Asymmetric synthesis of (+)-castanospermine through enol ether metathesis–hydroboration/oxidation†

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An asymmetric synthesis of (+)-castanospermine is presented in which enol ether metathesis–hydroboration/oxidation is used for stereoselective installation of the *trans-trans* hydroxyl groups on the piperidine ring of the alkaloid.

(+)-Castanospermine (**1**, Fig. 1) is a polyhydroxylated indolizidine first isolated in 1981 from *Castanospermum australe*,[1] and later from *Alexa leiopetala*.[2] This alkaloid, because of its resemblance to glucose, is a strong inhibitor of α- and β-glucosidases. (+)-Castanospermine and certain of its derivatives have been advanced for possible use in the treatment of cancers, diabetes, viral infections, and immunosuppressive deficiencies.[3]

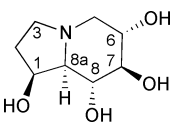

Fig. 1 (+)-Castanospermine (**1**).

Due to its biological activity and intrinsic complexity—an amino tetraol with five contiguous stereocenters—(+)-castanospermine has been the subject of numerous total synthesis studies over the past 30 years.[4] As four of the five stereocenters in this indolizidine correspond to those in D-glucose, it is not surprising that a majority of the syntheses to date have started from sugars. What is surprising, though, is that there are only four syntheses that are non chiral-pool,[4a–d] an approach that generally offers more flexibility for analog preparation. In a program aimed at the total synthesis of polyhydroxylated indolizidines from non chiral-pool starting material through [2 + 2] cycloaddition of dichloroketene to chiral enol ethers, (+)-castanospermine was targeted. Its efficient synthesis, which showcases a new approach to the often problematic introduction of the *trans-trans* triol array on six-membered rings, is described below.

The six membered-ring of indolozidines has been obtained[5] through ring-closing metathesis, but this approach has to date never been used for the synthesis of (+)-castanospermine. The formation of the *trans-trans* (all equatorial) triol arrangement found in (+)-castanospermine from a 6,7-dehydroindolizidine (e.g., **III**, X = H, Fig. 2) through overall *trans* dihydroxylation of the double bond is far from obvious: epoxidation, followed by ring opening, would be expected to lead to the alternative, undesired *trans* diol, embedded in a *trans-cis* array, as the major product through a more favorable transition state.[6] On the other hand, selective protection of the hydroxyl group(s) after *cis* dihydroxylation[5d] to permit subsequent inversion at C-6 would, if in fact feasible, most likely require several unattractive protection/deprotection steps. There was, though, an option that seemed worth exploring: modification of the above-mentioned ring-closing metathesis in which an alkoxy-substituted olefin would now be used as one of the olefinic partners.[7] We postulated that the hydroboration of the resultant cyclic enol ether (**III**, X = OR″) would lead directly to the required *trans-trans* hydroxyl stereochemistry on the six-membered ring because of steric shielding by the allylic substituent, which would be expected to force hydroboration to occur on the concave face of the molecule.[8]

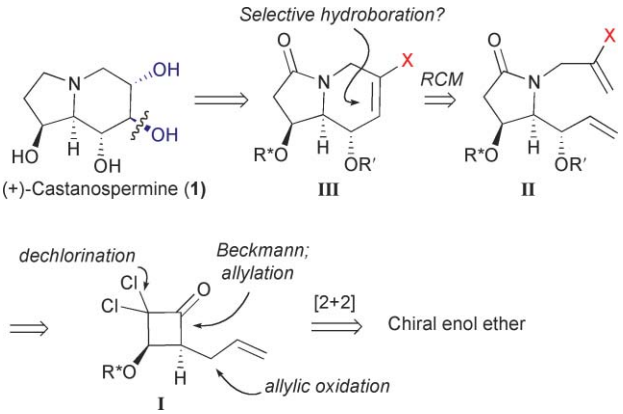

Fig. 2 Retrosynthetic analysis.

Hydroboration had never been applied to an alkoxy-substituted cyclic olefin with an allylic oxygen substituent. Therefore, to study the selectivity and efficiency of the proposed hydroboration, a model substrate was first prepared (Scheme 1). 3,5-Dimethoxypyridine[9] was reduced in the presence of benzyl chloroformate to afford an intermediate bis-enol ether, which was hydrolyzed with aqueous acid. The resulting vinylogous acid was etherified with diazomethane to yield the corresponding vinylogous ester **3**, which was reduced with lithium aluminium hydride to give piperidine **4** in good overall yield from **2**. A sample of **4** was converted into benzyl ether **5** to study the influence, if any, of hydroxyl-group protection on the stereochemical outcome of the hydroboration.

The hydroboration/oxidation was first tested by treatment of **4** with the borane-dimethyl sulfide complex in THF at 0 °C, followed by oxidation of the resulting organoborane using sodium

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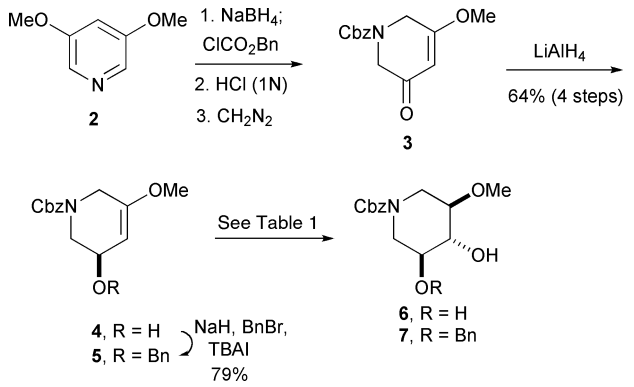


Scheme 1 Model substrate synthesis.

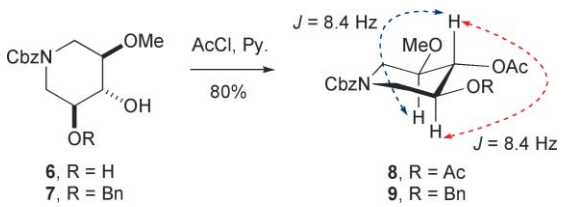
Table 1 Hydroboration of piperidines **4** and **5**

Entry	Cpd	Hydroboration	Oxidation	Yield[a]	dr[b]
1	**4**	$BH_3{\cdot}SMe_2$, THF	$NaOH/H_2O_2$	51%	> 98 : 2
2	**4**	$BH_3{\cdot}SMe_2$, THF	Me_3NO	[c]	
3	**4**	$BH_3{\cdot}SMe_2$, THF	$NaBO_3$	66%	> 98 : 2
4	**4**	$BH_3{\cdot}SMe_2$, Et_2O	$NaOH/H_2O_2$/EtOH	65%	> 98 : 2
5	**4**	9-BBN	$NaOH/H_2O_2$	[d]	
6	**4**	Catecholborane	$NaOH/H_2O_2$	[d]	
7	**5**	$BH_3{\cdot}SMe_2$, THF	$NaOH/H_2O_2$	61%	> 98 : 2
8	**5**	$BH_3{\cdot}SMe_2$, THF	$NaBO_3$	68%	> 98 : 2

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Only decomposition. [d] No hydroboration (starting material recovered).

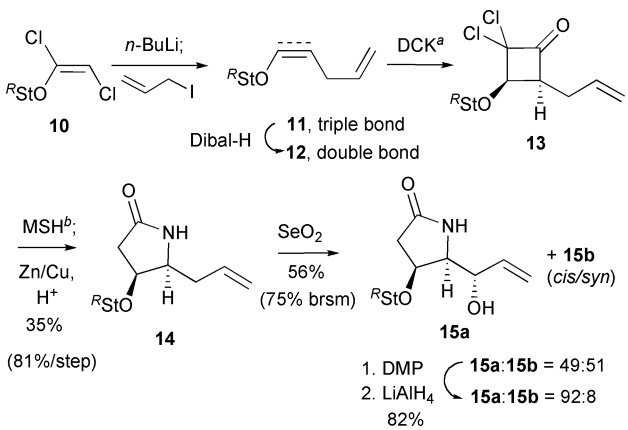
hydroperoxide. Encouragingly, the triol derivative **6** was isolated as a single isomer in 51% yield (Table 1, entry 1). Other oxidants that could improve the overall yield of the transformation were then tested: the use of trimethylamine *N*-oxide surprisingly led to complete decomposition of the intermediate borane adduct (entry 2), but sodium perborate did produce an improved yield (66%, entry 3). Performing the hydroboration in diethyl ether instead of THF, followed by sodium hydroperoxide oxidation in the presence of ethanol, was nearly as effective, however (entry 4). Neither 9-BBN nor catecholborane led to hydroboration (entries 5 and 6). The hydroboration/oxidation sequence (of entries 1 and 3) applied to the benzyl-protected derivative **5** again provided a single isomer **7** in good yield (entries 7 and 8), a better result once more being obtained with sodium perborate as the borane oxidant.

The relative configuration of triol derivatives **6** and **7** could be assigned by high-temperature NMR (to eliminate signal broadening due to conformers) of acetates **8** and **9** (Scheme 2). The two ^3J coupling constants of 8.4 Hz in **8** and **9** are diagnostic of diaxial relationships of the three contiguous carbinolic protons. Noe experiments provided additional proof of the all equatorial arrangement in both molecules.



Scheme 2 Relative configuration assignments.

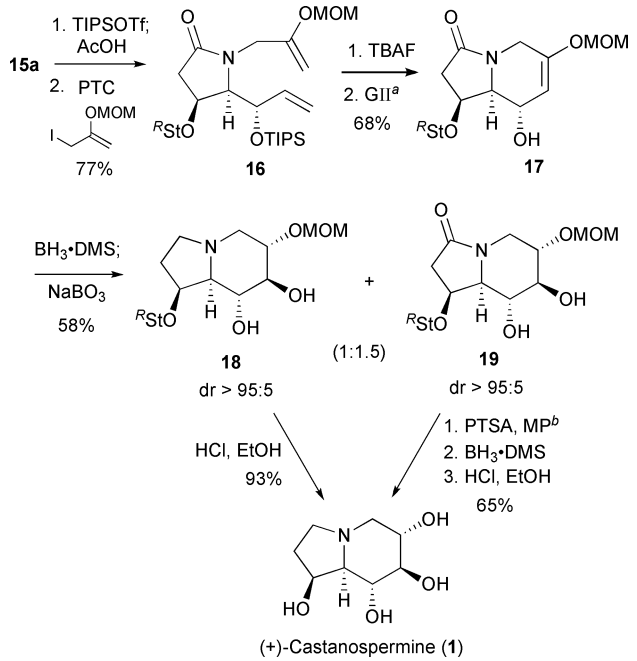
With the completely diastereoselective model-system results as support for our synthetic strategy, the synthesis of (+)-castanospermine was undertaken (Scheme 3). The preparation of intermediate **15a** began, as earlier,[5d] with the synthesis of dichloro enol ether **10**, which was generated by reaction of the potassium alkoxide of (*R*)-stericol[10] with trichloroethylene (79% yield). Treatment of **10** with butyllithium produced sequentially deprotonation, *cis* β-elimination, and chlorine–lithium exchange[11] to afford the intermediate lithio-ynol ether, which was allylated to give **11**. The ynol ether was next reduced by using Dibal-H at 50 °C to the corresponding enol ether **12**, which underwent diastereoselective cycloaddition with dichloroketene to provide dichlorocyclobutanone **13** (dr = 96:4). Beckmann ring expansion with Tamura's reagent and dechlorination then afforded γ-lactam **14** in 35% overall yield (5 steps, 81%/step). Allylic oxidation of **14** under Sharpless conditions afforded the corresponding allylic alcohols **15a**,**b** in 56% yield (75% brsm) as a 1:1 diastereomeric mixture.[12] The desired *cis-anti* isomer **15a** could be obtained as the major product (92:8 diastereoisomeric ratio) in 82% yield (2 steps) by applying an oxidation/reduction sequence to **15a**,**b**.[5d]



Scheme 3 Intermediate lactam **15a** synthesis. [a] DCK = dichloroketene. [b] MSH = *O*-mesitylenesulfonylhydroxylamine. St = 1-(2,4,6-triisopropylphenyl)ethyl. brsm = based on recovered starting material.

The allylic hydroxyl group was next protected as its triisopropylsilyl ether, which allowed *N*-alkylation with 3-iodo-2-(methoxymethoxy)prop-1-ene[13] under phase transfer conditions to proceed smoothly to give **16** in 77% overall yield (Scheme 4). The key ring-closing metathesis of **16** could not be achieved, though, despite considerable effort with a number of different catalysts under various reaction conditions. This failure can reasonably be ascribed, at least to some extent, to steric hindrance by the TIPS ether, which would favor formation of the ruthenium Fischer carbene, non-reactive in this system.[14] Pleasingly, after removal of the TIPS protecting group (TBAF, 87%), the diene readily underwent ring-closing metathesis in the presence of Grubbs II catalyst to produce **17** in 78% yield. This RCM product was accompanied by 9% of the ethyl ketone, the result of olefin isomerization in the allylic alcohol; the presence of benzoquinone did not significantly suppress its formation.[15]

With the cyclic enol ether **17** in hand, the above studied hydroboration/oxidation sequence could now be applied. To our delight, addition of excess borane-dimethyl sulfide complex followed by sodium perborate to **17** in THF afforded the product



Scheme 4 Completion of the synthesis. [a] GII = Grubbs 2nd generation catalyst. [b] MP = 2-methoxypropene.

of hydroboration/oxidation and lactam reduction **18**, together with the corresponding unreduced lactam **19** (1:1.5 ratio), *both as single isomers (dr > 95:5*), in a combined yield of 58%. Since efforts to increase the transformation of **17** into **18** at the expense of **19** proved unrewarding, diol **19** was converted into its acetonide derivative, which underwent smooth reduction with BH_3 to provide the protected indolizidine (70%, 2 steps). The cleavage of the numerous protecting groups in the two indolizidines with hydrochloric acid in ethanol led, in each case, to (+)-castanospermine in > 90% yield. The synthetically derived (+)-castanospermine ($[\alpha]^{20}_D$ +78.0 (*c* 0.75, H_2O), mp 204–206 °C (dec)) was spectroscopically and chromatographically identical with an authentic sample of the natural product.[16]

In summary, we have developed a new, efficient strategy, based on sequential enol ether metathesis—hydroboration/oxidation for the introduction of the all equatorial hydroxyl substituents on the six membered ring of (+)-castanospermine. Using this novel approach, a highly stereoselective non chiral-pool synthesis of (+)-castanospermine could be realized in 3.7% overall yield and 17 steps. Since several other biologically active polyol natural products share this *trans-trans* hydroxyl arrangement (inter alia, deoxynojirimycin, pancratistatin, siculinine, calystegin B_2), this metathesis–hydroboration/oxidation tandem should find additional application.

Acknowledgements

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