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Enantioselective organocatalyzed cascade reactions to highly functionalized quinolizidines

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ABSTRACT

An organocatalyzed one-pot Michael addition-Pictet–Spengler sequence of β-ketoamides and α,β-unsaturated aldehydes was developed, which provided access to highly substituted indolo[2,3-α]quinolizidines and benzo[α]quinolizidines in moderate to good yields and good to excellent enantioselectivities. For aromatic α,β-unsaturated aldehydes **1a**–**j** products **10a**–**r** containing a stable enol configuration were obtained.

1. Introduction

Increased focus has recently been placed on the development of organic cascade reactions that allow the formation of several bonds, whether C–C, C–O or C–N, from simple and readily available starting materials in one process.[1] In order to provide enantioselective synthesis of highly functionalized scaffolds effectively, a number of examples of asymmetric cascade catalysis has been developed.[2,3] Among them, cascade reactions catalyzed by primary or secondary chiral amines have attracted much interest, from which a diversity of highly substituted carbocycles and heterocycles have been generated.[3,4]

Indoloquinolizidine and benzoquinolizidine skeletons are found in a number of natural alkaloids (Fig. 1). Their structural diversity and stereochemical complexity have rendered them interesting synthetic targets.[5] Traditionally, optically pure quinolizidines are prepared from the chiral pool.[6] However, this strategy often requires multi-step functional group transformations and laborious protecting group manipulations. Therefore catalytic enantioselective methods to access these compounds would be highly desired.

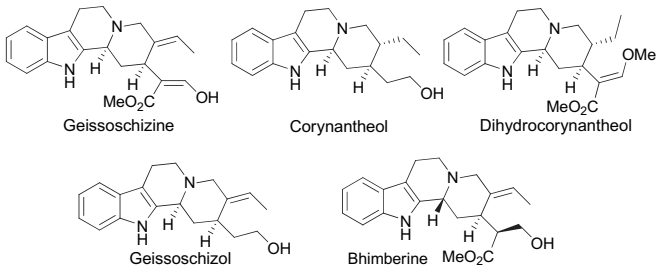

Fig. 1. Examples of indoloquinolizidine based natural alkaloids.

Although numerous asymmetric catalytic synthesis of quinolizidines have been developed recently,[7,8] relatively few utilized a cascade strategy.[8]

Recently, we and Franzén and co-workers independently reported efficient synthesis of highly functionalized quinolizidines by organocatalyzed enantioselective cascade reactions between α,β-unsaturated aldehydes and active methylene compounds, with good yield and high enantioselectivity achieved (Scheme 1).[8] To attain practical applicability to the total synthesis of natural alkaloids containing quinolizidine motifs, the development of more efficient asymmetric cascade synthesis of these structures is still highly desired.

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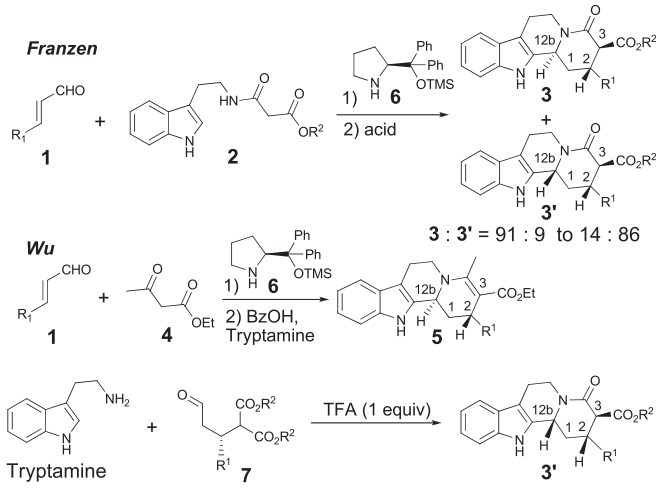
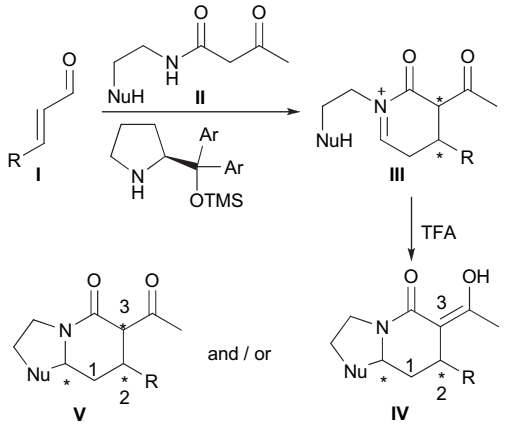


Scheme 1. Organocatalyzed asymmetric syntheses of highly substituted indoloquinolizidines.

Herein, we described a prolinol TMS ether[9] catalyzed cascade reaction of α,β-unsaturated aldehydes **I** and active methylene tethered tryptamine or homoveratrylamine **II** for the direct synthesis of indolo- or benzoquinolizidine (Scheme 2). Proceeding by conjugate addition of ketoamides **II** to α,β-unsaturated aldehydes **I** catalyzed by the prolinol ether catalyst, followed by acid-catalyzed intramolecular Pictet–Spengler cyclization via *N*-acylimminium ion **III**,[10,11] this cascade would effectively provide multi-ring heterocycles **IV** or **V** enantioselectively. Since most of the quinolizidine-based alkaloids contain an ethyl or an ethylidene group at C3, it would be convenient for further transformation with an acetyl group pre-installed using **II** as nucleophile.



Scheme 2. Concept of Michael addition-Pictet–Spengler cascade.

2. Results and discussion

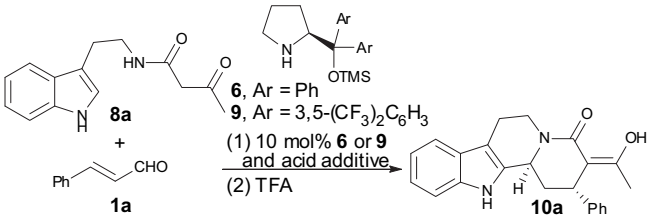
A model reaction between β-ketoamide **8a** and cinnamic aldehyde **1a** was examined under a set of reaction conditions (Table 1). The conjugate addition was conducted at 20 °C in DCM using **6** as catalyst (entry 1). After full conversion of amide **8a**, the reaction mixture was diluted with DCM, followed by addition of stoichiometric amount of TFA, and stirred at 20 °C for 30 min. Indoloquinolizidine **10a** was isolated as a single diastereomer in 45% yield and 69% ee (entry 1). It was interesting that **10a**, with phenyl group at C2 adopted a stable enol configuration and the formation of ketone tautomer was negligible.

After obtaining the initial result, a brief screen of solvents was conducted; with toluene as a solvent, higher enantioselectivity was achieved, whereas the yield was much lower (entry 2); chloroform led to both lower yield and enantioselectivity than DCM (entry 3); in solvents, such as THF and methanol almost no product was formed (entries 4, 5); DCM proved to be the best solvent in terms of yield (entry 1). Catalyst **9** with bulkier aryl substituents delivered better enantioselectivity without loss of reactivity (entry 6).

In attempts to improve the yield, a set of acid additives was next screened (entries 7–10). It was shown that the reaction gave the highest yield of the product without loss of enantioselectivity by using 4-nitrobenzoic acid as the additive (entry 8). In the presence of acid additive, the reaction time for full consumption of start material ketoamide was shortened from 30 h to 16 h (entries 7–10).

After the optimized reaction conditions were determined (entry 8, Table 1), the scope of this cascade reaction was next examined (Table 2). We first investigated the one-pot cascade sequence employing α,β-unsaturated aldehydes **1b**–**j** as electrophiles

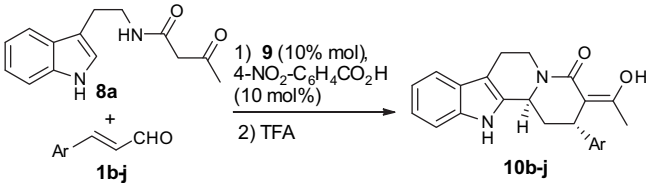
Table 1
Screening studies of cascade reaction between β-ketoamide **8a** and cinnamic aldehyde **1a**[a]



Entry	Cat	Additive	Solvent	*t* (h)	Yield (%)[b]	ee (%)[c]
1	**6**	—	DCM	30	45	69
2	**6**	—	Toluene	30	18	80
3[c]	**6**	—	$CHCl_3$	30	30	64
4	**6**	—	CH_3OH	30	—	—
5	**6**	—	THF	30	—	—
6	**9**	—	DCM	30	44	92
7	**9**	**A1**[d]	DCM	16	48	92
8	**9**	**A2**[d]	DCM	16	66	92
9	**9**	**A3**[d]	DCM	16	55	93
10	**9**	**A4**[d]	DCM	16	61	89

[a] General conditions: (step 1) **8a** (0.1 mmol), **1a** (0.15 mmol), **6** or **9** (10 mol %) and additive (10 mol %) in solvent (0.2 mL) at 20 °C; (step 2) TFA (1 equiv), solvent (0.3 mL) at 20 °C.
[b] Yield referred to isolated pure product.
[c] Enantiomeric excess was determined by chiral HPLC analysis.
[d] **A1**: BzOH; **A2**: 4-NO_2–$C_6H_4CO_2H$; **A3**: 3,5-$(NO_2)_2C_6H_3CO_2H$; **A4**: Acetic acid.

Table 2
Asymmetric cascade reaction of **8a** and α,β-unsaturated aldehydes **1b**–**j**[a]



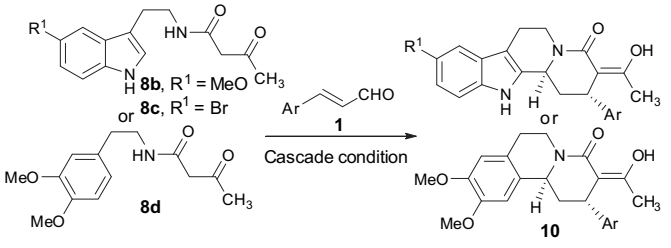
Entry	Ar, **1**	**10**	*t* (h)	Yield (%)[b]	ee (%)[c]
1	2-Br–C_6H_4, **1b**	**10b**	16	73	93
2	3-Br–C_6H_4, **1c**	**10c**	24	56	94
3	4-Br–C_6H_4, **1d**	**10d**	16	70	97
4	4-Cl–C_6H_4, **1e**	**10e**	16	76	94
5	2,4-Cl_2–C_6H_3, **1f**	**10f**	24	78	98
6	4-F–C_6H_4, **1g**	**10g**	16	90	92
7	4-NO_2–C_6H_4, **1h**	**10h**	24	66	95
8	2-MeO–C_6H_4, **1i**	**10i**	60	95	85
9	4-MeO–C_6H_4, **1j**	**10j**	60	70	77

[a] See footnote a of Table 1, DCM used as a solvent.
[b] Yield referred to isolated pure product.
[c] Enantiomeric excess was determined by chiral HPLC analysis.

and β-ketoamide **8a** as nucleophile. As shown in Table 2, the domino reaction proceeded well for aromatic α,β-unsaturated aldehydes bearing electron-donating or electron-withdrawing substituents on aryl ring, providing the products in moderate to good yields as single diastereoisomers. For aldehydes **1b**–**h** having electron-withdrawing substituents on aryl ring, the enantioselectivities of **10b**–**h** were in the range of 92–98% ee (entries 1–7). However, α,β-unsaturated aldehydes **1i** and **j** with electron-donating substituents gave the cyclized products with lower enantioselectivities (entries 8 and 9).

To further illustrate the power of this catalytic enantioselective cascade reaction, other nucleophiles **8b**–**d** (Table 3) were examined under the same reaction conditions for **8a**. The methoxyl substituted **8b** and bromo substituted **8c** served as good nucleophiles, providing the desired products in moderate to good yields and good enantioselectivities (entries 1 and 2). The reaction yields are in agreement with the fact that bromo-indolyl ring is less electron-rich than the methoxyl analogue.

Table 3
Further expanding of substrate scope[a]



Entry	8	1	10	*t* (h)	Yield (%)[b]	ee (%)[c]
1	**8b**	**1a**	**10k**	24	76	94
2	**8c**	**1a**	**10l**	24	56	87
3	**8d**	**1a**	**10m**	24	76	95
4	**8d**	**1b**	**10n**	30	86	92
5	**8d**	**1d**	**10o**	24	90	90
6	**8d**	**1f**	**10p**	18	85	86
7	**8d**	**1i**	**10q**	18	85	79
8	**8d**	**1j**	**10r**	18	81	89

[a] See footnote a of Table 2.
[b] Yield referred to isolated pure product.
[c] Enantiomeric excess was determined by chiral HPLC analysis.

We were pleased to find that **8d** also worked well in the reaction conditions, affording the benzoquinolizidine products in good yields and enantioselectivities (entries 3–8). To our delight, in all cases, only one diastereoisomer was observed.

The absolute configuration of the cyclization products were determined to be 2*R*,12b*S* for indoloquinolizidines and 2*R*,11b*S* for benzoquinolizidines by single crystal X-ray diffraction analysis of **10n** (Fig. 2).[12] The stereochemistry at C2 position of **10n** originated from conjugate addition of active methylene nucleophile **8d** to α,β-unsaturated aldehyde **1b** catalyzed by chiral prolinol TMS

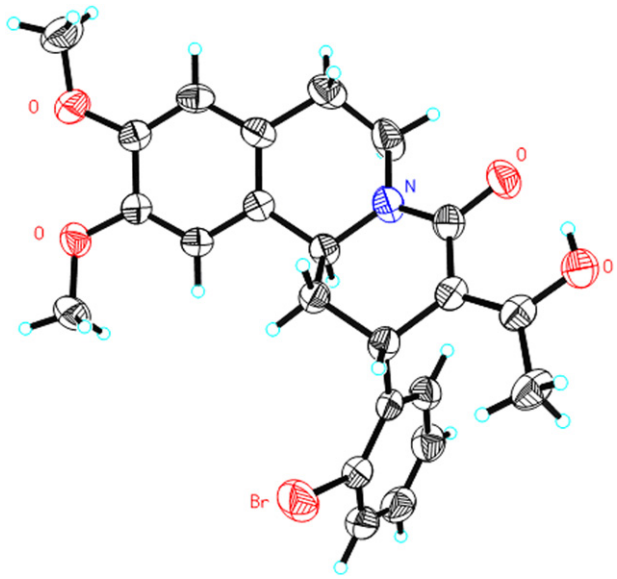


Fig. 2. X-ray structure of **10n**.

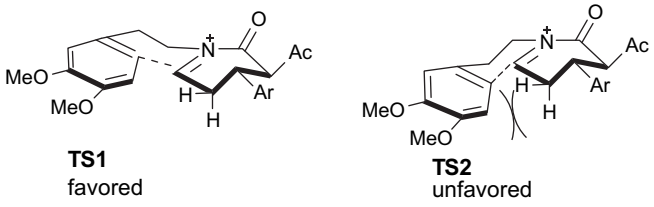
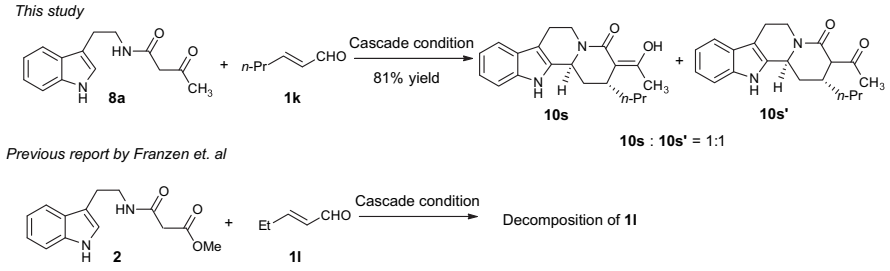


Fig. 3. Putative transition states in cyclization.

ether **9**.[9] The substrate controlled formation of 11b-position chirality could be exemplified by the transition states depicted in Fig. 3. Diastereoisomer **10n** formed exclusively due to less steric interaction between the equatorial β-proton and the 3,4-dimethoxyphenyl moiety in **TS1**, as compared to that between the axial α-proton and the 3,4-dimethoxyphenyl moiety in **TS2**.

Indoloquinolizidines and benzoquinolizidines with alkyl substituents at C2 position are common intermediates in the total synthesis of some natural alkaloids.[6] As pointed out in previous report by Franzén and Zhang, cascade reactions between aliphatic α,β-unsaturated aldehyde and indole tethered active methylene compound **2** resulted in decomposition of aldehyde.[8b] In our case, the cascade reactions between **8a** and **1k** proceeded smoothly to afford the cyclized products (Scheme 3). Surprisingly, a mixture of inseparable ketone and enol (**10s** and **10s'**) was formed. And such tautomeric pairs were inseparable by chromatography. Methylene



Scheme 3. Cascade reactions employing aliphatic α,β-unsaturated aldehyde.

compound **8** in our study was more reactive as compared with **2** in Franzén and co-workers' report.

3. Conclusions

In summary, we have developed an operationally simple asymmetric organocatalyzed cascade process for the preparation of indoloquinolizidines and benzoquinolizidines. The highly functionalized products were obtained from readily available reagents in moderate to good yields and good to excellent enantioselectivities. Moreover, the aliphatic α,β-unsaturated aldehydes, which were inactive substrates in the previous protocol reported by Franzén and co-workers,[8a,b] worked well and afforded indoloquinolizidines as a mixture of ketone and enol tautomers. Application of this method in total synthesis of natural alkaloids is currently underway in our laboratory and will be reported in due course.

4. Experimental

4.1. General information

Thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) or iodine. Flash column chromatography was performed on silica gel H (10–40 μ). NMR spectra were recorded on Bruker AM500 (500 MHz). Chemical shifts (δ) are given in parts per million relative to TMS, coupling constants (J) in hertz. Optical rotations were taken on JASCO P1030. High-resolution mass spectra were recorded on Bruker ApeXIII 7.0 TESLA FTMS. Enantiomeric excesses were determined by chiral HPLC using a Waters or Shimadzu instrument.

4.2. Procedure for the synthesis of 8a–d

To a solution of tryptamine (4.5 g, 28 mmol) in dry dichloroethane (30 mL) was added dropwise fresh diketene (2.2 g, 26 mmol) for 0.5 h at 0 °C. The mixture was stirred for 12 h at 0 °C. After evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel (AcOEt/Hexane 1/1) to afford **8a** (6.0 g, 94% yield) as a white solid.

*4.2.1. N-(2-(1H-Indol-3-yl)ethyl)-3-oxobutanamide (**8a**)*[13]. White solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 8.25–8.40 (br, 1H), 7.59 (d, J=7.5 Hz, 1H), 7.34 (d, J=8 Hz, 1H), 7.15–7.25 (m, 1H), 7.10–7.12 (m, 1H), 7.02 (s, 1H), 6.94 (s, 1H), 3.60 (t, J=6.5 Hz, 2H), 3.30 (s, 2H), 2.98 (t, J=6.5 Hz, 2H), 2.18 (s, 3H).

*4.2.2. N-(2-(5-Methoxy-1H-indol-3-yl)ethyl)-3-oxobutanamide (**8b**)*[14]. White solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 8.85 (s, 1H), 7.25 (s, 1H), 7.18 (d, J=8.5 Hz, 1H), 7.08–7.12 (m, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 6.79–6.82 (m, 1H), 3.78 (s, 3H), 3.48–3.58 (m, 2H), 3.21 (s, 2H), 2.85–2.93 (m, 2H), 2.08 (s, 3H).

*4.2.3. N-(2-(5-Bromo-1H-indol-3-yl)ethyl)-3-oxobutanamide (**8c**).* White solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 9.01 (s, 1H), 7.64 (s, 1H), 7.10–7.20 (m, 3H), 6.94 (s, 1H), 3.47–3.53 (m, 2H), 3.27 (s, 2H), 2.83–2.87 (m, 2H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 204.5, 166.1, 135.0, 129.1, 124.6, 123.7, 121.1, 112.9, 112.3, 112.1, 49.8, 39.9, 30.7, 24.9.

*4.2.4. N-(3,4-Dimethoxyphenethyl)-3-oxobutanamide (**8d**).* White solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 6.93–6.99 (br, 1H), 6.81 (d, J=8 Hz, 1H), 6.70–6.75 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.51 (t, J=7 Hz, 2H), 3.38 (s, 2H), 2.77 (t, J=7 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 204.6, 165.5, 149.1, 147.8, 131.4, 120.7, 112.0, 111.5, 56.0, 55.9, 49.7, 41.0, 35.3, 31.1.

4.3. General procedure for catalytic cascade reaction: preparation of compounds 10a–r

To a mixture of catalyst **9** (0.01 mmol, 0.1 equiv) and benzoic acid (0.01 mmol, 0.1 equiv) in DCM (0.2 mL) was added β-ketoamide **8** (0.1 mmol, 1 equiv) under an atmosphere of N_2. Followed by the addition of α,β-unsaturated aldehyde **1** (0.15 mmol, 1.5 equiv). The reaction was stirred at 20 °C and followed by TLC. After full consumption of β-ketoamide **8**, the reaction mixture was diluted with DCM (0.3 mL). Then TFA (0.1 mmol, 1 equiv) was added. The reaction mixture was stirred at 20 °C for 0.5 h. The reaction mixture was diluted with DCM (5 mL) and washed with saturated $NaHCO_3$ (3 mL). The aqueous phase was extracted with DCM (2×5 ml). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with a petroleum ether and ethyl acetate mixture to give pure compounds **10**.

*4.3.1. (2S,12bS,Z)-3-(1-Hydroxyethylidene)-2-phenyl-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10a**).* Pale yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.63 (s, 1H), 7.64 (s, 1H), 7.50 (d, J=7.5 Hz, 1H), 7.35–7.40 (m, 2H), 7.27–7.29 (m, 4H), 7.15 (t, J=7.5 Hz, 1H), 7.11 (t, J=7.5 Hz, 1H), 5.17–5.20 (m, 1H), 4.49 (d, J=10.5 Hz, 1H), 4.06–4.08 (m, 1H), 2.82–2.89 (m, 3H), 2.42 (dt, J=13 and 3 Hz, 1H), 2.16 (td, J=13 and 5 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.1, 170.2, 143.7, 136.3, 132.8, 132.4, 129.2, 127.5, 127.2, 126.9, 122.4, 120.1, 111.2, 109.9, 97.2, 51.7, 39.3, 38.2, 37.4, 21.3, 19.0; $[\alpha]_D^{25}$ −73.0 (c 0.50, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{23}N_2O_2)^+$ 359.1754, found 359.1756; HPLC (Phenomenex amylose-2, Hexane/Isopropanol=1:1, Flow rate=1.00 mL/min, λ=220 nm): t_R=4.50 min (minor enantiomer), t_R=5.52 min (major enantiomer).

*4.3.2. (2R,12bS,Z)-2-(2-Bromophenyl)-3-(1-hydroxyethylidene)-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10b**).* Pale yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.64 (s, 1H), 7.72 (s, 1H), 7.64 (d, J=7.5 Hz, 1H), 7.49 (d, J=7.5 Hz, 1H), 7.28–7.32 (m, 2H), 7.20 (d, J=7.5 Hz, 1H), 7.10–7.18 (m, 3H), 5.20–5.22 (m, 1H), 4.49 (d, J=11.5 Hz, 1H), 4.41–4.42 (m, 1H), 2.81–2.94 (m, 3H), 2.50 (d, J=13 Hz, 1H), 2.02–2.12 (m, 1H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.7, 170.2, 142.4, 133.5, 132.5, 129.7, 128.8, 127.9, 126.8, 122.3, 119.9, 118.4, 111.0, 110.0, 97.4, 49.1, 39.3, 38.1, 34.2, 21.2, 19.0; $[\alpha]_D^{25}$ −36.5 (c 0.52, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{22}N_2O_2Br)^+$ 437.0859, found 437.0858; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=9.98 min (minor enantiomer), t_R=21.62 min (major enantiomer).

*4.3.3. (2S,12bS,Z)-2-(3-Bromophenyl)-3-(1-hydroxyethylidene)-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10c**).* Yellow solid; ^{1}H NMR (CDCl3, 500 M): δ 15.68 (s, 1H), 7.68 (s, 1H), 7.40–7.52 (m, 3H), 7.10–7.32 (m, 5H), 5.17 (d, J=11.5 Hz, 1H), 4.46 (d, J=12 Hz, 1H), 4.04–4.06 (m, 1H), 2.81–2.92 (m, 3H), 2.40 (d, J=13 Hz, 1H), 2.10–2.20 (m, 1H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.6, 170.0, 146.2, 136.4, 132.4, 130.7, 130.6, 130.3, 126.9, 126.3, 123.3, 122.4, 120.0, 118.5, 111.0, 110.2, 96.5, 48.9, 39.3, 38.1, 37.4, 21.2, 19.1; $[\alpha]_D^{25}$ −70.9 (c 0.54, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{22}N_2O_2Br)^+$ 437.0859, found 437.0856; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=10.03 min (minor enantiomer), t_R=27.49 min (major enantiomer).

*4.3.4. (2S,12bS,Z)-2-(4-Bromophenyl)-3-(1-hydroxyethylidene)-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10d**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.66 (s, 1H), 7.68 (s, 1H), 7.48–7.52 (m, 3H), 7.27 (d, J=8 Hz, 1H), 7.10–7.18 (m, 4H), 5.14–5.19 (m, 1H), 4.45 (d, J=12 Hz, 1H), 4.02–4.04 (m, 1H), 2.82–2.90 (m, 3H), 2.38 (dt, J=12 and 2.5 Hz, 1H), 2.16 (td, J=12 and

5 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (CDCl3, 125 M): δ 173.4, 170.0, 151.6, 142.7, 136.4, 132.5, 132.1, 129.4, 126.9, 122.4, 120.0, 118.5, 111.0, 110.1, 96.7, 48.9, 39.3, 37.8, 37.3, 21.2, 19.0; $[\alpha]_D^{25}$ −28.4 (*c* 0.55, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{22}N_2O_2Br)^+$ 437.0859, found 437.0858; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=14.78 min (minor enantiomer), t_R=60.72 min (major enantiomer).

*4.3.5. (2S,12bS,Z)-2-(4-Chlorophenyl)-3-(1-hydroxyethylidene)-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10e**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.65 (s, 1H), 7.66 (s, 1H), 7.50 (d, *J*=7.5 Hz, 1H), 7.10–7.40 (m, 7H), 5.16–5.19 (m, 1H), 4.45 (d, *J*=12 Hz, 1H), 4.03–4.05 (m, 1H), 2.80–2.91 (m, 3H), 2.38 (d, *J*=12 Hz, 1H), 2.15 (td, *J*=12 and 4.5 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (CDCl3, 125 M): δ 173.4, 170.0, 142.2, 136.4, 132.8, 132.5, 129.4, 126.9, 122.4, 120.0, 118.5, 111.0, 110.2, 96.8, 48.9, 39.3, 37.7, 37.4, 21.2, 19.0; $[\alpha]_D^{25}$ −37.5 (*c* 0.80, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{22}N_2O_2Cl)^+$ 393.1364, found 393.1366; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=16.86 min (minor enantiomer), t_R=42.70 min (major enantiomer).

*4.3.6. (2R,12bS,Z)-2-(2,4-Dichlorophenyl)-3-(1-hydroxyethylidene)-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10f**).* ^{1}H NMR ($CDCl_3$, 500 M): δ 15.66 (s, 1H), 7.74 (s, 1H), 7.45–7.52 (m, 3H), 7.22–7.30 (m, 2H), 7.10–7.18 (m, 3H), 5.17–5.22 (m, 1H), 4.45 (d, *J*=13 Hz, 1H), 4.39–4.41 (m, 1H), 2.82–2.94 (m, 3H), 2.48 (dt, *J*=13 and 2.5 Hz, 1H), 2.08 (td, *J*=13 and 4 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.8, 170.1, 139.5, 136.4, 133.8, 133.6, 132.2, 130.4, 130.0, 127.6, 126.8, 122.4, 120.0, 118.4, 111.0, 110.1, 96.8, 49.1, 39.3, 35.3, 34.0, 21.2, 19.0; $[\alpha]_D^{25}$ −43.1 (*c* 0.56, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{21}N_2O_2Cl_2)^+$ 427.0975, found 427.0972; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=9.41 min (minor enantiomer), t_R=24.64 min (major enantiomer).

*4.3.7. (2S,12bS,Z)-2-(4-Fluorophenyl)-3-(1-hydroxyethylidene)-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10g**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.65 (s, 1H), 7.72 (s, 1H), 7.50 (d, *J*=7.5 Hz, 1H), 7.23–7.32 (m, 3H), 7.16 (t, *J*=7.5 Hz, 1H), 7.02–7.13 (m, 3H), 5.13–5.19 (m, 1H), 4.46 (d, *J*=12 Hz, 1H), 4.05–4.06 (m, 1H), 2.77–2.95 (m, 3H), 2.40 (d, *J*=12 Hz, 1H), 2.15 (td, *J*=12 and 4.5 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.3, 170.0, 160.9, 139.3, 136.4, 132.6, 129.2, 129.1, 126.9, 122.3, 120.0, 118.5, 115.7, 111.0, 97.2, 48.9, 39.3, 37.5, 37.5, 21.2, 19.0; $[\alpha]_D^{25}$ −37.2 (*c* 0.55, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{22}N_2O_2F)^+$ 377.1660, found 377.1656; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=16.61 min (minor enantiomer), t_R=34.74 min (major enantiomer).

*4.3.8. (2S,12bS,Z)-3-(1-Hydroxyethylidene)-2-(4-nitrophenyl)-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10h**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.71 (s, 1H), 8.23 (d, *J*=13 Hz, 2H), 7.70 (s, 1H), 7.47–7.52 (m, 3H), 7.28 (d, *J*=8 Hz, 1H), 7.17 (t, *J*=7 Hz, 1H), 7.12 (t, *J*=7 Hz, 1H), 5.16–5.21 (m, 1H), 4.44 (d, *J*=12 Hz, 1H), 4.18–4.20 (m, 1H), 2.84–2.90 (m, 3H), 2.46 (dt, *J*=12 and 3.5 Hz, 1H), 2.25 (td, *J*=12 and 4.5 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.9, 169.8, 151.6, 147.1, 136.4, 132.0, 128.6, 126.8, 124.3, 122.5, 120.1, 118.6, 111.0, 110.4, 96.2, 48.9, 39.4, 38.5, 37.1, 21.2, 19.1; $[\alpha]_D^{25}$ +11.8 (*c* 0.45, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{21}N_3O_4Na)^+$ 426.1424, found 426.1424; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=24.80 min (minor enantiomer), t_R=58.67 min (major enantiomer).

*4.3.9. (2S,12bS,Z)-3-(1-Hydroxyethylidene)-2-(2-methoxyphenyl)-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10i**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.60 (s, 1H), 7.64 (s, 1H), 7.49 (d, *J*=7.5 Hz, 1H), 7.24–7.31 (m, 2H), 7.05–7.19 (m, 3H), 6.92–6.97 (m, 2H), 5.16–5.21 (m, 1H), 4.47 (d, *J*=12 Hz, 1H), 4.39–4.40 (m, 1H), 3.96 (s, 3H), 2.79–2.93 (m, 3H), 2.48 (d, *J*=12 Hz, 1H), 2.01 (td, *J*=12 and 4.5 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 172.7, 170.5, 156.7, 136.3, 133.1, 131.5, 128.9, 128.1, 127.0, 122.1, 120.7, 119.8, 118.4, 110.9, 110.5, 109.8, 97.6, 55.6, 49.6, 39.2, 34.5, 32.2, 21.3, 18.8; $[\alpha]_D^{25}$ +124.8 (*c* 0.52, $CHCl_3$); HRMS (ESI) calcd for $(C_{24}H_{25}N_2O_3)^+$ 389.1860, found 389.1861; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4: 1, Flow rate=0.65 mL/min, λ=220 nm): t_R=8.07 min (minor enantiomer), t_R=14.25 min (major enantiomer).

*4.3.10. (2S,12bS,Z)-3-(1-Hydroxyethylidene)-2-(4-methoxyphenyl)-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10j**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.61 (s, 1H), 7.72 (s, 1H), 7.49 (d, *J*=7.5 Hz, 1H), 7.27–730 (m, 1H), 7.09–7.20 (m, 4H), 6.90 (d, *J*=8.5 Hz, 2H), 5.15–5.20 (m, 1H), 4.48 (d, *J*=10 Hz, 1H), 4.00–4.02 (m, 1H), 3.81 (s, 3H), 2.79–2.92 (m, 3H), 2.39 (dt, *J*=10 and 3 Hz, 1H), 2.12 (td, *J*=10 and 4.5 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.0, 170.2, 158.6, 136.4, 135.6, 132.9, 128.6, 126.9, 122.2, 120.0, 118.4, 114.3, 111.0, 110.0, 97.5, 55.4, 49.0, 39.3, 37.6, 37.4, 21.3, 18.9; $[\alpha]_D^{25}$ +10.2 (*c* 0.55, $CHCl_3$); HRMS (ESI) calcd for $(C_{24}H_{25}N_2O_3)^+$ 389.1860, found 389.1861; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.65 mL/min, λ=220 nm): t_R=12.20 min (minor enantiomer), t_R=23.78 min (major enantiomer).

*4.3.11. (2S,12bS,Z)-3-(1-Hydroxyethylidene)-9-methoxy-2-phenyl-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10k**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.62 (s, 1H), 7.55 (s, 1H), 7.37 (t, *J*=7.5 Hz, 2H), 7.27 (t, *J*=6.5 Hz, 2H), 7.14 (d, *J*=9 Hz, 1H), 6.94 (d, *J*=2.5 Hz, 1H), 6.80 (dd, *J*=9 and 2.5 Hz, 1H), 5.16–5.19 (m, 1H), 4.45–4.48 (m, 1H), 4.05–4.07 (m, 1H), 3.84 (s, 3H), 2.75–2.83 (m, 3H), 2.40 (dt, *J*=12 and 3 Hz, 1H), 2.15 (td, *J*=12 and 4 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.2, 170.5, 154.4, 143.7, 133.7, 131.4, 129.0, 127.7, 127.4, 127.0, 112.2, 111.7, 109.9, 100.5, 97.2, 56.0, 49.0, 39.3, 38.2, 37.5, 21.3, 19.0; $[\alpha]_D^{25}$ −17.7 (*c* 0.57, $CHCl_3$); HRMS (ESI) calcd for $(C_{24}H_{25}N_2O_3)^+$ 389.1860, found 389.1861; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=14.75 min (minor enantiomer), t_R=29.15 min (major enantiomer).

*4.3.12. (2S,12bS,Z)-9-Bromo-3-(1-hydroxyethylidene)-2-phenyl-1,2,3,6,7,12b-hexahydroindolo[2,3α]quinolizin-4(12H)-one (**10l**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.58 (s, 1H), 7.82 (s, 1H), 7.60 (d, *J*=1.5 Hz, 1H), 7.36 (d, *J*=7.5 Hz, 2H), 7.28 (d, *J*=6.5 Hz, 2H), 7.20–7.23 (m, 3H), 7.12 (d, *J*=8.5 Hz, 1H), 5.13–5.18 (m, 1H), 4.47 (d, *J*=12 Hz, 1H), 4.06–4.08 (m, 1H), 2.70–2.88 (m, 3H), 2.42 (dt, *J*=12 and 3 Hz, 1H), 2.65 (td, *J*=12 and 4 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.3, 170.2, 143.6, 135.0, 134.2, 129.2, 128.7, 127.6, 127.1, 125.0, 121.1, 113.1, 112.4, 109.7, 97.1, 48.9, 39.2, 38.2, 37.3, 21.1, 19.0; $[\alpha]_D^{25}$ −44.2 (*c* 0.04, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{22}N_2O_2Br)^+$ 437.0859, found 437.0858; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.65 mL/min, λ=220 nm): t_R=9.39 min (minor enantiomer), t_R=20.41 min (major enantiomer).

*4.3.13. (2S,11bS,Z)-3-(1-Hydroxyethylidene)-9,10-dimethoxy-2-phenyl-2,3,6,7-tetrahydro-1H-pyrido[2,1α]isoquinolin-4(11bH)-one (**10m**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.57 (s, 1H), 7.32–7.42 (m, 2H), 7.25–7.30 (m, 3H), 6.60 (s, 1H), 6.36 (s, 1H), 4.87–4.90 (m, 1H), 4.31 (d, *J*=12 Hz, 1H), 4.00–4.02 (m, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 2.81–2.91 (m, 2H), 2.65 (d, *J*=12 Hz, 1H), 2.44 (d, *J*=13 Hz, 1H), 2.04 (td, *J*=12 and 4 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 172.6, 169.9, 148.6, 147.8, 144.0, 131.5, 128.8, 127.7, 127.6, 126.8, 111.5, 108.7, 97.4, 56.3, 56.0, 51.5, 39.4, 38.9, 38.5, 29.0, 18.9; $[\alpha]_D^{25}$ −103.9 (*c* 0.51, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{26}NO_4)^+$ 380.1856, found 380.1852; HPLC (Daicel Chiralpak

ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=14.62 min (minor enantiomer), t_R=17.33 min (major enantiomer).

*4.3.14. (2R,11bS,Z)-2-(2-Bromophenyl)-3-(1-hydroxyethylidene)-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1α]isoquinolin-4 (11bH)-one (**10n**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.58 (s, 1H), 7.63 (d, J=8 Hz, 1H), 7.28 (t, J=7.5 Hz, 1H), 7.13–7.19 (m, 2H), 6.61 (s, 1H), 6.37 (s, 1H),4.88–4.91 (m, 1H), 4.31–4.35 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.88–2.90 (m, 2H), 2.66–2.68 (m, 1H), 2.52 (dt, J=13.5 and 3 Hz, 1H), 1.94 (td, J=13.5 and 5 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.1, 170.0, 147.9, 147.8, 142.7, 133.5, 129.8, 128.6, 128.1, 127.8, 127.6, 123.8, 111.5, 108.8, 97.6, 56.4, 56.0, 51.6, 38.9, 38.3, 36.2, 28.9, 18.9; $[\alpha]_D^{25}$ −88.5 (c 0.75, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{25}NO_4Br)^+$ 458.0962, found 458.0971; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.65 mL/min, λ=220 nm): t_R=8.63 min (minor enantiomer), t_R=13.97 min (major enantiomer).

*4.3.15. (2S,11bS,Z)-2-(4-Bromophenyl)-3-(1-hydroxyethylidene)-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1α]isoquinolin-4 (11bH)-one (**10o**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.59 (s, 1H), 7.49 (d, J=8.5 Hz, 2H), 7.16 (d, J=8.5 Hz, 2H), 6.60 (s, 1H), 6.34 (s, 1H), 4.86–4.90 (m, 1H), 4.27 (dd, J=12 and 3 Hz, 1H), 3.96–3.97 (m, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.82–2.87 (m, 2H), 2.64 (d, J=13 Hz, 1H), 2.37 (dt, J=12 and 3 Hz, 1H), 2.03 (td, J=12 and 4.5 Hz, 1H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 172.9, 169.8, 147.9, 147.9, 143.1, 132.0, 129.5, 128.0, 127.6, 120.7, 111.6, 108.6, 96.9, 56.3, 56.0, 51.4, 39.3, 38.9, 38.1, 28.9, 18.9; $[\alpha]_D^{25}$ −28.4 (c 0.77, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{25}NO_4Br)^+$ 458.0962, found 458.0971; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.65 mL/min, λ=220 nm): t_R=11.74 min (minor enantiomer), t_R=14.22 min (major enantiomer).

*4.3.16. (2R,11bS,Z)-2-(2,4-Dichlorophenyl)-3-(1-hydroxyethylidene)-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1α]isoquinolin-4 (11bH)-one (**10p**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.60 (s, 1H), 7.47 (d, J=2 Hz, 1H), 7.22–7.24 (m, 1H), 7.12 (d, J=8 Hz, 1H), 6.61 (s, 1H), 6.35 (s, 1H), 4.87–4.93 (m, 1H), 4.34–4.35 (m, 1H), 4.28 (dd, J=12 and 3 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.83–2.89 (m, 2H), 2.67 (d, J=14.5 Hz, 1H), 2.46 (dt, J=12 and 3 Hz, 1H), 1.95 (td, J=12 and 3.5 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 173.2, 169.9, 147.9, 147.9, 139.8, 133.8, 133.3, 130.5, 130.0, 127.8, 127.6, 127.4, 111.6, 108.6, 97.0, 56.4, 56.0, 51.6, 38.9, 36.0, 35.5, 28.9, 18.9; $[\alpha]_D^{25}$ −65.5 (c 0.75, $CHCl_3$); HRMS (ESI) calcd for $(C_{23}H_{24}NO_4Cl_2)^+$ 448.1077, found 448.1083; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.7 mL/min, λ=220 nm): t_R=12.58 min (minor enantiomer), t_R=17.78 min (major enantiomer).

*4.3.17. (2S,11bS,Z)-3-(1-Hydroxyethylidene)-9,10-dimethoxy-2-(2-methoxyphenyl)-2,3,6,7-tetrahydro-1H-pyrido[2,1α]isoquinolin-4 (11bH)-one (**10q**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.52 (s, 1H), 7.24–7.27 (m, 1H), 7.07 (dd, J=7.5 and 1.5 Hz, 1H), 6.90–6.96 (m, 2H), 6.60 (s, 1H), 6.38 (s, 1H), 4.84–4.87 (m, 1H), 4.30–4.35 (m, 2H), 3.93 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 2.85–2.89 (m, 2H), 2.64–2.67 (m, 1H), 2.50 (dt, J=13 and 3 Hz, 1H), 1.89 (td, J=13 and 4 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 172.2, 170.3, 156.8, 147.8, 147.7, 131.9, 129.1, 128.7, 127.9, 127.7, 120.6, 111.5, 110.6, 109.0, 97.8, 56.4, 56.0, 55.5, 52.1, 39.0, 36.4, 32.4, 29.0, 18.7; $[\alpha]_D^{25}$ +129.0 (c 0.69, $CHCl_3$); HRMS (ESI) calcd for $(C_{24}H_{28}NO_5)^+$ 410.1962, found 410.1967; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.65 mL/min, λ=220 nm): t_R=10.08 min (minor enantiomer), t_R=16.61 min (major enantiomer).

*4.3.18. (2S,11bS,Z)-3-(1-Hydroxyethylidene)-9,10-dimethoxy-2-(4-methoxyphenyl)-2,3,6,7-tetrahydro-1H-pyrido[2,1α]isoquinolin-4 (11bH)-one (**10r**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.54 (s, 1H), 7.18 (d, J=8.5 Hz, 2H), 6.90 (d, J=8.5 Hz, 2H), 6.60 (s, 1H), 6.37 (s, 1H), 4.86–4.89 (m, 1H), 4.31 (dd, J=13 and 3 Hz, 1H), 3.95–3.96 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 2.80–2.91 (m, 2H), 2.63–2.68 (m, 1H), 2.40 (dt, J=13 and 3 Hz, 1H), 2.00 (td, J=13 and 4.5 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 M): δ 172.5, 169.9, 158.4, 147.8, 135.9, 128.7, 128.4, 128.2, 127.6, 114.2, 111.5, 108.7, 97.6, 56.3, 56.0, 55.4, 51.5, 39.6, 38.9, 37.6, 29.0, 18.8; $[\alpha]_D^{25}$ +87.3 (c 0.71, $CHCl_3$); HRMS (ESI) calcd for $(C_{24}H_{28}NO_5)^+$ 410.1962, found 410.1967; HPLC (Daicel Chiralpak ADH, Hexane/Isopropanol=4:1, Flow rate=0.65 mL/min, λ=220 nm): t_R=14.00 min (major enantiomer), t_R=14.72 min (minor enantiomer).

*4.3.19. Mixture of ketone and enol tautomers (**10s** and **10s'**).* Yellow solid; ^{1}H NMR ($CDCl_3$, 500 M): δ 15.1 (s, 0.5H), 7.90–8.00 (m, 1H), 7.48–7.53 (m, 1H), 7.32–7.38 (m, 1H), 7.10–7.20 (m, 2H), 5.10–5.20 (m, 1H), 4.80–4.90 (m, 1H), 3,37 (m, 0.5H), 2.70–2.93 (m, 3.5H), 2.33–2.43 (m, 1H), 2.26 (s, 1.5H), 2.07–2.21 (m, 1H), 1.99 (s, 1.5H), 1.80–1.83 (m, 0.5H), 1.37–1.55 (m, 4H), 0.3–1.03 (m, 3H).

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Supplementary data

The original spectra of ^{1}H NMR, ^{13}C NMR and HPLC of all products are supplied. The supplementary data files are to be used as an aid for the refereeing of the paper only. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.007. These data include MOL files and InChIKeys of the most important compounds described in this article.

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