

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/45648145>

Total Synthesis of (-)-Apicularen A

ARTICLE *in* ORGANIC LETTERS · SEPTEMBER 2010

Impact Factor: 6.36 · DOI: 10.1021/ol101753y · Source: PubMed

CITATIONS

18

READS

14

2 AUTHORS, INCLUDING:



Sanjay Palimkar

Advinus Therapeutics

12 PUBLICATIONS 492 CITATIONS

SEE PROFILE

Total Synthesis of (–)-Apicularen A

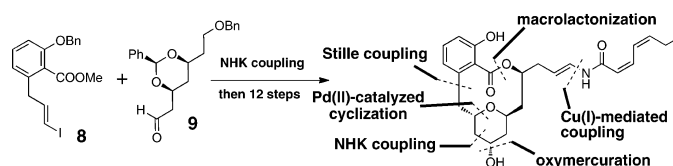
Sanjay S. Palimkar and Jun'ichi Uenishi*

Kyoto Pharmaceutical University, Misasagi Yamashina, Kyoto 607-8412, Japan

juenishi@mb.kyoto-phu.ac.jp

Received July 27, 2010

ABSTRACT



A convergent total synthesis of (–)-apicularen A, a highly cytostatic 12-membered macrolide, has been accomplished. The key steps include assembling of iodoalkene **8** and aldehyde **9** by Nozaki–Hiyama–Kishi (NHK) coupling, stereospecific construction of 2,6-*trans*-disubstituted dihydropyran by Pd(II)-catalyzed 1,3-chirality transfer reaction, and Yamaguchi macrolactonization. Introduction of the (2Z,4Z)-heptadienamide moiety in the side chain by an efficient Cu(I)-mediated coupling completed the total synthesis.

Kunze et al. reported the isolation of (–)-apicularen A (**1**) from a variety of strains of the myxobacterial genus *Chondromyces* in 1998.¹ Subsequently, the gross structure of **1** including the relative and absolute stereochemistry was determined.² Biological studies revealed **1** to be highly cytostatic to a wide range of human cancer cell lines such as ovarian, prostate, lung, kidney, cervix, leukemia, and histiocytic cells with IC₅₀ values in the range of 0.23–6.79 nM.¹ In addition, recent reports indicated that **1** exhibited antiangiogenesis properties,^{3a} induced apoptosis,^{3b,c} produced nitric oxide,^{3d} acted as a novel specific V-ATPase inhibitor,^{3e,f} and was a promising new microtubule-targeting compound.^{3g}

From a structural point of view, **1** is characterized by a number of motifs such as a 2,6-*trans*-tetrahydropyran ring

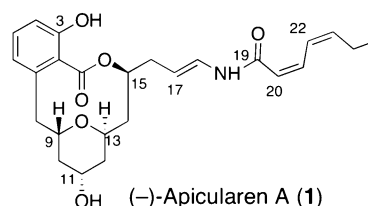


Figure 1. Structure of (–)-Apicularen A.

embedded in a 12-membered salicylate macrolactone and four stereogenic centers within the macrolactone core which bears a highly unsaturated *N*-acylenamine side chain.

Because of its fascinating molecular architecture and potent biological activity, **1** has been targeted by a number of synthetic research groups. To date, four total syntheses of **1**⁴ have been achieved along with four formal total syntheses.⁵ A number of synthetic efforts⁶ as well as syntheses of analogues⁷ have also been reported.

(1) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075–1080.

(2) Jansen, R.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **2000**, 913–919.

(3) (a) Kwon, H. J.; Kim, D. H.; Shik, J. S.; Ahn, J. W. *J. Microbiol. Biotechnol.* **2002**, *12*, 702–705. (b) Hong, J.; Yamaki, K.; Ishihara, K.; Ahn, J.-W.; Zee, O.; Ohuchi, K. *J. Pharm. Pharmacol.* **2003**, *55*, 1299–1306. (c) Hong, J.; Ishihara, K.; Zee, O.; Ohuchi, K. *Planta Med.* **2005**, *71*, 306–312. (d) Hong, J.; Yokomakura, A.; Nakano, Y.; Ban, H. S.; Ishihara, K.; Ahn, J.-W.; Zee, O.; Ohuchi, K. *J. Pharmacol. Exp. Ther.* **2005**, *312*, 968–977. (e) Hong, J.; Yokomakura, A.; Nakano, Y.; Ishihara, K.; Kaneda, M.; Onodera, M.; Nakahama, K.; Morita, I.; Niikura, K.; Ahn, J.-W.; Zee, O.; Ohuchi, K. *FEBS Lett.* **2006**, *580*, 2723–2730. (f) Huss, M.; Sasse, F.; Kunze, B.; Jansen, R.; Steinmetz, H.; Ingenhorst, G.; Zeeck, A.; Wiczorek, H. *BMC Biochem.* **2005**, *6*, 13. (g) Kim, J.-S.; Lee, Y.-C.; Nam, H.-T.; Li, G.; Yun, E.-J.; Song, K.-S.; Seo, K.-S.; Park, J.-H.; Ahn, J.-W.; Zee, O.; Park, J.-I.; Yoon, W.-H.; Lim, K.; Hwang, B.-D. *Clin. Cancer Res.* **2007**, *13*, 6509–6517.

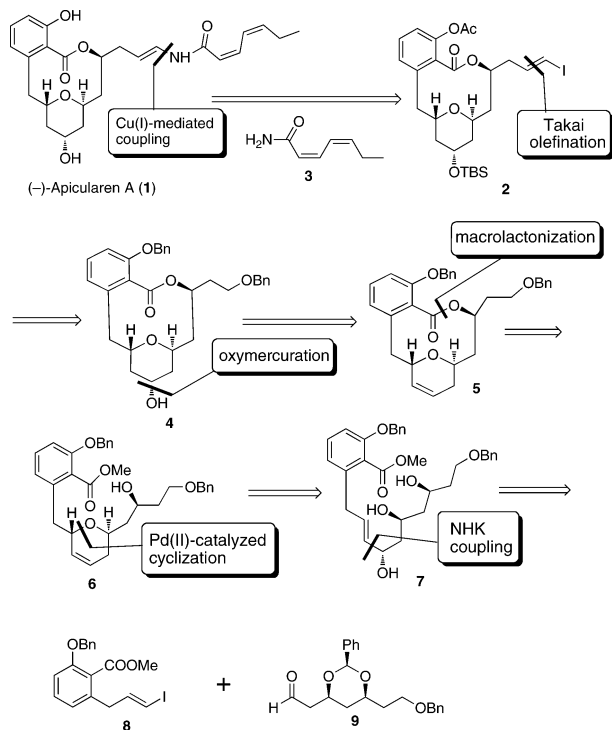
(4) (a) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217–1220. (b) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701–3704. (c) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430. (d) Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5821–5823.

(5) (a) Graetz, B. R.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357–3360. (b) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1289–1292. (c) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087–6090. (d) Jung, Y.-H.; Kim, Y. J.; Lee, J.; Tae, J. *Chem.-Asian J.* **2007**, *2*, 656–661.

Our interest in the synthesis of (–)-apicularen A stemmed from its molecular architecture of a bridged 2,6-*trans*-tetrahydropyran located in a 12-membered macrolactone ring. Recent work in our laboratory has provided a facile access to stereodefined either 2,6-*cis*- or *trans*-disubstituted dihydropyran and tetrahydropyran rings by using Pd(II)-catalyzed 1,3-chirality transfer reactions.^{8,9} We sought to apply our Pd(II)-catalyzed cyclization strategy to the synthesis of **1**. Herein, we report the total synthesis of (–)-apicularen A using the Pd(II)-catalyzed cyclization for the construction of the core 2,6-*trans*-tetrahydropyran ring.

Our retrosynthetic plan is outlined in Scheme 1. Nicolaou et al.^{4b} introduced a conjugated (*Z,Z*)-dienamide moiety by Cu(I)-

Scheme 1. Retrosynthetic Plan of (–)-Apicularen A



catalyzed coupling of iodoalkene with (2Z,4Z)-heptadienamide **3** under Shen and Proco's conditions¹⁰ before the macrolactonization because the poor result was obtained in the coupling after the macrolactonization.^{7a,5a} Although Panek et al. successfully attached the side chain amide,^{4c} the coupling was performed only in 40% yield after the macrolactonization.

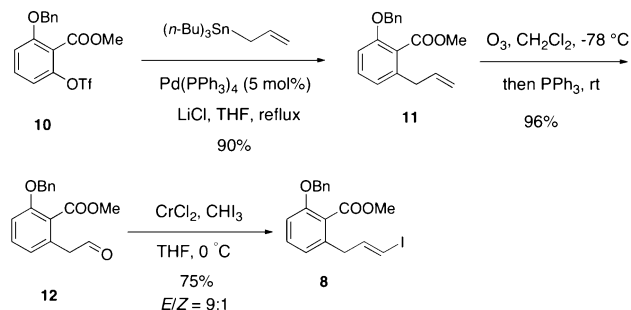
However, we anticipated that formation of **1** could be achieved by using the mild and efficient procedure developed

(6) (a) Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, 41, 8069–8073. (b) Kühnert, S.; Maier, M. E. *Org. Lett.* **2002**, 4, 643–646. (c) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2002**, 43, 8507–8510. (d) Yadav, J. S.; Kumar, N.; Prasad, A. R. *Synthesis* **2007**, 1175–1178. (e) Poniatowski, A. J.; Floreancig, P. E. *Synthesis* **2007**, 2291–2296.

(7) (a) Nicolaou, K. C.; Kim, D. W.; Baati, R.; O'Brate, A.; Giannakakou, P. *Chem.—Eur. J.* **2003**, *9*, 6177–6191. (b) Petri, A. F.; Sasse, F.; Maier, M. E. *Eur. J. Org. Chem.* **2005**, 1865–1875. (c) Jundt, L.; Höfle, G. *J. Nat. Prod.* **2007**, *70*, 1377–1379. (d) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549–5552. (e) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104–116.

by Buchwald et al.¹¹ Thus, Cu(I)-catalyzed coupling of iodoalkene **2** with (2Z,4Z)-hepta-2,4-dienamide **3** could be expected at a late stage by this improved protocol. Further, the disconnection of macrolactone indicates that it could be realized by classical Yamaguchi macrolactonization.¹² We envisioned that the 2,6-*trans*-disubstituted 2,5-dihydro-2*H*-pyran ring system in **6** could be constructed by a regio- and stereospecific Pd(II)-catalyzed cyclization in conjunction with a 1,3-chirality transfer.⁸ We planned to synthesize allylic alcohol **7**, the precursor of the Pd(II)-catalyzed cyclization, by Nozaki–Hiyama–Kishi (NHK) coupling,¹³ and the alcohol **7** would be derived from two advanced fragments, iodoalkene **8** and aldehyde **9**. The fragments **8** and **9** could be prepared from their respective starting materials.

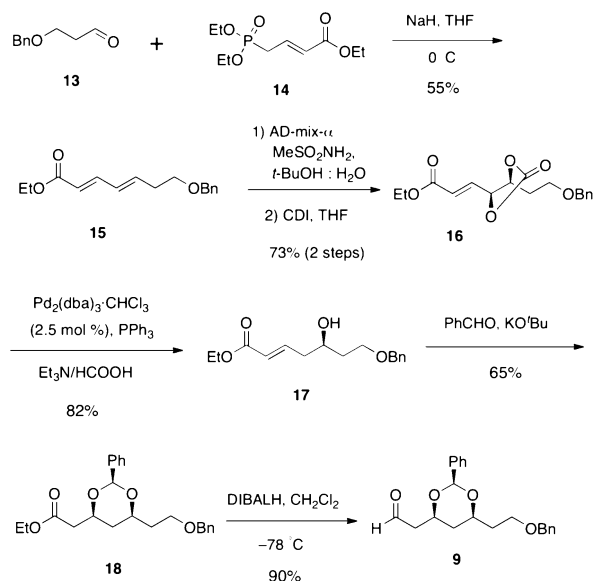
Scheme 2. Synthesis of Iodoalkene 8



In the synthesis of aromatic fragment **8** (Scheme 2), the Stille coupling of **10**¹⁴ with allyltributyltin in the presence of cat. [Pd(PPh₃)₄] gave terminal alkene **11** in 90% yield.

Ozonolysis of **11** provided aldehyde **12** in 96%, which was subjected to Takai iodoolefination¹⁵ to give **8** in 75% yield with high selectivity (*E*:*Z* = 9:1). Synthesis of fragment **9** com-

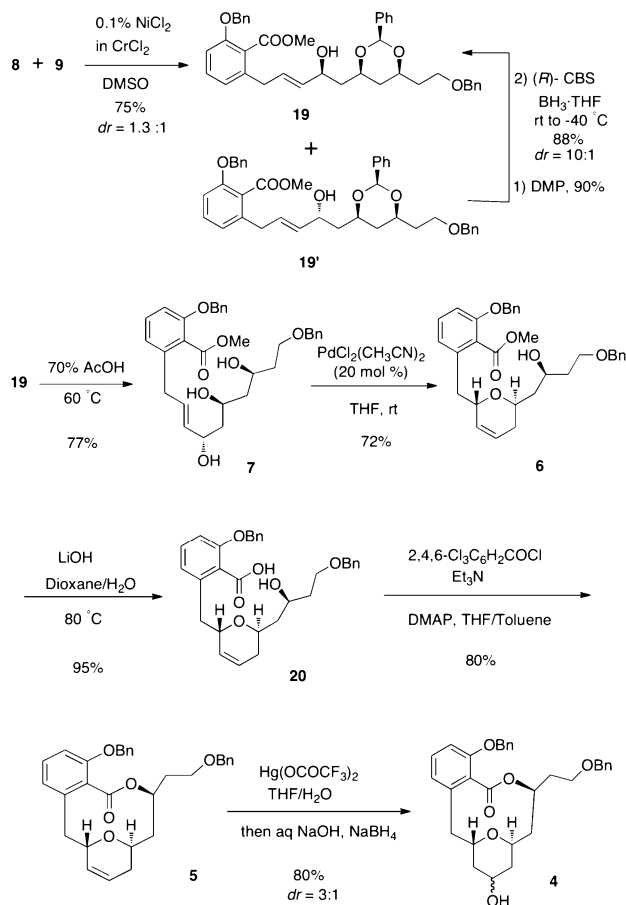
Scheme 3. Synthesis of Aldehyde 9



menced with aldehyde **13**¹⁶ (Scheme 3). The Horner–Wadsworth–Emmons reaction of **13** with triethyl phosphonate ester **14**¹⁷ afforded (*2E,4E*)-dienoate **15** in 55% yield (*E:Z* > 30:1). Sharpless asymmetric dihydroxylation of **15** afforded a diol, which was converted to cyclic carbonate **16** by treatment with carbonyldiimidazole (CDI) in 73% overall yield. Reduction of cyclic carbonate in the presence of Pd catalyst with formic acid provided δ -hydroxy- α,β -unsaturated ester **17** in 82% yield. The δ -hydroxy enoate **17** was transformed into the benzylidene acetal **18** in 65% yield by using the Evans protocol.¹⁸ Finally, reduction of the ester by DIBALH gave **9** in 90% yield.

For the synthesis of macrolactone core **4** (Scheme 4), the fragments **8** and **9** were assembled by NHK coupling¹³ to

Scheme 4. Synthesis of Core Structure



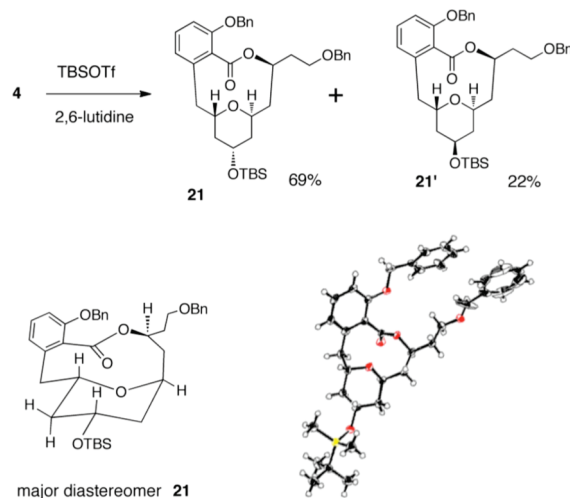
provide a mixture of diastereomeric allylic alcohols **19** and **19'** (*dr* = 1.3:1) in 43 and 32% yields, respectively. The undesired isomer **19'** was converted to **19** via Dess–Martin

oxidation¹⁹ followed by diastereofacial selective reduction of the resulting ketone using (*R*)-CBS reagent²⁰ in 72% yield of **19** along with 7% of **19'** for the two steps.

Deprotection of the benzylidene group of **19** under the mild acidic conditions gave triol **7** in 77% yield. When compound **7** was subjected to the Pd(II)-catalyzed cyclization, gratifyingly the reaction proceeded smoothly in the presence of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ in THF to give the desired 2,6-*trans*-dihydropyran **6** in 72% yield as a single diastereomer. Hydrolysis of the methyl ester using LiOH gave seco acid **20** in 95% yield.

Further important goals of our synthetic procedure were to install the macrolactone ring and an α -hydroxy group at the C-11 position regio- and stereoselectively. Yamaguchi macrolactonization of **20** proceeded to give core macrolactone **5** in 80% yield. Electrophilic reaction occurred from the β -face on the dihydropyran ring in this case. An oxymercuration and successive reductive demercuration installed the desired stereoinduction of the C-11 hydroxy group from the α -face. Treatment of **5** with $\text{Hg}(\text{OCOCF}_3)_2$ in THF and water followed by reductive demercuration with NaBH_4 gave the desired C-11 α -hydroxy product **4** preferentially as a mixture with the corresponding β -hydroxy isomer in a 3:1 ratio.

Scheme 5. Silylation of **4** and X-ray Crystal Structure of **21**



(8) (a) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron: Asymmetry* **2005**, 16, 1299–1303. (b) Kawai, N.; Lagrange, J.-M.; Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006**, 71, 4530–4537. (c) Kawai, N.; Lagrange, J.-M.; Uenishi, J. *Eur. J. Org. Chem.* **2007**, 2808–2814. (d) Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem.-Asian J.* **2008**, 3, 473–484.

(9) (a) Uenishi, J.; Ohmi, M. *Angew. Chem., Int. Ed.* **2005**, 44, 2756–2760. (b) Hande, S. M.; Uenishi, J. *Tetrahedron Lett.* **2009**, 50, 189–192.

(10) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, 2, 1333–1336.

(11) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, 5, 3667–3669.

(12) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, 52, 1989–1993.

(13) (a) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, 108, 5644–5646. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, 108, 6048–6050.

(14) (a) Bracher, F.; Krauss, J.; Bornatsch, A. *Nat. Prod. Lett.* **2000**, 14, 305–310. (b) De Silva, R.; Donate, P. M.; De Silva, G. V. J.; Pedersoli, S.; Aleman, C. *J. Braz. Chem. Soc.* **2005**, 16, 626–633.

(15) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, 108, 7408–7410.

(16) Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, 49, 2301–2309.

(17) Bennacer, B.; Trubuil, D.; Rivalle, C.; Grieson, D. S. *Eur. J. Org. Chem.* **2003**, 4561–4568.

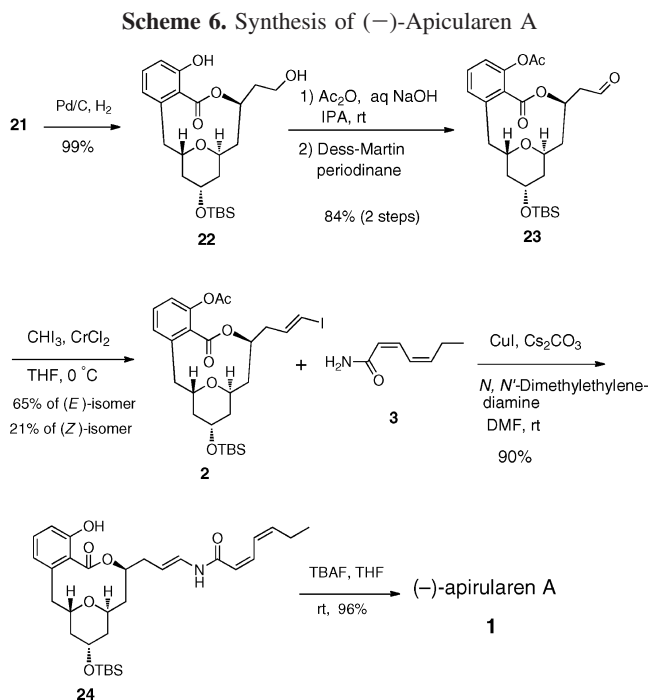
(18) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, 58, 2446–2453.

(19) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, 113, 7277–7287.

(20) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, 37, 1986–2012.

These diastereomers were separated after leading to silyl ethers **21** and **21'**. Silylation of **4** with TBSOTf gave the desired **21** along with undesired **21'** in 69% and 22% yields, respectively. The stereochemistry of the major diastereomer **21** was confirmed by the X-ray crystallographic analysis (Scheme 5).

The remaining task for completion of the synthesis addressed the functionalization of the side chain, which is outlined in Scheme 6. Hydrogenolysis of both *O*-benzyl groups gave **22**



in 99% yield. The chemoselective protection of the phenol with acetic anhydride followed by Dess–Martin oxidation of the

primary alcohol gave aldehyde **23** in 84% overall yield. Takai iodoolefination¹⁵ of **23** gave (*E*)-iodoalkene **2** in 65% yield after the separation of (*Z*)-isomer (21% yield). Initially, we attempted to couple the key intermediate **2** with **3**, in THF at 60 °C under Buchwald's conditions,¹¹ but only a trace amount of the desired product **24** was isolated. However, when this coupling reaction was conducted with an excess of CuI (2 equiv) in DMF at room temperature, the reaction improved dramatically, and the chemical yield increased to 90%. Fortunately, the acetate was removed under the coupling conditions. Finally, desilylation of **24** with TBAF provided (–)-apicularen A (**1**) in 96% yield.

The physical and spectroscopic data (¹H, ¹³C, IR, HRMS) as well as specific rotation were fully identical with those reported for the naturally occurring (–)-**1**.²

In summary, the total synthesis of (–)-apicularen A has been accomplished in 19 linear steps from aldehyde **13**. The key features of this total synthesis included: (i) assembly of (*E*)-iodoalkene and substituted heptanal by NHK coupling; (ii) stereospecific construction of 2,6-*trans*-disubstituted dihydropyran by Pd(II)-catalyzed 1,3-chirality transfer reaction; (iii) Yamaguchi macrolactonization to construct the 12-membered lactone ring with dihydropyran bridge; (iv) regio- and stereoselective introduction of the α-hydroxy group at the C-11 position by oxymercuration and reductive demercuration; and (v) highly efficient Cu(I)-mediated coupling of the iodoalkene with the dienamide under mild conditions.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL101753Y