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

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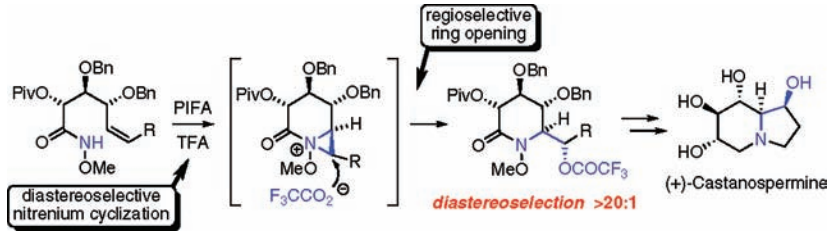
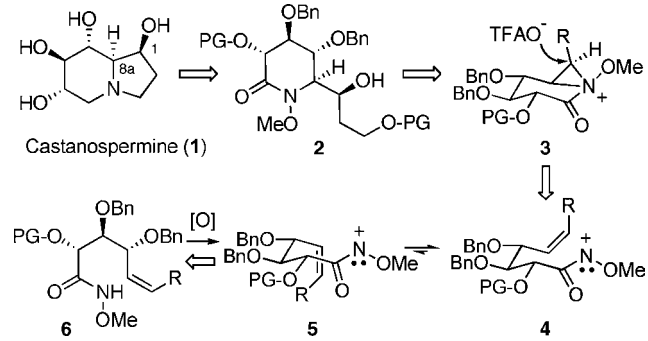
ABSTRACT



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 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

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



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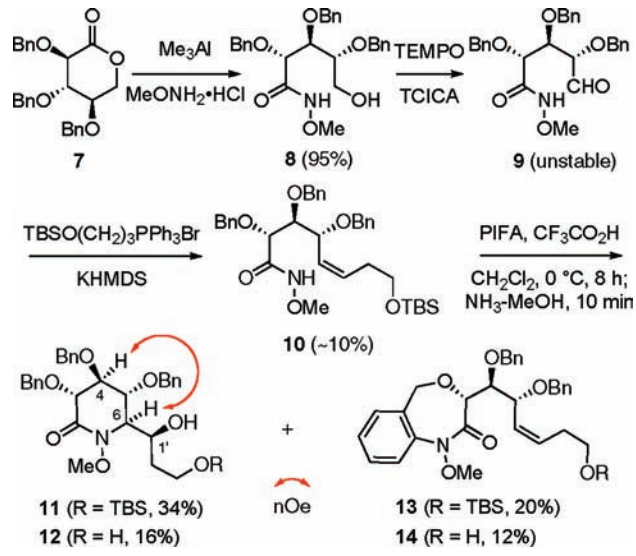
antibiotic-associated pseudomembranous colitis, a leading cause of infectious diarrhea in hospitals worldwide.[7]

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 our 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 reterosynthetic 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-*gluco*-hydroxamate **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) position[15] and hydrolysis of the resulting triflouroacetate 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 strain[16] 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 Me_3Al[19] to provide *O*-methyl hydroxamate **8** in excellent yield (Scheme 2). Chemoselective oxidation of the 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-

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



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MDS[22] provided **10** in poor yield. Inefficiencies of preparation notwithstanding, we proceeded to investigate the key cyclization step using this substrate.

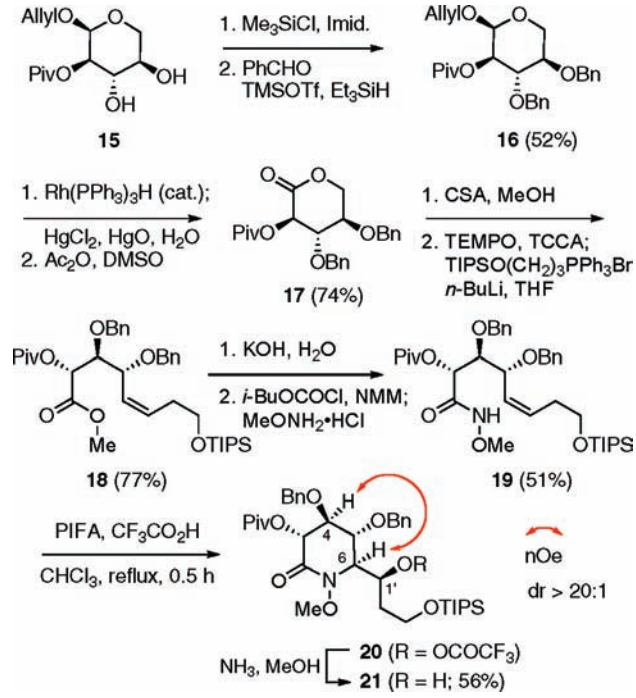
Upon exposure to phenyliodine bis(triflouroacetate) (PIFA) and trifluoroacetic acid in CH_2Cl_2, hydroxamate **10** underwent slow cyclization to form a mixture of products which following in situ ammonolysis of the trifluoroacetate adducts were separated by flash chromatography to provide compounds **11** and **13** and their desilyated 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 benzaldehyde[25] 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 $HRh(PPh_3)_3$ in THF provided the corresponding enol ether which without isolation was hydrolyzed with $HgCl_2$−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, Ac_2O).[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 bromide[28] 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 $CHCl_3$ 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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(21) Upon standing for 12 h at room temperature, compound **9** underwent cyclization to form a mixture of cyclic carbinolamine diastereomers.

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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 conformation[31] 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 $PdCl_2$, provided (+)-castanospermine (**1**). The ^1H and ^{13}C NMR spectral data obtained from this material were identical to those reported for the natural product. In addition, the optical rotation of synthetic **1** ($[\alpha]_{24}^D$ −86.0; *c* 0.1, MeOH) closely matched that of the natural product ($[\alpha]_{25}^D$ −87.2; *c* 2.1, MeOH).[34]

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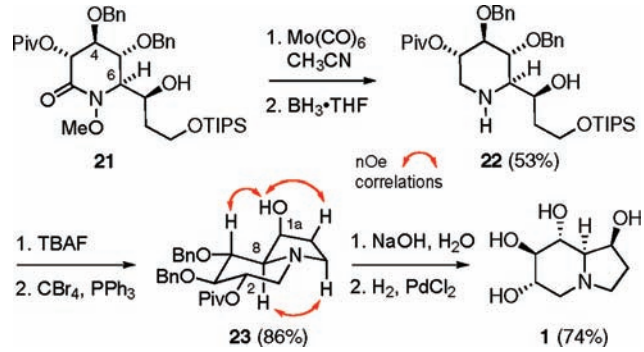
Scheme 4. Total Synthesis of (+)-Castanospermine (**1**)



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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