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Cascade Reactions: Catalytic Synthesis of Functionalized 1,3-Dihydroisobenzofuran and Tetrahydrofuran Derivatives by Sequential Nucleophilic Ring Opening–Heterocyclization–Oxidative Carbonylation of Alkynyloxiranes

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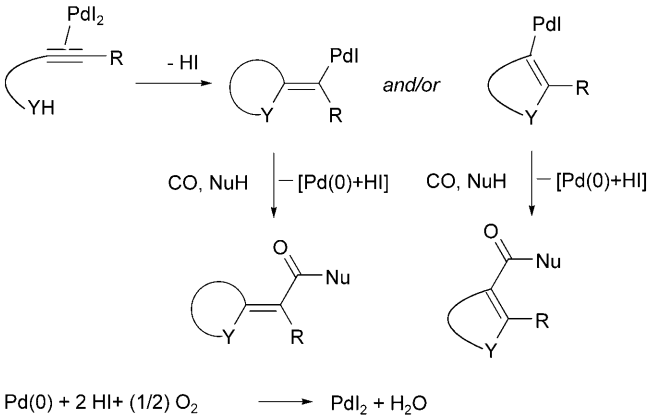
Abstract: Differently substituted alkynyloxiranes were efficiently converted into functionalized 1,3-dihydroisobenzofurans and tetrahydrofuran derivatives in fair to good yields by a new cascade reaction, consisting of a sequential nucleophilic ring opening–heterocyclization–oxidative carbonylation process. Reactions were carried out at 80–100 °C and under a 3:1 mixture of carbon monoxide and air (total pressure = 32–42 atm at 25 °C) in methanol or acetonitrile/methanol mixtures in the presence of catalytic amounts of palladium diiodide in conjunction with an excess of potassium iodide. The nucleophilic species beginning the cascade process by regioselective attack to the less hindered carbon of the oxirane ring can be methanol itself or iodide anions.

Keywords: carbonylation; cyclization; heterocycles; oxiranes; palladium

Introduction

Sequential catalytic reactions offer considerable advantages compared with the conventional synthetic procedures in terms of efficiency, selectivity, atom and energy economy.[1] The application of such processes has proved to be very valuable for performing the synthesis of functionalized five- and six-membered heterocyclic compounds.[2] In particular, we have previously reported the synthesis of a variety of carbonylated heterocycles by a sequential process involving the intramolecular nucleophilic attack to a triple bond coordinated to Pd(II) followed by carbonylation (Scheme 1).[2f,p,3] These reactions are carried out with an acetylenic substrate, bearing a suitably placed oxygen or nitrogen nucleophilic group (such as an alcoholic, amino, carbonyl, amido, or carboxylic group) in the presence of a carbon monoxide/air mixture, an external nucleophile NuH (such as an alcohol or an amine), and a catalytic system based on PdI_2 in conjunction with an excess of KI.[2f,p,3]



Scheme 1. Intramolecular nucleophilic attack to a triple bond followed by a carbonylation step in the presence of PdI_2/KI as catalytic system.

It is well known that a simple ethereal group is not reactive enough to act as a nucleophile in this kind of reactions, because of its high stability under a wide range of reaction conditions. Accordingly, very few examples are known in the literature regarding their use as nucleophiles in metal-catalyzed heterocyclization reactions, limited to substrates of particular reactivity. For example, the higher reactivity of the acetal C–O bond in comparison with that of simple ethers was favorably exploited in the palladium-catalyzed synthesis of indenol ethers from arylalkynes bearing *ortho*-acetals.[4] Similarly, alkynyl derivatives containing an allyl ether group showed good reactivity in the platinum-catalyzed rearrangement of enynes.[5] Selected *o*-alkynylallyloxybenzene derivatives were also advantageously used for palladium-catalyzed allylating–heteroannulation reactions[6] and for sequential homobimetallic palladium-catalyzed heterocyclization reactions.[3a,b]

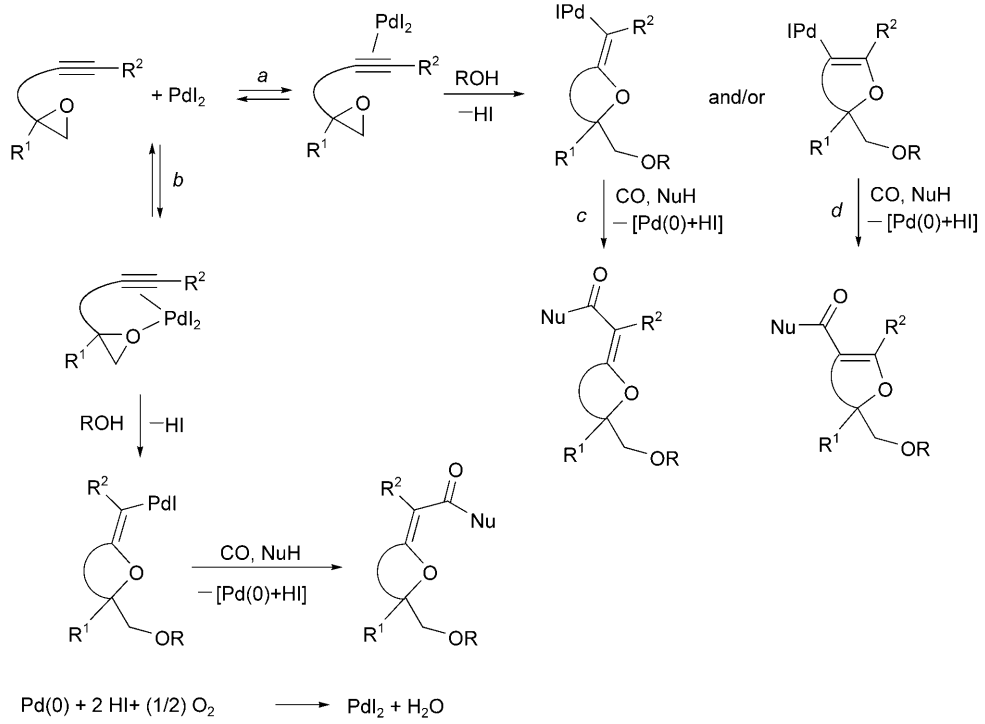
In this work, we have investigated the possibility to use the epoxide function as a potential nucleophile for the PdI_2/KI-catalyzed oxidative cyclization–alkoxycarbonylation reaction of acetylenic substrates.[7] Alkynyloxiranes derivatives have been recently used in reactions affording heterocyclic compounds in the presence of gold and ruthenium catalysts.[8]

The cleavage of an epoxide ring by attack of a nucleophile at the less substituted carbon[9] could favor the intramolecular nucleophilic attack by the epoxide oxygen to the triple bond coordinated to Pd(II), thus affording a heterocyclic organopalladium intermediate. At this point a carbonylation step would complete the process, with formation of the final carbonylated heterocyclic derivative (Scheme 2).

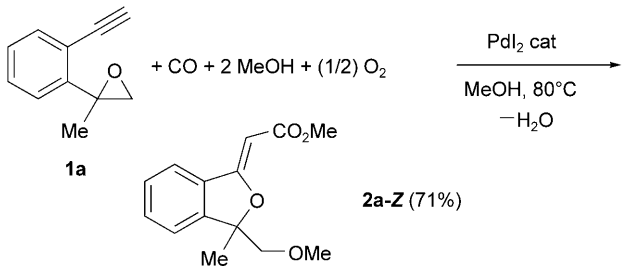
According to the general mechanistic pathways shown in Scheme 1, the nucleophilic attack by the epoxide oxygen may occur in an *anti* fashion, when PdI_2 is coordinated on the opposite site with respect to the epoxide moiety (Scheme 2, path *a*). This would lead to either an *anti-exo-dig* or an *anti-endo-dig* cyclization mode (Scheme 2, paths *c* and *d*, respectively). On the other hand, PdI_2, a Lewis acidic component of our catalytic system, could also assist the epoxide ring cleavage through the formation of a Pd(II)-chelate complex;[10] in this case, a *syn-exo-dig* cyclization would occur (Scheme 2, path *b*).

Results and Discussion

The first experiments were carried out using 2-(2-ethynylphenyl)-2-methyloxirane **1a**, easily prepared in three steps starting from commercially available 1-(2-bromophenyl)ethanone (see the Supporting Information for details). The PdI_2-catalyzed carbonylation of **1a**, carried out in MeOH in the presence of an excess of KI (KI/PdI_2 molar ratio = 10), under 32 bar (at 25 °C) of 3/1 mixture of CO-air at 80 °C for 24 h led to the product **2a-*Z*** in 71% isolated yield (79% by GLC, Scheme 3). The structure of **2a-*Z*** was unequivo-



Scheme 2. Alternative pathways for the oxidative cyclization–alkoxycarbonylation reaction of acetylenic substrates bearing an oxirane moiety.



Scheme 3. Oxidative cyclization–alkoxycarbonylation reaction of 2-(2-ethynylphenyl)-2-methyloxirane **1a**.

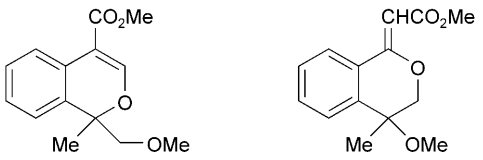


Figure 1. Possible isomers of **2a-*Z*** in the PdI_2/KI-catalyzed oxidative carbonylation of **1a**. See text for details.

cally established by spectroscopic techniques, including NOESY experiments. Small amounts (*ca.* 2%) of the *E* stereoisomer, **2a-*E***, were also detected by GLC and GLC-MS analysis (Table 1, entry 2). The assignment of the geometry around the double bond of the two isomers **2a-*Z*** and **2a-*E*** was based on the chemical shift of the aromatic proton in *ortho* to the double bond (7-H). In the case of the (*Z*) isomer the chemical shift is 7.62 ppm while for (*E*) isomer this proton undergo a significant influence by CO_2Me group and the chemical shift is above 8 ppm. Furthermore ^1H-^1H NOESY experiments show a clear dipolar interaction between the olefinic proton and 7-H only in the case of the (*Z*) isomer.

Formation of **2a-*Z*** clearly corresponds to a *syn*-5-*exo-dig* cyclization pathway, which means that, under the conditions mentioned above, the mechanism shown in Scheme 2, path *b*, is preferentially followed.

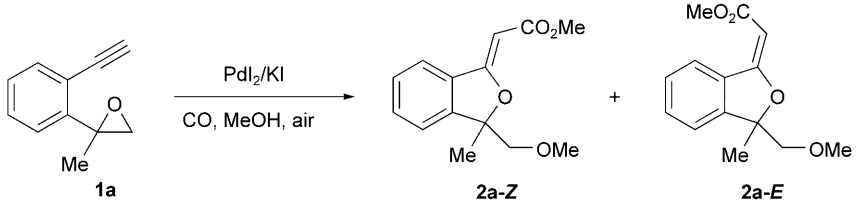
No appreciable interconversion of product **2a-*Z*** to **2a-*E*** occurred under the reaction conditions. Moreover, no formation of isomeric 6-membered products (Figure 1), either deriving from a 6-*endo-dig* pathway (Scheme 2, path *d*) or from an initial nucleophilic attack of MeOH at the more substituted carbon of the epoxide moiety of **1a**, was observed.

Different conditions of temperatures and solvent mixtures for the carbonylation reaction of **1a** were then tested, and the results are shown in Table 1 (entries 3–6). As can be seen, slightly higher yields of **2a-*Z*** and **2a-*E*** (86% and 4% respectively) were observed working at 100 °C in a 4:1 mixture of MeCN-MeOH (entry 6). On the other hand, an increase of the total pressure to 42 atm did not cause a significant effect on yields and selectivities.

In order to expand the synthetic scope of the reaction, a variety of substrates containing different substituents on the triple bond and on the aromatic ring were subjected to the carbonylation conditions optimized for **1a**, either in MeOH or in MeCN-MeOH mixtures, at 80–100 °C. The results obtained are shown in Table 2.

In most cases substrates **1** were converted into the corresponding (*Z*)-1-methoxymethyl-1-methyl-3-(methoxycarbonyl)methylene-1,3-dihydroisobenzofuran derivatives **2-*Z*** along with 1-iodomethyl-1-methyl-3-(methoxycarbonyl)methylene-1,3-dihydroisobenzofur-

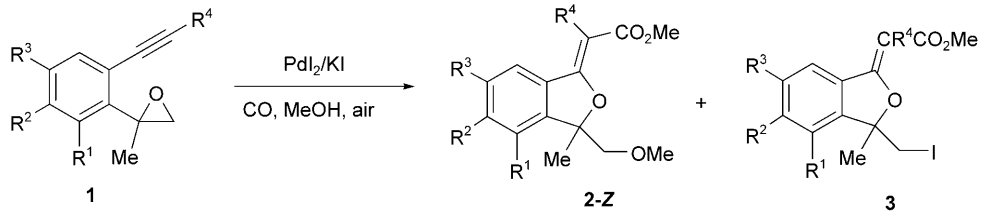
Table 1. Carbonylation reactions of 2-(2-ethynylphenyl)-2-methyloxirane **1a** under different conditions.[a]



Entry	Temperature [°C]	Solvent	Conversion of **1a** [%][b]	Yield of **2a-*Z*** [%][c]	Yield of **2a-*E*** [%][c]
1[d]	80	MeOH	36	28	
2	80	MeOH	94	79 (71)	2
3	100	MeOH	99	52	2
4	80	MeCN-MeOH (17:1)	41	25	
5	80	MeCN-MeOH (4:1)	77	63	
6	100	MeCN-MeOH (4:1)	99	86	4

[a] All reactions were carried out in 4 mL of solvent in the presence of PdI_2 (0.067 mmol), KI (0.67 mmol), **1a** (2.0 mmol) under 32 atm total pressure (at 25 °C) of a 3:1 mixture CO-air for 24 h.
[b] Determined by GLC.
[c] GLC yield (isolated yield) based on starting **1a**.
[d] Reaction time was 8 h.

Table 2. Synthesis of functionalized 1,3-dihydroisobenzofurans *via* PdI_2/KI-catalyzed sequential ring opening–heterocyclization–alkoxycarbonylation of 2-(2-alkynylphenyl)oxiranes **1b–i**.[a]



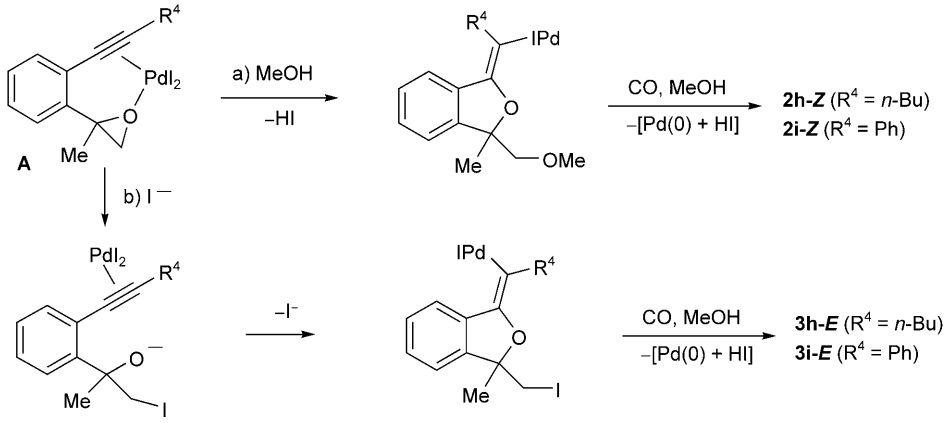
Entry	**1**	R^1	R^2	R^3	R^4	Solvent	Temp. [°C]	Conversion of **1** [%][b]	**2-*Z***	Yield of **2-*Z*** [%][c]	**3-*Z***	Yield of **3-*Z*** [%][c]	**3-*E***	Yield of **3-*E*** [%][c]
1	**1b**	H	H	Me	H	MeOH	80	81	**2b-*Z***	58 (50)	**3b-*Z***	11		
2	**1b**	H	H	Me	H	MeCN-MeOH	100	83	**2b-*Z***	45	**3b-*Z***	16		
3[d]	**1b**	H	H	Me	H	MeCN-MeOH	100	82	**2b-*Z***	47	**3b-*Z***	20 (12)		
4	**1c**	H	OMe	H	H	MeOH	80	91	**2c-*Z***	77 (70)	**3c-*Z***	5		
5	**1c**	H	OMe	H	H	MeCN-MeOH	100	92	**2c-*Z***	46	**3c-*Z***	23		
6[d]	**1c**	H	OMe	H	H	MeCN-MeOH	100	90	**2c-*Z***	34	**3c-*Z***	41 (33)		
7	**1d**	H	F	H	H	MeOH	80	80	**2d-*Z***	35 (28)	**3d-*Z***	25		
8	**1d**	H	F	H	H	MeCN-MeOH	100	83	**2d-*Z***	30	**3d-*Z***	31		
9[d]	**1d**	H	F	H	H	MeCN-MeOH	100	84	**2d-*Z***	24	**3d-*Z***	40 (31)		
10[e]	**1d**	H	F	H	H	MeCN-MeOH	100	70	**2d-*Z***	17	**3d-*Z***	38		
11	**1e**	F	H	H	H	MeOH	80	77	**2e-*Z***	55 (47)				
12	**1f**	H	OMe	OMe	H	MeCN-MeOH	100	81	**2f-*Z***	69 (60)				
13[f]	**1g**	H	H	H	TMS	MeCN-MeOH	100	81	**2a-*Z***[g]	69				
14[h]	**1h**	H	H	H	Bu	MeOH	80	85	**2h-*Z***	36 (27)			**3h-*E***	6
15	**1h**	H	H	H	Bu	MeCN-MeOH	100	76	**2h-*Z***	35			**3h-*E***	20
16[d]	**1h**	H	H	H	Bu	MeCN-MeOH	100	80	**2h-*Z***	35			**3h-*E***	28 (21)
17	**1i**	H	H	H	Ph	MeOH	80	82	**2i-*Z***	25 (19)			**3i-*E***	17
18	**1i**	H	H	H	Ph	MeCN-MeOH	100	83	**2i-*Z***	24			**3i-*E***	23
19[d]	**1i**	H	H	H	Ph	MeCN-MeOH	100	81	**2i-*Z***	23			**3i-*E***	31 (25)

[a] Unless otherwise noted, all reactions were carried out in 4 mL of solvent (pure MeOH or a 4:1 mixture MeCN-MeOH) in the presence of PdI_2 (0.067 mmol), KI (0.67 mmol), **1** (2.0 mmol) under 32 atm total pressure (at 25 °C) of a 3:1 mixture CO-air for 24 h.
[b] Determined by GLC.
[c] GLC yield (isolated yield) based on starting **1**.
[d] KI/PdI_2 molar ratio was 20.
[e] KI/PdI_2 molar ratio was 30.
[f] Reaction time was 36 h.
[g] Desilylation occurred under the reaction conditions, so the product formed was **2a-*Z***.
[h] The reaction also led to the formation of 2-(2-hex-1-ynylphenyl)-2-methoxypropan-1-ol **4h** in 35% GLC yield (25% isolated).

an derivatives **3** (Table 2). These latter products clearly derive from an initial nucleophilic attack by the iodide anion on the epoxide ring.[11] It was proved that the formation of methoxylated and iodinated products derive from two competing pathways which predominate over each other depending on the reaction conditions and substrate structures. As expected, formation of **3** became more favored by increasing the KI concentration (entries 3, 6, 9, 16, and 19). Thus an increase of the KI/PdI_2 molar ratio to 30:1, led to higher selectivity towards product **3**, but depressed the reaction conversion as shown in entries 9 and 10.

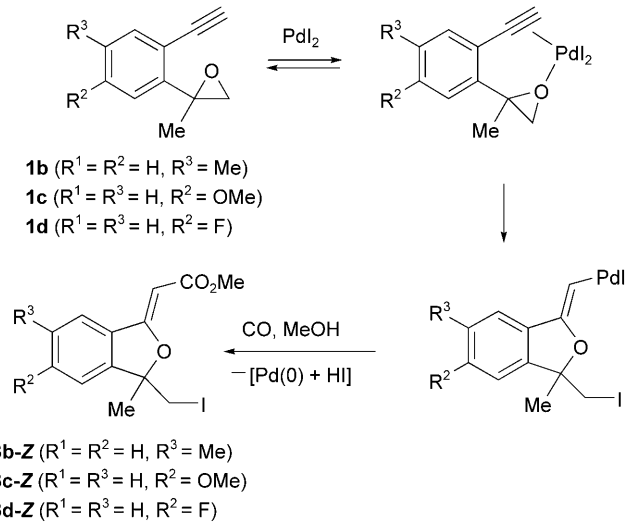
As can be seen from Table 2, entries 13–19, substrates bearing an internal triple bond, such as **1g** (R^4 = TMS), **1h** (R^4 = *n*-Bu), and **1i** (R^4 = Ph), led to less satisfactory results with respect to substrates bearing a terminal triple bond **1a–f** (R^4 = H) (Table 1, entries 2 and 6, and Table 2, entries 1–12). This can be explained on the basis of steric effects lowering coordination ability to PdI_2 of an internal triple bond compared to a terminal triple bond.[2f,p,q,3] As we already observed in other PdI_2-catalyzed oxidative carbonylations,[2f,p,q,3] desilylation occurred in the case of trimethylsilyl-substituted substrate **1g** (R^4 = TMS), with selective formation of the dihydroisobenzofuran derivative **2a-*Z*** (R^4 = H) in 69% yield (entry 13).

Interestingly, substrates such as **1h** and **1i**, substituted with an alkyl or a phenyl group in the triple bond,



Scheme 4. Attack of MeOH (path *a*) or I^- anion (path *b*) in the presence of a substituent on the triple bond ($R^4 = n$-Bu or Ph).

afforded the corresponding iodinated products with *E* rather than *Z* stereochemistry (**3h-*E*** and **3i-*E***, respectively). This could be related to the remarkable steric hindrance of the chelate complex **A**; in case of I^- anion attack to the epoxide ring (Scheme 4, path *b*), PdI_2 is forced to rotate around the triple bond in an *anti* mode to the oxirane moiety. As a consequence, a benzyl alkoxide intermediate is formed, which, as expected,[3e] selectively undergoes *anti*-5-*exo-dig* cyclization to give the final product with *E* geometry. If MeOH attacks the oxirane unit, HI elimination can reduce the steric hindrance in complex **A** thus leading to the *Z* isomer (Scheme 4, path *a*). On the other hand, in the absence of a substituent on the triple bond ($R^4 = H$), iodide attack occurs after chelation to PdI_2, thus leading to the product with *Z* geometry (Scheme 5). This is confirmed by the structure of product **3d-*Z*** determined by single crystal X-ray diffraction analysis (Figure 2).[12]



Scheme 5. Formation pathway of **3b–d-*Z*** compounds.

In the case of substrate **1h** ($R^4 = n$-Bu), under the conditions of entry 14 (Table 2), a non-cyclized product **4h**, corresponding to MeOH attack on the more substituted carbon of the epoxide moiety (Scheme 6), was also isolated from the reaction mixture in 25% yield. This result shows that neither a 6-*exo-dig* cyclization nor a 7-*endo-dig* cyclization is favored under the reaction conditions.

With the aim of expanding the scope of the reaction, we also tested the reactivity of a non-cyclic epoxyalkyne substrate, such as 2-ethyl-2-(2-methyloxiranyl)pent-4-ynoic acid methyl ester **5**. Thus, the oxidative carbonylation of **5** (1 mmol), carried out at 85 °C in a 1:1 mixture of MeCN-MeOH (2 mL total) in the presence of PdI_2 (0.033 mmol) and KI (0.66 mmol) under 42 atm (at 25 °C) of a 17:4 mixture of CO-air, led to the desired 5-[(methoxycarbonyl)methylene]tetrahydrofuran derivatives **6** and **7** in fairly good total isolated yield (53%, Scheme 7).

This result is noteworthy, if one considers the significantly higher conformational mobility of **5** as compared to that of substrates **1**. The higher conformational mobility of **5** with respect to **1** may, however, be responsible for the observed *E* stereochemistry around the exocyclic double bond of both **6** and **7**. In fact, this mobility may prevent chelation of the oxirane oxygen and the triple bond to PdI_2, thus hindering a 5-*endo-dig* mechanism. As a consequence, the *anti*-5-*exo-dig* pathway becomes favored, leading to the final products with *E* geometry (Scheme 8).

Finally, we tested amines instead of alcohols as nucleophiles in our new cascade reaction. When substrate **1a** was allowed to react in MeCN at 100 °C for 24 h, in the presence of piperidine (piperidine:**1a** molar ratio = 3:1), PdI_2 (3.3 mol%) and KI (KI/PdI_2 molar ratio = 20), under 40 atm (at 25 °C) of a 4:1 mixture CO-air, [2-(3-iodomethyl-3-methyl-3*H*-isobenzofuran-1-ylidene)-1-piperidin-1-yl]ethanone **8** was selectively obtained in 49% isolated yield

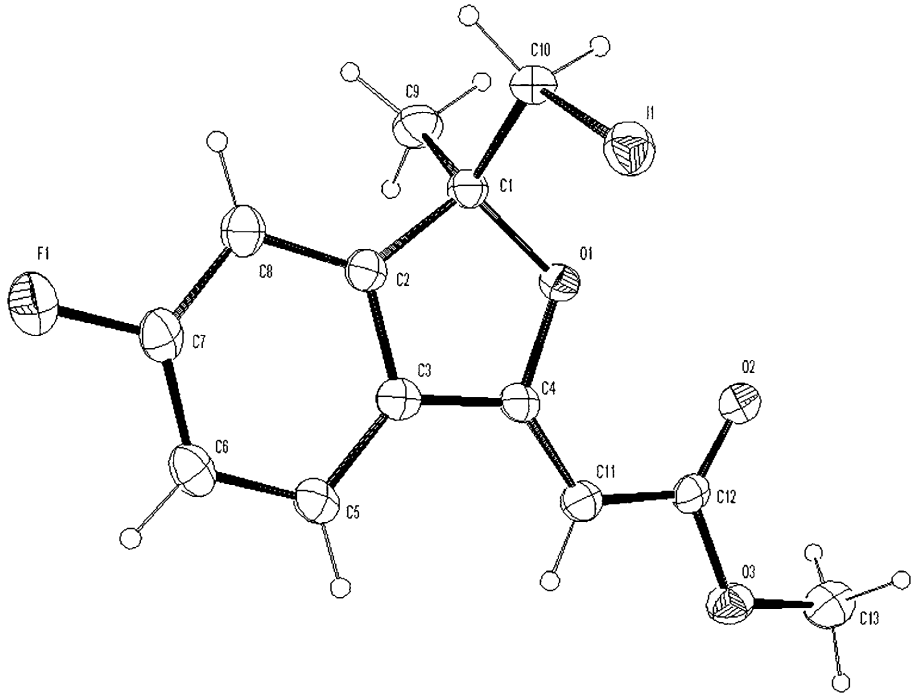
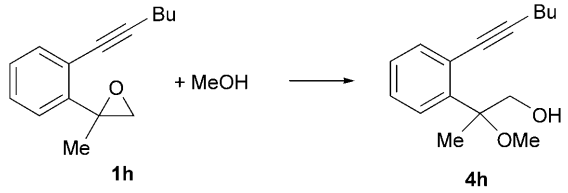
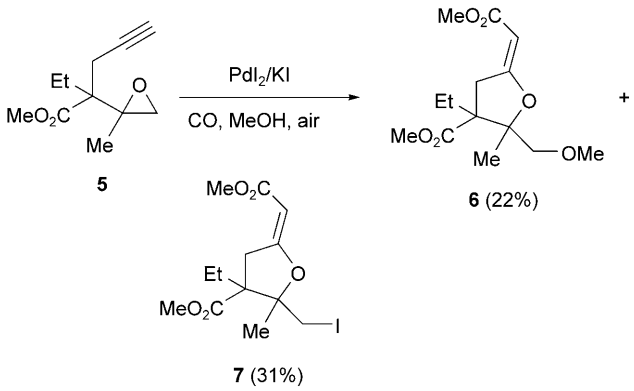


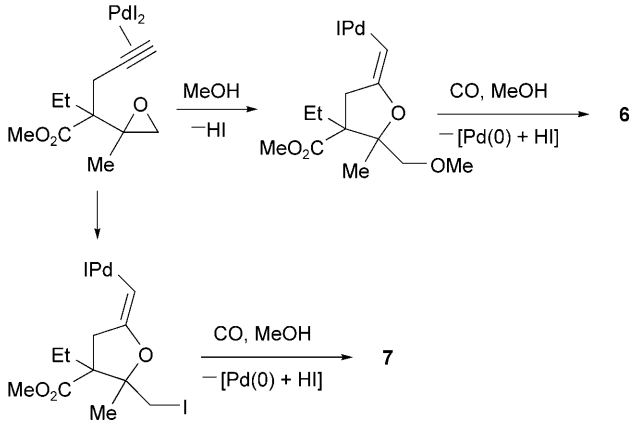
Figure 2. ORTEP view and labelling scheme for compound **3d-*Z***.



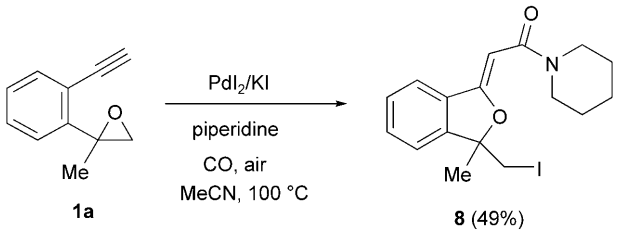
Scheme 6. MeOH attack to the more substituted carbon of **1h**.



Scheme 7. Oxidative cyclization–alkoxycarbonylation reaction of **5**.



Scheme 8. Formation pathway of **6** and **7**.



Scheme 9. Oxidative cyclization–aminocarbonylation reaction of **1a**.

(Scheme 9). This result shows that, under these conditions, ring opening of the epoxide ring is initiated by the iodide anion, while the amine intervenes in the final aminocarbonylation step.

Conclusions

Summing up, we have demonstrated that highly functionalized 1,3-dihydroisobenzofuran and tetrahydro-

furan derivatives can be successfully obtained in one step from alkynyloxiranes through a novel sequential nucleophilic ring opening–heterocyclization–oxidative carbonylation process, catalyzed by PdI_2 in conjunction with an excess of KI. Different mechanistic pathways may be at work, depending on the nature of the substrate and the nucleophile, and on reaction conditions. This new cascade reaction allows a direct entry to these important classes of heterocyclic derivatives, which would be difficult to synthesize by "classical" approaches not involving organometallic catalysis.

Experimental Section

General Remarks

Solvents and chemicals were reagent grade and were used without further purification. MeCN was dried over 3 Å molecular sieves and stored under nitrogen. All reactions were analyzed by TLC and by GLC using a 30 m SE-30 capillary column. Column chromatography was performed on silica gel 60 (70–230 mesh). Melting points were measured with an Electrothermal apparatus and are uncorrected. Electron impact mass spectra [*m/z*, relative intensity (%)] were determined with a GC-MS apparatus at 70 eV ionization energy. Infrared (IR) spectra were recorded on an FT-IR 5700 spectrophotometer. Elemental analyses were performed at our analytical laboratory. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, using the solvent as internal standard (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. The reported configurations (*E* or *Z*) were assigned on the basis of decoupling, COSY, and NOESY correlation experiments, and of X-ray diffraction analysis for compound **3d-*Z***.

General Procedure for the Catalytic Synthesis of 1,3-Dihydroisobenzofuran Derivatives 2 and 3 by Sequential Nucleophilic Ring Opening–Heterocyclization–Oxidative Methoxycarbonylation of 2-(2-Alkynylphenyl)oxiranes 1a–i (Tables 1 and 2)

A 45-mL stainless steel autoclave was charged with PdI_2 (24.0 mg, 0.067 mmol), KI (111 mg, 0.67 mmol, or 222 mg, 1.34 mmol - see Tables 1 and 2) and a solution of **1** (2 mmol) in pure MeOH or in a 4:1 MeCN/MeOH mixture (4 mL of solvent – see Tables 1 and 2). The autoclave was then sealed. While the mixture was stirred, the autoclave was charged with CO (24 atm) and air (up to 32 atm), and then heated at the required temperature (80 or 100 °C) for 24 h–36 h (see Tables 1 and 2). After cooling, the autoclave was degassed and opened. The solvent was evaporated under reduced pressure, and products **2** and **3** were separated by column chromatography (SiO_2) using suitable mixtures of hexane-EtOAc as eluent (see the characterization data for products for details regarding the eluent and for the yields obtained in each case).

General Procedure for the Catalytic Synthesis of Tetrahydrofuran Derivatives 6 and 7 by Sequential Nucleophilic Ring Opening–Heterocyclization–Oxidative Methoxycarbonylation of 2-Ethyl-2-(2-methyloxiranyl)pent-4-ynoic Acid Methyl Ester 5

A 45-mL stainless steel autoclave was charged with PdI_2 (12.0 mg, 0.033 mmol), KI (111 mg, 0.67 mmol) and a solution of **5** (196 mg, 1 mmol) in a 1:1 MeCN/MeOH mixture (2 mL of solvent). The autoclave was then sealed. While the mixture was stirred, the autoclave was charged with CO (34 atm) and air (up to 42 atm), and then heated at 85 °C) for 24 h. After cooling, the autoclave was degassed and opened. The solvent was evaporated under reduced pressure and products **6** (pale yellow oil, yield: 63 mg, 22%) and **7** (pale yellow oil, yield: 119 mg, 31%) were separated by column chromatography (SiO_2) using 40:60 hexane-EtOAc as eluent.

General Procedure for the Catalytic Synthesis of 2-(3-Iodomethyl-3-methyl-3*H*-isobenzofuran-1-ylidene)-1-piperidin-1-ylethanone 8 by Sequential Nucleophilic Ring Opening–Heterocyclization–Oxidative Aminocarbonylation of 2-(2-Ethynylphenyl)-2-methyloxirane 1a

A 45-mL stainless steel autoclave was charged with PdI_2 (24.0 mg, 0.067 mmol), KI (222 mg, 1.34 mmol) and a solution of **1a** (316 mg, 2 mmol) and piperidine (510 mg, 6 mmol) in pure MeCN (4 mL). The autoclave was then sealed. While the mixture was stirred, the autoclave was charged with CO (32 atm) and air (up to 40 atm), and then heated at 100 °C for 24 h. After cooling, the autoclave was degassed and opened. The solvent was evaporated under reduced pressure and product **8** was separated by column chromatography (SiO_2) using 85:15 hexane-EtOAc as eluent: yield: 390 mg (49%).

(*Z*)-3-Methoxycarbonylmethylene-1-methoxymethyl-1-methyl-3*H*-isobenzofuran (2a-*Z*): Yield: 71% (Table 1, entry 2); eluent: hexane-EtOAc 90:10; pale yellow oil. IR (film): $\nu = 2941$ (m), 1715 (s), 1621 (s), 1463 (m), 1100 (s), 810 (m), 772 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.62$ (further split d, $J = 7.9$ Hz, 1H, CH aromatic), 7.50–7.42 (m, 2H, CH aromatic), 7.33 (ddd, $J = 7.9$, 7.0, 1.9 Hz, 1H, CH aromatic), 5.64 (s, 1H, C=CH), 4.34 (d, $J = 11.1$ Hz, 1H, C*H*H), 4.10 (d, $J = 11.1$ Hz, 1H, CH*H*), 3.70 (s, 3H, CO_2CH_3), 3.16 (s, 3H, OCH_3), 1.50 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 166.0$, 161.2, 138.1, 130.7, 128.4, 127.8, 125.5, 124.8, 92.7, 71.5, 71.1, 51.1, 50.7, 20.6; MS: $m/z = 248$ (M^+, 85), 233 (38), 217 (57), 203 (80), 185 (41), 159 (95), 144 (50), 129 (100), 115 (91), 101 (33), 79 (27), 59 (25); anal. calcd. for $C_{14}H_{16}O_4$: C 67.73, H 6.50; found: C 67.84, H 6.56.

(*Z*)-3-Methoxycarbonylmethylene-1-methoxymethyl-1,5-dimethyl-3*H*-isobenzofuran (2b-*Z*): Yield: 50% (Table 2, entry 1); eluent: hexane-EtOAc 90:10; pale yellow oil. IR (film): $\nu = 2945$ (m), 1715 (s), 1625 (s), 1607 (s), 1434 (m), 1102 (s), 821 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.45$ (br s, 1H, CH aromatic), 7.37 (d, $J = 7.9$ Hz, 1H, CH aromatic), 7.27 (further split d, $J = 7.9$ Hz, 1H, CH aromatic), 5.63 (s, 1H, C=CH), 4.34 (d, $J = 11.0$ Hz, 1H, C*H*H), 4.07 (d, $J = 11.0$ Hz, 1H, CH*H*), 3.70 (s, 3H, CO_2CH_3), 3.14 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3), 1.48 (s, 3H, CH_3); ^{13}C NMR

($CDCl_3$): δ = 166.1, 161.5, 138.3, 134.9, 131.6, 127.6, 126.0, 124.9, 92.4, 71.8, 70.9, 51.1, 50.8, 21.2, 20.4; MS: *m/z* = 262 (M^+, 100), 247 (61), 231 (63), 217 (65), 199 (52), 185 (28), 173 (96), 158 (50), 143 (73), 129 (65), 128 (98), 115 (85), 91 (21), 59 (20); anal. calcd. for $C_{15}H_{18}O_4$: C 68.68, H 6.92; found: C 68.83, H 6.99.

(*Z*)-1-(Iodomethyl)-3-methoxycarbonylmethylene-1,5-dimethyl-3*H*-isobenzofuran (3b-*Z*): Yield: 12% (Table 2, entry 3); eluent: hexane-EtOAc 90:10; pale yellow oil. IR (film): ν = 2930 (m), 1719 (s), 1621 (s), 1603 (s), 1421 (m), 1100 (s), 794 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.42 (s further split, 1H, CH aromatic), 7.33 (d, *J* = 7.8 Hz, 1H, CH aromatic), 7.26 (d further split, *J* = 7.8 Hz, 1H, CH aromatic), 5.61 (s, 1H, C=CH), 3.79 (s, 3H, CO_2CH_3), 3.58 (d, *J* = 10.6 Hz, 1H, C*H*HI), 3.45 (d, *J* = 10.6 Hz, 1H, CH*H*I), 2.34 (s, 3H, CH_3), 1.71 (s, 3H, CH_3); MS: *m/z* = 358 (M^+, 8), 217 (100), 199 (32), 185 (18), 172 (26), 141 (14), 128 (35), 115 (26), 59 (7); anal. calcd. for $C_{14}H_{15}IO_3$: C 46.95, H 4.22; found: C 46.83, H 4.17.

(*Z*)-6-Methoxy-3-methoxycarbonylmethylene-1-methoxymethyl-1-methyl-3*H*-isobenzofuran (2c-*Z*): Yield: 70% (Table 2, entry 4); eluent: hexane-EtOAc 85:15; pale yellow oil. IR (film): ν = 2946 (m), 2837 (w), 1713 (s), 1601 (s), 1492 (m), 1288 (m), 1253 (m), 1160 (s), 1101 (s), 808 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.56 (d, *J* = 8.7 Hz, 1H, CH aromatic), 6.97 (d, *J* = 2.6 Hz, 1H, CH aromatic), 6.84 (dd, *J* = 8.7, 2.6 Hz, 1H, CH aromatic), 5.51 (s, 1H, C=CH), 4.28 (d, *J* = 10.9 Hz, 1H, C*H*H), 4.11 (d, *J* = 10.9 Hz, 1H, CH*H*), 3.83 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 1.47 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ = 166.2, 161.8, 140.5, 131.8, 127.5, 120.0, 114.3, 109.5, 90.8, 71.3, 71.2, 55.4, 51.2, 50.7, 21.3; MS: *m/z* = 278 (M^+, 100), 263 (9), 247 (45), 233 (31), 220 (30), 201 (14), 189 (31), 175 (25), 159 (33), 145 (15), 115 (15), 59 (13); anal. calcd. for $C_{15}H_{18}O_5$: C 64.74, H 6.52; found C 64.86, H 6.57.

(*Z*)-1-Iodomethyl-6-methoxy-3-methoxycarbonylmethylene-1-methyl-3*H*-isobenzofuran (3c-*Z*): Yield: 33% (Table 2, entry 6); eluent: hexane-EtOAc 85:15: pale yellow oil. IR (film): ν = 2945 (m), 1718 (s), 1607 (s), 1497 (m), 1279 (m), 1250 (m), 1168 (s), 1104 (s), 803 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.53 (d, *J* = 8.6 Hz, 1H, CH aromatic), 6.95 (d, *J* = 2.6 Hz, 1H, CH aromatic), 6.83 (dd, *J* = 8.6, 2.6 Hz, 1H, CH aromatic), 5.49 (s, 1H, C=CH), 3.81 (s, 3H, CO_2CH_3), 3.68 (s, 3H, OCH_3), 3.55 (d, *J* = 10.7 Hz, 1H, C*H*HI), 3.43 (d, *J* = 10.7 Hz, 1H, CH*H*I), 1.71 (s, 3H, CH_3); MS: *m/z* = 374 (M^+, 25), 343 (9), 233 (100), 215 (10), 201 (14), 191 (18), 159 (14), 145 (15), 115 (19); anal. calcd for $C_{14}H_{15}IO_4$: C 44.94, H 4.04; found: C 45.12, H 4.09.

(*Z*)-6-Fluoro-3-methoxycarbonylmethylene-1-(methoxymethyl)-1-methyl-3*H*-isobenzofuran (2d-*Z*): Yield: 28% (Table 2, entry 7); eluent: hexane-EtOAc 90:10. ^1H NMR ($CDCl_3$): δ = 7.65 (dd, *J* = 8.9, 5.2 Hz, 1H, CH aromatic), 7.21 (dd, *J* = 9.0, 2.7 Hz, 1H, CH aromatic), 7.05 (td, *J* = 8.7, 2.8 Hz, 1H, CH aromatic), 5.59 (s, 1H, C=CH), 4.31 (d, *J* = 11.0 Hz, 1H, C*H*H), 4.16 (d, *J* = 11.0 Hz, 1H, CH*H*), 3.72 (s, 3H, CO_2CH_3), 3.22 (s, 3H, OCH_3), 1.51 (s, 3H, CH_3); MS: *m/z* = 266 (M^+, 100), 251 (31), 235 (68), 221 (77), 203 (36), 189 (32), 177 (69), 162 (48), 147 (78), 133 (67), 59 (25); anal. calcd. for $C_{14}H_{15}FO_4$: C 63.15, H 5.58; found: C 63.26, H 5.53.

(*Z*)-6-Fluoro-1-iodomethyl-3-methoxycarbonylmethylene-1-methyl-3*H*-isobenzofuran (3d-*Z*): Yield: 31% (Table 2, entry 9); eluent: hexane-EtOAc 90:10. ^1H NMR ($CDCl_3$): δ = 7.53 (dd, *J* = 8.5, 4.6 Hz, 1H, CH aromatic), 7.15 (td, *J* = 8.4, 2.3 Hz, 1H, CH aromatic), 7.07 (dd, *J* = 7.8, 2.1 Hz, 1H, CH aromatic), 5.43 (s, 1H, C=CH), 3.74 (s, 3H, CO_2CH_3), 3.66 (d, *J* = 10.9 Hz, 1H, C*H*H), 3.60 (d, *J* = 10.9 Hz, 1H, CH*H*), 1.87 (s, 3H, CH_3); MS: *m/z* = 362 (M^+, 21), 331 (11), 221 (100), 189 (15), 133 (19); anal. calcd. for $C_{13}H_{12}FIO_3$: C 43.12, H 3.34; found: C 42.97, H 3.29.

(*Z*)-7-Fluoro-3-methoxycarbonylmethylene-1-methoxymethyl-1-methyl-3*H*-isobenzofuran (2e-*Z*): Yield: 47%; eluent: hexane-EtOAc 90:10 (Table 2, entry 11). ^1H NMR ($CDCl_3$): δ = 7.50 (dd, *J* = 8.0, 1.0 Hz, 1H, CH aromatic), 7.36 (td, *J* = 8.1, 5.2 Hz, 1H, CH aromatic), 7.16 (ddd, *J* = 10.9, 8.1, 1.0 Hz, 1H, CH aromatic), 5.66 (s, 1H, C=CH), 4.37 (d, *J* = 11.6 Hz, 1H, C*H*H), 4.02 (d, *J* = 11.6 Hz, 1H, CH*H*), 3.73 (s, 3H, CO_2CH_3), 3.22 (d, *J* = 0.9 Hz, 3H, OCH_3), 1.64 (d, *J* = 3.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ = 165.9, 160.8 (d, $J_{C,F}$ = 249.4 Hz), 130.0 (d, $J_{C,F}$ = 8.9 Hz), 129.7 (d, $J_{C,F}$ = 9.1 Hz), 121.7 (d, $J_{C,F}$ = 3.4 Hz), 121.6 (d, $J_{C,F}$ = 2.6 Hz), 118.3 (d, $J_{C,F}$ = 23.7 Hz), 116.2 (d, $J_{C,F}$ = 23.3 Hz), 94.3, 72.6, 68.1, 51.5, 50.9, 20.2 (d, $J_{C,F}$ = 7.9 Hz); MS: *m/z* = 266 (M^+, 63), 251 (24), 235 (42), 221 (100), 203 (33), 189 (27), 177 (52), 165 (29), 147 (52), 133 (46), 88 (20), 59 (12); anal. calcd. for $C_{14}H_{15}FO_4$: C 63.15, H 5.58; found: C 63.31, H 5.61.

(*Z*)-5,6-Dimethoxy-3-methoxycarbonylmethylene-1-methoxymethyl-1-methyl-3*H*-isobenzofuran (2f-*Z*): Yield: 60%; eluent: hexane-EtOAc 85:15 (Table 2, entry 12): pale yellow oil. IR (film): ν = 2940 (m), 1710 (s), 1600 (s), 1512 (s), 1465 (m), 1274 (s), 1159 (s), 1102 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.02 (s, 1H, CH aromatic), 6.92 (s, 1H, CH aromatic), 5.50 (s, 1H, C=CH), 4.29 (d, *J* = 11.0 Hz, 1H, C*H*H), 4.11 (d, *J* = 11.0 Hz, 1H, CH*H*), 3.91 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 1.47 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ = 166.1, 161.4, 151.8, 148.8, 132.4, 120.0, 107.4, 106.8, 91.1, 71.4, 71.0, 56.0, 55.9, 51.3, 50.8, 21.8; MS: *m/z* = 308 (M^+, 100), 293 (55), 277 (75), 245 (73), 219 (33), 189 (41), 175 (20), 59 (12); anal. calcd. for $C_{16}H_{20}O_6$: C 62.33, H 6.54; found: C 62.48, H 6.58.

(*Z*)-3-[(2-Butyl-2-methoxycarbonyl)methylene]-1-methoxymethyl-1-methyl-3*H*-isobenzofuran (2h-*Z*): Yield: 27%; eluent: hexane-EtOAc 90:10 (Table 2, entry 14); pale yellow oil. IR (film): ν = 2955 (s), 2930 (s), 2871 (s), 1711 (s), 1619 (m), 1460 (s), 1283 (m), 1117 (s), 1082 (s), 763 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.44–7.41 (m, 1H, CH aromatic), 7.38–7.31 (m, 2H, CH aromatic), 7.27–7.24 (m, 1H, CH aromatic), 4.17 (d, *J* = 10.8 Hz, 1H, C*H*H), 3.84 (d, *J* = 10.8 Hz, 1H, CH*H*), 3.57 (s, 3H, CO_2CH_3), 3.16 (s, 3H, OCH_3), 2.50 (t, *J* = 7.6 Hz, 2H, C=CCH_2), 1.51 (s, 3H, CH_3), 1.51–1.35 (m, 4H, CH_2CH_2), 0.92 (t, *J* = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ = 171.1, 160.9, 137.7, 129.2, 128.9, 128.8, 127.0, 123.8, 105.9, 72.3, 71.6, 51.2, 51.1, 30.6, 27.5, 22.3, 19.0, 13.9; MS: *m/z* = 304 (M^+, 10), 272 (14), 229 (100), 201 (30), 186 (20), 171 (22), 156 (16), 143 (30), 128 (21), 115 (35), 59 (55); anal. calcd. for $C_{18}H_{24}O_4$: C 71.03, H 7.95; found: C 71.11, H 8.01.

(*E*)-3-[(2-Butyl-2-methoxycarbonyl)methylene]-1-iodomethyl-1-methyl-3*H*-isobenzofuran (3h-*E*): Yield: 21% (Table 2, entry 16); eluent: hexane-EtOAc 90:10; pale yellow oil. IR (film): ν = 2953 (s), 2928 (s), 2868 (m), 1703 (s), 1613 (s), 1463 (s), 1444 (m), 1096 (s), 1054 (m), 952 (m), 763 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.66–8.63 (m, 1H, CH

aromatic), 7.44–7.38 (m, 2H, CH aromatic), 7.26–7.22 (m, 1H, CH aromatic), 3.81 (s, 3H, CO_2CH_3), 3.58 (d, J= 10.6 Hz, 1H, C*H*HI), 3.45 (d, J=10.6 Hz, 1H, CH*H*I), 2.55 (t, J=7.0 Hz, 2H, C=CCH_2), 1.75 (s, 3H, CH_3), 1.58–1.35 (m, 4H, CH_2CH_2), 0.94 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=169.2, 162.0, 147.4, 131.5, 130.1, 128.8, 127.2, 120.3, 106.7, 85.6, 51.1, 31.0, 27.9, 25.6, 22.6, 14.2, 14.0; MS: m/z=400 (M^+, 10), 369 (5), 357 (25), 259 (100), 212 (40), 170 (18), 144 (22), 115 (41), 59 (10); anal. calcd. for $C_{17}H_{21}O_3I$: C 51.01, H 5.29; found: C 51.17, H 5.34.

2-[2-(Hex-1-ynyl)phenyl]-2-methoxypropan-1-ol (4h): Yield: 25% (Table 2, entry 14); eluent: hexane-EtOAc 90:10; pale yellow oil. IR (film): ν=3448 (m), 2929 (s), 2871 (s), 2225 (w), 1461 (m), 1259 (m), 1075 (s), 1032 (s), 760 (s) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=7.42 (dd, J=7.8, 1.5 Hz, 1H, CH aromatic), 7.36 (dd, J=7.8, 1.7 Hz, 1H, CH aromatic), 7.28 (td, J=7.8, 1.7 Hz, 1H, CH aromatic), 7.20 (td, J=7.8, 1.5 Hz, 1H, CH aromatic), 4.55 (t, J=5.6 Hz, 1H, OH), 3.83 (dd, J=11.2, 5.6 Hz, 1H, C*H*H-OH), 3.67 (dd, J=11.2, 5.6 Hz, 1H, CH*H*-OH), 3.10 (s, 3H, OCH_3), 2.43 (t, J= 6.8 Hz, 2H, ≡C-CH_2), 1.60 (s, 3H, CH_3), 1.56–1.41 (m, 4H, CH_2CH_2), 0.91 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6): δ=144.1, 134.3, 127.5, 127.2, 126.5, 121.1, 94.5, 80.7, 80.0, 66.1, 49.7, 30.0, 21.3, 20.0, 18.5, 13.3; MS: m/z=246 (M^+, 2), 215 (100), 159 (41), 128 (20), 115 (15); anal. calcd. for $C_{16}H_{22}O_2$: C 78.01, H 9.00; found: C 77.88, H 8.96.

(*Z*)-3-[(2-Methoxycarbonyl-2-phenyl)methylene]-1-methoxymethyl-1-methyl-3*H*-isobenzofuran (2i-*Z*): Yield: 19% (Table 2, entry 17); eluent: hexane-EtOAc 90:10; pale yellow oil. IR (film): ν=2971 (s), 2944 (s), 1703 (s), 1611 (m), 1442 (s), 1272 (m), 1083 (s), 775 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.47–7.32 (m, 3H, CH aromatic), 7.29–7.23 (m, 2H, CH aromatic), 7.20–7.03 (m, 4H, CH aromatic), 4.13 (d, J=10.9 Hz, 1H, C*H*H), 3.88 (d, J=10.9 Hz, 1H, CH*H*), 3.78 (s, 3H, CO_2CH_3), 3.21 (s, 3H, OCH_3), 1.70 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=168.7, 159.1, 141.8, 132.6, 128.7, 128.0, 127.7, 126.4, 126.3, 126.2, 126.0, 120.6, 104.8, 73.1, 71.9, 52.2, 51.9, 21.5; MS: m/z=324 (M^+, 45), 279 (100), 233 (15), 205 (36), 191 (24), 175 (39), 115 (25), 77 (20), 59 (15); anal. calcd. for $C_{20}H_{20}O_4$: C 74.06, H 6.21; found: C 73.95, H 6.23.

(*E*)-1-(Iodomethyl)-3-[(1-methoxycarbonyl-2-phenyl)methylene]-1-methyl-3*H*-isobenzofuran (3i-*E*): Yield: 25% (Table 2, entry 19); eluent: hexane-EtOAc 90:10; pale yellow oil. IR (film): ν=2962 (s), 1700 (s), 1596 (m), 1413 (m), 1263 (s), 1060 (s), 1027 (s), 864 (m), 793 (s), 742 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=8.43–8.40 (m, 1H, CH aromatic), 7.51–7.43 (m, 4H, CH aromatic), 7.40–7.35 (m, 2H, CH aromatic), 7.30–7.26 (m, 2H, CH aromatic), 3.80 (s, 3H, CO_2CH_3), 3.57 (d, J=10.7 Hz, 1H, C*H*HI), 3.49 (d, J= 10.7 Hz, 1H, CH*H*I), 1.72 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=169.0, 160.3, 147.5, 135.9, 131.6, 130.6, 129.8, 129.0, 127.8, 126.6, 126.3, 120.4, 106.8, 86.9, 51.8, 25.3, 13.8; MS: m/z= 420 (M^+, 33), 279 (100), 234 (10), 205 (17), 191 (15), 115 (20), 77 (10), 59 (9); anal. calcd. for $C_{19}H_{17}O_3I$: C 54.30, H 4.08; found: C 54.21, H 4.12.

(*E*)-3-Ethyl-5-(methoxycarbonylmethylene)-2-methoxymethyl-2-methyltetrahydrofuran-3-carboxylic acid methyl ester (6): Yield: 22% (Scheme 7); eluent: hexane-CH_2Cl_2 40:60; pale yellow oil. IR (film): ν=2954 (m), 1730 (s), 1704 (s), 1644 (s), 1434 (m), 1359 (m), 1258 (m), 1122 (s), 1094 (s), 1024 (s), 798 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=5.25 (t, J=1.5 Hz, 1H, C=CH), 3.69 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.63–3.55 (m, 2H), 3.41–3.33 (m, 2H), 3.23 (s, 3H, OCH_3), 1.95–1.86 (m, 1H, C*H*HCH_3), 1.47–1.34 (m, 1H, CH*H*CH_3), 1.37 (s, 3H, CH_3), 0.86 (t, J=7.4 Hz, 3H, CH_2CH_3); MS: m/z=286 (M^+, 14), 255 (16), 241 (28), 227 (14), 209 (100), 181 (18), 69 (11), 59 (10); anal. calcd. for $C_{14}H_{22}O_6$: C 58.73, H 7.74; found: C 58.87, H 7.69.

(*E*)-3-Ethyl-2-iodomethyl-5-(methoxycarbonylmethylene)-2-methyltetrahydrofuran-3-carboxylic acid methyl ester (7): Yield: 31% (Scheme 7); eluent: hexane-CH_2Cl_2 40:60; pale yellow oil. IR (film): ν=2948 (s), 2880 (s), 1735 (s), 1706 (s), 1650 (s), 1435 (s), 1358 (s), 1241 (m), 1125 (s), 825 (m), 730 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=5.35 (t, J=1.6 Hz, 1H, C=CH), 3.73 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.58 (further split d, J=13.6 Hz, 1H), 3.37 (dd, J=13.6, 1.4 Hz, 1H), 3.30 (further split d, J=10.9 Hz, 1H, C*H*HI), 3.15 (d, J= 10.9 Hz, 1H, C*H*HI), 2.08–1.94 (m, 1H, C*H*HCH_3), 1.55 (s, 3H, CH_3), 1.51–1.38 (m, 1H, CH*H*CH_3), 0.84 (t, J=7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=172.1, 171.4, 168.5, 91.7, 87.0, 57.0, 52.4, 50.7, 36.4, 26.9, 21.1, 11.9, 9.4; MS: m/z=382 (M^+, 30), 353 (56), 323 (100), 291 (22), 209 (14), 163 (22), 69 (18), 59 (15); anal. calcd. for $C_{13}H_{19}IO_5$: C 40.85, H 5.01; found: C 40.73, H 4.96.

(*Z*)-[2-(3-Iodomethyl-3-methyl-3*H*-isobenzofuran-1-ylidene)-1-piperidin-1-yl]ethanone (8): Yield: 49% (Scheme 8); eluent: hexane-EtOAc 85:15; pale yellow oil. IR (film): ν=2934 (s), 2855 (s), 1655 (s), 1604 (s), 1442 (s), 1253 (m), 1019 (m), 948 (w), 761 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.54–7.35 (m, 3H, CH aromatic), 7.29–7.25 (m, 1H, CH aromatic), 5.54 (s, 1H, =CH), 3.69–3.50 (m, 6H), 1.79 (s, 3H, CH_3), 1.73–1.51 (m, 6H, 3 CH_2); ^{13}C NMR ($CDCl_3$, 230 K): δ=165.6, 158.0, 145.4, 133.0, 130.6, 129.2, 121.0, 120.9, 89.5, 88.4, 48.5, 42.6, 26.7, 25.7, 25.6, 24.7, 15.0; MS: m/z=397 (M^+, 25), 313 (100), 286 (18), 270 (26), 256 (32), 242 (20), 186 (24), 158 (80), 145 (52), 129 (28), 115 (50), 84 (60), 69 (12); anal. calcd. for $C_{17}H_{20}INO_2$: C 51.40, H 5.07; found: C 51.51, H 5.09.

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