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Blocking group-directed diastereoselective total synthesis of (±)-α-noscapine

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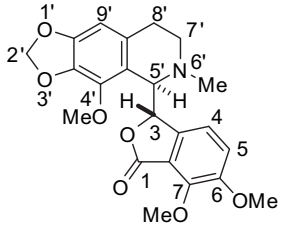
ABSTRACT

A new approach for the diastereoselective synthesis of (±)-α-noscapine, a phthalide tetrahydroisoquinoline alkaloid exhibiting several biological activities, is described. The strategy features a blocking group-directed Bischler–Napieralski reaction followed by diastereoselective reduction (α/β>23:1). One of the key intermediates, phthalide-3-carboxylic acid, could be efficiently prepared from simple benzoic acid derivative and glyoxylic acid in one-pot.

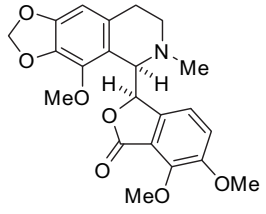
1. Introduction

Opium alkaloid (−)-α-noscapine (narcotine), which was originally isolated from *Papaver somniferum L.*,[1] is a classical non-addictive antitussive agent without significant toxicity.[2] It has been found that (−)-α-noscapine also displays other potential clinical utilities[3] for the treatment of cancer, stroke, anxiety, cerebral edema, and so on. Natural noscapine (α- or *erythro*-form) contains two contiguous chiral carbon centers: C-5′ at tetrahydroisoquinoline ring and C-3 at phthalide framework. In contrast, its diastereoisomers (β-noscapine, *threo*-form) are synthetic compounds[4] exhibiting less biological activities.

Clinically used (−)-α-noscapine can be provided through extraction from plant resource[5] or possible resolution of synthetic (±)-α-noscapine (**1**). So far, the total synthesis of (±)-α-noscapine is still limited. The pioneer work was reported by Robinson and Perkin[6] who constructed C5′–C3 bond through direct condensation between cortanine and meconine, which were produced by degradation of natural (−)-α-noscapine. Shono et al.[7] developed zinc-promoted reductive coupling of 3-bromo-meconine to the iminium salt of cotarnine to construct C5′–C3 bond. Alternatively, Kerekes and Bognár.[8] and Szántay et al.[9] synthesized tetrahydroisoquinoline skeleton through Bischler–Napieralski reaction after formation of C5′–C3 bond. However, the main problem for these procedures was formation of nearly equivalent (±)-β-noscapine and/or other regioisomers. Therefore, efficient diastereoselective total synthesis of (±)-α-noscapine without production of any undesired regioisomers is still very important.



α-noscapine (*erythro*-form)



β-noscapine (*threo*-form)

2. Results and discussion

Herein, we report a new approach employing Bischler–Napieralski cyclization as a key step for the total synthesis of (±)-α-noscapine (Scheme 1). We envisioned that by installing a removable blocking group (such as Br) onto C-9′ position,[10] the formation of undesired regioisomers (C5′–C9′ connection) would be exclusively avoided during Bischler–Napieralski cyclization. The produced imine could be diastereoselectively reduced into tetrahydroisoquinoline. The intermediate **2** could be obtained from meconine-3-carboxylic acid (**3a**) and arylethylamine **4**. We would also describe here a facile synthesis of **3a** from commercially available carboxylic acid **5a** and glyoxylic acid (**6**).

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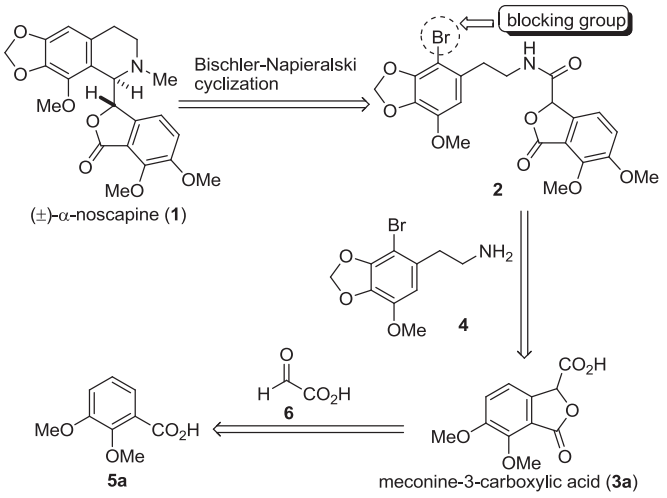


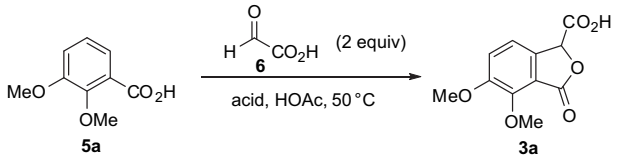
Scheme 1. Retrosynthetic analysis of (±)-α-noscapine.

3-Substituted-phthalides are very important molecules as valuable pharmacological compounds and versatile building blocks for medicinal chemistry.[11] Among them, phthalide-3-carboxylic acid derivatives, such as **3a** are supposed to be potentially useful intermediates for the synthesis of many phthalide tetrahydroisoquinoline alkaloids.[12] The preparation of phthalide-3-carboxylic acids have been well documented over the past decades,[13] however, those procedures inevitably involved many unsatisfactory aspects, such as the use of strong organic base (LDA) or very toxic reagent (KCN or $Pb(OAc)_4$), air/moisture-sensitive conditions, multi-steps' sequence, low reaction yield, and so on.

We gratifyingly found that meconine-3-carboxylic acid (**3a**) could be easily prepared from simple 2,3-dimethoxybenzoic acid (**5a**) and glyoxylic acid (**6**) in the presence of concentrated sulfuric acid with acetic acid as solvent at 50 °C in one-pot (Table 1, entry 2 vs 1). Two equivalents of sulfuric acid were found to be optimal for high yield (entry 3 vs 2 and 4). The reaction could also proceed similarly in trifluoroacetic acid as solvent (entry 10). Further optimization studies revealed that the use of other Brønsted acids (entries 5 and 6) or Lewis acids (entries 7–9) afforded poor to moderate yield. In addition, neither use of other solvent (e.g., entry 11) nor elevation of reaction temperature (entry 12) could improve the reaction yield furthermore.

We then applied the above optimal reaction conditions for other benzoic acid derivative substrates. The results are shown in Table 2. Electron-donating groups seemed to be important for the reaction. Phthalide-3-carboxylic acids **3b–f** were easily obtained in up to 81% yield.

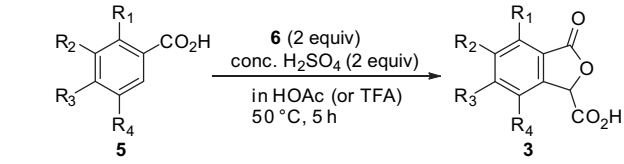
Table 1
Optimization of the reaction between **5a** and **6**

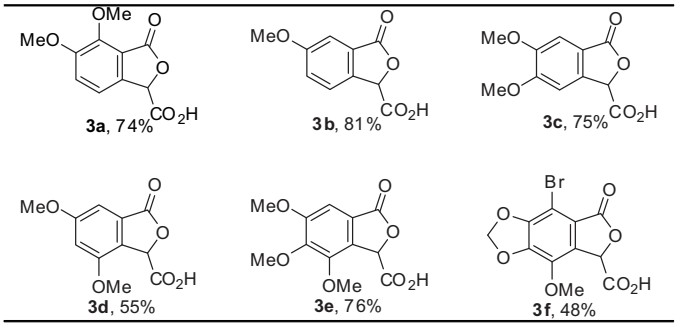


Entry[a]	Acid (equiv)	Time (h)	Yield[b](%)
1	None	20	0
2	H_2SO_4 (1.0)	5	46
3	H_2SO_4 (2.0)	5	80
4	H_2SO_4 (3.0)	5	64
5	TfOH (2.0)	5	61
6	TsOH (2.0)	5	8
7	$BF_3 \cdot Et_2O$ (2.0)	20	67
8	$TiCl_4$ (2.0)	20	25
9	$ZnCl_2$ (2.0)	20	18
10[c]	H_2SO_4 (2.0)	5	77
11[d]	H_2SO_4 (2.0)	5	14
12[e]	H_2SO_4 (2.0)	5	77

[a] Reactions were carried out with 0.1 mol of **5a** and 0.2 mol of **6** in 50 mL HOAc at 50 °C.
[b] Determined by HPLC analysis.
[c] Reaction was run in 50 mL TFA.
[d] Reaction was run in 50 mL THF.
[e] Reaction was run at 60 °C.

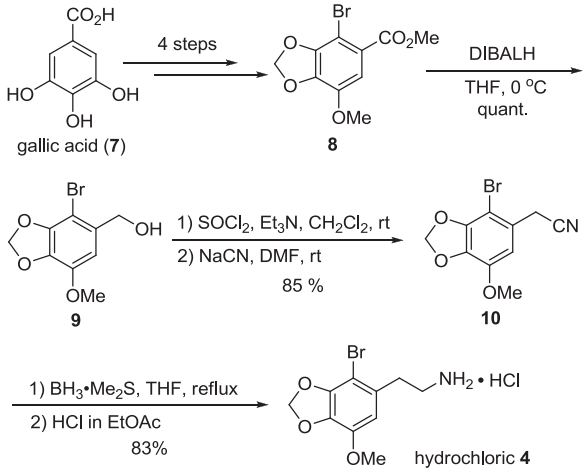
Table 2
Concise synthesis of some phthalide-3-carboxylic acids (**3**)[a]





[a] The reactions were carried out with 0.1 mol of **5** and 0.2 mol of **6** with H_2SO_4 in 50 mL HOAc (**3a–e**) or in 50 mL TFA (**3f**) at 50 °C for 5 h. The isolated yield was shown for each product.

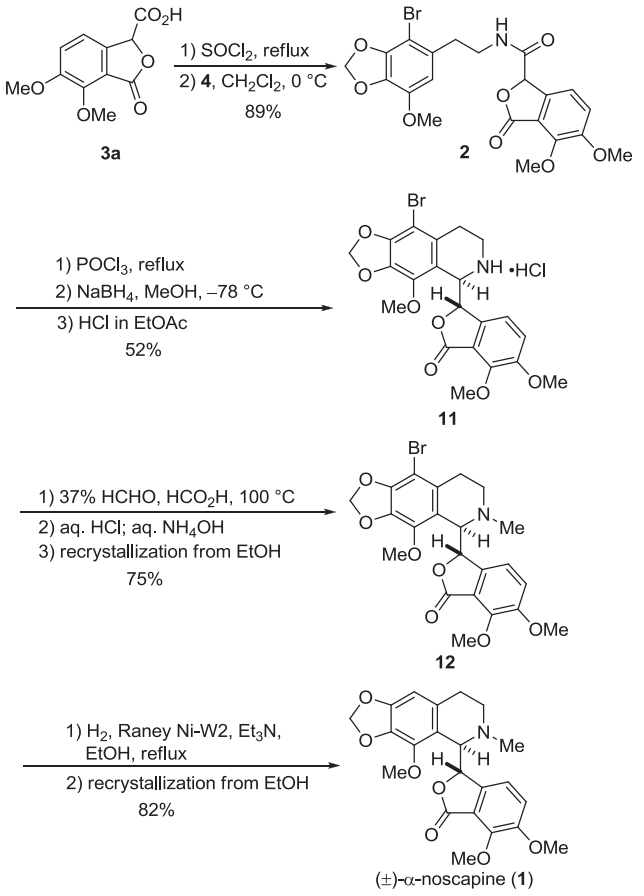
The synthesis of another intermediate **4** (Scheme 2) commenced with the transformation of commercially available gallic acid (**7**) into the bromo-substituted aryl carboxylate **8**,[14] which was quantitatively reduced into the benzyl alcohol **9** by DIBALH at 0 °C. Subsequent cyanation took place to afford the nitrile **10** in 85% yield over two steps. Next, reduction of the nitrile into primary amine was achieved with $BH_3 \cdot Me_2S$ in refluxed THF.[15] Further treatment of the amine with hydrochloric ethyl acetate afforded stable hydrochloric **4**. Thus, blocking group Br was successfully installed and was ready for the completion of our total synthesis of (±)-α-noscapine.



Scheme 2. Synthesis of intermediate **4**.

With the meconine-3-carboxylic acid **3a** and hydrochloric **4** in hand, we easily conducted the amide formation (C5′–C3 bond

formation) from the acyl chloride of **3a** and free amine **4** in 89% yield (Scheme 3). The next step was typical Bischler–Napieralski reaction in the presence of $POCl_3$. As we had expected, cyclization smoothly occurred to afford labile imine, which was then directly reduced to generate tetrahydroisoquinoline. After extensive tuning of this reduction, it was found that low reaction temperature was crucial for the high diastereoselectivity and relatively high yields by using $NaBH_4$ or $NaBH_3CN$ (Table 3, entries 1–6, 100 mg scale). In the case of L-Selectride, the reduction did not occur at −78 °C (entry 7). Eventually, the reaction was scaled up as described in entry 8 (3.0 g scale) by $NaBH_4$ at −78 °C to give the intermediate in 52% isolated yield with >23:1 dr.[16] Subsequently, Eschweiler–Clarke reaction took place to furnish N-methylation compound **12** in 75% yield. Finally, the tetrahydroisoquinoline underwent atmospheric hydrogenation in the presence of Raney Ni-W2 to remove the blocking group Br cleanly.[17] Further recrystallization afforded pure (±)-α-noscapine (**1**) in 82% yield over two steps.

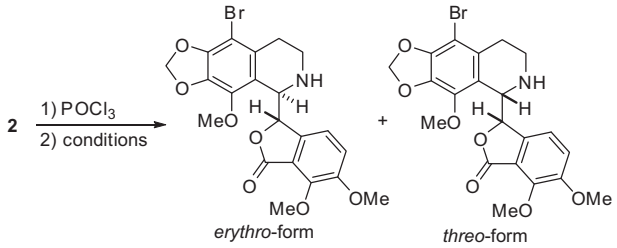


Scheme 3. Completion of the synthesis of **1**.

3. Conclusions

In summary, the first diastereoselective total synthesis of (±)-α-noscapine has been completed. The prominent features of our strategy include: (i) a concise synthesis of key intermediate phthalide-3-carboxylic acid from benzoic acid derivative and glyoxylic acid in the presence of concentrated sulfuric acid with HOAc or TFA as solvent; (ii) the installation of Br as a removable blocking group to avoid the formation of undesired regioisomers in Bischler–Napieralski cyclization; and (iii) highly diastereoselective reduction with $NaBH_4$ at low temperature afforded desired *erythro*-type phthalide tetrahydroisoquinoline structure. It should also be noted here some intermediates (such as **4** and **10**–**12**) were easily purified by recrystallization without performing column chromatography.

Table 3
Investigation of the diastereoselective reduction



Entry[a]	Reducing agent (3.0 equiv)	Temp (°C)	dr[b] (α/β)	Yield[c] (%)
1	$NaBH_4$	0	13:1	55
2	$NaBH_4$	−25	16:1	57
3	$NaBH_4$	−50	22:1	61
4	$NaBH_3CN$	−50	11:1	56
5	$NaBH_4$	−78	23:1	62
6	$NaBH_3CN$	−78	15:1	58
7[d]	L-Selectride	−78	ND	trace
8	$NaBH_4$	−78	28:1	52

[a] Reactions were run in methanol for 10 h. Entries 1–7 were carried out on 100 mg scale, whereas entry 8 was on 3.0 g scale.
[b] The dr (α/β or *erythro*/*threo*) was determined by LC–MS and HPLC analysis of the crude reaction mixture.
[c] HPLC yield for entries 1–7, and isolated yield for entry 8.
[d] Reaction was run in THF for 10 h.

4. Experimental section

4.1. General information

Infrared (IR) spectra were recorded on a Bruker IFS 55 Fourier transform infrared spectrophotometer. NMR spectra were recorded on Bruker ARX-300 MHz or 600 MHz spectrometer. Chemical shifts in $CDCl_3$ or DMSO-d_6 were reported in the scale relative to TMS or DMSO-d_5 (0 or 2.50 ppm for ^1H NMR), and $CDCl_3$ or DMSO-d_6 (77.0 or 39.6 ppm for ^{13}C NMR) as an internal reference, respectively. HRMS were measured on a Bruker MicrOTOF-Q spectrometer. HPLC and LC–MS analysis was carried out on the same liquid chromatographic systems, containing Agilent HP1100 LC/MS Ion Trap SL (positive mode; Phenomen kromasil C18 column; 30 °C; methanol/aqueous ammonium acetate (10 mM)/formic acid=50/50/0.4 (v/v%) as mobile phase; 0.5 mL/min. HPLC was detected by UV at 234 nm. MS was detected by 4000 V capillary voltage; 8 L/min drying gas flow at 325 °C; 30 psi nebulizing gas pressure; helium as collision gas). Column chromatography was performed with silica gel (300–400 mesh). Melting points were determined with Fisher–Johns melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was freshly distilled over sodium benzophenone ketyl. Toluene and dichloromethane were distilled from CaH_2. Reactions were carried out using flame-dried glasswares in dry solvents under an argon atmosphere unless otherwise stated.

4.2. Experimental procedures

*4.2.1. General procedure for the synthesis of phthalide-3-carboxylic acid 3 (**3a**–**e**).* A mixture of the aromatic carboxylic acid **5** (0.1 mol), glyoxylic acid monohydrate (**6**) (0.2 mol), concd H_2SO_4 (10.7 mL, 0.2 mol) and glacial acetic acid (50.0 mL) was stirred at 50 °C for 5 h until the completion of the reaction indicated by TLC. It was cooled to room temperature, then poured into ice water. The formed precipitate was filtered, washed with cold water, and dried to give the phthalide-3-carboxylic acid **3**.

*4.2.1.1. 1,3-Dihydro-4,5-dimethoxy-3-oxo-1-isobenzofurancarboxylic acid (**3a**).* Yield: 73%; white solid, mp

157–159 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.49 (d, 1H, J=8.3 Hz), 7.32 (d, 1H, J=8.3 Hz), 6.00 (s, 1H), 3.90 (s, 3H), 3.85 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$): δ 171.6, 166.8, 153.6, 148.6, 135.6, 119.6, 117.5, 116.7, 75.5, 62.5, 56.8; IR (KBr) 3308, 1775, 1598, 1497, 1454, 1273, 1168, 1042, 1024 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{11}O_6$ $[M+H]^+$ 239.0550, found 239.0554.

*4.2.1.2. 1,3-Dihydro-5-methoxy-3-oxo-1-isobenzofurancarboxylic acid (**3b**).* Yield: 81%; white solid, mp 169–171 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.88 (br s, 1H), 7.62 (d, 1H, J=8.70 Hz), 7.40 (d, 1H, J=8.70 Hz), 7.37 (s, 1H), 6.13 (s, 1H), 3.86 (s, 3H); ^{13}C NMR(75 MHz, DMSO-d_6): δ 169.5, 168.4, 160.9, 137.4, 125.8, 124.1, 123.2, 107.8, 77.3, 56.0; IR (KBr) 3428, 2843, 2636, 1782, 1735, 1622, 1493, 1291 cm^{-1}; HRMS (ESI): calcd for $C_{10}H_9O_5$ $[M+H]^+$ 209.0444, found 209.0448.

*4.2.1.3. 1,3-Dihydro-5,6-dimethoxy-3-oxo-1-isobenzofurancarboxylic acid (**3c**).* Yield: 75%; white solid, mp 203–205 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.32 (s, 1H), 7.15 (s, 1H), 6.04 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR(75 MHz, DMSO-d_6): δ 169.7, 168.5, 155.0, 150.9, 139.5, 116.0, 106.1, 104.5, 76.9, 56.3, 56.1; IR (KBr) 3239, 3006, 2945, 1778, 1604, 1500, 1457, 1318 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{11}O_6$ $[M+H]^+$ 239.0550, found 239.0553.

*4.2.1.4. 1,3-Dihydro-5,7-dimethoxy-3-oxo-1-isobenzofurancarboxylic acid (**3d**).* Yield: 55%; white solid, mp 184–187 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.94 (s, 2H), 5.88 (s, 1H), 3.86 (s, 6H); ^{13}C NMR(75 MHz, DMSO-d_6): δ 169.7, 168.1, 163.0, 155.1, 127.2. 126.1, 105.6, 99.3, 77.0, 56.3, 56.2; IR (KBr) 3463, 2940, 2842, 2527, 1962, 1735, 1625, 1498, 1329, 1031 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{11}O_6$ $[M+H]^+$ 239.0550, found 239.0555.

*4.2.1.5. 1,3-Dihydro-5,6,7-trimethoxy-3-oxo-1-isobenzofurancarboxylic acid (**3e**).* Yield: 76%; white solid, mp 139–142 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.90 (br s, 1H), 7.22 (s, 1H), 6.00 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 169.4, 156.8, 148.0, 147.2, 129.2, 120.4, 103.1, 75.7, 61.2, 60.9, 56.6; IR (KBr) 3430, 3017, 2954, 1872, 1725, 1615, 1482, 1615, 1482, 1352, 1109 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{13}O_7$ $[M+H]^+$ 239.0656, found 239.0659.

*4.2.2. 8-Bromo-4-methoxy-5,7-dihydro-7-oxo-1,3-benzodioxole-5-carboxylic acid (**3f**).* A mixture of 2-bromo-5-methoxy-3,4-methylenedioxybenzoic acid (2.8 g, 10.0 mmol), glyoxylic acid monohydrate (1.84 g, 20.0 mmol), concd H_2SO_4 (1.1 mL, 20.0 mmol), and trifluoroacetic acid (5.0 mL) was stirred at 50 °C for 5 h until the completion of the reaction indicated by TLC. It was cooled to room temperature, poured into ice water (50 mL), and extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (50 mL×2), dried over anhydrous Na_2SO_4, filtered through a short silica gel pad and concentrated in vacuo to give the title compound **3f** (1.6 g). Yield: 48%; white solid, mp 180–182 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.34 (s, 1H), 6.30 (s, 1H), 5.87 (s, 1H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.7, 166.8, 150.2, 142.3, 136.6, 134.7, 116.3, 104.1, 90.3, 75.4, 59.9; IR (KBr) 3430, 2922, 2317, 1780, 1626, 1497, 1439, 1331, 1122, 1056 cm^{-1}; HRMS (ESI), calcd for $C_{11}H_8BrO_7$ $[M+H]^+$ 330.9448, found 330.9447.

*4.2.3. Methyl 4-bromo-7-methoxy-1,3-benzodioxole-5-carboxylate (**8**).* Prepared from commercially available gallic acid in four steps.[14] Yield: 57% (for four steps); white solid, mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.13 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 147.9, 142.2, 138.3, 124.2, 112.3, 102.4, 94.5, 56.7, 52.3; IR (KBr) 2949, 2838, 1855, 1724, 1625, 1595, 1488, 1432, 1326, 936, 757 cm^{-1}; HRMS (ESI): calcd for $C_{10}H_{10}BrO_5$ $[M+H]^+$ 288.9706, found 288.9713.

*4.2.4. 4-Bromo-7-methoxy-1,3-benzodioxole-5-methanol (**9**).* To a solution of **8** (14.4 g, 50.0 mmol) in THF (100.0 mL) at 0 °C was added dropwise DIBALH (1.0 mol/L in hexane, 150.0 mL, 150.0 mmol). This mixture was stirred at 0 °C for 30 min, then quenched by aq Rochelle salt (1 mol/L, 200 mL). It was evaporated in vacuo to remove the organic solvents, and water (100 mL) and CH_2Cl_2 (100 mL) was added to the residue. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (100 mL×2). The combined organic layer was washed with brine (150 mL×2), dried over anhydrous Na_2SO_4, filtered through a short silica gel pad and concentrated in vacuo to give **9** (13.0 g) as a white solid. Yield: 99%; mp 139–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H), 6.06 (s, 2H), 4.68 (d, 2H, J=6.24 Hz), 3.91 (s, 3H), 1.88 (t, 1H, J=6.24 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.0, 142.9, 135.0, 133.5, 108.4, 102.0, 93.3, 64.5, 56.7; IR (KBr) 3213, 2904, 1628, 1446, 1342, 1161, 1106, 1036, 699 cm^{-1}; HRMS (ESI): calcd for $C_9H_9BrO_4Na$ $[M+Na]^+$ 282.9576, found 282.9571.

*4.2.5. 4-Bromo-7-methoxy-1,3-benzodioxole-5-acetonitrile (**10**).* To a stirred solution of **9** (13.0 g, 50.0 mmol) and Et_3N (7.7 mL, 0.55 mol) in CH_2Cl_2 (200 mL), $SOCl_2$ (5.5 mL, 75.0 mmol) was added dropwise at 0 °C. The mixture was gradually warmed to 30 °C and then kept at this temperature for 4 h. It was cooled, and then poured into ice water (150 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL×2). The combined organic extracts were successively washed with brine (100 mL×2) and saturated aq $NaHCO_3$ (100 mL), dried over anhydrous Na_2SO_4, filtered through a short silica gel pad and concentrated in vacuo. The obtained crude was dissolved in DMF (100 mL), and NaCN (2.7 g, 55.0 mmol) was added. The mixture was stirred at room temperature overnight and poured into water (250 mL). The precipitate was filtered, washed with water (20 mL×2) and dried. The crude was recrystallized from EtOH to give **10** (11.5 g) as a white solid. Yield: 85%; mp 171–173 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.65 (s, 1H), 6.02 (s, 2H), 3.86 (s, 3H), 3.69 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 146.6, 142.0, 134.6, 122.1, 116.1, 108.2, 101.2, 93.4, 56.0, 22.8; IR (KBr) 2978, 2909, 2248, 1637, 1490, 1445, 1327, 1175, 815, 699 cm^{-1}; HRMS (ESI): calcd for $C_{10}H_8BrNO_3Na$ $[M+Na]^+$ 291.9581, found 291.9580.

*4.2.6. 4-Bromo-7-methoxy-1,3-benzodioxole-5-ethanamine hydrochloride (hydrochloric **4**).* To a solution of **10** (6.7 g, 25.0 mmol) in THF (30.0 mL), borane–methyl sulfide complex in THF (1.0 mol/L, 50.0 mL, 50.0 mmol) was added slowly at 50 °C. After the reaction mixture was refluxed for 10 h, it was quenched with methanol (5.0 mL) at 0 °C and concentrated in vacuo. The residue was boiled with aq HCl (1.0 mol/L, 100 mL) for 1 h, and then cooled. After it was extracted off with ether (30 mL×2), the remaining aqueous layer was adjusted pH 12 with aq NaOH (2.0 mol/L), and extracted with ethyl acetate (100 mL×3). The organic layer was washed with brine (150 mL×2), dried over anhydrous Na_2SO_4. The organic was rotately distilled to around 30 mL, and treated with 1.0 mol/L hydrochloric ethyl acetate (30 mL) at 0 °C. The formed white solid was filtered and dried to give hydrochloric **4** (6.4 g). Yield: 83%; white solid, mp 231–233 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.91 (br s, 2H), 6.70 (s, 1H), 6.08 (s, 2H), 3.83 (s, 3H), 2.90–2.96 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 146.8, 142.6, 134.3, 129.9, 110.3, 101.9, 94.3, 56.6, 32.2; IR (KBr) 3400, 3051, 2897, 2014, 1628, 1496, 1434, 1165, 1104, 933, 822 cm^{-1}; HRMS (ESI): calcd for $C_{10}H_{13}BrNO_3$ $[M+H]^+$ 274.0073, found 274.0079.

*4.2.7. N-[2-(4-bromo-7-methoxy-1,3-benzodioxol-5-yl)ethyl]-1,3-dihydro-4,5-dimethoxy-3-oxo-1-isobenzofurancarboxamide (**2**).* A

mixture of **3a** (2.4 g, 10 mmol) and $SOCl_2$ (10.0 mL) was refluxed for 2 h, and vacuum evaporated to remove the excess $SOCl_2$. Then the residue was dissolved in CH_2Cl_2 (20 mL) and a solution of compound **4** (5.48 g, 20.0 mmol) in CH_2Cl_2 (20 mL) was added slowly at 0 °C. After the addition, it was further stirred for 1 h, and the hydrochloric **4** (2.3 g) was recovered by filtration. The filtrate was washed with brine (30 mL×2), dried over anhydrous Na_2SO_4, filtered through a short silica gel pad and concentrated in vacuo to give the title compound **2** (4.4 g). Yield: 89%; white solid, mp 174–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$,): δ 7.51–7.49 (m, 1H), 7.27–7.25 (m, 1H), 6.58 (s, 1H), 6.33 (s, 1H), 6.02 (s, 2H), 5.63 (s, 1H), 4.10 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 3.50 (q, 2H, J=13.2, 6.6 Hz), 2.86 (t, 2H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 153.2, 148.2, 147.0, 142.8, 137.5, 134.3, 131.1, 119.9, 118.3, 116.0, 109.6, 101.8, 95.2, 62.3, 56.8, 39.2, 34.6; IR (KBr) 3352, 2939, 1762, 1677, 1498, 1435, 1274, 1166, 1025, 935 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{21}BrNO_8$ $[M+H]^+$ 494.0440, found 494.0445.

*4.2.8. (±)-α-3-(9-Bromo-5,6,7,8-tetrahydro-4-methoxy-1,3-dioxolo [4,5-g]isoquinolin-5-yl)-6,7-dimethoxy-1(3H)-isobenzofuranone hydrochloride (**11**).* A mixture of the amide **2** (2.96 g, 6.0 mmol) and $POCl_3$ (22.9 mL, 0.25 mol) was refluxed for 2.0 h. It was concentrated, and then vacuum evaporated twice with dry toluene (25 mL×2) for complete removal of the excess $POCl_3$. The residue in methanol (60 mL) was portionwisely added $NaBH_4$ (0.68 g, 18.0 mmol) at −78 °C. It was further stirred at the temperature for 10.0 h, and quenched with 1.0 mol/L hydrochloric methanol (12.0 mL). After rotary removal of methanol, the residue was dissolved in water (50 mL). The aqueous solution was neutralized with 10% aqueous ammonia and extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with brine (30 mL×3), and dried over anhydrous Na_2SO_4. Following the removal of CH_2Cl_2, it was dissolved in ethyl acetate (10.0 mL) and then treated with 1.0 mol/L hydrochloric ethyl acetate (8.0 mL, 8.0 mmol) at 0 °C. The obtained crude was recrystallized from ethanol to give pure *erythro*-**11** as a white solid (1.60 g). Yield: 52%; mp 221–223 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.36 (d, 1H, J=8.3 Hz), 6.56 (d, 1H, J=8.3 Hz), 6.13 (s, 1H), 6.11 (s, 1H), 5.81 (s, 1H, J=3.3 Hz), 4.76 (s, 1H, J=3.3 Hz), 3.88 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 2.90–2.85 (m, 1H), 2.47–2.43 (m, 1H), 2.35–2.28 (m, 1H); ^{13}C NMR(75 MHz, DMSO-d_6): δ 166.2, 152.6, 147.7, 147.0, 139.0, 138.8, 134.0, 127.0, 120.4, 118.6, 117.4, 112.9, 102.0, 95.1, 77.8, 61.7, 59.0, 56.8, 52.0, 37.4, 24.8; IR (KBr) 3430, 3144, 2995, 2904, 1763, 1613, 1493, 1449, 1265, 1032 cm^{-1}; HRMS (ESI) : calcd for $C_{21}H_{21}BrNO_7$ $[M+H]^+$ 478.0496, found 478.0500.

*4.2.9. (±)-α-3-(9-Bromo-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxy-1(3H)-isobenzofuranone (**12**).* After the mixture of compound **11** (0.51 g, 1.0 mmol) in 37% formaldehyde (2.0 mL, 26.6 mmol) and 88% formic acid (5.0 mL) was stirred at 100 °C for 2 h, it was concentrated in vacuo. The residue was treated with aq HCl (1.0 mol/L, 12.0 mL) and activated charcoal (0.1 g) at 70 °C for 1 h. Following the filtration, the aqueous layer was adjusted pH 10 with 10% aqueous ammonia at 0 °C, and extracted with CH_2Cl_2 (10 mL×3). The combined organic layer was washed with brine (10 mL×3), dried over anhydrous Na_2SO_4 and concentrated to give the crude, which was further recrystallized from ethanol to afford the title compound **12** (0.37 g). Yield: 75%; white solid, mp 152–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (d, 1H, J=8.2 Hz), 6.31 (d, 2H, J=8.2 Hz), 6.03 (s, 2H), 5.50 (d, 1H, J=4.5 Hz), 4.34 (d, 1H, J=4.5 Hz), 4.10 (s, 3H), 3.99 (s, 3H), 3.89 (s, 3H), 2.76–2.64 (m, 2H), 2.52 (s, 3H), 2.48–2.43 (m, 1H), 2.01–1.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 152.3, 147.8, 146.5, 141.2, 140.0, 134.2, 130.3, 119.6, 119.0, 118.3, 117.5, 101.0, 95.5, 81.3, 62.3, 60.9, 59.4, 56.8, 48.4, 45.2, 25.9; IR (KBr) 3437, 2942, 2849, 2798, 1755, 1610, 1499, 1441, 1265, 1032, 942 cm^{-1}; HRMS (ESI): calcd for $C_{22}H_{23}BrNO_7$ $[M+H]^+$ 492.0652, found 492.0655.

*4.2.10. (±)-α-Noscapine (**1**).* A mixture of 12 (0.25 g, 0.5 mmol), Et_3N (0.14 mL, 1.0 mol), Raney Ni-W2 (0.2 g) and ethanol (20 mL) was refluxed for 30 h under atmospheric hydrogen. After filtration and removal of the solvent, the residue was treated with CH_2Cl_2 (20 mL). The organic layer was washed with brine (10 mL×2), dried over anhydrous Na_2SO_4 and concentrated to give the crude, which was recrystallized from ethanol to afford α-noscapine (**1**) as a pure product (0.17 g). Yield: 82%; white solid. The data of (±)-α-noscapine (*erythro*-1) is in accordance with lit.[9,18] mp 231–234 °C (lit.[9] 234–236 °C); ^{1}H NMR (300 MHz, $CDCl_3$):δ6.95 (d, 1H, J=8.2 Hz), 6.30 (s, 1H), 6.07 (d, 1H, J=8.2 Hz), 5.93 (s, 2H), 5.57 (d, 1H, J=4.1 Hz), 4.39 (d, 1H, J=4.1 Hz), 4.09 (s, 3H), 4.04 (s, 3H), 3.86 (s, 3H), 2.64–2.57 (m, 1H), 2.54 (s, 3H), 2.41–2.29 (m, 2H), 1.95–1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$):δ 168.1, 152.1, 148.3, 147.6, 141.1, 140.4, 134.0, 132.1, 120.2, 118.1, 117.6, 117.1, 102.3, 100.7, 81.8, 62.3, 60.8, 59.4, 56.7, 50.0, 46.3, 28.1; IR (KBr) 3430, 2941, 2317, 1756, 1623, 1496, 1273, 1086, 1035, 1008 cm^{-1}; HRMS (ESI), calcd for $C_{22}H_{24}NO_7$ $[M+H]^+$ 414.1547, found 414.1545.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra are provided. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.05.060.

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