Stereoselective Decarboxylation of a Geminal Dicarboxylic Acid. Synthesis of *cis*-5-(Hydroxymethyl)-D-proline Derivatives

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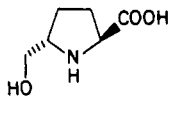
For studies of unnatural α-amino acids that can induce strong conformational biases when incorporated into proteins, we required *trans*-5-(hydroxymethyl)-L-proline (**1**) and were attracted by a scheme outlined by Witkop[1] in which racemic **1** and its diastereomer **2a** were formed as unwanted and uncharacterized major products from **3** by ring closure, hydrolysis, and decarboxylation.[2] Although Witkop's route proved to be unworkable as a source of **1**, it provided the conceptual focus for the work reported here.



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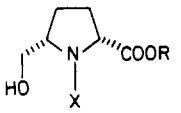
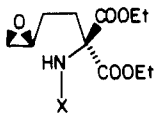
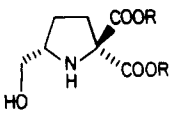


2a, X=R=H
2b, X=$COOCH_2Ph$, R=CH_3

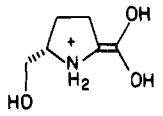


3, X=CHO
4, X=$COOCH_2Ph$
5, X=H

In particular, we were attracted by the possibility that in a suitable solvent the neighboring hydroxymethyl group might be involved in a chain of hydrogen bonds that would direct protonation of the α-carbon of the enolic intermediate **7** formed in the decarboxylation of **6b**, thus generating **1** stereoselectively.



6a R=Et
b R=H



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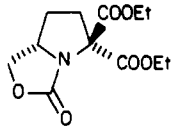
The required **6a** for testing this proposal was generated in 50% yield by (1) alkylation[3] of the sodium salt of (*N*-carbobenzoxyamino)malonate[4] with (*R*)-4-iodo-1,2-epoxybutane[5] and (2) hydrogenolysis of the Cbz group to yield **5**, followed by spontaneous ring closure.

In ethyl acetate solution hydrogenolysis of the benzyl group occurs cleanly without reduction of the epoxide,[6] and under these conditions ring closure occurs spontaneously to form **6a** in a 4.5:1 ratio with the isomeric piperidine. Hydrolysis of **6a** and decarboxylation of the resulting diacid (3 M HCl, reflux, 5h) gave selective formation of the cis acid **2a** together with traces of **1** (12:1 ratio); protonation of **7** thus occurs stereoselectively trans to the hydroxymethylene function. Although **2b** could not be induced to lactonize, its structure was established by oxidation and esterification to the corresponding 2,5-pyrrolidinedicarboxylate which had no detectable optical activity.

An important clue concerning the origin of the selectivity in the decarboxylation step is provided by the behavior of the constrained cyclic urethane **8** upon selective hydrolysis of the ester functions and decarboxylation. A



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2.5:1 mixture of the cyclic urethanes of **1** and **2a** is formed. Evidently the steric constraint of the urethane function has the effect of shifting the oxymethylene function from the locus of the enediol function of the intermediate in the decarboxylation. This in turn dramatically shifts the stereochemical outcome of the reaction. The most reasonable explanation for the selective trans protonation of **7** is steric shielding, perhaps augmented by an intramolecular hydrogen bond between the hydroxyl and ammonium groups. Though not useful for our original purpose, this simple route to chiral **2a** may have heuristic value for the planning of stereoselective synthesis of other pyrrolidine derivatives.

Experimental Section

NMR spectra were obtained on a Burker WM 250-MHz spectrophotometer using tetramethylsilane as the internal standard. IR spectra were obtained with a Perkin-Elmer 283B spectrophotometer. Optical rotations were measured with an Autopol III polarimeter. Mass spectra were obtained with a Varian MATT 8000 mass spectrometer. Elemental analyses were performed by MultiChem Laboratories, Lowell, MA. Merck silica gel 60 (0.040–0.063 mm) was employed for column chromatography. TLC was performed on Merck, precoated, silica gel 60 plates.

Preparation of 4: Ethyl 2-[((*N*-Benzyloxy)carbonyl)-amino]-2-carbethoxy-5(*R*),6-epoxyhexanoate. In a flame-dried flask under N_2 was dissolved 165 mg (7.17 mmol, 1.0 equiv) of Na metal in 10 mL of absolute EtOH. Once the Na had reacted, 2.45 g (7.93 mmol, 1.1 equiv) of diethyl (*N*-carbobenzoxyamino)malonate dissolved in 3 mL of absolute EtOH was added. After the mixture stood for 10 min the solvent was evaporated under high vacuum, and 5 mL of dry CH_3CN was added to the residue and evaporated. The crude malonate salt was dissolved in 14 mL of dry Me_2SO.

In a separate, flame-dried flask under N_2 was dissolved 2.14 g (10.8 mmol, 1.5 equiv) of (*R*)-4-iodo-1,2-epoxybutane in 3 mL of dry Me_2SO. To this was added dropwise over 10 min the malonate salt solution prepared as described above. After the mixture was stirred for 13 h at 23 °C the reaction solution was poured into 50 mL of 1 N HCl and extracted with 3 × 25 mL of EtOAc. The combined organic extracts were washed: 2 × 15 mL of 1 N HCl and 2 × 15 mL of brine. The EtOAc was dried ($MgSO_4$), filtered, and evaporated to an orange oil. Flash chromatography (1:1 Et_2O/hexane) followed by evaporation yielded 1.97 g (73%) of pure **4** as a clear oil: $[\alpha]^{22}_D$ +3.6° (*c* 1.67, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.35 (5 H, s), 6.19 (1 H, s), 5.10 (2 H, s), 4.27–4.19 (4 H, q, *J* = 6.9 Hz), 2.88 (1 H, br s), 2.73–2.69 (1 H, t, *J* = 4.4 Hz), 2.52–2.45 (1 H, m), 2.43–2.39 (1 H, m), 1.47–1.37 (2 H, m), 1.26–1.19 (6 H, t, *J* = 7.0 Hz); IR ($CHCl_3$) 3410 (NH), 1725 (ester C=O), 1710 (urethane C=O) cm^{-1}; TLC, R_f 0.45 (7:3 Et_2O/hexane).

Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found: C, 60.23; H, 6.60; N, 3.64.

Preparation of 6a: 5(*S*)-(Hydroxymethyl)-2,2-dicarbethoxypyrrolidine. To a solution of 1.97 g (5.19 mmol) of **4** in 45 mL of EtOAc in a Parr pressure vessel was added 0.20 g of 10% Pd–C. The resulting mixture was hydrogenated at 23 °C and 50 psi for 2.5 h; the catalyst was removed by filtration and the filtrate was evaporated to a crude oil. Flash chromatography (EtOAc) followed by evaporation yielded 0.88 g (69%) of pure **6a** as a clear oil: $[\alpha]^{22}_D$ −48° (*c* 0.59, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.30–4.10 (4 H, m), 3.60–3.48 (2 H, m), 3.42–3.33 (1 H, m), 3.0–2.0 (2 H, br s), 2.58–2.46 (1 H, m), 2.25–2.13 (1 H, m), 1.94–1.68 (2 H, m), 1.33–1.23 (6 H, m); IR ($CHCl_3$) 3460 (OH), 3350 (NH), 1720 (ester

(1) Witkop, B.; Fultz, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 192.
(2) Morita, K.; Irreverra, F.; Sakiyama, F.; Witkop, B. *J. Am. Chem. Soc.* **1963**, *85*, 2824.
(3) Cruickshank, P. A.; Fishman, M. *J. Org. Chem.* **1969**, *34*, 4060.
(4) Frankel, M.; Harnik, M.; Levin, Y. *J. Am. Chem. Soc.* **1952**, *74*, 3873.
(5) (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 1208. (b) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304.
(6) Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic: New York, 1967; p 478.

0022-3263/86/1951-2377$01.50/0

C=O) cm^{-1}; MS, *m/e* 246 ($M^+ + 1$), 214 ($M^+ - CH_2OH$), 172 ($M^+ - CO_2CH_2CH_3$); TLC, R_f 0.50 (EtOAc).

Preparation of 6b and 2b: 5(*S*)-(Hydroxymethyl)-2-(*R*)-carboxypyrrolidine and *N*-Carbobenzoxy-5(*S*)-(hydroxymethyl)-2(*R*)-carbomethoxypyrrolidine. 6a (880 mg, 3.59 mmol) was dissolved in 12 mL of 4 N NaOH and stirred at room temperature. After 17 h 10 mL of concentrated HCl was carefully added, and the resulting solution was brought to reflux. After 5 h reflux was stopped, and KOH pellets were added to bring the pH to 12. The solution was chilled to 0 °C and 0.80 mL (5.6 mmol, 1.5 equiv) of carbobenzoxy chloride dissolved in 15 mL of dioxane and 15 mL of H_2O was added. The reaction stirred at 0 °C for 1 h, then at room temperature. After 20 h the solution was poured into a separating funnel and washed three times with Et_2O. The aqueous layer was acidified to pH 2 with concentrated HCl and extracted four times with EtOAc. The combined EtOAc extracts were dried ($MgSO_4$), filtered, and evaporated. A crude oil remained, 416 mg (41%). This oil was dissolved in 5 mL of THF and treated with excess CH_2N_2 in ether. The excess CH_2N_2 was quenched with excess AcOH, and the solvent was evaporated to an oil from which **2b** was obtained pure by flash chromatography (4:1 EtOAc/hexane); 308 mg (29% from **6a**) of a clear oil was obtained: $[\alpha]^{22}_D$ +9.6° (*c* 0.27, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.45–7.25 (5 H, m), 5.25–5.05 (2 H, m), 4.55 -4.40 (1 H, m), 4.20–3.95 (2 H, m), 3.90–3.20 (2 H, m), 3.80, 3.65 (3 H, 2 s), 2.30–1.85 (4 H, m), 1.65 (1 H, br s); IR ($CHCl_3$) 3560 (OH), 1735 (ester C=O), 1700 (urethane C=O) cm^{-1}; TLC, R_f 0.63 (EtOAc); MS, *m/e* 294 ($M^+ + 1$), 293 (M^+), 262 ($M^+ - OCH_3$), 234 ($M^+ - CO_2CH_3$).

Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.43; N, 4.78. Found: C, 61.67; H, 6.58; N, 5.00. HRMS calcd for $C_{15}H_{19}NO_5$ 293.1263, found, 293.1262.

***cis*-*N*-Carbobenzoxy-2,5-dicarbomethoxypyrrolidine. 2b** (84.5 mg, 0.288 mmol) was dissolved in 5 mL of acetone and treated with 0.60 mL of 8 N chromic acid (4.8 mmol, 16.6 equiv). After the mixture was stirred for 1 h at room temperature 1.0 mL of isopropyl alcohol was added. After an additional hour at room temperature, the chromium salts were removed by filtration. The filtrate was evaporated to a green oil, which was dissolved in 15 mL of Et_2O and washed with 3 × 5 mL of brine. The Et_2O was dried ($MgSO_4$), filtered, and evaporated to a clear oil. This oil was dissolved in 4 mL of THF and treated with excess CH_2N_2. Excess AcOH was added to quench the excess CH_2N_2. The solvent was evaporated. The oil that remained was dissolved in 15 mL of Et_2O and washed with 3 × 5 mL of saturated $NaHCO_3$ and 1 × 5 mL of brine. The Et_2O was evaporated, leaving a crude oil. Flash chromatography (1:1 EtOAc/hexane) yielded one compound, a clear oil, 6.14 mg (66%): $[\alpha]^{22}_D$ 0.0° (*c* 1.54, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.34 (5 H, s with shoulders), 5.19, 5.14 (2 H, 2 d, *J* = 12 Hz), 4.53–4.48 (1 H, t, *J* = 4 Hz), 4.46–4.40 (1 H, t, *J* = 5 Hz), 3.78 (3 H, s), 3.65 (3 H, s), 2.30–2.10 (4 H, m); TLC, R_f 0.54 (1:1 EtOAc/hexane); MS, m/e 321 (M^+), 262 ($M^+ - CO_2CH_3$).

Preparation of 8: 5,5-Dicarbethoxytetrahydro-1*H*-pyrrolo[1,2-*c*]oxazol-3-one.[7] Racemic **6a** (560 mg, 2.28 mmol) and 1.53 g (9.44 mmol) of 1,1'-carbonyldiimidazole were dissolved in 20 mL of anhydrous benzene under N_2, and the solution was brought to reflux. After 15.5 h the benzene was cooled and evaporated. The tan oil that remained was dissolved in 50 mL of EtOAc and washed: 3 × 10 mL of 1 N HCl, 1 × 10 mL of saturated $NaHCO_3$, and 1 × 10 mL of brine. The EtOAc was dried ($MgSO_4$), filtered, and evaporated. **8** (479 mg, 78%) was obtained as a clear oil: ^1H NMR ($CDCl_3$) δ 4.60–4.54 (1 H, t, *J* = 7.5 Hz), 4.35–4.17 (6 H, m), 2.72–2.54 (2 H, m), 2.17–2.07 (1 H, m), 2.03–1.90 (1 H, m), 1.37–1.25 (6 H, m); IR ($CHCl_3$) 1770 (urethane C=O), 1750 (ester C=O) cm^{-1}; TLC, R_f 0.65 (EtOAc); MS, *m/e* 271 (M^+), 227 ($M^+ - CO_2$), 198 ($M^+ - CO_2CH_2CH_3$).

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(7) Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975**, *5*, 47.

Registry No. 2a, 102208-90-2; **2b**, 102108-00-9; **2b** (R = H), 102108-01-0; **4**, 102107-97-1; **6a**, 102107-98-2; (±)-**6a**, 102208-91-3; **8**, 102107-99-3; diethyl (*N*-carbobenzoxyamino)malonate, 3005-66-1; (*R*)-4-iodo-1,2-epoxybutane, 76282-42-3; carbobenzoxy chloride, 501-53-1; *N*-carbobenzoxy-2(*R*)-carbomethoxy-5(*S*)-carboxypyrrolidine, 102108-02-1; diethyl (*N*-carbobenzoxyamino)malonate sodium salt, 102108-03-2; *cis*-*N*-carbobenzoxy-2,5-dicarbomethoxypyrrolidine, 22328-84-3.

Lithium Diphenylphosphide as a Reagent for the Dehydroxylation of α-Hydroxy Ketones

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As a result of our interest in the utility of a number of phosphorus-containing materials as intermediates in synthesis, we have developed a unique method for the dehydroxylation of α-hydroxy ketones. This new reaction allows facile access to α-methylene ketones of the type RC(O)CH_2R by reduction of the corresponding α-hydroxy ketones. The latter are, in turn, available in good yields by chlorotrimethylsilyl-mediated acyloin condensations[1] of the appropriate esters. To date, the two most commonly employed reagent combinations for dehydroxylation of α-hydroxy ketones are red phosphorus/iodine[2] or trimethylsilyl iodide/sodium thiosulfate.[3] In this paper we would like to report the successful application of a readily available phosphorus-derived reagent to accomplish the same transformation. Thus, lithium diphenylphosphide (LDP) has been used to reduce a wide variety of α-hydroxy ketones to their analogous α-methylene ketones (Scheme I).

The utility of LDP as a reagent for the epoxide-mediated inversion of olefin stereochemistry has been reported previously.[4] This reaction proceeds via stereospecific epoxide ring-opening by LDP. The intermediate formed is treated with methyl iodide thereby effecting quarternization of phosphorus to give a betaine. Subsequent fragmentation of the betaine, usually at room temperature, produces an olefin and methyldiphenylphosphine oxide. This methodology has been employed to isomerize a variety of olefins via their epoxide derivatives, most notably, the conversion of *cis*- to *trans*-cyclooctene in >90% yield with >99.5% isomeric purity[5] (Scheme II).

We have investigated the effect of similar reaction conditions on α-hydroxy ketones with the thought that a similar mechanism could result in their dehydroxylation. Indeed, treatment of benzoin with 2 equiv of LDP at room temperature followed by quenching with methyl iodide and acetic acid gave desoxybenzoin in 76% yield after chromatography over silica gel. This reaction is not limited in its scope to benzoin-like molecules, but can be extended to include aliphatic, cyclic, and heteroaromatic systems as well. Good yields were obtained in all cases studied (Table I).

(1) For a review of the Me_3SiCl method, see: Ruchlmann, K. *Synthesis* **1971**, 236–253.
(2) Ho, T. L.; Wong, C. M. *Synthesis* **1975**, 161.
(3) Ho, T. L. *Synth. Commun.* **1979**, *9*, 665–668.
(4) Bridges, A. J.; Whitham, G. H. *Chem. Commun.* **1974**, 142. Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1971**, *93*, 4070–4072. Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822–825.
(5) Vedejs, E.; Snoble, K. A. J.; Fuchs, P. L. *J. Org. Chem.* **1973**, *38*, 1178–1183.

0022-3263/86/1951-2378$01.50/0