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Stereocontrolled Syntheses of Polyhydroxy Indolizidines, Including 8a-Epi-, 6,8a-Diepi- and 1,6-Diepi-castanospermine, Starting from Malic Acid

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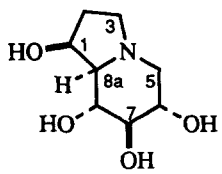
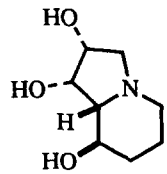
Abstract: Stereocontrolled total syntheses of one trihydroxy indolizidine **15** and three tetrahydroxy indolizidines, **17**, **21** and **23** – all diastereoisomers of castanospermine – are described which use malic acid as the only chiral starting material.

Polyhydroxy indolizidines have aroused considerable interest because of their inhibition of various glycosidases[1,2] and they have been investigated as possible treatments for diabetes,[3] cancer[4] and viral infections[5] (including HIV). The inhibition is presumably due to the resemblance between the protonated indolizidines and the transition states in glycoside hydrolysis, which have cationic oxonium ion character. The naturally occurring indolizidine castanospermine has the same stereochemistry at C-6, 7, 8 and 8a as C-2, 3, 4 and 5 of glucose and it is not surprising, therefore, that it inhibits glucosidases much more strongly than other types of glycosidase. However, this stereochemical relationship does not always hold good: 6-epicastanospermine is not a very good inhibitor of mannosidases even though it has the mannose stereochemistry, whereas swainsonine, which superficially bears much less resemblance to mannose, is a potent inhibitor of certain mannosidases.[6] Given that the inhibitory properties of polyhydroxy indolizidines cannot be reliably predicted, it is important that as many polyhydroxy indolizidines as possible are synthesised and tested for their biological activity.



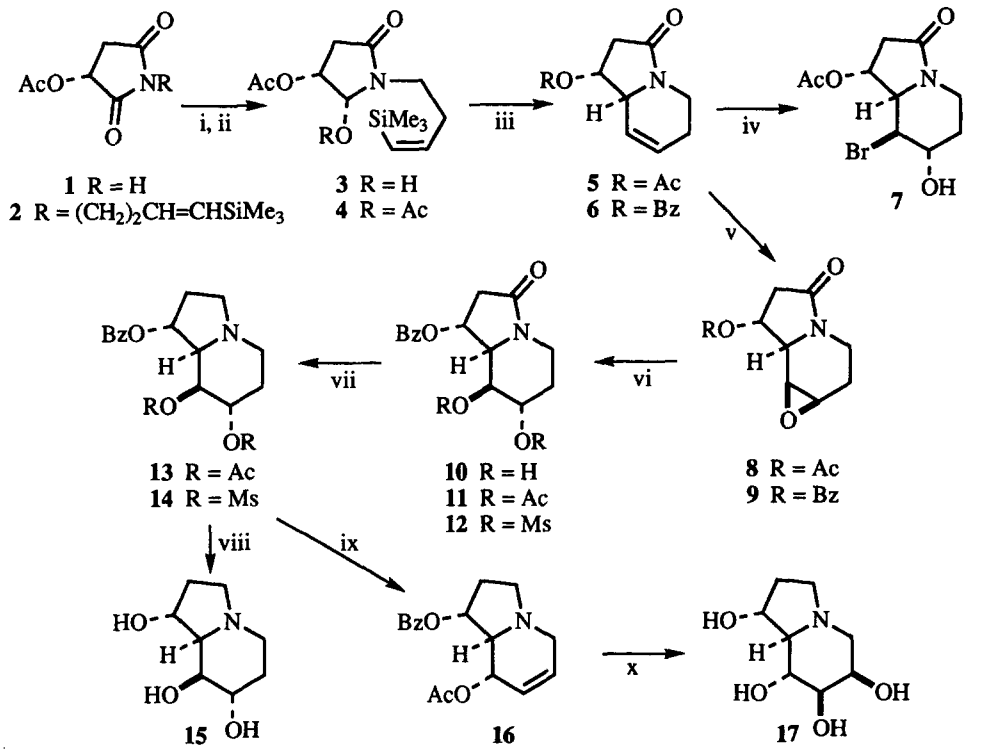
Castanospermine



Swainsonine

There have been a large number of reported syntheses of polyhydroxy indolizidines[7] including ones of castanospermine,[8] swainsonine[9] and epimers of these compounds.[6,8,10,11] The majority of these syntheses, however, have started from carbohydrates or other starting materials containing multiple chiral centres. This means that the syntheses lack flexibility, often being applicable to only one or two diastereoisomers and one absolute stereochemistry. Our approach has been the opposite – to start from a compound with only one chiral centre, which is readily available in either absolute configuration, and to use this chiral centre to control the formation of all the remaining chiral centres.

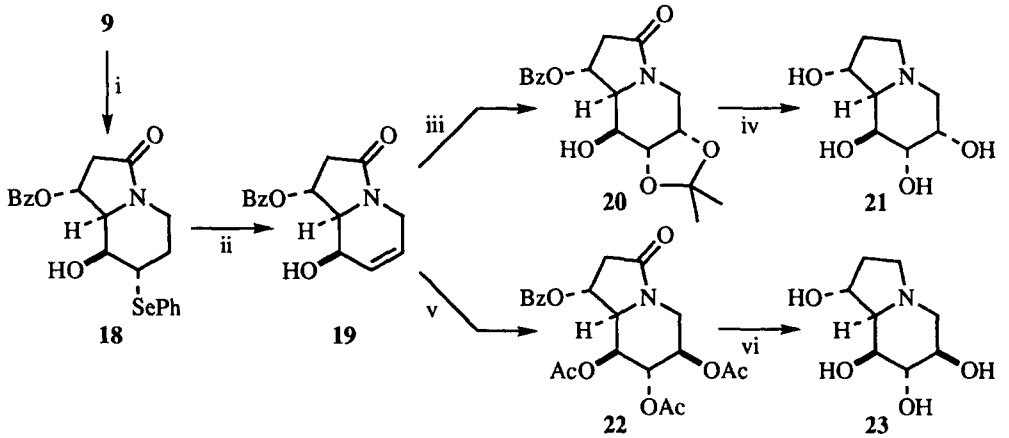
Our chosen starting material was malic acid which was converted to the acetoxysuccinimide **1** by published procedures.[12] Racemic malic acid was used for the development of the chemistry but both enantiomers are commercially available and inexpensive and the chemistry should work just the same in the optically active series. The imide **1** was converted into its *N*-(4-trimethylsilyl-3-butenyl) derivative[13] **2** using the corresponding alcohol under Mitsunobu conditions.[12,14–16] Reduction with $NaBH_4$ gave predominantly the hydroxylactam **3** with only a trace of the alternative diastereoisomer. The stage was now set for the key cyclisation to give the indolizidine skeleton **5** *via* an acyliminium ion intermediate. It was found, however, that the cyclisation of **3** in TFA did not proceed as readily or as cleanly as the previously reported[15] reaction of the hydroxylactam lacking the acetoxy group. This may be because neighbouring group participation from the acetoxy group reduces the reactivity of the acyliminium ion. A number of different conditions were tried for the cyclisation and eventually it was found that conversion of hydroxylactam **3** into its acetate **4** followed by treatment with boron trifluoride etherate in dichloromethane[16] gave the indolizinone **5** cleanly and in good yield. Only one diastereoisomer was detected and this was shown to be the expected isomer **5** by an X-ray crystal structure of the bromohydrin **7**, made by treatment of **5** with *N*-bromosuccinimide in THF–water (9:1).



Scheme 1. *Reagents: i*, $Me_3SiCH{=}CH(CH_2)_2OH$, DEAD, Ph_3P, 87%; $NaBH_4$, 94%; *ii*, Ac_2O, pyr, DMAP, 85%; *iii*, $BF_3.OEt_2$, 72%; Et_3N, MeOH, H_2O then BzCl, Et_3N, DMAP, 84%; *iv*, NBS, THF, H_2O, 77%; *v*, mCPBA, 76%; *vi*, H^+, THF, H_2O then ii, 52% or MsCl, pyr, 41%; *vii*, $BH_3.Me_2S$; *viii*, aq. NH_3, 37% (2 steps); *ix*, Bu_4NOAc, 25%; *x*, OsO_4, NMO then viii, 53%.

Epoxidation of the alkene **5** with *m*-chloroperbenzoic acid (mCPBA) gave the β-epoxide **8** as the major product and a minor amount of the inseparable α-epoxide (ratio 4:1). This α-epoxide was also formed by treatment of the bromohydrin **7** with t-BuOK, thus confirming its stereochemistry. In the absence of other substituents, the exo (α) face of the fused bicyclic system would be the less hindered. Presumably electrophilic attack on the β-face of alkene **5** (as seen in **7** and **8**) is due to steric hinderance by the acetoxy group. Accordingly this ester was hydrolysed and replaced by the bulkier benzoate **6** so as to exert greater control over the stereochemistry of the epoxidation. Indeed, treatment with mCPBA now gave the β-epoxide **9** with only 10% of a separable minor compound, probably the α-epoxide, being produced. Acid-catalysed ring-opening of the epoxide was effected with Dowex-50 (H^+) in THF–water to give the *trans*-diaxial diol **10**. In order to convert this to our first target molecule, 1,7,8-trihydroxyindolizidine **15**, the diol was acetylated and the lactam **11** then reduced with borane–dimethyl sulphide complex to give the indolizidine triester **13** (initially as a stable boron complex which required acid treatment or heating in ethanol to liberate the amine[9a]). Hydrolysis with aqueous ammonia and purification by ion exchange chromatography then gave the triol **15**.

Axial hydroxyl groups on adjacent positions such as those at C-7 and 8 of indolizidine **15** are not found in commonly occurring sugars and so we next investigated the possibility of inverting their stereochemistry. Mesylation of the diol **10** followed by borane reduction of the dimesylate **12** gave indolizidine **14**. Treatment with tetrabutylammonium acetate, using conditions reported to effect inversion in similar systems,[17] unexpectedly gave the allylic acetate **16**. It would seem that the acetate anion acted first as a base causing elimination of the C-7 mesylate group and then subsequently as a nucleophile displacing the now allylic mesylate at C-8. The yield of **16** is as yet low but it has not been optimised and it seems likely that stronger bases might be more effective at promoting the initial elimination. The 6,7-double bond of **16** allows further functionalisation leading to 1,6,7,8-tetrahydroxyindolizidines related to castanospermine. For example *cis*-dihyroxylation, using a catalytic amount of osmium tetroxide with *N*-methylmorpholine-*N*-oxide (NMO) occurred as expected *trans* to the acetoxy group on C-8 and hydrolysis of the ester groups as before gave 1,6-diepicastanospermine **17**. This compound has the mannose stereochemistry, it has been made before in optically active form[1,18] and was tested as an inhibitor of certain glycosidases but it showed surprisingly little inhibition, even of a mannosidase.[1]



Scheme 2. *Reagents: i*, PhSeNa, 75%; *ii*, mCPBA, 76%; *iii*, OsO_4, NMO, 57%; $Me_2C(OMe)_2$, H^+, 96%; *iv*, $BH_3.Me_2S$, 75%; H^+, H_2O then aq. NH_3, 100%; *v*, $VO(acac)_2$, ^tBuOOH, 79%; KOAc, AcOH then Ac_2O, pyr, DMAP, 87%; *vi*, $BH_3.Me_2S$, 46%; aq. NH_3, 100%.

An alternative route to a 6,7-double bond and hence to 1,6,7,8-tetrahydroxy-indolizidines involved opening the epoxide **9** with the phenylselenide anion to give selenide **18**. Oxidation with mCPBA then gave allylic alcohol **19** *via* the selenoxide. Osmylation of **19** again occurred *trans* to the substituent on C-8 (*i.e.* on the α-face this time); the water-soluble triol was isolated as its 6-*O*,7-*O*-isopropylidene derivative **20**, reduced with borane and deprotected to give 6,8a-diepicastanospermine **21**.[10] Alternatively, epoxidation of the allylic alcohol **19** using vanadyl acetoacetonate and t-butyl hydroperoxide gave the β-epoxide due to delivery from the allylic alcohol group. Opening of the epoxide with potassium acetate in acetic acid occurred by attack at C-7 to give the diaxial product and acetylation of the free hydroxyls gave the triacetate **22**. Reduction and deprotection as before then gave the third 1,6,7,8-tetrahydroxyindolizidine isomer, 8a-epicastanospermine **23**.[10]

In conclusion, the syntheses described here have shown that a variety of tri- and tetra-hydroxy indolizidines can be synthesised in a fully stereocontrolled manner starting with just the one chiral centre in malic acid. All the reactions proceeded with a high degree of stereoselectivity – indeed the only reaction in which a second diastereoisomer was detected is the epoxidation of **6** to **9** and even here the ratio of isomers was 10:1. Clearly there are alternative reactions still to be explored which should give access to further diastereoisomers of polyhydroxyindolizidines and work on this is in progress.

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REFERENCES

1. Winchester, B. G.; Cenci di Bello, I.; Richardson, A. C.; Nash, R. J.; Fellows, L. E.; Ramsden, N. G.; Fleet, G. W. J. *Biochem. J.* **1990**, *269*, 227–231 and references therein.
2. Elbein, A. D. *FASEB J.*, **1991**, *5*, 3055–3063.
3. Hodgson, J. *BioTechnology* **1991**, *9*, 609–613.
4. Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215–5222; Dennis J. W. *Cancer Res.* **1986**, *46*, 5131–5136.
5. Sunkara, P. S.; Kang, M. S.; Bowlin, T. L.; Liu, P. S.; Tyms, A. S.; Sjoerdsma, A. *Ann. N. Y. Acad. Sci.* **1990**, *616*, 90–96; Liu, P. S.; Hoekstra, W. J.; King, C.-H. R. *Tetrahedron Lett.* **1990**, *31*, 2829–2832.
6. Elbein, A. D.; Szumilo, T.; Sanford, B. A.; Sharpless, K. B.; Adams, C. *Biochemistry* **1987**, *26*, 2502–2510.
7. Michael, J. P. *Nat. Prod. Rep.* **1994**, *11*, 17–39; Takahata, H.; Momose, T. in *The Alkaloids*, Vol 44; Cordell, G. A. Ed.; Academic Press: San Diego, 1993; pp. 189–256.
8. Reviewed in Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045–4066.
9. (a) Carpenter, N. M.; Fleet, G. W. J.; Cenci di Bello, I.; Winchester, B. G.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1989**, *30*, 7261–7264; (b) Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100–8112; (c) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420–422.
10. Burgess, K.; Chaplin, D. A.; Henderson, I.; Pan, Y. T.; Elbein, A. D. *J. Org. Chem.* **1992**, *57*, 1103–1109.
11. Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083–6089; Tadano, K.; Iimura, Y.; Hotta, Y.; Fukabori, C.; Suami, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3885–3892.
12. Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653–3656.
13. All new compounds gave satisfactory NMR, IR and elemental analyses or high-resolution mass spectra.
14. Choi, J. K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959–3969.
15. Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097-6107.
16. Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591–2596.
17. Casiraghi G.; Spanu, P.; Rassu, G.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1994**, *59*, 2906–2909.
18. Burgess, K.; Chaplin, D. A. *Tetrahedron Lett.* **1992**, *33*, 6077–6080.

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