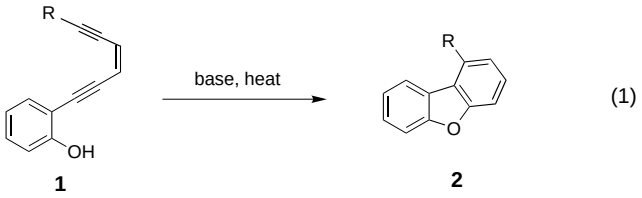
A Route to 5-Substituted Dibenzofurans by Anionic Cycloaromatization of 2-(6-substituted 3-hexen-1,5-diynyl)phenyl *tert*-butyldimethyl ethers and Related Molecules**

Ming-Jung Wu,* Chia-Ying Lee, and Chi-Fong Lin

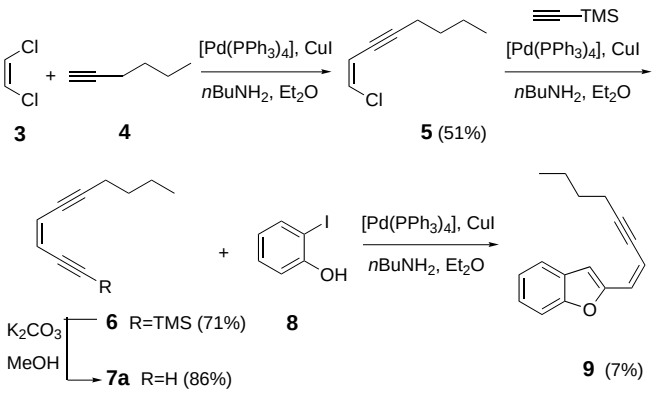
It is well-known that in a certain period of the life cycle of lichens or living-plant wood tissues a number of unique antimicrobial compounds are produced. The production of such compounds is thought to be a result of the secondary metabolism or as a part of their dynamic defense systems.[1] The biphenyl- or dibenzofuran-containing phytoalexins show manifold biological activities and have attracted much attention for chemical syntheses and biological studies.[2]

The dibenzofuran skeletons were usually generated by an acid-catalyzed ring-closure reaction of 2,2′-dihydroxybiphenyl compounds[3] or by cyclization of diaryl ethers with palladium.[4] Recently, we reported the anionic cycloaromatization of enediynes promoted by nucleophilic addition to prepare a variety of aromatic compounds.[5] We believe that 2-(6-substituted 3(*Z*)-hexen-1,5-diynyl)phenols (**1**) could undergo intramolecular anionic cycloaromatization to give dibenzofurans (**2**) under alkaline conditions. [Eq. (1)]



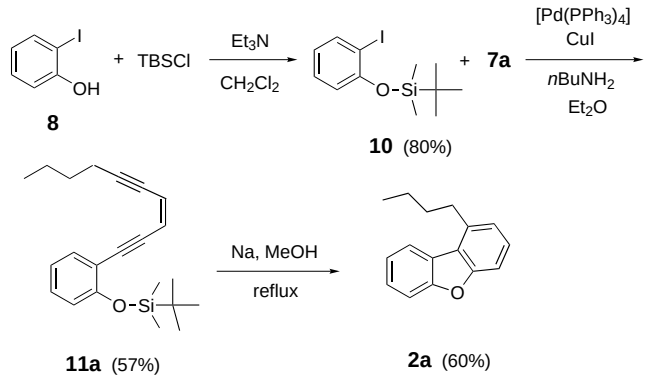
(1)

An attempt to synthesize compound **1** was carried out by using *cis*-1,2-dichloroethene (**3**; Scheme 1) as a starting material. The palladium-catalyzed coupling reaction of **3** with 1-hexyne (**4**) under Sonogashira reaction conditions[6] gave the vinyl chloride **5** in 51% yield. Compound **5** was then coupled with trimethylsilylacetylene under the same reaction conditions to give the enediyne **6** in 71% yield. Desilylation of **6** was carried out by treatment of **6** with potassium carbonate in dry methanol to form **7a** in 86% yield. Finally, the enediyne **7a** was coupled with 2-iodophenol (**8**) using tetrakis(triphenylphosphane)palladium as a catalyst to give the benzofuran **9** in 7% yield and a recovered 50% yield of the starting phenol **8** (Scheme 1). The failure to obtain the desired 2-(3(*Z*)-decen-1,5-diynyl)phenol (**1a**) may be attributed to the acidic proton of the phenol, which could cause the acid-catalyzed cyclization to give the benzofuran **9** instead of the dibenzofuran **2a**.



Scheme 1. Synthesis of the benzofuran **9** from a dichloroethene precursor. TMS = trimethylsilyl.

We anticipated that the protection of the phenolic proton, following the treatment of the product with a base would allow us to synthesize dibenzofurans. Thus, 2-(3(*Z*)-decen-1,5-diynyl)phenyl *tert*-butyldimethylsilyl ether (**11a**; Scheme 2) was prepared by palladium-catalyzed coupling reaction of (*Z*)-3-decen-1,5-diyne (**7a**) with 2-iodophenyl *tert*-butyldimethylsilyl ether (**10**) in 57% yield. Treatment of compound **11a** with sodium methoxide methanol heated under reflux for 16 h gave, after column chromatography, 5-butyldibenzofuran (**2a**) in 60% yield.



Scheme 2. Palladium-catalyzed coupling of **10** and **7a**, and subsequent cyclization of the product **11a** (see Table 1).

After the synthesis of dibenzofuran by the described method, we turned our attention to testing the generality of this cyclization reaction. Thus, various enediynylphenyl *tert*-butyldimethylsilyl ethers **11b–j** (Table 1) were prepared.[7] Treatment of **11b–j** with sodium methoxide under the same reaction conditions gave compounds **2b–j** in 50–94% yields. Other reaction conditions have also been examined for this cyclization reaction to synthesize dibenzofurans. The results show that treatment of **11b** and **11e** with potassium carbonate in refluxing methanol gave the dibenzofurans **2b** and **2e**, respectively, in yields comparable to those obtained by Method A.

Compound **11k** was prepared from *p-tert*-butylphenol.[8] Treatment of **11k** with sodium methoxide in refluxing

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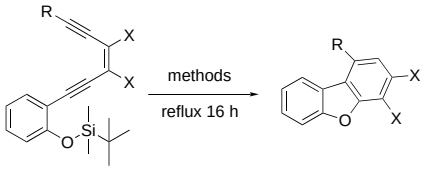
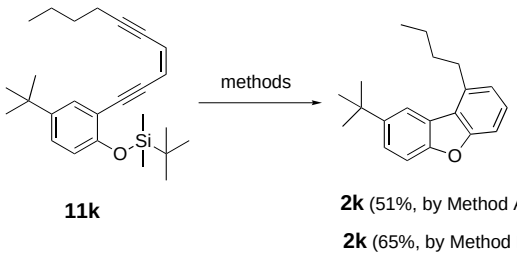
Table 1. Generation of 5-substituted dibenzofurans and related molecules.



Conditions				Yield
Method A: Na, MeOH				
X, X =	H, H	**11b**	$R = C_5H_{11}$	**2b** (56%)
		11c	$R = C_7H_{15}$	**2c** (50%)
		11d	$R = C_3H_6OTHP$	**2d** (57%)
X, X =		**11e**	$R = C_4H_9$	**2e** (93%)
		11f	$R = C_5H_{11}$	**2f** (94%)
		11g	$R = C_7H_{15}$	**2g** (92%)
		11h	$R = C_3H_6OTHP$	**2h** (91%)
X, X =		**11i**	$R = C_4H_9$	**2i** (75%)
		11j	$R = C_5H_{11}$	**2j** (75%)
Method B: K_2CO_3, MeOH				
		11b		**2b** (56%)
		11e		**2e** (93%)

THP = tetrahydropyran

methanol gave **2k** in 51% yield. On the other hand, treatment of **11k** with potassium carbonate in refluxing methanol gave **2k** in 65% yield. [Eq. (2)]



(2)

In conclusion, we have presented an efficient method for the synthesis of a series of 5-substituted dibenzofurans and related molecules in moderate to good yields by anionic cycloaromatization of enediynes.

Experimental Section

General procedure for methanolysis of **11** (Method A): Freshly cut sodium metal (5 mmol) was added to a solution of 2-(6-substituted 3(*Z*)-hexen-1,5-diynyl)phenyl *tert*-butyldimethylsilyl ethers (1 mmol) in 10 mL of methanol, the solution was heated to reflux and stirred for 16 h. After cooling to room temperature, the methanol was removed in vacuum. Saturated NaCl(aq.) was added to the residue, and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$(s). After filtration and removal of solvent, the residue was purified by column chromatography to give the separated products. Method B: The reaction conditions were the same as described in Method A, but the sodium was replaced with potassium carbonate (5 mmol).

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[7] Characterization data: **2a**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.98$ (dd, $J = 7.4$, 1.8 Hz, 1H), 7.51–7.32 (m, 4H), 7.13 (dd, $J = 6.6$, 1.6 Hz, 1H), 3.15 (t, $J = 7.4$ Hz, 2H), 1.84–1.72 (m, 2H), 1.57–1.26 (m, 2H), 1.00 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 156.3$, 156.0, 138.6, 126.9, 126.4, 124.3, 123.0, 122.6, 122.3, 122.2, 111.5, 109.0, 33.5, 31.9, 22.7, 14.0 ppm; HRMS (EI) calcd for $C_{16}H_{16}O$ 224.1201, found 224.1207. **2b**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.98$ (dd, $J = 7.8$, 2.0 Hz, 1H), 7.60 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.50–7.32 (m, 4H), 7.13 (dd, $J = 7.0$, 1.8 Hz, 1H), 3.13 (t, $J = 7.6$ Hz, 2H), 1.85–1.77 (m, 2H), 1.56–1.38 (m, 4H), 0.92 ppm (t, $J = 7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 156.2$, 156.0, 138.7, 126.9, 126.5, 124.6, 123.0, 122.6, 122.3, 122.1, 111.5, 109.1, 33.8, 31.9, 29.5, 22.6, 14.1 ppm; HRMS (EI) calcd for $C_{17}H_{18}O$ 238.1358, found 238.1360. **2c**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.01$ (dd, $J = 8.0$, 1.2 Hz, 1H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.63 (dd, $J = 7.6$ Hz, 1H), 7.56–7.41 (m, 2H), 7.32–7.21 (m, 2H), 4.61 (t, $J = 3.2$ Hz, 1H), 3.96–3.85 (m, 2H), 3.61–3.47 (m, 2H), 2.69 (t, $J = 6.4$ Hz, 2H), 2.04–1.84 (m, 2H), 1.75–1.48 ppm (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 156.4$, 156.0, 138.7, 126.9, 126.4, 124.3, 123.0, 122.6, 122.3, 122.2, 111.5, 109.0, 33.8, 31.9, 29.7, 29.6, 22.6, 21.0, 14.2 ppm; HRMS (EI) calcd for $C_{20}H_{22}O_3$ 310.1569, found 310.1570. **2d**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.96$ (dd, $J = 7.8$, 1.0 Hz, 1H), 7.59 (dt, $J = 7.6$, 1.0 Hz, 1H), 7.57–7.32 (m, 4H), 7.13 (dd, $J = 7.6$, 1.4 Hz, 1H), 3.13 (t, $J = 7.6$ Hz, 2H), 1.85–1.73 (m, 2H), 1.53–1.23 (m, 8H), 0.90 ppm (t, $J = 7.8$ Hz, 3H); HRMS (EI) calcd for $C_{19}H_{22}O$ 266.1671, found 266.1672. **2e**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.02$ (dd, $J = 8.0$, 1.2 Hz, 1H), 7.73 (d, $J = 1.2$ Hz, 1H), 7.62 (dd, $J = 7.6$, 0.8 Hz, 1H), 7.55–7.51 (m, 2H), 7.36 (td, $J = 8.0$, 1.6 Hz, 1H), 7.31–7.22 (m, 3H), 2.57 (t, $J = 6.8$ Hz, 2H), 1.73–1.67 (m, 2H), 1.66–1.50 (m, 2H), 0.99 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 154.1$, 154.0, 134.0, 131.1, 129.2, 127., 127.6, 126.4, 124.5, 122.8, 121.2, 120.5, 111.0, 105.4, 96.1, 80.5, 30.5, 22.0, 19.4, 13.6 ppm; HRMS (EI) calcd for $C_{20}H_{18}O$ 274.1358, found 274.1346. **2f**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.06$ (dd, $J = 7.0$, 0.8 Hz, 1H), 7.78 (s, 1H), 7.67–7.54 (m, 3H), 7.46–7.23 (m, 4H), 2.58 (t, $J = 7.0$ Hz, 3H), 1.78–1.61 (m, 2H), 1.61–1.28 (m, 4H), 0.96 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 154.1$, 154.0, 134.0, 131.1, 129.2, 127.7, 127.6, 126.4, 124.5, 122.7, 121.1, 120.5, 110.9, 105.4, 96.2, 80.5, 31.2, 28.2, 22.2, 19.8, 13.9 ppm; HRMS (EI) calcd for $C_{21}H_{20}O$ 288.1515, found 288.1513. **2g**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.03$ (dd, $J = 7.2$, 1.2 Hz, 1H), 7.75 (s, 1H), 7.74–7.52 (m, 4H), 7.44–7.21 (m, 4H), 2.56 (t, $J = 7.0$ Hz, 2H), 1.76–1.68 (m, 2H), 1.56–1.27 (m, 8H), 0.90 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 154.2$, 154.1, 134.0, 131.1, 129.2, 127.8, 127.6, 126.4, 124.5, 122.7, 121.2, 120.6, 111.0, 105.4, 96.2, 80.5, 31.7, 29.0, 28.9, 28.5, 22.6, 19.8, 14.0 ppm; HRMS (EI) calcd for $C_{23}H_{24}O$ 316.1828, found 316.1823. **2h**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.42$ (dt, $J = 8.0$, 1.2 Hz, 1H), 8.21 (dd, $J = 8.0$, 0.8 Hz, 1H), 7.91 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.73 (dt, $J = 8.0$, 0.8 Hz, 1H), 7.61–7.37 (m, 5H), 4.68 (t, $J = 4.0$ Hz, 1H),

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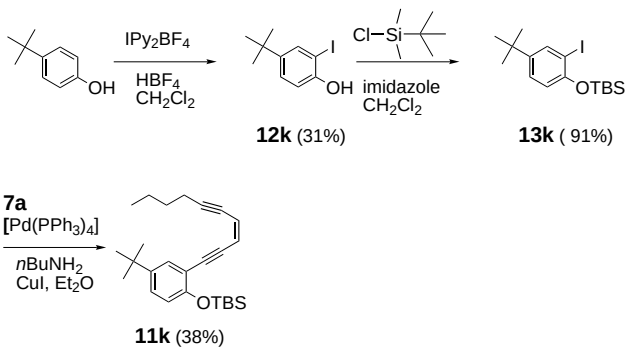
3.98–3.91 (m, 2H), 3.60–3.53 (m, 2H), 3.40–3.35 (m, 2H), 2.21–2.14 (m, 2H), 1.93–1.57 ppm (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 155.9$, 152.2, 135.3, 133.0, 127.6, 126.1, 125.7, 125.5, 124.8, 122.9, 122.2, 121.9, 120.8, 120.0, 118.4, 111.7, 98.8, 66.8, 62.1, 30.9, 30.6, 29.6, 25.4, 19.5 ppm; HRMS (EI) calcd for $C_{24}H_{24}O_3$ 224.1201, found 224.1207. **2i**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.49$ (s, 1H), 8.06 (s, 1H), 7.93–7.87 (m, 1H), 7.82 (s, 1H), 7.79–7.46 (m, 5H), 7.36–7.24 (m, 2H), 2.60 (t, $J = 6.8$ Hz, 2H), 1.77–1.37 (m, 4H), 1.00 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 154.5$, 154.2, 134.0, 132.4, 132.3, 132.0, 131.3, 128.3, 127.9, 127.2, 127.1, 126.8, 126.8, 125.9, 124.6, 122.8, 121.2, 118.3, 110.9, 105.8, 30.6, 29.7, 19.5, 13.6 ppm; HRMS (EI) calcd for $C_{24}H_{20}O$ 324.1515, found 324.1512. **2j**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.50$ (s, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.80–7.29 (m, 8H), 2.60 (t, $J = 6.8$ Hz, 2H), 1.83–1.22 (m, 6H), 0.95 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta =$ 154.3, 154.1, 134.1, 132.4, 132.3, 132.0, 131.4, 128.3, 127.3, 127.1, 126.9, 126.8, 126.5, 125.8, 124.6, 122.8, 121.2, 119.0, 111.0, 105.8, 31.3, 29.6, 22.3, 19.8, 14.0 ppm; HRMS (EI) calcd for $C_{25}H_{22}O$ 338.1671, found 338.1667. **2k**: ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.99$ (t, $J = 1.2$ Hz, 1H), 7.52 (d, $J = 1.4$ Hz, 2H), 7.44–7.31 (m, 2H), 7.11 (dd, $J = 6.8$, 1.4 Hz, 1H), 3.15 (t, $J = 7.6$ Hz, 2H), 1.89–1.74 (m, 2H), 1.65–1.50 (m, 2H), 1.45 (s, 9H), 1.03 ppm (t, $J = 7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta =$ 156.7, 154.2, 145.6, 138.4, 126.6, 124.1, 123.9, 122.9, 122.5, 118.7, 110.7, 109.0, 34.7, 33.8, 32.0, 31.8, 22.9, 14.0 ppm; HRMS (EI) calcd for $C_{20}H_{24}O$ 280.1828, found 280.1816.

[8] Treatment of *p-tert*-butylphenol with bis(pyridium)iodonium(I)tetrafluoroborate (Ipy_2BF_4) gave 2-iodo-4-*tert*-butylphenol in 31% yield. Compound **12k** was treated with *tert*-butyldimethylsilyl chloride using imidazole as a base to give **13k** in 91% yield. Finally, compound **13k**



was coupled with **7a** using palladium as a catalyst to give **11k** (TBS = *tert*-butyldimethylsilyl) in 38% yield.

The $HfCl_4$-Mediated Diels–Alder Reaction of Furan**

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7-Oxabicyclo[2.2.1]hept-2-ene derivatives are useful intermediates for the synthesis of natural products such as carbohydrates and prostaglandins.[1] One of the most straightforward methods for the construction of the 7-oxabicyclo[2.2.1]hept-2-ene skeleton is the Diels–Alder reaction between furan and appropriate dienophiles. However, the facile retro-Diels–Alder reaction and the low reactivity of furan as a diene, as a result of its aromatic character, make the Diels–Alder reaction of furan one of the most difficult cycloadditions.[2] In addition to the use of highly reactive dienophiles in the Diels–Alder reaction,[3] several methods have been developed to overcome these difficulties, such as the use of high pressure[4] or Lewis acid mediated reactions.[5] Although several Lewis acids have been reported to promote the reaction efficiently, there are problems in terms of generality. For example, $BF_3{\cdot}OEt_2$ is a good catalyst for methyl acrylate but a poor promoter for other dienopliles,[5c] ZnI_2 is suitable for acrylonitrile but not for α,β-unsaturated esters,[5a] while methyl vinyl ketone and acrylonitrile are activated by $BiCl_3$.[5l] Some Lewis acids supported on silica gel have also been utilized for the promotion of a particular dienophile with furan.[5e,g,i,j] However, low *endo*/*exo* selectivity is generally obtained because of the facile retro-Diels–Alder reaction. Herein we report the *endo*-selective Diels–Alder reaction of furan with α,β-unsaturated esters catalyzed by $HfCl_4$.

First, we looked for an appropriate Lewis acid using the reaction of furan and dimethyl maleate as a model and employing furan as the solvent (40 equiv). The reaction was performed in the presence of an equimolar amount of Lewis acid at room temperature for 15 h. Of the several Lewis acids screened,[6] $HfCl_4$ was found to have suitable Lewis acidity to promote the Diels–Alder reaction in moderate yield (60%).[7] Although most of the reported Lewis acids lose their Lewis acidity by coordination with furan, which acts as a Lewis base, $HfCl_4$ still activates α,β-unsaturated esters efficiently even in the presence of an excess amount of furan. Next, the use of a solvent was examined, and CH_2Cl_2 was found to be the best with respect to both yield and *endo*/*exo* selectivity.[8] For example, the Diels–Alder reaction of dimethyl maleate and furan proceeds in CH_2Cl_2 at −20 °C within 5 h to afford the cycloadduct in good yield (91%) and high diastereoselectivity

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