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STEREOSELECTIVE SYNTHESIS OF DIASTEREOMERIC BERBERINE ALKALOIDS, *O*-METHYLCORYTENCHIRINE AND CORALYDINE

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This paper is dedicated to Prof. Yasuyuki Kita on the occasion of his 77th birthday.

Abstract – Racemic total synthesis of diastereomeric berberine alkaloids, *O*-methylcorytenchirine and coralydine, was achieved from the common isoquinoline intermediate of norlaudanosine. The relative stereochemistry of C8-C14 was successfully constructed by favorable axial attack of nucleophiles to the iminium of dihydroprotoberberines.

INTRODUCTION

Berberines are a class of isoquinoline alkaloids containing two aromatic rings and quinolizidine skeletons (Figure 1). These alkaloids have a wide range of biological activities;[1] for example, javaberine (**1**) inhibits lipopolysaccharide-induced tumor necrosis factor-α and nitric oxide production[2] and theoneberine (**2**) exhibits antimicrobial activity against Gram-positive bacteria.[3] Recent studies revealed that C8-substituted berberines have I_{Kr} potassium channel blocking activity[4] and antimicrobial activity.[5]

Corytenchirine (*trans*-**3a**), 8-methyl substituted protoberberine in an H8-H14 *trans* relationship, was first isolated from *corydalis ochotensis* by Kametani and co-workers.[6] Coralydine (*cis*-**3b**)[7] is an H8-H14 *cis* diastereomer of *O*-methylcorytenchirine (*trans*-**3b**), and these compounds were reported to exhibit inhibitory activity against human cytochrome P450.[8] Many research groups have accomplished the total synthesis of *O*-methylcorytenchirine (*trans*-**3b**)[9] and coralydine (*cis*-**3b**),[10] but few have reported the stereoselective synthesis of *both* diastereomeric protoberberines *trans*/*cis*-**3b** from a *common* synthetic intermediate.[11] The most straightforward synthesis of **3b** was a Pictet-Spengler cyclization of norlaudanosine (**6**) with acetaldehyde reported by Kouklovsky, but the reaction was not stereoselective (Scheme 1).[12]

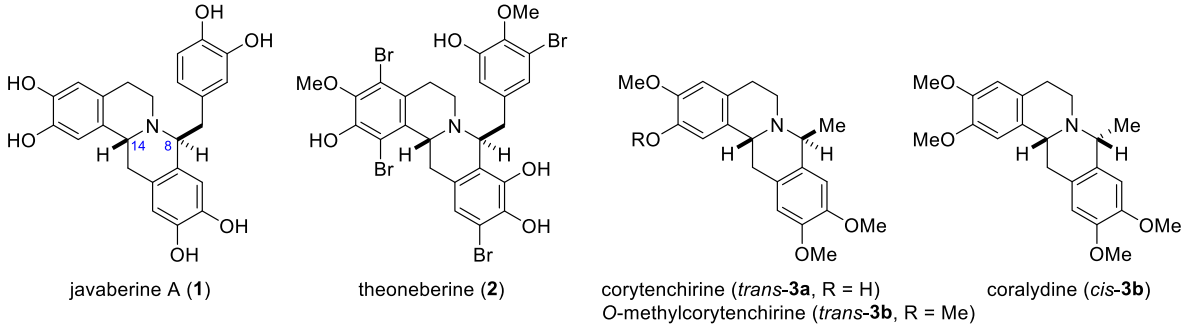
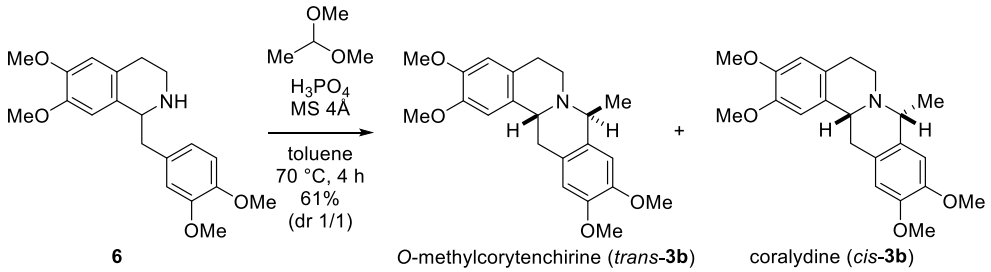
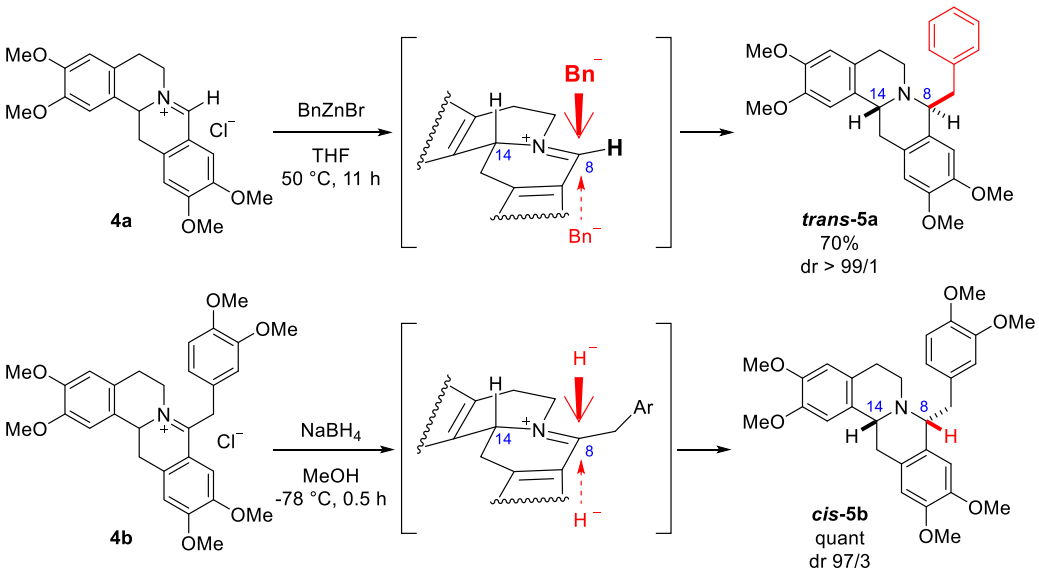


Figure 1. C8-Substituted tetrahydroprotoberberine alkaloids



Scheme 1. Pictet-Spengler cyclization of **6** reported by Kouklovsky's group



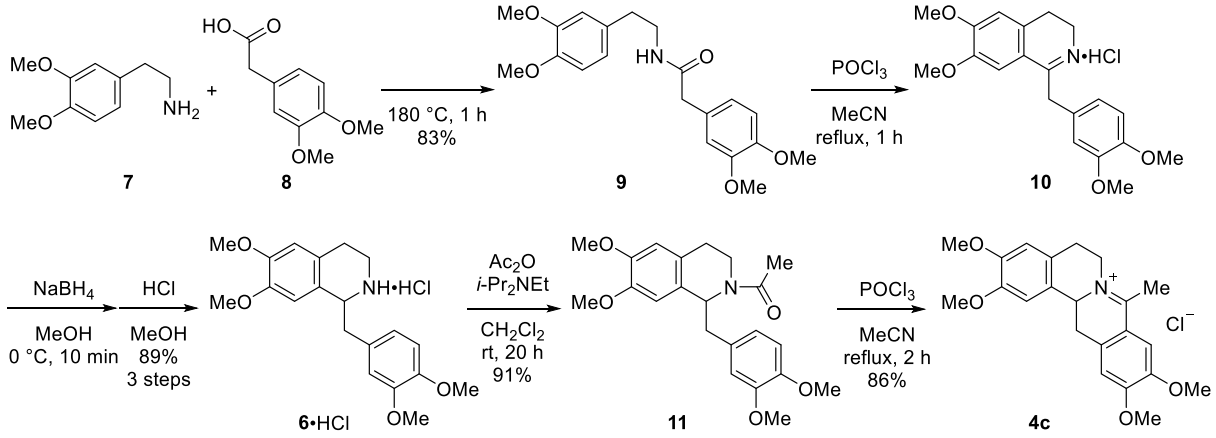
Scheme 2. Our previous study of stereoselective construction of C8-benzyl group of protoberberines

We previously reported stereoselective construction of the C8-benzyl group of tetrahydroprotoberberine based on nucleophilic axial attack of an iminium of dihydroprotoberberines.[13] The addition of benzylzinc halide to the iminium **4a** afforded H8-H14 *trans* 8-benzylprotoberberine *trans*-**5a** with excellent stereoselectivity (Scheme 2). On the other hand, H8-H14 *cis* 8-benzylprotoberberine *cis*-**5b** was synthesized by hydride reduction of iminium **4b**.[13,14] In these reactions, nucleophiles of the benzyl

group or hydride approached from the same side of the H14 of iminiums **4a** and **4b**, which were available from the *common* tetrahydroisoquinoline norlaudanosine (**6**). To verify our synthetic strategy of C8-substituted protoberberines, herein we report racemic total synthesis of diastereomeric alkaloids coralydine (*cis*-**3b**) and *O*-methylcorytenchirine (*trans*-**3b**) from norlaudanosine (**6**).

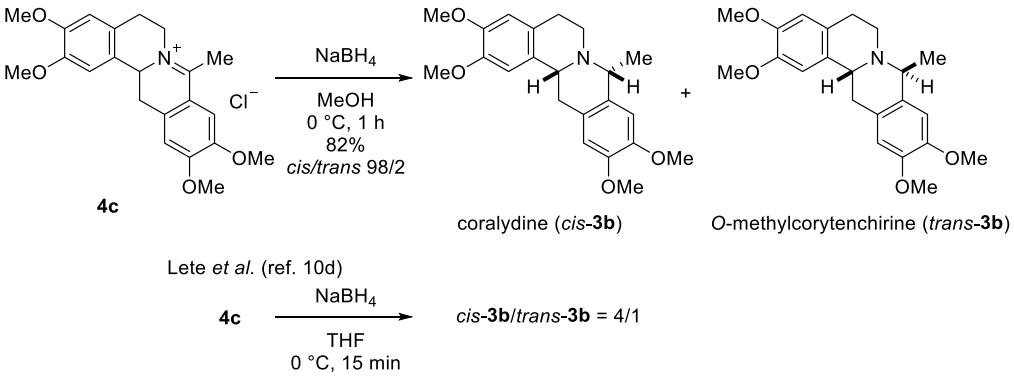
RESULTS AND DISCUSSION

We first examined the synthesis of coralydine (*cis*-**3b**). The *common* intermediate of norlaudanosine (**6**) was easily synthesized from commercially available homoveratrylamine (**7**) and homoveratric acid (**8**) in 3 steps: amidation, Bischler-Napieralski cyclization, and $NaBH_4$ reduction.[14] Next, norlaudanosine hydrochloride (**6**•HCl) was treated with acetic anhydride to give acetamide **11** in 91% yield, and the subsequent Bischler-Napieralski cyclization afforded iminium **4c** in 86% yield (Scheme 3). It is noteworthy that these reactions did not require any column chromatography to purify the products **9**, **6**, **11**, and **4c**.



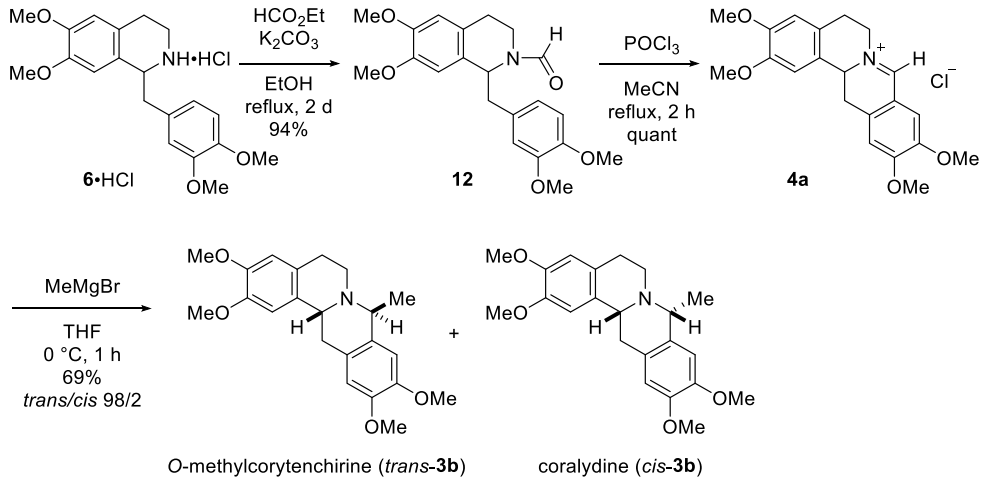
Scheme 3. Preparation of iminium **4c**

Reduction of iminium **4c** was previously examined by Lete's group using $NaBH_4$ in THF to give a diastereomeric mixture of coralydine (*cis*-**3b**) and *O*-methylcorytenchirine (*trans*-**3b**) with 4/1 dr.[10d] Although the diastereoselectivity was moderate under their reaction conditions, the stereoselectivity had room for improvement. In our previous report, we observed excellent diastereoselectivity (dr 97/3) for the reduction of benzyliminium **4b** with $NaBH_4$ in MeOH (Scheme 2).[14,15] Solvent choice was also important in the reduction of **4c**; thus, treatment of iminium **4c** with $NaBH_4$ in MeOH afforded coralydine (*cis*-**3b**) and *O*-methylcorytenchirine (*trans*-**3b**) with excellent 98/2 dr in 82% yield (Scheme 4).[16]



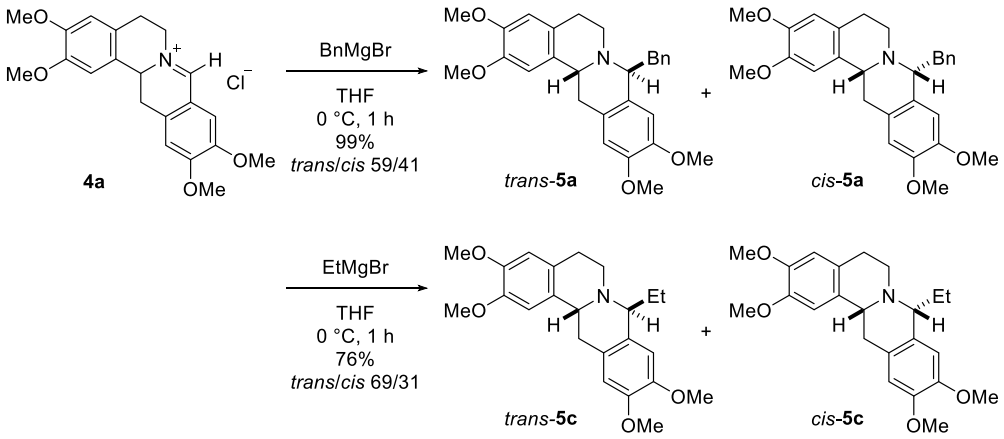
Scheme 4. Diastereoselective synthesis of coralydine (*cis*-**3b**)

Next, we examined the diastereoselective synthesis of *O*-methylcorytenchirine (*trans*-**3b**). As we previously reported, iminium **4a** was prepared from norlaudanosine (**6**) by formylation and Bischler-Napieralski cyclization.[13] We found that the addition of MeMgBr to iminium **4a** was highly stereoselective to give *O*-methylcorytenchirine (*trans*-**3b**) and coralydine (*cis*-**3b**) with excellent 98/2 dr in 69% yield (Scheme 5).



Scheme 5. Diastereoselective synthesis of *O*-methylcorytenchirine (*trans*-**3b**)

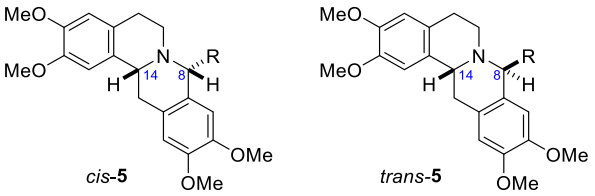
We also examined other Grignard reagents for the addition reaction to iminium **4a**. The addition of BnMgBr to iminium **4a** afforded a diastereomeric mixture of *trans*- and *cis*-**5a** with 59/41 dr in 99% yield. On the other hand, the reaction of EtMgBr was more stereoselective to give *trans*- and *cis*-**5c** with 69/31 dr in 76% yield (Scheme 6).

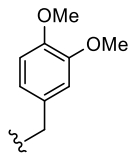


Scheme 6. Diastereoselectivity in the addition of Grignard reagents to iminium **4a**

The relative stereochemistry of C8-substituted protoberberines **5** was determined on the basis of the characteristic NMR chemical shifts of H14 and C14 (Table 1). We previously determined the relative configuration of *trans*- and *cis*-**5b** by NOE experiments, and found that H14 of *cis*-**5b** (3.65 ppm) appeared at a higher field than that of *trans*-**5b** (4.39 ppm). In addition, the C14 of *cis*-**5b** (58.5 ppm) appeared at lower field than that of *trans*-**5b** (50.8 ppm).[14,17] This tendency was also observed for *O*-methylcorytenchirine (*trans*-**3b**) and coralydine (*cis*-**3b**). On the basis of this criterion, the major isomers of **5a** and **5c** in Scheme 6 were assigned to the trans configuration.

Table 1. H14 and C14 NMR chemical shifts of **3b** and **5a-c**.



compound	R	*cis*-**5** H14 δ (ppm)	*cis*-**5** C14 δ (ppm)	*trans*-**5** H14 δ (ppm)	*trans*-**5** C14 δ (ppm)
5a	Bn	3.68	58.8	4.42	51.1
5b[a]		3.65	58.5	4.39	50.8
5c	Et	3.67	58.7	4.26	50.4
3b	Me	3.70	59.0	4.23	50.4

[a] See ref. 14.

It is likely that small nucleophiles such as hydride and methyl group prefer to approach from the same side of the H14 of iminium **4a** to show high diastereoselectivities (Scheme 4 and 5). In the case of bulky alkyl groups such as benzyl, alkylzinc halide would be useful toward realizing high stereoselectivity as we previously reported (Scheme 2).[13]

CONCLUSION

Racemic total synthesis of diastereomeric protoberberines of *O*-methylcorytenchirine (*trans*-**3b**) and coralydine (*cis*-**3b**) was achieved in a highly stereoselective manner from the *common* intermediate of norlaudanosine (**6**). Addition of nucleophiles to iminium of dihydroprotoberberines **4** is a very useful strategy for a stereoselective synthesis of C8-substituted protoberberines.

EXPERIMENTAL

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were measured in $CDCl_3$ unless otherwise mentioned. Chemical shift values were expressed in ppm relative to an internal reference of tetramethylsilane (0 ppm) in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. ^{13}C peak multiplicity assignments were made on the basis of DEPT data. IR spectroscopy of oil and solid samples was measured as neat liquid films and KBr pellets, respectively. Coupling constants were shown in Hertz. 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. Norlaudanosine (**6**) and iminium **4a** were synthesized as we previously reported.[13,14]

1-(1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (11)

To the suspension of **6**•HCl (3.8 g, 10 mmol) in CH_2Cl_2 (20 mL) were added *i*-Pr_2NEt (4.3 mL, 25 mmol) and Ac_2O (1.134 mL, 12 mmol) at 0 °C. The mixture was stirred for 20 h at room temperature, and then quenched with water (20 mL). The mixture was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration followed by recrystallization (hexane/AcOEt 20/27) gave **11** (3.51 g, 91%) as a colorless solid.

^{1}H NMR (rotamer ratio 55/45): 1.64 (1.35H, s), 2.15 (1.65H, s), 2.61 (0.55H, td, *J* = 4.6, 16), 2.68 (0.45H, ddd, *J* = 2.3, 4.1, 16.1), 2.78 (0.55H, ddd, *J* = 5.2, 9.2, 16.1), 2.89 (0.45H, ddd, *J* = 6.3, 12.1, 16.1), 2.95 (0.55H, dd, *J* = 8.0, 13.2), 2.99 (0.45H, dd, *J* = 5.2, 14.3), 3.06-3.16 (1.45H, m), 3.43 (0.55H, ddd, *J* = 4.6, 9.2, 13.2), 3.63 (2.2H, m), 3.78 (1.65H, s), 3.84, 3.85, 3.86, 3.87 (8.7H, s x 4), 4.75-4.80 (0.90, m), 5.62 (0.55H, dd, *J* = 5.2, 8.1), 6.21 (0.55H, s), 6.51 (0.45H, s), 6.55 (0.55H, dd, *J* = 2.0, 8.3), 6.58 (0.55H, s), 6.619 (0.55H, d, *J* = 2.0), 6.628 (0.45H, d, *J* = 2.0), 6.634 (0.45H, s), 6.70 (0.45H, dd, *J* = 2.0, 8.3), 6.72 (0.55H, d, *J* = 8.3), 6.83 (0.45H, d, *J* = 8.3). ^{13}C NMR: 21.1 (CH_3), 22.0 (CH_3), 27.8 (CH_2), 28.4 (CH_2),

34.9 (CH_2), 41.75 (CH_2), 41.80 (CH_2), 42.4 (CH_2), 54.0 (CH), 55.6 (CH_3), 55.7 (CH_3), 55.76 (CH_3 x 2), 55.81 (CH_3 x 2), 55.9 (CH_3), 56.0 (CH_3), 59.2 (CH), 110.0 (CH), 110.66 (CH), 110.69 (CH), 110.73 (CH), 111.3 (CH), 111.5 (CH), 112.6 (CH), 112.7 (CH), 121.6 (CH), 121.9 (CH), 125.6 (C), 126.6 (C), 127.8 (C), 128.2 (C), 130.1 (C), 130.6 (C), 146.9 (C), 147.2 (C), 147.50 (C), 147.54 (C), 147.99 (C), 148.03 (C), 148.5 (C), 148.9 (C), 169.3 (C), 169.6 (C). IR: 2937, 1634, 1519. EIMS *m/z*: 385 (M+). HRMS-ESI *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{27}NNaO_5$, 408.1787; found, 408.1773. Mp 101-107 °C.

2,3,10,11-Tetramethoxy-8-methyl-5,6,13,13a-tetrahydroisoquinolino[3,2-*a*]isoquinolin-7-ium chloride (4c)

To a suspension of **11** (1.77 g, 4.6 mmol) in MeCN (15 mL) was added $POCl_3$ (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 **4c** (1.59 g, 86%) as a yellow solid.

^{1}H NMR: 3.08 (3H, s), 3.10-3.14 (2H, m), 3.22 (1H, ddd, *J* = 4.0, 11.5, 16.1), 3.39 (1H, dd, *J* = 4.9, 16.9), 3.906 (3H, s), 3.913 (3H, s), 3.99 (3H, s), 4.02 (1H, m), 4.04 (3H, s), 4.68 (1H, dt, *J* = 13.2, 3.9), 5.25 (1H, m), 6.75 (1H, s), 6.80 (1H, s), 6.93 (1H, s), 7.39 (1H, s). ^{13}C NMR: 20.3 (CH_3), 28.6 (CH_2), 35.2 (CH_2), 50.4 (CH_2), 56.1 (CH_3), 56.5 (CH_3), 56.7 (CH_3), 56.9 (CH_3), 59.3 (CH), 109.2 (CH), 110.7 (CH), 111.0 (CH), 112.9 (CH), 120.2 (C), 124.1 (C), 125.6 (C), 134.0 (C), 148.8 (C x 2), 149.1 (C), 156.6 (C), 175.3 (C). IR: 2974, 1604, 1550, 1521. HRMS-DART *m/z*: $[M - Cl]^+$ calcd for $C_{22}H_{26}NO_4$, 368.1862; found, 368.1853.

Coralydine (*cis*-3b)[6b,10d]

Iminium **4c** (162 mg, 0.4 mmol) was dissolved in MeOH (2 mL), and $NaBH_4$ (121 mg, 3.2 mmol) was slowly added at 0 °C. The mixture was stirred for 1 h at 0 °C and then concentrated. To the mixture were added brine (1 mL), water (1.5 mL), and $CHCl_3$ (5 mL). The separated aqueous layer was extracted with $CHCl_3$ (2 x 5 mL). The combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt 1/1) gave a mixture of *cis*- and *trans*-**3b** (121 mg, 82%, *cis*/*trans* 98/2) as yellow needles of mp 142-144 °C. A part of a diastereomeric mixture of **3b** (*cis*/*trans* 98/2) was recrystallized from EtOH gave pure coralydine as white needles.

^{1}H NMR: 1.55 (3H, d, *J* = 6.3), 2.47 (1H, dt, *J* = 2.9, 11.5), 2.72 (1H, br d, *J* = 15.5), 2.87 (1H, dd, *J* = 11.5, 15.5), 3.08 (1H, ddd, *J* = 5.2, 11.5, 15.5), 3.13 (1H, dd, *J* = 2.9, 15.5), 3.39 (1H, ddd, *J* = 2.9, 5.2, 11.5), 3.70-3.73 (2H, m), 3.87 (3H, s), 3.88 (6H, s), 3.89 (3H, s), 6.23 (1H, s), 6.65 (1H, s), 6.69 (1H, s), 6.75 (1H, s). ^{13}C NMR: 22.0 (CH_3), 29.7 (CH_2), 36.6 (CH_2), 47.1 (CH_2), 55.8 (CH_3 x 2), 56.01 (CH_3), 56.03 (CH_3), 59.0 (CH), 59.3 (CH), 108.8 (CH), 109.5 (CH), 111.1 (CH), 111.2 (CH), 126.8 (C), 127.0

(C), 130.4 (C), 131.4 (C), 147.25 (C), 147.31 (C), 147.5 (C x 2). IR: 3002, 2935, 2834, 1607, 1514, 1465, 1256. HRMS-DART *m/z*: $[M + H]^+$ calcd for $C_{22}H_{28}NO_4$, 370.2018; found, 370.2019.

_O_–Methylcorytenchirine (*trans*-3b) [6b,9c,9d]

To the suspension of iminium **4a** (130 mg, 0.33 mmol) in THF (4 mL) was added MeMgBr (3.0 M solution in THF, 0.2 mL, 0.6 mmol) at 0 °C, and the mixture was stirred for 1 h at 0 °C. To the residue was added satd $NaHCO_3$ aq (5 mL) and the resulting mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt 1/1) gave a mixture of *trans*- and *cis*-**3b** (84 mg, 69%, *trans*/*cis* 98/2) as yellow solids.
^{1}H NMR: 1.40 (3H, d, *J* = 6.9), 2.75-3.06 (6H, m), 3.85 (3H, s), 3.87 (6H, s), 3.89 (3H, s), 4.12 (1H, m), 4.23 (1H, dd, *J* = 4.6, 11.5), 6.588 (1H, s), 6.594 (1H, s), 6.62 (1H, s), 6.70 (1H, s). ^{13}C NMR: 18.0 (CH_3), 29.6 (CH_2), 35.7 (CH_2), 47.2 (CH_2), 50.4 (CH), 55.8 (CH_3 x 2), 55.97 (CH_3), 56.00 (CH_3), 59.2 (CH), 109.2 (CH), 109.9 (CH), 111.2 (CH), 111.5 (CH), 125.4 (C), 126.6 (C), 130.9 (C), 132.0 (C), 147.33 (C), 147.36 (C), 147.39 (C), 147.5 (C). IR: 2962, 2933, 2833, 1611, 1515, 1464, 1258. HRMS-DART *m/z*: $[M + H]^+$ calcd for $C_{22}H_{28}NO_4$, 370.2018; found, 370.2006.

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

trans-**5a**: ^{1}H 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). ^{13}C NMR: 29.6 (CH_2), 34.1 (CH_2), 40.5 (CH_2), 47.2 (CH_2), 51.1 (CH), 55.4 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 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 $C_{28}H_{32}NO_4$, 446.2331; found, 446.2336.

cis-**5a**: ^{1}H 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). ^{13}C NMR: 30.2 (CH_2), 36.8 (CH_2), 43.7 (CH_2), 49.0 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 56.2 (CH_3), 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 $C_{28}H_{32}NO_4$, 446.2331; found, 446.2325.

8-Ethyl-2,3,10,11-tetramethoxy-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (5c)

trans-**5c**: ^{1}H NMR: 1.08 (3H, t, *J* = 7.5), 1.67 (1H, m), 1.85(1H, m), 1.83-1.86 (1H, m), 2.72-2.88 (4H, m), 3.00-3.10 (2H, m), 3.52 (1H, dd, *J* = 5.4, 8.3), 3.84 (3H, s), 3.866 (3H, s), 3.873 (3H, s), 3.88 (3H, s), 4.26 (1H, dd, *J* = 6.3, 10.9), 6.56 (1H, s), 6.61 (1H, s), 6.63 (2H, s). ^{13}C NMR: 12.5 (CH_3), 29.2 (CH_2), 29.7 (CH_2), 32.1 (CH_2), 46.7 (CH_2), 50.4 (CH), 55.9 (CH_3), 56.0 (CH_3), 56.08 (CH_3), 56.14 (CH_3), 66.7 (CH), 109.8 (CH), 110.7 (CH), 111.5 (CH), 111.9 (CH), 125.5 (C), 126.4 (C), 130.8 (C), 132.1 (C), 147.2 (C), 147.3 (C), 147.6 (C x 2). IR: 3017, 2928, 2855, 2833, 1610, 1516, 1464, 1261. HRMS-DART *m/z*: $[M + H]^+$ calcd for $C_{23}H_{30}NO_4$, 384.2175; found, 384.2164.

cis-**5c**: ^{1}H-NMR: 0.72 (3H, t, *J* = 7.5), 1.81 (1H, m), 2.12 (1H, m), 2.45 (1H, ddd, *J* = 2.9, 11.5, 11.5), 2.67 (1H, d, *J* = 15.5), 2.81 (1H, t, *J* = 11.5, 15.5), 3.02-3.09 (2H, m), 3.29 (1H, m), 3.67 (1H, d, *J* = 10.9), 3.76 (1H, m), 3.87 (6H, s), 3.890 (3H, s), 3.895 (3H, s), 6.63 (1H, s), 6.66 (1H, s), 6.67 (1H, s), 6.77 (1H, s). ^{13}C NMR: 7.9 (CH_3), 27.1 (CH_2), 30.1 (CH_2), 37.1 (CH_2), 47.4 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 56.2 (CH_3), 58.7 (CH), 63.9 (CH), 109.2 (CH), 109.5 (CH), 111.1 (CH), 111.5 (CH), 127.6 (C), 128.7 (C), 129.9 (C), 131.0 (C), 147.2 (C), 147.4 (C), 147.6 (C), 147.7 (C). IR: 2961, 2933, 2832, 2743, 1611, 1513, 1464, 1255. HRMS-DART *m/z*: $[M + H]^+$ calcd for $C_{23}H_{30}NO_4$, 384.2175; found, 384.2164.

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