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

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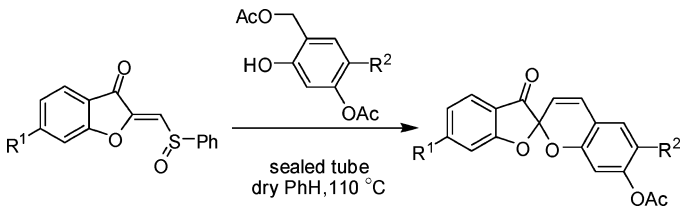
ABSTRACT



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.

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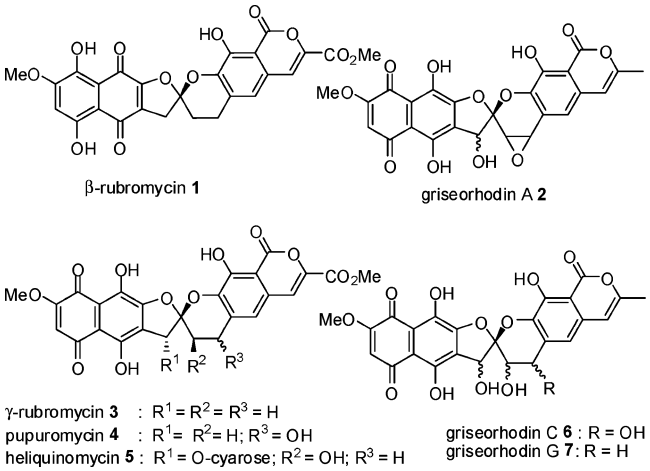
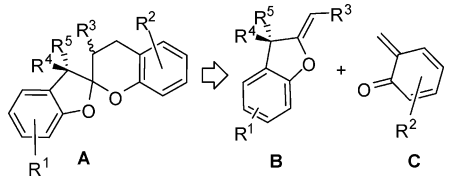


Figure 1. Spirocyclic natural products.

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.

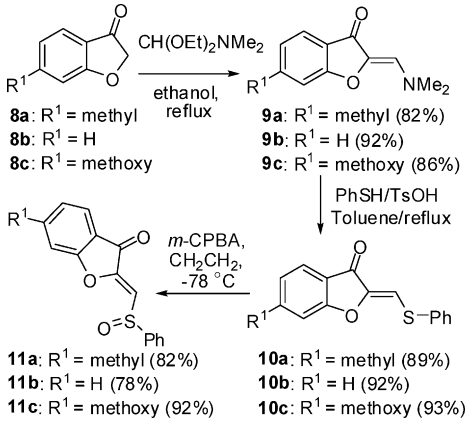
Scheme 1. Proposed Retrosynthesis of the [5,6] Aromatic Spiroketal Skeletons



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**.

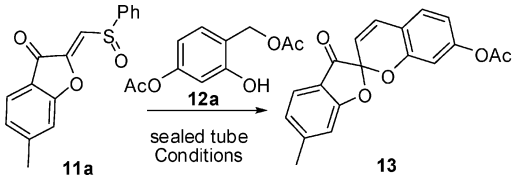
The dienophiles corresponding to **B** were synthesized from the commercially available 3(2H)-benzofuranones **8a**−**8c**[5] in a three-step sequence. Ketones **8a**−**8c** were first transformed to **9a**−**9c**, respectively, according to the method reported by Merour et al.[5] The newly introduced 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.

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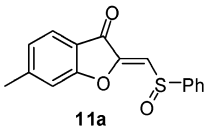
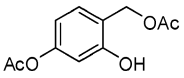
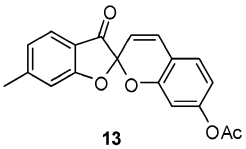
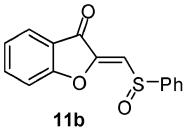
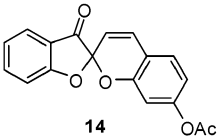
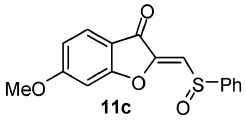
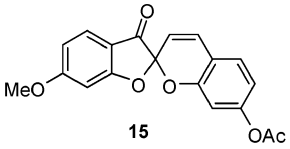
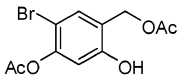
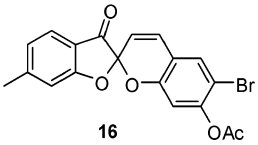
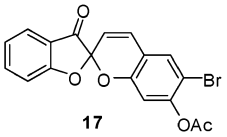
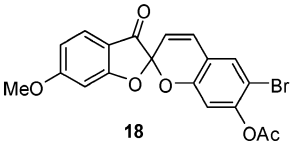
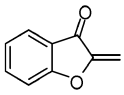
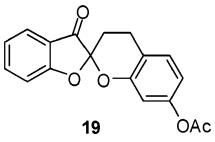
Table 2. Cycloaddition of Dienophiles **11a**−**11c, 20** with *o*-Quinone Methides Precursor **12a, 12b**[a]

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.

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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.

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