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A concise approach to (+)-1-*epi*-castanospermine

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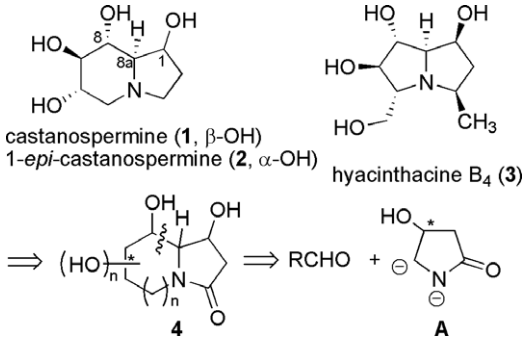
Abstract—A concise enantioselective synthesis of (+)-1-*epi*-castanospermine (**2**) is described, which featured the use of chiral non-racemic tetramic acid derivative **5** as a synthetic equivalent of the challenging synthon **A** through a highly diastereoselective vinylogous Mukaiyama type reaction.

Sugar mimetics, such as polyhydroxylated pyrrolidine, piperidine, pyrrolizidine, and indolizidine alkaloids, known as azasugars, show important bioactivities.[1] Among them, castanospermine (**1**), an alkaloid first isolated[2] from the seeds of *Castanospermum australe* and then from the dried pod of *Alexa leiopetala*, has attracted considerable attention. Because of its powerful inhibitory activities toward α- and β-glucosidases,[3] castanospermine (**1**) shows considerable potential as an antiviral agent in the treatment of HIV,[4] hepatitis C,[5] and HSV-1[6] infections. Castanospermine and its stereomers also have potential use in the inhibition of progression of multiple sclerosis,[7] angiogenesis, cancer,[8] and diabetes.[9] Several stereomers of castanospermine have also been isolated from natural sources.[10] The synthetic 1-*epi*-castanospermine (**2**)[11] was suggested to possess anti-HIV activity, and thus constitutes a valuable synthetic target for biological activities evaluation.

In addition, these alkaloids also provide a natural platform for exploring new synthetic methodologies. So far numerous strategies have been developed for the enantioselective synthesis of castanospermine and other polyhydroxylated alkaloids as well as their stereomers.[11,12] However, novel, efficient, and flexible methods are still highly demanding. That the carbanionic synthon **A**-based strategy as illustrated retrosynthetically in Scheme 1[13,14] is conceptually attractive for a general approach to the azasugars such as castanospermine (**1**) and hyacinthacine B_4 (**3**).[15]



Scheme 1. Retrosynthetic analysis of polyhydroxylated alkaloids (azasugars).

Although a number of umpoled methods have been developed,[16] and the generation of chiral non-racemic *N*-α-carbanion of 4-hydroxy-2-pyrrolidinone **A** has been reported,[13,17] the C–C bond formation based on synthon **A** remains a challenging problem in carbanion chemistry due to quick proton exchange[17] or β-elimination if the hydroxyl group is protected.[13,18] Recently, we reported a flexible approach to 5-alkyl tetramic acid derivatives based on the C-5 alkylation of tetramic acid derivative **5**, which was used as a synthetic equivalent of 4-hydroxy-2-pyrrolidinone 5-carbanionic synthon **A**.[19,20] With the aim to develop a general asymmetric approach to polyhydroxylated alkaloids, we now describe the extension of this method from alkylation to α-hydroxyalkylation and the asymmetric synthesis of 1-*epi*-castanospermine (**2**).

Keywords: Castanospermine; Tetramic acid; Synthon; Mukaiyama type reaction.
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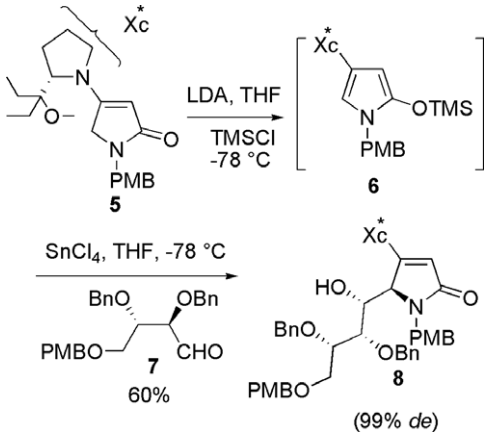


Scheme 2.

Our initial efforts have been devoted to explore the use of the vinylogous enolate derived from tetramic acid derivative **5**. Unfortunately, although the alkylation of this enolate shows excellent diastereoselectivities,[19] its reaction with *iso*-butanal gave four diastereomers with a modest ratio of 2:4:27:67.

In the light of the high diastereoselectivities observed in the vinylogous aldol reaction of heterocyclic silyloxy dienes,[21,22] extensively studied by Casiraghi and co-workers, we turned our attention to explore the use of the vinylogous silyl enol ether[23] **6**, easily derived from the tetramic acid derivative **5** (Scheme 2). Accordingly, compound **5** was treated with LDA in THF at −78 °C for 1 h. The resulted vinylogous enolate was quenched with trimethylsilyl chloride and allowed to warm up to −10 °C, and then stirred for 2 h. The in situ generated vinylogous silyl enol ether **6** was reacted, in the presence of tin tetrachloride at −78 °C, with 4-*O*-(4-methoxybenzyl)-2,3-bis-(*O*-benzyl)-L-threose (**7**)[24] for 3.5 h. To our delight, the desired hydroxyalkylated product **8** was obtained as the sole product in 60% yield. Both the ^{1}H and ^{13}C NMR spectra of the product are quite complex, a 2.2:1 ratio of mixture was observed. The fact that the HPLC analysis showed only one product in 99% de allowed us to assume that the complex peaks which appeared in both the ^{1}H and ^{13}C NMR spectra of **8** are rotameric in nature, which is due to the slow rotation around the C–N bond.[18] To confirm this assumption, both the ^{1}H and ^{13}C NMR spectra of **8** were recorded in DMSO-d_6 at 20 °C and 95 °C, respectively. The peaks of the minor isomer disappeared at 95 °C and reappeared when the temperature returned to 20 °C. These NMR experiments show that the aldol products observed in the NMR spectra are rotamers instead of diastereomers, as observed previously.[19] This was confirmed at a later stage (**8**→**10**). The stereochemical assignment was also carried out at a later stage (vide infra), which revealed that the newly formed stereocenters are *erythro* (*anti*), and the relationship with the adjacent stereocenter is *threo* (*syn*).

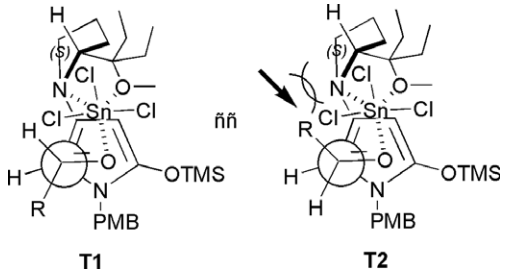
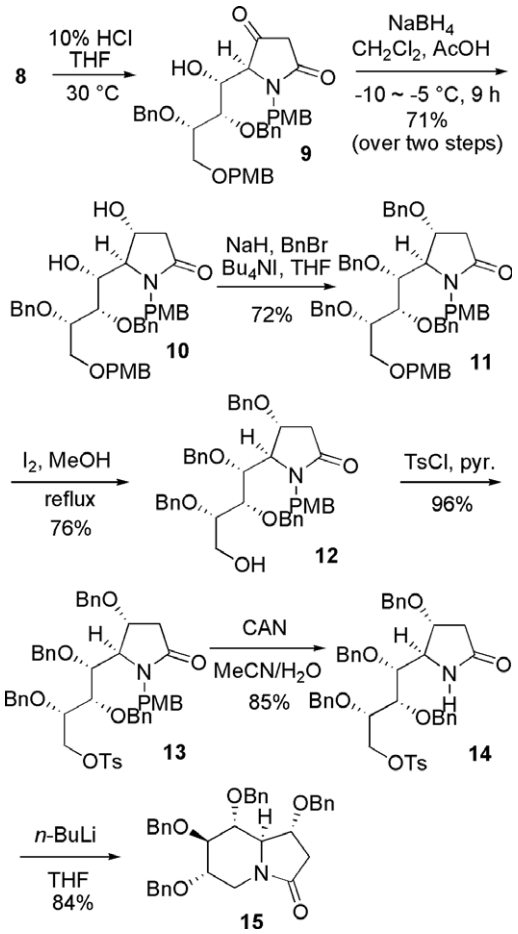


Figure 1.

Thus the vinylogous Mukaiyama type reaction between **6** and **7** established the correct configurations required for the synthesis of castanospermine and its C-1 epimer. This stereoselection can be rationalized by transition state[21,22] **T1**, which is favored over **T2** (Fig. 1). The reaction of **6** with aldehyde **7** is distinct from those reported by Casiraghi not only in the stereoselection, but also in the reaction conditions used for their formations (in THF at −78 °C versus in diethyl ether at −85 °C).

Now the stage was set for the synthesis of 1-*epi*-castanospermine (**2**) (Scheme 3). To this end, compound **8** was treated with a 10% HCl solution in THF at 30 °C to give the desired tetramic acid **9**, and then compound **9** was treated with $NaBH_4$[25] in the presence of HOAc at −10 to −5 °C for 9 h to give **10** as the sole diastereomer judged by the NMR analysis. The two hydroxyl groups



Scheme 3.

were protected (NaH, BnBr, n-Bu_4NI) to afford the desired di-benzylated product **11** in 72% yield. Treatment of compound **11** with I_2 in refluxing methanol[26] resulted in the selective cleavage of the *O*-PMB group, which furnished alcohol **12** in 76% yield.

Tosylation of alcohol **12** (*p*-TsCl/pyr.) led to tosylate **13** in 96% yield. Cleavage of the *N*-PMB group under Yoshimura's conditions[27] (CAN, $MeCN/H_2O = 9:1$) for 5 h at rt gave the desired lactam **14** in 85% yield. The key cyclization of **14** was undertaken by treating with *n*-BuLi in THF at −78 °C for 0.5 h, then allowed to warm up and stir overnight. The desired indolizidinone **15** was obtained in 84% yield. The relative stereochemistry of **15** was determined, first by ^1H–^1H COSY and ^1H–^{13}C HMQC experiments to make the proton assignments, and then by NOESY experiment. These experiments not only allowed determining the *erythro* (*anti*)/*threo* (*syn*) relationship of the stereocenters formed by the vinylogous Mukaiyama type reaction (**6**→**8**), but also determined the stereochemistry of the reduction (**9**→**10**), which indicated a 1,3-*syn* relationship between the C-3 and C-5.

The stereochemistry of the reduction ($NaBH_4$ in HOAc/CH_2Cl_2) can be understood by Evan's directed reduction model[25] (Fig. 2). In this singular situation merging an alicyclic-cyclic β-hydroxy ketone system, the formation of the 1,3-*syn*-diol can be explained by the Evans' model (intramolecular hydride delivery).

The subsequent reduction of **15** with borane dimethyl sulfide complex ($BH_3{\cdot}SMe_2$) proceeded smoothly to give indolizidine **16** in 92% yield (Scheme 4). Finally, cleavage of the four benzyl groups in **16** was achieved by Pd/C-catalyzed transfer hydrogenolysis, which gave 1-*epi*-castanospermine (**2**) {$[\alpha]_D^{22}$ +3.8 (*c* 0.54, MeOH); lit.[11] $[\alpha]_D$ +6 (*c* 0.45, H_2O); $[\alpha]_D^{25}$ +3.8 (*c* 0.5, MeOH); $[\alpha]_D^{22}$ +6.2 (*c* 0.15, MeOH); for the antipode: $[\alpha]_D^{22}$ −4 (*c* 1.2, MeOH); $[\alpha]_D^{22}$ −3.1 (*c* 1.86, MeOH)} in quantitative yield. The ^1H and ^{13}C NMR spectral data of the synthetic material are in consistent with those reported.[11]

In summary, chiral non-racemic tetramic acid derivative **5** is demonstrated to be a good synthetic equivalent to synthon **A**, via highly diastereoselective vinylogous Mukaiyama type reaction with an aldehyde. An application of the present method to the asymmetric synthesis of (+)-1-*epi*-castanospermine (**2**) was achieved in 10 steps and 14.8% overall yield from **5**. Further application of synthon **A**-based method in the asymmetric synthesis of castanospermine and other azasugars using

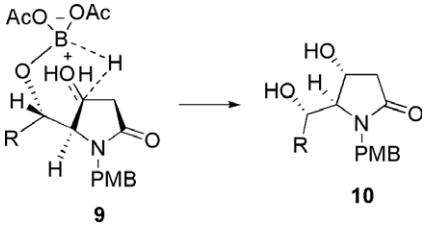
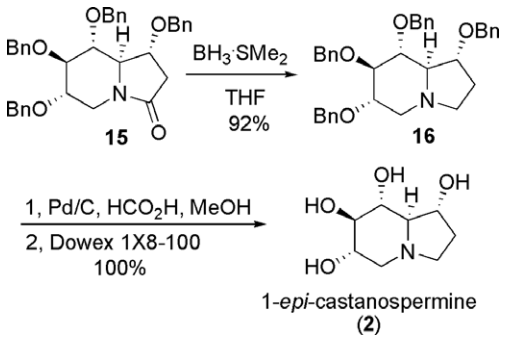


Figure 2.



Scheme 4.

achiral aldehydes is in progress in these laboratories and will be reported in due course.

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