

A RADICAL APPROACH TO BHARATAMINE, A UNIQUE PROTOBERBERINE ALKALOID FROM *ALANGIUM LAMARCKII*

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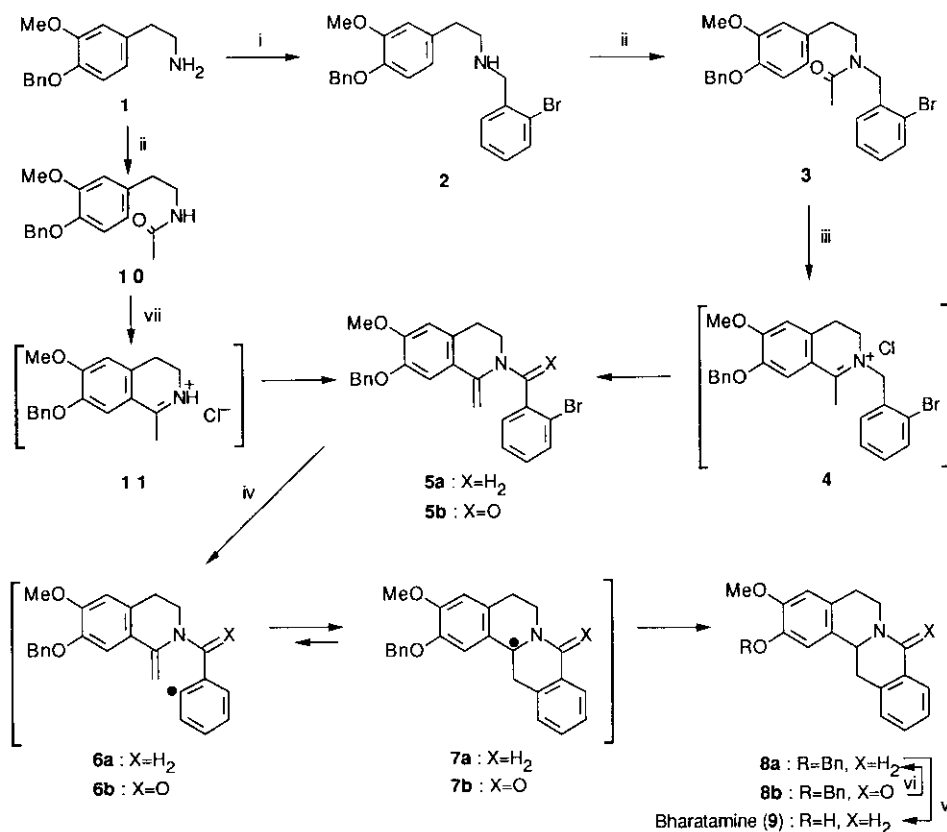
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Abstract — Bharatamine, a unique racemic protoberberine alkaloid from *Alangium Lamarckii*, has been synthesized via aryl radical-initiated 1,6-cyclization as the key step.

Bharatamine¹ (**9**) is a unique racemic protoberberine alkaloid isolated from the seeds of *Alangium lamarckii* and the sole naturally occurring protoberberine alkaloid unoxxygenated at ring D. We report herein a simple route² to this alkaloid employing the recent developed aryl radical-initiated 1,6-cyclization³ as the key step.

Treatment of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine⁴ (**1**) with *o*-bromobenzaldehyde followed by sodium borohydride in the same flask afforded the secondary amine (**2**) in good yield. On sequential acetylation and Bischler-Napieralski cyclization⁵ **2** furnished the enamine (**5a**) via the amide (**3**) and the iminium salt (**4**) after basic work-up. Exposure of **5a**⁶ to 1.5 equiv. of tri-*n*-butyltin hydride in the presence of a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) in benzene at reflux temperature brought about aryl radical-initiated 1,6-cyclization^{3,7} to give the penultimate intermediate *O*-benzylbharatamine (**8a**) in 20% overall yield via radical intermediates **6a** and **7a**. Overall yield of **8a** from the starting amine (**1**) was 15.4% in 4 steps. Conversion of **8a** to bharatamine (**9**) could be carried out in 80.0% yield by refluxing it with ethanolic hydrochloric acid followed to the established method.^{2b}

In order to improve overall yield, the amine **1** was first transformed into the acetamide (**10**), in 79.7% yield, which was sequentially cyclized and acylated with *o*-bromobenzoyl chloride to afford the enamide (**5b**) in 54.2% yield. On reflux with 2 equiv. of tri-*n*-butyltin hydride in benzene in the presence of a catalytic amount of AIBN, **5b** furnished the lactam (**8b**), in 50.4% yield, which was



Scheme 1

Reagents and conditions: (i) 2-bromobenzaldehyde, benzene, reflux, then NaBH₄, MeOH; (ii) AcCl, Et₃N, CH₂Cl₂; (iii) POCl₃, benzene, reflux, then NH₄OH; (iv) ⁿBu₃SnH, AIBN (cat.), benzene, reflux; (v) 10% HCl-EtOH, reflux; (vi) LiAlH₄, THF, reflux; (vii) POCl₃, benzene, reflux, then Et₃N, *o*-Br-C₆H₄COCl, CH₂Cl₂.

reduced with lithium aluminum hydride to afford the penultimate intermediate (**8a**) in 90.9% yield.

Overall yield of **8a** from the starting amine **1** via the second route was 19.8% in 5 steps.

EXPERIMENTAL SECTION

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Mass spectra were recorded with a JEOL-O1SG-2 instrument, ir spectra with a

JASCO A102 spectrophotometer, and ^1H nmr on a JEOL-JNM-FX90A spectrometer. Reaction were carried out under argon.

***N*-(2-Bromobenzyl)-2-(4-benzyloxy-3-methoxyphenyl)ethylamine (2)** — A solution of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (1) (872 mg, 3.42 mmol) and 2-bromobenzaldehyde (0.48 ml, 4.10 mmol) in benzene (20 ml) was refluxed for 5 h with removal of water using a Dean-Stark apparatus. After evaporation of the solvent under reduced pressure, the residue in MeOH (10 ml) was reduced with NaBH_4 (194 mg, 5.13 mmol) at 0°C with stirring. After 30 min, the mixture was diluted with sat. aq. NaHCO_3 and extracted with CH_2Cl_2 . The extract was washed with brine, dried over MgSO_4 , and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (50 g) using a mixture of AcOEt-hexane (1:1 v/v) as eluent to give the secondary amine (2) as a pale yellow oil; yield: 1.16 g (80.6%). Ir (neat): ν_{max} : 3250 cm^{-1} ; ^1H nmr (CDCl_3): δ 1.58 (s, 1H, exchangeable with D_2O), 2.77 – 2.86 (m, 4H), 3.86 (s, 5H), 5.13 (s, 2H), 6.69 – 6.87 (m, 3H), 6.99 – 7.57 (m, 9H); ms (m/z): 428 (M^+), 426 (M^+), 228.198. *Anal.* Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_2$ [$(\text{C}_{23}\text{H}_{24}\text{O}_2\text{NBr}) (\text{M}^+) - \text{C}_8\text{H}_8\text{NBr}$] and $\text{C}_8\text{H}_9\text{NBr}$ [$\text{C}_{23}\text{H}_{24}\text{O}_2\text{NBr} (\text{M}^+) - \text{C}_{15}\text{H}_{15}\text{O}_2$]: 228.1149 and 197.9918. Found: 228.1154 and 197.9926.

***N*-[2-(4-Benzyloxy-3-methoxyphenyl)ethyl]-*N*-(2-bromobenzyl)acetamide (3)** — To a stirred solution of 2 (1.23 g, 3.05 mmol) and triethylamine (0.25 ml, 3.66 mmol) in CH_2Cl_2 (15 ml) was added acetyl chloride (0.25 ml, 3.66 mmol) dropwise at 0°C . After stirring at room temperature for 1 h, the mixture was treated with sat. aq. NaHCO_3 and the organic layer was separated. The organic layer was washed with brine, dried over MgSO_4 , and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (55 g) using a mixture of AcOEt-hexane (1:1 v/v) as eluent to give the amide (3) as a colorless oil; yield: 1.37 g (95.6%). Ir (neat) ν_{max} : 1650 cm^{-1} ; ^1H nmr (CDCl_3): δ 2.04 (s, 3H x 1/2), 2.07 (s, 3H x 1/2), 2.69 – 2.90 (m, 2H), 3.43 – 3.61 (m, 2H), 3.86 (s, 3H), 4.40 (s, 1H), 4.74 (s, 1H), 5.13 (s, 2H), 6.51 – 6.91 (m, 3H), 7.01 – 7.61 (m, 9H); ms (m/z): 469 ($\text{M}^+ + 1$), 91 (100%). *Anal.* Calcd for $\text{C}_{25}\text{H}_{26}\text{O}_3\text{NBr}$: 467.1096. Found: 467.1064.

***O*-Benzylbharatamine (8a) from The Amide (3)** — A solution of the amide (3) (1.37 g, 2.92 mmol) and phosphoryl chloride (0.57 ml, 6.13 mmol) in benzene (20 ml) was refluxed for 12 h. After cooling, the mixture was diluted with hexane to form a precipitate and the supernatant solution was discarded by decantation. After washing three times with hot hexane, the precipitate was

made basic with 30% NH_4OH and extracted with CH_2Cl_2 . The extract was dried over MgSO_4 and evaporated under reduced pressure to give the crude enamine (**5a**) (1.01 g) which was used for the next reaction without further purification.

The crude enamine (**5a**) thus obtained was refluxed in benzene (13 ml) with tri-*n*-butyltin hydride (1.2 ml, 4.48 mmol) for 1 h in the presence of 2,2'-azobisisobutyronitrile (AIBN) (36 mg, 0.22 mmol). After cooling the mixture was stirred with 10% aq. KF for 30 min and the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 , evaporated under reduced pressure, and purified by chromatography on a silica gel column (70 g) using a mixture of Et_2O -hexane (1:2 v/v) as eluent to give *O*-benzylbharatamine (**8a**) as pale yellow fine crystals after recrystallization from CH_2Cl_2 - Et_2O ; yield: 166 mg (20.0% overall from **3**); mp 98 – 102 °C (lit.^{2b} mp 98 °C). Ir (Nujol) ν_{max} : 1610, 1510 cm^{-1} ; ^1H nmr (CDCl_3): δ 2.56 – 4.00 (m, 9H), 3.87 (s, 3H), 5.15 (s, 2H), 6.64 (s, 1H), 6.76 (s, 1H), 7.12 – 7.54 (m, 9H); ms (m/z): 370 ($\text{M}^+ - 1$), 91 (100%). Spectral data were virtually identical with those reported.^{2b}

Bharatamine^{2b} (9) ——— A solution of *O*-benzylbharatamine (**8a**) (16.8 mg, 0.05 mmol) in a mixture of 10% HCl (1 ml) and EtOH (1 ml) was refluxed for 12 h. After cooling the mixture was made basic with sat. aq. NaHCO_3 and extracted with CH_2Cl_2 . The extract was washed with brine, dried over MgSO_4 , evaporated under reduced pressure, and purified by chromatography on a silica gel column (2 g) using a mixture of AcOEt-hexane (1:1 v/v) as eluent to give bharatamine (**9**) as colorless needles after recrystallization from CHCl_3 -pet. ether; yield: 10 mg (80.0%); mp 186.5 – 188 °C (natural:¹ mp 182 – 183 °C). Ir (Nujol) ν_{max} : 3300 cm^{-1} ; ^1H nmr (CDCl_3): δ 2.55 – 4.12 (m, 9H), 3.86 (s, 3H), 6.59 (s, 1H), 6.83 (s, 1H), 7.07 – 7.36 (m, 4H); ms (m/z): 281 (M^+), 176, 104. Spectral data were identical with those reported for natural product.¹

***N*-2-(4-Benzyloxy-3-methoxyphenyl)ethylacetamide (10)** ——— To a stirred solution of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (**1**) (2.49 g, 9.69 mmol) and triethylamine (2.8 ml, 20.0 mmol) in CH_2Cl_2 (50 ml) was added acetyl chloride (0.76 ml, 10.7 mmol) dropwise at 0 °C. After stirring at room temperature for 4 h, the mixture was treated with sat. aq. NaHCO_3 and the organic layer was separated. The organic layer was washed with brine, dried over MgSO_4 , and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column (100 g) using a mixture of MeOH- CH_2Cl_2 (1:20 v/v) as eluent to give the amide (**10**) as a colorless amorphous solid; yield: 2.33 g (79.7%). Ir (neat) ν_{max} : 3300, 1640 cm^{-1} ; ^1H nmr (CDCl_3): δ 1.93 (s, 3H), 2.73 (t, $J=6.8$ Hz, 2H), 3.48 (m, 2H), 3.87 (s, 3H), 5.13 (s, 2H), 6.59 – 6.87 (m, 3H), 7.28 –

7.86 (m, 5H); *ms* (*m/z*): 299 (*M*⁺), 91 (100%). *Anal.* Calcd for C₁₈H₂₁O₃N: 299.1520. Found: 299.1557.

The Enamide (5b) from The Amide (10) — A solution of the amide (10) (1.45 g, 4.84 mmol) and phosphoryl chloride (1 ml, 11.1 mmol) in benzene (20 ml) was refluxed for 12 h. After cooling, the mixture was diluted with hexane to form a precipitate and the supernatant solution was discarded by decantation. After washing three times with hot hexane, the precipitate was treated with triethylamine (2.0 ml, 14.5 mmol) in benzene (20 ml) followed by 2-bromobenzoyl chloride (0.7 ml, 5.3 mmol) at ~5 °C and the mixture was stirred at room temperature for 30 min. The mixture was filtered through Celite and the filtrate was evaporated under reduced pressure, and the residue was purified by chromatography on a silica gel column (60 g) using a mixture of Et₂O-hexane (1:1 v/v) as eluent to give the enamide (5b) as a amorphous solid; yield: 1.19 g (54.2% from 10). *Ir* (neat) *v*_{max}: 1630 cm⁻¹; ¹H nmr (CDCl₃): δ 3.02 – 3.19 (m, 2H), 3.89 (s, 3H), 4.13 (br s, 2H), 4.48 (br s, 1H), 5.10 (s, 3H), 6.63 (s, 1H), 6.98 (s, 1H), 7.21 – 7.53 (m, 9H); *ms* (*m/z*): 464 (*M*⁺), 91 (100%). *Anal.* Calcd for C₂₅H₂₂O₃Br: 463.0783. Found: 463.0747.

The Lactam (8b) from The Enamide (5b) — A solution of the enamide (5b) (1.10 g, 2.44 mmol), tri-*n*-butyltin hydride (1.4 ml, 5.12 mmol), and 2,2'-azobisisobutyronitrile (AIBN) (43 mg, 0.24 mmol) in benzene (15 ml) was refluxed for 3 h. After cooling, the mixture was stirred with 10% aq. KF for 30 min and the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄, evaporated under reduced pressure, and purified by chromatography on a silica gel column (60 g) using a mixture of AcOEt-hexane (1:2 v/v) as eluent to give the lactam (8b) as colorless needles after recrystallization from EtOH; yield: 475 mg (50.4%); mp 166.5 – 168.0 °C. *Ir* (Nujol) *v*_{max}: 1655 cm⁻¹; ¹H nmr (CDCl₃): δ 2.75 – 3.10 (m, 5H), 3.89 (s, 3H), 4.67 – 5.03 (m, 2H), 5.16 (s, 2H), 6.71 (s, 2H), 7.13 – 7.53 (m, 8H), 8.01 – 8.17 (m, 1H); *ms* (*m/z*): 385 (*M*⁺), 91 (100%). *Anal.* Calcd for C₂₅H₂₃O₃N: 385.1678. Found: 385.1706.

O-Benzylbharatamine (8a) from The Lactam (8b) — A solution of the lactam (8b) (83 mg, 0.22 mmol) and LiAlH₄ (17 mg, 0.44 mmol) in THF (3 ml) was refluxed for 1 h. After cooling the mixture was treated with 30% NH₄OH and the mixture was diluted with Et₂O. After filtration through Celite, the organic layer was dried over MgSO₄, evaporated under reduced pressure, and purified by chromatography on a silica gel column (5 g) using a mixture of AcOEt-hexane (1:1 v/v) as eluent to give O-benzylbharatamine (8a) as a pale yellow fine crystals after recrystallization from AcOEt-

CH₂Cl₂-Et₂O; yield: 75 mg (90.9%); mp 98 – 102 °C. Spectroscopic data were identical with those of the material obtained via the enamine (5a).

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