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, for example, javaberine (1) inhibits lipopolysaccharide-induced tumor necrosis factor-α and nitric oxide production and theoneberine (2) exhibits antimicrobial activity against Gram-positive bacteria. Recent studies revealed that C8-substituted berberines have I{	extsubscript{Kr}} potassium channel blocking activity and antimicrobial activity. Corytenchirine (trans-3a), 8-methyl substituted protoberberine in an H8-H14 trans relationship, was first isolated from corydalis ochotensis by Kametani and co-workers. Coralydine (cis-3b) is an H8-H14 cis diastereomer of O-methylcorytenchirine (trans-3b), and these compounds were reported to exhibit inhibitory activity against human cytochrome P450. Many research groups have accomplished the total synthesis of O-methylcorytenchirine (trans-3b) and coralydine (cis-3b), but few have reported the stereoselective synthesis of both diastereomeric protoberberines trans/cis-3b from a common synthetic intermediate. The most straightforward synthesis of 3b was a Pictet-Spengler cyclization of norlaudanosine (6) with acetaldehyde reported by Koukovsky, but the reaction was not stereoselective (Scheme 1).
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.\textsuperscript{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.\textsuperscript{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 NaBH₄ reduction. 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.

Reduction of iminium 4c was previously examined by Lete’s group using NaBH₄ in THF to give a diastereomeric mixture of coralydine (cis-3b) and O-methylcorytenchirine (trans-3b) with 4/1 dr. 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 NaBH₄ in MeOH (Scheme 2). Solvent choice was also important in the reduction of 4c; thus, treatment of iminium 4c with NaBH₄ in MeOH afforded coralydine (cis-3b) and O-methylcorytenchirine (trans-3b) with excellent 98/2 dr in 82% yield (Scheme 4).
Next, we examined the diastereoselective synthesis of \(\text{O}-\text{methylcorytenchirine (} \text{trans-3b})\). As we previously reported, iminium 4a was prepared from norlaudanosine (6) by formylation and Bischler-Napieralski cyclization.\(^{13}\) We found that the addition of \(\text{MeMgBr}\) to iminium 4a was highly stereoselective to give \(\text{O}-\text{methylcorytenchirine (} \text{trans-3b})\) and \(\text{coralydine (} \text{cis-3b})\) with excellent 98/2 dr in 69% yield (Scheme 5).

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

<table>
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<tr>
<th>compound</th>
<th>R</th>
<th>cis-5 H14 δ (ppm)</th>
<th>cis-5 C14 δ (ppm)</th>
<th>trans-5 H14 δ (ppm)</th>
<th>trans-5 C14 δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Bn</td>
<td>3.68</td>
<td>58.8</td>
<td>4.42</td>
<td>51.1</td>
</tr>
<tr>
<td>5b(^{a})</td>
<td>OMe</td>
<td>3.65</td>
<td>58.5</td>
<td>4.39</td>
<td>50.8</td>
</tr>
<tr>
<td>5c</td>
<td>Et</td>
<td>3.67</td>
<td>58.7</td>
<td>4.26</td>
<td>50.4</td>
</tr>
<tr>
<td>3b</td>
<td>Me</td>
<td>3.70</td>
<td>59.0</td>
<td>4.23</td>
<td>50.4</td>
</tr>
</tbody>
</table>

\(^{a}\)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
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 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(1H)-yl)ethan-1-one (11)
To the suspension of 6•HCl (3.8 g, 10 mmol) in CH2Cl2 (20 mL) were added i-Pr2NEt (4.3 mL, 25 mmol) and Ac2O (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 CHCl3 (3 x 50 mL). The combined organic layers were washed with brine and dried over Na2SO4. Concentration followed by recrystallization (hexane/AcOEt 20/27) gave 11 (3.51 g, 91%) as a colorless solid.

1H 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), 3.40-3.6 (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), 6.65 (0.55H, s), 6.619 (0.55H, d, J = 2.0), 6.638 (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). 13C NMR: 21.1 (CH3), 22.0 (CH3), 27.8 (CH2), 28.4 (CH2), 822 HETEROCYCLES, Vol. 103, No. 2, 2021
34.9 (CH₂), 41.75 (CH₂), 41.80 (CH₂), 42.4 (CH₂), 54.0 (CH), 55.6 (CH₃), 55.7 (CH₃), 55.76 (CH₃ x 2), 55.81 (CH₃ x 2), 55.9 (CH₃), 56.0 (CH₃), 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 C22H27NNaO5, 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 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 4c (1.59 g, 86%) as a yellow solid.

1H 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). 13C NMR: 20.3 (CH₃), 28.6 (CH₂), 35.2 (CH₂), 50.4 (CH₂), 56.1 (CH₃), 56.5 (CH₃), 56.7 (CH₂), 56.9 (CH₃), 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 C22H26NO4, 368.1862; found, 368.1853.

Coralydine (cis-3b)₆₉,₁₀

Iminium 4c (162 mg, 0.4 mmol) was dissolved in MeOH (2 mL), and NaBH₄ (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 CHCl₃ (5 mL). The separated aqueous layer was extracted with CHCl₃ (2 x 5 mL). The combined organic layers were dried over Na₂SO₄. 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.

1H 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). 13C NMR: 22.0 (CH₃), 29.7 (CH₂), 36.6 (CH₂), 47.1 (CH₂), 55.8 (CH₃ x 2), 56.01 (CH₃), 56.03 (CH₃), 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)**

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\textsubscript{3} aq (5 mL) and the resulting mixture was extracted with CHCl\textsubscript{3} (3 x 10 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{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. 

**trans-5a:** 1H 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). 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.

**cis-5a:** 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 (1H, s), 3.68 (1H, m), 3.86 (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). IR: 1610, 1511. HRMS-ESI m/z: [M + H]+ calcd for C_{28}H_{32}NO_{4}, 446.2331; found, 446.2336.

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

trans-5a: 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). IR: 1610, 1511. HRMS-ESI m/z: [M + H]+ calcd for C_{28}H_{32}NO_{4}, 446.2331; found, 446.2336.

cis-5a: 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 (1H, s), 3.68 (1H, m), 3.86 (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). IR: 1610, 1511. HRMS-ESI m/z: [M + H]+ calcd for C_{28}H_{32}NO_{4}, 446.2331; found, 446.2335.

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8-Ethyl-2,3,10,11-tetramethoxy-5,8,13,13a-tetrahydro-6H-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), 3.86 (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 (1H, 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), 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, s), 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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REFERENCES AND NOTES


8. K. A. Salminen, A. Meyer, L. Jerabkova, L. E. Korhonen, M. Rahnasto, R. O. Juvonen, P. Imming,


16. Similar solvent effect was also observed in the reduction of 4b (Scheme 2). See ref. 13.

17. These differences would be derived from the conformation of B/C ring of berberine 5, namely quinolizidine moiety. See ref. 11a.