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Ambident Effect of a *p*-Sulfinyl Group for the Introduction of Two Carbon Substituents to Phenol Rings: A Convergent Synthesis of Diverse Benzofuran Neolignans

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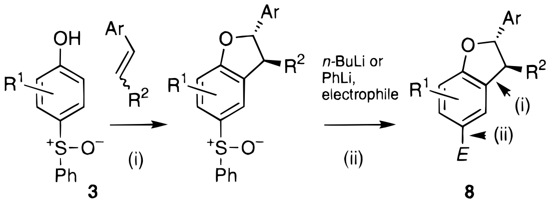
ABSTRACT



A convergent synthesis of diversely substituted benzofuran neolignans (8) is described employing a single *p*-sulfinyl group on the phenols (3) as an ambident functional group for two types of carbon–carbon bond-forming reactions: (i) the direct synthesis of the dihydrobenzofuran skeletons through an aromatic Pummerer-type reaction and (ii) the *ipso*-substitution of the sulfur functional group by carbon substituents through a ligand exchange reaction.

Naturally occurring benzofuran neolignans such as liliflol B (**1**), obovatinol, and kadsurenone (**2**) show important biological activities, i.e., cytotoxicity, inhibition of cell proliferation, inhibition of the platelet-activating factor (PAF)-induced effects, etc., and have attracted much attention on their effective syntheses.[1−5] The characteristic structure of these compounds involves the substituted phenyl group at the C-2 position, methyl or hydroxymethyl group at the C-3 position, carbon substituents at the C-5 position, and an oxygen functional group at the C-6 or C-7 position of the benzofuran skeleton (Figure 1).

The reported syntheses of these compounds were primarily performed through the [3 + 2] cycloaddition of 1-phenyl-1-propenes to *p*-quinones and their derivatives.[2−4] However, they are not always efficient due to unsatisfactory yields of the cycloadducts and/or the limitation of the substrates. Especially, lack of an effective method for the introduction of a variety of carbon substituents at the C-5 position of the skeleton has been an obstacle for the synthesis of various derivatives. In this Letter, we present a novel and general synthesis of benzofuran neolignans (**8**) containing diverse substituents which provides a solution to the above-mentioned problems. Our method utilizes the ambident effect of the sulfinyl group of *p*-sulfinylphenols, viz., (i) the direct synthesis of the dihydrobenzofuran skeleton (**5**) from the

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(1) For reviews, see: Ward, R. S. *Nat. Prod. Rep*. **1993**, *10*, 1−28. Ward, R. S. *Nat. Prod. Rep*. **1995**, *12*, 183−205. Ward, R. S. *Nat. Prod. Rep*. **1997**, *14*, 43−74.

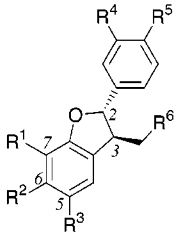
(2) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc*. **1977**, *99*, 8073−8075. Büchi, G.; Chu, P.-S. *J. Org. Chem*. **1978**, *43*, 3717−3719. Horne, D. A.; Yakushijin, K.; Büchi, G. *Tetrahedron Lett.* **1999**, *40*, 5443−5447.

(3) (a) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch, K. O., Jr.; Ray, J. E. *J. Org. Chem*. **1994**, *59*, 6567−6587. (b) Engler, T. A.; Chai, W. *Tetrahedron Lett*. **1996**, *37*, 6969−6970. (c) Engler, T. A.; Chai, W.; LaTessa, K. O. *J. Org. Chem*. **1996**, *61*, 9297−9308.

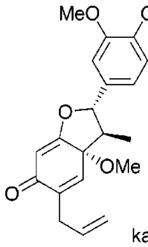
(4) Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem*. **1991**, *56*, 1979−1981. Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S *J. Org. Chem*. **1992**, *57*, 2135−2143.

(5) Ponpipom, M. M.; Bugianesi, R. L.; Brooker, D. R.; Yue, B. Z.; Hwang, S. B.; Shen T. Y. *J. Med. Chem*. **1987**, *30*, 136−142.

10.1021/ol0001261 CCC: $19.00



R^1=	R^2=	R^3=	R^4=	R^5=	R^6=	
H	OH	$CH_2CH{=}CH_2$	OMe	OMe	H	liliflol B (**1**)
OMe	H	CHO	H	OH	H	obovatinol
OMe	H	CH=CHMe	OCH_2O		H	licarin B
OMe	H	$(CH_2)_3OH$	OMe	OMe	OH	3',4-*O*-dimethyl-cedrusin

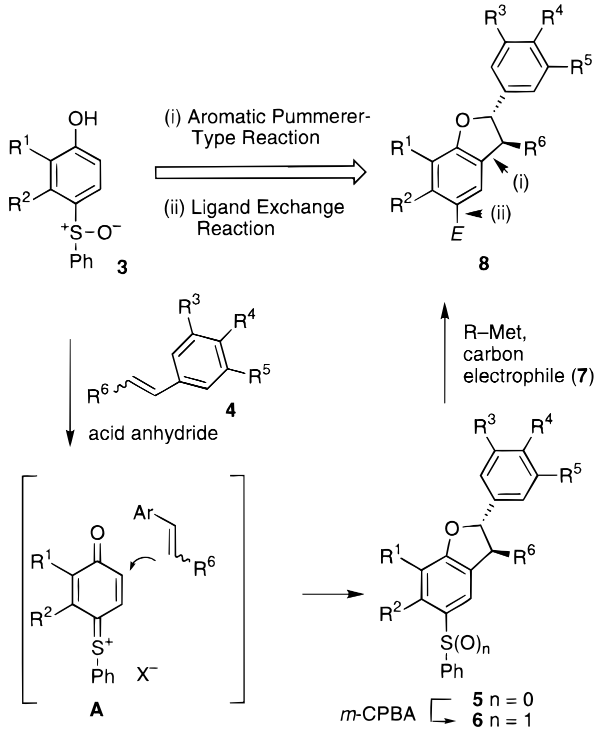


kadsurenone (**2**)

Figure 1. Benzofuran neolignans.

p-sulfinylphenols (**3**) through an aromatic Pummerer-type reaction and (ii) *ipso*-substitution of the sulfur group by a carbon substituent through a ligand exchange reaction of the sulfoxides (**6**) (Scheme 1).

Scheme 1. Synthesis of Substituted Dihydrobenzofurans (**8**)



Recently we have reported that treatment of *p*-sulfinylphenols (**3**) with $(CF_3CO)_2O$ caused the aromatic Pummerer-type reaction to generate the quinone thionium intermediates (**A**), to which 1,2-addition of the counteranion, X = $CF_3CO_2^-$, occurred to give *p*-quinones and/or *p*-quinone mono-*O*,*S*-acetals.[6] We anticipated that a similar reaction in the presence of a carbon nucleophile (**4**) would bring about carbon–carbon bond formation on the same intermediate (**A**). In this case, the preferential 1,4-addition of **4** to the conjugated $C{=}S^+$ system was expected due to the stronger electron-withdrawing nature of the $C{=}S^+$ group than that of the C=O group.[7,8]

At first, we examined the feasibility of this reaction using a simple *p*-sulfinylphenol (**3a**; $R^1 = R^2 = H$) and a nucleophile (**4a**; $R^3 = R^4 = OMe$, $R^5 = H$, $R^6 = Me$). After several trials that involved changing the acid anhydrides, solvents, and the addition order of the chemicals, we found that the addition of **3a** (1.0 equiv) to a solution of $(CF_3CO)_2O$ (1.4 equiv) and **4a** (1.05 equiv) in CH_3CN at −40 °C caused regiospecific carbon−carbon bond formation followed by spontaneous cyclization of the benzylic cation intermediate to give the product **5a** (81% yield) as a single regio- and stereoisomer (Table 1, run 1).[9] Formation of the *p*-benzoquinone was not observed in this reaction.

Application of this method to the *p*-sulfinylphenols (**3a**−**f**) with various substituents and styrene derivatives (**4a**−**g**) (1.1−1.6 equiv to **3**) readily afforded the corresponding products (**5a**−**k**) (Table 1). Several aspects are worth mentioning: (1) The reaction was generally completed below 0 °C within 60 min. (2) Products were obtained in good-to-high yields via the regioselective 1,4-addition of **4** to the less congested, conjugated $C{=}S^+$ system of **A**, which was independent of the substituents (R^1 and R^2); however, the methoxymethyl (MOM) ether (**5j**) was an exception (run 10). (3) The *trans*-adducts were exclusively obtained even from a mixture of *E*- and *Z*-olefins (**4a**, **4c**, and **4g**). (4) Introduction of typical substituents of the natural neolignans, i.e., alkoxy- or hydroxyphenyl group to the C-2 position and methyl or oxymethyl group to the C-3 position, was successfully attained using the corresponding olefins (**4**). (5) The naphthol (**3f**) was used to prepare the unnatural neolignan skeleton (**5k**) (run 11).

Next, *ipso*-substitution of the sulfur groups of **5** by carbon substituents was investigated by utilizing the ligand exchange reaction of the sulfoxides (**6**), readily prepared from **5** in high yields (Table 1). This reaction generates the arylmetal intermediates (**D**) via the sulfurane intermediates (**C**),[10] which

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(6) (a) Akai, S.; Takeda, Y.; Iio, K.; Yoshida, Y.; Kita, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1013−1014. (b) Akai, S.; Takeda, Y.; Iio, K.; Takahashi, K.; Fukuda, N.; Kita, Y. *J. Org. Chem.* **1997**, *62*, 5526−5536. (c) Kita, Y.; Takeda, Y.; Matsugi, M.; Iio, K.; Gotanda, K.; Murata, K.; Akai, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1529−1531. (d) Kita, Y.; Akai, S.; Fujioka, H. *J. Synth. Org. Chem. Jpn. (Special Issue in English)* **1998**, *56*, 963−974. (e) Akai, S.; Kita, Y. *Org. Prep. Proc. Int.* **1998**, *30*, 603−629.

(7) For related reactions of the *p*-sulfinylphenol, see: King, R. R. *J. Org. Chem.* **1978**, *43*, 3784−3785.

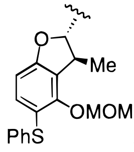
(8) For related reactions of the *o*-sulfinylphenols, see: Jung, M. E.; Kim, C.; von dem Bussche, L. *J. Org. Chem.* **1994**, *59*, 3248−3249. Jung, M. E.; Jachiet, D.; Khan, S. I.; Kim, C. *Tetrahedron Lett.* **1995**, *36*, 361−364.

(9) The addition of **4a** or $(CF_3CO)_2O$ as the last component and the use of $(CF_3SO_2)_2O$ and $(ClCH_2CO)_2O$ as an acid anhydride gave **5a** in low yields (trace−60%).

Table 1. Preparation of **5** from **3** and **4** and Oxidation of **5** to **6**[a]

run	**3**[b]	**4**[b]	temp, °C	**5**	$R^1 =$	$R^2 =$	$R^3 =$	$R^4 =$	$R^5 =$	$R^6 =$	% yield	**6**	% yield
1	**3a**	**4a**	−40	**5a**	H	H	OMe	OMe	H	Me	81		
2	**3a**	**4b**	−40	**5b**	H	H	H	OMe	H	H	88	**6b**	94
3	**3a**	**4c**	−40	**5c**	H	H	OMe	OH	H	H	55		
4	**3a**	**4d**	25	**5d**	H	H	H	H	H	H	58		
5	**3a**	**4e**	−40	**5e**	H	H	OMe	OMe	H	CH_2OAc	78		
6	**3a**	**4f**	−40	**5f**	H	H	OMe	OMe	OMe	H	85		
7	**3b**	**4g**	−40	**5g**	OMe	H	OCH_2O		H	Me	83	**6g**	98
8	**3c**	**4b**	0	**5h**	allyl	H	H	OMe	H	Me	90		
9	**3d**	**4g**	0	**5i**	H	OMe	OCH_2O		H	Me	67	**6i**	90
10	**3e**	**4a**	0	**5j**	H	OMOM	OMe	OMe	H	Me	46[c]	**6j**	99
11	**3f**	**4g**	−40	**5k**	CH=CHCH=CH		OCH_2O		H	Me	76	**6k**	84

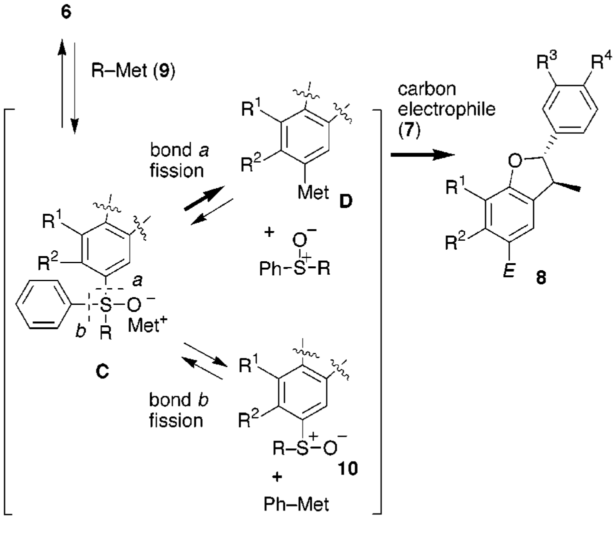
[a] Typical procedure for the preparation of **5**: into a solution of **4a** (0.29 mmol) and $(CF_3CO)_2O$ (0.35 mmol) in anhydrous CH_3CN (5 mL) at −40 °C was added a solution of **3a** (0.23 mmol). The reaction mixture was stirred at the same temperature for 30 min and quenched with saturated $NaHCO_3$. After the usual workup, the product was isolated by flash column chromatography on SiO_2. [b] R^1 and R^2 of **3** and R^3−R^6 of **4** are the same as those of the corresponding product (**5**). [c] A regioisomer (**5l**) was obtained in 28% yield.



5l

in turn react with a carbon electrophile (**7**) to give **8** (Scheme 2). The key in this transformation was the selective fission of bond *a* in **C** bearing two similar phenyl ligands,[11] and it was attained by choice of a suitable organometallic reagent (**9**), viz., PhLi for sulfoxides (**6i** and **6j**) with oxygen functional groups at their *ortho*-position and naphthylsulfoxide (**6k**) and *n*-BuLi for other types of sulfoxides.[12]

Scheme 2. Ligand Exchange Reaction of **6**



Five types of sulfoxides (**6b**, **g**, **i**, **j**, and **k**) were treated with an appropriate lithium reagent (**9**), and the resulting intermediates (**D**) were reacted with **7** (Table 2). In the cases of **6b** and **6g**, it was critical to add **7** immediately after the addition of *n*-BuLi (runs 1 and 2), because a 10 min delay caused exclusive formation of protonated products (**8**, $E =$ H). Carbonyl compounds such as DMF, $ClCO_2Me$, EtCHO, and acrylaldehyde were sufficiently employed to introduce C_1- or C_3-groups. On the other hand, the use of allyl iodide or allyl bromide for **6j** did not yield any allylated product (**8je**), and the iodinated product (**8**, $E =$ I) and/or the protonated product were obtained. However, the reaction with

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(10) For reviews, see: Oae, S. *Rev. Heteroatom Chem.* **1991**, *4*, 195−225. Satoh, T. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 481−489. Satoh, T. *Farumashia* **1999**, *35*, 1225−1229.

(11) Little is known about the selectivity of bond fission on unsymmetrical biphenyl sulfoxides, see: Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1987**, *28*, 2727−2730. Ogawa, S.; Furukawa, N. *J. Org. Chem.* **1991**, *56*, 5723−5726. Furukawa, N.; Ogawa, S.; Matsumura, K.; Fujihara, H. *J. Org. Chem.* **1991**, *56*, 6341−6348.

(12) The selectivity of the breaking bonds *a* and *b* was estimated by the ratio of the products, **8** ($E =$ H) and **10**, obtained by quenching the reaction mixture of **6** and **9** with MeOH. The use of PhLi (5 equiv) for **6i**, **6j**, and **6k** exclusively provided **8** ($E =$ H) but did not cause any reaction for other sulfoxides. The use of *n*-BuLi (5 equiv) resulted in moderate ratios (2.2−3.4:1) for **6b**, **6g**, and **6k** and a good ratio (>8:1) for **6i**. MeMgBr and PhMgBr brought about no reaction, and *t*-BuLi caused nonselective formation of the products.

(13) All new compounds (**5**, **6**, and **8**) were fully characterized by $^1H/^{13}C$ NMR and IR spectroscopic data as well as elemental analyses or high resolution mass spectroscopies. The product (**1**) was identical (mp and $^1H/^{13}C$ NMR) with the authentic sample.[3a]

(14) For preparation of **3** by direct introduction of the *p*-sulfinyl groups into the phenols, see: Chasar, D. W.; Pratt, T. M. *Phosphorus Sulfur* **1978**, *5*, 35−40. For the indirect preparation of **3**, see ref 6b.

(15) The sulfinyl group is known as a strong directing group for the *ortho*-lithiation of aromatic rings, see: Quesnelle, C.; Iihama, T.; Aubert, T.; Perrier, H.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2625−2628 and references therein.

(16) A dual use of a sulfinyl group for stereocontrolled C−C bond formation and subsequent regiocontrolled enol generation was reported, see: Posner, G. H.; Hulce, M.; Mallamo, J. P.; Drexler, S. A.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 5244−5246.

Table 2. Reaction of **6** with Various Carbon Electrophiles (**7**)[a]

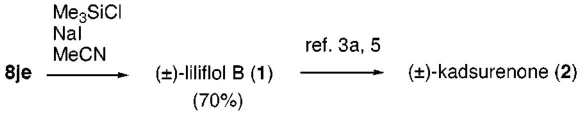
					8					
run	**6**	**9** (equiv)	**7**		$R^1 =$	$R^2 =$	$R^3 =$	$R^4 =$	*E* =	% yield
1	**6b**	*n*-BuLi (5)	DMF	**8ba**	H	H	H	OMe	CHO	61
2	**6g**	*n*-BuLi (5)	DMF	**8ga**	OMe	H	OCH_2O		CHO	56
3	**6i**	PhLi (5)	DMF	**8ia**	H	OMe	OCH_2O		CHO	93
4	**6j**	PhLi (2)	DMF	**8ja**	H	OMOM	OMe	OMe	CHO	85
5	**6j**	PhLi (2)	$ClCO_2Me$	**8jb**	H	OMOM	OMe	OMe	CO_2Me	72
6	**6j**	PhLi (2)	EtCHO	**8jc**	H	OMOM	OMe	OMe	CH(OAc)Et	52[b]
7	**6j**	PhLi (2)	$CH_2{=}CHCHO$	**8jd**	H	OMOM	OMe	OMe	$CH(OAc)CH{=}CH_2$	65[b]
8	**6j**	PhLi (5)	$CH_2{=}CHCH_2Br$	**8je**	H	OMOM	OMe	OMe	$CH_2CH{=}CH_2$	57[c]
9	**6k**	PhLi (5)	DMF	**8ka**	CH=CHCH=CH		OCH_2O		CHO	90

[a] General procedure: *n*-BuLi or PhLi was added to a THF solution of **6** at −78 °C, and **7** (5 equiv) was added immediately (for runs 1, 2) or after 15 min (for runs 3−9). The crude reaction mixture was stirred at −78 °C for 30−60 min, quenched with saturated $NaHCO_3$, and worked up as usual. The product (**8**) was isolated by flash column chromatography on SiO_2. [b] Isolated after acetylation. [c] A solution of CuI (5 equiv) and LiCl (5 equiv) in THF was added to a solution of the lithiated substrate in THF at −78 °C, and the mixture was stirred at 0 °C for 15 min. Allyl bromide (5 equiv) was added, and the reaction mixture was stirred at 0 °C for 60 min. The remainder of the procedure was same as the general procedure.

allyl bromide after metal exchange from lithium to copper afforded **8je** (run 8).[13]

Deprotection of the MOM group of **8je** using Me_3SiCl−NaI gave (±)-liliflol B (**1**) in 70% yield.[13] Conversion of **1** to (±)-kadsurenone (**2**), the PAF antagonist, has been reported (Scheme 3).[3a,5]

Scheme 3. Synthesis of (±)-Liliflol B (**1**) and (±)-Kadsurenone (**2**)



In conclusion, a new convergent synthesis of diverse benzofuran neolignans (**8**) from three components, viz., *p*-sulfinylphenols (**3**),[14] 1-aryl-1-propenes (**4**), and carbon electrophiles (**7**), was developed. This protocol features the dual effect of the sulfinyl group for two types of carbon−carbon bond-forming reactions and is unique from the viewpoint that a single functional group can produce the regiocontrolled introduction of multicarbon chains under the selected conditions.[15,16] The umpolung reactivity of the phenols to the corresponding highly reactive *p*-quinone thionium ions under nonoxidative, mild conditions is also noteworthy. An extensive study of these methodologies is now under investigation in our laboratory.

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