Synthesis of 11-Deoxy-13,14-dihydro-8-azaprostaglandin E_1

P. A. Zoretic* and J. Chiang[1]

Department of Chemistry, Southeastern Massachusetts University, North Dartmouth. Massachusetts 02747

Received January 7, 1977

The synthesis of 11-deoxy-13,14-dihydro-8-azaprostaglandin E_1 is reported. The synthetic sequence to 11-deoxy-8-aza-13,14-dihydroprostaglandin E_1 involves the construction of a 5-substituted 2-pyrrolidinone containing an intact C_8 side chain.

Recently Bolliger and Muchowski[2] and DeKoning and co-workers[3] reported the synthesis of 11-deoxy-8-azaprostaglandin E_1. In this paper we would like to communicate our synthesis of 11-deoxy-8-aza-13,14-dihydroprostaglandin E_1 (**9**). The synthetic approach to **9** involves the construction of a 5-substituted 2-pyrrolidinone nucleus containing an intact C_8 side chain as outlined below (Scheme I).

Reaction of *n*-hexanoyl chloride (**1**) with ethylene[4] in the presence of $AlCl_3$ in chloroform at 0°C yielded a 42:58 mixture of 1-chloro-3-octanone (**2**) and 3-oxo-1-octene (**3**) as determined by NMR. The mixture of chloro ketone **2** and vinyl ketone **3** was reacted with excess nitromethane in the presence of sodium methoxide in methanol at room temperature to afford 1-nitro-4-nonanone (**4**) in 42% yield. Ketalization of **4** with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid gave 1-nitro-4,4-ethylenedioxononane (**5**, 89%). Reaction of **5** with methyl acrylate[5] in the presence of Triton B at 90–95°C for 5 h and subsequent chromatography on silica gel G and elution with an ether–hexane solution afforded methyl 4-nitro-7,7-ethylenedioxydodecanoate in 45% yield.

Catalytic reduction of 4-nitro-7,7-ethylenedioxydodecanoate in the presence of R(Ni)W-4[6] in ethanol with hydrogen at 47 psi yielded a mixture of the ketal lactam **6** and uncyclized ketal amino ester. This mixture was refluxed in benzene for 5 h and chromatography of the crude reaction product on silica gel G afforded the pure ketal lactam **6** in 54% yield.

Reaction of **6** with sodium hydride in refluxing THF and subsequent alkylation with methyl 7-bromoheptanoate followed by chromatography on silica gel G gave the lactam ketal ester **7** (59%).

Hydrolysis of the lactam ketal ester **7** with an aqueous methanolic sodium hydroxide solution at room temperature followed by acidification and concomitant hydrolysis of the ketal moiety with an aqueous HCl–THF solution at room temperature and subsequent chromatography on silica gel G yielded the keto acid **8** in 56% yield. Reduction of the keto acid **8** with sodium borohydride[7] in an aqueous sodium bicarbonate solution between 0 and 20°C afforded a C_{15} epimeric mixture of the acid alcohols **9** in 76% yield. An attempt to separate the epimeric acid alcohols **9** by preparative TLC using analytical silica gel plates and employing different solvent systems failed. In each case the alcohols appeared as one elongated spot. The epimeric mixture of acid alcohols[8] **9** was found to be active in inhibiting gastric acid secretion.

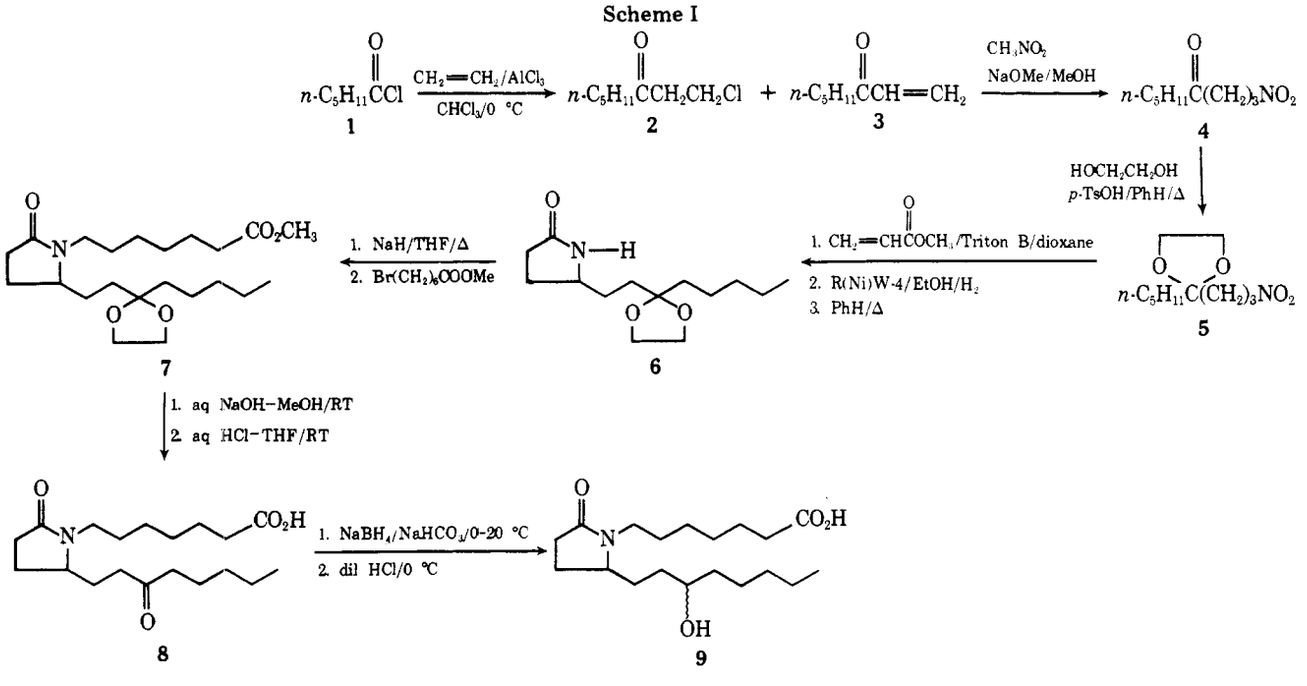
Experimental Section

1-Chloro-3-octanone (2) and 3-Oxo-1-octene (3). Chloroform (400 mL) was placed in a 1-L three-neck flask fitted with an addition funnel, mechanical stirrer, and inlet tube. A mercury bubbler was connected to the addition funnel and the chloroform was deaerated with nitrogen. Aluminum chloride (94.5 g, 0.71 mol) was added all at once to the chloroform under nitrogen. To this heterogeneous mixture, hexanoyl chloride (96 g, 0.71 mol) was added over a 5-min period. A homogeneous solution was obtained after addition of the hexanoyl chloride.

The reaction mixture was cooled to 0 °C with an ice bath and ethylene was bubbled into the reaction mixture at a rate so that excess ethylene was not escaping from the reaction vessel. Ethylene was allowed to bubble through the reaction mixture at 0 °C for 5.5 h, and the reaction mixture was allowed to stand overnight at 0 °C.

The reaction mixture was poured into a cold aqueous HCl solution (10% HCl, 700 mL, and 700 mL of ice) and extracted with chloroform

Scheme I



(500 mL). The chloroform layer was washed with a 10% HCl solution (2 × 700 mL), water (1 L), a 10% $NaHCO_3$ solution (700 mL), 5% $NaHCO_3$ solution (500 mL), and water.

The chloroform layer was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving a yellow oil. Distillation of the oil afforded 82.1 g of a mixture of 1-chloro-3-octanone (**2**) and 3-oxo-1-octene (**3**): bp 52–65 °C (12 mm); NMR (CCl_4) δ 3.77 ($ClCH_2$, t), 2.85 ($ClCH_2CH_2CO$–, t), 2.42 ($ClCH_2CH_2COCH_2$– and CH_2=$CHCOCH_2$–, t), 0.96 (t), 6.18–6.38 (m), 5.60–5.90 (m); IR (neat) 1780 and 1695 cm^{-1}. NMR analysis indicated that the mixture consisted of 42% of **2** and 58% of **3**. The reaction mixture was utilized directly in the synthesis of **4**.

1-Nitro-4-nonanone (4). Methanol (1 L) was placed in a 3-L three-neck flask fitted with a mechanical stirrer, water condenser, and nitrogen inlet tube, and was deaerated with nitrogen. Sodium methylate (54.0 g, 1.0 mol) was added under nitrogen and the resulting solution was allowed to cool to room temperature.

To this solution, nitromethane (335 g, 5.5 mol) was added all at once under nitrogen and the reaction mixture was stirred for 10 min. During this time period, a turbid solution resulted. A mixture of 1-chloro-3-octanone (**2**) and 3-oxo-1-octene (**3**) (75.1 g) was added all at once to the turbid solution under nitrogen. After addition, the reaction mixture became warm and a yellow color resulted. The reaction mixture was stirred for 14.5 h at room temperature. During the stirring period, the reaction mixture developed a deep orange juice color.

Ice-cold 10% HCl (800 mL) was added to the reaction mixture and the resulting solution was divided into four equal portions. To each portion, 700 mL of H_2O was added and the resulting mixture was extracted twice with 350 mL of chloroform. The chloroform extracts were combined and washed with water, and dried over anhydrous magnesium sulfate. Concentration of the chloroform solution and distillation of the yellow oil afforded 42.5 g (42%) of 1-nitro-4-nonanone (**4**): bp 108 °C (0.45 mm); NMR (CCl_4) δ 4.42 (t, 2 H), 2.06–2.62 (m, 6 H), 1.14–1.77 (m, 6 H), 0.97 (t, 3 H); IR (neat) 1715, 1550, and 1375 cm^{-1}.

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.54; H, 9.24; N, 7.28.

1-Nitro-4,4-ethylenedioxynonane (5). A mixture of 1-nitro-4-nonanone (**4**, 135.0 g, 0.722 mol), ethylene glycol (216 g, 3.48 mol), *p*-toluenesulfonic acid (2.0 g, 0.011 mol), and 700 mL of benzene was placed in a 2-L flask fitted with a Dean-Stark trap, condenser, and drying tube. The resulting mixture was refluxed for 24 h. During this period of time 18 mL of water was collected. The reaction mixture was allowed to cool to room temperature and was poured into a 2% $NaHCO_3$ solution (1 L). Ethyl ether (200 mL) was added and the organic layer was separated and washed with two 1-L portions of a 2% $NaHCO_3$ solution and twice with 1 L of water. The organic layer was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving 186 g of an oil. Distillation of the oil afforded 148.7 g (89%) of 1-nitro-4,4-ethylenedioxynonane (**5**): bp 110–117 °C (0.2 mm); NMR (CCl_4) δ 4.50 (t, 2 H), 3.90 (s, 4 H), 1.20–2.80 (m, 12 H), and 0.93 (t, 3 H); IR (neat) 1560 and 1375 cm^{-1}.

Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.24; H, 9.25; N, 6.00.

8-[5′-Oxo-(2′-pyrrolidinyl)]-6,6-ethylenedioxyoctane (6). A solution of 1-nitro-4,4-ethylenedioxynonane (**5**, 144.0 g, 0.623 mol) dissolved in 600 mL of dioxane was placed in a 1-L three-neck flask fitted with an addition funnel, condenser, and nitrogen inlet tube. The apparatus was connected to a mercury bubbler and the solution was deaerated with nitrogen. A 40% solution of Triton B (0.0623 mol, 26.2 mL) was added under nitrogen and the resulting solution was stirred for 10 min. During this time period the reaction mixture became yellow-orange. Methyl acrylate (58.9 g, 0.685 mol) was added all at once under nitrogen and the resulting mixture was stirred at 90–95 °C for 5 h.

The reaction mixture was cooled to room temperature and poured into a 3% oxalic acid solution (600 mL). Water (1 L) was added and the resulting mixture was extracted with three 800-mL portions of chloroform. The chloroform extracts were combined and washed with water, twice with 500 mL of a 1.5% sodium bicarbonate solution, and then water. The chloroform solution was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving 204 g of a dark yellow oil. Distillation of the oil afforded 121 g (61%) of crude methyl 4-nitro-7,7-ethylenedioxydodecanoate, bp 155–185 °C (0.6–1.0 mm). During the distillation some decomposition was observed.

The crude methyl 4-nitro-7,7-ethylenedioxydodecanoate was chromatographed using silica gel G and elution with an ether–hexane solution afforded 89.1 g (45%) of pure 4-nitro-7,7-ethylenedioxydodecanoate: NMR (CCl_4) δ 4.50 (m, 1 H), 3.88 (s, 4 H), 3.66 (s, 3 H), 1.10–2.50 (m, 16 H), and 0.90 (t, 3 H); IR (neat) 1745, 1555, and 1375 cm^{-1}.

Methyl 4-nitro-7,7-ethylenedioxydodecanoate (21.5 g, 0.068 mol) was dissolved in 150 mL of absolute ethanol and placed in a Parr shaker bottle. Raney nickel W-4 (approximately 20 g) was added and the resulting mixture was reduced at 47 psi on a Parr shaker. Hydrogen (13 psi) was taken up over a 43.5-h period. The reaction mixture was filtered through Celite 545 with suction and the residue was washed with chloroform. The filtrate was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, affording 17.4 g of an oil.

The oil (17.4 g) was dissolved in 75 mL of benzene and was refluxed for 5 h. The reaction mixture was allowed to cool to room temperature and the benzene solution was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving 17 g of an oil.

The oil was chromatographed on silica gel G and elution with chloroform and methanol–chloroform solutions afforded 13 g of an oil. The oil was dissolved in ether. The ether solution was extracted with a dilute solution of oxalic acid and then washed with a 1.5% $NaHCO_3$ solution and water. The ether layer was dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator, giving 9.4 g (54%) of the lactam ketal **6**: NMR (CCl_4) δ 8.53 (s, 1 H), 3.84 (s, 4 H), 3.50 (m, 1 H), 1.10–2.50 (m, 16 H), and 0.90 (t, 3 H); IR (neat) 1680 and 3220 cm^{-1}.

Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.47; H, 9.82; N, 5.39.

Methyl 8-Aza-9-oxo-15,15-ethylenedioxyprostanoate (7). A 300-mL three-neck flask fitted with a nitrogen inlet tube, condenser, and glass stopper was deaerated with nitrogen. A 50% sodium hydride–mineral oil suspension (1.3 g, 0.027 mol) and dry THF (130 mL) were placed in the flask under nitrogen. A solution of the lactam ketal **6** (6.2 g, 0.024 mol) dissolved in 20 mL of THF was added all at once under nitrogen and the resulting mixture was refluxed for 4.5 h. A solution of methyl 7-bromoheptanoate (6.3 g, 0.028 mol) dissolved in 10 mL of THF was then added all at once under nitrogen and the reaction mixture was refluxed for 18.5 h.

The reaction mixture was cooled to room temperature and poured into 400 mL of water. The resulting milky-white suspension was extracted with five 200-mL portions of chloroform. The chloroform extracts were combined and dried over anhydrous magnesium sulfate. Concentration of the chloroform solution afforded 10.7 g of an oil. Chromatography of the oil using silica gel G and elution with ether–hexane solutions afforded 5.7 g (60%) of the lactam ketal ester **7**: NMR (CCl_4) δ 3.88 (s, 4 H), 3.60 (s, 3 H), 3.15–3.58 [m, 1 H (–NCH)], 2.55–3.15 [m, 2 H (>$NCCH_2$–)], 2.18–2.50 [m, 4 H (–CH_2–C(=O)O and –CH_2C(=O)N<)], 1.1–2.10 (m, 24 H), and 0.90 (t, 3 H); IR (neat) 1740 and 1690 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_5$: C, 66.47; H, 9.89; N, 3.52. Found: C, 66.14; H, 9.83; N, 3.23.

8-Aza-13,14-dihydro-9,9-dioxoprostanoic Acid (8). The lactam ketal ester **7** (2.5 g, 0.0063 mol) was dissolved in an aqueous methanolic sodium hydroxide solution [NaOH (284 mg, 0.0071 mol), 24 mL of MeOH, and 10 mL of H_2O] and stirred at room temperature for 22 h.

The reaction mixture was poured into 150 mL of H_2O and extracted with an ether–chloroform solution. The ether–chloroform extracts contained a negligible amount of ester.

The aqueous layer was acidified and extracted with chloroform. The chloroform extracts were combined and dried over anhydrous magnesium sulfate and filtered, and concentration of the chloroform solution on a rotary evaporator afforded 2.4 g of an oil.

The oil (2.4 g) was dissolved in an aqueous HCl–THF solution (25 mL of THF and 25 mL of 10% HCl) and stirred at room temperature for 5 h. The reaction mixture was poured into H_2O and extracted with 2 × 125 mL of chloroform. The combined chloroform extracts were washed with H_2O, dried, and filtered, and concentration on a rotary evaporator afforded 2.0 g of the crude lactam keto acid **8**. Crude **8** was chromatographed using silica gel G and elution with a methanol–ether solution afforded 1.2 g (56%) of pure **8**: NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.10–2.04 (m), 2.10–2.55 (m) [26 H], 2.60–3.10 (m) and 3.11–3.90 (m) [3 H], and 7.60 (s, broad 1 H); on addition of D_2O the resonance peak at δ 7.6 disappeared; IR (neat) 1640 and 1750–1700 cm^{-1} (shoulder).

Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 66.87; H, 9.65; N, 4.08.

15α- and 15β-11-Deoxy-8-aza-13,14-dihydroprostaglandin E_1 (9). The lactam keto acid **8** (4.0 g, 0.012 mol) was dissolved in a 5% $NaHCO_3$ solution (60 mL) and cooled to 0 °C with an ice bath. $NaBH_4$ (760 mg, 0.02 mol) was added in small portions over a 1.5-h period. The reaction mixture was allowed to warm to 20 °C over a 1.25-h pe-

riod, and then cooled to 0 °C. At 0 °C the reaction mixture was acidified with 10% HCl and extracted immediately with 2 × 200 mL of chloroform. The chloroform extracts were combined, washed with H_2O, and dried over anhydrous magnesium sulfate and concentration of the chloroform solution on a rotary evaporator yielded 5.0 g of an oil. The oil was chromatographed using silica gel G and elution with a methanol–ether solution afforded 3.1 g (76%) of an epimeric mixture of 15α- and 15β-11-deoxy-8-aza-13,14-dihydroprostaglandin E_1 (**9**): NMR ($CDCl_3$) δ 0.91 (t), 1.05–1.93 (m) [23 H], 1.95–2.63 (m, 6 H), 2.65–3.95 (m, 4 H), and 7.10 [s (broad, CO_2H and OH), 2 H]; IR (neat) 1725 and 1665 cm^{-1}.

Anal. Calcd for $C_{19}H_{35}NO_4$: C, 66.82; H, 10.33; N, 4.10. Found: C, 66.84; H, 10.11; N, 4.03.

Acknowledgment. We would like to thank the A. H. Robins Co. for a grant in support of this work; Mr. John Forehand for mass spectra data; Mr. Malcolm Stone for microanalysis and Mr. Ashby F. Johnson, Jr., for NMR spectra and for coordinating the data obtained from the Robins Co.; and Dr. W. E. Conrad of S. M. U. for helpful discussions. One of us (J.C.) would like to thank S. M. U. for a teaching assistantship.

Registry No.—**1**, 142-61-0; **2**, 62005-96-3; **3**, 4312-99-6; **4**, 62005-97-4; **5**, 62005-98-5; **6**, 62005-99-6; **7**, 62006-00-2; **8**, 62006-01-3; 15α-**9**, 62006-02-4; 15β-**9**, 62006-03-5; nitromethane, 75-52-5; ethylene glycol, 107-21-1; methyl 4-nitro-7,7-ethylenedioxydodecanoate, 62006-04-6; methyl 7-bromoheptanoate, 54049-24-0.

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Synthesis of L-Prolyl-L-leucylglycine Alkylamides[1]

John Matsoukas, Paul Cordopatis, and Dimitrios Theodoropoulos*

Laboratory of Organic Chemistry, University of Patras, Patras, Greece

Received December 15, 1976

The synthesis of H-Pro-Leu-Gly-$NHCH_3$ and related alkylamido derivatives by a new general approach is described. The preferred conformation of H-Pro-Leu-Gly-$NHCH_3$ is assumed to be identical with that of H-Pro-Leu-Gly-NH_2. Also α-benzyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate β-methylamide and α-benzyl N^{α}-*tert*-butyloxycarbonyl-L-glutamate β-methylamide were synthesized.

The C-terminal tripeptide of oxytocin, H-Pro-Leu-Gly-NH_2, has been suggested to be the natural factor inhibiting the release of melanocyte-stimulating hormone (MRIF). Indeed there exists an enzymic system in rat hypothalamic extracts which can form MRIF activity on using oxytocin as a substrate.[2,3] On the other hand, the replacement of a carboxamide proton in position 9 of oxytocin by a methyl group (a) eliminates the agonistic properties of the hormone, but not its binding capacity, and (b) exerts potent inhibitory oxytocin-induced avian vasodepressor response.[4] In view of these considerations, we thought it of interest to synthesize H-Pro-Leu-Gly-$NHCH_3$ and its analogues with enhanced lipophilicity (Table II) as possible agents of potent and selective clinical value. This paper provides experimental details on the synthesis of certain L-prolyl-L-leucylglycine alkylamides by a new general approach and some information concerning the conformation of H-Pro-Leu-Gly-$NHCH_3$.

Results and Discussion

Firstly, the tripeptide derivative, Z-Pro-Leu-Gly-$NHCH_3$, was synthesized in a stepwise manner using *N*-Trt-glycine[5] as the starting material. This compound was condensed via the mixed-anhydride method[6] with methyl-, ethyl-, and propylamine, respectively, yielding the corresponding *N*-alkylamido derivatives in good yields (Table I). Since methylamide has a very low boiling point, its hydrochloride salt, dissolved in tetrahydrofuran–water (6:4), was used alternatively. Liberation of the amine in situ was brought about by addition of triethylamine. In fact the latter modification enabled us also to prepare α-benzyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate β-methylamide and its L-glutamic analogue in satisfactory yield. On the contrary, prolonged reaction time of methylamine under anhydrous conditions facilitated the formation of the cyclic aspartoyl methylimide derivative. Its structure is based on elemental analysis and spectral data (see Experimental Section). As expected the ^1H NMR spectrum in Me_2SO-d_6 lacks aromatic protons. Since the NCH_3 protons are located under the large $(CH_3)_2SO$ peak, this solvent was replaced with CD_3OD and the NCH_3 protons were shown then clearly as a singlet in the region of δ 2.7. In contrast, the ^1H NMR spectrum of the noncyclic product (a) displays a doublet at δ 2.7 due to coupling with the amide proton and a singlet at δ 7.35 attributed to the aromatic protons.