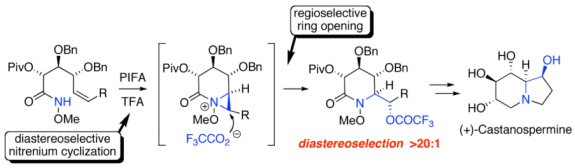
Published in final edited form as:
Org Lett. 2010 November 19; 12(22): 5330–5333. doi:10.1021/ol102371x.

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

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 antibiotic-associated pseudomembranous colitis, a leading cause of infectious diarrhoea 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 inhibitors11,12 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.

wardropd@uic.edu.

Supporting Information Available Experimental procedures and characterization data for all new compounds.

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) position15 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 pseudo-chair **4**, thereby avoiding the 1,3-allylic strain16 present in boat-like conformer **5**.17

Our initial route towards (+)-castanospermine (**1**) commenced from tribenzyl D-glucono-δ-lactone (**7**),18 which underwent ring opening with the methoxylamine in the presence of Me_3Al19 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 KHMDS22 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. In order 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 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 $CHCl_3$ at reflux, rapidly afforded **20**, which was isolated as a single diasteroisomer 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 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 $PdCl_2$, provided (+)-castanospermine (**1**). The ^{1}H 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** ($[\alpha]_{24D}$ − 86.0; *c* 0.1, MeOH) closely matched that of the natural product ($[\alpha]_{25D}$ −87.2; *c* 2.1, MeOH).34

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

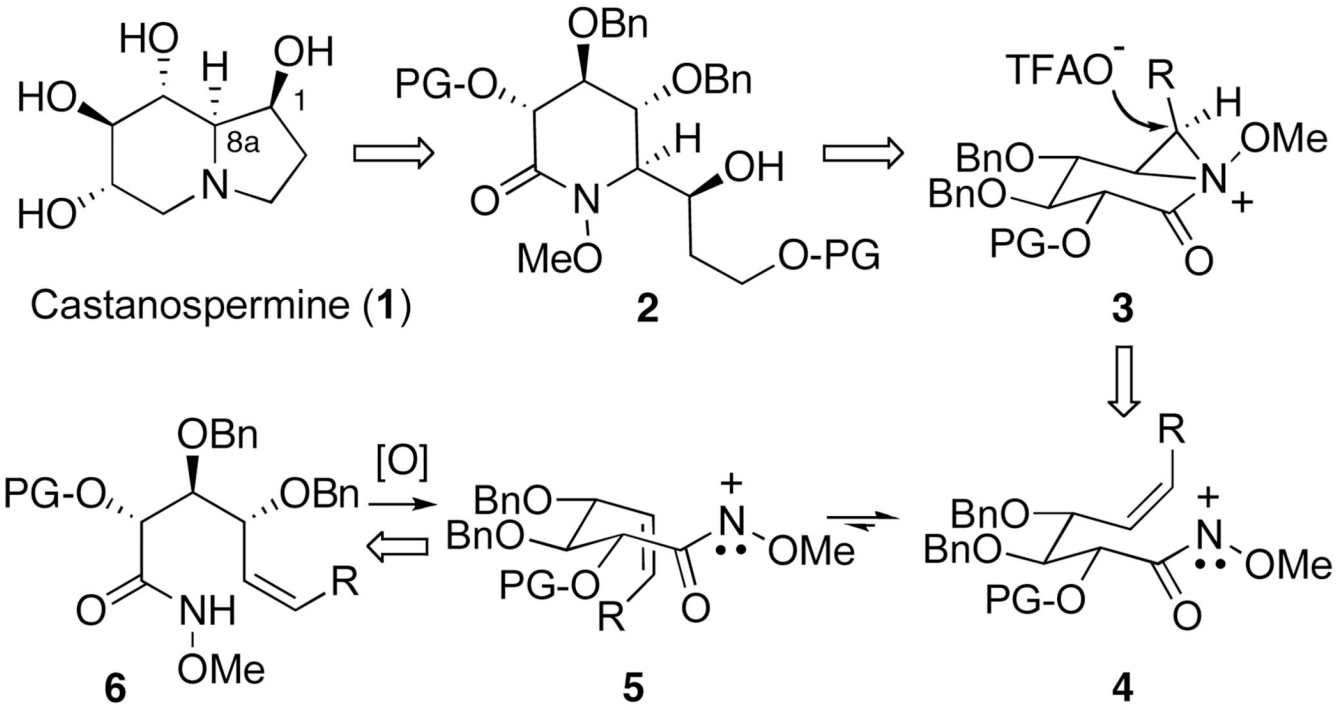
Acknowledgments

We thank the National Institutes of Health (GM-67176) and the University of Illinois at Chicago for financial support of this work.

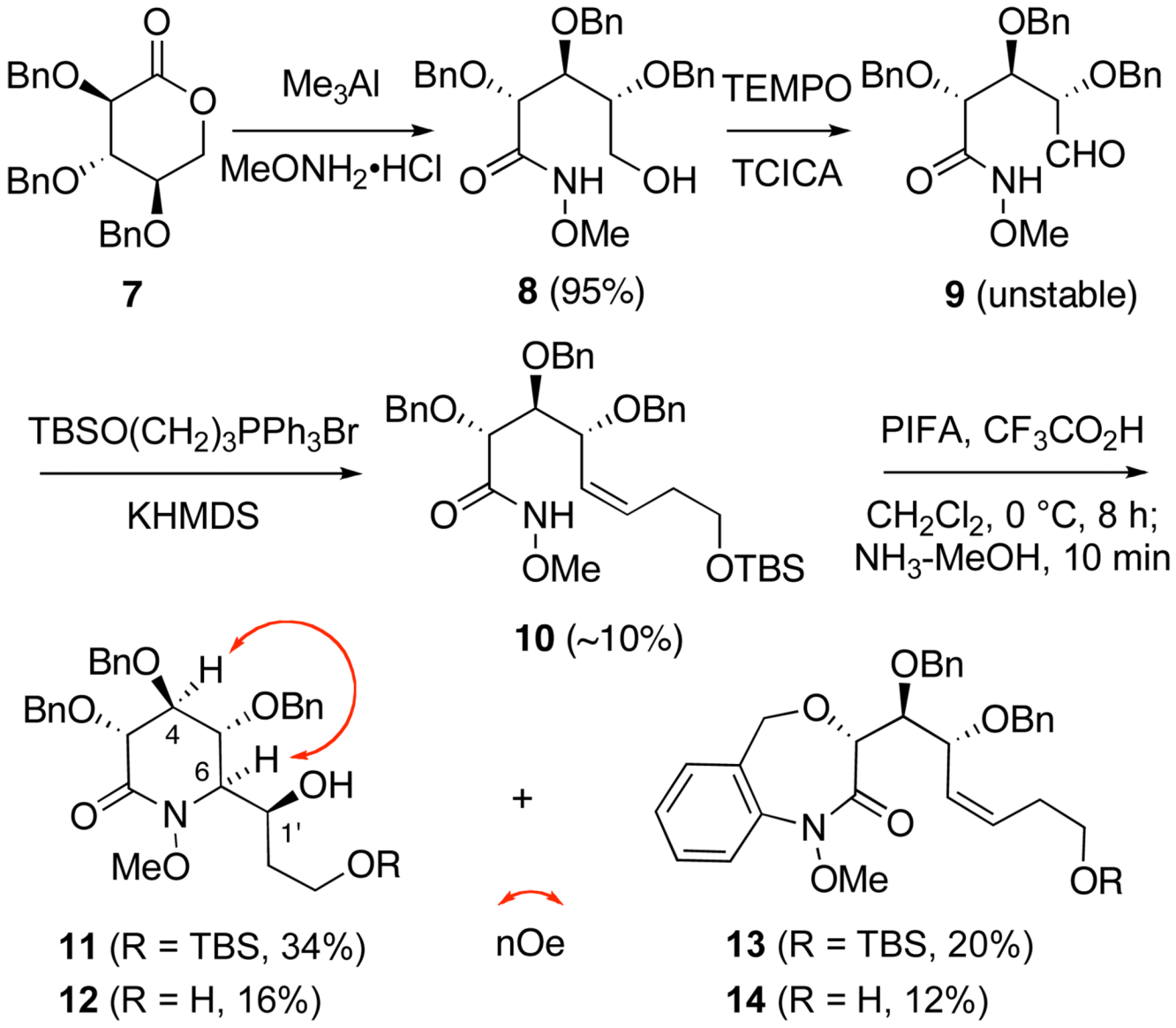
References

1. (a) Hohenschutz LD, Bell EA, Jewess PJ, Leworthy DP, Pryce RJ, Arnold E, Clardy J. Phytochemistry. 1981; 4:811. (b) Nash RJ, Fellows LE, Dring JV, Stirton CH, Carter D, Hegarty MP, Bell EA. Phytochemistry. 1988; 5:1403.
2. (a) Saul R, Chambers JP, Molyneux RJ, Elbein AD. Arch. Biochem. Biophys. 1983; 221:593. (β-glucosidase, β-glucocerebrosidase, β-xylosidase); [PubMed: 6404222] (b) Trugnan G, Rousset M, Zweibaum A. Febs Lett. 1986; 195:28. (sucrase); [PubMed: 2867936] (c) Campbell BC, Molyneux RJ, Jones KC. J. Chem. Ecol. 1987; 13:1759. (disaccharidases); (h) Scofield AM, Rossiter JT, Witham P, Kite GC, Nash RJ, Fellows LE. Phytochemistry. 1990; 29:107. (thioglucosidase); (i) Valaitis AP, Bowers DF. Insect Biochem. Mol. Biol. 1993; 23:599. (trehalase). [PubMed: 8353520]
3. (a) Gloster T, Meloncelli P, Stick R, Zechel D, Vasella A, Davies G. J. Am. Chem. Soc. 2007; 129:2345. [PubMed: 17279749] (b) Pan YT, Hori H, Saul R, Sanford BA, Molyneux RJ, Elbein AD. Biochemistry. 1983; 22:3975. [PubMed: 6615812] (c) Sasak VW, Ordovas JM, Elbein AD, Berninger RW. Biochem. J. 1985; 232:759. [PubMed: 3004419] (d) Ellmers BR, Rhinehart BL, Robinson KM. Biochem. Pharmacol. 1987; 36:2381. [PubMed: 3300654] (e) Foddy L, Hughes RC. Eur. J. Pharmacol. 1988; 175:291.
4. (a) Gloster TM, Davies GJ. Org. Biomol. Chem. 2010; 8:305. [PubMed: 20066263] (b) Winchester BG. Tetrahedron: Asymmetry. 2009; 20:645.
5. (a) Durantel D. Curr. Opin. Invest. Drugs. 2009; 10:860. (HCV). (b) Tanaka Y, Kato J, Kohara M, Galinski M. Antiviral Res. 2006; 72:1. (parainfluenza). [PubMed: 16730076] (c) Whitby K, Pierson T, Geiss B, Lane K, Engle M, Zhou Y, Doms R, Diamond M. J. Virol. 2005; 79:8698. (dengue virus). [PubMed: 15994763] (d) Whitby K, Taylor D, Patel D, Ahmed P, Tyms A. Antivir. Chem. Chemother. 2004; 15:141. (bovine viral diarrhoea virus/HCV). [PubMed: 15266896] (e) Ahmed SP, Nash R, Bridges C, Taylor D, Kang M, Porter E, Tyms A. Biochem. Biophys. Res. Commun. 1995; 208:267. (HSV-2). [PubMed: 7887939] (f) Bridges C, Brennan T, Taylor D, McPherson M, Tyms A. Antiviral Res. 1994; 25:169. (HIV-1). [PubMed: 7847878]
6. Jank T, Ziegler MO, Schulz GE, Aktories K. FEBS Lett. 2008; 582:2277. [PubMed: 18505687]
7. Lyras D, O'Connor J, Howarth P, Sambol S, Carter G, Phumoonna T, Poon R, Adams V, Vedantam G, Johnson S, Gerding D, Rood J. Nature. 2009; 458:1176. [PubMed: 19252482]
8. For recent syntheses of castanospermine, see: (a) Liu G, Wu TJ, Ruan YP, Huang PQ. Chem.-Eur. J. 2010; 16:5755. (b) Jensen T, Mikkelsen M, Lauritsen A, Andresen TL, Gotfredsen CH, Madsen R. J. Org. Chem. 2009; 74:8886. [PubMed: 19856948] (c) Ceccon J, Danoun G, Greene AE, Poisson JF. Org. Biomol. Chem. 2009; 7:2029. [PubMed: 19421437] (d) Machan T, Davis AS, Liawruangrath B, Pyne SG. Tetrahedron. 2008; 64:2725. (e) Karanjule NS, Markad SD, Shinde VS, Dhavale DD. J. Org. Chem. 2006; 71:4667. [PubMed: 16749803] (f) Zhao ZM, Song L, Mariano PS. Tetrahedron. 2005; 61:8888. (g) Cronin L, Murphy PV. Org. Lett. 2005; 7:2691. [PubMed: 15957923] .
9. (a) For a review of recent total syntheses of castanospermine and related α-glucosidase inhibitors, see: Wardrop DJ, Waidyarachchi SL. Nat. Prod. Reports. 2010; 27:1413.. (b) For a review of earlier syntheses of castanospermine, see: López MD, Cobo J, Nogueras M. Curr. Org. Chem. 2008; 12:718..
10. For bioactive analogs of castanospermine, see: (a) Louvel J, Botuha C, Chemla F, Demont E, Ferreira F, Pérez-Luna A. Eur. J. Org. Chem. 2010:2921. (b) Pluvinage B, Ghinet MG, Brzezinski R, Boraston AB, Stubbs KA. Org. Biomol. Chem. 2009; 7:4169. [PubMed: 19795054] (c) Aguilar-Moncayo M, Mellet CO, Fernández JMG, Garcia-Moreno MI. J. Org. Chem. 2009; 74:3595. [PubMed: 19334717] (d) Aguilar-Moncayo M, Gloster TM, Turkenburg JP, Garcia-Moreno MI, Mellet CO. (e) Davies GJ, Fernández JMG. Org. Biomol. Chem. 2009; 7:2738. [PubMed: 19532990] (f) Benltifa M, Garcia Moreno MI, Ortiz Mellet C, Garcia Fernández JM, Wadouachi A. Bioorg. Med. Chem. Lett. 2008; 18:2805. [PubMed: 18420407] .
11. Bowen EG, Wardrop DJ. J. Am. Chem. Soc. 2009; 131:6062. [PubMed: 19361223]

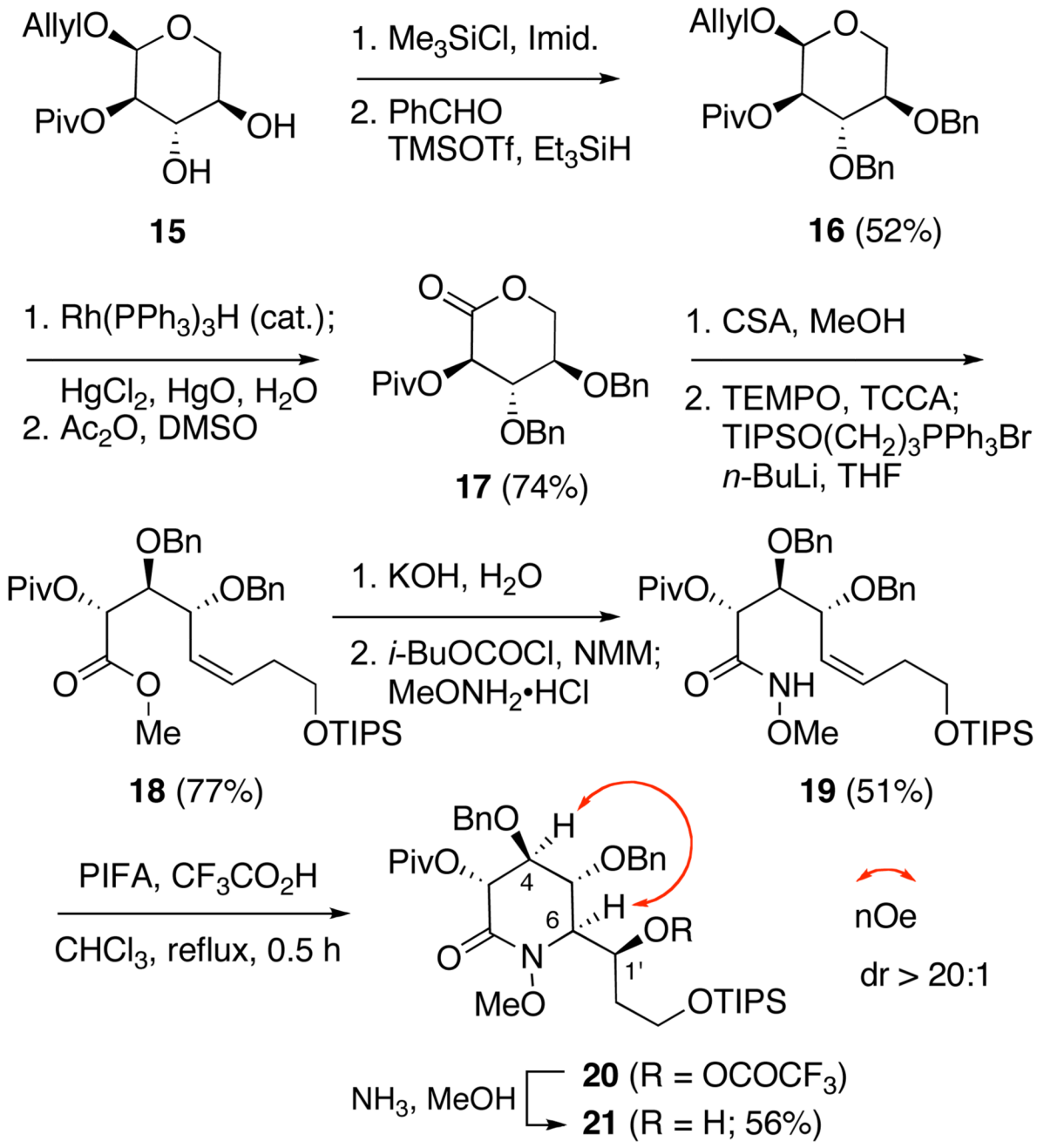
12. See reference 9a.
13. Wardrop DJ, Bowen EG, Forslund RE, Sussman AD, Weerasekera SL. J. Am. Chem. Soc. 2010; 132:1188. [PubMed: 19788297]
14. (a) Rudchenko VF, Ignatov SM, Kostyanovsky RG. Chem. Commun. 1990:261. (b) Vedejs E, Sano H. Tetrahedron Lett. 1992; 33:3261. (c) Hoffman RV, Christophe NB. J. Org. Chem. 1988; 53:4769.
15. For regioselective ring opening of a 1-azabicyclo[4.1.0]heptane-based aziridinium ion, see: D'hooghe MD, Vanlangendonck T, Törnroos KW, De Kimpe N. J. Org. Chem. 2006; 71:4678. [PubMed: 16749806] . (b) Reference 13.
16. Hoffmann RW. Chem. Rev. 1989; 89:1841.
17. For a related conformational analysis made in reference to an intramolecular Huisgen alkene-azide cycloaddition, see: Zhou Y, Murphy PV. Org. Lett. 2008; 10:3777. [PubMed: 18672879] .
18. López R, Fernández-Mayorala A. J. Org. Chem. 1994; 59:737.
19. (a) Takahashi H, Hitomi Y, Iwai Y, Ikegami S. J. Am. Chem. Soc. 2000; 122:2995. (b) Basha A, Lipton M, Weinreb SM. Tetrahedron Lett. 1977; 18:4171.
20. De Luca L, Giacomelli G, Porcheddu A. Org. Lett. 2001; 3:3041. [PubMed: 11554838]
21. Upon standing for 12 h at room temperature, compound **9** underwent cyclization to form a mixture of cyclic carbinolamines diastereomers.
22. Glebocka A, Sicinski R, Plum L, Clagett-Dame M, Deluca H. J. Med. Chem. 2006; 49:2909. [PubMed: 16686534]
23. Kikugawa Y, Shimado M, Matsumoto K. Heterocycles. 1994; 37:293.
24. Prepared in two steps, from D-xylose: Rosenberg H, Riley A, Marwood R, Correa V, Taylor C, Potter B. Carbohydr. Res. 2001; 332:53. [PubMed: 11403088] .
25. Hatakeyama S, Mori H, Kitano K, Yamada H, Nishizawa M. Tetrahedron Lett. 1994; 35:4367.
26. (a) Boons G, Burton A, Isles S. Chem. Commun. 1996; 141 (b) Uma R, Davies M, Crévisy C, Grée R. Eur. J. Org. Chem. 2001:3141. (c) Corey EJ, Suggs JW. J. Org. Chem. 1973; 38:3224.
27. Albright JD, Goldman L. J. Am. Chem. Soc. 1965; 18:4214.
28. For details of preparation, see: Supporting Information and Clayden J, Knowles FE, Baldwin IR. J. Am. Chem. Soc. 2005; 127:2412. [PubMed: 15724994] .
29. Oxidation of *O*-alkyl hydroxamates can also lead to the formation of thermally unstable *N*,*N*′-dialkoxy-*N*,*N*′-diacylhydrazines:. (a) De Almeida MV, Barton DHR, Bytheway I, Ferreira JA, Hall MB, Liu W, Taylor DK, Thomson L. J. Am. Chem. Soc. 1995; 117:4870. (b) Cooley JH, Mosher MW, Khan MA. J. Am. Chem. Soc. 1968; 90:1867. (c) Crawford RJ, Raap R. J. Org. Chem. 1963; 28:2419..
30. (a) Glover SA. Adv. Phys. Org. Chem. 2008; 42:35. (b) Glover SA, Rauk A. J. Chem. Soc., Perkin Trans. 2002; 2:1740. (c) Glover SA, Hammond GP. J. Org. Chem. 1998; 63:9684.
31. Boudreault N, Ball RG, Bayly C, Bernstein MA, Leblanc Y. Tetrahedron. 1994; 50:7947.
32. Cicchi S, Goti A, Brandi A, Guarna A, De Sarlo F. Tetrahedron Letters. 1990; 31:3351.
33. Appel R. Angew. Chem. Int. Ed. 1975; 14:801.
34. Scheider MJ, Ungemach FS, Broquist HP, Harris TM. Tetrahedron. 1983; 39:29.



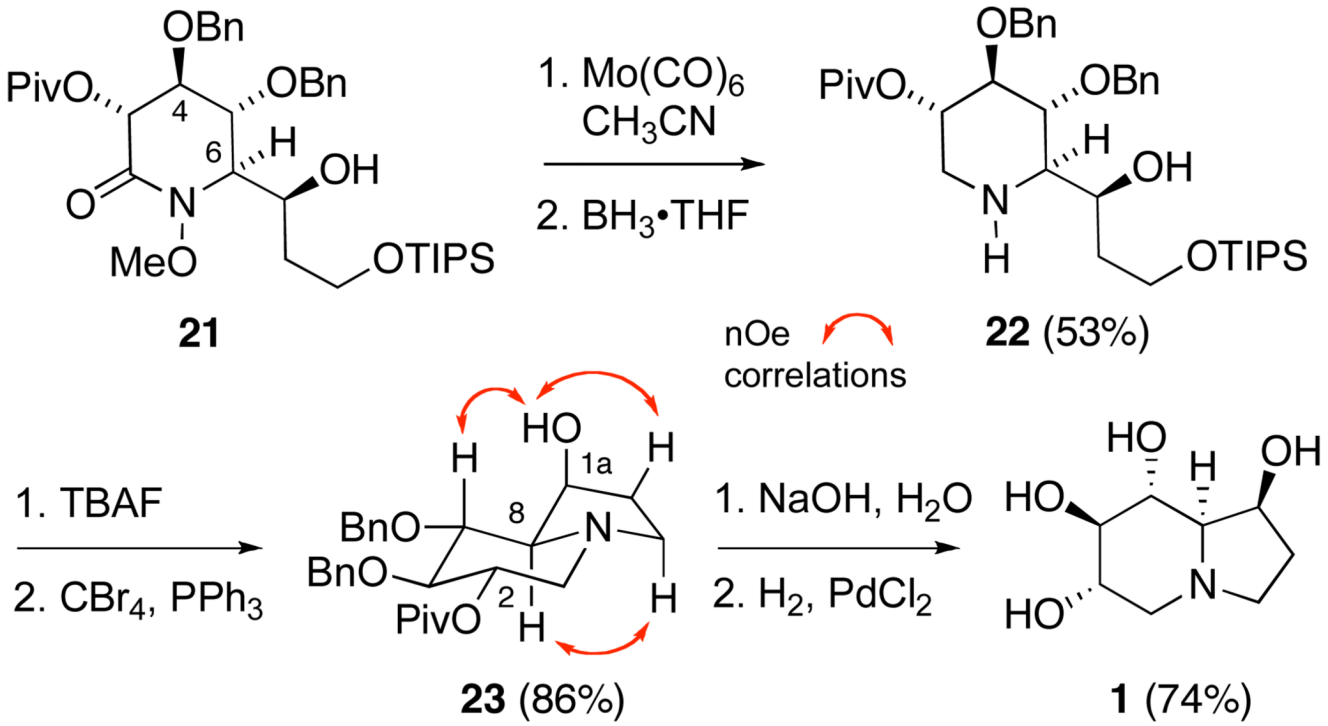
Scheme 1.
Retrosynthetic Analysis of Castanospermine (**1**).



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



Scheme 3.
2nd Generation Route to (+)-Castanospermine (**1**).



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