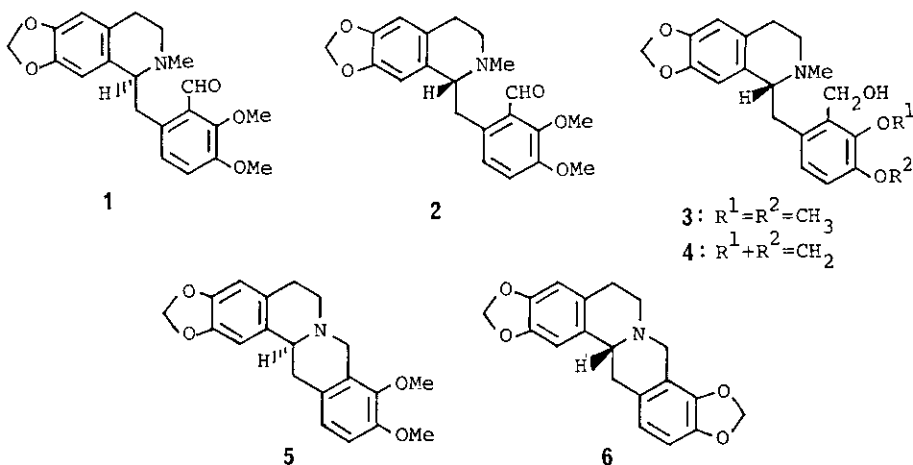


THE ABSOLUTE CONFIGURATION OF (+)-CANADALINE

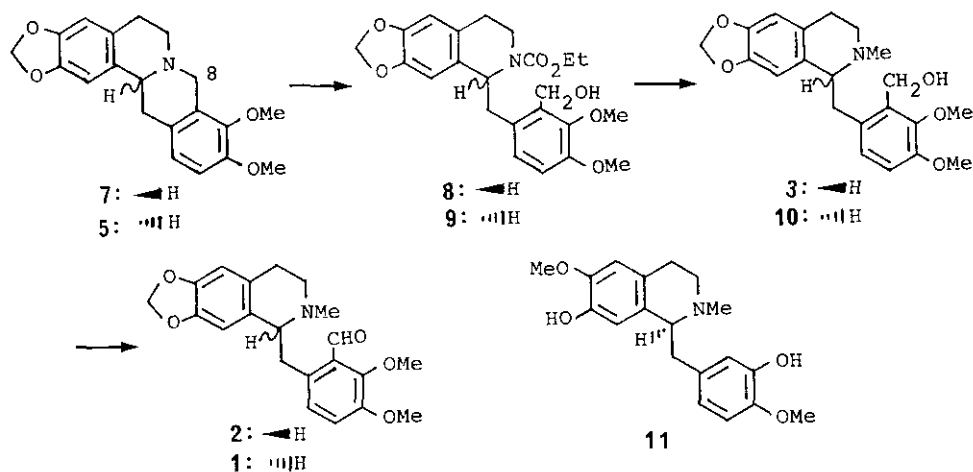
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Abstract—The absolute configuration of natural (+)-canadaline (1) was established to be S-configuration by its biomimetic synthesis from S-(–)-canadine (5).

(+)-Canadaline (1),¹ isolated from *Hydrastis canadensis* L. is a representative secoberberine alkaloid.² Its racemate has been synthesized from 8-benzyltetrahydroberberine³ through the Hofmann degradation and from tetrahydroberberine^{4,5} through C₈-N bond cleavage using ethyl chloroformate.⁶ The absolute configuration of (+)-canadaline (1) is still unknown even though its R-configuration (2) has been speculated from the facts that canadalisol (3), reduction product of (+)-canadaline, is dextrorotatory⁷ and a related alkaloid (+)-corydalisol (4)



has R-configuration. The configuration of **4** has been confirmed by chemical correlation with (+)-stylopine (**6**) of known chirality.⁸ We describe here determination of the absolute configuration of (+)-canadaline (**1**) by its synthesis as an optically active form from S(-)-canadine (**5**) according to our previous method.⁵



Optical resolution of (+)-tetrahydroberberine using d-camphorsulfonic acid resulted in (+)-canadine (**7**) [mp 133-134°C; $[\alpha]_D +272^\circ$ (c 0.912, CHCl₃) (lit.⁹ mp 131-132°C; $[\alpha]_D +299^\circ$ (c 0.929, CHCl₃))] and (-)-canadine (**5**) [mp 133-135°C; $[\alpha]_D -314^\circ$ (c 0.94, CHCl₃) (lit.¹⁰ mp 132-133°C; $[\alpha]_D -297.5^\circ$ (c 1, CHCl₃))] as an almost optically pure form. At first we intended to synthesize canadaline starting from R-(+)-canadine. Reaction of **7** with ethyl chloroformate in chloroform under reflux for 24 h, followed by treatment with silver nitrate in aqueous acetone caused C₈-N bond cleavage and substitution of the resulting chloride to afford the alcohol (**8**) in 79% yield from **7**. Reduction of **8** with lithium aluminum hydride in tetrahydrofuran furnished the N-methyl alcohol, (+)-canadalisol (**3**) [87%; mp 128-130°C; $[\alpha]_D +26^\circ$ (c 0.1, CHCl₃)]. The product was oxidized with pyridinium chlorochromate (PCC) in dichloromethane in the presence of sodium acetate to provide (-)-canadalisaldehyde (**2**) [63%; mp 114-116°C; $[\alpha]_D -38^\circ$ (c 0.1, CHCl₃)].

(-)-Canadaline (**2**) was identical with natural canadaline in ¹H-nmr spectral

comparison, however the sign of its specific rotation is opposite to that of natural (+)-canadalinine ($[\alpha]_D +43^\circ$ (c 0.5, CHCl_3)).¹ The absolute configuration of natural (+)-canadalinine is therefore S-configuration (1) but not R-configuration (2) assumed before.

In order to obtain a direct proof of S-configuration of (+)-canadalinine, natural (+)-canadalinine was synthesized from S(-)-canadalinine (5) through a similar procedure described above. S(-)-Canadalinine (5) was converted via 9 to (-)-canadalinol (10) [67% from 5; mp 130-131°C ($[\alpha]_D -37^\circ$ (c 0.1, CHCl_3))], which was oxidized with PCC to afford (+)-canadalinine (1) [58%, mp 117-119°C (lit.¹ mp 117-118°C); ($[\alpha]_D +44^\circ$ (c 0.1, CHCl_3))]. Synthetic (+)-canadalinine was shown to be identical with natural canadalinine in ¹H-nmr spectra. Thus, the absolute configuration of (+)-canadalinine was completely established to be S-configuration. It was found that canadalinine and canadalinol showed opposite sign in their specific rotation in spite of the same absolute configuration. Usually N-methyl-tetrahydrobenzylisoquinoline alkaloids with positive or negative specific rotation have S- or R-configuration, respectively.¹¹ This rule cannot be applied to corydalinol and canadalinol possessing an extra hydroxymethyl group at C-10, however canadalinine having an extra formyl group follows this rule, suggesting that conformation of canadalinine has normal anti relationship between the N-methyl group and the lower aromatic ring whereas corydalinol and canadalinol have abnormal syn relationship due to a hydrogen bonding.

Recently S(-)-corydalinol¹² was isolated and considered to be derived from S-(+)-reticuline (11),¹² which is the main biogenetic source for isoquinoline alkaloids. The present result suggests that canadalinine is also biosynthesized from S-(+)-reticuline via S(-)-canadalinine.

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