A Synthesis of the Amaryllidaceae Alkaloid Pratosine

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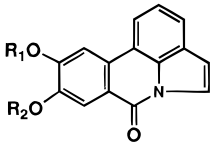
A synthesis of pratosine by thermolysis of the Michael adduct obtained from 5-hydroxy-8,9-dimethoxy-6(5*H*)-phenanthridone and methyl propiolate is described.

Pyrrolophenanthridine alkaloids, isolated from the bulbs of several *Crinum* species (Amaryllidaceae), comprise a group of tetracyclic lactams such as hippadine (**1**),[1−3] pratosine (**2**),[3] pratorinine (**3**),[2−6] and pratorimine (**4**).[2−6] The ability of hippadine to reversibly inhibit fertility in male rats[4] and the antitumor[7,8] activity of some members of this family of alkaloids have prompted the development of various synthetic methods[9] for these substances.



1 $R_1,R_2 = CH_2$

2 $R_1 = R_2 = Me$

3 $R_1 = H$; $R_2 = Me$

4 $R_1 = Me$; $R_2 = H$

We report here[10] the application of our previously described method[11] to the synthesis of pratosine (**2**) (Scheme 1), the characterization of various products formed in the key-transformation (**8** → **2**) and attempts to circumvent some of these undesired side-reactions.

Results and Discussion

The benzohydroxamic acid, derived from *N*-phenylhydroxylamine and 2-bromo-4,5-dimethoxybenzoyl chloride, and $BF_3{\cdot}Et_2O$ afforded the boron compound **5**[12] as a white solid, mp 158−159 °C, in more than 90% yield. Photolysis of a benzene solution of **5** using a Pyrex filter gave the cyclic borate **6**[12] from which the requisite hydroxamic acid **7** was liberated by aqueous hydrolysis. A base-catalyzed Michael addition of **7** to methyl propiolate provided the enol−ether **8**. Heating a solution of **8** in wet DMSO (0.03% H_2O v/v) under reflux (35 min) followed by workup and purification by preparative TLC led to the isolation of pratosine (**2**) in low yield (9%). Slow addition of the vinyl ether **8** to boiling DMSO containing H_2O and maintaining the reflux temperature (30 min) did not significantly alter the yield of the alkaloid, nor did systematic variation of the H_2O content (0.03% to 1%) in DMSO or of the temperature (130−180 °C). Optimal results were obtained by performing the thermolysis on a small scale for a shorter length of time (10 min) (50 mg; 3 mL wet DMSO, 0.03% in H_2O), combining five such experiments, and then working up the reaction mixture for products. By this process (see Experimental Section), the following substances were isolated and identified as: pratosine (**2**, 17%), 8,9-dimethoxy-6(5*H*)-phenanthridone[13] (**9**, 25%), *N*-(formylmethyl)-8,9-dimethoxy-6(5*H*)-phenanthridone (**10**, 15%), and 4-carbomethoxypratosine (**11**, 33%) (cf. Schemes 2 and 3).

The structure of aldehyde **10** follows from its exact molecular weight (M^+ 297.1010; $C_{17}H_{15}O_4N$ requires 297.1001) and spectral characteristics. The IR spectrum contained bands at 1710, 2830, and 1640 cm^{-1} consistent with the presence of an aldehyde and a δ-lactam group. The ^{1}H-NMR signals at δ 9.74 (1H, s, C*H*O), 5.24 (2H, s, CH_2CHO), 7.07, 7.33, 7.47, 7.62, 7.91, and 8.19 ppm (1H intensity each) and the lack of any exchangeable hydrogen with D_2O showed unambigously that the amide was tertiary.

Location of the CO_2Me group at C-4 and not at C-5 of the pyrrolophenanthridine nucleus in **11** was made on the basis of two strongly deshielded protons at δ 8.41 (1H, dd, $J_1 = 8$ and $J_2 = 3$ Hz, H-3) and 8.57 (1H, s, H-5) ppm in the ^{1}H-NMR spectrum. The corresponding hydrogens of pratosine resonated at δ 7.76 and 8.07 ppm, respectively.

Mechanistically the formation of the aldehyde **10** (Scheme 2) involves formally a 1,3-rearrangement of the vinyl ether **8**, followed by hydrolysis and decarboxylation of the resulting β-keto carboxylic acid. Heating **10** in wet DMSO under conditions of the formation of pratosine did not give the latter, indicating that **10** is not the precursor of **2**.

Although the generation of the phenanthridone **9** most probably occurs via homolysis of the weak N−O bond and subsequent quenching of the resulting amidyl radical,[14,15] the isolation of ester **11** (cf. Scheme 3) and pratosine (**2**) sheds some light on the nature of the various competitive processes that occur on thermolysis of **8**. Formation of **2** can be envisaged to occur by a sequence of reactions involving a 3,3-sigmatropic rearrangement to yield the aldehyde ester **12**, a nucleophilic attack of the nitrogen on the more electrophilic carbonyl carbon of the aldehyde group to form **13**, and hydrolysis of the ester **13** to produce the free acid **14**, which suffers decarboxylation with simultaneous loss of the hydroxyl group. Alternatively, the aldehyde ester **12** can suffer hydrolysis and decarboxylation, prior to cyclization to form aldehyde **15**, which on ring closure and elimination of H_2O generates alkaloid **2**. The same aldehyde ester (**12**) on cyclization and dehydration leads to pratosine 4-carboxylic ester (**11**). It thus became apparent that, in order to achieve a respectable yield of **2**, the hydroly-

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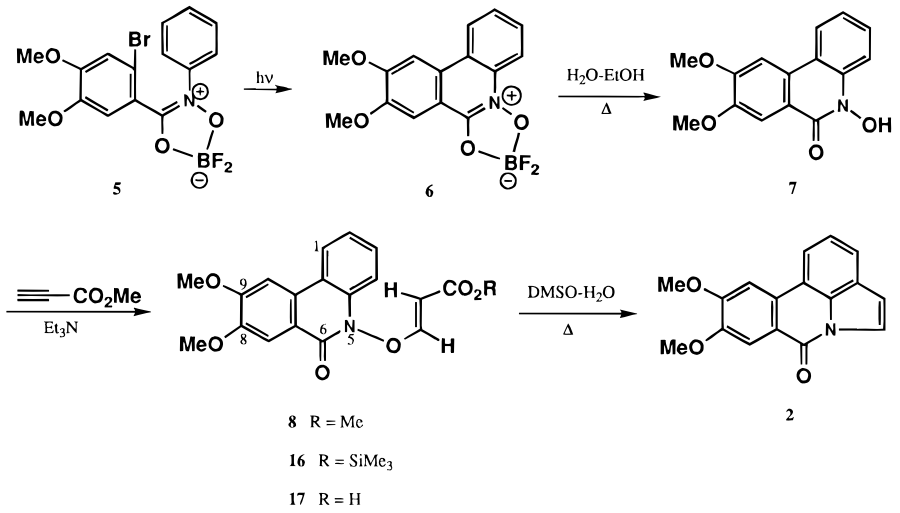
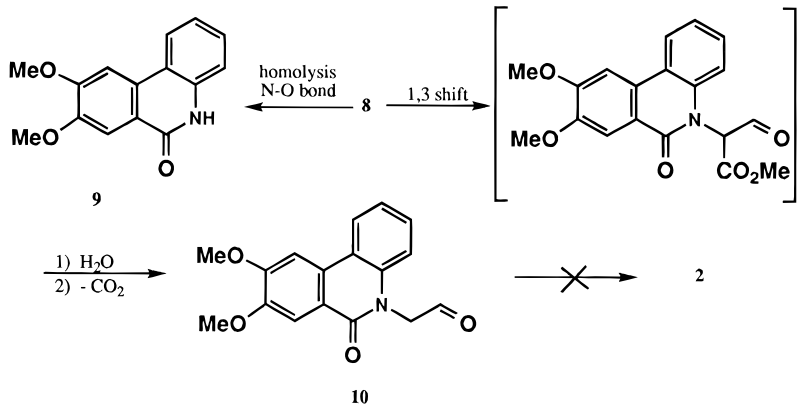
Scheme 1. Synthetic Scheme for Pratosine (**2**)



Scheme 2. Formation of **9** and **10** from **8**



sis of the ester group in **8** should occur prior to the 3,3-rearrangement, before the intermediate **13** is formed, or before dehydration of **13** occurs. Because the latter two conditions are difficult to realize experimentally, attempts were made to satisfy the first by the use of trimethylsilyl propiolate (since selective hydrolysis of **16** to the acid **17** can be brought about under neutral conditions, eg., by methanolysis). Accordingly, the reaction of trimethylsilyl propiolate[16] with two simple hydroxamic acids, *N*-phenylacetohydroxamic and *N*-phenylbenzohydroxamic acids, was performed to define appropriate experimental conditions for the necessary Michael addition to occur. However, no such addition took place under a variety of conditions, and the starting material either remained virtually unaltered at room temperature or yielded an intractable mixture under more drastic conditions (reflux, excess propiolate). Failure to obtain the Michael adduct with the silyl ester, which contrasts starkly with the behavior of the corresponding methyl ester, can be ascribed to one of two reasons. Either the nucleophile attacks the silicon atom, resulting in a simple transfer of the trimethylsilyl group to form the *O*-silyl ether of the hydroxamic acid, which regenerates the free hydroxamic acid with exceptional ease (viz. on chromatoplates used for monitoring the reaction), or the presence of the silicon atom in the β position, with respect to the carbonyl group in the electrophile, stabilizes the β carbon to such an extent that addition becomes unviable.

Attempts to force nucleophilic addition to the betaine,[17] obtained from triethylamine and propiolic acid, which had been shown to react with nucleophiles such as alkoxide[18] to furnish a β-alkoxyacrylic acid, with the hydroxamate anion (derived from **7**) proved to be unfruitful.

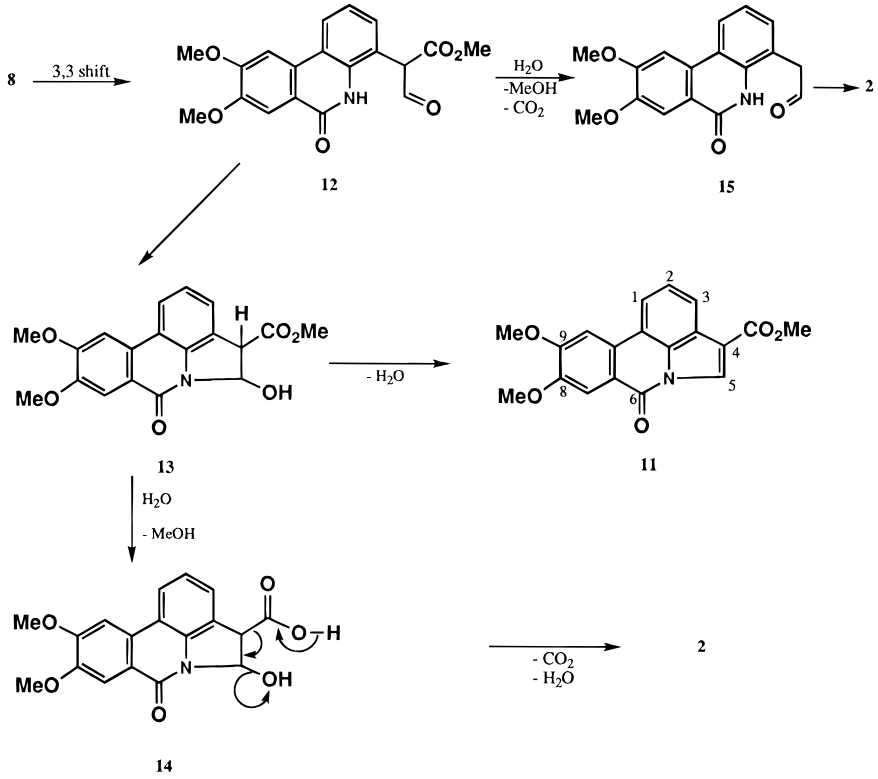
Experimental Section

General Experimental Procedures. Melting points were determined with a hot-stage microscope Reichert Thermovar and are uncorrected. IR were recorded with a Perkin-Elmer 157 Gand 683 grating infrared spectrophotometer, and frequencies are reported in cm^{-1}. ^1H-NMR spectra were obtained at 300 MHz with a Varian unit 300 spectrometer. Chemical shifts are reported in ppm downfield from TMS. HREIMS were measured in a Kratos MS-25 RF instrument using electron impact at 70 eV. Elemental analyses were carried out at the micro-analytical division of DTIQ-INETI, Queluz, Portugal.

N-Phenyl-2-bromo-4,5-dimethoxybenzohydroxamic acid: prepared, in 73% yield, from 2-bromo-4,5-dimethoxybenzoyl chloride and *N*-phenylhydroxylamine in ether, in the presence of K_2CO_3, mp 143−145 °C (from C_6H_6/*n*-hexane); found C, 51.48; H, 4.38; N, 3.88; $C_{15}H_{14}BrNO_4$ requires C, 51.56; H, 4.01; N, 3.98%.

2,2-Difluoro-4-phenyl-5-(2′-bromo-4′,5′-dimethoxyphenyl)-1,3-dioxo-4-azo-2-borocyclopent-4-ene (5). A mixture of the above acid (5.74 g) in dry

Scheme 3. Suggested Mechanism for the Formation of **2** and **11** from **8**



ether (400 mL) and freshly distilled BF_3-etherate (4 mL) was refluxed (30 min) and then allowed to stand at room temperature (24 h). The white crystalline solid that separated was filtered and crystallized (C_6H_6/*n*-hexane) to give the boron complex **5** (5.8 g, 90% yield), mp 158−159 °C; found C, 45.17; H, 3.32; N, 3.48; $C_{15}H_{13}BBrF_2NO_4$ requires C, 45.04; H, 3.28; N, 3.50%.

5-Hydroxy-8,9-dimethoxy-6(5*H*)-phenanthridone (7). The boron complex **5** (1 g) dissolved in dry C_6H_6 (130 mL) was irradiated (30 h) with a mercury lamp (Philips HPR 125W) using a Pyrex filter at 37 °C. The white crystalline precipitate of **6** that formed was decanted, washed with dry Et_2O, and dried to afford the cyclic boron complex **6** (mp 318−320 °C; 90% yield). A suspension of this compound (1 g) in H_2O (25 mL) and EtOH (50 mL) was heated to reflux (24 h). The mixture was cooled to 0 °C, and the solid **7**, collected by filtration, afforded the cyclic hydroxamic acid **7** (803 mg), mp 243−245 °C (from EtOH); found C, 66.24; H, 4.85; N, 5.27; $C_{15}H_{13}NO_4$ requires C, 66.41; H, 4.83; N, 5.17%.

***trans*-Methyl *β*-[6(5*H*)-Oxo-8,9-dimethoxyphenanthridinyl]-5-oxy]acrylate (8).** A mixture of the above compound **7** (500 mg), dry methyl propiolate (0.27 mL), and triethylamine (0.21 mL) in dry acetonitrile (200 mL) was stirred at room temperature (48 h). Evaporation of the solvent under reduced pressure and crystallization of the resulting brown solid (MeCN/*n*-hexane) afforded the thermally unstable acrylate derivative **8** in a reasonably pure state, mp 134−137 °C (dec); 82% yield; ν_{max} (KBr) 1715, 1660, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (3H, s), 4.04 (3H, s), 4.11 (3H, s), 5.42 (1H, d, J = 12 Hz), 7.88 (1H, d, J = 12 Hz). Attempts to purify the material by further crystallization served only to cause more decomposition.

Thermolysis of 8. The above acrylate (**8**) (50 mg) in DMSO (3 mL) containing H_2O (0.03%; v/v) was heated to reflux (10 min). The reaction mixtures from five such experiments were combined and poured into ice-water (100 mL). Rapid extraction with EtOAc and evaporation of solvent, after drying (Na_2SO_4) yielded a brown residue that was subjected to column chromatography (silica) using EtOAc/petroleum ether (1:1) as the eluent. The least polar substance, pratosine (**2**), was obtained as a white solid (17%), mp 238−240 °C (from CH_2Cl_2), lit.[3] mp 238−240 °C. Its chemical shifts (δ values) for various protons and ν_{max} data (IR) were identical to those recorded[3] for the alkaloid. Continued elution afforded a mixture of the aldehyde **10** and the amide **9**, which was rechromatographed on silica. Elution with EtOAc yielded the aldehyde **10**, crystallizing from ether/CH_3OH as a white solid (15%), mp 195−205 °C; ν_{max} (KBr) 2830 (*CH*O), 1710 (*CH*=*O*), 1640 (N−*C*=*O*)·cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04 (3H, s), 4.11 (3H, s), 5.24 (2H, s), 7.07 (1H, d, J = 8 Hz), 7.33 (1H, t, J = 8 Hz), 7.47 (1H, t, J = 8 Hz), 7.62 (1H, s), 7.91 (1H, s), 8.19 (1H, d, J = 8 Hz), 9.74 (1H, s); HREIMS M^+ 297.1010; $C_{17}H_{15}NO_4$ requires 297.1001.

The later fractions were evaporated to yield the phenanthridone **9** (25%), mp 296−298 °C, [lit.[12] mp 300−302 °C], ν_{max} (KBr) 3140−2840 (NH), 1650, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.91 (3H, s), 4.02 (3H, s), 7.23 (1H, t, J = 7.5 Hz), 7.33 (1H, d, J = 7.5 Hz), 7.43 (1H, t, J = 7.5 Hz), 7.71 (1H, s), 7.98 (1H, s), 8.39 (1H, d, J = 8 Hz), 11.50 (1H, s, exchangeable with D_2O). Evaporation of the aqueous solution under reduced pressure and high-vacuum sublimation of the residue afforded 4-carbomethoxypratosine (**11**) (33%) mp 320−321 °C, ν_{max} 1710, 1670 cm^{-1}, ^1H NMR (DMSO-d_6) δ 3.94 (3H, s), 3.96 (3H, s), 4.08 (3H, s), 7.63 (1H, t, J = 7.5 Hz), 7.87 (1H, s), 8.02 (1H, s), 8.13 (1H, dd, J_1 = 8 and J_2 = 3Hz), 8.41 (1H, dd, J_1 = 8 and J_2 = 3Hz), 8.57 (1H, s); HREIMS M^+ 337.0945; $C_{19}H_{15}O_5N$ requires 337.0950.

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