

A SIMPLE SYNTHESIS OF THE INDOLE ALKALOID BIPOLARAMIDE AND ITS DERIVATIVES¹⁾

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The first total synthesis of bipolaramide was achieved in 47% overall yield from (2S)-2,3-dihydroindole-2-carboxylic acid in three steps, utilizing thallium chemistry. Some derivatives, with dihalogeno or dialkenyl substituents at the 4 and 11 positions of (6aS-cis)-6a,7,13a,14-tetrahydropyrazino[1,2-a:4,5-a']diindole-6,13-dione have also been prepared.

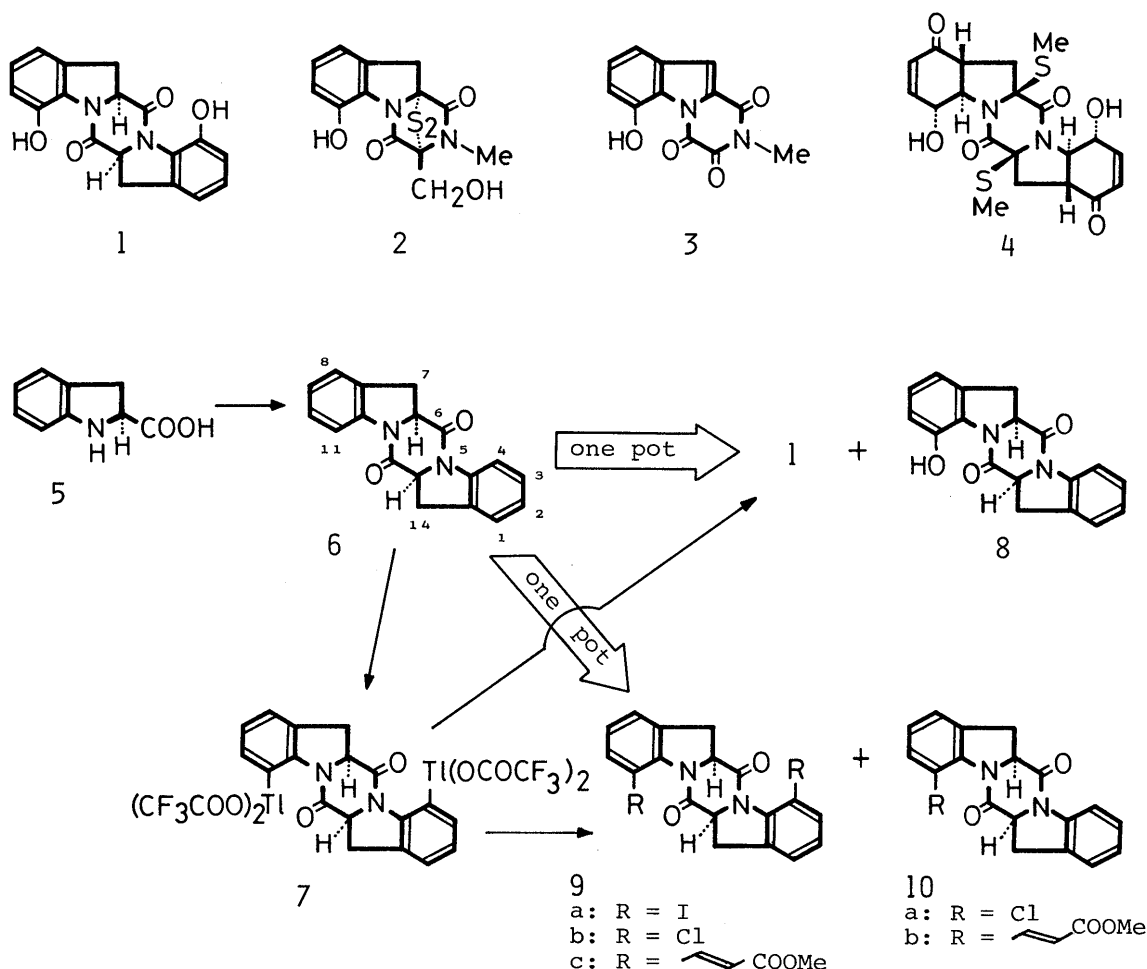
KEYWORDS bipolaramide; indole alkaloid; thallium chemistry; thallation-palladation method; 4,11-disubstituted (6aS-cis)-6a,7,13a,14-tetrahydropyrazino[1,2-a:4,5-a']diindole-6,13-dione; total synthesis

Bipolaramide ((-)-1) is an indole alkaloid isolated from cultures of *Bipolaris sorokiniana* in 1985 by Steyn and co-workers.²⁾ Many structurally related indole alkaloids are reported, such as dehydrogliotoxin³⁾ (2), dioxopiperazinoindole⁴⁾ (3), and exserohilone⁵⁾ (4). These alkaloids have either a 7-hydroxy-1-acyl-indole or a 7-hydroxy-2,3-dihydroindole structure as a common skeleton. An attempt to achieve total synthesis of the alkaloids and their derivatives makes it necessary to develop a new functionalization reaction working effectively at the 7-position of 1-acyl-2,3-dihydroindole. To meet this requirement, and based on our synthetic philosophy,⁶⁾ we have developed a straightforward and regioselective novel synthesis method utilizing thallium chemistry.⁷⁾ Here, we report the successful application of our method to the first simple total synthesis of (-)-1. We also describe the synthesis of some derivatives carrying dihalogeno or dialkenyl substituents in place of the dihydroxy groups at the 4 and 11 positions of (-)-1.

First, commercially available (2S)-2,3-dihydroindole-2-carboxylic acid ((-)-5, $[\alpha]_D^{20}$ -13.3° (c=0.30, MeOH)) was transformed to (6aS-cis)-6a,7,13a,14-tetrahydropyrazino[1,2-a:4,5-a']diindole-6,13-dione ((-)-6, mp 270-271°C, $[\alpha]_D^{23}$ -3.45° (c=0.61, CHCl₃)) in 76% yield, using 1,3-dicyclohexylcarbodiimide (3 mol eq) in tetrahydrofuran at room temperature for 1 h. The next thallation of (-)-6 with thallium tris(trifluoroacetate) (2.4 mol eq) in trifluoroacetic acid at room temperature for 24 h afforded dithallated compound ((-)-7, mp 198°C (dec.), $[\alpha]_D^{22}$ -82.7° (c=0.208, DMSO)) in 51% yield. Subsequent treatment of (-)-7 with cupric sulfate pentahydrate (CuSO₄·5H₂O, 10 mol eq) in N,N-dimethylformamide (DMF)-water (H₂O) (1:1, v/v) at 132°C for 3 h produced the monohydroxylated compound ((-)-8, mp 226-227°C, $[\alpha]_D^{26}$ -127° (c=0.251, CHCl₃)) and (-)-1 (mp 299-301°C, $[\alpha]_D^{22}$ -203° (c=0.286, acetone)) in 5% and 62% yields, respectively. ¹H-NMR (400 MHz), ¹³C-NMR (100.4 MHz), and IR spectra, admixed mp, $[\alpha]_D$, and tlc behavior of the synthetic (-)-1 were identical with those of bipolaramide ((-)-1).²⁾ In a simple one-pot reaction, (-)-1 was also prepared in 35% overall yield, together with a 5% yield of (-)-8 by the thallation of (-)-6, followed by treatment with CuSO₄·5H₂O.

Treatment of (-)-7 with potassium iodide (20 mol eq) in H₂O at room temperature for 1 h afforded diiodo compound ((-)-9a, mp 266-267°C, $[\alpha]_D^{23}$ -514.9° (c=0.255, CHCl₃)) in 20% yield. Under similar reaction conditions, (-)-9a was obtained from (-)-6 in 29% overall yield in a one-pot procedure. An attempt to improve the yield of (-)-9a by treating (-)-7 with cuprous iodide (2 mol eq) and I₂ (3 mol eq) in DMF^{8d)} resulted in a poor yield (16%). But chlorine was successfully introduced by treating (-)-7 with cupric chloride (10 mol eq) in DMF at 122°C for 5 h, affording the dichloro compound ((-)-9b, mp 304-306°C (dec.), $[\alpha]_D^{24}$ -470.2° (c=0.258, CHCl₃)) in 78% yield. By the one-pot procedure, (-)-9b was obtained from (-)-6 in 46% overall yield, together with a 3% overall yield of the monochloro compound ((-)-10a, mp 245-246°C, $[\alpha]_D^{25}$ -301.5° (c=0.202, CHCl₃)).

The thallation-palladation method⁸⁾ was also successfully used to synthesize alkenylated derivatives of (-)-1. Thus, the reaction of (-)-7 with methyl acrylate in the presence of a catalytic amount of palladium acetate in DMF produced the dialkenylated compound ((-)-9c, mp 194-195°C, $[\alpha]_D^{28}$ -487.6° (c=0.178, CHCl₃)) and the monoalkenylated compound ((-)-10b, mp 272-273°C, $[\alpha]_D^{26}$ -406.7° (c=0.195, CHCl₃)) in 30% and 34% yields,



respectively. One-pot synthesis of (-)-9c and (-)-10b from (-)-6 was also carried out with 13% and 24%, respectively.

In conclusion, we have developed a simple method for synthesizing bipolaramide. We had already described the thallation-palladation method,⁸⁾ and various kinds of derivatives of (-)-1 can be produced by applying it to the key dithallated compound ((-)-7). Applying the improved Heck reaction⁹⁾ to (-)-9a should also be promising for producing various derivatives needed for evaluating their pharmacological activities.

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