Bis(trimethylsilyl)ketene Acetals as C,O-Dinucleophiles: One-Pot Formation of Polycyclic γ- and δ-Lactones from Pyridines and Pyrazines

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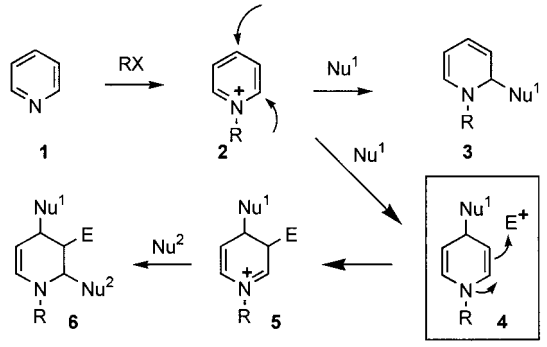
Keywords: Bis(trimethylsilyl)ketene acetals / Pyridines / Methyl chloroformate / Nucleophilic additions / γ- and δ-lactones / Pyrazines

Bis(trimethylsilyl)ketene acetals react with pyridines, quinoline and isoquinoline in the presence of stoichiometric amounts of methyl chloroformate to give the corresponding dihydropyridine-, dihydroquinoline- and dihydroisoquinoline-substituted carboxylic acids in satisfactory yields. The regio- and diastereoselectivities of the addition reactions, together with the presence or absence of rotamers, have been established. The isolated acids react with peracids to give β-hydroxy-δ-lactones through an intramolecular reaction. Similar lactonizations could also be brought about directly from the azaaromatic compounds in one-pot reactions with silica gel, iodine or bromine. In these cases δ-lactones or β-halo-δ-lactones were produced. The behaviour of pyrazines in these transformations is peculiar, since methyl chloroformate on its own induces the formation, through interaction with both nitrogen atoms, of polycyclic γ-lactones, a reaction formally reminiscent of the double nucleophilic addition of the same ketene acetals to (arene)tricarbonylchromium complexes. Most of the new structures were assigned through X-ray crystal structure determinations.

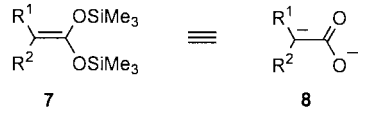
Introduction

Pyridines are versatile starting materials for the synthesis of complex heterocyclic compounds. Among their reactions, the addition of nucleophiles attracted our attention especially: it is known that pyridine (**1**) and its derivatives, once activated as in **2** (Scheme 1), react with a large variety of nucleophiles to afford substituted dihydropyridines **3** and **4**.[1–8] Moreover, the resulting dihydropyridines can in turn be reactivated via iminium intermediates **5** to undergo second nucleophilic additions. These finally yield highly substituted tetrahydropyridines **6**, products of overall double nucleophilic addition reactions on the azaaromatic frameworks, used in pioneering work by Wenkert[9] for crucial steps in the synthesis of alkaloids and also by Lavilla[10,11] in both inter- and intramolecular ways for the synthesis of polycyclic systems starting from pyridines.

There were two points of interest in this regard for our ongoing chemistry. The first was the *formation of dihydropyridines* through *mononucleophilic* addition reactions, since we had demonstrated that, besides the established importance of dihydropyridine derivatives as therapeutic agents,[12–14] such compounds could also be used for the biomimetic reduction of Fischer carbene complexes.[15–17] The second was the *dinucleophilic addition reactions*, since we had discovered that bis(trimethylsilyl)ketene acetals **7** constitute an original class of ketene acetals among nucleophiles,[18–21] as they can behave as *1,3-carbon,oxygen dinucleophiles* **8** in one-pot reactions, as the result of successive cleavage of both oxygen–silicon bonds (Scheme 2).



Scheme 1.



Scheme 2.

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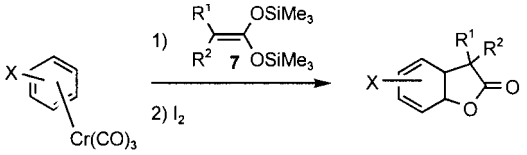
 DOI: 10.1002/ejoc.200500162

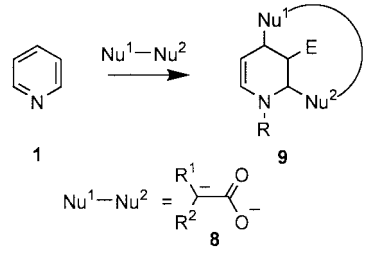
This special reactivity allowed us to synthesize, inter alia, γ-lactones, through formal [2+3] cycloadditions of these dinucleophiles to suitably activated carbon–carbon double bonds in (arene)tricarbonylchromium complexes (Scheme 3), in tricarbonyl(triene)chromium complexes and in (π-allyl)palladium complexes.[22–27]



Scheme 3.

Common to all of these transformations are the following features: *transition metals are involved* stoichiometrically or catalytically either in one or in the two steps of the nucleophilic additions, and carboxylic acids or their derivatives can be isolated as intermediates in the first steps of these reactions.

In the case of azaaromatic compounds, this approach might lead, *without any metal*, to polycyclic lactones **9**, since the two nucleophilic centres (Nu^1–Nu^2 = **8**) are potentially already present in the starting ketene acetals **7** (Scheme 4). Confirmation of this hypothesis was reported in a preliminary communication.[28]



Scheme 4.

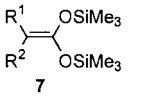
The purpose of this paper is firstly to describe and establish the scope and the limits of the first step in these transformations, the monoaddition of bis(trimethylsilyl)ketene acetals to pyridines, quinoline and isoquinoline, and secondly to outline the one-pot transformations of the same substrates and pyrazines into polycyclic δ- and γ-lactones.

Results and Discussion

Formation of Acids

Reaction of Pyridines with the Bis(trimethylsilyl) Ketene Acetals 7a–j Derived from Saturated Carboxylic Acids – Scope of the Reaction

Enol ethers and a few alkyl(trimethylsilyl)ketene acetals have been shown by Akiba to add to pyridines in the presence of methyl chloroformate to afford 4-oxoalkyl- and 4-carbalkoxy-substituted pyridines regioselectively after oxidation.[29,30] On the other hand, the addition of ketone enolates to pyridinium triflates has also been outlined.[31] However, the general, direct formation of carboxylic-substituted pyridines through the use of bis(trimethylsilyl)ketene acetals had not been described to the best of our knowledge, although an early example of the addition of the bis(trimethylsilyl)ketene acetal **7a** derived from acetic acid and giving the corresponding ester has been outlined.[32] We therefore treated pyridine and a series of substituted pyridines, quinoline and isoquinoline with the ketene acetals **7a–j** derived from saturated carboxylic acids,[33] bearing various substituents on the α-carbon atom, and also with those derived from unsaturated carboxylic acids **7k–o**.



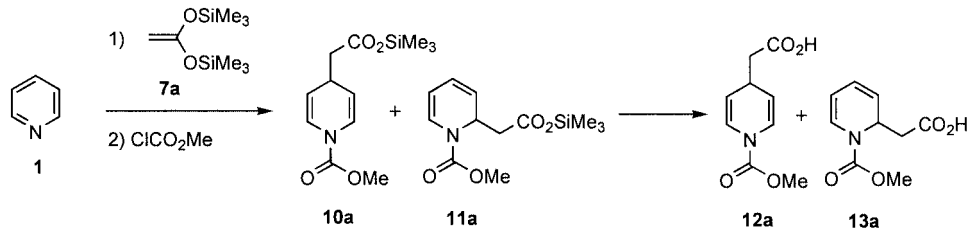
7

a $R^1 = R^2 = H$
b $R^1 = R^2 = Me$
c $R^1\ R^2 = (CH_2)_5$
d $R^1 = H\ R^2 = Me$
e $R^1 = H\ R^2 = Et$
f $R^1 = H\ R^2 = i$Pr
g $R^1 = H\ R^2 = t$Bu
h $R^1 = H\ R^2 = Ph$
i $R^1 = H\ R^2 = SiMe_3$
j $R^1 = H\ R^2 = OPh$
k $R^1 = H\ R^2 = CH{=}CH_2$
l $R^1 = Me\ R^2 = CH{=}CH_2$
m $R^1 = H\ R^2 = MeC{=}CH_2$
n $R^1 = H\ R^2 = CH_2CH{=}CH_2$
o $R^1 = H\ R^2 = (CH_2)_2CH{=}CH_2$

Five types of reactions have been examined: (1) those involving the simplest ketene acetal **7a** ($R^1 = R^2 = H$) and pyridine and affording C-2 and C-4 regioisomers, each as a mixture of rotamers;[34,35] (2) those involving symmetrically substituted ketene acetals [e.g., **7b**, $R^1 = R^2 = Me$ or **7c**, $R^1R^2 = (CH_2)_5$], which gave single isomers, again as mixtures of rotamers; (3) those involving monosubstituted ketene acetals, such as **7h** ($R^1 = H$, $R^2 = Ph$), which also gave single regioisomers but could give pairs of observable diastereoisomers (for substituted pyridines) through the formation of two adjacent stereogenic centres; (4) those involving substituted pyridines (e.g., 2-methylpyridine), which in the case of $R^1 = R^2 = Me$ gave single isomers as apparently unique rotamers but which for $R^1 \neq R^2$ might give pairs of observable diastereoisomers due to the fact that two adjacent stereogenic centres are formed; and (5) those involving pyridines bearing an electron-attracting substituent, which gave single isomers, in most cases with no discernible rotamers.

Reactions with Pyridine

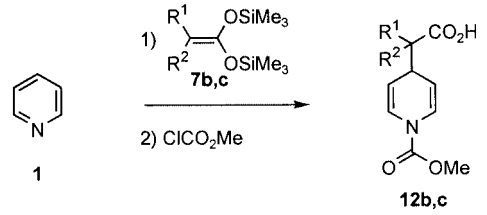
When methyl chloroformate was added to a solution of pyridine (**1**) and bis(trimethysilyl)ketene acetal **7a** in dichloromethane at room temperature, the formation of two fairly polar, separable products was observed. According to their physical data, these compounds are, as expected, two *regioisomers* (Scheme 5). The ^{1}H NMR spectrum of each isomer, taken at room temperature, was in agreement with the presence of a 1:1 mixture of two *rotamers*. In the case of the more abundant isomer **12a** (48%) this was supported by signals appearing for the two C(2)–H protons as two distinct broad doublets at $\delta = 6.68$ and 6.81 ppm ($J = 8$ Hz), all other protons giving single yet rather broad signals. This is also apparent in the ^{13}C NMR spectrum, since the carbon atoms of the two double bonds gave rise to four distinct signals, at δ = 123.2, 123.6 and 108.2, 108.6 ppm. The NMR spectrum of the minor product **13a** (20%), showing four vicinal protons of the 1,2-dihydropyridine, was also in agreement with the presence of two rotamers. It is noteable



Scheme 5.

that the intermediate trimethylsilyl esters **10a** and **11a** could be detected by NMR prior to hydrolysis.

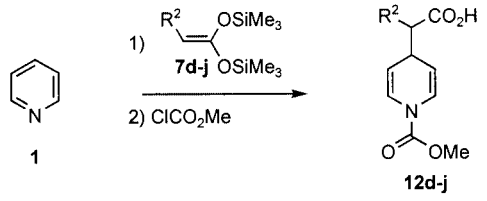
The symmetrically substituted ketene acetals **7b** and **7c** [$R^1 = R^2 = Me$, $R^1R^2 = (CH_2)_5$], however, gave single products, again as 1:1 mixtures of two rotamers (Scheme 6).



Scheme 6.

Fast rotamer interconversion occurred upon heating of chloroform solutions of **12b** to 50 °C (see Supporting Information).

In the cases of the monosubstituted ketene acetals **7d–j** ($R^1 = H$, R^2 = Me, Et, *i*Pr, *t*Bu, Ph, $SiMe_3$, OPh), the outcomes of the reactions (Scheme 7) were simpler than expected: only one regioisomer was formed, as two rotamers, in each instance. Especially diagnostic were the signals in



Scheme 7.

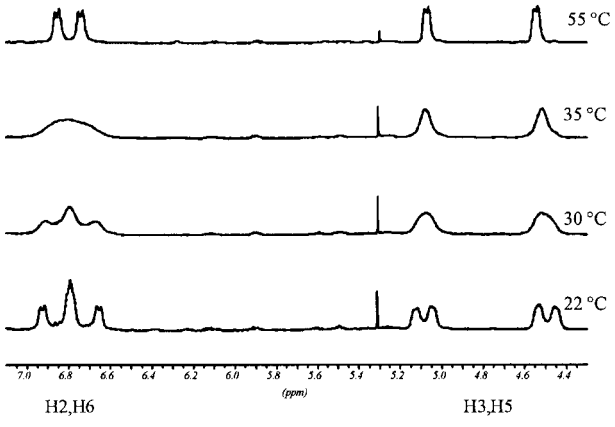
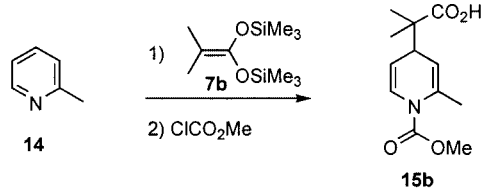


Figure 1. ^{1}H NMR (400 MHz) spectra of **12h** at various temperatures.

the ^{13}C NMR spectra, since the carbon atoms of the two double bonds gave rise to four specific signals. Heating of an NMR sample of **12h** at 55 °C simplified its spectra to a great extent (Figure 1), with four distinct signals for the vinylic protons indicating the presence of a stereogenic centre.

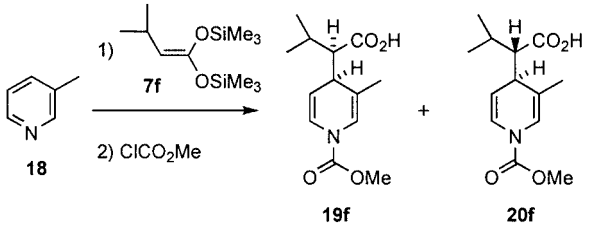
Reactions with Substituted Pyridines

Deactivation of the pyridine nucleus towards nucleophilic additions is generally observed for electron-donating substituents in the sequence C-3 < C-2 < C-4. Nevertheless, the expected addition products were obtained. Thus, 2-picoline (**14**) reacted with the ketene acetal **7b** ($R^1 = R^2$ = Me) to give a single product **15b** as an oil in 70% yield (Scheme 8).



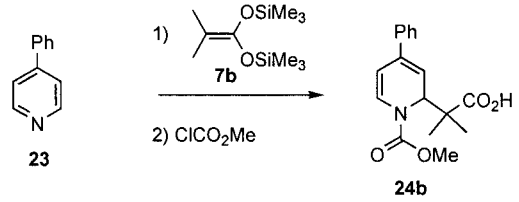
Scheme 8.

The ^{1}H NMR spectrum showed sharp signals for all the protons, an indication of the absence of rotamers. This was also confirmed by the ^{13}C NMR spectrum, since all the signals were single. Clearly, rotation around the partial C–N double bond is completely inhibited by the presence of the α-methyl group. A similar result was observed for 2-vinylpyridine **16**, which gave **17** (see Exp. Sect.). Interestingly, 3-picoline (**18**) and the monosubstituted ketene acetal **7f** (R^2 = *i*Pr) (Scheme 9) gave a 65% yield of a separable mixture of two diastereomeric C-4 addition products **19f** and **20f** (de, 86%) and, as expected, 4-picoline gave only a very low (10%) yield of an unstable C-2 addition product.

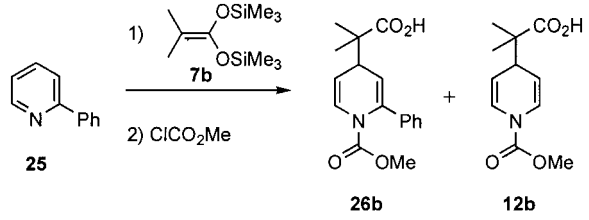


Scheme 9.

As far as pyridines **21**, **23** and **25**, each bearing the electron-withdrawing phenyl group, are concerned, by far the best result was obtained with 3-phenylpyridine (**21**), with the C-4 addition product **22b** being isolated in 90% yield. Whilst 4-phenylpyridine (**23**) provided a single C-2 addition product **24b** in a low (30%) yield (Scheme 10), 2-phenylpyridine (**25**) surprisingly reacted only in dichloromethane at reflux, sluggishly affording (20% yield) a 1:1 mixture of the expected acid **26b** and of **12b**, the result of the loss of the phenyl substituent [36–38] (Scheme 11).

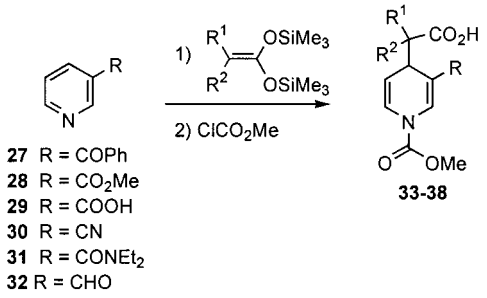


Scheme 10.



Scheme 11.

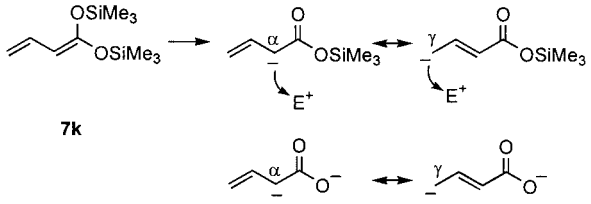
The introduction of more strongly electron-withdrawing groups was expected to have two opposite effects: (1) such pyridines are less prone to react with methyl chloroformate, whilst (2) in contrast, once activated as a pyridinium chloroformates, they should be more reactive towards nucleophiles. A third effect might be observable by NMR in the form of a lowering of the barrier to rotation around the N–C double bond and as a consequence, the absence of rotamers at room temperature. This was indeed the case. Thus, treatment of a series of 3-substituted pyridines (**27**, R = COPh; **28**, R = CO_2Me; **29**, R = CO_2H, **30**, R = CN; **31** R = $CONEt_2$; **32**, R = CHO) with the ketene acetals [R^1 = R^2 = Me, R^1R^2 = $(CH_2)_5$] provided the expected 3,4-disubstituted pyridines **33**–**38** in good to medium yields (90–42%) (Scheme 12). 3-Benzoylpyridine and **7b**, for example, afforded the expected C-4 addition product **33b**. Unlike in the previous examples, the various vinylic protons gave rise to sharp signals, and no splitting of the signals for the carbons of the double bonds was observed. It is thus clear that fast rotation around the C–N bond of the carbamate takes place even at room temperature. It is worthwhile to note here that no Mukaiyama-type[19,20] reaction was observed in the case of 3-pyridinecarboxaldehyde (**32**), which gave the expected C-4 addition product **38c**. Because of steric hindrance, no rotamers were observed in the case of the C-4 addition product **40b** (30% yield) originating from 2-benzoylpyridine (**39**), whereas methyl pyridine-4-carboxylate (**41**) gave a 2:1 inseparable mixture of the C-2 and C-4 isomers **42b** and **43b** (90%) and 4-cyanopyridine (**44**) yielded a 1:1 mixture of **45b** and **46b** (70%) (vide infra).



Scheme 12.

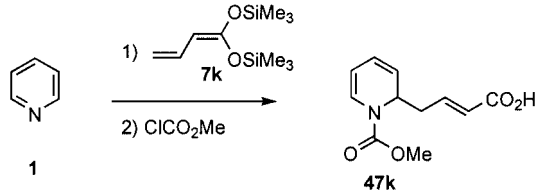
Reactivity of Pyridines towards Ketene Acetals 1k–o Derived from Unsaturated Acids

Depending on the reaction conditions, electrophiles react with enolates originating from conjugated ketene acetals such as **7k** to give either α- or γ-addition products (kinetic vs. thermodynamic addition)[39–44] (Scheme 13). We had already observed that such ketene acetals could also behave as 1,3-dinucleophiles since they add at low temperature to, for example, (arene)tricarbonylchromium complexes to give γ,δ-unsaturated γ-lactones.[23,24] At room temperature, however, the same treatment gave α,β-unsaturated acids as the result of γ-monoaddition reactions, so we investigated the behaviour towards pyridine of a series of ketene acetals **7k**–**o** derived from but-3-enoic, 2-methylbut-3-enoic, 3-methylbut-3-enoic, pent-4-enoic and hex-5-enoic acids.



Scheme 13.

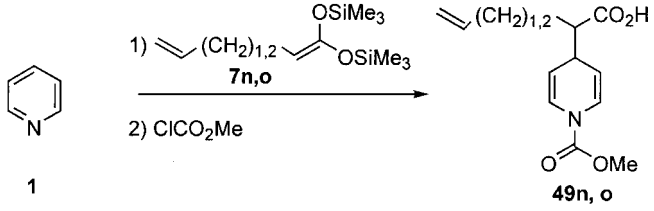
In the cases of the ketene acetals **7k**–**m**, only products originating from the γ-addition to the C-2 position of pyridine were observed both at low temperature and at room temperature (Scheme 14).



Scheme 14.

According to their ^{13}C NMR spectra, these products are indeed both conjugated carboxylic acids and 1,2-dihydropyridines, with the carbon atoms of the two conjugated

double bonds in **47k** giving split signals at δ = 125.49 and 124.93, 106.34 and 105.91, 122.43 and 122.84, and 121.21 and 121.05 ppm, which again indicates the presence of rotamers. Deactivation of the pyridine nucleus – as in nicotinamide, for instance – did not change the course of the reaction since an 85% yield of the C-2 addition product **48k** was formed (see the Exp. Sect.). As expected, the ketene acetals derived from pent-4-enoic and hex-5-enoic acids gave the C-4 addition products **49n** and **49o** in 85 and 55% yields, respectively, each as two rotamers (Scheme 15).



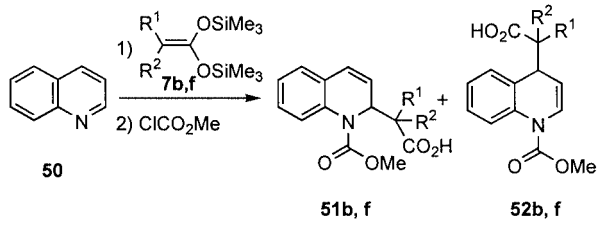
Scheme 15.

Reactions of Bis(trimethylsilyl)ketene Acetals with Quinolines and Isoquinolines

One of the drawbacks of most of the *protected* dihydropyridines described up to now is their instability.[1,10] Indeed, easy degradation through aerial oxidation most often takes place (vide infra). Since dihydroquinolines and dihydroisoquinolines are known to be more stable than simple dihydropyridines,[45] yet reactive enough to reduce carbene complexes,[46] and as the addition products are also potentially important targets, attempts were made to introduce acid functions in these substrates directly.

As already established for carbon nucleophiles,[47,48] the ketene acetal **7a** gave a single C-2 addition product **51a** in 90% yield with quinoline (**50**) (Scheme 16). However, **7b** and **7f** gave separable mixtures of the C-2 and C-4 isomers, their respective ratios depending on the natures of the substituents (Scheme 17).

Scheme 16.



Scheme 17.

Moreover, in this latter example, each regioisomer was formed as a mixture of diastereoisomers (*de* 30% for **51f**), which were also separated in the case of the more abundant **51f**.

Crystals of **51f** (R^1 = H, R^2 = *i*Pr) suitable for an X-ray determination could be grown. A DIAMOND projection of this compound appears in Figure 2. Three points are worthy of comment: (1) the six atoms C(2), C(10), C(16), O(3), O(4) and N(1) are almost coplanar, the sum of the angles around the nitrogen atom being equal to 356°, an observation that reflects the delocalization of the nitrogen doublet with formation of an N–C double bond [N(1)–C(16) = 1.363(3) Å] and a C–O single bond [C(16)–O(3) = 1.207(3) Å], (2) the introduced substituent at C-2 and the carbamate function are in a *trans*-opposite relationship with respect to the plane of the bicyclic system, so no intramolecular hydrogen bond can exist between the acid and the carbamate, and (3) an intermolecular hydrogen bond exists between one acid group and the carbonyl group of the carbamate of a second molecule, giving rise to a zig-zag arrangement in the crystal lattice (Figure 3).

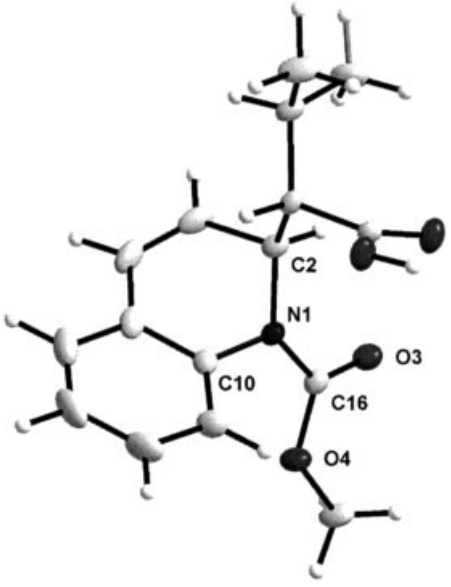


Figure 2. DIAMOND view of compound **51f**.

It is thus likely, as confirmed by NMR, that this compound exists as a single rotamer for steric reasons, the carbamate being in a constraint geometry with the methoxy group oriented towards the aromatic ring.

The behaviour towards ketene acetals derived from unsaturated carboxylic acids has also been examined: these gave the expected C-2 addition products in good to excellent yields (75–95%). In the case of the conjugated ketene acetal **7k** the thermodynamic product **53k** was obtained (Scheme 18; no rotamers present at room temperature), but **7m** produced **53m** as an inseparable mixture of two isomers around the carbon–carbon double bond of the conjugated acid. For the pentenoic acid derived ketene acetal **7n** a 3:1

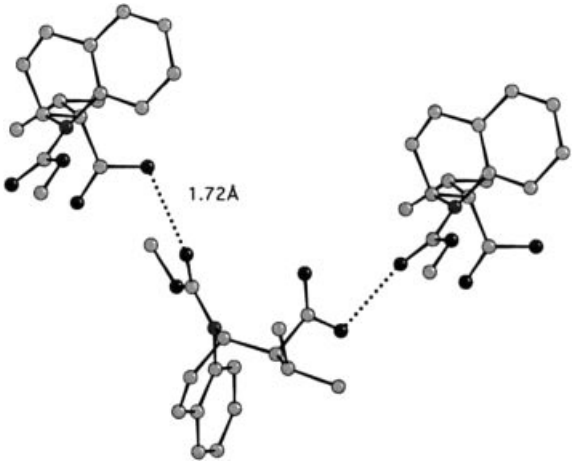
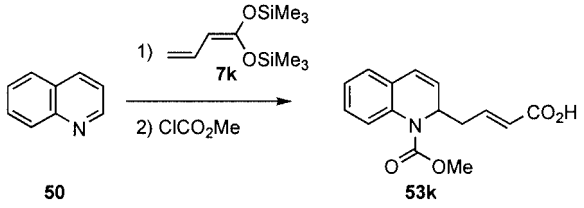


Figure 3. Evidence for intermolecular hydrogen bonds in compound **51f**.

mixture of the C-2 and C-4 addition products **54n** and **55n** (95% yield), each as two diastereoisomers, was isolated (Scheme 19).



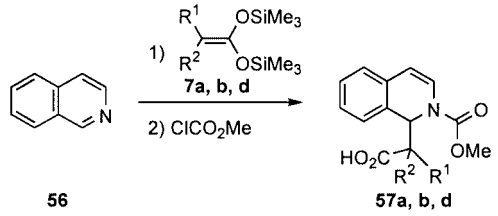
Scheme 18.

Isoquinoline (**56**) in turn gave, as expected, only the C-1 addition products with **7a**, **7b** and **7d**. At room temperature these exist either as two rotamers (in the case of **57a**, R^1 = R^2 = H) or, for bulky substituents such as in **57b** (R^1 = R^2 = Me), as single rotamers (Scheme 20).

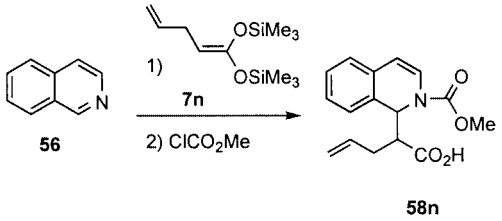
Diastereoisomers were obtained in the cases of the monosubstituted ketene acetals **7d** (R^1 = H, R^2 = Me, **57d**; *de* 20%) and **7n** (R^1 = H, R^2 = allyl, **58n**; *de* 90%, Scheme 21), each as two rotamers.

Finally, **7k** gave the C-1 addition adduct **59k** as two rotamers (Scheme 22).

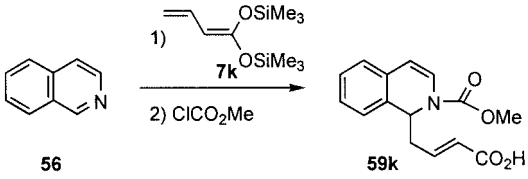
It therefore appears that (1) the addition of ketene acetals of type **7** to nitrogen-containing aromatic compounds can be regarded as a transformation of broad scope, providing new carboxylic acid substituted dihydropyridines, -quinolines and -isoquinolines, some of the reactions taking place with high diastereoselectivity, and (2) no special activation of the ketene acetals is necessary, since the various acylated



Scheme 20.



Scheme 21.

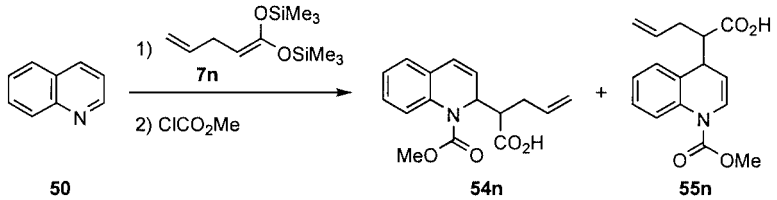


Scheme 22.

pyridines are electrophilic enough to react per se, though the role of the chloride ions probably has to be taken into account in the activation step.

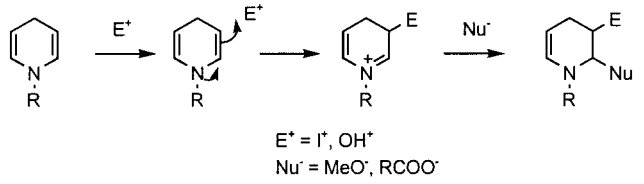
Transformation of Pyridines and Derivatives into Lactones

A parallel between the interaction of bis(TMS)ketene acetals with (arene)tricarbonylchromium complexes and their interaction with pyridines in carbon–carbon bond-formation reactions had already been sketched out. In the first case activation is linked to the coordination of the metal ion to the double bonds, whilst in the second case activation is the result of interaction between the nitrogen atom and methyl chloroformate. For the oxygen–carbon bond formation, the key point, in the case of (arene)chromium complexes, is the interaction of the intermediate anionic complex with an electrophile (oxidant), iodine, and the simultaneous cleavage of the remaining silicon–oxygen bond. This affords a bicyclic γ-lactone.[22,23] Pioneering work on *nonbiomimetic* transformations of dihydropyridines in their interaction with various oxidants (electrophiles E^+) has been reported in a series of recent papers by Lavilla and co-



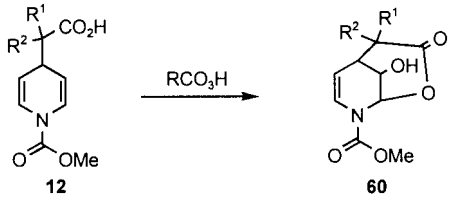
Scheme 19.

workers.[10,11,49,50] Among those directly related to the transformation of carboxylic acid bearing dihydropyridines into lactones are their reactions with iodine in the presence of nucleophiles and with peracids RCO_3H. In the intermolecular version this gave rise to successive electrophilic (I^+, HO^+) and nucleophilic (MeO^-, RCO_2^-) addition reactions onto the dihydropyridine carbon–carbon double bonds (Scheme 23).



Scheme 23.

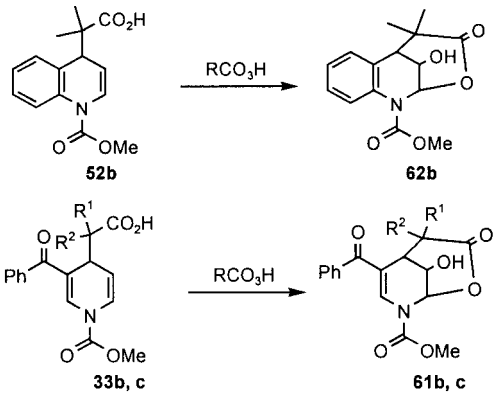
Since 1,4-dihydropyridines are known to react with *m*-chloroperbenzoic acid to give *trans*-hydroxy esters upon *intermolecular* transient epoxide opening reactions induced by *m*-chlorobenzoic acid,[10] we could reasonably expect double nucleophilic additions of bis(trimethyl)ketene acetals to pyridines and related heterocycles. In other words, acids of the general structure **12** (Scheme 24) might provide lactones **60** under the same conditions, the *intramolecular* reaction prevailing over the intermolecular reaction. This was indeed confirmed and has appeared in a preliminary communication.[28]



Scheme 24. Hydroxylactonisation reactions.

Thus, addition of 1.2 equiv. of *m*-chloroperbenzoic acid to a dichloromethane solution of the acid **12b** gave, after 2 h at room temperature and silica gel purification, a viscous oil (75%). According to the ^1H NMR spectrum, no *m*-chlorobenzoate substituent was present in the new compound, which, however, contained only one double bond (NCH=: δ = 6.81 and 6.91 ppm; CH=: δ = 5.08 and 5.15 ppm) and existed as two rotamers. The presence of a lactone was confirmed by the ^{13}C NMR spectrum, which exhibits – besides signals at δ = 152.70 and 152.83 ppm – a signal at δ = 174.05 ppm. Moreover, a signal typical of the NCHO proton of a lactone appears at δ = 6.25 and 6.40 ppm (δ = 80.83 and 81.21 ppm). Signals for a secondary alcohol at δ = 4.79 ppm (δ = 45.60 ppm), together with H–H and H–C NMR experiments, corroborated structure **60b**.

A few other examples confirmed the general behaviour of these acids towards peracids. Thus, under the same conditions, the quinoline-derived acid **52b** gave the hydroxy lactone **62b** in 30% yield, whereas the deactivated dihydropyridines **33b** and **33c** afforded the hydroxy lactones **61b** and **61c** in 50 and 35% yields, respectively (Scheme 25).



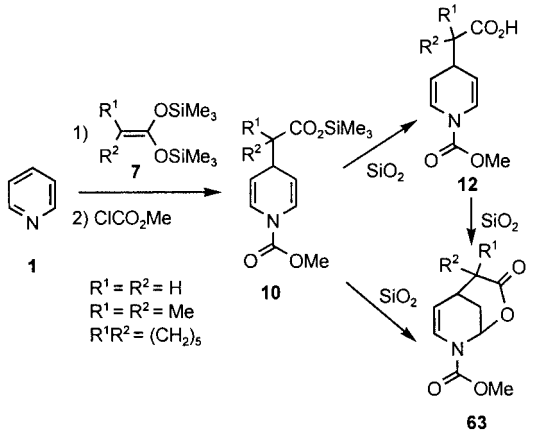
Scheme 25.

Protolactonisation Reactions

Though the transformation of the dihydropyridine-substituted acids into hydroxylactones is interesting, the need for isolation and purification of the rather unstable acids (vide supra, Scheme 24) prior to their interaction with a peracid was a drawback. The search for a direct, one-pot transformation of the pyridines into lactones was therefore essential, but attempts to transform the acids into lactones by the classical protolactonization reaction failed.[51,52]

The following observations gave us a first solution to this problem: the interaction of the ketene acetal **7b** with pyridine in the presence of methyl chloroformate afforded the expected dihydropyridine **12b** (vide supra) after *fast* silica gel chromatography, but during longer lasting purifications by the same technique, a second, slightly more polar, product (m.p. 108 °C, 5–10% yield) was isolated as a white solid. The ^1H NMR spectrum confirmed that only one single disubstituted carbon–carbon double bond remained in the new product. Indeed, signals for the NCH= and the CCH= protons appear, as in the dihydropyridine **12b**, at δ = 6.71 and 6.83 ppm (as two doublets) and at δ = 5.15 (complex signal), respectively. The shapes and the multiplicities of these signals agree with the presence of rotamers. Two new singlets, each due to one proton, appear at low field, at δ = 6.27 and 6.41 ppm, whereas three high-field signals are also observed. The ^{13}C NMR data confirmed the presence of the methoxycarbonyl group but also of a new signal for a carbonyl group at δ = 176.21, different from the carbonyl group of the acid **12b** (δ_C = 183.60 ppm), and also of a methylene group at δ = 27.33 ppm. H–H and C–H COSY NMR spectra finally allowed structure **63b** to be assigned to this new compound (Scheme 26).

It is likely that the double bond of the dihydropyridine behaves as an ene carbamate, which is protonated on silica gel to give an electrophilic iminium salt. This interacts intramolecularly with the carboxyl group to give a δ-lactone. The yield of this transformation could be improved firstly by heating the isolated acid **12b** either in dichloromethane or in benzene in the presence of silica gel (**12b**: SiO_2 = 2×10^{-3} mol: 1.5 g): this indeed provided the lactone **63b** in much better yield (90% conversion by NMR) but upon purification only 40% of the lactone could be recovered. Sec-



Scheme 26.

ondly, silica gel could just be added to the crude trimethylsilyl ester **10b**: *this constituted the standard procedure* since it provided the lactone **63b** much more rapidly (24 vs. 48 h) in an almost quantitative yield. Similarly, treatment of either the acid or its precursor with a molar solution of HCl in diethyl ether (1 equiv.) provided an 80% yield (by NMR) of the same lactone at room temperature after 4 h. This latter reaction appeared to be reversible, however, as evidenced by the formation of the corresponding acid upon evaporation of the solvent.

Scope of the Reaction: Transformation of the Esters 10a–d and 10f into the Lactones 63a–d and 63f – X-ray structures of the Lactones 64b and 66b

The transformation of these esters into the related lactones was general in scope, and the yields of the reactions, under the standard conditions established for the preparation of **63b**, were dependent on the natures of the substituents R^1 and R^2 on the ketene acetals: the bulkier the substituents, the better the yields. This was also confirmed in the case of 3-methylpyridine (**18**), which gave **64a** and **64b**. The presence of a phenyl group on the pyridine ring increased the yield of the transformation even further (**21** → **65b**, 80%). Finally, the structures of these new lactones could be assessed through an X-ray crystal analysis of **64b**. A CAMERON projection (Figure 4) confirms the formation of the six-membered lactone, with the two hydrogen atoms at the ring junction in a *cis* relationship. Moreover, no major steric hindrance would impede the free rotation of the methoxycarbonyl group, consistent with the presence, according to the NMR spectra, of two rotamers at room temperature.

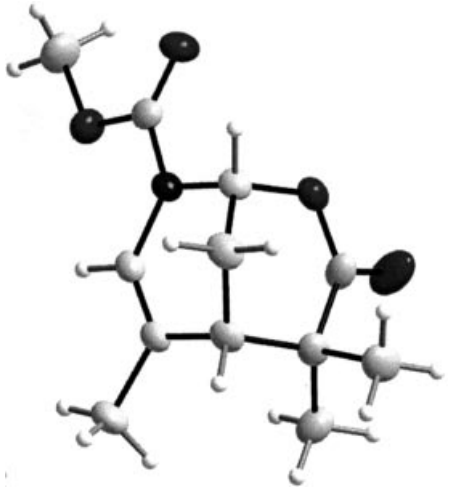
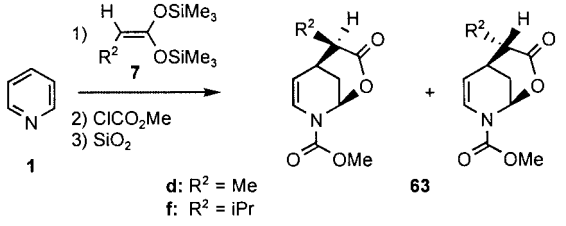


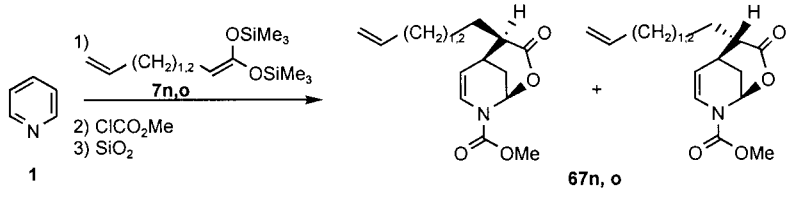
Figure 4. DIAMOND view of compound **64b**.

Further examples warrant a comment. Firstly, the transformations of **10d** and **10f** generated by treatment of pyridine with **7d** and **7f** and containing a stereogenic and a prostereogenic centre, gave, as expected, mixtures of two diastereoisomers [**63d** (4:1), separable in the case of **63f** (10:1)] (Scheme 27). Secondly, although an extra double bond potentially capable of undergoing a lactonization reaction was present in the acids **49n** and **49o**, the only isolated products corresponded to **67n** and **67o**, again as mixtures of diastereoisomers (5:2) (Scheme 28).



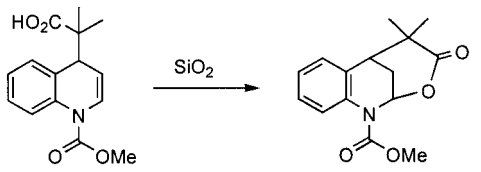
Scheme 27.

The one-pot transformations of quinoline and isoquinoline were also examined. As far as quinoline was concerned, the two acids **51b** and **52b** were separately subjected to the standard conditions: **52b** ($R^1 = R^2 = Me$) gave a separable mixture of the starting acid and the corresponding lactone **66b** (32% yield) (Scheme 29), the structure of which was again established by X-ray diffraction analysis (Figure 5).



Scheme 28.

No lactone, however, was formed from **51b**. Similarly, isoquinoline, which afforded only C-1 addition acids, did not produce lactones.



Scheme 29.

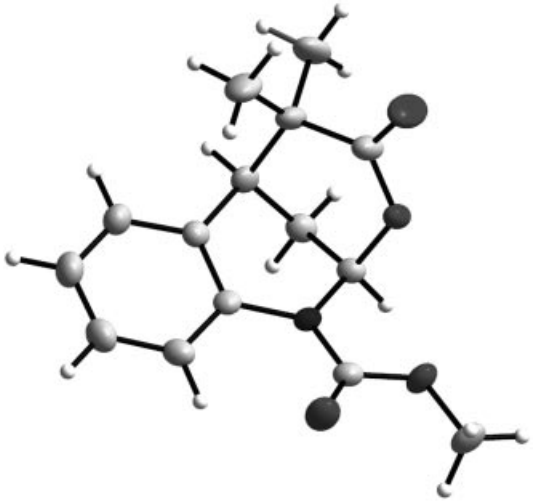
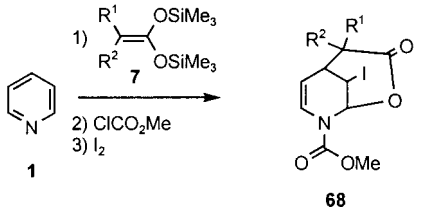


Figure 5. DIAMOND view of compound **66b**.

Iodo- and Bromolactonization Reactions: Peculiar Behaviour of Bromine

One of the major and best studied transformations of γ,δ-unsaturated carboxylic acids is their conversion into halolactones in the presence of either iodine or bromine.[53] This can be carried out in the presence or in the absence of water and a base. These transformations have even been extended to unsaturated esters, alkylsilyl esters among them.[53] This reaction therefore seemed appropriate for the one-pot transformation of pyridine and its derivatives into δ-lactones through the formation of intermediate unsaturated trimethylsilyl esters in which the polarities of the carbon–carbon double bonds would be set by the presence of the nitrogen atom. Thus, treatment of a mixture of pyridine and bis(TMS)ketene acetal **7b** in dichloromethane, first with 1 equiv. of methyl chloroformate at room temperature and then, after 1 h, with an excess of iodine and aqueous sodium hydrogencarbonate at room temperature gave, after 2 h at room temperature, a 90% yield of **68b** (Scheme 30).



Scheme 30.

According to its NMR spectra, **68b** contains both a lactone (δ_C = 173.8 ppm) and a methoxycarbonyl group (δ_C = 152.5 ppm). The presence of a single carbon–carbon double bond, together with a high-field signal for a methine group (δ_C = 13.6 ppm), and of a new low-field signal for one proton (δ_H = 5.09 ppm), are consistent with the addition of both the carboxylate and iodide to the second carbon–carbon double bond with formation of an iodolactone. One- and two-dimensional NMR experiments are fully in agreement with a structure such as **68b**.

Scope of the Transformation

Pyridine and simple substituted ketene acetals **7d** and **7h** gave the same type of iodolactones **68d** and **68h** in 10 and 73% yields (see Exp. Sect.). Small crystals suitable for X-ray analysis were grown from **68h** and allowed the unambiguous assessment of their structure (Figure 6), the C–I bond being *trans* to both the new carbon–carbon and carbon–oxygen bonds.

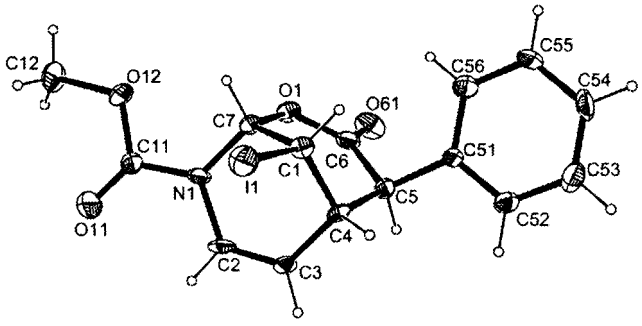
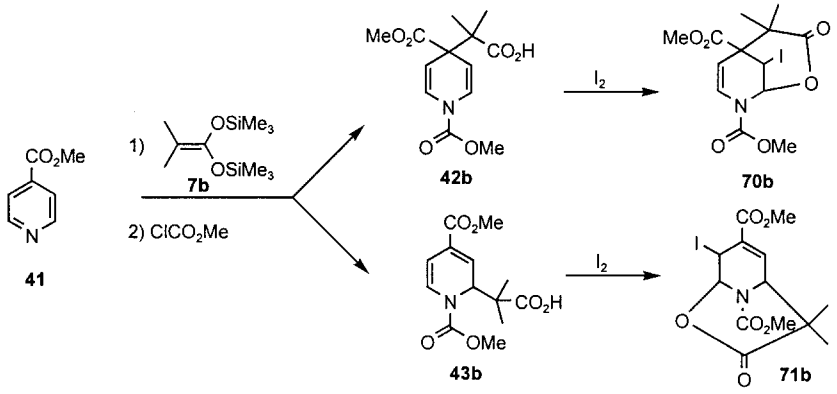
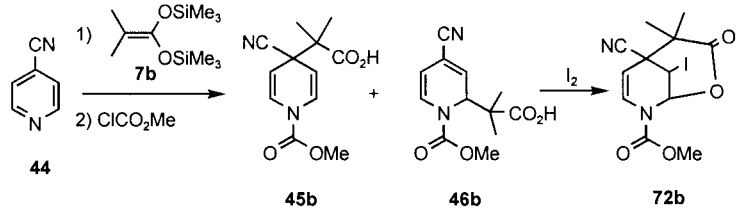


Figure 6. ORTEP view of compound **68h**.

In order to obtain insight into the factors governing the regiochemistry of the cyclization reaction, several substituted pyridines were also examined. Of interest were the transformations of the pyridines **41** and **44** (Scheme 31). Pyridine **41** afforded an inseparable 2:1 mixture of the two regioisomeric acids **42b** and **43b**, via the corresponding TMS esters, in 87% yield. The one-pot reaction fortunately gave two *separable* iodolactones **70b** and **71b** (30 and 10% yield). According to the NMR spectroscopic data, the lactone **70b** is similar to those obtained previously, whereas the second product **71b** is the result of the lactonization of the C-2 acid **43b** to C-6. Three carbonyl groups (signals at at δ = 153.84, 163.83 and 172.46 ppm) are present in this compound, which also shows high- and low-field signals at δ = 17.93 and 84.47 ppm. H–H and C–H COSY experi-



Scheme 31.

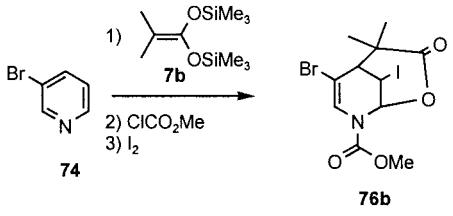


Scheme 32.

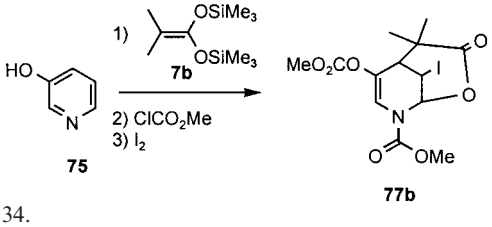
ments are in agreement with structure **71b**, in which the lactone bridges the carbamate group, so no vinylogous addition of iodine to the dihydropyridine carbon–carbon double bond of **43b** took place.

The direct iodolactonization of the acids **45b** and **46b** (70%, 1:1 mixture) originating from 4-cyanopyridine (**44**), however, provided a single iodolactone **72b** in 22% yield (Scheme 32).

A much better result was observed in the case of 2-benzoylpyridine **33**, which gave the lactone **73b** in 87% yield, the benzoyl group activating both the addition of the ketene acetal and the addition of the iodonium ion. Although the conversion of 3-bromo- and 3-hydroxypyridines (**74** and **75**) into the corresponding acids occurred in satisfactory yields, their direct transformation into the iodolactones **76b** and **77b** (observed in the form of the carbonate) were less satisfactory, since extensive decomposition was observed during the purification steps (isolated products 32 and 5% yields vs. 53 and 40% yields before purification) (Schemes 33 and 34). The bromoiodolactone **76b**, which shows the presence of two rotamers in the NMR spectra, clearly displays two broad singlets for the HC=N proton and a signal for the quaternary CBr= carbon atom at δ = 99.35 ppm. It could be isolated as white crystals (m.p. 161 °C) and its structure firmly established by X-ray diffraction crystallography (Figure 7).



Scheme 33.



Scheme 34.

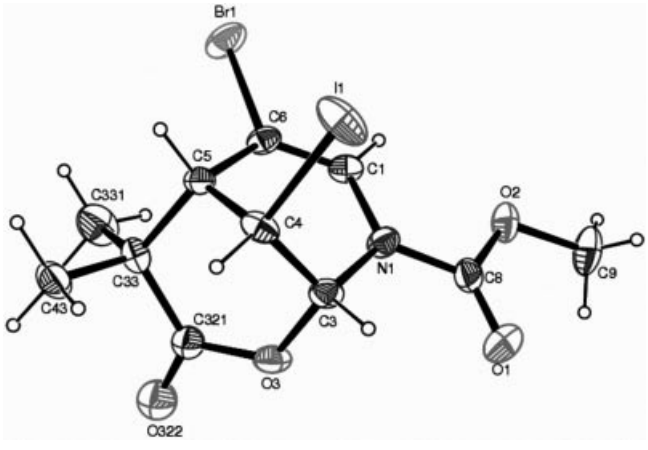


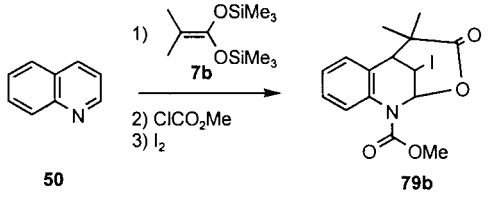
Figure 7. ORTEP view of compound **76b**.

Dihydropyridines derived from unsaturated acids gave the same types of iodolactones: no lactones involving the external, monosubstituted double bonds were observed. Thus, pyridine, upon successive treatment with the ketene acetals **7n** or **7o** and then with iodine, gave the iodolactones

78n and **78o** in 82 and 55% yields, respectively, and as mixtures of diastereoisomers (2:5 vs. 1:5).

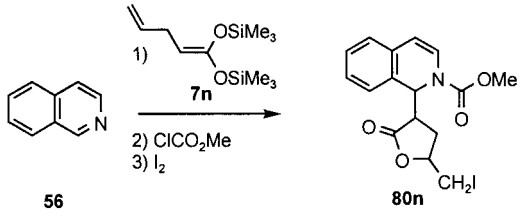
Iodolactones from Quinoline and Isoquinoline

Quinoline (**50**) behaved like pyridine: a 60% yield of the expected iodolactone **79b** was obtained from its successive treatment with the ketene acetal **7b** and with iodine. Although the intermediate acids were formed as a 4:1 mixture of C-4/C-2 regioisomers, no lactone originating from the C-2 isomer was observed (Scheme 35).



Scheme 35.

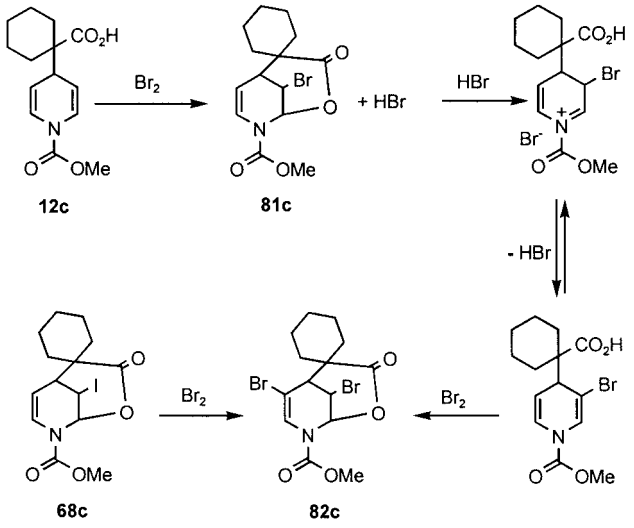
Even so, however, no iodolactone was obtained from isoquinoline (**56**) and **7b**, whilst its treatment first with the ketene acetal **7n** and then with iodine, consistent with its behaviour in the protolactonization reaction, gave the tricyclic iodolactone **80n** as a mixture of diastereoisomers. The ^{1}H NMR spectrum confirmed the presence of the double bond of the starting dihydroisoquinoline [C(4)–H, C(5)–H: δ = 5.84–6.00 and 6.80–7.00 ppm] and the absence of signals for the terminal double bond of the intermediate trimethylsilyl ester. The ^{13}C NMR spectrum agrees with the formation of a γ-lactone (δ = 175.07 ppm) and with the presence of iodine, a low-field signal due to a methylene group occurring at δ = 7.35 ppm (Scheme 36).



Scheme 36.

Surprising Bromolactonization Reactions

Bromine, like iodine, is known to induce the formation of halolactones from unsaturated acids.[53] In contrast to iodine, bromine gave no well-defined products in the presence of water. Starting from the acid **12c** and an excess of bromine in dichloromethane, however, did result in the formation of a lactone (δ_{CO} = 171.75 ppm) as two rotamers **82c** (Scheme 37). Surprisingly, according to the NMR spectra, the newly formed crystalline product did not correspond to the expected **81c**: only one olefinic proton, giving a singlet at δ = 7.28 ppm (δ = 7.16 ppm for the second rotamer), remained, although the expected signal at δ = 4.92 ppm for the CHBr proton was present. The NMR spectra of this new compound are indeed very close to those of the bromoiodolactone **76b** (vide supra).

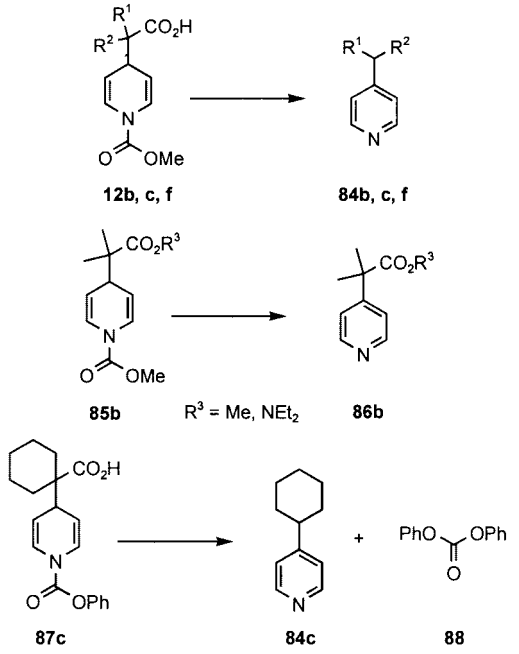


Scheme 37.

As confirmed by the mass spectrum, through the presence of excess bromine, a second bromine atom had been introduced in the substrate. This was confirmed as treatment of the acid **12c** with 1 equiv. of bromine indeed gave the expected bromolactone **81c** (with trace amounts of the dibromolactone **82c**). Interestingly, the same dibromolactone **82c** was obtained upon treatment of the iodolactone **68c** with bromine (2 equiv.) (Scheme 37). Similarly, 4-cyanopyridine (**44**) led to dibromolactone **83c** (see Exp. Sect.). These multiple introduction of halides and halide exchange reactions can be attributed to reversible opening and closure of the lactone ring.[54]

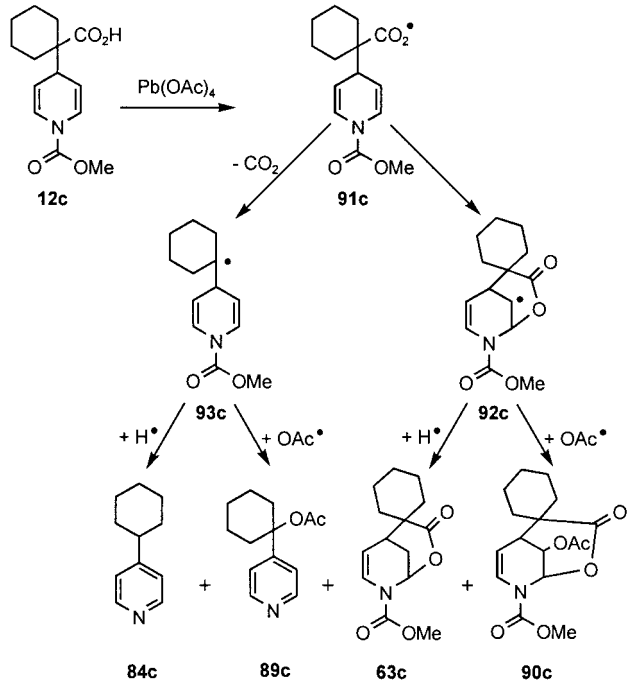
Miscellaneous: Air and Lead Tetraacetate Oxidation Reactions

As already mentioned, even *N*-(methoxycarbonyl)dihydropyridines are unstable to oxygen and give, by biomimetic routes, pyridines via pyridinium derivatives, or polymeric materials.[55–61] Similar behaviour was observed for most of the carboxylic acid substituted dihydropyridines here. Aside from those bearing a quaternary carbon atom at C-4, dihydropyridines of the general structure **12** underwent fast degradation at room temperature, producing the substituted pyridines through decarboxylation/demethoxycarbonylation. Thus, **12b**, **12c** and **12f**, either at room temperature or at reflux in toluene, in the presence of oxygen, gave the pyridines **84b**, **84c** and **84f**. In contrast, the acid derivatives **85** (R^3 = Me, NEt_2), which are far more stable than the corresponding acids, gave pyridines **86** through demethoxycarbonylation at reflux in toluene. The fates of the nitrogen substituents in these degradation reactions could also be established: when starting from the *N*-(phenoxycarbonyl)-dihydropyridine **87c**, a 30% yield of phenyl carbonate **88** was obtained, together with the substituted pyridine **84c** (50%) (Scheme 38).



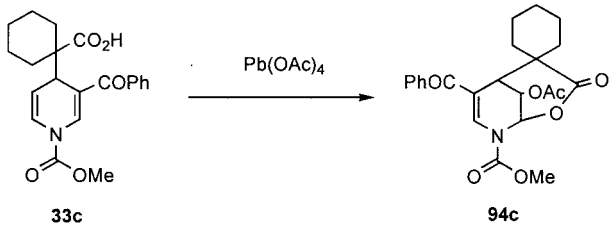
Scheme 38.

Finally, in order to try to bring possible radical degradations to the fore, the acid **12c** was subjected to treatment with lead tetraacetate in benzene at reflux.[62] Within minutes, this had resulted in the formation of a rather complex mixture of products, which were separated and characterized as **84c**, **89c**, the known lactone **63c**, and the acetoxy lactone **90c** in 18, 20, 8, and 14% yields, respectively (Scheme 39). It is likely that this transformation successively involves the radicals **91c**, **92c** and **93c**, with loss of carbon dioxide. Classical termination reactions would then provide the observed products.



Scheme 39.

The more functionalized acid **33c** behaved similarly and gave the lactone **94c** (Scheme 40).

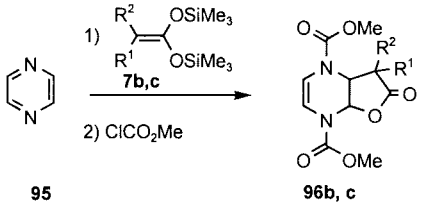


Scheme 40.

Peculiar Behaviour of Pyrazines towards Bis(trimethylsilyl)-ketene Acetals: Direct Formation of *γ-Lactones*

Successive formations of iminium derivatives are the two similar key steps allowing the direct transformation of pyridines and their derivatives into *δ-lactones*, through successive interactions of the nitrogen atom with a first electrophile, methyl chloroformate, and of a double bond of the produced dihydropyridines with a second electrophile, an acid or a halogen. However, the use of an excess of methyl chloroformate did not give rise to the formation of lactones. Nevertheless, this might be possible through the introduction of a second nitrogen atom in the aromatic ring, and has been successively achieved in transformations of pyrazines into bicyclic *γ-lactones*.[67]

Treatment of pyrazine **95** first with the ketene acetal **7b** and then with 3 equiv. of methyl chloroformate thus gave a single crystalline product **96b** in 47% yield after 2 h at room temperature (Scheme 41). Both the mass spectrum and the NMR spectroscopic data confirmed the formation of a bicyclic lactone through addition of 1 equiv. of **7b** to the doubly activated pyrazine moiety.



Scheme 41.

Especially diagnostic signals for two methoxycarbonyl groups appeared in the NMR spectrum at δ = 3.76 and 3.73 ppm, and for only two methyl groups, as singlets, originating from the ketene acetal **7b** at δ = 1.35 and 1.09 ppm. The ^{13}C NMR spectroscopic data (δ_{co} = 178.2, 153.6 and 152.9 ppm) confirmed the presence of both a γ-lactone and the two methoxycarbonyl groups. Pyrazine behaved similarly with the ketene acetal **7c**, affording the lactone **96c** in 58% yield. The structures of these lactones were finally confirmed by an X-ray analysis (Figure 8). Addition of an extra ring to pyrazine, as in quinoxaline **97**, did not modify

the course of the reaction since the corresponding lactone **98b** was obtained in 75% yield.

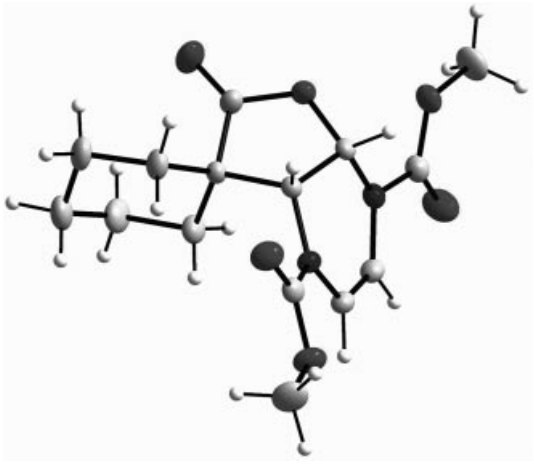
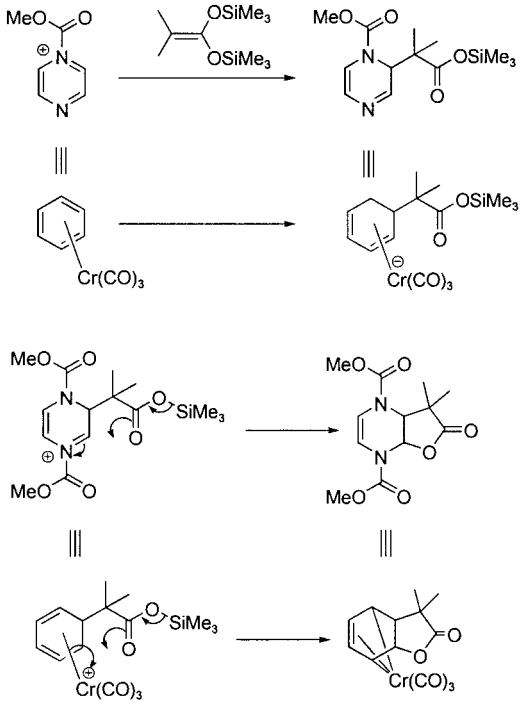


Figure 8. DIAMOND view of compound **96c**.

These transformations can be considered equivalent to double nucleophilic additions of bis(trimethylsilyl)ketene acetals to (arene)tricarbonylchromium complexes, since in both cases a γ-lactone is formed as the result of a double activation reaction, in the first example by a metal, in the second by an acylating agent, methyl chloroformate (Scheme 42). The difference between the two systems lies in the fate of the activating groups: in the last step of the metal-driven reaction the metal ion is lost, leading to a metal-free diene, whereas in the case of pyrazine the two methoxycarbonyl groups remain on the new addition product, which therefore contains only one carbon–carbon double bond.



Scheme 42.

Conclusions

In summary, a large series of new functionalized dihydropyridines and their derivatives has been obtained in satisfactory yields by treatment of nonactivated bis(trimethylsilyl)ketene acetals with activated azaaromatic compounds. The transformation of these nitrogen-containing acids and, more interestingly, of their trimethylsilyl ester precursors into lactones of various sizes by an intramolecular one-pot approach has been outlined. The scope and the limitations of these reactions were established, confirming the high nucleophilicity of ketene acetals[68,69] and the great potential properties of a special class of these derivatives, bis(trimethylsilyl)ketene acetals, as 1,3-carbon,oxygen dinucleophiles.

Experimental Section

General Remarks: All reactions were performed under dry argon. Solvents were distilled from sodium/benzophenone ketyl (diethyl ether, tetrahydrofuran), phosphorus pentoxide (dichloromethane) and saturated with argon. Merck silica gel (type 60, 0.063–0.200 mm) was used for column chromatography. ^{1}H NMR: Bruker AC 200 (200 MHz), Bruker ARX 400 (400 MHz). ^{13}C NMR: Bruker AC 200 (50 MHz), Bruker ARX 400 (100 MHz). All NMR spectra were recorded in $CDCl_3$ unless stated otherwise, with $CHCl_3$ as internal standard. MS and HRMS: JEOL MS 700. M.p.: Reichert melting point apparatus, the reported values are uncorrected. TLC: Merck silica gel plates (60 F_{254}, 0.25 mm).

Synthesis of Bis(trimethylsilyl)ketene Acetals: The saturated and conjugated ketene acetals were prepared in two steps (via trimethylsilyl esters) from the corresponding acids by reported procedures.[33] Similarly, pent-4-enoic and hex-5-enoic acids gave compounds **7n** and **7o.**

1,1-Bis(trimethylsilanyloxy)penta-1,4-diene (7n): 74% yield, liquid, b.p. 80 °C/15 Torr. ^{1}H NMR: δ = 0.25 (s, 18 H), 2.71(d, J = 6 Hz, 2 H), 3.60 (t, J = 6 Hz, 1 H), 4.90 (m, 2 H), 5.80 (m, 1 H) ppm. ^{13}C NMR: δ = 0.3, 29.6, 80.0, 113.2, 139.9, 159.9 ppm.

1,1-Bis(trimethylsilanyloxy-hexa-1,5-diene (7o): 66% yield, liquid, b.p. 90 °C/15 Torr. ^{1}H NMR: δ = 0.21 (m, 18 H), 2.96 (m, 4 H), 3.57 (s, 1 H), 4.99 (m, 2 H), 5.80 (m, 1 H) ppm. ^{13}C NMR: δ = 0.5, 25.9, 35.0, 82.8, 115.0, 139.0, 150.8 ppm.

Synthesis of Dihydropyridines: A dichloromethane solution (10 mL) of methyl chloroformate (5 mmol) was slowly added at room temperature to a solution of bis(trimethylsilyl)ketene acetal (3.5 mmol) and pyridine (2.5 mmol) in dichloromethane (40 mL). Stirring for 2 h followed by evaporation of the solvent gave an oil, which was chromatographed on silica gel [AcOEt/petroleum ether (PE), 30:70].

Methyl 4-Carboxymethyl-4*H*-pyridine-1-carboxylate (12a): 48% yield (0.24 g), white crystals, m.p. 87 °C. ^{1}H NMR: δ = 2.42 (d, J = 7.4 Hz, 2 H), 3.37 (m, 1 H), 3.41 (s, 3 H), 4.86 (m, 2 H), 6.68 and 6.81 (d, J = 8 Hz, 2 H), 9.00 (s, 1 H) ppm. ^{13}C NMR: δ = 29.37, 42.99, 53.54, 108.21, 108.63, 123.22, 123.58, 151.90, 177.19 ppm. MS: calcd. for $C_9H_{14}N_2O_4$ $[M + NH_3]^+$ 215; found 215.

Methyl 4-(1-Carboxy-1-methylethyl)-4*H*-pyridine-1-carboxylate (12b): 70% yield (0.35 g), white crystals, m.p. 98 °C. ^{1}H NMR: δ = 1.14 (s, 6 H), 3.37 (s, 1 H), 3.79 (s, 3 H), 4.85 (m, 2 H), 6.80 and

6.95 (d, J = 7.5 Hz, 2 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 21.30, 40.19, 47.17, 53.57, 105.68, 106.02, 124.66, 124.96, 151.90, 183.60 ppm. HRMS: calcd. for $C_{11}H_{16}NO_4$ [M + H]$^+$ 226.100; found 224.09.

Methyl 4-(1-Carboxycyclohexyl)-4*H*-pyridine-1-carboxylate (12c): 70% yield (0.47 g), white crystals, m.p. 120 °C. ^{1}H NMR: δ = 1.4 (m, 10 H), 3.17 (s, 1 H), 3.78 (s, 3 H), 4.80 (m, 2 H), 6.81 and 6.94 (d, J = 7.5 Hz, 2 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 23.52–30.08, 41.48, 52.96, 53.52, 105.45, 105,65, 124.45, 124.68, 151.90, 180.6 ppm. MS: calcd. for $C_{14}H_{22}N_2O_4$ [M + NH_3]$^+$ 283; found 283.

Methyl 4-(1-Carboxyethyl)-4*H*-pyridine-1-carboxylate (12d): 37% yield (0.20 g), yellow liquid. ^{1}H NMR: δ = 1.03 (d, J = 8 Hz, 3 H), 2.35 (m, 1 H), 3.35 (d, J = 4 Hz, 1 H), 3.68 (s, 3 H), 4.66 (m, 2 H), 6.68 and 6.80 (d, J = 8 Hz, 2 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 29.37, 35.17, 45.03, 53.34, 105.51, 106.01, 107.90, 108.14, 124.09, 151.76, 177.52 ppm.

Methyl 4-(1-Carboxypropyl)-4*H*-pyridine-1-carboxylate (12e): 40% yield (0.23 g), yellow liquid. ^{1}H NMR: δ = 0.91 (t, J = 7 Hz, 3 H), 1.58 (dt, J_1 = J_2 = 7 Hz, 2 H), 2.59 (t, J = 7 Hz, 1 H), 3.33 (s, 1 H), 3.78 (s, 3 H), 4.84 (m, 2 H), 6.75 and 6.84 (d, J = 7 Hz, 2 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 12.12, 21.06, 35.07, 53.46, 54.06, 106.56, 106.58, 107.97, 107.99, 123.75, 124.77, 151.90, 178.50 ppm.

Methyl 4-(1-Carboxy-2-methylpropyl)-4*H*-pyridine-1-carboxylate (12f): 30% yield (0.18 g), liquid. ^{1}H NMR: δ = 0.96 (t, J = 6.4 Hz, 6 H), 2.10 (m, 1 H), 2.19 (m, 1 H), 3.35 (m, 1 H), 3.77 (s, 3 H), 4.89 (m, 2 H), 6.71 and 6.84 (d, J = 8 Hz, 2 H), 10.2 (s, 1 H) ppm. ^{13}C NMR: δ = 19.25, 20.85, 26.01, 32.60, 53.42, 59.27, 107.11, 107.18, 107.53, 123.58, 123.60, 151.85, 178.79 ppm. MS: calcd. for $C_{12}H_{20}N_2O_4$ [M + NH_3]$^+$ 257; found 257.

Methyl 4-(1-Carboxy-2,2-dimethylpropyl)-4*H*-pyridine-1-carboxylate (12g): 90% yield (0.56 g), white crystals, m.p. 180 °C. ^{1}H NMR: δ = 1.01 (s, 9 H), 2.17 (d, J = 4 Hz, 1 H), 3.31 (d, J = 4 Hz, 1 H), 3.74 (s, 3 H), 4.90 (m, 2 H), 6.67 and 6.78 (d, J = 8 Hz, 2 H), 11.00(s, 1 H) ppm. ^{13}C NMR: δ = 28.52, 32.16, 33.06, 34.67, 53.44, 107.84, 108.18, 109.51, 109.88, 123.06, 123.40, 151.83, 178.73 ppm.

Methyl 4-[Carboxy(phenyl)methyl]-4*H*-pyridine-1-carboxylate (12h): 75% yield (0.52 g), yellow liquid. ^{1}H NMR: δ = 3.43 (s, 1 H), 3.60 (m, 1 H), 3.70 (s, 3 H), 4.45 and 5.00 (m, 1 H), 6.54 and 6.68 (d, J = 6.6 Hz, 1 H), 6.68 and 6.82 (d, J = 6.6 Hz, 1 H), 7.30 (s, 5 H), 10.7 (s, 1 H) ppm. ^{13}C NMR: δ = 36.15, 53.53, 59.95, 106.33, 106.76, 107.30, 107.72, 123.56, 123.88, 124.16, 124.94, 135.85 ppm. MS: calcd. for $C_{15}H_{18}N_2O_4$ [M + NH_3]$^+$ 291; found 291.

Methyl 4-[Carboxy(trimethylsilanyl)methyl]-4*H*-pyridine-1-carboxylate (12i): 70% yield (0.47 g), liquid. ^{1}H NMR: δ = 0.17 (s, 9 H), 2.15 (d, J = 8 Hz, 1 H), 3.50 (m, 1 H), 3.79 (s, 3 H), 4.95 (m, 2 H), 6.71 and 6.84 (m, 2 H), 10.7 (s, 1 H) ppm. ^{13}C NMR: δ = –0.88, 21.43, 32.32, 53.84, 108.75, 109.23, 109.80, 109.83, 123.48, 123.93, 124.16, 124.59, 152.23, 180.57 ppm.

Methyl 4-[Carboxy(phenoxy)methyl]-4*H*-pyridine-1-carboxylate (12j): 75% yield (0.54 g), white crystals, m.p. 120 °C. ^{1}H NMR: δ = 3.67 (m, 1 H), 3.77 (s, 3 H), 4.50 (d, J = 5.2 Hz, 1 H), 4.94 (m, 2 H), 6.8–7.2 (m, 7 H), 10.5 (s, 1 H) ppm. ^{13}C NMR: δ = 36.88, 53.74, 80.05, 104.12, 104.25, 104.68, 104.72, 115.45, 122.09, 125.01, 125.20, 129.68, 151.98, 157.82, 174.20 ppm. HRMS: calcd. for $C_{15}H_{16}NO_5$ [M + H]$^+$ 290.0950; found 289.0905.

Methyl 2-Carboxymethyl-2*H*-pyridine-1-carboxylate (13a): 20% yield (0.10 g), viscous liquid. ^{1}H NMR: δ = 2.52 (m, 2 H), 3.72 (s, 3 H), 5.19 (m, 2 H), 5.60 (m, 1 H), 5.91 (m, 1 H), 6.56 and 6.68 (d, J = 8 Hz, 1 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 29.28, 42.90, 53.40, 105.86, 106.21, 120.73, 121.20, 122.23, 124.43, 125.12, 153.78, 175.80 ppm.

Methyl 4-(1-Carboxy-1-methylethyl)-2-methyl-4*H*-pyridine-1-carboxylate (15b): 70% yield (0.39 g), yellow liquid. ^{1}H NMR: δ = 1.18 (s, 6 H), 2.10 (s, 3 H), 3.30 (s, 1 H), 3.74 (s, 3 H), 4.73–4.91 (m, 2 H), 6.92 (d, J = 8 Hz, 1 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 20.93, 21.04, 22.07, 41.13, 47.10, 53.02, 107.16, 108.97, 127.76, 135.56, 152.56, 183.63 ppm. MS: calcd. for $C_{12}H_{20}N_2O_4$ [M + NH_3]$^+$ 257; found 257.

Methyl 4-(1-Carboxy-1-methylethyl)-2-vinyl-4*H*-pyridine-1-carboxylate (17b): 40% yield (0.25 g), yellow liquid. ^{1}H NMR: δ = 0.99 (s, 3 H), 1.02 (s, 3 H), 3.17 (m, 1 H), 3.62 (s, 3 H), 4.82 (m, 2 H), 4.99 (m, 1 H), 5.25 (m, 1 H), 6.36 and 6.41 (d, 1 H), 6.79 (d, J = 8 Hz, 1 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 20.79, 21.20, 41.10, 47.15, 53.14, 107.88, 109.32, 112.87, 127.41, 134.43, 138.63, 152.40, 183.15 ppm. MS: calcd. for $C_{13}H_{20}N_2O_4$ [M + NH_3]$^+$ 251; found 251.

Methyl 4-(1-Carboxy-1-methylethyl)-3-methyl-4*H*-pyridine-1-carboxylate (19b): 60% yield (0.38 g), white crystals, m.p. 100 °C. ^{1}H NMR: δ = 1.13 (s, 6 H), 1.64 (s, 3 H), 3.37 (s, 1 H), 3.78 (s, 3 H), 4.88 (m, 1 H), 6.64 and 6.77 (s, 1 H), 6.81 and 6.99 (m, 1 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 21.21, 25.88, 40.18, 46.65, 53.43, 105.32, 105.52, 115.08, 115.38, 121.43, 121.60, 124.51, 124.70, 151.87, 184.70 ppm. MS: calcd. for $C_{12}H_{20}N_2O_4$ [M + NH_3]$^+$ 257; found 257.

Methyl 4-(1-Carboxycyclohexyl)-3-methyl-4*H*-pyridine-1-carboxylate (19c): 75% yield (0.53 g), white solid, m.p. 150 °C. ^{1}H NMR: δ = 1.1–2.1 (m, 10 H), 1.77 (s, 3 H), 3.22 (d, J = 5.6 Hz, 1 H), 3. 85 (s, 3 H), 4.97 (m, 1 H), 6.72 and 6.85 (s, 1 H), 6.92 and 7.06 (d, J = 8 Hz, 1 H), 10.5 (m, 1 H) ppm. ^{13}C NMR: δ = 21.1–31.6, 47.17, 53.21, 53.85, 106.21, 115.03, 115.32, 122.14, 122.45, 125.08, 125.53, 152.43, 184.04 ppm. MS: calcd. for $C_{15}H_{24}N_2O_4$ [M + NH_3]$^+$ 297; found 297.

Methyl 4-(1-Carboxy-2-methylpropyl)-3-methyl-4*H*-pyridine-1-carboxylate (19f and 20f): 65% yield (global) (0.42 g), liquid. **Major Compound:** ^{1}H NMR: δ = 0.84 (m, 6 H), 1.56 (s, 3 H), 2.08 (m, 1 H), 2.47 (m, 1 H), 3.37 (t, J = 4 Hz, 1 H), 3.84 (s, 3 H), 5.12 (m, 1 H), 6.64 and 6.82 (s, 1 H), 6.83 and 6.97 (d, J = 8 Hz, 1 H), 10.5 (s, 1 H) ppm. ^{13}C NMR: δ = 19.71, 21.85, 22.74, 25.85, 27.50, 39.42, 53.79, 106.80, 107.16, 116. 41, 116.79, 120.27, 120.57, 123.70, 124.13, 152.28, 181.11 ppm. **Minor Compound:** ^{1}H NMR: δ = 0.98 (m, 6 H), 1.76 (s, 3 H), 2.06 (m, 1 H), 2.41 (m, 1 H), 3.27 (t, J = 4 Hz, 1 H), 3.78 (s, 3 H), 4.89 (m, 1 H), 6.64 and 6.82 (s, 1 H), 6.83 and 6.97 (d, J = 8 Hz, 1 H), 10.5 (s, 1 H) ppm. ^{13}C NMR: δ = 19.99, 21.82, 22.09, 26.41, 38.20, 53.42, 104.90, 105.22, 115.71, 116.25, 120.12, 120.45, 124.28, 124.60, 152.30, 179.24 ppm. MS: calcd. for $C_{13}H_{22}N_2O_4$ [M + NH_3]$^+$ 271; found 271.

Methyl 4-(1-Carboxy-1-methylethyl)-3-phenyl-4*H*-pyridine-1-carboxylate (22b): 90% yield (0.67 g), white solid, m.p. 154 °C. ^{1}H NMR: δ = 0.83 (s, 3 H), 1.02 (s, 3 H), 3.75 (s, 3 H), 3.97 (d, J = 3.4 Hz, 1 H), 4.96 (m, 1 H), 6.9–7.3 (m, 7 H), 10.5 (s, 1 H) ppm. ^{13}C NMR: δ = 18.71, 21.03, 42.57, 48.23, 53.66, 106.39, 120.02, 126.4–128.5, 140.53, 152.02, 183.45 ppm. $C_{17}H_{19}NO_4$ (301.3): C 67.76, H 6.36, N 4.65; found C 67.64, H 6.52, N 4.48.

Methyl 2-(1-Carboxy-1-methylethyl)-4-phenyl-2*H*-pyridine-1-carboxylate (24b): 30% yield (0.23 g), yellow liquid. ^{1}H NMR: δ = 1.15 (s, 6 H), 3.67 (s, 3 H), 5.21 and 5.32 (s, 1 H), 5.32–5.70 (m, 2 H), 6.80 and 6.98 (d, J = 3.6 Hz, 1 H), 7.2–7.3 (m, 5 H), 11.3 (s, 1 H) ppm. ^{13}C NMR: δ = 19.66, 50.13, 53.53, 57.53, 108.28, 114.48, 125.1–128.5, 138.63, 155.14, 182.12 ppm. MS: calcd. for $C_{17}H_{22}N_2O_4$ [M + NH_3]$^+$ 319; found 319.

Methyl 4-(1-Carboxy-1-methylethyl)-2-phenyl-4*H*-pyridine-1-carboxylate (26b): 10% yield (0.08 g), liquid. ^{1}H NMR: δ = 1.14 (s, 3 H), 1.16 (s, 3 H), 3.35 (s, 1 H), 3.72 (s, 3 H), 5.40 (m, 2 H), 7.02 (d, J = 4 Hz, 1 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 20.86, 41.87, 52.95, 53.47, 109.15, 112.91, 125.79, 125.8–138.4, 152.66, 183.15 ppm. $C_{17}H_{19}NO_4$ (301.3): C 67.76, H 6.36, N 4.65; found C 68.55, H 6.37, N 4.65.

Methyl 3-Benzoyl-4-(1-carboxy-1-methylethyl)-4*H*-pyridine-1-carboxylate (33b): 90% yield (0.74 g), white solid, m.p. 154 °C. ^{1}H NMR: δ = 0.96 (s, 3 H), 1.01 (s, 3 H), 3.69 (s, 3 H), 4.07 (d, J = 6 Hz, 1 H), 5.05 (dd, J_1 = 6 Hz, J_2 = 8 Hz, 1 H), 6.80 (d, J = 8 Hz, 1 H), 7.2–7.6 (m, 6 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 20.19, 22.37, 39.27, 48.25, 54.28, 108.81, 118.45, 123.99, 128.4–137.6, 151.63, 182.16, 196.41 ppm. $C_{18}H_{19}NO_5$ (329.3): C 65,64, H 5.81, N 4.25; found C 65,93, H 5.88, N 4.18.

Methyl 3-Benzoyl-4-(1-carboxycyclohexyl)-4*H*-pyridine-1-carboxylate (33c): 90% yield (0.83 g), white solid, m.p. 165 °C. ^{1}H NMR: δ = 1.0–2.0 (m, 10 H), 3.76 (s, 3 H), 4.02 (m, 1 H), 5.15 (m, 1 H), 6.90 (d, J = 8 Hz, 1 H), 7.4–7.7 (m, 6 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 23.3–30.3, 40.44, 54.08, 54.28, 108.49, 118.53, 123.97, 129.2–137.7, 151.73, 180.58, 196.41.

Dimethyl 4-(1-Carboxy-1-methylethyl)-4*H*-pyridine-1,3-dicarboxylate (34b): 65% yield (0.46 g), white solid, m.p. 161 °C. ^{1}H NMR: δ = 0.99 (s, 3 H), 1.01 (s, 3 H), 3.65 (s, 3 H), 3.77 (m, 1 H), 3.82 (s, 3 H), 5.09 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1 H), 6.90 (d, J = 6 Hz, 1 H), 7.97 (m, 1 H), 11.0 (s, 1 H) ppm. ^{13}C NMR: δ = 20.36, 21.93, 39.63, 48.52, 51.98, 54.62, 108.44, 109.30, 124.69, 134.93, 151.97, 168.41, 183.45 ppm. $C_{13}H_{17}NO_6$ (283.3): C 55.12, H 6.05, N 4.94; found C 54.77, H 6.34, N 5.00.

Dimethyl 4-(1-Carboxy-1-methylethyl)-4*H*-pyridine-1,3-dicarboxylate (35b): 42% yield (0.28 g), white solid, m.p. 340 °C. ^{1}H NMR (MeOD): δ = 0.99 (s, 3 H), 0.96 (s, 3 H), 3.70 (d, J = 8 Hz, 1 H), 3.78 (s, 3 H), 5.04 (d, J = 8 Hz, 1 H), 6.87 (d, J = 8 Hz, 1 H), 7.92 (m, 1 H), 10.50 (s, 2 H) ppm. ^{13}C NMR (MeOD): δ = 20.09, 23.42, 40.32, 49.80, 54.78, 109.73, 110.10, 125.22, 135.46, 153.11, 171.09, 180.37 ppm. $C_{12}H_{15}NO_6$ (269.2): C 53.53, H 5.62, N 5.2; found C 53.90, H 6.23, N 5.29.

Methyl 4-(1-Carboxy-1-methylethyl)-3-cyano-4*H*-pyridine-1-carboxylate (36b): 46% yield (0.29 g), white solid, m.p. 146 °C. ^{1}H NMR: δ = 1.11 (s, 3 H), 1.26 (s, 3 H), 3.52 (d, J = 5 Hz, 1 H), 3.82 (s, 3 H), 4.94 and 4.98 (d, J = 5 Hz, 1 H), 6.85 (m, 1 H), 7.59 (s, 1 H), 11.2 (s, 1 H) ppm. ^{13}C NMR: δ = 20.30, 22.05, 41.03, 48.22, 54.56, 90.24, 106.69, 119.12, 123.97, 138.23, 150.58, 181.57 ppm. MS: calcd. for $C_{12}H_{17}N_3O_4$ [M + NH_3]$^+$ 268; found 268.

Methyl 4-(1-Carboxy-1-methylethyl)-3-diethylcarbamoyl-4*H*-pyridine-1-carboxylate (37b): 90% yield (0.73 g), liquid. ^{1}H NMR: δ = 1.12 (m, 12 H), 3.27 (t, J = 7 Hz, 2 H), 3.58 (t, J = 7 Hz, 2 H), 3.81 (s, 3 H), 5.00 (m, 1 H), 6.88 (m, 1 H), 7.13 (m, 1 H), 8.9 (s, 1 H) ppm. ^{13}C NMR: δ = 13.23, 20.82, 22.09, 41.70, 41.86, 48.03, 53.89, 107.49, 113.89, 123.84, 126.14, 151.79, 170.84, 180.83 ppm. MS: calcd. for $C_{16}H_{24}N_3O_5$ [M + NH_3]$^+$ 342; found 342.

Methyl 4-(1-Carboxycyclohexyl)-3-formyl-4*H*-pyridine-1-carboxylate (38c): 50% yield (0.37 g), yellow solid, m.p. 160 °C. ^{1}H NMR: δ = 0.9–1.9 (m, 10 H), 3.68 (d, J = 5 Hz, 1 H), 3.86 (s, 3 H), 5.19 (dd, J_1 = 5 Hz, J_2 = 8 Hz, 1 H), 6.93 (d, J = 8 Hz, 1 H), 7.74 (s, 1 H), 9.38 (s, 1 H), 11.0 (s, 1 H) ppm. ^{13}C NMR: δ = 22.2–28.85, 37.38, 52.75, 53.53, 107.94, 119.11, 123.38, 152.87, 179.00, 189.78 ppm.

Methyl 2-Benzoyl-4-(1-carboxy-1-methylethyl)-4*H*-pyridine-1-carboxylate (40b): 30% yield (0.25 g), liquid. ^{1}H NMR: δ = 1.16 (s, 6 H), 3.38 (m, 1 H), 3.51 (s, 3 H), 4.96 (m, 1 H), 5.36 (m, 1 H), 6.92 (d, J = 8 Hz, 1 H), 7.4–7.7 (m, 5 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 21.34, 21.47, 39.27, 47.23, 53.39, 107.31, 116.99, 126.73, 128.4–137.7, 151.49, 182.73, 190.10 ppm.

Methyl 2-(3-Carboxyallyl)-2*H*-pyridine-1-carboxylate (47k): 90% yield (0.51 g), liquid. ^{1}H NMR: δ = 2.25 and 2.51 (m, 2 H), 3.72 (s, 3 H), 4.79 and 4.92 (m, 1 H), 5.25 (m, 1 H), 5.48 (m, 1 H), 5.80 (d, J = 15Hz, 1 H), 5.90 (m, 1 H), 6.58 and 6.72 (d, J = 7 Hz, 1 H), 6.99 (m, 1 H), 10.8 (s, 1 H) ppm. ^{13}C NMR: δ = 37.06, 37.20, 51.21, 51.35, 53.43, 105.91, 106.34, 121.05, 121.21, 122.43, 122.84, 123.51, 124.93, 125.49, 146.35, 146.49, 153.95, 171.34 ppm. MS: calcd. for $C_{11}H_{16}N_2O_4$ [M + NH_3]$^+$ 241; found 241.

Methyl 2-(3-Carboxybut-2-enyl)-2*H*-pyridine-1-carboxylate (47l): 55% yield (0.33 g), liquid. ^{1}H NMR: δ = 1.73 and 1.75 (s, 3 H), 2.24 and 2.54 (m, 2 H), 3.74 (s, 3 H), 4.78 and 4.91 (m, 1 H), 5.20 and 5.30 (m, 1 H), 5.46 (m, 1 H), 5.87 (m, 1 H), 6.57 and 6.70 (d, J = 6.4 Hz, 1 H), 6.83 and 6.88 (m, 1 H), 10.2 (s, 1 H) ppm. ^{13}C NMR: δ = 12.05, 12.43, 32.27, 33.42, 51.32, 53.36, 53.87, 105.77, 106.24, 121.4–129.8, 139.12, 141.17, 151.86, 153.90, 173.10 ppm.

Methyl 2-(3-Carboxy-2-methylallyl)-2*H*-pyridine-1-carboxylate (47m): 25% yield (0.16 g), liquid. ^{1}H NMR: δ = 1.91, 1.96, 2.13 and 2.21 (s, 3 H), 2.6 (m, 2 H), 3.70 and 3.76 (s, 3 H), 4.82 (m, 1 H), 5.39 (m, 1 H), 5.50 (m, 1 H), 5.64 and 5.73 (s, 1 H), 5.92 (m, 1 H), 6.65 and 6.75 (d, J = 8 Hz, 1 H), 10.8 (s, 1 H) ppm. ^{13}C NMR: δ = 19.26, 26.05, 27.06, 30.94, 32.30, 36.48, 36.90, 42.17, 44.57, 50.16, 50.50, 51.10, 53.49, 106.30, 106.60, 108.59, 109.11, 117.52, 118.18, 118.39, 122.45, 122.95, 124.38, 124.59, 125.43, 157.86, 158.88, 171.65 ppm.

Methyl 2-(3-Carboxyallyl)-3-diethylcarbamoyl-2*H*-pyridine-1-carboxylate (48k): 85% yield (0.69 g), liquid. ^{1}H NMR: δ = 1.15 (m, 6 H), 2.52 (m, 2 H), 3.38 (m, 4 H), 3.77 (s, 3 H), 5.33 (m, 1 H), 5.33 and 5.43 (m, 1 H), 5.76 (d, J = 14 Hz, 1 H), 6.13 (m, 1 H), 6.75 and 6.85 (m, 1 H), 6.92 (m, 1 H), 11.5 (m, 1 H) ppm. ^{13}C NMR: δ = 13.41, 14.20, 36.33, 52.17, 53.66, 60.48, 123.4–127.5, 145.49, 145.79, 153.50, 154.22, 169.20, 170.21 ppm.

Methyl 4-(1-Carboxybut-3-enyl)-4*H*-pyridine-1-carboxylate (49n): 85% yield (0.51 g), liquid. ^{1}H NMR: δ = 2.36 (m, 3 H), 3.41 (s, 1 H), 3.79 (s, 3 H), 4.82 (m, 2 H), 5.02 (m, 2 H), 5.76 (m, 1 H), 6.81 and 6.90 (d, J = 8 Hz, 2 H), 8.9 (m, 1 H) ppm. ^{13}C NMR: δ = 31.94, 34.95, 51.67, 53.61, 106.76, 107.64, 116.92, 124.44, 135.43, 151.89, 179.48 ppm.

Methyl 4-(1-Carboxypent-4-enyl)-4*H*-pyridine-1-carboxylate (49o): 55% yield (0.42 g), liquid. ^{1}H NMR: δ = 1.60 and 2.00 (m, 4 H), 2.84 (m, 1 H), 3.82 (s, 3 H), 5.00 (m, 2 H), 5.60 and 5.78 (m, 2 H), 5.93 and 6.03 (d, J = 8 Hz, 1 H), 6.83 and 6.99 (d, J = 8 Hz, 1 H), 7.2 (m, 4 H), 9.8 (m, 1 H) ppm. ^{13}C NMR: δ = 27.72, 31.74, 50.53, 53.75, 57.06, 111, 00, 111,25, 116.01, 124.8–131.0, 137.65, 154.51, 179.66 ppm.

Methyl 2-Carboxymethyl-2*H*-quinoline-1-carboxylate (51a): 90% yield (0.61 g), white solid, m.p. 123 °C. ^{1}H NMR: δ = 2.32 (d, J = 6.5 Hz, 2 H), 3.64 (s, 3 H), 5.30 (dt, J_1 = J_2 = 6.5 Hz, 1 H), 5.96 (dd, J_1 = 6.5 Hz, J_2 = 9.2 Hz, 1 H), 6.35 (d, J = 9.2 Hz, 1 H), 6.9–7.9 (m, 4 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 37.65, 49.05, 53.18, 111.94, 121.37, 124.5–133.6, 154.51, 176.04 ppm. MS: calcd. for $C_{13}H_{17}N_2O_4$ [M + NH_3]$^+$ 265; found 265.

Methyl 2-(1-Carboxy-1-methylethyl)-2*H*-quinoline-1-carboxylate (51b): 20% yield (0.14 g), white solid, m.p. 150 °C. ^{1}H NMR: δ = 0.97 (s, 3 H), 1.17 (s, 3 H), 3.78 (s, 3 H), 5.43 (d, J = 7.5 Hz, 1 H), 6.00 (dd, J_1 = J_2 = 7.5 Hz, 1 H), 6.61 (d, J = 7.5 Hz, 1 H), 7.0–7.4 (m, 4 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 19.51, 22.10, 48.63, 53.35, 57.62, 124.6–136.2, 153.94, 182.02 ppm.

Methyl 2-(1-Carboxy-2-methylpropyl)-2*H*-quinoline-1-carboxylate (51f): 55% yield (global) (0.40 g). **Major Product:** White solid, m.p. 190 °C. ^{1}H NMR: δ = 0.94 (d, J = 6.8 Hz, 3 H), 1.09 (d, J = 6.8 Hz, 3 H), 1.96 (m, 1 H), 2.43 (dd, J_1 = 4.8 Hz, J_2 = 10.6 Hz, 1 H), 3.74 (s, 3 H), 5.41 (m, 1 H), 6.09 (dd, J_1 = 6 Hz, J_2 = 9.6 Hz, 1 H), 6.59 (d, J = 9.6 Hz, 1 H), 7.10 (m, 2 H), 7.23 (m, 1 H), 7.47 (m, 1 H), 10.8 (s, 1 H) ppm. ^{13}C NMR: δ = 17.60, 21.64, 26.88, 51.73, 53.31, 53.74, 125.0–127.8, 134.41, 154.88, 177.35 ppm. $C_{16}H_{19}NO_4$ (289.3): C 66.42, H 6.62, N 4.84; found C 65.96, H 6.58, N 4.84. **Minor Product:** ^{1}H NMR: δ = 0.86 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 1.95 (m, 1 H), 2.23 (dd, J_1 = 4 Hz, J_2 = 9 Hz, 1 H), 3.70 (s, 3 H), 5.26 (m, 1 H), 6.09 (dd, J_1 = 6 Hz, J_2 = 10 Hz, 1 H), 6.47 (d, J = 10 Hz, 1 H), 6.9–7.2 (m, 4 H), 10.5 (s, 1 H) ppm. ^{13}C NMR: δ = 17.63, 21.54, 26.89, 51.00, 51.10, 53.30, 121.0–128.8, 155.19, 177.47 ppm.

2-[Carboxy(trimethylsilanyl)methyl]-2*H*-quinoline-1-carboxylate (51i): 50% yield (0.42 g), liquid. ^{1}H NMR (400 MHz): δ = 0.15 (s, 9 H), 2.33 (d, J = 5.4 Hz, 1 H), 3.78 (s, 3 H), 5.57 (m, 1 H), 6.27 (dd, J_1 = 4.4 Hz, J_2 = 3 Hz, 1 H), 6.51 (d, J = 4.4 Hz, 1 H), 7.0–7.2 (m, 4 H), 10.5 (m, 1 H) ppm. ^{13}C NMR: δ = –1.97, 41.95, 50.38, 53.40, 125.0–127.7, 133.97, 152.98, 179.16 ppm. MS: calcd. for $C_{16}H_{24}N_2O_4Si$ [M + NH_3]$^+$ 337; found 337.

4-(1-Carboxy-1-methylethyl)-4*H*-quinoline-1-carboxylate (52b): 60% yield (0.41 g), white solid, m.p. 146 °C. ^{1}H NMR: δ = 1.05 (s, 3 H), 1.13 (s, 3 H), 3.78 (d, J = 7.5 Hz, 1 H), 3.86 (s, 3 H), 5.31 (dd, J_1 = J_2 = 7.5 Hz, 1 H), 7.1–7.9 (m, 5 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 20.10, 22.27, 45.23, 48.65, 53.51, 110.35, 121.9–137.7, 153.01, 183.73 ppm. MS: calcd. for $C_{15}H_{20}N_2O_4$ [M + NH_3]$^+$ 293; found 293.

Methyl 4-(1-Carboxy-2-methylpropyl)-4*H*-quinoline-1-carboxylate (52f): 10% yield (0.08 g), liquid. ^{1}H NMR: δ = 0.90 (d, J = 8 Hz, 3 H), 1.00 (d, J = 8 Hz, 3 H), 2.06 (m, 1 H), 2.34 (dd, J_1 = 5 Hz, J_2 = 6 Hz, 1 H), 3.66 (m, 1 H), 3.82 (s, 3 H), 5.36 (dd, J_1 = J_2 = 6 Hz, 1 H), 6.9–7.2 (m, 4 H), 7.87 (d, J = 8 Hz, 1 H), 10 (s, 1 H) ppm. ^{13}C NMR: δ = 21.54, 21.76, 27.38, 53.30, 53.48, 57.80, 111.12, 121.5–129.7, 153.04, 178.24 ppm.

Methyl 2-(3-Carboxyallyl)-2*H*-quinoline-1-carboxylate (53k): 90% yield (0.61 g), white solid, m.p. 110 °C. ^{1}H NMR: δ = 2.35 (m, 2 H), 3.79 (s, 3 H), 5.18 (m, 1 H), 5.74 (d, J = 15.4 Hz, 1 H), 6.01 (dd, J_1 = 9 Hz, J_2 = 5.6 Hz, 1 H), 6.52 (d, J = 9 Hz, 1 H), 6.98 (m, 1 H), 7.0–7.5 (m, 4 H), 10.7 (s, 1 H) ppm. ^{13}C NMR: δ = 36.15, 51.53, 53.32, 123.4–127.9, 133.97, 146.50, 154.84, 171.36 ppm.

Methyl 2-(3-Carboxy-2-methylallyl)-2*H*-quinoline-1-carboxylate (53m): 75% yield (global) (0.53 g), white solid. **Major Product:** ^{1}H NMR: δ = 2.25 (m, 5 H), 3.73 (s, 3 H), 5.27 (m, 1 H), 5.49 (s, 1 H), 6.03 (dd, J_1 = 9 Hz, J_2 = 6.2 Hz, 1 H), 6.50 (d, J = 9 Hz, 1 H), 7.0–7.5 (m, 4 H), 10.9 (s, 1 H) ppm. ^{13}C NMR: δ = 19.25, 44.04, 50.72, 53.25, 118.12, 124.6–127.9, 133.74, 157.92, 171.66 ppm. **Minor Product:** ^{1}H NMR: δ = 1.94 (s, 3 H), 2.70 (m, 2 H), 3.74 (s, 3 H), 5.40 (m, 1 H), 5.77 (s, 1 H), 6.04 (dd, J_1 = 9 Hz, J_2 = 6.2 Hz, 1 H), 6.52 (d, J = 9 Hz, 1 H), 7.0–7.5 (m, 4 H), 10.9 (s, 1 H) ppm. ^{13}C NMR: δ = 26.58, 36.20, 52.19, 53.25, 118.12, 124.6–129.2, 134.20, 158.69, 171.80 ppm. HRMS: calcd. for $C_{16}H_{18}NO_4$ [M + H]$^+$ 288.119; found 288.123.

Methyl 2-(1-Carboxybut-3-enyl)-2*H*-quinoline-1-carboxylate (54n): 95% yield (global with **55n**) (0.67 g), liquid. ^{1}H NMR: δ = 2.2–2.6 (m, 3 H), 3.75 (s, 4 H), 5.03 (m, 2 H), 5.27 (m, 1 H), 5.67 (m, 1 H), 6.07 (m, 1 H), 6.58 (d, J = 8 Hz, 1 H), 7.13 (m, 3 H), 7.51 (d, J = 8 Hz, 1 H), 9.9 (m, 1 H) ppm. ^{13}C NMR: δ = 32.01, 48.80, 53.22, 53.34, 117.45, 124.8–128.0, 134.54, 155.22, 178.18 ppm. MS: calcd. for $C_{16}H_{20}N_2O_4$ [M + NH_3]$^+$ 287; found 287.

Methyl 4-(1-Carboxybut-3-enyl)-4*H*-quinoline-1-carboxylate (55n): Liquid. ^{1}H NMR: δ = 2.0–2.6 (m, 3 H), 3.78 (m, 1 H), 3.87 (s, 3 H), 5.03 (m, 2 H), 5.31 (m, 1 H), 5.67 (m, 1 H), 7.2 (m, 4 H), 7.99 (d, J = 8 Hz, 1 H), 9.8 (s, 1 H) ppm. ^{13}C NMR: δ = 32.01, 39.93, 52.63, 53.57, 109.03, 109.33, 117.16, 121.46, 125.2–128.49, 135.07, 136.83, 153.06, 179.37 ppm.

Methyl 1-Carboxymethyl-1*H*-isoquinoline-2-carboxylate (57a): 90% yield (0.57 g), white solid, m.p. 126 °C. ^{1}H NMR: δ = 2.58 and 2.62 (d, J = 6 Hz, 2 H), 3.73 (s, 3 H), 5.81 (m, 2 H), 6.72 and 6.87 (d, J = 12Hz, 1 H), 7.00 (m, 4 H), 11.00 (s, 1 H) ppm. ^{13}C NMR: δ = 39.29, 49.05, 53.18, 111.94, 121.37, 124.5–133.6, 154.51, 176.04 ppm. MS: calcd. for $C_{13}H_{17}N_2O_4$ [M + NH_3]$^+$ 265; found 265.

Methyl 1-(1-Carboxy-1-methylethyl)-1*H*-isoquinoline-2-carboxylate (57b): 90% yield (0.61 g), white solid, m.p. 158 °C. ^{1}H NMR: δ = 1.08 (s, 3 H), 1.21 (s, 3 H), 3.79 (s, 3 H), 5.75 (m, 2 H), 6.85 (d, J = 4 Hz, 1 H), 7.0–7.3 (m, 4 H), 11.3 (s, 1 H) ppm. ^{13}C NMR: δ = 20.99, 22.41, 50.38, 53.67, 59.98, 110.91, 124.6–128.2, 154.88, 182.16 ppm. $C_{15}H_{17}NO_4$ (275.3): C 65.64, H 5.81, N 4.25; found C 64.77, H 6.22, N 5.06.

Methyl 1-(1-Carboxyethyl)-1*H*-isoquinoline-2-carboxylate (57d): 58% yield (global) (0.38 g), white solid. **Major Product:** ^{1}H NMR: δ = 1.03 (m, 3 H), 2.75 (dq, J_1 = J_2 = 8 Hz, 1 H), 3.71 (s, 3 H), 5.51 and 5.63 (d, J = 8 Hz, 1 H), 5.82 and 5.91 (d, J = 8 Hz, 1 H), 6.72 and 6.89 (d, J = 8 Hz, 1 H), 6.9–7.2 (m, 4 H), 9.3 (s, 1 H) ppm. ^{13}C NMR: δ = 13.43, 13.70, 44.97, 45.47, 43.18, 53.59, 56.59, 57.07, 110.19, 110.43, 124.5–130.5, 154.06, 154.26, 179.84, 179.94 ppm. MS: calcd. for $C_{14}H_{18}N_2O_4$ [M + NH_3]$^+$ 279; found 279. **Minor Product:** ^{1}H NMR: δ = 0.88 (m, 3 H), 2.85 (dq, J_1 = J_2 = 8 Hz, 1 H), 3.71 (s, 3 H), 5.45 and 5.59 (d, J = 8 Hz, 1 H), 5.84 and 5.93 (d, J = 8 Hz, 1 H), 6.78 and 6.93 (d, J = 8 Hz, 1 H), 7.0–7.2 (m, 4 H), 8.2 (s, 1 H) ppm. ^{13}C NMR δ = 12.71, 12.83, 42.46, 42.66, 53.29, 53.63, 57.42, 57.95, 109.51, 109.77, 124.8–130.6, 153.71, 153.89, 179.21, 179.68 ppm.

Methyl 1-(1-Carboxybut-3-enyl)-1*H*-isoquinoline-2-carboxylate (58n): 70% yield (global) (0.51 g), liquid. **Major Product:** ^{1}H NMR: δ = 1.93 (m, 1 H), 2.28 (m, 1 H), 2.86 (m, 1 H), 3.78 (s, 3 H), 5.00 (m, 2 H), 5.63 (m, 2 H), 5.93 and 6.02 (d, J = 7 Hz, 1 H), 6.81 and 6.96 (d, J = 7 Hz, 1 H), 7.1 (m, 4 H), 10.2 (m, 1 H) ppm. ^{13}C NMR: δ = 32.21, 32.39, 47.93, 48.08, 53.40, 53.70, 56.81, 57.4, 110.04, 110.24, 117.14, 124.4–130.8, 134.54, 134.77, 153.69, 178.38, 178.79 ppm. **Minor Product:** ^{1}H NMR: δ = 2.28 (m, 1 H), 2.42 (m, 1 H), 2.86 (m, 1 H), 3.73 (s, 3 H), 5.00 (m, 2 H), 5.60 (m, 2 H), 5.91 and 6.00 (d, J = 7 Hz, 1 H), 6.77 and 6.94 (d, J = 7 Hz, 1 H), 7.1 (m, 4 H), 10.2 (m, 1 H) ppm. ^{13}C NMR: δ = 32.60, 32.90, 50.29, 50.85, 53.40, 56.20, 60.60, 110.50, 110.86, 117.14, 124.4–130.8, 134.54, 134.77, 154.01, 178.38 ppm.

Methyl 1-(3-Carboxyallyl)-1*H*-isoquinoline-2-carboxylate (59k): 85% yield (0.50 g), white solid, m.p. 125 °C. ^{1}H NMR: δ = 2.47 and 2.57 (m, 2 H), 3.80 and 3.84 (s, 3 H), 5.39 and 5.55 (t, J = 6 Hz, 1 H), 5.66 and 5.74 (s, 1 H), 5.84 and 5.93 (d, J = 7.8 Hz, 1 H), 6.79 and 6.92 (d, J = 8 Hz, 1 H), 7.0–7.2 (m, 5 H), 10.9(s, 1 H) ppm. ^{13}C NMR: δ = 38.60, 38.82, 53.60, 54.66, 55.26, 108.90, 109.19, 123.5–131.1, 146.43, 146.61, 153.49, 153.87, 171.32 ppm.

Hydroxylactonisation: *m*-Chloroperbenzoic acid (2.4 mmol) was added to a dichloromethane solution (10 mL) of the acid (2 mmol). After 2 h, the remaining acid was neutralized with an aqueous solution of sodium hydroxide (10%, 10 mL). Evaporation of the solvent gave an oil, which was chromatographed on silica gel (AcOEt/PE, 30:70).

Methyl 9-Hydroxy-4,4-dimethyl-3-oxo-2-oxa-8-aza-bicyclo[3.3.1]-non-6-ene-8-carboxylate (60b): 75% yield (0.36 g), liquid. ^{1}H NMR:

δ = 1.37 (s, 3 H), 1.42 (s, 3 H), 1.60 (s, 1 H), 2.39 (s, 1 H), 3.48 (s, 3 H), 4.79 (s, 2 H), 5.08 and 5.15 (m, 1 H), 6.25 and 6.40 (s, 1 H), 6.81 and 6.91 (d, J = 6 Hz, 1 H) ppm. ^{13}C NMR: δ = 26.02, 27.17, 42.52, 42.60, 45.60, 46.17, 51.04, 80.83, 81.21, 103.52, 103.93, 121.84, 152.70, 152.83, 174.05 ppm.

Methyl 6-Benzoyl-9-hydroxy-4,4-dimethyl-3-oxo-2-oxa-8-aza-bicyclo[3.3.1]non-6-ene-8-carboxylate (61b): 50% yield (0.86 g), white solid, m.p. 190 °C. ^{1}H NMR: δ = 1.17 (s, 3 H), 1.42 (s, 3 H), 3.35 (m, 1 H), 3.77 (s, 3 H), 4.68 (m, 1 H), 6.11 (m, 1 H), 7.3–7,7 (m, 7 H) ppm. ^{13}C NMR: δ = 26.45, 28.08, 39.76, 43.73, 54.64, 58.49, 116.96, 128.5–137.4, 152.50, 175.06, 195.85 ppm. HRMS: calcd. for $C_{18}H_{19}NO_6$ [M + 1]$^+$ 346.1212; found 346.1291.

Methyl 6′-Benzoyl-9′-hydroxy-3′-oxospiro[cyclohexane-1,4′-(2-oxa-8-azabicyclo[3.3.1]non-6-ene)]-8′-carboxylate (61c): 35% yield (0.26 g), yellow solid, m.p. 206 °C. ^{1}H NMR: δ = 1.1–1.8 (m, 10 H), 3.65 (s, 1 H), 3.74 (s, 3 H), 4.74 (m, 1 H), 6.08 (m, 1 H), 7.3–7.6 (m, 7 H) ppm. ^{13}C NMR: δ = 21.13–25.21, 37.30, 47.76, 54.60, 57.84, 117.09, 128.67–137.03, 152.51, 174.53, 195.78 ppm.

Methyl 13-Hydroxy-12,12-dimethyl-11-oxo-10-oxa-8-azatricyclo-[7.3.1^{1,9}.0^{2,7}]trideca-2,4,6-triene-8-carboxylate (62b): 30% yield (0.17 g), white solid, m.p. 140 °C. ^{1}H NMR: δ = 1.08 (s, 3 H), 1.50 (s, 3 H), 2.87 (s, 1 H), 3.00 (s, 1 H), 3.84 (s, 3 H), 4.66 (s, 1 H), 6.37 (s, 1 H), 7.0–7.3 (m, 4 H) ppm. ^{13}C NMR: δ = 26.48, 29.18, 43.28, 48.83, 53.69, 60.51, 82.96, 120.56–133.42, 154.40, 174.96 ppm. MS: calcd. for $C_{15}H_{17}NO_5$ [M]$^+$ 291; found 291.

Protolactonisation: Dry silica gel (1.5 g, 25 mmol) was added to the dichloromethane solutions obtained after the reaction between the pyridines (2 mmol) and the acetals. Stirring for 2 h at reflux, followed by evaporation of the solvent, gave an oil, which was chromatographed on silica gel (AcOEt/PE, 35:65).

Methyl 3-Oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (63a): 15% yield (0.06 g), liquid. ^{1}H NMR: δ = 1.43 (d, J = 6.5 Hz, 1 H), 1.96 and 2.11 (m, 2 H), 2.54 (m, 1 H), 3.38 (d, J = 6.5 Hz, 1 H), 3.75 (s, 3 H), 5.12 (m, 1 H), 6.30 and 6.43 (m, 1 H), 6.66 and 6.83 (m, 1 H) ppm. ^{13}C NMR: δ = 25.17, 25.68, 28.85, 29.79, 47.69, 53.69, 78.87, 79.17, 111.90, 112.43, 122.08, 123.65, 156.65, 172.22 ppm.

Methyl 4,4-Dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (63b): 40% yield (0.18 g), white solid, m.p. 108 °C. ^{1}H NMR: δ = 1.30 (s, 6 H), 1.86 (m, 1 H), 2.10 (m, 1 H), 2.56 (m, 1 H), 3.77 (s, 3 H), 5.15 (m, 1 H), 6.27 and 6.41 (s, 1 H), 6.71 and 6.83 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 24.27, 25.50, 27.33, 34.31, 43.60, 53.68, 79.70, 79.91, 107.87, 108.37, 122.35, 122.10, 152.44,176.21 ppm. $C_{11}H_{15}NO_4$: C 58.66, H 6.71, N 6.22; found C 58.59, H 7.07, N 5.86.

Methyl 3′-Oxospiro[cyclohexane-1,4′-(2-oxa-8-azabicyclo[3.3.1]non-6-ene)-8-carboxylate (63c): 45% yield (0.24 g), white solid, m.p. 132 °C. ^{1}H NMR: δ = 1.48 (m, 11 H), 2.56 (m, 2 H), 3.75 (s, 3 H), 5.10 (m, 1 H), 6.22 and 6.36 (s, 1 H), 6.68 and 6.81 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.76–27.77, 32.41, 33.33, 47.14, 53.61, 78.62, 78.87, 107.12, 107.61, 122.52, 122.78, 152.40, 175.91 ppm. $C_{14}H_{19}NO_4$ (265.3): C 63.38, H 7.22, N 5.28; found: C 63.54, H 7.38, N 5.36.

Methyl 4-Methyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (63d): 25% yield (0.1 g), liquid. **Major Product:** ^{1}H NMR: δ = 1.20 (d, J = 8 Hz, 3 H), 2.03 and 2.26 (d, J = 14 Hz, 2 H), 2.41 (m, 1 H), 2.58 (m, 1 H), 3.75 (s, 3 H), 5.07 (m, 1 H), 6.29 and 6.43 (s, 1 H), 6.67 and 6.80 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 14.15, 14.85, 28.15, 29.80, 42.15, 53.80, 76.46, 106.20, 106.81, 123.41, 125.46, 149.27, 173.02 ppm. **Minor Product:** ^{1}H NMR: δ = 1.26 (d, J = 8 Hz, 3 H), 1.83 and 2.26 (d, J = 14Hz, 2 H), 2.41 (m, 1 H), 2.58 (m, 1 H), 3.75 (s, 3 H), 5.07 (m, 1 H), 6.29 and 6.43 (s, 1 H), 6.65 and 6.78 (d, J = 8 Hz, 1 H) ppm.

Methyl 4-Isopropyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (63f): 32% yield (0.15 g), white solid. **Major Product:** ^{1}H NMR: δ = 0.95 (d, J = 6.5 Hz, 3 H), 0.99 (d, J = 6.5 Hz, 3 H), 1.86 (m, 1 H), 2.08 (m, 1 H), 2.2–2.4 (m, 2 H), 2.58 (m, 1 H), 3.74 (s, 3 H), 5.07 and 5.18 (t, J = 6.5 Hz, 1 H), 6.29 and 6.44 (s, 1 H), 6.71 and 6.84 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.82, 21.26, 23.71, 24.01, 25.31, 25.68, 29.82, 30.06, 53.03, 53.25, 53.66, 79.44, 79.72, 110.14, 110.69, 122.71, 122.95, 152.42, 171.74 ppm. **Minor Product:** ^{1}H NMR: δ = 1.00 (d, J = 6.8 Hz, 3 H), 1.12 (d, J = 6.8 Hz, 3 H), 2.02 (m, 1 H), 2.2–2.4 (m, 3 H), 2.67 (m, 1 H), 3.79 (s, 3 H), 5.09 and 5.20 (t, J = 6.8 Hz, 1 H), 6.31 and 6.46 (s, 1 H), 6.71 and 6.85 (d, J = 3.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.64, 21.62, 23.74, 25.99, 26.24, 28.44, 29.02, 53.06, 53.47, 53.68, 78.95, 79.20, 107.33, 107.83, 122.75, 122.97, 152.41, 152.49, 171.65 ppm.

Methyl 6-Methyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (64a): Isolated as by-product of the preparation of the acids; 16% yield (0.07 g), liquid. ^{1}H NMR: δ = 1.65 (s, 3 H), 1.90 (m, 1 H), 2.20 (m, 1 H), 2.56 (m, 2 H), 3.71 (s, 3 H), 5.52 (m, 1 H), 6.26 and 6.40 (s, 1 H), 6.42 and 6.55 (s, 1 H) ppm. ^{13}C NMR: δ = 18.84, 26.74, 28.14, 35.36, 53.55, 78.84, 117.34, 117.66, 152.56, 169.12 ppm.

Methyl 4,4,6-Trimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (64b): 50% yield (0.24 g), white solid, m.p. 122 °C. ^{1}H NMR: δ = 1.23 (s, 3 H), 1.24 (s, 3 H), 1.70 (m, 4 H), 1.94 (m, 1 H), 2.52 (m, 1 H), 3.67 (s, 3 H), 6.11 and 6.23 (m, 1 H), 6.46 and 6.57 (s, 1 H) ppm. ^{13}C NMR: δ = 22.33, 25.59, 28.58, 39.65, 43.38, 53.51, 78.93, 116.69, 118.03, 152.38, 176.23 ppm. MS: calcd. for $C_{12}H_{17}NO_4$ [M + 1]$^+$ 240; found 240.

Methyl 4,4-Dimethyl-3-oxo-6-phenyl-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (65b): 80% yield (0.48 g), white solid, m.p. 172 °C. ^{1}H NMR: δ = 0.89 (s, 3 H), 1.28 (s, 3 H), 1.84 and 2.63 (m, 2 H), 2.87 (m, 1 H), 3.74 (s, 3 H), 6.27 and 6.40 (m, 1 H), 6.95–7.14 (m, 6 H) ppm. ^{13}C NMR: δ = 25.74, 28.26, 36.32, 43.61, 53.54, 78.91, 119.89, 121.31–128.52, 152.21, 176.23 ppm. $C_{17}H_{19}NO_4$ (301.3): C 67.76, H 6.36, N 4.65; found C 67.63, H 6.34, N 4.63.

Methyl 12,12-Dimethyl-11-oxo-10-oxa-8-azatricyclo[7.3.1^{1,9}.0^{2,7}0]-trideca-2(7),3,5-triene-8-carboxylate (66b): 32% yield (0.18 g), white solid, m.p. 130 °C. ^{1}H NMR: δ = 1.16 (s, 3 H), 1.49 (s, 3 H), 2.06 (m, 1 H), 2.77 (m, 1 H), 2.82 (m, 1 H), 3.88 (s, 3 H), 6.61 (m, 1 H), 7.0–7.3 (m, 3 H), 8.30 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 24.97, 26.07, 29.08, 41.91, 42.42, 53.75, 81.84, 120.6–134.0, 153.93, 175.80 ppm. $C_{15}H_{17}NO_4$ (275.3): C 65.44; H 6.22, N 5.09; found C 64.90, H 6.23, N 4.81.

Methyl 4-Allyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (67n): 49% yield (0.23 g), liquid. ^{1}H NMR: δ = 2.0–2.6 (m, 3 H), 2.85 and 2.91 (m, 1 H), 3.80 (s, 3 H), 5.0–5.1 (m, 3 H), 5.75 (m, 1 H), 6.36 and 6.48 (s, 1 H), 6.76 and 6.88 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 26.13, 28.43, 33.78, 47.09, 54.09, 79.88, 106.29, 106.708, 118.09, 118.64, 123.71, 135.47, 152.80, 172.36 ppm. MS: calcd. for $C_{12}H_{15}NO_4$ [M + 1]$^+$ 238; found 238.

Methyl 4-But-3-enyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (67o): 48% yield (0.24 g), liquid. ^{1}H NMR: δ = 1.45 (m, 1 H), 2.00 (m, 3 H), 2.55 (m, 2 H), 4.62 and 4.69 (s, 1 H), 4.84 (m, 3 H), 6.12 and 6.26 (s, 1 H), 6.64, 6.67, 6.76 and 6.79 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 7.83, 12.62, 28.17, 28.79, 30.44, 30.84, 36.02, 36.25, 37.04, 37.44, 47.97, 53.94, 81.97, 82.39, 102.84, 103.28, 106.57, 107.00, 116.03, 116.39, 136.26, 136.72, 152.23, 152.42, 169.87, 170.10 ppm.

Iodolactonisation: Iodine (530 mg, 2.1 mmol) and a saturated solution of sodium hydrogencarbonate (10 mL) were added to the dichloromethane solutions obtained after the reactions between the pyridines (2 mmol) and the acetals. After 1 night, the mixture was treated with a solution of sodium bisulfite in order to eliminate the remaining iodine. The aqueous phase was washed twice with Et_2O (10 mL). Concentration of the organic layers gave an oil, which was chromatographed on silica gel (AcOEt/PE, 40:60).

Methyl 9-Iodo-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (68a): 50% yield (0.08 g), yellow liquid. ^{1}H NMR: δ = 2.9 (m, 3 H), 3.87 (s, 3 H), 4.76 (s, 1 H), 5.13 (m, 1 H), 6.32 and 6.46 (s, 1 H), 6.83 and 6.96 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 15.69, 33.63, 33.83, 39.42, 54.56, 82.50, 83.02, 106.68, 107.13, 122.54, 153.09, 167.41 ppm.

Methyl 9-Iodo-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (68b): 60% yield (0.42 g), yellow liquid. ^{1}H NMR: δ = 1.20 and 1.30 (s, 6 H), 2.33 (d, J = 6 Hz, 1 H), 3.78 (s, 3 H), 5.09 (m, 2 H), 6.19 and 6.34 (s, 1 H), 6.75 and 6.87 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 13.64, 26.12, 27.26, 44.37, 44.51, 46.66, 54.08, 82.69, 83.18, 104.99, 105.42, 121.79, 152.50, 152.67, 173.88 ppm. HRMS: calcd. for $C_{11}H_{15}INO_4$ $[M + H]^+$ 352.0046; found 352.0040.

Methyl 9′-Iodo-3′-oxospiro[cyclohexane-1,4′-(2-oxa-8-azabicyclo[3.3.1]non-6-ene)]-8′-carboxylate (68c): 90% yield (0.75 g), yellow solid, m.p. 158 °C. ^{1}H NMR: δ = 1.1–2.0 (m, 10 H), 2.73 and 2.76 (s, 1 H), 3.78 (s, 3 H), 5.0 (m, 2 H), 6.14 and 6.29 (s, 1 H), 6.75 and 6.87 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 14.38, 21.66, 25.50, 33.63, 33.82, 38.79, 50.75, 54.36, 81.95, 82.44, 104.55, 105.02, 122.39, 152.75, 173.89 ppm.

Methyl 9-Iodo-4-methyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (68d): 10% yield (0.07 g), yellow liquid. ^{1}H NMR: δ = 1.25 and 1.28 (s, 3 H), 2.63 (m, 1 H), 2.85 (m, 1 H), 3.80 (s, 3 H), 4.69 and 4.79 (m, 1 H), 5.05 (m, 1 H), 6.22 and 6.38 (m, 1 H), 6.79 (m, 1 H) ppm. ^{13}C NMR: δ = 12.56, 15.25, 16.14, 39.15, 44.57, 54.10, 82.52, 97.44, 122.47, 146.49, 170.77 ppm.

Methyl 9-Iodo-3-oxo-4-phenyl-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (68h): 73% yield (0.58 g), white solid, m.p. 134 °C. ^{1}H NMR: δ = 2.17 and 2.28 (d, J = 6.5 Hz, 1 H), 2.87 (m, 1 H), 3.88 (s, 3 H), 4.80 (m, 1 H), 5.29 (m, 1 H), 6.37 and 6.53 (m, 1 H), 6.89 and 7.02 (d, J = 8 Hz, 1 H), 7.1–7.4 (m, 5 H) ppm. ^{13}C NMR: δ = 15.90, 40.53, 41.07, 41.61, 54.26, 55.94, 82.61, 83.10, 104.35, 104.81, 122.39, 127.3–129.5, 135.97, 152.60, 168.78 ppm.

Dimethyl 9-Iodo-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-5,8-dicarboxylate (70b): 30% yield (0.25 g), white solid, m.p. 194 °C. ^{1}H NMR: δ = 1.33 (s, 3 H), 1.36 (s, 3 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 5.18 and 5.21 (s, 1 H), 5.37 and 5.45 (d, J = 4 Hz, 1 H), 6.24 and 6.39 (s, 1 H), 6.74 and 6.87 (d, J = 4 Hz, 1 H) ppm. ^{13}C NMR: δ = 17.63, 23.93, 25.17, 49.46, 52.75, 54.30, 82.60, 83.09, 105.32, 105.78, 121.14, 121.36, 152.23, 152.40, 168.33, 173.21 ppm. $C_{13}H_{16}INO_6$ (409.2): C 38.16, H 3.94, N 3.42; found C 37.98, H 3.98, N 3.40.

Dimethyl 8-Iodo-4,4-dimethyl-2-oxo-3-oxa-9-azabicyclo[3.3.1]non-6-ene-7,9-dicarboxylate (71b): 10% yield (0.08 g), liquid. ^{1}H NMR: δ = 1.24 (s, 3 H), 1.29 (s, 3 H), 3.77 (s, 3 H), 3.80 and 3.82 (s, 3 H), 4.63 and 4.76 (d, J = 5 Hz, 1 H), 5.12 and 5.14 (s, 1 H), 6.55 and 6.69 (s, 1 H), 6.97 and 7.01 (d, J = 5 Hz, 1 H) ppm. ^{13}C NMR: δ = 17.93, 18.36, 22.25, 25.77, 25.96, 46.74, 47.00, 52.72, 53.25, 53.90, 54.43, 84.47, 85.01, 130.32, 130.82, 134.12, 134.78, 153.49, 153.84, 163.83, 172.21, 172.46 ppm. MS: calcd. for $C_{13}H_{17}INO_6$ $[M + 1]^+$ 410; found 410.

Methyl 5-Cyano-9-iodo-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (72b): 22% yield (0.17 g), yellow solid, m.p. 194 °C. ^{1}H NMR: δ = 1.50 (s, 3 H), 1.53 (s, 3 H), 3.82 (s, 3 H), 5.0 (m, 2 H), 6.23 and 6.37 (s, 1 H), 6.85 and 6.97 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 14.46, 24.82, 25.33, 47.64, 49.23, 54.99, 102.31, 118.44, 123.37, 152.37, 171.34 ppm.

Methyl 7-Benzoyl-9-iodo-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (73b): 87% yield (0.79 g), yellow solid, m.p. 158 °C. ^{1}H NMR: δ = 1.24 (s, 3 H), 1.33 (s, 3 H), 2.50 and 2.52 (dd, J_1 = J_2 = 2 Hz, 1 H), 3.47 (s, 3 H), 4.93 (m, 1 H), 5.41 and 5.44 (s, 1 H), 6.32 and 6.34 (d, J = 2 Hz, 1 H), 7.3 (m, 3 H), 7.77 (d, J = 7 Hz, 2 H) ppm. ^{13}C NMR: δ = 13.07, 26.06, 27.04, 45.00, 46.83, 54.06, 83.80, 113.01, 128.67, 128.98, 133.25, 134.04, 135.79, 152.18, 172.94, 188.63 ppm. MS: calcd. for $C_{18}H_{21}IN_2O_5$ $[M + NH_3]^+$ 473; found 473.

Methyl 6-Bromo-9-iodo-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (76b): 32% yield (0.28 g), white solid, m.p. 161 °C. ^{1}H NMR: δ = 1.38 (s, 3 H), 1.52 (s, 3 H), 2.62 (s, 1 H), 3.81 (s, 3 H), 4.95 (m, 1 H), 6.13 and 6.29 (s, 1 H), 7.13 and 7.26 (s, 1 H) ppm. ^{13}C NMR: δ = 12.50, 26.14, 28.12, 46.43, 52.92, 54.39, 81.25, 81.69, 99.35, 122.89, 151.65, 172.85 ppm. MS: calcd. for $C_{11}H_{13}BrINO_4$ $[M]^+$: 429, 430; found 447, 448. $C_{11}H_{13}BrINO_4$ (430.0): C 30.72, H 3.05, N 3.26; found C 31.01, H 3.03, N 3.27.

Dimethyl 9-Iodo-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-6,8-dicarboxylate (77b): 5% yield (0.05 g), white solid, m.p. 192 °C. ^{1}H NMR: δ = 1.35 and 1.37 (s, 6 H), 2.60 (m, 1 H), 3.80 (s, 6 H), 4.93 (m, 1 H), 6.16 and 6.32 (s, 1 H), 7.02 and 7.11 (s, 1 H) ppm. ^{13}C NMR: δ = 10.50, 10.73, 25.61, 27.40, 27.50, 45.99, 47.29, 47.66, 54.28, 55.58, 81.79, 82.32, 114.46, 131.93, 132.36, 132.90, 133.10, 151.94, 153.49, 172.81 ppm.

Methyl 4-Allyl-9-iodo-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (78n): 82% yield (0.60 g), yellow liquid. ^{1}H NMR: δ = 2.10 (m, 1 H), 2.30 (m, 1 H), 2.60 (m, 2 H), 3.79 (s, 3 H), 5.00 (m, 1 H), 5.10 (m, 3 H), 5.70 (m, 1 H), 6.25 and 6.41 (s, 1 H), 6.81 and 6.92 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 12.34, 33.72, 36.29, 49.59, 54.16, 82.35, 107.00, 117.5, 122.60, 134.00, 152.61, 169.60 ppm.

Methyl 4-But-3-enyl-9-iodo-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (78o): 50% yield (0.38 g), liquid. ^{1}H NMR: δ = 1.5 (m, 1 H), 2.00 (m, 3 H), 2.56 (m, 2 H), 3.66 (s, 3 H), 4.61 and 4.69 (s, 1 H), 4.84 (m, 3 H), 6.12 and 6.26 (s, 1 H), 6.64 and 6.67 and 6.76 and 6.79 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 16.31, 28.17, 30.85, 36.02, 36.25, 37.40, 37.44, 47.98, 48.10, 53.94, 81.87, 82.39, 102.84, 103.28, 106.57, 107.00, 116.03, 116.39, 121.74, 122.49, 136.26, 136.72, 152.23, 152.42, 170.10, 172.43 ppm. MS: calcd. for $C_{13}H_{16}INO_4$ $[M + 1]^+$ 378; found 378.

Methyl 13-Iodo-12,12-dimethyl-11-oxo-10-oxa-8-azatricyclo[7.3.1^{1,9}.0^{2,7}]trideca-2(7),3,5-triene-8-carboxylate (79b): 60% yield (0.48 g), yellow solid, m.p. 136 °C. ^{1}H NMR: δ = 1.14 (s, 3 H), 1.48 (s, 3 H), 3.84 (s, 1 H), 3.85 (s, 3 H), 5.37 (m, 1 H), 6.60 (m, 1 H), 7.01–7.31 (m, 4 H) ppm. ^{13}C NMR: δ = 18.35, 25.48, 26.56, 45.19, 50.7, 53.69, 84.41, 120.27–137.29, 153.45, 173.42 ppm. MS: calcd. for $C_{15}H_{17}INO_4$ $[M + 1]^+$ 402; found 402.

Methyl 1-(5-Iodomethyl-2-oxo-tetrahydrofuran-3-yl)-1*H*-isoquinoline-2-carboxylate (80n): 70% yield (0.58 g), yellow liquid. ^{1}H NMR: δ = 2.00 (m, 1 H), 2.39 (m, 1 H), 2.97 and 3.00 (m, 1 H), 3.13 and 3.32 (m, 2 H), 3.82 (s, 3 H), 4.19 and 4.43 (m, 1 H), 5.60 and 5.68 (m, 1 H), 5.84 and 6.00 (m, 1 H), 6.80 and 6.89 (m, 1 H), 7.0–7.4 (m, 4 H) ppm. ^{13}C NMR: δ = 7.35, 30.45, 46.96, 54.02, 54.71, 55.02, 76.08, 108.32, 110.66, 124–129, 153.83, 175.07 ppm. MS: calcd. for $C_{16}H_{19}IN_2O_4$ $[M + NH_3]^+$ 431; found 431.

Bromolactonisation: Bromine (1 or 2 equiv.) was added to a dichloromethane solution (10 mL) of the acid (2 mmol), cooled to –78 °C. After heating to room temp. and treatment with a solution of sodium bisulfite in order to eliminate the remaining bromine, the aqueous layer was washed twice with Et_2O (10 mL). Concentration gave an oil, which was chromatographed on silica gel (AcOEt/PE, 40:60).

Methyl 9′-Bromo-3′-oxospiro[cyclohexane-1,4′-(2-oxa-8-azabicyclo[3.3.1]non-6-ene)]-8′-carboxylate (81c): 40% yield (0.28 g), yellow solid, m.p. 116 °C. ^{1}H NMR: δ = 1.2–2.0 (m, 10 H), 2.79 (d, J = 4.5 Hz, 1 H), 3.79 (s, 3 H), 4.78 and 4.82 (s, 1 H), 4.96 and 5.06 (t, J = 6.5 Hz, 1 H), 6.13 and 6.29 (s, 1 H), 6.77 and 6.90 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.57, 21.27, 25.20, 33.43, 33.55, 36.81, 37.06, 37.70, 50.09, 54.00, 80.18, 80.62, 103.14, 103.54, 122.10, 152.53, 152.72, 173.64 ppm. MS: calcd. for $C_{14}H_{19}BrNO_4$ $[M + 1]^+$ 344; found 344.

Methyl 6′,9′-Dibromo-3′-oxospiro[cyclohexane-1,4′-(2-oxa-8-azabicyclo[3.3.1]non-6-ene)]-8′-carboxylate (82c): 70% yield (0.59 g), yellow solid, m.p. 138 °C. ^{1}H NMR: δ = 1.2–2.1 (m, 10 H), 3.04 (s, 1 H), 3.80 (s, 3 H), 4.89 and 4.93 (s, 1 H), 6.06 and 6.21 (s, 1 H), 7.16 and 7.29 (s, 1 H) ppm. ^{13}C NMR: δ = 20.43, 20.58, 24.17, 31.36, 34.00, 35.65, 35.94, 45.79, 49.25, 53.34, 78.09, 78.56, 96.06, 96.77, 122.79, 124.39, 139.34, 150.67, 171.75 ppm. $C_{14}H_{17}Br_2NO_4$ (420.9): C 39.74, H 4.05, N 3.31; found C 40.42, H 4.03, N 3.15.

Methyl 6,9-Dibromo-5-cyano-4,4-dimethyl-3-oxo-2-oxa-8-azabicyclo[3.3.1]non-6-ene-8-carboxylate (83b): 36% yield (0.30 g), liquid. ^{1}H NMR: δ = 1.58 (s, 3 H), 1.63 (s, 3 H), 3.85 (s, 3 H), 5.04 (s, 1 H), 6.20 and 6.35 (s, 1 H), 7.28 and 7.40 (s, 1 H) ppm. ^{13}C NMR: δ = 24.16, 24.43, 26.18, 37.82, 38.07, 49.55, 54.90, 78.92, 79.49, 115.06, 124.82, 150.99, 170.18, 170.77.

Miscellaneous

Preparation of the Acid Derivatives: The reactions were carried as above with the corresponding mono(TMS)ketene acetals Me_2C=$C(OSiMe_3)(OEt)$ and Me_2C=$C(OSiMe_3)(NEt_2)$ for **85** or with $ClCO_2Ph$ for **87**.

Methyl 4-(1-Methoxycarbonyl-1-methylethyl)-4*H*-pyridine-1-carboxylate (85b, R^3 = Me): 70% yield (0.42 g), liquid. ^{1}H NMR: δ = 1.03 (s, 6 H), 3.26 (s, 1 H), 3.58 (s, 3 H), 3.70 (s, 3 H), 4.65 (m, 2 H), 6.71 and 6.83 (d, J = 8 Hz, 2 H) ppm. ^{13}C NMR: δ = 20.74, 39.79, 46.50, 51.06, 52.70, 105.03, 105.39, 120.45, 123.88, 124.10, 149.16, 150.98, 176.39 ppm.

Methyl 4-(1-Diethylcarbamoyl-1-methylethyl)-4*H*-pyridine-1-carboxylate (85b, R^3 = NEt$_2$): 50% yield (0.37 g), liquid. ^{1}H NMR: δ = 1.03 (t, J = 7.5 Hz, 6 H), 1.11 (s, 6 H), 3.27 (q, J = 7.5 Hz, 4 H), 3.48 (s, 1 H), 3.73 (s, 3 H), 4.70 (m, 2 H), 6.73 and 6.87 (d, J = 8 Hz, 2 H) ppm. ^{13}C NMR: δ = 13.45, 23.05, 40.27, 41.96, 47.12, 53.28, 106.70, 106.91, 124.25, 124.61, 151.86, 174.93 ppm. MS: calcd. for $C_{15}H_{27}N_3O_3$ $[M + NH_3]^+$ 298; found 298.

Phenyl 4-(1-Carboxycyclohexyl)-4*H*-pyridine-1-carboxylate (87c): 95% yield (0.78 g), white solid, m.p. 106 °C. ^{1}H NMR: δ = 1.1–2.0 (m, 10 H), 3.17 (s, 1 H), 4.90 (m, 2 H), 6.75 and 6.87 (d, J = 8 Hz, 2 H), 7.2 (m, 5 H), 10.5 (s, 1 H) ppm. ^{13}C NMR: δ = 23.49, 26.23, 30.73, 41.42, 52.87, 106.40, 106.95, 120.89, 121.46, 124.61, 126.30, 129.45, 149.87, 150.55, 181.51 ppm.

Aerial Oxidation of Dihydropyridines: A dichloromethane or toluene solution of the dihydropyridine **12** was kept in contact with air for several days. After concentration, the oil, which was chromatographed on silica gel (AcOEt/EP 30:70), gave **84b**, **84c**, and **84f** (yields: 80, 50, and 60%), the properties of which are similar to those of the known products.[63–65] The same process applied to **85b** gave **86b**, which for R^3 = OMe is similar to a compound (60% yield) described in the literature.[66] Similarly, **87c** gave **84c** (50%), **88** (30%), and a trace of lactone **63c**.

***N*,*N*-Diethyl-2-(pyridin-4-yl)isobutyramide (86b, R^3 = NEt$_2$):** 42% yield, liquid. ^{1}H NMR: δ = 0.69 (t, J = 7 Hz, 3 H), 1.05 (t, J = 7 Hz, 3 H), 1.45 (s, 6 H), 2.73 (d, J = 7 Hz, 2 H), 3.27 (q, J = 7 Hz, 2 H), 7.08 (d, J = 6 Hz, 2 H), 8.48 (d, J = 6 Hz, 2 H) ppm. ^{13}C NMR: δ = 12.63, 13.63, 27.88, 40.71, 41.82, 46.78, 120.19, 150.07, 155.80, 173.71.

Lead Acetate Oxidation: A benzene solution containing **12c** (1.8 g, 6.8 mmol) and $Pb(OAc)_4$ (3.8 g, 8.1 mmol) was heated at reflux for 2 h. Evaporation of the solvent, followed by extraction with dichloromethane and filtration of the brown residue, gave an oil, which was chromatographed on silica gel (CH_2Cl_2/PE, 70:30).

1-(Pyridin-4-yl)cyclohexyl Acetate (89c): 20% yield (0.30 g), white solid, m.p. 106 °C. ^{1}H NMR: δ = 1.1–1.8 (m, 10 H), 2.09 (s, 3 H), 7.22 (d, J = 4 Hz, 2 H), 8.55 (d, J = 4 Hz, 2 H) ppm. ^{13}C NMR: δ = 22.08, 25.42, 35.95, 53.92, 81.57, 119.96, 150.42, 154.91, 169.72 ppm.

Methyl 9′-Acetoxy-3′-oxospiro[cyclohexane-1,4′-(2-oxa-8-azabicyclo[3.3.1]non-6-ene)]-8′-carboxylate (90c): 14% yield (0.30 g), white solid, m.p. 126 °C. ^{1}H NMR: δ = 1.2–1.8 (m, 10 H), 2.08 (s, 3 H), 2.95 (m, 1 H), 3.79 (s, 3 H), 4.69 (m, 1 H), 4.85 (m, 1 H), 6.78–6.88 (m, 2 H) ppm. ^{13}C NMR: δ = 20.95, 21.92, 22.57, 25.19, 29.31, 31.82, 36.39, 48.05, 53.86, 72.11, 73.02, 102.37, 102.63, 124.37, 153.18, 169.18, 179.04 ppm. MS: calcd. for $C_{16}H_{22}NO_6$ $[M + 1]^+$ 324; found 324.

Methyl 9′-Acetoxy-6′-benzoyl-3′-oxospiro[cyclohexane-1,4′-(2-oxa-8-azabicyclo[3.3.1]non-6-ene)]-8′-carboxylate (94c): 14% yield (0.30 g), yellow solid, m.p. 170 °C. ^{1}H NMR: δ = 1.2–1.9 (m, 10 H), 2.04 (s, 3 H), 3.75 (m, 1 H), 3.84 (s, 3 H), 5.04 (dd, J_1 = 2 Hz, J_2 = 6 Hz, 1 H), 6.95 (d, J = 2 Hz, 1 H), 7.3–7.7 (m, 6 H) ppm. ^{13}C NMR: δ = 20.75, 21.14, 22.07, 24.98, 30.33, 34.13, 40.99, 48.04, 54.55, 73.06, 73.23, 118.32, 128.75, 129.37, 132.71, 136.10, 152.75, 168.90, 177.92, 194.41 ppm. MS: calcd. for $C_{20}H_{22}NO_7$ $[M + 1]^+$ 428; found 428.

Reaction of Pyrazine: A dichloromethane solution (10 mL) of methyl chloroformate (10 mmol) was slowly added at room temperature to a solution of bis(trimethylsilyl)ketene acetal (3.5 mmol) and pyridine (2.5 mmol) in dichloromethane (40 mL). Stirring for 2 h, followed by evaporation of the solvent, gave an oil, which was chromatographed on silica gel (AcOEt/PE, 70:30).

Dimethyl 7,7-Dimethyl-6-oxo-4a,6,7,7a-tetrahydrofuro[2,3-*b*]pyrazine-1,4-dicarboxylate (96b): 47% yield (0.34 g), white solid, m.p. 70 °C. ^{1}H NMR: δ = 1.09 (s, 3 H), 1.35 (s, 3 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 4.80 and 4.89 (d, J = 9 Hz, 1 H), 6.2 (m, 3 H) ppm. ^{13}C NMR: δ = 19.80, 25.90, 44.29, 53.77, 53.96, 60.70, 80.70, 110.36, 110.85, 153.04, 153.67, 178.28 ppm.

Dimethyl 7′,7′-Dimethyl-6′-oxospiro[cyclohexane-1,4′-(4a,6,7,7a-tetrahydrofuro[2,3-*b*]pyrazine)]-1′,4′-dicarboxylate (96c): 58% yield (0.47 g), white solid, m.p. 130 °C. ^{1}H NMR: δ = 1.6–1.8 (m, 10 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 4.91 (d, J = 8 Hz, 1 H), 6.17 (m, 3 H) ppm. ^{13}C NMR: δ = 21.09, 21.54, 25.07, 28.80, 34.92, 46.21, 54.06, 61.45, 80.97, 111.54, 112.23, 154.41, 154.10, 176.88 ppm. MS: calcd. for $C_{15}H_{23}N_2O_6$ $[M + NH_3]^+$ 342; found 342.

Dimethyl 3,3-Dimethyl-2-oxo-2,3,3a,9a-tetrahydrofuro[2,3-*b*]quinoxaline-4,9-dicarboxylate (97b): 75% yield (0.50 g), white solid, m.p. 165 °C. ^{1}H NMR: δ = 1.25 (s, 3 H), 1.46 (s, 3 H), 3.83 (s, 3 H), 3.92 (s, 3 H), 5.25 (d, J = 8 Hz, 1 H), 7.05 (d, J = 8 Hz, 1 H), 7.3 (m, 4 H) ppm. ^{13}C NMR: δ = 18.82, 26.57, 44.04, 53.71, 53.89,

66.21, 85.26, 125.63, 125.81, 126.30, 129.58, 130.71, 153.58, 155.05, 178.03 ppm.

Crystallographic Data: Crystallographic data (excluding structure factors) for the structures **51f**, **64b**, **66b**, **68h**, **76b** and **98b** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-232996, -232999, -232997, -178733, -263793 and -233000, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Supporting Information (see footnote on page 1 of this article): Room-temperature ^{1}H NMR (400 MHz) spectra of **12b**, **12d**, **12h** and ^{1}H NMR (400 MHz) spectra of **12b** at various temperatures:

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Received: March 4, 2005
Published Online: July 20, 2005

