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A PALLADIUM-CATALYZED CARBON-CARBON BOND FORMATION OF CONJUGATED DIENONES

A MACROCYCLIC DIENONE LACTONE MODEL FOR THE CARBOMYCINS

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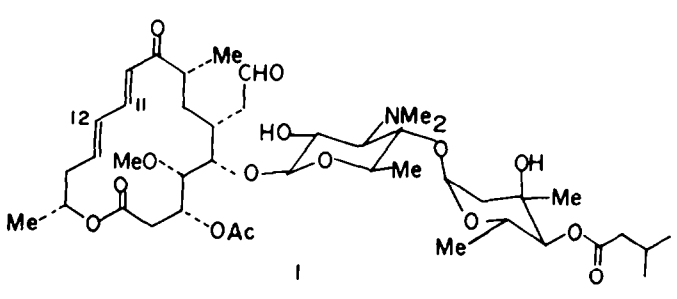
Abstract—A Pd catalyzed coupling of terminal vinylic iodides with methyl vinyl ketone and related enones to produce dienones is described. The application of this method to macrocyclization is demonstrated in a model system for the agylcone of carbomycin B.

Our studies relating to the synthesis of carbonolide B, the aglycone of the antibiotic carbomycin B (**1**), have focused upon developing a method for C_{11}–C_{12} macrocyclization. Transition metals, by virtue of their chemoselectivity, appear as suitable candidates for achieving such a goal. Cu[1], Ni[2], Pd[3], and Ti-W[4] have been employed in the construction of both medium and large rings containing limited functionality.

Alkenylcuprates have been demonstrated to add to propargylic esters to produce dienoates.[5] Dienoates are formed when alkenylalanes and β-bromo-acrylates are exposed to Pd (0) catalysis.[6] Alkenyl mercurials add to ethyl acrylate under the influence of $PdCl_2$ to produce π-allyl complexes of β,γ unsaturated esters,[7] while $Ni(AcAc)_2$ catalyzes the conjugate addition of alkenylzirconium reagents to α,β-unsaturated ketones in the reductive (i.e. Michael) sense.[8] Alkenyl boronic acids provide dienoates when condensed with methyl acrylate in the presence of palladium acetate.[9] For these methods to be successful in an intramolecular reaction, the formulation of the organometallic moiety must be compatible with a variety of reactive functionality.

The coupling sequence is believed to occur by initial reduction of the catalyst to Pd(0) species followed by oxidative addition of the vinyl halide (ostensibly with retention of configuration) to form an alkenyl Pd(II) intermediate. Addition of the complex to the unsaturated carbonyl compound and subsequent oxidative elimination provides the dienoate and a hydridopalladium halide which, in turn, is deprotonated by triethylamine (present in the reaction medium) to regenerate the ligand-bound Pd(0) catalyst.[9]

Heck has principally employed vinylic bromides in his studies and has demonstrated that vinyl iodide and *E*- and-*Z*-1-iodo-1-hexene are viable substrates in the reaction of methyl acrylate with 1 mol% $Pd(OAc)_2(Ph_3P)_2$ at 100°. If the reaction were to be successful under mild conditions, the more reactive vinylic iodides would have to be employed. Accordingly, when *E*-1-iodo-1-octene (**2a**) was coupled with 1.5 equivalents of methyl vinyl ketone (MVK) in the presence of 5 mol % of $PdCl_2(Ph_3P)_2$ (entry 1, Table 1) or 5 mol % of $Pd(OAc)_2(Ph_3P)_2$ (entry 2) at 60° for 60 hr, only 30–35% of the *E,E*-dienone **4a** was obtained reflecting a six-fold



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RESULTS AND DISCUSSION

The seminal studies of Heck,[9] involving the Pd-catalyzed oxidative coupling of vinyl halides with methyl acrylate to form dienoates, held promise for the realization of our goal. The vigorous conditions of these reactions (100°), the frequent lack of solvent, the formation of Diels–Alder adducts from the resultant dienoates, and the inability of α,β-unsaturated ketones to participate successfully in these reactions,[9,10] prompted us to explore conditions which would ameliorate this situation.[11] turnover in catalyst. These initial results were encouraging, but in need of substantial improvement.

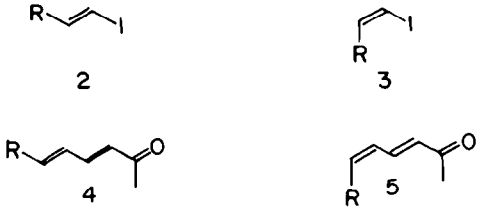


Table 1.

Entry	Iodide	Unsat. Carbonyl	Catalyst (mol %)[a]	Solvent	Temp., °C	Time, h[b]	Product, % Yield[c,d]
1	2a	MVK	A (5)[e]	$PhCH_3$	60	60	30, (E,E)[d]
2	2a	MVK	B (5)[e]	$PhCH_3$	60	60	35, (E,E)[d]
3	2a	MVK	C (10)	CH_3CN	55	3	81, (E,E:E,Z > 20:1)[f]
4	2a	MVK	C (10)	THF	55	3	72, (E,E:E,Z > 20:1)[g]
5	2a	MVK	C (1)	CH_3CN	55	24	69, (E,E:E,Z > 20:1)[f]
6	3a	MVK	C (10)	CH_3CN	55	4	81, (E,Z:E,E = 4:1)[f]
7	3a	MVK	C (10)	THF	35	5.25	low (mostly 3a)
8	2b	MVK	C (20)	THF	35	6.25	78, (E,E:E,Z > 20:1)[f]
9	2b	MVK	D (20)	THF	25	4.5	75, (E,E:E,Z > 10:1)[f]
10	2b	MVK	C (10)	CH_3CN	55	2.5	85, (E,E:E,Z > 8:1)[f,h]
11	2b	MVK	C (1)	CH_3CN	55	4	88, (E,E:E,Z > 5:1)[f,h]
12	2b	MA	C (10)	CH_3CN	55	3	73, (E,E)[i]
13	2b	13	C (10)	THF	25	8.5	71, (E,E)[i]
14	3b	MVK	C (10)	THF	55	3.75	62, (E,E:E,E = 77:23)[g]
15	3b	MVK	C (1)	CH_3CN	55	21	76, (E,Z:E,E = 60:40)[f]
16	PhI	MVK	C (10)	CH_3CN	55	5	<5, (E-PhCH=CHCOCH$_3$)
17	p-$NO_2C_6H_4I$	MVK	C (10)	CH_3CN	55	3.25	70, (E-p$NO_2C_6H_4$CH=CHCOCH$_3$)[m]
18	11	-	C (100)	THF	25	11[j]	low ~ 10%
19	11	-	C (100)	CH_3CN	25	11[k]	55, (E,E)[l]
20	7	MVK	C (10)	CH_3CN	55	3.25	N.R.

a) A = $PdCl_2(Ph_3P)_2$, B = $Pd(OAc)_2(Ph_3P)_2$, C = $PdCl_2(CH_3CN)_2$, D = $PdCl_2(PhCN)_2$, b) Time required for disappearance of iodide, c) Isolated by SiO_2 chromatography unless stated otherwise, d) Yields determined by GC using hexadecane as an internal standard, e) K_2CO_3 employed in addition to Et_3N, f) Isomer ratio determined by GC, g) Isomer ratio determined by NMR, h) Approximately 5% impurities, i) E,Z isomer was not detected by ^1H NMR, j) Addition time = 10 h, k) Addition time = 9.75 h, l) E,Z-isomer was not detected by ^1H NMR or GC, m) mp 112.0-113.0°C, lit. mp 110°C, Baeyer, A.; Becker, P., Chem. Ber., 1883, 16, 1968.

It was thought that pre-reduction of the Pd catalyst and the use of a weaker ligand than triphenylphosphine would facilitate the reaction. When $PdCl_2(CH_3CN)_2$[12] (10 mol %) was employed as a catalyst in acetonitrile and pre-reduced with formic acid at 25°, followed by heating at 55°, dienones **4a** (*E,E*) and **5a** (*E,Z*) were produced (> 20:1, respectively) in 81% yield (8-fold turnover) in only 3 hr (entry 3). The reaction was slightly less efficient in THF (entry 4) but it was able to be conducted in 69% yield (69-fold turnover) with 1 mol % catalyst in MeCN for 24 hr (entry 5).

The *Z*-isomer of 1-iodo-1-octene (**3a**) provided an 81% yield of dienones, wherein the *E,Z*-isomer predominated over the *E,E*-isomer in a 4/1 ratio (entry 6). This reaction was somewhat slower in acetonitrile than its *trans* counterpart. When THF was employed as a solvent (entry 7), a low yield (< 10%) of the dienones was obtained and the *Z*-iodo-octene was recovered. Since THF was found to be a suitable solvent for the *E*-isomer, this implies a slower rate of oxidative addition of the *Z*-iodo-octene to the Pd(0)-acetonitrile complex. The decomposition of the catalyst by dissociation to Pd metal (precipitation) in THF is faster than oxidative addition of the *Z*-iodo-octene. In acetonitrile, the complex is stabilized by mass action and, consequently, permits the oxidative addition to occur. The faster rate of consumption of the *E*-iodo-octene compared to the *Z*-isomer was observed when 2 equivalents of an equal mixture of the two iodides were permitted to compete for 4 equivalents of MVK in the presence of 1 mol % of catalyst. Over a period of two days, the *E*-iodide was totally consumed while the *Z*-isomer was still present.

Since *E*-5-iodo-4-penten-2-ol (**6**) was to play a role in our intramolecular cyclization studies, we investigated the reactivity of *E*- and *Z*-1-iodo-4-acetoxy-1-pentene. Both $PdCl_2(CH_3CN)_2$ and $PdCl_2(PhCN)_2$ at 20 mol % successfully produced the dienones **4b** and **5b** in THF solution at 25–35° when the *E*-vinylic iodide was employed. The *E*-vinylic iodide **2b**, as was the case with **2a**, reacted faster than its *Z*-isomer. Use of 1 mol % of $PdCl_2(CH_3CN)_2$ resulted in consumption of the *E*-isomer in 4 hr (55°, MeCN), while 21 hr were required to consume the *Z*-isomer.

In all reactions involving the $PdCl_2(RCN)_2$ catalyst and MVK, the major dienone was always the one possessing the stereochemistry of the vinylic iodide employed. The partial isomerization of the *E,Z*-isomer appears to occur prior to reductive elimination of the Pd complex from the substrate, presumably via a π-allyl complex, as has been invoked by Heck.[9]

In an experiment with methyl acrylate (MA), *E*-vinylic iodide **2b** provided the *E,E*-dienoate, uncontaminated with other double bond isomers (entry 12).

Iodobenzene provided only a 5% yield of 4-phenyl-3-buten-2-one. However, *p*-iodonitrobenzene provided 4-(*p*-nitrophenyl)3)buten-2-one in 70% yield. *Z*-1-Bromo-1-octene (**7**) failed to react under conditions which were successful for the vinylic iodides.

These preliminary studies set the stage for an investigation of the applicability of this method in an intramolecular reaction as a model for carbonolide B. The synthesis of the required iodo enone **11** is outlined in the Scheme.

It was necessary to effect the cyclization of compound **11** under conditions of high dilution. In view of the instability of the catalyst during the prolonged addition of the substrate, a stoichiometric amount of "catalyst" was employed to maintain active catalyst during the course of the addition and to permit the ring closure to be performed at 25°. As in the cases of the intermolecular reaction, MeCN (entry 19) was found to be a better solvent than THF (entry 18). The known[13] macrocyclic dienone **12** was readily produced in 55% yield. The inability of THF to function as a viable solvent with *E*-iodide **11**, in contrast to intermolecular reactions of *E*-iodides **2a** and **2b**, can be ascribed to the irreversible decomposition of the catalyst in the absence of a sufficient concentration of vinylic iodide **11** to permit oxidative addition.

An alternative approach to macrocyclic lactone **12** could invoke initial carbon–carbon bond formation followed by lactonization. The coupling reaction (entry 13) between *E*-vinylic iodide **2b** and methyl-9-oxo-10-undecenoate (**13**) (1 equiv) was successfully performed at 25° (THF) under catalytic conditions.

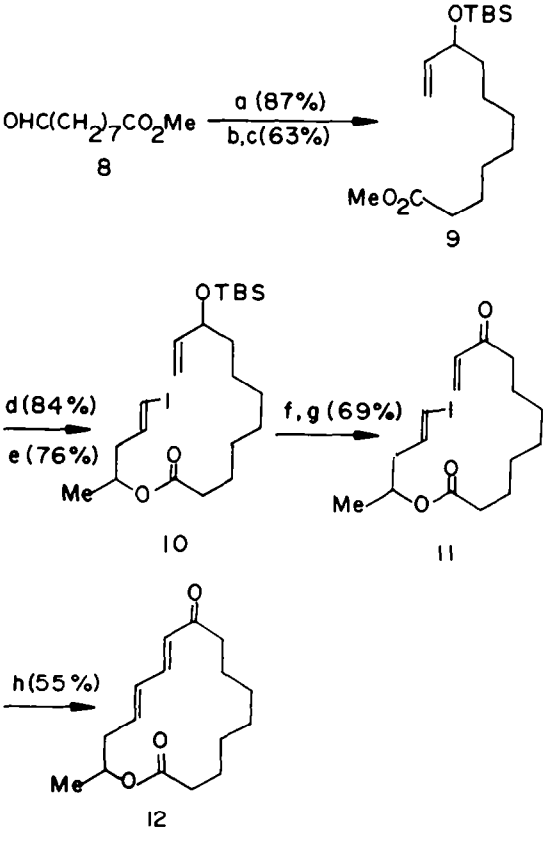
Studies are currently under way to apply these methods to the synthesis of carbonolide B.

EXPERIMENTAL

General procedures. M.ps were determined on a Fisher–Johns m.p. apparatus and are uncorrected. All reactions were performed under N_2. In most cases, liquids were introduced into the reaction vessel via syringe.

Anhyd THF and ether were freshly distilled from sodium benzophenone ketyl. MeCN, toluene, DMF, and CH_2Cl_2 were distilled from calcium hydride. Formic acid was distilled from phthalic anhydride.

IR spectra were obtained on a Nicolet 7000 FT-IR. ^1H NMR spectra were recorded on a Varian EM-390 spectrometer



Scheme 1. (a) HC≡CLi, (b) H_2, $Pd/BaSO_4$, (c) t-$BuMe_2SiCl$, DMAP, Et_3N, (d) LiOH, DME-H_2O, (e) **6**, DCC, DMAP, Et_2O, (f) n-$Bu_4N^+F^-$, THF, (g) MnO_2, (h) entry 19, Table 1.

(90 MHz), a Varian EM-360 spectrometer (60 MHz), or a Bruker HX-270 spectrometer (270 MHz) using TMS as an internal standard. ^{13}C NMR spectra were recorded on a Jeol FX-90 spectrometer (22.5 MHz) or a Bruker HX-270 spectrometer (67 MHz) using $CDCl_3$ as internal standard. Chemical shifts are reported in ppm (δ) downfield from TMS. Mass spectra were recorded on a Hewlett-Packard 5985 gas chromatograph/mass spectrometer. Electron impact mass spectra (EIMS) were obtained at 70 eV, and chemical ionization mass spectra (CIMS) utilized methane as the ionizing gas. UV spectra were obtained on a Bausch and Lomb spectronic 200 UV. Gas chromatographic (GC) analyses were performed on a Perkin–Elmer 3920 instrument equipped with a flame ionization detector.

Column chromatography was performed by the method of Still.[14]

Methyl 9-hydroxyundec-10-ynoate. THF (120 mL) was cooled to −70° and acetylene gas (735 mL; 0.033 mol) was added slowly via a gas-tight syringe.[15] The mixture was treated with a 2.9 M soln of n-BuLi (9.8 mL; 0.028 mol) in hexane. After the clear soln had been stirred for 30 min at −70°, 8[13] (4.76 g, 0.026 mol) in 30 mL THF was slowly added. The mixture was stirred for 15 min at −70°, warmed to 0°, and diluted with water (10 mL). The mixture was concentrated *in vacuo* and diluted with ether (100 mL). The organic layer was washed with water (2 × 50 mL) and the combined aqueous extracts were washed with ether (100 mL). Evaporation of the dried $MgSO_4$ organic extracts afforded methyl 9-hydroxyundec-10-ynoate (4.76 g; 87%) as a pale yellow oil: IR (CCl_4) 3620 and 1735 cm^{-1}; ^1H NMR (CCl_4) (90 MHz) 1.20–1.97 (m, 12H), 2.13–2.40 (m, 3H), 3.63 (s, 3H), 4.13–4.40 (m, 1H). (Found: C, 68.11; H, 9.71. Calc. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50).

Methyl 9-hydroxyundec-10-enoate. A soln of methyl 9-hydroxyundec-10-ynoate (4.94 g, 0.023 mol) and pyridine (0.7 mL) in 200 mL EtOH was stirred under H_2 at 25° in the presence of $Pd/BaSO_4$ (0.51 g). The reaction was monitored by gas chromatography (6 ft 5% Carbowax 20 M column) for the disappearance of starting material. The mixture was filtered through Celite and concentrated *in vacuo* to afford 4.49 g of methyl-9-hydroxyundec-10-enoate as an oil: IR (neat) 3456, 3078, and 1740 cm^{-1}; ^1H NMR (CCl_4) (90 MHz) 1.18–1.88 (m, 12H), 2.05–2.42 (m, 3H), 3.62 (s, 3H), 3.82–4.15 (m, 1H), 4.92–5.32 (m, 2H), 5.60–6.02 (m, 1H); CIMS, *m/e* (relative intensity) 215 (P + 1, 2.1), 197 (P-OH, 58.7), 165 (P-H_2O-CH_3O, 100).

Methyl-9-t-butyldimethylsilyloxyundec-10-enoate (**9**). A soln of methyl-9-hydroxyundec-10-enoate (4.49 g, 0.021 mol), 4-dimethylaminopyridine (0.85 g, 0.007 mol), Et_3N(2.56 g, 0.025 mol) and t-butyldimethylsilylchloride (3.51 g, 0.023 mol) in 40 mL CH_2Cl_2 was stirred for 37 hr at 25°.[16] The mixture was concentrated *in vacuo* and diluted with ether (50 mL). The organic soln was washed successively with brine (50 mL) and water (50 mL). Evaporation of the dried ($MgSO_4$) organic extract gave a crude mixture which was chromatographed on silica gel. Elution with hexanes-EtOAc (25:1) afforded 4.77 g (63% from the alkynyl alcohol) of **9** as a pale yellow oil: IR (neat) 3078 and 1743 cm^{-1}; ^1H NMR (CCl_4) (90 MHz) 0.03 (s, 6H), 0.88 (s, 9H), 1.17–1.73 (m, 12H), 2.10–2.33 (m, 2H), 3.57 (s, 3H), 3.90–4.13 (m, 1H), 4.83–5.17 (m, 2H), 5.52–5.93 (m, 1H); (Found: C, 65.91; H, 11.06. Calc. for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04).

9-t-Butyldimethylsilyloxyundec-10-enoic acid. A soln of **9** (5.39 g, 0.016 mol) and $LiOH·H_2O$ (3.45 g, 0.082 mol) in 220 mL DME:H_2O (2.5:1) was stirred at 25° for 3 days. The mixture was concentrated under reduced pressure and diluted with H_2O (100 mL). The aqueous soln was washed with ether (2 × 25 mL), acidified with 10% NaH_2PO_4 aq. and extracted with ether (4 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to afford 9-t-butyldimethylsilyloxyunedec-10-enoic acid (3.99 g; 84%) as a yellow oil: IR (neat) 3647–2281 (br), 3077, and 1710 cm^{-1}; ^1H NMR (CCl_4) (90 MHz) 0.88 (s, 9H), 1.17–1.83 (m, 12H), 2.17–2.43 (m, 2H), 3.90–4.17 (m, 1H), 4.87–5.20 (m, 2H), 5.53–5.97 (m, 1H), 11.13 (br. s, 1H); CIMS, *m/e* (relative intensity) 315 (P + 1, 9.3), 297 (P-OH, 14.8), 281 (P-CH_3-H_2O, 48.9).

(E)-*1-Iodo-4-acetoxy-1-pentene* (**2b**). Compound **6** was prepared in 34% yield (crude) from 4-pentyn-2-ol (Farchan) by the method of Zweifel.[17] ^1H NMR (CCl_4) (90 MHz) 1.16 (d, 3H, J = 7 Hz), 2.00–2.27 (m, 2H), 3.60–4.00 (m, 1H), 6.05 (d, 1H, J = 15 Hz), 6.49 (m, 1H).

A soln of crude (*E*)-**6** (5.81 g, 0.027 mol), pyridine (19.6 g, 0.25 mol) and Ac_2O (21.6 g, 0.21 mol) was stirred for 10 hr at 25°. The mixture was diluted with water (50 mL) and ether (50 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed successively with sat $NaHCO_3$ aq (4 × 25 mL) and brine (25 mL). Evaporation of the dried ($MgSO_4$) organic layer under reduced pressure gave a yellow oil which was chromatographed on silica gel. Elution with hexanes–EtOAc (50:1) gave *E*-**2b** (4.74 g; 69%) as a pale yellow oil: IR (neat) 3053 and 1737 cm^{-1}; ^1H NMR ($CDCl_3$) (270 MHz) 1.30 (d, 3H, J = 5.4 Hz), 2.10 (s, 3H), 2.33-2.40 (m, 2H), 4.87-4.99 (m, 1H), 6.12 (dt, 1H, J = 14.5 Hz, 1.5 Hz), 6.43 (dt, 1H, J = 14.7 Hz, 7.3 Hz); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 19.1, 20.9, 41.7, 68.5, 77.4, 140.9, 169.6; CIMS *m/e* (relative intensity) 255 (P + 1, 48.4), 195 (P + 1–CH_3CO_2H, 100.0), 194 (P–CH_3CO_2H, 26.6). Analysis by gas chromatography (5% Carbowax 20 M) indicated > 95% purity.

5'-Iodepent-4'-en-2'-yl 9-t-butyldimethylsilyloxyundec-10-enoate (**10**). A soln of 9-t-butyldimethylsilyoxyundec-10-enoic acid (4.15 g, 0.014 mmol), **6** (3.22 g, 0.015 mol), DCC (3.12 g, 0.015 mol), and 4-dimethylaminopyridine (0.189 g, 0.0015 mol) in 40 mL ether was stirred for 38 hr at 25°.[18] The mixture was filtered and concentration of the filtrate *in vacuo* gave a crude oil which was chromatographed on silica gel. Elution with hexanes-EtOAc (50:1) afforded **10** (5.35 g; 76%) as a clear, colorless oil: IR (neat 3075, 3056, and 1737 cm^{-1}; ^1H NMR (CCl_4) (90 MHz) 0.88 (s, 9H), 1.15–1.78 (m, 15H), 2.08–2.38 (m, 4H), 3.92–4.15 (m, 1H), 4.75-5.20 (m, 3H) , 5.52–5.95 (m, 1H), 6.07 (d, 1H, J = 15 Hz), 6.28–6.97 (m, 1H).

5'-Iodopent-4'-en-2'-yl 9-undec-10-enoate (**11**). Dry $Bu_4N^+F^-$(3.48 g, 13.3 mmol, prepared by heating $Bu_4N^+F^-·3H_2O$ at 80° under high vacuum overnight) was treated with a THF (5 mL) soln of **10** (721 mg, 1.42 mmol). The mixture was stirred for 71 hr at 25°, concentrated *in vacuo*, and diluted with ether (30 mL). The ether soln was washed with water (30 mL), dried ($MgSO_4$), and evaporated to afford 565 mg of a clear oil consisting of the hydroxy ester: ^1H NMR (CCl_4) (90 MHz) 1.13–1.73 (m, 15H) 2.10–2.37 (m, 4H), 2.83 (br. s, 1H), 3.83–4.10 (m, 1H), 4.67–5.27 (m, 3H), 5.57–5.90 (m, 1H), 6.05 (d, 1H, J = 15 Hz), and 6.23–6.63 (m, 1H).

A mixture of the crude alcohol and active MnO_2 (2.97 g) in CH_2Cl_2 (70 mL) was stirred for 4.5 hr at 25°. The suspension was filtered and concentrated *in vacuo* to give a crude mixture which was chromatographed on silica gel. Elution with hexanes–EtOAc (10:1) afforded 383 mg (69% from **10**) of **11** as a clear colorless oil: IR (neat) 3053, 1730, 1699, and 1680 cm^{-1}; ^1H NMR (270 MHz), $CDCl_3$) 1.21 (d, 3H, J = 6.6 Hz), 1.27–1.36 (m, 6H), 1.53–1.69 (m, 4H), 2.24–2.32 (m, 4H), 2.58 (t, 2H, J = 7.0 Hz), 4.91–4.98 (m, 1H), 5.81 (dd, 1H, J = 9.9 Hz, 1.5 Hz), 6.11 (td, 1H, J = 14.3 Hz, 1.5 Hz), 6.17–6.37 (m, 2H), 6.41–6.52 (m, 1H); ^{13}C NMR ($CDCl_3$) (22.5 MHz) 19.4, 23.8, 24.9, 29.0, 34.5, 39.5, 42.0, 68.6, 77.5, 127.7, 141.5, 173.0, 200.7; CIMS *m/e* (relative intensity) 393 (P + 1, 11.2), 199 (P–C_5H_6I, 11.8), 181 (P–C_5H_8OI, 100).

E,E-16-*Methyl-oxacyclohexadeca-11,13-diene-2,10-dione* (**12**). A stirred MeCN (4 mL) soln of $PdCl_2(MeCN)_2$ (82 mg, 0.32 mmol), Et_3N (262 mg, 2.60 mmol) and formic acid (42 mg, 0.91 mmol) at 25° was treated dropwise (syringe pump) with a MeCN (8 mL) soln of **11** (118 mg, 0.30 mmol) over a period of 9.75 hr. The mixture was stirred for an additional 1.5 hr at 25°, filtered through Florisil, and concentrated *in vacuo* to give a deep red oil which was chromatographed on silica gel. Elution with hexanes–EtOAc (10:1 and 5:1) afforded 44 mg (55%) of **12** as a white crystalline solid: m.p. 76.0–77.0°; UV (EtOH) λ_{max} = 274 nm (ϵ = 8500); IR (neat) 3030, 1727, 1688, 1658, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) (270 MHz) 1.12–1.37 (m, 6H), 1.28

(d, 3H, J = 6.2 Hz, –CH$_3$), 1.67 (m, 4H), 2.18–2.64 (m, 6H), 5.10 (m, 1H, CH$_3$CHO$_2$C–), 6.06 (ddd, 1H, J = 15.0 Hz, 9.0 Hz, 5.5 Hz, –CH=CH–CH=CHCO–), 6.19 (d, 1H, J = 15.4 Hz, =CHCO–), 6.19 (dd, 1H, J = 10.3 Hz, 15.4 Hz, –CH=CH–CH=CHCO–), 7.02 (dd, 1H, J = 10.3 Hz, 15.4 Hz, –CH=CH–CH=CHCO–); ^{13}C NMR ($CDCl_3$) (22.5 MHz), 20.6, 25.0, 26.2, 27.6, 28.0, 35.0, 40.3, 40.4, 68.7, 128.7, 131.8, 139.6, 142.3, 173.0, 200.8; EIMS (70 ev) *m/e* (relative intensity) 264 (P, 65.5), 249 (P–CH$_3$, 100.0).

(E)-1-*Iodo*-1-*octene* (**2a**). This substance was prepared by the method of Schwartz.[19] ^{1}H NMR (CCl_4) (90 MHz) 0.68–1.05 (m, 3 H), 1.08–1.68 (m, 8 H), 1.85–2.22 (m, 2 H), 5.95 (d, 1 H, J = 15 Hz), 6.28–6.68 (m, 1H); ^{13}C NMR ($CDCl_3$) (22.5 MHz) 14.0, 22.5, 28.3, 28.6, 31.5, 36.0, 74.2, 146.7; CIMS *m/e*, (relative intensity) 267 (P + 29, 25.2), 239 (P + 1, 39.0), 193 (P + 1–C_4H_8, 67.0).

Analysis by GC on a 6 ft 5% Carbowax 20 M column indicated >95% purity.

(Z)-1-*Iodo*-1-*octene* (**3a**). (*Z*)-1-Iodo-1-octyne was prepared from 1-octyne in 58% yield: bp 93° (30 mm); IR (neat) 2187 cm^{-1}; ^{1}H NMR (CCl_4) (90 MHz) 0.73–1.03 (m, 3H), 1.13–1.67 (m, 8H), 2.13–2.47 (m, 2H). Analysis by GC on a 6 ft 5% Carbowax 20 M column indicated >98% purity. Reduction of the iodoalkyne with diimide provided *Z*-1-iodo-1-octene in 38% yield:[9] IR (neat) 3069 and 1608 cm^{-1}; ^{1}H NMR (CCl_4) (90 MHz) 0.73–1.00 (m, 3H), 1.17–1.70 (m, 8H), 1.93–2.27 (m, 2H), 5.97–6.30 (m, 2H); ^{13}C NMR ($CDCl_3$) (22.5 MHz) 14.0, 22.5, 27.9, 28.7, 31.6, 34.6, 82.0, 141.2; CIMS, *m/e* (relative intensity) 267 (P + 29, 18.4), 239 (P + 1, 9.5), 193 (P + 1–C_4H_8). GC analysis on a 6 ft 5% Carbowax 20 M column indicated >98% purity.

1-*Iodo*-4-*acetoxy*-1-*pentyne*. A soln of 4-pentyn-2-ol (598 mg, 7.11 mmol) in ether (15 mL) at −78° was treated slowly with 6.2 mL (14 mmol) of a 2.3 M soln of n-BuLi in hexane. The soln was stirred for 1 hr at −78°, treated with solid I_2 (0.9 g, 7.1 mmol), and then warmed to 25°. After the mixture had been stirred for 4 hr, the soln was added to water (50 mL) and the aqueous layer was extracted with ether (4 × 25 mL). Evaporation of the dried ($MgSO_4$) organic layers under reduced pressure afforded 0.83 g (56%) in 5-iodo-4-pentyn-2-ol as a yellow oil: ^{1}H NMR ($CDCl_3$) (60 MHz) 1.25 (d, 3H, J = 6 Hz), 2.54 (d, 2H, J = 6 Hz), 3.99 (m, 1H).

A soln of 5-iodo-4-pentyn-2-ol (1.36 g, 6.48 mmol) in 3.8 mL pyridine (3.7 g, 47 mmol) was treated with 3.4 mL Ac_2O (3.7 g, 36 mmol) at 0°. The mixture was stirred overnight at 25°. The mixture was added to ice-water (100 mL) and the aqueous layer was extracted with ether (5 × 40 mL). The combined organic layers were washed successively with sat $NaHCO_3$ aq., 0.5 M HCl, and brine. Evaporation of the dried ($MgSO_4$) organic layer under reduced pressure afforded 1.54 g (94%) of 1-iodo-4-acetoxy-1-pentyne as a yellow oil: ^{1}H NMR ($CDCl_3$) (90 MHz) 1.32 (d, 3H, J = 6 Hz), 2.05 (s, 3H), 2.62 (d, 2H, J = 6 Hz), 4.96 (m, 1H).

(Z)-1-*Iodo*-4-*acetoxy*-1-*pentene* (**3b**). (*Z*)-**3b** was prepared from 1-iodo-4-acetoxy-1-pentyne in 43% yield:[9] IR (neat) 3072 and 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$) (270 MHz) 1.26 (d, 3H, J = 6.3 Hz), 2.04 (s, 3H), 2.42 (br. t., 2H, J = 6.6 Hz), 5.04 (qt, 1H, J = 6.3 Hz, 6.6 Hz), 6.16–6.24 (m, 1H), 6.37 (d, 1H, J = 7.7 Hz). ^{13}C NMR ($CDCl_3$) (67 MHz) 19.5, 21.2, 40.7, 69.0, 85.0, 136.4, 170.4; CIMS *m/e* (relative intensity) 25–5 (P + 1, 3.7), 195 (P + 1–CH_3CO_2H). Analysis by GC on a 6 ft 5% Carbowax 20 M column indicated >95% purity.

Methyl 9-*oxo*-*undec*-10-*enoate* (**13**). A suspension of methyl 9-hydroxyundec-10-enoate (2.25 g, 0.010 mol) and active MnO_2 (16.5 g) in CH_2Cl_2 (250 mL) was stirred for 8 hr at 25°. An additional 5.67 g of MnO_2 was added and the mixture was stirred for 3.5 hr. The mixture was filtered and the volatiles were removed *in vacuo* to give a yellow oil which was chromatographed on silica gel. Elution with hexanes-EtOAc (10:1 and 5:1) afforded 1.38 g (62%) of **13** as a pale yellow oil: IR (neat) 1737, 1702, and 1684 cm^{-1}; ^{1}H NMR (CCl_4) (90 MHz) 1.17–1.87 (m, 10H), 2.24 (t, 2H, J = 7 Hz), 2.52 (t, 2H, J = 7H), 3.60 (s, 3H), 5.72 (dd, 1H, J = 9 Hz, 4 Hz), 5.97–6.50 (m, 2H); (Found: C, 67.84; H, 9.53. Calc. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50%).

General procedure for the palladium assisted intermolecular coupling of vinylic iodides with α,β unsaturated ketones and esters. Solns containing the vinylic iodide (1 eq), Et_3N (8 eq), $PdCl_2(CH_3CN)_2$ (0.01 eq to 0.2 eq) and MVK (5 eq) in MeCN (THF) were treated with formic acid (1 eq) at 25°. The mixtures were stirred at the prescribed temp until GC analysis (6 ft 5% Carbowax 20 M column) indicated complete disappearance of the vinylic iodide. The solns were filtered through Florisil and the volatiles were removed under reduced pressure. The products were isolated by silica gel chromatography using mixtures of hexanes–EtOAc mixtures as eluents.

(E,E)-8-*Acetoxy*-3,5-*nonadien*-2-*one* (**4b**). UV (EtOH) λ_{max} = 269 nm (ϵ = 27,000); IR (neat) 1735, 1690, and 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$) (270 MHz) 1.24 (d, 3H, J = 6.6 Hz), 2.03 (s, 3H), 2.27 (s, 3H), 2.41–2.47 (m, 2H), 4.94–5.06 (m, 1H), 6.05–6.15 (m, 2H), 6.24 (dd, 1H, J = 15.8 Hz, 11.0 Hz), 7.09 (dd, 1H, J = 15.8 Hz, 10.3 Hz); ^{13}C NMR ($CDCl_3$) (22.5 MHz), 19.4,20.9, 26.8, 39.1, 69.3, 129.5, 131.3, 142.6, 169.9, 197.9; (Found: C, 67.43, H, 8.27. Calc. for $C_{11}H_{16}O_3$: C, 67.32, H, 8.22).

(E,E)-3,5-*Dodecadien*-2-*one* (**4a**). UV (EtOH) λ_{max} = 273 nm (ϵ = 21,080); IR (neat) 1690 and 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$) (270 MHz) 0.84–0.95 (m, 3H), 1.22–1.51 (m, 8H), 2.15–2.22 (m, 2H), 2.27 (s, 3H), 6.05 (d, 1H, J = 15.8 Hz), 6.16–6.20 (m, 2H), 7.05–7.14 (m, 1H); ^{13}C NMR ($CDCl_3$) (67 MHz) 13.86, 22.36, 28.49, 28.65, 31.43, 32.93, 26.91, 128.58, 128.64, 143.84, 145.61, 198.49; (Found: C, 79.92, H, 11.19. Calc for $C_{12}H_{20}O$: C, 79.94, H, 11.18).

Methyl(E,E)-7-*acetoxy*-2,4-*octadienoate*. UV (EtOH) λ_{max} = 257 nm (ϵ = 24,400); IR (neat) 1734 and 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$) (270 MHz) 1.23 (d, 3H, J = 6.2 Hz), 2.03 (s, 3H), 2.39–2.45 (m, 2H), 3.74 (s, 3H), 4.93–5.02 (m, 1H), 5.83 (d, 1H, J = 15.4 Hz), 6.05 (dt, 1H, J = 15.4 Hz, 7.7 Hz), 6.23 (dd, 1H, J = 15.4 Hz, 11.0 Hz), 7.26 (dd, 1H, J = 15.4 Hz, 10.3 Hz); ^{13}C NMR ($CDCl_3$ (22.5 MHz) 19.3, 20.8, 39.0, 51.1, 69.3, 119.7, 130.7, 138.2, 144.1, 166.9, 169.9; (Found: C, 62.22, H, 7.63. Calc. for $C_{11}H_{16}O_4$: C, 62.25, H, 7.60).

(E,Z) *and* (E,E)-3,5-*Dodecadien*-2-*one* (**5a** + **4a**). UV (EtOH) λ_{max} = 276 NM (E = 21,600); IR (neat) 1690 and 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) (270 MHz) 0.87–0.91 (m, 3H), 1.24–1.49 (m, 8H), 2.26–2.35 (m, 2H), 2.29 (s, 3H), 5.91 (dt, 1H, J = 11.0 Hz, 7.7 Hz), 6.02–6.20 (m, 2H), 7.46 (ddd, 1H, J = 15.4 Hz, 11.4 Hz, 0.7 Hz); ^{13}C NMR ($CDCl_3$) (67 MHz) 13.9, 22.4, 28.2, 28.7, 29.2, 31.5, 27.5 [126.7, 130.1, 137.9, 142.6 (olefinic H of E,Z-isomer)], 128.7, 143.9, 145.7 (olefinic H of *E,E*-isomer)], 198.6; (Found: C, 79.90, H, 11.19. Calc. for $C_{12}H_{20}O$: C, 79.94, H, 11.18). Analysis by GC on a 6 ft 5% Carbowax 20 M column indicated a 4:1 mixture of (*E,Z*):(*E,E*) isomers.

(E,Z) *and* (E,E)-8-*Acetoxy*-3,5-*nonadien*-2-*one* (**5b** + **4b**). IR (neat) 1737, 1690, and 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) (270 MHz) 1.23–1.27 (m, 3H), 2.02 + 2.04 [each s, total 3H, $OCOCH_3$; 2.02 (*E,Z*-isomer): 2.04 (*E,E*-isomer) = 4:1], 2.28 + 2.31 [each s, total 3H, $COCH_3$; 2.28 (*E,E*-isomer): 2.31 (*E,Z*-isomer) = 1:4], 2.45–2.70 (m, 2H), 4.92–5.05 (m, 1H), 5.89 (dd, 1H, J = 10.3 Hz, 8.1 Hz, δ-vinyl H of *E,Z*-isomer), 6.05–6.13 (m, 2H, α and δ-vinyl H of *E,E*-isomer), 6.18 (d, 1H, J = 15.4 Hz, α-vinyl H of *E,Z*-isomer), 6.25 (t, 1H, J = 11.0 Hz, γ-vinyl H of *E,Z*-isomer), 6.19–6.30 (m, 1H, γ-vinyl H of *E,E*-isomer), 7.09 (dd, 1H, J = 15.4 Hz, 9.9 Hz, β-vinyl H of *E,E*-isomer), 7.44 (dd, 1H, J = 15.4 Hz, 11.4 Hz, β-vinyl H of *E,Z*-isomer); ^{13}C ($CDCl_3$) (67 MHz) 19.4, 20.9, 26.9, 27.4, 34.2, 39.1 (*E,Z*-isomer, 69.5, 129.2, 131.0, 135.9, 137.1) (*E,E*-isomer, 69.3, 129.5, 131.3, 139.0, 142.8), 170.2, 198.3. CIMS *m/e* (relative intensity) 197 (P + 1, 12.1), 137 (P + 1–CH_3CO_2, 100.0).

Methyl(E,E)-9-*oxo*-15-*acetoxy*-10,12-*hexadecadienoate*. A soln of **13** (1.00 g, 4.7 mmol), (*E*-**2b** (1.30 g, 5.12 mmol), Et_3N (3.79, 37.52 mmol), $PdCl_2$ $(MeCN)_2$ (11.9 mg, 0.46 mmol) and formic acid (211 mg, 4.59 mmol) was stirred in THF (30 mL) for 8.5 hr at

25° providing the dienone as a yellow oil: UV (EtOH) λ_{max} = 271 nm (ϵ = 22,900); IR (neat) 1740, 1690, and 1665 cm^{-1}; ^1H NMR ($CDCl_3$) (270 MHz) 1.23 (d, 3H, J = 6.2 Hz), [1.25–1.37, 1.55–1.68 (m, 10H)], 2.03 (s, 3H), 2.30 (t, 2H, J = 7.5 Hz), 2.40–2.46 (m, 2H), 2.54 (t, 2H, J = 7.5 Hz), 3.66 (s, 3H), 4.96–5.03 (m, 1H), 6.03–6.13 (m, 2H), 6.22 (dd, 1H, J = 10.0 Hz, 15.5 Hz), 7.11 (dd, J = 15.4 Hz, J = 9.9 Hz); ^{13}C NMR ($CDCl_3$) (22.5 MHz): 19.4, 21.0, 24.0, 24.7, 28.9, 33.8, 39.2, 40.3, 51.2, 69.4, 128.7, 131.4, 138.8, 141.7, 170.1, 173.9, 200.4; (Found: C, 67.20, H, 8.96. Calc. for $C_{19}H_{30}O_5$: C, 67.43, H, 8.93).

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