A Deoxygenative [1,2]-Hydride Shift Rearrangement Converting Cyclic *cis*-Diol Monotosylates to Inverted Secondary Alcohols[1]

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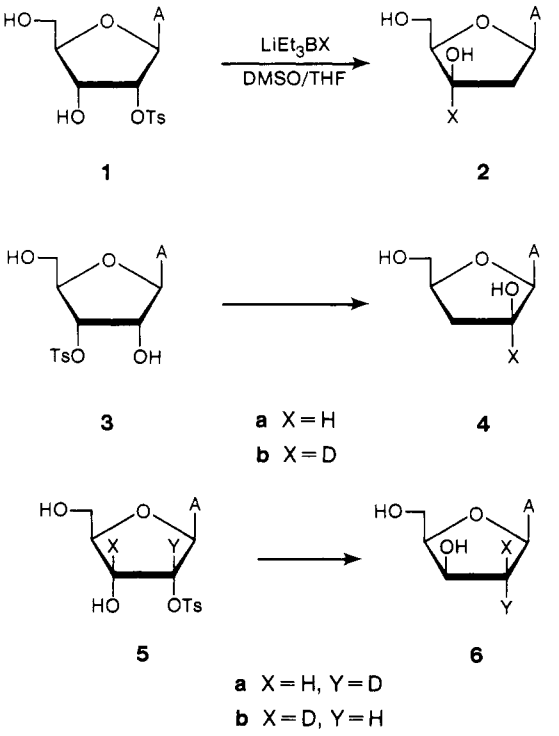
The component entry step for de novo biosynthesis of DNA involves 2'-deoxygenation of ribonucleoside di- or triphosphates by ribonucleotide reductase enzyme complexes.[2] We now report a high-yield stereoselective deoxygenative rearrangement of ribonucleoside 2'(or 3')-monotosylates to give the inverted 2'(or 3')-deoxy threo products. Interesting similarities exist between the presently described reaction and a proposed sequence[3] for the ribonucleotide reductase conversion. Our [1,2]-hydride shift rearrangement proceeds smoothly at ambient temperature by using excess lithium triethylborohydride (LTBH) in tetrahydrofuran (THF) or dimethyl sulfoxide (Me_2SO)/THF solutions.

We had examined the reactivity of 2'-*O*-tosyladenosine[4] (**1**) in our investigation of methods for the specific deoxygenation[5] and substitution[6] at C2' of ribonucleosides. It is a sluggish substrate for S_N2 reactions with common nucleophiles and undergoes alternative decomposition reactions[4] at elevated temperatures as noted with other purine nucleoside derivatives.[7] We also explored reaction of **1** with LTBH since a remarkable reductive displacement reactivity with alkyl tosylates had been reported for this reagent.[8]

A solution of 421 mg (1 mmol) of **1** in 10 mL of anhydrous Me_2SO under dry nitrogen was treated with 10 mL of 1 M LTBH/THF and the resulting solution was stirred at ambient temperature (~21 °C) for 14 h. Careful quenching with 5 mL of H_2O was followed by concentration of the solution to a syrup in vacuo and chromatography on a column of Dowex 1×2(OH^-) resin using H_2O as eluant. The product was recrystallized from MeOH to give 247 mg (98%) of 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine[9,10] (**2a**), mp 220–221 °C. No trace of the expected erythro isomer (2'-deoxyadenosine) was detected. Use of LTBD resulted in an analogously clean conversion of **1** to 9-(2-deoxy-3-deuterio-β-D-*threo*-pentofuranosyl)adenine[10] (**2b**).

The generality of this rearrangement was found to include the isomeric 3'-*O*-tosyladenosine[11] (**3**). Treatment of **3** under identical conditions gave 9-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine[9,10] (**4a**), mp 205–206 °C, or its 2'-deuterio derivative[10] (**4b**) in ~82% yields. Cleavage of the adenine base occurred to ~18%.

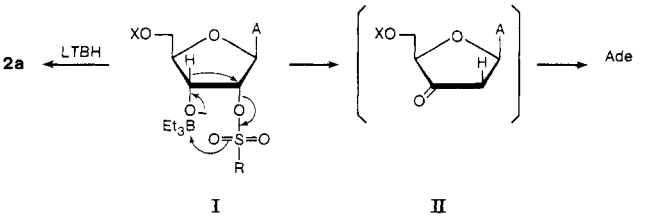
Specifically labeled 2'-(**5a**) and 3'-deuterio-2'-*O*-tosyladenosine[11] (**5b**) were prepared and subjected to the rearrangement conditions. The 9-(2-deoxy-2-deuterio-β-D-*threo*-pentofuranosyl)adenines[10] with a 2(*R*) (**6a**) and 2(*S*) (**6b**) configuration were obtained from **5a** and **5b**, respectively.



The absence of participation or direct effects by the primary (C5') alcohol group was verified with 5'-*O*-trityl- and 5'-*O*-(*tert*-butyldiphenylsilyl)-2'-*O*-tosyladenosine.[11] Both of these lipophilically protected compounds were soluble in THF. The rearrangement reactions were complete within 3 h at ambient temperature in THF whereas these substrates in Me_2SO/THF required the longer time period. The 5'-*O*-protected derivatives of **2a** were isolated in ~92% yields by preparative thin-layer chromatography. Both 2'-*O*-(methylsulfonyl)adenosine and 2'-*O*-((2,4,6-triisopropylphenyl)sulfonyl)adenosine[11] underwent the reductive rearrangement smoothly to give **2a**.

The noted experiments using labeled substrates or LTBD define the origin of atoms and the cleanly stereoselective [1,2]-hydride shift with accompanying inversion of *both* of the C2' and C3' centers. A logical sequence for the conversion of **1** → **2a** would involve expulsion of triethylboron tosylate from the boronate complex I to give a 2'-deoxy-3'-keto intermediate II. Stereoselective reduction of II by excess LTBH would give **2a**. However, treatment of **1** with <6 equiv of LTBH resulted in diminished yields of **2a** and a complementary amount of adenine was produced (e.g., with 3 equiv of LTBH ~90% cleavage to adenine occurred). Also, none of the epimeric erythro alcohol was observed in any of the reactions.

We recently have reported that treatment of 5'-*O*-trityl-2'-deoxyadenosine with chromium trioxide/pyridine/acetic anhydride results in spontaneous β-elimination of the base from the transient 2'-deoxy-3'-ulosyl intermediate (II, A = adenin-9-yl, X = trityl) to give a conjugated dihydrofuranone plus adenine.[1b] In addition,



treatment of the more stable 5'-*O*-trityl-3'-ketothymidine derivative (II, A = thymin-1-yl, X = trityl) with sodium borohydride resulted in formation of the threo and erythro alcohols in a ratio of ~8.5:1.[1b,12]

(1) (a) This contribution constitutes: Nucleic Acid Related Compounds. 45. (b) For the previous paper in this series, see: Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron*, in press.

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(10) These compounds were characterized completely by melting point, UV, ^1H and ^{13}C NMR, and mass spectroscopy, thin-layer chromatography, electrophoresis (0.1 M borate buffer at pH 10.0), and elemental microanalysis.

(11) Syntheses of these compounds will be described in our full paper.

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It would appear that expulsion of triethylboron tosylate from I to give II results in the spontaneous β-elimination of adenine before reduction of the free carbonyl function takes place. However, in the presence of >6 equiv of LTBH, association of a second triethyl borohydride species at the α-face may occur and promote a more closely "concerted" sequence. The hydride shift from C3′ to C2′ with Walden displacement of tosylate may be accompanied by hydride transfer from a second boron to C3′ with inversion of the boronate-substituted carbon or by rapid reduction of a transient trigonal boron–carbonyl complex at the α-face.

A sequence postulated for the ribonucleotide reductase mediated deoxygenation is initiated by abstraction of H3′, departure of O2′ (possible loss of the 3′-hydroxyl proton to give a 3′-ketone[3c]), external hydrogen transfer to C2′ at the α-face, and return of the originally abstracted H3′ to C3′ from the β-face.[3] Our present rearrangement includes certain features of that sequence, but the [1,2]-hydride shift to C2′ on the β-face and hydride transfer to C3′ at the α-face result in inversion of both chiral centers in contrast to the double-retention stereochemistry of the enyzmatic process.

Our new conversion provides convenient access to inverted deoxypentofuranosyl compounds that are difficult to obtain by conventional methods.[9,13] Compound **4a** is the core nucleoside of an unusual plant bacteriocin, agrocin 84.[14] This rearrangement provides other useful carbohydrate derivatives by efficient synthetic routes. Details of its application with other nucleoside bases and anomers and the experimental and spectral data will be reported.

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Supplementary Material Available: Spectroscopic and analytical data for compounds **2a,b**, **3**, **4a,b**, and **6a,b** (2 pages). Ordering information is given on any current masthead page.

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Regiospecific Metal-Catalyzed Ring Expansion of Aziridines to β-Lactams

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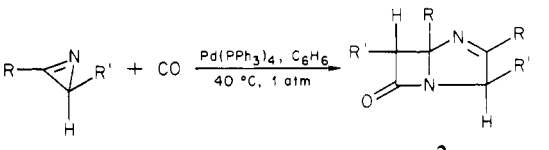
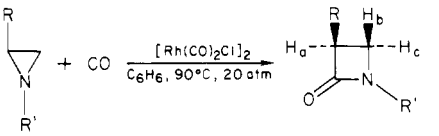
Three-membered ring compounds undergo interesting cleavage reactions in the presence of transition-metal complexes.[1] Of particular and practical value are those processes in which the metal complex functions as a catalyst and not as a stoichiometric reagent. In 1981, one of us[2] reported a novel approach to the synthesis of bicyclic β-lactams. Exposure of an azirine (**1**) to carbon monoxide and a catalytic amount of tetrakis(triphenylphosphine)palladium(0), at 40 °C and 1 atm, afforded the heterocycles **2** in reasonable yields. Attempts to synthesize monocyclic



1 2

β-lactams from azirines by metal-catalyzed carbonylation (and reduction) failed. It seemed conceivable that the desired monocyclic β-lactams could be prepared by the carbonylation of aziridines, the saturated three-membered ring heterocycles, under appropriate conditions. In fact, the mechanism first proposed for the formation of **2** from **1** involved the generation of a fused aziridine which then could be carbonylated to **2**. However, neither monocyclic nor bicyclic aziridines react with carbon monoxide under conditions used for the conversion of **1** to **2**.[3] While this result was disappointing in terms of monocyclic β-lactam formation, we knew that, in some cases, rhodium(I) and palladium(0) can effect the same kinds of reactions with one or the other metal complex being superior for a particular transformation (e.g., formation of vinyl isocyanates from aziridines).[3] We now wish to report the direct, regiospecific, rhodium-catalyzed carbonylation of aziridines to β-lactams.

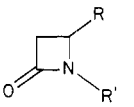
Treatment of *N-tert*-butyl-2-phenylaziridine (**3**, R = Ph, R′



3 4

= $(CH_3)_3C$) with carbon monoxide in benzene, using chlorodicarbonylrhodium(I) dimer as the catalyst (20:1 ratio of **3**/catalyst), at 90 °C and 20 atm, afforded the β-lactam **4**, R = Ph, R′ = $(CH_3)_3C$, in quantitative yield. The β-lactam was identified on the basis of analytical (Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.08; H, 8.44; N, 6.95) and spectral data. In particular the infrared carbonyl stretching frequency occurred at 1740 cm^{-1}, and the proton magnetic resonance spectrum displayed a typical 12-line AMX spectrum for the three protons attached to the carbon atoms of the heterocyclic ring. Carbon-13 magnetic resonance and mass spectral data are also in accord with the assigned structure (see Table I for pertinent nuclear magnetic resonance and mass spectral data).

β-Lactams were also formed in quantitative yields with **3**, R = Ph, *p*-BrC_6H_4, *p*-PhC_6H_4 and R′ = *tert*-butyl or 1-adamantyl, as reactants (aziridines were prepared by standard literature methods).[4] In all instances, the reaction was completely regiospecific with none of the isomeric β-lactam **5** being detected.



5

Note that, in order for reaction to occur under the described conditions, the R′ group must not contain acidic hydrogens on carbon adjacent to the heterocyclic nitrogen atom. If it does (e.g., R′ = $PhCH_2$) then ring cleavage of **3** occurs to give a complex mixture of products. However, one can achieve the synthesis of the desired benzylic compound by simply carbonylating *N*-(trimethylsilyl)-**2**-phenylaziridine to **4**, R = Ph, R′ = $Si(CH_3)_3$ and exposing the latter to benzyl chloride and tetrabutylammonium fluoride. This result is of relevance to the synthesis of nocardicin type antibiotics.[5] Another rhodium(I) complex, 1,5-cyclooctadienerhodium(I) chloride dimer, is also an effective catalyst for converting **3** to **4**. However, the dimer of 1,5-hexadiene-

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