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SYNTHETIC APPROACHES TO STEREOISOMERS AND ANALOGUES OF CASTANOSPERMINE

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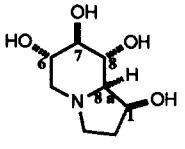
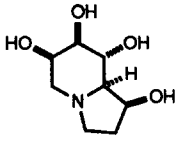
Contents

1. Introduction

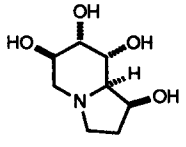
The 1,6,7,8-tetrahydroxyindolizidine, castanospermine (**1**), isolated from the seeds of the Australian legume *Castanospermum australe* [1] and the dried pod of *Alexa leiopetala*,[2] is a potent competitive and reversible inhibitor of several glucosidases.[1,3 - 13] It has the potential for the treatment of diabetes,[14,15] obesity,[16] cancer[5,15,17 - 21] and viral infections,[22,23] including HIV-1.[24 - 33] Other polyhydroxyindolizidines isolated from natural sources, 6-*epi*castanospermine (**2**),[34] 6,7-di*epi*castanospermine (**3**)[35] and swainsonine (**4**),[36,37] are also inhibitors of certain glycosidases; specifically **2**, and to a lesser extent **3**, inhibit amyloglucosidase[34,35,38,39] and **4** is a potent mannosidase inhibitor.[40 - 43] It is likely that other stereoisomers and analogues of these compounds will also inhibit glycosidases resulting in potentially interesting and useful biological properties.



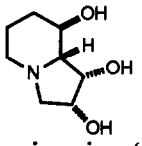
castanospermine (1)



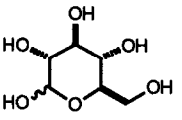
6-*epi*castanospermine (2)



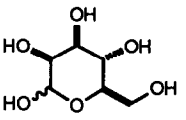
6,7-di*epi*castanospermine (3)



swainsonine (4)

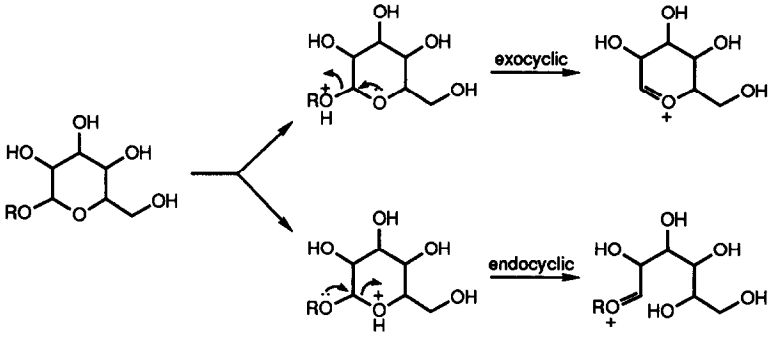


glucopyranose



mannopyranose

The mechanism(s) by which glycosidases process the oligosaccharides of glycoproteins has not been elucidated, although the generally accepted pathway involves acid-catalyzed cleavage of the exocyclic (anomeric) carbon-oxygen bond giving a cyclic oxonium ion.[16,44 - 56] Another possibility is acid-catalyzed cleavage of the endocyclic (ring) carbon-oxygen bond resulting in an acyclic oxonium ion.[56 - 58]



It is difficult to rationalize the exact role of polyhydroxyindolizidines as inhibitors due to this mechanistic uncertainty, but two postulates have been forwarded:[57] (i) when protonated within the active site of the enzyme, they mimic cyclic oxonium ion intermediates; and, (ii) the protonated forms mimic transition states leading to acyclic oxonium ions.

One might anticipate the best inhibitors of certain glycosidases would be those polyhydroxyindolizidines with the closest stereochemical correlation with the pyranose form of the sugar processed.[11,52] However, 6-*epi*castanospermine (**2**) resembles mannopyranose yet it is a poor inhibitor of several mannosidases,[34] and swainsonine (**4**) does not seem to resemble any hexose in the pyranose form, yet it is a potent mannosidase inhibitor.[41] A recent molecular modeling study proposes good glycosidase inhibitors can be either analogues of the putative glycopyranosyl cation intermediate, or mimics of the carbohydrate in its ground state.[59] For mannosidase inhibitors, it has also been suggested correlation with mannofuranose is important,[39] but other calculations indicate that structures similar to the mannopyranosyl cation, not mannose itself, exhibit the more potent activity.[60] It is clear that knowledge of the particular glycosidase mechanism is necessary to predict the inhibitory properties of these molecules. Without this information, the only reliable way to formulate structure/activity relationships for these compounds is to synthesize analogues and stereoisomers and determine their biological activities.

A number of syntheses of stereoisomers of 1,6,7,8-tetrahydroxyindolizidines and other analogues have been developed and they are reviewed here. Most of these target castanospermine (**1**) itself, reflecting the importance placed on this molecule; in fact, several of the other compounds are produced as by-products of these routes. Discussion of the various analogues is limited to deoxy, *O*-acyl and heteroatom-substituted derivatives of the basic

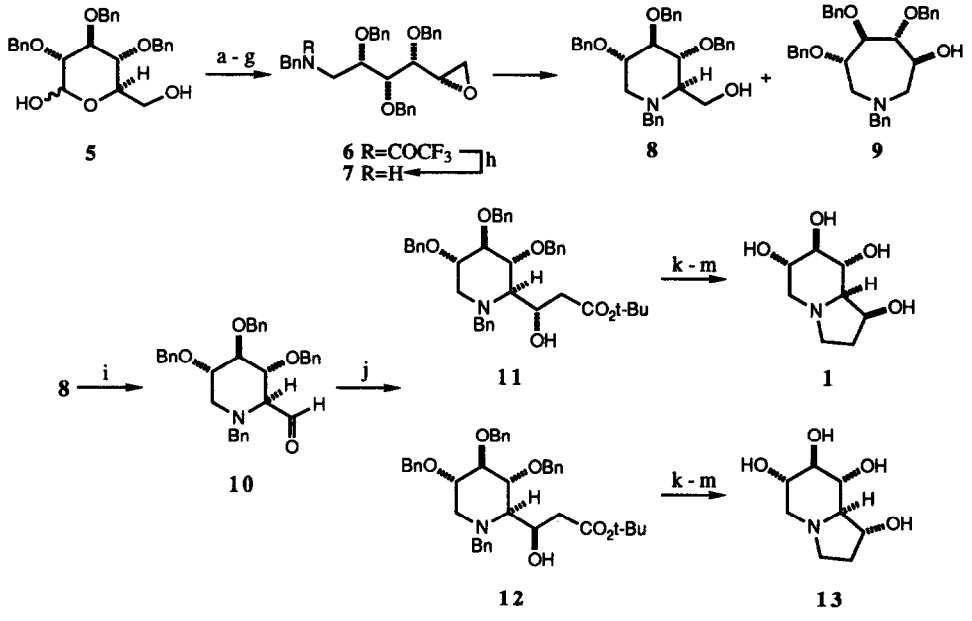
1,6,7,8-tetrahydroxyindolizidine skeleton; compounds such as the 1,2,8-trihydroxyindolizidine swainsonine (**4**) are not discussed.

2. Syntheses of 1,6,7,8-Tetrahydroxyindolizidines

Due to their "sugar-like" structure it is not surprising that most syntheses of 1,6,7,8-tetrahydroxyindolizidines utilize carbohydrate starting materials. Hexoses and their derivatives are often used, with four of the five chiral centers required in the product already present. There is also a strategy based on the utilization of pentoses. Ideally the remaining chiral center(s) should be introduced with good stereocontrol to obtain individual stereoisomers for biological testing; the apparent advantage of generating more than one compound from one synthesis is often offset by difficult diastereomeric separations.

2.1. Non-stereoselective Syntheses from Carbohydrate Starting Materials

The first total synthesis of castanospermine (**1**) established it's absolute stereochemistry {(1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine, (Scheme 1)}.[61]

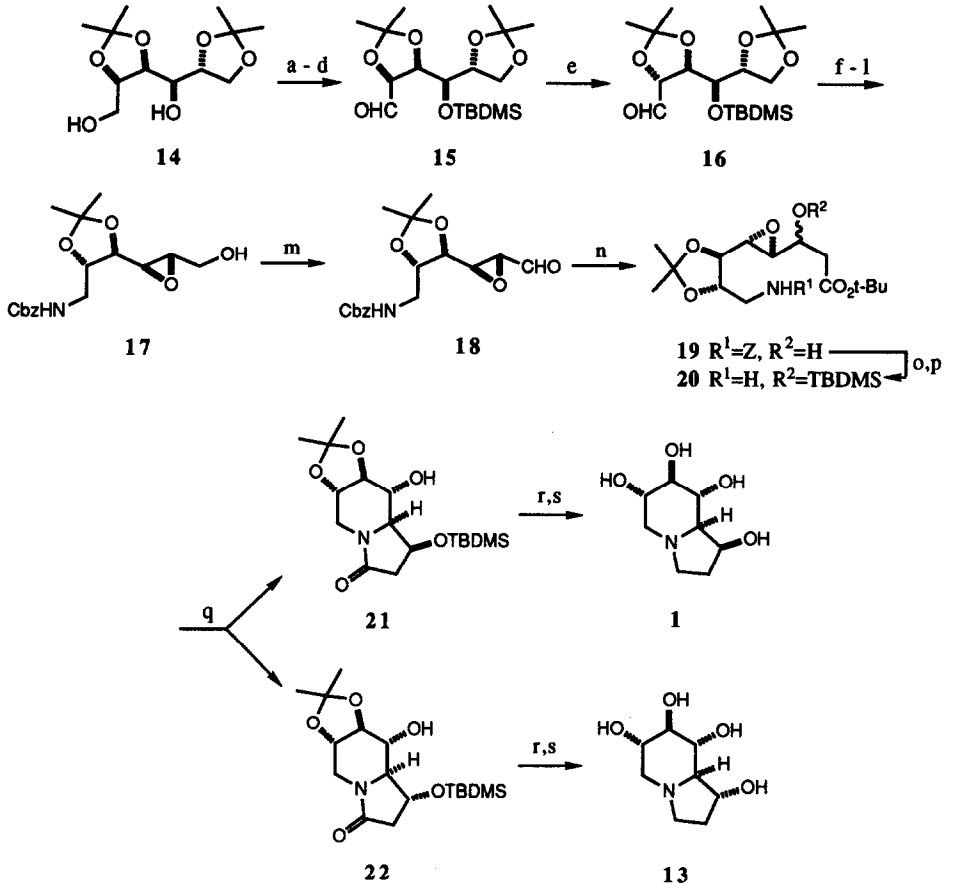


Scheme 1. (a) $BnNH_2$ (10 eq.), $CHCl_3$; (b) $LiAlH_4$, THF, reflux, 5 h; (c) trifluoroacetylation; (d) *t*-$BuMe_2SiCl$, imidazole; (e) mesylation; (f) *n*-Bu_4NF, THF; (g) MeONa, MeOH; (h) $NaBH_4$, EtOH, 40 °C; (i) DMSO, $(COCl)_2$, then NEt_3; (j) *t*-butyl lithioacetate; (k) hydrogenolysis; (l) TFA, H_2O, 60 °C, 3 h; (m) DIBAL.

2,3,4-Tri-*O*-benzyl-D-glucopyranose (**5**) was transformed into the amide epoxide **6** over seven steps. Cleavage of the amido group of **6** with $NaBH_4$ gave aminoepoxide **7** which spontaneously cyclized to give 45 % of the desired piperidine **8** and the azepane **9**. After separation of these structural isomers by chromatography, Swern oxidation of **8** furnished the unstable aldehyde **10** which was immediately reacted with *t*-butyl lithioacetate. This aldol reaction

resulted in a 1:1 mixture of diastereomers (**11** and **12**) which were separated by chromatography. The less polar epimer **11** was subsequently transformed in three steps to castanospermine (**1**), while an analogous series of reactions converted **12** into 1-*epi*castanospermine (**13**).

Another synthesis of castanospermine (**1**) and 1-*epi*castanospermine (**13**), though relatively long and low yielding, was accomplished using an analogous strategy (Scheme 2).[62]

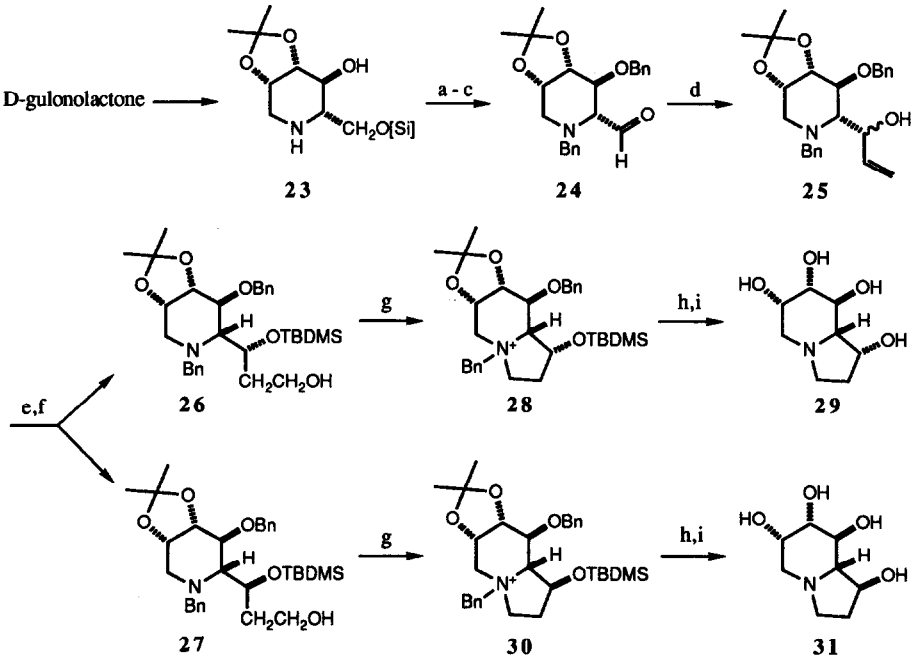


Scheme 2. (a) BzCl, pyridine, 25 °C; (b) TBDMSCl, imidazole, DMF, 80 °C; (c) 1 M NaOH, MeOH, 25 °C; (d) DMSO, DCC, TFA, pyridine, benzene, 25 °C; (e) K_2CO_3 (3 eq.), MeOH, 25 °C; (f) H_2NOH·HCl, $NaHCO_3$, EtOH, H_2O, 60 °C; (g) $LiAlH_4$, THF, 25 °C; (h) CbzCl, THF, H_2O, 0 °C; (i) TsOH (0.1 eq.), MeOH:H_2O (9:1), 15 °C; (j) *n*-Bu_4NF, THF, 0 °C; (k) MsCl, pyridine, 5 °C; (l) MeONa, (1,4 eq.), MeOH, 20 °C; (m) CrO_3·2pyridine, CH_2Cl_2, 5 °C; (n) *t*-butyl lithioacetate; (o) TBDMSCl, imidazole, DMF, 80 °C; (p) H_2, 10 % Pd-C, EtOH; (q) methoxyethanol, reflux; (r) BH_3-THF, THF, reflux; (s) 6 M HCl, THF, reflux.

Surprisingly, the starting material **14** was derived from D-mannose.[63] This necessitated epimerization of the original α-chiral center of the sugar, to produce the stereochemistry required; transformation of **14** in four steps to the aldehyde **15**, was followed by treatment with K_2CO_3 in MeOH to effect this epimerization. The resulting aldehyde **16** was then converted in seven steps to the alcohol/epoxide **17** which was subsequently oxidized to the

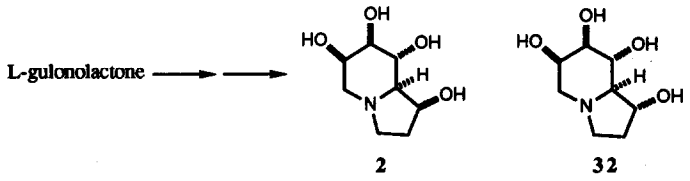
aldehyde **18**. Without isolation, **18** was reacted with *t*-butyl lithioacetate to give **19** as an approx. 1:1 mixture of epimers; hence, as in the first synthesis, the final chiral center was created via a non-stereoselective aldol reaction. Conversion of **19** via hydroxyl protection and subsequent hydrogenolysis to the amine **20**, was followed by a double-cyclization reaction on reflux in methoxyethanol. The resulting epimeric indolizidones **21** and **22** were separated by silica gel chromatography. Reduction of **21** with borane-THF complex followed by treatment with 6 M HCl afforded castanospermine (**1**). Similarly, the other epimer **22** was converted into 1-*epi*castanospermine (**13**).

Non-stereoselective nucleophilic attacks on hexose-derived aldehydes were also used to establish the remaining chiral centers in syntheses of four other stereoisomers of castanospermine;[38,39] in this case, a Grignard reaction rather than an aldol reaction was used (Schemes 3 and 4). Thus, lactam **23**, derived from D-gulonolactone,[64] was converted into **24** in three steps (Scheme 3). Treatment of aldehyde **24** with vinylmagnesium bromide gave alcohol **25**, as a near 1:1 mixture of epimers. Protection of the hydroxyl in **25** followed by hydroboration/oxidation of the double bond gave the epimers **26** and **27**, which were separated by flash chromatography. Mesylation of the alcohol **26** resulted in spontaneous cyclization to the quaternary ammonium salt **28**. Subsequent complete deprotection of **28** afforded L-6-*epi*castanospermine (**29**). Similarly, the other diastereomer **27** was converted via **30** into L-1,6-di*epi*castanospermine (**31**).



Scheme 3. (a) BnBr, NaH, THF, *n*-Bu_4NI; (b) $LiAlH_4$, $AlCl_3$; (c) DMSO, $(COCl)_2$, CH_2Cl_2, -40 °C, then Et_3N; (d) vinyl magnesium bromide, THF, 25 °C; (e) TBDMSCl, imidazole, DMF; (f) BH_3-THF, THF, then alkaline H_2O_2; (g) MsCl, Et_3N, CH_2Cl_2; (h) H_2, Pd black, MeOH; (i) TFA, H_2O.

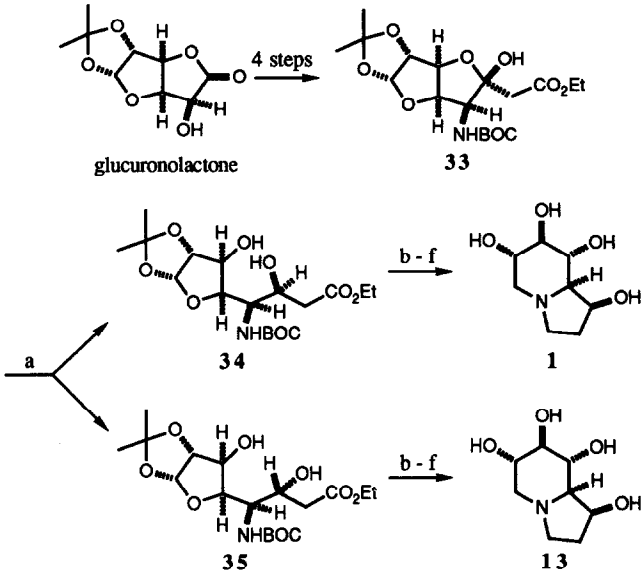
The same route starting with L-gulonolactone gave the enantiomeric products 6-*epi*castanospermine (**2**) and 1,6-di*epi*castanospermine (**32**) (Scheme 4).



Scheme 4.

The biological activities of these four castanospermine stereoisomers were also investigated. 6-*Epi*castanospermine (**2**) strongly inhibits fungal amyloglucosidase, while L-6-*epi*castanospermine (**29**), L-1,6-di*epi*castanospermine (**31**) and 1,6-di*epi*castanospermine (**32**) do not show any significant activity against this enzyme. Stereoisomer **2** also moderately inhibits α-D-glucosidase from human liver but is not very active against other liver glycosidases, while **32** does not significantly inhibit any of the glycosidases tested. Compounds **2** and **32** do not inhibit α-L-fucosidase and their enantiomers (**29** and **31**) are not active against HIV.[27]

An attempt was recently made to synthesize castanospermine (**1**) using a shorter and more selective route (Scheme 5).[65] However, while there are only ten steps in this synthesis, it is again not very selective, hence, it does not show a significant improvement on methodology already described.

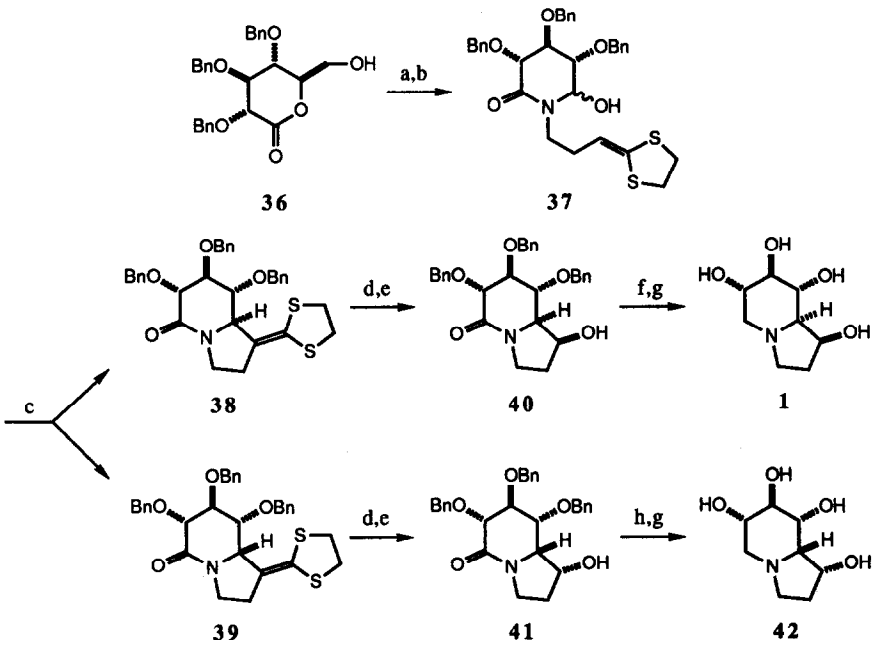


Scheme 5. (a) H_2 (45-50 psi), PtO_2, EtOAc, 20 h; (b) HCO_2H (98 %), CH_2Cl_2, 0-5 °C, 2 h, then 25 °C, 6 h; (c) Dowex 1X2 (OH-) resin, H_2O; (d) $LiAlH_4$ (5.0 eq.), THF, reflux, 20 h; (e) CF_3CO_2H (90 %), 25 °C, 20 h; (f) H_2 (50 psi), 5 % Pt on C, H_2O, 20 h.

The starting material, glucuronolactone, was converted in four steps to the hemiketal **33** (a single anomer at C-6).[66] It was hoped to establish the final chiral center by a stereoselective reduction of the "disguised" ketone carbonyl group of **33**. However, catalytic hydrogenation of **33** over PtO_2 gave a 7:2 epimeric mixture of **34**:**35**, from which the desired diastereomer (**34**) had to be separated by chromatography; other reducing reagents were even less

selective for the production of **34**. The amine **34** was then transformed into castanospermine (**1**) in five steps. Epimer **35** was similarly converted into 1-*epi*castanospermine (**13**) by an analogous series of reactions.

A novel approach to castanospermine (**1**), is based on an intramolecular cyclization to an enantiomerically pure cyclic acyliminium ion intermediate (Scheme 6).[67] The mesylate of the alcohol **37**, the precursor of this reactive intermediate, was derived in three steps from 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone (**36**). This sequence involves destruction of one of the four existing chiral centers. Mesylation of **37** was followed by spontaneous formation of the acyliminium ion intermediate, then cyclization to give the epimers **38** and **39**. The cyclization was repeated under a variety of conditions, but they all were similarly non-selective resulting in approximately equal amounts of the two epimers **38** and **39**, necessitating chromatographic separation. Subsequent oxidation of **38** with singlet oxygen produced an unstable ketone, which was then reduced selectively by L-Selectride to the indolizidone **40**, although in only 39 % yield from **38**. Reduction of **40** followed by hydrogenolysis gave castanospermine (**1**). The other epimer **39** was also transformed into the ketone and then selectively reduced with L-Selectride to give indolizidone **41**. Subsequent reduction followed by hydrogenolysis of **41** gave 1,8a-di*epi*castanospermine (**42**).

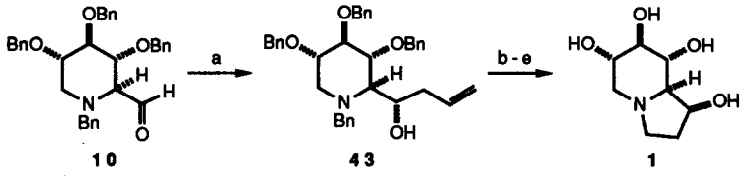


Scheme 6. a) 2-(3-aminopropylidene)-1,3-dithiane, MeOH; (b) $Pb(OAc)_4$, CH_3CN, then AcOH; (c) Et_3N, MsCl, CH_2Cl_2; (d) $^1O_2$, CCl_4, MeOH; (e) L-Selectride, THF; (f) BH_3-DMS, THF; (g) H_2, 10 % Pd on C, MeOH, HCl; (h) $LiAlH_4$, THF.

2.2. Stereoselective Syntheses from Carbohydrate Starting Materials

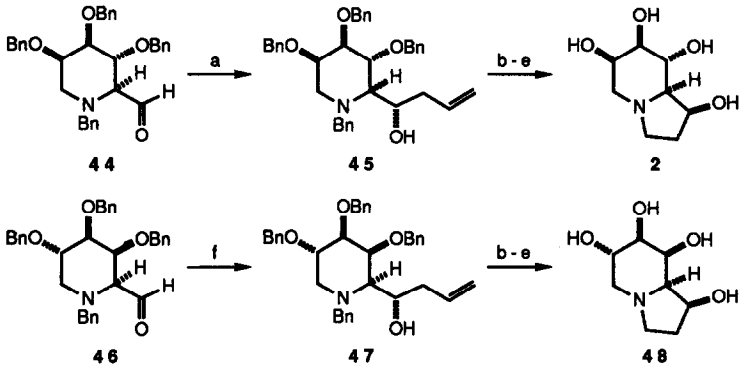
Methodology developed by Ganem involves establishing a chiral center via stereoselective Sakurai allylations of hexose-derived aldehydes.[68] This strategy was used to prepare castanospermine (**1**) and the two stereoisomers 6-*epi*castanospermine (**2**) and 8-*epi*castanospermine (**48**) (Schemes 7 and 8). Synthesis of **1** involved chelation-

controlled Sakurai allylation of the D-glucose-derived aldehyde **10** (allyltrimethylsilane/$TiCl_4$/CH_2Cl_2), which formed **43** with excellent stereocontrol (only one diastereomer could be detected by NMR) (Scheme 7). The alcohol **43** was subsequently transformed into castanospermine (**1**).



Scheme 7. a) allyltrimethylsilane (3.6 eq.), $TiCl_4$ (2.4 eq.), CH_2Cl_2, -85 °C, 15 h; (b) O_3, CH_2Cl_2, -78 °C; (c) $NaBH_4$, EtOH; (d) MsCl, Et_3N, CH_2Cl_2; (e) H_2, Pd-C.

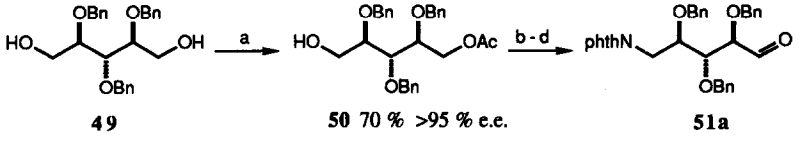
Good stereocontrol was also exhibited in the Sakurai allylations with the analogous aldehydes **44** (derived from D-mannose)[69] and **46** (derived from D-galactose),[70] (Scheme 8). The products **45** and **47** were then converted into 6-*epi*castanospermine (**2**) and 8-*epi*castanospermine (**48**) respectively, by a series of steps analogous to the synthesis of **1**.



Scheme 8. a) allyltrimethylsilane (3.6 eq.), $TiCl_4$ (2.4 eq.), CH_2Cl_2, -85 °C, 15 h; (b) O_3, CH_2Cl_2, -78 °C; (c) $NaBH_4$, EtOH; (d) MsCl, Et_3N, CH_2Cl_2; (e) H_2, Pd-C; (f) allyltri-*n*-butylstannane, $TiCl_4$, CH_2Cl_2.

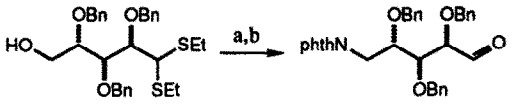
A stereoselective allylation was also used to prepare three other stereoisomers of castanospermine.[71] In this case, the aldehyde substrates were pentose-derived, and a chiral allylating reagent was used to establish the remaining two chiral centers with defined relative and absolute configuration.

Aldehyde **51a** was prepared utilizing an efficient lipase-catalyzed, enantiogroup selective monoacylation of the *meso* diol **49**, derived from adonitol (Scheme 9).[72]

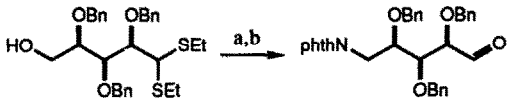


Scheme 9. a) *Candida cylindracea* (4.0 mass eq.), vinyl acetate, hexanes; (b) phthalimide, DEAD, PPh_3, THF; (c) TsOH, MeOH; (d) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2.

Subsequent simple chemical manipulations of the monoacetate **50** gave **51a**. The other two aldehydes **51b** and **51c** were obtained from dithioacetals **52** and **53**[73] derived from L-arabinose and D-xylose respectively (Scheme 10). Each dithioacetal was subjected to a Mitsunobu reaction with phthalimide to insert the *N*-functionality and then deprotected, to give **51b** and **51c**.



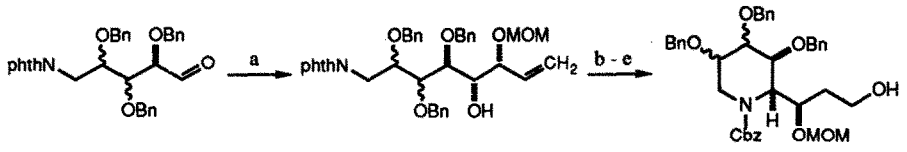
52 **51b**



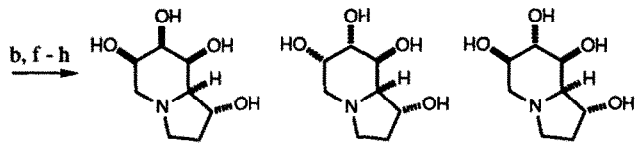
53 **51c**

Scheme 10. a) phthalimide, DEAD, PPh_3, THF; (b) $HgCl_2$, $CaCO_3$, MeCN:H_2O 1:10.

Since both enantiomers of the allylating reagent are readily available, the one which is stereochemically matched[74] with the Felkin-Anh bias[75 - 77] of the aldehyde was used; this ensured good stereocontrol in the formation of the two new chiral centers. For the aldehydes **51a - c** where the α-chiral center is *R* in each case, this necessitated allylation with the reagent derived from (1*R*)-(+)-α-pinene (Scheme 11).



51a - c **54a - c** **55a - c**



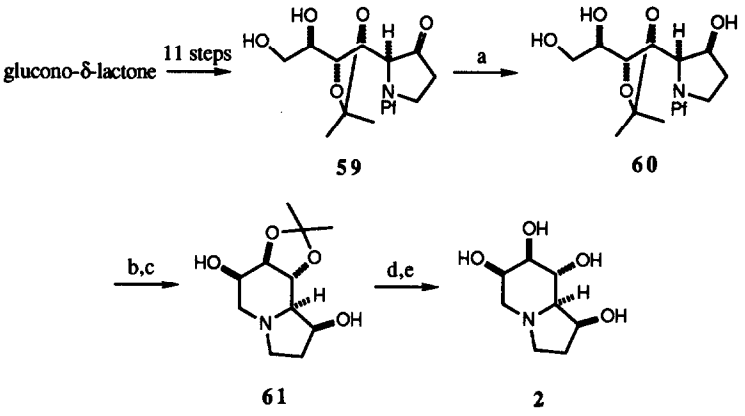
56 **57** **58**

Scheme 11. a) Z-(MOMO)CHCHCH$_2$^{d}BIpc$_2$, BF_3.OEt_2, then H_2O_2, $NaHCO_3$; (b) MsCl, NEt_3; (c) $MeNH_2$; (d) CbzCl, $NaHCO_3$; (e) BH_3-THF, then H_2O_2, $NaHCO_3$; (f) H_2, cat. Pd/C, MeOH; (g) $HCl_{(aq)}$; (h) ion-exchange.

The products **54a - c** were subsequently cyclized and then transformed into the alcohols **55a - c**. Mesylation of **55a - c** followed by exhaustive hydrogenolysis facilitated the second cyclization to the indolizidine and almost complete deprotection. Removal of the methoxymethyl ether furnished the target compounds 1,6,8-tri*epi*castanospermine (**56**), 1,7,8-tri*epi*castanospermine (**57**) and 1,6,7,8-tetra*epi*castanospermine (**58**) respectively.

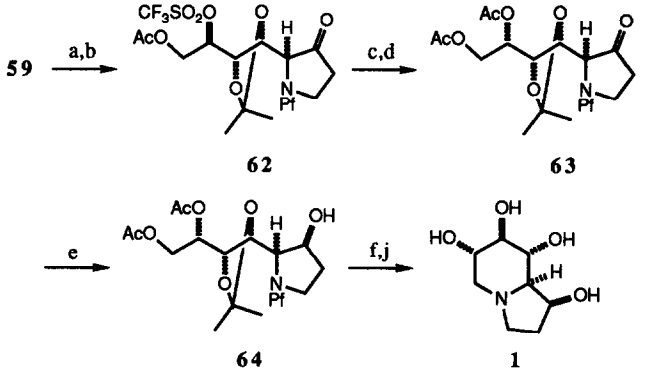
Rapoport recently developed methodology to prepare castanospermine (**1**) and 6-*epi*castanospermine (**2**) based on the stereoselective reduction of a cyclic ketone[78]. Synthesis of **2** involved conversion of glucono-δ-lactone into **59** in eleven steps (Scheme 12). Reduction of ketone **59** gave alcohol **60**, as a single epimer. Selective tosylation

of **60** followed by removal of the phenylfluorenyl (Pf) group effected cyclization to give the protected indolizidine **61**, which was then deprotected to give 6-*epi*castanospermine (**2**).



Scheme 12. (a) $NaBH_4$; (b) tosylation; (c) H_2, Pd-C, NaOAc; (d) CF_3COOH; (e) Dowex 50W.

Synthesis of castanospermine (**1**) was accomplished by inversion of the C-6 hydroxyl group of alcohol **59** (Scheme 13).



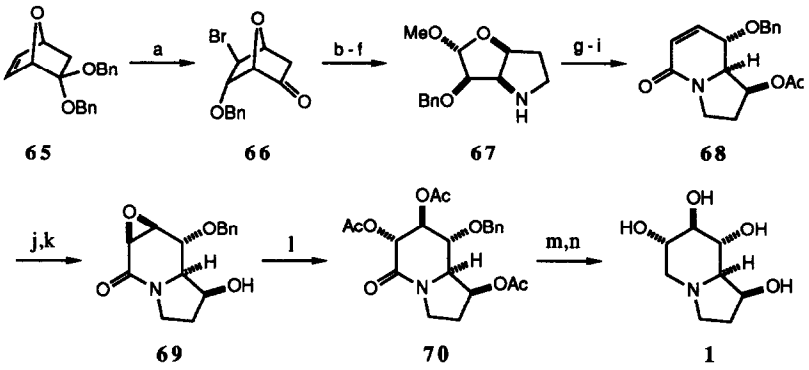
Scheme 13. a) Ac_2O, pyridine; (b) triflic anhydride, pyridine; (c) *n*-Bu_4NOAc; (d) acetic anhydride, pyridine, DMAP; (e) $NaBH_4$; (f) K_2CO_3; (g) tosylation; (h) H_2, Pd on C, NaOAc; (i).CF_3COOH; (j) Dowex 50W.

Selective acylation of **59** followed by formation of the triflate ester gave **62**, which without isolation was reacted with acetate anion to give the inverted acetate **63**. Reduction of ketone **63** gave a single alcohol **64**. After deacetylation of **64**, the resulting triol was converted into castanospermine (**1**) by a series of steps analogous to the synthesis of **2**.

2.3. Syntheses from Non-Carbohydrate Starting Materials

Only two syntheses of castanospermine stereoisomers have been performed that use non-carbohydrate starting materials. A preparation of castanospermine (**1**) is based on the bromine addition to 7-oxabicyclo[2.2.1]hept-5-en-2-one benzyl acetal (**65**) (Scheme 14).[79,80] Bromination occurred exclusively on the less-hindered convex face of

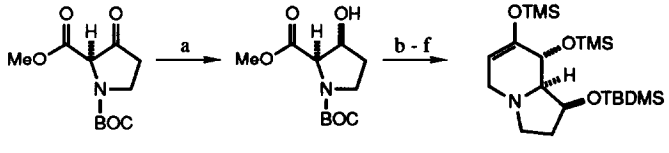
65 and this was followed by stereoselective migration of the *endo* BnO group of the acetal to give **66**. Subsequent conversion of **66** in five steps to **67**, included introduction of *N*-functionality. Amidation then acetylation of pyrrolidine **67** was followed by cyclization to **68** by an intramolecular Wittig-Horner condensation. Conversion of **68** into epoxide **69** was followed by regioselective opening with H_2O and then acylation to give triacetate **70**. Reduction of **70** followed by debenzylation gave D-castanospermine (**1**). Both enantiomers of **65** are available, hence L-castanospermine could also be synthesized by this route (although no such preparation has been reported).

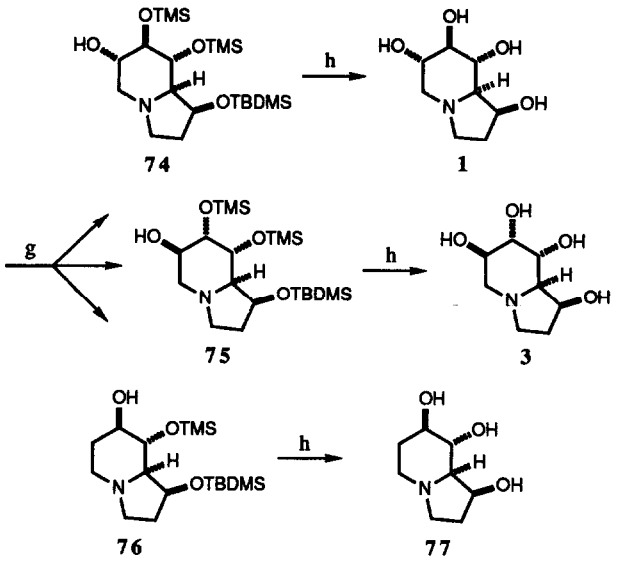


Scheme 14. a) Br_2, CH_2Cl_2, -80 °C; (b) MCPBA, $NaHCO_3$, CH_2Cl_2, 5 to 20 °C; (c) MeOH, $SOCl_2$, 20 °C, 24 h; (d) DIBAL, THF, -50 to -20 °C; (e) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (f) 12 % NH_3, 1:1 EtOH:H_2O, 70 °C, 5 h; (g) $ClCH_2COCl$, pyridine, CH_2Cl_2, -5 to +8 °C; (h) Ac_2O, c H_2SO_4, 5 °C, 2 h; (i).$(EtO)_3P$, 130 °C, 7 h, then K_2CO_3, EtOH, 20 °C, 12 h, then Ac_2O, pyridine, DMAP, 20 °C, 48 h; (j) Br_2, 1:2 AcOH:Ac_2O, AgOAc, 9 °C; (k) MeOH, $SOCl_2$, 20 °C, 17 h, then 2-*tert*butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene, CH_3CN, 20 °C, 35 min; (l) H_2O, 100 °C, 4.5 h, then Ac_2O, pyridine, DMAP, 20 °C, 48 h; (m) BH_3-Me_2S, THF, 20 °C, 15 h; (n) H_2, 10 % Pd-C, 5:1 THF:H_2O, 20 °C, 24 h.

A chemoenzymatic route to castanospermine (**1**) and 6,7-di*epi*castanospermine (**77**) has also been developed (Scheme 15).[81] Initial enzyme-catalyzed reduction of β-ketoester **71** to give alcohol **72** was efficient and very selective (80 %, >99 % e.e.); subsequent conversion of **72** to **73** (five steps) included cyclization via an intramolecular acyloin condensation. Hydroboration/oxidation of **73** resulted in the formation of the final two chiral centers, although not selectively; a mixture of diastereomeric alcohols **74** and **75** and another by-product **76** resulted. After separation by silica gel chromatography, desilylation of **74**, **75** and **76** afforded castanospermine (**1**), 6,7-di*epi*castanospermine (**3**) and 6-deoxycastanospermine (**77**) respectively.

Recently, 6,7-di*epi*castanospermine (**3**) has also been isolated from the seeds of *Castanospermum australe*.[35] Investigation of it's glycosidase inhibitory properties revealed it is a moderately good inhibitor of amyloglucosidase and a relatively weak inhibitor of β-glucosidase. It does not inhibit α- or β-galactosidase, α- or β-mannosidase, or α-L-fucosidase.



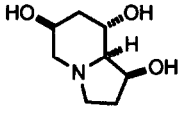


Scheme 15. a) *Didodascus sp.*, Vogel's medium, 72 h; (b) TBDMSCl, imidazole, CH_2Cl_2, 24 °C, 2 h; (c) 1:4 TFA:CH_2Cl_2, then Et_3N (3.0 eq.), methyl acrylate (1.5 eq.), EtOH; (d) Na (4.2 eq.), TMSCl (5.0 eq.), toluene, reflux; (e) DBU, CH_2Cl_2, 24 °C, 48 h; (f) TMSCl, $LiN(TMS)_2$, -78 °C, THF; (g) BH_3-Me_2S (2.0 eq.), THF, -78 to +25 °C, 12 h, then Me_3NO (10 eq.), toluene, reflux; (h) *n*-Bu_4NF, THF, 0 °C to +25 °C, 2 h.

3. Analogues of 1,6,7,8-Tetrahydroxyindolizidines

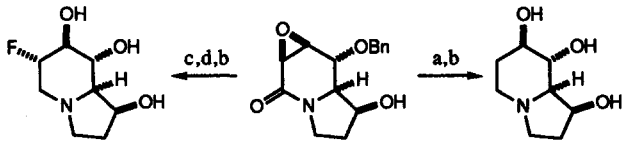
3.1. Deoxy Analogues

The only 1,6,7,8-tetrahydroxyindolizidine deoxy analogue to be isolated from nature is 7-deoxy-6-*epi*castanospermine (**78**).[82] It inhibits amyloglucosidase and yeast α-glucosidase, but is significantly less active than swainsonine (**4**) and the naturally-occurring 1,6,7,8-tetrahydroxyindolizidines **1-3**.



7-deoxy-6-*epi*castanospermine (78)

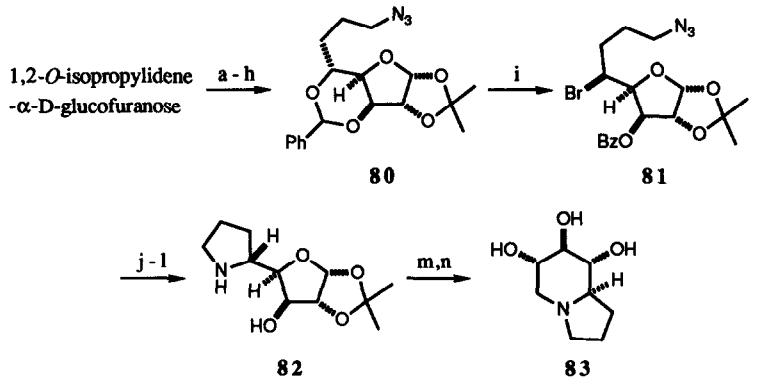
Other deoxy analogues have been synthesized and they also possess interesting biological activity.[10] Vogel prepared 6-deoxycastanospermine (**77**) together with 6-deoxy-6-fluorocastanospermine (**79**) utilizing intermediate **69** (Scheme 16).[80,83] Reduction followed by hydrogenolysis of **69** gave 6-deoxycastanospermine (**77**). Alternatively, regioselective ring-opening of the epoxide in **69** with fluoride anion gave a fluoro intermediate which was subsequently converted into 6-deoxy-6-fluorocastanospermine (**79**). 6-Deoxycastanospermine (**77**) was also isolated as a by-product in Sih's synthesis of castanospermine (**1**) (see Scheme 15).[81]



79 **69** **77**

Scheme 16. a) BH_3-Me_2S, THF, 20 °C, 4 d; (b) H_2, Pd-C, MeOH, HCO_2H, 20 °C, 16 h; (c) HF-Et_3N, 2-*t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene, 95 °C, 2 d, then Ac_2O, pyridine, DMAP, 20 °C, 4 d; (d) BH_3-Me_2S, THF, 20 °C, 1 d, then HCl, MeOH, H_2O, 70 °C, 4 d.

1-Deoxycastanospermine (**83**) was synthesized to probe the importance of the 1-hydroxyl group for biological activity (Scheme 17);[84,85] this molecule possesses four chiral centers that can be derived from D-glucose.



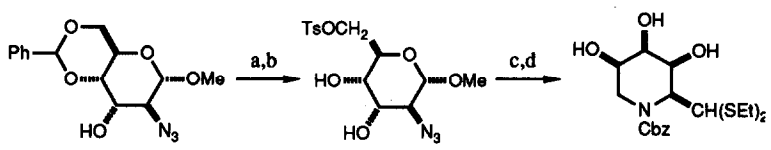
80 **81** **82** **83**

Scheme 17. a) C-6 benzoylation; (b) benzylidene formation; (c) C-6 debenzoylation; (d) PCC, powdered molecular sieves, CH_2Cl_2, then $Ph_3P{=}CHCO_2Et$; (e) H_2, 10 % Pd-C, EtOH; (f) $LiAlH_4$, Et_2O; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C; (h) NaN_3, DMF; (i) NBS, $BaCO_3$, CCl_4; (j) NaOMe, MeOH; (k) $SnCl_2$, MeOH, 60 °C; (l) NaOAc, EtOH, then CbzCl, $NaHCO_3$, EtOH:H_2O (1:1); (m) AcOH:H_2O (1:4); (n) H_2, 10 % Pd-C, MeOH.

Conversion of 1,2-*O*-isopropylidene-α-D-glucofuranose in eight steps to azide **80** was followed by the most important reaction in the sequence, formation of the L-*ido*-octose derivative **81** with a leaving group at C-5 via oxidative bromination of the benzylidene acetal in **80**. This was subsequently converted into the pyrrolidine **82**. Thus, double inversion at C-5 produced the five-membered ring with the configuration required by the product. Deprotection of **82** and intramolecular reductive amination furnished 1-deoxycastanospermine (**83**).

1-Deoxycastanospermine (**83**) was tested against a wide range of enzymes from the human liver; it has low activity against glucosidases compared to castanospermine (**1**) implying the 1-hydroxyl group is an important feature for glucosidase inhibition.[10,85]

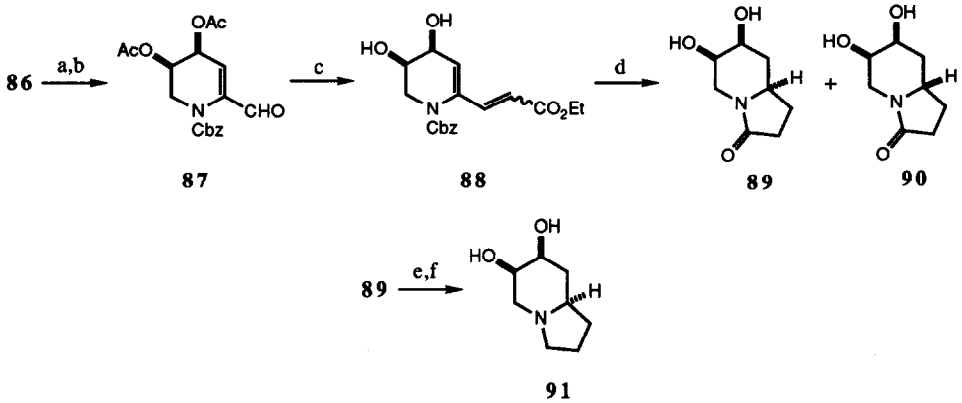
D-Glucose was also used to prepare 1,8-dideoxy-6-*epi*castanospermine (**91**) and 1-deoxy-6,8-di*epi*castanospermine (**95**) (Schemes 19 and 20).[86,87] The key intermediate **86** for both routes was synthesized from the known methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (**84**) (Scheme 18). The penultimate step in this sequence involved intramolecular displacement of the tosylate at C-6 of **85** by a 2-amino function formed via reduction of the azide.



84 85 86

Scheme 18. a) AcOH:H_2O 1:4 ; (b) TsCl, pyridine; (c) H_2, 10 % Pd-C, EtOH, then NaOAc, EtOH, reflux, then CbzCl, $NaHCO_3$, EtOH:H_2O 1:1; (d) EtSH, HCl, $CHCl_3$.

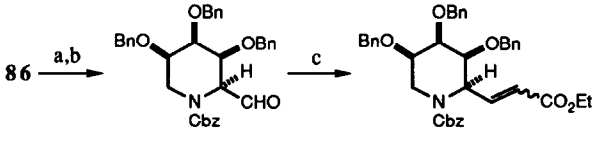
For the synthesis of 1,8-dideoxy-6-*epi*castanospermine (**91**), intermediate **86** was first converted into aldehyde **87** (Scheme 19); this involved destruction of two of the four chiral centers. Subsequent chain extension of **87** via reaction with carboethoxymethylene triphenylphosphorane gave **88**. Hydrogenation and then cyclization of **88** gave the epimeric lactams **89** and **90** in a ratio of 15:1.; the major product, lactam **89**, resulted from delivery of hydrogen to the least hindered face. After separation by flash chromatography, **89** was converted into 1,8-dideoxy-6-*epi*castanospermine (**91**).



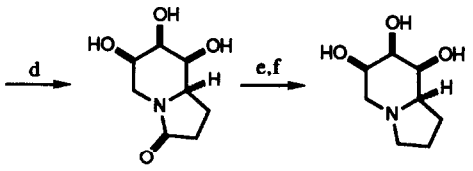
87 88 89 90 91

Scheme 19. a) Ac_2O, pyridine ; (b) $HgCl_2$, $CdCO_3$, Me_2CO:H_2O 1:9; (c) $Ph_3P{=}CHCO_2Et$, CH_3CN, then NaOMe, MeOH; (d) H_2, 10 % Pd-C, EtOH, then NaOAc, EtOH, reflux; (e) Ac_2O, pyridine; (f) BH_3-Me_2S, THF, then NaOMe, MeOH.

For the synthesis of 1-deoxy-6,8-di*epi*castanospermine (**95**) from **86** chain extension was again achieved via reaction with carboethoxymethylene triphenylphosphorane, but the aldehyde substrate **92** was synthesized using modified conditions, so that all the existing chirality was retained (Scheme 20). Hydrogenation followed by cyclization of the product **93** gave **94** which was then converted into 1-deoxy-6,8-di*epi*castanospermine (**95**).



92 93



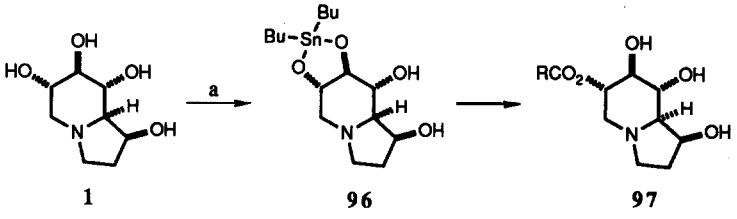
Scheme 20. a) BnBr, NaH, DMF ; (b) $HgCl_2$, $CdCO_3$, Me_2CO:H_2O 1:9; (c) Ph_3P=$CHCO_2Et$, CH_3CN; (d) H_2, 10 % Pd-C, EtOH, then NaOAc, EtOH, reflux, then H_2, 10 % Pd-C, AcOH, 48 h; (e) Ac_2O, pyridine; (f) BH_3-Me_2S, THF, then NaOMe, MeOH.

When tested against a wide range of enzymes originating from human liver, neither 1,8-dideoxy-6-*epi*castanospermine (**91**) or 1-deoxy-6,8-di*epi*castanospermine (**95**) showed any significant activity.

3.2. *O*-Acyl Analogues

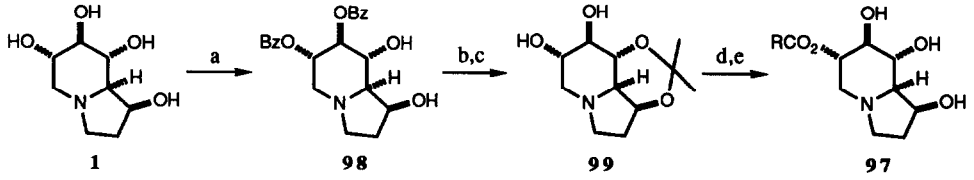
Several *O*-acyl derivatives of castanospermine are more active than castanospermine (**1**) with respect to inhibition of HIV replication.[31] Due to the similar reactivity of the four secondary hydroxyl groups, synthesis of these derivatives by regioselective acylation of **1** using conventional methods, presents a formidable challenge.

A simple one-pot procedure for the acylation of the 6-hydroxyl of **1** involves reaction with dibutyltin oxide followed by acyl chloride (Scheme 21).[88] It is probable that attack at the sterically less crowded 6-OH group leads to preferential formation of the intermediate 6,7-stannylidene **96**, which in turn activates the C-6 position to subsequent acylation affording the 6-*O*--acylcastanospermine derivative **97**.



Scheme 21. (a) Bu_2SnO (1.1 eq.), MeOH, reflux, 45 min, then RCOCl (5.0 eq.), Et_3N (5.0 eq.), 25 °C, 2 h

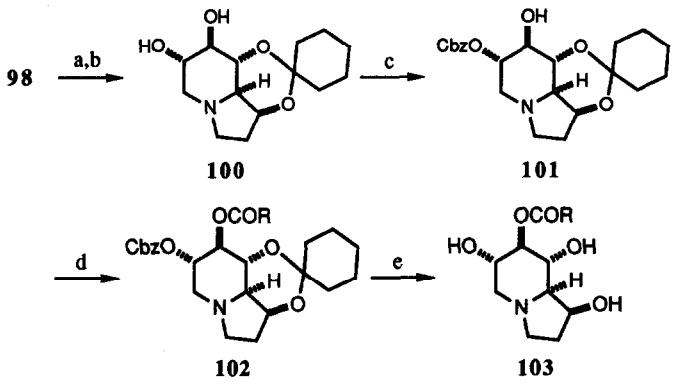
The syntheses of 6-*O* - and 7-*O*-acyl derivatives of castanospermine (**97** and **103** respectively) via conventional chemical manipulation have also been accomplished (Schemes 22 and 23).[89]



Scheme 22. (a) BzCl (2.2 eq.), pyridine, 0 °C-25 °C, 3 d; (b) 2-methoxypropene, *p*-TsOH·H_2O, DME, 55 °C; (c) NaOMe, MeOH, 25 °C; (d) RCOCl, CH_2Cl_2; (e) EtOH, HCl.

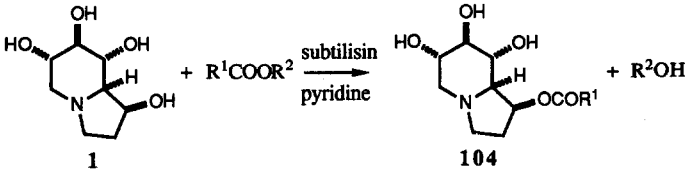
For the synthesis of **97**, selective dibenzoylation of castanospermine (**1**) gave the hydrochloride of 6,7-di-*O*-benzoylcastanospermine (**98**) as the major product (Scheme 22). Protection of the remaining two hydroxyl groups as the acetonide followed by debenzoylation gave **99**. Selective C-6 acylation of **99** followed by deprotection gave the 6-*O*-acylcastanospermine derivatives **97**.

A similar strategy was used to synthesize the 7-*O*-acyl derivatives **103** (Scheme 23). Conversion of **98** into the diol **100** was followed by formation of the hydrochloride of the C-6 carbamate **101**; no reaction at the C-7 hydroxyl occurred. Acylation of the remaining C-7 hydroxyl group gave **102** which was then deprotected stepwise resulting in the 7-*O*-acylcastanospermine derivative **103**.



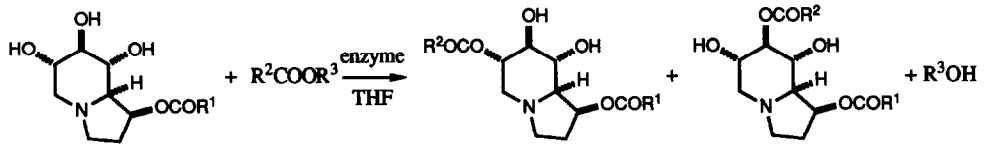
Scheme 23. (a) 1-methoxycyclohexene, CH_3SO_3H, DME, reflux; (b) 1 M NaOH, THF, 25 °C; (c) CbzCl, DMAP, CH_2Cl_2, 25 °C; (d) RCOCl, Et_3N, CH_2Cl_2; (e) H_2, 10 % Pd-C, EtOH, 18 h, then HCl, EtOH.

O-Acyl derivatives of castanospermine have also been synthesized via an alternative and quicker route involving the use of enzymes. The proteolytic enzyme subtilisin Carlsberg acylates castanospermine (**1**) with high regioselectivity and broad substrate specificity to give a wide variety of the 1-*O*-acyl derivatives **104** (Scheme 24).[90 - 92]



Scheme 24.

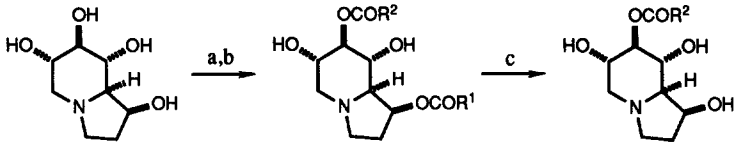
Further acylation of the 1-*O*-acyl derivatives **104**[91,92] in THF catalyzed by subtilisin Carlsberg results in predominant acylation at the C-6 hydroxyl to give the 1,6-di-*O*-acyl derivatives **105**. Alternatively, use of Porcine Pancreatic Lipase results in formation of the 1,7-di-*O*-acyl derivatives **106** as the major product (Scheme 25). No triesters or 1,8-diesters are formed in either case.



104 105 106

Scheme 25.

A three step enzymatic synthesis of the 7-*O*-acylcastanospermine derivatives **103** using similar methodology has also been accomplished (Scheme 26).[91,92] Monoacylation of **1** at the C-1 hydroxyl catalyzed by subtilisin followed by a second acylation at the C-7 hydroxyl catalyzed by the lipase *Chromobacterium viscosum* gave the 1,7-di-*O*-acyl derivative **106**. Subsequent selective hydrolysis of the C-1 acyl group catalyzed by subtilisin gave the 7-*O*-acylcastanospermine derivative **103**.

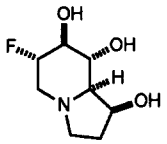


1 106 103

Scheme 26. (a) subtilisin, R^1COCl, pyridine; (b) lipase CV, R^2COCl, THF; (c) subtilisin, phosphate buffer (pH 6.0).

3.3. Heteroatom-Substituted Analogues

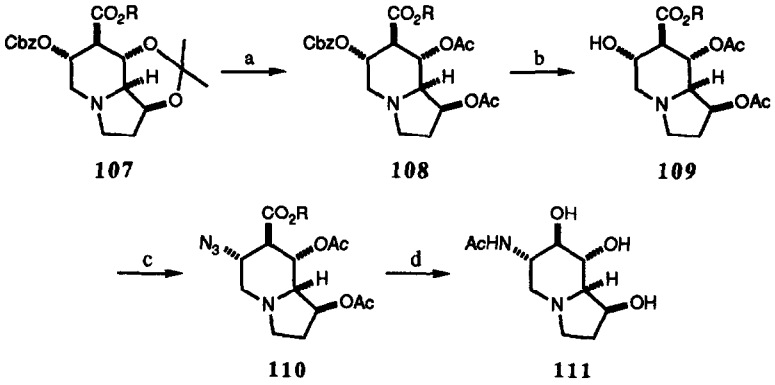
Vogel synthesized 6-deoxy-6-fluorocastanospermine (**79**) utilizing intermediate **68** which was also used to synthesize castanospermine (**1**) and 6-deoxycastanospermine (**77**) (Scheme 16).



79

The conjugate acid of 6-deoxy-6-fluorocastanospermine (**79-H⁺**) (pK_a = 5.09) was found to be stronger than castanospermine-H⁺ (**1-H⁺**) (pK_a = 6.01) and this can be attributed to the inductive effect of the fluoro substituent. Since the ionized form of the nitrogen is very important for inhibition, modification of the pK_a's of castanospermine derivatives could lead to profound changes in biological activity.

A synthesis of 6-acetamido-6-deoxycastanospermine (**111**) has recently been described (Scheme 27).[93] The isopropyl ketal **107** was synthesized analogously to the cyclohexyl ketal **102** (Scheme 23).[89] Removal of the ketal protecting group followed by peracetylation gave **108**. Selective deprotection of the 6-hydroxyl gave alcohol **109** which was then mesylated and converted into azide **110** by two successive invertive displacements. Deprotection of the remaining alkoxy groups, reduction of the azide and *N*-acetylation afforded 6-acetamido-6-deoxycastanospermine (**111**).



Scheme 27. (a) HCl, MeOH, then Ac_2O, pyridine; (b) Pd-C, MeOH, cyclohexene; (c) mesyl chloride, Et_3N, then NaI, EtOAc, then NaN_3, DMF; (d) NaOMe, MeOH, then Pd-C, H_2, then Ac_2O, acetone, H_2O.

6-Acetamido-6-deoxycastanospermine (**111**) was found to be a very potent inhibitor of β-*N*-acetylglucosaminidases from several sources.

4. Conclusions

Synthetic strategies outlined above describe the preparations of twelve of the possible thirty-two stereoisomers of 1,6,7,8-tetrahydroxyindolizidine plus other analogues; the stereoisomers are shown in Figure 1.

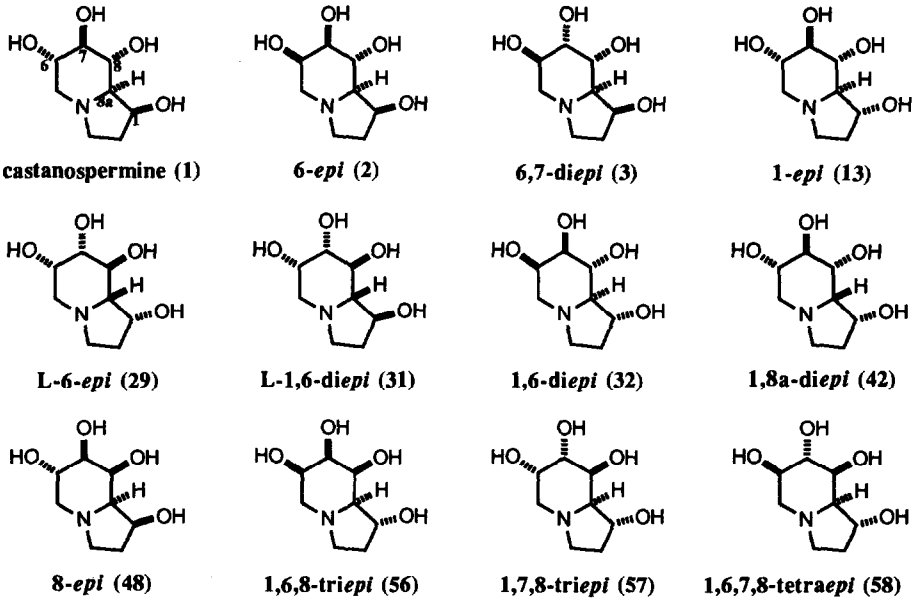


Figure 1. 1,6,7,8-Tetrahydroxyindolizidines isolated or synthesized to date.

References for these approaches and the known biological activities of these compounds are given in the Table.

Table. Stereoisomers of 1,6,7,8-Tetrahydroxyindolizidine: A Summary

compound	hexose corresponding to 6,7,8,8a-stereochemistry	references
castanospermine (**1**)	D-glucose	isolation from *Castanospermum australe*[1] and the dried pod of *Alexa leiopetala*[2] synthesis from D-glucose[61,68] synthesis from D-mannose[62] synthesis from glucuronolactone[65] synthesis from 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone[67] synthesis from glucono-δ-lactone[78] synthesis from 7-oxabicyclo[2.2.1]hept-5-en-2-one benzyl acetal[79,80] synthesis from non-carbohydrate starting material[94] enzyme-mediated synthesis[81] activity[1,3 - 33]
6-*epi* (**2**)	D-mannose	isolation[34] synthesis from L-gulonolactone[38,39] synthesis from D-mannose[68] synthesis from glucono-δ-lactone[78] activity[10,34,38,39]
6,7-di*epi* (**3**)	D-altrose	isolation[35] enzyme-mediated synthesis[81] activity[35]
1-*epi* (**13**)	D-glucose	synthesis from D-glucose[61] synthesis from D-mannose[62] synthesis from glucuronolactone[65]
L-6-*epi* (**29**)	L-mannose	synthesis from D-gulonolactone[38,39] activity[38,39]
L-1,6-di*epi* (**31**)	L-mannose	synthesis from D-gulonolactone[38,39] activity[38,39]
1,6-di*epi* (**32**)	D-mannose	synthesis from L-gulonolactone[38,39] activity[10,38,39]
1,8a-di*epi* (**42**)	L-idose	synthesis from 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone[67]
8-*epi* (**48**)	D-galactose	synthesis from D-galactose[68]
1,6,8-tri*epi* (**56**)	L-talose	synthesis from adonitol[71]
1,7,8-tri*epi* (**57**)	L-galose	synthesis from L-arabinose[71]
1,6,7,8-tetra*epi* (**58**)	L-idose	synthesis from D-xylose[71]

Despite significant efforts directed towards syntheses of stereoisomers of 1,6,7,8-tetrahydroxyindolizidine, over half have yet to be reported or isolated, and relatively few analogues have been prepared.[94] However, the useful biological activities exhibited by some of these compounds indicate other derivatives are of interest; consequently, further development of chemical methodologies for the syntheses of these compounds are a matter of some importance.

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