

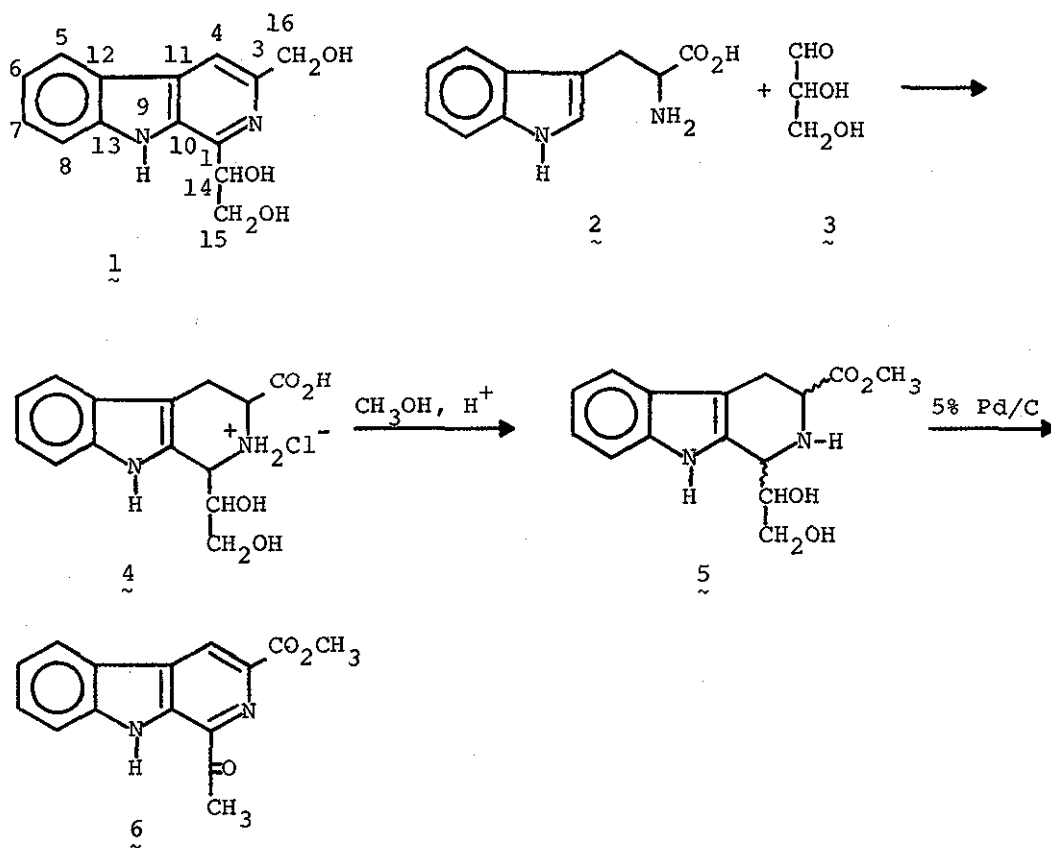
Synthesis of the Antibiotic, ( $\pm$ )-PyridindololGeng Wu, Etsuji Yamanaka, and James M. Cook<sup>\*</sup>,Department of Chemistry, University of Wisconsin-Milwaukee,  
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Pictet-Spengler condensation of tryptophan methyl ester **7** with glyceraldehyde acetonide **8** in refluxing benzene provided the 1,2,3,4-tetrahydro  $\beta$ -carboline **9** in good yield. The  $\beta$ -carboline was then converted in three steps to the  $\beta$ -galactosidase inhibitor, pyridindolol **1**.

Pyridindolol (**1**), a  $\beta$ -galactosidase inhibitor produced by Streptomyces alboverticillatus, was first isolated and identified by Umezawa and coworkers.<sup>1,2</sup> We now wish to report the total synthesis of ( $\pm$ )-pyridindolol (**1**).

The first attempts to synthesize **1** in our laboratories were based on a biogenetic approach. Pictet-Spengler reaction of dl-tryptophan (**2**) with dl-glyceraldehyde (**3**) in an acidic media<sup>3</sup> provided the diol **4** in moderate yield (Scheme I). This diol was then esterified to provide the methyl ester **5**, which was subsequently treated with 5% Pd/C to generate the fully aromatic  $\beta$ -carboline system. However, instead of the desired methoxycarbonyl derivative of **1** the product of this reaction was the methyl ketone **6** [mp 219-220°; IR (CHCl<sub>3</sub>) 3420, 1720, 1670 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  2.90 (s, 3H), 4.05 (s, 3H), 7.20-7.70 (m, 3H), 8.10 (d, J = 8 Hz, 1H), 8.90 (s, 1H), 10.40 (s, 1H); MS: m/e 268 (M<sup>+</sup>)]. The

SCHEME I

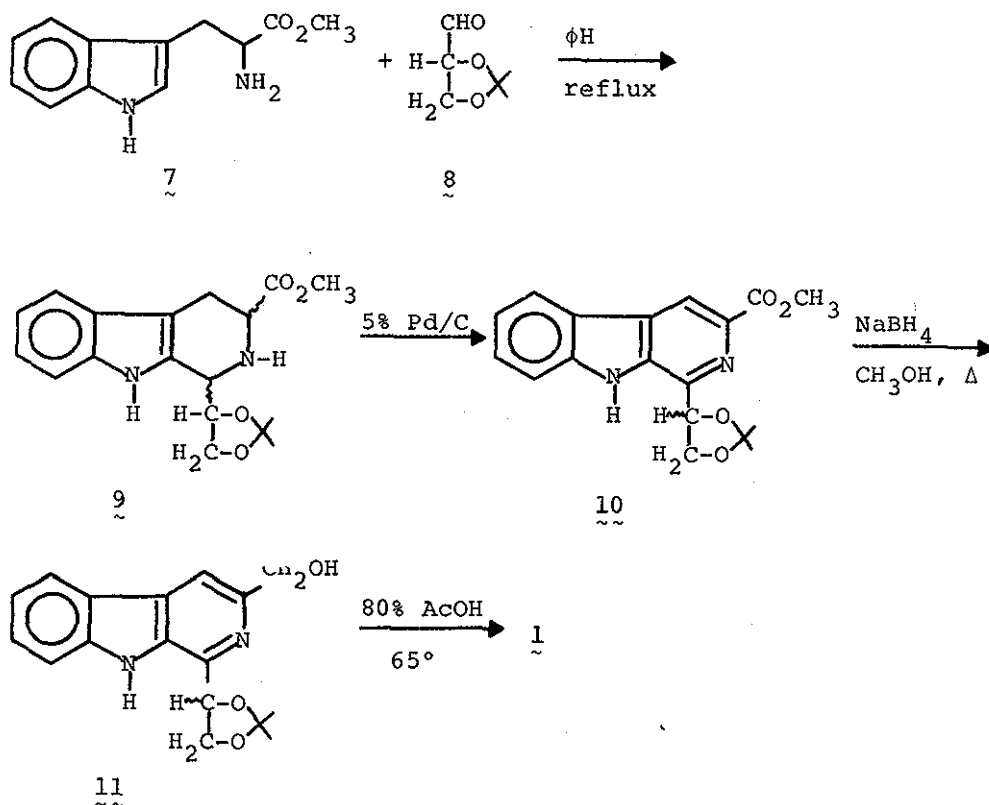


ketone 6 gave a positive test with 2,4-dinitrophenylhydrazine and a negative test with Tollen's reagent, in complete agreement with the assigned structure.

It was felt that some difficulty might be encountered in converting 5 to the 3-methoxycarbonyl derivative of 1, since 1,2,3,4-tetrahydro-8-carbolines with hydroxymethyl substituents attached to position 1 are rather labile;<sup>3-5</sup> therefore, the

need for protecting the hydroxyl functions to prevent loss of water was addressed. During work on the synthesis of other 1,2,3,4-tetrahydro- $\beta$ -carbolines, it had been found that Pictet-Spengler reactions of tryptophan methyl ester with acid labile aldehydes could be carried out in high yield in non-acidic aprotic media.<sup>6</sup> These conditions would permit the use of a protected glyceraldehyde molecule which would otherwise be labile in acidic media. Many simple attempts to prepare a functionalized glyceraldehyde species were unsuccessful; however, the acetonide of D-glyceraldehyde was obtained relatively easily from D-mannitol by the combined methods of Vargha<sup>7</sup> and Fischer.<sup>8</sup> Pictet-Spengler condensation of tryptophan methyl ester with the aldehyde 8 in refluxing benzene provided a 90% yield of a mixture of diastereomers represented by structure 9: [IR (film) 3435, 3400, 3000, 1740  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.38 (s, 3H), 1.50 (s, 3H), 2.22 (s, 1H), 2.90 (m, 2H), 2.50-4.50 (m with 3 sharp singlets, 8H), 6.90-7.60 (m, 4H), 8.40 (s, 1H); MS:  $m/e$  330 ( $\text{M}^+$ )]. Since the chirality at positions 1 and 3 of ring C would be destroyed on conversion to the  $\beta$  carboline 10 (Scheme II), no attempt was made to separate this mixture. The mixture of diastereomers 9 showed an overall rotation in the levorotary direction, which indicated that complete racemization had not occurred during reaction in refluxing benzene: heating 7 with 8 in an aqueous acidic medium would have led to a racemic mixture of 9. Aromatization of 9 with 5% Pd/C in refluxing cumene gave the  $\beta$ -carboline 10; however, this base was optically inactive. Not only had the chirality at positions 1 and 3 been

SCHEME II

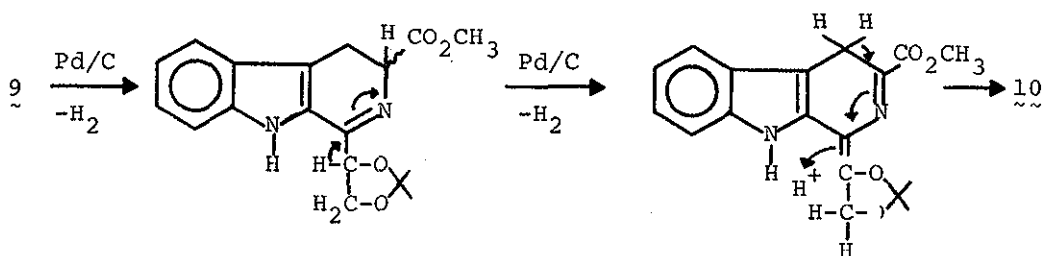


destroyed under these conditions, but racemization of the D-acetonide had also occurred. The structure of the  $\beta$ -carboline 10 was confirmed by IR, NMR, and mass spectroscopy [mp 220-222°, IR (film) 3430, 3000, 1720, 1620, 1250  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.55 and 1.60 (2s, 6H), 4.05 (s, 3H), 4.50 (m, 2H), 5.65 (t, 3H), 7.15-7.65 (m, 3H), 8.10 (d,  $J = 7.5 \text{ Hz}$ , 1H), 8.70 (s, 1H), 9.60 (s, 1H); MS:  $m/e$  326 ( $\text{M}^+$ )]. The methyl ester 10 was reduced to

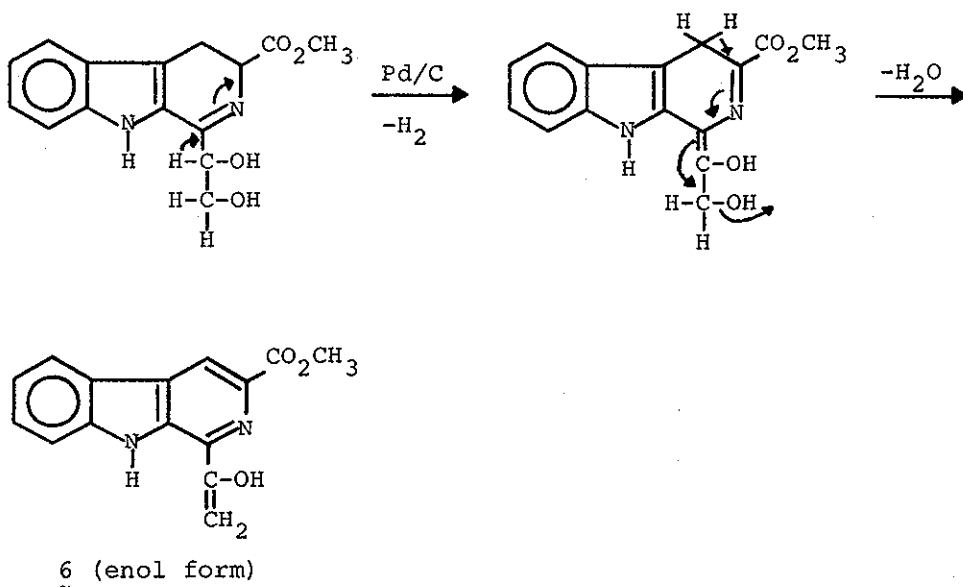
the alcohol 11 by stirring with  $\text{NaBH}_4$  in refluxing methanol<sup>9</sup> or reaction with lithium borohydride [mp 124-125°, IR (film) 3435, 3420-3100, 3000, 1630; NMR ( $\text{CDCl}_3$ )  $\delta$  1.57 (s, 6H), 4.40 (m, 2H), 4.80 (s, 2H), 5.52 (t, 1H), 7.00-7.56 (m, 3H), 7.78 (s, 1H), 8.00 (d,  $J = 8$  Hz, 1H), 9.15 (s, 1H); MS:  $m/e$  298 ( $\text{M}^+$ )]. Removal of the acetonide group was carried out in 70% yield by warming 11 in 80% acetic acid for 25 hrs.<sup>10</sup> The spectral data for the triol 1 (mp 169-170°, lit.<sup>1</sup> mp 167-168°) obtained by this procedure were identical in all respects to the published data for pyridindolol (1), except for the optical rotation which in our case was zero.

A possible mechanism for the racemization of the chiral center of the acetonide during the aromatization process, which is also consistent with the formation of the methyl ketone 6 generated from 5, is outlined in Scheme III. The common feature of both reactions is the introduction of the 1,2-double bond in ring C of the tetrahydro- $\beta$ -carboline as shown in Scheme III. The other steps are proposed to follow as illustrated.

SCHEME III



SCHEME III (contd)

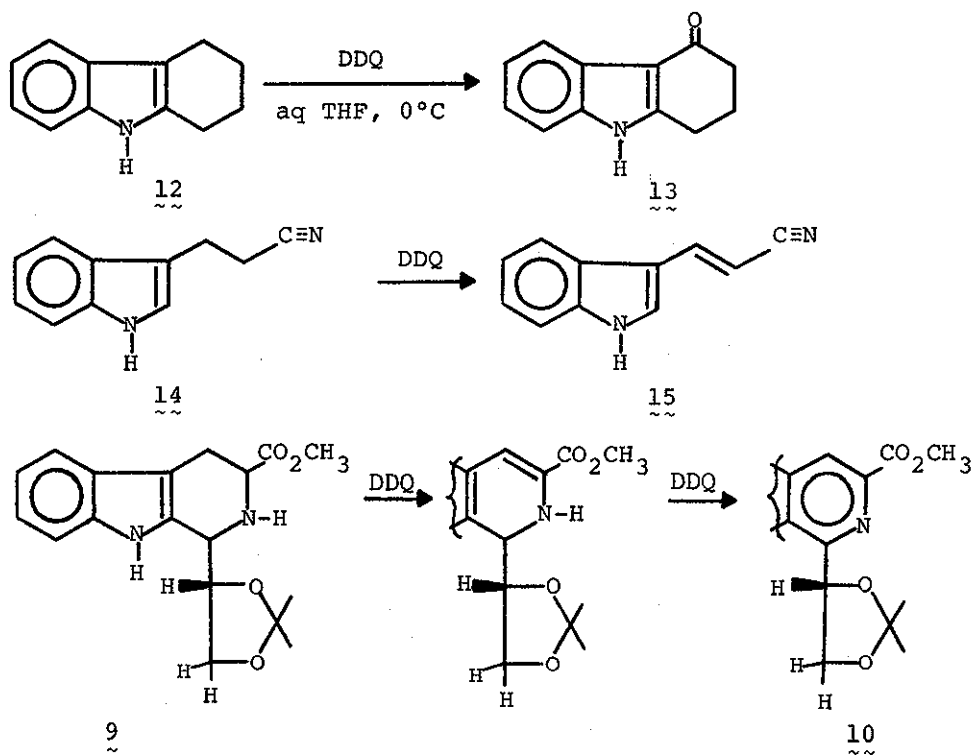


To test this hypothesis, other methods to convert 9 to 10 were considered. The introduction of unsaturation at the 3,4-position of ring C, followed by removal of hydrogens across the C(1)-N(2) bond to furnish the fully aromatic  $\beta$ -carboline 10, seemed particularly attractive.

Oikawa and Yonemitsu have recently reported that the four position of tetrahydrocarbazole 12 is selectively attacked by DDQ in aqueous solution<sup>11</sup> to provide an 83% yield of the 4-oxo derivative 13. Similarly, LeQuesne and coworkers have observed that the cyanoindole (14) on treatment with DDQ was dehydrogenated in high yield to provide the  $\alpha$ - $\beta$  unsaturated nitrile 15.<sup>12</sup> Therefore, the tetrahydro  $\beta$ -carboline 9, slightly enriched in the S isomer, was stirred in benzene with DDQ. The

yield of this reaction was only 45%; however, the  $\beta$ -carboline 10 obtained was optically active with a rotation ( $\alpha_D^{23} = 5.5^\circ$ ) in the dextrorotary direction (see Scheme IV). Reduction of the

## SCHEME IV



methyl ester and cleavage of the acetonide (see above) provided pyridindolol ( $\alpha_D^{23} = 7.7^\circ$ ). Clearly the retention of some optical activity supports the mechanisms outlined in Scheme III (Pd/C) and Scheme IV (DDQ), for introduction of the 3-4 double bond followed by aromatization of ring C precludes racemization via the enamine, illustrated in Scheme III for the Pd/C oxidation.

Pyridindolol enriched in either the (+) isomer (D-acetonide) or the natural isomer (L-acetonide) can be prepared by this method from D-mannitol and L-mannitol, respectively. However, the optically active glyceraldehyde-acetonides will racemize overnight even on standing at low temperature.<sup>13</sup> The acetonide must be used immediately and we were never able to isolate 8 optically pure. The Pictet-Spengler product 9 was obtained on a 10 gram scale ( $\alpha_D^{23^\circ} = -11^\circ$ ), and was converted to pyridindolol ( $\alpha_D^{23^\circ} = 7.7^\circ$ ). With smaller amounts of material the tetrahydro  $\beta$ -carboline 9 could be formed in higher optical purity ( $\alpha_D^{23^\circ} = -25^\circ$ ) but significant amounts are not yet available to convert 9 to the natural product.

In conclusion, it appears that preparation of  $\beta$ -carboline alkaloids in optically active form can be accomplished via Pictet-Spengler condensations in aprotic solvents. In the glyceraldehyde-D-acetonide case it does not seem possible to obtain pyridindolol ( $\alpha_D^{23^\circ} = -49^\circ$ ),<sup>1</sup> optically pure, on a practical basis; however, the reaction in aprotic media does perhaps provide a means to achieve this objective with aldehydes less prone to racemization.

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References and Notes

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