

# Asymmetric Synthesis of 5-Substituted $\gamma$ -Lactones and Butenolides via Nucleophilic Additions to Oxycarbenium Ions Derived from 5(R)-(Menthyloxy)-4(R)-(phenylsulfanyl)-2(3H)-dihydrofuranone

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Optically active 5-alkyl-substituted butenolides and  $\gamma$ -lactones are attractive building blocks in natural product synthesis<sup>1</sup> and comprise structural moieties frequently present in, e.g., insect pheromones,<sup>2</sup> cardenolides,<sup>3</sup> lignans, and flavor components.<sup>4</sup> Efficient and stereoselective synthetic routes to these products in enantiomerically pure form are highly desirable.<sup>5</sup> As part of our explorative studies toward the use of 5(R)-(menthyloxy)-2(5H)-furanone (**1**) as a chiral synthon,<sup>6,7</sup> the enantioselective synthesis of a number of naturally occurring lignans has been reported.<sup>8</sup>

5(R)-(Menthyloxy)-2(5H)-furanone (**1**) reacts with thiophenol and a catalytic amount of triethylamine to give stereospecifically and in excellent yield the trans addition product **2** (Scheme 1), which features an attractive functional group arrangement to generate  $\alpha$ -sulfanyl oxycarbenium ion **3**. Here we report the fast and highly stereoselective transformations of **2** to 5-alkyl-substituted 4-(phenylsulfanyl)-2(3H)-dihydrofuranones **4** or 4-(menthyloxy)-3-(phenylsulfanyl) carboxylic acids **5**, which are precursors for butenolides and  $\gamma$ -lactones.

Various methods for C–C bond formation via Lewis acid-mediated reactions of acetals with nucleophiles have been developed.<sup>9</sup> As demonstrated by a number of groups,<sup>10</sup> there is a mechanistic divergence between  $S_N2$ -

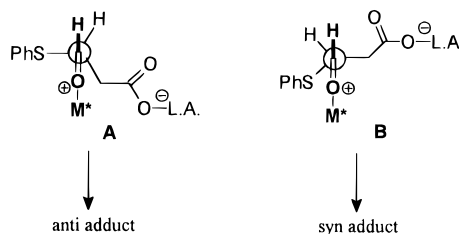
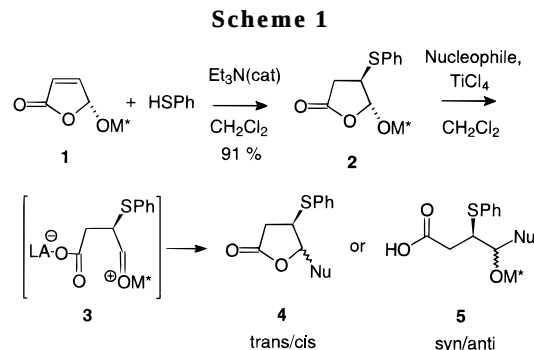


Figure 1.



and  $S_N1$ -type processes. It has been shown that Lewis acid-mediated additions of silylated nucleophiles to  $\alpha$ - and  $\beta$ -sulfanyl-substituted aldehydes proceed with excellent diastereoselectivities.<sup>11</sup> Furthermore, reactions of  $\alpha$ -sulfanyl acetals with carbon nucleophiles have been studied by Saigo and co-workers.<sup>12</sup> In furanone **2**, an  $\alpha$ -sulfanyl-substituted, mixed acyloxy–alkoxy acetal moiety is present, and upon treatment with a Lewis acid it is observed that the acyloxy acetal bond is always broken<sup>13</sup> and this reaction path leaves only two likely intermediates (Figure 1). The stereoselectivity of these reactions can be rationalized by the Felkin–Ahn model, and conformers **A** and **B** lead to anti and syn adducts, respectively. Conformer **A** is preferred, and in most cases the anti adduct is the only detectable diastereomer.

When 4(R)-(phenylsulfanyl)-substituted furanone **2** is treated at  $-70^\circ\text{C}$  with 1–2 equiv of  $\text{TiCl}_4$  in the presence of a variety of nucleophiles such as allylsilanes, silyl enol ethers, or diorganozinc reagents a very fast reaction occurs. After a reaction time of 5 min and subsequent aqueous workup,  $\beta,\gamma$ -substituted acids **5** are isolated in 56–72% yield and in most cases with a diastereomeric ratio  $>98:2$  according to  $^1\text{H}$  and  $^{13}\text{C}$  NMR (Scheme 2, path A, Table 1, entries 2, 4, 6, 8, and 12). In addition to the acids **5** small amounts of lactones **4** (5–20%) are also found in the crude product, but these could be easily separated.

When the addition of nucleophiles **9–16** is performed in the presence of 2 equiv of  $\text{TiCl}_4$  for 1 min at ambient temperature, followed by aqueous workup, the lactones **4** are obtained. In a few cases small amounts of the acids **5** ( $\leq 10\%$ ) are also formed. Apparently, the intermediate **6** is activated by the excess of Lewis acid present, and upon addition of water hydrolysis to the hydroxy acid **8**

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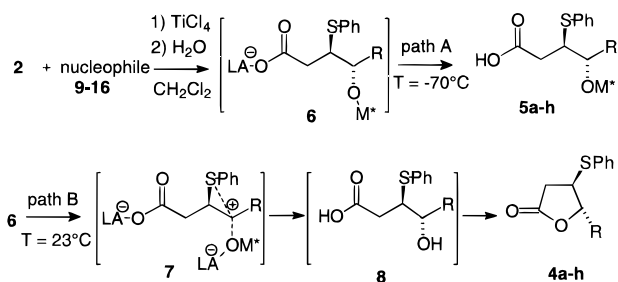
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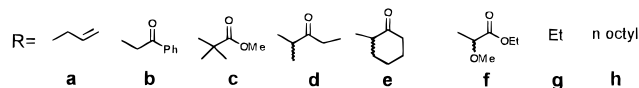
Scheme 2

Table 1. Additions of Nucleophiles to Oxycarbenium Ions Derived from **2**

| Entry | Nucleophile | T ( $^\circ\text{C}$ ) | time (min) | Product (R)  | (ratio a) | Yield <sup>b</sup> % | trans : cis <sup>c</sup><br>(anti : syn <sup>c</sup> ) |
|-------|-------------|------------------------|------------|--------------|-----------|----------------------|--------------------------------------------------------|
| 1     |             | 23                     | 1          | <b>4a/5a</b> | (>9 : 1)  | 50                   | 92 : 8                                                 |
| 2     |             | -70                    | 5          | <b>5a/4a</b> | (8 : 2)   | 56                   | 9 : 1                                                  |
| 3     |             | 23                     | 1          | <b>4b/5b</b> | (>9 : 1)  | 65                   | >98 : 2                                                |
| 4     |             | -70                    | 5          | <b>5b/4b</b> | (8 : 2)   | 59                   | >98 : 2                                                |
| 5     |             | 23                     | 1          | <b>4c/5c</b> | (>9 : 1)  | 66                   | >98 : 2                                                |
| 6     |             | -70                    | 5          | <b>5c/4c</b> | (9 : 1)   | 72                   | >98 : 2                                                |
| 7     |             | 23                     | 1          | <b>4d/5d</b> | (>9 : 1)  | 74                   | >98 : 2 <sup>d</sup>                                   |
| 8     |             | -70                    | 5          | <b>5d/4d</b> | (8 : 2)   | 52                   | >98 : 2 <sup>d</sup>                                   |
| 9     |             | 23                     | 1          | <b>4e/5e</b> | (>9 : 1)  | 57                   | >98 : 2 <sup>d</sup>                                   |
| 10    |             | 23                     | 1          | <b>4f/5f</b> | (>9 : 1)  | 74                   | 53 : 47 <sup>d</sup>                                   |
| 11    |             | 23                     | 2          | <b>4g/5g</b> | (>9 : 1)  | 56                   | 9 : 1                                                  |
| 12    |             | -70                    | 5          | <b>5g/4g</b> | (9 : 1)   | 57                   | >98 : 2                                                |
| 13    |             | 23                     | 5          | <b>4h/5h</b> | (>9 : 1)  | 53                   | >98 : 2                                                |

<sup>a</sup>Ratio determined by  $^1\text{H}$  NMR. <sup>b</sup>Isolated yield of the major isomer.

<sup>c</sup>Ratio determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR of the crude product. <sup>d</sup>Diastereomeric ratio of the exocyclic stereogenic center was in the order of 6 : 4 in all four cases (entry 7-10).

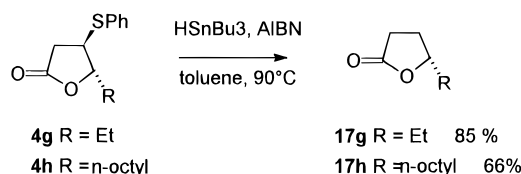


followed by lactonization takes place (Scheme 2, path B). A key feature of the second Lewis acid-mediated step is the stereoselective cleavage of the auxiliary group assisted by the  $\alpha$ -sulfanyl functionality. Except for **4f**, trans lactones **4** are formed as the major, or in most cases only detectable, diastereomer. Even in the few cases (entries 1 and 11, Table 1) where small amounts of cis lactones **4** were obtained, these could be separated by simple column chromatography using silica gel.

Single crystal X-ray analysis of **4b** confirmed the trans relationship of the substituents at  $\text{C}_4$  and  $\text{C}_5$ .<sup>21</sup> The trans configuration for the products **4a-e,g,h** has been assigned by comparison on the basis of  $^1\text{H}$  NMR coupling constants and on the expected mechanistic similarity in this reaction for all nucleophiles used.<sup>14</sup>

The enantiomerically pure 5(S)-alkyl-4(R)-(phenylsulfanyl)-2(3H)-dihydrofuranones **4** are excellent precursors for 5-alkyl-substituted butenolides or butanolides,<sup>15,16</sup> whereas the phenylsulfanyl substituent allows a number

Scheme 3



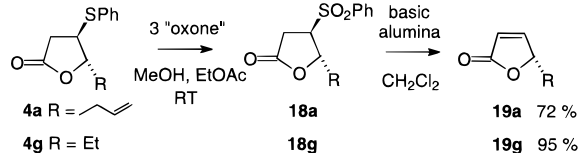
**4g** R = Et

**4h** R = n-octyl

**17g** R = Et 85 %

**17h** R = n-octyl 66 %

Scheme 4



**4a** R =

**4g** R = Et

**18a**

**18g**

**19a** 72 %

**19g** 95 %

of synthetically useful transformations. Reductive desulfurization of **4** could best be performed with  $\text{Bu}_3\text{SnH}$ /AIBN and provided enantiomerically pure 5(S)-alkyl-2(3H)-dihydrofuranones **17** (Scheme 3). The flavor components and insect pheromones<sup>4</sup> 5(S)-ethyl-2(3H)-dihydrofuranone (**17g**) [85% yield,  $[\alpha]_D = -50$  (c 1, MeOH) (lit.<sup>17</sup>  $[\alpha]_D = -53.2$  (c 1, MeOH))] and 5(S)-octyl-2(3H)-dihydrofuranone (**17h**) [66% yield,  $[\alpha]_D = -35$  (c 0.48, MeOH) (lit.<sup>17</sup>  $[\alpha]_D = -36.8$  (c 0.3, MeOH))] were obtained using this procedure.

Alternatively, 5(S)-alkyl-2(5H)-furanones **19** are accessible via the sulfones **18** (Scheme 4). Oxidation of **4** with Oxone<sup>18</sup> and subsequent elimination with basic alumina in  $\text{CH}_2\text{Cl}_2$  gave the corresponding 5(S)-alkyl-2(5H)-furanones **19** in good yields.<sup>19</sup> For example, 5(S)-ethyl-2(5H)-furanone (**19g**) [95% overall yield,  $[\alpha]_D = +105$  (c 4.1,  $\text{CH}_2\text{Cl}_2$ ) (lit.<sup>20</sup> for 5(R)-**19g**  $[\alpha]_D = -97.6$  (c 2.08,  $\text{CH}_2\text{Cl}_2$ ))] and 5(S)-(1-prop-2-enyl)-2(5H)-furanone (**19a**) (72% overall yield,  $[\alpha]_D = +105$  (c 1.08, MeOH)) were obtained using this procedure.

In conclusion, we have demonstrated that **2** is a valuable synthon for the synthesis of 3,4-disubstituted carboxylic acids, 5-substituted butenolides, and  $\gamma$ -lactones in enantiomerically pure form.

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**Supporting Information Available:** Experimental procedures for the Lewis acid mediated additions and spectroscopic data for compounds **4a-h** and **5a,b,c,d,g**. (5 pages).

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