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Synthesis and preliminary biological evaluation of a compound library of triazolylcyclitols

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ABSTRACT

A small library of compounds was prepared by a combination of toluene dioxygenase (TDO)-catalyzed enzymatic dihydroxylation and copper(I)-catalyzed Hüisgen cycloaddition. Some compounds were obtained by coupling an alkyne and a conduritol derivative, while more complex structures were obtained by a double Hüisgen reaction of a dialkyne and two molecules of the cyclitol. The compounds were fully characterized and subjected to preliminary biological screening.

1. Introduction

Hygromycin A (**1**) is a natural antibiotic amide compound isolated in 1953 from *Streptomyces hygroscopicus*.[1] It exhibits moderate activity against gram-positive and gram-negative bacteria.[1,2] It shows excellent activity against *Treponema hyodysenteriae*, the microorganism responsible for porcine dysentery.[3] and also exhibits immunosuppressant activity since it inhibits the proliferation of lymphocytes.[4] The structure of hygromycin A consists of three chemically well-defined substructures or residues, including cyclitol, cynnamoyl and furanose. This constitution makes it ideal for sequential structure variation and combinatorial approaches. In fact scientists from Pfizer have disclosed studies on several analogs with modifications in the three subunits.[5–7] Among the findings, it is noteworthy that there is a structure of an analogue that lacks the sugar subunit but shows the same potency as the natural antibiotic (Fig. 1).[8]

Since 2008, our groups in Brazil and Uruguay have been jointly involved in the synthesis of small libraries of natural product-like compounds by combined enzymatic and transition metal catalysis.[9–11] These compounds typically contained two subunits with one polar cyclitol derivative and an apolar aromatic or alkenyl residue. In addition, triazole-containing structures have been increasingly investigated as drug candidates since the emergence of the 'click chemistry' concept.[12–14] Moreover, amides and triazoles are bioisosteric and that has allowed the substitution of the former group by a triazole ring in several bioactive molecules.[15,16] This precedent prompted us to envision a class of molecules of moderate complexity (Fig. 1) that can relate to hygromycin A and could be rapidly built by combining azidocyclitols and alkynes in a diversity-oriented fashion.

2. Results and discussion

2.1. Synthesis

Our strategy involved the initial preparation of azidocyclitols **6** and **7**. The chemoenzymatic routes to these azides (or their chlorine analogues) have been previously described,[9,17–19] and their application to cyclitol synthesis was also demonstrated in a recent review.[20] *trans*-Hydroxyazide **6** was prepared by a short and efficient sequence that delivered the desired compound in four steps and an overall yield of 82%[9] from homochiral bacterial metabolite **5**, which was ultimately derived from bromobenzene (**4**) in a high-yield biotransformation (Scheme 1).[21,22] In a similar fashion, but involving a double inversion sequence, *cis*-bromoazide **7** was prepared in overall yield of 78%.[17]

Azides **6** and **7** are remarkable synthons that allow for further functionalization by metal catalyzed coupling at the vinyl bromine,

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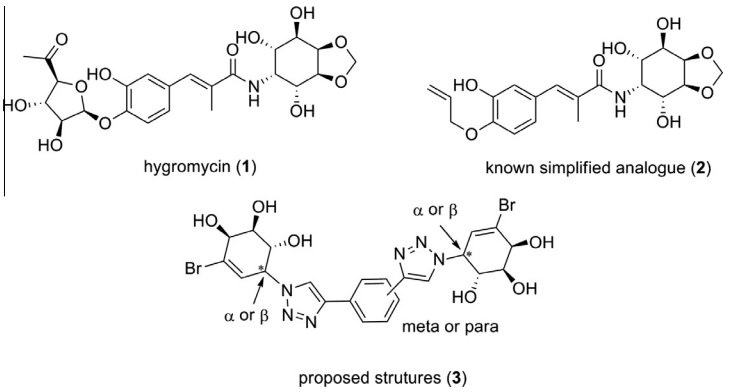
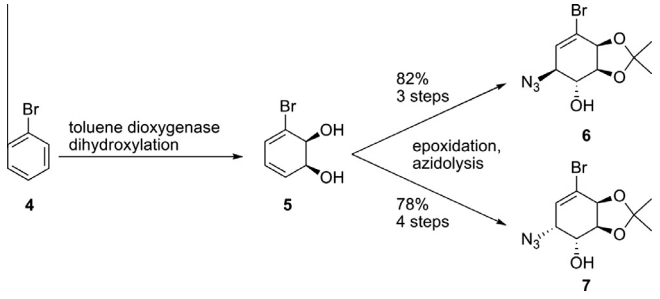


Figure 1. Structure of hygromycin A (**1**), a known synthetic analogue (**2**) and the proposed structurally related structures (**3**).

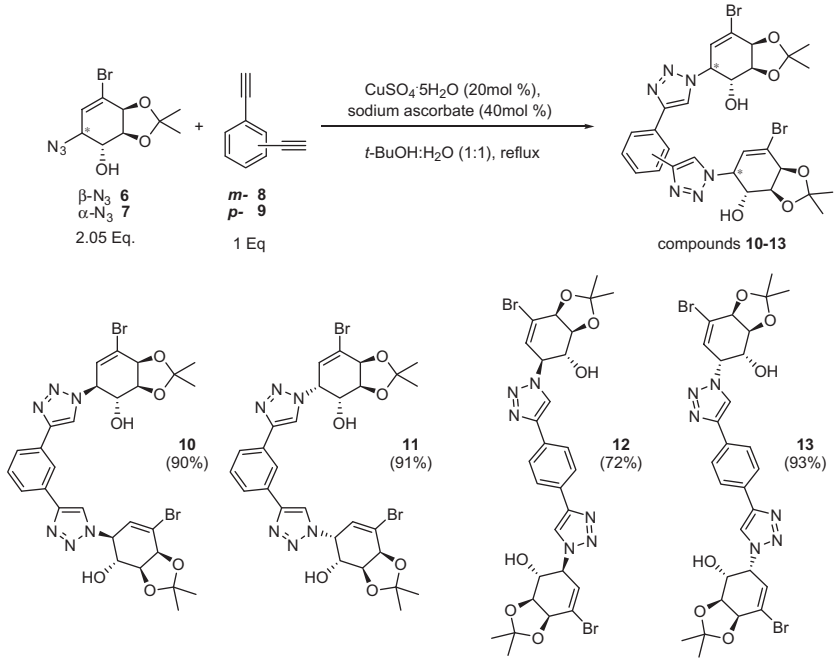


Scheme 1. Strategy used for the synthesis of the epimeric azidocyclitols.

esterification of the hydroxyl group or modification of the azide by reduction or cycloaddition. In this research, we explored their reaction with dialkynes **8** and **9** in order to prepare up to 10 combined structures by Hüisgen cycloaddition.

The simultaneous double Huisgen cycloaddition of a dialkyne has recently been used to prepare complex structures. In 2008, Wyszogrodzka and Haag[23] described the preparation of glycerol dendrimers centered in an aromatic ring, and in 2011 Ehlers et al.[24] synthesized triaryl α-helix mimics by a similar strategy. Previuosly, in 2010 the group of Fokin had reacted a dialkyne with benzyl azide in the absence of a metal catalyst.[25] In the light of these precedents, we decided to explore the simultaneous reaction of more complex secondary azides to build triazolylconduritol conjugates. Four dimers (**10**–**13**) (Scheme 2) were prepared by direct double cycloaddition between 2 equiv of the azide and one equivalent of the dialkyne. Two extra structures (**14** and **15**) were synthesized by sequential cycloadditon of two different conduritols with the dialkyne with intermediate isolation of the triazolylconduritols **16**–**19** (Schemes 3 and 4).

The reaction between azide **7** and alkyne **9** was used to find the best reactions conditions for double or single cycloaddition. A series of experiments were performed as depicted in Table 1. We searched for conditions to maximize the yield and minimize the reaction time with a minimum excess of any of the reactants. The use of Cu(II) and sodium ascorbate in a *t*-BuOH/H_2O (1:1) mixture was a better option than Cu(I) in THF (entries a and b), and the reaction was much faster at reflux conditions (90 °C) than at room temperature (entries c and e). The use of microwave heating did



Scheme 2. Double Hüisgen cycloaddition.