

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-A³ reaction (up to 4% overall yield and 88–97% ee), and based on Noyori catalytic ATH of enamine (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).

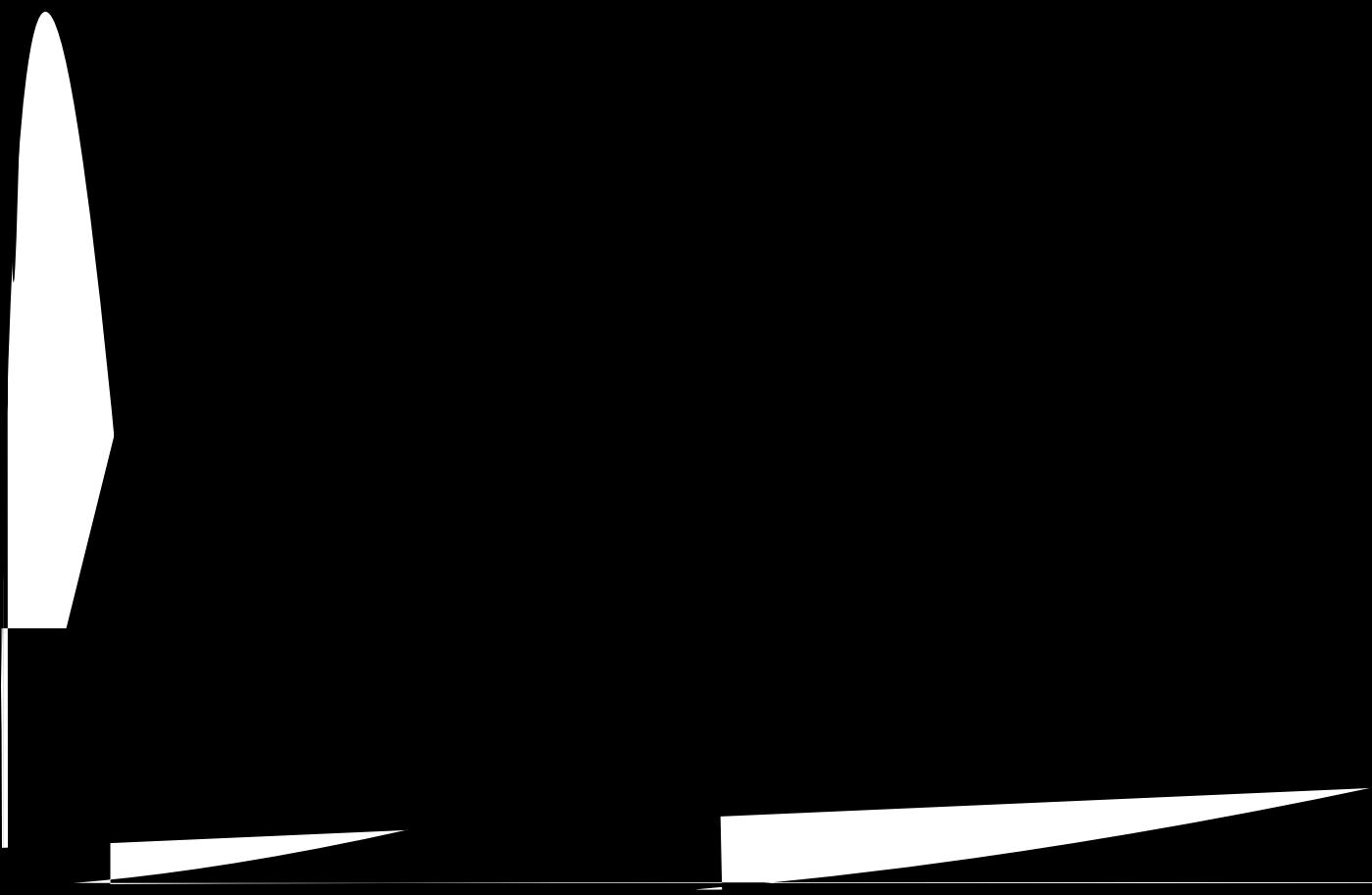
The retrosynthetic analysis of tetrahydroprotoberberine alkaloids 1–4 are depicted in Scheme 2. Inspired by the emerging field of transition-metal-catalyzed enantioselective hydrogenation of enamine as a powerful tool for the construction of chiral cyclic tertiary amines in asymmetric synthesis,⁹ the stereogenic center (14S) 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 hydroxylalkylation/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

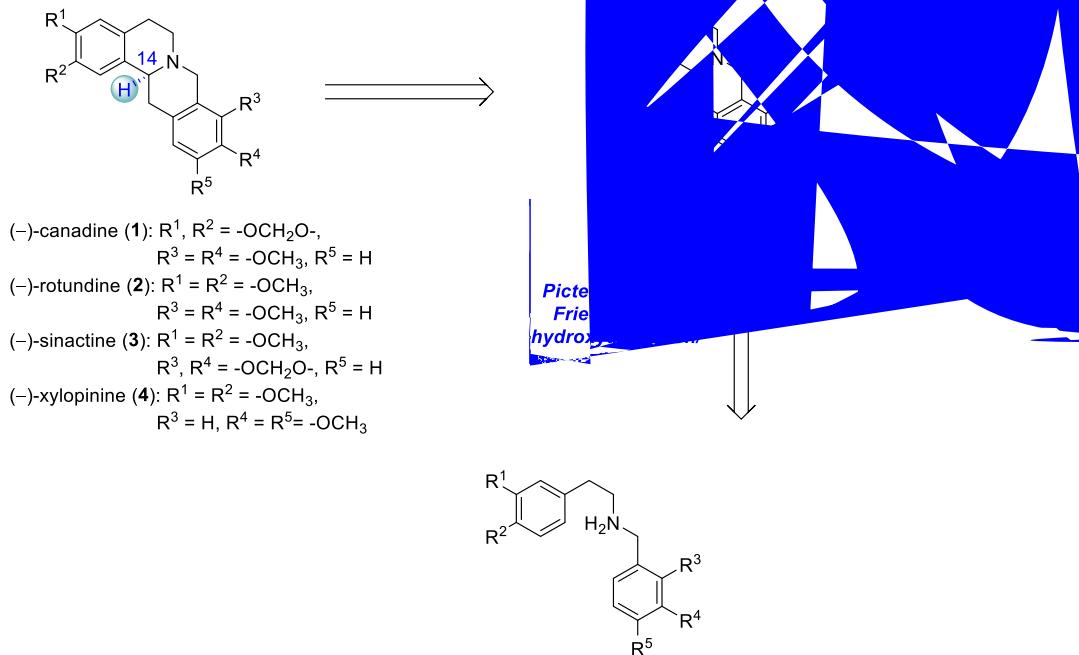
RESULTS AND DISCUSSION

Our synthesis commenced with the fully continuous flow synthesis of secondary amine hydrochlorides 6a–6d from the commercially available corresponding disubstituted phenylethylenamines 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 H₂ into another fixed-bed reactor containing 10% Pd(OH)₂/C dispersed by SiO₂ (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 hydroxylalkylation/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 AlCl₃ 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 ¹H NMR analysis, and no observed product upon work-up (entries 2 and 3).



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 phenylethyamines 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.

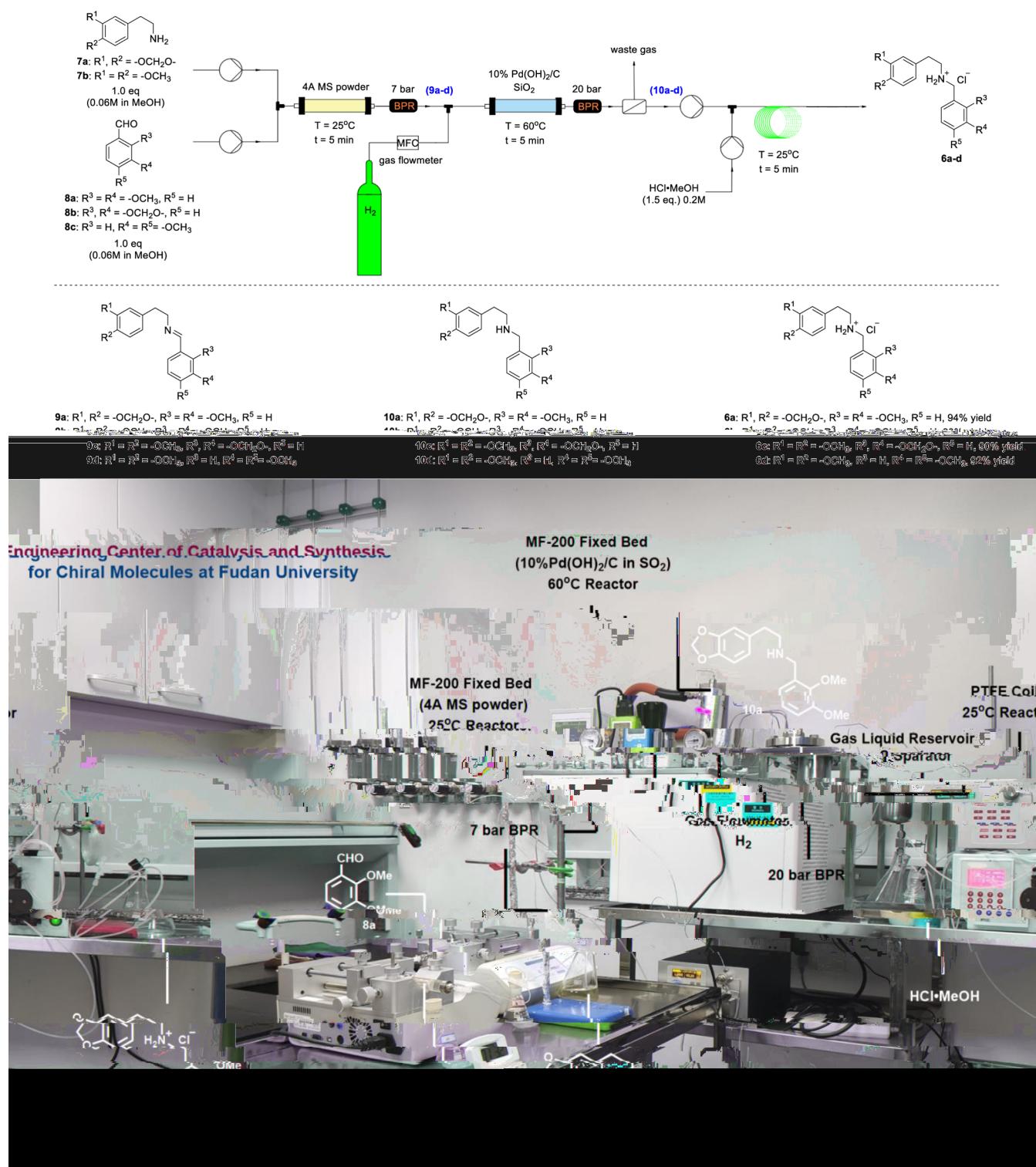
EXPERIMENTAL SECTION

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 phenylethyamines 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). ^1H NMR spectra were recorded at 400 or 600 MHz (Bruker) and $^{13}\text{C}\{1\}$ NMR spectra were recorded at 100 or 150 MHz (Bruker). Chemical shifts are reported in parts per million (ppm) downfield from CDCl_3 ($\delta = 7.26$ ppm), DMSO-d_6 ($\delta =$

2.50 ppm) for ^1H NMR and relative to the central CDCl_3 resonance ($\delta = 77.16$ ppm), the central DMSO-d_6 resonance ($\delta = 39.50$ ppm) for $^{13}\text{C}\{1\}$ 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-(Benzod[*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. ^1H 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).

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

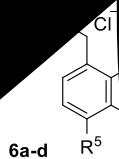


¹³C{¹H} NMR (100 MHz, DMSO-d₆): 156.4, 152.6, 148.7, 147.1, 145.4, 133.7, 129.3, 124.1, 121.8, 118.0, 114.7, 109.3, 108.0, 100.6, 62.6, 61.2, 55.8, 36.5. IR (neat): 2893.5, 2833.7, 1577.8, 1476.7, 1241.9, 1086.5, 1036.6, 1000.7, 881.9, 808.5, 774.2, 594.2 cm⁻¹. HRMS (ESI) m/z: calcd for C₁₈H₂₀NO₄ [M + 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 H₂ 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 SiO₂ (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 a cold 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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vacuo without purification as a yellow oil. ^1H NMR (400 MHz, chloroform-d): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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 $\text{C}_{18}\text{H}_{22}\text{NO}_4$ [M + H] $^+$, 316.1543; found, 316.1563.

2-(Benzod[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 Et₂O at room temperature for 12 h and then filtered to a solid 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. ^1H NMR (400 MHz, DMSO-d₆): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, DMSO-d₆): 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 $\text{C}_{18}\text{H}_{22}\text{NO}_4$ [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. ^1H NMR (400 MHz, chloroform-d): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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,

Table 2. Completion of Total Synthesis of 1–4 via Enzymatic Polymerization of 5a–5d^a

Reaction Time (h)	Yield (%)	Product
1	~50	1a
2	~60	1a
3	~70	1a
4	~80	1a
5	~85	1a
6	~90	1a
7	~95	1a
8	~98	1a
9	~99	1a
10	~99	1a
11	~99	1a
12	~99	1a
13	~99	1a
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369	~99	1a
370	~99	1a
371	~99	1a
372	~99	1a
373	~99	1a
374	~99	1a
375	~99	1a
376	~99	1a
377	~99	1a
378	~99	1a
379	~99	1a
380	~99	1a
381	~99	1a
382	~99	1a
383	~99	1a
384	~99	1a
385	~99	1a
386	~99	1a
387	~99	1a
388	~99	1a
389	~99	1a
390	~99	1a
391	~99	1a
392	~99	1a
393	~99	1a
394	~99	1a
395	~99	1a
396	~99	1a
397	~99	1a
398	~99	1a
399	~99	1a
400	~99	1a
401	~99	1a
402		

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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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 $\text{C}_{19}\text{H}_{26}\text{NO}_4$ [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 °C, ^1H NMR (400 MHz, chloroform-d): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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 $\text{C}_{19}\text{H}_{26}\text{NO}_4$ [M + Cl]⁺, 332.1856; found, 332.1866.

Fully Continuous Flow Synthesis of Secondary Amine Hydrochloride 6c. (E)-1-(Benzod[*d*][1,3]dioxol-4-yl)-N-(3,4-dimethoxyphenyl)ethanimine (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): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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 $\text{C}_{18}\text{H}_{20}\text{NO}_4$ [M + H]⁺, 314.1387; found, 314.1387.

N-(Benzod[*d*][1,3]dioxol-4-ylmethyl)-2-(3,4-dimethoxyphenyl)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): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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 $\text{C}_{18}\text{H}_{22}\text{NO}_4$ [M + H]⁺, 316.1543, found, 316.1548.

N-(Benzod[*d*][1,3]dioxol-4-ylmethyl)-2-(3,4-dimethoxyphenyl)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 °C, ^1H NMR (400 MHz, chloroform-d): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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 $\text{C}_{18}\text{H}_{22}\text{NO}_4$ [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): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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, 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 $\text{C}_{19}\text{H}_{24}\text{NO}_4$ [M + H]⁺, 330.1700; found, 330.1700.

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 °C, ^1H NMR (400 MHz, chloroform-d): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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 $\text{C}_{19}\text{H}_{26}\text{NO}_4$ [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 °C, ^1H NMR (400 MHz, chloroform-d): 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). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, chloroform-d): 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 $\text{C}_{19}\text{H}_{26}\text{NO}_4$ [M + Cl]⁺, 332.1856; found, 332.1866.

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 MgSO₄ (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. MgSO₄ 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 Na₂SO₄ 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 °C, ^1H NMR (600 MHz, chloroform-d): 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). $^{13}\text{C}\{\text{H}\}$ NMR (150 MHz, chloroform-d): 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 $\text{C}_{20}\text{H}_{20}\text{NO}_4$ [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

short flash column chromatography (DCM/MeOH = 100:1 to 80:1). A yellow solid, mp = 171.4–173.8 °C (lit.¹⁶ 170 °C). ¹H NMR (600 MHz, chloroform-d): 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). ¹³C{¹H} NMR (150 MHz, chloroform-d): 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 C₂₁H₂₄NO₄ [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. ¹H NMR (400 MHz, chloroform-d): 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). ¹³C{¹H} NMR (100 MHz, chloroform-d): 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 C₂₀H₂₀NO₄ [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. ¹H NMR (400 MHz, chloroform-d): 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). ¹³C{¹H} NMR (100 MHz, chloroform-d): 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 C₂₁H₂₄NO₄ [M + H]⁺, 354.1700; found, 354.1620.

General Procedure C of Ir-Catalyzed Enantioselective Hydrogenation: for the Synthesis of Tetrahydropyroberber-

chromatography (DCM/MeOH = 200:1 to 50:1) to give (S)-canadine (1) (926 mg, 92%) as a pale yellow solid, mp = 130.2–133.3 °C [lit.¹⁷ 134 °C], [α]_D²⁰ 281.3 (c 1.0, CHCl₃) [lit.¹⁷ [α]_D²⁰ 291 (c 0.93, CHCl₃)]. 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.

ACKNOWLEDGMENTS

This work was supported by the Fundamental Research Funds for the Central Universities (YJ201805 and YJ201864).

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