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

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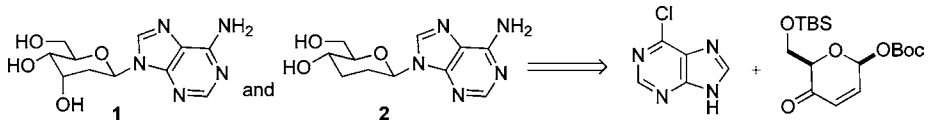
ABSTRACT



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 miharamycin[8]). 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 deoxyadenosine possess obvious structural and configurational similarities to the corresponding ribofuranose adenosines **3** and **4** (Figure 1).

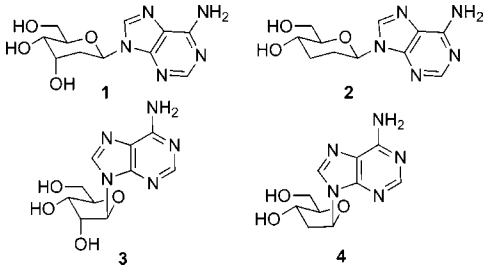


Figure 1. Adenosines and hexopyranosyl nucleosides.

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.[10−12] The interest in analogues of **3** and **4** has also led to the development of many novel nucleoside structures with anticancer and/or antiviral activity.[12]

(1) Onuma, S.; N., Y.; Saito, Y. *Bull. Chem. Soc. Jpn*. **1966**, *39*, 1091. For its synthesis, see: Nomoto, S.; Shimoyama, A. *Tetrahedron Lett.* **2001**, *42*, 1753−1755.

(2) (a) Fox, J. J.; Kuwada, Y.; Watanabe, K. A.; Ueda, T.; Whipple, E. B. *Antimicrob. Agents Chemother*. **1964**, 518−529. (b) For its synthesis, see: Watanabe, K. A.; Falco, E. A.; Fox, J. J. *J. Am. Chem. Soc.* **1972**, *94*, 3272−3274.

(3) Ennifar, S.; Das, B. C.; Nash, S. M.; Nagarajan, R. *J. Chem. Soc., Chem. Commun.* **1977**, 41−42. For its synthesis, see: (b) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657−9659. (c) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524−2536.

(4) Harada, S.; Mizuta, E.; Kishi, T. *J. Am. Chem. Soc.* **1978**, *100*, 4895−4897.

(5) Takahashi, A.; Ikeda, D.; Naganawa, H.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1986**, *39*, 1041−1046.

(6) (a) Ito, T.; Ohba, K.; Koyama, M.; Sezaki, M.; Tohyama, H.; Shomura, T.; Fukuyasu, H.; Kazuno, Y.; Niwa, T.; Kojima, M.; Niida, T. *J. Antibiot*. **1984**, *37*, 931−934. (b) For its synthesis, see: Buchanan, J. G.; Stoddart, J.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, *11*, 1417−1426.

(7) (a) Watanabe, K. A.; Matsuda, A.; Itoh, T. *Can. J. Chem.* **1981**, *59*, 468−472. (b) For its synthesis, see: Watanabe, K. A.; Matsuda, A.; Itoh, T. *Can. J. Chem*. **1981**, *59*, 468−72.

(8) Seto, H.; Koyama, M.; Ogino, H.; Tsuruoka, T.; Inouye, S.; Otake, N. *Tetrahedron Lett.* **1983**, *24*, 1805−1808. (b) For synthetic efforts toward miharamycin, see: Czernecki, S.; Franco, S.; Horns, S.; Valery, J.-M. *Tetrahedron Lett.* **1996**, *37*, 4003−4006.

(9) *Recent Advances in Nucleosides: Chemistry and Chemotherapy*; Chu, C. K., Ed.; Elsevier Science: Amsterdam, 2002.

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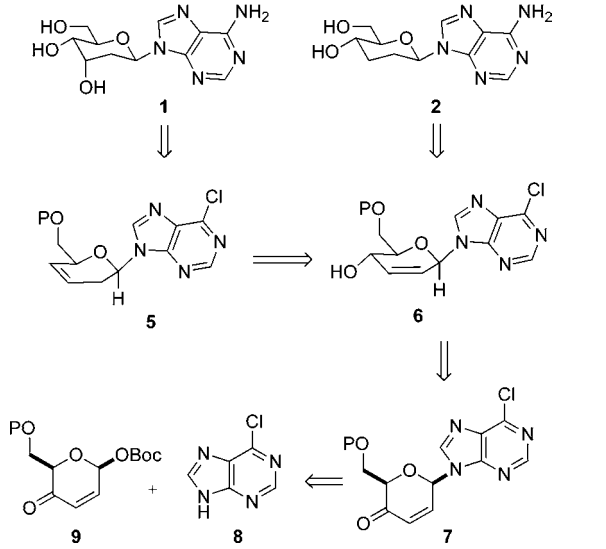
While there has been significant synthetic effort toward the synthesis of adenosine analogues,[9] we were interested in preparing pyrano-analogues of this class of compounds from an achiral starting material using enantioselective catalysis to set the asymmetry (de novo synthesis). In addition, we were 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-*tert*-butoxycarboxy-2*H*-pyran-3(6*H*)-ones into 2-substituted 6-alkoxy-2*H*-pyran-3(6*H*)-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 analogues 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 homoadenosine analogues (***ent***)-**1** and (***ent***)-**2**.[17]

We envisioned that both the homoadenosine **1** and the deoxyhomoadenosine **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

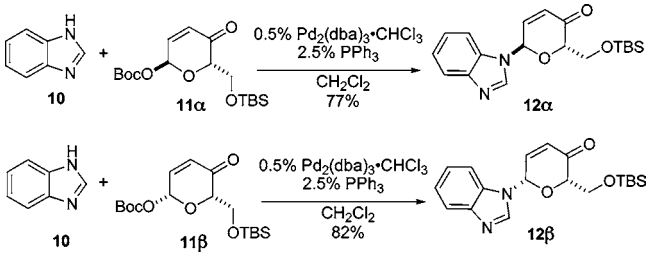
Scheme 1. Retrosynthetic Analysis of Adenosine Analogues



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 homoadenosine **1** via a diastereoselective dihydroxylation followed by amination.

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 **12**α and **12**β in good yield with complete stereocontrol (Scheme 2).

Scheme 2. Pd-Catalyzed *N*-Glycosylation: Model Study



Our initial attempts at post-glycosylation modification of these *N*-glycosides with the α-anomers were not encouraging. The pyranone **12**α was readily reduced to give the C-4 allylic alcohol **13**α. This reduction, however, occurred with less stereocontrol at C-4 (4:1) as compared to $NaBH_4$ reductions of pyranones with C-1 α-oxygen substituents.[20] The post-glycosylation chemistry for these *N*-glycosides diverged with the *O*-glycosides during our attempts to modify the double bond of pyran **13**α. To our surprise, all attempts to either dihydroxylate or reduce **13**α were unsuccessful (Scheme 3).

(10) (a) Nord, L. D.; Dalley, N. K.; McKernan, P. A.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1044−54. (b) Zorbach, W. W.; Saeki, S. *J. Org. Chem.* **1964**, *29*, 2018−2019.

(11) For the synthesis of **2**, see ref 12 and: Groebke, K.; Hunziker, J.; Fraser, W.; Peng, L.; Diederichsen, U.; Zimmermann, K.; Holzner, A.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta* **1998**, *81*, 375−474.

(12) (a) Leutzinger, E. E.; Meguro, T.; Townsend, L. B.; Shuman, D. A.; Schweizer, M. P.; Stewart, C. M.; Robins, R. K. *J. Org. Chem.* **1972**, *37*, 3695−3703. (b) Boehringer, M.; Roth, H. J.; Hunziker, J.; Goebel, M.; Krishnan, R.; Giger, A.; Schweizer, B.; Schreiber, J.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta* **1992**, *75*, 1416−1477.

(13) (a) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3037−3038. (b) For carbacyclic analogues, see: Trost, B. M.; Madsen, R.; Guile, S. D.; Elia, A. E. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1569−1572. (c) Trost, B. M.; Madsen, R.; Guile, S. D. *Tetrahedron Lett.* **1997**, *38*, 1707−1710.

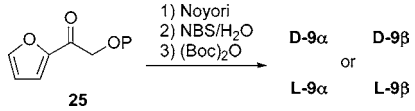
(14) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406−12407.

(15) (a) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428−3429. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921−3924. (c) Babu, R. S.; O'Doherty, G. A. *J. Carbohydr. Chem.* **2005**, *24*, 169−177.

(16) For the Pd-catalyzed *N*-glycosylation of indolocarboazoles, see: Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005−2008.

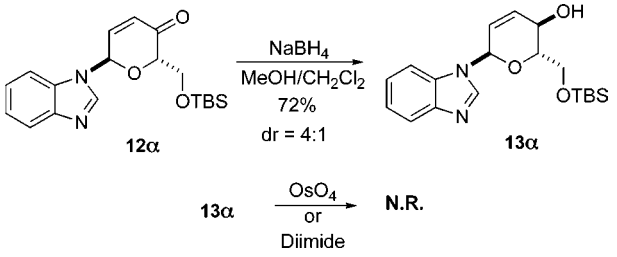
(17) While our approach has the flexibility to prepare either D- or L-pyranonosides, we targeted the L-enantiopodes of both **1** and **2** (i.e., **(*ent*)-1** and **(*ent*)-2**), because of our interest in comparing the antitumor activity of **(*ent*)-1** to **1**.

(18) Pyranones such as **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, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005−1009.



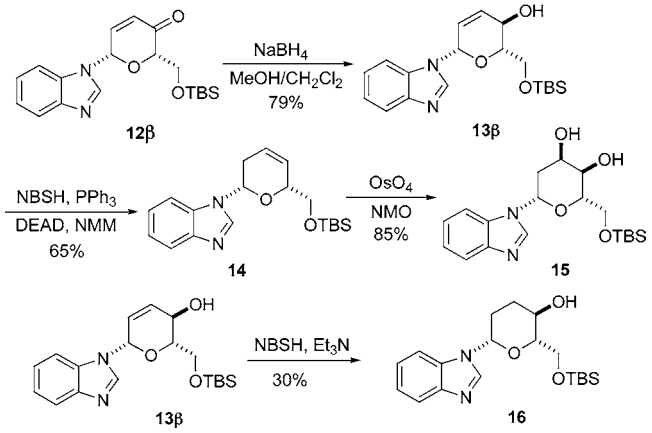
(19) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492−4493. (b) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841−4844. (c) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

Scheme 3. Post-Glycosylation Modification of **12**α



To our relief, our difficulties with the α-anomer did not occur with the *β*-isomers (Schemes 4−7). Reduction of the

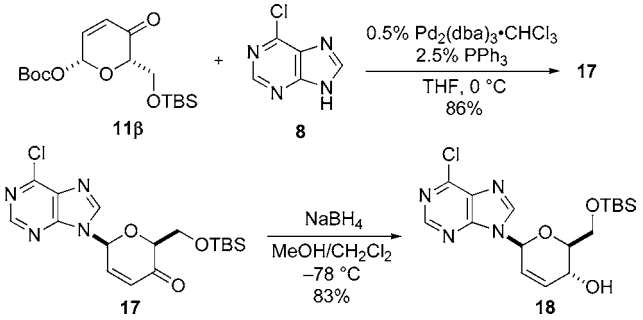
Scheme 4. Post-Glycosylation Modification of **12***β*



pyranone **12***β* using $NaBH_4$ at −78 °C gave exclusively allylic alcohol **13***β*.[21] Subjecting alcohol **13***β* to Myers' reductive 1,3-transposition condition (NBSH, PPh_3/DEAD, NMM, −30 °C to rt) provided the rearranged olefin **14** in good yield (65%). Dihydroxylation of **14** using the Upjohn conditions (OsO_4/NMO) gave the diol **15** in 85% yield. In contrast to the oxidation chemistry, **13***β* could also be reduced, although not in high yield. Thus, exposing **13***β* to excess diimide precursor (NBSH/Et_3N) gave the 2,3-dideoxypyranose **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 (H_2, 5% Pd/C in MeOH), which occurred with complete hydrogenolysis 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 **11***β* and commercial available 6-chloropurine **8**. The pyranone **11***β* was easily prepared in only two steps from furfural alcohol.[14,15] Thus, Pd-catalyzed coupling of **11***β* and **8** gave exclusively the 6-chloropurine glycosylated pyranone **17** in 86% yield (Scheme 5). Diastereoselective reduction of enone **17** with

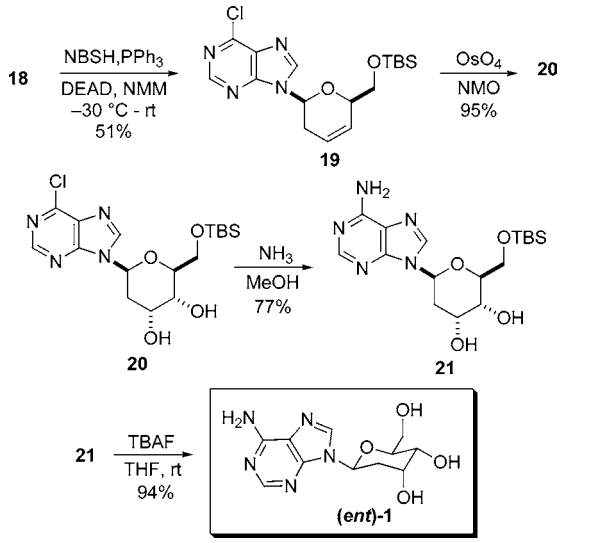
Scheme 5. Enantioselective Synthesis of Allylic Alcohol **18**



$NaBH_4$ 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, PPh_3/DEAD, NMM, −30 °C to rt) provided olefin **19** in 51% yield (Scheme 6).

Scheme 6. Enantioselective Synthesis of Homoadenosine



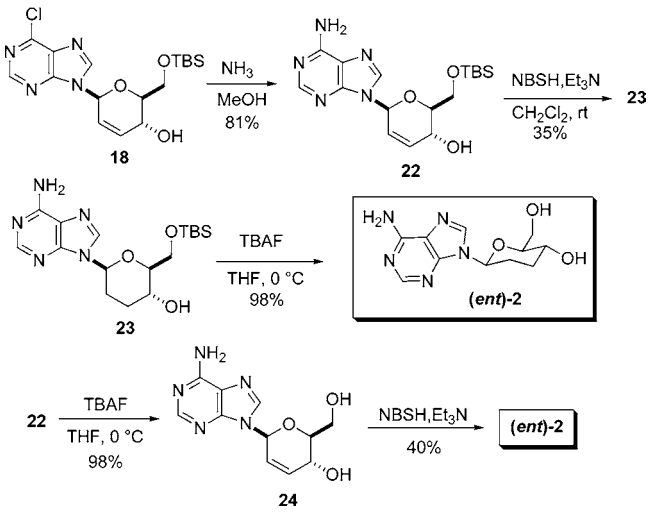
Dihydroxylation of the olefin **19** under Upjohn conditions (OsO_4/NMO) exclusively gave the diol product **20** (95%), which when exposed to ammonia in methanol (room temperature for 48 h) gave amine **21** in 77% yield. Finally, the silyl ether was deprotected with TBAF to give the desired 2-deoxy-*β*-L-*ribo*-hexopyranose **(*ent*)-1** (94%).

Commencing with the same advance intermediate **18**, another adenosine analogue homo-2′-deoxyadenosine **(*ent*)-2**

(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, K. D.; Johnston, B. D.; Green, D. F. and Pinto, B. M. *J. Org. Chem.* **2000**, *65*, 220−226. (b) Vaino, A. R.; Szarek, W. A. *J. Org. Chem.* **2001**, *66*, 1097−1102.

(21) This came to us as a surprise because previously we have found that the $NaBH_4$ reduction of 6-alkoxy-*β*-pyran-2-ones produces a mixture of diastereomers; see: Zhou, M.; O'Doherty, G. A. Unpublished results.

Scheme 7. Enantioselective Synthesis of Homo-2′-deoxyadenosine **2**



was also synthesized (Scheme 7). The allylic alcohol **18** was exposed to the diimide reduction conditions (NBSH, Et_3N) 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 NH_3/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 six steps and 2,3-dideoxy-β-L-*ribo*-hexopyranose **(*ent*)-2** was prepared in five steps from Boc-protected pyranone (nine and eight 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.[10−12] The synthesis of other potential analogues and evaluation of the biological activity of these compounds are ongoing.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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