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Total Synthesis of (−)-Canadine, (−)-Rotundine, (−)-Sinactine, and (−)-Xylopinine Using a Last-Step Enantioselective Ir-Catalyzed Hydrogenation

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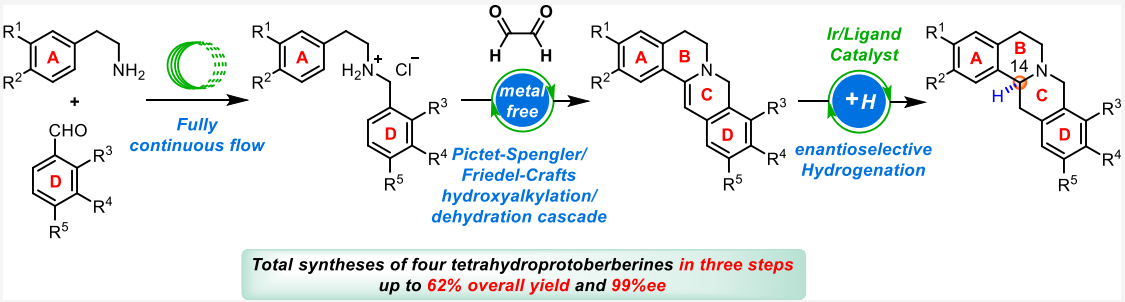

ABSTRACT: A concise asymmetric total synthesis of a group of tetrahydroprotoberberine alkaloids, (−)-canadine, (−)-rotundine, (−)-sinactine, and (−)-xylopinine, has been accomplished in three steps from the commercially available corresponding disubstituted phenylethylamine and disubstituted benzaldehyde. Our synthesis toward these four alkaloids took advantage of the following strategy: in the first step, we achieved an efficient and sustainable synthesis of secondary amine hydrochlorides via a fully continuous flow; in the second step, we developed a Pictet−Spengler reaction/Friedel−Crafts hydroxyalkylation/dehydration cascade for the construction of the dihydroprotoberberine core structure (ABCD-ring); and in the last step, Ir-catalyzed enantioselective hydrogenation was employed for the introduction of the desired stereochemistry at the C-14 position in the tetrahydroprotoberberine alkaloids. This work significantly expedites the asymmetric synthesis of the entire tetrahydroprotoberberine alkaloid family as well as a more diverse set of structurally related non-natural analogues.

INTRODUCTION

(−)-Canadine (**1**), (−)-rotundine (**2**), (−)-sinactine (**3**), and (−)-xylopinine (**4**), isolated from the plants of various species of *Corydalis* and *Stephania*,[1] are naturally occurring family members of tetrahydroprotoberberine alkaloids, as shown in Figure 1. Structurally, tetrahydroprotoberberine alkaloids embrace a 5,8,13,14-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine tetracyclic ring system bearing one stereogenic center at the C-14 position, with oxygen-containing functionalities at the C-2 and C-3 positions of the A-ring and C-9, C-10 or C-10, C-11 positions of the D-ring. The extraordinary range of biological properties displayed by these alkaloids, including (among other things) antimicrobial,[2] anti-inflammatory,[3] antipsychotic,[4] and analgesic activities,[5] have attracted significant attention although probably not as much as the capacities of some of them to act as potent and highly selective inhibitors of the a_{1A}-adrenoceptor, D_2/D_1 dopamine receptor, and 5-HT_{1A} receptor. As such, certain tetrahydroprotoberberine alkaloids in these alkaloids have come to be regarded as important leads for the development of new antagonists for the a_{1A}-adrenoceptor, D_2/D_1 dopamine receptor, and 5-HT_{1A} receptor.[6]

Certainly, an impressive range of derivatization and analogue programs have been launched on this basis, and considerable efforts have even led to a number of clinical trials.[4,6a,b,7]

Owing to the distinctive molecular architecture promising biological activities as well as the limited natural accessibility of this alkaloid family **1**−**4**, there has been substantial interest in the asymmetric total synthesis of these and other tetrahydroprotoberberine alkaloids. To date, a variety of approaches have been developed to address the enantioselective total synthesis of tetrahydroprotoberberines **1**−**4** (Scheme 1).[8] These works include the following: (i) Schore's synthesis via chiral Meyers' formamidine auxiliary-induced substitution and silyl-directed Pictet−Spengler cyclization for **1**−**3** (up to 51% overall yield and 55−60% ee).[8a] (ii) Enders' seven-step synthesis of **2** (17% overall yield and 89% ee) from 3,4-

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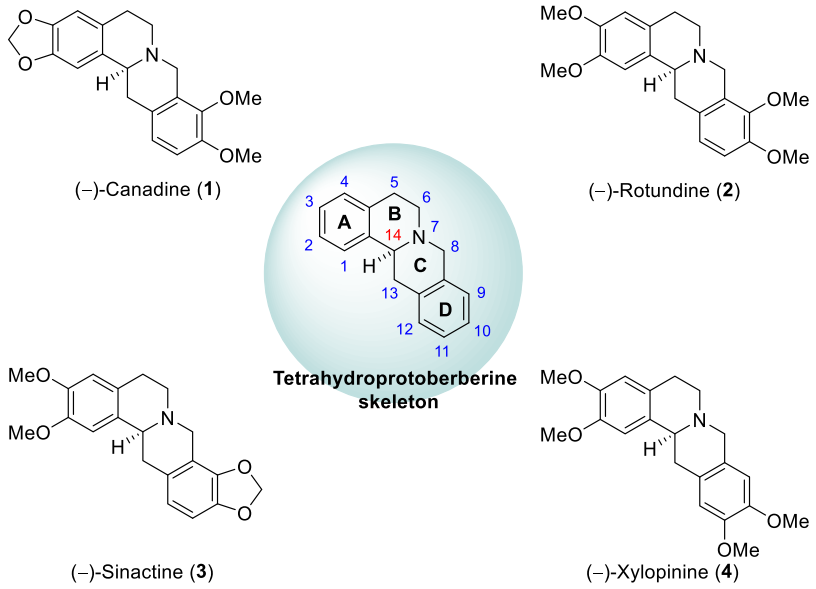

Figure 1. Representative examples of tetrahydroprotoberberine alkaloids.

dimethoxybenzaldehyde featuring (R)-*1*-amino-*2*-methoxymethylpyrrolidine (RAMP)-directed 1,2-addition/cyclization.[8b] (iii) Two highly enantioselective routes involving a sulfinyl-directed addition/cyclization and a sulfinyl-induced Pictet−Spengler reaction by employing aryl-substituted sulfoxide and arylsulfinyl imines as substrates to access **1**−**2** (up to 30% overall yield) and **4** (52% overall yield), developed by the Mastranzo group.[8c,d] (iv) Davis' formal asymmetric total synthesis of **4** (18% overall yield) that relied upon chiral sulfinyl auxiliary-induced addition/cyclization.[8e] (v) Doye's synthesis of **4** (55% overall yield and 93% ee) using Noyori's asymmetric transfer hydrogenation (ATH) of cyclic imine.[8f] (vi) Tong's two catalytic synthetic approaches toward **1**−**4** via asymmetric redox-A^3 reaction (up to 4% overall yield and 88−97% ee), and based on Noyori catalytic ATH of enanime (up to 12% overall yield and 77−99% ee).[8g] While these investigations constitute great progress, there is still room for improvement in synthetic efficiency, for example, higher enantioselectivity control and finding a more efficient method to install the tetracyclic ring core. In this article, we report a general strategy that allows asymmetric total synthesis of tetrahydroprotoberberine alkaloids, (−)-canadine (**1**), (−)-rotundine (**2**), (−)-sinactine (**3**), and (−)-xylopinine (**4**).

The retrosynthetic analysis of tetrahydroprotoberberine alkaloids **1**−**4** are depicted in Scheme 2. Inspired by the emerging field of transition-metal-catalyzed enantioselective hydrogenation of enamine as a powerful tool for the construction of chiral cyclic tertiary amines in asymmetric synthesis,[9] the stereogenic center (14*S*) at the C-14 position on the C-ring in these tetrahydroprotoberberine natural products **1**−**4** could be potentially installed from dihydroberberine **5** via a late-stage Ir-catalyzed enantioselective hydrogenation of cyclic enamine. The annulation of the dihydroprotoberberine tetracyclic core of **5** would be possible by a Pictet−Spengler/Friedel−Crafts hydroxyalkylation/dehydration cascade from the secondary amine hydrochloride **6** and glyoxal,[10] which would wait us to achieve. The required amine hydrochlorides **6** could be accessed in three steps from simple commercially available disubstituted phenylethylamines **7** and disubstituted benzaldehydes **8** under continuous flow conditions.[11]

RESULTS AND DISCUSSION

Our synthesis commenced with the fully continuous flow synthesis of secondary amine hydrochlorides **6a**−**6d** from the commercially available corresponding disubstituted phenylethylamines **7a** and **7b** and disubstituted benzaldehydes **8a**−**8c** in a continuous flow (Scheme 3). As depicted in Scheme 3, a methanol solution of **7a** and **7b** combined with **8a**−**8c** through a T-mixer was pumped into an MF-200 fixed-bed reactor (Shenzhen E-Zheng Tech Co., Ltd) packed with 4A MS powder (2 mL internal volume) at room temperature and 7 bar back-pressure with a residence time of 5 min, giving imines **9a**−**9d**, respectively. The reactor effluent was subjected to catalytic hydrogenation with H_2 into another fixed-bed reactor containing 10% $Pd(OH)_2/C$ dispersed by SiO_2 (5 mL internal volume) at 60 °C and 20 bar back-pressure with a 5 min residence time to provide the corresponding secondary amines **10a** and **10b**. The reaction liquid was combined with a 0.2 M methanol solution of hydrochloric acid and introduced into a PTFE reactor coil (5 mL, 0.8 mm i.d.) at room temperature with a residence time of 5 min; the desired secondary amine hydrochlorides **6a**−**6d** were obtained in 90−94% total yield.

With substantial quantities of building blocks **6a**−**6d** in hand, we sought to investigate the Pictet−Spengler reaction/Friedel−Crafts hydroxyalkylation/dehydration cascade reaction to access the dihydroprotoberberines **5a** and **5b**, which turned out to be of paramount importance. To the best of our knowledge, there are no examples reported using secondary amine derivatives and glyoxal via this novel cascade reaction for the synthesis of dihydroprotoberberines (Table 1). First, we employed a mixture of **6a** and excess glyoxal in dichloromethane (DCM) in the presence of anhydrous $AlCl_3$ at 60 °C; the cascade reaction unfortunately gave trace amounts of product **5a** in our hands (entry 1). Switching other acids such as TfOH and 98% HCOOH gave a minor product **5a**, as detected by ^{1}HNMR analysis, and no observed product upon work-up (entries 2 and 3).

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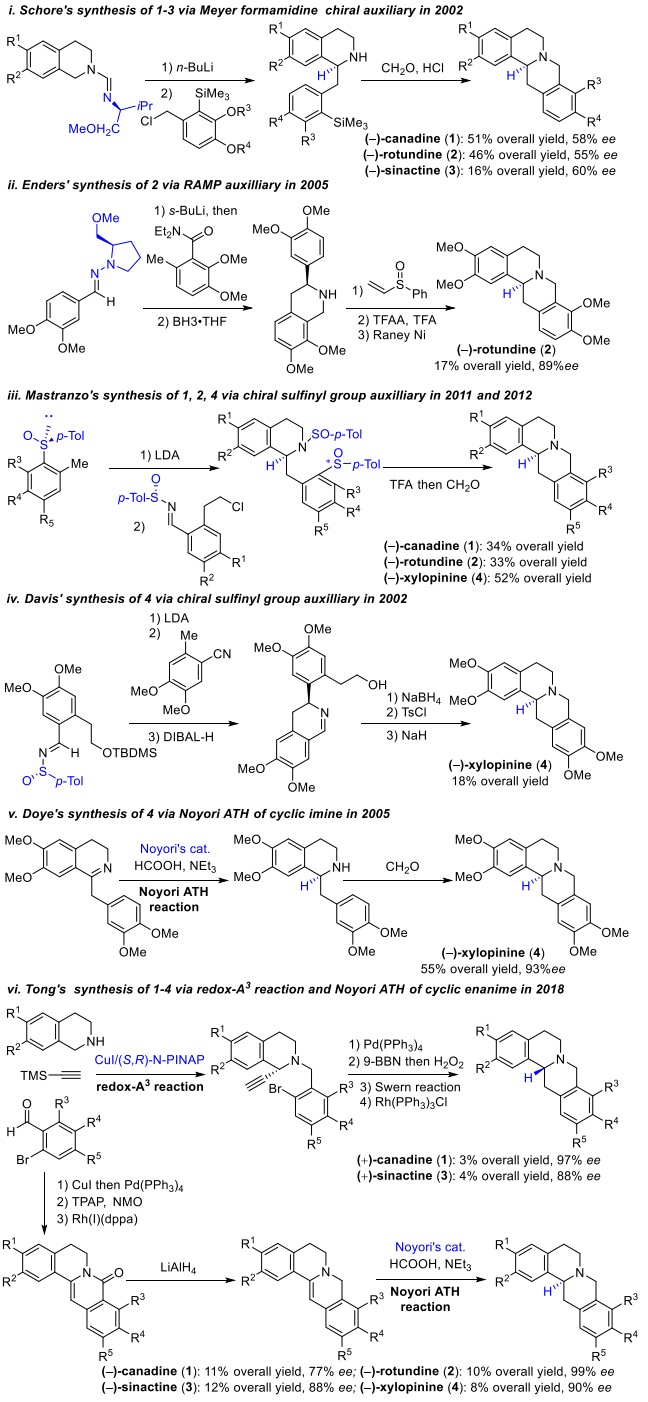
Scheme 1. Previous Asymmetric Synthesis of 1−4



While using TFA in place of $AlCl_3$, TfOH, and 98% HCOOH under the same conditions gave only a very low yield of **5a** (10% yield, entry 4). The sole use of excess 98% HCOOH was in vain for this transformation (entry 5). When the reaction temperature was increased to 80 °C, the yield of **5a** was improved to 30% under the conditions, as shown in entry 6 of Table 1. Alternatively, the reaction of **6a** with 2.0 equiv boric acid in 98% HCOOH at 80 °C for 12 h produced **5a** in 50% yield (entry 7). The best combination was 2.0 equiv boric acid/3.5 equiv NaCl as the additive/98% HCOOH/80 °C/12 h, which clearly provided the desired product **5a** in 71% isolated yield (entry 8). The cascade process was also applied to three other secondary amine hydrochloride substrates **6b**−**6d** under the optimal reaction conditions, delivering the corresponding dihydroprotoberberine derivatives **5b**−**5d** with similar outcomes (entries 9−11).

As mentioned before, the most challenging part of this work was the asymmetric synthesis of tetrahydroprotoberberine alkaloid molecules to accomplish the installation of a stereocenter at the C-14 position. An Ir-catalyzed enantioselective hydrogenation of **5a**−**5d** was an efficient and feasible strategy to build up this C-14 chirality, thus completing the total synthesis of (−)-canadine, (−)-sinactine, (−)-rotundine, and (−)-xylopinine (**1**−**4**). Initially, the Ir-catalyzed enantioselective hydrogenation of dihydroberberine **5a** was performed to evaluate the chiral ligands **L1**−**L7** based on reaction conditions recently reported for the total syntheses of (−)-20-*epi*-vincamine and (−)-20-*epi*-eburnamonine by the Ir-catalyzed asymmetric imine hydrogenation/lactamization cascade (Table 2).[12,13] The hydrogenation of **5a** catalyzed by a 1.0 mol % Ir/ligand **L1** complex, generated in situ from 0.5 mol % $[Ir(COD)Cl]_2$ and 2.0 mol % (*R*)-MONOPHOS ligand **L1**, was completed within 3 days in toluene/acetic acid (v/v = 9:1) under 80 atm H_2 at room temperature using KI as an additive, yielding the product (*R*)-**5a** with the opposite configuration of natural (−)-canadine (**1**) in high yields and moderate enantioselectivity (91%, −46% ee, entry 1). Whereas almost no enantioselectivity control was observed in the case of ligands **L2**−**L6** (entries 2−6). Subsequent investigations were focused on ferrocene-based ligand **L7** with the (*S*,*S*)-*f*-BINAPHANE moiety and proved to be the privileged ligand for this catalytic hydrogenation reduction in 94% yield and 82% ee (entry 7). Replacement of KI with I_2, TBAI, or LiI as the additive dramatically improved the level of enantioselectivity of (−)-canadine (1) (entries 8−10). However, KBr gave the best results (92%, 96% ee, entry 11). Several solvent systems were screened to find their promoting effect in this hydrogenation. Unfortunately, a moderate enantioselectivity (48% ee) was obtained when MeOH/AcOH (9:1) was used (entry 12). The mixed solvent system of trifluoroethanol/AcOH (9:1) gave a poor result in terms of enantioselectivity albeit a high yield (80%, less than 10% ee, entry 13). Pleasingly, EtOAc/AcOH (9:1) and DMF/AcOH (9:1) showed very good performances in terms of yield and enantiomeric ratios (87%, 94% ee and 88%, 94% ee, respectively, entries 14−15). However, a 9:1 ratio of DCM/AcOH provided the best results, affording the best yield and the highest enantioselectivity (93%, 99% ee, entry 16). However, the exact reason was not clear at this stage. Additionally, a gram-scale reaction of **5a** was carried out using 0.1% of Ir catalyst, and the desired product (−)-canadine (1) was obtained in 92% yield and 98% ee (entry 17), indicating that the Ir-catalyzed hydrogenation is reliable and practical.

Not surprisingly, our optimized hydrogenation conditions were extended to other dihydroprotoberberines **5b**−**5d**, completing the total synthesis of corresponding tetrahydroprotoberberine alkaloids (−)-rotundine (2), (−)-sinactine (3), and (−)-xylopinine (4) in excellent yields and enantioselectivities (95% yield and 97% ee; 90% yield and 92% ee; and 91% yield and 91% ee, respectively, entries 18−20). The ^{1}HNMR, ^{13}CNMR, and Fourier transform infrared (FT-IR) spectra and specific rotation of the synthetic (−)-**1**−(−)-**4** matched those recorded for the originally corresponding isolated natural products, respectively (see the Supporting Information for more details).[14]

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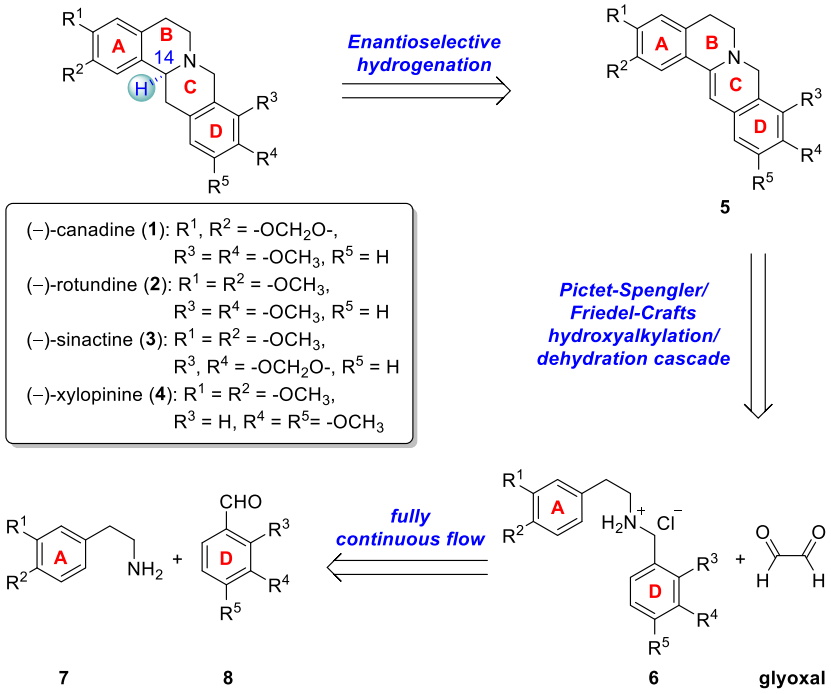
Scheme 2. Retrosynthetic Analysis of 1−4



CONCLUSIONS

In conclusion, the total synthesis of tetrahydroprotoberberine alkaloids (**1**−**4**) was accomplished in three steps starting from disubstituted phenylethylamines **7** and disubstituted benzaldehydes **8**. The key steps in this synthesis were a cascade cyclization via Pictet−Spengler reaction/Friedel−Crafts hydroxyalkylation/dehydration and an Ir-catalyzed asymmetric hydrogenation. This work demonstrated the power of the Pictet−Spengler reaction/Friedel−Crafts hydroxyalkylation/dehydration cascade for the straightforward annulation of dihydroprotoberberine alkaloids and the Ir-catalyzed enantioselective hydrogenation of enamine for the concise introduction of absolute configuration at the C-14 position. The synthetic strategy could be applied to the asymmetric construction of other related tetrahydroprotoberberine alkaloids and more related non-natural analogues. Further investigations highlighting the applicability of this uniform strategy for other bioactive alkaloid families and their derivatives to study their biology are currently underway in our laboratory and will be reported in due course.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, solvents were purified and dried according to standard methods prior to use. All reactions that require heating employed an oil bath as a heat source. The starting materials phenethylamines **7a** and **7b** and benzaldehydes **8a**−**8c** were commercially available. All the reactions were monitored by thin-layer chromatography (TLC) and were visualized under UV light. The product purification was conducted using silica gel column chromatography. TLC characterization was performed with precoated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (200−300 mesh). All new compounds were characterized by NMR spectroscopy, high-resolution mass spectroscopy (HRMS), FT-IR spectroscopy, and melting point (mp, for solids). ^{1}H NMR spectra were recorded at 400 or 600 MHz (Bruker) and ^{13}C{1H} NMR spectra were recorded at 100 or 150 MHz (Bruker). Chemical shifts are reported in parts per million (ppm) downfield from $CDCl_3$ (δ = 7.26 ppm), DMSO-d_6 (δ = 2.50 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm), the central DMSO-d_6 resonance (δ = 39.50 ppm) for ^{13}C{1H} NMR spectroscopy. Coupling constants are given in Hz. Chemical shifts (δ) were reported as ppm downfield from tetramethylsilane, and the following abbreviations were used to identify the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad, and all combinations thereof can be explained by their integral parts. HRMS spectra were recorded on a Bruker microTOF Q III by the ESI method. FTIR spectra were recorded on a PerkinElmer Spectrum Two FT-IR spectrometer. Melting points (mp) were recorded on an SRS optic melting point apparatus. In each case, enantiomeric ratios were determined by HPLC analysis on a chiral column in comparison with an authentic racemate, using a Daicel Chiralpak ADH column (250 × 4.6 mm). UV detection was performed at 210 nm. All starting materials, reagents, and solvents were purchased from commercial suppliers (Aldrich, Alfa, TCI, Adamas, etc.) and used as supplied unless otherwise stated.

General Procedure A: for Fully Continuous Flow Synthesis of Secondary Amine Hydrochloride 6a. *(E)-N-(2-(Benzo[d][1,3]-dioxol-5-yl)ethyl)-1-(2,3-dimethoxy phenyl)methanimine (**9a**).* The flow system adopted a two-feed microreactor consisting of a fixed-bed reactor (MF-200, Shenzhen E-Zheng Tech. Co., Ltd) containing 4A MS powder (7.5 g) (2 mL internal volume). Phenylethylamine **7a** (1.65 g, 10.0 mmol, 1 equiv) was dissolved in degassed MeOH (167 mL) and pumped into the microreactor through feed A (flow rate: 0.2 mL/min), while the mixture containing disubstituted benzaldehyde **8a** (1.66 g, 10.0 mmol, 1 equiv) and degassed MeOH (167 mL) was introduced into the microreactor through feed B (flow rate: 0.2 mL/min). The back-pressure regulator was attached to the output line to maintain a stable system pressure of 7 bar. The reaction mixture was pumped at an overall flow rate of 1.0 mL/min at 25 °C with a 5 min residence time. The reaction mixture was collected in a cumulative 250 mL conical flask to afford a methanol solution of imine **9a** (0.03 M in MeOH) for the next reaction without post-processing. Analytically, the imine **9a** sample was obtained after concentrating in vacuo without purification as a pale yellow solid; mp = 53.3−55.3 °C. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.53 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.75−6.70 (m, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 5.90 (s, 2H), 3.87 (s, 3H), 3.84 (t, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 2.93 (t, *J* = 7.2 Hz, 2H).

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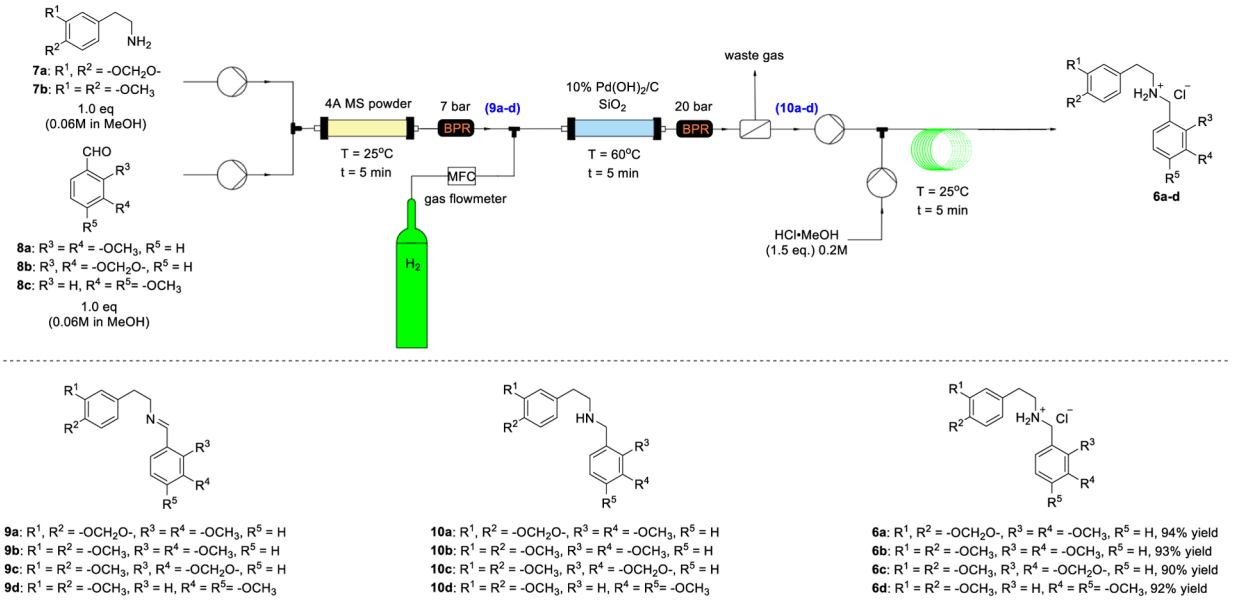
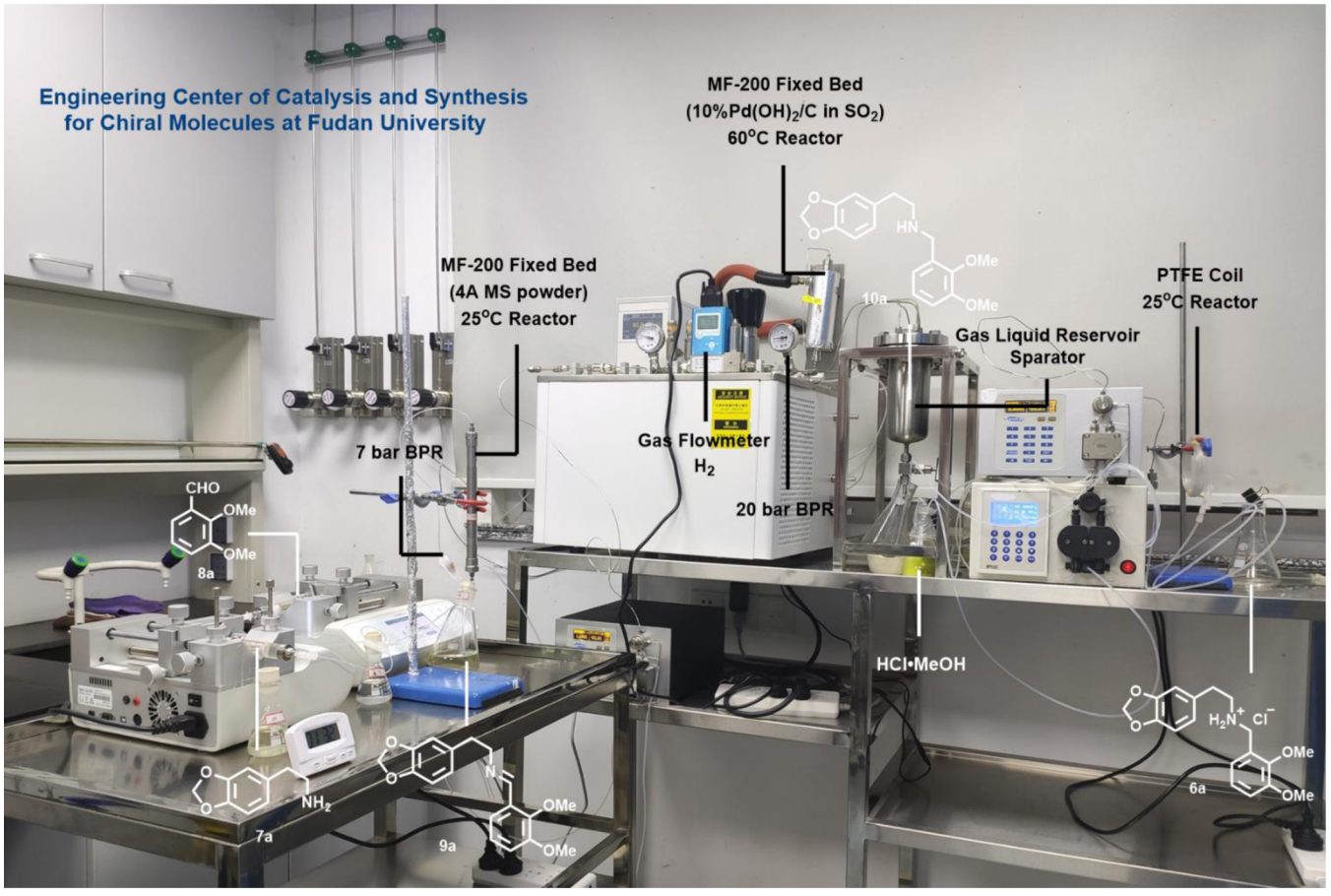
Scheme 3. Fully Continuous Flow Synthesis of Secondary Amine Hydrochlorides 6a–6d



9a: R1, R2 = -OCH2O-, R3 = R4 = -OCH3, R5 = H
9b: R1 = R2 = -OCH3, R3 = R4 = -OCH3, R5 = H
9c: R1 = R2 = -OCH3, R3, R4 = -OCH2O-, R5 = H
9d: R1 = R2 = -OCH3, R3 = H, R4 = R5= -OCH3

10a: R1, R2 = -OCH2O-, R3 = R4 = -OCH3, R5 = H
10b: R1 = R2 = -OCH3, R3 = R4 = -OCH3, R5 = H
10c: R1 = R2 = -OCH3, R3, R4 = -OCH2O-, R5 = H
10d: R1 = R2 = -OCH3, R3 = H, R4 = R5= -OCH3

6a: R1, R2 = -OCH2O-, R3 = R4 = -OCH3, R5 = H, 94% yield
6b: R1 = R2 = -OCH3, R3 = R4 = -OCH3, R5 = H, 93% yield
6c: R1 = R2 = -OCH3, R3, R4 = -OCH2O-, R5 = H, 90% yield
6d: R1 = R2 = -OCH3, R3 = H, R4 = R5= -OCH3, 92% yield



$^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ 156.4, 152.6, 148.7, 147.1, 145.4, 133.7, 129.3, 124.1, 121.8, 118.0, 114.7, 109.3, 108.0, 100.6, 62.6, 61.2, 55.8, 36.5. IR (neat): 2893.5, 2833.7, 1577.8, 1476.7, 1241.9, 1086.5, 1036.6, 1000.7, 881.9, 808.5, 774.2, 594.2 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{18}H_{20}NO_4$ $[M + H]^+$, 314.1387; found, 314.1392.

*2-(Benzo[d][1,3]dioxol-5-yl)-N-(2,3-dimethoxybenzyl)ethan-1-amine (**10a**).* The solution of crude **9a** obtained above in MeOH (0.03 M) was pumped at a flow rate of 1.0 mL/min and combined with the H_2 stream (flow rate 0.1 L/min) at the T-piece connector, which then entered the 3.2 mL reactor coil (1/16 in. outer diameter). The reactor output was then passed through a fixed-bed reactor (MF-200, Shenzhen E-Zheng Tech. Co., Ltd) containing 10% $Pd(OH)_2/C$ (2.0 g) and SiO_2 (40 mesh, 20.0 g) (5 mL internal volume) at 60 °C with 5 min residence time. The outlet of the fixed bed was connected to a back-pressure regulator to control a stable system pressure of 20 bar. The reaction mixture was collected in a 250 mL conical flask to afford a methanol solution of secondary amine **10a** (0.03 M in MeOH) for the next reaction without post-processing. Analytically, the secondary amine **10a** sample was obtained after concentrating in

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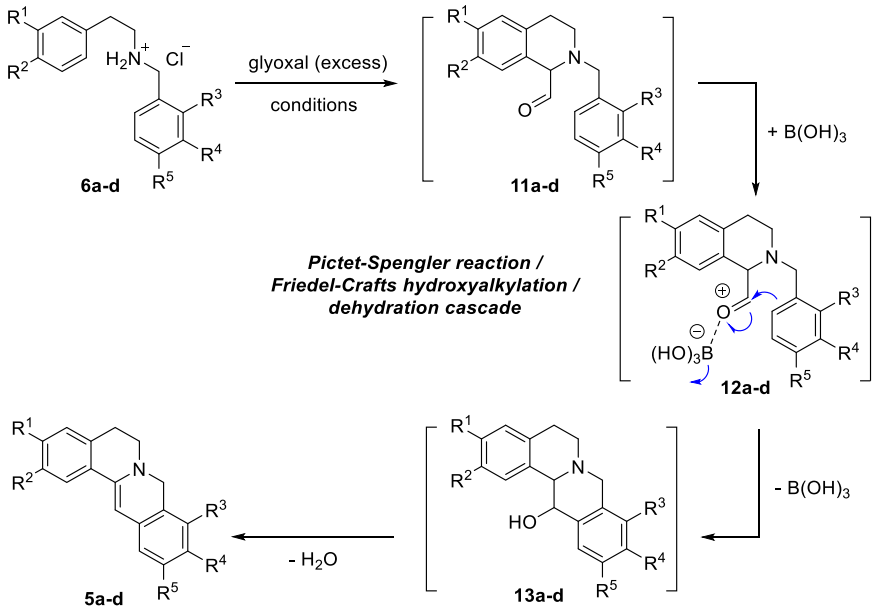
Table 1. Synthesis of Dihydroprotoberberines 5a−5d under Different Conditions



6a, **5a**: R^1, R^2 = -OCH_2O-, R^3 = R^4 = -OCH_3, R^5 = H
6b, **5b**: R^1 = R^2 = -OCH_3, R^3 = R^4 = -OCH_3, R^5 = H
6c, **5c**: R^1 = R^2 = -OCH_3, R^3, R^4 = -OCH_2O-, R^5 = H
6d, **5d**: R^1 = R^2 = -OCH_3, R^3 = H, R^4 = R^5= -OCH_3

entry	sub.	conditions	yield (%)[a]
1	**6a**	$AlCl_3$ (1.2 equiv), DCM, 60 °C, 12 h	trace
2	**6a**	TfOH (1.2 equiv), DCM, 60 °C, 12 h	trace
3	**6a**	98% HCOOH (1.2 equiv), DCM, 60 °C, 12 h	trace
4	**6a**	TFA (1.2 equiv), DCM, 60 °C, 12 h	10
5	**6a**	98% HCOOH, 60 °C, 12 h	16
6	**6a**	98% HCOOH, 80 °C, 12 h	30
7	**6a**	$B(OH)_3$ (2.0 equiv), 98%HCOOH, 80 °C, 12 h	50
8	**6a**	$B(OH)_3$ (2.0 equiv), NaCl (3.5 equiv), 98%HCOOH, 80 °C, 12 h	76 (71)[b]
9	**6b**	$B(OH)_3$ (2.0 equiv), NaCl (3.5 equiv), 98%HCOOH, 80 °C, 12 h	69[b]
10	**6c**	$B(OH)_3$ (2.0 equiv), NaCl (3.5 equiv), 98%HCOOH, 80 °C, 12 h	62[b]
11	**6d**	$B(OH)_3$ (2.0 equiv), NaCl (3.5 equiv), 98%HCOOH, 80 °C, 12 h	70[b]

[a]Yield determined by ^{1}HNMR spectroscopy with 1,3,5-trimethyl 1,3,5-benzenetricarboxylate as the internal standard. [b]Isolated yield.

vacuo without purification as a yellow oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.00 (t, J = 8.0 Hz, 1H), 6.88−6.80 (m, 2H), 6.74−6.66 (m, 2H), 6.64 (d, J = 8.0 Hz, 1H), 5.90 (s, 2H), 3.85 (s, 3H), 3.81 (s, 2H), 3.79 (s, 3H), 2.82 (t, J = 6.4 Hz, 2H), 2.76−2.68 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 152.7, 147.7, 147.4, 145.9, 134.1, 124.0, 121.8, 121.7, 111.5, 109.2, 108.3, 100.9, 60.8, 55.8, 50.8, 48.8, 36.3. IR (neat): 2940, 2830.4, 1482.1, 1442.1, 1243.1, 1222, 1036.8, 1003.3, 873.5, 807.7, 766.7, 592.2, 420.6 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{18}H_{22}NO_4$ $[M + H]^+$, 316.1543; found, 316.1563.

*2-(Benzo[d][1,3]dioxol-5-yl)-N-(2,3-dimethoxybenzyl)ethan-1-aminium Chloride (**6a**).* The flow system adopted a two-feed microreactor consisting of a 5.0 mL piece of PTFE tube with an internal diameter of 0.8 mm (1/16 in. outer diameter) and a length of 10 m. The solution of the above secondary amine **10a** in MeOH (0.03 M) was pumped into the microreactor through feed A (flow rate: 0.8 mL/min), while the mixture containing HCl/MeOH (0.2 M, 1.5 equiv) was introduced into the microreactor through feed B (flow rate: 0.2 mL/min). The reaction mixture was pumped at an overall flow rate of 1.0 mL/min at 25 °C with a 5 min residence time. The reaction mixture was collected in a separate 100 mL round-bottom flask. The system was allowed to reach a steady state by waiting three residence times prior to collecting the product in 15 min. The reaction mixture was evaporated in vacuo. The residue was slurried with Et_2O at room temperature for 12 h and then filtered to afford secondary amine hydrochloride **6a** in 94% yield, 3.3 g (in three steps from phenylethylamine **7a** and benzaldehyde **8a**), corresponding to a production rate of 505 mg/h. Hydrochloride **6a** was obtained as a white solid; mp = 144.7−147.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.47 (s, 2H), 7.21 (dd, J = 5.6, 3.6 Hz, 1H), 7.15−7.09 (m, 2H), 6.87−6.83 (m, 2H), 6.70 (dd, J = 8.0, 1.6 Hz, 1H), 5.98 (s, 2H), 4.11 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.10−3.00 (m, 2H), 2.98−2.90 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 152.3, 147.4, 147.1, 146.0, 131.0, 125.4, 124.1, 122.4, 121.7, 113.8, 109.0, 108.4, 100.9, 60.6, 55.8, 47.9, 44.2, 30.9. IR (neat): 2941.9, 2697.7, 2606.9, 1584.37, 1485.9, 1443.81, 1227.4, 1094.4, 1034.7, 996.6, 730.9, 588.7 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{18}H_{22}NO_4$ $[M - Cl]^+$, 316.1543; found, 316.1563.

Fully Continuous Flow Synthesis of Secondary Amine Hydrochloride 6b. *(E)-N-(3,4-Dimethoxyphenethyl)-1-(2,3-dimethoxyphenyl) Methanimine (**9b**).* The methanol solution of imine **9b** (0.03 M in MeOH) was prepared from phenylethylamine **7b** and benzaldehyde **8a** according to the procedure of **9a**. Analytically, imine **9b** sample was obtained after concentrating in vacuo without purification as a yellow oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.50 (s, 1H), 7.54 (dd, J = 7.9, 1.6 Hz, 1H), 7.12−7.03 (m, 1H), 6.96 (dd, J = 8.1, 1.6 Hz, 1H), 6.76 (dd, J = 10.6, 2.0 Hz, 3H), 3.87 (s, 5H), 3.83 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 2.96 (t, J = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 157.6, 152.9, 149.4, 148.8, 147.4, 132.7, 130.0, 124.3, 121.0, 118.8, 114.3, 112.6, 111.3, 63.8, 61.8, 56.0, 55.9, 55.9, 37.1. IR (neat): 2934.9, 2833.1, 1638, 1581.5, 1513.6, 1461.4, 1259.6, 1232.5, 1139.5, 1026.7, 1002.4, 756.4,

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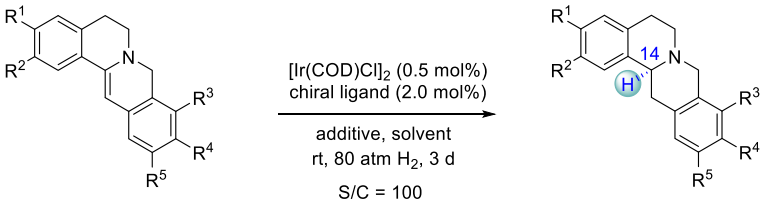
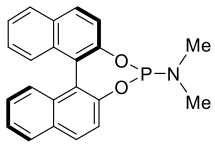
Table 2. Completion of Total Synthesis of 1−4 via Ir-Catalyzed Enantioselective Hydrogenation of 5a−5d[a]

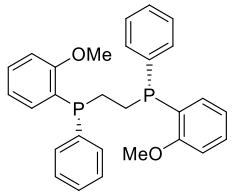


dihydroprotoberberine **5a-d** → tetrahydroprotoberberine **1-4**

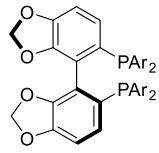
5a, (–)-canadine (1): R^1, R^2 = -OCH_2O-, R^3 = R^4 = -OCH_3, R^5 = H
5b, (–)-Rotundine (2): R^1 = R^2 = -OCH_3, R^3 = R^4 = -OCH_3, R^5 = H
5c, (–)-Sinactine (3): R^1 = R^2 = -OCH_3, R^3, R^4 = -OCH_2O-, R^5 = H
5d, (–)-Xylopinine (4): R^1 = R^2 = -OCH_3, R^3 = H, R^4 = R^5= -OCH_3



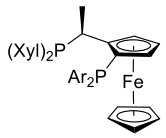
L1: (*R*)-MONOPHOS



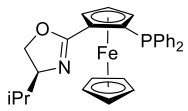
L2: (*R,R*)-DIPAMP



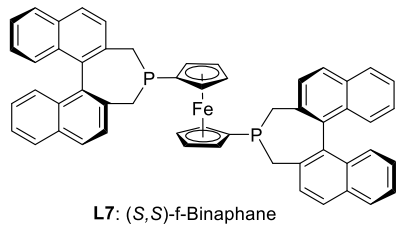
L3: (*R*)-DM-SEGPHOS
[Ar = 3,5-(Me)2-Ph]



L4: (S,R_P)-BTFM-Xyliphos
[Ar = 3,5-$(CF_3)_2$-Ph]
L5: Josiphos SL-J404-1
[Ar = Naphthyl]



L6: (*S,S*)-*i*Pr-FOXAP



L7: (*S,S*)-f-Binaphane

entry	sub.	lig.	solvent[b]	add.	yield (%)[c]	ee (%)[d]
1	**5a**	**L1**	Tol/AcOH	KI	91	46 (*R*)
2	**5a**	**L2**	Tol/AcOH	KI	61	1 (*S*)
3	**5a**	**L3**	Tol/AcOH	KI	80	8 (*S*)
4	**5a**	**L4**	Tol/AcOH	KI	71	2 (*S*)
5	**5a**	**L5**	Tol/AcOH	KI	76	1 (*S*)
6	**5a**	**L6**	Tol/AcOH	KI	76	2 (*S*)
7	**5a**	**L7**	Tol/AcOH	KI	94	82 (*S*)
8	**5a**	**L7**	Tol/AcOH	I2	86	92 (*S*)
9	**5a**	**L7**	Tol/AcOH	TBAI	88	93 (*S*)
10	**5a**	**L7**	Tol/AcOH	LiI	85	94 (*S*)
11	**5a**	**L7**	Tol/AcOH	KBr	92	96 (*S*)
12	**5a**	**L7**	MeOH/AcOH	KBr	82	48 (*S*)
13	**5a**	**L7**	TFE/AcOH	KBr	80	9 (*S*)
14	**5a**	**L7**	EtOAc/AcOH	KBr	87	94 (*S*)
15	**5a**	**L7**	DMF/AcOH	KBr	88	94 (*S*)
16	**5a**	**L7**	DCM/AcOH	KBr	93	99 (*S*)
17[e,f]	**5a**	**L7**	DCM/AcOH	KBr	92	98 (*S*)
18	**5b**	**L7**	DCM/AcOH	KBr	95	97 (*S*)
19	**5c**	**L7**	DCM/AcOH	KBr	90	92 (*S*)
20	**5d**	**L7**	DCM/AcOH	KBr	91	91 (*S*)

[a]Reaction conditions: Ir/ligand/additive/substrate = 1:2:10:100, [substrate] = 0.1 M, room temperature, 3d, 80 atm H_2. [b]Solvent/AcOH ratio was 9:1 (v/v). [c]Isolated yield. [d]Determined by chiral HPLC analysis. [e]1.0 g scale. [f]0.1 mol % $[Ir(COD)Cl]_2$ (S/C = 500).

641.5 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{19}H_{24}NO_4$ $[M + H]^+$, 330.1700; found, 330.1704.

*N-(2,3-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)ethan-1-amine (**10b**).* The methanol solution of secondary amine **10b** was prepared from imine **9b** according to the procedure of **10a**. Analytically, the compound **10b** sample was obtained after concentrating in vacuo without purification as a pale yellow oil. ^1H NMR (400 MHz, chloroform-*d*): δ 6.99 (t, *J* = 8.0 Hz, 1H), 6.83 (t, *J* = 6.4 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.76−6.70 (m, 2H), 3.85 (s,

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9H), 3.81 (s, 2H), 3.78 (s, 3H), 2.85 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-d): δ 152.7, 148.9, 147.5, 147.4, 134.1, 132.8, 123.9, 121.7, 120.7, 112.0, 111.4, 111.4, 60.8, 56.0, 55.9, 55.8, 50.7, 48.8, 36.1. IR (neat): 2934.1,2832, 1586.7, 1513.5, 1462.3, 1259.7, 1232, 1139.3, 1076, 1026.6, 1006.3, 749.7, 633 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{26}NO_4$ $[M + H]^+$, 332.1856; found, 332.1880.

*N-(2,3-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)ethan-1-aminium Chloride (**6b**).* The secondary amine hydrochloride **6b** was prepared from secondary amine **10b** according to the procedure of **6a** in 93% yield, 3.4 g (in three steps from phenylethylamine **7b** and benzaldehyde **8a**), corresponding to a production rate of 528 mg/h. The hydrochloride salt of **6b** was obtained as a white solid, mp = 96.2−98.4 °C, ^1H NMR (400 MHz, chloroform-d): δ 9.74 (s, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.76−6.64 (m, 3H), 4.24 (s, 2H), 3.86 (s, 3H), 3.84−3.77 (m, 9H), 3.17−3.08 (m, 2H), 3.03 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-d): δ 152.5, 149.2, 148.1, 147.9, 129.1, 124.7, 123.6, 123.2, 120.9, 113.9, 112.0, 111.5, 61.2, 56.0, 56.0, 55.8, 47.4, 45.1, 32.0. IR (neat): 2938.2, 2834.6, 2752.6, 1588.7, 1515.3, 1460.8, 1260.2, 1232.2, 1141.5, 1083.4, 1024.9, 730.2, 698.3, 632.4 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{26}NO_4$ $[M - Cl]^+$, 332.1856; found, 332.1866.

Fully Continuous Flow Synthesis of Secondary Amine Hydrochloride 6c. *(E)-1-(Benzo[d][1,3]dioxol-4-yl)-N-(3,4-dimethoxyphen-ethyl)methanimine (**9c**).* The methanol solution of imine **9c** (0.03 M in MeOH) was prepared from phenylethylamine **7b** and benzaldehyde **8b** according to the procedure of **9a**. Analytically, imine **9c** sample was obtained after concentrating in vacuo without purification as a pale yellow oil, ^1H NMR (400 MHz, chloroform-d): δ 8.23 (s, 1H), 7.24−7.20 (m, 1H), 6.87−6.83 (m, 2H), 6.81−6.76 (m, 2H), 6.75 (s, 1H), 6.04 (s, 2H), 3.88−3.83 (m, 5H), 3.82 (s, 3H), 2.96 (t, J = 7.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-d): δ 156.8, 148.8, 148.3, 147.5, 146.9, 132.6, 121.7, 120.9, 120.7, 118.9, 112.6, 111.3, 110.2, 101.7, 64.2, 56.0, 55.8, 37.2. IR (neat): 2903.4, 2833.7, 1644.5, 1513.5, 1449.7, 1235.6, 1138.7, 1025.7, 927.2, 773.1, 725.3637.6, 543.5 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{18}H_{20}NO_4$ $[M + H]^+$, 314.1387; found, 314.1387.

*N-(Benzo[d][1,3]dioxol-4-ylmethyl)-2-(3,4-dimethoxyphen-yl)-ethan-1-amine (**10c**).* The methanol solution of secondary amine **10c** was prepared from imine **9c** according to the procedure of **10a**. Analytically, the compound **10c** sample was obtained after concentrating in vacuo without purification as a pale yellow oil. ^1H NMR (400 MHz, chloroform-d): δ 6.81−6.75 (m, 2H), 6.74 (s, 2H), 6.73−6.70 (m, 2H), 5.90 (s, 2H), 3.85 (s, 3H), 3.85 (s, 3H), 3.79 (s, 2H), 2.87 (t, J = 6.8 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-d): δ 149.0, 147.5, 147.3, 145.6, 132.7, 122.3, 121.9, 121.6, 120.7, 112.0, 111.3, 107.5, 100.8, 56.0, 55.9, 50.6, 48.2, 35.9. IR (neat): 2933.3, 2903.4, 2833.7, 1513.4, 1454.1, 1234.1, 1138.6, 1026.2, 927, 761.7, 726.1, 632, 463.4 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{18}H_{22}NO_4$ $[M + H]^+$: 316.1543, found, 316.1548.

*N-(Benzo[d][1,3]dioxol-4-ylmethyl)-2-(3,4-dimethoxyphen-yl)-ethan-1-aminium Chloride (**6c**).* The secondary amine hydrochloride **6c** was prepared from secondary amine **10c** according to the procedure of **6a** in 90% yield, 3.1 g (in three steps from phenylethylamine **7b** and benzaldehyde **8b**), corresponding to a production rate of 505 mg/h. Hydrochloride **6c** was obtained as a white solid. mp = 143.3−144.6 °C. ^1H NMR (400 MHz, chloroform-d): δ 10.04 (s, 2H), 7.17 (d, J = 7.6 Hz, 1H), 6.81 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.74−6.68 (m, 3H), 5.98 (s, 2H), 4.07 (s, 2H), 3.83 (s, 6H), 3.16−2.99 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-d): δ 149.3, 148.2, 147.7, 147.2, 129.1, 123.8, 122.6, 120.9, 112.2, 111.6, 111.5, 109.9, 101.5, 56.1, 56.0, 48.0, 44.4, 31.9. IR (neat): 2936.3, 2761.7, 1515.7, 1457.3, 1238, 1141.1, 1026.1, 925.7, 780.1, 730.5, 631.7, 464.4 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{18}H_{22}NO_4$ $[M - Cl]^+$, 316.1543; found, 316.1550.

Fully Continuous Flow Synthesis of Secondary Amine Hydrochloride 6d. *(E)-N-(3,4-Dimethoxyphenethyl)-1-(3,4-dimethoxyphenyl) Methanimine (**9d**).* The methanol solution of imine **9d** (0.03 M in MeOH) was prepared from phenylethylamine **7b** and benzaldehyde **8c** according to the procedure of **9a**. Analytically, the imine **9d** sample was obtained after concentrating in vacuo without purification as a pale yellow solid. mp = 81.5−83.0 °C. ^1H NMR (400 MHz, chloroform-d): δ 8.04 (s, 1H), 7.44−7.38 (m, 1H), 7.10 (dd, J = 8.4, 1.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.81−6.72 (m, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.84 (s, 3H), 3.83−3.80 (m, 2H), 3.79 (s, 3H),2.94 (t, J = 7.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-d): δ 161.2, 151.5, 149.5, 148.8, 147.5, 132.8, 129.6, 123.1, 121.0, 112.7, 111.4, 110.6, 108.8, 63.4, 56.1, 56.1, 56.1, 55.9, 37.3. IR (neat): 2933.6, 2833.5, 1586, 1509.5, 1460.7, 1259.6, 1232.4, 1136, 1022.3, 806.9, 762.5,616.8 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{24}NO_4$ $[M + H]^+$, 330.1700; found, 330.1708.

*N-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)ethan-1-amine (**10d**).* The methanol solution of secondary amine **10d** was prepared from imine **9d** according to the procedure of **10a**. Analytically, the compound **10d** sample was obtained after concentrating in vacuo without purification as a white solid. mp = 84.6−86.3 °C. ^1H NMR (400 MHz, chloroform-d): δ 6.83 (s, 1H), 6.81−6.77 (m, 3H), 6.73 (d, J = 8.8 Hz, 2H), 3.86 (s, 6H), 3.85 (s, 6H), 3.74 (s, 2H), 2.87 (t, J = 6.8 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-d): δ 149.0, 149.0, 148.1, 147.5, 133.1, 132.7, 120.7, 120.3, 112.0, 111.4, 111.1, 56.0, 55.9, 53.8, 50.7, 36.0. IR (neat): 2933.9, 2832.7, 1511.4, 1459.9, 1257.9, 1231.5, 1136.6, 1024.7, 805.3, 761.6,634 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{26}NO_4$ $[M + H]^+$, 332.1856; found, 332.1863.

*N-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)ethan-1-aminium Chloride (**6d**).* The secondary amine hydrochloride **6d** was prepared from secondary amine **10d** according to the procedure of **6a** in 92% yield, 3.3 g (in three steps from phenylethylamine **7b** and benzaldehyde **8c**), corresponding to a production rate of 528 mg/h. Hydrochloride **6d** was obtained as a white solid. mp = 166.9−168.3 °C. ^1H NMR (400 MHz, chloroform-d): δ 10.02 (s, 2H), 7.31 (s, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.74 (t, J = 8.0 Hz, 2H), 6.68 (d, J = 7.2 Hz, 2H), 3.95 (s, 5H), 3.82 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 3.10−3.02 (m, 2H), 3.01−2.92 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-d): δ 150.0, 149.5, 149.3, 148.2, 129.1, 123.1, 122.2, 120.8, 113.4, 112.2, 111.6, 111.0, 56.4, 56.1, 56.0, 55.8, 51.1, 47.7, 32.0. IR (neat): 1518.2, 1465.3, 1263.4, 1161, 1140.1, 1025.8, 895.7, 814.4, 731, 702.9, 639.9 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{26}NO_4$ $[M - Cl]^+$, 332.1856; found, 332.1868.

General Procedure B: for the Synthesis of Dihydroprotoberberine Alkaloids 5. To a solution of glyoxal (570 μL, 5.0 mmol, 20.0 equiv, 40% wt in water) in 98% HCOOH (2 mL) were added NaCl (51 mg, 0.86 mmol, 3.5 equiv) and $MgSO_4$ (1.0 g). The mixture was stirred at room temperature for 0.5 h; then, secondary amine hydrochloride **6** (0.25 mmol, 1.0 equiv) and $B(OH)_3$ (31 mg, 0.5 mmol, 2.0 equiv) were added and the mixture was stirred at 80 °C for 12 h under argon in a sealed tube. $MgSO_4$ was filtered through celite and the organic collection was transferred into a 100 mL round-bottom flask. The mixture solution was quenched with 2 M NaOH aq., the pH was adjusted to 10, and then extracted with DCM (3 × 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated in vacuum. The resulting residue was purified by short silica column flash chromatography (DCM/MeOH = 100:1) to give the corresponding dihydroprotoberberine alkaloids **5**.

*Dihydroberberine (**5a**).* Dihydroberberine **5a** was prepared from **6a** in 71% yield, 60 mg, according to the general procedure B after short flash column chromatography (DCM/MeOH = 100:1 to 80:1). A dark yellow solid, mp = 150.4−152.8 °C (lit.[15] 155−161 °C). ^1H NMR (600 MHz, chloroform-d): δ 7.17 (s, 1H), 6.74 (d, J = 9.0 Hz, 2H), 6.58 (s, 1H), 5.95 (s, 1H), 5.94 (s, 2H), 4.32 (s, 2H), 3.84 (s, 6H), 3.13 (t, J = 6.0 Hz, 2H), 2.87 (t, J = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, chloroform-d): δ 150.5, 147.4, 146.8, 144.6, 141.8, 128.9, 128.7, 124.7, 122.3, 118.9, 111.6, 108.0, 103.9, 101.4, 96.5, 60.9, 56.1, 49.5, 49.2, 23.0. IR (neat): 2932.1, 2833.1, 1596.5, 1478.7, 1452.1, 1346, 1267.4, 1225.1, 1082.1, 1028, 815.3, 737.4, 646.5, 443.6 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{20}H_{20}NO_4$ $[M + H]^+$, 338.1387; found, 338.1376.

*Dihydropalmatine (**5b**).* Dihydropalmatine **5b** was prepared from **6b** in 69% yield, 61 mg, according to the general procedure B after

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short flash column chromatography (DCM/MeOH = 100:1 to 80:1). A yellow solid, mp = 171.4−173.8 °C (lit.[16] 170 °C). ^{1}H NMR (600 MHz, chloroform-*d*): δ 7.18 (s, 1H), 6.75 (s, 2H), 6.60 (s, 1H), 5.99 (s, 1H), 4.33 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.15 (t, *J* = 6.0 Hz, 2H), 2.90 (t, *J* = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz, chloroform-*d*): δ 150.5, 149.1, 147.9, 144.7, 141.8, 128.8, 127.5, 123.3, 122.2, 118.8, 111.6, 110.7, 106.8, 95.9, 60.9, 56.2, 56.1, 56.0, 49.6, 49.3, 29.5. IR (neat): 2998, 2953.2, 1602.6, 1506.4, 1450.2, 1362.9, 1271.5, 1184.7, 1107.4, 1019.4, 862.4, 809.9, 649.9, 585.2, 406.1 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{21}H_{24}NO_4$ [M + H]$^+$, 354.1700; found, 354.1608.

*Dihydroepiberberine (**5c**).* Dihydroepiberberine **5c** was prepared from **6c** in 62% yield, 52 mg, according to the general procedure B after short flash column chromatography (DCM/MeOH = 100:1 to 80:1). A dark yellow solid,[8g] mp = 162.8−164.7 °C. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.17 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.60 (s, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 1H), 5.93 (s, 2H), 4.25 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.14 (t, *J* = 5.6 Hz, 2H), 2.90 (t, *J* = 5.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 149.1, 147.9, 145.4, 142.8, 141.5, 129.6, 127.5, 123.3, 116.0, 110.7, 110.0, 107.5, 106.7, 101.0, 96.6, 56.2, 56.0, 49.3, 49.0, 29.5. IR (neat): 2925.9, 2831.7, 1509.9, 1455.3, 1373.8, 1216.3, 1157, 1062.3, 1016.8, 852.9, 810, 775.4, 481.6 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{20}NO_4$ [M + H]$^+$, 338.1387; found, 338.1302.

*Dihydropseudopalmatine (**5d**).* Dihydropseudopalmatine **5d** was prepared from **6d** in 70% yield, 62 mg, according to the general procedure B after short flash column chromatography (DCM/MeOH = 100:1 to 80:1). A yellow solid,[8g] mp = 182.3−184.5 °C. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.19 (s, 1H), 6.63 (s, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 6.02 (s, 1H), 4.19 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.13 (t, *J* = 6.0 Hz, 2H), 2.90 (t, *J* = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 149.1, 148.7, 147.9, 146.8, 142.1, 127.8, 127.4, 123.2, 120.1, 110.7, 109.3, 107.1, 106.7, 96.3, 56.4, 56.1, 56.1, 56.0, 55.1, 49.4, 29.5. IR (neat): 2997.4, 2929.1, 2833.9, 1610.1, 1512.4, 1461.8, 1346.9, 1256.8, 1141.5, 1100.1, 1022.3, 855.6, 730.1, 562.8 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{21}H_{24}NO_4$ [M + H]$^+$, 354.1700; found, 354.1620.

General Procedure C of Ir-Catalyzed Enantioselective Hydrogenation: for the Synthesis of Tetrahydroprotoberberine Alkaloids 1−4. A mixture of $[Ir(COD)Cl]_2$ (1.0 mg, 1.5 μmol, 0.5 mol %) and (*S*,*S*)-*f*-BINAPHANE (5 mg, 6.0 μmol, 2.0 mol %) was dissolved in a degassed mixed-solvent DCM/AcOH (v/v = 9:1, 3 mL) in an argon atmosphere, and the resulting solution was allowed to stir at room temperature for 30 min. Then, the dihydroprotoberberine alkaloids **5** (0.3 mmol, 1.0 equiv) and KBr (3.5 mg, 0.03 mmol, 10 mol %) were added. The mixture was transferred to an autoclave, which was purged (3 × 10 atm) and charged with H_2 (80 atm); then, the reaction was stirred at 25 °C for 72 h. The hydrogen gas was released slowly, and the solution was quenched with sat. Na_2CO_3 aq. The resulting mixture was extracted with DCM (3 × 5 mL). The combined organic phase was dried with Na_2SO_4 and evaporated in vacuum. The resulting residue was purified by silica gel chromatography to give the tetrahydroprotoberberine alkaloids **1**−**4**.

*(−)-Canadine (**1**).* (−)-Canadine (**1**) was prepared from **5a** in 93% yield, 94 mg, according to the general procedure C after flash column chromatography (DCM/MeOH = 50:1). A pale yellow solid, mp = 132.8−134.8 °C (lit.[17] 134 °C). ^{1}H NMR (400 MHz, chloroform-*d*): δ 6.86 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 1H), 6.59 (s, 1H), 5.91 (s, 2H), 4.24 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 6H), 3.60−3.48 (m, 2H), 3.29−3.04 (m, 3H), 2.91−2.75 (m, 1H), 2.73−2.54 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 150.4, 146.2, 146.0, 145.2, 130.9, 128.7, 127.9, 127.8, 124.0, 111.1, 108.5, 105.6, 100.8, 60.3, 59.7, 56.0, 54.0, 51.5, 36.5, 29.7. IR (neat): 2901.3, 2832.2, 2744.8, 1483.7, 1387.7, 1274.9, 1219, 1082, 1035.2, 936.4, 858.4, 732.7, 506.1, 438 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{22}NO_4$ [M + H]$^+$, 340.1543; found, 340.1543. $[\alpha]_D^{20}$ −290.8 (c 1.0, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ −291 (c 0.93, $CHCl_3$)]. The product was analyzed by HPLC to determine the enantiomeric excess: 99.9% ee (CHIRALPAK ADH, hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, *T* = 30 °C, 210 nm), t_R(major) = 10.1 min, t_R(minor) = 6.4 min.

*(−)-Rotundine (**2**).* (−)-Rotundine (**2**) was prepared from **5b** in 95% yield, 101 mg, according to the general procedure C after flash column chromatography (DCM/MeOH = 50:1). A pale yellow solid, mp = 135.8−137.8 °C (lit.[18] 141−142 °C). ^{1}H NMR (400 MHz, chloroform-*d*): δ 6.88 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 1H), 6.62 (s, 1H), 4.25 (d, *J* = 15.6 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86−3.84 (m, 6H), 3.56 (d, *J* = 15.2 Hz, 2H), 3.27 (dd, *J* = 15.6, 3.6 Hz, 1H), 3.23−3.10 (m, 2H), 2.89−2.79 (m, 1H), 2.74−2.60 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 150.2, 147.5, 147.4, 145.1, 129.7, 128.7, 127.7, 126.7, 123.8, 111.4, 111.0, 108.6, 60.1, 59.3, 56.1, 55.9, 55.8, 54.0, 51.5, 36.3, 29.1. IR (neat): 2926.9, 2836.9, 2736.3, 1609.1, 1510.7, 1491.8, 1453.2, 1255, 1227.9, 1139.6, 1078.6, 1027.9, 858.3, 783.3, 509, 426 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{21}H_{26}NO_4$ [M + H]$^+$, 356.1856; found, 356.1860. $[\alpha]_D^{20}$ −263.2 (c 0.9, $CHCl_3$) [lit.[18] $[\alpha]_D^{20}$ −269.0 (c 0.8, $CHCl_3$)]. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (CHIRALPAK ADH, hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, *T* = 30 °C, 210 nm), t_R(major) = 11.2 min, t_R(minor) = 6.2 min.

*(−)-Sinactine (**3**).* (−)-Sinactine (**3**) was prepared from **5c** in 90% yield, 95 mg, according to the general procedure C after flash column chromatography (DCM/MeOH = 50:1). A pale orange solid, mp = 162.4−165.5 °C (lit.[19] 175 °C). ^{1}H NMR (400 MHz, chloroform-*d*): δ 6.73 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.62 (s, 1H), 5.96 (s, 1H), 5.93 (s, 1H), 4.11 (d, *J* = 15.2 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.63−3.52 (m, 2H), 3.28 (dd, *J* = 16.0, 3.2 Hz, 1H), 3.20−3.10 (m, 2H), 2.87−2.77 (m, 1H), 2.73−2.60 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 147.5, 147.4, 145.0, 143.3, 129.5, 128.6, 126.7, 121.0, 116.9, 111.3, 108.5, 106.7, 101.0, 59.4, 56.1, 55.8, 53.0, 51.3, 36.3, 29.1. IR (neat): 2890.1, 2833.9, 1511.1, 1455.5, 1357.3, 1253, 1137.4, 1035, 1019.3, 911.2, 797.3, 756.1, 591.6, 477.2 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{21}NO_4$ [M + H]$^+$, 340.1543; found, 340.1548. $[\alpha]_D^{20}$ −279.1 (c 0.6, $CHCl_3$) [lit.[19] $[\alpha]_D^{20}$ −312 (c 0.37, $CHCl_3$)]. The product was analyzed by HPLC to determine the enantiomeric excess: 92% ee (CHIRALPAK ADH, hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, T = 30 °C, 210 nm), t_R(major) = 27.6 min, t_R(minor) = 13.0 min.

*(−)-Xylopinine (**4**).* (−)-Xylopinine (**4**) was prepared from **5d** in 91% yield, 97 mg, according to the general procedure C after flash column chromatography (DCM/MeOH = 50:1). A pale yellow solid, mp = 176.9−178.7 °C (lit.[8e] 177−178 °C). ^{1}H NMR (400 MHz, chloroform-*d*): δ 6.74 (s, 1H), 6.66 (s, 1H), 6.62 (s, 1H), 6.58 (s, 1H), 3.95 (d, *J* = 14.6 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.68 (d, *J* = 14.4 Hz, 1H), 3.62−3.56 (m, 1H), 3.25 (dd, *J* = 16.0, 3.2 Hz, 1H), 3.15 (d, *J* = 7.2 Hz, 2H), 2.89−2.79 (m, 1H), 2.71−2.57 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*): δ 147.7, 147.6, 147.5, 147.5, 129.9, 126.8, 126.4, 126.4, 111.5, 111.5, 109.1, 108.6, 59.7, 58.4, 56.1, 56.1, 56.0, 55.9, 51.5, 36.5, 29.1. IR (neat): 2928.3, 2833.7, 1610, 1514.3, 1461.9, 1354.9, 1257.8, 1142.7, 1101.1, 1022.7, 856, 729.9 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{21}H_{26}NO_4$ [M + H]$^+$, 356.1856; found, 356.1852. $[\alpha]_D^{20}$ −262.3 (c 0.6, $CHCl_3$) [lit.[8e] $[\alpha]_D^{20}$ −282.4 (c 0.7, $CHCl_3$)]. The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (CHIRALPAK ADH, hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, *T* = 30 °C, 210 nm), t_R(major) = 53.5 min, t_R(minor) = 14.7 min.

Synthesis of (−)-Canadine (1) on a Gram Scale with 0.1 mol % Ir Catalyst. A mixture of $[Ir(COD)Cl]_2$ (2.0 mg, 3.0 μmol, 0.1 mol %) and (*S*,*S*)-*f*-BINAPHANE (9.6 mg, 12.0 μmol, 0.4 mol %) was dissolved in a degassed mixed-solvent DCM/AcOH (v/v = 9:1, 30 mL) in an argon atmosphere, and the resulting solution was allowed to be stirred at room temperature for 30 min. Then, dihydroberberine **5a** (1.0 g, 3.0 mmol, 1.0 equiv) and KBr (35 mg, 0.3 mmol, 10 mol %) were added. The mixture was transferred to an autoclave, which was purged (3 × 10 atm) and charged with H_2 (80 atm); then, the reaction mixture was stirred at 25 °C for 72 h. The hydrogen gas was released slowly, and the solution was quenched with sat. Na_2CO_3 aq. The resulting mixture was extracted with DCM (3 × 50 mL). The combined organic phase was dried with Na_2SO_4 and evaporated in vacuum. The resulting residue was purified by silica gel

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chromatography (DCM/MeOH = 200:1 to 50:1) to give (−)-canadine (**1**) (926 mg, 92%) as a pale yellow solid, mp = 130.2−133.3 °C (lit.[17] 134 °C), $[\alpha]_D^{20}$ −281.3 (c 1.0, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ −291 (c 0.93, $CHCl_3$)]. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (CHIRALPAK ADH, hexane/*i*-PrOH = 80/20, flow rate: 1.0 mL/min, T = 30 °C, 210 nm), t_R(major) = 9.7 min, t_R(minor) = 6.2 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00602.

Experimental procedures, HPLC data, compound characterization, NMR spectra, and HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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