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Straightforward access to tetrahydropyridine and piperidine-fused fluorolactones from pyridines and bis(trimethylsilyl)ketene acetals

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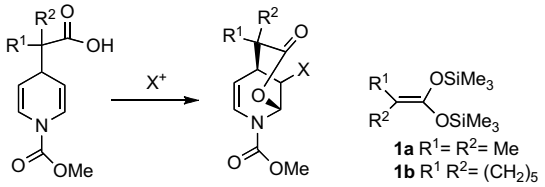
ABSTRACT

The interaction of bis(trimethylsilyl)ketene acetals with various pyridines provides a direct, general, diastereoselective access to fluorolactones via the formation of dihydropyridine-substituted carboxylic acids. These in turn reacted with selectfluor as the source of electrophilic fluorine. Whereas a discrimination of the double bonds devoid of fluorine and those bearing fluorine was observed in the case of electrophiles such as iodine, bromine and peracids, no such differentiation took place in the case of selectfluor since, besides 3,5-difluorolactones, the formation of *gem*-difluorolactones also took place. Moreover, the formation of two stereoisomeric fluorolactones during the lactonization of tetrahydropyridine-substituted carboxylic acids, obtained upon the interaction of (trimethylsilyl)ketene acetals with the previous lactones, could be ascribed to conformational modifications. In all the cases examined a *trans*, *diaxial* addition of the electrophile and of the carboxylate is observed. The stereochemical outcome of these reactions was assessed both by NMR spectroscopy and by X-ray crystallography.

1. Introduction

The use of ketene acetals **1** as dinucleophiles for the transformation of aromatic or aliphatic carbon–carbon double bonds either into γ- or δ-lactones has provided access to a large class of new polyheterocycles some of which disclose promising biological properties.[1,2] In the case of pyridines, these cycloadditions evolved via the formation of isolable dihydropyridines **2**. The scope and the limits of the reaction together with its extension to other aza- and diazaaromatics have been disclosed in a series of recent papers.[3–7] Although dihydropyridines belong to a class of organic compounds possessing a wide range of interesting chemical and biological properties,[8a–e] their unstability towards oxygen[8d] can constitute a serious drawback. This was also observed in the case of the dihydropyridines described herein: a slow, spontaneous N-deprotection/decarboxylation reactions of dihydropyridines **2** led indeed to 4-alkyl substituted pyridines.[5] However, owing to the presence of a carboxylic acid in the introduced side-chain, in β to an enecarbamate function, compounds **2** led very easily, in some cases even in the lone presence of silica gel, to stable δ-lactones **3** fused to a tetrahydropyridine[5] (Scheme 1). Since the lactones **3** gave back, in the presence of acids, the starting dihydropyridines **2**, they could be considered as masked (or protected) dihydropyridines. Moreover, in the presence of Lewis acids, they led upon a series of push–pull ring-opening/nucleophilic addition/ring-closing reactions to highly functionalized, piperidine-fused lactones[9] (vide infra).



2 **3**

1a $R^1 = R^2 = Me$
1b $R^1\ R^2 = (CH_2)_5$

Scheme 1.

These ring-closure reactions (Scheme 1) were not only induced by silica gel or protic acids but occurred also with a series of different electrophiles such as Br^+, I^+, HO^+, from, respectively, bromine, iodine and peracids, allowing thus to introduce various functionalities in β to the nitrogen atom of these substrates: due to the polarization of the carbon–carbon double bonds promoted by the carbamate function, a regiospecific lactonization was observed in all the cases examined so far. These results prompted us to consider the addition of electrophilic fluorine by the same means in order to get access to new fluorinated lactones.[10] It is indeed well

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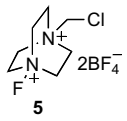


5

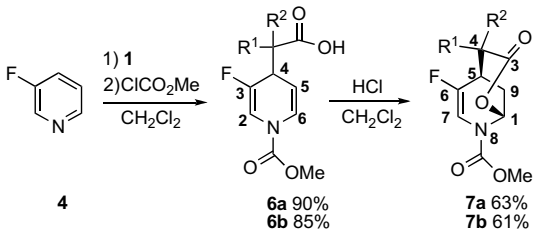
Scheme 2.

established that the introduction of fluorine in organic compounds might lead on the one hand to biologically active compounds and on the other hand, in the case of biologically active compounds, might also deeply modify their activity, e.g., uracil versus fluorouracil.[11a–e] Three possibilities existed for the introduction of fluorine in the new lactones: first, using the same approach as above, the addition of electrophilic fluorine to the functionalized dihydropyridines. Second, starting from commercially available fluorinated pyridines and carrying out the same series of transformations. And third, synthesizing fluorinated bis(trimethylsilyl)ketene acetals, which might allow the introduction of fluorine during the first step of these transformations.

The purpose of this paper is to demonstrate the feasibility of the two first approaches and that the aforementioned intramolecular cyclization, succeeding to the C-4-addition of various bis(TMS)ketene acetals to pyridine and substituted pyridines, can indeed constitute an efficient means to introduce the fluorine atom in these substrates. Starting either from the simple dihydropyridines **2** or from the tetrahydropyridines **17**, new monofluorinated lactones could be obtained. Furthermore, starting from the commercially available 3-fluoropyridine **4**, two fluorine atoms might be introduced, leading to a series of polyfluorinated lactones, some of which were unexpected. Their synthesis, structure and mechanism of formation will be outlined and discussed.

2. Results and discussion

Both the electrophilic fluorinations of activated double bonds and of the double bonds of unsaturated carboxylic acids are known: the former leads, in the presence of external nucleophiles, to fluorinated/functionalized substrates whereas the latter gives access to an important class of compounds, fluorolactones.[12] Several electrophilic fluorinating agents have been used in the literature for that purpose among which 1-chloromethyl 4-fluoro-1,4-diazoniabicyclo(2.2.2)octane bis (tetrafluoroborate) or Selectfluor **5** (F-TEDA–CH_2Cl 2 BF_4), which is now one of the most popular, and



4 **6a** 90% **6b** 85% **7a** 63% **7b** 61%

Scheme 3.

which leads to fluorinated compounds under mild conditions and in satisfactory yields.[13] Precedents for the oxidation of dihydropyridines with various electrophiles among which *N*-fluoropyridinium triflate and *N*-fluorodibenzenesulfonimide in the presence of external nucleophiles can nevertheless be found in the literature: Lavilla and co-workers observed indeed the formation, in a stereocontrolled manner, of axially 3-fluorinated tetrahydropyridines (Scheme 2).[14]

We have therefore carried out such reactions both on *N*-carbomethoxy dihydropyridines **2** and on 3-fluoro-*N*-carbomethoxy dihydropyridines **6** (R^1=R^2=Me; R^1 R^2=$(CH_2)_5$).

The starting dihydropyridines **2** and **6** were prepared according to a published method and isolated as white solids in good yields (85–90%).[5,6] The new fluorinated dihydropyridines **6** were characterized by ^1H and ^{13}C NMR and the presence of fluorine was confirmed by ^{19}F NMR spectroscopy. [15] Thus, the ^1H NMR spectrum of **6b** (mp 133 °C) exhibited, as for the non-fluorinated dihydropyridine **2b**, the presence of two rotamers, the carbamate giving for example two signals at δ 151.30 and 151.62 ppm. The spectra of **6b** could be compared to those of the dihydropyridine obtained upon the use of triflic anhydride as the activating agent for which no rotamers exist.[6] More significant as far as the presence of fluorine is concerned were the ^{19}F and ^{13}C NMR data.[14] The ^{19}F spectrum disclosed two broad signals, at δ −131.8 and −132.4 ppm, whereas the ^{13}C NMR spectrum was consistent with the suggested structure, C-3 giving rise to two doublets at δ 147.7 and 148.2 (J=249 Hz), all of the other carbons of the dihydropyridine ring but C-6 being coupled to the fluorine atom (Scheme 3).

Attempts to carry out the lactonization reaction in the presence of silica gel as for the non-fluorinated dihydropyridines **2a**,**b** failed. However, the use of anhydrous HCl in diethyl ether, at low temperature, led in the case of **6b**, after base washings, to a new compound the physical properties of which were consistent with those of the lactone **7b**, existing again as two rotamers (Table 1). Thus the ring closure took place as expected yet selectively on the more nucleophilic carbon–carbon double bond, C(5)–C(6).

2.1. Halolactonizations of 3-fluorodihydropyridines

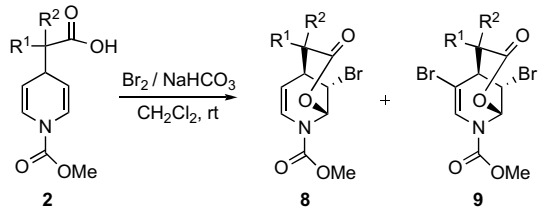
2.1.1. Fluoro, bromo-, fluoro, iodo- and fluoro, hydroxylactones

As already reported in a previous paper,[5] the ring-closure reaction of these carboxylic acid-substituted dihydropyridines was not only induced by protic acids, but also by various sources of electrophiles, among which bromine. However, the reaction was not selective since a mixture of the expected bromolactone **8** and dibromolactone **9** was obtained from **2**. The reasons behind this behaviour have been given (Scheme 4).

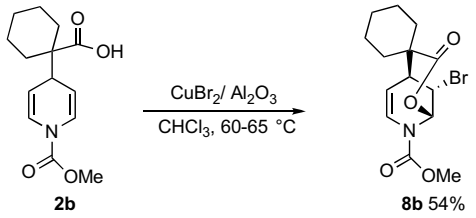
Before applying those cyclization reactions to the fluorodihydropyridines such as **6**, it appeared necessary to find out a potential reagent for the selective introduction of bromine in these dihydropyridines. Data from the literature on the use of copper(II) bromide on alumina as a potential source of electrophilic bromine to promote the lactonization of unsaturated carboxylic acids allowed us to settle that problem.[16] Indeed, the reaction carried out as stated by Zibuck, on dihydropyridine **2b**, led to a selective, 54% yield of the known bromolactone **8b** (Scheme 5).

Table 1
^1H (400 MHz) and ^{13}C NMR (100 MHz) data of fluorolactones **7b** and **10**–**12b**, δ, ppm, J, Hz, br s, broad singlet

	Yield (%)	^1H NMR (δ)				^{13}C NMR (δ)				
		H^1	H^5	H^7	H^9	C^1	C^3	C^5	C^7	C^9
7b	61	6.34 and 6.19	2.92, J_{HF}=12	6.91 and 6.79, J_{HF}=10	2.53	77.8 and 77.6	174.5	32.4 and 31.2, J_{CF}=21	107.4, J_{CF}=41	23.4 and 23.0, J_{CF}=6
10b	98	6.27 and 6.10	3.11, J_{HF}=11	7.01 and 6.88, J_{HF}=9	4.79	79.9 and 79.5	172.4	41.9 and 41.5	107.1 and 107.0, J_{CF}=40	35.9 and 35.5, J_{CF}=7
11b	82	6.29 and 6.13	3.06, J_{HF}=11	7.0 and 6.87, J_{HF}=10	4.93	81.0 and 80.4	172.4	43.2 and 43.1, J_{CF}=21	107.1, J_{CF}=40	11.0 and 10.7, J_{CF}=7
12b	27	6.10 and 5.93	2.94, J_{HF}=10.5	6.99 and 6.85, J_{HF}=9	4.48 and 4.44	79.3 and 79.0	173.6	40.2, br s	107.6, J_{CF}=40	59.4 and 58.9

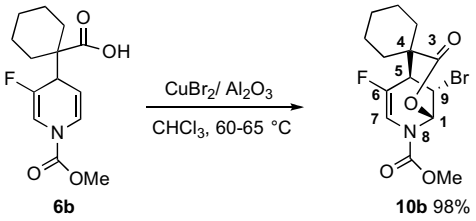


Scheme 4.



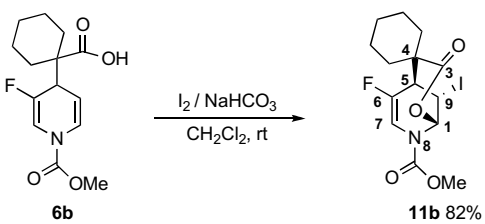
Scheme 5.

When the same transformation was carried out on dihydropyridine **6b**, an almost quantitative yield of a single compound **10b** was observed. The properties of this new compound were again in agreement with the absence of an acid and thus with the formation of a δ-lactone. Especially significant was the ^{13}C NMR spectrum, which showed signals for the carbonyl-carbon at δ 172.43 ppm, for the fluorine-substituted double bond, as in **7b**, at δ 145.8 and 146.5 ppm, as two doublets J=250 Hz for C-6, and at δ 107.11 and 107.02 ppm, as two doublets J=40 Hz for C-7; for C-5, as two doublets, $^{2}J_{CF}$, 21 Hz, at δ 41.8 and 41.46 ppm; for C-9, as two doublets, $^{3}J_{CF}$, 7 Hz at δ 35.87 and 35.52 ppm; and, for C-1, as two singlets at δ 79.50 and 79.91 ppm. Moreover, the ^{19}F spectrum displayed two singlets for the two rotamers at δ −132.60 and −133.30 ppm (Scheme 6).

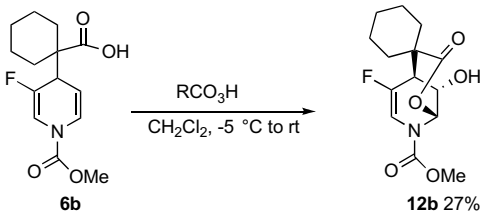


Scheme 6.

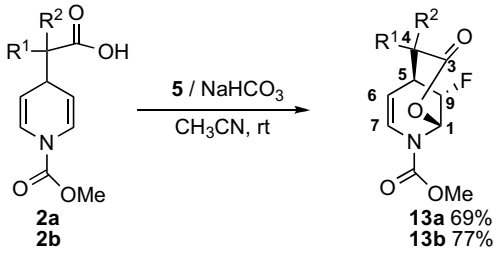
Similarly, when the classical iodolactonization was applied to **6b**, a single lactone **11b** was obtained in 82% yield as an off-white solid, mp 145 °C, the NMR data of which were in all respect comparable to those of **10b**, the signal for C-9 being highly shielded and appearing now at δ 10.73 and 11.04 ppm for the two rotamers as two doublets, $^{3}J_{CF}$=7 Hz (Table 1, Scheme 7).



Scheme 7.



Scheme 8.



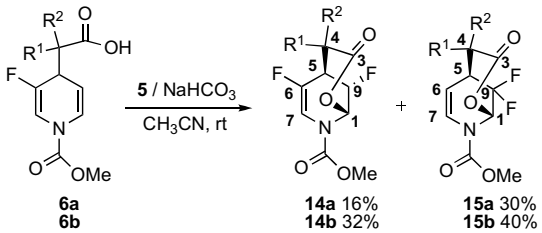
Scheme 9.

Finally, the interaction of **6b** with a slight excess of *m*-chloroperbenzoic acid led to a crystalline compound in 27% yield, mp 197 °C, the physical data of which were in agreement with those of the expected hydroxylactone **12b** (see Table 1 and the Experimental section).

2.1.2. *Monofluoro- and difluorolactones*

In view of planned attempts to generate in an enantioselective way fluorolactones of the type **13**, we chose selectfluor **5** as the source of electrophilic fluorine. This reagent has indeed been used for the synthesis of α-fluoro-γ-lactones, starting from unsaturated carboxylic acids, and, in conjunction with chiral alkaloids, for the enantioselective synthesis of fluoroketones starting from activated olefins such as enol ethers.[17] Besides the simple dihydropyridines **2** containing two identical double bonds, the reaction was also carried out on dihydropyridines **6** bearing already a fluorine atom on one of the double bonds and for which a marked difference of reactivity between these two double bonds has indeed been observed in the case of HCl (vide supra); and then on tetrahydropyridine **17** obtained from **3a**, which under typical acidic conditions (HCl in diethyl ether), appeared reluctant to undergo the lactonization reaction into **18**.

Thus, the reaction of **2a** in acetonitrile with a slight excess of selectfluor in the presence of sodium bicarbonate led to a single new compound **13a**, which was purified by silica gel chromatography. The new compound, isolated as white crystals (69%, mp 116 °C), a lactone, δCO, 174.16 ppm, contained a secondary fluorine atom according to its ^{1}H and ^{19}F NMR spectra with signals corresponding to two rotamers, at δ 5.40 and 5.37 ppm and at δ 198.10 and −199.3 ppm (J=48 Hz), C-1 and C-5 being coupled to fluorine, J=27 and 22 Hz. The *trans*-diaxial geometry of the two substituents of the double bond, the oxygen of the lactone and the fluorine atom in **13a** was confirmed by a single crystal X-ray structure on a related



Scheme 10.

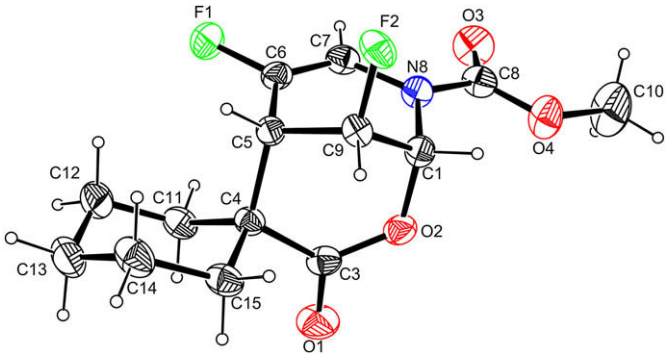


Figure 1. X-ray structure of compound **14b**.

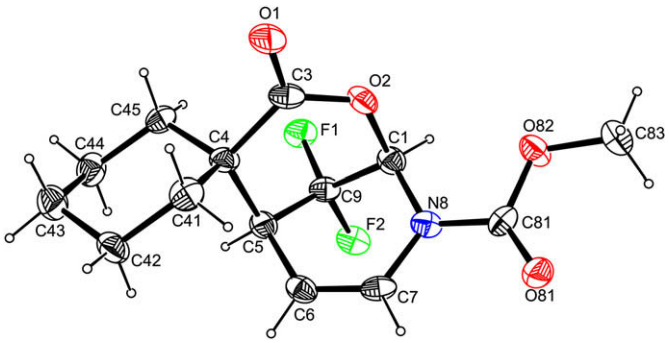
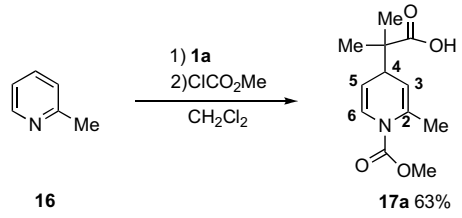


Figure 2. X-ray structure of compound **15b**.



Scheme 11.

fluorolactone **14b** (vide infra). Similarly, **2b** led to **13b** in 77% yield (white crystals, mp 141 °C) (Scheme 10).

When however the same reaction was carried out on **6b**, a complete transformation of the starting compound was again observed, leading, according to TLC, to two products. They could be separated by silica gel chromatography and obtained both as solids. To the more polar product (mp 140 °C, 32%) was assigned structure **14b** on the basis of its NMR data and finally on an X-ray structure determination. The presence of two kinds of fluorine atoms was also confirmed by the ^{19}F NMR spectrum, which disclosed indeed four signals for the two rotamers at δ −134.8 and −134.2 ppm, as singlets (for F-6), and at δ −198.4 and −198.7 ppm, as doublets of doublets, J=47 and 7 Hz, for F-9. Confirmation of these assignments came from a crystal structure determination as shown in Figure 1, and which agrees with both the regiochemistry of the cyclization and the *trans*, *axial* configuration of the introduced fluorine with respect to the lactone bridge.[18]

As far as the second less polar product **15b** (mp 110 °C, 40%) was concerned, its ^{13}C NMR spectrum was also especially meaningful. It confirmed the presence of a geminal difluorinated carbon appearing as a triplet (J=248 Hz).[19] This was also assessed by the ^{19}F NMR spectrum, which disclosed two nonequivalent fluorine signals (two doublets) at −117.2 and −112.1 ppm, $^{2}J_{FF}$=248 Hz. All these data were secured by a single crystal X-ray structure determination (Fig. 2).[20]

Similar results were observed in the case of **6a**, which led to a mixture of **14a** and **15a** (46% yield, 35/65).

2.2. Halolactonizations of methyldihydropyridine

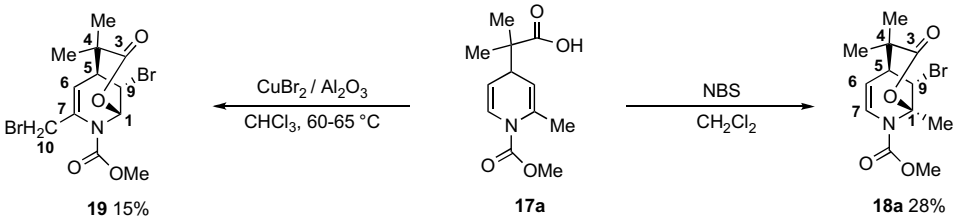
2.2.1. Bromolactonizations

Since the course of the lactonization reactions of unsaturated carboxylic acids is dominated by electronic control and thus, highly dependent on the nature of the substituents on the double bond,[21a,b] we choose 2-picoline **16** as an example of substrate, the methyl group of which might stabilize a positive charge in α to the nitrogen atom in the corresponding dihydropyridine. The interaction of **16** with the ketene acetal **1a** led, in the presence of a slight excess of methylchloroformate, to the expected dihydropyridine **17a** (63% yield) (Scheme 11).

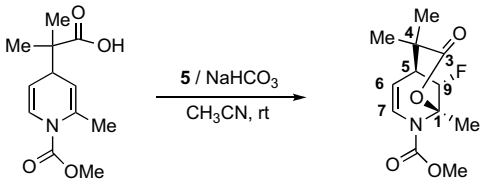
Surprisingly, however, no lactone was formed upon its interaction with HCl in diethyl ether: only decomposition of the starting material was observed. In the case of electrophilic bromine, the result was highly dependent on the nature of the source of Br^{+}. Whereas NBS in dichloromethane led to the expected bromolactone **18a** (see the Experimental section), in which the cyclization took place on the more stable C-2 carbocation, $CuBr_2$/Al_2O_3 in chloroform led unexpectedly to a dibrominated lactone **19**, the structure of which could be assigned by NMR spectroscopies. The ^{1}H NMR spectrum of **18a** disclosed signals for one disubstituted double bond at δ 6.87 ppm, 5.03 ppm, a signal for a methyl group, as a singlet, at δ 2.15 ppm, and a signal, as a triplet at δ 4.57 ppm assignable to H^{9}. The ^{13}C NMR spectrum confirmed the presence of a lactone, at δ 174.71 ppm. In the case of **19**, the typical signals for a lactone (δ_{CO}, 173.15 ppm; $\delta_{C\text{-}1}$, 83.29 ppm) and for a single proton of a double bond at δ 5.36 ppm were again observed. However, the absence of a signal for a third methyl group and the presence of a system of two doublets at δ 4.75 and 4.31, J=10 Hz, confirmed the formation of a CH_2Br group. This result could be considered as the indication of a radicalar-type reaction for the $CuBr_2$-induced bromolactonization of dihydropyridines (Scheme 12).

2.2.2. Fluorolactonization

Finally, the neatest reaction was observed with selectfluor **5**: its interaction with **17a** led to a single fluorolactone, the structure of which was fully in agreement with **20a**. The NMR data confirmed



Scheme 12.



Scheme 13.

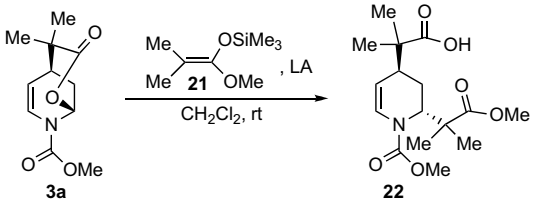
the presence of a lactone, δ_{CO}, 174.67 ppm, of a methyl group as a singlet at δ 2.16 ppm, of a secondary fluorine, giving a signal at δ 4.99 ppm (dt, J=48 and 2.5 Hz) (Scheme 13).

2.3. Electrophilic fluorination of the carboxylic acid-substituted tetrahydropyridine: formation of a *cis equatorial, axial* fluorolactone

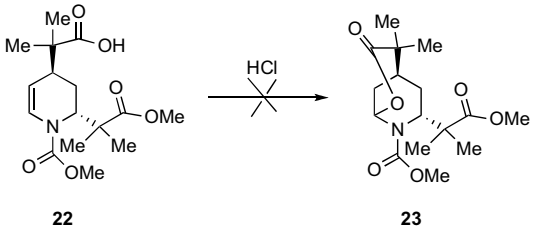
In a previous paper,[9] we already demonstrated that lactones of the type **3** are interesting precursors of tetrahydropyridines. Indeed, **3a** led, upon ring-opening/nucleophilic addition of a second mono(trimethylsilyl)ketene acetal **21**, to **22** (Scheme 14).

Although **22** contained an unsaturated carboxylic acid, which might lead to a new lactone **23** upon an electrophile-induced ring-closing reaction akin to the transformation of **2** into **3** (Scheme 1), no such reaction was observed upon its treatment with HCl (Scheme 15).

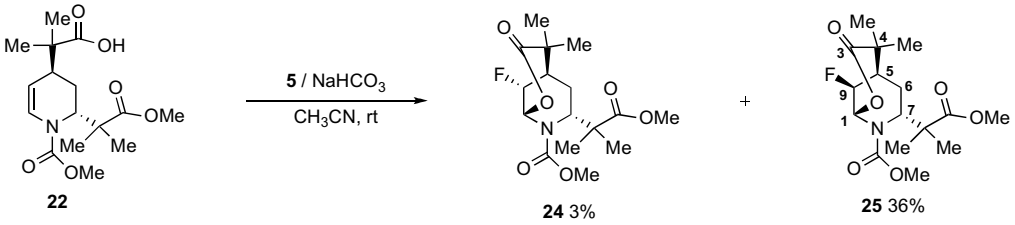
Considering the success of electrophilic fluorine in the previous ring-closing reactions (Schemes 8 and 9), we submitted compound **22** to selectfluor under the same conditions as above. Such



Scheme 14.



Scheme 15.



Scheme 16.

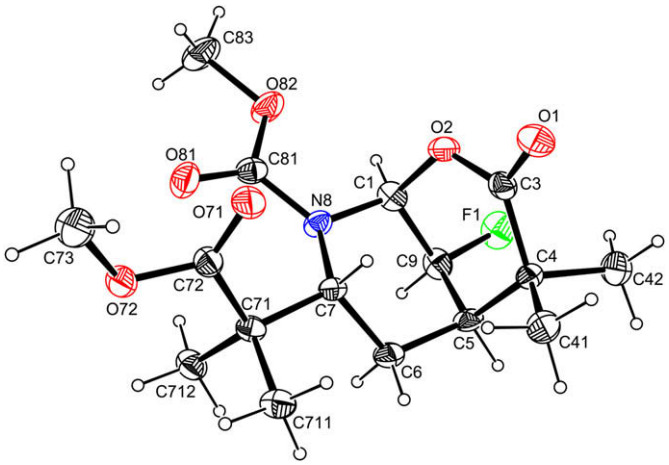
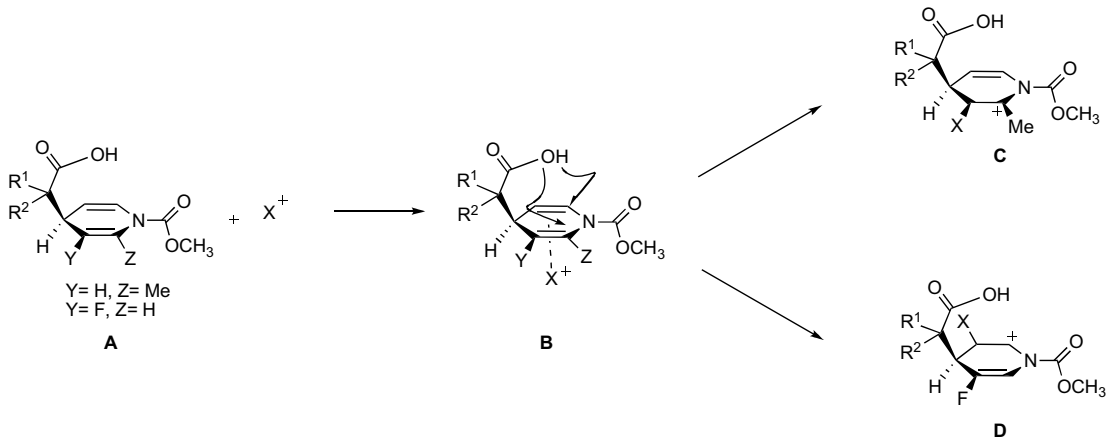


Figure 3. X-ray structure of compound **25**.

a reaction was interesting on several points of view. First, whereas in the case of **6a**,**b**, the acid function had the choice between two differently substituted double bonds, in the case of **22** the double bond might react with either of the two nucleophiles present in the molecule, the carboxylic acid at C-4 or the methyl carboxylate at C-2. It has indeed been shown by Lourie and co-workers that norbornene-carboxylic acids and their methyl esters behaved similarly towards selectfluor, giving in both cases the expected intramolecular lactonization products.[12a] Second, we observed that the Lewis-acid mediated opening of the lactone ring in **3a**,**b** led, depending on the nature of the substituents on the ketene acetals either to the expected tetrahydropyridines or more surprisingly, to new lactones, upon interaction of the substituted acetic acid function at C-2 with the C-5, C-6 carbon–carbon double bond. The interaction of **22** with selectfluor led indeed to two difficult-to-separate compounds, the less polar being the minor one. Silica gel column chromatography allowed nevertheless their resolution (Scheme 16).

To the major, more polar product, obtained as a crystalline solid (36%, mp 142 °C) was given structure **25** on the following grounds. The ^{13}C NMR spectrum confirmed the disappearance of the double bond and the formation of a δ-lactone (δ_{CO}, 176.8 ppm). The ^{19}F NMR spectrum was in agreement with the incorporation of fluorine, giving a doublet at δ −184.83 ppm, J=48 Hz, thus with a fluorine on a secondary carbon. This appeared also in the ^{13}C NMR spectrum, which disclosed two doublets at δ 86.64 ppm (J=186 Hz) for the carbon bearing a fluorine atom (C-9), and at δ 84.65 (J=29 Hz) for carbon C-1. The ^{1}H NMR fitted also with such a structure, H-9 giving a doublet of doublets with a large, J=48 Hz, and a small, J=2.5 Hz, coupling constant. A final assessment of the structure was obtained from an X-ray single crystal analysis (Fig. 3), which shows the fluorine atom in an equatorial position, *cis* to the lactone, the substituent at C-7 being *trans* to the lactone function.[22]



Scheme 17.

The physical data, and especially the NMR spectra of the less polar, less abundant compound (3%, isolated as an oil) of that reaction agreed with a structure such as **24**, the isomer of **25**, in which the fluorine is *axial* and *trans* with respect to the lactone. Although the ^{1}H and ^{13}C spectra do not show deep differences with those of **25**, the chemical shift of the fluorine atom is quite different, going from −184.83 in **25** to −195.8 in **24**, an observation, which is in agreement with data from the literature for equatorial versus axial geometries.[8d] Interestingly, the stereochemistry of the fluorine atom has also an impact on the chemical shifts of the two hydrogens at C-6: whereas for the compound **25**, the two hydrogens appear as doublets of multiplets at δ 2.04 and 1.92 ppm, in **24**, the chemical shifts for the two hydrogens are quite different, one of them giving a complex signal at δ 2.23 ppm, the signal of the second one being shifted upfield and appearing at δ 1.61 ppm.

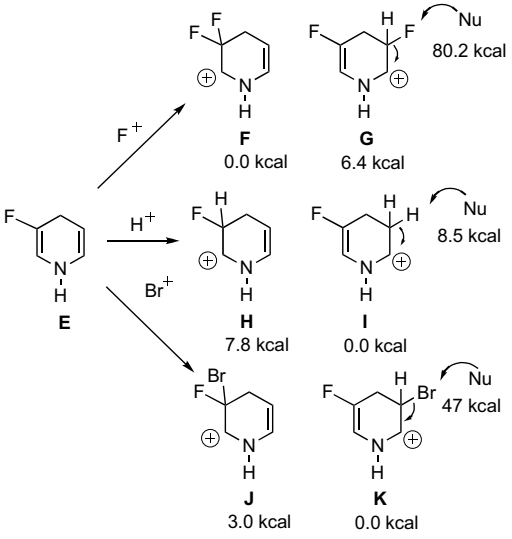
2.4. Comments on the regioselectivity of the lactonization reactions

Two modifications, the consequences of which were disclosed above, have been introduced in the starting pyridines: first, the introduction of a methyl group in α to the nitrogen atom, as in 2-picoline, and the introduction of a fluorine atom in β to the nitrogen atom, as in 3-fluoropyridine. The former would lead to dihydropyridines reacting with electrophiles X^{+} to give as an intermediate the more stable carbocationic species **C** and then the corresponding lactone[23] (Scheme 17).

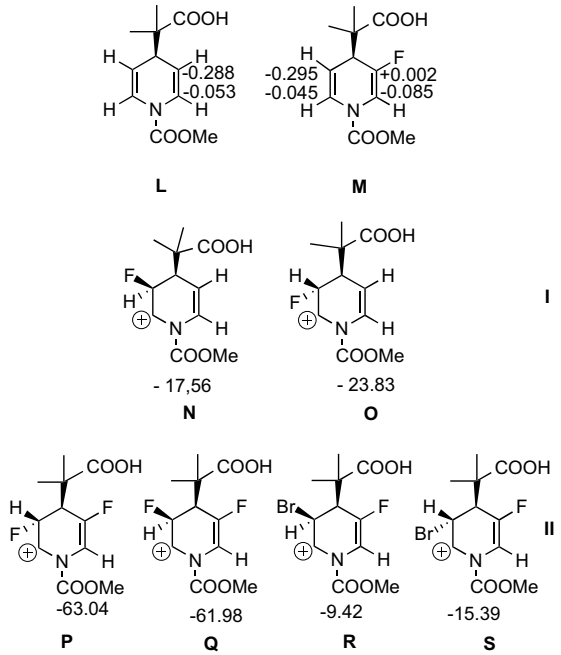
The latter would lead, due to the destabilising effect of a fluorine atom in β to a carbocation, to an intermediate such as **D**, and then to the corresponding lactone.[24] Accordingly, all the electrophiles X^{+} should react with these dihydropyridines in the same way. This was however not the case.

The general behaviour of electrophiles different from F^{+} towards dihydropyridines **6a**,**b** giving in all the cases examined, *trans*, *diaxial* lactones upon their interaction with the double bond lacking fluorine can be understood, at a first glance, since fluorine decreases the electron density at the double bond (Scheme 19, I, L vs M). Electrophilic additions should therefore be more difficult: it is thus not surprising that only one of the two possible regioisomers is formed with HCl.[25]

The special behaviour of electrophilic fluorine towards fluorodihydropyridines **6a**,**b** showing any discrimination between the



Scheme 18. Relative energies of the carbocationic species obtained upon interaction of various electrophiles with 1,4-fluoro-3-dihydropyridine.



Scheme 19. Respective charge distributions on substituted 1,4-dihydropyridines and formation enthalpies of the carbocationic species obtained therefrom.

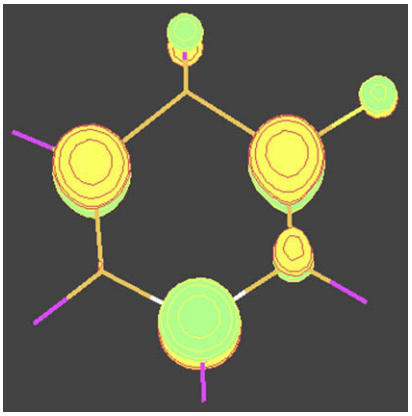
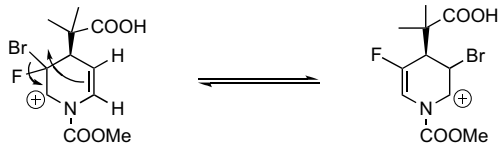


Figure 4. HO of 1,4-fluoro-3-dihydropyridine.



Scheme 20.

double bond devoid of fluorine and the double bond bearing already a fluorine atom was surprising. It led, besides the expected fluorolactones **14a**,**b**, to the formation of interesting geminated difluorinated compounds **15a**,**b**, a type of structure of limited accessibility.[19] Results from the literature confirmed however that activated double bonds, such as enol ethers, bearing fluorine in α to the oxygen atom, could indeed be transformed into *gem*-difluoro derivatives upon their interaction with selectfluor.[26] However, in those special cases, selectfluor had no choice since no other double bond was present in the starting material.

If the reactions are under kinetic control, then one has to consider the localization of the highest occupied orbital (HO) of the starting non-symmetric fluorodihydropyridine, which would interact with the electrophiles.[27] Somewhat surprisingly, the HO (Fig. 4) is almost equally distributed over the carbons C-4 and C-6 (Fig. 4): it is therefore likely that the destabilising effect of fluorine is partially compensated by the presence of the nitrogen atom.

This observation is thus in agreement with the formation of two fluorolactones in almost equal amounts. What about the lactones **7** (X^+=H^+), **10** (X^+=Br^+) and **11** (X^+=I^+)? In those cases, the kinetic products were not observed. The addition of the electrophiles to dihydropyridine can lead in each case to two carbocationic intermediates. As shown in Scheme 18, the more stable carbocation results from the addition of X^+ to the double bond, which does not bear fluorine. This means that for X^+=H^+, Br^+, I^+ equilibration must occur since the thermodynamic products are observed.

Experimentally, the reversibility of the lactonization reaction for X^+=H had already been established.[5] Nucleophile-assisted cleavage of the C–H bond in **I** costs only 8.5 kcal mol^{-1} according to calculations (Nu=NH_3). In contrast, cleavage of the C–F bond in **G** would cost 80.2 kcal mol^{-1}, confirming the irreversibility of the reaction. It is thus not surprising to observe the kinetic products in the case of F^+.

Finally, for X^+=Br^+ in **K**, the energy required for the cleavage of the C–Br bond is in between, 47 kcal mol^{-1}, yet too high. However, a rearrangement via an intramolecular transposition of Br^+ might also be possible, the cleavage of the C–Br bond requiring in that case only 25.8 kcal mol^{-1} (Scheme 20).

Further points warrant also a comment. The stereochemical outcome of the lactonization reaction of the dihydropyridines giving *trans*, *diaxial* fluorolactones **13a**,**b** is thus the same whatever the nature of the halogen (or electrophile) although different mechanisms have to be put forward.[8d,24] This result is in agreement with calculations, since the addition of X^+ *trans* with respect to the substituent at C-4 is favoured in all the cases examined, by 6.5 kcal mol^{-1} for X^+=F, and by 6.0 kcal mol^{-1} for X^+=Br (Scheme 19, II P, Q, R, S).

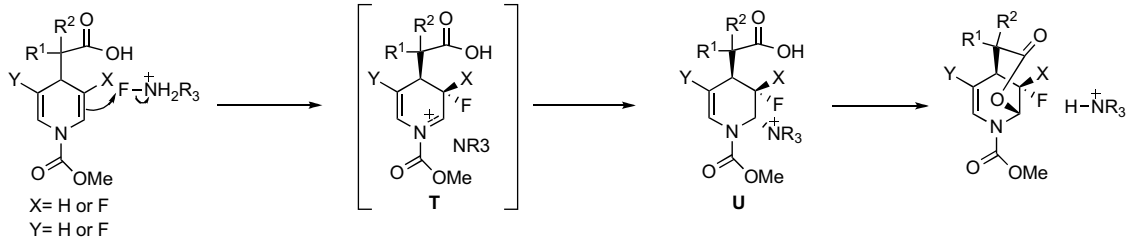
Finally, the formation of two stereoisomers in the fluorination reaction of tetrahydropyridine **22**, the major one bearing an equatorial fluorine, *cis* with respect to the lactone, is at a first sight in contradiction with the results obtained with the dihydropyridines **2a**,**b**. The mechanism of the fluorination of non-activated and of activated double bonds has been the subject of several publications.[8d,24b]

The general accepted pathways for heteroatom-polarized double bonds involve a *syn* addition of the elements of selectfluor, the fluorine atom being attached in β with respect to the heteroatom.[24b]

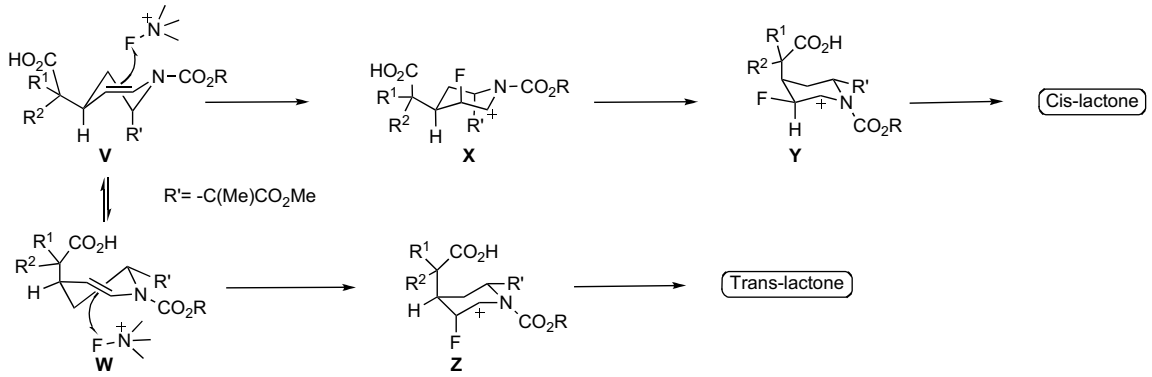
This is followed by a substitution of the TEDA–CH_2Cl group either by an external or by an internal nucleophile, via an S_N2 or S_N1 type reaction (via **T** or **U**, Scheme 21). Whereas the nature of the products obtained from norbornene-carboxylic acids could only be explained via the formation of carbocationic intermediates, both pathways could be observed when glycals were subjected to selectfluor. No SET processes were involved in these transformations.

The preferential formation of the lactone **25** could be assigned to stereochemical aspects. Indeed, the disubstituted tetrahydropyridine can adopt two half-chair conformations **V** and **W**, **V** being much more stable than **W** as a result of a 1,3 and a 1,4-diaxial strains existing in **W** between the bulky substituent at C-3 and the methoxycarbonyl group on nitrogen, and the hydrogen at C-3 and the substituent at C-4 (Scheme 22).

A nucleophilic addition of the double bond in **V** to the electrophilic fluorine of selectfluor would lead to **X** in which the introduced fluorine is *axial*.[28] A conformational inversion to **Y** will then allow the intramolecular lactonization to the observed major *cis* lactone **25**. This might take place either via the *syn* addition product of the elements of selectfluor, or rather, due to the close



Scheme 21.



Scheme 22.

proximity of the carboxylate, directly via a carbocationic (or iminium) intermediate. Similarly, the minor conformer **W** would give the intermediate **Z**, and then the *trans* lactone **24** (Scheme 22). Therefore, in all the cases a *trans*, *axial* introduction of fluorine is observed, followed by a *trans* addition of the TMS ester, the last step involving either an S_N2 or an S_N1 reaction.

3. Conclusion

Thanks to the regioselective interaction of bis(trimethyl)ketene acetals with activated pyridines, a broad series of new carboxylic acid-substituted dihydropyridines could be synthesized. These dihydropyridines are prone to cyclization reactions, leading to lactones among which new fluorolactones. These new lactones reacted in turn with trimethylsilylketene acetals to give tetrahydropyridine-substituted carboxylic acids, which led, upon lactonization reactions, to new lactones, and especially to piperidine-fused fluorolactones. Mechanistic considerations allowed us to explain the regioselectivities of these lactonization reactions. Work is in progress to adapt these fluorination reactions to tackle their enantiomeric aspects and to apply them to other azaaromatic derivatives.

4. Experimental

4.1. General

Reactions were run under an inert atmosphere. Dichloromethane and CH_3CN were distilled on P_2O_5. Column chromatography was performed using 70–230 mesh silica. Melting points were obtained on a Koffler bank and are uncorrected. Nuclear magnetic resonance spectra were recorded on Bruker AV 400 or AC 250 spectrometers. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.25 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad), coupling constant in hertz and integration. Chemical shifts for ^{19}F NMR spectra are recorded in parts per million from fluorotrichloromethane using trifluorotoluene resonance as the internal standard. Chemical shifts for ^{13}C are recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (77.1 ppm) as the internal standard. Analyses were performed by the Service de Microanalyse I.C.S.N.-C.N.R.S.

*4.1.1. 2-(3-Fluoro-1-(methoxycarbonyl)-1,4-dihydropyridin-4-yl)-2-methylpropanoic acid (**6a**)*

To a dry 100 mL round-bottomed flask purged with argon were added 3-fluoropyridine **4** (0.65 mL, 7.5 mmol) and bis-(trimethylsilyl)ketene acetal **1a** (2.65 mL, 9.75 mmol). Dry dichloromethane (40 mL) was added and the mixture was cooled to 0 °C. A solution of methylchloroformate (1.21 mL, 15.8 mmol) in dichloromethane (5 mL) was added dropwise with a dropping funnel. The mixture was allowed to warm up to room temperature and stirred for 12 h. After evaporation of the solvent under reduced pressure, the crude residue was chromatographed on silica gel. Elution with ethylacetate/petroleum ether gave **6a** as a white solid, mp=122 °C (1.64 g, 90%). Two rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.04 and 6.92 (d, J=10 Hz, 1H, H^2), 6.91 and 6.80 (d, J=8 Hz, 1H, H^6), 4.96 and 4.89 (br s, 1H, H^5), 3.80 (s, 3H, OCH_3), 3.78 (t, J=4 Hz, 1H, H^4), 1.18 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 182.3 (COOH), 151.6 and 151.3 ($NCOOCH_3$), 149.7 and 147.2 (d, J=250 Hz, C^3), 124.6 and 124.2 (C^6), 110.2 and 109.7 (d, J=44 Hz, C^2), 105.1 and 104.9 (d, J=13 Hz, C^5), 53.9 and 53.8 (OCH_3), 46.2 ($C^{1'}$), 43.5 and 43.2 (d, J=21 Hz, C^4), 22.2 and 21.8, 21.40 and 21.2 (2 CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −134.4 and −133.9 (br s).

*4.1.2. 1-(3-Fluoro-1-(methoxycarbonyl)-1,4-dihydropyridin-4-yl) cyclohexanecarboxylic acid (**6b**)*

Same procedure as above with bis(trimethylsilyl)ketene acetal **1b** (2.65 mL, 9.75 mmol). Compound **6b** was obtained as a white solid, mp=133 °C (1.8 g, 85%). Two rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.0 and 6.95 (d, J=5 Hz, 1H, H^2), 6.91 and 6.81 (d, J=6 Hz, 1H, H^6), 4.97 and 4.87 (br s, 1H, H^5), 3.8 (s, 3H, OCH_3), 3.57 (t, J=5.5 Hz, 1H, H^4), 1.10–2.10 (m, 10H, $5CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 181.3 (COOH), 151.6 and 151.3 ($NCOOCH_3$), 148.2 and 147.7 (d, J=249 Hz, C^3), 124.7 and 124.3 (C^6), 110.3 and 110.2 (d, J=44 Hz, C^2), 104.9 and 104.7 (d, J=14 Hz, C^5), 53.8 (OCH_3), 52.1 ($C^{1'}$), 45.0 (d, J=21 Hz, C^4), 30.4, 30.2, 28.8, 25.5, 23.6 ($5CH_2$). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −132.4 and −131.8 (br s).

*4.1.3. 2-(1-(Methoxycarbonyl)-2-methyl-1,4-dihydropyridin-4-yl)-2-methylpropanoic acid (**17a**)*

Same procedure as above with 2-picoline **16** (0.99 mL, 10 mmol), bis(trimethylsilyl)ketene acetal **1a** (2.55 mL, 11 mmol), and methylchloroformate (1.61 mL, 21 mmol). Compound **17a** was obtained as an oil (1.51 g, 63%). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.94 (d, J=7.5 Hz, 1H, H^6), 4.79 (ddd, J=2.5, 7.5 Hz, 1H, H^5), 4.60 (m, 1H, H^3), 3.75 (s, 3H, OCH_3), 3.23 (t, J=5 Hz, 1H, H^4), 2.18 (s, 3H, CH_3^2), 1.12 (s, 3H, CH_3^7), 1.11 (s, 3H, CH_3^7). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 183.3 (*C*OOH), 152.7 ($NCOOCH_3$), 135.6 (C^2), 127.8 (C^6), 108.6 (C^3), 107.4 (C^5), 53.1 (OCH_3), 47.2 (C^7), 41.3 (C^4), 22.5 (CH_3^2), 21.5 (CH_3^7), 21.4(CH_3^7). HRMS calcd for $C_{12}H_{17}NO_4Na$ ($M+Na^+$): 262.10498, found: 262.10479.

*4.1.4. Methyl 6-fluoro-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-carboxylate (**7a**)*

To a solution of dihydropyridine **6a** (443 mg, 1.823 mmol) in dry CH_2Cl_2 was added dropwise with syringe a solution of HCl in

diethyl ether (2 mL, 1 M, 2.01 mmol). The mixture was stirred for 3 days at room temperature. A saturated solution of $NaHCO_3$ (10 mL) was added. The mixture was decanted and the water phase extracted twice with $CHCl_3$, then the organic phase was washed with brine and dried over Na_2SO_4 and finally concentrated under reduced pressure. Compound **7a** was obtained as a white solid, mp=106 °C (281 mg, 63%). Two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.92 and 6.79 (d, J=9 Hz, 1H, H^7), 6.41 and 6.26 (br s, 1H, H^1), 3.82 and 3.80 (s, 3H, OMe), 2.58 (m, 1H, H^9), 2.43 (d, J=12 Hz, 1H, H^5), 1.96 (m, 1H, H^9), 1.40, 1.39 and 1.37 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8 (C^3), 152.2 and 151.9 (NCO), 148.4 and 147.4 (d, J=250 Hz, C^6), 107.4 (d, J=42 Hz, C^7), 78.7 and 78.5 (C^1), 54.0 and 53.9 (OCH_3), 42.8 and 42.7 (C^4), 38.3 and 38.2 (d, J=22 Hz, C^5), 27.2, 27.1, 25.3, (Me), 23.8 (d, J_{CF}=6 Hz, C^9). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −128.21 and −128.98 (br s).

4.1.5. Methyl 6-fluoro-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1′-cyclohexane]-8-carboxylate (**7b**)

Same procedure as above with dihydropyridine **6b** (566 mg, 2 mmol) and HCl solution (2.2 mL, 1 M, 2.2 mmol). Compound **7b** was obtained as a white solid, mp=128 °C (347 mg, 61%). Two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.91 and 6.79 (d, J_{HF}=10 Hz, 1H, H^7), 6.34 and 6.19 (br s, 1H, H^1), 3.79 (s, 3H, OMe), 2.92 (d, J_{HF}=12 Hz, 1H, H^5), 2.53 (br s, 1H, H^9), 2.15–1.40 (m, 11H, $5CH_2$ and H^9). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5 (C^3), 152.2 and 151.9 (NCO), 149.6 and 148.8 (d, J_{CF}=250 Hz, C^6), 107.4 (d, J_{CF}=41 Hz, C^7), 77.8 and 77.6 (C^1), 53.9 and 53.8 (OCH_3), 46.5 (C^4), 33.5 (CH_2), 32.6 (CH_2), 32.4 and 31.2 (d, J_{CF}=21 Hz, C^5), 25.3 (CH_2), 23.4 and 23.0 (d, J_{CF}=6 Hz, C^9), 21.2 (CH_2), 20.7(CH_2). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −129.4 and −130.1 (br s).

4.1.6. Methyl 9-bromo-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1′-cyclohexane]-8-carboxylate (**8b**)

To a solution of dihydropyridine **2b** (265 mg, 1 mmol) in dry $CHCl_3$ (70 mL) were added $CuBr_2$ (1.338 g, 6 mmol) and Al_2O_3 (612 mg, 6 mmol). The mixture was heated to 60–65 °C for 17 h. After filtration through Celite, and evaporation of the solvent under reduced pressure, the crude was chromatographed on silica gel. Compound **8b** was obtained as a yellow solid, mp=116 °C (187 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.90 and 6.77 (d, J=8 Hz, 1H, H^7), 6.29 and 6.13 (br s, 1H, H^1), 5.06 and 4.96 (m, 1H, H^6), 4.82 and 4.78 (m, 1H, H^9), 3.79 (s, 3H, OMe), 2.79 (m, 1H, H^9), 2.10–1.20 (m, 10H, $5CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6 (C^3), 152.7 and 152.5 (NCO), 122.1 (C^7), 103.5 and 103.1 (C^6), 80.6 and 80.2 (C^1), 54.0 (OCH_3), 50.1 (C^4), 37.7 (C^9), 37.1 and 36.8 (C^5), 33.5, 33.3, 25.1, 21.2, 20.6 ($5CH_2$). MS: for $C_{14}H_{21}BrN_2O_4$ [M+NH_3]: 361.

4.1.7. Methyl 9-bromo-6-fluoro-3-oxo-2-oxa-8-azaspiro[bicyclo-[3.3.1]non[6]ene-4,1′-cyclohexane]-8-carboxylate (**10b**)

Same procedure as above with dihydropyridine **6b** (237 mg, 0.84 mmol), $CuBr_2$ (1.123 g, 5.02 mmol), and Al_2O_3 (512 mg, 5.02 mmol). Compound **10b** was obtained as a yellow solid, mp=154 °C (293 mg, 98%). Two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.01 and 6.88 (d, J_{HF}=9 Hz, 1H, H^7), 6.27 and 6.10 (br s, 1H, H^1), 4.79 (m, 1H, H^9), 3.84 (s, 3H, OMe), 3.11 (d, J_{HF}=11 Hz, 1H, H^5), 2.13–1.26 (m, 10H, $5CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4 (C^3), 152.4 and 152.1 (NCO), 146.5 and 145.8 (d, J_{CF}=250 Hz, C^6), 107.1 and 107.0 (d, J_{CF}=40 Hz, C^7), 79.9 and 79.5 (C^1), 54.3 and 54.2 (OCH_3), 49.4 (C^4), 41.9 and 41.5 (d, J_{CF}=21 Hz, C^5), 35.9 and 35.5 (d, J_{CF}=7 Hz, C^9), 33.7, 33.6, 25.1, 21.2, 20.5 ($5CH_2$). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −132.6 and −133.3 (br s).

4.1.8. Methyl 6-fluoro-9-iodo-3-oxo-2-oxa-8-azaspiro[bicyclo-[3.3.1]non[6]ene-4,1′-cyclohexane]-8-carboxylate (**11b**)

To a solution of dihydropyridine **6b** (403 mg, 1.424 mmol) and I_2 (380 mg, 1.495 mmol) in dry CH_2Cl_2 was added a saturated solution of $NaHCO_3$ (10 mL). The mixture was stirred at room temperature for 17 h then transferred into a separating funnel and decanted. The aqueous phase was extracted three times with CH_2Cl_2. The organic phase was washed with a solution of $NaHSO_3$ then with water, dried on Na_2SO_4 and concentrated under reduced pressure. Compound **11b** was obtained as a white solid, mp=145 °C (dec) (477 mg, 82%). Two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.0 and 6.87 (d, J_{HF}=10 Hz, 1H, H^7), 6.29 and 6.13 (br s, 1H, H^1), 4.93 (br s, 1H, H^9), 3.85 (s, 3H, OMe), 3.06 (d, J_{HF}=11 Hz, 1H, H^5), 2.12–1.40 (m, 10H, $5CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4 (C^3), 152.4 and 152.0 (NCO), 146.5 and 145.8 (d, J_{CF}=250 Hz, C^6), 107.1 (d, J_{CF}=40 Hz, C^7), 81.0 and 80.4 (C^1), 54.3 and 54.2 (OCH_3), 49.9 and 49.8 (C^4), 43.2 and 43.1 (d, J_{CF}=21 Hz, C^5), 33.7, 33.3, 25.1, 21.3, 20.6 ($5CH_2$), 11.0 and 10.7 (d, J=7 Hz, C^9). Anal. Calcd for $C_{14}H_{17}FINO_4$: C, 41.09; H, 4.19; N, 3.42. Found: C, 41.57; H, 4.22; N, 3.34.

4.1.9. Methyl 6-fluoro-9-hydroxy-3-oxo-2-oxa-8-azaspiro[bicyclo-[3.3.1]non[6]ene-4,1′-cyclohexane]-8-carboxylate (**12b**)

To a suspension of metachloroperbenzoic acid (414 mg, 2.4 mmol) in dry CH_2Cl_2 (10 mL) cooled to −5 °C was added a solution of dihydropyridine **6b** (566 mg, 2 mmol) in CH_2Cl_2 (10 mL). After 10 min, the ice bath was taken off and the mixture allowed to stir at room temperature for 3 h. A NaOH solution (10%, 10 mL) was added, the mixture was transferred into a separating funnel and decanted. The aqueous phase was extracted three times with $CHCl_3$. The organic phase was washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude was chromatographed on silica gel. Lactone **7b** (57 mg, 10%) eluted first then **12b** was obtained as a white solid, mp=197 °C (162 mg, 27%). Two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.0 and 6.86 (d, J=9 Hz, 1H, H^7), 6.10 and 5.93 (br s, 1H, H^1), 4.48 and 4.44 (br s, 1H, H^9), 3.78 (s, 3H, OMe), 2.95 (d, =10.5 Hz, 1H, H^5), 2.00–1.21 (m, 10H, $5CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6 (C^3), 153.0 and 152.7 (NCO), 130.9 and 128.8 (C^6), 146.9 and 145.2 (d, J=250 Hz, C^6), 107.6 (d, J=40 Hz, C^7), 79.3 and 79.0 (C^1), 59.4 and 58.9 (C^9), 54.2 and 54.1 (OCH_3), 47.6 (C^4), 40.2 (br s, C^5), 33.8, 33.2, 25.3, 21.3, 20.6 ($5CH_2$). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −131.8 ppm and −132.5 ppm (br s). Anal. Calcd for $C_{14}H_{18}FNO_5$: C, 56.18; H, 6.06; N, 4.68. Found: C, 56.44; H, 5.85; N, 4.59.

4.1.10. Methyl 9-fluoro-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (**13a**)

To a solution of dihydropyridine **2a** (497 mg, 2.21 mmol) in CH_3CN (35 mL) was added $NaHCO_3$ (264 mg, 3.14 mmol), then selectfluor (870 mg, 2.46 mmol). The mixture was stirred for 2 days at room temperature. Cold water was added (10 mL), the mixture was transferred into a separating funnel and decanted. The aqueous phase was extracted three times with $CHCl_3$. The organic phase was washed twice with a dilute solution of HCl, once with water, and dried over Na_2SO_4. The solvent was removed under reduced pressure. Compound **13a** was obtained as a white solid, mp=116 °C (371 mg, 69%). Two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.96 and 6.82 (d, J_{HF}=8 Hz, 1H, H^7), 6.42 and 6.26 (br s, 1H, H^1), 5.40 and 5.37 (d, J=48 Hz, 1H, H^9), 5.09 and 5.00 (t, J=8 Hz, H^6), 3.83 (s, 3H, OMe), 2.45 (d, J_{HF}=8 Hz, 1H, H^5), 1.42 (s, 3H, Me), 1.36 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.1 (C^3), 152.9 and 152.6 (NCO), 122.4 and 122.4 (C^7), 103.6 and 103.3 (C^6), 78.5 (d, J_{CF}=197 Hz, C^9), 78.3 (d, J_{CF}=27 Hz, C^1), 54.0 (OCH_3), 44.5 and 44.4 (C^4), 39.6 (t, J=20 Hz, C^5), 27.4 and 27.3 (Me), 26.0 (Me). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −198.1 and −199.3 (dd, J=48 and J=8 Hz). Anal. Calcd for $C_{11}H_{14}FNO_4$: C, 54.32; H, 5.80; N, 5.76. Found: C, 54.21; H, 5.83; N, 5.56.

4.1.11. Methyl 9-fluoro-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non-[6]ene-4,1′-cyclohexane]-8-carboxylate (**13b**)

Same procedure as above with dihydropyridine **2b** (589 mg, 2.22 mmol), $NaHCO_3$ (261 mg, 3.11 mmol) and selectfluor (864 mg,

2.44 mmol). Compound **12b** was obtained as a white solid, mp=141 °C (484 mg, 77%). Two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 and 6.84 (d, J_{HF}=8 Hz, 1H, H^7), 6.39 and 6.23 (br s, 1H, H^1), 5.34 and 5.31 (d, J=48 Hz, 1H, H^9), 5.03 and 4.97 (br s, 1H, H^6), 3.82 (s, 3H, OMe), 2.88 (br s, 1H, H^5), 2.00–1.23 (m, 10H, $5CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.9 (C^3), 152.9 and 152.7 (NCO), 122.8 and 122.7 (C^7), 102.9 and 102.6 (C^6), 78.7 and 78.6 (d, J_{CF}=185 Hz, C^9), 77.4 and 77.1 (t, J_{CF}=27 Hz, C^1), 54.0 (OCH_3), 48.3 and 48.2 (C^4), 33.8 (CH_2), 33.6 and 33.3 (d, J_{CF}=22 Hz, C^5), 32.9, 25.2, 21.3, 20.5 ($4CH_2$). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −198.8 and −198.9 (d, J=48 Hz). Anal. Calcd for $C_{14}H_{18}FNO_4$: C, 59.35; H, 6.40; N, 4.94. Found: C, 58.92; H, 6.22; N, 4.64.

4.1.12. *Methyl 9,9-difluoro-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (**15a**) and methyl 6,9-difluoro-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non[6]ene-8-carboxylate (**14a**)*

Same procedure as above with dihydropyridine **6a** (474 mg, 1.95 mmol), $NaHCO_3$ (180 mg, 2.15 mmol) and selectfluor (761 mg, 2.15 mmol). The crude was chromatographed on silica gel, **15a** was obtained as a white solid, mp=106 °C (142 mg, 30%) then **14a** as a white solid too, mp=120 °C (91 mg, 16%). Compound **15a**: two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.87 and 6.75 (d, J=6.5 Hz, 1H, H^7), 6.24 and 6.07 (br s, 1H, H^1), 5.09 and 5.01 (br s, 1H, H^6), 3.85 (s, 3H, OMe), 2.58 (m, 1H, H^5), 1.50 and 1.49 (s, 3H, CH_3), 1.38 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1 (C^3), 152.3 and 152.0 (NCO), 122.2 and 122.0 (C^7), 115.5 (t, J=246 Hz, C^9), 104.0 (C^6), 80.1 and 79.4 (d, J=34 Hz, C^1), 54.3 (OMe), 44.5 (C^4), 42.0 (m, C^5), 28.9 (Me), 27.4 (CH_3). HRMS calcd for $C_{11}H_{13}F_2NO_4Na$ ($M+Na^+$): 284.07049, found: 284.07010. Compound **14a**: two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.01 and 6.88 (d, J=9 Hz, 1H, H^7), 6.36 and 6.20 (br s, 1H, H^1), 5.33 (d, J=48 Hz, 1H, H^9), 3.82 (s, 3H, OMe), 2.70 (t, J=9 Hz, 1H, H^5), 1.42, 1.41 and 1.40 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.7 (C^3), 152.6 and 152.2 (NCO), 145.8 and 145.2 (d, J=246 Hz, C^6), 107.2 and 107.1 (d, J=40 Hz, C^7), 77.8 and 77.5 (dd, J=193, 6 Hz, C^9), 77.4 and 77.2 (t, J=26 Hz, C^1), 54.2 and 54.1 (OMe), 43.6 (m, C^5 and C^4), 27.2 and 27.1 (CH_3), 25.6 (CH_3). HRMS calcd for $C_{11}H_{13}F_2NO_4Na$ ($M+Na^+$): 284.07049, found: 284.07016.

4.1.13. *Methyl 9,9-difluoro-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]-non[6]ene-4,1′-cyclohexane]-8-carboxylate (**15b**) and methyl 6,9-difluoro-3-oxo-2-oxa-8-azaspiro[bicyclo[3.3.1]non[6]ene-4,1′-cyclohexane]-8-carboxylate (**14b**)*

Same procedure as above with dihydropyridine **6b** (566 mg, 2 mmol), $NaHCO_3$ (201.6 mg, 2.4 mmol) and selectfluor (849.6 mg, 2.4 mmol). The crude was chromatographed on silica gel, **15b** was obtained as a white solid, mp=110 °C (242 mg, 40%) then **14b** as a white solid too, mp=140 °C (190 mg, 32%). Compound **15b**: two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.88 and 6.75 (d, J=8 Hz, 1H, H^7), 6.20 and 6.03 (d, J=4 Hz, 1H, H^1), 5.04 (m, 1H, H^6), 3.84 (s, 3H, OMe), 3.00 (m, 1H, H^5), 2.20–1.00 (m, 10H, $5CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.7 (C^3), 152.2 and 152.0 (NCO), 122.6 and 122.4 (C^7), 116.0 (t, J=248 Hz, C^9), 103.2 (C^6), 79.0 and 78.3 (d, J=34 Hz, C^1), 54.1 (OMe), 48.4 (C^4), 36.1 (m, C^5), 36.0, 35.8, 35.6, 34.9, 34.8, 34.3, 25.0, 20.9, 20.8 ($5CH_2$). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −112.1 (d, J_{FF}=251 Hz, F_1^9), −117.2 (d, J=251 Hz, F_2^9). Anal. Calcd for $C_{14}H_{17}F_2NO_4$: C, 55.81; H, 5.69; N, 4.65. Found: C, 55.78; H, 5.71; N, 4.59. Compound **14b**: two rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 and 6.90 (d, J=9 Hz, 1H, H^7), 6.33 and 6.17 (br s, 1H, H^1), 5.31 (d, J=47 Hz, 1H, H^9), 3.83 (s, 3H, OMe), 3.18 (t, J=9 Hz, 1H, H^5), 2.10–1.35 (m, 10H, $5CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.6 (C^3), 152.6 and 152.2 (NCO), 146.1 and 145.4 (d, J=247 Hz, C^6), 107.6 and 107.3 (d, J=40 Hz, C^7), 78.3 and 77.9 (dd, J=200 and J=6 Hz, C^9), 76.7 and 76.4 (t, J=26 Hz, C^1), 54.2 and 54.13 (OMe), 47.77 (C^4), 38.35 and 37.98 (d, J=17 Hz, C^5), 33.98, 33.90, 33.07, 25.15, 21.3, 20.5 ($5CH_2$). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −134.2 and −134.8 (br s, F^6), −198.4 and 198.7 (dd, J=47 and J=7 Hz, F^9). Anal. Calcd for $C_{14}H_{18}FNO_4$: C, 55.81; H, 5.69; N, 4.65. Found: C, 55.69; H, 5.75; N, 4.51.

4.1.14. *Methyl 9-bromo-1,4,4-trimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (**18a**)*

To a solution of dihydropyridine **17a** (428 mg, 1.79 mmol) in dry CH_2Cl_2 (40 mL) was added *N*-bromosuccinimide (350.66 mg, 1.97 mmol) and the mixture was stirred for 17 h. Water was added, the mixture was transferred into a separating funnel and decanted. The organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude was chromatographed on silica gel. Compound **18a** was obtained as an oil (158 mg, 28%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.9 (d, J=8.5 Hz, 1H, H^7), 5.1 (ddd, J=2.2, 6.3, 8.5 Hz, 1H, H^6), 4.6 (t, J=2.2 Hz, 1H, H^9), 3.74 (s, 3H, OMe), 2.4 (dd, J=2.2 Hz, 1H, H^5), 2.1 (s, 3H, CH_3^1), 1.4 (s, 3H, CH_3^4), 1.3 (s, 3H, CH_3^4). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7 (C^3), 152.6 (NCO), 124.9 (C^7), 104.1 (C^6), 90.9 (C^1), 53.5 (OCH_3), 48.6 (C^9), 46.1 (C^4), 44.4 (C^5), 27.9 (CH_3^1), 26.8 (CH_3^4), 25.4 (CH_3^4). HRMS calcd for $C_{12}H_{16}BrNO_4Na$ ($M+Na^+$): 341.01885, found: 341.01875.

4.1.15. *Methyl 9-bromo-7-(bromomethyl)-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (**19**)*

Same procedure as for the synthesis of **8b** was used with dihydropyridine **17a** (523 mg, 2.19 mmol), $CuBr_2$ (2.93 g, 13.14 mmol), Al_2O_3 (1340 mg, 13.14 mmol). Compound **19** was obtained as an oil (129 mg, 15%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.41 (dd, J=2, 3.8 Hz, 1H, H^1), 5.3 (dd, J=2, 6 Hz, 1H, H^6), 4.8 (m, 1H, H^9), 4.7 (d, J=10 Hz, 1H, H^{10}), 4.3 (d, J=10 Hz, 1H, H^{10}), 3.8 (s, 3H, OMe), 2.4 (m, 1H, H^5), 1.4 (s, 3H, CH_3^4), 1.3 (s, 3H, CH_3^4). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 173.1 (C^3), 152.5 (NCO), 152.8 (C^7), 110.7 (C^6), 83.3 (C^1), 54.1 (OCH_3), 46.1 (C^5), 43.6 (C^4), 37.6 (C^9), 32.4 (C^{10}), 26.9 (CH_3^4), 25.9 (CH_3^4).

4.1.16. *Methyl 9-fluoro-1,4,4-trimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (**20a**)*

Same procedure as for the synthesis of **13a** was used with dihydropyridine **17a** (499 mg, 2.09 mmol), $NaHCO_3$ (193 mg, 2.3 mmol) and selectfluor (814 mg, 2.3 mmol). Compound **20a** was obtained as a white solid, mp=108 °C (154 mg, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.93 (d, J=8.5 Hz, 1H, H^7), 5.01 (ddd, J=2, 6, 8.5 Hz, 1H, H^6), 4.99 (dt, J=2.5, 48 Hz, 1H, H^9), 3.78 (s, 3H, OMe), 2.42 (ddd, J=2.8, 6, 8 Hz, 1H, H^5), 2.16 (s, 3H, Me^1), 1.41 (s, 3H, Me^4), 1.35 (s, 3H, Me^4). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7 (C^3), 152.9 (NCO), 125.2 (C^7), 103.0 (C^6), 88.2 (C^1), 87.3 (d, J=190 Hz, C^9), 53.6 (OCH_3), 45.2 (d, J=8.5 Hz, C^4), 40.3 (d, J=17 Hz, C^5), 27.4 (Me^4), 25.6 (Me^1), 25.5 (Me^4). HRMS calcd for $C_{12}H_{16}FNO_4Na$: ($M+Na^+$): 280.09556, found: 280.09519.

4.1.17. *Methyl 9-fluoro-7-(1-methoxy-2-methyl-1-oxopropan-2-yl)-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]nonane-8-carboxylates (**24**) and (**25**)*

Same procedure as above with compound **22** (373 mg, 1.14 mmol), $NaHCO_3$ (134 mg, 1.6 mmol) and selectfluor (445 mg, 1.25 mmol). The crude was chromatographed on silica gel. Compound **24** was obtained as an oil (14 mg, 3%) then **25** as a white solid, mp=142 °C (141 mg, 36%). Compound **24** (F *trans*) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.38 (d, J=4 Hz, 1H, H^1), 5.05 (dt, J=48 and 4 Hz, 1H, H^9), 3.88 (dd, J=4 and 13 Hz, 1H, H^7), 3.62 (s, 6H, 2 OMe), 2.18 (m, 1H, H^5), 2.04 (m, 1H, H^6), 1.92 (m, 1H, H^6), 1.20 (s, 3H, Me), 1.18 (s, 3H, Me), 1.12 (s, 3H, Me), 1.10 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz): δ: 177.0 (C^3), 174.5 (CO ester), 156.2 (NCO), 82.5 (d, J=24 Hz, C^1), 78.7 (d, J=184 Hz, C^9), 53.4 (OCH_3), 53.0 (OCH_3), 52.2 (C^7), 46 (C^4), 41.2 (C^{10}), 39.8 (d, J=16 Hz, C^5), 29.6 (Me), 26.5 (Me), 24.7 (Me), 22.0 (C^6); 18.7 (Me). ^{19}F NMR ($CDCl_3$, 376 MHz): δ: −195.8 (d, J=48 Hz). **25** (F *cis*) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.43 (dt, J=8 and 2.5 Hz, 1H, H^1), 4.78 (dd, J=48, 4 and 2.5 Hz, 1H, H^9), 3.99 (d, J=4 and 12 Hz, 1H, H^7), 3.64 (s, 3H, OMe), 3.62 (s, 3H, OMe), 2.34

(m, 1H, H^5), 2.23 (m, 1H, H^6), 1.61 (m, 1H, H^6), 1.43 (s, 3H, Me), 1.34 (s, 3H, Me), 1.10 (s, 3H, Me), 1.09 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 176.8 (C^3), 174.8 (CO ester), 155.8 (NCO), 86.6 (d, J=186 Hz, C^9), 84.6 (d, J=29 Hz, C^1), 53.6 (OCH_3), 52.8 (OCH_3), 52.0 (C^7), 46.1 (C^4), 39.8 (C^{10}), 39.5 (d, J=16 Hz, C^5), 31.2 and 31.1 (Me), 27.9 (C^6), 26.9 (Me), 25.6 (Me), 18.9 (Me). ^{19}F NMR ($CDCl_3$, 376 MHz) δ: −184.8 (d, J=48 Hz). Anal. Calcd for $C_{16}H_{24}FNO_6$: C, 55.64; H, 7.00; N, 4.06. Found: C, 55.46; H, 7.31; N, 3.99.

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