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Synthesis of New Polycyclic γ- and δ-Lactones upon Activation of, and Nucleophilic Additions to, Diazines: Influence of the Activating Agents

A. Garduno-Alva,[a] Y. Xu,[b][‡] N. Gualo-Soberanes,[a] J. Lopez-Cortes,[a] H. Rudler,*[b] A. Parlier,[b] M. C. Ortega-Alfaro,[c] C. Alvarez-Toledano,[a] and R. A. Toscano[a]

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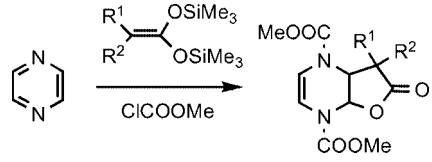
The reaction of bis(trimethylsilyl)ketene acetals **2** with N-heterocycles containing either one or two nitrogen atoms in the presence of triflic anhydride has been examined and the structures of the resulting products compared with those obtained by using methyl chloroformate as the activating agent. Whereas pyridine, pyrazine, quinoxaline and pyrimidine led to the same type of fused δ- or γ-lactones **4**, **6**, **8**, **10** and **11** as with methyl chloroformate, the behaviour of pyridazine appeared to be peculiar. In the presence of methyl chloroformate, this heterocycle led to δ-lactones **16** via stable dihydropyridazines, with triflic anhydride, the direct formation of γ-lactones **20** was observed.

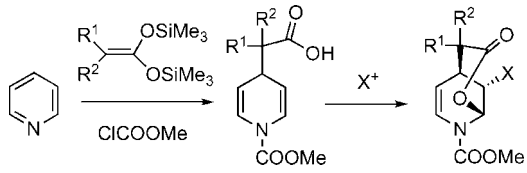
Introduction

The use of ketene acetals as potential 1,3-dinucleophiles has emerged as a very powerful method for the synthesis of lactones from both simple aromatic compounds as well as from aza-aromatics.[1] Whereas in the first case the activation of the aromatic substrates was the result of the coordination of their double bonds to a transition metal, in the second case the activation of the aza-aromatics occurred through the nitrogen atoms via the formation of pyridinium salts. These transformations were first carried out on pyridine and its derivatives: it is a two-step process giving isolable intermediate monoaddition products, carboxylic acid substituted dihydropyridines.[2] These could be oxidized in a non-biomimetic way to afford tetrahydropyridine-fused δ-lactones.[1b,3] Among the oxidizing agents X^+, the more efficient are derived from HCl, I_2, Br_2 and $ArCO_3H$ (Scheme 1).



Scheme 1.

Both the monoaddition products, the various dihydropyridines, and the diaddition products, the fused lactones, might be considered potentially important from a biological point of view.[4] No less important as far as their biological implications are concerned are diazine derivatives, which could be obtained by similar means: pyrazine and quinoxaline were even more straightforward as the presence of two nitrogen atoms, which might both be activated towards nucleophilic addition upon interaction with alkyl chloroformates, allowed for the direct formation of γ-lactones upon successive, formal additions of the two termini of the dinucleophiles to the two carbon–nitrogen double bonds of these substrates[1b,5] (Scheme 2).



Scheme 2.

The purpose of this paper is to show that the double nucleophilic addition reaction of ketene acetals, which leads to lactones, can be extended to other diazines such as pyrimidine and pyridazine, but that the course of the reaction may be dependent on the nature of the nitrogen-activating agent. Therefore, we shall first make a comparison between the behaviour of two types of activating agents, alkyl chloroformates and triflic anhydride [$(CF_3SO_2)_2O$], in the reac-

[a] Instituto de Quimica, Universidad Nacional Autonoma de México (UNAM),
Circuito Exterior s/n, Ciudad Universitaria, 04510 México D.F., México
[b] Laboratoire de Chimie Organique, UMR CNRS 7611, Université P. M. Curie,
Case 47, 4 place Jussieu, 75252 Paris Cedex 5, France
Fax: +33-1-44273787
E-mail: henri.rudler@upmc.fr
[c] Facultad de Quimica, Universidad Nacional Autonoma de México (UNAM),
Circuito Exterior s/n, Ciudad Universitaria, 04510 México D.F., México
[‡] Present address: Aster Print Pigments,
Shanghai, China

tions with pyridine and pyrazines, and then describe the special behaviour of pyridazine in these dinucleophilic addition reactions.

Results and Discussion

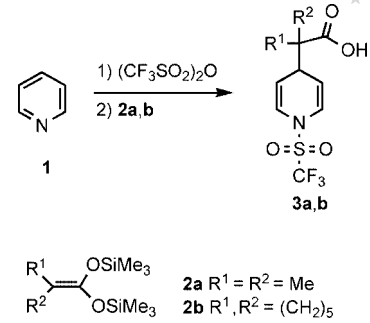
According to the literature, pyridines functionalized at C-4 are best obtained upon their activation with either alkyl chloroformates or triflic anhydride followed by the addition of various C-nucleophiles.[6–12] Each method has its advantages and disadvantages: triflic anhydride is expensive but gives high yields of stable pyridinium salts and then high yields of addition products. In the case of methyl chloroformate, which is cheap, the pyridinium salts are unstable and must be used as soon as they are formed. Also, the yields of the addition products are somewhat lower. There is a further difference that is significant: 1-methoxycarbonyl-1,4-dihydropyridines, in contrast to the corresponding triflates, exist as two rotamers, a fact that can complicate their analyses by NMR spectroscopy. In order to determine the effect, if any, of the activating agent on the course of these reactions, we carried out a series of experiments with both methyl chloroformate and triflic anhydride.

Reaction of Pyridine, Pyrazine and Quinoxaline with Bis(trimethylsilyl)ketene Acetals in the Presence of Triflic Anhydride: Formation of the Expected δ- and γ-Lactones

Triflic anhydride is known to activate pyridine towards nucleophilic addition reactions: it has been used by one of us in alkylamine-induced pyridine ring-opening reactions,[13,14] and by Katritzky et al. in the preparation of 4-(2-oxoalkyl)pyridines from pyridine and ketones.[15]

In this work we observed that the use of ketene acetals in conjunction with triflic anhydride led, in the case of pyridine, to results similar to those obtained with methyl chloroformate as the activating agent. Thus, the one-pot reaction of pyridine first with 1 equiv. of triflic anhydride at –30 °C and then, at the same temperature, with 1.5 equiv. of the ketene acetal **2a** led, after 10 hours at room temperature, to **3a** (yield 75%, m.p. 108 °C), the expected dihydropyridine (Scheme 3). The NMR spectra of this compound were in all respects comparable to those of the methoxycarbonyl-protected dihydropyridines shown in Scheme 1, all of the protons of the dihydropyridine ring appearing, however, as isolated multiplets due to the absence of rotamers. Compound **2b** behaved similarly leading to **3b** in 96% yield (white solid, m.p. 134 °C).

Crystals suitable for X-ray structure determination were grown from dichloromethane/hexane solutions.[16] The molecular structure is shown in Figure 1 and confirms the suggested structure, the planar geometry around the nitrogen atom and a general bent geometry of the dihydropyridine ring similar to that previously reported.[13,15] Interestingly, these acids appear as classical dimers formed via the carboxy groups. This is in contrast to acids bearing the methoxycarbonyl group, which appear in the unit cell as hydrogen-bonded polymers,[1b] the acid of one molecule being hydrogen-bonded to the oxygen of the methoxycarbonyl of another molecule.



Scheme 3.

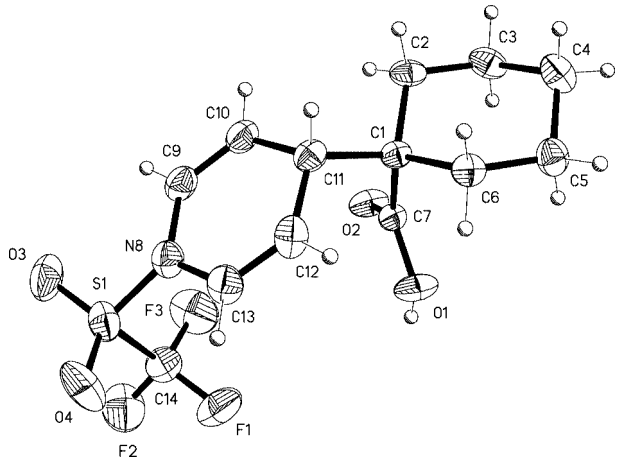
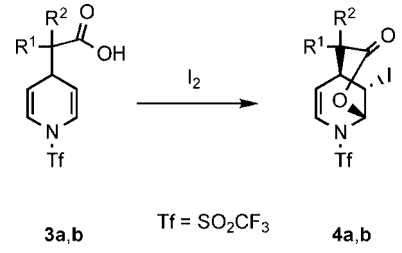


Figure 1. X-ray structure of compound **3b**.

Surprisingly however, the intramolecular lactonization reaction in the presence of acids did not occur: neither extended contact with silica gel nor reaction with HCl led to the expected lactones.[1b] Nevertheless, under the same conditions employed for the dihydropyridines bearing a methoxycarbonyl group, **3b** reacted with iodine to give a single crystalline compound (yield 96%, m.p. 132 °C), the physical data of which agreed in all respects with structure **4b**, the corresponding iodo-lactone showing typical signals for CO at δ = 171.7 ppm and for C–I at δ = 27.1 ppm (Scheme 4).



Scheme 4.

A final assessment was made by performing an X-ray structure determination, which showed indeed (Figure 2) the presence of iodine, as expected, *trans* with respect to the lactone bridge.[16] Compound **3a** reacted similarly and led to **4a** (yield 74%, m.p. 111 °C).

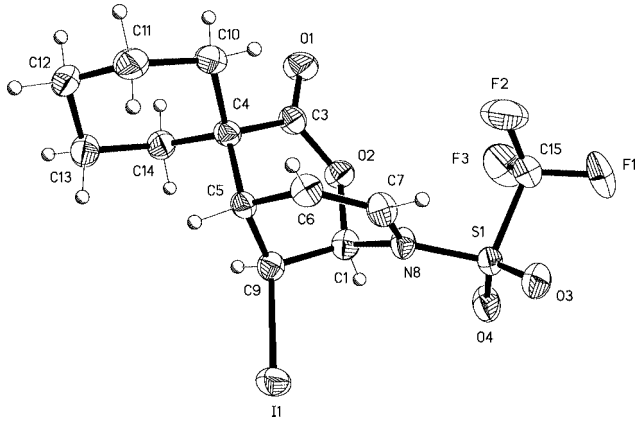
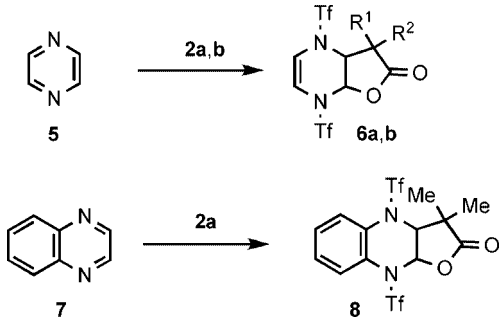


Figure 2. X-ray structure of compound **4b**.

The reactions of pyrazine (**5**) and quinoxaline (**7**) with ketene acetals in the presence of methyl chloroformate have already been outlined: they led in both cases to γ-lactones upon successive activation of the two nitrogen atoms (Scheme 5).[5] The reaction of pyrazine (**5**) and quinoxaline (**7**) with 1 equiv. of the ketene acetal **2a** in the presence of 2 equiv. of triflic anhydride followed the same course: the formation in each case of a single compound, a γ-lactone, upon double nucleophilic addition of the ketene acetal. Thus, **5** led to **6a**, and with **2b** to **6b**, in 47 and 50% yields, respectively, isolated as white solids.



Scheme 5.

Their physical data were in all respects comparable to those of the previously reported compounds. Similarly, quinoxaline (**7**) led upon reaction with **2a** to the lactone **8** (yield 41%, m.p. 187 °C) (Scheme 5). The structures of these γ-lactones were assessed by an X-ray analysis carried out on **8** (Figure 3), which confirmed the addition of the 1,3-dinucleophile to the carbon–nitrogen double bonds of the starting compounds.[16]

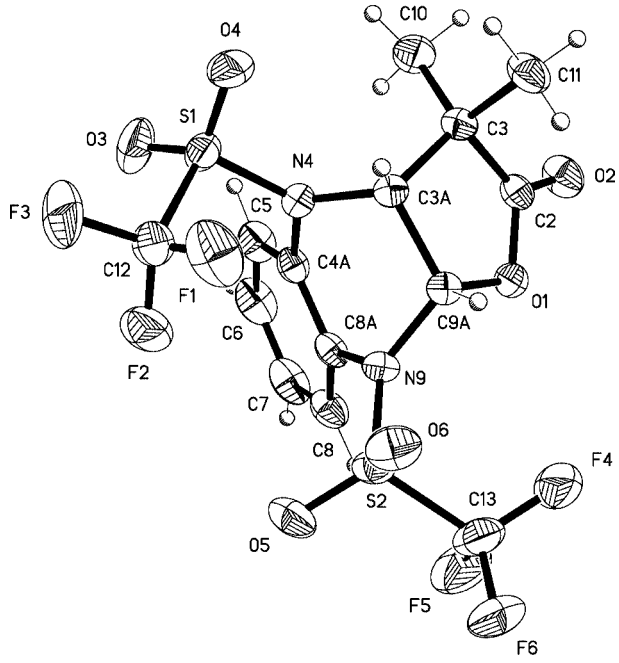
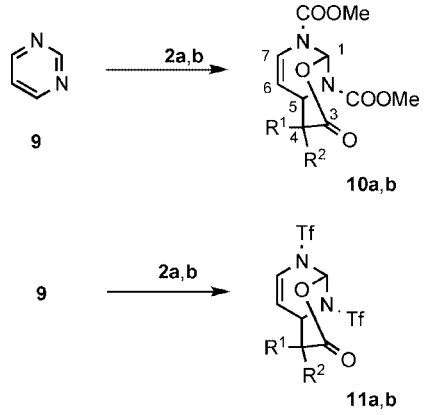


Figure 3. X-ray structure of compound **8**.

Reaction of Bis(trimethylsilyl)ketene Acetals with Pyrimidine

The importance of pyrimidine (**9**) in biochemistry as part of the skeleton of nucleic acids and as its oxygenated derivatives is clear.[17] Much work has already been carried out to achieve nucleophilic addition reactions on this substrate. Especially rewarding as far as the present work is concerned are the double nucleophilic addition reactions described by Akiba and co-workers on activated pyrimidinium nuclei involving carbon nucleophiles, which gave 2,4-disubstituted tetrahydropyrimidines.[18] No monoadducts, such as dihydropyrimidines, were observed upon activation with acetyl chloride. It was therefore likely that pyrimidine would react in the same way with 1 equiv. of a ketene acetal to give directly a diaddition product, once again a δ-lactone. And that was the case: activation with both methyl chloroformate or triflic anhydride led to the expected products. Thus, the reaction of pyrimidine (**9**) with 1 equiv of ketene acetal **2a** and 3 equiv. of methyl chloroformate led to a single compound (yield 42%, oil), the NMR spectroscopic data of which agreed with a structure such as **10a**, a 2,4-diaddition product. It is a δ-lactone with a signal at δ = 173.85 ppm. The COSY NMR spectrum confirmed the presence of a highly deshielded signal, a singlet at δ = 7.65 ppm, which was attributed to the isolated proton 1-H. An HMQC correlation indicated that the signal at δ = 53.56 ppm in the ^{13}C NMR spectrum was attributable to C-5. This carbon bears a proton that is correlated with 6-H (at δ_H = 5.31 ppm; δ_C = 104.99 ppm), a proton of the double bond. Under similar conditions, pyrimidine (**9**) reacted with **2b** to give **10b** as an oil in 90% yield (Scheme 6).



Scheme 6.

Activation with triflic anhydride led to similar products: thus, pyrimidine (**9**) with a two-fold excess of triflic anhydride and ketene acetals **2a**,**b** led to **11a** (yield 42%, m.p. 78 °C) and **11b** (yield 55%, m.p. 88 °C), respectively. The spectroscopic data were again in agreement with the expected structures. Confirmation of the structure of these double addition products came from an X-ray analysis (Figure 4) carried out on crystals of **11a**, which again indicated a planar geometry around the two nitrogen atoms.[16]

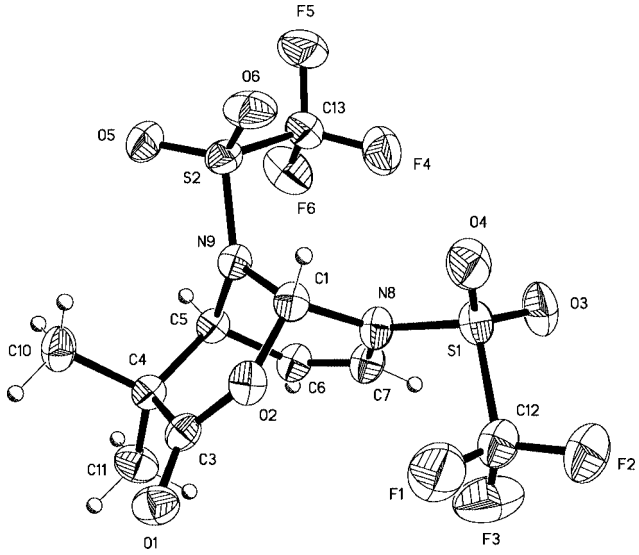
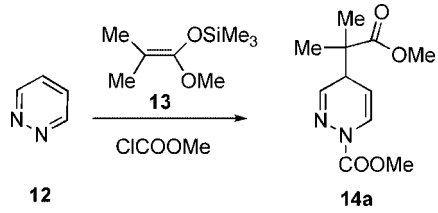


Figure 4. X-ray structure of compound **11a**.

Reaction of Pyridazine with Ketene Acetals − The Activation Agent Makes the Difference: Formation of δ- Versus γ-Lactones

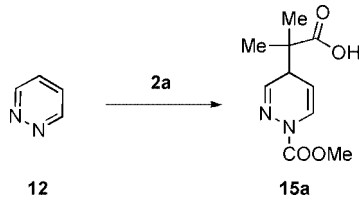
Methyl Chloroformate Activation: Formation of a δ-Lactone upon Iodocyclization via an Isolable Dihydropyridazine

The reaction of pyridazine (**12**) with mono(trimethylsilyl)ketene acetals of the type **13** in the presence of ethyl chloroformate has previously been studied by Akiba and co-workers; they observed the formation of only a C-4 monoaddition product.[18] We observed similar behaviour for the reaction of **12** and **13** in the presence of methyl chloroformate, leading to **14a** (Scheme 7).



Scheme 7.

It was therefore evident that a bis(trimethylsilyl)ketene acetal **2a** would behave similarly. And that was indeed the case. Even with 2 equiv. of methyl chloroformate and 2 equiv. of bis(trimethylsilyl)ketene acetal **2a**, pyridazine (**12**) led, upon purification by silica gel column chromatography, to a single monoaddition product, the acid **15a** (Scheme 8), isolated as a solid (yield 62%, m.p. 124 °C). The NMR spectroscopic data of this acid were only slightly different to those of the corresponding ester **14a** (see the Exp. Sect.).



Scheme 8.

Confirmation of the suggested structure came from an X-ray analysis carried out on a single crystal of **15a**.[16] Figure 5 indicates indeed that the addition took place at C-4, and that the six atoms of the cycle lie almost in the same plane. This structure, and especially the arrangement of the molecules in the lattice, warrants a special comment. Indeed, compound **15a** crystallized in the orthorhombic system with space group $Pca2_1$ and with two independent molecules of opposite stereochemistry in the asymmetric unit. In both molecules the 1,4-dihydropyridazine ring is in an almost planar boat conformation (mean plane deviations, for molecule A: 0.067 Å; for molecule B: 0.0815 Å). Moreover, the two independent components in **15a** are linked, forming homochiral endless chains along the *a* axis by a combination of simultaneous O–H···N hydrogen bonds and O–H···O interactions. These chains assemble in an antiparallel mode, forming a unique double-stranded helix (Figure 6) by virtue of π-stacking interactions (Figure 5) between the methyl 1,4-dihydropyridazine-1-carboxylate moieties.

When dihydropyridazine **15a** was treated with iodine in the presence of an aqueous saturated solution of sodium hydrogen carbonate for 3 days, the formation of a new product was observed. After removal of excess iodine, the

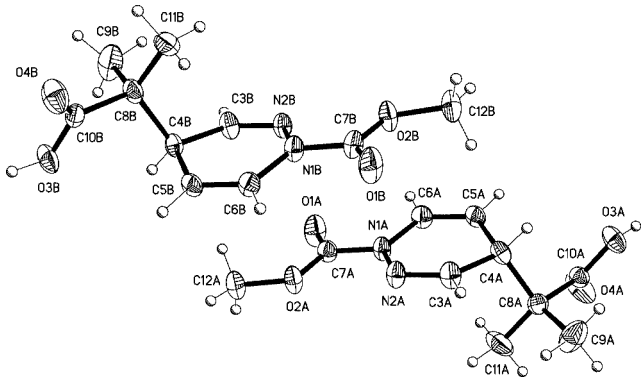


Figure 5. X-ray structure of compound **15a**.

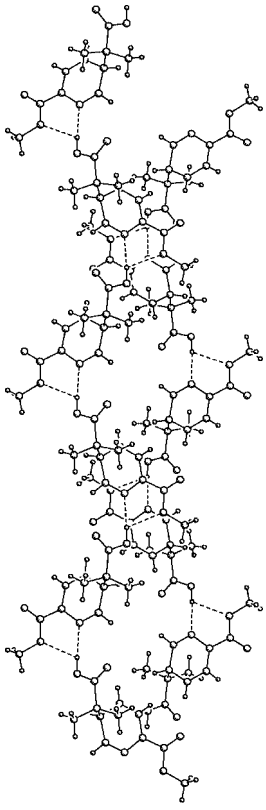
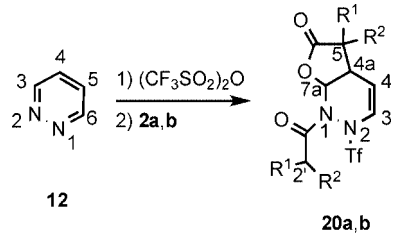


Figure 6. Helix structure of **15a** in the crystal lattice.

organic residue was subjected to silica gel column chromatography. A single crystalline compound **16a** was isolated (yield 79%, m.p. 116 °C, decomposition). The NMR spectroscopic data agreed with the presence of two carbonyl groups: δ = 172.4 ppm for the δ-lactone and δ = 154.0 ppm for the methoxycarbonyl group. Moreover, the presence of a secondary iodine was confirmed by signals at δ = 4.91 and 27.5 ppm, respectively, in the ^{1}H and ^{13}C NMR spectra (Scheme 9).

A single-crystal analysis carried out on **16a** (Figure 7) confirmed these data and again, as expected, the *trans* relationship between the lactone bridge and the iodine.[16] It appeared, therefore, that the intermediate dihydropyridazines **15a**,**b** behaved like 1,4-dihydropyridines, the lactonization reaction taking place upon interaction of the carboxy group with the polarized γ,δ-carbon–carbon double bonds of these substrates.



Scheme 9.

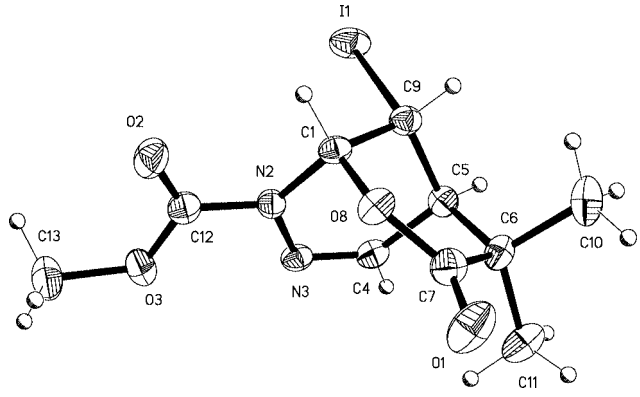


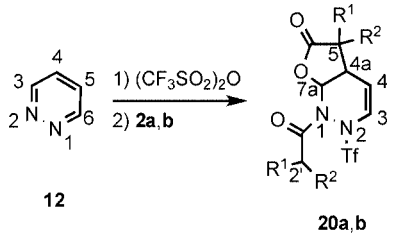
Figure 7. X-ray structure of compound **16a**.

Triflic Anhydride Activation of Pyridazine: Direct Formation of γ-Lactones

The reactivity was absolutely different when 2 equiv. of triflic anhydride were added at –30 °C to a dichloromethane solution of pyridazine (**12**) and after 10 min at the same temperature 2 equiv. of bis(trimethylsilyl)ketene acetal **2a** were also added. After slow heating to room temperature and stirring for 12 h, a new product was isolated upon silica gel chromatography (yield 20%, m.p. 94 °C). The ^{13}C NMR spectrum first confirmed the introduction of the SO_2CF_3 group and seemed also in agreement with the presence of a γ-lactone, with a signal at δ = 179.91 ppm in the ^{13}C NMR spectrum arising from the CO group as well as a band at 1786 cm^{-1} in the IR spectrum. In the same spectra, the presence of another carbonyl function was also observed (at 176.89 ppm and 1720 cm^{-1}, respectively). Surprisingly, besides signals for four different protons, signals for four methyl groups were also apparent in the ^{1}H NMR spectrum, two of them as singlets at δ = 1.27 and 1.44 ppm, two of them as doublets at δ = 1.08 and 1.22 ppm (J = 7.0 Hz). This was in agreement with the introduction of the elements of 2 equiv. of the ketene acetal. These latter signals more probably belonged, therefore, to an isopropyl group in an asymmetric environment, a structural feature also confirmed by the presence of a heptet at δ = 3.19 ppm, integrat-

ing for one proton. Among the signals of the isolated protons of the ring system, three of them were highly deshielded: δ = 6.91 (2 H) and 5.43 (1 H) ppm. Two were attributable to those of a double bond, as in **14a** or **15a**, and one to the typical deshielded N–CH–O proton of these lactones, an observation that was also in agreement with the presence of a signal at δ = 80.76 ppm in the ^{13}C NMR spectrum.

Similar features appeared in the NMR spectra of the product obtained by reaction of **12** with **2b** (31% yield, m.p. 114 °C). Its ^{1}H NMR spectrum clearly showed signals for the two coupled hydrogen atoms of the double bond, which appeared as two doublets at δ = 6.95 and 5.43 ppm (J = 8 Hz), and for the OCHN proton at δ = 6.87 ppm, which appeared as a doublet (J = 6 Hz). Taken together with the mass spectra, and with the structure of **14a** or **15a** obtained upon activation with methyl chloroformate, these data seemed to support structures **20a**,**b**, which arise from nucleophilic attack of the carbon and oxygen termini of the dinucleophile at C-4 and C-3 of pyridazine, respectively (Scheme 10).



Scheme 10.

The structures of the two products were assessed by X-ray analysis.[16] As shown for **20a** in Figure 8, a γ-lactone *cis*-fused to a tetrahydropyridazine had indeed formed, one nitrogen bearing a trifluoromethanesulfonyl group, as expected from the NMR spectroscopic data, the other one, surprisingly, an acyl group, originating most probably from the starting ketene acetal. Both nitrogen atoms adopt a planar geometry due to electron delocalization either on the oxygen atoms of the triflyl or on the oxygen of the amide. Thus, in contrast to what was observed with methyl chloroformate, a surprising, novel, direct activation of the two nitrogen atoms takes place, which allows the double nucleophilic addition to occur.

A mechanism for the formation of **20a**,**b** can be suggested. Although nucleophilic addition to the intermediate imine **18** seemed possible, the nature and origin of the electrophile on the nitrogen atom were not clear in the absence of any ester derivatives of the acid employed as the starting material.[1] It is therefore likely that the intermediate dihydropyridazine **18**, formed upon reaction of the ketene acetals with the starting iminium triflate **17**, underwent a Me_3-SiOTf-mediated cyclization, leading in the presence of excess ketene acetals **2** to the adduct **19**, and, after hydrolysis of the α-TMS amide, loss of the TMS group to give the

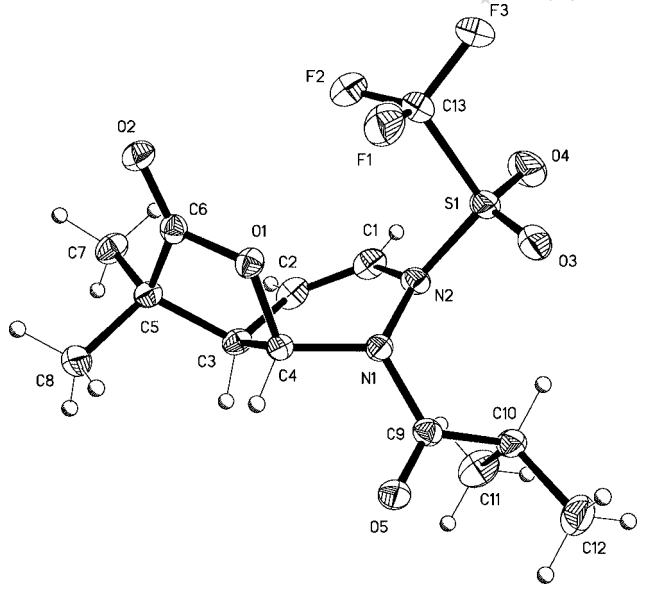
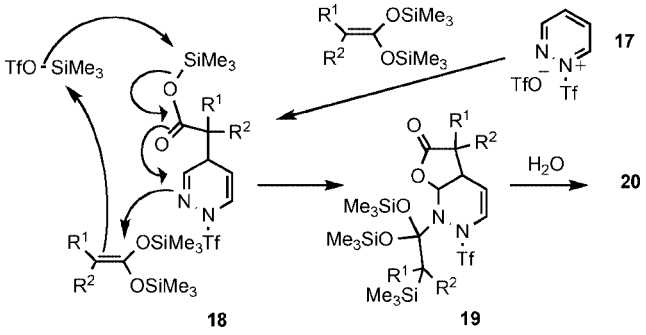


Figure 8. X-ray structure of compound **20a**.

observed amide **20**.[19] Such an evolution of intermediate **18** cannot take place when the activation is promoted by methyl chloroformate (Scheme 11).



Scheme 11.

Conclusions

As a general rule, the reaction of pyridines, pyrazines, quinoxalines and pyrimidines with ketene acetals of the type **2** led to a series of δ- and γ-lactones whatever the nitrogen activating agent. Note, in the case of pyridine, no spontaneous or acid-mediated lactonization of the intermediate trifluoromethanesulfonyl-substituted dihydropyridines was observed. In the case of pyridazine, strikingly different behaviour was observed. An intermediate dihydropyridazine was isolated upon activation with methyl chloroformate. This intermediate then reacted with iodine, similarly to the dihydropyridines **3**, to give a δ-lactone. No such intermediate was observed in the case of triflic anhydride; the interaction of the second nitrogen atom with an activated ketene acetal promoted a direct, intramolecular reaction

of the oxygen terminus of the ketene acetal with the electrophilic carbon of an imine, leading to a γ-lactone. Finally, almost all of the new products described herein have been characterized by X-ray crystallography.

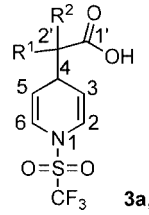
Experimental Section

General Information: Reactions were run under inert argon. All glassware was dried in an oven prior to use. Anhydrous solvents were obtained by distillation under an inert atmosphere over sodium benzophenone for THF, and P_2O_5 for dichloromethane. Column chromatography was performed using 70–230 mesh silica gel. Melting points were obtained with a Kofler hot-plate and are uncorrected. Nuclear magnetic resonance spectra were recorded with a Bruker AV 400 or JEOL Eclipse +300 spectrometer. Chemical shifts for the ^{1}H NMR spectra were 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 (*J*) in Hz and integration. Chemical shifts for the ^{13}C NMR spectra were recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (δ = 77.1 ppm) as the internal standard. IR spectra were recorded with a Nicolet FT-1 Magna 750 spectrometer using KBr pellets. Mass spectra were recorded with a JEOL JMS-AX 505 HA spectrometer at 70 eV using the electronic impact (EI) technique. The ketene acetals **2a** and **2b** were prepared according to published methods.[20]

General Procedure for the Synthesis of Compounds 3a and 3b: Trifluoromethanesulfonic anhydride was added by syringe to a solution of pyridine in dry dichloromethane (20 mL) cooled to –30 °C and under an inert atmosphere. The formation of a white precipitate was observed. After 10 min, the corresponding bis(trimethylsilyl)ketene acetal was added. After 5 min, the mixture was warmed to room temperature and stirred for 17 h. Water was added (30 mL), the mixture was transferred to a separating funnel and decanted. The aqueous phase was extracted four times with dichloromethane. Base extraction followed by reacidification and extraction with dichloromethane (Na_2CO_3 then HCl) allowed the acid to be isolated as a white solid after evaporation of the solvent under reduced pressure.

Compound **3a** ($C_{10}H_{12}F_3NO_4S$, *M* = 299 g/mol) was prepared starting from pyridine (0.5 mL, 0.511 g, 6.47 mmol), trifluoromethanesulfonic anhydride (1 mL, 1.8258 g, 6.47 mmol) and acetal **2a** (2.25 mL, 2.25 g, 9.705 mmol) and was obtained as a white solid, m.p. 108 °C (1.46 g, 4.87 mmol, 75%). IR: $\tilde{\nu}$ = 1706 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.30 (s, 1 H, COOH), 6.55 (d, *J* = 7.7 Hz, 2 H, 2-H and 6-H), 5.09 (d, *J* = 3.03 Hz, 2 H, 3-H and 5-H), 3.39 (s, 1 H, 4-H), 1.18 (s, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.4 (COOH), 119.6 (*J* = 324.79 Hz, CF_3), 123.8 (C-2), 109.6 (C-2′), 46.8 (C-5), 39.4 (C-4), 21.3 (CH_3) ppm. MS (EI): *m*/*z* (%) = 298 (20) $[M - 1]^+$, 212 (100) $[M - 87]^+$.

Compound **3b** ($C_{13}H_{16}F_3NO_4S$, *M* = 339 g/mol) was prepared starting from pyridine (2 mL, 2.044 g, 25.88 mmol), trifluoromethanesulfonic anhydride (4.34 mL, 7.29 g, 25.88 mmol) and acetal **2b** (7 mL, 7.0312 g, 25.88 mmol) and was obtained as a white solid, m.p. 134 °C (8.46 g, 24.93 mmol, 96%). IR: $\tilde{\nu}$ = 1688 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.27 (s, 1 H, COOH), 6.54 (d, *J* = 8 Hz, 2 H, 2-H and 6-H), 5.10 (dd, *J* = 8, 4 Hz, 2 H, 3-H and 5-H), 3.19 (s, 1 H, 4-H), 2.04 (m, 4 H, CH_2), 1.67 (m, 2 H, CH_2), 1.17–1.39 (m, 4 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.7 (COOH), 119.5 (*J* = 324.79 Hz, CF_3), 120.9 (C-2), 108.5 (C-3), 50.2 (C-2′), 38.6 (C-4), 33.6, 33.4, 25.1, 20.7, 20.3 (CH_2) ppm. MS (EI): *m*/*z* = 338 $[M - 1]^+$.

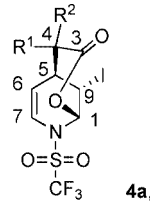


3a,**b**

General Procedure for the Synthesis of Lactones 4a and 4b: A dichloromethane solution (5 mL) of iodine was added through a cannula followed by a saturated solution of $NaHCO_3$ (10 mL) to a solution of *N*-(trifluoromethylsulfonyl)-1,4-dihydro-4-pyridinylethanoic acid (**3**) in dry dichloromethane (40 mL) under an inert atmosphere. The mixture was stirred at room temperature for 4 d. Then a 10% solution of Na_2SO_3 was added (40 mL), the mixture was transferred to a separating funnel and decanted. The aqueous phase was extracted four times with dichloromethane. The organic phase was dried with Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude residue was purified by column chromatography. Elution with ethyl acetate/petroleum ether gave **4**.

Compound **4a** ($C_{10}H_{11}F_3INO_4S$, *M* = 425 g/mol) was prepared starting from **3a** (0.508 g, 1.69 mmol) and iodine (0.457 g, 1.8 mmol) and was obtained as a yellow solid, m.p. 111 °C (0.5386 g, 1.26 mmol, 74%). IR: $\tilde{\nu}$ = 1762 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.56 (d, *J* = 8 Hz, 7-H), 6.07 (br. s, 1 H, 1-H), 5.38 (m, 1 H, 6-H), 5.09 (ddd, *J* = 1.95, 1.9, 1.7 Hz, 1 H, 9-H), 2.51 (dd, *J* = 4.4, 1.9 Hz, 1 H, 5-H), 1.47 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7 (C=O), 119 (q, *J* = 300 Hz, CF_3), 120.5 (C-7), 109 (C-6), 84.6 (C-1), 46.3 (C-4), 44.0 (C-5), 27.1 (C-9), 26.0 (CH_3) ppm. MS (EI): *m*/*z* (%) = 425 (60) $[M]^+$, 338 (100) $[M - 87]^+$, 212 (40) $[M - 213]^+$.

Compound **4b** ($C_{13}H_{15}F_3INO_4S$, *M* = 465 g/mol) was prepared starting from **3b** (0.5 g, 1.47 mmol) and iodine (0.37 g, 1.47 mmol) and was obtained as a yellow solid, m.p. 132 °C (0.6626 g, 1.42 mmol, 96%). IR: $\tilde{\nu}$ = 1753 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.57 (d, *J* = 8.4 Hz, 1 H, 7-H), 6.04 (m, 1 H, 1-H), 5.37 (dt, *J* = 2.6, 1.9 Hz, 1 H, 6-H), 5.05 (d, *J* = 1.8 Hz, 1 H, 9-H), 2.90 (d, *J* = 6.3 Hz, 1 H, 5-H), 1.46–2.07 (m, 10 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7 (C=O), 119.4 (*J* = 319.3 Hz, CF_3), 120.8 (C-7), 108.3 (C-6), 83.8 (C-1), 50.1 (C-4), 38.5 (C-5), 33.5 (CH_2), 33.1 (CH_2), 32.4 (C-9), 25.1 (CH_2), 21.3 (CH_2), 20.7 (CH_2) ppm. MS (EI): *m*/*z* = 464 $[M - 1]^+$.



4a,**b**

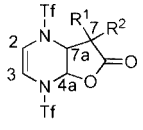
Synthesis of Lactones 6a and 6b from Pyrazine (5), and Lactone 8 from Quinoxaline (7): The same procedure as described for the synthesis of **3a** and **3b** was used. The crude was purified by column chromatography. Elution with ethyl acetate/petroleum ether gave **6** or **8**.

Compound **6a** ($C_{10}H_{10}F_6N_2O_6S_2$, *M* = 432 g/mol) was prepared starting from **5** (0.290 mL, 0.300 g, 3.74 mmol), trifluoromethane-

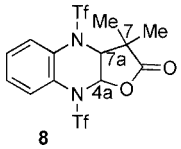
sulfonic anhydride (1.26 mL, 2.11 g, 7.49 mmol) and acetal **2a** (1 mL, 0.960 g, 4.11 mmol) and was obtained as a white solid, m.p. 128 °C (0.759 g, 1.76 mmol, 47%). IR: $\tilde{\nu}$ = 1809 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.39 (m, 2 H, 2-H and 3-H), 6.22 (d, J = 7.56 Hz, 1 H, 4a-H), 4.83 (d, J = 7.83 Hz, 1 H, 7a-H), 1.43 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.43 (C=O), 126, 121, 117, 113 (2 CF_3), 116.06 (C-2), 114.06 (C-3), 82.94 (C-4a), 66.25 (C-7a), 43.69 (C-7), 25.49 (CH_3), 20.11 (CH_3) ppm. MS (EI): m/z (%) = 432 (50) $[M]^+$, 299 (100) $[M - 133]^+$, 271 (30) $[M - 161]^+$, 229 (30) $[M - 203]^+$, 201 (40) $[M - 231]^+$.

Compound **6b** ($C_{13}H_{14}F_6N_2O_6S_2$, M = 472 g/mol) was prepared starting from **5** (0.485 mL, 0.500 g, 6.24 mmol), trifluoromethanesulfonic anhydride (2.1 mL, 3.52 g, 12.48 mmol) and acetal **2b** (3.4 mL, 3.4 g, 12.48 mmol) and was obtained as a white solid, m.p. 111 °C (1.472 g, 3.12 mmol, 50%). IR: $\tilde{\nu}$ = 1792 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.45 (d, J = 5.34 Hz, 1 H, 2-H), 6.36 (d, J = 5.49 Hz, 1 H, 3-H), 6.16 (d, J = 7.83 Hz, 1 H, 4a-H), 4.76 (d, J = 7.83 Hz, 1 H, 7a-H), 2.1–1.5 [m, 10 H, $(CH_2)_5$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.19 (C=O), 126, 121, 117, 113 (2 CF_3), 117.57 (C-2), 113.98 (C-3), 82.86 (C-4a), 67.28 (C-7a), 45.12 (C-7), 34.49, 29.23, 24.49, 20.94, 20.49 [$(CH_2)_5$] ppm. MS (EI): m/z (%) = 472 (40) $[M]^+$, 339 (100) $[M - 133]^+$, 311 (35) $[M - 161]^+$, 283 (5) $[M - 189]^+$, 213 (35) $[M - 259]^+$.

Compound **8** ($C_{14}H_{12}F_6N_2O_6S_2$, M = 482 g/mol) was prepared starting from **7** (0.27 mL, 0.300 g, 2.3 mmol), trifluoromethanesulfonic anhydride (0.775 mL, 1.3 g, 7.46 mmol) and acetal **2a** (0.59 mL, 0.590 g, 2.5 mmol) and was obtained as a white solid, m.p. 187 °C (0.454 g, 0.943 mmol, 41%). IR: $\tilde{\nu}$ = 1809 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.41 (m, 4 H, arom.), 6.66 (d, J = 7.56 Hz, 1 H, 4a-H), 5.09 (d, J = 7.68 Hz, 1 H, 7a-H), 1.42 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.39 (C=O), 130.14, 129.14, 127.17, 125.15 (arom.), 122.06, 121.33, 117.76, 117.07 (CF_3), 87.04 (C-4a), 70.54 (C-7a), 43.63 (C-7), 26.50 (CH_3), 19.42 (CH_3) ppm. MS (EI): m/z (%) = 482 (30) $[M]^+$, 349 (20) $[M - 133]^+$, 263 (100) $[M - 219]^+$, 130 (20) $[M - 352]^+$.



6a,b

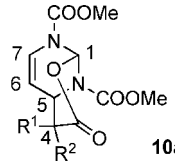


8

Synthesis of Lactones 10a and 10b from Pyrimidine (9): Methyl chloroformate (0.769 mL, 0.940 g, 10 mmol) in dichloromethane (10 mL) was slowly added at room temperature to a solution of bis(trimethylsilyl)ketene acetal **2a** or **2b** (3.5 mmol) and pyrimidine (**9**) (0.197 mL, 0.20 g, 2.5 mmol) in dichloromethane (40 mL). Stirring for 2 h followed by evaporation of the solvent gave an oil, which was purified by column chromatography. Elution with ethyl acetate/petroleum ether gave **10a** or **10b**.

Compound **10a** ($C_{12}H_{16}N_2O_6$, M = 284 g/mol) was obtained as an oil (0.30 g, 1.05 mmol, 42%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1 H, 1-H), 6.84 (d, J = 8 Hz, 1 H, 7-H), 5.31 (m, 1 H, 6-H), 4.42 (m, 1 H, 5-H), 3.84 (s, 6 H, OCH_3), 1.35 (s, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.85 (C=O), 151.48 (CO_2CH_3), 122.19 (C-7), 104.99 (C-6), 85.17 (C-1), 54.29 (OCH_3), 53.56 (C-5), 45.49 (C-4), 26.08 and 22.60 (CH_3) ppm. HRMS: calcd. for $C_{12}H_{17}N_2O_6$ [MH] 285.1087; found 285.1084.

Compound **10b** ($C_{15}H_{20}N_2O_6$, M = 324 g/mol) was obtained as an oil (0.730 g, 2.25 mmol, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (s, 1 H, 1-H), 6.83 (d, J = 8 Hz, 1 H, 7-H), 5.27 (m, 1 H, 6-H), 4.83 (m, 1 H, 5-H): 3.86 (s, 6 H, OCH_3), 1.18–1.76 [m, 10 H, $(CH_2)_5$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.40 (C=O), 151.90 (CO_2CH_3), 124.90 (C-7), 105.00 (C-6), 87.20 (C-1), 54.90 (OCH_3), 53.20 (C-5), 45.48 (C-4), 30.08–23.52 [$(CH_2)_5$] ppm. MS: calcd. for $C_{15}H_{21}N_2O_6$ [MH] 325; found 325.

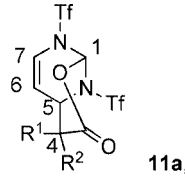


10a,b

Synthesis of Lactones 11a and 11b from Pyrimidine (9): The same procedure as described for the synthesis of **3a** and **3b** was used. The crude was purified by chromatography. Elution with ethyl acetate/petroleum ether gave **11**.

Compound **11a** ($C_{10}H_{10}F_6N_2O_6S_2$, M = 432 g/mol) was prepared starting from **9** (0.3 mL, 0.304 g, 3.8 mmol), trifluoromethanesulfonic anhydride (1.256 mL, 2.11 g, 7.5 mmol) and acetal **2a** (1.74 mL, 1.74 g, 7.5 mmol) and was obtained as a white solid, m.p. 78 °C (0.689 g, 1.59 mmol, 42%). IR: $\tilde{\nu}$ = 1774 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.14 (s, 1 H, 1-H), 6.67 (d, J = 8.67 Hz, 1 H, 7-H), 5.59 (m, 1 H, 6-H), 4.26 (d, J = 5.22 Hz, 1 H, 5-H), 1.49 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.17 (C=O), 125.58, 121, 117, 112.83 (CF_3), 121.55 (C-7), 107.07 (C-6), 87.01 (C-1), 56.31 (C-5), 44.94 (C-4), 25.75 (CH_3), 22.27 (CH_3) ppm. MS (EI): m/z (%) = 432 (5) $[M]^+$, 299 (30) $[M - 133]^+$, 213 (5) $[M - 219]^+$, 122 (10) $[M - 310]^+$, 70 (100) $[M - 362]^+$.

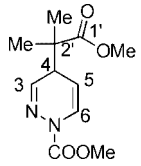
Compound **11b** ($C_{13}H_{14}F_6N_2O_6S_2$, M = 472) was prepared starting from **9** (0.3 mL, 0.300 g, 3.8 mmol), trifluoromethanesulfonic anhydride (1.26 mL, 2.11 g, 7.5 mmol) and acetal **2b** (2 mL, 2.04 g, 7.5 mmol) and was obtained as a white solid, m.p. 88 °C (0.986 g, 2.09 mmol, 55%). IR: $\tilde{\nu}$ = 1775 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.09 (s, 1 H, 1-H), 6.67 (d, J = 8.67 Hz, 1 H, 7-H), 5.56 (m, 1 H, 6-H), 4.60 (d, J = 5.22 Hz, 1 H, 5-H), 2.12–1.36 [m, 10 H, $(CH_2)_5$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.75 (C=O), 125.5, 121, 117, 113 (2 CF_3), 121.67 (C-7), 106.68 (C-6), 86.33 (C-1), 52.41 (C-5), 48.42 (C-4), 32.46, 30.71, 24.75, 20.71 $(CH_2)_5$ ppm. MS (EI): m/z (%) = 472 (5) $[M]^+$, 339 (40) $[M - 133]^+$, 213 (5) $[M - 259]^+$, 110 (100) $[M - 362]^+$.



11a,b

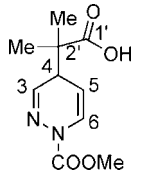
Synthesis of Ester 14a from Pyridazine (12): The same procedure as described for the synthesis of **10a** and **10b** was used. Compound **14a** was prepared starting from methyl chloroformate (0.769 mL, 0.940 g, 10 mmol), monosilylated ketene acetal **13** (0.710 mL, 0.609 g, 3.5 mmol) and pyridazine (**12**) (0.181 mL, 0.20 g, 2.5 mmol) as an oil, which was purified by column chromatography. Elution with ethyl acetate/petroleum ether gave **14a** ($C_{12}H_{16}N_2O_4$, M = 240 g/mol) as an oil (0.480 g, 2.0 mmol, 80%). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.88 (d, J = 8 Hz, 1 H, 6-H), 6.69 (m, 1 H, 3-H), 4.64 (m, 1 H, 5-H), 3.62 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3), 3.06 (m, 1 H, 4-H), 0.94 and 0.90 [s, 6 H, $(CH_3)_2$-C] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.00 (CCO_2CH_3),

152.5 (NCO_2CH_3), 143.3 (C-3), 124.9 (C-6), 101.7 (C-5), 53.9 (OCH_3), 52.10 (OCH_3), 47.0 (C-2′), 39.80 (C-4), 21.64 [$(CH_3)_2C$] ppm.



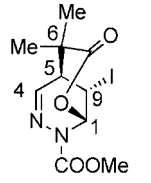
14a

Synthesis of Acid 15a from Pyridazine (12): The same procedure as described above was used. Compound **15a** was prepared starting from methyl chloroformate (0.579 mL, 0.708 g, 7.5 mmol), bis(trimethylsilyl)ketene acetal **2a** (1.74 mL, 1.74 g, 7.5 mmol) and pyridazine (**12**) (0.3 mL, 0.304 g, 3.8 mmol) as an oil, which was purified by chromatography. Elution with ethyl acetate/petroleum ether gave **15a** ($C_{10}H_{14}N_2O_4$, M = 226 g/mol) as a white solid, m.p. 124 °C (0.532 g, 2.38 mmol, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.00 (s, 1 H, COOH), 7.18 (d, J = 8 Hz, 1 H, 6-H), 6.96 (m, 1 H, 3-H), 4.96 (m, 1 H, 5-H), 3.91 (s, 3 H, OCH_3), 3.38 (m, 1 H, 4-H), 1.26 and 1.22 [s, 6 H, $(CH_3)_2C$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.7 (COOH), 152.6 (CO_2CH_3), 143.4 (C-3), 125.0 (C-6), 101.7 (C-5), 54.2 (OCH_3), 46.9 (C-2′), 39.5 (C-4), 21.5 [$(CH_3)_2C$] ppm. MS (EI): m/z (%) = 226 (3) $[M]^+$, 139 (100) $[M - 87]^+$, 95 (90) $[M - 131]^+$.



15a

Synthesis of Lactone 16a from Acid 15a: The same procedure as described for the synthesis of **4a** and **4b** was used. Compound **16a** was prepared starting from **15a** (0.3 g, 1.33 mmol) and iodine (0.68 g, 2.66 mmol). The crude residue was purified by column chromatography. Elution with ethyl acetate/petroleum ether gave **16a** ($C_{10}H_{13}IN_2O_4$, M = 352 g/mol) as a yellow solid, m.p. 116 °C (dec.) (0.370 g, 1.051 mmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 (s, 1 H, 1-H), 6.48 (s, 1 H, 4-H), 4.91 (m, 1 H, 9-H), 3.96 (s, 3 H, OCH_3), 2.66 (m, 1 H, 5-H), 1.45 and 1.47 [s, 6 H, $(CH_3)_2$-C] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (CO), 154.0 (CO_2CH_3), 142.1 (C-4), 80.91 (C-1), 54.7 (OCH_3), 46.2 (C-6), 45.2 (C-5), 27.5 (C-9), 25.7 [$(CH_3)_2C$] ppm. MS (EI): m/z (%) = 352 (20) $[M]^+$, 265 (7) $[M - 87]^+$, 181 (100) $[M - 171]^+$, 137 (70) $[M - 215]^+$.

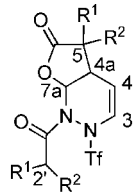


16a

Synthesis of Lactones 20a and 20b from Pyridazine (12): The same procedure as described for the synthesis of **3a** and **3b** was used. The crude was purified by chromatography. Elution with ethyl acetate/petroleum ether gave **20**.

Compound **20a** ($C_{13}H_{17}F_3N_2O_5S$, M = 370 g/mol) was prepared starting from **12** (0.275 mL, 0.304 g, 3.8 mmol), trifluoromethanesulfonic anhydride (1.26 mL, 2.11 g, 7.5 mmol) and acetal **2a** (1.74 mL, 1.74 g, 7.5 mmol) and was obtained as a white solid, m.p. 94 °C (0.274 g, 0.741 mmol, 20%). IR: $\tilde{\nu}$ = 1786 (C=O lactone), 1720 (NCO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (d, J = 8 Hz, 2 H, 3-H and 7a-H), 5.43 (dd, J = 8, 3 Hz 1 H, 4-H), 3.19 (m, 1 H, 2′-H), 2.89 (m, 1 H, 4a-H), 1.44 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.22 (d, J = 7 Hz, 3 H, CH_3), 1.08 (d, J = 7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.91 (C=O lactone), 176.89 (NC=O), 125.88 (C-3), 112.59 (C-4), 80.76 (C-7a), 45.17 (C-5), 41.92 (C-4a), 30.90 (C-2′) 25.62 (5-CH_3), 20.56 (5-CH_3), 19.77 (2′-CH_3), 18.56 (2′-CH_3) ppm. MS (EI): m/z (%) = 370 (5) $[M]^+$, 237 (10) $[M - 133]^+$, 213 (100) $[M - 157]^+$, 167 (50) $[M - 203]^+$.

Compound **20b** ($C_{19}H_{125}F_3N_2O_5S$, M = 450 g/mol) was prepared starting from **12** (0.275 mL, 0.304 g, 3.8 mmol), trifluoromethanesulfonic anhydride (1.26 mL, 2.11 g, 7.5 mmol) and acetal **2b** (2 mL, 2.04 g, 7.5 mmol) and was obtained as a white solid, m.p. 114 °C (0.530 g, 1.178 mmol, 31%). IR: $\tilde{\nu}$ = 1777 (C=O lactone), 1709 (NCO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.95 (d, J = 8 Hz, 1 H, 3-H), 6.87 (d, J = 6 Hz, 1 H, 7a-H), 5.43 (dd, J = 8, 3 Hz, 1 H, 4-H), 3.08 (m, 1 H, 2′-H), 2.87 (m, 1 H, 4a-H), 1.85–1.25 (m, 20 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.90 (C=O lactone), 175.92 (NC=O), 126.46 (C-3), 112.15 (C-4), 80.75 (C-7a), 49.44 (C-5), 40.79 (C-4a), 38.50 (C-2′), 32.70, 29.89, 29.19, 28.30, 25.71, 25.54, 25.04, 24.91, 22.44, 21.96 (CH_2) ppm. MS (EI): m/z (%) = 450 (3) $[M]^+$, 317 (5) $[M - 133]^+$, 213 (100) $[M - 237]^+$.



20a,**b**

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