

Diastereoselective Nitrenium
Ion-Mediated Cyclofunctionalization:
Total Synthesis of (+)-Castanospermine

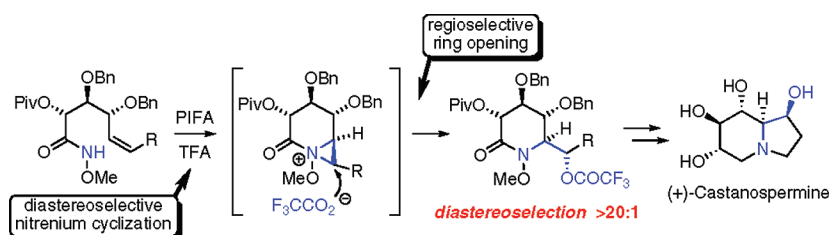
Edward G. Bowen and Duncan J. Wardrop*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street,
Chicago, Illinois 60607-7061, United States

wardropd@uic.edu

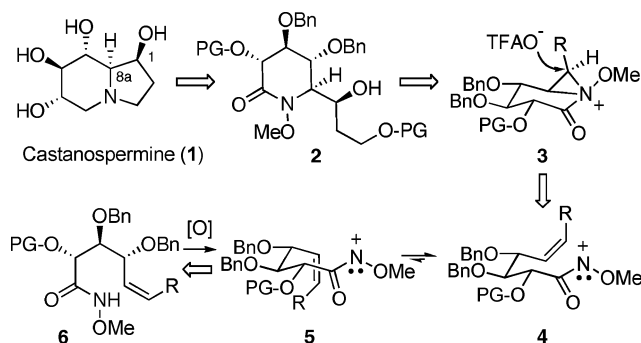
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ABSTRACT



The asymmetric total synthesis of the α -glucosidase inhibitor (+)-castanospermine is reported. The central theme in our approach to this polyhydroxylated alkaloid is the simultaneous generation of the piperidine ring and the C-1/8a *erythro* stereodiad through the diastereoselective, oxamidation of an unsaturated *O*-alkyl hydroxamate. This process is believed to proceed sequentially via singlet acylnitrenium and aziridinium ion intermediates.

(+)-Castanospermine (**1**), a polyhydroxylated indolizidine alkaloid originally isolated from the seeds of the Moreton Bay chestnut tree (*Castanospermum australe*),¹ displays a prestigious range of biological activities which stem from its role as a glycosidase inhibitor (Scheme 1).² Compound **1**'s ability to inhibit endoplasmic reticulum (ER) glucosidase I is of particular significance since this leads to the abrogation of normal glycoprotein trafficking,³ a process critical to a host of cellular functions as well as the coat protein biogenesis of enveloped viruses.⁴ From a drug-development standpoint, compound **1** has elicited considerable interest

Scheme 1. Retrosynthetic Analysis of Castanospermine (**1**)

since it displays activity against several human viral pathogens, including HCV, parainfluenza, dengue virus, HSV-2, and HIV-1.⁵ Most recently, castanospermine has also been found to inhibit the Rho/Ras-glycosylating action of *Clostridium difficile* toxin B,⁶ which is the major virulence factor of this Gram-positive bacteria and the causative agent of

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antibiotic-associated pseudomembranous colitis, a leading cause of infectious diarrhea in hospitals worldwide.⁷

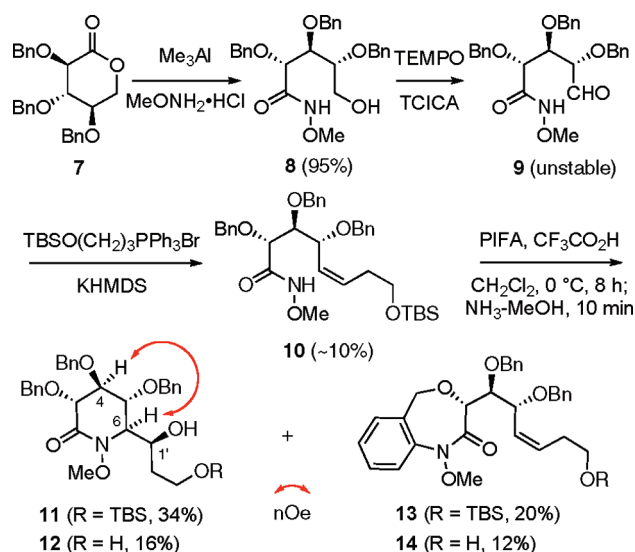
Given the biological activity of castanospermine, it is understandable that almost 30 years after its initial isolation this alkaloid remains a relevant and popular synthetic target.^{8,9} That minor structural/stereochemical alterations to **1** lead to dramatic alterations in glycosidase selectivity only adds further impetus to the development of new synthetic routes to this natural product.¹⁰ In light of our ongoing interest in the synthesis of α -glucosidase inhibitors^{11,12} and having recently reported a versatile oxamidation method for the preparation of α -hydroxyalkyl lactams involving the intramolecular addition of acylnitrenium ions to alkenes,¹³ we were prompted to consider whether this methodology might be gainfully employed in the enantioselective preparation of (+)-castanospermine. Herein, we report the successful implementation of this idea through the use of a substrate-controlled nitrenium ion oxamidation reaction.

From a retrosynthetic perspective, we envisioned that the indolizidine ring of **1** could be generated from α -hydroxyalkyl lactam **2** through a sequence of reduction and ring

closure (Scheme 1). In turn, this compound would be accessed through the cyclization of the nitrenium ion generated upon the oxidation of methyl D-glucosaminide **6**. Since singlet nitrenium ions are known to undergo concerted addition to alkenes,¹⁴ this reaction would generate bicyclic aziridinium ion **3**, which upon concerted, regioselective ion-pair collapse at the external (α) position¹⁵ and hydrolysis of the resulting trifluoroacetate ester adduct would provide δ -lactam **2** and thereby establish the C-1/8a *erythro* stereodiad of the natural product. Regarding the diastereoselectivity of the addition process, we anticipated that cyclization of the nitrenium ion generated from **6** would preferentially proceed via a transition state resembling pseudochair **4**, thereby avoiding the 1,3-allylic strain¹⁶ present in boatlike conformer **5**.¹⁷

Our initial route toward (+)-castanospermine (**1**) commenced from tribenzyl D-glucono- δ -lactone (**7**),¹⁸ which underwent ring opening with the methoxylamine in the presence of Me₃Al¹⁹ to provide *O*-methyl hydroxamate **8** in excellent yield (Scheme 2). Chemoselective oxidation of the

Scheme 2. Initial Route to (+)-Castanospermine (**1**)



primary alcohol, using TEMPO and trichloroisocyanuric acid (TCICA),²⁰ now generated unstable aldehyde **9**.²¹ Exposure of this substrate to the ylide generated from 3-(*tert*-butyldimethylsilyloxy)propyl phosphonium bromide and KH-

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MDS²² provided **10** in poor yield. Inefficiencies of preparation notwithstanding, we proceeded to investigate the key cyclization step using this substrate.

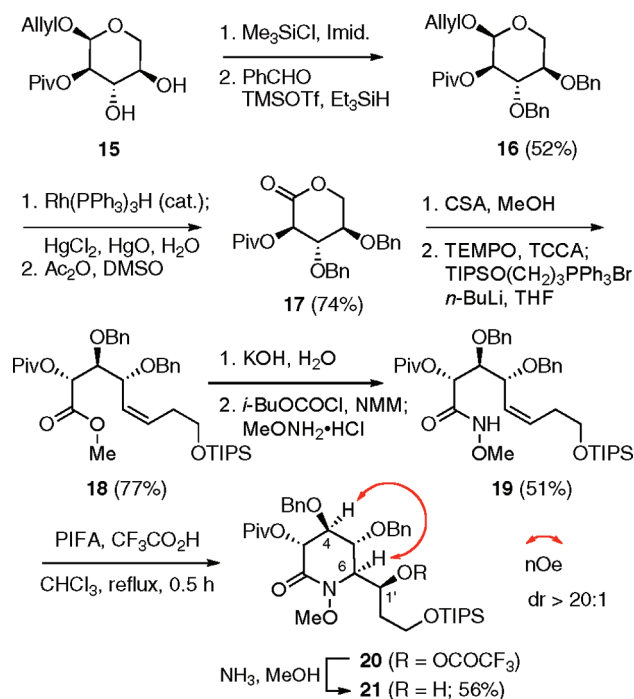
Upon exposure to phenyliodine bis(trifluoroacetate) (PIFA) and trifluoroacetic acid in CH₂Cl₂, hydroxamate **10** underwent slow cyclization to form a mixture of products which following in situ ammonolysis of the trifluoroacetate adducts were separated by flash chromatography to provide compounds **11** and **13** and their desilylated counterparts **12** and **14**. The unanticipated formation of 1,4-oxazepan-3-ones **13** and **14** presumably arises from competitive interception of the nitrenium ion intermediate by the C-3 benzyl ether in **10**.²³ More encouragingly, oxamidation products **11** and **12** were isolated as single diastereomers, which NOSEY experiments indicated were of the desired stereochemistry at C-6.

In light of the involvement of the C-3 O-protecting group during cyclization and the inefficiency of the preceding Wittig reaction, a number of alterations to our synthetic plan were clearly mandated. Accordingly, we decided to evaluate alternative protecting groups that would not irreversibly trap the putative *N*-acylnitrenium ion. To impede loss of the TBS silyl ether under the acidic reaction conditions, a TIPS protecting group was chosen as a more robust surrogate.

Our plan thus amended, the second-generation, and ultimately successful, route to (+)-castanospermine commenced from α -D-xylopyranoside **15**,²⁴ which through reductive etherification of the corresponding (bis)trimethylsilyl ether using benzaldehyde²⁵ was converted to dibenzyl ether **16** (Scheme 3). While direct deallylation of **16** proved to be unexpectedly challenging and failed with a number of reagents, a stepwise approach to this task ultimately proved successful. Thus, exposure of **16** to catalytic HRh(PPh₃)₃ in THF provided the corresponding enol ether which without isolation was hydrolyzed with HgCl₂–HgO to afford a mixture of lactol anomers in good overall yield.²⁶ Conversion of these products to lactone **17** while sluggish with PDC or PCC proceeded with high efficiency under the Albright–Goldman conditions (DMSO, Ac₂O).²⁷

In preparation for installation of the pendant alkene, methanolysis of **17** in the presence of camphorsulfonic acid provided the corresponding δ -hydroxy ester in high yield. Addition of a phosphate buffer (pH 7) prior to workup, to prevent transesterification to **17**, was found to be a prerequisite for the success of this reaction. Oxidation of the primary alcohol, again using TEMPO and TCICA, and

Scheme 3. Second-Generation Route to (+)-Castanospermine (**1**)



treatment of the aldehyde with the ylide generated from (3-isopropylsiloxy)propyltriphenylphosphonium bromide²⁸ then provided **18** in high overall yield. Chemoselective saponification of the methyl ester was now accomplished by the treatment of **18** with aqueous KOH (0.1 M, 3 equiv) in THF and MeOH. Formation of oxamidation substrate **19** was then accomplished by conversion of **18** to the corresponding mixed anhydride, which was treated with methoxylamine hydrochloride.

Disappointingly, exposure of compound **19** to PIFA in the presence of trifluoroacetic acid at room temperature failed to effect cyclization and instead generated an intractable mixture of products.²⁹ Fortunately, performing this reaction at higher temperature, accomplished by adding **19** to a solution of PIFA and trifluoroacetic acid in CHCl₃ at reflux, rapidly afforded **20**, which was isolated as a single diastereoisomer after in situ ammonolysis of the trifluoroacetate adduct. That **19** does not undergo cyclization at ambient temperature, in contrast to compound **10**, may reflect a decrease in the stability of the intermediate nitrenium ion, which in this case could be destabilized by the presence of a more electron-withdrawing, α -acyloxy substituent. This interpretation is consistent with our current belief that

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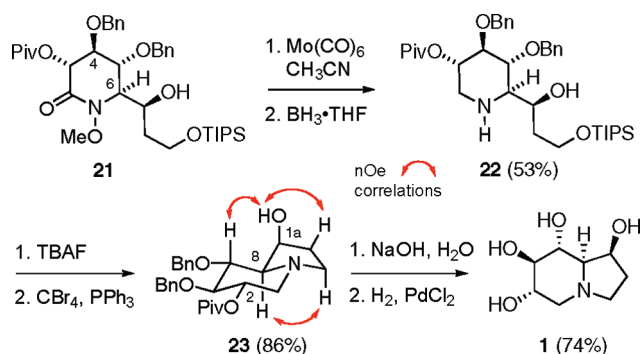
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formation of this N-electrophile is rate limiting and may occur from an *N*-methoxy-*N*-trifluoroacetoxy, or anomeric, amide.³⁰

As with piperidinones **11** and **12**, a 2D NOESY experiment conducted upon **21** revealed a correlation between H-4 and H-6, which together with the absence of interactions between H-3 and H-5 is diagnostic of a half-chair conformation³¹ and confirms the relative stereochemistry at C-6 (Scheme 3).

Treatment of compound **21** with Mo(CO)₆ in aqueous acetonitrile now cleaved the N–O bond and provided the corresponding *NH*-lactam,³² which was reduced with borane to yield piperidine **22**. Removal of the TIPS ether, using TBAF in THF, then provided the corresponding amino-2,4-diol in excellent yield. Selective bromination of this primary alcohol and in situ cyclization to indolizidine **23** was now accomplished by recourse to Appel's conditions.³³ Reflecting the relatively hindered environment at the C-2 position, saponification of the pivalate ester now proceeded slowly at room temperature to provide the 6,7-di-*O*-benzyl ether of castanospermine, albeit in high yield. With the C-1a stereocenter now constrained within the indolizidine ring system, unambiguous assignment of stereochemistry was possible through a NOSEY experiment (Scheme 4). Finally, removal of the benzyl ethers, via hydrogenolysis in the presence of PdCl₂, provided (+)-castanospermine (**1**). The ¹H and ¹³C NMR spectral data obtained from this material were identical to those reported for the natural product. In addition, the optical rotation of synthetic **1** ([α]₂₄^D –86.0; *c* 0.1, MeOH) closely matched that of the natural product ([α]₂₅^D –87.2; *c* 2.1, MeOH).³⁴

Scheme 4. Total Synthesis of (+)-Castanospermine (**1**)



In conclusion, we have developed a 15-step synthesis of (+)-castanospermine (**1**) in which the C-1/8a stereodiad is established through the diastereoselective oxamidation of an unsaturated *O*-alkyl hydroxamate. That this process was found to be stereospecific with respect to alkene geometry supports our current belief that the oxamidation proceeds via the concerted ring opening of a bicyclic aziridinium ion formed upon the addition of a singlet nitrenium ion to the pendant alkene. Extension of this valuable methodology to the preparation of other azasugars is now in progress.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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