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# A CHEMOENZYMATIC SYNTHESIS OF (+)-CASTANOSPERMINE

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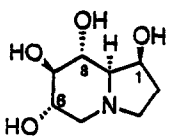
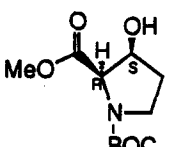
Summary: A chemoenzymatic synthesis of (+)-castanospermine (1) from the chiral building block, 2, is described.

Castanospermine, 1, a polyhydroxylated indolizidine alkaloid[1], has attracted the attention of many synthetic chemists because of its antiretroviral activity against the human immunodeficiency virus (HIV), thereby providing the prospect of an alternative chemotherapeutic agent for the treatment of AIDS[2]. This plant alkaloid is a potent inhibitor of α-glucosidase-I[3], an enzyme that is essential for the normal processing of the N-linked oligosaccharide moiety of glycoproteins. With one exception[5], the total syntheses[4] of 1 that have already been reported utilize monosaccharides as starting materials which limits the flexibility for structural modifications. We herein present a concise chemo-enzymatic total synthesis of 1 to demonstrate the usefulness of biocatalytic methodology and to offer unique opportunities for the synthesis of new structural analogs of 1.

We envisaged that 1 may be constructed from the building block, 2, which in turn may be prepared in the desired enantiomerically-pure form using biocatalytic methodology.

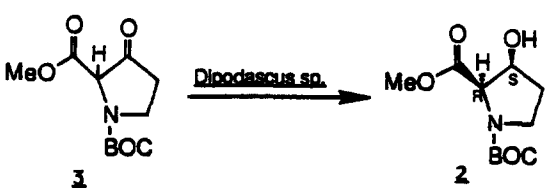



1




2

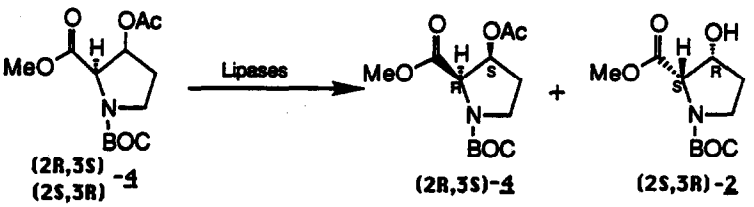
Although Cooper *et al.*[6] were the first to achieve the stereoselective reduction of a similar keto ester, in 70% chemical yield using Bakers' yeast, the optical purity of the product was only moderate (80% ee) due to the presence of multiple enzymes of opposite stereochemical preference in this yeast.[7] We therefore examined a wide variety of microorganisms with a view to discovering a more suitable one to catalyze this asymmetric reduction. Of the ones examined, we found that the yeast *Dipodascus sp.* was uniquely suited for this transformation. In the Vogel's medium, this microorganism catalyzed the conversion of 3 to 2 ($[\alpha]_D^{25}$ +30.0°C, 1.0, $CH_2Cl_2$) in 80% chemical and >99% optical yield in 72 hours.




3 2

Alternatively, 2 also may be obtained via the enantioselective hydrolysis of (±)-4[9] using microbial lipases. The results of Table 1 clearly show that the lipases of *Candida cylindracea* and *Pseudomonas sp.* (AK) were highly chemo- and enantioselective towards (±)-4 (E = >100).[10] These lipases preferentially catalyzed the cleavage of the 3R-acetoxy group and by controlling the extent of conversion either 4 (2R,3S) or 2 (2S,3R) may be obtained in enantiomerically pure form.

Table 1. Lipase-catalyzed Enantioselective Hydrolysis of (±)-4

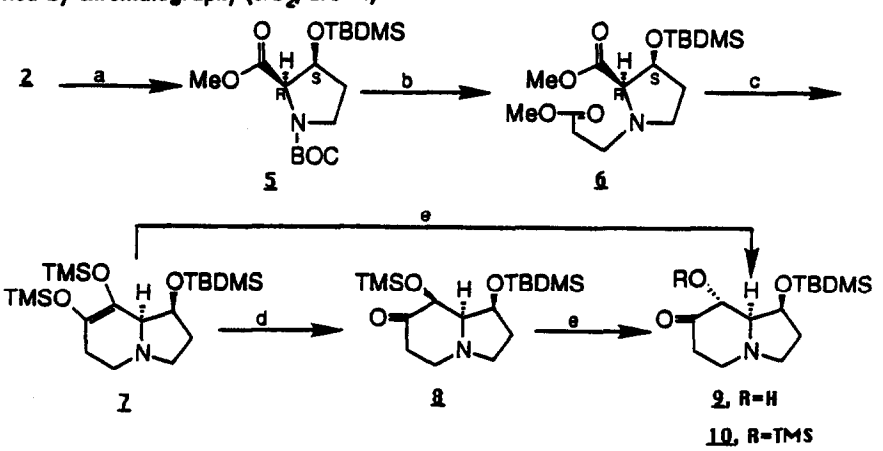



(2R,3S) (2S,3R) -4 → (2R,3S)-4 + (2S,3R)-2

| Lipase | Substrate % ee | Product % ee | Conversion % | E |
|---|---|---|---|---|
| *Candida cylindracea* | >99 | >99 | 50 | >100 |
| *Pseudomonas sp.* (AK) | >99 | >99 | 50 | >100 |
| Porcine pancreas | >99 | 64 | 61 | 22 |

Having the requisite chiron 2 in quantity, we then proceeded to the synthesis of 1 using the reaction sequence shown in Scheme 1. After conversion of 2 into 5 (TBDMSCl, imidazole, 96%), the latter was transformed into the diester, 6, by treatment with 20% $CF_3COOH$ in $CH_2Cl_2$ (v/v) followed by removal of volatiles. The resulting salt was treated with $Et_3N$ and methyl acrylate (95% overall). Acyloin condensation[11] of 6 in the presence of an excess of TMSCl afforded the bistrimethylsilyloxy derivative, 7 (75%) (Scheme 1). Interestingly, 7 could be purified by chromatography ($SiO_2$, EtOAc).

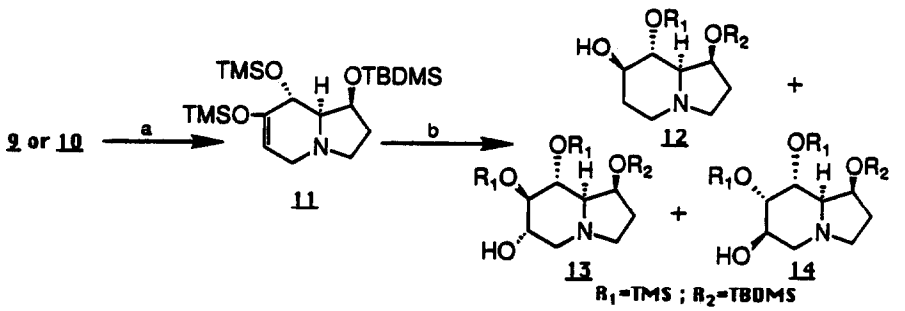
Scheme 1




a) TBDMSCl, imidazole, $CH_2Cl_2$, 24°C, 2h; b) [i] $CF_3CO_2H/CH_2Cl_2$, 20% (v/v); [ii] $Et_3N$ (3 eq), methyl acrylate (1.5 eq), EtOH; c) Na (4.2 eq), TMSCl (5 eq), toluene reflux; d) glacial HOAc, NaOAc (10%), 24°C, 2h; e) DBU, $CH_2Cl_2$, 24°C, 48h.

Several known procedures[12] were examined with a view to removing the silyl groups in **7**, but all of these gave low yields of products. However, treatment of **7** (HOAc-NaOAc) afforded a mixture of **8** (31%) and **10** (18%), which was readily separated by sg chromatography (10-60% EtOAc/hex.). Apparently, under acidic conditions the hydroxyl group at C-8 partially epimerized. The inversion of the C-8 center was more completely achieved by stirring **8** with DBU in $CH_2Cl_2$ (25°C, 24h) to furnish a mixture of **9** and **10** (1:1) (56% yield). Although the conventional methods of hydrolysis of silyl enol ethers are carried out in acidic media, we observed that a crude preparation of **7** could be directly converted into a mixture of **9** and **10** (60% overall from **6**) by stirring **7** with an excess of DBU in $CH_2Cl_2$. The mechanism of this interesting transformation is currently under investigation.

Either **9** or **10** was quantitatively converted into **11** [$LiN(TMS)_2$; -78°C, TMSCl]. Hydroboration [$BH_3$; $Me_2S$ (2 eq), -78°C→25°C] of **11** followed by subsequent oxidation[13] [$(CH_3)_3NO$/toluene, reflux, 1.5 h] of the borane complex gave a mixture of **12** (15%), **13** (24%), and **14** (32%), which were separated by sg chromatography (20% EtOAc/hex.). Compounds **13** and **14** offer the opportunity for the preparation of the C-6 O-acyl derivatives, which exhibit more potent antiretroviral activity than (+)-**1**.[14] Desilylation ($n\text{-}Bu_4N^+F^-$, THF, 0°C to 25°C, 2 hr) of **13** afforded (+)-castanospermine (**1**) (90%), $[\alpha]_D$ +75° (c, 0.7, $H_2O$); reported[15] $[\alpha]_D$ +79°. Similarly, desilylation of **12** gave 6-deoxycastanospermine, $[\alpha]_D$ +32° (c, 0.7, $CHCl_3$) and **14** yielded 6,7-diepicastanospermine, $[\alpha]_D$ +25° (c, 0.6, $H_2O$).[16]




a) TMSCl, $LiN(TMS)_2$, -78°C, THF; b) [i] $BH_3$; $Me_2S$ (2 eq), THF, -78°C to 25°C, 12h; [ii] $Me_3NO$ (10 eq), toluene, reflux.

We are currently examining the diastereoselectivity of the hydroboration of **11**. The results of these studies will be reported at a later date.

Acknowledgment

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