

REGIOSPECIFIC AND STEREOSELECTIVE CONVERSION OF  
RIBONUCLEOSIDES TO 3'-DEOXYNUCLEOSIDES. A HIGH YIELD  
THREE-STAGE SYNTHESIS OF CORDYCEPIN FROM ADENOSINE.<sup>1</sup>

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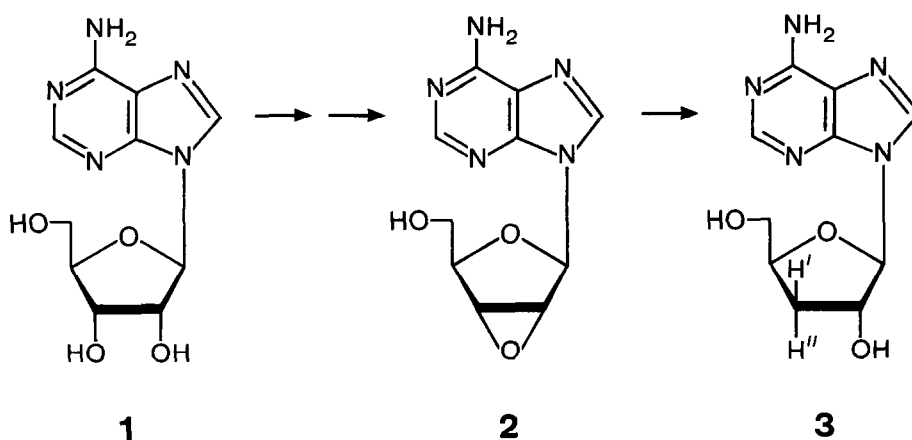
*Summary:* Treatment of 2',3'-anhydroadenosine (obtained<sup>2</sup> in 92% yield from adenosine) with lithium triethylborohydride (or deuteride) gave cordycepin (or its 3'(R)-deuterio derivative) in ~90% overall yields with no 2'-deoxy isomer detected.

Cordycepin represents the first reported nucleoside antibiotic. Its isolation was described in 1951<sup>3</sup> and its correct structure was defined as 3'-deoxyadenosine (3) in 1964.<sup>4</sup> Cordyceps militaris was shown to convert 3'-tritioadenosine to labeled cordycepin. This reduction is thought to resemble the overall process of deoxygenation of ribonucleoside 5'-di- or triphosphates to 2'-deoxynucleotides.<sup>5</sup> However, no stereochemical and mechanistic determinations for the biosynthesis of cordycepin have paralleled the careful studies with the ribonucleotide reductases.<sup>6</sup> Cordycepin is converted intracellularly into its 5'-mono, di, and triphosphates. The latter product can terminate normal 3'-phosphodiester polymer elongation upon incorporation onto a growing RNA. It has been found recently that cordycepin interferes with the processing of nuclear transcribed RNA. A number of biological effects of cordycepin and coenzyme analogues that have created a resurgence of interest in this antibiotic have been reviewed.<sup>5</sup>

Over twenty publications involving syntheses of cordycepin are in the literature beginning with the pioneering studies of Todd, Baker and Goodman, and Walton and Holly and their coworkers<sup>7</sup> and extending forward to recent efforts involving non-chiral precursors<sup>8</sup> and free radical mediated reductions.<sup>9</sup> However, the majority of these suffer from low to moderate overall yields resulting from inefficient sugar moiety trans-

formations or routes that give 2' and 3' isomers. Two very recent reports<sup>9c,10</sup> illustrate difficulties involved with selective 2',5'-diprotection for thionocarbonate reduction approaches<sup>11</sup> to the synthesis of 3'-deoxynucleosides. Most reported routes would not provide highly stereoselective incorporation of hydrogen isotopes.

We had noted borohydride induced opening of nucleoside epoxides some time ago.<sup>12</sup> Brown's examination of epoxide reductions using lithium triethylborohydride<sup>13</sup> has been extended to pyranose sugar epoxides.<sup>14</sup> We now report conversion of adenosine to 3'-deoxyadenosine via the ribo-epoxide in ~90% overall yield using reactions that proceed readily at or below room temperature. Incorporation of deuterium at C3' with inverted stereochemistry can be effected.



Conversion of adenosine (1) to the 2',3'-trans bromo-acetates using  $\alpha$ -acetoxyisobutyryl bromide in "moist acetonitrile"<sup>15</sup> followed by treatment of that mixture with amberlite IRA-400(OH<sup>-</sup>) resin gave crystallized 2',3'-anhydroadenosine (2) in 92% yield.<sup>2</sup> A deoxygenated solution of 500 mg (2 mmol) of 2 in 50 mL of dry Me<sub>2</sub>SO was cooled to ~10°C with stirring and treated under nitrogen with 25 mL of a cold (~4°C) solution of 1 M LiEt<sub>3</sub>BH/THF. Stirring (under N<sub>2</sub>) in an ice-water bath was continued for 1 h with gradual warming to room temperature overnight. Cautious addition of 50 mL of 5% HOAc/H<sub>2</sub>O followed by careful purging of the pyrophoric triethylborane with a stream of N<sub>2</sub> and evaporation in vacuo gave a yellow syrup. This material was dissolved in H<sub>2</sub>O and chromatographed on Dowex 1-X2(OH<sup>-</sup>)<sup>16</sup> using a H<sub>2</sub>O wash followed by elution with MeOH/H<sub>2</sub>O (3:7). Recrystallization of the colorless solid eluate residue from 95% EtOH gave 492 mg (98%) of cordycepin, mp 224-225°C (Lit.<sup>7c</sup> mp 224-225°C), mass

spectrum  $m/z$  251.1018 (calcd. for  $M^+$  251.1018), Anal. Calcd. for  $C_{10}H_{13}N_5O_3$ : C, 47.80; H, 5.21; N, 27.88. Found: C, 47.84; H, 5.21; N, 27.92. Parallel reduction of 1 mmol of **2** using  $LiEt_3BD$  gave 242 mg (96%) of **3** ( $H' = D$ ), mp 225°C, mass spectrum  $m/z$  252.1083 (calcd. for  $M^+$  252.1081).

Analogous reduction of 9-(2,3-anhydro- $\beta$ -D-lyxofuranosyl)adenine<sup>12</sup> gave the 3'/2'-deoxy threo products<sup>17</sup> with ~86:14 regioselectivity. This deuterated 3'-deoxy threo product (easily separated<sup>16</sup> from the minor 2'-deoxy isomer) was inverted<sup>18</sup> at C2' to give the 3'(S)-deuterio-3'-deoxy-adenosine (**3**,  $H'' = D$ ) diastereomer. Evaluation of  $^1H$  NMR spectra allowed unequivocal assignment of the signal for the pro-S  $H3''$  at  $\delta$  1.92 and the pro-R  $H3'$  at  $\delta$  2.26 (in  $Me_2SO-d_6$ ) in harmony with cis shielding of  $H3''$  by the 2'-OH group of **3**.

This straightforward three-stage sequence should be applicable for the regioselective synthesis of 3'-deoxynucleosides from ribonucleosides whose structural features allow formation of the ribo-epoxide function and use of "Super Hydride" reduction. Analysis of chemical shifts and first order high field  $^1H$  NMR coupling constants for these stereodefined models for cordycepin biosynthetic studies will be presented in a full paper including synthetic details and  $^{13}C$  NMR parameters for a number of deoxy and O'-alkyl nucleosides obtained by treatment of nucleoside epoxides with reducing hydrides in alcohols.

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1. (a) This contribution constitutes: Nucleic Acid Related Compounds. 49. (b) For the previous paper in this series see: D. K. Buffel, C. McGuigan, and M. J. Robins, *J. Org. Chem.*, in press.
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15. The proportions of added acetonitrile/water should read (100:1) and not (10:1) as reported on page 367, paragraph 3, line 2 of Ref. 2. We regret any inconvenience this transcriptional error may have caused.
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