ORGANIC LETTERS

2013
Vol. 15, No. 18
4742–4745

Construction of 2-Substituted-3-Functionalized Benzofurans via Intramolecular Heck Coupling: Application to Enantioselective Total Synthesis of Daphnodorin B

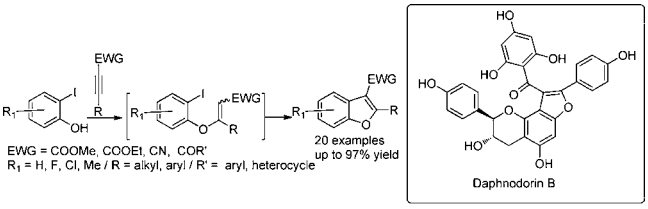
Hu Yuan,[†,‡] Kai-Jian Bi,[†] Bo Li,[†] Rong-Cai Yue,[†] Ji Ye,[†] Yun-Heng Shen,[†] Lei Shan,[†] Hui-Zi Jin,[*,‡] Qing-Yan Sun,[*,§] and Wei-Dong Zhang[*,†,‡]

Department of Phytochemistry, School of Pharmacy, Second Military Medical University, Shanghai 200433, China, School of Pharmacy, Shanghai Jiao Tong University, Shanghai 200240, China, and Department of Organic Chemistry, School of Pharmacy, Second Military Medical University, Shanghai 200433, China

wdzhangy@hotmail.com; sqy_2000@163.com; kimhz@sjtu.edu.cn

Received July 25, 2013

ABSTRACT



A novel approach was developed for the synthesis of 2-substituted-3-functionalized benzofurans, using an intramolecular Heck reaction which was further applied in the first enantioselective total synthesis of Daphnodorin B.

Benzofuran is an important class of heterocycles present in a wide variety of biologically important molecules,[1] such as BNC105[2] and Amiodarone,[3] and natural products such as Daphnodorin A and B[4a−c] which display a wide array of biological activities, including α-glucosidase inhibitory activities,[4d] antifungal and insecticidal activities,[4e] 12-lipoxygenase inhibitory activities,[4f,g] human chymase-dependent angiotensin II inhibitory activities,[4h] and antitumor properties.[4i,j] Different types of substitution patterns in these heterocycles provide new opportunities for drug discoveries and other applications in material science. Thus synthetic access to benzofurans is of considerable interest, and numerous approaches to this scaffold have been disclosed in the literature.[5] In general, these approaches give only moderate yields or yield benzofurans

[†] Department of Phytochemistry, Second Military Medical University.
[‡] School of Pharmacy, Shanghai Jiao Tong University.
[§] Department of Organic Chemistry, Second Military Medical University.

(1) For selected reviews, see: (a) Miyata, O.; Takeda, N.; Naito, T. *Heterocycles* **2009**, *78*, 843. (b) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (e) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641.

(2) Flynn, B. L.; Gill, G. S.; Grobelny, D. W.; Chaplin, J. H.; Paul, D.; Leske, A. F.; Lavranos, T. C.; Chalmers, D. K.; Charman, S. A.; Kostewicz, E.; Shackleford, D. M.; Morizzi, J.; Hamel, E.; Jung, M. K.; Kremmidiotis, G. *J. Med. Chem.* **2011**, *54*, 6014.

(3) Singh, S. N.; Fletcher, R. D.; Fisher, S. G.; Singh, B. N.; Lewis, H. D.; Deedwania, P. C.; Massie, B. M.; Colling, C.; Layyeri, D. *New Eng. J. Med.* **1995**, *333*, 77.

(4) (a) Baba, K.; Takeuchi, K.; Hamasaki, F.; Kozawa, M. *Chem. Pharm. Bull.* **1985**, *33*, 416. (b) Baba, K.; Takeuchi, K.; Hamasaki, F.; Kozawa, M. *Chem. Pharm. Bull.* **1986**, *34*, 595. (c) Baba, K.; Takeuchi, K.; Dio, M.; Inoue, M.; Kozawa, M. *Chem. Pharm. Bull.* **1986**, *34*, 1540. (d) Zhou, T.; Zhang, S.-W.; Liu, S.-S.; Cong, H.-J.; Xuan, L.-J. *Phytochem. Lett.* **2010**, *3*, 242. (e) Inamori, Y.; Takeuchi, K.; Baba, K.; Kozawa, M. *Chem. Pharm. Bull.* **1987**, *35*, 3931. (f) Sakuma, S.; Fujimoto, Y.; Tsunomor, M.; Tagano, S.; Nishida, H.; Baba, K.; Fujita, T. *Prostag. Leukotr. Ess.* **1998**, *58*, 143. (g) Takai, S.; Jin, D.; Sakaguchi, M.; Kirimura, K.; Ikeda, J.; Baba, K.; Fujita, T.; Miyazaki, M. *Prostag. Leukotr. Ess.* **1999**, *60*, 135. (h) Takai, S.; Sakaguchi, M.; Jin, D.; Baba, K.; Miyazaki, M. *Life Sci.* **1999**, *64*, 1889. (i) Zheng, W.-F.; Gao, X.-W.; Gu, Q.; Chen, C.-F.; Wei, Z.-W.; Shi, F. *Int. Immunopharmacol.* **2007**, *7*, 128. (j) Zheng, W.-F.; Gao, X.-W.; Chen, C.-F.; Tian, R.-X. *Int. Immunopharmacol.* **2007**, *7*, 117.

10.1021/ol4021095
Published on Web 09/05/2013

of limited structural diversity. We envisage that if we were able to prepare *o*-iodoaryl vinyl ethers *via* a conjugate addition procedure from *o*-iodophenols and activated alkynes, the subsequent intramolecular Heck reaction would regiospecifically provide us the corresponding 2-substituted-3-functionalized benzofurans. Herein, we report the versatile route to 2-substituted-3-functionalized benzofurans and its application to the total synthesis of Daphnodorin B (Figure 1).

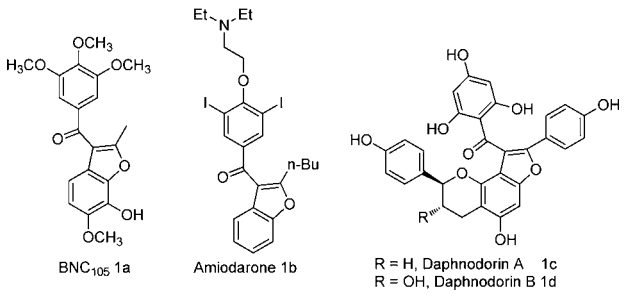
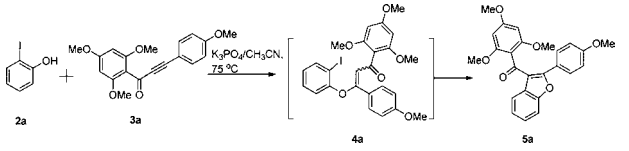


Figure 1. Bioactive compounds containing 2-substituted-3-functionalized benzofuran scaffold.

Our initial studies focused on the synthesis of a model substrate (*o*-iodoaryl vinyl ether **4a**, Table 1), which was available from a conjugate addition procedure employing *o*-iodophenol with ynone **3a** in the presence of a base at 75 °C in CH_3CN. Different bases such as DBU, *t*-BuOK, Pyridine, DIPEA, K_3PO_4, Et_3N, DABCO, Ag_2CO_3, and K_2CO_3 were tried to promote the conjugate addition, and K_3PO_4 (100 mol %) gave the highest yield (> 99%) of **4a** as a pair of *Z*/*E* isomers mixture (≈ 1:1). Fortunately, the subsequent intramolecular Heck reaction of **4a** proceeded smoothly without separation of the *Z*- and *E*-isomers.

We next screened the effect of the palladium source and ligand on the intramolecular Heck reaction of the model substrate by using Ag_2CO_3 as base at 115 °C in CH_3CN, and the results are summarized in Table 1. The model reaction could be catalyzed by Pd^{II} or Pd^0 complexes, such as $Pd(OAc)_2$, $PdBr_2$, $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$ in the absence of additional ligand. From Table 1, the reactivity of the Pd catalytic system decreases in the following order for the cyclization reaction: $Pd(OAc)_2/PPh_3 \approx Pd(OAc)_2/P(o\text{-tol})_3 > PdBr_2/PPh_3 \approx Pd(PPh_3)_4 > Pd(OAc)_2/dppf \approx Pd(OAc)_2/BINAP > Pd(OAc)_2/PBu_3 \approx Pd(PPh_3)_4/Et_3N > Pd_2(dba)_3/BINAP$ (Table 1, entries 1−9). It is evident that PPh_3 and $P(o\text{-tol})_3$ could accelerate the reaction, while $P(o\text{-tol})_3$ was not utilized in this work due to its air sensitivity and higher cost compared to PPh_3.

Table 1. Effect of Palladium/Ligand and Base on the Reaction[a]



entry	palladium/ligand	yield(%)
1	$Pd(OAc)_2/PBu_3$	29
2	$Pd(OAc)_2$/dppf	52
3	$Pd(OAc)_2/PPh_3$	75
4	$Pd(OAc)_2/P(o\text{-tol})_3$	73
5	$Pd(OAc)_2$/BINAP	47
6	$Pd_2(dba)_3$/BINAP	11
7	$PdBr_2/PPh_3$	68
8	$Pd(PPh_3)_4/Et_3N$[b]	28
9	$Pd(PPh_3)_4$	63

[a] Optimal reaction conditions: **2a**/**3a** 1:1 (1 equiv), Pd (5 mol %), Ligand (10 mol %), Ag_2CO_3 (1 equiv), CH_3CN, 115 °C, 15 h. Isolated yields. [b] Et_3N was employed instead of Ag_2CO_3.

Next, the substrate scope of the reaction was explored with a range of *o*-iodophenols with ynones. Under our optimized conditions, substrates with electron-donating or -withdrawing groups or electron-neutral substituents were successfully transformed into the corresponding 2-substitued-3-aroyl-benzofurans (**5a**−**k**) in good to excellent yields (Scheme 1). A chloro substituent on the aryl part of the *o*-iodophenols (**5i**/**j**) was tolerated in this transformation. In the case of **5a** and **5i**−**k**, lower yields were obtained, which might be attributed to the large steric effect of bulky ynones (**3a**/**b**) and 3-chloro-2-iodophenol.

With these encouraging results in hand, we decided to further probe the reaction scope by employing other alkynes bearing electron-withdrawing substituents, such as cyano or carboalkoxy groups. To our delight, all the substrates employed yielded corresponding 2-substitued-3-functionalized benzofurans (**8a**−**i**) in high yields (Scheme 2).

Finally, we note that the aryl chloride moieties in **5i**/**j** and **8b**/**h** can be exploited in a subsequent synthetic modification. For example, Suzuki−Miyaura cross-coupling reactions can enable further diversification.[5c,6] The nitrile group can be utilized for further transformations.[7]

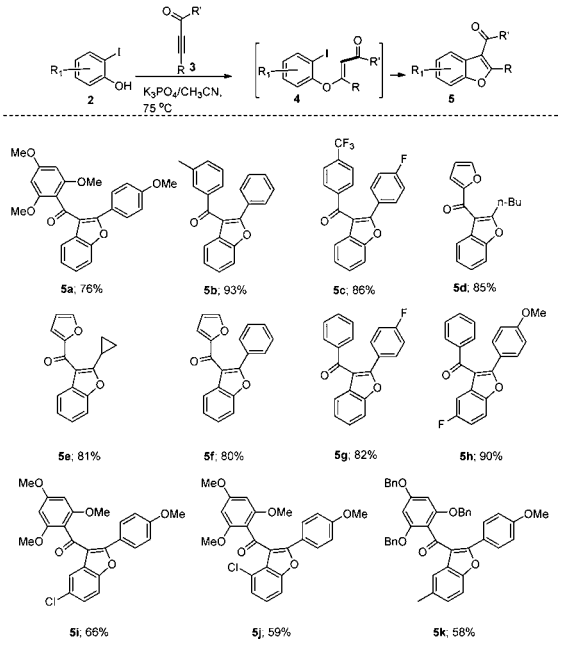
With a set of new synthetic methodologies in hand, we turned our attention to the total synthesis of Daphnodorin B.

(5) For selected papers on the synthesis of benzofurans, see: (a) Ye, S.-Q.; Liu, G.; Pu, S.-Z.; Wu, J. *Org. Lett.* **2012**, *14*, 70. (b) Yin, B.-L.; Cai, C.-B.; Zeng, G.-H.; Zhang, R.-Q.; Li, X.; Jiang, H.-F. *Org. Lett.* **2012**, *14*, 1098. (c) Liu, Y.; Ma, S.-M. *Org. Lett.* **2012**, *14*, 720. (d) Schevenels, F.; Markó, I. E. *Org. Lett.* **2012**, *14*, 1298. (e) Li, C.-L.; Zhang, Y.-C.; Li, P.-H.; Wang, L. *J. Org. Chem.* **2011**, *76*, 4692. (f) Markina, N. A.; Chen, Y.; Larock, R. C. *Tetrahedron* **2013**, *69*, 2701. (g) Henke, B. R.; Aquino, C. J.; Birkemo, L. S.; Croom, D. K.; Dougherty, R. W., Jr.; Ervin, G. N.; Grizzle, M. K.; Hirst, G. C.; James, M. K.; Johnson, M. F.; Queen, K. L.; Sherrill, R. G.; Sugg, E. E.; Suh, E. M.; Szewczyk, J. W.; Unwalla, R. J.; Yingling, J.; Willson, T. M. *J. Med. Chem.* **1997**, *40*, 2706. (h) Ma, D.-W.; Cai, Q.; Xie, X.-A. *Synlett* **2005**, 1767. (i) Stork, G.; Yamashita, A.; Adams, J.; Schulte, G. R.; Chesworth, R.; Miyazaki, Y.; Farmer, J. J. *J. Am. Chem. Soc.* **2009**, *131*, 11402. (j) Liao, Y.; Smith, J.; Fathi, R.; Yang, Z. *Org. Lett.* **2005**, *7*, 2707. (k) Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 2607. (l) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297.

(6) Kudo, M.; Perseghini, G.; Fu, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282.

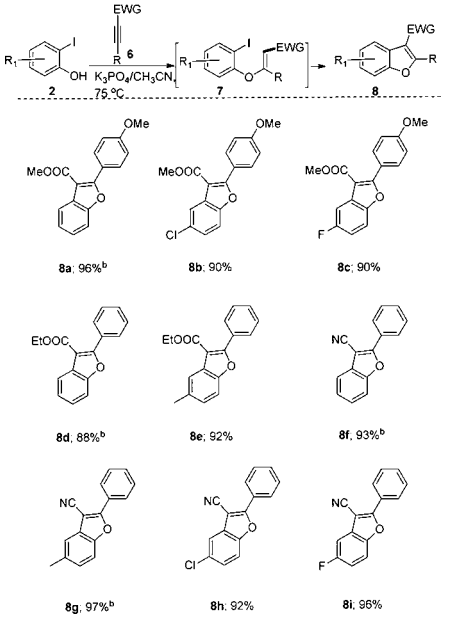
(7) Rappoport, Z., Ed. *Chemistry of the Cyano Group*; John Wiley & Sons: London, 1970.

Scheme 1. Examples of 2-Substitued-3-aroyl-benzofurans[a]



[a] Reaction conditions: **2**/**3** 1:1 (1 equiv), $Pd(AcO)_2$ (5 mol %), PPh_3 (10 mol %), Ag_2CO_3 (1 equiv), CH_3CN, 115 °C, 15 h. Isolated yields.

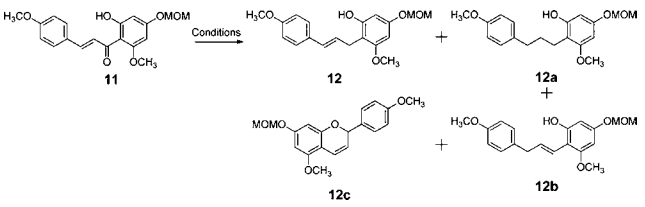
Scheme 2. Extending the Scope of Reaction[a]



[a] Optimal reaction condition: **2**/**6** 1:1 (1 equiv), $Pd(AcO)_2$ (5 mol %), PPh_3 (10 mol %), Ag_2CO_3 (1 equiv), CH_3CN, 115 °C, 15 h. Isolated yields. [b] Known compounds, the ^1H, ^{13}CNMR, and IR spectra are identical to those of an authentic sample.

Our synthetic efforts (Scheme 3) commenced with the commercially available 2,4,6-trihydroxyacetophenone **9** to obtain selectively protected 6-hydroxy phenylacetone. Treatment of **9** with 2 equiv of methoxymethyl chloride (MOMCl) and *N*,*N*-diisopropylethylamine in methylene chloride afforded 2,4-dimethoxymethyl 6-hydroxy phenylacetone whose free phenol group was methylated, followed by deprotection of the MOM group at the ortho-position with 1 M HCl in MeOH, which afforded **10** in 72% yield. Condensation of anisaldehyde with **10** was achieved *via* a Claisen–Schmidt reaction[8] to give the chalcone **11** in 99% yield. Decarbonylation of **11** using lithium aluminum hydride and $AlCl_3$[9] proved overly harsh and resulted in a complex mixture (Table 2, entry 1).

Table 2. Decarbonylation of **11**



entry	conditions	yield (%) **12/12a/12b/12c**
1	$LiAlH_4$, $AlCl_3$	complex mixture
2	$(CH_3O)_3SiH$, ZnI_2	44/0/28/0
3	ClCOOEt, Et_3N; $NaBH_4$	35/33/0/32
4	ClCOOEt, Et_3N; $NaBH_4$, $CeCl_3 \cdot 7H_2O$	93/0/0/7

Two reduced isomers involving double-bond transfer were observed when the trialkoxylsilane/ZnI_2 system[10] was employed (Table 2, entry 2). Minami's method[11] performed by employing ethyl chloroformate and sodium borohydride in a two-step sequence afforded the over-reduced product and cyclic byproduct (Table 2, entry 3). Finally, the excellent 1,2-reduction selectivity and yield of **12** were obtained by using an improved methodology of Minami's method we reported (Table 2, entry 4).[12]

Sharpless asymmetric dihydroxylation was attempted in the presence of the free phenol and proved unsuccessful. Therefore, the phenol was protected as the TBDMS ether, providing the substituted diphenylpropene in almost quantitative yield. With the TBDMS group in place, asymmetric dihydroxylation proceeded smoothly using AD-mix-α in a mixture of *tert*-butyl alcohol and water (1:1), affording the TBS protected diol **13** in 88% yield and 94.1% ee. Attempts to add CH_2Cl_2 or acetone did produce **13** but in low yield and ee. The TBS-ether of diol **13** was cleaved using tetrabutylammonium fluoride (TBAF) to afford the triol with a free phenolic hydroxyl group. The attempt to convert the triol in one step into the

(8) Sharma, P. K.; He, M.; Jurayj, J.; Gou, D.-M.; Lombardy, R.; Romanczyk, L. J., Jr.; Schroeter, H. *Molecules* **2010**, *15*, 5595.

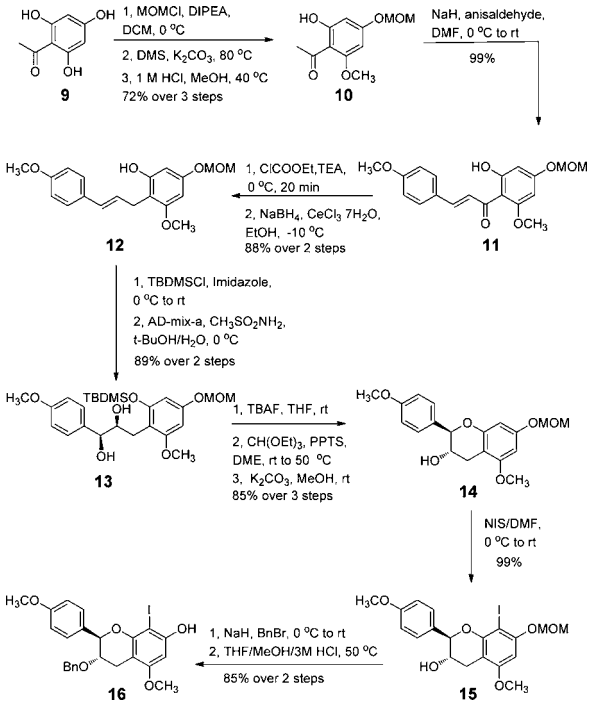
(9) Hase, T. *Acta Chem. Scand.* **1968**, *22*, 2845.

(10) Li, J.-Y.; Peng, J.-J.; Bai, Y.; Chen, L.-Z.; Lai, G.-Q. *Phosphorus, Sulfur, and Silicon* **2011**, *186*, 1621.

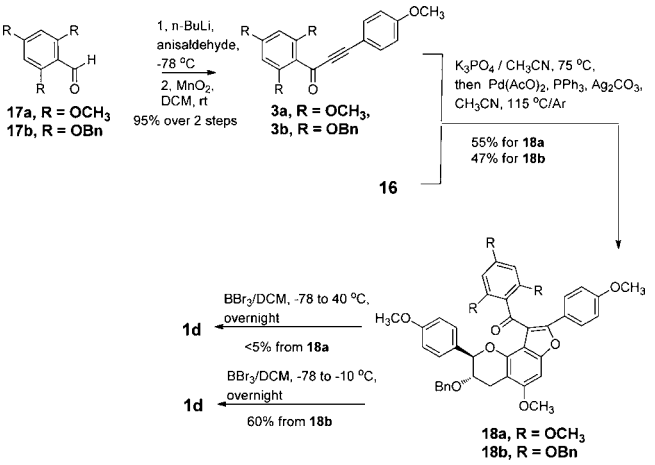
(11) Minami, N.; Kijima, S. *Chem. Pharm. Bull.* **1979**, *27*, 1490.

(12) Yuan, H.; Chen, H.; Jin, H.-Z.; Li, B.; Yue, R.-C.; Ye, J.; Shen, Y.-H.; Shan, L.; Sun, Q.-Y.; Zhang, W.-D. *Tetrahedron Lett.* **2013**, *54*, 2776.

Scheme 3. Synthesis of *o*-Iodophenol **16**



Scheme 4. Total Synthesis of Daphnodorin B



enantiomerically pure flavan-3-ol **14** by a Mitsunobu reaction[13] afforded the desired compound in only 51% yield and 95.8% ee. Treatment of triol with triethyl orthoformate in the presence of catalytic pyridinium *p*-toluenesulfonate (PPTS) and succedent removal of the formate ester by using K_2CO_3 in methanol[14] gave the flavan-3-ol **14** in 88% yield and 97.3% ee over two steps. 8-Iodo derivative **15** was readily prepared in 99% yield by reacting **14** with 1 equiv of recrystallized NIS in DMF at rt.[15] The free hydroxyl group in **15** was protected by benzylation, followed by deprotection of MOM ether with 3 M HCl, affording *o*-iodophenol **16**, which underwent conjugate addition and subsequent intramolecular Heck reaction with ynones **3a/b** to generate the fully protected Daphnodorin B (**18a/b**, Scheme 4). Deprotection of **18a** with 1 M BBr_3 yielded a mixture of selectively demethylated products since demethylation of a methoxy group *para* to a carbonyl functional group seems to be less effective.[16] Finally, deprotection of **18b** with a benzyloxy group *para* to a carbonyl functional group furnished Daphnodorin B (**1d**) whose spectral data were in agreement with those reported in literature.[4b,d,17]

In conclusion, syntheses of various 2-substituted-3-functionalized benzofurans were achieved *via* a conjugate addition procedure from *o*-iodophenols and activated alkynes and a subsequent intramolecular Heck reaction, which was illustrated by an enantioselective total synthesis of natural product Daphnodorin B.

Acknowledgment. The work was supported by the program NCET Foundation, NSFC (81230090), partially supported by Global Research Network for Medicinal Plants (GRNMP), King Saud University, Shanghai Leading Academic Discipline Project (B906), Key laboratory of drug research for special enorthoformatevironments, PLA, Shanghai Engineering Research Center for the Preparation of Bioactive Natural Products (10DZ2251300), the Scientific Foundation of Shanghai China (12401900801, 09DZ1975700, 09DZ1971500, 10DZ1971700), National Major Project of China (2011ZX09307-002-03), and National Key Technology R&D Program of China (2012BAI29B06).

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

(13) Krohn, K.; Ahmed, I.; John, M. *Synthesis* **2009**, *5*, 779.
(14) Li, L.-H.; Chan, T.-H. *Org. Lett.* **2001**, *3*, 739.
(15) Tarascou, I.; Barathieu, K.; André, Y.; Pianet, I.; Dufourc, E. J.; Fouquet, E. *Eur. J. Org. Chem.* **2006**, *23*, 5367.
(16) (a) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W.; Somvichien, N. *Tetrahedron Lett.* **1966**, *7*, 4153. (b) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289. (c) Quillinan, A. J.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1329. (d) Mihigo, S. O.; Mammo, W.; Bezabih, M.; Andrae-Marobela, K.; Abegaz, B. M. *Bioorg. Med. Chem.* **2010**, *18*, 2464.
(17) Chen, R.-J.; Cao, S.-W.; Ruan, Z. *Chem. Nat. Compd.* **2009**, *45*, 534.

The authors declare no competing financial interest.