



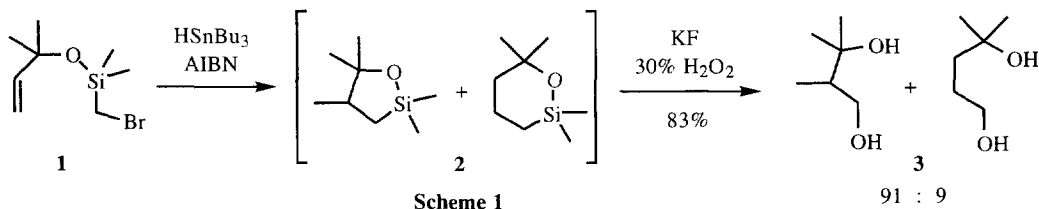
## Highly Regioselective Intramolecular Hydroxymethylation of $\alpha,\beta$ -Unsaturated Carboxylic Acids

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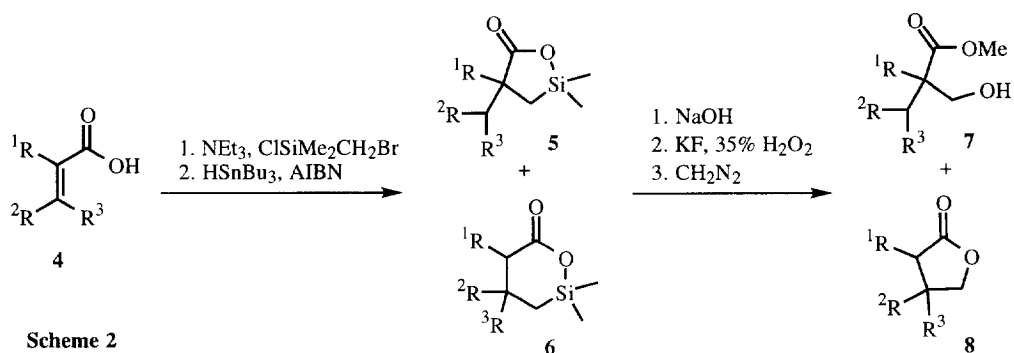
**Abstract:** A convenient synthesis of hydroxy esters **7** and lactones **8** by starting from easily available  $\alpha,\beta$ -unsaturated carboxylic acids **4** is described. The key step of this transformation is a hitherto unknown radical cyclization of silyl esters, which exhibits a high degree of regioselectivity through steric and orbital control. Copyright © 1996 Elsevier Science Ltd

Silicon-tethered reactions have become increasingly attractive for the selective formation of carbon-carbon bonds and were recently comprehensively reviewed.<sup>1</sup> In combination with the oxidation of the carbon-silicon bond,<sup>2</sup> this methodology was applied abundantly in organic synthesis. Among the various strategies, radical cyclizations offer an especially powerful option, which was demonstrated in the pioneering work of Nishiyama and Stork.<sup>3</sup> Thus, by starting from an easily available allyl silyl ether **1**, the regioisomeric diols **3** were synthesized by reaction with tributyltin hydride and Tamao oxidation<sup>4</sup> of the cyclic intermediates **2** (Scheme 1). This methodology was extended to highly functionalized allyl silyl ethers,<sup>5</sup>



homoallyl silyl ethers,<sup>6</sup> propargyl silyl ethers,<sup>7</sup> and tandem cyclizations.<sup>8</sup> Surprisingly, no examples for analogous transformations of  $\alpha,\beta$ -unsaturated silyl esters exist in literature. This is remarkable, since electron-acceptor-substituted olefins represent ideal substrates for intermolecular radical additions.<sup>9</sup>

Herein we present a convenient protocol for the synthesis and cyclization of silyl esters, which provides an easy route to hydroxy esters **7** and lactones **8**. Thus, the  $\alpha,\beta$ -unsaturated carboxylic acids **4** were transformed into the corresponding bromomethyl silyl esters, which upon reaction with tributyl tin hydride afford the silalactones **5** and **6** by 5-*exo* and 6-*endo* cyclization (Scheme 2). The relatively low conversions (Table 1) are due to the lability of the silyl esters under the reaction conditions. The removal of the tin compounds, which is often a problem in radical reactions, was conveniently achieved by extraction with 0.5 N NaOH and separation of the cyclization products as sodium salts. Tamao oxidation<sup>4</sup> and esterification with diazomethane afforded the hydroxy esters **7** and lactones **8** in moderate to good overall yields (Table 1).

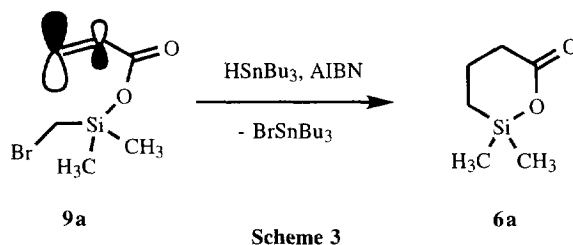


**Table 1.** Hydroxymethylation of Carboxylic Acids **4**

entry	acid	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	conv. (%) <sup>[a]</sup>	cyclizations		oxidations	
						<b>5</b> : <b>6</b> <sup>[b]</sup>	ester <b>7</b> (%) <sup>[c]</sup>	lactone <b>8</b> (%) <sup>[c]</sup>	
1	<b>4a</b>	H	H	H	> 95	< 3:97	-	24 <sup>[d]</sup>	
2	<b>4b</b>	H	Me	H	54	48:52	30	33	
3	<b>4c</b>	Me	Me	H	64	< 3:97 <sup>[e]</sup>	-	67 <sup>[e]</sup>	
4	<b>4d</b>	H	Me	Me	52	> 97:3	74	-	
5	<b>4e</b>	H	Ph	H	47	> 97:3	72	-	

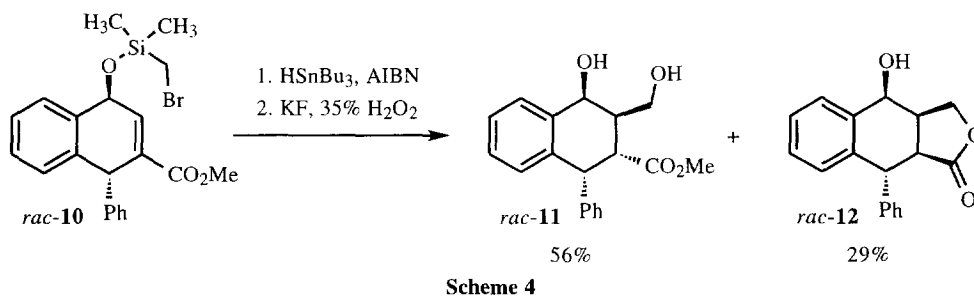
[a] After the radical reactions acids **4** were obtained due to the lability of the silyl esters. [b] Determined by <sup>1</sup>H NMR analysis of the crude product mixture. [c] Yield of isolated product after silica gel chromatography based on conversion of acid **4**. [d] The low yield is due to the formation of oligomers. [e] *cis:trans* = 65:35.

As shown in Table 1, the regioselectivities of the cyclizations (5-*exo* versus 6-*endo*) strongly depend on the substitution pattern of the double bond. Severe steric interactions control the reactions of tiglic acid (**4c**) and 3,3-dimethylacrylic acid (**4d**) (entries 3 and 4). Thus, the radical cyclization exclusively takes place at the less substituted end of the double bond, to afford selectively lactone **8c** and hydroxy ester **7d**. In contrast to steric control, the regioselective 6-*endo* cyclization of the silyl ester **9a** derived from acrylic acid (**4a**) (entry 1) is rationalized in terms of orbital control (Scheme 3). For nucleophilic, carbon-centered radicals the



interaction with the LUMO is crucial,<sup>10</sup> which has the largest coefficient at the 4-position of acrylic ester **9a**. Therefore, the silalactone **6a** is obtained selectively as a result of the 6-*endo* cyclization. The importance of orbital interactions becomes evident by the comparison with the analogous reaction of allyl silyl ether **1** (Scheme 1). In this case, the energy gap between the SOMO and LUMO is larger and, thus, the kinetically favored 5-*exo* cyclization predominates.<sup>11</sup> Only crotonic acid (**4b**) affords a mixture of regioisomeric silalactones **5** and **6** (entry 2), since steric repulsions and favorable orbital interactions are counterbalanced. Instead, the highly selective 5-*exo* cyclization of the silyl ester derived from cinnamic acid (**4e**) (entry 5) can be rationalized by an increase in the LUMO coefficient  $\alpha$  to the ester group, which is in accordance with analogous reactions of cinammyl alcohols.<sup>12</sup>

Finally, the more highly functionalized  $\alpha,\beta$ -unsaturated ester *rac*-**10** was subjected to an intramolecular hydroxymethylation to afford hydroxy ester *rac*-**11** and lactone *rac*-**12** in good overall yields (Scheme 4).<sup>13</sup>



The first stereocenter is introduced exclusively *cis* to the hydroxy group, whereas, the hydrogen transfer step is less selective. Under the reaction conditions, the *cis*-configured epimer directly affords the lactone **12**. Both cyclization products **11** and **12** represent precursors for the synthesis of podophyllotoxin analogues, which are important chemotherapeutic agents.<sup>14</sup>

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13. Selected spectroscopic data for *rac*-**11**: IR (KBr) 3342 1719 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 5.07 (d, 1H, *J* = 3.4, 1-H), 4.64 (d, 1H, *J* = 6.2, 4-H), 3.99 (dd, 1H, *J* = 11.3, 3.1, 11-H), 3.97 (dd, 1H, *J* = 11.3, 4.5, 11'-H), 3.65 (dd, 1H, *J* = 12.3, 6.2, 3-H), 3.54 (s, 3H, OMe), 2.43 (m, 1H, 2-H). *rac*-**12**: IR (KBr) 3445 1738 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>OD): δ 4.70 (d, 1H, *J* = 5.5, 1-H), 4.51 (d, 1H, *J* = 3.4, 4-H), 4.39 (dd, 1H, *J* = 9.5, 8.2, 11-H), 4.28 (dd, 1H, *J* = 9.5, 3.9, 11'-H), 3.72 (dd, 1H, *J* = 10.7, 3.4, 3-H), 3.99 (dddd, 1H, *J* = 10.7, 8.2, 5.5, 3.9, 2-H).
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