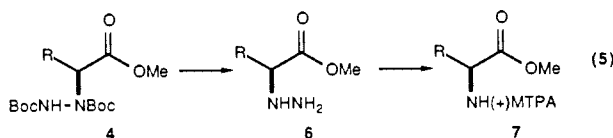


5f (R = CMe₃) were also subjected to the same reaction sequence with equal success¹¹ in yields ranging from 83% to 94%. Since the diastereomeric purity of the derived MTPA amides 7c (R = CH₂Ph), 7e (R = CHMe₂), and 7f (R = CMe₃) was 200:1, racemization, which could have presented a problem during either transesterification or hydrazine reduction, proved to be inconsequential (eq 5).



In summary, the electrophilic "amination" of chiral enolates with DBAD provides an expedient approach to the synthesis of both α -hydrazino¹² and α -amino acids. This methodology nicely complements the chiral glycinate alternatives reported by others.^{2a,2b}

Acknowledgment. Support has been provided by the National Science Foundation (CHE-8501707) and the National Institutes of Health (GM-33328). The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is also acknowledged for providing NMR facilities.

Supplementary Material Available: Detailed general procedures for enolate amination, transesterification, and hydrolysis and full spectral data (13 pages). Ordering information given on any current masthead page.

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Amination of Chiral Enolates by Dialkyl Azodiformates. Synthesis of α -Hydrazino Acids and α -Amino Acids[†]

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Received July 11, 1986

The natural occurrence of about 700 nonprotein amino acids as well as the importance of the approximately 20 amino acids common in proteins has stimulated recent work on asymmetric synthesis of such compounds.¹⁻³ Their structural analogues, α -hydrazino acids (1), are effective inhibitors of certain amino acid metabolizing enzymes, especially ammonia lyases⁴ and pyridoxal phosphate dependent proteins.⁵ As a result, some α -

[†] Presented in part at the International Symposium on the Chemistry of Natural Products, June 23-26, 1985, Edmonton, Alberta, Canada.

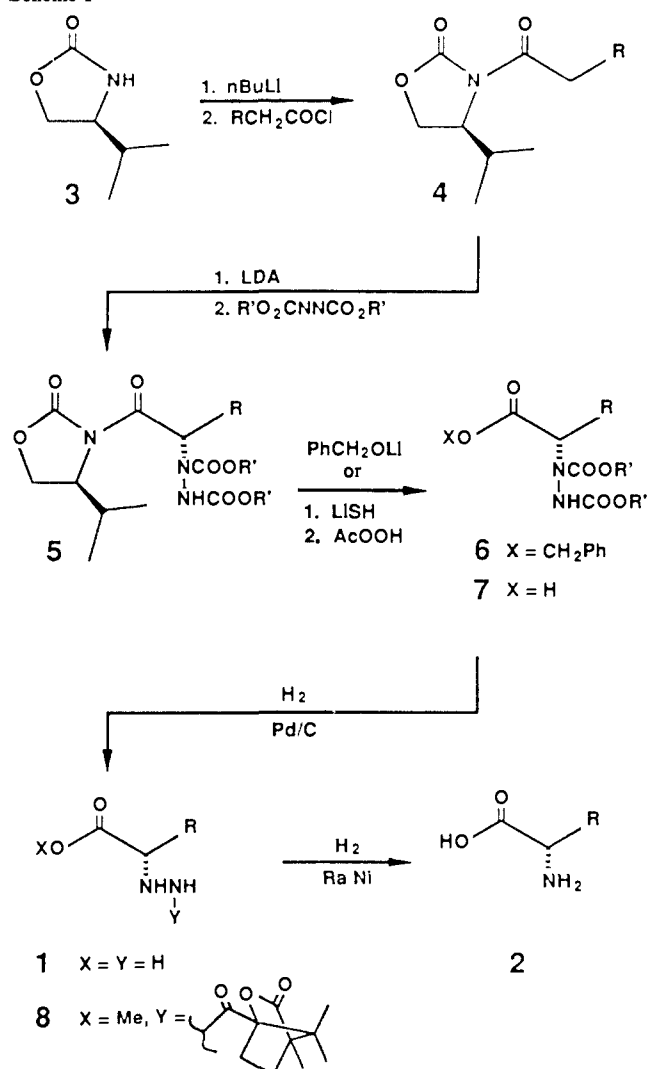
(1) See: Evans, D. A., et al., preceding paper in this issue. Professor Evans has independently developed similar methodology. We are deeply indebted to him for generously sharing his unpublished results with us after we learned of each other's work in July 1985.

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Scheme I



hydrazino acids (1) possess antibiotic activity^{5d,6} or produce interesting physiological effects.⁷ These attributes and the known conversion of 1 to the parent α -amino acids (2) by nitrosation⁸ make an efficient stereospecific synthesis of these analogues highly desirable. Most previous syntheses of 1 have involved reduction of α -diazo esters,⁹ nitrosation and reduction of α -amino acids,¹⁰ Hofmann rearrangement of α -ureido acids,^{8,11} or treatment of α -halo carboxylic acids with hydrazine.¹² Frequently these procedures suffer from loss of optical purity or low yields. We

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Table I. Amination of Enolates of **4** with R'O₂CNNCO₂R'

entry	R	R'	% yield of 5 ^a	diastereomeric ratio of 5 ^b	yield of 6 or 7 ^a	yield of 1 ^a	enantiomeric ratio of 1 ^c
a	Me	CH ₂ Ph	91	90:10 ^d	82 ^e 93 ^f	98 92	88:12 72:28 ^g
b	CH ₂ Ph	Me	83	69:31			
c	CH ₂ Ph	Et	88	75:25			
d	CH ₂ Ph	CH ₂ Ph	90	94:6	85 ^e 87 ^f	82 92	94:6 88:12
e	CH ₂ Ph	C(CH ₃) ₃	88	93:7	97 ^f	81 ^h	83:17 ^g
f	CH(CH ₃) ₂	CH ₂ Ph	85	97:3	86 ^f	98	97:3
g	Me	C(CH ₃) ₃	92		74 ^f	83 ^h	86:14 ^g

^aSee supplementary material for experimental procedures. Yield of isolated compounds. ^bDiastereomeric ratio determined by HPLC ($\pm 2\%$). ^cDiastereomeric ratio determined by GC of **8** ($\pm 0.5\%$). ^dStructure of major diastereomer is shown. ^eCleavage with LiSH to produce **7**. ^fCleavage with PhCH₂OLi to produce **6**. ^gEnantiomeric ratio determined by optical rotation. ^hDeprotected by hydrogenolysis followed by treatment with trifluoroacetic acid.

now report¹ that α -hydrazino acids (**1**) are easily accessible in good yield and optical purity through amination of chiral enolates by dialkyl azodiformates, and that the corresponding α -amino acids (**2**) are readily obtained by Raney nickel hydrogenolysis of **1**.

Previous studies by Evans and co-workers had shown that enolates of chiral carboximides **4** attack a variety of electrophiles with high diastereoselectivity.¹³ This suggested that a source of electrophilic nitrogen¹⁴⁻¹⁷ could provide a short sequence for stereospecific introduction of this element at the α -position of a carboxylic acid. When preliminary experiments indicated that most of these electrophilic nitrogen reagents^{14,15} are unsuitable, attention shifted to dialkyl azodiformates. Stolle, Carpino, and others had demonstrated that some carbon nucleophiles (e.g., Grignard reagents¹⁶) can add to azodiformates or related *N*-acyl azo compounds in the desired fashion.^{16,17} Thus, the chiral carboximides **4** (Scheme I), obtained by *N*-acylation of oxazolidinone (**3**), were converted to their respective *Z* lithium enolates¹³ (1.1 equiv of LDA, THF, -78°C) and a solution of the dialkyl azodiformate¹⁸ (1.1 equiv, 0.8 M in THF, -78°C) was added. The reactions were then immediately quenched by addition of NH₄Cl (5% in H₂O) to give the aminated carboximides **5** in good yield (Table I). The diastereomeric ratios, as determined by HPLC,¹⁹ indicate that the substitution of both the dialkyl azodiformate and the acyl side chain of **4** influence the selectivity. As the size of the R' group on the aminating reagent increases the ratio improves (Me < Et < CH₂Ph \approx *t*-Bu). Similarly, greater bulk of the acyl side chain also increases the diastereoselectivity (Me < CH₂Ph < *i*-Pr). The reaction is extremely rapid even at -110°C , and

such lower temperatures do not alter the diastereomeric ratios significantly.²⁰ Since the diastereomers of **5** are generally difficult to separate by conventional column chromatography, the use of more hindered dibenzyl or di-*tert*-butyl azodiformates is synthetically advantageous.

Methods for removal of the chiral oxazolidinone moiety were also examined. The transesterification method (PhCH₂OLi, 2 equiv, THF, 0°C , 15 min) reported for other carboximides^{13b} often caused some epimerization at the newly aminated center in our cases. Thus **5f** was transformed to **6f** with no loss of stereochemistry, but under similar conditions **5d** gave **6d** with 11% racemization.²¹ To avoid this, cleavage with hydrosulfide anion (HS⁻) was investigated because of its increased nucleophilicity and decreased basicity.²³ Since loss of stereochemistry with alkoxide (PhCH₂OLi) probably occurs after departure of the oxazolidinone moiety,^{13c} reaction of **5** with anhydrous LiSH (10 equiv, THF, 20°C , 10 min) has the additional advantage of generating the anion of the thiol acid, which is less prone to deprotonation at the α -position than an ester. Treatment of the resulting reaction mixture with 1:1 THF/peracetic acid (40% in H₂O) gives the carboxylic acids **7** in 76–85% yield after medium-pressure reverse-phase chromatography (RP-8, 3:1 MeOH/H₂O). Compounds **6** and **7** were hydrogenolyzed to the free α -hydrazino acids (**1**), which were converted to **8** for stereochemical analysis.²¹ In the cases studied (Table I), the amount of racemization (if any) is less than 1%, using the hydrosulfide cleavage.

Since Raney nickel²⁴ was known to hydrogenolyze the nitrogen–nitrogen bond of hydrazine derivatives,²⁵ this approach was used to convert the α -hydrazino acids (**1**) to the parent α -amino acids (**2**). In a typical example, hydrogenation of **1d** (R = CH₂Ph) with Raney nickel (500 psi, 10% aqueous HOAc) produced L-phenylalanine in 97% yield without detectable racemization.²⁶

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(20) In several cases the diastereomeric ratios of **5** could be determined by ¹H NMR spectroscopy. Although standard conditions (CDCl₃, 298 K) produce spectra with broad peaks due to restricted rotation, spectra with sharp signals could be obtained at elevated temperatures (toluene-*d*₈, 374 K).

(21) Enantiomeric ratios of **6** or **7** were determined by hydrogenolysis (H₂, 5% Pd/C, THF/HCl (6 N) 10:1) to the free α -hydrazino acid salt (**1**), which was then converted to the diastereomeric camphanamide methyl esters (**8**) by using (–)-camphanoyl chloride followed by diazomethane.²² The mixture was analyzed by gas chromatography (DB-17, 15 m \times 0.53 mm bonded FSOT column, 170°C for 2 min, $2^\circ\text{C}/\text{min}$ to 250°C , 250°C for 5 min, 9.5 psi).

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Hence the amination of enolates derived from **4** with dibenzyl or di-*tert*-butyl azodiformates provides an efficient route for conversion of carboxylic acid derivatives to both chiral α -hydrazino acids (**1**) and α -amino acids (**2**).

Acknowledgment. We thank Professor David A. Evans (Harvard University) for valuable discussions and suggestions.¹ Financial support from the National Institutes of Health (GM 29826), the Alberta Heritage Foundation for Medical Research, and the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Supplementary Material Available: Experimental descriptions, analytical procedures, and spectral data for new compounds (12 pages). Ordering information is given on any current masthead page.

Photoinduced Reversible Conformational Transition of Polypeptide Solid Membranes

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Received March 12, 1986

The photocontrol of physical and chemical properties of polymer gels and membranes with photochromic residues has been the subject of numerous recent investigations.¹⁻⁴ Photoinduced conformational changes of polypeptides in solution have been observed for poly(L-aspartates)⁵⁻⁹ and poly(L-glutamates),¹⁰⁻¹⁴ with azobenzene derivatives in their side chains. No report has appeared, however, on photoinduced α -helix to coil transition of polypeptide solid membrane. We report here on the photocontrol of the secondary structure of polypeptide solid membranes composed of poly(L-glutamic acid) (PGA) containing pararosanine (rose) groups in the polymer side chains based on a cooperative effect between photodissociation of the pararosanine moiety and

Scheme I

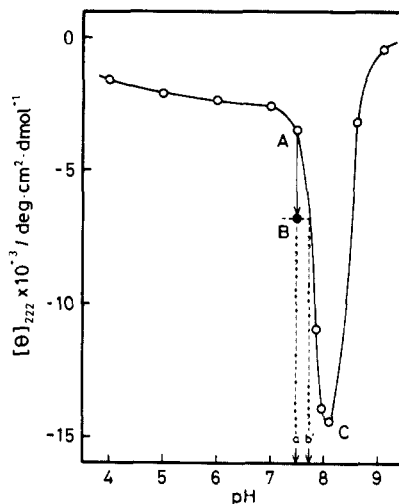
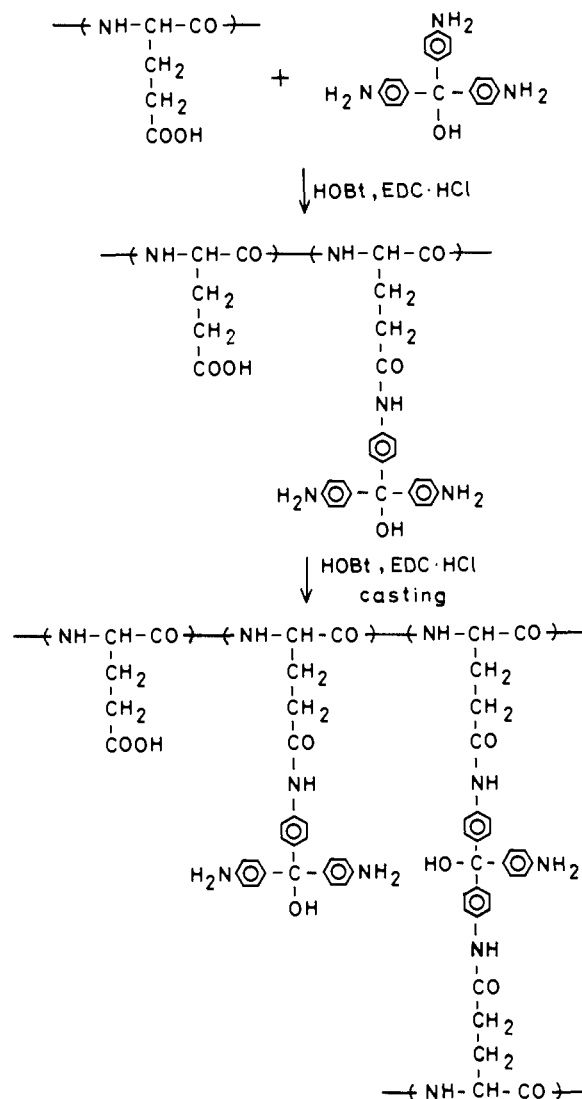


Figure 1. pH dependence of minimum ellipticity, $[\theta]_{222}$, of a dark-adapted membrane of poly(L-glutamic acid) containing 10.5 mol % pararosanine groups in aqueous solution at 25 °C.

the induced acid dissociation of the L-glutamic acid group in the membrane.

PGA polymers with incorporated pararosanine groups (rose-PGA) were synthesized by the condensation reaction of PGA with pararosanine in the presence of *N*-hydroxybenzotriazole (HOBT) and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide

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