Triple Reductive Amination Approach to Polyhydroxyindolizidine Alkaloids: A Total Synthesis of Castanospermine

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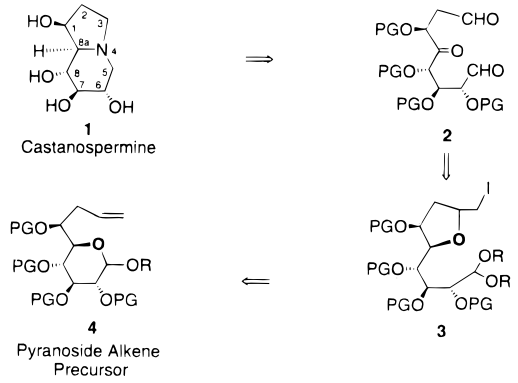
The polyhydroxindolizidine alkaloids, of which castanospermine **1** is one of the more prominent derivatives, are noted for their powerful glycosidase inhibitory activity.[1] Analogs have been used as biochemical tools and have been examined as chemotherapeutic agents in the treatment of several disorders,[2] including cancer[3] and HIV-I.[4] It is commonly believed that their enzyme inhibitory activity is related to their carbohydrate-like structure.[5] The variation of enzyme specificity with stereochemistry appears to be consistent with this hypothesis, and this has led to considerable interest in analog design and synthesis.[5−7]

Several syntheses center on the introduction of one or more new carbinol centers in a sugar template, leading to conversion to the bicyclic indolizidine framework. Noncarbohydrate approaches are becoming increasingly popular with the advancement in methodologies for enantio- and stereoselective synthesis of polyhydroxylated compounds. Many of the published procedures suffer from poor stereoselectivity and inefficient protecting group chemistry, especially with respect to handling of the amino residue. In view of the latter we envisaged a strategy in which a carbohydrate-derived tricarbonyl precursor **2** is converted in a single step to the target indolizidine skeleton via a triple reductive amination reaction (Scheme 1).[5,8,9] Notwithstanding questions of stereoselectivity and the formation of di- and triaminated products, this approach capitalizes on the use of a carbohydrate precursor and on the fact that the amino residue is introduced at a late stage in the synthesis and with concomitant formation of the indolizidine framework. Herein we illustrate the general features of this strategy by the synthesis of castanospermine.

In common with previous sugar based syntheses, the three carbinol centers C6, C7, and C8 in the target may

Scheme 1



be identified in a D-glucose precursor.[10] The remaining carbinol center at C1 would have to be introduced at an 'off-ring' position of a monosaccharide template. A more challenging proposition was the practical preparation of the tricarbonyl functionality. Toward this goal, we anticipated the use of a pyranoside alkene precursor **4**. The alkenyl residue serves as a novel protecting group device since treatment of **4** with halonium ions in the presence of an alcohol gives the iodotetrahydrofuran−acetal product **3**, which is primed for transformation to the desired tricarbonyl precursor, under relatively mild conditions.[11]

The synthesis begins with the known aldehyde **5**, which is available on a large scale and in four straightforward steps from methyl α-D-glucopyranoside.[12] Allylation of **5** under the conditions developed by Whitesides (allyl bromide, Sn, CH_3CN/H_2O, ultrasound) led to a 9:1 ratio of alcohol epimers in 83% yield.[13,14] Chromatographic separation and benzylation of the major product gave **6**, which was smoothly converted within 30 min, on treatment with iodonium dicollidine perchlorate (IDCP)/CH_2Cl_2/MeOH, to a mixture of iodo-THF's. Zinc-mediated reductive elimination of the crude product led to the alkenyl acetal−alcohol **7** in 74% overall yield from the pyranoside alkene **6**. The conversion of **7** to the requisite tricarbonyl intermediate was achieved in 90% yield via a three-step sequence of reactions: alcohol oxidation using the Swern's procedure to the ketone **8**, followed by alkene ozonolysis and acetal hydrolysis. ^{1}H and ^{13}CNMR analysis of the product showed no evidence of the free bis-aldehyde **9**; instead, the mass spectrum and the presence of several acetal resonances suggested a mixture of lactol isomers (e.g., **9′**) and/or hydrate formation (Scheme 2).

Treatment of the presumed bis-aldehyde derivative in anhydrous methanol, with 1.5 equiv of ammonium formate and 30 equiv of sodium cyanoborohydride over 24 h, led to the formation of a major compound **10** in 53% yield together with an intractable mixture of several minor, highly polar components (∼20%). Within the

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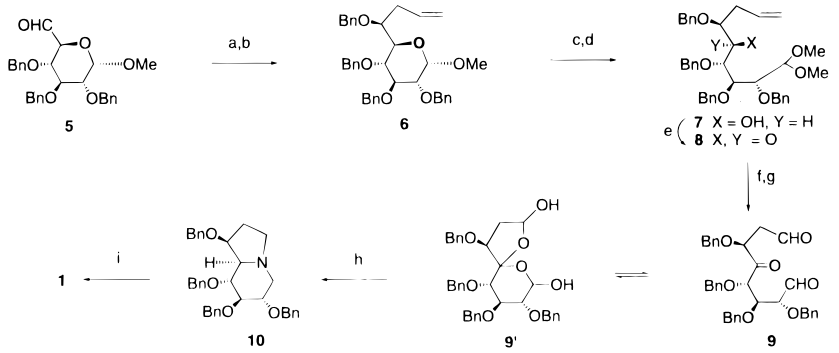
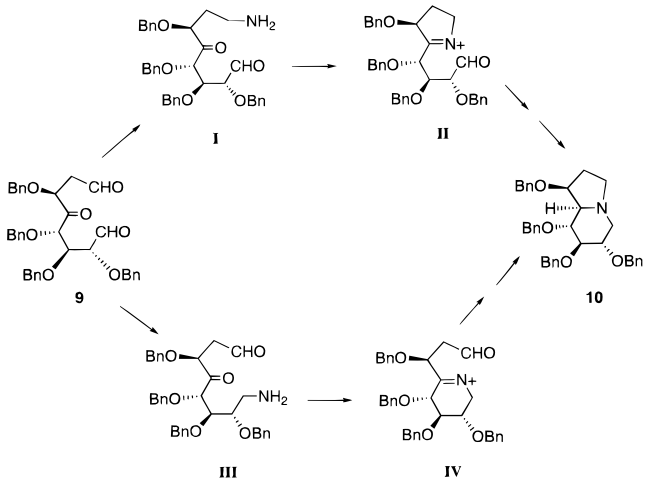
Scheme 2[a]

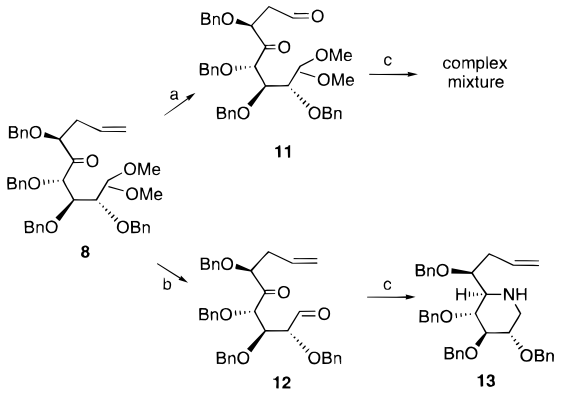


[a] Key: (a) allyl bromide, Sn, CH_3CN-H_2O (10:1), ultrasound; (b) BnBr, NaH, *n*-Bu_4NI, DMF; (c) IDCP, CH_2Cl_2–MeOH; (d) Zn, 95% EtOH, Δ; (e) Swern oxidation; (f) O_3, CH_2Cl_2, −78 °C then Ph_3P; (g) THF–9 M HCl; (h) 1.3 equiv of NH_4HCO_2, 30 equiv of $NaCNBH_3$, MeOH; (i) 10% Pd/C, MeOH–HCOOH.

Scheme 3



Scheme 4[a]



[a] Key: (a) O_3, CH_2Cl_2, −78 °C then Ph_3P; (b) THF–9 M HCl; (c) 1.3 equiv of NH_4HCO_2, 30 equiv of $NaCNBH_3$, MeOH.

limits of NMR detection less than 5% of the C8a epimer was observed. Hydrogenolysis of **10** gave a product that was identical with natural castanospermine[15] (mp, IR, NMR, α_D). The overall yield from **5** was 22% over nine steps.

The preponderance of monoamination vs di- and triaminated products suggests that initial reductive amination on **9** occurs preferentially at one of the aldehyde groups and the resulting primary amine undergoes stereoselective cyclization to the pyrrolidine or piperidine, giving the indolizidine, before appreciable di- and triamination occurs, i.e., **9** → **III** → **IV** → **10** or **9** → **I** → **II** → **10** (Scheme 3). Therefore, comparison of the double reductive amination of **11** and **12** with regard to the facility and stereoselectivity of the reaction might be insightful as to the preferred sequence (Scheme 4).

Substrates **11** and **12** were obtained via ozonolysis or hydrolysis, respectively, on the ketone **8**, used in the previous sequence. Each was individually subjected to the identical amination conditions used on the tricarbonyl substrate **9**. The reaction of **11** was sluggish and gave an intractable mixture of products. On the other hand, **12** behaved in a fashion similar to **9**. A single product **13** of identical C8a configuration to **10** was obtained in 54% yield over 24 h.[16] This stereochemical result and the difference in reactivity of **11** vs **12** appears to be more in agreement with a pathway through the six-membered iminium ion **IV**, i.e., **9** → **III** → **IV** → **10**, rather than one which involves the five membered intermediate **II**, i.e., **9** → **I** → **II** → **10** (Scheme 3).

In addition to its synthetic significance, this result has biosynthetic implications, since it has been proposed that the variation in the configuration at C8a is related to the timing of reduction of a cyclic iminium ion relative to introduction of the C1-alcohol.[17] The application of these results to the synthesis of other polyhydroxyindolizidines and of related alkaloid ring systems is currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and NMR spectra for **1** and **6**–**13** (20 pages).

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