mol) was added to the flask and the contents were allowed to stir at room temperature for 4 days. The volatile components were removed by simple distillation and the residue was distilled in vacuo, collecting 44.6 g of liquid boiling between 75 and 80 °C/0.10 mmHg. Iodotrimethylsilane (19 mL, 26.7 g, 0.13 mol) was added to the resultant oil, and the mixture was heated at 100 °C for 1 day with gradual darkening of the solution. The color change is believed to be due to the formation of I_2. Additional $ISiMe_3$ (10 mL, 14.0 g, 0.07 mol) was added and the reaction mixture was again heated for 34 h. The volatile components were removed in vacuo. The resultant oil was decolorized by stirring over acid-washed zinc powder and vacuum distilled through a simple distillation apparatus to yield 44.4 g of a light brown oil. The oil was redistilled through a simple distillation apparatus to yield 41.5 g (0.106 mol, 64%) of the title compound as an oil, which partially solidified in the cold water condenser: bp 88–92 °C (0.3 mmHg); ^{19}F NMR −118.0 ppm (d) $^2J_{F,P}$ = 102 Hz; ^{31}P NMR −16.3 ppm (t); ^1H NMR 0.35 ppm (s, $P(OSiMe_3)_2$), 0.38 (s, CO_2SiMe_3).

Hydrolysis of Trimethylsilyl Difluoro[bis(trimethylsiloxy)phosphinyl]acetate. Trimethylsilyl difluoro[bis(trimethylsiloxy)phosphinyl]acetate (41.5 g, 0.106 mol) was dissolved in 300 mL of distilled water in a separatory funnel. The resultant organic phase was separated, and the aqueous phase was extracted with 6 × 50 mL portions of benzene. The bulk of the water was removed by rotary evaporation to yield difluorophosphonoacetic acid as a clear, hygroscopic oil: ^{19}F NMR (H_2O, $CFCl_3$ external standard) −117.6 ppm (d) $J_{P,F}$ = 89 Hz; ^{31}P NMR 0.8 ppm (t).

Dicyclohexylammonium Difluorophosphonoacetate. To an Erlenmeyer flask which contained an aqueous solution of difluorophosphonoacetic acid, which had been formed by dissolution of trimethylsilyl difluoro[bis(trimethylsiloxyphosphinyl)]acetate (1.60 g, 0.004 mol) in 10 mL of distilled water, was added dicyclohexylamine (0.39 mL, 0.35 g, 0.002 mol). Evaporation of the water over a hot plate and recrystallization of the residue from a 1:5 methanol/acetone mixture gave 0.06 g (0.0002 mol, 5%) of the title compound as a single crop of white needles: mp 210–212 °C dec.

Anal. Calcd for $C_{14}H_{26}F_2NO_5P$: C, 47.06; H, 7.33; N, 3.92. Found: C, 47.17; H, 7.07; N, 3.76.

Ethyl Difluoro(dichlorophosphinyl)acetate (11). Ethyl difluoro(diethoxyphosphinyl)acetate (10.0 g, 0.038 mol) was added to a round-bottomed flask which was equipped with a Teflon-coated spin bar and was connected to a nitrogen bubbler. Bromotrimethylsilane (10.3 mL, 11.9 g, 0.078 mol) was added to the flask and the contents were stirred at room temperature. After 2 weeks the volatile components were removed in vacuo. The residue was dissolved in 10 mL of CCl_4 and added dropwise to a solution of PCl_5 (20.0 g, 0.096 mol) dissolved in 75 mL of CCl_4. The homogeneous mixture was stirred overnight at room temperature. The solvent and phosphorus oxychloride were removed by simple distillation, and the resultant oil was distilled to give 7.8 g (0.032 mol, 84%) of the title compound: bp 45–47 °C (0.1 mmHg); ^{19}F NMR −112.0 ppm (d) $^2J_{P,F}$ = 125 Hz; ^{31}P NMR 24.6 ppm (t); ^1H NMR ($SOCl_2$) 1.37 ppm (t) $^3J_{H,H}$ = 7.0 Hz, 4.45 (q); IR (neat) 2995 (w, C—H), 1300 (s, P=O), 1155 (s).

Acknowledgment. We thank the National Science Foundation, the Air Force Office of Scientific Research, and the National Institutes of Health for support of this work.

Registry No. 1, 17843-01-5; 2, 113161-58-3; 3, 113161-59-4; 4 (R = Et), 82845-20-3; 4 (R = *i*-Pr), 82845-21-4; 4 (R = Bu), 82845-22-5; 6, 97480-49-4; 7, 113161-61-8; 8, 91410-83-2; [8] [dicyclohexylamine], 91410-86-5; [8]Na_2, 91410-87-6; 9, 91410-84-3; 10, 91410-85-4; 11, 113161-62-9; $(EtO)_2P(O)CF_2Cl$, 113161-60-7; $(EtO)_2P(O)CF_2Br$, 65094-22-6; $(i\text{-}PrO)_2P(O)CF_2O_2Et$, 113161-63-0; $(n\text{-}BuO)_2P(O)CF_2CO_2Et$, 113161-64-1; $(EtO)_2P(O)CF_2C(O)SEt$, 113161-65-2; $(EtO)_2P(O)CF_2H$, 1478-53-1.

Synthesis of 6,6-Pentamethylene-2-aminosuberic Acid. A Key Intermediate in the Synthesis of Dicarba Analogues of Vasopressin Antagonists

James F. Callahan,* Kenneth A. Newlander, Heidemarie G. Bryan, William F. Huffman, Michael L. Moore, and Nelson C. F. Yim

Department of Peptide Chemistry, Smith Kline & French Laboratories, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939

Received October 28, 1987

Two complementary syntheses of the unnatural amino acid, 6,6-cyclopentamethylene-2-aminosuberic acid, Pas (2) are described. The first, starting from methyl cyclohexanecarboxylate (4), yields in ten steps racemic Boc-Pas(OBzl)-OH (3) which is suitably protected for solid phase peptide synthesis. The second method involves the stereospecific synthesis of optically pure Boc-Pas(OBzl)-OH (3L) utilizing the electrochemical coupling, via the Kolbe method of the monobenzyl ester of 1,1-cyclohexanediacetic acid (13) and Boc-L-Glu-OBzl (14). The optical purity of 3L was confirmed by chiral gas chromatographic analysis of its *N*-pentafluoropropionyl diisopropyl ester derivative 15L.

The replacement of the cysteine residue in position one of vasopressin with the deaminocysteine derivative β-mercapto-β,β-cyclopentamethylenepropionic acid, Pmp[1] (1), has been shown to be one of the key factors involved in the development of antagonists of the renal vasopressin (V_2) receptor.[2] In order to enhance the chemical and metabolic stability of these vasopressin antagonists and to begin to evaluate the role the disulfide bond plays in the biologically active conformation, the synthesis of the

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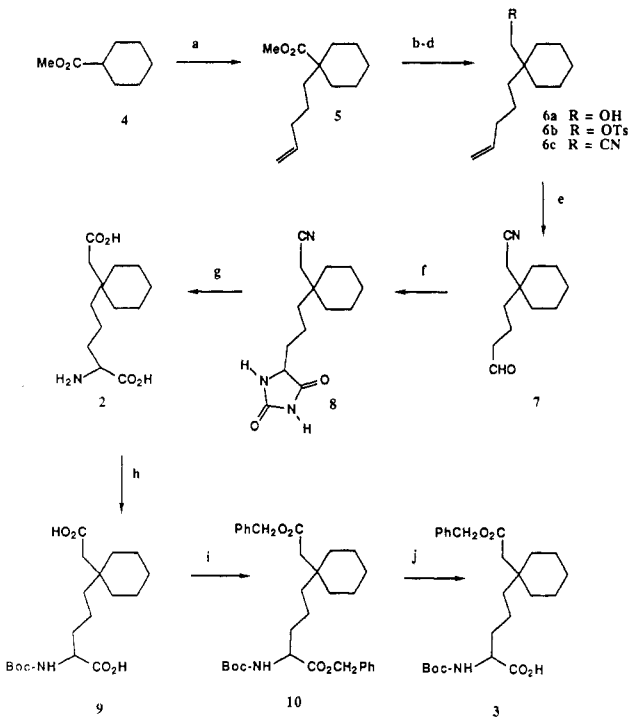
0022-3263/88/1953-1527$01.50/0

Scheme I[a]

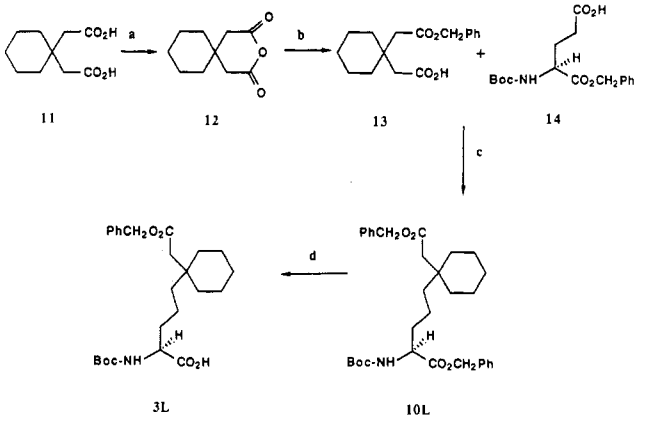


[a] (a) LDA, THF, −78 °C; $CH_2{=}CH(CH_2)_3I$, −78 to 0 °C (84%); (b) $LiAlH_4$, Et_2O; (c) TsCl, pyridine; (d) NaCN, DMSO, reflux (68% from **5**); (e) O_3, MeOH, −78 °C; Me_2S, −78 to 25 °C (63%); (f) $(NH_4)_2CO_3$, NaCN, EtOH, H_2O, reflux; (g) $Ba(OH)_2$, H_2O, 160 °C; ion exchange:BioRad AG 50W-X8 (27% from **7**); (h) $(Boc)_2O$, *t*-BuOH, 1 N NaOH; 1 N HCl (98%); (i) $PhCH_2OH$, DCC, DMAP (63%); (j) 1 N NaOH (1 equiv), dioxane; 1 N HCl (97%).

corresponding dicarba analogues was undertaken. A prerequisite of this study was the development of a synthesis of the unnatural amino acid 6,6-cyclopentamethylene-2-aminosuberic acid, Pas (**2**). We report a practical method for the synthesis of differentially protected racemic Pas **3** which is readily amenable to large scale preparation as well as a stereospecific synthesis which utilizes the Kolbe electrolysis method[3] to yield optically pure **3**.

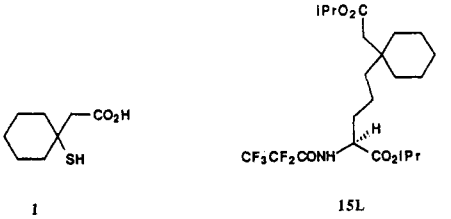
Initially it was felt that a straightforward, unambiguous synthesis of Pas **3** suitably protected for solid phase peptide synthesis would supply the material needed for the peptide program. The synthesis of differentially protected racemic Pas **3** is outlined in Scheme I. Methyl cyclohexanecarboxylate (**4**) was treated with lithium diisopropylamide in THF at −78 °C and the resulting enolate was alkylated with 5-iodopent-1-ene to give **5**. The ester **5** was homologated in three steps to the nitrile **6** which was then treated with ozone in methanol at −78 °C followed by reductive workup with methyl sulfide to afford **7** which contained the functionality needed for conversion to the desired amino acid. The aldehyde **7** was converted to the corresponding hydantoin **8** which was hydrolyzed in aqueous $Ba(OH)_2$ at 160 °C to the amino acid **2**, which was isolated by ion exchange chromatography over BioRad 50W-X8 resin.[4] The α-amino group of **2** was protected as its *tert*-butoxycarbonyl (Boc) derivative **9**, which was then converted to the Boc, dibenzyl ester **10** with 1,3-dicyclohexylcarbodiimide/4-(dimethylamino)pyridine and benzyl alcohol. Taking advantage of the steric hinderance imposed on the ω ester by the cyclohexane ring, it was possible to selectively hydrolyze **10** with 1 equiv of base to give Boc-D,L-Pas(OBzl)-OH (**3**) which is suitably protected for use in solid phase peptide synthesis.

Scheme II[a]



[a] (a) AcCl, 60 °C, 3 h; (b) $PhCH_2OH$, pyridine, toluene, 100 °C, 24 h (88%); (c) e^-, Na, pyridine, MeOH, 20–25 °C, 9 h, (18%); (d) 1 N NaOH (1 equiv), dioxane; 1 N HCl.

As our interest in dicarba vasopressin antagonists increased, we began work on the development of a synthesis of optically pure Pas. One possible synthesis would involve the electrochemical coupling via the Kolbe method[3] of a monoester of 1,1-cyclohexanediacetic acid (**13**) with a suitably protected L-glutamic acid **14** (Scheme II). This synthesis was not without precedent since the electrochemical coupling of differentially protected glutamic acids was known to proceed in moderate yield;[5] however the effects of a neopentyl substituent on one of the carboxylic acids involved in the coupling could not be predicted. Treatment of 1,1-cyclohexanediacetic anhydride (**12**)[6] with benzyl alcohol and pyridine in toluene at 100 °C for 18 h afforded the monobenzyl ester **13** in excellent yield. A mixture of the half-ester **13** and Boc-L-Glu-OBzl (**14**) (1:1.6 ratio) was oxidatively coupled at a platinum electrode (Kolbe electrolysis) to give a complex mixture of products.[3,5] The crude reaction mixture was first purified by flash chromatography and the fractions containing product were pooled and purified by gravity chromatography to give the desired protected L-Pas **10L** in 18% yield. Selective base hydrolysis of the dibenzyl ester **10L** afforded the monoester **3L**. The optical purity of **3L** was determined by chiral gas chromatographic analysis (Chirasil-Val III, Alltech Associates, Inc.) of its *N*-pentafluoropropionyl, diisopropyl ester derivative **15L**.[7] None (<1%) of the corresponding D antipode was seen.



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In conclusion we have developed two complementary syntheses of Pas suitably protected for use in solid phase peptide synthesis.

Experimental Section

General. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 90 MHz on a Varian EM390 spectrometer. Chemical shifts are reported in δ units from the internal standard tetramethylsilane. Optical rotations were measured at the sodium D line on a Perkin-Elmer 241 polarimeter using a 1-dm cell. Mass spectra were taken on a Finnigan Model 3300 mass spectrometer. Gas chromatography was performed on a Hewlett Packard 5890 instrument using an Alltech Associates Chirasil-Val III NON-PAKD (20 m × 0.53 mm) column. TLC was carried out on Analtech silica gel GF plates and both flash and gravity chromatography were carried out on Merck 60 (230–400 mesh) silica gel. Tetrahydrofuran was distilled from sodium ketyl immediately before use. Methyl cyclohexanecarboxylate and 1,1-cyclohexanediacetic acid were obtained from the Aldrich Chemical Co. and Boc-L-Glu-OCH_2Ph was obtained from Bachem Inc.

Methyl 1-(5-Pent-1-enyl)cyclohexanecarboxylate (5). A solution of lithium diisopropylamide was prepared by adding 2.7 M *n*-butyllithium (hexane) (37.0 mL, 100 mmol) to a solution of diisopropylamine (15.0 mL, 109 mmol) in dry tetrahydrofuran (170 mL) at −78 °C under argon and then stirring the subsequent mixture at −78 °C for 20 min. Methyl cyclohexanecarboxylate (4) (13.0 mL, 91 mmol) was added to the solution and the reaction mixture was stirred for 30 min at −78 °C. 5-Iodopent-1-ene (18 g, 91.8 mmol) was added, the reaction was continued at −78 °C for 10 min, and the mixture was then slowly brought to room temperature. The reaction mixture was diluted with water, acidified (pH 2) with 3 N hydrochloric acid, and extracted with ether. The ether extracts were washed with saturated sodium thiosulfate (aqueous), dried over magnesium sulfate, and evaporated at reduced pressure to give 16 g (84%) of **5**: ^{1}H NMR ($CDCl_3$) δ 6.00–5.50 (m, 1 H), 5.17–4.77 (m, 2 H), 3.63 (s, 3 H), 2.27–1.70 (m, 4 H), and 1.70–0.97 (m, 12 H).

1-(Cyanomethyl)-1-(5-pent-1-enyl)cyclohexane (6c). The methyl ester **5** (16 g, 76.0 mmol) was added to a solution of lithium aluminum hydride (4.6 g, 120.9 mmol) in tetrahydrofuran (205 mL) at room temperature and the resulting mixture was heated at reflux for 3 h. The reaction was cooled to 0 °C, treated sequentially with water (5 mL), 3 N sodium hydroxide solution (5 mL), and water (15 mL), and then filtered. The filtrate was dried over magnesium sulfate, refiltered, and evaporated to give **6a**: ^{1}H NMR ($CDCl_3$) δ 6.17–5.60 (m, 1 H), 5.20–4.80 (m, 2 H), 3.40 (s, 2 H), and 2.43–0.80 (m, 17 H).

The crude alcohol **6a** was dissolved in pyridine (89 mL) and treated with *p*-toluenesulfonyl chloride (27 g, 142.5 mmol) at 0 °C for 4 h. The reaction mixture was poured into water and extracted with petroleum ether, petroleum ether/ethyl ether (1:1), and ethyl ether. The combined organic extracts were washed with 0.5 N HCl (aqueous), saturated sodium bicarbonate (aqueous), and water, dried over magnesium sulfate, filtered, and evaporated to give **6b**: ^{1}H NMR ($CDCl_3$) δ 7.98–7.20 (m, 4 H), 6.03–5.53 (m, 1 H), 5.13–4.78 (m, 2 H), 3.82 (s, 2 H), 2.43 (s, 3 H), and 2.23–0.73 (m, 16 H).

The crude tosylate **6b** from above was dissolved in dimethyl sulfoxide (219 mL) with sodium cyanide (13.6 g, 279 mmol). The resulting mixture was heated at 150 °C for 18 h. The reaction mixture was then cooled, poured onto saturated ammonium chloride (aqueous), and extracted with petroleum ether. The organic extracts were dried, filtered, and evaporated. Purification of the residue using flash chromatography (silica gel; 15% ethyl acetate/hexane) gave 9.9 of **6c** (68% yield from **5**): ^{1}H NMR ($CDCl_3$) δ 6.12–5.57 (m, 1 H), 5.20–4.87 (m, 2 H), 2.30 (s, 2 H), 2.23–1.82 (m, 2 H), and 1.50 (br s, 14 H).

1-(Cyanomethyl)-1-(3-formylpent-1-yl)cyclohexane (7). The nitrile **6c** (4.9 g, 25.6 mmol) was dissolved in methanol (80 mL). The resulting solution was cooled to −78 °C and treated with ozone [from a Welsbach ozone generator] until residual ozone was left in solution (blue color). The crude ozonide was treated with methyl sulfide (20 mL) at −78 °C and, then, slowly warmed to room temperature. After 18 h, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel; 20% ethyl acetate/hexane) to give 3.1 g (63%) of **7**: ^{1}H NMR ($CDCl_3$) δ 9.80 (br s, 1 H), 2.63–2.38 (m, 2 H), 2.33 (s, 2 H), and 1.47 (br s, 14 H).

2-Amino-5-[1-(carboxymethyl)cyclohexyl]pentanoic Acid (2). The aldehyde **7** (3.1 g, 16 mmol) was dissolved in 60% aqueous ethanol (30 mL) and treated with sodium cyanide (860 mg, 17.6 mmol) and ammonium carbonate (4.0 g, 41.6 mmol). The resulting solution was heated at reflux for 18 h. Excess carbonate was removed by heating the reaction mixture at 90 °C for 1 h without a condenser. The remaining solvent was removed at reduced pressure. The crude product was dissolved in hot ethanol, filtered, and evaporated under reduced pressure to give the crude hydantoin **8**: mass spectra, m/e $(M + H)^+$ 264.

The unpurified hydantoin **8** was suspended in water with barium hydroxide octahydrate (12.0 g, 38 mmol) and heated in a sealed tube at 170 °C for 96 h. The reaction mixture was cooled, diluted with water, and filtered. The filtrate was passed over a BioRad AG 50W-X8 ion exchange column and the desired product was eluted off the column with 1 N ammonium hydroxide (aqueous). Evaporation of the ammonium hydroxide eluent gave 1.1 g (27%) of the amino acid **2** which was used without further purification. An analytical sample was obtained by recrystallization from water/ethanol: mp 248–249 °C dec; ^{1}H NMR (TFA-*d*) δ 4.50 (t, 1 H, J = 6 Hz), 2.57 (s, 2 H), 2.40–1.97 (m, 2 H), and 1.82–1.27 (m, 14 H); mass spectrum, m/e $(M + H)^+$ 258. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.60; H, 8.83; N, 5.54.

Benzyl 2-(Boc-amino)-5-[1-(carbobenzoxymethyl)cyclohexyl]pentanoate (10). The amino acid **2** (1.1 g, 4.27 mmol) was dissolved in 1 N sodium hydroxide solution (45 mL) and *tert*-butyl alcohol (45 mL), and the mixture was treated at room temperature with di-*tert*-butyl dicarbonate (980 mg, 4.5 mmol) for 48 h. The reaction mixture was washed with hexane, acidified with sodium bisulfate, and extracted with ethyl acetate. The combined organic extracts were dried, filtered, and evaporated to give 1.5 g (98%) of **9**.

The crude Boc diacid **9** (1.34 g, 3.75 mmol) in methylene chloride (30 mL) was then treated with benzyl alcohol (1.94 mL, 18.75 mmol), 4-(dimethylamino)pyridine (1.01 g, 8.25 mmol), and 1,3-dicyclohexylcarbodiimide (1.70 g, 8.25 mmol) at room temperature, and the mixture was stirred at room temperature for 72 h. The reaction mixture was then filtered and evaporated at reduced pressure and the residue was dissolved in ethyl acetate which was washed with 3 N hydrochloric acid, dried over $MgSO_4$, and evaporated at reduced pressure. Purification of the residue by flash chromatography (silica gel, 15% ethyl acetate/hexane) gave 1.27 g (63%) of **10**: ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 10 H), 5.15 (d, J = 2.4 Hz, 2 H), 5.07 (s, 2 H), 5.05–4.70 (m, 1 H), 4.50–4.05 (m, 1 H), 2.27 (s, 2 H), 1.45 (s, 9 H), and 2.00–1.03 (m, 16 H); mass spectrum, m/e $(M + H)^+$ 448.

2-(Boc-amino)-5-[1-(carbobenzoxymethyl)cyclohexyl]-pentanoic Acid (3). The Boc diester **10** (1.27 g, 2.36 mmol) was dissolved in dioxane (15 mL) and treated with 2.5 mL of 1 N sodium hydroxide solution at room temperature under argon for 4 h. The reaction mixture was acidified (pH 2) with 3 N hydrochloric acid and evaporated at reduced pressure. The residue was dissolved in ethyl acetate, washed with 3 N hydrochloric acid, dried over $MgSO_4$, and evaporated at reduced pressure. The residue was purified by flash chromatography (silica gel, 5% methanol/chloroform) to give 1.03 g (97%) of **3**: ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5 H), 5.07 (s, 2 H), 5.20–4.80 (m, 1 H), 4.42–4.05 (m, 1 H), 2.32 (s, 2 H), 1.43 (s, 9 H), and 2.08–1.07 (m, 16 H).

1,1-Cyclohexanediacetic Anhydride (12). Acetyl chloride (35 mL, 492 mmol) was added to 1,1-cyclohexanediacetic acid (**11**) (25 g, 125 mmol) in a round-bottom flask and the suspension was heated at 60 °C on an oil bath (after about 15 min the suspension became clear). After 3 h, the flask was attached to a short path condenser and was heated at 100 °C under vacuum to remove volatile byproducts to give upon cooling to room temperature the anhydride **12**: ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 4 H), 1.45 (m, 10 H).

1,1-Cyclohexanediacetic Acid Monobenzyl Ester (13). Toluene (25 mL), benzyl alcohol (14.2 mL, 137 mmol), and pyridine (10.1 mL, 125 mmol) were added to 1,1-cyclohexanediacetic anhydride (**12**) and the resulting solution was stirred at 100 °C for 18 h. The reaction was taken into ethyl acetate, washed

with 1 N HCl (aqueous) and saturated NaCl (aqueous), dried over $MgSO_4$, filtered, and then evaporated to give 38 g of thick oil **13**. Analysis by gas chromatography indicated 92.2% purity with the major impurity being benzyl alcohol: ^1H NMR ($CDCl_3$) δ 11.0 (s, 1 H), 7.25 (s, 5 H), 5.0 (s, 2 H), 2.5 (s, 2 H), 1.4 (br s, 10 H).

Benzyl 2-(L-Boc-amino)-5-[1-(carbobenzoxymethyl)-cyclohexyl]pentanoate (10L). Sodium (0.15 g) was added to a large metal beaker containing methanol (200 mL) followed by pyridine (80 mL), 1,1-cyclohexanediacetic acid monobenzyl ester (**13**) (35 g, 121 mmol), and *N*-α-Boc-L-Glu-α-benzyl ester (**14**) (25 g, 74 mmol) dissolved in methanol (40 mL). The solution was electrolized with vigorous mechanical stirring at 100 V and 2.5 A between two platinum plates (25 × 50 mm) spaced 2-mm apart. The temperature of the reaction was kept between 20 and 25 °C by the aid of a 2-propanol/dry ice bath. After 9 h, TLC indicated most of **14** was reacted. The reaction mixture was evaporated to give a brown oil which was taken into 1:1 ethyl acetate/*n*-hexane. The precipitate was filtered off and the filtrate was washed two times with dilute HCl (aqueous), two times with 1 N Na_2CO_3 (aqueous), and once with saturated NaCl (aqueous), dried over $MgSO_4$, filtered, and evaporated to give an oil. The majority of the impurities were removed by flash chromatography (silica gel, 5–10% ethyl acetate/*n*-hexane). Final purification was achieved on a 3.0 × 100 cm silica gel gravity column eluted with 7% ethyl acetate/*n*-hexane. A pure fraction contained 7.17 g (18%) of **10L**. This material was identical with the racemic material **10** except that it was optically active: $[\alpha]_D$ −14.7° (*c* = 0.1025 g/mL, methanol).

2-(Boc-amino)-5-[1-(carbobenzoxymethyl)cyclohexyl]-pentanoic Acid (3L). The optically pure Boc diester **10L** was hydrolyzed under the same conditions as **10** to give material that was identical with racemic **3** except that it was optically active: $[\alpha]_D$ +0.40° (*c* 0.1008 g/mL, methanol). Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33, N, 3.13. Found: C, 66.87; H, 8.33; N, 3.07.

Chiral GC Analysis of 3L. The optical purity of **3L** was confirmed by chiral gas chromatographic analysis. In order to analyze the protected amino acid **3L** by GC, it was necessary to convert **3L** to its *N*-pentafluoropropionyl, diisopropyl ester **15L**. Hydrolysis of **10L** with 6 N HCl at 100 °C for 18 h gave after evaporation the HCl salt of **2L**. The amino acid salt **2L** was esterified with HCl/2-propanol at 100 °C for 30 min, evaporated, and then aceylated with pentafluoropropionic anhydride in CH_2Cl_2 at 100 °C for 15 min to give **15L**. The D,L standard **15** was prepared in a similar manner from **2**. GC analysis of **15L** on the Chirasil-Val III column (isothermal, 175 °C) showed only a single enantiomer.

Acknowledgment. We acknowledge Lewis B. Killmer, Jr. of the Department of Physical and Structural Chemistry for the mass spectra and Edith A. Reich of the Department of Analytical Chemistry for elemental analysis.

Registry No. **2**, 113009-17-9; **3**, 113009-18-0; **3L**, 113084-43-8; **4**, 4630-82-4; **5**, 113009-19-1; **6a**, 113009-20-4; **6b**, 113009-26-0; **6c**, 113009-27-1; **7**, 113009-21-5; **8**, 113009-22-6; **9**, 113009-23-7; **10**, 113009-24-8; **10L**, 113084-42-7; **11**, 4355-11-7; **12**, 1010-26-0; **13**, 113009-25-9; **14**, 30924-93-7; CH_2=$CH(CH_2)_3I$, 7766-48-5.

An Unusual Substituent Effect on Elimination vs Fragmentation Reactions of the Dianions of 5-Fluorouracil–Alkene Photoadducts. Preparation of Cyclobutane-Annelated Uracils

John S. Swenton* and John G. Jurcak

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

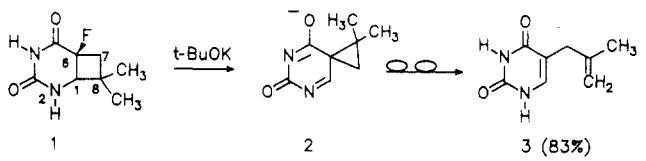
Received October 16, 1987

Acetone-sensitized photocycloadditions of 5-fluorouracil to methyl vinyl ether, 2-methoxypropene, and ketene dimethyl acetal give good yields of the respective 8,8-disubstituted-6-fluoro-2,4-diazabicyclo[4.2.0]octane-3,5-diones. Whereas the dianions of cycloadducts of 5-fluorouracil and alkyl-substituted alkenes afford high yields of 5-substituted uracils, the products from 2-methoxypropene and ketene dimethyl acetal give predominantly cyclobutane-annelated uracils derived from syn elimination of hydrogen fluoride. Deuterium labeling studies support the proposed mechanism of elimination. Heating 8,8-dimethoxy-2,4-diazabicyclo[4.2.0]oct-1(6)-ene-3,5-dione, obtained from hydrogen fluoride elimination of the 5-fluorouracil–ketene dimethyl acetal photoadduct, in the presence of *N*-phenylmaleimide or dimethyl acetylenedicarboxylate, gives Diels–Alder adducts derived from trapping the thermally generated diene.

Introduction

The availability of functionalized benzocyclobutenes coupled with the cycloaddition reactions of their thermally generated *o*-quinodimethane forms has made these compounds useful synthetic intermediates.[1] Heterocyclic analogues of benzocyclobutenes and their respective *o*-quinodimethane forms are less common. Although the pyridine analogues of benzocyclobutenes have been prepared via pyrolysis routes,[2] their chemistry has not been extensively studied.

Several years ago we envisioned a preparation of pyrimidine analogues of benzocyclobutenes from an elimination reaction of the readily available cycloaddition products of 5-fluorouracil and alkenes. However, reaction of these photoaddition products with excess KO-*t*-Bu gave 5-substituted uracils (i.e., **1** → **3**) in excellent yields,[3] not the expected cyclobutenes. Labeling and kinetic studies favored rearrangement of the dianion of **1** to form a spirocyclic intermediate **2** which then yielded **3**.



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