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Synthesis of an all-*cis* intermediate of ticagrelor

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ABSTRACT

A six step conversion of the common carbocyclic nucleoside precursor **8** into the all-*cis* key intermediate for the synthesis of ticagrelor analogs is reported. The method involves two oxidation/stereoselective reduction sequences for both the C—O and C—N bonds. Inversion of stereochemistry was confirmed by analysis of spin couplings between the hydrogens at the junction of the 1,3-dioxolane and cyclopentane rings.

Introduction

Carbocyclic nucleosides (CNs) are compounds possessing important antiviral, antitumor, and antibiotic activities.[1] Naturally occurring CNs—aristeromycin (**1**)[2] and neplanocin A (**2**)[3] served as an inspiration for the design and synthesis of many unnatural analogs.[4] Some of these, entecavir (**3**),[5] carbovir (**4**),[6] abacavir (**5**),[7] and ticagrelor (**6**),[8] have found application as drugs (Fig. 1).

The stereochemistry of many CNs analogs is similar to that of the natural nucleosides. However, this similarity is not required to effect biological activities and there are examples of bioactive nucleoside analogs in which one stereogenic center has been inverted.[4b–d,f] Interestingly, all-*cis* CNs, in which two stereocenters are inverted, have not been broadly investigated. However, these compounds have occasionally been reported as part of general synthetic approaches to CNs (Scheme 1).[9]

These examples show that all-*cis* CNs can be formed, at least as minor products, during the synthesis of APIs (active pharmaceutical ingredients) in the pharmaceutical industry. Therefore, access to this scaffold is particularly important in drug development processes in order to determine their levels in APIs.

During the course of our research aimed at the synthesis of ticagrelor impurities, we developed a synthesis of all-*cis* **7** from previously reported carbocycle **8**. All-*cis* **7**, where the C-1 and C-4 stereocenters are inverted, is an analog of **9**, a key intermediate previously used in the synthesis of ticagrelor. We considered that with all-*cis* **7** in hand, all-*cis* ticagrelor may also be prepared (Scheme 2).

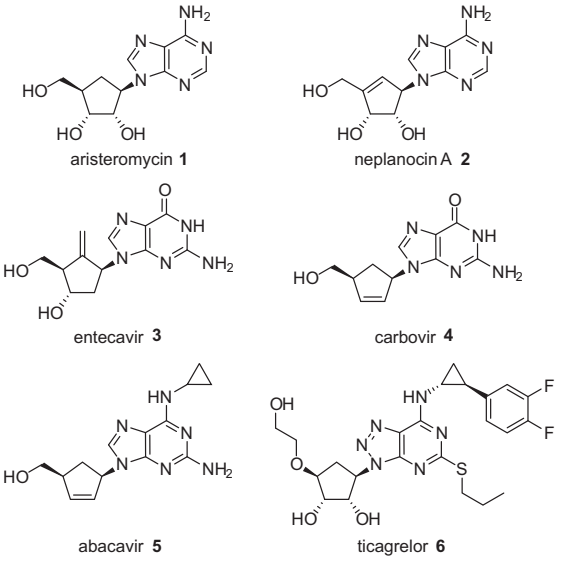

Figure 1. Selected carbocyclic nucleoside natural products and analogs.

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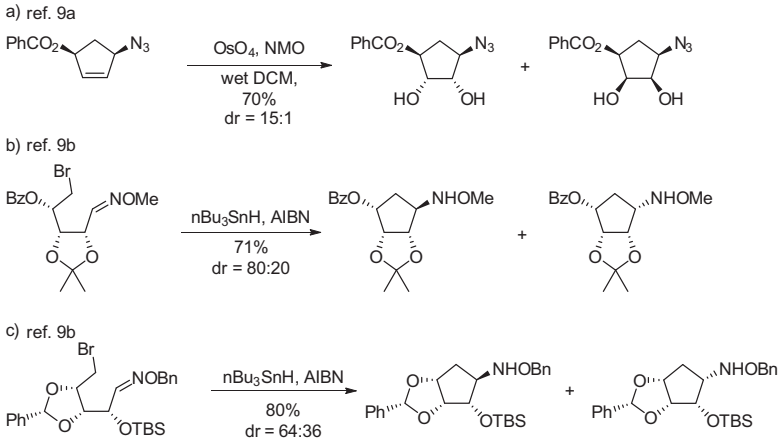
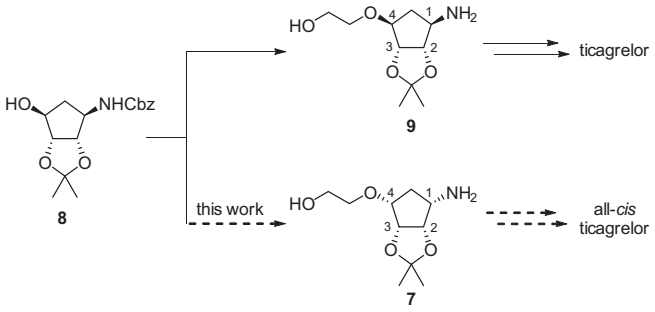
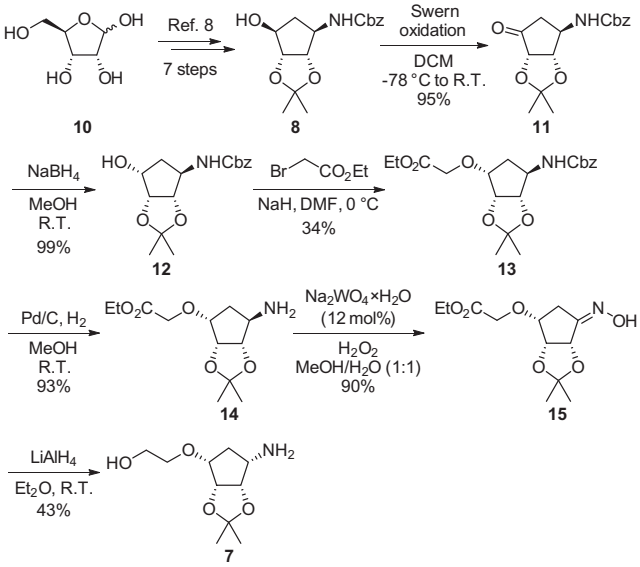


Scheme 1. Studies toward all-*cis* CNs.



Scheme 2. An outline of the study.



Scheme 3. Synthesis of all-*cis* **7**.

Results and discussion

Our strategy for inversion of the configuration at C-1 and C-4 involved oxidation of the C—O and C—N bonds to the ketone and imine, respectively, followed by reduction with metal hydrides. We envisioned that steric hindrance induced by the 1,3-dioxolane ring should preferentially favor exposure of one face of the cyclopentane ring to hydride attack (Fig. 2).

Our synthesis began with compound **8**, which was obtained from D-ribose (**10**) in 7 steps according to a previously published route.[8] The C-4 stereochemistry was inverted in two high yielding steps. First, the secondary alcohol was oxidized to ketone **11** under Swern conditions before reduction with $NaBH_4$ to exclusively afford alcohol **12**.

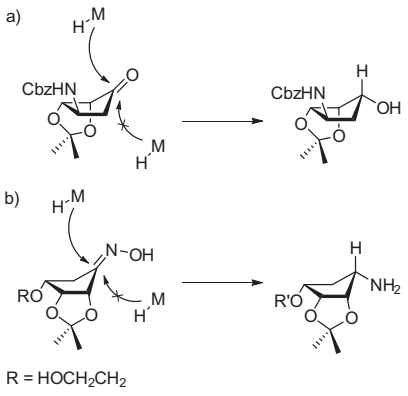


Figure 2. Proposed stereoselectivity for reduction of the C=O and C=N bonds.

Before transformation of the C—N bond to the C=N bond, the secondary alcohol was needed to be protected. The CH_2CO_2Et group was selected because it could be converted into the $HOCH_2$-CH_2 unit present in ticagrelor, during reduction of the C=N bond. Williamson etherification using ethyl bromoacetate proved to be a difficult transformation, giving **13** in only 34% yield. Presumably, both the steric hindrance of the secondary alcohol and the relatively acidic proton of the NHCbz group made this reaction difficult.

The Cbz protecting group was removed under standard conditions providing amine **14** in 93% yield which was smoothly converted, in a tungsten-catalyzed process[10] with hydrogen peroxide as the external oxidant, to oxime **15** in 90% yield. Reduction of both oxime and esters moieties in **15** with $LiAlH_4$ provided amine **7** in 43% yield (Scheme 3).

The stereochemistry of compounds **12** and **7** was assigned according to their ^1H and 2D NMR spectra and by comparison with the spectra of uninverted **8** and **9** (Fig. 3).

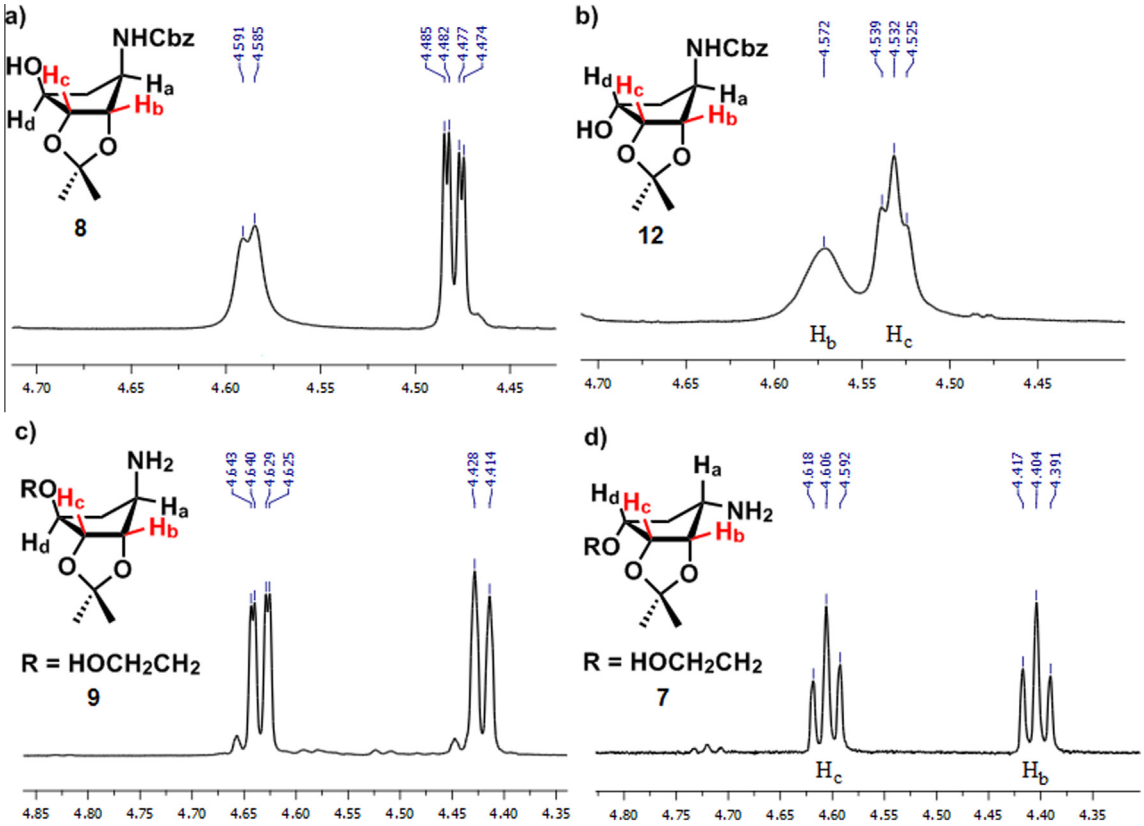


Figure 3. Stereochemistry determination by ^{1}H NMR.

Hydrogens H_b and H_c from the 1,3-dioxolane ring junction were diagnostic for determining the stereochemistry. In uninverted alcohol **8**, protons H_b and H_c gave a broad doublet (J = 4.2 Hz) and a doublet of doublets (J_1 = 5.6 Hz, J_2 = 2.1 Hz). Since the broad doublet at 4.59 ppm was not well resolved, differences between J coupling values from coupled hydrogens occurred. The COSY spectrum of **8** showed that neither H_a–H_b nor H_c–H_d proton pairs were coupled; therefore we could not determine which peak came from H_b or H_c (Fig. 3a). In alcohol **12**, however, with an inverted secondary alcohol, the dihedral angles H_c–C–C–H_d and H_c–C–C–H_b should have similar values and hence, J values for couplings H_c–H_d and H_c–H_b should also be similar. Indeed, H_c was a broad triplet with J = 4.9 Hz (Fig. 3b). This assignment was confirmed by 2D NMR spectra. The comparison of ^{1}H NMR spectra of **9** and **7** led to the conclusion that protons H_b and H_c in **7** must be *cis* to H_a and H_d as both H_b and H_c gave triplets (J = 5.2 Hz) (Fig. 3c and d).

Conclusion

In conclusion, we have reported a new and efficient method for the transformation of alcohol **8**, easily accessible from D-ribose, into all-*cis* **7**. This transformation was achieved by oxidation/reduction sequences applied to both the secondary alcohol and the primary amine. All-*cis* **7** obtained by this method may be used in the synthesis of an all-*cis* analog of ticagrelor. The stereochemistry of the inverted products was confirmed by ^{1}H NMR spectroscopy.

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Supplementary data

Supplementary data (methods, experimental procedures, and characterization data, as well as copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.074.

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