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Second-generation total synthesis of aplyronine A featuring Ni/Cr-mediated coupling reaction

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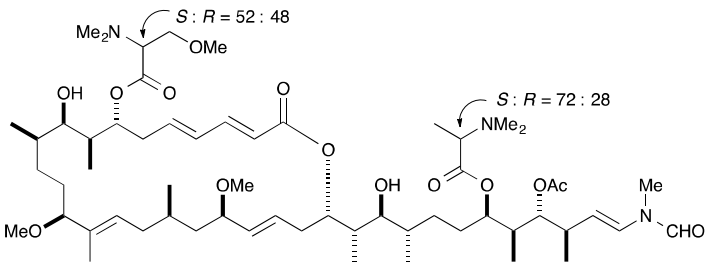
Second-generation total synthesis of aplyronine A, a potent antitumor marine macrolide, was achieved using Ni/Cr-mediated coupling reactions as key steps. The overall yield of the second-generation synthetic pathway of aplyronine A was 1.4%, obtained in 38 steps based on the longest linear sequence. Compared to our first-generation synthetic pathway of aplyronine A, the second-generation synthesis greatly improved both the yield and number of steps. In particular, we improved the stereoselectivity in the construction of the C13 stereogenic center and the C14–C15 (*E*)-trisubstituted double bond using the asymmetric Ni/Cr-mediated coupling reaction. Furthermore, we established efficient reaction conditions for the asymmetric Ni/Cr-mediated coupling reaction between the C21–C28 segment and C29–C34 segment. Thus, this coupling reaction proceeded with an equimolar ratio of each segment.

Introduction

Aplyronine A (**1**) is a marine macrolide isolated from the Japanese sea hare *Aplysia kurodai* by Yamada and co-workers (Fig. 1).[1] Aplyronine A (**1**) exhibited strong cytotoxicity against HeLa S_3 cells *in vitro*, and potent antitumor activities *in vivo* against P388 leukemia, Lewis lung carcinoma, and Ehrlich carcinoma.[2] Previously, we have revealed structure–activity relationships,[3] target proteins,[4] and mechanisms of action of aplyronine A (**1**)[5] based on organic synthesis. Aplyronine A (**1**) possesses unique mechanisms of action. Thus, aplyronine A (**1**) forms a 1 : 1 : 1 heterotrimeric complex with actin and tubulin, and inhibits tubulin polymerization. Like aplyronine A (**1**), FK-506 and rapamycin are known to induce protein–protein interactions (PPIs) in natural products.[6] In addition, inhibitors of tubulin polymerization, such as vinblastine, have been clinically important drugs, especially for breast cancer.[7] Therefore, aplyronine A (**1**) can be expected to become a lead compound in novel-type anticancer drugs.



aplyronine A (**1**)

Fig. 1 Structure of aplyronine A (**1**)

The potent and unique biological activities of aplyronine A (**1**) have made it an attractive synthetic target.[8] Several groups have reported approaches to synthesizing aplyronine A (**1**) and its related derivatives. In 2013, Paterson and co-workers achieved total synthesis of aplyronine C,[9] which is a natural analogue of aplyronine A (**1**). Prior to that report, we described the first total synthesis of aplyronine A (**1**).[10] This synthesis made it possible to evaluate *in vivo* antitumor activities, and to prepare chemical probes to elucidate the mechanisms of

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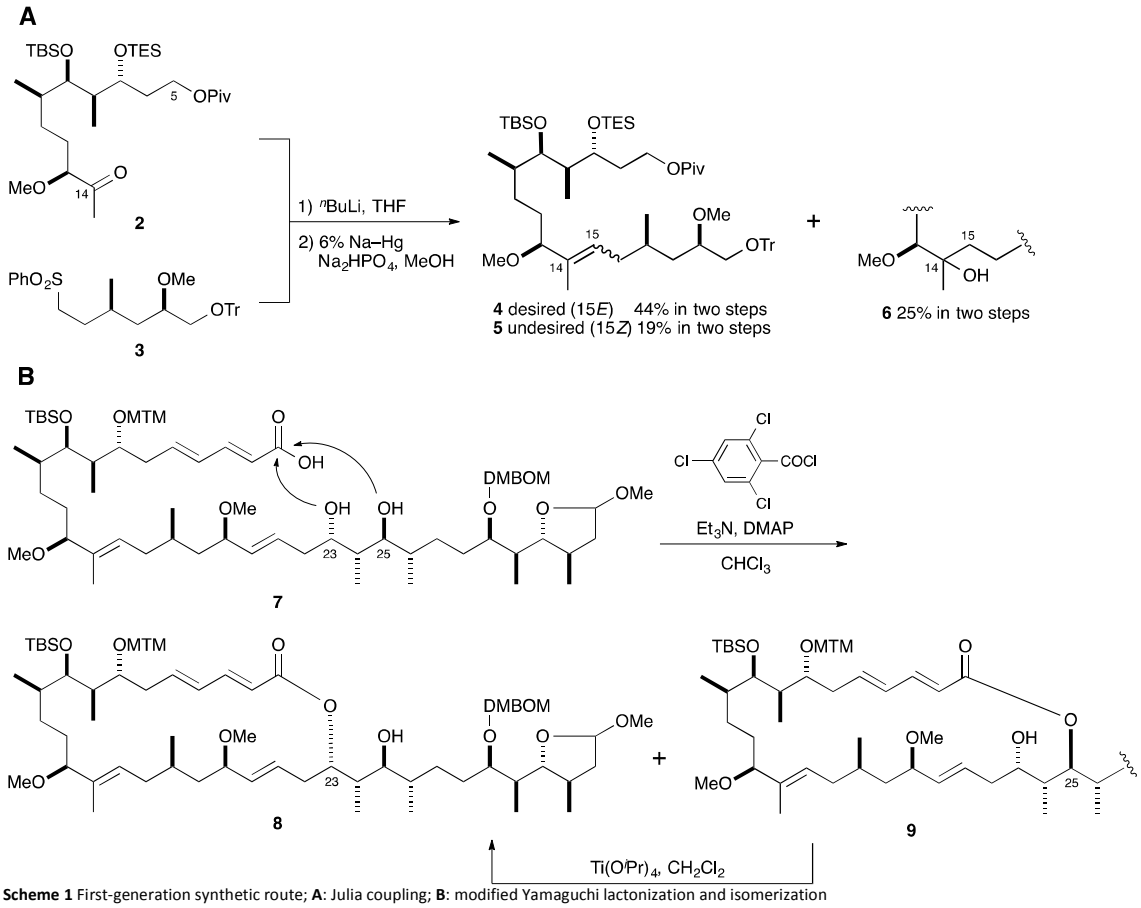
action of aplyronine A (**1**). However, our previous synthetic route included a few steps with low yield and poor stereoselectivity. We therefore sought an efficient second-generation route to aplyronine A (**1**) and its derivatives that could provide a practical supply for further biological studies. Here, we describe the efficient second-generation total synthesis of aplyronine A (**1**), featuring Ni/Cr-mediated coupling reactions as key steps.

In our first-generation total synthesis of aplyronine A (**1**),[10] we constructed the C14–C15 (*E*)-trisubstituted double bond using Julia coupling because of the advantage that recovering the unreacted sulfone segment was much easier than using Wittig phosphonium salts.[11] However, Julia coupling between ketone **2** and sulfone **3**, and the subsequent reduction of the hydroxy sulfone, produced undesired (*Z*)-olefin **5** (19%) and C14 tertiary alcohol **6** (25%), along with the desired (*E*)-olefin **4** (44%) (Scheme 1A). In addition, when macrolactonization of seco-acid **7**, which has two hydroxy groups at C23 and C25 as possible reaction sites, was conducted under the modified Yamaguchi conditions,[12] the desired 24-membered lactone **8** and the undesired 26-membered lactone **9** were produced in a ratio of ca. 4 : 3. Therefore, the undesired 26-membered lactone **9** had to be isomerized to 24-membered lactone **8** *via* an ester exchange reaction with $Ti(O^iPr)_4$ (Scheme 1B). We consider that these problems of poor stereoselectivity and/or regioselectivity could be improved by using the Ni/Cr-mediated coupling reaction.[13] In 2012, we reported the synthesis of the aplyronine A–mycalolide B hybrid molecule consisting of the macrolactone portion in aplyronine A (**1**) and the side chain portion in mycalolide B, with featuring Ni/Cr-mediated coupling reactions as key steps.[14] This synthesis improved the problems outlined above. Thus, we planned the second-generation total synthesis of aplyronine A (**1**) based on the synthetic strategy of the aplyronine A–mycalolide B hybrid molecule.



Scheme 1 First-generation synthetic route; **A**: Julia coupling; **B**: modified Yamaguchi lactonization and isomerization

Results and discussion

The second-generation retrosynthetic pathway of aplyronine A (**1**) is shown in Scheme 2. Aplyronine A (**1**) would be obtained from **10**, the same intermediate as in our first-generation synthesis.[10] The macrolactone portion in **10** might be assembled from cyclization precursor **11** using the intramolecular Ni/Cr-mediated coupling (Nozaki–Hiyama–Takai–Kishi coupling) reaction.[13] Cyclization precursor **11** can be constructed by intermolecular esterification between carboxylic acid **12** and alcohol **13**. In our previous work,[15] carboxylic acid **12**, which is the C1–C19 segment, was prepared

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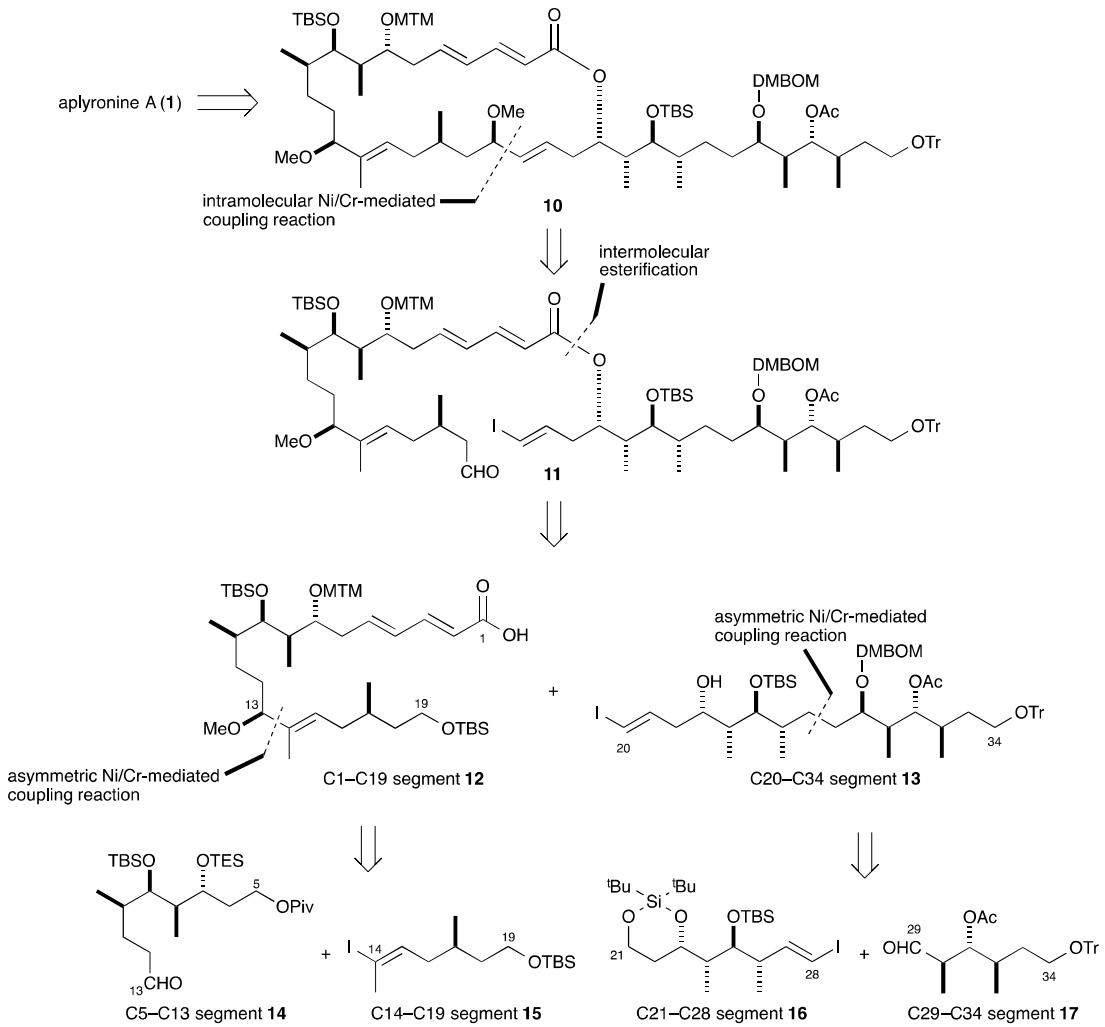
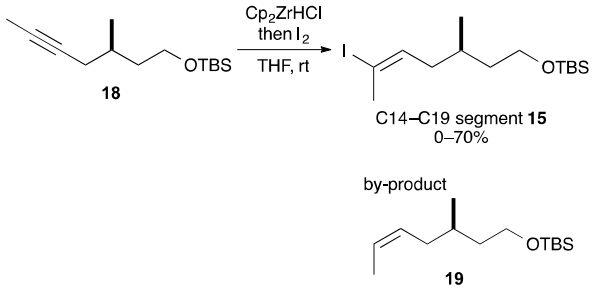
from aldehyde **14** and iodoolefin **15** by an asymmetric Ni/Cr-mediated coupling reaction.[16] This strategy has the benefit of forming the C14–C15 (*E*)-trisubstituted double bond and the C13 stereogenic center simultaneously. In addition, the C20–C34 segment **13** might also be obtained from iodoolefin **16** and aldehyde **17**[14] by an asymmetric Ni/Cr-mediated coupling reaction followed by hydrogenation.



Scheme 2 Retrosynthetic pathway of aplyronine A (**1**)

In our preliminary report,[15] iodoolefin **15** was stereoselectively constructed from compound **18** by a regioselective hydrozirconation with Schwartz's reagent (Scheme 3).[17] However, this reaction was not reproducible (0–70%) and afforded reduced compounds, such as **19**, as by-products in some cases. Thus, preparation of iodoolefin **15** required optimization.



Scheme 3 Previous synthetic route: hydrozirconation of **18**

We attempted the silylcupration of internal alkyne in **18**, with subsequent iododesilylation (Table 1).[18] Thus, treatment of **18**

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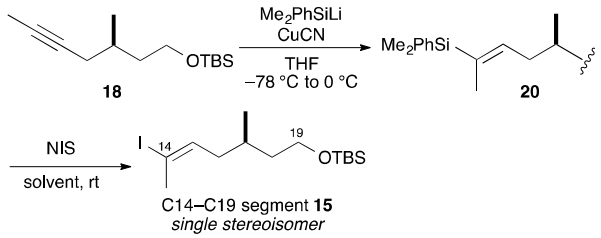
with CuCN and $PhMe_2SiLi$[19] gave vinylsilane **20** as a single isomer with quantitative yield. We next tried iododesilylation of **20** with NIS. The Holton and Zakarian groups reported stereoselective iododesilylation with NIS in hexafluoroisopropanol.[20] We attempted to reproduce the Zakarian-reported conditions[20b] to obtain the desired iodoolefin **15** in moderate yields (entries 1 and 2). Treatment of vinylsilane **20** with NIS in MeCN–THF (3 : 1) afforded the desired iodoolefin **15** as a single isomer (entry 3).[21] This modification made the reaction reproducible and increased the yield of the desired iodoolefin **15** to 96% in two steps.

Table 1 Iododesilylation of **18**

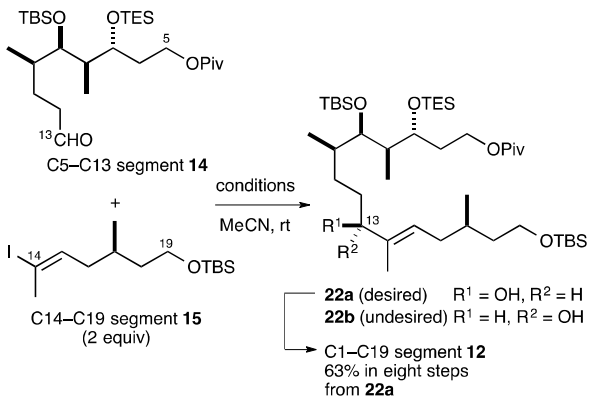


Entry	Solvent	**15** in two steps (from **18**)
1	$(CF_3)_2CHOH$	39%
2	$(CF_3)_2CHOH$–CH_2Cl_2 (4:1)	58%
3	MeCN–THF (3:1)	96%

We next investigated the Ni/Cr-mediated coupling reaction between the C5–C13 segment **14**[15] and C14–C19 segment **15** (Table 2). The constructions of trisubstituted olefins *via* asymmetric Ni/Cr-mediated coupling reaction have been few and far between, and investigation of this reaction was a synthetic challenge.[22] We first tried the Ni/Cr-mediated coupling reaction under standard conditions (0.1 w/w% $NiCl_2/CrCl_2$, DMSO)[13] without a chiral ligand. We found the reaction was completed to give the desired coupling compound **22** in 96% yield as a 1 : 1 diastereomixture at C13. This result suggested that the stereochemistry of C13 could be controlled by the Ni/Cr-mediated coupling reaction with a chiral ligand. Thus, we screened several known chiral sulfonamide ligands for the asymmetric Ni/Cr-mediated coupling reactions,[15] but known sulfonamide ligands with high yield and stereoselectivity were not found in this screening.[15b] Results of the screening, however, led to the following conclusions: (1) a large substituent on the sulfonamide group prevented the transmetalation of the vinyl-Ni(II) species to Cr(III) ones and thereby decreased the yield of the coupling product; (2) a large substituent on the oxazoline ring induced the high stereoselectivity because of its steric hindrance; and (3) electron-donating substituents on the benzene ring improved the stereoselectivity due to enhanced affinity to Cr, which reduced the ligand-free Ni/Cr-mediated coupling reaction.[15] Therefore, in consideration of all the above, we designed and synthesized chiral ligand **21**, which has a large ^{t}Bu group on the oxazoline ring, a small methyl group on the sulfonamide group, and three methoxy groups on the benzene ring, based on the chiral sulfonamide ligands developed by Kishi (Fig. 2).[15]

We used our modified ligand **21** to carry out an asymmetric Ni/Cr-mediated coupling reaction between the C5–C13 segment **14** and C14–C19 segment **15** (Table 2). In entry 1, the coupling reaction with ligand **21** (8.0 equiv) and $CrCl_2$ (8.0 equiv) yielded the coupling compound **22** as a diastereomeric mixture (**22a**/**22b** = 3.7 : 1, quantitative yield).[15,23] We speculated that one reason for the low diastereoselectivity was that there was insufficient formation of the Cr–ligand complex. Thus, we next tried a coupling reaction with $CrCl_2$ (3.1 equiv) and a small excess (against $CrCl_2$) of ligand **21** (3.5 equiv), and found that the diastereoselectivity was greatly improved (**22a**/**22b** = 7.3 : 1, 88% yield) (entry 2). The C13 isomers **22a** and **22b** were separated by silica gel column chromatography, and the desired **22a** was converted into the C1–C19 segment **12** by our previously established synthetic route (63% in eight steps).[15] The undesired **22b** could be inverted into the former by Mitsunobu reaction[24] or the oxidation–asymmetric reduction sequence.

Table 2 Optimization of the asymmetric Ni/Cr-mediated coupling reaction for improving stereoselectivity



Entry	$NiCl_2$(dppp) (equiv)	$CrCl_2$ (equiv)	Ligand **21** (equiv)	Proton-sponge® (equiv)	Yield (%) **22a** + **22b**	*d.r.*[a]
1	0.60	8.0	8.0	8.0	quant	3.7 : 1
2	0.15	3.1	3.5	3.0	88	7.3 : 1

[a] calculated by ^{1}H NMR

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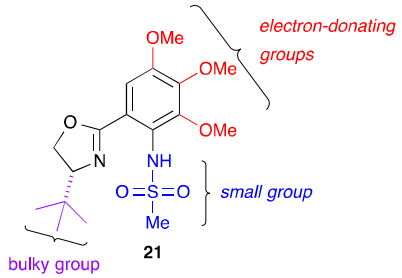
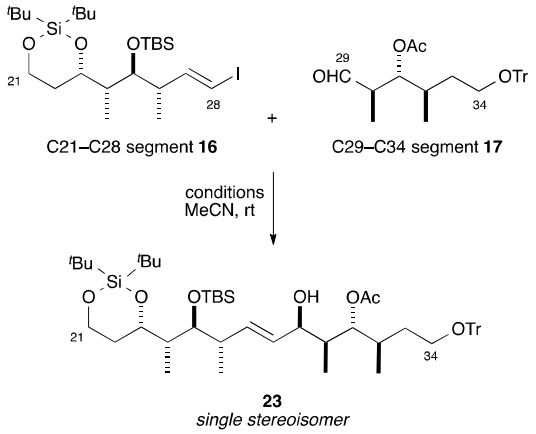


Fig. 2 Modified chiral sulfonamide ligand **21**

We next examined the synthesis of the C20–C34 segment **13**. The C21–C28 segment **16** and C29–C34 segment **17** were synthesized using as key steps the Mukaiyama Sn(II)-promoted aldol reaction,[25] Takai olefination,[26] and Roush crotylboration,[27] respectively (see the ESI†). Thus, we attempted the Ni/Cr-mediated coupling reaction between the C21–C28 segment **16** and C29–C34 segment **17** (Table 3). We first checked the substrate controllability of the chiral methyl group at the α-position of the aldehyde group in **17**. The ligand-free Ni/Cr-mediated coupling reaction (1 w/w% $NiCl_2/CrCl_2$, DMSO)[13] proceeded through the Felkin–Anh model to give priority to the desired diastereomer **23**. However, the yield and diastereoselectivity were moderate (50% yield, 4.6 : 1). Thus, we next examined the Ni/Cr-mediated coupling reaction with our modified chiral sulfonamide ligand **21**.[15] In entry 1, the asymmetric Ni/Cr-mediated coupling reaction proceeded smoothly to afford coupling compound **23** at an 80% yield as a single diastereomer.[23] In this case, the coupling reaction was performed with 2.0 equiv of vinyl iodide **16**. Generally, ca. 1.5–2.0 equiv of a vinyl iodide against an aldehyde is used for the Ni/Cr-mediated coupling reaction. However, because the preparation of vinyl iodide **16** required more steps than that of aldehyde **17** in this case, we investigated the molar ratio of vinyl iodide **16** and aldehyde **17** in this asymmetric Ni/Cr-mediated coupling reaction.[28] In entry 2, the asymmetric Ni/Cr-mediated coupling reaction with an equimolar mixture of vinyl iodide **16** and aldehyde **17** gave the desired allylic alcohol **23** in 56% yield. Also, this coupling reaction proceeded slowly, and led to the decomposition of aldehyde **17**. In this result, the coupling yield was decreased from entry 1. However, the yield in entry 2 was acceptable when the consumption of vinyl iodide **16** was considered. Thus, we next optimized the coupling conditions using an equimolar mixture of vinyl iodide **16** and aldehyde **17**. For the enhanced reaction rate, we attempted this coupling reaction at a higher concentration, but the yield was slightly decreased (entry 3). We assumed that the cause of the decreased yield was that the reaction system was rendered acidic by the sulfonamide proton in ligand **21**. In entry 4, the reduction of each reagent to half the original amount was found to give the best yield (64%). Therefore, we improved the condition of the asymmetric Ni/Cr-mediated coupling reaction with an equimolar mixture of vinyl iodide **16** and aldehyde **17**.

Table 3 Optimization of the asymmetric Ni/Cr-mediated coupling reaction



Entry	**16** (equiv)	$NiCl_2$(dppp) (equiv)	$CrCl_2$ (equiv)	Ligand **21** (equiv)	Proton-sponge® (equiv)	Conc. (mM)	Yield (%)
1	2	0.5	10	10	10	15	80%[a]
2	1	0.5	10	10	10	15	56%
3	1	0.5	10	10	10	30	49%
4	1	0.2	5	5	5	30	64%

[a] The yield was calculated from aldehyde **17**.

Next, we attempted to synthesize the C20–C34 segment **13** from the desired coupling compound **23**. Reduction of the olefin in **23** and subsequent protection of the secondary hydroxy group gave DMBOM [{(3,4-dimethoxybenzyl)oxy}methyl] ether,[10] which was converted into diol **24** by selective desilylation of the silylene acetal group. Silylation of the diol group in **24** with TES groups gave di-TES ether, which was transformed into aldehyde **25** by selective removal of the primary TES group and oxidation of the resultant primary hydroxy group. Aldehyde **25** was converted into the C20–C34 segment **13** by Takai olefination[26] and selective removal of the TES group. Although C20–C34 segment **13** was obtained as an inseparable mixture of olefin stereoisomers (*E* / *Z* = 4.5 : 1), the stereoisomers could be chromatographically separated after several steps.

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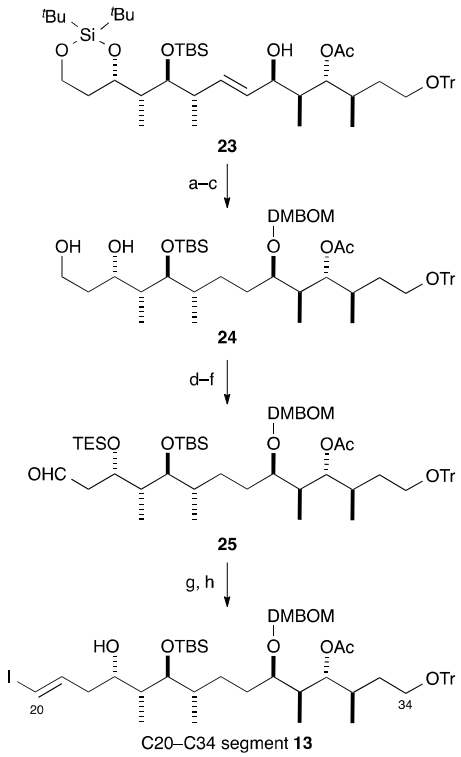
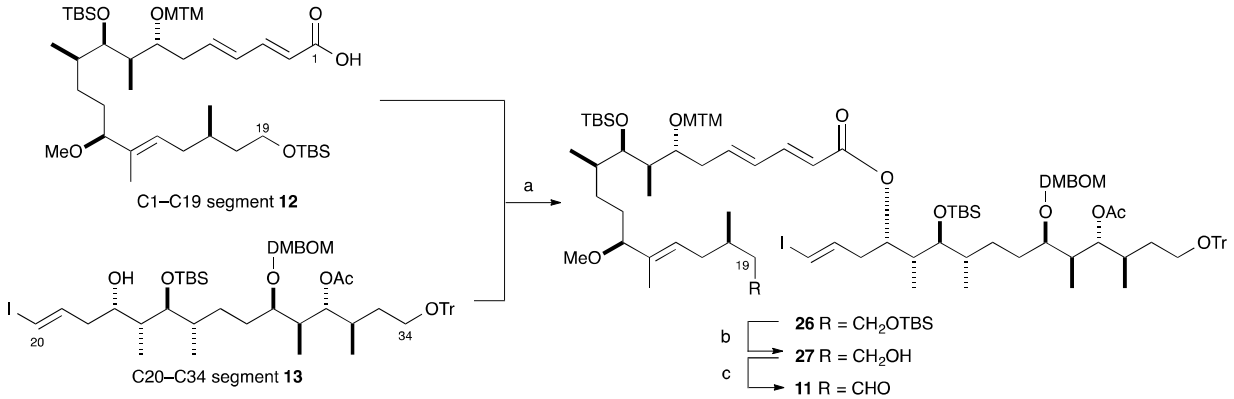


Scheme 4 Synthesis of C20–C34 segment **13**. *Reagents and conditions*: (a) H_2, $Pd(OH)_2/C$, $NaHCO_3$, EtOH, rt, 92%; (b) DMBOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 30 °C, 94%; (c) $^{n}Bu_4NF$, AcOH, THF, –5 °C, 91%; (d) TESCl, imidazole, DMF, rt, quant; (e) NH_4F, MeOH, rt, quant; (f) Dess–Martin peropdinane, py, CH_2Cl_2, rt, 93%; (g) $CrCl_2$, CHI_3, THF, rt, 91%, E/Z = 4.5 : 1; (h) AcOH, H_2O, THF, rt, 86%.

With both fragments C1–C19 segment **12** and C20–C34 segment **13** in hand, synthesis of a precursor for intramolecular Ni/Cr-mediated coupling reaction was examined next. In preparation for this, we followed our synthetic route for the aplyronine A–mycalolide B hybrid molecule (Scheme 5).[14] Thus, the C1–C19 segment **12** and C20–C34 segment **13** were esterified *via* Yamaguchi conditions[29] to give ester **26**, the *O*[19] TBS group of which was selectively removed to provide alcohol **27**. The resultant primary hydroxy group of **27** was oxidized to afford aldehyde **11** as a cyclization precursor.



Scheme 5 Synthesis of a precursor for the intramolecular Ni/Cr-mediated coupling reaction. *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, toluene, rt, 96%; (b) AcOH, H_2O, THF, rt, 93%; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 90%.

The intramolecular Ni/Cr-mediated coupling reaction was examined next (Table 4). Treatment of aldehyde **11** with 2.0 w/w% $NiCl_2/CrCl_2$ in DMSO (c = 10 mM)[13] gave the desired cyclization compound **28** (54%) and its diastereomer **29** (35%) (entry 1).[23] This intramolecular Ni/Cr-mediated coupling reaction proceeded smoothly at a 26-times higher concentration than that of the modified Yamaguchi macrolactonization[12] in our first-generation total synthesis of aplyronine A (**1**) (c = 0.39 mM).[30] The stereoisomer at the C20–C21 double bond could be separated after the intramolecular Ni/Cr-mediated coupling reaction of **11**. Then, we examined the asymmetric intramolecular Ni/Cr-mediated coupling reaction of **11** using our modified chiral ligand **30** (*ent*-**21**) (entry 2). Unexpectedly, the yield and diastereoselectivity of this cyclization were not improved (**28**: 41%, **29**: 18%). We thought that steric hindrance of vinyl–Cr(III)/ligand complex of **11** interfered with the intramolecular addition to the aldehyde

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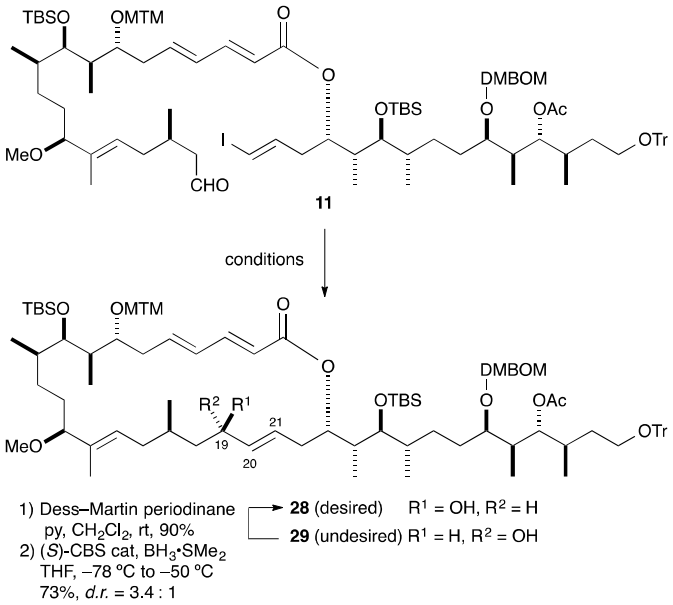
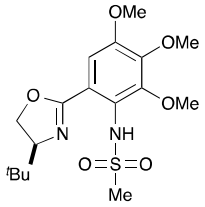
group. The undesired diastereomer **29** could be converted into the desired allylic alcohol **28** by oxidation of by using a sequence of Dess–Martin oxidation and CBS reduction.[31] To convert undesired diastereomer **29** into desired allylic alcohol **28**, we followed the procedure reported by Paterson.[9b]

Table 4 Intramolecular Ni/Cr-mediated coupling reaction of **11**



Entry	Conditions	Solvent	Yield (%) 28	29
1	2.0 w/w% $NiCl_2/CrCl_2$ ($NiCl_2$: 0.1 equiv, $CrCl_2$: 5.0 equiv)	DMSO (10 mM)	54	35
2	$NiCl_2$(dppp) (0.05 equiv), $CrCl_2$ (12 equiv), Ligand **30** (12 equiv), Proton-sponge® (11 equiv)	MeCN (2 mM)	41	18



Ligand **30**

Methylation of the hydroxy group at C19 in allylic alcohol **28** afforded methyl ether **10**, which was our intermediate in the first-generation total synthesis of aplyronine A (**1**) (Scheme 6).[10] The methyl ether **10** gave spectral data (^{1}H NMR and ^{13}C NMR spectroscopy, HRMS, and optical rotation) that were in full agreement with those of our authentic intermediate.[3a] To convert methyl ether **10** into aplyronine A (**1**), we followed our first-generation total synthesis (see the ESI†). The ^{1}H NMR data of synthetically obtained aplyronine A (**1**) were in good agreement with those of natural aplyronine A (**1**) (see the ESI†).

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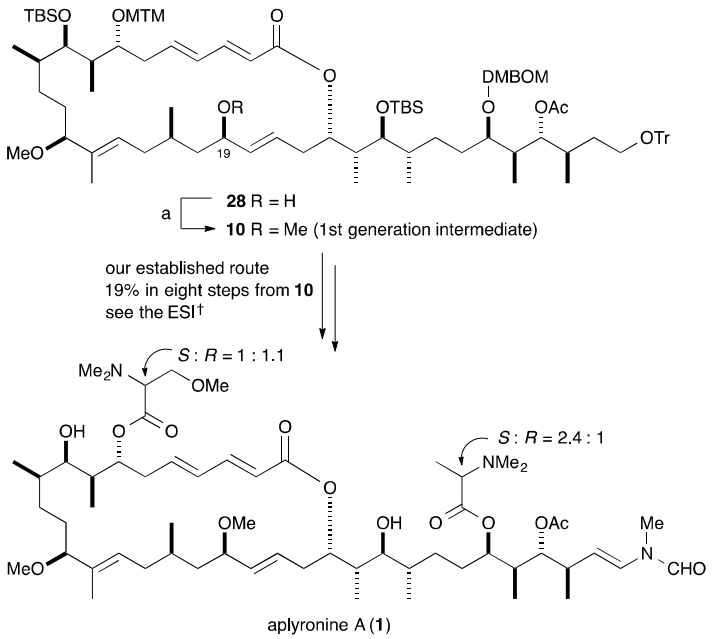

Scheme 6 Second-generation total synthesis of aplyronine A (**1**). *Reagents and conditions*: (a) MeI, NaH, THF, 35 °C, 90%.

Conclusions

In conclusion, we achieved second-generation total synthesis of aplyronine A (**1**). The overall yield of the second-generation synthetic pathway of aplyronine A (**1**), based on the longest linear sequence, was 1.4% in 38 steps (the total number of steps was 80 from the commercial materials.), a considerable improvement over our first-generation synthetic pathway of aplyronine A (**1**), which gave 0.39% overall yield in 47 steps in the longest linear sequence. We especially improved the stereoselectivity of the construction of the C13 stereogenic center and the C14–C15 (*E*)-trisubstituted double bond using the asymmetric Ni/Cr-mediated coupling reaction. Moreover, we established efficient reaction conditions for the asymmetric Ni/Cr-mediated coupling reaction between the C21–C28 segment **16** and the C29–C34 segment **17**. This coupling reaction proceeded well with an equimolar ratio of each segment. We consider that this synthetic strategy, which uses Ni/Cr-mediated coupling reactions as key steps, could be useful for the preparation of structurally diverse derivatives of aplyronine A (**1**). In fact, we have prepared aplyronine A (**1**) and an aplyronine A–mycalolide B hybrid molecule using this strategy. The strategy is now being applied to the synthesis of other derivatives based on aplyronine A (**1**) for development of lead compounds of novel-type anticancer agents.

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