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Stereoselective Synthesis of (S)- and (R)-Penciclovir Triphosphate and their Activity Against Viral Enzymes. Z. J. Lesnikowski, A. S. Juodawlkis, R. M. Lloyd, Jr., and R. F. Schinazi.* Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine and VA Medical Center, Decatur, GA 30033, USA.

Penciclovir (PCV) is a selective inhibitor of herpes simplex virus (HSV), varicella-zoster virus (VZV), and hepatitis B virus (HBV). In herpesvirus infected cells, the active form of PCV is its triphosphate (PCVTP) which can exist in enantiomeric forms. (*S*)-PCVTP was the only enantiomer found in HSV-1 and VZV infected cells, but about 10% of (*R*)-enantiomer was formed in HSV-2 infected cells. Therefore, it was important to develop methodology for the synthesis of both enantiomers of the triphosphate for comparison of activity against viral and cellular enzymes. A combined chemical and enzymatic approach was developed for the synthesis of (*R*)- and (*S*)-PCVTP. Partial enzymatic hydrolysis of *O*,*O*-bisisobutyryl-PCV with *Bacillus licheniformis* protease led to enriched (*S*)-*O*-monoisobutyryl-PCV, as established by chiral chromatography. Phosphorylation of (*S*)-*O*-monoisobutyryl-PCV, followed by removal of isobutyryl protection, produced the (*R*)-enriched PCVTP. The corresponding (*S*)-PCVTP was synthesized *via* phosphorylation of (*R*)-O-monomethoxytrityl-PCV prepared from (*S*)-monoisobutyryl-PCV. We demonstrated, for the first time, that one of the enantiomers is markedly more potent than the other against HIV-1 reverse transcriptase (RT). PCVTP was shown to be an effective inhibitor and DNA chain terminator of HIV-RT. These results support the concept that PCV should be an effective inhibitor of both HSV and HIV in doubly infected cells. The demonstration of differing biochemical activities of the PCVTP enantiomers confirms the need for improved synthesis of nucleotides with greater enantiomeric purity.