A SIMPLE SYNTHESIS OF THE INDOLE ALKALOID BIPOLARAMIDE AND ITS DERIVATIVES[1)]

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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.

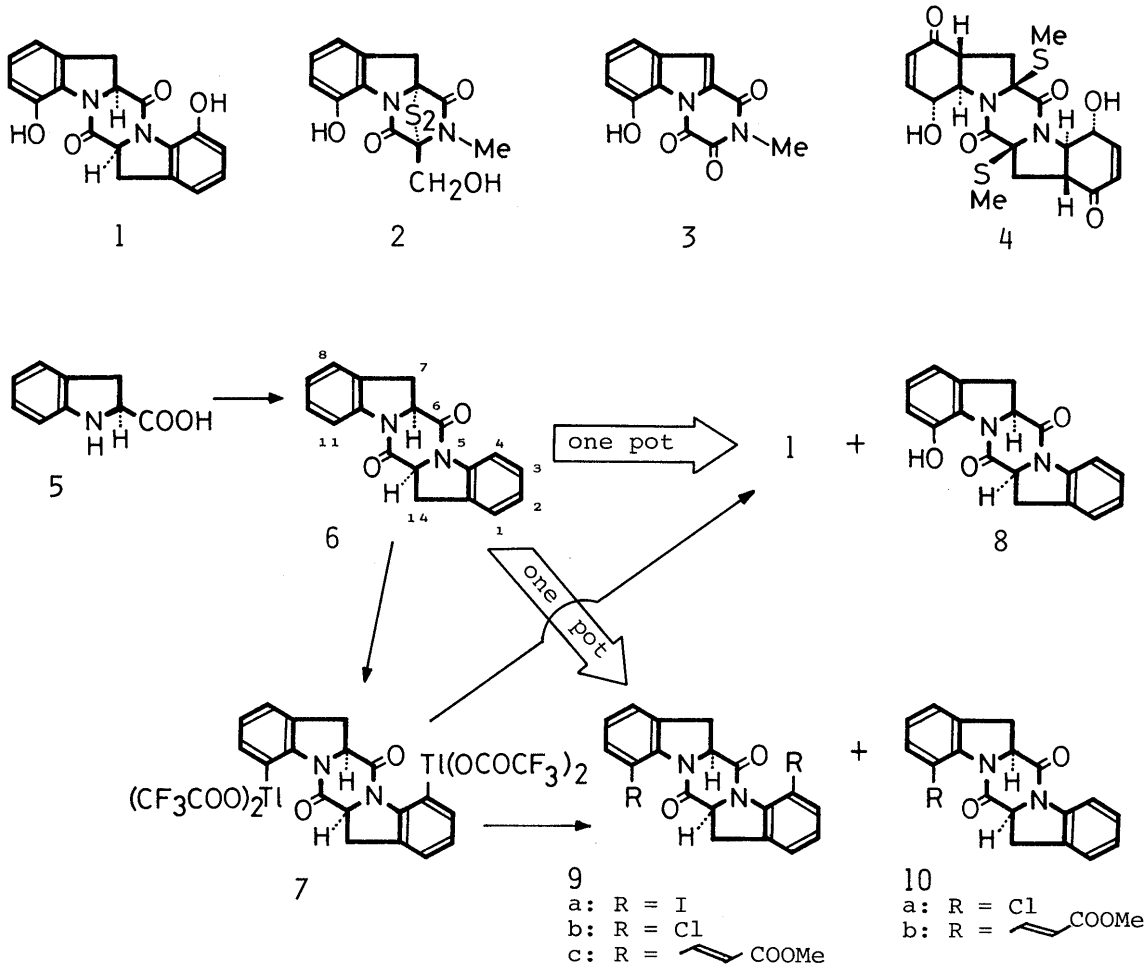
KEYWORDS bipolaramide; indole alkaloid; thallium chemistry; thallation-palladation method; 4,11-disubstituted (6aS-cis)-6a,7,13a,14-tetrahydropyrazino[1,2-a:4,5-a']diindole-6,13-dione; total synthesis

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 dehydrogliotoxin[3)] (2), dioxopiperazinoindole[4)] (3), and exserohilone[5)] (4). These alkaloids have either a 7-hydroxy-1-acylindole 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, $CHCl_3$)) 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 ($CuSO_4 \cdot 5H_2O$, 10 mol eq) in N,N-dimethylformamide (DMF)-water (H_2O) (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, $CHCl_3$)) and (-)-1 (mp 299-301°C, $[\alpha]_D^{22}$ -203° (c=0.286, acetone)) in 5% and 62% yields, respectively. ^{1}H-NMR (400 MHz), ^{13}C-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 $CuSO_4 \cdot 5H_2O$.

Treatment of (-)-7 with potassium iodide (20 mol eq) in H_2O at room temperature for 1 h afforded diiodo compound ((-)-9a, mp 266-267°C, $[\alpha]_D^{23}$ -514.9° (c=0.255, $CHCl_3$)) 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 I_2 (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, $CHCl_3$)) 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, $CHCl_3$)).

The thallation-palladation method[8)] 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, $CHCl_3$)) and the monoalkenylated compound ((-)-10b, mp 272-273°C, $[\alpha]_D^{26}$ -406.7° (c=0.195, $CHCl_3$)) 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 reaction[9] to (-)-9a should also be promising for producing various derivatives needed for evaluating their pharmacological activities.

ACKNOWLEDGMENT The authors express their cordial gratitude to Dr. R. Vleggaar for providing us with precious alkaloid, bipolaramide.

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(Received September 25, 1989)