A NEW GENERAL SYNTHETIC ROUTE FOR 1-SUBSTITUTED 4-OXYGENATED β-CARBOLINES[1)]

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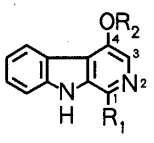
Two naturally occurring 1-substituted 4-methoxy-β-carboline (**1b,c**) were synthesized from ethyl indole-2-carboxylate (**5b**) and its 1-benzyl derivative (**5a**), respectively. The synthesis routes involved elaboration of the ester group of **5a,b**, cyclization of the substituent at the 2-position toward the 3-position of the indole nucleus, and functionalization at the 1-position of the β-carboline nucleus by a modified Reissert reaction. The β-carbolines (**1b,c**) thus prepared should be mother compounds for the synthesis of their congeners.

KEYWORDS indole; β-carboline; cyclization; PPA; Reissert reaction; synthesis

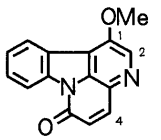
4-Oxygenated β-carboline alkaloids[2)] have become a large family in β-carboline alkaloids recently. Representative examples (**1,2,3,**and **4**) are shown in Fig. 1. Some compounds of them show interesting biological activities,[3,4,5)] but systematic research for biological evaluation has not been done, probably because of their poor isolation yields from natural sources. Thus, we are sure that their syntheses will have some pharmaceutical importance. Two compounds, crenatine[1c,6,7)] (**1a**) and 1-methoxycanthin-6-one[9)] (**3**), were synthesized earlier, but their synthetic routes are not suitable for the general synthesis of their congeners. In this paper we report a new synthesis of 1-functionalized 4-methoxy-β-carbolines (**1b** and **1c**), which are natural products themselves and at the same time mother compounds leading to the general synthesis of their congeners.

Fig. 1



1, 2

	R_1	R_2	
1a	Et	Me	(crenatine)
1b	COMe	Me	
1c	CO_2Me	Me	
1d	$CH=CH_2$	Me	
1e	$CH(OH)CH_2OH$	Me	
2a	CHO	H	
2b	CO_2Me	H	



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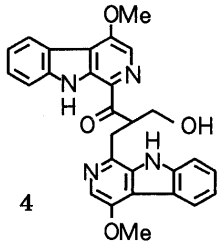

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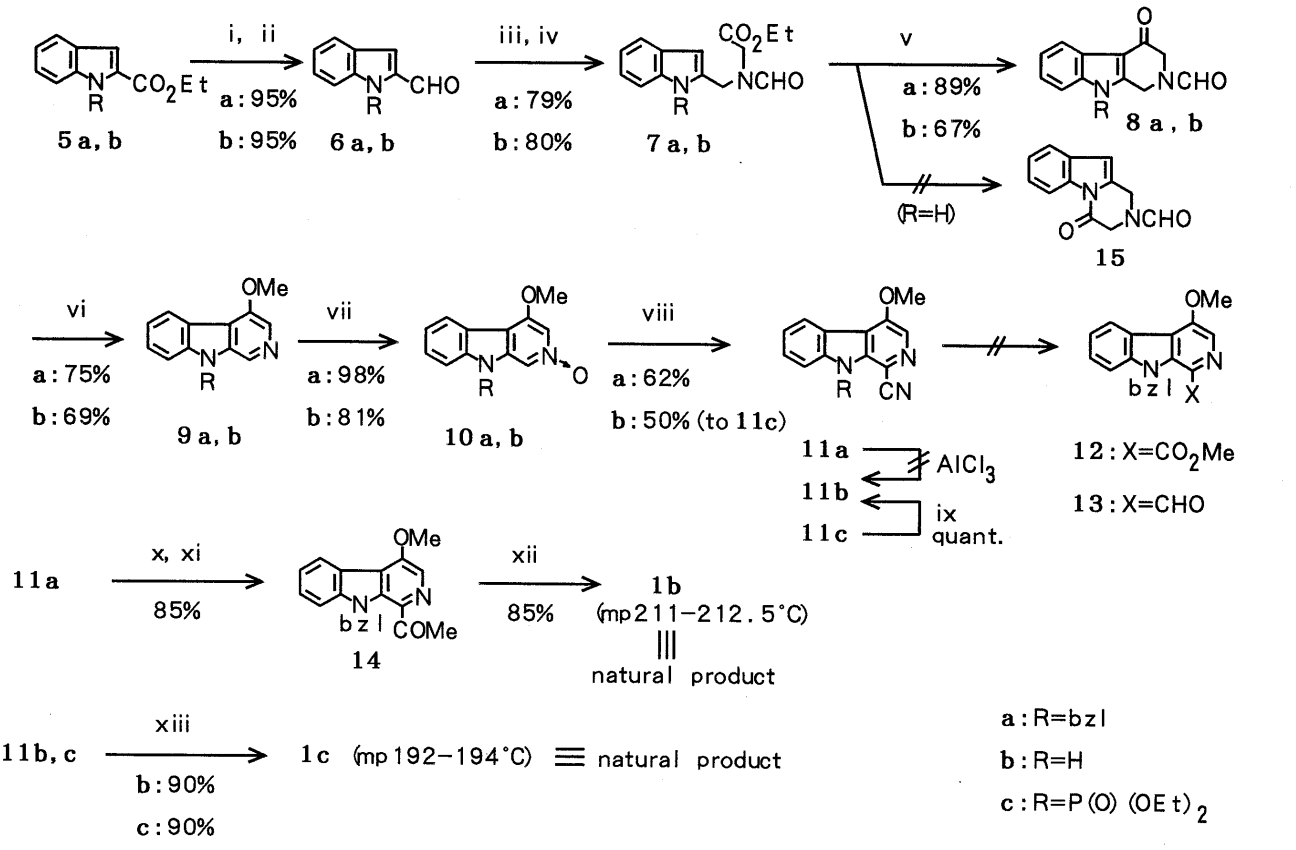
Strategy for the synthetic route is based on our route for crenatine,[1c,7)] in which construction of the C-ring consisted of very little cyclization[8)] from the C_2- to C_3-position of the indole nucleus. The synthesis shown in Chart 1 was started with the N-protected ethyl indole-2-carboxylate (**5a**), which was elaborated to the glycine derivative (**7a**) in a good yield. Cyclization of **7a** with PPA occurred naturally at the C_3-position to give the cyclic ketone (**8a**). It is an advantageous feature in the present route

that the cyclization step simultaneously forms the C_4-oxygen functionality of the β-carboline nucleus. A combination of O-methylation and the following dehydrogenation of **8a** to **9a** was conducted by modification of Cook's methods[9]; that is, use of chloranil as a dehydrogenating agent resulted in shortening the reaction time and increasing the yield. C_1-Functionalization of **9a** was achieved by a modified Reissert reaction with diethyl phosphorocyanidate[10] (DEPC) via the N-oxide (**10a**). The modification of the cyano group of **11a** with HCl/MeOH [to methyl ester (**12**)] or with DIBAL [to the aldehyde (**13**)] for converting the nitrile (**11a**) into natural products was unsuccessful, while **11a** was converted to the 1-acetyl compound (**14**) by the reaction with MeLi, followed by treatment with SiO_2. And last, the debenzylation of **14** by our method[11] gave the target compound (**1b**) very smoothly. The synthetic **1b** (mp 211–212.5°C) was identical with the natural one (mp 208°C) in all respects.

To overcome the difficulty that the cyano group of the 9-benzyl compound (**11a**) could not be converted to ester group as mentioned above, debenzylation of **11a** to **11b** was tried. However, no debenzylation occurred. Thus, **11b** was synthesized from ethyl indole-2-carboxylate (**5b**) according to the synthesis of the N-benzyl compound (**11a**). A problem in the NH-series was at the cyclization of the NH-glycine derivative (**7b**). Two cyclization directions were possible[12] for **7b** (1- and 3-positions, giving **8b** and **15**). Fortunately cyclization occurred exclusively at the desired 3-position. Reissert reaction of the N-oxide (**10b**) with DEPC gave the N-phosphorylated 1-cyano compound (**11c**) but not the NH 1-cyano compound (**11b**); that is, N-phosphorylation occurred concurrently with the Reissert reaction. Dephosphorylation was successful with KOH to give **11b** quantitatively. Treatment of both **11b** and **11c** with HCl/MeOH easily gave the 1-ester



Reagents and conditions : i) $LiAlH_4$ / THF, rt, ii) MnO_2 / CH_2Cl_2, rt, iii) H-Gly-OEt, $NaBH_3CN$ / MeOH, rt, iv) HCO_2Et, rt, v) PPA, 60° C, vi) $(CH_3O)_2C(CH_3)_2$, TsOH, chloranil / benzene, rt, vii) m-CPBA / CH_2Cl_2, rt, viii) DEPC, Et_3N / dioxane, reflux, ix) KOH / CH_3CN-H_2O, rt, x) MeLi / THF -50° C, xi) SiO_2, xii) $AlCl_3$ / benzene, rt, xiii) HCl-MeOH, rt.

Chart 1[13]

(**1c**, mp 192-194°C), which was identical with the natural product (mp 191-192°C).

The synthetic **1b** and **1c** should also serve as starting compounds for the synthesis of their congeners (**1**, **2**, **3**, and **4**). Yields of the benzyl series was superior to those of the NH series in each step. However, debenzylation by $AlCl_3$ in benzene is not necessarily successful for various 1-substituents, while the NH series is feasible for every step. Thus, the two routes are complementary.

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