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A Regio- and Stereocontrolled Approach to Pyranosyl *C*-Nucleoside Synthesis

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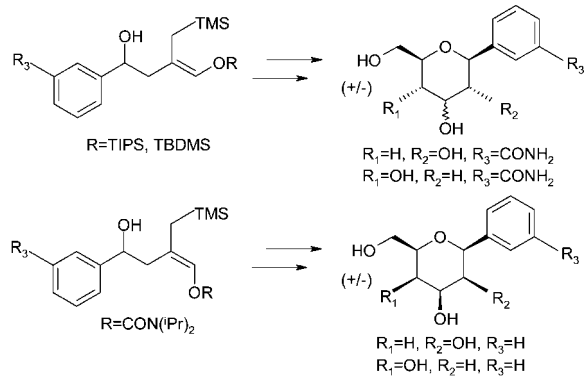
ABSTRACT



Six novel diastereomerically pure *C*-nucleosides have been synthesized from nonchiral starting materials, using the ene/intramolecular Sakurai cyclization reaction demonstrating a simple, general, and stereocontrolled approach to pyranosyl *C*-nucleosides.

C-Nucleosides form a unique class of nucleosides in which the glycosidic C−C bond between the sugar moiety (usually ribose) and heterocycle is resistant to chemical and enzymatic cleavage. *C*-Nucleosides, such as benzamide riboside **1** and tiazofurin **2** (Figure 1), are precursors to inhibitors of nicotinamide adenine dinucleotide (NAD) dependent enzymes such as oxidoreductases[1] and glycohydrolases,[2,3] being converted to dinucleotide cofactor analogues such as **3** (Figure 1).[4]

For instance, inosine monophosphate dehydrogenase (IMPDH), the enzyme which catalyzes the NAD-dependent conversion of inosine 5′-monophosphate (IMP) to guanosine 5′-monophosphate (GMP), is key to the synthesis of guanine nucleotides.[5] It has been discovered that human IMPDH exists as two isoforms, types I and II. The level of IMPDH activity is much greater in several tumors as compared with

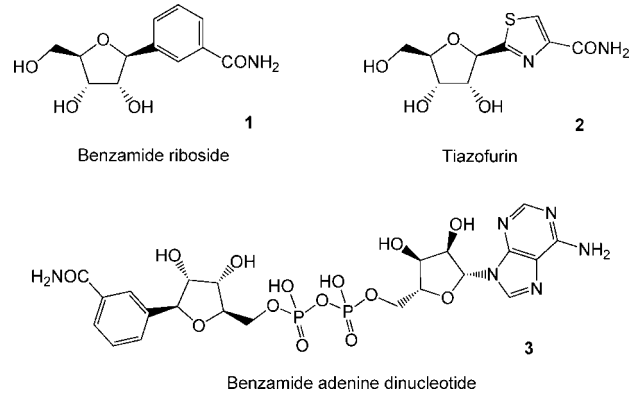


Figure 1. Known antiproliferative agents.

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(1) Jager, W.; Salamon, A.; Szekeres, T. *Cur. Med. Chem.* **2002**, *9*, 781.
(2) Migaud, M. E.; Pederick, R. L.; Bailey, V. C.; Potter, B. V. L. *Biochemistry* **1999**, *38*, 9105.
(3) Batoux, N. E.; Paradisi, F.; Engel, P. C.; Migaud, M. E. *Tetrahedron* **2004**, *60*, 6609.
(4) Gharehbaghi, K.; Grunberger, W.; Jayaram, H. N. *Curr. Med. Chem.* **2002**, *9*, 743.

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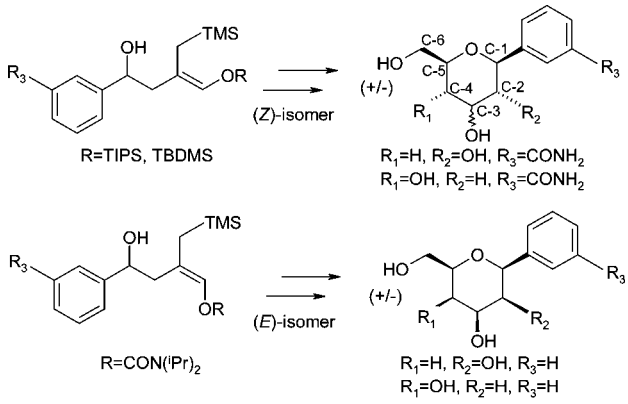
normal tissue[5] with the up-regulation of the type II isoform in these rapidly replicating cells. Selective inhibition of this dominant species, with reduced toxicity toward type I, would be antiproliferative. Agents, such as benzamide riboside **1**, are very potent antiproliferatives but also display high cytotoxic activity toward healthy cells.[4] Consequently, it is essential to synthesize novel *C*-nucleosides that possess structural diversity to increase specific recognition in order to optimize enzyme and cell selectivity and maintain high levels of inhibition. Our focus is therefore on obtaining benzamide riboside analogues that will be incorporated as nicotinamide adenine dinucleotide mimics with potential to be selective inhibitors of IMPDH. Although a number of routes exist for the preparation of *C*-nucleosides, their scope is very limited and lengthy.[6–10] Herein, we report our initial results in the establishment of a novel and stereocontrolled route for the construction of a range of diastereomerically pure pyranosyl *C*-nucleosides.

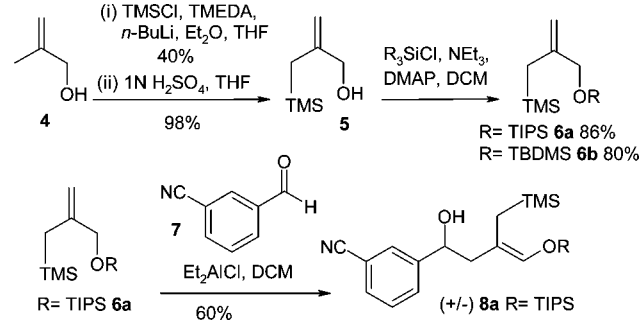
Recently, Markó developed an efficient procedure for the preparation of diastereomerically pure *exo*-methylene pyrans, using the tandem ene/intramolecular Sakurai cyclization (IMSC) of aldehydes with an allylsilane or an allylcarbamate.[11–15] This route, which offers great potential to a wide range of D/L nucleoside analogues incorporating the essential C−C glycosidic bond, has never before been applied to the preparation of nucleoside mimetics (Scheme 1).[16]

Scheme 1. Generic Structures of Synthetic Targets



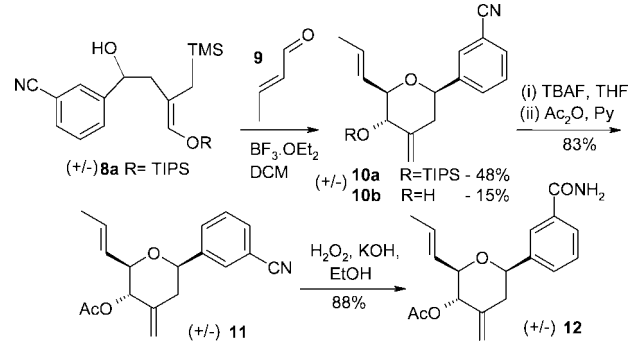
Starting from the allyl alcohol **4**, our initial strategy involved the synthesis of allylsilane **5** in bulk using Trost's conditions. The latter uses *n*-butyllithium and tetramethylethyldiamine as base to deprotonate methallyl alcohol **4** and traps the resulting carbanion with chlorotrimethylsilane.[17] Allylsilane **5** was obtained in modest yields, with media polarity critically affecting the outcome. Introduction of a triisopropylsilyl (TIPS) moiety on compound **6** was required in order to achieve higher yields in the subsequent synthetic steps. The ene-reaction of allylsilane **6a** with 3-cyanobenzaldehyde **7**, promoted by diethylaluminium chloride (Et_2AlCl) led to the (*Z*)-homoallylic alcohol **8a** with complete control of the double bond geometry (Scheme 2).[11]

Scheme 2. Ene Reaction



Subsequent condensation with an appropriate second aldehyde thereafter provided the framework for the desired *C*-nucleoside (Scheme 3) due to the pseudoequatorial positions adopted by the silyloxy and cyanoaromatic ring in the oxycarbonium chairlike transition state.[11] However, the hydroxymethylene moiety that would be introduced at the C5-position of the *exo*-methylene pyrans could not directly be set in place in good yields due to the lack of reactivity of α-hydroxyaldehydes toward the IMSC.[11]

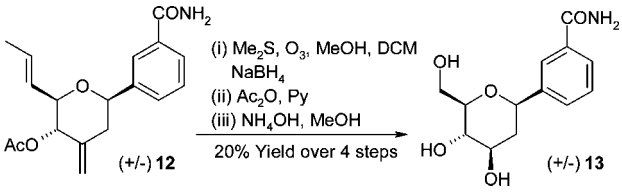
Scheme 3. IMSC with Crotonaldehyde



(5) Chen, L.; Petrelli, R.; Felczak, K.; Gao, G.; Bonnac, L.; Yu, J. S.; Bennett, E. M.; Pankiewicz, K. W. *Curr. Med. Chem.* **2008**, *15*, 650.
(6) Krohn, K.; Dorner, H.; Zukowski, M. *Curr. Med. Chem.* **2002**, *9*, 727.
(7) Ramesh, N. G.; Balasubramanian, K. K. *Eur. J. Org. Chem.* **2003**, *23*, 4477.
(8) Schramm, V. L.; Tyler, P. C. *Curr. Top. Med. Chem.* **2003**, *3*, 525.
(9) Franchetti, P.; Cappellacci, L.; Grifantini, M.; Jayaram, H. N.; Goldstein, B. M. *ACS Symp. Ser.* **2003**, *839*, 212.
(10) Shaban, M. A. E.; Nasr, A. Z. *Adv. Heterocycl. Chem.* **1997**, *68*, 223.
(11) Markó, I. E.; Dumeunier, R.; Leclercq, C.; Leroy, B.; Plancher, J. M.; Mekhalfia, A.; Bayston, D. J. *Synthesis—Stuttgart* **2002**, 958.
(12) Leroy, B.; Markó, E. I. *Tetrahedron Lett.* **2001**, *42*, 8685.
(13) Leroy, B.; Markó, E. I. *Tetrahedron Lett.* **2000**, *41*, 7225.
(14) Pospisil, J.; Kumamoto, T.; Marko, I. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3357.
(15) Leroy, B.; Markó, E. I. *J. Org. Chem.* **2002**, *67*, 8744.
(16) For clarity purposes, carbohydrate numbering has been used in the text C-1 corresponding to the etheral carbon linked to benzamide.
(17) Trost, B. M.; Chan, M. D. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.

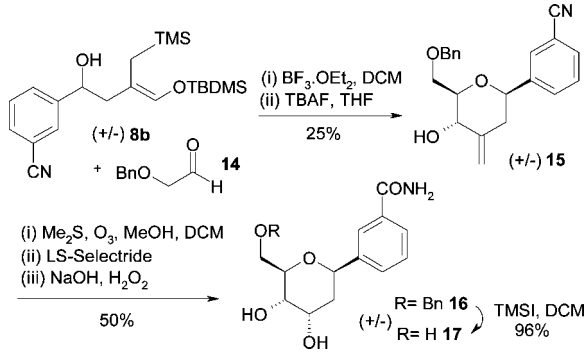
Hence, **8a** was cyclized with crotonaldehyde **9** activated by BF_3•OEt_2, which was the most proficient Lewis acid at catalyzing this synthetic step. The diastereomerically pure silyl-protected *exo*-methylene tetrahydropyran **10a** was obtained along with the free alcohol **10b**. Deprotection using tetrabutylammonium fluoride (TBAF) and subsequent reprotection (for handling purposes) of the crude mixture using acetic anhydride in pyridine led to dialkene **11**. The amide functionality was then introduced by base-mediated hydrolysis of the nitrile in **11** (Scheme 3). The hydroxyl groups at C-6 and C-3 were introduced by oxidative cleavage of the alkenes in **12** followed by reduction of the dicarbonyl intermediate. Subsequent acetylation of these hydroxyls, purification, and acetyl removal then yielded the final *C*-nucleoside **13** in 20% overall yield over four steps (Scheme 4).[18]

Scheme 4. Synthesis of Benzamide Riboside Analogue **13**



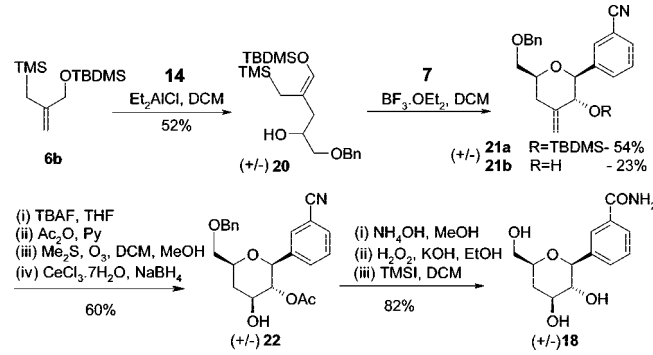
The IMSC was attempted with α-benzyloxyacetaldehyde **14**, knowing that the electron-withdrawing nature of the α-hydroxy substituent would hinder the cyclization pathway.[11] Indeed, as anticipated, the IMSC reaction did occur in low yields and provided a mixture of silylated and desilylated material. In situ removal of the *tert*-butyldimethylsilyl (TBDMS) moiety provided the *exo*-methylene tetrahydropyran **15** in 25% yield over two steps. This tetrahydropyran was then ozonized to give an isolable ketone intermediate that was selectively reduced with LS-Selectride; hydration of the nitrile occurred during workup to produce **16**. Cleavage of the benzyl ether at O-6 with TMSI yielded the *syn*-configured *C*-nucleoside **17** (Scheme 5).

Scheme 5. Stereocomplementary *Syn*-Configuration **17**



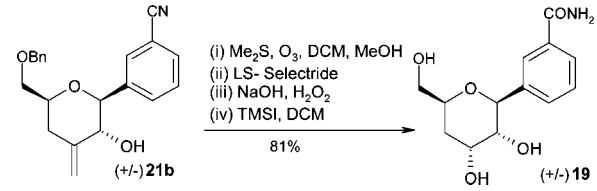
In order to access the regioisomers **18** and **19**, the sequence of aldehyde addition was exchanged. The α-benzyloxyacetaldehyde **14** underwent the ene reaction with allylsilane **6b** to give the (*Z*)-alkene intermediate **20** in satisfactory yields. The benzamide pyrans **21a** and **21b** were then obtained by IMSC with 3-cyanobenzaldehyde **7** (Scheme 6).

Scheme 6. Synthesis of Regioisomer **18**



Repetition of the procedures used for the synthesis of the previous analogues, including selective reduction of a ketone using sodium borohydride and cerium trichloride yielded the *C*-nucleoside **18** (Scheme 6). The 2,3-*syn*-triol **19** was also obtained quite readily (Scheme 7).

Scheme 7. Synthesis of Regioisomer **19**



Attention now turned to constructing the 1,2-*syn* and 4,5-*syn* stereoisomers **23** and **24** (Figure 2). Using the described ene-silyl chemistry, these isomers were not obtainable, as this methodology was exclusive to the (*Z*)-isomer, as described by Markó.

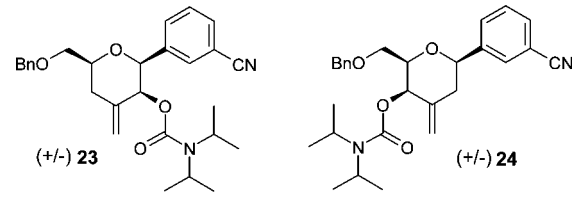


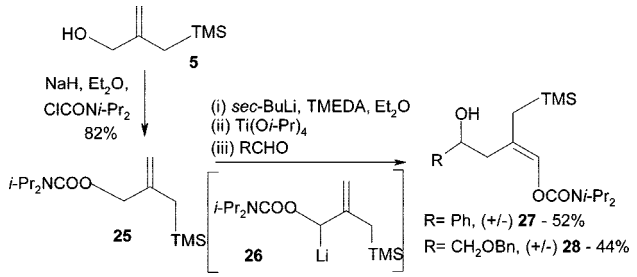
Figure 2. 1,2-*syn*-**23** and 4,5-*syn*-**24** stereoisomers.

Instead, Markó's group adopted an allyl-metalation protocol to achieve this type of stereochemistry.[15] Using this

(18) Stereochemistry determined by NOE studies and *J* values from ^{1}H NMR.

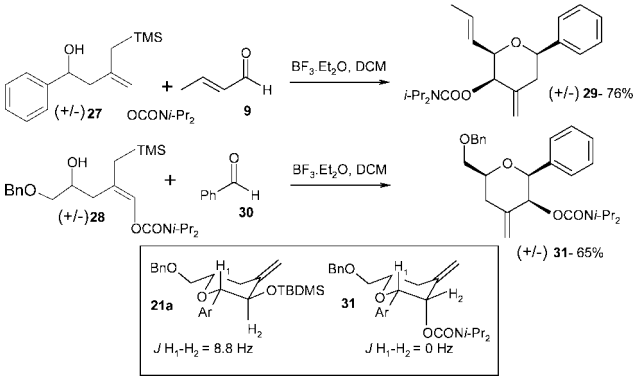
procedure, allylsilane **5** was condensed with diisopropylcarbamoyl chloride to obtain **25**. The lithiated species **26** was treated with titanium tetraisopropoxide followed by benzaldehyde or α-benzyloxyacetaldehyde to access **27** and **28**, respectively (Scheme 8). The enol carbamates **27** and **28** were

Scheme 8. Ene-ICMS Strategy Using Carbamate Intermediate



isolated as single geometric (*E*)-isomers that smoothly underwent IMSC with crotonaldehyde **9** to give **29** and with benzaldehyde **30** to give **31**, respectively. ^{1}H NMR assignments helped support the nature of each stereoisomer; they were consistent with the literature, and the geometries of the starting enol ethers (Scheme 9).[11–15] Ozonolysis and

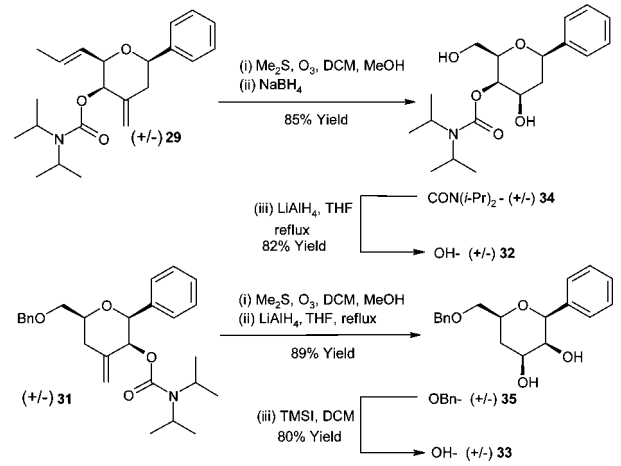
Scheme 9. Pyran **29** and **31** via IMSC



reduction of the *exo*-cyclic alkenes in carbamates **29** and **31** proceeded much more efficiently compared with the corresponding silyl derivatives. Unfortunately, lithium aluminum hydride was the only reagent that could effectively remove the carbamate protecting group from the C-2 or C-4 position of the tetrahydropyrans. It is, however, incompatible with nitrile functionality.[15]

As a consequence, the amide functionality was difficult to introduce or maintain throughout the synthesis when using the carbamate-promoted ene-ICMS chemistry to access the benzamide riboside derivatives from **23** and **24**. Alternative synthetic sequences and oxazoline chemistry are currently under investigation to overcome this difficulty. Compound **32** possessing a 3,4-*syn* stereochemistry, and its counterpart, compound **33** possessing a 2,3-*syn* stereochemistry were two isomers synthesized using this sequence. Work is currently being carried out to obtain the *anti*-configured isomers (Scheme 10).

Scheme 10. Synthesis of Isomers **32** and **33**



In summary, we have applied an established methodology to a new synthetic purpose: the preparation of racemic D/L pyranosyl *C*-nucleosides. Consequently, the first simple, general, and stereocontrolled approach to these nucleosides has been realized. With ongoing work, this approach should broaden the methodologies available for novel *C*-nucleoside synthesis. Notwithstanding their racemic nature, these benzamide riboside analogues have potential antiproliferative activity. Those best mimicking nicotinamide riboside are likely to offer crucial information on enzyme-NAD recognition processes and enhance our knowledge of their biological and conformational importance and assist in future rational drug design.

Acknowledgment. This work was supported by DEL and GSK.

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

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