$J_{4a,5}$ = 4 Hz, $J_{4b,5}$ = 8 Hz), 7.49 (t, 2, H3, H5 of Ph, J_{ortho} = 8 Hz), 7.62 (tt, 1, H4 of Ph, J_{ortho} = 8 Hz, J_{meta} = 1.5 Hz), 8.12 (dd, 1, H2, H6, J_{ortho} = 8 Hz, J_{meta} = 1.5 Hz), 9.65 (d, 1, H6, $J_{5,6} > 1$ Hz); MS, m/e (relative intensity) 278 (<1, M^+), 249 (2, M - CHO), 233 (1, M - EtO), 145 (10, M - Bz - C_2H_4), 128 (7, M - Bz - OEt), 105 (100, Bz).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.36; H, 6.54.

Ethyl 5,7-Di-*O*-benzoyl-2,3,4-trideoxy-D-*erythro*-heptonate (20). A stirred solution of **16** (115 mg, 0.37 mmol) in pyridine (1.5 mL) was cooled to 0–5 °C, and a solution of benzoyl chloride (54 mg, 0.38 mmol) was added dropwise. The mixture was kept at room temperature overnight and was then evaporated. Flash chromatography on a short column (1:1 ethyl acetate–hexane) eluted the triester. The pooled fractions were washed with dilute phosphoric acid to remove traces of pyridine and then with sodium hydrogen carbonate solution. Drying and evaporation gave **20** as a colorless syrup (125 mg, 81.5%): $[\alpha]^{25}_D$ +19.08° (*c* 0.14, chloroform) (lit.[18c] $[\alpha]^{25}_D$ +17.2%); 200-MHz NMR ($CDCl_3$) δ 1.24 (t, 3, Me of Et, J = 7 Hz), 1.7–2.0 (m, 4, H3, H4), 2.38 (t, 2, H2, $J_{2,3}$ = 7 Hz), 2.88 (d, 1, OH, $J_{6,OH}$ = 5 Hz), 4.13 (q, 2, CH_2 of Et, J = 7 Hz), 4.24 (m, 1, H6), 4.42 (dd, 1 H7a, $J_{6,7a}$ = 6 Hz and J_{gem} = 12 Hz), 4.58 (dd, 1, H7b, $J_{6,7b}$ = 3.5 Hz and J_{gem} = 12 Hz), 5.31 (m, 1, H5).

Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.35. Found: C, 66.68; H, 6.55.

Registry No. 1, 71160-24-2; 2, 72059-45-1; 3, 111689-68-0; 4, 111689-69-1; 5, 111717-54-5; 6, 111689-70-4; 7, 103795-36-4; 8, 111689-73-7; 9, 111689-71-5; 10, 111689-74-8; 11, 111689-72-6; 12, 111768-78-6; 14, 82493-58-1; 16, 82493-57-0; 18, 73957-99-0; 20, 80311-46-2; D-arabinose, 10323-20-3; D-arabinose dipropyl mercaptal, 107618-44-0; 2,3:4,5-di-*O*-isopropylidene-D-arabinose dipropyl mercaptal, 107418-31-5; triethyl phosphonoacetate, 867-13-0; (*E*)-4,5-*O*-isopropylidene-D-*glycero*-pent-2-enose, 4757-80-6.

Synthesis of Semisynthetic Dipeptides Using *N*-Carboxyanhydrides and Chiral Induction on Raney Nickel. A Method Practical for Large Scale

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Methods useful for both laboratory and large-scale syntheses of the ACE inhibitors enalapril and lisinopril are described. The requisite dipeptides L-alanyl-L-proline and N^ϵ-(trifluoroacetyl)-L-lysyl-L-proline were prepared via *N*-carboxyanhydride (NCA) chemistry. These dipeptides undergo facile reductive alkylation with ethyl 2-oxo-4-phenylbutyrate over Raney nickel with high stereoinduction to afford the direct precursors of enalapril maleate and lisinopril. Kinetic and structural rationalizations are presented for understanding success or failure in forming NCAs and in their subsequent conversions to dipeptides.

Angiotensin-converting enzyme (ACE) inhibition is an effective therapy for the control of hypertension and congestive heart failure.[1a,b] We describe herein three- and five-step convergent syntheses of the ACE inhibitors N^2-[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline (enalapril, **1a**)[2a,b] and N^2-[(*S*)-1-carboxy-3-phenylpropyl]-L-lysyl-L-proline (lisinopril, **2a**)[2a,c] from alanine and lysine, respectively, without need for classical protection group chemistry (Scheme I).

Previously reported syntheses of **1a** and **2a** suffered from poor yields due to length and/or poor diastereoselectivity in forming the desired asymmetry at the new optical center.[3a-d] Our approach centers about a reductive amination procedure whereby Schiff base formation followed by catalytic low-pressure hydrogenation in ethanol over Raney nickel affords **1a** and **7a** in 80–90% yield with high diastereoselectivity: **1a**(*SSS*):**1b**(*RSS*) = 87:13[4a] and **7a**(*SSS*):**7b**(*RSS*) = 95:5.[4a,b] The requisite dipeptides L-alanyl-L-proline (**5a**) and N^ϵ-(trifluoroacetyl)-L-lysyl-L-proline (**5b**) were readily prepared in kilogram quantities via *N*-carboxyanhydride (NCA) chemistry in water after first mastering the effects of the countercation and of the organic cosolvent during condensation, and by gaining an initimate understanding of the details of NCA formation.

Results and Discussion

A. Enalapril Maleate (17). *N*-Carboxyanhydride Formation. Except for a recent high-yielding but costly and multistep procedure for the preparation of Ala-NCA (**4a**) from Boc-alanine and oxalyl chloride,[5a] the literature suggests that only moderate yields (60–80%) can be expected for its direct preparation from alanine (**3a**) and phosgene.[5b,c] This is likely due to the near total insolubility of alanine (or alanine hydrochloride) in the reacting medium, which affords a sluggish reaction and thus allows time for side reactions to occur. We now report the preparation of Ala-NCA (**4a**) in 95% yield (unisolated) directly from alanine via an optimized Fuchs–Farthing procedure[5c] (Scheme II) similar to that recommended by Goodman.[5b]

(1) (a) Cleary, J. D.; Taylor, J. W. *Drug Intell. Clin. Pharm.* **1986**, *20*, 177–186. (b) Todd, P. A.; Heel, R. C. *Drugs* **1986**, *31*, 198–248.

(2) (a) Harris, E. E.; Patchett, A. A.; Tristram, E. W.; Wyvratt, M. J. U.S. Patent 4 374 829, 1982. (b) Enalapril is marketed under the trade name Vasotec (Merck & Co., Inc.). (c) Lisinopril will be marketed under the tradenames Prinivil (Merck & Co., Inc.) and Zestril (ICI).

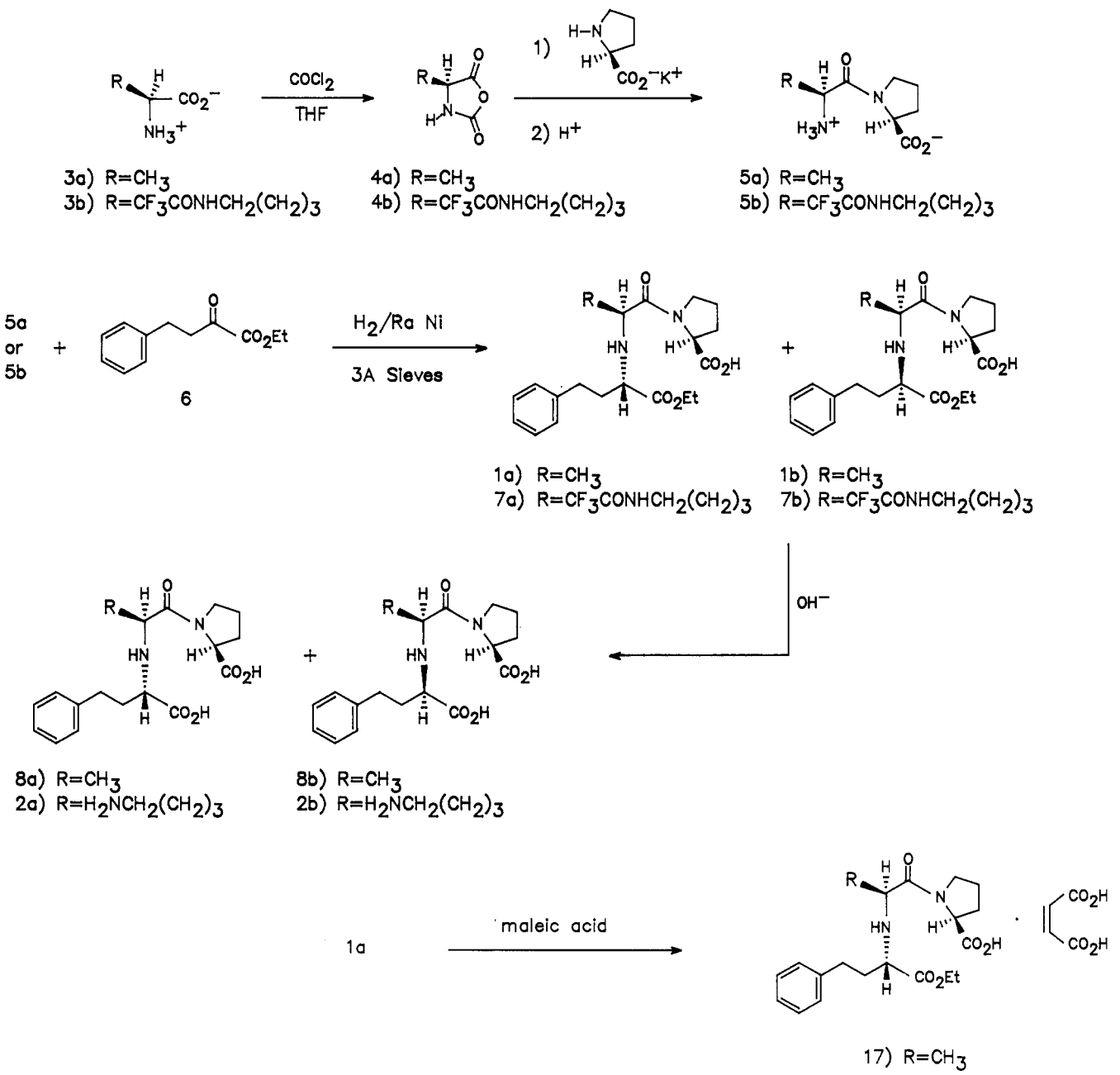
(3) (a) Wyvratt, M. J.; Tristram, E. W.; Ikeler, T. J.; Lohr, N.; Joshua, H.; Springer, J. P.; Arison, B.; Patchett, A. A. *J. Org. Chem.* **1984**, *49*, 2816–2819. (b) Kaltenbronn, J. S.; DeJohn, D.; Krolls, U. *Org. Prep. Proced. Int.* **1983**, *15*, 35–40. (c) Urbach, H.; Henning, R. *Tetrahedron Lett.* **1984**, *25*, 1143–1146. (d) Wu, M. T.; Douglas, A. W.; Ondeyka, D. L.; Payne, L. G.; Ikeler, T. J.; Joshua, H.; Patchett, A. A. *J. Pharm. Sci.* **1985**, *74*, 352–354.

(4) (a) Blacklock, T. J.; Butcher, J. W.; Shuman, R. F. *Pept.: Struct. Funct., Proc. Am. Pept. Symp., 9th, 1985* **1985**, 787–790. (b) Blacklock, T. J.; Shuman, R. F., U.S. Patent pending.

(5) (a) Mobashery, S.; Johnston, M. *J. Org. Chem.* **1985**, *50*, 2200–2202. (b) Fuller, W. D.; Verlander, M. S.; Goodman, M. *Biopolymers* **1976**, *15*, 1869–1871. (c) Farthing, A. *J. Chem. Soc.* **1950**, 3222–3229.

0022-3263/88/1953-0836$01.50/0

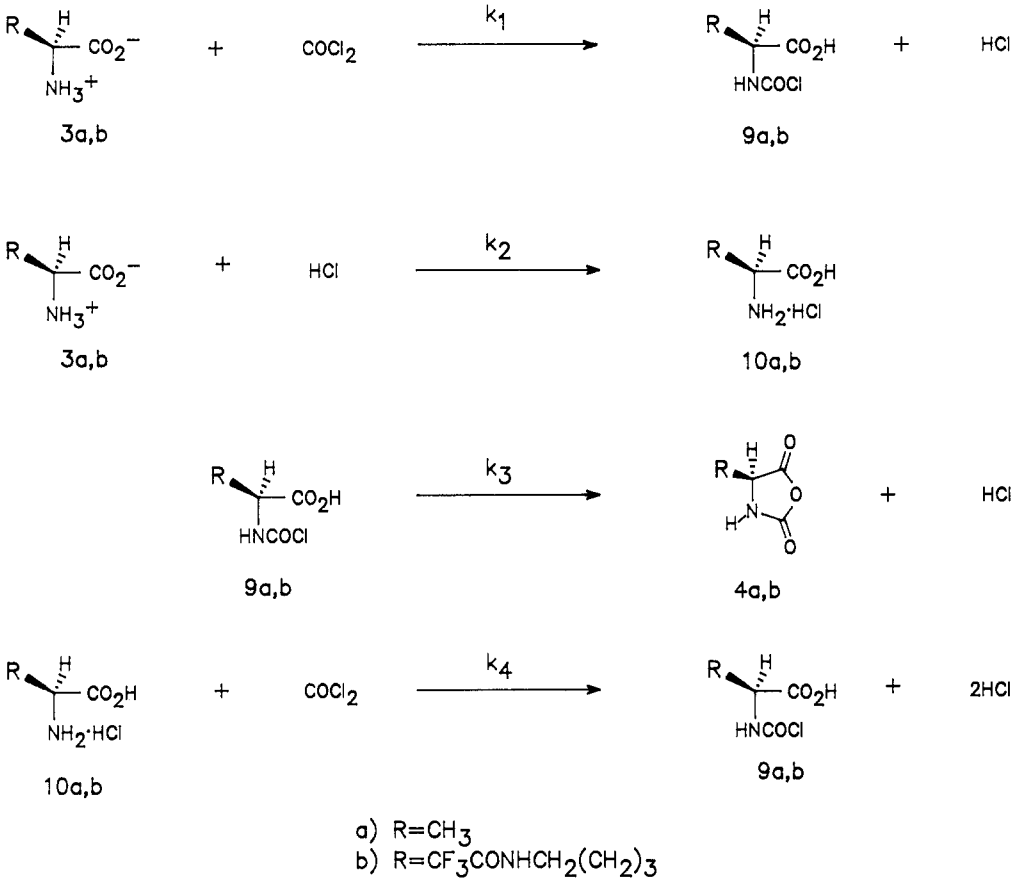
Scheme I



Alanine (**3a**) was reacted with a preformed 4 M solution of phosgene in THF; this removed phosgene as a rate-limiting reagent, and any large-scale thermal contribution due to the heat of solvation of phosgene with THF was eliminated. Upon addition of **3a** to the phosgene/THF solution at 15–20 °C, a rapid, self-limiting exotherm occurred due to initial formation of *N*-chlorocarbonyl amino acid **9** (k_1) followed immediately by formation of amino acid hydrochloride **10** (k_2). Thus, very rapidly, between 33% and 50% of the amino acid was converted to **9**, the amount depending on the relationship of k_2 to k_3 (k_2, being dependent on proton transfer, is assumed to be very fast). The reaction was then allowed to continue until complete dissolution (reaction) of the remaining amino acid hydrochloride had occurred (k_4). The initial stage of the reaction was generally complete within 4 h (as signified by dissolution of alanine and/or its hydrochloride salt) with minimal ring opening of THF by hydrogen chloride. Traditionally this observation has been used to signify the end of reaction. Instead, we found that ring closure of **9** to the corresponding NCA (k_3) at 30 °C or below was indeed much slower than expected and, in some cases, k_3 was observed to be proportional to the concentration of **9** in the THF/HCl mixture (this phenomenon is currently under further investigation). Accordingly, once alanine hydrochloride was no longer visually evident, the reaction mixture was concentrated to remove excess phosgene and HCl and allowed to stand until cyclization was complete. Subsequent dilution with THF followed by concentration removed most of the remaining HCl to afford an NCA solution sufficiently pure for direct use. Alternatively, the NCAs could be crystallized by addition of hexanes. While purity of an NCA (solution or crystal) could be determined by van Slyke CO_2 assay,[6] quantitative derivatization with monomethylamine to a methyl amide[7] is a general proce-

(6) The NCA solution was subjected to acidic hydrolysis and the CO_2 evolved measured coulometrically. This method is not specific for NCA since *N*-chlorocarbonyl acid chloride and residual phosgene both evolve CO_2 under acidic hydrolysis.

Scheme II. Simplified Mechanistic Pathway to NCA Formation



a) R=CH_3
b) R=$CF_3CONHCH_2(CH_2)_3$

dure which more accurately reflects the true NCA content.

Purity of the tetrahydrofuran used as solvent for NCA synthesis was found to be critical in some instances to success or failure in preparing NCAs. Dimethylformamide (DMF), a common low-level contaminant in many bulk solvents, was found to catalyze a significant reaction loss to the corresponding *N*-chlorocarbonyl amino acid chloride **12** (Scheme III). This product (**12**) was identified by ^{13}C NMR and presumably arises from a Vilsmeier–Haack-type intermediate. At levels of DMF as low as 1 ppt (part per thousand), a nearly quantitative yield of **12** was obtained. This side reaction seriously affects the yield of any NCA reaction if rates k_5 and/or k_6 effectively compete with k_3. Once any acid chloride has formed, subsequent NCA formation from **11** or **12** is precluded. Whether k_5, k_6, or k_7 is rate determining depends primarily on the relationship of k_1 to k_3. If $k_1 \gg k_3$, then k_6 is the primary determinant of **12**. Conversely, if $k_3 \gg k_1$, then k_5 must account for the formation of **12**. Solvent contamination as above may be a primary cause for some low-yielding NCA reactions attempted by other workers.

An alternative pathway to compounds such as **12** was previously established by Iwakura and co-workers.[8] This reaction sequence involves HCl-promoted ring opening of an NCA to form the amino acid chloride hydrochloride **11**. Continued reaction with phosgene affords **12**. Since formation of **12a** or **12b** was not observed under our reaction conditions of below 30 °C and with DMF-free THF, this pathway can be discounted.

Peptide Formation. An efficient large-scale synthesis of peptides via NCA chemistry, which by definition controls overreaction (oligomerization and/or polymerization), has long been the goal of many chemists. The attractiveness of the NCA coupling method lies in its simplicity. It can be described as conceptually simple and elegant, and yet is has been thought to be virtually impossible to achieve utility on a commercially important scale. Yet to avoid classical peptide coupling methodology, compressing at least three chemical steps through protection and activation into one step, makes it well worth pursuit. Throughout the entire condensation reaction, the molecular bulk of the reactants remains with the newly formed peptide. The only byproduct, carbon dioxide, is easily eliminated, and the condensation sequence may be rapidly repeated to build polypeptides requiring only control of pH. Furthermore, the NCA method has been shown to be virtually racemization free.[9]

Many of the general arguments previously presented attempt to rationalize NCA condensation/polymerization in terms of pK_a's, thermal stability of carbamate intermediates, reaction medium pH, and mixing.[10] A factor frequently overlooked is the combined substituent effects of both NCA (electrophile) and the nucleophile (free amine, NCA *N*-anion, amino acid, hydroxyl anion, dipeptide anion, etc.). NCAs having very bulky substituents

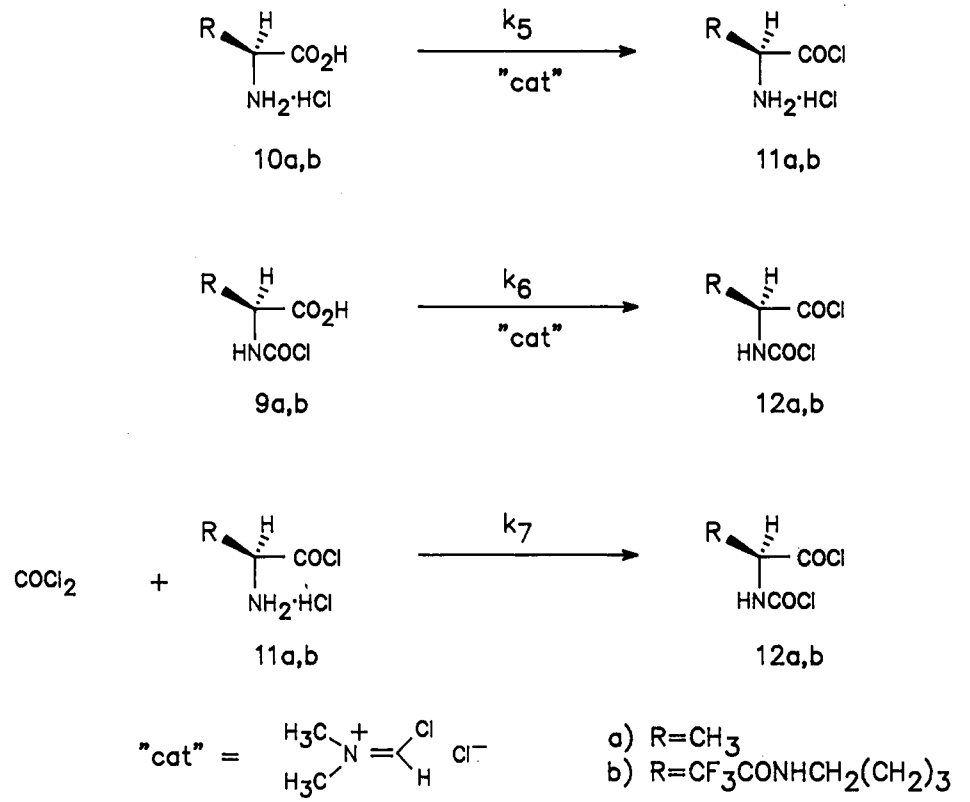
(7) An aliquot of the NCA solution was added rapidly to an excess of monomethylamine dissolved in THF at 0 °C. After reaction had ceased, the mixture was assayed by HPLC against the appropriate *N*-methylamide standard. *N*-Chlorocarbonyl acid chloride impurities and residual phosgene form ureas and/or hydantoin derivatives and not simple *N*-methyl amides; thus this method is specific for NCA. The generality of this method will be discussed in a forthcoming publication.

(8) Iwakura, Y.; Uno, K.; Kang, S. *J. Org. Chem.* **1965**, *30*, 1158–1161.

(9) (a) Denkewalter, R. G.; Schwam, H.; Strachan, R. G.; Beesley, T. E.; Veber, D. F.; Schoenewaldt, E. F.; Barkemeyer, H.; Palaveda, J. J., Jr.; Jacob, T. A.; Hirschmann, R. *J. Am. Chem. Soc.* **1966**, *88*, 3163–3164. (b) Manning, J. M.; Moore, S. *J. Biol. Chem.* **1968**, *243*, 5591.

(10) Blacklock, T. J.; Hirschmann, R.; Veber, D. F. In *The Peptides*; Meienhofer, J. H., Udenfriend, S., Eds.; Academic: San Diego, CA, 1987; pp 39–102.

Scheme III. DMF + Phosgene Catalyzed Pathway to *N*-Chlorocarbonyl Acid Chloride during NCA Formation



seldom polymerize. In fact, Phe-NCA affords a 90% yield of dipeptide, even at 20 °C, when condensed with an equimolar amount of glycine benzyl ester.[11] On the basis of this observation and studies of N- and α-substituent-related effects of NCAs toward homopolymerization and/or dipeptide formation by Akiyama et al.[12] and Oya and Takahashi,[11] respectively, one can conclude that the extent of polymerization is roughly inversely proportional to the bulk of the α-substituent of the NCA and directly proportional to the bulk of the nucleophile, and also that the nature of the nucleophile may frequently be the controlling factor. Clearly, condensation of Ala-NCA with proline is likely one of the more difficult to achieve efficiently due to the above factors. Consequently, a literature search revealed few examples of NCA condensations with either proline or Ala-NCA.

The method for peptide bond formation reported by Iwakura et al.[13,14] seemed most promising for the preparation of **5a**, but initial attempts using Ala-NCA (**4a**, crystalline and pure) and proline according to their methodology afforded extensive oligomerization, thus indicating that its application is not without limitation. When Ala-NCA was condensed with sodium prolinate in a sodium carbonate buffered water/acetonitrile medium, the reaction mixtures either froze at the recommended temperature and/or the sodium prolinate/sodium carbonate mixture crystallized. Thus, once fully reacted, the product mixture contained as much as 40% oligomers. Warming the reaction mixture alleviated the freezing problem, but it did not reduce the degree of oligomerization. At the recommended 0.1 M concentration, dipeptide yield was shown to be inversely related to addition time and directly related to mixing efficiency. When the addition time of the Ala-NCA was decreased from several minutes to less than 5 s, the yield of dipeptide increased from about 65% to 90%. This increase was greatly attenuated when the reaction was carried out at a concentration approaching 1 M. We discovered, however, that when both the buffer and countercation were changed from sodium to potassium, the reaction could be run at higher concentrations (greater than 0.5 M with respect to the aqueous phase) and at 0 °C without encountering solubility problems. As a consequence, the yield of L-alanyl-L-proline exceeded 90%. Subsequently, a distinct correlation with the group I metals vs yield of dipeptide was noted. Under identical conditions, including concentration, yields pro-

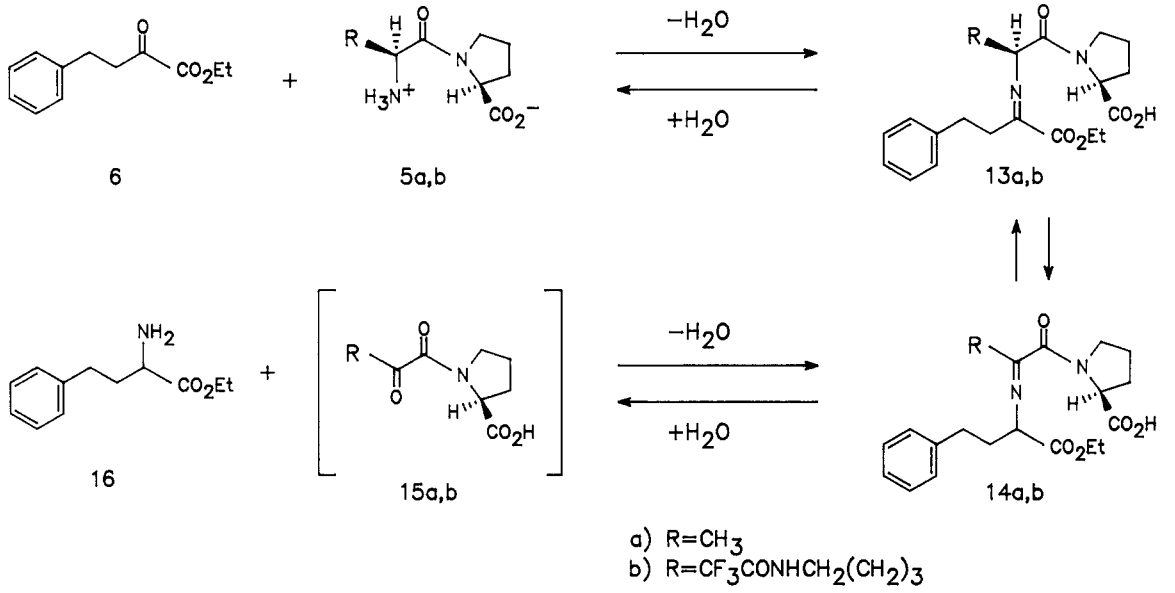
Table I. Effect of Reaction Parameters on Condensation Yield between L-Proline and L-Alanine *N*-Carboxyanhydride (4a)[a,b]

MOH	buffer	NCA:proline: base:buffer	addn time, s	temp, °C	% yield Ala-Pro (HPLC assay)[c] based on NCA
LiOH	Li_2CO_3	1.00:1.05:1.05: 1.00	4	−0→−5[d]	80.4
NaOH	Na_2CO_3	1.00:1.05:1.00: 1.00	5	−5→−2	78.2
KOH	K_2CO_3	1.00:1.02:1.00: 1.00	5	−5→0	90.5
RbOH	Rb_2CO_3	1.00:1.02:1.00: 1.00	5	−5→0	90.8
CsOH	Cs_2CO_3	1.00:1.02:1.00: 1.00	5	−5→0	93.3

[a] Solvent = 1:1 CH_3CN/H_2O. Combined volume of reaction solvents = 1000 mL; i.e., 1:1 CH_3CN/H_2O = 500 mL of CH_3CN plus 500 mL of H_2O. [b] NCA added = 0.261 mol. The Ala-NCA was dissolved in CH_3CN and assayed prior to use. [c] See method in Experimental Section. [d] Solids present prior to and throughout run.

(11) Oya, M.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 439–441.
(12) Akiyama, M.; Hasegawa, M.; Takeuchi, H.; Shimizu, K. *Tetrahedron Lett.* **1979**, 2599–2600.
(13) Iwakura, I.; Uno, K.; Oya, M.; Katakai, R. *Biopolymers* **1970**, *9*, 1419–1427.
(14) Katakai, R.; Oya, M.; Uno, K.; Iwakura, Y. *Biopolymers* **1971**, *10*, 2199–2208.

Scheme IV. Transamination Pathway to Ethyl 2-Amino-4-phenylbutyrate



gressively increased as the group I counterion increased in atomic number, i.e., the highest yield of 93% was obtained when the cesium cation was employed[15] (see Table I). Use of THF instead of acetonitrile gave comparable results, thus simplifying use of the Ala-NCA solution.

As a practical matter, the resulting salt-laden aqueous L-alanyl-L-proline solution was dehydrated by azeotropic vacuum distillation with 1-butanol and the slurry used directly in the next step (reductive amination). Alternatively, crystalline L-alanyl-L-proline could be isolated as one of three distinct allotropes from an alcoholic solution similarly dehydrated and filtered free of salts.

Reductive Amination. Catalytic hydrogenation of the presumed imine formed between L-alanyl-L-proline (**5a**) and ethyl 2-oxo-4-phenylbutyrate (**6**)[16a] (EtOH, 3A molecular sieves) affords enalapril free base (**1a**, *S,S,S* configuration) and its *R,S,S* diastereomer **1b**. Diastereoselectivity was found to be remarkably dependent on the choice of catalyst; Raney nickel afforded the highest ratio of 87:13 **1a**(*SSS*):**1b**(*RSS*) (see Table II). Reaction workup consisted of filtering the catalyst and molecular sieves, and a solvent exchange from ethanol to ethyl acetate readied crude enalapril for crystallization as its maleate salt.

Isolation. Whereas enalapril (**1a**) was found to be relatively stable as a solution in ethanol, in ethyl acetate it cyclized to its diketopiperazine at the rate of approximately 1%/h. Addition of maleic acid to crude enalapril in ethyl acetate afforded crude crystalline enalapril maleate with good rejection of the *R,S,S* diastereomer. Recrystallization from water afforded enalapril maleate essentially free of *R,S,S* diastereomer.

B. Lisinopril (2a). *N*-Carboxyanhydride Formation. N^{ϵ}-(Tfa)-L-lys-NCA (**4b**) was prepared in 97% yield (unisolated) via a similarly optimized Fuchs–Farthing procedure (see Ala-NCA (**4a**) above). This NCA too could be crystallized by addition of hexanes. To ensure sole and complete reaction of the α-amino group over the ϵ-amino group of lysine required that the ϵ-amino group be suitably protected from subsequent chemistry in the synthesis, and yet be easily removed at the appropriate stage. The trifluoroacetyl (Tfa) group appeared uniquely suited for this task; it survived the highly acidic conditions of NCA formation, the brief moderately basic low-temperature condensation with proline, and reductive alkylation, and yet it was easily removed via basic hydrolysis. The N^{ϵ}-(Tfa)-L-Lys precursor (**3b**) to NCA **4b** was prepared in 85% yield from ethyl trifluoroacetate and L-lysine in aqueous sodium hydroxide. It is well-known that N^{ϵ}- vs N^{α}-acylation of lysine is directly related to pH; N^{ϵ}-acylation is favored at higher pH and is nearly exclusive above pH 11.[18] We found ethyl trifluoroacetate[19] (easily prepared from ethanol and trifluoroacetic acid) to be a higher yielding alternative to trifluoroacetic anhydride[20] or to the odoriferous *S*-ethyl trifluorothioacetate.[20,21]

Table II. Reductive Amination Catalyst and Reducing Agent Screen Affording Diastereomeric Pairs 1a and 1b and 7a and 7b

catalyst	normalized diastereomeric ratio **1a**(*SSS*):**1b**(*RSS*)	normalized diastereomeric ratio **7a**(*SSS*):**7b**(*RSS*)
5% Pt/C	50:50	50:50
5% Rh/C	50:50	
5% Ru/C	40:60	
P-1 nickel boride (wet)[18a]		
P-2 nickel bromide[18b]	50:50	
IrO_2 (Adams' catalyst)	60:40	
Raney nickel (Grace no. 28)	87:13	95:5
Pd/C	60:40	53:47
chemical reduction $NaBH_3(CN)$	50:50	50:50[3d]

Peptide Formation. In contrast to the preparation of

(15) Blacklock, T. J.; Shuman, R. F. U.S. Patent 4510083, 1985, Eur. Patent 127108, 1984.

(16) (a) For a discussion on the asymmetric hydrogenation of Schiff bases derived from α-keto esters and chiral amino acid esters, see: Harada, K.; Shiono, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1367–1370. (b) Witkop, B.; Beiler, T. W. *J. Am. Chem. Soc.* **1954**, *76*, 5589–5596.

(17) (a) Brown, C. A.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 1003. (b) Brown, H. C.; Brown, C. A. *J. Am. Chem. Soc.* **1963**, *85*, 1005.

(18) Leclerc, J.; Benoiton, L. *Can. J. Chem.* **1968**, *46*, 1047–1051.

(19) Curphey, T. J. *J. Org. Chem.* **1979**, *44*, 2805–2807. Curphey has promoted the use of ethyl trifluoroacetate for the N-derivatization of amino acids. To our knowledge, he has not applied his methodology to a dibasic amino acid such as lysine. Our use of ethyl trifluoroacetate for the N^{ϵ}-derivatization of lysine will be discussed in a forthcoming publication.

(20) Use of trifluoroacetic anhydride for the derivatization of lysine yields predominantly N^{ϵ}-(Tfa)-L-Lys. See: Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; p 915.

(21) Schallenberg, E. E.; Calvin, M. *J. Am. Chem. Soc.* **1955**, *77*, 2779–2783.

L-alanyl-L-proline (**5a**) described above, the buffered biphasic condensation of N^{ϵ}-(Tfa)-L-Lys-NCA (**4b**) with potassium prolinate proceeded in somewhat higher yield (92% vs 89%) than did the similar condensation with Ala-NCA, and it did not require as careful control of reaction parameters. Addition time of **4b** proved to be less critical, and extensive oligomerization was not observed even when addition time was extended to 15 min. We attribute this phenomenon to the bulky α-substituent effect as previously discussed.

Reductive Amination. Similar diastereoselectivity with respect to catalyst choice as was observed with **5a** was also observed for the reductive condensation between N^{ϵ}-(Tfa)-L-Lys-L-Pro (**5b**) and ethyl 2-oxo-4-phenylbutyrate (**6**). Raney nickel afforded a remarkable 95:5 ratio of the desired *S,S,S* diastereomer **7a** (see Table II) to the corresponding *R,S,S* diastereomer **7b**.

The probability of Schiff base formation is implied and supported by appearance of a byproduct, ethyl 2-amino-4-phenylbutyrate (**16**).[16a,b] This material (**16**), which likely forms via the pathway shown in Scheme IV, was observed to steadily increase in prehydrogenation mixtures that were allowed to stand for several hours in the presence of Raney nickel under a nitrogen atmosphere. Hydrogenation without delay, however, minimized transamination. No attempt was made to identify the conjugate α-keto derivative **15b**. Although transamination products **15a** and **16** were not detected in the preparation of enalapril, their formation seems likely.

Saponification/Hydrolysis. Simultaneous removal of the N^{ϵ}-trifluoroacetyl protecting group (hydrolysis) and saponification of the ethyl ester was accomplished in near quantitative yield in aqueous hydroxide (pH greater than 11, 40 °C). The Tfa group, which proved to be remarkably stable through prior reactions, briefly withstanding pH 12.5 at 0 °C during the NCA condensation reaction and cold aqueous bicarbonate for extended periods, began to hydrolyze at pH greater than 10 at 40 °C. Although not necessary for the target synthesis, we were unable to effect a clean selective deprotection of the trifluoroacetamide moiety over the ethyl ester using only control of pH and temperature.

Isolation. Large-scale desalination of crude water-soluble lisinopril (**2a**) from the aqueous salt-laden saponification mixture was accomplished equally well on Dowex ion-exchange resin (acid cycle) and on SP-207 resin,[22] a nonionic brominated polystyrene/divinylbenzene copolymer. Both resins gave comparable results. Vacuum concentration of the product-rich cuts and crystallization from 90% ethanol afforded lisinopril (**2a**) containing less than 1% *R,S,S* diastereomer. A final crystallization from water gave pure **2a** (isolated as its dihydrate solvate) in greater than 70% recovery.[23]

Experimental Section

^{13}C NMR spectra for compounds **4a**, **4b**, **12a**, and **12b** were recorded on a Varian CFT-20 spectrometer (80 MHz) in THF (0.3 M) with acetone-d_6 as an external lock and referenced to the low-field signal of THF (δ 67.4). Other NMR spectra were recorded on a Varian XL-100 or on a Bruker 250-MHz spectrometer as noted. FTIR spectra were obtained on a Nicolet 7199 spectrophotometer. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus. UV spectra were obtained on a Cary 210 spectrophotometer. Specific rotations were recorded on a Perkin-Elmer 241 polarimeter.

We note that reagent grade THF from reputable laboratory supply houses does not generally contain DMF. Bulk supplies however were frequently found contaminated. All THF was assayed for DMF by capillary gas chromatography using a Varian 3700 chromatograph equipped with a 30m DB-210 column supplied by J. & W. Scientific (0.32 mm i.d. × 0.5 μm film) and operated at 60 °C isothermal for 2 min followed by a ramp to 200 °C at 20 °C/min. Helium pressure was maintained at 10 psig; injection, 1.5 μL; t_R DMF, 6.0 min; t_R BHT (antioxidant), 8.5 min. Optimum yields of NCA were obtained when DMF levels were at <1 ppm.

Direct Colorimetric Titration of (2-Phenylethyl)magnesium Bromide. This nonaqueous, direct colorimetric titration of (2-phenylethyl)magnesium bromide is an adaptation of the elegant and general method published by Watson and Eastham.[24]

A 125-mL filter flask was fitted with a rubber stopper carrying a nitrogen inlet and a 25-mL buret. In the flask under nitrogen were placed 1–2 mg of 2,2′-biquinoline as an indicator, a magnetic stirring bar, and 25 mL of the (2-phenylethyl)magnesium bromide reaction mixture. This stirred, maroon-colored solution was titrated with 1 N 2-butanol in xylene. Titration was accompanied with decolorization to a light gray end point with a tinge of green. The amount of 2-butanol required to achieve the end point is equivalent to the amount of (2-phenylethyl)magnesium bromide in the 25-mL aliquot.

The chemical basis for this method lies in the formation of a red to purple complex of an organolithium or organomagnesium reagent with 2,2′-biquinoline and its subsequent decolorization (titration) with 2-butanol to a light gray end point tinged with green. Bases other than the organometallic reagent (e.g., MgO, $Mg(OH)_2$, Mg(OH)Br) are not measured by this method, whereas such bases may contribute to unrealistic answers with conventional aqueous acid titration.

Ethyl 2-Oxo-4-phenylbutyrate (6). Magnesium turnings (12.1 g, 0.5 mol) were placed in sieve-dried THF (25 mL) under nitrogen. A small amount (~8 mL) of (2-bromoethyl)benzene (92.5 g, 70.6 mL, 0.5 mol) dissolved in dry THF (300 mL) was added to the magnesium slurry and stirred for a few minutes with warming until the reaction commenced. The remainder of the (2-bromoethyl)benzene solution was added dropwise over 1 h to maintain reflux, then the reaction mixture was aged at reflux for an additional 1 h. The reaction mixture was cooled to 25 °C, and the supernatant Grignard solution was sampled and titrated. See titration method above.

In a separate flask, diethyl oxalate (88.2 g, 81.2 mL, 0.6 mol) was dissolved in dry THF (100 mL) and cooled to −10 °C. The solution of (2-phenylethyl)magnesium bromide was sucked under nitrogen through a sintered-glass filter into a dropping funnel. The reaction temperature was held at −10 °C as the solution of Grignard reagent was added dropwise over 1 h to the diethyl oxalate. The sintered-glass funnel and dropping funnel were then rinsed with dry THF (100 mL), and the rinse was added to the batch. The reaction mixture was allowed to stand for 15 min and then quenched by addition of 3 N HCl (145 mL).

Hexane (500 mL) was added, and the bottom aqueous layer was discarded. The organic phase was washed with saturated sodium chloride (100 mL), saturated sodium bicarbonate (100 mL) for 1 h, and repeatedly with saturated sodium chloride (100 mL for each wash), until the aqueous layer measured pH 5.3–5.5. The organic phase was dried by stirring with anhydrous sodium sulfate (200 g) for 30 min. The solids were filtered and washed with hexane, and the combined layers were concentrated to an oil at ≤80 °C.

The crude keto ester (93 g) was vacuum distilled in glass at 105–110 °C (0.2–0.3 mm) to afford a rich cut of 45.8 g (76% recovery).

Analytically pure ethyl 2-oxo-4-phenylbutyrate was obtained via two successive distillations of the above material and was identical in all respects with that previously reported.[25]

L-Alanine *N*-Carboxyanhydride (4a). Phosgene (250 g, 2.52 mol) was introduced with rapid stirring into a dry 1-L water-

(22) Mitsubishi Chemical Industries Ltd., New York, NY.

(23) For chemical reasons, our reference to lisinopril throughout the text has disregarded solvation. Lisinopril (**2a**) is correctly defined as the crystalline dihydrate solvate. Other crystalline solvates have been observed.

(24) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(25) Weinstock, L. M.; Currie, R. B.; Lovell, A. V. *Synth. Commun.* **1981**, *11*(2), 943–946.

jacketed reaction flask containing 500 mL of sieve-dried THF (Karl Fischer titration (KF) = 0.021 mg/mL) under nitrogen. The reaction flask was cooled to maintain ≤15 °C. L-Alanine (34.9 g, 0.392 mol; milled to a particle-size distribution of 10–15 μm) was introduced rapidly as a slurry in 100 mL of dry THF, and the temperature rose to 24 °C. Rapid stirring was maintained while the temperature of the reaction mixture was brought to 30 °C. After 3.5 h at 30 °C, the reaction mixture became transparent. A mild vacuum (60 mm at the source) was then applied to the reaction vessel while the temperature of the mixture was lowered and maintained at 20 °C. The vacuum (pump) was then increased, allowing the excess phosgene, tetrahydrofuran, and hydrogen chloride to distill from the product. The phosgene/tetrahydrofuran/hydrogen chloride mixture was collected in a dry ice trap at −78 °C. Concentration was continued until a volume of 100 mL was reached. THF (185 mL) was added, and concentration was continued to aid removal of residual phosgene/hydrogen chloride to a minimum volume of 100 mL. This flushing procedure was repeated twice more. Unisolated Ala-NCA, suitable for use as is in solution with THF, was analyzed for NCA content[7] and used directly for amide (peptide) formation.

Alternatively, Ala-NCA was crystallized via addition of hexanes (400 mL) to the above concentrate, filtered under N_2, and sucked dry to afford 47.4 g (79%) of product, identical in all respects with the material reported by Bailey:[26] ^{13}C NMR (THF) δ 172 (s), 153 (s), 54 (s), 17 (s).

Effect of Dimethylformamide as a Solvent Contaminant on NCA Formation. An amount of dimethylformamide (DMF) corresponding to 234 ppm solvent concentration relative to THF was added to the above reaction mixture prior to phosgene introduction. After normal reaction times and workup, the corresponding ratio of L-Ala-NCA (**4a**) to *N*-(chlorocarbonyl)alanyl chloride (**12a**, R = CH_3) was measured by ^{13}C NMR to consist of 23% **4a**:77% **12a**.[27]

Similar results were observed for the preparation of N^{ϵ}-(Tfa)-Lys-NCA (**4b**, R = $CF_3CONHCH_2CH_2(CH_2)_3$). DMF concentrations of 10 and 833 ppm gave **4b**:**12b** ratios of 74:26 and 3:97, respectively.[27]

N-Chlorocarbonyl amino acid chlorides **12a** and **12b** were identified by their ^{13}C NMR spectra and their characteristic acid chloride and *N*-chlorocarbonyl bands in the FT infrared spectrum (1801 cm^{-1}, COCl; 1775 cm^{-1}, NCOCl). Subsequent conversion to the corresponding isocyanato acid chloride was not observed in either case. ^{13}C NMR: **12a** (THF) δ 174 (s), 148 (s), 61 (s), 16 (s); **12b** (THF) 174 (s), 157 (q, J_{CF}^2 = 36 Hz), 148 (s), 117 (q, J_{CF}^1 = 290 Hz), 65 (s), 40 (s), 30 (s), 29 (s), 23 (s).

L-Alanyl-L-proline (5a). A solution consisting of potassium hydroxide (15.4 g corrected, 0.274 mol), potassium carbonate (36.1 g, 0.261 mol), and proline (31.5 g, 0.274 mol) in water (500 mL) was prepared and cooled to 0 °C. A solution of Ala-NCA (30 g, 0.261 mol) in THF (60 mL) was cooled to 0 °C. This solution was added to the rapidly stirred carbonate solution over 5 s. The temperature rose to 9 °C. The mixture was stirred at 5–10 °C for 15 min. Stirring was discontinued, and the product solution (pH 9.4–10.2) was removed, weighed, and assayed to contain 44.7 g (92%) of alanylproline by ion-pairing reversed-phase liquid chromatography against an external standard (column, Du Pont Zorbax C-8 (4.6 mm × 25 cm); eluant, 90:10 A:B isocratic @ 2 mL/min, A = 0.015 M heptanesulfonic acid sodium salt in water adjusted to pH 2.2 with H_3PO_4 (~1 mL/L), B = CH_3CN: detector, UV at 210 nm; temperature 50 °C; t_R alanylproline ≃7.0 min). The solution was adjusted to pH 5.7 with 50% H_2SO_4 (~30 mL). Some potassium sulfate precipitated. The resultant slurry was then rendered anhydrous (see next section) for subsequent reductive alkylation or stored at <0.5 °C under nitrogen.

Effects of Alternative Salt/Buffer Combinations for the Preparation of Dipeptides 5a and 5b. The effects of alternative salt/buffer counterions was determined by substituting the corresponding alkali metal hydroxide and carbonate salt for potassium hydroxide and potassium carbonate respectively in the procedures described for **5a** and **5b**.

N^2-[(*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline Maleate (Enalapril Maleate) (17). An aqueous slurry containing L-alanyl-L-proline (**5a**, 133.6 g of slurry assayed at 69.6 mg/g solution; 9.3 g dry basis, 0.05 mol) was concentrated under high vacuum (pump) in a 40 °C bath to a volume of ~20 mL. 1-Butanol (90 mL) was added, and concentration under high vacuum was continued to afford 50 g of a thick slurry with a water content (KF) of ≤0.5% (5 mg/mL). To this was added absolute ethanol (75 mL), and the resulting slurry was transferred to a 500-mL Parr glass shaker bottle. To the hydrogenation bottle were also added powdered 3A molecular sieves (18 g, Linde (Union Carbide)), Grace no. 28 Raney nickel (0.5 tsp) stored in absolute ethanol, and ethyl 2-oxo-4-phenylbutyrate (12.9 g, 0.0625 mol, corrected for purity). These were rinsed in with absolute ethanol (25 mL), and the mixture was hydrogenated at a constant 40 psi of hydrogen for 18 h at 23–28 °C. Hydrogen uptake was normally 100–120% of theory due to concomitant reduction of the α-keto ester. The batch was vented, purged thoroughly with nitrogen, and filtered through 8 g of Supercel and the filter cake washed with ethanol (160 mL). The pH of the combined filtrate was adjusted to 4.25–4.30 with 12 N HCl, as determined by titration of a 1-mL aliquot diluted with water and ethyl acetate. The mixture was concentrated to 40 g, the slurry was filtered through Supercel (3 g), and the cake was washed with ethyl acetate (25 mL). To the combined filtrate was added more ethyl acetate (50 mL) followed by maleic acid (5.22 g, 0.045 mol). The resulting product was filtered after stirring for a few hours and washed with ethyl actate (100 mL). Drying under vacuum to a constant weight afforded 19.2 g (78%) of N^2-[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline maleate (**17**): mp 145.5–146 °C; $[\alpha]^{25}_D$ 42.2° (*c* 1, MeOH); ^{13}C NMR (CD_3OD) δ 174.7 (s), 170.3 (s), 169.9 (s), 168.8 (s), 141.2 (s), 136.2 (s), 129.7 (s), 129.5 (s), 127.5 (s), 63.8 (s), 60.6 (s), 60.0 (s), 56.1 (s), 48.0 (s), 33.2 (s), 31.9 (s), 30.0 (s), 25.9 (s), 15.7 (s), 14.4 (s). Anal. Calcd for $C_{24}H_{32}N_2O_9$: C, 58.53; H, 6.55; N, 5.69. Found: C, 58.55; H, 6.64; N, 5.64.

Evaluation of Alternative Reducing Agents/Catalysts for 1a and 7a. The effect of alternative hydrogenation catalysts for reductive amination (see Table II) was determined by substituting the appropriate catalyst for Raney nickel in the procedures described for **17** and **7a**. The ratios of *S,S,S* and *R,S,S* diastereomers were determined by HPLC.

N^{ϵ}-(Trifluoroacetyl)-L-lysine *N*-Carboxyanhydride (4b). Phosgene (62 g, 0.63 mol) was charged to a 1-L jacketed glass vessel containing dry tetrahydrofuran (THF, 400 mL) under dry nitrogen at 0 °C. The temperature of the solution was brought to 10 °C and the solution stirred rapidly while a slurry of N^{ϵ}-(trifluoroacetyl)-L-lysine (47.5 g, 0.196 mol) in THF (150 mL) was charged in one portion. Remaining solid was rinsed in with additional THF (50–100 mL). The temperature of the mixture rose to 20 °C. External heating was applied, and the temperature of the reaction mixture was brought to 30 °C and maintained for 2.5 h. The reaction temperature was then lowered to 20 °C, and a mixture of phosgene, THF, and HCl was distilled off at 20 mmHg. Heat was applied to the vessel jacket so that an internal temperature of 10–15 °C was maintained. Care was taken during the initial stages of concentration to prevent foaming. When the volume had reached 200 mL, an additional 200 mL of THF was added and concentration was continued. When the volume again reached 200 mL, an additional 200 mL of THF was added and concentration was continued until a final volume of 200 mL was attained. The batch was allowed to stand at 25 °C for 4 h to assure complete cyclization of the *N*-chlorocarbonyl intermediate **9b** to NCA: **9b** ^{13}C NMR (THF) δ 172 (s), 158 (q, J_{CF}^2 = 36 Hz), 147 (s), 117 (q, J_{CF}^1 = 288 Hz), 56 (s), 40 (s), 31 (s), 29 (s), 24 (s). An additional 200 mL of THF was added, and concentration was continued until a final volume of 150 mL was attained. At this point the concentrate was filtered and any filter cake was washed with 100 mL of THF. The combined filtrate and wash was assayed for NCA content.[7] The yield of **4b** was 50.0 g (95%).

Alternatively **4b** could be crystallized by the addition of hexanes to the above concentrate. Filtration afforded 46.3 g (88%) of N^{ϵ}-(Tfa)-Lys-NCA;[28] ^{13}C NMR (THF) δ 171 (s), 158 (q, J_{CF}^2 =

(26) Bailey, J. L. *J. Chem. Soc.* **1950**, 3461–3466.

(27) No ^{13}C NMR signals inconsistent with either NCA or *N*-chlorocarbonyl acid chloride were observed, leading to our belief that under our reaction conditions these are the only products formed.

(28) The preparation of N^{ϵ}-(Tfa)-L-Lys-NCA has previously been reported by: Sela, M.; Arnon, R.; Jacobson, I. *Biopolymers* **1963**, *1*(6), 517–525.

36 Hz), 153 (s), 117 (q, J_{CF}^1 = 288 Hz), 58 (s), 40 (s), 32 (s), 29 (s), 23 (s).

N^{ϵ}-(Trifluoroacetyl)-L-lysyl-L-proline (5b). A solution containing L-proline (10.1 g, 0.0874 mol), potassium hydroxide (4.89 g, 0.0874 mol), and potassium carbonate (17.3 g, 0.125 mol) in THF (250 mL) and deionized water (325 mL) was prepared in a 1-L internally baffled reaction flask and cooled to 0 °C. Care was taken not to go below 0 °C to avoid freezing. The pH of the reaction mixture registered about 13.25 when measured with a silver/silver chloride electrode at 0 °C. The mixture was stirred vigorously as a solution of N^{ϵ}-(trifluoroacetyl)-L-lysine *N*-carboxyanhydride (**4b**, 22.3 g, 0.0833 mol) in THF (concentration ca. 0.2 g of NCA/g of solution) was added over 5 s. Within 20 s the reaction temperature rose to 12 °C, and the pH of the mixture dropped to 9.9. After 2 min total time from the addition of the NCA, pH adjustment to 5.8 with concentrated sulfuric acid (ca. 9 mL) was begun. This adjustment was made in two stages to attenuate CO_2 evolution.

The resulting solution containing some suspended solids was concentrated to about 300 mL and extracted with ethyl acetate (200 mL). The yield of N^{ϵ}-(trifluoroacetyl)-L-lysyl-L-proline (**5b**) in the aqueous phase was 26.6 g (94%) by reversed-phase HPLC as measured against an external standard (column, Hamilton 10μ PRP-1 (4.1 mm × 23 cm); eluant, 95:5 A:B isocratic @ 2 mL/min, A = 0.01 M H_3PO_4 in H_2O adjusted to pH 3.2 with Et_3N, B = CH_3CN; detector, UV at 210 nm; temperature 50 °C; t_R **5b** ≃5.8 min). Concentration was then continued at ≤40 °C until a volume of 150 mL was attained. 1-Butanol (100 mL) was added, and concentration was continued until a volume of 100 mL was obtained. Precipitation of salts occurred as the water content of the batch diminished. An additional 100 mL of 1-butanol was added, and concentration was resumed until a volume of 100 mL was attained. This flushing procedure was repeated, each time adding 100 mL of 1-butanol followed by concentration to 100 mL until a final Karl Fischer titration of the mixture indicated <0.2% H_2O. The resulting slurry was filtered, and the salt cake was washed with three 55-mL portions of anhydrous ethanol. The combined filtrate and washes were stored at 0–5 °C until used.

N^{ϵ}-(Trifluoroacetyl)-L-lysyl-L-proline (**5b**) was characterized by formation of its dicyclohexylamine salt. A portion of the above filtrate containing 2 g of **5b** was lyophilized, slurried in 12 mL of warm 2-propanol, and filtered. The filtrate was stirred as 1 equiv of dicyclohexylamine (1.6 g, 1.8 mL, 5.9 mmol) was added via syringe in one portion. Crystallization generally ensued within 15 min. After 24 h, the (Tfa)-Lys-Pro DCHA salt was filtered, washed with 6 mL of cold 2-propanol, sucked dry under nitrogen, and further dried in vacuo at 50 °C to constant weight. The yield of N^{ϵ}-(trifluoroacetyl)-L-lysyl-L-proline dicyclohexylamine salt was 2.4 g (78%): mp 146.5–147.5 °C; ^{13}C NMR (D_2O) δ 180.2 (s), 180.0 (s), 176.9 (s), 175.5 (s), 159.5 (q, J_{CF}^2 = 37 Hz), 116.8 (q, J_{CF}^1 = 286 Hz), 63.1 (s), 62.9 (s), 54.2 (s), 53.0 (s), 52.6 (s), 48.3 (s), 48.0 (s), 40.5 (s), 40.4 (s), 34.1 (s), 33.9 (s), 32.3 (s), 30.2 (s), 30.0 (s), 28.6 (s), 28.5 (s), 25.4 (s), 25.3 (s), 24.9 (s), 23.3 (s), 23.1 (s), and 22.9 (s). Anal. Calcd for $C_{25}H_{43}N_4O_4F_3$: C, 57.71; H, 8.20; N, 10.8. Found: C, 57.9; H, 8.00; N, 10.8.

N^{ϵ}-(Trifluoroacetyl)-N^{α}-[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-lysyl-L-proline (7a). A mixture (approximately 270 mL) of alcoholic **5b** (26.0 g, 0.0766 mol) and Grace no. 28 Raney nickel (2.5 tsp, newly washed free of water by decantation with absolute ethanol) was prepared. Powdered 3A molecular sieves (12 g) were added. The mixture was stirred for 30 min to achieve ≤0.1% H_2O. Ethyl 2-oxo-4-phenylbutyrate (19.8 g, 0.0958 mol) and an additional 24 g of 3A molecular sieves (Linde) were added, and the entire mixture was hydrogenated at 40 psi of hydrogen, 25 °C, for 16 h (hydrogen uptake was usually 130% of theory, 0.0996 mol based on **5b**). Hydrogen was vented from the vessel by displacement with nitrogen. The reaction mixture was filtered under nitrogen, and the filter cake was washed three times with ethanol (250-mL portions). The combined filtrates and washes were then assayed by reversed-phase HPLC against an external standard (column, Hamilton 10μ PRP-1 (4.1 mm × 23 cm); eluant, 65:35 A:B isocratic @ 2 mL/min, A = 0.01 M H_3PO_4 in H_2O adjusted to pH 3.2 with Et_3N, B = CH_3CN; detector, UV at 210 nm; temperature 50 °C; t_R **7a** ≃ 7.4 min, t_R **7b** ≃10.5 min). The yield of **7a** was 33.4 g (87.5%). Diastereomer content (**7b**) was 5 area % relative to **7a** at 210 nm.

The combined filtrate and decant washes were concentrated under vacuum at <40 °C to a volume of 100 mL. The reaction mixture was vented, and a freshly prepared solution of sodium bicarbonate (0.5 N, 192 mL, 0.096 mol) was added at such a rate so as to control carbon dioxide evolution. The pH of the reaction mixture registered about 7.0. The mixture was chased free of remaining ethanol by further vacuum concentration at <30 °C until a volume of 125 mL was attained. By this time the pH rose to 8.35. An additional 200 mL of water was added. The batch was cooled to 20 °C and extracted with 2 × 200 mL of toluene, allowing at least 30 min settling time between extractions. The product layer was then subjected to the saponification/hydrolysis described in the next step.

Alternatively **7a** was isolated via the following workup. The combined filtrate and wash from above was concentrated under vacuum to a thick viscous liquid and chased free of ethanol by addition of water (175 mL) and further concentration at <40 °C to a volume of 150 mL. Stirring was continued as the biphasic mixture of water and product was diluted with methylene chloride (175 mL) and an additional 175 mL of water. It was cooled to 5 °C and maintained there throughout the following extraction procedure. The pH of the mixture, initially about 6.7, was adjusted upward to 9.2 with 50% NaOH (~2.5 mL). The layers were thoroughly mixed, and the bottom methylene chloride layer was removed. The aqueous layer was washed twice more with methylene chloride (2 × 150 mL). Fresh methylene chloride (175 mL) was added to the combined aqueous layer, and the pH of the mixture, now about 9.8, was adjusted downward to 4.6 with concentrated hydrochloric acid (~5 mL). The bottom methylene chloride product layer was drawn off and saved. The aqueous layer was extracted twice more with methylene chloride (2 × 100 mL). The combined methylene chloride extracts were dried over sodium sulfate (50 g), filtered, and concentrated under vacuum to a thick oil. The oil, ~35 g, was dissolved in *tert*-butyl methyl ether (225 mL) at 45 °C, and the solution was seeded (or scratched to induce crystallization) and cooled slowly over 4 h to 5 °C. After 18 h, the mixture was warmed to 20 °C and cyclohexane (85 mL) was added at the rate of 1 mL/min. It was then cooled to 5 °C over 4 h, aged overnight, and filtered. The product cake was washed with cold 1:1 cyclohexane/methyl *tert*-butyl ether solution (35 mL) and sucked dry. Residual solvent was removed under vacuum at 25 °C to afford a first-crop yield of 54.8 g (47%) of **7a**. A second crop could be obtained in variable yield by concentrating the filtrate to an oil and crystallizing the product in similar fashion to above. Recrystallization of first-crop **7a** (4.5 mL of *tert*-butyl methyl ether/g of **7a**) followed by addition of hexanes afforded 50 g of pure **7a** (91% recovery): mp 74–77 °C; $[\alpha]^{25}_{405}$ −53.8°, $[\alpha]^{25}_{D}$ −24.7 (*c* 1, 0.1 N HCl/CH_3OH); ^{13}C NMR ($CDCl_3$) δ 174.3 (s), 173.7 (s), 173.1 (s), 157.4 (q, J_{CF} = 36.7 Hz), 140.9 (s), 128.3 (s), 126.0 (s), 116.0 (q, J_{CF}^2 = 287.7 Hz), 61.0 (s), 59.4 (s), 57.6 (s), 47.0 (s), 39.6 (s), 34.4 (s), 32.0 (s), 31.8 (s), 28.5 (s), 28.2 (s), 24.8 (s), 22.1 (s), 14.2 (s), 14.0 (s). Anal. Calcd for $C_{25}H_{34}N_3O_6F_3$: C, 56.71; H, 6.43; N, 7.94. Found: C, 56.73; H, 6.54; N, 7.75.

N^2-[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl-L-proline (Lisinopril) (2a). The aqueous bicarbonate solution of **7a** (33.4 g, 0.0631 mol) was heated with stirring to 40 °C, and the solution was adjusted to pH 12.5 with 50% sodium hydroxide and maintained at 40 °C for 4 h. The reaction mixture was cooled to 20 °C, and its pH was adjusted to 8.0 with concentrated hydrochloric acid (approximately 14 mL). Methylene chloride (200 mL) was added, and the pH of the reaction mixture was further adjusted to 5.0–5.2 with concentrated hydrochloric acid (approximately 10 mL). The lower methylene chloride layer was removed, and the upper product layer was concentrated in vacuo to 125 mL. The yield of crude lisinopril (**2a**) was 25.3 g (99%) as measured by HPLC against an external standard (column, Du Pont Zorbax C-8 (4.6 mm × 25 cm); eluant, 96:4 A:B isocratic @ 1.8 mL/min, A = 0.02 M NaH_2PO_4 in water adjusted to pH 5.0 with 5% NaOH, B = CH_3CN; detector, UV at 210 nm; temperature 50 °C; t_R lisinopril (**2a**) ≃6.0 min, t_R **2b** ≃9.0 min). A similar solution of crude lisinopril (**2a**, 40.0 assay g), contaminated primarily with its *R,S,S* diastereomer **2b**, was adjusted to pH 5.0–5.2 and concentrated to ~8 wt % solution. This was charged to a column (5.0 × 50 cm) containing 1.5 L of SP-207[23] resin previously equilibrated with water.[29] The column was eluted with

water at a rate of 1 bed volume/h. Elution of the salt contaminants (mainly sodium chloride) occurred within the first 3 bed volumes. Its presence or absence was monitored by a test of the eluate with a few drops of aqueous 1 N silver nitrate [a positive test (precipitate) indicated the presence of salts]. Once salt elution had ceased, the eluant was switched to 25% ethanol in water (v/v), and the product was eluted in the next 2–3 bed volumes. The product rich cuts generally contained 39.2 g (98%) of lisinopril (**2a**).

Alternatively, crude lisinopril was concentrated to a 15–20 wt % solution and charged to a Dowex 50W-x2 (H^+ cycle) resin column (5 × 50 cm). The column was eluted with deionized water at a rate of 1.25 bed volumes/h. When the column eluate showed a negative halide test with silver nitrate, usually within 2–3 bed volumes, the eluting solvent was changed to 0.2 N ammonium hydroxide. The product eluted in the next 2 bed volumes. The product cuts were combined and assayed for total lisinopril content. Recovery was 39.0 g (99%).

Combined salt-free rich cuts of lisinopril (**2a**, 13.95 g by HPLC assay; see conditions above) containing 5–7 area % (HPLC) of the *R,S,S* isomer **2b** were concentrated under vacuum to 215 mL. The pH was adjusted to 5.2 ± 0.2 with 28–30% ammonium hydroxide, and the mixture was decolorized with Darco KB (0.7 g). After filtration the carbon cake was washed with ethanol (40 mL) and the combined filtrate was further concentrated to 32.6 g (ca. 43 wt % solution). Ethanol (250 mL) was added to afford a solution which was 13 wt % in water. Haze was removed by filtration. The filter was washed with ethanol (30 mL), and the filtrates were combined. The resulting clear solution was concentrated under vacuum to 42 g. Ethanol (160 mL) was added, and the water content was measured to be 4–6%. Throughout, the water content was monitored carefully to assure that crystallization would occur from 94–96% ethanol to afford a monohydrate crystal and reject about one-half of the *R,S,S* diastereomer. The solution was seeded with 0.3 g of lisinopril monohydrate and stirred for 12 h at 20–25 °C. The product was filtered and washed with absolute ethanol (50 mL). The product was dried under vacuum at 60 °C to afford 13.84 g of crude lisinopril, 96 wt % (89% corrected anhydrous basis) recovery. The *R,S,S* isomer content was 1.0–2.5 area % by HPLC.

Recrystallization of 2a. Twenty-five grams of crude lisinopril (**2a**) (anhydrous basis) was added to water (300 mL). The slurry was warmed to 60 °C to afford a pale yellow solution. The solution was cooled to 25 °C and filtered to remove insoluble materials. Thirty milliliters of water was used as a wash, and the filtrates were combined. Water was removed under vacuum to afford 75 g of clear concentrate (2 mL of water/g of lisinopril). This was seeded with 0.5 g of lisinopril dihydrate. The slurry was warmed and stirred at 45 ± 1 °C until it became very thick. This normally required 24 h. The slurry was then allowed to cool to room temperature and stirred for another 24 h. The thick slurry was filtered, and the cake was washed with water (50 mL). The product was dried under vacuum to a constant weight at 50–55 °C and then equilibrated at 68% relative humidity to afford 20.5 g of **2a** (75% recovery corrected for hydrated water): $[\alpha]^{25}_{405}$ −120.8° (*c* 1, $Zn(OAc)_2$ buffer 0.025 M, pH 6.4); ^{13}C NMR (1 N DCl) δ 175.71, 171.44, 167.32, 140.53, 129.65, 129.50, 127.58, 60.53, 60.11, 59.73, 48.70, 39.89, 31.92, 31.21, 30.02, 29.49, 27.20, 25.39, 21.57. Anal. Calcd for $C_{21}H_{31}N_3O_5 \cdot 2H_2O$: C, 57.13; H, 7.99; N, 9.52. Found: C, 57.04; H, 7.90; N, 9.38.

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Registry No. **1a**, 75847-73-3; **1b**, 76420-74-1; **2a**, 76547-98-3; **3b**, 10009-20-8; **4a**, 2224-52-4; **4b**, 42267-27-6; **5a**, 13485-59-1; **5b**, 103300-89-6; **5b**·DCHA, 103300-90-9; **6**, 64920-29-2; **7a**, 103300-91-0; **7b**, 112246-14-7; **9b**, 112139-31-8; **12a**, 112139-29-4; **12b**, 112139-30-7; **17**, 76095-16-4; (2-bromoethyl)benzene, 103-63-9; diethyl oxalate, 95-92-1; L-alanine, 56-41-7; L-proline, 147-85-3; Raney nickel, 7440-02-0.

(29) Initial preparation of the SP-207 resin requires washing the resin with 3 bed volumes of acetone/methanol/water (1:1:2) followed by equilibration of the column with deionized water.