



## Synthetic studies on the taxane skeleton: effective construction of eight-membered carbocyclic ring by palladium-catalyzed intramolecular $\alpha$ -alkenylation of a methyl ketone

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### ABSTRACT

A new method for the construction of the eight-membered carbocyclic ring in the taxane skeleton is described. The palladium-catalyzed intramolecular  $\alpha$ -alkenylation of a methyl ketone effectively constructed the eight-membered carbocyclic ring in the taxol model compound. To the best of our knowledge, this reaction is the first example of forming an eight-membered carbocyclic ring by the palladium-catalyzed intramolecular  $\alpha$ -alkenylation of a ketone.

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Taxol (Fig. 1) has been a challenging synthetic target because of its complexity as well as the highly strained eight-membered ring included in the central part of the 6–8–6 tricyclic structure.<sup>1–7</sup> Since medium carbocyclic rings (8–11-membered rings) are generally difficult to construct due to the transannular strain, the development of synthetic methods for medium carbocyclic rings holds promise for organic synthesis.

We have recently reported that the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction effectively constructed compounds with the taxane skeleton (**1–3**, Fig. 2).<sup>8</sup> However, these products lack an oxygen atom around the newly formed C–C bond, requiring further introduction of an oxygen atom to complete the total synthesis of taxol.<sup>9</sup> This oxidation would be problematic because the strained structure of the advanced intermediate would be labile under oxidation conditions. We therefore undertook the development of an alternative method for producing the eight-membered carbocyclic ring with an oxygen atom around the newly formed C–C bond. We report herein the palladium-catalyzed intramolecular  $\alpha$ -alkenylation of a methyl ketone that generates a taxol model compound with the 6–8–6 taxane skeleton in excellent yield.

Despite the potential utility of the palladium-catalyzed coupling reaction of ketones with aryl halides or alkenyl halides, this chemistry has been left unexplored.<sup>10</sup> However, it attracted attention when some research groups published intermolecular<sup>11</sup> as well as intramolecular<sup>12a,b</sup> palladium-catalyzed  $\alpha$ -arylation of ketones in 1997, and this reaction has been studied extensively.<sup>12c,d,13</sup>

On the other hand, the palladium-catalyzed intramolecular  $\alpha$ -alkenylation of a ketone was first reported by Piers in 1990,<sup>14</sup>

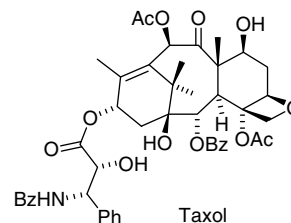


Figure 1. Structure of taxol.

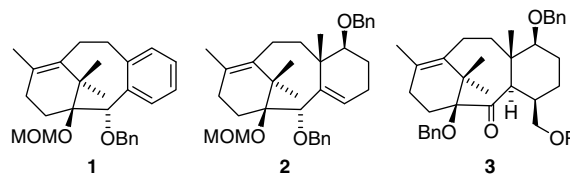
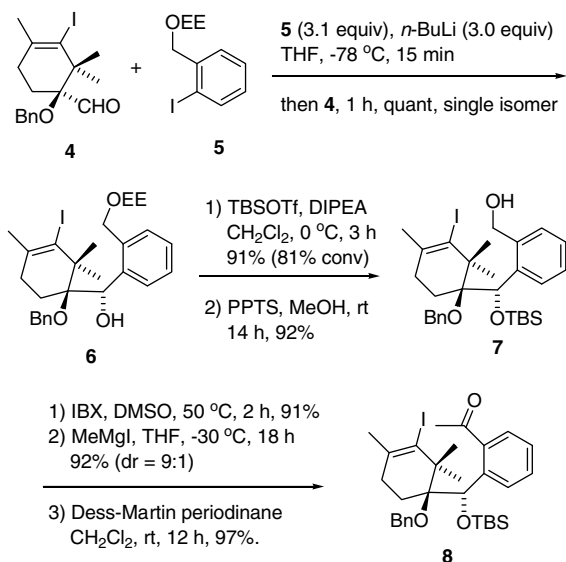


Figure 2. Compounds with the taxane skeleton prepared by the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction.

and 10 years later, the amino-tethered variant has been developed<sup>15,16h</sup> and utilized for natural product synthesis.<sup>16</sup> However, its application to constructing medium carbocyclic rings has never been reported. Therefore, we pursued the possibility of a palladium-catalyzed intramolecular  $\alpha$ -alkenylation for the construction of the eight-membered carbocyclic ring included in the taxane skeleton.

Considering that the yield of **1** in the intramolecular palladium-catalyzed reaction was comparable with those of **2** and **3**, the palladium-catalyzed ring closure of methyl ketone **8** (Scheme 1) would be a proper model reaction for construction of the real

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Scheme 1. Preparation of methyl ketone 8.

taxane skeleton. Moreover, the C-bound palladium enolate has been known to be operative in the palladium-catalyzed arylation of a ketone and a methyl ketone provides the stable C-bound palladium enolate.<sup>13</sup> Therefore, we selected methyl ketone **8** as the most suitable substrate for studying the palladium-catalyzed intramolecular  $\alpha$ -alkenylation.

Methyl ketone **8** was prepared as shown in Scheme 1. Thus, coupling reaction of a readily available iodide **5** with known aldehyde **4**<sup>8a</sup> successfully provided alcohol **6** quantitatively as a single diastereomer. TBS ether formation of alcohol **6** and subsequent selective removal of the ethoxyethyl group under mild acidic conditions afforded alcohol **7**. IBX oxidation,<sup>17</sup> methylation with Grignard reagent, and Dess–Martin oxidation then furnished methyl ketone **8**.

The palladium-catalyzed intramolecular  $\alpha$ -alkenylation of methyl ketone **8** was first carried out by use of Pd(PPh<sub>3</sub>)<sub>4</sub> (30 mol %) and potassium *tert*-butoxide (3.0 equiv) in THF at 60 °C, and it gratifyingly provided the desired product **9** in 58% yield after 24 h (Table 1, entry 1). Stereochemistry of the product **9** was confirmed by the NOE experiments (Fig. 3).

As the protodeiodinated by-product **10** formed in 20% yield in entry 1, we attempted to optimize the reaction conditions. The reaction time was fixed at 24 h and the effect of the solvent was surveyed. In CPME (cyclopentyl methyl ether), the yield was increased to 76%, but the reaction proceeded slowly, leaving 10% of methyl ketone **8** even at 100 °C (entry 2). The yield decreased to 40% in 1,4-dioxane (entry 3) and in DME, only by-product **10** formed (entry 4). The low yields in entries 3 and 4 could arise from the decomposition of methyl ketone **8** observed. No product was obtained in DMF and only decomposition of methyl ketone **8** occurred (entry 5). Decomposition of methyl ketone **8** was observed in heptane, too, diminishing the yield to 61% (entry 6). However, benzene (entry 7) afforded a yield comparable to that with CPME. Finally, toluene was found to be the best solvent, improving the yield to 82%.

Next we examined the effect of the base. Sodium *tert*-butoxide diminished the yield to 72% (Table 2, entry 1), while K<sub>3</sub>PO<sub>4</sub><sup>18</sup> retarded the reaction (entry 2). Cesium carbonate improved the yield to 91% (entry 3) and, ultimately, the yield was further increased to 96% by use of potassium phenoxide (entry 4).<sup>15d,18</sup> These results suggested that a weak base was enough to cause the palladium-catalyzed reaction.

Table 1

Entry	Solvent	Temp (°C)	Yield <sup>a</sup> (%)		
			9	10	8
1	THF	60	58	20	0
2	CPME	100	76	13 <sup>b</sup>	10 <sup>b</sup>
3	1,4-Dioxane	100	40	27	0 <sup>c</sup>
4	DME	80	0	26	0 <sup>c</sup>
5	DMF	100	0	0	0 <sup>c</sup>
6	Heptane	100	61	7	0 <sup>c</sup>
7	Benzene	80	76	20	0
8	Toluene	100	82	8	0

<sup>a</sup> Isolated yields.

<sup>b</sup> Isolated yields. The ratio was determined by <sup>1</sup>H NMR because a mixture of **10** and **8** was inseparable.

<sup>c</sup> Decomposition of methyl ketone **8** occurred.

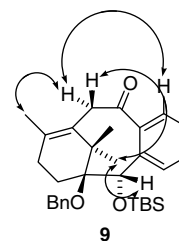
Figure 3. NOE correlations in the NOESY spectra of **9**.

Table 2

Entry	Base	Yield <sup>a</sup> (%)		
		9	10	8
1	<i>t</i> -BuONa	72	6	0
2	K <sub>3</sub> PO <sub>4</sub>	48	4 <sup>b</sup>	46 <sup>b</sup>
3	Cs <sub>2</sub> CO <sub>3</sub>	91	6	0
4	PhOK	96	3	0

<sup>a,b</sup> See the footnotes to Table 1.

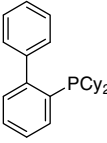
The effect of the ligand was also examined utilizing Pd<sub>2</sub>(dba)<sub>3</sub> (15 mol %) and various phosphine ligands (60 mol % for monodentate ligand and 30 mol % for bidentate ligand). The reaction of **8** in the absence of phosphine ligand proceeded slowly (Table 3, entry 1)<sup>19</sup> and the reaction with PPh<sub>3</sub> (60 mol %) provided **9** in 88% yield (entry 2), indicating that use of Pd(PPh<sub>3</sub>)<sub>4</sub> is superior in this reaction. PCy<sub>3</sub> did not change the yield (entry 3), but all other monodentate and bidentate ligands shown in Table 3 diminished the yield (entries 4–11). Although the relationship between the ligand and the yield is difficult to explain, it is worth noting that almost no product was formed in the reactions using P(*o*-tol)<sub>3</sub> (entry 4) and P(*t*-Bu)<sub>3</sub> (entry 5).

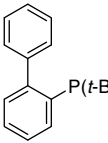
Further studies revealed that the reaction under the optimized conditions was found to be completed after 2 h (Table 4, entry

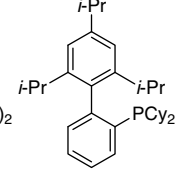
Table 3

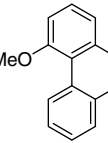
$\text{Pd}_2(\text{dba})_3$  (15 mol%)  
 ligand  
 $\text{PhOK}$  (3.0 equiv)  
 toluene, 100 °C, 24 h

**8**  $\xrightarrow{\hspace{10em}}$  **9** + **10**

  
**11**

  
**12**

  
**13**

  
**14**

Entry	Ligand (mol %)	Yield <sup>a</sup> (%)		
		<b>9</b>	<b>10</b>	<b>8</b>
1	—	51	7 <sup>b</sup>	41 <sup>b</sup>
2	PPh <sub>3</sub> (60)	88	3	0
3	PCy <sub>3</sub> (60)	95	4	0
4	P( <i>o</i> -tol) <sub>3</sub> (60)	2	16 <sup>b</sup>	77 <sup>b</sup>
5	P( <i>t</i> -Bu) <sub>3</sub> (60)	0	25 <sup>b</sup>	61 <sup>b</sup>
6	dppp (30)	86	8	0
7	dppf (30)	84	4	0
8	<b>11</b> (60)	52	47	0
9	<b>12</b> (60)	73	Trace	0
10	<b>13</b> (60)	80	9	0
11	<b>14</b> (60)	90	7	0

<sup>a,b</sup> See the footnotes to Table 1.

Table 4

$\text{Pd}(\text{PPh}_3)_4$  (Table 4)  
 $\text{PhOK}$  (3.0 equiv)  
 toluene, 100 °C, 2 h

**8**  $\xrightarrow{\hspace{10em}}$  **9** + **10**

Entry	Pd(PPh <sub>3</sub> ) <sub>4</sub> (mol %)	Yield <sup>a</sup> (%)		
		<b>9</b>	<b>10</b>	<b>8</b>
1	30	96	3	0
2	20	95	4	0
3	10	85	10	0
4	5	85	10	0

<sup>a</sup> Isolated yields.

1), providing the same yields as those in entry 4 of Table 2. Moreover, when the catalyst loading was reduced to 20 mol % (entry 2), the results were comparable with those in entry 1. Reducing the catalyst loading to 10 mol %, reduced the yield to 85% (entry 3), but the same results were obtained by use of 5 mol % of the catalyst (entry 4).

In summary, the palladium-catalyzed intramolecular  $\alpha$ -alkenylation of a methyl ketone was found to be effective for the construction of the eight-membered carbocyclic ring. Although the exceptionally high yield of the palladium-catalyzed reaction of **8** could arise from the Thorpe–Ingold effect and the limited anion formation at one  $\alpha$ -carbon, it is worth noting that an eight-membered carbocyclic ring has been prepared in 96% yield. To the best of our knowledge, this reaction is the first example of forming an eight-membered carbocyclic ring by the palladium-catalyzed intramolecular  $\alpha$ -alkenylation of a methyl ketone. Considering that the yield of **1** in the palladium-catalyzed reaction was comparable with those of **2** and **3**, application of the palladium-catalyzed ring

closure for construction of the real taxane skeleton would be promising.

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