Short step syntheses of a natural product, 6-cyano-5-methoxy-12-methylindolo[2,3-a]carbazole and novel 6-aminoindolo[2,3-a]-thiazolo[5,4- c]carbazoles

SHORT STEP SYNTHESES OF A NATURAL PRODUCT, 6-CYANO-5-METHOXY-12-METHYLINDOLO[2,3-*a*]CARBAZOLE AND NOVEL 6-AMINOINDOLO[2,3-*a*]-THIAZOLO[5,4-*c*]CARBAZOLES[1]

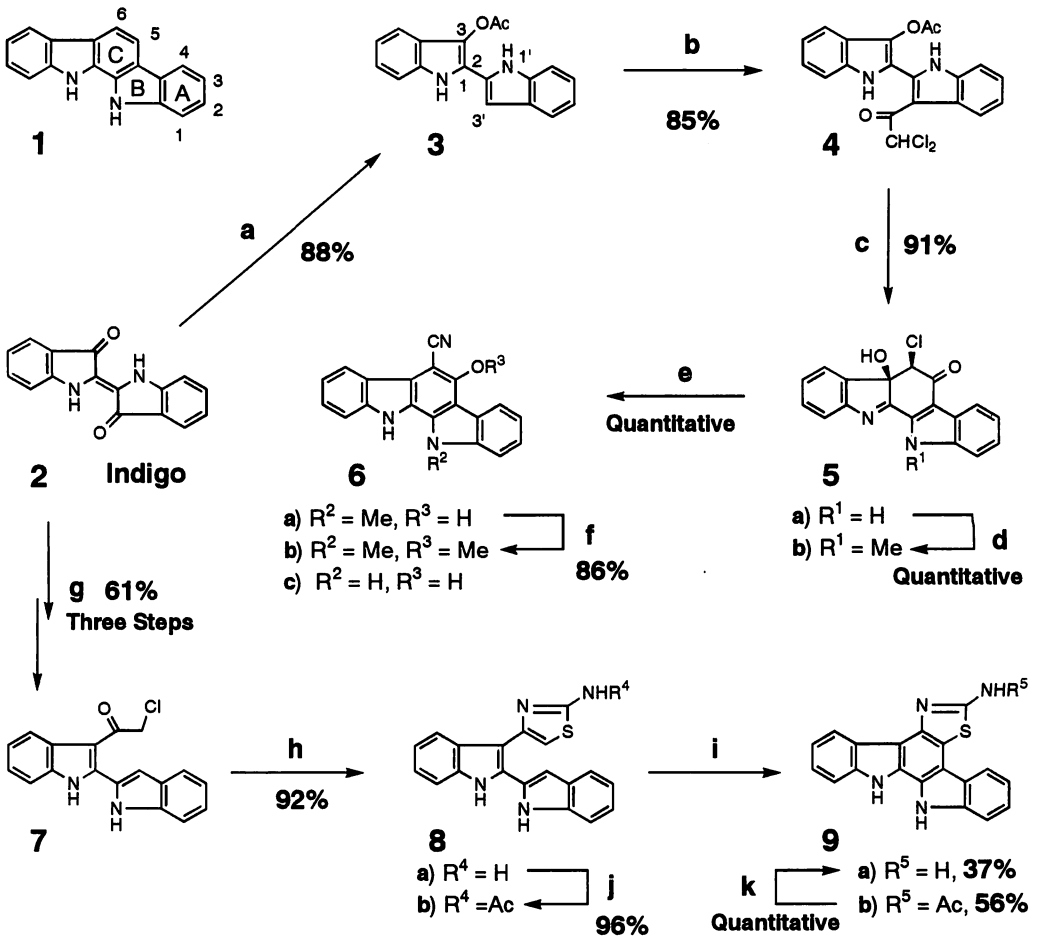
Hiroyuki Hayashi, Yoshiaki Suzuki, and Masanori Somei*
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract ——— Starting from indigo, simple synthetic methods for 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole and novel 6-aminoindolo[2,3-*a*]thiazolo-[5,4-*c*]carbazoles are achieved using only conventional reagents.

Indolo[2,3-*a*]carbazole (**1**, Scheme 1) is a common skeleton of a class of compounds such as staurosporine,[2a] tjipanazoles,[2b] BE-13793C,[2c] and so on. We have expected that manipulation of **1** is a promising method for finding a new biologically active compound. As a simple derivative of **1**, we have focused our attention to cytotoxic and antiviral 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole (**6b**), isolated from blue-green alga *Nostoc sphaericum* (strain EX-5-1) by Moore and co-workers.[3] Although we have established two synthetic routes to **6b** in the previous communications,[4] their overall yields (13% and 5%, respectively) are still not satisfactory to carry out structure-activity relationship project. Now, we wish to report a satisfactory six step synthetic method for **6b** from indigo (**2**). In addition, simple preparation of novel 6-aminoindolo[2,3-*a*]thiazolo[5,4-*c*]carbazoles (**9a** and **9b**) is also developed.

First, 3-acetoxy-2,2'-biindolyl (**3**), prepared in one step from **2** in 88% yield,[4] reacted with dichloroacetyl chloride in refluxing ethyl acetate to give 3-acetoxy-3'-dichloroacetyl-2,2'-biindolyl (**4**) in 85% yield. Treatment of **4** with aqueous 1.3% ammonia in MeOH-DMF at room temperature afforded *cis*-6-chloro-6a-hydroxy-5-oxo-5,6,6a,12-tetrahydroindolo[2,3-*a*]carbazole[5] (**5a**) in 91% yield. Methylation of **5a** with dimethyl sulfate in the presence of K_2CO_3 produced 12-methyl compound (**5b**) in a quantitative yield. A novel reductive cyanation of **5b** was found to produce **6a** in a quantitative yield by the reaction with NaCN in DMF-H_2O. Finally methylation of **6a** with diazomethane afforded **6b** in 86% yield. Thus the natural product (**6b**) is available in six steps with an overall yield of 59% using only conventional reagents. The originality rate[6] for **6b** from **2** is 57% based on our three reaction steps, **a**, **c**, and **e**.

Scheme 1



a) Sn, AcOH, Ac_2O, 64—66°C; b) $Cl_2CHCOCl$, EtOAc, reflux; c) aq. 1.3% NH_3, MeOH, DMF, rt; d) Me_2SO_4, K_2CO_3, rt; e) NaCN, DMF, H_2O, 70°C; f) CH_2N_2, rt; g) i) Zn, AcOH, Ac_2O; ii) NaOMe, MeOH, then Salcomine, O_2 ; iii) $ClCH_2COCl$, benzene, reflux; h) $(NH_2)_2CS$, MeOH, reflux; i) nitrobenzene, 190—225°C; j) Ac_2O, pyridine, rt; k) NaOH, MeOH, reflux.

On the other hand, 3-chloroacetyl-2,2'-biindolyl (**7**) was prepared in three steps with an overall yield of 61% from **2** as described before.[4] Treatment of **7** with thiourea in refluxing MeOH afforded 3-(2-aminothiazol-4-yl)-2,2'-biindolyl (**8a**) in 92% yield. Subsequent oxidative cyclization of **8a** proceeded in refluxing nitrobenzene to give 6-aminoindolo[2,3-*a*]thiazolo[5,4-*c*]carbazole (**9a**) in 37% yield. Similar cyclization of **8b**, prepared in 96% yield by reacting **8a** with Ac_2O-pyridine, produced **9b** in 56% yield. Alkaline hydrolysis of **9b** with NaOH-MeOH afforded a quantitative yield of **9a**. According to the present synthetic methodology, it would be possible to obtain compounds fused with various heterocycles[7] on the

C ring of **1**, since a chloroacetyl group of **7** is suitable for forming heterocycles.

With useful building blocks at hand such as **6a**, **9a**, and **6c** which is available from **5a** as reported previously,[4] the structure-activity relationship project is in progress.

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REFERENCES AND NOTES

1. This is Part 90 of a series entitled "The Chemistry of Indoles". Part 89: K. Yamada and M. Somei, *Heterocycles*, 1998, **48**, 2481. All new compounds gave satisfactory spectral data and elemental analyses. **4**: mp 227—229°C (decomp); **5a**: mp 236—238°C (decomp); **5b**: mp 223—225°C (decomp); **6a**: mp >300°C; **8a**: mp 238—241°C (decomp); **8b**: mp 240°C (decomp); **9a**: mp 140—141°C; **9b**: mp >300°C.
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7. Related indolo[2,3-*a*]oxazolo[4,5-*c*]carbazol-6-one and indolo[2,3-*a*]imidazolo[4,5-*c*]carbazol-6-one derivatives were reported: E. R. Pereira, M. Prudhomme, M. Sancelme, M. Ollier, D. Severe, J. F. Riou, H. Crevel, J. P. Savineau, D. Fabbro, and T. Meyer, *Chem. Pharm. Bull.*, 1997, **45**, 733 and references cited therein.

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