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De Novo Asymmetric Synthesis of Homo-Adenosine via a Palladium Catalyzed *N*-Glycosylation

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Abstract

A highly stereoselective synthesis of L-2-deoxy- β -ribo-hexopyranosyl nucleosides from 6-chloropurine and Boc-protected pyranone has been developed. Our approach relies on the iterative application of a palladium catalyzed *N*-glycosylation, diastereoselective reduction and reductive 1,3-transposition. This strategy is amenable to prepare various natural and unnatural hexopyranosyl nucleosides analogues.

The hexopyranosyl nucleosides make up a large and varied class of natural products (e.g. blasticidin,¹ gougerotin,² hikizimycin,³ mildiomycin,⁴ the bagougeramines,⁵ SF-2140,⁶ the pentopyranines,⁷ and miharamycin⁸). In addition to displaying intriguing structures, they also possess distinct biological activities.⁹ Inspired by these natural products, chemists have made two hexopyranosyl nucleosides 2-deoxy- β -D-ribo-hexopyranose adenosine (**1**)¹⁰ and 2,3-dideoxy- β -D-ribo-hexopyranose adenosine (**2**).¹¹ These homologous nucleosides of adenosine and deoxy-adenosine possess obvious structural and configurational similarities to the corresponding ribofuranose adenosines **3** and **4** (Figure 1). Biological studies of these ring-expanded analogues (**1** and **2**) have led to the discovery of several pyrano-nucleotide analogues with both antitumor and antiviral activity.^{10,11,12} The interest in analogs of **3** and **4** has also led to the development of many novel nucleoside structures with anticancer and/or antiviral activity.¹²

While there has been significant synthetic effort toward the synthesis of adenosine analogs,⁹ we were interested in preparing pyrano-analogues of this class of compounds from an achiral starting material using enantioselective catalysis to set the asymmetry (de novo synthesis). In addition, we were interested in a synthesis that allows for the diastereoselective installation of the base at C-1. Our retrosynthetic analysis of **1** and **2** was particularly influenced by Trost's de novo synthesis of the nucleosides.¹³

As part of our efforts working toward the de novo synthesis of carbohydrates, we discovered a palladium catalyzed glycosylation reaction that selectively converts 2-substituted 6-*t*-butoxycarboxy-2H-pyran-3(6H)-ones into 2-substituted 6-alkoxy-2H-pyran-3(6H)-ones with complete retention of configuration.¹⁴ This methodology has been extended toward the preparation of several natural/unnatural mono-, di- and trisaccharides.¹⁵ To test the breadth of this methodology, we set out to prepare various analogs of pyranose adenosines (**1** and **2**). To accomplish this goal, we needed to extend the palladium glycosylation reaction to nitrogen

nucleophiles (e.g. benzimidazole and purines).¹⁶ Herein we describe our successful efforts to prepare the homo-adenosine analogues **1** and **2**.¹⁷

We envisioned that both the homo-adenosine **1** and the deoxy-homo-adenosine **2** could be prepared from the β -pyranone **7**, which in turn could be prepared by a palladium catalyzed glycosylation of the β -Boc-pyranone **9** with chloropurine **8** (Scheme 1).¹⁸ A diastereoselective reduction of **7** should provide **6**, which could be converted into **2** by olefin reduction and replacement of the chlorine with ammonia. We imagined that the routes would diverge at allylic alcohol **6**. A Myers' reductive 1,3-transposition of allylic alcohol **6** should provide alkene **5**,¹⁹ which should be converted into homo-adenosine **1** via a diastereoselective dihydroxylation followed by amination.

In order to test the strategy, we carried out a model study using benzimidazole **10** and pyranone **11**. The Pd catalyzed *N*-glycosylation of benzimidazole **10** and pyranone **11** successfully gave the desired glycosylated pyranone **12a** and **12b** in good yield with complete stereo-control (Scheme 2).

Our initial attempts at post-glycosylation modification of these *N*-glycosides with the α -anomers were not encouraging. The pyranone **12a** was readily reduced to give the C-4 allylic alcohol **13a**. This reduction, however, occurred with less stereocontrol at C-4 (4:1) as compared to NaBH₄ reductions of pyranones with C-1 α -oxygen substituents.²⁰ Where the post-glycosylation chemistry for these *N*-glycosides diverged with the *O*-glycosides was during our attempts to modify the double bond of pyran **13a**. To our surprise all attempts to either dihydroxylate or reduce **13a** were unsuccessful.

To our relief, our difficulties with the α -anomer did not occur with the β -isomers (Schemes 4–7). Reduction of the pyranone **12b** using NaBH₄ at –78 °C gave exclusively allylic alcohol **13b**.²¹ Subjecting alcohol **13b** to Myers' reductive 1,3-transposition condition (NBSH, PPh₃/DEAD, NMM, –30 °C to rt) provided the rearranged olefin **14** in good yield (65%). Dihydroxylation of **14** using the Upjohn conditions (OsO₄/NMO) gave the diol **15** in 85% yield. In contrast to the oxidation chemistry, **13b** could also be reduced, although not in high yield. Thus exposing **13b** to excess diimide precursor (NBSH/Et₃N) gave the 2,3-dideoxy pyranose **16** in low yield (30%) but with good recovery of starting material (50%). While the yield of **16** was low, this procedure was superior to traditional hydrogenation (H₂, 5% Pd/C in MeOH), which occurred with complete hydrolysis of the C-1 benzimidazole.

These successful model studies inspired us to synthesize the adenosine analogues.¹⁷ Our synthesis commenced with the coupling of Boc protected pyranone **11b** and commercial available 6-chloropurine **8**. The pyranone **11b** was easily prepared in only 2 steps from furfural alcohol.^{14,15} Thus, Pd catalyzed coupling of **11b** and **8** give exclusively the 6-chloropurine glycosylated pyranone **17** in 86% yield (Scheme 5). Diastereoselective reduction of enone **17** with NaBH₄ at –78 °C provided the allylic alcohol **18** in 83% yield. The stereochemistry of the alcohol was assigned by analysis of coupling constants (e.g. J_{H4-H5} = 7.8 Hz).

With this advanced intermediate **18** in hand, efforts were taken to reductively rearrange the allylic alcohol into olefin **19**. Exposing allylic alcohol **18** to the Myers' reductive rearrangement conditions (NBSH, PPh₃/DEAD, NMM, –30 °C to rt) provided olefin **19** in 51% yield (Scheme 6). Dihydroxylation of the olefin **19** under Upjohn conditions (OsO₄/NMO) exclusively gave the diol product **20** (95%), which when exposed to ammonia in methanol (room temperature for 48 hr) gave amine **21** in 77% yield. Finally, the silyl ether was deprotected with TBAF to give the desired 2-deoxy- β -L-ribo-hexopyranose (*ent*)-**1** (94%).

Commencing with the same advance intermediate **18**, another adenosine analogue homo-2'-deoxyadenosine (*ent*)-**2** was also synthesized (Scheme 7). The allylic alcohol **18** was exposed

to the diimide reduction conditions (NBSH, Et₃N) giving the desired reduced alcohol in very low yield. We envisioned that the 6-chloro group in the purine ring may be a problem and decided to carry out the amination first. Thus the allylic alcohol **18** was treated with NH₃/MeOH to afford the amine **22** in 81% yield. The diimide reduction of olefin **22** gave the reduced product **23** (35%, with 55% recovered starting material). Finally, TBS-deprotection with TBAF provided the 2,3-dideoxy- β -L-ribo-hexopyranose (*ent*)-**2** in good yield (98%). By switching the reaction sequence (TBAF then diimide), a slightly higher yielding approach to (*ent*)-**2** was achieved (39% for the two steps).

In summary, a highly enantio- and diastereoselective procedure for the preparation of hexopyranose adenosine analogues has been developed. The 2-deoxy- β -L-ribo-hexopyranose (*ent*)-**1** was synthesized only in 6 steps and 2,3-dideoxy- β -L-ribo-hexopyranose (*ent*)-**2** was prepared in 5 steps from Boc-protected pyranone (9 and 8 steps from an achiral acylfuran, respectively). In addition to being the first synthesis of the L-sugar forms of **1** and **2**, this synthesis is the first to diastereoselectively install the purine base at the anomeric center.^{10, 11, 12} The synthesis of other potential analogues and evaluation of the biological activity of these compounds are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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16. For the Pd-catalyzed N-glycosylation of indolocarbrazoles, see: Trost BM, Krische MJ, Berl V, Grenzer EM. *Org Lett* 2002;4:2005–2008. [PubMed: 12049503]
17. While our approach has the flexibility to prepare either D- or L-pyranonosides, we targeted the L-enantiopodes of both 1 and 2 (i.e. (*ent*)-1 and (*ent*)-2), because of our interest in comparing the antitumor activity of (*ent*)-1 to 1.
18. Pyranones like 9 can be prepared in three steps from acylfuran 25. Not only can 9 be easily prepared in either enantiomeric form (D/L) but also in its α - or β -configuration, see: ^{ref. 15c} and Li M, Scott JG, O'Doherty GA. *Tetrahedron Lett* 2004;45:1005–1009.

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20. The differences in the stability and post-glycosylation modification in the α - and β -benzimidazole glycosides as well as the comparison to the O-glycosides are not without precedent. Similar phenomena for anomeric imidazoles have been described as a reverse anomeric effect, see: (a) Randell KD, Johnston BD, Green DF, Pinto BM. *J Org Chem* 2000;65:220–226. [PubMed: 10813919] (b) Vaino AR, Szarek WA. *J Org Chem* 2001;66:1097–1102. [PubMed: 11312934]
21. This came to us as a surprise because previously we have found that the NaBH₄ reduction of 6-alkoxy- β -pyran-2-ones produces a mixture of diastereomers, see: Zhou, M.; O'Doherty, G. A., unpublished results.

Figure 1.
Adenosines and hexopyranosyl nucleosides

Scheme 1.
Retrosynthetic analysis of adenosine analogs

Scheme 2.
Pd catalyzed *N*-glycosylation, model study

Scheme 3.
Post-glycosylation modification of **12α**

Scheme 4.
Post-glycosylation modification of **12β**

Scheme 5.
Enantioselective synthesis of allylic alcohol **18**

Scheme 6.
Enantioselective synthesis of homo-adenosine

Scheme 7.
Enantioselective synthesis of homo-2'-deoxyadenosine **2**