Synthetic Approaches to 3'-Azido-3'-deoxythymidine and Other Modified Nucleosides

Michael E. Jung* and John M. Gardiner

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

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Summary: An efficient stereospecific total synthesis of AZT (nine steps from crotonaldehyde) is reported in which the chirality is introduced via Sharpless epoxidation and therefore intermediates for the synthesis of both D- and L-AZT are easily produced.

The modified nucleoside, 3'-azido-3'-deoxythymidine (AZT or zidovudine, I) is currently the best known drug for the treatment of HIV infections.1 It was first synthesized in 1964 by Horwitz and co-workers as a potential antitumor agent.2 Since then several other syntheses of AZT have been developed, all of which begin with either AZT or zidovudine, which is currently the best known drug for the treatment of HIV infections.3 However, upon pretreatment of BOC-Phe-F either the D- or L-enantiomer is obtained. Another approach, involving Sharpless epoxidation, has been used to produce 20% of each enantiomer.4

Our synthesis is shown in Scheme I. Crotonaldehyde (2) was converted into a mixture of the E and Z isomers of 1-(trimethylsilyloxy)-1,3-butadiene (3), a compound that is also commercially available. Condensation of this silyloxy diene 3 with methyl orthoformate using zinc chloride led to formation without significant racemization. Similar results are expected for most of the other naturally occurring proteinogenic amino acids. However, upon pretreatment of BOCH-Phe-F with 2 equiv of triethylamine in methylene dichloride for periods of 1, 5, 8, and 10 min prior to addition of alanine methyl ester hydrochloride, the one-phase procedure in CH2Cl2 led to formation of 1-2, 14.3, 23.1, and 26.3% of the DL-dipeptide, respectively. Thus one can expect rapid risk-free coupling via appropriate standard techniques for these new, stable acylating agents in the case of typical proteinogenic amino acids.

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Supplementary Material Available: Preslected procedures for the preparation and NMR data for the amino acid fluorides and dipeptide esters and 1H NMR spectra illustrating the racemization tests (7 pages). Ordering information is given on any current masthead page.

References

Regioselective, Palladium-Catalyzed Hetero- and Carboannulation of 1,2-Dienes Using Functionally Substituted Aryl Halides

Richard C. Larock,* Norman G. Berrios-Peña, and Colleen A. Fried

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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Summary: Aryl halides bearing heteroatom- or potential carbonan-containing functionality in the ortho position react regioselectively with 1,2-dienes in the presence of a palladium catalyst and a carbonate base to afford five- and six-membered ring hetero- and carbocycles in high yield.

Annulation processes are among the most important reactions in organic chemistry.1 Few, however, have...