

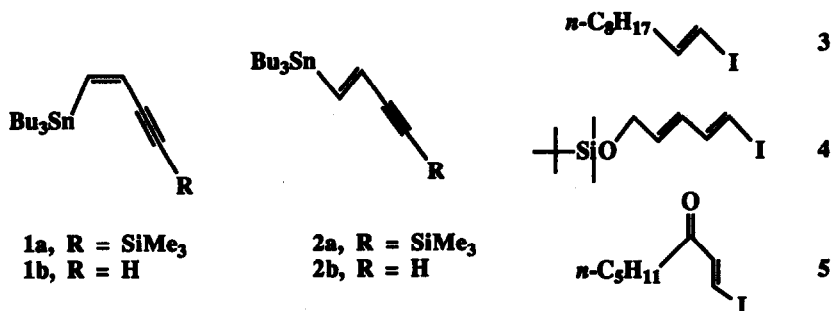
## Polyene Constructions *via* Palladium Couplings of Activated Triflates with Stannylated Enynes

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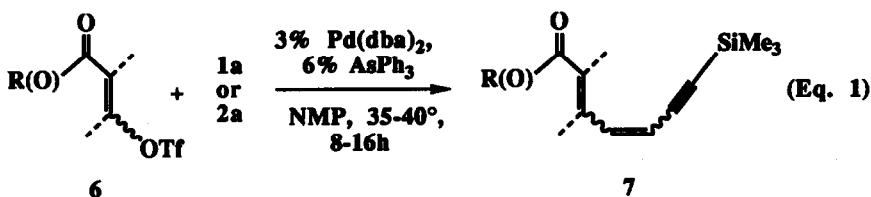
**Summary:** Polyenes of defined olefin geometries can be prepared in high yields from conjugated enol triflates and enyne linchpins under the influence of catalytic amounts of Pd(0).

As part of our continuing interest in polyene macrolide total synthesis,<sup>1</sup> we have begun to focus on developing general methods for conjugated polyene constructions.<sup>2</sup> Although the controlled assembly of sp<sup>3</sup> centers in these and related polyacetate and propionate-derived natural products has been achieved with remarkable success,<sup>3</sup> by contrast, very little attention has been directed toward the realization of quick entries to their polyene portions. Utilized multi-step approaches<sup>4</sup> rely heavily on traditional Wittig/Horner-Emmons chemistry,<sup>5</sup> or on McGarvey's more recent, reiterative sequence involving aldehydes and Wollenberg's lithiated alkoxybutadiene.<sup>6</sup> Transition metal-based organometallic linchpins, on the other hand, offer promise here in that olefin geometries are normally maintained, and conditions for their vinyl-vinyl couplings are oftentimes mild and efficient.<sup>7</sup> We now report our initial results in this area which suggest that conjugated tri- and tetraenones/oates, or higher homologs, will be obtainable using the proper matching of reaction partners *via* the intermediacy of organopalladium species.

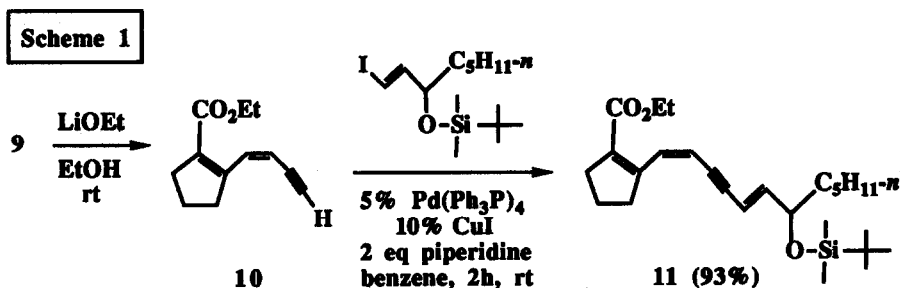
Linchpins **1a** and **2a** were prepared according to the procedure of Magriotis.<sup>8</sup> Stille couplings<sup>9</sup> with vinyl iodides such as **3** and **4** employing various combinations of Pd/solvent/additive mixtures [*e.g.*, Pd(Ph<sub>3</sub>P)<sub>4</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>(PhCN)<sub>2</sub>, PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, Pd(dba)<sub>2</sub>/(furan)<sub>3</sub>P in DMF, CH<sub>2</sub>Cl<sub>2</sub>, or N-methyl-2-pyrrolidone (NMP), with or without LiCl] at room temperature gave low yields of polycynes (<38%), clearly an indication of the perturbation exerted by the conjugated alkyne residue in **1a/2a**.<sup>10</sup> Even an activated iodide (*e.g.*, **5**) afforded only 40% of the desired coupling product with **1a** after 24h. Switching to the triflate analog **6**, however, led to a very clean and efficient process *utilizing 1:1 ratios of reactants*, generalized by Equation 1. Table 1 lists a number of examples demonstrating the generality of the method.<sup>11</sup>



Several additional points can be made, including (1) both triflates and fluorosulfonates<sup>12</sup> (entries 1,2) react with equal facility; (2) the couplings are essentially stereospecific;<sup>13</sup> (3) removal of the Me<sub>3</sub>Si moiety in 1a/2a is readily accomplished with K<sub>2</sub>CO<sub>3</sub> in MeOH to give 1b/2b; identical reaction of the desilylated linchpin (*i.e.*, a terminal acetylene), however, leads to coupling at *both* termini of the linchpin in *ca.* 50% yield; none of the desired product was observed.

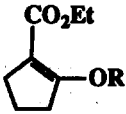
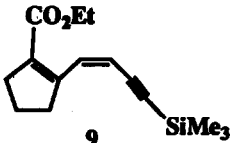
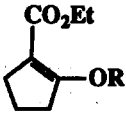
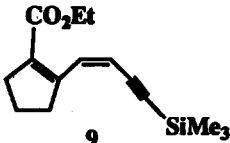
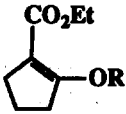
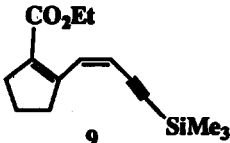
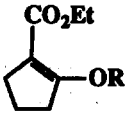
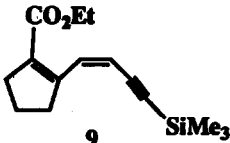
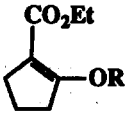
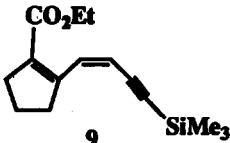
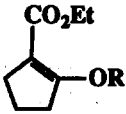
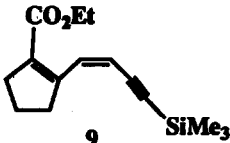


Products 7 could be manipulated further at the acetylenic terminus (after desilylation, *vide supra*, 85-90%). For example, dienynoate 10 undergoes straightforward coupling<sup>14</sup> to the vinyllog 11 in good yield (Scheme 1). Other related transformations are also envisioned (*e.g.*, Boland reduction,<sup>15</sup> I<sub>2</sub> initiated isomerization<sup>4b</sup>), as are applications in synthesis. These studies will be reported in due course.



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Table 1. Palladium(0)-mediated couplings of linchpins 1a and 2a with activated triflates.

Entry	Vinyl sulfonate <sup>a</sup>	Linchpin <sup>b</sup>	Product <sup>c</sup>	Yield(%) <sup>d</sup>
1		1a		90
2	8b, R = SO <sub>2</sub> F	1a		91
3		1a		92
4		1a		94
5		1a		80 <sup>f</sup>
6		2a		79
7		2a		85

<sup>a</sup>Prepared from the corresponding  $\beta$ -keto esters according to ref. 16. <sup>b</sup>See ref 8.

<sup>c</sup>Fully characterized by IR, NMR, MS, and HRMS data. <sup>d</sup>Isolated. <sup>e</sup>Geometry assigned on the basis of an NOE experiment. <sup>f</sup>Isolated in a 80:20 ratio as a mix of E:Z isomers.

## References and Notes

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  - Simple vinyl stannanes (e.g., vinyltributylstannane) are known to couple with activated vinyl triflates; cf. Houpiis, I.N., *Tetrahedron Lett.*, **1991**, 32, 6675; see also, Scott, W.J., Kling, J.K., Hettrick, C.M., *J. Org. Chem.*, **1991**, 56, 1489.
  - A representative procedure for the preparation of **9** is as follows: In an argon flushed flask were placed Pd(dba)<sub>2</sub> (5.20 mg, 0.009 mmol), triphenylarsine (5.50mg, 0.018 mmol),<sup>17</sup> and triflate **8a** (0.30 mmol) to which dry N-methylpyrrolidone (3 mL) was added. The resulting solution became pale yellow after 5 to 10 min. At this point, vinyl stannane **1a** (0.30 mmol) was added. The reaction was stirred under argon at 35–40°C for 8 to 16 h. After being allowed to cool to room temperature, the dark solution was treated with aqueous HCl (0.2 M, 10 mL), and the aqueous layer was extracted with diethyl ether (60 mL). The combined organic layers were washed successively with aqueous NaHCO<sub>3</sub> (20 mL) and H<sub>2</sub>O (2 x 10 mL), dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo* to give a dark oily residue. Purification by column chromatography (silica gel, hexane/ethyl acetate, 95:5, R<sub>f</sub> = 0.37) afforded the diyne **9** (70.75 mg, 90%) as a colorless oil; IR (neat) cm<sup>-1</sup> 2400, 2140, 1710, 1600, 1410, 1250, 1200, 1110, 1035, 1000, 850; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ 7.48 (1H, d, J = 12.0Hz), 5.68 (1H, d, J = 12.0Hz), 4.18 (2H, q, J = 7.2Hz), 3.10 (2H, t, J = 7.8Hz), 2.64 (2H, t, J = 7.8Hz), 1.86 (2H, quint, J = 7.7Hz), 1.27 (3H, t, J = 7.0Hz), 0.18 (9H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>) δ 165.40, 151.30, 134.35, 133.30, 112.05, 104.40, 103.75, 60.00, 35.85, 33.55, 22.00, 14.25, -0.45; EIMS (rel int) 262 (M<sup>+</sup>, 35), 247(18), 234(29), 219(44), 203(34), 175(33), 73(100); HREIMS calcd for C<sub>15</sub>H<sub>22</sub>O<sub>2</sub>Si (M<sup>+</sup>): 262.1389; found 262.1392.
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  - In the case of the cyclohexenone derivative (Table 1, entry 5), however, analysis of the crude reaction mixture (by GC) revealed that a 89:11 ratio of Z:E coupling products was formed initially, which was converted to a 80:20 E:Z mix upon purification (silica gel).
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