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Study on the reactivity of enantiopure (*S*)-6-oxopipecolic acid and corresponding pyridoisoquinolines under acid conditions

Peter Šafář,[a] Štefan Marchalín,*[a,b] Barbora Balónová,[c] Michal Šoral,[d] Ján Moncol,[e] Alina Ghinet,[f,g,h] Benoît Rigo,[f,g] and Adam Daïch*,‡[b]

Dedication ((optional))

Abstract: Enantiopure *N*-benzyl 6-oxopipecolic acid, obtained from (*S*)-2-aminoadipic acid, was evaluated under π-cationic cyclization conditions. If the combination of $SOCl_2/AlCl_3$ seems to be superior in terms of the reaction yields, use of PPA, $(CF_3CO)_2O/BF_3.Et_2O$, and Eaton's reagent is also very interesting since in addition to the expected keto-lactam, reduced- and oxidized keto-lactam, enamides and enamidones containing CF_3CO- residue are isolated. Mechanisms leading to these products as well as the ones resulting from their acidic treatment were proposed and discussed with the help, in some cases, of univocal transformations and X-ray analysis.

Introduction

Heterocyclic systems constitute probably the largest and most varied family of organic compounds. They occupy a privileged position as pivotal sources for novel scaffolds with synthetic, therapeutic and industrial ramifications.[1] Octahydro-indolizine and octahydro-quinolizine alkaloids commonly known as indolizidines and quinolizidines, respectively, constitute a family of 5,6- and 6,6-nitrogen-fused bicycloalkanes. The latter have received considerable attention by virtue of their varied and pharmaceutically useful biological actions as potential antiviral, antitumor, immunomodulator agents as well as glycosidase inhibitors.[2] Of particular interest are indolizidines and quinolizidines fused to π-aromatic nucleus, represented by the popular plant metabolites, belonging to the phenanthro-indolizidine and phenanthroquinolizidine, classes of alkaloids (Figure 1). More importantly, phenanthroquinolizidines despite their lower natural occurrence compared to corresponding phenanthroindolizidines exhibit very interesting biological properties. Thus, in addition to their strong activities as anti-inflammatory, antitumor and cytotoxic agents at low, i.e. submicromolar concentrations against different cancer cell lines, some of them including particularly both enantiomers of the same product (7-methoxycryptopleurine for example), have shown important antiviral activity against tobacco mosaic virus (TMV).[3] Again a difference between *R*- and *S*-stereomers on the activity was observed outlining the pivotal role of the stereochemistry of the pyramidal nitrogen atom at the ring junction as postulated before in many reports. Since phenanthroquinolizidines are generally more potent compared to phenanthroindolizidines, allied to their unique mode of action unlike those of the marketed anticancer drugs, phenanthro-quinolizidines have received recently intensive attention not only due to medicinal chemistry issues[4] but also from the synthetic point of view.[5]

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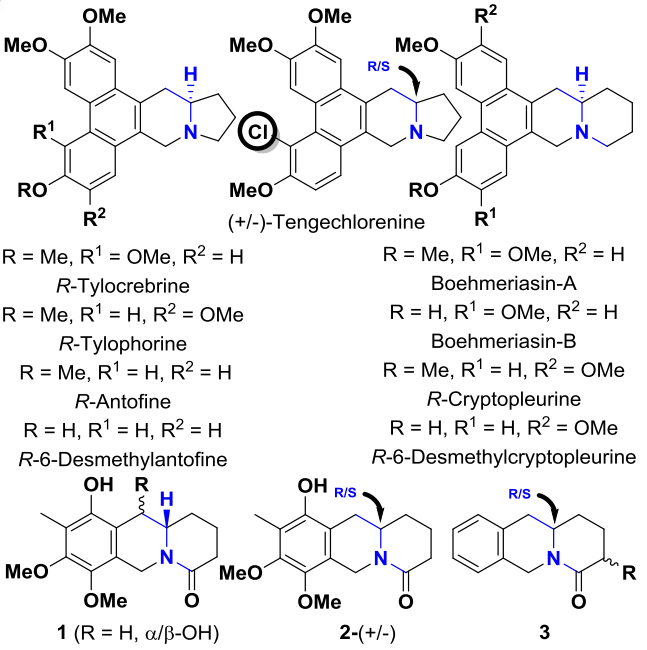


Figure 1. Representative phenanthroindolizidine and phenanthroquinolizidine alkaloids and their synthetic analogues **1-3**.

The simple aromatic analogues of these phenanthroquinolizidines were however very scarce and only few examples of advanced intermediates for the synthesis of chiral aromatic δ-amino-acids[6] and a natural potent antitumor Saframycin-A were reported.[7] On our part, we have been strongly involved for decades in the elaboration of novel indolizidines **4** (n=1) and quinolizidines **5** (n=2) fused to aromatic[8] or heteroaromatic[9] nuclei and the study of their reactivity to obtain divers compounds with biological profiles as farnesyltransferase (FTase),[10] tubulin[11] and glycosidase[12] inhibitors. During these investigations, enantiopure, abundant and cost-effective glutamic acid (or pyroglutamic acid; PGA) and 2-aminoadipic acid were used as starting materials both as a nitrogen atom source and a chiral pool (Figure 2).

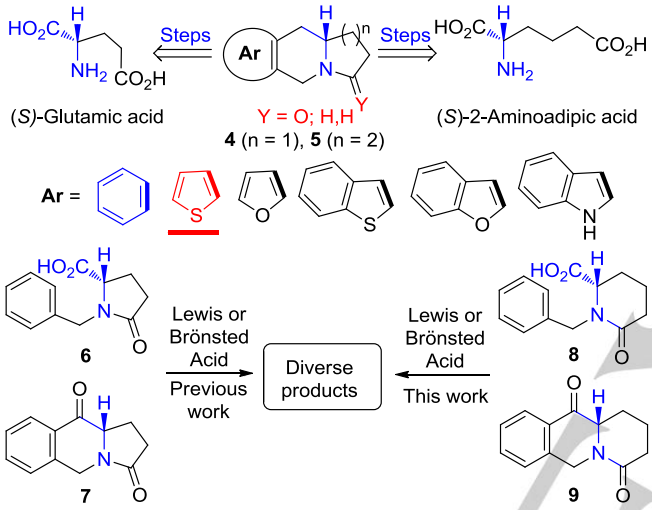


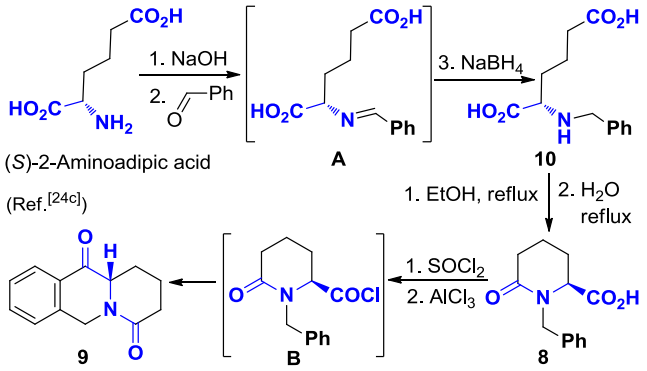
Figure 2. Retrosynthetic scheme leading to phenanthroindolizidine and phenanthroquinolizidine aromatic analogues **7** and **9** starting from natural carboxylic acids such as (*S*)-glutamic acid and (*S*)-2-aminoadipic acid.

Elsewhere, the influence of the ring size of saturated compounds on their reactivity and properties is of prime importance to synthetic chemists.[13] In the lactam series too, this was observed for alkylation,[14] hydrolysis[15] and silylation reactions,[16] reactions with Bredereck's reagent[17] or polymerization ability.[18] Moreover, it was postulated that exocyclic double bonds stabilize 5-membered rings but destabilize 6-membered ones.[19] This impact of the ring size of lactams[20] could be associated with the relative order of basicity[21] and electron donor capacity; the 6-membered ring being the strongest electron donor while 5- and 7-membered ring shown very similar properties.[22] However, in some three component reactions involving stabilization of exocyclic *N*-acyliminium salts, pyrrolidinone leads to good results while lactams possessing 6-, 7- and 12-carbons in the nucleus do not react.[23]

We are strongly implicated in *γ*- and δ-lactams reactivity and in that context we have found that an important part of the chemistry of *N*-benzyl pyroglutamic acid (*γ*-lactams), and corresponding ketone obtained after Friedel-Crafts cyclization, is governed by the formation of *N*-acyliminium salts followed by a hydride transfer during acid treatment. The chemistry of δ-lactam containing acid has been, for its part, much less studied since only the results of the behavior of *N*-arylmethyl piperidone-6-carboxylic acid under acid conditions in benzene[24] series and thiophene[25] series were reported, however with different reactivity profile. Because the importance of the exposed scaffolds,[26] *γ*-lactams and δ-lactams containing heterocycle for pharmaceutical and agrochemical industry,[27] we describe herein our finding on the reactivity of enantiopure (*S*)-1-benzyl-6-oxopipecolic acid (**8**) and corresponding tricyclic ketone **9**. This fits perfectly in our previous work on γ-lactams starting from (*S*)-1-benzyl pyroglutamic acid (**6**) and ketone **7** (Figure 2).[8] Some aspects of the reactivity of these δ-lactams containing an acid or ketone function will be taken in consideration, relying both on chemical and spectroscopic investigations, including X-ray crystallographic analysis, and when possible, on the most plausible reaction mechanism

Results and Discussion

Our work was initiated by considering first the behavior of *N*-benzyl piperidone-6-carboxylic acid (**8**). Although this compound has already been described in a patent,[28] we have described it recently through an easy three-step synthesis in very good yields as highlighted in Scheme 1. This comprises reductive amination of benzaldehyde by mixing commercially available (*S*)-2-aminoadipic acid and benzaldehyde in aqueous alkaline media (2M NaOH), followed by borohydride reduction of the imine **A**, intramolecular peptide coupling of the resulting (*S*)-*N*-benzyl aminoadipic acid (**10**)[24c] followed finally by the reflux of the dicarboxylic acid **10** in ethanol and water. We then turned our attention to intramolecular Friedel-Crafts acylation of the acid **8**. We have found that, contrary to the (*S*)-*N*-thienylmethyl pipecolic acids,[25] with (*S*)-*N*-benzyl 6-oxopipecolic acid (**8**), the best results were obtained with $SOCl_2$ and $AlCl_3$ (Method **A**), giving the expected ketone **9** in good yield (71%). Under these conditions, the $AlCl_3$-catalyzed cyclization reaction of the non-isolated acid chloride **B** needs only fifteen minutes of time. The obtained ketone **9** was properly characterized by ^{1}H-^{1}H, ^{1}H-^{13}C, ^{1}H-^{15}N and even ^{13}C-^{13}C NMR correlation methods, thus explicitly proving its structure.

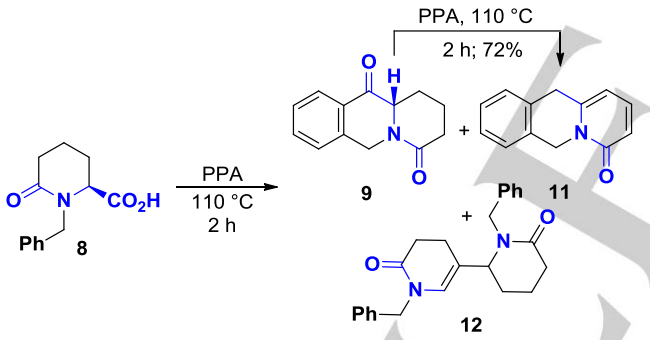


Scheme 1. Synthesis of enantiopure tricyclic ketone **9** from (*S*)-2-aminoadipic acid under Friedel-Crafts reaction using $SOCl_2$/$AlCl_3$.[24c]

It is worth mentioning that these cyclization conditions are effective in producing thieno-(or furo) indolizidindiones,[9a,d,e] benzothienoindolizidindiones[9f,g] as well as phenanthro-quinolizidindiones.[24a,b] In addition, the best yields of the cyclization were obtained when the reaction time was very short (15 minutes), its prolongation leading to drastic decreases of reaction yields (e.g., 20% after 2 hours) due to the rapid decomposition of materials. However, this is reminiscent of the formation of many by-products observed during the cyclization of *N*-arylmethyl pyroglutamic acids of type **6**, studies that led to new interesting enantiopure fused indolizidindiones analogues of **7** (Scheme 1).[8a,e,f, 29-33]

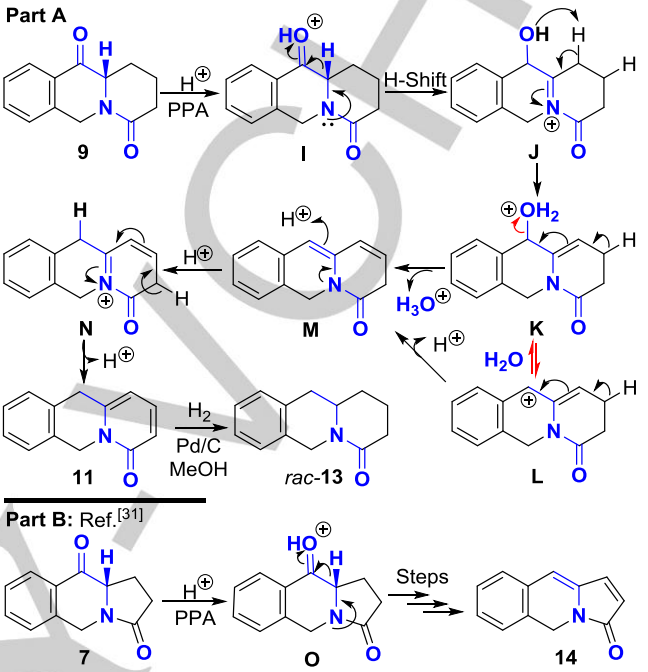
In the light of these observations, we were interested to enlarge the scope of the π-cationic cyclization of (*S*)-*N*-benzyl aminoadipic acid (**8**). Here we consider other conditions we explored before in pyrrolidinone series[8f,29] and unique piperidinone containing a thiophene nucleus.[25] Among them, we envisioned to use PPA (Method **B**), TFAA/BF_3.Et_2O (Method **C**) and Eaton's reagent (Method **D**). This in order to compare the results with those obtained in fused *γ*-lactam series starting from *N*-substituted (*S*)-pyroglutamic acids hoping to gain some insights in this cyclization process.

Thus, in neat PPA at 100-105 °C under conditions of the Method **B**, carboxylic acid **8** provides the expected pyrido-isoquinolindione **9**, oxidized pyridoisoquinolone **11** and piperidin-yldihydropyridinone **12**, respectively, in 57%, 30% and 5.6% yields (Scheme 2).



Scheme 2. Reaction of carboxylic acid **8** under Friedel-Crafts conditions using neat PPA (Method **B**).

The formation of oxidized pyridoisoquinolone **11** can be explained by the transformation of the initially formed tricyclic ketone **9** in the reaction medium (PPA). Our proposed mechanism (Scheme 3, **Part A**) is similar to the one proposed by Rigo's group[31] for the conversion of pyrroloisoquinolindione **7** to the corresponding pyrroloisoquinolinone **14** (Scheme 3, **Part B**). However, in our case evidently the diene **M** is not the ultimate product as observed in the *N*-benzylpyroglutamic series (product **14**), due to its isomerization to the thermodynamically more stable conjugated tricyclic dienone **11**. Alternatively, when the starting compound was ketone **9**, we have obtained after heating with PPA lactam **11** as the sole reaction product in good yield (72% after crystallization). Previously, we have found that in the case of *N*-thienylmethyl-6-oxopipecolic acids, the corresponding ketones are not susceptible for transformations to thieno analogues of dienone **11**, owing to their higher stability in acidic reaction conditions.[25]



Scheme 3. Plausible mechanism of the formation of pyridoisoquinolinone **11** from ketone **9 (Part A)** and diene **14** from **7 (Part B)** in PPA.

The structure of pyridoisoquinoline **11** was confirmed by its catalytic hydrogenation yielding in good yield (72%) the known *rac*-**13** lactam,[34] which was identified without ambiguity by single-crystal X-ray diffraction analysis (Figure 3).[35]

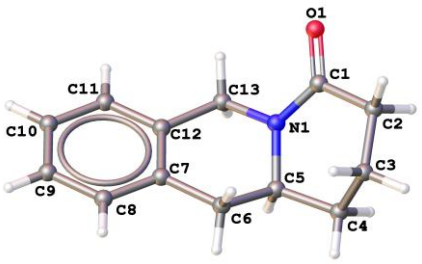
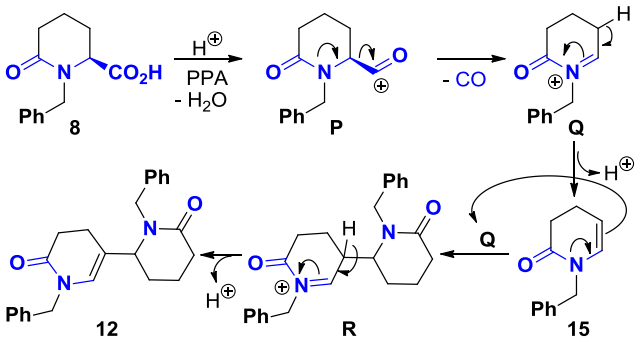


Figure 3. Stick drawing of (±)-2,3,11,11*a*-tetrahydro-1*H*-pyrido[1,2-*b*]isoquino-lin-4(6*H*)-one (**13**).

As shown in Scheme 4, the formation of the bis-lactam **12** can be explained by the formation of the acylium cation **P** under acid conditions, followed by elimination of carbon monoxide CO and deprotonation of the stable cyclic *N*-acyliminium intermediate **Q**. Electrophilic substitution of the being formed enamide **15** with the cyclic electrophile species **Q** afforded ultimately, via the *N*-acyliminium species **R**, the product **12** as a racemate (Scheme 4). The structure of racemic **12** has been confirmed by an

expanded series of 2D NMR measurements (including ^{1}H-^{15}N HMBC and ^{13}C-^{13}C INADEQUATE) and ultimately by single-crystal X-ray diffraction (Figure 4).[36]



Scheme 4. Proposed mechanism for the formation of bis-lactam product **12**.

As planned above, another Method **C** consisting of the use of the combination of TFAA and $BF_3.Et_2O$ to promote the Friedel-Crafts cyclization of carboxylic acid **8** was attempted.[29b] Interestingly, under these cyclization conditions, bis-lactam **12** and two piperidin-2-ones **15** and **16**, respectively, in yields of 17% (**12**), 13% (**15**) and 5.6% (**16**), were obtained in addition to the expected ketone **9** as the major product (Scheme 5).

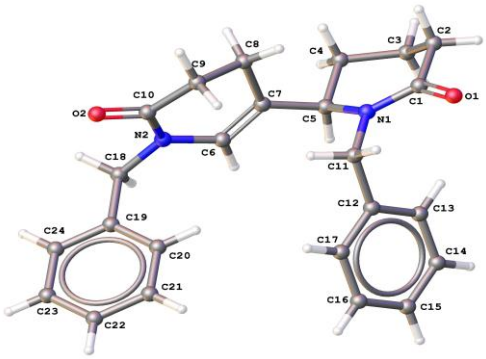
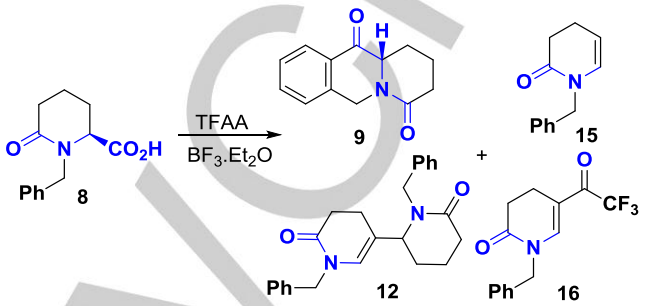


Figure 4. Stick drawing of (±)-1-benzyl-5-(1-benzyl-6-oxopiperidin-2-yl)-3,4-dihydropyridin-2(1*H*)-one (**12**).

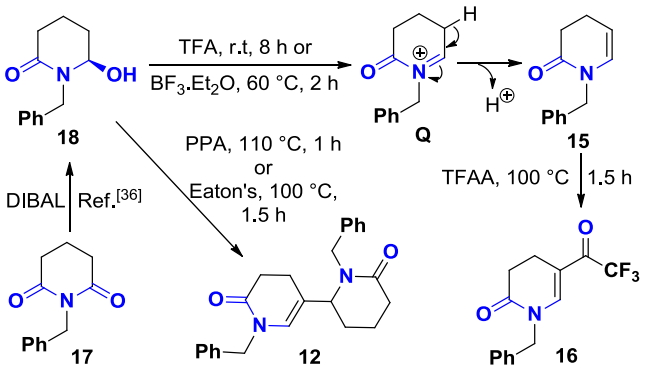
The elucidation of the structure of the trifluoroacetyl derivative **16** was hampered by intriguing ^{19}F-^{13}C couplings observed in its ^{13}C NMR spectrum. According to the signal assignments obtained from basic 2D NMR methods two $^{4}J_{CF}$ coupling were observable whilst the $^{3}J_{CF}$ coupling constant between the CF_3-group's fluorines and the carbon bearing the trifluoroacetyl group was of a far lower value than the ^{13}C peak linewidth (0.4 Hz full width at half maximum without apodization). The assignment was supported by the correlations observed in ^{1}H-^{15}N HMBC. To unambiguously prove the connectivity within the structure, a ^{13}C-^{13}C INADEQUATE spectrum was acquired, proving the original assumption about the signal assignment and securing the expected structure of **16**. It should be noted that the complete ^{13}C-^{13}C correlation appeared in the INADEQUATE spectrum, despite the ^{19}F-^{13}C interactions present within the molecule.

As we can see, in this reaction the most favourable process under these conditions starts with the decarbonylation of the acylium cation **P** leading to the *N*-acyliminium species **Q**, which provide similarly the enamide **15** and the bis-lactam derivative **12**. The product **16** was formed by acylation of the enamide **15** with TFAA. Similarly, the course of this reaction was also observed with the *N*-thienylmethyl-6-oxopipecolic acid.[25]



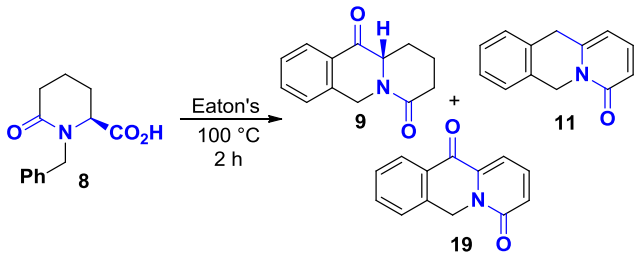
Scheme 5. The reaction of (*S*)-*N*-benzyl 6-oxopipecolic acid (**8**) with TFAA and $BF_3.Et_2O$ (Method **C**).

As we expected, all these pyridinone systems **12**, **15** and **16** could be independently prepared univocally from easily available 1-benzyl-6-hydroxypiperidin-2-one (**18**) as the precursor of *N*-acyliminium intermediate **Q** (Schemes 4 and 6). Along this line, the requisite 1-benzyl-6-hydroxypiperidin-2-one (**18**)[37] was prepared in three steps starting from glutaric anhydride, by chemoselective DIBAL-H reduction of *N*-benzyl glutarimide (**17**) as the key and earliest step of the sequence.[38] Next we tested the reaction under acidic conditions with different reagents enabling selective transformation of starting hydroxyl lactam **18** to lactams **12**, **15** and **16**. After careful checking of the reaction conditions, we have found that depending on the temperature, the use of TFA and TFAA, respectively, it afforded in good yields lactam **15** as well as trifluoroacetyl derivative **16** as was reported. The latter was generated by acylation of enamidone **15** acting as nucleophile followed by deprotonation of the *N*-acyliminium intermediate. For the preparation of bis-lactam **12**, the reagent of choice is PPA or Eaton´s reagent under heating (Scheme 6).



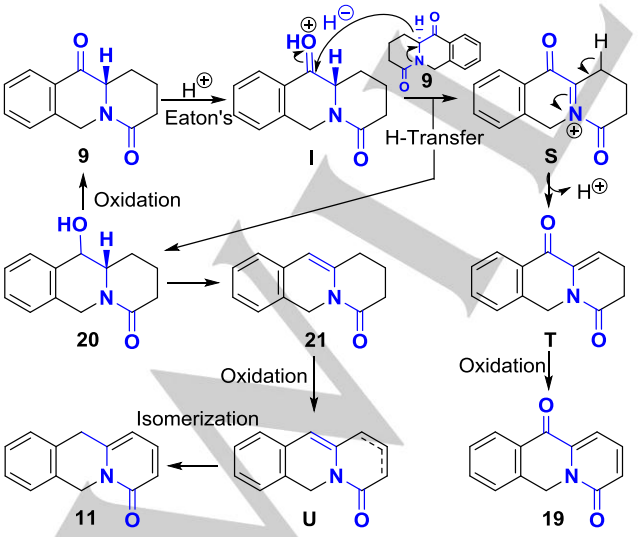
Scheme 6. Preparation of lactams **12**, **15** and **16** starting from hydroxyl lactam **18** via *N*-acyliminium chemistry.

In the ultimate attempt, we have tested Eaton's reagent (P_2O_5/$MeSO_3H$: 1/10 w/w) at 90 °C according to the Method **D** we had earlier used for π-cationic cyclization of *N*-substituted pyroglutamic acids.[29b] Under these conditions, (*S*)-*N*-benzyl-6-oxopipecolic acid (**8**) afforded, after 2 hours, a complex mixture from which we were able to extract three products. The latter were identified as the tricyclic lactams **9**, **11** and **19**, isolated in yields of 17%, 9% and 49%, respectively (Scheme 7).



Scheme 7. The reaction of (*S*)-*N*-benzyl 6-oxopipecolic acid (**8**) with Eaton's reagent (Method **D**).

The formation of **19** takes place after protonation of ketone **9** and interfacial hydride transfer in acidic environment provided by Eaton's reagent. This compares well with results obtained both in the pyrroloisoquinolinone **14** and in pyridoisoquinolinone **11** series when PPA was used as an activator (Scheme 3, **Parts A** and **B**). Thus, it starts with ketone **9** protonation into the cation **I** followed by hydride migration leading to the *N*-acyliminium salt **S** and the alcohol **20** (Scheme 8). Alcohol **20** furnished the starting ketone **9** by oxidation or enamide **21** by dehydration. The latter intermediate afforded ultimately the tricyclic pyridone **11**, after an allylic oxidation and isomerization.[31] The keto-lactam **19** is finally obtained by considering the unstable *N*-acyliminium species **S** generated in the second step after its deprotonation followed by a thermodynamically favorable oxidation via the enamido-ketone **T** never isolated in the reaction media.



Scheme 8. Plausible mechanism of the formation of pyridoisoquinolinone **11** from ketone **9** when treated with Eaton's reagent.

For the sake of comparison, the results obtained for the π-cationic cyclization of (*S*)-*N*-benzyl 6-oxopipecolic acid (**8**) under different acidic conditions have been summarized in Table 1.

Table 1. Products from catalyzed cyclization of acid **8** (δ-lactams) compared to the ones obtained from *N*-arylmethyl glutamic acid of type **6** (γ-lactams).[a]

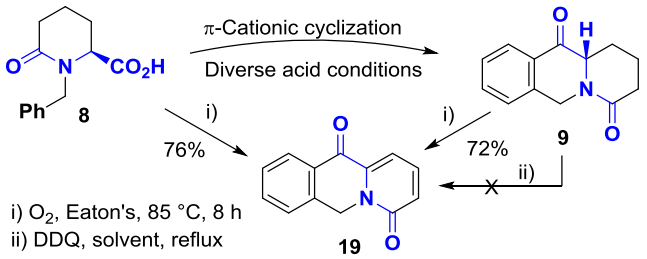
Acid[b]	Lactam **9**	Lactam **11**	Bis-lactam **12**	Enamide **15**	Enamidone **16**	Lactam **19**
Method **A**	**71**	no[f]	no	no	nep	no
" [c]	**65-78**[e]	no	no	no	nep	no
Method **B**	**26**	**21**	**15**	no	nep	no
" [c]	no	no	no	-[g]	nep	no
Method **C**	**57**	no	**12**	**13**	**6**	no
" [c]	**30-70**[e]	no	no	**17-33**[e]	no	no
Method **D**	**49**	**9**	no	no	nep	**17**
" [c]	no	no	no	-[g]	nep	no

[a] The ratio of isolated products in %. [b] Method used: $SOCl_2$/$AlCl_3$ (Method **A**), PPA (Method **B**), TFFA/BF_3.Et_2O (Method **C**) and P_2O_5/$MeSO_3H$ (Method **D**). [c] Results from (*S*)-*N*-arylmethyl glutamic acid (**6**). [d] Not expected product: nep. [e] Many other by-products were isolated. [f] Not obtained: no. [g] Only products of *N*-acyliminium cations trapping with aryl were obtained.

From the results summarized in Table 1, it appeared that the treatment of *N*-substituted pyroglutamic acids of type **6** (pyrrolidinone series) with PPA (Method **B**) or TFAA/BF_3.Et_2O (Method **C**) often induced a decarbonylation process to generate stable *N*-acyliminium salts. The latter in the absence of nucleophiles, produces *N*-substituted 1*H*-pyrrol-2(5*H*)-ones similar to the enamide **15** and/or their ancillary α-hydroxy lactams after hydrolysis in the reaction media. However, the case of *N*-benzyl oxopiperidine carboxylic acid (**8**) is more complex; depending on the exact conditions up to six different products could be formed. Among those the expected ketone **9** can be isolated in 26 to 71% yields. To the best of our knowledge, dimers comparable to **12** in pyrrolidinone series were never reported neither from *N*-acyliminium salt generated *in situ* nor from corresponding enamide obtained by its dehydration.[39] Enaminocarbonyl lactam analogous to **16** were for their part obtained only when starting from amino acrylates[40] or from oxidation of *N*-benzyl azepinones.[41] On the other hand, the reaction of the nucleophilic enamide **15** with TFAA leads to the trifluoroacetyl ketone **16** (Method **C**). Related reactions were already observed when chlorosulfonyl isocyanate was opposed to dihydropyridone **15** as partner[42] as well as in the *N*-thienyl-methyl tetrahydropyridone series.[25]

Importantly, these results confirm again the high impact of the ring size of saturated aza-compounds on the course of the π-cationic cyclization and the relative stability of the tricyclic systems towards the reaction conditions.

Having evoked constantly the hydride transfer and oxidation processes in the various proposed mechanisms (Schemes 3 and 8), we next decided to examine the truthfulness of these suggestions. Thus for the confirmation of the essential participation of oxidation process (by air oxygen) in the last step of transformation of carboxylic acid **8** and corresponding ketone **9** into tricyclic keto-pyridone **19** in a domino process, we have carried out these reactions in the presence of oxygen (see Scheme 9).



Scheme 9. Transformation of *N*-benzyl 6-oxopipecolic acid (**8**) and ketone **9** into pyridoisoquinoline **19** under oxidative conditions.

We were delighted to see that these reactions conditions (modified Method **D**) in both cases were clean and provided the expected 4*H*-pyrido[1,2-*b*]isoquinoline-4,11(6*H*)-dione (**19**) as the sole domino product in good yields of 76% and 72%, respectively, when starting from **8** and **9**. Alternatively, we noticed that all attempts to aromatize ketone **9** into keto-pyridone **19** by heating with freshly crystallized DDQ in boiling benzene or toluene were unsuccessful.[37] Finally, the structure of product **19** was confirmed by single-crystal X-ray diffraction analysis (Figure 5).[43]

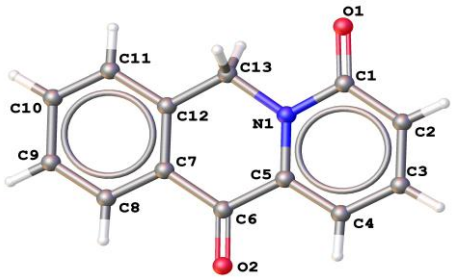
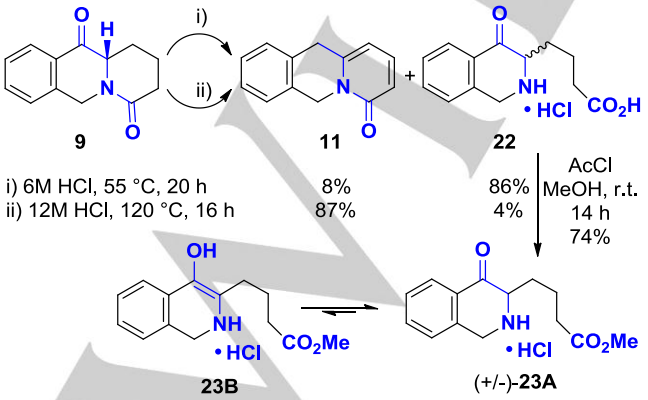


Figure 5. Stick drawing of 4*H*-pyrido[1,2-*b*]isoquinoline-4,11(6*H*)-dione (**19**).

Based on our previous reports[31] outlining an intermolecular shift in the transformation of pyrrolo[1,2-*b*]isoquinoline-3,10-dione (**7**) into 3-(4-hydroxy-3-isoquinolinyl)propanoic acid with concentrated hydrochloric acid solutions, treatment of tricyclic ketone **9** with different HCl solutions was intended (Scheme 10).



Scheme 10. Hydrolysis of ketone **9** in hydrochloric acid conditions.

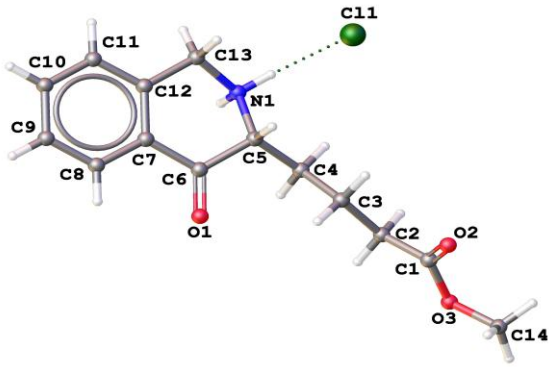


Figure 6. Stick drawing of racemic methyl 4-(4-oxo-1,2,3,4-tetrahydroiso-quinolin-3-yl)butanoate (**23A**).

As shown in Scheme 10, the hydrolysis of the tricyclic lactam **9** in acidic media leads to the formation of two compounds identified to be the tricyclic pyridone **11** and the novel and racemic amino-acid **22** in different ratios depending on the HCl solution concentration. Because the acid **22** could not be sufficiently purified, for better characterization it was converted to the corresponding methyl ester **23** (e.g., AcCl, MeOH, r.t., 14 h; 74%), which was purified by crystallization from dry methanol. The structure of **23** was ultimately established by X-ray crystallographic analysis (Figure 6)[44] confirming that both isoquinolines **22** and **23** are racemic. This owes to the easy racemization of the initially formed aminoketo-acid (S)-4-(4-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)butanoic acid (**23A**) in acidic medium *via* the enol form **23B** (Scheme 10).

The physicochemical and spectral data of the product **11** obtained here by a domino process, consisting on reduction →dehydration→oxidation→isomerization, are in full agreement with the derivative, prepared by reaction of ketone **4** with PPA (Method **B**, Scheme 2). In addition its structure was established by an X-ray crystallographic analysis (Figure 7).[45]

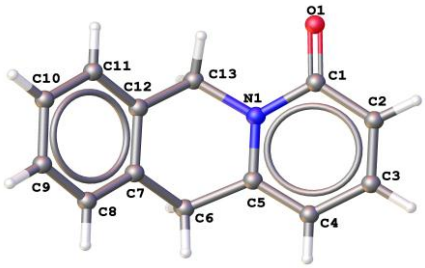
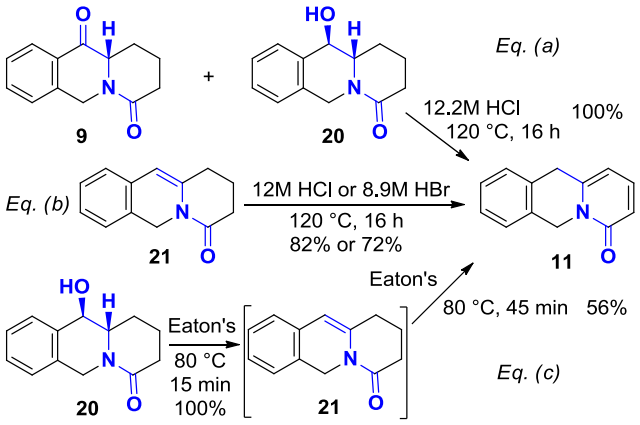


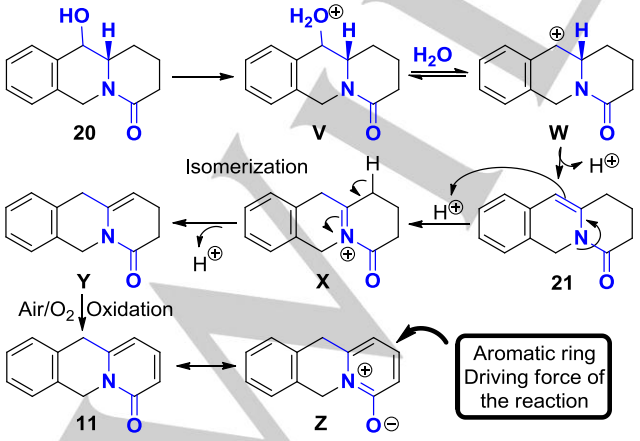
Figure 7. Stick drawing of 6,11-dihydro-4*H*-pyrido[1,2-*b*]isoquinolin-4-one (**11**).

We then continued to explore mechanistic considerations in connection with the reaction mechanisms proposed in Schemes 3 and 8 because of the wish to enhance our knowledge about these transformations. In this perspective, the synthesis and reactivity of alcohol **20** and enamide **21** as advanced intermediates for the production of tricyclic systems **11** and **19** as ultimate products in certain acid-catalyzed Friedel-Crafts cyclization was envisioned.



Scheme 11. Short pathways leading to tricyclic pyridone **11**.

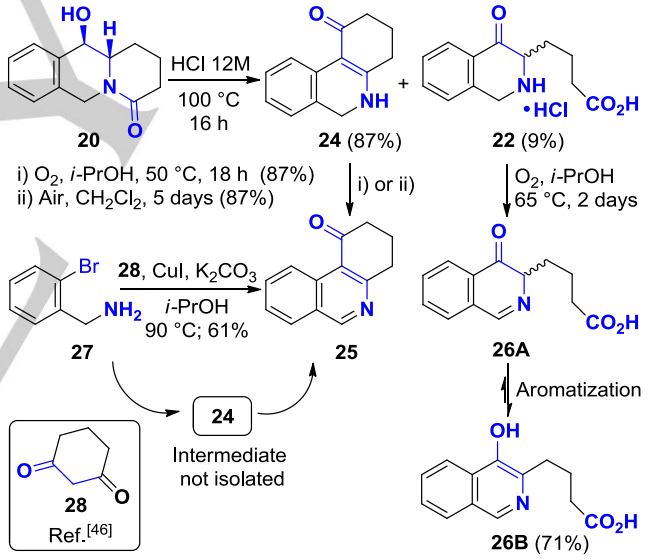
As highlighted in Scheme 11 three reactions were realized. The reaction of an equimolar mixture of ketone **9** and the corresponding pure *trans*-diastereomer of alcohol **20**, obtained by diastereoselective reduction of **9** (e.g., $NaBH_4$, MeOH, 0–5 °C; 73.5%)[35a] with 12.2M HCl resulted in the formation of tricyclic pyridone **11** in quantitative yield (*Eq. (a)*). This clearly implies the generation of alcohol **20** from the ketone in the reaction media by the protonation of ketone **9** followed by intermolecular hydride transfer evoked in the beginning of the proposed reaction mechanism (Schemes 3 and 8). In the same line, the treatment of tricyclic enamide **21** with hydrochloric acid (12M) or hydrobromic acid (8.9M) solution resulted in the formation of the expected tricyclic pyridone **11** in 82% and 72% yields, respectively (*Eq. (b)*). This reaction indicates that allylic oxidation of enamide **21** followed by dienic isomerization occurred along with the formation of pyridone **11** from carboxylic acid **8** or ketone **9**. We then anticipated that the treatment of alcohol **20** with Eaton's reagent (e.g., Eaton's reagent, 80 °C, 1 h) would allow the formation of the expected tricyclic system **11**. Again the product **11** was obtained in 100% then 56% yield (*Eq. (c)*) demonstrating the pivotal role of alcohol **20** as proposed in the reaction mechanisms above.



Scheme 12. Plausible mechanism of the formation of **21** and **11** starting from the tricyclic ketone **9** in hydrochloric acid conditions via the alcohol **20**.

All independent reactions given are in perfect agreement with the mechanism proposed for the formation of the tricyclic system **11** in Scheme 8 as reproduced in Scheme 12. Thus, alcohol **20** was generated *in situ* by a hydride migration followed by proton displacement accompanied by the *N*-acyliminium salt **S** (Scheme 8). Protonation of **20**, the dehydration of the formed intermediate **V** and the following deprotonation of **W** provides the enamide **21**. In the latter, the hydrogen in allylic position is acidic enough to enable its isomerization into enamide **Y** (never isolated from the reaction media) by protonation/deprotonation of the *N*-acyliminium species **X**. The tricyclic system **11** stabilized by the semi-aromatic pyridinium form **Z** was obtained ultimately by oxidation (air, O_2).

These results demonstrate the efficacy of the treatment of tricyclic enamide **21** with a hydrochloric acid solution (12M) leading to the formation of tricyclic pyridone **11** via a domino allylic oxidation/ isomerization (*Eq. (b)*, Schemes 12, 13). In this context the behavior of alcohol **20** under same acid conditions was considered. Thus, the reaction of **20** at 100 °C for 16 h (Scheme 13) provided interestingly a separable mixture of the acid hydrochloride **22** and the tetrahydrophenanthridin-1(2*H*)-one (**24**) in yields of 9% and 87%, respectively.



Scheme 13. Treatment of enantiopure alcohol **20** with 12M hydrochloric acid solution under same conditions as for the tricyclic ketone **9**.

Further post oxidation of tetrahydrophenanthridin-1(2*H*)-one (**24**) under two different conditions were realized and lead to the formation, in exactly the same yield of 87%, of the known 3,4-dihydrophenanthridin-1(2*H*)-one (**25**). The latter was previously obtained in a domino process consisting in a CuI-catalyzed coupling (2-bromophenyl)methanamine (**27**) and cyclohexane-1,3-dione (**28**) followed by spontaneous oxidation.[46] Since the characterization of **25** in its first report was not complete, the structure of this product was then established by X-ray crystallographic analysis among others (Figure 8).[47] Similarly, the oxidation of the minor product, acid hydrochloride **22**, by

using oxygen as oxidant (Scheme 13) resulted in the formation of 4-(4-hydroxyisoquinol-in-3-yl)-butanoic acid (**26B**) as the thermodynamically stable product via the imine-one **26A** (71% yield).

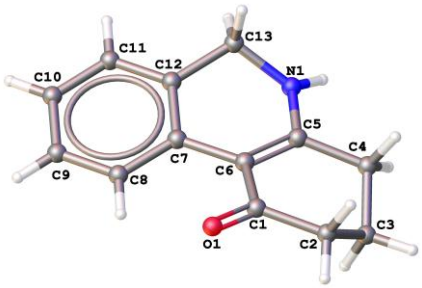
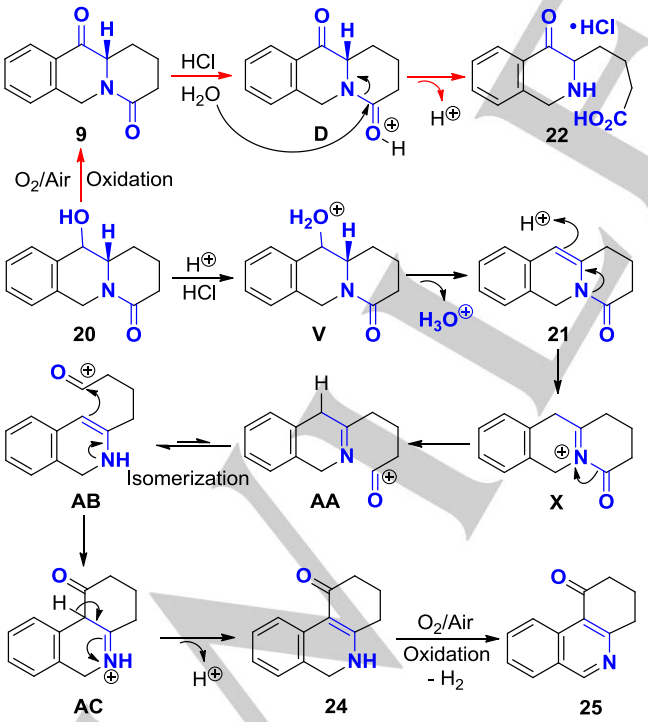


Figure 8. Stick plot of 3,4-dihydro-phenanthridin-1(2*H*)-one (**24**).

Mechanistically speaking (Scheme 14), the co-formation of the acid hydrochloride **22** (isolated in only 9% yield) supposes the transformation of the alcohol **20** into the corresponding ketone **9**. This is made possible by the presence air oxygen in the reaction medium. The oxidation is then followed by the lactam cleavage activated by hydrochloride acid via the intermediate **D** as mentioned in aromatic and heteroaromatic fused indolizine series.[8a,9h,31b,33a,48] This fact is also confirmed by the obtained result when the ketone **9** is directly treated with an hydrochloric acid solution. Under these conditions the reaction provides to same product **22** with 86% yield in the best case (Scheme 10).



Scheme 14. Plausible mechanism of the formation of carboxylic acid **22**, ketones **24** and **25** starting from the tricyclic alcohol **20** under hydrochloric acid conditions.

As for the formation of 3,4-dihydrophenanthridin-1(2*H*)-one (**25**), it can be explained by the possible mechanism highlighted in Scheme 14. Thus, starting alcohol **20**, under acid conditions (HCl 12M), undergoes the tricyclic enone **21** formation *via* the intermediacy of protonated species **V** (Schemes 3, 8). Product **21** after protonation with HCl furnish the stable *N*-acyliminium cation **X** which would cleave into the acylium intermediate **AA**. The latter imine in equilibrium with enamine **AB** by isomerization can lead to the cyclized product **25** after π-cationic cyclization into **AC**, its deprotonation into enamino-ketone **24** followed ultimately by air oxidation. In our case, we were able to isolate the fused enaminone **24** as the major reaction product in 87% yield (Scheme 13).

Conclusions

In summary, we reported here the treatment of (*S*)-*N*-benzyl 6-oxopiperidine carboxylic acid (δ-lactam) (**8**) under various Friedel-Crafts conditions - a process richer and more complex than reported for the corresponding (*S*)-*N*-substituted pyroglutamic acids (γ-lactams) earlier. In short, we have shown that the standard protocol using Method **A** ($SOCl_2/AlCl_3$) is superior in terms of yields of the expected tricyclic keto-lactam. On the other hand, approaches using PPA (Method **B**), $(CF_3CO)_2O/BF_3.Et_2O$ (Method **C**) and Eaton's reagent (Method **D**) are also very interesting since parallel to the expected keto-lactam (26-71% yields), other keto-lactams, uncyclized enamide monomers and dimers as well as enamidones containing a CF_3CO fragment in certain cases are isolated generally in good overall yields.

From these results, it appears that the use of Methods **B** and **C** often induces a decarbonylation process to generate stable *N*-acyliminium salts in addition to the acylium cation. The Method **A** provides only the ketone **9** (the Friedel-Crafts product) in contrary to carboxylic acids in γ-lactams which furnished in addition to the π-cationic cyclization compounds many other by products. To the best of our knowledge, dimers in γ-lactams series were never reported either from *N*-acyliminium salt generated *in situ* or from corresponding enamide obtained by its dehydration, contrary to the results reported in this paper dealing with δ-lactams derivatives (Methods **B, C**). On the other side, reaction of the nucleophilic uncyclised enamide with TFAA leads to the trifluoroacetyl ketone (Method **C**). If similar behaviour was never observed in δ-lactams series, a related reaction has already been observed in the *N*-thienylmethyl tetrahydro-pyridone series reported by our group.

The use of Method **D** demonstrates the formation of keto-lactam *via* the acylium species accompanied by interesting events, namely the protonation of ketone **9**, followed by an interfacial hydride transfer and oxidation. These events were observed also with other methodologies used herein and in the case of the γ-lactams series. These phenomena were proved by independent reactions driven from tricyclic ketone alone or mixed with corresponding alcohol in the presence of air/oxygen or not. In this context, treatment of tricyclic alcohol with HCl resulted not only in the cleaved amino-keto-acid product which

re-aromatize spontaneously to functioned isoquinoline but also to original tetrahydrophenanthridin-1(2*H*)-one (**24**) and corresponding 3,4-dihydrophenanthridin-1(2*H*)-one (**25**).

Finally, these results confirm once again the high impact of the ring size of saturated aza-compounds on the course of the π-cationic cyclization. They confirm also the relative stability of the tricyclic systems in δ-lactams series compared to the ones in *γ*-lactams towards the acidic reaction conditions.

Experimental Section

Crystallography: Data collection and cell refinement for **11**, **12**, **13**, **19**, **23A** and **24** were carried out using diffractometer Stoe StadiVari using Pilatus3 R 300K detector at 100 K, and using CuKα radiation (λ = 1.54186 Å, microfocus source Xenocs Genix3D Cu HF) The structures were solved using program SHELXT[49] or SuperFlip,[50] and refined by a full-matrix least-squares procedure with the SHELXL (ver. 2018/3),[49] and drawn with the OLEX2 package.[51] Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC nos° 1839259–1839264) for the products. Copies of the data can be obtained free of charge at the following address: http://www.ccdc.cam

General Remarks. Melting points were obtained using a Boetius apparatus and are corrected. Commercial reagents were used without further purification. All solvents were distilled before use. Flash column liquid chromatography (FLC) was performed on silica gel Kieselgel pore size 60 Å (40–63 μm particle size, 230–400 mesh particle size) and analytical thin-layer chromatography (TLC) was performed on aluminium plates pre-coated with either 0.2 mm (DC-Alufolien, Merck) or 0.25 mm silica gel 60 F254 (ALUGRAM-SIL G/UV254, Macherey-Nagel). The compounds were visualized by UV fluorescence and by dipping the plates in an aqueous H_2SO_4 solution of cerium sulphate/ammonium molybdate followed by charring with a heat gun. HPLC analyses were performed on Varian system 9012 with diode array Varian 9065 polychrom UV detector: column CC 250/3 Nucleosil 120-5 C18, 250x3 mm (Macherey Nagel). Mobile phase: solvent A: water/acetonitrile/methanesulfonic acid (1000/25/1), solvent B: water/acetonitrile/methanesulfonic acid (25/1000/1), elution mode: gradient with 5-50% solvent B, flow rate: 0.65 ml/min, UV detection: 210 nm (DAD), 35 °C, 20 min. GC-MS analyses were performed on GC MS Varian Saturn 2100 T, ion trap MS detector, 70 eV. Column: Varian, FactorFour capillary column VF -5ms 30mx0.25 mm ID, DF=0.25. Optical rotations were measured with a POLAR L-IP polarimeter (IBZ Messtechnik) with a water-jacketed 10.000 cm cell at the wavelength of the sodium line D (λ = 589 nm). Specific rotations are given in units of 10^{-1} deg.cm^2.g^{-1} and concentrations are given in g/100 mL. Infrared spectra were recorded on a Nicolet 5700 FT-IR spectrometer as ATR discs (ATR) or as thin films on ATR plates (film). NMR spectra were recorded on a VNMRS 600 NMR spectrometer (Varian) with operating frequencies 599.76 MHz for ^{1}H, 564.28 MHz for ^{19}F, 150.82 MHz for ^{13}C and 60.78 MHz for ^{15}N nuclei. The spectrometer was equipped by an inverse triple resonance probe and a standard double channel X/H tunable probe with the possibility to tune the high frequency channel to the resonance frequency of ^{19}F. NMR spectra from all samples were measured in $CDCl_3$, d_6-DMSO or CD_3OD at 25 °C. Chemical shifts (δ) are quoted in ppm; the chemical shift axes were calculated using the reference signals of TMS (for ^{1}H and ^{13}C NMR), $CFCl_3$ (for ^{19}F NMR) and CH_3NO_2 (for ^{15}N NMR). These axes were shifted using an automatic re-calculation system exploiting the ^{2}H signal of the used solvent; for the precise correction of the chemical shift axes, the ^{1}H and ^{13}C signals of TMS (present in spectra obtained in $CDCl_3$; 0.000 ppm), ^{1}H signals of residual d_5-DMSO (2.50 ppm) and CD_2HOD (3.31 ppm), and the ^{13}C signals of d_6-DMSO (39.52 ppm) and CD_3OD (49.00 ppm) were used as references. Depending on the possibilities and amount of information needed to provide the best possible structural proof ^{1}H, standard ^{13}C, quantitative ^{13}C, ^{13}C-attached proton test, ^{15}N with inverse gated ^{1}H decoupling, and ^{19}F NMR measurements were underdone, supported by ^{1}H-^{1}H COSY (with gradient coherence selection and with/without zero quantum filtering), ^{1}H-^{13}C HSQC (with varied use of gradient coherence selection, adiabatic 180 ° pulses on the ^{13}C channel and non-uniform sampling), ^{1}H-^{13}C HMBC (with gradient coherence selection and varied use of adiabatic 180 ° pulses on the ^{13}C channel and semi-selective ^{13}C excitation with WURST2i[52] pulses), ^{13}C-^{13}C INADEQUATE (with an adiabatic 180 ° pulse for compound **12** and with a universal 180 ° rotation pulse[53] for compounds **9** and **16**), f2-coupled Perfect CLIP-HSQC[54] and ^{1}H-^{15}N HMBC (with gradient coherence selection) spectra. Experimental and processing parameters, together with raw NMR data are available on demand from the authors. For the precise extraction of chemical shift and *J*-coupling values manual spin simulation was performed if needed in the spin simulation package built in the MestReNova software (version 11.0.2-18153). The elemental analyses were carried out by the microanalysis laboratory of IRCOF, F-76130 Mt. St. Aignan, France or carbon, nitrogen, hydrogen and sulfur content was determined by elemental analysis, using an analyser Vario Macro Cube. High-resolution spectrometry was performed on Micromass Q-Tof Micro MS system with ESI$^+$ ionization (measured mass represents M+Na$^+$) and LC-MS chromatographic separation was performed on Agilent 1260B LC-MS system using HALO C18 column (2,1 × 50 mm, 5.0 *μ*m particle size). A 10 min gradient elution was performed at 1,5 mL/min flow rate as following: maintain H_2O/MeOH with 0,1% formic acid from 5% to 100%. MS detector used combined ionization (ESI + APCI) in positive mode, 50% scan and 50% SIM. All samples for analysis and NMR spectroscopy were dried for 48 hours at Laboratory Freeze Dryer Alpha 2-4 LDplus Lyophilizer.

(*S*)-1,2,3,11*a*-Tetrahydro-4*H*-pyrido[1,2-*b*]isoquinoline-4,11(6*H*)-dione (9). Method A: To a solution of a freshly crystallized carboxylic acid **8** (23.33 g, 0.1 moL) in dry CH_2Cl_2 (750 mL) was added thionyl chloride (10.9 mL, 0.15 moL) at 0 °C. The mixture was stirred under reflux for 4 h, and then cooled to -5 °C. Under vigorous stirring, dry $AlCl_3$ (33.3 g, 0.25 moL) was added in small portions. The mixture was stirred for 15 min. at 0 °C, cold water (220 mL) was added carefully. The two pure layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (50 mL). After washing with brine, the CH_2Cl_2 phase was dried with $MgSO_4$ and concentrated. The resulting product was purified by flash column chromatography (400 g SiO_2, 4 cm x 125 cm, CH_2Cl_2, CH_2Cl_2/MeOH 50:1) to yield a light yellow solid. Recrystallization from toluene/n-heptane (3:2) gave **9** (9.25 g, 71%) as light yellow crystals; mp: 105.4-109.4 °C. See the Supporting Information part for complete NMR signal assignment.

Method B: A mixture of freshly crystallized carboxylic acid **8** (1.75 g, 7.5 mmol) and freshly prepared PPA (45 g) was heated at 100 °C for 1 h. The reaction mixture was cooled, neutralized with a saturated Na_2CO_3 solution and the aqueous layer was extracted with CH_2Cl_2 (3 x 45 mL). The combined extracts were washed with H_2O (3 x 30 mL), brine (30 mL) and dried (Na_2SO_4). Evaporation of the solvent afforded a dark-yellow oil (1.37 g) as a mixture of products **9**, **11** and **12,** which was separated and purified by chromatography (30 mm x 120 cm, 100 g SiO_2, CH_2Cl_2, CH_2Cl_2/MeOH 250:1, CH_2Cl_2/MeOH 50:1) on a silica gel column. After chromatography we isolated (*S*)-1,2,3,11*a*-tetrahydro-4*H*-pyrido[1,2-*b*]-isoquinoline-4,11(6*H*)-dione (**9**) as a light yellow solid in 26% yield (421 mg), 6,11-dihydro-4*H*-pyrido[1,2-*b*]isoquinolin-4-one (**11**) as light yellow crystals in 21% yield (305 mg) and finally 1-benzyl-5-(1-benzyl-6-oxopiperidin-2-yl)-3,4-dihydropyridin-2(1*H*)-one (**12**) as light yellow crystals in 15% yield (210 mg).

Method C: A stirred mixture of freshly crystallized acid **8** (1.17 g, 5 mmol) and trifluoroacetic anhydride (TFAA, 1.26 mL, 10 mmol) in dry 1,2-dichloroethane (50 mL) was heated at 45 °C for 45 min., then cooled with an ice bath and boron trifluoride etherate ($BF_3.Et_2O$, 5.7 mL, 46 mmol) was added. After stirring at 60 °C for 18 h under nitrogen atmosphere solvents were evaporated, then a saturated solution of K_2CO_3 in water (150 mL) was added and the mixture was stirred at room temperature for 5 min. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL); the organic phase was washed with water and dried (Na_2SO_4). Evaporation of the solution afforded a yellow oil (1.02 g) as a mixture of **9**, **12**, **15** and **16**, which was purified by slow chromatography (30 mm x 120 cm, 100 g SiO_2, CH_2Cl_2, CH_2Cl_2/MeOH 600:1, CH_2Cl_2/MeOH 400:1, CH_2Cl_2/MeOH 100:1, CH_2Cl_2/MeOH 30:1) on a silica gel column. After chromatography the products were identified to be (*S*)-1,2,3,11*a*-tetrahydro-4*H*-pyrido [1,2-*b*]isoquinoline-4,11 (6*H*) dione (**9**) as yellow crystals in 57% yield (615 mg), 1-benzyl-5-(1-benzyl-6-oxopiperidin-2-yl)-3,4-dihydropyridin-2(1*H*)-one (**12**) as yellow crystals in 17% yield (154 mg), 1-benzyl-3,4-dihydropyridin-2(1*H*)-one (**15**) as colorless crystals in 13% yield (121 mg) and finally 1-benzyl-5-(2,2,2-trifluoroacetyl)-3,4-dihydropyridin-2(1*H*)-one (**16**) as a colorless oil in 5.6% yield (79 mg).

Method D: A mixture of freshly prepared carboxylic acid **8** (2.33 g, 10 mmol) and Eaton's reagent (P_2O_5/CH_3SO_3H/1/10 w/w) (25 mL) was heated at 90 °C for 1 h. The reaction mixture was cooled and ice (20 g) and water (80 mL) were added carefully. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were diluted with AcOEt (200 mL), washed with saturated Na_2CO_3 (50 mL), H_2O (30 mL), brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give crude yellow semi-crystalline solid (2.88 g) which was purified by chromatography (30 mm x 120 cm, 120 g SiO_2, CH_2Cl_2, CH_2Cl_2/MeOH 200:1, CH_2Cl_2/MeOH 100:1, CH_2Cl_2/MeOH 30:1 as eluent) on a silica gel column. The chromatography purification provided 358 mg (17% yield) of (*S*)-1,2,3,11*a*-tetrahydro-4*H*-pyrido [1,2-*b*]isoquinoline-4,11(6*H*)-dione (**9**), 177 mg (9% yield) of 6,11-dihydro-4*H*-pyrido[1,2-*b*]isoquinolin-4-one (**11**) and ultimately 1.01 g (49% yield) of 4*H*-pyrido[1,2-*b*]isoquinoline-4,11(6*H*)-dione (**19**).

6,11-Dihydro-4*H*-pyrido[1,2-*b*]isoquinolin-4-one (11). The keto-amide **9** (1.08 g, 5 mmol) was added to PPA (15 g) at 80 °C and the mixture was then heated at 110 °C for 2 h in an argon atmosphere (TLC monitoring). After cooling to room temperature, 20 ml of cold water was added and the mixture was neutralized slowly with a saturated solution of Na_2CO_3. The aqueous layer was extracted with AcOEt (3 x 60 mL), the combined organic layers were dried, concentrated and the resulting dark-red oil (1.0 g) was purified by column chromatography (80 g SiO_2, 25 mm x 75 cm, CH_2Cl_2, CH_2Cl_2/MeOH, 50:1) to give diene-lactam **11** (889 mg, 90% yield) as a light yellow oil, which crystallizes when standing on air slowly. Recrystallization from a mixture of cyclohexane/*n*-heptane (5:1) gave pure diene (489 mg, 72% yield) as light yellow crystals; mp 99.1-99.8 °C; R_f = 0,45 (CH_2Cl_2/*i*-PrOH; 10:1), IR (ṽ, cm^{-1}, ATR): 3033, 2968, 1650, 1590, 1573, 1544, 1490, 1459, 1433, 1423, 1414, 1340, 1315, 1269, 1223, 1186, 1153, 1142, 1113, 1054, 958, 945, 885, 840, 794, 774, 754, 719, 707, 656, 617, 564, 541, 508, 429. HRMS: (ESI) Calculated for $C_{13}H_{11}NO$ (197.24) $[M+Na]^+$: 220.0733, found 220.0732. See the Supporting Information part for complete NMR signal assignment.

1-Benzyl-5-(1-benzyl-6-oxopiperidin-2-yl)-3,4-dihydropyridin-2(1*H*)-one (12). Hydroxy-amide **18** (411 mg, 2 mmol) was added to trifluoroacetic acid (TFA, 10 mL) at r.t. and the mixture was then heated at 100 °C for 5 h in an argon atmosphere (TLC monitoring). After cooling to room temperature, TFA was evaporated, then a saturated solution of sodium carbonate in water (20 mL) was added and the mixture was stirred at room temperature for 5 min. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL); the organic phase was washed with water and dried. Evaporation afforded a yellow oil, which was purified by chromatography (20 mm x 70 cm, 55 g SiO_2, CH_2Cl_2, CH_2Cl_2/methanol 100:1) on a silica gel column – the procedure afforded dimer **12** (532 mg, 71% yield) as a light yellow oil which slowly solidifies. Crystallization from dry n-heptane provide pure **12** (480 mg, 64 %), mp 108.1-109.8 °C. R_f = 0.47 (CH_2Cl_2/*i*-PrOH; 10:1), IR (ṽ, cm^{-1}, ATR): 3028, 2945, 1668, 1634, 1495, 1438, 1400, 1379, 1358, 1325, 1298, 1270, 1182, 1146, 1072, 1027, 989, 944, 862, 850, 728, 696, 655, 607, 496, 459. HRMS: (ESI) Calculated for $C_{24}H_{26}N_2O_2$ (374.48) $[M+Na]^+$: 397.1886, found 397.1882. See the Supporting Information part for complete NMR signal assignment.

(*R,S*)-1,2,3,6,11,11*a*-Hexahydro-4*H*-pyrido[1,2-*b*]isoquinolin-4-one (*rac*-13). 10% Pd-C (60 mg) was added to a solution of freshly crystalized 6,11-dihydro-4*H*-pyrido[1,2-*b*]isoquinolin-4-one (**11**) (394.0 mg, 2.0 mmol) in dry methanol (25 mL). The solution was stirred for 6 h under a pressure of hydrogen at 203 kPa (TLC monitoring). After completion, the solution was filtered through a Celite pad to remove the catalyst and concentrated in *vacuo*. The crude product (390 mg) was chromatographed on silica gel (20 mm x 75 cm, 80 g SiO_2, eluent: CH_2Cl_2/methanol 50:1) to afford pure *rac*-**13** (338 mg, 84% yield) as a colorless oil, which quickly crystallized on standing. After crystallization from *i*-hexane, the product *rac*-**13** was obtained as colorless crystals (298 mg, 74% yield); m.p. 80.6-81.3 °C. R_f = 0.19 (AcOEt/*i*-hexane 3:1). HRMS: (ESI) Calculated for $C_{13}H_{15}NO$ (201.27) $[M+Na]^+$: 224.1046, found 224.1043. Spectral data of **13** was consistent with data reported in the literature.[34b]

1-Benzyl-3,4-dihydropyridin-2(1*H*)-one (15). Hydroxy-amide **18**[37] (411 mg, 2 mmol) was added to trifluoroacetic acid (TFA, 10 mL) at room temperature. The solution was stirred at room temperature for 6 h, solvent was evaporated and the residue was dissolved in CH_2Cl_2. The solution was extracted with aqueous sodium bicarbonate, aqueous phases were washed with CH_2Cl_2 again. CH_2Cl_2 and the organic phases were dried (sodium sulfate) then evaporated giving a yellow oil which was purified by chromatography (20 mm x 70 cm, 80 g SiO_2, CH_2Cl_2, CH_2Cl_2/methanol 250:1) on a silica gel column – the procedure afforded olefin **15** (318 mg, 85%) as a colorless oil, which slowly crystallized on standing. Recrystallization from *n*-pentane gave olefin **15** (266 mg, 71% yield) as colorless crystals; mp 41.6-42.3 °C (reported as colorless oil)[38]. R_f = 0.68 (CH_2Cl_2/*i*-PrOH; 10:1). HRMS: (ESI) Calculated for $C_{12}H_{13}NO$ (187.24) $[M+Na]^+$: 210.0889, found 210.0886. See the Supporting Information for NMR signal assignment. Spectral data of **15** were consistent with data reported in the literature.[38]

1-Benzyl-5-(2,2,2-trifluoroacetyl)-3,4-dihydropyridin-2(1*H*)-one (16). *N*-Benzyldihydropyridine-2(1*H*)-one (**15)** (187 mg, 1 mmol) was added slowly to trifluoroacetic anhydride (TFAA, 10 mL) and the mixture was then heated at 80 °C for 2 hours in an ace round-bottom pressure flask with a magnetic stir bar. After cooling to room temperature, TFAA was evaporated, then a saturated solution of sodium carbonate in water (20 mL) was added and the mixture was stirred at room temperature for 5 min. The aqueous phase was extracted with dichloromethane (3 x 50 mL); the organic phase was washed with water and dried. Evaporation afforded a pink oil, which was purified by chromatography (20 mm x 70 cm, 55 g SiO_2, CH_2Cl_2, CH_2Cl_2/methanol 500:1) on silica gel column gave trifluoroacetyl **16** (224 mg, 79 % yield) as a colorless oil. R_f = 0.78 (CH_2Cl_2/*i*-PrOH; 10:1), IR (ṽ, cm^{-1}, ATR): 3033, 1707, 1677, 1619, 1496, 1454, 1367, 1331, 1265, 1195, 1163, 1132, 1082, 1029, 972, 908, 884, 745, 721, 698, 664, 598, 532, 498, 426. HRMS: (ESI) Calculated for $C_{14}H_{12}F_3NO_2$ (283.25) $[M+Na]^+$: 306.0712, found 306.0708. See the Supporting Information part for complete NMR signal assignment.

4*H*-Pyrido[1,2-b]isoquinoline-4,11(6*H*)-dione (19). A flask containing freshly crystallized carboxylic acid **8** (467 mg, 2 mmol) or freshly

crystallized dione **9** (431 mg, 2 mmol) was dried *in vacuo* for 0.5 h before it was charged with oxygen. To this flask was added Eaton´s reagent (8 mL). The mixture was stirred at 85 °C for 12 h in an oxygen atmosphere. After cooling to room temperature, 10 mL of cold water was added and the mixture was neutralized slowly with a saturated solution of Na_2CO_3. The aqueous layer was extracted with 3 x 25 mL of CH_2Cl_2, the combined organic layers were dried, concentrated and the resulting dark-yellow oil (428 mg from **8** and 402 mg from **9**) was purified by column chromatography (80 g SiO_2, 25 mm x 85 cm, CH_2Cl_2, CH_2Cl_2/MeOH, 50:1) to give keto-diene **19** (320 mg, 76% yield from **3** and 303 mg, 72% yield from **9**) as light yellow crystals. Recrystallization from a mixture of acetone/*n*-pentane (5:1) gave pure keto-diene **19** (257 mg, 61% yield calculated when starting from **8** and 249 mg, 59% yield calculated when starting from **9**) as light yellow crystals; mp 178.8-181.4 °C; R_f = 0,49 (CH_2Cl_2/*i*-PrOH; 10:1), IR (ṽ, cm^{-1}, ATR): 3309, 3066, 2962, 2449, 1643, 1603, 1580, 1454, 1398, 1350, 1297, 1255, 1208, 1179, 1162, 1143, 1107, 1058, 999, 971, 951, 905, 867, 734, 723, 686, 634, 614, 554, 484, 436. HRMS: (ESI) Calculated for $C_{13}H_9NO_2$ (211.22) $[M+Na]^+$: 234.0525, found 234.0521. See the Supporting Information par for complete NMR signal assignment.

3-(3-Carboxypropyl)-4-oxo-1,2,3,4-tetrahydroisoquinolinium chloride (22). Ketone **9** (2.17 g, 10 mmol) was stirred at 55 °C for 16 h in a mixture of 37% HCl (12 mL) and water (10 mL) in an ace round-bottom pressure flask with a magnetic stir bar. After cooling, the reaction mixture was concentrated to dryness and the obtained oil was vigorously stirred overnight with dry CH_2Cl_2 (150 ml). Acid **22** precipitated upon stirring at room temperature. The solid (2.32 g, 86% yield) was filtered off, [TLC (Silica gel): R_f = 0.19 (AcOEt: MeOH, 10:1), ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.94 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.73 (td, *J* = 7.5, 1.3 Hz, 1H), 7.53 (t, *J* = 7.1 Hz, 2H), 4.58 (d, *J* = 16.1 Hz, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.31 (t, *J* = 6.0 Hz, 1H), 2.37 (ddd, *J* = 19.8, 11.7, 5.2 Hz, 2H), 2.15 – 2.05 (m, 1H), 1.89 – 1.75 (m, 3H)] and the organic phase was washed with water, dried (Na_2SO_4), and evaporated. The yellow oil obtained was purified by silica gel column chromatography (10 x 400 mm, 40 g SiO_2, eluent: CH_2Cl_2/MeOH, 50:1) to afford pale yellow crystals of diene **11** (158 mg, 8% yield). Because the acid could not be sufficiently purified, for better characterization it was converted to the corresponding methyl ester.

3-(4-Methoxy-4-oxobutyl)-4-oxo-1,2,3,4-tetrahydroisoquinolinium chloride (23). Acetyl chloride (0.64 mL, 9 mmol, 3 eq.) was added to a stirred mixture of acid hydrochloride **22** (HCl, 810 mg, 3 mmol) in anhydrous MeOH (5 mL) at 0 °C. The mixture was stirred for 14 h at room temperature. The solid ester hydrochloride (600 mg, 71% yield) was filtered off and the filtrate was evaporated to dryness, the resulting oil was dissolved in a minimum amount of water, neutralized with saturated Na_2CO_3 and extracted 3 times with DCM (total, 60 mL). The organic phase was washed with saturated NaCl solution, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (15 mm x 75 cm, 60 g SiO_2, eluent: AcOEt-MeOH, 25:1) to afford pale crystals (165 mg, 19% yield). Crystallization of the combined esters from methanol provided pure **23** (630 mg, 74% yield) as white crystals, mp 179.1-180.5 °C. TLC (Silica gel): R_f = 0.58 (AcOEt: MeOH, 10:1). IR (ṽ, cm^{-1}, ATR) = 2942, 2736, 2688, 2624, 2577, 2474, 2349, 1729, 1704, 1604, 1562, 1455, 1437, 1371, 1315, 1274, 1259, 1215, 1190, 1159, 1119, 1087, 1057, 995, 982, 951, 923, 889, 820, 758, 736, 672, 640, 579, 525, 480, 432. LC-MS, Calculated for $C_{14}H_{18}ClNO_3$ (283.75) $[M]^+$: *m/z* 283 (100%). See the Supporting Information part for NMR signal assignment.

6,11-Dihydro-4H-pyrido[1,2-*b*]isoquinolin-4-one (11). Using the procedure as described for the synthesis of acid **22** from ketone **9** (1.09 g, 5 mmol) in a 37% HCl (25 mL) at 115 °C for 16 h. The acid **22** (54 mg, 4% yield) and diene **11** (860 mg, 87% yield) were obtained. The physicochemical and spectral data of the compound obtained are in full agreement with the derivative prepared by reaction of ketone **9** with PPA as described above**.**

Preparation of 11 from ketone 9 and alcohol 20. Using the procedure as described for the synthesis of acid **22** from an equimolar mixture of ketone **9** (215 mg, 1 mmol) and alcohol **20** (217 mg, 1 mmol) in 37% HCl (10 mL) at 110 °C for 24 h. The yellow oil obtained after evaporation of dichloromethane was purified by silica gel column chromatography (10 x 450 mm, 60 g SiO_2, eluent: CH_2Cl_2/MeOH, 50:1) to afford pale yellow crystals of diene **11** (144 mg, 73% yield). The physicochemical and spectral data of the compound obtained are in full agreement with the derivative **11** prepared above by reaction of ketone **9** with PPA**.**

3,4,5,6-Tetrahydrophenanthridin-1(2*H*)-one (24). Using the procedure as described for the synthesis of acid **22** from alcohol **20** (869 mg, 4 mmol) in a 37% HCl (20 mL) at 110 °C for 18 h. Acid hydrochloride **22** (97 mg, 9% yield) was obtained after filtration. Then concentration of dichloromethane gave a yellow semi-crystalline mass which after purification by silica gel column chromatography (25 x 600 mm, 100 g SiO_2, eluent: AcOEt/MeOH 30:1) gave the crude enaminone **24** (694 mg, 87% yield). Crystallization from a mixture of AcOEt/*n*-heptane provided pure **24** (540 mg, 68% yield) as light yellow crystals, mp 181.2-184.7 °C. TLC (Silica gel): R_f = 0.53 (AcOEt: MeOH, 10:1). IR (ṽ, cm^{-1}, ATR) = 3242, 3099, 2945, 1608, 1574, 1530, 1483, 1445, 1422, 1397, 1369, 1328, 1285, 1271, 1204, 1175, 1143, 1114, 1082, 1053, 1034, 1010, 837, 810, 727, 652, 581, 536, 504, 443, 433. ^{1}H NMR (600 MHz, CD_3OD) δ 8.41 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.12 (dddd, *J* = 8.0, 7.3, 1.4, 0.7 Hz, 1H), 7.03 (ddd, *J* = 7.5, 7.3, 1.3 Hz, 1H), 6.93 (ddq, *J* = 7.5, 1.4, 0.8 Hz, 1H), 4.47 (app s, 2H), 2.50 (app t, *J* = 6.3 Hz, 2H), 2.42 (app t, *J* = 6.4 Hz, 2H), 1.92 – 1.81 (m, 2H). ^{13}C NMR (151 MHz, CD_3OD) δ 195.18, 166.85, 132.36, 128.02, 127.75, 126.37, 126.01, 125.89, 105.59, 46.12, 38.96, 30.20, 21.77. HRMS: (ESI) Calculated for $C_{13}H_{13}NO$ (199.25) $[M+Na]^+$: 222.0889, found 222.0892.

3,4-Dihydrophenanthridin-1(2*H*)-one (25). Method A: Solution of *i*-PrOH (5 mL) and water (1 mL) was bubbled with O_2 for 10 min. The tetrahydrophenanthridinone **24** (200 mg, 1 mmol) was added and then stirred at 50 °C in an oxygen atmosphere for 18 h to give 100% of isoquinoline **25** with a total yield of 78% after crystallization from *n*-heptane.

Method B: The tetrahydrophenanthridinone **24** (200 mg, 1 mmol) was dissolved in DCM (25 mL) and stirred 5 days on air give 100% of isoquinoline **25** with total yield of 76% after crystallization from *n*-heptane, mp 102.1-104.3°C (light yellow crystals). TLC (Silica gel): R_f = 0.62 (AcOEt: MeOH, 10:1). IR (ṽ, cm^{-1}, ATR) = 2954, 2480, 1742, 1626, 1581, 1497, 1435, 1373, 1350, 1319, 1297, 1244, 1173, 1136, 1103, 1045, 991, 935, 866, 754, 741, 681, 590, 548, 488, 409. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.39 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.84 (ddd, *J* = 8.6, 6.9, 1.4 Hz, 1H), 7.62 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 3.35 (t, *J* = 6.2 Hz, 2H), 2.81 (dd, *J* = 7.4, 6.0 Hz, 2H), 2.25 (dq, *J* = 7.7, 6.5 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.73, 160.82, 156.77, 133.89, 133.47, 128.42, 127.81, 127.23, 125.94, 120.85, 40.53, 33.60, 21.84. HRMS: (ESI) Calculated for $C_{13}H_{11}NO$ (197.23) $[M+Na]^+$: 220.0733, found 220.0736

4-(4-hydroxyisoquinolin-3-yl)butanoic acid (26B). Solution of *i*-PrOH (5 mL) and water (0.5 mL) was bubbled with O_2 for 5 min. The tetrahydro-isoquinole **22** (270 mg, 1 mmol) was added and then stirred at 65 °C in an oxygen atmosphere for 48 h to give 100% of isoquinolinecarboxylic acid **26b** with a total yield of 71% after crystallization from water. This product melted at mp 102.1-104.3 °C (white crystals, the substance gets a pale pink color after a few weeks). TLC (Silica gel): R_f = 0.49 (AcOEt: MeOH, 10:1). IR (ṽ, cm^{-1}, ATR) = 3185, 2638, 2260, 2042, 1695, 1651,

1616, 1587, 1429, 1421, 1394, 1273, 1235, 1199, 1154, 1092, 966, 883, 846, 769, 714, 661, 636, 552, 545, 519, 475, 435. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.79 (s, 1H, OH), 8.45 (d, *J* = 8.2 Hz, 1H), 8.28 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.12 (t, *J* = 7.5 Hz, 1H), 7.91 (t, *J* = 7.5 Hz, 1H), 3.09 (t, *J* = 7.5 Hz, 2H), 2.33 (t, *J* = 7.3 Hz, 2H), 2.08 – 1.99 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.91, 147.63, 146.27, 138.48, 135.84, 129.95, 129.63, 126.87, 125.91, 122.83, 32.71, 31.90, 24.03. HRMS: (ESI) Calculated for $C_{13}H_{13}NO_3$ (231.25) $[M+Na]^+$: 254.0788, found 254.0791.

Isomerization of 21 to pyridone 11 in hydrochloric acid solution. Using the procedure as described for the synthesis of **22** from 2,3-dihydro-1*H*-pyrido[1,2-*b*]isoquinolin-4(6*H*)-one (**21**) (190 mg, 1 mmol) in a 37% HCl (15 mL) at 120 °C for 10 h. The yellow oil obtained after cooling and concentration of dichloromethane was purified by silica gel column chromatography (20 x 600 mm, 100 g SiO_2, eluent: CH_2Cl_2/MeOH, 50:1) – the procedure provided pale yellow crystals of dienone **11** in 82% yield (161 mg). The physicochemical and spectral data of both compounds obtained are in full agreement with the derivative prepared by reaction of ketone **9** with PPA as described above.

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[35] **Crystal Data** for product **13**, $C_{13}H_{15}NO$ (M = 201.26 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 8.2461(7) Å, b = 14.6728(13) Å, c = 9.0290(7) Å, β = 108.738(6)°, V = 1034.55(15) Å^3, Z = 4, T = 100 K, μ(CuKα) = 0.640 mm^{-1}, *Dcalc* = 1.292 g/cm^3, 12302 reflections measured (11.332° ≤ 2Θ ≤ 142.728°), 1983 unique (R_{int} = 0.0643, R_{sigma} = 0.0478) which were used in all calculations. The final R_1 was 0.0480 (I > 2σ(I)) and wR_2 was 0.1170 (all data), CCDC no. 1839260.

[36] **Crystal Data** for product **12**, $C_{24}H_{26}N_2O_2$ (M = 374.47 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 10.6028(3) Å, b = 9.5288(2) Å, c = 19.5497(5) Å, β = 95.633(2)°, V = 1965.61(9) Å^3, Z = 4, T = 100 K, μ(CuKα) = 0.637 mm^{-1}, *Dcalc* = 1.265 g/cm^3, 18384 reflections measured (9.092° ≤ 2Θ ≤ 143.986°), 3748 unique (R_{int} = 0.0205, R_{sigma} = 0.0165) which were used in all calculations. The final R_1 was 0.0356 (I > 2σ(I)) and wR_2 was 0.0936 (all data), CCDC no. 1839259.

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[43] **Crystal Data** for $C_{13}H_9NO_2$ (*M* =211.21 g/mol) (**19**): monoclinic, space group $P2_1/c$ (no. 14), a = 13.9334(8) Å, b = 4.9033(3) Å, c = 14.6482(7) Å, β = 112.990(4)°, V = 921.27(9) Å^3, Z = 4, T = 100 K, μ(CuKα) = 0.849 mm^{-1}, *Dcalc* = 1.523 g/cm^3, 12369 reflections measured (6.892° ≤ 2Θ ≤ 155.562°), 1709 unique (R_{int} = 0.0402, R_{sigma} = 0.0391) which were used in all calculations. The final R_1 was 0.0378 (I > 2σ(I)) and wR_2 was 0.0946 (all data), CCDC no. 1839261.

[44] **Crystal Data** for product **23**, $C_{14}H_{18}ClNO_3$ (M = 283.74 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 5.3473(3) Å, b = 11.6243(6) Å, c = 22.6116(15) Å, V = 1405.51(14) Å^3, Z = 4, T = 100 K, μ(CuKα) = 2.446 mm^{-1}, *Dcalc* = 1.341 g/cm^3, 86165 reflections measured (7.82° ≤ 2Θ ≤ 143.056°), 2737 unique (R_{int} = 0.0397, R_{sigma} = 0.0118) which were used in all calculations. The final R_1 was 0.0293 (I > 2σ(I)) and wR_2 was 0.0807 (all data), CCDC no. 1839263.

[45] **Crystal Data** for product **11**, $C_{13}H_{11}NO$ (M = 197.23 g/mol): orthorhombic, space group *P*bca (no. 61), a = 7.4420(2) Å, b = 22.1357(9) Å, c = 12.0860(4) Å, V = 1990.97(12) Å^3, Z = 8, T = 100 K, μ(CuKα) = 0.664 mm^{-1}, *Dcalc* = 1.316 g/cm^3, 17240 reflections measured (7.988° ≤ 2Θ ≤ 143.034°), 1911 unique (R_{int} = 0.0628, R_{sigma} = 0.0336) which were used in all calculations. The final R_1 was 0.0397 (I > 2σ(I)) and wR_2 was 0.1039 (all data), CCDC no. 1839262.

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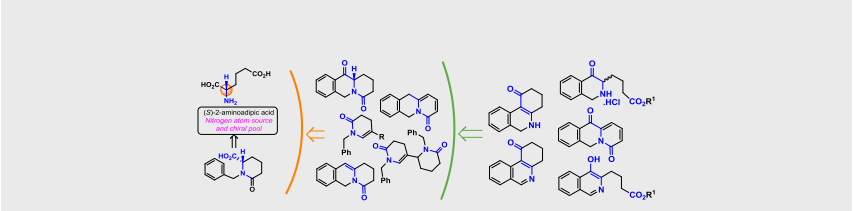

Enantiopure *N*-benzyl 6-oxopipecolic acid, generated from (*S*)-2-aminoadipic acid, was evaluated under different π-cationic cyclization conditions. If the combination of $SOCl_2$/$AlCl_3$ seems to be superior in terms of the reaction yields, use of other activators resulted in the change of the reaction profile and thus, interestingly, in the diversification of the aza-heterocyclic systems.

Fused aza-heterocyclic systems

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Study on the reactivity of enantiopure (*S*)-6-oxopipecolic acid and corresponding pyridoisoquinolines under acid conditions