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Oxidative Degradation of L-Ascorbic Acid Acetals to 2',3'-Dideoxy-3'-Oxaribofuranosides. Synthesis of Enantiomerically Pure 2',3'-Dideoxy-3'-Oxacytidine Stereoisomers as Potential Antiviral Agents

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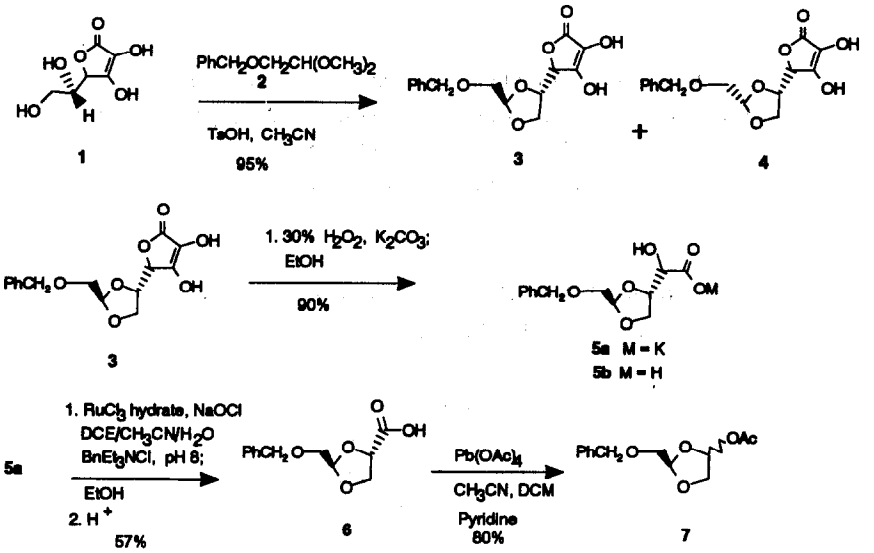
Abstract: Enantiomerically pure 2',3'-dideoxy-3'-oxacytidine nucleoside analogues were synthesized from L-ascorbic acid in eight steps and good overall yield.

The discovery of 3'-azido-3'-deoxythymidine[2] (AZT), 3'-fluoro-3'- deoxythymidine[3] (FLT), 2',3'-dideoxycytidine[4] (DDC) and 2',3'-dideoxyinosine[4] (DDI) as potent inhibitors of the HIV virus, the causative agent of acquired immunodeficiency syndrome (AIDS), has stimulated intensive efforts in targeting nucleoside analogues as potential anti-HIV agents. Clinical studies have shown adverse toxicities associated with AZT, FLT, DDC and DDI and resistant virus strains are emerging. Recently, Belleau and coworkers reported the anti-HIV activity of a novel series of 2',3'-dideoxy-3'-thia and 2',3'-dideoxy-3'-oxa nucleoside analogues.[5] The 3'-thia series features 3TC which was found equipotent to its enantiomer in antiviral activity against HIV-1 and 2 and considerably less cytotoxic.[6] 3TC possesses the "unnatural" L-sugar configuration[6] and is currently in clinical trials. Racemic 2',3'-dideoxy-3'-oxacytidine was found to be highly toxic and its anti-HIV activity could not be assessed. In this paper, we wish to report a novel and practical process for the synthesis of 2',3'-dideoxy-3'-oxaribofuranosides and their transformations to 3'-oxacytidine analogues corresponding to D and L-sugar configuration. Recently, Chu et al. reported the synthesis of dioxolane nucleoside analogues possessing the "natural" D sugar configuration in 12 steps from 1,6-anhydro-D-mannose.[7]

With precedents in the work of Abushanab[8] and others[9], L-ascorbic acid 1 was envisaged as a useful starting material. Condensation of 1 with benzyloxyacetaldehyde dimethylacetal[10] 2 in acetonitrile in the presence of TsOH afforded a (1:1) mixture of diastereomers 3 and 4 in excellent isolated yield (Scheme 1). Initial attempts to prepare 3 and 4 by using TsOH or MSA in benzene or toluene, $SnCl_2$[11] or titanium tetraisopropoxide in ethyl acetate were unsatisfactory.

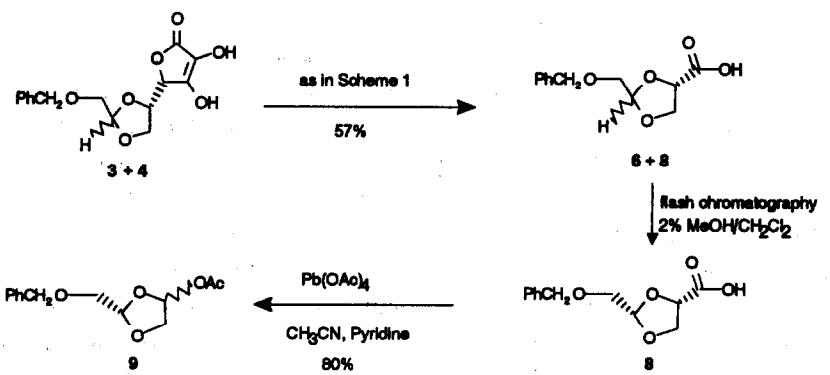
Fractional crystallization of a crude mixture of 3 and 4 using benzene and ethyl acetate mixtures provided compound 3 in > 98% de (HPLC). Intermediate 4 was isolated in 60% de by fractional crystallization from benzene. Degradation of 3 to acid 6 was

Scheme 1



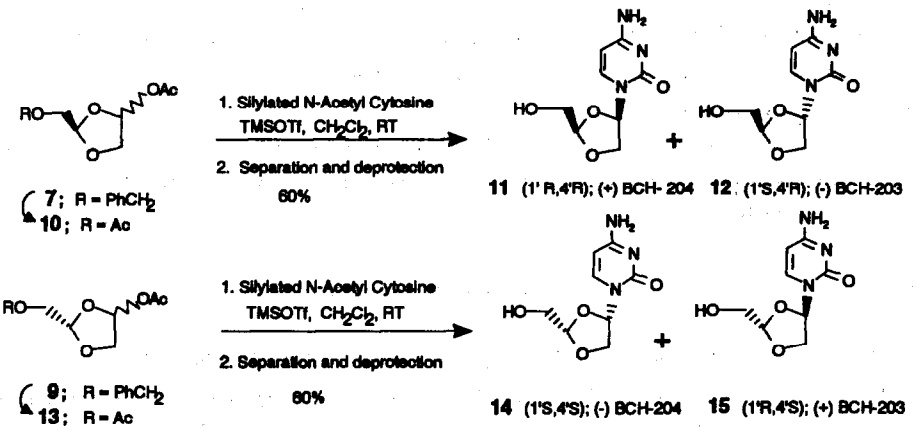
achieved in two steps. Oxidative degradation of **3** with basic H_2O_2, followed by extraction with hot ethanol furnished **5a** in excellent yield. In the second step, Ruthenium trichloride - catalyzed sodium hypochlorite oxidation (Wolfe oxidation)[12] of **5a** under controlled pH conditions[11] afforded acid **6**. The presence of benzyltriethylammonium chloride enhanced substantially the rate of formation of **6**. In a similar fashion, a 1:4 mixture of **3** and **4** was converted to **6** and **8** from which the less polar acid **8** was easily isolated by flash chromatography[13] (Scheme 2).

Scheme 2



Conversion of the carboxyl group in **6** or **8** to the acetoxy group was achieved by oxidative decarboxylation induced by lead tetraacetate in acetonitrile[10,14] to produce the acetates **7** or **9** in good yield. The coupling of **7** or **10** with silylated N-acetylcytosine in the presence of the Lewis acid TMSOTf[15] produced a mixture of nucleoside analogues **11** and **12** in 1:1 ratio. Separation and deprotection afforded enantiomerically pure **11** and **12**. Similarly, **14** and **15** were obtained (Scheme 3). The anti-HIV activity of **11**, **12**, **14** and **15** was determined in whole cell assay (MT-4, RF strain of HIV-1) at concentrations up to 100 μg/ml. The trans analogues **12** and **15** were found to be inactive and not toxic. Compound **14** was cytotoxic whereas **11** was very active (IC_{50} = 0.045 μg/ml) but somewhat cytotoxic (ID_{50} = 10 μg/ml). Details of the anti-HIV activity will be reported elsewhere.

Scheme 3



In conclusion, we present here a novel and practical entry to enantiomerically pure 2',3'-dideoxy-3'-oxaribofuranosides and their couplings to furnish all BCH-203 and BCH-204 stereoisomers from a common starting material. The cis analogue emerged as a potent anti-HIV agent.

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13. Selected physical and spectral data:

3 m.p. 127.6°C, $[\alpha]^{20}_d$ -8.8° (c, 1.0, MeOH), ^{1}H NMR (DMSO-d_6) δ 3.44 (d,2H,J=3.8Hz), 3.83 (dd,1H,J=6.7Hz), 4.19 (t,1H,J=7.1Hz), 4.27-4.35 (m,1H), 4.50 (s,2H), 4.79 (d,1H,J=2.8Hz), 5.01 (t,1H,J=3.7Hz), 7.21-7.40 (m,5H), 8.55 (bs,1H), 11.3 (bs,1H). ^{13}C NMR (DMSO-d_6) δ 66.21, 70.88, 72.84, 73.62, 74.89, 103.72, 118.45, 127.90, 127.95, 138.28, 152.79, 170.43.

We thank Dr. R. Storer and the computational chemistry department of GGR for a single cyrstal X-ray structure determination.

4 oil, $[\alpha]^{20}_d$ +18.6° (c,1.2,MeOH), ^{1}H NMR (DMSO-d_6) δ 3.35-3.50 (m,2H), 3.90-4.10 (m,2H), 4.20-4.30 (m,1H), 4.49 (s,2H), 4.75 (d,1H,J=3.3Hz), 5.02 (t,1H,J=4.2Hz), 7.20-7.37 (m,5H), 8.54 (bs,1H), 11.35 (bs,1H). 13C NMR (DMSO-d6) δ 65.79, 70.47, 72.50, 73.76, 74.22, 102.79, 118.29, 127.49, 128.26, 138.09, 152.06, 170.08.

6 oil, $[\alpha]^{26}_d$ -28.2°(c,1.0,$CHCl_3$), ^{1}H NMR (DMSO-d_6) δ 3.50 (d,2H,J= 3.7Hz), 3.86 (dd,1H,J=8.0 Hz, 5.2Hz), 4.17 (t,1H,J=7.8Hz), 4.53 (s,2H), 4.57 (dd,1H,7.4Hz,5.2Hz), 5.15 (t,1H,J=3.9Hz), 7.20-7.40 (m,5H), 12.7 (bs,1H). ^{13}C NMR (DMSO-d_6) δ 67.41, 70.13, 72.52, 73.21, 103.18, 127.53, 128.28, 138.09, 172.16.

8 oil $[\alpha]_d$ +4.6° (c,1.0,$CHCl_3$). ^{1}H NMR (DMSO-d_6) δ 3.54 (m,2H), 4.56 (dd,1H, J=4.7Hz, 6.9Hz), 5.11 (t,1H,J=4.1Hz), 7.20-7.40 (m,5H), 12.7 (bs,1H).

11 m.p. 173-175°C Lit.[7] m.p. 181-183°C, $[\alpha]_d^{22}$ + 35.2° (C, 1.0, MeOH) Lit.[7] $[\alpha]_d^{25}$ + 21.0° (C, 1.0, MeOH). ^{13}C NMR (DMSO-d_6) δ 60.76, 71.46, 81.37, 94.30, 105.41, 141.32,155.76, 166.25. Chiral HPLC (>99% ee).

12 m.p. 188-190°C Lit[7] m.p. 185°C, $[\alpha]_d^{22}$ - 68.5° (C, 0.5, MeOH) Lit. $[\alpha]_d^{25}$ - 25.2 (C, 1.0, MeOH).^{13} C NMR (DMSO-d_6) δ 62.14, 70.52, 83.11, 94.40, 105.81, 140.90, 155.62, 166.20. Chiral HPLC (>99% ee).

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10 and 13 were derived from 7 and 9 respectively, by hydrogenolysis (10% Pd/C) and acetylation (70% yield).

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