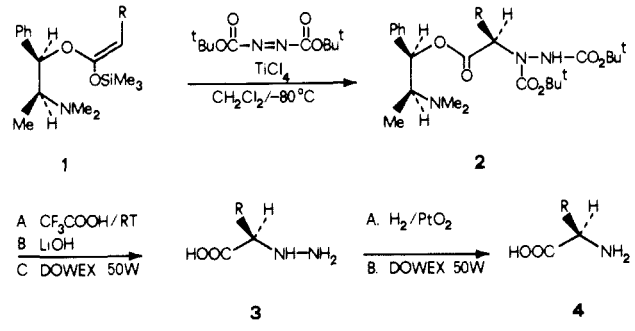
Table I. α-Hydrazino and α-Amino Acid Synthesis Using (1*R*,2*S*)-*N*-Methylephedrine

R	2, % yield	3, % yield	4, % yield	4		
				% ee (from crude 3)	% ee (from 3 after crystallization[b])	absolute config
CH_3	70[a]	78[b]	92	90.6[c]	≥98[c]	*R*
CH_2Ph	45[a]	81[b]	89[d]	91.0[d]	≥98[d]	*R*
$CH_2CH(CH_3)_2$	70[a]	81[b]	91	81.5[c]	≥98[c]	*R*
CH_2CH_3	65[a]	80[b]	93	84.0[c]	≥98[c]	*R*
$(CH_2)_3CH_3$	45[a]	78[b]	90	78.0[c]	≥98[c]	*R*

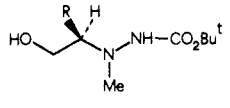
[a] The major stereoisomer can be separated and isolated by flash chromatography. [b] By use of the isolated major stereoisomer **2**, or by recrystallization of the α-hydrazino acid from EtOH–H_2O, ≥98% enantiomerically pure compound **3** was obtained. [c] The α-hydrazino acid hydrochloride was hydrogenolyzed (H_2–PtO_2) in water: by use of increasing amounts of HCl (from 0.1 to 6.0 N), increasing degrees of racemization were observed. [d] Hydrogenolysis of the α-hydrazino acid hydrochloride (H_2–PtO_2) in aqueous 0.05 N HCl gave *R*-cyclohexyl alanine with no racemization (see: Waser, E.; Brauchli, E. *Helv. Chim. Acta* **1924**, *7*, 740). Data reported in the table refer to (*R*)-cyclohexylalanine.

Scheme I



1 2 3 4

of the amination products with remarkable stereoselectivity (Table I).[13] The crude adducts **2** can be reduced (LAH, Et_2O, room temperature) to give *N*-methylephedrine and β-hydrazino alcohols **5**. Alcohol **5** (R = Me) was transformed into the stereoisomeric



5

Mosher esters ((−)-MTPA-Cl, Py, CCl_4),[14] and the diastereoisomeric excess was checked by 200-MHz ^1H NMR (≥95:5). Alternatively the crude adducts **2** were hydrolyzed (CF_3COOH, room temperature, 1.5 h) to give α-hydrazino esters which were saponified (LiOH, MeOH–H_2O, room temperature).[15] The mixture was then acidified, evaporated, and chromatographed on Dowex W50-X8 ion-exchange resin to give α-hydrazino acids **3** which were obtained ≥98% optically pure with a single recrystallization process. Reduction with H_2/PtO_2 gave the corresponding α-amino acids in high yield. The enantiomeric excess was checked by $[\alpha]_D$ comparison and by HPLC[16] or, much more efficiently, capillary VPC[17] using chiral columns.

In summary, a new practical method for the preparation of α-hydrazino acids and of natural and unnatural α-amino acids in both the *R* and *S* configuration has been developed.

Efforts to further expand the scope and utility of this methodology are presently under active investigation in this laboratory.

Registry No. (*E*)-**1** (R = Me), 98171-04-1; (*E*)-**1** (R = CH_2Ph), 103836-61-9; (*E*)-**1** (R = CH_2Pr-*i*), 103836-62-0; (*E*)-**1** (R = Et), 103836-63-1; (*E*)-**1** (R = Bu), 103836-64-2; **2** (R = Me), 103836-65-3; **2** (R = CH_2Ph), 103836-66-4; **2** (R = CH_2Pr-*i*), 103836-67-5; **2** (R = Et), 103836-68-6; **2** (R = Bu), 103836-69-7; **3** (R = Me), 21028-13-7; **3** (R = CH_2Ph), 1202-30-8; **3** (R = CH_2Pr-*i*), 24292-07-7; **3** (R = Et), 103883-01-8; **3** (R = Bu), 103883-02-9; **4** (R = Me), 338-69-2; **4** (R = CH_2Ph), 673-06-3; **4** (R = CH_2Pr-*i*), 328-38-1; **4** (R = Et), 2623-91-8; **4** (R = Bu), 327-56-0; **5** (R = Me), 103836-70-0; DTBAD, 870-50-8; CH_3COCl, 75-36-5; $PhCH_2COCl$, 103-80-0; *i*-$PrCH_2COCl$, 108-12-3; CH_3CH_2COCl, 79-03-8; $CH_3(CH_2)_3COCl$, 638-29-9; (1*R*,2*S*)-*N*-methylephedrine, 552-79-4; (1*R*,2*S*)-*N*-methylephedrine acetate, 74111-77-6; (1*R*,2*S*)-*N*-methylphedrine 2-phenylethanoate, 103836-59-5; (1*R*,2*S*)-*N*-methylphedrine 3-methylbutanoate, 103836-60-8; (1*R*,2*S*)-*N*-methylphedrine propanoate, 53135-04-9; (1*R*,2*S*)-*N*-methylphedrine pentanoate, 74059-53-3.

Supplementary Material Available: Detailed experimental procedures for the reactions, analyses, optical rotations, and spectroscopic data (^1H NMR, IR) for the compounds (9 pages). Ordering information is given on any current masthead page.

(12) Steric hindrance has a negative effect on the condensation reaction. For example in the case of N-methylephedrine isovalerate (R = *i*-Pr) yields were poor (ca. 35%).

(13) Both DTBAD and the ephedrine NMe_2 group are expected to bind to $TiCl_4$, which usually ligates two-electron-donating molecules to form cis-octahedral, six-coordinate complexes. Therefore the conformational freedom of the system is likely to be dramatically reduced, and the C–N bond formation occurs on the six-coordinate metal in a highly stereoselective way.

(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(15) Optically pure *N*-methylephedrine was recovered here by CH_2Cl_2 extraction (≥95%).

(16) Supelcosil^R LC-(*R*)-urea: the amino acids were injected as PTH derivatives (see: Edman, P. *Acta Chem. Scand.* **1950**, *4*, 277).

(17) Chirasil-Val III FSOT Column (AllTech Associates, Inc.): the amino acids were injected as TFA isopropyl ester derivatives (see: Parr, W.; Howard, R. Y. *Anal. Chem.* **1975**, *47*, 951).

Stereoselective Amination of Chiral Enolates. A New Approach to the Asymmetric Synthesis of α-Hydrazino and α-Amino Acid Derivatives

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Nonproteinogenic and rare enantiomerically pure amino acids[1] are important constituents in peptide-derived chemotherapeutics. As a consequence, the development of new reaction methodology which provides an expedient, general approach to the synthesis of this family of compounds continues as an active area of investigation.[2] Recent advances in this field have featured the development of several highly effective chiral glycine enolate synthons which may be employed in diastereoselective alkylation reactions (eq 1).[2b] The purpose of this paper is to report a complementary approach to the synthesis of α-amino acids via the electrophilic amination of chiral enolates (eq 2). One positive attribute of this latter process is that its scope is not so strictly defined by the alkyl (aryl) substituent in the given amino acid target. Such constraints are quite apparent in the related alkylation reactions (eq 1).

(1) For a recent review, see: Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.

(2) (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103–1104. (b) Schollkolpf, U. *Top. Curr. Chem.* **1983**, *109*, 66–84. (c) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5402. (d) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106–112.

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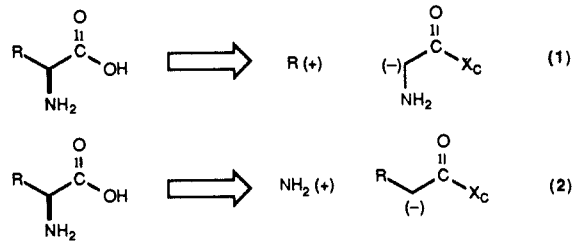
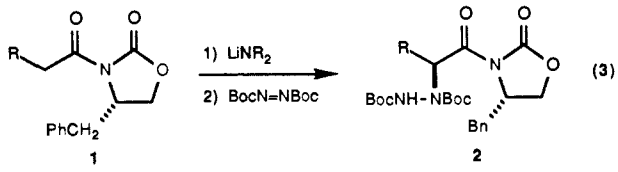


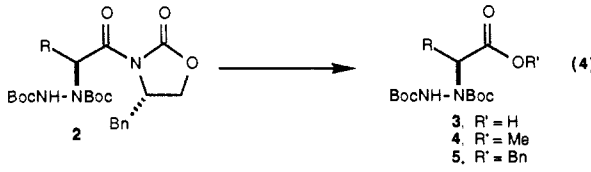
We have found that the commercially available reagent, di-*tert*-butyl azodicarboxylate (DBAD),[3] reacts readily with the lithium enolates derived from the *N*-acyloxazolidones **1**[4,5] to provide the hydrazide adducts **2** in excellent yield (eq 3).[6] The



scope of this reaction is evident from the data provided in Table I. In all instances the lithium enolates derived from **1** reacted virtually instantaneously with DBAD at −78 °C. All reactions were characteristically free of byproducts with the exception of 1–3% of the unwated C_2 hydrazide diastereomer which may be easily removed by chromatography on silica gel. In all of these chromatographic resolutions, a stereoregular elution order was observed with the major diastereomer **2** exhibiting the greater mobility.[7,8]

In a typical experimental procedure, a cooled (−78 °C) solution of the lithium enolate derived from **1** (0.12 M in THF)[4] is treated with a precooled solution of 1.2 equiv of DBAD (0.19 M in CH_2Cl_2) via cannulation. After a reaction time of 1–3 min, the reaction is quenched with 2.5 equiv of glacial acetic acid. A conventional isolation procedure and subsequent chromatographic purification affords the diastereomerically pure (>300:1) hydrazides **2** in yields exceeding 90% (Table I).

Each of the adducts **2** was then subjected to three types of reactions which might facilitate the nondestructive removal of the oxazolidone auxiliary (eq 4): hydrolysis (2.3 equiv of LiOH, 2:1



THF–H_2O, 3 h, 0 °C), methanolysis (2.0 (equiv of MeOMgBr, 0.08 M in MeOH, 30 min, 0 °C), and benzyl alcohol transesterification[4] (2.0 equiv of $PhCH_2OLi$, 0.14 M in THF, 2 h, −50 °C). These reactions were surveyed on the representative hydrazides **2c** (R = CH_2Ph), **2d** (R = Ph), **2e** (R = $CHMe_2$), and **2f** (R = CMe_3) (Table II). For the hydrazide **2c**, where the R substituent is not sterically demanding, hydrolysis, methanolysis, and lithium benzyl oxide transesterification (entries A–C) each proceeded in good yield with no perceptible racemization (vide infra). Hydrazide **2d** (R = Ph) was selected as a substrate which should be exceptionally prone to racemization during either hydrolysis or transesterification. Hydrolysis of **2c** with LiOH under the previously defined conditions (entry D) proved to be uniquely effective in providing the derived acid **3d** (R = Ph) with no more than 2% racemization. In contrast, the more highly basic conditions required for the transesterification to the benzyl ester **5d** (R = Ph) caused considerable racemization (entry F). As the steric requirement of the R substituent in hydrazide **2** is increased, exocyclic carbonyl reactivity is suppressed. As an example, the methanolysis of hydrazide **2e** (R = $CHMe_2$) affords **4e** in only 12% yield, the balance of the reaction product being derived from methanolysis at the oxazolidone carbonyl center. Under such circumstances, we have systematically noted that lithium benzyl oxide is the reagent of choice for carrying out the desired transesterification without attendant racemization.[4] For example, the conversion of **2e** (R = $CHMe_2$) to benzyl ester **5e** may be realized under the previously defined conditions (16 h, −50 °C) in good yield (entry H). Benzyl transesterification may even be successfully carried out on **2f** (R = CMe_3); however, excessive reaction times (50 h, −50 °C) must be tolerated (entry I).

Table I. Stereoselective "Amination" of *N*-Acyloxazolidones (eq 3)

entry	imide **1** R	kinetic ratio[a] (2*S*:2*R*)	yield, %[b] **2**
A	Me	98:2	92[c]
B	$CH_2CH{=}CH_2$	98:2	94
C	CH_2Ph	97:3	91
D	Ph	97:3	96
E	$CHMe_2$	98:2	95
F	CMe_3	>99:1	96

[a] Ratios determined by HPLC analysis. [b] Values refer to isolated yields of isomerically pure (2*S*:2*R* > 300:1) adduct. [c] Isolated yield of the diastereomeric mixture.

Table II. Transesterification (Hydrolysis) of Hydrazide Adducts (eq 4)

entry	substrate **2**	product[a]	yield, %	ee, %[b]
A	**2c**, R = CH_2Ph	**3c**	82	>99
B	**2c**	**4c**	89	>99
C	**2c**	**5c**	96	>99
D	**2d**, R = Ph	**3d**	84	98
E	**2d**	**4d**	71	93
F	**2d**	**5d**	89	22
G	**2e**, R = $CHMe_2$	**4e**	12	>99
H	**2e**	**5e**	82	>99
I	**2f**, R = CMe_3	**5f**	51	>99

[a] Specific reaction conditions for hydrolysis, methanolysis, and benzyl alcohol transesterification are reported in text. [b] The ee values were determined by gas chromatographic analysis of the derived MTPA amides **7**.

Finally, we have found that hydrazides **3**–**5** are practical precursors to enantiomerically pure α-hydrazino and α-amino acid derivatives. In a representative example, hydrazido acid **3d** (R = Ph) was esterified (CH_2N_2) and deprotected to **6d** with 1:1 CF_3CO_2H–CH_2Cl_2 (30 min, 25 °C). The resulting solution was directly hydrogenated over Raney nickel catalyst (550 psi of H_2, 4 h, 25 °C).[9] The unpurified product, obtained after filtration through Celite and solvent removal, was acylated with (+)-MTPA chloride[10] (2.0 equiv) and triethylamine (4.0 equiv, CH_2Cl_2, 3 h, 25 °C) to afford the amide **7d** (R = Ph) in 99% yield for the three steps. Diastereomer analysis by gas chromatography revealed a 99:1 mixture of C_2 isomers. This result establishes that the conversion of **2d** to **7d** via the illustrated four-step sequence is accompanied by a negligible loss in enantiomeric purity. The purified benzyl esters **5c** (R = CH_2Ph), **5e** (R = $CHMe_2$), and

(3) Carpino, L. A.; Terry, P. H.; Crowley, D. J. *J. Org. Chem.* **1961**, *26*, 4336–4340. DBAD purchased from Fluka Chemical Co.

(4) For a general procedure for the generation of these enolates, see: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

(5) For the related oxygenation of these enolates, see: Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348.

(6) For prior reports documenting the reaction of enolates with azodicarboxylates, see: (a) Huisgen, R.; Jakob, F. *Justus Liebigs Ann. Chem.* **1954**, 590. (b) Diels, O.; Behncke, H. *Chem. Ber.* **1924**, *57*, 653.

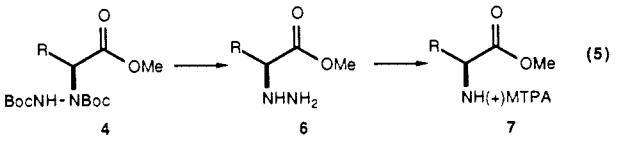
(7) Similar chromatographic behavior has also been noted for the related α-hydroxy carboximides.[5]

(8) The utility of related oxazolidone heterocycles in the chromatographic resolution of amino acids has recently been reported: Nagao, Y.; Kumagai, T.; Yamada, S.; Fujita, E.; Inoue, Y.; Nagase, Y.; Aoyagi, S.; Abe, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2361–2367.

(9) Although freshly prepared W-2 Raney nickel catalyst may be used, we have found that the commercially available catalyst (Aldrich Chemical Co.) is acceptable. The catalyst to substrate ratio was 3 g (damp weight) of catalyst per 1.0 mmol of substrate.

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

5f (R = CMe_3) were also subjected to the same reaction sequence with equal success[11] in yields ranging from 83% to 94%. Since the diastereomeric purity of the derived MTPA amides **7c** (R = CH_2Ph), **7e** (R = $CHMe_2$), and **7f** (R = CMe_3) 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-hydrazino[12] 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.

(11) Benzyl esters **5c**, **5e**, and **5f** were converted to the derived methyl esters **4** via successive hydrogenolysis (5% Pd–C, H_2, EtOAc) and diazomethane treatment.

(12) α-Hydrazino acids have been prepared from *N*-benzyl α-amino acids via a multistep procedure: Achiwa, K.; Yansada, S. *Tetrahedron Lett.* **1975**, 2700–2704.

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

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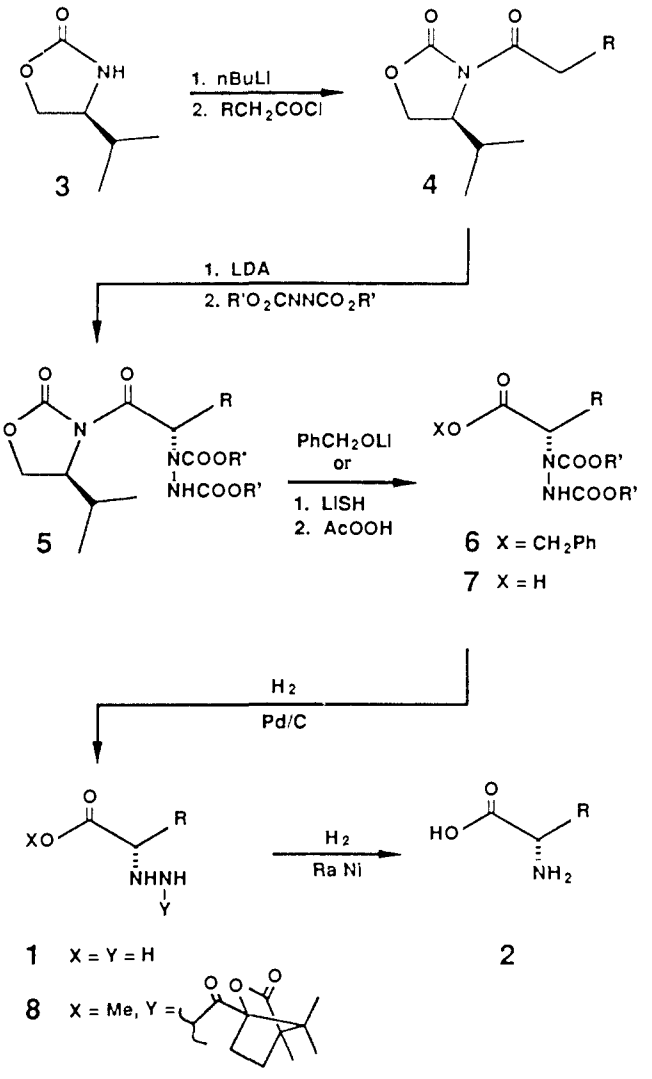
Received July 11, 1986

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 lyases[4] and pyridoxal phosphate dependent proteins.[5] As a result, some α-

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 nitrosation[8] 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

† 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.

(2) *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985.

(3) For some recent examples, see references in: (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103–1104. (b) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833–1843. (c) Schöllkopf, U.; Neubauer, H. J.; Hauptreif, M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1066–1067. (d) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1131–1132. (e) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105–7109. (f) Fitzner, J. N.; Shea, R. G.; Fankhauser, J. E.; Hopkins, P. B. *J. Org. Chem.* **1985**, *50*, 417–419.

(4) (a) Munier, R. L.; Bompeix, G. *C. R. Acad. Sci., Ser. 3* **1985**, *300*, 203–206. (b) Brand, L. M.; Harper, A. E. *Biochemistry* **1976**, *15*, 1814–1821.

(5) For leading references, see the following. (a) Histidine decarboxylase (PLP type): Tanase, S.; Guirard, B. M.; Snell, E. E. *J. Biol. Chem.* **1985**, *260*, 6738–6746. (b) Aspartate aminotransferase: Yamada, R. H.; Wakabayashi, Y.; Iwashima, A.; Hasegawa, T. *Biochim. Biophys. Acta* **1985**, *831*, 82–88. (c) Ornithine decarboxylase: Takano, T.; Takigawa, M.; Suzuki, F. *J. Biochem. (Tokyo)* **1983**, *93*, 591–598. (d) Diaminopimelate decarboxylase: Kelland, J. G.; Arnold, L. D.; Palcic, M. M.; Pickard, M. A.; Vederas, J. C. *J. Biol. Chem.*, in press.

(6) (a) Morley, J. S.; Payne, J. W.; Hennessey, T. D. *J. Gen. Microbiol.* **1983**, *129*, 3701–3708. (b) Morley, J. S.; Hennessey, T. D.; Payne, J. W. *Biochem. Soc. Trans.* **1983**, *11*, 798–800. (c) Parsons, J. L.; Klosterman, H. J.; Ninnemann, J. L. *Antimicrob. Agents Chemother.* **1967**, 415–421.

(7) (a) Markle, R. A.; Hollis, T. M.; Cosgarea, A. J. *Exp. Mol. Pathol.* **1986**, *44*, 21–28. (b) Amrhein, N.; Wenker, D. *Plant Cell. Physiol.* **1979**, *20*, 1635–1642. (c) Kusunoki, S.; Yasumasu, I. *Dev. Biol.* **1978**, *67*, 336–345. (d) Brand, L. M.; Harper, A. E. *Biochim. Biophys. Acta* **1976**, *444*, 294–306.

(8) LiBassi, G.; Ventura, P. Monguzzi, R.; Pifferi, G. *Gazz. Chim. Ital.* **1977**, *107*, 253–255.

(9) Takamura, N.; Yamada, S. *Chem. Pharm. Bull.* **1976**, *24*, 800–803.

(10) Achiwa, K.; Yamada, S. *Tetrahedron Lett.* **1975**, 2701–2704.

(11) Gustafsson, H. *Acta Chem. Scand., Ser. B* **1975**, *B29*, 93–98.

(12) (a) Sawayama, T.; Kinugasa, H.; Nishimura, H. *Chem. Pharm. Bull.* **1976**, *24*, 326–329. (b) Niedrich, H.; Koller, G. *J. Prakt. Chem.* **1974**, *316*, 729–740. (c) Sletzinger, M.; Firestone, R. A.; Reinhold, D. F.; Rooney, C. S.; Nicholson, W. H. *J. Med. Chem.* **1968**, *11*, 261–263.

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