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Stereoselective Syntheses of 3′-Hydroxyamino- and 3′-Methoxyamino-2′,3′-Dideoxynucleosides

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ABSTRACT: Aminonucleosides are used as key motifs in medicinal and bioconjugate chemistry; however, existing strategies toward 3′-hypernucleophilic amines systems do not readily deliver deoxyribo-configured products. We report diastereoselective syntheses of deoxyribo- and deoxyxylono-configured 3′-hydroxyamino- and 3′-methoxyamino-nucleosides from 3′-imine intermediates. The presence or absence of the 5′-hydroxyl-group protection dictates facial selectivity via inter- or intramolecular delivery of hydride from BH₃ (borane). Protecting group screening gave one access to previously unknown 3′-methoxyamino-deoxyguanosine derivatives.

Scheme 1. Several Hydride-Transfer Agents Were Explored and Each Delivered Deoxyxylono-Configured Product 2 Exclusively

Sebesta et al.⁸ and Matsuda and co-workers¹⁰ successfully synthesized 2′-(alkoxyamino)uridines via the intramolecular nucleophilic substitution upon 2,2′-O-anhydrouridines derivatives. Thus, we attempted nucleophilic substitution at the 3′-position of 2,3′-anhydrothymidine with methoxylamine under a range of reaction conditions; however, surprisingly, we only observed a hydrolytic opening of the anhydro-linkage. Stereoselective reduction of 3′-keto nucleosides to ribonucleosides via intramolecular delivery of hydride, tethered through a free 5′-hydroxy group, has been reported.⁹ Moreover, Matsuda and co-workers¹⁰ reported that 3′-(hydroxyamino) uridine with a ribo-configuration 5a can be obtained from the corresponding 3′-hydroxyiminouridine 4a by treatment with NaBH₄/AcOH (Scheme 2). Thus, we...
attempted the reduction of imine 4b under similar conditions; however, poor conversion to 5b was observed (Scheme 2). This result aligns with the findings of Tronchet et al., who used NaBH₃CN upon 1 under acidic conditions to obtain low levels of the deoxyribomethoxyamino-product 5b as part of a complex mixture that prevented the isolation of pure material. We then explored the application of the borane-tetrahydrofuran complex for the reduction of 4b, which we expected to show higher reactivity and higher levels of conversion. To our delight, we obtained 3'-methoxyamino-thymidine 5b with the desired deoxyriboconfiguration exclusively in 72% yield (Scheme 3). We were also able to reduce protected imine 1 with BH₃·THF to give deoxoxylo-configured product 2 in a yield of 70%. We sought to confirm the absolute configurations of the deprotected 3'-methoxyamino-products 5b and 6 by 2D NMR spectroscopy. Unfortunately, the signals arising from the 3'-H [NCH-(OMe)], 4'-H (OCH), and the 5'-H (OCH₂OTBS) protons were overlapping in the ¹H NMR spectra, thus preventing clear assignments by NOESY correlations. We also attempted

Scheme 2. Stereoselective Reduction of Uridine-Based Oxime 4a₁b Is Observed but Not for the Thymidine Analog 4b

Scheme 3. Stereoselective Syntheses of Deoxyribo- and Deoxxylo-Configured 3'-Methoxyamino-Thymidines

"Arrows on structures 7 and 8 indicate observed NOESY correlations."
similar analyses using the 5′-TBS-protected systems 2 and 3; however, we encountered the same signal overlap problems. Thus, in order to increase the chemical shifts of the 5′-H signals and, to a lesser extent, 4′-H signals, we prepared 5′-tosyl derivatives 7 and 8. This strategy allowed us to distinguish and assign each of the proton signals around the sugar rings. The deoxyribo-isomer 7 did not show NOESY correlation between the 3′- and the 1′-protons, whereas correlations were clearly observed for the deoxyxylo-isomer 8. Additionally, in the case of deoxyribo-isomer 7, NOESY signals were observed between the 3′-proton and thymine nucleobase, along with the expected NOESY correlation between the 4′- and the 1′-protons. The xylo-isomer 8 also showed the expected 4′–1′ NOESY correlations.

In order to gain mechanistic insights into the proposed intramolecular hydride delivery via complexation of the boron to the free hydroxyl group at the 5′-position, we carried out 11B NMR experiments.10 The 5′-TBS protected thymidine imine 1 and deprotected 3′-methoxyimino thymidine 4b were treated with B(OMe)3 in THF-d8. Starting with the addition of 0.5 equiv of B(OMe)3, 11B NMR spectra were recorded for multiple additions of 0.5 equiv of B(OMe)3 up to 2.5 equiv. Figure 1 gives evidence for B–N complexation via the imine nitrogen of 5′-TBS-protected 3′-methoxyimino-thymidine 1 via a signal at 19.19 ppm, which persists even after overnight incubation with 2.5 equiv of B(OMe)3. In the case of the 5′-hydroxy 3′-methoxyimino-thymidine 4b, we observed two distinct signals at 22.98 ppm (RO–B–N) and 19.20 ppm that indicate the complexation of boron with the free hydroxyl group at the 5′-position and B–N complex, respectively (Figure 1).11 Taken together, these simple experiments support the idea of a critical role for 5′-OH complexation in the reduction of 4b to deliver the deoxyribo-configuration observed in 5b.

On the basis of our promising results with the thymidine system, we applied the same strategies to the adenosine and yadenosine system12 afforded the deoxyriboethoxymethyamine product 10 exclusively, which was derivatized at the 5′-position (Figure 2) to minimize conformational changes and, thus, confirm configuration (see the Supporting Information).14,1b

We then moved on to explore the application of our BH3-THF reduction strategies toward guanosine systems. Guanosine systems present significant synthetic challenges because of their poor solubility properties.13 With this in mind, we attempted reductions on the 5′-OTBS-N-isobutyroyl-protected methoxyimino-derivative of deoxyguanosine and the analogous 5′-OH system12 using BH3·THF. These reactions resulted in the reduction of the imines to the desired deoxyxylo-product (11b) and deoxyribo-product (11a) in 85% and 70% yield, respectively, but the isobutyroyl group was also reduced. Thus, we moved to a N-DMT-protected substrate, which tolerated BH3·THF to yield the deoxyribo-product 12 after TBS protection, as its tosic acid salt in 80% yield upon deprotection of the DMT group (Figure 3). The configurations of the derivatives of all guanosine products were confirmed by NOESY analysis of the 5′-derivatives (see the Supporting Information).

Next, we explored the BH3·THF reductions of 3′-hydroxymimino systems. The unprotected 3′-hydroxymimino-thymidine derivative14 13a was reduced by BH3·THF stereo-selectively to give deoxyribo-configured 14a15 as the major product alongside the deoxyxylo-derivative 14b16 in a 4:1 ratio, where the mixture could be separated by column chromatography. On the other hand, the 5′-TBS-protected 3′-hydroxymimino-thymidine derivative 13b1b afforded the deoxyxylo-product 1517 exclusively. The NMR spectra of the TBS-protected deoxyribo-derivative 16 and deoxyxylo-isomer 15 matched NMR data reported by Tronchet et al.26 (Scheme 4). This strategy was also successfully applied to deoxycytidine and deoxycytidines systems to afford mixtures of deoxyribo- and deoxyxylo-isomers, in ~4:1 ratios, which could also be isolated by chromatography. The products were derivatized to 17a, 17b, and 18 to minimize conformational equilibration14.
and thus allow differentiation between the deoxyribo- and deoxyxylo-products through NOESY assignments. Bis-TBS-protected 3′-hydroxyamino-cytidine derivative 17a exhibited NOESY correlations between the 3′-proton and the 6-(nucleobase)-proton, whereas the debenzoylated-deoxyxylo-derivative 17b exhibited 1′-H to 3′-H NOESY correlation. Similarly, the TBS-protected-deoxyribo-3′-hydroxyamino-adenosine 18 exhibited NOESY correlations between the protons 3′- and 8-H of the nucleobase (Figure 4).

Kojima et al. demonstrated that 3′-hydroxylamine systems can be further reduced to 3′-amines by Pd/C and hydrogen to afford 3′-amino-ribonucleoside analogs. We applied the same methodology to hydroxylamino-systems 14a and 15, and we were pleased to observe clean conversion to the corresponding amine systems 19 and 20 in 89% and 75% yield, respectively (Scheme 5).

In conclusion, we have developed efficient, direct strategies to obtain deoxyribo- and deoxyxylo-isomers of 3′-methoxyamino- and 3′-hydroxyamino-deoxynucleosides, from common

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**Scheme 4. Synthesis of Deoxyribo- and Deoxyxylo-Configured 3′-Hydroxyamino Thymidine Derivative**

**Scheme 5. Synthesis of 3′-Aminonucleoside Systems via Catalytic Reductions of Hydroxylamines**
intermediates, via stereoselective reductions of the corresponding 3′-imino deoxynucleosides using BH$_3$·THF. Our approach has delivered ribo-configured deoxynucleosides in good yields, which are otherwise difficult to obtain. To the best of our knowledge, the ribo-deoxycytidine derivative 9a, deoxyadenosine derivative 10, and ribo- and xylo-deoxyguanosine derivatives 11a–c and 12 containing the 3′-methoxyamino-functionality are novel compounds.

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