Tetrahedron Letters 50 (2009) 7274–7279

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An intramolecular journey of a carboxyl group around 1,2-dihydropyridines: multisite δ- versus γ-lactonization reactions

Andrée Parlier [a], Catherine Kadouri-Puchot [a], Sandra Beaupierre [a], Nathalie Jarosz [a], Henri Rudler [a,*], Louis Hamon [a], Patrick Herson [a], Jean-Claude Daran [b]

[a] Institut Parisien de Chimie Moléculaire UMR CNRS 7201, Université Pierre et Marie Curie, CC 47, 4 Place Jussieu 75252 Paris Cedex 5, France
[b] Laboratoire de Chimie de Coordination, 205 Route de Narbonne 31077 Toulouse Cedex 4, France

ARTICLE INFO

Article history:
Received 7 September 2009
Revised 2 October 2009
Accepted 7 October 2009
Available online 31 October 2009

Keywords:
1,2-Dihydropyridines
Lactones
Ring-closing/ring-opening
Rearrangements
Synthetic methods

ABSTRACT

In contrast to substituted 4-acetic acid 1,4-dihydropyridines, giving only δ-lactones upon intramolecular reactions, 2-substituted 1,2-dihydropyridines led, besides to δ-lactones, also to new, structurally interesting γ-lactones as the result of a bromine-induced carbon-carbon double bond 'Umpolung'.

1. Introduction

The applications of dihydropyridines have already a long and interesting history due to their involvement as fundamental reducing agents in living systems, a property which was mimetically extended to organic[1] and even to organometallic chemistries.[2] Last but not the least, dihydropyridines are also highly valuable and nowadays essential in pharmaceutical sciences: they are part of the chemist's range of tools for the synthesis of highly elaborate molecules. Yet, their non-biomimetic transformations, mainly developed by Lavilla et al.,[3] emerged also as part of important strategic starting material in organic synthesis. Inspired by the use of bis (TMS) ketene acetals as dinucleophiles for the synthesis of a broad range of γ-lactones,[4] we also focused our attention these last few years on the transformations of pyridines via dihydropyridines, according to such a route.[5]

Intramolecular reactions induced by electrophiles allowed us indeed to synthesize, starting from C-4 acetic acid derived 1,4-dihydropyridines **A** (Fig. 1), a broad range of tetrahydropyridine- and piperidine-fused lactones **B** and **D** and especially fluorolactones (e.g., **X** = F in **B**) of biological relevance.[6] The key transformations relied on easy, stereoselective cascade ring-closing to **B**, ring-opening to **C**, and ring-closing reactions to **D**, leading to two types of products, δ-lactones **B** and **D**, as summarized in Figure 1. Due to the symmetry of dihydropyridines **A**, and to the presence in the substrate of a directing group, a polarized ene-carbamate, the lactonization reactions led only to one type of lactones, δ-lactones **B**, and as expected for substrates containing the double bond within a ring, with complete stereocontrol. The acid-promoted ring-opening reactions of lactones **B** led stereoselectively to the dihydropyridines **C**. For R = H in **C**, re-lactonization reactions involving only the substituent at C-2 occurred to give **D** regioselectively.

The purpose of the present Letter is to describe an even more complex trip of the carboxyl group, starting from C-2-functionalized 1,2-dihydropyridines, giving upon halolactonizations inter alia, new fluorolactones, interesting on a biological point of view, and upon unexpected bromolactonizations/solvolytic rearrangements, piperidinelactones, precursors of azasugars.

2. Results

2.1. Fluorolactones and hydroxylactones

Although C-2-functionalized dihydropyridines can be obtained upon the interaction of ketene acetals with activated pyridines, the reaction suffers from two drawbacks: either, mixtures of C-2 and C-4 regioisomers were formed, depending on the substituent on the pyridine-ring, or the selective C-2 regioisomer was observed only in limited cases, for example, with the non-substituted ketene acetal **1** ($R^1 = R^2 = H$).[5b] However, we found that the C-4 *t*-Bu-substituted pyridine was the substrate of choice for the introduction of

* Corresponding author. Tel.: +33 (0)144275092; fax: +33 (0)144273787.
E-mail address: henri.rudler@upmc.fr (H. Rudler).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.038

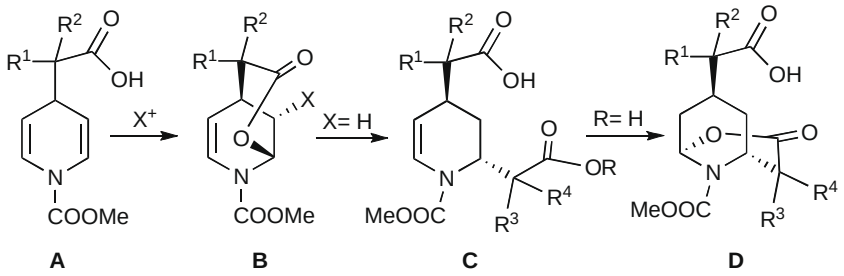


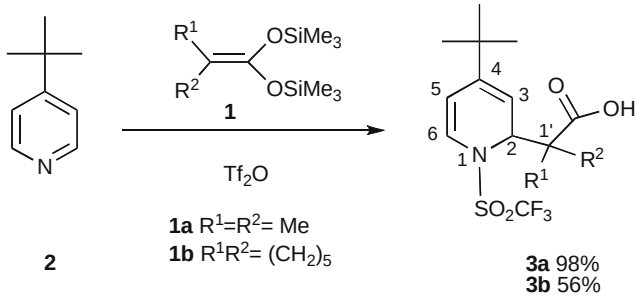
Figure 1. Ring-closing and ring-opening reactions of 1,4-dihydropyridines.

substituents in C-2, and thus for the selective synthesis of 1,2-dihydropyridines (Scheme 1).

Thus, the ketene acetals $R^1R^2C{=}C(OSiMe_3)_2$ **1a,b** ($R^1 = R^2 = Me$ and $R^1R^2 = (CH_2)_5$) reacted with 4 *t*-Bu pyridine **2** in the presence of triflic anhydride to give selectively the corresponding 1,2-addition products **3a** (98%, white solid, mp 118 °C) and **3b** (56%, white solid, mp 178 °C). The interaction of Selectfluor (1-chloromethyl 4-fluoro-1,4-diazoniabicyclo (2.2.2) octane bis (tetrafluoroborate))[7] with **3a** and **3b** led in each case to two compounds **4a,b** and **5a,b**, respectively, in 46% and 65% overall yields and separable by column chromatography (Scheme 2).

Especially significant were the ^1H NMR data of **4b** showing up two doublets at δ 6.70 and 5.53 ppm (J = 8.5 Hz) for H-7 and H-8, a multiplet at δ 5.35 ppm for H-9 (ddd, J = 46.5, 3.5 and 2 Hz), and a multiplet at δ 4.38 (dd, J = 7 and 3.5 Hz) for H-5, the presence of fluorine being established by ^{19}F NMR with signals at δ −73.6 (d, J = 20 Hz) and −215.2 (dqt, J = 46, 16, 2 Hz), respectively, for the fluorine of the triflate and the fluorine of the lactone.

Confirmation of the structure of these C-4 cyclization products came from an X-ray analysis carried out on **4a** (Fig. 2).[8]



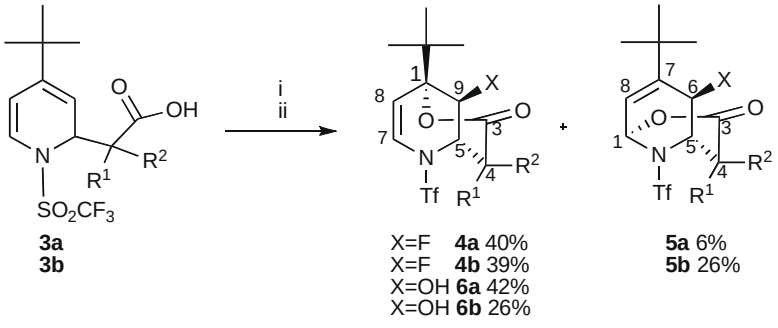
Scheme 1. Synthesis of dihydropyridines **3**. Reagent and conditions: CH_2Cl_2, 0 °C to rt, 17 h.

The hydroxylactonization reactions carried out on **3a,b** by means of *m*-chloroperbenzoic acid led to a single compound **6a,b** which could again be fully characterized by NMR experiments and by a single crystal structure determination on **6b** (Fig. 3) as C-4 lactonization products.[9]

2.2. Bromolactones

Three approaches were used for the bromolactonization reaction of **3a,b**,[10] the two classical one's involving *N*-bromosuccinimide, and a more unusual one, using copper bromide. Under classical kinetic conditions, with NBS in ice-cold dichloromethane, in the presence of sodium hydrogenocarbonate, a single, rather unstable product formed rapidly from **3a**. Its NMR data taken after half an hour of reaction were in agreement with structure **9a** and were very close to those of fluorolactones **4**. Indeed, the ^1H NMR spectrum disclosed signals at δ 6.66 and 5.43 ppm again as a doublet (J = 10 Hz) and a doublet of doublets (J = 10, 2.5 Hz), at δ 4.72, t, J = 2.5 Hz) and at δ 4.28 ppm (d, J = 2.5 Hz). After one night at room temperature, **9a** could only be detected in trace amounts. Besides, two new products, the ^1H NMR data of which were in agreement with those of **7a** and **8a** were observed.

The same mixture of products was obtained, respectively, in 67% and 45% yields from **3a,b** when the reaction was carried out under thermodynamic conditions, using NBS in anhydrous dichloromethane as a source of Br^+. According to their NMR data these products differed only by the position of the introduced bromine. Their structure, as C-6 lactonization products, was ascertained by an X-ray analysis carried out on 7**b** (Fig. 4).[11] This also confirmed the stereochemical outcome of these reactions. Finally, the interaction of **3a,b** with $CuBr_2$ on Al_2O_3 as a source of 'electrophilic' bromine, in refluxing chloroform,[12] gave in each case a single product, stable with respect to the purification conditions (silica gel column chromatography), the physical data of which were in all respect identical to those of **7a** and **7b** (Scheme 3).



Scheme 2. Synthesis of fluoro- and hydroxylactones. Reagents and conditions: (i) X = F selectfluor, CH_3CN, $NaHCO_3$, rt, 17 h.; (ii) X = OH *m*-chloroperbenzoic acid, CH_2Cl_2, rt, 3 d.

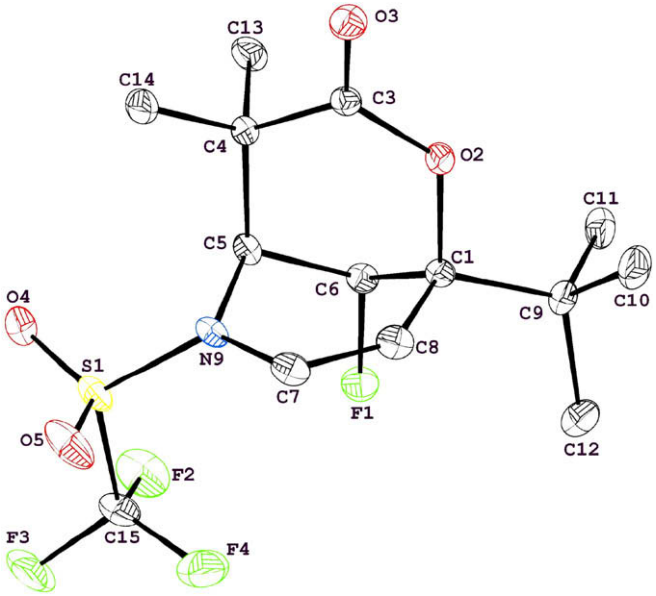


Figure 2. X-ray structure of compound **4a**.

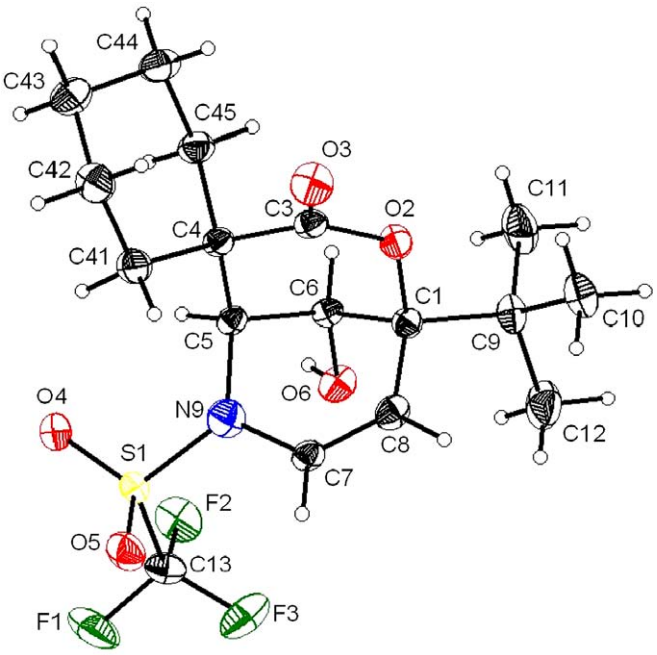


Figure 3. X-ray structure of compound **6b**.

2.3. Solvolysis reactions of bromolactones 7: formation of new γ-lactones

Although stable on silica gel, compounds **7** underwent surprising but, as far as the resulting structures are concerned, highly rewarding solvolysis reactions. These reactions were easy and fast in the case of alcohols, taking place at room temperature, but occurred slower and under more drastic conditions in the case of water. Thus, the interaction of **7b** with alcohols (MeOH or EtOH) at room temperature led to new types of lactones, for the first time γ-lactones **10b** and **11b**, respectively, in 91% and 94% yields (Scheme 4).

Their structure was again ascertained both by NMR and by an X-ray analysis carried out on **10b** (Fig. 5)[13] confirming the presence of a γ-lactone, and of a trisubstituted double bond. It is interesting to notice here, as far as its straightforward synthesis is concerned, that compounds **10b** could be obtained directly and almost quantitatively during the interaction of dihydropyridine **3b** with $CuBr_2$ in the presence of ethanol-stabilized $CHCl_3$.

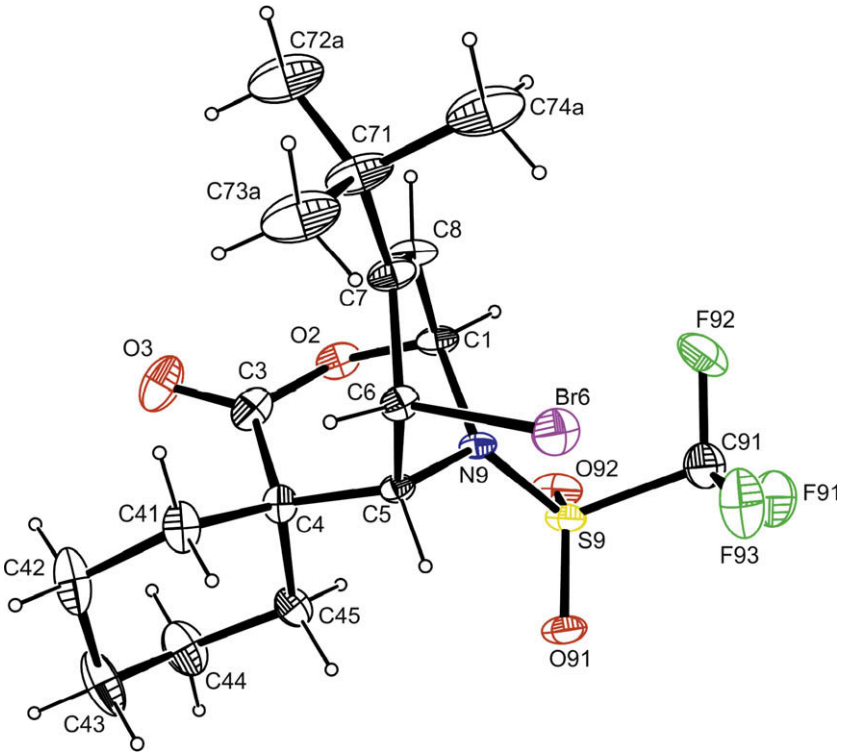
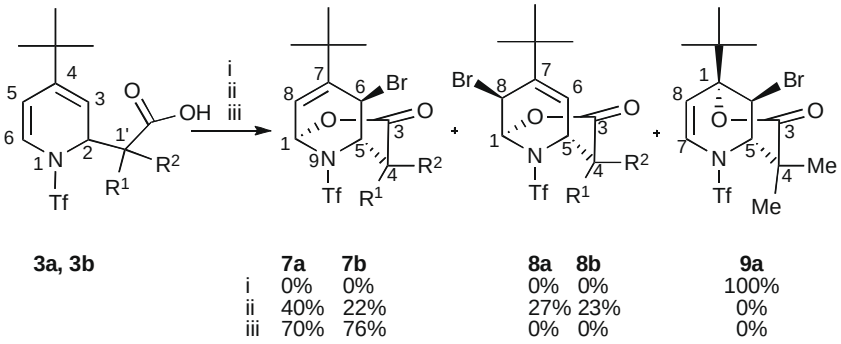
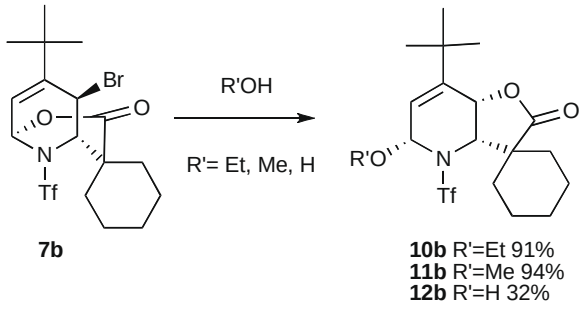


Figure 4. X-ray structure of compound **7b**.



Scheme 3. Synthesis of bromolactones. Reagents and conditions: (i) NBS, $NaHCO_3$, CH_2Cl_2, 0 °C, 1 h; (ii) NBS, CH_2Cl_2, rt, 17 h; (iii) $CuBr_2$, Al_2O_3, ethanol free $CHCl_3$, 65 °C, 36 h.



Scheme 4. Solvolysis reactions of bromolactone **7b**.

Similarly, bromolactone **7b** reacted with water in refluxing THF to give the corresponding alcohol **12b** in 32% yield. However, no reaction was observed between **8b** and MeOH, even under reflux.

3. Discussion

Starting from cationic species, resulting from the interaction of an electrophile with the dihydropyridines, a rationale for all of these transformations, based on calculations and previous results in the field can be suggested. The calculations of the structures and energies of the different species were performed using the semiempirical AM1 Hamiltonian in the AMPAC[14] or GAMESS[15] suite of programs. The structures of the different cations were first optimized in the AMPAC using the default BFGS Algorithm minimizing the gradient norm. Ab initio calculations for some species were also performed using STO3G or 631G atomic basis using GAMESS. Atomic charges have been calculated using the Mulliken Population Analysis.[16] These calculations were run on RS/6000 System Regatta Power 4 machines.

In the case of Br^+, under kinetic control, the addition of the halide occurs at C-3, which is also the more negatively charged carbon (Fig. 7). The intermediate cation **E** is stabilized both by the *t*-Bu group and by the introduced bromine (in the form of a bridged bromonium ion) (Fig. 6).

Moreover, the bromination being very fast and reversible, the structure of the final product will only be dependent on the site of interaction of the carboxylate, where the more positive charge is, thus at C-4 as in **E**, giving **9.** The transformation of dihydropyridine **3** into lactone **9** being reversible, it might give back, as intermediates the bridged bromonium ions **F** and **G**.

The intramolecular ring-closing reaction would then provide the observed thermodynamically more stable bridging lactones **7** and **8**, in agreement with calculations and previous observations.[5d] The formation of a single product during the interaction of $CuBr_2$ with dihydropyridines **3** is somewhat surprising, since a mixture

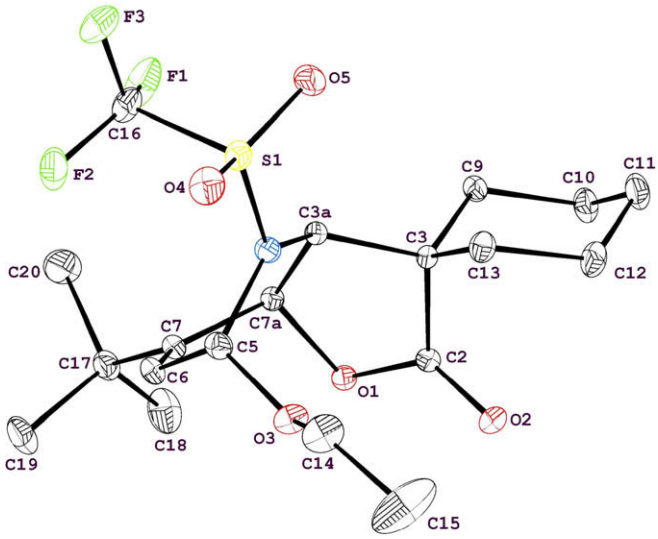


Figure 5. X-ray structure of compound **10b**.

of lactones was expected, the reaction taking place also under thermodynamic conditions. However, on one hand the nature of the intermediates formed with that reagent might be questioned since in the case of 2-methyldihydropyridine, products arising rather from a radical reaction were observed.[17]On the second hand, the conditions of the reaction are quite different.

As far as the other electrophiles are concerned and according to the literature data, and our previous conclusions, F^+ reacting with dihydropyridines **3a,b** leads to the formation, in the first irreversible step, of a kinetic product therefore upon the addition of fluorine to carbon C-3.[17,18] A *syn*-addition of the corresponding counterion of Selecfluor, or the direct formation of carbocationic species might then occur either at C-4 (stabilization by the *t*-Bu group but β-destabilization by fluorine)[19] or at C-6 (stabilization by the nitrogen atom). An intramolecular substitution (or addition) would then result in the formation of the two observed and more stable products **4** and **5** in agreement with the calculated data.

The formation of piperidinelactones **10–12** might be ascribed to a concerted, alcohol-mediated opening of the lactone-ring to the iminium **H**, addition of an alcoholate exclusively to the less hindered face of the intermediate **H** trans to Br, to give **I**. This is followed by a highly thermodynamically favorable γ-lactonization reaction to **10** (Fig. 8).

That, however, no reaction was observed between **8b** and MeOH, even under reflux, can be inferred to a more favorable intramolecular ring-closing reaction: even if the lactone-ring would open to give the iminium **J**, no reaction with an external

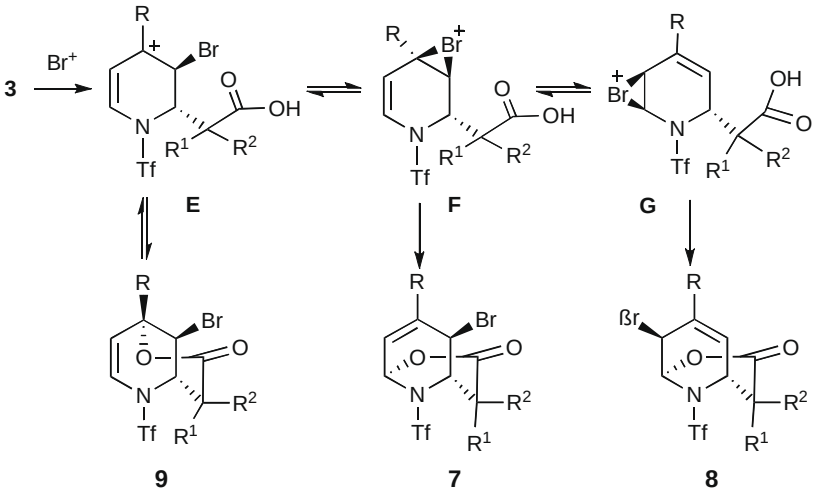


Figure 6. Bromolactonizations of dihydropyridines **3**: mechanistic aspects.

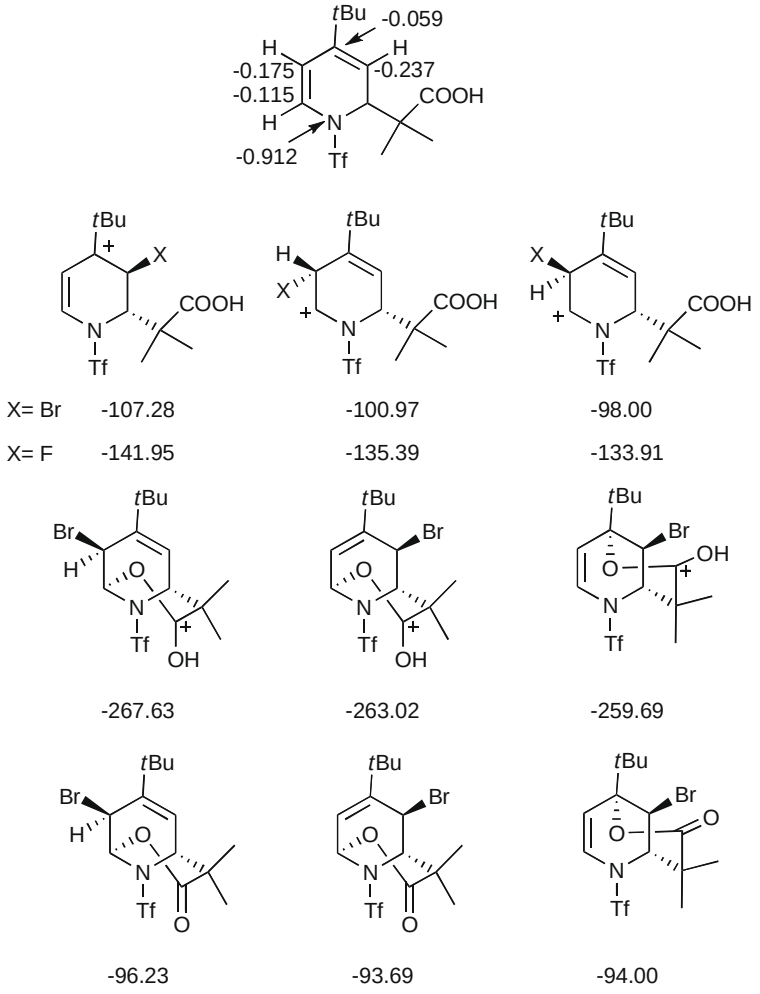


Figure 7. Respective charge distributions on substituted 1,4-dihydropyridines and formation enthalpies of the carbocationic species obtained therefrom.

nucleophile would take place, since the reverse reaction, giving back the starting lactone, is, according to our previous observations, highly favoured[6d] (Fig. 9). Such a result is also supported by the calculations which indeed confirm that among the bromolactones **8b** is thermodynamically the most stable.

4. Conclusions

As a conclusion, it appears that functionalized 1,2-dihydropyridines such as those described herein are the precursors of choice for the synthesis of diversely tetrahydropyridine-fused lactones,

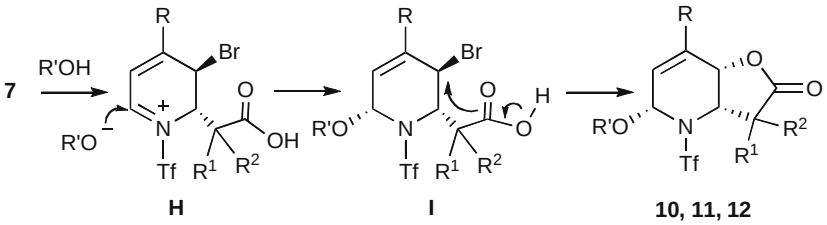


Figure 8. Solvolysis rearrangement reactions of bromolactones **7**.

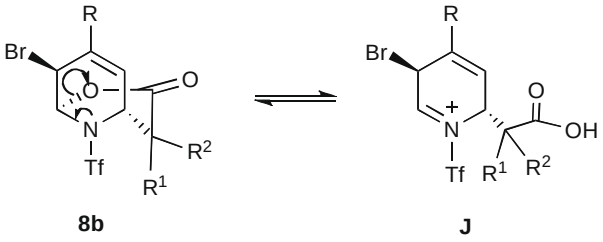


Figure 9.

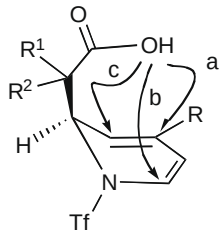


Figure 10. Observed ring-closure sites of 1,2-dihydropyridines **3**.

the reaction conditions promoting a series of ring-closing/ring-opening/ring-closing transformations and directing the sites of the lactonization reactions.

The formation of piperidinelactones **10–12** via the route **c** in only a few high-yielding steps from pyridine, besides the expected δ-lactones via the routes **a** and **b** (Fig. 10), is very interesting on a synthetic point of view since they can be considered as valuable and close starting materials for the synthesis of azasugars.[20]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.038.

References and notes

1. (a) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223–243; (b) Kellog, R. M. *Top. Curr. Chem.* **1982**, *101*, 111–145; (c) Sobolev, A.; Franssen, M. C. R.; Vigante, B.; Cekavius, B.; Zhalubovskis, R.; Kooijman, H.; Spek, A. L.; Duburs, G.; de Groot, A. *J. Org. Chem.* **2002**, *67*, 401–410; (d) Kumar, R.; Chandra, R.. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 2001; Vol. 78, pp 269–313; (e) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141–1156; (f) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int Ed.* **2004**, *43*, 6660–6662; (g) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32–33; (h) Zhu, X.-Q.; Zou, H.-L.; Yuan, P.-W.; Liu, Y.; Cao, L.; Cheng, J.-P. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1857–1861; (i) Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* **2004**, *60*, 6649–6655.
2. (a) Rudler, H.; Audouin, M.; Parlier, A.; Martin-Vaca, B.; Goumont, R.; Durand-Réville, T.; Vaissermann, J. *J. Am. Chem. Soc.* **1996**, *118*, 12045–12058; (b) Rudler, H.; Parlier, A.; Certal, V.; Vaissermann, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3417–3419; (c) Rudler, H.; Parlier, A.; Durand-Réville, T.; Martin-Vaca, B.; Audouin, M.; Certal, V.; Vaissermann, J. *Tetrahedron* **2000**, *56*, 5001–5027; (d) Rudler, H.; Parlier, A.; Certal, V.; Lastenet, G.; Audouin, M.; Vaissermann, J. *Eur. J. Org. Chem.* **2004**, 2471–2502; (e) Rudler, H.; Parlier, A.; Peregrina, M. P.; Vaissermann, J. *Organometallics* **2005**, *24*, 1–3.
3. (a) Lavilla, R.; Gullon, F.; Baron, X.; Bosch, J. *Chem. Commun.* **1997**, 213–214; (b) Lavilla, R.; Coll, O.; Kumar, R.; Bosch, J. *J. Org. Chem.* **1998**, *63*, 2728–2730; (c) Lavilla, R.; Baron, X.; Coll, O.; Gullon, F.; Masdeu, C.; Bosch, J. *J. Org. Chem.* **1998**, *63*, 10001–10005. and references cited therein.
4. Bellassoued, M.; Chelain, E.; Collot, J.; Rudler, H.; Vaissermann, J. *J. Chem. Soc., Chem. Commun.* **1999**, 187–189.
5. (a) Rudler, H.; Denise, B.; Parlier, A.; Daran, J.-C. *Chem. Commun.* **2002**, 940–941; (b) Rudler, H.; Denise, B.; Xu, Y.; Parlier, A.; Vaissermann, J. *Eur. J. Org. Chem.* **2005**, 3724–3744; (c) Garduno-Alva, A.; Xu, Y.; Gualo-Soberanes, N.; Lopez-Cortes, J.; Rudler, H.; Parlier, A.; Ortega-Alfaro, M. C.; Alvarez-Toledano, C.; Toscano, R. A. *Eur. J. Org. Chem.* **2008**, 3714–3723; (d) Xu, Y.; Rudler, H.; Denise, B.; Parlier, A.; Chaquin, P.; Herson, P. *Tetrahedron Lett.* **2006**, *47*, 4541–4544.
6. (a) Lourie, L. F.; Serguchev, Y. A.; Shevchenko, G. V.; Ponomenko, M. V.; Chernega, A. N.; Rusanov, E. B.; Howard, J. A. K. *J. Fluorine Chem.* **2006**, *127*, 377–385; (b) Meng, W.-D.; Qing, F.-L. *Curr. Top. Med. Chem.* **2006**, *6*, 1499–1528; (c) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11; (d) Bégué, J. P.; Bonnet-Delpon, D. *Chimie bioorganique et médicinale du fluor*; EDP Sciences/CNRS: Paris, 2005.; (e) Singh, R. P.; Shree, J. M. *Acc. Chem. Res.* **2004**, *37*, 31–34; (f) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319.
7. (a) Banks, R. E.; Murtagh, V.; Tsiliopoulous, E. *J. Fluorine Chem.* **1991**, *52*, 389–401; (b) Lal, G. S. *J. Org. Chem. Soc.* **1993**, *58*, 2791–2796; (c) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31–44.
8. Crystal data for **4a**: $C_{14}H_{19}F_4NO_4S$, $M = 373.09$, triclinic, space group $P\bar{1}$, $a = 6.2206(18)$ Å, $b = 11.368(2)$ Å, $c = 13.016(4)$ Å, $V = 838.6(4)$ Å^3, $Z = 2$, (MoKα, $\lambda = 0.71073$) $T = 200$ K, R_1, wR_2 $[I > 2\sigma(I)] = 0.0540$, R_1, wR_2 (all data) = 0.169. CCDC 717522.
9. Crystal data for **6b**: $C_{17}H_{24}F_3NO_5S$, $M = 474.333$, monoclinic, space group Cc, $a = 10.0005(8)$ Å, $b = 17.8028(16)$ Å, $c = 10.8951(12)$ Å, $V = 1907.2(3)$ Å^3, $Z = 4$, $D_c = 1.43$ g cm^{-3}, (MoKα, $\lambda = 0.71073$) $T = 200$ K, R_1, wR_2 $[I > 2\sigma(I)] = 0.046$, 0.100. CCDC 738889.
10. For a review on halolactonization reactions, see: Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273–5308. and references cited therein.
11. Crystal data for **7b**: $C_{16}H_{23}BrF_3NO_4S$, $M = 474.333$, *hexagonal*, space group $P6_5$, $a = 10.3064(2)$ Å, $b = 10.3064(2)$ Å, $c = 33.2508(14)$ Å, $V = 3058.77(15)$ Å^3, $Z = 6$, $D_c = 1.496$ g cm^{-3}, (MoKα, $\lambda = 0.71073$) $T = 180$ K, R_1, wR_2 $[I > 2\sigma(I)] = 0.0367$, 0.0831. CCDC 717647.
12. Rood, G. A.; DeHaan, J. M.; Zibuck, R. *Tetrahedron Lett.* **1996**, *37*, 157–158.
13. Crystal data for **10b**: $C_{19}H_{28}F_3NO_5S$, $M = 399.132$, monoclinic, space group $P21/n$, $a = 11.1055(14)$ Å, $b = 10.7290(8)$ Å, $c = 19.388(2)$ Å, $V = 2216.6(4)$ Å^3, $Z = 4$, (MoKα, $\lambda = 0.71073$) $T = 200$ K, R_1, wR_2 $[I > 2\sigma(I)] = 0.040$. CCDC 717523.
14. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaya, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1337–1363.
15. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
16. Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833–1840.
17. Rudler, H.; Parlier, A.; Hamon, L.; Herson, P.; Chaquin, P.; Daran, J.-C. *Tetrahedron* **2009**, *65*, 5552–5562.
18. Rudler, H.; Parlier, A.; Hamon, L.; Herson, P.; Daran, J.-C. *Chem. Commun.* **2008**, 4150–4152.
19. (a) Bach, R. D.; Henneike, H. F. *J. Am. Chem. Soc.* **1970**, *92*, 5589–5602; (b) Differding, E.; Rüegg, G. M. *Tetrahedron Lett.* **1991**, *32*, 3815–3818; (c) Vincent, S. P.; Burkart, M. D.; Tsai, C.-Y.; Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5264–5279; (d) Albert, M.; Dax, K.; Ortner, J. *Tetrahedron* **1998**, *54*, 4839–4848.
20. (a) Wee, A. G. H.; Fan, G.-J. *Org. Lett.* **2008**, *10*, 3869–3872; (b) Fan, G.-J.; Wang, Z.; Wee, A. G. H. *Chem. Commun.* **2006**, 3732–3734; (c) Szolcsanyi, P.; Gracza, T.; Koman, M.; Pronayova, N.; Liptaj, T. *Tetrahedron: Asymmetry* **2000**, *11*, 2579–2597.