# An Efficient and General Synthesis of Furan-2-acetic Esters by Palladium-Catalyzed Oxidative Carbonylation of (*Z*)-2-En-4-yn-1-ols

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A variety of (*Z*)-2-en-4-yn-1-ols have been carbonylated under oxidative conditions to give substituted furan-2-acetic esters in good yields. The cyclization−alkoxycarbonylation process occurs in alcoholic media at 50−70 °C and under 100 atm pressure of a 9:1 mixture of carbon monoxide and air in the presence of catalytic amounts of $PdI_2$ in conjunction with KI. The proposed reaction pathway involves the in situ isomerization of the initially formed (*E*)-2-[(alkoxycarbonyl)methylene]-2,5-dihydrofuran species, which in some cases have been isolated and shown to be the intermediates.

## Introduction

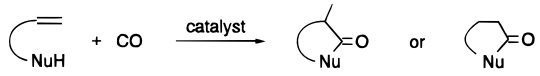
Carbonylation of unsaturated compounds containing a suitably placed nucleophilic group is an important method for the synthesis of functionalized heterocyclic compounds.[1] When carbon monoxide inserts between the nucleophilic and the unsaturated moieties of the substrate, an endocyclic carbonyl group is obtained in the final product (cyclocarbonylation), as shown, for example, in Scheme 1.[2]

In other cases, however, carbonylation is accompanied by ring closure without CO incorporation into the cycle, so that an external carbonyl group is obtained in the final product, as depicted, for example, in Scheme 2.

This kind of reactivity has been observed in the oxidative cyclization−alkoxycarbonylation of 4-en-1-ols, 5-en-1-ols, 4-en-1-amines, 5-en-1-amines, unsaturated ureas, and carbamates.[3] Ring closure followed by carbonylation has also been reported in the case of 2-alkynylanilines and 2-alkynylphenols to give *β*-(methoxycarbonyl)indoles or *β*-(methoxycarbonyl)benzofurans, respectively.[4] Recently, we described the oxidative cyclization−alkoxycarbonylation of prop-2-ynylamides[5] and of propynylureas[6] to give nitrogen heterocycles and the sequential oxidative carboxylation−cyclization−alkoxycarbonylation of propynylamines to give 5-[(alkoxycarbonyl)methylene]oxazolidin-2-ones.[7]

We now give a full account of the $PdI_2$/KI-catalyzed oxidative cyclization−alkoxycarbonylation of (*Z*)-2-en-4-yn-1-ols to obtain furan-2-acetic esters in good yields (eq 1). To our knowledge, this is the first example of synthesis

**Scheme 1**




**Scheme 2**

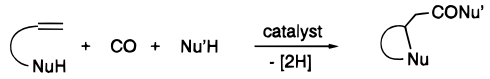



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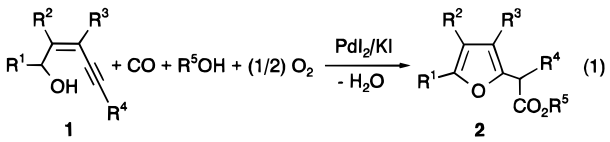
**Table 1. Synthesis of Furan-2-acetic Esters 2 by $PdI_2$/KI-Catalyzed Oxidative Carbonylation of (*Z*)-2-En-4-yn-1-ols 1 in MeOH ($R^5$ = Me), $P_{CO}$ = 90 atm, $P_{Air}$ = 10 atm, $T$ = 70 °C, 0.22 mmol of Substrate/mL MeOH[a]**

| entry | enynol **1** | $R^1$ | $R^2$ | $R^3$ | $R^4$ | KI/$PdI_2$ | **1**/$PdI_2$ | time (h) | yield of **2**[b] (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | H | H | Me | H | 50 | 1000 | 15 | 82 (73) |
| 2[c] | **1a** | H | H | Me | H | 200 | 1000 | 15 | 51 (44) |
| 3 | **1b** | H | H | Et | H | 50 | 1000 | 15 | 65 (57) |
| 4 | **1c** | H | H | Ph | H | 10 | 1000 | 15 | 62 (51) |
| 5 | **1d** | H | H | Me | Bu | 40 | 50 | 24 | 50 (45) |
| 6 | **1e** | H | H | Me | Ph | 30 | 30 | 24 | 73 (64) |
| 7 | **1f** | H | H | H | Bu | 50 | 100 | 15 | 59 (50)[d] |
| 8 | **1g** | H | Et | H | Bu | 50 | 1000 | 15 | 76 (68)[d] |
| 9 | **1h** | H | Ph | H | Bu | 50 | 1000 | 15 | 80 (75)[d] |
| 10 | **1i** | H | Et | Ph | Ph | 50 | 50 | 24 | 58 (53) |
| 11 | **1j** | H | Et | H | TMS | 300 | 1000 | 15 | 81 (70)[e] |
| 12 | **1k** | H | Ph | H | TMS | 300 | 1000 | 15 | 55 (50)[e] |
| 13 | **1l** | Pr | H | H | TMS | 50 | 1000 | 15 | 67 (58)[e] |
| 14 | **1m** | Et | H | Me | H | 300 | 1000 | 20 | 64 (55) |
| 15 | **1n** | Et | Et | H | Bu | 500 | 2000 | 15 | 65 (58) |
| 16 | **1o** | Ph | H | Me | H | 100 | 200 | 30 | 68 (58)[d] |

[a] All reactions were carried out on a 3−10 mmol scale based on enynol **1**. [b] GLC yield (isolated yield) based on **1**. Substrate conversion was practically quantitative in all cases. [c] Reaction carried out in BuOH ($R^5$ = Bu). [d] Yield after addition of diluted $H_2SO_4$ to the reaction mixture followed by stirring at room temperature for 1 h (see text for details). [e] $R^4$ = H in the final product **2** (see text for details).

of furanacetic derivatives via carbonylation of acyclic precursors.[8]

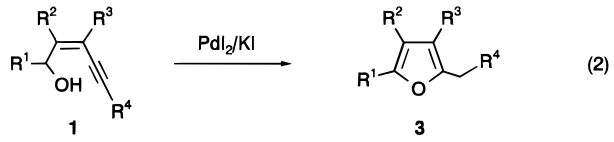



Furan-2-acetic acid derivatives are a very interesting class of compounds, known to be useful intermediate for the synthesis of biologically active molecules.[9]

## Results

Enynols **1** with different substitution patterns were subjected to carbonylation. The most representative results obtained are collected in Table 1.

**Enynols (*Z*)-HOCH$_2$CH=C(R$^3$)C≡CH.** The first carbonylation experiments were carried out using the commercially available (*Z*)-3-methylpent-2-en-4-yn-1-ol **1a**. This enynol was initially reacted in methanol under the same reaction conditions we previously used for the oxidative dicarbonylation of propynyl alcohols and 3-yn-1ols to give $\beta$- and $\gamma$-lactone derivatives,[2m] i.e., $T$ = 70 °C, $P_{tot}$ = 20 atm, CO/air = 3:1, KI/$PdI_2$ molar ratio = 10, substrate concentration = 0.22 mmol/mL MeOH. With 0.05% of catalyst, after 4 h GLC analysis indicated complete substrate conversion. The main reaction product was identified as 2-(methoxycarbonyl)methyl-3-methylfuran **2a** (48%). 2,3-Dimethylfuran **3a** (12%), formed by a competitive cycloisomerization reaction (eq 2),[10] was




also detected in the reaction mixture. Furan **3a** was not an intermediate for the formation of **2a**, as it was recovered unreacted under the reaction conditions. Unidentified heavy compounds accounted for the remaining products. Formation of the latter could be minimized by increasing the KI/$PdI_2$ molar ratio, even though the reaction rate was slowed owing to the competition between the iodide ligands and the substrate for coordination to palladium. For example, by reacting **1a** under the above-mentioned conditions, but using 50 mol of KI per mol of palladium, after 4 h, GLC yields of **2a** and **3a** were 62 and 14%, respectively, with a substrate conversion of 90%.

Selectivity in carbonylated product **2a** was significantly improved by working at higher CO partial pressure. Apparently, increasing the CO pressure tends to favor carbon monoxide insertion against the protonolysis pathway leading to **3a**. Thus, when the reaction was carried out at 100 atm (CO/air = 3:1; substrate/KI/$PdI_2$ molar ratio = 1000:50:1) after 15 h the **2a**/**3a** ratio was about 10 with a total GLC yield of 80%. Still better results were obtained by further increasing the $P_{CO}$ up to 90 atm at 100 atm of total pressure. Under these conditions, the yield of **2a** was as high as 82% (73% isolated yield, entry 1 of Table 1), **3a** being still formed in 8% yield. The reaction occurred even at 60 °C, although with less satisfactory results (**2a**, 55%; **3a**, 7% at 80% conversion after 15 h). Only products deriving from dialkoxycarbonylation of the triple bond [11] were obtained from (*E*)-3-methylpent-2-en-4-yn-1-ol, so *Z* stereochemistry of the double bond is a necessary condition for the occurrence of the cyclization−alkoxycarbonylation process.

When methanol was replaced by butan-1-ol under the same conditions of entry 1, 2-(butoxycarbonyl)methyl-3-methylfuran **2a′** was formed in 26% yield together with unidentified heavy products. A better yield of **2a′** was obtained by working with a KI/$PdI_2$ molar ratio of 200 rather than 50 (51% GLC, 44% isolated, entry 2).

Under the optimized conditions established for **1a** ($T$ = 70 °C, $P_{tot}$ = 100 atm, CO/air = 9:1, substrate/KI/$PdI_2$ molar ratio = 1000:50:1), other (*Z*)-enynols containing an alkyl substituent at C-3 reacted in a very similar

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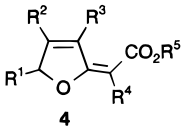
way, as exemplified by (*Z*)-3-ethylpent-2-en-4-yn-1-ol **1b** (entry 3; 3-ethyl-2-methylfuran **3b** was also formed in 9% yield). Analogous substrates containing an aryl group rather than an alkyl, such as **1c**, were much less reactive, and the KI/$PdI_2$ molar ratio had to be decreased in order to achieve acceptable reaction times. Luckily, in this case the competitive cycloisomerization process was very slow even when KI/$PdI_2$ = 10, so a satisfactory yield of the desired 2-(methoxycarbonyl)methyl-3-phenylfuran **2c** could still be obtained (entry 4).

**Enynols (*Z*)-$HOCH_2CH{=}C(R^3)C{\equiv}CR^4$.** (*Z*)-Enynols bearing substituents at both C-3 and C-5 were much less reactive compared with the corresponding (*Z*)-enynols with a terminal triple bond, as expected in view of their lower coordination ability to the metal center. For example, under the same conditions reported in entry 1, (*Z*)-3-methylnon-2-en-4-yn-1-ol **1d** afforded only a 4% yield of the expected furan-2-acetate **2d** and 0.5% of 3-methyl-2-pentylfuran **3d** after 15 h at 14% substrate conversion. A faster reaction was observed when the substrate/$PdI_2$ molar ratio was lowered down to 100. Conversion of **1d** was about 60% after 15 h and almost quantitative after 40 h, with 57% GLC yield of **2d** (51% isolated) and 20% of **3d**. Similar results were obtained with **1d**/KI/$PdI_2$ molar ratio = 50:40:1 after 24 h [yield of **2d** = 50% (45% isolated, entry 5), **3d** = 25%]. (*Z*)-3-Methyl-5-phenylpent-2-en-4-yn-1-ol **1e** behaved similarly. After 15 h under the conditions of entry 1 its conversion was only 3%, which became 92% after 24 h using **1e**/KI/$PdI_2$ molar ratio = 30:30:1, with a 73% GLC yield (64% isolated) of 2-[(methoxycarbonyl)(phenyl)methyl]-3-methylfuran **2e** and only traces of the cycloisomerization product, 2-benzyl-3-methylfuran **3e** (entry 6). The same results were obtained after 50 h using **1e**/KI/$PdI_2$ molar ratios of 100:50:1.

**Enynols (*Z*)-$HOCH_2CH{=}CH{\equiv}CR^4$.** (*Z*)-Enynols bearing no substituents on the double bond turned out to be more reactive compared with the corresponding 3-substituted ones. For example, (*Z*)-non-2-en-4-yn-1-ol **1f** attained almost complete conversion after only 15 h using a **1f**/KI/$PdI_2$ molar ratio of 100:50:1, while **1d** reacted in 24 h with 2% of $PdI_2$. This can be understood, since the triple bond, which must necessarily coordinate to the metal center at the beginning of the catalytic cycle, is now sterically less hindered. Interestingly, GC/MS analysis of the reaction crude deriving from **1f** showed the presence of two isomeric products, both corresponding to oxidative cyclization−methoxycarbonylation, in addition to small amounts (6%) of 2-pentylfuran **3f**. Carbonylation products were separated by column chromatography and characterized by IR and $^1$H NMR spectroscopies. The less abundant isomer (23%) was the expected 2-[1-(methoxycarbonyl)pentyl]furan **2f**, while the other one (39%) was (*E*)-2-[1-(methoxycarbonyl)pentylidene]-2,5-dihydrofuran **4f**.




**4**

**f** $R^1{=}R^2{=}R^3{=}H$, $R^4{=}Bu$, $R^5{=}Me$
**g** $R^1{=}R^3{=}H$, $R^2{=}Et$, $R^4{=}Bu$, $R^5{=}Me$
**h** $R^1{=}R^3{=}H$, $R^2{=}Ph$, $R^4{=}Bu$, $R^5{=}Me$

*E* stereochemistry was established unequivocally by $^1$H NMR spectroscopy. The chemical shift of the proton attached at C-3 adsorbs downfield at 7.3 ppm, and on the basis of the $^1$H NMR data reported in the literature on isomeric compounds with a 2,4-dienoic arrangement,[12] this value is compatible only with an *E* stereochemistry of the α,*β* double bond. Moreover, the NOESY spectrum shows a distinct NOE interaction between the protons of the $-CO_2CH_3$ group and the C-3 proton, together with a weaker NOE interaction between the same methyl protons and the C-4 proton; no NOE is observed between the C-3 proton and the α protons of the pentylidene moiety. Product **4f** was proved to be the intermediate for the formation of **2f**. In fact, when the reaction time was prolonged to 40 h, GLC yields of **2f** and **4f** were 53 and 7%, respectively, **3f** being also formed in 5% yield. Furthermore, **4f** could be converted quantitatively into **2f** by acid-catalyzed isomerization at room temperature. Thus, the carbonylation mixture obtained after 15 h (3 mmol substrate scale) was added to 10% $H_2SO_4$ (1 mL) and the resulting mixture allowed to stir at room temperature for 1 h. GLC analysis indicated complete conversion of **4f** into **2f** (59% GLC yield based on starting **1f**, 50% isolated, entry 7). Obviously, from a practical point of view, the latter procedure (15 h carbonylation followed by one-pot acid-catalyzed isomerization) is more convenient compared with the previous one (carbonylation followed by in situ isomerization, requiring at least 40 h reaction time) for the synthesis of **2f**.

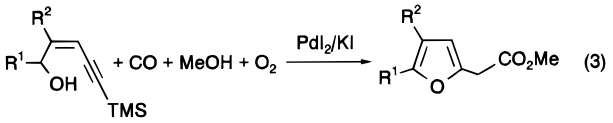
**Enynols (*Z*)-$HOCH_2CR^2{=}CH{\equiv}CR^4$.** (*Z*)-Enynols bearing a substituent at C-2 were more reactive than the corresponding enynols with no substituents on the double bond. This is due to the fact that the unfavorable steric repulsion between the substituent and the $CH_2OH$ moiety is relieved going through the transition state leading to cyclization. Thus, (*Z*)-2-ethylnon-2-en-4-yn-1-ol **1g** reacted in 15 h with a $PdI_2$/KI/substrate molar ratio of 1:50:1000 to give 4-ethyl-2-[1-(methoxycarbonyl)pentyl]-furan **2g** (29% GLC yield) and (*E*)-4-ethyl-2-[1-(methoxycarbonyl)pentylidene]-2,5-dihydrofuran **4g** (50%) at total conversion. This reaction can be compared with that reported in entry 7 for **1f**, which required 1% of catalyst. The *E* stereochemistry for **4g** was assigned on the basis of the chemical shift of H-3 ($\delta$ = 7.1 ppm). Carbonylation followed by one-pot acid-catalyzed isomerization afforded directly **2g** in high yield (76% GLC, 68% isolated, entry 8). Similar results were obtained using (*Z*)-2-phenylnon-2-en-4-yn-1-ol **1h**. The reaction carried out with a $PdI_2$/KI/substrate molar ratio of 1:50:1000 for 15 h led to the formation of 2-[1-(methoxycarbonyl)pentyl]-4-phenylfuran **2h** (22% GLC yield) and (*E*)-2-[1-(methoxycarbonyl)-pentylidene]-4-phenyl-2,5-dihydrofuran **4h** (60%) at total conversion. As usual, the chemical shift of H-3 ($\delta$ = 7.7) was indicative of *E* stereochemistry for **4h**. Carbonylation followed by one-pot acid-catalyzed isomerization afforded directly **2h** in high yield (80% GLC, 75% isolated, entry 9).

**Enynols (*Z*)-$HOCH_2CR^2{=}CR^3C{\equiv}CR^4$.** (*Z*)-Enynols bearing a substituent on both olefinic carbons could also be used successfully. Thus, (*Z*)-3,5-diphenyl-2-ethylpent-2-en-4-yn-1-ol **1i** reacted in 24 h (**1i**/KI/$PdI_2$ molar ratio = 50:50:1) to give the desired furanacetic ester **2i** in 58% GLC yield (53% isolated, entry 10), together with 10% of 2-benzyl-4-ethyl-3-phenylfuran **3i**.

**Enynols (*Z*)-$HOCH_2CR^2{=}CH{\equiv}CSiMe_3$.** As we al-

(12) (a) Alcaide, B.; Casarrubios, L.; Domínguez, G.; Retamosa, A.; Sierra, M. A. *Tetrahedron* **1996**, *52*, 13215−13226. (b) Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1995**, *78*, 129−144. (c) Nikles, M.; Bur, D.; Séquin, U. *Tetrahedron* **1990**, *46*, 1569−1578. (d) Crombie, L.; Crombie, W. M. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1267−1274.

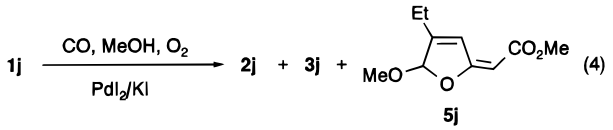
ready reported,[10b] (*Z*)-enynols with a substituent at C-2 and a terminal triple bond were not stable during the purification procedures and could not be tested. However, 4-substituted furan-2-acetates were obtained directly by the reaction of 2-substituted (*Z*)-5-trimethylsilyl-2-en-4-yn-1-ols, since the TMS group was lost in the course of the oxidative carbonylation process (eq 3).




**1j** $R^1$=H, $R^2$=Et
**1k** $R^1$=H, $R^2$=Ph
**1l** $R^1$=Pr, $R^2$=H

**2j** $R^1$=H, $R^2$=Et
**2k** $R^1$=H, $R^2$=Ph
**2l** $R^1$=Pr, $R^2$=H

For example, the reaction of (*Z*)-2-ethyl-5-trimethylsilylpent-2-en-4-yn-1-ol **1j** carried out under the same conditions used for **1g** afforded after 15 h 4-ethyl-2-[(methoxycarbonyl)methyl]furan **2j** in 37% yield together with another product corresponding to further oxidative methoxylation, (*E*)-3-ethyl-2-methoxy-5-(methoxycarbonyl)methylene-2,5-dihydrofuran **5j** (7%). Small amounts (1%) of 4-ethyl-2-methylfuran **3j** were also detected in the reaction mixture (eq 4). Unidentified heavy products accounted for the conversion of substrate (96%).



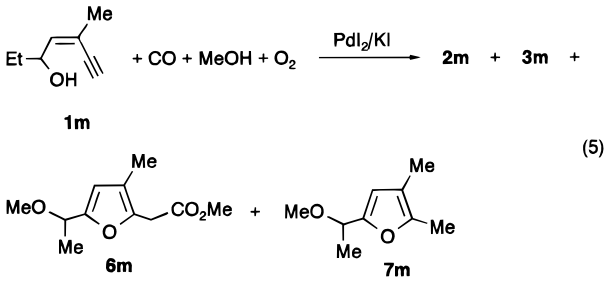

**5j**

The side reactions leading to **5j** and to the heavy products were suppressed by increasing the KI/$PdI_2$ molar ratio. Working with a **1j**/KI/$PdI_2$ molar ratio = 1000:300:1, GLC analysis after 15 h indicated an 81% yield of **2j** (70% isolated, entry 11) and 15% of **3j** at total substrate conversion, without any formation of **5j**. Under the same conditions, (*Z*)-2-phenyl-5-trimethylsilylpent-2-en-4-yn-1-ol **1k** afforded after 15 h a 55% GLC yield (50% isolated, entry 12) of 2-(methoxycarbonyl)methyl-4-phenylfuran **2k** at total substrate conversion.

***(Z)*-Enynols Bearing a Secondary Alcoholic Group.** (*Z*)-Enynols bearing a secondary alcoholic group and no substituent on C-2, C-3, and C-5 were not stable during the purification procedures. For example, purification of crude (*Z*)-oct-3-en-1-yn-5-ol (obtained by deprotection of the triple bond of (*Z*)-1-trimethylsilyloct-3-en-1-yn-5-ol **1l** with KF in MeOH) by transfer distillation afforded the cycloisomerization product, 5-methyl-2-propylfuran **3l**, in practically quantitative yield. However, as in the case of **1j** and **1k**, oxidative carbonylation of **1l**, carried out under the optimized conditions established for **1a** (entry 1), led directly to the desired furan-2-acetic ester **2l** in satisfactory yield (67% GLC, 58% isolated, entry 13) (eq 3).

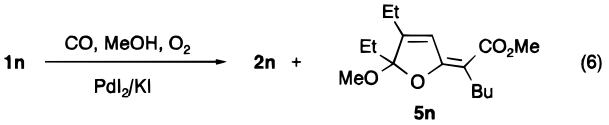
Oxidative carbonylation of 1,3-dialkyl substituted (*Z*)-enynols was in some cases accompanied by partial methoxylation of the α carbon of $R^1$. For example, by reacting (*Z*)-3-methylhept-3-en-1-yn-5-ol **1m** under the same conditions of entry 1, after 15 h methoxylated furans **6m** (20%) and **7m** (9%) were obtained together with **2m** (36%) and **3m** (4%) (eq 5).

As in the case of **1j**, formation of methoxylation products **6m** and **7m** was strongly curtailed by increasing the KI/$PdI_2$ molar ratio. Working with a substrate/KI/$PdI_2$ molar ratio = 1000:300:1, after 20 h GLC yields of



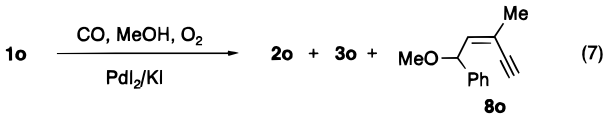

**2m**, **3m**, **6m**, and **7m** were 64% (55% isolated), 9%, 4%, and 3%, respectively (entry 14).

With 1,2-dialkyl-substituted enynols, such as (*Z*)-4-ethylundec-4-en-6-yn-3-ol **1n**, methoxylation preferentially occurred at C-2 on the ring, as already observed in the case of **1j**. The reaction of **1n** carried out with a substrate/KI/$PdI_2$ molar ratio = 2000:100:1 afforded after 15 h a mixture of furan-2-acetate **2n** and (*E*)-2,3-diethyl-2-methoxy-5-[1-(methoxycarbonyl)pentylidene]-2,5-dihydrofuran **5n** in 46% and 20% GLC yield, respectively (eq 6). As usual, the reaction could be made selective toward **2n** simply by increasing the KI/$PdI_2$ molar ratio. Working with a ratio of 500, only **2n** was obtained (65% GLC yield, 58% isolated, entry 15).




**5n**

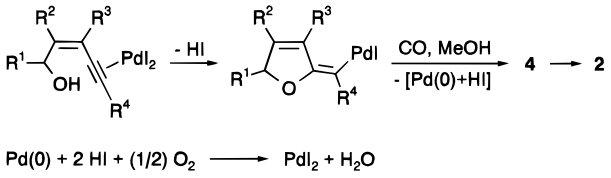
A different kind of side reaction was observed with substrates bearing an aryl substituent at C-1, resulting in partial etherification of the alcoholic function. For example, by reacting (*Z*)-3-methyl-1-phenylpent-2-en-4-yn-1-ol **1o** under the same conditions reported in entry 1, after 15 h a 24% GLC yield of 1-methoxy-1-phenyl-3-methylpent-2-en-4-yne **8o** was obtained together with 46% of the desired 2-(methoxycarbonyl)methyl-3-methyl-5-phenylfuran **2o** and 1% of the cycloisomerization product 2,3-dimethyl-5-phenylfuran **3o** (eq 7).



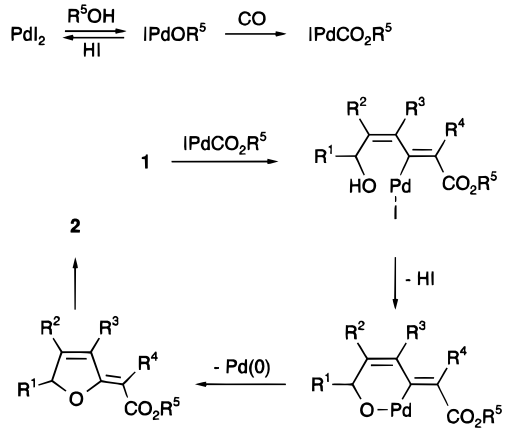

**8o**

As we already reported in the case of dimethyl hydroxymethylmaleate,[11] this side reaction could be easily minimized by working at lower temperature, even though the reaction rate was decreased. The reaction carried out at 50 °C rather than 70 °C, with a **1o**/KI/$PdI_2$ molar ratio = 200:100:1, reached almost quantitative substrate conversion after about 30 h, to give a 55% GLC yield of **2o**, 5% of **8o**, and 4% of **3o**. GLC−MS analysis of the reaction crude indicated also the presence of a product isomeric with **2o** (13%), which, however, could not be isolated by the conventional chromatographic techniques. It is very likely that this product corresponds to the nonaromatic precursor of **2o**, analogously to what observed with other substrates. This was confirmed by the fact that it slowly converted into **2o** under the reaction conditions. When the same reaction as before was analyzed after 52 h rather than 30 h, the yield of **2o** was 65%, the isomer being still present in 3% yield together with **8o** (8%) and **3o** (4%). From a practical point of view, 30 h carbonylation followed by one-pot acid-catalyzed

**Scheme 3**




**Scheme 4**




isomerization was again the easiest way of synthesizing **2o** (68% GLC yield, 58% isolated, entry 16).

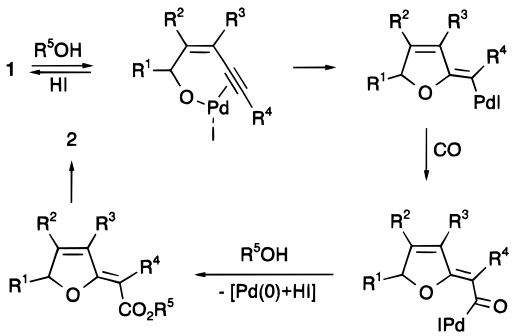
## Discussion

Formation of furan-2-acetic esters starting from (*Z*)-2-en-4-in-1-ols corresponds to oxidative alkoxyalkoxycarbonylation of the triple bond and isomerization (eq 1). These two processes occur in sequence, since, as discussed before, the nonaromatic carbonylation products (*E*)-2-[(alkoxycarbonyl)methylene]-2,5-dihydrofurans **4** proved to be the intermediates in the formation of **2**. According to what has been previously reported on palladium(II)-catalyzed intramolecular nucleophilic attack on carbon−carbon multiple bond followed by alkoxycarbonylation,[3,5−7] the most likely mechanism for the Pd-promoted alkoxyalkoxycarbonylation of (*Z*)-enynols involves an anti-*exo*-*dig* intramolecular nucleophilic attack of the hydroxyl group on the triple bond coordinated to Pd(II) [13] followed by alkoxycarbonylation (Scheme 3). The *E* stereochemistry invariably observed in dihydrofurans **4** is in agreement with this mechanistic hypothesis.

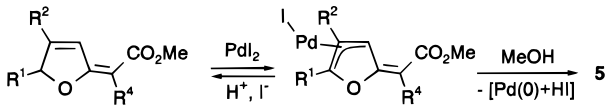
It is worth noting that in the case of simple alk-1-ynes,[11] propynyl alcohols,[2h,m] and 3-yn-1-ols[2m] the catalytic system based on $PdI_2$/KI selectively catalyzed the oxidative *di*alkoxycarbonylation of the triple bond. In the latter cases, the key intermediates for product formation were acylpalladium species formed by syn addition of an alkoxycarbonylpalladium complex to the triple bond followed by carbon monoxide insertion.

With (*Z*)-2-en-4-yn-1-ols, methoxycarbonylpalladium species could still be at work, since the vinylpalladium complex resulting from addition of I−Pd−$CO_2$Me to the triple bond could undergo hydroxyl attack on palladium followed by reductive elimination (Scheme 4). However, owing to the syn character of the addition of alkoxycarbonylpalladium and alkoxypalladium species on the triple bond,[2m,11,14] such a mechanism would lead to (*Z*)-2-[(alkoxycarbonyl)methylene]-2,5-dihydrofurans rather than the actually isolated *E* isomers. Accordingly, the mechanistic pathway depicted in Scheme 4 does not play a significant role in the present reaction.

**Scheme 5**




**Scheme 6**




**j** $R^1=R^4=H$, $R^2=Et$
**n** $R^1=R^2=Et$, $R^4=Bu$

The mechanism shown in Scheme 5, which implies the formation of an alkoxypalladium species from the alcoholic function of the substrate, rather than from the solvent, followed by triple-bond insertion and alkoxycarbonylation, can also be ruled out for similar reasons.

Exclusion of the mechanisms shown in Schemes 4 and 5 further confirms the validity of that shown in Scheme 3.

The occurrence of some byproducts deserves a short comment. Formation of methoxylated dihydrofurans **5j** and **5n** is remarkable, since it presupposes C−H activation. It is likely that the nonaromatic precursors of **2j** and **2n** are palladated on the ring to give $\pi$-allyl complexes, which then undergo nucleophilic attack by methanol to give **5** (Scheme 6).[15] Apparently, a large excess of iodide anions shifts the equilibrium of formation of the $\pi$-allylpalladium complex to the left by mass effect.

Compounds **6m** and **7m** were shown to derive from **2m** and **3m**, respectively. For example, **3m** partially converted into **7m** when reacted under the reaction conditions. A $\pi$-allylpalladium complex is probably involved also in this case[16] (Scheme 7).

Methoxylation of the hydroxylic function, observed with **1o**, probably results from the reaction of the allylic moiety with the [Pd(0) + HI] species[17] ensuing from the oxidative process, with formation of a particularly stable $\pi$-allylpalladium intermediate in which the allyl system is conjugated to the phenyl substituent. This intermediate readily undergoes methanol attack on the less

(13) See, for example, ref 1b and references therein.

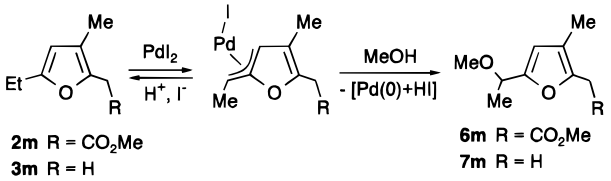
(14) (a) Murray, T. F.; Varma, V.; Norton, J. R. *J. Am. Chem. Soc.* **1977**, *99*, 8085−8087. (b) Murray, T. F.; Norton, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 4107−4119. (c) Calderazzo, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 299−311.

(15) It is well-known from the literature that nucleophilic attack on $\pi$-allylpalladium complexes usually occurs on the less hindered carbon of the allyl system (see, for example, ref 1b and references therein). In the present case, however, the nucleophilic attack occurs exclusively at C-5 since it leads to a more stable double bond.

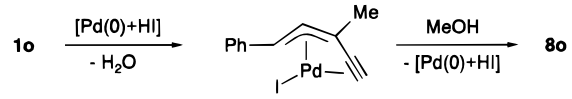
(16) Nucleophilic attack by methanol occurs preferentially at the α-alkyl carbon owing to the partial aromatic character of the transition state leading to **6m** or **7m**.

(17) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Mol. Catal. A* **1996**, *111*, 43−48.

**Scheme 7**




**Scheme 8**




hindered carbon to give **8o**. The stereoselectivity of the reaction can be ascribed to the simultaneous coordination of the triple bond, which stabilizes the complex arrangement leading to the *Z* isomer (Scheme 8).

## Conclusions

In conclusion, we have described a new, direct, and efficient synthetic route to furan-2-acetic esters via Pd-catalyzed oxidative carbonylation of readily available (*Z*)-2-en-4-yn-1-ols. Despite the multifunctional character of the substrates and the oxidative conditions employed, the reaction is very selective. In the case of substrates particularly prone to undergo undesired side reactions, the process can be easily directed with high selectivity toward the cyclization−alkoxycarbonylation pathway by slightly modifying the reaction conditions. Also, isolation of the nonaromatic precursors of the final products has allowed us to gain insight into the reaction mechanism.

## Experimental Section

**General Methods.** Melting points are uncorrected. $^1$H NMR spectra were run on $CDCl_3$ solutions with $Me_4Si$ as internal standard and recorded at 300 MHz. Chemical shifts and coupling constants (*J*) are given in ppm ($\delta$) and in Hz, respectively. IR spectra were taken on a FT-IR spectrometer. Mass spectra were obtained at 70 eV on a GC−MS apparatus. Microanalyses were performed at our analytical laboratory. All reactions were analyzed by TLC on silica gel 60 $F_{254}$ or by GLC using capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70−230 mesh). Preparative thin-layer chromatography (PTLC) was carried out on silica gel 60 $F_{254}$ plates. Starting (*Z*)-2-en-4-yn-1-ols **1** were prepared according to published procedures.[10b] (*Z*)-1-Trimethylsilyloct-3-en-1-yn-5-ol **1l** was prepared by Pd/Cu-catalyzed coupling between (*Z*)-1-iodohex-1-en-3-ol[18] and trimethylsilylacetylene, as described below. All other materials were commercially available and were used without further purification.

Known products **2a**,[9i,19] **3d**,[10b] **3e**,[20] **3f**,[21] **3i**,[10b] and **3o**[20] were characterized by comparison with literature data. Low-boiling furans **3a**, **3b**, **3j**, and **3m** were not isolated and were characterized by GC−MS comparison with the pure products obtained by cycloisomerization of the corresponding (*Z*)-enynols.[10b]

**(*Z*)-1-Trimethylsilyloct-3-en-1-yn-5-ol 1l.** The method of Alami[22] was employed. To a cooled (0 °C), stirred mixture of $Pd(PPh_3)_4$ (1.8 g, 1.56 mmol) and CuI (0.59 g, 3.1 mmol) in pyrrolidine (10 mL) was added under nitrogen a solution of (*Z*)-1-iodohex-1-en-3-ol [18] (7.0 g, 31.0 mmol) in pyrrolidine (20 mL), followed by stirring for 5 min. A solution of TMSC≡CH (6.0 g, 61.1 mmol) in pyrrolidine (6 mL) was then added dropwise at 0 °C. After being stirred at 0 °C for 5 h, the reaction mixture was diluted with $Et_2O$ and quenched at 0 °C with saturated $NH_4Cl$. The aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with brine and dried over $Na_2SO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (9:1 hexane/ethyl acetate) to obtain pure **1l** as a colorless oil (5.8 g, 95%): IR (neat) 3338, 2150, 1251, 844 cm$^{-1}$; $^1$H NMR $\delta$ 5.93 (dd, $J$ = 11.0, 8.3, 1 H), 5.55 (dd, $J$ = 11.0, 1.0, 1 H), 4.75−4.64 (m, 1 H), 1.70−1.34 (m, 4 H), 0.96 (t, $J$ = 7.3, 3 H), 0.20 (s, 9 H); MS *m/e* 196 (1, M$^+$), 181 (30), 75 (90), 73 (100).

**Deprotection of 1l with KF in MeOH.** To a stirred solution of **1l** (0.5 g, 2.55 mmol) in MeOH (4.5 mL) was added KF (215 mg, 3.71 mmol), and the mixture was allowed to stir at room temperature for 5 h. The reaction was quenched with water (50 mL), the aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with brine. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure. $^1$H NMR of the residue was in agreement with the expected (*Z*)-oct-3-en-1-yn-5-ol: $\delta$ 5.99 (ddd, $J$ = 11.2, 8.3, 1.0, 1 H), 5.53 (ddd, $J$ = 11.2, 2.4, 1.0, 1 H), 4.74−4.64 (m, 1 H), 3.14 (dd, $J$ = 2.4, 1.0, 1 H), 1.70−1.32 (m, 4 H), 0.95 (t, $J$ = 7.3, 3 H). MS *m/e* 124 (1, M$^+$), 81 (100), 53 (76). However, purification by transfer distillation gave in practically quantitative yield 5-methyl-2-propylfuran **3l**, whose spectral properties agreed with that reported:[23] IR (neat): 2961, 1570, 1456, 1220, 778 cm$^{-1}$; $^1$H NMR $\delta$ 5.84 (s, 2 H), 2.54 (t, $J$ = 7.3, 2 H), 2.25 (s, 3 H), 1.64 (sext, $J$ = 7.3, 2 H), 0.95 (t, $J$ = 7.3, 3 H); MS *m/e* 124 (13, M$^+$), 95 (100).

**Carbonylation Procedure.** Oxidative carbonylation reactions were carried out in alcoholic media at 50−70 °C under 100 atm of a 9:1 mixture of carbon monoxide and air, in the presence of catalytic amounts of $PdI_2$ (0.05−3%) in conjunction with an excess of KI (10−500 mol per mol of palladium). In a typical experiment, a 300 mL stainless steel autoclave was charged in the presence of air with $PdI_2$, KI, and the appropriate (*Z*)-2-en-4-yn-1-ol (3−10 mmol) dissolved in MeOH or BuOH. The autoclave was pressurized with air (10 atm) and CO (up to 100 atm of total pressure) and heated at 70 °C with stirring for the required time. Reaction times, substrate/KI/$PdI_2$ molar ratios, and substrate concentration are indicated in Table 1.

**Separation of Products.** Products were separated by column chromatography after removal of the solvent under reduced pressure: **2a** (pentane/AcOEt from 95:5 to 9:1, colorless oil). **2a′** (hexane/AcOEt from 99:1 to 95:5, colorless oil): IR (neat) 1742, 1168, 735 cm$^{-1}$; $^1$H NMR $\delta$ 7.27 (d, $J$ = 2.0, 1 H), 6.21 (d, $J$ = 2.0, 1 H), 4.11 (t, $J$ = 6.8, 2 H), 3.60 (s, 2 H), 1.99 (s, 3 H), 1.66−1.51 (m, 2 H), 1.45−1.28 (m, 2 H), 0.92 (t, $J$ = 7.3, 3 H); MS *m/e* 196 (14, M$^+$), 95 (100). **2b** (95:5 hexane/AcOEt, colorless oil): IR (neat) 1744, 1212, 1165, 740 cm$^{-1}$; $^1$H NMR $\delta$ 7.28 (d, $J$ = 1.8, 1 H), 6.26 (d, $J$ = 1.8, 1 H), 3.70 (s, 3 H), 3.62 (s, 2 H), 2.38 (q, $J$ = 7.6, 2 H), 1.14 (t, $J$ = 7.6, 3 H); MS *m/e* 168 (25, M$^+$), 109 (100). **2c** (99:1 hexane/acetone, pale yellow oil): IR (neat) 1742, 1121, 761, 701 cm$^{-1}$; $^1$H NMR $\delta$ 7.42−7.26 (m, 6 H), 6.54 (d, $J$ = 1.9, 1 H), 3.79 (s, 2 H), 3.74 (s, 3 H); MS *m/e* 216 (67, M$^+$), 157 (100), 129 (62), 128 (61). Products **3d** and **2d** were eluted in this order using 98:2 hexane/AcOEt. **2d** (pale yellow oil): IR (neat) 1743, 1226, 1167, 741 cm$^{-1}$; $^1$H NMR $\delta$ 7.27 (d, $J$ = 1.7, 1 H), 6.18 (d, $J$ = 1.7, 1 H), 3.68 (s, 3 H), 3.67 (t, $J$ = 7.8, 1 H), 2.10−1.83 (m, 2 H), 2.00 (s, 3 H), 1.39−1.13 (m, 4 H), 0.87 (t, $J$ = 7.2, 3 H); MS *m/e* 210 (15, M$^+$), 151 (55), 95 (100). Compounds **3e** and **2e** were eluted in this order using 9:1 hexane/AcOEt. **2e** (pale yellow oil): IR (neat) 1745, 1201, 1160, 732 cm$^{-1}$; $^1$H NMR $\delta$

(18) Beruben, D.; Marek, I.; Normant, J. F.: Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488−2501.
(19) Piotti, M. E.; Alper, H. *J. Org. Chem.* **1997**, *62*, 8484−8489.
(20) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089−13102.
(21) McKeown, N. B.; Chambrier, I.; Cook, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1169−1177.
(22) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403−6406.
(23) Heyns, K.; Stute, R.; Scharmann, H. *Tetrahedron* **1966**, *22*, 2223−2235.

7.36−7.23 (m, 6 H), 6.20 (d, $J$ = 2.0, 1 H), 5.05 (s, 1 H), 3.74 (s, 3 H), 1.96 (s, 3 H); MS *m/e* 230 (7, $M^+$), 171 (100), 128 (24). Products **3f**, **2f**, and **4f** were eluted in this order using a concentration gradient of hexane/AcOEt from 99:1 to 95:5. **2f** (colorless oil): IR (neat) 1743, 1160, 736 $cm^{-1}$; $^1H$ NMR $\delta$ 7.34 (dd, $J$ = 2.0, 1.0, 1 H), 6.32 (dd, $J$ = 2.9, 2.0, 1 H), 6.18 (dd, $J$ = 2.9, 1.0, 1 H), 3.70 (t, $J$ = 7.8, 1 H), 3.70 (s, 3 H), 2.08−1.85 (m, 2 H), 1.40−1.20 (m, 4 H), 0.89 (t, $J$ = 7.1, 3 H); MS *m/e* 196 (14, $M^+$), 137 (46), 81 (100). **4f** (pale yellow oil): IR (neat) 1694, 1625, 1112, 787 $cm^{-1}$; $^1H$ NMR $\delta$ 7.35 (dt, $J$ = 6.4, 2.4, 1 H), 6.69 (dt, $J$ = 6.4, 2.0, 1 H), 4.98 (dd, $J$ = 2.4, 2.0, 2 H), 3.72 (s, 3 H), 2.37 (t, $J$ = 7.3, 2 H), 1.47−1.22 (m, 4 H), 0.91 (t, $J$ = 7.1, 3 H); MS *m/e* 196 (21, $M^+$), 165 (18), 153 (62), 93 (100). Compounds **2g** and **4g** were eluted in this order using 99:1 hexane/AcOEt. **2g** (colorless oil): IR (neat) 2959, 1743, 1162 $cm^{-1}$; $^1H$ NMR $\delta$ 7.12−7.10 (m, 1 H), 6.08 (d, $J$ = 0.7), 3.71 (s, 3 H), 3.64 (t, $J$ = 7.7, 1 H), 2.40 (qd, $J$ = 7.5, 1.3, 2 H), 2.05−1.79 (m, 2 H), 1.41−1.20 (m, 4 H), 1.16 (t, $J$ = 7.5, 3 H), 0.89 (t, $J$ = 7.1, 3 H); MS *m/e* 224 (18, $M^+$), 165 (57), 109 (100). **4g** (colorless oil): IR (neat) 1694, 1628, 1610, 1112 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 7.07−7.04 (m, 1 H), 4.86−4.83 (m, 2 H), 3.71 (s, 3 H), 2.38−2.27 (m, 4 H), 1.46−1.23 (m, 4 H), 1.20 (t, $J$ = 7.5, 3 H), 0.90 (t, $J$ = 7.0, 3 H); MS *m/e* 224 (21, $M^+$), 181 (75), 121 (100). Products **2h** and **4h** (in a mixture with **2h**) were eluted in this order using 99:1 hexane/AcOEt. **4h** was subsequently separated from **2h** by PTLC using 8:2 hexane/$Et_2O$ as eluent and crystallized from MeOH at − 20 °C. **2h** (colorless oil): IR (neat) 1741, 1154, 751 $cm^{-1}$; $^1H$ NMR $\delta$ 7.64 (d, $J$ = 1.0, 1 H), 7.50−7.44 (m, 2 H), 7.39−7.31 (m, 2 H), 7.28−7.20 (m, 1 H), 6.53−6.51 (m, 1 H), 3.73 (s, 3 H), 3.72 (t, $J$ = 7.7, 1 H), 2.12−1.86 (m, 2 H), 1.43−1.24 (m, 4 H), 0.90 (t, $J$ = 6.9, 3 H); MS *m/e* 272 (41, $M^+$), 213 (48), 157 (100). **4h** (pale yellow solid, mp 72−73 °C): IR (neat) 1691, 1606, 1121 $cm^{-1}$; $^1H$ NMR $\delta$ 7.71 (t, $J$ = 2.0, 1 H), 7.50−7.35 (m, 5 H), 5.32−5.29 (m, 2 H), 3.76 (s, 3 H), 2.41 (t, $J$ = 7.3, 2 H), 1.52−1.29 (m, 4 H), 0.92 (t, $J$ = 7.1, 3 H); MS *m/e* 272 (34, $M^+$), 229 (89), 169 (100), 141 (42), 115 (51). Compounds **3i** and **2i** were eluted in this order using a concentration gradient of hexane/AcOEt from 99:1 to 9:1. **2i** (pale yellow solid, mp = 62−63 °C): IR (neat) 1745, 1202, 1155, 702 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 7.47−7.22 (m, 11 H) 5.00 (s, 1 H) 3.69 (s, 3 H), 2.45−2.30 (m, 2 H), 1.07 (t, $J$ = 7.3, 3 H); MS *m/e* 320 (7, $M^+$), 261 (100). Products **2j** and **5j** were eluted in this order using 95:5 hexane/AcOEt. **2j** (pale yellow oil): IR (neat) 1745, 1261, 1204, 1157 $cm^{-1}$; $^1H$ NMR $\delta$ 7.13 (q, $J$ = 1.1, 1 H), 6.14−6.11 (m, 1 H), 3.72 (s, 3 H), 3.65 (d, $J$ = 0.7, 2 H), 2.41 (qd, $J$ = 7.6, 1.1, 2 H), 1.16 (t, $J$ = 7.6, 3 H); MS *m/e* 168 (25, $M^+$), 109 (100). **5j** (pale yellow oil): IR (neat) 1706, 1652, 1621, 1105 $cm^{-1}$; $^1H$ NMR $\delta$ 7.18−7.15 (m, 1 H), 5.82−5.80 (m, 1 H), 5.29−5.27 (m, 1 H), 3.70 (s, 3 H), 3.43 (s, 3 H), 2.45−2.18 (m, 2 H), 1.21 (t, $J$ = 7.3, 3 H); MS *m/e* 198 (17, $M^+$), 169 (100), 139 (21). Furanacetate **2k** was eluted using hexane/AcOEt from 95:5 to 9:1 and further purified by repeated crystallization from MeOH at −25 °C to give a white solid: mp = 91−92 °C: IR (KBr) 1720, 1257, 755 $cm^{-1}$; $^1H$ NMR $\delta$ 7.66 (s, 1 H), 7.50−7.23 (m, 5 H), 6.57 (s, 1 H), 3.76 (s, 3 H), 3.74 (s, 2 H); MS *m/e* 216 (61, $M^+$), 157 (100), 128 (65). Furanacetate **2l** was eluted using hexane/AcOEt from 95:5 to 9:1 (colorless oil): IR (neat) 1747, 1221, 1014, 785 (m) $cm^{-1}$; $^1H$ NMR $\delta$ 6.10 (d, $J$ = 2.7, 1 H), 5.92 (d, $J$ = 2.7, 1 H), 3.72 (s, 3 H), 3.64 (s, 2 H), 2.56 (t, $J$ = 7.3, 2 H), 1.64 (sext, $J$ = 7.3, 2 H), 0.94 (t, $J$ = 7.3, 3 H); MS *m/e* 182 (31, $M^+$), 153 (32), 123 (100), 111 (31). Compounds **7m**, **2m**, and **6m** were eluted in this order using 95:5 hexane/AcOEt. **7m** (colorless oil): IR (neat) 1449, 1109, 1084, 734 $cm^{-1}$; $^1H$ NMR $\delta$ 6.03 (s, 1 H), 4.25 (q, $J$ = 6.6, 1 H), 3.27 (s, 3 H), 2.19 (s, 3 H), 1.92 (s, 3 H), 1.47 (d, $J$ = 6.6, 3 H); MS *m/e* 154 (23, $M^+$), 139 (68), 123 (100). **2m** (colorless oil): IR (neat): 1745, 1167, 1010, 806 $cm^{-1}$; $^1H$ NMR $\delta$ 5.81 (s, 1 H), 3.71 (s, 3 H), 3.58 (s, 2 H), 2.58 (q, $J$ = 7.6, 2 H), 1.94 (s, 3 H), 1.19 (t, $J$ = 7.6, 3 H); MS *m/e* 182 (17, $M^+$), 123 (100). **6m** (colorless oil): IR (neat) 1742, 1266, 740 $cm^{-1}$; $^1H$ NMR $\delta$ 6.10 (s, 1 H), 4.29 (q, $J$ = 6.6, 1 H), 3.71 (s, 3 H), 3.62 (s, 2 H), 3.28 (s, 3 H), 1.97 (s, 3 H), 1.47 (d, $J$ = 6.6, 3 H); MS *m/e* 212 (31, $M^+$), 197 (100), 181 (87), 139 (42). Products **2n** and **5n** were eluted in this order using 99:1 hexane/AcOEt. **2n** (colorless oil): IR (neat) 1744, 1160 $cm^{-1}$; $^1H$ NMR $\delta$ 5.99 (s, 1 H), 3.70 (s, 3 H), 3.60 (t, $J$ = 7.7, 1 H), 2.53 (t, $J$ = 7.3, 2 H), 2.30 (t, $J$ = 7.3, 2 H), 2.06−1.73 (m, 2 H), 1.42−1.16 (m, 4 H), 1.15 (t, $J$ = 7.3, 3 H), 1.11 (t, $J$ = 7.3, 3 H), 0.89 (t, $J$ = 7.3, 3 H); MS *m/e* 252 (19, $M^+$), 193 (100), 137 (66). **5n** (colorless oil): IR (neat) 1698, 1637, 1617, 1118 $cm^{-1}$; $^1H$ NMR $\delta$ 7.21−7.18 (m, 1 H), 3.74 (s, 3 H), 3.06 (s, 3 H), 2.41 (t, $J$ = 7.3, 2 H), 2.14 (qd, $J$ = 7.3, 1.5, 2 H), 2.04−1.70 (m, 2 H), 1.51−1.27 (m, 4 H), 1.24 (t, $J$ = 7.3, 3 H), 0.91 (t, $J$ = 7.3, 3 H), 0.78 (t, $J$ = 7.3, 3 H); MS *m/e* 282 (6, $M^+$), 253 (100). Compounds **3o**, **8o**, and **2o** were eluted in this order using a concentration gradient hexane/AcOEt from 98:2 to 9:1. **8o** (colorless oil): IR (neat) 3290, 1098, 1081, 699 $cm^{-1}$; $^1H$ NMR $\delta$ 7.42−7.23 (m, 5 H), 5.83 (dq, $J$ = 9.1, 1.3, 1 H), 5.22 (d, $J$ = 9.1, 1 H), 3.36 (s, 3 H), 3.22 (s, 1 H), 1.90 (d, $J$ = 1.3, 3 H); MS *m/e* 186 (90, $M^+$), 171 (100), 128 (87), 77 (85). **2o** (pale yellow oil): IR (neat) 1742, 1167, 761 $cm^{-1}$; $^1H$ NMR $\delta$ 7.65−7.57 (m, 2 H), 7.39−7.30 (m, 2 H), 7.26−7.18 (m, 1 H), 6.49 (s, 1 H), 3.72 (s, 3 H), 3.68 (s, 2 H), 2.03 (s, 3 H); MS *m/e* 230 (31, $M^+$), 171 (100).

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**Supporting Information Available:** Characterization data for all new compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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