Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 4541–4544
Tetrahedron Letters

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

Yiming Xu,[a] Henri Rudler,[a,*] Bernard Denise,[a] Andrée Parlier,[a] Patrick Chaquin[b] and Patrick Herson[c]

[a]*Laboratoire de Chimie Organique, UMR 7611-CNRS, Institut de Chimie Moléculaire Université Pierre et Marie Curie, France*
[b]*Laboratoire de Chimie Théorique, UMR 7616 UPMC-CNRS, France*
[c]*Laboratoire de Chimie Inorganique et des Matériaux Moléculaires, UMR 7071 UPMC-CNRS, T. 44-45 4 place Jussieu, 75252 Paris Cedex 5, France*

Received 10 April 2006; revised 27 April 2006; accepted 2 May 2006

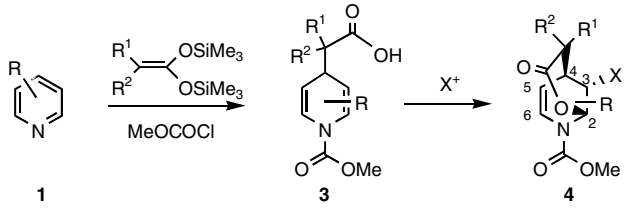
This letter is dedicated to Dr. Bernard Denise, who deceased on November 4th 2005

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

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-dinucleophiles[5] 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 dihydropyridines[8] 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 various functional groups (X = I, Br, OH, OAc). Both steps could be carried out as one-pot reactions (Scheme 1).



Scheme 1.

These new lactones can be considered as special semicyclic 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 exmple, 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

Keywords: Dihydropyridines; Lactone; Ketene acetals; Nucleophilic additions; Tetrahydropyridines; Piperidines.
* Corresponding author. Tel.: +33 (0)144275092; fax: +33 (0)144275504; e-mail: rudler@ccr.jussieu.fr

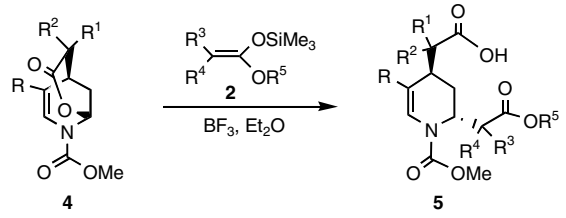
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.004

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 ($R^5 = CH_3$, CH_2CH_3) and bis(OTMS) ketene acetals **2** ($R^5 = TMS$) in the presence of Lewis acids.

Thus when a dichloromethane solution of lactone **4a** ($X = H$, $R = H$, $R^1 = R^2 = Me$) was stirred first at −60 °C with a slight excess of ketene acetal **2a** ($R^3 = R^4 = H$, $R^5 = Et$) 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 (δ CO, 183.37 ppm, δ H, 11.00 ppm), as a mixture of rotamers, one of the double bonds being still present with signals at δ 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**.

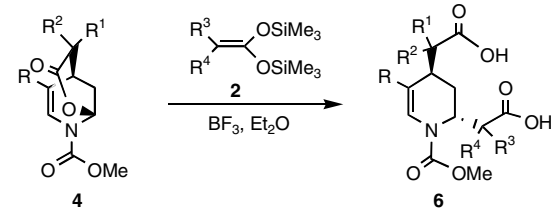
The ketene acetals **2c** ($R^3 = R^4 = H$, $R^5 = SiMe_3$) and **2d** behaved similarly leading to **6a** and **6b**. This appeared clearly in the NMR spectra of **6a** which showed signals at δ 177.19 and 184.11 ppm and at δ 10.80 and 11.00 ppm, for two acid functions, the remaining double bond giving signals at δ 4.70 and δ 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.

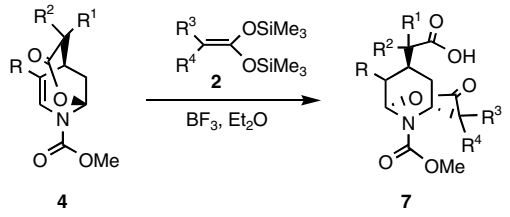
Table 2. Ring-opening/ring-closing reactions of lactones **4**

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 (δ 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** (δ 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.

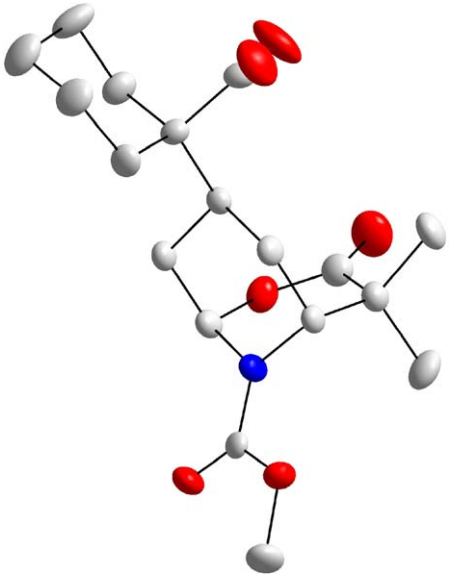
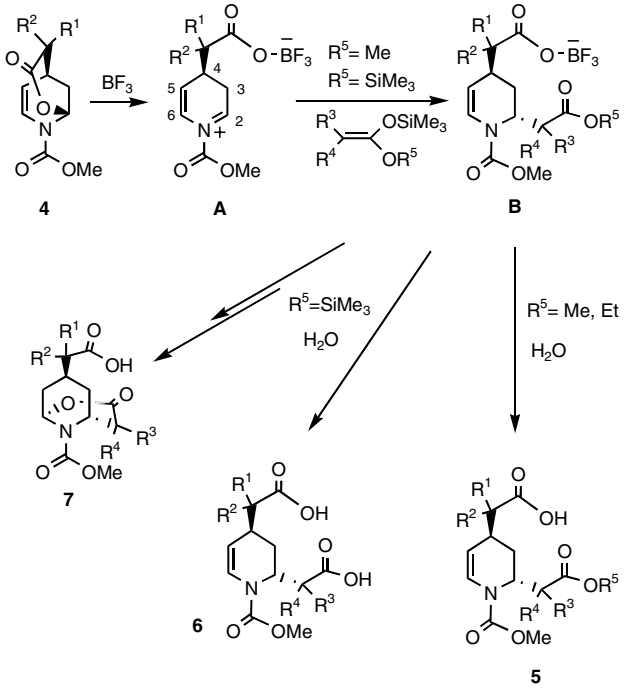


Figure 1. *Diamond* view of compound **7c** demonstrating the ring-opening of **4b** and the new ring-closing reaction.

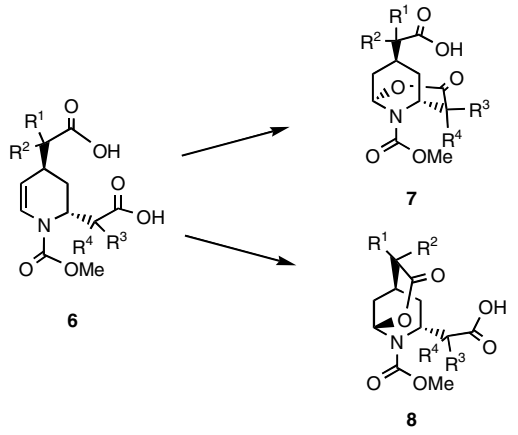
that the lactone ring opened as indicated above (Scheme 2) and that the entering nucleophile indeed substituted position C-2 with inversion giving an acid linked to C-4. However, a consecutive nucleophilic addition of the introduced carboxylate took place at C-6 leading to a new lactone which is now bridged by the carbamate. According to the NMR, two rotamers in non-equivalent amounts are present at room temperature. The planar geometry around nitrogen is indicative of a complete delocalization of its doublet over the oxygen atom of the carbamate, with formation of a strong supramolecular hydrogen bond with the proton of the acid function of a second molecular unit.

A tentative mechanism (Scheme 5) which could account for the complete set of results involves the interaction of the carbonyl group of the lactones with the Lewis acid, leading selectively to the iminium derivatives **A**. The ketene acetals **2** acting as a C-nucleophile add then to C-2 giving 2,4-disubstituted tetrahydropyridine intermediates **B**. These new intermediates might then give upon hydrolysis either monoesters **5** of the diacids, or diacids **6**, or suffer cyclization as such or via diacids **6** to the new lactones **7**.[14]

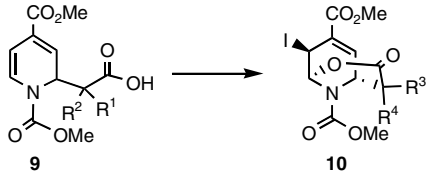
We wondered therefore on the one side why such intermediates **B** (or the diacids **6**) gave in some special cases lactones, and on the other side why these lactones had structure **7** rather than **8** (Scheme 6). Indeed, we had already observed both types of lactonization, the 4-substituted dihydropyridine acids **3** giving very easily and stereoselectively lactones **4**[4a,c] (Scheme 1), the 2-substituted dihydropyridine **9** leading to the carbamate-bridged iodolactone **10** upon its interaction with iodine (Scheme 7),[4b] and a peracid-mediated intramolecular addition of the hydroxyl group of **4** (X = OH) to its



Scheme 5.



Scheme 6.



Scheme 7.

carbon–carbon double bond giving a substituted piperidine.[15]

However, there is a great difference between those substrates and diacids **6**: in contrast to the three previous examples, two internal nucleophiles are in competition in **6** for the addition to the remaining carbon–carbon double bond.

Theoretical calculations have been carried out at the B3LYP/6-31G(d,p) level, using the Gaussian series of programs[16] on three selected diacids **6d** ($R^1 = R^2 = R^3 = R^4 = H$), **6a** ($R^1 = R^2 = Me$, $R^3 = R^4 = H$), and **6e** ($R^1 = R^2 = R^3 = R^4 = Me$) and their corresponding lactones **7** and **8**. The results indicate that, as far as their potential energy is concerned, whatever the nature of the four substituents, the more stable lactone is **7**. Nevertheless, non-negligible differences in the zero point energy (ZPE) and thermal corrections between the lactones and their open form, which is entropy favoured, can be expected.

For that purpose, and for the sake of simplicity, thermodynamic data have been calculated on a monoacid model and the corresponding lactone. They reveal that the relative energy of **6** is overestimated by ca. 2 kcal mol^{-1} due to the ZPE correction and by ca. 3.8 kcal mol^{-1} due to Gibbs free energy corrections. After these corrections, it appears that lactone **7** remains more stable than the diacid in the case of the more substituted compound ($R^1 = R^2 = R^3 = R^4 = Me$) and more important that diacid **6** is the more stable species in the two other cases ($R^1 = R^2 = R^3 = R^4 = H$, and $R^1 = R^2 = H$, $R^3 = R^4 = Me$). According to these results, it appears that if the reaction is under thermodynamic control, then the intermediate acids **6** should indeed evolve as observed

experimentally. A further indication comes from the interaction of lactone **7c** with BF_3 etherate in the presence of a ketene acetal: no further addition reaction is observed. Therefore, no delocalization of the nitrogen doublet, which would lead to a new iminium ion, can take place. Lactone **7** can thus be considered as a potential sink in these transformations.

That picoline would not lead to a lactone of type **7** might be inferred to either steric hindrance or to the fact that the double bond of the corresponding dihydropyridine is much less polarized.

It appears therefore that by adjusting adequately the nature of the substituents on the ketene acetals and on the starting lactones, it is possible to drive these addition reactions either towards the formation of tetrahydropyridines or towards the formation of highly substituted piperidines in a highly stereoselective way. Efforts in this area will be devoted to the synthesis of the same types of structure in an enantioselective way.

References and notes

1. (a) Beak, P.; Stehle, N. W.; Wilkinson, T. J. *Org. Lett.* **2000**, *2*, 155–158; (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446.
2. (a) Elliot, R. L.; Kopecka, H.; Lin, N.-H.; He, Y.; Garvey, D. S. *Synthesis* **1995**, 772–774; (b) Basha, F. Z.; Debernadis, J. F. *Pure Appl. Chem.* **1994**, *66*, 2201–2204; (c) Li, N. H.; Carrera, G. M., Jr.; Anderson, D. J. *J. Med. Chem.* **1994**, *37*, 3542–3553.
3. (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813; (b) Boto, A.; Hernandez, A.; de Leon, Y.; Suarez, E. *J. Org. Chem.* **2001**, *66*, 7796–7803.
4. (a) Rudler, H.; Denise, B.; Parlier, A.; Daran, J. C. *J. Chem. Soc., Chem. Commun.* **2002**, 940–941; (b) Rudler, H.; Denise, B.; Xu, Y.; Parlier, A.; Vaissermann, J. *Eur. J. Org. Chem.* **2005**, 3724–3744; (c) Rudler, H.; Denise, B.; Xu, Y.; Vaissermann, J. *Tetrahedron Lett.* **2005**, *46*, 3449–3451.
5. (a) Bellassoued, M.; Chelain, E.; Collot, J.; Rudler, H.; Vaissermann, J. *J. Chem. Soc., Chem. Commun.* **1999**, 187–188; (b) Rudler, H.; Parlier, A.; Cantagrel, F.; Bellassoued, M. *J. Chem. Soc., Chem. Commun.* **2000**, 771–772; (c) Rudler, H.; Comte, V.; Garrier, E.; Bellassoued, M.; Chelain, E.; Vaissermann, J. *J. Organomet. Chem.* **2001**, *621*, 284–298; (d) Rudler, H.; Harris, P.; Parlier, A.; Cantagrel, F.; Denise, B.; Bellasssoued, M.; Vaissermann, J. *J. Organomet. Chem.* **2001**, *624*, 186–202; (e) Rudler, H.; Alvarez, C.; Parlier, A.; Aldeco-Perez, E.; Denise, B.; Xu, Y.; Vaissermann, J. *Tetrahedron Lett.* **2004**, *45*, 2409–2411; (f) Rudler, H.; Parlier, A.; Alvarez-Toledano, C.; Vaissermann, J. *J. Organomet. Chem.* **2005**, *690*, 4087–4089.
6. For recent applications of this methodology see, (a) Ullah, E.; Rotzoll, S.; Schmidt, A.; Michalik, D.; Langer, P. *Tetrahedron Lett.* **2005**, 8997–8999; (b) Ullah, E.; Langer, P. *Synlett* **2004**, *15*, 2782–2784.
7. For the use of dianions derived from carboxylic acids see, (a) Creger, P. L. *J. Org. Chem.* **1972**, *37*, 1907–1917; (b) Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521–578; (c) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125–4149.
8. For a general review on non-biomimetic reactions of dihydropyridines and applications see, (a) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141–1156; (b) Lavilla, R.; Coll, O.; Nicolas, M.; Sufi, B. A.; Torrents, J.; Bosch, J. *Eur. J. Org. Chem.* **1999**, 2997–3003; (c) Stout, D. V.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223–243; (d) Kumar, R.; Chandra, R. *Adv. Heterocycl. Chem.* **2001**, *78*, 269–313.
9. Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.
10. Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352.
11. Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1250–12517.
12. Fogain-Ninkam, A.; Daïch, A.; Decroix, B.; Netchitaïlo, P. *Eur. J. Org. Chem.* **2003**, 4273–4278, and references therein.
13. For related ring-closure reactions at oxygen see also, Wong, Y.; Marazano, C.; Gnecco, D.; Génisson, Y.; Chiaroni, B.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729–733.
14. Crystal data for **7c**: $M = 353.42$, monoclinic, space group $P2_1$, $a = 6.2200(6)$, $b = 10.0566(7)$, $c = 14.2760(10)$ Å, $\alpha = 90°$, $\beta = 95.969(6)°$, $\gamma = 90°$, $V = 888.15$ Å^3, $Z = 2$, $\rho = 1.32$ g cm^{-3}, $\lambda(\mathrm{MoK}_\alpha) = 0.71073$ Å, $\mu = 0.99$. KAPPACCD-Enraf Nonius diffractometer. Of 6176 reflections collected, 1812 unique data used for refinement. Final $R = 0.0577$, ($R_w = 0.0607$). CCDC-298172 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge crystallographic Data Centre via E.
15. Xu, Y.; Aldeco-Perez, E.; Rudler, H.; Parlier, A.; Alvarez, C. *Tetrahedron Lett.* **2006**, *47*, doi:10.1016/j.tetlet.2006.05.006.
16. Frisch, M. J. In *Gaussian 03, Revision C.02*; Gaussian, Inc.: Wallingford CT, 2004.