DOI: 10.1002/cjoc.201400612

A Versatile Total Synthesis of 8-Oxyberberine and Oxohomoberberines

Yun He, Yang Zheng, Li Hai, and Yong Wu*

Key Laboratory of Drug Targeting and Drug Delivery System of the Education Ministry, Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu, Sichuan 610041, China

The total syntheses of 8-oxyberberine and oxohomoberberines were accomplished starting from commercially available 5-bromobenzo[*d*][1,3]dioxole, piperonal and sesamol in high total yield. The key steps involved a modified Pomeranz-Fritsch reaction and the intramolecular Heck cyclization. This approach is short, convenient and suitable for the preparation of homoberberine analogues.

Keywords synthetic method, total synthesis, oxohomoberberines, modified Pomeranz-Fritsch reaction, intramolecular Heck cyclization

Introduction

8-Oxyberberine (**1a**, Figure 1) is a significant natural compound which was isolated from *Acangelisia gusanlung*, *Cocculus orbiculatus*, *Phellodendron amurense* and *Argemone mexicana* Linn.[1] Due to its biological properties such as antitumor, antiarrhythmic and anti-inflammatory activities, scientists have concentrated on the structural modification of 8-oxyberberine for decades.[2]

Changes in the skeleton of natural alkaloids have proved beneficial. Cheng *et al*. modified the 8-oxyberberine to get the 8,8-dialkyldihydroberberines (8,8-DDBs) and investigated their anti-diabetic activity in 2010.[3] The 8,8-DDBs (**I**, Figure 1) promoted glucose uptake and AMPK phosphorylation in L6 myoblasts while it also reduced glucose levels in diabetic mice.

Mitiglinide (trade name Glufast, **II**, Figure 1) is an isoindole compound for the treatment of type 2 diabetes.[4a] Interestingly, the similar isoindole-skeletons have been also observed in Gliclazide (**III**，Figure 1) and Glisindamide (**IV**, Figure 1) which were shown to have an antiatherogenic effect in type 2 diabetes.[4b] Thus, it can be expected that the novel compound **1b** (Figure 1) which was introduced the isoindole moiety to the B-ring of 8-oxoberberine shared structural homology with the chemical compounds mentioned earlier and possessed hypoglycemic ability unique to their parent natural berberine.

In addition, We also found that the azepane ring in the sulfonylurea derivatives, Glidazamide (**V**, Figure 1) and Glisoxepide (**VI**, Figure 1) which inspired us into enlarging the B-ring of 8-oxyberberine to design the novel compound **1c** and **1d** (Figure 1).[4c]

However, our group found that previously reported methods were unsuitable for the synthesis of target compounds because of low overall yields and needing complicated starting materials.[5] Thus, the development of a convenient and short approach for the oxohomoberberines is demanded.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. All manipulations involving air-sensitive materials were performed under argon. TLC was performed using precoated silica gel GF254 (0.2 mm), while column chromatography was performed using silica gel (100－200 mesh). The melting point was measured on a YRT-3 melting point apparatus (Shantou Keji instrument & Equipment Co. Ltd, Shantou, China). ^{1}H NMR spectra were taken on a Varian INOVA400 (Varian, Palo Alto, CA, USA) using $CDCl_3$, DMSO-d_6 and D_2O as solvent. Chemical shifts are expressed in δ, with tetramethylsilane (TMS) functioning as the internal reference, and coupling constants (J) were expressed in Hz. Mass spectra were recorded on a Bruner AmaZon SL (Bruker Daltonics, German).

2-(Benzo[*d*][1,3]dioxol-5-yl)ethanol (5a) A solution of ethylene oxide (6.6 g, 0.15 mol) in dry THF (100 mL) was added dropwise to the solution of benzo[*d*][1,3]dioxol-5-ylmagnesium bromide (13 g, 0.058 mol) in 90 mL of dry THF within 1 h at 0 ℃.

* E-mail: tgxx903@163.com
Received September 7, 2014; accepted October 7, 2014; published online November 3, 2014.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201400612 or from the author.

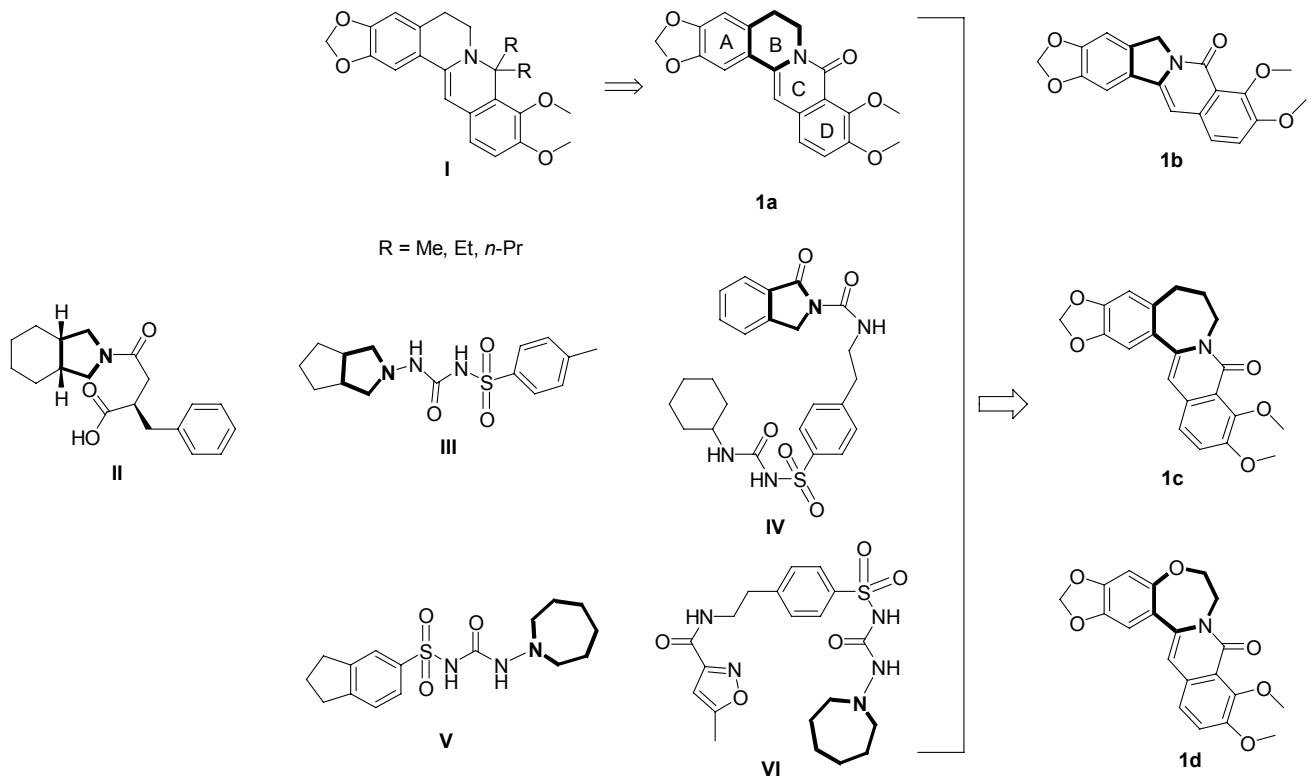


Figure 1 Important molecules in the discovery of hypoglycemic activity of berberine analogues.

After addition, the reaction mixture was allowed to warm to room temperature for 2 h. Then 10 mL of saturated NH_4Cl was added to quench the reaction. The resulting mixture was extracted with diethyl ether (100 mL×3). The combined organic layer was washed with 20 mL of brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified in vacuum to afford **5a** (22.4 g, 0.135 mmol, 90%) as colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 6.755 (d, J= 7.6 HZ, 1H, ArH), 6.719 (s, 1H, ArH), 6.673 (d, J=7.6 Hz, 1H, ArH), 5.926 (s, 2H, OCH_2O), 3.802 (t, J=6.4 Hz, 2H, CH_2), 2.779 (t, J=6.4 Hz, 2H, CH_2).

5b was prepared following the procedure of Harrowven *et al*.[7]

(6-Iodo-1,3-benzodioxol-5-yl)-methanol (**6b**) To a cooled (−5 ℃) solution of piperonyl alcohol **5b** (0.93 g, 6.11 mmol) in $CHCl_3$ (13 mL) were added iodine (1.73 g, 6.8 mmol) and silver trifluroacetate (1.5 g, 6.79 mmol). After stirring for 30 min the reaction was filtered through Celite. The filtrate was washed with saturated $Na_2S_2O_3$ (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow solid. Recrystallization from $CHCl_3$ gave iodine **6b** (1.47 g, 5.29 mmol, 87%) as a white solid. m.p. 108－110 ℃; ^{1}H NMR (400 Hz, $CDCl_3$) δ: 7.232 (s, 1H, ArH), 6.986 (s, 1H, ArH), 5.975 (s, 2H, OCH_2O), 4.588 (s, 2H, $ArCH_2O$), 2.031 (br. s, 1H, OH).

5-(Bromomethyl)-6-iodo-1,3-benzodioxole (**7b**) Concentrated HBr (48%, 4 mL) was slowly added to the alcohol **6b** (1 g, 3.6 mmol) and the resulting suspension was stirred for 2 h at room temperature, then extracted with DCM (30 mL×3). The combined organic phases were washed with Na_2CO_3 (2 mol/L, 50 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give benzyl bromide **7b** (1.1 g, 3.3 mmol, 90%) as a white soild which was used without further purification in the next step. m.p. 72－74 ℃; ^{1}H NMR (400 Hz, $CDCl_3$) δ: 7.248 (s, 1H, ArH), 6.964 (s, 1H, ArH), 5.993 (s, 2H, OCH_2O), 4.557 (s, 2H, $ArCH_2Br$).

3 and **4** were prepared following the procedure of Yang *et al*.[6]

3-(3,4-Methlenedioxyphenyl)-1-propanol (**5c**) The flask was charged with $NaBH_4$ (1.91 g, 51 mmol), acid **4** (3.27 g, 16.8 mmol) and THF (40 mL). After the flask was cooled to 0 ℃ in an ice bath, a solution of iodine (4.27 g, 16.8 mol) dissolved in 40 mL of THF was added slowly and dropwise over 30 min resulting in vigorous evolution of hydrogen. After addition of the iodine was complete and gas evolution had ceased, the flask was heated to reflux for 12 h and then cooled to room temperature, and methanol was added cautiously until the mixture became clear then the mixture was extracted with DCM (30 mL × 3). The combined organic phases were washed with Na_2CO_3 (2 mol/L, 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give benzylic propanol **5c** (2.55 g, 14 mmol, 84%) as a yellow oil which was used without further purification in the next step. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 6.719 (d,

J=7.6 Hz, 1H, ArH), 6.684 (s, 1H, ArH), 6.632 (d, *J*=7.6 Hz, 1H, ArH), 5.904 (s, 2H, OCH_2O), 3.648−3.616 (m, 2H, CH_2), 2.629−2.591 (m, 2H, CH_2), 2.506 (s, 1H, OH), 1.861−1.790 (m, 2H, CH_2).

5-(2-Bromoethoxy)benzo[*d*][1,3]dioxole (5d) The mixture of sesamol **2d** (2 g, 14.5 mmol), sodium hydroxide (695 mg, 17 mmol), TBAB (467 mg, 1.4 mmol) and alcohol (20 mL) was cooled to 30 ℃ after it was heated and refluxed for 1 h. 1,2-Dibromoethane (3.76 mL, 43.4 mmol) was added, heated and refluxed for 24 h, and it was condensed, extracted with ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give a residue, which was purified by silica gel column chromatography using AcOEt/PE (1∶10) as a white solid (1.9 g, 7.8 mmol, 53%). m.p. 74−76 ℃; ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 6.702 (d, *J*=7.2 Hz, 1H, ArH), 6.519 (s, 1H, ArH), 6.342 (d, *J*=7.2 Hz, 1H, ArH), 5.921 (s, 2H, OCH_2O), 4.211 (t, *J*=4.4 Hz, 2H, CH_2), 3.598 (t, *J*=4.4 Hz, 2H, CH_2).

3-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)propan-1-ol (6c) A solution of I_2 (6.66 g, 26 mmol) in dry $CHCl_3$ (15 mL) was added over a suspension of CF_3COOAg (6.28 g, 28 mmol) and propanol **5c** (3.94 g, 22 mmol) in dry $CHCl_3$ (20 mL). After the reaction mixture was stirred at room temperature for 2 h, the resulting AgI precipitate was filtered, and the filtrate was washed with saturated $Na_2S_2O_3$ (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a yellow solid. Recrystallisation from Et_2O gave iodine **6c** (5.35 g, 17 mmol, 80%) as a white solid. m.p. 28−30 ℃; ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 7.210 (s, 1H, ArH), 6.709 (s, 1H, ArH), 5.931 (s, 2H, OCH_2O), 3.701−3.668 (m, 2H, CH_2), 2.742−2.703 (m, 2H, CH_2), 1.923 (br s, 1H, OH), 1.855−1.769 (m, 2H, CH_2).

2-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)ethanol (6a) **6a** was prepared as the above step (yield 89%) as a yellow oil. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 7.212 (s, 1H, ArH), 6.818 (s, 1H, ArH), 5.929 (s, 2H, OCH_2O), 4.876 (br. s, 1H, OH), 3.653 (t, *J*=7.2 Hz, 2H, CH_2), 2.867 (t, *J*=7.2 Hz, 2H, CH_2).

5-(2-Bromoethoxy)-6-iodobenzo[*d*][1,3]dioxole (7d) **7d** was prepared as the above step (yield=83%) as a brown solid. m.p. 91−93 ℃; ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 7.166 (s, 1H, ArH), 6.533 (s, 1H, ArH), 5.959 (s, 2H, OCH_2O), 4.236 (t, *J*=6.8 Hz, 2H, CH_2), 3.648 (t, *J*=6.8 Hz, 2H, CH_2).

5-(3-Bromopropyl)-6-iodobenzo[*d*][1,3]dioxole (7c) A solution of the iodine **6c** (1 g, 3.2 mmol) in dry CH_2Cl_2 (10 mL) at 0 ℃ was treated with CBr_4 (1.14 g, 3.4 mmol) followed by the portionwise addition of triphenylphosphine (0.9 g, 3.4 mmol). The reaction was allowed to warm to room temperature and monitored by TLC. After no starting material was detected, the solvent was removed under reduced pressure. The resulting solid was resuspended in a 1∶1 mixture of Et_2O/pentane and filtered through a pad of silica. The solvent was removed under rotary evaporator to provide the crude bromide **7c** (1.02 g, 2.8 mmol, 87.5%) as a yellow oil, which was carried on to the next step without any further purification. ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 7.200 (s, 1H, ArH), 6.707 (s, 1H, ArH), 5.928 (s, 2H, OCH_2O), 3.428−3.395 (m, 2H, CH_2), 2.793−2.755 (m, 2 H, CH_2), 2.115−2.045 (m, 2H, CH_2).

5-(2-Bromoethyl)-6-iodobenzo[*d*][1,3]dioxole (7a) **7a** was prepared as the above step **(**yield 91%**)** as a yellow solid. m.p. 82−84 ℃; ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 7.234 (s, 1H, ArH), 6.776 (s, 1H, ArH), 5.968 (s, 2H, OCH_2O), 3.499 (t, *J*=7.6 Hz, 2H, CH_2), 3.186 (t, *J*=7.6 Hz, 2H, CH_2).

7,8-Dimethoxyisoquinolin-1(2*H*)-one (10) To 2,3-dimethoxybenzoic acid (**8**) (2 g, 11 mmol) was added $SOCl_2$ (20 mL), and the mixture was stirred at 80 ℃ for 1 h, then the remaining $SOCl_2$ was removed. To the residue in dry DCM (20 mL) at 0 ℃ was added DIPEA (3 mL, 16.9 mmol). The reaction was stirred for 4 min at 0 ℃ before adding 2,2-dimethoxyethanamine (0.9 g, 8 mmol). The reaction was allowed to warm to room temperature and stirred for 20 h. The reaction was washed with 1 equiv. HCl (50 mL), water (50 mL), saturated $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and concentrated to give the *N*-(2,2-dimethoxyethyl) benzamide (**9**) as a yellow oil. To **9** (2.49 g, 9.25 mmol) was added 80% H_2SO_4 (25 mL) at 0 ℃. The reaction was allowed to warm to room temperature and stirred for 22 h. It was then poured over ice and then quenched with saturated $NaHCO_3$. The aqueous solution was extracted with DCM (30 mL × 3). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 7,8-dimethoxyisoquinolin-1(2*H*)-one **10 (**1.63 g, 8 mmol, 86%**)** as a yellow solid which was used without purification. m.p. 150−152 ℃; ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 11.183 (br s, 1H, NH), 7.358 (d, *J*=8.4 Hz, 1H, ArH), 7.288 (d, *J*=8.4 Hz, 1H, ArH), 7.058 (d, *J*=7.2 Hz, 1H, CH=CH), 6.442 (d, *J*=7.2 Hz, 1H, CH=CH), 3.999 (s, 3H, OCH_3), 3.954 (s, 3H, OCH_3); ^{13}C NMR (400 Hz, $CDCl_3$) *δ*: 155.6, 152.7, 149.1, 128.6, 127.7, 124.8, 119.8, 117.7, 105.5, 60.9, 56.1; LC-MS *m*/*z*: 206.1 [M+H].

2-(2-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)-7,8-dimethoxyisoquinolin-1(2*H*)-one (11a) To 7,8-dimethoxyisoquinolin-1(2*H*)-one **10 (**0.26 g, 1.28 mmol**)** and dry DMF (10 mL) was added 60% sodium hydride in mineral oil (0.06 g, 1.54 mmol). The resulting suspension was allowed to stir at 0 ℃ for 1 h. Compound **7a** (0.5 g, 1.4 mmol) in dry DMF (5 mL) was added and the reaction was allowed to watm to room temperature. This suspension was allowed to stir for an additional 15 h. It was then poured into 50 mL water and extracted with DCM (30 mL×3). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give 2-(2-(6-iodobenzo[*d*][1,3]dioxol-5-yl)-ethyl)-7,8-dimethoxyisoquinolin-1(2*H*)-one (**11a**) (0.527 g, 1.1 mmol, 78.5%) as a yellow solid. m.p. 159−161 ℃; ^{1}H NMR (400 Hz, $CDCl_3$) *δ*: 7.317 (d, *J*=8.8 Hz, 1H, ArH), 7.264 (s, 1H, ArH), 7.220 (d, *J*=8.8

Hz, 1H, ArH), 6.819 (d, J=7.2 Hz, 1H, CH=CH), 6.800 (s, 1H, ArH), 6.301 (d, J=7.2 Hz, 1H, CH=CH), 5.940 (s, 2H, OCH_2O), 4.084 (t, J=7.2 Hz, 2H, CH_2), 4.006 (s, 3H, OCH_3), 3.947 (s, 3H, OCH_3), 3.136 (t, J=7.2 Hz, 2H, CH_2); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 160.066, 151.572, 149.468, 148.556, 147.221, 134.195, 132.732, 129.953, 124.305, 122.778, 118.650, 118.386, 116.041, 105.371, 101.537, 87.779, 61.568, 56.746, 49.609, 39.373; LC-MS *m*/*z*: 480.0 [M+H].

2-((6-Iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-7,8-dimethoxyisoquinolin-1(2*H*)-one (11b) To 7,8-dimethoxyisoquinolin-1(2*H*)-one (**10**) (0.12 g, 0.59 mmol) and dry DMF (10 mL) was added 60% sodium hydride in mineral oil (0.03 g, 0.76 mmol). The resulting suspension was allowed to stir at 0 ℃ for 1h. Benzyl bromide **7b** (0.24 g, 0.7 mmol) in dry DMF (5 mL) was added and the reaction was allowed to watm to room temperature. This suspension was allowed to stir for an additional 15 h. It was then poured into 50 mL water and extracted with DCM (30 mL×3). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give 2-((6-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-7,8-dimethoxyisoquinolin-1(2*H*)-one (**11b**) (0.293 g, 0.63 mmol, 90%) as a yellow solid. m.p. 144−146 ℃; ^1H NMR (400 Hz, $CDCl_3$) δ: 7.327 (d, J=8.4 Hz, 1H, ArH), 7.250 (s, 1H, ArH), 7.236 (d, J=8.4 Hz, 1H, ArH), 6.899 (d, J=7.6 Hz, 1H, CH=CH), 6.653 (s, 1H, ArH), 6.370 (d, J=7.6 Hz, 1H, CH=CH), 5.919 (s, 2H, OCH_2O), 5.135 (s, 2H, CH_2), 3.974 (s, 3H, OCH_3), 3.943 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 160.109, 151.836, 149.651, 148.829, 147.889, 132.556, 132.476, 129.085, 122.086, 120.804, 118.676, 118.486, 108.808, 106.026, 101.688, 86.366, 61.594, 56.704, 55.502; LC-MS *m*/*z*: 466.04 [M+H].

2-(3-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)propyl)-7,8-dimethoxyisoquinolin-1(2*H*)-one (11c) **11c** was prepared as the above step (yield 93%) as a yellow solid. m.p. 148−150 ℃; ^1H NMR (400 Hz, $CDCl_3$) δ: 7.308 (d, J=8.4 Hz, 1H, ArH), 7.236 (s, 1H, ArH), 7.208 (d, J=8.4 Hz, 1H, ArH), 6.925 (d, J=7.6 Hz, 1H, CH=CH), 6.749 (s, 1H, ArH), 6.360 (d, J=7.6 Hz, 1H, CH=CH), 5.942 (s, 2H, OCH_2O), 4.035−3.998 (m, 2H, CH_2), 3.984 (s, 3H, OCH_3), 3.939 (s, 3H, OCH_3), 2.760−2.705 (m, 2 H, CH_2), 2.065−2.007 (m, 2H, CH_2); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 159.916, 151.556, 149.426, 148.342, 146.632, 136.874, 134.812, 132.577, 129.749, 121.872, 118.465, 118.333, 109.010, 105.396, 101.379, 87.535, 61.480, 56.673, 48.562, 37.789, 29.614; LC-MS *m*/*z*: 494.10 [M+H].

2-(2-((6-Iodobenzo[*d*][1,3]dioxol-5-yl)oxy)ethyl)-7,8-dimethoxyisoquinolin-1(2*H*)-one (11d) **11d** was prepared as the above step (yield 79%) as a white solid. m.p. 188−190 ℃; ^1H NMR (400 Hz, $CDCl_3$) δ: 7.323 (d, J=3.2 Hz, 1H, ArH), 7.302 (d, J=3.2 Hz, 1H, ArH), 7.230 (d, J=8.8 Hz, 1H, CH=CH), 7.122 (s, 1H, ArH), 6.444 (s, 1H, ArH), 6.385 (d, J=8.8 Hz, 1H, CH=CH), 5.909 (s, 2H, OCH_2O), 4.376 (t, J=4.8 Hz, 2H, CH_2), 4.266 (t, J=4.8 Hz, 2H, CH_2), 3.977 (s, 3H, OCH_3), 3.931 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 160.241, 152.278, 151.532, 149.467, 148.861, 142.623, 133.066, 132.011, 122.039, 120.665, 118.812, 117.590, 105.033, 101.731, 95.749, 73.069, 68.181, 61.550, 56.794, 49.156; LC-MS *m*/*z*: 496.02 [M+H].

8-Oxyberberine (1a) A mixture of 2-(2-(6-iodobenzo[*d*][1,3]dioxol-5-yl)ethyl)-7,8-dimethoxyisoquinolin-1(2*H*)-one (**11a**) (0.3 g, 0.625 mmol), palladium(II) acetate (0.03 g, 0.125 mmol), PCy_3 (0.073 g, 0.25 mmol), Ag_2CO_3 (0.086 g, 0.312 mmol) and potassium carbonate (0.173 g, 1.25 mmol) in 5 mL of anhydrous acetonitrile was purged with nitrogen and refluxed at 120 ℃ for 8 h. At this time the reaction was complete (as monitored by TLC). After cooled down, the resulting solid was collected by filtration, washed with 2 mL of acetonitrile, and concentrated *in vacuo* to get a brown solid which was purified by column chromatography on silica gel eluting with PE/acetone gradient (50∶1−1∶15) as a yellow solid **1a** (0.165 g, 0.47 mmol, 75%). m.p. 238−240 ℃; ^1H NMR (400 Hz, $CDCl_3$) δ: 7.32 (d, J=8.4 Hz, 1H, ArH), 7.286 (s, 1H, ArH), 7.268 (s, 1H, ArH), 7.213 (s, 1H, ArH), 6.71 (d, J=8.4 Hz, 1H, ArH), 6.007 (s, 2H, OCH_2O), 4.290 (t, J=6.4 Hz, 2H, CH_2), 4.014 (s, 3H, OCH_3), 3.949 (s, 3H, OCH_3), 2.889 (t, J=6.4 Hz, 2H, CH_2); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 160.248, 153.788, 151.613, 149.508, 148.113, 141.819, 132.919, 131.127, 130.886, 130.346, 122.027, 119.179, 107.991, 105.663, 98.198, 73.665, 66.944, 62.343, 56.238, 48.333; LC-MS *m*/*z*: 352.1 [M+H]. Anal. calcd for $C_{20}H_{17}NO_5$: C 68.37, H 4.88, N 3.99; found C 68.21, H 4.94, N 4.02.

8,9-Dimethoxy-[1,3]dioxolo[4',5':5,6]isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (1b) A mixture of 2-((6-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-7,8-dimethoxyisoquinolin-1(2*H*)-one (**11b**) (0.1 g, 0.2 mmol), palladium(II) acetate (0.01 g, 0.04 mmol), PCy_3 (0.024 g, 0.08 mmol), Ag_2CO_3 (0.03 g, 0.1 mmol) and potassium carbonate (0.06 g, 0.4 mmol) in 5 mL of anhydrous acetonitrile was purged with nitrogen and refluxed at 120 ℃ for 14 h. At this time the reaction was complete (as monitored by TLC). After cooled down, the resulting solid was collected by filtration, washed with 2 mL of acetonitrile, and concentrated *in vacuo* to get a brown solid which was purified by column chromatography on silica gel eluting with PE/acetone gradient (100∶1−1∶10) as a yellow solid **1b** (0.0521 g, 0.154 mmol, 77%). m.p. 140−142 ℃; ^1H NMR (400 Hz, $CDCl_3$) δ: 7.345 (s, 2H, ArH), 7.135 (s, 1H, ArH), 6.990 (s, 1H, ArH), 6.742 (s, 1H, ArH), 6.077 (s, 2H, OCH_2O), 5.053 (s, 2H, CH_2), 4.030 (s, 3 H, OCH_3), 3.961 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 159.894, 151.010, 149.688, 140.518, 139.874, 133.923, 131.908, 127.514, 122.311, 121.878, 118.833, 118.465, 103.750, 101.857, 100.626, 96.240, 61.756, 56.845, 51.891; LC-MS *m*/*z*: 338.2 [M + H], 360.2 [M + Na]. Anal. calcd for $C_{19}H_{15}NO_5$: C 67.65, H 4.48, N 4.15; found C 67.43, H 4.59, N 4.20.

CHINESE JOURNAL OF CHEMISTRY

10,11-Dimethoxy-6,7-dihydro[1,3]dioxolo[4'',5'':4',5']benzo[1',2':3,4]azepino[1,2-*b*]isoquinolin-9(5*H*)-one (1c) **1c** was prepared as the above step (yield＝42%) as a yellow oil. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 7.329 (d, J＝8.8 Hz, 1H, ArH), 7.240 (s, 1H, ArH), 7.004 (s, 1H, ArH), 6.721 (s, 1H, ArH), 6.382 (s, 1H, ArH), 6.016 (s, 2H, OCH_2O), 5.074－5.0273 (m, 1H, CH), 4.022 (s, 3H, OCH_3), 3.954 (s, 3H, OCH_3), 3.187－3.110 (m, 1H, CH), 2.626－2.520 (m, 2H, CH_2), 2.422－2.338 (m, 1H, CH), 1.899－1.835 (m, 1H, CH); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 159.979, 151.645, 149.519, 148.288, 146.359, 142.309, 134.882, 132.677, 129.805, 121.901, 120.919, 118.568, 109.063, 108.183, 105.466, 101.265, 61.523, 56.754, 48.854, 32.679, 30.596; LC-MS *m*/*z*: 366.2 [M＋H]. Anal. calcd for $C_{21}H_{19}NO_5$: C 69.03, H 5.24, N 3.83; found C 69.10, H 5.45, N 3.78.

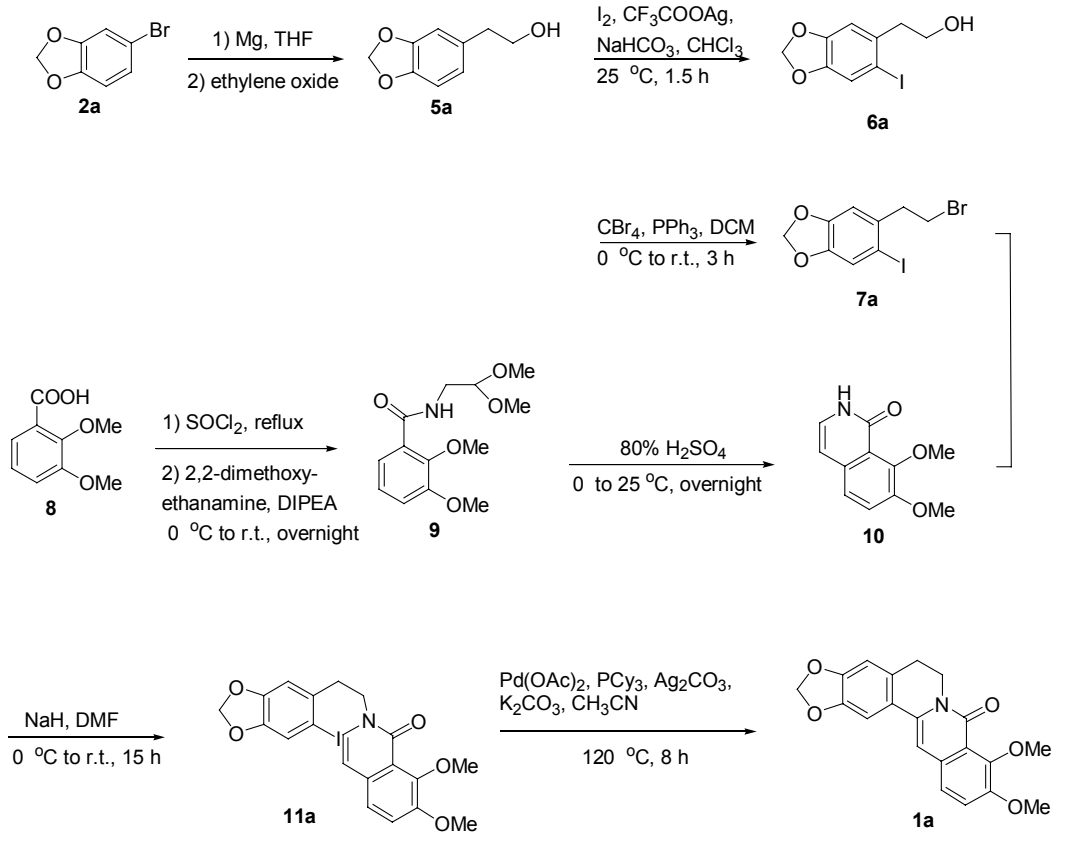
10,11-Dimethoxy-6*H*-[1,3]dioxolo[4'',5'':4',5']-benzo[1',2':6,7][1,4]oxazepino[4,5-*b*]isoquinolin-9(7*H*)-one (1d) **1d** was prepared as the above step (yield 39%) as a yellow oil. ^{1}H NMR (400 Hz, $CDCl_3$) δ: 7.301 (s, 1H, ArH), 7.218 (s, 1H, ArH), 7.029 (d, J＝7.2 Hz, 1H, ArH), 6.661 (d, J＝7.2 Hz, 1H, ArH), 6.454 (s, 1H, ArH), 5.887 (s, 2H, OCH_2O), 4.304 (t, J＝4.4 Hz, 2H, CH_2), 4.252 (t, J＝4.4 Hz, 2H, CH_2), 3.975 (s, 3H, OCH_3), 3.935 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 160.247, 153.798, 151.653, 149.558, 148.213, 141.839, 132.929, 131.147, 122.394, 119.069, 107.891, 105.683, 101.115, 98.098, 73.665, 66.974, 61.593, 56.837, 49.106; LC-MS *m*/*z*: 368.6 [M＋H]. Anal. calcd for $C_{20}H_{17}NO_6$: C 65.39, H 4.66, N 3.81; found C 65.42, H 4.59, N 3.78.

Results and Discussion

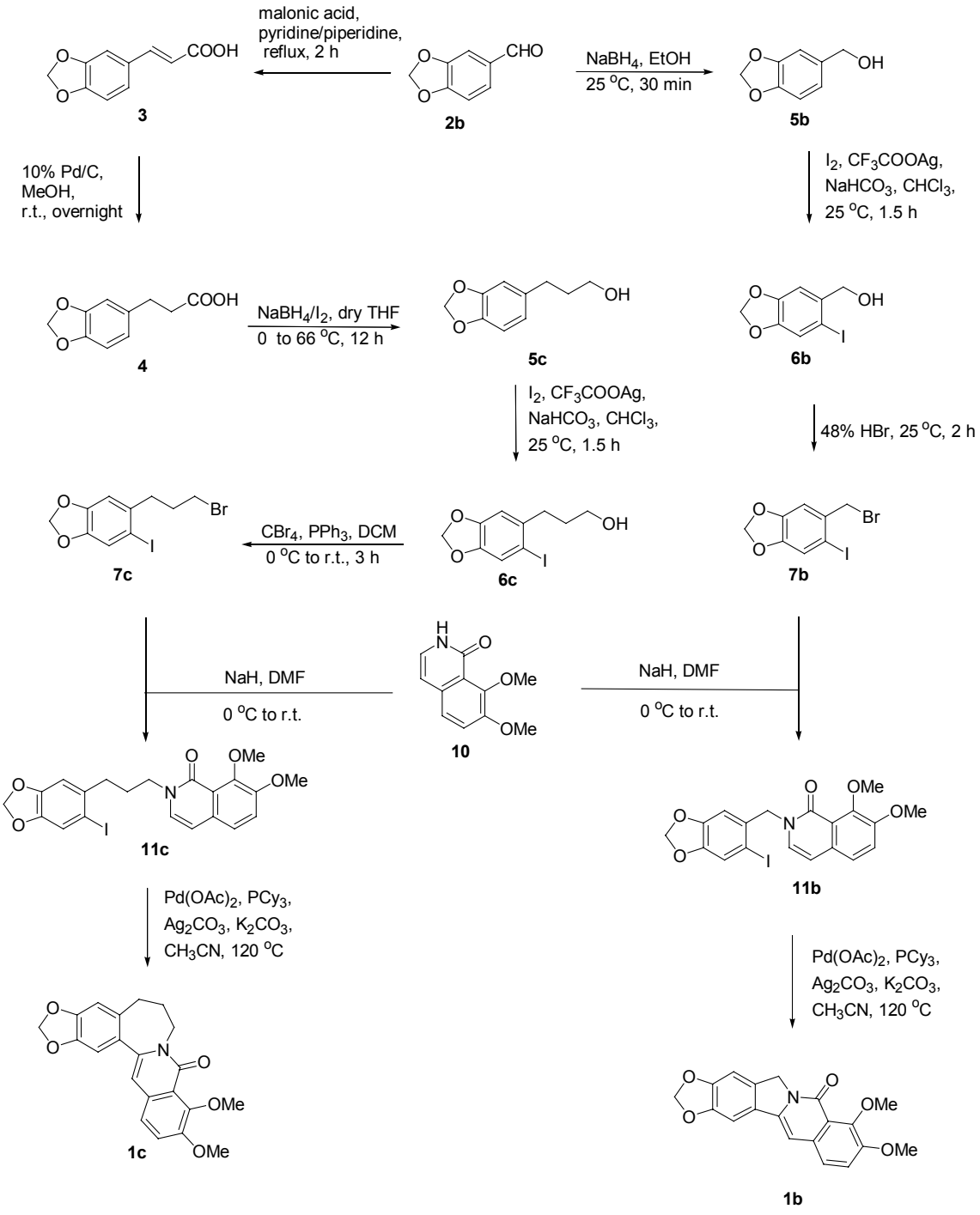
Our strategy for the synthesis of 8-oxyberberine **1a** is shown in Scheme 1. The corresponding 2-phenylethanol **5a** was readily prepared by Grignard reaction of benzo[*d*][1,3]dioxol-5-ylmagnesium bromide with ethylene oxide in dry THF. The iodination reaction of alcohol **5a** was performed with I_2 and CF_3COOAg to give compound **6a**.[7,8] Appel-Lee synthesis of compound **7a** was from **6a**.[9]

The synthesis of oxohomoberberine **1b** and **1c** is shown in Scheme 2. Knoevenagel condensation of malonic acid and commercially available piperonal **2b** in pyridine/piperidine gave the corresponding acids **3**, followed by palladium-catalyzed hydrogenation to form acid **4** that was used without purification in the next step.[6] Piperonal **2b** was also reduced to benzylic alcohol **5b** by using $NaBH_4$ while the $NaBH_4/I_2$ system was chosen to deoxidize the acid **4** to yield benzylic propanol **5c**. The iodination reaction of alcohol **5b** and propanol **5c** was performed with I_2 and CF_3COOAg to give compound **6b** and compound **6c**, respectively.[7,8] Appel-Lee synthesis of 1-(3-bromopropyl)-2-iodobenzene (**7c**) was from **6c**.[9] Meanwhile, the benzyl bromide **7b** was prepared from **6b** with 48% aqueous HBr, identically in

Scheme 1 Synthesis of 8-oxyberberine (**1a**)



Scheme 2 Synthesis of oxohomoberberines **1b** and **1c**



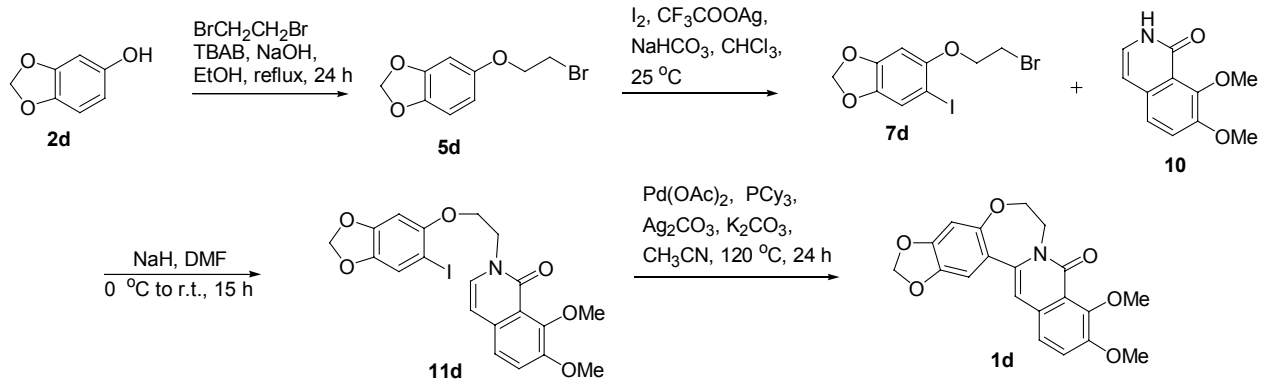
all aspects with the Harrowven's report.[8]

The synthesis of oxohomoberberine **1d** is shown in Scheme 3. Compound **5d** was prepared by the reaction of sesamol **2d** with ethylene dibromide in EtOH. Then, compound **7d** was prepared from **5d** by Appel-Lee synthesis.[9]

Treatment of benzoic acid **8** with $SOCl_2$ and 2,2-dimethoxyethanamine resulted in *N*-(2,2-dimethoxyethyl)benzamide (**9**) without purification followed by cyclization to form the isoquinolinone core **10** as a modified Pomeranz-Fritsch reaction in Scheme 1.[10] The isoquinolinone **10** was treated with NaH and bromo compound **7a**, **7b**, **7c** or **7d** (respectively) to afford the key intermediates — *N*-substituted isoquinoline-1(2*H*)-one **11a**, **11b**, **11c** and **11d**.[11]

Next, we turned our attention to the cyclization of **11a**, **11b**, **11c** and **11d**. Among the existing method of cyclization, the closest competing methodology to the intramolecular Heck reaction is radical cyclization.[12] Although both methods typically give efficient exo ring closure, radical cyclization (usually mediated by *n*-Bu_3SnH) is often characterized by reduction leading

Scheme 3 Synthesis of oxohomoberberine **1d**



to a reductive cyclization. Heck reaction is generally not reductive because beta-hydride elimination is the usual outcome. In addition, another drawback of radical cyclization is the use of stoichiometric quantities of *n*-Bu_3SnH, which is highly toxic, difficult to separate from the reaction products, and poses disposal challenges. Due to the above analysis, we chose the Heck intramolecular cyclization for the exo ring closure as the most powerful method in five or seven-membered ring systems. Thus, the optimized reaction condition for the Heck intramolecular cyclization was $Pd(OAc)_2$ (0.2 equiv.), PCy_3 (0.4 equiv.), Ag_2CO_3 (0.5 equiv.), and K_2CO_3 (2 equiv.) in CH_3CN heated at 120 ℃ for 8—24 h.

Conclusions

In summary, we have successfully presented a synthetic route for the synthesis of 8-oxyberberine **1a** with high total yield of 43% from 5-bromobenzo[*d*][1,3]-dioxole (**2a**) in 7 steps. Meanwhile, we firstly described the synthesis of the oxohomoberberines **1b**, **1c** and **1d** in 46.2% (7 steps), 22.9% (9 steps), and 14% (6 steps) overall yields, respectively. Considering oxyberberine possesses excellent hypoglycemic activity, our work might provide an efficient synthetic route for its pharmacological derivatives.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (No. 81373259).

References

[1] (a) Zhang, J. S.; Chen, Z. L. *Planta Med.* **1991**, *57*, 457; (b) Chang, F. R.; Wu, Y. C. *J. Nat. Prod.* **2005**, *68*, 1056; (c) Zhu, Q. K.; Zhou, J. Y.; Zhang, G.; Liao, H. *Chin. J. Chem.* **2012**, *30*, 2533.

[2] (a) Min, Y. D.; Kwon, H. C.; Yang, M. C.; Lee, K. H.; Choi, S. U.; Lee, K. R. *Arch. Pharm. Res.* **2007**, *30*, 58; (b) Chi, J. F.; Chu, S. H.; Lee, C. S. *Br. J. Pharmacol.* **1996**, *118*, 503.

[3] Cheng, Z.; Chen, A. F.; Wu, F.; Sheng, L.; Zhang, H. K. *Bioorg. Med. Chem.* **2010**, *18*, 5915.

[4] (a) Malaisse, W. J. *Expert Opinion on Pharmacotherapy* **2008**, *9*, 2691; (b) Katakami, N.; Yamasaki, Y.; Hayaishi, O, R.; Ohtoshi, K. *Diabetologia* **2004**, *47*, 1906; (c) Breuer, H.; Hoehn, H. *Chimica Therapeutica* **1973**, *8*, 659.

[5] (a) Yang, P.; Song, D. Q.; Li, Y. H.; Kong, W. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4675; (b) Lee, C. S.; Yu, T. C.; Luo, J. W.; Cheng, Y. Y.; Chuang, C. P. *Tetrahedron Lett.* **2009**, *50*, 4558; (c) Chen, A. F.; Zhao, K.; Zhang, H. K.; Gan, X. W.; Lei, M.; Hu, L. H. *Monatsh Chem.* **2012**, *143*, 825.

[6] Yang, S. X.; Kang, T. N.; Rui, C. H. *Chin. J. Chem.* **2011**, *29*, 2394.

[7] Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387.

[8] Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311.

[9] Fillion, E.; Trepanier, V. E.; Heikkinen, J. J. *Organometallics* **2009**, *28*, 3518.

[10] Cody, J. A.; Ahmed, I.; Tusch, D. J. *Tetrahedron Lett.* **2010**, *51*, 5585.

[11] Berry, J. M.; Watson, C. Y.; Whishm, W. J. D.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, *8*, 1147.

[12] Orito, K.; Satoh, Y.; Nishizawa, H.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 2535.

(Pan, B.; Qin, X.)

