Rearrangement of 3-(4,5-dimethoxy -2-vinylphenyl)-2-methyl -5-nitroisoquinolin -1(2*H*)-one to 2-(6,7-dimethoxy -1-oxoisoquinolin -2(*1H*)-yl)-*N*-methylbenzamide: a mechanistic proposal

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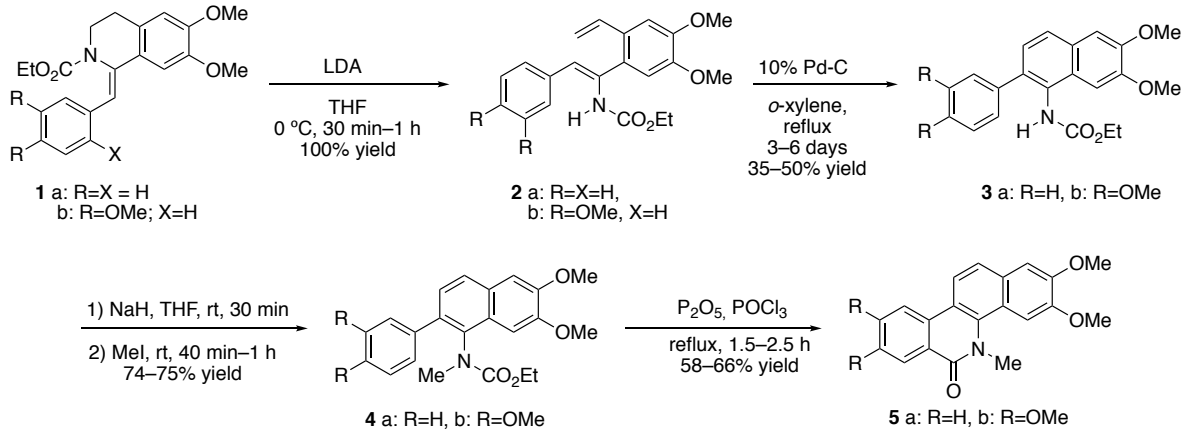
1-Benzylisoquinolines are biogenetic precursors of a wide range of natural products of pharmacological interest, including benzo[*c*]phenanthridines, which exhibit antineoplastic activity. This pharmacological property has been related with the presence of a 2-phenylheteronaphthalene subunit embedded in its structural framework.

As a part of our past work on isoquinolines, we reported in 2010 a novel access to 2-phenylnaphthalenes **3** from 1-benzylideneisoquinolines **1** via the novel (*Z*)-alkyl 2-phenyl-1-(2-vinylphenyl)vinylcarbamates **2**, and their transformation into benzo[*c*]phenanthridin-1-ones **4** (Scheme 1).[1]



1 a: R=X = H
b: R=OMe; X=H

2 a: R=X=H,
b: R=OMe, X=H

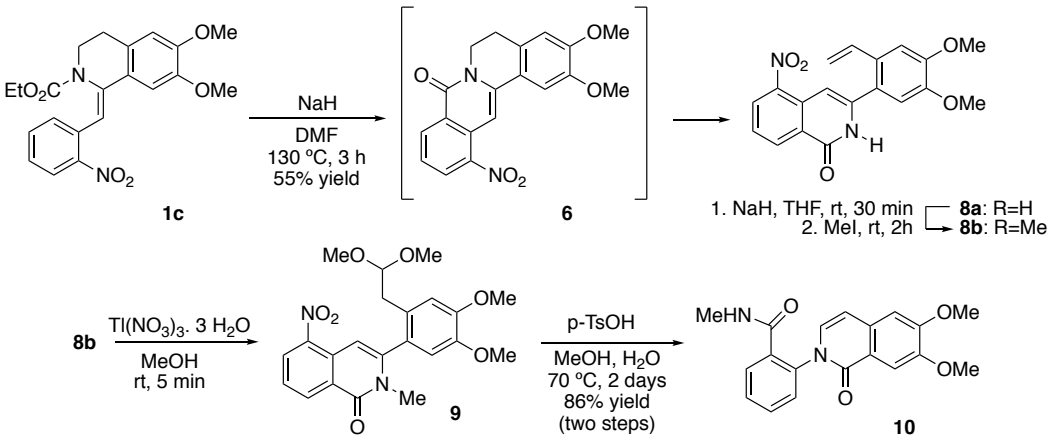
3 a: R=H, b: R=OMe

4 a: R=H, b: R=OMe

5 a: R=H, b: R=OMe

Scheme 1

Treatment of the known 1-benzylideneisoquinoline **1a** with LDA at 0 °C provided the styrylurethane **2a** resulting from a Hoffman-like elimination resulting on the cleavage of its C3-N bond. Ulterior reflux of a solution of compound **2a** in *o*-xylene containing 10 % Pd/C provided phenylnaphthalene derivative **3a** as a result of a thermically induced electrocyclic cyclization. After, compound **3a** was easily converted into its *N*-methyl derivative **4a** by treatment with MeI in a basic medium. Finally, benzo[*c*]phenanthridine **5a** was easily by a Bischler-Napieralski cyclization carried out by refluxing a solution **4a** and P_2O_5 in $POCl_3$. This strategy for the synthesis of benzo[*c*]phenanthridin-1-ones **5a** was also applied to the preparation of benzo[*c*]phenanthridine **5b**, via compounds **2b**, **3b** and **4b**.

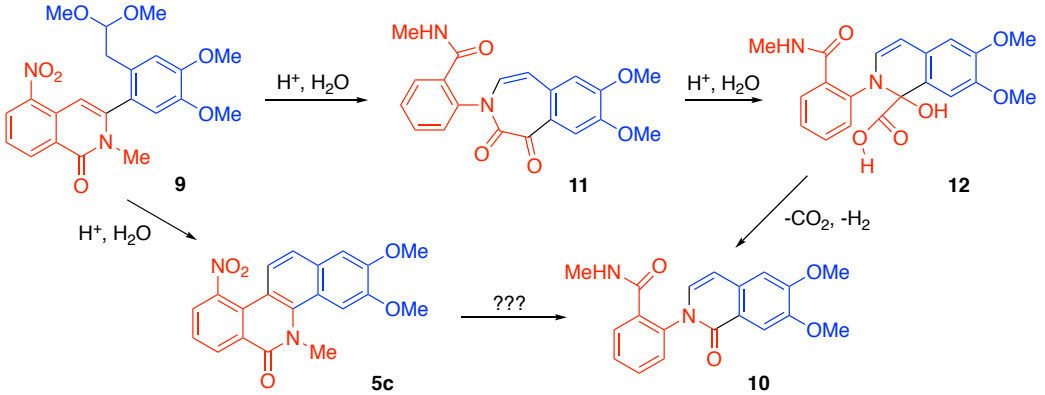


Scheme 2

Proceeding as for **1a** and **1b**, reaction of compound **1c** with LDA in THF at 0 °C for 1.5 h gave a complex reaction mixture. However, when a solution of compound **1c** and NaH in DMF was heated at 130 °C for 3 h, the isoquinoline **8a** resulted, probably by means of a nitro facilitated thermal electrocyclic cyclization of **1a** involving its *N*-ethoxycarbonyl substituent. This resulted in the formation of protoberberine derivative **6**, which could spontaneously be converted into compound **8a** by a Hofmann-like elimination by the action of hydride.

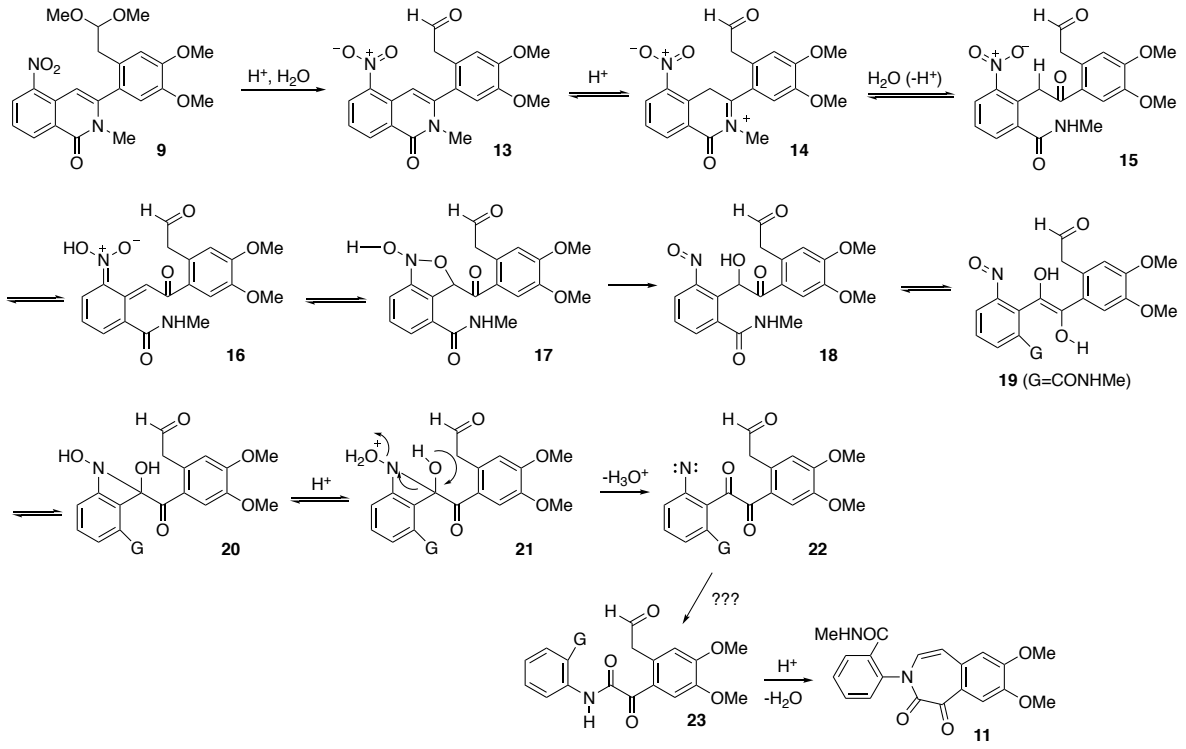
Methylation of **8a** provided **8b**, which when subjected to the conditions for the transformation of 2a into **3a** did not gave the expected benzophenanthridine **5c**. Alternatively, **8b** was subjected to a known protocol for the transformation of 3-(2-vinylphenyl)-isoquinolin-1(2*H*)-ones (**8**) benzo[*c*]phenanthridin-1-ones (**5**). The treatment of **8b** with thallium trinitrate allowed us to obtain the acetal derivative **9**, which was directly solved in a MeOH/H2O mixture and heated at 70 ºC for two days, after adding *p*-toluensulfonic acid.[2] Surprisingly, the resulting compound was the isoquinolin-1-one **10.**

Compound **10** could result from the expected **5c**, via an unknown rearrangement. But, although this possibility was not discarded, we assumed that the nitro group prevents the cyclization required for the transformation of compound **9** into benzo[**c**]phenanthridine **5c** in favor of a novel, complex rearrangement involving the transformation of **9** into the benzazepindione **11**. A benzylic acid rearrangement could explain the transformation of compound **11** into compound **12**, which could undertook a decarboxylative oxidation leading the isoquinoline **10** (Scheme 3).



Scheme 3

Transformation of nitroisoquinoline **9** into benzazepindione **11** could occur via the mechanism depicted in Scheme 4.



Scheme 4

Hydrolysis of ketal **9** provided nitroisoquinoline **13**. Protonation of this compound resulted in the formation of its conjugated acid **14**, which spontaneously opened to the corresponding δ-ketoacid amide **15**. Isomerization of this compound to compound **16** is followed by an intramolecular Michael-like reaction leading to the complex oxazole **17**. The opening of the oxazole ring of this compound gave the nitroso δ-ketoacid amide **18**, which undertook a cyclization, via its enol **19**, that provided the complex benzazetidine **20**. Protonation of this compound, followed by the opening of the azetidine ring of the resulting conjugate acid **21** could explain the formation of the key nitrene **22**, that should rearrange to the α-ketophenylacetic acid amide **23**, precursor of the benzazepindione **11**.

This mechanistic proposal for the striking transformation of isoquinoline 9 into isoquinoline 10 is open to discussion. Any comment or alternative mechanism will be welcomed.

References

1. Treus, M.; Salas; C. O.; González, M. A.; Estévez, J. C.; Tapia, R. A.; Estévez, R. J. (*Z*)-Ethyl 2-phenyl -1-(2-vinylphenyl)vinylcarbamates. Part 1: Synthesis and preliminary studies on their divergent transformation into benzo[*c*]phenanthridines and 2-phenyl-1,4-naphthoquinones. *Tetrahedron* **2010**, *66*, 9986e9995, DOI 10.1016/j.tet.2010.10.035.
2. (a) Hanaoka, M.; Motonishi, T.; Mukai, C. J. Chem. Soc., *Chem. Commun.* **1984**, 718; (b) Hanaoka, M.; Motonishi, T.; Mukai, C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2253