Synthesis of *(E)*-7-[[2-[4-(*m*-Trifluoromethylphenoxy)-3α and 3β-Hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]]heptanoic Acids

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The synthesis of an 8-aza-PGE_1 analog, *(E)*-7-[[2-[4-(*m*-trifluoromethylphenoxy)-3α and 3β-hydroxy-1-butenyl]-5-oxo-pyrrolidinyl]]heptanoic acids is reported.

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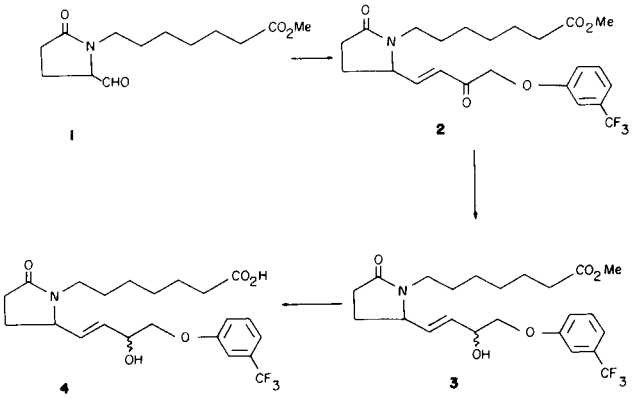
Hetero prostaglandin analogs have been shown to possess biological properties paralleling that of the natural prostaglandins. Recently we reported (2,3) the synthesis of 8-aza-PGE_1 and 8-aza-PGE_2. Of special interest in the 8-aza-PGE_1 series was the finding that the diasteromeric mixture of the 15α and 15β analogs effectively interrupted pregnancy (4,5) in the hamster and displayed only minimal smooth muscle activity relative to $PGF_{2\alpha}$.

Since it was determined that the 8-aza-PGE_1 analogs displayed minimal smooth muscle activity, we were interested in modifying the C-8 side chain to ascertain if such analogs would possess enhanced biological activity. Of particular interest was the report by the ICI group (6,7) that 16-aryloxyprostaglandins display potent luteolytic activity. Herein we report the synthesis of the 16-aryloxy-8-aza-PGE_1 analogs **4**.



Reaction of aldehyde **1** (2) with the lithium salt of dimethyl [2-oxo-3-(3-trifluoromethylphenoxy)]propyl phosphonate (7) in tetrahydrofuran at 0° and subsequent chromatography afforded enone **2**. Reduction of **2** with a methanolic sodium borohydride solution at -23° gave an epimeric mixture of the ester alcohols **3**. Hydrolysis of the ester alcohols **3** with an aqueous methanolic sodium hydroxide solution at room temperature followed by acidification and subsequent chromatography yielded an epimeric mixture of acids **4**. Analysis (tlc) of **3** and **4** in a variety of solvent systems showed the ester alcohols **3** as one round spot and the alcohol acids **4** as an elongated spot. The alcohol esters **3** and the alcohol acids **4** were found not to be effective in interrupting pregnancy in the hamster.

EXPERIMENTAL

The 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.

(E)-Methyl 7-[[2-[4-(*m*-Trifluoromethylphenoxy)-3-oxo-1-butenyl]-5-oxo-1-pyrrolidinyl]]heptanoate.

Dimethyl [2-oxo-3-(3-trifluoromethylphenoxy)]propyl phosphonate (3.9 g, 0.012 mole) in 25 ml of tetrahydrofuran was cooled to -70° under nitrogen. A hexane solution of 2.4 *M* *n*-butyl lithium (4.98 ml, 0.012 mole) was added *via* syringe and the reaction mixture was allowed to warm to 0° and stirred for 30 minutes. Aldehyde **1** (2.30 g, 0.0090 mole) in 25 ml of tetrahydrofuran was added all at once, the reaction mixture was stirred at 0° for 2 hours, and then stirred at room temperature for 8 hours.

The reaction mixture was poured into 200 ml of a brine-ice mixture and extracted with three 200 ml portions of methylene chloride. The organic portions were combined, washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* giving an oil. The oil was chromatographed on a silica gel G and elution with ether hexane solutions afforded (1.2 g, 30%) of *(E)*-methyl 7-[2-[4-(*m*-trifluoromethylphenoxy)-3-oxo-1-butenyl]-5-oxo-1-pyrrolidinyl]heptanoate (**2**); nmr (deuteriochloroform): δ 3.73 (s, 3H) and 4.60-4.90 (m, 2H); ir (neat): 1735 and 1680 cm^{-1}.

Anal. Calcd. for $C_{23}H_{28}F_3NO_5$: C, 60.65; H, 6.20; N, 3.08. Found: C, 60.36; H, 5.98; N, 3.00.

(E)-Methyl 7-[[2-[4-(*m*-Trifluoromethylphenoxy)-3α and 3β-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]]heptanoates.

Sodium borohydride (0.18 g, 0.0046 mole) was cooled to -23° (dry ice-carbon tetrachloride) under nitrogen. Enone **2** (0.83 g, 0.0018 mole) in 10 ml of absolute methanol was added all at once and the reaction was stirred at -23° for 3.5 hours. The reaction mixture was poured into 100 ml of brine and extracted with three 100 ml portions of methylene chloride. The combined organic portions were dried (magnesium sulfate), filtered and concentrated *in vacuo*, giving an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions afforded (0.75 g, 90%) of *(E)*-methyl 7-[2-[4-(*m*-trifluoromethylphenoxy)-3α and 3β-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]heptanoates (**3**); nmr (deuteriochloroform): δ 3.76 (s, 3H), 5.84-6.18 (m, 2H), 7.14-7.88 (m, 4H); ir (neat): 3400 (br), 1730 and 1660 cm^{-1}.

Anal. Calcd. for $C_{23}H_{30}F_3NO_5$: C, 60.39; H, 6.61; N, 3.06. Found: C, 60.21; H, 6.60; N, 3.13.

(E)-7-[[2-[4-(*m*-Trifluoromethylphenoxy)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]]heptanoic Acids.

To a solution of alcohols **3** (0.40 g, 0.88 mmole) in 6 ml of methanol was added an aqueous sodium hydroxide solution [sodium hydroxide (0.07 g, 0.0018 mole) and 3 ml of water]. The reaction mixture was stirred for 12 hours at room temperature, poured into 40 ml of water, and ex-

tracted with two 30 ml portions of ether. The aqueous layer was acidified and extracted with two 30 ml portions of chloroform. The combined chloroform solutions were washed with 30 ml of brine, dried (magnesium sulfate), filtered and concentrated *in vacuo*, giving an oil. Chromatography of the oil on silica gel G and elution with methanol-ether solutions afforded (280 mg, 72%) of *(E)*-7-[[2-[4-(*m*-Trifluoromethylphenoxy)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]]heptanoic acids (4); nmr (deuteriochloroform): δ 5.76-6.76 (m, 4H, vinyl; carboxyl and hydroxyl protons), and 7.05-7.80 (m, 4H), ir (neat): 3300 (br), 1710 and 1650 cm^{-1}.

Anal. Calcd. for $C_{22}H_{22}F_3NO_5$: C, 59.59; H, 6.36; N, 3.16. Found: C, 59.55; H, 6.49; N, 3.00.

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REFERENCES AND NOTES

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(4) The interruption of pregnancy test was assayed at the National Institute of Child Health and Human Development. The diastereomeric mixture of 15α and 15β-8-aza-PGE_1 showed 100% interruption of pregnancy at a dose of 50 ug/kg in the hamster with only 0.03% of the smooth muscle activity of $PGF_{2\alpha}$.

(5) The interruption of pregnancy test was carried out as described by Giannia and coworkers (*Contraception*, **9**, 507 (1974)) with the exception that one male per female was used instead of one male per three females.

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