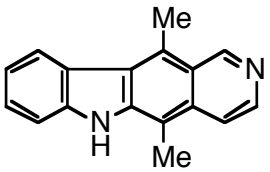
HETEROCYCLES, Vol. 53, No. 10, 2000, pp. 2123-2125, Received, 3rd July, 2000

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

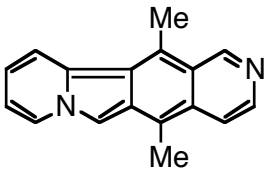
Yasuyoshi Miki*, Noriko Nakamura, Ryota Yamakawa, Hajime Hibino, Hiroko Hachiken, and Ko-ichi Matsushita
Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1, Kowakae, Higashi-Osaka 577-8502, Japan

Abstract – Reaction of indolizine-1,2-dicarboxylic anhydride with (3-bromo-4-pyridyl)triisopropoxytitanium gave 2-(3-bromoisonicotinoyl)-3-ethoxycarbonylindolizine-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,[1] and many useful methods for its synthesis have been reported.[2,3] From the viewpoint of biological interest many ellipticine analogues, including other heterocycles,[2,4] 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[5] and the reactivity of 3-ethoxycarbonylindolizine-1,2-dicarboxylic anhydride (**3**) toward Grignard reagents.[6] 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**.



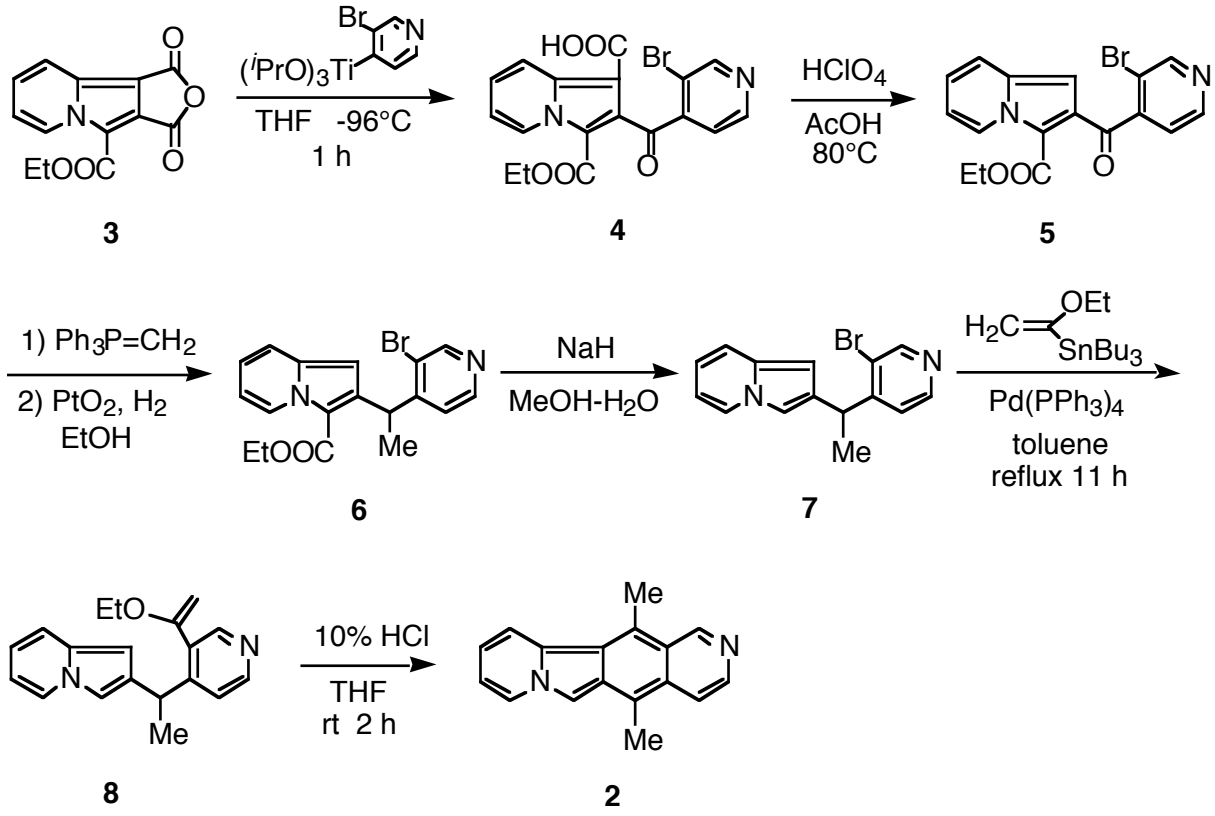
Ellipticine (**1**)



2

3-Ethoxycarbonylindolizine-1,2-dicarboxylic anhydride (**3**)[6] reacted with a (3-bromo-4-pyridyl)-triisopropoxytitanium[4] 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%$HClO_4$ in AcOH, 30

min, 80°C) of **4** furnished the ketone (**5**)(79%), which was converted by reaction of $Ph_3P=CH_2$ (81%), followed by catalytic reduction (H_2, PtO_2 in EtOH, 6 h, 73%) to 1-(3-bromo-4-pyridyl)-1-(3-ethoxy-carbonyl-2-indolizinyl)ethane (**6**). Removal of the ester group of **6** was performed under basic hydrolysis condition (NaH in MeOH and H_2O, 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.



3 **4** **5**

6 **7**

8 **2**

REFERENCES AND NOTE

1. L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Aust. J. Chem.*, 1967, **20**, 2715.
2. For reviews, see G. W. Gribble, *Synlett*, 1991, 289; G. W. Gribble, 'Advances in Heterocyclic Natural Product Synthesis,' Vol. 1, p. 43, ed. by W. Pearson, Jai Press Inc., London, 1990; V. K. Kansal and P. Potier, *Tetrahedron*, 1986, **42**, 2389; G. W. Gribble and M. G. Saulnier, *Heterocycles*, 1985, **23**, 1277; M. J. E. Hewlins, A.-M. O.-Campos, and P. V. R. Shannon, *Synthesis*, 1984, 289; M. Sainsbury, *Synthesis*, 1977, 437.

3. G. W. Gribble, M. G. Saulnier, M. P. Sibi, and J. A. O.-Nutaitis, *J. Org. Chem.*, 1984, **49**, 4518; C. May and C. J. Moody, *J. Chem. Soc. Perkin Trans. 1*, 1988, 247; S. Hibino and E. Sugino, *J. Heterocycl. Chem.*, 1990, **27**, 1751; D. A. Davis and G. W. Gribble, *Tetrahedron Lett.*, 1990, **31**, 1081; S. P. Modi, M. A. Michael, and S. Archer, *Tetrahedron,* 1991, **47**, 6539; C.-K. Sha and J.-F. Yang, *Tetrahedron*, 1992, **48**, 10645; G. W. Gribble, D. J. Keavy, D. A. Davis, M. G. Saulnier, B. Pelcman, T. C. Barden, M. P. Sibi, E. R. Olson, and J. J. BelBruno, *J. Org. Chem.*, 1992, **57**, 5878; G. W. Gribble, M. G. Saulnier, J. A. O.-Nutaitis, and D. M. Ketcha, *ibid.*, 1992, **57**, 5891; M. T. Diaz, A. Cobas, E. Guitián, and L. Castedo, *Synlett,* 1998, 157; M. Ishikura, A. Hino, and N. Katagiri, *Heterocycles*, 2000, **53**, 11.
4. C. Rivalle, C. Ducrocq, and E. Bisagni, *J. Chem. Soc. Perkin Trans. I*, 1979, 138; R. L. Weinkauf, A. Y. Chen, C. Yu, L. Liu, L. Barrows, and E. J. LaVoie, *Bioorg. Med. Chem.*, 1994, **2**, 781.
5. Y. Miki, Y. Tada, N. Yanase, H. Hachiken, and K. Matsushita, *Tetrahedron Lett.*, 1996, **37**, 7753; Y. Miki, Y. Tada, and K. Matsushita, *Heterocycles*, 1998, **48**, 1593.
6. Y. Miki, N. Nakamura, R. Yamakawa, H. Hachiken, and K. Matsushita, *Heterocycles*, 2000, **53**, 2143.
7. Compound (**2**): mp 172-173°C (MeOH-ether). ^{1}H-NMR ($CDCl_3$) δ: 2.90 (3H, s, 5-CH_3 or 12-CH_3), 3.34 (3H, s, 5-CH_3 or 12-CH_3), 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^+) calcd for $C_{17}H_{14}N_2$: 246.1157. Found: 246.1182.