DOI: 10.1002/ejoc.200900195

New Efficient Route to Fused Aryltetrahydroindolizinones via *N*-Acyliminium Intermediates

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

Keywords: Iminium / Indolizinones / Carbonylation / Lithiation / Nitrogen heterocycles

Straightforward routes to fused tetrahydroindolizinones by two routes **A** and **B**, starting either from 2-formylbenzoic acid and esters or from β-hydroxy lactones via acyl iminium ions, are described. A plausible mechanism and limitations are given.

Introduction

Protein kinases, and in particular Cyclin Dependant Kinases (CDKs), play vital roles in the regulation of the cell division cycle (G1 to S phase) by controlling the transition between the different phases of the process.[1] Deregulation of the cell cycle causes an uncontrolled cell proliferation that has been strongly linked to the molecular pathology of cancer.[2] The search for small-molecule inhibitors of CDKs is therefore one of the most active fields for the development of anticancer chemotherapy.[3] In spite of their apparent molecular diversity, flavopyridol,[4] purvanolol[5] and pyrido[2,3-*d*]pyrimidin-7-one[6] (Figure 1) have all been reported to be strong CDK inhibitors. In the indolocarbazole series, UCN-01 (7-hydroxystraurosporin),[7] a non-specific CDK inhibitor that has been entered into clinical trials, was also well known to interact with the ATP-binding pocket.[8] Simultaneously, Lilly's group and our laboratory have proposed the simpler (het)arylcarbazoles **I**, which can act as kinase inhibitors (Figure 1).

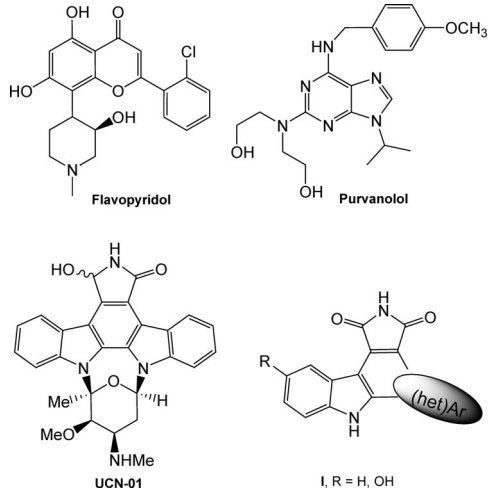


Figure 1. Stong kinase inhibitors.

These planar molecules operate in the active site as competitive inhibitors of ATP. Molecular modelling and crystallographic data have shown, in particular, the crucial role of one specific carbonyl group, which engages in direct interaction with the Leu83 residue, in the active site.[9–11]

Another class of potent CDK inhibitors has also emerged from molecular modelling and topological binding similarity. The diarylurea scaffold was proposed and, interestingly, during the optimization of the aryl counterpart it was additionally shown that the tetrahydropyrrolo[2,1-*a*]-isoindol-5-one framework **II** (Figure 2) can also bind with the enzyme (IC_{50} 42 nM). Moreover, the carbonyl group of the isoindole nucleus created an additional hydrogen bond, which could explain the remarkable activities of the new designed compounds[12,13] (Figure 2). A lot of work has also been devoted to the isoindolo[2,1-*a*]isoquinolinone type **IV**, because this core is often encountered in natural products and biologically active compounds. Several synthetic pathways under anionic, basic, acidic, or Lewis acid conditions have been envisaged. They have started from anhydrides,[14] phthalimides,[15] β-hydroxy or β-phenylsulfanyl lactams[16,17] or 2-formylbenzoic acids.[18]

Alternative methods such as condensations of imines with acetylene[19] or with an ester function[20] and treatment of an enamine with an aryl iodide[21] have also been reported. Whereas most of the previous strategies led easily to bis-aromatic fused heterocycles, synthetic pathways to design compounds of type **V** immediately appeared to be

[a] Institut de Chimie Organique et Analytique, (1) Université d'Orléans, (2) UMR CNRS 6005,
Rue de Chartres, B. P. 6759, 45057 Orléans Cedex 2, France
E-mail: sylain.routier@univ-orleans.fr
[b] Clermont Université, ENSCCF, Laboratoire de Chimie des Hétérocycles et des Glucides,
B. P. 10448, 63000 Clermont-Ferrand
E-mail: Yves.Troin@univ-bpclermont.fr

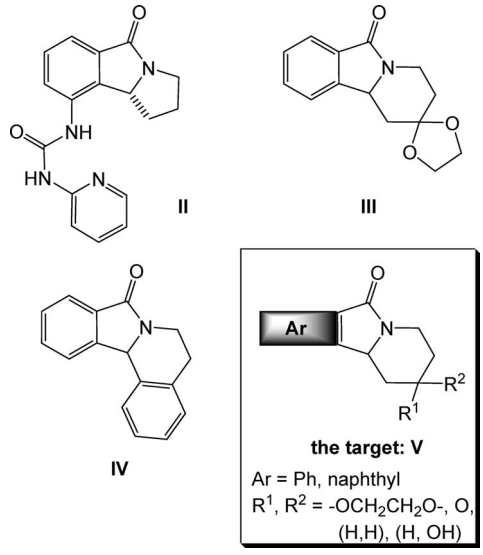


Figure 2. New isoindolones **II**, **III**, **IV** and the target **V**.

critical. Only a few publications have reported the synthesis of the targeted tetrahydropyrido[1,2-*a*]isoindolone core, through intramolecular reactions either between a β-ethoxy lactam and a terminal alkene[22] or between a β-hydroxy lactam and a methyl ketone.[23] Both reactions also required strongly acidic conditions and the common reported mechanism involved the formation of an acyliminium ion, which was further trapped either by an alkene or by an enol.

We have recently described a stereoselective route to the hexahydropyrido[2,1-*a*]isoindole skeleton **III** from readily available starting materials.[24] This work prompted us to explore the generalization of the synthetic method to the production of various compounds of type **V** (Figure 2).

We therefore now set out to explore the scope and limitations of this reaction through the introduction of several substituents on the aromatic ring. In order to allow a complete mechanism to be proposed, and to corroborate the presence of some intermediates in the aryl series, 2-formylbenzoic acids, 2-formylbenzoic acid esters or β-alkoxy lactones were used as starting materials. Two synthetic pathways were also envisaged and fully studied (Figure 3).

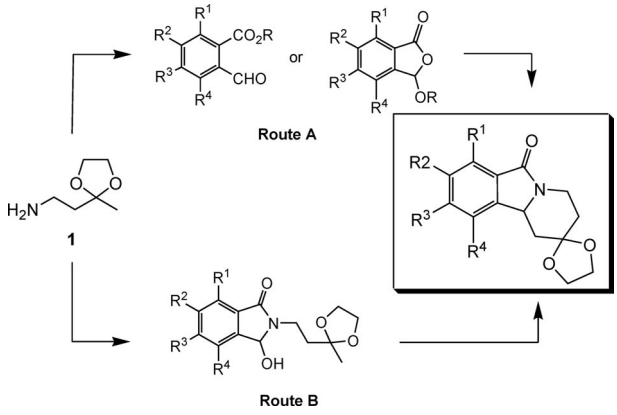


Figure 3. Synthetic routes A and B.

In a second undertaking, an extension to the naphthyl series, allowing the preparation of the corresponding targets, was achieved. To the best of our knowledge, most of the reported structures were unknown and the method described here offers chemists new heterocyclic tools for the development of complex and original structures.

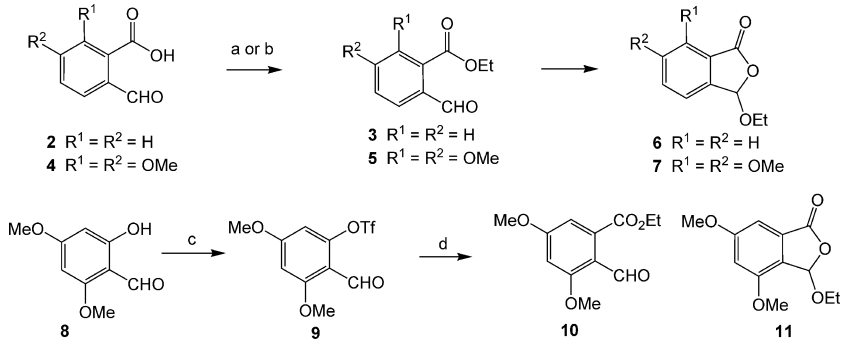
Results and Discussion

Aryl Series

As in our preliminary investigations,[24] we first prepared the protected β-amino ketone **1** (Figure 3), which was easily isolated in three steps by conventional procedures.[25] Ethyl 2-formylbenzoate (**3**, Scheme 1) was obtained in a good yield from the corresponding acid **2** by treatment with $SOCl_2$ and dry EtOH. From the starting 3,4-dimethoxy derivative **4**, the same reaction afforded the attempted ester **5** and the very stable β-ethoxy lactone **7**[26] in 68% and 30% yields respectively. On the other hand, compounds **6** or **7** could be quantitatively obtained by addition of $SOCl_2$ to solutions containing the corresponding acids **2** or **4** before the introduction of EtOH. This result could be explained by the prior formation of the acyl chloride, favouring the intramolecular cyclization into the expected β-ethoxy lactone.[27]

In order to investigate the electronic effect of the methoxy substituent on the yield of the targeted compounds, we also prepared the 3,5-dimethoxy-6-formyl derivative **10** (Scheme 1) from 2-hydroxy-4,6-dimethoxybenzaldehyde (**8**).[28] Treatment of **8** with an excess of Tf_2O in the presence of Et_3N in dichloromethane at –20 °C, followed by additional stirring at room temperature for an additional four hours, furnished the expected triflate **9** in a 68% yield. Subsequent carbonylation was next performed under CO in the presence of a catalytic amount of $Pd(OAc)_2$, dppp and Et_3N at reflux in a mixture of DMSO and EtOH for 12 h, leading to ethyl 2-formyl-3,5-dimethoxybenzoate (**10**)[29] in a 44% yield together with the corresponding β-ethoxy lactone **11**, formed in a 32% yield. All attempts to increase the yield by exchanging dppp for Xantphos®, by adding H_2O (to form a carboxylic acid) or by reducing the amount of catalyst (0.1 vs. 0.25 equiv.) were unfruitful.[30]

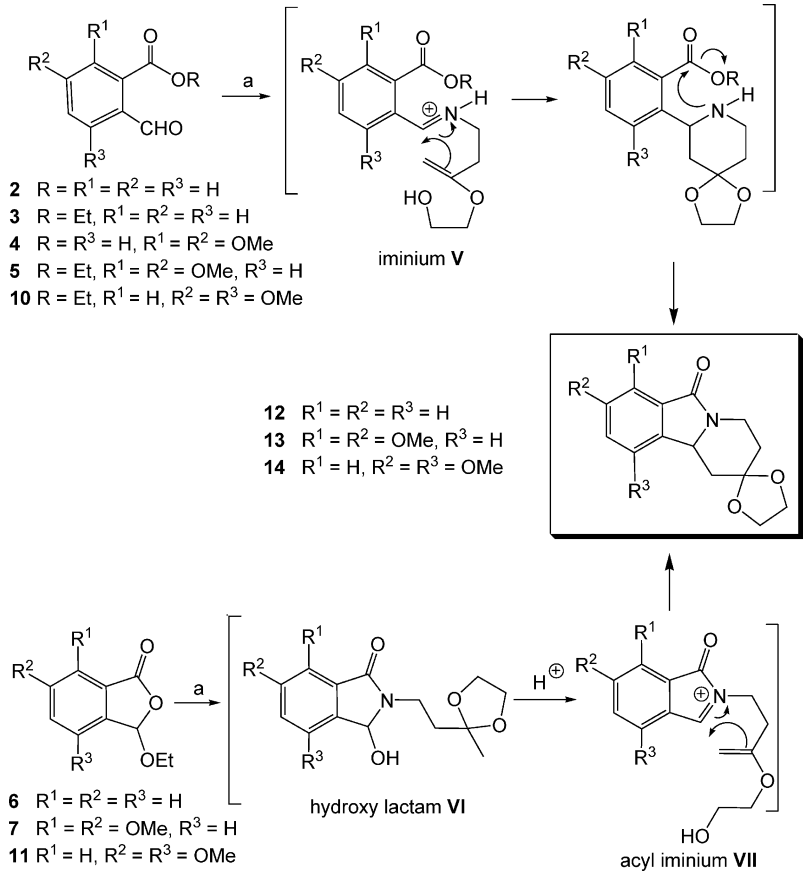
With the targeted phenyl intermediates (**3**–**5**, **6**, **7**, **10**, **11**) now to hand, we investigated their reactions with our primary amine **1** in order to form the tetrahydropyrido[2,1-*a*]-isoindolone core. All reactions were carried out in boiling toluene under a Dean–Stark apparatus in the presence of APTS (1.5 equiv.), standard conditions that have been used before.[24] From the starting formylbenzoic acids **2** and **4**, the fused heterocycles **12** and **13** were easily isolated in one-step fashion in 77 and 55% yields, respectively (Scheme 2).[24] The formation of **12** was achieved in 12 h, whereas for compound **13**, 20 h at reflux were necessary, indicating the influence of the electron-releasing groups in the reaction. With the assumption of an intramolecular Mannich reaction mechanism, we could first presume the formation of the piperidine ring, followed by an intramolec-



Scheme 1. Synthesis of compounds **6**, **7**, **10** and **11**; reagents and conditions: a) $SOCl_2$ (1.2 equiv.), EtOH, 0 °C to room temp., 12 h, *from* ***2***: **3** 85%; *from* ***4***: **5** 68% and **7** 30%. b) $SOCl_2$ (1.2 equiv.), 0 °C to r.t, 1 h then EtOH, 12 h, *from* ***2***: **6** 99%, *from* ***4****:* **7** quant. c) Tf_2O (4.0 equiv.), Et_3N (4.0 equiv.), CH_2Cl_2, –20 °C to room temp., 4 h, 68%. d) $Pd(OAc)_2$ (0.25 equiv.), dppp (0.25 equiv.), Et_3N (2.0 equiv.), CO atmosphere, DMSO/EtOH (4:1), 130 °C, 12 h, **10** 44% and **11** 32%.

ular cyclization on the carboxylic group as the limiting factor, implying the release of water, a poor leaving group. Moreover, the 6-OMe group might form an intramolecular hydrogen bond with the carboxylic acid, modifying its electrophilic character and relative configuration and so diminishing the reactivity of the carbonyl group towards nitrogen addition. In this way the increase in the reaction time and the decrease in the relative yield could be explained.

When the corresponding reactions were carried out with the 2-formylbenzoic esters **3**, **5** and **10**, the proposed hydrogen bond was not formed and ethanol, a more favourable leaving group, was released. Although no notable improvement was observed when starting from **3** (compound **12** was obtained in a 70% yield), the ester effect was clearly established when starting from the dimethoxylated ester **5**, which afforded **13** in a 75% yield. Surprisingly, the use of **10** led



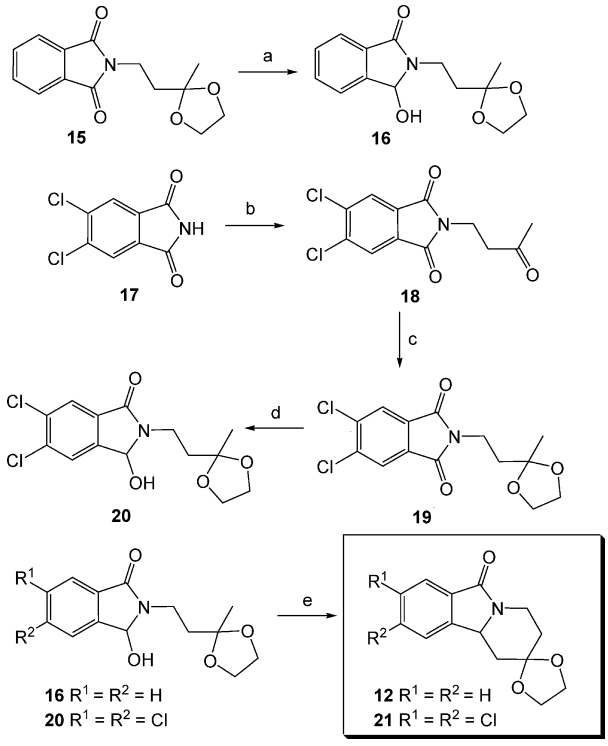
Scheme 2. Synthesis of compounds **12**, **13** and **14**; reagents and conditions: a) **1** (1.1 equiv.), APTS (1.5 equiv.), toluene, reflux, *from* ***2***: 12 h, **12** 77%; *from* ***3***: 12 h, **12** 77%; *from* ***4***: 20 h, **13** 55%; *from* ***5***: 12 h, **13** 69%; *from* ***6***: 12 h, **12** 60%; *from* ***10***: 12 h, **14** 54%.

to compound **14** in only a 54% yield after 12 h. Increasing the reaction time only increased the degradation of the reaction mixture. As the sole difference between the two starting materials **5** and **10** was the shift of one of the two OMe groups from the 6-position to the 3-position, we could assume that in this case the combined electronic and steric effects of the OMe group at C-3 might play an important role in modifying the limiting factors of the reaction. In conclusion, the formation of the tetrahydropyrido[2,1-*a*]isoindolones **12**–**14** in one step appears to be easier from the esters than from the carboxylic acids and these reactions are sensitive to the presence of electron-rich groups in the aldehyde or acid functions.

The next investigations were into the utility of the β-ethoxy lactones **6**, **7** and **11**. Although the unsubstituted compound **6** reacted easily with amine **1** to afford the isoindolone **12** in a 60% yield, the dimethoxy-substituted lactones **7** and **11** did not afford the corresponding cycloadducts **13** and **14**. Because the conversion of **6** into **12** could be explained by strong stability of the starting material under acidic conditions, the mechanism had to be modified slightly. The addition of the amine **1** onto the lactone led to an amide **VI**, which, by an intramolecular elimination, afforded the β-hydroxy or (more probably, because EtOH is a more better leaving group; vide supra) -ethoxy lactam **VI**; acidic catalysis formed the more stable acyl iminium ion **VII** (rather than iminium ion **V**), which further cyclised to afford compound **12**. Here also, the non-formation of the methoxy analogues **13** and **14** could be attributed to steric hindrance at the point of the formation of the postulated intermediates. These observations prompted us to prepare β-hydroxy lactams of type **VII**, which should lead, by the proposed mechanism, to the targeted tetrahydropyrido[2,1-*a*]-isoindolones **12**.

In order to confirm the mechanism we decided to prepare β-hydroxy lactams of type **VI** to verify their reactivities in the synthesis of tetrahydropyrido[2,1-*a*]isoindolones. Compound **16** (Scheme 3) was prepared easily and quantitatively from **15**[31] by monoreduction of the phthalimide with $NaBH_4$ in MeOH at room temperature over 1 h.[32] Analogously with **16**, the hydroxy lactam **20** was also prepared quantitatively by reduction of the protected phthalimide **19**, itself obtained from phthalimide **17**[33] by Raphael's protocol.[31] After overnight heating in toluene and in the presence of APTS, compound **16** had afforded the cycloadduct **12** in an 85% yield, whereas compound **20** under the same conditions gave the hexahydropyrido[2,1-*a*]isoindolone **21** in a 75% yield. The two chlorine atoms have no effect on the efficiency of the cycloaddition, but in this case no steric constraints could be involved. The synthesis of β-hydroxy lactams of type **VI** appeared here to be a good alternative by which to perform the reaction by an intramolecular process.

Two methods to build the hexahydropyrido[2,1-*a*]isoindolone core were now available. The first route (**A**) is compatible with symmetrical or dissymmetrical phenyl substrates. Generalization of this method nevertheless required the preparation of the substituted 2-formylbenzoic acids or



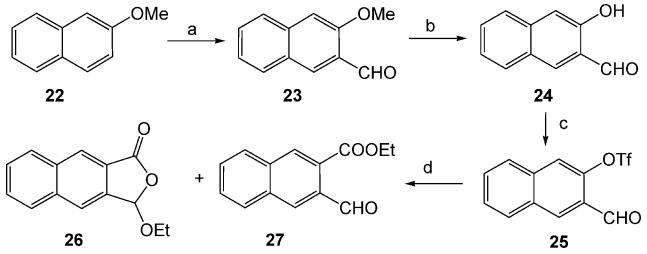
Scheme 3. Synthesis of compounds **12** and **21**; reagents and conditions: a) $NaBH_4$ (6.0 equiv.), MeOH, 0 °C to room temp., 1 h, quant. b) methyl vinyl ketone (1.0 equiv.), Triton B (0.4 equiv.), AcOEt, reflux, 13 h, 97%; c) ethyleneglycol, APTS (cat.), toluene, reflux, 12 h, quant. d) $NaBH_4$, MeOH/THF, 1:1, –20 °C to room temp., 1 h 30, quant.; e) APTS (1.5 equiv.), toluene, reflux, 12 h *from **16***: **12** 85%; *from **20**:* **21** 75%.

2-formylbenzoic acid esters, which implied a synthetic challenge. The second route (**B**) started from anhydrides or imides and led to the hexahydropyrido[2,1-*a*]isoindolones in only a few steps after purification of the β-hydroxy lactam intermediates. This attractive method was certainly less affected by the presence of substituents on the phenyl ring. From starting unsymmetrical anhydrides or phthalimides, this method implied the development of regioselective reductions or the further separation of the two regioisomers. With a pool of alternatives now to hand, we next applied our methods to naphthalene analogues and completed the family of related hexahydropyrido[2,1-*a*]isoindolones.

Naphthyl Series

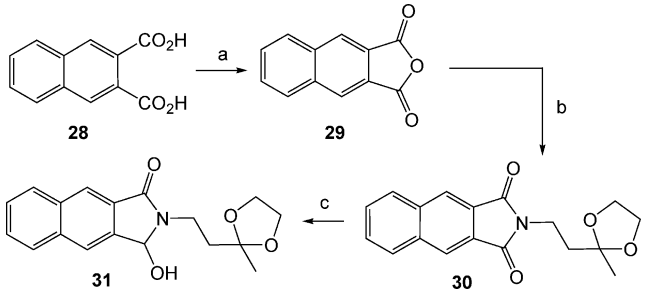
Direct application of route **A** implied the preparation of the corresponding 2-formyl carboxylic acid or carboxylic ester. From the starting 2-methoxynaphthalene **22** (Scheme 4) we first achieved a regioselective formylation at the 3-position by use of a slight excess of *n*-BuLi (–78 °C to room temperature) in dry THF and DMF as electrophile. Aldehyde **23**[34] was isolated in 75% yield. Demethylation was next performed, with BBr_3 (1.2 equiv.), to afford the naphthol **24**[35] after 1 h in 87% yield. The triflate **25** was then obtained in the presence of Tf_2O and Et_3N (from 0 °C to room temperature) after 5 h without any difficulty and

in a near quantitative yield. Palladium-catalysed carbonylation was next performed under carbon monoxide (atmospheric pressure) with $Pd(OAc)_2$ as catalyst, together with Et_3N at reflux in a mixture of DMSO and EtOH. With Xantphos® as ligand the reaction once more failed, as above, whereas introduction of dppp led to the desired ester **27** in a 39% yield after 18 h. Under these conditions the β-ethoxy lactone **26** was concomitantly formed in a 30% yield. However, changing the solvent for DMF led, after 24 h at 100 °C, to the compound **26** as the sole isolated product in a 97% yield, in confirmation of the efficiency of the carbonylation step.



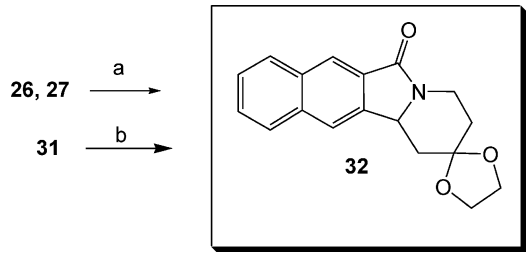
Scheme 4. Synthesis of compounds **26** and **27**; reagents and conditions: a) i) *n*BuLi (1.5 equiv.), THF –78 °C, 1 h, ii) DMF (2.0 equiv.), –78 °C to room temp., 1 h, 75%. b) BBr_3 (1.2 equiv.), CH_2Cl_2, –10 °C to room temp., 1 h, 87%. c) Tf_2O (4.0 equiv.), Et_3N (4.0 equiv.), CH_2Cl_2, –5 °C to room temp., 5 h, 98%; d) $Pd(OAc)_2$ (0.1 equiv.), dppp (0.1 equiv.), Et_3N (2.0 equiv.), DMSO/EtOH, 4:1, CO pressure, 100 °C, 24 h, **26** 30% and **27** 39%, in DMF 100 °C, 24 h, **26** 97%.

To perform route **B**, hydroxy lactam **31** (Scheme 5) was now the target. The 2,3-dicarboxylic acid **28**[36] was therefore transformed into the naphthalenic anhydride **29**[37] in boiling acetic anhydride in 90% yield (Scheme 5). The phthalimide **30** was next obtained by heating at reflux with amine **1** (1.1 equiv.) in a mixture of toluene and Et_3N (0.1 equiv.) in a near quantitative yield. Monoreduction with an excess of $NaBH_4$ in a MeOH/THF mixture led without any difficulties to the β-hydroxy lactam **31** in a 91% yield.



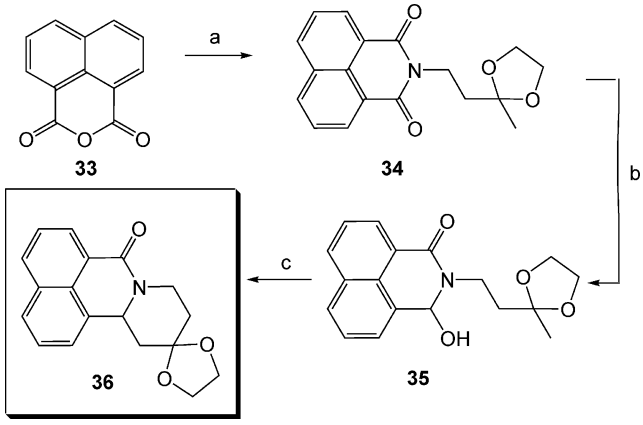
Scheme 5. Synthesis of compound **31**; reagents and conditions: a) acetic anhydride, reflux, 1 h 30, 90%. b) **1** (1.1 equiv.), Et_3N (cat.), toluene, Dean–Stark, reflux, 12 h, 98%. c) $NaBH_4$ (6.0 equiv.), MeOH/THF, 2.5:1, –30 °C to 0 °C, 2 h, 91%.

For route **A**, the intermolecular indolizination was performed in the presence of **1** (1.2 equiv.) under the same conditions as described before. From **27**, the tetrahydrobenzo[*f*]pyrido[2,1-*a*]isoindolone **32** was obtained in a moderate yield of 30% (Scheme 6), whereas the very stable β-ethoxy lactone **26** did not react with amine **1**. Numerous modifications of the experimental conditions (increasing the reaction time or microwave irradiation) were next developed, but all attempts were unsuccessful. By route **B**, β-hydroxy lactam **31** afforded cycloadduct **32** in a much better yield of 70%.



Scheme 6. Preparation of compound **32**; reagents and conditions: a) **1** (1.1 equiv.), toluene, reflux, 12 h, *from* **27**: **32** 30%. b) APTS (1.5 equiv.), toluene, Dean–Stark, reflux, 12 h, *from* ***31****:* **32** 70%.

To complete the study, we started from the commercially available 1,8-naphthalenic anhydride **33**, which was transformed in two steps (treatment with amine **1** to give **34**, followed by a monoreduction) into the β-hydroxy lactam **35** in a 92% overall yield. The β-hydroxy lactam **35** was produced more efficiently than **31** by route **B** and furnished the new tetrahydroazabenzo[*de*]anthracenone **36** in 80% yield (Scheme 7).



Scheme 7. Synthesis of compound **36**; reagents and conditions: a) **1** (1.1 equiv.), toluene, reflux, 12 h, quant. b) $NaBH_4$ (6.0 equiv.), MeOH/THF, 2.5:1–10 °C to room temp., 1 h, 92%. c) APTS (1.5 equiv.), toluene, Dean–Stark, reflux, 12 h, 80%.

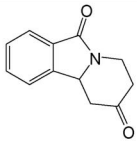
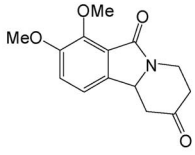
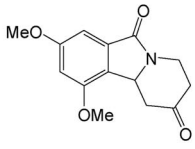
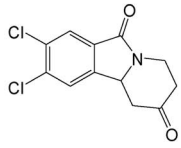
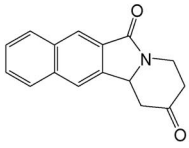
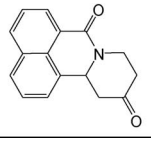
At this stage, route **A** appeared to be less efficient in the naphthyl series. From **27**, however, water was appearing in the Dean–Stark apparatus and the reaction mixture was yellow-orange-coloured, a sign of imine formation. Some hypotheses to explain the failure of route **A** can be put forward: 1) the transformation into the acyl iminium ion could be a limiting factor, 2) the electron-rich naphthalene ring could decrease the electrophilic character of the ester carbonyl function, or 3) the β-ethoxy lactone **26** was too stable and did not react with **1**. All results relating to route **A** in the naphthyl series were consistent with those obtained in the phenyl series. By route **B**, the symmetry of the unsubstituted aromatic moiety furnished a very attractive synthesis

to construct new tetracyclic fused structures possessing the targeted tetrahydroindolizinone core and ultimately its azabenzoanthracenone analogue. In validation, the two reactions with β-hydroxy lactams **31** or **35** were very efficient, the acyliminium ions were also produced without any difficulty, and the electronic factors of the aromatic ring were abolished.

Acetal Removal

We next turned our attention to the final removal of the acetal functionality. From starting compounds **12**–**14**, **31**, **32** and **36**, the reactions were also performed at reflux in a mixture containing aqueous hydrochloric solution (10%) and acetone (Table 1).

Table 1. Acetal deprotections.

Entry	SM[a]	Conditions	Products		Yields[b]
1	**12**	10% aq. HCl, acetone, reflux, 1.5 h		**37**	quant.
2	**13**	see entry 1		**38**	81%
3	**14**	see entry 1		**39**	79%
4	**21**	see entry 1, but 3 h		**40**	quant.
5	**32**	see entry 1, but 2 h		**41**	quant.
6	**36**	see entry 1, but 3 h		**42**	quant.

[a] SM: starting material. [b] Yields indicated are of isolated products.

After a few hours, in the phenyl or the naphthyl series, the attempted ketones **37** and **40**–**42** were isolated in quantitative yields. The use of the methoxylated compounds **13** and **14**, which were also more acid-sensitive, led to **38** and **39** in 81 and 79% yields, respectively.

Conclusions

We describe straightforward routes to fused tetrahydroindolizinones. These compounds were obtained, in a single step (route **A**), by acidic condensation of a keto-protected 1,3-amino ketone and 2-formylbenzoic acid or 2-formylbenzoic acid ester derivatives. A postulated mechanism involving the formation of an acyl iminium ion has been given and we showed that modifications of the electronic or steric parameters (i.e. electron-releasing substituents and electron-rich aromatic systems) strongly affect the yields.

Because the use of a β-hydroxy lactone indicated the presence of a β-hydroxy lactam as hypothetical intermediate, we also prepared compounds of this type by selective reduction of the corresponding phthalimides, which successfully cyclised to the fused tetrahydroindolizinones in the aromatic series through the direct formation of the acyl iminium ion (route **B**). The targeted tetrahydroindolizinones obtained were deprotected, leading to useful and reactive ketones, which could be used further to introduce molecular diversity.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded on Bruker 250 or 400 MHz instruments in $CDCl_3$ or [D_6]DMSO. The chemical shifts are reported in ppm (δ scale) and all J values are in Hz. 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 with a Perkin–Elmer PARAGON 1000 PC instrument and values are reported in cm^{-1}. IR spectra were also recorded with an Avatar 320 instrument (from KBr pellets) or in combination with the ATR (Ge) technique. Mass spectra (ion-spray technique) were performed with a Perkin–Elmer Sciex PI300 instrument, HRMS were measured in Clermont Ferrand, France (Centre Regional de Mesures Physiques, CRMP). Monitoring of the reactions was performed by TLC (Merck 60 F_{254} silica gel plates). Spots were visualized by UV light at 254 and 356 nm. Flash chromatography columns were performed with silica gel 60 (0.063–0.200 mm, Merck). Spectral data obtained for the following compounds are in accordance with the literature: **1**,[25] **3**,[26] **5**,[26] **6**,[26] **7**,[26] **10**,[28] **15**,[31] **23**,[35] **24**,[35] **26**[35] and **29**.[37]

General Procedure A or Carbonylations: Triethylamine (Et_3N) and dppp as ligand were successively added to a solution of the desired triflate (1.6 mmol) in a mixture of dimethyl sulfoxide and ethanol (DMSO/EtOH 4:1). The mixture was stirred for 10 min with CO bubbling. $Pd(OAc)_2$ was added, and the reaction mixture was heated and stirred vigorously under CO pressure. After cooling, the mixture was washed with a solution of saturated sodium chloride and extracted three times with ethyl acetate. The combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography to afford the desired compounds. From **9** the reaction was performed with $Pd(OAc)_2$ (0.25 equiv.), dppp (0.25 equiv.) and Et_3N (2.0 equiv.) at 130 °C for 12 h to give compounds **10** in 44% yield and **11** in 32% yields. From **25**, the reaction was performed with $Pd(OAc)_2$ (0.1 equiv.), dppp (0.1 equiv.) and Et_3N (2.0 equiv.) at 100 °C for 24 h to give compounds **26** in 30% yield and **27** in 39% yield. Alternatively, **26** could be obtained from **25**

in 97% yield by use of dimethylformamide (DMF) as solvent at 100 °C.

General Procedure B for Cyclizations: A solution of aldehyde or β-ethoxy lactone (1.0 mmol), 2-(2-methyl-1,3-dioxolan-2-yl)ethylamine (**1**, 1.1 equiv.) and *p*-toluenesulfonic acid (1.5 equiv.) in toluene (20 mL) was heated at reflux under a Dean–Stark apparatus for the desired time. From β-hydroxy lactam, the previously used amine **1** was also employed. The cooled mixture was washed with saturated aqueous $NaHCO_3$ (20 mL) and 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.

General Procedure C for Acetal Removal: A mixture containing the protected heterocycle (0.3 mmol), an aqueous solution of HCl (10%, 1 mL) and acetone (5 mL) was heated at reflux for the desired time. After cooling, the crude product was diluted with water (20 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure to afford a crude material that was next purified by flash chromatography.

2-Formyl-3,5-dimethoxyphenyl Trifluoromethanesulfonate (9): Triethylamine (2.8 mL, 20.0 mmol) and triflic anhydride (Tf_2O, 3.4 mL, 20.0 mmol) were added slowly and dropwise, under argon at –20 °C, to a solution of **8** (910 mg, 5.0 mmol) in dichloromethane (100 mL). The system was allowed to stand at room temperature for 4 h. Water (20 mL) was added, and the aqueous phase was extracted first with dichloromethane (20 mL) and then with ethyl acetate (20 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give **9** (1.02 g, 68%) as a white solid: m.p. 95–96 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.31 (s, 1 H, CHO), 6.50 (d, J = 2.2 Hz, 1 H), 6.39 (d, J = 2.1 Hz, 1 H), 3.95 (s, 3 H, OMe), 3.90 (s, 3 H, OMe) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 185.8 (CHO), 165.5 (Cq), 164.4 (Cq), 150.0 (Cq), 118.8 (q, J = 320.7 Hz, CF_3), 112.0 (Cq), 101.0 (CH), 97.9 (CH), 56.6 (OMe), 56.2 (OMe) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1680 (CHO), 1423 (S–O), 1195 (C–O), 1227 (C–C), 1068 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{10}F_3O_6S$ $[M + H]^+$ 314.0150; found 315.0147.

3-Ethoxy-4,6-dimethoxy-2-benzofuran-1(3*H*)-one (11): Compound **11** was obtained by General Procedure **A** from **9** after purification by flash chromatography (petroleum ether/ethyl acetate, 4:1) as a white solid (32%); m.p. 121–122 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.90 (d, $^2J_{H,H}$ = 1.9 Hz, 1 H), 6.67 (d, $^2J_{H,H}$ = 1.9 Hz, 1 H), 6.36 (s, 1 H, CH), 3.91–3.82 (m, 2 H, CH_2), 3.88 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 1.31 (t, $^3J_{H,H}$ = 7.07 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 169.0 ($C{=}O_{amide}$), 163.9 (Cq), 156.2 (Cq), 130.2 (Cq), 125.7 (Cq), 105.4 (CH), 101.5 (CH), 99.1 (CH), 65.4 (CH_2), 56.1 (OMe), 56.0 (OMe), 15.3 (CH_3) ppm. IR (NaCl): $\tilde{\nu}$ = 1631 (C=O), 1455 (C=C aromatic), 1338 (C–O) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{14}O_5Na$ $[M + Na]^+$ 261.0739, found 261.0738.

1′,3′,4′,10b′-Tetrahydro-6′*H*-spiro[1,3-dioxolane-2,2′-pyrido[2,1-*a*]-isoindol]-6′-one (12): Compound **12** was obtained by General Procedure **B** from **2**, **3** or **6** after purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) in 77%, 70% and 60% yields, respectively, as a white solid; m.p. 160–161 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.70 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.40 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.30 (m, 2 H), 4.45 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 2.5 Hz, 1 H, H_{4eq}), 4.32 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 5.5 Hz, 1 H, H_{10b}), 3.95–3.90 (m, 4 H, 2 × OCH_2), 3.10 (td, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 12.5, $^3J_{H,H}$ = 2.5 Hz, 1 H, H_{4ax}), 2.20 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 3.0 Hz, 1 H, H_{1eq}), 1.65 (dd, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 2.0 Hz, 1 H, H_{3eq}), 1.50 (m, 1 H, H_{3ax}), 1.23 (t, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 12.5 Hz, 1 H, H_{1ax}) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 165.7 (C=O), 144.7 (Cq), 131.7 (Cq), 131.0 (Cq), 127.8 (Cq), 124.8 (Cq), 121.3 (Cq), 107.0 (*O*-Cq-O), 64.5 (OCH_2), 64.3 (OCH_2), 56.5 (CH), 39.8 (CH_2), 36.1 (CH_2), 33.5 (CH_2) ppm. IR (NaCl): $\tilde{\nu}$ = 1689 (C=O) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{15}NO_3$ $[M + H]^+$ 245.1052; found 245.1054.

7′,8′–Dimethoxy-1′,3′,4′,10b′-tetrahydro-6′*H*-spiro[1,3-dioxolane-2,2′-pyrido[2,1-*a*]isoindol]-6′-one (13): Compound **13** was obtained by General Procedure **B** from **4** and **5** after purification by flash chromatography (petroleum ether/EtOAc 1:2) in 55% and 75% yields, respectively, as a yellow solid; m.p. 107–108 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.03 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 6.95 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 4.40 (m, 2 H, H_{10b} + H_{4eq}), 4.05 (s, 3 H, OCH_3), 4.05–3.95 (m, 4 H, 2 × OCH_2), 3.83 (s, 3 H, OCH_3), 3.10 (td, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 12.5, $^3J_{H,H}$ = 3.5 Hz, 1 H, H_{4ax}), 2.20 (m, 1 H, H_{1eq}), 1.75 (m, 1 H, H_{3eq}), 1.59 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 13.0, $^3J_{H,H}$ = 6.0 Hz, 1 H, H_{3ax}), 1.31 (t, $^2J_{H,H}$ = 13.0 Hz, $^3J_{H,H}$ = 13.0 Hz, 1 H, H_{1ax}) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 164.3 (C=O), 152.5 (Cq), 147.4 (Cq), 138.5 (Cq), 124.4 (Cq), 116.6 (Cq), 116.1 (Cq), 107.6 (O-Cq-O), 64.8 (OCH_2), 64.6 (OCH_2), 62.6 (CH), 56.7 (OCH_3), 55.7 (OCH_3), 40.7 (CH_2), 36.3 (CH_2), 33.9 (CH_2) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1685, (C=O) 1498, 1280, 1086, 1054 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{19}NO_5$ $[M + H]^+$ 305.1263; found 305.1266.

8′,10′-Dimethoxy-1′,3′,4′,10b′-tetrahydro-6′*H*-spiro[1,3-dioxolane-2,2′-pyrido[2,1-*a*]isoindol]-6′-one (14): Compound **14** was obtained by General Procedure **A** from **10** after purification by flash chromatography (petroleum ether/ethyl acetate, 1:2) in a 54% yield and as a white solid; m.p. 169–170 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.94 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H), 6.57 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H), 4.56 (dd, $^3J_{H,H}$ = 12.0, $^3J_{H,H}$ = 4.0 Hz, 1 H, H_{10b}), 4.54 (ddd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 5.6, $^3J_{H,H}$ = 1.7 Hz, 1 H, H_{4eq}), 4.07–4.02 (m, 4 H, 2 × OCH_2), 3.85 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.24 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 13.0, $^3J_{H,H}$ = 4.0 Hz, 1 H, H_{4ax}), 2.54 (ddd, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 3.8, $^3J_{H,H}$ = 2.4 Hz, 1 H, H_{3eq}), 1.87–1.77 (m, 1 H, H_{1eq}), 1.68 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 13.0, $^3J_{H,H}$ = 5.6 Hz, 1 H, H_{3ax}), 1.30 (t, $^3J_{H,H}$ = 12.5, $^3J_{H,H}$ = 12.5 Hz, 1 H, H_{1ax}) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 166.3 (C=O), 161.9 (Cq), 155.5 (Cq), 134.8 (Cq), 125.9 (Cq), 107.8 (O-Cq-O), 102.5 (CH), 98.1 (CH), 65.0 (OCH_2), 64.8 (OCH_2), 56.0 (OMe), 55.7 (CH), 55.6 (OMe), 39.3 (CH_2), 36.8 (CH_2), 34.3 (CH_2) ppm. IR (NaCl): $\tilde{\nu}$ = 1672 (C=O), 1501 (C=C arom.), 1140 (C–N) cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{20}NO_5$ $[M + H]^+$ 305.1341; found 306.1329.

3-Hydroxy-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2,3-dihydroisoindol-1-one (16): $NaBH_4$ (128 mg, 3.4 mmol) was slowly added portionwise at –20 °C, under an inert atmosphere, to a solution of **15** (740 mg, 2.3 mmol) in a tetrahydrofuran/methanol (20.0 mL/25.0 mL) mixture. The mixture was stirred at this temperature for 30 min and the temperature was then allowed to rise to 0–5 °C for 1 h. Water (6.0 mL) and saturated $NaHCO_3$ (15.0 mL) were successively added. The mixture was extracted with dichloromethane (3 × 30.0 mL) and with ethyl acetate (50.0 mL). After evaporation of the combined organic layers, the crude material was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5) to give **18** (750 mg, quant.) as a white solid; m.p. 135–136 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 7.85–7.81 (m, 2 H), 7.72–7.68 (m, 2 H), 6.78 (d, $^2J_{H,H}$ = 8.7 Hz, 1 H, OH), 5.91 (d, $^2J_{H,H}$ = 8.7 Hz, 1 H, CH), 3.94 (s, 4 H, 2 × OCH_2), 3.82 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, NCH_2), 2.08 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, NCH_2CH_2), 1.38 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 163.6 (C=O),

133.4 (2×CH), 132.2 (2×Cq), 123.2 (2×CH), 108.0 (O-Cq-O), 78.4 (CH), 64.8 (2×OCH_2), 36.5 (NCH_2), 33.7 (NCH_2CH_2), 23.9 (CH_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 3253 (OH), 1680 (C=O amide), 1419 (C–O), 1419 (C–C) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{17}NO_4Na$ $[M + Na]^+$ 286.1055; found 286.1047.

5,6-Dichloro-2-(3-oxobutyl)-1*H*-isoindole-1,3(2*H*)-dione (18): 3,4-Dichlorophthalimide (**17**, 650 mg, 3.0 mmol), methyl vinyl ketone (0.3 mL, 3.0 mmol) and benzyltrimethylammonium hydroxide (40% in methanol, 0.2 mL, 1.2 mmol) in ethyl acetate (10.0 mL) were stirred at reflux for 18 h. Evaporation to dryness under reduced pressure and recrystallization from ethanol give **20** (835 mg, 97%) as white crystals; m.p. 133–134 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.92 (s, 2 H), 3.95 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, NCH_2), 2.87 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, NCH_2CH_2), 2.18 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 205.6 (C=O), 166.2 (2×C=O), 139.1 (2×Cq), 131.2 (2×Cq), 125.6 (2×CH), 41.4 (NCH_2), 33.6 (NCH_2CH_2), 30.1 (CH_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1712 (CO ketone), 1692 (CO amide), 1390 (C–C), 734 (C–Cl) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{10}Cl_2NO_3$ $[M + H]^+$ 286.0038; found 286.0026.

5,6-Dichloro-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (19): A solution of ketone **18** (490 mg, 1.6 mmol), ethylene glycol (0.2 mL, 3.4 mmol) and *p*-toluenesulfonic acid (cat) in toluene (10.0 mL) was heated at reflux overnight under a Dean–Stark apparatus. The cooled solution was washed with a solution of sat. $NaHCO_3$ (3×10 mL). The aqueous layers were extracted with ethyl acetate (10 mL) and the combined organic layers were dried, filtered and concentrated under reduced pressure. The crude material slowly crystallized from ethanol to afford **19** (566 mg, quant.) as a white solid; m.p. 136–137 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.91 (s, 2 H), 3.92 (s, 4 H, 2×OCH_2), 3.82 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, NCH_2), 2.07 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, NCH_2CH_2), 1.36 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 166.5 (2×C=O), 138.9 (2×Cq), 131.5 (2×Cq), 125.4 (2×CH), 108.8 (O-Cq-O), 64.8 (2×OCH_2), 36.2 (NCH_2), 34.1 (NCH_2CH_2), 23.9 (CH_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1704 (CO amide), 1382 (C–O), 1031 (C–C), 742 (C–Cl) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{13}Cl_2NO_4Na$ $[M + Na]^+$ 352.0119; found 352.0126.

5,6-Dichloro-3-hydroxy-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]isoindolin-1-one (20): Compound **20** was obtained as described for compound **16**, starting from **19**. The crude material was purified by flash chromatography on silica gel (dichloromethane/methanol, 95:5) to give **20** (quant.) as a white solid; m.p. 197–198 °C. ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 7.86 (s, 1 H), 7.84 (s, 1 H), 6.74 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, OH), 5.85 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, CH), 3.92–3.97 (brs, 4 H, 2×OCH_2), 3.72–3.60 (m, 1 H, NCH_2), 3.41–3.29 (m, 1 H, NCH_2), 2.02–1.84 (m, 2 H, NCH_2CH_2), 1.28 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ= 163.6 (C=O), 144.8 (Cq), 134.5 (Cq), 132.3 (Cq), 132.1 (Cq), 125.8 (CH), 124.0 (CH), 108.0 (O-Cq-O), 79.9 (CH), 64.0 (OCH_2), 63.9 (OCH_2), 36.4 (NCH_2), 34.6 (NCH_2CH_2), 23.6 (CH_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 3253 (OH), 1680 (C=O amide), 1419 (C–O), 1419 (C–C), 705 (C–Cl) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{15}Cl_2NO_4Na$ $[M + Na]^+$ 354.0276; found 354.0272.

8′,9′-Dichloro-1′,3′,4′,10b′-tetrahydro-6′*H*-spiro[1,3-dioxolane-2,2′-pyrido[2,1-*a*]isoindol]-6′-one (21): Compound **21** was obtained from **20** by General Procedure **B** after purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) in a 75% yield and as a white solid; m.p. 204–205 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 7.50 (s, 1 H), 4.57 (dd, $^3J_{H,H}$ = 12.5, $^3J_{H,H}$ = 4.0 Hz, 1 H, H_{10b}), 4.45 (ddd, $^2J_{H,H}$ = 13.4, $^3J_{H,H}$ = 5.7, $^3J_{H,H}$ = 1.4 Hz, 1 H, H_{4eq}), 4.12–4.06 (m, 4 H, 2×OCH_2), 3.24 (td, $^2J_{H,H}$ = 13.4, $^3J_{H,H}$ = 13.4, J = 3.9 Hz, 1 H, H_{4ax}), 2.28 (ddd, J = 13.0, J = 3.8, J = 3.9 Hz, 1 H, H_{3eq}), 1.87–1.80 (m, 1 H, H_{1eq}), 1.67 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 5.7 Hz, 1 H, H_{3ax}), 1.41 (t, $^3J_{H,H}$ = 12.5 Hz, 1 H, H_{1ax}) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 164.2 (C=O), 144.2 (Cq), 136.0 (Cq), 133.2 (Cq), 132.3 (Cq), 125.9 (CH), 124.1 (CH), 107.3 (O-Cq-O), 65.0 (OCH_2), 64.9 (OCH_2), 56.5 (CH), 40.2 (CH_2), 36.8 (CH_2), 33.9 (CH_2) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1680 (CO amide), 1419 (C–O), 1076 (C–C), 746 (C–Cl) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{13}Cl_2NO_3$ $[M + H]^+$ 314.0351; found 314.0337.

3-Formyl-2-naphthyl Trifluoromethanesulfonate (25): Triethylamine (1.0 mL, 7.0 mmol) and then, dropwise, triflic anhydride (1.2 mL, 7.0 mmol) were added at 0 °C, under inert atmosphere, to a stirred solution of **24** (300 mg, 1.7 mmol) in dichloromethane (30.0 mL). Stirring was continued at 0 °C for 30 min and then at room temperature for 5 h. Water (25 mL) was added. The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. The resulting crude solid was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) to give **25** (517 mg, 98%) as a yellow solid; m.p. 69–70 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 10.31 (s, 1 H, CHO), 8.48 (s, 1 H), 8.05 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H), 7.92 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.81 (s, 1 H), 7.76–7.64 (m, 2 H) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 187.2 (CHO), 145.3 (Cq), 135.8 (Cq), 135.2 (CH), 131.6 (Cq), 130.7 (CH), 129.9 (CH), 128.5 (CH), 128.2 (CH), 126.7 (Cq), 121.0 (Cq), 119.6 (q, J = 119.6 Hz, CF_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1696 (C=O aldehyde), 1419 (C=C arom.), 1211 (C–C), 1133 (C–N), 1068 (C–F) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_8F_3O_4S$ $[M + H]^+$ 305.0095; found 305.0013.

3-Ethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (26): Compound **26** was obtained from **25** in DMF by General Procedure **A** after purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) in a 97% yield and as a yellow solid; m.p. 179–180 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.49 (s, 1 H), 8.05–7.96 (m, 2 H), 8.02 (s, 1 H), 7.70–7.58 (m, 2 H), 6.53 (s, 1 H, CH), 4.11–3.85 (m, 2 H, CH_2), 1.36 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 168.9 (C=O), 139.2 (Cq), 136.4 (Cq), 134.1 (Cq), 130.1 (CH), 129.2 (CH), 128.8 (CH), 127.7 (CH), 127.0 (CH), 124.4 (Cq), 123.2 (CH), 102.7 (CH), 65.9 (CH_2), 15.3 (CH_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1766 (C=O lactone), 1420–1460 (C=C arom.), 1326 (C–O), 1089 (C–C) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{12}O_3Na$ $[M + Na]^+$ 251.0684; found 251.0672.

Ethyl 3-Formyl-naphthalene-2-carboxylate (27): Compound **27** was obtained by General Procedure **A** from **25** after purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) in a 39% yield and as a yellow solid; m.p. 67–68 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 10.70 (s, 1 H, CHO), 8.50 (s, 1 H), 8.44 (s, 1 H), 8.03–7.96 (m, 2 H), 7.71–7.65 (m, 2 H), 4.50 (q, $^4J_{H,H}$ = 7.1 Hz, 2 H, CH_2), 1.47 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 192.3 (CHO), 166.8 (C=O), 134.4 (Cq), 134.0 (Cq), 133.5 (Cq), 132.1 (CH), 130.8 (CH), 129.7 (CH), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.1 (Cq), 62.0 (CH_2), 14.5 (CH_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 2919 (CH aldehyde), 1704 (C=O ester), 1684 (C=O aldehyde), 1280 (C–C) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{12}O_3Na$ $[M + Na]^+$ 251.0684; found 251.0683.

2-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-benzo[*f*]isoindole-1,3(2*H*)-dione (30): A mixture of anhydride **29** (400 mg, 2.0 mmol), 2-(2-methyl-1,3-dioxolan-2-yl)ethylamine (**1**, 260 mg, 2.0 mmol) and triethylamine (some drops, cat.) in toluene (60.0 mL) was heated at reflux at 150 °C overnight under a Dean–Stark apparatus. After cooling, the mixture was washed with water (20 mL) and ex-

tracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure to give **31** (610 mg, 98%) as a yellow solid; m.p. 135–136 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.32 (s, 2 H), 8.05 (dd, $^3J_{H,H}$ = 6.0, $^3J_{H,H}$ = 3.5 Hz, 2 H), 7.69 (dd, $^3J_{H,H}$ = 6.3, $^3J_{H,H}$ = 3.1 Hz, 2 H), 4.03–3.92 (m, 4 H, 2 × OCH_2), 3.89 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, NCH_2), 2.13 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2), 1.41 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 168.1 (2 × CO), 135.6 (2 × Cq), 130.4 (2 × CH), 129.2 (2 × CH), 128.1 (2 × Cq), 124.6 (2 × CH), 108.9 (O-Cq-O), 64.8 (2 × OCH_2), 36.4 (NCH_2), 34.0 (CH_2), 23.9 (CH_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1691 (C=O amide), 1367 (C–O acetal), 1189 (C–N), 1040 (C–C) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{17}NO_4$ [M + Na]$^+$ 334.1055; found 334.1043.

3-Hydroxy-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2,3-dihydro-1*H*-benzo[*f*]isoindol-1-one (31): Compound **32** was obtained from **30** as described for compound **16**, after 2 h. The crude product was purified by flash chromatography on silica gel to give **32** (91%) as a white solid; m.p. 197–198 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.26 (s, 1 H, OH), 8.16–8.08 (m, 2 H), 7.67–7.57 (m, 2 H), 6.66 (d, $^2J_{H,H}$ = 9.2 Hz, 1 H), 5.99 (d, $^2J_{H,H}$ = 9.2 Hz, 1 H), 3.90 (br s, 4 H, 2 × OCH_2), 3.81–3.69 (m, 1 H, N-CH_2), 3.49–3.34 (m, 1 H, NCH_2), 2.13 (m, 2 H, CH_2), 1.31 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 165.5 (CO), 140.3 (Cq), 134.7 (Cq), 133.0 (Cq), 129.8 (Cq), 129.3 (CH), 128.3 (CH), 127.6 (CH), 126.6 (CH), 122.5 (CH), 122.2 (CH), 108.1 (O-Cq-O), 80.6 (CH), 64.0 (2 × OCH_2), 36.5 (NCH_2), 34.6 (CH_2), 23.7 (CH_3). IR (ATR-Ge): $\tilde{\nu}$ = 1203 (C–O), 1047 (C–C), 778 (CH arom.) cm^{-1}. SM (IS) (*m*/*z*): 314.5 [M + H]$^+$.

1,3,4,12b-Tetrahydro-6*H*-spiro[benzo[*f*]pyrido[2,1-*a*]isoindole-2,2′-1,3-dioxolan]-6-one (32): Compound **32** was obtained by General Procedure **B** from **27** and **31** after purification by flash chromatography (petroleum ether/ethyl acetate, 1:2) in 30% and 70% yields, respectively, as a white solid; m.p. 129–130 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.00 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H), 7.90 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H), 7.80 (s, 1 H), 7.62–7.52 (m, 2 H), 4.75 (dd, $^2J_{H,H}$ = 12.1, $^3J_{H,H}$ = 3.8 Hz, 1 H, H_{12b}), 4.55 (ddd, $^2J_{H,H}$ = 13.3, $^3J_{H,H}$ = 5.6, $^3J_{H,H}$ = 1.4 Hz, 1 H, H_{4eq}), 4.16–4.00 (m, 4 H, 2 × OCH_2), 3.29 (td, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 13.0, $^3J_{H,H}$ = 3.9 Hz, 1 H, H_{4ax}), 2.42 (ddd, $^2J_{H,H}$ = 12.8, $^3J_{H,H}$ = 3.8, $^3J_{H,H}$ = 2.4 Hz, 1 H, H_{1eq}), 1.90–1.84 (m, 1 H, H_3), 1.72 (td, $^3J_{H,H}$ = 12.8, $^3J_{H,H}$ = 12.8, $^3J_{H,H}$ = 5.6 Hz, 1 H, H_{1ax}), 1.48 (m, 1 H, H_3) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 164.5 (CO), 140.4 (Cq), 134.4 (Cq), 132.5 (Cq), 130.0 (Cq), 129.2 (CH), 127.9 (CH), 127.5 (CH), 126.2 (CH), 122.9 (CH), 120.9 (CH), 106.7 (O-Cq-O), 64.2 (–OCH_2), 63.9 (OCH_2), 56.1 (CH), 39.9 (CH_2), 36.2 (CH_2), 33.4 (CH_2) ppm. IR (NaCl): $\tilde{\nu}$ = 1703 cm^{-1} (C=O amide), 1644 (C=C), 1424 (C=C aromatic), 1391 (C–O), 1265 (C–C) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{18}NO_3$ [M + H]$^+$ 296.1287; found 296.1288.

2-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (34): A mixture of anhydride **33** (991 mg, 5.0 mmol) and 2-(2-methyl-1,3-dioxolan-2-yl)ethylamine (**1**, 720 mg, 5.5 mmol) in toluene (60.0 mL) was heated at reflux overnight under a Dean–Stark apparatus. After cooling, the mixture was washed with water (40 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure to give **34** (1.60 g, quant.) as a yellow solid; m.p. 137–138 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.61 (dd, $^3J_{H,H}$ = 7.3, $^4J_{H,H}$ = 1.0 Hz, 2 H), 8.21 (dd, $^3J_{H,H}$ = 8.3, $^4J_{H,H}$ = 0.9 Hz, 2 H), 7.76 (t, $^3J_{H,H}$ = 8.1 Hz, 2 H), 4.35–4.29 (m, 2 H, NCH_2), 4.03–3.97 (m, 4 H, 2 × OCH_2), 2.14–2.08 (m, 2 H, NCH_2CH_2), 1.48 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 164.2 (2 × C=O), 134.0 (2 × CH), 131.3 (2 × Cq + 2 × CH), 127.1 (2 × CH), 122.9 (2 × Cq), 109.1 (O-Cq-O), 64.8 (2 × OCH_2), 36.4 (2 × CH_2), 24.0 (CH_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1698 (C=O amide), 1647 (C=C), 1568 (C=C arom.), 1343 (C–O), 1234 (C–C) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{17}NO_4$ [M + Na]$^+$ 334.1055; found 334.1061.

3-Hydroxy-2-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-1-one (35): Compound **35** was obtained from **34** (92%) as described for compound **16**, as a yellow solid; m.p. 174–175 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.23 (d, $^3J_{H,H}$ = 7.1 Hz, 1 H), 8.17 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H), 8.03 (dd, $^3J_{H,H}$ = 7.3, $^4J_{H,H}$ = 1.9 Hz, 1 H), 7.72–7.66 (m, 3 H), 6.69 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H), 6.16 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, OH), 3.98–3.86 (m, 1 H, NCH_2), 3.90 (br s, 4 H, 2 × OCH_2), 3.66–3.54 (m, 1 H, NCH_2), 2.08–2.01 (m, 1 H, NCH_2CH_2), 1.31 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 161.6 (C=O), 132.1 (Cq), 131.6 (CH), 131.5 (CH), 127.5 (CH), 126.5 (CH), 126.4 (CH), 126.2 (CH), 126.1 (CH), 126.0 (Cq), 124.0 (CH), 108.3 (O-Cq-O), 79.9 (CH), 64.0 (2 × OCH_2), 40.3 (NCH_2), 36.5 (CH_2), 23.9 (CH_3) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1199 (C–O), 1044 (C–C), 771 (CH arom.) cm^{-1}. SM (IS) (*m*/*z*): 314 [M + H]$^+$.

9,10,12,12a-Tetrahydro-7*H*-spiro[benzo[*de*]pyrido[2,1-*a*]isoquinoline-11,2′-[1,3]dioxolan]-7-one (36): Compound **36** was obtained by General Procedure **B** from **35** after purification by flash chromatography (petroleum ether/ethyl acetate, 3:2) in an 80% yield and as a white solid; m.p. 157–158 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.38 (dd, $^3J_{H,H}$ = 7.2, $^4J_{H,H}$ = 1.1 Hz, 1 H), 7.97 (dd, $^3J_{H,H}$ = 8.3, $^4J_{H,H}$ = 1.0 Hz, 1 H), 7.80 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H), 7.60 (dd, $^3J_{H,H}$ = 8.2, $^3J_{H,H}$ = 7.3 Hz, 1 H), 7.52 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.37 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H), 5.20–5.07 (m, 2 H, H_{12a} and H_9), 4.15–4.00 (m, 4 H, 2 × OCH_2), 3.01 (dt, $^2J_{H,H}$ = 13.8, $^3J_{H,H}$ = 8.1 Hz, 1 H, H_9), 2.12 (d, $^2J_{H,H}$ = 12.9 Hz, 1 H, H_{12}), 1.96 (d, $^2J_{H,H}$ = 12.2 Hz, 1 H, H_{12}), 1.90–1.85 (m, 2 H, H_{10}) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 161.6 (C=O), 132.6 (Cq), 132.0 (Cq), 131.6 (CH), 127.6 (Cq), 126 ppm. (CH), 126.5 (CH), 126.4 (Cq), 126.1 (CH), 124.2 (CH), 123.0 (CH), 107.2 (O-Cq-O), 64.8 (2 × OCH_2), 57.9 (CH), 47.7 (CH_2), 40.8 (CH_2), 35.2 (CH_2) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1638 (C=O amide), 1615 (C=C arom.), 1071 (C–C) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{18}NO_3$ [M + H]$^+$ 296.1287; found 296.1284.

1,3,4,10b-Tetrahydropyrido[2,1-*a*]isoindole-2,6-dione (37): Compound **37** was obtained from **12** after 1 h 30 min by General Procedure **C** with purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) as a white solid (quant.); m.p. 123–124 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.90 (d, $^3J_{H,H}$ = 6.8 Hz, 1 H), 7.62–7.52 (m, 2 H), 7.42 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H), 4.82–4.73 (m, 1 H, H_4), 4.71 (dd, $^3J_{H,H}$ = 12.5, $^3J_{H,H}$ = 3.9 Hz, 1 H, H_{1eq}), 3.46–3.34 (m, 1 H, H_4), 3.02 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 4.2 Hz, 1 H, H_1), 2.59–2.54 (m, 2 H, H_3), 2.25 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 12.5 Hz, 1 H, H_{1ax}) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 205.9 (C=O), 166.5 (C=O), 144.3 (C_q), 132.1 (C_q), 131.7 (C_q), 129.0 (C_q), 124.3 (CH), 121.9 (CH), 57.9 (CH), 46.5 (CH_2), 39.9 (CH_2), 37.5 (CH_2) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1692 (CO ketone), 1775 (CO amide), 1245 (C–O), 1073–1051 (C–N) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{12}NO_2$ [M + H]$^+$ 202.0868; found 202.0884.

7,8-Dimethoxy-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindole-2,6-dione (38): Compound **38** was obtained from **13** after 1 h 30 min by General Procedure **C** with purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) as a white solid (81%); m.p. 157–158 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.12 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H), 7.04 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H), 4.77–4.68 (m, 1 H, H_4), 4.60 (dd, $^3J_{H,H}$ = 11.9, $^3J_{H,H}$ = 4.2 Hz, 1 H, H_{10b}), 4.10 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.39–3.28 (m, 1 H, H_4), 2.94 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 4.2 Hz, 1 H, H_{1eq}), 2.57–2.51 (m, 2 H, H_3),

2.23 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 11.9 Hz, 1 H, H_{1ax}) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 206.1 (C=O), 164.7 (C=O), 153.0 (Cq), 147.6 (Cq), 137.5 (Cq), 123.7 (Cq), 116.9 (CH), 116.6 (CH), 62.6 (OMe), 56.7 (CH + OMe), 46.9 (CH_2), 39.8 (CH_2), 37.3 (CH_2) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1720 (CO ketone), 1672 (CO amide), 1264 (C–O), 1084–1048 (C–N), 828–807 (CH arom.) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{16}NO_4$ $[M + H]^+$ 262.1079; found 262.1068.

8,10-Dimethoxy-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindole-2,6-dione (39): Compound **39** was obtained from **14** after 1 h 30 min by General Procedure **C** with purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) as a white solid (79%); m.p. 101–102 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.96 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H), 6.60 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H), 4.76–4.69 (m, 1 H, H_4), 4.65 (dd, $^3J_{H,H}$ = 12.1, $^3J_{H,H}$ = 4.0 Hz, 1 H, H_{10b}), 3.87 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.46–3.34 (m, 1 H, H_4), 3.20 (dd, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 4.0 Hz, 1 H, H_{1eq}), 2.58–2.52 (m, 2 H, H_3), 2.14 (dd, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 12.1 Hz, 1 H, H_{1ax}) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 206.7 (C=O), 166.5 (C=O), 162.3 (Cq), 155.4 (Cq), 134.1 (Cq), 125.1 (Cq), 102.8 (CH), 98.3 (CH), 56.4 (CH), 56.0 (OMe), 55.6 (OMe), 45.8 (CH_2), 39.9 (CH_2), 37.6 (CH_2) ppm. IR (NaCl): $\tilde{\nu}$ = 1685 cm^{-1} (C=O ketone), 1620 (C=C arom.), 1501 (C=C arom.), 1137 (C–C) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{16}NO_4$ $[M + H]^+$ 262.1079; found 262.1073.

8,9-Dichloro-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindole-2,6-dione (40): Compound **40** was obtained from **21** after 3 h by General Procedure **C** with purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) as a white solid (quant.); m.p. 260 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.95 (s, 1 H), 4.94 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 4.3 Hz, 1 H, H_{10b}), 4.38 (ddd, $^2J_{H,H}$ = 13.1, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ = 2.7 Hz, 1 H, H_{4eq}), 3.46 (td, $^2J_{H,H}$ = 11.5, $^3J_{H,H}$ = 5.0 Hz, 1 H, H_{3eq}), 3.01 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 4.3 Hz, 1 H, H_{1eq}), 2.61–2.53 (m, 1 H, H_{4ax}), 2.42–2.37 (m, 1 H, H_{3ax}), 2.34 (dd, $^3J_{H,H}$ = 14.0, $^3J_{H,H}$ = 12.5 Hz, 1 H, H_{1ax}) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 205.7 (C=O), 163.3 (C=O), 145.0 (Cq), 134.4 (Cq), 132.0 (Cq), 131.6 (Cq), 125.3 (CH), 124.7 (CH), 56.2 (CH), 44.5 (CH_2), 38.6 (CH_2), 36.7 (CH_2) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1692 (CO ketone), 1427 (C–O), 1243(C–C), 758 (C–Cl) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{10}Cl_2NO_2$ $[M + H]^+$ 270.0089; found 270.0088.

1,3,4,12b-Tetrahydrobenzo[*f*]pyrido[2,1-*a*]isoindole-2,6-dione (41): Compound **41** was obtained from **32** after 2 h by General Procedure **C** with purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) as a white solid (quant.); m.p. 249–250 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.42 (s, 1 H), 8.06–8.02 (m, 1 H), 7.95–7.91 (m, 1 H), 7.83 (s, 1 H), 7.66–7.55 (m, 2 H), 4.88 (dd, $^3J_{H,H}$ = 11.5, $^3J_{H,H}$ = 4.8 Hz, 1 H, H_{12b}), 4.85–4.80 (m, 1 H, H_4), 3.49–3.37 (m, 1 H, H_4), 3.10 (dd, $^2J_{H,H}$ = 14.0, J = 4.2 Hz, 1 H, H_{1eq}), 2.63–2.57 (m, 2 H, H_3), 2.34 (dd, J = 14.0, J = 11.5 Hz, 1 H, H_{1ax}) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 205.8 (CO), 166.4 (CO), 139.3 (Cq), 135.3 (Cq), 133.4 (Cq), 129.8 (CH), 129.4 (CH), 128.3 (CH), 128.2 (Cq), 126.9 (CH), 124.8 (CH), 121.0 (CH), 57.9 (CH), 47.2 (CH_2), 40.1 (CH_2), 37.8 (CH_2) ppm. IR (NaCl): $\tilde{\nu}$ = 1676 cm^{-1} (C=O ketone), 1429–1357 (C=C arom.), 1246 (C–C), 1164 (C–N) cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{14}NO_2$ $[M + H]^+$ 252.1025; found 252.1017.

9,10,12,12a-Tetrahydro-7*H*,11*H*-benzo[*de*]pyrido[2,1-*a*]isoquinoline-7,11-dione (42): Compound **42** was obtained from **36** after 3 h by General Procedure **C** with purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) as a white solid (quant.); m.p. 147–148 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.44 (dd, $^3J_{H,H}$ = 7.2, $^4J_{H,H}$ = 1.1 Hz, 1 H), 8.04 (dd, $^3J_{H,H}$ = 8.3, $^4J_{H,H}$ = 1.0 Hz, 1 H), 7.86 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H), 7.65 (dd, $^3J_{H,H}$ = 8.2, $^3J_{H,H}$ = 7.3 Hz, 1 H), 7.56 (dd, $^3J_{H,H}$ = 8.2, $^3J_{H,H}$ = 7.2 Hz, 1 H), 7.35 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H), 5.35 (ddd, $^2J_{H,H}$ = 13.3, $^3J_{H,H}$ = 6.6, $^3J_{H,H}$ = 2.3 Hz, 1 H, H_{9eq}), 5.25 (dd, $^3J_{H,H}$ = 12.0, $^3J_{H,H}$ = 3.4 Hz, 1 H, H_{12a}), 3.09 (dt, $^3J_{H,H}$ = 12.0, $^3J_{H,H}$ = 12.0, J = 4.2 Hz, 1 H, H_{12ax}), 2.88–2.80 (m, 1 H, H_{9ax}), 2.74–2.58 (m, 3 H, H_{12eq} and H_{10}) ppm. ^{13}C NMR (62.6 MHz, $CDCl_3$): δ = 205.9 (C=O), 162.1 (C=O), 132.7 (Cq), 132.2 (CH), 130.4 (Cq), 127.3 (Cq + 2 × CH), 126.7 (CH), 126.4 (CH), 123.5 (Cq), 123.2 (CH), 59.0 (CH), 53.1 (CH_2), 42.0 (CH_2), 41.6 (CH_2) ppm. IR (ATR-Ge): $\tilde{\nu}$ = 1708 (CO ketone), 1639 (CO amide), 1464 (C–O), 1272 (C–C) cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{14}NO_2$ $[M + H]^+$ 252.1025; found 252.1019.

Acknowledgments

We thank the Cancéropôle Grand Ouest (grant to S. R.) and the Ligue Contre le Cancer Region Centre for financial support.

[1] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, P. Walter, in: *Molecular Cell Biology*, Garland, New York, 4th ed., **2002**, chapter 17.
[2] A. Kamb, N. A. Gruis, J. Weaver-Feldhaus, Q. Liu, K. Harshman, S. V. Tavtigian, E. Stockert, R. S. Day III, B. E. Johnson, M. H. Skolnick, *Science* **1994**, *264*, 436–440.
[3] a) P. L. Toogood, *Med. Res. Rev.* **2001**, *21*, 487–498; b) A. Huwe, R. Mazitschek, A. Giannis, *Angew. Chem. Int. Ed.* **2003**, *42*, 2122–2138; c) N. Kong, N. Fotouhi, P. M. Wovkulich, J. Roberts, *Drugs Future* **2003**, *28*, 881–896; d) S. Blagden, J. de Bono, *Curr. Drugs Targets* **2005**, *6*, 325–335; e) G. I. Shapiro, *J. Clin. Oncol.* **2006**, *24*, 1770–1783.
[4] J. Pines, *Trends Biochem. Sci.* **1993**, *18*, 195–197.
[5] N. S. Gray, L. Wodicka, A. W. Thunnissen, T. C. Norman, S. Kwon, F. H. Espinoza, D. O. Morgan, G. Barnes, S. LeClerc, L. Meijer, S. Kim, D. J. Lockhart, P. G. Schultz, *Science* **1998**, *281*, 533–538.
[6] M. Barvian, D. H. Boschelli, E. Cossrsrow, A. Fattaey, A. Fristch, D. Fry, P. Harvey, P. R. Keller, M. Garrett, F. La, W. Leopold, D. McNamara, M. Quin, S. Trump-Kallmeyer, P. Toogood, E. Zhang, *J. Med. Chem.* **2000**, *43*, 4606–4616.
[7] S. Akinaga, K. Sugiyama, T. Akiyama, *Anti-Cancer Drug Des.* **2000**, *15*, 43–52.
[8] B. Zhao, M. J. Bower, P. J. McDevitt, H. Zhao, S. T. Davis, K. O. Johanson, S. M. Green, N. O. Concha, B. B. S. Zhou, *J. Biol. Chem.* **2002**, *277*, 46609–46615.
[9] M. M. Faul, T. A. Engler, K. A. Sullivan, J. L. Grutsch, M. T. Clayton, M. J. Martinelli, J. M. Pawlak, M. Le Tourneau, D. S. Coffey, S. W. Pedersen, S. P. Kolis, K. Furness, S. Malhotra, R. S. Al-awar, J. E. Ray, *J. Org. Chem.* **2004**, *69*, 2967–2975.
[10] S. Routier, P. Peixoto, J. Y. Mérour, G. Coudert, C. Bailly, A. Pierre, S. Léonce, D. H. Caignard, *J. Med. Chem.* **2005**, *48*, 1401–1413.
[11] S. Routier, J. Y. Mérour, N. Dias, G. Coudert, C. Bailly, A. Pierré, S. Léonce, D. H. Caignard, *J. Med. Chem.* **2006**, *49*, 789–799.
[12] T. Honma, K. Hayashi, T. Aoyama, N. Hashimoto, T. Machida, K. Fukasawa, T. Iwama, C. Ikeura, M. Ikuta, I. Suzuki-Takahashi, Y. Iwasawa, T. Hayama, S. Nishimura, H. J. Morishima, *J. Med. Chem.* **2001**, *44*, 4615–4627.
[13] T. Honma, T. Yoshizumi, N. Hashimoto, K. Hayashi, N. Kawanishi, K. Fukasawa, T. Takaki, C. Ikeura, M. Ikuta, I. Suzuki-Takahashi, T. Hayama, S. Nishimura, H. Morishima, *J. Med. Chem.* **2001**, *44*, 4628–4640.
[14] a) E. V. Boltukhina, F. I. Zubkov, E. V. Nikitina, A. V. Varlamov, *Synthesis* **2005**, 1859–1875; b) F. I. Zubkov, E. V. Boltukhina, K. F. Turchin, R. S. Borisov, A. V. Varlamov, *Tetrahedron* **2005**, *61*, 4099–4113.

[15] T. Bousquet, J. F. Fleury, A. Daïch, P. Netchitaïlo, *Tetrahedron* **2006**, *62*, 706–715.
[16] W. Zhang, A. Zheng, Z. Liu, L. Yang, Z. Liu, *Tetrahedron Lett.* **2005**, *46*, 5691–5694.
[17] R. Hunter, P. Richards, *Tetrahedron Lett.* **2000**, *41*, 3755–3758.
[18] A. R. Katritzky, S. Mehta, H. Y. He, *J. Org. Chem.* **2001**, *66*, 148–152.
[19] Y. Yamamoto, K. Kinpara, T. Saigoku, H. Nishiyama, K. Itoh, *Org. Biomol. Chem.* **2004**, *2*, 1287–1294.
[20] H. Heaney, K. F. Shuhaibar, *Tetrahedron Lett.* **1994**, *35*, 2751–2752.
[21] D. Brown, R. Grigg, V. Sridharan, V. Tambyrajah, *Tetrahedron Lett.* **1995**, *36*, 8137–8140.
[22] J. P. Gesson, J. C. Jacquesy, D. Rambaud, *Tetrahedron* **1993**, *49*, 2239–2248.
[23] A. W. Lochead, G. R. Proctor, M. P. L. Caton, *J. Chem. Soc. Perkin Trans. 1* **1984**, 2477–2489.
[24] A. Alsarabi, J. L. Canet, Y. Troin, *Tetrahedron Lett.* **2004**, *45*, 9003–9006.
[25] C. H. Heathcock, S. W. Davidsen, S. G. Mills, M. A. Sanner, *J. Org. Chem.* **1992**, *57*, 2531–2544.
[26] C. F. Morrison, D. J. Burnell, *Org. Lett.* **2000**, *2*, 3891–3892.
[27] D. O. Morgan, W. D. Ollis, S. P. Stanforth, *Tetrahedron* **2000**, *56*, 5523–5534.
[28] R. Cordoba, A. Csaky, J. Plumet, *Arkivoc* **2004**, *4*, 94–99.
[29] M. V. Paradkar, S. A. Kukarni, R. Augustine, A. A. Ranade, *J. Chem. Res. Synopses* **2000**, *364–366*, 944–956.
[30] a) R. Lou, M. Van Alstine, X. Sun, M. P. Wentland, *Tetrahedron Lett.* **2003**, *44*, 2477–2480; b) K. R. Gibson, L. Hitzel, R. J. Mortishire-Smith, U. Gerhard, R. A. Jelley, A. J. Reeve, M. Rowley, A. Nadin, A. P. Owens, *J. Org. Chem.* **2002**, *67*, 9354–9360.
[31] A. M. Islam, R. A. Raphael, *J. Chem. Soc.* **1955**, 3151–3154.
[32] M. Othman, P. Pigeon, B. Decroix, *Tetrahedron* **1997**, *53*, 2495–2504.
[33] K. Kacprzak, *Synth. Commun.* **2003**, *33*, 1499–1507 and references therein.
[34] D. G. Batt, J. D. Maynard, J. J. Petraitis, J. E. Shaw, W. Galbraith, R. R. Harris, *J. Med. Chem.* **1990**, *33*, 360–370.
[35] G. Coll, J. Morey, A. Costa, J. Saa, *J. Org. Chem.* **1988**, *53*, 5345–5348.
[36] M. Brzaszcz, K. Kloc, M. Maposah, J. Mlochowski, *Synth. Commun.* **2000**, *30*, 4425–4434.
[37] Z. Y. Wang, D. M. Du, D. Wu, W. T. Hua, *Synth. Commun.* **2003**, *33*, 1275–1283.

Received: February 25, 2009
Published Online: May 7, 2009

