strained ring compound. 1,2-Dihydrocyclopenta[*jk*]-fluorene, a carbon analogue of **4**, has, for example, been shown[7] to possess a "bent" benzene ring. On the other hand, that no trace of **4** was detected when **3** was generated either photolytically or thermally in solution at much lower temperatures suggests that high energy is required for **4** to be formed. Thus, **4** would be expected to undergo bond cleavage at the pyrolysis temperature. If the respective bond strengths, ring strains, and stabilities of the biradicals that would be formed by bond cleavage are taken into account, then there are three possible bonds, i.e., a, b, and c, which may be cleaved upon thermolysis. Breaking bond a would be favored because the doubly stabilized biradical **5** would be formed. Unfortunately, however, one cannot easily draw a reasonable pathway leading from **5** to the observed product. Hence, breaking bond a seems unproductive. Cleavage of bond b, on the other hand, would produce diradical **6**, which could isomerize to **8** by way of a somewhat unusual 1,2-phenyl shift. 1,2-Shifts of aryl groups in free radicals are not unprecedented.[8] Moreover, the isomerization of **6** to **8** would be favored because a more stable biradical would be formed. Biradical **8** could then rearrange to the stable aromatic compound **2** by way of a 1,4-hydrogen shift. Cleavage of bond c would also release ring strain in **4** and form biradical **7**. This species could undergo a 1,3 O → C shift of the bridging methylene chain to yield biradical **8**. Although the pathway triggered by the cleavage of bond b seems most reasonable, more detailed studies, which would include theoretical calculations, are required.

One would expect **4** not to be unduly unstable because its carbon analogue has been isolated.[7] All attempts to isolate, or even to detect, **4** were, however, unsuccessful. The apparent instability of **4** can be explained, at least in part, in terms of chemical activation.[9] Because a high energy of activation is required to form **3** and also because the subsequent insertion of the carbene into the C–H bond of the methoxy group is highly exothermic, a highly reactive **4** is produced, one that is much more energetic than the pyrolysis temperature would indicate. Therefore, **4** fragments as soon as it forms.

Reports of the gas-phase rearrangements of carbenes have been heavily weighted with those that deal with substituted phenylcarbenes and diphenylcarbenes, probably because such species undergo repeated carbene to carbene rearrangement until they are trapped by a proximate reactive center to yield stable products that are often synthetically useful. In marked contrast, almost no reports of the gas-phase reactions of fluorenylidene systems have appeared because such species obviously infrequently undergo similar rearrangements and, therefore, are not expected to give any useful products. The reaction described here is the first example of a gas-phase reaction of fluorenylidene that produces a significant product in fairly good yield in "one-pot" fashion. The reaction is driven by the relief of ring strain in the initially formed product **4**, which is the result of an interaction of the carbene center and the substituent at the 1-position. The reaction, therefore, should be applicable to other 1-substituted fluorenylidenes. Investigations of such a possibility are in progress in this laboratory.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

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(8) Wilt, J. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. I, pp 346–356.
(9) Wentrup, C. *Reactive Molecules*; Wiley-Interscience: New York, 1984; p 162 ff and references cited therein.

tert-Butyloxycarbonyl and Benzyloxycarbonyl Amino Acid Fluorides. New, Stable Rapid-Acting Acylating Agents for Peptide Synthesis

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Summary: A new class of rapid-acting acylating agents, α-BOC and Z amino acid fluorides are obtained as stable, often crystalline, compounds by treatment of the protected amino acid with cyanuric fluoride.

Recently the synthesis of stable FMOC amino acid fluorides substituted in the side chain with *tert*-butyloxycarbonyl (BOC) and other acid-sensitive *tert*-butyl-bearing protecting groups was described.[1] Generally the corresponding acid *chlorides* bearing such side chains were either too sensitive to be obtained or were subject to facile degradation on storage. Similarly, α-BOC-protected amino acid chlorides are not accessible except in situ at very low temperatures.[2] Long-term storage is not practical. The corresponding benzyloxycarbonyl (Z) derivatives are more stable and were in fact synthesized and used by Bergmann and Zervas[3] during the early days of rational peptide synthesis following the classic discovery of the Z function. Unfortunately even these chlorides proved not to be generally storable, undergoing both hydrolysis and conversion to the corresponding Leuch's anhydrides[4] and mainly for that reason rapidly went out of fashion. Very recently new in situ methods for the preparation of Z amino acid chlorides have been described.[5] At least partly in response to the problems encountered by early investigators in the

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(2) Losse, G.; Wehrstedt, K.-D. *Z. Chem.* **1981**, *21*, 148.
(3) Bergmann, M.; Zervas, L. *Chem. Ber.* **1932**, *65*, 1192.
(4) See, for example: (a) Bergmann, M.; Zervas, L.; Ross, W. F. *J. Biol. Chem.* **1935**, *111*, 245. (b) Goldschmidt, S.; Lautenschlager, W.; Kolb, B.; Zunach, G. *Chem. Ber.* **1964**, *97*, 2434. (c) Ronwin, E. *Can. J. Chem.* **1957**, *35*, 1031. (d) Bergmann, M.; Zervas, L.; Schleich, H.; Lienert, F. *Hoppe-Seyler's Z. Physiol. Chem.* **1932**, *212*, 72.
(5) (a) Schmidt, U.; Kroner, M.; Beutler, U. *Synthesis* **1988**, 475. (b) Munyemana, F.; Frisque-Hesbain, A.-M.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* **1989**, 3077.

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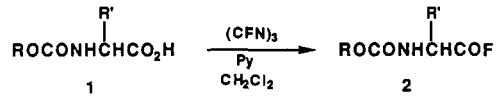
practical utilization of simple Z-protected amino acid chlorides numerous special coupling agents were devised for both stepwise and segment peptide bond formation.[6] With such reagents the greater stability that is traded for lesser reactivity, clearly important in the case of segment coupling, has not unequivocally been shown to be necessary in the case of stepwise coupling.

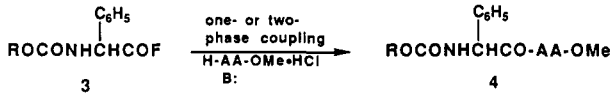
It has now been found, consonant with our experience in the FMOC series, that both α-BOC and α-Z amino acid fluorides **2** can be readily synthesized, via cyanuric fluoride, often in crystalline form, although, especially in the *t*-BOC series, they differ from their FMOC analogues in requiring being held at refrigerator temperatures for long-term storage. When the conversion of **1** (R = *t*-Bu, R′ = Bn)



to the corresponding fluoride was attempted by refluxing the cyanuric fluoride–methylene dichloride reaction mixture, the only product obtained was the corresponding Leuch's anhydride.[7]

Some of the acid fluorides synthesized during the course of this work are collected in Table I along with key physical properties. In the BOC series all such fluorides were obtained in crystalline form except for those derived from valine, isoleucine, proline, and *O*-benzylthreonine. Z derivatives showed a lesser tendency to crystallize (fluorides from valine, proline, β-*tert*-butylaspartic acid, γ-*tert*-butylglutamic acid, ε-BOC-lysine and *O*-*tert*-butylserine were obtained as oils). For those acid fluorides obtainable only as oils, identity, as established by IR and NMR data, was confirmed by conversion to at least one known solid dipeptide derivative. These are collected in Table II.

As previously noted for reactions involving FMOC amino acid fluorides,[1] the relative stability of these new reagents is not compromised by low reactivity. Coupling reactions require only a few minutes and proceed without racemization under appropriate conditions. Initial racemization tests involved the highly sensitive α-phenylglycine derivatives **3**. Racemization is readily visualized on coupling



with alanine methyl ester by an NMR technique at both the methyl ester and *C*-methyl residues.[8,9] Whether two-phase or one-phase coupling procedures were adopted, no significant racemization (<1%) was observed with either BOC- or Z-α-phenylglycine fluoride. In the case of the diastereomeric pair, Z-Phg-Ala-OMe (δ_{OMe}: LL 3.699; DL 3.783), the sensitivity of the NMR method was confirmed with preformed mixtures containing 1% and 2% of the DL isomer in the presence of the LL form. Coupling to a more hindered amino acid ester is expected to be more

Table I. BOC and Z Amino Acid Fluorides[a]

compound	yield (%)[b]	mp (°C)[c]	$[\alpha]_D$ (c 1, EtOAc), 22 °C
BOC-Gly-F	89.0	52–4	
BOC-Ala-F	65.4	62–4	−17.2
BOC-Val-F[d]	86.8	36–8	+6.8
BOC-Leu-F[e]	68.0	55–7	−17.4
BOC-Ile-F	77.3		+10.9
BOC-Pro-F	87.6		−35.2
BOC-Phe-F	75.8	66–8	−27.9
BOC-D-Phe-F	73.8	67–9	+28.2
BOC-Trp-F[f]	78.4	114 dec	−15.9
BOC-Ser(Bn)-F[e]	65.8	37–8	+13.9
BOC-Thr(Bn)-F	93.2		+22.6
BOC-Lys(Z)-F	78.0	84–6	−7.2
BOC-Asp(OBn)-F	89.0	52–4	−13.2
BOC-Met-F[e]	59.8	32–4	−23.5
BOC-Glu(OBn)-F	81.0	50–1	−14.5
BOC-Tyr(Bn)-F	80.0	58–60	−19.0
BOC-Cys(Bn)-F	67.0	52–3	−42.7
BOC-Phg-F	75.0	54–6	+106.0
BOC-D-Phg-F	72.7	56–8	−106.3
Z-Gly-F	83.3	45–7	
Z-Ala-F[g]	78.0	39–41	−7.8
Z-Val-F	81.0		+10.2
Z-Pro-F	82.9		−33.5
Z-Phe-F	73.3	87–8	−36.4
Z-D-Phe-F	78.3	84–6	+34.8
Z-Lys(BOC)-F	87.5		−5.5
Z-Asp(O-*t*-Bu)-F	70.0	42–4	+4.8
Z-Glu(O-*t*-Bu)-F	83.8		−17.2
Z-Met-F	82.5		−23.0
Z-Ser(*t*-Bu)-F	89.6		+28.2
Z-Phg-F	81.4	75–7	+82.0
Z-D-Phg-F	84.7	76–8	−82.5

[a] General procedure. To a stirred solution of the BOC or Z amino acid (2 mmol) in dry CH_2Cl_2 (5 mL) and pyridine (2 mmol, 162 μL) kept under a N_2 atmosphere was added cyanuric fluoride (10 mmol, 900 μL) at −20 to −10 °C. A precipitate or emulsion formed and gradually increased in amount. In selected cases the reaction was followed by TLC. Quenching a small amount of the reaction mixture in dry methanol, waiting for 10–15 min, and spotting on a TLC plate (SiO_2) generally showed the methyl ester but no residual free acid after 45 min (elution by $CHCl_3$/MeOH/HOAc 9/1/0.1). After stirring at −10 °C for 1 h, crushed ice was added along with 10 mL of additional CH_2Cl_2. The organic layer was separated and the aqueous layer extracted once with 5 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were extracted with 10 mL of ice-cold water and dried ($MgSO_4$), and the solvent was removed with a rotary evaporator at room temperature. Recrystallization once from CH_2Cl_2–hexane or hexane alone gave the pure acid fluoride. In more recent preparations less cyanuric fluoride (about 2 mmol per mol of acid) was used. [b] Yields given are of pure isolated fluorides following a single crystallization. Additional recrystallizations did not always enhance the purity. HPLC analyses as previously reported[1] for the corresponding FMOC analogues were carried out in selected cases and revealed small amounts of free acid. [c] Where no melting point is given the compound was obtained as a clear, colorless oil. Exhaustive evacuation of the oils at 5 mm or less helps to ensure efficient drying. Retention of significant amounts of water may lead to slow hydrolysis on standing. All crystalline compounds gave elemental analyses for C, H, and N that agreed with theoretical values (±0.3%). All fluorides in the table showed infrared carbonyl absorption near 1847 cm^{-1} (range 1833–1859 cm^{-1}). All oily products were derivatized as an appropriate dipeptide. See Table II. [d] In this case long evacuation with an oil pump caused the oil to solidify. The solid was not further recrystallized but identified by conversion to a known dipeptide as noted for other fluorides obtained as oils. See Table II. [e] Recrystallized from hexane alone. [f] Two recrystallizations were necessary in this case to remove a yellow byproduct. [g] Ether–hexane was used for recrystallization in this case.

(6) Jones, J. H. In *The Peptides*; Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1979; Vol. 1, p 65.

(7) Often obtained as an oil, the Leuch's anhydride was also obtained once as a crystalline solid [mp 90–92 °C; IR (KBr) 3362 (NH), 1852, 1777 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 2.9–3.3 (m, 2, $CH_2C_6H_5$), 4.55 (m, 1, CH), 6.6 (s, 1, NH), 7.2–7.45 (m, 5, phenyl)] identified by comparison of properties with those described: Daly, W. H.; Poche, D. *Tetrahedron Lett.* **1988**, 5859. Interestingly when either BOC-Phe-F or Z-Phe-F were refluxed in anhydrous THF for 2 h the crystalline protected amino acid fluorides were recovered unchanged upon removal of solvent.

(8) Carpino, L. A. *J. Org. Chem.* **1988**, *53*, 875.

(9) (a) Davies, J. S.; Thomas, R. J.; Williams, M. K. *Chem. Commun.* **1975**, 76. (b) Davies, J. S.; Mohammed, A. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2982. (c) Davies, J. S.; Thomas, R. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1639. (d) Davies, J. S.; Hakeem, E. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1387.

Table II. Dipeptide Esters via Coupling of BOC and Z Amino Acid Fluorides[a]

dipeptide[b]	recryst solvent	prep method	yield, %[c]	mp, °C[d]	α_D, deg, t[d]
BOC-Val-Gly-OEt[e]	ether/hexane	*f*	69.7	66–8[e]	−26.8 (*c* 0.5, EtOH), 22
			(92.7)	(98–9)	(−28.3, *c* 1, EtOH, 25)
BOC-Ile-Gly-OMe[g]	cyclohexane	*f*	76.7	74–6	−11.4 (*c* 0.5, DMF), 22
			(93.3)	(83–4)	(−11.8, *c* 1, DMF, 21)
BOC-Pro-Phe-OMe[h]	Et_2O/hexane	*f*	74.5	71–2	−54.1 (*c* $CHCl_3$), 22
			(93.1)	(74–6)	(−53, 25)
BOC-Thr(Bn)-Phe-OMe[i]	hexane	*f*	76.5	80–2	+7.6 (*c* 1, MeOH), 22
			(92.6)	(85–7.5)	(+7.8, 20)
BOC-Phg-Ala-OMe[j]	CH_2Cl_2/hexane	*k*	82.0	126–8	+45.0 (*c* 1, DMF), 22
			(95.1)		
BOC-D-Phg-Ala-OMe[j]	CH_2Cl_2/hexane	*k*	78.5	109–111	−76.8 (*c* 0.5, DMF), 22
			(94.7)		
Z-Phg-Ala-OMe[j]	CH_2Cl_2	*k*	75.7	173–5	+34.5 (*c* 1, DMF), 22
			(91.2)		
Z-D-Phg-Ala-OMe[j]	CH_2Cl_2	*k*	72.8	175–7	−59.5 (*c* 1, DMF), 22
			(91.9)		
Z-Phg-Aib-OMe[j]	CH_2Cl_2/hexane	*k*	71.1	122–4	+51.8 (*c* 1, DMF), 22
			(89.5)		
Z-D-Phg-Aib-OMe[j]	CH_2Cl_2/hexane	*k*	73.7	122–4	−52.5 (*c* 1, DMF), 22
			(93.8)		
BOC-Phg-Aib-OMe[j]	CH_2Cl_2/hexane	*k*	74.3	82–5	+64.4 (*c* 1, DMF), 22
BOC-D-Phg-Aib-OMe[j]	CH_2Cl_2/hexane	*k*	72.4	83–5	−62.9 (*c* 0.5, DMF), 22
BOC-Phe-Ala-OMe[i]	CH_2Cl_2/hexane	*f*	75.8	100–2	−18.5 (*c* 0.5, MeOH), 22
			(91.4)	(98–9)	(−18.0, 25)
BOC-D-Phe-Ala-OMe[j]	hexane	*f*	72.2	82–4	−3.6 (*c* 1, DMF), 22
			(94.6)		
Z-Val-Gly-OEt[m]	EtOH	*f*	65.8	160–61	−4.8 (*c* 1, EtOAc), 22
			(92.3)	(169–70)	(−6.0, 24)
Z-Pro-Ala-OMe[n]	EtOAc/hexane	*f*	69.7	75–7	−74.2 (*c* 1, EtOH), 22
			(89.1)	(79–80)	(−74.0, *c* 2, EtOH, 28)
Z-Glu(O-*t*-Bu)-Ala-OMe[o]	CH_2Cl_2/hexane	*f*	73.2	94–6	−12.8 (*c* 1, DMF), 22
			(94.4)	(99–101)	(−12.5, 23)
Z-Ser-Gly-OEt[p,q]	CH_2Cl_2/hexane	*f*	80.7	93–5	−6.2 (*c* 0.5, EtOH), 22
			(99.2)	(106–7)	(−5.9, *c* 1, EtOH, 20)
Z-Met-Gly-OEt[q]	$CHCl_3$/hexane	*f*	78.7	91–3	−18.6 (*c* 1, EtOH), 22
			(94.5)	(96–7)	(−18.6, *c* 4.5, EtOH, 27)
Z-Lys(BOC)-Gly-O-*t*-Bu[r]	ether/hexane	*f*	73.4	56–8	−14.5 (*c* 1, MeOH), 22
			(93.8)	(67–8)	(−13.5, *c* 2.1, MeOH, 23)

[a] Dipeptides derived from proteinogenic amino acids were those obtainable only as oily protected amino acid fluorides and were used for characterization by comparison with reported data. Those derived from α-phenylglycine were used for racemization studies as described below, see footnote *k*. [b] Known dipeptide properties were compared with recorded data. [c] The yield is given of purified material obtained by crystallization from the solvent listed. The crude yield is given in parentheses. [d] The reported mp and rotation data are given in parentheses. The concentration is omitted if it is the same as reported. [e] Schnabel, E. *Liebigs Ann. Chem.* **1965**, *688*, 238. After melting at 66–68 °C the liquid resolidified and then melted at 86–88 °C. The single, higher mp reported was not observed although the rotation data agreed with the literature results and the IR and NMR data were consistent with the assigned structure. [f] As an example 241 mg (1.1 mmol) of BOC-Val-F in 10 mL of CH_2Cl_2 was added over a period of 60 s to a stirred solution of H-Gly-OEt·HCl (139 mg, 1 mmol) in 10 mL of H_2O containing 170 mg of $NaHCO_3$. The mixture was stirred at room temperature for 20 min (after 5–10 min IR examination showed the acid fluoride band at 1845 cm^{-1} to have essentially disappeared). After washing of the CH_2Cl_2 solution two times each with 5% HCl, 10% $NaHCO_3$, and H_2O, the dried solution was evaporated in vacuo and the crude dipeptide recrystallized from ether–hexane to give the pure dipeptide (see table for characterization data). [g] Niedrich, H. *Chem. Ber.* **1967**, *100*, 3273. [h] Paul, R.; Anderson, G. W. *J. Org. Chem.* **1962**, *27*, 2094. [i] Zeigler, A. R.; Anfinsen, C. B. *J. Am. Chem. Soc.* **1973**, *95*, 880. [j] New dipeptides showed consistent IR and ^1H NMR spectral data and satisfactory elemental analyses for C, H, and N (±0.3%). [k] Racemization tests involving the coupling of BOC- and Z-Phg-F were carried out via either two-phase techniques (as given in footnote *f* above or as described.[12] One-phase couplings were carried out by addition of the acid fluoride in dry CH_2Cl_2 to a solution of the amino acid ester hydrochloride and 2 equiv of diisopropylethylamine or *N*-methylmorpholine in CH_2Cl_2 over a period of 60 s.[8] Workup followed the two-phase technique. For dipeptides derived from α-aminoisobutyric acid methyl ester (H-Aib-OMe) the chiral shift reagent tris[3-((trifluoromethyl)hydroxymethylene)-(+)-camphorato]europium(III) (Aldrich 17-649-4) was added in order to visualize any possible loss of chirality. In this case 20 mg of the pure enantiomeric dipeptide esters were dissolved in 0.5 mL of $CDCl_3$ and separately treated with varying amounts of shift reagent. Separation of appropriate peaks was first visible with 5 mg of shift reagent, with the effect being maximized after 10 mg had been added. Additional shift reagent caused little effect except for broadening. The initial methyl ester peak appeared at 3.717 ppm; after addition of 10 mg of shift reagent the L and D isomers showed this peak at 3.964 and 3.844, respectively. Correspondingly the α,α-dimethyl groups initially at 1.517 ppm split into two peaks for the L isomer at 1.671 and 2.218 ppm and for the D isomer at 1.741 and 2.063. [l] Nitecki, D. E.; Halpern, B.; Westley, J. W. *J. Org. Chem.* **1968**, *33*, 864. [m] Bergel, F.; Stock, J. A. *J. Chem. Soc.* **1960**, 3658. [n] (a) Schröder, E. *Liebigs Ann. Chem.* **1946**, 679, 207. (b) Savige, W. E. *Aust. J. Chem.* **1961**, *14*, 664. [o] Meienhofer, J. Z. *Naturforsch* **1964**, *19b*, 114. [p] In this case the coupling of oily Z-Ser(*t*-Bu)-F with H-Gly-OEt gave in 78.8% (93.9%) yield the dipeptide Z-Ser(*t*-Bu)-Gly-OEt, mp 68–70 °C, α^{22}_D +6.8 (*c* 0.5, EtOH). Since the melting point and specific rotation of the dipeptide ester could not be located, the ester was treated with TFA/CH_2Cl_2 to give the free hydroxy dipeptide ester cited. [q] Yamada, S.; Takeuchi, Y. *Tetrahedron Lett.* **1971**, 3595. [r] Walshaw, K. B.; Young, G. T. *J. Chem. Soc.* **1965**, 786.

demanding.[10] Reaction of BOC-Phg-F or Z-Phg-F with α-aminoisobutyric acid methyl ester by the two-phase method led to no significant racemization (<1%). In this case a chiral shift reagent[11] was added to the crude product in order to detect any racemized dipeptide. When Z-Phg-Aib-OMe was prepared by the one-phase method[8] using DIEA as base in CH_2Cl_2 13.2–15.3% contamination by the D enantiomer was observed. Upon starting with

(10) Compare: Goodman, M.; McGahren, W. J. *Tetrahedron* **1967**, *23*, 2031.

(11) (a) Goering, H. L.; Eikenberry, J. N.; Koermer, G. S. *J. Am. Chem. Soc.* **1971**, *93*, 5913. (b) McGreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038.

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

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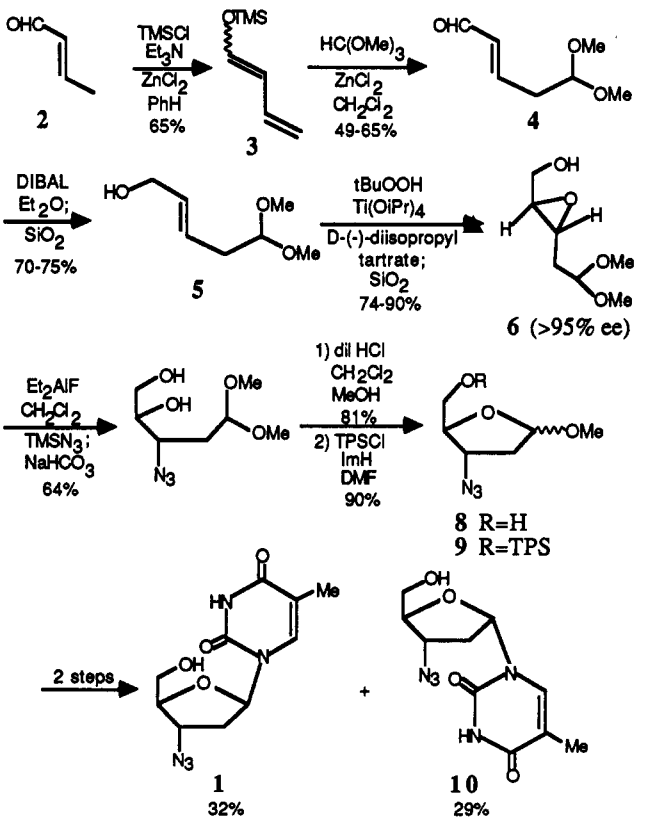
Summary: An efficient stereospecific total synthesis of AZT (nine steps from crotonaldehyde) is reported in which the chirality is introduced via Sharpless epoxidation and therefore intermediates for the synthesis of both D- and L-AZT are easily produced.

The modified nucleoside, 3′-azido-3′-deoxythymidine (AZT or zidovudine, **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-

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