Palladium-Catalyzed Intramolecular Alkyne–Carbon Monoxide–Alkene Insertion Cascade for Synthesis of α-Methylenecyclopentenones

Nathan C. Ihle and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

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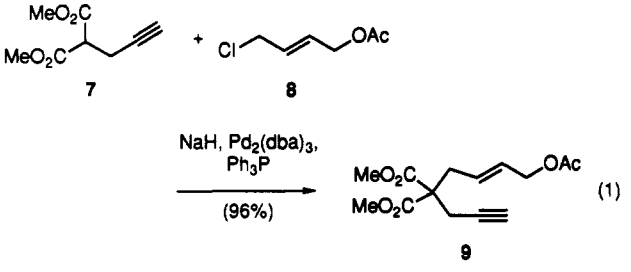
A method for the construction of α-methylenecyclopentenones fused to five-membered rings using a palladium catalyst is reported. The procedure involves the formation of π-allylpalladium intermediates that undergo sequential intramolecular alkyne insertion, carbon monoxide insertion, intramolecular alkene insertion, and β-hydride elimination. Examples of the cyclization are seen in eq 2 and Scheme III.

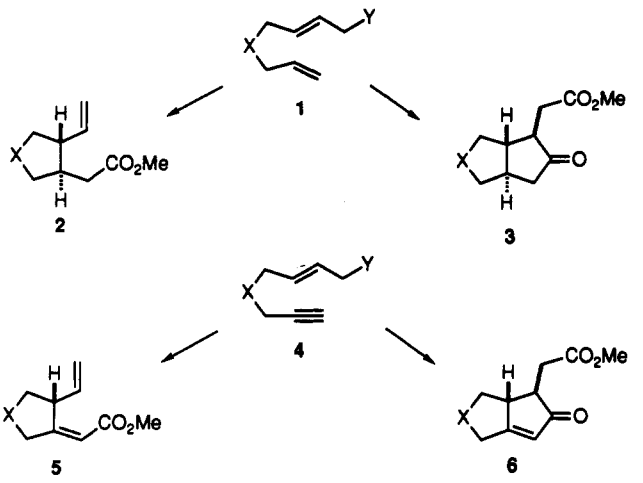
The transition-metal-mediated cyclization–carbonylation of 1,6-dienes and 6-en-1-ynes has been extensively developed and has become a useful method of synthesis of bicyclooctanones and bicyclooctenones.[1] The various modifications on this basic theme include the intramolecular Pauson–Khand reaction,[2] Negishi's zirconium-based method,[3] and Oppolzer's "metallo–ene" procedure.[4] The latter process can give either mono- or bicyclization, depending on the metal catalyst used and on the substitution pattern of the substrate (Scheme I). Of these useful transformations, the cyclizations of 1,6-dienes (1 → 2 or 3) have been studied more than the corresponding cyclizations of 6-en-1-ynes (4 → 5 or 6). In connection with a synthesis project underway in these laboratories, we sought to use Oppolzer's methodology to accomplish one of the latter transformations, analogous to 4 → 5. To our surprise, the reaction took an unexpected course and delivered instead an α-methylenecyclopentenone in good yield. In this paper, we report our brief investigation and optimization of this discovery.

To explore the proposed cyclization–carbonylation reaction an appropriate eneyne with which to screen reaction conditions was needed. Malonate derivative **9**, easily prepared by the palladium-catalyzed allylation[5] of malonate 7[6] by chloroacetate 8[7] (eq 1), was chosen for these studies.

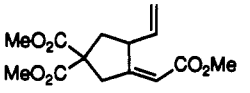


(1)

Scheme I



With this enyne in hand we set about exploring its reactivity under various conditions. As has already been mentioned, it was expected that reaction of **9** with palladium(0) in the presence of carbon monoxide and methanol would lead to the formation of **10**. However,



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this product was never found in more than trace quantities. Instead, the bicyclic compound **11** proved to be the dominant product under a variety of reaction conditions. Through a series of optimization studies it was found that a protic solvent is required for the observed reactivity, with THF/water mixtures giving the best results. Of the ligands tested, Ph_3P proved most effective. The ratio of metal to ligand is also important. When more than 1 equiv of ligand per metal was used the yields were greatly reduced. Also important was the presence of added LiCl, a common additive in carbonylation reactions. Both the commercially-available $Pd_2(dba)_3$ and its easily synthesized chloroform solvate[8] served as convenient sources of palladium(0), allowing easy control over the structure and

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(2) (a) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. (b) Simonian, S. O.; Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Mikaelian, G. S.; Tarasov, V. A.; Ibragimiv, I. I.; Caple, R.; Troen, D. E. *Tetrahedron Lett.* **1986**, *27*, 1245. (c) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *37*, 5289.
(3) Negishi, E. I.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.
(4) (a) Oppolzer, W.; Keller, T. H.; Bedoya-Zurita, M.; Stone, C. *Tetrahedron Lett.* **1989**, *30*, 5883. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. (c) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941. (d) Oppolzer, W.; Xu, J.-Z.; Stone, C. *Helv. Chim. Acta* **1991**, *74*, 465. (e) Oppolzer, W.; Keller, T. H.; Kuo, D. L.; Pachinger, W. *Tetrahedron Lett.* **1990**, *31*, 1265. (f) Yoo, S.-E.; Lee, S.-H.; Yi, K.-Y.; Jeong, N. *Tetrahedron Lett.* **1990**, *31*, 6877. (g) Oppolzer, W.; Ando, A. *Chimia* **1992**, *46*, 122. (h) Keese, R.; Guidetti-Grept, R.; Herzog, B. *Tetrahedron Lett.* **1992**, *33*, 1207.
(5) Nyström, J.-E.; Bäckvall, J.-E. *J. Org. Chem.* **1983**, *48*, 3947.
(6) Dötz, K. H.; Popall, M. *Tetrahedron* **1985**, *41*, 5797.
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(8) Ukai, T.; Kawaqura, H.; Ishii, Y. *J. Organomet. Chem.* **65**, *1974*, 253.

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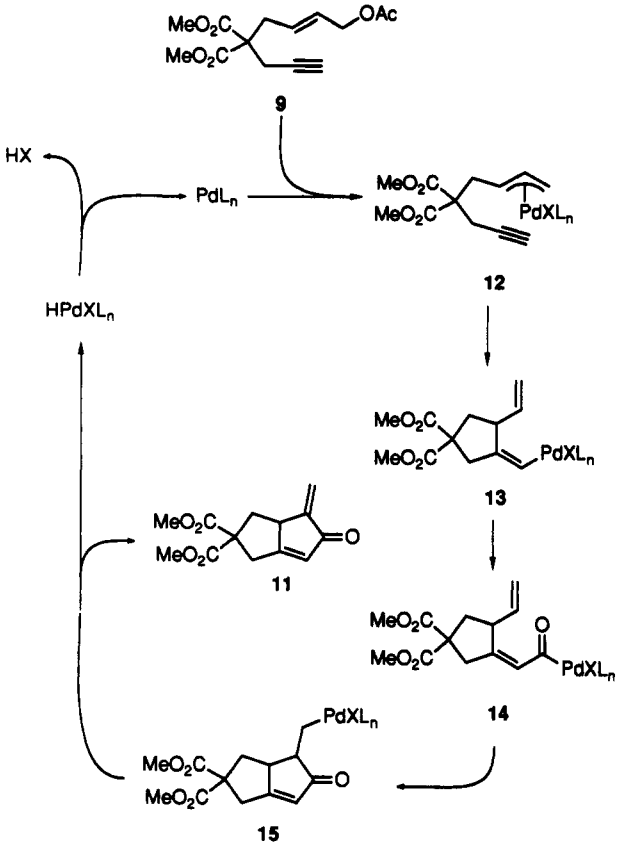
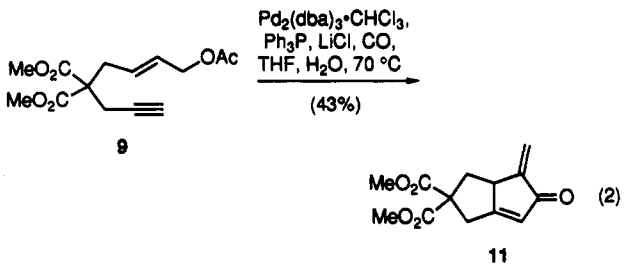
Scheme II

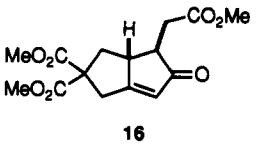


stoichiometry of added phosphine. The best results are shown in eq 2. The product is rather unstable, and crude (NMR) yields appear to be significantly better than the isolated yield reported in eq 2.



The formation of this bicyclic α-methylenecyclopentenone can easily be rationalized as shown in Scheme II. As expected, the palladium(0) complex undergoes oxidative addition to the allyl ester, forming the π-allylpalladium intermediate **12**, which inserts the alkyne in an intramolecular ring-forming step. Carbonylation of **13** follows, and then, rather than undergoing reaction with solvent, a second intramolecular insertion takes place, this time with the alkene. The resulting alkylpalladium **15** suffers β-hydride elimination releasing the organic product, and loss of HX regenerates the palladium(0) catalyst.

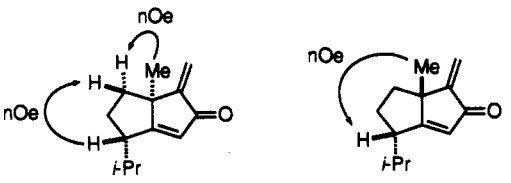
This mode of reaction is not entirely unprecedented. Analogous nickel- and palladium-catalyzed cyclizations provide mixtures of monocyclic and bicyclic products related to the products that would result from carbonylation of intermediates **14** and **15** in Scheme II.[4a,e,9] What is striking, however, is the difference between our results (predominant formation of the β-elimination product **11**) and those of Oppolzer, who observed the exclusive formation of enone triester **16** when the reactions were



carried out in HOAc rather than aqueous THF.[4] We see evidence for the formation of related products under some of the conditions investigated, but always as minor components. There are several possible explanations for this different reaction course.[10] First, it is possible that in acetic acid the rate of carbonylation for alkylpalladium intermediate **15** is faster than β-hydride elimination. It is also possible that intermediate **15** is in equilibrium with a CO-inserted acylpalladium species and that the rate of trapping of this species might affect the branching ratio. Oppolzer's conditions employ more equivalents of triphenylphosphine, which would retard β-elimination. On the other hand, since we employ LiCl as an additive in our reactions, the key intermediate **15** might have X = Cl in our case, whereas X = acetate in Oppolzer's case. It is possible that the presence of a chloride ligand could enhance the rate of β-elimination.

This interesting reaction cascade was further investigated with four other simple substrates (**18**, **20**, **22**, and **24**; Scheme III). Each of these enynes was successfully cyclized upon treatment with Pd(0). Equation 2 and Scheme III illustrate several features of the method. Both acetates (e.g., **9**, **18**) and benzoates (e.g., **20**, **22**, **24**) serve for the generation of the requisite π-allylpalladium. Furthermore, either the internal or terminal isomer of the allyl ester can be used. Finally, methyl substitution at the 3-position of the allyl group is not detrimental, and these cyclizations provide angularly-methylated bicyclic products in acceptable yield.

As shown in Scheme III, cyclization of enyne **24** provided isomers **28a** and **28b** in a ratio of 73:27. The relative configuration was established by difference NOE experiments and coupling constant analysis:



In summary, this paper reports the discovery of a new palladium-catalyzed intramolecular cyclization procedure for the preparation of α-methylenecyclopentenones fused to five-membered rings, materials of obvious utility for the synthesis of polyquinane natural products.

Experimental Section

General. THF was distilled from Na/benzophenone, and CH_2Cl_2 was distilled from CaH_2. Crude extracts were dried over $MgSO_4$ and concentrated with a rotary evaporator. NMR spectra were measured as $CDCl_3$ solutions. Tris(dibenzylidineacetone)-dipalladium(0), $Pd_2(dba)_3$, was obtained from the Aldrich Chemical Co. (catalog no. 32,877-4). We found that the $CHCl_3$ solvate,

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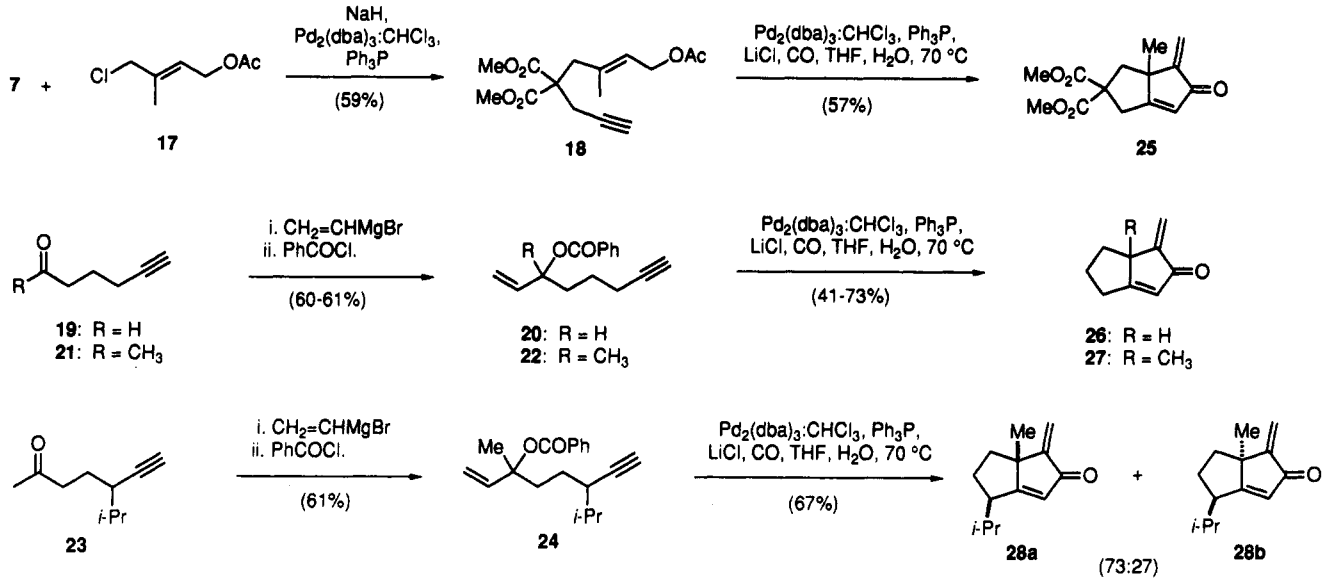
(10) We thank a reviewer for several useful suggestions pertaining to this point.

Scheme III



prepared by a literature procedure[8] or by recrystallization of the commercial $Pd_2(dba)_3$ from $CHCl_3$, gave better yields.

Methyl (*E*)-6-Acetoxy-2-(methoxycarbonyl)-2-propargylhex-4-enoate (9). Dimethyl 2-propargylmalonate (7) (1.22 g, 7.17 mmol) was added over 5 min to a suspension of 0.40 g of NaH (50% oil dispersion; 8.3 mmol of NaH) in 10 mL of THF cooled to 0 °C and then warmed to rt for 10 min. This enolate solution was added to a solution of 40 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (39 μmol), 82 mg of Ph_3P (310 μmol), and 1.13 g (7.61 mmol) of 1-acetoxy-4-chloro-2-butene (8) in 5 mL of THF. After 20 min the reaction mixture was poured into 1% HCl and extracted twice with ether, and the organic layers were washed with brine. The crude material was purified by flash chromatography on a 50- × 150-mm column, eluting with 5:1 hexanes–EtOAc to obtain 1.94 g of enyne 9, *E*:*Z* = 20:1 (6.88 mmol, 96%). ^1H NMR (400 MHz): δ 2.04 (t, *J* = 2.6 Hz, 1), 2.06 (s, 3), 2.79 (d, *J* = 2.7 Hz, 2), 2.82 (d, *J* = 7.4 Hz, 2), 3.75 (s, 6), 4.50 (d, *J* = 6.2 Hz, 2), 5.59 (dt, *J* = 15.3, 7.4 Hz, 1), 5.73 (dt, *J* = 15.3, 6.2 Hz, 1). ^{13}C NMR (100 MHz): δ 20.90 (CH_3), 22.78 (CH_2), 35.02 (CH_2), 52.80 (CH_3), 56.80 (C), 64.39 (CH_2), 71.64, 78.54, 128.44 (CH), 129.28 (CH), 169.95 (C), 170.65 (C). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.55; H, 6.39.

7,7-Bis(methoxycarbonyl)-4-methylenebicyclo[3.3.0]oct-1-en-3-one (11). In a Schlenk tube fitted with a cold finger condenser were placed $Pd_2(dba)_3{\cdot}CHCl_3$ (35 mg, 34 μmol), Ph_3P (17.1 mg, 65 μmol), LiCl (65 mg, 1.53 mmol), and THF (5 mL). After 5 min, 2.5 mL of degassed H_2O was added to the burgundy solution, followed by a solution of 389 mg (1.38 mmol) of enyne 9 in 5 mL of THF. Carbon monoxide was bubbled through the solution for 2 min, and a 1-atm blanket was maintained while the yellow solution was heated in a 70 °C bath for 24 h. The mixture was poured into 1% HCl and extracted three times with ether, and the organic layers were washed with 1% NaOH and brine. The crude product was purified by medium-pressure liquid chromatography (MPLC), eluting with 2:1 hexanes–EtOAc, to obtain the rather unstable dienone 11 (147.6 mg, 43%). GC analysis of this and other reactions implied that the crude yields were much better than indicated; however, the instability of the product precluded the accurate determination of yields by GC. ^1H NMR (500 MHz): δ 1.78 (t, *J* = 12.6 Hz, 1), 2.90 (dd, *J* = 12.9, 8.0 Hz, 1), 3.32 (ABXdt, *J* = 18.8, 1.2 Hz, 1), 3.38 (ABXdt, *J* = 18.8, 1 Hz, 1), 3.76 (s, 3), 3.82 (s, 3), 3.61 (br t, *J* = 9 Hz, 1), 5.39 (t, *J* = 0.8 Hz, 1), 6.04 (d, *J* = 1.8 Hz, 1), 6.14 (br s, 1). ^{13}C NMR (125 MHz): δ 35.11 (CH_2), 36.96 (CH_2), 48.36 (CH), 53.14 (CH_3), 53.33 (CH_3), 61.05 (C), 116.03 (CH_2), 126.73 (CH), 145.56 (C), 170.91 (C), 171.81 (C), 179.86 (C), 196.53 (C). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.16; H, 5.95.

Methyl (*E*)-6-Acetoxy-2-(methoxycarbonyl)-4-methyl-2-propargylhex-4-enoate (18). Dimethyl 2-propargylmalonate 7[6] (1.22 g, 7.17 mmol) was added over 5 min to a suspension of 0.41 g of NaH 50% oil dispersion (8.5 mmol) in 10 mL of THF cooled to 0 °C. This enolate solution was warmed to rt and added to a solution of 80 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (77 μmol) and 216 mg of Ph_3P (820 μmol) in 5 mL of THF. To this solution was added 1.39 g (9.2 mmol) of 1-acetoxy-4-chloro-2-methyl-2-butene (17).[7] After 1 h the reaction mixture was poured into 1% HCl and extracted twice with ether, and the organic layers were washed with brine. The crude material (*E*:*Z* 20:1) was purified by Kügelrohr distillation (115–145 °C (0.2 Torr)) and MPLC on silica, eluting with 10:1 hexanes–EtOAc, to obtain 1.25 g (59%) of 18. ^1H NMR (500 MHz): δ 1.64 (br s, 4), 2.05 (s, 3), 2.80 (d, *J* = 2.7 Hz, 2), 2.86 (br s, 2), 3.75 (s, 6), 4.56 (d, *J* = 6.9 Hz, 2), 5.50 (br t, *J* = 6.8 Hz, 1). ^{13}C NMR (125 MHz): δ 17.18 (CH_3), 20.92 (CH_3), 22.68 (CH_2), 41.21 (CH_2), 52.76 (CH_3), 56.65 (C), 60.90 (CH_2), 71.94, 78.94, 124.79 (CH), 135.70 (C), 170.33 (C), 170.90 (C). Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.61; H, 6.70.

Oct-1-en-7-yn-3-yl Benzoate (20). Vinylmagnesium bromide (0.76 M in THF, 21.3 mL, 16.2 mmol) was cooled to 0 °C (slurry), and a solution of 5-hexynal[11] (1.554 g, 16.2 mmol) in 10 mL of THF was added over 10 min. After 15 min more, 1.9 mL (16 mmol) of benzoyl chloride was added and the mixture was warmed to rt for 1 h before quenching with saturated NH_4Cl, extracting twice with ether, and washing the organic layers with saturated $NaHCO_3$ and brine. The crude material was distilled (bulb-to-bulb, ot 80–110 °C (0.2 Torr)) and purified by MPLC with 20:1 hexanes–ether to obtain 2.21 g (60%) of benzoate 20. ^1H NMR (500 MHz): δ 1.61–1.71 (m, 2), 1.84–1.94 (m, 2), 1.97 (t, *J* = 2.7 Hz, 1), 2.26 (td, *J* = 7.0, 2.6 Hz, 2), 5.23 (dt, *J* = 10.5, 1.1 Hz, 1), 5.34 (dt, *J* = 17.3, 1.3 Hz, 1), 5.52 (br q, *J* = 6.1 Hz, 1), 5.90 (ddd, *J* = 17.3, 10.5, 6.2 Hz, 1), 7.45 (br t, *J* = 6.4 Hz, 2), 7.56 (tt, *J* = 7.4, 1.3 Hz, 1), 8.07 (dm, *J* = 7 Hz, 2). ^{13}C NMR (125 MHz): δ 18.21 (CH_2), 24.01 (CH_2), 33.24 (CH_2), 68.76, 74.68 (CH), 83.82, 116.89 (CH_2), 128.34 (CH), 129.57 (CH), 130.38 (C), 132.92 (CH), 136.18 (CH), 165.76 (C). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.00; H, 7.04.

3-Methyloct-1-en-7-yn-3-yl Benzoate (22). A solution of vinylmagnesium bromide (0.76 M in THF, 34 mL, 26 mmol) was cooled to 0 °C (whereupon it turned to a slurry), and a solution of 6-heptyn-2-one[12] (2.68 g, 24.4 mmol) in 15 mL of THF was added over 10 min. After 10 min more, 3.4 mL (29 mmol) of benzoyl chloride was added and the mixture was warmed to rt for 4 h before quenching with saturated NH_4Cl, extracting twice with ether, and washing the organic layers with brine. MPLC, eluting with 50:1 hexanes–EtOAc gave 3.59 g (61%) of benzoate 22. ^1H NMR (500 MHz): δ 1.65 (dt, *J* = 16.7, 7.1 Hz, 2), 1.70 (s, 3), 1.97 (t, *J* = 2.7 Hz, 1), 1.99 (dm, *J* = 7.1 Hz, 1), 2.12 (dm, *J* = 7.0 Hz, 1 H), 2.23 (td, *J* = 7.1, 2.6 Hz, 2), 5.20 (d, *J* = 10.8 Hz, 1), 5.28 (d, *J* = 17.4 Hz, 1), 6.08 (dd, *J* = 17.5, 11.0 Hz, 1), 7.43 (br t, *J* = 7.9 Hz, 2), 7.54 (br t, *J* = 7.4 Hz, 1), 8.01 (br d, *J* = 7.1 Hz, 2). ^{13}C NMR (125 MHz): δ 18.59 (CH_2), 22.87 (CH_2),

(11) Adams, T. C.; Combs, D. W.; Caves, G. D., Jr.; Hauser, F. M. *J. Org. Chem.* **1981**, *46*, 4582.

23.80 (CH_3), 39.22 (CH_2), 68.62, 83.29, 84.07, 113.54 (CH_2), 128.27 (CH), 129.45 (CH), 131.44 (C), 132.66 (CH), 141.58 (CH), 165.17 (C). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.25; H, 7.55.

7,7-Bis(methoxycarbonyl)-5-methyl-4-methylenebicyclo-[3.3.0]oct-1-en-3-one (25). In a Schlenk tube fitted with a cold-finger condenser were placed $Pd_2(dba)_3$·$CHCl_3$ (5.9 mg, 5.7 μmol), Ph_3P (3.9 mg, 15 μmol), LiCl (5 mg, 0.1 mmol), and 1 mL of THF. After 5 min 1 mL of degassed H_2O was added. To this burgundy mixture was added a solution of 56.0 mg of enyne **18** (0.19 mmol) in 2 mL of THF. The solution was saturated by bubbling CO through it for 1 min, and a 1-atm blanket was maintained while the yellow solution was heated in a 70 °C bath for 22 h. The mixture was poured into 1% NaOH and extracted twice with ether, and the organic layers were washed with brine. The crude product (approx 57% yield) was purified by flash chromatography on 10- × 150-mm silica, eluting with 10:1 hexanes–EtOAc, to obtain 17.4 mg (35%) of **25**. Tan crystals, mp 78.0–79.0 °C, were obtained by recrystallization from 4:1 hexanes–EtOAc. ^1H NMR (500 MHz): δ 1.24 (s, 3), 2.20 (d, J = 13.6 Hz, 1), 2.67 (d, J = 13.6 Hz, 1), 3.27 (d, J = 17.3 Hz, 1), 3.48 (dd, J = 17.2, 2.2 Hz, 1), 3.72 (s, 3), 3.83 (s, 3), 5.30 (s, 1), 5.97 (s, 1), 6.07 (d, J = 2.0 Hz, 1). ^{13}C NMR (125 MHz): δ 25.39 (CH_3), 34.14 (CH_2), 42.35 (CH_2), 52.10 (C), 53.29 (CH_3), 53.40 (CH_3), 60.18 (C), 114.30 (CH_2), 125.58 (CH), 152.13 (C), 171.41 (C), 171.97 (C), 182.82 (C), 196.51 (C). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.62; H, 6.09.

4-Methylenebicyclo[3.3.0]oct-1-en-3-one (26). In a Schlenk tube fitted with a cold-finger condenser were placed $Pd_2(dba)_3$·$CHCl_3$ (28 mg, 27 μmol), Ph_3P (14.6 mg, 56 μmol), LiCl (90 mg, 2.1 mmol), 10 mL of THF, and 0.25 mL of dodecane (GC standard). After 10 min 10 mL of degassed H_2O was added. To this burgundy mixture was added a solution of enyne **20** (498 mg, 2.18 mmol) in 20 mL of THF. The solution was saturated by bubbling CO through it for 2 min, and a 1-atm blanket was maintained while the yellow solution was heated in a 70 °C bath for 48 h. The mixture was poured into 1% HCl and extracted three times with ether, and the organic layers were washed with brine. After drying ($MgSO_4$), the solution was filtered through Florisil eluting with additional ether, and a GC yield of 73% was determined. Due to the volatility of the product solvent was removed by fractional distillation at 1 atm. The crude product was purified by MPLC, eluting with 2:1 petroleum ether–ether, and an analytical sample was prepared by prep GC (SE-30). Pure **26** proved to be very unstable, tending to polymerize in a matter of min or h at rt. ^1H NMR (500 MHz): δ 1.22 (tt, J = 11.9, 9.2 Hz, 1), 2.08–2.15 (m, 2), 2.24 (m, 1), 2.58 (ABXdt, J = 18.6, 8.2 Hz, 1), 2.68 (ABXdm, J = approx 15 Hz, 1), 3.39 (br tm, J = 9.6, 1.5 Hz, 1), 5.33 (br d, J = 0.5 Hz, 1), 5.99 (dd, J = 2.0, 0.8 Hz, 1), 6.09 (br s, 1). ^{13}C NMR (125 MHz): δ 25.89 (CH_2), 26.23 (CH_2), 28.87 (CH_2), 50.06 (CH), 114.81 (CH_2), 125.91 (CH), 146.78 (C), 186.27 (C), 198.03 (C). HR/MS m/z calcd for $C_9H_{10}O$: 134.0732, found 134.0732.

5-Methyl-4-methylenebicyclo[3.3.0]oct-1-en-3-one (27). In a Schlenk tube fitted with a cold-finger condenser were placed $Pd_2(dba)_3$·$CHCl_3$ (13.4 mg, 12.9 μmol), Ph_3P (6.7 mg, 26 μmol), LiCl (15 mg, 0.3 mmol), and 1 mL of THF. After 5 min 2 mL of degassed H_2O was added. To this burgundy mixture was added a solution of enyne **22** (54.7 mg, 0.226 mmol) in 1 mL of THF. The solution was saturated by bubbling CO through it for 1 min, and a 1-atm blanket was maintained while the yellow solution was heated in a 70 °C bath for 18 h. Dodecane (25 μL, GC standard) was added, the mixture was quenched in 1% HCl and extracted twice with ether, and the organic layers were washed with brine. After drying ($MgSO_4$), the product was filtered through Florisil, eluting with additional ether, and a GC yield of 41% was determined.[12] Due to the volatility of the product solvent was removed by fractional distillation at 1 atm. The crude product was purified by MPLC, eluting with 10:1 hexanes–EtOAc, and an analytical sample of **27** was prepared by prep GC (SE-30). ^1H NMR (500 MHz): δ 1.23 (s, 3), 1.46 (dt, J = 12.0, 10.2 Hz, 1), 1.90 (br dd, J = 12.4, 8.0 Hz, 1), 2.01 (tddm, J = 10.4, 4.4, 1.4 Hz, 1), 2.38 (m, 1), 2.60 (br ABXddd, J = 17.9, 8.9, 5.7 Hz, 1), 2.71 (ABXdddd, J = 17.9, 11.9, 4.4, 2.1 Hz, 1), 5.26 (br s, 1), 5.94 (br s, 1), 6.00 (br s, 1). ^{13}C NMR (125 MHz): δ 23.65 (CH_2), 24.46 (CH_3), 24.71 (CH_2), 34.33 (CH_2), 52.63 (C), 113.25 (CH_2), 124.66 (CH), 152.83 (C), 189.44 (C), 197.83 (C).

6-Isopropyl-3-methyloct-1-en-7-yn-3-yl Benzoate (24). A solution of vinylmagnesium bromide (7.8 mL of 1.02 M in THF, 7.96 mmol) was added over 10 min to a solution of ketone **23**[13] (1.098 g, 7.22 mmol) in 10 mL of THF at 0 °C. After 10 min more, 1.26 mL (10.8 mmol) of benzoyl chloride was added and the mixture was warmed to rt for 4.5 h. The mixture was quenched into NH_4Cl and extracted twice with ether, and the organic layers were washed with saturated $NaHCO_3$ and then brine. The crude product was purified by MPLC, eluting with 50:1 hexanes–EtOAc, to obtain 1.254 g (61%) of benzoate **24**. ^1H NMR (500 MHz): δ 0.95–0.99 (m, 6), 1.8–1.62 (m, 2), 1.69/1.71 (s, 3), 1.98 (m, 1), 2.07–2.12 (m, 2), 2.18–2.25 (m, 2), 5.198/5.206 (dd, J = 11.1, 0.8 Hz, 1), 5.267/5.286 (dd, J = 17.4, 0.7 Hz, 1), 6.07/6.10 (dd, J = 17.6, 11.0 Hz, 1), 7.43 (br t, J = 7.7 Hz, 2), 7.54 (br t, J = 7.7 Hz, 1), 8.02 (dm, J = 8 Hz, 2). ^{13}C NMR (125 MHz): δ 18.24/18.29, 21.02, 23.62/23.84, 26.69/26.73 (CH_2), 31.08/31.1, 38.23 (CH_2), 38.73/38.74, 70.48, 83.37/83.55, 85.82, 113.49/113.52 (CH_2), 128.25 (CH), 129.43 (CH), 131.47/131.51 (C), 132.62 (CH), 141.57/141.73 (CH), 165.18 (C). Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.49; H, 8.40.

(5*SR*,8*RS*)- and (5*RS*,8*RS*)-8-Isopropyl-5-methyl-4-methylenebicyclo[3.3.0]oct-1-en-3-one (28a and 28b). In a Schlenk tube fitted with a cold-finger condenser were placed $Pd_2(dbd)_3$·$CHCl_3$ (9.1 mg, 8.8 μmol), Ph_3P (4.7 mg, 18 μmol), LiCl (10 mg, 0.2 mmol), and 1 mL of THF. After 5 min 1 mL of degassed H_2O was added. To this burgundy mixture was added a solution of 59.8 mg (0.21 mmol) of enyne **24** and 10 μL of dodecane (GC standard) in 2 mL of THF. The solution was saturated by bubbling CO through it for 1 min, and a 1-atm blanket was maintained while the yellow solution was heated in a 70 °C bath for 22 h. The mixture was poured into 1% HCl and extracted with ether and the organic layer washed with brine. GC analysis indicated 67% crude yield. Flash chromatography on 15- × 150-mm silica, eluting with 20:20:1 hexanes–CH_2Cl_2–ether, provided 18.8 mg (47%) of **28a** and **28b** as a 2.7:1 mixture. Semipreparative HPLC on μPartisil, eluting with 50:1 hexanes–EtOAc, resulted in separation of diastereomers, with the minor component, **28b** eluting first. NOE difference experiments and coupling constant evaluation permitted the unequivocal assignment of configuration in both **28a** and **28b**.

Isomer 28a. ^1H NMR (400 MHz): δ 1.02 (apparent t, J = 6.8 Hz, 6), 1.25 (s, 3), 1.42 (dm, J = 8.1 Hz, 1), 1.67 (m, 1), 1.88–1.98 (m, 2), 2.20 (m, 1), 2.43 (br q, J = 8 Hz, 1), 5.20 (s, 1), 5.88 (s, 1), 5.99 (br s, 1). ^{13}C NMR (100 MHz): δ 21.63 (CH_3), 22.05 (CH_3), 25.12 (CH_3), 31.22 (CH_2), 33.94 (CH), 34.86 (CH_2), 47.91 (CH), 53.42 (C), 112.63 (CH_2), 127.54 (CH), 153.77 (C), 191.43 (C), 197.71 (C). HRMS: calcd for $C_{13}H_{18}O$ 190.1358, found 190.1362.

Isomer 28b. ^1H NMR (400 MHz): δ 0.86 (d, J = 6.8 Hz, 3), 1.04 (d, J = 6.7 Hz, 3), 1.25 (s, 3), 1.43 (dt, J = 12.1, 9.9 Hz, 1), 1.72 (dddd, J = 13.4, 10.2, 5.5, 2.4 Hz, 1), 1.86 (ddd, J = 12.4, 8.3, 2.3 Hz, 1), 2.00 (heptd, J = 6.7, 5.6 Hz, 1), 2.25 (m, 1), 2.85 (dtd, J = 11.3, 5.5, 2.1 Hz, 1), 5.23 (s, 1), 5.91 (s, 1), 5.99 (d, J = 1.9 Hz, 1). ^{13}C NMR (100 MHz): δ 18.31 (CH_3), 21.70 (CH_3), 25.87 (CH_3), 26.64 (CH_2), 29.49 (CH), 33.84 (CH_2), 43.93 (CH), 53.00 (C), 112.95 (CH_2), 123.44 (CH), 153.10 (C), 191.36 (C), 197.66 (C). HRMS: calcd for $C_{13}H_{18}O$ 90.1358, found 190.1352.

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Supplementary Material Available: ^1H NMR spectra of compounds **26**, **27**, **28a**, and **28b** and IR spectra of all compounds reported (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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