

# Study on the Alkylation Reaction at C-5 of Bicyclic Acetal Compounds 6,8-Dioxabicyclo[3.2.1]octane System

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Bicyclic acetals in the 6,8-dioxabicyclo[3.2.1]octane series are very useful intermediates for the synthesis of other important structures. Since the discovery by Mundy in 1985 of the transformation of bicyclic acetals into  $\delta,\epsilon$ -unsaturated ketones,<sup>1,2</sup> which has been used for the synthesis of solenopsin A,<sup>1</sup> Douglas-Fir tussock moth pheromone<sup>1</sup> and the formal synthesis of sirenin,<sup>3</sup> our group has developed the direct synthesis of 1,5-diketone,<sup>4</sup> *cis*-1,2-cyclopentanediol,<sup>5</sup> 2,6-disubstituted pyridine<sup>6</sup> and 2,3,6-trisubstituted pyridine derivatives.<sup>7</sup>

The investigation of the functionalization on this highly utilizable acetal **1** has been essential and especially the introduction of alkyl group at C-5 was critical to the synthesis of Douglas-Fir tussock moth pheromone,<sup>1</sup> multistriatin<sup>8</sup> and brevicomin<sup>9</sup> etc.

We now report the introduction of alkyl group at C-5 of bicyclic acetal **1** via dianion **5** (an alkoxide and a carbanion) from the dihydropyranol **4**, which was easily prepared from acrolein **2**,<sup>10</sup> followed by cyclization (Scheme 1). The preparation of carbanions derived from certain simple vinyl ethers has been described by Baldwin<sup>11</sup> and allyl ethers by Evans<sup>12</sup> and Still.<sup>13</sup> However, the feasibility of extension to the cyclic systems was not apparent and the conversion to carbanion was relatively insufficient and not consistent.<sup>14</sup>

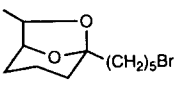
Initial attempts for the preparation of a dianion by deprotonation of dihydropyranol **4** with *n*-BuLi in ether or THF and *sec*-BuLi in THF were unpromising. We turned to *t*-BuLi and observed complete deprotonation (monitored by <sup>1</sup>H NMR) with 2.5 equivalents of the lithium reagent at -78

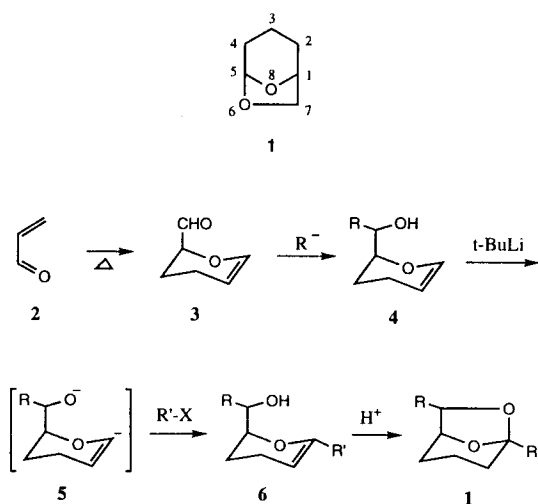
°C (1 hr) in small volume of THF. Competition by THF for the alkyl lithium reagent was occurring; however, at least 0.5 equivalent of THF was essential to dissociate the aggregated lithium reagent to the reactive complex.<sup>15</sup> Any excess lithium reagent is conveniently destroyed by addition of excess THF.<sup>16</sup>

As expected, the alkyl halides react with the carbanion rather than react with the alkoxide to give the C-C bond instead of the O-C bond formation (Table 1). Some limitations are encountered in the reaction with alkyl halides. Short-chain primary alkyl halides (Entries a, c, d) are generally less- or un-reactive as well as more hindered alkylating agents (Entry f). Only the cyclized product **1** (R'=H) without alkylation at C-5 was obtained in these case. The use of dimethyl sulfate as an alkylating reagent instead of methyl iodide gave only a same result. Long chain alkyl halides are easily reacted with the vinylic carbanion to give the alkylated alcohol **6** which was cyclized to the bicyclic compound **1** via acidic work-up with 10% aqueous HCl solution.<sup>17</sup>

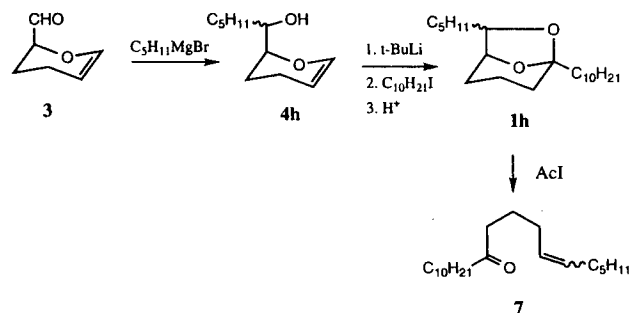
This methodology has been utilized for the synthesis of Douglas-Fir tussock moth pheromone (Scheme 2). Acrolein dimer **3** was reacted with two equivalents of *n*-pentyl magnesium bromide to give 85% yield of dihydropyranol **4h**. Two equivalents of *t*-butyllithium was added to this alcohol in 0.5 N concentration of THF at -78 °C and stirred for an hour. Dodecyl iodide (1.2 equiv.) was added to the reaction mixture at 0 °C and stirred for 2 hours at room temperature.

Table 1. Alkylation at C-5 of bicyclic acetal compounds

Entry	Dihydropyranol (4)	Substrate (R'X)	Yield (%)
a	R=H	CH <sub>3</sub> I	0
b	H	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> Br	90
c	CH <sub>3</sub>	CH <sub>3</sub> I	0
d	CH <sub>3</sub>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> Br	35 (exo/endo 64:36)
e	CH <sub>3</sub>	Br(CH <sub>2</sub> ) <sub>5</sub> Br	81 (exo/endo 65:35)
f	CH <sub>3</sub>		0
g	(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	Br(CH <sub>2</sub> ) <sub>5</sub> Br	73 (exo/endo 70:30)
h	(CH <sub>2</sub> ) <sub>4</sub> CH	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> I	85 (exo/endo 60:40)



Scheme 1.



Scheme 2.

Acidic work-up using 10% aqueous HCl solution gave 85% yield of cyclized *exo/endo* (60/40) mixture **1h** which was treated with acetyl iodide<sup>2</sup> to yield *cis/trans* (40/60) mixture of Douglas-Fir tussock moth pheromone **7** (27%). It was noted that *exo*-bicyclic acetal gave *trans*-pheromone and *endo* gave *cis*-pheromone selectively.<sup>2</sup> The *cis/trans* (40/60) mixture of the 6-heneicosen-11-ones turned out to be more active as a pheromone than pure material isolated from female tussock moth.<sup>18</sup>

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- Undesirable side products and non-homogeneous systems could be avoided by dilution with THF to 0.1-1.0 M in anions which were stable in THF once formed.
- Typical spectroscopic data for bicyclic acetal; *exo*-5-(*n*-bromopentyl)-7-methyl-6,8-dioxabicyclo[3.2.1]octane (**1e**) <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.19 (q, *J*=6.4 Hz, 1H, C7-H), 4.02 (br s, 1H, C1-H), 3.39 (t, *J*=6.8 Hz, 2H), 1.9-1.39 (m, 14H), 1.16 (d, *J*=5.9 Hz, 3H, C7-CH<sub>3</sub>); MS *m/z* 278 (*M*<sup>+</sup>+2), 276 (*M*<sup>+</sup>), 234, 232, 179, 177, 100 (base), 69, 55, 41; HRMS Calcd for C<sub>12</sub>H<sub>21</sub>O<sub>2</sub>Br 276.0725, Found 276.0717.  
*endo*-5-(*n*-bromopentyl)-7-methyl-6,8-dioxabicyclo[3.2.1]octane (**1e**) <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.14 (br s, 2H, C1-H and C7-H), 3.39 (t, *J*=6.8 Hz, 2H), 1.9-1.39 (m, 14H), 1.31 (d, *J*=5.9 Hz, 3H, C7-CH<sub>3</sub>); MS *m/z* 278 (*M*<sup>+</sup>+2), 276 (*M*<sup>+</sup>), 250, 248, 234, 232, 197, 179, 177, 155, 135, 100, 82, 69 (base), 55, 41; HRMS Calcd for C<sub>12</sub>H<sub>21</sub>O<sub>2</sub>Br 276.0725, Found 276.0724.
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## Convenient One-Pot Synthesis of Vinyl Selenides

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A number of useful functional group transformations can be achieved with vinyl selenides.<sup>1</sup> Owing to their ability to stabilize carbanionic intermediates for further functionalization and/or easy removal of the metalloids, they have been widely used in organic synthesis. The preparation of vinyl selenides generally implies multiple step procedures involving addition of electrophilic selenium on triple or double bonds followed by elimination reaction<sup>2</sup> or Wittig-type reactions with  $\alpha$ -selenated ylides.<sup>2,5</sup> Various vinyl selenides have been prepared by the reaction of phosphorus tetraiodide or triiodide with selenoacetals or seleno esters,<sup>2f</sup> the reduction of phenyl selenoalkynes,<sup>2d</sup> the reaction of alkynyl trialkyl borates,<sup>2e</sup> alkenylboranes, and alkenyl mercurials with selenyl halides or diaryl selenides,<sup>2d</sup> the addition of selenic acids<sup>2f,6</sup> and selenols<sup>7</sup> on alkynes, and the syn-elimination of selenoacetal monoselenoxides.<sup>8</sup> Recently, stereoselective syntheses of (*E,E*)-1-arylselenobutadienes<sup>9</sup> and 1-halo-1-selenoalkanes<sup>10</sup> were also reported.

Preparation of vinyl selenides through the Horner-Emmons reaction has also been reported.<sup>4</sup> But this method of using iodomethyl phosphonate and PhSeNa for starting materials needs to isolate the intermediate diethyl phenylselenomethyl phosphonate and suffers from the limited availability of starting material.

Recently, we reported the synthetic method for ketene selenoacetals<sup>3a</sup> and vinyl tellurides<sup>3b</sup> starting from dialkyl methylphosphonate. As an extension of these works, we here report a convenient one-pot synthesis of vinyl selenides from readily available dialkyl alkylphosphonates and PhSeBr. This method is based upon modification of Horner-Emmons reaction without isolation of its intermediate.

To obtain diethyl phenylselenomethylphosphonate, diethyl methylphosphonate was treated with PhSeBr in the presence of 1.0 equivalent of LDA. We obtained only 30% of diethyl 1,1-bis(phenylseleno)methylphosphonate probably due to the H-Li exchange reaction between diethyl lithiophosphonate and diethyl phenylselenomethyl phosphonate which was ge-