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The Synthesis of Roeharmine and (-)-1,2,3,4-Tetrahydroroeharmine

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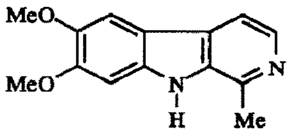
Abstract: *The total synthesis of roeharmine 1 as well as an enantiospecific synthesis of (-)-1,2,3,4-tetrahydroroeharmine 2 has been achieved via the Pictet-Spengler reaction as a key step. The optical rotation of synthetic (-)-2 was found to be higher than that reported for the natural product. A possible mechanism for the racemization of 2 upon exposure to acid has been proposed and serves as a warning to alkaloid chemists who isolate ring-A alkoxylated indole alkaloids under acidic conditions.*

There has been a long standing interest in our laboratory in the total synthesis of complex indole alkaloids *via* the enantiospecific Pictet-Spengler reaction as a key step.[1a,b] Recently, the isolation of four new *Roemaria* alkaloids (see for example 1 and 2)[2] has attracted our attention. The 6,7-ring-A *bis*methoxylated substitution pattern of these β-carbolines is identical to that found in the potent convulsant DMCM.[3] This latter β-carboline was shown to reverse the effects of a lethal dose of pentobarbital in mice.[3] In addition, the low optical rotation of 2 suggested that a tetrahydro β-carboline of this type might undergo racemization when subjected to the acid/base conditions employed during the standard isolation procedure.[2] In this report we wish to disclose the synthesis of roeharmine 1 and (-)-1,2,3,4-tetrahydroroeharmine 2, as well as propose a mechanism for the racemization of 2 upon exposure to acid.[4]

From a retrosynthetic perspective, both alkaloids 1 and 2 can be envisaged to arise from the Pictet-Spengler reaction of 5,6-dimethoxytryptamine 3 with acetaldehyde. Although the commercially available 5,6-dimethoxyindole 4 is relatively expensive, it can be prepared on multigram scale by way of the Moody azide pyrolysis.[5,6] As illustrated in Scheme 1, condensation of 3,4-dimethoxy benzaldehyde (80g) with methyl azido acetate (221g) furnished the α-azidocinnamate 6 (95g) as a crystalline solid.[5,6] Slow addition of a solution (xylene) of azide 6 (90g) to boiling xylene (145°C) furnished a 90% yield of the indoles 7 and 8 in a ratio of 1:10. The desired indole 8 was produced with high regioselectivity and was easily separated from indole 7 by fractional crystallization on multigram scale. The ester function from 8 was removed (*via* 9) under standard conditions[6] to provide the 5,6-dimethoxyindole 4.



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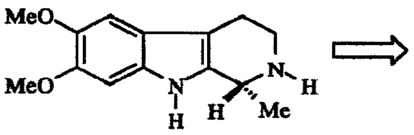

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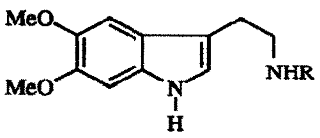
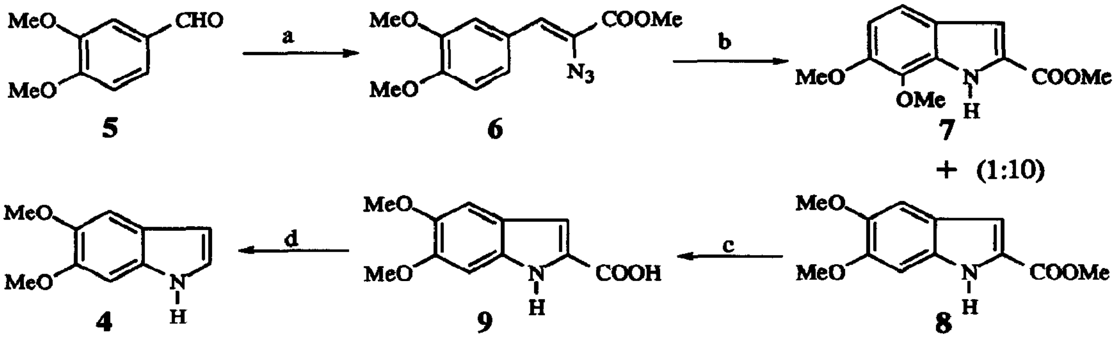


3

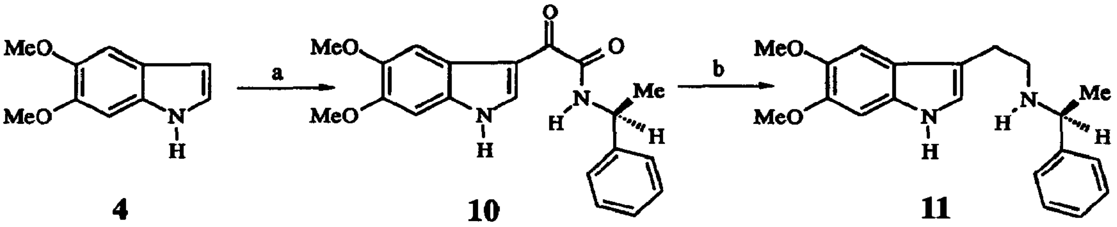
Scheme 1



Reagents & Conditions: a) N_3CH_2COOMe, NaOMe, MeOH, -8°C to 5°C, 4h, 75%; b) xylenes, 140° to 145°C, 90%; c) 2N NaOH(aq), 100°C, 6h, 90%; d) copper powder, quinoline, reflux, 2h, 82%.

Initial attempts to transform indole **4** to the optically active tryptamine **11** *via* the glyoxamide **10** employing the conditions of Speeter and Anthony[7] were successful, albeit in low yield. However, modification of this procedure has now dramatically improved this process and provided a route to tryptamines even when primary amines are employed. Treatment of indole **4** with oxalyl chloride in ether[7] furnished the 5,6-dimethoxyindolyl-3-glyoxalyl chloride as an insoluble solid, which on reaction with (S)-α-methylbenzylamine hydrochloride in the presence of excess triethylamine in dichloromethane afforded the glyoxamide **10** in 75% yield. Reduction of both oxygen functions of glyoxamide **10** with AlH_3, generated *in situ* in THF,[8] provided the desired tryptamine **11** in yields ranging from 85 to 90% with no racemization of the chiral auxillary.

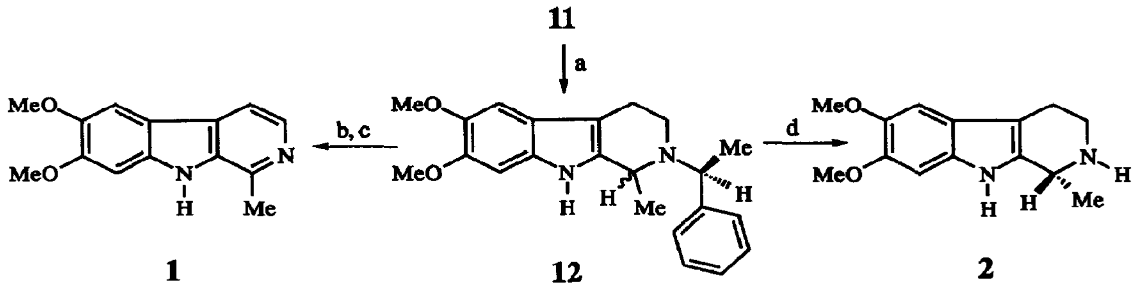
Scheme 2



Reagents & Conditions: a) i) oxalyl chloride, ether, 0°C, 45 min., ii) (S)-(-)-α-methylbenzylamine hydrochloride, CH_2Cl_2, Et_3N , 0 to 25°C, 4h, 75%; b) AlH_3, THF, 0 to 25°C, 4h, 85 to 90%.

As illustrated in Scheme 3, Pictet-Spengler condensation of **11** with acetaldehyde under the nonacidic aprotic conditions developed by Soerens et al.[9] furnished **12** as a mixture of diastereomers in a ratio of 1.8:1. Although the diastereoselectivity was disappointing, the two diastereomers of **12** could be separated with ease. For the preparation of **1** this was not necessory. The mixture of tetrahydro β-carbolines **12** was subjected to catalytic debenzylation, followed by aromatization over activated manganese dioxide in refluxing benzene[10] to afford **1**. The spectral data of synthetic **1** were identical to that reported for the natural product.[2]

Scheme 3

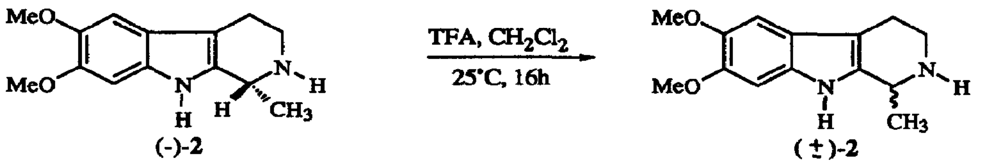


Reagents & Conditions: a) acetaldehyde, benzene, sealed tube, 85 to 90°C, 18h, 95%; b) NH_4CO_2H, (10%) Pd/C, EtOH, 25°C, 8h; c) MnO_2, benzene, 85°C, 4h, 55%; d) i) separation, ii) NH_4CO_2H, (10%) Pd/C, EtOH, 25°C, 8h, 72%.

Chromatographic separation of the major diastereomer of **12** by flash chromatography (silica gel) was then followed by catalytic transfer hydrogenation (pH 7-8) to provide (-)-1,2,3,4-tetrahydroroeharmine **2**, the spectral properties of which were identical to the natural product[2] except for the optical rotation. The specific rotation of **2** was found to be -18° (c= 1.04, MeOH), while that reported for the natural product was -4° (c= 0.12, MeOH).[2]

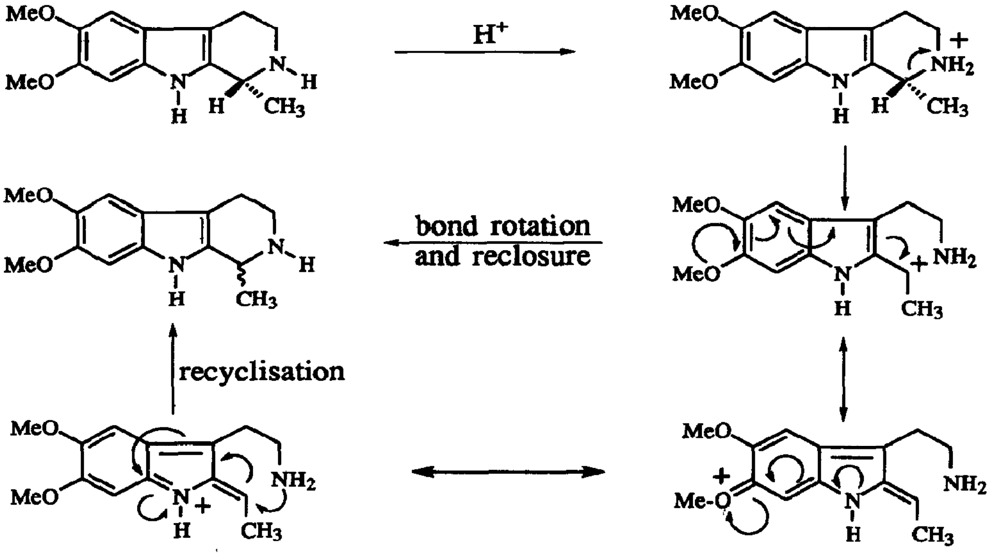
It was believed that the (-)-1,2,3,4-tetrahydroroeharmine **2** had undergone partial racemization during the acid/base mediated isolation procedure.[2] To test this hypothesis, optically pure **2**[11] was exposed to trifluoroacetic acid in dichloromethane at room temperature, as illustrated in Scheme 4. The proton NMR spectrum and R_f of the alkaloid which resulted was unchanged; however, the optical rotation of this material was now -0.8°. Based on this experiment, it is believed that the mechanism of racemization of **2** occurred as illustrated in Scheme 5. Racemization has occured *via* cleavage across the C(1)-N(2) bond in agreement with previous work from this laboratory.[12a,b] This postulated mechanism outlined in Scheme 5 is further supported by reaction of optically pure (-)-**2** with CF_3COOD in dichloromethane at 25°C. Although deuterium incorporation occurred at C(5) and C(8), no deuterium was found at C(1) of **2**, the optical rotation of this material was found to be near 0°.

Scheme 4



Although these β-carbolines are alkaloids of simple structure, the results observed here are important for all chemists who employ acidic conditions during isolation of ring-A methoxylated indole alkaloids. Care must be taken to avoid exposure of these bases to acid to prevent the opportunity for racemization. In addition, it is strongly believed the racemization of (-)-tetrahydroharmine reported by Brossi[13] occures *via* the pathway outlined in Scheme 5. It is important to note that both the Pictet-Spengler reaction under nonacidic conditions[9] and catalytic transfer hydrogenation (pH 7-8) were both key to the synthesis of optically pure (-)-**2**. Further studies on this mechanism of epimerization [cleavage across the C(1)-N(2) bond], as well as the synthesis of related indole alkaloids will be reported in due course.

Scheme 5



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