# A Novel Route to Cross-Conjugated 4-Oxo-5-alkylidene-2-cyclopentenecarboxylates by Pd(0)-Catalyzed Vicinal Carbonylation of 4-En-2-ynyl Carbonates

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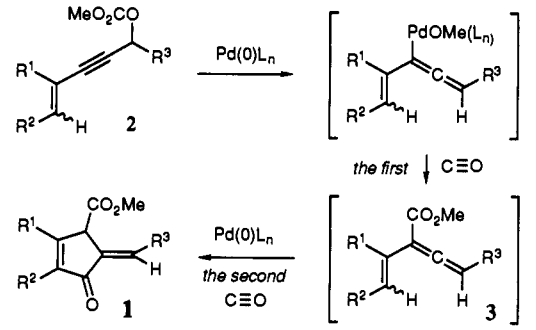
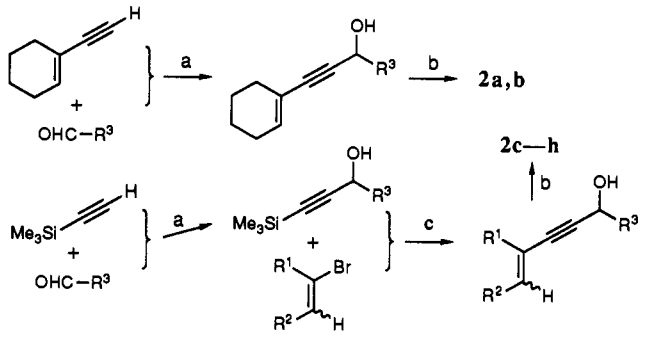
Direct introduction of carbon monoxide (CO) into an acetylenic sp carbon by transition-metal complexes is an important process to construct $\alpha,\beta$-unsaturated carbonyl functions in organic chemistry.[1] The syntheses of a variety of cyclopentenone derivatives have been demonstrated on the basis of such a process where *one* CO incorporation into the sp carbon is almost invariably featured.[2] To the best of our knowledge, however, no effort has been recorded so far to vicinally introduce *two* COs into both sp carbons in a stepwise manner by a Pd(0) species[3] in which the second CO triggers cyclopentenone ring closure. To our delight, we have succeeded in realizing, for the first time, single-pot vicinal carbonylation-carbacyclization of the 4-en-2-ynyl carbonates **2** by Pd(0) catalyst providing the 4-oxo-5-alkylidene-2-cyclopentenecarboxylates (**1**) via the conjugated enallenes **3** (Scheme I). The cyclpentenone ring closure triggered by the second CO proceeds in such a way that the carbonyl carbon links to the allenyl central and alkenyl terminal carbons.

**Scheme I**



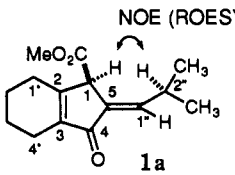

**Scheme II**[a]




[a] (a) (1) EtMgBr, (2) aldehyde; (b) EtMgBr then $ClCO_2Me$; (c) $Pd(PPh_3)_4$/CuI.

The starting 4-en-2-ynyl carbonates **2a–h** were synthesized via a series of routine reactions, as shown in Scheme II. The carbonylation process has smoothly proceeded in a mixed solvent system such as $C_6H_6$–$CH_3CN$–MeOH (4:2:1) in the presence of $Pd(OAc)_2$ (10 mol %) and a bidentate phosphine such as 1,3-bis(diphenylphosphino)propane (DPPP) or 1,2-bis(diphenylphosphino)ethane (DPPE) (10 mol %)[4] at room temperature during 4–24 h under atmosphere of CO (5 kg/cm²) to give **1a–h** in high yields, which are listed in Table I, while a monodentate ligand such as triphenylphosphine was not effective at all.[5]

The structures of **1a–h** were indicated by IR, UV, and NMR spectroscopy and elemental analyses. The following information obtained with regard to **1a** is representative. The $^{13}C$ NMR clearly pointed to the appendage of one more carbon to **2a**, with a signal at 194.8 ppm strongly suggesting the presence of an $\alpha,\beta$-unsaturated ketone function in **1a**. This deduction was supported by the IR[6] and, further, by the UV[7] analyses. The $^{13}C$ NMR also indicated the presence of three unprotonated and one protonated olefinic carbons, the latter of which was revealed to be positioned adjacent to the methine carbon of the isopropyl group on the basis of both COSY and HETCOR information. The HMBC and ROESY experiments of **1a** led to a final confirmation that **1a** should bear a cross-conjugated dienone backbone with an exocyclic double bond of (*E*) geometry, as indicated below.




Major long-range C—H correlations observed (HMBC):
C(1)—H(1"); C(2)—H(1); C(2)—H(1');
C(3)—H(4'); C(4) (C=O)—H(1");
C(5)—H(1); $O_2C$—H(1);
C(1")—$CH_3$; C(2")—$CH_3$.

In order to gain more insight into the present reaction with regard to not only a mechanism but also scope and limitation, the following reactions have been conducted (Scheme III). Firstly,

(1) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum Press: New York, 1991. Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65–72. For Pd-ctalyzed carbonylations of acetylenes, see: Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, Heidelberg, 1980; pp 159–162.

(2) Pd: Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761–6763. Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, *107*, 8289–8291. Zr: Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568–2569. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832. Negishi, E.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 917–920. Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336–3346. Wender, P. A.; McDonald, F. E. *Tetrahedron Lett.* **1990**, *31*, 3691–3694. Co: Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1971**, 36–37; *J. Chem. Soc., Perkin Trans. I* **1973**, 975–977. Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. I* **1973**, 977–981. Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855–5860. La Belle, B. E.; Knudsen, M. J.; Olmstead, M. M.; Hope, H.; Yanuck, M. D.; Schore, N. E. *J. Org. Chem.* **1985**, *50*, 5215–5222. Carceller, E.; García, M. L.; Moyano, A.; Pericàs, M. A.; Serratosa, F. *Tetrahedron* **1986**, *42*, 1831–1839. Schore, N. E.; Rowley, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 5224–5225. Smit, W. A.; Simonyan, S. O.; Tarasov, V. A.; Mikaelian, G. S.; Gybin, A. S.; Ibragimov, I. I.; Caple, R.; Froen, D.; Kreager, A. *Synthesis* **1989**, 472–476. Magnus, P.; Slater, M. J.; Principe, L. M. *J. Org. Chem.* **1989**, *54*, 5148–5153. Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289–5292. Schore, N. E. *Org. React.* **1991**, *40*, 1–90. Ni: Cassar, L.; Chiusoli, G. P.; Guerrieri, F. *Synthesis* **1973**, 509–523. Camps, F.; Coll, J.; Llebaria, A.; Moretó, J. M. *Tetrahedron Lett.* **1988**, *29*, 5811–5814. Oppolzer, W.; Keller, T. H.; B.-Zurita, M.; Stone, C. *Tetrahedron Lett.* **1989**, *30*, 5883–5886. Camps, F.; Llebaria, A.; Moretó, J. M.; Pagès, L. *Tetrahedron Lett.* **1992**, *33*, 109–112; 113–114. Rh: Doyama, K.; Joh, T.; Takahashi, S.; Shiohara, T. *Tetrahedron Lett.* **1986**, *27*, 4497–4500; *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4353–4360.

(3) Vicinal carbonylations of acetylenic sp carbons employing Pd(II) salts and Pd(0) complex have been reported: Tsuji, J.; Morikawa, M.; Iwamoto, N. *J. Am. Chem. Soc.* **1964**, *86*, 2095. Tsuji, J.; Nogi, T. *J. Am. Chem. Soc.* **1966**, *88*, 1289; *J. Org. Chem.* **1966**, *31*, 2641–2643. Chiusoli, G. P.; Venturello, C.; Merzoni, S. *Chem. Ind.* **1968**, 977. Nogi, T.; Tsuji, J. *Tetrahedron* **1969**, *25*, 4099–4108. Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Chem. Commun.* **1992**, 1007–1008.

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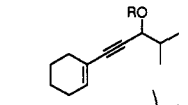
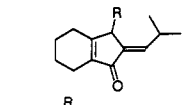
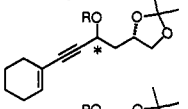
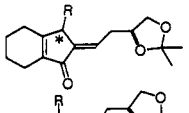
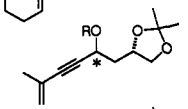
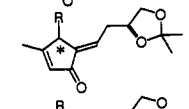
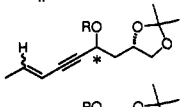
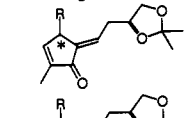
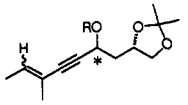
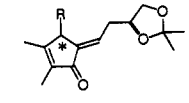
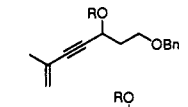
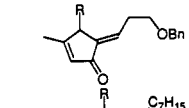
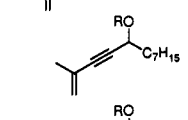
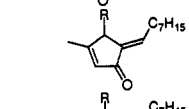
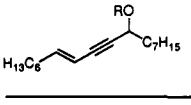
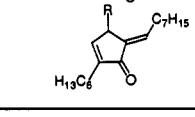
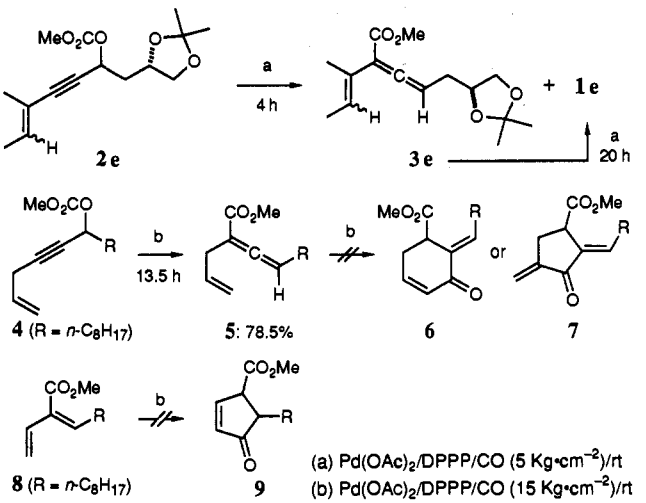
**Table I.** Vicinal Carbonylation-Carbacyclization of the Carbonates **2a–h**[a]

| carbonate[b,c] | | time/h | product[b,c] | | yield/%[d] |
|---|---|---|---|---|---|
|  | 2a | 8.0 |  | 1a | 81 |
|  | 2b | 4.0 |  | 1b | 82 |
|  | 2c | 8.0 |  | 1c | 70 |
|  | 2d | 24.0 |  | 1d | 69 |
|  | 2e | 24.0 |  | 1e | 70 |
|  | 2f | 8.0 |  | 1f | 69 |
|  | 2g | 6.5 |  | 1g | 73 |
|  | 2h | 8.0 |  | 1h | 64 |

[a] Conducted at room temperature in $C_6H_6$–$CH_3CN$–MeOH (4:2:1) under CO atmosphere (5 kg/cm²) in the presence of $Pd(OAc)_2$–DPPP (1:1) (10 mol %). [b] R = $CO_2Me$. [c] Diastereomeric mixture (1:1) with regard to the C* centers. [d] For purified product by $SiO_2$ column chromatography, yields obtained by using DPPE were essentially the same (within ±1%) as these values.

to attest to the structure of the first-stage products **3**,[8] we have attempted their isolation, which, however, for most entries in Table I, was unsuccessful even if the reactions were intermitted at the initial stage. Fortunately, as an only exception, the carbonate **2e** provided a mixture of **3e** (64%) and **1e** (22%) after 4 h, the former of which indeed afforded **1e** (60%) on further exposure to the carbonylation conditions (room temperature, 22 h). This result led us to the definite conclusion that the allene carboxylates **3** should undoubtedly be a precursor for **1**. Secondly, the carbonylations of the 1,4-enyne **4** terminated at the allene ester **5** (79%) and did not pattern after the conversion **3** → **1**, never leading to the cyclized products **6** and **7** to an any extent even under higher CO pressure (15 kg/cm²); the 1,3-diene ester **8** was also recovered intact under the same conditions.[9] These data imply that a conjugated enallene system is a necessary requirement for the incorporation of the second molecule of carbon

**Scheme III**




monoxide, perhaps via an oxidative addition of the intermediate **3** to Pd(0) species to probably afford a palladacycle intermediate. The rationalization of this point, however, must await future mechanistic studies.

In summary, the newly developed Pd(0)-mediated vicinal carbonylation can be executed in a single pot at room temperature under atmosphere of CO (5 kg/cm²) without any serious problem and leads to products of high chemical purity after conventional column chromatography. It should be emphasized that selection of an appropriate phosphine ligand is crucial to the success of our approach, though the realization of the present process has indeed arisen, in part, from the confluence of several interesting known elementary reactions mediated by transition-metal complexes.[1-3,8] In any event, the reaction has significant synthetic value because the molecular architecture of this type has not been involved within the scope of previous methods for the synthesis of related structures employing transition-metal complexes.[2,10] In addition, a broad range of substitution patterns is tolerated, coupled with ready availability of starting materials and simplicity of their conversion to **2**; therefore, the vicinal carbonylation-carbacyclization would promise much profit to organic synthesis. Biological assays of **1** are currently another of our concerns because of their structural similarity to the clavulone family[11] or sarkomycin,[12] and investigation of such assays is in progress.[13]

**Acknowledgment.** We are grateful to the SC-NMR Laboratory of Okayama University for 500-MHz NMR experiments.

**Supplementary Material Available:** Synthesis procedures and spectroscopic ($^1H$ and $^{13}C$-NMR) and analytical data for compounds **1** and **2** (5 pages). Ordering information is given on any current masthead page.

(4) $Pd(OAc)_2$ was used after concentration of a soluble part in hot benzene to dryness. Also, DPPP was used after recrystallization from ethanol.

(5) The reaction of **2a**, for instance, employing $Pd(OAc)_2$–$Ph_3P$ (1:2) (10 mol %) resulted in the formation of **1a** in only 8% yield after 24 h, **2a** (90%) being recovered intact.

(6) $\nu$(C=O): 1740 and 1700 cm⁻¹. $\nu$(C=C): 1683 and 1661 cm⁻¹.

(7) Observed $\lambda_{max}$ = 255 nm ($\epsilon$ 15 900); $\lambda_{max}$ = 254 nm calculated on the basis of the structure.

(8) For the formation of 2,3-dienyl carboxylates from propargyl carbonates, see: Tsuji, J.; Sugiura, T.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 731–734. Evidence supporting the intervention of this structure has previously been reported for the related transformation: Mandai, T.; Suzuki, S.; Ikawa, A.; Murakami, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1991**, *32*, 7687–7688.

(9) The unsubstituted (**2**, $R^1$ = $R^2$ = H) or electron-withdrawing version (**2**, $R^1$ = Cl, $R^2$ = H) resulted in the formation of deteriorated mixtures or the total recovery of the starting **2** ($R^1$ = Cl, $R^2$ = H), respectively.

(10) Merour, J. Y.; Roustan, J. L.; Charrier, C.; Collin, J. *J. Organomet. Chem.* **1973**, *51*, C24–C25. Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950–952. Tamao, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286–1288.

(11) Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1982**, *23*, 5171–5174; **1983**, *24*, 1549–1552. Iguchi, K.; Yamada, Y.; Kikuchi, H.; Tsukitani, Y. *Tetrahedron Lett.* **1983**, *24*, 4433–4434.

(12) For the synthesis of sarkomycin, see: Linz, G.; Weetman, J.; Hady, A.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5599–5602, and references cited therein.

(13) The observed results of bioassays with the synthetic product such as **1f–h** for P388 and KB cell lines were 2.5, 6.0, 4.0 and 5.0, 15, 4.0 ($IC_{50}$/$\mu$g mL⁻¹), respectively.