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New Developments of the Parham Cyclization Process. Applications in Natural Products Synthesis.

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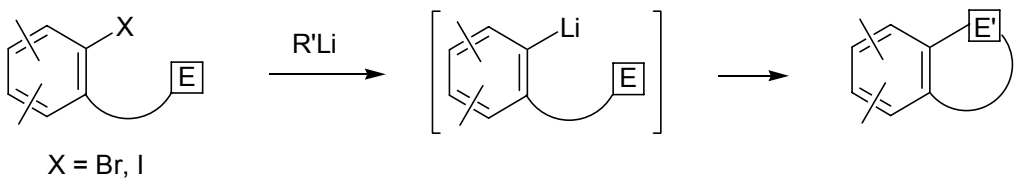
Introduction

The Parham cyclization process occupies a place of choice in the arsenal of the synthetic tactics for the assembling of carbo and heterocyclic systems. The protocol developed by Parham hinges upon aromatic lithiation, usually carried out by lithium-halogen exchange, and subsequent reaction with an internal electrophile [1] (Scheme1).



Scheme 1.

This technique has been widely used in heterocyclic synthesis mainly in alkaloid total synthesis but applications for the elaboration of five-membered lactams are scarce [2].

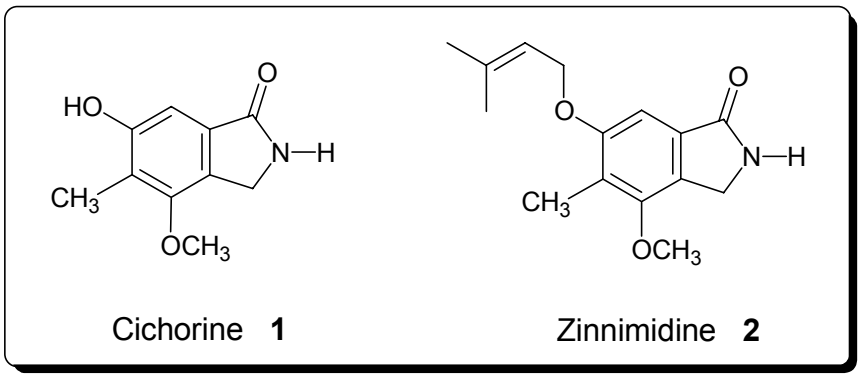
Results and discussion

In the course of our ongoing project dealing with the synthesis and subsequent biological evaluation of a variety of isoindolinone-centered natural products we herein wish to disclose an efficient synthetic approach to the isoindolinone ring system and further synthetic developments for the elaboration of structurally different naturally occurring compounds.

1. Synthesis of poly and differentially substituted isoindolinones. Total Synthesis of cichorine and zinnimidine.

1.1. Introduction.

Cichorine (**1**) and zinnimidine (**2**) have been isolated from phytopathogenic fungi from the genus *Alternaria* [3]. They are implicated in diseases of commercially important plants namely through necrosis of the tips and margins of infected specimen.



Cichorine **1** Zinnimidine **2**

We have developed a new synthetic approach to these poly and diversely substituted compounds which hinges upon the application of the Parham cyclization process to the bromoarylcarbamate **3**. Retrosynthetic analysis led to the disconnections indicated in Fig. 1 for the synthetically challenging construction of this parent compound with an exquisite arrangement of diverse and dense functionalities.

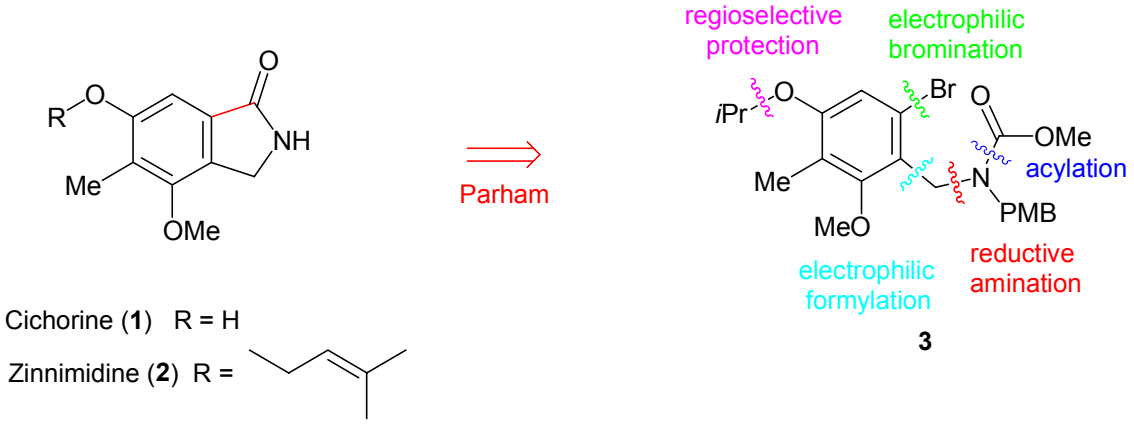
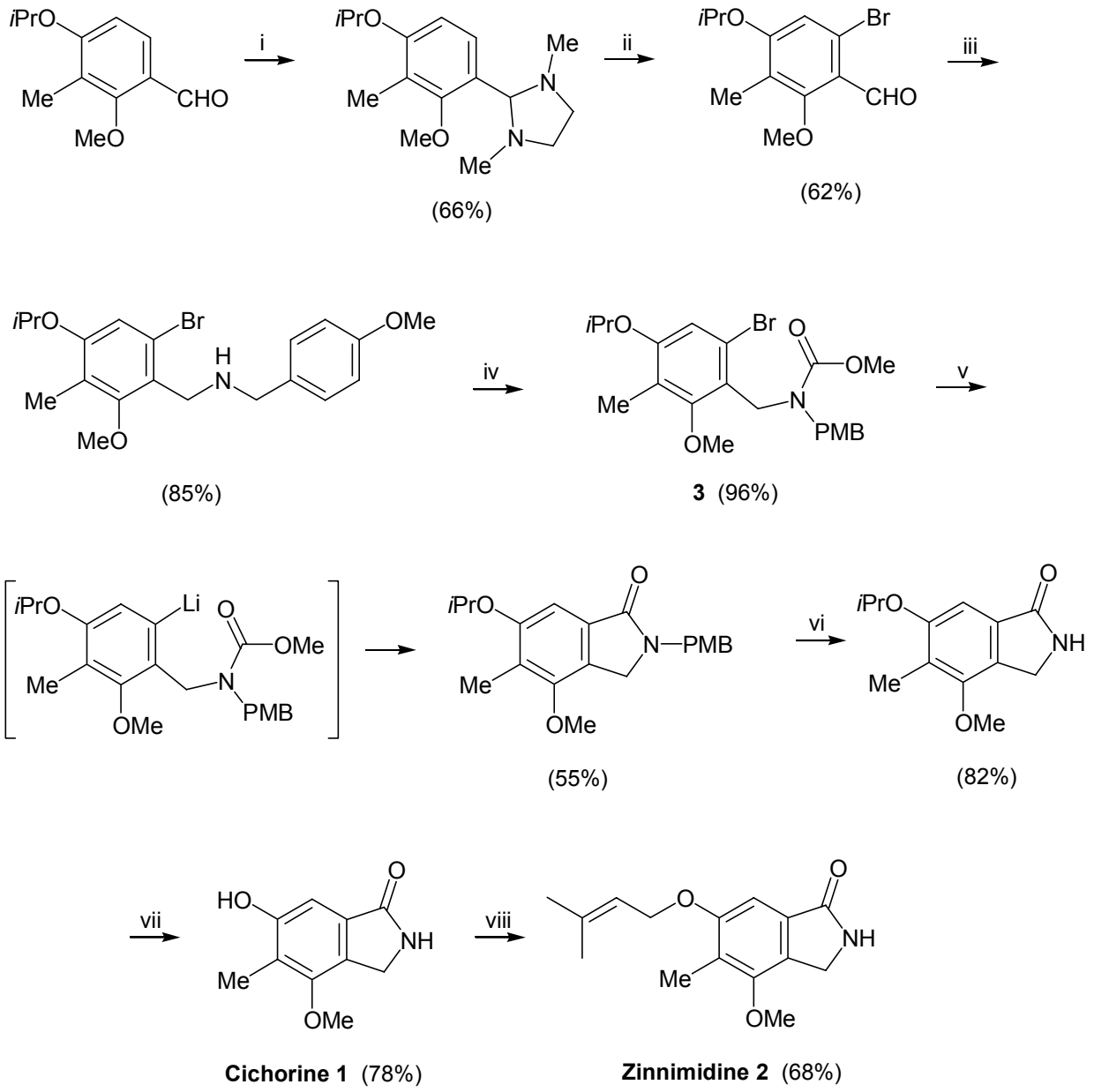


Figure 1.

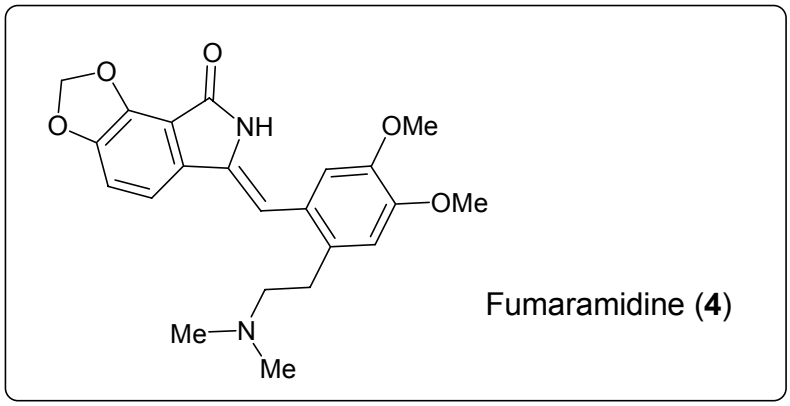
1.2. Total synthesis of cichorine and zinnimidine.



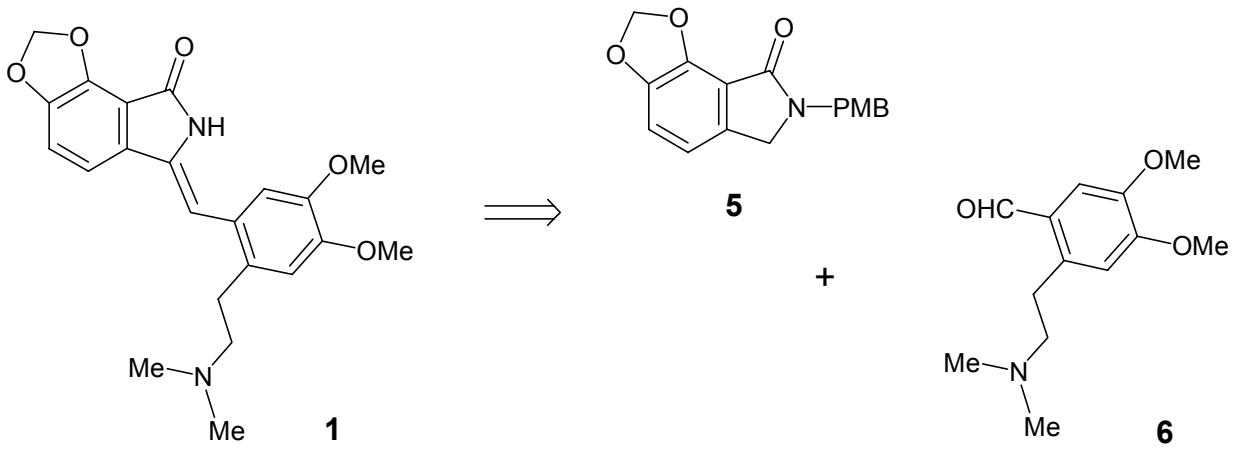
Scheme 2. *Reagents and conditions:* (i) *N,N'*-dimethylethylenediamine, toluene, reflux, 3 h; (ii) *t*BuLi, Et_2O, Ar, −30 °C, then 20 °C, 6 h, then −30 °C, $(BrCl_2C)_2$, then 20 °C 12 h, then HCl 10%, 20 °C, 30 min; (iii) *p*−$CH_3OC_6H_4CH_2NH_2$, toluene, reflux, 3 h, then $NaBH_4$, MeOH, 20 °C, 2 h; (iv) ClCOOMe, NEt_3, CH_2Cl_2, 0 °C, then 20 °C, 3 h; (v) *t*BuLi, THF, −100 °C, Ar, 30 min; (vi) TFA, anisole, reflux, 48 h; (vii) BCl_3, CH_2Cl_2, −78 °C, 2 h; (viii) 1-bromo-3-methylbut-2-ene, K_2CO_3, acetone, reflux, 12 h.

2. *Application to the synthesis of arylmethyleneisoindolinones. Total synthesis of fumaramidine.*

The creeper *Fumaria parviflora Lam* (*Fumariaceae*) is widespread in Pakistan where its extracts are used in folk medicine as blood purifier and in the treatment of diseases and diarrhea. [4] From the strongly basic extracts of dried plant material four enelactams including fumaramidine (**4**) were isolated [5] but the question arises whether this compound is present in the natural source or is formed in the course of its isolation. No total synthesis of this alkaloid has appeared in print.

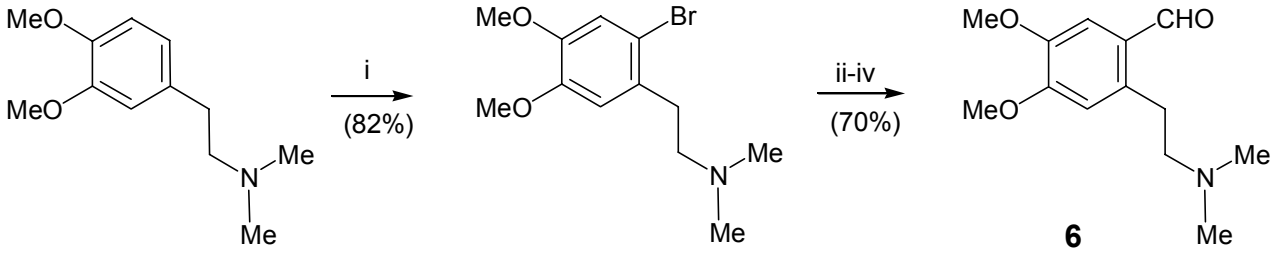


We assumed that fumaramidine (**4**) would conceivably be assembled by sequential basic treatment of the protected isoindolinone **5** , quenching with the appropriate aldehyde **6**, E1cb elimination and ultimate deprotection (retrosynthetic Scheme 3).



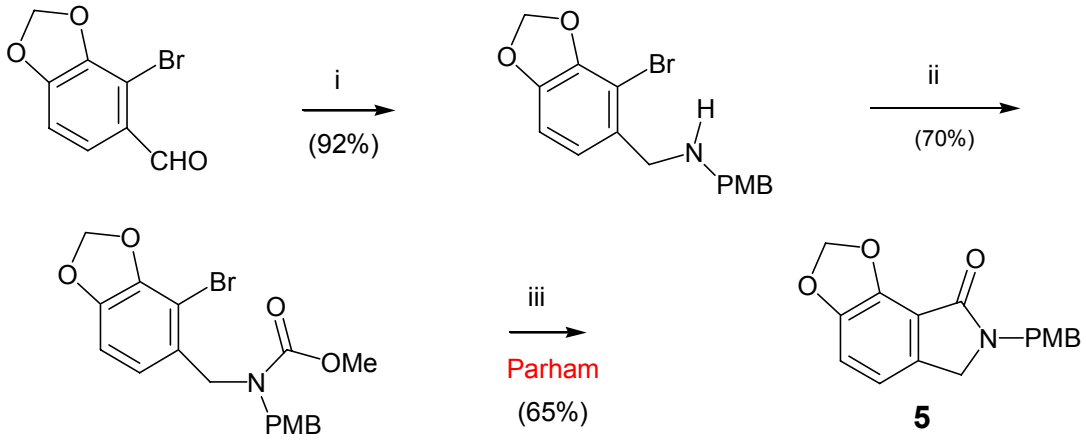
Scheme 3.

2.1. Synthesis of the first partner **6**.



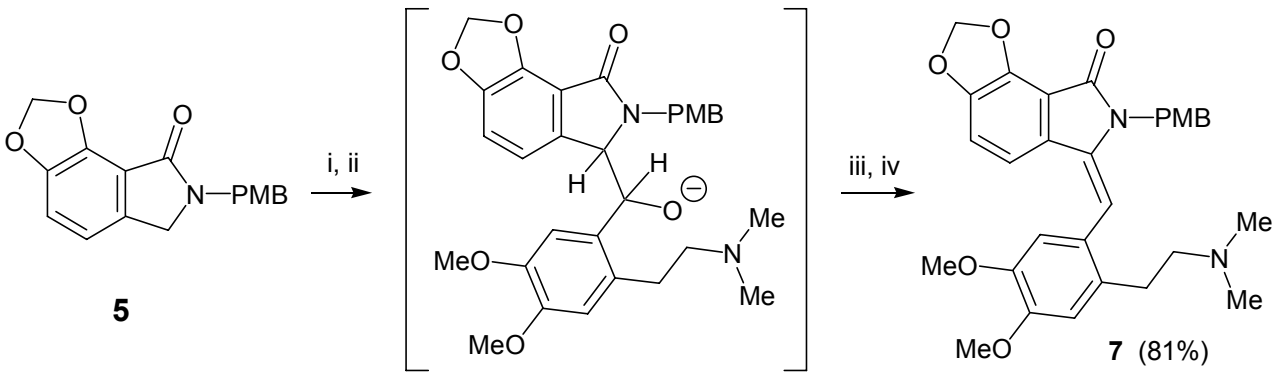
Scheme 4. *Reagents and conditions:* (i) Br_2, AcOH, AcONa, rt, 16 h; (ii) *n*BuLi, THF, -78 °C; (iii) DMF, -78 °C, 1 h; (iv) -78 °C to rt, then H_3O^+.

2.2. Application of the Parham protocol for the assemblage of the requisite isoindolinone **5**.



Scheme 5. *Reagents and conditions:* (i) *p*-Methoxybenzylamine, MeOH, then $NaBH_4$; (ii) ClCOOMe, Et_2O, 0 °C; (iii) *t*BuLi, THF, -90 °C, 30 min, then -40 °C, H_3O^+.

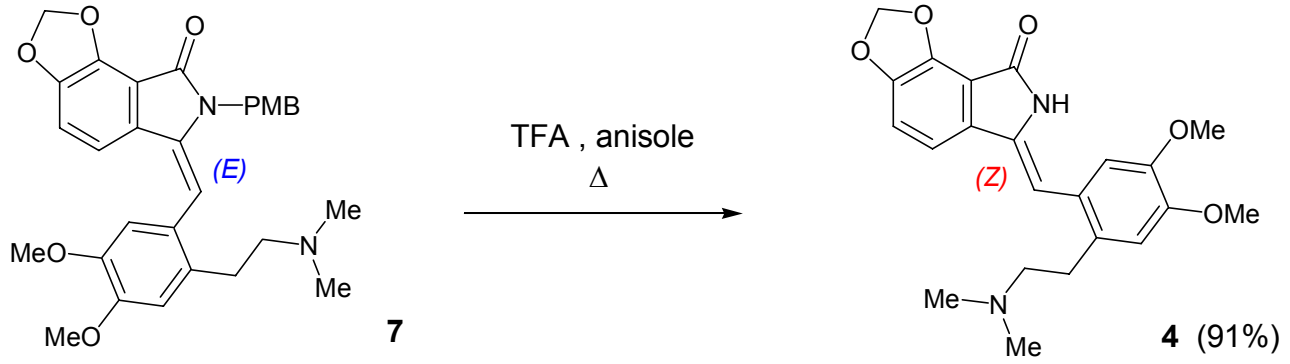
2.3. Assembling of the target enelactame **4**.



Scheme 6. *Reagents and conditions:* (i) KHMDS, THF, -78 °C; (ii) **6**, THF; (iii) Me_3SiCl, THF, -78 °C; (iv) KHMDS, -78 °C to rt.

2.4. Final deprotection.

Ultimate treatment of **7** with TFA-anisole triggers off the removal of the benzyl lactam protection and the formation of the mandatory *Z* configured stereoisomer **4**.



Scheme 7.

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