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Studies toward the total synthesis of eletefine: an efficient construction of the AB ring system

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ABSTRACT

Synthetic studies toward eletefine, a novel stephaoxocane alkaloid, were undertaken in an attempt to provide a general methodology to aid in the synthesis of other novel stephaoxocanes. An efficient construction of the AB ring system with increased functionality is described which presents a flexible approach to synthesizing the C and D rings of eletefine.

1. Introduction

Isoquinoline alkaloids are an important class of biologically active natural products.[1] Among this class is the stephaoxocane family of natural products which consists of eight structurally interesting compounds (Fig. 1).[2–7] The tetracycles contain a remote alcohol stereocenter, an oxygen bridge, and uncommon unsaturation at the bridgehead carbons. Our synthetic interest in the stephaoxocanes results from the potential biological activity and the unusual structures of the family members. Eletefine (**1**) was logically the first member to prepare in our campaign to synthesize members of the stephaoxocane family. Eletefine was first isolated in 1998 from the roots of *Cissampelos glabberima*[2] harvested in northeastern Brazil and later from the roots of *Stephania longa*[8] in southern China. Both plant species belong to the family Menispermacae, members of which have been used in traditional medicine to treat a wide range of symptoms. The *Cissampelos* species have been used to treat symptoms of asthma and urinary tract infections,[8] while *S. longa* has been used in traditional Chinese medicine to reduce fever, inflammation, and to fight dysentery.[3]

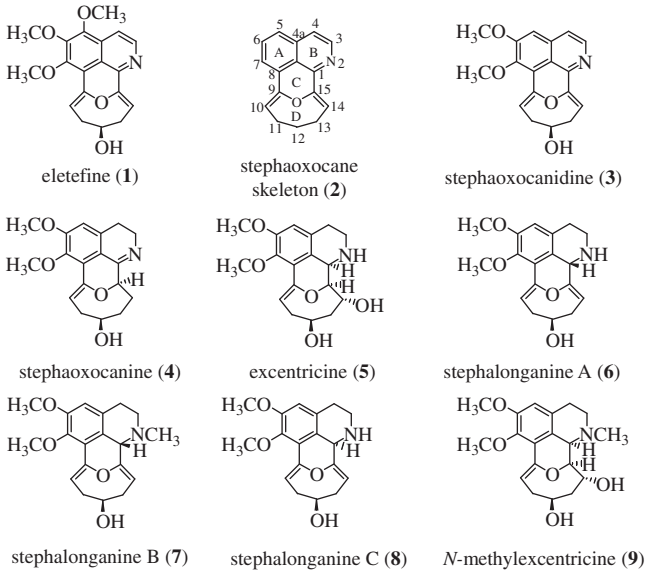

Figure 1. The stephaoxocane family of alkaloids.

Previous synthetic work on the stephaoxocane skeleton has been completed by Kaufman, who most recently completed the synthesis of the carbon skeleton of excentricine without the oxygen bridge or alcohol functionality.[9–11] However, to date a successful synthesis of a stephaoxocane has not been achieved. Herein, we report the successful synthesis of a properly functionalized isoquinoline AB rings system and the development of key carbon–carbon bond-forming reactions toward our efforts in preparing the CD rings of eletefine.

2. Results and discussion

A retrosynthetic analysis of our proposed route begins by simplifying the novel divinyl oxygen bridge into ynoate **10** (Scheme 1). Therefore, a successful completion of eletefine is envisioned to be achieved after completing the carbon–carbon bond-forming reactions at C1 and C8 (stephaoxocane numbering) to join the top and bottom fragments of the target. The formation of the C1–C15 bond may be realized using a Sonogashira coupling reaction between γ-lactone fragment **11** and isoquinoline **12**. Both anionic and acidic conditions may be proposed to form C8–C9 bond. The convergent retrosynthetic analysis of eletefine is rapidly dissected to a γ-lactone **11** and an isoquinoline fragment **12**.

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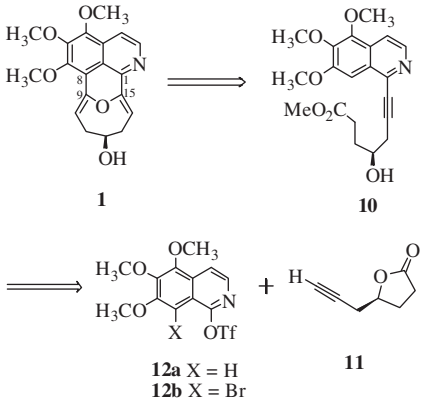
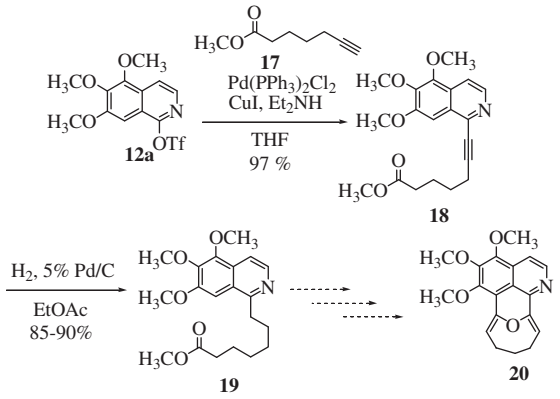
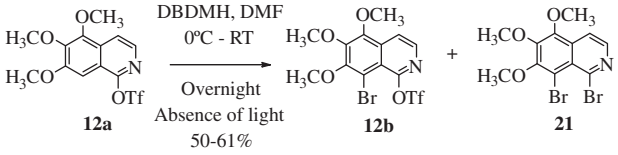


Scheme 1. Proposed retrosynthetic analysis of eletefine (**1**).



Scheme 3. Coupling the model alkyne **17** to triflate **12a** using a Sonogashira reaction.



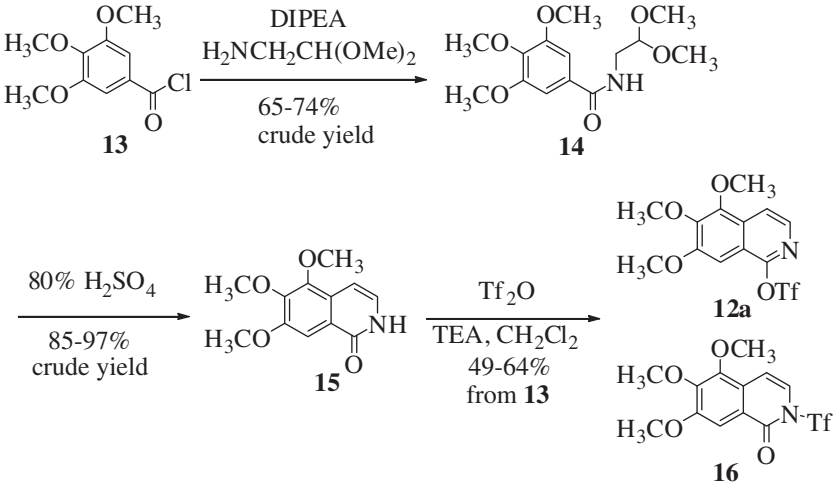
Scheme 4. Bromination of triflate **12a** to brominated triflate **12b**.

Construction of the A and B rings of eletefine began with the amidation of commercially available 3,4,5-trimethoxybenzoyl chloride **13** with aminoacetaldehyde dimetyl acetal in CH_2Cl_2 with diisopropylamine as a base to give moderate yields of amide **14** (Scheme 2). Amide **14** was in turn cyclized to isoquinoline **15** via a modified Pomeranz–Fritsch reaction.[12] The concentration of the sulfuric acidic conditions was tuned to effect the cyclization of amide **14** without degradation. Triflation of isoquinolone **15** provided a 6:1 ratio of **12a** to **16** in an overall yield of 49–64% from acyl chloride **13**. The triflated mixture is the first point of purification in the route. The *N*- and *O*-triflate compounds may be readily separated using silica gel chromatography. To our knowledge this is the first report of an N-triflation observed when triflating an isoquinolone.

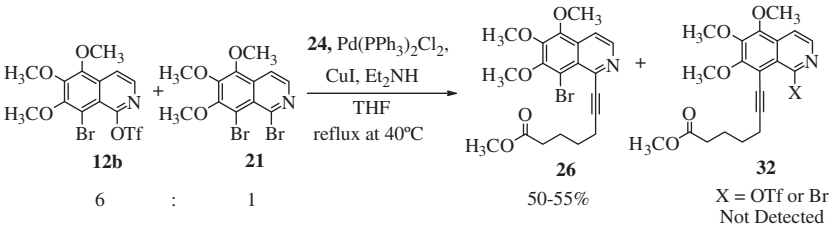
Currently, a readily available model alkyne fragment **17** is being used to explore the final stages of the synthetic route, which will provide *des*-hydroxyeletefine (**20**) (Scheme 3). *Des*-hydroxyeletefine is not chiral and may prove to be an interesting analogue for biological studies. Triflate **12a** easily underwent the Sonogashira coupling reaction with model alkyne **17** in excellent yield. Efforts to cyclize either alkyne **18** or alkane **19** under acidic conditions to form the 10-membered ring only hydrolyzed the ester to the corresponding carboxylic acids. The rigidity of alkyne **18** and in turn the inherent strain of having three sp^2 and two sp carbons in a 10-membered ring limit the viability of cyclizing alkyne **18**. The cyclization of ester **19** is not limited by strain, but by entropy.[13]

Preparation of a bis-functionalized isoquinolone fragment offers further opportunities to develop other routes toward the total synthesis of eletefine. The bromination of triflate **12a** resulted in a ratio of 3–4:1 of brominated triflate **12b** and bis-brominated **21** prior to purification using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH). Various brominating reagents were explored including Br_2 and NBS, however DBDMH was chosen due to its ease of use and favorable results.[14] Optimization of the bromination conditions led us to utilize 1.5 equiv of DBDMH at 0 °C in the absence of light (Scheme 4).

Silica gel chromatography provided a mixture of brominated triflate **12b** and dibromo **21** in a 6:1 ratio in acceptable yields. Dibromo **21** slowly degrades on silica gel, which explains the difference in ratios of **12b** to **21** and may provide an opportunity for further degradation and then purification to obtain pure brominated triflate **12b**. Regardless, the mixture of **12b** and **21** was used in the following reaction without detriment, as both provided the same product. When a mixture of the two compounds underwent a Sonogashira coupling reaction under mild heating, alkyne **22** was observed as the product in moderate yields. Interestingly, alkyne



Scheme 2. Synthesis of triflated isoquinolone **12a**.



Scheme 5. Sonogashira reaction with a mixture of brominated triflate **12b** and dibrominated **21**.

23 was not observed (Scheme 5). Despite the presence of two halogenated sites on dibromo **21**, the oxidative addition of the palladium complex occurred alpha to the nitrogen atom. This result is consistent with the results obtained by Stoltz et al. in 2004, where a single product was observed from a Suzuki coupling reaction with a dibrominated compound.[15]

3. Conclusions

In the preparation of isoquinolone **12**, a robust route was developed to prepare triflate **12a** in 49–64% yield from commercially available acid chloride **13** with only one purification step. Also, a mixture of *O*-triflate **12a** and *N*-triflate **16** was reported. Currently, we are surveying a number of different acid chlorides with varying electronic properties to determine the scope and generality of the modified Pomeranz–Fritsch reaction to prepare isoquinolones. Additionally, a useful bis-functionalized isoquinolone **12b** intermediate was prepared that can be envisioned to undergo carbon–carbon bond formation at the C-1 carbon using Pd coupling chemistry or at the C-8 carbon with a lithium halogen exchange reaction followed by addition of a carbon electrophile. Ongoing work toward the total synthesis of eletefine will take advantage of the flexibility of bis-functionalized isoquinolone fragment **12b**.

Acknowledgments

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Supplementary data

Supplementary data (experimentals for the preparation of compounds **12a**–**b**, **14**–**18**, and **22** including spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.058.

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