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Determination of the absolute configuration of picrasidine Y, a naturally occurring β-carboline alkaloid

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ABSTRACT

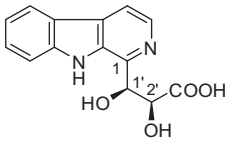
The absolute configuration of picrasidine Y, a β-carboline alkaloid isolated from *Picrasma quassioides* (Simaroubaceae), has not been determined. To determine the absolute configuration of picrasidine Y, we synthesized stereoisomers of picrasidine Y through 7-step chemical reactions using tartaric acid as a starting material. Moreover, we extended the scope of application of this synthetic method to canthin-5,6-dione compounds. The absolute configuration of natural picrasidine Y was elucidated based on comparisons of chemically synthesized isoforms with the naturally occurring compound in ^{1}H and ^{13}C NMR spectra, specific optical rotation, HPLC analysis with chiral columns, computational molecular simulation, and analysis with the CD exciton chirality method.

Picrasma quassioides and other plants in the *Picrasma* genus of the Simaroubaceae family are used as bitter stomachics for gastritis, loss of appetite, and indigestion in Chinese and Japanese traditional medicine. In addition to limonoids, a large number of β-carboline and canthinone alkaloids have been isolated from these plants.[1–19] Furthermore, these alkaloids have been reported to have a variety of biological activities, including PTP1B-inhibition, anti-inflammatory activity, cAMP-phosphodiesterase inhibition, and cytotoxicity.[6,14,17–19] Picrasidine Y (**1**) isolated from *P. quassioides* is a β-carboline alkaloid, and the absolute configuration of the propionic acid side chain at position 1 of the backbone structure has not been determined (Fig. 1).[16] In the present study, we synthesized stereoisomers of picrasidine Y through 7-step chemical reactions using tartaric acid as a starting material. We then determined the absolute configuration of natural picrasidine Y (**1**) by comparing chemically synthesized isoforms with the naturally occurring compound in ^{1}H and ^{13}C NMR spectra, specific optical rotation, HPLC analysis with chiral columns, computational molecular simulation, and analysis with the CD exciton chirality method.

Stereoisomers of picrasidine Y were synthesized from L-tartaric acid (2*R*,3*R*, **2a**), D-tartaric acid (2*S*,3*S*, **2b**), and *meso*-tartaric acid (**2c**) (Scheme 1). The synthetic methods for these compounds are explained using the one starting from L-tartaric acid (**2a**) as a representative.

L-tartaric acid (**2a**) was treated with acetic anhydride to yield the *O*-protected acid anhydride **3a** in one step, which was then converted to the half-ester **4a** with methanol. The carboxylic acid was converted to the acid chloride **5a** with thionyl chloride. The production of **5a** was monitored by ^{1}H NMR spectroscopy. Specifically, after the 2 h reaction, a broad signal at δ_H 9.84 and two doublet signals at δ_H 5.72 and 5.75 assignable, respectively, to the carboxylic acid and two methine protons in **4a** disappeared, and the new methine proton signals shifted to lower field (δ_H 5.83 and 5.91) were observed. Next, **5a** was allowed to react with bubbling hydrogen in the presence of 5% Pd-$BaSO_4$ in a xylene reflux to obtain aldehyde **6a** through the Rosenmund reduction. The structure of **6a** was confirmed by the appearance of a low-field signal at δ_H 9.45 for the aldehyde moiety in the ^{1}H NMR spectrum and the downfield shift of a carbonyl signal at δ_C 194.7 in the ^{13}C NMR spectrum.

Next, **6a** was treated with tryptamine in the presence of trifluoroacetic acid (TFA) to construct the β-carboline backbone through



Picrasidine Y (**1**)

Figure 1. Chemical structure of natural occurring picrasidine Y.

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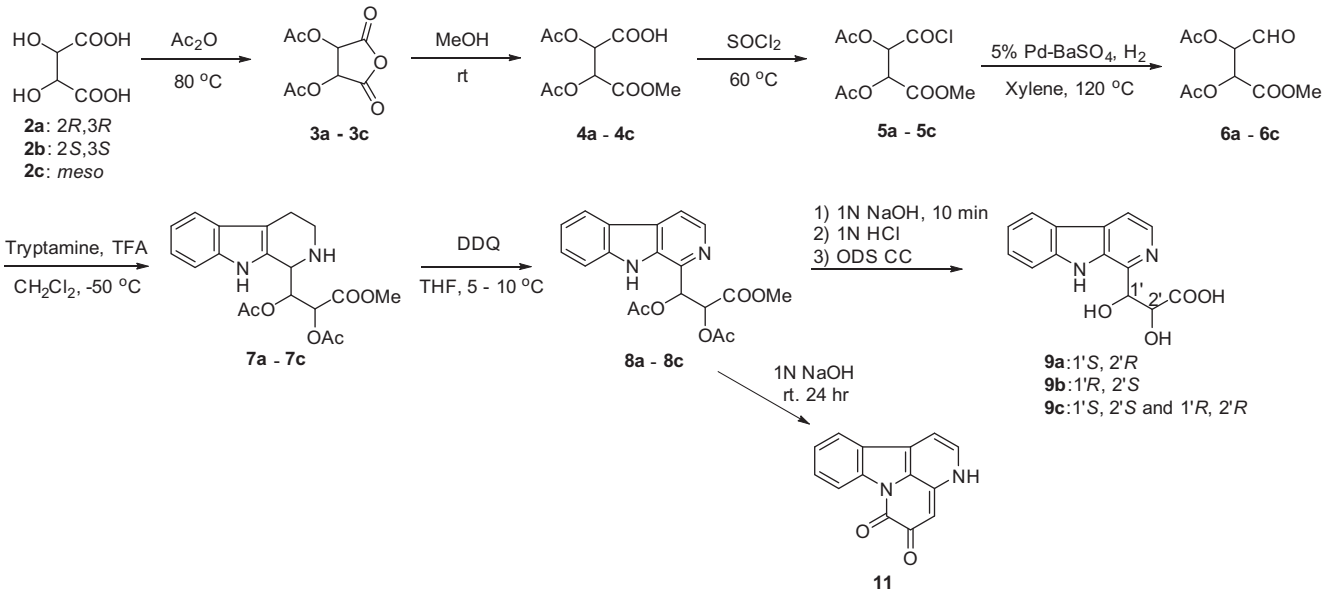

Scheme 1.

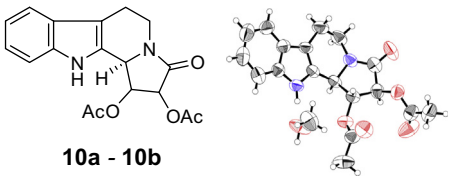

Figure 2. Chemical structure of **10a** and **10b**, and ORTEP structure of compound **10a**.

the Pictet–Spengler reaction. When this reaction was carried out at room temperature, the carbonyl part of the methyl ester group of **6a** reacted with the amino group at position 2 to release methanol and form an amide bond, and thereby compound **10a** containing a 5-membered ring was produced in a large amount (Fig. 2). However, when the reaction was carried out at −50 °C, the production of the by-product **10a** was suppressed and the desired 1,2,3,4-tetrahydro-β-carboline **7a** was obtained.

Compound **7a** was an epimer as a new chiral center was created at position 1 of β-carboline. DDQ oxidation of **7a** at or below 10 °C yielded compound **8a** containing the aromatized C ring. Finally, the deprotective deacetylation of compound **8a** yielded 1′*S*,2′*R*-picrasidine Y (**9a**).

It is worth noting that the compound **8a** was converted to a highly-fluorescent canthin-5,6-dione compound (**11**) by a 24 h agitation in MeOH at 50 °C or in 1 N NaOH at room temperature (Scheme 1). The mechanism underlying production of compound **11** presumably involves lactam ring formation through the indole NH and the carbonyl group, followed by dehydration to yield compound **11**. Canthin-5,6-dione derivatives represent a major group of alkaloids found in *P. quassioides* and have been reported to show the potent anticancer cytotoxicity and PTP1B inhibitory activity.[18,19] Using the synthetic method described here, it may be possible to synthesize chemical derivatives with longer alkyl chains or other substituting groups after constructing the canthin-5,6-dione backbone.

1′*R*,2′*S*-picrasidine Y (**9b**) and a mixture of enantiomers 1′*S*, 2′*S*- and 1′*R*,2′*R*-picrasidine Y (**9c**) were synthesized from *D*-tartaric acid (2*S*,3*S*, **2b**) and *meso*-tartaric acid (**2c**), respectively, with methods similar to those described above. ^{1}H and ^{13}C NMR data of optical isomers synthesized, **9a** (1′*S*,2′*R*), **9b** (1′*R*,2′*S*), and **9c** (1′*S*,2′*S* and 1′*R*,2′*R*) were compared with those of the natural picrasidine Y (**1**). The spectra of the natural picrasidine Y (**1**) were completely identical to those of **9c**, but were slightly different from those of **9a** (1′*S*,2′*R*) and **9b** (1′*R*,2′*S*). While the specific rotation for the natural compound was $[\alpha]_D^{25}$ -30°, the values for **9a** and **9b** were +104° and -104°, respectively, revealing large differences. The natural picrasidine Y (**1**) was also chromatographically compared with synthesized optical isomers **9a** (1′*S*,2′*R*), **9b** (1′*R*,2′*S*), and **9c** (1′*S*,2′*S* and 1′*R*,2′*R*) using chiral HPLC analysis (CHIRAL PAK AD-RH 0.46 × 15 cm, mobile phase CH_3CN/H_2O = 2:3, flow rate: 0.5 mL/min) (Fig. 3). The analytical peak of the natural compound **1** was similar in retention time (3.55 min) to one of the peaks detected for the racemic **9c** synthesized from *meso*-tartaric acid, but differed from **9a** and **9b**. These data indicate that the absolute configuration of picrasidine Y (**1**) is either 1′*S*,2′*S* or 1′*R*,2′*R* in **9c**, and have ruled out the possibility that **9a** or **9b** has the same configuration as **1**.

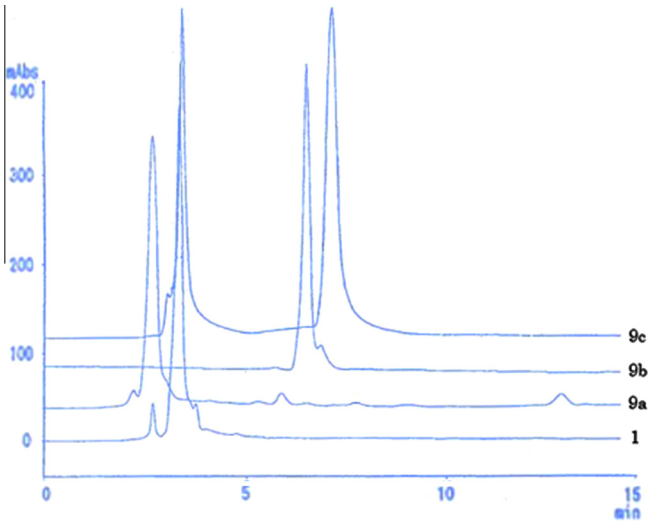

Figure 3. Chiral HPLC. HPLC chromatograms of natural and synthetic picrasidine Y. Daicell AD-RH 4.6 mm I.d × 150 mm, and an isocratic mode of 40% MeCN (aq) in 15 min was used with detection at 254 nm.

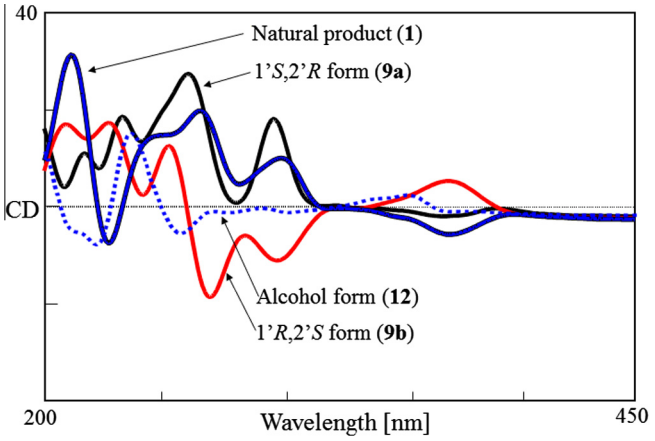

Figure 4. CD spectra of picrasidine Y (**1**) and synthetic compounds (1′*S*,2′*R* form (**9a**), 1′*R*,2′*S* form (**9b**), and alcohol form of **9a** (**12**)).

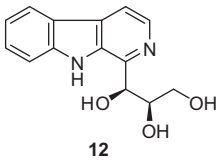

Figure 5. Chemical structure of **12**.

It is plausible that two chromophores of picrasidine Y, β-carboline backbone, and the carbonyl group, produce the Cotton effect via exciton interactions.[20] Therefore, the absolute configuration of picrasidine Y was finally determined by the CD exciton chirality method. Although picrasidine Y compounds showed a complex exciton-split Cotton effect, we focused on major transition moments at 370 nm and 290 nm (Fig. 4). For **9a** (1′*S*,2′*R*), a weak negative Cotton effect and a positive Cotton effect were observed at 370 nm and 290 nm, respectively. Compound **12** (Fig. 5), an alcohol obtained by reducing the carbonyl group of **9a** with $LiAlH_4$, showed no Cotton effect at 270–390 nm, suggesting that exciton interactions between the two chromophores of picrasidine Y compounds, the β-carboline backbone and carbonyl group, underlie the Cotton effect. In other words, the natural compound **1** and **9a** (1′*S*,2′*R*) showed negative chirality, whereas **9b** (1′*R*,2′*S*) showed positive chirality.

Conformation that could yield such chirality was examined by molecular computation with Discovery 4.1 software. For computation, a state satisfying small *J* values of positions 1′ and 2′ was estimated, when a hydrogen bond between the carbonyl group and the indole NH was taken into consideration. Namely, an angle of −67.8° gave the calculated $J_{1'H,\ 2'H}$ = 2.1 Hz by Karplus model for **9a** (1′*S*,2′*R*), an angle of +64.5° gave $J_{1'H,2'H}$ = 2.4 Hz for **9b** (1′*R*,2′*S*), an angle of −52.6° gave $J_{1'H,2'H}$ = 3.6 Hz for **9c** (1′*S*,2′*S*), and an angle of +52.8° gave $J_{1'H,2'H}$ = 3.6 Hz for **9c** (1′*R*,2′*R*).[21] These computed values do not contradict the observed values. These results suggest that a pseudo-octacyclic ring structure is formed by hydrogen bonding between the carbonyl group and the indole NH in a solution state, allowing protons at position 1′ and 2′ to be arranged in a gauche conformation and stabilized. Figure 6 recapitulates estimation of the torsion axis between two electric transition moments in the carbonyl group and the β-carboline backbone of the picrasidine Y compounds (four enantiomers). Specifically, it could be estimated that 1′*S*,2′*R* (**9a**) and 1′*S*,2′*S* show negative chirality, whereas 1′*R*,2′*S* (**9b**) and 1′*R*,2′*R*

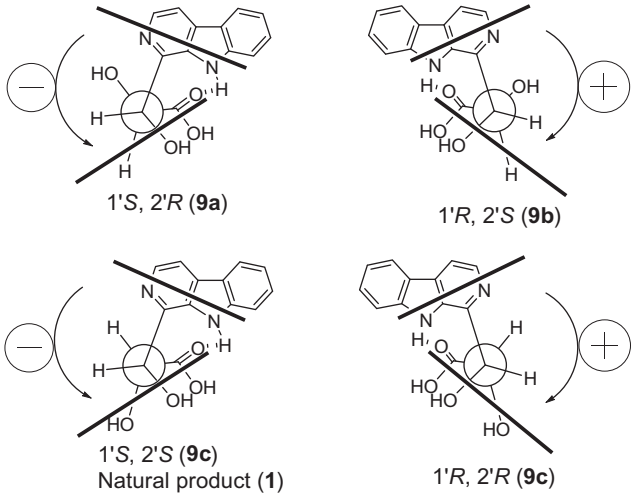

Figure 6. CD exciton chirality of picrasidine Y.

show positive chirality. By applying this estimated result to the natural compound **1**, the configuration of **1** was determined to be 1′*S*,2′*S*.

In summary, to determine the absolute configurations of picrasidine Y, enantiomers of picrasidine Y were successfully synthesized by constructing the β-carboline backbone from tryptamine and using enantiomers of tartaric acid as sources of the asymmetric carbon at position 1. Furthermore, the scope of application of this synthetic method was extended to canthin-5,6-dione compounds. In the meanwhile, the absolute configuration of the natural picrasidine Y was suggested to be either 1′*S*,2′*S* or 1′*R*,2′*R*, based on comparisons of ^1H and ^{13}C NMR spectral data and specific optical rotation values, and HPLC analysis using chiral columns. Finally, its absolute configuration was determined to be 1′*S*,2′*S* using molecular computational methods and the CD exciton chirality method.

Supplementary data

Supplementary data (experimental and spectroscopic data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.079.

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