If correct, this mechanism would suggest the chemical significance of a NADH-flavin couple in the native P-450 system.[4]

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Electrophilic Glycinates: New and Versatile Templates for Asymmetric Amino Acid Synthesis

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The number of naturally occurring α-amino acids has grown substantially beyond the roughly 20 amino acids normally found in proteins; over 500 are now known.[1] In addition, there has been a tremendous surge of interest in the asymmetric preparation of relatively inaccessible unnatural amino acids whose potential biological properties and general synthetic utility are just beginning to be realized. Of the methods presently available, there is a general lack of access to optically pure α-monosubstituted α-amino acids and derivatives in both the D and L configuration. Several groups have recently reported the asymmetric alkylation of amino acid derived enolates[2] to furnish α-disubstituted amino acids and, in one approach,[3] the enolates of optically active lactim ethers of diketopiperazines furnishes the α-monosubstituted α-amino acids. The more classical approaches involving the asymmetric hydrogenation of prochiral dehydro amino acid derivatives[4] or hydrogenation of chiral dehydro amino acid derivatives[5] suffer from the range of substitution accessible on the α-"R" group and the variations in the percent asymmetric synthesis (i.e., % ee). In this preliminary account, we wish to report a new and general method for preparing both D- and L-α-monosubstituted α-amino acids via C-C bond-forming reactions on *electrophilic* glycinates[6] that is complementary to the existing enolate-based methodologies.

According to Tischler et al.,[7] D,L-*erythro*-α,β-diphenyl-β-hydroxyethylamine is efficiently resolved on large scale through the agency of the derived glutamate salts to furnish both optically pure antipodes of **1**.[7] Sequential N-alkylation with ethyl bromoacetate (Et_3N, THF, 25 °C), Schotten-Baumann acylation (BnOCOCl, $NaHCO_3$(aq), CH_2Cl_2), and cyclization (catalytic *p*-TsOH, PhH, reflux) furnished the optically pure lactone **2** (mp

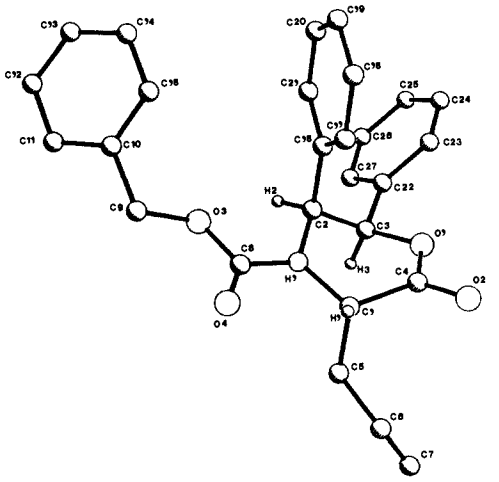
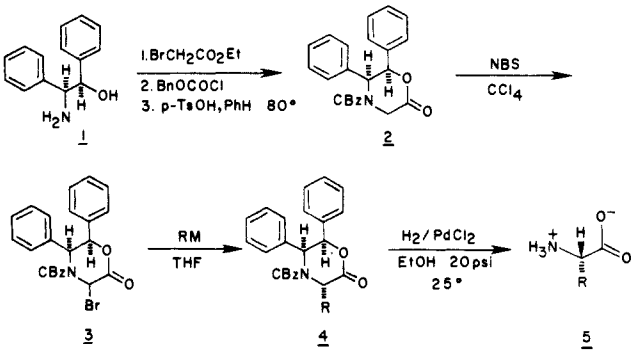


Figure 1. Molecular Structure of **4** (R = $CH_2CH{=}CH_2$). Atoms are shown as spheres of fixed, arbitrary radius.

Scheme I



200 °C; $[\alpha]^{25}_D$ −66.7°, *c* 0.815, CH_2Cl_2) in 65% overall yield from **1**. Bromination of **2** was realized by treatment with 1 equiv of NBS in warm CCl_4 to afford after filtration of insoluble succinimide the bromide **3** as an amorphous white powder. The bromide **3** is produced in essentially quantitative yield[8] (crude, by ^1H NMR) but decomposes upon exposure to silica gel chromatography. The bromide can be stored indefinitely as a solid in the dark and is directly used for the subsequent C-C coupling reactions as described in Scheme I.

The bromoglycinate **3** is a very reactive electrophile toward a variety of carbon nucleophiles; those described herein constitute a superficial initial screening and are representative of many possible extensions and variations. A typical procedure is described below for the preparation of β-ethylaspartate.

To a stirred solution of lactone **2** (0.2 g, 0.51 mmol) in refluxing CCl_4 (60 mL) was added NBS (0.11 g, 0.62 mmol). The mixture was allowed to reflux for 35 min, cooled to 0 °C, filtered, and evaporated to afford the bromide **3** as a white powder which was used directly for the next step. The bromide **3** (0.108 g, 0.23 mmol) was dissolved in THF (4 mL) and the (*tert*-butyldimethylsilyl)ketene acetal of ethyl acetate (0.11 mL, 0.58 mmol) was added followed by a solution of anhydrous $ZnCl_2$ (1.5 mL of a 0.17 N solution in THF) at 25 °C. The reaction was allowed to stir for 1 h at 25 °C, poured into H_2O, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (3:1, hexanes/EtOAc) to afford 78.6 mg (71%) of the lactone **4** (R = CH_2CO_2Et). This material was dissolved in absolute EtOH (3 mL) plus THF (1 mL), $PdCl_2$ (13.2 mg) was added, and the system was flushed with H_2 and hydrogenated at 20 psi for 24 h at 25 °C. Filtration of the catalyst through Celite, concentration, and addition of Et_2O precipitates the zwitterionic amino acid (**5**, R = CH_2CO_2Et) (25 mg, quantitative) as a white powder. The percent asymmetric synthesis (% ee) on this and the other amino acids listed in the table was determined by acylating[9] the crude amino acid with (+)-α-methoxy-α-(tri-

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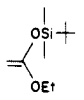
Table I

RM	reactn condtns	yield 4	amino acid 5[a]	% ee
	1.2$ZnCl_2$, THF, 25 °C, 1 h	71%	D-β-ethylaspartate	96.6
	1.2$ZnCl_2$, THF, 25 °C	54%	L-homophenylalanine	96.9
	2$ZnCl_2$, THF, 25 °C, 3 days	68%	L-norvaline, L-allylglycine[b]	98.3
MeZnCl	THF, 25 °C, 1 h	46%	L-alanine	96.8
$Me_2CuCNLi_2$	THF, −78 °C, 30 min	28%		
$Bu_2CuCNLi_2$	THF, −78 °C 30 min	48%	L-norleucine	99.5

[a] The conversions of 4 → 5 proceed in essentially quantitative yields in all cases. [b] The conversion of 4 → 5 is carried out with Li/NH_3/EtOH.

fluoromethyl)phenylacetyl chloride and examination of the crude mixture by ^{19}F and ^1H NMR and comparison to the authentic diastereomers prepared from the racemic amino acids. We have also found that for substrates containing unsaturated functionality, such as the allyl case, the conversion of 4 → 5 can be performed by a dissolving metal reduction ($Li/NH_3(l)$/EtOH) and thus precludes the saturation of the olefin (see Table I for allylglycine).

The substrate 3 is best suited for coupling with "neutral" carbon nucleophiles, such as the silyl enol ethers; the diminished yields for the more basic organometallic reagents is due to competing reduction of 3 → 2. Examination of the crude coupling reaction mixtures (3 → 4) provided no evidence for the formation of alternative diastereoisomers (4); the diastereoselectivity of the nucleophilic additions to 3 in the cases studied is, therefore, excellent.

A single-crystal X-ray analysis of 4 (R = $CH_2CH{=}CH_2$) has been performed[10] as shown in Figure 1. The structure clearly shows that the nucleophile has attacked 3 or putative iminium species from the least hindered face to furnish, from the D series (of 1) after hydrogenation, L-norvaline as expected. This trend is followed for most of the carbon nucleophiles examined thus far. The notable and curious exception, however, was found in the preparation of β-ethyl aspartate. From the D-series lactone, D-β-ethylaspartate is produced in >96% ee which indicates that the resulting lactone 4 (R = CH_2CO_2Et) must possess the all-syn configuration. The molecular structure of 4 (R = $CH_2CH{=}CH_2$), shown in Figure 1, shows that the tetrahydrooxazinone has adopted a twist-boat conformation that situates the phenyl ring at C-2 (X-ray numbering) in a pseudoaxial orientation. It is reasonable to assume that a reactive intermediate derived from 3 would also have a similar conformation, since that shown avoids A strain as well as 1,3-diaxial interactions that would be experienced in alternative conformations.

It must be concluded that the *tert*-butyldimethylsilyl enol ether of ethyl acetate is selectively coupling from the sterically more encumbered face or that epimerization of an initially formed anti isomer to the syn isomer occurs under the reaction conditions. Efforts are under way to elucidate the factors governing this anomalous, yet highly selective, coupling reaction.

In summary, a new and potentially highly versatile method[11,12] for the preparation of natural and unnatural α-amino acids in both the D and L configuration has been developed. The percent asymmetric synthesis (% ee) for the cases studied herein are uniformly high, and the entire sequence beginning with benzoin[7] proceeds with efficiency, requiring only a single chromatographic isolation at the stage of 4. Efforts to further expand the scope and utility of this methodology are presently under active investigation in these laboratories.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for financial support of this work and an NIH Research Career Development Award (to R.M.W.). We also wish to express thanks to Professor Dave Evans for helpful discussions and communicating their results to us in a related system prior to publication.

Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom positions for the crystal structure of 4; ^1H NMR spectra of amino acids obtained without purification from the hydrogenation of 4, and listing of spectroscopic and analytical data for all new compounds (14 pages). Ordering information is given on any current masthead page.

(8) It was not possible to assign the relative configuration of the crude bromide due to slow conformational exchange on the ^1H NMR time scale.
(9) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.
(10) Data were collected on an Nicolet R3m X-ray diffractometer. All crystallographic computations were carried out using the SHELXTL program library (written by G. M. Sheldrick and supplied by Nicolet XRD for the Data General Eclipse S/140 computer in the crystallographic laboratory at Colorado State University). Lattice constants a = 29.325 (11) Å; b = 10.326 (1) Å; c = 25.316 (7) Å, β = 142.79 (1)°, monoclinic (C centered). R = 0.0711, R_w = 0.0637, GOF = 1.31.
(11) An example of racemic amino acid synthesis via electrophilic glycinates has recently appeared in addition to that mentioned in ref 6; see: O'Donnell, M. J.; Falmagne, J. B. *Tetrahedron Lett.* **1985**, *26*, 699.
(12) Various attempts at generating the enolate anions of 2 and 4 followed by electrophilic quenching resulted in decomposition only.

New Approach to Pyrrolo[1,2-*a*]indoles Using Azomethine Ylides‡

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In this paper we describe an efficient method to form the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole nucleus which is based on 1,3-dipolar cycloaddition methodology. We expect that this method will prove amenable toward the synthesis of more complex mitosene derivatives.[1-5]

We have previously found that α-cyano silyl amines are useful and convenient synthons for azomethine ylides.[6] In the light of our earlier findings, we envisioned a convenient approach to the pyrrolo-indole nucleus to lie along the pathway (i.e., 1 → 3) illustrated in Scheme I. The development of this strategy was based on literature reports that (cyanomethyl)amines can function

‡ Dedicated to Rolf Huisgen on the occasion of his 65th birthday.
† Alexander von Humboldt Senior Scientist, 1985; University of Wurzburg.
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(2) Rebek, J. R.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1671.
(3) Kametani, T.; Kigawa, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1607.
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