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Divergent Synthesis of Aminocyclopentitol Analogues via Stereoselective Amination of Cyclic Polybenzyl Ether with Chlorosulfonyl Isocyanate

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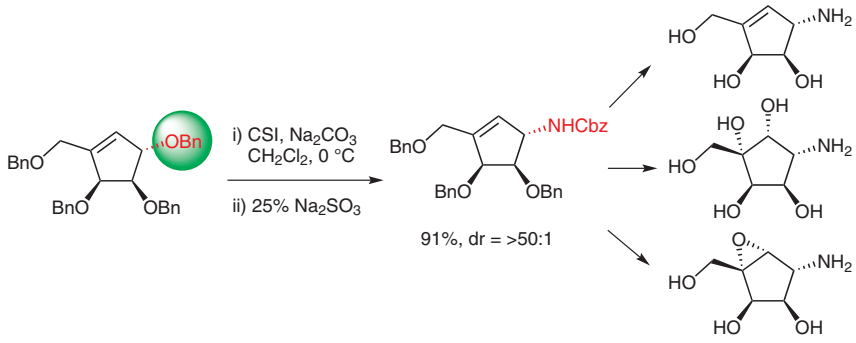

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Abstract The divergent synthesis of some novel aminocyclopentitol analogues was concisely achieved from readily available D-galactose via the highly diastereoselective amination of carbocyclic polybenzyl ether using chlorosulfonyl isocyanate, diastereoselective dihydroxylation, and epoxidation as the key steps.

Key words amination, aminocyclopentitol, chlorosulfonyl isocyanate, divergent synthesis, ether

Recent years have witnessed a great deal of attention in the preparation and biological evaluation of carbocyclic amino alcohols, which either exist in nature or constitute crucial core structures of several natural products.[1] This class of molecules involves two typical substructures such as aminocyclopentitol and aminocyclohexitol. Among the well-known examples of aminocyclopentitol are mannostatin A (**1**)[2] and trehazolin (**2**),[3] as shown in Figure 1. Aminocyclopentitol scaffold has been also found in a range of carbocyclic nucleosides such as neplanocin A (**3**)[4] and its unsaturated analogue (–)-aristeromycin (**4**).[5] Due to the absence of a true glycosidic bond, carbocyclic nucleosides are more chemically stable and not involved in the action of the enzymes that cleave the N-glycosidic linkage in conventional nucleosides.[6] Thus carbocyclic amino alcohol moiety have been the focus of much attention in the development of new therapeutic agents.[7] The unsaturated carbasugar valienamine A (**5**) is known as a representative aminocyclohexitol, and displays a highly potent inhibitor of α-glucosidases in the human digestive tract.[8] In addition, valienamine A (**5**) is an essential core unit in many kinds of pseudooligosaccharides, for example, acarbose, validamycins, amylostatins, adiposins, salbostatin, and acarviosin.[9]

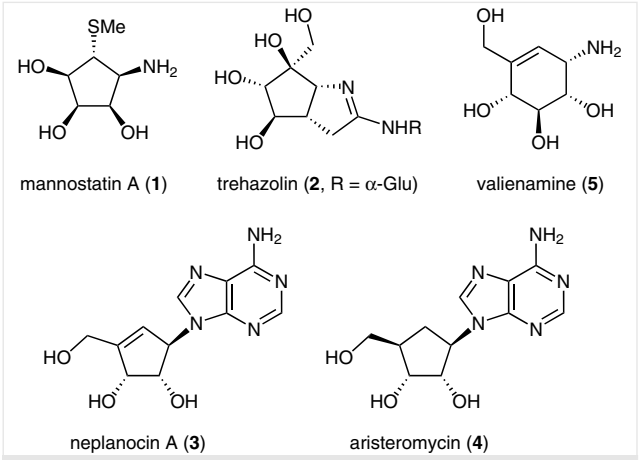
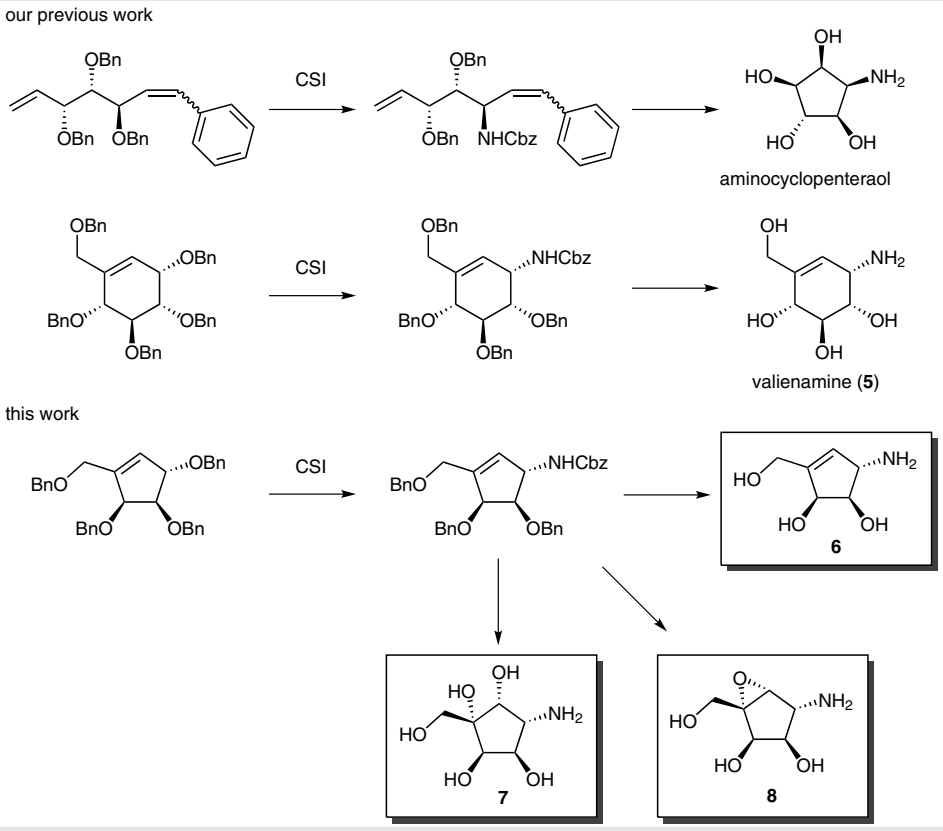


Figure 1 Structures of typical carbocyclic amino alcohols

Carbocyclic amino alcohols can be considered as structural analogues of carbohydrates, in which an oxygen atom in furanose and pyranose rings is replaced by a methylene group, containing a basic nitrogen group at the anomeric center in the protonated form. General mode of biological action is presumed to proceed via mimicking of the glycopyranosyl cation in the transition state of the glycosidase-catalyzed reaction.[10] However, glycosidase inhibitory effect of carbocyclic amino alcohols in term of structural and stereochemical features still remains to be explored. Therefore, the preparation of new analogues could provide not only a better understanding of glycosidase functioning but also lead to more active inhibitors, which can be used for the treatment of carbohydrate-metabolism-related disorders.



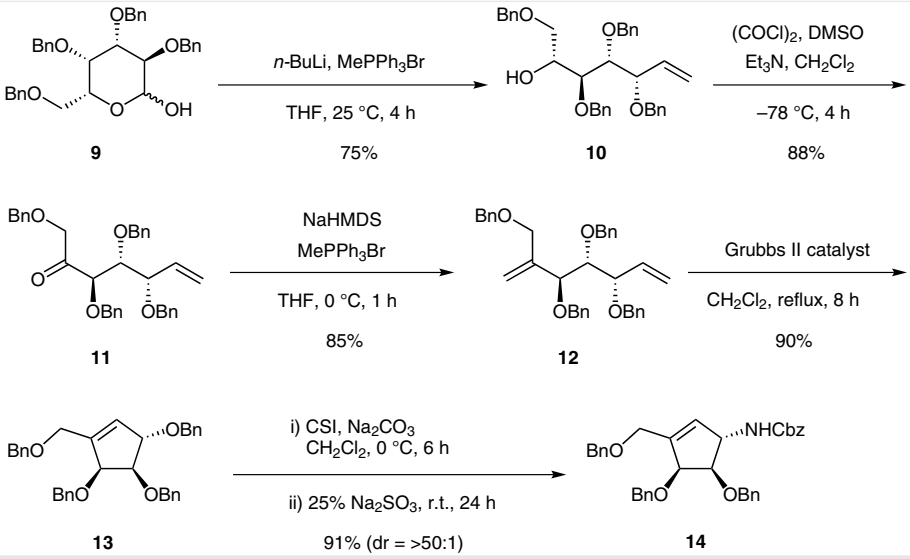
Scheme 1 Synthetic strategy for carbocyclic amino alcohols

In our previous works, we reported a convenient synthetic route for the preparation of stereoisomeric 5-amino-1,2,3,4-cyclopentanetetrols[11] using linear polybenzyl ethers and valienamine (**5**)[12] using cyclic polybenzyl ethers based on our amination methodology (Scheme 1).

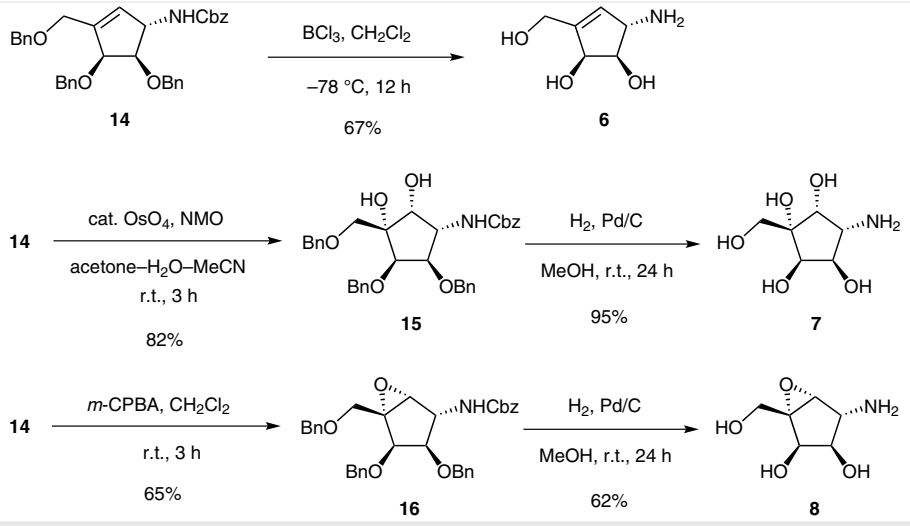
In connection with our ongoing research program on the total synthesis of biologically active compounds through stereoselective amination of polybenzyl ethers using chlorosulfonyl isocyanate,[13] we herein report a divergent synthetic protocol for the synthesis of new three carbocyclic amino alcohols via the diastereoselective amination of cyclopentene polybenzyl ether using chlorsulfonyl isocycante (CSI).

Our investigation was initiated from the construction of carbocyclic polybenzyl ether **13**, which can be converted into the protected amino alcohol **14** via our amination methodology. Thus, the synthesis of **13** began with the benzyl-protected lactol **9** derived from D-galactose according to the reported literature (Scheme 2).[14]

Wittig reaction of **9** followed by Swern oxidation of a secondary alcohol provided the ketone **11** in high yields. Subsequent Wittig reaction of **11** afforded the diene **12**, which was subjected with second-generation Grubbs catalyst in refluxing CH_2Cl_2 to give the carbocyclic polybenzyl ether **13** in 90% yield. Next, the diastereoselectivity of the reaction between **13** and CSI was examined under various reaction conditions. After extensive screening of reaction conditions, we found that the reaction of **13** with CSI in dichloromethane at 0 °C for six hours gave the our desired product **14** in 91% yield with an excellent level of diastereoselectivity (*anti*/*syn* = >50:1). However, other solvents such as CCl_4, Et_2O, and toluene were relatively less effective under otherwise identical conditions (see Supporting Information for the detailed optimizations). It should be noted that the reaction exclusively afforded the *anti*-amino alcohol product in all cases, and trace amounts of *syn* compound were observed by ^1H NMR analysis. The *anti* selectivity can be explained by competition between S_Ni mechanism and S_N1 mechanism.[13c] In general, the S_Ni mechanism leads to retention of stereochemistry via a four-centered transition state by the formation of a tight ion pair. Another plausible S_N1 mechanism may cause the generation of a carbocation intermediate, which can provide the racemization of products. However, in the case of *anti*-dibenzyl ether **13**, *anti*-amino alcohol **14** can be exclusively obtained due to retention of stereochemistry via S_Ni mechanism and the facile approach of $^-NCO_2Bn$ species to the less sterically hindered face on a carbocation intermediate. In addition, the regioselective substitution at this secondary allylic position can be expected because the regioselectivity is controlled



Scheme 2 Synthesis of carbocyclic polybenzyl ether **13** and its diastereoselective amination using CSI



Scheme 3 Synthesis of aminocyclopentitols

by steric congestion and the stability of the carbocation intermediate. Namely, the less hindered secondary allylic OBn is more reactive than other secondary or allyl one to provide our desired product.

Based on the above results, we next focused on the synthesis of aminocyclopentitols **6**–**8**, as illustrated in Scheme 3. Unsaturated aminotriol **6**[15] was readily obtained by a removal of protection groups using BCl_3 in 67% yield. In addition, dihydroxylation or epoxidation of **14** diastereoselectively provided **15** or **16** as major products. Finally, hydrogenative debenzylation of **15** and **16** afforded highly functionalized aminocyclopentitols **7**[16] and **8**[17] in good yields, respectively.

In conclusion, we described a concise synthesis of new and highly functionalized aminocyclopentitols starting from readily available D-galactose via highly diastereoselective amination of cyclic benzylic ether with retention of stereochemistry using chlorosulfonyl isocyanate, diastereoselective dihydroxylation, and epoxidation as the key steps. It is believed that this synthetic strategy can be applied to the preparation of a broad range of biologically active compounds containing a chiral amine moiety.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380227.

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(15) **Characterization Data of 6**
R_f = 0.26 (CH_2Cl_2–MeOH–EtOH–NH_4OH = 5:2:2:1); $[\alpha]^{25}_D$ +38.96 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD): δ = 5.71 (d, *J* = 1.2 Hz, 1 H), 4.46 (d, *J* = 5.4 Hz, 1 H), 4.21–4.16 (m, 2 H), 3.83–3.77 (m, 2 H). ^{13}C NMR (125 MHz, CD_3OD): δ = 146.9, 128.3, 79.2, 73.3, 61.2, 59.0. HRMS (EI): *m/z* calcd for $C_6H_{11}NO_3$ $[M]^+$: 145.0739; found: 145.0742.

(16) **Characterization Data of 7**
R_f = 0.17 (CH_2Cl_2–MeOH–EtOH–NH_4OH = 5:3:3:1); $[\alpha]^{25}_D$ –36.8 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, D_2O): δ = 4.43–4.39 (m, 1 H), 4.25 (d, *J* = 8.7 Hz, 1 H), 4.00 (d, *J* = 4.8 Hz, 1 H), 3.82 (d, *J* = 12.3 Hz, 1 H), 3.63 (d, *J* = 12.0 Hz, 1 H), 3.62–3.57 (m, 1 H). ^{13}C NMR (125 MHz, D_2O): δ = 81.4, 74.1, 73.7, 67.9, 62.4, 56.7. HRMS (EI): *m/z* calcd for $C_6H_{13}NO_5$ $[M]^+$: 179.0794; found: 179.0795.

(17) **Characterization Data of 8**
R_f = 0.23 (CH_2Cl_2–MeOH–EtOH–NH_4OH = 5:2:1:1). $[\alpha]^{25}_D$ –42.8 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, D_2O): δ = 4.30–4.23 (m, 2 H), 3.87 (dd, *J* = 7.8, 5.4 Hz, 1 H), 3.77 (s, 1 H), 3.66 (d, *J* = 13.2 Hz, 1 H), 3.57 (d, *J* = 8.1 Hz, 1 H). ^{13}C NMR (125 MHz, D_2O): δ = 74.8, 68.6, 66.2, 61.8, 57.9, 56.2. HRMS (EI): *m/z* calcd for $C_6H_{11}NO_4$ $[M]^+$: 161.0688; found: 161.0689.