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D-(−)-ribose: 3*R*, 4*S*, 5*R*
L-(+)-ribose: 3*S*, 4*R*, 5*S*
D-(−)-lyxose: 3*S*, 4*R*, 5*R*

From D-(−)-ribose: 1*R*, 2*R*, 3*S*, 4*R*
From L-(+)-ribose: 1*S*, 2*S*, 3*R*, 4*S*
From D-(−)-lyxose: 1*R*, 2*S*, 3*R*, 4*S*

Overall yield: 11-22%

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Convenient syntheses of orthogonally protected aminocyclopentitols from aldopentoses

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ABSTRACT

Orthogonally protected aminocyclopentitols were synthesized from commercially available aldopentoses using a convenient three-step procedure that does not require protection of the free anomeric hydroxyl group of the starting carbohydrate. The synthesized compounds are important building blocks with potential use in medicinal chemistry and drug discovery.

Aminocyclopentitols are structural motifs that are present in a number of pharmacologically important natural products and drugs. Neplanocin A[1] and aristeromycin[2] are naturally occurring carbocyclic analogues of adenosine that demonstrate antiviral and antitumor activities. Allosamidin,[3] mannostatins A and B,[4] and trehazolin[5] are natural glycosidase inhibitors that have received significant attention as lead compounds in drug discovery for diseases such as diabetes and cancer, and for viral and bacterial infections, and Gaucher's disease.[4] The aminocyclopentitol structure is also present in peramivir,[6] which is a selective influenza neuraminidase inhibitor, and in ticagrelor,[7] which is a reversible $P2Y_{12}$ receptor antagonist for the prevention of thrombosis (Figure 1).

Considering the pharmacological importance of aminocyclopentitols, convenient methods for the synthesis of these compounds are highly desirable. In this context, we focused on orthogonally protected aminocyclopentitol **1** (Scheme 1). The synthesis of this compound from protected D-(+)-ribono-1,4-lactone **2** was first reported by Marco-Contelles *et al.*[8] We wanted to prepare compound **1** from the commercially available and inexpensive D-(–)-ribose, by combining procedures available in the literature into our initial synthetic plan (Scheme 1).

However, after careful analysis of this plan, a number of potential problems were identified. The synthesis required the protection of the free anomeric hydroxyl group of D-(–)-ribose in the form of a lactone **2**. The reagents for the protection and deprotection steps were uninviting, as the protection step is either an oxidation of the free anomeric hydroxyl group of D-(–)-ribose to lactone **3** using hazardous bromine in aqueous $NaHCO_3$,[9] or an oxidation with the expensive $RhH(PPh_3)_4$-benzalacetone system.[10] Additionally, the deprotection step involves reduction of lactone **4** to hemiacetal **5** with the highly flammable diisobutylaluminium hydride (DIBAL-H).[11-13]

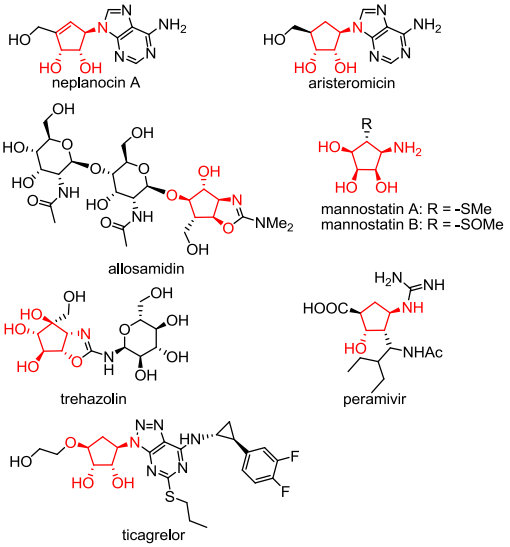

Figure 1. Examples of biologically important natural aminocyclopentitols and aminocyclopentitol-based drugs.

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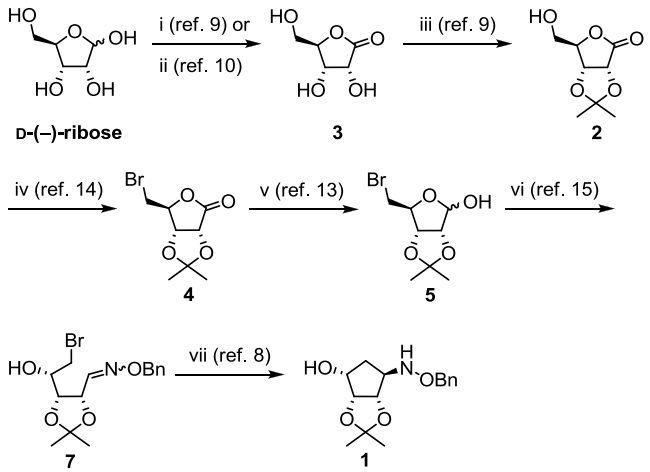
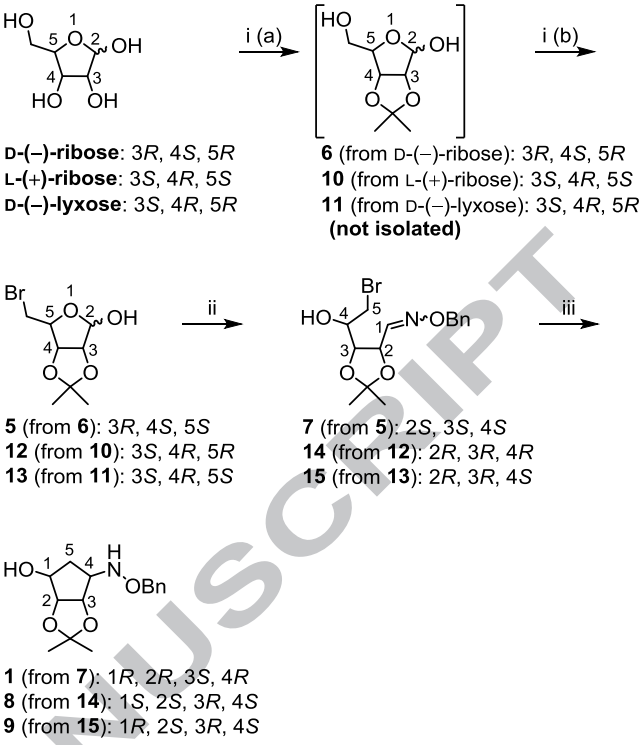


Scheme 1. Synthetic plan for the preparation of compound **1** from D-(–)-ribose based on the steps published in the literature. Reagents and conditions: i. (a) Br_2, $NaHCO_3$, H_2O, 0 °C, 110 min, (b) $NaHSO_3$, 0 °C; ii. benzalacetone, $RhH(PPh_3)_4$ (cat.), anhydrous DMF, 40 °C, under argon, 1.5 h, 99%; iii. anhydrous acetone, 2,2-dimethoxypropane, conc. H_2SO_4 (cat.), r.t., 50 min, 73% from D-(–)-ribose, (b) Ag_2CO_3, r.t.; iv. (a) PPh_3, NBS, CH_2Cl_2, 10–25 °C, 2.5 h, (b) $BaCO_3$, reflux, 15 min, 80%; v. (a) DIBAL-H, anhydrous PhMe or anhydrous THF, –80 °C, 30 min, under argon, (b) MeOH, r.t., 30 min, 95%; vi. $BnONH_3^+Cl^-$, pyridine, CH_2Cl_2, H_2O, reflux, 18 h; 95%; vii. (a) $(n\text{-}Bu)_3SnH$, AIBN (cat.), PhMe, reflux, under argon, 6 h, (b) Et_2O, 15% KF aq, overnight, 75%.

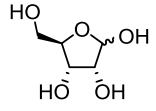
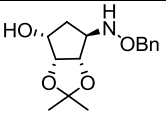
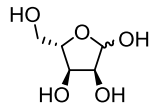
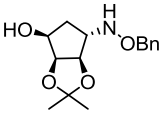
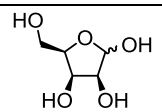
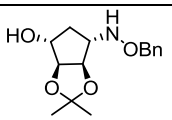
In our attempts to make the synthesis of compound **1** more convenient, we eliminated the initial protection of the free anomeric hydroxyl group of D-(–)-ribose. We converted the starting aldopentose into bromide **5** in two steps, without purification of the intermediate **6**. The first stage was the conversion of D-(–)-ribose into its 2,3-*O*-isopropylidene derivative **6**.[16] The crude acetonide **6** was then treated with PPh_3 and *N*-bromosuccinimide (NBS) in *N*,*N*-dimethylformamide (DMF) to give the bromide **5** in 28% yield from D-(–)-ribose, after purification by flash column chromatography. The bromide was converted into the oxime **7** using a literature procedure,[15] in 93% yield. For the free-radical carbocyclization of compound **7** into orthogonally protected aminocyclopentitol **1**, the radical initiator 2,2′-azobis(2-methylpropionitrile) (AIBN) as used in the literature procedure,[8] was replaced with the less hazardous 1,1′-azobis(cyclohexanecarbonitrile) (ABCN). The yield of this carbocyclization step was 77% (Scheme 2). The overall yield for the preparation of compound **1** from D-(–)-ribose using this three-step procedure was 20% (Table 1), while the calculated overall yield of the six-step procedure reported in the literature was 40% (Scheme 1).

We were thus able to make the synthesis of compound **1** more convenient by reducing the number of steps from six to three, and by avoiding reactions that required the use of some hazardous reagents. To confirm the general applicability of our procedure, we converted L-(+)-ribose into compound **8**, in 22% overall yield, and D-(–)-lyxose into compound **9**, in 11% yield, thus obtaining two additional stereoisomeric aminocyclopentitols (Scheme 2, Table 1).



Scheme 2. Reagents and conditions: i. (a) acetone, conc. H_2SO_4 (cat.), r.t., 18 h, (b) PPh_3, NBS, DMF, 0 °C to r.t., 20 h, 28% for **5** from D-(–)-ribose, 38% for **12** from L-(+)-ribose, 18% for **13** from D-(–)-lyxose; ii. $BnONH_3^+Cl^-$, pyridine, CH_2Cl_2, H_2O, reflux, 18 h, 93% for **7** from **5**, 82% for **14** from **12**, 93% for **15** from **13**; iii. (a) $(n\text{-}Bu)_3SnH$, ABCN (cat.), PhMe, reflux, argon, 6 h, (b) Et_2O, 20% KF aq, 12 h, 77% for **1** from **7**, 71% for **8** from **14**, 68% for **9** from **15**.

Table 1.
Orthogonally protected aminocyclopentitols **1, 8** and **9** obtained from aldopentoses.

Starting aldopentose	Final orthogonally protected aminocyclopentitol	Overall yield (%)[b]
 D-(–)-ribose	 **1**	20
 L-(+)-ribose	 **8**	22
 D-(–)-lyxose	 **9**	11

[b]Isolated yield of pure product

As the configurations at C1, C2 and C3 of compounds **1**, **8** and **9** are the same as in the corresponding starting aldopentose, we were able to determine the configuration at C4 of these compounds using NOESY spectroscopy. In compounds **1** and **8**, where the hydroxyl group and the benzylhydroxylamino group are in the *trans* configuration, proton H1′ correlates more intensely with one of the protons H5′, while proton H4′ correlates more intensely with the other H5′ proton (Figure 2). In compound **9**, where the hydroxyl group and the benzylhydroxylamino group are in *cis*

configuration, proton H1′ and proton H4′ correlate more intensely with the same H5′proton (Figure 2).

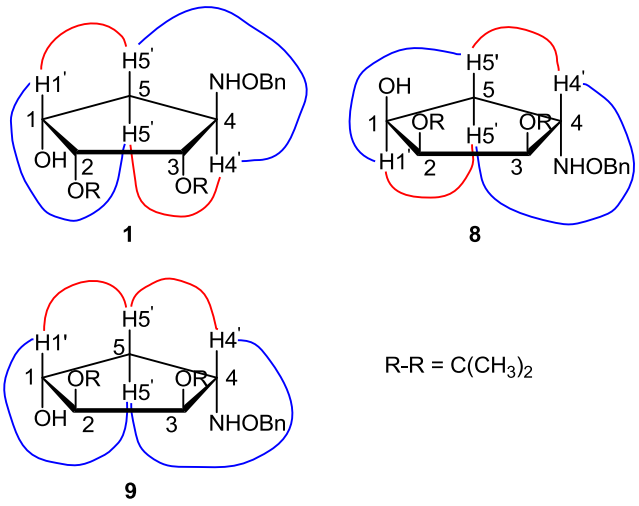


Figure 2. NOESY correlations of **1**, **8** and **9**.

To conclude, we have successfully synthesized orthogonally protected aminocyclopentitols from commercially available aldopentoses using a convenient three-step procedure. The aminocyclopentitols thus prepared are building blocks with potential use in medicinal chemistry and drug discovery.

Acknowledgment

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Supplementary data

Supplementary data associated with this article (general methods, experimental procedures, compound characterization, and ^{1}H NMR and ^{13}C NMR spectra of all synthesized compounds) can be found in the online version, at (*insert link here*).

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