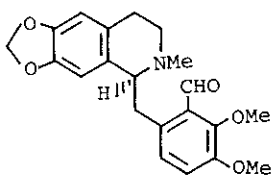
THE ABSOLUTE CONFIGURATION OF (+)-CANADALINE

Miyoji Hanaoka,* Kazuyoshi Nagami, and Shingo Yasuda
Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa 920, Japan

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 secoberbine alkaloid.[2] Its racemate has been synthesized from 8-benzyltetrahydroberberine[3] through the Hofmann degradation and from tetrahydroberberine[4,5] through C_8-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 dextrorotatory[7] and a related alkaloid (+)-corydalisol (**4**)



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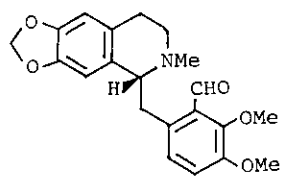

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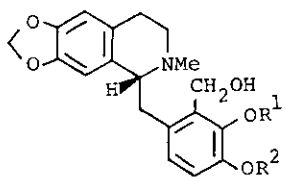
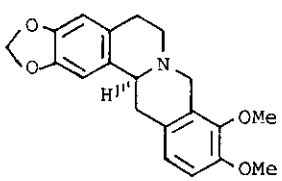


3: $R^1=R^2=CH_3$
4: $R^1+R^2=CH_2$



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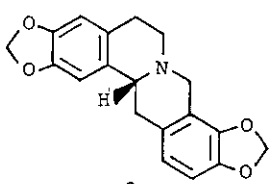
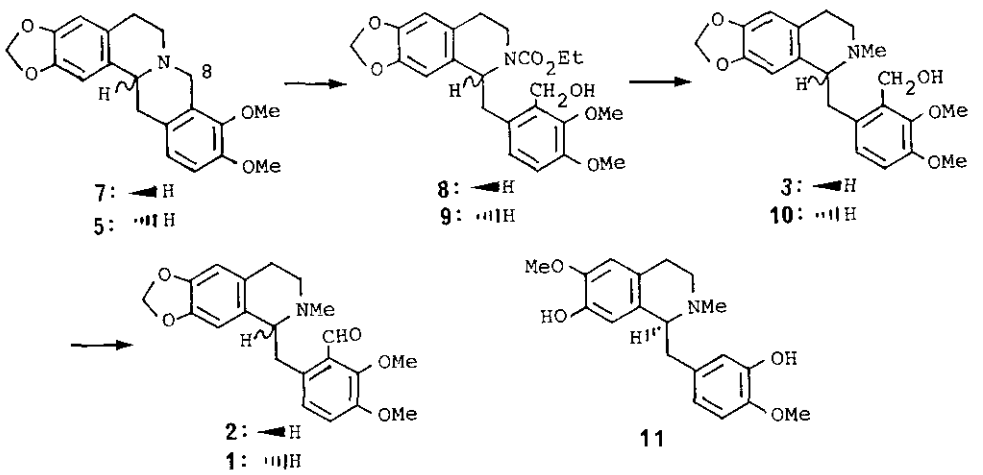


6

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° (c 0.912, $CHCl_3$) (lit.[9] mp 131-132°C; $[\alpha]_D$ +299° (c 0.929, $CHCl_3$))] and (-)-canadine (**5**) [mp 133-135°C; $[\alpha]_D$ -314° (c 0.94, $CHCl_3$) (lit.[10] mp 132-133°C; $[\alpha]_D$ -297.5° (c 1, $CHCl_3$))] 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 C_8-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° (c 0.1, $CHCl_3$)*]. The product was oxidized with pyridinium chlorochromate (PCC) in dichloromethane in the presence of sodium acetate to provide (-)-canadaline (**2**) [63%; mp 114-116°C; $[\alpha]_D$ -38° (c 0.1, $CHCl_3$)].

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

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

In order to obtain a direct proof of S-configuration of (+)-canadaline, natural (+)-canadaline was synthesized from S-(-)-canadine (**5**) through a similar procedure described above. S-(-)-Canadine (**5**) was converted via **9** to (-)-canadalisol (**10**) [67% from **5**; mp 130-131°C $[\alpha]_D$ -37° (c 0.1, $CHCl_3$)], which was oxidized with PCC to afford (+)-canadaline (**1**) [58%, mp 117-119°C (lit.[1] mp 117-118°C); $[\alpha]_D$ +44° (c 0.1, $CHCl_3$)]. Synthetic (+)-canadaline was shown to be identical with natural canadaline in ^{1}H-nmr spectra. Thus, the absolute configuration of (+)-canadaline was completely established to be S-configuration. It was found that canadaline and canadalisol 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 corydalisol and canadalisol possessig an extra hydroxymethyl group at C-10, however canadaline having an extra formyl group follows this rule, suggesting that conformation of canadaline has normal anti relationship between the N-methyl group and the lower aromatic ring whereas corydalisol and canadalisol have abnormal syn relationship due to a hydrogen bonding.

Recently S-(-)-corydalisol[12] 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 canadaline is also biosynthesized from S-(+)-reticuline via S-(-)-canadine.

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