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New Different Synthetic Approaches to the Isoindoloisoquinolone Skeleton. Total Synthesis of Nuevamine.

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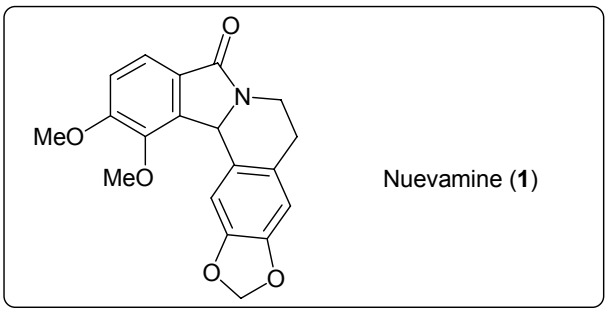
Introduction

Nuevamine (**1**) is the first isoindolo[1,2–*a*]isoquinolinone known to occur in nature and can still be considered the lone representative of this class of isoquinoline alkaloids. Initially the structure of this natural product which has been isolated from *Berberis darwinii Hook*, gathered in southern Chile, in the vicinity of Cuidad Osorno, [1] was erroneously assigned but later revision led unambiguously to structure **1** [2].

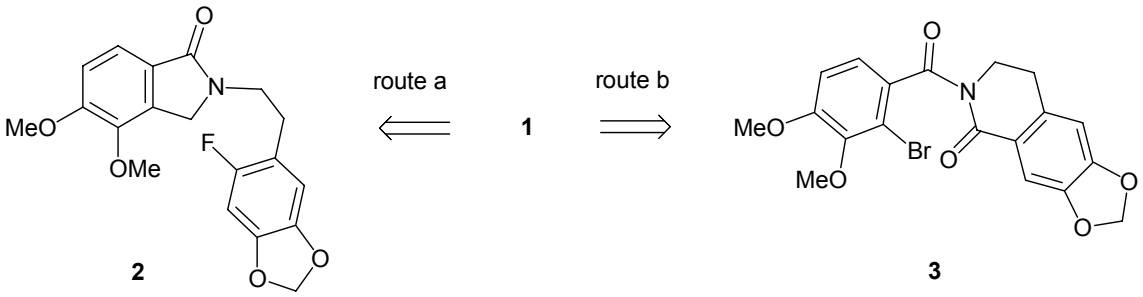


Nuevamine (**1**)

This alkaloid is an eminent member of the isoindoloisoquilinone family, but all of the synthetic methods developed for the construction of this class of tetracyclic lactams [3] are inadequate for the synthesis of this unique natural product.

Results and discussion

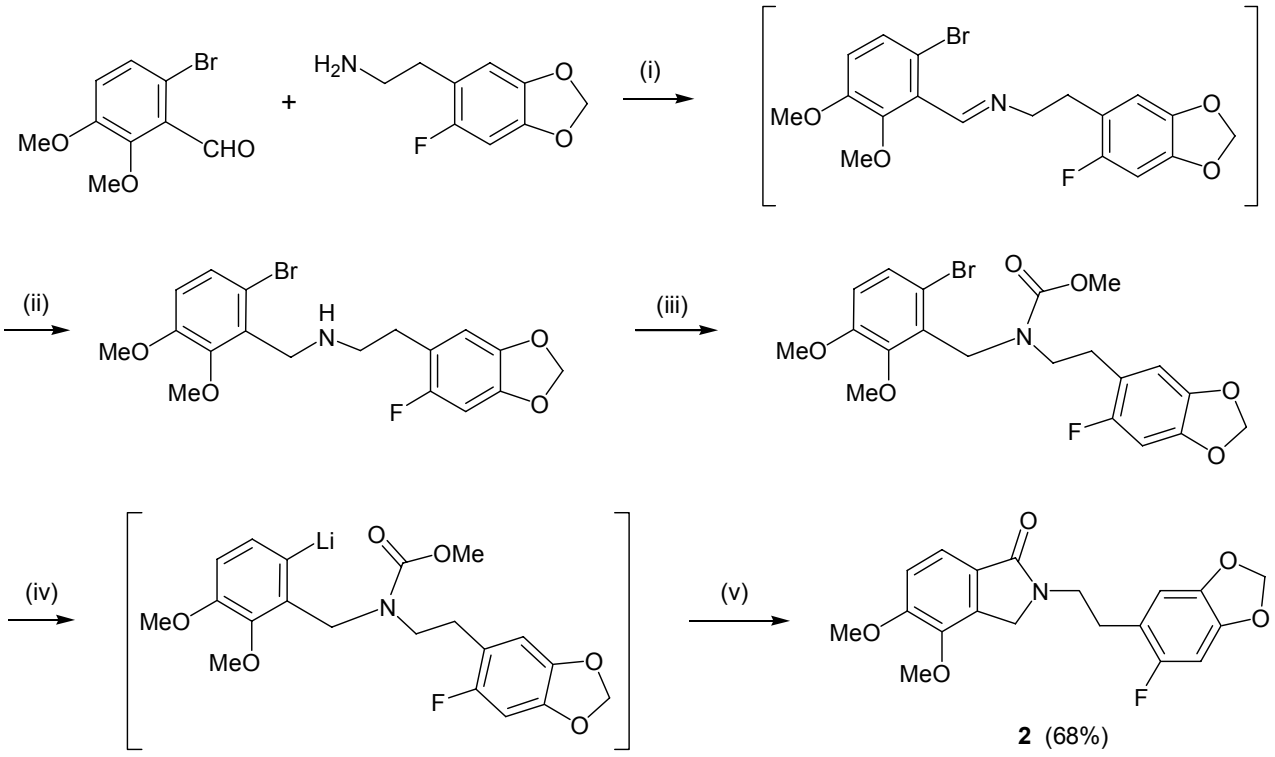
We have then developed two conceptually and tactically different synthetic approaches to isoindoloisoquinolinones illustrated by the total synthesis of this alkaloid.
The first one hinges upon the aryne-mediated cyclization induced by basic treatment of the preliminary assembled model **2** (Scheme 1 - synthetic route a).
The second strategy relies on the Parham cyclization of the parent compound **3** for the construction of the lactam ring in the ultimate step (Scheme 1 - synthetic route b).



Scheme 1.

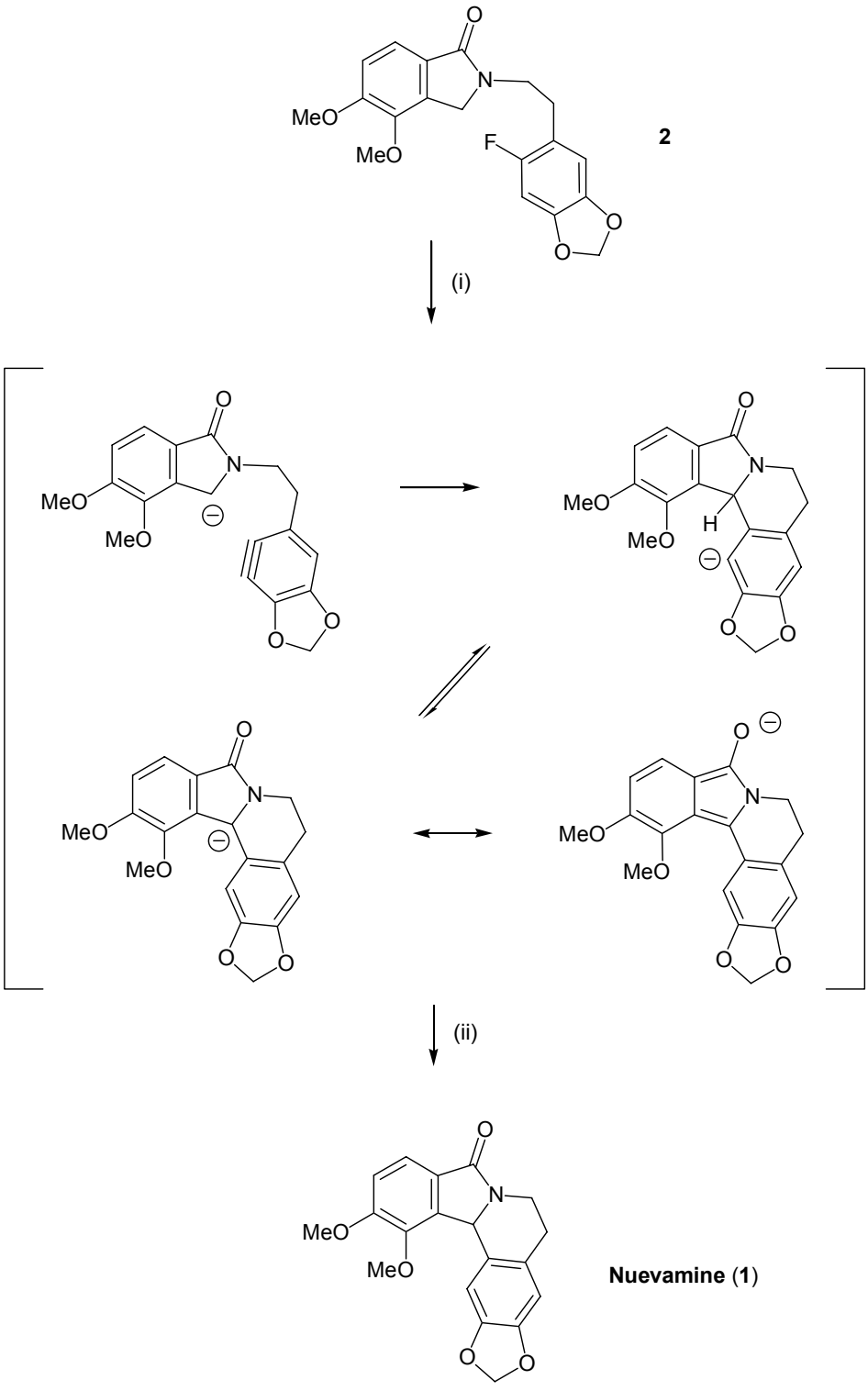
1. New synthetic approach to the isoindoloisoquinolone framework. Total synthesis of nuevamine (1) *through route a.*

1.1. Synthesis of the compound **2**



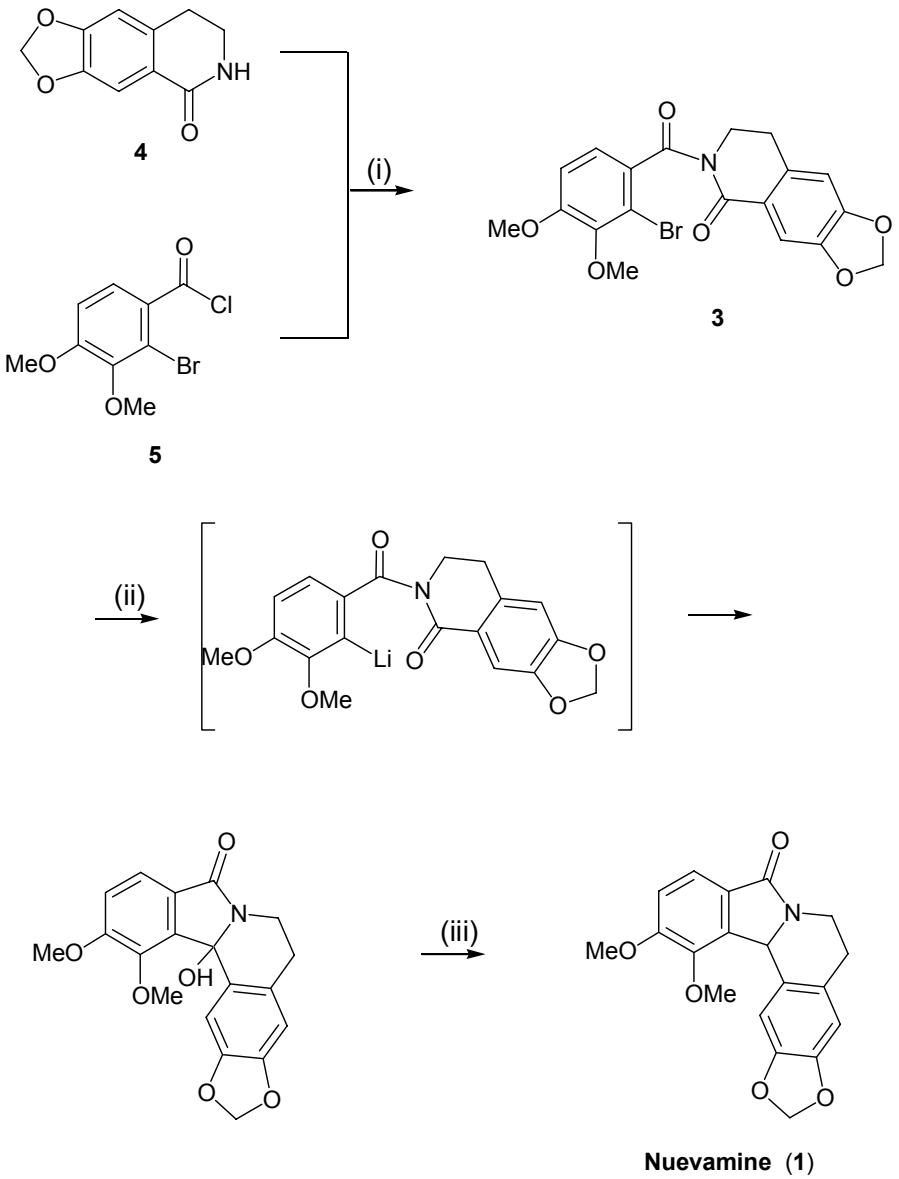
Scheme 2. *Reagents and conditions:* (i) toluene, PTSA, reflux; (ii) $NaBH_4$, MeOH, 20 °C; (iii) ClCOOMe, CH_2Cl_2, NEt_3; (iv) *t*BuLi, THF, -100 °C; (v) -100 °C to rt, H_3O^+.

1.2. Synthesis of nuevamine (**1**) through aryne-mediated cyclization.



Scheme 3. *Reagents and conditions:* (i) KHMDS (2 equiv), THF, -78 °C; (ii) -78 °C to rt, H_30^+.

2. New synthetic approach to the isoindoloisoquinolone framework. Total synthesis of nuevamine (1) *through route b.*



Scheme 4. *Reagents and conditions:* (i) **4**, *n*BuLi, THF,-78 °C to 20 °C, 30 min, then -78 °C, **5** in THF, -78 °C to 20 °C, 2 h; (ii) *t*BuLi, THF,-100 °C, 30 min; (iii) Et_3SiH (2 equiv), TFA (1 equiv), CH_2Cl_2, 20 °C, 2 h.

Conclusion

In summary we have identified two novel and flexible synthetic approaches to isoindoloisoquinolinones. The simplicity and the versatility of these two processes have been emphasized by the total synthesis of the naturally occurring alkaloid nuevamine and we believe that this work demonstrates a general new methodology for the preparation of similar structurally modified isoindoloisoquinolinone alkaloids.

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