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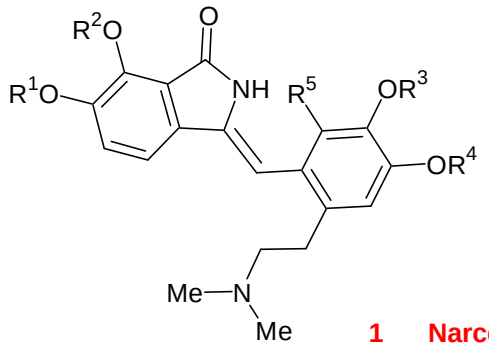
First Total Synthesis of Narceine Imide

Axel Couture,* Eric Deniau, Pierre Grandclaudon, Marc Lamblin

UMR 8009 "Chimie Organique et Macromoléculaire", associée à l'ENSCL,
Laboratoire de Chimie Organique Physique,
Bâtiment C3(2), Université des Sciences et Technologies de Lille 1,
F-59655 Villeneuve d'Ascq Cédex, France
**Axel.Couture@univ-lille1.fr*

Introduction

The creeper *Fumaria parviflora Lam* (*Fumariaceae*) is widespread in Pakistan where it is commonly known as Pit Papra and where its extracts are used in folk medicine as a blood purifier and as an anthelmintic, as well as in the treatment of skin diseases and diarrhea [1]. The crude alkaloidal extracts have initially indicated the presence of seventeen isoquinoline bases [2] and additionally four enelactams, i.e; narceine imide (**1**), fumaramidine (**2**), fumaramine (**3**) and fumaridine (**4**) (Fig. 1) were isolated from the strongly basic ethanolic extracts of dried plant material [3].



1	**Narceine imide**	**$R^1 = R^2 = Me$; $R^3,R^4 = -CH_2-$; $R^5 = OMe$**
2	Fumaramidine	$R^1,R^2 = -CH_2-$; $R^3 = R^4 = Me$; $R^5 = H$
3	Fumaramine	$R^1,R^2 = R^3,R^4 = -CH_2-$; $R^5 = H$
4	Fumaridine	$R^1 = R^2 = Me$; $R^3,R^4 = -CH_2-$; $R^5 = H$

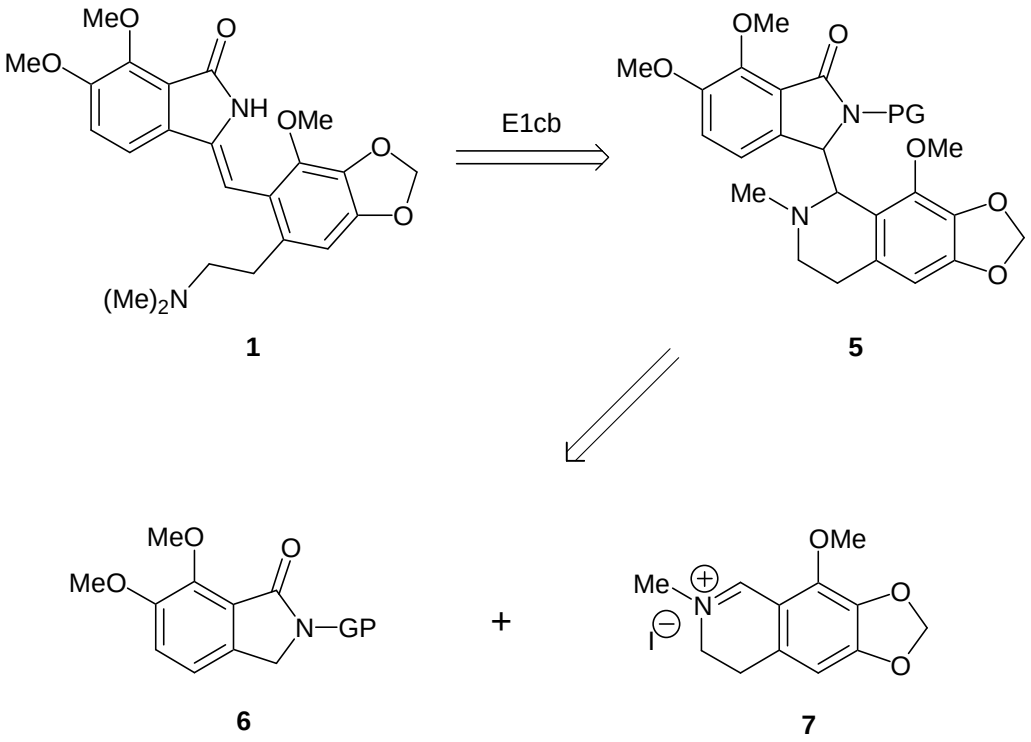
These enelactams are not generally considered to be true alkaloids but are regarded conceivably as artefacts formed during their basic extraction since their biogenetic precursors have been reported to be present in all the previously quoted *Fumariaceae* species [4.]

In the course of our ongoing project dealing with the synthesis of a variety of compounds comprising an arylmethyleneisoindolinone unit in opened [5] or in fused models [6] (e.g. aristolactams) we became interested in the synthesis of these enelactams and we embarked on the first total synthesis of the exemplary representative narceine imide **1**.

Results and Discussion

1. Retrosynthetic analysis

A conceptually new synthetic approach to this enelactamic compound **1**, bearing diverse and dense functionalities on the environmentally different aromatic units, has been developed and is presented in the Retrosynthetic Scheme.



1 **5**

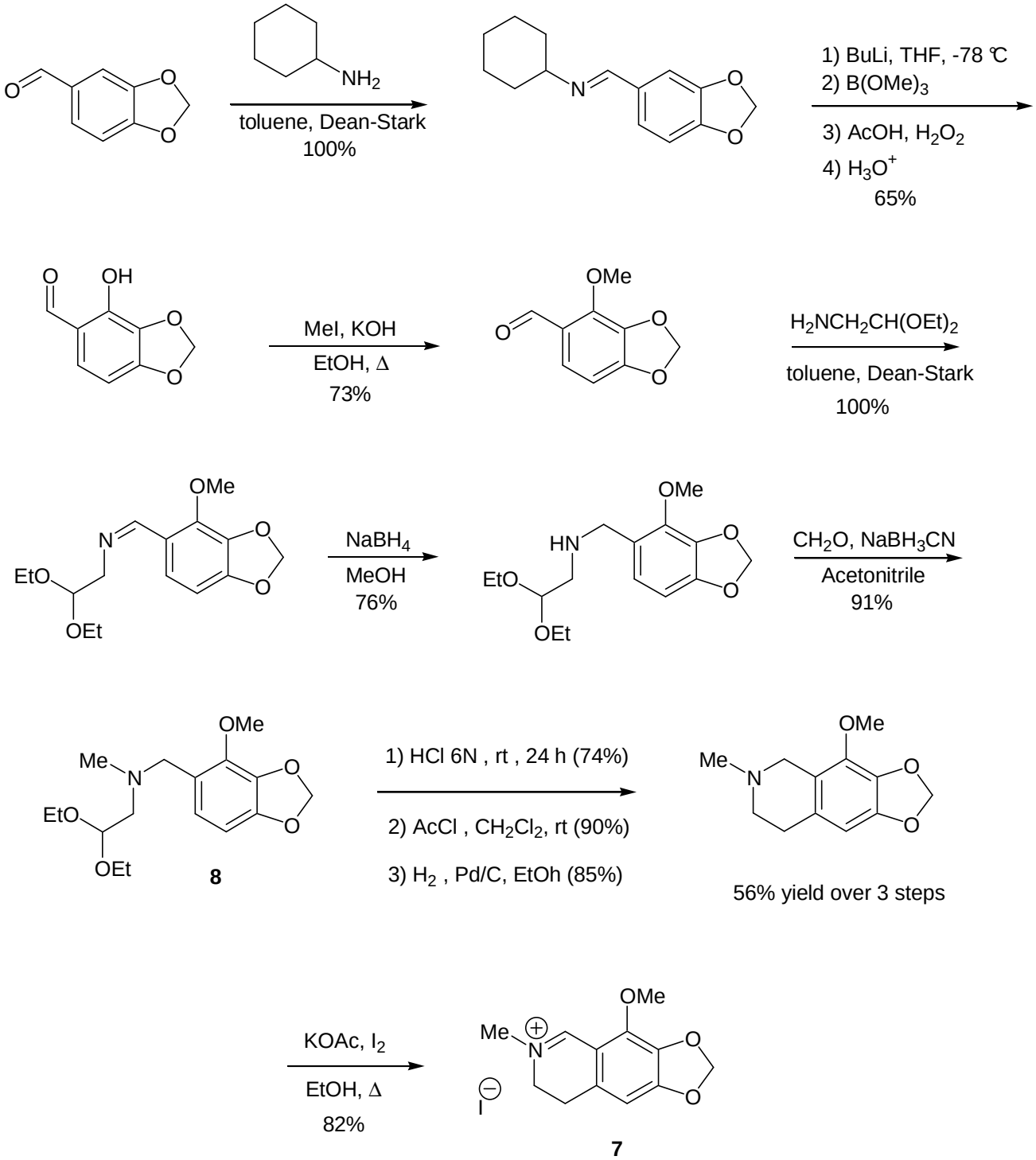
6 **7**

PG = protecting group

The key step was an E1cb elimination process applied to the polycyclic adduct **5** that allowed the creation of the pendant arylmethyene unit and the concomitant formation of the required dimethylaminoethyl chain present on the "southern" aromatic nucleus.
Adduct **5** could be in turn assembled by reaction of the metalated isoindolinone **6** with an iminium salt deriving from a suitably substituted isoquinoline **7**.

2. Construction of the Eschenmoser salt 7

The key step for the synthesis of the poly and diversely substituted isoquinolinium salt **7** was a Pomeranz-Fritsch type cyclization reaction of a suitably substituted aromatic aminoacetal **8**.



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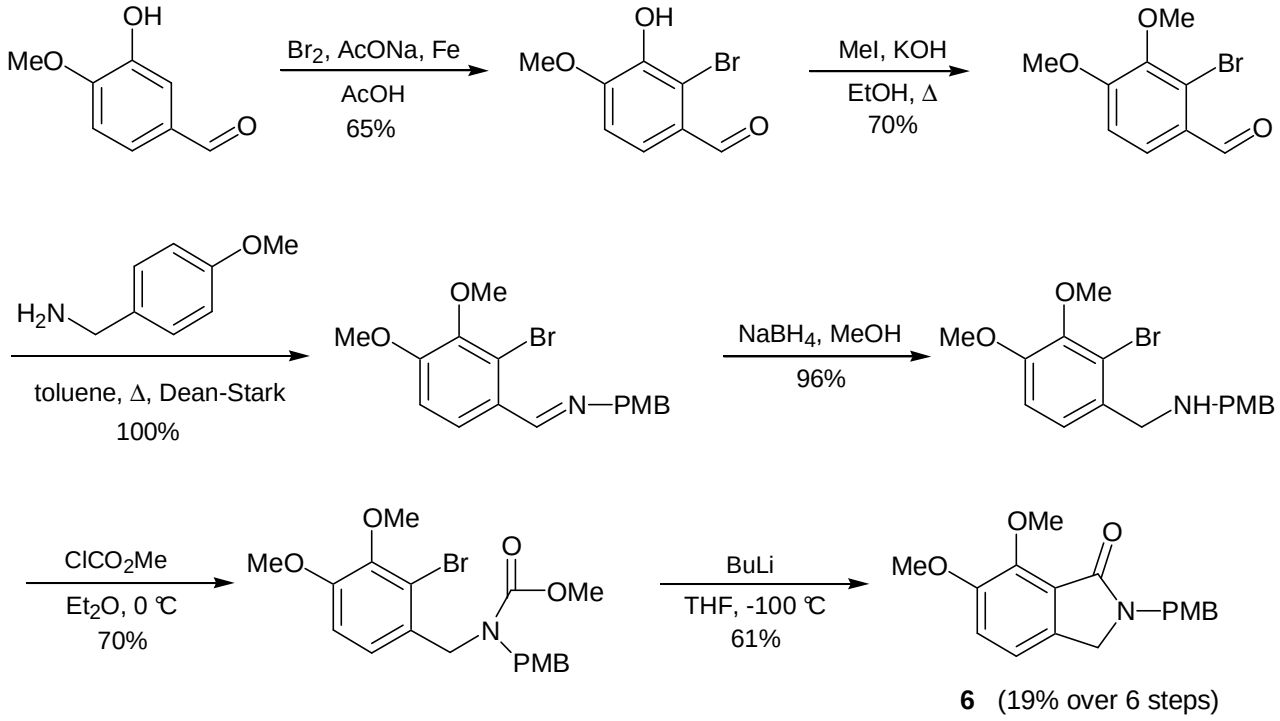
7

3. Elaboration of the parent dimethoxylated isoindolinone **6**

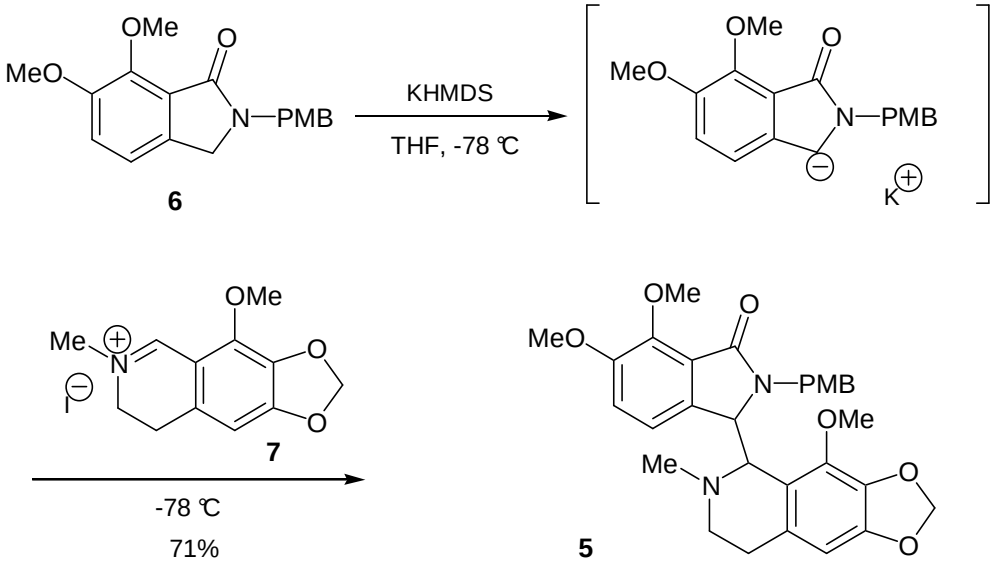
Our strategy for the construction of the five-membered lactam embedded in the isoindolinone framework was based upon the Parham cyclization process which hinges upon aromatic lithiation and subsequent reaction with an internal electrophile [7].



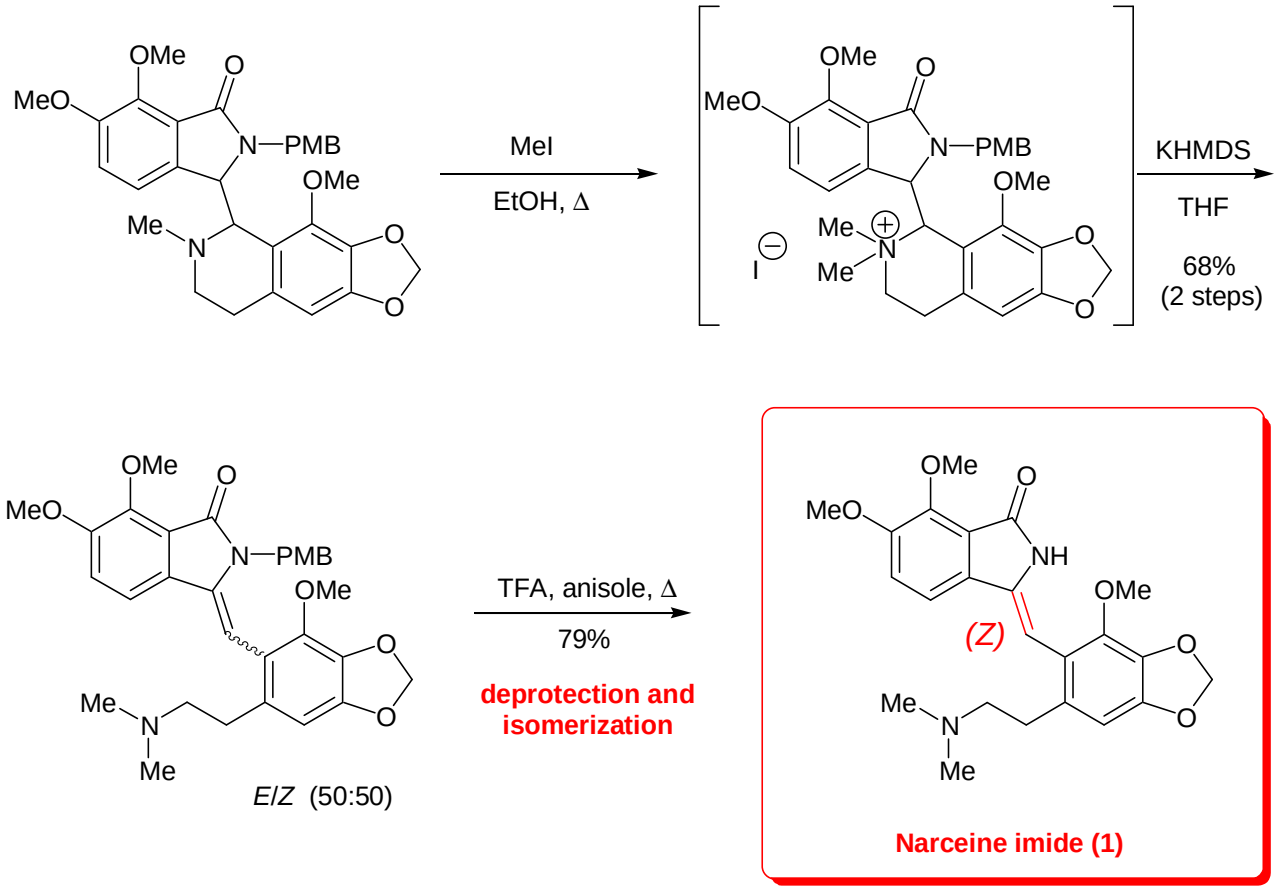
6 (19% over 6 steps)

4. Synthesis of the polyaza-adduct **5**

For the assembling of the congested adduct **5** we have taken advantage of the nucleophilicity of the benzylic α-aminocarbanionic species generated by basic treatment of the isoindolinone precursor **6** [8.]



5. The E1cb elimination / deprotection-isomerization sequence. Total synthesis of narceine imide (1)



It is noteworthy that the choice of the *para*-methoxybenzyl (PMB) group as the lactam protecting group was rewarded here since deprotection at high temperature under acidic conditions delivered the thermodynamically more stable (*Z*)-configurated natural product **1**. The target alkaloid **1** was obtained with a 38% yield over the last four steps.

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