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Synthesis and biological evaluation of 12 allenic aromatic ethers

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Abstract—Twelve allenic aromatic ethers, some of them are natural products isolated from the mangrove fungus *Xylaria* sp. 2508 in the South China Sea, were synthesized. Their antitumor activities against KB and KBv200 cells were determined. All these compounds demonstrated cytotoxic potential, ranging from weak to strong activity. The analysis of structure–activity relationships suggested that the introduction of allenic moiety could generate or enhance cytotoxicity of these phenol compounds.

About 150 natural products with an allenic or cumulenic structure moiety are known today.[1] Inspired by the intriguing biological activities of many allenic natural products, allenic moieties are now introduced in the compounds which have the pharmacologically activity. The many functionalized allenes thus obtained exhibit impressive activities, such as enzyme inhibitor activities, cytotoxic or antiviral activities, etc.[1]

Naturally occurring allenic compounds can be found in microorganisms, fungi, higher plants, and insects. So far, only several allenic aromatic ethers, for example, chestersiene from the *Hypoxylon chestersii*,[2] **2b** from the *Clitocybe eucalyptorum*,[3] xyloallenoide A and **2f** from the mangrove fungus *Xylaria* sp. 2508[4] were isolated. Recently, we isolated four new allenic aromatic ethers (**2c**, **3a**–**c**) from the *Xylaria* sp. 2508 again.[5] In the preliminary bioassay, some natural allenic aromatic ethers showed antitumor activities against KB and KBv200 cells. The limited amounts of isolated materials prevented the study on their biological activities. Therefore, we synthesized 12 allenic aromatic ether analogs (see Fig. 1) to further explore the effect of allenic groups bioactivities of compounds. These compounds are the derivatives of allenic group linking to compounds **1**. Compound **2j** is analogous to the natural product xyloallenoide A.

In the synthesis of these allenic aromatic ethers, one key step was the preparation of 2,3-butadiene-1-ol (**6**). There were two methods to synthesize **6** (Scheme 1). The first method used 2-butyne-1,4-diol (**4**) as the starting material. Chlorination of **4** with thionyl chloride gave the monochloroalkyne (**5**), which was reduced with lithium aluminum hydride to give compound **6**,[6] but in our work, the yield of **6** was very low (15%), it was difficult to separate the monochloroalkyne (**5**) from the dichloroalkyne, and compound **5** was a severe skin irritant. We tried another method that Baeckstrom et al. reported,[7] which started through a Mannich reaction with diethylamine, formaldehyde, and 2-propynol. The resulting 4-diethylamine-2-butyn-1-ol (**7**) was methylated with dimethyl sulfate, then reduced with lithium hydride to afford **6** with a high yield of 71%. So the latter method was used to synthesize a series of compound **2**, and **3**.

Because **1a**–**h** were commercially available and **6** was also prepared, thus the series of compound **2** could be synthesized readily. Scheme 2 shows the synthesis of the compounds **2a**–**j**. 4-Bromo-1,2-butadiene (**8**) was prepared by bromination of **6** with phosphorus tribromide and trace amount of pyridine at 0 °C.[8]

Then, treatment of compound **8** with **1a**–**d** and **1g**–**j** in the presence of potassium carbonate gave **2a**–**d** and **2g**–**j**, respectively. Hydrolysis of compounds **2a** and **2b** with LiOH in THF–H_2O provided the corresponding acids **2e** and **2f**.

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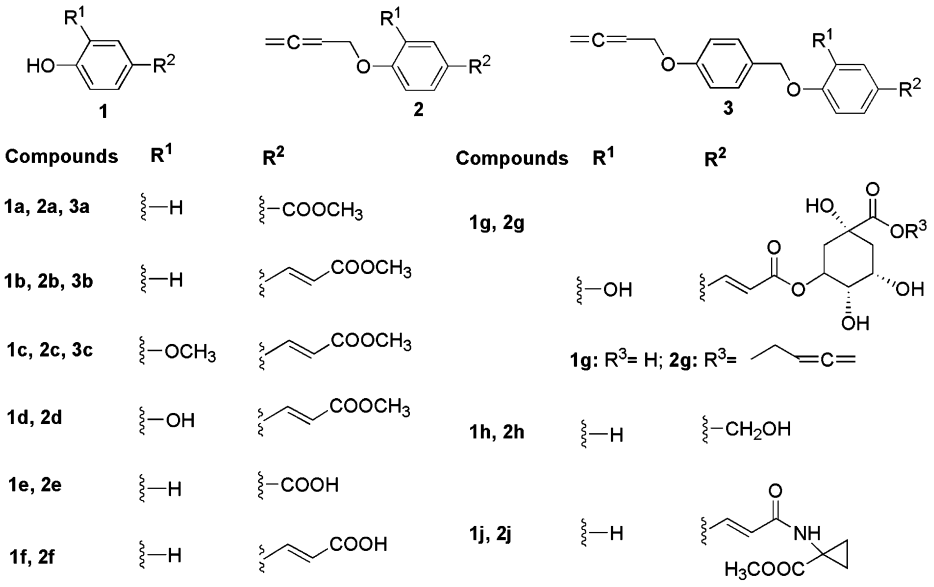
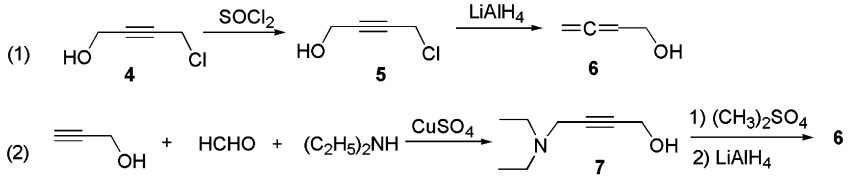
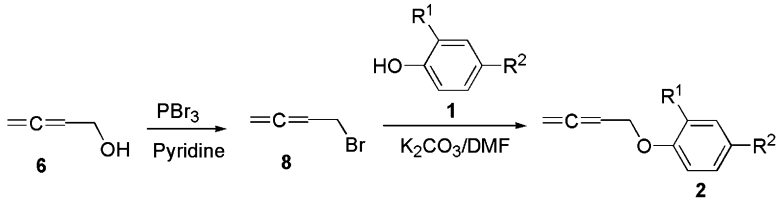


Figure 1. Structures of compounds **1a–j**, **2a–j**, and **3a–c**.



Scheme 1. Two methods to synthesize **6**.



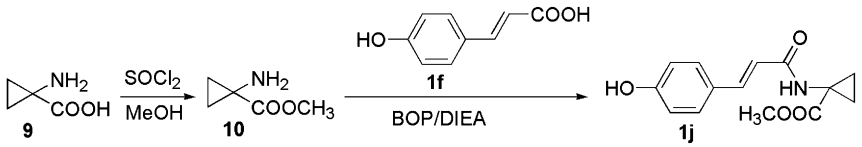
Scheme 2. Synthesis of **2a–j**.

In an attempt to study compound **2** analogs with two allenic moieties, we used an excess amount of compound **8** to react with caffeic acid methyl ester (**1d**) or chlorogenic acid (**1g**). Because the molecules of **1d** and **1g** contain two phenol hydroxyl groups, it was anticipated that they would form two allenic ethers in the excess amount of **8** (mole ratio 2.5:1 or 3.5:1). However, it was unexpected that only one OH formed allenic ether, the OH of R^1 did not react with **8** in the two compounds. Moreover, the carboxyl group of **1g** reacted with one allenic moiety formed the ester. The structures of these compounds were determined by the spectral data. Furthermore, the single crystals of **2g** were obtained by crystallization in EtOAc and PE.[9] The structure of **2g** was finally confirmed by X-ray diffractive technique.

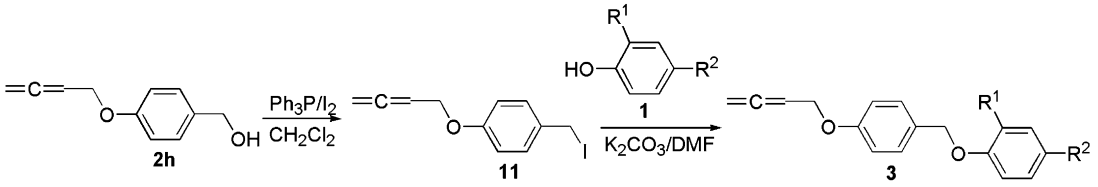
The method described in Scheme 3 allowed for the preparation of **1j**. The intermediate 1-amino-cyclo-propanecarboxylic acid methyl ester (**10**) was synthesized via 1-amino-cyclopropanecarboxylic (**9**) in the presence of thionyl chloride in methanol. Compound **10** then coupled with compound **1f** in the presence of BOP and DIEA in DMF to afford **1j**.

The synthesis of the compounds **3a–c** is presented in Scheme 4. Several methods for preparation of halide of **2h** were examined. When **2h** was treated with phosphorus tribromide or thionyl chloride, only a small amount of the corresponding halide was obtained. We tried to use the Ph_3P/I_2 reagent.[10] The iodide compound **11** was successfully synthesized with a good yield of 82%. Treatment of **11** with **1a–c** in the presence of potassium carbonate finally gave compounds **3a–c**, respectively.

The 12 allenic aromatic ethers, together with **1a–j**, **6**, **8**, and **10**, were evaluated in vitro for their ability to inhibit the growth of short-term cultured tongue cancer KB and KBv200 cell lines by a modified MTT (3-(4,5-dimethyl-



Scheme 3. Synthesis of **1j**.



Scheme 4. Synthesis of **3a**–**c**.

Table 1. Inhibitory activities of phenols and allenic aromatic ethers against tongue cancer KB and KBv200 cells in vitro

No.	IC_{50}[a] (μM)		No.	IC_{50}[a] (μM)		No.	IC_{50}[a] (μM)	
	KB	KBv200		KB	KBv200		KB	KBv200
1a	>200	>200	**2a**	22.52	20.86	**3a**	75.40	52.92
1b	123.1	101.2	**2b**	27.64	18.96	**3b**	48.76	55.47
1c	>200	>200	**2c**	17.36	18.27	**3c**	34.55	30.27
1d	>200	>200	**2d**	29.36	23.38	**6**	>200	>200
1e	>200	>200	**2e**	40.58	49.56	**8**	>200	>200
1f	>200	>200	**2f**	71.5	52.42	**10**	135.2	>200
1g	>200	>200	**2g**	53.10	35.68			
1h	>200	>200	**2h**	74.45	76.58			
1j	>200	>200	**2j**	48.06	77.03			

[a] Each experiment was independently performed three times and expressed as means. In addition, variation between the replicates was not greater than 4% of any given value.

thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay.[11,12] The IC_{50} values were also determined (Table 1).

As shown in Table 1, phenols, such as **1a** and **1c**–**j**, have no inhibitory activities against KB or KBv200 cells, while the corresponding allenic compounds **2a** and **2c**–**j** exhibited inhibitory activities against these two cells. Compound **1b** itself has weak inhibitory activity, with the IC_{50} values for KB/KBv200 of 123.1/101.2 μM, but the corresponding allenic compound **2b** has stronger activity, with IC_{50} values for KB/KBv200 of 27.64/18.96 μM. In fact, all the 12 allenic aromatic ethers exhibited cytotoxic potential, ranging from weak to strong activity. These data indicated that the introduction of allenic moiety to the phenol hydroxyl group could generate or enhance cytotoxicity of these phenols. Although the experiments were preliminary, it suggests that the allenic moiety is effective for the antitumor activities of these compounds.

Among the 12 allenic aromatic ethers, four compounds **2a**–**d** have significant cytotoxicities (IC_{50} < 30 μM). The introduction of OCH_3 (**2c**) or OH (**2d**) groups on the benzene ring of **2b** showed no influence on the activity. Compound **2g** has two allenic moieties (one is linked to the carboxyl group), but it did not exhibit better activity. Although compound **10** has weak inhibitory activity against KB cells with IC_{50} value of 135.2 μM, the introduction of this moiety into **2b** to form compound **2j** did not obtain the desired activity. It was also observed that simple allenic compounds **6** and **8** had no inhibitory activities against KB or KBv200 cells, whereas the allenic aromatic ethers **2** or **3** showed good inhibitory activities. Interestingly, when **2** and **3** have the same R^1, R^2 group, **2** showed better inhibitory activities than **3**. The structurally difference between them was that the latter has one more benzyloxy fragment.

In summary, we have synthesised 12 allenic aromatic ethers and identified their structures. Ten of them are new compounds, including four new natural products. Many of these allenic aromatic ethers showed potent and efficacious antitumor activities against KB and KBv200 cells. The analysis of structure–activity relationships suggested that the introduction of allenic moiety could generate or enhance cytotoxicity of these phenol compounds.

Acknowledgments

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Supplementary data

Synthetic details and characterization associated with this article are included in the Supporting Information. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.02.084.

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