Tetrahedron 66 (2010) 4647–4653

Contents lists available at ScienceDirect

Tetrahedron

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

New efficient access to fused (Het)Aryltetrahydroindolizinones via *N*-acyl iminium intermediates

Matteo Chiurato [a], Rajaa Boulahjar [a], Sylvain Routier [a,*], Yves Troin [b,*], Gérald Guillaumet [a]

[a] *Institut de Chimie Organique et Analytique, ICOA, Université d'Orléans, UMR CNRS 6005, Rue de Chartres, BP 6759, 45057 Orléans Cedex 2, France*
[b] *Clermont Université, ENSCCF, EA 987, LCHG, BP 10448, 63000 Clermont-Ferrand, France*

ARTICLE INFO

Article history:
Received 18 February 2010
Received in revised form 23 March 2010
Accepted 26 March 2010
Available online 14 April 2010

ABSTRACT

In this paper, we described the preparation of fused (Het)Aryltetrahydroindolizinones via *N*-acyl iminium intermediates. Two different routes were also explored to achieve the synthesis. The first one consists in the intramolecular reaction of β-hydroxylactams whereas the second route one is an intermolecular condensation between a 2-formylester or a β-alkoxylactone and an appropriate primary amine. We also developed two heterocyclic strategies to obtain the adequate unavailable starting materials in pyridine, pyrazine, quinoline, and quinaxoline series and then perform all inter or intramolecular reactions. Scope and limitations are given.

1. Introduction

Cyclin Dependant Kinases (CDKs) control the transition between the different phases of the cycle cell.[1] Their deregulation causes an uncontrolled cell proliferation which has been strongly linked to cancer.[2] One consequence is the contribution of research groups to design efficient CDK inhibitors. In this area, tetrahydropyrrolo[2,1-*a*]isoindol-5-one framework **I** (Fig. 1) are described to bind and fully inactivate the enzymes in the nanomolar range.[3]

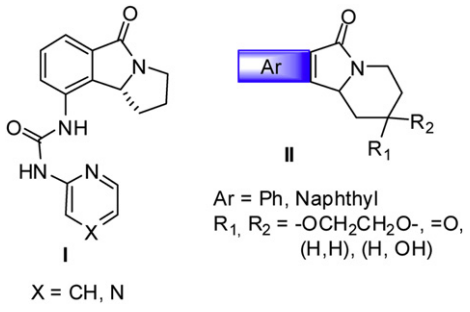


Figure 1. CDK inhibitors **I** and tetrahydropyrido[1,2-*a*]isoindolone **II**.

Only few examples related the synthesis of the targeted tetrahydropyrido[1,2-*a*]isoindolone core. For our own part, we have first described a stereoselective access to the hexahydropyrido[2,1-*a*]isoindole skeleton from readily available starting materials.[4] Then, we generalized this method in both phenyl and naphthyl series and described also compounds of type **II**.

We proposed two different routes and their related mechanism. The first route (route **A**) involved the direct condensation of the primary amine **1** with several 2-formylbenzoic acids, 2-formylesters or β-alkoxylactones. The second route (route **B**) required the preparation of a β-hydroxylactam, precursor of the *N*-acyl iminium anion, which led to the attempted fused heterocycle by intramolecular reaction. Nevertheless, no methods gave currently access to the hexahydropyrido[2,1-*a*]indolizine **IV**, the aza analogs of skeleton **II**. So we envisioned the application of our methodology to pyridinyl, pyrazinyl, quinolyl, and quinazolyl series (Fig. 2).

Due to limitations in the synthesis of some precursors, we focused our efforts in the preparation of heterocyclic β-hydroxylactams **III**, key intermediates of our route **A**. Our investigations in quinoline and quinazoline series gave the opportunity to evaluate the intramolecular route **B** by preparing the required *ortho* formylesters **V** and β-alkoxylactones **VI**. Finally, we performed all the intra and intermolecular reactions and final deprotections.

2. Results and discussion

2.1. Pyridine series

First assays were done in the pyridine series. Reaction of amine **1** with pyridine-2,3-dicarboxylic acid **2** was first realized in

* Corresponding authors. Tel.: +33 238 494 853; fax: +33 238 417 281; e-mail addresses: sylvain.routier@univ-orleans.fr (S. Routier), yves.troin@univ-bpclermont.fr (Y. Troin).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.03.100

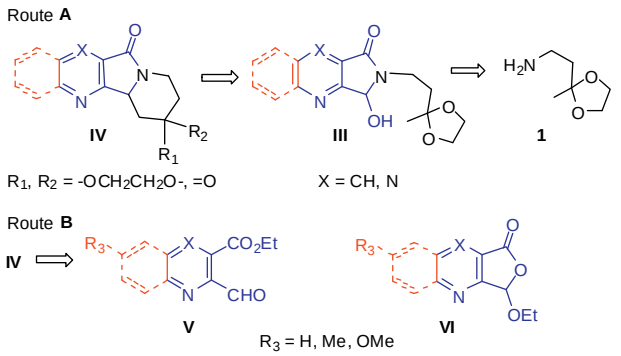
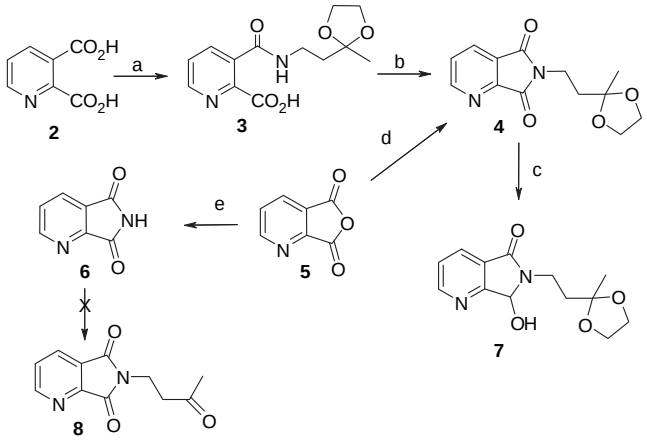


Figure 2. Retrosynthetic scheme.

standard conditions (EDCI, NEt_3) and furnished the attempted compound **3** in a 34% yield, which structure was confirmed by NMR experiments (HMQC $^1H/^{13}C$ NMR). However, changing EDCI for DCC considerably increases the yield (94%) and furnished regioselectively only one amide **3** (Scheme 1).



Scheme 1. Reagents and conditions: (a) **1** (1.0 equiv), DCC (2.0 equiv), THF, 4 h, 94%; (b) (i) $ClCO_2Et$ (1.1 equiv), NEt_3 (2.0 equiv), −100 °C to rt, 2 h, (ii) DMAP (2.0 equiv), 1 h, 50%; (c) $NaBH_4$ (1.1 equiv), THF/MeOH, −20 °C to 0 °C, 2 h, 80%; (d) **1** (1.1 equiv), Et_3N (0.5 equiv), toluene, 9 h, 50%; (e) CH_3CONH_2 (2.2 equiv), 165 °C, 2 h 30 min, quant.

Activation of the carboxylic acid function by treatment with ethyl chloroformate (1.1 equiv) and triethylamine (2.0 equiv), followed by heating in the presence of 4-dimethylaminopyridine (4-DMAP, 2.0 equiv) afforded the expected derivative **4** in a 50% yield. Alternatively, starting from anhydride **5**[5] and amine **1** led directly to compound **4**, in one step, in 50% yield. Changing the solvent (toluene for THF or DMF), or performing the reaction under microwave irradiation led only to minor yields. Compound **3** was still identified as a by-product, confirming here the regioselective reaction of amine **1** onto **2** and the difficulties to transform **3** into imide **4**.

A last method consisted in the transient preparation of imide **6**, which could be further transformed into **4** by Michael addition with methyl vinyl ketone (MVK) and acetalization. However, if compound **6**[6] was quantitatively obtained from anhydride **5**, all attempts to obtain **8** with MVK failed, probably due to the strong insolubility of **6** in most organic solvents.

The unsymmetrical framework of imide **4** led to two possibilities for the mono reduction step, which could occur either on each carbonyl group. This duality was demonstrated when a large excess of sodium borohydride was used (5.0 equiv) at 0 °C or room temperature, affording an inseparable mixture of the two regioisomers.[7] Nevertheless, by fine tuning of the temperature combined with the decrease of the amount of reducing agent (1.1 equiv) and the use of a mixture of THF and methanol, the regioselective reduction in position C-2 was obtained and compound **7** was isolated in a very good yield (80%), without any contamination by the other regioisomer, as it could be deducted from the spectroscopic data.

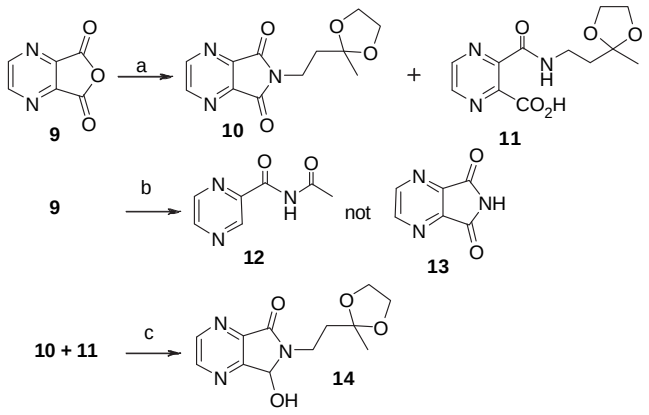
2.2. Pyrazine series

The symmetry of the pyrazine skeleton seemed more encouraging for the synthesis of the envisaged precursors using the same experimental protocol (vide supra). Starting from anhydride **9**,[8] condensation with amine **1** in the presence of a catalytic amount of triethylamine furnished a mixture of the cyclic structure **10** and the open one **11** (95%, **10**/**11**: 2/1 as evaluated by ^1H NMR spectroscopy), which could not be separated by chromatography as absorption on silica gel led only to compound **11**.[9]

Changing triethylamine for Hunig's base resulted only to the modification of the ratio of the two compounds (75%, **10**/**11**: 1/2). Using a coupling agent, such as DCC, or more acidic conditions gave no satisfactory results as untreatable mixtures were obtained.[10]

Best improvement was finally obtained by microwaves irradiation for 1 h at 180 °C in which starting material fully disappeared and compound **11** was the unique structure formed in 80% yield. With **11** now in hands in good yield we tried to transform **11** to **10** using acetic anhydride under microwave conditions but all attempts failed.[10b] Finally, as evocated for the preparation of compound **6**, reaction of **9** with acetamide could appear as a good alternative to prepare bicyclic amide **13**,[11] but such reaction furnished quantitatively the decarboxylated compound **12**[6c,12] with any trace of **13**.

At this time, we decided to perform the selective reduction using the best mixture of **10**/**11** (2/1) such obtained. Using the experimental procedure described before led to bad results even if a lot of conditions have been tried. On the other hand, best results were obtained by using $Mg(ClO_4)_2$ as complexing agent[13] (2.0 equiv) in combination with sodium borohydride (1.6 equiv) at −30 °C, and, by this way, the desired product **14** was isolated in a 63% yield from **9** (Scheme 2).

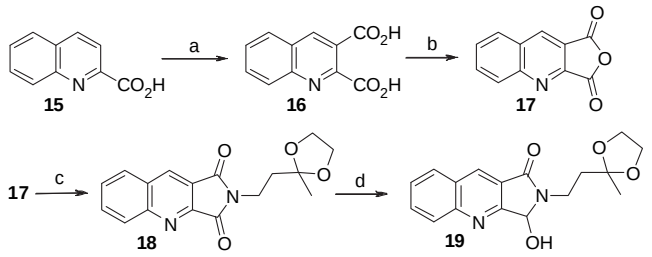


Scheme 2. Reagents and conditions: (a) **1** (1.1 equiv), NEt_3 (cat.), toluene, Dean–Stark apparatus, 48 h, **10**/**11** (2/1), 95%; (b) CH_3CONH_2 (2.2 equiv), 4 h 30 min, quant.; (c) $NaBH_4$ (1.6 equiv), $Mg(ClO_4)_2$ (2.0 equiv), −30 °C to rt, 1 h, from **9**: 63%.

2.3. Quinoline series

Once again, the dissymmetry of the aromatic skeleton forced us to try several synthetic pathways to obtain the desired compounds.

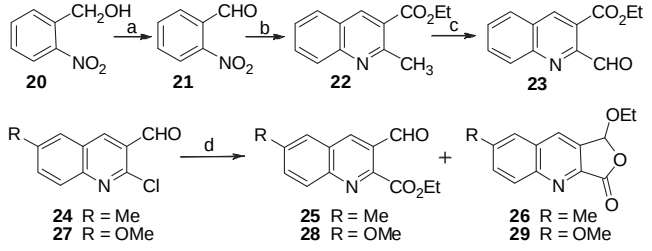
Starting from commercially available 2-quinolinyl carboxylic acid **15**, we performed a carbonylation reaction using an excess of LiTMP and dry CO_2 and so obtained the corresponding 2,3-diacidic compound **16**.[14] Dehydration to the corresponding anhydride **17**[15] was realized through treatment of **16** with acetic anhydride at reflux for 2 h (Scheme 3). Its purification, which was performed by sublimation, was accountable for the moderate yield of 55%.



Scheme 3. Reagents and conditions: (a) LiTMP (3.0 equiv), dry CO_2 gas, THF, −25 °C, 2 h, 80%; (b) Ac_2O, reflux, 1 h 30 min, 51%; (c) amine **1** (1.1 equiv), Et_3N (cat.), toluene, Dean–Stark apparatus, reflux, 12 h, 78%; (d) $NaBH_4$ (1.2 equiv), $Mg(ClO_4)_2$ (2.0 equiv), −25 °C, 2 h, quant.

Condensation of **17** with amine **1** led after 12 h to the desired imide **18** in a 78% yield. Mono and regioselective reduction was achieved as previously described (1.0 equiv of $Mg(ClO_4)_2$ and 1.2 equiv of $NaBH_4$, −25 °C, 2 h), furnishing the β-hydroxylactam **19** in a quantitative yield.

According to our previous results,[4] we tried also to prepare the two suitable precursors for the intermolecular process (route **B**). First model **23** was obtained in three steps from 2-aminobenzilic alcohol **20** (Scheme 4).



Scheme 4. Reagents and conditions: (a) MnO_2 (4.0 equiv), CH_2Cl_2, rt, 18 h, 97%; (b) ethylmethylmalonate (1.0 equiv), pyridine (cat.), EtOH, 12 h, 70%; (c) SeO_2 (2.0 equiv), xylene, 160 °C, 12 h, 89%; (d) CO atmosphere, $Pd(OAc)_2$ (0.1 equiv), Xantphos® (0.2 equiv), Et_3N (2.0 equiv), DMF/EtOH 1/1, 18 h, from **24**:**25** 69% and **26** 17%, from **27**:**28** 67% and **29** 16% (not pure enough to be fully characterized).

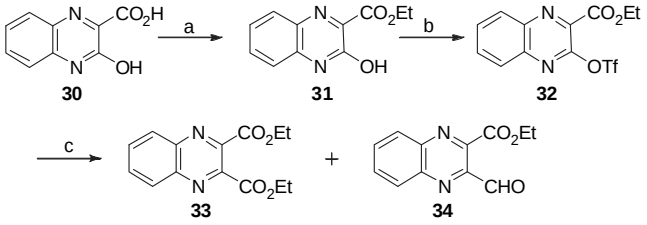
Oxidation with MnO_2 furnished aldehyde **21**[16], which reacted with ethylmethylmalonate to give quinolinic ester **22**.[17] Final oxidation of the methyl group with SeO_2 led to the targeted compound **23**[18] (overall yield 61%).

The second model **25** was issued from commercially available **24** and, in order also to investigate the possible electronic effect of a methoxy substituent on the yield, we made the same transformations on compound **27**, leading to **28**. So, palladium carbonylation[4,19] on compounds **24** using 1,3-bis(diphenylphosphino) propane (dppp) as catalyst led to the formation of the expected compounds **25** but in poor yields (<25%). Analogous results were obtained starting from **27**. Changing dppp for Xantphos® furnished now a mixture of compounds **25** and **26** in fair yield (86%) in which the open form was predominant (**25**/**26**: 8/2). The same reaction conducted with **27** furnished also a mixture of **28** and **29** (87%), and here again, the open form was predominantly formed (**28**/**29**: 8/2), showing once more that this reaction is very sensitive to the experimental conditions and the reactants.

2.4. Quinoxaline series

Due to the accessibility of the starting materials we decided to test only the intermolecular cyclization process (route **A**). Thus, commercial 3-hydroxy-quinoxaline-2-carboxylic acid **30** was treated with thionyl chloride in ethanol to give quantitatively the corresponding ester **31**.[20] Reaction of **31**, with an excess of Tf_2O in the presence of Et_3N in dichloromethane, at −10 °C furnished the expected triflate **32** in a 80% yield (Scheme 5).

Subsequent carbonylation,[19] as described for the preparation of compounds **25** and **28**, was next performed under CO atmosphere using a catalytic amount of $Pd(OAc)_2$, dppp, and Et_3N in a refluxing mixture of DMF and EtOH for 18 h, leading to diethyl quinoxalin-2,3-dicarboxylate **33**[21] in a 24% yield together with the non-expected aldehyde **34** formed in a 17% yield, which formation[22] traditionally required, in the palladacycle, the presence of an hydride source.[23] Et_3N can offer this opportunity by β-hydride elimination under palladium catalysis during the long reaction time (Scheme 5).



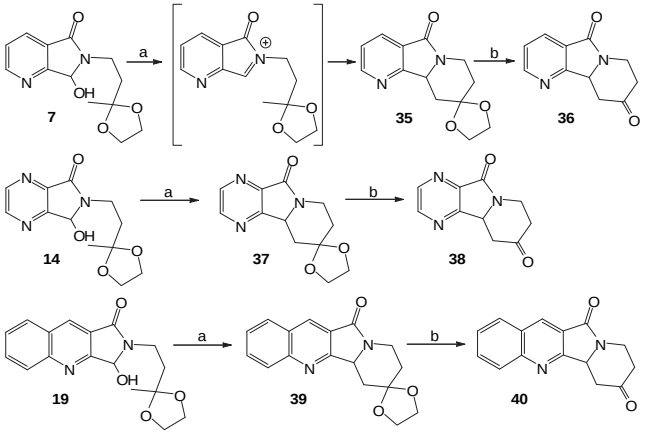
Scheme 5. Reagents and conditions: (a) $SOCl_2$, (3.0 equiv), EtOH, 0 °C, quant.; (b) triflic anhydride (4.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2, −10 °C, 80%; (c) CO atmosphere, $Pd(OAc)_2$ (0.1 equiv), dppp (0.1 equiv), Et_3N (2.0 equiv), DMF/EtOH 1/1, 18 h, **33** 24% and **34** 17%.

3. Cyclization reactions and final deprotections

Having now in hands the targeted precursors (**7**, **14**, **19**, **23**, **25**, **26**, **28**/**29**, and **34**), we now investigated their reactions in order to form the tetrahydropyrido[2,1-*a*]isoindolone core.

Trying out the intermolecular process (route **B**) was very disappointing as, starting either from **23**, **25**, **28**/**29** or **34**, in the presence of amine **1**, we were enable to isolate any cycloadduct although the amount of *p*-TsOH and the reaction time has been carefully checked. If these latter compounds led only to degradation, on the opposite, the ethoxylactone **26** proved to be very stable since no reaction occurred with amine **1** in the chosen experimental conditions, result in concordance with those observed in the presence of electron rich systems (i.e., methoxybenzene or naphthalene).[4]

Starting from derivatives **7**, **14**, and **19**, we now examined the intramolecular process (route **A**). All reactions were carried out in boiling toluene with a Dean–Stark apparatus in the presence of *p*-TsOH (1.5–3.5 equiv), standard conditions, which have been used before.[4] First reactions were performed with the pyrido-β-hydroxylactam **7**. So, addition of 1.5 equiv of *p*-TsOH led to the cycloadduct **35** in a low yield of 14% (Scheme 6). Postulating that the basicity of the nitrogen atom could have a strong influence



Scheme 6. Reagents and conditions: (a) *p*-TsOH (1.5–3.5 equiv) (see text and Experimental section), toluene, reflux, 12 h from **7**: **35** 30%, from **14**: **37** 20%, from **19**: **39** 40%; (b) 10% HCl, acetone, reflux, 1 h 30 *from* **35**, **37**, **39**: **36**, **38**, **40** quant. (*).

upon the necessary amount of *p*-TsOH, we increased its quantity to 2.5 equiv, and consequently, the yield rose up to 30%. Further increase to 3.5 equiv, or changing the reaction time did not have any significant influence on the resulting yield.

Similar results were obtained from pyrazine precursor **14** in which the two nitrogen atoms could intensify the neutralization of *p*-TsOH. So, the reaction was first conducted with only 0.5 equiv of acid and; in this case, we observed the formation of traces of cyclized compound **37**; whereas the use of 3.5 equiv of acid, in the same experimental conditions, led to **37** in 20% yield.

Same thought was applied to quinolinyl derivative **19**, which furnished the desired cycloadduct **39** in a 40% yield in the compromise use of 1.5 equiv of *p*-TsOH,[22] showing once more that reaction yield was strongly dependent from these interdependent factors.

Finally, the cycloadducts **35**, **37**, **39** were deacetalized in standard conditions, leading to corresponding keto-derivatives **36**, **38**, and **40** in acceptable to good yield; however a short reaction time (<2 h) and an additional step of neutralization was required to isolate the keto-derivatives without any difficulty.

4. Conclusion

In this paper we prepare new pyridinyl, pyrazinyl, quinolinyl, and quinazolinyl β-hydroxy lactames, β-alkoxylactones or β-formylesters in pyridine, pyrazine, quinoline, and quinazoline series. In addition, we described a straightforward access to fused (Het) Aryl tetrahydroindolizinones. The single step (route **B**) synthesis, by acidic condensation of a ketoprotected-1,3-aminoketone and β-alkoxylactones or β-formylesters unfortunately failed. Nevertheless, the intramolecular pathway involving the acidic cyclization of β-hydroxy lactames led to the targeted original pyridinic, pyrazinic, and quinoleinic-fused heterocycles. The targeted tetrahydroindolizinones such obtained were deprotected leading to useful and reactive ketones, which could be used further to introduce molecular diversity.

5. Experimental section

5.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded on a Brüker 250 or 400 MHz apparatus using $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in parts per million (δ scale) and all *J* values are in hertz. The following abbreviations are used: singlet (s), doublet (d), doubled doublet (dd), triplet (t), multiplet (m), quaternary carbon (Cq). Melting points are uncorrected. IR absorptions were recorded on a Perkin–Elmer PARAGON 1000 PC and values were reported in cm^{-1}. IR were also performed on Avatar 320 using KBr or equipped by an ATR (Ge) technique. Mass spectra (Ion Spray) were performed on a Perkin–Elmer Sciex PI300, HRMS in Clermont Ferrand, France (*Centre Regional de Mesures Physiques*, CRMP). Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). Spots were visualized by UV light at 254 and 356 nm. Flash chromatography columns were performed using silica gel 60 (0.063–0.200 mm, Merck).

5.2. General experimental procedures

*5.2.1. General procedure **A** for cyclizations.* In a Dean–Stark apparatus, a solution of aldehyde or β-ethoxylactone (1.0 mmol), 2-(2-methyl-[1,3]dioxolan-2-yl)-ethylamine **1** (1.1 equiv), and *p*-toluenesulphonic acid (1.5 equiv) in toluene (20 mL) was refluxed for the desired time (route **B**). On the other hand, starting from β-hydroxylactam compounds, reflux was conducted in the presence of *p*-toluenesulphonic acid (route **A**). In each case, the cooled mixture was washed with saturated aqueous $NaHCO_3$ (20 mL), extracted with ethyl acetate (3×20 mL). The combined organic layers were dried and concentrated under reduced pressure and the crude residue obtained was purified by flash chromatography.

*5.2.2. General procedure **B** for acetal deprotections.* A mixture containing the protected heterocyclic structure (0.3 mmol), an aqueous solution of 10% HCl (1 mL), and acetone (5 mL) was refluxed for the desired time. After cooling, the crude was diluted with water (20 mL), extracted with dichloromethane (2×20 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure to afford a crude material, which was next purified by flash chromatography.

5.3. Compound data

*5.3.1. N-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-5H-pyrrolo [3,4-b] pyridine-5,7(6H)-dione (**4**).* A round bottom flask equipped with a Dean–Stark apparatus was charged with a solution of pyridine-2,3-dicarboxylic anhydride **2** (895 mg, 6.0 mmol), 2-(2-methyl-[1,3]dioxolan-2-yl)-ethylamine **1** (790 mg, 6.0 mmol) in toluene (100 mL). Some drops of Et_3N (cat.) were added and the mixture was refluxed for 9 h. After cooling, water (50 mL) was added. Extractive workup (EtOAc then CH_2Cl_2) followed by drying on $MgSO_4$ gave, after evaporation, a residue, which was purified by flash chromatography (CH_2Cl_2/MeOH 98/2+1% Et_3N) to give **4** as a yellow solid (780 mg, 50%). Mp: 98–100 °C. IR (ATR-Ge, ν cm^{-1}): 2354–2341, 1717, 1398, 1372, 1161, 1055. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.96 (d, *J*=5.0 Hz, 1H), 8.16 (d, *J*=7.5 Hz, 1H), 7.65–7.60 (m, 1H), 3.94 (m, 4H), 3.89 (t, *J*=6.5 Hz, 1H), 2.11 (t, *J*=6.6 Hz, 1H), 1.37 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.3 (C=O), 166.2 (C=O), 155.1 (CH), 151.9 (Cq), 131.1 (CH), 127.5 (Cq), 127.3 (CH), 108.7 (O–Cq–O), 64.7 (2×CH_2), 36.2 (NCH_2), 33.8 (CH_2), 23.8 (CH_3). ESI-MS *m*/*z* 263.5 $[M+H]^+$, 280.5 $[M+NH_4]^+$.

*5.3.2. 7-Hydroxy-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (**7**).* To a solution of **4** in a mixture of THF/MeOH (1/1, 20 mL), cooled to −20 °C, and under an argon atmosphere was added, by portions, $NaBH_4$ (40 mg, 1.06 mmol). The mixture was stirred at this temperature for 30 min and then at 0 °C for 1 h 30 min (followed by TLC). When starting material has disappeared, the reaction was quenched with H_2O (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3×30 mL), the combined organic layers were washed with brine, and dried over $MgSO_4$. The concentrated residue (240 mg) was purified by flash chromatography (98:2, CH_2Cl_2/MeOH) to give **7** (200 mg, 80%) as a yellow solid. Mp: 116–118 °C. IR (ATR-Ge, ν cm^{-1}): 3314, 1689, 1669, 1414, 1161, 1055. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.67 (dd, *J*=5.0, 1.6 Hz, 1H), 8.07 (dd, *J*=7.5, 1.6 Hz, 1H), 7.43 (dd, *J*=7.5, 5.0 Hz, 1H), 6.70 (br s, 1H), 6.00 (s, 1H), 3.98–3.59 (m, 2H), 3.89 (br s, 4H), 2.16–2.09 (m, 2H), 1.38 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.2 (Cq), 163.8 (C=O), 152.1 (CH), 132.0 (CH), 126.4 (Cq), 124.7 (CH), 109.0 (O–Cq–O), 81.2 (CH), 64.7 (2×OCH_2), 36.9 (NCH_2), 35.1 (CH_2), 24.0 (CH_3). ESI-MS *m*/*z* 265.5 $[M+H]^+$, 282.5 $[M+NH_4]^+$.

*5.3.3. 6-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-5H-pyrrolo [3,4-b] pyrazine-5,7(6H)-dione (**10**).* According to the procedure described for the preparation of **4**, pyrazine-2,3-dicarboxylic anhydride **9** (150 mg, 1.0 mmol), 2-(2-methyl-[1,3]dioxolan-2-yl)-ethylamine **1** (130 mg, 1.0 mmol), and Et_3N (five drops, cat.) were dissolved in toluene (100 mL) and the mixture was refluxed for 24 h. After standard workup the residue was purified by flash chromatography (CH_2Cl_2/MeOH 97/3+1% Et_3N,) to give **10** (100 mg, 38%) as a yellow solid. Mp: 102–104 °C. IR (ATR-Ge, ν cm^{-1}): 1715, 1449–1402, 1369, 1161, 1053. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.93 (s, 2H), 3.97 (t, *J*=6.9 Hz,

2H), 3.97–3.92 (m, 4H), 2.15 (t, J=6.9 Hz, 2H), 1.36 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.1 (2×C=O), 148.9 (2×CH), 147.0 (2×Cq), 108.7 (O–Cq–O), 64.7 (2×OCH_2), 36.1 (NCH_2), 34.1 (CH_2), 23.8 (CH_3). ESI-MS m/z 264.5 $[M+H]^+$, 281.5 $[M+NH_4]^+$, 286.5 $[M+K]^+$.

*5.3.4. 3-({[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]amino}carbonyl) pyrazine-2-carboxylic acid (**11**).* Compound **11** (170 mg, 60%) was isolated during the purification of compound **10** as a yellow solid. Mp: 108–110 °C. IR (ATR-Ge, ν cm^{-1}): 3378, 2981–2885, 1660, 1161, 1039. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.68 (d, J=2.2 Hz, 1H), 8.63 (br s, 1H), 8.52 (d, J=2.2 Hz, 1H), 5.14 (br s, 1H), 4.02 (s, 4H), 3.61 (q, J=6.0 Hz, 2H), 2.03 (t, J=6.3 Hz, 2H), 1.39 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.3 (C=O), 164.3 (C=O), 145.2 (CH), 142.7 (Cq), 141.4 (CH), 109.6 (O–Cq–O), 64.8 (OCH_2), 64.7 (–OCH_2), 37.4 (N–CH_2), 35.1 (CH_2), 24.0 (CH_3). ESI-MS m/z 282.5 $[M+H]^+$.

*5.3.5. N-Acetylpyrazine-2-carboxamide (**12**).* A mixture of pyrazine-2,3-dicarboxylic anhydride **9** (900 mg, 6.0 mmol) and acetamide (790 mg, 13.3 mmol) was heated at reflux for 4 h. After cooling to room temperature the mixture was filtered, and the cake was washed with water and crystallized in hot ethanol to obtain **12** as a brown solid (1.42 g, quant.). Mp: 86–88 °C. IR (ATR-Ge, ν cm^{-1}): 3343, 1716, 1667, 1476, 1390, 1378. ^{1}H NMR (250 MHz, DMSO-d_6): δ 10.80 (br s, 1H), 9.25 (s, 1H), 8.26 (d, J=2.3 Hz, 1H), 7.80 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 170.7 (C=O), 162.5 (C=O), 148.4 (CH), 144.3 (CH), 143.8 (Cq), 143.3 (CH), 25.1 (CH_3). HRMS (EI): $C_7H_7N_3NaO_2$ $[M+Na]^+$ calcd 165.0436, found 188.0434.

*5.3.6. 7-Hydroxy-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one (**14**).* According to the procedure described for the preparation of **7**, compound **14** was obtained from a mixture of **10**/**11** (204 mg, 0.5 mmol, 2/1) adding magnesium perchlorate (245 mg, 1.5 mmol) in a mixture THF/MeOH 1:1 (20 mL) before the $NaBH_4$ (30 mg, 0.6 mmol) introduction. After standard workup, the resulting oil was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 96/4+1% Et_3N) to give **14** (125 mg, 90%) as a yellow solid. Mp: 141–143 °C. IR (ATR-Ge ν cm^{-1}): 3253, 1708, 1455–1420, 1378, 1142, 1052. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.74 (d, J=2.8 Hz, 1H), 8.68 (d, J=2.8 Hz, 1H), 5.98 (br s, 1H), 3.97 (s, 4H), 3.90–3.70 (m, 2H), 2.20–2.11 (m, 2H), 1.38 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.8 (C=O), 157.9 (Cq), 146.8 (CH), 146.6 (CH), 145.5 (Cq), 109.2 (O–Cq–O), 80.1 (CH), 64.7 (2×OCH_2), 36.8 (NCH_2), 35.6 (CH_2), 25.9 (CH_3). ESI-MS m/z 266.5 $[M+H]^+$, 283.5 $[M+NH_4]^+$.

*5.3.7. 2-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-1H-pyrrolo [3,4-b] quinoline-1,3(2H)-dione (**18**).* According to the procedure described for the preparation of **10**, quinolin-2,3-dicarboxylic anhydride **17** (1.24 g, 6.2 mmol), 2-(2-methyl-[1,3]dioxolan-2-yl)-ethylamine **1** (820 mg, 6.2 mmol), and Et_3N (five drops, cat.) were dissolved in toluene (100 mL) and the mixture was refluxed for 24 h. After standard workup the residue was purified by flash chromatography (CH_2Cl_2/MeOH 97/3+1% Et_3N,) to give **18** (1.50 g, 78%) as a white solid. Mp: 208–210 °C. IR (ATR-Ge, ν cm^{-1}): 1715, 1449–1402, 1369, 1161, 1053. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.42 (d, J=8.5 Hz, 1H), 8.06 (d, J=9.2 Hz 1H), 7.97–7.90 (m, 1H), 7.79–7.72 (m, 1H), 3.98 (t, J=6.7 Hz, 2H), 3.97–3.92 (m, 4H), 2.17 (t, J=7.0 Hz, 2H), 1.39 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.3 (C=O), 166.1 (C=O), 150.8 (Cq), 150.7 (Cq), 132.8 (CH), 132.6 (CH), 131.6 (CH), 130.0 (CH), 129.6 (CH), 128.9 (Cq), 123.1 (Cq), 108.9 (O–Cq–O), 64.8 (2×OCH_2), 36.2 (NCH_2), 34.2 (CH_2), 23.9 (CH_3). ESI-MS m/z 313.0 $[M+H]^+$.

*5.3.8. 1-Hydroxy-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (**19**).* According to the procedure described for the preparation of **7**, to a mixture of **18** (500 mg, 1.6 mmol) and magnesium perchlorate (360 mg, 1.6 mmol) in a mixture THF/MeOH 1:1 (25 mL/25 mL), were added in few portions $NaBH_4$ (180 mg, 4.8 mmol). Standard workup gave quantitatively **19** as a yellow solid. Mp: 208–210 °C; IR (ATR-Ge, ν cm^{-1}): 3406, 1654, 1527–1489, 1218, 1061. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.24 (d, J=8.3 Hz, 1H), 7.96 (d, J=8.3 Hz, 1H), 7.85 (t, J=7.6 Hz, 1H), 7.64 (t, J=7.6 Hz, 1H), 6.18 (s, 1H), 4.03–3.93 (m, 5H), 3.88–3.79 (m, 1H), 2.22 (t, J=7.2 Hz, 2H), 1.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2 (C=O), 162.6 (Cq), 149.3 (Cq), 132.9 (CH), 131.9 (CH), 129.7 (CH), 129.1 (CH), 128.3 (Cq), 127.8 (CH), 126.3 (Cq), 109.2 (O–Cq–O), 81.5 (CH), 64.8 (2×OCH_2), 37.1 (NCH_2), 35.6 (CH_2), 24.1 (CH_3). ESI-MS m/z 317.0 $[M+H]^+$.

*5.3.9. Ethyl-3-formyl-6-methylquinoline-2-carboxylate (**25**).* Under an argon atmosphere, to a solution **24** (330 mg, 1.6 mmol) in a mixture DMSO/EtOH 1:1 (80 mL) were added Et_3N (0.45 mL, 3.2 mmol) and Xantphos® (0.4 mmol, 0.25 equiv). The mixture was stirred for 10 min and saturated in CO pressure. At last $Pd(OAc)_2$ (90 mg, 0.4 mmol, 0.25 equiv) was added, and the reaction was vigorously stirred overnight at 150 °C under CO pressure. After cooling the mixture was washed with a solution of saturated NaCl (50 mL). The resulting mixture was extracted with EtOAc (3×90 mL), the combined organic layers were washed with brine, and dried over $MgSO_4$. The concentrated residue (240 mg) was purified by flash chromatography (petroleum ether/EtOAc 90/10,) to give **25** (69%) as a white solid. Mp: 90–92 °C. IR (ATR-Ge, ν cm^{-1}): 1684, 1594, 1260, 1121. ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.47 (s, 1H), 8.48 (s, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.57 (s, 1H), 7.56–7.52 (m, 1H), 4.62 (q, J=7.1 Hz, 2H), 2.48 (s, 3H), 1.50 (t, J=7.1 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 189.8 (CHO), 160.9 (C=O), 147.6 (Cq), 139.1 (CH), 134.8 (CH), 134.7 (Cq), 128.7 (CH and Cq), 127.1 (CH), 124.4 (CH), 120.0 (Cq), 62.4 (CH_2), 21.4 (CH_3), 14.6 (CH_3). HRMS (EI): $C_{14}H_{14}NO_3$ $[M+H]^+$ calcd 244.0974, found 244.0977.

*5.3.10. 1-Ethoxy-7-methyl-1H-furo[3,4-b]quinolin-3-one (**26**).* Compound **26** (17%) was isolated during the purification of **25** as a white solid. Mp: 192–194 °C. IR (ATR-Ge, ν cm^{-1}): 1773, 1578, 1504, 1382, 1329, 1097. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.27 (d, J=8.7 Hz, 1H), 7.73 (s, 1H), 7.71 (dd, J=8.7, 1.8 Hz, 1H), 6.57 (s, 1H), 4.14–3.92 (m, 2H), 2.61 (s, 3H), 1.37 (t, J=7.1 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.8 (C=O), 149.5 (Cq), 145.1 (Cq), 140.2 (Cq_{ar}), 134.2 (CH), 133.5 (Cq), 131.6 (CH), 130.9(CH), 129.5 (Cq), 127.3 (CH), 101.2 (CH), 66.4 (CH_2), 22.0 (CH_3), 15.2 (CH_3). HRMS (EI): $C_{14}H_{14}NO_3$ $[M+H]^+$ calcd 244.0974, found 244.0978.

*5.3.11. Ethyl-3-formyl-6-methoxyquinolin-2-carboxylate (**28**).* According to the procedure described for the preparation of **25**, compound **28** (69%) was obtained after purification by flash chromatography (petroleum ether/EtOAc 90/10,) as a white solid. Mp: 108–110 °C. IR (ATR-Ge, ν cm^{-1}): 1688, 1594, 1252, 1231. ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.49 (s, 1H), 8.49 (s, 1H), 7.74 (d, J=9.1 Hz, 1H), 7.34 (dd, J=9.1, 2.8 Hz, 1H), 7.11 (d, J=7.2 Hz, 1H), 4.61 (q, J=7.2 Hz, 2H), 3.91 (s, 3H), 1.50 (t, J=7.2 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 189.8 (CHO), 160.0 (C=O), 156.6 (Cq), 144.9 (CH), 138.3 (CH), 128.6 (CH), 124.9 (Cq), 124.8 (2×Cq), 119.9 (Cq), 107.3 (CH), 62.2 (CH_2), 55.6 (OCH_3), 14.6 (CH_3). ESI-MS m/z 260.5 $[M+H]^+$.

*5.3.12. Ethyl-3-hydroxy-quinoxaline-2-carboxylate (**31**).* To 0 °C and under argon atmosphere, carboxylic acid **30** (380 mg, 2.0 mmol) was dissolved in a mixture of $SOCl_2$ (0.5 mL, 6.0 mmol) in EtOH (10.0 mL). The mixture was stirred at this temperature for 30 min and then at room temperature overnight. Petroleum ether (40.0 mL) was added and the solvent was evaporated under reduced pressure. The crude solid was purified by chromatography on silica gel (petroleum ether/EtOAc 3/1) to give **31** (430 mg, quant.) as white solid.

Mp: 180–182 °C. IR (ATR-Ge, ν cm^{-1}): 2935, 1732, 1571, 1431, 1316, 1124, 1078. ^{1}H NMR (250 MHz, $CDCl_3$): δ 12.09 (s, 1H, OH), 7.95 (dd, 1H, J=8.3, 1.0 Hz, H_{ar}), 7.66–7.59 (m, 1H, H_{ar}), 7.50–7.37 (m, 2H, H_{ar}), 4.55 (q, 2H, J=6.8 Hz, CH_2), 1.48 (t, 3H, J=6.8 Hz, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.8 (C=O), 155.0 (Cq), 148.7 (Cq), 133.1 (CH), 132.5(Cq), 132.4 (Cq), 130.5 (CH), 125.3 (CH), 116.8 (CH), 62.9 (CH_2), 14.4 (CH_3). ESI-MS m/z 219.5 $[M+H]^+$, 236.5 $[M+NH_4]^+$.

*5.3.13. Ethyl-3-trifluoromethanesulfonyloxy-quinoxaline-2-carboxylate (**32**).* Under argon atmosphere, a solution of **31** (1.0 g, 4.6 mmol) in CH_2Cl_2 (70.0 mL) was cooled at −10 °C. Et_3N (2.6 mL, 18.4 mmol) and Tf_2O (3.1 mL, 18.4 mmol) were added. The reaction was stirred at room temperature. After complete conversion (monitored by TLC) water (20 mL) was added. The aqueous layers were extracted with CH_2Cl_2 (20 mL) and EtOAc (10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The dark oil was purified by chromatography on silica gel (petroleum ether/EtOAc 2/1) to give **32** (1.3 g, 80%) as white solid. Mp: 88–89 °C; IR (ATR-Ge, ν cm^{-1}): 1737, 1574–1420, 1324, 1126, 1084. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.36–8.32 (m, 1H, H_{ar}), 8.14–8.10 (m, 1H, H_{ar}), 7.99–7.94 (m, 2H, H_{ar}), 4.61 (q, 2H, J=7.2 Hz, CH_2), 1.51 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.1 (C=O), 147.8 (Cq), 141.5 (Cq), 141.0 (Cq), 137.5 (Cq), 134.2 (CH), 132.2 (CH), 130.5 (CH_{ar}), 129.0 (CH), 121.4 (CF_3), 63.8 (CH_2), 14.4 (CH_3). ESI-MS m/z 351.5 $[M+H]^+$.

*5.3.14. Diethyl quinoxaline-2,3-dicarboxylate (**33**).* Compound **33** was obtained following the same procedure **A** as described for compound **25**, starting from the triflate **32** by using a mixture (DMSO/EtOH 4/1) as solvent and dppp as a ligand. After purification by flash chromatography (petroleum ether/EtOAc 65/35) **33** was obtained as a yellow solid in 24% yield. Mp: 90–92 °C. IR (ATR-Ge, ν cm^{-1}): 2917, 2853, 1737, 1574, 1420, 1324, 1126, 1084. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.28–8.24 (m, 2H), 7.95–7.91 (m, 2H), 4.56 (q, J=7.1 Hz, 2H), 1.48 (t, J=7.1 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.9 (2×C=O), 144.3 (2×Cq), 141.5 (2×Cq), 132.6 (2×CH), 130.0 (2×CH), 63.0 (2×CH_2), 14.2 (2×CH_3). ESI-MS m/z 275.5 $[M+H]^+$.

*5.3.15. Ethyl-3-formylquinoxaline-2-carboxylate (**34**).* Compound **34** (17%) was obtained during the purification of **33** as a yellow solid. Mp: 92–94 °C IR (ATR-Ge, ν cm^{-1}): 2917, 2853, 1737, 1683, 1556, 1318, 1133, 1079. ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.55 (s, 1H), 8.34–8.30 (m, 1H), 8.22–8.18 (m, 1H), 7.92–7.86 (m, 2H), 4.61 (q, J=7.1 Hz, 2H), 1.52 (t, J=7.1 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 182.5 (CHO), 164.3 (C=O), 145.2 (2×Cq), 143.8 (2×Cq), 132.4 (CH), 131.1 (CH), 130.8 (CH), 129.5 (CH), 62.8 (CH_2), 14.5 (CH_3). ESI-MS m/z 231.5 $[M+H]^+$.

*5.3.16. 7′,8′,10′,10a′-Tetrahydro-5′H-spiro[1,3-dioxolane-2,9′-pyrido[2,3-a]indolizin]-5′-one (**35**).* According to the general procedure **A**, the compound **35** was obtained starting from **7** after purification by flash chromatography (CH_2Cl_2/MeOH 98/2) as yellow solid (30%). Mp: 132–134 °C. IR (ATR-Ge, ν cm^{-1}): 1696, 1584, 1408, 1081, 1026. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (dd, J=7.0, 1.6 Hz, 1H), 8.12 (dd, J=7.5, 1.6 Hz, 1H), 7.40 (dd, J=7.5, 5.0 Hz, 1H), 4.64 (dd, J=12.3, 4.0 Hz, 1H), 4.53 (ddd, J=13.5, 5.6, 1.6 Hz, 1H), 4.12–4.04 (m, 4H), 3.30 (td, J=13.0, 4.2 Hz, 1H), 2.55 (ddd, J=12.9, 4.0, 2.3 Hz, 1H), 1.89–1.84 (m, 1H), 1.74 (td, J=13.1, 5.3 Hz, 1H), 1.38 (t, J=12.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1 (C=O), 164.5 (Cq), 152.3 (CH), 132.1 (CH), 126.1 (Cq), 123.5 (CH), 107.4 (O–Cq–O), 64.9 (2×OCH_2), 58.3 (CH), 38.5 (CH_2), 36.6 (CH_2), 34.3 (CH_2). ESI-HRMS m/z calcd for $C_{13}H_{15}N_2O_3$ $[M+H]^+$: 247.1083, found 247.1071.

*5.3.17. 7,8,10,10a-Tetrahydropyrido[2,3-a]indolizine-5,9-dione (**36**).* According to the general procedure **B**, compound **36** was obtained starting from **35** after purification by flash chromatography (CH_2Cl_2/MeOH 98/2+1% Et_3N) in a quantitative manner. Mp: 230–232 °C; IR (ATR-Ge, ν cm^{-1}): 1698, 1429, 1383, 1294, 1147. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.44 (dd, J=7.2, 1.0 Hz, 1H), 8.25(dd, J=7.5, 1.0 Hz, 1H), 7.78 (t, J=7.8 Hz, 1H), 5.38 (dd, J=11.6, 4.0 Hz, 1H), 4.79 (ddd, J=14.0, 7.1, 3.0 Hz, 1H), 3.53–3.39 (m, 2H), 2.70–2.50 (m, 2H), 2.08 (dd, J=14.5, 11.7 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 204.4 (C=O), 164.1 (C=O), 139.2 (Cq), 135.3 (Cq), 130.7 (CH), 130.6 (CH), 127.6 (CH), 58.7 (CH), 44.5 (CH_2), 39.5 (CH_2), 37.3 (CH_2). ESI-HRMS m/z calcd for $C_{11}H_{11}N_2O_2$ $[M+H]^+$: 203.0821, found 203.0824.

*5.3.18. 7′,8′,10′,10a′-Tetrahydro-5′H-spiro[1,3-dioxolane-2,9′-pyrazino[2,3-a]-indolizin]-5′-one (**37**).* According to the general procedure **A**, the compound **37** was obtained starting from **14** after purification by flash chromatography (98:2+1% Et_3N, CH_2Cl_2/MeOH) as a white solid (20%). Mp: 155–156 °C; IR (ATR-Ge, ν, cm^{-1}): 3445, 1645, 1265. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.77 (d, J=2.6 Hz, 1H), 8.64 (d, J=2.6 Hz, 1H), 4.72 (dd, J=12.4, 4.0 Hz, 1H), 4.63 (ddd, J=13.4, 5.7, 1.7 Hz, 1H), 4.11–4.04 (m, 4H), 3.35 (td, J=13.0, 4.1 Hz, 1H), 2.53 (ddd, J=13.0, 3.9, 2.4 Hz, 1H), 1.95–1.85 (m, 1H), 1.76 (td, J=13.0, 5.7 Hz, 1H), 1.40 (t, J=12.6 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 159.0 (C=O), 146.1 (CH), 146.0 (CH), 130.0 (Cq), 128.1 (Cq), 107.0 (O–Cq–O), 65.1 (OCH_2), 65.0 (OCH_2), 56.2 (CH), 38.3 (CH_2), 37.2 (CH_2), 34.1 (CH_2). ESI-HRMS m/z calcd for $C_{12}H_{14}N_3O_3$ $[M+H]^+$: 248.1035, found 248.1033.

*5.3.19. 7,8,10,10a-Tetrahydropyrazino[2,3-a]indolizine-5,9-dione (**38**).* According to the general procedure **B**, compound **38** was obtained starting from **37** after purification by flash chromatography (CH_2Cl_2/MeOH 98/2+1% Et_3N) in a 94% yield as a white solid. Mp: >250 °C; IR (ATR-Ge, ν cm^{-1}): 1696, 1429, 1379, 1294, 1150. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.83 (d, J=2.6 Hz, 1H), 8.70 (d, J=2.6 Hz, 1H), 4.95–4.89 (m, 1H), 4.84 (dd, J=12.3, 4.5 Hz, 1H), 3.57–3.45 (m, 1H), 3.22 (ddd, J=14.5, 5.1, 1.0 Hz, 1H), 2.67–2.60 (m, 2H), 2.31 (dd, J=14.4, 12.2 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 204.0 (C=O), 162.9 (C=O), 158.3 (Cq), 146.7 (2×CH), 144.4 (Cq), 56.7 (CH), 44.0 (CH_2), 39.7 (CH_2), 38.1 (CH_2). ESI-HRMS m/z calcd for $C_{10}H_{10}N_3O_2$ $[M+H]^+$: 203.0773, found 204.0768.

*5.3.20. 5b′,6′,8′,9′-Tetrahydro-11′H-spiro[1,3-dioxolane-2,7′-indolizino[1,2-b]quinolin]-11′-one (**39**).* According to the general procedure **A**, the compound **39** was obtained starting from **19** after purification by flash chromatography (CH_2Cl_2/MeOH 99/1) as yellow solid (30%). Mp: 178–180 °C. IR (ATR-Ge, ν cm^{-1}): 2966, 1682, 1633, 1524, 1354, 1294, 1255, 1176. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.16 (d, J=8.5 Hz, 1H), 8.00 (dd, J=8.2, 1.1 Hz, 1H), 7.87–7.80 (m, 1H), 7.63 (m, 1H), 4.79 (dd, J=12.2, 4.0 Hz, 1H), 4.61 (ddd, J=13.7, 5.5, 1.8 Hz, 1H), 4.16–4.05 (m, 4H), 3.35 (td, J=12.6, 4.5 Hz, 1H), 2.67 (ddd, J=12.9, 4.0, 2.2 Hz, 1H), 1.92–1.74 (m, 2H), 1.47 (t, J=12.6 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.3 (C=O), 163.5 (Cq), 149.8 (Cq), 132.9 (CH), 131.5 (CH), 129.7 (CH), 129.3 (CH), 127.8 (Cq), 127.1 (CH), 123.8 (Cq), 107.4 (O–Cq–O), 65.0 (OCH_2), 64.9 (OCH_2), 59.1 (CH), 45.0 (CH_2), 40.1 (CH_2), 37.7 (CH_2); ESI-HRMS m/z calcd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1239, found 297.1237.

*5.3.21. 5b,6,8,9-Tetrahydroindolizino[1,2-b]quinoline-7,11-dione (**40**).* According to the general procedure **B**, compound **40** was obtained starting from **39** after purification by flash chromatography (CH_2Cl_2/MeOH 98/2+1% Et_3N) in a 64% yield as a pale yellow solid. Mp: 216 °C IR (ATR-Ge, ν cm^{-1}): 3412, 1691, 1634, 1508, 1422, 1265. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.18 (d, J=8.4 Hz, 1H), 8.03 (d, J=8.0 Hz, 1H), 7.87 (td, J=8.4, 1.4 Hz, 1H), 7.67 (td, J=8.0, 1.0 Hz, 1H), 4.92–4.90 (m, 1H), 4.86 (dd, J=8.9, 4.6 Hz, 1H), 3.54–3.52 (m, 1H), 3.33 (dd, J=14.5, 4.4 Hz, 1H), 2.66–2.60 (m, 2H), 2.36 (dd, J=14.4, 12.1 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 205.0 (C=O), 164.7 (C=O), 162.3 (Cq), 150.0 (Cq), 133.4 (CH), 131.2 (CH),

129.8 (CH), 129.5 (CH), 127.8 (Cq), 127.5 (CH), 122.9 (Cq), 59.1 (CH), 45.0 (CH_2), 40.1 (CH_2), 37.7 (CH_2). ESI-HRMS *m/z* calcd for $C_{15}H_{13}N_2O_2$ $[M+H]^+$: 253.0899, found 253.0970.

Acknowledgements

The authors thank the *Volubilis* Hubert Curien Program for a financial support to R.B.

References and notes

1. Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P. *Molecular Cell Biology*, 4th ed.; Garland: New York, NY, 2002, Chapter 17.
2. (a) Toogood, P. L. *Med. Res. Rev.* **2001**, *21*, 487–498; (b) Huwe, A.; Mazitschek, R.; Giannis, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2122–2138; (c) Kong, N.; Fotouhi, N.; Wovkulich, P. M.; Roberts, J. *Drugs Future* **2003**, *28*, 881–896; (d) Blagden, S.; de Bono, J. *Curr. Drugs Targets* **2005**, *6*, 325–335; (e) Shapiro, G. I. *J. Clin. Oncol.* **2006**, *24*, 1770–1783.
3. (a) Honma, T.; Hayashi, Y.; Aoyama, T.; Hashimoto, N.; Machida, T.; Fukasawa, K.; Iwama, T.; Ikeura, C.; Ikuta, M.; Suzuki-Takahashi, I.; Iwasawa, Y.; Hayama, T.; Hishimura, S.; Morishima, H. *J. Med. Chem.* **2001**, *44*, 4615–4627; (b) Honma, T.; Yoshizumi, T.; Hashimoto, N.; Hayashi, K.; Kawanishi, K.; Fukasawa, K.; Takaki, T.; Ikeura, C.; Ikuta, M.; Suzuki-Takahashi, I.; Hayama, T.; Nishimura, S.; Morishima, H. *J. Med. Chem.* **2001**, *44*, 4628–4640.
4. Chiurato, M.; Routier, S.; Troin, Y.; Guillaumet, G. *Eur. J. Org. Chem.* **2009**, 3011–3021.
5. (a) Vitry, C.; Bedat, J.; Prigent, Y.; Levacher, V.; Dupas, G.; Salliot, I.; Queguiner, G.; Bourguignon, J. *Tetrahedron* **2001**, *57*, 9101–9108; (b) Gribble, G. W.; Fletcher, G. L.; Ketcha, D. M.; Rajopadhye, M. *J. Org. Chem.* **1989**, *54*, 3264–3269; (c) Hemmerich, P.; Fallab, S. *Helv. Chim. Acta* **1958**, *41*, 498–513.
6. (a) Carpino, L. A.; Xia, J.; El-Faham, A. *J. Org. Chem.* **2004**, *69*, 54–61; (b) Blanco, M. M.; Levin, G. J.; Shapira, C. B.; Perillo, I. A. *Heterocycles* **2002**, *57*, 1881–1890; (c) Zhou, Z. L.; Navratil, J. M.; Cai, S. X.; Whittemore, E. R.; Espitia, S. A.; Hawkinson, J. E.; Tran, M.; Woodward, R. M.; Weber, E.; Keana, J. F. W. *Bioorg. Med. Chem.* **2001**, *9*, 2061–2071.
7. Othman, M.; Pigeon, P.; Decroix, B. *Tetrahedron* **1997**, *53*, 2495–2504; $LiEt_3BH$ (Super-Hydride®) has been also used for this kind of reaction, see: Padwa, A.; Brodney, M. A. *Arkivoc* **2002**, *vi*, 35–48.
8. Buckland, P. R. *J. Heterocycl. Chem.* **1980**, *17*, 397–398.
9. This transformation occurred even though the silica gel was washed with triethylamine in order to suppress the residual acidity. See Experimental section.
10. (a) Hitchins, G. J.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1757–1763; (b) Muth, M.; Bender, W.; Scharfenstein, O.; Holzgrabe, U.; Balaktova, E.; Trankle, C.; Mohr, K. *J. Med. Chem.* **2003**, *46*, 1031–1040; (c) Ganjian, I.; Khorshidi, M.; Lalezari, I. *J. Heterocycl. Chem.* **1991**, *28*, 1173–1175.
11. Tsuda, T.; Fujishima, K.; Ueda, H. *Agric. Biol. Chem.* **1981**, *45*, 2129–2130.
12. Schreier, H.; Gonzalez-Rothi, R. PCT Int. Appl. 199105771.
13. Goto, T.; Konno, M.; Saito, M.; Sato, R. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1205–1210.
14. (a) Maulding, D. R. *J. Heterocycl. Chem.* **1988**, *25*, 1777–1779; (b) Rebstock, A. S.; Mongin, F.; Trécourt, F.; Queguiner, G. *Tetrahedron Lett.* **2002**, *43*, 767–769.
15. Doehner R. F. Jr. US Patent 4910327 A (20/03/1990); 4925944 A (15/05/1990); 5892050 A (06/04/1999).
16. Anderson, K. W.; Dalvie, D. K. *J. Heterocycl. Chem.* **1993**, *30*, 1533–1536.
17. Huo, M.; Kuang, Y. Y.; Chen, F. E. *Org. Prep. Proced. Int.* **2004**, *36*, 331–336.
18. Gräf, E.; Troschütz, R. *Synthesis* **1999**, 1216–1222.
19. (a) Lou, R.; VanAlstine, M.; Sun, X.; Wentland, P. M. *Tetrahedron Lett.* **2003**, *44*, 2477–2480; (b) Gibson, K. R.; Hitzel, L.; Russell, J.; Mortishire-Smith, J.; Gerhard, U.; Gelley, R. A.; Reeve, A.; Rowley, M.; Nadin, A.; Owens, A. P. *J. Org. Chem.* **2002**, *67*, 9354–9360.
20. (a) Monge, A.; Palop, J. A.; Del Castillo, J. C.; Caldero, J. M.; Roca, J.; Romero, G.; Del Rio, J.; Lasheras, B. *J. Med. Chem.* **1993**, *36*, 2745–2750; (b) Eller, G. A.; Datterl, B.; Holzer, W. *J. Heterocycl. Chem.* **2007**, *44*, 1139–1143; (c) Haldar, P.; Dutta, B.; Guin, J.; Ray, J. K. *Tetrahedron Lett.* **2007**, *48*, 5855–5857.
21. Chattaway, F. D.; Humphrey, W. S. *J. Chem. Soc.* **1929**, 645–651.
22. Here too, increasing time of reflux or amount of acid did not introduce changes to the corresponding yield.
23. Morgan, D. O.; Ollis, D. W.; Stanforth, S. P. *Tetrahedron* **2000**, *56*, 5523–5534.