Synthesis of 8-Aza-15-hydroxy-7-oxo-12*S*-13*E*-Prostenoic Acids

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The synthesis of a prostaglandin E_1 analog, 8-aza-15-hydroxy-7-oxo-12*S*-13*E*-prostenoic acid, is reported.

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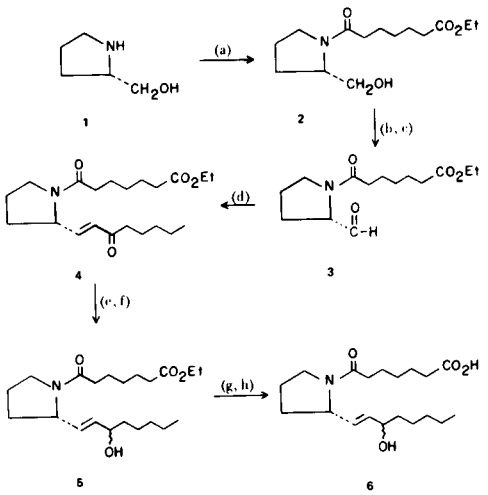
Recently we reported (2) the synthesis of 8-aza-7-oxo-10a-homoprost-13-enoic acids. These homo-8-aza-PGE_1 analogs were shown to inhibit gastric acid secretion. In this note we wish to report the synthesis of the 8-aza-15-hydroxy-7-oxo-12*S*-13*E*-prostenoic acids **6**, having the unnatural configuration at the C-12 position.

Reaction of ethyl 6-chloroformyl hexanoate with two equivalents of L-2-hydroxymethylpyrrolidine (**1**) in chloroform at 0°-20° for 3.0 hours afforded the optically active ester alcohol **2** (98%; [α] D -36.04°). Oxidation of the ester alcohol **2** with Collins reagent (3) in methylene chloride at 0° under nitrogen followed by treatment with sodium bisulfate monohydrate and subsequent chromatography on silica gel G gave a 52% yield of the ester aldehyde **3**.

Treatment of the ester aldehyde **3** with the lithium salt of dimethyl (2-oxoheptyl)phosphonate in tetrahydrofuran at 0° for 3.0 hours and subsequent chromatography on silica gel G afforded the enone **4** (68%; [α] D -33.35°). Reduction of the enone **4** with an ethanolic sodium borohydride solution at -40° for 3 hours and destruction of the excess sodium borohydride with a 10% ethanolic hydrochloric acid solution at -40° followed by chromatography yielded a 1:1 epimeric mixture of the optically active alcohol esters **5** (71%; [α] D -17.52°). Separation of the alcohol esters by preparative tlc in various solvent systems could not be achieved. In each case a single rounded spot was observed. Saponification of the ester alcohols **5** with an aqueous ethanolic sodium hydroxide solution at room temperature for 21 hours, followed by acidification and subsequent chromatography afforded an optically active epimeric mixture of the 15α- and 15β-hydroxy acids **6** (75%; [α] D -20.85°). The alcohol acids did not inhibit gastric acid secretion and displayed only mild activity (4) with respect to inhibiting platelet aggregation.



(a) Ethyl 6-chloroformyl hexanoate, chloroform, 0°-20°, 2.5 hours. (b) Collins reagent, 0°, 1.2 hours. (c) Sodium bisulfate monohydrate, 0°. (d) Lithium dimethyl(2-oxoheptyl)phosphonate, tetrahydrofuran, 0°, 3 hours. (e) Sodium borohydride, ethanol, -40°, 3 hours. (f) 10% Ethanolic hydrochloric acid, -40°. (g) Aqueous sodium hydroxide/ethanol, room temperature, 21 hours. (h) 10% Hydrochloric acid.

EXPERIMENTAL

Nmr spectra were recorded on a Jeolco Model c60HL spectrometer at 60 MHz with TMS as an internal standard. Infrared spectra were recorded on a Perkin Elmer Model 337 spectrometer.

1-(Ethyl-7-oxoheptanoate)-2*S*-hydroxymethylpyrrolidine (**2**).

A solution of L-2-pyrrolidinemethanol **1** (10.0 g., 0.10 mole) in 90 ml. of chloroform was cooled to 0°. Ethyl 6-chloroformyl hexanoate (10.3 g., 0.05 mole) in 30 ml. of chloroform was added at 0° over a 1.5 hour period. The addition funnel was rinsed with an additional 15 ml. of chloroform and the reaction was allowed to warm to room temperature over a 3 hour period.

The reaction was poured into 125 ml. of a 5% hydrochloric acid solution. An additional 125 ml. of chloroform was added to the above mixture and the organic layer was separated and washed consecutively with 150 ml. of a 5% hydrochloric acid solution, 125 ml. of water, 125 ml. of a 10% sodium bicarbonate solution and 125 ml. of water. The chloroform extract was dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator to afford 13.3 g. (98%) of the ester alcohol **2**; b.p., kugelrohr, 194-196° (0.04 mm); nmr (carbon tetrachloride): δ 4.51 (s, broad, OH), 4.11 (q) and 3.25-3.72 (m) [8H], 1.42-2.50 (m) and 1.26 (t) [17H]; ir (neat): 3400, 1745 and 1635 cm^{-1}; [α] D -36.04°.

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.62; H, 9.35; N, 5.07.

1-(Ethyl-7-oxoheptanoate)-2*S*-formylpyrrolidine (**3**).

q A three liter three-neck flask fitted with a mechanical stirrer and nitrogen inlet tube was deaerated with nitrogen. The ester alcohol **2** (6.6 g., 0.024 mole) dissolved in 1.5 ℓ. of dry methylene chloride was cooled to 0°. Collins reagent, chromium trioxide·2 pyridine (37.5 g., 0.145 mole) was added all at once under nitrogen and the reaction was allowed to stir at 0° for 1.2 hours. Powdered sodium bisulfate monohydrate (80.2 g.) was added and the resulting mixture was stirred for an additional 20 minutes at 0°.

The reaction solution was decanted and the residue was washed with 500 ml. of methylene chloride. The methylene chloride solutions were combined and washed with two 1 ℓ. portions of a 10% hydrochloric acid solution, two 1 ℓ. portions of a 10% sodium bicarbonate solution, and two 1 ℓ. portions of water. The methylene chloride extract was dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator to afford 6.7 g. of a crude brown oil. The oil was chromatographed immediately on silica gel G. Elution with ether-hexane solutions and ether afforded 3.4 g. (52%) of the ester aldehyde **3**; nmr (carbon tetrachloride): δ 1.25 (t) and 1.40-2.35 (m) [17H], 3.14-3.75 (m), 4.05 (q) and 4.28-4.50 (m) [5H] and 9.43 (d, 1.3 Hz); ir (neat) 1740 and 1650 cm^{-1}. The aldehyde **3** was not characterized further but used directly in the Wadsworth-Emmons reaction.

Ethyl 8-aza-7,15-dioxo-12*S*-13*E*-prostenoate (**4**).

A three-neck flask fitted with a condenser, nitrogen inlet tube, magnetic stirring bar, and serum cap was flamed and deaerated with nitrogen. Dimethyl(2-oxoheptyl)phosphonate (2.7 g., 0.012 mole) dissolved in 100 ml. of dry tetrahydrofuran was placed in the reaction vessel under nitrogen and cooled to 0°. A hexane solution of 2.5 *M n*-butyl lithium (4.8 ml., 0.012 mole) was added with a syringe and the reaction was stirred at 0° for 15 minutes. The ester aldehyde **3** (3.38 g., 0.0126 mole) in 40 ml. of dry tetrahydrofuran was added to the reaction all at once and the resulting reaction mixture was stirred at 0° for 3 hours.

The reaction mixture was poured into 200 ml. of a saturated sodium chloride solution and extracted with five 200 ml. portions of chloroform. The chloroform extracts were combined, washed with 150 ml. of water, dried over anhydrous magnesium sulfate, filtered and concentrated on a rotary evaporator to afford an oil. The oil was chromatographed on silica gel G. Elution with ether-hexane solutions yielded (3.0 g., 68%) of the enone **4**; nmr (carbon tetrachloride): δ 6.43-6.92 (m), 6.0 (d, J = 16.5 Hz) and 5.91 (d, J = 16.5 Hz) [2H]; 4.35-4.85 (m, 1H), 4.11 (q, 2H), 3.20-3.75 (m, broad, 2H), 1.10-2.67 (m), and 0.93 (t, distorted) [28H]; ir (neat): 1740 and 1650 (broad) cm^{-1}; [α] D -33.35°; mass spectrum: m/e 365 (M), 320 (M -OCH_2CH_3), 309 (M -$C_2H_5CH{=}CH_2$), 266 (M -$C_5H_{11}C{=}O$), 195 (M -O=C=CH-$(CH_2)_4$-CO_2Et), 194 (M -CH=CH-CO-C_5H_{11} or O=C-$(CH_2)_5CO_2Et$), 124 (M -O=C=CH-$(CH_2)_4CO_2Et$ and C_5H_{11}), and 96 (M -O=C=CH-$(CH_2)_4CO_2Et$ and $C_5H_{11}C{=}O$, or $C_5H_{11}C{=}O$, $CH_2{=}CH$-$(CH_2)_2$-CO_2Et and $CH_2{=}C{=}O$).

Anal. Calcd. for $C_{21}H_{35}NO_4$: C, 69.01; H, 9.65; N, 3.83. Found: C, 69.41; H, 9.71; N, 4.03.

Ethyl 8-aza-15-hydroxy-7-oxo-12*S*-13*E*-prostenoates (**5**).

A three-neck flask fitted with two addition funnels, a magnetic stirring bar, and a nitrogen inlet tube was flamed and deaerated with nitrogen. Sodium borohydride (0.50 g., 0.0132 mole) was placed in the reaction flask and the flask was cooled to -40°. Dry ethanol was added to obtain a clear ethanolic sodium borohydride solution at -40°. The enone **4** (2.4 g., 0.0066 mole) dissolved in 30 ml. of absolute ethanol was added all at once and the resulting mixture was stirred for 3 hours at -40°. Excess sodium borohydride was destroyed at -40° by addition of a 10% ethanolic hydrochloric acid solution and the reaction mixture was concentrated on a rotary evaporator. The resulting residue was poured into 100 ml. of water and extracted with four 125 ml. portions of chloroform. The chloroform extracts were combined, washed with 100 ml. of a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator to yield an oil. The oil was chromatographed on silica gel G. Elution with ether-hexane solutions afforded 1.7 g. (71%) of a 1:1 epimeric mixture of the ester alcohols **5**; nmr (carbon tetrachloride): δ 5.32-5.67 (m, 2H), 4.30-4.69 (m), 4.08 (q) and 3.0-3.70 (m) [7H], 1.09-2.50 (m) and 0.92 (t, distorted) [28H]; ir (neat): 3400 (broad), 1740 and 1635 (broad) cm^{-1}; [α] D -17.52°; mass spectrum m/e 367 (M), 350 (M -OH), 349 (M -H_2O), 322 (M -OCH_2CH_3), 296 (M -C_5H_{11}), 226 (M -C_5H_{11}-CHOH), 240 (M -CH=CH-CHOH-C_5H_{11}), 196 (M -O=C-$(CH_2)_5$-CO_2Et), 180 (M -O=C=CH-$(CH_2)_4CO_2Et$ and OH), 179 (M -O=C=CH-$(CH_2)_4CO_2Et$ and H_2O), 126 (M -O=C=CH-$(CH_2)_4CO_2Et$ and C_5H_{11}), 96 (M -O=C=CH-$(CH_2)_4CO_2Et$ and C_5H_{11}CHOH) and 70 (M -O=C=CH-$(CH_2)_4CO_2Et$ and C_5H_{11}-CHOH-CH=CH).

Anal. Calcd. for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.32; H, 10.21; N, 3.68.

8-Aza-15-hydroxy-7-oxo-12*S*-13*E*-prostenoic acids (**6**).

The ester alcohols **5** (870 mg., 0.00237 mole) were dissolved in 15 ml. of ethanol. An aqueous sodium hydroxide solution [sodium hydroxide (104 mg., 0.0026 mole) and 4.2 ml. of water] was added to the above solution and the resulting mixture was stirred at room temperature for 21 hours.

The reaction mixture was poured in 10 ml. of a 4% sodium hydroxide solution and extracted with two 50 ml. portions of ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with five 50 ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator to afford a yellow oil. The oil was chromatographed on silica gel G. Elution with ether-hexane solutions and ether yielded (0.6 g., 75%) of a C-15 epimeric mixture of the optically active alcohol acids **6**; nmr (deuteriochloroform): δ 5.90 (s, broad, CO_2H and OH), and 5.41-5.70 (m, CH=CH) [4H], 3.25-3.85 (m, 4H) and 1.05-2.75 (m) and 0.90 (t, distorted) [25H]; ir (neat): 3380 (broad), 1720 and 1610 cm^{-1}; [α] D -20-85°; mass spectrum: m/e 339 (M), 322 (M -OH), 321 (M -H_2O), 268 (M -C_5H_{11}), 238 (M -C_5H_{11}CHOH), 222 (M -CH=CH-$(CH_2)_2CO_2H$ and OH), 212 (M -CH=CH-CHOH-C_5H_{11}), 196 (M -$CO(CH_2)_5CO_2H$), 179 (M -$CO(CH_2)_5CO_2H$ and OH or O=C=CH-$(CH_2)_4CO_2H$ and H_2O.

Anal. Calcd. for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 67.55; H, 9.99; N, 4.12.

REFERENCES AND NOTES

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