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Click chemistry and biocatalysis for the preparation of pancratistatin analogs

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ABSTRACT

Tricyclic compounds that are advanced precursors for the synthesis of analogs of the antitumoral alkaloid pancratistatin were prepared by a short sequence that involved enzymatic dihydroxylation, epoxidation, and intramolecular Huisgen cycloaddition.

1. Introduction

Pancratistatin, narciclasine, lycoricidine, and related alkaloids isolated from the Amarillydaceae family exhibit strong biological activity and have been studied and tested as anticancer, antiviral, and antiparasitic agents. In fact the remarkable properties of crude extracts of several plants of the family have been recognized for centuries as it was nicely narrated by Kornienko and Evidente in an excellent review.[1] The synthetic problems involved in the preparations of this group of alkaloids are not trivial and several major research groups have engaged in the endeavor. Notably, the groups of Danishefsky,[2] Hudlicky,[3] Keck,[4] Magnus,[5] Rigby,[6] and Trost[7] among others have contributed with total syntheses. Several preparations of truncated or simplified analogs are known and the biological evaluation of those structures has allowed the recollection of data on the essential pharmacophoric requirements of the phenanthridone alkaloids to preserve biological activity. Independent and collaborative efforts of the Hudlicky, Pettit, and Kornienko groups[3c,8] as well as the work from McNulty[9] have rendered major contributions in this area.

Since 2004, our group has performed research in the enantioselective chemoenzymatic preparation of deoxycyclitols[10] and recently, we have explored the decoration of the cyclitol nucleus with triazolic structures obtained by Huisgen cycloaddition.[11] In light of the published work on pancratistatin analogs, we envisioned that the triazolic ring could be an interesting surrogate for the aromatic ring in pancratistatin and its congeners.

We conceived triazolic pancratistatin analogs (Fig. 1) where several of the known key elements of the pharmacophore could be present. The triazole could replace the aromatic ring and provide the required nitrogen atom, an acid or ester functionality could replace the oxygenated groups in ring A, a lactone could surrogate for lactam ring B, and finally a cyclitol with the minimum oxygen functionality to mimic ring C could complete the structure. The hydroxyl group on C1 is not essential but the α–β–β arrangement of the hydroxyls on C2, C3, and C4 is required for bioactivity. The incorporation of an indole ring into the general structure of the alkaloids was explored by Hudlicky[8b,12] but, to the best of our knowledge, the substitution of the aromatic ring A for a substituted triazole has not been studied before this Letter.

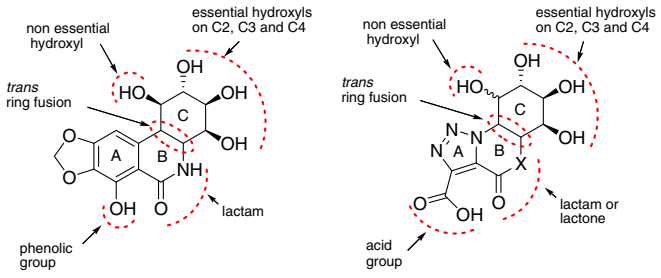

Figure 1. Key elements in the pancratistatin structure and the proposed triazolic analogs.

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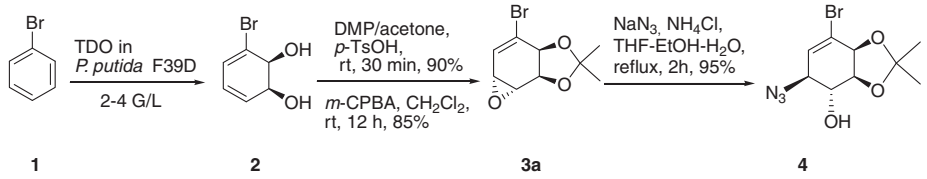
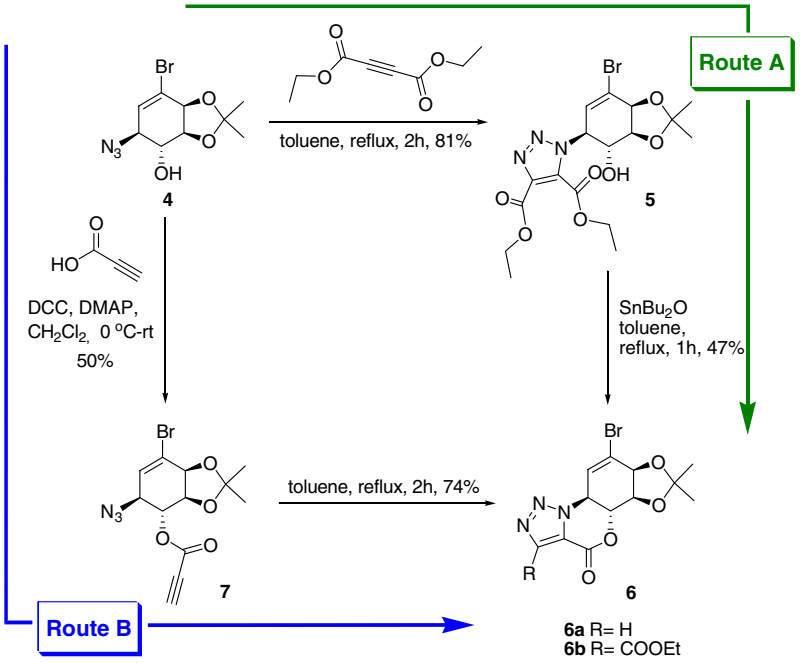


Scheme 1. Chemoenzymatic preparation of the bromoazide.



Scheme 2. Strategies toward phenanthridone alkaloid analogs.

2. Results and discussion

For the construction of the cyclitol ring C we followed the chemoenzymatic strategy developed by Hudlicky and that we have used extensively in the preparation of conduritols[12a] and particularly azidoconduritols.[12b] Bromobenzene (**1**) was enzymatically dihydroxylated by toluene dioxygenase (TDO) from Pseudomonas utilizing the strain *Pseudomonas putida* 39/D grown in a 2L fermenter following an in-house modification of the protocol described by Hudlicky et al. in Organic Synthesis.[13] That procedure can provide a weekly supply of 2–4 g of bromocyclohexadienediol **2** that are used in several research projects in our Department. Diol **2** was protected as the acetonide and the later was transformed into bromoepoxide **3a** with complete regio- and stereoselectivity. The epoxide was opened with sodium azide to provide the key compound **4** in 73% overall yield from diol **2** (Scheme 1).

With the azide in hand we explored the options to incorporate rings A and B. Previously, we have had success attaching triazole rings by means of Cu catalyzed Huisgen cycloaddition to this compound. In fact, we have prepared a small library of decorated cyclitols by combining Huisgen cycloaddition and Pd coupling, thus modifying the conduramine core at C2 (vinylic) and C6 (azide) (pancratistatin numbering). The nature of the Cu(I) catalysis rendered only 1,4-disubstituted triazoles by that strategy while for our current purposes we were in need of either a 1,5-disubstituted triazole or a 1,4,5-trisubstituted heterocycle. We, therefore, discarded the catalyzed version of the reaction and relied on the activation of the alkyne by a diester group or the entropic facilitation of the cycloaddition by an intramolecular reaction (Scheme 2). A similar approach has been disclosed in 2008 by Pericas et al. to prepare a library of tricyclic triazolooxazines with excellent yield and remarkable bioactivity.[14] We explored route A to access analogs of the phenolic alkaloids pancratistatin and narciclasine and route B for the less oxidized lycoricidine and 7-deoxypancratistatin analogs.

We initially explored route A by heating azide **4** and diethylacetylendicarboxylate (DADC) in refluxing toluene. The uncatalyzed Huisgen cycloaddition was complete in 2 h rendering triazole **5** in 81% isolated yield. Initially, we expected to observe also the con-

Table 1
Lactonization of hydroxydiester **5**

Entry	Reaction promoter	Solvent	*T* (°C)	Reaction time (h)	Product
1	DBU	THF	rt	20	Recovered **5**
2	DBU	THF	rt	120	**5**, **8** (traces)
3	DBU	THF	Reflux	120	**5**, **8** (traces)
4	DIPEA	Toluene	Reflux	48	Recovered **5**
5	DMAP	CH_2Cl_2	Reflux	48	Recovered **5**
6	NaH	THF	0–5	13	**8** (40%)
7	NaH	THF	Reflux	2.5	**8** (71%)
8	Dowex resin (weakly acidic)	CH_2Cl_2	Reflux	192	Deprotected **5**
9	Amberlyst resin (strongly acidic)	CH_2Cl_2	Reflux	48	Deprotected **5**, **8** (traces)
10	Novozym 435	Hexanes	30	24	**5**, **8** (traces)
11	Dibutyltin oxide	Toluene	Reflux	1	**6b** (47%)