Total Synthesis of Apoptolidin A
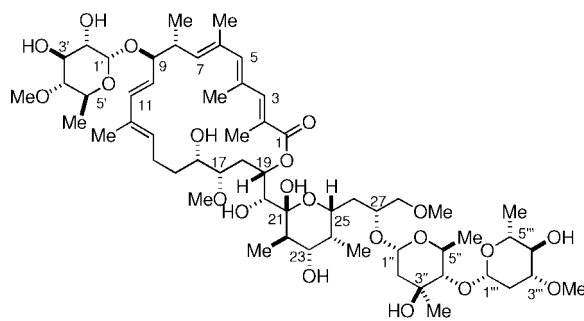
Michael T. Crimmins,* Hamish S. Christie, Alan Long, and Kleem Chaudhary

Venable and Kenan Laboratories of Chemistry, Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

crimmins@email.unc.edu

Received December 8, 2008

ABSTRACT

Apoptolidin A **1**

A highly convergent, enantioselective total synthesis of the potent antitumor agent apoptolidin A has been completed. The key transformations include highly selective glycosylations to attach the C27 disaccharide and the C9 6′-deoxy-L-glucose, a cross-metathesis to incorporate the C1–C10 trienoate unit, and a Yamaguchi macrolactonization to complete the macrocycle. Twelve stereocenters in the polypropionate segments and sugar units were established through diastereoselective chlorotitanium enolate aldol reactions.

Apoptolidins A–D (Figure 1) are secondary metabolites of *Nocardiopsis* sp. which are potent, selective inducers of programmed cell death in rat glia cells transformed with the adenovirus E1A oncogene. Apoptolidin A was isolated by Hayakawa in 1997, and its structure was elucidated by a combination of NMR spectroscopy and molecular modeling techniques.[1] The minor metabolites apoptolidins B, C, and D were recently isolated and identified by Wender.[2,3] Importantly, apoptolidin A has no effect on normal cells at concentrations as high as 88 μM, while the E1A transformed glial cells undergo apoptotic cell death when exposed to apoptolidin A at concentrations of 10 nM.[1] This selective activity of cancer therapeutics is a major factor in minimizing side effects of chemotherapeutic agents.

The apoptolidins have been the subject of intense synthetic and biological[4] investigations because of their potential as agents for the treatment of cancer.[5] Two total syntheses of
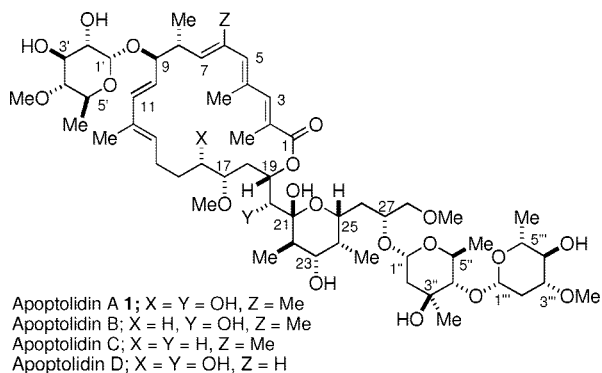

Figure 1. Structure of the apoptolidins.

Apoptolidin A **1**; X = Y = OH, Z = Me
Apoptolidin B; X = H, Y = OH, Z = Me
Apoptolidin C; X = Y = H, Z = Me
Apoptolidin D; X = Y = OH, Z = H

(1) (a) Kim, J. W.; Adachi, H.; Shin-ya, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1997**, *50*, 628. (b) Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita, K.; Seto, H. *J. Am. Chem. Soc.* **1998**, *120*, 3524.

(2) Wender, P. A.; Sukopp, M.; Longcore, K. *Org. Lett.* **2005**, *7*, 3025.

(3) Wender, P. A.; Longcore, K. *Org. Lett.* **2007**, *9*, 691.

(4) (a) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Chem. Biol.* **2001**, *8*, 71. (b) Salomon, A. R.; Zhang, Y. B.; Seto, H.; Khosla, C. *Org. Lett.* **2001**, *3*, 57. (c) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Proc. Natl. Acad. Sci.* **2000**, *97*, 14766.

(5) Daniel, P. T.; Koert, U.; Schuppan, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 872.

apoptolidin A,[6] several syntheses of the aglycon, known as apoptolidinone,[7] including one from our laboratory,[8] a number of partial syntheses,[9] as well as selective synthetic modifications[10] have been reported.
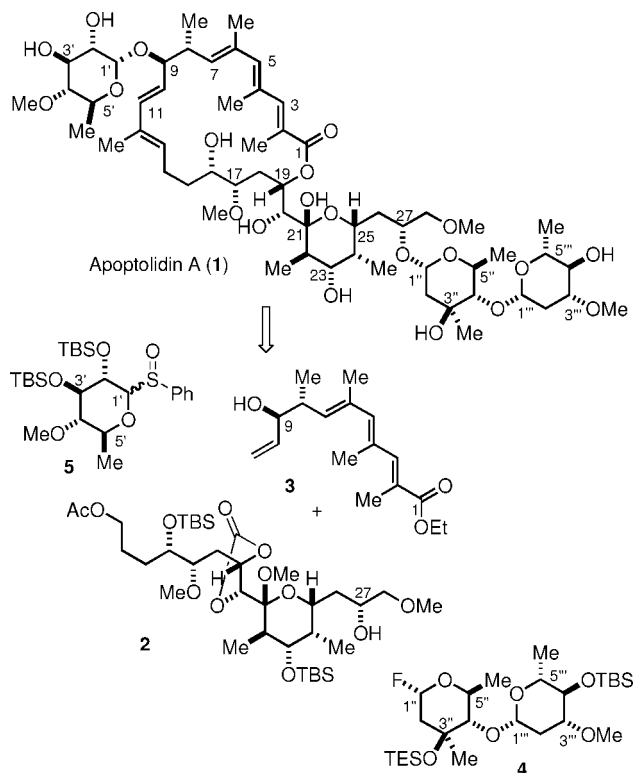
Apoptolidin A (**1**, Scheme 1) is comprised of a macrocyclic lactone and two unusual carbohydrate units attached through glycosidic linkages at the C9 and C27 hydroxyl groups. Our highly convergent approach to the synthesis of apoptolidin A focused initially on the individual preparation of the aglycon, apoptolidinone,[8] and the carbohydrate units,[9e] with the expectation that the approach to apoptolidinone

could be adapted to a synthesis of apoptolidin A by a late-stage attachment of the sugar units to advanced intermediates in the apoptolidinone synthesis.

The glycosyl fluoride **4** derived from L-olivomycose and D-oleandrose would be utilized to attach the required disaccharide at C27 of mixed ketal **2** or a similar advanced intermediate prior to incorporation of the trienoate **3**. Sulfoxide **5** would serve as the glycosylating agent for the incorporation of the 6′-deoxy-L-glucose unit at C9 either immediately before or after assembly of the C1−C10 and C11−C28 subunits via a stereoselective olefin cross-metathesis reaction. Mixed ketal **2** and trienoate **3** were advanced intermediates in our recently reported synthesis of apoptolidinone.[8]

The required glycosyl donors **4** and **5** for the incorporation of the sugar units were obtained as illustrated in Schemes 2 and 3. Each of the individual monosaccharide units were obtained by de novo synthesis through the application of a chlorotitanium glycolate aldol approach to establish the C4 and C5 stereocenters of each of the monosaccharides.[9e]
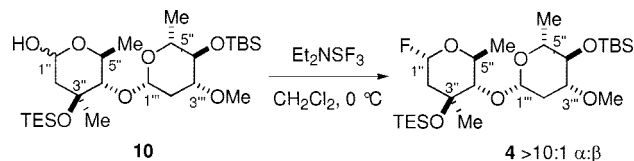
The necessary glycosyl fluoride **4** was accessed from the protected disaccharide **10** as shown in Scheme 2. Direct exposure of the hemiacetal **10** to DAST provided the glycosyl fluoride **4** ($>10:1$ α:β).[6c] Since the glycosyl fluoride was somewhat unstable, it was utilized in the subsequent glycosylation of the C27 hydroxyl group without further purification.

The synthesis of 6′-deoxy-L-glucose (the C9 sugar unit) donor **5** was readily accomplished from lactone **6**[9e] (Scheme 3). Protection of the diol as the corresponding TBS ether **7** was followed by reduction of the lactone with i-Bu$_2$AlH to deliver the protected 6′-deoxy-L-glucose **8**. The hemiacetal

(6) (a) Wehlan, H.; Dauber, M.; Fernaud, M. T. M.; Schuppan, J.; Mahrwald, R.; Ziemer, B.; Garcia, M. E. J.; Koert, U. *Angew. Chem., Int. Ed.* **2004**, *43*, 4597. (b) Wehlan, H.; Dauber, M.; Fernaud, M. T. M.; Schuppan, J.; Kieper, S.; Mahrwald, R.; Garcia, M. E. J.; Koert, U. *Chem. Eur. J.* **2006**, *12*, 7378. (c) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y. W.; Weyershausen, B.; Mitchell, H. J.; Wei, H. X.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433. (d) Nicolaou, K. C.; Li, Y. W.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443. (e) Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Sugita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3854. (f) Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Wei, H. X.; Weyershausen, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3849.

(7) (a) Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 2063. (b) Wu, B.; Liu, Q. S.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6673. (c) Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Chem. Eur. J.* **2006**, *12*, 7364. (d) Ghidu, V. P.; Wang, J. Q.; Wu, B.; Liu, Q. S.; Jacobs, A.; Marnett, L. J.; Sulikowski, G. A. *J. Org. Chem.* **2008**, *73*, 4949.

(8) Crimmins, M. T.; Christie, H. S.; Chaudhary, K.; Long, A. *J. Am. Chem. Soc.* **2005**, *127*, 13810.

(9) (a) Abe, K.; Kato, K.; Arai, T.; Rahim, M. A.; Sultana, I.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2004**, *45*, 8849. (b) Bouchez, L. C.; Vogel, P. *Chem. Eur. J.* **2005**, *11*, 4609. (c) Chang, S. S.; Xu, J.; Loh, T. P. *Tetrahedron Lett.* **2003**, *44*, 4997. (d) Craita, C.; Didier, C.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **2007**, 2411. (e) Crimmins, M. T.; Long, A. *Org. Lett.* **2005**, *7*, 4157. (f) Daniel, P. T.; Koert, U.; Schuppan, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 872. (g) Jin, B. H.; Liu, Q. S.; Sulikowski, G. A. *Tetrahedron* **2005**, *61*, 401. (h) Nicolaou, K. C.; Li, Y. W.; Weyershausen, B.; Wei, H. X. *J. Chem. Soc., Chem. Commun.* **2000**, 307. (i) Paquette, W. D.; Taylor, R. E. *Org. Lett.* **2004**, *6*, 103. (j) Schuppan, J.; Ziemer, B.; Koert, U. *Tetrahedron Lett.* **2000**, *41*, 621. (k) Sulikowski, G. A.; Lee, W. M.; Jin, B.; Wu, B. *Org. Lett.* **2000**, *2*, 1439. (l) Toshima, K.; Arita, T.; Kato, K.; Tanaka, D.; Matsumura, S. *Tetrahedron Lett.* **2001**, *42*, 8873. (m) Handa, M.; Scheidt, K. A.; Bossart, M.; Zheng, N.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1031. (n) Handa, M.; Smith, I. I. I.; W, J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1036.

(10) (a) Wender, P. A.; Jankowski, O. D.; Tabet, E. A.; Seto, H. *Org. Lett.* **2003**, *5*, 2299. (b) Wender, P. A.; Jankowski, O. D.; Tabet, E. A.; Seto, H. *Org. Lett.* **2003**, *5*, 487. (c) Wender, P. A.; Gulledge, A. V.; Jankowski, O. D.; Seto, H. *Org. Lett.* **2002**, *4*, 3819.

Scheme 3. Synthesis of the C9 Sugar Unit

Scheme 3. Synthesis of the C9 Sugar Unit
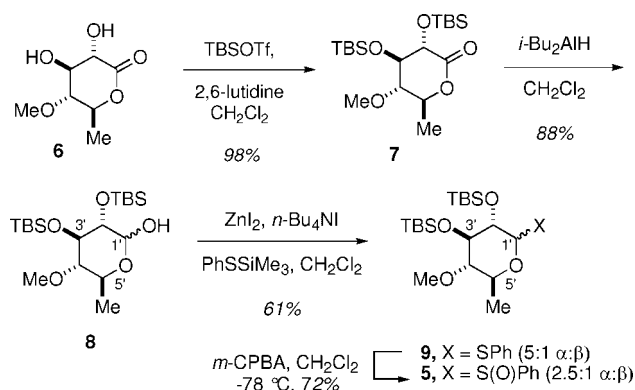
8 was converted to mixed acetal **9** ((5:1 α:β) by exposure to PhSSiMe₃ in the presence of ZnI₂. The required glycosyl donor **5** was obtained as a 2.5:1 mixture of isomers in 72% yield by oxidation of the thioacetal with *m*-CPBA.[6c]

The assembly of the four key subunits for the completion of the synthesis of apoptolidin A began with the modification of mixed ketal **2**. Mixed ketal **2** was an advanced intermediate from the recently completed synthesis of apoptolidinone, and was available in multigram quantities through 17 synthetic steps involving an interative aldol sequence.[8]

The key C11–C28 diene **12** was accessible by either of two sequences from hemiketal **2** as illustrated in Scheme 4.

Attachment of the C27 disaccharide could be accomplished in high yield (74%) with excellent stereoselectivity (7:1, α:β) by treatment of C27 alcohol **2** with stannous chloride in the presence of glycosyl fluoride **4**. The C13 acetate was selectively cleaved in the presence of the C19,20 carbonate whereupon the resulting primary alcohol was oxidized under Swern[11] conditions to produce aldehyde **11** in 89% yield. Two sequential Wittig olefinations completed the synthesis of diene **12** in 80% overall yield. Alternately, the diene unit could be incorporated prior to the attachment of the C27 discaccharide. The C27 alcohol **2** was protected as its triethylsilyl ether followed by removal of the C13 acetate and subsequent oxidation of the alcohol to the aldehyde **13**. Stabilized Wittig olefination of the aldehyde in chlorobenzene at 90 °C was accompanied by cleavage of the C27 TES ether. Methylenation of the unsaturated aldehyde provided the desired diene alcohol **14**. Stereoselective glycosylation of the C27 alcohol **14** as described previously for alcohol **2** delivered diene **12** in excellent yield.

Completion of the synthesis of apoptolidin A is illustrated in Scheme 5. Exposure of the alkenes **3**[8] and **12** to the Grubbs heterocyclic carbene catalyst [Cl₂(Cy₃P)(IMes)Ru=CHPh][12] provided the desired *E* isomer **15** through a critical complex cross-metathesis[8,13] in good yield (>95:5 *E*:*Z* by ¹H NMR analysis). An attempted cross-metathesis reaction failed when the reaction was performed after the glycosidation of the C9 oxygen. To complete the synthesis of apoptolidin A, attachment of the sugar unit at C9 and macrolactonization were

Scheme 4. Attachment of the C27 Disaccharide

Scheme 4. Attachment of the C27 Disaccharide
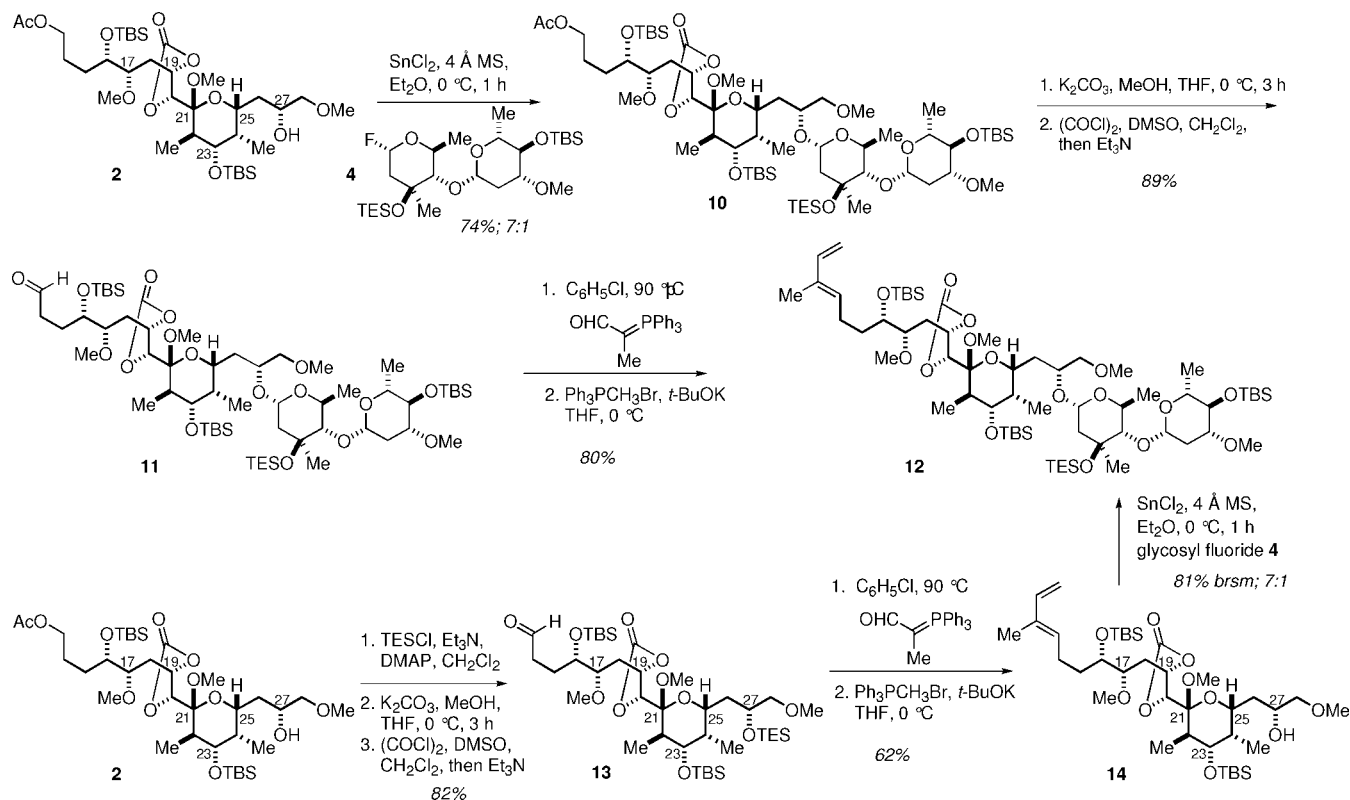
Scheme 5. Synthesis of Apoptolidin A
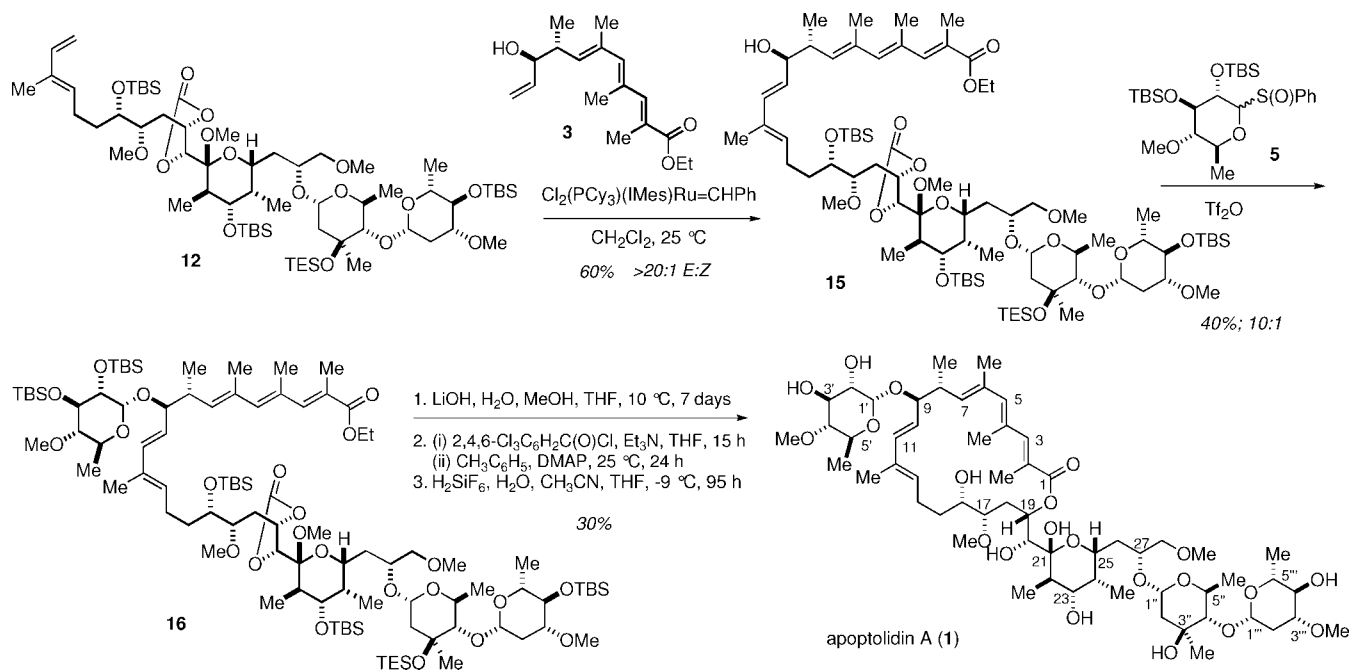
required. A mixture of alcohol **15** and sulfoxide **5** was exposed to triflic anhydride stereoselectively providing the glycoside **16**. Treatment of the ester **16** with LiOH at room temperature rapidly cleaved the carbonate group and eventually the ester, to give a good yield of the desired seco acid. Regioselective macrolactonization at C19 proceeded smoothly under Yamaguchi's conditions to deliver the macrolactone.[14] Finally, cleavage of the silyl ethers and hydrolysis of the mixed methyl acetal were effected in one operation with H_2SiF_6 to furnish apoptolidin A (**1**). Synthetic apoptolidin A was identical with an authentic sample.

The successful total synthesis utilized diastereoselective chlorotitanium aldol reactions to establish **12** (carbons 4′,5′; 4″,5″; 4‴,5‴; 8,9; 22,23; and 24,25) of the 24 stereocenters of apoptolidin A and exploited a complex cross-metathesis to assemble the two major fragments and construct the C10−C13 diene unit.

Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802829N

(11) Swern, D.; Mancuso, A. J.; Huang, S. *J. Org. Chem.* **1978**, *43*, 2480.

(12) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(13) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

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