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Asymmetric Aziridination of Cyclic Enones Using Chiral Diamine Catalysts and Its Application to the Total Synthesis of (−)-Agelastatin A

Yasuhiro Menjo, Akinari Hamajima, Neri Sasaki, and Yasumasa Hamada*

Graduate School of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

hamada@p.chiba-u.ac.jp

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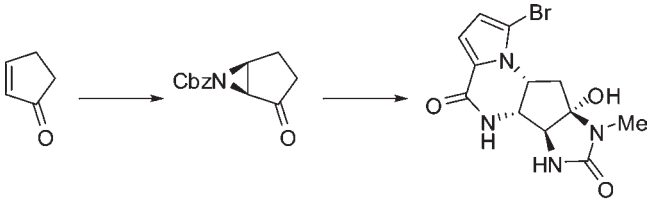
ABSTRACT



(−)-Agelastatin A

The asymmetric aziridination of cyclic enones with *N*-tosyloxycarbamates, using *N*-neopentyl 1,2-diphenylethylenediamine as a catalyst, and its application to the formal total synthesis of (−)-agelastatin A, using a one-pot silylation-selenylation procedure and the regioselective aziridine-opening by an azide anion as key steps, are described.

The chiral amine-catalyzed asymmetric reaction is one of the most studied areas of modern organic synthesis.[1] Many enantioselective reactions by various chiral amines have been developed to date. We have demonstrated that *N*-tosyloxycarbamates as a nitrogen source can be efficiently used for the asymmetric aziridination of enones using α,α-diphenylprolinol trimethylsilyl ether.[2−4] Chiral aziridines are useful synthetic intermediates with one or two stereogenic centers. They are effectively used for the synthesis of amino acids, natural products, and pharmaceuticals.[5,6] As part of such research, we examined the asymmetric aziridination of cyclic enones using new catalysts and found an efficient method.

The asymmetric aziridination of cyclic enones with *N*-tosyloxy *tert*-butylcarbamate (*p*TsONHBoc) using the cinchona alkaloid derivatives as organocatalysts has already been reported by Melchiorre and co-workers.[3k] They stated that the level of enantioselection depends on the structure of the *N*-tosyloxy alkylcarbamates and is moderate for 2-cyclopenten-1-one. We now describe an efficient asymmetric aziridination of cyclic enones using the *N*-neopentyl 1,2-diphenylethylenediamine catalyst **4** and its application in a formal total synthesis of (−)-agelastatin A.

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(2) Arai, H.; Sugaya, N.; Sasaki, N.; Makino, K.; Lectard, S.; Hamada, Y. *Tetrahedron Lett.* **2009**, *50*, 3329–3332.

(3) For the aziridinations using *N*-arenesulfonyloxycarbamates, see: (a) Lwowski, W.; Mairich, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3630–3637. (b) Banks, M. R.; Blake, A. J.; Cadogan, J. I. G.; Dawson, I. M.; Gosney, I.; Grant, K. J.; Gaur, S.; Hodgson, P. K. G.; Knight, K. S.; Smith, G. W. *Tetrahedron* **1992**, *48*, 7979–8006. (c) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synthesis* **2001**, *13*, 1975–1978. (d) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **2003**, *23*, 4549–4552. (e) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synlett* **2004**, 1083–1085. (f) Fioravanti, S.; Colantoni, D.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **2005**, *70*, 3296–3298. (g) Mohr, F.; Binfield, S. A.; Fettinger, J. C.; Vedernikov, A. N. *J. Org. Chem.* **2005**, *70*, 4833–4839. (h) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198–14199. (i) Lebel, H.; Lectard, S.; Parmentier, M. *Org. Lett.* **2007**, *9*, 4797–4800. (j) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8703–8706. (k) De Vincentiis, F.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Galzerano, P.; Melchiorre, P. *Chem. Asian J.* **2010**, *5*, 1652–1656. (l) Deiana, L.; Zhao, G.; Lin, S.; Dziedzic, P.; Zhang, Q.; Leijonmarck, H.; Córdova, A. *Adv. Synth. Catal.* **2010**, *352*, 3201–3207. (m) Deiana, L.; Dziedzic, P.; Zhao, G.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem.—Eur. J.* **2011**, *17*, 7904–7917.

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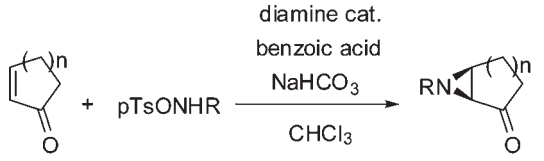
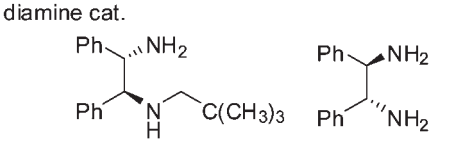
Table 1. Chiral Diamine-Catalyzed Aziridination of Cyclic Enones





entry[a]	cat.	*n*	product (R = Cbz)		product (R = Boc)	
1[b,c]	**4**	1	**1a**[d]	75% yield[e] 95% ee[f]	**1b**	89% yield 88% ee
2[b]	**5**	1	*ent*-**1a**	59% yield 59% ee	*ent*-**1b**	81% yield 71% ee
3	**4**	2	**2a**	84% yield 97% ee	**2b**	80% yield 97% ee
4	**4**	3	**3a**	83% yield 94% ee	**3b**	91% yield 92% ee

[a] Reaction was carried out with *p*TsONHR (0.20 mmol), a cyclic enone (0.24 mmol), benzoic acid (0.20 mmol), sodium hydrogen carbonate (1.0 mmol), diamine **4** or **5** (0.04 mmol) in chloroform (2 mL) at room temperature for 24 h. [b] Three equivalents of 2-cyclopenten-1-one were used. [c] Reaction time was 40 h. [d] Scale = 10 mmol. [e] Isolated yield. [f] Enantiomeric excess was determined by HPLC analysis.

First, some simple chiral 1,2-diamines for the aziridination of 2-cyclopenten-1-one, using *N*-tosyloxy benzylcarbamate (*p*TsONHCbz), were evaluated. Table 1 depicts selected examples of the diamine-catalyzed aziridination. The reaction was carried out with *p*TsONHR (1 equiv), a cyclic enone (1.2 equiv), benzoic acid (1 equiv), sodium hydrogen carbonate (5 equiv), and the diamine catalyst (20 mol %) in solvent at room temperature for 24 h. The presence of benzoic acid and sodium hydrogen carbonate were essential for a smooth reaction, preventing decomposition of the *N*-tosyloxy alkylcarbamates. To our delight, the primary-secondary diamine **4**,[7] which can be easily prepared from the commercially available chiral 1,2-diphenyethylenediamine (DPEN) **5**, exhibited an excellent enantioselectivity. The chiral aziridine **1a** was obtained in 75% yield with 95% ee, if the reaction was performed in chloroform in the presence of benzoic acid.[8] We have examined the scope of this new asymmetric aziridination. *p*TsONHCbz and *p*TsONHBoc as a nitrogen source were equally effective for this aziridination and produced the corresponding keto aziridines in good yields and with high enantioselectivities. Interestingly, in contrast to Melchiorre's case,[3k] the use of *p*TsONHCbz resulted in a somewhat higher enantioselectivity than *p*TsONHBoc. The introduction of the *N*-neopentyl group to DPEN was essential for high enantioselection. The reaction of 2-cyclohexen-1-one and 2-cyclohepten-1-one also efficiently proceeded to afford the corresponding aziridines with high enantioselectivity. The absolute configurations of the product were assigned by comparison of the known **1b** and ***ent*-1b** with the reported retention time in HPLC analysis.[3k]

Next, we turned our attention to application of this efficient asymmetric aziridination to the total synthesis of a natural product. (−)-Agelastatin A[9] isolated by Pietra and co-workers in 1993 from the Coral Sea sponge *Agelas dendromorpha* has received much attention because of its potent cytotoxicity against a wide range of cancer cell lines.[10] It is also known as an inhibitor of osteopontin-mediated adhesion, invasion, colony formation,[11] and glycogen synthase kinase-3β,[10a] a potential target for Alzheimer's disease, diabetes, and bipolar disorder. These remarkable biological activities coupled with its highly complex structure have made (−)-agelastatin A an attractive target for total synthesis. The structure comes from the 5,6,5,5-tetracyclic system that contains 4 contiguous chiral centers on the C-ring, and each of them is substituted with a nitrogen atom. To date, 11 research groups have reported racemic,[12,13a,1] and asymmetric[12,13b−13k,13m−13p] total syntheses of agelastatin A.

Among them, are stereoselective syntheses based on transition metal-catalyzed asymmetric reactions, transformations from naturally occurring chiral substances, or the enzymatic resolution of a racemic substrate. On the other

(4) For a review of α,α-diarylprolinol ethers, see: (a) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922–948. (b) Lattanzi, A. *Chem. Commun* **2009**, 1452–1463. (c) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876–7880.

(5) For reviews of aziridines, see: (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *32*, 247–258. (b) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657–669. (c) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2920. (d) Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715. (e) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509–1555.

(6) For recent examples of the enantioselective aziridination, see: (a) Hashimoto, T.; Nakatsu, H.; Yamamoto, K.; Watanabe, S.; Maruoka, K. *Chem. Asian J.* **2011**, *6*, 607–613. (b) Larson, S. E.; Li, G.; Rowland, G. B.; Junge, D.; Huang, R.; Woodcock, H. L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2188–2191. (c) Arroyo, Y.; Meana, Á.; Sant-Tejedor, M. A.; Alonso, I.; García Ruano, J. L. *Chem.—Eur. J.* **2010**, *16*, 9874–9883. (d) Bonifácio, V. D. B.; González-Bello, C.; Rzepa, H. S.; Prabhakar, S.; Lobo, A. M. *Synlett* **2010**, *1*, 145–149. (e) Huang, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 8892–8895. (f) Hashimoto, T.; Nakatsu, H.; Yamamoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 9730–9733. (g) Murakami, Y.; Takeda, Y.; Minakata, S. *J. Org. Chem.* **2011**, *76*, 6277–6285.

(7) Wang, M.; Lin, L.; Shi, J.; Liu, X.; Kuang, Y.; Feng, X. *Chem.—Eur. J.* **2011**, *17*, 2365–2368.

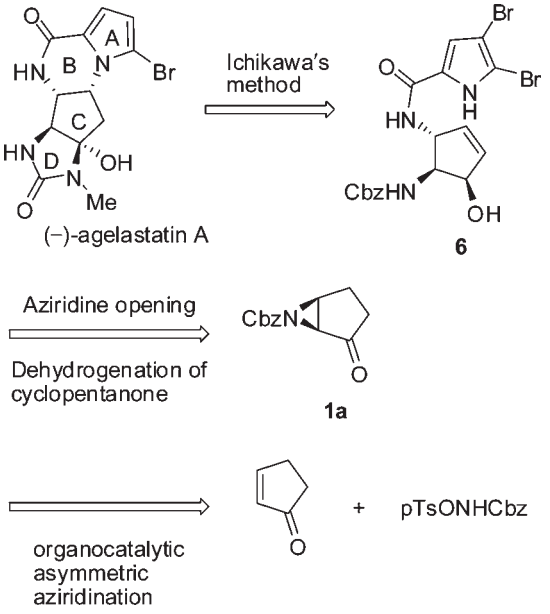
(8) In our preliminary experiments, the addition of sodium benzoate instead of benzoic acid and sodium hydrogen carbonate produced in somewhat the decreased yield and with enantiomeric excess (50%, 88% ee). Therefore, we employed a mixture of benzoic acid and sodium hydrogen carbonate.

(9) (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc. Chem. Commun* **1993**, 1305–1306. (b) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1895–1902.

(10) (a) Meijer, L.; Thunnissen, A. M.; White, A. W.; Garnier, M.; Nikolic, M.; Tsai, L. H.; Walter, J.; Cleverley, K. E.; Salinas, P. C.; Wu, Y. Z.; Biernat, J.; Mandelkov, E. M.; Kim, S. H.; Pettit, G. R. *Chem. Biol.* **2000**, *7*, 51–63. (b) Pettit, G. R.; Ducki, S.; Herald, D. L.; Doubek, D. L.; Schmidt, J. M.; Chapuis, J. C. *Oncol. Res.* **2005**, *15*, 11–20.

hand, organocatalytic reactions have never been applied for the total synthesis of (−)-agelastatin A.

Scheme 1. Retrosynthetic Analysis of **6**



In designing a synthetic plan to (−)-agelastatin A, we focused on Ichikawa's intermediate **6** for the construction of a B ring of agelastatin A.[13h] We envisioned that regioselective aziridine-opening of **1a** by a nitrogen nucleophile and dehydrogenation to the enone should produce Ichikawa's key intermediate **6** (Scheme 1).

With the chiral keto aziridine **1a** in hand, we attempted the synthesis of enone **7** by the phenylselenylation or Ito-Saegusa oxidation of **2a** (Figure 1). However, formation of the trimethylsilyl enol ether **8** from **1a** by the standard procedure (LDA or LiHMDS in THF at −78 °C, then TMSCl) failed due to its extreme sensitivity to hydrolysis, and the α-phenylselenylation of **1a** by the standard procedure (LDA in THF at −78 °C, then PhSeCl) produced an inseparable mixture of **9** and **10**. After several experiments, we found that Tanabe's procedure[14] for the preparation of silyl enol ethers was efficient for our case. Thus, **1a** was treated with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in the presence of DBU (0.2 equiv). The clean conversion of **1a** to the corresponding trimethylsilyl enol ether **8** was confirmed by the ^{1}H NMR analysis of the reaction mixture. The reaction mixture was directly treated with phenylselenyl chloride at −78 °C to give **9** in a satisfactory yield.[15]

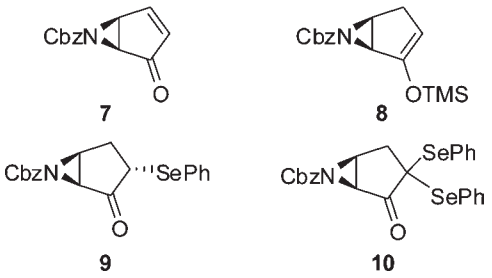


Figure 1. Enone **7** and enone's precursors **8**–**10**.

Several attempts at effecting the direct ring-opening of the keto aziridine **1a** or **9** with an azide anion were unsuccessful and resulted in decomposition of the starting materials. Finally, we found that the ring-opening reaction, after reduction of the ketone function of **9**, regioselectively proceeded to produce the corresponding product. Thus, **9** was reduced with sodium borohydride at −78 °C to give **11**, which was treated with sodium azide to produce the azide **12** in a good yield as a single isomer.[16] The nickel boride-catalyzed reduction of the azide, and the acylation of the resulting amine **13** with 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid **14** gave **15**. Finally, oxidative elimination of the phenylselenyl group furnished the chiral intermediate **6** of (−)-agelastatin A in a nearly quantitative yield (Scheme 2). Its spectroscopic data were identical with the reported values for **6**. The absolute configuration of the keto aziridine **1a** was unambiguously confirmed by comparison of the optical rotation of **6** ($[\alpha]_D^{23}$ = −200.9, *c* 1.62, chloroform) with the reported data ($[\alpha]_D^{15}$ = −223.4, *c* 0.56, chloroform).[13h]

In summary, we have discovered an asymmetric aziridination of cyclic enones catalyzed by a primary-secondary chiral diamine **4**, which can be readily prepared from the commercially available DPEN. The chiral keto aziridine **1a**

(11) Mason, C. K.; McFarlane, S.; Johnston, P. G.; Crowe, P.; Erwin, P. J.; Domostoj, M. M.; Campbell, F. C.; Manaviazar, S.; Hale, K. J.; El-Tanani, M. *Mol. Cancer Ther*. **2008**, *7*, 548–558.

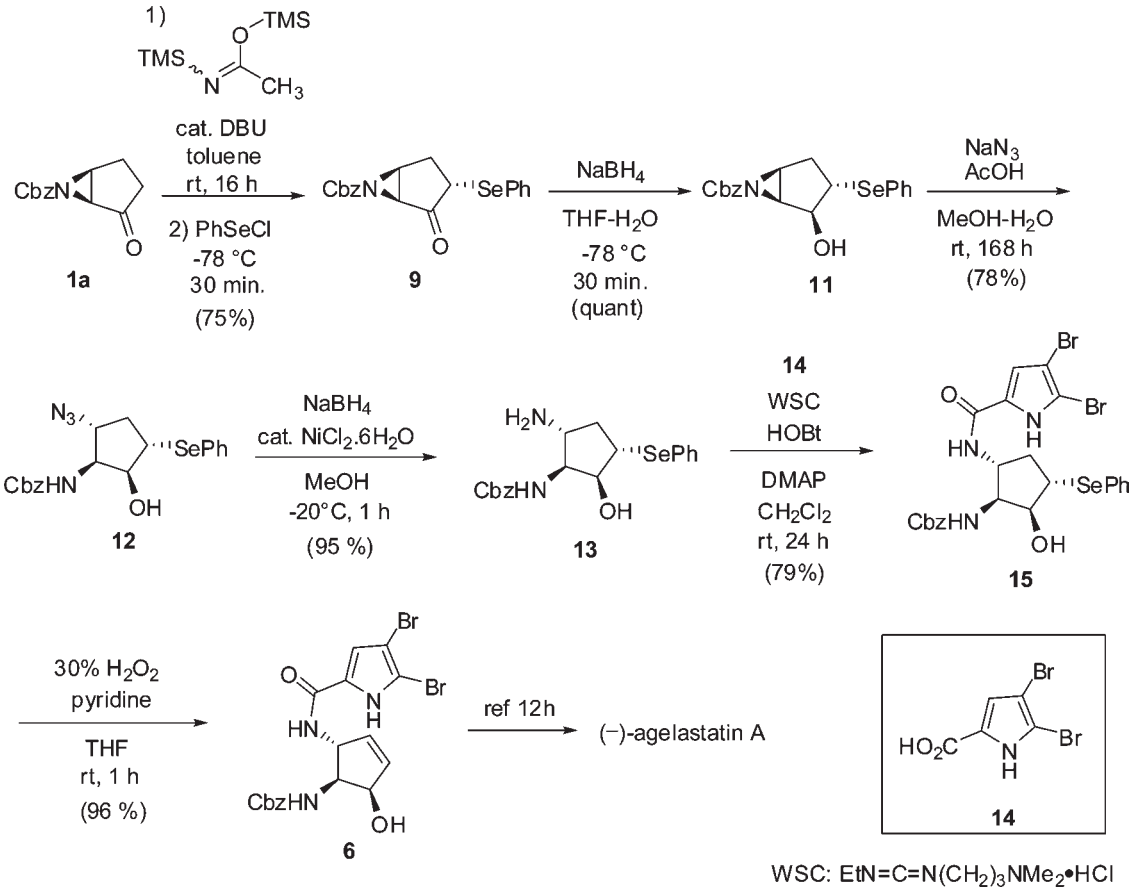
(12) For reviews of agelastatins, see: (a) Weinreb, S. M. *Nat. Prod. Rep*. **2007**, *24*, 931–948. (b) Dong, G. *Pure Appl. Chem*. **2010**, *82*, 2231–2246.

(13) (a) Stien, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.; Weinreb, S. M. *J. Am. Chem. Soc*. **1999**, *121*, 9574–9579. (b) Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc*. **2002**, *124*, 9060–9061. (c) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. *J. Org. Chem*. **2002**, *67*, 7096–7109. (d) Hale, K. J.; Domostoj, M. M.; Tocher, D. A.; Irving, E.; Scheinmann, F. *Org. Lett*. **2003**, *5*, 2927–2930. (e) Domostoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. *Org. Lett*. **2004**, *6*, 2615–2618. (f) Davis, F. A.; Deng, J. *Org. Lett*. **2005**, *7*, 621–623. (g) Trost, B. M.; Dong, G. *J. Am. Chem. Soc*. **2006**, *128*, 6054–6055. (h) Ichikawa, Y.; Yamaoka, T.; Nakano, K.; Kotsuki, H. *Org. Lett*. **2007**, *9*, 2989–2992. (i) Yoshimitsu, T.; Ino, T.; Tanaka, T. *Org. Lett*. **2008**, *10*, 5457–5460. (j) Davis., F. A.; Zhang, J.; Zhang, Y.; Qiu, H. *Synth. Commun*. **2009**, *39*, 1914–1919. (k) Yoshimitsu, T.; Ino, T.; Futamura, N.; Kamon, T.; Tanaka., T. *Org. Lett*. **2009**, *11*, 3402–3405. (l) Dickson, D. P.; Wardrop, D. J. *Org. Lett*. **2009**, *11*, 1341–1344. (m) Wehn, P. M.; Du Bois, J. *Angew. Chem., Int Ed*. **2009**, *48*, 3802–3805. (n) Hama, N.; Matsuda, T.; Sato, T.; Chida, N. *Org. Lett*. **2009**, *11*, 2687–2690. (o) Trost, B. M.; Dong, G. *Chem.—Eur. J*. **2009**, *15*, 6910–6919. (p) Movassaghi, M.; Siegel, D. S.; Han., S. *Chem. Sci*. **2010**, 561–566.

(14) Tanabe, Y.; Misaki, T.; Kurihara, M.; Iida, A.; Nishii, Y. *Chem. Commun* **2002**, 1628–1629.

(15) This phenylselenylation occurred from the less hindered face to afford trans-phenylselenide **9** as a single diastereomer.

Scheme 2. Formal Total Synthesis of (−)-Agelastatin A



was efficiently transformed into the known intermediate **6** of (−)-agelastatin A, in seven steps, and 30% overall yield, which represents a new formal total synthesis of (−)-agelastatin A.

(16) In the aziridine ring-opening reaction, the high regioselectivity can be explained by the steric interaction of the adjacent hydroxy group. Then, the azide anion attacks regioselectively at the remote position from the hydroxyl group to give **12**.

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Supporting Information Available. Supplemental information and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.