ORGANIC LETTERS

2013
Vol. 15, No. 15
4018–4021

Asymmetric Total Synthesis of (+)-Fusarisetin A via the Intramolecular Pauson–Khand Reaction

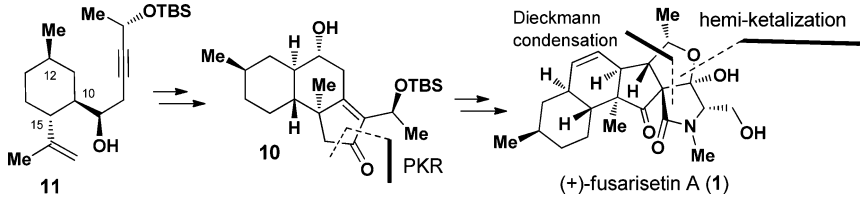
Jun Huang,[†,§] Lichao Fang,[†,§] Rong Long,[†] Li-Li Shi,[†] Hong-Juan Shen,[†] Chuang-chuang Li,[*,†] and Zhen Yang[*,†,‡]

Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China, and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), and Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China

licc@pkusz.edu.cn; zyang@pku.edu.cn

Received July 1, 2013

ABSTRACT



An asymmetic total synthesis of (+)-fusarisetin A has been achieved. The essential to our strategy was the application of the intramolecular Pauson–Khand reaction for the stereoselective construction of the *trans*-decalin subunit of (+)-fusarisetin A with a unique C16 quarternary chiral center. The developed chemistry offers an alternative to the IMDA reaction that has been used for fusarisetin A, and is applicable to analogue synthesis for biological evaluation.

(+)-Fusarisetin A (**1**, Figure 1)[1] represents an emerging class of anticancer agents structurally related to the members of the cytochalasin family of fungal metabolites.[2] This molecule has elicited considerable levels of biological interest because it exerts a potent inhibitory effect on metastasis in the MDA-MB-231 breast cancer cells, as well as inhibiting acinar morphogenesis (77 μM), cell migration (7.7 μM), and cell invasion (26 μM) in the same cell line without any significant cytotoxicity.[2] The structure of **1** was estblished by NMR and X-ray diffraction analyses,[1] as well as its total synthesis.[3]

Structurally, **1** is composed of 10 stereocenters and an unprecedented carbon skeleton consisting of a pentacyclic ring system comprising decalin (6/6) and tricyclic (5/5/5) moieties that are both decorated with a variety of different functionalities. The novel structural features of these fungal metabolites have led to the deployment of considerable synthetic efforts that have culminated in several successful total syntheses of **1** by the groups of Li in 2011[3] and Theodorakis[4] and Gao[5] in 2012.

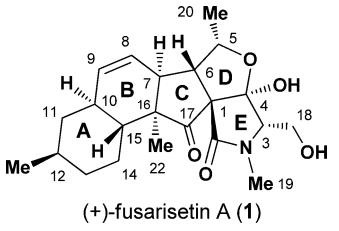


Figure 1. Structure of (+)-fusarisetin A (**1**).

[†] Peking University Shenzhen Graduate School.
[‡] Peking University.
[§] These authors contributed equally.

(1) Jang, J.-H.; Asami, Y.; Jiang, J.-P.; Kim, S.-O.; Shin, S.-S.; Hashizume, D.; Muroi, M.; Saito, T.; Oh, H.; Kim, B. Y.; Osada, H.; Ahn, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 6865.
(2) Li, J. Y.; Strobel, G. A.; Harper, J. K.; Lobkovsky, E.; Clardy, J. *Org. Lett.* **2000**, *2*, 767.
(3) Deng, J.; Zhu, B.; Lu, Z.-Y.; Yu, H.-X.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 920.
(4) (a) Xu, J.; Caro-Diaz, J. E.; Trzoss, L.; Theodorakis, E. A. *J. Am. Chem. Soc.* **2012**, *134*, 5072. (b) Xu, J.; Caro-Diaz, J. E.; Lacoske, M. H.; Hung, C.-I.; Jamora, C.; Theodorakis, E. A. *Chem. Sci.* **2012**, *3*, 3378.

10.1021/ol401831w
Published on Web 07/19/2013

During the course of the past two decades, the Pauson–Khand (PK) reaction[6] has emerged as a powerful method for the synthesis of cyclopentenones,[7] and the reaction has been successfully applied to the total syntheses of complex natural products.[8] Herein, we report our recent accomplishment of the total synthesis of (+)-fusarisetin A by using the PK reaction as a key step.

Retrosynthetically, (+)-fusarisetin A (**1**) could be made from amide **4** via the Dieckmann-type cyclization followed by hemiacetalization via the published protocol (Figure 2).[3] Amide **4** could in turn be generated via the aminolysis of the β-keto ester **5** with aminoester **6**.

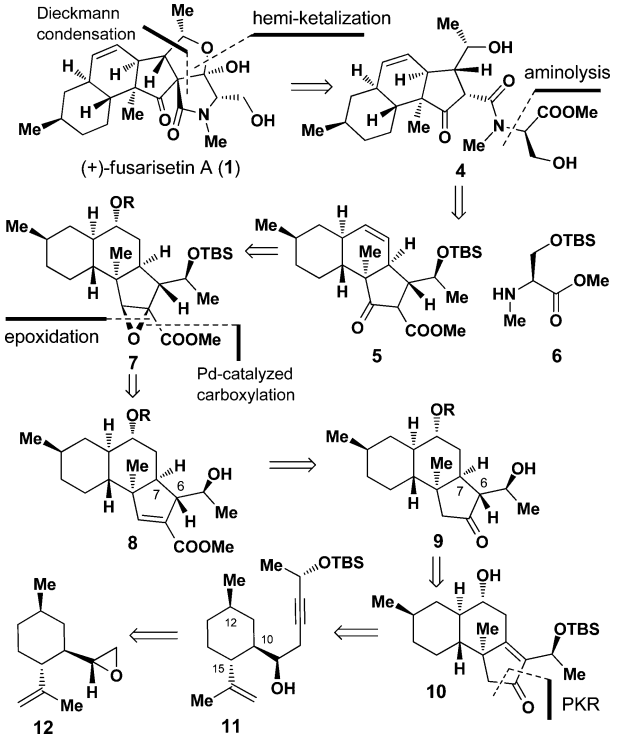


Figure 2. Retrosynthetic analysis of (+)-fusarisetin A (**1**).

It was envisaged that the ester **5** could be prepared from the epoxide ester **7** via a reductive epoxide-ring-opening reaction[9] followed by the oxidation of the resulting β-hydroxy ester. The epoxide ester **7** could be prepared by the epoxidation of **8**. Given that the Pd-catalyzed carbonylation of enol triflates has been reported as an effective method for the conversion of ketones to its corresponding α,β-unsaturated esters,[10] this approach was used for the construction of the α,β-unsaturated ester in **8** in a regiocontrolled manner from ketone **9**, which was itself derived from **10** via a stereoselective 1,4-reduction. It was also expected that enyne **11**, which already included three necessary chiral centers (C_{10}, C_{12}, and C_{15}), could be stereoselectively transformed into **10** via a transition metal catalyzed PK reaction. The precursor enyne **11** could be constructed from epoxide **12**,[11] which could itself be prepared by the known precudure.[12]

Our synthesis started with the synthesis of enone **10**. In the event, addition of chloromethylithium, generated from chloroiodomethane and *n*-BuLi, to aldehyde **13**[11] at −78 °C gave epoxide **12** in 72% yield,[12] together with its diastereoisomer **12a** in 12% yield (Scheme 1). Further reaction of epoxide **12** with lithium acetylide **14**[13] at −78 °C in THF in the presence of $BF_3 \cdot Et_2O$ gave the requisite enyne **11** in 60% yield.

Our attention then shifted to the intramolecular PK reaction of enyne **11**. To establish the optimal reaction conditions, the effects of a variety of different parameters (e.g., metal catalyst, additive, solvent, and temperature) on the outcome of the reaction were investigated. Several different transition metal complexes were tested, including $PdCl_2$ in the presence of tetramethyl thiourea (TMTU)[14] and $Co_2(CO)_8$ under a variety of different conditions in the presence of several different additives, including molecular sieves,[15] Me_2S,[16] water,[17] ethane-1,2-diol,[18] *N*-methylmorpholine-*N*-oxide (NMO),[19] trimethylamine-*N*-oxide (TMANO),[20] and TMTU.[14] The results indicated that the $Co_2(CO)_8$-mediated PK reaction was the most efficient method of those tested for the stereoselective construction of the quaternary stereogenic center at the C_{16} position of cyclopentenone **10**. Of the different solvents tested, including THF, benzene, toluene, and CH_3CN, toluene was found to provide the best results. The temperature for the reaction was evaluated at temperatures ranging from 70 to 130 °C, with 120 °C giving the best result. Taken together, an 82% yield

(5) Yin, J.; Wang, C.; Kong, L.-L.; Cai, S.-J.; Gao, S.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 7786.

(6) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977. (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc. D.: Chem. Commun.* **1971**, 36a.

(7) Illustrative reviews on the Pauson–Khand reaction: (a) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. (b) Schore, N. E. *Org. React.* **1991**, *40*, 1. (c) Schore, N. E. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier: New York, 1995; Vol. 12, p 703. (d) Jeong, N. *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 560.

(8) (a) Turlington, M.; Du, Y.; Ostrum, S. G.; Santosh, V.; Wren, K.; Lin, T.; Sabat, M.; Pu, L. *J. Am. Chem. Soc.* **2011**, *133*, 11780. (b) Hayashi, Y.; Inagaki, F.; Mukai, C. *Org. Lett.* **2011**, *13*, 1778. (c) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684. (d) Liu, Q.; Yue, G.; Wu, N.; Lin, G.; Li, Y.; Quan, J.; Li, C.-C.; Wang, G.; Yang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12072.

(9) (a) Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1996**, *61*, 5885. (b) Molander, G. A.; del Pozo Losada, C. *J. Org. Chem.* **1997**, *62*, 2935.

(10) (a) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985. (b) Cacchi, S.; Morera, E.; Orter, G. *Tetrahedron Lett.* **1986**, *26*, 1109.

(11) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526.

(12) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795.

(13) (a) Cotterill, A. S.; Gill, M.; Gimenez, A.; Milanovic, N. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3269. (b) Brimble, M. A.; Bryant, C. J. *Org. Biomol. Chem.* **2007**, *5*, 2858.

(14) Tang, Y. F.; Deng, L. J.; Zhang, Y. D.; Dong, G. B.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 1657.

(15) (a) Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Org. Lett.* **1999**, *1*, 1187. (b) Blanco-Urgoiti, J.; Dominguez, G.; Perez-Castells, J. *Synthesis* **2004**, *3*, 182.

(16) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771.

(17) Sugihara, T.; Yamaguci, M. *Synlett* **1998**, 1384.

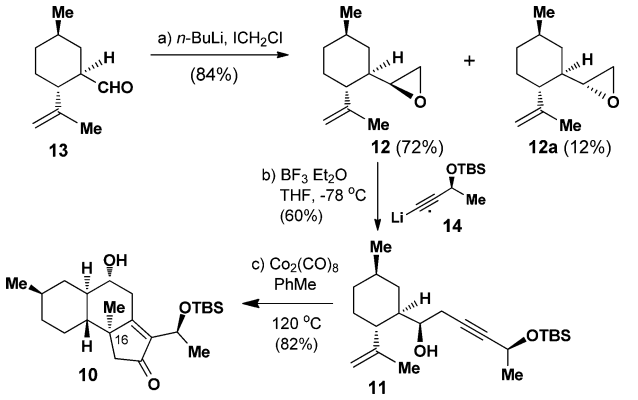
(18) Su, S.; Rodriguez, R. A.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 13922.

(19) (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289. (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. E.; Sunghee, H. *Synlett* **1991**, 204.

(20) Blanco-Urgoiti, J.; Casarrubios, L.; Perez-Castells, J. *Tetrahedron Lett.* **1999**, *40*, 2817.

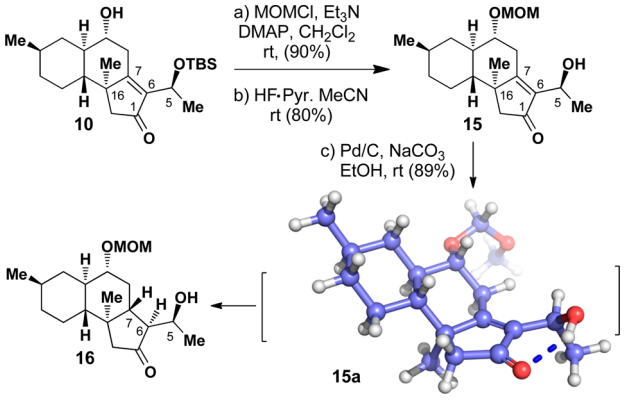
of product **10** with the desired quaternary chiral center was remarkably obtained when a stoichiometric amount of $Co_2(CO)_8$ was used at a reaction temperature of 120 °C under argon.

Scheme 1. Synthesis of Cyclopentanaphthalenone **10**



We then investigated the stereoselective reduction of enone **10** via hydrogenation. Initially, various conditions were attempted; however, no hydrogenation was observed, presumably because of the steric hindrance of the TBS group. We then decided to remove this silyl group. In the event, the hydroxyl group in **10** was first protected as its methoxy methyl ether (MOM), and the resultant MOM ether was then subjected to desilylaytion with HF·pyridine to afford product **15** (Scheme 2). Thus, under the hydrogenation conditions with Pd/C as a catalyst, **16** was obtained in 89% yield as a single isomer. However, the stereochemistries at the C6- and C7-positions in **16** were the opposite of what we expected. The stereochemistry of **16** was established via a 2D-NMR study (see Supporting Information for details).

Scheme 2. Synthesis of Compound **16**

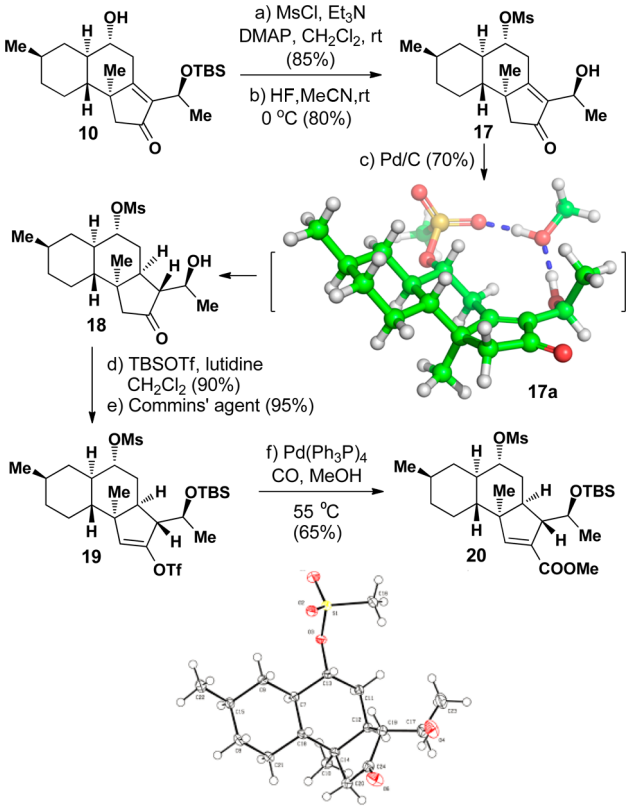


As a working hypothesis, it was assumed that an intramolecular H-bonding existed between the C5 hydroxyl and C1 carbonyl groups (see 3D structure of **15a** in Scheme 2), which regulated the C5 methyl group down and could lead the catalyst to approach the double bond from the top face, resulting in the formation of product **16** as the sole product. The *trans*-configuration[21] across the two newly generated chiral centers at C6 anf C7 suggested that the ketone-mediated epimerization[22] occurred during the reaction.

To generate the desired stereochemistry at the C7 position, the decision was taken to use mesylate as the protecting group in consideration of the tendency of mesylate[23] to form a H-bonding network with ethanol (solvent) and the C5 hydroxyl group. As a result, **16** would likely adopt its conformation as **17a** (see its 3D structure in Scheme 4). Thus, the C5 methyl group would block the catalyst to access the C6, C7 double bond from the top face, leading to the formation of **16** predominately.

To this end, **10** was reacted with MsCl in the presence of Et_3N/DMAP, followed by desilylation to afford **17** in 68% yield over the two steps (Scheme 3). Thus, hydrogenation of **17** under the same conditions as used before (i.e., Pd−C, EtOH, Et_3N, and H_2 under balloon pressure) effectively saturated the double bond and afforded **18** in 70% yield as the major product. The structure of **18** was confirmed by X-ray crystallographic analysis.

Scheme 3. Synthesis of Compound **20**



X-ray structure of **18**

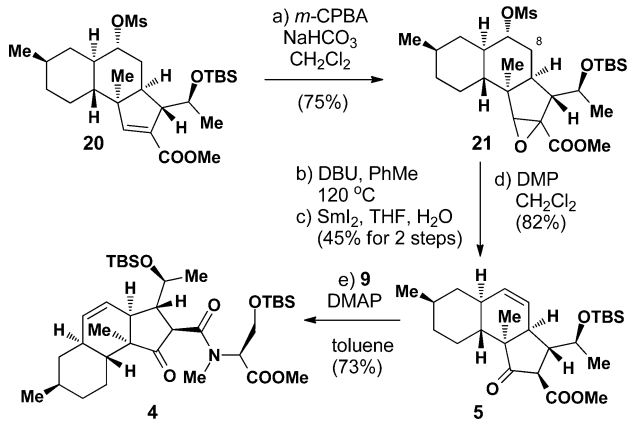
To continue our planned strategy toward the total synthesis of the target molecule, it was necessary to prepare the α,β-unsaturated ester **20** via the Pd-catalyzed esterification

(21) (a) Shizaki, M.; Niimi, Y.; Hoshino, O. *Tetrahedron Lett.* **2003**, *44*, 6029. (b) Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, *61*, 4053.

process from the precursor enol triflate **19** (Scheme 3). To this end, the hydroxyl group in ketone **18** was first protected as the corresponding TBS ether, and the resulting ketone was then reacted with Comins' reagent[24] in the presence of KHMDS as a base to give enol triflate **19** in 95% yield. Triflate **19** was subsequently subjected to a Pd-catalyzed carbonylative esterification reaction[25] to give **20** in 65% yield. This sequence conveniently established the α,β-unsaturated ester functionality necessary for the epoxidation to **21**. It is worthwhile to mention that the major side product observed in this reaction occurred as a consequence of reductive demesylation.

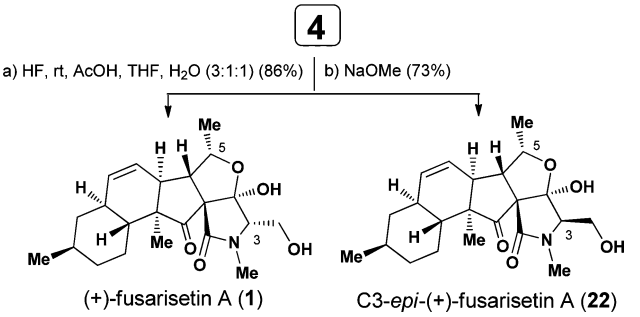
We then proceeded to synthesize the key intermediate amide **4** (Scheme 4). Although it was anticipated that the α,β-unsaturated ester in **20** would provide facile access to the corresponding epoxide in **21**, the treatment of substrate **21** with a variety of different oxidative agents, such as *tert*-butyl hydroperoxide (TBHP)/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[26] *m*-chloroperbenzoic acid (*m*-CPBA),[27] and H_2O_2/NaOH,[28] did not result in the formation of the desired product.

Scheme 4. Synthesis of Compound **4**



It was later established that epoxide **21** could be synthesized in a 75% yield as a single diastereoisomer by reaction of **20** with *m*-CPBA in the presence of $NaHCO_3$, presumably because $NaHCO_3$ could scavenge the generated chlorobenzoic acid, which might cause the formed product **21** decomposition.

Scheme 5. Completion of the Total Synthesis



No efforts were made at this stage to assign the stereochemistry at the newly formed epoxide centers because the stereochemistry at these positions would be eliminated in the subsequent steps. Thus, epoxide **21** was demesylated by treatment with DBU in refluxing toluene, followed by reductive epoxide opening with SmI_2, and the newly generated hydroxyl group was oxidized with DMP to give the corresponding β-keto ester **5** in 37% yield for three steps. Thus, aminolysis proceeded smoothly when the β-keto ester **5** was reacted with the aminoester **6**, and amide **4** was formed in 73% yield.

To complete the total synthesis, amide **4** was first treated with HF to remove the TBS groups, and the resulting ester was then treated with NaOMe in MeOH to undergo the planned transannulation process, and (+)-fusarisetin A (**1**) and (+)-C3-*epi*-fusarisetin A (**22**) were formed in a ratio of 6/4 in a combined yield of 73% (Scheme 5). The spectroscopic data (^{1}H and ^{13}C NMR spectra, HRMS analyses, and optical rotation) of the synthesized sample (**1**) were fully consistent with the corresponding data for the naturally occurring fusarisetin A.[1] The structure of (+)-C3-*epi*-fusarisetin A (**25**) was deduced by the analysis of its NMR spectra, as well as its epimerization tendency of the C3 position during the base-mediated Dieckmann cyclization.

In conclusion, we have developed a concise synthetic strategy for the total synthesis of (+)-fusarisetin A (**1**) in 16 steps from the commercially available aldehyde **13**. Essential to our strategy was the application of the intramolecular PK reaction for the stereoselective construction of the cyclopentenone **10** with a unique C16 quaternary chiral center. The chemistry offers an alternative to the IMDA reaction that has been used for fusarisetin A and is applicable to analogue synthesis for biological evaluation.

Acknowledgment. Financial support from the National Science Foundation of China (91013004, 21072006, and 21072011) and National 863 Program (2013AA090203) is acknowledged.

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

The authors declare no competing financial interest.

(22) (a) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (b) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1960**, 4547. (c) Baggaley, K. H.; Brooks, S. G.; Green, J.; Redman, B. T. *J. Chem. Soc. C* **1971**, 2671.
(23) (a) Hunter, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5310. (b) Bissantz, C.; Kuhn, B.; Stahl, M. *J. Med. Chem.* **2010**, *53*, 5061.
(24) Comins, D.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(25) (a) Xu, J.; Trzoss, L.; Chang, W. K.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3672. (b) Nicolaou, K. C.; Ding, H.; Richard, J.-A.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 3815.
(26) (a) Krishna, P. R.; Reddy, P. S. *J. Comb. Chem.* **2008**, *10*, 426. (b) Fu, R.; Ye, J.-L.; Dai, X.-J.; Ruan, Y.-P.; Huang, P.-Q. *J. Org. Chem.* **2010**, *75*, 4230.
(27) (a) Rodilla, J. M. L.; Diez, D.; Urones, J. G.; Rocha, P. M. *Molecules* **2004**, *9*, 300. (b) Ruano, J. L. G.; Fajardo, C.; Fraile, A.; Martín, M. R. *J. Org. Chem.* **2005**, *70*, 4300.
(28) (a) Borrelly, S.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 727. (b) Yu, B.; Jiang, T.; Quan, W.; Li, J.; Pan, X.; She, X. *Org. Lett.* **2009**, *11*, 629.