($CDCl_3$) δ 138.5, 133.8, 128.3, 129.2, 133.5, 21.3; ^1H NMR ($CDCl_3$) δ 7.08–7.26 (m, 4 H), 2.35 (s, 3 H).

Tris[4-(trifluoromethyl)phenyl]phosphine, synthesized by the method of Miller and Grim:[17] mp 69–70 °C (lit.[17] mp 68–70 °C).

NMR Measurements. The ^{31}P NMR measurements were made on a JEOL-FX270 MHz instrument at 109.13 MHz. A total of 16 384 points were collected over a spectral width of 50 000 Hz, utilizing a pulse delay of 5 or 10 s. All the chemical shifts are reported relative to 85% H_3PO_4 by substitution. The proton and ^{13}C NMR data were also collected on a JEOL-FX270 MHz instrument and the data referenced to tetramethylsilane.

Kinetic Method. The rates of the reactions were determined by monitoring the disappearance of the phosphines at 290 nm on a Cary 14R UV spectrophotometer. The absorbances of the corresponding phosphine oxides were negligible at this wavelength. The peroxides were purified by five sublimations immediately before use, but the phosphines were used without further purification. Fresh 10-mL solutions of 2×10^{-2} M peroxide and 2×10^{-4} M phosphine were made up for each kinetic run. A 1.7-mL sample of each solution was added to a 1-cm cuvette thermostated at the desired temperature. The disappearance of the phosphine was monitored for 3 half-lives. Each reported rate is the average of three independent determinations.

Data Treatment. Each rate constant was determined by following the decrease in absorbance of PPh_3 at 290 nm for at least 3 half-lives and plotting ln $(A_0 - A_\infty)$ vs. time. All of the rate constants were obtained by linear regression analysis and the second-order rate constants by dividing the pseudo-first-order rate constants by the concentration of the peroxide. The activation parameters were determined by plotting ln (k/T) vs. $1/T$ and the confidence limits were calculated by the method of Bennett and Franklin[18] and propagated into the activation parameters at the 95% confidence level. For the Hammett studies, plots of log (k_X/k_H) vs. σ^+ were plotted and the confidence limits in the slope were determined by using a least-square fit to a straight line as described by Bevington.[19]

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Registry No. 1, 279-35-6; 2, 280-53-5; 3, 67105-55-9; 5a, 603-35-0; 5b, 13406-29-6; 5c, 18437-78-0; 5d, 1159-54-2; 5e, 1038-95-5; 5f, 855-38-9.

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An Efficient Synthesis of Ethyl LL-3-Amino-2-piperidone-6-carboxylate

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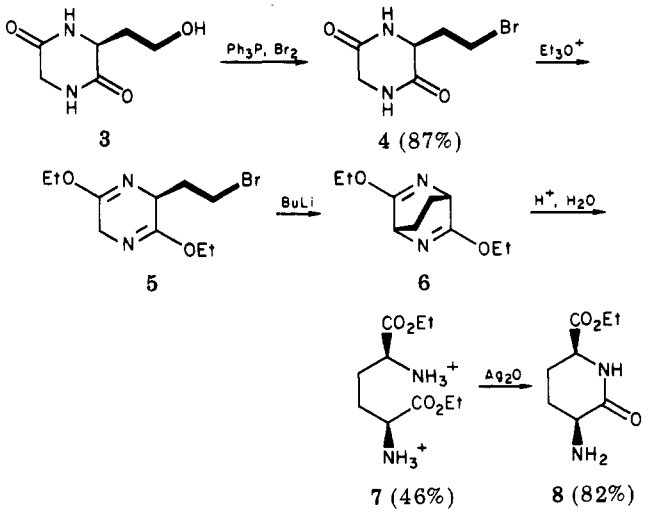
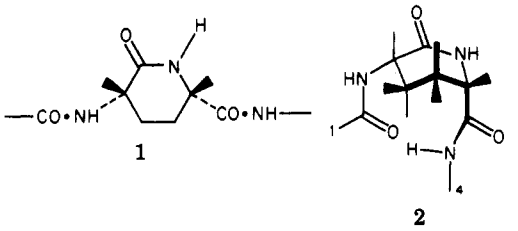
Control of the local conformations of the backbones of polypeptides and proteins offers new approaches to fundamental problems ranging from studies of mechanisms of protein folding[1] to developing useful pharmacological mimics of the peptide hormones.[2] As one of the commonest and simplest elements of secondary structure, the β-turn is a natural candidate for conformational control.[3] Elsewhere we have shown[4] that the 3-amino-2-piperidone-6-carboxylic acid residue (Acp, 1), when incorporated into short peptides, adopts conformation 2 in which the 3-acylamino substituent adopts a *pseudo* equatorial and the 6-carboxamido substituent a *pseudo* axial orientation. Thus, the α-carbon atoms of amino acid residues 1 and 4 are within the 6–7 Å of a generalized turn conformation.

Scheme I





Although we have previously reported a synthesis of LL-Acp from L-homoserine involving a high-temperature copper-catalyzed decarboxylation of 3,6-dioxo-2,5-diazabicyclo[2.2.2]octane-1-carboxylic acid,[5] variable racemization attends large-scale execution of this step. We report an alternative synthesis from L-homoserine outlined in Scheme I and based on the chiral amino acid synthesis of Schöllkopf.[6]

Diketopiperazine 3 is available in two steps (70%) from Cbz-Gly-OSu and L-homoserine lactone, followed by hydrogenation. Although NBS–phosphine could be used for conversion to 4, a cleaner preparation of crystalline 4 was achieved by means of bromine and triphenylphosphine.[8] The next three steps could be carried out without purification of intermediates, giving 7 in 46% yield, based on 4. No chromatographic separations are required in this reaction sequence which has been used to generate tens of grams of 7, a conveniently storable precursor of 8.

The efficiency of chiral induction at the second asymmetric center generated in 5 → 6 is in the range of 99.5%,

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as assessed by the conversion of an unrecrystallized sample of **7** to **8** and thence by reaction with the hydroxysuccinimide ester of Cbz-L-Pro-OH to Cbz-L-Pro-Acp-OEt. Separation of diastereomers of this species by HPLC is clean and can be used to detect less than 1% of the L,DD isomer.

It is noteworthy that the reaction of **5** with butyllithium occurs exceptionally cleanly, implying that alternative proton transfer or cyclization reactions are not competitive. Provided proton transfer does not lead to racemization of **5**, this ring closure is expected to be absolutely enantioselective. Thus the efficiency of this intramolecular chiral synthesis sets an upper limit on the chiral integrity that can be realized by the intermolecular Schöllkopf method.

Experimental Section

Proton NMR spectra were obtained on Brucker Model WM-250 or WM-270 instruments by Ms. J. Owens. Optical rotations were measured in a 1.0-dm thermostatted cell in a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. TLC was carried out on aluminum-backed silica gel 60 plates (F-254) and a EM Reagents in the following solvent systems: (A) chloroform–acetic acid (95:5); (B) chloroform–methanol (4:1); (C) chloroform–methanol (95:5); (D) hexane–ethyl acetate (4:1).

***N*-(Benzyloxycarbonyl)glycyl-L-homoserine Lactone.** To an ice-cold suspension of L-homoserine lactone hydrochloride (26.5 g, 193 mmol) in 400 mL of dichloromethane was added triethylamine (26.9 mL, 193 mmol) followed by the hydroxysuccinimide ester[7] of carbobenzoxyglycine (mp 111–113 °C, 61.0 g, 200 mmol). The reaction was stirred at 5 °C overnight, and the solution was washed with water (2 × 200 mL). The washings were extracted with dichloromethane (1 × 100 mL), and the organic solutions were pooled, dried (Na_2SO_4), and concentrated until a precipitate appeared. The mixture was kept at 5 °C for 5 h. The precipitate was collected by filtration, washed, and dried. The filtrate was concentrated and further material recovered in the same manner. The crude product (48.0 g) was recrystallized from acetonitrile to yield 44.7 g (79%) of white prisms: mp 114–116 °C; TLC R_f 0.44 (A).

Anal. Calcd for $C_{14}H_{16}O_5N_2$: C, 57.52; H, 5.52; N, 9.59. Found: C, 57.30; H, 5.36; N, 9.47.

3-L-(2-Hydroxyethyl)diketopiperazine (3). (Benzyloxycarbonyl)glycyl-L-homoserine lactone (17.54 g, 60.0 mmol) was dissolved in 300 mL of hot methanol and cooled to 5 °C. After addition of 10% Pd–C (1 g), the mixture was hydrogenated in a Parr apparatus, at 25 °C and 40 psi for 18 h. The mixture was diluted with 200 mL of methanol, brought to a boil, and filtered through Celite with the help of hot methanol. The filtrate was evaporated and the residue crystallized from 400 mL ethanol to give 8.33 g of **3** (88%) as white needles: mp 191–193 °C; $[\alpha]^{26}_D$ 46.6° (*c* 1.0, H_2O); ^1H NMR (Me_2SO-d_6) δ 1.82 (2 H, m), 3.50 (2 H, q), 3.63 (1 H, dd, 2.8 Hz and 17.6 Hz), 3.77 (2 H, d overlapping with broad m, 17.6 Hz), 4.57 (1 H, t, 4.9 Hz), 7.97 (1 H, s), 8.10 (1 H, s).

Anal. Calcd for $C_6H_{10}O_3N_2$: C, 45.56; H, 6.37; N, 17.72. Found: C, 45.67; H, 6.19; N, 17.67.

3-L-(2-Bromoethyl)diketopiperazine (4). A mixture of **3** (9.49 g, 60 mmol) and triphenylphosphine (17.31 g, 66 mmol) was dried in a desiccator under high vacuum for 2 h. Dry DMF (300 mL) was added via a cannula, and the mixture was cooled in an ice bath with stirring. When most of the solid had dissolved, bromine (3.4 mL, 66 mmol) was added dropwise over 0.5 h. The solution was stirred at 0 °C for 0.5 h and overnight at 5 °C. Dry methanol (1.5 mL) was added, and the solution was stirred, at 5 °C, for 1 h. The solution was evaporated to an oil, which was rubbed with ether (3 × 300 mL), yielding a sticky solid. The crude product was dissolved in 500 mL of hot methanol, cooled to room temperature, and diluted with 1.5 L of chloroform. Long, soft needles of product were obtained after storage overnight at 0 °C. These were collected by filtration, washed with chloroform–methanol (4:1) and chloroform, and dried under vacuum over P_2O_5. A second crop was recovered from the filtrates. The total yield was 11.57 g (87%): mp 195–196 °C; $[\alpha]^{26}_D$ 13.3° (*c* 1.08, H_2O); TLC R_f 0.51 (B); ^1H NMR (Me_2SO-d_6) δ 1.81 (2 H, m), 2.28 (2 H, m), 3.45–3.69 (3 H, m).

Diethyl L,L-2,5-Diaminoadipate Dihydrochloride (7). A. 2,5-Diethoxy-3-L-(2-bromoethyl)-3,6-dihydropyrazine (5). In this preparation all glassware was oven dried; all manipulations involving triethyloxonium tetrafluoroborate were carried out in a glovebag under dry N_2.

A solution of freshly prepared triethyloxonium tetrafluoroborate (16.79 g, 88.4 mmol) in 50 mL of dry dichloromethane was added to a suspension of 3-L-(2-bromoethyl)diketopiperazine (**4**, 6.63 g, 30.0 mmol) in 80 mL of dichloromethane. The suspension was stirred at 25 °C and under nitrogen for 18 h, in which time the solid had dissolved and a second liquid phase had separated. The mixture was stirred vigorously for 15 min with 300 mL of ice-cold 5% sodium bicarbonate and 125 mL of dichloromethane. The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The organic layers were pooled, dried ($MgSO_4$), and evaporated. Dry hexane was added to the residue and evaporated, yielding 6.24 g (75%) of an oil. TLC showed only trace impurities and no further purification was attempted: TLC R_f 0.75 (C); ^1H NMR ($CDCl_3$) δ 1.28–1.34 (6 H, overlapping t), 2.10 (1 H, m), 2.40 (1 H, m), 3.44–3.62 (2 H, m), 3.98–4.19 (7 H, m).

B. 3,6-Diethoxy-2,5-diazabicyclo[2.2.2]octa-2,5-diene (6). The oil **5** (6.1 g, 22 mmol) was dissolved in tetrahydrofuran and transferred via a cannula to an oven-dried, 500-mL round-bottomed flask. The solvent was evaporated, with care taken to exclude moisture. The flask and contents were kept in a desiccator under high vacuum and over P_2O_5 for 1 h, then 275 mL of tetrahydrofuran was added via a cannula, and the solution was cooled to −78 °C. Butyllithium (15.6 mL of 1.34 M hexane solution; 20.9 mmol) was added dropwise over 20 min. The solution was stirred at −78 °C for 3 h. (If significant amounts of **5** were present, more *n*-BuLi was added.) The amber solution was evaporated, and the residue was partitioned between 100 mL of ether and 100 mL of water. The layers were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The organic layers were pooled, washed with brine (1 × 25 mL), dried (Na_2SO_4), and evaporated to yield 4.01 g (91%) of an amber oil. TLC showed only traces of impurities, and **6** was used without further purification: TLC R_f 0.67 (C), 0.13 (D).

The above oil (4.01 g, 20.4 mmol) was dissolved in 100 mL of 0.5 N HCl, and the cloudy solution was kept at room temperature for 1 h. The solvent was then evaporated, ethanol was added, and the mixture was taken to dryness, leaving an amber solid. The product was crystallized from ethanol, yielding 2.44 g of a white crystalline solid: mp 215–216 °C. Five volumes of ether was added to the filtrate. The mixture was kept at 0 °C for 1 h. The product was collected by filtration and dried in a vacuum desiccator to yield 1.68 g of an off-white solid: mp 211–212 °C. A total of 4.12 g (66%) of **7** was obtained. The two crops were chromatographically and chemically indistinguishable and were used interchangeably for further transformations. The substance was usually stored in this form and converted into piperidone **8** immediately before use.

Anal. Calcd for $C_{10}H_{22}O_4N_2Cl_2$: C, 39.34; H, 7.27; N, 9.18. Found: C, 39.37; H, 7.26; N, 9.07.

Ethyl L,L-3-Amino-2-piperidone-6-carboxylate (8). Diethyl L,L-2,5-diaminoadipate dihydrochloride (**7**, 1.83 g, 6 mmol) was dissolved in 30 mL of water and 30 mL of ethanol. Silver oxide (1.46 g, 6.3 mmol) was added, and the mixture was stirred for 20 min. The mixture was filtered with the aid of Celite, and the solution was taken to dryness. The solid residue was dissolved in ethanol and passed through 10 g of neutral alumina, using 25 mL of ethanol as a rinse. The solvent was evaporated, leaving 913 mg (82%) of crystalline product: mp 90–92 °C; TLC R_f 0.29 (A), $[\alpha]^{25}_D$ 1.4° (*c* 0.3, CH_3OH); ^1H NMR (Py-d_5) δ 1.07 (3 H, t, 7.8 Hz), 1.5–2.3 (4 H, m), 2.4–2.9 (2 H, bs), 3.8–4.4 (4 H, m), 8.4 (1 H, bs); TLC R_f 0.29 (H).

Boc-L-Cys(Meb)-OSu (9).[9] An ice-cold mixture of Boc-Cys(Meb)-OH·DCHA (6.8 g, 13 mmol), 70 mL of H_2O, and 70 mL of ethyl acetate was stirred with 14.3 mL of 1 N sulfuric acid. After the solid dissolved, the layers were separated and the aqueous

(9) Meb = *p*-methoxybenzyl. See: Akabori, S.; Sakakibara, S.; Shimonishi, Y.; Nobuhara, Y. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 433–440.

layer was extracted with ethyl acetate (2 × 20 mL). The organic layers were combined, washed with water (1 × 10 mL) and brine (1 × 10 mL), and dried ($MgSO_4$). The solvent was evaporated, leaving Boc-L-Cys(Meb)-OH as an oil to which was added *N*-hydroxysuccinimide (1.5 g, 13 mmol) in 25 mL of tetrahydrofuran. The solution was cooled and dicyclohexylcarbodiimide (2.68 g; 13 mmol) was added, with 2 mL of tetrahydrofuran as a rinse. The reaction was stirred at 0 °C for 2 h. The solutions was filtered, and the filtrate was evaporated. The residue was crystallized from hot 2-propanol, yielding 4.2 g (74%) of white crystals: mp 80–86 °C. The crystals were used as such in subsequent transformations. A sample was recrystallized: mp 82–84 °C; $[\alpha]^{27}_D$ −48.0° (*c* 0.99, EtOAc).

Boc-L-Cys(Meb)-LL-Acp-OEt. Boc-L-Cys(Meb)-OSu (4.91 g, 11.2 mmol) was added to an ice-cold solution of H-LL-Acp-OEt (8, 2.08 g, 11.2 mmol) in 22 mL of dichloromethane, and the solution was stirred at 5 °C for 18 h. After evaporation, the residue was dissolved in 100 mL of ethyl acetate and washed with water (2 × 25 mL) and brine (1 × 25 mL). The washes were pooled and extracted with ethyl acetate (1 × 20 mL). The organic layers were pooled, dried ($MgSO_4$), and evaporated, leaving the product as a foam. Crystallization from chloroform–petroleum ether yielded 4.85 g (85%) of white crystals: mp 109–111 °C; TLC R_f 0.56 (A), 0.79 (B); ^{1}H NMR (Me_2SO-d_6) δ 1.20 (3 H, t, 7.1 Hz), 1.39 (9 H, s), 1.86–2.18 (4 H, m), 2.71–2.81 (2 H, m), 3.71 (5 H), 4.00–4.26 (5 H, m), 6.84 (2 H, d, 8.4 Hz), 6.92 (1 H, d, 8.4 Hz), 7.23 (2 H, d, 8.4 Hz), 7.78 (1 H, s), 8.09 (1 H, d, 7.5 Hz).

Anal. Calcd for $C_{24}H_{35}O_7N_3S$: C, 56.56; H, 6.92; N, 8.24; S, 6.29. Found: C, 56.49; H, 6.75; N, 8.24; S, 6.36.

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Registry No. 3, 89959-25-1; 4, 89959-26-2; 5, 89959-27-3; 6, 89959-28-4; 7, 90025-86-8; 8, 84245-61-4; 9, 66413-65-8; Boc-Cys(Meb)-OH·DCHA, 31025-14-6; Boc-L-Cys(Meb)-OH, 18942-46-6; Boc-L-Cys(Meb)-LL-Acp-OEt, 89975-16-6; L-homoserine lactone hydrochloride, 2185-03-7; carbobenzoxyglycine hydroysuccinimide ester, 2899-60-7; *N*-(benzyloxycarboyl)glycyl-L-homoserine lactone, 89959-29-5.

A Palladium-Catalyzed Synthesis of Ketones from Acid Chlorides and Organozinc Compounds

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The reaction of acid halides and organometallic compounds (i.e., Zn, Cd, Mg) has historically been frequently used for ketone synthesis. Although organozinc compounds were generally employed prior to the 1930s, organocadmium reagents were subsequently demonstrated to be more satisfactory.[1] Recently, several transition-metal-catalyzed coupling reactions of acid chlorides and organometallic reagents to form ketones have been reported.[2-11] Of these, the most selective and general route appears to be the palladium-catalyzed reaction between acid chlorides and organotin compounds.[5]

We have found that the reaction between acid chlorides and organozinc compounds is catalyzed by palladium complexes to produce ketones in higher yields, selectivities, and rates than the uncatalyzed reaction. The reaction proceeds under mild conditions (0–23 °C) and is general in scope (see Table I). Ketones can be prepared by the reactions between primary and secondary alkylzinc reagents and alkyl acid chlorides (i.e., 4-octanone and 2-methyl-3-hexanone, respectively), arylzincs and alkyl acid chlorides (i.e., acetophenone), and alkylzincs and aryl acid chlorides (i.e., valerophenone). Thus, the reaction of di-*n*-butylzinc (prepared in situ by the reaction of *n*-butylmagnesium chloride with a slight excess of zinc chloride) with butanoyl chloride in the presence of benzylchlorobis(triphenylphosphine)palladium[12] (**1**) in THF/Et_2O gave 4-octanone in nearly quantitative yield (GC analysis, see Table I).[13] Under the same conditions, the uncatalyzed reaction gave a 5% yield of 4-octanone (~7% conversion, 60% selectivity). A 92% isolated yield of 4-octanone (greater than 99% pure) was obtained by using the palladium-catalyzed method on a large scale (see Experimental Section).

Reactions involving aryl acid chlorides differed from those using alkyl acid chlorides in that the corresponding aryl aldehyde was formed as a significant byproduct. Thus the reaction between benzoyl chloride and di-*n*-butylzinc in the presence of **1** in THF/Et_2O solution gave benzaldehyde (40%) in addition to the desired product, valerophenone (53%). We suggest the byproduct is formed by the β-hydrogen elimination of a palladium alkyl intermediate and the resulting palladium aroylhydrido species undergoing reductive elimination to yield benzaldehyde. The selectivity to benzaldehyde was affected both by the nature of the catalyst and solvent as shown in Table I. In general, the byproduct benzaldehyde was minimized by either using diethyl ether as the sole solvent or (dppf)$PdCl_2$[14] (**2**) as the catalyst. The best yield to valerophenone (97%) was obtained by using the combination of **2** and diethyl ether. This trend was also seen for the reaction between di-*n*-butylzinc and terephthaloyl chloride (see Table I).

Another example of the dependency of the solvent on selectivity was observed in the synthesis of 2-methyl-3-hexanone from butanoyl chloride and diisopropylzinc. Although in THF/Et_2O solutions of **1**, 2-methyl-3-hexanone was formed in 95% yield, surprisingly, 4-heptanone (4%) was the byproduct. The formation of 4-heptanone requires the isomerization of the isopropyl to an *n*-propyl group before reaction with acid chloride. In solutions of **1** in diethyl ether as the sole solvent, the yield of the byproduct 4-heptanone decreased to ~0.5%. In contrast to the aryl acid chloride results, changing the catalyst from **1** to **2** did not affect the yield of 4-heptanone.

Tetrakis(triphenylphosphine)palladium (**3**), although less active than **1**, is also an effective catalyst for this ketone synthesis. Under the same conditions shown in

† ARCO Chemical Co. is a division of Atlantic Richfield Co.

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