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## TOTAL SYNTHESIS OF 8-EPI-JAVABERINE A AND JAVABERINE A

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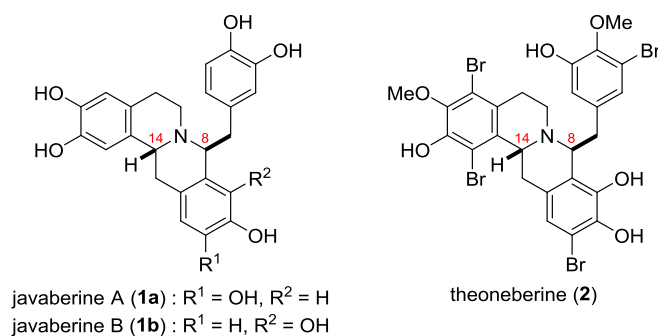
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This paper is dedicated to Prof. Victor Snieckus on the occasion of his 77<sup>th</sup> birthday.

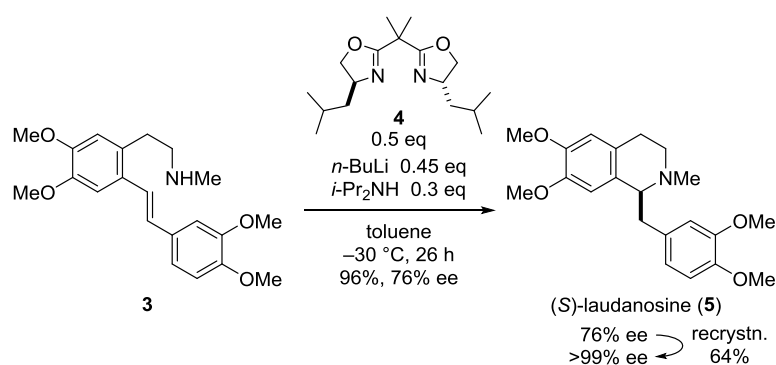
**Abstract** – The total synthesis of berberine alkaloid javaberine A was examined. The B/C ring of berberine was successfully constructed by sequential Bischler–Napieralski cyclization–reduction protocols, and final demethylation afforded both javaberine A and its epimer.

## INTRODUCTION

Berberine alkaloid javaberine **1**, isolated from the Portulacaceae plant *Talinum paniculatum* GAERTNER in 2001 by Yoshikawa and co-workers, inhibits lipopolysaccharide-induced tumor necrosis factor- $\alpha$  and nitric oxide production.<sup>1</sup> Related alkaloid theoneberine **2**, isolated in 1992, has antimicrobial activity against Gram-positive bacteria.<sup>2</sup> These alkaloids comprise an 8-benzyltetrahydroprotoberberine skeleton,<sup>3</sup> and the *cis* relationship of H-14 and the 8-benzyl group is a characteristic feature (Figure 1).<sup>4</sup> We previously reported the chiral bisoxazoline **4**–lithium diisopropylamide-catalyzed asymmetric intramolecular hydroamination of aminoalkene **3** for the synthesis of isoquinoline alkaloid (*S*)-laudanosine (**5**) (Scheme 1).<sup>5–7</sup> Herein we report the total synthesis of javaberine A (**1a**) starting from benzyltetrahydroisoquinoline. Our synthetic strategy is expected to provide the asymmetric total synthesis of benzylberberine alkaloids by combining our intramolecular hydroamination approach toward the asymmetric synthesis of benzyltetrahydroisoquinoline.<sup>5</sup>



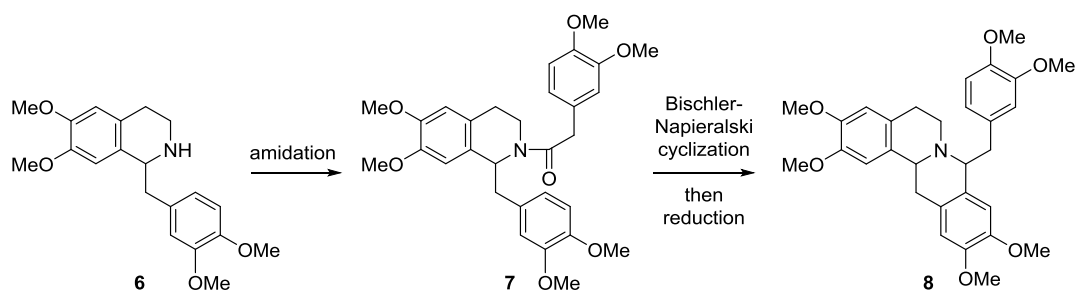
**Figure 1.** 8-Benzylprotoberberine alkaloids javaberine (**1**) and theoneberine (**2**)



**Scheme 1.** Asymmetric synthesis of (*S*)-laudanosine (**5**) by intramolecular hydroamination

## RESULTS AND DISCUSSION

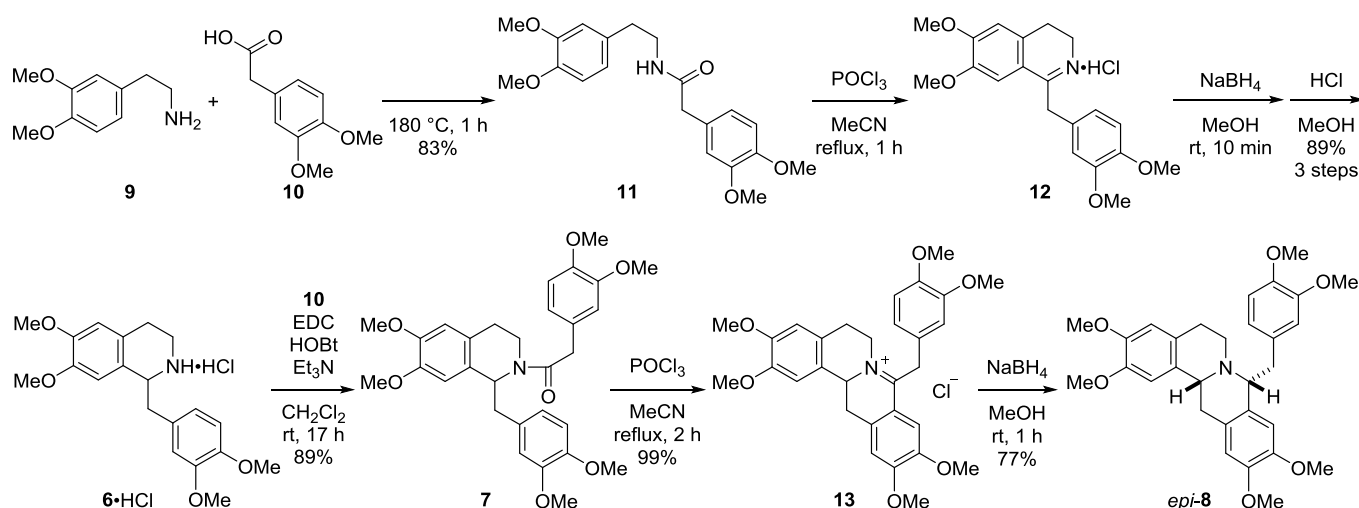
Our synthetic strategy is based on the amidation–Bischler–Napieralski cyclization–reduction sequence, as shown in Scheme 2. Starting tetrahydroisoquinoline **6** was expected to be prepared by *N*-demethylation of laudanosine (**5**), which was synthesized by asymmetric intramolecular hydroamination as previously reported (Scheme 1).<sup>5a</sup>



**Scheme 2.** Amidation and Bischler–Napieralski cyclization strategy from tetrahydroisoquinoline **6**

Tetrahydroisoquinoline **6** was prepared as a racemic HCl salt by amidation of 3,4-dimethoxyphenethylamine **9** with 3,4-dimethoxyphenylacetic acid **10**, Bischler–Napieralski

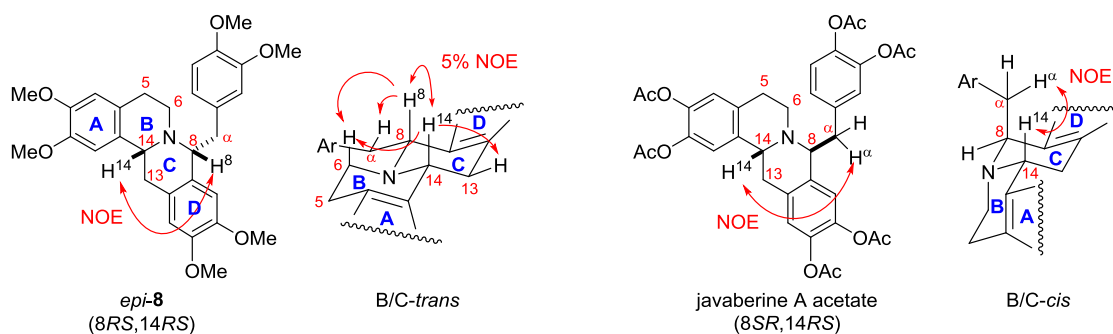
cyclization of amide **11**, and NaBH<sub>4</sub> reduction of **12**, according to published procedures.<sup>8,9</sup> Condensation of amine hydrochloride **6**·HCl with 3,4-dimethoxyphenylacetic acid **10** by EDC–HOBt gave amide **7** in 89% yield. Bischler–Napieralski cyclization of **7** with phosphoryl chloride smoothly proceeded to give iminium **13**,<sup>10</sup> whose reduction with NaBH<sub>4</sub> in MeOH at 0 °C afforded cyclization product *epi*-**8**,<sup>11</sup> corresponding to the epimer of hexamethyl-javaberine A, in 77% yield as a single diastereomer (Scheme 3).



**Scheme 3.** Amidation–Bischler–Napieralski cyclization–reduction sequence

### Determination of the relative configuration of *epi*-**8**

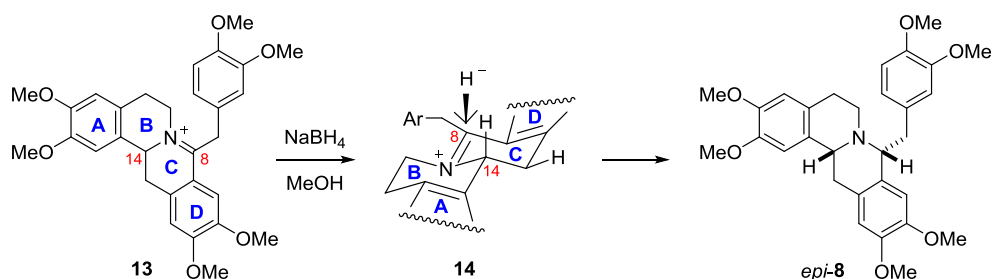
The relative configuration of *epi*-**8** was determined to be (8*RS*,14*RS*) as shown in Figure 2 by NOE correlation between H<sup>14</sup> and H<sup>8</sup>. NMR was performed to analyze the conformation of the B/C ring. According to the reported NMR of benzylprotoberberine,<sup>12</sup> H<sup>14</sup> proton at 3.6±0.2 ppm and the C<sup>14</sup> carbon at 58.4±0.3 ppm indicates a B/C-*trans* conformation, whereas a chemical shift of the H<sup>14</sup> proton at 4.3±0.2 ppm and the C<sup>14</sup> carbon at 49–52 ppm indicates the B/C-*cis* conformation. The chemical shifts of *epi*-**8** in CDCl<sub>3</sub> were 3.65 ppm (H<sup>14</sup>) and 58.5 ppm (C<sup>14</sup>), suggesting a B/C-*trans* conformation. The presence of Bohlmann bands (2834, 2811, 2773, 2741 cm<sup>-1</sup>) in the IR spectra of *epi*-**8** also suggested the *trans* form at the B/C ring junction.<sup>13</sup> On the other hand, the conformation of javaberine A hexaacetate was reported to be B/C-*cis* based on NMR (4.40 ppm of H<sup>14</sup> and 50.2 ppm of C<sup>14</sup> in CDCl<sub>3</sub>) and IR (absence of Bohlmann bands), and the NOE correlation between H<sup>14</sup> and the H<sup>α</sup> methylene proton indicated an (8*SR*,14*RS*) configuration.<sup>1</sup> Based on these findings, our synthesized *epi*-**8** corresponded to an epimer of hexamethyl-javaberine A.



**Figure 2.** Relative configuration and conformation of *epi-8* and javaberine A acetate. NOE correlation was shown in red arrows.

### Stereochemical pathway in the reduction of iminium **13**

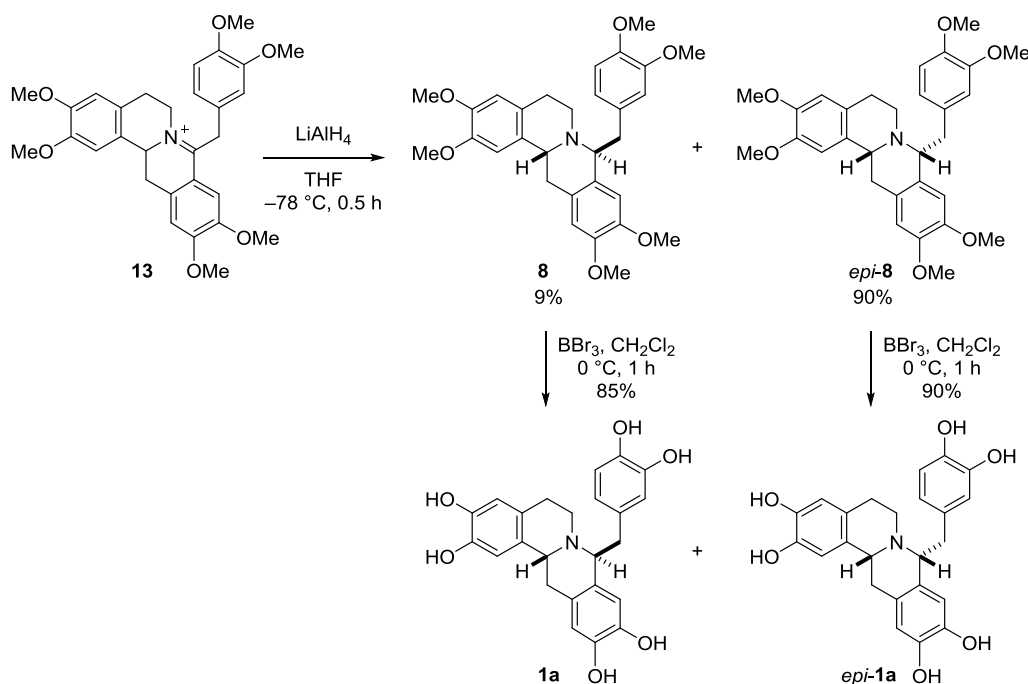
The 8-benzyltetrahydroprotoberberine framework was successfully constructed by this route; however, only unnatural diastereomer was obtained. The reduction of iminium **13** proceeded preferentially through an axial attack of hydride via conformation **14** to give *epi-8* (Scheme 4).



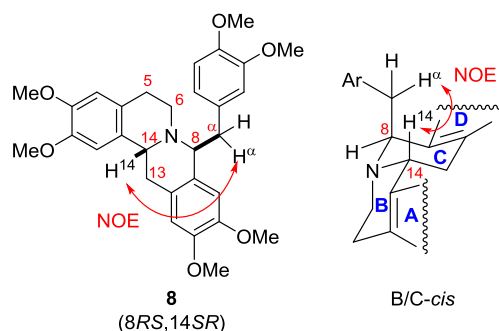
**Scheme 4.** Plausible stereochemical pathway of iminium **13** reduction to **8** through **14**.

### Total synthesis of javaberine A and 8-*epi*-javaberine A

Lithium aluminum hydride reduction of iminium **13** at  $-78\text{ }^{\circ}\text{C}$  for 0.5 h gave desired diastereomer **8** (9%) bearing the same relative stereochemistry as javaberine A, as well as *epi-8* in 90% yield (Scheme 5). Reduction of **13** with other hydride reagents ( $\text{LiAlH}(\text{O}t\text{-Bu})_3$ , DIBAL,  $\text{LiAlH}_4\text{-Me}_3\text{Al}^{14}$ ) at  $-78\text{ }^{\circ}\text{C}$  also gave desired **8**, although the ratio of **8**/*epi-8* was almost 1/10. The relative configuration of **8** was determined by NOE correlation between  $\text{H}^{14}$  and  $\text{H}^{\alpha}$  of the methylene proton (Figure 3). Moreover, the conformation at the B/C ring junction of **8** was revealed to be *cis* based on NMR (4.39 ppm of  $\text{H}^{14}$  and 50.8 ppm of  $\text{C}^{14}$  in  $\text{CDCl}_3$ ) and IR (absence of Bohlmann bands). These data are very similar to those of javaberine A hexaacetate (Figure 2).<sup>1</sup> Diastereomers **8** and *epi-8* were separated by column chromatography, and finally, demethylation of **8** and *epi-8* furnished racemic javaberine A (**1a**) and 8-*epi*-javaberine A (*epi-1a*), respectively (Scheme 5).



**Scheme 5.** Total synthesis of javaberine A (**1a**) and 8-*epi*-javaberine A (*epi-1a*)



**Figure 3.** Relative configuration and conformation of **8**. NOE correlation was shown in red arrows.

The fact that tetrahydroisoquinoline **6** could be synthesized by *N*-demethylation of laudanosine (**5**), which could be asymmetrically prepared by intramolecular hydroamination,<sup>5a</sup> was encouraging for the asymmetric total synthesis of javaberine A.

## CONCLUSION

In conclusion, Bischler–Napieralski cyclization–reduction protocols were successfully used to construct an 8-benzyltetrahydroprotoberberine framework.  $\text{NaBH}_4$  reduction of iminium intermediate **13** stereoselectively proceeded to give the product corresponding to the epimer of javaberine A. Although  $\text{LiAlH}_4$  reduction predominately afforded the epimer, a product with the same configuration as javaberine A was also obtained. Final demethylation afforded both javaberine A and its epimer. Asymmetric total synthesis of these alkaloids will be reported in due course.

## EXPERIMENTAL

$^1\text{H}$  NMR (500 MHz) and  $^{13}\text{C}$  NMR (125 MHz) were measured in  $\text{CDCl}_3$  unless otherwise mentioned. Chemical shift values were expressed in ppm relative to an internal reference of tetramethylsilane (0 ppm) in  $^1\text{H}$  NMR and  $\text{CDCl}_3$  (77.0 ppm) in  $^{13}\text{C}$  NMR.  $^{13}\text{C}$  peak multiplicity assignments were made based on DEPT data. IR spectroscopy of oil and solid samples were measured as neat liquid films and KBr pellets, respectively. Coupling constants were shown in Herz. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. The wave-numbers of maximum absorption peaks of IR spectroscopy were presented in  $\text{cm}^{-1}$ . Column chromatography was performed using silica gel as a stationary phase.

### ***N*-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide (11)**<sup>8</sup>

A mixture of 3,4-dimethoxyphenethylamine **9** (9.2 mL, 55.8 mmol) and homoveratric acid **10** (9.4 g, 48 mmol) was heated at 180 °C for 1 h. After cooled to room temperature, the residue was recrystallized from EtOH (40 mL) to give amide **11** (14.4 g, 83%) as white solids of mp 122.0-124.0 °C.

$^1\text{H}$  NMR: 2.68 (2H, t,  $J = 6.6$ ), 3.45 (2H, dt,  $J = 6.6, 6.6$ ), 3.48 (2H, s), 3.83 (6H, s), 3.86 (3H, s), 3.88 (3H, s), 5.40 (1H, br s), 6.52 (1H, d,  $J = 8.0$ ), 6.62 (1H, s), 6.67-6.72 (3H, m), 6.80 (1H, d,  $J = 8.0$ ).

### **1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (12)**<sup>8</sup>

A mixture of amide **11** (4.96 g, 13.8 mmol) and phosphoryl chloride (2.6 mL, 27.8 mmol) in anhydrous MeCN (40 mL) was refluxed for 1 h under Ar. After concentration, the residue was crystallized by an addition of AcOEt. The solids were filtered and washed with AcOEt to give crude 3,4-dihydroisoquinoline hydrochloride **12** (6.48 g) as yellow solids of mp 114-117 °C.

$^1\text{H}$  NMR: 3.02 (2H, t,  $J = 8.0$ ), 3.83 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 3.96-3.99 (5H, m), 4.38 (2H, s), 6.78 (1H, d,  $J = 8.3$ ), 6.79 (1H, s), 6.85 (1H, dd,  $J = 2.0, 8.3$ ), 6.98 (1H, d,  $J = 2.0$ ), 7.34 (1H, s).

### **1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (6•HCl)**<sup>9</sup>

To a stirred suspension of crude 3,4-dihydroisoquinoline hydrochloride **12** (6.48 g) in MeOH (50 mL) was slowly added  $\text{NaBH}_4$  (0.8 g, 21 mmol) at 0 °C under Ar. The mixture was stirred for 10 min at room temperature and then concentrated. After an addition of brine (16 mL) and MeCN (30 mL), the resulting mixture was partitioned between AcOEt (30 mL) and  $\text{H}_2\text{O}$  (30 mL). The aqueous layer was extracted twice with AcOEt–MeCN (30 mL, 1:1). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated to give yellow oil, which was dissolved in MeOH (10 mL). HCl in MeOH (5% solution, 20 mL) was added to the solution, and then concentrated. The residue was crystallized by an addition of  $\text{Et}_2\text{O}$ , and the solids were filtered and washed with  $\text{Et}_2\text{O}$  to give **6•HCl** (4.67 g, 89% for 3 steps) as white solids of mp 211-215 °C.

$^1\text{H}$  NMR: 2.91 (1H, m), 3.16-3.24 (3H, m), 3.36 (1H, m), 3.56 (1H, m), 3.60 (3H, s), 3.80 (3H, s), 3.85 (6H,

s), 4.73 (1H, m), 6.17 (1H, s), 6.58 (1H, s), 6.72 (1H, d,  $J = 8.0$ ), 6.77-6.79 (2H, m), 9.77 (1H, br s), 10.35 (1H, br s).

$^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ):<sup>9b</sup> 3.01-3.05 (2H, m), 3.16-3.29 (2H, m), 3.41 (1H, m), 3.53 (1H, m), 3.60 (3H, s), 3.72 (3H, s), 3.83 (6H, s), 4.73 (1H, m), 6.36 (1H, s), 6.73 (1H, s), 6.83-6.89 (2H, m), 7.00 (1H, m).

### **1-(1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-(3,4-dimethoxyphenyl)ethanone (7)**

A mixture of **6**•HCl (5.7 g, 15 mmol), homoveratric acid **10** (2.94 g, 15 mmol), HOBt (2.28 g, 16.8 mmol), EDC (3 mL, 16.8 mmol) and  $\text{Et}_3\text{N}$  (6.3 mL, 45 mmol) in  $\text{CH}_2\text{Cl}_2$  (300 mL) was stirred at room temperature for 17 h. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (100 mL) and was washed with 10% HCl (30 mL x 2), satd  $\text{NaHCO}_3$  (30 mL) and brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtrated and evaporated to afford yellow solids. Recrystallization from EtOH (135 mL) gave amide **7** (6.96 g, 89%) as yellow solids of mp 148–150 °C.

$^1\text{H}$  NMR (the ratio of rotamer is 66/34): 2.49-2.61 (1.32H, m), 2.70 (0.34H, m), 2.92 (0.34H, m), 2.93 (0.66H, dd,  $J = 8.0, 13.2$ ), 2.98 (0.34H, dd,  $J = 5.2, 13.7$ ), 3.02 (0.34H, d,  $J = 16.0$ ), 3.07 (0.34H, dd,  $J = 9.2, 13.7$ ), 3.10 (0.66H, dd,  $J = 5.8, 13.2$ ), 3.19 (0.34H, m), 3.24 (0.34H, d,  $J = 16.0$ ), 3.38 (0.66H, m), 3.61 (1.98H, s), 3.67 (1.02H, s), 3.68-3.73 (1.98H, m), 3.75 (1.98H, s), 3.80 (1.98H, s), 3.83-3.84 (6H, m), 3.86 (1.02H, s), 3.87 (3H, s), 3.88 (1.02H, s), 4.82 (0.34H, m), 4.92 (0.34H, dd,  $J = 5.2, 9.2$ ), 5.67 (0.66H, dd,  $J = 5.8, 8.0$ ), 6.18 (0.66H, s), 6.39 (0.34H, s), 6.43-6.45 (0.68H, m), 6.15-6.52 (1.32H, m), 6.62-6.80 (4.66H, m), 6.84 (0.34 H, d,  $J = 8.6$ ).  $^{13}\text{C}$  NMR: 27.9 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_2$ ), 35.2 ( $\text{CH}_2$ ), 39.6 ( $\text{CH}_2$ ), 41.1 ( $\text{CH}_2$ ), 41.2 ( $\text{CH}_2$ ), 41.8 ( $\text{CH}_2$ ), 42.4 (CH), 54.0 (CH), 56.6 ( $\text{CH}_3$ ), 55.8 ( $\text{CH}_3$ ), 55.93 ( $\text{CH}_3$ ), 55.96 ( $\text{CH}_3$ ), 55.99 ( $\text{CH}_3$ ), 56.1 ( $\text{CH}_3$ ), 58.6 (CH), 110.1 (CH), 110.82 (CH), 110.89 (CH), 110.93 (CH), 111.2 (CH), 111.4 (CH), 111.5 (CH), 111.6 (CH), 111.8 (CH), 111.9 (CH), 112.8 (CH), 112.9 (CH), 120.8 (CH), 120.9 (CH), 121.9 (CH), 122.1 (CH), 125.6 (C), 126.7 (C), 127.5 (C), 127.7 (C), 128.0 (C), 128.3 (C), 130.5 (C), 130.7 (C), 147.0 (C), 147.4 (C), 147.69 (C), 147.72 (C), 147.9 (C), 148.2 (C), 148.3 (C), 148.9 (C), 145.1 (C), 170.1 (C), 170.4 (C). IR: 1630. HRMS-ESI  $m/z$ :  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{30}\text{H}_{35}\text{NNaO}_7$ , 544.2311; found, 544.2300.

### **8-(3,4-Dimethoxybenzyl)-2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydroisoquinolino[3,2-*a*]isoquinolin-7-ium chloride (13)**

A mixture of amide **7** (5.21 g, 10 mmol) and phosphoryl chloride (1.9 mL, 20 mmol) in anhydrous MeCN (30 mL) was refluxed for 2 h under Ar. Concentration followed by recrystallization from EtOH (320 mL) gave **13** (5.32 g, 99%) as yellow cubes of mp 170-174 °C.

$^1\text{H}$  NMR: 2.89-2.99 (2H, m), 3.13 (1H, dd,  $J = 16.6, 16.6$ ), 3.42 (1H, dd,  $J = 4.6, 16.6$ ), 3.80 (1H, m), 3.83 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 3.91 (3H, s), 3.92 (3H, s), 4.06 (3H, s), 4.67-4.72 (2H, m), 4.91 (1H, d,  $J = 16.6$ ), 5.31 (1H, dd,  $J = 4.6, 16.6$ ), 6.44 (1H, dd,  $J = 1.7, 8.6$ ), 6.67 (1H, s), 6.75 (1H, d,  $J = 8.6$ ), 6.82 (1H,

s), 6.87 (1H, d,  $J = 1.7$ ), 6.99 (1H, s), 7.43 (1H, s).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ): 28.1 (CH<sub>2</sub>), 34.5 (CH<sub>2</sub>), 35.5 (CH<sub>2</sub>), 50.4 (CH<sub>2</sub>), 55.5 (CH<sub>3</sub>), 55.6 (CH<sub>3</sub>), 55.7 (CH<sub>3</sub>), 55.9 (CH<sub>3</sub>), 56.4 (CH<sub>3</sub>), 56.5 (CH<sub>3</sub>), 59.4 (CH), 109.9 (CH), 111.0 (CH), 111.3 (CH), 112.28 (CH), 112.32 (CH), 113.7 (CH), 119.4 (C), 119.9 (CH), 125.0 (C), 125.8 (C), 126.7 (C), 135.3 (C), 148.1 (C x 2), 148.1 (C), 148.3 (C), 149.1 (C), 155.8 (C), 175.1 (C). IR: 1608, 1518, 1466, 1372, 1280, 1259. HRMS-ESI  $m/z$ :  $[\text{M}-\text{Cl}]^+$  calcd for C<sub>30</sub>H<sub>34</sub>NO<sub>6</sub>, 504.2386; found, 504.2371.

**(8SR,13aSR)-8-(3,4-Dimethoxybenzyl)-2,3,10,11-tetramethoxy-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline (*epi*-8)**

Iminium **13** (1.08 g, 2 mmol) was dissolved in MeOH (10 mL), and NaBH<sub>4</sub> (0.6 g, 16 mmol) was slowly added at 0 °C. The mixture was stirred for 1 h at room temperature and then concentrated. To the mixture were added brine (5 mL) and CHCl<sub>3</sub> (10 mL), and the separated aqueous layer was extracted with CHCl<sub>3</sub> (10 mL x 2). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Desired diastereomer **8** was not observed in crude NMR. The resulting crude mixture was crystallized by an addition of Et<sub>2</sub>O. After concentration, the crude was recrystallized from EtOH (20 mL) to give *epi*-**8** (0.78 g, 77%) as yellow needles of mp 142–144 °C.

$^1\text{H}$  NMR: 2.47 (1H, dd,  $J = 11.0, 14.6$ ), 2.65 (1H, m), 2.68 (1H, m), 2.96 (1H, dd,  $J = 2.0, 15.2$ ), 3.04 (1H, dd,  $J = 5.2, 14.3$ ), 3.07 (1H, dd,  $J = 5.2, 14.3$ ), 3.11 (1H, m), 3.40 (1H, m), 3.65 (1H, d,  $J = 11.2$ ), 3.67 (3H, s), 3.75 (3H, s), 3.81 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 3.88 (3H, s), 3.99 (1H, dd,  $J = 5.2, 5.2$ ), 6.49 (1H, s), 6.54 (1H, d,  $J = 1.9$ ), 6.58 (1H, s), 6.60 (1H, dd,  $J = 1.9, 8.0$ ), 6.63 (1H, s), 6.67 (1H, d,  $J = 8.0$ ), 6.74 (1H, s).  $^{13}\text{C}$  NMR: 30.1 (CH<sub>2</sub>), 36.7 (CH<sub>2</sub>), 42.7 (CH<sub>2</sub>), 48.8 (CH<sub>2</sub>), 55.6 (CH<sub>3</sub>), 55.75 (CH<sub>3</sub>), 55.77 (CH<sub>3</sub>), 55.8 (CH<sub>3</sub> x 2), 56.0 (CH<sub>3</sub>), 58.5 (CH), 65.4 (CH), 108.8 (CH), 110.0 (CH), 110.5 (CH), 110.8 (CH), 111.3 (CH), 113.3 (CH), 122.3 (CH), 127.2 (C), 128.5 (C), 129.5 (C), 130.6 (C), 131.4 (C), 147.0 (C x 2), 147.1 (C), 147.2 (C), 147.4 (C), 147.9 (C). IR: 2932, 2834, 2811, 2773, 2741, 1612, 1512, 1261. FABMS  $m/z$ : 506  $[\text{M}+\text{H}]^+$ . HRMS-FAB  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for C<sub>30</sub>H<sub>36</sub>NO<sub>6</sub>, 506.2543; found, 506.2558.

NOE experiment was performed in C<sub>6</sub>D<sub>6</sub>. Irradiation of H<sup>8</sup> (3.98 ppm) yielded an appreciable NOE (5%) at H<sup>14</sup> (3.80 ppm), H<sup>α</sup> (3.11 ppm), and H<sup>6</sup> (2.62 ppm), respectively. Irradiation of H<sup>14</sup> (3.80 ppm) yielded an appreciable NOE (5%) at H<sup>8</sup> (3.98 ppm), H<sup>6</sup> (2.62 ppm), and H<sup>13</sup> (2.98 ppm), respectively.

$^1\text{H}$  NMR (C<sub>6</sub>D<sub>6</sub>): 2.55 (1H, d,  $J = 15.7, \text{H}^5$ ), 2.62 (1H, ddd,  $J = 3.2, 11.8, 11.8, \text{H}^6$ ), 2.73 (1H, dd,  $J = 10.9, 14.9, \text{H}^{13}$ ), 2.98 (1H, dd,  $J = 2.3, 14.9, \text{H}^{13}$ ), 3.11 (1H, dd,  $J = 4.0, 14.3, \text{H}^\alpha$ ), 3.15 (1H, dd,  $J = 5.5, 14.3, \text{H}^\alpha$ ), 3.21 (1H, m, H<sup>5</sup>), 3.32 (1H, m, H<sup>6</sup>), 3.36 (3H, s), 3.43 (3H, s), 3.44 (3H, s), 3.48 (3H, s), 3.50 (3H, s), 3.52 (3H, s), 3.80 (1H, d,  $J = 10.9, \text{H}^{14}$ ), 3.98 (1H, dd,  $J = 4.0, 5.5, \text{H}^8$ ), 6.43 (1H, s), 6.539 (1H, d,  $J = 8.3$ ), 6.543 (1H, s), 6.58 (1H, s), 6.66 (1H, d,  $J = 1.7$ ), 6.72 (1H, dd,  $J = 1.7, 8.3$ ), 6.76 (1H, s).



**(8SR,13aRS)-8-(3,4-Dimethoxybenzyl)-2,3,10,11-tetramethoxy-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline (8)**

To the suspension of  $\text{LiAlH}_4$  (75.9 mg, 2 mmol) in THF (2 mL) was added iminium **13** (108 mg, 0.2 mmol) in THF (1 mL) at  $-78^\circ\text{C}$ . The mixture was stirred for 1 h at  $-78^\circ\text{C}$ , and quenched with water (0.1 mL), 10% NaOH (0.1 mL) and water (0.3 mL) and then filtered through a Celite pad. The filtrate was dried over  $\text{Na}_2\text{SO}_4$  and concentrated. Column chromatography (hexane/AcOEt 2/3 to 1/3) gave *epi*-**8** (91 mg, 90%) as yellow solids and **8** (9.0 mg, 9%) as yellow amorphous solids of mp  $75\text{--}77^\circ\text{C}$ .

$^1\text{H}$  NMR: 2.79–3.00 (6H, m), 3.12 (1H, m), 3.26 (1H, m), 3.57 (3H, s), 3.77 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 3.94 (1H, dd,  $J = 6.9, 6.9$ ), 4.39 (1H, dd,  $J = 4.6, 11.5$ ), 5.99 (1H, s), 6.58 (1H, s), 6.63 (1H, s), 6.66–6.68 (3H, m), 6.78 (1H, d,  $J = 8.0$ ).  $^{13}\text{C}$  NMR: 29.4 ( $\text{CH}_2$ ), 33.6 ( $\text{CH}_2$ ), 40.2 ( $\text{CH}_2$ ), 46.8 ( $\text{CH}_2$ ), 50.8 (CH), 55.4 ( $\text{CH}_3$ ), 55.7 ( $\text{CH}_3 \times 2$ ), 55.79 ( $\text{CH}_3$ ), 55.88 ( $\text{CH}_3$ ), 55.94 ( $\text{CH}_3$ ), 66.6 (CH), 109.2 (CH), 110.8 (CH), 110.9 (CH), 111.0 (CH), 111.5 (CH), 113.2 (CH), 121.9 (CH), 125.2 (C), 126.1 (C), 128.9 (C), 131.2 (C), 132.7 (C), 146.2 (C), 147.2 (C), 147.3 (C), 147.4 (C), 147.5 (C), 148.5 (C). IR: 3002, 2935, 1610, 1515, 1465, 1261. HRMS-ESI  $m/z$ :  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{30}\text{H}_{35}\text{NNaO}_6$ , 528.2362; found, 528.2363.

NOE experiment was performed in acetone- $d_6$ . Irradiation of  $\text{H}^{14}$  (4.37 ppm) yielded an appreciable NOE (5%) at  $\text{H}^a$  (3.14, 2.80 ppm) and  $\text{H}^6$  (2.94 ppm).

$^1\text{H}$  NMR (acetone- $d_6$ ): 2.65–2.82 (6H, m), 2.94 (1H, dd,  $J = 4.6, 16.6$ ), 3.06 (1H, m), 3.14 (1H, dd,  $J = 6.9, 13.7$ ), 3.55 (3H, s), 3.65 (3H, s), 3.73 (6H, s), 3.75 (3H, s), 3.79 (3H, s), 3.95 (dd, 1H,  $J = 6.9, 6.9$ ), 4.37 (dd, 1H,  $J = 4.6, 11.5$ ), 6.27 (1H, s), 6.62 (1H, s), 6.65 (1H, s), 6.67 (1H, d,  $J = 8.2$ ), 6.78–6.83 (3H, m).  $^{13}\text{C}$  NMR (acetone- $d_6$ ): 29.6 ( $\text{CH}_2$ ), 32.9 ( $\text{CH}_2$ ), 40.4 ( $\text{CH}_2$ ), 46.7 ( $\text{CH}_2$ ), 50.6 (CH), 55.0 ( $\text{CH}_3$ ), 55.17 ( $\text{CH}_3$ ), 55.21 ( $\text{CH}_3$ ), 55.3 ( $\text{CH}_3$ ), 55.4 ( $\text{CH}_3$ ), 55.5 ( $\text{CH}_3$ ), 66.3 (CH), 110.5 (CH), 111.5 (CH), 111.9 (CH), 112.0 (CH), 112.4 (CH), 114.1 (CH), 121.9 (CH), 125.9 (C), 126.4 (C), 129.8 (C), 132.0 (C), 133.4 (C), 147.1 (C), 147.8 (C), 147.95 (C), 148.02 (C), 148.1 (C), 149.2 (C).

**Javaberine A (1a)**

To the solution of **8** (20 mg, 0.04 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was added  $\text{BBr}_3$  (0.6 mL, 0.6 mmol, 1 M solution in  $\text{CH}_2\text{Cl}_2$ ) at  $0^\circ\text{C}$ . The mixture was stirred for 1 h, and then MeOH (2 mL) was added. After concentration, the residue was dissolved in MeOH (1 mL), and  $\text{Et}_3\text{N}$  (0.1 mL) was added to neutralize. Concentration followed by reprecipitation (MeOH/ $\text{CHCl}_3$ ) gave **1a** (14.2 mg, 85%) as pale yellow solids of mp  $190\text{--}194^\circ\text{C}$ .

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ): 2.81 (1H, dd,  $J = 11.5, 17.5$ ), 2.86–2.95 (2H, m), 3.04 (1H, m), 3.24 (1H, dd,  $J = 5.8, 17.5$ ), 3.28–3.36 (3H, m), 4.30 (1H, m), 4.63 (1H, m), 5.96 (1H, s), 6.41 (1H, d,  $J = 8.0$ ), 6.54 (1H, s), 6.57 (1H, s), 6.59 (1H, d,  $J = 1.2$ ), 6.64 (1H, s), 6.68 (1H, d,  $J = 8.0$ ).  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ ): 27.3 ( $\text{CH}_2$ ), 34.2 ( $\text{CH}_2$ ),

40.8 (CH<sub>2</sub>), 48.1 (CH<sub>2</sub>), 53.4 (CH), 67.9 (CH), 113.8 (CH), 115.7 (CH), 115.9 (CH), 116.2 (CH), 116.4 (CH), 118.0 (CH), 122.4 (CH), 123.0 (C), 123.4 (C), 127.8 (C), 130.0 (C), 144.7 (C), 145.4 (C), 145.6 (C), 146.3 (C), 146.5 (C). IR: 3373, 1618, 1525, 1376, 1261. HRMS-ESI *m/z*: [M+H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>24</sub>NO<sub>6</sub>, 422.1604; found, 422.1599.

### 8-*epi*-Javaberine A (*epi*-1a)

To the solution of *epi*-8 (25 mg, 0.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added BBr<sub>3</sub> (0.5 mL, 0.5 mmol, 1 M solution in CH<sub>2</sub>Cl<sub>2</sub>) at 0 °C. The mixture was stirred for 1 h, and then MeOH (2 mL) was added. After concentration, the residue was dissolved in MeOH (1 mL), and Et<sub>3</sub>N (0.1 mL) was added to neutralize. Concentration followed by reprecipitation (MeOH/CHCl<sub>3</sub>) gave *epi*-1a (19 mg, 90%) as yellow solids of mp 186–192 °C.

<sup>1</sup>H NMR (CD<sub>3</sub>OD): 2.44 (1H, dt, *J* = 3.4, 11.5), 2.50-2.56 (2H, m), 2.90-2.99 (4H, m), 3.32 (1H, m), 3.50 (1H, d, *J* = 10.3), 3.79 (1H, m), 6.49-6.51 (4H, m), 6.63 (1H, d, *J* = 8.0), 6.67 (1H, d, *J* = 1.7), 6.68 (1H, s). <sup>13</sup>C NMR (CD<sub>3</sub>OD): 29.3 (CH<sub>2</sub>), 36.0 (CH<sub>2</sub>), 43.2 (CH<sub>2</sub>), 47.8 (CH<sub>2</sub>), 61.0 (CH), 67.3 (CH), 113.4 (CH), 114.5 (CH), 115.7 (CH), 116.0 (CH), 116.3 (CH), 117.6 (CH), 121.9 (CH), 126.0 (C), 126.9 (C), 128.7 (C), 129.3 (C), 131.9 (C), 144.8 (C), 144.95 (C), 145.00 (C), 145.2 (C), 145.4 (C), 146.2 (C). IR: 3397, 2851, 2695, 2584, 1609, 1524, 1450, 1279. HRMS-ESI *m/z*: [M+H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>24</sub>NO<sub>6</sub>, 422.1604; found, 422.1589.

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