ORGANIC LETTERS

2008
Vol. 10, No. 5
721−724

An Efficient Synthesis of Highly Functionalized [5,6] Aromatic Spiroketals by Hetero-Diels–Alder Reaction

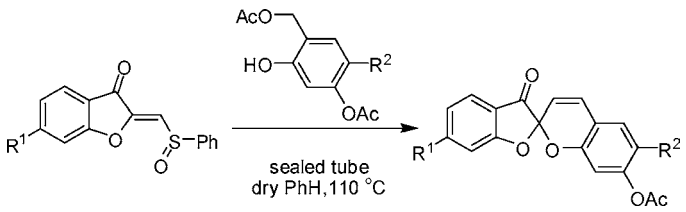
Guanglian Zhou, Jianrong Zhu, Zhixiang Xie,* and Ying Li*

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P.R. China

xiezx@lzu.edu.cn; liying@lzu.edu.cn

Received December 3, 2007

ABSTRACT



A hetero-Diels–Alder reaction of vinyl sulfoxides with *o*-quinone methides precursor constructs highly functionalized [5,6] aromatic spiroketal skeletons in moderate to good yields with high regioselectivity. The two functional groups (ketone and olefin) can be further subjected to many synthetic transformations.

The [5,6] aromatic spiroketal skeleton is found in a wide range of bioactive natural products such as heliquinomycin (**1**) and its analogues (Figure 1).[1] The interesting biological activity and structures of these compounds have stimulated many studies of [5,6] aromatic spiroketal skeleton construction. Even though there is progress that has been achieved in this area in recent years,[2] the synthesis of highly functionalized [5,6] aromatic spiroketal skeletons remains a formidable challenge.[2c,d] Our interest in these structures has given rise to diverse methods for their expeditious synthesis.

On the basis of our previous work on synthesis of [6,6] aromatic spiroketal skeletons,[3] we attempted to synthesize highly functionalized [5,6] aromatic spiroketal skeletons (Scheme 1) that would be applicable for most of the natural products containing the [5,6] aromatic spiroketal skeletons. To the best of our knowledge, there is no report of the synthesis of functionalized [5,6] aromatic spiroketals using a hetero-Diels−Alder reaction. In this letter, we report our successful execution of this strategy.

(1) (a) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Tetrahedron Lett.* **1966**, *22*, 3525. (b) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Chem. Ber.* **1969**, *102*, 126. (c) Brockmann, H.; Zeeck, A. *Chem. Ber.* **1970**, *103*, 1709. (d) Coronelli, C.; Pagani, H.; Bardone, M. R.; Lancini, G. C. *J. Antibiot.* **1974**, *27*, 161. (e) Bardone, M. R.; Martinelli, E.; Zerilli, L. F.; Cornelli, C. *Tetrahedron* **1974**, *30*, 2747. (f) Stroshane, R. M.; Chan, J. A.; Rubalcaba, E. A.; Garetson, A. L.; Aszalos, A. A.; Roller, P. P. *J. Antibiot.* **1979**, *32*, 197. (g) Chino, M.; Nishikawa, K.; Umekia, M.; Hayashi, C.; Yamazaki, T.; Tsuchida, T.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 752. (h) Chino, M.; Nishikawa, K.; Tsuchida, T.; Sawa, R.; Nakamura, H.; Nakamura, K. T.; Muraoka, Y.; Ikeda, D.; Naganawa, H.; Sawa, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 143.

(2) (a) Capecchi, T.; de Koning, C. B.; Michael, J. P. *Tetrahedron Lett.* **1998**, *39*, 5429. (b) Capecchi, T.; de Koning, C. B.; Michael, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2681. (c) Qin, D.; Ren, R. X.; Siu, T.; Zheng, C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4709. (d) Siu, T.; Qin, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4713. (e) Tsang, K. Y.; Brimble, M. A.; Bremner, J. B. *Org. Lett.* **2003**, *5*, 4425. (f) Waters, S. P.; Fennie, M. W.; Kozlowski, M. C. *Tetrahedron Lett.* **2006**, *47*, 5409. (g) Lindsey, C. C.; Wu, K. L.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2365. (h) Waters, S. P.; Fennie, M. W.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 3243. (i) Sö1rgel, S.; Azap, C.; Reissig, H-U. *Org. Lett.* **2006**, *8*, 4875. (j) Tsang, K. Y.; Brimble, M. A. *Tetrahedron* **2007**, *63*, 6015. (k) Akai, S.; Kakiguchi, K.; Nakamura, Y.; Kuriwaki, I.; Dohi, T.; Harada, S.; Kubo, O.; Morita, N.; Kita, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 7458.

(3) Zhou, G. L.; Zheng, D. P.; Da, S. J.; Xie, Z. X.; Li, Y. *Tetrahedron Lett.* **2006**, *47*, 3349.

10.1021/ol7029068 CCC: $40.75
Published on Web 02/12/2008

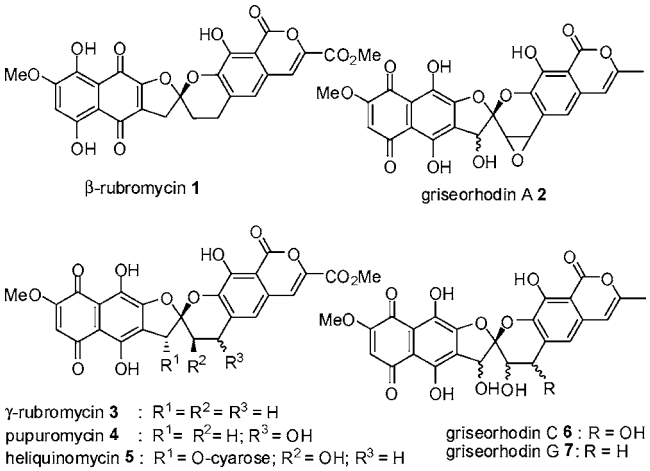
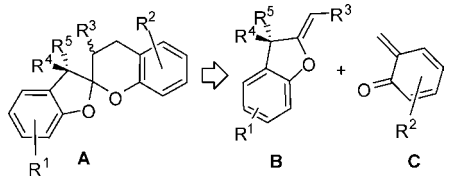


Figure 1. Spirocyclic natural products.

As shown in Scheme 1, the [5,6] aromatic spiroketal skeleton **A** could arise from a cycloaddition between the enol ethers **B** and *o*-quinone methides **C**. The 2-methylene-2,3-dihydrobenzofuran structure in **B** is readily isomerized to 2-methylbenzofurans,[3] so a suitable functional group was required at the 3 position of **B** to stabilize the exocyclic double bond. Considering the hydroxyl in **2** and **5**−**7**, the carbonyl group could be the ideal choice in the dienophile.

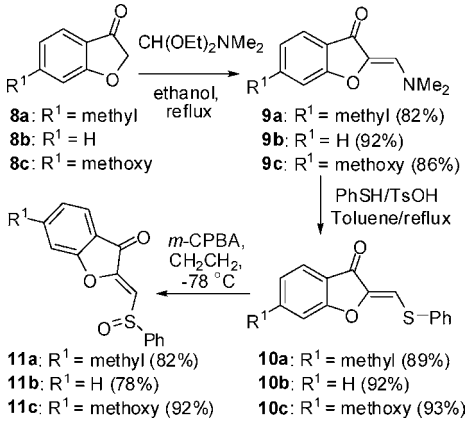
Scheme 1. Proposed Retrosynthesis of the [5,6] Aromatic Spiroketal Skeletons



A sulfoxide group on the dienophile has been found to control the regiochemistry of its Diels−Alder cycloadditions with a wide range of cyclic and acyclic dienes.[4] The domino Diels−Alder reaction/pyrolytic sulfoxide elimination as a general one-pot strategy was reported by Carreño.[4] We therefor chose a sulfoxide group for R^3 in dienophile **B**.

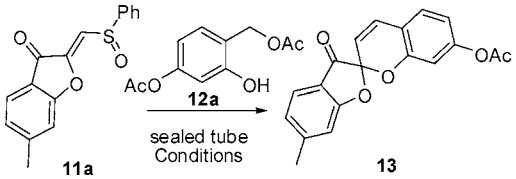
The dienophiles corresponding to **B** were synthesized from the commercially available 3(2H)-benzofuranones **8a**−**8c**[5] in a three-step sequence. Ketones **8a**−**8c** were first transformed to **9a**−**9c**, respectively, according to the method reported by Merour et al.[5] The newly introduced dimethylamino group in **9a**−**9c** was then substituted with benzenthiol (1.1 equiv benzenethiol in toluene), giving rise to the thioethers **10a**−**10c**. Oxidation of **10a**−**10c** with *m*-CPBA (1.0 equiv in CH_2Cl_2 under −78 °C) afforded the vinyl sulfoxides **11a**−**11c**[6] efficiently (good yield for three steps) (Scheme 2).

Scheme 2. Synthesis of Dienophiles



With the enol ether dienophile **B** in hand, we began the study of hetero-Diels−Alder cycloadditions, choosing **11a** as a model dienophiles. These reactions were performed under a range of conditions, and the results are shown in Table 1. The *o*-quinone methides precursor **12a**[3] and the enol ether **11a** reacted in analytical benzene at 110 °C in a sealed tube giving the desired spiroketal product **13** as a single

Table 1. Cycloaddition of *o*-Quinone Methides Precursor with Vinyl Sulfoxides



entry	time (h)	solvent	temp. (°C)	catalysis	yield (%)
1	39	PhH[a]	110	no	10
2	39	PhH[b]	110	no	55
3	40	PhH[b]	100	no	26
4	39	PhH[b]	120	no	51
5	50	PhH[b]	120	no	53
6	47	$PhCH_3$[b]	120	no	9
7	39	PhH[b]	110	$AlCl_3$	22
8	39	PhH[b]	110	$BF_3{\cdot}Et_2O$	0
9	39	PhH[b]	110	$TiCl_4$	0

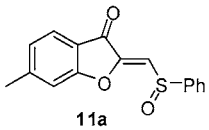
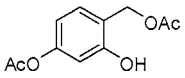
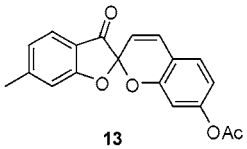
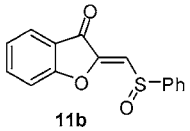
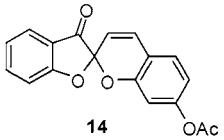
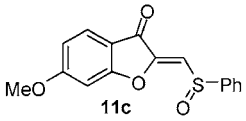
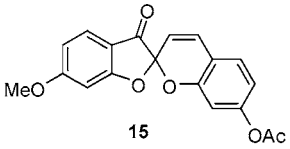
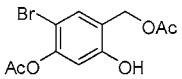
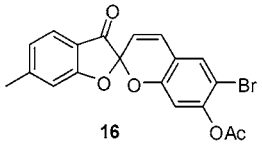
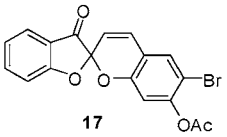
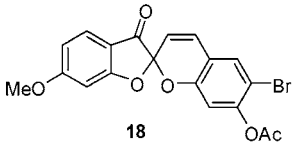
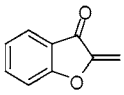
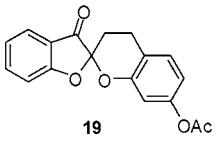
[a] Analytical PhH without purification. [b] Solvent was dried by distillation over Na/K.

(4) For selected reports on Diels−Alder reactions of vinyl sulfoxides, see: (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717. (b) Carreño, M. C.; García Ruano, J. L.; Toledo, M. A.; Urbano, A.; Remor, C. Z.; Stefani, V.; Fischer, J. *J. Org. Chem.* **1996**, *61*, 503. (c) Carreño, M. C.; Hérnandez-Sánchez, R.; Mahugo, J.; Urbano, A. *J. Org. Chem.* **1999**, *64*, 1387. (d) Carreño, M. C.; Susana, G-C.; Urbano, A,; Vitta, C. D. *J. Org. Chem.* **2000**, *65*, 4355.

(5) Merour, J. Y.; Cossais, F. *J. Heterocycl. Chem.* **1991**, *28*, 1875.

(6) Olsen, R. K.; Shao, R-l. *J. Org. Chem.* **1996**, *61*, 5852.

Table 2. Cycloaddition of Dienophiles **11a**−**11c, 20** with *o*-Quinone Methides Precursor **12a, 12b**[a]

entry	dienophile	*o*-quinone methides precursor	spiroketal product	yield (%)[b]
1	 **11a**	 **12a**	 **13**	55
2	 **11b**	**12a**	 **14**	58
3	 **11c**	**12a**	 **15**	62
4	**11a**	 **12b**	 **16**	76
5	**11b**	**12b**	 **17**	90
6	**11c**	**12b**	 **18**	86
7	 **20**	**12a**	 **19**	46

[a] All reactions were carried out in a sealed tube, PhH (dried by distillation over Na/K) as solvent, 110 °C for 39 h. [b] Yields were calculated after column chromatography.

regioisomer (entry 1) in 10% yield. As expected, the elimination of the sulfoxide group took place spontaneously following the cycloaddition. No intermediate cycloadducts were detected. The use of dry benzene as solvent improved the yield to 55% (entry 2). Reducing the reaction temperature to 100 °C decreased the yield to 26% (entry 3). Raising the reaction temperature to 120 °C resulted in a little decrease in the yield to 51% (entry 4). The better result (53% yield) was obtained when the reaction time was extended to 50 h (entry 5). When dry toluene was used as the solvent, the yield was reduced to 9% (entry 6). The effect of some Lewis acids was also examined. It was found that the yield of spiroketal product **13** decreased greatly in the presence of catalytic amount of $AlCl_3$ (entry 7). Additon of $BF_3{\cdot}Et_2O$ and $TiCl_4$ turned the reaction mixture red, and no spiroketal product was detected (entries 8−9).

The hetero-Diels−Alder cycloaddition was further examined between the enol ethers **11a**−**c** and *o*-quinone methides **12a** and **12b**.[7] As shown in Table 2, entries 1−6, substituents on the aryl ring of the benzofuranone had no apparent effect on the hetero-Diels−Alder reaction. In contrast, a 4-bromo electron-withdrawing substituent of the *o*-quinone methide precursor **12b** increased the yield to a great extent (entries 4−6). When there was no sulfoxide moiety in dienophile such as compound **20**,[8] the yield of the corresponding spiroketal product **19** was reduced to 46% (entry 7). It is noteworthy that the spiroketal products **13**−**18** were obtained in moderate to good yield without any isomeric impurities. The sulfoxide moiety served not only as a good leaving group to form the styrene but also increased the yield (entries 1−7) and ensured high regioselectivity.

In conclusion, we have developed a facile and effective strategy for the synthesis of highly functionalized [5,6]

(7) Prepared the compound **12b**; see Supporting Information.
(8) Prepared the compound **20**; see Supporting Information.

aromatic spiroketal products. A sulfoxide proved to be a good precursor of the styrene in our model compounds. Synthetic studies toward natural spiroketal products employing this newly developed hetero-Diels−Alder reaction method are underway in this laboratory.

Acknowledgment. We are grateful for the financial support of the National Natural Science Foundation of China (Grant Nos. 20272020, 20672050, and 20621091). We also thank Dr. Scott McN. Sieburth of Temple University for helpful discussions.

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

OL7029068