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The synthesis of precursor of FP- (+) DTBZ

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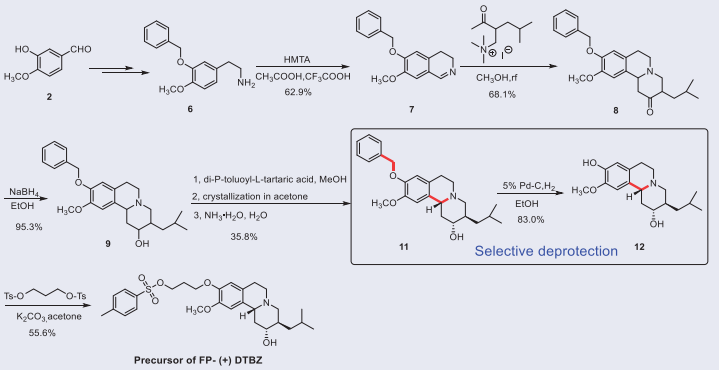
ABSTRACT

A synthetic route to the precursor of FP- (+) DTBZ was disclosed, in which 3-hydroxy-4-methoxybenzaldehyde was employed as a starting material. In the method, the benzyl-protecting protocol and the *in-situ* Diels-Alder reaction made the procedure more practical because of the mild conditions for selectively deprotection and the accelerated reaction process.

GRAPHICAL ABSTRACT



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Positron Emission Computed Tomography; VMAT2 imaging agents; precursor of FP- (+) DTBZ; synthesis

Introduction

Studies have shown the early detection and monitoring of neurodegenerative diseases including Parkinson's disease (PD), Alzheimer's disease (AD), dementia with Lewy bodies (DLB), other dementias, and movement disorders are a very significant unmet medical need. The brain positron emission computed tomography (PET) can be used for diagnosis of Parkinson's disease.[1]

Vesicular Monoamine Transporter 2 (VMAT2), a membrane bound protein, is a biomarker for Parkinson's disease.[2] DTBZ and its derivatives (Figure 1), labeled with positron emitting isotopes such as [^{11}C] and [^{18}F], were used as PET radioligands for examining VMAT2[3,4] and the density of VMAT2 determined by [^{18}F] DTBZ was well,

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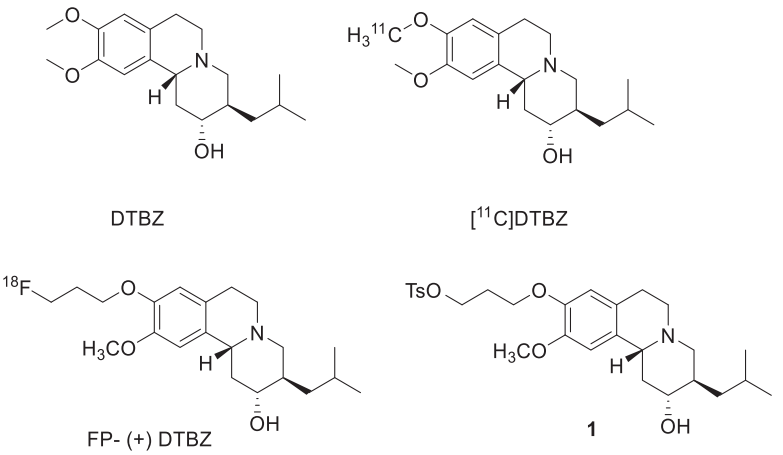


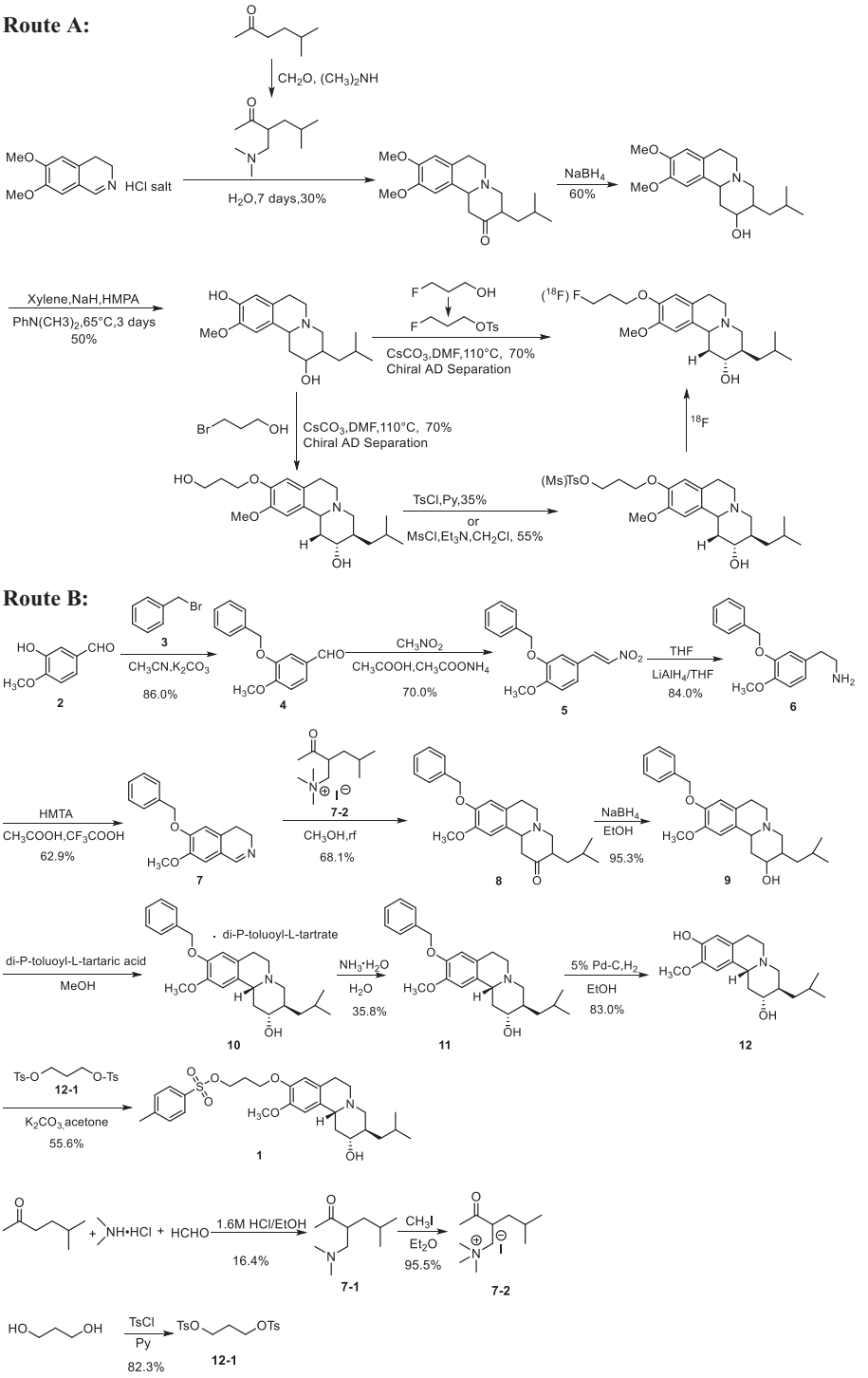
Figure 1. Structures of DTBZ, [^{11}C] DTBZ, FP- (+) DTBZ and precursor **1**.

inversely correlated with the severity of Parkinson's disease.[5] 9-[^{18}F] fluoropropyl-(+)-dihydrotetrabenazine ([^{18}F] AV-133, FP- (+) DTBZ) targeting VMAT2 was employed as brain PET tracer. FP- (+) DTBZ is currently under Phase II/III clinical trials to verify its validity in the diagnosis of neurodegenerative diseases including dementia with Lewy bodies and Parkinson's disease.[5–7] In this paper, we described a procedure for the synthesis of the precursor of FP- (+) DTBZ.

Results and discussion

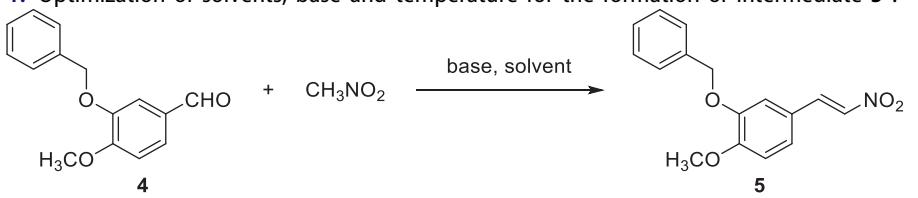
About its synthesis, Hank et al. reported a route (Scheme 1, Route A)[8] using 6,7-dimethoxy-3,4-dihydroisoquinoline as the starting material, which was not commercially available. Besides, the second step required seven days with yield only of 30%. In addition, harsh condition was employed to remove the methoxyl group and it was difficult to remove the mono 3-methoxyl selectively. Therefore, we optimized an economical and practical synthetic route based on Liu's work (Scheme 1, Route B[9]). This synthetic route from commercially available 3-hydroxy-4-methoxy benzaldehyde involved benzyl protection, Henry reaction, reduction, Pictet–Spengler reaction, *in-situ* Diels–Alder cyclization, resolution of chiral isomers, debenzylation, and etherification.

The substituted 2-nitrovinyl benzene **5** was prepared via the benzyl protocol and the Henry reaction, which converted to the substituted phenyl ethanamine **6** via the reduction. Initially, we attempted to prepare the intermediate **5** under the conditions of Aldol condensation, but no satisfactory result was obtained (Table 1, entries 1–4). After repeatedly exploration, Henry reaction was employed to achieve this goal and the intermediate **5** was obtained by adding **4**, ammonium acetate, and nitromethane into a solvent of acetic acid at 93 °C (entry **6**). As for the next step of reduction, strong reductant of lithium aluminum hydride (LAH) was selected to reduce the double bond and nitro group simultaneously. Much lower yield was obtained when adding LAH at ambient temperature because of the generation of impurities (Table 2, entry 1). However, when decreasing feeding temperature and reaction temperature, no product was obtained



Scheme 1. Reported and modified synthetic routes of precursor **1**.

Table 1. Optimization of solvents, base and temperature for the formation of intermediate **5**[a].

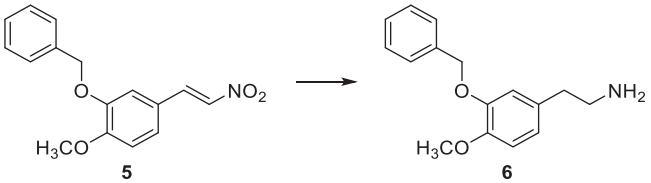


4 **5**

Entry	CH_3NO_3 (equie)	Solvent	Base (equie)	Temp (°C)	Yield (%)
1	1.1	toluene	Piperidine (0.15)	110	<10%
2	1.1	MeOH	NaOH (1.0)	0	<10%
3	1.1	MeOH	NaOH (1.0)	0→10	<10%
4	1.5	MeOH	NaOH (2.0)	0→10	<10%
5	3	CH_3COOH	CH_3COONH_4 (2.4)	50	ND[b]
6	3	CH_3COOH	CH_3COONH_4 (2.4)	93	70.0%

[a]Standard conditions: **4** (40.6 g, 167.7 mmol); [b]not detected by TLC analysis.

Table 2. Optimization of temperature for the formation of intermediate **6**[a].



5 **6**

Entry	Temp (°C)	Yield (%)
1	33→66	17.3
2	0→25	ND[b]
3	0→66	84.0

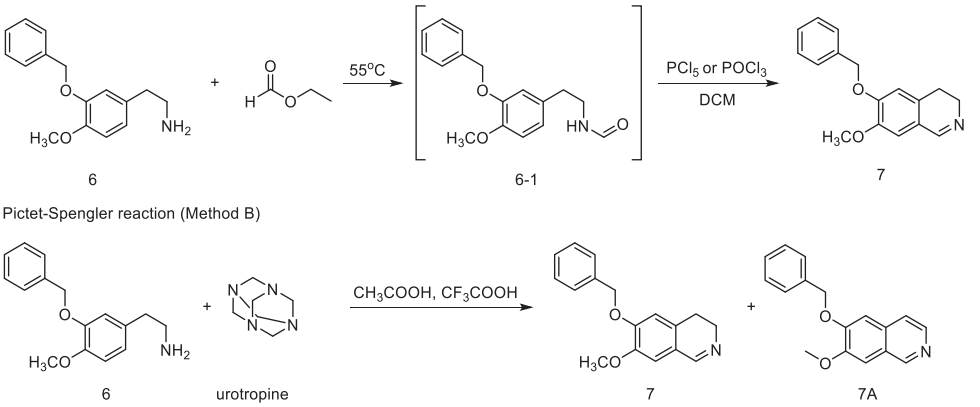
[a]Standard conditions: **5** (19.3 g, 67.7 mmol), the THF solution of $LiAlH_4$ (2.5 M, 108 mL, 270 mmol). [b]Not detected by TLC analysis.

(entry 2). An attempt at reducing the feeding temperature and raising the reaction temperature step by step was success to obtain a higher yield (entry 3).

The Bischler–Napieralski reaction was employed to synthesize dihydro isoquinoline intermediate **7**, but we abandoned the approach after several failed attempts due to the low yield (Table 3, entries 1–6). Eventually, intermediate **7** was obtained with acceptable yield of 62.9% via the Pictet–Spengler reaction with urotropine. In the process, the yield was increased by 10% by raising the reaction temperature from 60 to 90 °C (entries **7, 8**). We tried to increase the yield by further raising the temperature, but the impurity **7 A** was increased when the temperature raised to 110–120 °C (entry **9**). Isomerization may occur easily during high reaction temperature, therefore, 90 °C was selected as the optimal condition.

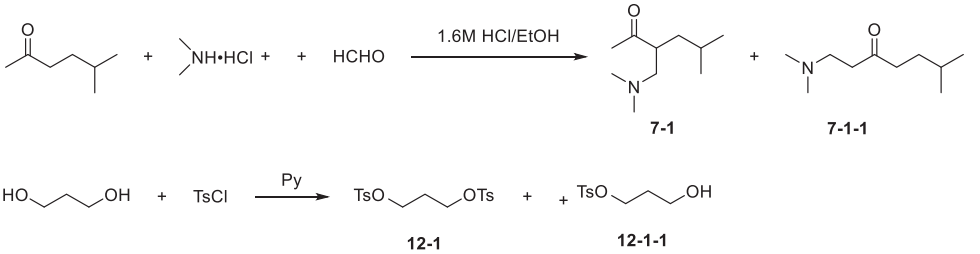
Tertiary amine **7-1** was synthesized via Mannich reaction, but the reaction always produced isomer **7-1-1** which could not be reduced by changing reaction time, reaction temperature, or feeding amount of dimethylamine and polyformaldehyde (Scheme 2). However, the isomer **7-1-1** would increase when reducing the reaction temperature to ambient temperature or below. Compound **12-1** was synthesized from propane-1,3-diol and p-toluenesulfonyl chloride, but when the reaction was carried out at the ambient temperature, the monosulfonate **12-1-1** was the major product (Scheme 2). Therefore, we obtained **12-1** with an acceptable yield when the reaction was carried out below 0 °C.

Table 3. Optimization of temperature for the formation of intermediate **7**[a].



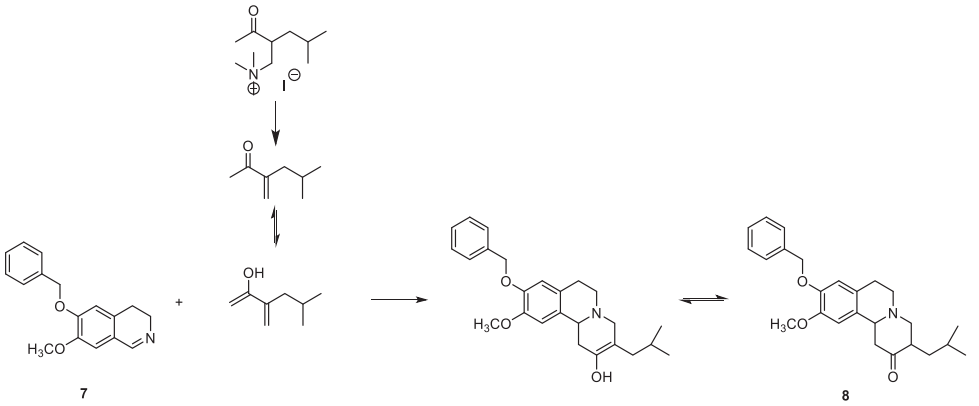
Entry	Method	Dehydrant (equie)	Solvent	Temp (°C)	Yield (%)
1	A	$POCl_3$ (3.3)	–	105	<5
2	A	$POCl_3$ (3.3)	–	60	<5
3	A	$POCl_3$ (1.5)	DCM	25	<10
4	A	PCl_5 (1.5)	DCM	25	<5
5	A	PCl_5 (1.5)	DCM	−5→25	<10
6	A	PCl_5 (1.5)	DCM	−5→44	<10
7	B			60	55.7
8	B			90	64.5
9	B			120	26.9

[a]Standard conditions for method A: **6** (7.9 g, 30 mmol); standard conditions for method B: **6** (7.9 g, 30 mmol), trifluoroacetic acid (12 mL), hexamethylenetetramine (12.9 g, 92 mmol), acetic acid (48 mL).



Scheme 2. The synthesis of intermediates **7-1** and **12-1**.

The *in-situ* Diels-Alder cyclization followed by the elimination of the quaternary ammonium **7-2** salt furnished ketone **8**. Compared with the route reported by Hank et al.[8], tertiary amine **7-1** first reacts with iodomethane to form quaternary ammonium **7-2** instead of directly reacting with the intermediate **7**, which greatly accelerated the reaction process for the preparation of ketone **8**. Also, the possible mechanism for the formation of ketone **8** was shown in Scheme 3. After the reduction of the ketone **8**, the racemic compound **11** was carefully resoluted with di-*p*-toluoyl-*L*-tartaricdi-*p*-toluoyl-*L*-tartaric acid in acetone. Under normal pressure and room temperature conditions, the 3-OBn of the optical pure **11** was selectively deprotected to give the key intermediate **12** via Pd-catalysed hydrogenation while keeping the C–N bond of the benzylamine structure in the substituted isoquinoline undestroyed. The intermediate **12** could be easily converted to the final key precursor **1** via reacted with **12-1**.



Scheme 3. The possible mechanism for the formation of ketone **8**.

Conclusion

We provide an economical and practical route to synthesize the key precursor of FP-(+) DTBZ and it is acceptable from both reaction conditions and yield standpoint. The advantages of the method are the benzyl ether protecting group removed selectively under mild conditions and the *in-situ* Diels–Alder reaction accelerating the process of cyclization.

Experimental section

General

Reagents and solvents were obtained from commercial suppliers and used without further purification. Melting points were determined with a X-4 digital apparatus and were uncorrected. Specific rotation was determined with a WZZ-automatic polarimeter. ^{1}H nuclear magnetic resonance (NMR) spectra were collected using a Bruker ARX-600 apparatus and using tetramethylsilane (TMS) as an internal standard. Electrospray ionization mass spectrometry (ESI-MS) data were obtained using an Agilent 1100 Series MSD Trap (SL) apparatus. The reactions were monitored by thin-layer chromatography (TLC; HG/T2354-92, GF254) and compounds septated by TLC were visualized with UV light.

Synthesis of 9-(benzyloxy)-3-isobutyl-10-methoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-one (8)

The intermediate **7** (4.3 g, 16.0 mmol) and quaternary ammonium **7-2** (6.5 g, 20.7 mmol) were added to a solution of methanol (40 mL) and the mixture was stirred at reflux for 31 h. Then, the mixture was cooled to ambient temperature and dissolved in DCM (100 mL) and H_2O (50 mL), then organic phase was collected and washed with brine (100 mL) before being dried over anhydrous sodium sulfate. The sodium sulfate was filtered off and the filtrate was concentrated in vacuum to afford white solid **8** (4.3 g, 68.1%). Mp 119–121 °C (Lit.[3] Mp 133–135 °C). MS(ESI): $m/z = 394.3$ $[M+H]^+$. ^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) 7.43 (d, $J = 7.4$ Hz, 2H), 7.38–7.34 (m, 2H), 7.32–7.28

(m, 1H), 6.65 (s, 1H), 6.58 (s, 1H), 5.12 (s, 2H), 3.84 (s, 3H), 3.49 (s, 1H), 3.27 (s, 1H), 3.08 (d, 2H), 2.91 (d, $J = 13.3$ Hz, 1 H), 2.66 (dd, 4H), 2.35 (s, 1H), 1.83–1.78 (m, 1H), 1.69–1.62 (m, 1H), 1.06–1.01 (m, 1H), 0.91 (t, $J = 6.6$ Hz, 6H).

Synthesis of (2 R,3R,11bR)-9-(benzyloxy)-3-isobutyl-10-methoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol.di-P-toluoyl-L-tartrate (10) and (2 R,3R,11bR)-9-(benzyloxy)-3-isobutyl-10-methoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol (11)

The intermediate **9** (3.6 g, 9.0 mmol) was added to a solution of methanol (140 mL) and the mixture was stirred. When the reaction temperature rose to 45 °C, di-*p*-toluoyl-tartaric acid (3.5 g, 9.0 mmol) was added and the mixture was stirred at 45 °C for 0.5 h. Then, the mixture was cooled to ambient temperature and concentrated in vacuum to afford white solid (7.5 g), which was recrystallized twice from acetone to afford (2 R,3R,11bR)-9-(benzyloxy)-3-isobutyl-10-methoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a]isoquinolin-2-ol.di-P-toluoyl-*L*-tartrate **10**.

The tartrate **10** (2.4 g, 3.1 mmol) was dissolved in H_2O (200 mL) and the pH was adjusted to 10 with 25% ammonium hydroxide, then the solution was extracted with DCM (200 mL). Organic phase was washed with brine (200 mL) before being dried over anhydrous sodium sulfate. The sodium sulfate was filtered off and the filtrate was concentrated in vacuum to afford white solid **11** (1.3 g, 35.8%). Mp 133–136 °C (Lit.[3] Mp 139–141 °C). $[\alpha]_D^{20} = +53.3°$ (c = 1, chloroform) (lit[9]. $[\alpha]_D^{20} = +58.3°$ (c = 1, chloroform)).

Synthesis of (2 R,3R,11bR)-3-isobutyl-10-methoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinoline-2,9-diol (12)

The intermediate **11** (1.3 g, 3.2 mmol) and 5% Pd-C (0.1 g) were added to a solution of anhydrous ethanol (50 mL) and the mixture was stirred at 25 °C for 48 h at a hydrogen atmosphere. Then the mixture was concentrated in vacuum to remove ethanol to afford white solid **12** (0.8 g, 83.0%). Mp 216–218 °C (Lit.[4] Mp 206–208 °C). MS(ESI): $m/z = 306.3$ $[M + H]^+$. ^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) 6.65 (s, 2H), 3.85 (s, 3H), 3.40 (td, $J = 10.5$, 4.6 Hz, 1H), 3.16 (s, 1H), 3.07 (d, $J = 10.5$ Hz, 2H), 3.01 (s, 1H), 2.67–2.53 (m, 2H), 2.47 (s, 1H), 2.07–1.96 (m, 1H), 1.77 (s, 1H), 1.72–1.67 (m, 2H), 1.62–1.49 (m, 2–H), 1.25 (s, 1H), 1.09–1.04 (m, 1H), 0.93 (dd, $J = 13.0$, 6.5 Hz, 6H).

Synthesis of 3-(((2 R,3R,11bR)-2-hydroxy-3-isobutyl-10-methoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-9-yl)oxy)propyl 4-methylbenzenesulfonate (1)

The intermediate **12** (0.53 g, 1.74 mmol), **12-1** (1.50 g, 5.21 mmol) and potassium carbonate (0.60 g, 4.34 mmol) were added to a solution of acetone (50.0 mL). After stirred at 65 °C for 48 h,the mixture was cooled to ambient temperature and concentrated in vacuum to remove acetone. The residue was dissolved in DCM (80 mL) and the organic phase was washed with H_2O (50 mL) and brine (100 mL) before being dried over

anhydrous sodium sulfate. The sodium sulfate was filtered off and the filtrate was concentrated in vacuum to afford white solid **1** (0.50 g, 55.6%). Mp 115–120 °C. MS(ESI): $m/z = 518.3$ $[M+H]^+$. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{39}NO_6S$ 518.2498, found 518.2594. $[\alpha]_D^{20} = +29.09°$ ($c = 1$, chloroform). ^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) 7.76 (d, $J = 8.2$ Hz, 2H), 7.28 (s, 2H), 6.65 (s, 1H), 6.52 (s, 1H), 4.29–4.23 (m, 2H), 4.00–3.96 (m, 2H), 3.76 (s, 3H), 3.40 (s, 1H), 3.08 (t, 4H), 2.60 (t, $J = 17.8$ Hz, 2H), 2.48 (s, 1H), 2.40 (s, 3H), 2.14 (p, $J = 6.1$ Hz, 2H), 2.04–1.98 (m, 1H), 1.73–1.68 (m, 2H), 1.58 (d, $J = 10.7$ Hz, 2H), 1.09–1.05 (m, 1H), 0.94 (dd, $J = 12.5$, 6.5 Hz, 6H).

Full experimental detail, ^{1}H spectra, MS spectra are explained in the supplementary material.

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