ORGANIC LETTERS

2011
Vol. 13, No. 5
900–903

Toward the Second Generation Synthesis of Aplyronine A: Stereocontrolled Assembly of the C1−C19 Segment by Using an Asymmetric Nozaki−Hiyama−Kishi Coupling

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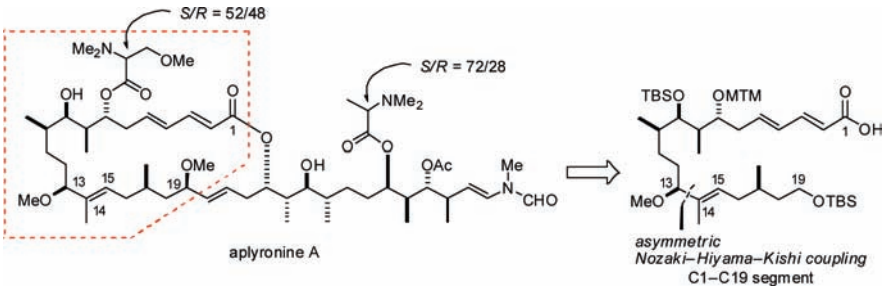
Received December 7, 2010

ABSTRACT



An efficient synthesis of the C1−C19 segment of aplyronine A is described. Stereoselective construction of the C14−C15 (*E*)-trisubstituted double bond and the C13 stereocenter was achieved by using an asymmetric Nozaki−Hiyama−Kishi coupling.

Aplyronine A (**1**), isolated from the sea hare *Aplysia kurodai* in 1993 by Yamada and co-workers, is a potent cytotoxic and antitumor macrolide (Figure 1).[1] Furthermore, aplyronine A (**1**) inhibits the polymerization of globular actin (G-actin) to fibrous actin (F-actin) by sequestering G-actin and forming a 1:1 complex, and also depolymerizes F-actin by a severing mechanism.[2] Thus, aplyronine A (**1**) is expected to be a new type of anticancer chemotherapeutic agent. Its complex structure and potent biological activities have attracted considerable attention from the synthetic community.[3]

Although we have previously accomplished the first total synthesis of aplyronine A (**1**),[4] our previous route involved a few steps that showed both low yield and poor selectivity. In particular, Julia coupling between ketone **2**

(1) (a) Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020. (b) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8501. (c) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Nisiwaki, M.; Tsukada, I.; Mizuta, K.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8505. (d) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Tsukada, I.; Tsuboi, T.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7441.

(2) Saito, S.; Watabe, S.; Ozaki, H.; Kigoshi, H.; Yamada, K.; Fusetani, N.; Karaki, H. *J. Biochem.* **1996**, *120*, 552.

(3) (a) Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037. (b) Paterson, I.; Woodrow, M. D.; Cowden, C. J. *Tetrahedron Lett.* **1998**, *39*, 6041. (c) Paterson, I.; Blakey, S. B.; Cowden, C. J. *Tetrahedron Lett.* **2002**, *43*, 6005. (d) Calter, M. A.; Guo, X. *Tetrahedron* **2002**, *58*, 7093. (e) Calter, M. A.; Zhou, J. *Tetrahedron Lett.* **2004**, *45*, 4847. (f) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501. (g) El-Awa, A.; Fuchs, P. *Org. Lett.* **2006**, *8*, 2905.

(4) (a) Kigoshi, H.; Ojika, M.; Suenaga, K.; Mutou, T.; Hirano, J.; Sakakura, A.; Ogawa, T.; Nisiwaki, M.; Yamada, K. *Tetrahedron Lett.* **1994**, *35*, 1247. (b) Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; Mutou, T.; Sakakura, A.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7443. (c) Suenaga, K.; Ishigaki, T.; Sakakura, A.; Kigoshi, H.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 5053. (d) Kigoshi, H.; Suenaga, K.; Mutou, T.; Ishigaki, T.; Atsumi, T.; Ishikawa, H.; Sakakura, A.; Ogawa, T.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 5326.

10.1021/ol1029657
Published on Web 01/26/2011

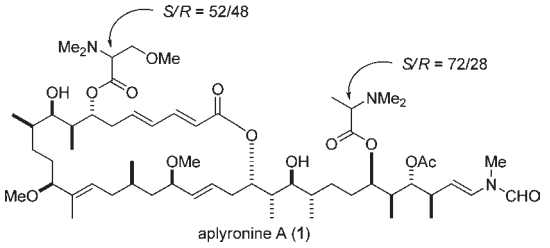
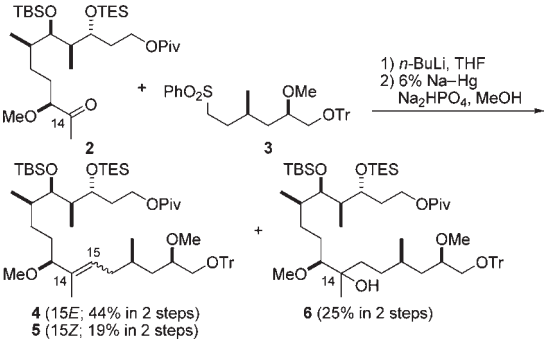


Figure 1. Structure of aplyronine A (**1**).

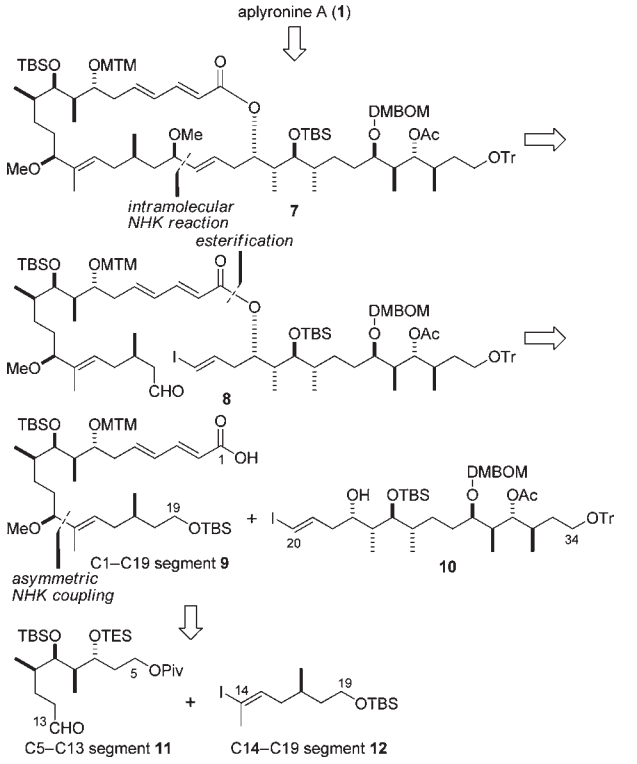
Scheme 1. Our Previous Work



and sulfone **3** and subsequent reduction yielded the undesired (*Z*)-olefin **5** (19%) and the C14 tertiary alcohol **6** (25%) along with the desired (*E*)-olefin **4** (44%) (Scheme 1). Therefore we planned to develop stereoselective construction of the C14−C15 (*E*)-trisubstituted double bond for the second generation total synthesis of aplyronine A (**1**), which would provide a practical supply of **1** for further biological studies. Herein we describe an efficient stereocontrolled construction of the C1−C19 segment of aplyronine A (**1**).

The second generation retrosynthetic analysis of aplyronine A (**1**) is shown in Scheme 2. Aplyronine A (**1**) would be obtained from **7**, the same intermediate as that in the first generation synthesis.[4b,c] The macrolactone part in **7** can be constructed by an intramolecular Nozaki−Hiyama−Kishi (NHK) reaction[5] of compound **8**. Disconnection of the ester moiety of **8** provides carboxylic acid **9** and alcohol **10**. The C1−C19 segment **9** can be derived from aldehyde **11** and iodoolefin **12** by an asymmetric NHK coupling[6] as a key step. This strategy has the benefit of constructing the

Scheme 2. Second-Generation Retrosynthetic Analysis of Aplyronine A (**1**)



C14−C15 (*E*)-trisubstituted double bond and the C13 stereocenter at once. Also, construction of trisubstituted olefins by using an asymmetric NHK coupling has never been reported to date, and investigation of this reaction was a synthetic challenge.

Synthesis of the C5−C13 segment **11** started from alcohol **13**,[4b,c] which was the intermediate in our first generation synthesis of aplyronine A (**1**) (Scheme 3). The secondary hydroxy group in **13** was protected as a TES ether, and the benzyl group was removed. The resulting primary alcohol was converted into tosylate **14**. We next attempted three-carbon homologation of **14** using allylmagnesium bromide in the presence of Cu(I) salt[7] to obtain not the homologue compound but the depivaloyl compound. However, the use of excess allylmagnesium bromide without Cu(I) salt in boiling Et_2O gave the terminal olefin **15** in good yield (92%) with concomitant cleavage of the pivaloyl group. Reprotection of the resulting hydroxy group in **15** with a pivaloyl group and dihydroxylation of the terminal olefin gave a diol, which was readily converted into the desired aldehyde **11** as a C5−C13 segment by oxidative cleavage in two steps and 97% yield.

Iodoolefin **12** as a C14−C19 segment was prepared as follows (Scheme 4). Oxidation of alcohol **16**[8] provided

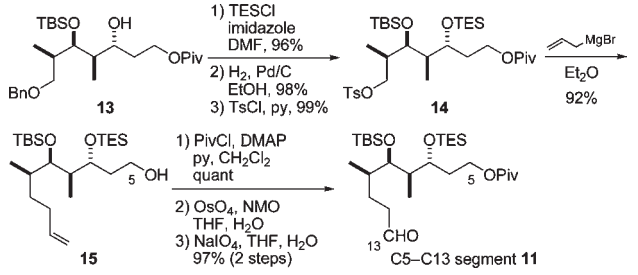
(5) (a) Jin, H.; Uenichi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (c) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.

(6) (a) Wan, Z.-K.; Choi, H.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431. (b) Choi, H.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435. (c) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031. (d) Namba, K.; Cui, S.; Wang, J.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5417. (e) Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387.

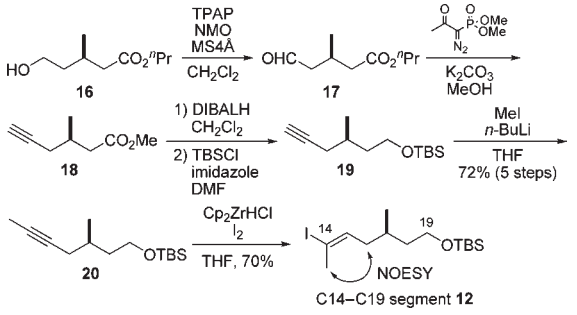
(7) (a) Kotsuki, H.; Miyazaki, A.; Ochi, M.; Sims, J. J. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 721. (b) Wipf, P.; Uto, Y.; Yoshimura, S. *Chem.—Eur. J.* **2002**, *8*, 1670.

(8) Ito, H.; Inoue, T.; Iguchi, K. *Org. Lett.* **2008**, *10*, 3873.

Scheme 3. Synthesis of C5−C13 Segment **11**



Scheme 4. Synthesis of C14−C19 Segment **12**



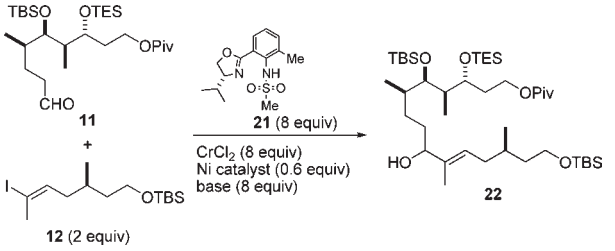
aldehyde **17**, which was subjected to an Ohira−Bestmann reaction[9] to yield acetylene **18** with concomitant transesterification by MeOH. The methyl ester group in **18** was reduced by DIBALH, and the resulting alcohol was subsequently converted into the TBS ether **19**. Introduction of the methyl group to the terminal alkyne of **19** with *n*-BuLi/MeI gave **20** in 72% yield from **16** (five steps). Regioselective hydrozirconation of compound **20** by Schwartz's reagent[10] followed by quenching with iodine afforded the C14−C19 segment **12** in 70% yield. The stereochemistry of the resulting (*E*)-trisubstituted double bond of **12** was determined by the NOESY correlation between the allylic methylene protons and the vinyl methyl protons.

With both fragments **11** and **12** in hand, an asymmetric NHK coupling reaction was next examined. First, we optimized the solvent and Ni catalyst (Table 1). The coupling reaction between **11** and **12** using $CrCl_2$/$NiCl_2$/ligand **21**/Et_3N/THF reported by Kishi and co-workers[6a] gave the coupling product **22**, but the yield was only 7% (entry 1). Next, we screened solvents by using $NiCl_2$·DMP as a Ni catalyst and proton-sponge as a base (entries 2−4).[6c,d] From these results, this coupling reaction was the most efficient in CH_3CN (entry 4).[6c,d] In entries 4−6, we screened an assortment of Ni catalysts based on Kishi's reports.[6c,d] The reaction with $NiCl_2$(dppp) in CH_3CN gave the best result in this case (entry 6); however, we could not satisfy the stereoselectivity under this condition

(9) Ohira, S. *Synth. Commun.* **1989**, *58*, 561.

(10) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed.* **1976**, *15*, 333.

Table 1. Optimization of Reaction Conditions: Solvent and Ni Catalyst



entry	Ni catalyst	solvent	base	yield (%)[a]
1	$NiCl_2$	THF	Et_3N	7[c]
2	$NiCl_2$·DMP[b]	THF	proton-sponge	58[c]
3	$NiCl_2$·DMP[b]	DME	proton-sponge	0
4	$NiCl_2$·DMP[b]	CH_3CN	proton-sponge	86[c]
5	$NiCl_2$	CH_3CN	proton-sponge	82[c]
6	$NiCl_2$(dppp)	CH_3CN	proton-sponge	96 (S/R = 2.8:1)[d]

[a] Isolated yield calculated from **11**. [b] $NiCl_2$·DMP: 2,9-dimethyl-1,10-phenanthroline−$NiCl_2$ complex. [c] The stereoselectivity was not determined. [d] The stereochemistry was confirmed by modified Mosher's method.

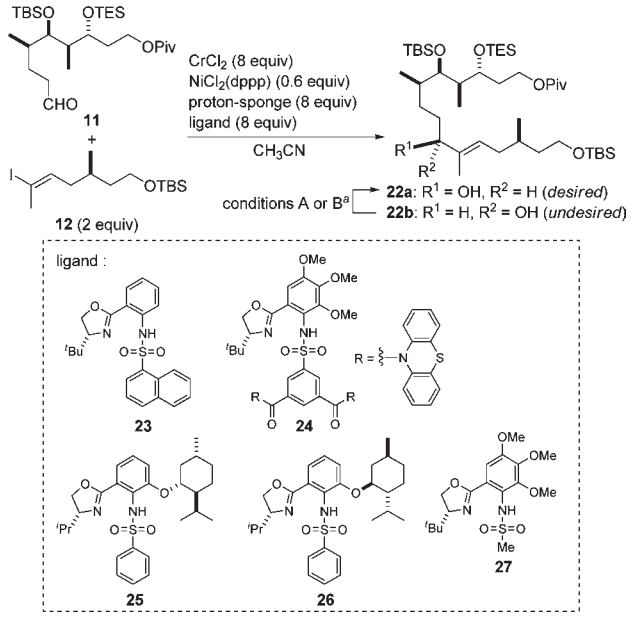
(S/R = 2.8:1).[11] Therefore, we next screened chiral sulfonamide ligands of an asymmetric NHK coupling.

The investigation of an asymmetric NHK coupling with several chiral sulfonamide ligands is summarized in Table 2. Attempts at an asymmetric NHK coupling with chiral sulfonamide ligands, such as **23**[6a,c] or **24**,[6d] improved the stereoselectivity, but the yields were low (entries 1 and 2). The ligand **25** recently developed by Kishi and co-workers[6e] and its diastereomer **26** were also tested and gave excellent yields, but the stereoselectivities were low (2.8:1 for **25**, 2.0:1 for **26**) (entries 3 and 4). From these results, we assumed that (1) a large substituent on the sulfonamide group prevented the transmetalation of the vinyl-Ni(II) species to Cr(III) 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 the enhanced affinity to Cr. Thus, we designed and synthesized ligand **27**,[12] 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. As expected, the coupling reaction with ligand **27** gave the best result: **22a**/**22b** = 3.7:1, 100% yield (entry 5). Furthermore, the reagent loadings were successfully reduced

(11) (a) The stereochemistry was confirmed by the modified Mosher's method (see Supporting Information). (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(12) Ligand **27** was prepared from a known aniline (see Supporting Information).[6c]

Table 2. Optimization of Chiral Sulfonamide Ligands



entry	ligand	yield (%)[b]	dr[c,d] 22a/22b
1	**23**	46	3.4:1
2	**24**	40	3.9:1
3	**25**	98	2.8:1
4	**26**	100	2.0:1
5	**27**	100	3.7:1

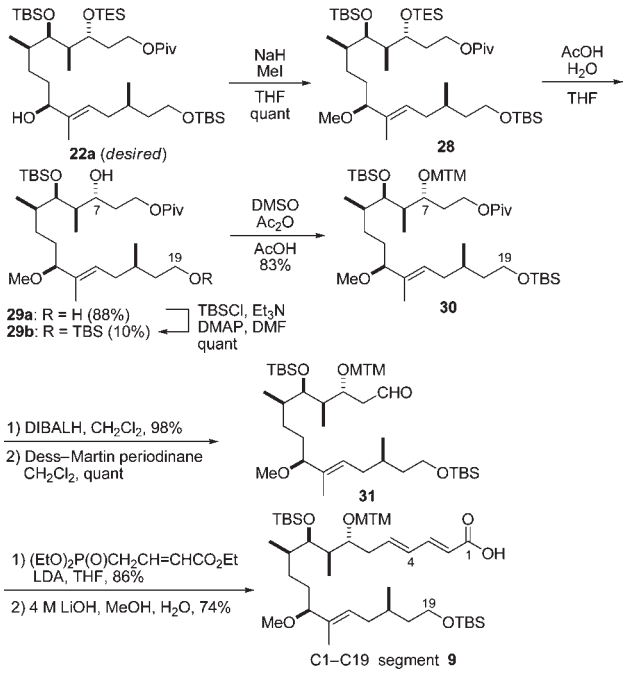
[a] Conditions A: (1) Dess−Martin periodinane, py, CH_2Cl_2, 98%, (2) (*R*)-CBS catalyst, $BH_3 \cdot SMe_2$, THF, 89% (> 95:5 dr). Conditions B: (1) *p*-$NO_2C_6H_4CO_2H$, PPh_3, DEAD, THF, 97%, (2) K_2CO_3, MeOH, 96%. [b] Isolated yield calculated from **11**. [c] The ratio was determined by ^1H NMR analysis. [d] The stereochemistry was confirmed by modified Mosher's method.

to 4 equiv of $CrCl_2$, 0.1 equiv of $NiCl_2$(dppp), 4 equiv of proton-sponge, and 4 equiv of ligand **27** without loss of product yield or stereoselectivity. The two diastereomers **22a** and **22b** were separated by flash column chromatography. Paterson and co-workers achieved stereoselective introduction of the C13 hydroxy group by using CBS reduction[13] of a similar ketone.[3b] We followed this procedure, and oxidation of C13 epimer **22b** with Dess−Martin periodinane followed by CBS reduction[13] afforded the desired isomer **22a**. Alternatively, C13 epimer **22b** could be converted to the desired isomer **22a** via a Mitsunobu reaction[14] in good yield.

To convert **22a** into C1−C19 segment **9**, we followed our first generation synthetic strategy (Scheme 5). *O*-Methylation of the C13 hydroxy group in **22a** with NaH/MeI gave methyl ether **28** in quantitative yield. Treatment of **28** with aqueous acetic acid in THF afforded diol **29a** (88%) along with alcohol **29b** (10%). The C19 hydroxy group in **29a** was reprotected as a TBS ether, and the remaining C7

(13) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
(14) Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme 5. Synthesis of C1−C19 Segment **9**



secondary hydroxy group was protected as an MTM ether to give compound **30**. Reductive cleavage of the pivaloyl group in **30** by DIBALH and oxidation of the resulting hydroxy group with Dess−Martin periodinane gave aldehyde **31**. The Horner−Wadsworth−Emmons reaction of **31** with $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$ afforded α,β,γ,δ-unsaturated ester in 86% yield, which contained a small amount (about 5%) of (4*Z*)-isomer. The minor (4*Z*)-isomer can be separated by HPLC at a later stage in the synthesis.[4b,d] Finally, hydrolysis of the ethyl ester group with LiOH in aqueous methanol afforded C1−C19 segment **9**.

In conclusion, we have developed a stereocontrolled synthesis of the C1−C19 segment **9** of aplyronine A, featuring an asymmetric NHK coupling reaction between aldehyde **11** and iodoolefin **12** to construct the C14−C15 (*E*)-trisubstituted double bond and the C13 stereocenter in one step. Studies on the synthesis of the C20−C34 segment **10** and further investigation toward the second generation total synthesis of aplyronine A are in progress.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research, from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan; by a grant from the Uehara Memorial Foundation; and by a grant from the Suntory Institute for Bioorganic Research (SUNBOR GRANT).

Supporting Information Available. Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.