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The convergent synthesis and anticancer activity of broussonetinines related analogues

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ABSTRACT

The convergent synthesis of broussonetinines related congeners **3** and **4** with the simple C_{13} alkyl side chain and differently configured pyrrolidine skeleton has been achieved. Our approach relied on the [3,3]-sigmatropic rearrangements of chiral allylic substrates derived from D-xylose. Cross metathesis of the common oxazolidinone intermediates **7** and **8** with tridec-1-ene followed by alkylative cyclization completed the construction of both *C*-alkyl iminosugars. The targeted compounds **3** and **4** were screened for antiproliferative/cytotoxic activities against multiple cancer cell lines by MTT assay. Compound **3** exhibited very good in vitro potency on Caco-2 and Jurkat cell lines with IC_{50} value of 5.1 μM and 5.8 μM, respectively.

1. Introduction

Broussonetines, along with diastereomeric broussonetinines, the representative structures of which are illustrated by broussonetine C (**1**) and broussonetinine A (**2**), were isolated by Kusano and co-workers [1] from the branches of the Asian deciduous tree *Broussonetia kazinoki* (Fig. 1). They represent a class of more than 30 well-identified and characterized polyhydroxylated pyrrolidine alkaloids, which possess variable side chains with the diverse types of functionalization [1]. Most of these *C*-alkyl iminosugars demonstrated significant glycosidase inhibitory activities with IC_{50} values in the micromolar to nanomolar range [1–3] and as such are expected to be promising anticancer [4], antidiabetic [5], antiviral [6] and anti-inflammatory agents [7], and pharmacological chaperones [8]. Due to these potent biological properties, several synthetic methods towards naturally occurring broussonetines [2,3,9] and their related analogues [2-3,8b,9d] have been reported.

In our continuing studies based on the feasibility of the [3,3]-sigmatropic rearrangements in the total synthesis of sphingoid base-like natural products and their analogues [10] we were interested in investigating the use of such transformation as the key reaction for the construction of broussonetinines related congeners, which possess the simple C_{13} hydrocarbon fragment. Herein, we would like to report the total synthesis and antiproliferative activity of two iminosugars **3** and **4**, starting from D-xylose. While this manuscript was in preparation, we published the approach towards other diastereomeric analogues of our final compounds **3** a **4** together with their cytotoxic profile [11]. Part of the reported synthetic strategy [11] is here effectively applied.

2. Results and discussion

2.1. Chemistry

As shown in Fig. 2, our retrosynthetic route to broussonetinines analogues **3** and **4** would involve pyrrolidine core construction through the intramolecular S_N2 cyclization of open chain scaffolds **5** and **6**, respectively. We planned to install the C_{13} side segment in

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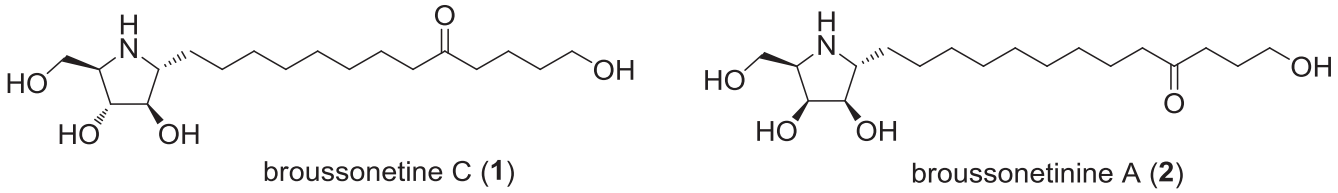


Fig. 1. Structures of broussonetine C (**1**) and broussonetinine A (**2**).

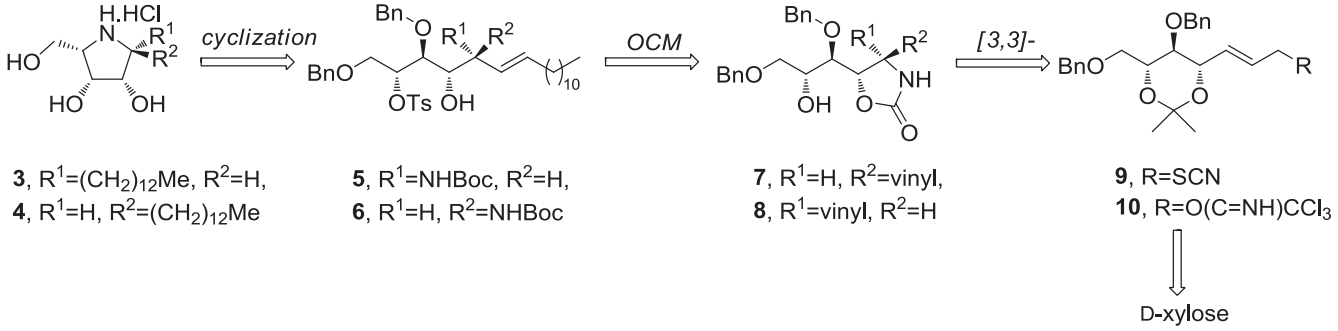
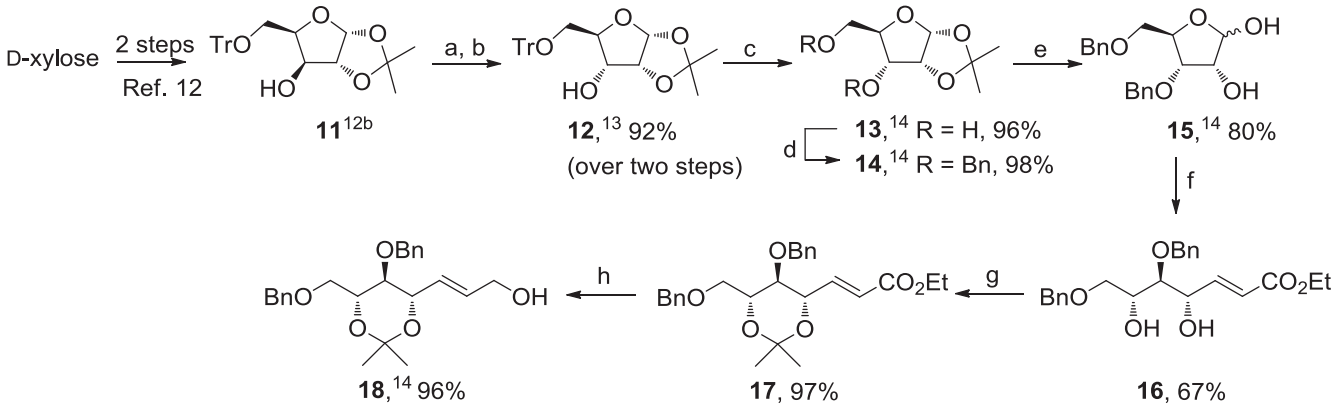


Fig. 2. Retrosynthetic route towards broussonetinines related analogues **3** and **4**.

5 and **6** via cross metathesis chemistry of the common oxazolidinones **7** and **8**, which could be constructed by the [3,3]-sigmatropic rearrangements of the allylic substrates **9** and **10** derived from D-xylose.

The commercially available D-xylose was modified into the known 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-xylofuranose **11** [12b] according to the literature [12] (Scheme 1). The conversion of the C-3 stereochemistry in **11** was achieved through an oxidation-highly diastereoselective reduction protocol, affording the corresponding 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranose **12** [13] in 92% yield over two steps via formation of the 1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*erythro*-pentofuranos-3-ulose [13]. Removal of the *O*-trityl protecting group in **12** (CSA, MeOH/CH_2Cl_2) and subsequent treatment of the resulting diol **13** [14] (96%) with BnBr produced 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose **14** [14] in 94% yield from **12**. Exposure of **14**—80% TFA resulted in cleavage of the isopropylideneketal fragment to provide lactol **15** [14] (80%) as a mixture of anomers. Wittig reaction of **15** with the stable ylide reagent ($Ph_3P=CHCO_2Et$) produced (*E*)-α,β-unsaturated ester **16** (67%, $J = 15.7$ Hz, this coupling constant value unambiguously supported an (*E*)-relationship between vinyl protons). It should be noted that no trace of the second geometric isomer was detected in the crude ^{1}H NMR spectrum. The lower yield is most likely due to generation of the minor unidentified side products. Further attempts to improve the efficiency of the olefination turned out to be ineffective and afforded **16** in the similar or lower amounts. After protection of the diol moiety in **16** with 2,2-DMP, the ester functionality in the created acetonide **17** (97%) was then reduced with DIBAl-H to give the corresponding alcohol **18** [14] (96%, 43% overall yield starting from **11**).

With the construction of the allylic scaffold **18** accomplished (Scheme 1), we were now in a position to examine the key [3,3]-sigmatropic rearrangements. For this purpose, compound **18** was converted into the appropriate substrates **9** and **10**, respectively. Thiocyanate **9** (93%) was produced via the known [10d] two-step approach involving the formation of a mesylate intermediate. On the other hand, the corresponding imidate **10** was prepared by treatment of **18** with Cl_3CCN and catalytic amounts of DBU and was used immediately in the Overman transformation [15] without purification (Scheme 2). The microwave-promoted thermal aza-



Scheme 1. *Reagents and conditions:* (a) IBX, MeCN, reflux, 93%; (b) $NaBH_4$, EtOH/CH_2Cl_2, 0 °C→rt, 99%; (c) CSA, MeOH/CH_2Cl_2, rt; (d) BnBr, NaH, DMF, TBAI, 0 °C→rt; (e) 80% TFA, rt; (f) $Ph_3P=CHCO_2Et$, CH_2Cl_2, benzoic acid, rt; (g) 2,2-DMP, *p*-TsOH, CH_2Cl_2, rt; (h) DIBAl-H, CH_2Cl_2, −30 °C.