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A divergent route to 9, 10-oxygenated tetrahydroprotoberberine and 8-oxoprotoberberine alkaloids: synthesis of (±)-isocorypalmine and oxypalmatine

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Abstract

A new route which is germane to the synthesis of 9,10-oxygenated tetrahydroprotoberberines and 8-oxoprotoberberines is described. The route features the use of a diester (**14**) generated from reaction of dimethylmalonate with an aryl halide in the presence of *n*-butyllithium. The amide **17** prepared in subsequent steps is a versatile precursor for the synthesis of tetrahydroprotoberberine and 8-oxoprotoberberine scaffolds using standard high-yielding reactions. In this manner, (±)-isocorypalmine and oxypalmatine have been synthesized in 23% and 22 % yields respectively.

Keywords

THPB; Tetrahydroprotoberberine; Isocorypalmine; Oxypalmatine; 8-oxoprotoberberine

1. Introduction

The tetracyclic tetrahydroprotoberberine (THPB) alkaloids are a sub-group of isoquinoline alkaloids that have displayed interesting biological activities - for example as antimicrobial,^{1,2} antitumor,^{3,4} antifungal⁵ and anti-cholinesterase agents.^{6,7} There have also been several reports on THPBs as central nervous system receptor (particularly dopamine receptor) ligands with potential as antipsychotic agents.^{8–10} The core tetracyclic nucleus of naturally occurring THPBs is usually decorated with hydroxyl or alkoxy substituents in the aromatic A and D rings.

The THPB (–)-isocorypalmine (ICP, **1**) is a natural product that has been isolated from a number of *Corydalis* species.^{11,3} (–)-ICP was recently reported to reduce the rewarding effects of cocaine in mice via acting on dopamine receptors.¹² As such, (–)-ICP is a

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Supplementary Material

NMR spectra for all new compounds.

promising molecule towards the development of anti-cocaine therapeutics. Several methods have been developed for the synthesis of the THPB core. Among them, closure of ring C via a Mannich reaction on a benzyltetrahydroisoquinoline (BTHIQ) substrate (**3**; Figure 2) has been most utilized owing to the relative ease with which the BTHIQ precursors can be prepared. However, the Mannich method is non-ideal for the synthesis of 9,10-oxygenated THPBs, since Mannich reaction on the required BTHIQ substrate yields both the 9,10- (**4**) and 10,11-oxygenated (**5**) THPBs (often giving the latter either predominantly or exclusively).^{13,14}

Use of bromine as a blocking group (at the incipient C12 position of the THPB nucleus; **6**) has been used to circumvent this problem. However, this strategy lengthens the synthesis, is often low yielding and may be less desirable for the synthesis of more structurally rich THPBs.^{14–16}

Enantioselective synthesis of THPBs has been accomplished via reduction of intermediate BTHIQs with Noyori catalysts.^{10,17,18} Sun et al recently reported an enantioselective synthesis of several 9,10-oxygenated THPBs (including **1**) via key lactone precursors typified by **7**. Here, condensation of a phenethylamine with **7**, gave an amide.¹⁰ Further synthetic manipulations eventually transformed the aromatic ring of **7** into ring D of the THPB core. However, the synthesis overall is lengthy (>10 steps) and preparation of lactones such as **7** is known to be problematic, particularly on large scale.^{19,20}

These troublesome issues with synthesis of 9,10-oxygenated THPBs prompted an investigation into alternative routes to prepare molecules with this structural feature. In this paper, we report our efforts in this regard as applied to the synthesis of (\pm)-ICP. The route described may also be modified to prepare oxidized 8-oxoprotoberberine congeners - exemplified herein in our synthesis of oxypalmatine (**2**).

2. Results and Discussion

We envisaged that the 9,10-methoxylated THPB core (**8**) could be prepared via the amide intermediate **9** (Figure 3). This intermediate in turn is derivable from the diester **10** (via amide coupling with the corresponding aliphatic acid). Compound **10** we reasoned, would serve as an easily reachable synthetic surrogate for the isochroman **7**. The diester **10** would be prepared from aryl bromide **11**.

This general approach was applied to the synthesis of (\pm)-ICP as depicted in Scheme 1. Commercially available bromo cresol **12** was protected as the ethoxymethyl ether by reaction with chloromethoxyethane affording **13**. (We considered that the ethoxymethyl ether group could be selectively removed later so that various C10 alkoxy analogues in addition to ICP itself could be prepared). Thereafter reaction of **13** with *n*-butyllithium in the presence of dimethylmalonate gave diester **14**.^{21,22} This reaction presumably proceeds via nucleophilic attack of malonate anion on a benzyne intermediate generated from dehydrobromination of **13**.²³ Selective hydrolysis of the aliphatic ester group was accomplished with K₂CO₃ in refluxing H₂O:MeOH to give acid **15**. This acid was coupled

to readily available amine **16**²⁴ with carbonyldiimidazole (CDI) to provide key amide precursor **17**.

Bischler-Napieralski cyclization on amide **17** proved to be successful with POCl₃ as dehydrating agent and acetonitrile as solvent. This cyclization was fortuitously accompanied by simultaneous removal of the ethoxymethyl protecting group. Other dehydrating conditions (neat POCl₃, P₂O₅ or PCl₅) and solvents (dichloromethane or toluene) were tried but gave inferior yields of imine product. Bischler-Napieralski cyclization was followed by immediate reduction (due to instability of the intermediate imines of this type) with NaBH₄ to afford the 8-oxotetrahydroprotoberberine **18**. The C10 phenol of **18** was methylated to give **19**. Reduction of the 8-oxo group of **19** with LAH provided an intermediate tertiary amine which was subsequently heated with concentrated HCl, thus effecting debenzoylation to give (±)-ICP.

The success of this route propelled us to investigate an analogous asymmetric route to (–)-ICP. We presumed that this could be easily accomplished by replacing NaBH₄ as the reducing agent in Scheme 1 (**17** to **18**) with Noyori's asymmetric hydrogenation method.²⁵ The chiral 8-oxotetrahydroprotoberberine thus formed (i.e., analogous to **18**) would then be transformed to (–)-ICP by using the identical sequence of reagents that was used in Scheme 1. Thus, Bischler-Napieralski cyclization on amide **17** was performed as described in Scheme 1 (Scheme 2).

The imine formed was then subjected to Noyori's asymmetric hydrogenation conditions. To our surprise this did not yield the desired chiral 8-oxotetrahydroprotoberberine **20**. Instead the 8-oxoprotuberberine **21** was produced. One possible cause for failure of the reduction is due to formation (and subsequent isomerization) of an acyl iminium ion formed from reaction of the imine nitrogen (from Bischler-Napieralski reaction) with the aryl ester group. Another possibility is that when the imine derived from **17** (ie compound **22**) is subjected to Noyori reduction conditions, isomerization of the imine to an enamine precedes the cyclization of ring C. Treatment of the **22** with triethylamine (the base used in the Noyori reduction) gives **21**. Presumably, the isomerization/cyclization steps occur at a faster rate than Noyori reduction.

Through this attempt to achieve an enantioselective synthesis of (–)-ICP, it was recognized that naturally occurring 8-oxoprotuberberines could be synthesized by variations of this method. Previous syntheses of the 8-oxoprotuberberine skeleton have required several synthetic steps and/or suffer from low-yielding steps.^{26–30} Thus to demonstrate the pliability of the route, compound **21** was transformed to the natural product oxypalmatine (**2**, Scheme 2) by removal of the C2 benzyl group followed by Williamson ether methylation. Insofar as synthesis of oxypalmatine is concerned, this method is comparable to published methods in both yield and number of steps (7 steps and 22% overall yield for the present synthesis; 9 steps 10% yield for the previous synthesis).³¹

3. Conclusions

Herein, a new synthesis of (\pm)-ICP is delineated which features the use of the easily obtainable diester intermediate **14**. (\pm)-ICP was prepared in 9 steps from readily available precursors in 23% overall yield. The route is attractive due to its efficiency and practical ease; no chromatographic purification was necessary for a number of steps. The yield obtained is comparable to a reported synthesis of (\pm)-ICP.³² However, enantioselective preparation of (–)-ICP by modifications to this route remains to be optimized. The key amide intermediate (**17**) that is used for (\pm)-ICP synthesis can also be used to prepare a 9,10-oxygenated-8-oxoprotoberberine core, and we adapted this method to prepare oxypalmatine (**2**). Hence, the route examined here is a versatile one for the preparation of 9,10-oxygenated THPBs as well as their 8-oxoprotoberberine analogs.

4. Experimental section

General methods

All moisture-sensitive and oxygen-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere. Solvents and all other reagents were purchased at the highest commercial quality from Aldrich and Fisher Scientific USA and used without further purification, unless otherwise stated. Anhydrous sodium sulfate was used as drying agent for work-up of reactions. HRESIMS spectra were obtained using an Agilent 6520 QTOF instrument. ¹H NMR and ¹³C NMR spectra were recorded using Bruker DPX-500 spectrometer (operating at 500 MHz for ¹H; 125 MHz, for ¹³C) using CDCl₃ as solvent unless stated otherwise. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ¹H NMR and CDCl₃ (δ 77.0 ppm) in ¹³C NMR unless stated otherwise. Chemical shift (δ 0.00 ppm) values are reported in parts per million and coupling constants in Hertz (Hz). Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). Reactions were monitored by TLC with Whatman Flexible TLC silica gel G/UV 254 precoated plates (0.25 mm). TLC plates were visualized by UV (254 nm) and by staining in an iodine chamber. Flash column chromatography was performed with silica gel 60 (EMD Chemicals, 230–400 mesh, 0.063 mm particle size).

4-Bromo-1-(ethoxymethoxy)-2-methoxybenzene (**13**)

Compound **12** (8.0 g, 39 mmol) and diisopropylethyl amine (13.7 mL, 78.8 mmol) were stirred in DCM (100 mL) at 0 °C for 15 min. Ethoxychloromethyl ether (5.48 mL, 59.1 mmol) was added dropwise to the solution at 0 °C. The solution was allowed to stir at rt for 1 h. The reaction mixture was washed with 0.1N HCl (120 mL). The organic layers were combined, dried over sodium sulfate and evaporated to dryness to give **13** (10.1 g, 98%) as a brownish oil. This product was used in the subsequent reaction without any further purification: ¹H NMR (CDCl₃, 500 MHz) δ 7.06–7.00 (m, 3H), 5.26 (s, 2H), 3.86 (s, 3H), 3.76 (q, J = 7 Hz, 2H), 1.22 (t, J = 7 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 150.5, 145.9, 123.6, 117.7, 115.2, 114.4, 94.2, 64.5, 56.1, 15.1; HRMS (ESI) m/z calcd. for C₁₀H₁₃BrO₃ ([M+Na]⁺), 282.9940, found 282.9942.

Methyl 3-(ethoxymethoxy)-2-methoxy-6-(2'-methoxy-2'-oxoethyl) benzoate (14)

Diisopropylamine (11.5 mL, 84.3 mmol) was stirred in dry THF (100 mL) at $-78\text{ }^{\circ}\text{C}$ in an oven-dried round bottom flask for 15 min. *n*-Butyllithium (2.5 M in hexane, 100 mL) was added and the solution was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Dimethylmalonate (18.9 mL, 164 mmol) in 60 mL dry THF was added. The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and a solution of **13** (10.0 g, 38.3 mmol) in 50 mL dry THF was added. After 45 min, the reaction mixture was quenched with a saturated solution of ammonium chloride. THF was evaporated and the crude mixture was extracted with dichloromethane ($4 \times 100\text{ mL}$). The solvent was reduced *in vacuo* and the crude product was purified via flash chromatography on silica gel (10% acetone/hexanes) to afford compound **14** (6.5 g, 54%) as a yellowish oil: $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.20 (d, $J = 9\text{ Hz}$, 1H), 6.96 (d, $J = 9\text{ Hz}$, 1H), 5.26 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.75 (q, $J = 7\text{ Hz}$, 2H), 3.68 (s, 3H), 3.62 (s, 2H), 1.23 (t, $J = 7\text{ Hz}$, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 171.5, 167.6, 149.8, 147.6, 129.0, 126.5, 125.6, 118.0, 93.8, 64.6, 61.7, 52.2, 52.1, 38.4, 15.1; HRMS (ESI) m/z calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_7$ ($[\text{M} + \text{Na}]^+$), 315.1101, found 315.1104.

2-[4'-(Ethoxymethoxy)-3'-methoxy-2'-(methoxycarbonyl)phenyl]acetic acid (15)

Compound **14** (5.8 g, 18 mmol) and potassium carbonate (5.1 g, 37 mmol) were refluxed in a 1:1 water/methanol mixture (150 mL) for 1 h. The methanol was evaporated and the crude mixture was acidified with 0.1N HCl. The solution was extracted with ethyl acetate ($3 \times 100\text{ mL}$) and dried over sodium sulfate. Filtration and evaporation of the ethyl acetate extract afforded **15** (5.2 g, 95%) as a yellowish oil. This was used in the next step without purification: $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.21 (dd, $J = 8, 3\text{ Hz}$, 1H), 6.97 (dd, $J = 8, 3\text{ Hz}$, 1H), 5.26 (d, $J = 2\text{ Hz}$, 2H), 3.90 (d, $J = 4\text{ Hz}$, 3H), 3.88 (d, $J = 2\text{ Hz}$, 3H), 3.76 (q, $J = 2\text{ Hz}$, 2H), 3.64 (s, 2H), 1.27-1.21 (m, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 171.1, 168.8, 150.0, 147.9, 128.3, 126.6, 125.4, 118.5, 93.7, 64.6, 61.7, 52.7, 38.9, 15.1; HRMS (ESI) m/z calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_7$ ($[\text{M} + \text{Na}]^+$), 321.0945, found 321.0948.

Methyl 6-{2'-[(4''-(benzyloxy)-3''-methoxyphenethyl)amino]-2'-oxoethyl}-3-(ethoxymethoxy)-2-methoxybenzoate (17)

Compound **15** (5.0 g, 17 mmol) was dissolved in 60 mL THF and stirred at $0\text{ }^{\circ}\text{C}$ for 15 min. 1,1'-Carbonyldiimidazole (2.7 g, 17 mmol) was added portion-wise to the solution at $0\text{ }^{\circ}\text{C}$ and the mixture allowed to stir at rt for 1 h. A solution of **16** (4.3 g, 17 mmol) in 60 mL THF was added to the above reaction mixture at $0\text{ }^{\circ}\text{C}$ and allowed to stir overnight at rt. THF was evaporated and the residue was dissolved in 150 mL dichloromethane and washed with sodium bicarbonate and 0.1N HCl consecutively. The organic layer was dried, filtered and concentrated *in vacuo* to afford **17** (7.0 g, 78%) as a brown oil: $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.43 (d, $J = 7\text{ Hz}$, 2H), 7.37 (t, $J = 8\text{ Hz}$, 2H), 7.29 (t, $J = 7\text{ Hz}$, 1H), 7.18 (d, $J = 9, 1\text{ Hz}$), 6.98 (d, $J = 9\text{ Hz}$, 1H), 6.74 (d, $J = 8\text{ Hz}$, 1H), 6.68 (d, $J = 2\text{ Hz}$, 1H), 6.50 (dd, $J = 8, 2\text{ Hz}$, 1H), 6.16 (t, $J = 5\text{ Hz}$, 1H), 5.25 (s, 2H), 5.11 (s, 2H), 3.88 (s, 6H), 3.84 (s, 3H), 3.75 (q, $J = 7\text{ Hz}$, 2H), 3.40-3.39 (m, 3H), 2.67 (t, $J = 7\text{ Hz}$, 2H), 1.23 (t, $J = 7\text{ Hz}$, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 170.3, 168.4, 149.7, 149.6, 147.3, 146.7, 137.4, 132.1, 128.8, 128.5, 128.5, 127.8, 127.3, 127.3, 126.8, 126.1, 120.6, 118.5, 114.2, 112.4, 93.8, 71.1, 64.7, 61.6,

55.9, 52.6, 41.2, 40.9, 35.2, 15.1; HRMS (ESI) m/z calcd. for $C_{30}H_{35}NO_8$ ($[M+Na]^+$), 560.2255, found 560.2260.

2-(Benzyloxy)-10-hydroxy-3,9-dimethoxy-5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one (**18**)

Compound **17** (5.0 g, 9.3 mmol) and $POCl_3$ (6.95 mL, 74.4 mmol) were refluxed in 60 mL acetonitrile for 3 h. The solvent was evaporated and the residue was dissolved in 120 mL DCM. The resulting solution was washed with sodium bicarbonate and then dried over sodium sulfate. The organic solvent was removed *in vacuo* and methanol (100 mL) was added. Sodium borohydride (1.4 g, 37 mmol) was added at 0 °C and the mixture allowed to stir for 6 h. The reaction was quenched with water and methanol was evaporated. The residue was extracted with DCM (3 × 80 mL). The organic layer was dried, filtered and evaporated to dryness to afford **18** (3.2 g, 79%). It was used in the next step without further purification: 1H NMR ($CDCl_3$, 500 MHz) δ 7.44 (d, $J = 7$ Hz, 2H), 7.37 (t, $J = 8$ Hz, 2H), 7.29 (t, $J = 7$ Hz, 1H), 7.06 (d, $J = 10$ Hz, 1H), 6.84 (d, $J = 10$ Hz, 1H), 6.71 (s, 1H), 6.68 (s, 1H), 6.01 (s, 1H), 5.15 (s, 2H), 4.99 (d, $J = 10$ Hz, 1H), 4.68 (dd, $J = 16, 4$, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 2.93-2.70 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.6, 149.0, 148.8, 147.3, 146.9, 137.0, 130.7, 128.6, 128.6, 128.1, 127.9, 127.5, 127.4, 127.4, 122.8, 121.5, 118.1, 112.6, 111.9, 71.6, 62.4, 56.1, 54.9, 38.9, 38.3, 29.4; HRMS (ESI) m/z calcd. for $C_{26}H_{25}NO_5$ ($[M+H]^+$), 432.1805, found 432.1809.

2-(Benzyloxy)-3,9,10-trimethoxy-5,8,13,13a-tetrahydro-6H-isoquinolino[3,2-a]isoquinoline (**19**)

Compound **18** (0.03 g, 0.07 mmol) was dissolved in 5 mL DMF. Potassium carbonate (0.02 g, 0.1 mmol) and methyl iodide (0.013 mL, 0.21 mmol) were added and reaction mixture was stirred at rt for 6 h. DMF was evaporated and 0.1 N HCl (15 mL) was added. The crude mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried and concentrated to yield **19** (0.027 g, 91%) which was used in the next step without further purification: 1H NMR ($CDCl_3$, 500 MHz) δ 7.46 (t, $J = 7$ Hz, 2H), 7.38 (t, $J = 7$ Hz, 2H), 7.31 (t, $J = 7$ Hz, 1H), 6.83 (d, $J = 9$ Hz, 1H), 6.78 (d, $J = 8$ Hz, 1H), 6.75 (s, 1H), 6.64 (s, 1H), 5.14 (s, 2H), 4.20 (d, $J = 16$ Hz, 1H), 3.88 (s, 3H), 3.85 (s, 6H), 3.53-3.46 (m, 2H), 3.20-3.07 (m, 3H), 2.75-2.60 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.7, 152.1, 150.9, 148.0, 147.9, 137.0, 131.7, 128.6, 128.6, 127.9, 127.7, 127.6, 127.3, 127.3, 123.9, 122.0, 118.1, 111.4, 109.1, 71.4, 61.7, 56.2, 55.97, 54.9, 39.3, 38.2, 29.5; HRMS (ESI) m/z calcd. for $C_{27}H_{27}NO_5$ ($[M+H]^+$), 446.1962, found 446.1968.

(±)-Isocorypalmine [(±1)]

Compound **19** (0.02 g, 0.05 mmol) in 5 mL THF was added to a suspension of lithium aluminum hydride (0.005 g, 0.1 mmol) and the reaction mixture allowed to heat at reflux for 1 h. The reaction mixture was allowed to cool to rt and excess of lithium aluminum hydride was quenched with water. THF was evaporated and the crude mixture was extracted with dichloromethane (4 × 10 mL). The organic layer was evaporated and the resulting crude product was refluxed in a mixture of methanol (5 mL) and concentrated hydrochloric acid (3 mL) for 3 h. Methanol was evaporated and the resulting mixture was basified with ammonia

solution, and extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried, filtered and concentrated to give the crude product, which was purified by flash column chromatography on silica gel (2% – 5% MeOH/DCM) to give (±)-Isocorypalmine (0.012 g, 81%); mp: 216–221 °C (lit.³³ 219–222 °C); ¹H NMR (CDCl₃, 500 MHz) δ 6.87 (d, *J* = 8 Hz, 1H), 6.83 (s, 1H), 6.78 (d, *J* = 8 Hz, 1H), 6.60 (s, 1H), 4.24 (d, *J* = 16 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 6H), 3.55–3.51 (m, 2H), 3.28–3.14 (m, 3H), 2.81 (dd, *J* = 16, 12 Hz, 1H), 2.68–2.61 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 150.2, 145.1, 145.0, 143.9, 130.6, 128.7, 127.9, 126.1, 123.9, 111.3, 110.9, 110.6, 60.2, 59.2, 55.9, 55.9, 54.0, 51.6, 36.3, 29.7; HRMS (ESI) *m/z* calcd. for C₂₀H₂₃NO₄ ([M+H]⁺), 342.1700, found 342.1704.

2-(Benzyloxy)-10-hydroxy-3,9-dimethoxy-5,6-dihydro-8H-isoquinolino[3,2-a]isoquinolin-8-one: (21)

Compound **17** (0.2 g, 0.4 mmol) and POCl₃ (0.28 mL, 3.0 mmol) were refluxed in 10 mL acetonitrile for 3 h. The solvent was evaporated and the residue was dissolved in 25 mL DCM. The resulting solution was washed with sodium bicarbonate and then dried over sodium sulfate. The organic solvent was removed *in vacuo* and the residues were dissolved in 10 mL dry DCM. Triethylamine (1.6 mL, 0.10 mmol) was added to the solution and allowed to stir at rt for 2 h. The reaction mixture was washed with 0.1N HCl and extracted with DCM (3 × 15 mL). The combined organic layer was evaporated and concentrated to yield **21** (0.11 g, 70%) which was used in the next step without further purification: ¹H NMR (CDCl₃, 500MHz) δ 7.49 (d, *J* = 7 Hz, 2H), 7.40 (t, *J* = 7 Hz, 2H), 7.35–7.30 (m, 2H), 7.27 (s, 1H), 7.20 (d, *J* = 9 Hz, 1H), 6.75 (s, 1H), 6.60 (s, 1H), 5.21 (s, 2H), 4.31 (t, *J* = 6 Hz, 2H), 4.05 (s, 3H), 3.93 (s, 3H), 2.92 (t, *J* = 6 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 159.7, 151.0, 147.7, 147.6, 145.5, 136.9, 135.3, 132.2, 129.0, 128.5, 128.5, 127.9, 127.4, 127.4, 122.9, 122.3, 121.1, 118.1, 111.3, 111.0, 101.4, 71.9, 62.6, 56.0, 39.4, 28.2; HRMS (ESI) *m/z* calcd. for C₂₆H₂₃NO₅ ([M+H]⁺), 430.1649, found 430.1652.

Oxypalmatine (2)

Compound **21** (0.015 g, 0.033 mmol) was refluxed in a mixture of methanol (10 mL) and concentrated HCl (5 mL) for 3 h. Methanol was evaporated and the resultant mixture was basified with ammonia solution, and extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried and concentrated to give a crude product, which was used in the next step without further purification. Crude residues were dissolved in 5 mL DMF. Potassium carbonate (0.014 g, 0.10 mmol) and methyl iodide (0.013 mL, 0.20 mmol) were added and reaction mixture was stirred at rt for 6 h. DMF was evaporated and 0.1 N HCl (10 mL) was added. The crude mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried the crude product was purified by flash column chromatography on silica gel (1% – 3% methanol/dichloromethane) to yield oxypalmatine (**2**) (0.01 g, 79%); mp: 178–185 °C (lit.³¹ 181–183 °C); ¹H NMR (CDCl₃, 500 MHz) δ 7.33 (d, *J* = 9 Hz, 1H), 7.3 (d, *J* = 9 Hz, 1H), 7.23 (s, 1H), 6.76 (s, 1H), 6.73 (s, 1H), 4.32 (t, *J* = 6 Hz, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 2.93 (t, *J* = 6 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 160.3, 151.4, 150.1, 149.6, 148.4, 135.6, 132.4, 128.5, 122.3, 122.1, 119.4, 118.9, 110.5, 107.5, 100.9, 61.6, 56.9, 56.24, 56.0, 39.4, 28.2; HRMS (ESI) *m/z* calcd. for C₂₁H₂₁NO₅ ([M+H]⁺), 368.1492, found 368.1497.

Supplementary Material

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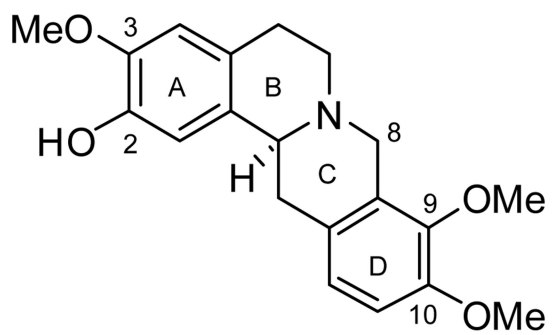
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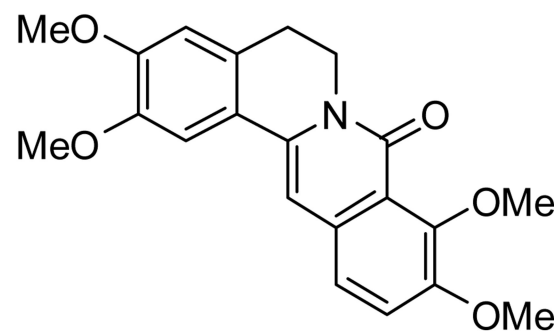
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(-)-isocorypalmine(1)



oxypalmatine(2)

Figure 1.
Structures of (-)-ICP and oxypalmatine

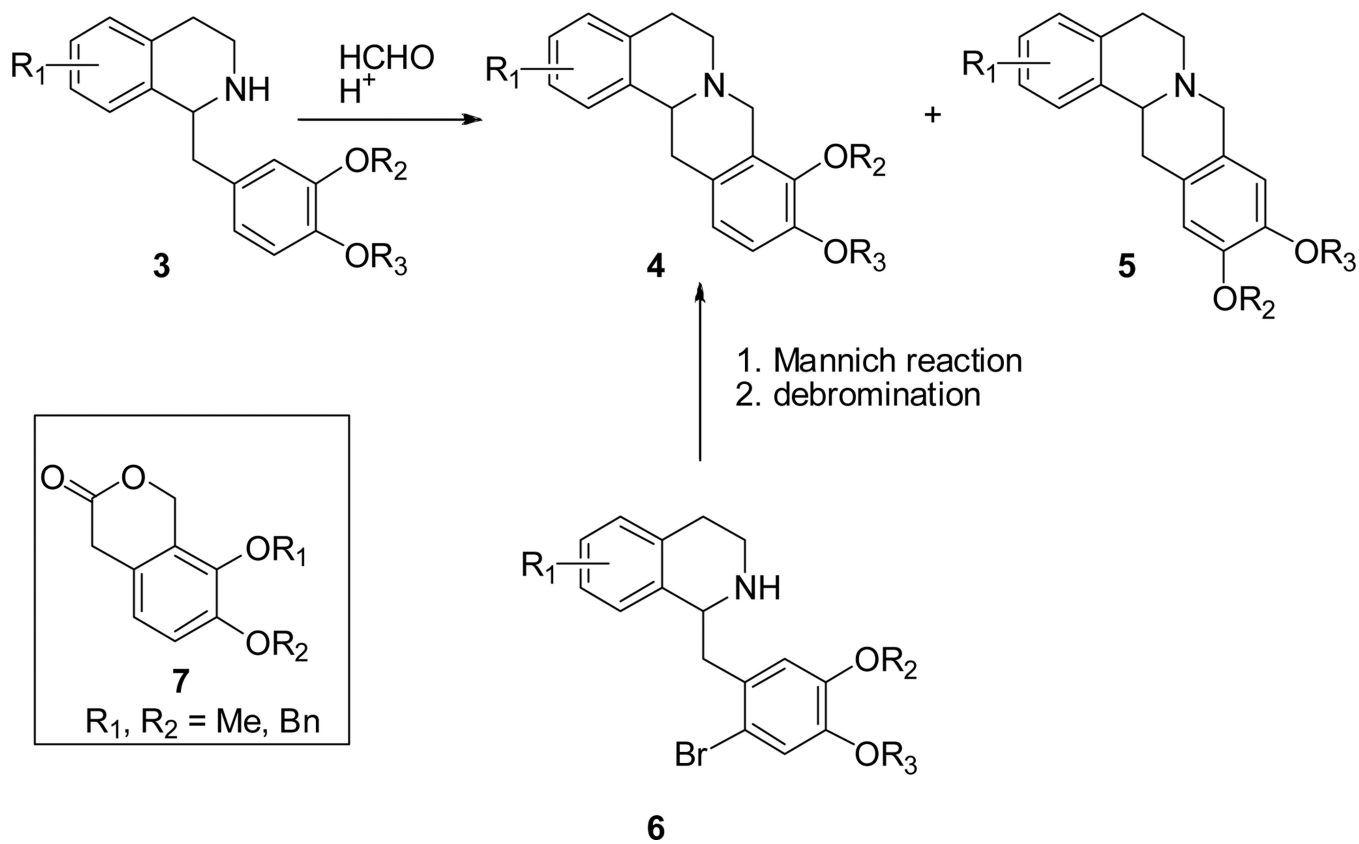


Figure 2.
Synthesis of 9, 10-oxygenated THPBs

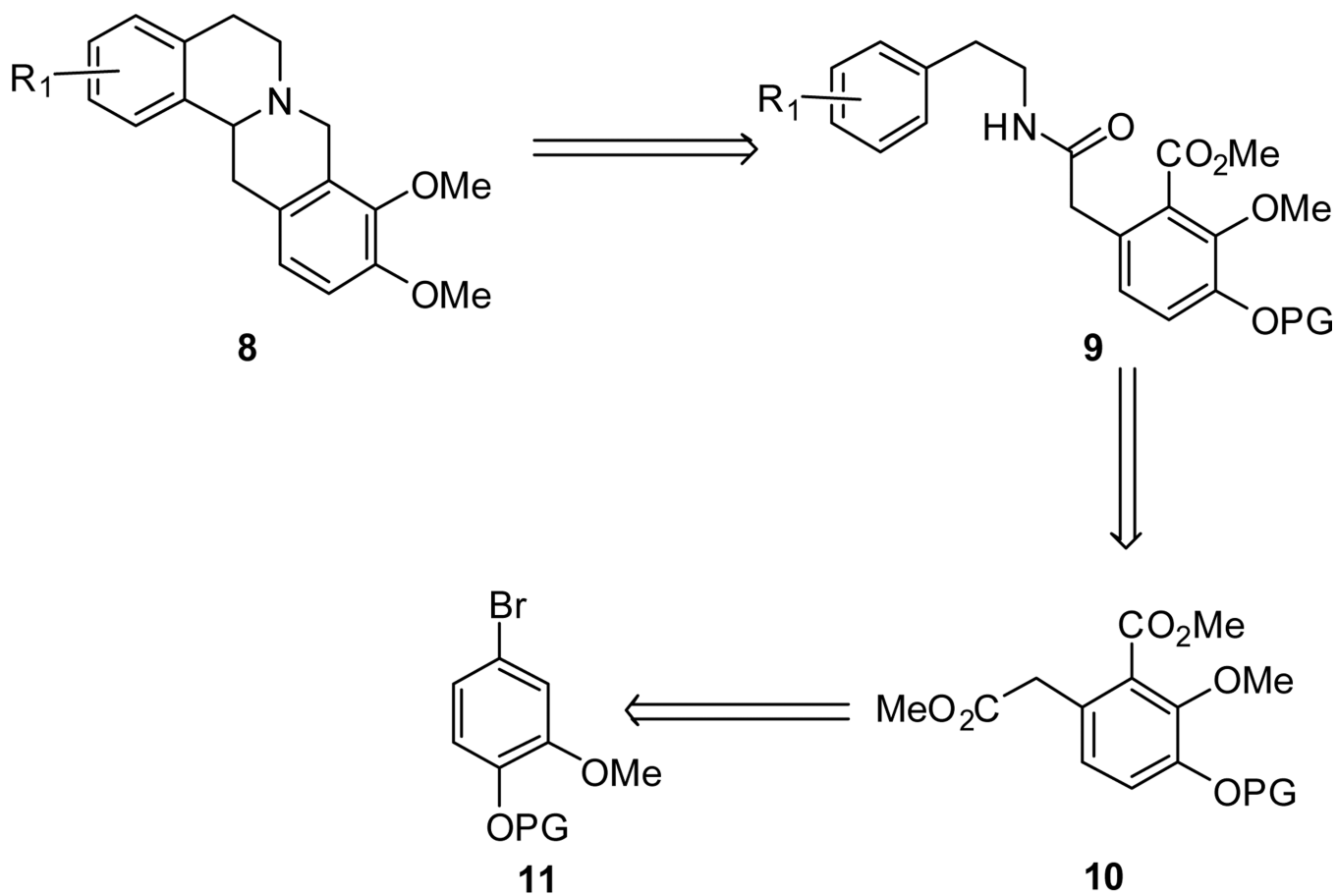
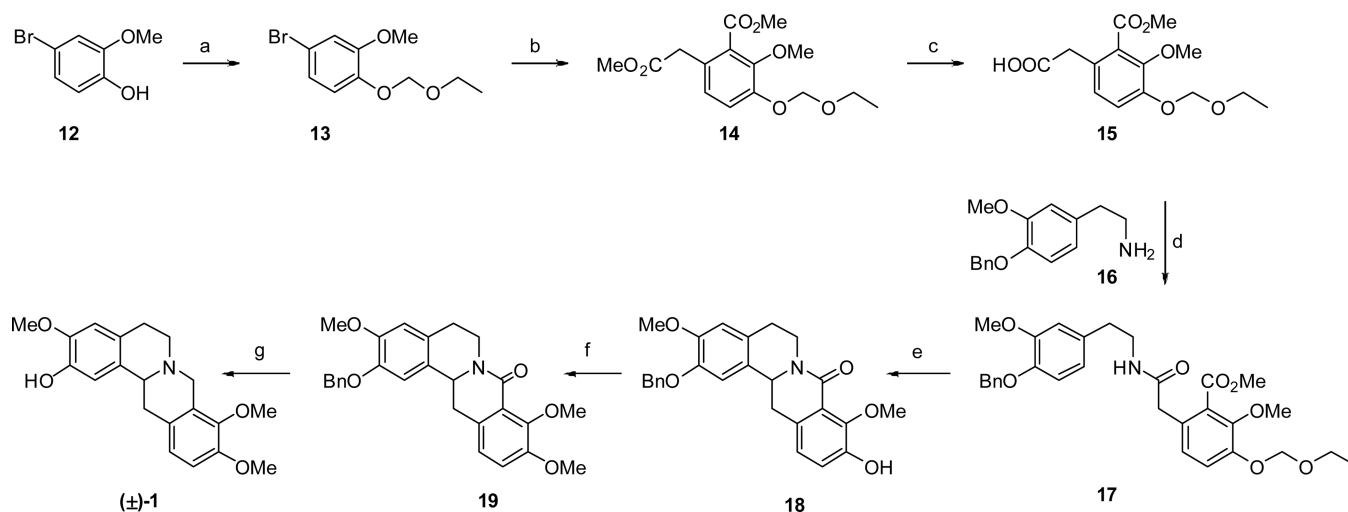
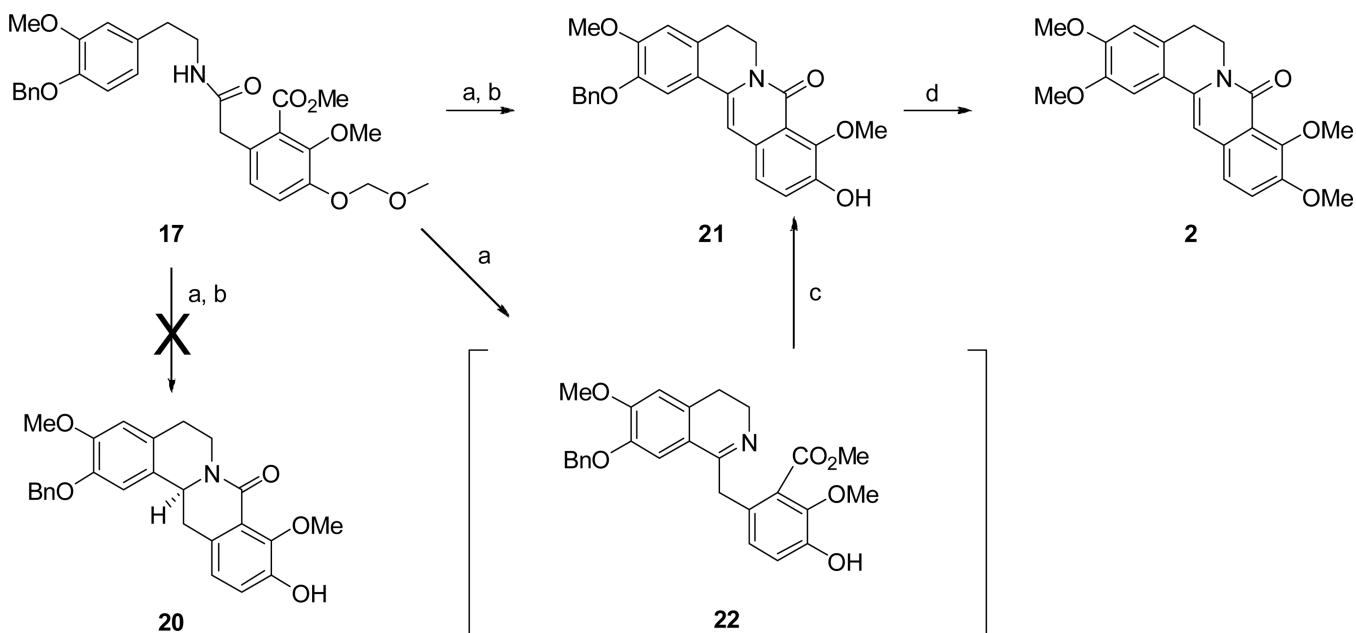


Figure 3.
Retrosynthetic analysis to THPB core



Scheme 1. Synthesis of (±)-Isocorypalmine (1)

Reagents and conditions: (a) DIPEA, (chloromethoxy)ethane, DCM, 98%; (b) DIPA, *n*-BuLi, DMM, THF, $-78\text{ }^{\circ}\text{C}$, 54%; (c) K_2CO_3 , 1:1 $\text{H}_2\text{O}/\text{MeOH}$, reflux, 95%; (d) CDI, **16**, THF, 78%; (e) i) POCl_3 , CH_3CN , reflux; ii) NaBH_4 , MeOH, 79% over 2 steps; (f) CH_3I , K_2CO_3 , DMF, 91%; (g) i) LAH, THF, reflux; ii) conc. HCl, MeOH, reflux; 81% over 2 steps.



Scheme 2. Synthesis of oxypalmitine (2)

Reagents and conditions: (a) POCl₃, CH₃CN, reflux; (b) Ru[(*R,R*)-Tsdpen](η₆-p-cymene), DMF, HCOOH/TEA, rt, 53% over 2 step ; (c) Et₃N, DCM, 2h, 70% over 2 steps; (d) i) conc. HCl, MeOH, reflux; ii) CH₃I, K₂CO₃, DMF, 79%, over 2 steps;