# Synthesis of (*E*)-8-Aza-11-Deoxy-15α- and 15β-hydroxyprost-13-en-1-ol

*P. A. Zoretic,* C. Bhakta, N. D. Sinha and J. Jardin*

Department of Chemistry, Southeastern Massachusetts University, N. Dartmouth, MA 02747

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The synthesis of a prostaglandin $E_1$ analog, (*E*)-8-aza-11-deoxy-15α- and 15β-hydroxyprost-13-en-1-ol, is reported.

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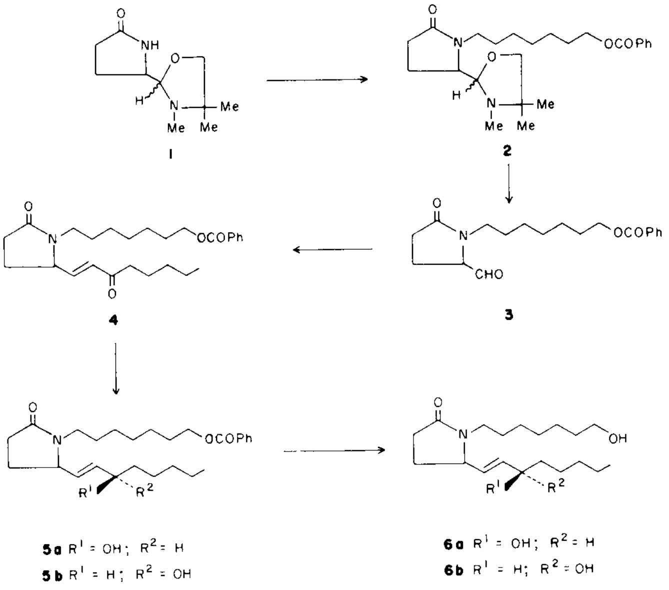
Prostaglandins are known to possess potent biological properties. An intense interest, during the past several years, has developed in the synthesis of prostaglandin analogs with the intent of developing analogs that would be biologically more specific than the natural occuring prostaglandins and orally active. Recently we reported (1,2) the synthesis of 8-aza-PGE$_1$ and 8-aza-PGE$_2$. The 8-aza-PGE analogs have been shown to possess biological properties paralleling that of the natural E series.

In an effort to correlate structural-reactivity relationships in the 8-aza-PGE series, we were interested in synthesizing the 8-aza-PGE-diol analogs (**6**) to determine if these analogs would possess agonistic properties or act as prostaglandin antagonists.



Alkylation of the sodium salt of **1** with 7-bromoheptyl benzoate in refluxing THF gave the esters **2**. Hydrolysis of **2** with an aqueous trifluoroacetic acid-THF solution at room temperature and subsequent chromatography yeilded aldehyde **3**. Reaction of **3** with the lithium salt of dimethyl (2-oxo-heptyl)phosphonate in THF at 0° afforded enone **4**. Reduction of **4** with an ethanolic sodium borohydride solution at -23° afforded a 1:1 mixture of the ester alcohols **5a** and **5b**. Extensive column chromatography of the C-15 alcohol esters **5a** and **5b** on silica gel G and elution with ether-hexane solutions yielded a faster moving (less polar) diastereisomer and a slower moving (more polar) isomer. The less polar and the more polar compounds were tentatively assigned to the 15β-epimer **5a** and the 15α-epimer **5b**, respectively, in analogy with the characteristic tlc behavior of methyl 11-deoxy-15-epi-PGE$_1$ and 11-deoxy-PGE$_1$.

Hydrolysis of **5a** and **5b** with aqueous methanolic sodium hydroxide solution at room temperature and subsequent acidification afforded the diols **6a** and **6b**, respectively. The diols were found (3) to be active in inhibiting gastric acid secretion. The diols were also shown to display only weak anti-hypertensive activity.

## EXPERIMENTAL

The nmr spectra were recorded on a Joelco Model c60HL spectrometer at 60 MHz with TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrometer.

### 2-[5-Oxo-1-(7-benzoyloxyheptyl)-2-pyrrolidinyl]-3,4,4-trimethyloxazolidines.

A 50% suspension of sodium hydride in mineral oil (4.47 g, 0.093 mole) was added to 100 ml of dry tetrahydrofuran under nitrogen. The oxazolidines **1** (16.6 g, 0.084 mole) dissolved in 125 ml of tetrahydrofuran was added dropwise over a 45 minute period with stirring. The reaction mixture was stirred at room temperature for 1.5 hours, heated to 50° for 1.5 hours and then cooled to room temperature. 7-Bromoheptyl benzoate (25.3 g, 0.085 mole) dissolved in 30 ml of tetrahydrofuran was added dropwise over a 20 minute period and the reaction mixture was refluxed for 5 days. The solvent was removed *in vacuo*, the residue poured into 250 ml of water and extracted with four 500 ml portions of chloroform. The organic extracts were combined, washed with brine (400 ml), dried (magnesium sulfate) and concentrated *in vacuo*, giving an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions afforded (18.0 g, 51%) of 2-[5-oxo-1-(7-benzoyloxyheptyl)-2-pyrrolidinyl]-3,4,4-trimethyloxazolidines (**2**); nmr (carbon tetrachloride): δ 1.01 and 1.12 (s, 6H, gem dimethyls), 1.19-3.75 (m) and 2.17 (s. NCH$_3$) [22H], 3.95-4.45 (m, 3H), 7.05-7.55 (m, 3H) and 7.73-8.11 (m, 2H); ir (neat): 1715 and 1685 cm$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{36}N_2O_4$: C, 69,20; H, 8.71; N, 6.72. Found: C, 69.50; H, 8.73; N, 7.02.

### 1-[(7-Benzoyloxyheptyl)-2-formyl-5-oxo]pyrrolidine.

The oxazolidines **2** (17.5 g, 0.0421 mole) was dissolved in an aqueous trifluoroacetic acid tetrahydrofuran solution [17.5 ml of tetrahydrofuran, 17.5 ml of water and 8.6 g (0.0754 mole) of trifluoroacetic acid] and stirred at room temperature for 4.0 hours. The reaction mixture was poured into 350 ml of chloroform and extracted with 200 ml of a 10% hydrochloric acid solution, water (100 ml), 200 ml of a 10% sodium bicarbonate solution and brine (150 ml). The organic solution was dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford an oil.

The oil was chromatographed on silica gel G and elution with ether and methanolic ether solutions afforded (10.7 g, 77%) of 1-[7-benzoyloxyheptyl)-2-formyl-5-oxo]pyrrolidine (3); nmr (deuteriochloroform): $\delta$ 1.04-2.67 (m), 2.70-4.09 (m), 4.23 (t) [19H], 7.10-7.60 (m, 3H), 7.70-8.15 (m, 2H), 9.50 (d, 1H, J = 3.0 Hz); ir (neat): 1725 (br) and 1680 (br) $cm^{-1}$. The aldehyde was not characterized further but submitted directly in the Wadsworth-Emmons reaction.

### (*E*)-[1-(7-Benzoyloxyheptyl)-2-(3-oxo-2-octenyl)-5-oxo]pyrrolidine.

Dimethyl (2-oxoheptyl)phosphonate (6.56 g, 0.0295 mole) in 160 ml of dry tetrahydrofuran was cooled to 0° under nitrogen. A hexane solution of 2.3*M* *n*-butyllithium (12.8 ml, 0.0294 mole) was added with a syringe and the reaction mixture was stirred at 0° for 20 minutes. Aldehyde **3** (10.3 g, 0.031 mole) in 140 ml of tetrahydrofuran was added all at once; an additional 70 ml of tetrahydrofuran was added and the reaction mixture was stirred at 0° for 3.5 hours.

The reaction mixture was poured into 500 ml of a brine-ice mixture and extracted with three 500 ml portions of chloroform. The organic solutions were combined, washed with brine (150 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo,* giving an oil. The oil was chromatographed on silical gel G and elution with ether-hexane solutions afforded (8.2 g, 63%) of (*E*)-[1-(7-benzoyloxyheptyl)-2-(3-oxo-2-octenyl)-5-oxo]pyrrolidine (**4**); nmr (deuteriochloroform): $\delta$ 0.92 (t), 1.07-3.10 (m), 3.05-3.90 (m) [27H], 3.95-4.55 (m,3H), 6.12 (d, $J_{13,14}$ = 15.8 Hz) and 6.63 (d, d, $J_{13,14}$ = 16 Hz, $J_{13,14}$ = 15.8 Hz) [2H], 7.20-7.75 (m, 3H), 7.85-8.30 (m, 2H); ir (neat): 1725, 1685 and 1645 $cm^{-1}$.

*Anal.* Calcd. for $C_{26}H_{37}NO_4$: C, 73.04; H, 8.72; N, 3.28. Found: C, 73.18; H, 9.01; N, 3.26.

### (*E*)-[1-(7-Benzoyloxyheptyl)-2-(3$\alpha$ and 3$\beta$-hydroxy-2-octenyl)-5-oxo]pyrrolidines.

Sodium borohydride (1.65 g, 0.0434 mole) was cooled to -23° (dry ice-carbon tetrachloride) under nitrogen. Absolute methanol was added to obtain a methanolic-sodium borohydride solution at -23°. Enone **4** (7.4 g, 0.0173 mole) in 50 ml of methanol was added all at once and the reaction was stirred at -23° for 4.5 hours.

The reaction mixture was poured into 400 ml of cold brine and extracted with four 400 ml portions of chloroform. The combined organic solutions were washed with brine (400 ml), dried (magnesium sulfate), filtered and cancentrated *in vacuo,* giving an oil. The oil was chromatographed on silica gel G. Rechromatography of the enriched fractions on silica gel and elution with ether-hexane solutions afforded (1.65 g, 22%) of *E*-[1-(7-benzoyloxyheptyl)-2-(3$\beta$-hydroxy-2-octenyl)-5-oxo]pyrrolidine (5a); nmr (carbon tetrachloride): $\delta$ 0.90 (t, distorted), 1.10-4.06 (m), 4.21 (t) [32H]; 5.04-5.67 (m, 2H); 7.35-7.75 (m, 3H), and 7.94-8.31 (m, 2H); ir (neat): 3435 (br), 1725 and 1680 (br) $cm^{-1}$; and (2.4 g, 32%) of *E*-[1-(7-benzoyloxyheptyl)-2-(3$\alpha$-hydroxy-2-octenyl)-5-oxo]-pyrrolidine (**5b**); nmr (carbon tetrachloride): $\delta$ 0.88 (t, distorted), 1.05-4.02 (m) and 4.17 (t) [32H]; 5.0-5.83 (m, 2H), 7.04-7.57 (m, 3H) and 7.71-8.16 (m, 2H); ir (neat): 3400 (br), 1720 and 1680 (br) $cm^{-1}$ and (2.0 g, 27%) of a mixture of **5a** and **5b** as determined by tlc analysis.

*Anal.*Calcd. for $C_{26}H_{39}NO_4$ (**5a**): C, 72.69; H, 9.15; N, 3.26. Found: C, 72.95; H, 9.15; N, 3.13.

*Anal.*Calcd. for $C_{26}H_{39}NO_4$ (**5b**): C, 72.69; H, 9.15; N, 3.26. Found: C, 72.41; H, 9.20; N, 3.25.

### (*E*)-8-Aza-11-deoxy-15$\beta$-hydroxyprost-13-en-1-ol.

To a solution of the 15-epi alcohol **5a** (1.1 g, 0.00256 mole) in 15 ml of methanol was added an aqueous sodium hydroxide solution [sodium hydroxide (0.21 g, 0.0053 mole) and water (5 ml)]. The reaction mixture was stirred for 20 hours at room temperature; diluted with 50 ml of water and extracted with three 200 ml portions of chloroform. The organic solution was washed with brine (100 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo,* giving an oil. The oil was chromatographed on silica gel G and elution with ether and methanolic ether solutions afforded (0.75 g, 90%) of (*E*)-8-aza-11-deoxy-15$\beta$-hydroxyprost-13-en-1-ol (**6a**); nmr (deuteriochloroform): $\delta$ 0.89 (t, distorted), 1.05-1.91 (m) [18H], 1.94-4.26 (m, 12H) and 5.03-5.91 (m, 2H); ir (neat): 3400 (br) and 1675 $cm^{-1}$.

*Anal.* Calcd. for $C_{19}H_{35}NO_3$: C, 70.11; H, 10.84; N, 4.30. Found: C, 70.22; H, 10.97; N, 4.25.

### (*E*)-8-Aza-11-deoxy-15$\alpha$-hydroxyprost-13-en-1-ol.

To a solution of the 15$\alpha$-alcohol **5b** (2.0 g, 0.0047 mole) in 28 ml of methanol was added an aqueous sodium hydroxide solution [sodium hydroxide (0.5 g, 0.0125 mole) and water (7 ml)]. The reaction mixture was stirred for 20 hours at room temperature, diluted with water (100 ml) and extracted with three 150 ml portions of chloroform. The organic solution was washed with brine (250 ml), dried (magnesium sulfate), filtered, and concentrated *in vacuo,* giving an oil. Chromatography of the oil on silica gel and elution with ether and methanolic ether solutions afforded (1.5 g, 98%) of (*E*)-8-aza-11-deoxy-15$\alpha$-hydroxyprost-13-en-1-ol (**6b**); nmr (deuteriochloroform): $\delta$ 0.92 (t, 3H), 1.10-1.90 (m) [19H], 1.94-4.26 (m, 12H) and 5.03-5.91 (m, 2H); ir (neat): 3400 and 1675 $cm^{-1}$.

*Anal.* Calcd. for $C_{19}H_{35}NO_3$: C, 70.11; H, 10.84; N, 4.30. Found: C, 70.33; H, 10.96; N, 4.50.

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## REFERENCES AND NOTES

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(2) P. A. Zoretic, N. D. Sinha and B. Branchaud, *Synth. Commun.*, 7, 299 (1977).

(3) Drs. D. Atkinson and H. Vidrio, Instituto Miles De Terapeutica Experimental Division De Laboratories Miles De Mexico, conducted the biological testing.