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Stereoselective synthesis of benzoquinolizidines and related homologues via intramolecular addition to dihydropyridones

Piotr Szcześniak, Artur Ulikowski, Olga Staszewska-Krajewska, Grzegorz Lipner, Bartłomiej Furman *

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

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ABSTRACT

An efficient method for the synthesis of benzoquinolizidine and benzoindolizidine alkaloid scaffolds is described. The synthetic strategy is based on the lithium–halogen exchange-initiated intramolecular conjugate addition of aryllithiums to 2,3-dihydro-4-pyridones. A similar cyclization was also carried out under free radical conditions providing the expected cyclic compounds, although with significantly lower yields. The effects of chain length and acceptor substitution pattern on the feasibility of ring construction were studied.

1. Introduction

Benzoquinolizidine alkaloids represent a small class of natural products which have attracted considerable attention because of their interesting biological activity. Among them, emetine, isolated from the roots of *Cephalis acuminate*,[1] possesses antiprotozoic properties[2] and activity in the treatment of lymphatic leukemia.[3] Furthermore, it used to be applied as an emetic. Tubulosine has been isolated from the dried fruits of *Alangium lamarckii*[4] and the sap of *Pogonopus speciosus*.[5] It is remarkably active against several cancer cell lines[6] and has been studied for a variety of other biological activity, such as inhibition of protein biosynthesis[7] and HIV reverse transcriptase inhibitory activity.[8] Tetrabenazine is an orphan drug for the symptomatic treatment of hyperkinetic movement disorder[9] and tetrahydroberberine has significant potential as an antimicrobial drug (Fig. 1).[10]

A number of useful methods for the synthesis of these alkaloids have been developed.[11] The most commonly used are different strategies for cyclization leading to the formation of azabicyclic scaffolds. These synthetic methods include: asymmetric aza-Michael additions,[12] organocatalytic *exo*-type aza-Michael additions,[13] intramolecular domino aza-Michael addition/Darzens reaction,[14] domino Knoevenagel/hetero-Diels–Alder reaction.[15]

The utility of the presented strategy depends mainly on the availability of suitable precursors, usually synthesized by multistep syntheses. Therefore, the development of a more reliable and expeditious synthetic methodology, especially a useful solution to address the problem associated with benzoindolizidine and benzoquinolizidine ring system construction, is still desirable for the synthesis of this biologically important class of natural products.

We envisioned that the target benzoindolizidine and benzoquinozilidine scaffolds could be obtained via intramolecular anionic or radical cyclization of 2,3-dihydro-4-pyridones bearing an *ortho*-bromophenyl group in the side-chain. Corresponding enaminones are easily prepared via one-pot Mannich-Michael cyclocondensation reaction (formal aza-Diels–Alder reaction). The retrosynthetic plan we intended to use to achieve this goal is illustrated in Scheme 1.

Cyclic enaminones, particularly 6-membered enaminones (2,3-dihydro-4-pyridones), are extraordinarily versatile intermediates for the synthesis of piperidine-containing molecules.[16] Indeed, this heterocycle exists in numerous drugs and drug candidates as an indispensable binding element. Moreover, the piperidine moiety is prevalent in various structural classes of bioactive natural products.[17] We have previously described the synthetic utility of enaminones in azabicycloalkane synthesis.[18,19] For instance, we described a stereoselective approach to unsaturated indolizidines involving Lewis acid-mediated tandem Mannich/Michael reactions and the rhodium-catalyzed intramolecular conjugate addition of

* Corresponding author. Tel.: +48 22 3432053; fax: +48 22 6326681; e-mail address: furbar@icho.edu.pl (B. Furman).

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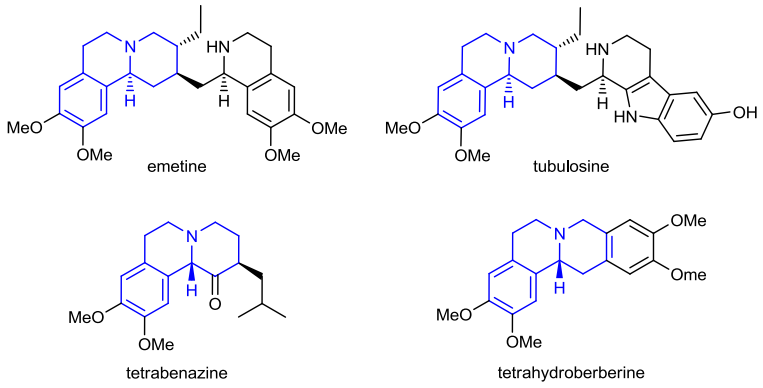
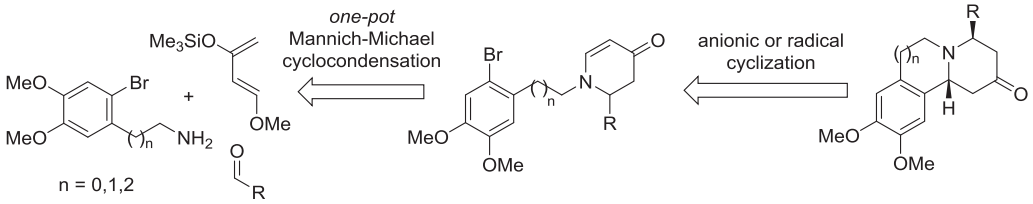


Fig. 1. Representative quinolizidine alkaloids.



Scheme 1. The cyclocondensation–cyclization methodology.

vinylstannanes. Such methodology was recently used as a key step in the synthesis of racemic Lazubine I.[20] In this article we demonstrate the application of cyclic enaminones in the stereoselective synthesis of benzoquinolizidines and their related homologues (5- and 7-membered rings). Our methodology is based on the intramolecular cyclization reaction of 2,3-dihydro-4-pyridones bearing an *ortho*-bromophenyl group in the side-chain.

2. Results and discussion

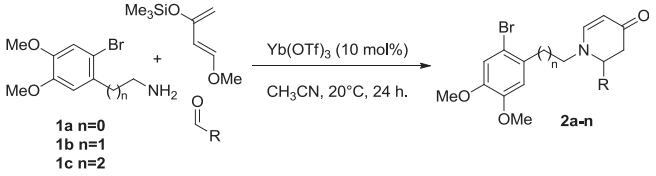
As we demonstrated previously, acyclic imines undergo the reaction with Danishefsky's diene[21] to afford the corresponding 2,3-dihydropyridin-4(1*H*)-ones in the presence of a catalytic amount of $Yb(OTf)_3$[18–20] We applied that simple protocol to the direct synthesis of dihydropyridones **2a**–**n** (Table 1). The primary amines **1a**–**c** were synthesized from commercially available compounds according to known procedures.[22] The direct three-component, $Yb(OTf)_3$-catalyzed coupling reaction between aldehydes, amines **1a**–**c** and Danishefsky's diene afforded the corresponding adducts **2a**–**n** in good yields (Table 1).

As shown in Table 1, the overall yield of the reaction showed no dependence on the nature of starting substrates and various types of aromatic and aliphatic aldehydes were cleanly and rapidly converted to the corresponding 2-substituted 2,3-dihydropyridones.

With the desired 2,3-dihydro-4-pyridones **2a**–**n** in hand, we initiated the study of the lithium–halogen exchange-initiated cyclization reaction. Largely through the pioneering work of Parham and co-workers, lithium–halogen exchange reactions in aromatic systems have been shown to be possible in the presence of a variety of common electrophilic groups (CO_2H, CO_2R, CN, $CONR_2$, CX, C=NR).[23]

With these indications and after a few unsuccessful attempts we found that the mixture of *t*-BuLi and HMPA promoted the anionic cyclization to give the corresponding benzoquinolizidines **3a**–**f** and benzoindolizidines **3g**–**l** in good yields and with excellent stereoselectivity (Table 2). We determined that the major isomers exhibit a *trans*-arrangement at H-4 and H-10b for **3a**–**f**, H-4 and H-11b for **3g**–**l**, and H-4 and H-12b for **3m**–**n**. The stereochemical assignment in each of the adducts **3a**–**n** was firmly established by NOE

Table 1
The scope of dihydropyridone synthesis

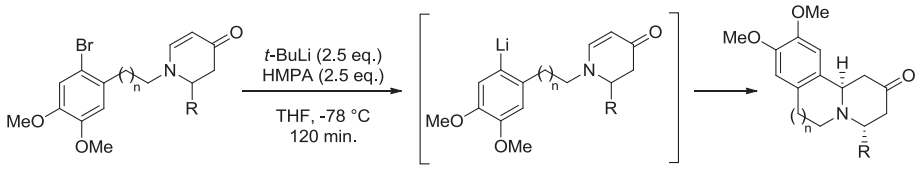


Entry	Amine	n	R	Product	Yield (%)[a]
1	**1a**	0	Ph	**2a**	87
2	**1a**	0	4-Br–C_6H_4	**2b**	84
3	**1a**	0	4-MeO–C_6H_4	**2c**	75
4	**1a**	0	2-Furyl	**2d**	70
5	**1a**	0	CO_2Et	**2e**	72
6	**1a**	0	*i*-Pr	**2f**	84
7	**1b**	1	Ph	**2g**	81
8	**1b**	1	4-Br–C_6H_4	**2h**	87
9	**1b**	1	4-MeO–C_6H_4	**2i**	74
10	**1b**	1	2-Furyl	**2j**	66
11	**1b**	1	CO_2Et	**2k**	65
12	**1b**	1	*i*-Pr	**2l**	70
13	**1c**	2	Ph	**2m**	86
14	**1c**	2	CH_2CH_2–C_6H_5	**2n**	55

[a] All yields are isolated yields after purification by column chromatography.

experiments as well as X-ray analysis of compound **3j**. In each of the analyzed compounds, the NOE spectrum showed no correlation between protons at C-4 and C-10b for **3a**–**f**, C-4 and C-11b for **3g**–**l**, or C-4 and C-12b for **3m**–**n**. We noted also that the nature of the **R** substituent on the enaminones doesn't significantly affect the overall yield and diastereoselectivity of the cyclization reaction. The anionic cyclization also proved effective in the synthesis of 7-membered analogues of benzoquinolizidines **3m**–**n**. In this case, the intramolecular addition of the aryllithium compound to enaminones **2m**–**n** proceeded in low yield, but nonetheless with good stereoselectivity. We noted that in this case the aryllithium compound is substantially protonated by the solvent molecules. The results of the investigation on the anionic cyclization are summarized in Table 2.

Table 2
The scope of anionic cyclization



2a-n **3a-n**

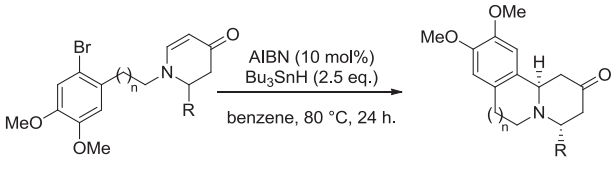
Entry	Substrate	n	R	Product	Yield (%)[a]	*trans/cis*[b]
1	**2a**	0	Ph	**3a**	72	*trans*
2	**2b**	0	4-Br–C_6H_4	**3b**	34	*trans*
3	**2c**	0	4-OMe-C_6H_4	**3c**	69	*trans*
4	**2d**	0	2-Furyl	**3d**	63	*trans*
5	**2e**	0	CO_2Et	**3e**	38	99.5/0.5
6	**2f**	0	*i*-Pr	**3f**	63	99.5/0.5
7	**2g**	1	Ph	**3g**	71	*trans*
8	**2h**	1	4-Br–C_6H_4	**3h**	25	*trans*
9	**2i**	1	4-MeO–C_6H_4	**3i**	74	*trans*
10	**2j**	1	2-Furyl	**3j**	61	*trans*
11	**2k**	1	CO_2Et	**3k**	32	99.5/0.5
12	**2l**	1	*i*-Pr	**3l**	68	*trans*
13	**2m**	2	Ph	**3m**	20	99.5/0.5
14	**2n**	2	CH_2CH_2–C_6H_5	**3n**	19	99.5/0.5

[a] All yields are isolated yields after purification by column chromatography.
[b] Determined by HPLC.

Next, we investigated the radical cyclization reaction of a variety of substituted 2,3-dihydro-4-pyridones **2**. Recently, Ishibashi has reported a simple access to oxindoles via the intramolecular cyclization reaction of in situ generated aryl radicals to enaminones.[24] Working from these results, we found that a mixture of Bu_3SnH and a catalytic amount of AIBN promoted the radical cyclization to give the corresponding benzoquinolizidines and benzoindolizidines in moderate yields and with high diastereoselectivity (Table 3). The radical cyclization needed a longer reaction time and higher temperature. However, the stereochemical assignment of radical cyclization products was the same as observed for the anionic process.

The stereochemical outcome of these cyclizations is rationalized in Scheme 2. Similar stereochemical preferences in Michael additions have been reported previously.[25] We postulate that in the transition state the nitrogen lone pair occupies an axial position while the R group prefers the equatorial position. The cyclization proceeds preferably *anti* to the R group, providing the adduct exhibiting the *trans* arrangement of protons, which was confirmed by X-ray analysis.[26] This rule applies to both the anionic and the radical cyclization (Scheme 2).

Table 3
The scope of radical cyclization



2a-l **3a-l**

Entry	Substrate	n	R	Product	Yield (%)[a]	*trans/cis*[b]
1	**2a**	0	Ph	**3a**	53	*trans*
2	**2b**	0	4-Br–C_6H_4	**3b**	34	*trans*
3	**2c**	0	4-OMe-C_6H_4	**3c**	42	*trans*
4	**2d**	0	2-Furyl	**3d**	53	*trans*
5	**2e**	0	CO_2Et	**3e**	38	99.5/0.5
6	**2f**	0	*i*-Pr	**3f**	32	99.5/0.5
7	**2g**	1	Ph	**3g**	75	*trans*
8	**2h**	1	4-Br–C_6H_4	**3h**	20	*trans*
9	**2i**	1	4-MeO–C_6H_4	**3i**	34	*trans*
10	**2j**	1	2-Furyl	**3j**	34	*trans*
11	**2k**	1	CO_2Et	**3k**	25	99.5/0.5
12	**2l**	1	*i*-Pr	**3l**	42	*trans*

[a] All yields are isolated yields after purification by column chromatography.
[b] Determined by HPLC.

3. Conclusion

In summary, a novel method for the stereoselective construction of benzoindolizidine and benzoquinolizidine scaffolds has been described. The structure and relative stereochemistry of the cyclization products was confirmed by NMR and X-ray analysis. The generality of this method was further tested with different ring sizes, where dihydropyridones with a bromoaryl function located in the side-chain underwent cyclization to give 6,7,6-fused ring systems.

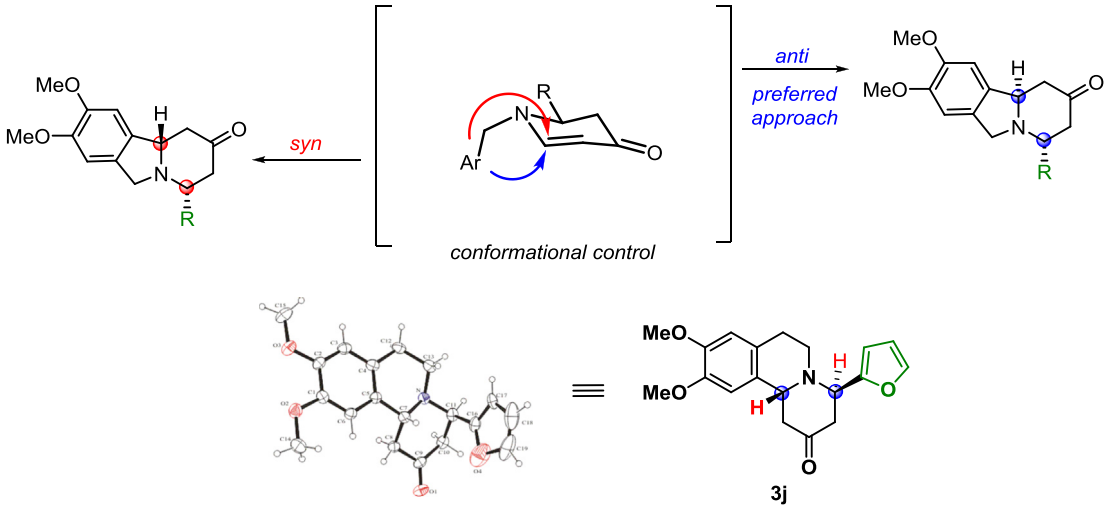
4. Experimental section

4.1. General

Column chromatography was performed on Merck silica gel, grade 60 (230–400 mesh). TLC plates were visualized with UV and/or staining with phosphomolybdic acid. ^1H and ^{13}C NMR spectra were recorded on Bruker AM500 (500 MHz) and Varian (400 MHz) spectrometers and the chemical shifts are reported in parts per million with TMS as an internal standard (δ=0 ppm). Signal multiplicities are abbreviated as follows: s–singlet, d–doublet, t–triplet, q–quartet, m–multiplet. Infrared (IR) spectra were recorded using Perkin Elmer FTIR-1600 infrared spectrophotometer. High-resolution mass spectra were recorded using a Mariner PerSeptive Biosystems mass spectrometer with time-of-flight (TOF) detector. Unless stated otherwise, all reagents and solvents were purchased from commercial sources and used without additional purification.

4.2. General procedure for enaminone 2a–m synthesis via the Lewis acid-catalyzed one-pot aza-Diels–Alder reaction of Danishefsky's diene with imines generated in situ

To a solution of amine **1a–c** (0.5 mmol) in CH_2Cl_2 and molecular sieves 4 Å (50 mg) the corresponding aldehyde (0.5 mmol) was added dropwise. The flask was shielded from light with aluminum foil and



Scheme 2. Stereochemical model of the cyclization and the crystal structure of **3j**.

the reaction mixture was stirred over 8 h. The solution was filtered through a pad of Celite and evaporated under reduced pressure. The obtained crude imine was dissolved in dry MeCN (4 ml) without purification and cooled to 0 °C. $Yb(OTf)_3$ (31 mg, 0.05 mmol, 10 mol %) and Danishefsky's diene (117 μl, 0.6 mmol, 1.2 equiv) were added under argon. The reaction mixture was warmed to rt and stirred over 6 h (TLC monitoring). The reaction was quenched by saturated aqueous $NaHCO_3$ (5 ml). After phase separation, the organic layer was washed three times with CH_2Cl_2 (10 ml), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography to give the corresponding enaminones (**2a**–**m**).

*4.2.1. 1-(2-Bromo-4,5-dimethoxybenzyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one (**2a**).* Colorless solid; mp 47–48 °C; isolated yield 175 mg (87%); R_f 0.35 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 3H), 7.29–7.26 (m, 3H), 7.02 (s, 1H), 6.60 (s, 1H), 5.07 (d, J=7.7 Hz, 1H), 4.55 (t, J=7.0 Hz, 1H), 4.35–4.29 (m, 2H), 3.68 (s, 3H), 3.81 (s, 3H), 2.93 (dd, J=16.5, 7.4 Hz, 1H), 2.66 (dd, J=16.5, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.9, 153.9, 149.6, 148.7, 138.6, 129.1, 128.3, 126.9, 116.0, 114.5, 112.8, 98.5, 60.9, 57.2, 56.2, 56.1, 43.4; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{20}O_3N^{79}Br$ [M+] 401.0632 found 401.0645; IR (film, CH_2Cl_2) ν_{max}: 1638, 1592, 1507, 1439, 1262, 1030 cm^{-1}.

*4.2.2. 1-(2-Bromo-4,5-dimethoxybenzyl)-2-(4-bromophenyl)-2,3-dihydropyridin-4(1H)-one (**2b**).* Colorless solid; mp 107–108 °C; isolated yield 202 mg (84%); R_f 0.38 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.47 (m, 2H), 7.26 (d, J=7.7 Hz, 1H), 7.16–7.14 (m, 2H), 7.02 (s, 1H), 6.60 (s, 1H), 5.07 (d, J=7.7 Hz, 1H), 4.49 (t, J=7.0 Hz, 1H), 4.34–4.29 (m, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 2.93 (dd, J=16.4, 7.5 Hz, 1H), 2.59 (dd, J=16.4, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 153.6, 149.7, 148.7, 137.6, 132.2, 128.6, 126.2, 122.2, 116.1, 114.5, 112.7, 98.7, 60.2, 57.3, 56.3, 56.2, 43.24; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{19}O_3N^{79}Br_2$ [M+] 478.9732 found 478.9718; IR (film, CH_2Cl_2) ν_{max}: 1639, 1588, 1571, 1507, 1379, 1262, 1221, 1205, 1166 cm^{-1}. **(2b*):** isolated yield 51%; HPLC: Chiralpak® OD-H, 100% *i*-PrOH, flow 0.25 ml/min, UV 325 nm, R_t 49.8 min(minor), 60.9 min(major).

*4.2.3. 1-(2-Bromo-4,5-dimethoxybenzyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (**2c**).* Yellow solid; mp 92–94 °C; isolated yield 162 mg (75%); R_f 0.33 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–7.18 (m, 3H), 7.02 (s, 1H), 6.89–6.85 (m, 2H), 6.60 (s, 1H), 5.06 (d, J=7.7 Hz, 1H), 4.49 (m, 1H), 4.30–4.23 (m, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 2.88 (dd, J=16.4, 7.2 Hz, 1H), 2.65 (dd, J=16.4, 7.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 159.6, 153.7, 149.5, 148.7, 130.6, 128.2, 126.7, 116.0, 114.4, 114.3, 112.7, 98.4, 60.5, 56.9, 56.2, 56.1, 55.3, 43.7; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{22}NO_4^{79}Br$ [M+] 431.0732 found 431.0751; IR (film, CH_2Cl_2) ν_{max}: 1639, 1591, 1510, 1379, 1259, 1165, 1030, 771 cm^{-1}.

*4.2.4. 1-(2-Bromo-4,5-dimethoxybenzyl)-2-(furan-2-yl)-2,3-dihydropyridin-4(1H)-one (**2d**).* Colorless oil; isolated yield 137 mg (70%); R_f 0.36 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 1H), 7.07 (s, 1H), 7.02 (d, J=7.7 Hz, 1H) 6.8 (s, 1H), 6.3 (m, 1H), 6.29 (m, 1H), 5.03 (dd, J=7.7, 0.7 Hz, 1H), 4.64 (dd, J=7.0, 4.6 Hz, 1H), 4.53 (d, J=14.9 Hz, 1H), 4.36 (d, J=14.9 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.88 (dd, J=16.4, 7.0 Hz, 1H), 2.72 (ddd, J=16.4, 4.6, 0.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 152.2, 151.3, 149.7, 148.7, 142.6, 126.9, 116.2, 114.5, 112.9, 110.4, 108.6, 98.4, 57.6, 56.3, 56.2, 54.0, 39.8; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{18}NO_4^{79}Br$ [M+] 391.0419 found 391.0431; IR (film, CH_2Cl_2) ν_{max}: 1640, 1587, 1506, 1439, 1377, 1262, 1207, 1166, 1029, 741 cm^{-1}.

*4.2.5. Ethyl 1-(2-bromo-4,5-dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (**2e**).* Colorless oil; isolated yield 163 mg (82%); R_f 0.27 (60% acetone in hexanes); chromatography (50% acetone in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, J=7.7, 1.2 Hz, 1H), 7.07 (s, 1H), 6.82 (s, 1H), 5.02 (d, J=7.7 Hz, 1H), 4.53–4.45 (m, 2H), 4.23 (q, J=7.2 Hz, 2H), 4.09 (ddd, J=6.2, 3.9, 1.1 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.83–2.80 (m, 2H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 169.9, 153.2, 149.9, 148.8, 126.5, 116.1, 114.9, 113.3, 99.5, 62.1, 58.8, 58.7, 56.3, 56.2, 38.0, 14.1; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{20}NO_5^{79}Br$ [M+] 397.0525 found 397.0542; IR (film, CH_2Cl_2) ν_{max}: 1734, 1642, 1590, 1507, 1378, 1262, 1166, 1027, 801 cm^{-1}.

*4.2.6. 1-(2-Bromo-4,5-dimethoxybenzyl)-2-isopropyl-2,3-dihydropyridin-4(1H)-one (**2f**).* Colorless oil; isolated yield 136 mg (74%); R_f 0.35 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.08–7.05 (m, 2H), 6.79 (s, 1H), 4.92 (dd, J=7.4, 0.7 Hz, 1H), 4.56, (d, J=15.3 Hz, 1H), 4.38 (d, J=15.3 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.26 (m, 1H), 2.69–2.64

(m, 1H), 2.42 (dd, *J*=16.7, 2.4 Hz, 1H), 2.29 (m, 1H), 0.98 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 153.0, 149.6, 148.9, 127.6, 116.0, 113.8, 111.8, 97.5, 61.8, 58.1, 56.3, 56.2, 36.5, 29.2, 19.7, 18.0; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{22}NO_3{}^{79}Br$ [M+] 367.0783 found 367.0801; IR (film, CH_2Cl_2) ν_{max} 1636, 1588, 1507, 1261, 1207, 1164, 1030 cm^{-1}.

*4.2.7. 1-(2-Bromo-4,5-dimethoxyphenethyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one (**2g**).* Colorless oil; isolated yield 169 mg (81%); R_f 0.29 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 7.06 (d, *J*=7.7 Hz, 1H), 6.97 (s, 1H), 6.48 (s, 1H), 5.0 (d, *J*=7.7 Hz, 1H), 4.62 (dd, *J*=8.7, 7.0 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.34–3.25 (m, 2H), 2.89–2.76 (m, 2H), 2.79–2.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 153.8, 148.6, 148.5, 138.6, 129.0, 128.9, 128.3, 127.1, 115.6, 114.1, 113.3, 98.7, 61.6, 56.14, 56.08, 53.2, 43.8, 35.5; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{22}O_3NO^{79}Br$ [M+] 415.0783 found 415.0796; IR (film, CH_2Cl_2) ν_{max} 1635, 1591, 1578, 1509, 1439, 1383, 1257, 1218, 1165, 1033, 792, 701 cm^{-1}.

*4.2.8. 1-(2-Bromo-4,5-dimethoxyphenethyl)-2-(4-bromophenyl)-2,3-dihydropyridin-4(1H)-one (**2h**).* Colorless oil; isolated yield 215 mg (87%); R_f 0.27 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H), 7.19–7.17 (m, 2H), 7.07 (d, *J*=7.7 Hz, 1H), 6.98 (s, 1H), 6.51 (s, 1H), 5.03 (d, *J*=7.7 Hz, 1H), 4.65–4.45 (m, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.34–3.30 (m, 2H), 2.95–2.90 (m, 2H), 2.83 (dd, *J*=15.6, 7.6 Hz, 1H), 2.65 (dd, *J*=15.6, 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 153.7, 148.7, 148.6, 137.7, 132.2, 128.7, 128.6, 122.3, 115.7, 114.2, 113.2, 98.9, 61.0, 56.2, 56.1, 53.3, 43.5, 35.6; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{21}NO_3{}^{79}Br_2$ [M+] 492.9888 found 492.9879; IR (film, CH_2Cl_2) ν_{max} 1635, 1586, 1509, 1439, 1383, 1258, 1219, 1165, 1035, 1010, 791 cm^{-1}. **(2h*):** isolated yield 48%; HPLC: Chiralpak® OD-H, 100% *i*-PrOH, flow 0.25 ml/min, UV 325 nm, R_t 53.6 min (minor), 65.9 min (major).

*4.2.9. 1-(2-Bromo-4,5-dimethoxyphenethyl)-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (**2i**).* Colorless oil; isolated yield 165 mg (74%); R_f 0.31 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 7.08 (d, *J*=7.6 Hz, 1H), 7.02 (s, 1H), 6.96–6.91 (m, 2H), 6.51 (s, 1H), 5.04 (d, *J*=7.6 Hz, 1H), 4.62 (dd, *J*=9.0, 7.0 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.35–3.28 (m, 2H), 2.91–2.83 (m, 2H), 2.77–2.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 159.6, 153.8, 148.52, 148.46, 130.7, 129.0, 128.4, 115.7, 114.3, 114.1, 113.4, 98.6, 61.1, 56.15, 56.10, 55.3, 53.0, 44.0, 35.5; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{24}NO_4{}^{79}Br$ [M+] 445.0889 found 445.0881.; IR (film, CH_2Cl_2) ν_{max} 1635, 1586, 1509, 1439, 1383, 1258, 1219, 1165, 1035, 1010, 791 cm^{-1}.

*4.2.10. 1-(2-Bromo-4,5-dimethoxyphenethyl)-2-(furan-2-yl)-2,3-dihydropyridin-4(1H)-one (**2j**).* Colorless oil; isolated yield 134 mg (66%); R_f 0.34 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J*=1.8, 0.8 Hz, 1H), 7.01 (s, 1H), 6.86 (d, *J*=7.5 Hz, 1H) 6.6 (s, 1H), 6.35 (dd, *J*=3.3, 1.8 Hz, 1H), 6.32 (dd, *J*=3.3, 0.8 Hz, 1H), 4.98 (d, *J*=7.5 Hz, 1H), 4.69–4.64 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.48–3.43 (m, 2H), 2.96–2.90 (m, 2H), 2.80–2.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 152.7, 151.1, 148.7, 148.5, 142.7, 128.8, 115.7, 114.2, 113.5, 110.4, 108.7, 98.1, 56.2, 56.1, 54.6, 53.9, 39.9, 36.1; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{20}NO_4{}^{79}Br$ [M+] 405.0555 found 405.0545; IR (film, CH_2Cl_2) ν_{max} 1635, 1583, 1509, 1439, 1383, 1258, 1219, 1165, 1033, 771 cm^{-1}.

*4.2.11. Ethyl 1-(2-bromo-4,5-dimethoxyphenethyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (**2k**).* Colorless oil; isolated yield 134 mg (65%); R_f 0.36 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.98 (d, *J*=7.5 Hz, 1H), 6.70 (s, 1H), 4.96 (d, *J*=7.5 Hz, 1H), 4.21 (q, *J*=7.2 Hz, 2H), 4.09–4.05 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.59 (dd, *J*=14.3, 7.0 Hz, 1H), 3.46 (dd, *J*=14.3, 6.9 Hz, 1H), 3.00–2.96 (m, 2H), 2.81–2.80 (m, 2H), 1.27 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 170.0, 153.6, 148.7, 148.6, 128.7, 115.7, 114.3, 113.3, 99.0, 62.1, 59.6, 56.2, 55.4, 38.0, 36.0, 29.2, 14.1; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{22}NO_5{}^{79}Br$ [M+] 411.0681 found 411.0697; IR (film, CH_2Cl_2) ν_{max} 1735, 1637, 1589, 1510, 1463, 1384, 1258, 1218, 1188, 1166, 1027, 791 cm^{-1}.

*4.2.12. 1-(2-Bromo-4,5-dimethoxyphenethyl)-2-isopropyl-2,3-dihydropyridin-4(1H)-one (**2l**).* Colorless oil; isolated yield 134 mg (70%); R_f 0.28 (50% acetone in hexanes); chromatography (40% acetone in hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.89 (d, *J*=6.5 Hz, 1H), 6.67 (s, 1H), 4.83, (d, *J*=6.5 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.51–3.44 (m, 2H), 3.29–3.18 (m, 1H), 2.94–2.90 (m, 2H), 2.60 (dd, *J*=16.6, 7.3 Hz, 1H), 2.37 (dd, *J*=16.6, 3.7 Hz, 1H), 2.30–2.10 (m, 1H), 0.96–0.89 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.7, 152.6, 148.7, 148.5, 128.7, 115.8, 114.1, 113.7, 97.3, 62.3, 56.1, 54.6, 52.8, 37.0, 36.9, 29.0, 19.7, 18.1; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{24}NO_3{}^{79}Br$ [M+] 381.0936 found 381.0955; IR (film, CH_2Cl_2) ν_{max} 1632, 1585, 1509, 1464, 1385, 1259, 1220, 1165, 1032, 790, 731 cm^{-1}.

*4.2.13. 1-(3-(2-Bromo-4,5-dimethoxyphenyl)propyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one (**2m**).* Colorless oil; isolated yield 151 mg (70%); R_f 0.42 (20% acetone in hexanes); chromatography (30% acetone in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 7.19 (d, *J*=7.6 Hz, 1H), 6.98 (s, 1H), 6.59 (s, 1H), 5.08 (d, *J*=7.6 Hz, 1H), 4.66 (dd, *J*=7.8, 7.3 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.19–3.13 (m, 2H), 2.90 (dd, *J*=16.4, 7.5 Hz, 1H), 2.71(dd, *J*=16.4, 7.5 Hz, 1H), 2.67–2.61 (m, 1H), 2.58–2.49 (m, 1H), 1.87–1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 154.2, 148.5, 148.1, 138.5, 131.8, 129.0, 128.3, 127.0, 115.7, 114.0, 112.7, 98.4, 61.0, 56.2, 56.1, 53.1 43.6, 33.0, 29.1; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{24}NO_3{}^{79}Br$ [M+] 429.0940 found 429.0957; IR (film, CH_2Cl_2) ν_{max} 1636, 1592, 1578, 1508, 1442, 1383, 1257, 1216, 1164, 1030, 701 cm^{-1}.

*4.2.14. 1-(3-(2-Bromo-4,5-dimethoxyphenyl)propyl)-2-phenethyl-2,3-dihydropyridin-4(1H)-one (**2n**).* Colorless oil; isolated yield 167 mg (73%); R_f 0.38 (20% acetone in hexanes); chromatography (30% acetone in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (m, 3H), 7.23–7.13 (m, 2H), 7.0 (s, 1H), 6.94 (d, *J*=7.5 Hz, 1H), 6.65 (s, 1H), 4.94 (d, *J*=7.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.51–3.46 (m, 1H), 3.30–3.14 (m, 2H), 2.82 (dd, *J*=16.5, 6.8 Hz, 1H), 2.78–2.58 (m, 3H), 2.57–2.42 (m, 2H), 2.21–2.08 (m, 1H), 1.95–1.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 152.4, 148.5, 148.2, 140.7, 131.8, 128.6, 128.2, 126.2, 115.7, 113.9, 112.8, 97.0, 56.2, 56.1, 55.6, 53.4, 39.1, 32.9, 31.6, 30.0, 29.8; HRMS (ESI-TOF) *m/z* calcd for $C_{24}H_{28}NO_3{}^{79}Br$ [M+] 457.1253 found 457.1264; IR (film, CH_2Cl_2) ν_{max} 1633, 1584, 1508, 1454, 1441, 1383, 1256, 1216, 1164, 1030, 752, 700 cm^{-1}.

4.3. General procedure for anionic cyclization

To a solution of enaminone **2a**–**m** (0.2 mmol) in dry THF (5 ml) HMPA (87 ul, 0.5 mmol, 2.5 equiv) and *t*-BuLi 1.7 M (in pentane) (295 ul, 0.5 mmol, 2.5 equiv) were added under argon at −78 °C. The reaction mixture was stirred at −78 °C for 2 h (TLC monitoring). After the substrate was consumed, the reaction mixture was warmed to −10 °C and quenched with H_2O (10 ml). After phase separation, the organic layer was washed three times with CH_2Cl_2 (10 ml), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography to give the corresponding adducts (**3a**–**m**).

4.4. General procedure for radical cyclization

To a solution of enaminone **2a**–**l** (0.1 mmol) in benzene (15 ml) tributyltin hydride (Bu_3SnH) (32 ul, 0.12 mmol 1.2 equiv) and AIBN (3.2 mg, 0.02 mmol, 20 mol %) were added under argon. The reaction mixture was stirred at 80 °C for 16 h (TLC monitoring). After the substrate was consumed, the reaction mixture was evaporated under reduced pressure. The crude product was diluted with acetonitrile (10 ml), and washed three times with hexanes. The acetonitrile phase was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography to give the corresponding adducts (**3a**–**l**).

4.4.1. (4R,10bR*)-8,9-Dimethoxy-4-phenyl-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-2(6H)-one (**3a**).* Yellow solid; mp 101–103 °C; isolated yield 47 mg (72%) for anionic cyclization, 17 mg (53%) for radical cyclization; R_f 0.24 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ: 7.30–7.14 (m, 5H), 6.39 (s, 1H), 6.34 (s, 1H), 4.62–4.56 (m, 1H), 4.00 (d, J=12.7 Hz, 1H), 3.87 (dd, J=11.2, 3.5 Hz, 1H), 3.58–3.53 (m, 1H), 3.41 (m, 6H), 2.58 (dd, J=16.7, 11.2 Hz, 1H), 2.50–2.44 (m, 2H), 2.34 (dd, J=16,1, 12.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.0, 150.3, 150.0, 143.4, 134.2, 130.7, 128.9, 128.8, 107.1, 106.4, 96.4, 62.8, 61.7, 58.7, 56.0, 55.9, 48.1, 44.8; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{21}NO_3$ [M+] 323.1523 found 323.1511; IR (film, CH_2Cl_2) ν_{max} 1718, 1507, 1454, 1356, 1224, 1190, 1111, 756, 702 cm^{-1}.

4.4.2. (4R,10bR*)-4-(4-Bromophenyl)-8,9-dimethoxy-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-2(6H)-one (**3b**).* Yellow solid; mp 136–137 °C; isolated yield 27 mg (34%) for anionic cyclization, 14 mg (34%) for radical cyclization; R_f 0.28 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.34 (d, J=8.4 Hz, 2H), 7.16–7.13 (s, 2H), 6.94 (d, J=8.3 Hz, 2H), 6.42 (s, 1H), 6.34 (s, 1H), 4.44 (t, J=5.0 Hz, 1H), 3.92 (m, 1H), 3.47–3.43 (m, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 2.48–2.38 (m, 2H), 2.35–2.25 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.6, 150.4, 150.1, 142.4, 134.0, 132.0, 130.5, 129.0, 121.4, 107.0, 106.4, 62.2, 61.7, 58.6, 56.0, 55.9, 47.8, 44.7; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{20}NO_3{}^{79}Br$ [M+] 401.0634 found 401.0623; IR (film, CH_2Cl_2) ν_{max} 1719, 1508, 1325, 1224, 1191, 1112, 1009, 839 cm^{-1}.

4.4.3. (4R,10bR*)-8,9-Dimethoxy-4-(4-methoxyphenyl)-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-2(6H)-one (**3c**).* Orange solid; mp 122–124 °C; isolated yield 49 mg (69%) for anionic cyclization, 15 mg (42%) for radical cyclization; R_f 0.32 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ: 7.34 (d, J=8.6 Hz, 2H), 6.92 (d, J=8.6 Hz, 2H), 6.73–6.66 (m, 2H), 4.48 (t, J=5.0 Hz, 1H), 3.88–3.80 (m, 1H), 3.49–3.45 (m, 1H), 3.45 (s, 3H), 3.42–3.39 (m, 6H), 3.32 (dd, J=12.3, 3.2 Hz, 1H), 2.99 (d, J=13.6 Hz, 1H), 2.75–2.58 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 205.1, 154.7, 152.7, 147.7, 132.1, 131.9, 129.8, 128.8, 114.7, 108.4, 105.1, 67.6, 65.2, 59.7, 55.1, 52.3, 52.7, 48.0, 42.7; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{23}NO_4$ [M+] 353.1632 found 353.1621; IR (film, CH_2Cl_2) ν_{max} 1715, 1511, 1464, 1306, 1247, 1224, 1175, 1112, 1033, 839 cm^{-1}.

4.4.4. (4R,10bR*)-4-(Furan-2-yl)-8,9-dimethoxy-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-2(6H)-one (**3d**).* Dark brown oil; isolated yield 39 mg (63%) for anionic cyclization, 17 mg (53%) for radical cyclization; R_f 0.35 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ: 7.06 (dd, J=1.8, 0.8 Hz, 1H), 6.48 (s, 1H), 6.30 (s, 1H), 6.12 (m, 1H), 6.05 (dd, J=3.2, 1.8 Hz, 1H), 4.23–4.18 (m, 2H), 4.09 (dd, J=11.8, 2.2 Hz, 1H), 3.89 (dd, J=11.8, 2.2 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 2.68–2.63 (m, 2H), 2.58 (dd, J=15.3, 6.2 Hz, 1H), 2.29 (dd, J=14.4, 11.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ: 205.5, 154.6, 150.0, 149.9, 142.2, 134.8, 131.3, 110.3, 108.3, 107.5, 106.1, 60.4, 56.1, 56.0, 55.6, 54.0, 46.3, 44.1; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{19}NO_4$ [M+] 313.1312 found 313.1325; IR (film, CH_2Cl_2) ν_{max} 1712, 1505, 1465, 1366, 1320, 1217, 1188, 1112, 1018, 747 cm^{-1}.

4.4.5. (4R,10bR*)-Ethyl 8,9-dimethoxy-2-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindole-4-carboxylate (**3e**).* Yellow oil; isolated yield 24 mg (38%) for anionic cyclization, 12 mg (38%) for radical cyclization; R_f 0.29 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ: 6.50 (s, 1H), 6.34 (s, 1H), 4.64 (dd, J=11.4, 2.6 Hz, 1H), 4.27 (dd, J=11.5, 2.5 Hz, 1H), 3.94–3.88 (m, 3H), 3.74 (dd, J=6.8, 3.6 Hz, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 2.70 (dd, J=14.2, 3.1 Hz, 1H), 2.63 (dd, J=15.2, 3.5 Hz, 1H); 2.39 (dd, J=15.2, 6.8 Hz, 1H); 2.21 (dd, J=14.2, 11.5 Hz, 1H), 0.58 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 204.2, 170.9, 150.2, 150.1, 134.9, 131.0, 107.4, 106.0, 61.0, 60.6, 58.8, 55.9, 55.7, 46.3, 45.0, 42.0, 14.3; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{21}NO_5$ [M+] 319.142 found 319.141; IR (film, CH_2Cl_2) ν_{max} 1726, 1689, 1499, 1292, 1198, 1122, 1027 cm^{-1}.

4.4.6. (4R,10bR*)-4-Isopropyl-8,9-dimethoxy-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-2(6H)-one (**3f**).* Yellow oil; isolated yield 36 mg (63%) for anionic cyclization, 9 mg (32%) for radical cyclization; R_f 0.33 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ: 6.54 (s, 1H), 6.38 (s, 1H), 4.46 (dt, J=11.9, 3.4 Hz, 1H), 4.14 (d, J=12.1 Hz, 1H), 3.72 (ddd, J=12.1, 3.4, 0.7 Hz, 1H), 3.49 (s, 3H), 3.47 (s, 3H), 2.71–2.68 (m, 1H), 2.35 (dd, J=15.5, 3.5 Hz, 1H), 2.28 (d, J=2.4 Hz, 2H), 2.13 (dd, J=15.5, 11.9 Hz, 1H), 1.74 (m, 1H), 0.92 (d, J=6.8 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 208.0, 150.1, 149.9, 135.5, 130.6, 107.3, 106.4, 64.3, 62.2, 58.2, 56.1, 56.0, 45.2, 39.1, 30.8, 19.4, 17.2; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{23}NO_3$ [M+] 289.168 found 289.168; IR (film, CH_2Cl_2) ν_{max} 1716, 1506, 1351, 1322, 1222, 1190, 1113, 1002 cm^{-1}.

4.4.7. (4R,11bR*)-9,10-Dimethoxy-4-phenyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (**3g**).* Colorless solid; mp 139–141 °C; isolated yield 48 mg (71%) for anionic cyclization, 25 mg (75%) for radical cyclization; R_f 0.36 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35–7.29 (m, 5H), 6.60 (s, 1H), 6.47 (s, 1H), 4.54 (t, J=5.1 Hz, 1H), 4.07 (dd, J=8.9, 4.9 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.28–3.24 (m, 1H), 2.95–2.80 (m, 5H), 2.78 (ddd, J=15.0, 4.1, 1.1 Hz, 1H), 2.71 (dd, J=14.8, 9.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.0, 152.3, 147.4, 139.5, 128.7, 128.3, 128.1, 127.5, 126.0, 111.5, 108.9, 96.9 63.9, 55.9, 54.2, 46.9, 46.5, 43.6, 29.7 28.7; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{23}NO_3$ [M+] 337.1678 found 337.1695; IR (film, CH_2Cl_2) ν_{max} 1706, 1610, 1517, 1451, 1357, 1256, 1232, 1129, 1021, 769, 702 cm^{-1}.

4.4.8. (4R,11bR*)-4-(4-Bromophenyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (**3h**).* Colorless solid; mp 128–129 °C; isolated yield 21 mg (25%) for anionic cyclization, 8 mg (20%) for radical cyclization; R_f 0.31 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.48–7.44 (m, 2H), 7.28–7.24 (m, 2H), 6.60 (s, 1H), 6.45 (s, 1H), 4.14 (t, J=5.0 Hz, 1H), 4.08 (dd, J=14.6, 7.1 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.30–3.24 (m, 1H), 2.89–2.84 (m, 4H), 2.75–2.61 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 206.1, 150.4, 149.6, 142.6, 135.5, 133.2, 128.7, 128.2, 122.3, 110.2, 108.9, 63.9, 58.9, 55.9, 52.2, 46.9, 45.1, 41.5, 30.2; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{22}{}^{79}BrNO_3$ [M+] 415,0785 found 415,0742; IR (film, CH_2Cl_2) ν_{max} 1716, 1510, 1337, 1256, 1232, 1189, 1131, 851 cm^{-1}.

4.4.9. (4R,11bR*)-9,10-Dimethoxy-4-(4-methoxyphenyl)-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (**3i**).* Colorless

solid; mp 123–125 °C; isolated yield 54 mg (74%) for anionic cyclization, 12 mg (34%) for radical cyclization; R_f 0.28 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.30–7.25 (m, 2H), 6.89–6.85 (m, 2H), 6.61 (s, 1H), 6.48 (s, 1H), 4.44 (t, J=5.0 Hz, 1H), 4.08 (dd, J=9.5, 4.9 Hz, 1H), 3.85–3.79 (m, 10H), 3.29–3.23 (m, 1H), 2.95–2.70 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 209.1, 158.8, 147.6, 147.4, 131.6, 129.2, 128.8, 126.0, 113.6, 111.5, 108.9, 63.4, 55.8, 55.2, 54.0, 46.9, 46.5, 43.7, 29.7, 28.7; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{25}NO_4$ [M+] 367.1784 found 367.17957; IR (film, CH_2Cl_2) ν_{max} 1707, 1463, 830 cm^{-1}.

4.4.10. (4R,11bR*)-4-(Furan-2-yl)-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (**3j**).* Colorless solid; mp 109–111 °C; isolated yield 40 mg (61%) for anionic cyclization, 11 mg (34%) for radical cyclization; R_f 0.33 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ: 7.04 (dd, J=1.9, 0.8 Hz, 1H), 6.40 (s, 1H), 6.19 (s, 1H), 6.16 (m, 1H), 6.03 (dd, J=3.3, 1.8 Hz, 1H), 4.10 (t, J=4.6 Hz, 1H), 3.87 (dd, J=11.2, 3.3 Hz, 1H), 3.43 (s, 3H), 3.31 (s, 3H), 2.97–2.85 (m, 3H), 2.71–2.65 (m, 1H), 2.59–2.57 (m, 2H), 2.52–2.46 (m, 1H), 2.33 (dd, J=14.5, 11.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ: 205.8, 153.6, 148.8, 148.8, 142.2, 129.8, 126.4, 112.7, 110.2, 109.7, 109.5, 59.2, 55.7, 55.7, 54.6, 49.0, 48.1, 43.7, 30.2; HRMS (ESI-TOF) m/z calcd for $C_{19}H_{22}NO_4$ [M+H$^+$] 328.1543 found 328.1557; IR (film, CH_2Cl_2) ν_{max} 1713, 1465, 743 cm^{-1}.

4.4.11. (4R,11bR*)-Ethyl-9,10-dimethoxy-2-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline-4-carboxylate (**3k**).* Yellow oil; isolated yield 21 mg (32%) for anionic cyclization, 8 mg (25%) for radical cyclization; R_f 0.35 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.6 (s, 1H), 6.53 (s, 1H), 4.18–4.14 (m, 3H), 4.01 (dd, J=6.3, 1.7 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.17–2.62 (m, 7H), 2.39 (dd, J=14.9, 11.2 Hz, 1H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 201.5, 163.5, 148.6, 144.8, 124.3, 123.1, 106.1, 106.0, 61.7, 60.6, 59.2, 57.0, 53.9, 51.7, 46.7, 45.3, 42.5, 12.1; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{23}NO_5$ [M+] 333.1576 found 333.1589; IR (film, CH_2Cl_2) ν_{max} 1724, 1465, 818 cm^{-1}.

4.4.12. (4R,11bR*)-4-Isopropyl-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (**3l**).* Yellow oil; isolated yield 41 mg (68%) for anionic cyclization, 13 mg (42%) for radical cyclization; R_f 0.34 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.62 (s, 1H), 6.50 (s, 1H), 4.19 (dd, J=11.5, 3.3 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.35–3.29 (m, 1H), 3.13–3.05 (m, 1H), 2.86–2.79 (m, 2H), 2.75–2.60 (m, 3H), 2.54–2.48 (m, 1H), 2.44 (dd, J=14.0, 3.4 Hz, 1H), 1.72 (ddd, J=16.7, 12.9, 6.5 Hz, 1H), 0.97 (d, J=6.9 Hz, 3H), 0.95 (d, J=6.9 Hz, 3H); NMR (50 MHz, $CDCl_3$) δ: 210.4, 155.2, 150.9, 133.2, 134.5, 101.2, 100.4, 67.2, 65.2, 59.4, 57.1, 55.8, 44.2, 40.1, 32.8, 28.6, 18.3, 16.9; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{25}NO_3$ [M+] 303.1834 found 303.1823; IR (film, CH_2Cl_2) ν_{max} 1706, 1465, 732 cm^{-1}.

4.4.13. (4R,12bR*)-10,11-Dimethoxy-4-phenyl-1,3,4,7,8,12b-hexahydrobenzo[c]pyrido[1,2-a]azepin-2(6H)-one (**3m**).* Yellow oil; isolated yield 14 mg (20%) for anionic cyclization; R_f 0.27 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.22 (m, 5H), 6.76 (s, 1H), 6.72 (s, 1H), 4.86 (dd, J=5.5, 2.4 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.65 (dd, J=9.5, 4.0 Hz, 1H), 3.16–2.94 (m, 5H), 2.74 (dd, J=14.6, 5.8 Hz, 1H), 2.61 (dd, J=16.1, 9.5 Hz, 1H), 2.51 (dd, J=16.1, 4.0 Hz, 1H), 1.51–1.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.8, 147.2, 146.3, 141.3, 135.2, 132.2, 128.6, 128.2, 127.7, 113.4, 112.4, 59.7, 57.9, 56.0, 55.8, 54.6, 50.2, 47.1, 36.2, 24.2; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{25}NO_3$ [M+] 351.1834 found 351.1824; IR (film, CH_2Cl_2) ν_{max} 1707, 1454, 705 cm^{-1}.

4.4.14. (4S,12bR*)-10,11-Dimethoxy-4-phenethyl-1,3,4,7,8,12b-hexahydrobenzo[c]pyrido[1,2-a]azepin-2(6H)-one (**3n**).* Yellow oil; isolated yield 14 mg (19%) for anionic cyclization; R_f 0.31 (50% AcOEt in hexanes); chromatography (40% AcOEt in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28–7.10 (m, 5H), 6.65 (s, 1H), 6.61 (s, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.41–3.37 (m, 1H), 3.15–2.57 (m, 6H), 2.47–2.37 (m, 2H), 2.33–2.20 (m, 2H), 1.74–1.50 (m, 1H), 1.27–1.22 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.8, 147.2, 146.5, 141.8, 132.4, 128.5, 128.3, 128.2, 126.0, 113.4, 112.0, 60.8, 56.0, 55.9, 53.0, 47.6, 46.6, 33.9, 31.8, 31.5, 29.7, 25.8; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{29}NO_3$ [M+] 379.2147 found 379.2161; IR (film, CH_2Cl_2) ν_{max} 1705, 1458, 706 cm^{-1}.

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26. Crystallographic data for the structure **3j** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1459295. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [e-mail: deposit@ccdc.cam.ac.uk].