Tetrahedron: *Asymmetry* 26 (2015) 1145–1149

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric total synthesis of (*S*)-isocorydine

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ARTICLE INFO

Article history:
Received 19 June 2015
Accepted 3 September 2015
Available online 3 October 2015

ABSTRACT

The asymmetric total synthesis of (*S*)-isocorydine, a potential drug for the cure of hepatocellular carcinoma, is described. Asymmetric transfer hydrogenation of 3,4-dihydroisoquinoline using a chiral Ru(II) catalyst was applied to the synthesis of isocorydine as the key step, in which the ee value achieved is up to 99%. The overall yield is 9.4% after 12 synthetic procedures.

1. Introduction

Isocorydine (Fig. 1), a tetracyclic aporphine alkaloid, which is abundant in natural resources, such as *Dicranostigma leptopodum* (Maxim.) Fedde, *Stephania brachyandra* Diets, and *Dactylicapnos scandens* (D. Don) Hutch., has wide bioactivities including antiarrhythmic, vasodilation, antihypoxic, and so on.[1] In 2010, isocorydine hydrochloride tablets were approved as a prescription drug by the China Food and Drug Administration to act as spasmolytic analgesics to cure the pain caused by spasms of the stomach, intestines, gallbladder, and pancreas.[2] Recent studies have showed that isocorydine from *Papaveraceae* sp. had an inhibitory effect on the growth of hepatocellular carcinoma cell lines through the induction of G2/M phase cell cycle arrest and apoptosis.[3] Further research indicated that isocorydine could decrease the percentage of side population cells dramatically in hepatocellular carcinoma cell lines and sensitized cancer cells to doxorubicin, a conventional clinical drug for hepatocellular carcinoma. The xenograft model revealed that isocorydine selectively reduced the size and weight of the side population-induced tumor masses in vivo. The growth of side population cells arrested in G2/M in the early stage of isocorydine treatment; later it induced apoptosis. Furthermore, the expression of programed cell death 4, a tumor suppressor gene, was increased after treatment with isocorydine. These findings implied that isocorydine is a potential therapeutic drug for targeting the side population cancer cells of hepatocellular carcinoma.[4] Considering the intermediate anticancer ability of isocorydine and high dosage needed to achieve an effect on hepatocellular carcinoma, a series of derivatives of isocorydine have been prepared in order to increase the anticancer activity compared with isocorydine, among which 8-amino-isocorydine was a potential drug for the treatment of liver carcinoma due to its good inhibitory effect on murine hepatoma H_{22}-induced tumors.[5]

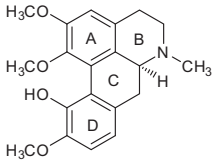

Figure 1. Chemical structure of isocorydine.

In general, isocorydine is extracted by chromatographic methods using silica gel columns from natural plants such as *Dicranostigma leptopodum* (Maxim.) Fedde, *Stephania brachyandra* Diets, and *Dactylicapnos scandens* (D. Don) Hutch. In particular, isocorydine has been abundantly extracted by our team from *Dicranostigma leptopodum* (Maxim.), which is mainly distributed in the northwest of China and used as a folk medicine for the treatment of tonsillitis and hepatitis, and long term inflammation.[6] Generally, isocorydine was obtained from isocorydine-derived plants through extraction with ethanol or methanol, acidification of the extract, alkalization, extraction with chloroform, and chromatography on a silica gel column. The maximum yield of isocorydine extracted from plants so far is 0.125%.[5,6] The disadvantages of this common method using silica gel column chromatography to obtain isocorydine, include the waste of solvent, time, and labor, an excess use of toxic solvent, which in turn can cause damage to the environment and also cause harm to human health, the high cost of production,

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http://dx.doi.org/10.1016/j.tetasy.2015.09.008
0957-4166/

low efficiency, and so on. Moreover, with the restriction of isocorydine from natural sources, it is necessary to develop a simple and efficient synthetic method for isocorydine to solve the resource problem and provide technical support for studying the synthesis of isocorydine derivatives in future work. Although several total syntheses[7] of isocorydine have been reported, the asymmetric synthesis of isocorydine has not yet been studied. Herein, an asymmetric synthetic route of isocorydine was developed and the overall yield was 9.4% after 12 steps with an ee value up to 99%. The purification of the intermediate products in this route was simplified using recrystallization or removing further purification altogether. Hence the need for flash column chromatography was minimized, which would impede future production of isocorydine on a large scale. Meanwhile, the need for toxic solvents and labor was also reduced and thus this route would be an environmentally friendly method.

2. Results and discussion

Due to the restriction of isocorydine from a natural resource and the good anticancer activities of isocorydine[3,4] and isocorydine derivatives against hepatocellular carcinoma,[5] there is a need to develop a synthetic method to obtain isocorydine. Based on the various synthetic methods of aporphine alkaloids and a retrosynthetic analysis of isocorydine, we realized that the key points of the synthetic route to isocorydine were the construction of the tetracyclic structure and the stereogenic center. The B ring was firstly constructed via a Bischler–Napieralski reaction by which the dihydroisoquinoline fragment in isocorydine could be built. The C ring could be constructed by an intramolecular coupling reaction using a transition metal and finally the tetracyclic structure of isocorydine was successfully established. The stereogenic center of isocorydine was created using suitably designed chiral Ru(II) complexes developed by Noyori et al.[8] The synthetic route to isocorydine is designed and described in Scheme 1.

3-Hydroxy-4-methoxybenzaldehyde **1** was chosen as the starting material, through aromatic electrophilic substitution of hydrogen by bromine to obtain compound **2** in 65% yield after recrystallization from ethanol.[9] The phenolic hydroxyl was protected by a benzyl group to give compound **3** in 86% yield, which could be readily removed in the final step.[10] The reduction of the formyl group by $NaBH_4$ at room temperature[11] provided the benzylic alcohol **4** in 90% yield. The substitution of hydroxyl by chloride[12] gave benzylic chloride **5** in 99% yield. Substitution of the chloride by cyano[12] afforded phenylacetonitrile **6** in 84% yield, which extended the carbon chain. Hydrolysis of the cyano group with sodium hydroxide provided the key intermediate trisubstituted phenylacetic acid **7** in 83% yield after recrystallization from ethyl acetate.[13] Acid **7** and 3,4-dimethoxyphenethylamine **8** were heated at 175 °C for 3 h to obtain amide **9** in 89% yield after recrystallization in ethyl acetate.[14] The subsequent Bischler–Napieralski reaction of amide **9** with $POCl_3$ in CH_3CN gave the B ring via cyclodehydration to give 3,4-dihydroisoquinline **10** in 95% yield, which is unstable at room temperature and thus should be used directly in the next step without further purification.[15] Imine **10** underwent asymmetric hydrogenation using the Noyori chiral catalyst RuCl[(*R*,*R*)-TsDPEN](*p*-cymene)] **15** to provide tetrahydroisoquinoline **11** in 80% yield and with 99% ee, followed by N-methylation[16] to obtain phenylalkyltetrahydroisoquinoline **12** in 93% yield. Intramolecular coupling of phenylalkyltetrahydroisoquinoline **12** using $Pd(OAc)_2$ to construct ring C provided compound **13** in 50% yield,[17] after which hydrolysis of the protecting benzyl group furnished the target product isocorydine **14**.

The key enantioselective reduction step using a Noyori transfer hydrogenation is a powerful method for the hydrogenation of cyclic imines and has also been demonstrated to enantioselectively hydrogenate dihydroisoquinolines[14,18] with excellent selectivities (93–95% ee). The single enantiomer 1,2,3,4-tetrohydroisoquinloine **11** was obtained with high ee under N_2 in DMF, in the presence of catalyst **15** and formic acid/triethylamine (v/v = 5/2). Purification of the free amine **11** was successfully carried out by treatment of the acid hydrochloride during the work-up procedure and product **11** was precipitated as its hydrochloride salt. Another key step was the construction of the C ring with $Pd(OAc)_2$, K_2CO_3 and PPh_3 under N_2 in *N*,*N*-dimethylacetamide. The mechanism of the intramolecular coupling reaction involved in the oxidative addition, involved C–H activation and reductive elimination.[19]

3. Conclusion

A feasible synthetic route for the asymmetric total synthesis of (*S*)-isocorydine has been developed. The enantiomeric excess of the asymmetric hydrogenation of 3,4-dihydroisoquinolie reached 99% with the use of Noyori's catalyst. The overall yield is 9.4% after 12 steps. This study uses regular reactions and reagents and provides the synthesis of isocorydine and sufficient material for future studies on structure–activity relationships.

4. Experimental

4.1. General

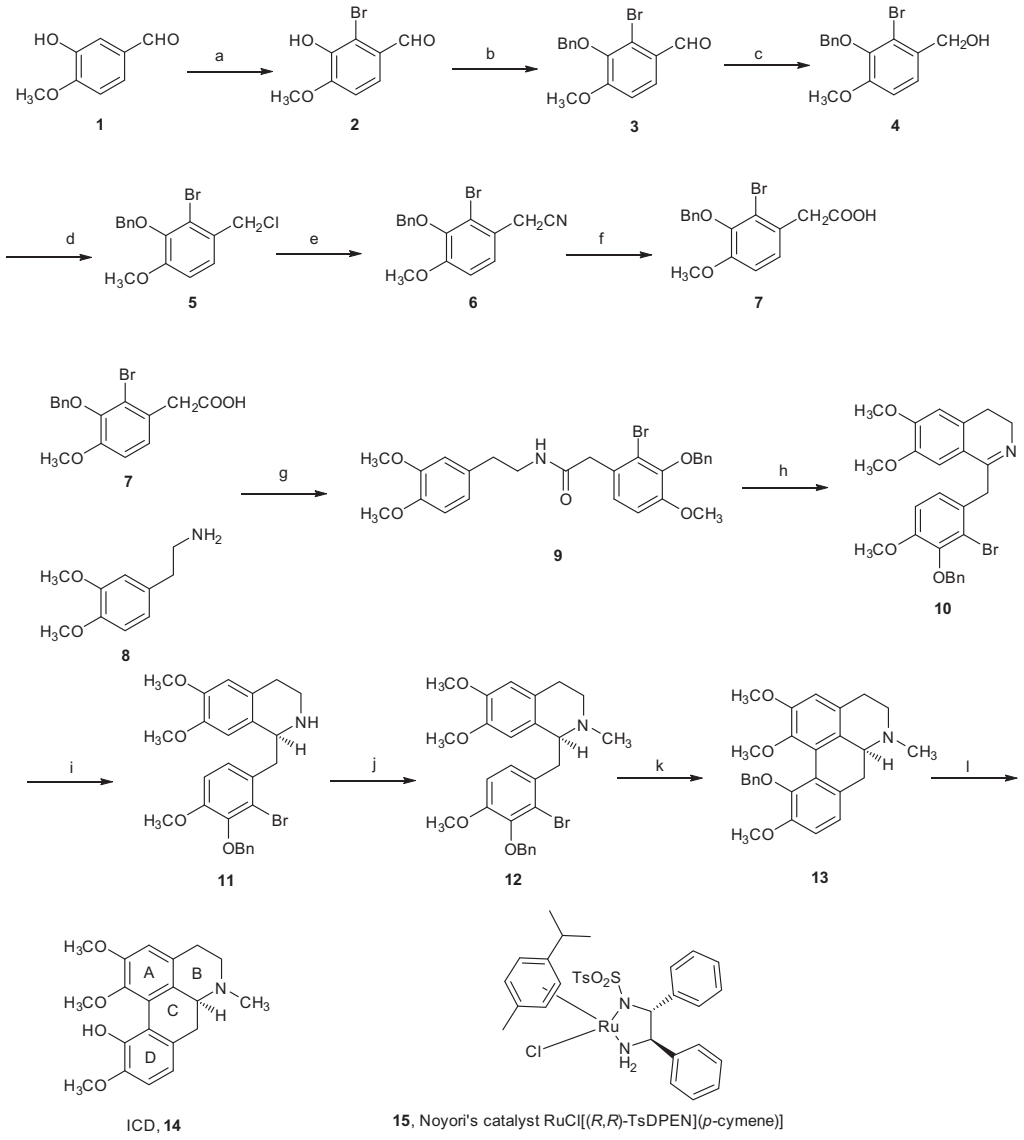
3-Hydroxy-4-methoxybenzaldehyde, 3,4-dimethoxypheny lethylamine, chiral catalyst RuCl[(*R*,*R*)-TsDPEN](*p*-cymene)] **15**, and palladium acetate $Pd(OAc)_2$ were purchased from J&K Scientific Ltd. The Pd/C (10%) catalyst was purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Column chromatography was performed on silica gel (200–300 mesh, Qingdao Hailang Silica Gel Desiccant Co., Ltd, Qingdao, China). TLC was carried out on silica gel GF254 (Qingdao Haiyang Chemical Co., Ltd, Qingdao, China), and spots were visualized under UV light. The solvents were purified by standard procedures and other reagents were purchased from commercial vendors and were used without further purification. NMR spectra were recorded on a Varian INOVA-400 MHz-FTNMR spectrometer with TMS as the internal standard. HRMS (ESI) was recorded on a Bruker Apex II. The enantiomeric excess was determined by Waters 515 system equipped with a ChiralPAK IB column and a UV detector.

4.1.1. 2-Bromo-3-hydroxy-4-methoxybenzaldehyde 2

To a mixture of **1** (10.0 g, 0.066 mol), NaOAc (10.8 g, 0.132 mol), Fe powder (0.34 g, 0.006 mol) was added acetic acid (60 mL), and then the mixture was stirred for 30 min at room temperature. Next, Br_2 (3.5 mL, 0.07 mol) in 15 mL of acetic acid was slowly added to the above mixture at room temperature. The mixture was stirred for another 3 h at the same temperature. Ice-water (125 mL) was then added into the mixture and stirred for another 1 h and filtered. The solid was dried and then recrystallized from EtOH to give **2** as a gray solid (9.9 g, 65%). ^{1}H NMR (400 MHz, Acetone-d_6): δ 10.23(s, 1H, –CHO), 7.49 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H, $-OCH_3$); ^{13}C NMR (100 MHz, Acetone-d_6): δ 192.1, 154.7, 146.0, 129.0, 123.5, 114.5, 111.7, 57.8. HRMS (ESI): m/z calcd for $[M+Na]^+$ $C_8H_7BrNaO_3$ 252.9471, obsd 252.9454.

4.1.2. 3-Benzyloxy-2-bromo-4-methoxybenzaldehyde 3

Compound **2** (9.9 g, 0.043 mol) was dissolved in anhydrous DMF (108 mL). Benzyl bromide (8.55 g, 0.50 mol) was then added slowly, followed by K_2CO_3 (14.3 g, 0.11 mol). The yellow mixture was stirred violently at room temperature for 2.5 h. The mixture



Scheme 1. Synthesis of (*S*)-isocorydine. Reagents and conditions: (a) Br_2, NaOAc, AcOH, rt, 65%; (b) BnBr, K_2CO_3, DMF, rt, 86%; (c) $NaBH_4$, CH_3OH, rt, 90%; (d) $SOCl_2$, DMF, CH_2Cl_2, 0 °C, 99%; (e) KCN, DMF, H_2O, 100 °C, 84%; (f) NaOH, 1,4-dioxane, CH_3OH, H_2O, 100 °C, 83%; (g) 170 °C, N_2, 89%; (h) $POCl_3$, CH_3CN, N_2; (i) Ru(II) catalyst (**15**, CAS: 192139-92-7), HCOOH/NEt_3 = 5:2, DMF, N_2, 8 h, rt, 80%; (j) HCHO, $NaBH_4$, CH_3OH, 93%; (k) $Pd(OAc)_2$, K_2CO_3, PPh_3, *N*,*N*-dimethylacetamide, 175 °C, 50%; (l) Pd/C, H_2, MeOH, 86%.

was parted into an ether–water mixture (1:1, 200 mL of each) and stirred. The organic and aqueous layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layer was washed with water (2 × 100 mL) and saturated NaCl (100 mL), dried over anhydrous Na_2SO_4, and concentrated to give **3** as a white solid (11.8 g, 86%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.54–7.34 (m, 5H), 7.27 (d, J = 8.4 Hz, 1H), 5.01 (s, 2H, –CH_2–), 3.97 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 190.8, 159.0, 144.9, 137.1, 128.8, 128.7, 128.6, 127.4, 127.2, 122.2, 112.6, 74.5 (–CH_2), 57.1 HRMS (ESI): m/z calcd for $[M+Na]^+$ $C_{15}H_{13}BrNaO_3$ 342.9940, obsd 342.9939.

4.1.3. 3-Benzyloxy-2-bromo-4-methoxypenzyl alcohol 4

To a solution of **3** (6.6 g, 0.021 mol) in methanol (50 mL) was added $NaBH_4$ (0.5 g, 0.013 mol). After stirring for 2 h at room temperature, the mixture was evaporated and the residue was dissolved in $CHCl_3$ (40 mL). The organic layer was washed with water (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated to give **4** as a white solid (6.0 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53–7.34 (m, 5H), 7.24 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 4.95 (s, 2H), 4.46 (s, 2H, –CH_2–), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.6, 144.6, 137.5, 134.2, 128.7, 128.6, 128.4, 123.7, 117.2, 112.3, 74.3, 63.0 (–CH_2–), 56.6. HRMS (ESI): m/z calcd for $[M+Na]^+$ $C_{15}H_{15}BrNaO_3$ 345.0097, obsd 345.0099.

4.1.4. 3-Benzyloxy-2-bromo-4-methoxybenzyl chloride 5

To the solution of **4** (6.0 g, 0.019 mol) dissolved in freshly distilled CH_2Cl_2 (60 mL), a catalytic amount of DMF (31 μL) was added. With continuous stirring, $SOCl_2$ (2.3 mL, 32 mmol) was added to the reaction mixture. After 1 h of stirring at 0 °C, the solvent and excess $SOCl_2$ were removed on a rotary evaporator to give **5** as a white solid (6.3 g, 99%). The product was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.32 (m, 5H), 7.19 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 5.01 (s, 2H), 4.68 (s, 2H, –CH_2–), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 145.6, 137.0, 129.6, 128.3, 128.3, 128.0, 126.1,

120.4, 111.2, 74.6, 56.1, 46.6 (–CH_2Cl). HRMS (ESI): m/z calcd for $[M+Na]^+$ $C_{15}H_{14}BrClNaO_2$ 362.9758, obsd 362.9776.

4.1.5. 3-Benzyloxy-2-bromo-4-methoxybenzyl cyanide 6

Compound **5** (6.3 g, 19 mmol) was dissolved in DMF (28 mL). Next, KCN (5.4 g, 83 mmol) and water (8 mL) were added and the mixture was heated at 100 °C for 2.5 h. The reaction mixture was cooled to temperature, diluted with water (22 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The exacts were washed with water (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated to give **6** as a red oil (5.4 g, 84%). The product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53–7.35 (m, 5 H), 7.31 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 4.98 (s, 2H), 4.00 (s, 2 H, –CH_2–), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.5, 145.5, 137.3, 128.7, 128.7, 128.5, 125.9, 123.7, 119.5 (–CN), 118.6, 112.8, 74.4, 56.6, 24.1 (–CH_2–). HRMS (ESI): m/z calcd for $[M+Na]^+$ $C_{16}H_{14}BrNNaO_2$ 354.0100, obsd 354.0106.

4.1.6. 3-Benzyloxy-2-bromo-4-methoxyphenylacetic acid 7

Compound **6** (5.4 g, 16 mmol) in methanol (57.6 mL) and 1,4-dioxane (19.2 mL) was refluxed with NaOH (13.6 g, 0.34 mol) in water (6.4 mL) for 25 h at 100 °C. Evaporation left an oily residue, which was dissolved in water (25 mL). The aqueous solution was acidified with concentrated HCl to pH = 2 in an ice bath, and then the solution was extracted with ethyl acetate (3 × 40 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated to give a yellow solid, which was then recrystallized from ethyl acetate to give **7** as a white solid (4.6 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.39 (s, 1H, –COOH), 7.53–7.34 (m, 5H), 7.15 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 4.94 (s, 2H), 3.85 (s, 3H), 3.68 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2 (–COOH), 152.7, 144.9, 137.6, 128.7, 128.6, 128.4, 128.3, 127.4, 120.7, 112.3, 74.3, 56.6, 41.3. HRMS (ESI): m/z calcd for $[M+Na]^+$ $C_{16}H_{15}BrNaO_4$ 373.0046, obsd 373.0058.

4.1.7. 2-(3-Benzyloxy-2-bromo-4-methoxyphenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide 9

A mixture of compound **7** (1.4 g, 4 mmol) and compound **8** (0.7 g, 4 mmol) contained in a 250 mL four-neck-flask was evacuated and refilled with nitrogen and then placed in an oil bath at 170 °C while passing a slow continuous stream of nitrogen over the solid. The mixture was heated for another 3 h at which point compound **7** had completely melted. The reaction mixture was cooled to room temperature, and the residue was dissolved in CH_2Cl_2 (18 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL), aqueous HCl (10%, 2 × 4 mL), and brine (8 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated by rotary evaporation to provide a brown solid, which was recrystallized from hot ethyl acetate to provide **9** as a white solid (1.82 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (t, J = 4.0 Hz, –CONH–, 1H), 7.54–7.34 (m, 5H), 7.03 (s, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 6.72 (d, J = 8.0 Hz, 1H), 4.93 (s, 2H), 3.84 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.52 (s, 2H), 3.31 (dd, J = 6.0, 12.4 Hz, 2H), 2.67 (t, J = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4 (–CONH–), 152.5, 149.1, 147.7, 144.9, 137.6, 132.4, 129.2, 128.7, 128.6, 128.4, 127.0, 120.9, 120.6, 113.1, 112.4, 112.2, 74.2, 56.6, 56.0, 55.9, 42.6, 40.9, 35.2. HRMS (ESI): m/z calcd for $[M+Na]^+$ $C_{26}H_{28}BrNNaO_5$ 538.1024, obsd 538.1007.

4.1.8. 1-(3-Benzyloxy-2-bromo-4-methoxy)benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline 10

To a solution of amide **9** (2.2 g, 4.3 mmol) in dry CH_3CN (95 mL) was added $POCl_3$ (2.4 mL). The mixture was heated at reflux under N_2 for 2 h, and then it was cooled to room temperature and concentrated to yield yellow oil which was dissolved in CH_2Cl_2 (20 mL) which was adjusted to pH 7–8 with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined CH_2Cl_2 layer was washed with NaCl solution (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated to give **10** as a yellow solid (2.05 g, 95%) which is unstable at room temperature.[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.33 (m, 5H), 7.02 (d, J = 8.0 Hz, 1H), 6.91 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.97 (s, 1H), 5.01 (s, 2H), 4.18 (s, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.74 (t, J = 8.0 Hz, 2H), 2.70 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz , $CDCl_3$): δ 165.5, 152.3, 150.8, 147.4, 145.4, 137.2, 131.6, 130.4, 128.4, 128.3, 128.0, 124.9, 121.3, 120.6, 111.6, 110.2, 109.2, 74.5, 56.2, 56.0, 55.9, 47.1, 42.0, 25.7. HRMS (ESI): m/z calcd for $[M+H]^+$ $C_{26}H_{27}BrNO_4$ 496.1118, obsd 496.1109.

4.1.9. (*S*)-1-(3-Benzyloxy-2-bromo-4-methoxy)benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 11

Freshly prepared imine **10** (2.05 g, 4 mmol) was dissolved in anhydrous DMF, and the solution was degassed for 10 min with N_2. Next, RuCl[(*R*,*R*)-TsDPEN](*p*-cymene)] **15** (CAS: 192139-92-7) (26 mg, 1 mol %) was added followed by HCOOH/NEt_3 (v/v = 5:2, 2.4 mL), and the reaction mixture was stirred at room temperature for 8 h under N_2. The reaction was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate (50 mL × 3). The combined organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated to yield green oil which was relatively pure, but was rather unstable at room temperature. Therefore, the crude greenish product was converted into its HCl salt by treatment with concentrated HCl–MeOH–diether (v/v/v = 1:100:100) ether solution at −20 °C to obtain a light greenish solid **11**·HCl (1.81 g, 80%, >99% ee of the free base). $[\alpha]_D^{24}$ = +63.0 (c 1.12, CH_2Cl_2). HPLC (Chiralpak IB, UV 230, isopropanol/hexane 1:4, 1.0 mL/min), t_r [(*S*)-stereomer] 29.816 min and t_r [(*R*)-stereomer] 35.483 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.32 (m, 5H), 6.99 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 6.59 (s, 1H), 5.05 (s, 2H), 4.24 (dd, J = 3.6, 9.6 Hz, 1H, –CH–), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.35–3.21 (m, 2H), 2.98–2.92 (m, 2H), 2.75 (t, J = 4.0 Hz, 2H), 2.34 (br, 1H, –NH–); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 147.6, 147.1, 145.5, 137.2, 131.6, 130.6, 128.4, 128.3, 128.0, 127.1, 126.7, 120.9, 111.8, 111.3, 109.8, 74.6, 56.2, 56.0, 55.9, 54.8, 42.8, 40.0, 29.4. HRMS (ESI): m/z calcd for $[M+H]^+$ $C_{26}H_{29}BrNO_4$ 498.1274, obsd 498.1275.

4.1.10. (*S*)-1-(3-Benzyloxy-2-bromo-4-methoxy)benzyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinloine 12

To a solution of **11** (1.02 g, 2.04 mmol) in MeOH (64 mL) was added formalin (37%, 4.2 mL). After the mixture was stirred for 30 min at room temperature, it was cooled to 0 °C, after which $NaBH_4$ (2.32 g, 6.13 mmol) was slowly added and the reaction mixture was warmed to room temperature. Stirring for additional 40 min and evaporation of the solvents produced a colorless solid, which was dissolved in 1 M NaOH (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous $NaSO_4$, filtered, and the solvents removed to give **12** as a light yellow solid (0.973 g, 93%). $[\alpha]_D^{24}$ = +70.0 (c 1.03, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.31 (m, 5H), 6.75 (d, J = 8 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.57 (s, 1H), 5.94 (s, 1H), 5.03 (dd, J = 8.0, 16.0 Hz, 2H), 3.89 (t, J = 8.0 Hz, 1H, –CH–), 3.82 (s, 3H), 3.82 (s, 3H), 3.52 (s, 3H), 3.30–3.25 (m, 2H), 2.91–2.83 (m, 2H), 2.63–2.58 (m, 2H), 2.52 (s, 3H, –NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 147.3, 146.2, 145.2, 137.2, 132.2, 129.0, 128.4, 128.3, 128.0, 127.5, 125.9, 121.1, 111.4, 111.3, 111.0, 74.6, 62.1, 56.2, 55.8, 55.4, 46.0, 42.5, 40.9, 25.0. HRMS (ESI): m/z calcd for $[M]^+$ $C_{27}H_{30}BrNO_4$ 512.1431, obsd 512.1340.

4.1.11. (*S*)-11-Benzyloxy-5,6,6a,7-tetrahydro-1,2,10-trimethoxy-6-methyl-4*H*-dibenzo[de,g]quinoline 13

To a solution of compound **12** (0.88 g, 1.7 mmol) in *N*,*N*-dimethylacetamide (4 mL) were added $Pd(OAc)_2$ (0.21 g, 0.9 mmol), PPh_3 (0.46 g, 1.8 mmol), and K_2CO_3 (0.50 g, 3.6 mmol). The mixture was placed in a 100 mL three-neck-flask, degassed for 10 min and then stirred for 1 h at 175 °C with a slow continuous stream of nitrogen. After cooling to room temperature, the reaction mixture was loaded onto a deactivated silica gel column and eluted with ethyl acetate–hexane (v/v = 1:20–3:7) to give **13** as a brown oil (0.35 g, 50%). $[\alpha]_D^{24}$ = +190.0 (*c* 1.02, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.31 (m, 5H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.69 (s, 1H), 4.96 (dd, *J* = 10.0, 20.0 Hz, 2H), 4.13–4.07 (m, 1H, –CH–), 3.82 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.53–3.43 (m, 2H), 3.28–3.24 (m, 2H), 3.21–3.15 (m, 2H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 149.3, 146.6, 145.1, 136.7, 128.6, 128.4, 128.2, 128.1, 126.7, 121.9, 120.5, 120.2, 111.5, 111.4, 111.1, 74.6, 70.8, 56.2, 56.0, 55.3, 53.1, 51.2, 37.5, 23.6. HRMS (ESI): *m*/*z* calcd for $[M+H]^+$ $C_{27}H_{30}NO_4$ 432.2169, obsd 432.2154.

4.1.12. (*S*)-Isocorydine 14

Compound **13** (0.35 g, 0.8 mmol) was placed in methanol (18 mL) and the solution was heated to 80 °C until the compound was dissolved. Next, 10% Pd/C (37 mg) was added to the above solution and stirred under an H_2 atmosphere (0.3 MPa) for 6 h. After the Pd/C catalyst was filtered off, the solvents were removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2/CH_3OH = 50:1, v/v) to furnish the target compound isocorydine (0.23 g, 86%). $[\alpha]_D^{24}$ = +200.0 (*c* 1.05, MeOH) {lit.[20] $[\alpha]_D^{23}$ = +205.0 (*c* 0.2, MeOH)}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (s, 1H, –OH), 6.99 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 4.08–4.04 (m, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 3.39–3.36 (m, 2H), 3.26–3.17 (m, 2H), 3.08–2.98 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.9, 149.1, 144.5, 144.3, 127.2, 126.5, 125.2, 123.4, 119.3, 119.2, 112.0, 111.8, 62.2, 61.6, 56.4, 51.8, 49.0, 41.4, 32.3, 26.0. HRMS (ESI): *m*/*z* calcd for $[M+H]^+$ $C_{20}H_{24}NO_4$ 342.1700, obsd 342.1697. The NMR data corresponded with those in the literature.[21]

Acknowledgments

This work was supported by 'West Light Program', of the Chinese Academy of Sciences (090NKCA127) and the Science and Technology Program of Gansu (1304FKCA062).

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