Z-D-Phg-F 15.5–16.6% of the L form was obtained. Clearly in the case of especially sensitive, sterically hindered couplings the two-phase method[8,12] is more protective of chiral integrity.

As expected, in the case of BOC- or Z-Phe-F either the one- or two-phase methods were suitable for peptide bond formation without significant racemization. Similar results are expected for most of the other naturally occurring amino acids. However, upon pretreatment of BOC-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 CH_2Cl_2 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.

Acknowledgment. We are indebted to the National Science Foundation (NSF CHE-9003192) and the National Institutes of Health (GM-09706) for support of this work. The National Science Foundation is also thanked for grants used to purchase the high-field NMR spectrometers used in this research.

Supplementary Material Available: Preselected 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.

(12) Beyermann, M.; Bienert, M.; Niedrich, H.; Carpino, L. A.; Sadat-Aalaee, D. *J. Org. Chem.* **1990**, *55*, 721.

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

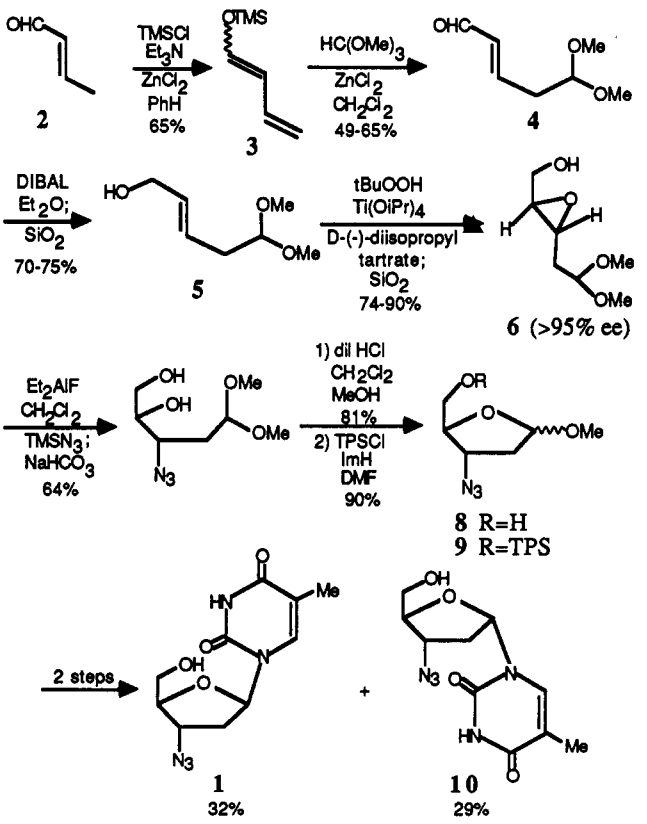
Received January 30, 1991

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, **1**) 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,[3] all of which begin with either a nucleoside (usually thymidine) or a sugar derivative (D-xylose, D-mannose, etc.), so that the asymmetry of the product **1** is derived directly from the chiral starting material used (a chiron approach). We now describe a short synthesis of D-AZT (**1**) from noncarbohydrate starting materials that utilizes instead a chiral catalyst approach, namely, a Sharpless epoxidation process to afford the required asymmetry. We have shown that this approach can also be used to prepare an intermediate for construction of the enantiomer L-AZT.

Our synthesis is shown in Scheme I. Crotonaldehyde (**2**) was converted into a mixture of the *E* and *Z* isomers

Scheme I



of 1-(trimethylsilyloxy)-1,3-butadiene (**3**),[4] a compound that is also commercially available. Condensation of this silyloxy diene **3** with methyl orthoformate using zinc chloride as catalyst gave the enal acetal **4** in 49–65% yield after Kugelrohr distillation.[5] This preparation of **4** resulted in a higher proportion (>95%) of the *E*-alkene ge-

(1) For reviews on chemotherapeutic strategies in the treatment of AIDS, see: (a) Norbeck, D. W. *Ann. Rep. Med. Chem.* **1990**, *25*, 149. (b) Yarchoan, R.; Mitsuya, H.; Broder, S. *Ann. Rep. Med. Chem.* **1988**, *23*, 251. (c) Mansuri, M. M.; Martin, J. C. *Ann. Rep. Med. Chem.* **1988**, *23*, 161; *Ann. Rep. Med. Chem.* **1987**, *22*, 147.

(2) Horwitz, J. P.; Chua, J.; Noel, M. *J. Org. Chem.* **1964**, *29*, 2076.

(3) (a) Rideout, J. L.; Barry, D. W.; Lehrman, S. N.; St. Clair, M. H.; Furman, P. A.; Freeman, G. A. DE 3,608,606; *Chem. Abstr.* **1987**, *106*, P38480b. (b) Rideout, J. L.; Barry, D. W.; Lehrman, S. N.; St. Clair, M. H.; Furman, P. A.; Beacham, L. M., III; Le Blanc, H. S.; Freeman, G. A. EP 199,451; *Chem. Abstr.* **1987**, *107*, P52002z. (c) Zaitseva, V. E.; Dyatkina, N. B.; Krayevskii, A. A.; Skaptsova, N. V.; Turina, O. V.; Gnuchev, N. V.; Gottikh, B. P.; Azhaev, A. V. *Bioorg. Khim.* **1984**, *10*, 670. (d) Rideout, J. L.; Freeman, G. A.; Shaver, S. R. EP 287,215; *Chem. Abstr.* **1989**, *111*, P23912y. (e) Wilson, J. D.; Almond, M. R.; Rideout, J. L. EP 295,090; *Chem. Abstr.* **1989**, *111*, P23914a. (f) Wellcome Foundation Ltd. JP 63 255,295 (88 255,295); *Chem. Abstr.* **1989**, *111*, P7758x. (g) Hayauchi, Y.; Lockhoff, O. DE 3,705,794; *Chem. Abstr.* **1988**, *109*, P211404s. (h) Chu, C. K.; Beach, J. W.; Ullas, G. V.; Kosugi, Y. *Tetrahedron Lett.* **1988**, *29*, 5349. (i) Fleet, G. W. J.; Son, J. C.; Derome, A. E. *Tetrahedron* **1988**, *44*, 625.

(4) (a) Ishida, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1161. (b) Cazeau, P.; Frainnet, E. *Bull. Soc. Chim. Fr.* **1972**, 1658.

(5) Makin, S. M.; Raifel'd, Yu. E.; Zil'berg, L. L.; Arshava, B. M. *Zh. Org. Khim.* **1984**, *20*, 210.

0022-3263/91/1956-2614$02.50/0

ometry than other routes (e.g., a Wadsworth–Emmons reaction on the mono dimethyl acetal of malondialdehyde). Reduction of the enal **4** gave the allylic alcohol **5** in 87% crude yield (70% after chromatography).[6] The chirality necessary for the final product was introduced by a Sharpless epoxidation, namely, treatment of **5** with D-(−)-diisopropyl tartrate, *tert*-butyl hydroperoxide, and titanium tetraisopropoxide at −20 °C for 2 days to afford, after workup and chromatography, the desired epoxy alcohol **6** in 74% yield.[7] The optical purity of **6** was shown by examination of the ^{1}H NMR of the Mosher ester to be >95% ee (the corresponding ester of racemic **6** was prepared for comparison). The key step of this synthesis involves the regioselective opening of the epoxy alcohol **6** with azide. After much experimentation with a wide variety of reagents and conditions,[8-10] we found that diethylaluminum fluoride[11] cleanly promoted the desired regioselective opening of **6** with trimethylsilyl azide to furnish, after quenching with bicarbonate and chromatography, the desired azido diol **7** in 64% yield. We see no evidence for the production of any of the opposite regioisomer in this reaction, although not all of the material can be accounted for. With the two non-anomeric stereocenters set, all that remained in the synthesis was to cyclize to the methyl furanoside and attach the thymine base. Cyclization was accomplished quite easily by stirring a mixture of the azido diol **7** in dichloromethane with a few drops of 1.5% HCl in aqueous methanol for 5 min at 23 °C to give, after silica gel chromatography, the desired methyl furanoside **8** as a mixture of α and β anomers in 81% yield.[12] These anomers could be separated by further chromatography or preparative TLC and their ^{1}H NMR and ^{13}C NMR spectra matched the published data.[3i] Silylation of the alcohol **8** under standard conditions gave the *tert*-butyldiphenylsilyl (TPS) ether **9** in 90% yield. The final attachment of the base has already been carried out by Fleet,[3i] namely, Vorbrüggen coupling[13] of **9** with bis(trimethylsilyl)thymine and treatment with fluoride to give, after flash chromatographic separation, D-AZT (**1**) (32%) and its α-epimer **10** (29%). This ends a nine-step synthesis of optically pure D-AZT (**1**) from crotonaldehyde, which should be applicable for the production of other 3′-substituted 2′,3′-dideoxynucleosides (via addition of other nucleophiles to **6**) as well as 2′,3′-dideoxynucleosides (via regioselective reduction of **6**).[14]

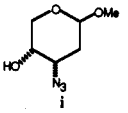
Since the asymmetry is introduced from an external chiral catalyst or promoter, one can prepare the enantiomeric series as well. Epoxidation of **5** using L-(+)-diisopropyl tartrate gave the enantiomer of **6** in comparable yield and purity. This epoxy alcohol was converted via the identical sequence of steps into the enantiomer of **9**. L-AZT should be readily available from this methyl L-furanoside by the standard Vorbrüggen coupling. This route to L nucleosides may be of use in the preparation of substrates for antisense oligonucleotide therapy.[15]

We have thus synthesized the important antiviral agent D-AZT (**1**) from crotonaldehyde (**2**) by a route that should be general enough for the preparation of analogues and that should allow the preparation of the enantiomeric series as well from the same starting material.

Acknowledgment. We thank the National Institutes of Health (AI-26692) for their generous support.

Supplementary Material Available: Experimental details and compound characterization data for compounds prepared (6 pages). Ordering information is given on any current masthead page.

(6) Hughes, P.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 3260.
(7) We have only used the stoichiometric version of the Sharpless asymmetric epoxidation procedure and have not attempted to carry out this reaction by the catalytic procedure.
(8) For example, treatment of **6** with trimethylsilyl azide and titanium tetraisopropoxide under the normal conditions[9] for nucleophilic opening of an epoxy alcohol gave the corresponding trimethylsilyl ether of **6** as the major product in only moderate yield (50–67%). Use of diazido titanium diisopropoxide[9,10] as the catalyst in refluxing benzene gave the desired azido diol **7** in poor yield again along with the trimethylsilyl ether of **6** as the major product.
(9) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.
(10) (a) Choukroun, R.; Gervais, D. *J. Chem. Soc., Dalton Trans.* **1980**, 1800. (b) Blandy, C.; Choukroun, R.; Gervais, D. *Tetrahedron Lett.* **1983**, *24*, 4189.
(11) Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, 599.
(12) Treatment of a more concentrated solution of **7** under similar conditions leads mainly to the methyl pyranoside i rather than **8** for as yet unknown reasons. Isomerization of i into **8** is also possible under acidic conditions.



i

(13) (a) For other examples of this coupling to give AZT, see: Dyatkina, N. B.; Kraevskii, A. A.; Azhaev, A. V. *Bioorg. Khim.* **1986**, *12*, 1048. (b) Reference 3h.
(14) We have not yet examined in a systematic way the addition of other nucleophiles to the epoxy alcohol **6** but based on the Sharpless work,[9] we would expect nucleophiles to add well. We have carried out the reduction of **6** with DIBAL, which gave in about 60% yield a mixture of regioisomers in which the desired 5,5-dimethoxypentane-1,2-diol was the major isomer. We are currently studying the conversion of this compound into 2′,3′-dideoxynucleosides.
(15) For reviews, see: (a) Miller, P. S.; Ts'O; P. O. *Ann. Rep. Med. Chem.* **1988**, *23*, 295. (b) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543. (c) For a specific example of the use of enantio-DNA, see: Fujimori, S.; Shudo, K.; Hashimoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7436.

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

Received January 18, 1991

Summary: Aryl halides bearing heteroatom- or potential carbanion-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

0022-3263/91/1956-2615$02.50/0