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Synthetic Route to Rare Isoindolones Derivatives

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The isoindolone scaffold is present in many biologically active compounds. Here, we have developed a shorter and more efficient synthesis of tetrahydropyrido[2,1-*a*]isoindolone. The key step of this approach is a cyclization to form the γ-lactam ring under Shibasaki's conditions. Thus, tetrahydropyrido[2,1-*a*]isoindolone and superior analogues, namely hexahydroazepino[2,1-*a*]isoindolone and hexahydroazocino[2,1-*a*]isoindolone, have been prepared in only three steps in 39, 25, and 19 % overall yields, respectively. This novel strategy offers a shorter alternative to existing procedures.

Introduction

Some of the natural alkaloids isolated from *Berberis*, for example Lennoxamine and Magallanesine, contain the isoindolone skeleton. This scaffold is widely present in biologically active compounds, including non-nucleoside HIV-1 reverse transcriptase inhibitors,[1] inhibitors of tubulin polymerization,[2] kinases inhibitors,[3] antiobesity agents,[4] TNF-α inhibitors,[5] and urotensin-II receptor antagonists (Figure 1).[6] The pharmaceutical importance of these compounds has led medicinal chemists to develop many synthetic approaches to prepare these heterocycles.[7]

In 2012, Valmerins were developed as serine and threonine kinase inhibitors, especially for cyclin-dependent protein kinases and glycogen synthase kinase 3, which are validated targets for therapies such as leukemia, solid tumors, and Alzheimer's disease (Figure 2). The biological activity of Valmerins has been evaluated both in vitro and in vivo, and Routier et al. proved the drugability of these Valmerins through their efficacy on tumor growth inhibition in mice xenogreph models.[8]

Although the attractiveness of Valmerins is established, the first described synthetic access to these tetrahydropyrido[2,1-*a*]isoindolone scaffolds in seven steps limits the upscaling and modulation of the tricyclic scaffold. The principal synthetic approach used to access to tetrahydropyrido[2,1-*a*]isoindolones is based on the generation of an *N*-acyliminium ion in situ, followed by addition of the appropriate nucleophilic reagents.[9] Moreover access to the hexahydro azepino and azocino[2,1-*a*]isoindolones scaffolds is rarely described.[7a,10] To circumvent these limitations, we revisited the existing synthetic access to this scaffold, and set up a novel alternative strategy. The main advantages of the new approach include a reduced number of steps and

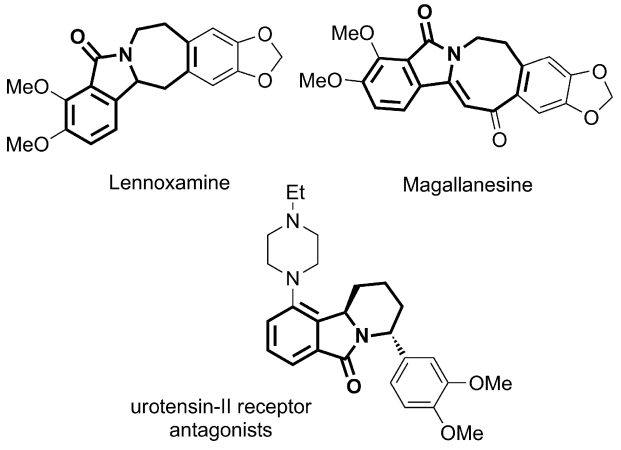

Figure 1. Examples of natural and biologically active compounds containing the isoindolone ring.

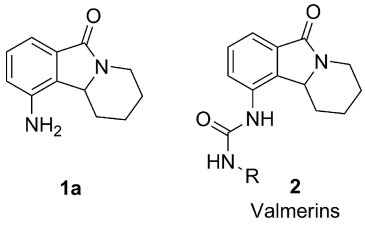

Figure 2. Structures of tetrahydropyrido[2,1-*a*]isoindolone **1a** and Valmerins derivatives **2**.

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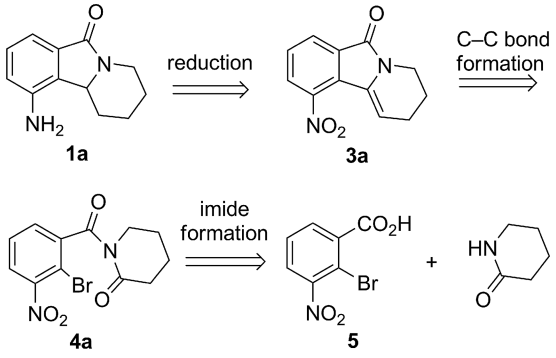
increased global yields, and the route provides flexibility for medicinal chemists in terms of chemical access and substitution patterns.

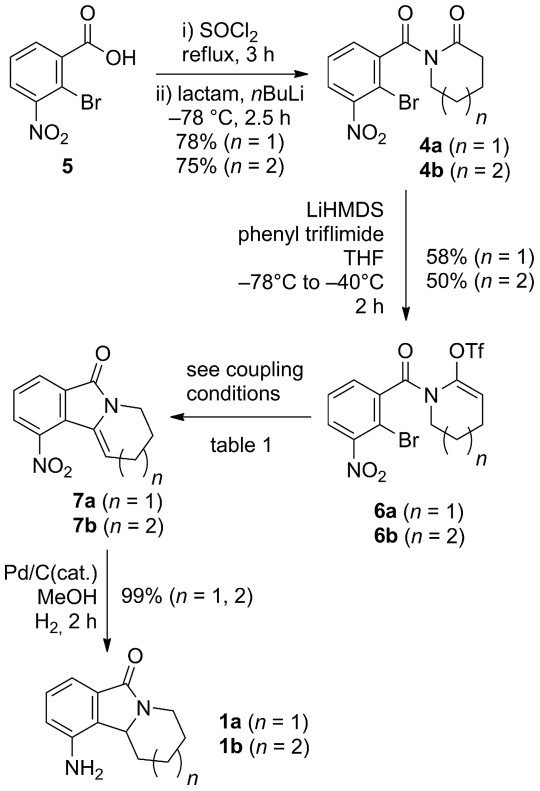
We thus propose in this paper to follow an original retrosynthetic pathway (Scheme 1) that offers, as a key step, an intramolecular C_{sp2}–C_{sp2} bond formation from imide **4a**. In this strategy, the acylated enamine intermediate **3a** results from the coupling reaction between a vinyl triflate and an aryl bromide or from the condensation of the aryl anion, generated in situ, on the imide. Precursor **4a** is prepared from carboxylic acid **5** and commercially available lactams.



Scheme 1. Retrosynthetic pathway used to access tetrahydropyrido[2,1-*a*]isoindolone **1a**.

Results and Discussion

The first synthetic route we explored was the Pd-mediated cross-coupling reaction between an aromatic bromide and a vinylic derivative formed from the enolate form of **4a** (triflate or analogue). The formation of **4a** (Scheme 2) was achieved by treatment of commercially available 2-bromo-3-nitrobenzoic acid (**5**) with thionyl chloride to give the corresponding acyl chloride quantitatively, which was immediately added to a solution of deprotonated (*n*-butyllithium, –78 °C) δ-valerolactam. Such a procedure afforded the desired imide **4a** in 78% yield. Triflation of **4a** was achieved by using LiHMDS as a base at low temperature and quenching the oxanion with phenyltriflimide to furnish the desired vinyl trifluoromethanesulfonate **6a** in 58% yield. To achieve C_{sp2}–C_{sp2} bond formation, a range of conditions for the intramolecular coupling reaction were tested (Table 1).



Scheme 2. Synthetic route using an intramolecular coupling reaction.

First, we followed the method described by Le et al., namely a palladium-catalyzed intramolecular coupling reaction between aryl and vinyl halides mediated by indium.[11] Under these conditions with a catalytic amount of Pd/C or $Pd(PPh_3)_4$ and one equivalent of 100 mesh indium, only starting material or degradation products were obtained (Table 1, entry 1). By using only palladium(II) catalyst under basic conditions [10 mol-% $PdCl_2$(dppf) with K_3PO_4; dppf = 1,1′-bis(diphenylphosphino)ferrocene] un-

Table 1. Conditions used for intramolecular cyclization of **6a**.

Entry	Conditions				Yield [%][a]
	Catalyst system	Solvent	*T* [°C]	*t* [h]	
1	Pd/C or $Pd(PPh_3)_4$ (0.025 equiv.), In (1.0 equiv.), LiCl (1.5 equiv.)	DMF	100	3	–[b]
2	$PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv.), K_3PO_4 (2.0 equiv.)	1,4-dioxane/water (9:1)	120	2	30
3	$Pd(OAc)_2$ (0.1 equiv.), dppp (0.2 equiv.), K_3PO_4 (2.0 equiv.)	1,4-dioxane/water (9:1)	120 (300 W)	2	–[b]
4	$PdCl_2$ (0.1 equiv.), Davephos (0.2 equiv.), K_3PO_4 (2.0 equiv.)	1,4-dioxane/water (9:1)	120	18	–[c]
5	$PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv.), K_3PO_4 (2.0 equiv.)	THF	reflux	16	22
6	$Pd(PPh_3)_4$ (0.1 equiv.), K_3PO_4 (2.0 equiv.)	THF	reflux	16	–[b]
7	Cu powder (10.0 equiv.), $Pd_2(dba)_3$ (0.1 equiv.)	DMSO	80	2	31
8	Cu powder (10.0 equiv.), $PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv.)	DMSO	50	2	–[b]
9	Cu powder (10.0 equiv.)	DMSO	50	2	24
10	1. $PdCl_2(PPh_3)_2$ (0.05 equiv.), PPh_3 (0.1 equiv.), B_2Pin_2 (1.5 equiv.), K_2CO_3 (2.0 equiv.)	1,4-dioxane	r.t.	3	40
	2. $Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.2 equiv.), K_3PO_4 (2.0 equiv.)	water	100	1.5	
11	$Pd(PPh_3)_4$ (0.2 equiv.), LiCl (20.0 equiv.), $Me_3SnSnMe_3$ (1.2 equiv.)	1,4-dioxane	120	16	54

[a] Isolated yield. [b] Degradation. [c] Inseparable mixture of product and starting material.

der microwave activation, the desired coupling product **7a** was afforded in 30% isolated yield (entry 2). Other Pd sources (either as Pd^0 or Pd^{II}) were tested unsuccessfully (entries 3, 4, and 6). Replacement of the 1,4-dioxanne/water mixture as solvent by tetrahydrofuran (THF) gave similar results (entry 5 vs. 2).

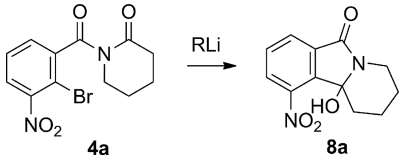
The disappointing yields prompted us to explore other conditions. Banwell et al. described the intermolecular formation of C–C bonds between aryl halides and vinyl halides by using an excess of copper(0) and a catalytic amount of palladium source [e.g., $Pd(PPh_3)_4$, $PdCl_2(dppf)$ or Pd_2dba_3].[12] In our case, these conditions led to the desired product **7a** in only 31% yield (entry 7) with a Pd^0 source, and none with a palladium(II) catalyst (entry 8). It should be noted that **7a** was obtained in similar yield (entry 9) without the palladium catalyst.

We then envisioned an intramolecular palladium-catalyzed Suzuki–Miyaura coupling reaction. The borylation of vinyl triflate **6a** in situ followed by C–C cross-coupling reaction of the vinyl borane with the aryl bromide gave the desired product **7a** in 40% yield (entry 10).[13] Encouraged by this increase in yield, we evaluated the tin-mediated Stille–Kelly reaction. This has been performed by using hexamethylditin in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give **7a** in 54% yield (entry 11).[14]

With the acylenamine in hand, the final step was achieved by simultaneous Pd^0 catalyzed hydrogenation of alkene and nitro functions in quantitative yield. To summarize, the tetrahydropyrido[2,1-*a*]isoindolone **1a** has been synthesized in four steps with an overall yield of 24% (instead of seven steps, 28% overall yield).

By following the same synthetic scheme, the hexahydroazepino[2,1-*a*]isoindolone **1b** was obtained in 12% overall yield. Notably, Stille–Kelly coupling gave **7b** in only 33% yield because of steric hindrance. Nevertheless, to our knowledge, this synthetic route is the first approach that allows the preparation of hexahydroazepino[2,1-*a*]isoindolones such as **1b** in only four steps.

To increase the cyclization yield further, we used a second strategy involving C–C bond formation by nucleophile addition of in situ generated aryl anion on the imide. Thus, we investigated the intramolecular reaction involving lithiated anions on imide **4a**. First, the formation of the corresponding organolithium intermediate via a metal-halogen exchange was examined (Scheme 3).



Scheme 3. Cyclization by using Parham's conditions.

Wolf et al. previously used Parham's conditions to induce such intramolecular cyclizations of *N*-acyl-2-bromobenzamides.[15] By using *n*BuLi at low temperature for 2 h (Table 2, entry 1),[16] the desired product **8a** was formed in 20% yield, but concomitant formation of many byproducts was observed (e.g., nucleophilic addition of *n*BuLi on imide function). At lower temperature, cyclization occurred in 34% yield (entry 2). In addition to this method, Moreau et al. reported the synthesis of Nuevamine by using *t*BuLi instead of *n*BuLi.[17] Unfortunately, compound **8a** was obtained in only 15% yield (entry 3) under these conditions. The use of an excess of *t*BuLi led only to complete degradation (entry 4).

Table 2. Conditions for intramolecular cyclization of **4a**.

Entry	Conditions	Yield [%][a]
1	*n*BuLi (1.1 equiv.), THF, –78 °C, 3 h	20
2	*n*BuLi (1.1 equiv.), THF, –100 °C, 3 h	34
3	*t*BuLi (2.2 equiv.), THF –78 °C then r.t., 16 h	15
4	*t*BuLi (4.0 equiv.), THF, –78 °C then r.t., 16 h	–[b]

[a] Isolated yield. [b] Degradation.

Based on these results, we evaluated a milder strategy with which to form the aryl anion. Shibasaki et al. reported cyclization by using a stannyl aryl anion generated on aryl halide from $Me_3SiSnBu_3$ and fluoride or chloride ion (Scheme 4).[18]

Scheme 4. Cyclization by using Shibasaki's conditions.

Several solvents, temperature, and halogen source were assayed to optimize this two-step cascade. First, by using fluoride sources [e.g., cesium fluoride and tetrabutylammonium fluoride (TBAF)] to generate the tributyltin anion (Table 3, entries 1–3), the desired cyclized compound **8a** was obtained in moderate yield (up to 42%). The use of a chloride source allowed **8a** to be accessed with better yields. Whereas the use of either tetraethylammonium chloride (Et_4NCl) or cesium fluoride in *N*,*N*-dimethylformamide (DMF) gave similar results (entry 4 vs. entry 1), benzyl triethyl ammonium chloride (Et_3BnNCl) in DMF appeared to be the best system, and yields under these conditions increased to 51% (entry 5).

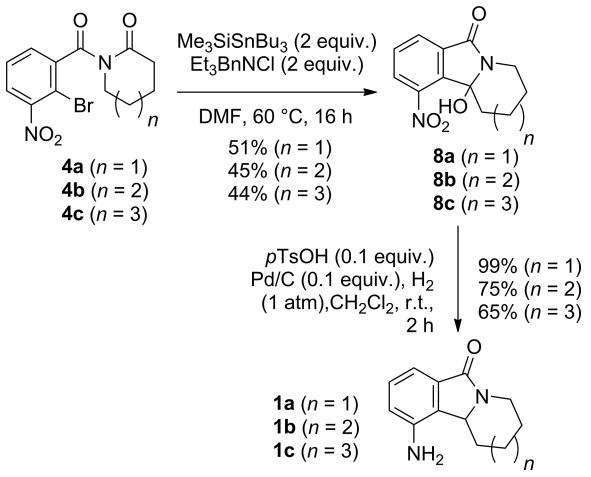
Table 3. Conditions for intramolecular cyclization of **4a**.

Entry	Conditions[a]	Yield [%][b]
1	CsF (2 equiv.), DMF, 0 °C then room temp., 16 h	42
2	CsF (2 equiv.), DMF, 0 °C then 60 °C, 16 h	17
3	TBAF (2 equiv.), THF, 0 °C, 2 h	20
4	$Et_4N^+Cl^-$ (2 equiv.), DMF, 0 °C then room temp., 16 h	39
5	$Et_3BnN^+Cl^-$ (2 equiv.), DMF, 0 °C then 60 °C, 16 h	51
6	$Et_3BnN^+Cl^-$ (2 equiv.), THF, 0 °C then reflux, 24 h	30
7	$Et_3BnN^+Cl^-$ (2.0 equiv.), DMA, 0 °C then 60 °C, 0.5 h	17
8	$MgOTf_2$ (2.0 equiv.), DMF, 0 °C then 60 °C, 16 h	13
9	LiOTf (2.0 equiv.), DMF, 0 °C then 60 °C, 1 h	51
10	LiOTf (3.0 equiv.), DMF, 0 °C then 60 °C, 16 h	20[c]

[a] Carried out with 2.0 equiv. $Me_3SiSnBu_3$. [b] Isolated yield. [c] Carried out with 3.0 equiv. $Me_3SiSnBu_3$.

Finally, Lewis acids were tested in place of halide ions. Whereas magnesium triflate in DMF gave poor yields of cyclized product (13%, entry 8), and cooper triflate [Cu(OTf)$_2$] proved unsuccessful (result not shown), surprisingly, the use of two equivalents of LiOTf in DMF at 60 °C furnished **8a** in a satisfactory 51% yield (entry 9). The use of an excess or a stoichiometric amount of reagent did not improve the reactivity (entry 10).

To achieve the sequence, a one-pot, three-step procedure was used: (1) elimination of the tertiary alcohol upon treatment with TsOH followed by (2) reduction of the resulting alkene concomitantly with (3) reduction of the nitro group to give **1a** in quantitative yield. By using this alternative route, **1a** was obtained in a global yield of 39% in three steps. Having the optimized conditions for cyclization in hand, this strategy was then applied to superior analogues, which gave improved yields compared with those obtained through the aforementioned Stille–Kelly strategy. Thus, the hexahydroazepino[2,1-*a*]isoindolone **1b** and the hexahydroazocino[2,1-*a*]isoindolone **1c** were prepared in three steps in an overall yield of 25 and 19%, respectively (Scheme 5).



Scheme 5. Second route to isoindolones **1a**–**c**.

Conclusions

In this study, we have developed a shorter synthetic route to isoindolone derivatives fused to six-, seven-, and eight-membered rings. This optimization led us to develop two methods to create such complex tricyclic derivatives in only three steps. The tetrahydropyrido[2,1-*a*]isoindolone **1a** was obtained in three steps with an overall yield of 39% (vs. 28% in seven steps as described by Routier et al.).[8] In contrast to the other reported strategies, this synthesis allowed easy access to superior analogues; thus, the hexahydroazepino[2,1-*a*]isoindolone **1b** and the hexahydroazocino[2,1-*a*]-isoindolone **1c** were prepared in 25 and 19% overall yields, respectively. This work will be fully applied to medicinal chemistry programs and to the design of kinases inhibitors and in the preparation of novel Valmerins generations.

Experimental Section

General: Column chromatography purifications were performed on silica gel (40–63 μm) from Macherey–Nagel. Thin-layer chromatography (TLC) was carried out on Merck DC Kieselgel 60 F-254 aluminum sheets. Compounds were visualized by either illumination with a short-wavelength UV lamp (λ = 254 nm) or by staining with a 3.5% (w/v) phosphomolybdic acid solution in absolute ethanol. Anhydrous solvents were purchased from Sigma–Aldrich or dried by following standard procedures (CH_2Cl_2: distillation over P_2O_5, THF: distillation over Na/benzophenone).

Microanalyses were carried out with a Carlo–Erba 1106. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with a Bruker DPX 300 spectrometer (Bruker, Wissembourg, France). Chemical shifts are expressed in parts per million (ppm) from $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm), [D$_6$]DMSO (δ_H = 2.50 ppm, δ_C = 39.52 ppm), or CD_3OD (δ_H = 3.31 ppm, δ_C = 49.00 ppm). *J* values are expressed in Hz. Mass spectra were obtained with a Finnigan LCQ Advantage MAX (ion trap) apparatus equipped with an electrospray source or with a Shimadu GC–MS-GP 2010 apparatus by using direct injection and isobutane chemical ionization. Melting points were measured with a Stuart SMP30 melting-point apparatus.

Imide Synthesis. General Procedure A: To a solution of thionyl chloride (32.0 equiv.) was added 2-bromo-3-nitrobenzoic acid (1.0 equiv.), and the resultant mixture was stirred and heated at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated. To a solution of lactam (1.1 equiv.) in anhydrous THF (0.1 mol/L), *n*-butyllithium (2.5 M in hexane, 1.05 equiv.) was added at –78 °C. The mixture was stirred for 0.5 h at –78 °C and a solution of acyl chloride dissolved in anhydrous THF (1.3 mol/L) was slowly added. The mixture was stirred at –78 °C for 2.5 h then the reaction was quenched with aq. satd. NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic layer was washed successively with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

Vinyl Triflate Synthesis. General Procedure B: To a solution of hexamethyldisilazane (1.2 equiv.) in anhydrous THF (1.4 mol/L) at 0 °C was added *n*-butyllithium (2.5 M in hexane, 1.2 equiv.), and the resultant mixture was stirred for 0.5 h. After cooling at –78 °C, a solution of imide (1.0 equiv.) contained in anhydrous THF (0.4 mol/L) was added slowly and the resultant mixture was stirred for 0.5 h. *N*-Phenyltrifluoromethanesulfonimide (1.2 equiv.) contained in anhydrous THF (1.1 mol/L) was added and the mixture was stirred at –40 °C for 3 h. The reaction was quenched with aq. satd. NH_4Cl and the aqueous layer was extracted with EtOAc. The combined organic layer was washed successively with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

Cyclization by Stille–Kelly Coupling. General Procedure C: To a solution of vinyl triflate (1.0 equiv.) in anhydrous and degassed dioxane (0.12 mol/L) in a sealed tube, was added LiCl (2.0 equiv.), hexamethylditin (1.2 equiv.), and Pd(PPh$_3$)$_4$ (0.2 equiv.). The resultant mixture was stirred and heated to reflux for 16 h, then the reaction was quenched with a satd. aq. solution of potassium fluoride. The aqueous layer was extracted with Et_2O and the combined organic layer was washed successively with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

Reduction. General Procedure D: To a solution of enamide (1 equiv.) in degassed methanol (0.1 mol/L) was added Pd/C (0.1 equiv., 10 wt.-% loading) and the mixture was stirred under

hydrogen for 2 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure.

Cyclization by Stannyl Anion. General Procedure E: To a solution of imide (1.0 equiv.) in anhydrous DMF (0.16 mol/L) was added benzyltriethylammonium chloride (2.0 equiv.) and the solution was cooled to 0 °C. The solution was vigorously stirred, tributyl(trimethylsilyl)stannane was slowly added, then the mixture was heated at 70 °C for 16 h. After cooling to room temperature, the reaction was quenched with a satd. aq. solution of potassium fluoride. The aqueous layer was extracted with EtOAc and the combined organic layer was washed successively with water then brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

Elimination and Reduction. General Procedure F: To a solution of cyclized compound (1 equiv.), in anhydrous and degassed CH_2Cl_2 (0.2 mol/L) was added *p*-toluenesulfonic acid (0.1 equiv.) and Pd/C (0.1 equiv., 10 wt.-%) and the mixture was stirred under hydrogen (1 atm) overnight. The mixture was degassed, filtered through Celite, and the filtrate was washed with a satd. aq. solution of $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure without further purification.

1-(2-Bromo-3-nitrobenzoyl)piperidin-2-one (4a): General procedure A was followed by using 2-bromo-3-nitrobenzoic acid (**5**; 2.15 g) and 2-piperidone (0.89 g). Purification by flash chromatography (cyclohexane/EtOAc, 7:3 v/v) gave **4a** (2.09 g, 78%) as a pale-yellow solid; m.p. 103–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (dd, J = 8.0, 1.7 Hz, 1 H), 7.49 (t, J = 7.8 Hz, 1 H), 7.39 (dd, J = 7.8, 1.7 Hz, 1 H), 3.93 (t, J = 6.5 Hz, 2 H), 2.54 (t, J = 6.5 Hz, 2 H), 2.00–1.88 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 169.0, 150.1, 143.7, 130.3, 128.5, 125.1, 110.0, 44.9, 34.1, 22.3, 20.5 ppm. MS (CI): m/z = 327, 329. $C_{12}H_{11}BrN_2O_4$ (327.13): calcd. C 44.06, H 3.39, N 8.56; found C 43.99, H 3.43, N 8.48.

1-(2-Bromo-3-nitrobenzoyl)azepan-2-one (4b): General procedure A was followed by using 2-bromo-3-nitrobenzoic acid (**5**; 800 mg) and caprolactam (377 mg). Purification by flash chromatography (cyclohexane/EtOAc, 7:3 v/v) gave **4b** (769 mg, 75%) as a pale-yellow solid; m.p. 145–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (dd, J = 8.0, 1.6 Hz, 1 H), 7.49 (t, J = 8.0 Hz, 1 H), 7.34 (dd, J = 7.7, 1.6 Hz, 1 H), 4.11–4.08 (m, 2 H), 2.71–2.67 (m, 2 H), 1.85–1.84 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.5, 168.2, 150.1, 144.0, 129.8, 128.4, 124.9, 110.0, 43.8, 39.0, 29.4, 28.3, 23.7 ppm. $C_{13}H_{14}N_2O_4$ (262.26): calcd. C 45.77, H 3.84, N 8.21; found C 45.58, H 3.96, N 7.86.

1-(2-Bromo-3-nitrobenzoyl)azocan-2-one (4c): General procedure A was followed by using 2-bromo-3-nitrobenzoic acid (**5**; 2 g) and 1-aza-2-cyclooctanone (1.1 g). Purification by flash chromatography (cyclohexane/EtOAc, 7:3 v/v) gave **4c** (1.78 g, 66%) as a pale-yellow solid; m.p. 108–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (dd, J = 8.0, 1.6 Hz, 1 H), 7.47 (t, J = 8.0 Hz, 1 H), 7.33 (dd, J = 7.7, 1.6 Hz, 1 H), 4.11–4.08 (m, H), 2.71–2.67 (m, H), 1.85–1.84 (m, 4 H), 1.62 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3, 168.6, 150.2, 144.1, 129.5, 128.4, 124.8, 110.4, 43.5, 36.1, 29.3, 29.1, 26.1, 24.1 ppm. $C_{14}H_{15}BrN_2O_4$ (355.19): calcd. C 47.34, H 4.26, N 7.89; found C 47.26, H 4.30, N 7.72.

1-(2-Bromo-3-nitrobenzoyl)-1,4,5,6-tetrahydropyridin-2-yl Trifluoromethanesulfonate (6a): General procedure B was followed by using imide **4a** (543 mg). Purification by flash chromatography (cyclohexane/EtOAc, 7:3) gave **6a** (442 mg, 58%) as a pale-yellow solid; m.p. 95–96 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 55 °C): δ = 8.09 (dd, J = 7.9, 1.6 Hz, 1 H), 7.76 (t, J = 7.9 Hz, 1 H), 7.68 (dd, J = 7.7, 1.7 Hz, 1 H), 5.70 (t, J = 3.9 Hz, 1 H), 3.59 (s, 2 H), 2.38–2.32 (m, 2 H), 1.92–1.84 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 55 °C): δ = 165.1, 150.6, 139.0, 138.0, 131.1, 129.6, 125.9, 118.0 (q, J = 319 Hz), 110.1, 110.0, 46.3, 21.8, 21.4 ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO, 55 °C): δ = –73.20 ppm. MS (CI): m/z = 460, 458, 230, 228. $C_{13}H_{10}BrF_3N_2O_6S$ (459.19): calcd. C 34.00, H 2.20, N 6.10, S 6.98; found C 34.02, H 2.22, N 5.98, S 7.05.

1-(2-Bromo-3-nitrobenzoyl)-4,5,6,7-tetrahydro-1*H*-azepin-2-yl Trifluoromethanesulfonate (6b): General procedure B was followed by using imide **4b** (300 mg). Purification by flash chromatography (cyclohexane/EtOAc, 7:3 v/v) gave **6b** (208 mg, 50%) as a brown oil. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.95 (dd, J = 7.8, 1.8 Hz, 1 H), 7.63 (t, J = 7.8 Hz, 1 H), 7.57 (dd, J = 7.7, 1.8 Hz, 1 H), 5.84 (s, 1 H), 4.05 (s, 2 H), 2.70 (s, 2 H), 1.74 (s, 4 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 328 K): δ = 176.2, 167.3, 150.0, 143.3, 129.4, 129.3, 128.8, 124.0, 120.0 (q, J = 275 Hz), 108.7, 42.7, 27.5, 22.9, 22.8 ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO, 328 K): δ = –77.56 ppm. MS (CI): m/z = 474, 472, 326, 324, 230, 228, 184, 182. $C_{14}H_{13}F_3N_2O_6S$ (394.32): calcd. C 35.53, H 2.56, N 5.92, S 6.78; found C 35.74, H 2.99, N 5.58, S 6.31.

10-Nitro-3,4-dihydropyrido[2,1-*a*]isoindol-6(2*H*)-one (7a): General procedure C was followed by using vinyl triflate **6a** (100 mg). Purification by flash chromatography (cyclohexane/EtOAc, 4:1 v/v) gave **7a** (27 mg, 54%) as a pale-yellow solid; m.p. 79–80 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.21 (dd, J = 8.1, 1.0 Hz, 1 H), 8.08 (dd, J = 7.6, 1.0 Hz, 1 H), 7.70 (t, J = 7.6 Hz, 1 H), 6.67 (t, J = 4.8 Hz, 1 H), 3.88–3.84 (m, 1 H), 2.54 (dd, J = 11.0, 6.1 Hz, 1 H), 2.05–1.97 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 164.8, 145.4, 133.7, 132.2, 130.8, 129.1, 128.8, 127.6, 118.5, 40.0, 24.3, 21.6 ppm. MS (CI): m/z = 230.

10-Nitro-7,8,9,10-tetrahydro-5*H*-azepino[2,1-*a*]isoindol-5-one (7b): General procedure C was followed by using vinyl triflate **6b** (148 mg). Purification by flash chromatography (cyclohexane/EtOAc, 4:1 v/v) gave **7b** (25 mg, 33%) as a pale-yellow solid; m.p. 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (dd, J = 7.8, 1.0 Hz, 1 H), 7.91 (dd, J = 8.0, 1.0 Hz, 1 H), 7.55 (t, J = 7.8 Hz, 1 H), 6.35 (t, J = 6.1 Hz, 1 H), 4.05–4.02 (m, 2 H), 2.58 (dd, J = 12.0, 6.0 Hz, 2 H), 1.99–1.92 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 144.5, 134.5, 132.2, 128.8, 127.8, 127.6, 127.3, 117.9, 42.6, 26.9, 26.6, 26.4 ppm. MS (ESI$^+$): m/z = 245 [M + H]$^+$. $C_{13}H_{12}N_2O_3$ (244.25): calcd. C 63.93, H 4.95, N 11.47; found C 63.72, H 5.12, N 11.03.

10-Amino-1,2,3,4-tetrahydropyrido[2,1-*a*]isoindol-6(10b*H*)-one (1a): General procedure D was followed by using **7a** (103 mg) to give **1a** (90 mg, 99%). NMR spectra are in accordance with those reported previously.[8]

10-Amino-7,8,9,10,11,11a-hexahydro-5*H*-azepino[2,1-*a*]isoindol-5-one (1b): General procedure D was followed by using **7b** (25 mg) to give **1b** (22 mg, 99%) as a pale-yellow solid; m.p. 163–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.22 (m, 2 H), 6.79 (dd, J = 7.0, 1.7 Hz, 1 H), 4.53 (dd, J = 6.3, 4.5 Hz, 1 H), 4.00 (ddd, J = 14.0, 7.8, 3.3 Hz, 1 H), 3.71 (s, 2 H), 3.36 (ddd, J = 14.0, 8.5, 2.7 Hz, 1 H), 2.38–2.28 (m, 1 H), 2.00–1.92 (m, 1 H), 1.85–1.66 (m, 4 H), 1.54–1.43 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 141.0, 133.8, 130.2, 129.3, 118.2, 113.5, 60.0, 43.6, 31.0, 29.6, 26.6, 25.7 ppm. MS (ESI$^+$): m/z = 217 [M + H]$^+$. $C_{13}H_{16}N_2O$ (216.28): calcd. C 72.19, H 7.46, N 12.95; found C 71.91, H 7.37, N 12.91.

10b-Hydroxy-10-nitro-1,2,3,4-tetrahydropyrido[2,1-*a*]isoindol-6(10b*H*)-one (8a): General procedure E was followed by using imide **4a** (50 mg). Purification by flash chromatography (petroleum ether/EtOAc, 7:3 v/v) gave **8a** (19 mg, 51%) as a pale-yellow solid; m.p.

159–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (dd, J = 8.2, 1.0 Hz, 1 H), 8.19 (dd, J = 7.5, 1.0 Hz, 1 H), 7.71 (dd, J = 8.2, 7.5 Hz, 1 H), 4.37–4.31 (m, 1 H), 4.06 (s, 1 H), 3.26 (td, J = 13.1, 3.4 Hz, 1 H), 2.71 (dt, J = 5.3, 2.4 Hz, 1 H), 2.22–2.08 (m, 1 H), 1.86–1.81 (m, 2 H), 1.42 (ddd, J = 13.5, 8.5, 3.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 143.9, 141.7, 135.0, 131.0, 130.1, 127.7, 87.5, 37.1, 34.7, 24.9, 19.3 ppm. MS (ESI$^+$): m/z = 249 [M + H]$^+$. $C_{12}H_{12}N_2O_4$ (248.24): calcd. C 58.06, H 4.87, N 11.29; found C 58.18, H 4.97, N 11.26.

11a-Hydroxy-1-nitro-7,8,9,10,11,11a-hexahydro-5*H*-azepino[2,1-*a*]-isoindol-5-one (8b): General procedure E was followed by using imide **4b** (500 mg). Purification by flash chromatography (petroleum ether/EtOAc, 7:3 v/v) gave **8b** (175 mg, 45%) as a pale-yellow solid; m.p. 127–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (dd, J = 8.2, 1.0 Hz, 1 H), 8.13 (dd, J = 7.4, 1.0 Hz, 1 H), 7.70 (t, J = 9.0 Hz, 1 H), 4.41 (s, 1 H), 4.11–4.03 (m, 1 H), 3.35 (ddd, J = 14.3, 10.3, 3.9 Hz, 1 H), 2.65 (dd, J = 15.2, 7.8 Hz, 1 H), 2.25 (ddd, J = 15.2, 10.5, 1.3 Hz, 1 H), 1.88–1.76 (m, 3 H), 1.71–1.66 (m, 1 H), 1.56–1.48 (m, 1 H), 0.90–0.78 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 144.0, 141.3, 135.3, 131.0, 129.4, 128.2, 91.6, 39.6, 38.7, 29.5, 26.3, 22.8 ppm. MS (ESI–): m/z = 261 [M – H]$^-$. HRMS (ESI–): m/z calcd. for $C_{13}H_{14}N_2O_4$ 261.0881; found 261.0878.

12a-Hydroxy-1-nitro-8,9,10,11,12,12a-hexahydroazocino[2,1-*a*]isoindol-5(7*H*)-one (8c): General procedure E was followed by using imide **4c** (500 mg). Purification by flash chromatography (petroleum ether/EtOAc, 7:3 v/v) gave **8c** (170 mg, 44%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (dd, J = 8.2, 1.0 Hz, 1 H), 8.16 (dd, J = 7.4, 1.0 Hz, 1 H), 7.71 (t, J = 12.0 Hz, 1 H), 4.27 (s, 1 H), 4.01 (dt, J = 14.8, 4.9 Hz, 1 H), 3.42 (ddd, J = 14.8, 10.9, 4.0 Hz, 1 H), 2.48–2.41 (m, 1 H), 2.19–2.12 (m, 1 H), 1.73–1.61 (m, 2 H), 1.56–1.45 (m, 2 H), 1.25–1.14 (m, 2 H), 0.96–0.81 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 144.3, 140.3, 135.5, 131.1, 129.6, 128.0, 91.1, 39.1, 31.8, 26.4, 25.8, 23.7, 22.3 ppm. HRMS (ESI–): m/z calcd. for $C_{14}H_{16}N_2O_4$ 275.1037; found 275.1032.

10-Amino-1,2,3,4-tetrahydropyrido[2,1-*a*]isoindol-6(10b*H*)-one (1a): General procedure F was followed by using **8a** (30 mg) to give **1a** (24 mg, 99%). NMR spectra are in accordance with those described previously.[8]

10-Amino-7,8,9,10,11,11a-hexahydro-5*H*-azepino[2,1-*a*]isoindol-5-one (1b): General procedure F was followed by using **8b** (100 mg) to give **1b** (62 mg; 75%). NMR spectra are in accordance with those reported above.

1-Amino-8,9,10,11,12,12a-hexahydroazocino[2,1-*a*]isoindol-5(7*H*)-one (1c): General procedure F was followed by using **8c** (170 mg) to give **1c** (92 mg, 65%) as a pale-yellow solid; m.p. 172–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 2 H), 6.79 (dd, J = 7.3, 1.3 Hz, 1 H), 4.50 (t, J = 4.2 Hz, 1 H), 4.19 (dt, J = 14.2, 5.4 Hz, 1 H), 3.72 (s, 2 H), 3.16 (ddd, J = 14.2, 9.8, 4.0 Hz, 1 H), 2.31–2.26 (m, 1 H), 2.19–2.13 (m, 2 H), 1.76–1.50 (m, 2 H), 1.45–1.32 (m, 3 H), 1.17–1.13 (m, 1 H), 0.92–0.85 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 141.2, 134.3, 129.3, 129.2, 118.3, 113.8, 60.5, 42.1, 27.3, 27.1, 25.6, 24.0, 22.1 ppm. HRMS (ESI$^+$): m/z calcd. for $C_{14}H_{18}N_2O$ [M + H]$^+$ 231.1492; found 231.1492.

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[1] A. Mertens, H. Zilch, B. Koenig, W. Schaefer, T. Poll, W. Kampe, H. Seidel, U. Leser, H. Leinert, *J. Med. Chem.* **1993**, *36*, 2526–2535.
[2] M. Lorion, V. Agouridas, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron Lett.* **2010**, *51*, 5146–5149.
[3] a) 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; b) 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. Morishima, *J. Med. Chem.* **2001**, *44*, 4615–4627.
[4] D. A. Wacker, J. G. Varnes, S. E. Malmstrom, X. Cao, C.-P. Hung, T. Ung, G. Wu, G. Zhang, E. Zuvich, M. A. Thomas, W. J. Keim, M. J. Cullen, K. W. Rohrbach, Q. Qu, R. Narayanan, K. Rossi, E. Janovitz, L. Lehman-McKeeman, M. F. Malley, J. Devenny, M. A. Pelleymounter, K. J. Miller, J. A. Robl, *J. Med. Chem.* **2007**, *50*, 1365–1379.
[5] K. S. Kumar, P. M. Kumar, K. A. Kumar, M. Sreenivasulu, A. A. Jafar, D. Rambabu, G. R. Krishna, C. M. Reddy, R. Kapavarapu, K. Shivakumar, K. K. Priya, K. V. L. Parsa, M. Pal, *Chem. Commun.* **2011**, *47*, 5010–5012.
[6] a) D. K. Luci, E. C. Lawson, S. Ghosh, W. A. Kinney, C. E. Smith, J. Qi, Y. Wang, L. K. Minor, B. E. Maryanoff, *Tetrahedron Lett.* **2009**, *50*, 4958–4961; b) W. A. Kinney, D. K. Luci, B. E. Maryanoff, S. Ghosh, E. C. Lawson, US20100029616A1.
[7] a) F. Csende, F. Miklos, G. Stajer, *Curr. Org. Chem.* **2012**, *16*, 1005–1050; b) K. Speck, T. Magauer, *Beilstein J. Org. Chem.* **2013**, *9*, 2048–2078.
[8] R. Boulahjar, A. Ouach, C. Matteo, S. Bourg, M. Ravache, R. l. Guével, S. Marionneau, T. Oullier, O. Lozach, L. Meijer, C. Guguen-Guillouzo, S. Lazar, M. Akssira, Y. Troin, G. Guillaumet, S. Routier, *J. Med. Chem.* **2012**, *55*, 9589–9606.
[9] a) I. A. I. Ali, *Monatsh. Chem.* **2014**, *145*, 803–810; b) A. K. Maity, S. Roy, *J. Org. Chem.* **2012**, *77*, 2935–2941; c) M. Chiurato, S. Routier, Y. Troin, G. Guillaumet, *Eur. J. Org. Chem.* **2009**, 3011–3021; d) J. G. Pierce, D. L. Waller, P. Wipf, *J. Organomet. Chem.* **2007**, *692*, 4618–4629; e) A. E. Alsarabi, J.-L. Canet, Y. Troin, *Tetrahedron Lett.* **2004**, *45*, 9003–9006.
[10] a) B. Miller, S. Mao, K. M. G. Rosenker, J. G. Pierce, P. Wipf, *Beilstein J. Org. Chem.* **2012**, *8*, 1091–1097; b) A. Daïch, S. Marchalin, P. Pigeon, B. Decroix, *Tetrahedron Lett.* **1998**, *39*, 9187–9190; c) F. D. King, A. E. Aliev, S. Caddick, D. A. Tocher, *Org. Biomol. Chem.* **2011**, *9*, 1547–1554.
[11] P. H. Lee, D. Seomoon, K. Lee, *Org. Lett.* **2005**, *7*, 343–345.
[12] M. G. Banwell, B. D. Kelly, O. J. Kokas, D. W. Lupton, *Org. Lett.* **2003**, *5*, 2497–2500.
[13] E. G. Occhiato, F. Lo Galbo, A. Guarna, *J. Org. Chem.* **2005**, *70*, 7324–7330.
[14] a) T. R. Kelly, Q. Li, V. Bhushan, *Tetrahedron Lett.* **1990**, *31*, 161–164; b) A. B. Smith, A. H. Davulcu, Y. S. Cho, K. Ohmoto, L. Kürti, H. Ishiyama, *J. Org. Chem.* **2007**, *72*, 4596–4610; c) R. Grigg, A. Teasdale, V. Sridharan, *Tetrahedron Lett.* **1991**, *32*, 3859–3862; d) R. Olivera, R. SanMartin, I. Tellitu, E. Domínguez, *Tetrahedron* **2002**, *58*, 3021–3037.
[15] M. S. Hendi, K. J. Natalie Jr., S. B. Hendi, J. A. Campbell, T. D. Greenwood, J. F. Wolfe, *Tetrahedron Lett.* **1989**, *30*, 275–278.

[16] W. E. Parham, C. K. Bradsher, *Acc. Chem. Res.* **1982**, *15*, 300–305.
[17] A. Moreau, A. Couture, E. Deniau, P. Grandclaudon, *Eur. J. Org. Chem.* **2005**, 3437–3442.
[18] a) M. Mori, N. Kaneta, M. Shibasaki, *J. Organomet. Chem.* **1994**, *464*, 35–40; b) M. Mori, N. Kaneta, N. Isono, M. Shibasaki, *Tetrahedron Lett.* **1991**, *32*, 6139–6142; c) M. Mori, N. Isono, H. Wakamatsu, *Synlett* **1999**, 269–280; d) M. Mori, N. Isono, N. Kaneta, M. Shibasaki, *J. Org. Chem.* **1993**, *58*, 2972–2976; e) M. Mori, A. Hashimoto, M. Shibasaki, *J. Org. Chem.* **1993**, *58*, 6503–6504.

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