Convenient Synthesis of Polysubstituted 3-Iodofurans through the Tandem Ring-Opening/Cyclization Reaction of 1-Alkynyl-2,3-epoxy Alcohols

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Abstract: A novel method for the synthesis of highly substituted iodine-containing furans has been developed by the cyclization of 1-(arylethynyl)-2,3-epoxy alcohols (1-aryl-4,5-epoxyalk-1-yn-3-ols) with alcohols as nucleophiles under very mild reaction conditions. The resulting iodine-containing furans can be readily elaborated to more complex products using known organopalladium chemistry.

Key word: iodofuran, tandem reaction, epoxide, electrophilic cyclization

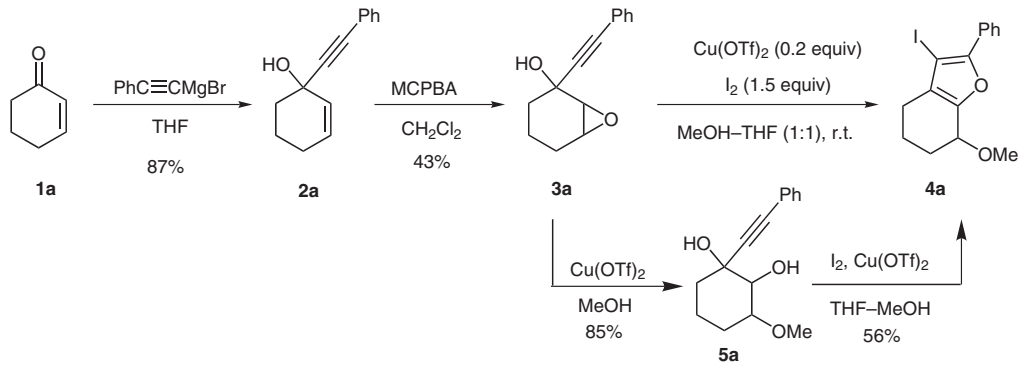
The furan core is one of the most important five-membered-ring heterocycles and it can be found in a number of natural products[1] and pharmaceuticals.[2] Encouraged by their important biological activity and great utility, a variety of methods have been developed for the synthesis of furans.[3,4] The transition-metal-catalyzed cyclization is an effective approach and many substrates such as an alkynyl or allenyl ketone,[5] alcohol,[6] or epoxide[7] can be subjected to cyclization in this way. In addition, the electrophilic cyclization of unsaturated compounds has also proven to be an efficient method for the one-step construction and functionalization of furan units.[8–11] This method provides an alternative route to complex furan derivatives.

Halofurans are important intermediates that provide an opportunity for further functionalization. In particular, iodo- and bromofurans are useful as substrates in a variety of C–C, C–N, or C–S bond-forming reactions.[12] Since the HOMO coefficient is greater for the α-C than for the β-C, electrophilic reactions at the 3- or 4-positions are generally more difficult than substitution at the 2- or 5-positions.[13]

In our efforts to develop new methodologies for the synthesis of heterocycles, we have succeeded in the construction of highly substituted 3-iodofurans by electrophilic cyclization of 1-aryl-4,5-epoxyalk-1-yn-3-ols. In this paper, we will report our results.

The synthesis of the starting materials is illustrated in Scheme 1 with **3a** as an example. Treatment of **1a** with the Grignard reagent of phenylacetylene afforded the allylic alcohol **2a**. Then epoxidation of the latter with 3-chloroperoxybenzoic acid yielded the (hydroxymethyl)oxirane **3a**.

Compound **3a** was then subjected to copper(II) triflate (0.2 equiv) in methanol at room temperature. The reaction afforded the epoxide ring-opening product of **5a** in 85% yield. Hence, we predicted that the iodofuran would be produced by the addition of iodine.[10b] When **3a** was exposed to the mixture of copper(II) triflate (0.2 equiv) and iodine (1.5 equiv) in methanol–tetrahydrofuran (1:1) for 12 hours, the product **4a** was separated in 35% yield; when the reaction time was prolonged to 24 hours at 20 °C, **4a** was obtained in 70% yield. Then, various Lewis



Scheme 1 General synthetic scheme to (hydroxymethyl)oxirane **3a** and its cyclization to give **4a**

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Table 1 Selection of the Catalyst[a]

Entry	Catalyst	Yield[b] (%)
1	I_2, K_2CO_3	0
2	$Cu(OTf)_2$, I_2	70
3	$Zn(OTf)_2$, I_2	45
4	$AlCl_3$, I_2	trace
5	$BF_3{\cdot}OEt_2$, I_2	0
6	$TiCl_4$, I_2	0
7	$CeCl_3{\cdot}7H_2O$, I_2	59
8	$LiClO_4{\cdot}3H_2O$, I_2	44

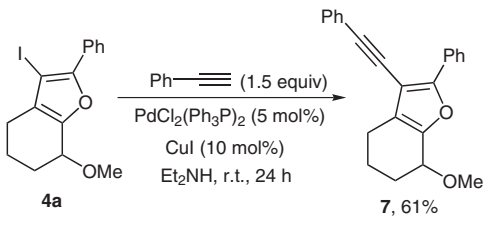
[a] All reactions were carried out using **3a** (0.20 mmol), catalyst (0.04 mmol), I_2 (0.30 mmol), MeOH–THF (1:1, 2 mL), 20 °C, 24 h.
[b] Isolated yields.

acids were examined and the results showed that copper(II) triflate was the most appropriate catalyst (Table 1).

Then various substrates were investigated and the results are summarized in Table 2. When ethanol and propan-2-ol were selected as the nucleophiles (entries 2 and 3), the yields were lower than that of methanol (**4a** > **4b** > **4c**). This result shows the steric hindrance of the alcohol greatly affects the yield. Alkynes bearing either electron-poor or electron-rich aryl groups are readily accommodated in the iodine-induced cyclizations (entries 4–7); **4d** and **4e** were obtained in 75% and 63% yields, which were higher than **4f** and **4g** although the latter proceeded more rapidly and the reaction was complete within four hours.

A range of acyclic substrates **3f–j** was also investigated and the yields of **4h–l** were comparable to that of the cyclic compounds; the results for various substituted aryl groups showed similar trends (entries 9–12). In addition to the successful cyclization of 1-aryl-5-phenyl-4,5-epoxypent-1-yn-3-ols **3f–j**, 2,3-epoxy-1-phenylhex-1-yn-3-ol (**3k**) afforded iodofuran **3m** in 58% yield.

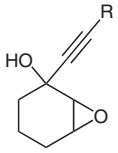
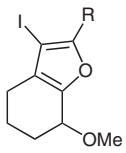
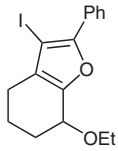
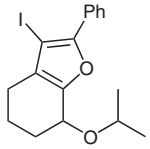
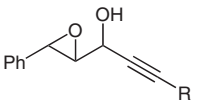
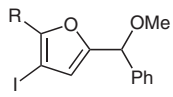
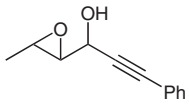
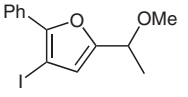
The utility of 3-iodofurans produced by this chemistry as useful synthetic intermediates for further elaboration was briefly investigated by the palladium-catalyzed Sonogashira reaction of **3a**, which afforded alkynylated product **7** in 61% yield (Scheme 2).



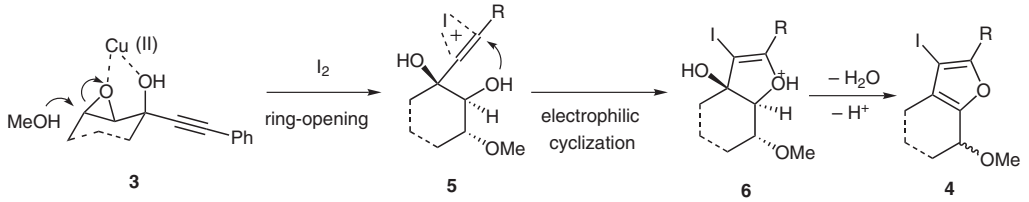
Scheme 2

An epoxide ring-opening/iodocyclization mechanism is proposed for this reaction[10b] (Scheme 3). The epoxide is regioselectively opened by the alcohol in the presence of the Lewis acid. Coordination of the electrophile to the triple bond promotes nucleophilic attack of the oxygen onto the triple bond to generate the intermediate **6**, which then undergoes *anti* elimination of water to produce iodofuran **4**. The (hydroxymethyl)oxirane **3** generated from the epoxidation of allylic alcohols with 3-chloroperoxybenzoic acid is a mixture of *threo* and *erythro* products especially for the acyclic allylic alcohols.[14] According to our proposed mechanism, the *threo* product would produce the

Table 2 Cyclization of 1-Aryl-4,5-epoxyalk-1-yn-3-ols[a]

Entry	Substrate	Nucleophile	Product	Yield[b] (%)
				
1	R = Ph **3a**	MeOH	**4a**	70
2	R = Ph **3a**	EtOH	 **4b**	56
3	R = Ph **3a**	*i*-PrOH	 **4c**	43
4	R = 4-BrC_6H_4 **3b**	MeOH	**4d**	75
5	R = 4-ClC_6H_4 **3c**	MeOH	**4e**	63
6	R = 4-$MeOC_6H_4$ **3d**	MeOH	**4f**	45[c]
7	R = 4-MeC_6H_4 **3e**	MeOH	**4g**	44[c]
		MeOH		
8	R = Ph **3f**	MeOH	**4h**	63
9	R = 4-BrC_6H_4 **3g**	MeOH	**4i**	69
10	R = 4-ClC_6H_4 **3h**	MeOH	**4j**	50
11	R = 4-$MeOC_6H_4$ **3i**	MeOH	**4k**	45[c]
12	R = 4-MeC_6H_4 **3j**	MeOH	**4l**	53[c]
13	 **3k**	MeOH	 **4m**	58

[a] All reactions were run under the following conditions, unless otherwise specified: **3** (0.20 mmol), $Cu(OTf)_2$ (0.04 mmol), I_2 (0.30 mmol), MeOH–THF (1:1, 2 mL), stirring, 20 °C, 24 h.
[b] Isolated yield.
[c] The reaction took 4 h.



Scheme 3

iodofuran **4** smoothly and the *erythro* product would not, which might be the reason for the moderate yield.

In conclusion, an efficient synthesis of highly substituted furans has been developed through the cyclization of 1-aryl-4,5-epoxyalk-1-yn-3-ols in the presence of alcohol. An iodide is readily introduced into the 3-position by using iodine as the electrophile. This methodology accommodates iodofurans in moderate to good yields under very mild reaction conditions. The resulting iodine-containing products can be readily elaborated to more complex products using known organopalladium chemistry.

Column chromatography was carried out on silica gel and the petroleum ether (PE) used was the fraction boiling in the range 60–90 °C. ^{1}H NMR spectra were recorded on 300 MHz or 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 75 MHz or 100 MHz in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and are uncorrected. All new compounds were further characterized by elemental analysis. Commercially available reagents and solvents were used without further purification. THF was distilled immediately before use from Na/benzophenone.

2-(Phenylethynyl)-7-oxabicyclo[4.1.0]heptan-2-ol (3a); Typical Procedure

A soln of EtMgBr was prepared using Mg turnings (6 mmol), EtBr (6 mmol), and THF (3 mL). Then phenylacetylene (6 mmol) was added dropwise and the mixture was stirred at 50 °C for 15 min. The soln was cooled to r.t. and a soln of cyclohex-2-enone (**1a**, 5 mmol) in THF (5 mL) was added dropwise. After the reaction was completed, sat. NH_4Cl soln was added. The aqueous phase was extracted with Et_2O. The combined organic phases were dried (anhyd $MgSO_4$) and concentrated. The crude product was purified by column chromatography (PE–EtOAc, 10:1) to give the alcohol **2a** (861 mg, 87%) as a colorless oil.

To the soln of **2a** (2 mmol) in CH_2Cl_2 (20 mL) was added MCPBA (3 mmol) portionwise at 0–5 °C. The mixture was stirred at r.t. overnight and then filtered. The organic solvent was washed with 5% aq $NaHSO_3$, 5% aq Na_2CO_3, and then thoroughly with H_2O. The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (PE–EtOAc, 10:1) to give **3a** (205 mg, 48%) as a colorless oil.

IR (neat): 3427, 2947, 2252, 1490, 909, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.67 (m, 2 H), 1.80–1.87 (m, 2 H), 1.89–1.92 (m, 2 H), 3.03 (s, 1 H), 3.41 (m, 1 H), 3.46–3.48 (m, 1 H), 7.27–7.32 (m, 3 H), 7.45–7.48 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 22.2, 34.1, 55.7, 58.3, 67.9, 85.5, 89.2, 122.1, 128.2, 128.5, 131.7.

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.62; H, 6.35.

2-[2-(4-Bromophenyl)ethynyl]-7-oxabicyclo[4.1.0]heptan-2-ol (3b)

White solid; yield: 50% for two steps; mp 62–64 °C.

IR (neat): 3433, 2949, 2253, 1486, 908, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54–1.56 (m, 2 H), 1.79–1.88 (m, 2 H), 1.90–1.95 (m, 2 H), 3.09 (s, 1 H), 3.42 (m, 1 H), 3.45–3.46 (m, 1 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.43 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 22.2, 34.1, 55.8, 58.2, 67.8, 84.6, 90.4, 122.0, 122.8, 131.4, 131.2.

Anal. Calcd for $C_{14}H_{13}BrO_2$: C, 57.36; H, 4.47. Found: C, 57.21; H, 4.68.

2-[2-(4-Chlorophenyl)ethynyl]-7-oxabicyclo[4.1.0]heptan-2-ol (3c)

White solid; yield: 55% for two steps; mp 49–51 °C.

IR (neat): 3436, 2949, 2253, 1490, 909, 735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55–1.64 (m, 2 H), 1.70–1.89 (m, 2 H), 1.90–1.93 (m, 2 H), 2.89 (s, 1 H), 3.41–3.46 (m, 2 H), 7.28 (d, *J* = 8.7 Hz, 2 H), 7.38 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 22.3, 34.2, 55.8, 58.2, 67.8, 84.4, 90.2, 120.6, 128.6, 133.0, 134.6.

Anal. Calcd for $C_{14}H_{13}ClO_2$: C, 67.61; H, 5.27. Found: C, 67.38; H, 5.33.

2-[2-(4-Methoxyphenyl)ethynyl]-7-oxabicyclo[4.1.0]heptan-2-ol (3d)

Colorless oil; yield: 41% for two steps.

IR (neat): 3411, 2947, 2254, 1510, 909, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.63 (m, 2 H), 1.79–1.83 (m, 2 H), 1.89–1.92 (m, 2 H), 2.67 (s, 1 H), 3.41–3.45 (m, 2 H), 3.81 (s, 3 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 7.39 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 22.3, 34.4, 55.2, 55.8, 58.4, 67.9, 85.5, 87.8, 113.9, 114.1, 133.3, 159.8.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.48; H, 6.45.

2-[2-(4-Methylphenyl)ethynyl]-7-oxabicyclo[4.1.0]heptan-2-ol (3e)

Colorless oil; yield: 45% for two steps.

IR (neat): 3413, 2945, 2250, 1510, 910, 734 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.65 (m, 2 H), 1.79–1.83 (m, 2 H), 1.87–1.92 (m, 2 H), 2.42 (s, 3 H), 2.74 (s, 1 H), 3.41–3.46 (m, 2 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 21.4, 22.3, 34.3, 55.8, 58.4, 67.9, 85.7, 88.5, 119.0, 129.0, 131.7, 138.7.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.08; H, 7.20

3-Phenyl-1-(3-phenyloxiran-2-yl)prop-2-yn-1-ol (3f)
Colorless oil; yield: 53% for two steps.

IR (neat): 3431, 2252, 1491, 909, 733 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (7:3 mixture of diastereoisomers) = 3.24–3.28 (m, 1 H), 3.41–3.44 (m, 1 H), 4.03 and 4.14 (2 d, J = 2.4 Hz, 1 H), 4.75–4.76 and 4.96–4.97 (2 m, 1 H), 7.19–7.41 (m, 8 H), 7.42–7.45 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (7:3 mixture of diastereoisomers) = 55.9, 56.2, 61.4, 62.1, 63.4, 64.1, 85.1, 85.8, 86.1, 86.6, 121.8, 125.7, 125.8, 128.2, 128.3, 128.4, 128.7, 131.8, 135.8, 136.0.

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.47; H, 5.82.

3-(4-Bromophenyl)-1-(3-phenyloxiran-2-yl)prop-2-yn-1-ol (3g)
White solid; yield: 38% for two steps; mp 86–88 °C.

IR (neat): 3432, 2254, 1486, 908, 733 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (3:7 mixture of diastereoisomers) = 2.70–2.73 (m, 1 H), 3.40–3.43 (m, 1 H), 4.03 and 4.12 (2 d, *J* = 2.1 Hz, 1 H), 4.73–4.76 and 4.93–4.95 (2 m, 1 H), 7.25–7.39 (m, 7 H), 7.42–7.45 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (3:7 mixture of diastereoisomers) = 55.9, 56.1, 61.4, 61.9, 63.1, 63.9, 85.1, 85.7, 86.1, 87.1, 120.8, 123.1, 125.8, 128.5, 131.6, 133.2, 135.8, 135.9.

Anal. Calcd for $C_{17}H_{13}BrO_2$: C, 63.02; H, 3.98. Found: C, 63.27; H, 4.15.

3-(4-Chlorophenyl)-1-(3-phenyloxiran-2-yl)prop-2-yn-1-ol (3h)
White solid; yield: 47% for two steps; mp 103–105 °C.

IR (neat): 3438, 2254, 1489, 909, 734 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (4:6 mixture of diastereoisomers) = 2.88–2.90 (m, 1 H), 3.41–3.42 (m, 1 H), 4.03 and 4.13 (2 d, *J* = 1.8 Hz, 1 H), 4.73–4.77 and 4.93–4.95 (2 m, 1 H), 7.25–7.38 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (4:6 mixture of diastereoisomers) = 55.9, 56.2, 61.4, 61.9, 63.2, 64.0, 85.1, 85.6, 86.0, 86.8, 120.3, 125.8, 125.9, 128.5, 128.6, 133.0, 134.8, 135.7, 135.9.

Anal. Calcd for $C_{17}H_{13}ClO_2$: C, 71.71; H, 4.60. Found: C, 71.38; H, 4.32.

3-(4-Methoxyphenyl)-1-(3-phenyloxiran-2-yl)prop-2-yn-1-ol (3i)
Colorless oil; yield: 35% for two steps.

IR (neat): 3419, 2254, 1490, 908, 733 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (7:3 mixture of diastereoisomers) = 2.89 (m, 1 H), 3.41–3.44 (m, 1 H), 3.80 (s, 3 H), 4.03 and 4.14 (2 d, *J* = 2.4 Hz, 1 H), 4.74–4.75 and 4.95–4.96 (2 m, 1 H), 6.81–6.85 (m, 2 H), 7.30–7.42 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (7:3 mixture of diastereoisomers) = 55.2, 55.9, 56.2, 63.4, 64.1, 83.7, 84.3, 86.2, 86.8, 113.9, 125.9, 125.9, 128.4, 128.5, 133.4, 136.1, 159.9.

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.20; H, 5.58.

1-(3-Phenyloxiran-2-yl)-3-(4-methylphenyl)prop-2-yn-1-ol (3j)
Colorless oil; yield: 40% for two steps.

IR (neat): 3440, 2253, 1509, 909, 739 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (6:4 mixture of diastereoisomers) = 2.38 (s, 3 H), 3.25 (s, 1 H), 3.41–3.42 (m, 1 H), 4.02 and 4.13 (2 d, *J* = 2.4 Hz, 1 H], 4.73–4.74 and 4.94–4.95 (2 m, 1 H), 7.06–7.09 (m, 2 H), 7.21–7.35 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (6:4 mixture of diastereoisomers) = 21.4, 55.9, 56.2, 61.5, 62.1, 63.4, 64.1, 84.4 85.1, 118.8, 125.8, 125.9, 128.3, 128.4,129.0, 131.7, 135.9, 136.1, 138.8.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.75; H, 6.39.

1-(3-Methyloxiran-2-yl)-3-phenylprop-2-yn-1-ol (3k)
Colorless oil; yield: 65% for two steps.

IR (neat): 3433, 2253, 1490, 911, 741 cm^{-1}.

^1H NMR (300 MHz, CDCl3): δ (5:5 mixture of diastereoisomers) = 1.29–1.34 (m, 3 H), 3.02–3.07 (m, 1 H), 3.09–3.26 (m, 2 H), 4.50–4.53 and 4.77–4.79 (2 m, 1 H), 7.26–7.28 (m, 3 H), 7.38–7.43 (m, 2 H).

^{13}C NMR (75 MHz, CDCl3): δ (5:5 mixture of diastereoisomers) = 16.8, 16.9, 52.5, 52.7, 60.7, 61.5, 62.5, 85.5, 85.7, 86.0, 86.1, 122.0, 128.2, 128.6, 131.7.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.53; H, 6.39.

Iodofurans 4; General Procedure
To a soln of **3** (0.20 mmol) in THF–MeOH (1:1, 2 mL) were added $Cu(OTf)_2$ (0.04 mmol) and I_2 (0.30 mmol). The mixture was stirred at 20 °C for until the reaction was complete (monitored by TLC). The soln was quenched with aq $Na_2S_2O_3$ and extracted with Et_2O. The combined organic phases were washed with sat. NaCl, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography to give iodofuran **4**.

3-Iodo-7-methoxy-2-phenyl-4,5,6,7-tetrahydrobenzofuran (4a)
Colorless oil.

IR (neat): 2938, 2821, 1602, 1481, 1444, 1090 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.77–1.91 (m, 3 H), 2.10–2.16 (m, 1 H), 2.21–2.31 (m, 1 H), 2.38–2.45 (m, 1 H), 3.52 (s, 3 H), 4.32 (t, *J* = 3.6 Hz, 1 H), 7.30–7.35 (m, 1 H), 7.39–7.44 (m, 2 H), 7.98 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 23.5, 29.5, 57.0, 66.2, 70.5, 126.3, 127.0, 128.0, 128.3, 130.4, 150.3, 150.6.

Anal. Calcd for $C_{15}H_{15}IO_2$: C, 50.87; H, 4.27. Found: C, 50.73; H, 4.19.

7-Ethoxy-3-iodo-2-phenyl-4,5,6,7-tetrahydrobenzofuran (4b)
Colorless oil.

IR (neat): 2932, 2864, 1603, 1481, 1444, 1088 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 6.9 Hz, 3 H), 1.67–1.78 (m, 2 H), 1.80–1.89 (m, 1 H), 2.01–2.09 (m, 1 H), 2.12–2.24 (m, 1 H), 2.30–2.38 (m, 1 H), 3.59–3.72 (m, 2 H), 4.32 (t, *J* = 3.6 Hz, 1 H), 7.21–7.26 (m, 1 H), 7.31–7.36 (m, 2 H), 7.89 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6, 18.8, 23.5, 29.9, 64.7, 66.2, 68.9, 126.3, 126.8, 128.0, 128.3, 130.5, 150.5, 150.6.

Anal. Calcd for $C_{16}H_{17}IO_2$: C, 52.19; H, 4.65. Found: C, 52.01; H, 4.45.

3-Iodo-7-isopropoxy-2-phenyl-4,5,6,7-tetrahydrobenzofuran (4c)
Colorless oil.

IR (neat): 2969, 2867, 1603, 1481, 1446, 1066 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.26 (m, 6 H), 1.76–1.84 (m, 2 H), 1.89–2.08 (m, 2 H), 2.19–2.29 (m, 1 H), 2.37–2.45 (m, 1 H), 3.90–3.98 (m, 1 H), 4.50 (t, *J* = 3.6 Hz, 1 H), 7.29–7.34 (m, 1 H), 7.39–7.44 (m, 2 H), 7.96 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 22.6, 22.8, 23.5, 30.8, 66.2, 66.5, 70.3, 126.2, 126.6, 127.9, 128.3, 130.6, 150.3, 150.7.

Anal. Calcd for $C_{17}H_{19}IO_2$: C, 53.42; H, 5.01. Found: C, 53.05; H, 4.78.

2-(4-Bromophenyl)-3-iodo-7-methoxy-4,5,6,7-tetrahydrobenzofuran (4d)
Colorless oil.

IR (neat): 2940, 2821, 1622, 1477, 1439, 1091 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75–1.94 (m, 3 H), 2.10–2.16 (m, 1 H), 2.20–2.30 (m, 1 H), 2.37–2.44 (m, 1 H), 3.53 (s, 3 H), 4.32 (t, *J* = 3.6 Hz, 1 H), 7.36 (d, *J* = 9.0 Hz, 2 H), 7.98 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 23.4, 29.3, 57.0, 66.9, 70.5, 122.0, 127.2, 127.6, 129.3, 131.5, 150.0, 150.3.

Anal. Calcd for $C_{15}H_{14}BrIO_2$: C, 41.60; H, 3.26. Found: C, 41.56; H, 3.15.

2-(4-Chlorophenyl)-3-iodo-7-methoxy-4,5,6,7-tetrahydrobenzofuran (4e)
Colorless oil.

IR (neat): 2940, 2821, 1622, 1474, 1439, 1088 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78–1.86 (m, 3 H), 2.09–2.16 (m, 1 H), 2.19–2.30 (m, 1 H), 2.37–2.40 (m, 1 H), 3.52 (s, 3 H), 4.31 (t, *J* = 3.6 Hz, 1 H), 7.52 (d, *J* = 9.0 Hz, 2 H), 7.86 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 23.5, 29.4, 57.0, 66.7, 70.5, 127.2, 127.5, 128.6, 128.9, 133.8, 149.7, 150.6.

Anal. Calcd for $C_{15}H_{14}ClIO_2$: C, 46.36; H, 3.63. Found: C, 46.48; H, 3.59.

3-Iodo-7-methoxy-2-(4-methoxyphenyl)-4,5,6,7-tetrahydrobenzofuran (4f)
Colorless oil.

IR (neat): 2936, 2837, 1611, 1493, 1459, 1252, 1087 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78–1.91 (m, 3 H), 2.10–2.16 (m, 1 H), 2.25–2.31 (m, 1 H), 2.37–2.44 (m, 1 H), 3.52 (s, 3 H), 3.85 (s, 3 H), 4.32 (t, *J* = 3.6 Hz, 1 H), 6.93 (d, *J* = 6.9 Hz, 2 H), 7.89 (d, *J* = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 23.5, 29.5, 55.3, 57.0, 64.7, 70.6, 113.7, 123.3, 126.8, 127.9, 149.8, 151.0, 159.4.

Anal. Calcd for $C_{16}H_{17}IO_3$: C, 50.02; H, 4.46. Found: C, 50.39; H, 4.31.

3-Iodo-7-methoxy-2-(4-tolyl)-4,5,6,7–tetrahydrobenzofuran (4g)
Colorless oil.

IR (neat): 2926, 2822, 1621, 1492, 1450, 1088 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79–1.90 (m, 3 H), 2.10–2.16 (m, 1 H), 2.21–2.30 (m, 1 H), 2.39–2.44 (m, 4 H), 3.51 (s, 3 H), 4.32 (t, *J* = 3.6 Hz, 1 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 7.84 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 21.3, 23.5, 29.6, 35.5, 57.0, 65.5 70.5, 126.3, 126.9, 127.8, 129.0, 138.0, 150.1, 151.0.

Anal. Calcd for $C_{16}H_{17}IO_2$: C, 52.19; H, 4.65. Found: C, 52.42; H, 4.58.

3-Iodo-5-[methoxy(phenyl)methyl]-2-phenylfuran (4h)
Colorless oil.

IR (neat): 2930, 2823, 1602, 1485, 1449, 1090 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42 (s, 3 H), 5.28 (s, 1 H), 6.32 (s, 1 H), 7.26–7.47 (m, 8 H), 7.95 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.1, 61.1, 78.6, 118.8, 126.2, 127.1, 128.2, 128.3, 128.5, 130.0, 138.3, 151.8, 154.8.

Anal. Calcd for $C_{18}H_{15}IO_2$: C, 55.40; H, 3.87. Found: C, 55.57; H, 3.95.

2-(4-Bromophenyl)-3-iodo-5-[methoxy(phenyl)methyl]furan (4i)
White solid; mp 96–98 °C.

IR (neat): 2941, 2820, 1617, 1474, 1452, 1073 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.41 (s, 3 H), 5.27 (s, 1 H), 6.31 (s, 1 H), 7.34–7.45 (m, 5 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.80 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.2, 61.8, 78.6, 119.0, 122.2, 127.1, 127.7, 128.4, 128.6, 128.9, 131.5, 138.1, 150.8, 155.2.

Anal. Calcd for $C_{18}H_{14}BrIO_2$: C, 46.07; H, 3.01. Found: C, 46.14; H, 3.01.

2-(4-Chlorophenyl)-3-iodo-5-[methoxy(phenyl)methyl]furan (4j)
White solid; mp 89–91 °C.

IR (neat): 2931, 2822, 1647, 1478, 1453, 1093 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42 (s, 3 H), 5.27 (s, 1 H), 6.31 (s, 1 H), 7.34–7.45 (m, 7 H), 7.86 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.2, 61.7, 78.6, 119.0, 127.1, 127.4, 128.4, 128.5, 128.6, 133.9, 138.2, 150.8, 155.1.

Anal. Calcd for $C_{18}H_{14}ClIO_2$: C, 50.91; H, 3.32. Found: C, 51.03; H, 3.24.

3-Iodo-2-(4-methoxyphenyl)-5-[methoxy(phenyl)methyl]furan (4k)
Colorless oil.

IR (neat): 2934, 2829, 1612, 1494, 1457, 1255 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.42 (s, 3 H), 3.83 (s, 3 H), 5.27 (s, 1 H), 6.27 (s, 1 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 7.33–7.46 (m, 5 H), 7.85 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3, 57.1, 59.9, 113.7, 118.7, 118.7, 122.9, 127.1, 127.9, 128.2, 128.5, 138.4, 152.1, 154.2, 159.5.

Anal. Calcd for $C_{19}H_{17}IO_3$: C, 54.30; H, 4.08. Found: C, 54.22; H, 3.91.

3-Iodo-5-[methoxy(phenyl)methyl]-2-(4-tolyl)furan (4l)
Colorless oil.

IR (neat): 2926, 2822, 1606, 1493, 1452, 1090 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.42 (s, 3 H), 5.3 (s, 1 H), 6.29 (s, 1 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 7.33–7.46 (m, 5 H), 7.80 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 57.1, 60.4, 78.7, 118.7, 126.2, 127.1, 127.3, 128.2, 128.5, 129.0, 138.2, 138.4, 152.1, 154.5.

Anal. Calcd for $C_{19}H_{17}IO_2$: C, 56.45; H, 4.24. Found: C, 56.54; H, 3.95.

3-Iodo-5-(1-methoxyethyl)-2-phenylfuran (4m)
Colorless oil.

IR (neat): 2929, 2820, 1603, 1482, 1444, 1116 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 5.7 Hz, 3 H), 3.34 (s, 3 H), 4.35 (q, 1 H), 6.47 (s, 1 H), 7.31–7.45 (m, 3 H), 7.96 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 56.4, 60.9, 71.9, 117.6, 126.2, 128.1, 128.3, 130.1, 151.3, 155.8.

Anal. Calcd for $C_{13}H_{13}IO_2$: C, 47.58; H, 3.99. Found: C, 47.55; H, 3.84.

7-Methoxy-2-phenyl-3-(phenylethynyl)-4,5,6,7-tetrahydrobenzofuran (7)
Colorless oil.

IR (neat): 2932, 2821, 2211, 1600, 1482, 1444, 1091 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.96 (m, 3 H), 2.10–2.15 (m, 1 H), 2.42–2.50 (m, 1 H), 2.63–2.69 (m, 1 H), 3.55 (s, 3 H), 4.36 (t, *J* = 3.6 Hz, 1 H), 7.25–7.55 (m, 8 H), 8.12 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 21.2, 29.4, 57.0, 70.6, 82.0, 95.5, 103.3, 123.6, 124.9, 127.9, 128.2, 128.4, 128.5, 130.7, 131.4, 149.4, 154.1.

Anal. Calcd for $C_{23}H_{20}IO_2$: C, 84.12; H, 6.24. Found: C, 84.18; H, 6.47.

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