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STEREOSELECTIVE CONSTRUCTION OF A BERBERINE C-8 BENZYL GROUP FOR THE SYNTHESIS OF JAVABERINE DERIVATIVES

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This paper is dedicated to Prof. Kaoru Fuji on the occasion of his 80th birthday.

Abstract – Diastereoselective synthesis of 8-benzyltetrahydroprotoberberines was examined. Although Stevens rearrangement of *N*-benzylxylopinine resulted in poor yield and diastereoselectivity, benzylation of tetracyclic iminium successfully gave H8-H14 *trans*-benzyltetrahydroprotoberberines with high stereoselectivity.

INTRODUCTION

Berberines are a class of isoquinoline alkaloids containing two aromatic rings and quinolizidine skeletons. These alkaloids have various substitution patterns of rings A and D, and a wide range of biological activities.¹ Among them, javaberine² and theoneberine³ have particularly interesting activities, such as inhibition of lipopolysaccharide-induced tumor necrosis factor- α and nitric oxide production (javaberine A), or antimicrobial activity against Gram-positive bacteria (theoneberine). Structurally, these compounds feature an 8-benzyltetrahydroprotoberberine skeleton with a *trans* relationship of H14 and H8.⁴

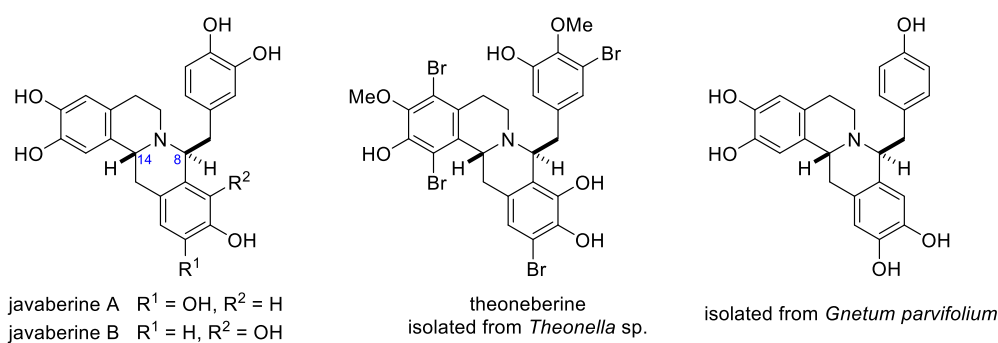
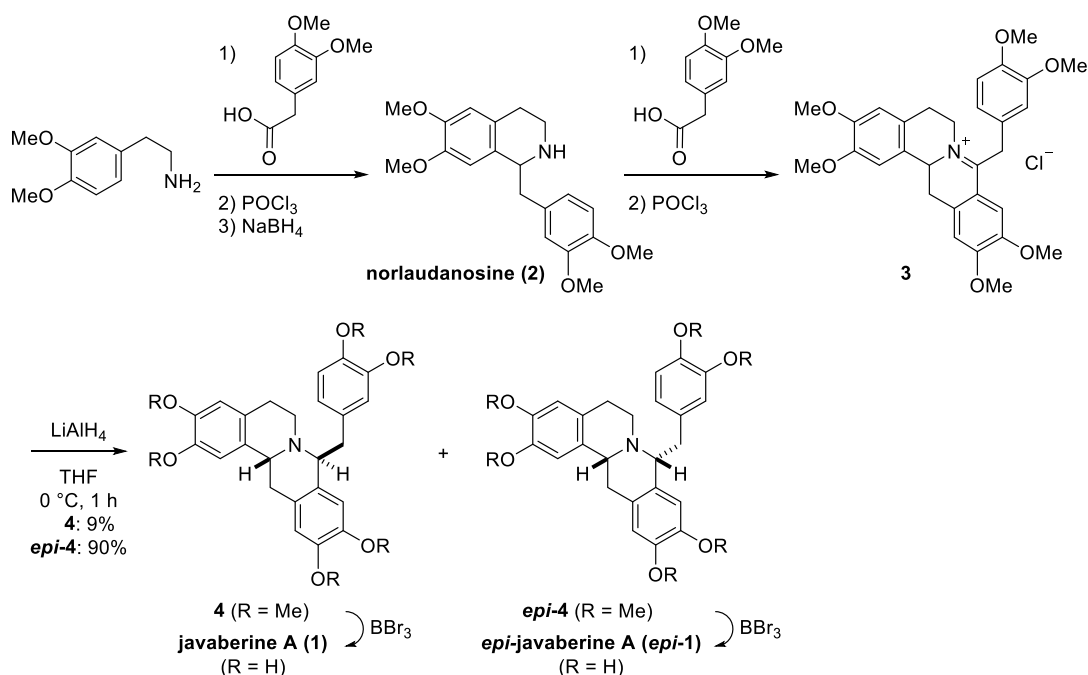


Figure 1. 8-Benzyltetrahydroprotoberberine alkaloids

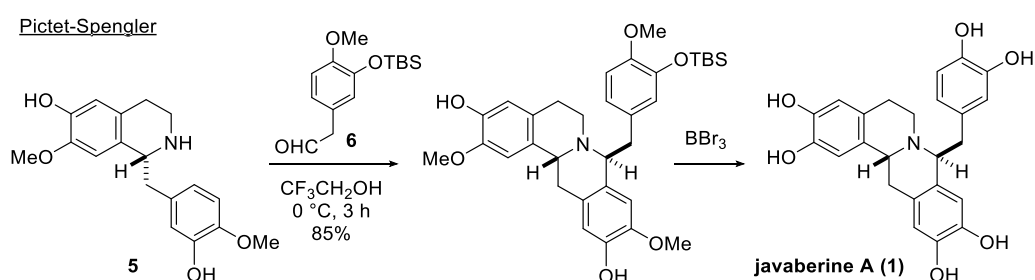
We previously reported the racemic total synthesis of *epi*-javaberine A (*epi*-1) and javaberine A (**1**) using an amidation–Bischler–Napieralski cyclization–reduction sequence, as shown in Scheme 1.⁵ In the reduction of iminium **3**, the major diastereomer was *epi*-4, an unnatural form of javaberine A (**1**), and improvement of the stereoselectivity remained unresolved. Herein, we report stereoselective construction of the C-8 benzyl group by benzylation of the iminium of dihydroprotoberberine.



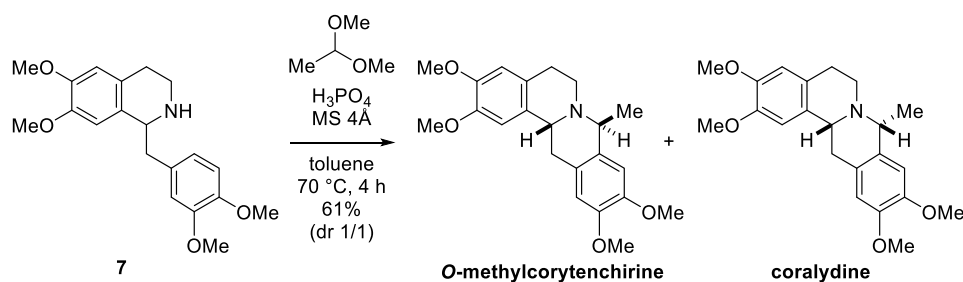
Scheme 1. Our previous racemic total synthesis of *epi*-javaberine A (*epi*-1) and javaberine A (**1**)

RESULTS AND DISCUSSION

Several groups have reported the stereoselective construction of C-8 substituents of protoberberines. The most successful of the approaches is the Pictet-Spengler cyclization of tetrahydroisoquinoline **5** with aldehyde **6** by Hiemstra's group,⁶ in which they considered the presence of free phenol OH to be essential for the high reactivity and diastereoselectivity (Scheme 2). On the other hand, Kouklovsky reported that Pictet-Spengler cyclization of **7** with acetaldehyde dimethyl acetal is not stereoselective (dr 1/1).⁷

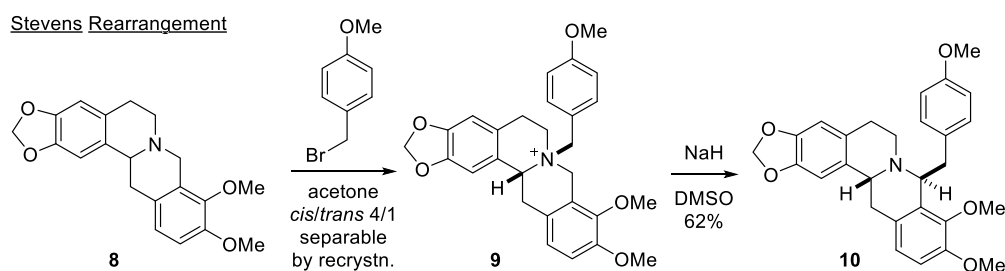


Scheme 2. Pictet-Spengler cyclization in Hiemstra's asymmetric total synthesis of javaberine A



Scheme 3. Pictet-Spengler cyclization with poor stereoselectivity in Kouklovsky's total synthesis of coralydine

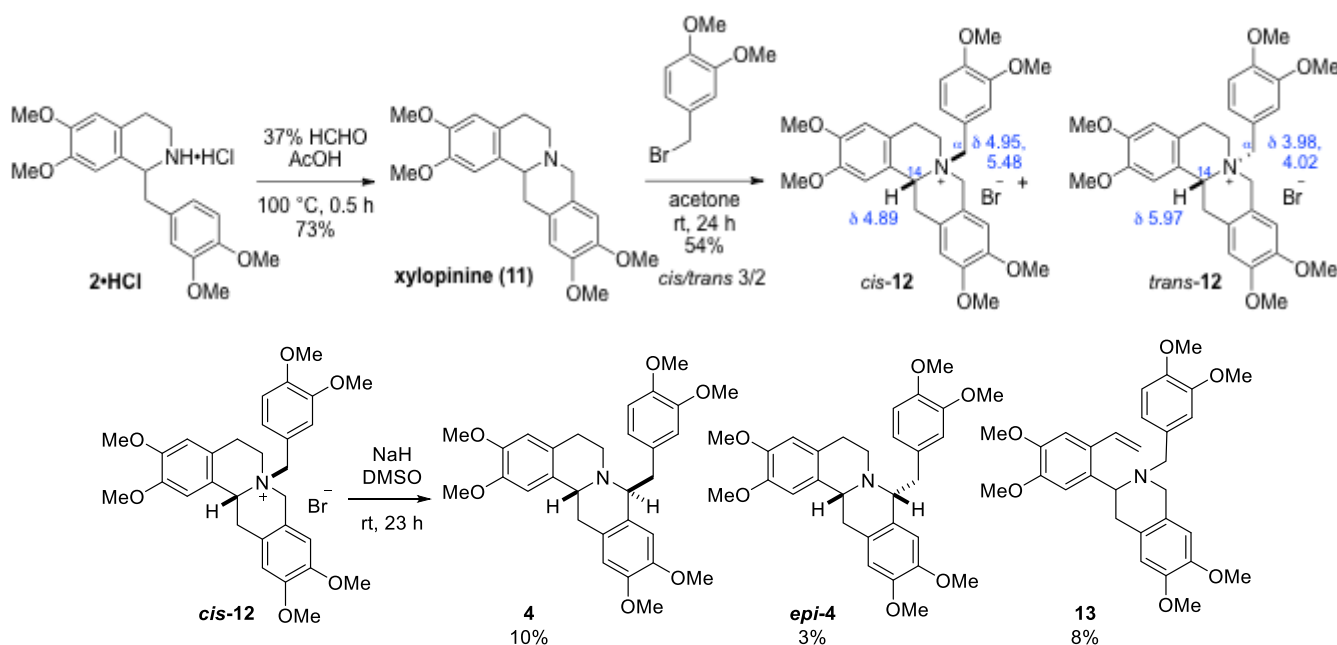
Valpuesta reported retaining the stereochemistry with another approach using Stevens rearrangement of benzylammonium **9** to give 8-benzylprotoberberine **10** (Scheme 4).⁸ Although the stereoselectivity of the rearrangement was extremely high, this strategy requires stereoselective preparation of H8-*N*-benzyl-*cis*-benzylammonium **9**, leading to *trans*-**10**. Obtaining pure *cis*-**9** requires recrystallization of the diastereomeric mixture of **9** (*cis/trans* 4/1) after benzylation of berberine **8**.



Scheme 4. The Stevens rearrangement reaction reported by Valpuesta

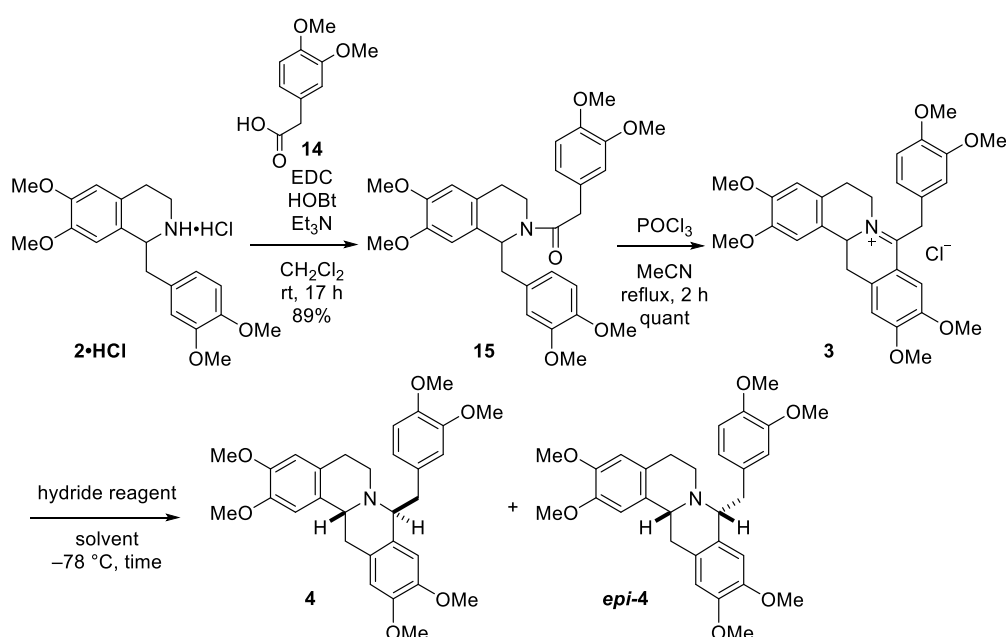
We also tried the Stevens rearrangement for the total synthesis of javaberine A, but found it difficult to prepare the *cis*-*N*-benzylammonium salt **12**. We first synthesized xylopinine (**11**) by Pictet-Spengler cyclization of norlaudanosine hydrochloride (**2·HCl**)⁹ with formaldehyde. Next, benzylation of xylopinine (**11**) by 3,4-dimethoxybenzyl bromide gave ammonium **12** with a *cis/trans* ratio of 56/44, which was almost unchanged by recrystallization from acetone (*cis/trans* ratio 56/44 to 60/40). These diastereomers were partially separated by NaBr-coated silica gel column chromatography¹⁰ to give *cis*-**12** (28%), *trans*-**12** (21%), and a diastereomeric mixture of **12** (25%, *cis/trans* ratio 31/69).¹¹ The relative stereochemistry of **12** was determined based on the chemical shifts of the H14 methine proton and H α methylene protons. Thus, the signals of H14 of the *cis* isomer and H α of the *trans* isomer appears at higher fields than that of the corresponding opposite isomers due to their conformations.⁸ Unfortunately, the Stevens rearrangement of *cis*-**12** with NaH and DMSO was not stereoselective, and both **4** (desired)

and *epi-4* (undesired) were obtained in 10% and 3% yield, respectively, with elimination product **13** obtained in 8% yield.



Scheme 5. Stevens rearrangement reaction of *cis-12*

We previously reported that reduction of iminium **3**, prepared from norlaudanosine (**2**) by amidation and Bischler-Napieralski cyclization, with LiAlH_4 affords H8-H14 *cis-epi-4* as a major product, and desired **4** was obtained in only 9% yield (Scheme 6 and Table 1).^{5,12} Although we screened other hydride reagents, the diastereoselectivity was not improved, and the yield of the desired **4** was less than 10% (Table 1).



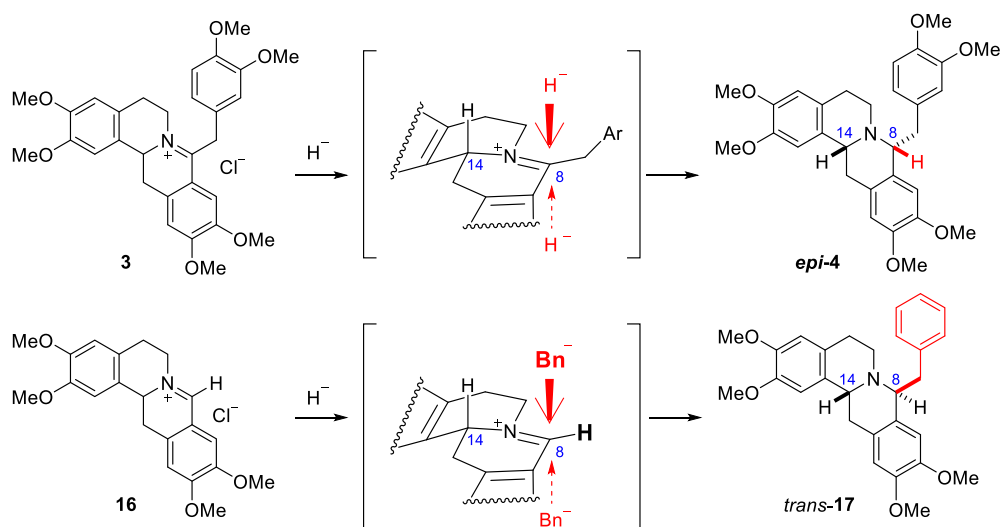
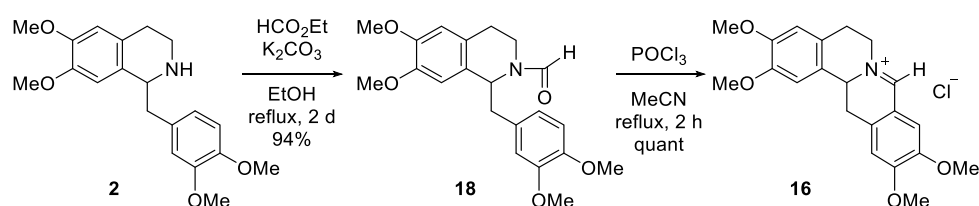
Scheme 6. Preparation of iminium **3** and its hydride reduction

Table 1. Reduction of iminium **3** to give **4** and *epi-4*^a

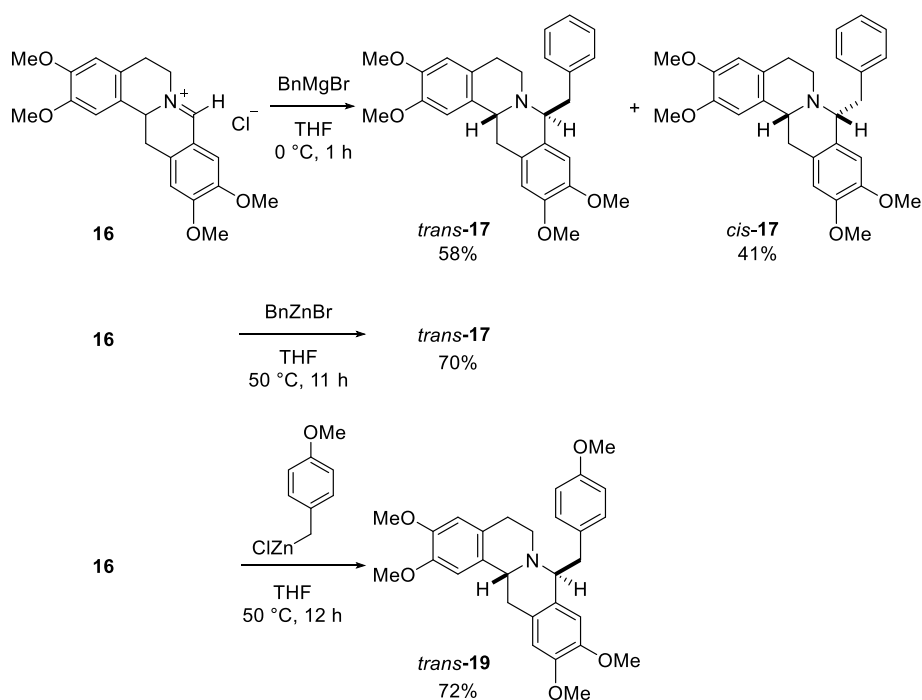
Entry	Reagent (equiv)	solvent	Time (h)	4 (%)	<i>epi-4</i> (%)
1	LiAlH ₄ (10)	THF	1	9	90
2	LiAlH ₄ (10), AlMe ₃ (10) ¹³	THF	1	9	90
3	LiAlH(O <i>t</i> -Bu) ₃ (10)	THF	1	7	76
4 ^b	NaBH ₄ (2)	MeOH	0.5	3	97
5 ^b	KBH ₄ (2)	MeOH	0.5	1	99
6 ^b	LiBH ₄ (2)	MeOH	0.5	1	99

^a All reactions were carried out at -78 °C. ^b The yields of **4** and *epi-4* was calculated by crude ¹H NMR.

The undesired diastereoselectivity in the reduction of iminium **3** was presumably due to kinetically-favored axial attack of hydride on iminium **3** to give *epi-4*.¹⁴ On the basis of this analysis, we expected that benzylation of iminium **16**, possessing a hydrogen instead of the 3,4-dimethoxyphenylmethyl group of **3**, would predominately afford **17** with the desired H14-H8 *trans* relationship through axial attack of the benzyl group (Scheme 7). Iminium **16** was synthesized from norlaudanosine **2** by formylation followed by Bischler-Napieralski cyclization (Scheme 8).

**Scheme 7.** Plausible stereochemical pathway of iminium **3** reduction and alkylation**Scheme 8.** Preparation of iminium **16**

We next examined the benzylation of iminium **16**. Adding benzylmagnesium bromide in THF at 0 °C proceeded smoothly to give the desired *trans*-**17** in 58% yield and *cis*-**17** in 41% yield.¹⁵ As expected, this benzylation strategy dramatically improved the diastereoselectivity for the construction of the C-8 benzyl group of protoberberines. To our delight, benzylzinc bromide was highly stereoselective, giving *trans*-**17** in 70% yield as a sole product. The addition of 4-methoxybenzylzinc chloride was also stereoselective to afford *trans*-**19** in 72% yield (Scheme 9).



Scheme 9. Stereoselective benzylation of iminium **16**

CONCLUSION

Stereoselective construction of the C-8 benzyl group of tetrahydroprotoberberine was successfully achieved in an H8-H14 *trans* manner by the addition of benzylzinc halide to an iminium of dihydroprotoberberine. We previously reported the H8-H14 *cis*-selective synthesis of C-8 benzyltetrahydroprotoberberine by hydride reduction of benzyliminium, and therefore selective preparation of both diastereomers is now established. These findings should be useful for biological studies of benzylprotoberberines.

EXPERIMENTAL

¹H NMR (500 MHz) and ¹³C NMR (125 MHz) were measured in CDCl₃ unless otherwise mentioned. Chemical shift values were expressed in ppm relative to an internal reference of tetramethylsilane (0 ppm) in ¹H NMR and CDCl₃ (77.0 ppm) in ¹³C NMR. ¹³C 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 cm^{-1} . Column chromatography was performed using silica gel as a stationary phase.

Xylopinine (**11**)¹⁶

A mixture of **2**•HCl (11.3 g, 29.7 mmol), 37% formaldehyde (18.8 mL, 30.0 mmol) and acetic acid (18.8 mL, 60.1 mmol) was heated at 100 °C for 30 min. After dilution with water (100 mL), the solution was basified with 28% ammonia solution (47 mL). To the mixture was added MeCN (100 mL) and brine (50 mL), and then the resulting mixture was extracted with AcOEt (100 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4 , and evaporated to afford a solid, which was recrystallized from EtOH (116 mL) to give **xylopinine (11)**, 7.95 g, 72%) as pale yellow solids of mp 156-159 °C.

11: ^1H NMR: 2.60-2.69 (2H, m), 2.86 (1H, dd, $J = 11.5, 16.0$), 3.12-3.18 (2H, m), 3.26 (1H, dd, $J = 4.0, 16.0$), 3.60 (1H, dd, $J = 4.0, 11.5$), 3.69 (1H, d, $J = 14.9$), 3.86-3.90 (12H, m), 3.95 (1H, d, $J = 14.9$), 6.58 (1H, s), 6.62 (1H, s), 6.67 (1H, s), 6.78 (1H, s).

7-(3,4-Dimethoxybenzyl)-2,3,10,11-tetramethoxy-5,6,7,8,13,13a-hexahydroisoquinolino[3,2-*a*]isoquinolin-7-ium bromide (**12**)

To a solution of xylopinine (**11**, 1.07 g, 3.0 mmol) in acetone (90 mL) was added 3,4-dimethoxybenzyl bromide (0.96 g, 4.15 mmol) and the mixture was stirred at room temperature for 24 h. The precipitate was collected by filtration to give pure *trans*-**12** (148 mg, 8%). The filtrate was concentrated, and the residue was suspended with acetone (10 mL). The precipitate was collected by filtration to give *cis/trans* mixture of **12** (941 mg, 54%, *cis/trans* 56/44). A part of the *cis/trans* mixture of **12** (456 mg, *cis/trans* 56/44) was purified by NaBr-coated silica gel column chromatography (silica gel was suspended with 12% NaBr in MeOH, and then was packed and eluted with $\text{CHCl}_3/\text{MeOH}$ 10/1) to give *cis*-**12** (128 mg, 28%), *trans*-**12** (97 mg, 21%), and a diastereomeric mixture of **12** (112 mg, 25%, *cis/trans* ratio 31/69).

cis-**12**: ^1H NMR: 3.02 (1H, dd, $J = 10.9, 18.3$), 3.23 (1H, dd, $J = 7.5, 18.3$), 3.42 (1H, dd, $J = 6.3, 18.3$), 3.57 (1H, ddd, $J = 9.7, 9.7, 18.3$), 3.73 (1H, m), 3.80 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 3.93 (6H, s), 3.94 (3H, s), 4.39 (1H, dd, $J = 8.6, 13.2$), 4.89 (1H, dd, $J = 6.3, 10.9$), 4.95 (1H, d, $J = 13.2$), 5.06 (1H, d, $J = 15.5$), 5.24 (1H, d, $J = 15.5$), 5.48 (1H, d, $J = 13.2$), 6.72 (1H, s), 6.73 (1H, s), 6.77 (1H, s), 6.81 (1H, s), 6.88 (1H, d, $J = 8.6$), 7.11 (1H, d, $J = 8.6$), 7.32 (1H, s).

trans-12: ^1H NMR: 3.25 (1H, dd, $J = 12.0, 18.0$), 3.36 (1H, dd, $J = 6.3, 18.0$), 3.51 (1H, m), 3.63 (1H, dd, $J = 6.9, 13.2$), 3.75 (3H, s), 3.84 (3H, s), 3.892 (3H, s), 3.894 (3H, s), 3.91 (3H, s), 3.92 (3H, s), 3.98 (1H, d, $J = 14.0$), 4.02 (1H, d, $J = 14.0$), 4.03 (1H, d, $J = 15.5$), 4.27 (1H, dd, $J = 6.3, 18.0$), 4.75 (1H, ddd, $J = 6.3, 13.2, 13.2$), 5.53 (1H, d, $J = 15.5$), 5.97 (1H, dd, $J = 6.3, 12.0$), 6.41 (1H, d, $J = 1.7$), 6.58 (1H, s), 6.83 (1H, s), 6.86-6.89 (2H, m), 6.91 (1H, d, $J = 8.0$), 7.12 (1H, s).

Stevens rearrangement of *cis*-12

A solution of NaH (49.6 mg, 1.24 mmol) in DMSO (1.67 mL, 21.7 mmol) was stirred for 90 min at 80 °C under argon. Once the dimethyl sodium was formed, *cis*-12 (58 mg, 0.1 mmol) was added and the mixture was stirred for 23 h at room temperature. The reaction mixture was poured onto ice. The precipitate was filtered off, and the filtrate was extracted from CHCl_3 . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The crude product was purified by silica-gel chromatography (hexane/AcOEt 1/1) to give **3** (5.1 mg, 10%), *epi*-**3** (1.5 mg, 3%), and **13** (4.0 mg, 8%).

3: ^1H 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}C NMR: 29.4 (CH_2), 33.6 (CH_2), 40.2 (CH_2), 46.8 (CH_2), 50.8 (CH), 55.4 (CH_3), 55.7 ($\text{CH}_3 \times 2$), 55.79 (CH_3), 55.88 (CH_3), 55.94 (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.

epi-**3:** ^1H NMR: 2.47 (1H, dd, $J = 11.0, 14.6$), 2.63-2.69 (2H, m), 2.96 (1H, dd, $J = 2.4, 14.6$), 3.05-3.16 (3H, m), 3.41 (1H, m), 3.65-3.67 (4H, m), 3.75 (3H, s), 3.81 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 3.88 (3H, s), 3.99 (1H, dd, $J = 4.3, 4.6$), 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}C NMR: 30.1 (CH_2), 36.7 (CH_2), 42.7 (CH_2), 48.8 (CH_2), 55.6 (CH_3), 55.8 (CH_3), 55.8 (CH_3), 55.9 ($\text{CH}_3 \times 2$), 56.0 (CH_3), 58.5 (CH), 65.4 (CH), 108.9 (CH), 110.1 (CH), 110.6 (CH), 110.9 (CH), 111.4 (CH), 113.4 (CH), 122.4 (CH), 127.3 (C), 128.6 (C), 129.6 (C), 130.7 (C), 131.5 (C), 147.1 ($\text{C} \times 2$), 147.2 (C), 147.3 (C), 147.5 (C), 148.1 (C). IR: 2932, 1612, 1512. MS (FAB) m/z : 506 $[\text{M}+\text{H}]^+$, 354, 192, 149. HRMS-FAB m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{36}\text{NO}_6$: 506.2543. Found: 506.2558.

13: ^1H NMR: 2.90 (dd, 1H, $J = 4.0, 16.6$), 2.94 (d, 1H, $J = 13.2$), 3.14 (dd, 1H, $J = 10.3, 16.6$), 3.39 (d, 1H, $J = 15.5$), 3.78-4.00 (m, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 5.24 (d, 1H, $J = 10.9$), 5.57 (d, 1H, $J = 17.8$), 6.48 (s, 1H), 6.57 (s, 1H), 6.79 (d, 1H, $J = 8.6$), 6.85 (d, 1H, $J = 8.6$), 6.86 (s, 1H), 7.04 (s, 1H), 7.12 (s, 1H), 7.35 (dd, 1H, $J = 10.9, 17.8$). ^{13}C NMR: 36.8

(CH₂), 55.78 (CH₃), 55.87 (CH₃ × 2), 55.90 (CH₃ × 2), 55.94 (CH₃), 58.8 (CH₂), 61.3 (CH), 108.8 (CH), 109.3 (CH), 110.4 (CH), 110.6 (CH), 110.8 (CH), 111.8 (CH), 113.9 (CH₂), 120.7 (CH) 126.1 (C), 126.4 (C), 129.3 (C), 131.8 (C), 133.2 (C), 134.3 (CH), 147.4 (C), 147.6 (C), 147.9 (C), 148.9 (C), 149.2 (C). IR: 3002, 2925, 2851, 1605, 1509, 1463. HRMS-ESI *m/z*: [M+Na]⁺ calcd for C₃₀H₃₅NNaO₆, 528.2362; found, 528.2340.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carbaldehyde (**18**)

To the suspension of **2**•HCl (1.9 g, 5.0 mmol) and K₂CO₃ (2.1 g, 150 mmol) in EtOH (20 mL) was added HCO₂Et (30 mL), and the mixture was reflux for 40 h. The mixture was concentrated, and the residue was recrystallized from EtOH to give **18** (1.70 g, 94%) as colorless needles of mp 133.0-134.0 °C.

18: ¹H NMR (the ratio of rotamer is 60/40): 2.61 (0.4H, m), 2.70 (0.6H, m), 2.78-2.93 (1.0H, m), 2.97-3.17 (2.6H, m), 3.27 (0.4H, ddd, *J* = 4.0, 11.5, 13.2), 3.56 (0.4H, ddd, *J* = 2.3, 6.3, 13.5), 3.69 (1.2H, s), 3.77 (1.2H, s), 3.843 (1.2H, s), 3.848 (1.2H, s), 3.857 (3.6H, s), 3.865 (1.8H, s), 3.88 (1.8H, s), 4.48 (0.6H, ddd, *J* = 1.8, 6.3, 13.2), 4.58 (0.6H, dd, *J* = 5.2, 9.2), 5.52 (0.4H, t, *J* = 6.3), 6.33 (0.4H, s), 6.55 (0.4H, s), 6.57 (0.6H, s), 6.58-6.61 (1.4H, m), 6.63 (0.6H, s), 6.66 (0.6H, dd, *J* = 8.0, 1.7), 6.74 (0.4H, d, *J* = 8.6), 6.82 (0.6H, d, *J* = 8.0), 7.71 (0.6H, s), 8.14 (0.4H, s). ¹³C NMR: 27.8 (CH₂), 29.2 (CH₂), 34.2 (CH₂), 41.0 (CH₂), 41.6 (CH₂), 43.2 (CH₂), 52.1 (CH), 55.89 (CH₃), 55.93 (CH₃), 55.97 (CH₃), 56.03 (CH₃), 56.07 (CH₃), 53.11 (CH₃), 53.17 (CH₃), 56.21 (CH₃), 59.1 (CH), 110.0 (CH), 110.4 (CH), 111.0 (CH), 111.3 (CH), 111.5 (CH), 111.7 (CH), 112.5 (CH), 112.9 (CH), 121.9 (CH), 122.1 (CH), 125.5 (C), 126.3 (C), 127.1 (C), 127.4 (C), 129.7 (C), 130.0 (C), 147.4 (C), 147.6 (C), 147.9 (C), 148.0 (C), 148.2 (C), 148.4 (C), 148.7 (C), 149.2 (C), 161.40 (CH), 161.44 (CH). IR: 1666, 1515. HRMS-ESI *m/s*: [M+Na]⁺ calcd for C₂₁H₂₅NNaO₅, 394.1630; found, 394.1621.

2,3,10,11-Tetramethoxy-5,6,13,13a-tetrahydroisoquinolino[3,2-*a*]isoquinolin-7-ium chloride (**16**)

To a suspension of **18** (1.70 g, 4.6 mmol) in MeCN (15 mL) was added POCl₃ (0.84 mL, 9 mmol), and the mixture was refluxed for 2 h. After cooled to room temperature, THF (20 mL) was added. The precipitate was collected by filtration to give **16** (1.80 g, quant) as a pale yellow solid.

16: ¹H NMR (CDCl₃): 3.03 (1H, d, *J* = 16.9), 3.10 (1H, dd, *J* = 16.9, 16.9), 3.26 (1H, m), 3.51 (1H, dd, *J* = 5.7, 16.9), 3.91 (3H, s), 3.92 (3H, s), 3.98 (3H, s), 4.04 (3H, s), 4.05 (1H, m), 4.80 (1H, d, *J* = 13.2), 5.19 (1H, dd, *J* = 5.7, 16.9), 6.74 (1H, s), 6.75 (1H, s), 6.93 (1H, s), 7.72 (1H, s), 9.83 (1H, br s). ¹³C NMR (DMSO-*d*₆): 27.9 (CH₂), 33.6 (CH₂), 54.5 (CH₂), 55.6 (CH₃), 55.8 (CH₃), 56.1 (CH₃), 56.5 (CH₃), 57.1 (CH), 109.6 (CH), 111.3 (CH), 111.6 (CH), 114.8 (CH), 117.2 (C), 124.5 (C), 125.1 (C), 134.6 (C), 148.05 (C), 148.16 (C), 148.22 (C), 156.5 (C), 165.0 (CH). IR (KBr): 1647, 1607, 1567, 1523, 1511, 1456. HRMS-ESI *m/s*: [M-Cl]⁺ calcd for C₂₁H₂₄NO₄, 354.1700; found, 354.1693.

Addition reaction of benzyl Grignard reagent to tetracyclic iminium 16

To the suspension of iminium **16** (206 mg, 0.53 mmol) in THF (5 mL) was added BnMgBr (0.5 M solution in THF, 1.8 mL, 0.9 mmol) at 0 °C, and the mixture was stirred for 1 h at 0 °C. To the mixture was added saturated aqueous NaHCO₃ (5 mL), and the whole was extracted with AcOEt (3 x 10 mL). The combined organic layers were dried over Na₂SO₄. Concentration and column chromatography (hexane/AcOEt 1/1) gave *trans*-**17** (138 mg, 58%) as a yellow solid and *cis*-**17** (97 mg, 41%) as a yellow solid.

trans-**17**: ¹H NMR: 2.81-2.93 (5H, m), 3.01 (1H, dd, *J* = 5.2, 16.6), 3.06 (1H, m), 3.33 (1H, dd, *J* = 5.7, 13.2), 3.47 (3H, s), 3.82 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 3.98 (1H, dd, *J* = 5.2, 8.6), 4.42 (1H, dd, *J* = 4.6, 11.5), 5.83 (1H, s), 6.57 (1H, s), 6.62 (1H, s), 6.70 (1H, s), 7.13 (2H, d, *J* = 7.5), 7.20 (1H, t, *J* = 7.5), 7.27 (2H, t, *J* = 7.5). ¹³C NMR: 29.6 (CH₂), 34.1 (CH₂), 40.5 (CH₂), 47.2 (CH₂), 51.1 (CH), 55.4 (CH₃), 55.9 (CH₃), 56.0 (CH₃), 56.1 (CH₃), 66.8 (CH), 109.4 (CH), 110.9 (CH), 111.1 (CH), 111.7 (CH), 125.3 (C), 126.1 (CH), 126.4 (C), 128.3 (CH), 129.1 (C), 130.1 (CH), 131.3 (C), 140.3 (C), 146.2 (C), 147.4 (C), 147.4 (C), 147.6 (C). IR: 1610, 1511. HRMS-ESI *m/z*: [M+H]⁺ calcd for C₂₈H₃₂N₁O₄, 446.2331; found, 446.2336.

cis-**17**: ¹H NMR: 2.56 (1H, dd, *J* = 11.9, 14.2), 2.64-2.69 (2H, m), 3.00 (1H, dd, *J* = 2.3, 15.2), 3.04 (1H, dd, *J* = 6.9, 14.2), 3.09-3.21 (2H, m), 3.40 (1H, m), 3.66 (3H, s), 3.68 (1H, m), 3.86 (3H, m), 3.867 (3H, s), 3.871 (3H, s), 4.01 (1H, m), 6.37 (1H, s), 6.59 (1H, s), 6.63 (1H, s), 6.74 (1H, s), 7.07 (2H, d, *J* = 7.4), 7.11-7.18 (3H, m). ¹³C NMR: 30.2 (CH₂), 36.8 (CH₂), 43.7 (CH₂), 49.0 (CH₂), 55.8 (CH₃), 55.9 (CH₃), 56.0 (CH₃), 56.2 (CH₃), 58.8 (CH), 65.7 (CH), 108.9 (CH), 110.0 (CH), 110.9 (CH), 111.5 (CH), 126.0 (CH), 127.4 (C), 127.9 (CH), 128.2 (C), 129.6 (C), 130.2 (CH), 130.6 (C), 139.3 (C), 147.0 (C), 147.1 (C), 147.3 (C), 147.5 (C). IR: 1610, 1512. HRMS-ESI *m/z*: [M+H]⁺ calcd for C₂₈H₃₂N₁O₄, 446.2331; found, 446.2325.

Addition reaction of 4-methoxybenzylzinc chloride to tetracyclic iminium 16

To the suspension of iminium **16** (130 mg, 0.33 mmol) in THF (4 mL) was added 4-methoxybenzylzinc chloride (0.5 M solution in THF, 2.0 mL, 1.0 mmol) at room temperature. The mixture was stirred for 12 h at 50 °C, and then quenched with 10% HCl (1 mL). The mixture was basified with saturated aqueous NaHCO₃ (15 mL) and was extracted with AcOEt (3 x 10 mL). The combined organic layers were dried over Na₂SO₄. Concentration and column chromatography (hexane/AcOEt 1/1) gave *trans*-**19** (113 mg, 72%) as a yellow solid.

trans-**19**: ¹H NMR: 2.78-2.91 (5H, m), 3.00 (1H, dd, *J* = 5.2, 16.6), 3.09 (1H, m), 3.26 (1H, *J* = 5.2, 13.2), 3.53 (3H, s), 3.79 (3H, s), 3.83 (3H, s), 3.87 (3H, s), 3.90-3.93 (4H, m), 4.41 (1H, dd, *J* = 5.2, 11.5), 5.90 (1H, s), 6.58 (1H, s), 6.63 (1H, s), 6.70 (1H, s), 6.82 (2H, d, *J* = 8.8), 7.05 (2H, d, *J* = 8.8). ¹³C NMR:

29.4 (CH₂), 33.8 (CH₂), 39.5 (CH₂), 46.9 (CH₂), 50.8 (CH), 53.3(CH₃), 54.8 (CH₃), 55.0 (CH₃), 55.6 (CH₃), 57.6 (CH₃), 66.7 (CH), 109.2 (CH), 110.8 (CH), 110.9 (CH), 111.5 (CH), 113.5 (CH), 125.1 (C), 126.2 (C), 128.9 (C), 130.8 (CH), 131.2 (C), 132.1 (C), 146.0 (C), 147.2 (C), 147.4 (C), 157.9 (C). IR: 1610, 1511. HRMS-ESI *m/z*: [M+H]⁺ calcd for C₂₉H₃₄N₁O₅, 476.2437; found, 476.2433.

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REFERENCES AND NOTES

1. a) M. A. Matulenko and A. I. Meyers, *J. Org. Chem.*, 1996, **61**, 573; (b) S. Gadhiya, S. Madapa, T. Kurtzman, I. L. Alberts, S. Ramsey, N.-K. Pillarsetty, T. Kalidindi, and W. W. Harding, *Bioorg. Med. Chem.*, 2016, **24**, 2060.
2. H. Shimoda, N. Nishida, K. Ninomiya, H. Matsuda, and M. Yoshikawa, *Heterocycles*, 2001, **55**, 2043.
3. J. Kobayashi, K. Kondo, H. Shigemori, M. Ishibashi, T. Sasaki, and Y. Mikami, *J. Org. Chem.*, 1992, **57**, 6680.
4. Q. Xu and M. Lin, *J. Nat. Prod.*, 1999, **62**, 1025.
5. Y. Yamamoto, Y. Tabuchi, A. Baba, K. Hideshima, M. Nakano, A. Miyawaki, and K. Tomioka, *Heterocycles*, 2014, **88**, 1311.
6. J. Kayhan, M. J. Wanner, S. Ingemann, J. H. van Maarseveen, and H. Hiemstra, *Eur. J. Org. Chem.*, 2016, 3705.
7. A. Pouihes, P. J. Baltaze, and C. Kouklovsky, *Synlett*, 2013, 1805.
8. (a) M. Valpuesta, A. Diaz, R. Suau, and G. Torres, *Eur. J. Org. Chem.*, 2004, 4313; (b) M. Valpuesta, A. Diaz, R. Suau, and G. Torres, *Eur. J. Org. Chem.*, 2006, 964; (c) M. Valpuesta, M. Ariza, A. Diaz, G. Torres, and R. Suau, *Eur. J. Org. Chem.*, 2010, 638.
9. Norlaudanosine **2** was prepared from homoveratrylamine and homoveratric acid as shown in Scheme 1. See ref. 5.
10. L. H. Bluhm and T. Li, *Tetrahedron Lett.*, 1998, **38**, 3623.
11. *Trans/cis* of *N*-benzylammonium salt **12** represents the relative configuration of H14 and *N*-benzyl group as shown in ref. 8a.
12. 8-Benzyltetrahydroprotoberberines showing a *cis*-relationship of H8 and H14 were also isolated from natural products, and therefore the hydride reduction of tetracyclic iminium such as **3** was useful for the synthesis of these alkaloids. (a) L. M. X. Lopes, *Phytochemistry*, 1992, **31**, 4005; (b) L. M. X. Lopes and E. Humpfer, *Phytochemistry*, 1997, **58**, 431.

13. (a) Y. Matsumura, K. Maruoka, and H. Yamamoto, [Tetrahedron Lett.](#), 1982, **23**, 1929; (b) G. Bringmann, R. Weirich, H. Reuscher, J. R. Jamen, L. Kinzinger, and T. Ortmann, *Liebigs Ann. Chem.*, 1993, 877.
14. Similar stereochemical pathway was proposed in an addition reaction of Grignard reagents to nitron of dihydroisoquinoline. J. Flores-Ferrándiz, N. Carter, M. J. González-Soria, M. Wasinska, D. Gill, B. Maciá, and V. Caprio, [Org. Biomol. Chem.](#), 2018, **16**, 6961.
15. *Trans/cis* of **17** and **18** represents the relative configuration of H8 and H14.
16. D. Mujahidin and S. Doye, [Eur. J. Org. Chem.](#), 2005, 2689.