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Stereoselective Total Synthesis of the Proposed Structure of 2-Epibotcinolide

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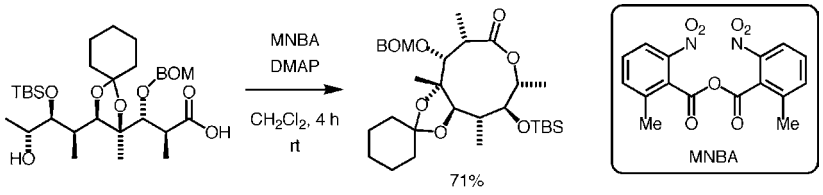
ABSTRACT



The total synthesis of *pseudo* 2-epibotcinolide (1b) through several featured synthetic approaches has been attained. First, the chiral linear precursors of the nine-membered ring compound is stereoselectively constructed by the asymmetric aldol reaction for producing *β*-hydroxy ester units. Second, the key cyclization reaction to form the nine-membered lactone moiety is efficiently achieved by the extremely facile and powerful mixed-anhydride method promoted by 2-methyl-6-nitrobenzoic anhydride (MNBA) with basic promoters.

Botcinolide was first isolated from a strain of the fungus *Botrytic cinerea* (UK185RRC) by Cutler et al. in 1993,[1] and *pseudo* 2-epimeric isomer, 2-epibotcinolide, was also extracted from the plant pathogen *Botrytic cinerea* (UCA992) by Collado et al. in 1996.[2] Other isomeric and homologous compounds were also prepared from a similar fungus,[3] and it was revealed that botcinolide and its relatives have a significant biological activity that inhibits the growth of several plants at low concentrations.

Although the structures of botcinolide (**1a**) and 2-epibotcinolide (**1b**) had been theorized to possess peculiar saturated nine-membered rings on the basis of a NMR analysis including enhanced NOE techniques (Figure 1), the revised forms of botcinolide (**2a**) and 2-epibotcinolide (**2b**) were recently proposed on the basis of a reinvestigation of the structure by Nakajima's group.[4]

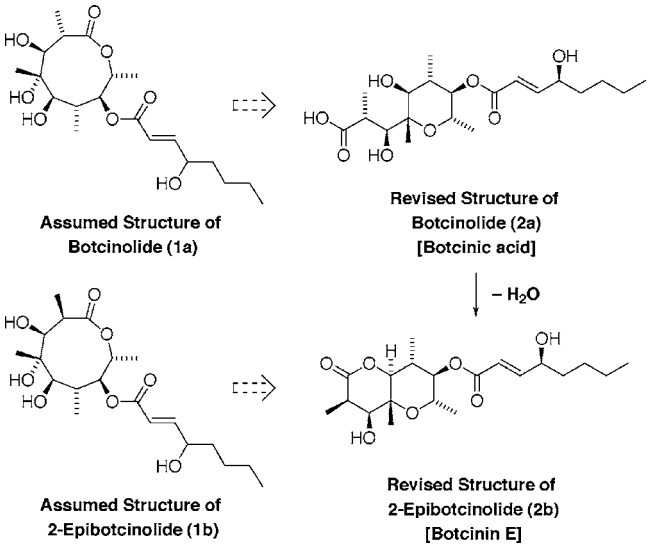


Figure 1. Reported structure of botcinolide (**1a**) and 2-epibotcinolide (**1b**).

Independently, we have quite recently reported a method for the preparation of the target molecule **1b** and ques-

(1) (a) Cutler, H. G.; Jacyno, J. M.; Harwood, J. S.; Dulik, D.; Goodrich, P. D.; Roberts, R. G. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1980−1982. (b) Jacyno, J. M.; Harwood, J. S.; Cutler, H. G.; Dulik, D. M. *Tetrahedron* **1994**, *50*, 11585−11592.

(2) Collado, I. G.; Aleu, J.; Hernandez-Galan, R.; Hanson, J. R. *Phytochemistry* **1996**, *42*, 1621−1624.

(3) (a) Cutler, H. G.; Parker, S. R.; Ross, S. A.; Crumley, F. G.; Schreiner, P. R. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 656−658. (b) Reino, J. L.; Hernández-Galán, R.; Durán-Patrón, R.; Collado, I. G. *J. Phytopathology* **2004**, *152*, 563−566. (c) Reino, J. L.; Durán-Patrón, R. M.; Daoubi, M.; Collado, I. G.; Hernández-Galán, R. *J. Org. Chem.* **2006**, *71*, 562−565.

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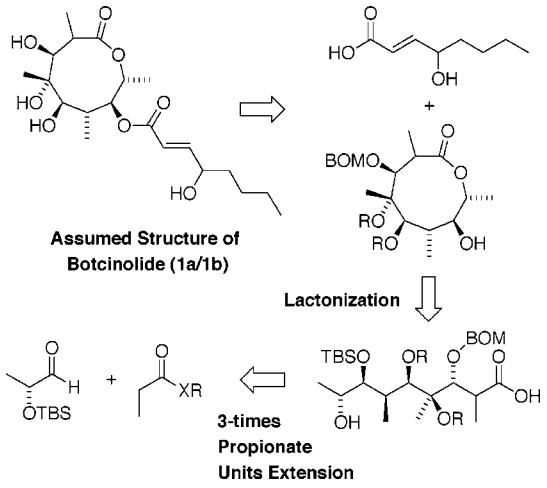
tionedthe structure of the proposed 2-epibotcinolide through its total synthesis.[5]

In this communication, we report an effective method for the synthesis of the saturated nine-membered lactone moiety of the presumed botcinolides and transformation to the proposed structure of 2-epibotcinolide (**1b**)[6] using the effective lactonization protocol accelerated by the substituted benzoic anhydride, a powerful dehydrating reagent, as part of our continuous efforts for the application of this new synthetic methodology to produce unusual structural lactones.[7]

Scheme 1. Synthesis of the Assumed Structure of Botcinolides via Lactonization



Scheme 1 illustrates the retrosynthetic route to the desired lactones **1a** and **1b**, which are divided into a lactone moiety and a side chain. It is postulated that all segments might be prepared using the asymmetric Mukaiyama aldol reaction via our universal strategy.[8]

We recently developed a new and rapid lactonization of ω-hydroxycarboxylic acids using symmetric substituted benzoic anhydrides, such as 2-methyl-6-nitrobenzoic anhydride (MNBA), as a coupling reagent.[7,9] Therefore, we planned to apply our effective monomer-selective lactone formation of the seco-acid to generate the desired nine-membered ring backbone, after assembling α-siloxyaldehyde and propionate templates to form the corresponding precursor (Scheme 1).

First, methyl (*R*)-lactate (**3**) was used as the starting material for the preparation of the chiral linear seco-acid **16** as shown in Scheme 2. The successive protection of **3** and reduction with DIBAL afforded the chiral α-siloxy aldehyde **4**, which in turn was treated with the enol silyl ether **5** derived from *S*-ethyl propanethioate using the chiral diamine−Sn(II) complex (**6**) combined with $^{n}Bu_2Sn(OAc)_2$.[8]

The asymmetric aldol reaction proceeded smoothly, and the corresponding γ-siloxy-β-hydroxy-α-methyl thioester **7**, which has the required stereochemistry, was exclusively obtained. The secondary hydroxyl group was protected as its TBS ether, and the reduction of the thioester moiety by the Fukuyama method produced the aldehyde **8**.[10]

Conventional three-carbon elongation using the successive Wittig reaction, reduction with L-Selectride and oxidation with TPAP/NMO yielded the seven-carbon unit aldehyde **9**. The second aldol reaction of **9** with lithium enolate derived from *S*-ethyl propanethioate took place with a moderate diastereoselectivity, and the linear nine-carbon polyoxygenated intermediate **10a** was predominantly produced. Relative configurations of **10a** and **10b** were assigned via the coupling constants of acetonide derivatives **11a** and **11b** as shown in Scheme 3. Absolute stereochemistry at the C3 position in **10a** was proved as *R* using MTPA ester protocol.[11] Although dihydroxylation of **10a** was examined under several reaction conditions, all of the reactions proceeded sluggishly to afford the corresponding γ-lactones **12** and **12″** in low yields, respectively (Scheme 3). The relative stereochemistry of **12** was determined after preparation of its benzylidene acetal as described in Supporting Information.

Then, the addition of two extra functionalities for the linear compound **10a** was attained by dihydroxylation of the double

(4) (a) Tani, H.; Koshino, H.; Sakuno, E.; Cutler, H. G.; Nakajima, H. *J. Nat. Prod.* **2006**, *69*, 722−725. (b) Tani, H.; Koshino, H.; Sakuno, E.; Nakajima, H. *J. Nat. Prod.* **2005**, *68*, 1768−1772.

(5) (a) Shiina, I.; Takasuna, Y.; Komiyama, Y. *Abstracts of Papers*, 85th National Meeting of the Chemical Society of Japan, Yokohama, 2005; Vol. 2, 1A142; (b) Shiina, I.; Takasuna, Y.; Komiyama, Y.; Suzuki, R.; Oshiumi, H. *Abstracts of Papers*, 86th National Meeting of the Chemical Society of Japan, Chiba, 2006; Vol. 2, 4L429; (c) Shiina, I.; Komiyama, Y.; Takasuna, Y.; Hitomi, S. *Abstracts of Papers*, 86th National Meeting of the Chemical Society of Japan, Chiba, 2006; Vol. 2, 4L430.

(6) Just before submitting our paper, Chakraborty et al. reported the synthesis of the nine-membered lactone core of botcinolides based on their independent methodology. They described that their prepared nine-membered ring corresponds to the assumed structure of 2-epibotcinolide (**1b**); however, there is a misunderstanding that the nine-membered ring produced by Chakraborty is not a precursor of 2-epibotcinolide (**1b**) but one of the diastereomers of **1b** originated at the C8 position. This means that Chakraborty reported the first synthesis of the lactone moiety of 2-epi-8-epibotcinolide. Carefully note the stereochemistry of the seco-acid (**19**, the number used in their paper): Chakraborty, T. K.; Goswami, R. K. *Tetrahedron Lett*. **2006**, *47*, 4917−4919.

(7) (a) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, 286−287. (b) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535−7539. (c) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822−1830. (d) Shiina, I.; Oshiumi, H.; Hashizume, M.; Yamai, Y.; Ibuka, R. *Tetrahedron Lett.* **2004**, *45*, 543−547. (e) Shiina, I. *J. Synth. Org. Chem. Jpn.* **2005**, *62*, 2−17. (f) Shiina, I.; Hashizume, M.; Yamai, Y.; Oshiumi, H.; Shimazaki, T.; Takasuna, Y.; Ibuka, R. *Chem. Eur. J.* **2005**, *11*, 6601−6608. (g) Shiina, I.; Hashizume, M. *Tetrahedron* **2006**, *62*, 7934−7939. See also: (h) Shiina, I.; Kawakita, Y. *Tetrahedron* **2004**, *60*, 4729−4733.

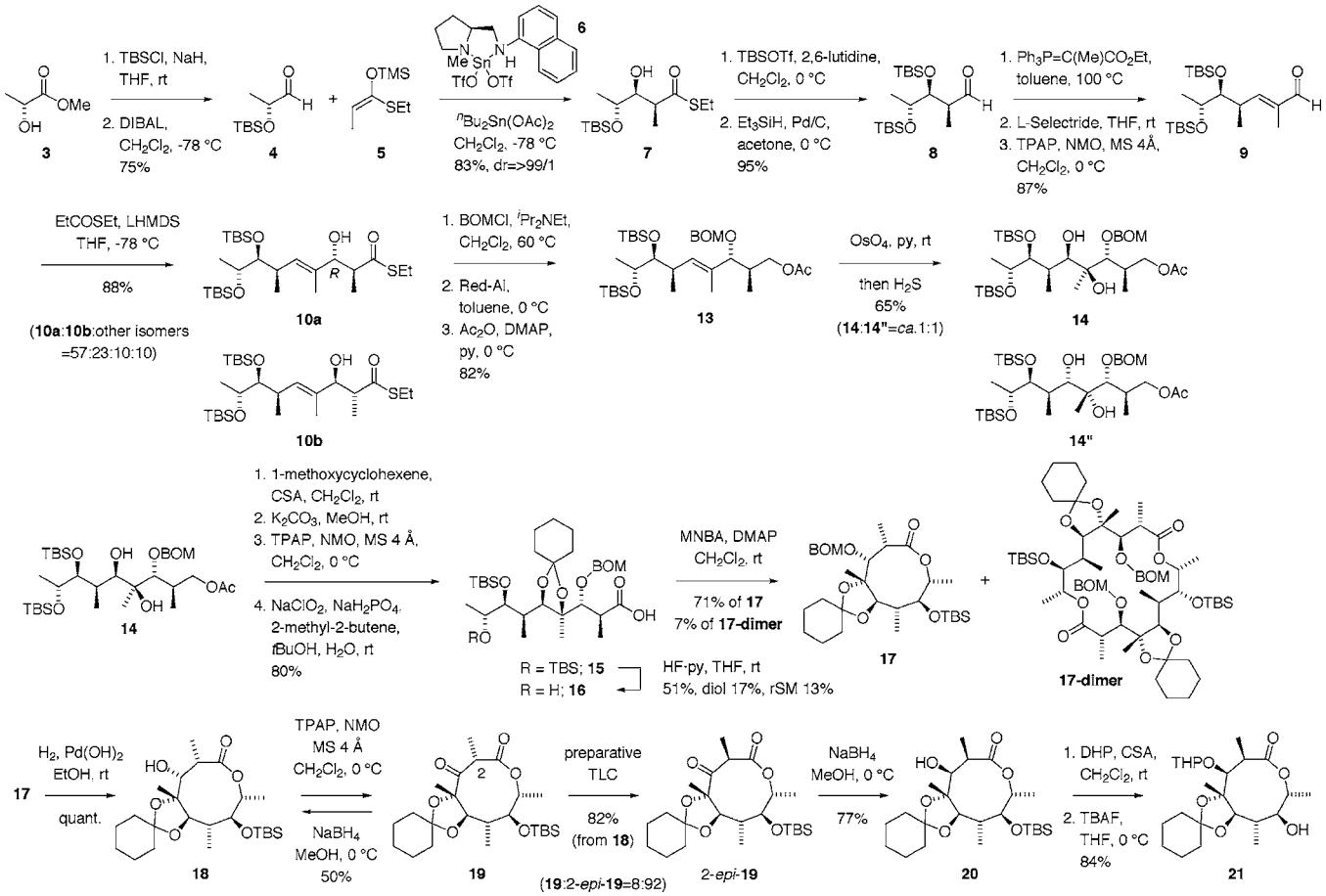
(8) (a) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett.* **1990**, 129−132. (b) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247−4252. (c) Shiina, I. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 105−165.

(9) (a) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021−3024. (b) Inoue, M.; Sasaki, T.; Hatano, S.; Hirama, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6500−6505. (c) Inoue, M. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 501−510. (d) Dinh, M.-T.; BouzBouz, S.; Peglion, J.-L.; Cossy, J. *Synlett* **2005**, 2851−2853. (e) Morita, M.; Mase, N.; Yoda, H.; Takabe, K. *Tetrahedron: Asymmetry* **2005**, *16*, 3176−3182. (f) Doi, T.; Iijima, Y.; Shin-ya, K.; Ganesan, A.; Takahashi, T. *Tetrahedron Lett.* **2006**, *47*, 1177−1180. (g) Hosokawa, S.; Seki, M.; Fukuda, H.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 2439−2442. (h) Nicolaou, K. C.; Xu, H. *Chem. Commun.* **2006**, 600−602. (i) Wu, Y.; Yang, Y.-Q. *J. Org. Chem.* **2006**, *71*, 4296−4301. (j) Tsuchikawa, H.; Matsushita, N.; Matsumori, N.; Muraka, M.; Oishi, T. *Tetrahedron Lett.* **2006**, *47*, 6187−6191.

(10) Fukuyama, T.; Lin, S.-C.; Li, L.-P. *J. Am. Chem. Soc.* **1990**, *112*, 7050−7051.

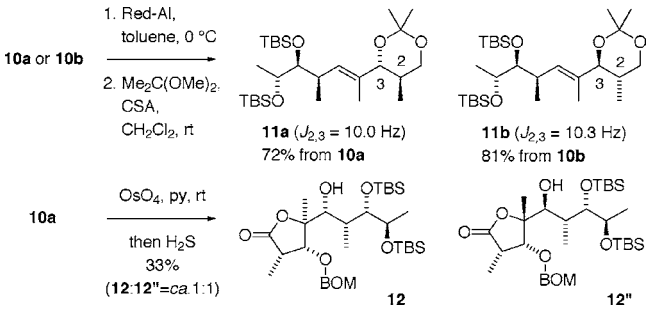
(11) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

Scheme 2. Synthesis of Nine-Membered Lactone Part of the Proposed Structure of Botcinolides



bond using OsO_4 in pyridine solvent after converting to **13** via three steps; that is, protection of the secondary hydroxyl group with the BOM group, reduction of the ester function, and protection of the resulting primary hydroxyl group (Scheme 2). It was confirmed that the produced diol **14** has the desired relative configuration by comparison of ^{1}H NMR data of the deacetylated **14** with those of a derivative of **12** (see details in Supporting Information).

Scheme 3. Determination of the Stereochemistry of **10a**, **10b**, and **12**



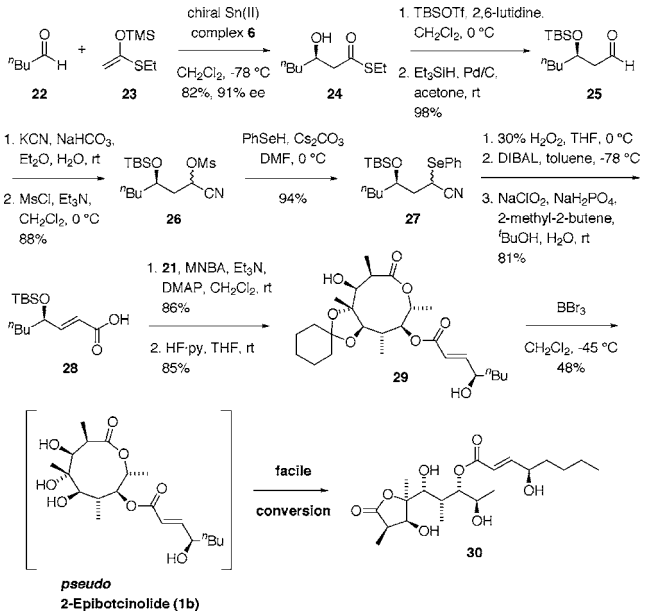
The produced diol **14** was converted to the corresponding cyclohexylidene derivative by treatment with 1-methoxycyclohexene and CSA, and the successive deacetylation of the protective group followed by gradual oxidation of the primary alcohol into the carboxylic acid **15** proceeded in high yield. The TBS protecting group at C8 was cleaved, and then the desired seco-acid **16** needed for the formation of the nine-membered ring was produced at last. Eventually, the lactonization of the seco-acid **16** was carried out in the presence of MNBA with DMAP, and the desired monomeric lactone **17** was obtained in 71% yield along with the dimeric lactide **17-dimer** (7%). Following the successful results of forming the novel saturated nine-membered lactone, which corresponds to the main skeleton of the assumed botcinolide structure, further studies focused on the derivation of this key compound **17** into one of the assumed naturally occurring botcinolides.

Before attaching the side chain on the backbone of the nine-membered lactone core, the stereochemistry of **17** was arranged by a transformation into the coupling fragment **21**. First, the BOM group of **17** was deprotected by hydrogenation using $Pd(OH)_2$, and the produced β-hydroxy lactone **18** was oxidized by the TPAP/NMO conditions. Epimerization at the α-position of the formed β-ketolactone **19** smoothly took place on silica gel and the 2-epimeric β-ketolactone 2-*epi*-**19** was obtained in good yield. Stereoselective reduction of the carbonyl group in 2-*epi*-**19** was also accomplished

using $NaBH_4$ in MeOH to afford the corresponding 2-epimerized β-hydroxy lactone **20**, which was then converted into the THP ether, and the TBS protective group was removed by TBAF to afford the key intermediate **21**. Relative configurations of **17** and **20** were assigned by NOE correlations with conformational analysis as described in Supporting Information.

The side chain **28** was synthesized starting from the achiral pentanal (**22**) by the asymmetric aldol reaction with enol silyl ether **23** derived from the *S*-ethyl ethanethioate using the chiral diamine−Sn(II) complex (**6**) as depicted in Scheme 4. The optically active aldol product **24** was protected as its

Scheme 4. Synthesis of the Proposed Structure of 2-Epibotcinolide



TBS ether, and the successive reduction to form an aldehyde **25**, which was further treated with KCN for the one-carbon homologation. Mesylation of a mixture of cyanohydrin and successive substitution of **26** with phenylselenol in the presence of Cs_2CO_3 afforded a mixture of the diastereomeric isomers **27**. Oxidative elimination of the phenylseleno group, followed by reduction with DIBAL and oxidation of the resulting aldehyde, yielded the corresponding α,β-unsaturated carboxylic acid **28**.[9a]

Finally, the coupling reaction between the main nine-membered ring **21** and the chiral side chain **28** was also investigated using MNBA esterification to form the desired lactone that involves all functionalities for producing the ideal structure of 2-epibotcinolide (**1b**). The coupling product was temporarily converted into the deprotected compound **29**, and the spectral data of the coupling product were compared with those of the natural 2-epibotcinolide and other botcinolide derivatives reported from several groups. However, the chemical shift especially of the methyne proton (4.9 ppm in CD_3OD) at C8 of the synthetic sample **29** is significantly different from the natural 2-epibotcinolide (3.7 ppm in CD_3OD), botcinolide (3.6 ppm), 4-*O*-methylbotcinolide (3.6 ppm), and 3-*O*-acetyl-2-epibotcinolide (3.7 ppm). Furthermore, the deprotection of **29** afforded the intramolecular trans-acylated compound **30**, which is facilely formed from the assumed nine-membered lactone **1b**. The structure of trans-acylated γ-lactone **30** was determined by the comparison with the spectral data of the other γ-lactones derived from aldols **10a** and **10b**.

Therefore, the proposed nine-membered ring structures of 2-epibotcinolide (**1b**) and other related compounds are extremely doubtful, and reassigned structures should be given for the exact determination of these true forms. In accordance with our representation of these results,[5] Nakajima's group has just shown the alternative structure of 2-epibotcinolide (**2b**) as depicted in Figure 1.[4]

It was experimentally determined that the proposed nine-membered ring structure of 2-epibotcinolide (**1b**) is very unstable and the ineluctable trans-lactonization easily occurred to form the corresponding γ-lactone **30**. Therefore, it is confirmed that there does not exist a naturally occurring saturated-type nine-membered ring lactone as a result of the synthetic approach for the proposed structure of 2-epibotcinolide (**1b**), although there are three kinds of monocyclic saturated eight-membered ring lactones, cephalosporolide D and octalactins A and B.

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

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