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Selective C-Acylation of 2-Aminoimidazo[1,2-*a*]pyridine: Application to the Synthesis of Imidazopyridine-Fused [1,3]Diazepinones

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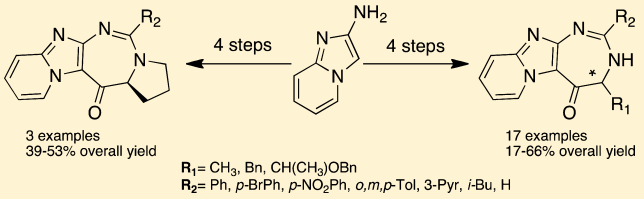
Supporting Information

ABSTRACT: A series of 20 optically pure 3,4-dihydro-5*H*-pyrido[1′,2′:1,2]imidazo[4,5-*d*][1,3]diazepin-5-ones which form a new family of azaheterocycle-fused [1,3]diazepines were synthesized in four steps with 17−66% overall yields. The key step consists of a selective C-acylation reaction of easily accessible 2-aminoimidazo[1,2-*a*]pyridine at C-3.



The concept of privileged structure, which is defined as "a single molecular framework able to provide ligands for diverse receptors",[1] has emerged as a powerful approach to increase the chances of discovering lead compounds. The first prototype of such structures, which led to many clinical and commercial successes, was the diazepine scaffold.[2,3] Since the discovery of the benzodiazepine family as central nervous system depressants, many synthetic derivatives, displaying a wide pharmacological spectrum including antithrombotic,[4] antibiotic,[5] and antitumor[6,7] properties, have been extensively developed. Much attention has been paid to the replacement of the fused benzene ring by a heterocyclic ring system such as thiophene,[8,9] pyrazole,[10,11] imidazole,[12] pyrrole,[13−15] indole,[16,17] furan,[13] etc. Among the different classes of diazepines, the [1,3]diazepines have been studied to a minor extent although their derivatives are also of interest due to their ability to bind multiple therapeutic targets. As an example, [1,3]-diazepines have shown inhibitory effects on HIV-1 protease,[18] lymphocyte-specific kinase (Lck),[19] AMP deaminase,[20] adenosine deaminase, and guanase,[21] as well as cytotoxic effects on Jurkat and glial cells[22] (for examples of biologically active [1,3]diazepines, see Figure 1). Consequently, the development of efficient methodologies for the synthesis of new heterocycle-fused [1,3]diazepine scaffolds could be of value for subsequent biological screening programs.

Imidazo[1,2-*a*]pyridine (IP), an aza analogue of indole, is an important pharmacophore and is widely found in many biologically active compounds exhibiting antibacterial,[23] antifungal,[24] antiviral,[25−27] antitumorous,[28,29] and anti-inflammatory[30] properties. Drug formulations containing imidazo[1,2-*a*]pyridines currently available on the market include alpidem (anxiolytic), zolpidem[31] (hypnotic), and zolimidine (antiulcer). Extensive studies have been performed to synthesize bioactive polyfused heterocyclic compounds with the IP ring.[28,32] However, a careful survey of the literature revealed that, among the numerous synthesized IP derivatives, and despite their promising activities for pharmaceutics, no IP-fused [1,3]diazepine has been reported so far. In light of our interest in accessing new skeletons containing the IP ring,[33] we report herein the synthesis of IP-fused [1,3]diazepines **1**.

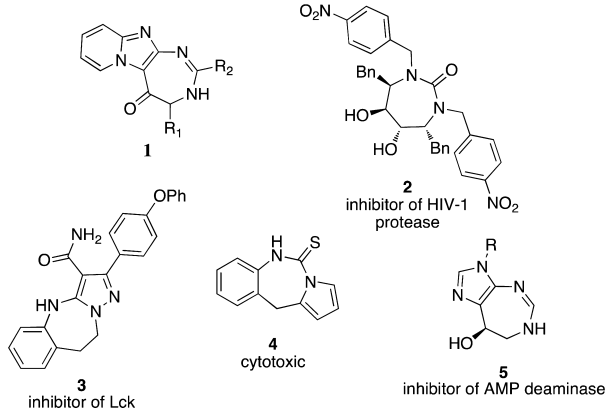


Figure 1. Representative examples of [1,3]diazepines.

In order to synthesize **1**, we envisioned the strategy described in Scheme 1 that consisted of condensation of 2-amino-3-acylimidazo[1,2-*a*]pyridines **7** with aldehydes. Oxidation led to 3,4-dihydro-5*H*-pyrido[1′,2′:1,2]imidazo[4,5-*d*][1,3]diazepin-5-one **1**. One of the most efficient reported methods to synthesize the key intermediates **7** is the alkylation of 2-chloropyridine with halomethyl ketones followed by nucleophilic chloride displacement with cyanamide and subsequent cyclization under basic conditions.[34] This method suffers from a low number of commercially available halomethylketones and from harsh reaction conditions, especially during alkylation of 2-chloropyridine. The direct acylation of 2-aminoimidazo[1,2-

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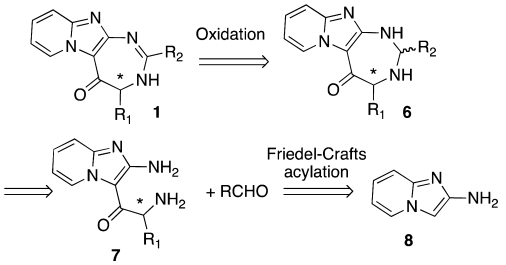
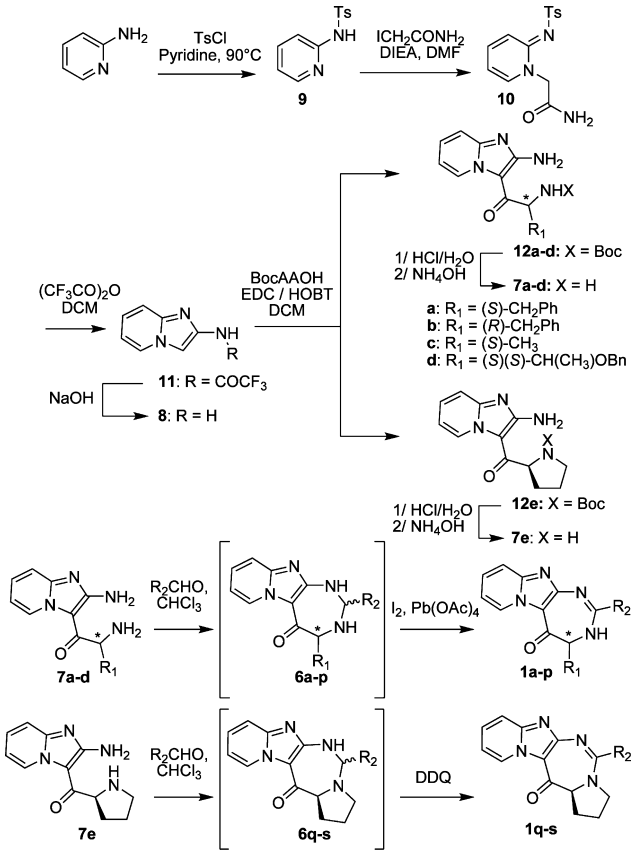
Scheme 1. Retrosynthetic Approach To Synthesize 3,4-Dihydro-5*H*-pyrido[1′,2′:1,2]imidazo[4,5-*d*][1,3]diazepin-5-ones



a]pyridine **8** is an alternate strategy. However, to the best of our knowledge, this option has never been considered.

2-Aminoimidazo[1,2-*a*]pyridine **8** was prepared as depicted in Scheme 2. 2-Aminopyridine was first reacted with

Scheme 2. Synthesis of 3,4-Dihydro-5*H*-pyrido[1′,2′:1,2]imidazo[4,5-*d*][1,3]diazepin-5-ones



tosylchloride in refluxing pyridine and then alkylated with iodoacetamide to give **10** in 91% yield. Electrocyclization of **10** with trifluoroacetic anhydride in dry dichloromethane afforded trifluoroacetamide **11** in 88% yield according to the method reported by Hamdouchi.[35] **8** was finally obtained by saponification of the trifluoroacetamide group.

IP is known to be an electron-rich aromatic ring[32,33,36,37] that could lead to electrophilic aromatic substitutions at C-3. However, the Friedel–Crafts acylation remains challenging and requires an excess of acylating reagent and strong temperature conditions.[38] In the case of 2-aminoimidazo[1,2-*a*]pyridine **8**, it could be expected that two different modes of addition, either N-addition or C-addition, could occur. It is known that aminoimidazole derivatives could give these two different modes of addition, depending on the electrophilic reagent used.[39] However, to the best of our knowledge, Friedel–Crafts acylation had never been studied with these ambivalent nucleophiles. In order to study the conditions to selectively acetylate compound **8** at C-3, *N*-Boc-L-Phe was selected as the acyl donor. Activation of the N-protected amino acid was performed at room temperature in dichloromethane using EDC/DMAP (1 equiv; 0.1 equiv) or isobutylchloroformate (1 equiv) with DIEA (1 equiv). Reactions were monitored by TLC on alumina oxide (DCM/EtOH, 99:1 v/v) and by HPLC. Whatever the tested conditions, 2-aminoimidazo[1,2-*a*]pyridine **8** was converted into an inseparable mixture consisting of N- and C-addition products (data not shown). No reaction occurred when *N*-Boc-L-Phe was activated into acid chloride with the Ghosez reagent. Selective C-acylation at C-3 was finally obtained when using EDC/HOBT (1 equiv; 1 equiv) in dichloromethane: the C-addition compound **12a** was isolated in 88% yield, while the N-addition product was only detected as a minor compound by LC-MS. While C-3 acyclation of IP generally required harsh conditions, compound **8** could be acylated at room temperature, probably due to the high reactivity of the enamine function. Moreover, the use of a soft activation method (i.e., EDC/HOBT) led to a C-acylation selectivity that could be seen as a powerful method to easily functionalize the IP skeleton.

The scope of the reaction was extended to three other *N*-Boc-amino acids, such as *N*-Boc-L-Ala, *N*-Boc-L-Thr(OBn), and *N*-Boc-L-Pro, which respectively led to compounds **12c–e** in 64, 61.5, and 88% yields. Intermediates **12** were finally unprotected by aqueous HCl, and the resulting hydrochloride salts were neutralized with aqueous ammonia.

To explore the formation of the IP-fused [1,3]diazepine scaffold, diamine **7a** was reacted with 1 equiv of *p*-nitrobenzaldehyde under various experimental conditions. Six different solvents were tested (i.e., toluene, THF, *n*-BuOH, 1,4-dioxane, chloroform, and acetonitrile) between 25 and 110 °C (Table 1). Reactions were monitored by TLC on alumina oxide (DCM/EtOH, 99:1 v/v). Diazepinones **6a** and **6a′** were isolated by chromatography on neutral alumina oxide as pure diastereomers. Their absolute configurations were ascertained by X-ray crystal structures of **6a** and **6a′** (see Supporting Information). The best yields were obtained when the reaction was performed at 50 °C in toluene or in dioxane as well as in refluxing chloroform (Table 1, entries 2, 4, and 9). The ratio of diastereomers appeared to be highly dependent on the conditions used. As examples, at 50 °C in toluene, **6a** and **6a′** were obtained in a 72:28 ratio, while at 110 °C, the diastereoselectivity was inversed to a 30:70 ratio (Table 1, entries 1 and 2). The best diastereoselectivity in the *cis*-diazepinone **6a** was obtained when the reaction was carried out at 50 °C in acetonitrile (Table 1, entry 10). Adding a Lewis acid such as $SnCl_2$ led to a decrease of the global yield (Table 1, entry 6).

^{1}H NMR experiments have revealed a slow interconversion of diastereomers **6a** and **6a′** at room temperature with a 30:70 equilibrium ratio. In order to obtain the desired 3,4-dihydro-5*H*-pyrido[1′,2′:1,2]imidazo[4,5-*e*][1,3]diazepin-5-one **1a**, diazepinones **6a** and **6a′** were oxidized with a mixture of lead tetraacetate and iodine in chloroform at room temperature.[40] **1a** was isolated in 90% yield.

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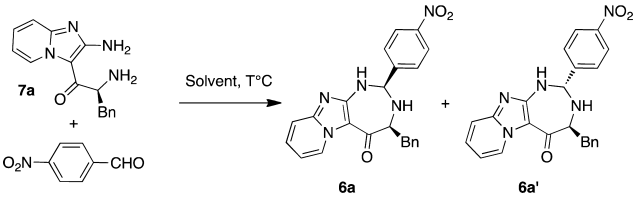
Table 1. Condensation of 2-Amino-3-acylimidazo[1,2-*a*]pyridine 7a and *p*-Nitrobenzaldehyde



entry	solvent	T (°C)	yield (%)[a]	6a/6a′
1	toluene	110	59	30/70
2	toluene	50	96	72/28
3	1,4-dioxane	25	70	90/10
4	1,4-dioxane	50	92	90/10
5	1,4-dioxane	105	81	50/50
6	1,4-dioxane[b]	50	50	22/78
7	THF	50	84	60/40
8	*n*-BuOH	50	83	72/28
9	chloroform	50	89	76/24
10	acetonitrile	50	80	95/5

[a]Reaction done with 50 mg of **7a** and 1 equiv of *p*-nitrobenzaldehyde in 2 mL of solvent. [b]Reaction done with 0.1 equiv of $SnCl_2$.

To investigate the scope of the process, the diamine **7a** and its enantiomer **7b** were reacted with various (hetero)aromatic and aliphatic aldehydes, such as benzaldehyde, *p*-bromobenzaldehyde, *o*,*m*,*p*-tolualdehyde, *p*-anisaldehyde, and isovaleraldehyde. While intermediate diazepinones **6** could be detected by LC-MS in most cases, they were not stable enough to be isolated: purification by chromatography on alumina oxide led to re-formation of aldehydes and diamine **7**. Therefore, to access diazepinones **1** anyway, we envisioned to perform aldehyde condensation and oxidation in a one-pot tandem procedure without any purification of the diazepinone intermediates **6**. Chloroform was chosen as a common solvent for both cyclization and oxidation reactions. Diamines **7** were stirred with 1 equiv of aldehyde at 60 °C overnight. The mixtures were then cooled to 25 °C, and a solution of iodine (1.1 equiv) and lead tetraacetate (1.1 equiv) was added. Stirring was maintained until completion (monitored by TLC). The reactions were quenched with 10% m/v sodium thiosulfate aqueous solution, then compounds were purified by chromatography on neutral alumina oxide. Results are summarized in Figure 2. The best yields of the cyclization/oxidation sequence were obtained with benzaldehyde bearing electron-withdrawing groups such as *p*-nitro and *p*-bromobenzaldehyde (Figure 2, compounds **1a,b**, respectively) and with 3-pyridinecarboxaldehyde (Figure 2, compound **1i**). The lack of racemization was ascertained by determination of optical rotation of both enantiomers (*S*)-**1b** ($[\alpha]^{20}_D$ = +1 (*c* 1.0, $CHCl_3$)) and (*R*)-**1b** ($[\alpha]^{20}_D$ = −1 (*c* 1.0, $CHCl_3$)) and by measuring their enantiomeric excesses by chiral HPLC (ee >99%). With benzaldehyde, *o*-, *m*-, and *p*-tolualdehydes, diazepinones were isolated with 41−54% overall yields (Figure 2, compounds **1c−f**). The use of *p*-methoxybenzaldehyde led to a strong decrease in yield (34% compared to 77% yield obtained with *p*-nitrobenzaldehyde). This could probably be due to the low stability of intermediate **6g**. Despite lower yields, the cascade reaction also tolerated aliphatic aldehydes like isovaleraldehyde (Figure 2, compounds **1h**). Conversely, it did not proceed with paraformaldehyde (Figure 2, compound **1j**). Nevertheless, **1j** could be quantitatively obtained by condensation of diamine **7a** with trimethylorthoformate, but it appeared to be highly unstable as soon as it was in solution. In

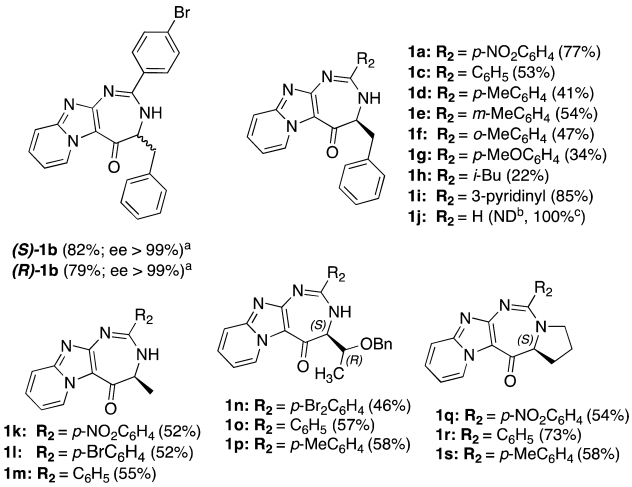


Figure 2. Synthesis of 3,4-dihydro-5*H*-pyrido[1′,2′:1,2]imidazo[4,5-*d*][1,3]diazepin-5-ones **1** (isolated yield after purification by chromatography on alumina oxide). ND: not detected. NI: not isolated. [a]Determined by chiral HPLC. [b]Using paraformaldehyde. [c]Using trimethylorthoformate.

order to study the influence of lateral chains, the procedure was tested on the alanine and threonine derivatives **7c** and **7d**. The nature of the substituent at the C-4 position was not a crucial factor since yields obtained with diamines **7c** and **7d** were in the same range as those obtained with **7a** (Figure 2, Compounds **1k−p**). On the other hand, while proline derivative **7e** proved to be easily converted into diazepinones **6**, the use of $I_2/Pb(OAc)_4$ as oxidant led in these cases to complex mixtures and low yields (data not shown). We therefore focused our attention on the optimization of oxidation conditions. This led us to choose DDQ instead of $I_2/Pb(OAc)_4$ for diamine **7e**. Using this modified procedure, the imidazopyridine-fused pyrrolodiazepinones **1q−s** were isolated with 54−73% yields (Figure 2, compounds **1q−s**).

In conclusion, we have developed a practical sequence for the synthesis of the IP-fused [1,3]diazepin-5-one heterocyclic scaffold. The key step was a Friedel−Crafts acylation at the C-3 position of the easily accessible 2-aminoimidazo[1,2-

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a]pyridine. Choice of conditions to activate amino acids, that is, use of EDC/HOBT, was decisive. After removal of the amino protecting group, the intermediate diamines were engaged in a two-step tandem procedure to access a library of 20 compounds in 22−85% overall yields. In light of the remarkable biological activities of diazepine derivatives, these unusual heterocycle-fused [1,3]diazepines are currently under investigation and results will be reported in due course.

EXPERIMENTAL SECTION

2-[2-{(*p*-Toluenesulfonyl)imino}pyridin-1-yl]acetamide 10: *i*-Pr_2NEt (7.7 mL, 5.7 g, 44.3 mmol, 1.1 equiv) was added to a suspension of 4-methyl-*N*-pyridin-2-ylbenzenesulfonamide **9**[41] (10 g, 40.3 mmol) in DMF (60 mL). To the resulting solution was added 2-iodoacetamide (8.2 g, 44.3 mmol, 1.1 equiv), and the mixture was stirred at rt for 24 h. DMF was removed in vacuo, water (250 mL) was added and the mixture was stirred for 1 h. The solid was collected by filtration and washed with water and dried in vacuo to give **10** as a white solid: yield 12.25 g (91%); mp 170−172 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.33 (s, 3H), 4.83 (s, 2H), 6.72 (t, 1H, J = 6.8 Hz), 7.27 (m, 3H), 7.37 (br s, 1H), 7.66 (d, 2H, J = 8.2 Hz), 7.71 (dd, 1H, J = 8.5, 6.8 Hz), 7.79 (br s, 1H), 7.99 (d, 1H, J = 6.8 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.9, 54.3, 110.7, 116.1, 126.0, 129.1, 140.9, 141.2, 141.5, 142.3, 155.3, 167.5; FT-IR γ_{max} (cm^{-1}) 767.2, 982.2, 1080.7, 1131.7, 1367.7, 1502.8, 1697.4, 3173.7; HPLC, T_r = 0.97 min; MS (ESI+) m/z 289.2 [M − NH_3]$^+$, 306.3 [M + H]$^+$, 611.4 [2M + H]$^+$; HRMS calcd for $C_{14}H_{16}N_3O_3S$ 306.0912, found 306.0915.

Trifluoro-*N*-imidazo[1,2-*a*]pyridin-2-yl-acetamide 11: In a suspension of compound **10** (5.4 g, 17.7 mmol) in dry CH_2Cl_2 (55 mL) at 0 °C was added trifluoroacetic anhydride (4.9 mL, 7.4 g, 35.2 mmol, 2 equiv), and the solution was stirred a rt for 4 h. The solution was washed with saturated sodium hydrogen carbonate solution (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo to give 3.56 g (88%) of **11** as a solid: mp 154−158 °C (dec). The Dimroth isomer trifluoro-*N*-imidazo[1,2-*a*]pyridine-3-ylacetamide was also detected by HPLC, T_r = 1.25 min (22%). Analysis of **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56 (br s, 1H), 6.90 (dd, 1H, J = 6.9, 7.8 Hz), 7.28 (dd, 1H, J = 9.1, 7.8 Hz), 7.49 (d, 1H, J = 9.1 Hz), 8.16 (d, 1H, J = 6.8 Hz), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 102.9, 113.3, 114.5 (q), 116.4, 126.0, 126.2, 139.3, 142.0, 154.9 (q); ^{19}F NMR ($CDCl_3$, 300 MHz) δ −74.8; FT-IR γ_{max} (cm^{-1}) 767, 982, 1080, 1131, 1252, 1368, 1461, 1502, 1630, 1697, 3174; HPLC, T_r = 1.08 min; MS (ESI+) m/z 230.1 [M + H]$^+$; HRMS calcd for $C_9H_6F_3N_3O$ 230.0541, found 230.0541.

Synthesis of 12a−e. To a suspension of 1 g of compound **11** (4.36 mmol) in 9 mL of aqueous 5 N sodium hydroxide solution was added 1 mL of THF. The solution was stirred at rt for 2 h. The solution was extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was dissolved in 40 mL of dichloromethane, and BocAAOH (4.76 mmol, 1.1 equiv), HOBt (650 mg, 4.8 mmol, 1.1 equiv), and EDC (850 μL, 4.8 mmol, 1.1 equiv) were added at 0 °C. The solution was stirred at rt for 4 h. The solution was washed with satured sodium hydrogen carbonate solution (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by chromatography (Al_2O_3, DCM/EtOH 99/1 v/v).

(2S)-2-Boc-amino-1-(2-aminoimidazo[1,2-a]pyridin-3-yl)-3-phenylpropan-1-one ***12a:*** White solid, m = 1.46 g, 88%, mp 182−184 °C; $[\alpha]_D^{20}$ = +54.2 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 9H), 3.10 (ABX, 2H), 5.27 (m, 1H), 5.98 (d, 1H, J = 8.4 Hz), 6.11 (br s, 1H), 6.84 (dd, 1H, J = 6.3, 7.8 Hz), 7.15 (m, 5H), 7.35 (m, 2H), 9.62 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 38.7, 55.5, 80.5, 108.3, 113.0, 114.3, 126.7, 128.4, 129.3, 129.4, 130.7, 137.0, 147.8, 156.7, 158.8, 184.9; FT-IR γ_{max} (cm^{-1}) 750.2, 1045.8, 1164.8, 1287.6, 1342.9, 1453.7, 1495.0, 1542.8, 1576.1, 1682.3, 2974.0, 3195.0, 3329.1; HPLC, T_r = 1.49 min; MS (ESI$^+$) m/z 381.2 [M + H]$^+$; HRMS calcd for $C_{21}H_{25}N_4O_3$ 381,1927, found 381.1930. **12b**: White solid, m = 1.40 g, 85%; $[\alpha]_D^{20}$ = +54.8 (c 1.0, $CHCl_3$).

(2S)-2-Boc-amino-1-(2-aminoimidazo[1,2-a]pyridin-3-yl)-propan-1-one ***12c:*** White solid, m = 848 mg, 64%, mp 160−162 °C; $[\alpha]_D^{20}$ = −69.8 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3H), 1.42 (s, 9H), 5.03 (quint, 1H, J = 7.2 Hz), 5.65 (d, 1H, J = 7.2 Hz), 5.97 (br s, 1H), 6.88 (t, 1H, J = 6.8 Hz), 7.39 (m, 2H), 9.60 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.5, 28.5, 50.3, 80.4, 107.6, 113.2, 114.4, 129.4, 130.7, 147.8, 156.4, 158.6, 185.9; FT-IR γ_{max} (cm^{-1}) 743, 758, 853, 1054, 1167, 1267, 1288, 1309, 1329, 1343, 1444, 1499, 1522, 1591, 1630, 1678, 2982, 3203, 3388; HPLC, T_r = 1.13 min; LC-MS (ESI$^+$) m/z 305.2 [M + H]$^+$; HRMS calcd for $C_{15}H_{21}N_4O_3$ 305.1614, found 305.1613.

(2S,3S)-2-Boc-amino-1-(2-aminoimidazo[1,2-a]pyridin-3-yl)-3-(benzyloxy)-butan-1-one ***12d:*** White solid, m = 1.14 g, 61.5%, mp 126−128 °C; $[\alpha]_D^{20}$ = −4.8 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, 3H, J = 6.2 Hz), 1.43 (s, 9H), 4.07 (m, 1H), 4.44 (d, 1H, J = 11.4 Hz), 4.64 (d, 1H, J = 11.4 Hz), 5.10 (dd, 1H, J = 8.4, 5.1 Hz), 5.86 (br s, 2H), 6.85 (dd, 1H, J = 7.2, 6.6 Hz), 7.24 (m, 5H), 7.31 (d, 1H, J = 8.8 Hz), 7.38 (d, 1H, J = 7.7 Hz), 9.62 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7, 28.5, 59.0, 74.6, 76.6, 80.1, 113.1, 114.4, 127.8, 127.9, 128.0, 128.5, 129.5, 130.7, 137.7, 147.8, 156.2, 158.9, 183.0; FT-IR γ_{max} (cm^{-1}) 742, 759, 1019, 1054, 1164, 1268, 1287, 1343, 1444, 1498, 1590, 1677, 2979, 3203, 3386; HPLC, T_r = 1.57 min; LC-MS (ESI$^+$) m/z 425.2 [M + H]$^+$; HRMS calcd for $C_{23}H_{29}N_4O_4$ 425.2189, found 425.2184.

(2-Aminoimidazo[1,2-a]pyridin-3-yl) [(2S)-Boc-pyrrolidin-2-yl]-methanone ***12e:*** White solid, m = 1.27 g, 88%, mp 184−186 °C; $[\alpha]_D^{20}$ = +56.2 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H), 1.90−2.11 (m, 3H), 2.30 (m, 1H), 3.45−3.70 (m, 2H), 5.13 (dd, 1H, J = 7.7, 3.0 Hz), 6.83 (t, 1H, J = 6.5 Hz), 6.90 (br s, 1H), 7.34 (m, 3H), 9.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.9, 28.5, 30.6, 47.5, 60.2, 80.1, 109.0, 112.9, 114.3, 128.9, 130.1, 147.3, 155.4, 158.8, 188.1; FT-IR γ_{max} (cm^{-1}) 756, 1051, 1125, 1161, 1344, 1403, 1446, 1495, 1592, 1678, 2977, 3139; HPLC, T_r = 1.39 min; LC-MS (ESI+) m/z 331.2 [M + H]$^+$; HRMS calcd for $C_{17}H_{23}N_4O_3$ 331.1770, found 331.1768.

Synthesis of 7a−e. One gram of compound **12a−e** in 5 mL of 12 N aqueous hydrochloric acid was stirred a rt for 1 h. The solution was treated with 28% aqueous ammonia solution and then extracted with chloroform (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo to lead compounds **7a−e** with 88, 88, 92, 91, and 82% yields, respectively (for spectra, see Supporting Information).

Synthesis of 6a and 6a′. To a solution of 50 mg of **7a** in 2 mL of dioxane was added 1 equiv of the appropriate *p*-nitrobenzaldehyde. The solution was stirred at 50 °C for 3 h. After cooling, the solution was concentrated under reduced pressure. The residue was dissolved in 20 mL of dichloromethane and washed with saturated sodium hydrogen carbonate (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by chromatography on alumina, eluted by CH_2Cl_2 then by CH_2Cl_2/EtOH (98:2 v/v).

(2S,4S)-4-Benzyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydro-5H-pyrido-[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***6a:*** White solid, m = 61 mg, 82%, mp 190−193 °C; $[\alpha]_D^{20}$ = −235.8 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.19 (dd, 1H, J = 13.7, 7.7 Hz), 3.43 (dd, 1H, J = 13.7, 4.1 Hz), 4.20 (1H, m), 5.41 (d, 1H, J = 9.4 Hz), 6.80 (d, 1H, J = 9.4 Hz), 6.89 (dd, 1H, J = 6.8, 8.0 Hz), 7.28 (m, 7H), 7.53 (d, 2H, J = 8.7 Hz), 8.09 (d, 2H, J = 8.7 Hz), 9.80 (d, 1H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.3, 67.9, 71.8, 109.4, 113.1, 113.7, 124.1, 126.7, 127.2, 128.5, 129.5, 129.6, 130.9, 138.1, 147.7, 147.9, 148.2, 156.7, 191.4; FT-IR γ_{max} (cm^{-1}) 695, 755, 834, 1244, 1338, 1348, 1406, 1480, 1512, 1567, 2920, 3214,3326; HPLC, T_r = 1.71 min; LC-MS (ESI$^+$) m/z 414.1 [M + H]$^+$; HRMS calcd for $C_{23}H_{20}N_5O_3$ 414.1566, found 414.1563. Single crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of a solution of **6a** in 1:1 tetrahydrofuran/ethanol mixture.

(2R,4S)-4-Benzyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydro-5H-pyrido-[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***6a′:*** White solid, m = 7 mg, 10%; mp 141−143 °C; $[\alpha]_D^{20}$ = +21.5 (c 1.0, DMSO); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 2.63 (dd, 1H, J = 9.0, 13.8 Hz), 3.28 (m,

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2H), 3.88 (dd, 1H, J = 9.0, 6.0 Hz), 5.66 (m, 1H), 6.99 (t, 1H, J = 6.9 Hz), 7.02 (m, 2H), 7.14 (m, 3H), 7.28 (d, 2H, J = 8.6 Hz), 7.38 (d, 1H, J = 8.8 Hz), 7.53 (dd, 1H, J = 8.8, 6.9 Hz), 7.96 (d, 2H, J = 8.8 Hz), 9.66 (d, 1H, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 37.1, 62.3, 66.9, 107.5, 112.1, 113.4, 123.0, 125.5, 127.7, 128.3, 128.4, 129.4, 130.5, 139.7, 146.5, 147.8, 149.0, 156.5, 190.7; FT-IR γ_{max} (cm^{-1}) 697, 744, 856, 987, 1257, 1286, 1310, 1342, 1474, 1510, 1546, 1581, 3029, 3298; HPLC, T_r = 1.71 min; LC-MS (ESI$^+$) m/z 414.1 [M + H]$^+$. Single crystals were obtained by crystallization in dichloromethane.

Synthesis of 1a−i and 1k−p. To a solution of 0.18 mmol of **7a−d** in 2 mL chloroform was added 1 equiv of the appropriate aldehyde. The solution was stirred at 60 °C for 6 h. After cooling, the mixture was added to a solution of iodine (72 mg, 0.28 mmol, 1.1 equiv) in 4 mL of chloroform. Finally, a solution of lead tetraacetate (118 mg, 0.28 mmol, 1.1 equiv) in 6 mL of chloroform was added. The solution was stirred at room temperature for 1−6 h (monitoring by TLC). The solution was washed with 10% m/v sodium thiosulfate aqueous solution (3 × 30 mL) and then with aqueous saturated sodium hydrogen carbonate solution (2 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by chromatography on alumina, eluted by dichoromethane.

(4S)-4-Benzyl-2-(4-nitrophenyl)-3,4-dihydro-5H-pyrido[1′,2′:1,2]-imidazo[4,5-d][1,3]diazepin-5-one ***1a:*** Yellow powder, m = 57 mg, 77%; mp 169−171 °C (dec); $[\alpha]_D^{20}$ = +27.4 (c 0.92, DMSO); two conformers detected by ^{1}H NMR in DMSO; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.71 (dd, 0.6H, J = 15.1, 3.6 Hz), 3.00 (dd, 1H, J = 13.9, 4.7 Hz), 3.20 (dd, 0.6H, J = 13.5, 13.3 Hz), 3.45 (dd, 1H, J = 13.5, 13.3 Hz), 4.13 (dd, 0.6H, J = 9.3, 4.7 Hz), 4.27 (m, 1H), 7.20 (m, 5H), 7.28 (m, 3H), 7.32 (d,1H, J = 7.3 Hz), 7.38 (d, 1H, J = 7.6 Hz), 7.71 (m, 3H), 7.82 (d, 2H, J = 8.3 Hz), 7.96 (d, 1.2H, J = 7.6 Hz), 8.25 (d, 2H, J = 8.8 Hz), 8.29 (d, 1.2H, J = 8.3 Hz), 8.82 (d, 1H, J = 6.8 Hz), 9.38 (d, 0.6H, J = 6.6 Hz), 9.50 (d, 1H, J = 6.4 Hz), 11.5 (s, 0.6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 35.4, 62.9, 114.1, 116.2, 123.2, 126.8, 127.7, 127.8, 128.0, 128.5, 129.4, 129.7, 130.2, 130.7, 136.6, 146.5, 149.1, 155.2, 182.2; FT-IR γ_{max} (cm^{-1}) 697, 760, 849, 1337, 1421, 1467, 1519, 1626, 2851, 2921; HPLC, T_r = 1.51 min; LC-MS (ESI$^+$) m/z 412.0 [M + H]$^+$; HRMS calcd for $C_{23}H_{18}N_5O_3$ 412.1410, found 412.1411.

(4S)-4-Benzyl-2-(4-bromophenyl)-3,4-dihydro-5H-pyrido [1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***1b:*** Brown solid, m = 65 mg, 82%; mp 102−107 °C (dec); $[\alpha]_D^{20}$ = +1.0 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (m, 1H), 3.40 (m, 1H), 4.27 (dd, 1H, J = 11.1, 4.1 Hz), 7.06 (m, 1H), 7.28−7.45 (m, 9H), 7.53 (m, 1H), 7.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.4, 63.2, 114.0, 116.3, 126.7, 127.0, 127.1, 127.2, 128.7, 129.0, 129.8, 130.5, 130.6, 130.7, 131.8, 134.2, 182.2; FT-IR γ_{max} (cm^{-1}) 699, 765, 1009, 1071, 1337, 1423, 1479, 1554, 1580, 1625, 2927; HPLC, T_r = 1.33 min; LC-MS (ESI$^+$) m/z 445.0 [M + H]$^+$, 447.0 [M + 2 + H]$^+$; HRMS calcd for $C_{23}H_{18}BrN_4O$ 445.0664, found 445.0665. (***R***)**-1b:** $[\alpha]_D^{20}$ = −1.0 (c 1.0, $CHCl_3$).

(4S)-4-Benzyl-2-phenyl-3,4-dihydro-5H-pyrido[1′,2′:1,2] imidazo-[4,5-d][1,3]diazepin-5-one ***1c:*** Yellow solid, m = 35 mg, 53%; mp 111−112 °C; $[\alpha]_D^{20}$ = +16.8 (c 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.14 (m, 1H), 3.43 (m, 1H), 4.24 (dd, 1H, J = 10.5, 4.2 Hz), 6.96 (t, 1H, J = 7.0 Hz), 7.24−7.44 (m, 12H), 7.60 (m, 2H), 9.52 (d, 1H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.5, 113.7, 115.9, 126.8, 128.5, 128.6, 128.8, 129.3, 129.9, 130.3, 131.7, 135.2, 146.2, 182.2; FT-IR γ_{max} (cm^{-1}) 698, 742, 1252, 1335, 1421, 1467, 1525, 1624, 2926; HPLC, T_r = 1.22 min; LC-MS (ESI$^+$) m/z 368 [M + H]$^+$; HRMS calcd for $C_{23}H_{19}N_4O$ 367.1548, found 367.1559.

(4S)-4-Benzyl-2-(4-methylphenyl)-3,4-dihydro-5H-pyrido-[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***1d:*** Yellow powder, m = 28 mg, 41%; mp 108−109 °C; $[\alpha]_D^{20}$ = +11.2 (c 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 3.11 (br s, 1H), 3.42 (br s, 1H), 4.24 (dd, 1H, J = 10.9, 4.0 Hz), 7.00 (t, 1H, J = 6.8 Hz), 7.10 (d, 2H, J = 8.0 Hz), 7.29−7.35 (m, 6H), 7.45 (m, 3H), 9.56 (d, 1H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 36.4, 67.5, 113.7, 116.2, 126.9, 128.6, 128.9, 129.2, 129.3, 129.8, 130.2, 132.4, 142.4, 146.6, 182.5; FT-IR γ_{max} (cm^{-1}) 698, 765, 1252, 1336, 1423, 1465, 1524, 1623, 2922; HPLC, T_r = 1.33 min; LC-MS (ESI$^+$) m/z 381 [M + H]$^+$; HRMS calcd for $C_{24}H_{21}N_4O$ 381.1715, found 381.1715.

(4S)-4-Benzyl-2-(3-methylphenyl)-3,4-dihydro-5H-pyrido-[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***1e:*** Orange powder, m = 37 mg, 54%; mp 85−87 °C; $[\alpha]_D^{20}$ = +13.7 (c 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 3.04 (m, 1H), 3.34 (d, 1H, J = 11.0 Hz), 4.18 (dd, 1H, J = 11.0, 4.2 Hz), 6.92 (dd, 1H, J = 6.9, 7.7 Hz), 7.05−7.29 (m, 11H), 9.46 (d, 1H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 36.4, 77.4, 113.8, 116.0, 126.3, 127.0, 128.4, 128.6, 128.8, 129.4, 129.8, 130.0, 130.3, 132.6, 135.0, 138.4, 139.7, 146.5, 146.9, 182.3; FT-IR γ_{max} (cm^{-1}) 764, 1253, 1336, 1424, 1465, 1557, 1625, 2921, 3027; HPLC, T_r = 1.33 min; LC-MS (ESI$^+$) m/z 414.1 [M + H]$^+$; HRMS calcd for $C_{24}H_{21}N_4O$ 381.1715, found 381.1712.

(4S)-4-Benzyl-2-(2-methylphenyl)-3,4-dihydro-5H-pyrido-[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***1f:*** Yellow powder, m = 32 mg, 47%; mp 83−85 °C; $[\alpha]_D^{20}$ = −10.7 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 3.30 (dd, 1H, J = 13.6, 9.4 Hz), 3.56 (dd, 1H, J = 13.6, 9.2 Hz), 4.11 (dd, 1H, J = 9.4, 9.2 Hz), 5.66 (d, 1H, J = 9.2 Hz), 6.84 (t, 1H, J = 6.6 Hz), 7.02−7.33 (m, 11H), 9.39 (d, 1H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.3, 37.0, 69.7, 113.6, 114.8, 126.1, 128.3, 129.4, 130.0, 130.1, 130.7, 131.2, 131.5, 135.8, 138.4, 140.0, 145.3, 152.7, 155.4, 181.5; FT-IR γ_{max} (cm^{-1}) 696, 767, 1250, 1335, 1422, 1462, 1523, 1625, 2920; HPLC, T_r = 1.33 min; LC-MS (ESI$^+$) m/z 381 [M + H]$^+$; HRMS calcd for $C_{24}H_{21}N_4O$ 381.1715, found 381.1710.

(4S)-4-Benzyl-2-(4-methoxyphenyl)-3,4-dihydro-5H-pyrido-[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***1g:*** Yellow powder, m = 24 mg, 34%; mp 108−109 °C; $[\alpha]_D^{20}$ = +22.3 (c 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (dd, 1H, J = 10.2, 11.0 Hz), 3.38 (m, 1H), 3.79 (s, 3H), 4.20 (dd, 2H, J = 11.0, 4.0 Hz), 6.77 (d, 2H, J = 8.4 Hz), 7.02 (t, 1H, J = 7.0 Hz), 7.21−7.32 (m, 6H), 7.51 (m, 3H), 9.57 (d, 1H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.2, 55.5, 77.4, 113.7, 113.9, 116.2, 127.0, 127.5, 128.6, 128.9, 129.8, 130.3, 130.9, 139.8, 146.6, 146.7, 147.0, 157.6, 162.8, 182.6; FT-IR γ_{max} (cm^{-1}) 698, 740, 1026, 1166, 1235, 1336, 1427, 1462, 1604, 1623, 2927; HPLC, T_r = 1.18 min; LC-MS (ESI$^+$) m/z 397.2 [M + H]$^+$; HRMS calcd for $C_{24}H_{21}N_4O_2$ 397.1665, found 397.1664.

(4S)-4-Benzyl-2-isobutyl-3,4-dihydro-5H-pyrido[1′,2′:1,2]imidazo-[4,5-d][1,3]diazepin-5-one ***1h:*** Pale yellow powder, m = 14 mg, 22%; mp 173−176 °C (dec); $[\alpha]_D^{20}$ = −23.0 (c 1, DMSO); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.79 (d, 6H, J = 6.6 Hz), 1.12 (dd, 1H, J = 18.4, 6.6 Hz), 1.98 (m, 1H), 2.24 (m, 2H), 2.88 (m, 1H), 3.17 (m, 1H), 3.89 (dd, 1H, J = 8.5, 4.5 Hz), 7.12−7.27 (m, 8H), 7.61 (m, 2H), 9.35 (d, 1H, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 22.0, 22.1, 26.9, 29.0, 36.1, 113.5, 115.4, 116.5, 126.1, 127.6, 128.1, 128.3, 129.2, 129.3, 130.4, 130.8, 131.6, 181.0; FT-IR γ_{max} (cm^{-1}) 698, 760, 1324, 1337, 1414, 1479, 1567, 1625, 2285, 2918, 2953; HPLC, T_r = 1.26 min; LC-MS (ESI$^+$) m/z 347.2 [M + H]$^+$; HRMS calcd for $C_{21}H_{23}N_4O$ 347.1872, found 347.1873.

(4S)-4-Benzyl-2-(3-pyridinyl)-3,4-dihydro-5H-pyrido[1′,2′:1,2]-imidazo[4,5-d][1,3]diazepin-5-one ***1i:*** Pale yellow powder, m = 55 mg, 85%; mp 87−89 °C; $[\alpha]_D^{20}$ = +10.9 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.85 (m,1H), 3.19−3.36 (m, 1H), 4.27 (m, 1H), 6.98 (t, 1H, J = 6.9 Hz), 7.17−7.25 (m, 7H), 7.55 (m, 2H), 8.00 (d, 1H, J = 7.5 Hz), 8.55 (d, 1H, J = 2.8 Hz), 9.51 (d, 1H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.2, 63.9, 114.0, 116.8, 123.3, 127.6, 128.6, 129.2, 129.6, 129.7, 130.5, 131.1, 131.4, 137.1, 149.6, 150.3, 152.2, 156.1, 157.9, 182.6; FT-IR γ_{max} (cm^{-1}) 700, 744, 919, 1025, 1078, 1202, 1254, 1337, 1412, 1427, 1472, 1558, 1584, 1622, 2923; HPLC, T_r = 1.07 min; LC-MS (ESI$^+$) m/z 368.0 [M + H]$^+$; HRMS calcd for $C_{22}H_{18}N_5O$ 368.1511, found 368.1515.

(4S)-4-Methyl-2-(4-nitrophenyl)-3,4-dihydro-5H-pyrido[1′,2′:1,2]-imidazo[4,5-d][1,3]diazepin-5-one ***1k:*** Pale yellow powder, m = 42 mg, 52%; mp 248−250 °C; $[\alpha]_D^{20}$ = +3.5 (c 1.0, DMSO); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.33 (d, 3H, J = 7.1 Hz), 4.05 (m, 1H), 7.19 (dd, 1H, J = 6.5, 8.9 Hz), 7.67 (m, 3H), 8.27 (d, 2H, J = 8.7 Hz), 8.37 (d, 2H, J = 8.7 Hz), 8.84 (d, 1H, J = 5.2 Hz), 9.48 (d, 1H, J = 6.7 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 15.5, 56.6, 111.9, 113.9, 116.1, 123.4, 127.8, 130.4, 141.7, 146.3, 149.2, 155.9, 157.3, 183.0; FT-IR γ_{max}

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(cm^{-1}) 698, 762, 850, 1340, 1422, 1470, 1515, 1627, 2927; HPLC, T_r = 0.98 min; LC-MS (ESI^+) m/z 336.2 $[M + H]^+$; HRMS calcd for $C_{17}H_{14}N_5O_3$ 336.1097, found 336.1093.

(4S)-4-Methyl-2-(4-bromophenyl)-3,4-dihydro-5H-pyrido-[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***1l:*** Orange powder, m = 46 mg, 52%; mp 142−243 °C; $[\alpha]_D^{20}$ = −6.8 (c 1.0, DMSO); ^1H NMR (DMSO-d_6, 300 MHz) δ 1.36 (d, 3H, J = 6.6 Hz), 3.99 (q, 1H, J = 6.6 Hz), 7.18 (dd, 1H, J = 8.3, 6.7 Hz), 7.65 (m, 2H), 7.73 (d, 2H, J = 8.0 Hz), 7.93 (d, 2H, J = 8.0 Hz), 9.45 (d, 1H, J = 6.7 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.0, 69.8, 113.7, 115.8, 115.9, 125.3, 127.7, 128.7, 130.4, 131.1, 131.3, 131.5, 131.7, 145.9, 166.9, 183.2; FT-IR γ_{max} (cm^{-1}) 743, 765, 1009, 1249, 1338, 1421, 1473, 1587, 1646, 2925, 3223; HPLC, T_r = 1.00 min; LC-MS (ESI^+) m/z 369.0 $[M + H]^+$, 371.1 $[M + 2 + H]^+$; HRMS calcd for $C_{17}H_{14}BrN_4O$ 369.0351, found 369.0.349.

(4S)-4-Methyl-2-phenyl-3,4-dihydro-5H-pyrido[1′,2′:1,2]imidazo-[4,5-d][1,3]diazepin-5-one ***1m:*** Yellow powder, m = 39 mg, 55%; mp 90−93 °C; $[\alpha]_D^{20}$ = −32.9 (c 0.82, $CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (d, 3H, J = 6.8 Hz), 4.11 (q, 1H, J = 6.8 Hz), 6.97 (t, 1H, J = 6.5 Hz), 7.47 (m, 5H), 8.0 (d, 2H, J = 7.0 Hz), 9.50 (d, 1H, J = 6.8 Hz), 11.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.7, 53.5, 108.9, 113.6, 114.0, 128.5, 128.8, 129.2, 130.1, 131.6, 135.3, 138.0, 147.7, 152.9, 158.4, 182.7; FT-IR γ_{max} (cm^{-1}) 762, 1252, 1335, 1420, 1470, 1623, 2927; HPLC, T_r = 0.85 min; LC-MS (ESI^+) m/z 291.2 $[M + H]^+$; HRMS calcd for $C_{17}H_{15}N_4O$ 291.1246, found 291.1246.

(4S)-4-[(1S)-1-(Benzyloxy)ethyl]-2-(4-bromophenyl)-3,4-dihydro-5H-pyrido[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***1n:*** Yellow oil, m = 35 mg, 46%; $[\alpha]_D^{20}$ = −11.3 (c 1.1, $CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (d, 3H, J = 5.8 Hz), 3.92 (d, 1H, J = 8.0 Hz), 4.09 (m, 1H), 4.33 (d, 1H, J = 10.5 Hz), 4.65 (d, 1H, J = 10.5 Hz), 7.04 (t, 1H, J = 6.9 Hz), 7.22−7.31 (m, 6H), 7.44 (d, 2H, J = 8.5 Hz), 7.53 (dd, 1H, J = 6.9, 8.5 Hz), 7.68 (d, 2H, J = 8.5 Hz), 8.7 (d, 2H, J = 8.5 Hz), 9.58 (d, 1H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7, 71.8, 72.1, 78.6, 114.1, 116.8, 127.0, 128.2, 128.4, 128.6, 128.7, 129.7, 130.6, 130.8, 131.4, 131.9, 132.1, 134.4, 137.7, 147.0, 180.5; FT-IR γ_{max} (cm^{-1}) 695, 760, 837, 1009, 1070, 1253, 1339, 1425, 1455, 1555, 1582, 1623, 2927, 2975, 3207; HPLC, T_r = 1.40 min; LC-MS (ESI^+) m/z 489.0 $[M + H]^+$, 491.0 $[M + 2 + H]^+$; HRMS calcd for $C_{25}H_{22}BrN_4O_2$ 489.0926, found 489.0932.

(4S)-4-[(1S)-1-(Benzyloxy)ethyl]-2-phenyl-3,4-dihydro-5H-pyrido-[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***1o:*** Yellow oil, m = 36 mg, 57%; $[\alpha]_D^{20}$ = −47.0 (c 0.9, $CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (d, 3H, J = 5.9 Hz), 4.07 (m, 1H), 4.34 (d, 1H, J = 9.0 Hz), 4.62 (d, 1H, J = 9.0 Hz), 6.97 (dd, 1H, J = 7.7, 6.9 Hz), 7.25 (m, 7H), 7.32 (d, 2H, J = 7.7 Hz), 7.46 (t, 2H, J = 7.7 Hz), 8.02 (d, 2H, J = 7.7 Hz), 7.63 (d, 1H, J = 8.5 Hz), 9.55 (d, 1H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7, 66.4, 71.8, 78.5, 113.7, 116.8, 128.0, 128.4, 128.5, 128.6, 129.3, 130.3, 130.4, 131.9, 135.7, 137.8, 147.2, 180.5; FT-IR γ_{max} (cm^{-1}) 744, 926, 1027, 1071, 1253, 1338, 1423, 1449, 1558, 1590, 1622, 2861, 2928, 3063, 3248; HPLC, T_r = 1.23 min; LC-MS (ESI^+) m/z 411.1 $[M + H]^+$; HRMS calcd for $C_{25}H_{23}N_4O_2$ 411.1821, found 411.1826.

(4S)-4-[(1S)-1-(Benzyloxy)ethyl]-2-(4-methylphenyl)-3,4-dihydro-5H-pyrido[1′,2′:1,2]imidazo[4,5-d][1,3]diazepin-5-one ***1p:*** Yellow oil, m = 38 mg, 58%; $[\alpha]_D^{20}$ = −23.8 (c 1.1, $CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (d, 3H, J = 6.1 Hz), 2.38 (s, 3H), 3.88 (d, 1H, J = 7.8 Hz), 4.10 (m, 1H), 4.38 (d, 1H, J = 10.1 Hz), 4.62 (d, 1H, J = 10.1 Hz), 6.85 (m, 1H), 6.98 (t, 1H, J = 6.9 Hz), 7.14 (d, 2H, J = 8.0 Hz), 7.30 (m, 4H), 7.40 (d, 1H, J = 7.7 Hz), 7.48 (dd, 1H, J = 8.0, 8.2 Hz), 7.65 (d, 1H, J = 6.9 Hz), 7.94 (m, 2H), 9.56 (d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.8, 21.6, 66.4, 71.8, 78.5, 113.6, 116.7, 126.6, 128.0, 128.4, 128.5, 129.2, 129.4, 130.4, 131.9, 132.8, 137.8, 142.6, 147.3, 180.6; FT-IR γ_{max} (cm^{-1}) 695, 763, 1337, 1425, 1455, 1555, 1621, 2857, 2923, 3257; HPLC, T_r = 1.30 min; LC-MS (ESI^+) m/z 425.1 $[M + H]^+$; HRMS calcd for $C_{26}H_{25}N_4O_2$ 425.1978, found 425.1972.

Synthesis of 1q−s. To a solution of 0.22 mmol of compound **7e** in 2 mL of chloroform was added 1 equiv of the appropriate aldehyde. The solution was stirred at 80 °C for 6 h. After cooling, DDQ (0.44 mmol, 2 equiv) was added to the reaction mixture. The solution was stirred at room temperature for 6 h (monitoring by TLC). The solution was washed with aqueous saturated sodium hydrogen carbonate solution (2 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The residue was purified by chromatography on alumina, eluted by dichloromethane.

(11aS)-7-(4-Nitrophenyl)-9,10,11,11a-tetrahydro-12H-pyrido-[2′,1′:2,3]imidazo[4,5-f]pyrrolo[1,2-c][1,3]diazepin-12-one ***1q:*** Yellow powder, m = 43 mg, 54%; mp 90−93 °C; $[\alpha]_D^{20}$ = −285 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 1.84−1.91 (m, 1H), 2.05−2.10 (m, 1H), 2.11−2.17 (m, 1H), 3.20 (m, 1H), 3.35 (ddd, 1H, J = 2.7, 7.4, 10.0 Hz), 3.78 (td, J = 6.5, 10.0 Hz), 4.18 (dd, 1H, J = 7.9, 1.7 Hz), 7.02 (td, 1H, J = 6.7, 1.2 Hz), 7.51 (ddd, 1H, J = 8.8, 6.7, 1.2 Hz), 7.67 (d, 1H, J = 8.8 Hz), 7.86 (dd, 1H, J = 8.8 Hz), 8.30 (d, 2H, J = 8.7 Hz), 9.52 (d, 1H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7, 25.5, 53.4, 65.0, 113.8, 114.8, 117.1, 123.8, 128.4, 130.2, 130.7, 142.6, 146.9, 149.0, 158.3, 158.5, 179.4; FT-IR γ_{max} (cm^{-1}) 709, 742, 853, 955, 1014, 1073, 1107, 1164, 1251, 1334, 1466, 1518, 1548, 1629, 2928; HPLC, T_r = 1.03 min; LC-MS (ESI^+) m/z 362.0 $[M + H]^+$; HRMS calcd for $C_{19}H_{16}N_5O_3$ 362.1253, found 362.1250.

(11aS)-7-Phenyl-9,10,11,11a-tetrahydro-12H-pyrido [2′,1′:2,3]-imidazo[4,5-f]pyrrolo[1,2-c][1,3]diazepin-12-one ***1r:*** White powder, m = 51 mg, 53%; mp 209−213 °C (dec); $[\alpha]_D^{20}$ = −204 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 1.82 (m, 1H), 2.03 (m, 1H), 2.13 (m, 1H), 3.15 (m, 1H), 3.32 (m, 1H), 3.91 (m, 1H), 4.14 (d, 1H, J = 7.1 Hz), 6.97 (t, 1H, J = 6.9 Hz), 7.38−7.48 (m, 5H), 7.67 (m, 3H), 9.50 (d, 1H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7, 25.6, 53.5, 65.0, 113.5, 114.6, 116.9, 128.5, 128.6, 129.9, 130.1, 130.8, 136.3, 146.8, 158.7, 161.2, 180.0; FT-IR γ_{max} (cm^{-1}) 700, 721, 747, 761, 785, 828, 851, 929, 956, 1030, 1069, 11239, 1249, 1306, 1333, 1392, 1421, 1464, 1540, 1623, 2953; HPLC, T_r = 1.24 min; LC-MS (ESI^+) m/z 317.1 $[M + H]^+$; HRMS calcd for $C_{19}H_{17}N_4O$ 317.1402, found 317.1400.

(11aS)-7-(4-Methylphenyl)-9,10,11,11a-tetrahydro-12H-pyrido-[2′,1′:2,3]imidazo[4,5-f]pyrrolo[1,2-c][1,3]diazepin-12-one ***1s:*** White powder, m = 42 mg, 58%; mp 106−111 °C (dec); $[\alpha]_D^{20}$ = −257 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 1.79 (m, 1H9, 2.01 (m, 1H), 2.12 (m, 1H), 2.37 (s, 3H), 3.14 (m, 1H), 3.32 (m, 1H), 3.95 (m, 1H), 4.15 (d, 1H, J = 7.4 Hz), 6.95 (td, 1H, J = 6.95, 1.0 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.45 (td, 1H, J = 8.5, 1.3 Hz), 7.60 (d, 2H, J = 8.0 Hz), 7.64 (d, 1H, J = 8.5 Hz), 9.50 (d, 1H, J = 6.95 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 24.7, 25.7, 53.5, 65.0, 113.5, 114.6, 116.9, 128.4, 129.2, 130.1 (2C), 133.3, 141.3, 146.8, 158.8, 161.3, 180.1; FT-IR γ_{max} (cm^{-1}) 698, 739, 761, 826, 959, 1071, 1141, 1251, 1334, 1440, 1467, 1536, 1624, 2924; HPLC, T_r = 1.01 min; LC-MS (ESI^+) m/z 331.1 $[M + H]^+$; HRMS calcd for $C_{20}H_{19}N_4O$ 331,1559, found 331.1541.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data of compounds **6a** and **6a′**. Chiral HPLC analyses of compounds (*R*)-**1b** and (*S*)-**1b** as well as ^1H and ^{13}C NMR spectra of compounds **10**, **11**, **12a−e**, **7a−e**, **6a**, and **1a−s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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