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「Stereoselective synthesis and biological evaluation of bioactive constituents from the Brazilian plant *Tabebuia avellanedae*」

ブラジル原産 *Tabebuia avellanedae* 由来活性成分の立体選択的合成および生物活性研究

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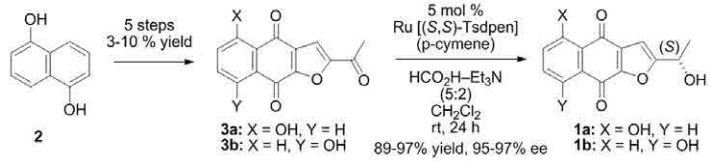
A series of naphthoquinones based on the naphtho[2,3-b]furan-4,9-dione skeleton such as (−)-5-hydroxy-2-(1'-hydoxyethyl)naphtho[2,3-b]furan-4,9-dione (**1a**) and its positional isomer,(−)-8-hydroxy-2-(1'-hydoxyethyl)naphtho[2,3-b]furan-4,9-dione (**1b**), which are secondary metabolites found in the inner bark of *Tabebuia avellanedae*, were stereoselectively synthesized and their biological activities were evaluated in conjunction with those of their corresponding enantiomers.

The stereoselective synthesis of **1a** and **1b** were accomplished similarly according to our preliminary synthesis of naphthoquinones.[1] 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 MnO2 afforded the naphthoquinone **3** in good yield. Subsequent Noyori reduction completed the stereoselective synthesis of **1a** and **1b** (89-97% yield, 96-97% ee). Compound **1a** exhibited potent antiproliferative effect against several human tumor cell lines, but its effect against some human normal cell lines was much lower than that of mitomycin. On the other hand, its enantiomer *(R)*- **1a** was less active toward the above tumor cell lines than 1a. The antiproliferative effect of **1b** against all tumor cell lines was significantly reduced. In addition to these result, **1a** was found to show modest antifungal and antibacterial activity against fungi and common Gram-positive bacteria. We also report the preclinical test of **1a**.

■日本語訳

ノウゼンカズラ科*Tabebuia avellanedae (Taheebo)*から単離された(−)-5-hydroxy-2-(1-hydroxyethyl)naphtho[2,3-b]furan-4,9-dione (**1a**)などのナフトキノン類に着目し研究を行っている[1]。化合物1a及び位置異性体である**1b**は天然からはごくわずかしか得られてこないために不斉合成法の開発を行った後に、抗腫瘍活性を中心とした詳細な生物活性評価を行うこととした。

文献に従い市販の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、MnO2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**1a**及び**1b**の立体選択的合成を達成した(89-97%収率、96-97%エナンチオマー過剰率)。合成して得られた光学活性体**1a**, **1b**、ケトン**3a**, **3b**のヒト腫瘍細胞に対する細胞毒性、がんの化学予防効果及び抗菌活性を調べた。化合物**1a**は数種のヒト腫瘍細胞株に対して強力な細胞増殖抑制活性を示したが、ヒト正常細胞に対する効果はマイトマイシンのそれよりずっと低かった。一方、そのエナンチオマーの活性は**1a**より弱かった。また、**1b**の細胞増殖抑制活性は著しく低下した。これら結果に加え、**1a**は真菌とグラム陽性菌に対して中程度の抗菌活性を示すことが明らかとなった。**1a**の前臨床試験の結果も併せて報告する。



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