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A greener enantioselective synthesis of the antiviral agent North-methanocarbathymidine (N-MCT) from 2-deoxy-D-ribose

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ABSTRACT

An enantioselective synthesis of suitably protected (1*R*,2*S*,4*S*,5*S*)-4-amino-1-(hydroxymethyl)bicyclo[3.1.0]hexan-2-ol, a key starting material for the synthesis of conformationally locked carbocyclic nucleosides, including the antiviral active North-methanocarbathymidine, is reported. Starting from 2-deoxyribose the target Boc-protected amine was prepared in 33% overall yield under conditions that are ecologically friendlier than previous methods.

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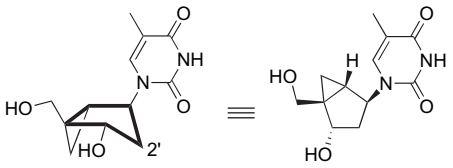
1. Introduction

The antiviral active and conformationally locked nucleoside, North-methanocarbathymidine (N-MCT, **1**), belongs to a group of carbocyclic nucleosides constructed on a bicyclo[3.1.0]hexane scaffold.[1] This scaffold was devised as a strategy to lock the embedded cyclopentane ring of N-MCT into a permanent North envelope ($_{2'}$E) conformation as it is defined in the pseudorotational cycle.[2] The antiviral activity of N-MCT is dependent on type I thymidine kinase (TK) from herpes simplex viruses (HSV-1 and HSV-2),[3–5] as well as from type II TK expressed in cowpox[6] and vaccinia viruses.[7] Once phosphorylated to the 5′-triphosphate level, N-MCTTP inhibits viral DNA synthesis. The compound reduces the mortality of mice infected with orthopoxviruses when administered intraperitoneally,[6] as well as when given orally to mice infected with HSV-1, even when treatment is initiated 76 h post-infection.[8] In addition, N-MCT has shown excellent in vitro activity against Kaposi's sarcoma-associated herpesvirus (KSHV), displaying greater potency than the reference compounds ganciclovir and cidofovir.[9] These combined properties suggest that N-MCT is bioavailable, safe, and orally effective, thus warranting further development.

We recently reported an improved synthesis of N-MCT involving the elaboration of the thymine ring from a suitable pseudosugar precursor.[10] Both convergent and linear strategies were compared side by side, but the linear strategy of building the pyrimidine ring from the corresponding carbobicyclic amine was found to more selective and easier to execute, plus the overall yield was comparable to that using a convergent approach. Therefore, the linear approach was selected for the large-scale synthesis of N-MCT. We now wish to report a novel enantioselective route toward the other half of the molecule, the carbobicyclic amine. This new synthesis circumvents many of the drawbacks encountered with other strategies reported earlier.



N-MCT (**1**)

Historically, our first approach (Route A, Fig. 1) was based on the orthogonally protected hexanol **2**—derived from the chiral cyclopentenone precursor (**3a**)—that was used in the synthesis of neplanocin A.[11,12] In this methodology, a regioselective cleavage of the contiguous *O*-isopropylidenetriol system with trimethylaluminum and a two-step radical deoxygenation to remove the extra hydroxyl group were necessary. This route, however, was unattractive from an economical and ecological point of view (4% overall yield, 13 steps from D-ribose). Formation of the

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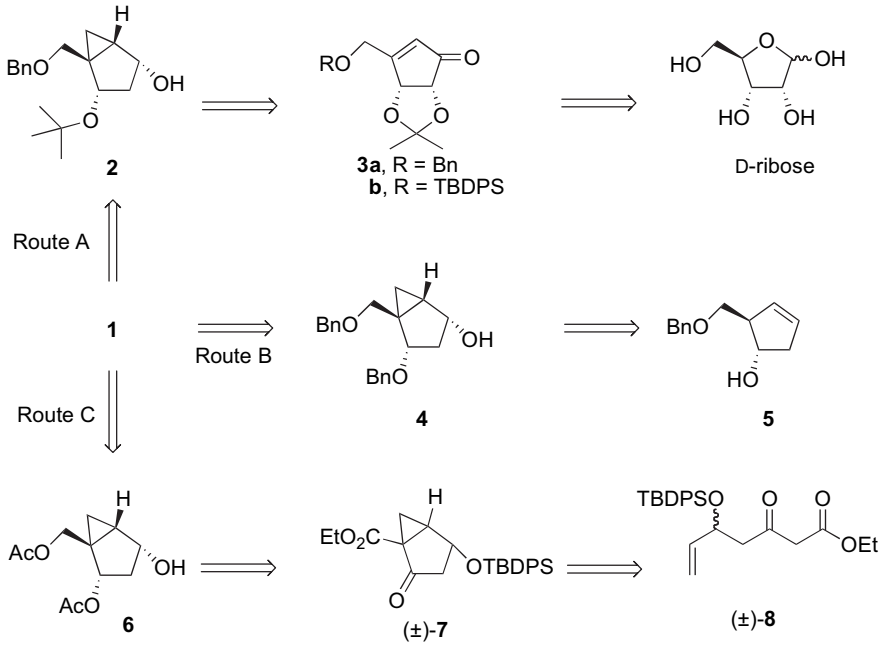

Figure 1. Synthetic strategies toward N-MCT (**1**).

equivalent cyclopentenone precursor (**3b**) by Jeong et al.[13] using ring-closing metathesis (RCM) was a significant improvement. However, for the purpose of synthesizing a 2′-deoxy analogue, such as N-MCT, the issue of removing the additional hydroxyl function still remained.

Another strategy that we utilized was based on the enantiomerically pure cyclopentenol **5** that was developed by Roberts et al.[14] for the synthesis of 2′-deoxycarbanucleosides (Route B, Fig. 1). This approach was very attractive because **5** could be used as a common precursor for making both North- and South-locked bicyclo[3.1.0]hexane nucleosides.[15,16] Although **5** could be obtained with excellent optical purity (>97% ee), the synthesis is extremely sensitive to air, moisture, and temperature, plus the overall yield is not optimal. Starting from cyclopentadiene—the precursor of **5**—the critical intermediate (1*S*,2*R*,4*S*,5*R*)-4-(benzyloxy)-5-(benzyloxymethyl)bicyclo[3.1.0]hexan-2-ol (**4**) was obtained in 10% overall yield after 10 steps. To our knowledge, no alternative synthesis of cyclopentenol **5** has been reported thus far.

Since the availability of **5** was a limiting factor, we next designed a very simple chemical approach toward the requisite racemic, bicyclo[3.1.0]hexane system that relied on a practical and efficient enzymatic step for chiral resolution (Route C, Fig. 1). The bicyclic system (±) **7** was formed in one step by a metal catalyzed ketocarbene cycloaddition after diazotation of the β-keto ester (±) **8**, which was easily obtained by an aldol reaction from cheap ethyl acetoacetate and acrolein.[17] However, despite the straightforwardness of this approach, half of the material was lost during the resolution of enantiomers, thus drastically reducing the overall yield of the diacetate **6** (13%, eight steps).

Based on the above considerations, we now wish to present an enantioselective approach that is inexpensive, environmentally friendlier, easy to handle, and most importantly, highly efficient. The recent publication by Michel and Strazewski on the improved synthesis of chiral cyclopentenone **3b**[18] and the utilization of natural 2-deoxy-D-ribose as rich chiral pool,[19] prompted us to investigate the possibility of preparing the bicyclic hexanol precursor **4** from this inexpensive building block. The retrosynthetic analysis for this novel route (Fig. 2) resembles in great part Jeong's initial approach toward chiral cyclopentenone **3b**.[13] In a previous communication,

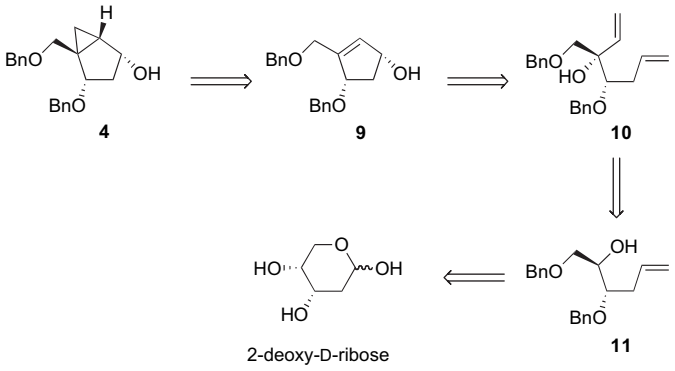

Figure 2. Retrosynthetic analysis of the novel strategy towards the N-MCT precursor **4**.

we have already shown that compound **4** could be obtained with high stereospecificity from the allylic cyclopentenol **9**,[20] which should be accessible from the α,ω-diene **10** via ring-closing metathesis (RCM),[21–26] followed by a palladium(II) catalyzed rearrangement of the resulting allylic system.[27,28] The RCM-precursor **10** is envisaged to arise from the stereospecific addition of a vinyl Grignard reagent to a ketone obtained from the oxidation of the corresponding alcohol **11**. Alcohol **11** is already a known compound that has been synthesized by Herdewijn et al.,[29] in four steps starting from 2-deoxy-D-ribose.

2. Results and discussion

The starting lactol **14** was prepared in three steps from 2-deoxy-D-ribose according to the literature procedure (Scheme 1). Although the synthesis has been described already,[30] we would like to comment on the methodology and report some useful modifications (Scheme 1). The purity of **14** greatly depends on reducing the amount of the pyranoside isomer **12′** formed during acetalization under acidic conditions (Table 1). Since the desired furanose form **12** is the kinetic product, while the pyranoside **12′** resembles the thermodynamic product,[31] we concluded that acetalization at lower temperatures should favor formation of the five-membered