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A concise sequential photochemical-metathesis approach for the synthesis of (+)-castanospermine and possible uniflorine-A stereoisomers

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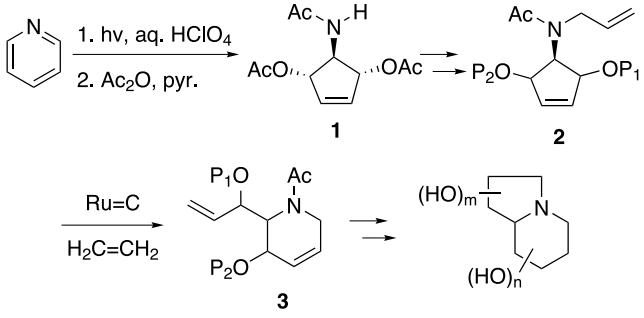
Abstract—A recently developed strategy for polyhydroxylated indolizidine ring construction has been applied to the synthesis of (+)-castanospermine and possible isomers of uniflorine-A. The routes to these targets rely on the use of the earlier discovered photocyclization reaction of pyridinium perchlorate in a concise route for preparation of a key *N*-allylacetamidocyclopentendiol intermediate. Ring rearrangement metathesis of this substance gives an allyl-tetrahydropyridine, which is then transformed to the targets by execution of regio- and stereo-controlled hydroxylation processes followed by indolizidine ring construction.

1. Introduction

Members of the polyhydroxylated indolizidine, natural product family have received continuous intense scrutiny from synthetic chemists owing to their densely functionalized, stereochemically rich structures and their biomedically relevant physiological properties.[1] Recently,[2] we described a unique and stereochemically flexible strategy for synthesis of functionalized indolizidines that relies on the combined use of photochemical and ring rearrangement metathesis (RRM) reactions in key ring building steps. The overall approach, outlined in Scheme 1, begins with the preparation of 4-amino-3,5-cyclopentendiol derivative **1** through photocyclization reaction of pyridinium perchlorate.[3,4] Transformation of this substances to *N*-acetamido-*N*-allylcyclopentenes **2** is then followed by ruthenium alkylidene[5] catalyzed RRM reactions[6] to generate the corresponding 6-allyltetrahydropyridines **3**. The RRM derived products contain an array of exocyclic and endocyclic alkene and potentially differentiated alcohol functionalities, which can be manipulated to both introduce the groups required for indolizidine ring formation and install target functionality.

In an earlier publication,[2] we described the advent of this strategy and its application to the synthesis of the potent



Scheme 1.

α-D-mannosidase and mannosidase II inhibitor, (−)-swainsonine (**8**). In the approach to this target (Scheme 2), regiocontrolled RRM reaction of allylacetamidocyclopentene **4** was employed to produce the tetrahydropyridine **5**. As a result of $A^{1,3}$-strain between the *N*-acetyl and 6-allyl groups, the corresponding acetate derivative exists predominantly in the diaxial conformation **6**, in which both faces of the endocyclic alkene group are blocked. Consequently, dihydroxylation of the exocyclic olefin in **6** takes place selectively to produce the requisite precursor **7** in the route to (−)-swainsonine.

Broad application of this strategy to a variety of naturally occurring, biomedically important indolizidines requires that methods be available to selectively manipulate the endocyclic alkene moiety in the RRM derived 6-allyl-tetrahydropyridine intermediates. (+)-Castanospermine, an

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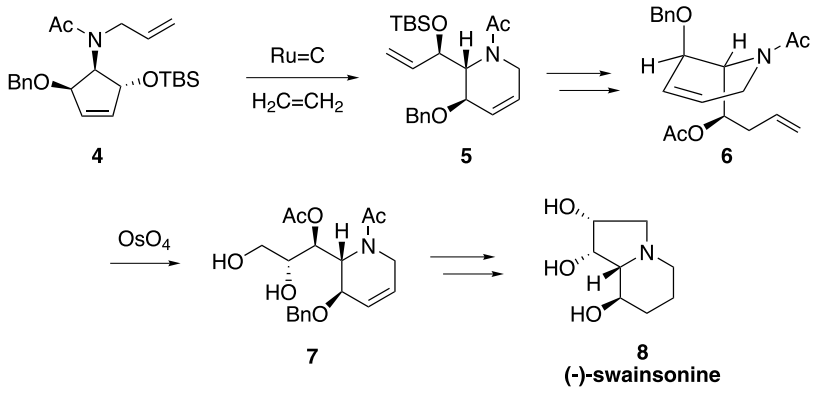
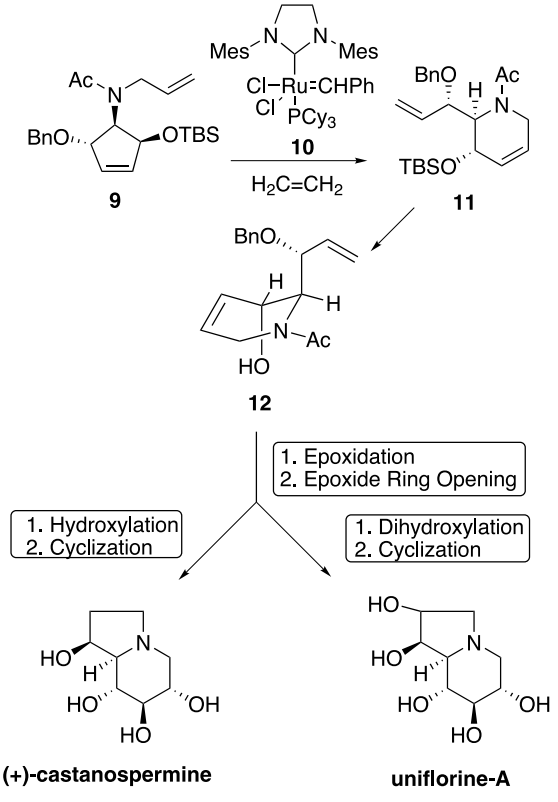


Scheme 2.

excellent glycosidase inhibitor,[7] is one of a group of targets, which can be approached by using this design variation. As depicted in Scheme 3, a possible route to (+)-castanospermine would employ RRM reaction of the *N*-acetamido-*N*-allylcyclopentene **9** to generate the tetrahydropyridine **11**. Based on $A^{1,3}$-strain considerations, the alcohol derivative **12** should exist in the diaxial conformation, in which the C-5 hydroxyl is perfectly aligned to guide selective α-face epoxidation of the internal alkene moiety. Trans-diaxial epoxide ring opening would then set the stage for cyclization to produce the tetrahydroxylated indolizidine skeleton of castanospermine. Importantly, this general strategy can be employed to design concise, stereoselective routes for the preparation of pentahydroxylated indolizidines that are potentially related to the incorrectly identified glycosidase inhibitor, uniflorine-A.[8] For this purpose, hydroxyl guided epoxidation of **12** and epoxide ring opening would be followed by dihydroxylation of the exocyclic olefin and indolizidine ring formation (Scheme 3).



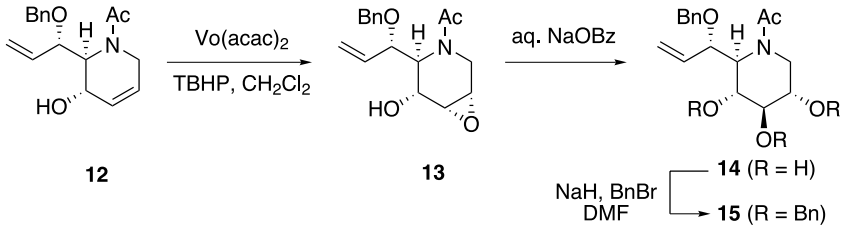
Scheme 3.

2. Results and discussion

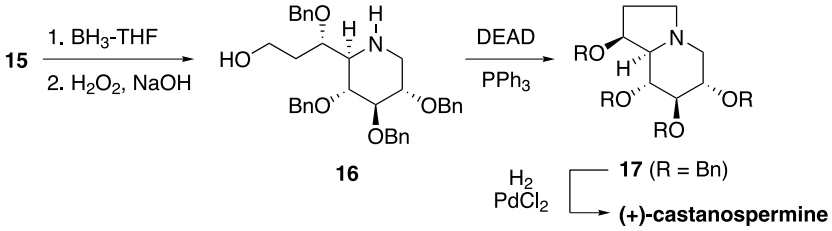
2.1. Synthesis of (+)-castanospermine

Earlier, we reported that RRM reaction of the enantiomerically enriched *cis*,*-trans*-*N*-allylacetamidocyclopentendiol derivative **9**, produced from pyridine by using a photochemical-enzymatic desymmetrization-alcohol inversion sequence, proceeds smoothly (93%) to furnish the corresponding 6-allyltetrahydropyridine **11**.[2] This highly regioselective process is performed by using the second generation, Grubbs ruthenium alkylidene catalyst **10**[5] in the presence of ethylene (Scheme 3). X-ray crystallographic analysis of endocyclic allylic alcohol **12**, generated by treatment of **11** with TBAF, clearly demonstrates that it exists in the diaxial conformation. This preference results from relief of $A^{1,3}$-strain caused by interactions between the *N*-acetyl and 6-allyl side chain in the alternative diequatorial conformation. A consequence of this preference is that the endocyclic hydroxyl group in **12** can be used advantageously to guide regio- and stereo-selective dihydroxylation reaction of the endocyclic alkene moiety. In the context of the current targets, the hydroxyl group is employed to direct selective epoxidation of **12** to produce the corresponding epoxy-alcohol **13**. Trans-diaxial ring opening of **13** under mild basic conditions then furnishes the *trans*,*trans*,*trans*-trihydroxy-piperidine **14**. Benzylation of **14** provides the tetrabenzyl ether **15** (Scheme 4), which serves as the key intermediate in routes to castanospermine and the possible uniflorine-A diastereomers.

Several approaches were explored to transform **15** to the corresponding terminal alcohol. The best method (albeit not fully satisfactory) for performing this operation was found to be one using the hydroboration–oxidation protocol. Accordingly, treatment of **15** with the BH_3–THF complex followed by NaOH–H_2O_2 oxidation produces the alcohol **16** (Scheme 5). Surprisingly the *N*-acetyl group is fortuitously removed under these conditions.[9] As expected this process also forms a minor amount of the *N*-ethyl analog of **16** by way of reduction of the amide group. An attempt to minimize this unwanted side reaction by using 9-BBN was not successful; **15** is recovered when treated with this



Scheme 4.

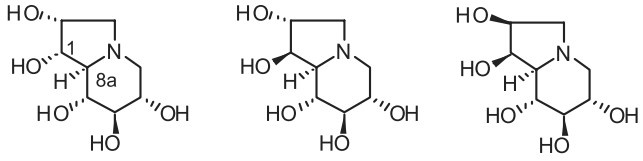


Scheme 5.

hydroboration agent. Indolizidine ring formation takes place when **16** is subjected to typical Mitsunobo cyclization conditions (DEAD–PPh_3) to yield indolizidine **17**. Hydrogenolytic removal of the benzyl protecting groups then generates the target, (+)-castanospermine. The physical and spectroscopic properties of the synthetic material match those reported for the natural product.[10]

2.2. Pentahydroxylated indolizidines potentially related to uniflorine-A

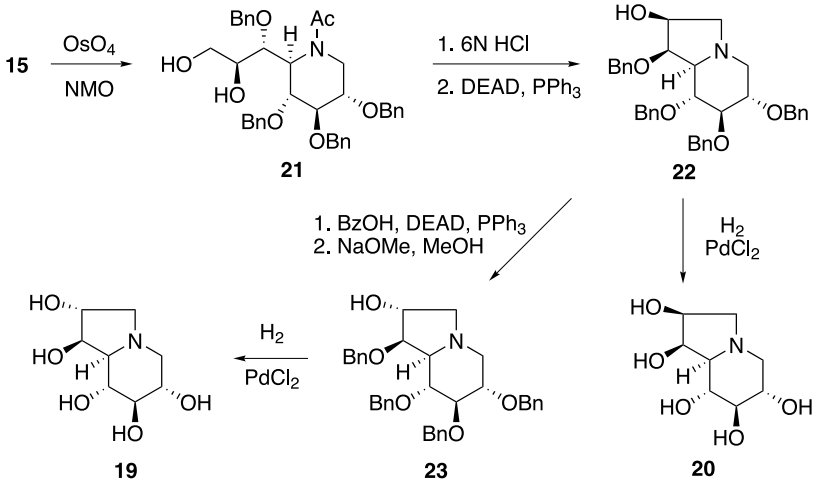
A novel pentahydroxylated indolizidine, uniflorine-A, was recently isolated from the tree *Eugenia uniflora L.* whose leaves are used in folk medicine as antidiarrhetics, antirheumatics and antidiabetics.[8a] The structure/stereochemistry of this substance was assigned by Arisawa and his co-workers[8a] as **18** based on NMR spectroscopic data. Recently, Pyne and his co-workers[8b] synthesized the putative uniflorine-A **18** by using an elegent pathway starting with L-xylose. However, the ^1H and ^{13}C NMR data of the synthetic material did not match those reported for the natural product by the Arisawa group. One significant difference between the natural and synthetic materials was found in their ^1H NMR spectra. Specifically, the H_1–H_{8a} coupling constant reported for uniflorine-A is 4.5 Hz while that of the synthetic material **18** is 7.7 Hz, as expected for the *anti*-relationship of these protons. This difference led Pyne to make the reasonable suggestion that 'uniflorine-A, if it is an indolizidine alkaloid, has the same H-1 stereochemistry as castanospermine'; that is, that H-1 and H-8a have a *syn* relationship.[8b]



Based on Pyne's conclusion, uniflorine-A could be one of the two pentahydroxylated indolizidines **19** or **20**, both of which have the trans,trans,trans-piperidine ring stereochemistry and *syn* relationships between H-1 and H-8a. The preparation of one of these, indolizidine **20**, was reported in 1996 by Fleet and his co-workers.[11] A comparison of their spectroscopic data with those reported by Arisawa (Table 1) indicates that uniflorine-A is not **20**. To our knowledge, indolizidine **19** has not been prepared previously. Owing to the potentially interesting biomedical properties of uniflorine-A and the fact that its structure/stereochemistry remains undefined, we have applied the RRM based strategy described above to the synthesis of the respective

Table 1. ^1H NMR spectroscopic data (D_2O) for uniflorine-A and the pentahydroxy-indolizidines **18**–**20**

	Chemical shifts (ppm)					Coupling constants (Hz)			
	Uniflorine-A[8a]	**18**[8b]	**19**	**20**[11]		Uniflorine-A[8a]	**18**[8b]	**19**	**20**[11]
H_1	4.18	3.82	4.08	4.06	H_1–H_2	4.5	7.3	0	5.3
H_2	4.35	4.11	4.25	4.24	H_1–H_{8a}	4.5	7.5	6.3	3.5
H_3	2.98	3.26	2.63	2.54	H_2–H_3	5.1	6.8	6.3	8.1
H_3	3.04	2.20	2.88	2.71	H_2–H_3	5.1	6.8	4.4	2.1
H_5	3.61	3.01	2.96	2.95	H_{8a}–H_8	7.7	9.2	10.2	9.7
H_5	3.76	2.09	1.91	1.91	H_8–H_7	7.7	9.0	9.1	9.5
H_6	2.76	3.46	3.42	3.42	H_7–H_6	9.0	9.0	9.1	9.1
H_7	3.81	3.20	3.13	3.12	H_6–H_5	6.4	10.9	9.1	10.6
H_8	3.94	3.25	3.48	3.47	H_6–H_5	3.8	5.5	5.2	5.1
H_{8a}	3.14	2.08	2.01	2.01	H_3–H_3	12.1	10.5	10.3	10.7
					H_5–H_5	11.8	10.7	10.9	10.6



Scheme 6.

unknown and known pentahydroxylated indolizidines **19** and **20**.

The divergent route to both targets (Scheme 6) begins with the protected piperidine **15**. Stereocontrolled catalytic osmylation of this substance cleanly produces the corresponding diol **21**. Amide hydrolysis and Mitsunobo cyclization is then employed to transform **21** to the pentahydroxy-indolizidine derivative **22**, which serves as a direct precursor (benzyl deprotection) of the known indolizidine **20**.[11] Indolizidine **19**, is also generated from **22** by using Mitsunobo hydroxyl inversion to form **23** followed by hydrogenolytic benzyl deprotection.

The physical and spectroscopic properties of **19** do not match those reported for uniflorine-A. Significant differences are found between the melting points and optical rotations of the synthetic material (mp 114–116 °C, $[\alpha]_0^{25}$ +22.7 (*c*, 0.07, H_2O))[8a] and naturally occurring substance (mp 175–178 °C, $[\alpha]_0$ −4.4 (*c*, 1.2, H_2O)). Equally different are the ^1H and ^{13}C NMR spectra of **19** and uniflorine-A (Table 1). Moreover, the properties reported for the natural product are not equivalent to those reported earlier for **20** by Fleet and his co-workers (Table 1).[11] To insure that the differences between the properties of the natural product and those determined for **19** and **20** are not a consequence of different protonation state, the hydrochloride salts of the of **19** and **20** were prepared. As with their neutral counterparts, the spectroscopic data for these salts do not match those obtained for uniflorine-A. Based on these results, we conclude that the glycosidase inhibitor uniflorine-A isolated by Arisawa and his co-workers does not have the structure and/or stereochemistry found in either of the three pentahydroxy indolizidines **18**–**20**.

3. Conclusions

The studies described above demonstrate the unique preparative potential of the strategy for functionalized indolizidine synthesis, that is, based on pyridinium salt photochemistry and ring rearrangement metathesis chemistry. In addition, the ability to develop concise stereocontrolled routes to members of the polyhydroxylated indolizidine family has been exploited in the synthesis of the interesting glycosidase inhibitor (+)-castanospermine. Finally, by using this chemistry we have demonstrated that the natural product uniflorine-A does not possess the pentahydroxylated indolizidine stereostructures represented by **19** and **20**.

4. Experimental

4.1. General

Each reaction was run under a dry nitrogen atmosphere. All reagents were obtained from commercial sources and used without further purification, and all solvents were dried by using the standard procedures. ^1H and ^{13}C NMR spectra were recorded by using $CDCl_3$ solutions, unless specified otherwise, and chemical shifts are reported in ppm relative to $CHCl_3$ (7.24 ppm for ^1H and 77.0 ppm for ^{13}C), which was used as a chemical shift internal standard for samples in $CDCl_3$. For spectra recorded on d_6-acetone solutions, chemical shifts are reported in ppm relative to d_5-acetone (2.05 ppm for ^1H and 29.92 ppm for ^{13}C). For spectra recorded using d_4-methanol, chemical shifts are reported in ppm relative to d_3-methanol (3.31 ppm for ^1H and 49.15 ppm for ^{13}C). ^{13}C NMR resonance assignments were aided by the use of the DEPT-135 technique to determine numbers of attached hydrogens. All compounds were isolated as oils unless otherwise specified and their purities were determined to be >90% by ^1H and ^{13}C NMR analysis. Column chromatography was performed by using 230–400 mesh silica gel as absorbent.

4.1.1. 1-Acetyl-2-(1-benzyloxyallyl)-3-hydroxy-4,5-epoxypiperidine 13. To a stirred solution of the known[2] allylic alcohol **12** (29 mg, 0.10 mmol) in 3 mL of CH_2Cl_2 at 0 °C was added vanadyl acetylacetonate (2 mg, 0.01 mmol) and 0.07 mL (5–6 M in decane) of *t*BuOOH. The resulting mixture was stirred at 25 °C for 5 h, diluted with 1 mL of satd $NaHSO_3$ and $CHCl_3$. The $CHCl_3$ layer was separated, washed with satd $NaHSO_3$, satd $NaHCO_3$ and satd NaCl,

dried and concentrated in vacuo giving a residue, which was subjected to column chromatography (silica gel, 1:1 acetone/hexane) to yield 15 mg (50%) of the epoxide **13**. $[\alpha]_D^{25}$ +26.6 (*c*, 0.13, $CHCl_3$); ^1H NMR (mixture of rotamers) 7.34–7.20 (m, 5H), 5.72–5.68 (m, 1H), 5.46 (d, *J*=10.0 Hz, 1H), 5.36 (d, *J*=16.6 Hz, 1H), 4.80 (d, *J*=15.4 Hz, 1H), 4.58 (d, *J*=11.9 Hz, 1H), 4.23 (dd, *J*=3.9, 11.9 Hz, 1H), 3.98–3.94 (m, 1H), 3.76 (m, 1H), 3.42 (m, 1H), 3.41 (m, 1H), 2.91 (d, *J*=15.3 Hz, 1H), 2.71 (d, *J*=9.0 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR rotamer A 172.3, 137.3, 134.7, 128.4, 127.9, 127.8, 127.6, 121.5, 78.4, 70.1, 62.6, 61.8, 52.6, 51.1, 36.5, 21.7; rotamer B 172.4, 137.3, 134.4, 128.4, 127.9, 127.8, 127.6, 119.5, 80.4, 71.1, 64.2, 58.5, 52.6, 49.7, 42.1, 21.9; HRMS (FAB) *m/z* 326.1358 (M+Na), calcd for $C_{17}H_{23}NO_5Na$ 326.1363.

4.1.2. 1-Acetyl-2-(1-benzyloxyallyl)-3,4,5-hydroxypiperidine 14. A solution of epoxide **13** (46 mg, 0.15 mmol) in 1 mL of water containing sodium benzoate (6 mg, 0.04 mmol) was stirred at 130 °C for 12 h, cooled and concentrated in vacuo giving a residue, which was subjected to column chromatography (silica gel, 3:2 acetone/hexane) to yield 27 mg (55%) of the triol **14**. $[\alpha]_D^{25}$ +7.2 (*c*, 0.1, CH_3OH); ^1H NMR (mixture of rotamers) 7.51–7.23 (m, 5H), 5.86–5.82 (m, 1H), 5.48–5.41 (m, 2H), 4.59 (d, *J*=11.9 Hz, 1H), 4.47–4.40 (m, 1H), 4.29–4.25 (m, 1H), 3.96 (d, *J*=10 Hz, 1H), 3.85 (s, 1H), 3.80 (s, 1H), 3.65 (d, *J*=15.2 Hz, 1H), 3.31 (s, 1H), 2.83 (d, *J*=14.1 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR rotamer A 175.7, 139.8, 137.1, 129.5, 129.1, 128.7, 121.4, 77.3, 71.2, 70.5, 69.9, 69.8, 66.1, 39.7, 22.2; rotamer B 174.3, 140.0, 137.4, 129.4, 129.1, 128.7, 120.5, 78.3, 71.9, 71.2, 71.1, 70.0, 60.0, 46.3, 22.2; HRMS (FAB) *m/z* 344.1482 (M+Na), calcd for $C_{17}H_{23}NO_5Na$ 344.1468.

4.1.3. 1-Acetyl-2-(1-benzyloxyallyl)-3,4,5-benzyloxypiperidine 15. To a solution of triol **14** (180 mg, 0.60 mmol) in 10 mL DMF at 0 °C was added sodium hydride (95%, 86 mg, 3.4 mmol), After stirring at 0 °C for 30 min, 0.5 mL of benzyl bromide was added and the solution was stirred for 2 h, diluted with ethyl acetate, washed with satd NaCl, dried and concentrated in vacuo giving a residue, which was subjected to column chromatography (silica gel, 1:2 EA/hexane) to give 330 mg (94%) of **15**. $[\alpha]_D^{25}$ +35.8 (*c*, 0.17, $CHCl_3$); ^1H NMR (mixtures of rotamers) 7.32–7.12 (m, 20H), 5.78–5.70 (m, 0.4H), 5.62–5.55(m, 0.6H), 5.31 (d, *J*=10.2 Hz, 0.6H), 5.25 (d, *J*=10.1 Hz, 0.4H), 5.16 (t, *J*=15.3 Hz, 1H), 4.72 (d, *J*=11.7 Hz, 1.3H), 4.68 (d, *J*=12.4 Hz, 1.2H), 4.60 (d, *J*=12.1 Hz, 1H), 4.54 (m, 2.2H), 4.41 (m, 2.9H), 4.21(d, *J*=12.0 Hz, 0.6H), 4.07 (m, 1.5H), 3.92 (d, *J*=9.2 Hz, 0.6H), 3.77 (m, 0.4H), 3.61 (m, 2.5H), 3.51 (m, 1H), 2.75 (d, *J*=14.7 Hz, 0.6H), 2.15 (s, 2.3H), 2.11 (s, 1.3H); ^{13}C NMR rotamer A 171.6, 138.1, 137.8, 128.0, 127.7, 127.1, 120.7, 75.5, 73.1, 73.0, 71.2, 70.7, 70.2, 69.5, 61.6, 35.6, 21.6; rotamer B 170.6, 137.7, 137.4, 127.9, 127.5, 127.4, 118.2, 81.1, 78.6, 78.3, 74.3, 73.4, 72.8, 70.8, 56.2, 45.1, 21.3; HRMS (FAB) *m/z* 614.2879 (M+Na), calcd for $C_{38}H_{41}NO_5Na$ 614.2877.

4.1.4. 2-(1-Benzyloxy-3-hydroxypropyl)-3,4,5-benzyloxypiperidine 16. To a solution of **15** (110 mg, 0.186 mmol) in 3 mL of THF was added $BH_3\cdot THF$ (0.5 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 3 h and 0.5 mL of 3 M NaOH and 1 mL of 30% hydrogen peroxide were added. The solution was stirred at 25 °C for 3 h and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo giving a residue, which was subjected to column chromatography (silica gel, 1:2 acetone/hexane) to give 33 mg (31%) of **16**. ^1H NMR 7.36–7.21 (m, 20H), 4.99 (d, *J*=10.7 Hz, 1H), 4.91 (d, *J*=11.1 Hz, 1H), 4.82 (d, *J*=10.7 Hz, 1H), 4.69 (d, *J*=10.9 Hz, 1H), 4.64 (d, *J*=11.7 Hz, 1H), 4.50 (d, *J*=11.1 Hz, 1H), 4.35 (d, *J*=11.1 Hz, 1H), 4.09 (d, *J*=11.1 Hz, 1H), 4.05 (d, *J*=6 Hz, 1H), 3.75 (t, *J*=11.4 Hz, 2H), 3.58 (t, *J*=9 Hz, 1H), 3.51 (m, 1H), 3.46 (t, *J*=9.5 Hz, 1H), 3.35 (m, 1H), 3.19 (dd, *J*=8.1 Hz, 13.8 Hz, 1H), 2.49–2.43 (m, 2H), 2.16 (m,1H); ^{13}C NMR 138.5, 138.3, 138.2, 137.9, 128.4, 128.0, 127.9, 127.9, 127.7, 127.5, 87.1, 80.8, 79.8, 75.8, 75.2, 72.8, 72.8, 70.6, 62.3, 55.3, 46.6, 34.2; HRMS (FAB) *m/z* 590.2894 (M+Na), calcd for $C_{36}H_{41}NO_5Na$ 590.2877.

4.1.5. 1,6,7,8-Tetrabenzyloxyindolizidine 17. A solution of **16** (20 mg, 0.035 mmol) in 2 mL THF containing PPh_3 (14 mg, 0.053 mmol), DEAD (9 mg, 0.05 mmol) was stirred at 25 °C for 12 h, diluted with satd $NaHCO_3$, and extracted with ethyl acetate. The ethyl acetate extracts were washed with satd NaCl, dried and concentrated in vacuo giving a residue, which was subjected to column chromatography (silica gel, 1:2 EA/hexane) to yield 18 mg (93%) of **17**. $[\alpha]_D^{25}$ +35.2° (*c*, 0.01, $CHCl_3$) (lit.[10] $[\alpha]_D^{25}$ +32 (*c*, 1.0, $CHCl_3$)); the spectroscopic data for this substance matched those previously reported.[10] ^1H NMR (C_6D_6) 7.43–7.16 (m, 20H), 5.18 (d, *J*=6.5 Hz, 1H), 5.15 (d, *J*=6.9 Hz, 1H), 5.01 (d, *J*=11.3 Hz, 1H), 4.92 (d, *J*=11.7 Hz, 1H), 4.57 (abq, *J*=12 Hz, 2H), 4.40 (d, *J*=11.7 Hz, 1H), 4.27 (t, *J*=9.2 Hz, 1H), 4.18 (d, *J*=11.7 Hz, 1H), 4.02–3.97 (m, 1H), 3.89 (ddd, *J*=5.0, 4.2, 9.5 Hz,1H), 3.76 (t, *J*=8.9 Hz, 1H), 3.24 (dd, *J*=5.0, 10.4 Hz, 1H), 2.97 (m, 1H), 2.08 (dd, *J*=4.9, 9.4 Hz, 1H), 1.99 (t, *J*=10.3 Hz, 1H), 1.89 (dd, *J*=8.6, 17.3 Hz, 1H), 1.86–1.79 (m,1H), 1.75–1.69 (m,1H); ^{13}C NMR 139.1, 138.9, 138.4, 138.1, 128.3, 128.3, 128.2, 128.1, 127.8, 127.4, 87.5, 79.1, 77.3, 75.6 (2), 74.2, 72.8, 71.6, 70.5, 54.5, 52.4, 29.7.

4.1.6. (+)-Castanospermine. A solution of **17** (15 mg, 0.027 mmol) in 3 mL ethyl acetate and 3 mL MeOH containing palladium chloride (22 mg, 0.013 mmol) under an atmosphere of hydrogen (1 atm) was stirred for 4 h at 25 °C, filtered through Celite. The filtrate was concentrated in vacuo giving a residue, which was subjected to ion-exchange chromatography (Dowex 1-X8, OH^- form, 100–200 mesh, eluted with water) to yield 5 mg (91%) of (+)castanospermine. $[\alpha]_D^{25}$ +20.6 (*c*, 0.05, H_2O) (lit.[10] $[\alpha]_D^{25}$ +70 (*c*, 0.33, H_2O)). The ^1H and ^{13}C NMR spectra of the synthetic material matched those reported previously.[10] ^1H NMR (D_2O) 4.24 (m, 1H), 3.64 (m, 2H), 3.35 (m, 1H), 3.19 (m, 1H), 3.14 (m, 1H), 2.35(m, 1H), 2.23 (m, 1H), 2.10–2.02 (m, 2H), 1.74–1.72 (m, 1H); ^{13}C NMR 79.1, 71.4, 70.2, 69.7, 69.0, 55.4, 51.6, 32.8.

4.1.7. 2-(1-Benzyloxy-2,3-dihydroxypropyl)-3,4,5-benzyloxypiperidine 21. To a solution of **15** (290 mg, 0.049 mmol) and NMO (172 mg, 1.47 mmol) in 30 mL acetone was added OsO_4 (0.7 mL, 7 mg in 10 mg/ml 1:1 acetone/water). The resulting solution was stirred for 4 h at 25 °C diluted with 3 mL satd $Na_2S_2O_5$, stirred for 30 min,

and filtered. The filtrate was concentrated in vacuo giving a residue, which was subjected to column chromatography (silica gel, 1:1 acetone/hexane) to yield 240 mg (78%) **21** along with 20 mg (6.5%) of the uncharacterized diastereomeric diol. $[\alpha]_D^{25}$ +50.8 (*c*, 0.14, $CHCl_3$); ^1H NMR 7.35–7.17 (m, 20H), 5.43 (s, 1H), 4.99 (d, $J=11.7$ Hz, 1H), 4.80 (abq, $J=6.5$ Hz, 2H), 4.63 (dd, $J=4.2$, 11.6 Hz, 2H), 4.55 (d, $J=9.2$ Hz, 1H), 4.50 (d, $J=8.3$ Hz, 1H), 4.39 (d, $J=11.4$ Hz, 1H), 4.07 (d, $J=11.4$ Hz, 1H), 3.75 (d, $J=6.4$ Hz, 1H), 3.73–3.66 (m, 7H), 3.38 (br s, 1H), 2.16 (s, 3H); ^{13}C NMR 173.2, 138.1, 137.9, 137.4, 128.5, 128.4, 128.0, 127.8, 127.6, 127.3, 85.3, 81.7, 79.2, 75.1, 74.7, 74.6, 74.3, 71.4, 70.1, 63.5, 57.0, 47.2, 21.3; HRMS (FAB) *m/z* 648.2912 (M+Na), calcd for $C_{38}H_{43}NO_7Na$ 648.2932.

4.1.8. 1,6,7,8-Tetrabenzyloxy-2-hydroxyindolizidine 22. A solution of **21** (120 mg, 0.19 mmol) in 4 mL THF and 4 mL 6 N HCl was stirred at 70 °C for 4 h, cooled and concentrated in vacuo to give a residue. A solution of the residue in 3 mL anhydrous pyridine containing 0.2 g molecular sieves, PPh_3 (63 mg, 0.24 mmol) and DEAD (42 mg, 0.24 mmol) was stirred at 0 °C for 4 h, diluted with satd $NaHCO_3$ and extracted with $CHCl_3$.The $CHCl_3$ extracts were washed with satd NaCl, dried and concentrated in vacuo to yield a residue, which was subjected to column chromatography (silica gel, 1:2 EA/hexane) to give 80 mg (74%) of **22**. $[\alpha]_D^{25}$ +40 (*c*, 0.032, $CHCl_3$); ^1H NMR 7.49–7.18 (m, 20H), 5.07 (d, $J=11.3$ Hz, 1H), 5.03 (d, $J=11.0$ Hz, 1H), 4.83 (d, $J=10.9$ Hz, 1H), 4.69–4.64 (m, 4H), 4.58 (d, $J=11.0$ Hz, 1H), 4.32 (br s, 1H), 4.18 (t, $J=5.6$ Hz, 1H), 3.90 (m, 1H), 3.78 (m, 1H), 3.62 (m, 1H), 3.29 (dd, $J=4.8$, 10.5 Hz, 1H), 3.22 (br s, 1H), 3.04 (d, $J=8.9$ Hz, 1H), 2.35 (dd, $J=6.3$, 10.3 Hz, 1H), 2.15 (m, 1H), 1.94 (t, $J=11.9$ Hz, 1H); ^{13}C NMR 138.9, 138.7, 138.3, 137.2, 128.5, 128.4, 128.4, 127.9, 127.1, 87.6, 79.1, 78.1, 76.8, 75.5, 74.4, 74.2, 72.8, 70.4, 69.9, 62.7, 54.2; HRMS (FAB) *m/z* 588.2702 (M+Na), calcd for $C_{36}H_{39}NO_5Na$ 588.2720.

4.1.9. 1,2,6,7,8-Pentahydroxyindolizidine 20. A solution of **22** (32 mg, 0.057 mmol) in 3 mL EA and 3 mL MeOH containing palladium chloride (22 mg, 0.013 mmol) under an atmosphere of hydrogen (1 atm) was stirred at 25 °C for 4 h and filtered through Celite. The filtrate was concentrated in vacuo giving a residue, which was subjected to ion-exchange chromatography (Dowex 1-X8, OH^- form, 100–200 mesh, eluted with water) to yield 11 mg (94%) of **20**. $[\alpha]_D^{25}$ +37.9 (*c*, 0.013, H_2O) (lit.[11] $[\alpha]_D^{25}$ +66.5 (*c*, 1.33, H_2O)). The ^1H and ^{13}C NMR spectra of this substance matched those reported earlier.[11] ^1H NMR (D_2O) 4.26 (m, 1H), 4.08 (m, 1H), 3.50–3.41 (m, 2H), 3.13 (t, $J=9.1$ Hz, 1H), 2.97 (dd, $J=5.1$, 10.8 Hz, 1H), 2.73 (dd, $J=2.1$, 11.0 Hz, 1H), 2.48 (dd, $J=8.1$, 10.7 Hz, 1H), 2.00 (dd, $J=3.5$, 9.7 Hz, 1H), 1.90 (t, $J=10.6$ Hz, 1H); ^{13}C NMR (D_2O) 81.1, 72.6, 72.2, 72.0, 71.6, 71.1, 61.8, 57.6.

4.1.10. 1,6,7,8-Tetrabenzyloxy-2-hydroxyindolizidine 23. A solution of **22** (60 mg, 0.11 mmol), benzoic acid (26 mg, 0.22 mmol), PPh_3 (58 mg, 0.022 mmol) and DEAD (37 mg, 0.22 mmol) in 3 mL THF was stirred at 25 °C for 12 h, diluted with satd $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with satd NaCl, dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (silica gel, 1:2 EA/hexane) to yield 62 mg of the inverted benzoate ester. ^1H NMR 8.06 (d, $J=8.1$ Hz, 2H), 7.56–7.50 (m, 1H), 7.50–7.34 (m, 2H), 7.33–7.13 (m, 20H), 5.49 (m, 1H), 5.01 (d, $J=11.0$ Hz, 1H), 4.93 (d, $J=11.5$ Hz, 1H), 4.86 (t, $J=11.5$ Hz, 2H), 4.71 (d, $J=11.0$ Hz, 1H), 4.59 (abq, $J=11.0$ Hz, 2H), 4.37 (m, 1H), 4.18 (d, $J=4.5$ Hz, 1H), 3.92 (t, $J=9.1$ Hz, 1H), 3.85–3.70 (m, 1H), 3.65–3.55 (m, 2H), 3.31 (dd, $J=4.2$ Hz, 9.4 Hz, 1H), 2.5 (dd, $J=4.1$, 9.5 Hz, 1H), 2.35 (dd, $J=5.2$, 10.2 Hz, 1H), 2.12 (t, $J=10.3$ Hz, 1H); ^{13}C NMR 165.6, 138.7 (2), 138.2, 137.3, 133.2, 129.5, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.3, 87.2, 82.1, 78.8, 76.4, 76.2, 75.5, 74.5, 72.8, 71.3, 69.3, 58.7, 54.2.

A solution of the inverted ester (60 mg, 0.11 mmol) in 10 mL MeOH containing sodium methoxide (54 mg, 1 mmol) was stirred for 12 h at 25 °C, diluted with 1 mL of water, and concentrated in vacuo giving a residue, which was subjected to column chromatography (silica gel, 1:1 acetone/hexane) to yield 44 mg (73%) of **23**. $[\alpha]_D^{25}$ +16.2 (*c*, 0.04, $CHCl_3$); ^1H NMR 7.33–7.20 (m, 20H), 4.99 (d, $J=10.9$ Hz, 1H), 4.84 (abq, $J=11.1$ Hz, 2H), 4.68–4.60 (m, 4H), 4.50 (d, $J=11.6$ Hz, 1H), 4.32 (t, $J=6.2$ Hz, 1H), 3.89 (dt, $J=4.6$, 9.2 Hz, 2H), 3.73–3.68 (m, 1H), 3.60–3.52 (m, 2H), 3.26 (dd, $J=4.9$, 10.5 Hz, 1H), 2.45 (dd, $J=4.6$, 9.3 Hz, 1H), 2.08–2.03 (m, 2H); ^{13}C NMR 139.0, 138.8, 138.3, 137.6, 128.3, 128.3, 127.9, 127.8, 127.3, 87.4, 85.2, 78.9, 77.0, 75.6, 75.3, 72.8, 71.3, 69.3, 61.7, 54.3; HRMS (FAB) *m/z* 588.2740 (M+Na), calcd for $C_{36}H_{39}NO_5Na$ 588.2720.

4.1.11. 1,2,6,7,8-Pentahydroxyindolizidine 19. A solution of **23** (42 mg, 0.074 mmol) in 3 mL EA and 3 mL MeOH containing palladium chloride (22 mg, 0.013 mmol). The mixture under an atmosphere of hydrogen (1 atm) was stirred at 25 °C for 4 h and filtered through Celite. The filtrate was concentrated in vacuo giving a residue, which was subjected to ion-exchange chromatography (Dowex 1-X8, OH^- form, 100–200 mesh, eluted with water) to yield 15 mg (98%) of **19**, mp 114–116 °C, $[\alpha]_D^{25}$ +22.7 (*c*, 0.07, H_2O); ^1H NMR (D_2O) 4.21 (t, $J=6.3$ Hz, 1H), 4.12 (d, $J=4.3$ Hz, 1H), 3.64–3.58 (m, 2H), 3.51 (dd, $J=7.1$, 10.3 Hz, 1H), 3.38 (t, $J=9.1$ Hz, 1H), 3.19 (dd, $J=5.2$, 10.9 Hz, 1H), 2.37 (dd, $J=4.4$, 10.2 Hz, 1H), 2.19–2.14 (m, 2H); ^{13}C NMR 81.2, 79.6, 78.9, 72.3, 71.7, 70.9, 61.9, 57.7; HRMS (FAB) *m/z* 228.0841 (M+Na), calcd for $C_8H_{15}NO_5Na$ 228.0842.

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Supplementary data

Supplementary data associated with this article can be

found, in the online version, at doi:10.1016/j.tet.2005.07.014. Contained in the supplementary data are ^{1}H and ^{13}C NMR spectra for compounds **13–17**, **19–23**, and synthetic (+)-castanospermine.

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