substituents were inevitable in these circumstances. In spite of this, the analyses described here are believed to have been quite successful in differentiating the various stereoelectronic effects exerted on the acidity by multiple substituents. No published example of Hammett-Taft-type correlation analysis has dealt with such complicated multiple substituent effects as does the present study. The use of different σ constants to reflect the effects of substituents at different locations was clearly justified. The quality of the results also validates the procedure used for the analysis of the ortho effect.[6]

Registry No. 1, 70757-08-3; 2, 70757-13-0; 3, 70757-16-3; 4, 133229-78-4; 5, 59431-90-2; 6, 70757-07-2; 7, 133229-79-5; 8, 133229-80-8; 9, 133229-81-9; 10, 133229-82-0; 11, 133229-83-1; 12, 70757-03-8; 13, 70756-87-5; 14, 133229-84-2; 15, 133229-85-3; 16, 133229-86-4; 17, 133229-87-5; 18, 133229-88-6; 19, 70756-90-0; 20, 133229-89-7; 21, 70757-02-7; 22, 133229-90-0; 23, 133229-91-1; 24, 133229-92-2; 25, 133270-12-9; 26, 79614-58-7; 27, 133229-93-3; 28, 79614-71-4; 29, 79614-70-3; 30, 79614-73-6; 31, 79614-85-0; 32, 79614-72-5; 33, 79614-64-5; 34, 79614-63-4; 35, 133229-94-4; 36, 79614-60-1; 37, 79622-59-6; 38, 79614-87-2; 39, 133229-95-5; 40, 133229-96-6; 41, 133229-97-7; 42, 133229-98-8; 43, 133229-99-9; 44, 133230-00-9; 45, 79614-88-3; 46, 79614-83-8; 47, 133230-01-0; 48, 83663-58-5; 49, 133230-02-1; 51, 133230-03-2; 52, 133230-04-3; 53, 133230-05-4; 54, 79614-96-3; 55, 79614-92-9; 56, 79614-93-0; 57, 133230-06-5; 58, 133230-07-6; 59, 133230-08-7.

Supplementary Material Available: Melting points and other analytical data for compounds 1-59 and absorption maxima and molar absorptivities for compounds 1-59 and their respective anions (5 pages). Ordering information is given on any current masthead page.

2-Amino-2-deoxyhexoses as Chiral Educts for Hydroxylated Indolizidines. Synthesis of (+)-Castanospermine and (+)-6-Epicastanospermine

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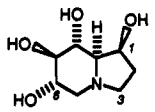
Received November 29, 1990

D-2-Amino-2-deoxyglucosaminic acid, obtained from D-glucosamine, and a D-2-amino-2-deoxymannosaminic acid derivative, obtained from D-glucono-δ-lactone, were derivatized and converted to the corresponding configurationally stable aldehydes. The *N*-(9-phenylfluoren-9-yl)-protected mannosamine derivative was readily transformed into a variety of configurationally stable α-amino ketones, thus providing convenient and versatile chiral educts. These educts may be envisaged as derivable from polyhydroxy α-amino acids. Examples of the utility of these chiral educts are provided by the efficient conversion of a D-mannosaminic acid derivative into the polyhydroxy indolizidine alkaloids (+)-castanospermine and (+)-6-epicastanospermine.

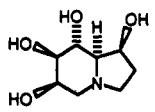
Introduction

Attaching a 9-phenylfluoren-9-yl group to the nitrogen of an α-amino acid has led to useful intermediates for the preparation of α-amino ketones and α-amino aldehydes of unusually high configurational stability.[1] We now report an extension of this methodology to 2-amino-2-deoxyhexoses as polyhydroxylated analogues of the simple amino acids, aldehydes, and ketones. We have also explored some selective transformations of these 2-aminohexoses. Our general strategy is demonstrated by the synthesis of the epimeric tetrahydroxyindolizidine alkaloids from a *N*-(9-phenylfluoren-9-yl)mannosamine derivative.

Castanospermine (1) and 6-epicastanospermine (2) are found in *Castanospermum australe*[2] and *Alexa leiopetala*,[3] respectively. Due to their biological activity, 1 and 2 have generated considerable interest. Castanospermine (1) is a potent inhibitor of several glycosidases[4] and shows anticancer,[5] antiviral,[6] and antiretroviral[7] activity. 6-Epicastanospermine (2) shows significant difference in its glycosidase inhibition activity,[8] due to the epimeric stereochemistry at C-6. In addition, recent studies have shown that selective derivatization of the hydroxyl groups of 1 can result in increased biological activity.[9]



1



2

Our objective was to develop an efficient route to an intermediate, derivable from a 2-amino-2-deoxyhexose, which could lead to the preparation of both castanospermine (1) and 6-epicastanospermine (2). To do so we planned to exploit the synthetic methodology developed for simple amino aldehydes.[1,10] The target intermediate

(1) (a) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239. (b) Lubell, W. D.; Rapoport, H. *J. Org. Chem.* **1987**, *109*, 236. (c) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511.

(2) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.

(3) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, *27*, 1403.

(4) (a) Pan, T. T.; Hori, H.; Saul, R.; Sanford, B. A.; Molyneux, R. J.; Elbein, A. D. *Biochemistry* **1983**, *22*, 3975. (b) Saul, R.; Chambers, J. P.; Molyneux, R. J. Elbein, A. D. *Arch. Biochem. Biophys.* **1983**, *221*, 593. (c) Campbell, B. C.; Molyneux, R. J.; Jones, K. C. *J. Chem. Ecol.* **1987**, *13*, 1759. (d) Szumilo, T.; Kaushal, G. P.; Elbein, A. D. *Arch. Biochem. Biophys.* **1986**, *247*, 261.

(5) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46* 5215.

(6) (a) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *PNAS* **1987**, *84*, 8120. (b) Sunkara, P. S.; Bowling, T. L.; Liu, P. S.; Sjoerdsma A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206.

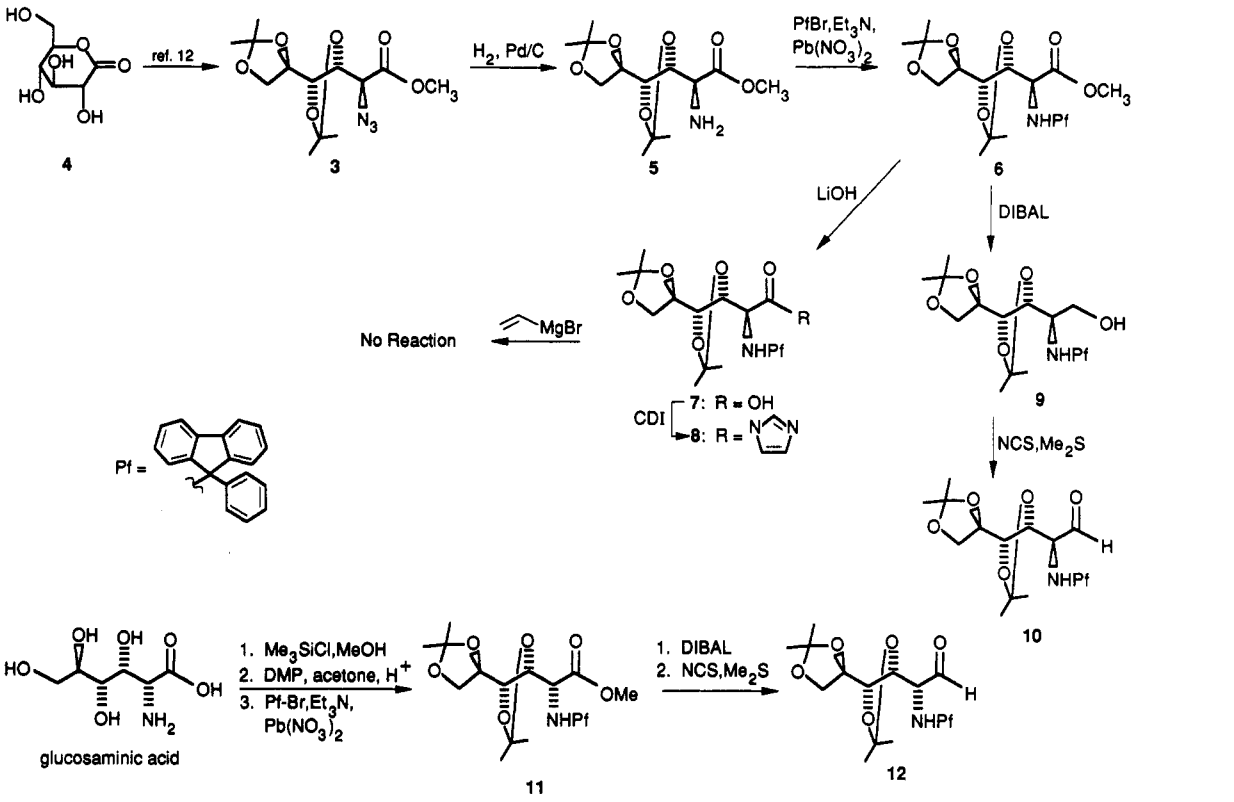
(7) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74.

(8) (a) Molyneux, R. J.; Roitman, J. N.; Dunnheim, G.; Szumilo, T.; Elbein, A. D. *Arch. Biochem. Biophys.* **1986**, *251*, 450. (b) Nash, R. J.; Fellows, L. E.; Girdnar, A.; Fleet, G. W. J.; Peach, J. M.; Watkin, D. J.; Hegarty, M. P. *Phytochemistry* **1990**, *29*, 1356.

(9) (a) Liu, P. S.; Hoekstrar, W. J.; King, C.-H. R. *Tetrahedron Lett.* **1990**, *31*, 2829. (b) Margolin, A. L., Delinck, D. L.; Whalon, M. R. *J. Am. Chem. Soc.* **1990**, *112*, 2849.

0022-3263/91/1956-3700$02.50/0

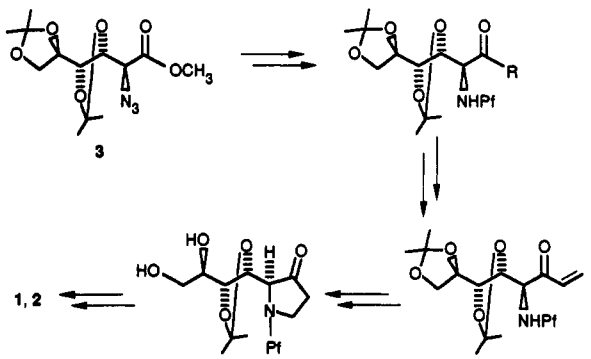
Scheme I. Synthesis of Protected D-2-Deoxy-2-aminomannose (10) and D-2-Deoxy-2-aminoglucose



should also represent a molecule in which selective transformations on the hydroxyl groups could also be effected. The reported syntheses[11] of 1 and 2 have the disadvantages of either including nonstereoselective steps or involving configurationally unstable α-amino aldehydes. Also the reported methods do not proceed from a central building block that is suitable for the synthesis of a number of isomeric polyhydroxylated cyclic nitrogen compounds.

Results and Discussion

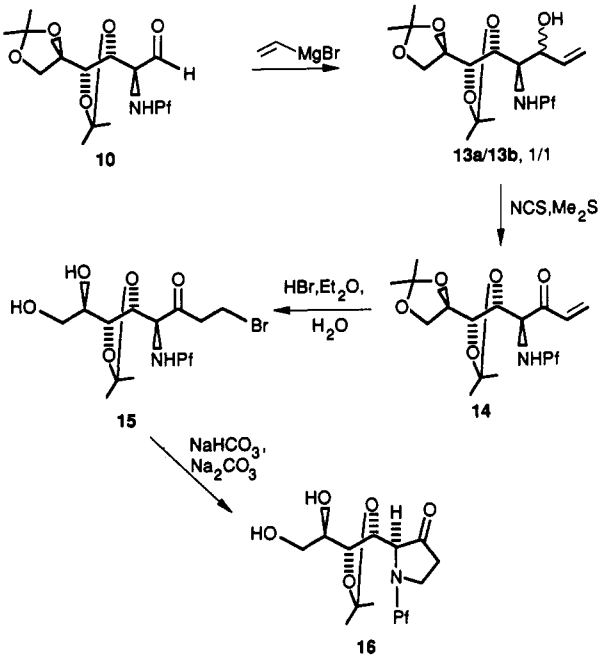
As our chiral educt we choose the manno azide 3[12] which has four stereocenters in the same absolute stereochemistry as required for C-6, C-7, C-8, and C-8a in 6-epicastanospermine (2). Starting with 3 we planned to synthesize an α-amino carbonyl compound which would allow the introduction of a C_2 unit via an organometallic reagent. This intermediate would then be cyclized to a five-membered ring ketone, whose configurational stability would be assured by the presence of the *N*-(9-phenylfluoren-9-yl) protecting group. By forming the new chiral center of C-1 from the pyrrolidinone we expected high stereoselectivity in the reduction of the cyclic ketone. We also anticipated selectivity in the removal of the terminal isopropylidene protecting group to give the α-amino ketone as the key intermediate of the synthesis. To demonstrate the usefulness of this concept we have synthesized castanospermine (1) and 6-epicastanospermine (2).



The manno azide 3 was synthesized in three easy steps from readily available glucono-δ-lactone (4) as described[12] and was then hydrogenated in the presence of palladium on charcoal (Scheme I). The resulting amine 5 was treated under standard conditions for introducing the 9-phenylfluoren-9-yl group,[1] and the resulting ester 6, a stable and crystalline compound, was obtained in 82% yield from 3. Hydrolysis of 6 with lithium hydroxide gave the free acid 7. Attempts to introduce the C_2 unit by direct treatment[10] of the acid 7 with vinylmagnesium bromide in THF failed as did attempts to affect this transformation by using the imidazolide 8. We then turned to the more reactive α-amino aldehyde 10. Excellent yields (90%) of the pure aldehyde 10 were obtained by reducing the ester 6 to the alcohol 9 and oxidizing[1c,13] to the aldehyde 10 (Scheme I). α-Amino aldehyde is configurationally stable and can be stored at room temperature without epimerisation at C-2.[14]

(10) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866.
(11) (a) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165. (b) Setoi, H.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 4617. (c) Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5492. (d) Fleet, G. W. J.; Ramsden, N. G.; Molyneux, R. J.; Jacob, G. S. *Tetrahedron Lett.* **1988**, *29*, 3603. (e) Reymond, J. L.; Vogel, P. *Tetrahedron Lett.* **1989**, *30*, 705. (f) Anzeveno, P. B.; Angell, P. T.; Creemer, L. J.; Whalon, M. R. *Tetrahedron Lett.* **1990**, *31*, 4321. (g) Fleet, G. W. J.; Ramsden, N. G.; Nash, R. J.; Fellows, L. E. *Carbohydr. Res.* **1990**, *205*, 269. (h) Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100. (i) An enzymatic synthesis of (+)-castanospermine has also been reported: Bhide, R.; Mortezali, R.; Scilimati, A.; Sih, C. J. *Tetrahedron Lett.* **1990**, *31*, 4827.
(12) (a) Regeling, H.; de Rouville, E.; Chittenden, G. J. F. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 461. (b) Csuk, R.; Hugener, M.; Vasella, A. *Helv. Chim. Acta* **1988**, *71*, 609.
(13) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

Scheme II. Synthesis of 3-Pyrrolidinone 16



Introduction of the C_2 unit with vinylmagnesium bromide in THF gave a 1/1 mixture of the diastereomeric allyl alcohols **13a** and **13b**, which was oxidized[1c,13] to the α,β-unsaturated ketone **14**.

Our synthetic plan required cyclization to the five-membered ring before reduction of the keto group in order to induce stereoselectivity in the introduction of the new chiral center at C-2 as shown in Scheme II. The best conditions to effect this transformation were to add HBr to the double bond by the action of HBr in diethyl ether at 0 °C. The bromide **15** was not isolated but treated with $NaHCO_3/Na_2CO_3$ in water to effect the cyclization. Partial deprotection of the 5,6-*O*-isopropylidene group occurred during the HBr addition due to traces of moisture in the reaction mixture. Since we sought specific removal of this primary–secondary isopropylidene group, 200 mol % of water was added to the reaction mixture. Under these conditions 70–80% yields of pure **16** resulted directly from **14**. From 2D NMR data it is clear that indeed the terminal isopropylidene group had been cleaved. Thus **16** represents the desired configurationally stable chiral building block in which the possibility clearly exists for carrying out selective transformations at at least three of the five oxygen functions.

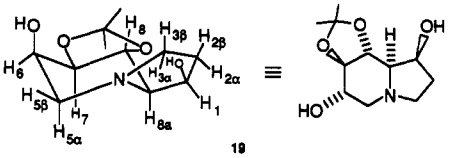
(+)-6-Epicastanospermine. To demonstrate the versatility of **16**, we targeted the synthesis of both **1** and **2**. Since four of the five stereocenters of 6-epicastanospermine (**2**) are already included in **16**, **2** is the more immediate synthetic target, and its synthesis is presented in Scheme III.

Simple reduction of **16** with $NaBH_4$ in ethanol gave a single isomer of **17** in almost quantitative yield. At that point we could not establish the configuration at the newly formed center. Proceeding with cyclization of the fused six-membered ring, we sought to tosylate the primary hydroxy group of **17**. The usual reaction conditions[15] for this transformation gave low conversions. However with (dimethylamino)pyridine (DMAP) instead of pyridine as a base tosylate **18** was obtained in 55% yield, together with 15–20% of a ditosylate. By turning to tosylation with *N*-methyltosylimidazolium triflate in the presence of *N*-methylimidazole,[16,17] yields of 66% of primary tosylate **18**, 8% of a ditosylate, and 15% of reisolated triol **17** were obtained.

Cyclization to the fused six-membered ring was effected by removal of the phenylfluorenyl group by hydrogenolysis in the presence of palladium on charcoal in methanol.[18] Nucleophilic ring closure then proceeded via displacement of the tosyloxy group, and the toluenesulphonic acid formed was neutralized by the sodium acetate[19] that had been added to the reaction. Pure **19** was obtained as an oil after chromatography. In order to determine the still unknown stereochemistry at C-1, a NOESY experiment was carried out and the data are summarized in Table I. On the basis of these data the stereochemistry of **19** can be assigned as shown. These results establish that attack of the reducing agent ($NaBH_4$) in the transformation of **16** to **17** is guided only by the steric hindrance of the polyhydroxy substituent at C-8.

To remove the remaining isopropylidene group, **19** was treated with trifluoracetic acid in dioxane/water. The free base form of 6-epicastanospermine (**2**) was obtained by ion exchange chromatography (Dowex 50W-X8) as an oil and was pure by NMR. By treatment of **2** with concd HCl, followed by removal of the solvent and two recrystallizations from methanol/diethyl ether, an analytically pure sample of 6-epicastanospermine hydrochloride (**20**) was obtained. No other epimers were present in this material, based on the 500-MHz NMR spectrum and doping experiments with castanospermine. Using both the free base and crystalline hydrochloride, we have established the

Table I. NOESY Data for Structure 19



19

proton	NOE observed[a]
H_1	H_8 (vw), H_{8a} (vs), $H_{2\alpha}$ (s), $H_{2\beta}$ (w)
$H_{2\alpha}$, $H_{3\alpha}$ (overlap)	$H_{2\beta}$ (vs), $H_{3\beta}$ (vs), $H_{5\alpha}$ (w), H_{8a} (vw)
$H_{2\beta}$	$H_{2\alpha}$ (vs), $H_{3\beta}$ (m)
$H_{3\beta}$	$H_{3\alpha}$ (vs), $H_{2\beta}$ (m)
$H_{5\alpha}$	$H_{3\alpha}$ (w), $H_{5\beta}$ (vs), H_6 (s), H_7 (s), H_{8a} (s)
$H_{5\beta}$	$H_{5\alpha}$ (vs), H_6 (s)
H_6	$H_{5\beta}$ (s), H_7 (s), H_8 (vw), $H_{5\alpha}$ (s)
H_7	$H_{5\alpha}$ (s), H_{8a} (s), H_8 (w), H_6 (s)
H_8	H_7 (w), H_1 (vw), H_6 (w), H_{8a} (w)
H_{8a}	$H_{5\alpha}$ (s), H_7 (s), H_8 (w), H_1 (vs), $H_{2\alpha}$ (w)

[a] Key: vw = very weak; w = weak; m = medium; s = strong; vs = very strong.

(14) This was shown by comparison of the high-field ^1H NMR data of **10** and its C-2 epimer **12**. The diastereomeric purity of **10** and **12** was better than 98%. Epimer **12** was prepared from glucosaminic acid; **11** is made by protection of hydroxyl functions after first preparing the methyl ester with trimethylsilyl chloride in methanol. This process leaves the nitrogen in a protonated form, so that it is not converted to the isopropylidene derivative in the subsequent treatment with DMP/acetone. Reaction with 9-phenylfluoren-9-yl bromide then gave **11**. Epimer **10** was prepared using the same procedure as for the preparation of **12** from **6**. The diasteremomeric purity of **10** and **12** was better than 99% as established by doping experiments with ^1H NMR.

(15) Cramer, F. D. In *Methods in Carbohydrate Chemistry*; Academic Press: New York, 1963; Vol. II.

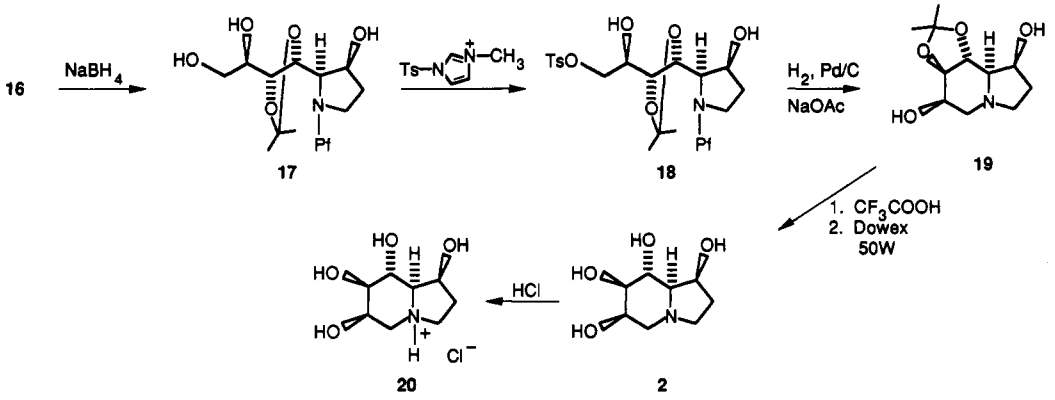
(16) Tosylimidazole[17] was treated at 0 °C with methyl triflate in THF; this cloudy mixture was then added to a solution of **17** and *N*-methylimidazole in THF at 0 °C. The reaction was carried out at 0 °C to rt over a period of 6–10 h.

(17) Staab, H. A.; Wendel, K. *Chem. Ber.* **1960**, *93*, 2902.

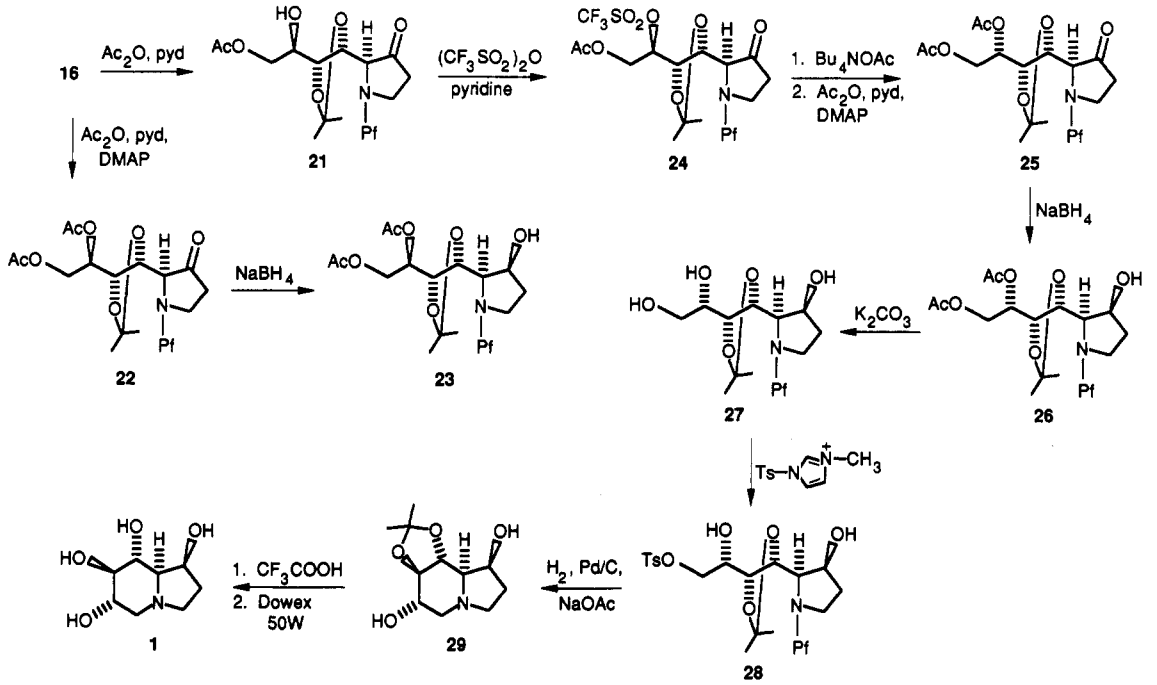
(18) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859.

(19) Bruce, I.; Fleet, G. W. J.; di Bello, I. C.; Winchester, B. *Tetrahedron Lett.* **1989**, *30*, 7257.

Scheme III. Synthesis of (+)-6-Epicastanospermine



Scheme IV. Synthesis of (+)-Castanospermine



optical rotation of (+)-6-epicastanospermine which has been variously reported.[8,11c,d]

(+)-Castanospermine (1). To prepare castanospermine from our versatile intermediate **16**, all that was required was inversion of the C-6 hydroxyl group (castanospermine numbering). This was accomplished as shown in Scheme IV by first treating **16** with excess acetic anhydride in pyridine to selectively acylate the primary hydroxyl and form the monoacetate **21** in yields of over 80%. If a catalytical amount of DMAP was added to the reaction mixture the diacetate **22** was obtained in 82% yield. Reduction of **22** to the corresponding hydroxy compound **23** was straightforward, and **23** represents a suitable starting material for selective transformations at C-1.

From monoacetate **21**, the triflate **24** was formed by reaction with triflic anhydride. It was not isolated; instead the reaction mixture was filtered through silica gel directly into a solution of excess tetra-*n*-butylammonium acetate[20,21] in acetonitrile. Crude inverted acetate **25** was isolated and was submitted to acetylation conditions (Ac_2O, pyridine, DMAP). This step was necessary, because trace amounts of water in the tetra-*n*-butylammonium acetate led to partial deacetylation during the inversion reaction. After purification **25** was obtained in 85% yield; a small amount of unreacted **21**, which was also acetylated, could easily be removed by chromatography. The reduction of the keto group once again gave only a single isomer of **26**. Treatment of **26** with potassium carbonate in methanol led to deacetylation to triol **27**, which we assume has the same stereochemistry at C-1 as **17**. Analogously to the epi series, **27** was converted to the tosylate **28**. Hydrogenolysis of **28** in the presence of palladium on charcoal and sodium acetate removed the phenylfluorenyl group and led to direct cyclization to indolizidine **29** in a yield of 89%. Castanospermine (**1**) was then generated by removal of the isopropylidene group with TFA, followed by ion exchange chromatography. ^1H NMR and ^{13}C NMR data and the optical rotation for recrystallized ($MeOH/Et_2O$) **1** are consistent with those reported.[2,11]

To further demonstrate the versatility of this synthetic strategy, we have prepared the corresponding protected 2-amino-2-deoxy-D-glucosamine derivative **12**. This proceeds readily and in high yield from D-glucosaminic acid. Subjection of protected aldehyde **12** to the same reaction scheme should result in polyhydroxyindolizidines with

(20) Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; J. Wiley: New York, 1972; Vol. 3, p 277; 1981; Vol. 9, p 442.
(21) (a) Mayer, H.; Rüttiman A. *Helv. Chim. Acta* **1980**, *63*, 1451. (b) Corey, E. J.; Terashima, S. *Tetrahedron Lett.* **1972**, 111.

inverted configuration at C-8a.

Conclusion

We have presented an efficient synthesis of the configurationally stable α-amino ketone **16** from the known azide **3** in a yield of 45% by applying the chemistry developed for α-amino acid and α-amino aldehydes to a configurationally stable 2-amino-2-deoxyhexose. Further manipulation has demonstrated that stereochemistry at C-1 and C-6 can be controlled by choice as can the configuration at C-8a by starting with 2-mannosamine or 2-glucosamine. From the D-mannosamine-derived pyrrolidinone **16**, efficient synthesis of both (+)-castanospermine (**1**) and (+)-6-epicastanospermine (**2**) have been developed.

Experimental Section

General Methods. Tetrahydrofuran (THF) was distilled immediately prior to use from potassium/benzophenone; acetonitrile, triethylamine (Et_3N), and 2,2-dimethoxypropane (DMP) were distilled from CaH_2; diethyl ether was distilled from NaH; methylene chloride (CH_2Cl_2) was purified by filtration through aluminum oxide, activity I. *N*-Chlorosuccinimide was recrystallized from acetic acid. Methyl triflate (MeOTf) was prepared by adding dimethyl sulfate to triflic acid and by subsequent distillation of the reaction mixture. All nonaqueous reactions were carried out under an inert (argon or nitrogen) atmosphere with magnetic stirring. Organic solutions were dried over $MgSO_4$ unless otherwise noted and evaporated with a Berkeley rotary evaporator. Chromatography on silica gel was carried out on Merck silica gel 60 (230–400 mesh). Analytical TLC was obtained on Merck silica gel coated aluminum sheets. Melting points are uncorrected. Proton and carbon magnetic resonance spectra were measured downfield relative to tetramethylsilane in $CDCl_3$ unless otherwise noted (values in ppm). All ^1H NMR spectra were recorded on a Nicolet 250 MHz spectrometer unless otherwise noted, where Bruker 400- and 500-MHz instruments were used. For spectra taken in D_2O, the HDO signal was set to 4.65 ppm as internal reference. IR spectra were obtained using KBr pellets unless otherwise noted. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley, CA.

Methyl 2-Azido-2-deoxy-3,4:5,6-di-*O*-isopropyl-D-mannonate (3) was prepared as described,[12] using triflic anhydride, prepared by distilling triflic acid twice from P_2O_5, and tetrabutylammonium azide (Bu_4NN_3), prepared from tetrabutylammonium hydrogen sulfate and sodium azide.[22]

Methyl 2-[(9-Phenylfluoren-9-yl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannonate (6). A solution of **3** (8.8 g, 28 mmol) in EtOAc (250 mL) was hydrogenated at atmosphere pressure with Pd/C (10%, 900 mg) for 24 h. The mixture was filtered, the filtrate was evaporated, and the oily residue was dissolved in CH_2Cl_2 (120 mL). 9-Phenylfluoren-9-yl bromide[13a] (11.2 g, 35.2 mmol), lead nitrate (11.2 g, 33.6 mmol), and triethylamine (2.88 g, 28 mmol) were added. The mixture was stirred for 48 h at rt, and then it was filtered and chromatographed on silica gel (hexane/EtOAc, 4/1). After recrystallization from hexane/EtOAc, 12.5 g, 82% yield, of pure **6** was obtained: mp 113 °C; $[\alpha]^{20}_D$ −142° (*c* 1.18, $CHCl_3$); ^1H NMR (500 MHz) δ 1.08, 1.29, 1.34, and 1.36 (4 s, 12 H), 2.81 (d, 1 H), 3.20 (bs, 1 H), 3.23 (s, 3 H), 3.9–4.02 (m, 3 H), 4.1 (2 dd, 2 H), 7.2–7.7 (m, 11 H), 7.7 (m, 2 H); ^{13}C NMR δ 25.2, 26.3, 27.1, 27.4, 51.5, 58.7, 66.7, 72.7, 76.7, 76.8, 77.0, 79.4, 81.8, 109.6, 110.3, 119.9, 120.0, 125.1, 126.1, 127.2, 127.4, 128.0, 128.2, 128.3, 128.5, 140.3, 141.0, 144.1, 148.3, 148.5, 174.0; IR 3305 s, 1730 s. Anal. Calcd for $C_{32}H_{35}O_6N$: C, 72.6; H, 6.6: N, 2.6. Found: C, 72.6; H, 6.7; N, 2.6.

Methyl 2-[(9-Phenylfluoren-9-yl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-gluconate (11). To a suspension of D-glucosaminic acid[23] (1.5 g, 7.6 mmol) in absolute methanol (35 mL) was slowly added trimethylsilyl chloride (1.5 g, 14 mmol).[24] The solution was stirred for 20 h, the methanol was evaporated, DMP/acetone (50 mL, 3/1) and toluenesulfonic acid (100 mg) were added, stirring was continued for 23 h at rt, the solvents were evaporated, and the residue was dissolved in CH_2Cl_2 (25 mL). 9-Phenylfluoren-9-yl bromide (4.8 g, 16.4 mmol), lead nitrate (5 g, 16.5 mmol), and triethylamine (350 mg, 16.8 mmol) were added. After the reaction mixture was stirred for 72 h at rt it was filtered, the filtrate was evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 4/1) to give 3.0 g (75%) of pure crystalline **11**: mp 123 °C; $[\alpha]^{20}_D$ +215° (*c* 0.32, $CHCl_3$); ^1H NMR (500 MHz) δ 1.28, 1.33, 1.42 and 1.58 (4 s, 12 H), 2.86 (dd, 1 H), 3.4 (s, 3 H), 3.43 (d, 1 H), 3.7 (m, 1 H), 3.81 (dd, 1 H), 4.05 (m, 2 H), 4.12 (m, 1 H), 7.4–7.8 (m, 13 H); ^{13}C NMR δ 25.2, 26.1, 27.2, 27.3, 51.6, 56.3, 66.5, 72.6, 76.2, 77.2, 80.3, 109.4, 110.0, 119.8, 119.9, 125.5, 126.1, 126.9, 127.2, 127.3, 128.0, 128.2, 128.3, 128.5, 140.2, 140.9, 144.4, 147.9, 148.7. IR 3310 m, 1740 s cm^{-1}. Anal. Calcd for $C_{32}H_{35}O_6N$: C, 72.6; H, 6.6; N, 2.6. Found: C, 72.6; H, 6.7; N, 2.6.

2-[(9-Phenylfluoren-9-yl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannitol (9). To a solution of ester **6** (4.6 g, 8.6 mmol) in toluene was added DIBAL (1 M in toluene, 28 mL, 28 mmol) at −78 °C. The solution was stirred for 30 min, 100 mL of 10% citric acid was added, and the solution was allowed to reach rt. The layers were separated, the aqueous layer was extracted twice with EtOAc, the combined organic layers were washed with water, dried, and evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 3/1) to give pure **9** as a foam (4.1 g, 94%): mp 51–53 °C; $[\alpha]^{20}_D$ +159° (*c* 1.18, $CHCl_3$); ^1H NMR δ 1.0, 1.2, and 2 at 1.25 (4 s, 12 H), 2.35 (m, 1 H), 2.75 (dd, 1 H), 3.35 (dd, 1 H); 360 (m, 1 H), 3.7–3.85 (m, 3 H), 4.05 (m, 1 H), 7.2–7.5 (m, 11 H), 7.8 (m, 2 H); IR 3450 s, 3305 s cm^{-1}. Anal. Calcd for $C_{31}H_{35}O_5N$: C, 74.25; H, 7.0; N, 2.8. Found: C, 74.0; H, 6.9; N, 2.8.

2-[(9-Phenylfluoren-9-yl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-glucitol was obtained from ester **11** in the same manner: oil; ^1H NMR δ 1.26, 1.30, 1.33 and 1.40 (4 s, 12 H), 2.40 (m, 1 H), 2.80 (bs, 1 H), 2.90 (dd, 1 H), 3.25 (bs, 1 H), 3.32 (dd, 1 H), 3.77 (dd, 1 H), 3.82 (m, 1 H), 3.92 (dd, 1 H), 4.02–4.10 (2 dd, 2 H), 7.2–7.7 (m, 13 H); IR (neat) 3500 s, 3310 s cm^{-1}.

2-[(9-Phenylfluoren-9-yl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannose (10). Dimethyl sulfide (2.4 mL) was added to as suspension of *N*-chlorosuccinimide (3.0 g, 22.4 mmol) in 100 mL of toluene at 0 °C. After stirring for 20 min at 0 °C a white precipitate was formed; the suspension was cooled to −25 °C, and 4 g (8 mmol) of **9** in 15 mL of toluene was added. After stirring for 5.5 h at −25 °C, 4 mL of triethylamine was added and the reaction mixture was stirred for 20 min, the suspension was allowed to reach rt. Water was added, the layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with water and brine, dried, and evaporated. After chromatography of the residue on silica gel (hexane/EtOAc, 3/1) **10** was obtained in 92% yield: mp 93–95 °C; $[\alpha]^{20}_D$ +16.9° (*c* 0.49, $CHCl_3$); ^1H NMR (500 MHz) δ 1.08, 1.18, 1.25, and 1.27 (4 s, 12 H), 2.82 (m, 1 H), 3.45 (bs, 1 H), 3.72 (dd, 1 H), 3.75–3.83 (m, 2 H), 3.93 (dd, 1 H), 4.02 (m, 1 H), 7.2–7.8 (m, 13 H), 9.27 (d, 1 H); IR 3305 s, 1720 s cm^{-1}. Anal. Calcd for $C_{31}H_{33}O_N$: C, 74.5; H, 6.7; N, 2.8. Found: C, 74.4; H, 6.9; N, 2.75.

2-[(9-Phenylfluoren-9-yl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-glucose (12) was obtained from the corresponding glucitol in the same way: oil; ^1H NMR (500 MHz) δ 1.19, 1.25, 1.29, and 1.40 (4 s, 12 H), 2.77 (bs, 1 H), 3.35 (m, 1 H), 3.62 (ss, 1 H), 3.93 (dd, 1 H), 3.95–4.05 (m, 3 H), 7.2–7.7 (m, 13 H), 9.25 (d, 1 H); IR (neat) 3305 s, 1720 s cm^{-1}.

2-[(9-Phenylfluoren-9-yl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidenemannosaminic Acid (7). To a solution of ester **6** (500 mg, 0.95 mmol) in 30 mL of dioxane/water, 1/1, was added lithium hydroxide (LiOH–H_2O, 550 mg). The mixture was stirred for 20 h at 60 °C, and then it was allowed to cool to rt. The pH was adjusted to 2 by the addition 2 N HCl. The solution was extracted twice with EtOAc, the combined organic layers were washed with water and brine and dried, and the solvent was evaporated to yield **7** as a foam (480 mg, 98%), which was used

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(23) Hardegger, E.; Lohse, F. *Helv. Chim. Acta* **1957**, *40*, 2383.

(24) Brook, M. A.; Chan, T. H. *Synthesis* **1983**, 201.

in the next reaction without further purification: ^{1}H NMR δ 1.12, 1.20, 1.23, and 1.30 (4 s, 12 H), 2.90 (d, 1 H), 3.65–3.75 (m, 3 H), 3.82 (dd, 1 H), 3.97 (dd, 1 H), 4.07 (dd, 1 H), 7.2–7.8 (m, 13 H). Anal. Calcd for $C_{31}H_{33}O_6N$: C, 72.2; H, 6.5; N, 2.7. Found: C, 72.4; H, 6.5; N, 2.6.

2-[(9-Phenylfluoren-9-yl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidene-1-vinyl-D-mannitol (13). A solution of vinylmagnesium bromide (prepared from 200 mg of magnesium and 600 mg of vinyl bromide in 8 mL of THF) was added to a solution of **10** (1.5 g, 3.0 mmol) in 35 mL THF at −40 °C. The reaction mixture was allowed to reach rt over a period of 1 h, 100 mL of 1 M NaH_2PO_4 was added, and the mixture was extracted three times with EtOAc. The combined EtOAc layers were washed with water and brine, dried, and evaporated, and the residue was chromatographed on silica gel (hexane/EtOAc, 3/1) to give **13** as a 1/1 mixture of diastereomers in 91% yield: mp 46–50 °C; ^{1}H NMR δ 0.95, 1.15, 1.17, 1.20, 1.26, and 1.30 (6 s, 12 H), 3.6 (m, 1 H), 3.3 (m, 1 H), 3.5 (m, 1 H), 3.6–4.0 (m, 5 H), 4.18 (m, 1 H), 5.05 (m, 1 H), 5.2 (dd, 1 H), 5.3 (dd, 1 H), 5.8 (m, 1 H), 7.2–7.5 (m, 11 H), 7.75 (m, 2 H); IR 3500 s, 3310 s cm^{-1}. Anal. Calcd for $C_{33}H_{37}O_5N$: C, 75.1; H, 7.1; N, 2.5. Found, C, 74.8, H, 7.0; N, 2.5.

2-[(9-Phenylfluoren-9-yl)amino]-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannose (14). Compound **14** was prepared from the mixture **13** using exactly the same oxidation procedure as described for the preparation of **10** and **12**. After chromatography on silica gel (hexane/EtOac, 3/1) **14** was obtained in a 92% yield: mp 114–115 °C; $[\alpha]^{20}_D$ −115° (*c* 0.18, $CHCl_3$); ^{1}H NMR δ 1.05, 1.22, 1.40, and 1.43 (4 s, 12 H), 3.05 (dd, 1 H), 3.47 (d, 1 H), 3.78 (dd, 1 H), 3.93 (dd, 1 H), 4.02 (dd, 1 H), 4.14 (dd, 1 H), 4.40 (dd, 1 H), 5.30 (dd, 1 H), 5.50 (dd, 1 H), 5.87 (dd, 1 H), 7.0–7.7 (m, 13 H); IR 3305 s, 1670 m, 1610 m cm^{-1}. Anal. Calcd for $C_{33}H_{35}O_5N$: C, 75.4: H, 6.7; N, 2.7. Found: C, 75.2; H, 6.7; N, 2.6.

2-(1′,2′-*O*-Isopropylidene-1′,2′,3′,4′-tetrahydroxybutyl)-3-oxo-*N*-(9-phenylfluoren-9-yl)pyrrolidine (16). A solution of vinyl ketone **14** (800 mg, 1.52 mmol) in 50 mL of absolute diethyl ether was cooled to 0 °C, and a solution of HBr in diethyl ether (saturated at 0 °C, 10 mL) and 54 μL (200 mol %) of water were added. After being stirred for 30 min, the reaction mixture was poured into a solution of $NaHCO_3$ and Na_2CO_3 (1.5 g and 2.0 g in 200 mL water) and stirred at rt for 2.5 h. The mixture was extracted with EtOAc (3×), the combined organic layers were washed with water and brine and dried, and the solvent was evaporated. After chromatography of the residue on silica gel (hexane/EtOAc, 2/3), **16** was obtained in 70–90% yield: mp >150 °C dec; $[\alpha]^{20}_D$ +213° (*c* 1.26, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.05 and 1.10 (2 s, 6 H), 2.3 (m, 2 H), 3.07 (m, 1 H), 3.19 (dd, 1 H), 3.20 (d, 1 H), 3.35 (m, 1 H), 3.41 (dd, 1 H), 3.62 (dd, 1 H), 3.70 (m, 1 H), 3.90 (dd, 1 H), 7.2–7.8 (m, 13 H); ^{13}C NMR δ 26.5, 26.7, 38.0, 44.7, 63.8, 64.7, 72.4, 76.5, 81.4, 109.3, 120.2, 120.3, 126.8, 127.1, 127.6, 127.7, 128.3, 128.5, 128.87, 140.2, 140.4, 142.6, 147.2, 148.3, 216.0; IR 3450 s, 1745 s cm^{-1}. Anal. Calcd for $C_{30}H_{31}O_5N$: C, 74.2: H, 6.4; N, 2.9. Found: C, 73.9; H, 6.4; N, 3.0.

2-(1′,2′-*O*-Isopropylidene-1′,2′,3′,4′-tetrahydroxybutyl)-3-hydroxy-*N*-(9-phenylfluoren-9-yl)pyrrolidine (17). To a solution of **16** (500 mg, 1.0 mmol) in absolute ethanol (25 mL) was added sodium borohydride (150 mg, 3.9 mmol) at 0 °C. After the mixture was stirred for 90 min at 0 °C, 20 mL of 1 M NaH_2PO_4 was added, and the reaction mixture was extracted with CH_2Cl_2/i-PrOH (4/1, 3×). The combined extracts were washed with half-saturated brine, dried, and evaporated, and the residue was chromatographed on silica gel (5% i-PrOH in CH_2Cl_2) to give **17** in 94% yield: mp 55–60 °C; $[\alpha]^{20}_D$ −245° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.95, 1.25 (2 s, 6 H), 1.8 (m, 1 H), 2.2 (m, 1 H), 2.55 (dd, 1 H), 3.1 (dd, 1 H), 3.2 (m, 1 H), 3.35 (m, 2 H), 3.5–3.75 (m, 3 H), 3.8 (dd, 1 H), 7.1–7.75 (m, 13 H); IR 3400 s cm^{-1}. Anal. Calcd for $C_{30}H_{33}O_5N$: C, 73.9; H, 6.8; N, 2.9. Found: C, 74.2; H, 6.9; N, 2.8.

2-(1′,2′-*O*-Isopropylidene-4′-*O*-tosyl-1′,2′,3′,4′-tetrahydroxybutyl)-3-hydroxy-*N*-(9-phenylfluoren-9-yl)-pyrrolidine (18). Method A. To a precooled solution (0 °C) of **17** (270 mg, 0.54 mmol) and DMAP (66 mg, 0.55 mmol) in dry CH_2Cl_2 (30 mL) was added tosyl chloride (144 mg, 0.75 mmol). The solution was stirred at 0 °C for 1 h, and then it was allowed to warm to rt and stirred for another 14 h. It was then diluted with EtOAc (50 mL) and filtered through silica gel (10 g). The silica gel was washed with CH_2Cl_2/EtOAc, 1/1. After evaporation of the filtrate and washings the residue was chromatographed on silica gel (EtOAc/CH_2Cl_2, 1/2) and **18** was obtained as a foam in 55% yield. A ditosylate was also isolated in 25% yield.

Method B. To a solution of 230 mg (1.05 mmol) tosylimidazolide (230 mg, 1.05 mmol) in THF (10 mL) was added methyl triflate (114 mL, 1.04 mmol), the mixture was stirred for 40 min at 0 °C, and then it was added to a solution of **17** (440 mg, 0.9 mmol) and *N*-methylimidazole (90 μL, 1.1 mmol) in THF (25 mL) at 0 °C. After the mixture was stirred for 6 h at 0 °C to rt, 0.1 M NaH_2PO_4 (50 mL) was added, and the reaction mixture was extracted with EtOAc (3×). The combined EtOAc extracts were washed with water and brine, dried, and evaporated. After chromatography of the residue on silica gel (hexane/EtOAc/CH_2Cl_2, 2/1/2) **18** was obtained in 66% yield: mp 86 °C dec; $[\alpha]^{20}_D$ −161° (*c* 0.45, $CHCl_3$); ^{1}H NMR δ 0.82, 1.10 (2 s, 6 H), 1.78 (ddd, 1 H), 2.15 (m, 1 H), 2.37 (s, 3 H), 2.58 (dd, 1 H), 3.00 (d, 1 H), 3.2 (m, 1 H), 3.46 (m, 1 H), 3.50 (m, 2 H), 3.65 (m, 1 H), 3.75 (dd, 1 H), 4.03 (dd, 1 H), 4.22 (dd, 1 H), 7.15–7.85 (m, 17 H); IR 3450 s, 1600 s, 1365 s, 1180 s cm^{-1}. Anal. Calcd for $C_{37}H_{39}O_7NS$: C, 69.2; H, 6.1; N, 2.2. Found: C, 69.0; H, 6.0; N, 2.1. The yield of the ditosylate was 8%, and 15% of starting material **17** was recovered. ^{1}H NMR of the ditosylate: δ 1.02 and 1.08 (2 s, 6 H), 1.72 (m, 1 H), 2.0 (m, 1 H), 2.45 and 2.47 (2 s, 6 H), 2.49 (m, 1 H), 3.05 (d, 1 H), 3.12 (m, 1 H), 3.3–3.5 (m, 2 H), 3.64 (dd, 1 H), 3.65 (m, 1 H), 3.77 (dd, 1 H), 3.91 (dd, 1 H), 4.15–4.23 (m, 2 H), 7.2–7.85 (m, 21 H).

1,6,7,8-Tetrahydroxy-7,8-*O*-isopropylideneindolizidine (19). A mixture of **18** (280 mg, 0.41 mmol), NaOAc (360 mg, 4.4 mmol), and Pd/C (10%, 60 mg) in MeOH (20 mL) was hydrogenated at atmospheric pressure. After 20 h the catalyst was filtered off, the filtrate was refluxed for 10 min, the MeOH was evaporated, and water (5 mL) was added. By the addition of 1 N NaOH, the pH was adjusted to 12–13, and the aqueous solution was extracted with CH_2Cl_2/i-PrOH (4/1, 5×). The combined organic layers were dried (Na_2SO_4) and evaporated. After chromatographing the residue on silica gel (CH_2Cl_2/i-PrOH, 6/1, 5% Et_3N) **19** was obtained in 92% yield as an oil: $[\alpha]^{20}_D$ −1.50° (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.45 (s, 3 H), 1.50 (s, 3 H), 1.87 (m, 1 H), 2.22 (dd, 1 H), 2.28 (m, 2 H), 2.39 (dd, 1 H), 3.19 (ddd, 1 H), 3.25 (dd, 1 H), 3.42 (dd, 1 H), 4.02 (dd, 1 H), 4.30 (m, 1 H), 4.38 (m, 1 H); ^{13}C NMR δ 26.7, 26.8, 34.8, 51.1, 55.3, 65.5, 70.0, 70.6, 70.7, 81.7, 110.7. Anal. Calcd for $C_{11}H_{19}O_4N$: C, 57.6; H, 8.3; N, 6.1. Found: C, 57.7; H, 8.2; N, 5.8.

6-Epicastanospermine (2). A solution of **19** (60 mg, 0.26 mmol) in trifluoroacetic acid/water/dioxane (1/1/1, 3 mL) was stirred for 24 h at rt. The solution was evaporated and then coevaporated with toluene. The remaining oil was subjected to ion-exchange chromatography (Dowex 50W-X8, eluting with 2 N NH_3 in water), and **2** was obtained as an oil in 84% yield: $[\alpha]^{20}_D$ +2.2° ± 0.5 (*c* 0.7, MeOH) (lit. $[\alpha]_D$ +8 (MeOH;[8] negative, no numerical value;[11c] +2 (MeOH)[11d]; see Table II); ^{1}H NMR (500 MHz) δ (D_2O) 1.55 (m, 1 H), 1.72 (dd, 1 H), 1.97 (dd, 1 H), 2.10 (dd, 1 H), 2.15 (m, 1 H), 2.89 (ddd, 1 H), 2.93 (dd, 1 H), 3.37 (dd, 1 H), 3.69 (dd, 1 H), 3.81 (m, 1 H), 4.24 (m, 1 H); ^{13}C NMR (D_2O) δ 35.1, 54.1, 57.7, 69.8, 71.3, 72.5, 74.0, 77.8.

6-Epicastanospermine Hydrochloride (20). To **2** was added concentrated HCl, and the solution was evaporated and then coevaporation with toluene. The crystalline residue was recrystallized two times from methanol/diethyl ether. No other epimers were present, based on the 500-MHz NMR analysis and doping experiments with castanospermine: mp >250 °C dec; $[\alpha]^{20}_D$ +2.6° ± 0.4 (*c* 0.395, 0.1 N NaOH in methanol, *c* calculated as the concentration of free base). Anal. Calcd for $C_8H_{16}O_4NCl$: C, 42.6; H, 7.1; N, 6.2. Found: C, 42.7; H, 7.2; N, 5.9.

Table II. Rotation of 6-Epicastanospermine (2)

source	$[\alpha]^{20}_D$, deg	source	$[\alpha]^{20}_D$, deg
2a	+2.2 ± 0.5	ref 11d[d]	+2
20b	+2.6 ± 0.4	ref 11c[e]	negative
ref 8[c]	+8		

[a] In methanol. [b] In 0.1 N NaOH in methanol, $[\alpha]^{20}_D$ calcd for concentration of free base. [c] In methanol, isolated natural material. [d] In methanol. [e] No values given, but authors state it is negative.

2-(1′,2′-*O*-Isopropylidene-1′,2′-dihydroxy-3′,4′-diacetoxybutyl)-3-oxo-*N*-(9-phenylfluoren-9-yl)pyrrolidine (22). A solution of **16** (550 mg, 1.13 mmol) in pyridine (10 mL) was cooled to 0 °C, and DMAP (25 mg) and acetic anhydride (2 mL) were added. After the mixture was stirred for 4 h at rt, citric acid (15%) was added to pH 2.5, and the reaction mixture was extracted with EtOAc (2×). The combined organic layers were washed with water and brine, dried, and evaporated. After chromatography of the residue on silica gel (hexane/EtOAc, 2/1) 525 mg (82%) of **22** was obtained: mp 55–58 °C; $[\alpha]^{20}_D$ +227° (*c* 0.45, $CHCl_3$); ^1H NMR δ 1.05 (s, 3 H), 1.15 (s, 3 H), 1.80 (s, 3 H), 2.00 (s, 3 H), 2.18 (t, 2 H), 3.15 (m, 1 H), 3.20 (m, 1 H), 3.60 (m, 3 H), 3.80 (dd, 1 H), 4.20 (dd, 1 H), 4.50 (m, 1 H), 7.1–7.5 (m, 11 H), 7.7 (m, 2 H). Anal. Calcd for $C_{34}H_{35}O_7N$: C, 71.7; H, 6.2; N, 2.4. Found: C, 71.4; H, 5.9; N, 2.4.

2-(1′,2′-*O*-Isopropylidene-1′,2′-dihydroxy-3′,4′-diacetoxybutyl)-3-hydroxy-*N*-(9-phenylfluoren-9-yl)pyrrolidine (23). The procedure to obtain compound **23** was the same as described for the conversion of **16** to **17**. After chromatography on silica gel, **23** was obtained in 92% yield: mp 60–62 °C; $[\alpha]^{20}_D$ −23° (*c* 0.72, $CHCl_3$): ^1H NMR δ 1.21 (s, 3 H), 1.22 (s, 3 H), 1.80 (m, 1 H), 1.95 (s, 3 H), 2.05 (s, 3 H), 2.61 (t, 1 H), 3.27 (m, 1 H), 3.47 (dd, 1 H), 3.55 (m, 1 H), 3.65 (d, 1 H), 3.95 (dd, 1 H), 4.02 (dd, 1 H), 4.11 (dd, 1 H), 4.20 (dd, 1 H), 4.73 (m, 1 H), 7.1–7.8 (m, 13 H). Anal. Calcd for $C_{34}H_{37}O_7N$: C, 7.1.4; H, 6.5; N, 2.4. Found: C, 71.3; H, 6.3; N, 2.4.

2-(1′,2′-*O*-Isopropylidene-1′,2′,3′-trihydroxy-4′-acetoxybutyl)-3-oxo-*N*-(9-phenylfluoren-9-yl)pyrrolidine (21). To a solution of **16** (600 mg, 1.23 mmol) in pyridine (10 mL) was added Ac_2O (240 mg, 2.36 mmol) at 0 °C. After being stirred for 20 h at 0 °C, the mixture was poured into 1 M NaH_2PO_4, 2 N HCl was added to pH 2, and the mixture was extracted with EtOAc (3×). The combined organic layers were washed with water, saturated $NaHCO_3$, and brine, dried, and evaporated. After chromatography of the residue on silica gel (hexane/EtOAc, 1/1), 470 mg (80%) of **21** was obtained: mp 57–60 °C; $[\alpha]^{20}_D$ +203° (*c* 0.75, $CHCl_3$); ^1H NMR δ 1.04 (s, 3 H), 1.07 (s, 3 H), 2.0 (s, 3 H), 2.25 (m, 2 H), 3.27 (m, 2 H), 3.63 (m, 3 H), 3.85 (m, 3 H), 7.2–7.7 (m, 13 H); IR 3480 m, 1740 s cm^{-1}. Anal. Calcd for $C_{32}H_{33}O_6N$: C, 72.8; H, 6.3; N, 2.6. Found: C, 72.42; H, 6.14; N, 2.60.

2-(1′,2′-*O*-Isopropylidene-1′,2′-dihydroxy-3′,4′-diacetoxybutyl)-3-oxo-*N*-(9-phenylfluoren-9-yl)pyrrolidine (25). To **21** (280 mg, 0.54 mmol) and pyridine (160 mL) in CH_2Cl_2 (mL) was added triflic anhydride (140 mL, 0.8 mmol) at −15 °C. After 20 min (TLC) the reaction mixture was filtered through a layer of silica gel (10 g) into a solution of tetrabutylammonium acetate (700 mg, 2.3 mmol) in CH_3CN (30 mL). This solution was stirred for 50 min at 40 °C, water was added, and the product was extracted into EtOAc (3×). The combined organic layers were washed with water and brine and dried, and the solvent was evaporated. The residue was dissolved in pyridine (6 mL), Ac_2O (0.5 mL) and DMAP (30 mg) were added, and the solution was stirred for 3 h at rt. The isolation procedure was the same as in the preparation of **22**. After chromatography on silica gel (hexane/EtOAc, 2/1) 233 mg (87%) of **25** was obtained as a foam: mp 49–50 °C; $[\alpha]^{20}_D$ +208° (*c* 1.25, $CHCl_3$); ^1H NMR δ 1.08 (s, 3 H), 1.13 (s, 3 H), 1.89 (s, 3 H), 1.90 (s, 3 H), 2.24 (m, 2 H), 3.01 (m, 1 H), 3.05 (dd, 1 H), 3.28 (m, 1 H), 3.61 (dd, 1 H), 3.55 (m, 1 H), 3.92 (dd, 1 H), 4.21 (dd, 1 H), 4.67 (m, 1 H), 7.2–7.65 (m, 13 H); IR 1750s cm^{-1}. Anal. Calcd for $C_{34}H_{35}O_7N$: C, 71.7; H, 6.2; N, 2.4. Found: C, 71.3; H, 6.2; N, 2.4.

2-(1′,2′-*O*-Isopropylidene-1′,2′-dihydroxy-3′,4′-diacetoxybutyl)-3-hydroxy-*N*-(9-phenylfluoren-9-yl)pyrrolidine (26). The procedure to prepare **26** from **25** was the same as described for the preparation of **17**. After chromatography on silica gel (hexane/EtOAc, 1/1), **26** was obtained in 93% yield: mp 63–65 °C; $[\alpha]^{20}_D$ −278° (*c* 0.82, $CHCl_3$); ^1H MR δ 1.04 (s, 3 H), 1.22 (s, 3 H), 2.02 (s, 3 H), 2.05 (s, 3 H), 2.60 (t, 2 H), 3.15 (m, 2 H), 3.4 (m, 1 H), 3.65 (m, 2 H), 3.83 (dd, 1 H), 4.00 (dd, 1 H), 4.30 (dd, 1 H), 5.45 (dd, 1 H), 7.1–7.7 (m, 13 H). IR 3500 m, 1745 s cm^{-1}. Anal. Calcd for $C_{34}H_{37}O_7N$: C, 71.4; H, 6.4; N, 2.4. Found: C, 71.1; H, 6.4; N, 2.4.

2-(1′,2′-*O*-Isopropylidene-1′,2′,3′,4′-tetrahydroxybutyl)-3-hydroxy-*N*-(9-phenylfluoren-9-yl)pyrrolidine (27). To a solution of **26** (350 mg, 0.62 mmol) in methanol (10 mL) was added 300 mg of potassium carbonate at 0 °C. After being stirred for 1 h at 0 °C the mixture was diluted with 100 mL of CH_2Cl_2/iPrOH, 4/1. The organic layer was washed with 1 M NaH_2PO_4, water, and brine and dried, and the solution was evaporated. The residue was chromatographed on silica gel (5% i-PrOH in CH_2Cl_2), and **27** was obtained in 93% yield: mp 81–83 °C; $[\alpha]^{20}_D$ −239° (*c* 0.72, $CHCl_3$); ^1H NMR δ 1.17 (s, 3 H), 1.25 (s, 3 H), 1.9 (m, 1 H), 2.1 (m, 1 H), 2.57 (t, 1 H), 3.15 (m, 1 H), 3.3 (m, 2 H), 3.45 (m, 1 H), 3.55 (m, 1 H), 3.78 (dd, 1 H), 3.8 (m, 1 H), 3.97 (dd, 1 H), 7.1–7.5 (m, 11 H), 7.7 (m, 2 H); IR 3450 s cm^{-1}. Anal. Calcd for $C_{30}H_{33}O_5N$: C, 73.9; H, 6.8; N, 2.9. Found: C, 73.9; H, 6.6; N, 2.7.

2-(1′,2′-*O*-Isopropylidene-4′-*O*-tosyl-1′,2′,3′,4′-tetrahydroxybutyl)-3-hydroxy-*N*-(9-phenylfluoren-9-yl)-pyrrolidine (28). Using method B, **28** was prepared from **27** as described for the preparation of **18**: yield, 65%, mp 81–83 °C dec; $[\alpha]^{20}_D$ −237° (*c* −0.3, $CHCl_3$); ^1H NMR δ 1.02 (s, 3 H), 1.32 (s, 3 H), 1.75 (m, 1 H), 2.07 (m, 1 H), 2.38 (s, 3 H), 2.48 (m, 2 H), 3.05 (d, 1 H), 3.11 (m, 1 H), 3.35 (m, 1 H), 3.50 (m, 1 H), 3.62 (dd, 1 H), 3.70 (dd, 1 H), 3.93 (m, 3 H), 7.05–7.80 (m, 17 H); IR 3500 m, 1365 s, 1180 s cm^{-1}. Anal. Calcd for $C_{37}H_{39}O_7NS$: C, 69.2; H, 6.1; N, 2.2. Found: C, 68.9; H, 6.2; N, 2.2.

1,6,7,8-Tetrahydroxy-7,8-*O*-isopropylideneindolizidine (29) was prepared from **28** as described for the preparation **19** from **18**: yield 89%; $[\alpha]^{20}_d$ +41.5° (*c* 0.41, $CHCl_3$); ^1H NMR (500 MHz) δ 1.46 (s, 3 H), 1.48 (s, 3 H), 1.82 (m, 1 H), 2.09 (dd, 1 H), 2.20 (dd, 1 H), 2.28 (m, 2 H), 3.15 (m, 1 H), 3.28 (dd, 1 H), 3.39 (dd, 1 H), 3.58 (dd, 1 H), 4.03 (ddd, 1 H), 4.36 (m, 1 H); ^{13}C NMR δ 26.5, 26.8, 34.1, 50.7, 55.7, 68.3, 69.4, 70.1, 73.2, 84.6, 111.3. Anal. Calcd for $C_{11}H_{19}O_4N$: C, 57.6; H, 8.5; N, 6.1. Found: C, 57.6; H, 8.5; N, 6.0.

Castanospermine (1) was prepared from **29** as described for the preparation of **2** from **19**: yield 95%; mp 210 °C dec on recrystallization from methanol/diethyl ether; $[\alpha]^{20}_D$ +81.9° (*c* 0.72, H_2O) (lit.[2] $[\alpha]^{20}_D$ +79.9° (*c* 0.93, H_2O)); ^1H NMR (500 MHz, D_2O) δ 1.69 (m, 1 H), 2.03 (dd, 1 H), 2.06 (m, 1 H), 2.22 (dd, 1 H), 2.32 (m, 1 H), 3.07 (ddd, 1 H), 3.15 (dd, 1 H), 3.30 (dd, 1 H), 3.58 (dd, 1 H), 3.60 (m, 1 H), 4.38 (m, 1 H); ^{13}C NMR (D_2O) δ 35.0, 53.9, 57.6, 71.2, 71.8, 72.3, 73.7, 81.2.

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