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A Multicomponent Reaction for the One-Pot Synthesis of 4-Aza-2,3-didehydropodophyllotoxin and Derivatives

Christophe Tratrat, Sylviane Giorgi-Renault,* and Henri-Philippe Husson*

Laboratoire de Chimie Thérapeutique, UMR 8638 associée au CNRS et à l'Université René Descartes, Faculté des Sciences Pharmaceutiques et Biologiques, 4 avenue de l'Observatoire,75270 Paris Cedex 06, France

S.Giorgi-Renault@pharmacie.univ-paris5.fr

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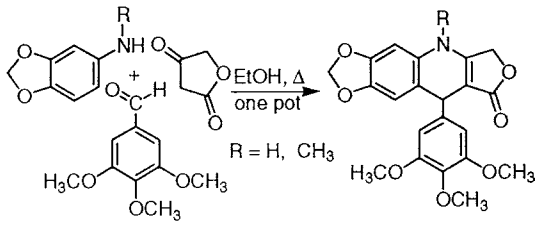
ABSTRACT



A convergent method has been found to prepare 4-aza-2,3-didehydropodophyllotoxin and derivatives in a one-pot procedure. The mechanism of the reaction between tetronic acid, anilines, and benzaldehydes is discussed.

Podophyllotoxin (Figure 1) is a plant lignan that inhibits microtubule assembly. Attempts to use it for the treatment of human neoplasia were mostly unsuccessful and complicated by side effects. Extensive structural modifications have been performed in order to obtain more potent and less toxic anticancer agents. This has led to etoposide and teniposide, two 4-epipodophyllotoxin glycoside derivatives which have been in clinical use as antineoplastic agents since the early 1970s. They are powerful DNA topoisomerase II inhibitors working through a mechanism of action entirely different from that of the parent natural podophyllotoxin. The potential of this series engendered considerable interest; however, no new analogue has been launched on the market. For various reasons, aza-analogues have held the attention of our group[1] and others.[2] In the 4-aza series, (−)-4-aza-4-deoxypodophyllotoxin has been prepared by partial synthesis starting from (−)-podophyllotoxin.[3]

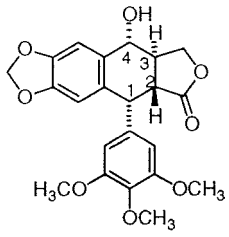


Figure 1. Structure of podophyllotoxin.

In this preliminary communication we disclose a straightforward synthesis of the unsaturated 4-aza-2,3-didehydropodophyllotoxins **6** and **12** (Table 1) according to a

(1) (a) Liénard, P.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron* **1993**, *49*, 3995. (b) Clémencin-Le Guillou, C.; Giorgi-Renault, S.; Quirion J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1997**, *38*, 1037. (c) Clémencin-Le Guillou, C.; Remuzon, P.; Bouzard, D.; Quirion, J.-C.; Giorgi-Renault, S.; Husson, H.-P. *Tetrahedron* **1998**, *54*, 83.

(2) For a review, see: Ramos, A. C.; Pelaez-Lamanié de Clairac, R.; Medarde, M. *Heterocycles* **1999**, *51*, 1443.

(3) Hitotsuyanagi, Y.; Kobayashi, M.; Morita, H.; Itokawa, H.; Takeya, K. *Tetrahedron Lett.* **1999**, *40*, 9107.

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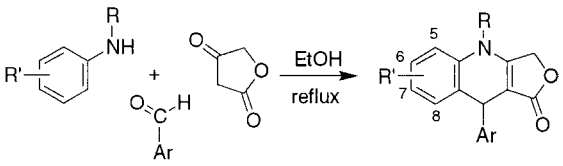
Table 1. Additional Examples Illustrating the Versatility of the One-Pot Reaction



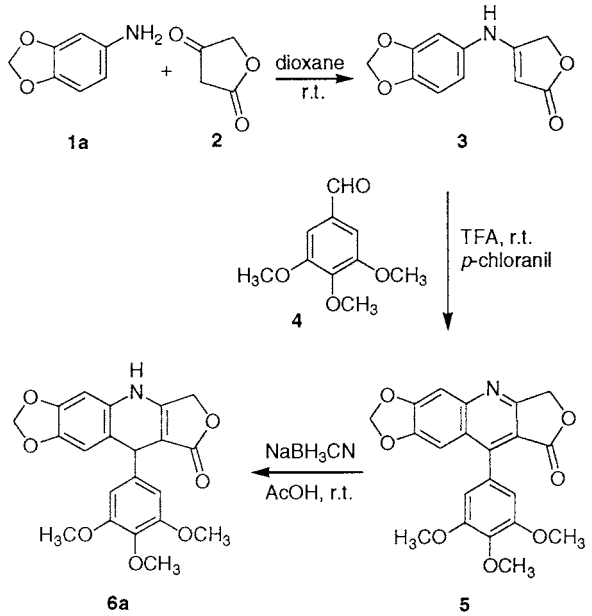
6a-c; 12a-e

	R	R′	Ar	yield (%)
6a	H	6,7-methylenedioxy	3,4,5-trimethoxyphenyl	92
6b	Me	6,7-methylenedioxy	3,4,5-trimethoxyphenyl	80
6c	$Me_2N(CH_2)_3$, HCl	6,7-methylenedioxy	3,4,5-trimethoxyphenyl	45
12a	H	6-hydroxy	3,4,5-trimethoxyphenyl	63
12b	H	6,7-dimethoxy	3,4,5-trimethoxyphenyl	94
12c	H	7,8-benzo	3,4,5-trimethoxyphenyl	59
12d	H	6,7-methylenedioxy	2,3,4-trimethoxyphenyl	83
12e	H	6,7-methylenedioxy	2-pyridyl	78

multicomponent reaction. The preparation and the potent activity of these new compounds have been patented,[4] and similar work has been published a few weeks after by Takeya et al.[5] Both approaches start with the same three components and take advantage of the intrinsic electrophilicity and nucleophilicity of tetronic acid **2**.

However, Takeya's method[5,6] (Scheme 1) is much less efficient, and the scope is more limited. It requires three steps: formation of enamine **3** between tetronic acid **2** and aniline **1a**; condensation−cyclization of the enamine with trimethoxybenzaldehyde **4** in TFA in the presence of *p*-chloranil at rt to give quinoline **5**;[6] and finally reduction of **5** with $NaBH_3CN$ in acetic acid affording the required azapodophyllotoxin **6a**.[5]

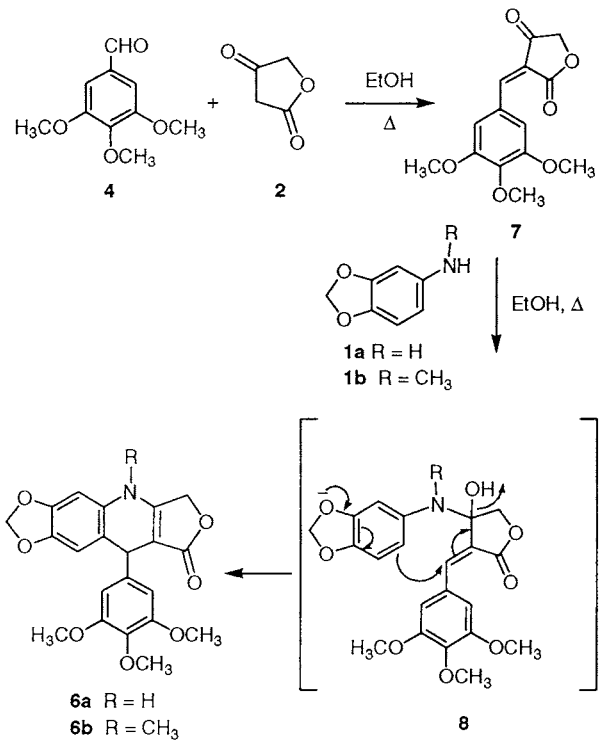
Scheme 1



In addition to the necessary reduction step, this method did not allow the preparation of *N*-substituted derivatives since attempts at alkylation of **6a** to form **6b** failed. This is a serious drawback as far as medicinal chemistry is concerned.

Simultaneously and independently, we carried out a different two-step strategy (Scheme 2) involving the pre-

Scheme 2



(4) Husson, H.-P.; Giorgi-Renault, S.; Tratrat, C.; Atassi, G.; Pierré, A.; Renard, P.; Pfeiffer, B. French patent no. 99.14771, Nov 24, 1999. Extension no. 00403255.3, Nov 22, 2000.

(5) Hitotsuyanagi, Y.; Fukuyo, M.; Tsuda, K.; Kobayashi, M.; Ozeki, A.; Itokawa, H.; Takeya, K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 315.

liminary formation of benzylidene 2,4-furandione **7** in HCl[7] which was subsequently reacted with aniline **1a** in refluxing ethanol to afford **6a** in 85% yield.

Encouraged by these great strides toward the target molecule, we tried a one-pot reaction in refluxing ethanol with the three commercially available compounds **1a**, **2**, and **4**. We were pleased to note the formation of **6a** in excellent yield (92%).[8]

Similarly, the *N*-methyl derivative **6b** was obtained starting with *N*-methylaniline **1b**, an important breakthrough since *N*-alkylated derivatives cannot be prepared otherwise. Accordingly, we have been able to prepare a library of azapodophyllotoxins using tetronic acid, aromatic aldehydes, and anilines.[4] Some examples are given in Table 1. The only limitation is for anilines that are to be substituted in the *meta*-position by electron donors groups.

The dramatic difference between the processes described in Schemes 1 and 2 deserves comment. In Scheme 1, the first intermediate **3** is a stabilized vinylogous amide whose electron pair on the nitrogen overlaps with the phenyl group and consequently is less delocalized into the π system of the α,β-carbon−carbon double bond. Consequently, **3** is poorly nucleophilic. Indeed we have verified that, in refluxing ethanol, no reaction occurs between enamine **3** and benzaldehydes. On the other hand the Japanese group indicated that, in the absence of *p*-chloranil, a reagent of high redox potential, carbocation **9** led to dismutation products **11** and **5** (Scheme 3). Therefore, they had to use TFA and *p*-chloranil to obtain the cyclized derivative **5** exclusively.[6]

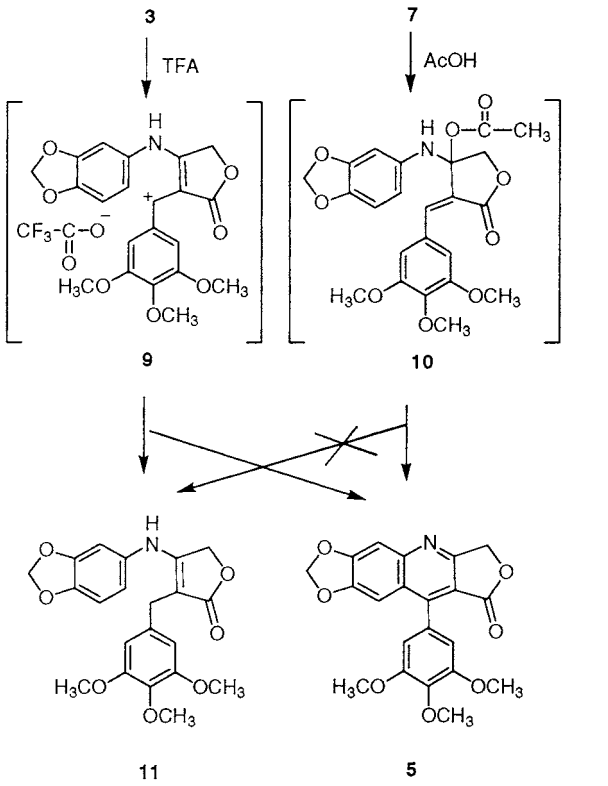
We suppose that, in our route (Scheme 2), reactive intermediate **8** was formed instead of the iminium ion. The labile hydroxy group of **8** is the driving force for the facile cyclization reaction without any dismutation reaction.

The main difference between the two routes is that the key intermediate **8** is easily generated in ethanol from benzylidene **7** to give a highly reactive carbinolamine whereas drastic acid catalysis conditions are necessary to trigger the transformation of the vinylogous amide **3**.

Interestingly from a mechanistic point of view, quinoline **5** was obtained as a single product in a one-pot procedure by refluxing tetronic acid **2**, aniline **1a**, and benzaldehyde **4** in acetic acid without any oxidative agent (Scheme 3).

It is worth highlighting the notable difference caused by the use of acetic acid instead of trifluoroacetic acid. The latter conditions are favorable for the dismutation leading to **5** and reduced compound **11** (Scheme 3). This resembles the behavior of the iminium ion formed in the Polonovski reaction, i.e., the action of an acid anhydride on an *N*-oxide.[9] The low nucleophilicity of trifluoroacetic acid leads to an ion pair whereas in the case of acetic acid an ester of carbinolamine may be formed as an addition product. Accordingly, intermediates **9** and **10** are the result of the reactivity of the iminium ion in the presence of acetate or trifluoroacetate anions. It is noteworthy that in refluxing acetic acid, facile aromatization of **6a** into **5** occurred, whereas under milder conditions (refluxing ethanol), only dihydroquinoline **6a** was isolated.

Scheme 3



In conclusion, the present method provides a useful alternative for the preparation of *N*-unsubstituted derivatives and opens the way to the *N*-substitutted 4-aza-2,3-didehydropodophyllotoxin series which cannot be prepared otherwise. The notable advantages of our methodology are mild conditions without any activation, fast reaction, and tolerance for structural diversity.

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Supporting Information Available: Full experimental details; characterization of 4-aza-2,3-didehydropodophyllotoxins. The material is available free of charge via the Internet at http://pubs.acs.org.

OL0200908

(6) Hitotsuyanagi, Y.; Kobayashi, M.; Fukuyo, M.; Takeya, K.; Itokawa, H. *Tetrahedron Lett.* **1997**, *38*, 8295.

(7) Zimmer, H.; Hillstrom, W. W.; Schmidt, J. C.; Seemuth, P. D.; Vögeli, R. *J. Org. Chem.* **1978**, *43*, 1541.

(8) **Typical Procedure.** A mixture of tetronic acid **2** (0.8 g; 8 mmol), 3,4-methylenedioxyaniline **1a** (1 g, 8 mmol), and 3,4,5-trimethoxybenzaldehyde **4** (1.57 g, 8 mmol) in ethanol (30 mL) was refluxed for 10 min. After being cooled, the precipitate was filtered off, washed with ethanol, and then recrystallized from ethanol to give 2.92 g (92% yield) of **6a** (mp > 260 °C, lit.[5] 271−274 °C).

(9) Grierson, D. *Org. React.* **1991**, *39*, 85.