Pergamon

Tetrahedron Letters, Vol. 37, No. 43, pp. 7753-7754, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01768-6

Reaction of Indole-2,3-dicarboxylic Anhydride with (3-Bromo-4-pyridyl)triisopropoxytitanium: Synthesis of Ellipticine

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Abstract: *N*-Benzylindole-2,3-dicarboxylic anhydride (1) was reacted with (3-bromo-4-pyridyl)triisopropoxytitanium to give 2-(3-bromoisonicotinoyl)indole-3-carboxylic acid (2) as the sole product in high yield, which could be converted to ellipticine in six steps. Copyright © 1996 Elsevier Science Ltd

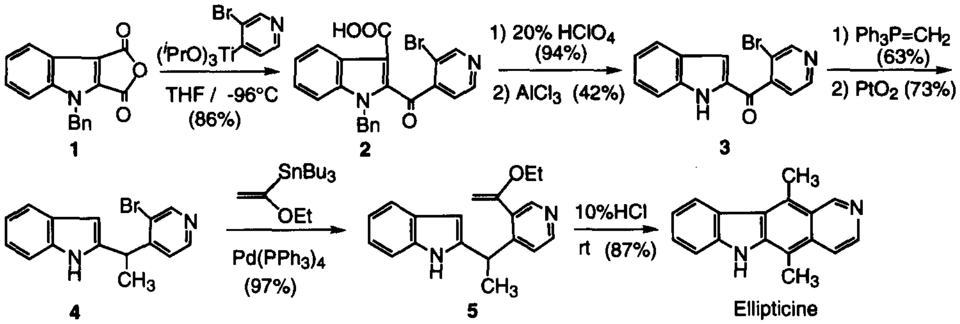
Ellipticine, 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, has potent antitumor activity[1] and many useful methods for its synthesis have been reported.[2,3] Although the Diels-Alder reaction of 4*H*-furo[3,4-*b*]indole,[4] pyrrolo[3,4-*b*]indole,[5] and pyrano[3,4-*b*]indol-3-one[6] with 3,4-pyridyne is the attractive synthetic methods of ellipticine, it produced a mixture of ellipticine and isoellipticine. Reaction of 4*H*-furo[3,4-*b*]indole with 5,6-dihydro-2-pyridinone afforded a sole adduct, but the transformation of the adduct to ellipticine resulted in low yield.[7] However, Gribble reported a useful synthesis of ellipticine by using the reaction of 2-lithio-1-(phenylsulfonyl)indole with 3,4-pyridinedicarboxylic anhydride.[8]

Recently we have reported a synthesis of murrayaquinone-A by using the selective reduction of *N*-benzylindole-2,3-dicarboxylic anhydride (1), in which the 2-carbonyl group is more reactive toward the nucleophile than the 3-carbonyl group,[9] following cycloaddition reaction of the corresponding furo[3,4-*b*]indole with methyl acrylate.[10] The nucleophilic reaction of *ortho*-halolithiopyridines is a convenient method for the preparation of numerous *ortho*-substituted halopyridines[11]. However, the reaction of enolizable ketones or unstable compounds toward a base with *ortho*-halolithiopyridines gave sometimes unacceptable results.[12] Seebach[13] reported that phenyltitanium compounds reacted with aldehydes to give the corresponding products in high yield, but the reactivity of *ortho*-haloltitaniumpyridines has not been extensively studied.

In this paper we report a simple and useful synthesis of ellipticine by regioselective reaction of **1** with a 4-pyridyltitanium derivative.

N-Benzylindole-2,3-dicarboxylic anhydride (**1**) reacted with a 3-bromo-4-pyridiyltitanium compound (prepared from 3-bromo-4-lithiopyridine[14] and $ClTi(OPr^i)_3$[15] in THF -96°C) to afford 2-acylindole-3-carboxylic acid (**2**) in 86% yield.[16] Decarboxylation and debenzylation ($AlCl_3$ in anisole,[17] 100°C) of **2** furnished ketone (**3**), which was changed by Wittig reaction, followed by catalytic reduction to 1-(3-bromo-4-

pyridyl)-1-(2-indolyl)ethane (**4**). Treatment of **4** with (1-ethoxyvinyl)tributyltin in the presence of tetrakis(triphenylphosphine)palladium(0) in refluxing toluene gave the corresponding ethoxyvinyl derivative (**5**), which was converted to ellipticine[18] in 87% yield by treatment with 10% hydrochloric acid in tetrahydrofuran.



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16. Reaction of the anhydride (**1**) with 3-bromo-4-lithiopyridine gave 2-acylindole-3-carboxylic acid (**2**) in 42% yield.
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18. Ellipticine: mp >300°C (MeOH) (lit.,[6] 312-314°C); ^{1}H-NMR (DMSO-d_6) δ 2.80 (3H, s, 5-CH$_3$), 3.27 (3H, s, 11-CH$_3$), 7.22-7.33 (1H, m, Ar), 7.49-7.61 (2H, m, Ar), 7.92 (1H, d, J = 6 Hz, H-4), 8.39 (1H, d, J = 8 Hz, H-10), 8.43 (1H, d, J = 6 Hz, H-3), 9.69 (1H, s, H-1), 11.25 (1H, s, NH); HRMS *m/z* calcd for $C_{17}H_{14}N_2$ (M^+) 246.1157, found 246.1185.

(*Received in Japan* 27 *May* 1996; *revised* 7 *August* 1996; *accepted* 10 *September* 1996)