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「Synthesis of bioactive constituents from the Brazilian plant *Tabebuia avellanedae* 2」

ブラジル原産*Tabebuia avellanedae*由来活性成分の合成研究2

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【目的】

ノウゼンカズラ科*Tabebuia avellanedae*（Taheebo）は、ブラジルから北アルゼンチンまでの南アメリカを原産とする大木である。本植物が、抗がん、抗真菌、抗菌、抗炎症等の効果を示す医薬資源として着目されたことから成分研究が進み、ナフトキノン類、アントラキノン類、ベンゾフラン化合物およびベンゼン誘導体等が単離された。その中でも、(−)-5-hydroxy-2-(1-hydroxyethyl) naphtho[2,3-b]furan-4,9-dione（1a）は様々な腫瘍細胞に対して強力な細胞毒性を示すと同時に強力な抗がん予防効果を持つこと既に報告している[1]。今回、1aの位置異性体である1bの不斉合成を行った。化合物1a及び1bの細胞毒性、がん予防効果及び抗菌活性についての結果と合わせて報告する。

【方法・結果】

文献に従い1,5-Dihydroxynaphthalene（2）を酸化して5-hydroxy-1,4-naphthoquinone（juglone）に変換した後、ジメチルアミンを用いて酸化的アミノ化を行うと位置異性体が各々48%と10%で得られた。酸加水分解、ヒドロフラン環構築、MnO_2酸化を経て、各々の異性体をケトン体3へと変換した後に、野依還元することで光学活性体1a及び1bを良好な化学収率、不斉収率にて得ることができた。合成して得られた光学活性体を用いて細胞毒性、がん予防効果及び抗菌活性を調べた。

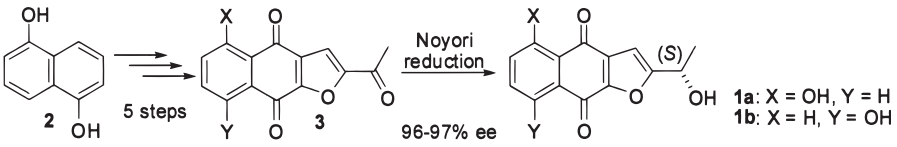
■English abstract

[Introduction]

The Bignoniaceae plant, *Tabebuia avellanedae Lorentz ex Griseb*, is a gigantic tropical tree native to South America from Brazil to north Argentina and has been known as a useful medicinal plant since the Incan Era. The stem bark of *T. avellanedae* has been utilized as a diuretic and as astringent, and as a folk remedy for the treatment of cancer and various diseases. Findings of the antitumor activity of an alcoholic extract of the stem bark of this plant and efforts to find clinically acceptable antitumor compounds led to the discovery of a series of naphthoquinones based on the naphtho[2,3-b]furan-4,9-dione skeleton such as (−)-5-hydroxy-2-(1'-hydoxyethyl) naphtho[2,3-b]furan-4,9-dione (1a) and its positional isomers, (±)-8-hydroxy-2-(1'-hydoxyethyl) naphtho[2,3-b] furan-4,9-dione (1b). We describe here the stereoselective synthesis of naphthoquinone 1a and 1b by utilizing Noyori reduction as a key step and their biological evaluation.

[Results and discussion]

The stereoselective synthesis of 1a and 1b were accomplished starting from commercially available 1,5-dihydroxynaphthalene (2). For the synthesis of juglone, compound 2 was oxidized with air in the presence of CuCl to give juglone. Oxidative amination of juglone with dimethylamine gave 2-dimethylaminojuglone and 3-dimetylaminojuglone in 48 and 10% yields, respectively. Deamination, construction of hydrofuran skeleton and oxidation with MnO_2 afforded the naphthoquinone 3 in good yield. Subsequent Noyori reduction accomplished the stereoselective synthesis of 1a and 1b (89-97% yield, 96-97% ee). Compound 1a and 1b displayed potent cytotoxicity against several human tumor cell lines, whereas it showed lower cytotoxicity against some human normal cell lines compared with that of mitomycin. In addition to these result, 1a was found to show modest antifungal and antibacterial activity against fungi and common Gram-positive bacteria.



1) Yamashita, M. *et al. Bioorg. Med. Chem. Lett*. 2007, *17*, 6417