

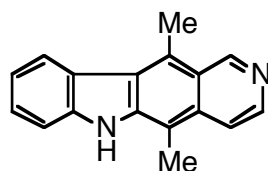
**REACTION OF 3-ETHOXYCARBONYLINDOLIZINE-1,2-DICARBOXYLIC ANHYDRIDE WITH (3-BROMO-4-PYRIDYL)-TRIISOPROPOXYTITANIUM: SYNTHESIS OF 5,12-DIMETHYL-INDOLIZINO[2,1-*g*]ISOQUINOLINE (ELLIPTICINE ANALOGUE)**

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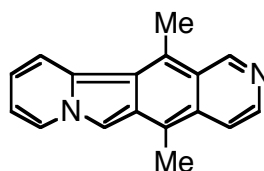
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**Abstract** – Reaction of indolizine-1,2-dicarboxylic anhydride with (3-bromo-4-pyridyl)triisopropoxytitanium gave 2-(3-bromoisonicotinoyl)-3-ethoxycarbonyl-indolizine-1-carboxylic acid as the sole product. The indolizine-1-carboxylic acid could be converted to 5,12-dimethylindolizine[2,1-*g*]isoquinoline in six steps.

Ellipticine (**1**), 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, has potent antitumor activity,<sup>1</sup> and many useful methods for its synthesis have been reported.<sup>2,3</sup> From the viewpoint of biological interest many ellipticine analogues, including other heterocycles,<sup>2,4</sup> have been synthesized. However, synthesis of the indolizine analogue (**2**) of ellipticine has not been reported. Recently, we showed that 1-benzylindole-2,3-dicarboxylic anhydride was a useful synthon in the synthesis of ellipticine<sup>5</sup> and the reactivity of 3-ethoxycarbonylindolizine-1,2-dicarboxylic anhydride (**3**) toward Grignard reagents.<sup>6</sup> In this communication, we report the reaction of indolizine-1,2-dicarboxylic anhydride (**3**) with a (3-bromo-4-pyridyl)triisopropoxytitanium and the synthesis of **2**.



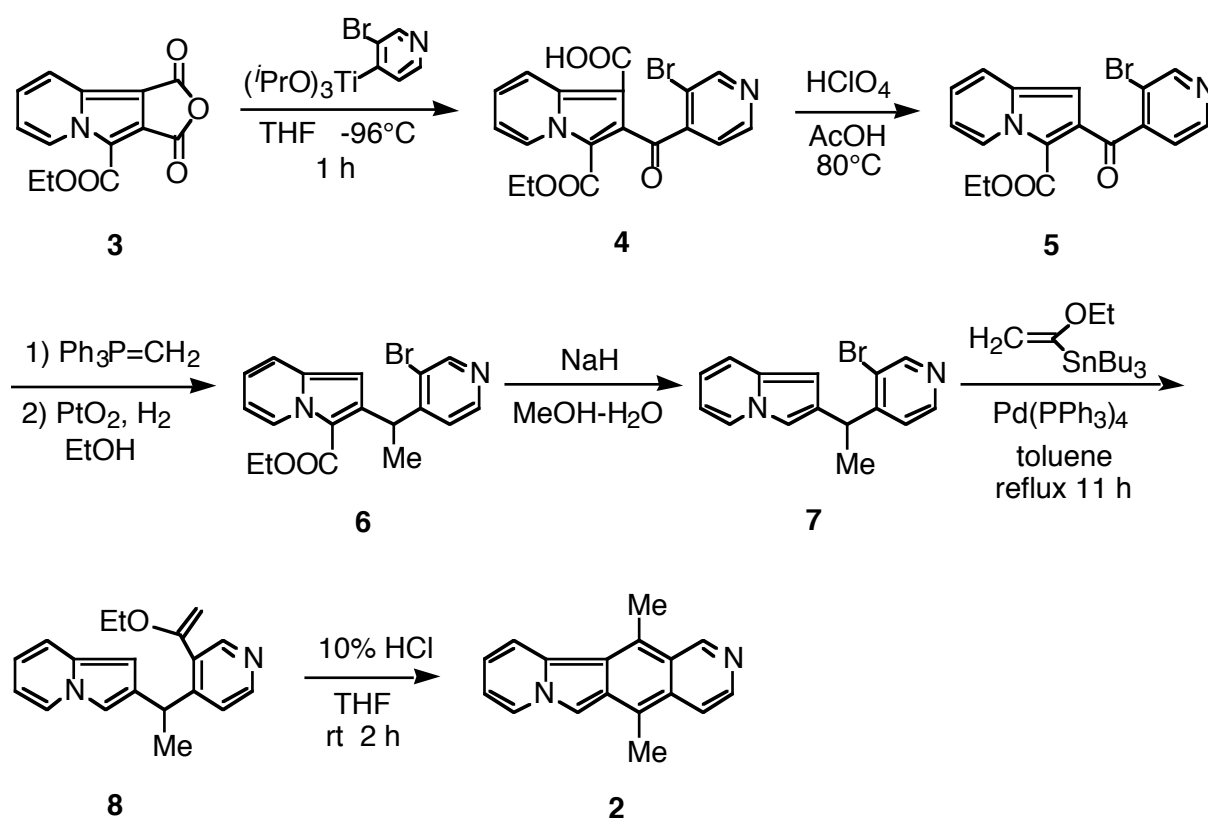
Ellipticine (**1**)



**2**

3-Ethoxycarbonylindolizine-1,2-dicarboxylic anhydride (**3**)<sup>6</sup> reacted with a (3-bromo-4-pyridyl)-triisopropoxytitanium<sup>4</sup> to afford 3-ethoxycarbonyl-2-(3-bromoisonicotinoyl)indolizine-1-carboxylic acid (**4**) in 59% yield. Under these reaction conditions 3-ethoxycarbonyl-1-(3-bromoisonicotinoyl)indolizine-2-carboxylic acid, an isomeric product of **4**, was not produced. Decarboxylation (20% HClO<sub>4</sub> in AcOH, 30

min, 80°C) of **4** furnished the ketone (**5**)(79%), which was converted by reaction of  $\text{Ph}_3\text{P}=\text{CH}_2$  (81%), followed by catalytic reduction ( $\text{H}_2$ ,  $\text{PtO}_2$  in  $\text{EtOH}$ , 6 h, 73%) to 1-(3-bromo-4-pyridyl)-1-(3-ethoxycarbonyl-2-indoliziny)ethane (**6**). Removal of the ester group of **6** was performed under basic hydrolysis condition ( $\text{NaH}$  in  $\text{MeOH}$  and  $\text{H}_2\text{O}$ , 15 h, reflux) to provide **7** (89%). Treatment of the bromo derivative (**7**) with (1-ethoxyvinyl)tributyltin in the presence of tetrakis(triphenylphosphine)palladium(0) in refluxing toluene gave the corresponding ethoxyvinyl derivative (**8**), which was converted to 5,12-dimethylindolizino[2,1-g]isoquinoline (**2**), an indolizine analogue of ellipticine, in 87% yield by treatment with 10% hydrochloric acid in THF.



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7. Compound (**2**): mp 172-173°C (MeOH-ether). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.90 (3H, s, 5-CH<sub>3</sub> or 12-CH<sub>3</sub>), 3.34 (3H, s, 5-CH<sub>3</sub> or 12-CH<sub>3</sub>), 6.45 (1H, ddd, *J* = 7, 6, 1 Hz, H-9), 6.76 (1H, s, H-6), 7.00 (1H, ddd, *J* = 9, 6, 1 Hz, H-10), 7.47 (1H, dt, *J* = 9, 1 Hz, H-11), 7.91 (1H, br d, *J* = 6 Hz, H-4), 8.42 (1H, d, *J* = 6 Hz, H-3), 8.91 (1H, br d, *J* = 7 Hz, H-8), 9.76 (1H, s, H-1). HRMS *m/z* (M<sup>+</sup>) calcd for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>: 246.1157. Found: 246.1182.