

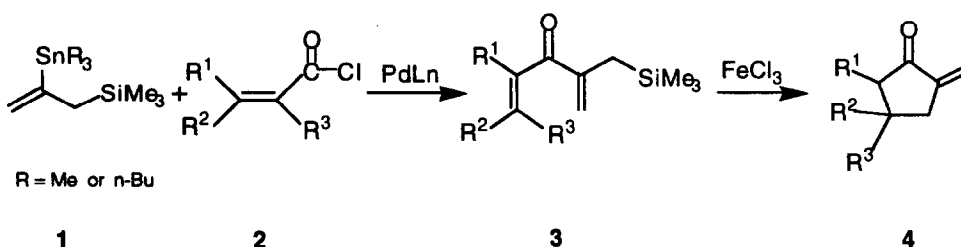
## SYNTHESIS OF $\alpha$ -METHYLENECYCLOPENTANONES VIA SILICON-DIRECTED NAZAROV REACTION OF $\alpha$ -TRIMETHYLSILYLMETHYL-SUBSTITUTED DIVINYL KETONES.

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*Reactions of  $\alpha$ -trimethylsilylmethyl-substituted divinyl ketones with  $FeCl_3$  gave  $\alpha$ -methylene-cyclopentanones. Thienyl and *N*-methylpyrrolyl ( $\alpha$ -trimethylsilylmethyl)vinyl ketones also underwent cyclization to afford the corresponding  $\alpha$ -methylene-cyclopentanones.*

$\alpha$ -Methylenecycloalkanone moiety is often found in biologically active natural products. Most synthetic methods known so far are based on the  $\alpha$ -methylenation of cycloalkanones.<sup>1</sup> A major limitation common to all of these methods was the lack of regioselectivity when unsymmetrical cycloalkanones were applied. We here present the regiospecific synthesis of  $\alpha$ -methylene-cyclopentanones from acyclic precursors,  $\alpha$ -trimethylsilylmethyl-substituted divinyl ketones **3** via silicon-directed Nazarov cyclization.<sup>2</sup> Recently, we found a facile synthesis of **3** via palladium-catalyzed cross-coupling of 2-stannyl-3-silylpropene **1** with  $\alpha,\beta$ -unsaturated acid chlorides **2**.<sup>3</sup>




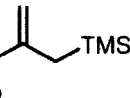
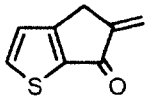
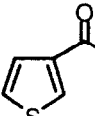
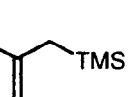
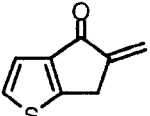
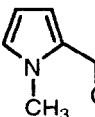
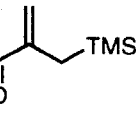
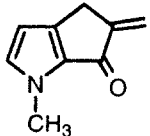
The reaction of **3** with anhydrous  $FeCl_3$  in dichloromethane gave the corresponding  $\alpha$ -methylene-cyclopentanones after purification by column chromatography on silica gel.<sup>4</sup> Some representative results are summarized in Table 1.



Among the Lewis acid tried,  $FeCl_3$  was found to be the most effective (entry d). In all experiments 2.0 equivalents of  $FeCl_3$  were used. Acyclic divinyl ketones **3a-e** reacted under mild conditions to give good yields of  $\alpha$ -methylene-cyclopentanones **4a-e**, respectively, uncontaminated with endo cyclic double-bond isomers (GC analysis).

When **3f** was treated with  $FeCl_3$  at  $-78^\circ\text{C}$  a myriad of products were formed. The products were difficult to isolate, however, the molecular ion of the dimers of **4f** at  $m/z$  300 was found in the GC-MS spectra of the reaction mixture (entry f). In case of **3g**, 5-methylene-2-cyclopentenone (**5**) was obtained (entry g). **5** was believed to be produced from the dehydrochlorination of **4g** during workup.

Table 1. Cyclization of **3**<sup>a</sup>

| Entry | <b>3</b>  |   |                | Lewis acid                        | Temp (°C) | Time (h) | <b>4</b><br>Yield (%) <sup>b</sup>  |
|-------|---|---|----------------|-----------------------------------|-----------|----------|---|
|       | R <sup>1</sup>  | R <sup>2</sup>  | R <sup>3</sup> |                                   |           |          |   |
| a     | H   | H   | H              | FeCl <sub>3</sub>                 | -30       | 2        | 49 (70)   |
| b     | H   | Me  | H              | FeCl <sub>3</sub>                 | -30       | 2        | 58 (82)   |
| c     | H   | Me  | Me             | FeCl <sub>3</sub>                 | -10       | 1.5      | 91 (97)   |
| d     | H   | Ph  | H              | FeCl <sub>3</sub>                 | -78       | 3        | 64  |
|       |   |   |                | BF <sub>3</sub> ·OEt <sub>2</sub> | -78       | 4        | 15  |
|       |   |   |                | EtAlCl <sub>2</sub> <sup>c</sup>  | -10       | 4        | 9   |
| e     | H   |    | H              | FeCl <sub>3</sub>                 | -78       | 2        | 55  |
| f     | (CH <sub>2</sub> ) <sub>4</sub>   | H   | H              | FeCl <sub>3</sub>                 | -78       | 5        | d   |
| g     | H   | Cl  | H              | FeCl <sub>3</sub>                 | -20       | 2        |  <b>5</b> , 68 |
| h     |   |   | H              | FeCl <sub>3</sub>                 | 30        | 2        |  65            |
| i     |  |  | H              | FeCl <sub>3</sub>                 | 30        | 2        |  52           |
| j     |  |  | H              | FeCl <sub>3</sub>                 | 30        | 2        |  48           |

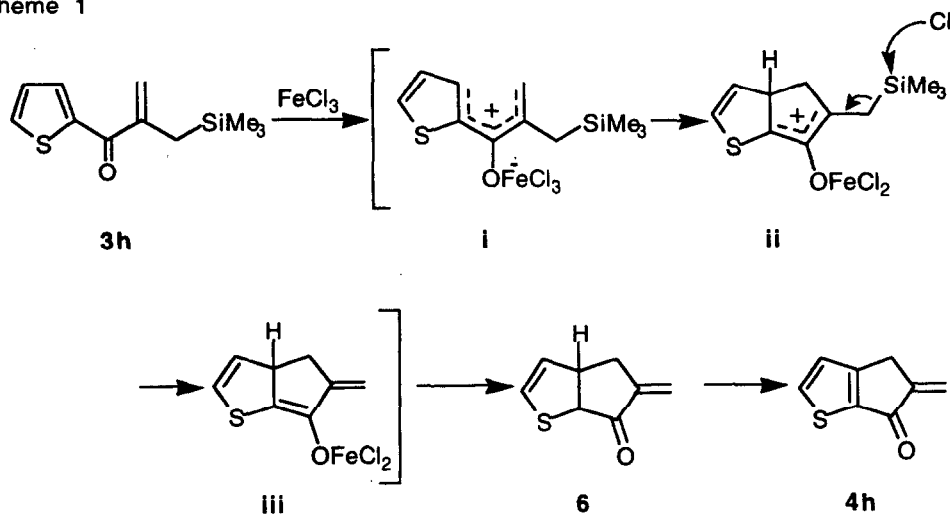
<sup>a</sup> Reaction was carried out in CH<sub>2</sub>Cl<sub>2</sub> at 0.02 M unless otherwise noted. <sup>b</sup> Isolated (GC) yield. Products were characterized by <sup>1</sup>H- and <sup>13</sup>C-NMR, and GC-MS.<sup>5</sup> <sup>c</sup> Toluene was used as a solvent. <sup>d</sup> See, Text.

The reaction of 2-thienyl and 3-thienyl vinyl ketones **3h** and **3i** with FeCl<sub>3</sub> at 30 °C afforded the corresponding α-methylenecyclopentanones **4h** and **4i**, respectively. 2-(N-methylpyrrolyl)

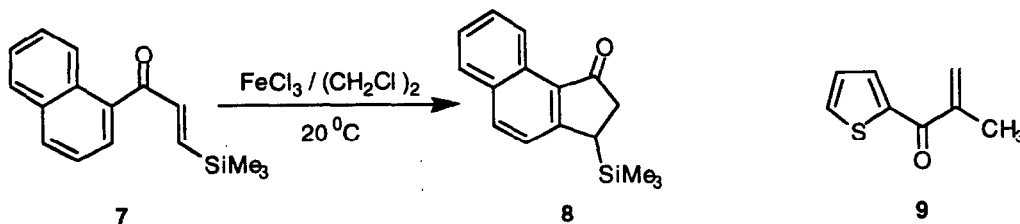
vinyl ketone **3j** similarly produced **4j**. It is quite interesting to note the attempted Nazarov cyclization of the vinyl monocyclic aryl ketone failed.<sup>6,7</sup>

A possible mechanistic rationale for the formation of **4h** is depicted in Scheme 1. The  $\text{FeCl}_3$ -complexed, pentadienylic cation precursor **i** undergoes a ring closure to cyclopentenyl cation **ii** followed by rapid loss of the silicon electrofuge to produce **iii**. The protonation of the resulting enolate **iii** would produce **6**, which is oxidized to **4h** by ferric chloride.<sup>9</sup>

Scheme 1



Such a competitive rapid loss of the silicon electrofuge than the proton from the intermediate **ii** was surprising because the loss of the proton from **ii** is a rearomatization process. This contrasts to the reaction of the ketone **7**, which loses a proton faster and rearomatizes to naphthalene with the silyl moiety remaining intact.<sup>8b</sup>

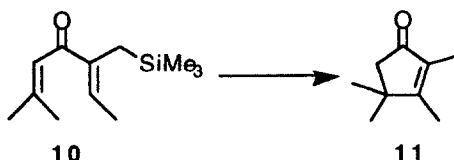


The striking success of the cyclization made us wonder whether the silicon was necessary at all. We therefore prepared the Si free substrate **9** by  $\text{F}^-$  induced protodesilylation of **3h**. When **9** was subjected to the similar reaction conditions, none of the cycloadduct was formed and only decomposed at elevated temperature. The presence of silyl moiety in the vinyl monocyclic aryl ketones is essential for the cyclization and controls the position of double bond.

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5. Spectral data for the selected  $\alpha$ -methylene-cyclopentanones are given below.

**4c**:  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.03 (s, 6H), 2.13 (s, 2H), 2.41 (s, 2H), 5.23 (s, 1H), 5.94 (s, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  28.32, 33.67, 44.66, 53.30, 117.47, 145.29, 206.68. **4e**:  $^1\text{H-NMR}$   $\delta$  2.40-2.60 (m, 2H), 2.65-2.90 (m, 2H), 3.60-3.75 (m, 1H), 5.39 (s, 1H), 6.07 (s, 1H), 6.80-7.26 (m, 3H);  $^{13}\text{C-NMR}$   $\delta$  34.57, 38.91, 46.79, 117.89, 123.31, 123.56, 126.86, 143.87, 147.19, 201.47; MS  $m/z$  178 ( $\text{M}^+$ , 66), 135 (12), 110 (23), 84 (22), 68 (100%). **4h**:  $^1\text{H-NMR}$   $\delta$  3.56 (s, 2H), 5.47 (s, 1H), 6.17 (s, 1H), 7.02 (d, 1H,  $J = 4.86$  Hz), 7.81 (d, 1H,  $J = 4.86$  Hz);  $^{13}\text{C-NMR}$   $\delta$  29.95, 47.31, 118.37, 123.74, 140.23, 142.79, 146.92, 162.77, 185.04; MS  $m/z$  150 ( $\text{M}^+$ , 54), 121 (100), 96 (16), 93 (11), 81 (9), 78 (17), 69 (25), 63 (7), 51 (12%). **4i**:  $^1\text{H-NMR}$   $\delta$  3.80 (s, 2H), 5.55 (s, 1H), 6.24 (s, 1H), 7.26-7.34 (m, 2H);  $^{13}\text{C-NMR}$   $\delta$  30.26, 117.93, 120.46, 130.31, 130.82, 146.86, 165.22, 185.78; MS  $m/z$  150 ( $\text{M}^+$ , 67), 121 (100), 96 (22), 78 (21), 51 (23%). **4j**:  $^1\text{H-NMR}$   $\delta$  3.41 (s, 2H), 3.86 (s, 3H), 5.39 (s, 1H), 6.07 (d, 1H,  $J = 2.4$  Hz), 6.10 (s, 1H), 6.95 (d, 1H,  $J = 2.4$  Hz);  $^{13}\text{C-NMR}$   $\delta$  26.51, 34.05, 104.84, 115.80, 134.96, 146.51, 149.30, 179.47, 211.10; MS  $m/z$  147 ( $\text{M}^+$ , 73), 118 (100), 104 (26), 91 (20), 78 (22), 77 (24), 51 (34%).

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