First Total Synthesis of the Pavine Alkaloid (±)-Neocaryachine and Its Optical Resolution

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The first total synthesis of (±)-neocaryachine (1) was achieved using a radical cyclization to produce the dibenzo-9-azabicyclo[3.3.1]nonane pavine skeleton, following a Bischler–Napieralski reaction to construct an intermediate benzylisoquinoline. The resulting racemic mixture was separated by chiral column chromatography to provide pure (+)- and (−)-1.

Key words pavine alkaloid; neocaryachine; total synthesis; optical resolution

Introduction

Pavine alkaloids are structurally based on dibenzo-9-azabicyclo[3.3.1]nonane, which contains two aromatic rings fused on opposite sides of an eight-membered ring bridged by a nitrogen atom. Various functional groups are found on the aromatic rings and the nitrogen atom. Pavine alkaloids have been reported in limited genera of only five plant families, including three genera Argeomeone, Eschschozia and Roemerea in the Papaveraceae, two genera Beilschmiedia and Cryptocarya in the Lauraceae, two genera Berberis and Leonortice in the Berberidaceae, one genus Thalictrum in the Ranunculaceae, and one genus Hernandia in the Hernandiaceae, and are biosynthesized through tetrahydrobenzylisoquinoline.1–3) Several total syntheses have been accomplished4–9) due to the interesting structures and biological activities of this compound class.10–13) However, to date, all synthesized pavine alkaloids have no functional group at the C-7 position. Thus, neocaryachine, which has hydroxyl at C-7, methoxy at C-8, methyl on nitrogen, and methylenedioxy at C-2/C-3, has not yet been synthesized. We describe here the first total synthesis of (±)-neocaryachine (1, Fig. 1) and its optical resolution by chiral column chromatography.

Results and Discussion

The retrosynthetic analysis began with the disconnection of the C-6 and C-6a bond, which could be formed by radical cyclization between the enamine and bromobenzene of 2 (Fig. 2). Benzylisoquinoline 3, the precursor of 2, could be constructed by a Bischler–Napieralski reaction of 4, obtained by amidation of 5 with 6. The two latter compounds would be synthesized from aldehydes 7 and 8, respectively.

According to a literature method,14) benzaldehyde 7 was converted to amine 5 in three steps, conversion to a nitroalkene, followed by methylation and reduction, in 52.3% overall yield (Chart 1). The substituted phenylacetic acid 6 was obtained from commercially available 2-bromo-3-hydroxy-4-methoxybenzaldehyde 8 in five steps, including benzyl protection of the phenol, reduction of the aldehyde, and homologation through cyanidation, in 83.8% overall yield.
natively, benzylisoquinoline 11 was converted quantitatively to carbamate 18, which is relatively stable compared with enamine 16. The radical cyclization of 18 under the above conditions produced pavine alkaloid 19 in a better 59% yield. However, the reduction of the carbamate to the methylamine of 17 using LiAlH4 failed due to decomposition. The obtained (±)-1 was further separated with chiral column chromatography to obtain both enantiomers. The retentions time were 7.36 and 19.42 min for (−)-1 and (+)-1, which exhibited an IC50 of single digit nM level.

CH2Cl2, and the mixture was stirred at room temperature for 2 h. Then, compound 11 (58.4 mg, 0.12 mmol) in methyl iodide (1.5 mL) was refluxed at 80°C for 3.5 h. After cooling to room temperature, the mixture was placed in an ice bath and its pH was adjusted to 8 by addition of saturated aqueous NaHCO3. After extraction with CH2Cl2 (60%), the organic layer was dried over anhydrous Na2SO4 and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give 10 as a colorless oil (149.0 mg, 91%).

1H-NMR (400 MHz, CDCl3) δ 7.57–7.35 (m, 5H), 7.07 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.75–6.68 (m, 3H), 5.94 (m, 2H), 5.80 (brs, 1H), 5.03 (s, 2H), 4.11 (m, 1H), 3.89 (s, 3H), 3.68 (d, J = 4.4 Hz, 2H), 3.61 (m, 1H), 3.17 (s, 3H), 3.14 (m, 1H); 13C-NMR (400 MHz, CDCl3) δ 169.9, 153.0, 147.9, 147.4, 145.7, 137.1, 132.9, 128.4, 128.3, 128.1, 127.7, 126.6, 121.1, 120.4, 111.6, 108.2, 106.6, 101.0, 81.9, 74.6, 56.7, 56.1, 45.6, 43.7; HRMS-FAB ([M + H]+) calcd for C25H21BrNO4, 478.0618, 480.0618; found, 478.0627, 480.0618.

To a solution of 10 (54.7 mg, 0.10 mmol) in dry CH2CN (2.0 mL) was added POCI3 (0.10 mL, 1.07 mmol). The mixture was heated at 50°C under N2 for 18 h. After cooling to room temperature, the mixture was placed in an ice bath and its pH was adjusted to 8 by addition of saturated aqueous NaHCO3. After extraction with CH2Cl2 (×3), the organic layer was dried over anhydrous Na2SO4 and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc/MeOH = 67:33:0.3) to give 11 as a pale orange solid (60%).

1H-NMR (400 MHz, CDCl3) δ 8.36 (d, J = 6.0 Hz, 1H), 7.57–7.60 (m, 2H), 7.43–7.34 (m, 5H), 7.08 (s, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 6.06 (s, 2H), 5.06 (s, 2H), 4.60 (s, 2H), 3.80 (s, 3H); 13C-NMR (600 MHz, CDCl3) δ 157.6, 152.1, 150.5, 148.4, 145.3, 141.5, 137.3, 134.9, 132.0, 128.5, 128.3, 128.0, 125.0, 124.5, 120.6, 119.5, 111.3, 103.1, 101.9, 101.6, 74.5, 56.1, 41.7; HRMS-FAB ([M + H]+) calcd for C25H21BrNO4, 478.0654, 480.0633; found, 478.0654, 480.0618.

A solution of 11 (58.4 mg, 0.12 mmol) in methyl iodide (1.5 mL) was refluxed at 80°C for 3.5 h. After cooling to room
temperature, the solid was collected by filtration and washed with Et₂O to give 14 as a yellow solid (58.8 mg, 78%).

1H-NMR (400 MHz, CDCl₃) δ 9.10 (d, J = 6.8 Hz, 1H), 8.13 (d, J = 6.8 Hz, 1H), 7.54–7.35 (m, 7H), 6.74 (d, J = 8.4 Hz, 1H), 6.29 (s, 2H), 6.22 (d, J = 8.0 Hz, 1H), 5.09 (s, 2H), 4.78 (s, 2H), 4.46 (s, 3H), 3.83 (s, 3H); (600 MHz, dimethyl sulfoxide (DMSO)-d₆) δ 8.62 (d, J = 7.2 Hz, 1H), 8.27 (d, J = 7.2 Hz, 1H), 7.90 (s, 1H), 7.75 (s, 1H), 7.54–7.35 (m, 5H), 6.91 (d, J = 8.4 Hz, 1H), 6.42 (s, 2H), 6.20 (d, J = 8.4 Hz, 1H), 5.03 (s, 2H), 4.88 (s, 2H), 4.16 (s, 3H), 3.80 (s, 3H); 13C-NMR

Table 1. Reduction Conditions for Conversion of 14 to 15 and 16

| Entry | NaBH₄ | Solvent | Temp. | Time* | Result (16:15) |
|-------|-------|---------|-------|-------|---------------|
| 1     | 1.0 eq| MeOH    | r.t.  | 10 min| 1:2           |
| 2     | 0.2 eq×3| MeOH    | 0°C   | 15 min×3| 2:1          |
| 3     | 0.2 eq×3| MeOH/DMF (10:1)| 0°C | 10 min×1 and 15 min×2| 1:2 |
| 4     | 0.2 eq×3| CH₃CN | 0°C   | 15 min×3| 0:1          |
| 5     | 0.2 eq×4| MeOH    | −20°C | 10 min×2 and 15 min×2| 1:1 |
| 6     | 1.1 eq| MeOH    | −20°C | 5 min   | 2:1          |
| 7     | 1.1 eq| MeOH    | −78°C | 5 min   | 10:1         |

*The reaction was monitored by TLC until starting material had almost disappeared. eq: equivalent.
To a solution of 14 (40.1 mg, 0.06 mmol) in dry MeOH (10.0 mL) was added NaBH₄ (2.73 mg, 0.07 mmol). After the mixture was stirred at 78°C under N₂ for 5 min, it was diluted with water and extracted with Et₂O. The organic layer was dried over Na₂SO₄ and concentrated to give a sensitive oil, which was used in the next step without further purification.

1H-NMR (400 MHz, CDCl₃) δ 7.57–7.33 (m, 5H), 6.70 (d, J = 8.8 Hz, 1H), 6.54 (d, J = 8.8 Hz, 1H), 6.46 (s, 1H), 6.04 (dd, J = 7.2, 1.6 Hz, 1H), 5.95 (s, 1H), 5.82 (dd, J = 1.6, 8.0 Hz, 2H), 5.28 (d, J = 7.2 Hz, 1H), 5.04 (s, 2H), 4.45 (t, J = 6.8 Hz, 1H), 3.85 (s, 3H), 3.11 (dd, J = 12.8, 6.8 Hz, 1H), 2.85 (dd, J = 12.8, 6.8 Hz, 1H), 2.79 (s, 3H).

(±)-7-Benzoyloxynorcarachine (17)

A solution of 16 (35.0 mg, 0.07 mmol) in dry toluene (50.0 mL) was refluxed in an Ar atmosphere at 130°C in an oil bath. A solution of AIBN (11.6 mg, 0.07 mmol) and Bu₃SnH (40.0 µL, 0.149 mmol) in dry toluene (5.0 mL) was added dropwise to the mixture, which was refluxed for 16.5 h. After the solvent was evaporated, the residue was purified by silica gel column chromatography (hexane/EtOAc/Et₂O) to give 17 as a colorless solid (approx. 2.0 mg, approx. 20%).

1H-NMR (400 MHz, CDCl₃) δ 7.52–7.33 (m, 3H), 6.76 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.55 (s, 1H), 6.38 (s, 1H), 5.84 (s, 1H), 5.80 (s, 1H), 5.22 (d, J = 11.2 Hz, 1H), 5.01 (d, J = 11.2 Hz, 1H), 4.16 (d, J = 5.6 Hz, 1H), 3.95 (d, J = 5.6 Hz, 1H), 3.84 (s, 3H), 3.38–3.21 (m, 2H), 2.67 (d, J = 16.4 Hz, 1H), 2.57 (d, J = 16.4 Hz, 1H), 2.39 (s, 3H); 13C-NMR (600 MHz, CDCl₃) δ 150.5, 146.2, 145.8, 144.3, 138.1, 132.0, 130.8, 128.5, 128.0, 127.9, 125.9, 125.0, 124.3, 111.2, 108.7, 106.9, 100.5, 74.3, 76.5, 55.8, 52.1, 40.7, 32.8, 32.6, 29.8; HRMS-FAB (m/z): [M + H]+ calcld for C₂₀H₂₄NO₄, 416.1826; found, 416.1818.

(±)-Neocarachine (I)

To a solution of 16 (8.90 mg, 0.02 mmol) in EtOH (2.0 mL) was added 5% Pd/C (13.8 mg). After being stirred at room temperature for 8 h with H₂, the reaction mixture was heated at 50°C and stirred for 33 h. The resulting mixture was filtered through Celite and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂/EtOH/Et₂N = 100:2:0.3) to give (±)-I as a colorless solid (5.0 mg, 72%).

1H-NMR (400 MHz, CDCl₃) δ 6.66 (d, J = 8.2 Hz, 1H), 6.58 (s, 1H), 6.50 (d, J = 8.2 Hz, 1H), 6.43 (s, 1H), 5.85 (d, J = 1.4 Hz, 1H), 5.80 (d, J = 1.4 Hz, 1H), 5.69 (s, 1H), 4.34 (d, J = 6.0 Hz, 1H), 3.98 (d, J = 6.0 Hz, 1H), 3.83 (s, 3H), 3.37 (dd, J = 6.0, 16.5 Hz, 1H), 3.32 (dd, J = 6.0, 16.5 Hz, 1H), 2.72 (d, J = 16.5 Hz, 1H), 2.59 (d, J = 16.0 Hz, 1H), 2.53 (s, 3H).

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials. NMR and IR spectra of compound 1, and NMR data of compounds 2–11 are available as supplementary materials.

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