Intramolecular 5- endo- Trig Aminomercuration of β-Hydroxy-γ-alkenylamines: Efficient Route to a Pyrrolidine Ring and Its Application for the Synthesis of (+)-Castanospermine and A...

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · JULY 2006

Impact Factor: 4.72 · DOI: 10.1021/jo0601617 · Source: PubMed

4 AUTHORS, INCLUDING:

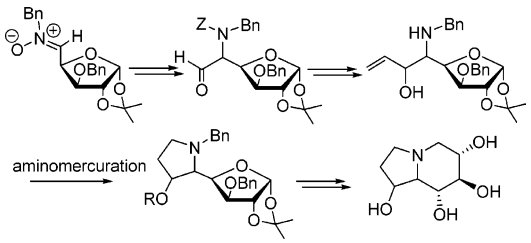
Shankar D Markad
AstraZeneca
12 PUBLICATIONS **286** CITATIONS
SEE PROFILE

Vaishali S Shinde
Savirtibai Phule Pune University
29 PUBLICATIONS **294** CITATIONS
SEE PROFILE

JOC*Note*

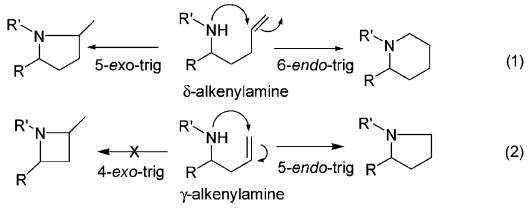
Intramolecular 5-*endo*-Trig Aminomercuration of *β*-Hydroxy-*γ*-alkenylamines: Efficient Route to a Pyrrolidine Ring and Its Application for the Synthesis of (+)-Castanospermine and Analogues†

Narayan S. Karanjule, Shankar D. Markad, Vaishali S. Shinde, and Dilip D. Dhavale*
Department of Chemistry, Garware Research Centre, University of Pune, Pune-411 007, India
ddd@chem.unipune.ernet.in
Received January 24, 2006



The intramolecular aminomercuration reaction of sugar-derived *β*-hydroxy-*γ*-alkenylamines **8a**−**c** undergoes 5-*endo*-trig cyclization in high yield. The sugar-substituted pyrrolidines thus obtained were elaborated to the synthesis of polyhydroxylated indolizidine alkaloids, namely, castanospermine **1a**, 1-*epi*-castanospermine **1b**, and 8a-*epi*-castanospermine **1c**, having promising glycosidase inhibitory activities.

The common occurrence of the pyrrolidine ring in natural products as well as its use as a chiral auxiliary[1] and ligand in asymmetric synthesis[2] led to the development of a number of inter- and intramolecular pathways for its construction.[3] In particular, intramolecular methodologies mainly involve either C−N bond formation,[4] including rhodium/copper carbenoid N−H insertion,[5] or metal-assisted C−C bond formation of aminoalkenes.[6] Among intramolecular metal-catalyzed hydroamination,[7] one of the most attractive methods is the stereoselective amido- and aminomercuration reactions of *δ*-alkenylamines that affords a 2-substituted pyrrolidine ring through preferable 5-*exo*-trig cyclization in addition to the 6-*endo*-trig cyclized piperidine ring skeleton in minor amounts (eq 1).[8] However, only a single report is known on the mercury(II)-mediated 5-*endo*-trig cyclization of *γ*-alkenylamine leading to the formation of a pyrrolidine ring.[8a,9] Although the intramolecular *exo*-trig nucleophilic addition reaction to a double bond for rings smaller than a five-membered ring is favored over the *endo*-trig,[10] we have recently demonstrated that the aryl- and sugar-substituted *γ*-alkenylamines led to the formation of the pyrrolidine ring via 5-*endo*-trig cyclization in the presence of mercury(II) salt in high yield (eq 2).[11] Inspired with this observation and as a part of our continuing interest in the synthesis of azasugars,[12] we have further investigated the intramolecular aminomercuration reaction with D-glucose derived *β*-hydroxy-*γ*-alkenylamines and noticed that 5-*endo*-trig cyclization is indeed a prominent process. The sugar-substituted pyrrolidine compounds thus obtained in high yield, are found to be the adequate precursors in the synthesis of azasugars.



Among azasugars, (+)-castanospermine **1a** (Figure 1) was isolated from the seeds of the Australian legume *Castanospermum australe*,[13a] as well as from the dried pod of *Alexa leiopetala*,[13b] known to have a significant glycosidase inhibitory activity.[14] In the search for a structure−activity relationship, a number of natural and unnatural analogues of **1a**, with variation in the number/position and stereochemistry of the hydroxyl

† Dedicated to Prof. N. S. Narasimhan.

(1) (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581−1590. (b) White, J. D.; Xu, Q.; Lee, C.-S.; Valeriote, F. A. *Org. Biomol. Chem.* **2004**, *2*, 2092−2102.

(2) (a) Fache, F.; Schultz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159−2232. (b) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16−17. (c) *Chiral Reagents for Asymmetric Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 2003. (d) Rogers, C. J.; Dickerson, T. J.; Brogan, A. P.; Janda, K. D. *J. Org. Chem.* **2005**, *70*, 3705−3708.

(3) (a) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927−964 and references therein. (b) Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979−1985. (c) Besev, M.; Engman, L. *Org. Lett.* **2002**, *4*, 3023−3025.

(4) (a) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221−3235. (b) Craig, D.; Jones, P. S.; Rowlands, G. J. *Synlett* **1997**, 1423−1428. (c) Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* **2000**, *2*, 385−388.

(5) Davis, F. A.; Wu, Y.; Xu, H.; Zhang, J. *Org. Lett.* **2004**, *6*, 4523−4525.

(6) (a) Coldham, I.; Hufton, R. *Tetrahedron Lett.* **1995**, *36*, 2157−2160. (b) Pedrosa, R.; Andres, C.; Duque-Soladana, J. P.; Mendiguchia, P. *Eur. J. Org. Chem.* **2000**, 3727−3730. (c) Bustos, F.; Gorgojo, J. M.; Suero, R.; Aurrecoechea, J. M. *Tetrahedron* **2002**, *58*, 6837−6842.

(7) (a) Bajracharya, G. B.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4883−4886. (b) Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959−1962. (c) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737−1739.

(8) For amido- and aminomercuration, see: (a) Perie, J. J.; Laval, J. P.; Roussel, J.; Lattes, A. *Tetrahedron* **1972**, *28*, 675−699. (b) Gasc, M. B.; Lattes, A.; Perie, J. J. *Tetrahedron* **1983**, *39*, 703−731. (c) Stipa, P.; Finet, J. P.; Le Moigne, F.; Tordo, P. *J. Org. Chem.* **1993**, *58*, 4465−4468. (d) Arnone, A.; Bravo, P.; Donadelli, A.; Resnati, G. *J. Chem. Soc., Chem. Commun.* **1993**, 984−985. (e) Le Moigne, F.; Tordo, P. *J. Org. Chem.* **1994**, *59*, 3365−3367. (f) Pecanha, E. P.; Verli, H.; Rodrigues, C. R.; Barreiro, E. J.; Fraga, C. A. M. *Tetrahedron Lett.* **2002**, *43*, 1607−1611. (g) Chikkanna, D.; Han, H. *Synlett* **2004**, 2311−2314.

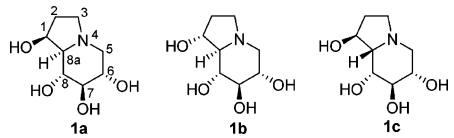
(9) The 5-*endo*-trig radical- and iodo-cyclization of *γ*-alkenylamines are known to give a pyrrolidine ring, see: (a) Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10765−10772. (b) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874−2883. (c) Lee, W. S.; Jang, K. C.; Kim, J. H.; Park, K. H. *Chem. Commun.* **1999**, 251−252.

(10) (a) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476−482. (b) Baldwin, J. E.; Thomas, R. C.; Kruce, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846−3852.

(11) Dhavale, D. D.; Jachak, S. M. *Molecules* **2005**, *10*, 893−900.

(12) (a) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065−1074. (b) Dhavale, D. D.; Markad, S. D.; Karanjule, N. S.; PrakashaReddy, J. *J. Org. Chem.* **2004**, *69*, 4760−4766. (c) Karanjule, N. S.; Markad, S. D.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *J. Org. Chem.* **2005**, *70*, 1356−1363. (d) Dhavale, D. D.; Jachak, S. M.; Karche, N. P.; Trombini, C. *Synlett* **2004**, 1549−1552 and references therein.

10.1021/jo0601617 CCC: $33.50
Published on Web 05/18/2006

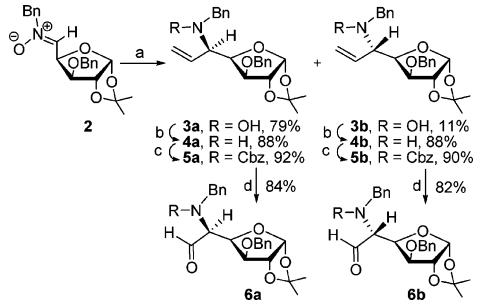


1a **1b** **1c**

FIGURE 1. Castanospermine and analogues.

groups at each carbon atom in the indolizidine ring skeleton, have been synthesized[12c,15] and evaluated for the glycosidase inhibition in the treatment of various diseases such as diabetes,[16] cancer,[17] and multiple scelerosis,[18] as well as viral infections including AIDS, hepatitis C, and HSV-1.[19] As a result of the highly oxygenated framework in **1a**−**c**, the chiron approach is the obvious choice for their synthesis.[20] In fact, the D-glucose type of hidden symmetry in **1** could be easily recognized in the trihydroxylated architect of the piperidine ring, wherein the C-6, 7, and 8 of **1** match with that of the C-2, 3, and 4 of D-glucose as far as the position and stereochemical aspects are concerned. However, the building of a pyrrolidine ring, with stereochemically well-defined hydroxylated carbon center C-1 of **1**, requires an asymmetric pathway. In general, the required carbinol center is generated first, followed by an intramolecular cyclization, to get the pyrrolidine ring skeleton. The use of the intramolecular aminomercuration strategy with D-glucose derived β-hydroxy-γ-alkenylamines for the formation of pyrrolidine ring and further elaboration to castanospermine **1a**, to the best of our knowledge, is not known. Our efforts toward the successful implementation of this methodology for the synthesis of castanospermine **1a**, 1-*epi*-castanospermine **1b**, and 8a-*epi*-castanospermine **1c** are reported herein.

SCHEME 1. 1,3-Addition of Vinylmagnesium Bromide[a]



[a] Reaction conditions: (a) vinylmagnesium bromide, TMSOTf, THF, −78 °C, 2 h, 90%; (b) Zn, $Cu(OAc)_2$, AcOH, 80 °C, 1 h; (c) $NaHCO_3$, CbzCl, MeOH−water (4:1), 3 h; (d) (i) NMO, $K_2OsO_4 \cdot 2H_2O$, acetone−water (8:1), 12 h; (ii) $NaIO_4$, acetone−water (9:1), 6 h.

A 1,3-addition reaction of vinylmagnesium bromide (3.0 eq.) to nitrone **2** in THF at 0 °C afforded a diastereomeric mixture of D-*gluco*- and L-*ido*-*N*-allylamines **3a** and **3b**, respectively, in the ratio of 55:45 (Scheme 1). The diastereoselectivity in favor of D-*gluco* isomer was achieved using TMSOTf (1 equiv) at −78 °C in dry THF, which gave **3a**/**3b** in the ratio 87/13.[21] The spectral and analytical data is found to be identical with that reported.[22] The N−O bond reductive cleavage in **3a** using zinc in acetic acid−water afforded *N*-benzylamino sugar **4a**,[22a] which on treatment with benzylchloroformate afforded *N*-Cbz protected allylamine **5a**.[23] Dihydroxylation of **5a** (potassium osmate, NMO), followed by a reaction with $NaIO_4$, afforded α-amino aldehyde **6a**. The similar reaction sequence with hydroxylamine **3b** afforded corresponding **4b**, **5b**, and α-amino aldehyde **6b** in good yields.[24] No epimerization at C-5 in **6a**,**b** was noticed under $NaIO_4$-mediated oxidative cleavage of the diol.

In the next step (Scheme 2), the reaction of vinylmagnesium bromide with D-*gluco*-configurated-α-amino aldehyde **6a** at −50 °C afforded a diastereomeric mixture of *anti*/*syn* products in the ratio 3:1, as is evident from the ^{1}H NMR spectrum of the crude product.[25] Our attempts to alter the diastereoselectivity as well as to separate the diastereomers by flash chromatography were unsuccessful,[26] therefore, the mixture was directly treated with 40% KOH in MeOH for 10 min at 90 °C, which afforded easily separable carbamates **7a** and **7b** in the ratio of 3:1. The

(13) (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811−814. (b) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirotn, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, *27*, 1403−1406.

(14) (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1987; Vol. 5. Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, Chapter 3. (b) Michael, J. P. *Nat. Prod. Rep.* **1990**, *9*, 485−523.

(15) (a) Svansson, L.; Johnston, B. D.; Gu, J.-H.; Patrik, B.; Pinto, B. M. *J. Am. Chem. Soc.* **2000**, *122*, 10769−10775. (b) Izquiedro, I.; Plaza, M. T.; Robles, R.; Mota, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 1015−1027. (c) Kefalas, P.; Grierson, D. S. *Tetrahedron Lett.* **1993**, *34*, 3555−3558. (d) Burgess, K.; Chaplin, D. A.; Henderson, I.; Pan, Y. T.; Elbein, A. D. *J. Org. Chem.* **1992**, *57*, 1103−1109. (e) Furneaux, R. H.; Mason, J. M.; Tyler, P. C. *Tetrahedron Lett.* **1995**, *36*, 3055−3058.

(16) Nojima, H.; Kimura, I.; Chen, F.-J.; Sugihara, Y.; Haruno, M.; Kato, A.; Asano, N. *J. Nat. Prod.* **1998**, *61*, 397−400.

(17) Pili, R.; Chang, J.; Partis, R. A.; Mueller, R. A.; Chrest, F. J.; Passaniti, A. *Cancer Res.* **1995**, *55*, 2920−2926.

(18) Walter, S.; Fassbender, K.; Gulbins, E.; Liu, Y.; Rieschel, M.; Herten, M.; Bertsch, T.; Engelhardt, B. *J. Neuroimmunol.* **2002**, *132*, 1−10.

(19) (a) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229−9233. (b) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8120−8124. (c) Sunkara, P. S.; Bowling, T. L.; Liu, P. S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206−210. (d) Whitby, K.; Taylor, D.; Patel, D.; Ahmed, P.; Tyms, A. S. *Antiviral Chem. Chemother.* **2004**, *15*, 141−151. (e) Bridges, C. G.; Ahmed, S. P.; Kang, M. S.; Nash, R. J.; Porter, E. A.; Tyms, A. S. *Glycobiology* **1995**, *5*, 249−253.

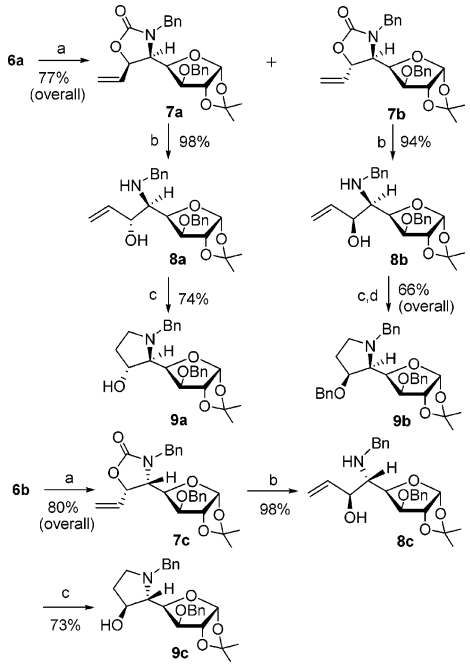
(20) For selected syntheses of **1a**, **1b**, and **1c**, see: (a) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046−3056. (b) Cronin, L.; Murphy, P. V. *Org. Lett.* **2005**, *7*, 2691−2693 and references therein. (c) Bartnicka, E.; Zamojski, A. *Tetrahedron* **1999**, *55*, 2061−2076. (d) Leeper, F. J.; Howard, S. *Tetrahedron Lett.* **1995**, *36*, 2333−2338. (e) Somfai, P.; Marchand, P.; Torsell, S.; Lindstrom, U. M. *Tetrahedron* **2003**, *59*, 1293−1299. (f) Zho, Z.; Song, L.; Marino, P. S. *Tetrahedron* **2005**, *61*, 8888−8894. (g) Zhao, H.; Hans, S.; Cheng, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761−1767. (h) Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5492−5494. (i) Zhao, H.; Mootoo, D. R. *J. Org. Chem.* **1996**, *61*, 6762−6763. (j) Zhao, H.; Hans, S.; Cheng, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *65*, 1761−1767.

(21) These results are consistent with our earlier studies on the 1,3-addition of methyl- and allyl-magnesium bromide, as well as silyl ketene acetal of ethyl acetate to nitrone **2**, in the presence of TMSOTf (1 equiv) at −78 °C in THF, which afforded a good diastereoselectivity in the favor of the D-gluco isomer (∼de 75%), see: (a) Saha, N. N.; Desai, V. N.; Dhavale, D. D. *Tetrahedron* **2001**, *57*, 39−46. (b) Dhavale, D. D.; Jachak, S. M.; Karche, N. P.; Trombini, C. *Synlett* **2004**, 1549−1552. (c) Dhavale, D. D.; Desai, V. N.; Sindkhedkar, M.; Mali, R. S.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1475−1486.

(22) Pedro Merino et al. reported the reaction of vinylmagnesium bromide with nitrone **2** using Et_2AlCl as a Lewis acid in which **3a** and **3b** were obtained in the ratio of 77:23, see: (a) Merino, P.; Anoro, S.; Franco, S.; Gascon, J. M.; Martin, V.; Merchan, F.; Revuelta, J.; Tejero, T.; Tunon, V. *Synth. Commun.* **2000**, 2989−3021. (b) Merino, P.; Anoro, S.; Castillo, E.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1887−1890. For reviews on the 1,3-addition of organometallic reagents to nitrones, see: (c) Lombardo, M.; Trombini, C. *Curr. Org. Chem.* **2002**, *6*, 695−713 and references therein.

(23) The ^{1}H and ^{13}C NMR spectra of compounds **5a**,**b** and **6a**,**b**, in which a *N*-Cbz group is present, showed doubling of signals. This was due to isomerization by restricted rotation around C═N, see: *Applications of NMR spectroscopy in organic chemistry*; Jackman, L. M., Sternhell, S., Eds.; Pergamon: Elmsford, NY, 1978; p 361.

SCHEME 2. 5-*endo*-Trig Cyclization of 8a−c[a]



[a] Reaction conditions: (a) (i) vinylmagnesium bromide, THF, −50 °C, 1 h; (ii) 40% KOH, MeOH, 90 °C, 10 min; (b) 40% KOH, MeOH, 90 °C, 48 h; (c) $Hg(OAc)_2$, THF−H_2O (1:1), $NaBH_4$, 3 h; (d) NaH, BnBr, TBAI, THF, 0 °C to room temperature, 6 h.

^{1}H NMR data of carbamates **7a** and **7b** allowed us to establish the absolute configurations at the newly generated C6 carbinol stereocenter, wherein the coupling constant between H-5 and H-6 is decisive. Thus, in **7a**, the H-5 appeared at δ 4.20 as a triplet with a high coupling constant. $J_{5,6}$ = 7.8 Hz, while in **7b**, the H-5 showed a narrow triplet at δ 4.25 with a small coupling constant, $J_{5,6}$ = 4.4 Hz. The large value of $J_{5,6}$ (7.8 Hz) in **7a** and the small value of $J_{5,6}$ (4.4 Hz) in **7b** indicated the *cis* and *trans* relative orientation of H-5 and H-6. Therefore, absolute configurations 5*S*,6*R* and 5*S*,6*S* were assigned for **7a** and **7b**, respectively. Similarly, the reaction of vinylmagnesium bromide with L-*ido*-configurated-α-amino aldehyde **6b** at −50 °C afforded only a single *anti*-diastereomer that on treatment with 40% KOH at 90 °C for 10 min afforded carbamate **7c**.[27]

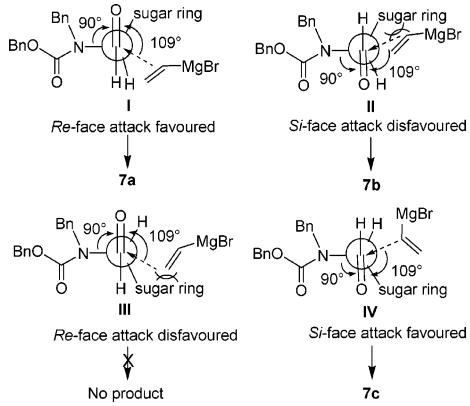


FIGURE 2. The Felkin−Anh models of **6a** and **6b**.

In the ^{1}H NMR spectrum of **7c**, the H-5 appeared as a doublet of doublets at δ 4.12, with a large coupling constant ($J_{5,6}$ = 7.7 Hz), indicating the *cis* relation of H-5 with H-6. This established the 5*R*,6*S* absolute configurations.

The observed stereoselectivity in the addition of the Grignard reagent to **6a** and **6b** could be explained in terms of the Felkin−Anh-like transition states (TSs). As shown in Figure 2, TS **I**/**II** and **III**/**IV** were considered for **6a** and **6b**, respectively, in which the more electronegative C−N group is placed at a right angle to the C=O bond.[28] In the case of **6a**, the *re*-face attack along the Burgi−Dunitz trajectory in TS **I** is favored over the *si*-face attack in TS **II**, as a result of the presence of the sugar ring, leading to the formation of the *anti* isomer **7a** as the major and the syn isomer **7b** as the minor product. In **6b**, the nucleophilic *re*-face attack in TS **III** is restricted due to the presence of the sugar ring and the C-3 benzyloxy substituent, while the *si*-face attack of the Grignard reagent in TS **IV**, which is free from any steric hindrance, provided the *anti* isomer **7c** as the only product.

In the subsequent step, carbamates **7a**−**c** were individually treated with 40% KOH at 90 °C for 48 h, and the corresponding β-hydroxy-γ-alkenylamines **8a**−**c** were isolated in good yields (Scheme 2). This one-pot two-step reaction probably involves the hydrolysis of carbamate to give in situ formation of carbamic acid, which undergoes decaboxylation to give the product. Having sugar-substituted β-hydroxy-γ-alkenylamine **8a**−**c** in hand, we have examined the intramolecular aminomercuration using mercury(II) salts. Thus, the reaction of **8a** and **8c** with mercury(II) acetate in THF−water at room temperature, followed by the reductive demercuration with $NaBH_4$, afforded exclusively 5-*endo*-trig-cyclized product **9a** and **9c** in 74 and 73% yield. Similarly, **8b** afforded a sugar-substituted pyrrolidine ring compound that was found to be relatively unstable over silica gel column, therefore, it was directly subjected to *O*-benzylation to afford dibenzylated pyrrolidine **9b**. Thus, the reaction was found to be compatible in the presence of β-hydroxyl functionality in **9a**−**c**. In fact, the presence of the β-hydroxyl group enhances the rate of aminomercuration by 6-fold as compared to that of the unsubstituted sugar γ-alkenylamine and aromatic γ-alkenylamine.[11]

The pyrrolidine derivatives **9a**−**c** were found to be the true intermediates for the synthesis of the target molecules. Thus, hydrogenolysis of *N*- and *O*-benzyl groups in **9a**, followed by selective amine protection, afforded a *N*-Cbz-protected com-

(24) The reaction of D-glucose-derived nitrone **2** with C-2 metalated thiazole followed by N−O bond cleavage, unmasking the thiazole functionality with MeOTf in acetonitrile then $NaBH_4$ in MeOH, and treatment with $HgCl_2$ in acetonitrile−water is known to give D-glucose-substituted *N*-benzyl-protected α-amino aldehydes; see: (a) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem.*−*Eur. J.* **1995**, *1*, 505−520. (b) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Scherrmann, M.-C.; Tejero, T. *J. Org. Chem*. **1997**, *62*, 5484−5496.

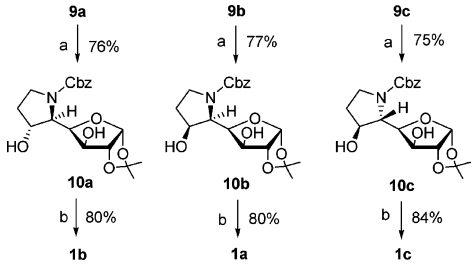
(25) Our results were found to be identical with that reported by J. Jurczak and co-workers in which the addition of vinylmagnesium bromide to −*N*(Bn)Cbz diprotected L-alaninal afforded syn/anti products in the ratio 23:77; see: (a) Gryko, D.; Urbanczyk-Lipkowska, Z.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 4059−4067. For a review on α-amino aldehydes, see: (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164.

(26) The reaction of **6a** with vinylmagnesium bromide (3.0 equiv) in THF at 0 °C marginally altered the selectivity, giving anti/syn products in the ratio of 2:1. An additional increase in the temperature did not improve the selectivity but lowers the combined yield (62%). Changing of the solvent to diethyl ether or toluene did not change the selectivity. Use of vinyllithium (3.0 equiv) in THF or in Et_2O at −50 °C afforded a 1:1 mixture of the anti/syn products in low yield. Performing the reaction at 0 °C also led to the same ratio, with a low combined yield (55%).

(27) The reaction at 0 °C also afforded a single diastereomer.

(28) Houck, K. N.; Paddon-Row, N. M.; Rondon, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, C. D.; Metz, J. T.; Li, Y. L.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117.

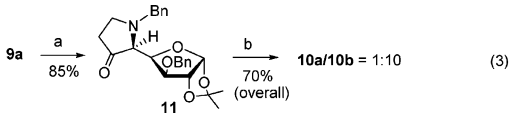
SCHEME 3. Synthesis of 1a−c[a]



[a] Reaction conditions: (a) (i) $HCOONH_4$, 10% Pd/C, MeOH, 80 °C, 1 h; (ii) $NaHCO_3$, CbzCl, MeOH−H_2O (9:1), 3 h; (b) (i) TFA−H_2O (3:2), 2.5 h; (ii) 10% Pd/C, MeOH, 80 psi, 12 h.

pound **10a** (Scheme 3). Finally, deprotection of the 1,2-acetonoide functionality using TFA−water followed by hydrogenation afforded 1-*epi*-castenospermine **1b** $[\alpha]_D = +7.0$ (*c* 0.5, MeOH) [lit[20b] $[\alpha]_D = +6.2$ (*c* 0.15, MeOH)]. The same sequence of reactions with **9b** and **9c** gave (+)-castenospermine **1a** $[\alpha]_D = +78.9$ (*c* 0.30, H_2O) [lit[20b] $[\alpha]_D = +78.6$ (*c* 0.25, H_2O)], and 8a-*epi*-castanospermine **1c** $[\alpha]_D = +30.0$ (*c* 0.4, MeOH) [lit[20c] $[\alpha]_D = +28.0$ (*c* 0.3, MeOH)], respectively. The *N*-Cbz-protected compounds **10b**,**c** and target molecules **1a**−**c** were characterized by spectral and analytical techniques, and the data for target molecules was found to be in agreement with that of what was reported.[20]

In the above sequence, the overall yield of (+)-castanospermine **1a** was affected due to the fact that the Grignard reaction of **6a** afforded the required diastereomer **7b** in a minor amount. Disappointed with these results, we thought of an alternative pathway to epimerize the C-6 hydroxyl group in **9a** (eq 3). Thus, pyrrolidine **9a** was treated under Swern oxidation reaction conditions, which afforded the α-amino ketone **11** in 85% yield. The $NaBH_4$ reduction of **11** in MeOH−water at −60 °C, followed by hydrogenolysis and selective amine protection, gave the required pyrrolidine **10b** as the major product (**10a**/**10b** = 1:10), which was converted to (+)-castanospermine **1a**. The formation of **10b** in major amount could be explained based on the preferred *re*-face hydride attack at the carbonyl carbon, as the *si*-face is sterically hindered due to the presence of the C-5-*N*-Bn group.



In conclusion, the 1,3-addition reaction of D-glucose-derived nitrone **2** with vinylmagnesium bromide, followed by N−O bond reductive cleavage, *N*-protection, and dihydroxylation followed by oxidative cleavage afforded α-amino aldehydes **6a**,**b** in high yield. The utility of **6a**,**b** was demonstrated in the synthesis of castanospermine **1a** and its analogues **1b** and **1c** using the intramolecular aminomercuration strategy.

Experimental Section

General Procedure for Aminomercuration. To a stirred solution of **8** (0.78 g, 1.83 mmol) in THF−water (1:1, 12 mL) was added $Hg(OAc)_2$ (1.16 g, 3.6 mmol), and the reaction mixture was stirred at room temperature for 3 h. Sodium borohydride (0.266 g, 7.2 mmol) was added over a period of 10 min. THF was removed under reduced pressure, and the residue was extracted with chloroform (15 mL × 3).

3-*O*-Benzyl-1,2-*O*-isopropylidene-5,7,8-trideoxy-5,8-(*N*-benzylamino)-6(*R*)-hydroxy-α-D-*glycero*-D-*gluco*-oct-1,4-furanose (9a). Purification using column chromatography (*n*-hexane/ethyl acetate = 8/2) afforded **9a** (0.58 g, 74%) as a thick liquid: R_f 0.52 (*n*-hexane/ethyl acetate = 3/2); $[\alpha]_D = -17.0$ (*c* 0.7, $CHCl_3$); IR (neat) 3550−3150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.45 (s, 3H), 1.62−1.78 (m, 1H), 1.86−2.06 (m, 1H), 2.10 (br s, exchanges with D_2O, 1H), 2.52 (q, $J = 9.6$ Hz, 1H), 2.80−3.00 (m, 2H), 3.45 (d, $J = 13.2$ Hz, 1H), 3.96 (d, $J = 13.2$ Hz, 1H), 4.01 (d, $J = 3.3$ Hz, 1H), 4.10 (dd, $J = 5.8$, 3.6 Hz, 1H), 4.39 (d, $J = 11.2$ Hz, 1H), 4.44 (dt, $J = 5.8$, 2.4 Hz, 1H), 4.64 (d, $J = 3.9$ Hz, 1H), 4.66 (d, $J = 11.2$ Hz, 1H), 5.90 (d, $J = 3.9$ Hz, 1H), 7.15−7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 26.9, 32.2, 52.3, 60.1, 71.1, 71.6, 74.0, 81.3, 81.5, 82.7, 104.7, 111.6, 126.8, 127.7 (s), 128.2 (s), 128.5, 128.6 (s), 136.5. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34. Found: C, 70.64; H, 7.46.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5,7,8-trideoxy-5,8-(*N*-benzylamino)-6(*S*)-*O*-benzyl-α-L-*glycero*-D-*gluco*-oct-1,4-furanose (9b). Sodium hydride (0.11 g, 2.7 mmol, 60% suspension) in THF (5.0 mL) was cooled to 0 °C, and the crude aminomercuration product (0.78 g, 0.84 mmol), prepared from **8b** in THF (5.0 mL), was added and stirred for 30 min. Benzyl bromide (0.37 g, 2.2 mmol) in THF (2.0 mL) and TBAI (0.1 g) was added and stirred for 6 h. Water (5.0 mL) was added, and the mixture was extracted with diethyl ether (20 mL × 3). The usual work up was performed, and purification by column chromatography (*n*-hexane/ethyl acetate = 9/1) afforded **9b** (0.48 g, 66%, overall) as a thick liquid: R_f 0.62 (*n*-hexane/ethyl acetate = 3/1); $[\alpha]_D = +4.0$ (*c* 0.5, $CHCl_3$); IR (neat) 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.51 (s, 3H), 1.64−1.86 (m, 2H), 2.30−2.50 (m, 1H), 3.00−3.18 (m, 1H), 3.22−3.50 (m, 2H), 3.98−4.25 (m, 3H), 4.38 (d, $J =$ 12.0 Hz, 1H), 4.50−4.72 (m, 5H), 5.95 (d, $J = 3.9$ Hz, 1H), 7.10−7.45 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 26.8, 30.0, 52.0, 60.4, 66.0, 71.1, 72.2, 79.7, 81.3, 82.9, 104.5, 111.5, 126.5, 127.1, 127.6, 127.7, 127.8 (s), 127.9 (s), 128.0 (s), 128.3 (s), 137.2, 138.9, 140.6. Anal. Calcd for $C_{32}H_{37}NO_5$: C, 74.54; H, 7.23. Found: C, 74.65; H, 7.31.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5,7,8-trideoxy-5,8-(*N*-benzylamino)-6(*R*)-hydroxy-β-L-*glycero*-L-*ido*-oct-1,4-furanose (9c). Purification by column chromatography (*n*-hexane/ethyl acetate = 8/2) afforded **9c** (0.56 g, 73%) as a thick liquid: R_f 0.52 (*n*-hexane/ethyl acetate = 6/4); $[\alpha]_D = -80.0$ (*c* 0.7, $CHCl_3$); IR (neat) 3600−3200, 1623 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.53 (s, 3H), 1.64 (dd, $J = 13.2$, 6.3 Hz, 1H), 1.86−2.03 (m, 1H), 2.11 (br s, exchanges with D_2O, 1H), 2.47 (ddd, $J = 11.0$, 9.1, 6.3 Hz, 1H), 2.78−2.94 (m, 2H), 3.40 (d, $J = 12.9$ Hz, 1H), 4.12 (d, $J = 3.3$ Hz, 1H), 4.13−4.20 (m, 1H), 4.27 (dd, $J = 8.0$, 3.3 Hz, 1H), 4.37 (d, $J = 12.4$ Hz, 1H), 4.51 (d, $J = 11.3$ Hz, 1H), 4.69 (d, $J = 3.9$ Hz, 1H), 4.75 (d, $J = 11.5$ Hz, 1H), 6.02 (d, $J = 3.9$ Hz, 1H), 7.15−7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.8, 32.9, 52.2, 59.6, 71.7, 72.8, 74.4, 80.9, 83.3, 84.1, 105.0, 111.3, 126.6, 127.9 (s), 128.0 (s), 128.2, 128.6 (s), 129.0 (s), 136.4, 139.3. Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34. Found: C, 70.69; H, 7.42.

Acknowledgment. We are grateful to Prof. M. S. Wadia for helpful discussions. We are thankful to CSIR, New Delhi, for the Senior Research Fellowships to N.S.K. and S.D.M. and for the financial assistance (Project No. 01(1906)/03/EMR-II).

Supporting Information Available: General experimental methods, procedure for the 1,3-addition reaction of vinylmagnesium bromide with nitrone **2** using TMSOTf, experimental procedures and spectral and analytical data for compounds **5a**,**b**, **6a**,**b**, **7a**−**c**, **8a**−**c**, **10a**−**c**, **11**, and **1a**−**c**, and copies of ^1H and ^{13}C NMR spectra of compounds **7a**−**c**, **8a**−**c**, **9a**−**c**, **10a**−**c**, **11**, and **1a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0601617