Pergamon

Tetrahedron Letters, Vol. 37, No. 46, pp. 8363-8366, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01931-4

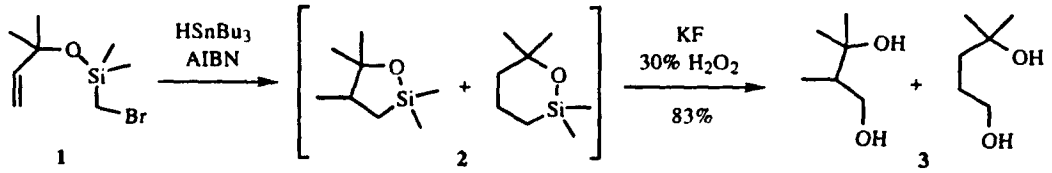
Highly Regioselective Intramolecular Hydroxymethylation of α,β-Unsaturated Carboxylic Acids

Torsten Linker*, Michael Maurer, and Frank Rebien

Institute of Organic Chemistry, University of Würzburg , Am Hubland, D-97074 Würzburg, Germany

Abstract: A convenient synthesis of hydroxy esters **7** and lactones **8** by starting from easily available α,β-unsaturated carbocylic 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

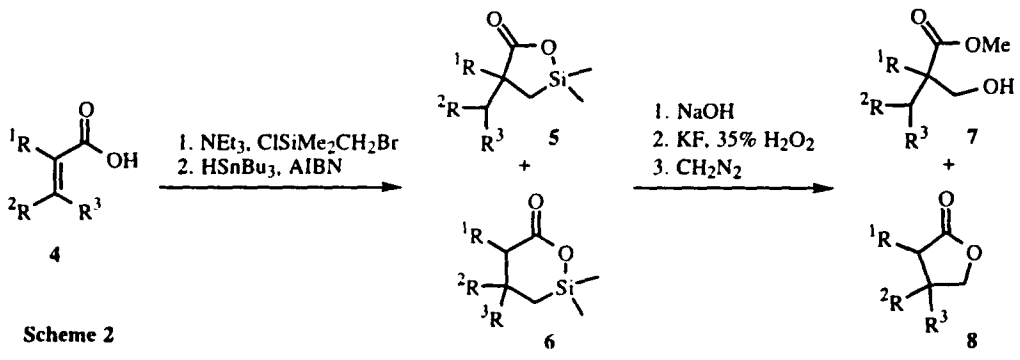
Silicon-tethered reactions have become increasingly attractive for the selective formation of carbon-carbon bonds and were recently comprehensively reviewed.[1] In combination with the oxidation of the carbon-silicon bond,[2] this methodology was applied abundantly in organic synthesis. Among the various strategies, radical cyclizations offer an especially powerful option, which was demonstrated in the pioneering work of Nishiyama and Stork.[3] 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[4] of the cyclic intermediates **2** (Scheme 1). This methodology was extended to highly functionalized allyl silyl ethers, [5]



Scheme 1

homoallyl silyl ethers,[6] propargyl silyl ethers,[7] and tandem cyclizations.[8] Suprisingly, no examples for analogous transformations of α,β-unsaturated silyl esters exist in literature. This is remarkable, since electron-acceptor-substituted olefins represent ideal substrates for intermolecular radical additions.[9]

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 α,β-unsaturated carbocylic 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 silylesters 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[4] and esterification with diazomethane afforded the hydroxy esters **7** and lactones **8** in moderate to good overall yields (Table 1).



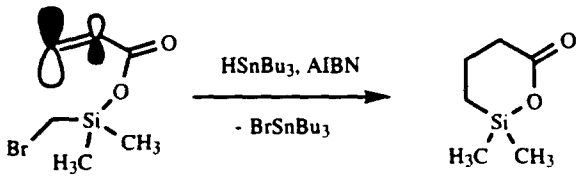
Scheme 2

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

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

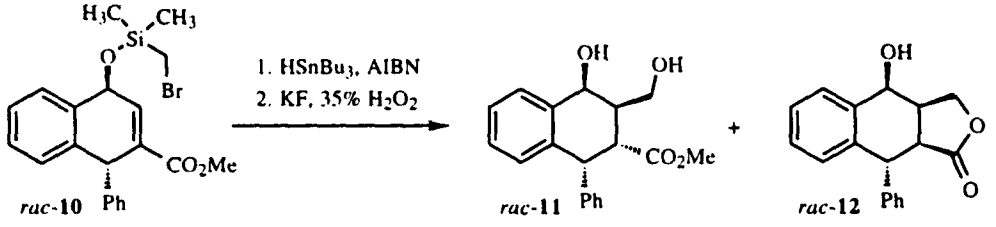


9a **6a**

Scheme 3

interaction with the LUMO is crucial,[10] 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.[11] 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 α to the ester group, which is in accordance with analogous reactions of cinammyl alcohols.[12]

Finally, the more highly functionalized α,β-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).[13]



rac-**10** *rac*-**11** *rac*-**12**

56% 29%

Scheme 4

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*-configurated 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.[14]

Acknowledgment

This work was generously supported by the Deutsche Forschungsgemeinschaft (Li 556/2-1, 556/3-1) and the Volkswagen-Stiftung. We thank Prof. Dr. W. Adam for his continuous encouragement.

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13. Selected spectroscopic data for *rac*-**11**: IR (KBr) 3342 1719 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 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^{-1}; ^1H NMR (200 MHz, CD_3OD): 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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(*Received in Germany* 28 *August* 1996; *revised* 23 *September* 1996; *accepted* 27 *September* 1996)