ORGANIC LETTERS

2010
Vol. 12, No. 24
5752−5755

Stereoselective Synthesis and Structural Correction of the Naturally Occurring Lactone Stagonolide G§

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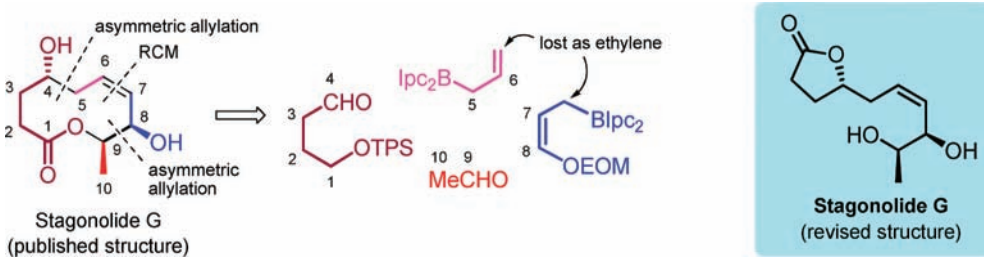
Received October 26, 2010

ABSTRACT



A convergent synthesis of the structure proposed for the naturally occurring lactone stagonolide G is described. All three stereocenters were created with the aid of asymmetric Brown allylations. The lactone ring was built by means of a ring-closing metathesis (RCM). The synthetic and the natural compound differed in their spectral properties. A new structure is now proposed for stagonolide G and demonstrated by means of a chemical transformation.

Stagonospora cirsii Davis is a pathogenic fungus which grows on the terrestrial plant *Cirsium arvense*, a noxious weed, and causes necrotic lesions on its leaves. The fungus, which has aroused interest as a potential myco-herbicidal agent, has been found to produce various toxic metabolites when grown in liquid culture. The first of these metabolites was reported in 2007 and named stagonolide (later called stagonolide A). The compound was assigned the structure depicted in Figure 1 on the basis of its NMR and other spectroscopic data.[1] Stagonolide A was shown to be a non-host-specific but selective phytotoxin.[2]

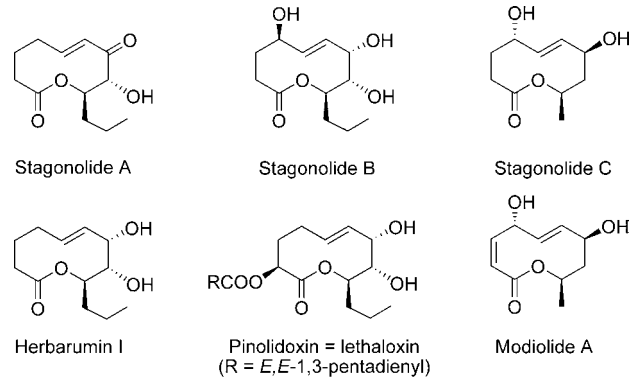


Figure 1. Structures of some stagonolides and other structurally related, naturally occurring 10-membered lactones.

§ Dedicated to the memory of Prof. R. Suau (deceased November 11, 2010).

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(1) Yuzikhin, O.; Mitina, G.; Berestetskiy, A. *J. Agric. Food Chem.* **2007**, *55*, 7707–7711.

10.1021/ol102599e
Published on Web 11/24/2010

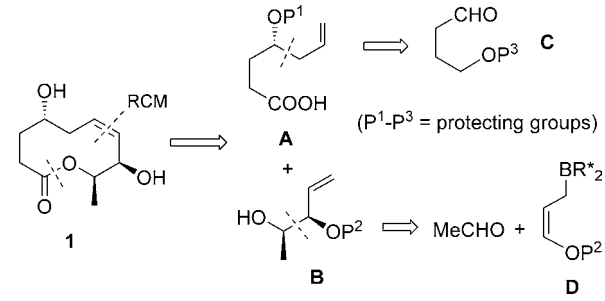
A short time later, further metabolites were isolated from the same fungus and named stagonolides B−I.[3] They also showed phytotoxic activity against *C. arvense*, although except for stagonolide H, the activity was much weaker than that of stagonolide A. Most particularly, stagonolide G was essentially inactive. Figure 1 shows the structures of three of the stagonolides.

The similarity of their structures with those of other bioactive 10-membered lactones of natural origin (see Figure 1)[4] has attracted the attention of several groups, who have devised stereoselective syntheses for lactones of this type. As a matter of fact, stagonolides A,[5] B,[5b,6] C,[7] F,[8] and G[9] have succumbed to total synthesis in the last 2 years.

In recent years, we have been involved in the total synthesis of several medium- and large-ring lactones.[10] In the present paper, we are disclosing our own synthesis of compound **1**, which has the structure proposed for stagonolide G. The retrosynthetic concept followed is presented in Scheme 1.

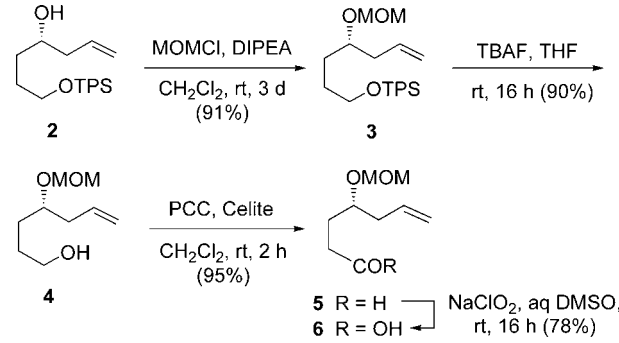
Retrosynthetic cleavage of the lactone C−O bond and the olefinic C=C bond (via ring-closing metathesis, RCM) in **1** leads to fragments **A** and **B**. Acid **A** can be referred via inverse allylation and functional group interchange to the protected 4-hydroxybutanal **C**. The monoprotected diol **B** should be amenable to preparation by means of an asymmetric α-alkoxyallylation[11] of acetaldehyde with the chiral (*Z*)-γ-alkoxyallylborane **D**.

Scheme 1. Retrosynthetic Analysis of Structure **1**



Homoallyl alcohol **2** was prepared as reported[12] by means of asymmetric Brown allylation of a silylated 4-hydroxy-butanal (Scheme 1, **C** with P^3 = TPS). Protection of the hydroxyl group as its MOM derivative[13] was followed by desilylation with TBAF to yield primary alcohol **4**.[14] All attempts at direct oxidation of **4** to acid **6** failed. However, PCC oxidation of alcohol **4** to aldehyde **5** followed by sodium chlorite oxidation[15] gave **6** in a fair overall yield (Scheme 2).

Scheme 2. Synthesis of Acid **6** (≡ **A**, P^1 = MOM)[a]



[a] Acronyms and abbreviations: TPS, *tert*-butyldiphenylsilyl; MOM methoxymethyl; TBAF, tetra-*n*-butylammonium fluoride hydrate; PCC, pyridinium chlorochromate; DIPEA, *N*,*N*-diisopropylethylamine.

In the only other, very recently published synthesis of stagonolide G,[9] a fragment equivalent to **B** (P^2 = Bn) was prepared through a nine-step sequence from D-glucose diacetonide. In the present synthesis, a shorter and more efficient sequence has been utilized (Scheme 3). Our first idea was to lithiate the MOM derivative of allyl alcohol and then treat the organolithium thus formed with *B*-methoxydiisopinocampheylborane (Ipc_2BOMe). The resulting chiral

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(3) (a) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Mitina, G.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 31–34. (b) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 1897–1901.

(4) For reviews on various synthetic, biosynthetic, or pharmacological aspects of medium-ring (8−11 membered) lactones, see: (a) Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365–375. (b) Shiina, I. *Chem. Rev.* **2007**, *107*, 239–273. (c) Ferraz, H. M. C.; Bombonato, F. I.; Longo, L. S., Jr. *Synthesis* **2007**, 3261–3285. (d) Ferraz, H. M. C.; Bombonato, F. I.; Sano, M. K.; Longo, L. S., Jr. *Quim. Nova* **2008**, *31*, 885–900. (e) Ishigami, K. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 971–979.

(5) (a) Srihari, P.; Kumaraswamy, B.; Rao, G. M.; Yadav, J. S. *Tetrahedron: Asymmetry* **2010**, *21*, 106–111. (b) Prabhakar, P.; Rajaram, S.; Reddy, D. K.; Shekar, V.; Venkateswarlu, Y. *Tetrahedron: Asymmetry* **2010**, *21*, 216–221. (c) Mohapatra, D. K.; Somaiah, R.; Rao, M. M.; Caijo, F.; Mauduit, M.; Yadav, J. S. *Synlett* **2010**, 1223–1226. (d) Srihari, P.; Rao, G. M.; Rao, R. S.; Yadav, J. S. *Synthesis* **2010**, 2407–2412.

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(8) Perepogu, A. K.; Raman, D.; Murty, U. S. N.; Rao, V. J. *Bioorg. Chem.* **2009**, *37*, 46–51.

(9) Srihari, P.; Kumaraswamy, B.; Bhunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 2903–2905.

(10) (a) Murga, J.; Falomir, E.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447–3449. (b) García-Fortanet, J.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 9822–9827. (c) García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron* **2007**, *63*, 12131–12137. (d) Díaz-Oltra, S.; Angulo-Pachón, C. A.; Kneeteman, M. N.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2009**, *50*, 3783–3785. (e) Díaz-Oltra, S.; Angulo-Pachón, C. A.; Murga, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2010**, *75*, 1775–1778. (f) Díaz-Oltra, S.; Angulo-Pachón, C. A.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Chem.−Eur. J.*, in press.

(11) For a review of this specific allylation type, see: Lombardo, M.; Trombini, C. *Chem. Rev.* **2007**, *107*, 3843–3879.

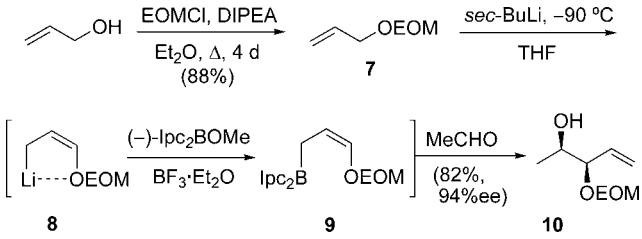
(12) Brimble, M. A.; Bryant, C. J. *Org. Biomol. Chem.* **2007**, *5*, 2858–2866. In our hands, **2** was obtained with an enantiomeric purity above 99% (see the Supporting Information).

(13) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; 4th ed.; John Wiley and Sons: New York, 2007; pp 30−38.

(14) Compound **4** has previously been prepared with a lower optical purity (84%) alongside a different reaction sequence: Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2801–2810.

(15) The reaction conditions for this oxidation were taken from ref 6b.

Scheme 3. Synthesis of Alcohol **10** (≡ **B**)[a]

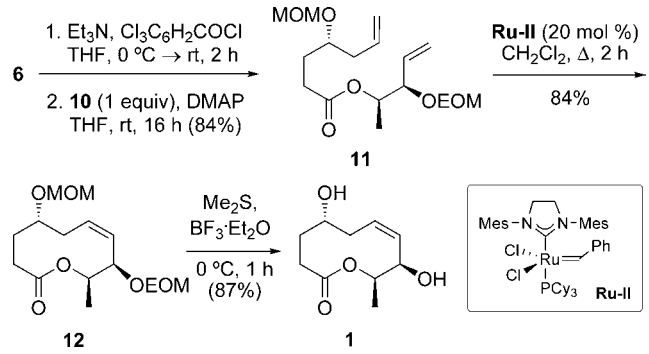


[a] Acronyms and abbreviations: Ipc, isopinocampheyl; EOM, ethoxymethyl.

allylborane would then be treated with acetaldehyde.[16] However, we faced considerable practical difficulties in obtaining the MOM derivative of allyl alcohol with an adequate purity.[17] In view of this drawback, we replaced the MOM group with the structurally similar EOM group.[18,19] Thus, protection of allyl alcohol gave compound **7**, which was then lithiated with *sec*-butyl lithium at low temperature. The resulting organolithium reagent **8** was treated at the same temperature with Ipc_2BOMe to yield the chiral (*Z*)-γ-alkoxyallylborane **9**, which was then allowed to react with acetaldehyde. This gave homoallyl alcohol **10** in 82% yield and 94% ee.[20]

Acid **6** and alcohol **10** were joined using the Yamaguchi procedure[21] (Scheme 4). The resulting ester **11** was then subjected to RCM[22] catalyzed by the second-generation ruthenium complex **Ru-II**.[23] This gave the 10-membered lactone **12** in 84% yield as a single *Z* stereoisomer.[24] Simultaneous cleavage of the two protecting groups was performed under the same mild conditions used previously for MOM groups[10a] and yielded lactone **1**. Surprisingly,

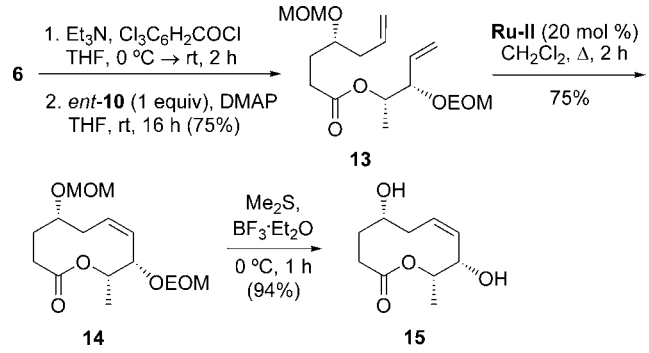
Scheme 4. Fragment Coupling and Last Steps of the Synthesis



however, the spectral data of synthetic **1** were found different from those reported for stagonolide G.[3b] This was a most unexpected result in view of the fact that structure **1** was assumedly confirmed with a total synthesis.[9]

As an alternative structural possibility, we prepared lactone **15**, a stereoisomer of **1**, as described in Scheme 5. First, *ent*-**10**

Scheme 5. Synthesis of **15**, a Stereoisomer of **1**



(the enantiomer of **10**) was prepared in the same way as the latter (Scheme 3) but using (+)-Ipc_2BOMe in the asymmetric allylation step. Then, **6** and *ent*-**10** were connected as above by means of the Yamaguchi procedure to yield ester **13**. This was followed by RCM to **14** and cleavage of the two protecting groups to yield **15**, epimeric of **1** at C-8 and C-9 (for numbering see Figure 2). Again, lactone **15** proved different from natural stagonolide G.

We found the fact very intriguing that the only previous, target-directed synthesis of stagonolide G reported the successful preparation of the natural compound.[9] Our synthetic structure being secured, we could only explain this result by assuming that some undetected mistake of the same type was made in both the initial structure assignment[3b] and the aforementioned synthesis. Since the C−H connectivities of the natural compound had been based on 2D NMR one-bond (HSQC) and also long-range (HMBC) heteronuclear correlations, the carbon framework should be correctly established.[3b] However, no HMBC three-bond through-oxygen correlations (O=*C*−

(16) This reaction has previously been performed with an *achiral* allylborane to yield the corresponding homoallyl alcohol in racemic form. See: Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Liebigs Ann. Chem.* **1985**, 2246–2260.

(17) This was due to the considerable volatility of this compound, which made it difficult to eliminate trace amounts of the solvent used in its preparation, at least at the small scale in which we were working. These solvent traces led to failure of the lithiation step.

(18) The lower volatility of the EOM derivative of allyl alcohol, as compared with the MOM derivative, permitted its preparation with an appropriate purity.

(19) For examples of use of the EOM protecting group in synthesis, see: (a) Boudier, A.; Hupe, E.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2294–2297. (b) Adrio, J.; Rodríguez-Rivero, M.; Carretero, J. C. *Chem.—Eur. J.* **2001**, *7*, 2435–2448. (c) Dakas, P.-Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N. *Chem.—Eur. J.* **2009**, *15*, 11490–11497. (d) Harris, D. A.; Powers, M. E.; Romesberg, F. E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3787–3790.

(20) The experimental procedure followed was adapted from that reported in: Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040–6041.

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

(22) For reviews on the uses of this reaction for the synthesis of macrocycles, see: (a) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830. (b) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086–6101. (c) Majumdar, K. C.; Rahaman, H.; Roy, B. *Curr. Org. Chem.* **2007**, *11*, 1339–1365.

(23) With the first-generation ruthenium catalyst $PhCH{=}RuCl_2(PCy_3)_2$, no reaction took place after 16 h of reflux in CH_2Cl_2.

(24) It is noteworthy that, except for stagonolide G, in all syntheses of other stagonolides where RCM was used, the *E* isomer was the predominant or the only isomer formed.

O−C−*H*) were presented in the original publication, such correlations being very useful to confirm the position of lactone carbonyl groups. Thus, we performed an HMBC experiment with our synthetic **1** and found such a correlation between the carbonyl ^{13}C NMR peak at 173.9 ppm and the H-9 signal at δ 5.06 (see the Supporting Information).

In view of these findings, we wondered whether the ring closure in the putative *seco*-acid precursor of stagonolide G (Figure 2) took place through the hydroxyl at C-8 (i.e., the

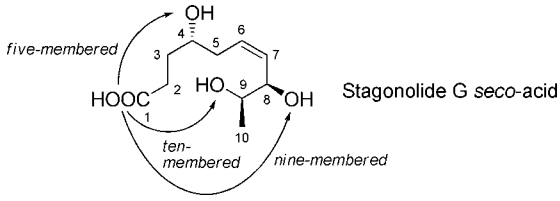


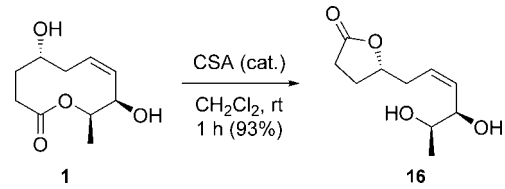
Figure 2. Alternative lactone ring closures available to stagonolide G *seco*-acid.

compound would be a nine-membered rather than a ten-membered lactone) or, perhaps more likely, through the hydroxyl at C-4 (i.e., a five-membered lactone). This is not without precedent, as five-membered lactones of this structural class have been found to coexist in the same organism with lactones of higher ring sizes.[25,26]

Although the NMR data of synthetic **1** were different from those reported for stagonolide G,[3b] an aged sample of the synthetic compound displayed additional NMR signals which were coincident with those of the natural product. Since $CDCl_3$ may contain traces of HCl, a solution of **1** was stirred at room temperature in the presence of a catalytic amount of camphorsulfonic acid. A new lactone **16** was then isolated in 93% yield with spectral data identical to those reported for the natural compound (Scheme 6). This indicates that a translactonization has taken place with formation of the thermodynamically more stable γ-lactone system.[27] The carbonyl band at 1765 cm^{-1} in the IR spectrum of **16** is also diagnostic of a five-membered lactone.[28]

Visible differences are observed between our optical rotation values and those reported in the literature. Thus, as indicated in this paper, compound **1** having the reported stagonolide G structure has $[\alpha]_D$ −24.2 (*c* 0.55, $CHCl_3$),

Scheme 6. Acid-Catalyzed Isomerization of the 10-Membered Lactone **1** to the Five-Membered Lactone **16** [a]



[a] Acronyms and abbreviations: CSA, camphorsulfonic acid.

whereas compound **16**, which has the actual structure, has $[\alpha]_D$ +21.8 (*c* 0.1, $CHCl_3$). A value of $[\alpha]_D$ +96 (*c* 0.1, $CHCl_3$) was given for stagonolide G in the original publication,[3b] and $[\alpha]_D$ +7 (*c* 0.3, $CHCl_3$) was the value reported for a putative synthetic stagonolide G.[9] Our compound **16** has a high optical purity, as demonstrated by the chiral HPLC analyses of its two precursors **6** (>99% ee) and **10** (94% ee). We believe therefore that the aforementioned literature values are affected by errors likely due to an inadequate purity.

While an adventitious translactonization in the course of the chromatographic isolation process may be invoked to explain the coexistence of a five-membered lactone with the other 10-membered lactones in *S. cirsii*,[3,26] there is still the open question that a previous synthesis of stagonolide G was claimed to give a product identical to the natural product.[9] The only reasonable explanation for this is that a translactonization inadvertently took place in the last step of the synthetic sequence. Indeed, this was a deprotection step in which two benzyl groups were cleaved under the influence of $TiCl_4$, a strong Lewis acid which can induce such kinds of processes, as previously observed.[29] It seems that the translactonization **1** → **16** under such conditions is competitive with, or even faster than, deprotection.

In summary, the structure of the stagonolide G isolated from *S. cirsii* turns out to be markedly different from the remaining lactones found in the same fungus. Most likely, the accordingly different molecular shape explains why stagonolide G, in contrast to the other lactones found in the fungus, is practically devoid of phytotoxic activity.[3b]

Acknowledgment. Financial support has been granted by the Spanish Ministry of Science and Technology by the BANCAJA-UJI foundation (Project No. P1-1B-2008-14) and by the Generalitat Valenciana (Project Nos. ACOMP/2009/113 and ACOMP/2010/246).

Supporting Information Available: Experimental procedures for the preparation and tabulated spectral data of all new compounds. Graphical NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Smith, C. J.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Jompa, J.; Tahir, A.; Ireland, C. M. *J. Nat. Prod.* **2000**, *63*, 142–145.

(26) For natural lactones containing additional free hydroxyl groups, the question remains open as to whether they all are true natural products or some of them are the result of translactonization process during the isolation. In the present case, it is not unlikely that the natural product actually has structure **1**, which then isomerized during the isolation to the more stable γ-lactone **16**.

(27) Freshly dissolved samples of **1** in $CDCl_3$ (taken from a bottle opened a few weeks prior to use) already showed incipient NMR signals of **16** after several minutes at room temperature. After 15 h, about 50% of **1** was converted into **16**. Interestingly, lactone **15** did not show this marked proclivity to acid-catalyzed translactonization.

(28) Lambert, J. B.; Shurvell, H. F.; Lightner, D. A.; Cooks, R. G. *Organic Structural Spectroscopy*; Prentice Hall: Upper Saddle River, 1998; p 193. An HMBC experiment with **16** further confirmed the presence of the γ-lactone ring (see the Supporting Information).

(29) Sharma, G. V. M.; Reddy, J. J.; Reddy, K. L. *Tetrahedron Lett.* **2006**, *47*, 6531–6535.