

Lactones from lactones: regio and diastereoselective double dinucleophilic additions of bis(OTMS) ketene acetals to pyridines

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This letter is dedicated to Dr. Bernard Denise, who deceased on November 4th 2005

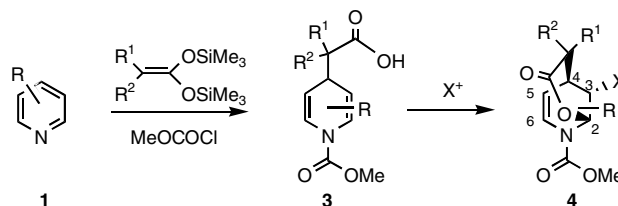
Abstract—Lactones from lactones: a cascade transformation is observed during two successive double nucleophilic additions of bis (TMS) ketene acetals to pyridines.

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Many natural products contain piperidine ring systems in their structure, from very simple monocyclic compounds to more complex ones such as alkaloids.¹ They very often have significant biological activity and in many cases have been used as therapeutic agents.² Moreover, these heterocyclic rings are also of a general interest in organic synthesis. Therefore, efforts to develop stereocontrolled syntheses of these classes of compounds remained unabated during the last years.³

We recently reported in a series of papers the synthesis of lactones fused to heterocyclic compounds starting from pyridines and their derivatives **1**.⁴

The transformation of pyridines **1** into lactones **4** involved the use of bis (OTMS) ketene acetals as C,O-dinucleophiles⁵ in conjunction with an electrophilic activating reagent such as methylchloroformate giving in the first step carboxylic acid-substituted dihydropyridines **3**.^{6,7} In the second step, a non-biomimetic transformation of the dihydropyridines⁸ involving one of their double bonds led to a series of lactones **4** bearing in β to nitrogen either a methylene group (X = H) or



Scheme 1.

various functional groups (X = I, Br, OH, OAc). Both steps could be carried out as one-pot reactions (Scheme 1).

These new lactones can be considered as special semi-cyclic N,O-acetals, the reactivity of which should be greatly enhanced due to the presence of the carbonyl group of the highly strained lactone: they might thus react very easily with electrophiles, for example, Lewis acids, giving upon ring-opening iminium derivatives, which in turn would react with nucleophiles at C-2.^{9–12} They contain also an ene-carbamate, the double bond of which might undergo addition of both electrophiles at C-5 and nucleophiles at C-6 upon delocalization of electrons from nitrogen to the double bond.

The purpose of this letter is to show that indeed both types of properties can be used to synthesize in a

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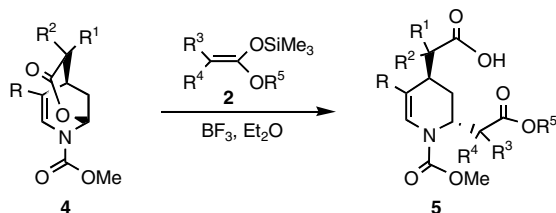
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diastereoselective way, on the one side highly functionalized tetrahydropyridines and on the other side polysubstituted piperidines as the result of concerted push–pull lactone opening/closing reactions. We therefore examined successively their behaviour towards O-alkyl O-TMS ($R^5 = \text{CH}_3, \text{CH}_2\text{CH}_3$) and bis(OTMS) ketene acetals **2** ($R^5 = \text{TMS}$) in the presence of Lewis acids.

Thus when a dichloromethane solution of lactone **4a** ($X = \text{H}, R = \text{H}, R^1 = R^2 = \text{Me}$) was stirred first at -60°C with a slight excess of ketene acetal **2a** ($R^3 = R^4 = \text{H}, R^5 = \text{Et}$) in the presence of either borontrifluoride etherate or trimethylsilylfluorosulfonate, then for 2 h at room temperature, a single new compound **5a** was isolated in 60% yield (Scheme 2).

According to its spectroscopic data, this compound resulted indeed from the addition of the ketene acetal to the lactone giving an acid ($\delta \text{CO}, 183.37 \text{ ppm}, \delta \text{H}, 11.00 \text{ ppm}$), as a mixture of rotamers, one of the double bonds being still present with signals at $\delta 107.28, 107.60, 127.10$ and 127.64 ppm . It is likely that the nucleophile enters in trans towards the lactone ring (*vide infra 7c*). As indicated in Table 1, a similar behaviour was observed in the case of ketene acetals **2a,b** and **4a–c**.

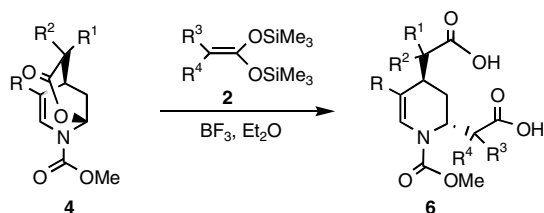
The ketene acetals **2c** ($R^3 = R^4 = \text{H}, R^5 = \text{SiMe}_3$) and **2d** behaved similarly leading to **6a** and **6b**. This appeared clearly in the NMR spectra of **6a** which showed signals at $\delta 177.19$ and 184.11 ppm and at $\delta 10.80$ and 11.00 ppm , for two acid functions, the remaining double bond giving signals at $\delta 4.70$ and $\delta 6.66$ and 6.79 ppm as in the starting lactone (Scheme 3).



Scheme 2.

Table 1. Ring-opening reactions of lactones **4**

R	R ¹	R ²	4	R ³	R ⁴	R ⁵	2	Yield (%)	5
H	Me	Me	4a	H	H	Et	2a	60	5a
H	Me	Me	4a	Me	Me	Me	2b	64	5b
H		(CH ₂) ₅	4b	H	H	Et	2a	63	5c
Me	Me	Me	4c	H	H	Et	2a	58	5d



Scheme 3.

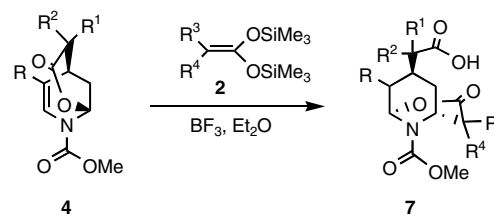
Table 2. Ring-opening/ring-closing reactions of lactones **4**

R	R ¹	R ²	4	R ³	R ⁴	2	Yield (%)	
H	Me	Me	4a	H	H	2c	51	6a
H	Me	Me	4a	Me	H	2d	56	6b
H	Me	Me	4a	Me	Me	2e	53	7a
H	Me	Me	4a	Ph	Me	2f	17	7b
H		(CH ₂) ₅	4b	Me	Me	2e	61	7c
Me	Me	Me	4c	Me	Me	2e	51	6c

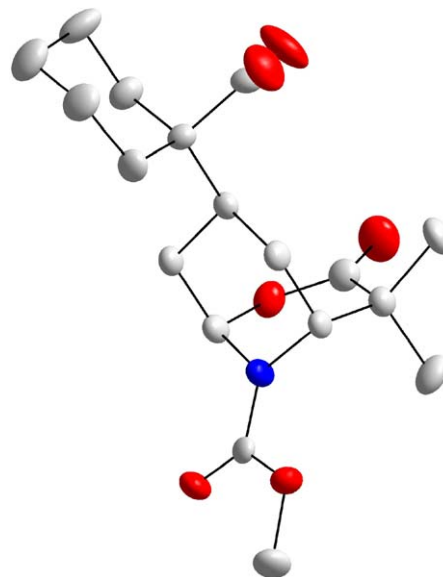
Lactone **4c** derived from 3-picoline led with **2e** to the diacid **6c** in 51% yield (Table 2). When instead the bis(OTMS) ketene acetals **2e,f** were used, the course of the reaction was different. Thus, under the same conditions, lactone **4a** and ketene acetal **2e** led selectively to **7a** in 53% yield (Scheme 4).

Surprisingly, this product contained both an acid and a lactone function ($\delta \text{CO}, 181.53$ and 175.58 ppm) but no double bond. A highly deshielded proton gave a signal at 6.23 and 6.35 ppm typical for a proton on a carbon bearing two heteroatoms as in the starting lactones **4a** ($\delta \text{C}, 82.20$ and 82.46 ppm for the two rotamers).

Lactone **4b** behaved similarly with **2e** giving a single addition product **7c** as white crystals (61% yield, mp 251°C) suitable for an X-ray analysis.¹³ Figure 1 reveals



Scheme 4.

Figure 1. Diamond view of compound **7c** demonstrating the ring-opening of **4b** and the new ring-closing reaction.

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