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Synthetic Methods for the Stereoisomers of Swainsonine and its Analogues

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Contents

1. Introduction

The (1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyindolizidine, (−)-swainsonine (**1**), which was first isolated from the fungus *Rhizoctonia leguminicola*[1] and later found in the Australian plant *Swainsona canescens*[2] (and has been produced from cultures of normal and transformed roots of *Swainsona galegifolia*[2d,e]), the North American spotted locoweed plant *Astragalus lentiginosus*[3] and the fungus *Metarhizium anisopline* F-3622,[4] is found to be an effective inhibitor of both lysosomal α-mannosidase[5,6] and mannosidase **II**[7] (lysosomal α-mannosidase is involved in the cellular degradation of polysaccharides and mannosidase **II** is a key enzyme in the processing of asparagine-linked glycoproteins[8]). It also has antimestastic,[9] antitumor-proliferative,[10] anticancer[11] (swainsonine is the first glycoprotein-processing inhibitor to be selected for clinical testing as an anticancer drug,[12] but its high cost has hindered clinical

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Abbreviations: AIBN, Azobis(isobutyronitrile); All, Allyl; Bn, Benzyl; BMS, Borane–dimethylsulfide complex; Boc, *t*-Butoxcarbonyl; Bu, Butyl; Bz, Benzoyl; CAN, Ceric ammonium nitrate; Cbz, Benzylcarbamyl; CSA, Camphorsulphonic acid; DAMP, 4-(*N*,*N*-Dimethylamino) pyridine; DAST, Diethylaminosulphur trifluoride; DBAD, Di-*t*-butyl azodicarboxylate; DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; DEAD, Diethyl azodicarboxylate; DCE, 1,2-Dichloroethane; DDQ, 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; DHQ-CLB, Sharpless asymmetric dihydroxylation reagent; DIBAL, Di-*i*-butylaluminium hydride; DIPT, Di-*i*-propyl tartrate; EE, 1-Ethoxyethoxy; DMP, 2,2-Dimethoxypropane; DMSO, Dimethyl sulphoxide; DPPA, Diphenylphosphorazidate; HMDS, Hexamethyldisilazane; HMPA, Hexamethylphosphoramide; Im_2CS, 1,1′-Thiocarbonyldiimidazole; LDA, Lithium di-*i*-propylamide; LHMDS, Lithium hexamethyldisilazide; *m*CPBA, *m*-Chloroperoxybenzoic acid; MEM, Methoxyethoxymethyl; MOM, Methoxymethyl; MPM, Methoxyphenylmethyl; Ms, Mesyl; M.S., Molecular sieve; NBS, *N*-Bromosuccinimide; NMO, *N*-Methylmorpholine *N*-oxide; NSA, 2-Naphthalenesulphonic acid; PCC, Pyridinium chlorochromate; PDC, Pyridinium dichromate; Pf, 9-Phenylfluororen-9-yl; Ph, Phenyl; Piv, Trimethylacetyl; PPTS, Pyridinium salt, *p*-Toluenesulphonic acid; pyr, Pyridine; rt, Room temperature; Ru-Cat, Bis-(tricyclohexylphosphane) benzylidene ruthenium dichloride; SUC-OTf, *O*-(Trifluoroacetate)-*N*-hydroxysuccinimide; TBAF, Tetrabutylammonium fluoride; TBDMS, *t*-Butyldiphenylsily; TBDPS, *t*-Butyldimethylsilyl; TBHP, *t*-Butylhydroperoxide; Tf, Trifluoromethylsulphonyl; TFA, Trifluoroacetic acid; Tf_2O, Trifluoromethylsulphonic anhydride; THF, Tetrahydrofuran; TIPS, Triisopropylsilyl; TMS, Trimethylsilyl; TMSOF, 2-(Trimethylsiloxy)furan; Tol, Tolyl.

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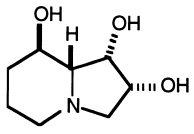
trials) and immunoregulating activity.[13] Swainsonine has been the subject of many other biological investigations,[14–16] e.g. its effects on murine survival and bone marrow proliferation,[14a] modification of glycan structure,[14b] activity of intestinal sucrase,[14c] rats appetite,[14d] aspartate transaminase activity,[14e] insulin and lectin binding,[14f] inhibition of tyrosinase activity,[14g] rat epididymal glycosidases,[14h] inhibition of the formation of the normal oligosaccharide chain of the G-protein of vesicular stomatitis virus[14i] and modulation of ricin toxicity,[14j,k] its biochemical and pathological effects in the pig,[14m] toxicity and lesion production,[14n] rate of clearance from animal tissues,[14o] effect on neuronal lysosomal mannoside storage disease,[14p–r] on inhibition of mammalian digestive disaccharidases,[14s] increasing the high-mannose glycoproteins in cultured mammalian cells,[14f] inducing a high mountain disease in calves,[14u] fucose incorporation in soy bean cells,[15a] normal human fibroblasts in culture,[15b] recycling of the transferrin receptor[15c] and inhibition of root length elongation[15d] have been investigated, and swainsonine is the principal toxin responsible for the induction of locoism.[15e]



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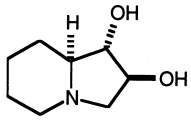

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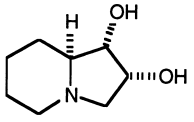

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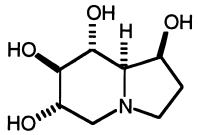

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The absolute configuration of (**1**) was deduced on the basis of biosynthetic,[17] asymmetric induction studies,[1b] and unambiguous nuclear magnetic resonance alignments,[18] although the relative stereochemistry of swainsonine was determined by X-ray crystallography.[19]

Other polyhydroxyindolizidines isolated from natural sources are lentiginosine (**2**) (8-deoxy-2, 8a-di-*epi*-swainsonie), isolated from the leaves of spotted locoweed, *Astragalus lentiginosus* var. *diphysus*,[20] 2-*epi*-lentiginosine (**3**) (8-deoxy-8a-*epi*-swainsonine), isolated from *Rhizoctonia lenguminicola*[21] (this alkaloid has been demonstrated to be a biosynthetic precursor to swainsonnine[1d]) and castanospermine (**4**), isolated from the seeds of the Australian legume *Castanospermum australe*[22] and the dried pod of *Alexa leiopetala*.[23]

Lentiginosine (**2**) is a selective and powerful inhibitor of amyloglucosidases found within the class of imino-sugars and their derivatives,[20a,24] and is twice as powerful as castanospermine (**4**). Castanospermine (**4**) is a potent competitive and reversible inhibitor of several glucosidases[25] and has potential for the treatment of cancer[26] and viral infections,[27] including HIV-1.[28]

There is no clear knowledge of the particular glycosidases mechanism(s), although there are two generally accepted pathways which involve acid-catalysed cleavage of the exocyclic (anomeric) carbon–oxygen bond giving a cyclic oxonium ion,[29] and the endocyclic (ring) carbon–oxygen bond resulting in an acyclic oxonium ion.[30] For mannosidase inhibitors, it has been suggested that correlation with mannofuranose is important,[31] but other calculations indicate that structures similar to the mannopyranosyl cation, not mannose itself, exhibit the more potent activity.[32]

The high potential for using these alkaloids in a wide range of biological applications makes them attractive targets for synthesis.[33] In particular, the preparation of unnatural epimers and other structural analogues of (−)-swainsonine (**1**) has created much interest since the biological activity of these compounds varies substantially with the number, position and stereochemistry of the hydroxy groups in the indolizidine skeleton. A number of syntheses of stereoisomers of 1,2,8-trihydroxyindolizidines and other analogues have been developed and they are reviewed here. Most of these target (−)-swainsonine (**1**) itself, reflecting the importance placed upon this molecule. Discussion of the various compounds is limited to trihydroxy analogues sharing the hydroxy groups of (**1**) in at least in two positions, 3-(hydroxymethyl)swainsonine analogues, and mono-deoxy and 1,2,7,8-tetrahydroxyindolizidines. Compounds such as castanospermine and 6,7,8-trihydroxyindolizidines are not discussed.

2. Syntheses of 1,2,8-Trihydroxyindolizidines

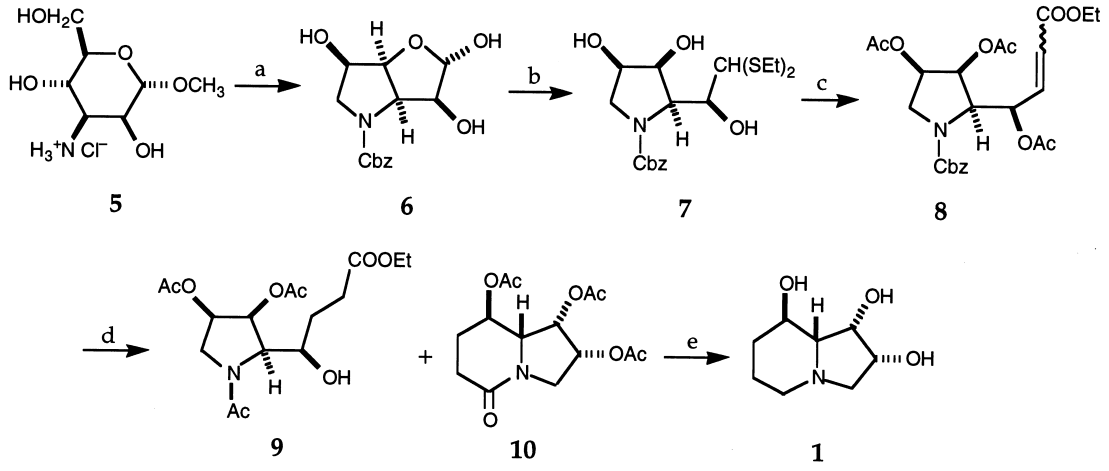
Due to their 'sugar-like' structure it is not surprising that many syntheses of 1,2,8-trihydroxyindolizidines utilise carbohydrate starting materials. Hexoses and their derivatives are often used with four chiral centres required in the product. There is also a strategy based on the utilisation of pentoses. Many syntheses of 1,2,8-trihydroxyindolizidines also employ non-carbohydrate starting materials.

2.1. Syntheses from carbohydrate starting materials

The first total synthesis of (−)-swainsonine (**1**) established its absolute stereochemistry (1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyindolizidine (Scheme 1).[34]

Compound **6** was obtained from the amino hydrochloride **5** over five steps in ~31% overall yield. Reaction of **6** with ethanethiol afforded the dithioacetal **7**. Acetylation of **7** was followed by $HgCl_2$–$CdCO_3$ oxidation and subsequent treatment with $Ph_3P{=}CHCO_2Et$ to give **8** as a non-separable 1:1 mixture of *E* and *Z* isomers. Hydrogenation of the *E*/*Z*-mixture **8** gave a 1:1 mixture of the lactam **10** and the product **9** and, after chromatographic separation, the lactam **10** was converted in two steps to (−)-swainsonine (**1**).

A similar methodology was applied with some modifications to prepare (−)-swainsonine (**1**) (Scheme 2).[35] The mesylate **11** was transformed into the dithioacetal **12** over six steps in 33% overall yield. Benzylation of **12** followed by detritylation and tosylation gave the pyrrolidine derivative **13**. Mercury(II) chloride oxidation of **13** and subsequent Horner–Emmons reaction furnished a mixture of *E*- and



Scheme 1. (a) 1—$NaHCO_3$, 1:1 EtOH–H_2O, CbzCl, rt, 2 h; 2—TsCl, pyr, rt, 36 h, 82% two steps; 3—H_2, 10% Pd on C, EtOH, then NaOAc, reflux, 8 h; 4—$NaHCO_3$, CbzCl, 2 h, 73% two steps; 5—HCl, 95–100°C, 16 h, 52%; (b) EtSH, conc. HCl, 74%; (c) 1—acetylation, 73%; 2—$HgCl_2$, $CdCO_3$, acetone, reflux, 30 min, 96%; 3—$Ph_3P{=}CHCO_2Et$, CH_3CN, reflux, 15 min, 86%; (d) H_2, 10% Pd on C, 2 h, **9** (25%) and **10** (25%); (e) 1—BMS, THF, under N_2, 71–94%; 2—$NaOCH_3$, CH_3OH, 3 h, 100%.

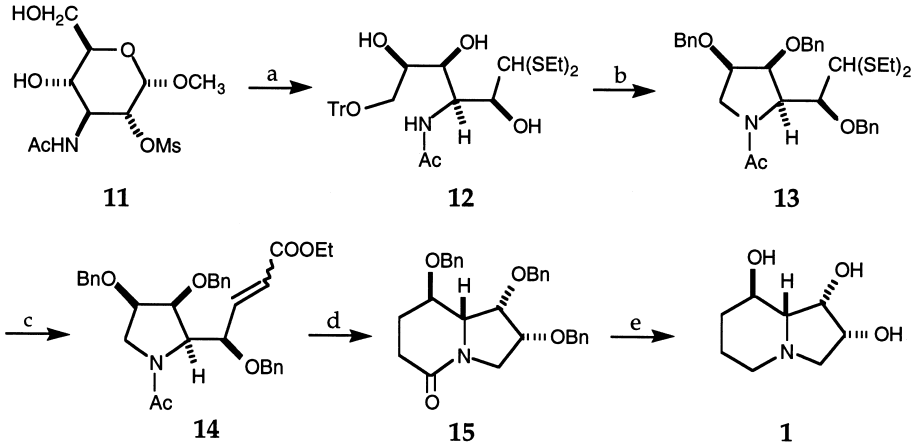
Z-**14** in a ratio of ~40:1. Catalytic hydrogenation of *E*- and *Z*-**14** followed by prolonged heating in aqueous ethanolic 15 M KOH in a sealed tube at 90°C afforded the lactam **15**. This was reduced with lithium aluminum hydride followed by debenzylation to afford (−)-swainsonine (**1**).

Another synthesis of (−)-swainsonine (**1**) was accomplished utilising D-mannose as the starting material (Scheme 3).[36] D-Mannose was transformed into the manno-azide (**16**) in eight steps, including double inversion at *C*-4, in 46% overall yield. Oxidation of the free hydroxyl group in **16** with PCC followed by treatment with $Ph_3P{=}CHCHO$ gave **17** in 60–65% yield and the dienal **19** in 12% yield, which were separated by chromatography. Prolonged hydrogenation of **17** and **18** followed by removal of the isopropylidene protecting group in **21** afforded (−)-swainsonine (**1**).

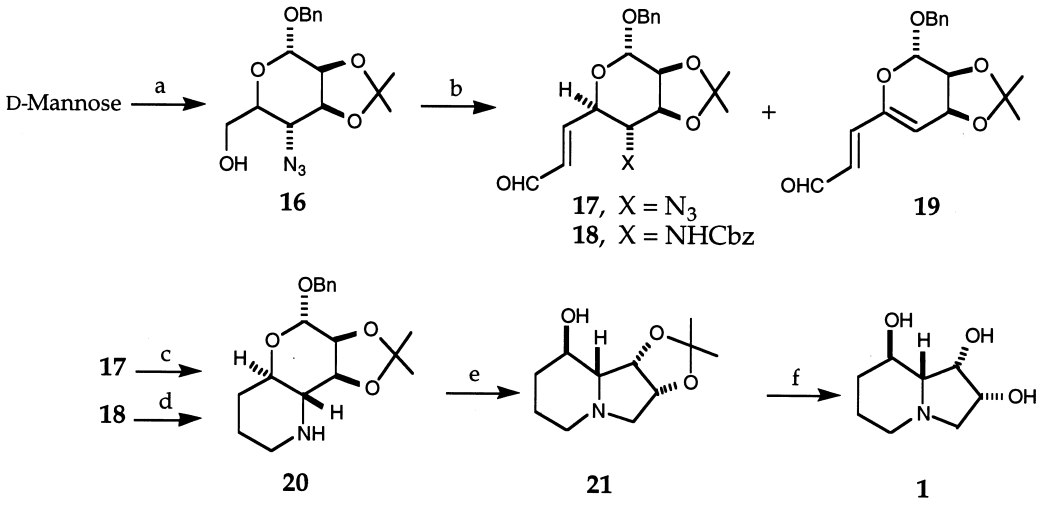
An attempt was made to synthesise the intermediate **20** utilising benzyl α-D-mannopyranoside (Scheme 4).[37]

The *p*-toluenesulfonate **23** was obtained from benzyl-α-D-mannopyranoside (**22**) in four steps in 55% overall yield. Two different synthetic routes were applied to **23** to produce **25**. Compound **23** underwent nucleophilic displacement with allylmagnesium chloride followed by desilylation and Swern oxidation to give **24**. Lemieux–Johnson degradation of **24** followed by treatment with diazomethane afforded compound **25** in 78% overall yield from **23**. Alternatively, compound **25** could be obtained from **23** in 56% yield in five steps comprising S_N2 displacement with sodium diethylmalonate to give **26**, followed by decarboxylation to give **27**, saponification, esterification and finally oxidation. Reduction of **25** followed by triflation and S_N2 displacement of triflate with sodium azide afforded the azide ester **28** and compound **29**. Hydrogenolysis of **28** followed by $LiAlH_4$ reduction of the lactam **30** gave **20**, in 48% overall yield from **25**.

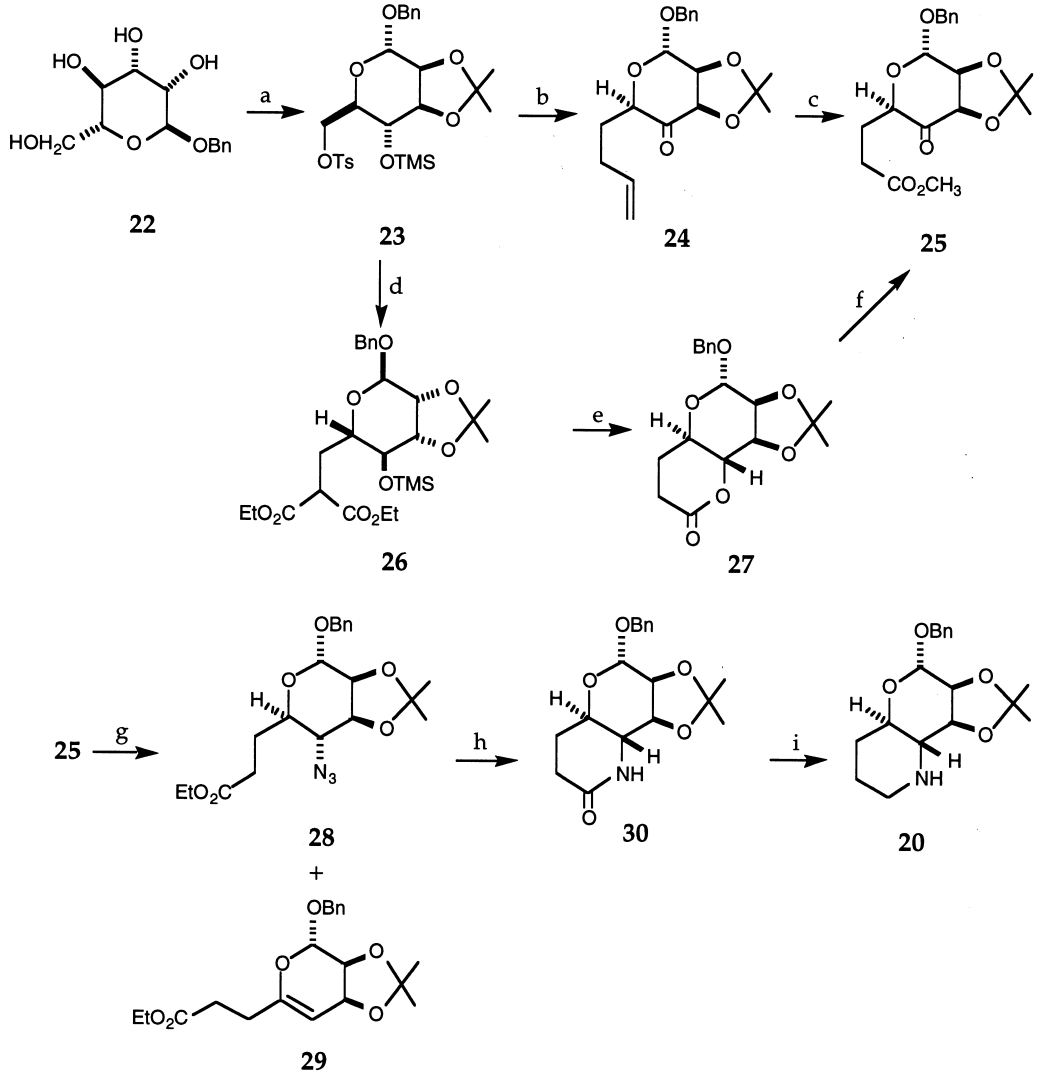
A similar synthesis of (−)-swainsonine (**1**), although



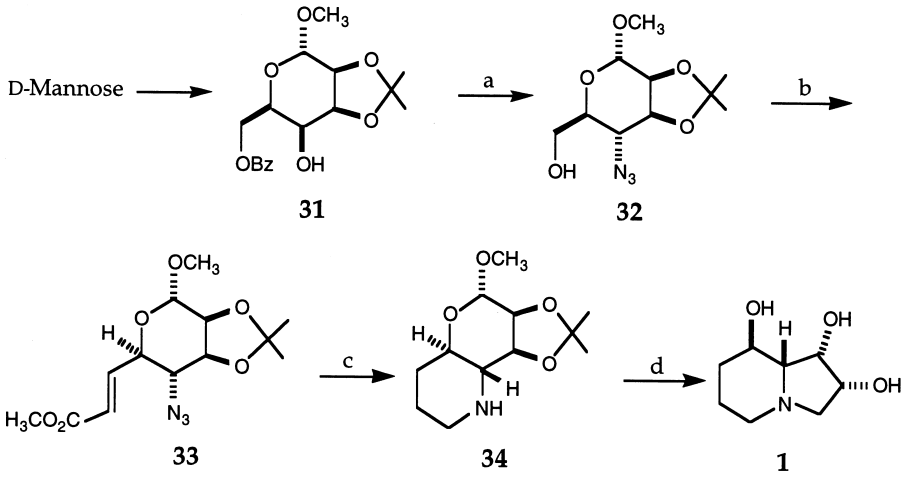
Scheme 2. (a) 1—NaOAc, $CH_3OCH_2CH_2OH$, reflux, 25 h, 61%; 2—2 M HCl, reflux, 13 h; 3—Ac_2O, pyr, 98%; 4—$NaOCH_3$, CH_3OH; 5—EtSH, HCl; 6—TrCl, pyr, DMAP, 55% three steps; (b) 1—BnBr, NaH, DMF; 2—TsOH·H_2O, CH_3OH, 35% two steps; 3—TsCl, pyr, 77%; 4—1,4-dioxane, NaOH, reflux, 30 min, 93%; (c) 1—$HgCl_2$, Ca_2CO_3, CH_3CN; 2—$Et_2P(O)CH_2CO_2Et$, NaH, THF, 4 h, 75% two steps; (d) 1—H_2, Raney nickel, 2 h, 94% for *E* and 70% for *Z*; 2—15 M KOH, EtOH, sealed tube, 90°C, 6 days, 54%; (e) 1—$LiAlH_4$, THF, reflux, 5 h, 74%; 2–20% $Pd(OH)_2$ on C, cyclohexene, reflux, 44 h, 72%.



Scheme 3. (a) 1—BnOH·HCl, 83%, 2—TBDPSCl, imidazole, DMF, rt, 6 h, 89–97%; 3—DMP, CSA, acetone, 100%; 4—PCC, CH_2Cl_2, rt, 2 h; 5—$NaBH_4$, EtOH, 81% two steps; 6—Tf_2O, pyr, CH_2Cl_2, −50→20°C; 7—NaN_3, DMF, rt, 68% two steps; 8—Bu_4NF, THF, rt, 4 h; (b) 1—PCC, 3 Å M.S., CH_2Cl_2, 45 min; 2—$Ph_3P{=}CHCHO$, 45 min, 68%, two steps; (c) H_2, 10% Pd on C, CH_3OH, 6 h; (d) 1—H_2, Pd-black, CH_3OH, 48 h; (e) H_2, Pd-black, AcOH, rt, 3 days, 60–87% for c, d and e; (f) TFA, D_2O, rt, 50 h, 74%.



Scheme 4. (a) 1—TsCl, pyr, rt, 75%; 2—DMP, NSA, acetone, rt, 94%; 3—TMSCl, Et_3N, THF, rt, 94%; (b) 1—allylMgBr, ether, 88%; 2—$Bu_4NF{\cdot}3H_2O$, THF, rt, 98%; 3—$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C, 95%; (c) 1—$NaIO_4$, $RuO_2{\cdot}H_2O$, CCl_4, CH_3CN, H_2O, rt, 15 h, 96%; 2—CH_2N_2, Et_2O, 100%; (d) $NaCH(COOEt)_2$, toluene, reflux, 87%; (e) DMSO, NaCl, H_2O, 145°C, 15 h, 70%; (f) 1—1 M KOH, CH_3OH, rt, 96%; 2—PCC, CH_2Cl_2, 15 h, rt, 95%; (g) 1—$NaBH_4$, EtOH, rt, 97%; 2—Tf_2O, pyr, −20°C, 88%; 3—NaN_3, DMF, 15 h, rt, 97%; (h) 1—H_2, Pd-black, rt, 6 h; 2—toluene, reflux, 1 h, 97% two steps; (i) $LiAlH_4$, THF, rt, 15 h, 89%.



Scheme 5. (a) 1—MsCl, pyr, 88%; 2—TFA, CH_3OH, rt, 30 min, 98%; 3—NaN_3, DMF, 110–115°C, 3 h, 77%; 4—TsOH, DMP, acetone; 5—KOH, CH_3OH, 98%; (b) 1—pyr-SO_3, DMSO, Et_3N, 10 min; 2—$Ph_3P{=}CHCO_2CH_3$, THF, rt, 4 days, 56% two steps; (c) 1—H_2, Pd-black CH_3OH; then CH_3OH, reflux, 12 h, 34%; 2—BH_3, THF; ice-cooling, 30 min, 78%; (d) 1—BCl_3, CH_3Cl, −78°C, 1.5 h→rt, 16 h; 2—$NaCNBH_3$, 1:1 H_2O–CH_3OH, 0.1 M HCl, rt, 24 h, 1.8%.

relatively long and giving very low yields, has been accomplished (Scheme 5).[38]

Oxidation of the azide **32**, derived from 6-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-talopyranoside (**31**) in five steps in 65% yield, followed by Wittig olefination, furnished the uronate *E*-**33** in 56% yield. Hydrogenation of **33** in the presence of palladium black, followed by refluxing in methanol and subsequent reduction of the lactam formed, afforded the cyclic amine **34** in 27% yield. Demethylation of **34** with boron trichloride, followed by reduction with sodium cyanoborohydride, gave (−)-swainsonine (**1**), but in only 1.8% yield.

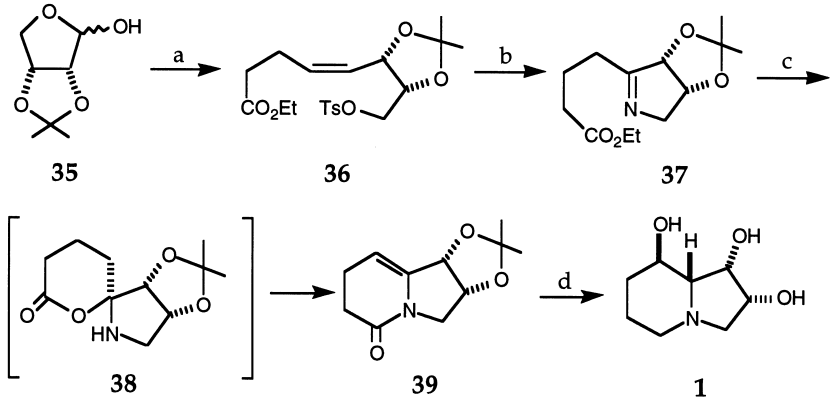
A short enantioselective synthesis of (−)-swainsonine (**1**) has been reported in seven steps from 2,3-*O*-isopropylidene-D-erythrose (**35**) in an overall yield of 35% (Scheme 6).[39a] The olefinic ester **36**, prepared from **35** in two steps, underwent tosyl displacement with NaN_3 and subsequently 1,3-dipolar cycloaddition to afford the imino ester **37** in 81% overall yield. Mild hydrolysis of **37**, followed by cyclisation in refluxing toluene via the lactone **38**, gave the desired lactam **39**. This was then treated with borane and hydrogen peroxide to produce the swainsonine acetonide as a single diastereomer and concomitant acid hydrolysis gave (−)-swainsonine (**1**).

Two patents[39b,c] describe the synthesis of (−)-swainsonine (**1**) utilising a similar methodology.

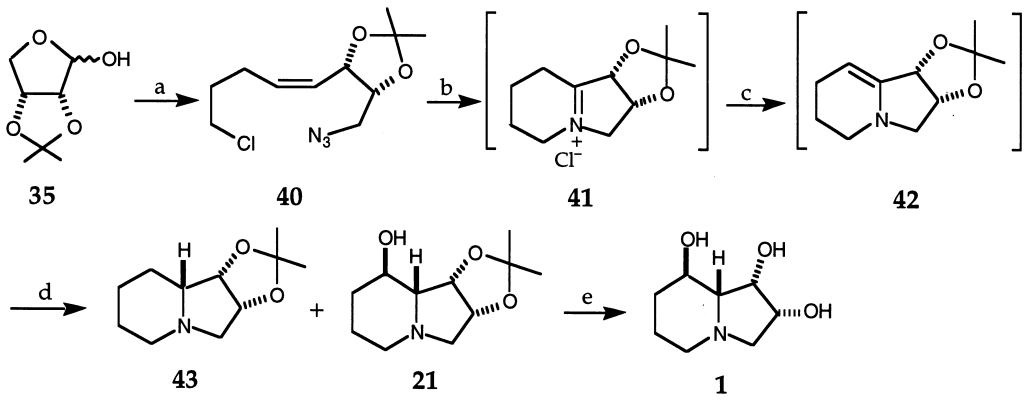
An analogous strategy employing D-erythrose led to the efficient synthesis of (−)-swainsonine (**1**) (Scheme 7).[40]

D-Erythrose was transformed into the azide **40** over three steps. Intramolecular cycloaddition of **40** in refluxing benzene produced the bicyclic iminium ion **41**, which was treated with *t*-butylamine followed by hydroboration of the enamine **42** using $NaOAc/H_2O_2$ to give the β-aminoalcohol **21** as the major product. Aqueous acid hydrolysis of **21** afforded (−)-swainsonine (**1**).

Multigram quantities of pure (−)-swainsonine (**1**) were prepared by reductive double cyclisation of an azide bearing two remote electrophilic sites (Scheme 8).[41a] The commercially available 2,3-*O*-isopropylidene-D-erythronolactone (**44**) was transformed into the allylic alcohol **45** over three steps in 73% overall yield. Johnson orthoester Claisen rearrangement conditions converted the mixture containing



Scheme 6. (a) 1—$EtO_2C(CH_2)_3P^+Ph_3Br^-$, $KN(TMS)_2$, THF, −78→0°C; 2—TsCl, Et_3N, CH_2Cl_2; (b) NaN_3, DMF, 70→100°C; 81% three steps; (c) 1—K_2CO_3, aq CH_3OH, rt, 12 h, 74%; 2—toluene, reflux in Dean–Stark trap, 30 h, 87%; (d) 1—BH_3, THF, 0°C→rt, overnight; then H_2O_2, NaOH, EtOH, reflux, 2 h, 79%; 2—6N HCl, THF, rt, overnight, 85%.



Scheme 7. (a) 1—$ClCH_2CH_2CH_2CH_2P^+Ph_3Br^-$, $KN(TMS)_2$, THF, −78°C→23°C, 2 h; 2—$(PhO)_2P(O)N_3$, PPh_3 $EtO_2CN{=}NCO_2Et$, THF, 23°C, 1 h; (b) PhH, reflux, 26 h; (c) *t*-$BuNH_2$, $KN(TMS)_2$; (d) BH_3–THF, 23°C, 10 h; then NaOAc, CH_3OH, H_2O_2, 23°C, 12 h, **21** (70%), **43** (7%); (e) 1—6N HCl, THF, 23°C, 12 h; 2—IRA-400 ion exchange chromatography, 85%.

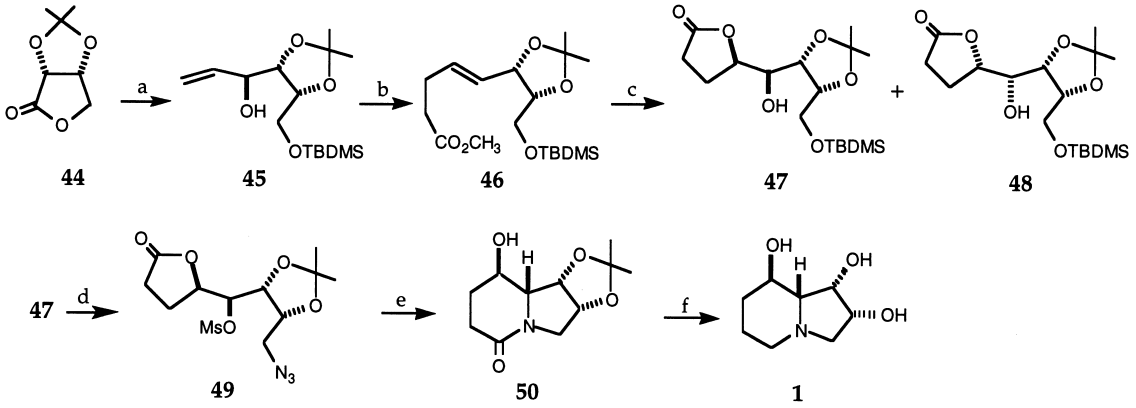
45 into the γ,δ-unsaturated ester **46** which, on Sharpless dihydroxylation, produced the lactones **47** and **48** in 70 and 9% yields, respectively.

After chromatographic separation, removal of the silyl protecting group from the lactone **47** and subsequent mesylation, followed by selective S_N2 displacement of the primary mesylate with sodium azide, the azide **49**, was produced. Hydrogenolysis of **49** followed by treatment with sodium methoxide effected a reductive double cyclisation to give the bicyclic lactam **50** in 75% yield. Reduction of **50** followed by acid hydrolysis gave (−)-swainsonine (**1**) in **20**% overall yield from the lactone **44**.

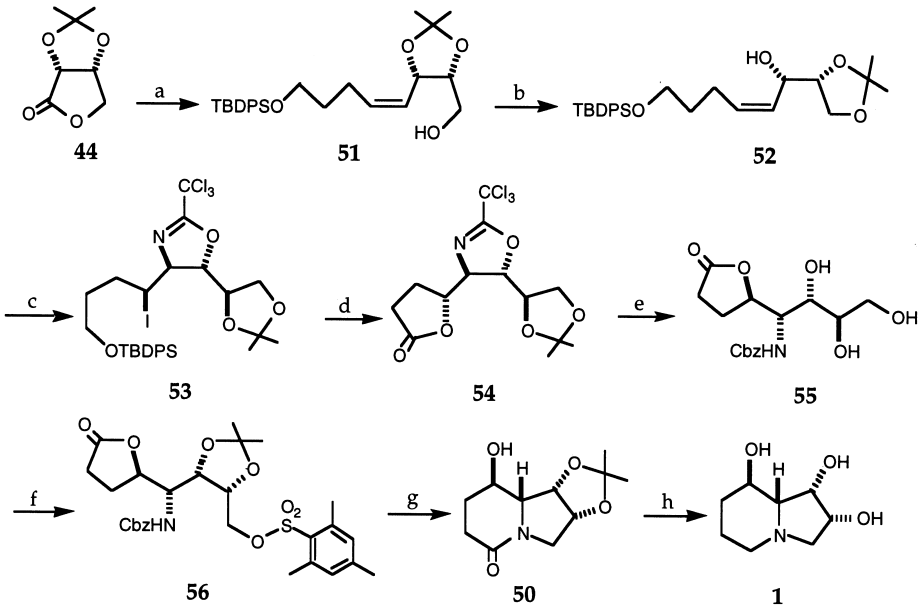
Two patents[41b,c] describe the synthesis of (−)-swainsonine (**1**) utilising a similar route.

The stereoselective iodoamination of a trichloroacetimidate derivative has been used as the key step for the synthesis of (−)-swainsonine (Scheme 9).[42] The lactone **44** was reduced by DIBAL followed by olefination to give a 15:1 mixture of the *cis*- and *trans*-olefin **6** in 82% yield. Rearrangement of the inner acetonide **51** to the outer acetonide **52** was achieved in acetone in the presence of TsOH. The allylic alcohol **52** was converted into the trichloroacetimidate followed by stereoselective iodoamination using iodine monobromide to afford the *trans*-oxazoline **53**. Removal of the silyl group in **53**, followed by oxidation of the primary hydroxyl group to the carboxylic acid, and heating with silver carbonate provided the lactone **54** in 57% overall yield. Complete deprotection of **54** followed by carbamate protection of the amino group generated gave the triol carbamate **55**. Selective sulfonation of the primary hydroxyl group in **55** followed by reaction of the dihydroxy groups with DMP afforded the acetonide **56**, which was hydrogenated to produce the lactam **50**. Reduction of **50** followed by deprotection gave (−)-swainsonine (**1**).

A methodology using an intramolecular cyclisation to an enantiomerically pure cyclic acyliminium ion intermediate in the synthesis of (−)-swainsonine has been developed (Scheme 10).[43] Treatment of D-(−)-lyxose (**57**) with 1-methoxycyclohexene followed by prolonged heating with Ag_2CO_3–Celite in benzene afforded the lactone **58**, which was converted into the hydroxylactam **59** in 32% overall yield from **57**. The formation of the indolizidine ring system was achieved, in 60% yield, by mesylation of

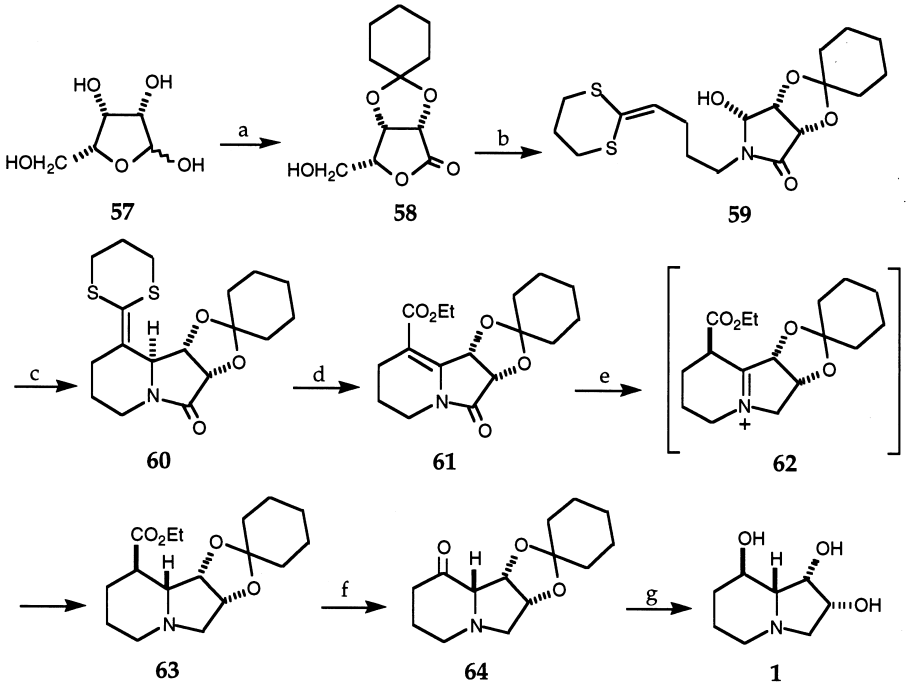


Scheme 8. (a) 1—DIBAL, CH_2Cl_2, −78°C, 2 h; 2—$CH_2{=}CHMgBr$, THF, −78→0°C, 6 h; 3—TBDMSCl, imidazole, THF–DMF, 0°C, 45 min, 73% (*anti*/*syn*=97:3); (b) $CH_3C(OCH_3)_3$, $EtCO_2H$, toluene, reflux, 24 h, 99%; (c) AD-Mix b, *t*-BuOH, $CH_3SO_2NH_2$, H_2O, 0→25°C, 18 h, then separate; (d) 1—Bu_4NF, THF, 0°C, 1.5 h, 84%; 2—MsCl, pyr, DMAP, 2°C, 16 h, 90%; 3—NaN_3, DMSO, 80°C, 36 h, 75%; (e) 1—H_2, $Pd(OH)_2$, CH_3OH, 6 h, 75%; 2—$NaOCH_3$, CH_3OH, reflux, 60 h; (f) 1—BMS, THF, 0°C, 30 min, rt, 2 h, 94%; 2—6N HCl, THF, rt, 12 h, Dowex OH^-, 96%.

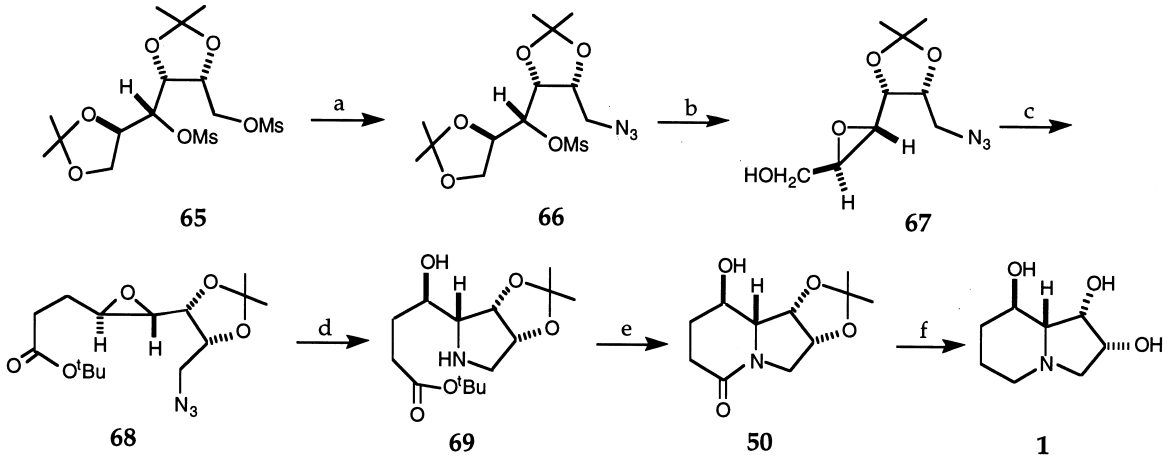


Scheme 9. (a) 1—DIBAL, CH_2Cl_2, −78°C; 2—TBDPSO$(CH_2)_4P^+Ph_3I^-$, *n*-BuLi, HMPA, THF, 0°C, 77% two steps; (b) TsOH, acetone, rt, 93%; (c) 1—Cl_3CCN, DBU, CH_3CN, CH_2Cl_2, 0°C; 2—1 equiv. DBU, IBr, CH_3CN, −60 to −50°C, 85–90%; (d) 1—NH_4F, CH_3OH, 45°C, 90%; 2—Swern oxidation; 3—$NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, aq. *t*-BuOH, rt; 4—Ag_2CO_3, PhH, 65–70°C, 62% three steps; (e) 1—TFA, H_2O, rt; 2—CbzCl, K_2CO_3, CH_3OH, 0°C, 90% two steps; (f) 1—2-mesitylenesulfonyl chloride, Et_3N, CH_2Cl_2, 0°C, 84%; 2—DMP, TsOH, acetone, rt, 97%, (g) H_2, 10% Pd on C, K_2CO_3, rt→reflux, 97%; (h) 1—BMS, THF, rt; 2—H_2O_2, NaOH, reflux, 97%; 3—6N HCl, rt, 92%.

the lactam **59** in the presence of triethyamine. Introduction of a C-8/C-8a double bond, followed by removal of the lactam carbonyl group from **61** with Meerwein's reagent and then treating with sodium cyanoborohydride, led to the correct stereochemistry at the ring junction in the lactam **60**, via reduction of the resultant iminium ion **62** from the less hindered convex face. Conversion of the ester **63** into the unstable C-8 ketone **64** followed by reduction with $NaBH_4$ or $LiAlH_4$ under a variety of conditions gave a mixture of epimers at C-8, favouring the axial alcohol (8-*epi*-swainsonine). Treatment of the ketone **64** with Na/NH_3 however, gave >95% of the desired equatorial alcohol, and removal of the cyclohexylidene ketal afforded (−)-swainsonine (**1**).



Scheme 10. (a) 1—1-methoxycyclohexene, $BF_3{\cdot}OEt_2$, THF, 78%; 2—Ag_2CO_3, Celite, PhH, 65%; (b) 1—H_2NR, CH_3OH; 2—$Pb(OAc)_4$, CH_3CN, 63%; (c) MsCl, Et_3N, CH_2Cl_2; then CH_3CN, 60%; (d) 1—NBS, EtOH, CH_3CN; 2—DBU, THF, 71% two steps; (e) 1—$Et_3O^+BF_4^-$, CH_2Cl_2; 2—$NaCNBH_3$, CH_3OH, 86% two steps; (f) 1—LDA, THF, O_2, 76%; 2—$LiAlH_4$, THF; 3—$NaIO_4$, H_2O; (g) 1—Na/NH_3, H_2O, THF, 45% for g and h; 2—6 M HCl, 95%.



Scheme 11. (a) NaN_3, DMF–H_2O, 62%; (b) 1—aq. CH_3OH, CSA, 56%; 2—saturated methanolic barium methoxide, 95%; (c) 1—Tf_2O, pyr; 2—$LiCH_2CO_2$ *t*-Bu, THF, 60% two steps; (d) H_2, Pd on C, EtOH, 80%; (e) $NaOCH_3$, CH_3OH, reflux, 92%; (f) 1—BMS, 70%; 2—TFA, 86%.

The synthesis of (−)-swainsonine (**1**) has also been achieved from the dimesylate **65**, which is readily available on a large scale from D-mannose (Scheme 11).[44]

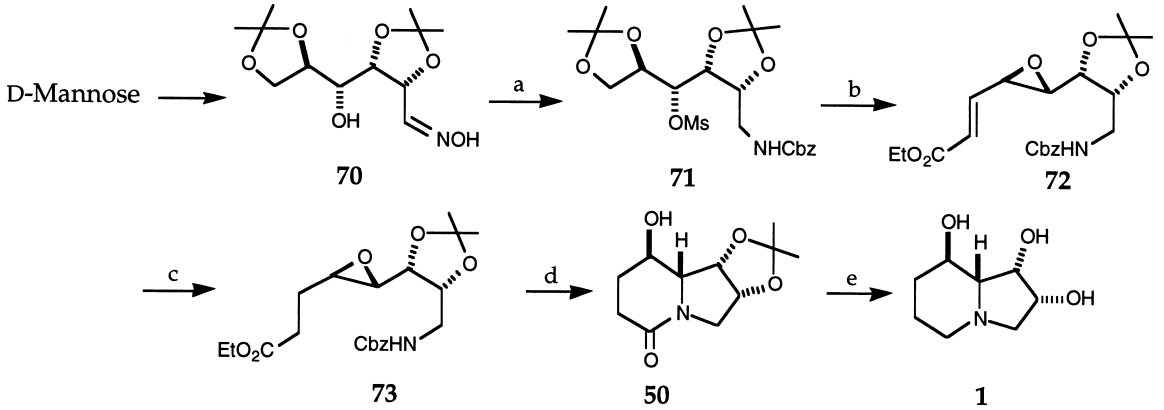
The dimesylate **65** was converted into the moderately unstable 4,5-anhydro-1-azido-1-deoxy-2,3-*O*-isopropylidene-D-talitol (**67**) via azide **66** in three steps. Triflation of the azido epoxide **67** followed by two-carbon elongation with lithium *t*-butyl acetate afforded **68**. Intramolecular double cyclisation of **68** furnished the lactam **50** via ester **69**. Reduction of **50** with borane–dimethyl sulfide complex (BMS) followed by acid hydrolysis gave (−)-swainsonine (**1**).

The synthesis of **1** from 4,5-anhydro-1-azido-1-deoxy-2,3-*O*-isopropylidene-D-talitol (**67**) has also been described in a patent.[45]

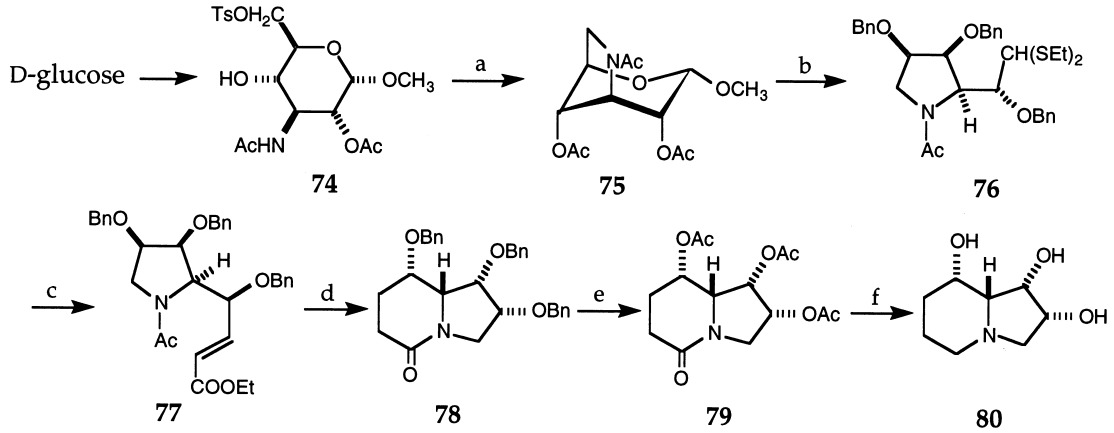
A short enantiospecific synthesis of (−)-swainsonine (**1**) from D-mannose has been achieved by a route involving a double cyclisation and the use of sodium borohydride for reducing the conjugated esters and lactams (Scheme 12).[46] The oxime **70** (obtained from D-mannose) was reduced with lithium aluminium hydride followed by acylation of the resulting amine and treatment with MsCl to produce the mesylate **71**. Partial hydrolysis of **71**, epoxidation, oxidation of the resulting epoxide, and Wittig reaction furnished the desired *trans*-α-β-unsaturated ester **72**, which was reduced smoothly with sodium borohydride to afford **73** in 58% yield. Hydrogenolysis of **73**, followed by refluxing in ethanol, gave the lactam **50**. Reduction of **50** using sodium borohydride and subsequent acid hydrolysis furnished (−)-swainsonine (**1**).

An attempt was made to synthesise of (−)-8-*epi*-swainsonine (**80**) and (−)-1,8-di-*epi*-swainsonine (**88**) (Schemes 13 and 14)[47] utilising a strategy similar to that used previously in the first synthesis of (−)-swainsonine (**1**) in Scheme 1.

Compound **74** (obtained from D-glucose) was heated in DMF in the presence of NaH followed by acetylation to give the acetylimino derivative **75** in 68% yield. Deacetylation of **75** and subsequent treatment with ethanethiol followed by benzylation afforded **76**. Two-carbon elongation of **76** provided the α,β-unsaturated ester **77**. Hydrogenolysis of **77** followed by intramolecular cyclisation gave the lactam **78** in 35% yield. Removal of the benzyl



Scheme 12. (a) 1—$LiAlH_4$, THF, rt; 2—CbzCl, THF–H_2O, 0°C; 3—MsCl, pyr, 0°C, 95% three steps; (b) 1—TsOH, CH_3OH–H_2O, rt, 3 days; 2—Amberlite IRA-400 (OH^-), 43%, recovery 33%; 3—Collins reagent, CH_2Cl_2, 5°C; 4—$Ph_3P{=}CHCO_2Et$, THF, 0°C, 43% two steps; (c) 10 equiv. $NaBH_4$, 10:1 EtOH–THF, reflux, 1 h, 58%; (d) 1—H_2, 10% Pd on C, EtOH; then EtOH, reflux 4 h, 60%; (e) 1–10 equiv. $NaBH_4$, 10:1 EtOH–THF, reflux 1 h, 60%; 2—6N HCl, THF, rt, 75%.



Scheme 13. (a) 1—NaH, DMF, 100°C, 30 min; 2—Ac_2O, pyr, 12 h, 68%; (b) 1—$NaOCH_3$, CH_3OH; 2—EtSH, HCl, 18 h, rt; 3—BnBr, NaH, DMF, rt, 20 min, 59%; (c) 1—$HgCl_2$, Ca_2CO_3, CH_3CN, H_2O, 4 h; 2—ethoxycarbonylmethylphosphonate, NH, rt, 3 h, 82%; (d) 1—H_2, Raney nickel T-4, 5 h, 86%; 2—KOH, EtOH, sealed tube, 120°C, 14 h; (e) 1—20% $Pd(OH)_2$ on C, EtOH, cyclohexene, reflux, 4 h; 2—Ac_2O, pyr, 84%; (f) 1—BMS, THF, rt, 2 h; 2—$NaHCO_3$, dioxane, 5 h, 64%; 3—HCl, reflux, 3 h, 86%.

protecting groups of **78** and subsequent acetylation furnished the lactam **79**, which was reduced with BMS followed by deprotection to give (−)-8-*epi*-swainsonine (**80**) (Scheme 13).

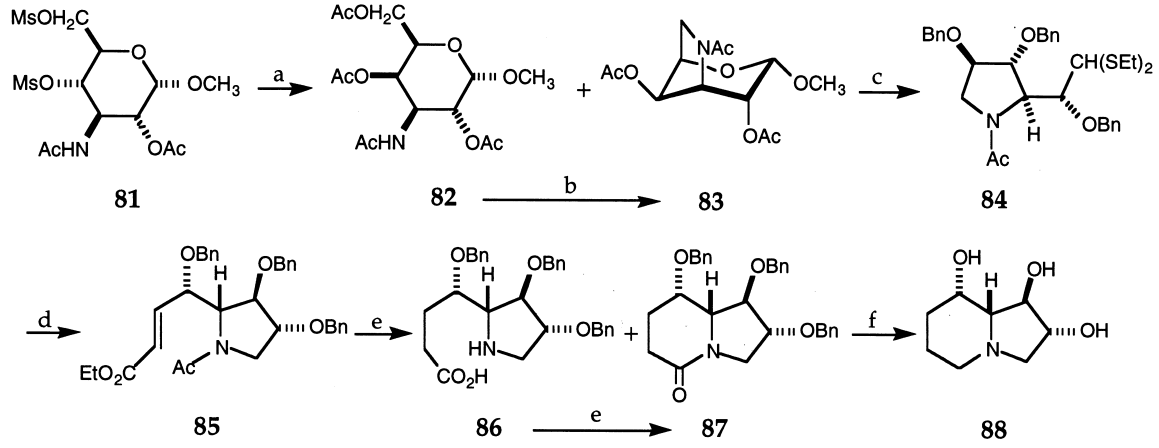
Solvolysis of the acetamide **81** followed by acetylation furnished the acetylimino derivative **83** (68%) and **82** (27%). Compound **82** was converted through compounds **84** and **85** to **83** by four steps in 18% yield. The acetylimine **83** was then converted to (−)-1,8-di-*epi*-swainsonine (**88**) by a series of steps analogous to the synthesis of (−)-8-*epi*-swainsonine (**80**) (Scheme 14).

A strategy similar to that used in the first published synthesis of (−)-swainsonine (**1**) was again applied to the synthesis of (−)-8-*epi*-swainsonine (**80**), except, that the 6-membered ring of the indolizidine framework was formed by an intramolecular Wadsworth–Emmons reaction (Scheme 15).[48]

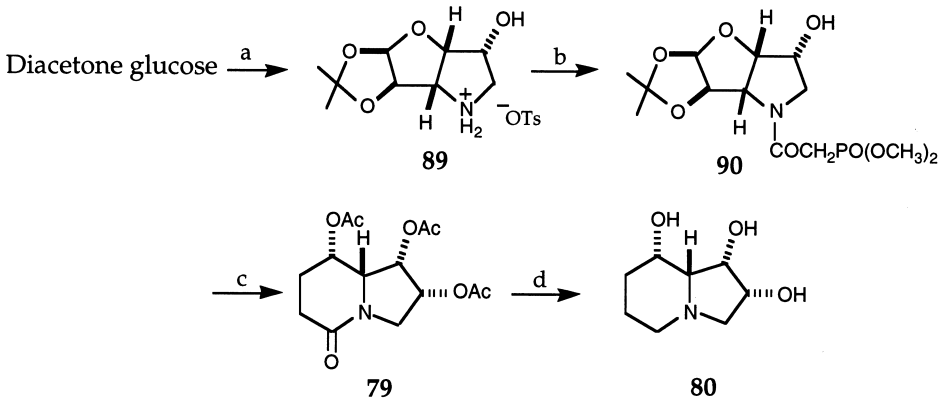
Diacetone glucose was converted into the tosylate salt **89** over seven steps in 53% overall yield. This was treated with dimethylphosphonoacetic acid to give the amide **90**. Acid hydrolysis of **90** and subsequent treatment with potassium carbonate to effect an intramolecular Wadsworth–Emmons reaction, followed by hydrogenation and acetylation, afforded the triacetate **79**. Treatment of **79** with BMS followed by Zemplén deacylation gave (−)-8-*epi*-swainsonine (**80**) in 12% overall yield from diacetone glucose.

3-Azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**91**) (obtained from D-glucose) was converted into (−)-2,8-di-*epi*-swainsonine (**96**) and (−)-8-*epi*-swainsonine (**80**) via a one-step cyclisation of the intermediates **92** and **97**, respectively, in a very low overall yield (Schemes 16 and 17).[49]

Mesylation of the azide **91** followed by deprotection of the isopropylidene group and olefination gave the intermediate **92**. Hydrogenation of **92** afforded **94** and **93**. Reduction of the lactam **94** followed by mesyl displacement with sodium benzoate afforded compound **95**, subsequent removal of the



Scheme 14. (a) 1—NaOAc, aq 90% 2-methoxyethanol, reflux, 6 h; 2—Ac_2O, pyr; (b) 1—$NaOCH_3$, CH_3OH, 30 min, rt; 2—TsCl, pyr, 10 h, −17→−10°C; 3—NaH, DMF, 100°C, 3 h; 4—Ac_2O, pyr; (c) 1—$NaOCH_3$, CH_3OH; 2—EtSH, HCl, 18 h, rt; 3—BnBr, NaH, DMF, rt, 20 min, 56%, three steps; (d) 1—$HgCl_2$, Ca_2CO_3, CH_3CN, H_2O, 4 h; 2—ethoxycarbonylmethylphosphonate, NaH, rt, 52% (e) 1—H_2, Raney nickel T-4, 3 h, 86%; 2—EtOH, KOH, 120°C sealed tube, 10 days, **86** (62%) and **87** (34%); (f) 1—20% $Pd(OH)_2$ on C, EtOH, cyclohexene, reflux, 4 h; 2—Ac_2O, pyr, 84%; 3—BMS, THF, rt, 2 h; 4—$NaHCO_3$, dioxane, 5 h, 64%; 5—HCl, reflux, 3 h, 55% three steps.



Scheme 15. (a) 1—Oxidation; 2—reduction; 3—Tf_2O, pyr; 4—NaN_3, DMF, 50°C; 5—mild acid hydrolysis; 6—TsCl, pyr, −10°C; 7—H_2, Pd-black, EtOH, 53% seven steps; (b) *N,N*-dicyclohexylcarbodiimide, $(CH_3O)_2P(O)CH_2CO_2H$, DMF, Et_3N, rt, 8 h, 87%; (c) 1—50% aq TFA, 50°C, 1 h; 2—K_2CO_3, 18-crown-6, DMF, 12 h; 3—H_2, Pd-black, EtOH, 1 h; 4—Ac_2O, pyr, 47% four steps; (d) 1—BMS, THF, rt, 1 h, 70%; 2—$NaOCH_3$, CH_3OH, 50°C, 2 h, 80%.

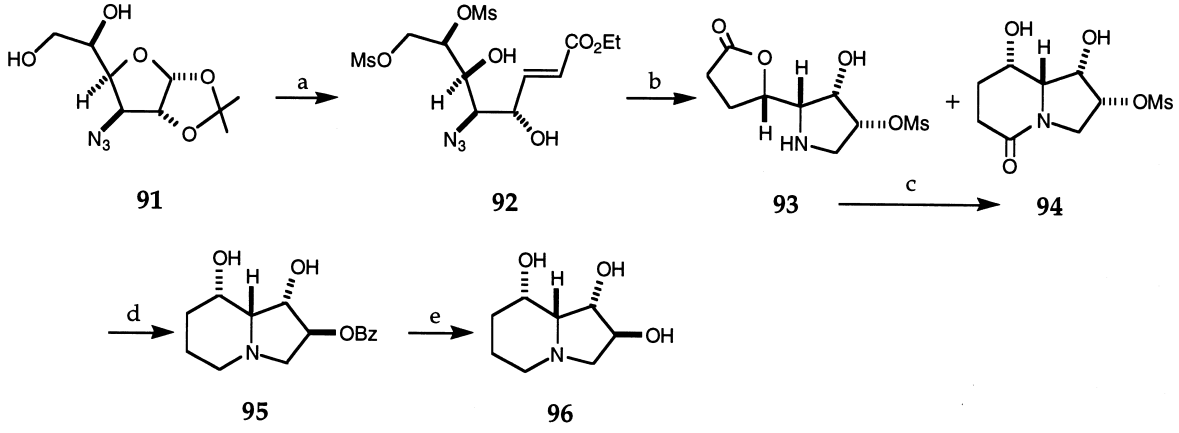
benzoyl group afforded (−)-2,8-di-*epi*-swainsonine (**96**). Partial mesylation of **91** to **97** and then following similar steps afforded (−)-8-*epi*-swainsonine (**80**).

Similar strategies were used to synthesise (−)-8,8a-di-*epi*-swainsonine (**103**) (Scheme 18),[50] (−)-8a-*epi*-swainsonine (**108**) (Scheme 19)[51] and (−)-2,8a-di-*epi*-swainsonine (**111**) (Scheme 20)[50] utilising the same starting material.

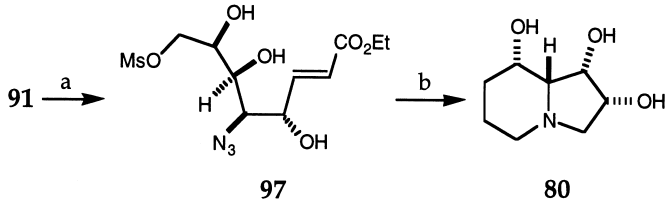
The synthesis of (−)-8,8a-di-*epi*-swainsonine (**103**) (Scheme 18) involved conversion of the inseparable olefinic mixture **99** (derived in six steps from the azide **98** in 39% overall yield) to the corresponding partially separable isopropylidene derivatives, which were reduced and then desilylated with fluoride ion to furnish the 2-piperidone derivative **100**. This was converted to the lactam **101** via two different routes in 41 and 67% overall yields. S_N2 Displacement of the mesyloxy group with NaOBz effected the inversion at C-8 of the lactam **101**, followed by reduction of compound **102** with BMS and, finally, complete deprotection furnished (−)-8,8a-di-*epi*-swainsonine (**103**).

The azide **98** (obtained from D-glucose) was converted to the azide **104** in five steps in 62% overall yield. Wittig olefination of **104** gave a 1:1 mixture of *E*- and *Z*-**105** in 54% yield. Hydrogenation of *E*-**105** and *Z*-**105** in the presence of Raney nickel afforded **106** in 67 and 73% yields, respectively. Intramolecular cyclisation of **106** afforded **107**. Reduction of **107** followed by debenzylation with iodotrimethylsilane gave (−)-8a-*epi*-swainsonine (**108**) (Scheme 19).

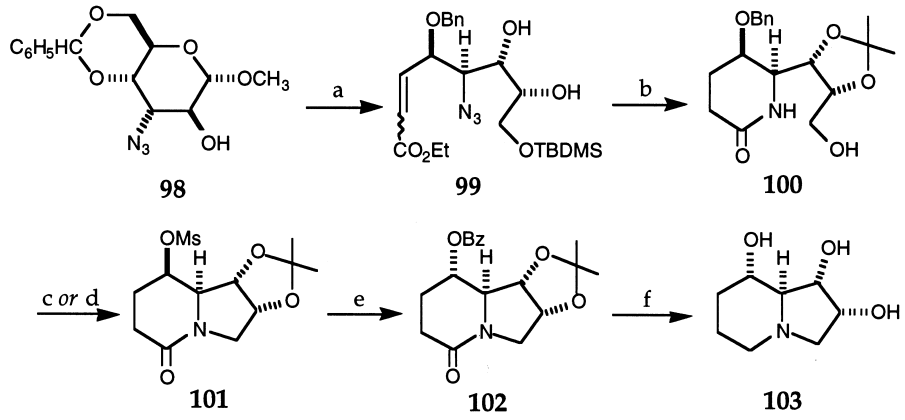
The (−)-8a-*epi*-swainsonine (**108**)[51] exhibited a 93%



Scheme 16. (a) 1—MsCl, pyr, 78%; 2—9:1 TFA–H_2O, rt, 5.5 h; 3—$Ph_3P{=}CHCO_2Et$, THF, reflux, 2 h, 71%, two steps; (b) H_2, 10% Pd on C, CH_3OH, **93** (30%) and **94** (19%); (c) 1:4 DMF–EtOH, reflux. 89%; (d) 1—$(TMS)_2NH$–TMSCl;2—BMs, THF, reflux, 28% two steps, 3—BzONa, DMF, 120°C, 54%; (e) $NaOCH_3$, CH_3OH, rt, 38%.



Scheme 17. (a) 7.5%; (b) 2.3%.



Scheme 18. (a) 1—NaH, DMF, BnBr, rt, 1 h, 94%; 2—80% aq AcOH, 100°C, 4 h; 3—Ac_2O, H_2SO_4, rt, 4 h; 4—$NaOCH_3$, CH_3OH, 82% three steps; 5—TBDMSCl, pyr, Et_3N, 3 h, 85%; 6—$Ph_3P{=}CHCO_2Et$, PhH, reflux, 3 h, 60%; (b) 1—DMP, acetone, CSA, 2 h, 84%; 2—H_2, Raney nickel W-4, EtOH, 36 h; 3—Bu_4NF, THF, 4 h, from *E*-isomer 82%, from *Z*-isomer 77%; (c) 1—MsCl, pyr, 40°C, 3 h, 77%; 2—20% $Pd(OH)_2$ on C, cyclohexene, EtOH, reflux, 14 h, 64%; 3—MsCl, pyr, 4 h 83%; (d) 1—20% $Pd(OH)_2$ on C, cyclohexene, EtOH, reflux, 12 h; 2—MsCl, pyr, 35°C, 5 h, 64%; 3—K_2CO_3, H_2O, dioxane, 90°C, 2 h 67% three steps; (e) NaOBz, DMF, 140°C, 30 min, 84%; (f) 1—BMS, THF, 0°C→rt, 2 h; then 10% aq $NaHCO_3$, 76%; 2—1 M HCl, reflux, 30 min, 84%.

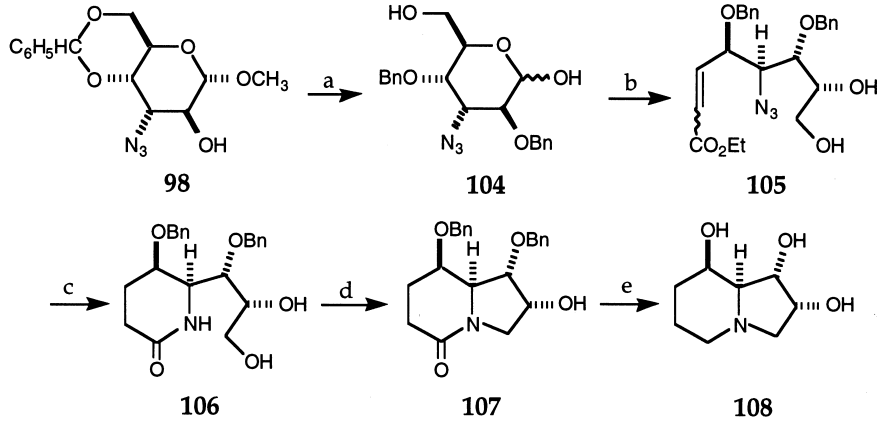
inhibition of human α-D-mannosidase at 1 mM concentration and at pH 4. Under the same conditions, (−)-swainsonine (**1**) showed a 99% inhibition of this enzyme.

O-Sulfonylation of **106** with excess methanesulfonyl chloride gave the 2-*O*-methyl derivative **109**. Inversion of the mesyloxy group in **109** with benzoate anion followed by debenzoylation furnished compound **110** which was similarly converted into (−)-2,8a-di-*epi*-swainsonine (**111**) (Scheme 20).[50]

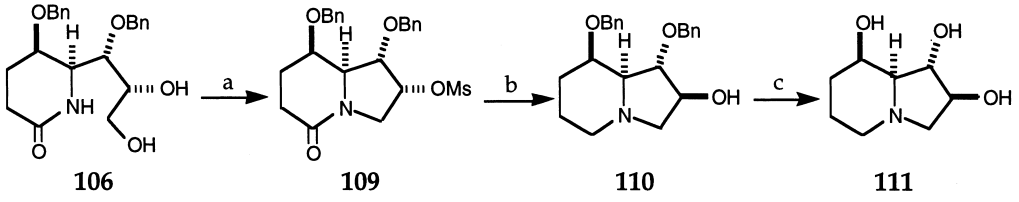
A methodology utilising 2,3-*O*-isopropylidene-L-erythrose (**112**) for the divergent syntheses of (−)-8a-*epi*-(**108**), (−)-8-*epi*-(**80**) and (−)-8,8a-di-*epi*-swainsonine (**103**) has been developed by Kim and Cha (Schemes 21–24).[52]

2,3-*O*-Isopropylidene-L-erythrose (**112**) was converted in 50–60% overall yield to **114** via **113a** or **115** via **113b** in five steps each, including condensation with hydroxylamine, reduction, protection, Swern oxidation and Wittig reaction (Scheme 21).

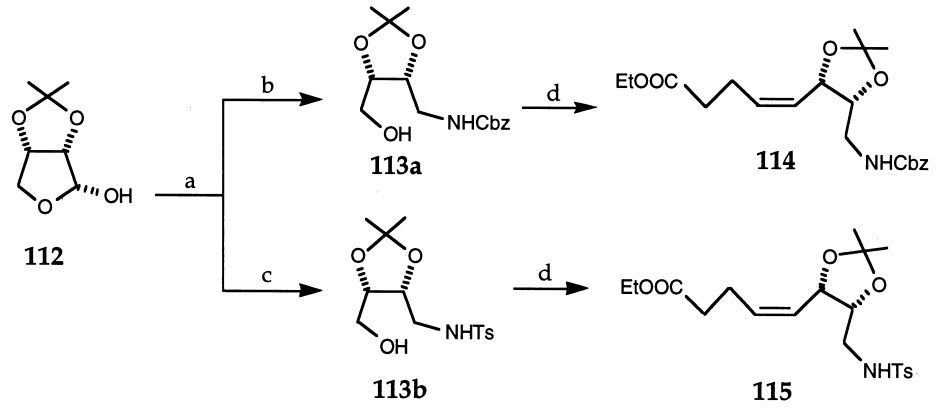
Epoxidation of **114** with *m*CPBA gave a 1:1 mixture of the epoxides **116** and **117** in 86% total yield. After separation of these structural isomers by chromatography, each epoxide underwent an intramolecular double cyclisation to give the



Scheme 19. (a) 1—1:1 AcOH–H_2O, 100°C; 2—TrCl, pyr, DMAP; 3—BnBr, NaH, DMF, 77% three steps; (b) 1—Ac_2O, H_2SO_4, 0°C; 2—$NaOCH_3$, CH_3OH, 80% two steps; (c) $Ph_3P{=}CHCO_2Et$, PhH, reflux, 54%, *Z*/*E* 1:1; (d) H_2, Raney nickel; 67% for *E*-isomer, 73% for *Z*-isomer; (e) TsCl, pyr, DMAP, 70–100°C, 10 h, 60%; (f) 1—BMS, THF, rt; then pyr, 84%; 2—iodotrimethylsilane, $CHCl_3$, 75%.



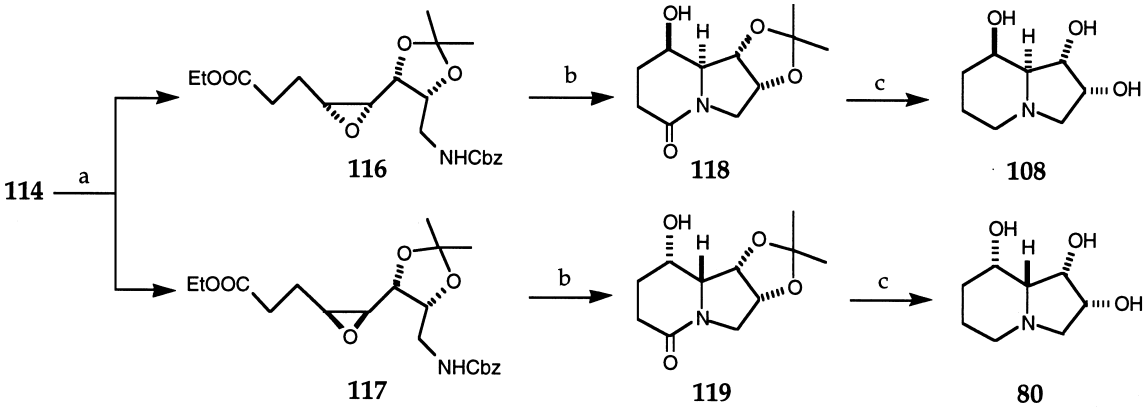
Scheme 20. (a) MsCl, pyr, 24 h, 64%; (b) 1—NaOBz, DMF, reflux, 3.5 h, 86%; 2—$NaOCH_3$, CH_2Cl_2, 0°C, 5 h; then rt, 4 h, 62%; (c) 1—BMS, THF, 0°C, 2 h, 76%; 2—iodotrimethylsilane, $CHCl_3$, 15 h; then CH_3OH, 2 h, 88%.



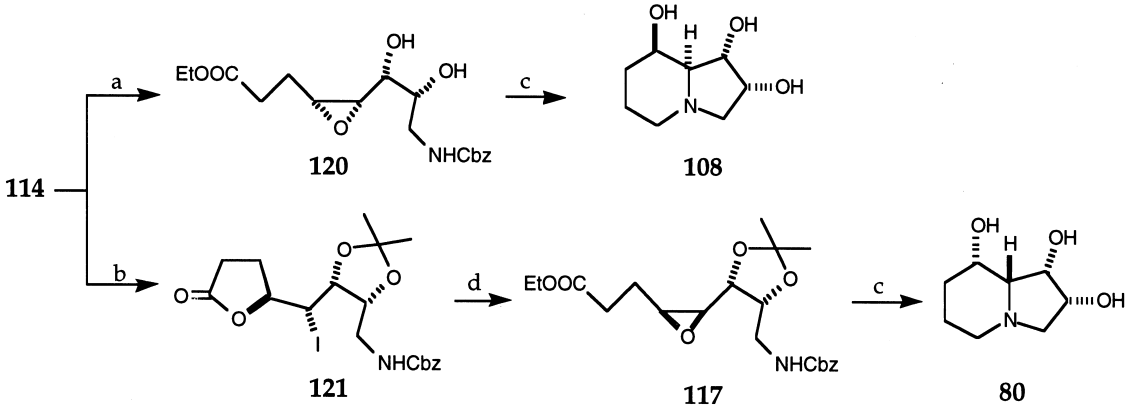
Scheme 21. (a) 1—$HONH_2HCl$, pyr, CH_3OH, 25°C; 2—$LiAlH_4$, THF, reflux, 3 h; (b) CbzCl, aq. $NaHCO_3$, THF, 25°C, 81% two steps; (c) TsCl, $NaHCO_3$, aq THF, 25°C, 54% for a and c; (d) 1—Swern oxidation; 2—$EtO_2C(CH_2)_3P^+Ph_3Br^-$, $KN(TMS)_2$, THF, −78→0°C, 50–60%.

lactams **118** and **119** followed by lactam reduction and acid hydrolysis to afford the desired alkaloids, (−)-8a-*epi*-swainsonine (**108**) and (−)-8-*epi*-swainsonine (**80**) in 50–60% overall yield from **116** and **117**, respectively (Scheme 22).

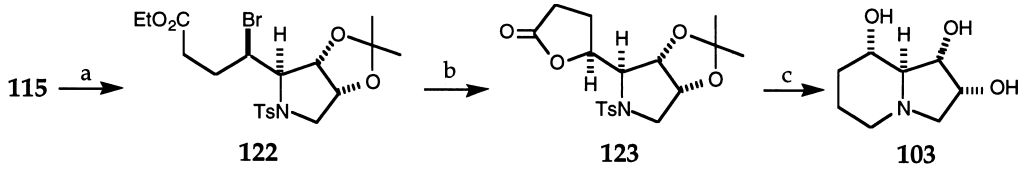
Good stereocontrol was exhibited in the acetal deprotection of **114** followed by epoxidation of the resulting diol to afford the epoxide **120** in a 5:1 diastereoselectivity. This was converted to the alkaloid, (−)-8a-*epi*-swainsonine (**108**), in four steps. On the other hand, basic hydrolysis of the ester **114**, followed by halolactonization of the resulting acid, afforded the lactone **121** in a 5:1 mixture of epimers. Conversion of **121** into the epoxide **117** was followed by a double cyclisation reaction to afford the lactam **119**, which was converted into (−)-8-*epi*-swainsonine (**80**) as described above (Scheme 23).



Scheme 22. (a) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 25°C, 24 h, 86%; (b) 1—H_2, 10% Pd on C, EtOH, 25°C; 2—EtOH, reflux, 80–90%; (c) 1—BH_3–THF, reflux, 4 h; 2—6N HCl, THF, 25°C, 83%.



Scheme 23. (a) 1—PPTS, CH_3OH, 25°C, 72 h, 90%; 2—*m*CPBA, $NaHCO_3$, CH_2Cl_2, 25°C, 24 h; (b) 1—K_2CO_3, 2:1 CH_3OH–H_2O, 25°C, 24 h, 84–90%; 2—I_2, $NaHCO_3$, CH_3CN, 0°C, 24 h, 60–90%; (c) 1—H_2, 10% Pd on C, EtOH, 25°C; 2—EtOH, reflux; 3—BH_3–THF, reflux, 4 h; 4—6N HCl, THF, 25°C; (d) K_2CO_3, EtOH, 25°C, 24 h, 88%.



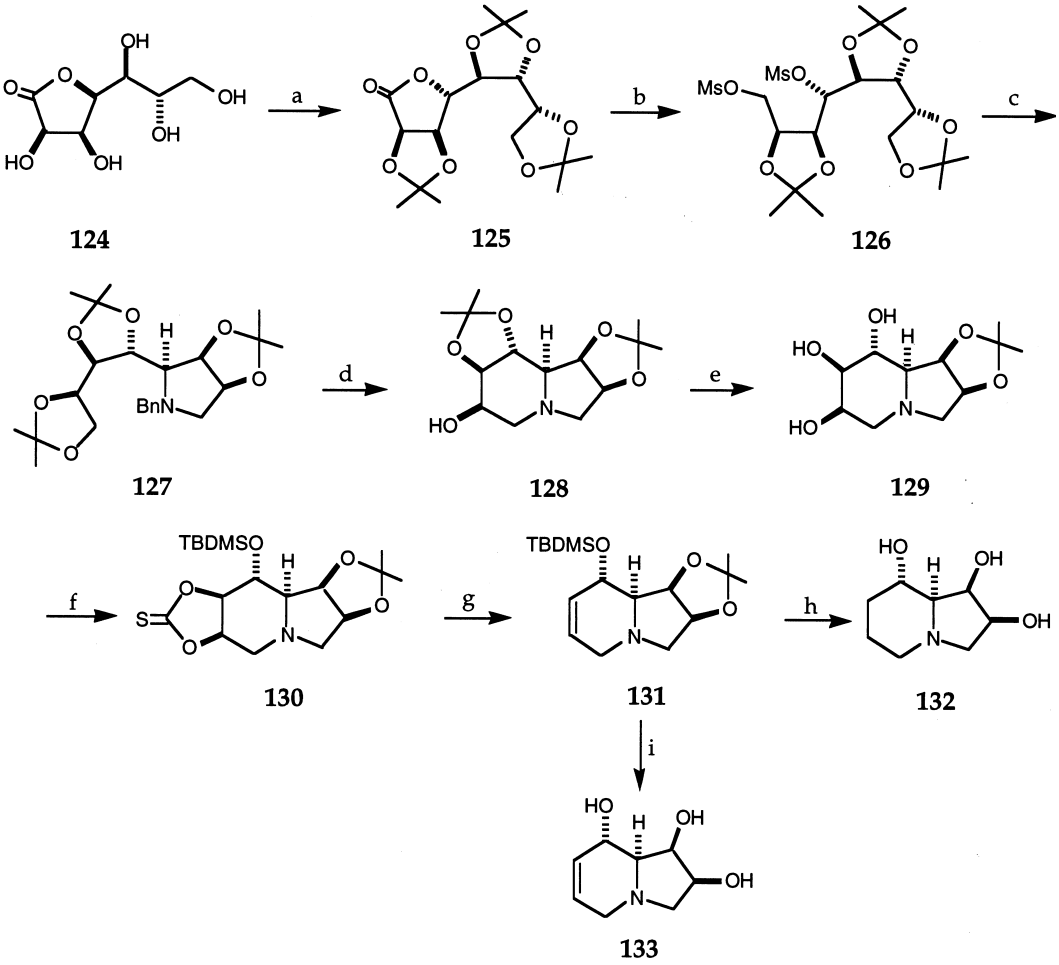
Scheme 24. (a) NBS, 5:2 DMF–H_2O, 0°C, 6 h, 71% (4:1 ds); (b) SiO_2, xylene, reflux, 48 h, 71%; (c) 1—Na, naphthalene, THF, 31%; 2—$LiAlH_4$, THF, reflux; 3—6N HCl, 25°C, 86%.

Haloamidation of **115** afforded a non-separable 4:1 mixture of the pyrrolidine **122** and its diastereomer in 71% yield, and this was subjected to the lactonization procedure of Takeda to give the lactone **123**. Detosylation of **123** followed by lithium aluminium hydride reduction and acid hydrolysis afforded (−)-8,8a-di-*epi*-swainsonine (**103**) in 13.5% overall yield from **115** (Scheme 24).

Syntheses of (+)-swainsonine (**132**) and dehydro-(+)-swainsonine (**133**) from the glucoheptonolactone (**124**) has been developed by Fleet and co-workers (Scheme 25).[53]

Reduction of the lactone **124** followed by one-carbon elongation and acetonation afforded the triacetonide lactone **125**. Reduction of **125** followed by mesylation afforded **126**, this was reflux with benzylamine to give the pyrrolidine **127**. Removal of the terminal isopropylidene group in **127**, followed by regioselective mesylation and intramolecular displacement, provided the bicyclic diacetonide **128** in 5% overall yield from **124**. Regioselective hydrolysis of **128** followed by reaction with 1,1′-thiocarbonylimidazole afforded **129**, this was then react with *t*-butyldimethylsilyl triflate to furnish the thionocarbonate **130**. Corey–Winter fragmentation of **130** gave the olefin **131** which underwent hydrogenation followed by complete deprotection to afford (+)-swainsonine (**132**) in 31% overall yield from **128**. Alternatively complete deprotection of **131** afforded dehydro-(+)-swainsonine (**133**).

(+)-Swainsonine (**132**) is the most potent L-rhamnosidase



Scheme 25. (a) 1—$NaBH_4$, H_2O; 2—NaCN, H_2O, rt, 68 h, reflux, 23 h, 19%; 3—H_2SO_4, acetone, rt, 16 h, 73%; (b) 1—$LiBH_4$, THF; 2—MsCl, pyr, DMAP, 91% two steps; (c) $BnNH_2$, 110°C, 2 days, 93%; (d) 1—TsOH, CH_3OH, 68%; 2—MsCl, pyr, DMAP, 91%; 3—H_2, Pd-black, EtOH, NaOAc, 62%; (e) 80% AcOH–H_2O, 85%; (f) Im_2CS, toluene; then TBDMSOTf, pyr, CH_2Cl_2, 72%; (g) $(EtO)_3P$, heat, 76%; (h) 1—H_2, Pd-black, EtOAc, 89%; 2—1:1 TFA–D_2O, 74%; (i) 1:1 TFA–D_2O, 80%.

(from *Penicillium decumbers*, IC_{50}=0.3 μM, K_i=0.45 μM) inhibitor yet described.[53]

2.2. Syntheses from non-carbohydrate starting materials

(−)-Swainsonine (**1**) and some of its isomers have been prepared utilising non-carbohydrate starting materials. Sharpless reported[54] the first non-carbohydrate route for the synthesis of (−)-swainsonine (**1**) in which the *N*-benzyl-*p*-toluenesulfonamide moiety provides a suitably protected nitrogen, to avoid this nitrogen acting as an internal nucleophile towards the epoxide function and the other transformations in the Masamune–Sharpless iterative process (Scheme 26).

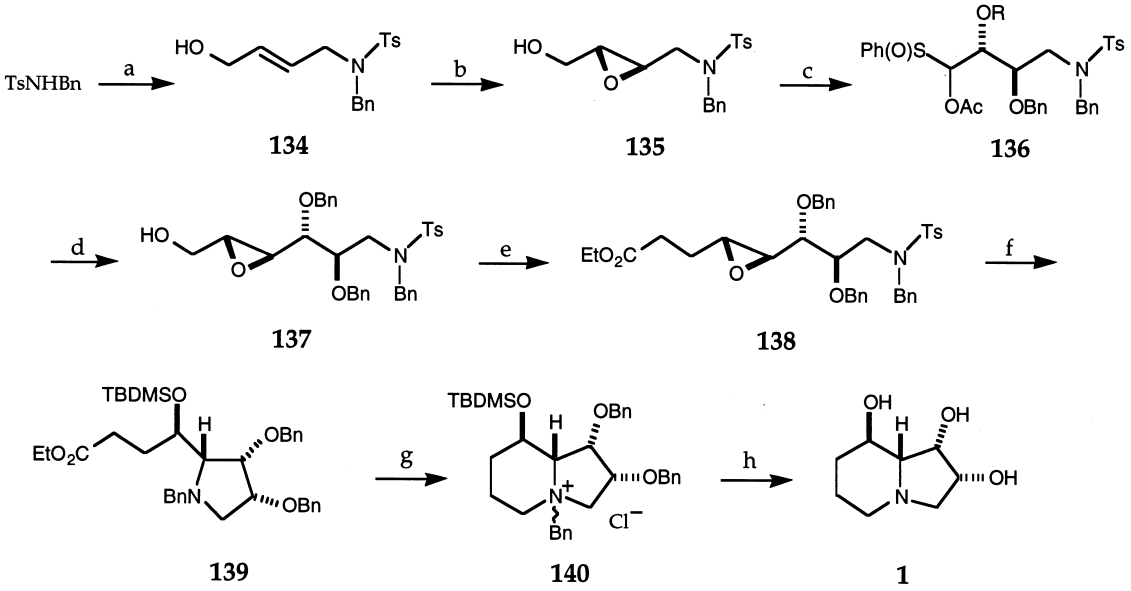
The olefin **134**, obtained from *N*-benzyl-*p*-toluenesulfonamide, underwent an asymmetric epoxidation to give the epoxy alcohol **135**, which was converted into the epoxy alcohol **137** via the tosyl **136** in nine steps in 29% overall yield from **134**. Moffatt oxidation of **137**, followed by direct addition of (carbethoxymethylene)–triphenylphosphorane and subsequent reduction of the resulting α,β-unsaturated ester, afforded the epoxy ester **138**. Sodium naphthalide removal of the tosyl protecting group in **138**, followed by intramolecular cyclisation and silyl protection furnished **139**, which was converted into the quaternary ammonium salt **140** via reduction and mesylation processes. Subsequent hydrogenolysis followed by desilylation gave (−)-swainsonine (**1**) in 6.6% overall yield for 21 steps.

An enantioselective synthesis of *anti* 1,2-diols has been developed using the reaction of 4-bromobutanal with (*S*,*S*)-**143** and this has been used as a key step in the synthesis of (−)-swainsonine (**1**) (Scheme 27).[55]

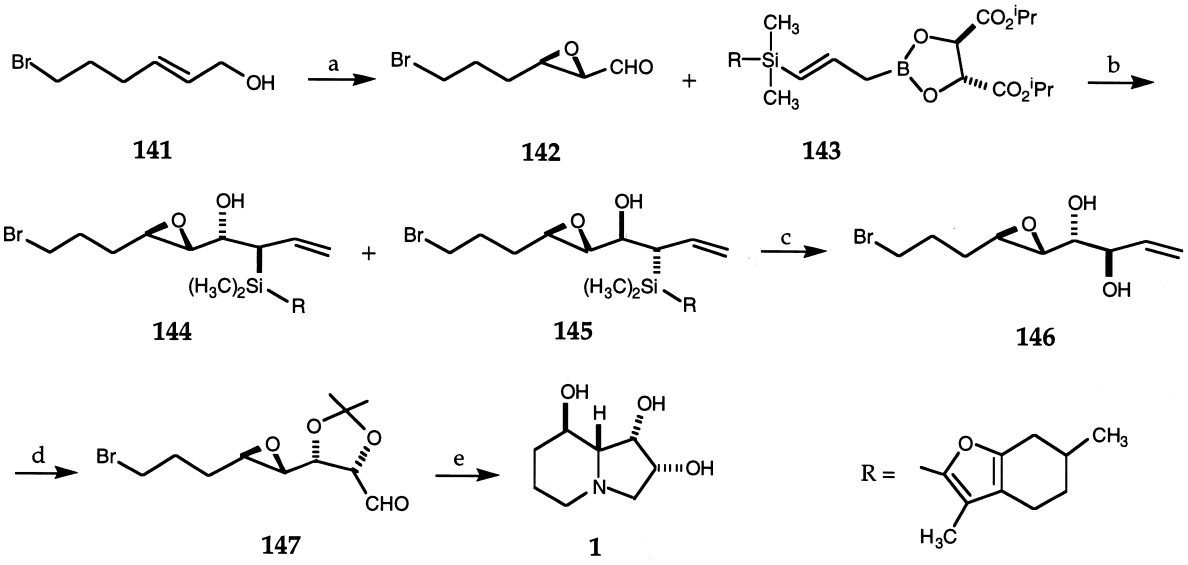
4-Bromobutanal was transformed to the allylic alcohol **141** via a Horner–Wadsworth–Emmons reaction followed by DIBAL reduction. Sharpless asymmetric epoxidation of **141** afforded the corresponding epoxy alcohol derivative which was 92% enantiomerically pure and which underwent Swern oxidation of the hydroxyl group to afford the aldehyde **142**, subsequent α-hydroxyallylation with (*S*,*S*)-**143** to afford **144** (73%) and **145** (8%); compound **144** was separated by recrystallization from hexane. A one-pot protodesilylation–oxidation reaction of **144** furnished the diol **146** in 85% yield. The acetonide of **146** underwent ozonolysis to provide the aldehyde **147**. Reductive amination of **147** was accomplished by intramolecular cyclisation followed by acid hydrolysis to afford (−)-swainsonine (**1**) in 16% overall yield from 4-bromobutanal.

A methodology for the stereoselective synthesis of *trans*-3-hydroxypipecolic esters has been extended to the diastereoisomers of (−)-swainsonine (**1**) (Scheme 28).[56] The β-keto ester **148** was converted into the α-hydrazino β-hydroxy ester **149** in three steps in 50% overall yield. Reductive ozonolysis of the double bond in **149** followed by mesylation of the primary alcohol provided **150**. Treatment of **150** with TFA followed by hydrogenolysis and cyclisation gave the ester **151**, which was converted via the alcohol **152** into the alkene **153** (*Z*/*E*=19:1) in five steps. Osmium dihydroxylation of the *Z*/*E* mixture of **153** gave **154** in 71% yield, as an optically pure diastereoisomer. Cleavage of the benzyl carbamate followed by acetonide protection furnished the lactam **155**, which was transformed into (−)-swainsonine (**1**) in 78% yield.

Another methodology involving a stereoselective osmium-catalysed dihydroxylation of an indolizidine double bond as a key step in the syntheses of (−)-8,8a-di-*epi*-swainsonine



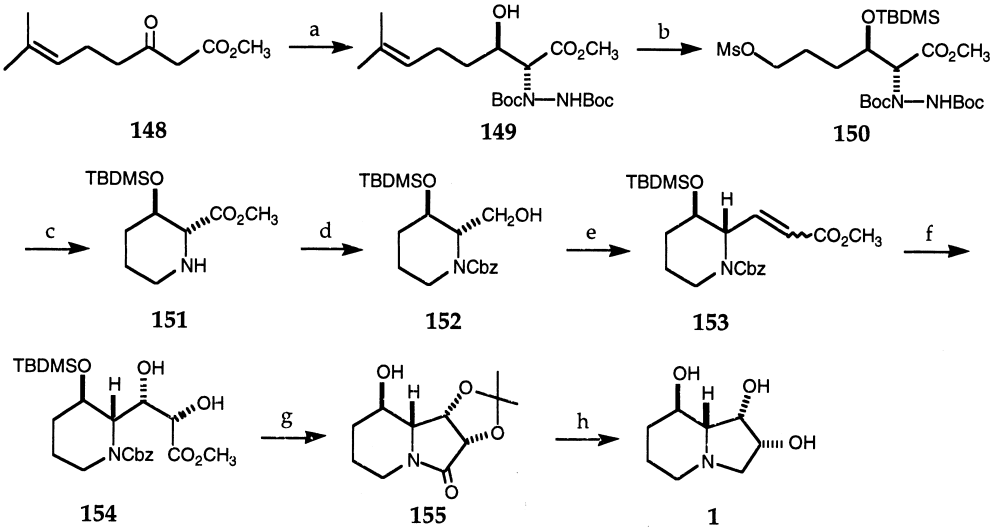
Scheme 26. (a) 1—NaH, (*E*)-$ClCH_2CH{=}CHCH_2Cl$, DMF, 0°C→rt, 6 h; 2—NaOAc, DMF, 120°C, 5 h; 3—K_2CO_3, CH_3OH, rt, 2 h, 68% three steps; (b) (−)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, −20°C, 2.5 h, 91%; (c) 1—PhSH, *t*-BuOH, 0.5N NaOH, 85°C, 5 h, 71%, 2—BnBr, NaH, *n*-Bu_4NI, THF, rt, 18 h, 91%; 3—*m*CPBA, CH_2Cl_2, −78°C, 2 h, 100%; (d) 1—Ac_2O, Tf_2O, 2,6-lutidine, rt, 3 h, 71%; 2—$LiAlH_4$, THF, 0°C, 30 min, 92%, 3—$(COCl)_2$, DMSO, DBU, CH_2Cl_2, −60°C, 30 min; 4—$(EtO)_2P(O)CH_2CO_2Et$, NaH, toluene, 0°C, rt; 5—DIBAL, toluene, −78°C, 1 h, 93%; 6—(−)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, −21°C, 21 h, 93%; (e) 1—Dicyclohexylcarbodiimide, DMSO, C_5H_5NHOTf, 5 h, 40°C, then $Ph_3P{=}CHCO_2Et$, 24 h, 89%, 2—$KO_2CN{=}NCO_2K$, pyr, AcOH, 40°C, 40 h, 85%; (f) 1—Na-naphthalene, DMF, −60°C, 30 min; 2—TBDMSOTf, Et_3N, CH_2Cl_2, 0°C, 1 h, 68%; 3—DIBAL, toluene, 0°C, 2 h, 79%; (g) MsCl, Et_3N, CH_2Cl_2, 0°C→rt, 18 h, 100%; (h) 1—H_2, Pd-black, 10% HCO_2H in CH_3OH, rt, 18 h, 100%; 2—Dowex 50W-X8, CH_3OH, 24 h, 84%.



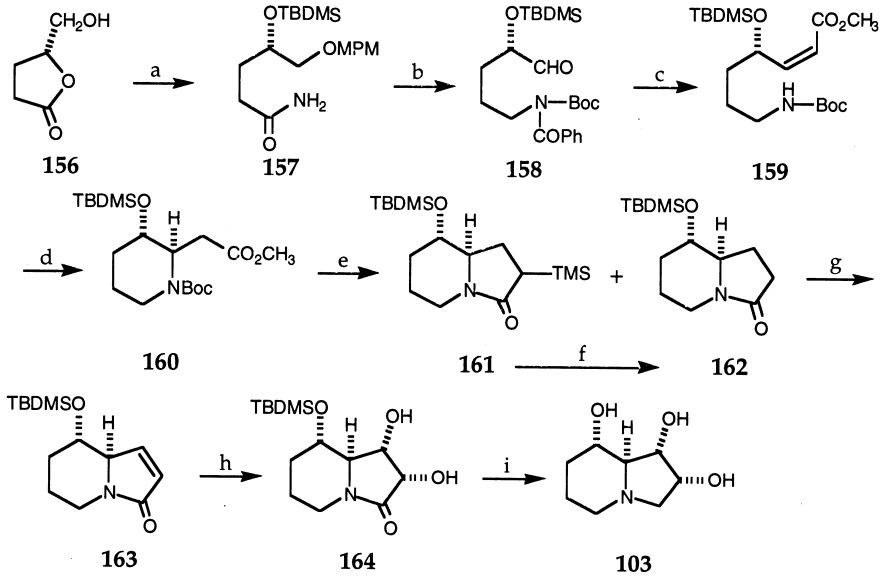
Scheme 27. (a) 1—$Ti(OiPr)_4$, D-(−)-DIPT, TBHP, 4 Å M.S., −20°C, 72%; 2—SO_3-pyr, DMSO, Et_3N, CH_2Cl_2, 78%; (b) toluene, 4 Å M.S., −78°C, 81%, (c) 1—TFA, THF, 0→23°C; 2—$KHCO_3$, KF, H_2O_2, THF–CH_3OH, 23°C, 85%; (d) 1—DMP, PPTS, CH_2Cl_2; 2—O_3, CH_2Cl_2, −78°C; then Ph_3P, 84%; (e) 1—NH_4OAc, CH_3OH, 3 Å M.S.; then $NaCNBH_3$, 71%; 2—6N HCl, THF, 92%.

(**103**) and (+)-swainsonine (**132**) has been developed (Schemes 29 and 30).[57] The butyrolactone (**156**), prepared from L-glutamic acid, was converted into the aldehyde **158** in eight steps. Wadsworth–Emmons type reaction of **158** followed by removal of the *E*-isomer and deprotection of the benzoyl group in the *Z*-isomer gave the *Z*-α,β-unsaturated ester **159**, which subsequently underwent intramolecular conjugate addition with complete diastereoselectivity to afford **160**. Intramolecular acyloin type condensation reaction between the carbamate and the ester group of **160** gave **161** (23%) and the desired **162** (20%). The lactam **161** was converted into the lactam **162** by heating with potassium carbonate. Subsequent phenylselenenylation of **162** followed by *cis*-dihydroxylation of **163** afforded the lactam **164**. This was converted into (−)-8,8a-di-*epi*-swainsonine (**103**) in two steps (Scheme 29).

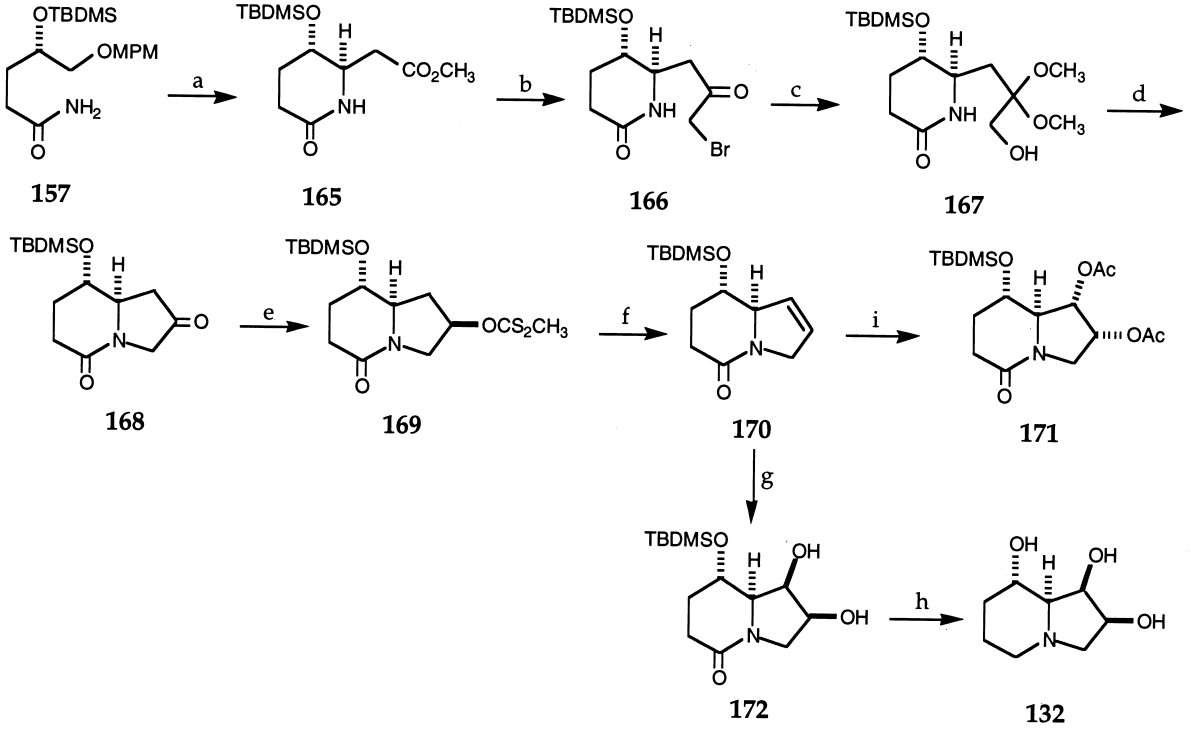
The lactam **165**, obtained from amine **157**, underwent a one-carbon elongation to give the bromoketone **166**, which failed to undergo a base-catalysed intramolecular cyclisation. Its methyl ketal **167**, however, was mesylated followed by cyclisation using potassium hydride and ketal hydrolysis to give the ketone **168**. This was converted to the olefin **170**



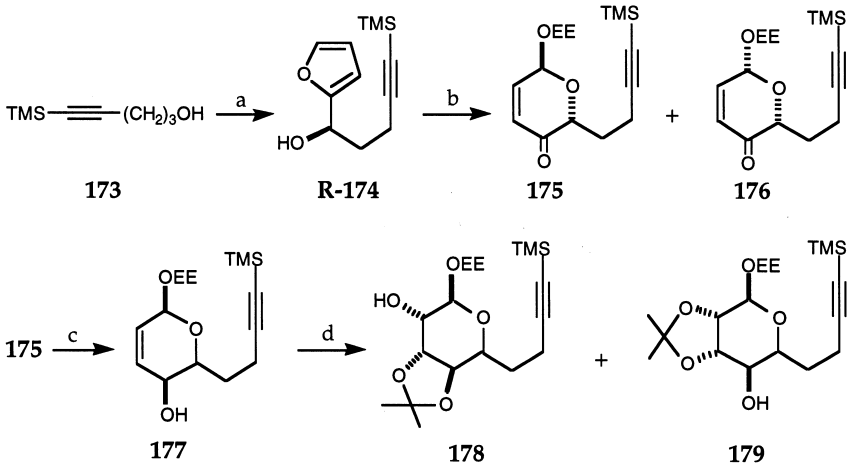
Scheme 28. (a) 1—H_2, $RuBr_2$[(R)-Binap] in situ (2%), CH_3OH, 50°C, 2 h, 98%; 2—CH_3ZnBr, THF, 0°C, 30 min; 3—LDA, THF, −78°C; 1 h, 4—DBAD, THF, −78°C, 30 min, 66% three steps; 5—2,6-lutidine, TBDMSOTf, CH_2Cl_2, −78°C, 2 h, 77%; (d) 1—O_3, CH_2Cl_2, −78°C, 1 h; 2—BMS, CH_2Cl_2, −78°C→rt, 16 h, 96%; 3—MsCl, pyr, 0°C, 1 h, 86%; (e) 1—TFA, CH_2Cl_2, 0°C→rt, 2 h; 2—H_2, Raney nickel, ultrasound, CH_3OH, rt, 2 h; 3—Et_3N, CH_2Cl_2, rt, 30 min, 75% three steps; (d) 1—CbzCl, DMAP, CH_3CN, 0°C→rt, 2.5 h, 74%; 2—$Ca(BH_4)_2$, 2:3 THF–EtOH, −20°C→rt, 45 min, 91%; (e) 1—$(COCl)_2$, DMSO, CH_2Cl_2, 10 min, −60°C; 2—Et_3N, 30 min, −60°C, then H_2O, 100%; 3—$(CF_3CH_2O)_2P(O)CH—CO_2CH_3K^+$, 18-crown-6, THF, −78°C, 2 h, 83%, *Z*/*E*=19:1; (f) OsO_4, $(CH_3)_3NO$, 19:1 acetone—H_2O, ultrasound, rt, 2 h, 71%; (g) 1—H_2, Pd on C, NaOAc, CH_3OH, rt, 2 h, 35°C, 90%; 2—DMP, Dowex H^+, 4 h, rt, 97%; (h) 1—BMS, THF, rt, 14 h; then EtOH and vacuum; 2—EtOH, reflux, 2 h, 81% two steps; 3—1N HCl, reflux, 30 min; then Dowex OH^-, 96%.



Scheme 29. (a) 1—NaH, MPMCl, THF, DMF, 76%; 2—NH_4OH, Et_2O, 0°C, 79%; 3—TBDMSCl, imidazole, DMF, 91%; (b) 1—$LiAlH_4$, Et_2O, reflux, 88%; 2—$(Boc)_2O$, Et_3N, CH_2Cl_2, 88%; 3—Bz_2O, KH, THF, 91%; 4—DDQ, CH_2Cl_2, H_2O, 96%; 5—DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, 100%, (c) 1—$(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$, 18-crown-6, KHMDS, toluene, −78°C, 95%, *Z*/*E*=3:1; separation; 2—$HN{=}C(NMe_2)_2$, CH_3OH, 96%; (d) *t*-BuOK, THF, −65→−45°C, 91%; (e) Na, TMSCl, toluene, reflux, 6 h; then aq NH_4Cl; (f) K_2CO_3, CH_3OH, 88%; (g) 1—LDA, PhSeBr, THF, 76%; 2—H_2O_2, pyr, 94%; (h) 1—OsO_4, NMO, acetone, H_2O, rt, 87%, α/β>12:1; 2—OsO_4, (*S*,*S*)-*N*,*N*′-di(3,3-dimethylbutyl)-2,2′-bipyrrolidine, CH_2Cl_2, −78°C; then $Na_2S_2O_5$, aq THF, reflux, 80%; or (*R*,*R*)-*N*,*N*′-di(3,3-dimethylbutyl)-2,2′-bipyrrolidine, CH_2Cl_2, −78°C; then $Na_2S_2O_5$, aq THF, reflux, 63%; (i) 1—2-methoxypropene, CSA, CH_2Cl_2, 74%; 2—BH_3, THF; then 1N HCl, reflux, 43%.



Scheme 30. (a) 1—KH, Boc-S, THF, −30→5°C, 81%; 2—DDQ, CH_2Cl_2, H_2O, 94%; 3—DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, 81%; 4—$(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$, 18-crown-6, KHMDS, toluene, −78°C, 85%, *Z*/*E*=4.3:1; separation; 5—TMSI, $CHCl_3$, 65%; 6—*t*-BuOK, THF, −55°C, 80%; (b) $LiCHBr_2$, THF, −90°C; then BuLi, −90°C, 59%; (c) 1—K_2CO_3, CH_3OH, 92%; (d) 1—MsCl, Et_3N, CH_2Cl_2, 94%; 2—KH, THF, 87%; 3—TsOH, acetone, 77%; (e) 1—$NaBH_4$, CH_3OH, 0°C, 98%; 2—NaH, THF, CS_2; then CH_3I, 98%, β:α=6.7:1; (f) 180°C, 68%; (g) OsO_4, NMO, acetone, H_2O, rt, 82%; (h) 1—TFA, THF, H_2O; then Ac_2O, pyridine, CH_2Cl_2, 84%, α/β=1:6.9; 2—BH_3–THF, reflux; K_2CO_3, CH_3OH; then 2 M HCl, reflux, 85%; (i) OsO_4, (*S*,*S*)-*N*,*N*′-di(3,3-dimethylbutyl)-2,2′-bipyrrolidine, CH_2Cl_2, −78°C; then $Na_2S_2O_5$, aq THF, reflux; then Ac_2O, pyr, DMAP, 93%; *or* (*R*,*R*)-*N*,*N*′-di(3,3-dimethylbutyl)-2,2′-bipyrrolidine, CH_2Cl_2, −78°C; then $Na_2S_2O_5$, aq THF, reflux; then Ac_2O, pyr, DMAP, 81%.



Scheme 31. (a) 1—Swern oxidation, 92%; 2-lithiofuran, THF, −78°C, 85%; 3-diisoprpyl-L-tartrate, CH_2Cl_2, 3 Å M.S., rt→−25°C; then titanium tetra-isopropoxide, 30 min, then *t*-BuOOH, 15 h, $FeSO_4{\cdot}7H_2O$, tartaric acid, 48%; (b) 1—NaOAc, NBS, aq THF, 100%; 2—ethyl vinyl ether, PPTS, 0°C, rt, 5 h, **175** (62%) and **176** (18%); (c) $LiAlH_4$, Et_2O, 0°C, 92%; (d) 1—OsO_4, Et_2O, pyr, rt, 10 h, 70%; 2—DMP, PPTS, DMF, 0°C, 10 h, **179** (74%) and **178** (15%).

via the lactam **169** in three steps. Asymmetric dihydroxylation of **170** with (*S*,*S*)- or (*R*,*R*)-*N*,*N*′-di(3,3-dimethylbutyl)-2,2′-bipyrrolidine–OsO_4 complex afforded α-diacetate **171** predominantly. However, the dihydroxylation under Upjohn conditions gave **172** with an α/β ratio of 1:6.9. The β-isomer was converted into (+)-swainsonine (**132**) by a series of steps analogous to the synthesis of **103** in Scheme 29 (Scheme 30).

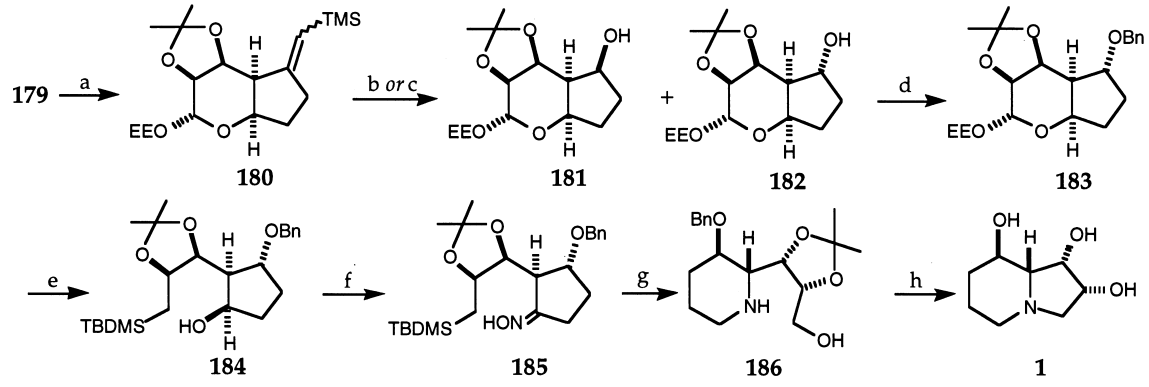
An enantiocontrolled synthesis of (−)-swainsonine (**1**) by ring transformation of a pyranone has been developed (Schemes 31 and 32).[58]

The optically active furfuryl alcohol (*R*)-**174** was obtained from **173** in three steps including Sharpless kinetic resolution to give the optical isomer (*R*)-**174**. Oxidative ring transformation of (*R*)-**174** followed by treatment with ethyl vinyl ether furnished **175** (62%) and **176** (18%). Subsequent reduction of **175** gave **177**, followed by dihydroxylation and formation of the acetonide to give the regioisomers **178** (15%) and **179** (74%) (Scheme 31).

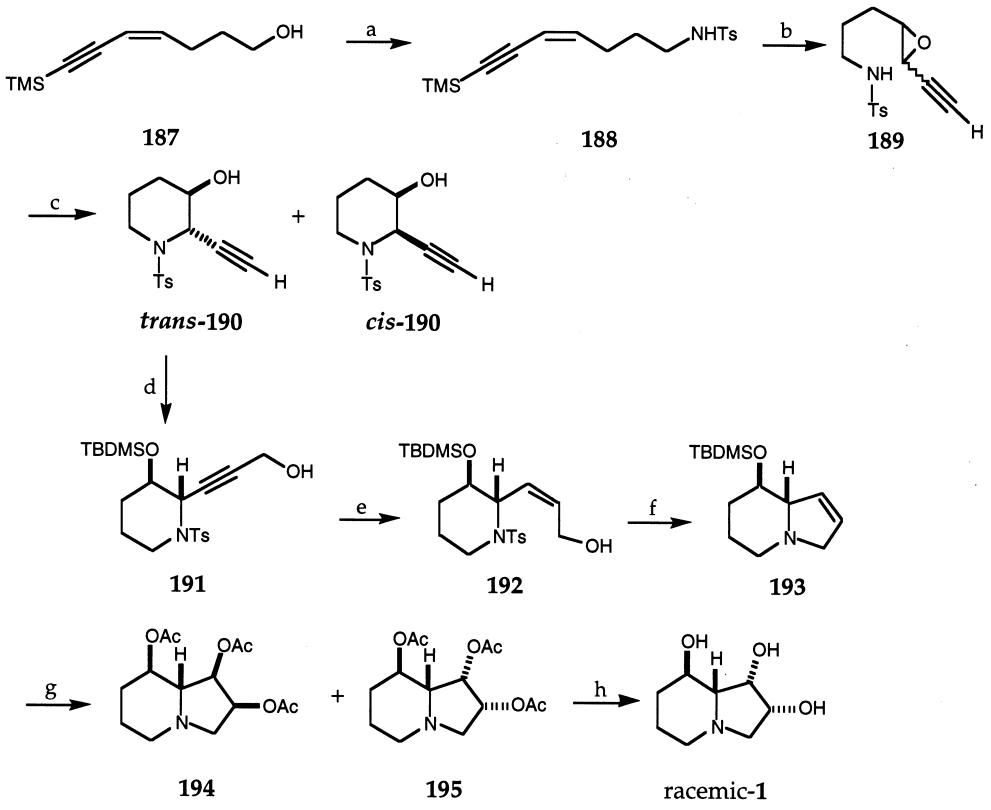
Radical cyclisation of the thiocarbonylimidazolo derivative of **179** afforded the silyl **180** followed by Lemieux–Johnson oxidation and reduction afforded the alcohols **181** (30%) and **182** (55%). The latter alcohol was converted via compounds **183** and **184** into the (*E*)-oxime **185** in five steps, and this underwent Beckmann rearrangement followed by desilylation to furnish **186**. Conversion of **186** into the indolizidine skeleton followed by reduction and complete deprotection afforded (−)-swainsonine (**1**) (Scheme 32).

endo Mode cyclisation methodology was used as a key step for the synthesis of (±)-swainsonine (racemic-**1**) (Scheme 33).[59]

Mitsunobu conditions followed by azido group reduction and tosylation of the alcohol **187** afforded the compound **188** in 79% overall yield. Desilylation followed by epoxidation and *endo* cyclisation of **188** gave *trans*-**190** (76%) and *cis*-**190** (9%). After chromatographic separation, *trans*-**190** was converted via compounds **191** and **192** into compound **193** in five steps. Subsequent dihydroxylation followed by



Scheme 32. (a) 1—Im_2CS, $ClCH_2CH_2Cl$, DMAP, rt, 5 h, 68%; 2—Bu_3SnH, AIBN, PhH, reflux, 30 min, 92%; (b) 1—OsO_4, *t*-BuOH, pyr, rt, 4.5 h; then $NaIO_4$; 2—$NaBH_4$, CH_3OH, **181** (96%); or (c) Na, liquid NH_3, 1:1 THF–EtOH, −78°C, 20 min, rt, 1 h, **181** (30%) and **182** (55%); (d) BnBr, Bu_4NI, NaH, THF, 0°C, 98%; (e) 1—2N HCl, THF, rt, 2 h, 98%; 2—$NaBH_4$, CH_3OH, CH_2Cl_2, 100%; 3—TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 10 h, 100%; (f) 1—NMO, 4 Å M.S., tetrapropylammonium perruthenate, rt, 30 min; then $NH_2OH{\cdot}HCl$, pyr, rt, 30 min, 86%; (g) 1—$SOCl_2$, 1 h, 83%; 2—Bu_4NF, THF, rt, 1 h, 100%; (h) 1—MsCl, Et_3N, DMAP, CH_2Cl_2, 0°C, 1 h; then K_2CO_3, 1,4-dioxane, 90°C, 1 h, 96%; 2—H_2, 20% $Pd(OH)_2$ on EtOH, rt, 1 h, 99%; 3—BMS, THF, rt, 1 h; then K_2CO_3, 65°C, 2 h, 99%; then hydrolysis.



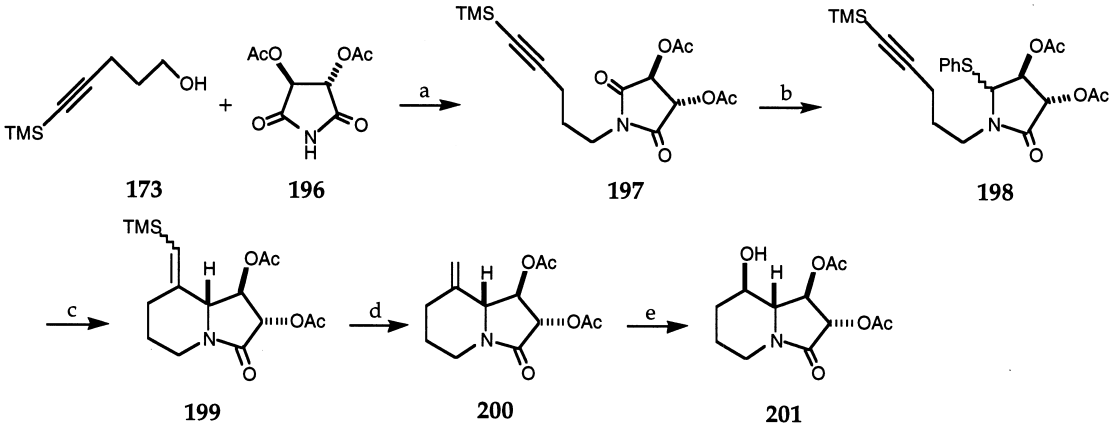
Scheme 33. (a) 1—HN_3, DEAD, PPh_3, 99%; 2—PPh_3, H_2O, 99%; 3—TsCl, Et_3N, 81%; (b) 1—Bu_4NF, THF, rt, 30 min, 96–99%; 2—*m*CPBA, CH_2Cl_2, rt, 24 h, (58%); (c) 1—$Co_2(CO)_8$, CH_2Cl_2, rt→−78°C, 30 min; 2—$BF_3{\cdot}OEt_2$, CH_2Cl_2, 10 min; 3—CAN, CH_3OH, 0°C, 30 min; *trans* (76%), *cis* (9%); (d) 1—TBDMSCl, imidazole, 99%; 2—*n*-BuLi, $(HCHO)_n$, 97%; (e) H_2, Lindlar cat., 99%; (f) 1—Na, naphthalene, THF, −78°C, 20 min; 2—CBr_4, PPh_3, Et_3N, 57%; (g) 1—OsO_4, NMO, acetone, rt, 2—Bu_4NF, THF, rt, 12 h; 3—Ac_2O, pyr, DMAP, 76% (7:1 mixture); (h) K_2CO_3, CH_3OH, rt, 1.5 h, 99%.

acetylation of **193** gave 1,2-di-*epi*-swainsonine triacetate **194** (9%) and swainsonine triacetate **195** (67%). Base treatment of **195** provided (±)-swainsonine (racemic-**1**).

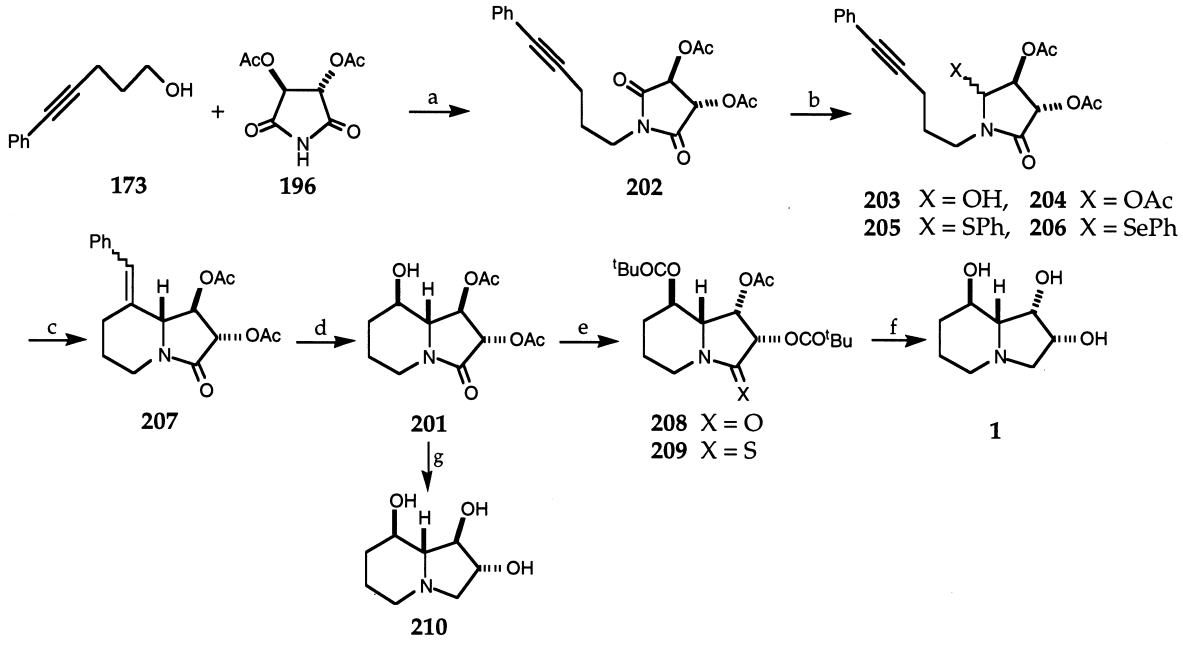
α-Acylamino radical cyclisation methodology was applied as a key step for the syntheses of (−)-swainsonine (**1**) and 1-*epi*-swainsonine (**210**) (Schemes 34 and 35).[60]

The imide **196** (derived from D-tartaric acid in 48% overall yield) underwent a Mitsunobu coupling reaction with **173** to give the imide **197**, which was converted into the radical precursor **198** in three steps in 49% overall yield from the imide **196**. Radical cyclisation of **198** furnished **199** followed by protodesilylation to give the olefin **200**. Subsequent ozonolysis followed by reduction of **200** gave **201** in 39% overall yield from **198** (Scheme 34).

The poor overall yield for the cyclisation and degradation of **198** to give the intermediate **201**. However, led to the use of an aryl group in place of the trimethylsilyl group to improve the overall yield for **201**. The tartarimide **202** was reduced to give **203**, this was converted via triacetate **204** into the



Scheme 34. (a) Ph_3P, $EtO_2CN{=}NCO_2Et$, THF; (b) 1—$NaBH_4$, CH_3OH; 2—Ac_2O, Et_3N, DMAP, CH_2Cl_2; 3—PhSH, TsOH; (c) *n*-Bu_3SnH, AIBN, PhH, reflux, 1 h, 70%; (d) *p*-$CH_3C_6H_4SO_2H$, CH_3CN, H_2O, rt, 48 h; then Ac_2O, Et_2O, Et_3N, DMAP, CH_2Cl_2, rt, 3 h, 64%; (e) O_3, CH_2Cl_2, −78°C; then $(CH_3)_2S$, 10 h; then $NaBH_4$, CH_3OH, −40°C, 1 h, 68%.

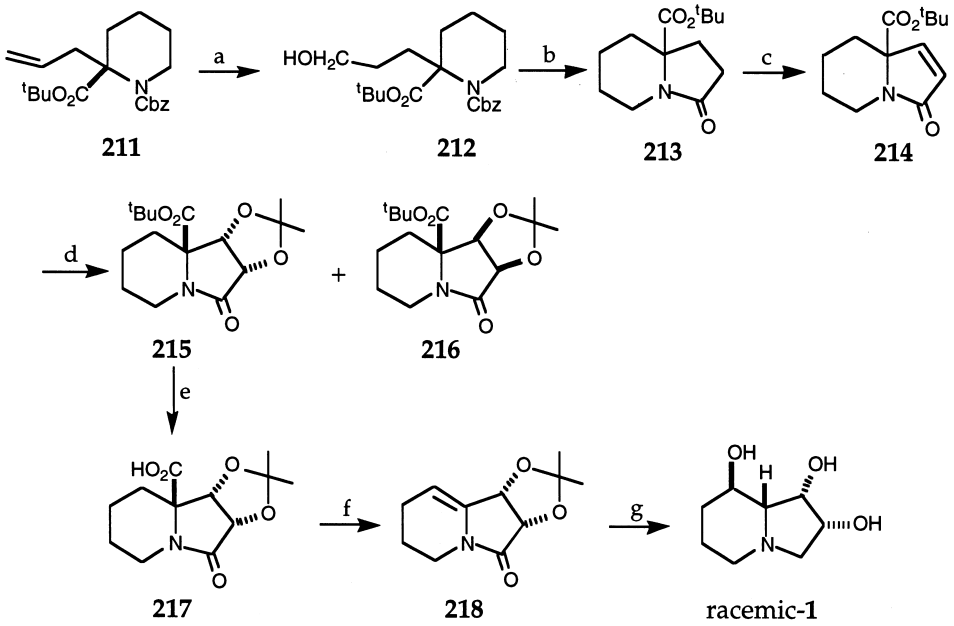


Scheme 35. (a) Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, 0°C, 15 min; then rt, 3.5 h, 96%; (b) 1—$NaBH_4$, CH_3OH, −7°C, 12 min, 91%; then Ac_2O, Et_3N, DMAP, CH_2Cl_2, 30 min, 96%; then PhSH, TsOH, rt, 45 min, 82%; or *n*-Bu_3P, PhSSPh, PhH, rt, 11 min, 77%; or PhSeH, TsOH, rt, 75 min, 90%; (c) *n*-Bu_3SnH, AIBN, PhH, reflux, 2 h, 91% (*Z*/*E*=1.2:1) from **205**, and 85% (*Z*/*E*=7.7:1) from **206**; (d) O_3, CH_3OH, then $(CH_3)_2S$, rt, 2.5 h; then $NaBH_4$, CH_3OH, −50 to −60°C, 74%; (e) 1—Me_3CCOCl, pyr, DMAP, rt, 27 h, 93%; 2—50% NH_3–CH_3OH, rt, 4 h; then Me_3CCOCl, pyr, rt, 27 h, 67%; 3—Tf_2O, pyr, CH_2Cl_2, 0°C, then KOAc, 18-crown-6, DMF, 29.5 h; then Ac_2O, Et_3N, DMAP, 45 min, **208** (85%); 4—Lawesson's reagent, toluene, reflux, 1 h, **209** (97%); (f) 1—Raney nickel W-2, EtOH, reflux, 1 h, 96%; 2—aq CH_3NH_2, CH_3OH, 48 h, 63%; (g) $LiAlH_4$, 25%.

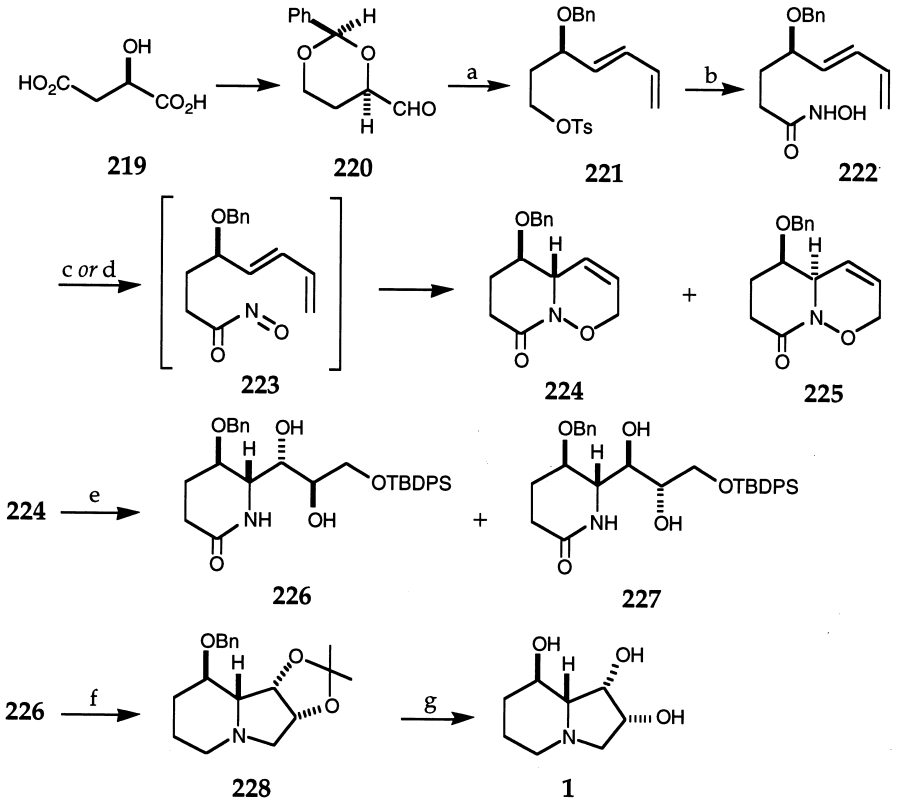
radical precursor **205** or **206** in two steps for each compound. Radical cyclisation of **205** and **206** afforded **207**, followed by ozonolysis and reduction to afford **201**. The indolizidine **201** was converted via the thiolactam **209** into (−)-swainsonine (**1**) in 14% overall yield from the imide **196**. Reduction of **201** with lithium aluminium hydride gave 1-*epi*-swainsonine (**210**) (Scheme 35).

Decarbonylation of an α-tertiary amino acid was used for the synthesis of (±)-swainsonine (racemic-**1**) (Scheme 36).[61]

The α-allyl derivative **211**, derived from DL-pipecolic acid, was converted via compounds **212** and **213** into the lactam **214** in four steps in 50% overall yield. Catalytic osmylation



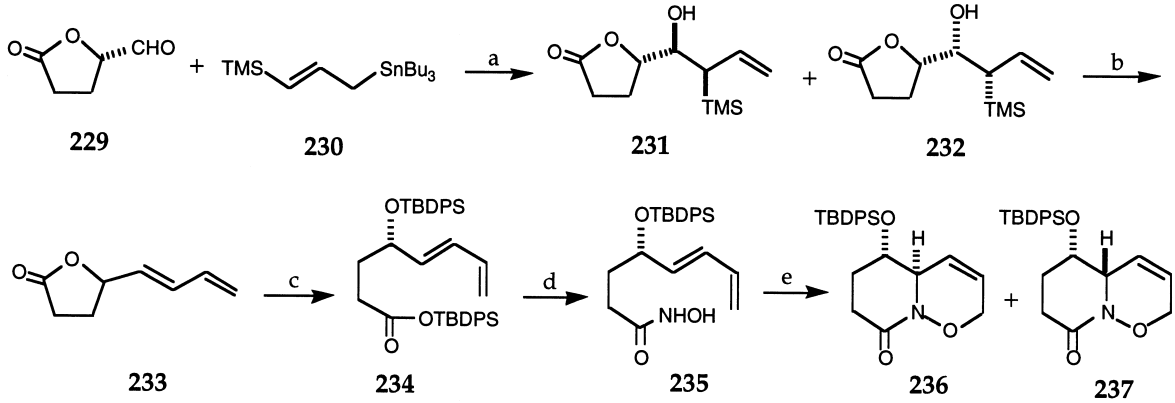
Scheme 36. (a) 1—BMS, THF, rt, 3 h; 2—H_2O_2, NaOH, EtOH, O°C→reflux, 1 h, 75% two steps; (b) 1—PDC, DMF, rt, 24 h, 95%; 2—CH_2N_2, ether, 100 %; 3—TFA, CH_2Cl_2 rt, 15 h, 100%; (c) 1—LDA, THR, −78°C; then PhSeCl, THF; then H_2O_2, AcOH, 0°C, 70% (d) 1—O_SO_4, NMO, acetone, H_2O, *t*-BuOH; 2—DMP, PPTS, CH_2Cl_2, **215** (57%) and **216** (28%); (e) TFA, CH_2Cl_2, 0°C, 100%; (f) 1—$(COCl)_2$, DCE, −10°C; 2—DPPA, Et_3N, toluene, 0°C, 75% two steps; (g) 1—BMS, THF, rt, 5 h; then H_2O_2, NaOH, reflux, 2 h, 85%; 2—6N HCl, rt, 15 h; then Dowex OH^-, 96%.



Scheme 37. (a) 1—CH_2=$CHCH_2P^+Ph_3Br^-$, *t*-BuOK, THF, rt, 20 min, 49%, 2—DIBAL, CH_2Cl_2, rt, 1.5 h, 96%; 3—*hv*, I_2, PhH, 30 min 69%; 4—TsCl, pyr, 0°C, 2 h, rt, 2 h, 95%; (b) 1—NaCN, DMSO, 60°C, 1 h, 99%; 2—NaOH, CH_3OH–H_2O, reflux, 9 h, 77%; 3—CH_2N_2, ether, 0°C, 15 min, 99%; 4—NH_2OH·HCl, KOH, CH_3OH, 0°C, 30 min, 96%; (c) Pr_4NIO_4, $CHCl_3$, 0°C, 10 min, **224** (41%) and **225** (30%); (d) Pr_4NIO_4, H_2O, 0°C, 10 min, **224** (69%) and **225** (16%); (e) 1—Na–Hg, Na_2HPO_4, EtOH, 1 h, 94%; 2—TBDPSCl, imidazole, DMF, rt, 1 h, 97%; 3—OsO_4, NMO, rt, 12 h, **226** (76%) and **227** (15%); (f) 1 DMP, PPTS, 55°C for 13 h, 99%; 2—$LiAlH_4$, THF, 71%; 3—CBr_4, PPh_3, Et_3N, 0°C, 30 min, 85%; (g) 1—H_2, $PdCl_2$, 30 min, 86%; 2—6N HCl, THF, rt, 14 h, 66%.

of **214** followed by isopropylidene protection gave the two acetonides **215** (57%) and **216** (28%). Compound **215** was converted into the carboxyl derivative **217**, which was then treated with oxalyl chloride followed by thermal fragmentation to give the enamide **218**. Treatment of **218** with excess BMS followed by alkaline hydroperoxide and subsequent acid hydrolysis furnished the target compound (±)-swainsonine (racemic-**1**) in 17% overall yield from **211**.

A chiral route to (−)-swainsonine (**1**) utilising an intramolecular asymmetric hetero Diels–Alder reaction of an acylnitroso diene under aqueous conditions has been described (Scheme 37).[62] The dioxane **220**, obtained from D-malic acid (**219**) in three steps, was converted via a Wittig reaction to a mixture of *Z*- and *E*-dienes which underwent ring-opening of the benzylidene acetal, followed by photoisomerization and tosylation to give **221**. Conversion of **221** into the hydroxamic acid **222** was achieved in four steps.



Scheme 38. (a) 1—BF_3·OEt_2, −78°C, 30 min; 2—aq $NaHCO_3$, −78°C→rt, 86% two steps; (b) *t*-BuOK, rt, 15 min, 94%; (c) 1—*n*-Pr_4NOH, THF, CH_3OH, rt, 30 min; 2—TBDPSCl, DMAP, rt, 3 days, 96% two steps; (d) 1—LiOH, THF, CH_3OH, H_2O, 94%; 2—SUC-OCOCF$_3$, THF, pyr, rt, overnight, 83%; 3—H_2NOH·HCl, $CHCl_3$, 0°C, 100%; (e) *n*-Pr_4NIO_4, CH_2Cl_2, −78→0°C, 30 min, 96%.

The hydoxamic acid **222** underwent [4+2] cycloaddition in water to give a 4.1:1 mixture of *trans*-**224** and *cis*-**225** via an acylnitrosodiene intermediate **223**. The oxazinolactam **224** was transformed diastereoselectively to **226** and **227** in a 4:1 ratio. Acetonation of the diol **226** followed by reduction with lithium aluminium hydride and intramolecular cyclodehydration gave the indolizidine **228**, which underwent hydrogenolytic removal of the benzyl group followed by acidic hydrolysis of the acetonide to afford (−)-swainsonine (**1**).

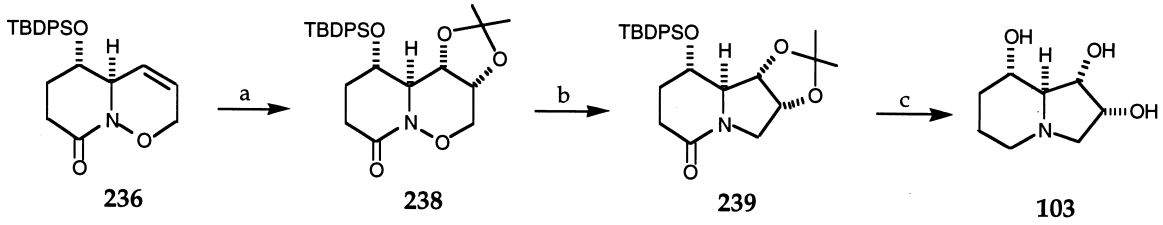
Another synthesis of swainsonine analogues utilising the intramolecular acylnitroso Diels–Alder reaction to form an indolizidine framework has been developed (Schemes 38–41).[63] L-glutamic acid was converted in three steps to carboxaldehyde γ-lactone **229**. Wittig reaction of **229** gave a poor yield of the desired 1,3-diene **233**, but its reaction with **230** in the presence of $BF_3{\cdot}OEt_2$ and aqueous $NaHCO_3$ afforded a mixture of diasterioisomers **231** and **232**, subsequent elimination of the α-hydroxysilane gave **233** in 81% yield. The diene **233** was converted via **234** into the diene **235** in five steps, this underwent intramolecular acylnitroso Diels–Alder reaction to give the bicyclic 1,2-oxazines **236** and **237** as a 2.4:1 mixture of diastereomers.

Catalytic osmylation of **236** followed by isopropylidene protection gave the triol **238** as a single diastereomer. Subsequent reductive cleavage of the N–O bond of **238**, followed by intramolecular cyclisation afforded **239** which underwent complete deprotection to furnish (−)-8,8a-di-*epi*-swainsonine (**103**) in 48% overall yield from **236** (Scheme 39). Similarly, the other epimer **237** was converted through the intermediate compounds **240** and **241** into (+)-1,2,8-tri-*epi*-swainsonine (**242**) in 37% overall yield from **237** (Scheme 40).

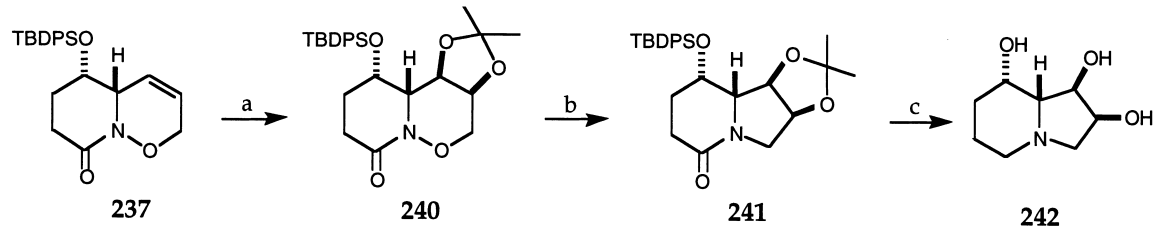
The C-8 hydroxyl of the lactam **243** (obtained from **238**) was mesylated and subsequent S_N2 displacement with benzoate anion gave **244**. Reduction followed by hydrolysis of **244** gave (−)-8a-*epi*-swainsonine (**108**) in 70% overall yield from **243** (Scheme 41).

A diastereoselective preparation of a trihydroxylated alkyl-substituted pyrrolidine has been extended to produce (−)-8a-*epi*-swainsonine (**108**) (Scheme 42).[64]

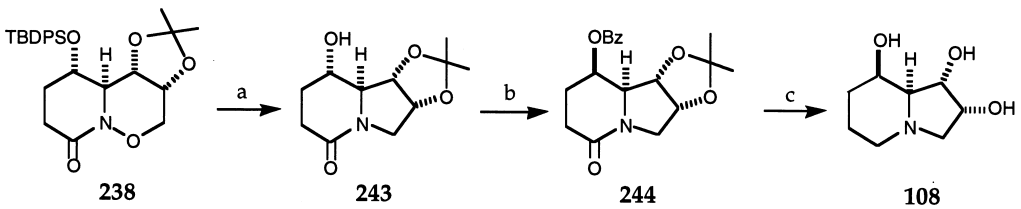
The silyloxypyrrole **246**, obtained from the lactam **245** in two steps, underwent aldol condensation followed by osmium-catalysed dihydroxylation to afford the diol **247**, which was protected as an acetonide followed by lactam reduction to give the alcohol **248**. Hydrogenolysis of **248** gave the acetonide of (−)-8a-*epi*-swainsonine **249**.



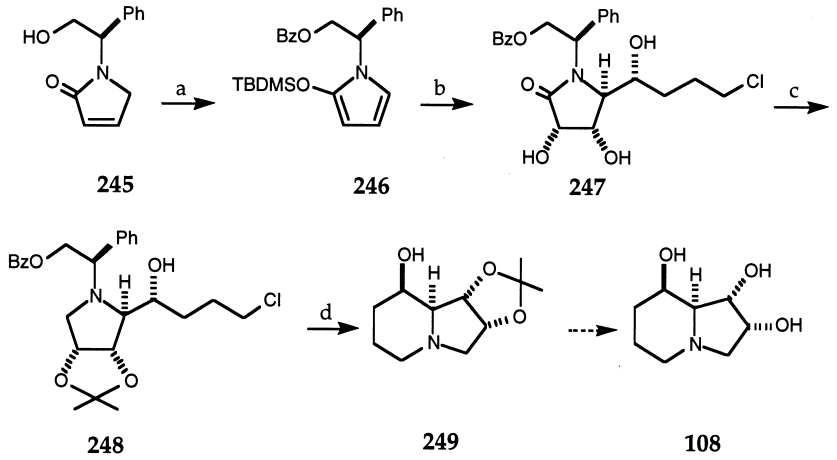
Scheme 39. (a) 1—OsO_4, NMO, THF, rt, 24 h; 2—DMP, Dowex (H^+), resin. rt, 4 h, 82% two steps; (b) 1—Na(Hg), EtOH, Na_2HPO_4, 0°C, 1 h; 2—MsCl, CH_2Cl_2, Et_3N, 0°C, 30 min; 3—K_2CO_3, dioxane, H_2O, 90°C, 5 h, 83% three steps; (c) 1—Bu_4NF, THF, 12 h, rt, 96%; 2—BMS, THF, rt, 4 h, 88%; 3—1N HCl, reflux, 30 min, 84%.



Scheme 40. (a) 1—OsO_4, NMO, THF, rt, 24 h; 2—DMP, Dowex (H^+), resin. rt, 4 h, 77% two steps; (b) 1—Na(Hg), EtOH, Na_2HPO_4, 0°C, 1 h; 2—MsCl, CH_2Cl_2, Et_3N, 0°C, 30 min; 3—K_2CO_3, dioxane, H_2O, 90°C, 5 h, 70% three steps; (c) 1—Bu_4NF, THF, 12 h, rt, 95%; 2—BMS, THF, rt, 4 h, 87%; 3—1N HCl, reflux, 30 min, 83%.



Scheme 41. (a) Bu_4NF, THF; (b) 1—MsCl, Et_3N, 0°C, 30 min; 2—NaOBz; DMF; reflux, 4 h, 86% two steps; (c) 1—BMS, THF, rt, 2 h; then K_2CO_3, CH_3OH, reflux, 4 h, 94%; 2—1N HCl, reflux, 30 min, 86%.

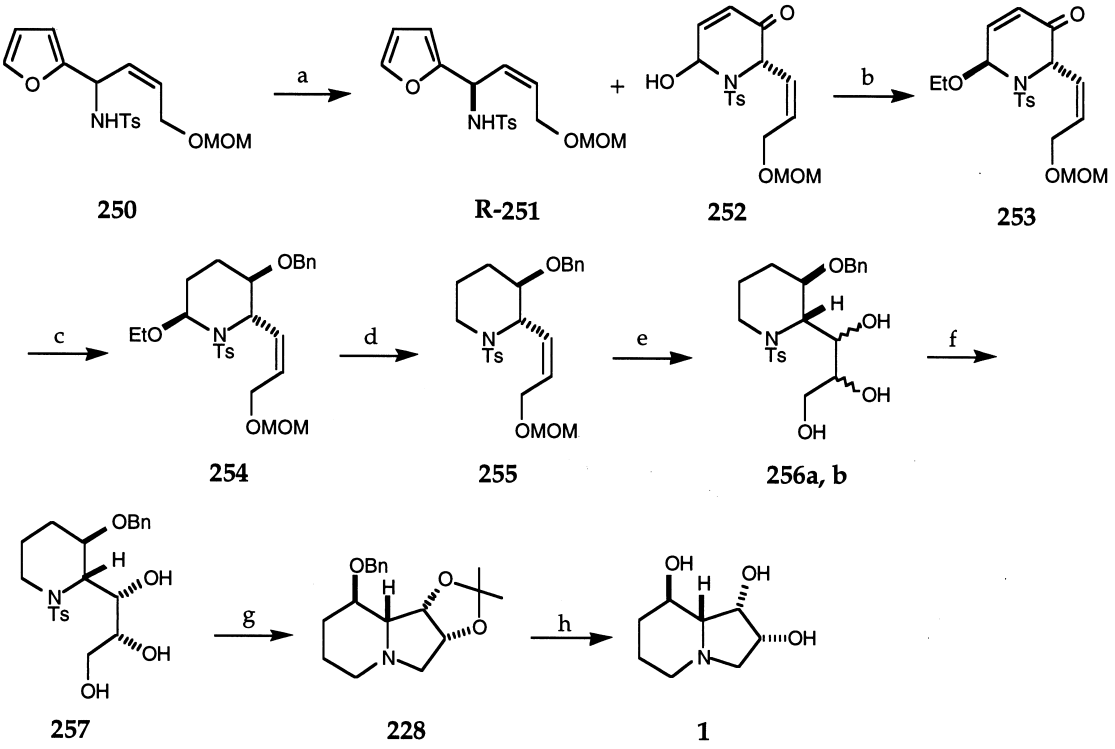


Scheme 42. (a) 1—BzCl, pyr, 0°C, 10 min; 2—TBDMSOTf, Et_3N, CH_2Cl_2 rt, 1 h, 57% two steps; (b) 1—$Cl(CH_2)_3CHO$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C, 3 h, 74% (80% de); 2—OsO_4, NMO, acetone–H_2O, 69% (78% de); (c) 1—DMP, TsOH, acetone, rt, 1.5 h, 99%; 2—$BH_3{\cdot}THF$, reflux, 5 h, 72%; (d) H_2, $Pd(OH)_2$, CH_3OH, 3 h, 65%.

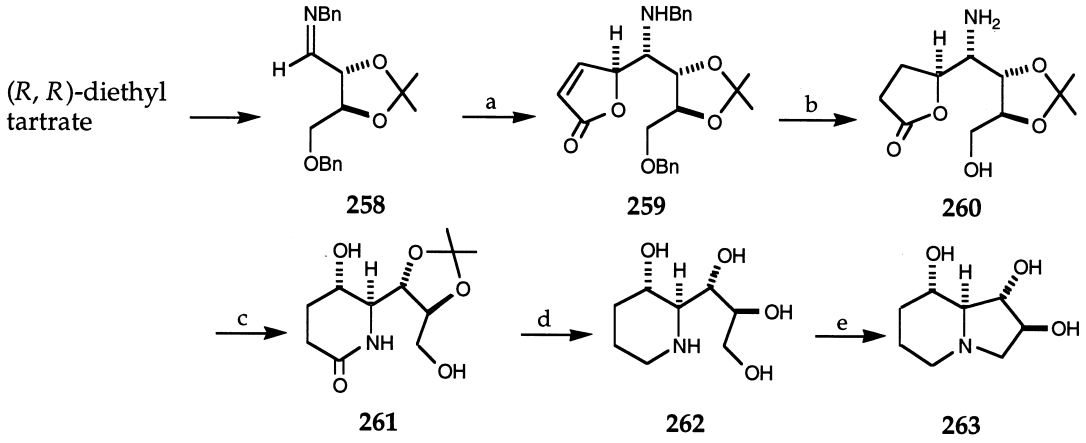
The synthesis of (−)-swainsonine (**1**) has been achieved utilising the kinetic resolution of an α-furfurylamide derivative and Sharpless asymmetric dihydroxylation as the key steps (Scheme 43).[65] Sharpless asymmetric epoxidation of the α-furfurylamide **250** produced the optically active dihydropyridone **252** (42%), which was converted through the intermediate compounds **253** and **254** into **255** in four steps. Dihydroxylation of **255** gave a 10:1 separable mixture of **256a** and its epimer **256b**. Removal of the methoxymethyl and tosyl protecting groups afforded **275**, which underwent intramolecular cyclisation to afford 8-benzyloxy-swainsonine. Direct debenzylation was not successful, but hydrogenolysis of the acetonide **228** followed by acid hydrolysis afforded (−)-swainsonine (**1**).

The syntheses of (+)-2,8,8a-tri-*epi*-swainsonine (**263**) and (−)-1-*epi*-swainsonine (**210**) utilising (*R*,*R*)- and (*S*,*S*)-diethyltartarate as the starting materials have been reported (Schemes 44 and 45).[66]

Enantiomeric L-threose *N*-benzylimine **258**, derived from (*R*,*R*)-diethyl tartarate, was converted into (+)-2,8,8a-tri-*epi*-swainsonine (**263**) via a stereospecific [4+4] homologative procedure using 2-(trimethylsiloxy)-furan



Scheme 43. (a) $Ti(OiPr)_4$, D-(−)-DIPT, TBHP, silica gel, CaH_2, CH_2Cl_2, 25°C, 2 days, ***R*-251** (46%) and **252** (42%); separation; (b) $HC(OEt)_3$, $BF_3{\cdot}OEt_2$, 4 Å M.S., ether, rt, 97%; (c) 1—$NaBH_4$, CH_3OH, −40→−30°C, 88%; 2—BnBr, NaH, Bu_4NI, THF, 96%; (d) $NaBH_4$, HCO_2H, −5→0°C, 90%; (e) OsO_4, NMO, DHQ-CLB, trace $CH_3SO_2NH_2$, acetone–H_2O, ultrasonication, **256a** (73%) and **256b** (7%); (f) TsOH, *t*-BuOH, reflux, 90%; (g) 1—Na, naphthalene, DMF, −60°C; 2—Ph_3P, CCl_4, Et_3N, DMF, 50%, 3—DMP, TsOH, CH_2Cl_2, 94%; (h) deprotection, 57%.



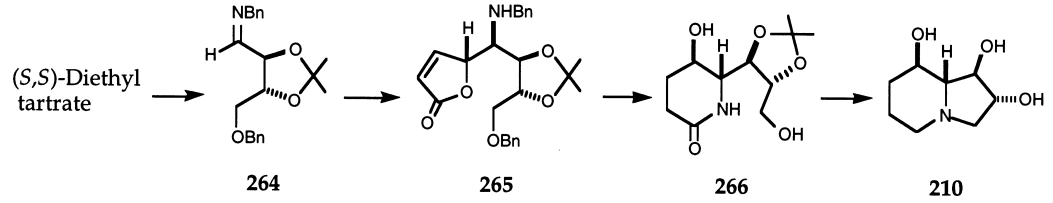
Scheme 44. (a) TMSOF, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −85°C, 4 h, 77%; (b) H_2, 10% Pd on C, NaOAc, THF, rt, 12 h, 90%; (c) DBU, PhH, reflux, 2 h, 95%; (d) 1—BMS, THF, rt, 30 min; 2—60% TFA, rt, 15 min; then Dowex (OH^-), 93%; (e) Ph_3P, CCl_4, Et_3N, DMF, rt, 1 h, 92%.

(TMSOF) to convert **258** into the eight-carbon skeleton of the indolizidine triols **259**. Hydrogenation of the butenolide **259** afforded the amine **260**, which underwent a ring expansion achieved by treatment with DBU in benzene at reflux, to give the δ-lactam **261**. Subsequent reduction of **261**, followed by acid hydrolysis of the isopropylidene protecting group afforded **262** which underwent an intramolecular cyclodehydration with Ph_3P–CCl_4, to furnish the desired (+)-2,8,8a-tri-*epi*-swainsonine (**263**) in 56% overall yield from **258** (Scheme 44).

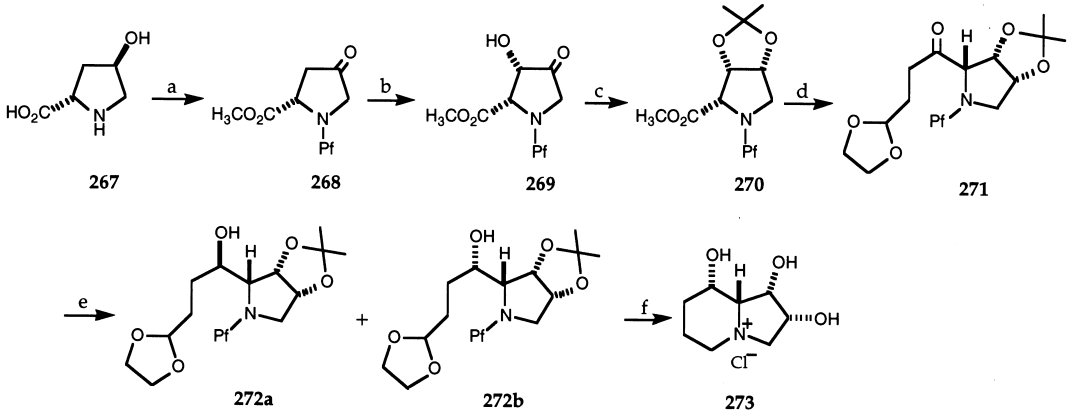
Similarly, (−)-1-*epi*-swainsonine (**210**) was obtained via the intermediate compounds **265** and **266** in 61% overall yield from D-threose *N*-benzylimine **264** by a series of steps analogous to the synthesis of **263** in Scheme 44 (Scheme 45).

A synthesis of 8-*epi*-swainsonine has been reported utilising *trans*-4-hydroxy-L-proline as the starting material (Scheme 46).[67]

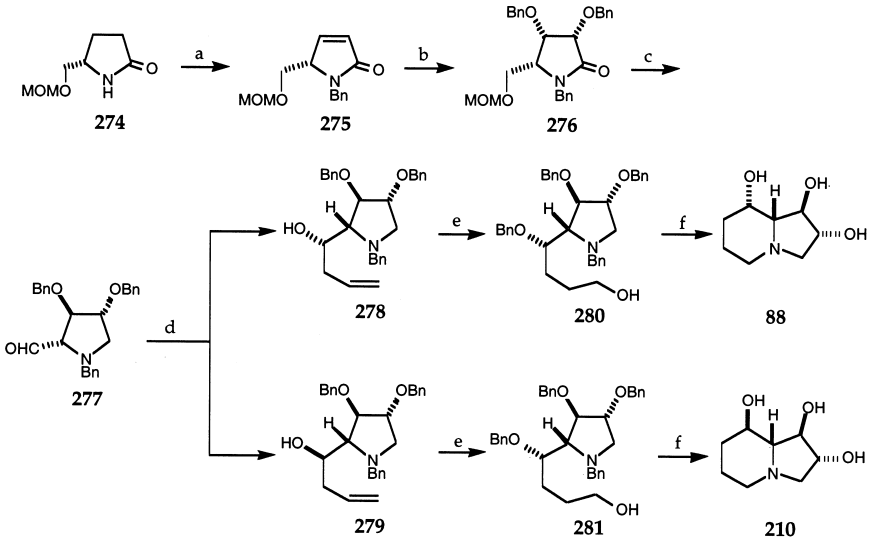
trans-4-Hydroxy-L-proline (**267**) was converted through the intermediate compounds **268** and **269** into the *N*-Pf proline ester **270** in 65% overall yield and subsequent Grignard reaction using 3-(1,3-dioxolane)-1-propyl magnesium bromide as the nucleophile afforded **271**, followed by reduction to afford the alcohols **272a** (18%) and **272b** (74%). After chromatographic separation, compound **272b** was



Scheme 45.



Scheme 46. (a) 1—$SOCl_2$, CH_3OH, 0°C, rt, 74 h, 100%; 2—TMSCl, Et_3N, CH_2Cl_2, reflux, 1 h; then PfBr, Et_3N, $Pb(NO_3)_2$, rt, 96 h, 82%; 3—$(COCl)_2$, DMSO, CH_2Cl_2, −60°C; then Et_3N, 100%; (b) 1—THF, NaHMDS, −78°C, 1.5 h; then MoOPH, THF, −78→−15°C, 2.5 h, 82%; (c) 1—$NaBH_4$, CH_3OH, THF, −78°C, 4 h, 100%; 2—DMP, PPTS, DMF, 5°C, 24 h, 97%; (d) $(CH_2O)_2CH(CH_2)_2MgBr$, THF, 3.5 h, −40→−5°C, 96%; (e) $LiEt_3BH$, THF, 0°C, 18 h, 92%; (f) 1—aq 5% HCl, THF, rt, 2 h; 2—H_2, 10% Pd on C, CH_3OH, 3 h, 94%; then AcOH 36 h.



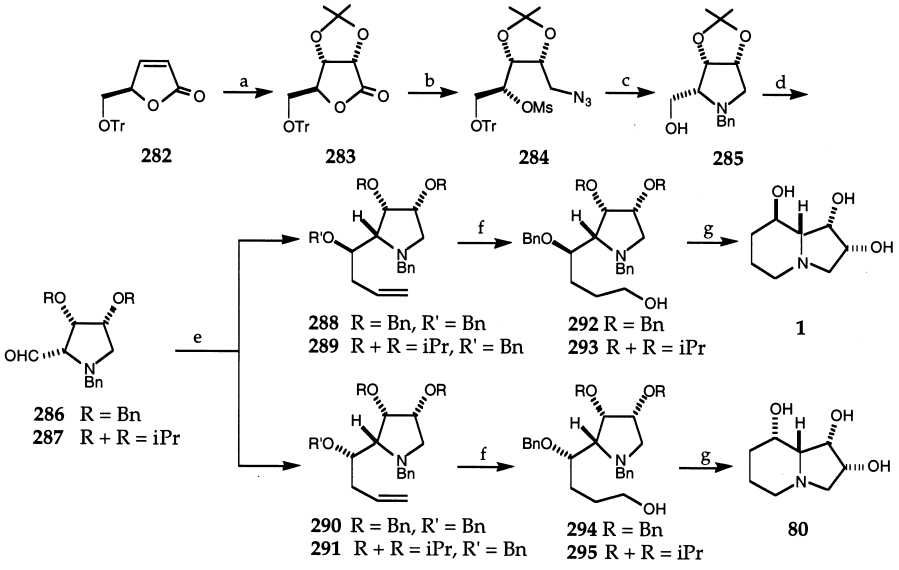
Scheme 47. (a) 1—NaH, BnBr, 1:1 THF–DMF, rt, 15 h, 95%; 2—LDA, THF, −78°C, 40 min; then PhSeCl, THF, −78°C, 15 min, 82%; 3—30% H_2O_2, EtOH, 15–20°C, 20 min, 84%; 4—OsO_4, NMO, 1:1 acetone–H_2O, rt, 13 h, 65%; 5—NaH, BnBr, DMF, rt, 3 h, 85%; (b) 1—$NaOCH_3$, CH_3OH–THF; 2—BMS, THF, reflux; then aq HCl; 3—oxidation; (d) 1—allylMgCl, THF, −78°C, 1 h; 2—lithium diallylcuprate, −78°C, ether, 30 min; or allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78°C, 1 h; 3—NaH, THF–DMF, BnBr, 3 h; (e) BH_3, THF, 40°C, 45 min then NaOH, H_2O_2, 60°C, 30 min, **280** (78%); **281** (67%); (f) 1—MsCl, Et_3N, CH_2Cl_2, rt, 6 h; 2—H_2, 10% Pd on C, EtOH, HCl, CH_3OH, rt, 12 h; then Dowex 50W-X8(H^+), **88** (67%); **210** (64%).

transformed into the 8-*epi*-swainsonine salt **273** in two steps in 44% overall yield from **267**.

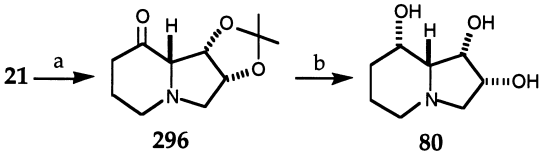
Ikota has reported[68] a stereoselective synthesis of (+)-1,8-di-*epi*-(**88**) and (−)-1-*epi*-swainsonine (**210**) from (*S*)-pyroglutamic acid (Scheme 47).

The aldehyde **277**, derived from (*S*)-pyroglutamic acid via the intermediate compounds **274**, **275** and **276**, was treated with allylmagnesium chloride to give **278** and **279** in a 1:1.6 ratio in 81% total yield, but an opposite ratio (2.2:1) of the epimers **278** and **279** was obtained in 68% total yield when lithium diallylcuprate was used as the reagent. Condensation of **277** with allyltrimethylsilane in the presence of $TiCl_4$, however, gave only **278** in 56% yield. The hydroxyl group generated in **278** was benzylated, followed by hydroboration–oxidation and subsequent mesylation, to give a bicyclic compound, which was hydrogenolysis to afford (+)-1,8-di-*epi*-swainsonine (**88**). The other epimer **279** was similarly converted into (−)-1-*epi*-swainsonine (**210**).

The aldehyde **286** (derived from **282** via the intermediate compounds **283**, **284** and **285**) was converted into (−)-swainsonine [through the intermediate compounds



Scheme 48. (a) 1—OsO_4, NMO, aq acetone; 2—DMP, acetone, *p*-TsOH; (b) 1—$LiAlH_4$, THF; 2—MsCl, pyr; 3—NaN_3, DMF, 130°C; (c) 1—H_2, Pd-black, EtOH; 2—BnBr, K_2CO_3, acetone, then conc. HCl, CH_3OH (1:99); (d) oxidation; or 1—MOMCl, *N,N*-diethylaniline; 2—10% HCl, CH_3OH, 40°C; 3—BnBr, NaH, DMF–THF; then 10% HCl, CH_3OH, 70°C; 4-oxidation; (e) 1—allylMgCl, THF, −78°C, 1 h; or allylMgCl, CuI, 5:1 THF–$(CH_3)_2S$, −78°C→rt, 1 h; or allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78°C, 2 h; 2—NaH, THF–DMF, BnBr, rt, 2 h; (f) BH_3, THF, 45°C, 1 h then 3N NaOH, H_2O_2, 60°C, 1 h; then 10% aq HCl, 60°C, 5 min; then 10% aq NaOH; (g) 1—MsCl, Et_3N, CH_2Cl_2, rt, 6 h, 2—0% aq HCl–CH_3OH, 70°C, 1 h; and/or H_2, 10% Pd on C, EtOH, HCl, CH_3OH, rt, 6 h.



Scheme 49. (a) DCC, DMSO; (b) 1—$NaBH_4$; 2–75% aq TFA; 18% for a and b.

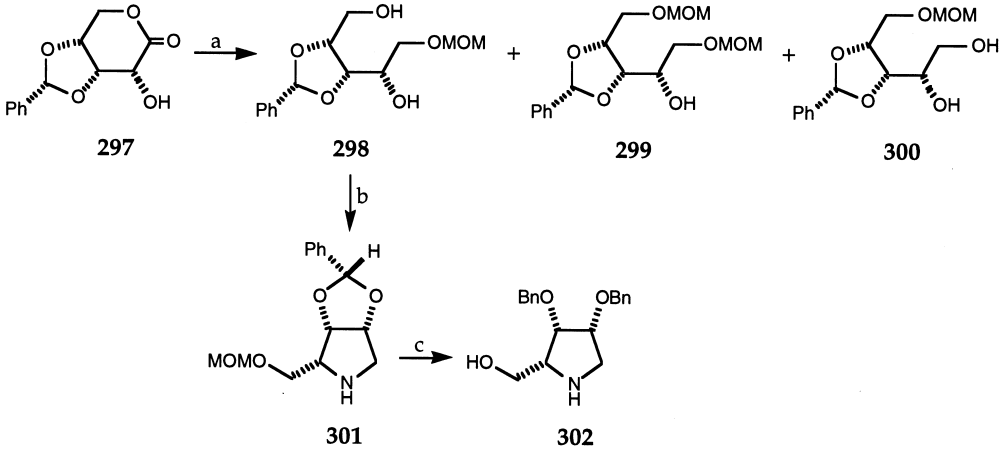
288, **289**, **292** and **293**] and 8-*epi*-swainsonine (through the intermediate compounds **290**, **291**, **294** and **295**) by a series of steps analogous to the synthesis of (+)-1,8-di-*epi*-swainsonine (**88**) in Scheme 47 (Scheme 48).[69]

8-*epi*-Swainsonine (**80**) has been obtained from swainsonine acetonide **21** via an oxidation–reduction of the free hydroxyl group at C-8 (Scheme 49).[70]

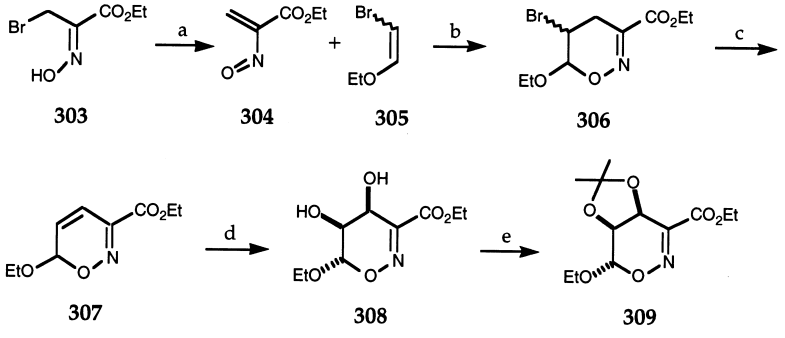
Facile syntheses of the pyrrolidine derivatives **302** and **313**, which are intermediates for the preparation of (−)-swainsonine (**1**) and some of its analogues shown in Schemes 47 and 48, have been developed (Schemes 50–52).[71]

Reduction of Zinner's lactone **297**, derived from D-ribonolactone, with lithium aluminum hydride followed by treatment with 1.3 equiv. of chloromethyl methyl ether gave **298** in 53% yield, together with **299** (10.5%) and **300** (5%). Compound **298** was separated and converted into the pyrrolidine **301** in three steps in 50% yield, which was converted to the desired pyrrolidine **302** in 13% overall yield from Zinner's lactone **297** (Scheme 50).[71a]

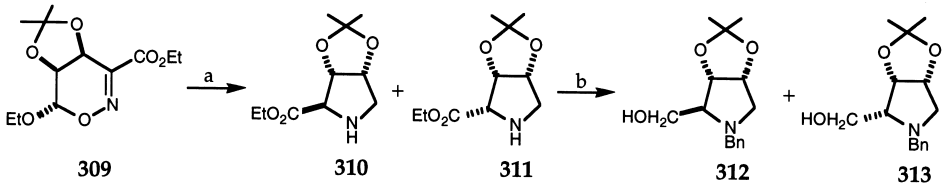
The 6*H*-1,2-oxazine **307**, derived from the α-halogenated oxime **303** and the β-bromoenol ether **305** via the intermediate compounds **304** and **306**, underwent *cis*-dihydroxylation with $KMnO_4$ to give the diol **308**, followed by isopropylidene protection to give the diastereomerically pure 1,2-oxazine **309** in 74% overall yield (Scheme 51).[71b]



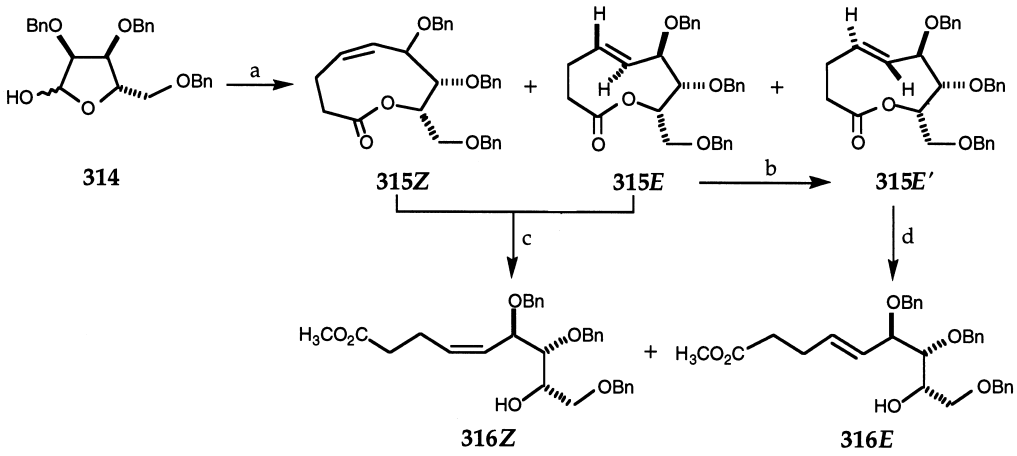
Scheme 50. (a) 1—$LiAlH_4$, THF, rt, 5 h, 92%; 2—Chloromethyl methyl ether, CH_2Cl_2, −10→−20°C, 32 h, total 68.5%; (b) 1—MsCl, pyr, 0°C, 15 h, 100%; 2—NaN_3, DMF, 110–120°C, 2.5 h, 69%; 3—H_2, Pd-black, EtOH, 73%; (c) 1—BnBr, K_2CO_3, acetone, rt, 2 h, 95%; 2–10% aq HCl, CH_3OH, 40°C, 2 h, 64%; 3—NaH, BnBr, DMF, THF, rt, 4 h, 92%; 4–10% aq HCl, CH_3OH, 70°C, 2 h, 96%.



Scheme 51. (a) Na_2CO_3; (b) *t*-$BuOCH_3$, rt, 6 days; (c) DBU, rt, 1 day; (d) $KMnO_4$, $MgSO_4$, EtOH, H_2O, −45°C→rt; (e) DMP, TsOH, acetone, rt, 74% overall yield.



Scheme 52. (a) 1—H_2, Pd on C, 2N HCl, EtOH; 2—DMP, TsOH, acetone, rt, 63%; (b) 1—BnCl, NaOH, K_2CO_3, EtOH, 50°C; 2—$LiAlH_4$, Et_2O, rt, 56%.



Scheme 53. (a) 1—CH_2=CHMgBr, THF, 0°C, 3 h, 97%; 2—$PhSeCH_2CH(OEt)_2$, PPTS, toluene, reflux, 4.5 h; 3—$NaIO_4$, $NaHCO_3$, CH_3OH, H_2O, 10 min, rt; 4—DBU, toluene, reflux, 24 h, 54%; (b) toluene, reflux, 24 h; (c) $NaOCH_3$, CH_3OH, separate, **316*Z*** (39%) and **316*E*** (37%); (d) $NaOCH_3$, CH_3OH, **316*E*** (91%).

Hydrogenolysis of **309** in acidic media followed by reprotection of the partially liberated hydroxy groups furnished the *cis*-dihydroxylated proline esters **310** and **311** in a 1:1 diastereomeric mixture. Benzylation followed by separation and reduction of **310** and **311** gave **312** (17%) and **313** (39%), respectively (Scheme 52).[71b]

3. Syntheses of 1,2,8-Trihydroxyindolizidine Analogues

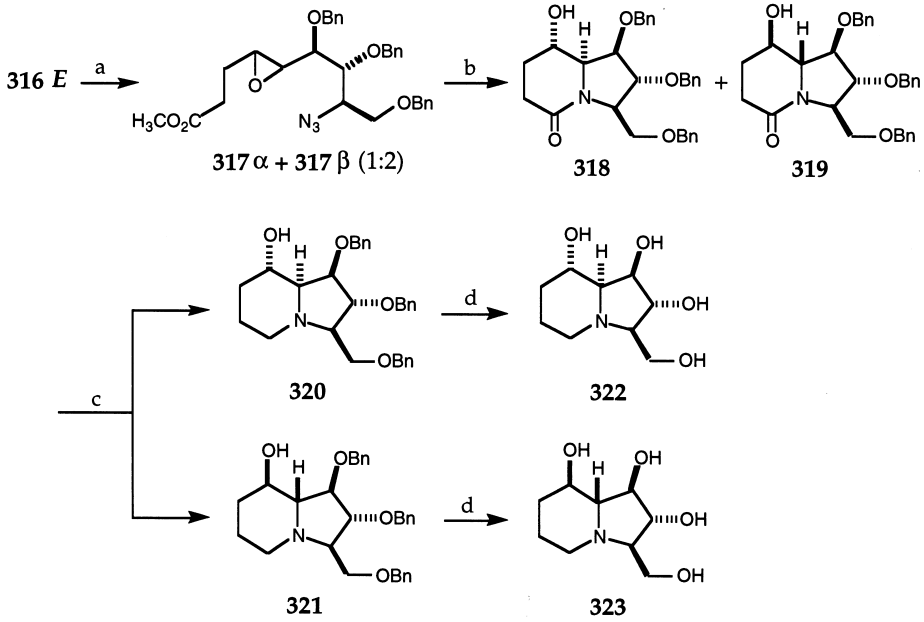
The syntheses of structural analogues of 1,2,8-trihydroxyindolizidines are currently of interest in connection with attempts to correlate structure with biological activity.

3.1. Syntheses of 3-(hydroxymethyl)-1,2,8-trihydroxyindolizidines

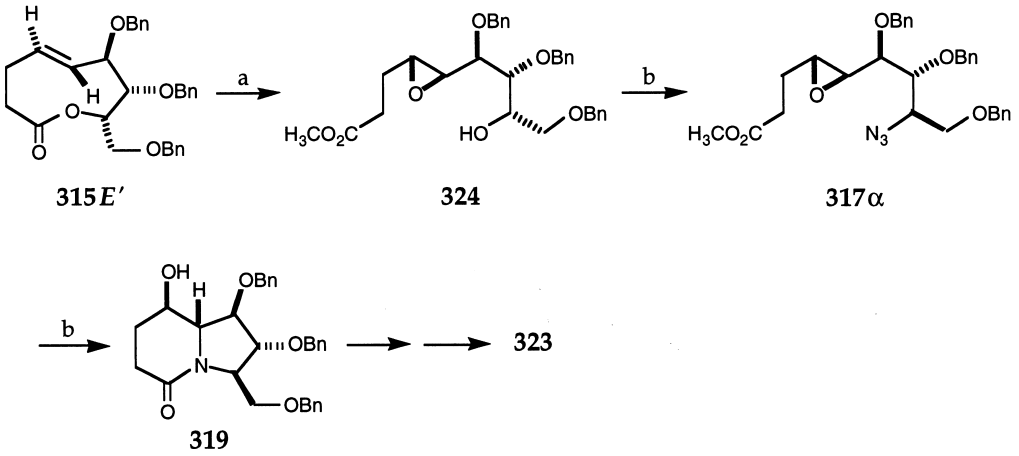
Swainsonine derivatives bearing a hydroxymethyl group at C-3 have been synthesised with the expectation that they will be potent mannosidase inhibitors and perhaps be useful as anticancer agents, as is the naturally occurring parent molecule.

The first examples of 3-(hydroxymethyl)indolizidines have been synthesised as illustrated in Schemes 53–56.[72]

Tri-*O*-benzyl-L-xylofuranose (**314**) was treated with vinylmagnesium bromide followed by acetal formation with (phenylseleno)acetaldehyde diethylacetal. Subsequent



Scheme 54. (a) 1—HN_3, PPh_3, DEAD, PhH, 82%; 2—*m*CPBA, CH_2Cl_2, rt, 24 h, 67%; (b) H_2, $Pd(OH)_2$, on C, CH_3OH, EtOAc, 4 h; 2—$NaOCH_3$, CH_3OH, reflux, 24 h, 79%; (c) BMS, THF, 6 h, rt, **320** (64%), **321** (32%); (d) H_2, Pd on C, HCl, CH_3OH; Dowex OH^-, **322** (88%), **323** (74%).



Scheme 55. (a) 1—*m*CPBA, CH_2Cl_2, 88%; 2—$NaHCO_3$, CH_3OH, THF, 89%; (b) HN_3, PPh_3, DEAD, PhH, 85%; (c) H_2, $Pd(OH)_2$ on C; then $NaOCH_3$, CH_3OH, reflux, 82%.

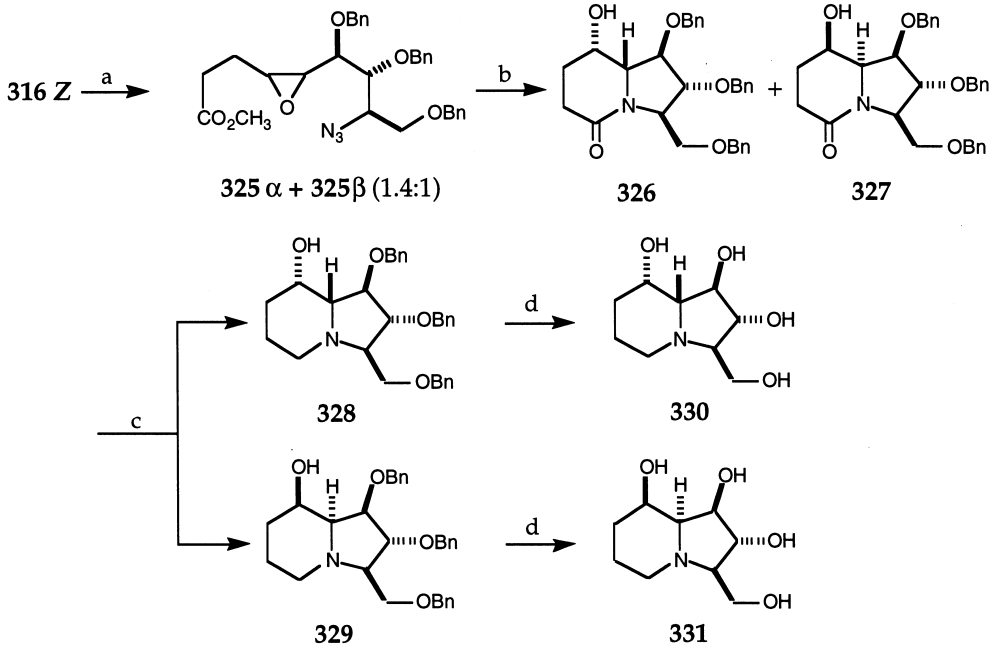
selenide oxidation followed by selenoxide elimination and Claisen rearrangement afforded a mixture of three products; chromatography afforded two fractions, the first containing **315*Z*** and **315*E*** in a 1:1 ratio and the second containing **315*E′***. Heating the purified mixture of **315*Z*** and **315*E*** in toluene gave a slow conversion of **315*E*** into **315*E′***. Methanolysis of the mixture of **315*Z*** and **315*E*** afforded **316*Z*** (39%) and **316*E*** (37%). Methanolysis of **315*E′*** gave **316*E*** (91%) (Scheme 53).

Conversion of **316*E*** to the mixture **317** using a Mitsunobu reaction with hydrazoic acid, followed by azide reduction and intramolecular cyclisation, gave the inseparable indolizidinones **318** and **319**, and these were reduced with borane, separated and debenzylated to give the desired compounds **322** and **323** (Scheme 54).

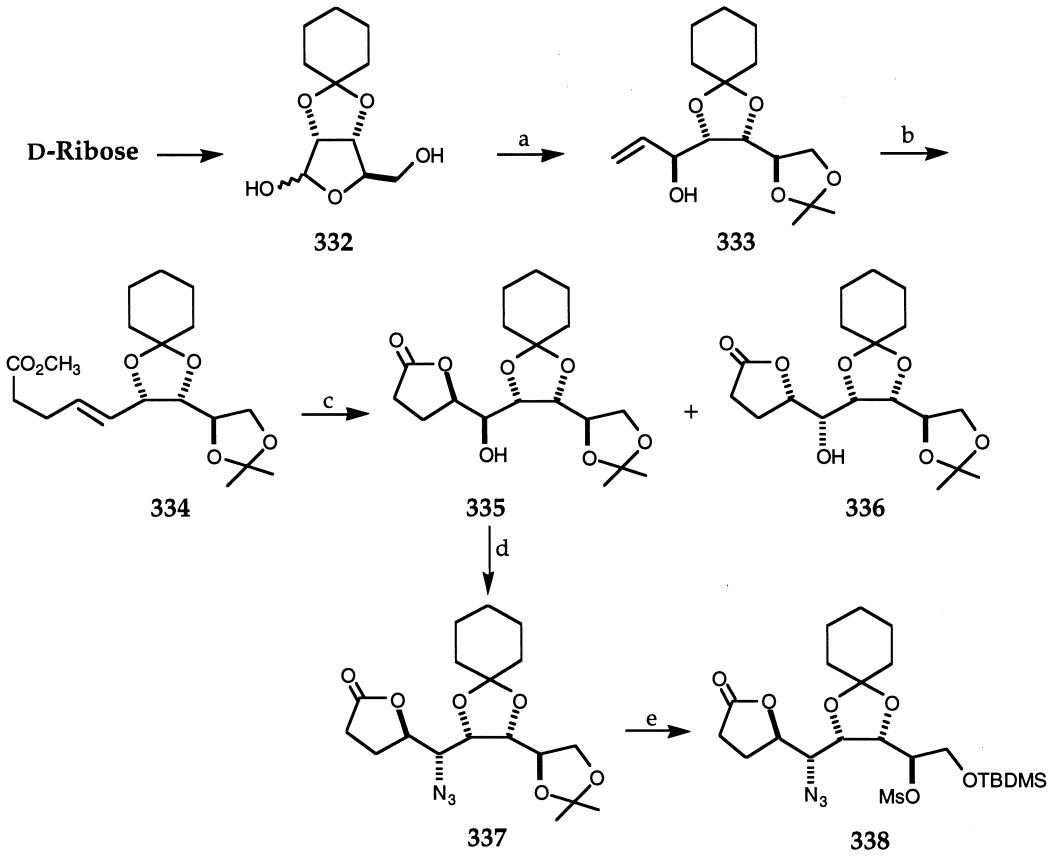
Epoxidation of **315E′** followed by mild transesterification with methanol afforded **324**, which was subjected to a Mitsunobu reaction followed by reductive double cyclisation to afford the indolizidinone **319** in 55% overall yield from **315*E′***. Compound **319** was similarly converted to the indolizidine **323** (Scheme 55).

Compound **316*Z*** reacted with hydrazoic acid followed by epoxidation to give an inseparable mixture of the diastereomeric *cis*-epoxides **325**α and **325**β which was converted into **330** and **331** by a series of steps analogous to the synthesis of compounds **322** and **323** (Scheme 56).

All four compounds **322**, **323**, **330** and **331** were found to be good inhibitors of amyloglucosidase (*Aspergillus niger*), but they did not inhibit β-glucosidase (almond) or



Scheme 56. (a) 1—HN_3, PPh_3 DEAD, PhH, 85%; 2—*m*CPBA, CH_2Cl_2, rt, 24 h, 75%; (b) H_2, $Pd(OH)_2$ on C, CH_3OH, EtOAc, 4 h; then $NaOCH_3$, CH_3OH, reflux, 24 h; separate, **326** (46%) and 327 (**33**%); (c) BMS, THF, 6 h, rt, **328** (62%), **329** (84%); (d) H_2, Pd on C, HCl, CH_3OH; Dowex OH^-, **330** (62%), **331** (82%).

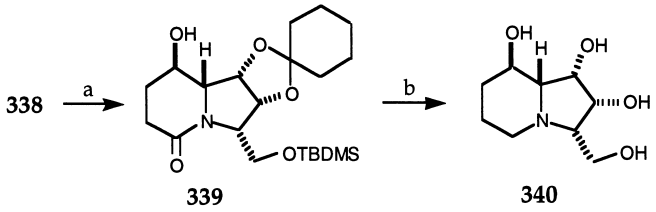


Scheme 57. (a) 1—*i*-PrMgBr, THF, 15 min; 2—CH_2=CHMgBr, THF, rt, 12 h; 3—DMP, PPTS, $MgSO_4$, THF, rt, 18 h, 70% three steps; (b) $MeC(OMe)_3$, $EtCO_2H$, toluene, refluex, 18 h, 99%;(c) $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, $K_3Fe(CN)_6$, K_2CO_3, 36 h, **335** (66%) and 336 (6%) from **333**; (d) 1—MsCl, pyr, DMAP, 2°C, 24 h; 2—*n*-Bu_4NN_3, THF, reflux, 48 h, 65% two steps; (e) 1—aq H_2SO_4, THF, *i*-PrOH, 18 h, 55%; 2—TBDMSCl, imidazole, THF, DMF, 1 h; 3—MsCl, pyr, DMAP, 2°C, 24 h, 84% two steps.

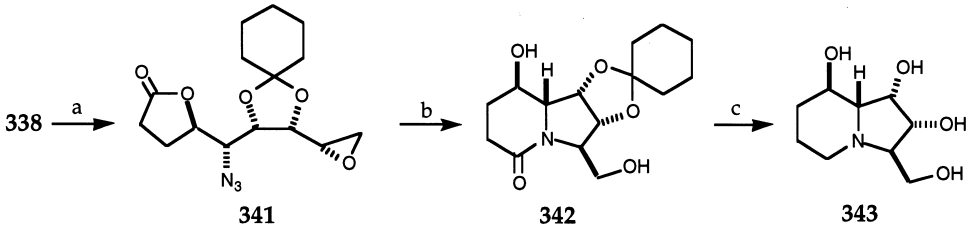
α-glucosidase (bakers yeast) and were only weak inhibitors of α-mannosidase (jack bean).

Attempt have been made to synthesise (3*S*)-(hydroxymethyl)swainsonine (**340**) and (3*R*)-(hydroxymethyl)swainsonine (**343**) starting with D-ribose, and involving a Claisen rearrangement, a Sharpless osmylation, and a reductive double cyclisation (Schemes 57–59).[73]

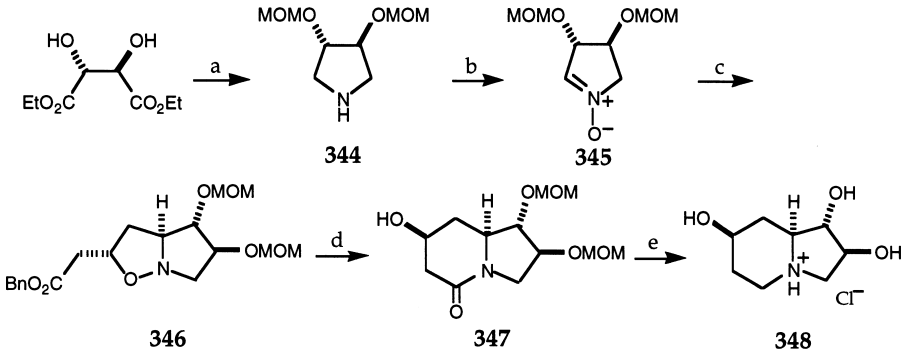
Deprotonation of 2,3-*O*-cyclohexylidene-D-ribose (**332**) was followed by addition of vinylmagnesium bromide to give a triol, which was reacted with acetone to give the



Scheme 58. (a) H_2, $Pd(OH)_2$ on C, CH_3OH, EtOAc, 2 h; then $NaOCH_3$, CH_3OH, reflux, 30 min, 77%; (b) 1—BMS, THF, rt, 4 h, 94%; 2—6N HCl, THF, rt, 24 h; then Dowex OH^-, 80%.



Scheme 59. (a) CsF, CH_3CN, reflux, 2 h, 96%; (b) H_2, $Pd(OH)_2$ on C, CH_3OH, EtOAc, 2 h; then $NaOCH_3$, CH_3OH, reflux, 60 h, 64%; (b) 1—BMS, THF, CH_2Cl_2, rt, 4 h, 99%; 2—6N HCl, THF, rt, 24 h; then Dowex OH^-, 75%.



Scheme 60. (a) 1—$(CH_3O)_2CH_2$, $CHCl_3$ 2 h, P_2O_5, 97%; 2—$LiAlH_4$, THF, −78°C→rt, 1 h, 75%; 2—MsCl, Et_3N, CH_2Cl_2, 0°C, 1 h, 84%; 4—$PhCH_2NH_2$, 60°C, 3 days, 89%; 5—H_2, $Pd(OH)_2$ on C, CH_3OH; (b) SeO_2, H_2O_2, acetone; (c) $CH_2{=}CHCH_2CO_2Bn$, toluene, reflux, 4 days, 44%; (d) Zn, HOAc, 60°C, 2 h, 83%; (e) 1—BMS; then EtOH, reflux, 95%; 2—6 M HCl; then EtOH, HCl, Et_2O, 75%.

allylic alcohol **333** as a single diastereomer. Application of a Johnson orthoester Claisen rearrangement to **333** gave the γ,δ-unsaturated ester **334**. Sharpless asymmetric dihydroxylation of **334** afforded the lactones **335** and **336**, the major product **335** was converted into the azide **337** which subsequently being converted into the azidomesylate **338** in three steps (Scheme 57).

Hydrogenolysis of **338** followed by heating with $NaOCH_3$ completed the intramolecular cyclisation, providing the indolizidinone **339**. Subsequent reduction followed by complete deprotection afforded (3*S*)-(hydroxymethyl)-swainsonine (**340**) in 8% overall yield from **332** (Scheme 58).

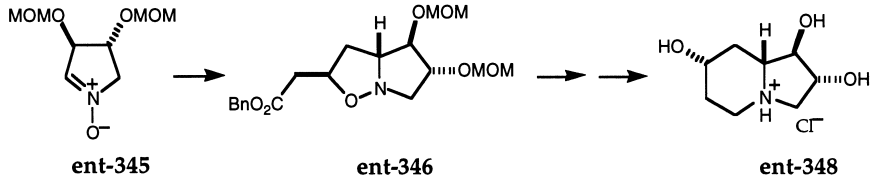
Conversion of **338** into the epoxide **341** was followed by hydrogenolysis and intramolecular cyclisation to produce the lactam **342**. Reduction of **342** followed by deprotection gave the target compound, (3*R*)-(hydroxymethyl)swainsonine (**343**), in 6% overall yield from **332** (Scheme 59).

These two hydroxymethyl-substituted swainsonine analogues **340** and **343** were found to be inhibitors of α-mannosidase (jack bean), but they were not as potent as (−)-swainsonine (**1**).

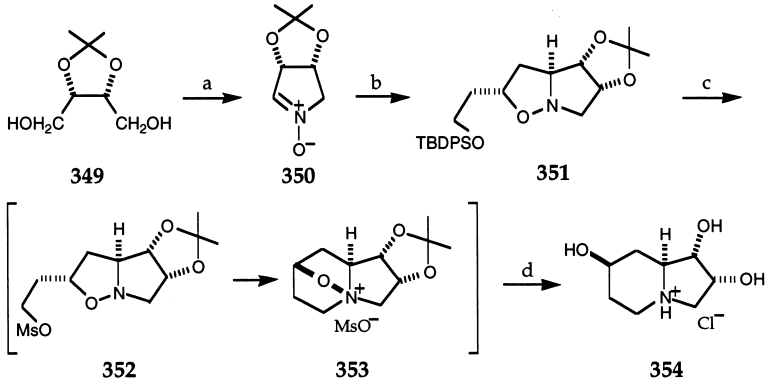
3.2. Syntheses of 1,2,7-trihydroxyindolizidines

Most of the reported syntheses of 1,2,7-trihydroxyindolizidines (swainsonine analogues having a hydroxy substituent at C-7 instead of C-8) utilise a cycloaddition to a 3,4-dihydroxypyrroline *N*-oxide.

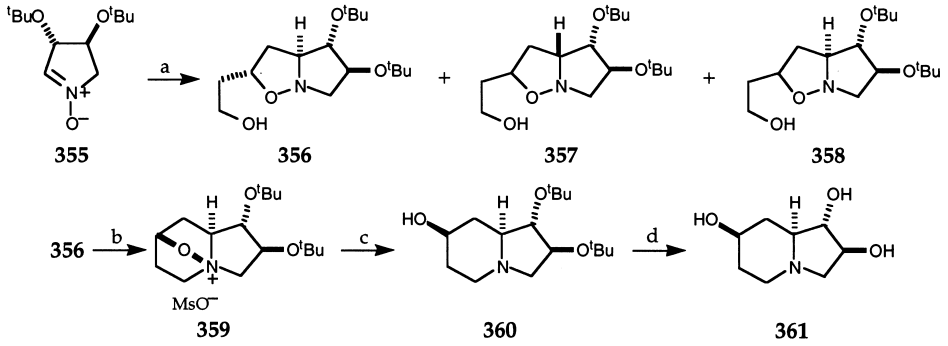
Diethyl L-tartrate was converted into the pyrrolidine **344** in five steps. Reaction with Davis reagent gave the nitrone **345**, which was treated directly with benzyl but-3-enoate to give **346**. Reductive cleavage of the N–O bond accompanied by cyclisation afforded the lactam **347**. Subsequent reduction followed by acid hydrolysis of **347** gave the salt **348** (Scheme 60).[74]



Scheme 61.



Scheme 62. (a) 1—MsCl, Et_3N, CH_2Cl_2, 84%, 2—$BnNH_2$, 65°C, 48 h, 84%; 3—H_2, $Pd(OH)_2$ on C, CH_3OH, 85%; 4—2-(phenylsulfonyl)-3-phenyloxaziridine, $CHCl_3$, 91%; (b) $CH_2{=}CHCH_2CH_2OTBDPS$, toluene, reflux, 92%; (c) 1—Bu_4NF, THF; 2—MsCl, pyr; (d) 1—H_2, Pd on C, EtOH, 74% three steps; 2—1:1 TFA–H_2O; then EtOH, HCl–Et_2O, 76%.



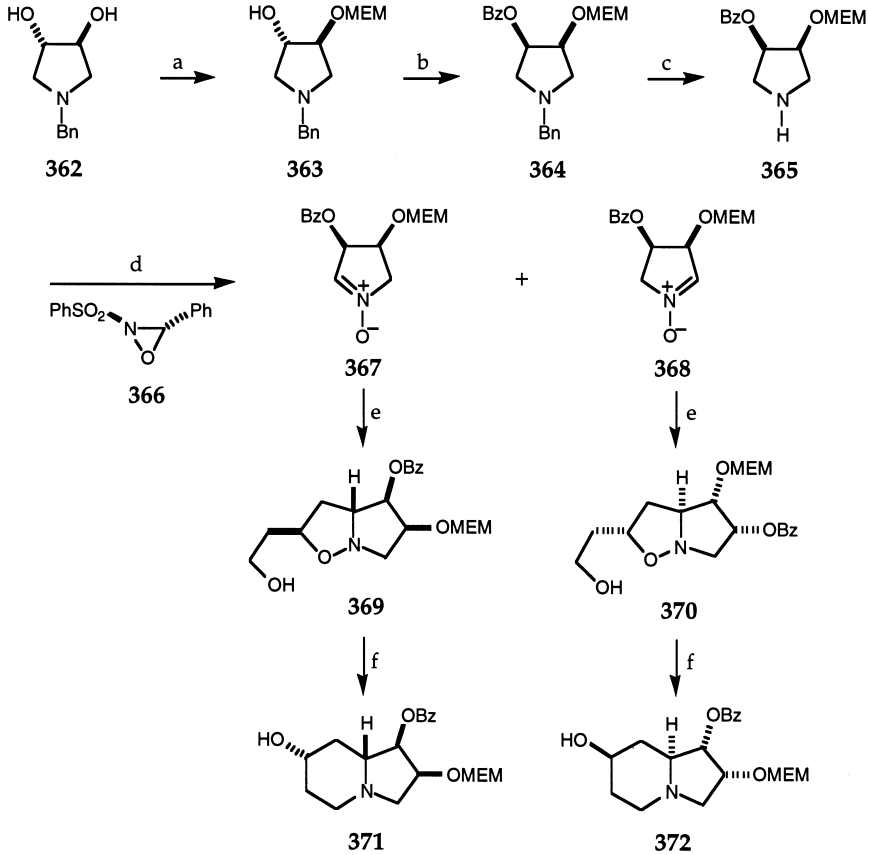
Scheme 63. (a) $CH_2{=}CHCH_2CH_2OH$, 60°C, 2 days, 100%; (b) MsCl, Et_3N, CH_2Cl_2; H_2, 10% Pd on C, CH_3OH, 24 h, 86%; (d) TFA, 24 h, 93%.

ent-**345** (obtained from diethyl D-tartrate) was converted into *ent*-**348** by a series of steps analogous to the synthesis of **348** (Scheme 61).[74] Compounds **348** and *ent*-**348** are inactive against HIV-1.

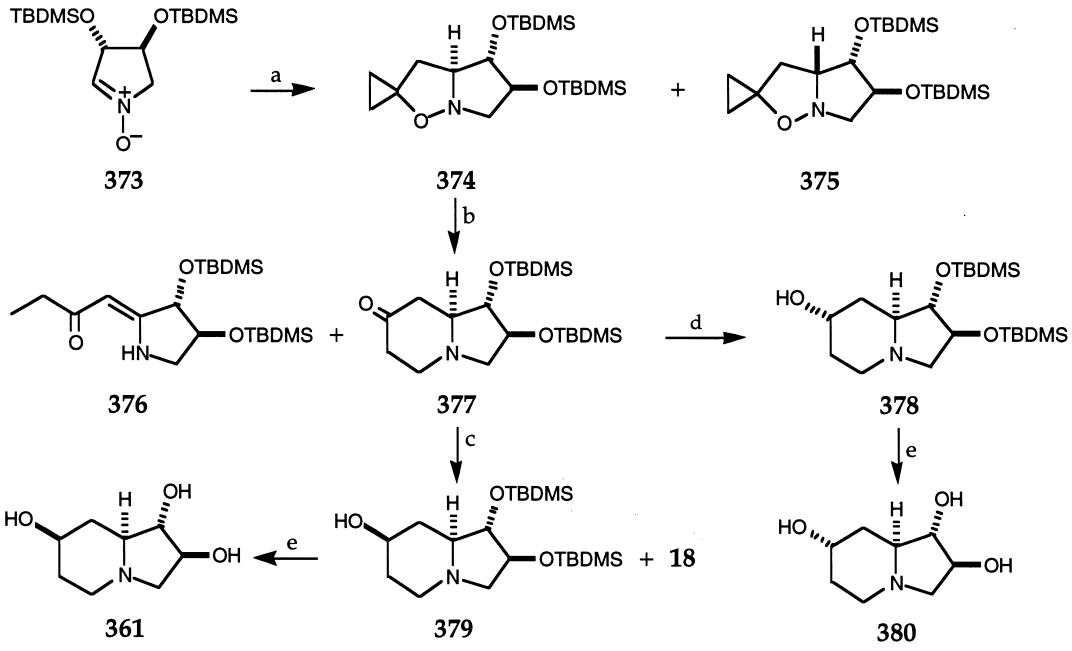
For the synthesis of the swainsonine analogue **354**, the diol **349** obtained from D- or L-arabinopyranose was treated with excess methanesulfonyl chloride, heated with benzylamine, followed by debenzylation and oxidation with Davis reagent to give the racemic nitrone **350**, which was treated with the homoallyl alcohol to give **351**. This was desilylated and transformed into the corresponding mesylate **352** which underwent internal S_N2 type attack by the bridgehead nitrogen in sito to give the salt **353**. Hydrogenation of **353** followed by acid hydrolysis afforded salt **354** (Scheme 62). The salt **354** showed no significant inhibition of the replication of HIV-1.[74b]

The nitrone **355** (derived from L-tartaric acid) was heated with the dipolarophile, 3-buten-1-ol, to give a 10:2:1 mixture of the diastereoisomers **356**, **357** and **358**. Compound **356** was separated by column chromatography in 79% yield, then transformed into the salt **359**. Reductive ring opening of **359** gave **360**, and deprotection of **360** gave (1*S*,2*S*,7*R*, 8a*S*)-trihydroxyindolizidine (**361**) (Scheme 63).[75]

For the syntheses of the swainsonine analogues, **371** and



Scheme 64. (a) NaH, MEMCl, THF, 0°C, 75 min, 61%; (b) Ph_3P, PhCOOH, DEAD, THF, 0°C→rt, 24 h, 76%; (c) 1—H_2 $Pd(OH)_2$ on C, CH_3OH, rt, 21 h, 100%; (d) CH_3Cl, 0°C, 20 min, rt, 40 min, **367** (33%), **368** (26%); (e) 1—Bu-3-en-1-ol, PhH, 60°C, 43 h, **369** (92%), **370** (97%); (f) 1—NEt_3, MsCl, CH_2Cl_2, 0°C; 2—H_2 10% Pd on C, CH_3OH, rt, 12 h, **371** (75%), **372** (57%).



Scheme 65. (a) methylenecyclopropane, PhH, sealed tube, 35°C, 11 days, **374** (63%) and **375** (~15%); (b) *o*-dichlorobenzene, 130°C, 3 h, **376** (31%) and **377** (41%); (c) $NaBH_4$, axial attack, 84%; (d) LS-Selectride, equatorial attack, 51%; (e) 40% aq HF, **361**, 75%; **380**, 89%.

enti-**372**, monoprotection of the *trans*-3,4-dihydroxypyrrolidine **362** (available from L-tartaric acid) with MEMCl afforded **363** in 61% yield, followed by inversion of the unprotected hydroxy group under Mitsunobu conditions to give the benzoate **364**. Debenzylation of **364** gave the optically pure pyrrolidine **365**. Oxidation of **365** was achieved by using *N*-benzenesulfonyl-*C*-phenyloxaziridine **366** to give the nitrones **367** (33%) and **368** (26%) which were converted into the major cycloadducts, **369** (7:1 *exo*/*endo*) and **370** (7:1 *exo*/*endo*), and these were separated and converted into the indolizidinols **371** and **372** (Scheme 64).[76]

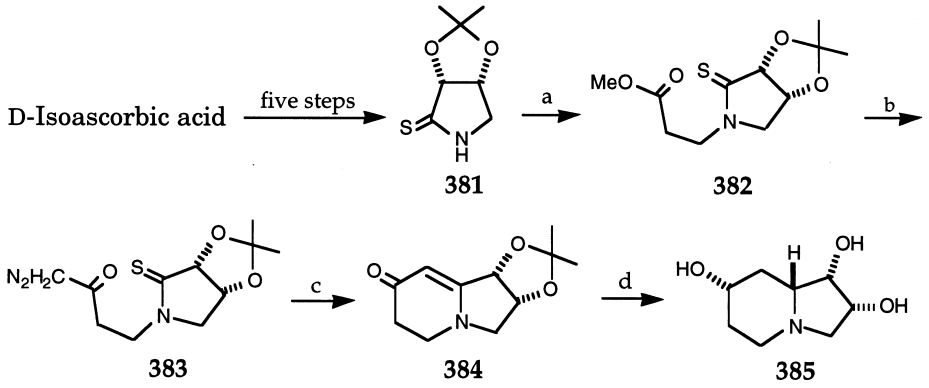
Another route utilising a 1,3-dipolar cycloaddition to methylenecyclopropane followed by thermal rearrangement has been used for the syntheses of the 1,2,7-trihydroxyindolizidines **361** and **380** (Scheme 65).[77]

The TBDMS-protected nitrone **373**, obtained in 22% overall yield from L-tartaric acid in five steps, was converted into the TBDMS-protected ketone **377** in two steps by the usual cycloaddition–thermal rearrangement procedure in 26% overall yield. The cycloaddition and rearrangement steps were similar to those used for the corresponding nitrone **373**. Reduction of **377** with $NaBH_4$ afforded a 94:6 mixture of the alcohols **378** and **379**. Reduction with the bulkier LS-selectride, however, afforded **378** as the sole product. Deprotection of **378** and **379** gave the corresponding (1*S*,2*S*,7*R*,8*aS*)-1,2,7-trihydroxyindolizidine (**361**) and (1*S*,2*S*,7*S*,8*aS*)-1,2,7-trihydroxyindolizidine (**380**).

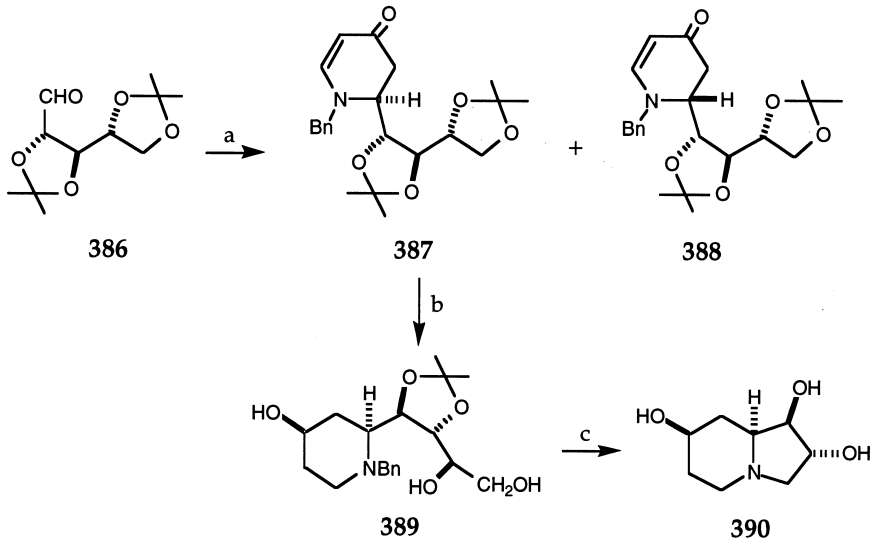
The compounds **361** (10 μM) and **380** (290 μM) are inhibitors of amyloglucosidase from *Aspergillus niger*.

Aza-Robinson annulation (Michael addition and thioamide-diazoketone cyclocondensation) has been used in the synthesis of 1,2,7-trihydroxyindolizidine (**385**) (Scheme 66).[78]

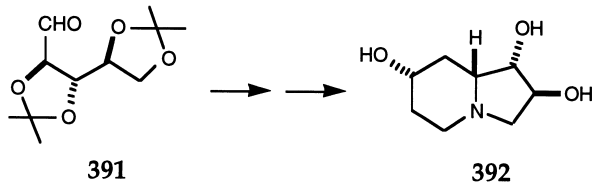
The thiopyrrolidone **381** was obtained in five steps from D-isoascorbic acid and Michael addition of **381** to methyl acrylate afforded **382** quantitatively. This was converted



Scheme 66. (a) Methyl acrylate, THF, NaOH, 25°C, 100%; (b) 1—NaOH, CH_3OH–H_2O, 25°C; 2—$ClCO_2Et$, CH_2Cl_2, 0°C; 3—CH_2N_2, CH_2Cl_2, Et_2O, 0°C; (c) 1—$[Rh(OAc)_2]_2$, PhH, reflux; 2—H_2, Raney nickel W2, acetone, 25°C; (d) 1—$LiAlH_4$, THF; 2—acid hydrolysis.



Scheme 67. (a) 1—$BnNH_2$, PhH, rt, 30 min; 2—CH_2=C($OSiMe_3$)CH=CHOMe, $ZnCl_2$, dioxane, rt, 1 h, **387** (65%) and **388** (14%); (b) 1—$NaBH_4$, EtOH, rt, 14 h, 99%; 2—AcOH, H_2O, 55°C, 10 h, 84%; (c) 1—$Pb(OAc)_4$ PhH, rt, 10 min; 2—TFA, H_2O, rt, 10 h; 3—H_2, Pd on C, AcOH, rt, 16 h 54% three steps.



Scheme 68.

into the diazoketone **383** in three steps in 56% overall yield. Cyclization of **383** in refluxing benzene with a catalytic amount of rhodium acetate followed by desulphurization with Raney nickel in acetone afforded the enaminone **384** in 60% yield from **383**. Treatment of **384** with an excess of lithium aluminium hydride was followed by deprotection to afford (1*S*,2*R*,7*S*,8a*R*)-1,2,7-trihydroxyindolizidine (**385**).

Cyclocondensation of azomethines with Danishefsky's diene has been used as a key step in the syntheses of the 1,2,7-trihydroxyindolizidines **390** and **392** (Schemes 67 and 68).[79]

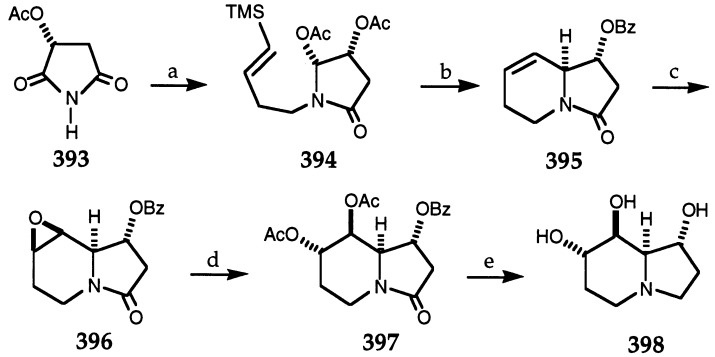
Condensation of the aldehydo-D-arabinose **386** with benzylamine followed by cyclocondensation with CH_2=C($OSiMe_3$)CH=CHOMe afforded a separable mixture of the diastereomers **387** (65%) and **388** (14%). Reduction of the olefin and keto functions of **387** in a single diastereomer was achieved by sodium borohydride and the product was subjected to partial hydrolysis of the terminal isopropylidene protecting group to give compound **389**. Glycol-cleaving oxidation followed by hydrolysis of the dioxolane ring and intramolecular reductive amination afforded **390** in a 29% overall yield from **386** (Scheme 67). Similarly, the aldehydo-L-arabinose **391** was converted into the triol **392** (Scheme 68).

Compound **390** competitively inhibits *Lupinus luteus* α-mannosidase and compound **392** is a β-glucosidase inhibitor (from sweet almond).[79]

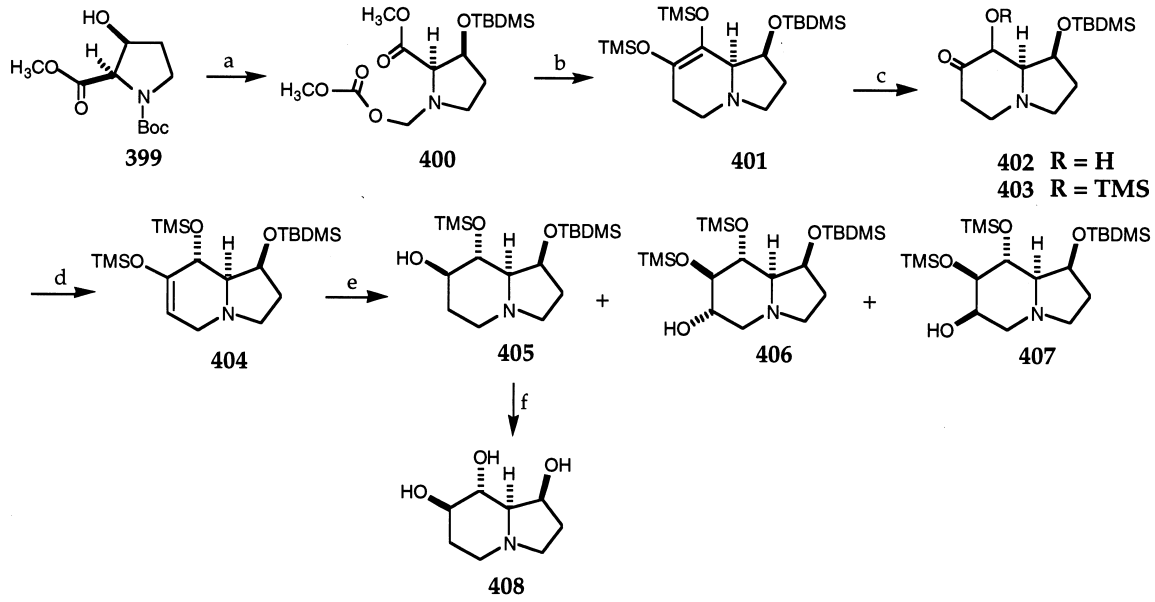
3.3. Syntheses of 1,7,8-trihydroxyindolizidines

A methodology starting from a compound with only one chiral centre was used to produce 1,7,8-trihydroxyindolizidine (Scheme 69).[80]

The acetoxysuccinimide **393** (obtained from malic acid) was converted into the lactam **394** under Mitsunobu conditions followed by $NaBH_4$ reduction. Ring closure of **394** afforded the optically pure indolizinone **395** through an



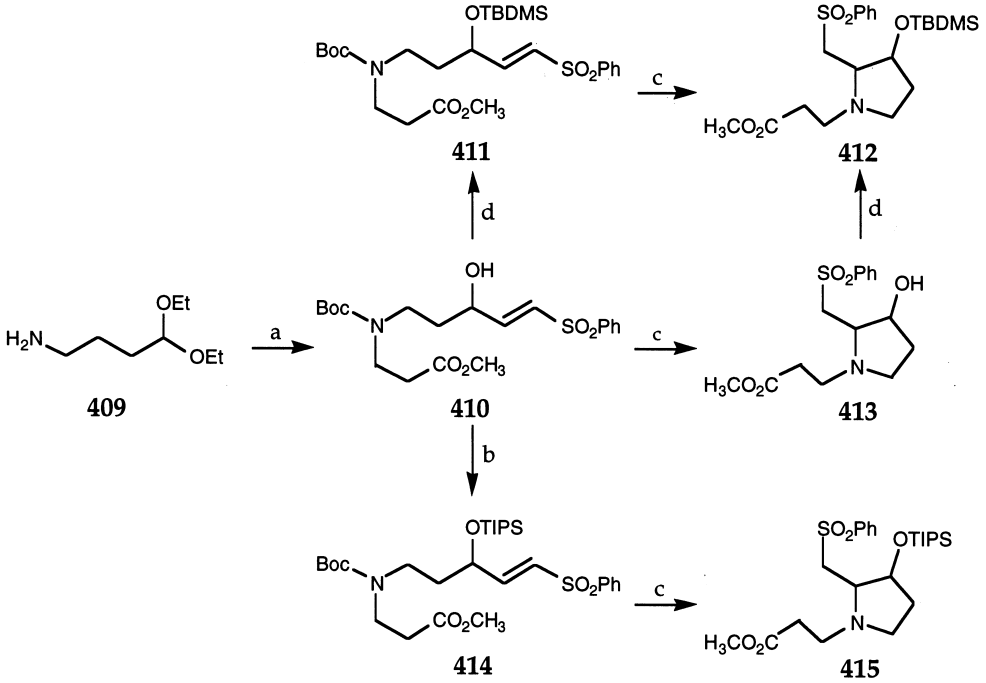
Scheme 69. (a) 1—Me_3SiCH=$CH(CH_2)_2OH$, DEAD, Ph_3P, 87%; $NaBH_4$, 94%; 2—Ac_2O, pyr, DMAP, 85%; (b) 1—BF_3·OEt_2, 72%; 2—Et_3N, CH_3OH, H_2O; then BzCl, Et_3N, DMAP, 84%; (c) *m*CPBA, 76%; (d) H^+, THF, H_2O; then Ac_2O, pyridine, DMPA, 52%; (e) 1—BMS, THF; 2—aq NH_3, 37% two steps.



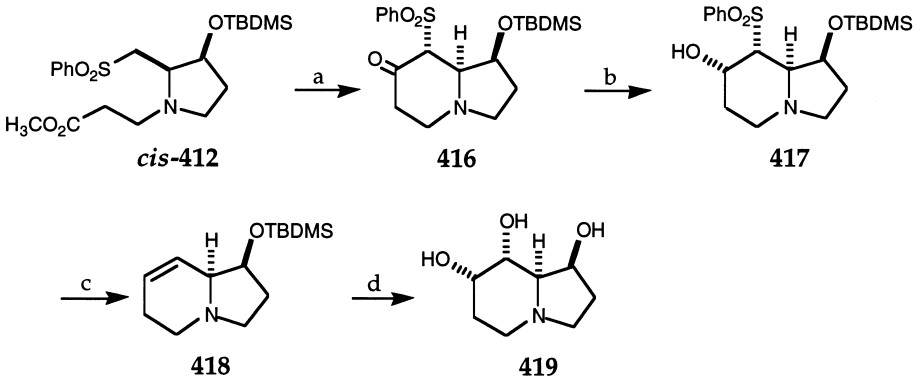
Scheme 70. (a) 1—TBDMSCl, imidazole, CH_2Cl_2, 24°C, 2 h, 96%; 2—1:4 TFA–CH_2Cl_2; then Et_3N, methyl acrylate, EtOH, 95%; (b) Na, TMSCl, toluene, reflux, 75%; (c) AcOH, NaOAc, 24°C; then DBU, CH_2Cl_2, 24°C, 48 h; or DBU, CH_2Cl_2, 24°C, 48 h; (d) TMSCl, LiN$(TMS)_2$, THF, −78°C; (e) BMS, THF, −78→25°C, 12 h; then $(CH_3)_3NO$, toluene, reflux, **405** (15%), **406** (24%) and **407** (32%); (f) *n*-Bu_4NF, THF, 0°C→25°C, 2 h.

acyliminium ion intermediate. Treatment of the benzoate **395** with *m*CPBA gave the β-epoxide **396** (76%) and the α-epoxide (10%). Subsequent acid-catalysed ring opening of the epoxide **396** followed by acetylation gave the *trans*-diaxial di-*O*-acetyl derivative **397**, which was reduced with BMS followed by deprotection to give 1,7,8-trihydroxyindolizidine **398** in 6% overall yield from **393**.

6-Deoxycastanospermine has been prepared as a by-product in a chemoenzymatic route to castanospermine and 6,7-di-*epi*-castanospermine (Scheme 70).[81] The alcohol **399** (derived from an enzyme-catalysed reduction of its corresponding β-ketoester) was converted into **400** (91%) followed by an intramolecular acyloin condensation in the presence of an excess of TMSCl afforded the silyl **401** which was converted into a 1:1 mixture of **402** and **403** in 60% yield, these were quantitatively converted into **404**. Hydroboration/oxidation of **404** gave a mixture of the



Scheme 71. (a) 1—CH_2=$CHCO_2CH_3$, EtOH, 0°C; then $(Boc)_2O$, CH_2Cl_2, rt, 82%; 2—$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 95%; 3—$PhSO_2CH_2SOTol$, piperidine, CH_2Cl_2, 0°C, 93%; (b) TIPS–triflate, 2,6-lutidine, CH_2Cl_2, 90%; (c) 1—TFA, CH_2Cl_2, 100%; 2—Et_3N, toluene, 0°C, R=H (96%, 81:19 *cis*/*trans*); or Et_3N, THF, −78°C, R=TIPS (93%, 10:90 *cis*/*trans*), R=TBDMS (88%, 19/81 *cis*/*trans*) (d) TBDMSCl, imidazole, DMAP, rt, 24 h.



Scheme 72. (a) TBDMSCl, imidazole, DMAP, rt, 24 h; (b) LHMDS, THF, 0°C, 100%; (c) $LiEt_3BH$, THF, −78°C, 70%; (d) 6% Na(Hg), CH_3OH, Na_2HPO_4; (e) OsO_4, $(CH_3)_3NO$, acetone–H_2O, rt, 4 days; then HCl; then Dowex OH^-, 49% from **417**.

diastereomeric alcohols **405**, **406** and **407**. After separation by silica gel chromatography, desilylation of **405** afforded 6-deoxycastanospermine (**408**).

γ-Hydroxy-α-β-unsaturated sulfones were used as a key step in the syntheses of 1,7,8-trihydroxy-indolizidine compounds (Schemes 71–73).[82]

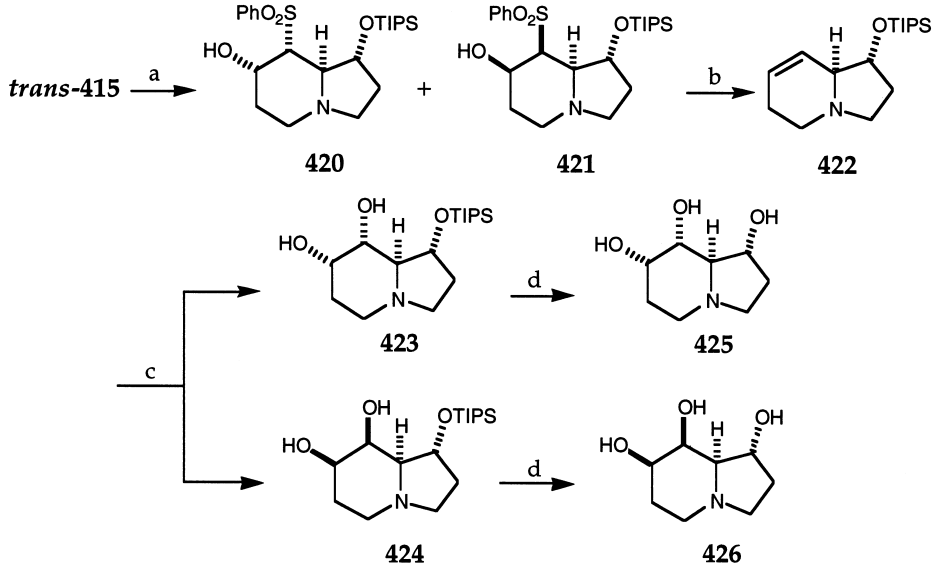
Conjugate addition of 4-aminobutyraldehyde diethyl acetal (**409**) to methylacrylate followed by protection of the secondary amine afforded a carbamate derivative, which underwent a condensation with (phenylsulfonyl)(*p*-tolyl-sulfinyl)methane to give the sulfone **410**. Cyclization of **410** (Et_3N, toluene) gave a *cis*-pyrrolidine **413** as the major isomer, where as the cyclisation of **411** and **414** was highly stereoselective in favour of the *trans*-isomer (Scheme 71).

Intramolecular Claisen-like condensation of *cis*-**412** (prepared in 71% overall yield from **410**) afforded **416** followed by reduction and Julia elimination afforded the olefin **418** which was immediately dihydroxylated and deprotected to afford the trihydroxylated indolizidine **419** (Scheme 72).

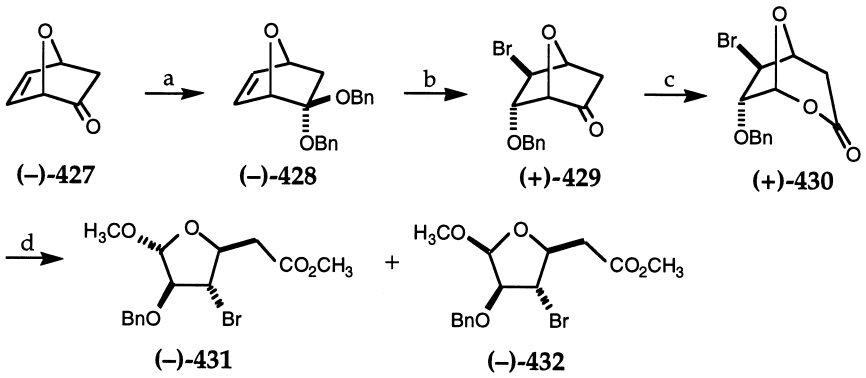
The trihydroxylated indolizidines **425** and **426** were prepared from *trans*-**415** following a similar reaction sequence to that used for **419**. *trans*-**415** Yielded a 1:1.5 mixture of the alcohols **420** and **421** which were converted via the olefin **422** into **423** and **424** and these were separated and deprotected to produce **425** and **426** (Scheme 73).

A preparation of the 1,7,8-trihydroxyindolizidine (**408**) [6-deoxycastanospermine] based on bromine addition to 7-oxabicyclo [2.2.1]hept-5-en-2-one benzyl acetal (**428**) has been developed (Schemes 74 and 75).[83] Bromination occurred exclusively on the less hindered convex face of **428** (obtained from **427**) and this was followed by stereo-selective migration of the *endo*-BnO group of the acetal to give **429**, which underwent Baeyer–Villiger oxidation to give **430** followed by acid hydrolysis to give a 4:1 mixture of the methyl furanosides **431** and **432** (Scheme 74).

Compound **431** was converted into **434** via the intermediate



Scheme 73. (a) LHMDS, THF, 0°C; then $NaBH_4$, **420** (31%) and **421** (48%); (b) 1—MsCl, CH_2Cl_2, Et_3N, rt, 4 h; 2—Na(Hg), CH_3OH, 82%; (c) OsO_4, $(CH_3)_3NO$, acetone–H_2O, rt, 4 h, **423** (52%) and **424** (27%); (d) HCl; then Dowex OH^-, 100%.



Scheme 74. (a) $BnOSi(CH_3)_3$, $CF_3SO_3Si(CH_3)_3$, CH_2Cl_2; (b) Br_2, CH_2Cl_2, −90°C, then aq $NaHCO_3$, −90°C, 98%; (c) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 5°C, 96%; (d) CH_3OH, $SOCl_2$.

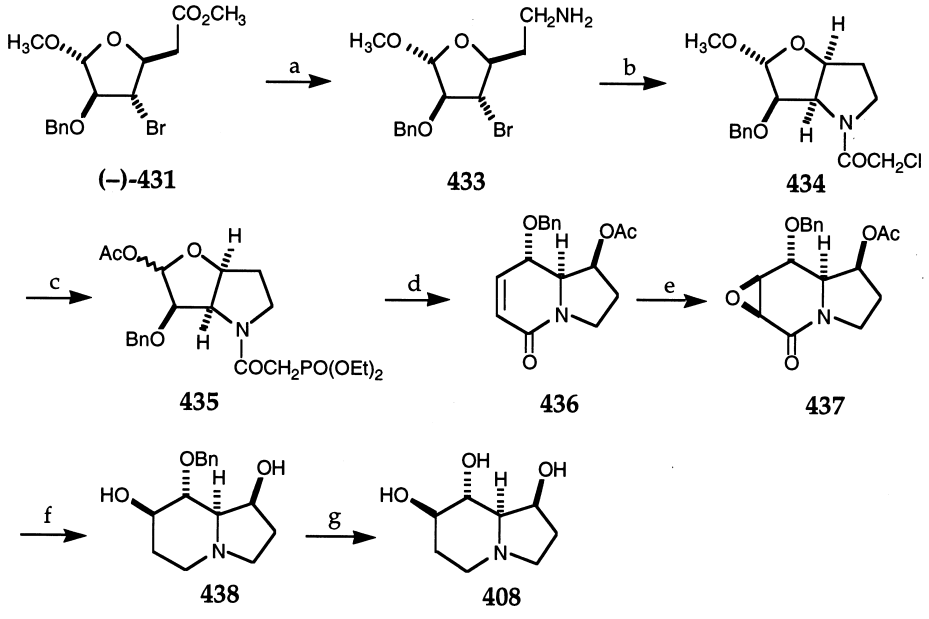
compound **433** in four steps, including introduction of *N*-functionality, amidation and acetylation. Acetolysis of **434** followed by Arbuzov reaction gave the corresponding phosphonoacetamide **435** which was immediately cyclisated to **436** by an intramolecular Wittig–Horner condensation. Conversion of **436** into the epoxide **437** was followed by treatment with BMS complex to give **438** which underwent hydrogenolysis to afford the 1,7,8-trihydroxyindolizidine (**408**) (Scheme 75).

3.4. Synthesis of 1,6,8-trihydroxyindolizidine

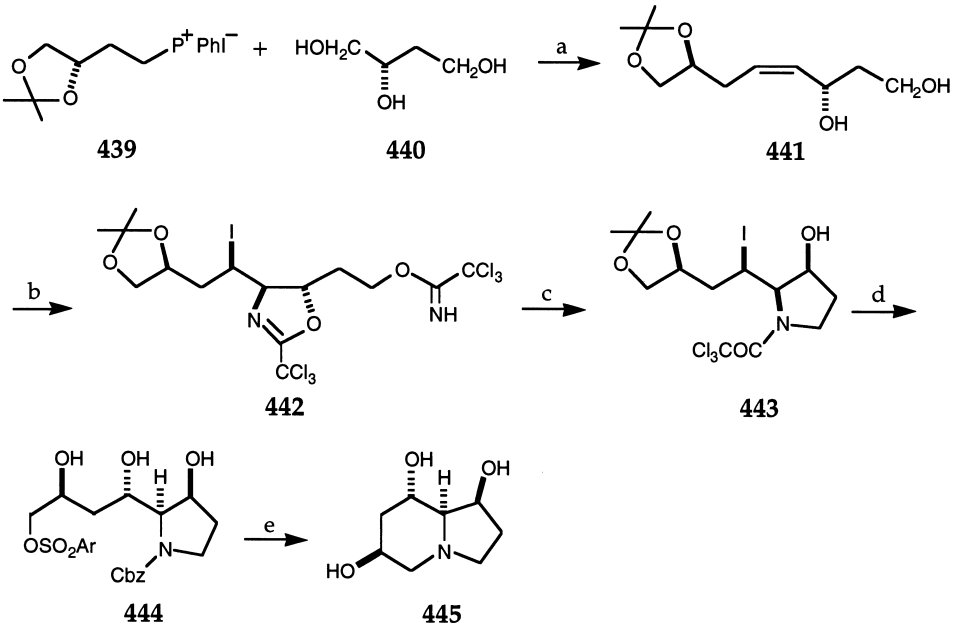
1,6,8-Trihydroxyindolizidine (7-deoxy-6-*epi*-castanospermine) (**445**) is the first trihydroxylated indolizidine to be isolated from the seeds of *Castanospermum australe*[84] and it is an inhibitor of amyloglucosidase and yeast α-glucosidase, but is significantly less active than its isomer (−)-swainsonine (**1**).

A synthetic route using an intramolecular iodoamidation of a *cis*-olefinic allylic trichloroacetimidate followed by stereoselective intramolecular iodocyclisation has led to the formation of (+)-7-deoxy-6-*epi*-castanospermine (**445**) (Scheme 76).[85]

Reaction of (*S*)-butane-1,2,4-triol (**440**) with the phosphonium salt **439** was followed by chemoselective hydrolysis to give the *cis*-olefinic allylic alcohol **441**. Treatment of **441** with trichloroacetonitrile followed by intramolecular iodoamidation afforded **442**, which underwent partial hydrolysis followed by Mitsunobu conditions to give the pyrrolidine **443**. Substitution of the iodo group in **443** with complete inversion was effected by refluxing in aqueous trifluoroacetic acid and the product generated was sequentially subjected to benzyl chloroformate and mesitylenesulfonyl chloride to afford the sulfonate **444**. After removal of the benzyloxy-carbonyl group of **444** by hydrogenation, cyclisation was achieved using



Scheme 75. (a) 1—DIBAL, THF, toluene, 100%; 2—MsCl, pyr, CH_2Cl_2; then 24% NH_3, EtOH, H_2O, 45°C, 1 day, 99%; (b) $ClCH_2COCl$, pyr, CH_2Cl_2; (c) Ac_2O, H_2SO_4, 0°C, 2 h; then $P(OEt)_3$, 130°C, 79% from **431**; (d) K_2CO_3, EtOH, 20°C, 3 days; then Ac_2O, DMAP, 49% from **431**; (e) 1—Br_2, AcOH, AgOAc, 90°C, 15 min, 70%; 2—$SOCl_2$, CH_3OH, 20°C, 17 h; then 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazophosphorine on polystyrene, 20°C, 35 min, 50%; (f) BMS, THF, 20°C, 4 days, 25%; (g) H_2, Pd on C; CH_3OH, HCO_2H, 20°C, 16 h, 97%.



Scheme 76. (a) 1—*p*-$CH_3OC_6H_4CHO$, PPTS, toluene, Dean–Stark trap, 120°C, 87%; 2—Swern oxidation; 3—*n*-BuLi, HMPA, THF, 78–0°C, 69%; 4—PPTS, H_3OH, 0°C, 86%, (b) Cl_3CCN, DBU, CH_3CN, 0°C; then IBr, K_2CO_3, CH_3CH_2CN, −78°C, 86%; (c) PPTS, CH_3OH, rt; then DEAD, Ph_3P, THF, 0°C, 82%; (d) aq TFA, reflux; then CbzCl, $NaHCO_3$, CH_3OH, 0°C; then 2,4,6—$Me_3C_6H_2SO_2Cl$, pyr, 0°C, 79%; (e) H_2, 10% Pd on C, CH_3OH; then Et_3N, reflux, 69%.

triethylamine at reflux in methanol to give (+)-7-deoxy-6-*epi*-castanospermine (**445**).

3.5. Syntheses of 1,2-dihydroxyindolizidines

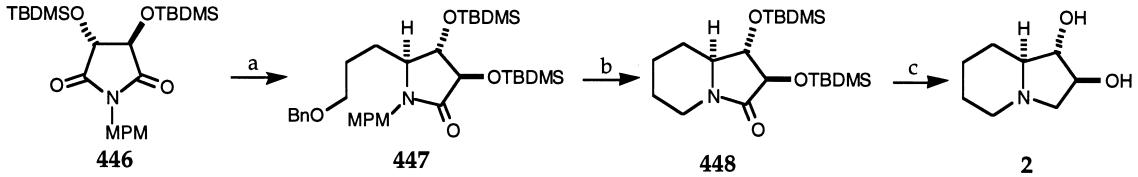
The following synthetic strategies describe the preparation of seven of the eight possible stereoisomers of 1,2-dihydroxyindolizine (8-deoxyswainsonine analogues), most of these being focused on (+)-lentiginosine (**2**).

The first asymmetric synthesis of naturally occurring lentiginosine from L-tartaric acid was achieved in 10% overall yield (Scheme 77).[86]

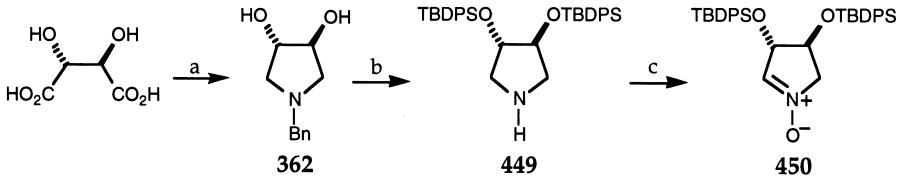
The imide **446** (obtained from L-tartaric acid in 53% yield) was treated with the Grignard reagent, $BnO(CH_2)_4MgBr$, followed by reductive deoxygenation with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to provide the lactam **447** which was 96.1% optically pure. Successive removal of the benzyl and MPM protecting groups from the lactam **447**, followed by mesylation and intramolecular cyclisation, gave the bicyclic amide **448**. Subsequent deprotection followed by reduction of the amide **448** gave (+)-lentiginosine (**2**).

The previously described 1,3-dipolar cycloaddition to methylenecyclopropane strategy which has been utilised for the synthesis of 1,2,7-trihydroxyindolizidine has been extended to the synthesis of 1,2-dihydroxyindolizidine (Schemes 78 and 79).[24a,87]

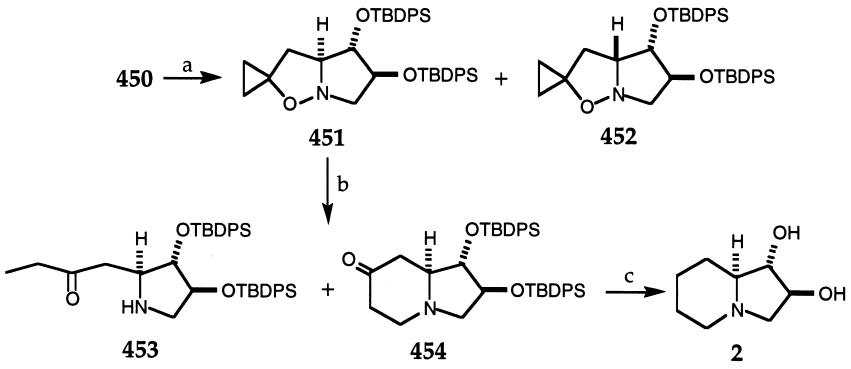
The *N*-benzyl-3,4-dihydroxypyrrolidine **362** (derived from L-(+)-tartaric acid in two steps) was silylated quantitatively



Scheme 77. (a) 1—$BnO(CH_2)_4MgBr$, THF, −78→0°C, 85%; 2—Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C, 95%; (b) 1—CAN, CH_3CN–H_2O, 0°C; then Pd-black, HCO_2H, *i*-PrOH, 27%; 2—MsCl, Et_3N, CH_2Cl_2; then NaH, THF, 90%; (c) 1—HCl, CH_3OH, 100%; 2—$LiAlH_4$, THF, reflux, 100%.



Scheme 78. (a) 1—$BnNH_2$; 2—BF_3, $NaBH_4$; (b) 1—TBDPSCl, imidazole, DMF, 60°C, 12 h, 100%; 2—H_2, $Pd(OH)_2$ on C, CH_3OH, 20°C, 3 days, 71%; (c) 30% H_2O_2, SeO_2, acetone, 20°C, 2 h, 53%.



Scheme 79. (a) methylenecyclopropane, PhH, rt, 7 days, 75%; (b) xylene, 140°C, 1.5 h, **454** (45%), **453** (55%); (c) 1—$TsNHNH_2$, CH_3OH, 7 h; 2—$NaBH_4$, 65°C, 20 h, 45%; 3—40% aq HF, CH_3CN, rt, 2 days, 70%.

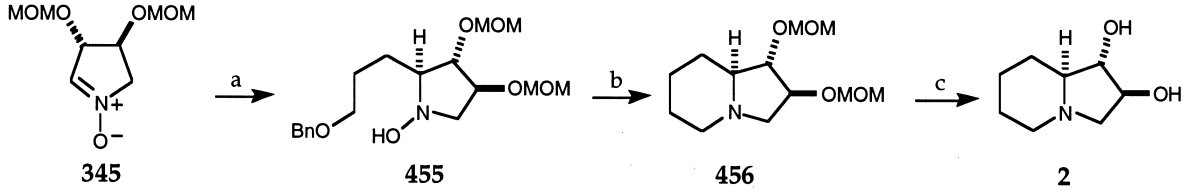
with TBDPSCl and debenzylated to give the pyrrolidine **449**. Subsequent oxidation of **449** with SeO_2/H_2O_2 produced the corresponding nitrone **450** in 18% overall yield from L-tartaric acid (Scheme 78).

The thermal rearrangement of 5-spirocyclopropane isoxazolidines has been used as a key step for the synthesis of (+)-lentiginosine (**2**). The protected nitrone **450** reacted with an excess of methylenecyclopropane to give a 10:1 mixture of the isoxazolidines **451** and **452** in 75% yield. Thermal rearrangement of the desired product **451** afforded the indolizidinone **454** (45%) and the enaminone isomer **453** (55%). Subsequent reduction of **454** followed by desilylation gave the (+)-lentiginosine (**2**) (Scheme 79).

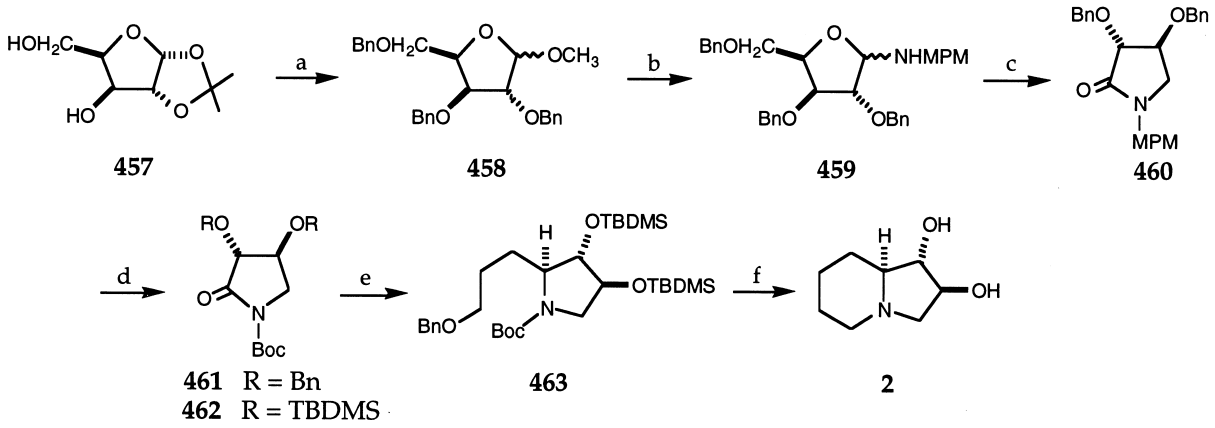
Another strategy utilising addition of a Grignard reagent into the 1,3-dipolar **345** was used in the preparation of 1,2-dihydroxyindolizidine (Scheme 80).[88]

The nitrone **345** (available in five steps from L-tartaric acid, Scheme 79) was treated with $BnO(CH_2)_4MgBr$ to give 2,3-*trans* **455** which was 95% optically pure. Hydrogenation of the hydroxylamine **455** followed by intramolecular displacement afforded the indolizidine **456**. Removal of the methoxymethyl groups in **456** gave (+)-lentiginosine (**2**) in 16% overall yield from L-tartaric acid.

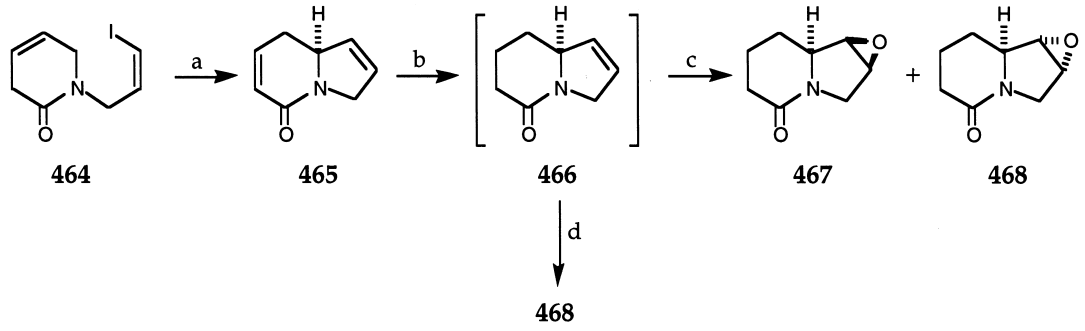
The stereoselective deoxygenation of an α-hydroxypyrrolidine has been used as a synthetic pathway to (+)-lentiginosine (**2**) (Scheme 81).[89]



Scheme 80. (a) $BnO(CH_2)_4MgBr$, THF, rt, 82%; (b) 1—H_2, Raney nickel; then $HCONH_4$, Pd on C, 76%; 2—Ph_3P, CCl_4. Et_3N, DMF, 88%; (c) HCl, CH_3OH, reflux, 91%.



Scheme 81. (a) 1—BnBr, NaH, THF, 93%; 2—HCl, CH_3OH, 93%; 3—BnBr, NaH, THF, 98%; (b) 1—80% AcOH, 100°C, 91%; 2—$MPMNH_2$, PhH–$CHCl_3$, 70°C, 4 Å M.S., 100%; (c) 1—$LiAlH_4$, THF, 83%; 2—PCC, 4 Å M.S., CH_2Cl_2, 58%; (d) 1—CAN, CH_3CN–H_2O, 81%; 2—$(Boc)_2O$, Et_3N, CH_2Cl_2, 96%; 3—Pd-black, 4.4% HCO_2H, CH_3OH, 40°C, 96%; 4—TBDMSCl, imidazole, DMF, 94%; (e) 1—$BnO(CH_2)_4MgBr$, THF, −78°C; 2—Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C, 55% two steps; (f) 1—Pd-black, 4.4% HCO_2H, CH_3OH, 40°C, 94%; 2—TsCl, pyr, 70%; 3—$BF_3{\cdot}OEt_2$, CH_2Cl_2, −20–0°C; then KOH, CH_3OH, 74%.



Scheme 82. (a) PdLn, Ag zeolite; (b) K-selectride, Et_2O, −78→0°C; (c) 30% H_2O_2, aq HCO_2H, **467** (65%) and **468** (5.4%) for b and d steps; *or m*CPBA, **467** (68%); (d) NBS, THF, Et_2O–H_2O then K_2CO_3, CH_3OH, 43% for b and d steps.

1,2-*O*-Isopropylidene-D-xylofuranose (**457**) was benzylated followed by heating in methanol containing HCl, and further benzylation of the free hydroxyl group to give **458**. Subsequent hydrolysis of **458** followed by amination afforded **459**, followed by reduction and oxidative degradation gave the optically pure lactam **460**. Nucleophilic addition to **461** followed by reductive deoxygenation led to moderately diastereoselective products. Nucleophilic addition of $BnO(CH_2)_4MgBr$ to **462** (derived from **460**) however, followed by reductive deoxygenation with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ afforded **463** with an extremely high stereoselectivity (98:2). Compound **463** was converted into (+)-lentiginosine (**2**) in 7% overall yield from **457**.

Functionalisation of the optically active oxoindolizine **465** (derived from an asymmetric Heck-type cyclisation of **464**) was used for the syntheses of (+)-lentiginosine (**2**) and (+)-1,2-di-*epi*-lentiginosine (**472**) (Schemes 82 and 83).[90]

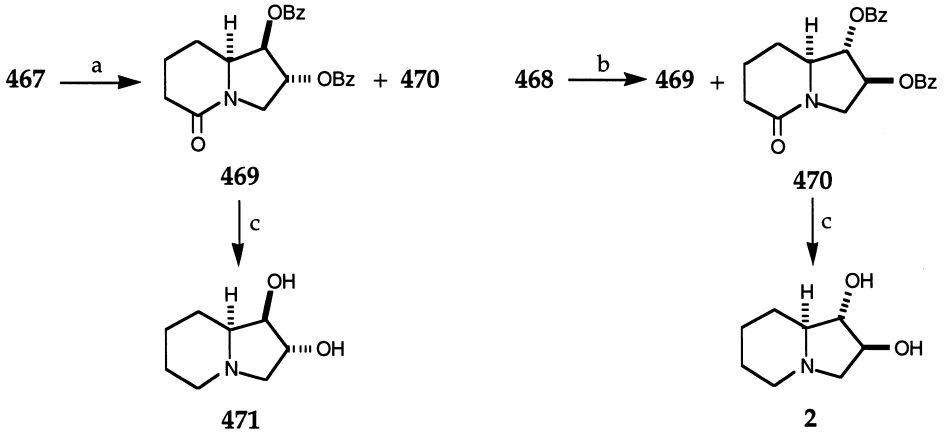
Regioselective reduction of the 6,7-double bond was achieved by K-selectride to give the intermediate **466**, which was either epoxidised with hydrogen peroxide to give the β-epoxide **467** (65%) and the α-epoxide **468** (5.4%), or with *m*CPBA to give **467** (68%). In contrast, treatment of **465** with K-selectride, NBS and potassium carbonate gave the α-epoxide **468** in 43% yield from **465** (Scheme 82). Regioselective opening of the epoxides **467** and **468** occurred at the less hindered C-2 position to give a mixture of the dibenzoates **469** and **470**, which were treated with $LiAlH_4$ to afford (+)-1,2-di-*epi*-lentiginosine (**471**) and (+)-lentiginosine (**2**), respectively (Scheme 83).

A method for the synthesis of 8a-*epi*-lentiginosine (**479**) via a ring-closing olefin metathesis has been developed (Scheme 84).[91]

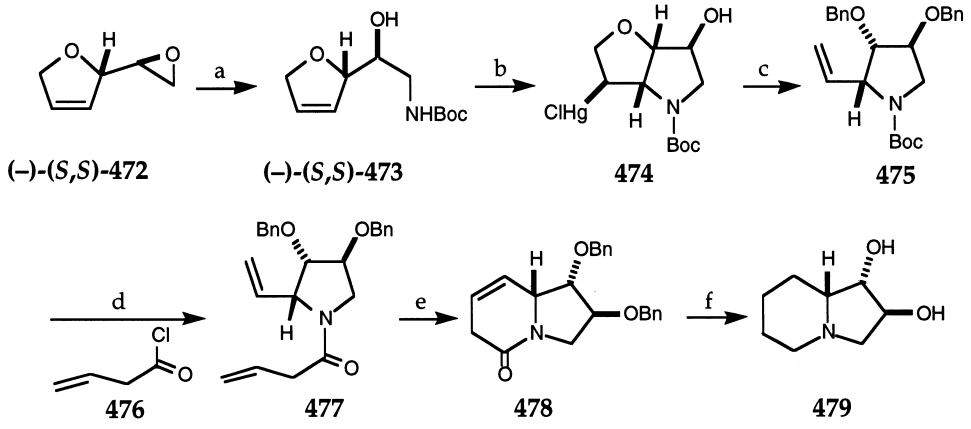
The dihydrofuran (*S*,*S*)-**472**, obtained from mannitol, was subjected to epoxide ring opening with sodium azide and protection with di-*t*-butyl carbonate to provide the amino-alcohol **473**, which was treated with mercury(II) trifluoroacetate to afford **474** via a highly stereoselective cyclisation. Dodecane-1-thiol effected the deoxymercuration of **474** and by protection as the dibenzyl ether gave the α-vinylpyrrolidine **475**. This was treated with trifluoroacetic acid, followed by acylation with **476** to give the amide **477**. A ruthenium carbene complex effected intramolecular cyclisation of **477** to the unsaturated lactam **478**. Reduction of the carbonyl group followed by hydrogenation afforded (−)-8a-*epi*-lentiginosine (**479**) in 13.4% overall yield from **473**.

A radical reduction at C-7 of 1,2,7-trihydroxyindolizidine derivatives has been used for the syntheses of 1,2-dihydroxyindolizidine compounds (Schemes 85 and 86).[75]

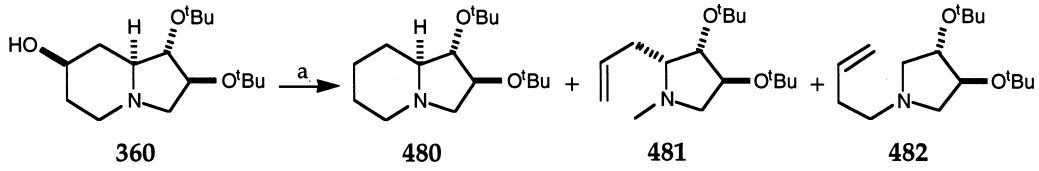
Reduction of the tosylate of compound **360** with lithium aluminium hydride gave only 16% of the desired protected lentiginosine **480** (Scheme 85).



Scheme 83. (a) 1—1:1 acetone:1% H_2SO_4, 70°C; 2—BzCl, pyr, DMAP, CH_2Cl_2, **469** (54%) and **470** (10%); (b) 1—1:1 acetone:1% H_2SO_4, 45°C; 2—BzCl, pyr, DMAP, CH_2Cl_2, **469** (29%) and **470** (59%); (c) $LiAlH_4$, Et_2O, 98% for **2** and 100% for **471**.



Scheme 84. (a) 1—NaN_3, CH_3OH–H_2O, $NaH_2PO_4{\cdot}H_2O$, rt, 60 h, 77%; 2—$LiAlH_4$, THF, rt, 1 h, reflux 2 h; 3—$(t\text{-BuOCO})_2O$, THF, rt, 24 h, 89% two steps; (b) $Hg(CF_3CO_2)_2$, THF, 0°C→rt, 30 min; then NaCl, H_2O, 77%; (c) 1—$n\text{-}C_{12}H_{23}SH$, CH_3OH, rt, 4 h, 67%; 2—NaH, BnBr, DMF, THF, −10°C, 5 h, 96%; (d) 1—TFA, CH_2Cl_2, rt, 30 min; 2—$CH_2{=}CHCH_2COCl$, Et_3N, THF, H_2O, 0°C→rt, 4 h, 90% two steps; (e) Ru-Cat, PhH, reflux, 2 h, 80%; (f) 1—$LiAlH_4$, THF, reflux, 5 h, 60%; 2—H_2, 10% Pd on C, CH_3OH, HCl, rt, 8 h; then NaOH, 91%.



Scheme 85. (a) 1—TsCl, pyr, 77%; 2—$LiAlH_4$, THF, 68°C, 3 h, **480** (16%), **481** (12%) and **482** (38%).

Radical deoxygenation of compound **360** via the thiocarbonylimidazolide **483** followed by deprotection afforded (+)-lentiginosine (**2**) in 63% overall yield from **360** (Scheme 86).

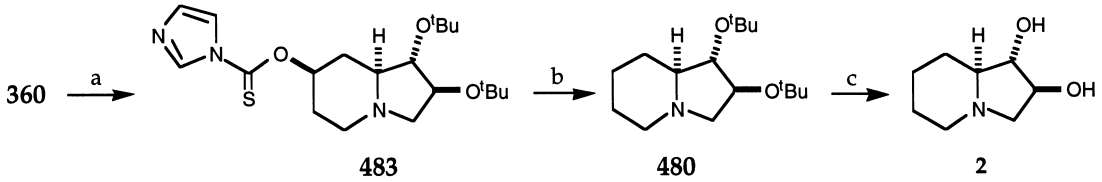
Conversion of the partially protected triol **484** into its imidazolythiocarbonyl derivative, followed by radical deoxygenation and deprotection afforded (+)-lentiginosine (**2**) (Scheme 87).[74]

Similarly, *ent*-**484** was converted into (−)-lentiginosine (*ent*-**2**) (Scheme 88).[74] Compounds **2** and *ent*-**2** are inactive against HIV-1.

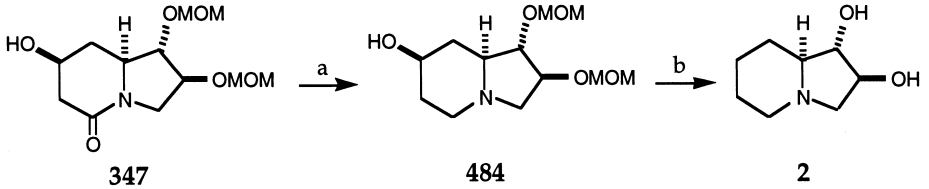
Swainsonine (**1**) was converted into the acetonide **21** and the unprotected C-8-hydroxyl group was removed by conversion into the S-methyldithiocarbonate **485** followed by reduction with tributyltin hydride to give the acetonide **486** in 62% yield. Deprotection followed by acetylation of **486** afforded the diacetate **487** (Scheme 89).[21]

1-[^{H}]-swainsonine {biosynthesised from 1-[^{H}]-1-hydroxyindolizidine} was converted into (1*S*,2*R*,8a*R*)-1-[^{H}]-1,2-dihydroxyindolizidine (**490**) via a radical deoxygenation of **489** as described earlier (Scheme 90).[92]

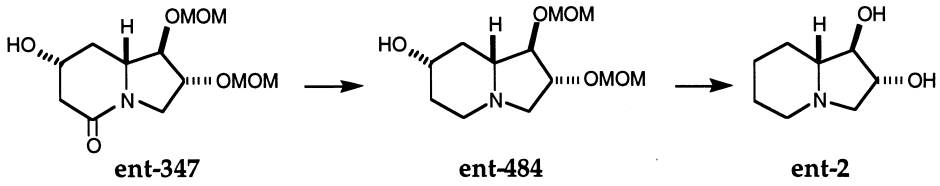
(1*S*,2*R*,8a*R*)-8a-[^{2}H]-1,2-dihydroxyindolizidine (**494**) was



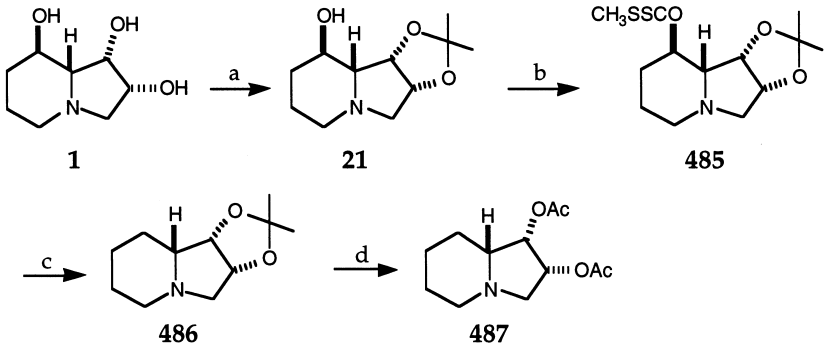
Scheme 86. (a) $Im_2C{=}S$, THF, 68°C, 2.5 h, 99%; (b) *n*-Bu_3SnH, AIBN, toluene, 110°C, 16 h, 68%; (c) TFA, 16 h, 93%.



Scheme 87. (a) BMS, THF, rt, 4 h; then EtOH, reflux, 3 h, 95%; (b) 1—Im_2CS, CH_2Cl_2, reflux, 2 h, rt, overnight, 83%; 2—Bu_3SnH, AIBN, toluene, reflux, 3 h, 53%; 3—6 M HCl, rt, overnight; then aq NH_3, 60%.



Scheme 88.



Scheme 89. (a) DMP, TsOH, acetone, 50°C, 2 days, 85%; (b) NaOH, CS_2, CH_3I, *n*-Bu_4NHSO_4, PhH, 55%; (c) Bu_3SnH, xylene, reflux, 48 h, 62%; (d) 2 M HCl, 80°C, 6 h; then Ac_2O, 60°C, 1 h, 83%, two steps.

prepared from the acetonide **491** via oxidation with mercuric(II) acetate to the 4,8a-iminium ion, which underwent stereospecific reduction with NaCNB[$^2H_3$] followed by deprotection (Scheme 91).[92]

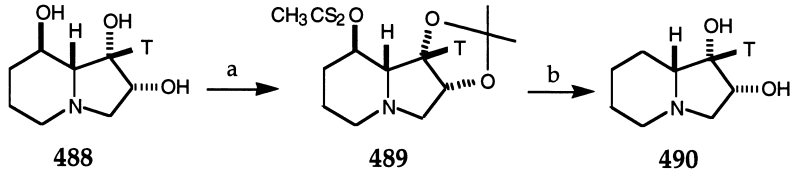
Facial routes to (−)- and (+)-lentiginosine have been developed based on Sharpless asymmetric dihydroxylation (Schemes 92 and 93).[93]

(*R*)-pipecolinic acid (**495**) was transformed into the (*E*)-ester **496** in four steps. Subsequent Sharpless asymmetric dihydroxylation of **496** gave an 11.5:1 mixture of the two diols **497a** and **497b**. Intramolecular cyclisation of the diol **497a** was effected by hydrogenation to give the lactam **498**. Reduction of **498** with BMS complex gave (−)-lentiginosine (*ent*-**2**) (Scheme 92). Similarly, (*S*)-pipecolinic acid (**499**) was transformed into (+)-lentiginosine (**2**) by a series of steps analogous to the synthesis of *ent*-**2** (Scheme 93).

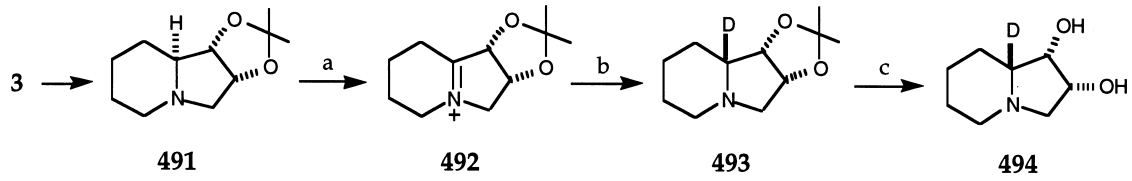
Intramolecular cycloaddition of **40** in refluxing benzene produced the bicyclic iminium ion **41** {previously used in the synthesis of (−)-swainsonine (**1**) in Scheme 7}[40] which underwent sodium borohydride reduction followed by acid hydrolysis of the isopropylidene group to provide (1*S*,2*R*,8a*R*)-1,2-dihydroxyindolizidine (**500**) in 49% overall yield from **40** (Scheme 94).[40]

The pyrrolidine **501** derived from chiral (*S*)-*N*-benzyloxycarbonyl-3-hydroxy-4-pentenylamine has been used as a starting material for the synthesis of (−)-*cis*-1,2-dihydroxyindolizidine (**3**) (Scheme 95).[94]

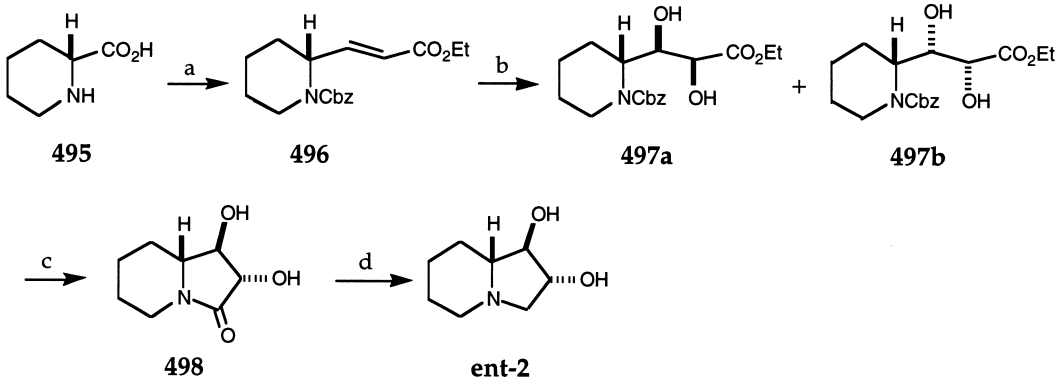
Reduction of the pyrrolidine **501** with DIBAL, followed by selective monotritylation, xanthation and thermolysis, furnished the 3-pyrroline **502** in 19% overall yield. Catalytic osmylation of **502** gave the diol **503** as a single diastereoisomer, which was converted into the acetonide **504** in three steps. Debenzyloxycarbonylation of **504** afforded the salt



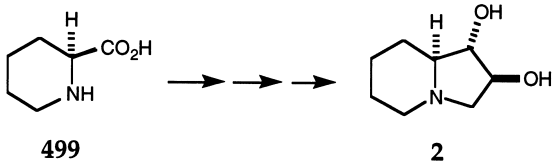
Scheme 90. (a) 1—DMP; 2—CS_2, CH_3I; (b) 1—Bu_3SnH; 2—2 M HCl, 80°C, 6 h.



Scheme 91. (a) $Hg(OAc)_2$, aq AcOH, reflux, 2 h; (b) H_2S, NaCNB[$^2H_3$]; (c) 2 M HCl, 80°C, 6 h; lyophilization.



Scheme 92. (a) 1—CbzCl, 4N NaOH, rt, 6 h; 2—BMS, THF, 0°C→rt, 10 h; 3—pyr-SO3, DMSO, 0°C→rt, 30 min; 4—$Ph_3P{=}CHCO_2Et$, PhH, 10 h; (b) AD-mix-β, 1:1 *t*-BuOH–H_2O, rt, 24 h; (c) H_2, 10% Pd on C, NaOAc, CH_3OH, 12 h; (d) BMS, THF, rt, 12 h.



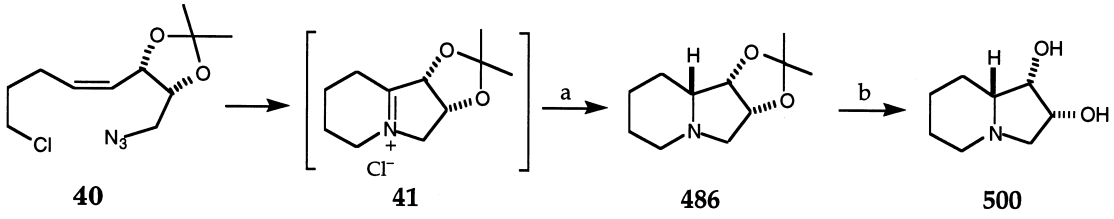
Scheme 93.

505, followed by treatment with aqueous K_2CO_3, gave the acetonide **506**, which was heated with 2 M HCl to give (−)-*cis*-1,2-dihydroxyindolizidine (**3**).

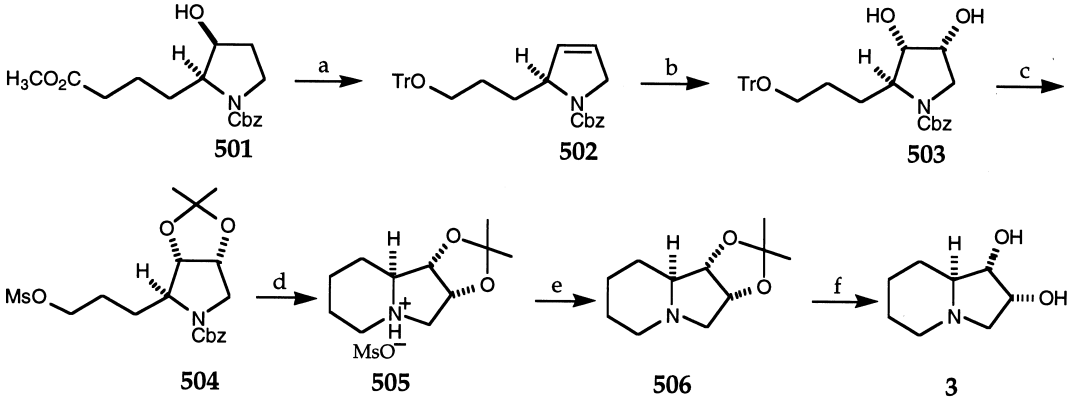
The acetonide **506** of the natural alkaloid, (−)-*cis*-1,2-dihydroxyindolizidine (**3**) formed by *Rhizoctonia leguminicola* was deprotected followed by acetylation to furnish the diacetate **507** (Scheme 96).[21]

A methodology applying the cyclisation of iminium ion and *N*-acyliminium ion intermediates to form the opposite absolute configuration of *cis*-1,2-dihydroxyindolizidines has been achieved (Schemes 97 and 98).[95]

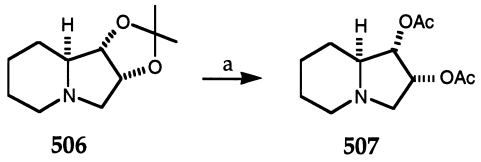
The enantiomerically pure lactone acetonide **44** (available on a large scale in 75% yield from D-isoascorbic acid) was reacted with **508** to give the amide intermediate **509**, which was then oxidised to give the hydroxylactam **510**. The cyclisation of **510** was repeated using a variety of standard activating agents, but these were all unsuccessful. Acetylation of **510** followed by cyclisation with $BF_3{\cdot}OEt_2$, however, provided the desired tetrahydroindolizinone **511**. Subsequent hydrogenation of **511** followed by reduction ($LiAlH_4$) and deprotection afforded (1*R*,2*S*,8a*R*)-1,2-dihydroxyindolizidine (*enti*-**3**) in 20% overall yield from **44** (Scheme 97).



Scheme 94. (a) $NaBH_4$, CH_3OH, 0°C, 1 h, 90%; (b) 6N HCl, THF, 23°C, 12 h, 54%.



Scheme 95. (a) 1—DIBAL; 2—TrCl, Et_3N, 37%; 3—NaH, CS_2, CH_3I; then 170°C, 52%; (b) OsO_4, NMO, 86%; (c) 1—HCl, CH_3OH; then DMP, TsOH, 84%; 2—MsCl, pyr; (d) H_2, $Pd(OH)_2$; (e) aq K_2CO_3, 70%; (f) 2 M HCl, 80°C.



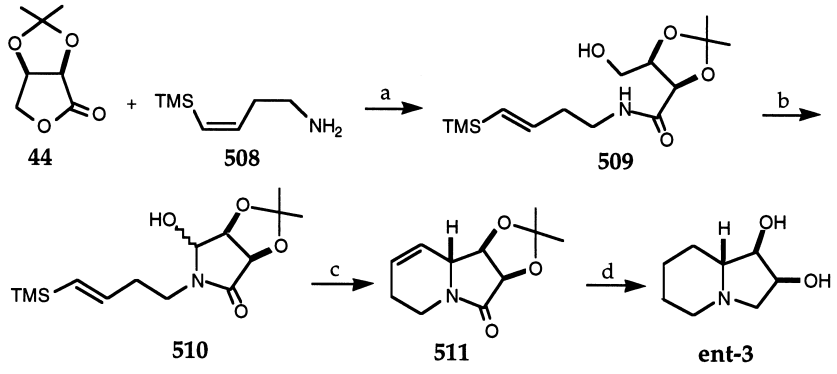
506 507

Scheme 96. (a) 1—2 M HCl, 16 h, 80°C; 2—Ac_2O, reflux, 3 h, 70%, two steps.

Mitsunobu condition failed to convert **509** into the lacton **512**, but methylation of **509** followed by cyclisation afforded **512** in 88% yield. Treatment of **512** with Lawesson's reagent to give the corresponding thioamide derivative was followed by reduction with $LiBEt_3H$ to give the 2-(ethylthio)pyrrolidine **513**. Iminium ion-vinylsilane cyclisation of **513** with $BF_3{\cdot}OEt_2$ afforded the tetrahydroindolizine **514** as a single stereoisomeric cyclisation product. Subsequent hydrogenation followed by deprotection furnished (1*S*,2*R*,8a*S*)-1,2-dihydroxyindolizidine (**3**) in 24% overall yield from **509** (Scheme 98).

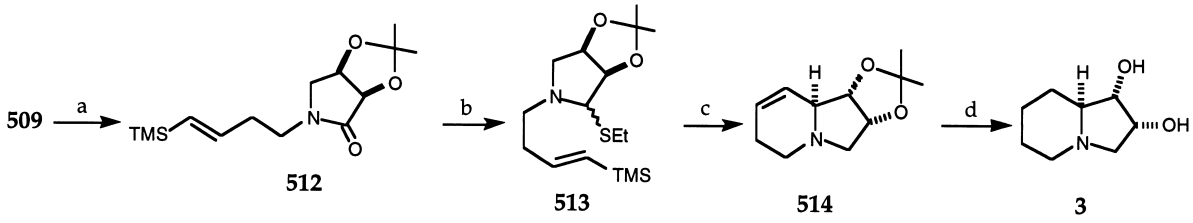
A methodology involving an α-alkylation of *N*-protected 3-pyrroline has been used for the synthesis of (±)-(1α,2α,8aα)-1,2-dihydroxyindolizidine (*rac*-**3**) (Scheme 99).[96]

3-Pyrroline (**515**), obtained by zinc/hydrochloric acid reduction of pyrrole, was converted into the urethane followed by alkylation with 1,4-dibromobutane to give the racemic α-alkylated compound **516** which was then treated with a catalytic amount of osmium tetraoxide to produce the *cis*-diol **518**. Further reaction with trimethylsilyl iodide followed by methanolysis of the resulting trimethylsilyl carbamate and cyclisation afforded *rac*-**3**, also obtained by reaction of **516** with trimethylsilyl iodide to give **517**, followed by dihydroxylation.



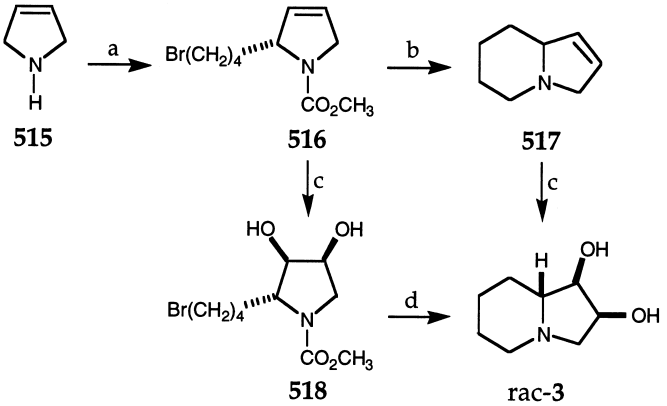
44 508 509 510 511 ent-3

Scheme 97. (a) $(CH_3)_3Al$, CH_2Cl_2; hexane, rt, 82%; (b) pyr-SO_3, DMSO, rt, 74%; (c) 1—Ac_2O, DMAP, CH_2Cl_2, −20°C, 95%; 2—$BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 72%; (d) 1—H_2, Pd on C, EtOAc, rt, 86%; 2—$LiAlH_4$, Et_2O, reflux, 78%; 3—2 M HCl, 80°C, 72%.



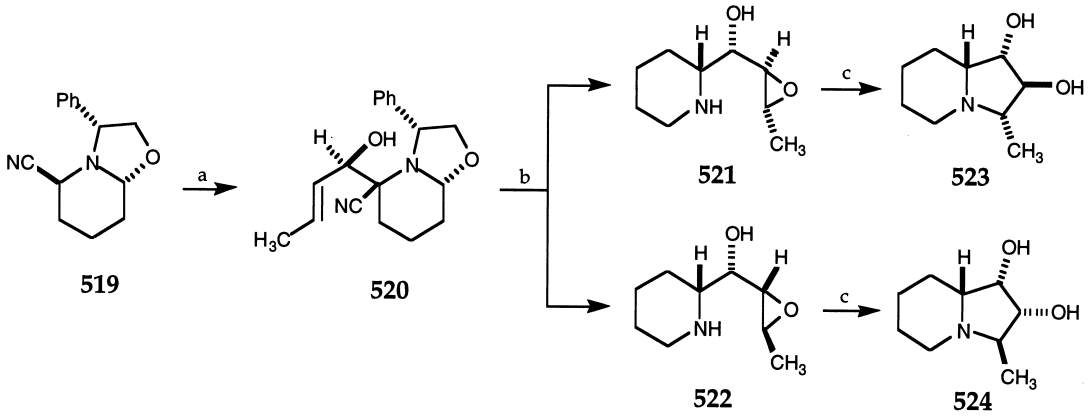
512 513 514 3

Scheme 98. (a) MsCl, Et_3N, CH_2Cl_2, 0°C→rt; then NaH, THF, rt, 88%; (b) 1—$(ArPS_2)_2$, HMPA, 100°C, 80%; 2—$BF_3{\cdot}OEt_2$, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, rt; 3—$LiBEt_3H$, THF, −78°C, 84%; (c) $Cu(OSO_2CF_3)_2$, THF, reflux, 73%; (d) 1—H_2, Pd on C, EtOAc, 24 h, 72%; 2—2 M HCl, 16 h, 80°C, 77%.



515 516 517 518 rac-3

Scheme 99. (a) 1—$ClCO_2CH_3$, Na_2CO_3, EtOH, rt, 2 h, 58%; 2—$Br(CH_2)_4Br$, $LiN(i\text{-}Pr)_2$, THF, −70°C, 70%; (b) $(CH_3)_3SiI$, CH_3OH, Na_2CO_3, 76%; (c) *t*-BuOH, H_2O_2, OsO_4, rt, 6 h, 91%; (d) $(CH_3)_3SiI$, PhH, 1 h, 50°C; then Na_2CO_3, CH_3OH, rt, 1 h, 45%.



Scheme 100. (a) crotonaldehyde, base; (b) 1—*m*CPBA; 2—H_2 (c) cyclisation.

rac-**3** Was found to be a weak inhibitor of both α-mannosidase (K_m 0.75×10^{-2} M) and α-glucosidase (K_m 1.1×10^{-2} M).

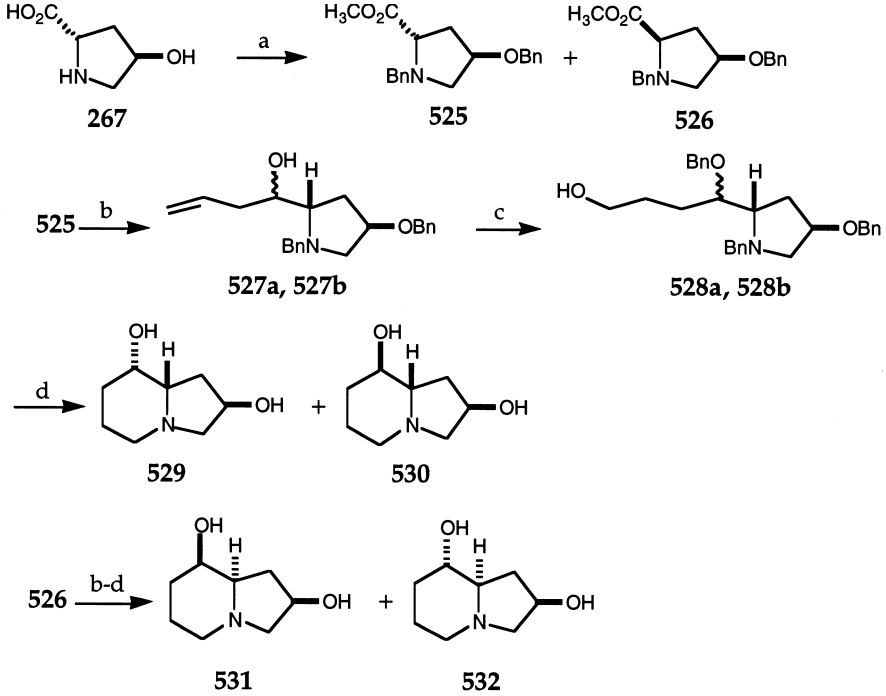
An asymmetric synthesis of the 3-methyl-1,2-dihydroxyindolizidines **523** and **524** has been developed (Scheme 100).[97] Addition of the anion of the chiral 2-cyano-6-oxazolopiperidine synthon **519** to crotonaldehyde gave the pentenyloxazolopiperidine **520** with enantioselective formation of the first hydroxyl group. Epoxidation of **520** followed by hydrogenation produced the epoxides, **521** and **522**, and subsequent cyclisation furnished **523** and **524**, respectively.

3.6. Syntheses of 2,8-dihydroxyindolizidines

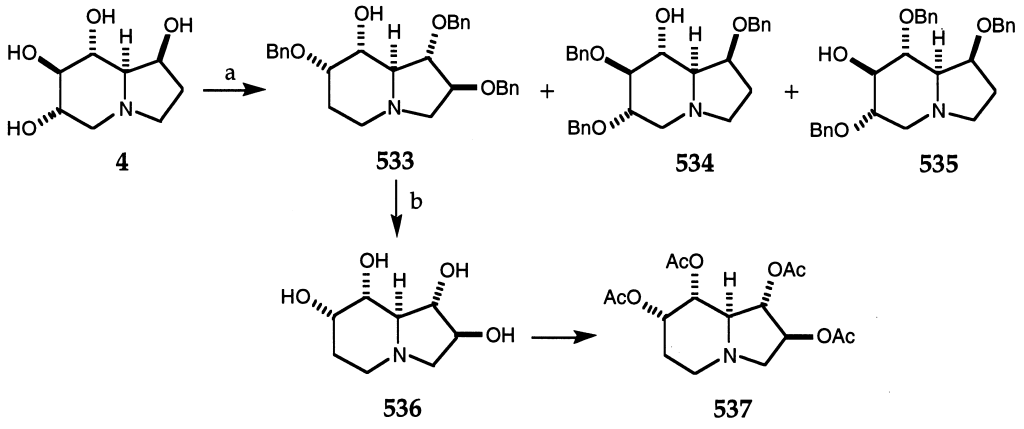
Four diastereomers of 2,8-dihydroxyindolizidines have been prepared from *trans*-4-hydroxy-L-proline (**267**) (Scheme 101).[98]

Esterification of optically pure *trans*-4-hydroxy-L-proline (**263**) followed by benzylation gave a separable mixture of the two epimers **525** and **526** in a 7:3 ratio in 70% total yield. Reduction of the ester function of **525** followed by Swern oxidation and a Grignard reaction afforded **527a** and **527b** in a 3:7 ratio in 70% total yield. Conversion of compounds **527a** and **527b** into **528a** and **528b** was followed by intramolecular displacement to afford **529** and **530**, respectively. The other epimer **526** was similarly, converted into **531** and **532**.

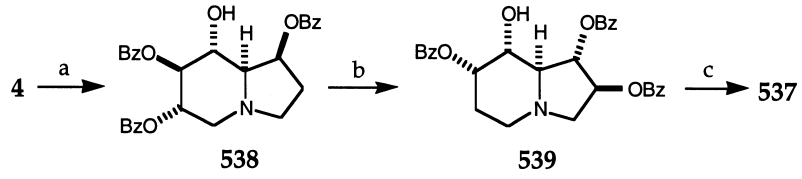
The (2*R*,8*S*,9*S*)-(**529**) and (2*R*,8*R*,9*R*)-2,8-dihydroxyindolizidines (**532**) showed a moderate inhibition of α-amyloglucosidase, whilst the (2*R*,8*R*,9*S*)-2,8-dihydroxyindolizidine (**530**) displayed a moderate activity against α-glucosidase.



Scheme 101. (a) 1—AcCl, CH_3OH, 96%; 2—BnBr, NaH, Bu_4NI, 0°C, 70–90%, 7:3, **525**:**526**; (b) $NaBH_4$, $CaCl_2$, 82–92%; $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 80–92%; AllylMgBr, 70% (3:7 ratio); (c) 1—BnBr, NaH, Bu_4NI, 70–75%; BH_3, $NaBO_3$, THF; (d) 1—MsCl, Et_3N, CH_2Cl_2, 90–93%; 2—H_2, 10% Pd on C, EtOH, HCl; then Dowex 50 W-X8 (H^+), 59–75%.



Scheme 102. (a) 1—Bu_2SnO, toluene, reflux, 2 h; then added BnBr, Bu_4NBr, reflux, 3 days; 2—LiSPr, DMSO, **533** (15%) and **534** (50%); (b) H_2, 20% $Pd(OH)_2$ on C, AcOH; then Ac_2O, pyr, 24 h, 64%.



Scheme 103. (a) 1—Bu_2SnO, toluene, reflux, 2 h; then added BzCl, −78°C, 60%; (b) DAST, CH_2Cl_2, 0°C, 1 h, 52%; (c) aq NH_4OH, rt, 3 days; then Ac_2O, pyr, 90%.

3.7. Syntheses of 1,2,7,8-tetrahydroxyindolizidines

Most of the reported 1,2,7,8-tetrahydroxyindolizidines (swainsonine analogues having a hydroxyl substituent at C-7) are obtained by a rearrangement of castanospermine (**4**) (Schemes 102–104).[99]

Selective benzylation of castanospermine (**4**) afforded 1,6,7-tri-*O*-benzylcastanospermine (**534**) in 50% yield containing a trace of **535** as well as the rearranged tribenzyl ether **533** (15%). Hydrogenation of **533** followed by acetylation afforded the acetate **537** (Scheme 102).

Treatment of the 1,6,7-tribenzoate **538** with DAST gave a product which did not contain fluorine and assignment the structure **539**; this was deprotected with NH_4OH in CH_3OH to produce **536** which was isolated as its tetraacetate **537** (Scheme 103).

Methylation of **540** followed by debenzylation afforded **541** and **542** (Scheme 104).

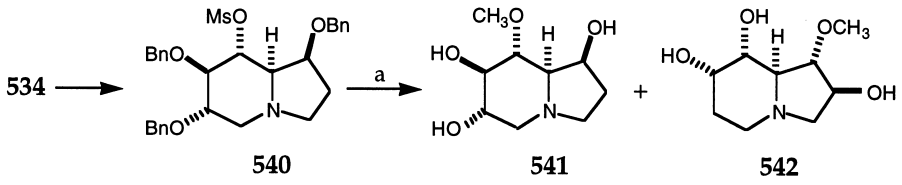
Radical reduction at *C*-6 of 1,2,6,7,8-pentahydroxyindolizidines was used for the synthesis of *trans*- and *cis*-hydroxy-(+)-swainsonine (Scheme 105).[53]

Conversion of **128** to its thionocarbonate **543** (68%) followed by deoxygenation and deprotection afforded *trans*-hydroxy-(+)-swainsonine **544** in 33% overall yield from **128**. Triflation of **128** followed by βα-elimination of the triflyl group afforded the enol ether **545**. Hydrogenation of **545** followed by acid hydrolysis provided *cis*-hydroxy-(+)-swainsonine **546** in 39% overall yield from **128**.

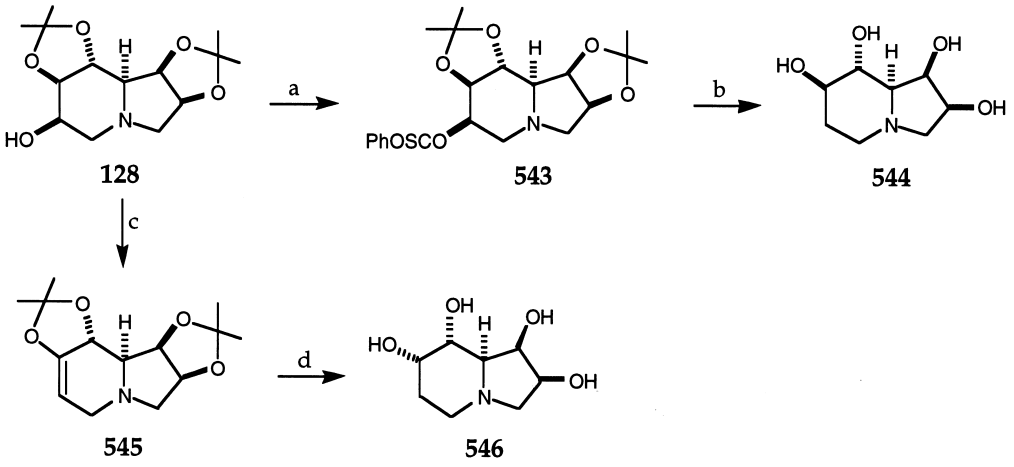
3.8. Miscellaneous analogues

Three patents[100] describe the syntheses of many partially protected swainsonine derivatives for use as immunoregulators.

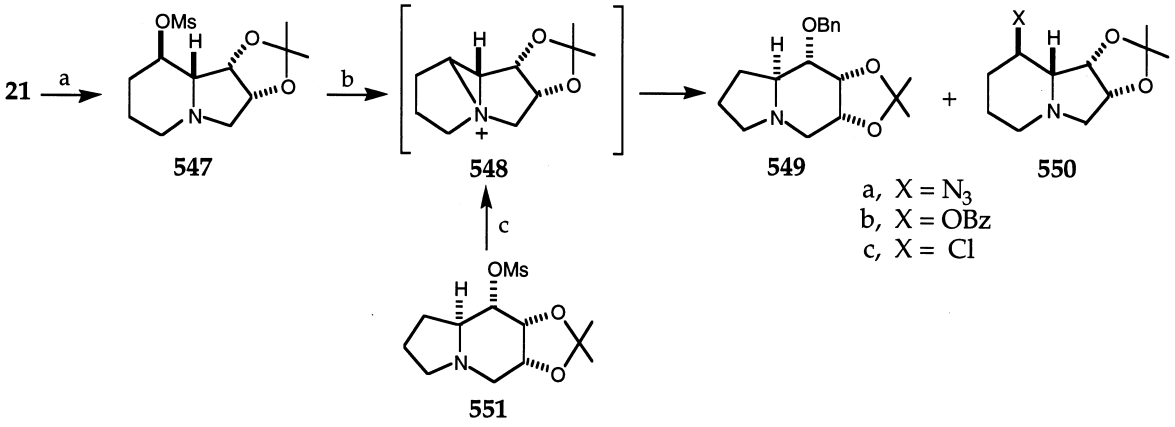
Mesylation of **21** gave compound **547**, which on heating with an anion (BzO^- and N_3^-) afforded the corresponding products **549** and **550** via the aziridinium ion intermediate **548**. Heating with Cl^- ion afforded only the thermodynamically stable rearranged product **549c**. Heating compound



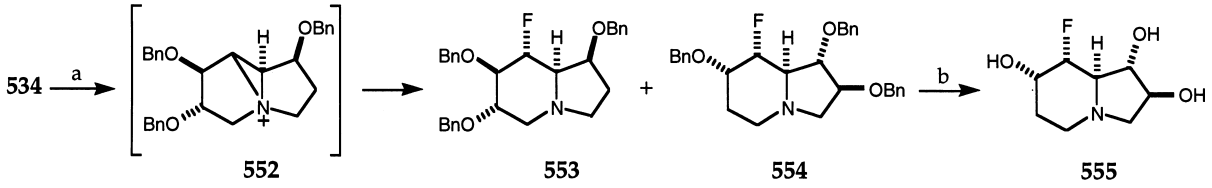
Scheme 104. (a) NaH, CH_3I, DMSO, overnight, NaSPr, DMSO; then 20% H_2, $Pd(OH)_2$ on C, AcOH, 3 days.



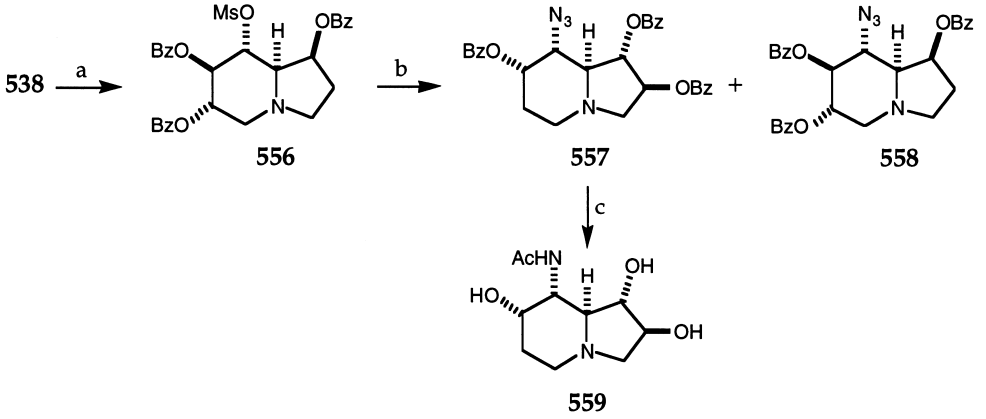
Scheme 105. (a) PhOCSCl, DMAP, CH_3CN, 68%; (b) 1—Bu_3SnH, AIBN, toluene, reflux, 59%; 2—1:1 TFA–D_2O, 81%; (c) Tf_2O, pyr, 61%; 2—DBU, THF, 100%; (d) 1—H_2, Pd-black, CH_3OH, 81%; 2—1:1 TFA–D_2O, 79%.



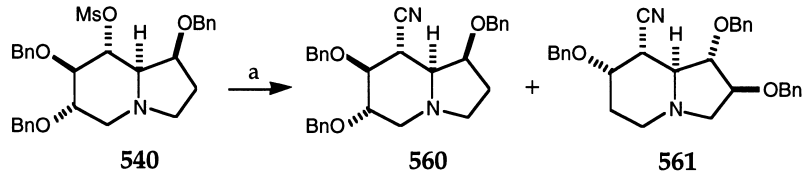
Scheme 106. (a) MsCl, pyr, 5°C, 95%; (b) NaN3, DMF, 100°C, **549** (60%) and **550** (17%); or NaOBz, DMF, 100°C, **549** (68%) and **550** (15%); *or* LiCl, DMF, 100°C, **549**, 100% (c) NaOBz, DMF, 100°C, **549** and **550**, total 40%.



Scheme 107. (a) DAST, CH_2Cl_2, 0°C, 2 days, **553** (16–20%) and **554** (26–30%); (b) H_2, 20% $Pd(OH)_2$ on C, HCl, EtOH, 24 h, 86%.



Scheme 108. (a) MsCl, pyr, rt, overnight; (b) NaN_3, HMPA, 80°C, 2 h, **557** (41%), **559** (56%); (c) H_2, 20% $Pd(OH)_2$ on C, EtOAc, EtOH, 24 h; then Ac_2O, pyr, $NaOCH_3$, CH_3OH, 95%.



540 560 561

Scheme 109. (a) KCN, DMSO, 90°C, 1 h, **560** (18–20%), **561** (30–36%) from **534**.

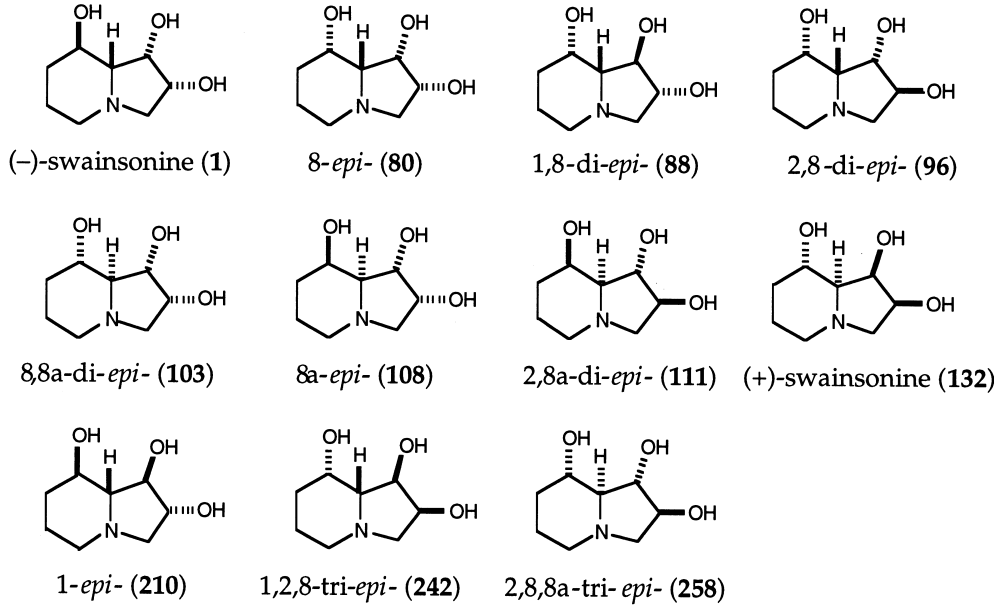


Figure 1. 1,2,8-Trihydroxyindolizidines synthesised to date.

551 with sodium benzoat, however, furnished a mixture of **549b** and **550b** (Scheme 106).[47b]

Treatment of **534** with DAST gave **553** and **554** via the aziridinium ion intermediate **552** as a mixture in a 2:3 ratio, hydrogenation of **554** affording the fluorinated octahydroindolizidinetriol **555** (Scheme 107).[99]

Mesylation of **538** afforded the methyl **556** followed by heating with sodium azide to give **557** and **558** in a 1:1.3 ratio. Subsequent reduction of the azide group followed by *N*-acetylation and debenzoylation of **557** furnished the compound **559** (Scheme 108).[99]

Treatment of **540** with potassium cyanide in warm DMSO gave the nitrile derivatives **560** and **561** in a 2:3 ratio through the aziridinium ion intermediate (**552**) (Scheme 109).[99]

4. Conclusions

The synthetic methods discussed in this review describe the preparation of 11 of the possible 16 stereoisomers of 1,2,8-trihydroxyindolizidine together with other analogues; the 11 stereoisomers are shown in Fig. 1.

The useful biological activities exhibited by certain of these swainsonine analogues indicate that other derivatives are of interest. Consequently, the further development of chemical methodologies for the syntheses of swainsonine and its analogues is a matter of some importance as this should allow a better understanding of the structure–activity relationships and lead to novel improved glycosidase compounds.

References

1. (a) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055. (b) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29. (c) Daniel, L. R.; Hagler, W. M. J.; Croom, W. J. J. *Biodeterior. Res.* **1994**, 85. (d) Harris, C. M.; Campbell, B. C.; Molyneux, R. J.; Harris, T. M. *Tetrahedron Lett.* **1988**, *29*, 4815. (e) Bartlett, H. S.; Wilson, M. E.; Croom, J. J.; Broquist, H. P.; Hagler, Winston, M. J. *Biodeterior. Res.* **1987**, *1*, 135; [*Chem. Abstr.* **1989**, *110*, 36551j]. (f) Broquist, H. P.; Mason, P. S.; Wickwire, B.; Homann, R.; Schneider, M. J.; Harris, T. M. *Plant Toxicol.* **1985**, 301. (g) Broquist, H. P. *J. Toxicol. Toxin Rev.* **1986**, *5*, 241 (review).
2. (a) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257. (b) Broquist, H. P. *Annu. Rev. Nutr.* **1985**, *5*, 391 (review). (c) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Plant Toxicol.* **1985**, 249. (d) Ermayanti, T. M.; McComb, J. A.; O'Brien, P. A. *J. Exp. Bot.* **1994**, *45*, 633. (e) Ermayanti, T. M.; McComb, J. A.; O'Brien, P. A. *Phytochemistry* **1994**, *36*, 313.
3. (a) Molyneux, R. J.; James, L. F. *Science* **1982**, *216*, 190.

(b) Molyneux, R. J.; James, L. F.; Panter, K. E.; Ralphs, M. H. *Phytochem. Anal.* **1991**, *2*, 125. (c) Davis, D.; Schwarz, P.; Hernandez, T.; Mitchell, M.; Warnock, B.; Elbein, A. D. *Plant Physiol.* **1984**, *76*, 972.

4. (a) Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 926. (b) Donaldson, M. J.; Bucke, C.; Adlard, M. W. *Microb. Util. Renewable Resour.* **1990**, *7*, 228. (c) Patrick, M.; Adlard, M. W.; Keshavarz, T. *Biotechnol. Lett.* **1993**, *15*, 997. (d) Sim, K. L.; Perry, D. *Mycol. Res.* **1995**, *99*, 1078. (e) Patrick, M. S.; Adlard, M. W.; Keshavarz, T. *Biotechnol. Lett.* **1995**, *17*, 433. (f) Patrick, M. S.; Adlard, M. W.; Keshavarz, T. *Enzyme Microb. Technol.* **1996**, *18*, 428. (g) Sim, K. L.; Perry, D. *Glycoconjugate J.* **1997**, *14*, 661. (h) Tamerler-Yildir, C.; Adlard, M. W.; Keshavarz, T. *Biotechnol. Lett.* **1997**, *19*, 919. (i) Tamerler, C.; Ullah, M.; Adlard, M. W.; Keshavarz, T. *FEMS Microbiol. Lett.* **1998**, *168*, 17. (j) Tamerler, C.; Keshavarz, T. *Biotechnol. Lett.* **1999**, *21*, 501.

5. (a) Dorling, P. R.; Huxtable, C. R.; Colegate, S. M. *Biochem. J.* **1980**, *191*, 649. (b) Molyneux, R. J.; James, L. F. *Mycotoxins Phytoalexins* **1991**, 637 (review). (c) Elbein, A. D. *FASEB J.* **1991**, *5*, 3055 (review). (d) Winchester, B.; Al Daher, S.; Carpenter, N. C.; Cenci di Bello, I.; Choi, S. S.; Fairbanks, A. J.; Feelt, G. W. J. *Biochem. J.* **1993**, *290*, 743. (e) Liao, Y. F.; Lal, A.; Moremen, K. W. *J. Biol. Chem.* **1996**, *271*, 28348. (f) Cenci di Bello, I.; Fleet, G. W. J.; Namgoong, S. K.; Tadano, K.; Winchester, B. *Biochem. J.* **1989**, *259*, 855. (g) Nagahashi, G.; Tu. S. I.; Fleet, G.; Namgoong, S. K. *Plant Physiol.* **1990**, *92*, 413. (h) McGee, C. M.; Murray, D. R. *J. Plant Physiol.* **1984**, *116*, 467. (i) Tulsiani, D. R. P.; Broquist, H. P.; Touster, O. *Arch. Biochem. Biophys.* **1985**, *236*, 427. (j) Dorling, P. R.; Huxtable, C. R.; Colegate, S. M.; Winchester, B. G. *Plant Toxicol.* **1985**, 255. (k) Elbein, A. D.; Szumilo, T.; Sanford, B. A.; Sharpless, K. B.; Adams, C. *Biochemistry* **1987**, *26*, 2502. (l) Winkler, J. R.; Segal, H. L. *J. Biol. Chem.* **1984**, *259*, 15369. (m) Cenci di Bello, I.; Dorling, P. R.; Winchester, B. *Biochem. J.* **1983**, *215*, 693. (n) Segal, H. L.; Winkler, J. R. *Prog. Clin. Biol. Res.* **1985**, *180*, 491. (o) Haeuw, J. F.; Strecker, G.; Wieruszeski, J. M.; Montreuil, J.; Michalski, J. C. *Eur. J. Biochem.* **1991**, *202*, 1257. (p) Jauhiainen, A.; Vanha-Perttula, T. *Int. J. Biochem.* **1987**, *19*, 267. (q) Tulsiani, D. R. P.; Touster, O. *J. Biol. Chem.* **1987**, *262*, 6506. (r) Vlasova, A. L.; Ushakova, N. A.; Preobrazhenskaya, M. E. *Biokhimiya* **1991**, *56*, 1479; [*Chem. Abstr.* **1991**, *115*, 229146t]. (s) Greenaway, V. A.; Naish, S.; Jessup, W.; Dean, R. T. *Biochem. Soc. Trans.* **1982**, *10*, 533. (t) Winchester, B. *Biochem. Soc. Trans.* **1984**, *12*, 522.

6. (a) Glick, M. C.; De Santis, R.; Santer, U. V. *Prog. Clin. Biol. Res.* **1985**, *175*, 229. (b) Greenaway, V. A.; Jessup, W.; Dean, R. T.; Dorling, P. R. *Biochim. Biophys. Acta* **1983**, *762*, 569. (c) De Gasperi, R.; Al Daher, S.; Winchester, B. G.; Warren, C. D. *Biochem. J.* **1992**, *286*, 55. (d) Stannard, B. S.; Gesundheit, N.; Thotakura, N. R.; Gyves, P. W.; Ronin, C.; Weintraub, B. D. *Biochem. Biophys. Res. Commun.* **1989**, *165*, 788.

7. (a) Elbein, A. D.; Solf, R.; Dorling, P. R.; Vosbeck, K. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 7393. (b) Kaushal, G. P.; Szumilo, T.; Pastuszak, I.; Elbein, A. D. *Biochemistry* **1990**, *29*, 2168. (c) Elbein, A. D.; Dorling, P. R.; Vosbeck, K.; Horisberger, M. *J. Biol. Chem.* **1982**, *257*, 1573. (d) Tulsiani, D. R. P.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, *257*, 7936. (e) Tulsiani, D. R. P.; Touster, O. *Arch. Biochem. Biophys.* **1983**, *224*, 594. (f) Dorling, P. R.; Colegate, S. M.; Huxtable, C. R. *Toxicon* **1983**, *3*, 93 (review). (g) Pastuszak, I.; Kaushal, G. P.; Wall, K. A.; Pan, Y. T.; Sturm, A.; Elbein, A. D. *Glycobiology* **1990**, *1*, 71.

8. Hubbard, S. C.; Ivatt, R. J. *Annu. Rev. Biochem.* **1981**, *50*, 555.

9. (a) Humphries, M. J.; Matsumoto, K.; White, S. L.; Molyneux, R. J.; Olden, K. *Cancer Res.* **1988**, *48*, 1410. (b) Dennis, J. W.; White, S. L.; Freer, A. M.; Dime, D. *Biochem. Pharmoacol.* **1993**, *46*, 1459. (c) Bowen, D.; Southerland, W. M.; Bowen, C. D.; Hughes, D. E. *Anticancer Res.* **1997**, *17*, 4345. (d) Chen, X.; Liu, B.; Ji, Y.; Li, J.; Zhu, Z.; Yin, H.; Lin, J. *Shanghai Yixue* **1998**, *21*, 256; [*Chem. Abstr.* **1998**, *129*, 254444k]. (e) Olden, K.; Mohla, S.; Newton, S. A.; White, S. L.; Humphries, M. J. *Ann. NY Acad. Sci.* **1988**, *551*, 421 (review). (f) Myc, A.; Kunicka, J. E.; Melamed, M. R.; Darzynkiewicz, Z. *Cancer Res.* **1989**, *49*, 2879. (g) Spearman, M. A.; Damen, J. E.; Kolodka, T.; Greenberg, A. H.; Jamieson, J. C.; Wright, J. A. *Cancer Lett.* **1991**, *57*, 7. (h) Welch, D. R.; Lobl, T. J.; Seftor, E. A.; Wack, P. J.; Aeed, P. A.; Yohem, K. H.; Seftor, R. E. B.; Hendrix, M. J. C. *Int. J. Cancer* **1989**, *43*, 449. (i) Yagel, S.; Feinmesser, R.; Waghorne, C.; Lala, P. K.; Breitman, M. L.; Dennis, J. W. *Int. J. Cancer* **1989**, *44*, 685. (j) Bowen, D.; Adir, J.; White, S. L.; Bowen, C. D.; Matsumoto, K.; Olden, K. *Anticancer Res.* **1993**, *13*, 841. (k) Newton, S. A.; White, S. L.; Humphries, M. J.; Olden, K. *J. Natl. Cancer Inst.* **1989**, *81*, 1024. (l) Liu, B.; Lin, Y.; Yin, H.; Chen, X. *Zhonghua Zhongliu Zazhi* **1998**, *20*, 168; [*Chem. Abstr.* **1999**, *130*, 20275z].

10. (a) Dennis, J. W. *Cancer Res.* **1986**, *46*, 5131. (b) Taylor, J. B.; Strickland, J. R. *J. Anim. Sci.* **1998**, *76*, 2857. (c) White, S. L.; Nagai, T.; Akiyama, S. K.; Reeves, E. J.; Grzegorzewski, K.; Olden, K. *Cancer Commun.* **1991**, *3*, 83. (d) Myc., A.; DeAngelis, P.; Lassota, P.; Melamed, M. R.; Darzynkiewicz, Z. *Clin. Exp. Immunol.* **1991**, *84*, 406. (e) Dennis, J. W.; Koch, K.; Beckner, D. *J. Natl. Cancer Inst.* **1989**, *81*, 1028. (f) Seftor, R. E. B.; Seftor, E. A.; Grimes, W. J.; Liotta, L. A.; Stetler-Stevenson, W. G.; Welch, D. R.; Hendrix, M. J. C. *Melanoma Res.* **1991**, *1*, 43.

11. (a) Galustian, C.; Foulds, S.; Dye, J. F.; Guillou, P. J. *Immunopharmacology* **1994**, *27*, 165. (b) Roberts, J. D.; Klein, J. L. D.; Palmantier, R.; Dhume, S. T.; George, M. D.; Olden, K. *Cancer Detect. Prev.* **1998**, *22*, 455 (review). (c) Olden, K.; Breton, P.; Grzegorzewski, K.; Yasuda, Y.; Gause, B. L.; Oredipe, O. A.; Newton, S. A.; White, S. L. *Pharmacol. Ther.* **1991**, *50*, 285 (review). (d) Olden, K.; Newton, S. A.; Nagai, T.; Yasuda, Y.; Grzegorzewki, K.; Breton, P.; Oredipe, O.; White, S. L. *Pigm. Cell Res. Suppl.* **1992**, *2*, 219 (review). (e) Dennis, J. W. *Semin. Cancer Biol.* **1991**, *2*, 411 (review). (f) Yagita, M.; Noda, I.; Maehara, M.; Fujieda, S.; Inoue, Y.; Hoshino, T.; Saksela, E. *Int. J. Cancer* **1992**, *52*, 664. (g) Korczak, B.; Dennis, J. W. *Int. J. Cancer* **1993**, *53*, 634. (h) Bowlin, T. L.; McKown, B. J.; Kang, M. S.; Sunkara, P. S. *Cancer Res.* **1989**, *49*, 4109. (i) Dennis, J. W.; Koch, K.; Yousefi, S.; VanderElst, I. *Cancer Res.* **1990**, *50*, 1867. (j) Breton, P.; Asseffa, A.; Grzegorzewski, K.; Akiyama, S. K.; White, S. L.; Cha, J. K.; Olden, K. *Cancer Commun.* **1990**, *2*, 333. (k) Pulverer, G.; Beuth, J.; Ko, H. L.; Yassin, A.; Ohshima, Y.; Roszkowski, K.; Uhlenbruck, G. *J. Cancer Res. Clin. Oncol.* **1988**, *114*, 217. (l) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215. (m) Grzegorzewski, K.; Newton, S. A.; Akiyama, S. K.; Sharrow, S.; Olden, K.; White, S. L. *Cancer Commun.* **1989**, *1*, 373. (n) Klein, J. L. D.; Roberts, J. D.; George, M. D.; Kurtzberg, J.; Breton, P.; Chermann, J. C.; Olden, K. *Br. J. Cancer* **1999**, *80*, 87.

12. (a) Das, P. C.; Roberts, J. D.; White, S. L.; Olden, K. *Oncol. Res.* **1995**, *7*, 425. (b) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935. (c) Goss, P. E.; Reid, C. L.; Bailey, D.; Dennis, J. W. *Clin. Cancer Res.* **1997**, *3*, 1077.

13. (a) Motohiro, H.; Kunio, N.; Hiroshi, T.; Junji, H.; Masanobu, K.; Hatsuo, A.; Hiroshi, I. Patent EP 104826; *Chem. Abstr.* **1984**, *101*, 28283x. (b) White, S. L.; Schweitzer, K.; Humphries, M. J.;

Olden, K. *Biochem. Biophys. Res. Commun.* **1988**, *150*, 615. (c) Yagita, M.; Saksela, E. *Scand. J. Immunol.* **1990**, *31*, 275. (d) Kino, T.; Inamura, N.; Nakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 936. (e) Stegelmeier, B. L.; Snyder, P. W.; James, L. F.; Panter, K. E.; Molyneux, R. J.; Gardner, D. R.; Ralphs, M. H.; Pfister, J. A. *Toxic Plants Other Nat. Toxicants* **1998**, 285. (f) Dennis, J. W.; Shah, R. N.; Ziser, L. Patent WO 9,846,602; *Chem. Abstr.* **1998**, *129*, 306525j.

14. (a) Oredipe, O. A.; White, S. L.; Grzegorzewski, K.; Gause, B. L.; Cha, J. K.; Miles, V. A.; Olden, K. *J. Natl. Cancer Inst.* **1991**, *83*, 1149. (b) Peyrieras, N.; Bause, E.; Legler, G.; Vasilov, R.; Claesson, L.; Peterson, P.; Ploegh, H. *EMBO J.* **1983**, *2*, 823. (c) Pan, Y. T.; Ghidoni, J.; Elbein, A. D. *Arch. Biochem. Biophys.* **1993**, *303*, 134. (d) Pritchard, D. H.; Huxtable, C. R. R.; Dorling, P. R. *Res. Vet. Sci.* **1990**, *48*, 228. (e) Baker, D. C.; James, L. F.; Hartley, W. J.; Panter, K. E.; Maynard, H. F.; Pfister, J. *Am. J. Vet. Res.* **1989**, *50*, 1396. (f) Kovacs, P.; Csaba, G. *Acta Microbiol. Hung.* **1993**, *40*, 351. (g) Takahashi, H.; Parsons, P. G. *J. Invest. Dermatol.* **1992**, *98*, 481. (h) Skudlarek, M. D.; Orgebin-Crist, M. C. *J. Reprod. Fertil.* **1988**, *84*, 611. (i) Kang, M. S.; Elbein, A. D. *J. Virol.* **1983**, *46*, 60. (j) Muldoon, D. F.; Stohs, S. J. *J. Appl. Toxicol.* **1994**, *14*, 81. (k) Foddy, L.; Feeney, J.; Hughes, R. C. *Biochem. J.* **1986**, *233*, 697. (l) Foddy, L.; Hughes, R. C. *Carbohydr. Res.* **1986**, *151*, 293. (m) Tulsiani, D. R. P.; Broquist, H. P.; James, L. F.; Touster, O. *Plant Toxicol.* **1985**, 279. (n) Stegelmeier, B. L.; Molyneux, R. J.; Elbein, A. D.; James, L. F. *Vet. Pathol.* **1995**, *32*, 289. (o) Stegelmeier, B. L.; James, L. F.; Panter, K. E.; Gardner, D. R.; Ralphs, M. H.; Pfister, J. A. *J. Anim. Sci.* **1998**, *76*, 1140. (p) Huxtable, C. R.; Dorling, P. R. *Acta Neuropathol.* **1985**, *68*, 65. (q) Huxtable, C. R.; Dorling, P. R.; Walkley, S. U. *Acta Neuropathol.* **1982**, *58*, 27. (r) De Balogh, K. K. I. M.; Dimande, A. P.; Van Der Lugt, J. J.; Molyneux, R. J.; Naude, T. W.; Welman, W. G. *Toxic Plants Other Nat. Toxicants* **1998**, 428. (s) Scofield, A. M.; Fellows, L. E.; Nash, R. J.; Fleet, G. W. J. *Life Sci.* **1986**, *39*, 645. (t) Elbein, A. D.; Pan, Y. T.; Solf, R.; Vosbeck, K. *J. Cell. Physiol.* **1983**, *115*, 265. (u) James, L. F.; Panter, K. E.; Broquist, H. P.; Hartly, W. J. *Vet. Hum. Toxicol.* **1991**, *33*, 217. (v) Khan, F. A.; Basu, D. *Indian J. Biochem. Biophys.* **1984**, *21*, 203. (w) Houri, J. J.; Ogier-Denis, E.; Bauvy, C.; Aubery, M.; Sapin, C.; Trugnan, G.; Codogno, P. *Eur. J. Biochem.* **1992**, *205*, 1169. (x) Kalathur S.; Seetharam, S.; Dahms, N. M.; Seetharam, B. *Arch. Biochem. Biophys.* **1994**, *315*, 8. (y) Sem, A.; Sambhara, S.; Chadwick, B. S.; Miller, R. G. *J. Cell. Physiol.* **1991**, *148*, 485. (z) Caroll, M.; Bird, M. M. *Int. J. Biochem.* **1991**, *23*, 1285.

15. (a) Hori, H.; Kaushal, G. P.; Elbein, A. D. *Plant Physiol.* **1985**, *77*, 687. (b) Chotai, K.; Jennings, C.; Winchester, B.; Dorling, P. *J. Cell. Biochem.* **1983**, *21*, 107. (c) Chen, W.; Li, X.; Shao, D.; Gu, J. *Shanghai Yike Daxue Xuebao* **1993**, *20*, 415; [*Chem. Abstr.* **1994**, *121*, 176613h]. (d) Stevens, K. L.; Molyneux, R. J. *J. Chem. Ecol.* **1988**, *14*, 1467. (e) Tulsiani, D. R. P.; Broquist, H. P.; James, L. F.; Touster, O. *Arch. Biochem. Biophys.* **1984**, *232*, 76. (f) Croom, W. J. J.; Hagler, W. M. J.; Froetschel, M. A.; Johnson, A. D. *J. Anim. Sci.* **1995**, *73*, 1499. (g) Warren, C. D.; Daniel, P. F.; Bugge, B.; Evans, J. E.; James, L. F.; Jeanloz, R. W. *J. Biol. Chem.* **1988**, *263*, 15041. (h) Kang, M. S.; Bowlin, T. L.; Vijay, I. K.; Sunkara, S. P. *Carbohydr. Res.* **1993**, *248*, 327. (i) Chae, B. S.; Ahn, Y. K.; Kim, J. H. *Yakhak Hoechi* **1998**, *42*, 75; [*Chem. Abstr.* **1998**, *128*, 278760r]. (j) Chae, B. S.; Ahn, Y. K.; Kim, J. H. *Arch. Pharmacol. Res.* **1997**, *20*, 545. (k) Chrispeels, M. J.; Vitale, A. *Plant Physiol.* **1985**, *78*, 704. (l) Daniel, P. F.; Warren, C. D.; James, L. F. *Biochem. J.* **1984**, *221*, 601. (m) Molyneux, R. J.; McKenzie, R. A.; O'Sullivan, B. M.; Elbein, A. D. *J. Nat. Prod.* **1995**, *58*, 878. (n) McNally, A. K.; DeFife, K. M.; Anderson, J. M. *Am. J. Pathol.* **1996**, *149*, 975. (o) Opara, K. N.; Okenu, D. M. N. *J. Parasitol. Dis.* **1996**, *20*, 145. (p) Shao, M.; Chin, C. C. Q.; Caprioli, R. M.; Wold, F. *J. Biol. Chem.* **1987**, *262*, 2973. (q) Schwarz, P. M.; Elbein, A. D. *J. Biol. Chem.* **1985**, *260*, 14452. (r) Abraham, D. J.; Sidebothom, R.; Winchester, B. G.; Dorling, P. R.; Dell, A. *FEBS Lett.* **1983**, *163*, 110. (s) Tropea, J. E.; Swank, R. T.; Segal, H. L. *J. Biol. Chem.* **1988**, *263*, 4309. (t) Bosch, J. V.; Tlusty, A.; McDowell, W.; Legler, G.; Schwarz, R. T. *Virology* **1985**, *143*, 342. (u) Dreyer, D. L.; Jones, K. C.; Molyneux, R. J. *J. Chem. Ecol.* **1985**, *11*, 1045. (v) Goussault, Y.; Warren, C. D.; Bugge, B.; Jeanloz, R. W. *Glycoconjugate J.* **1986**, *3*, 239. (w) Arumugham, R. G.; Tanzer, M. L. *Biochem. Biophys. Res. Commun.* **1983**, *116*, 922. (x) Huxtable, C. R.; Dorling, P. R. *Vet. Pathol.* **1983**, *20*, 727. (y) Broquist, H. P.; Mason, P. S.; Hagler, W. M.; Harris, T. M. *Appl. Environ. Microbiol.* **1984**, *48*, 386. (z) Ziegler, C.; Mersmann, G. *Biochim. Biophys. Acta* **1984**, *799*, 203.

16. (a) McLawhon, R. W.; Berry-Kravis, E.; Dawson, G. *Biochem. Biophys. Res. Commun.* **1986**, *134*, 1387. (b) Koettgen, E.; Beiswenger, M.; James, L. F.; Bauer, C. *Gastroenterology* **1988**, *95*, 100. (c) Tulsiani, D. R. P.; Broquist, H. P.; James, L. F.; Touster, O. *Arch. Biochem. Biophys.* **1988**, *264*, 607. (d) Tulsiani, D. R. P.; Skudlarek, M. D.; Orgebin-Crist, M. C. *Biol. Reprod.* **1990**, *43*, 130. (e) Tulsiani, D. R. P.; Touster, O. *J. Biol. Chem.* **1983**, *258*, 7578. (f) Winkler, J. R.; Segal. H. L. *J. Biol. Chem.* **1984**, *259*, 1958. (g) Dorling, P. R.; Huxtable, C. R.; Cenci di bello, I.; Winchester, B. *Biochem. Soc. Trans.* **1983**, *11*, 717. (h) Tulsiani, D. R. P.; Touster, O. *Arch. Biochem. Biophys.* **1992**, *296*, 556. (i) Costa, J.; Ricardo, C. P. P. *Plant Sci.* **1994**, *101*, 137. (j) Pulsipher, G. D.; Galyean, M. L.; Hallford, D. M.; Smith, G. S.; Kiehl, D. E. *J. Anim. Sci.* **1994**, *72*, 1561. (k) Stegelmeier, B. L.; James, L. F.; Panter, K. E.; Molyneux, R. J. *Vet. Hum. Toxicol.* **1995**, *37*, 336. (l) Daniel, P. F.; Newburg, D. S.; O'Neil, N. E.; Smith, P. W.; Fleet, G. W. J. *Glycoconjugate J.* **1989**, *6*, 229. (m) Larsson, O.; Engstroem, W. *Biochem. J.* **1989**, *260*, 597. (n) Van Kemenade, F. J.; Rotteveel, F. T. M., van den Broek, L. A. G. M.; Baars, P. A., van Lier, R. A. W.; Miedema, F. *J. Leukocyte Biol.* **1994**, *56*, 159. (o) Wang, S.; Panter, K. E.; Holyoak, G. R.; Molyneux, R. J.; Liu, G.; Evans, R. C.; Bunch, T. D. *Anim. Reprod. Sci.* **1999**, *56*, 19. (p) Lehrman, M. A.; Zeng, Y. *J. Biol. Chem.* **1989**, *264*, 1584. (q) Donaldson, M. J.; Broby, H.; Adlard, M. W.; Bucke, C. *Phytochem. Anal.* **1990**, *1*, 18. (r) Novikoff, P. M.; Touster, O.; Novikoff, A. B.; Tulsiani, D. P. *J. Cell Biol.* **1985**, *101*, 339.

17. Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 6863.

18. Kardono, L. B. S.; Kinghorn, A. D.; Molyneux, R. J. *Phytochem. Anal.* **1991**, *2*, 120.

19. Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1980**, *33*, 435.

20. Pastuszak, I.; Molyneux Russell, J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886.

21. Harris, T. M.; Harris, C. M.; Hill, J. E.; Ungemach, F. S.; Broquist, H. P.; Wickwire, B. M. *J. Org. Chem.* **1987**, *52*, 3094.

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

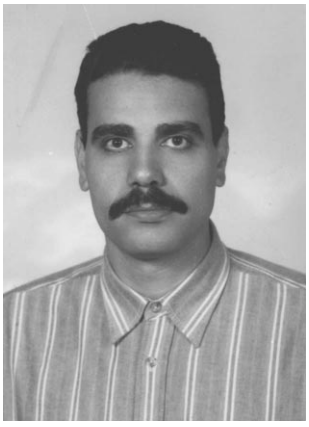
23. Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, *27*, 1403.

24. (a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806. (b) Cardona, F.; Goti, A.; Brandi, A.; Scarselli, M.; Niccolai, N.; Mangani, S. *J. Mol. Model.* **1997**, *3*, 249.

25. (a) Saul, R.; Chambers, J. P.; Molyneux, R. J.; Elbein, A. D. *Arch. Biochem. Biophys.* **1983**, *221*, 593. (b) Saul, R.; Ghidoni, J. J.; Molyneux, R. J.; Elbein, A. D. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 93. (c) Pan, Y. T.; Hori, H.; Saul, R.; Sanford, B. A.; Molyneux, R. J.; Elbein, A. D. *Biochemistry* **1983**, *22*, 3975. (d) 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.
26. (a) Sasak, V. W.; Ordovas, J. M.; Elbein, A. D.; Berninger, R. W. *Biochem. J.* **1985**, *232*, 759. (b) Trugnan, G.; Rousset, M.; Zweibaum, A. *FEBS Lett.* **1986**, *195*, 28. (c) Ostrander, G. K.; Scribner, N. K.; Rohrschneider, L. R. *Cancer Res.* **1988**, *48*, 1091. (d) Ahrens, P. B.; Ankel, H. *J. Biol. Chem.* **1987**, *262*, 7575.
27. (a) Sunkara, P. S.; Bowlin, T. L.; Liu, P. S.; Sjoerdsma, A. *Biochem. Biophys. Res. commun.* **1987**, *148*, 206. (b) Nichols, E. J.; Manager, R.; Hakomori, S.; Herscovics, A.; Rohrschneider, L. R. *Mol. Cell. Biol.* **1985**, *5*, 3467.
28. (a) Dagani, R. *Chem. Eng. News* **1987**, *June 29*, 25. (b) Gruters, R. A.; Neefies, J. J.; Tersmette, M.; De Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (c) Molyneux, R. J.; Roitman, J. N.; Dunnheim, G.; Szumilo, T.; Elbein, A. D. *Arch. Biochem. Biophys.* **1986**, *251*, 450. (d) Montefiori, D. C.; Robinson, W. E.; Mitchell, W. M. *Proc. Natl. Acad. Sci. USA* **1998**, *85*, 9248. (e) Tan, G. T.; Miller, J. F.; Kinghorn, A. D.; Hughes, S. H.; Pezzuto, J. M. *Biochem. Biophys. Res. Commun.* **1992**, *185*, 370. (f) Tan, G. T.; Pezzuoto, J. M.; Kinghorn, A. D.; Hughes, S. H. *J. Nat. Prod.* **1991**, *54*, 143.
29. (a) Kang, M. S.; Elbein, A. D. *Plant Physiol.* **1983**, *71*, 551. (b) Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744. (c) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171. (d) Withers, S. G.; Street, I. P. *J. Am. Chem. Soc.* **1988**, *110*, 8551. (e) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29. (f) Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 6554. (g) Dorling, P. R.; Huxtable, C. R.; Colegate, S. M. *Biochem. J.* **1980**, *191*, 649. (h) Withers, S. G.; Street, I. P.; P. Bird, P.; Dolphin, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7430. (i) Fuhrmann, U.; Bause, E.; Legler, G.; Ploegh, H. *Nature* **1984**, *307*, 755.
30. (a) Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 6554. (b) Post, C. B.; Karplus, M. *J. Am. Chem. Soc.* **1986**, *108*, 1317. (c) Fleet, G. W. J. *Tetrahedron Lett.* **1985**, *26*, 5073.
31. (a) Fleet, G. W. J.; Ramsden, N. G.; Nash, R. J.; Fellows, L. E.; Jacob, G. S.; Molyneux, R. J.; Cenci di Bello, I.; Winchester, B. *Carbohydr. Res.* **1990**, *205*, 269. (b) Segal, H. L.; Winkler, J. R. *Curr. Top. Cell. Regul.* **1984**, *24*, 229.
32. Winkler, D. A.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084.
33. (a) Herezegh, P.; Kovacs, I.; Sztaricskai, F. *Recent Prog. Chem. Synth. Antibiot. Relat. Microb. Prod.* **1993**, 751 (review). (b) Fellows, L. E.; Kite, G. C.; Nash, R. J.; Simmonds, M. S. J.; Scofield, A. M. *Recent Adv. Phytochem.* **1989**, *23*, 395 (review). (c) Reissig, H. U. *Org. Synth. Highlights* **1991**, 359 (review). (d) Takahata, M.; Momose, T. *The Alkaloids* **1993**, *44*, 189 (review). (e) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045 (review). (f) Nishimura, Y. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 10, 495pp (review). (g) Cossy, J.; Vogel, P. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1993; Vol. 11, 275pp (review). (h) Hashimoto, S.; Setoi, H.; Takeno, S.; Ito, Y. Patent JP 61,277,685; *Chem. Abstr.* **1987**, *106*, 138253y. (i) Takeno, S.; Setoi, H.; Hashimoto, S. Patent JP 61,227,566; *Chem. Abstr.* **1987**, *106*, 120131x. (k) Pearson, W. H.; Hembre, E. J. Patent WO 9,907,366; *Chem. Abstr.* **1999**, *130*, 196798m.
34. (a) Mezher, H. A.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 447. (b) Ali, M. H.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1985**, *136*, 225.
35. (a) Suami, T.; Tadano, K.; Iimura, Y. *Chem. Lett.* **1984**, 513. (b) Suami, T.; Tadano, K.; Iimura, Y. *Carbohydr. Res.* **1985**, *136*, 67. (c) Suami, T.; Tadano, K. Patent JP 60,218,389; *Chem. Abstr.* **1986**, *105*, 78823b.
36. (a) Bashyal, B. P.; Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083. (b) Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, *25*, 1853; Takatani, T.; Tsutsumi, H.; Yasuda, N. Patent JP 60,166,680; *Chem. Abstr.* **1986**, *105*, 134289w.
37. Bermejo Gonzalez, F.; Lopez Barba, A.; Ruano Espina, M. *Bull. Chem. Soc. Jpn* **1992**, *65*, 567.
38. Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1984**, 1201.
39. (a) Bennett, R. B.; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580. (b) Cha, J. K.; Bennett, R. B. Patent WO 9,006,311 *Chem. Abstr.* **1990**, *113*, 212415r. (c) Tropper, F.; Shah, R. N.; Sharma, P. Patent WO 9,921,858; *Chem. Abstr.* **1999**, *130*, 338281p.
40. Pearson, W. H.; Lin, K. C. *Tetrahedron Lett.* **1990**, *31*, 7571.
41. (a) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217. (b) Cha, J. K.; Bennett, R. B. Patent US 5,187,279; *Chem. Abstr.* **1993**, *118*, 255177k. (c) Pearson, W. H.; Hembre, E. J. Patent US 5,919,952; *Chem. Abstr.* **1999**, *131*, 73836k.
42. Kang, S. H.; Kim, G. T. *Tetrahedron Lett.* **1995**, *36*, 5049.
43. Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100.
44. Carpenter, N. M.; Fleet, G. W. J.; Cenci di Bello, I.; Winchester, B.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1989**, *30*, 7261.
45. Fleet, G. W. J. US Patent 5,023,340 *Chem. Abstr.* **1991**, *115*, 136472f.
46. Setoi, H.; Takeno, H.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 3948.
47. (a) Tadano, K.; Iimura, Y.; Hotta, Y.; Fukabori, C.; Suami, T. *Bull. Chem. Soc. Jpn* **1986**, *59*, 3885. (b) Iimura, Y.; Hotta, Y.; Fukabori, C.; Tadano, K.; Suami, T. *J. Carbohydr. Chem.* **1986**, *5*, 147.
48. Austin, G. N.; Baird, P. D.; Fleet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron* **1987**, *43*, 3095.
49. Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1985**, 31.
50. Tadano, K.; Morita, M.; Hotta, Y.; Ogawa, S.; Winchester, B.; Cenci di Bello, I. *J. Org. Chem.* **1988**, *53*, 5209.
51. (a) Tadano, K.; Hotta, Y.; Morita, M.; Suami, T.; Winchester, B.; Cenci di Bello, I. *Chem. Lett.* **1986**, 2105. (b) Tadano, K.; Hotta, Y.; Morita, M.; Suami, T.; Winchester, B.; Cenci di Bello, I. *Bull. Chem. Soc. Jpn* **1987**, *60*, 3667.
52. Kim, Y. G.; Cha, J. K. *Tetrahedron Lett.* **1989**, *30*, 5721.
53. (a) Davis, B.; Bell, A. A.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Jones, M. G.; Smith, C.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8565. (b) Bell, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1996**, *7*, 595. (c) Bell, A. A.; Pickering, L.; Watson, A. A.; Nash, R. J.; Griffiths, R. C.; Jones, M. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8561.
54. Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420.
55. (a) Hunt, J. A.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 501. (b) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112.
56. Ferreira, F.; Greck, C.; Genet, J. P. *Bull. Soc. Chim. Fr.* **1997**, *134*, 615.
57. Oishi, T.; Iwakuma, T.; Hirama, M.; Ito, S. *Synlett* **1995**, 404.
58. (a) Honda, T.; Hoshi, M.; Kanai, K.; Tsubuki, M. *J. Chem.*

Soc. Perkin Trans. I **1994**, 2091. (b) Honda, T.; Hoshi, M.; Tsubuki, M. *Heterocycles* **1992**, *34*, 1515.
59. Mukai, C.; Sugimoto, Y.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281.
60. Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022.
61. Martin-López, M. J.; Rodriguez, R.; Bermejo, F. *Tetrahedron* **1998**, *54*, 11623.
62. Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358.
63. Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083.
64. Dudot, B.; Micouin, L.; Baussanne, I.; Royer, J. *Synthesis* **1999**, 688.
65. (a) Zhou, W. S.; Xie, W. G.; Lu, Z. H.; Pan, X. F. *J. Chem. Soc., Perkin Trans. I* **1995**, 2599. (b) Zhou, W. S.; Xie, W. G.; Lu, Z. H.; Pan, X. F. *Tetrahedron Lett.* **1995**, *36*, 1291.
66. Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1993**, *58*, 3397.
67. Blanco, M. J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748.
68. (a) Ikota, N. *Chem. Pharm. Bull.* **1993**, *41*, 1717. (b) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1987**, *35*, 2140. (c) Ikota, N.; Hanaki, A. *Heterocycles* **1987**, *26*, 2369.
69. Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1990**, *38*, 2712.
70. Setoi, H.; Takeno, H.; Hashimoto, M. *Heterocycles* **1986**, *24*, 1261.
71. (a) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1988**, *36*, 1143. (b) Angermann, J.; Homann, K.; Reissig, H. U.; Zimmer, R. *Synlett* **1995**, 1014.
72. Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546.
73. Hembre, E. J.; Pearson, W. H. *Tetrahedron* **1997**, *53*, 11021.
74. (a) Mccaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429. (b) McCaig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939.
75. Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761.
76. Cicchi, S.; Nunes, J. J.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1998**, 419.
77. Goti, A.; Cardona, F.; Brandi, A.; Picasso, S.; Vogel, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1659.
78. Maggini, M.; Prato, M.; Ranelli, M.; Scorrano, G. *Tetrahedron Lett.* **1992**, *33*, 6537.
79. Herczegh, P.; Kovacs, I.; Szilagyi, L.; Zsely, M.; Sztaricskai, F.; Berecibar, A.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.* **1992**, *33*, 3133.
80. Leeper, F. J.; Howard, S. *Tetrahedron Lett.* **1995**, *36*, 2335.
81. Bhide, R.; Mortezaei, R.; Scilimati, A.; Sih, C. J. *Tetrahedron Lett.* **1990**, *31*, 4827.
82. (a) Carretero, J. C.; Arrayas, R. G. *J. Org. Chem.* **1995**, *60*, 6000. (b) Carretero, J. C.; Arrayas, R. G.; Storch De Gracia, I.; Adrio, J. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *120/121*, 347. (c) Carretero, J. C.; Arrayas, R. G. *J. Org. Chem.* **1998**, *63*, 2993. (d) Carretero, J. C.; Arrayás, R. G.; Storch De Gracia, I. *Tetrahedron Lett.* **1996**, *37*, 3379.
83. (a) Reymond, J. L.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1990**, 1070. (b) Reymond, J. L.; Pinkerton, A. A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128. (c) Reymond, J. L.; Vogel, P. *Tetrahedron Lett.* **1989**, *30*, 705.
84. Molyneux, R. J.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1990**, *53*, 609.
85. Kang, S. H.; Kim, J. S.; Youn, J. H. *Tetrahedron Lett.* **1998**, *39*, 9047.
86. Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455.
87. Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949.
88. Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706.
89. Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137.
90. Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398.
91. Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415.
92. Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940.
93. Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871.
94. Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron: Asymmetry* **1992**, *3*, 999.
95. Heitz, M. P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591.
96. Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1984**, *37*, 1503.
97. Ratovelomanana, V.; Vidal, L.; Royer, J.; Husson, H. P. *Heterocycles* **1991**, *32*, 879.
98. Na, H. S.; Choi, J.; Yu, J.; Shin, K. J.; Yoo, K. H.; Kim, D. J.; Park, S. W. *Heterocycles* **1998**, *48*, 2365.
99. (a) Furneaux, R. H.; Gainsford, G.; Mason, J. M.; Tyler, P. C.; Hartley, O.; Winchester, B. G. *Tetrahedron* **1995**, *51*, 12611. (b) Furneaux, R. H.; Mason, J. M.; Tyler, P. C. *Tetrahedron Lett.* **1994**, *35*, 3143.
100. (a) Takatani, T.; Tsutsumi, H.; Yasuda, N.; Hashimoto, S.; Setoi, H.; Takeno, S. Patent JP 60,193,986; *Chem. Abstr.* **1986**, *104*, 207151m. (b) Dime, D. Patent WO 9,309,117; *Chem. Abstr.* **1993**, *119*, 160615h. (c) Dime, D. Patent US 5,466,809; *Chem. Abstr.* **1996**, *124*, 117677w.

Biographical Sketch



Ahmed El Nemr was born 1962 in El Behera, Egypt. He received his BSc degree in chemistry with a general grade of excellent and his MSc degree from Alexandria University under the supervision of Professor El Sayed H. El Ashry, after which he was awarded his PhD in Engineering in Applied Chemistry by Keio University, Yokohama, Japan. He worked for six years as a researcher at the Institute of Bioorganic Chemistry, Kawasaki, Japan with Professor Tsutomu Tsuchiya. He is now working as a researcher and lecturer at the NIOF, Egypt. His research interests involve carbohydrate chemistry.