One-Pot Diastereoselective Preparation of α,β-Unsaturated-γ-Silylated-δ-Lactones: Application towards Natural Compounds

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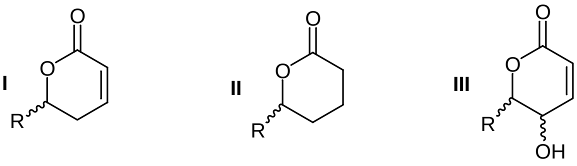
Abstract: Rearrangement of silylated vinyloxiranes into highly functionalized α-silylated-β,γ-unsaturated aldehydes occurs with total chirality transfer and retention of double bond configuration under Pd(0) catalysis. We show that this reaction is a versatile tool in the field of total stereoselective synthesis : enantiomerically pure lactones are obtained. The pheromone 6-*n*-undecyltetrahydro-2-pyrone **2** and massoilactone, 5-hydroxy-2-decenoic acid lactone **3**, are synthesized. We describe herein a novel highly diastereoselective route to α,β-unsaturated-γ-silylated-δ-substituted-δ-lactones **1**.

Key words: assymetric synthesis, lactones, natural products, palladium

Enantiomerically pure 6-substituted-5,6-dihydro-2*H*-pyran-2-ones (α,β-unsaturated-δ-lactones) **I** are key structural subunits of widely occurring natural products.[1-4] Their saturated analogues **II** are important aroma compounds[2] which are abundantly found in meat, dairy and fruit products. The 5-hydroxy derivatives **III** display diverse biological activities and appear as part of some antibiotic structures[5] (Scheme 1).

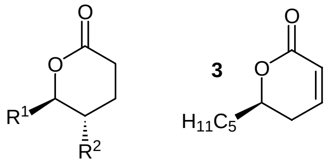


Scheme 1

Herein, we describe an enantioselective method to synthesize δ-lactones of type **I**, **II** and **III**, based on the utilization of α,β-unsaturated-γ-silylated-δ-substituted-δ-lactones **1** as key intermediates. Thus, we synthesized type **II** 6-*n*-undecyltetrahydro-2-pyranone **2**, the pheromone of the oriental hornet[6] called *Vespa orientalis* and type **I** 6-*n*-pentyl-5,6-dihydro-2-pyrone **3**, also known as massoilactone which is the major constituent of the bark oil of *Cryptocaria massoia*. Massoilactone **3**[7a, b] has also been isolated from cane molasses as a flavor product and from two species of ants as a defense substance. Type **III** δ-lactones may be obtained after oxidation of the carbon-silicon bond into a hydroxyl group to give the (+) Osmundalactone **4**[8]($R = CH_3$), (Scheme 2).

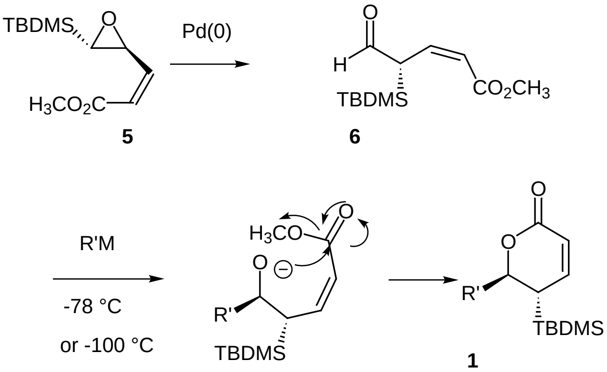
2 : $R^1 = C_{11}H_{23}$ $R^2 = H$

4: $R^1 = CH_3$ $R^2 = OH$



Scheme 2

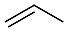
We present here a short stereoselective synthesis of compounds **2**[9] and **3**[7a]. We recently reported[10,11] that the silylated vinyloxiranes **5** rearrange into the α-silylated-β,γ-unsaturated aldehydes **6** with a complete transfer[10] of chirality and retention of the double bond configuration.[11] This stereoselective palladium-catalyzed 1,2-silicon shift, combined with the high diastereoselective alkylation[12,13] of aldehydes **6** led us to propose a one-pot transformation of the silylated vinylepoxides **5** into the δ-lactones **1** (Scheme 3).



Scheme 3

Enantiomerically pure silylated vinyloxiranes **5** were prepared using our previously described conditions[10a] and were submitted to a catalytic amount of zerovalent palladium generated in situ from $Pd(OAc)_2$ and $P(OPh)_3$. After checking the completion of the rearrangement by TLC, the organometallic reagent was added dropwise. The temperature was increased to reach room temperature in order to achieve complete cyclization. Grignard derivatives give the best chemical yields of lactones **1** (Table 1), with a very high degree of diastereoselectivity for the *anti* diastereomeric form of α,β-unsaturated-γ-silylated-δ-substi-

Table Preparation of δ-Lactones **1a**-**g**. Diastereomeric Ratio

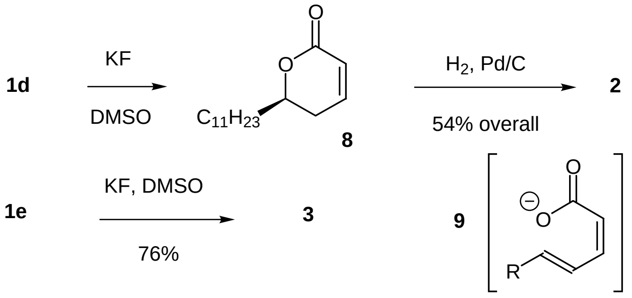
R'	Yield [%]	Product	d.e.[%][a]
CH_3	78	**1a**[b]	74
i-Pr	79	**1b**[b,c]	>96
t-Bu	90	**1c**[d]	>96
$C_{11}H_{23}$	73	**1d**[d]	>96
C_5H_{11}	70	**1e**[b]	>96
HC≡C—	70	**1f**[b]	>96
	60	**1g**[e]	>96

a) Measured by ^{1}H NMR. b) Purified as a white solid by recrystallisation. c) ee = 93-99%. The enantiomeric excesses were measured by chiral GC. They were checked to be equal to the starting vinyloxiranes'ees, proving that chirality is totally transferred through this one-pot procedure. d) Purified by flash chromatography on silica gel. e) Synthesized in a racemic form.

tuted-δ-lactones **1a-g**.[14] This selectivity can be explained by a Felkin model.[12,13]

Other alkylating agents have been added to aldehydes **6**. In the case of methyllithium and methylcerium dichloride (Scheme 4), the δ-lactone **1a** and the homoallylic alcohol **7** are isolated. The intermediate aldehyde **6** is also recovered. Alcohol **7** could be conveniently cyclized to lactone **1a** by Otera's procedure[15] in 85% yield. Grignard reagents led to higher yields of lactones probably due to magnesium-catalyzed transesterification.

Desilylation (Scheme 5) of lactones **1d** and **1e** was conducted in dimethyl sulfoxide at room temperature with a large excess of potassium fluoride. Lactone **1d** leads to the desilylated product **8**, which was directly hydrogenated to the pheromone **2**; whereas **1e** was directly transformed into the natural product **3**. Partial racemization of **1d** and **1e** during the desilylation process, led to less optical activity for **2** (α_D^{20} 9.47(c 0.95, THF)) and **3** (α_D^{20} -28.7 (c 1.02, $CHCl_3$)) than reported in litterature for **2**[16] and **3**.[17] Isolation of the acidic form of the intermediate conjugated carboxylate **9** gave an explanation for the loss of enantiomeric purity observed during the desilylation reaction which is currently under study in our group.



Scheme 5

In summary, this paper shows a simple and efficient general access to diastereomerically pure α,β-unsaturated-γ-silylated-δ-lactones **1**. The two natural lactones **2** and **3** could be synthesized in overall yields of 70-90%. These results also suggest that the enantiopure α,β-unsaturated-γ-silylated-δ-lactones are interesting building blocks for further 1,4-addition reactions on the α,β-unsaturated ester moiety and electrophilic additions on the allylsilane skeleton.

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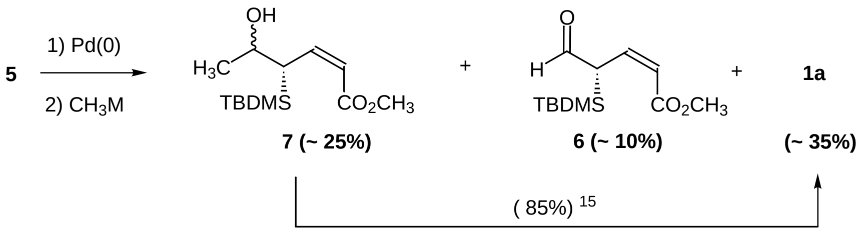

Scheme 4

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(14) General procedure for the preparation of compounds **1a-g** : Triphenyl phosphite (0.2 equiv, 0.4 mmol) was added via a syringe to a stirred solution of palladium diacetate (0.05 equiv, 0.1mmol) in freshly distilled THF (3mL). A solution of vinylepoxysilane **5a-g** (1 equiv, 2 mmol) in THF (10mL) was cannulated into the pale yellow reaction mixture. After completion of the rearrangement (checked by TLC), temperature was lowered to -78 °C and the Grignard reagent (1.1 equiv, 2.2 mmol) was added dropwise via a syringe to minimize temperature fluctuations. The mixture was stirred an additional hour at -78 °C. Then, under continuous stirring, the temperature was raised toward room temperature and the mixture was quenched by a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether, the organic layers were combined and dried over sodium sulfate. After filtration the solvent was evaporated under reduced pressure. The lactone was then purified by flash chromatography with a petroleum ether / ethyl acetate (9/1) eluent.

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