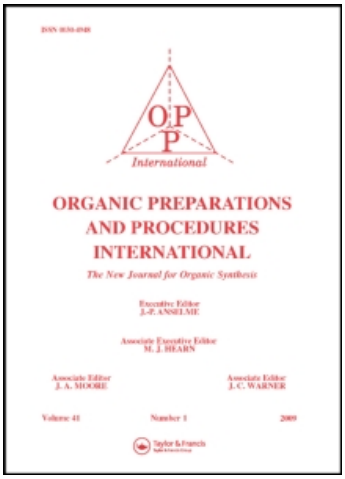

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SYNTHESIS OF 8,12-SECOPROSTAGLANDIN $F_{1\alpha}$, AN EICOSENOIC ACID ANALOGUE

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SYNTHESIS OF 8,12-SECOPROSTAGLANDIN $F_{1\alpha}$, AN EICOSENOIC ACID ANALOGUE

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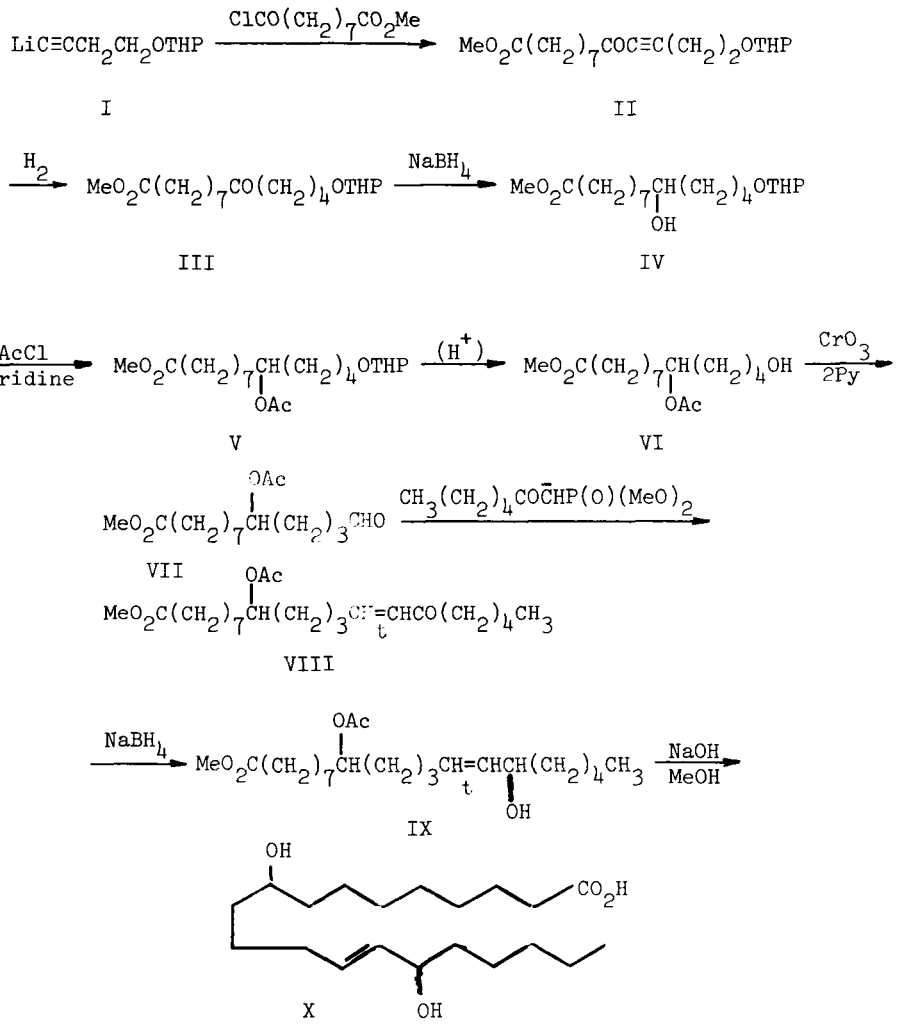
The synthesis of hetero 8,12-secoprostaglandins,[1] 11,12-secoprostaglandins,[2] 9,11-secoprostaglandins[3] and the synthesis of eicosatrienoic acid analogues[4] have recently been reported. These seco analogues have been shown to possess prostaglandin-like activity and also to act as prostaglandin antagonists. Herein we describe the synthesis of a novel eicosenoic acid analogue, 8,12-secoprostaglandin $F_{1\alpha}$ (X).

Reaction of the lithium salt of I with methyl-8-chloroformyl octanoate at -78° and subsequent chromatography afforded a 53% yield of the tetrahydropyranyl ester II. Catalytic reduction of II with hydrogen in the presence of 10% Pd/C gave a 71% yield of ketone III. Reduction of III with $NaBH_4$ in MeOH at 0° yielded the alcohols IV (82%) and subsequent acylation of IV with acetyl chloride in the presence of pyridine followed by chromatography afforded an 82% yield of the acetates V. Cleavage of the protecting group of V was accomplished with methanol in the presence of a catalytic amount of p-toluenesulfonic acid, giving the alcohol VI in 75% yield. Oxidation of VI with Collins reagent[5] afforded a 92% yield of aldehyde VII and subsequent treatment of VII with the lithium

salt of dimethyl (2-oxoheptyl)phosphonate at 0° gave an 83% yield of enone VIII. Hydride reduction of VIII with a meth-



anolic sodium borohydride solution at -23° afforded the alcohols IX in 76%. Tlc analysis of IX in several different solvent systems showed IX as one rounded spot. Saponification of IX with an aqueous methanolic sodium hydroxide solution at room temperature followed by acidification afforded a 75% yield of

the alcohol acids X. The alcohol acids X as well as the corresponding esters appeared as one elongated spot when subjected to tlc analysis in a variety of solvent systems. However on careful chromatography and subsequent crystallization two alcohol acids having melting points of 77-79° and 88-89.7° were obtained. The alcohol acids were shown to be effective in inhibiting gastric acid secretion[6] and were found to contract human bronchial muscle in vitro.[6]

EXPERIMENTAL

Methyl 9-Oxo-13-[(tetrahydro-2H-pyran-2-yl)oxy]tridec-10-ynoate (II).- A hexane solution of 2.4 M n-BuLi (20.83 ml, 0.05 mol) was added dropwise over a 10 min period to 1-[(tetrahydro-2H-pyranyl-2-yl)oxy]but-3-yne I (7.7 g, 0.05 mol) in 80 ml of THF at -78° under N_2, and the reaction mixture was stirred for 45 min. Methyl 8-chloroformyl octanoate (11.1 g, 0.05 mol) was added neat and the addition funnel was rinsed with 15 ml of THF. The reaction mixture was stirred at -78°C for 1 hr, poured into 300 ml of 10% $NaHCO_3$ and extracted with ether. The organic solution was washed with 100 ml of H_2O, dried (Na_2SO_4) and concentrated in vacuo. Chromatography of the oil on silica gel and elution with ether-hexane solutions and ether afforded 8.9 g (53%) of II; NMR (CCl_4): δ 0.90-1.95 (m, 16H), 2.0-2.81 (m, 6H), 3.13-4.05 (m) and 3.53 (s) [7H], and 4.45-4.46 (m, 1H); ir (neat): 2220, 1740 and 1675 cm^{-1}.

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94.
Found: C, 67.34; H, 8.77.

Methyl 9-Oxo-13-[(tetrahydro-2H-pyran-2-yl)oxo]tridecanoate (III).- To a solution of II (7.5 g, 0.022 mol) in 75 ml of

MeOH, was added 1.0 g of 10% Pd/C and the resulting reaction mixture was reduced with H_2 at 1 atm at room temperature. After two equivalents of H_2 was absorbed, the reaction was filtered through Celite with suction. The organic solution was diluted with 100 ml of ether, dried (Na_2SO_4) and concentrated in vacuo. Chromatography of the oil on silica gel and elution with ether-hexane solutions gave 5.3 g (71%) of III; NMR (CCl_4): δ 0.95-1.95 (m, 20H), 2.0-2.55 (m, 6H), 3.0-3.98 and 3.54 (s) [7H] and 4.33-4.60 (m, 1H); ir (neat): 1745 and 1710 cm^{-1}.

Anal. Calcd for $C_{19}H_{34}O_5$: C, 66.64; H, 10.01.

Found: C, 66.81; H, 10.05.

Methyl 9-Hydroxy-13-[(tetrahydro-2H-pyran-2-yl)oxy]tridecanoate (IV).- $NaBH_4$ (2.63 g, 0.0692 mol) in 70 ml of MeOH was cooled to 0°. Ketone III (16.95 g, 0.049 mol) in 200 ml of MeOH was added all at once and the reaction was stirred at 0° for 1.75 hr. The reaction mixture was poured into 1 ℓ of brine and extracted with five 250 ml portions of CH_2Cl_2. The organic solution was dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica gel and elution with ether-hexane solutions afforded 10.2 g of IV and a mixture of III and IV. $NaBH_4$ reduction of the mixture in MeOH at 0° and subsequent chromatography afforded an additional 3.6 g of IV. The combined hydride reduction gave 13.8 g (82%) of IV; NMR (CCl_4): δ 0.90-1.95 (m) and 2.20 (t, distorted) [26H], 2.67 (s, 1H, br), 3.0-4.0 (m) and 3.56 (s) [8H] and 4.30-4.60 (m, 1H); ir (neat): 3740 and 1740 cm^{-1}.

Anal. Calcd for $C_{19}H_{36}O_5$: C, 66.25; H, 10.53.

Found: C, 66.38; H, 10.41.

Methyl 9-Acetoxy-13[(tetrahydro-2H-pyran-2-yl)oxy]tridecanoate (V).- The alcohol IV (13.8 g, 0.040 mol) and pyridine (3.2 g, 0.040 mol) in 60 ml of CH_2Cl_2 was cooled to 0° and acetyl chloride (3.1 g, 0.040 mol) in 90 ml of CH_2Cl_2 was added dropwise with stirring and the reaction mixture was stirred at 0° for an additional 15 min. and then at room temperature for 3 hrs. The reaction mixture was poured into 250 ml of brine and extracted with three 150 ml portions of CH_2Cl_2. The organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel and elution with ether-hexane solutions gave 12.6 g (82%) of V; NMR (CCl_4): δ 1.0-1.85 (m), 1.87-2.55 (m) and 1.91 (s) [29H], 2.93-4.02 (m) and 3.53 (s) [7H], and 4.30-4.95 (m, 2H, OCHO and CHOCO); ir (neat): 1740 cm^{-1}.

Anal. Calcd for $C_{21}H_{38}O_6$: C, 65.26; H, 9.91.
Found: C, 65.35; H, 9.76.

Methyl 9-Acetoxy-13-hydroxytridecanoate (VI).- p-Toluenesulfonic acid (1.2 g) was added to the tetrahydropyranyl ester V (12.0 g, 0.031 mol) in 120 ml of MeOH and the reaction mixture was stirred at room temperature for 2 hrs. The reaction mixture was poured into 400 ml of 10% $NaHCO_3$ and extracted with four 150 ml portions of CH_2Cl_2. The organic solution was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel and elution with ether-hexane solutions afforded 7.0 g (75%) of VI; NMR (CCl_4): δ 0.95-1.93 (m, 18H), 1.96-2.65 (m) and 2.0 (s) [5H], 3.0-4.06 (m) and 3.60 (s) [6H], and 4.50-5.10 (m, 1H); ir (neat): 3470 and 1735 cm^{-1}.

Anal. Calcd for $C_{16}H_{30}O_5$: C, 63.55; H, 10.00.
Found: C, 63.40; H, 9.89.

Methyl 9-Acetoxy-12-formyldodecanoate (VII).- Collins reagent (17.9 g, 0.069 mol) was added to the alcohol VI (3.5 g, 0.0116 mol) in 900 ml of CH_2Cl_2 at 0° under N_2 and the reaction mixture was stirred at 0° for 1 hr. Powdered $NaHSO_4 \cdot H_2O$ (36 g) was added and the reaction mixture was stirred for an additional 20 min. The reaction solution was decanted and the residue washed with CH_2Cl_2. The organic solution was extracted with two 900 ml portions of 10% HCl, two 500 ml portions of 10% $NaHCO_3$ and 1 ℓ of H_2O. The organic solution was dried ($MgSO_4$) and concentrated in vacuo, giving a brown oil. The oil was passed through a short silica gel column with ether as the eluent to afford 3.2 g (92%) of VII; NMR (CCl_4): δ 1.98 (s), 3.53 (s) and 9.60 (s). The aldehyde was not characterized further but subjected to the Wadsworth-Emmons reaction.

(E)-Methyl 9-Acetoxy-15-oxoeicos-13-enoate (VIII).- A hexane solution of 2.4 M n-butyllitium (5.5 ml, 0.031 mol) was added with a syringe to dimethyl (2-oxoheptyl)phosphonate (2.9 g, 0.031 mol) in 35 ml of THF at 0° under N_2 and the reaction mixture was stirred for 20 min. Aldehyde VII (3.16 g, 0.0105 mol) in 25 ml of THF was added and stirring was continued for 3 hrs at 0°. The reaction mixture was poured in 500 ml of brine and extracted with three 200 ml portions of ether. The organic solution was washed with 100 ml of brine, dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica gel and elution with ether-hexane solutions afforded 3.5 g (83%) of VIII; NMR (CCl_4): δ 0.93 (t, distorted), 1.07-2.66 (m) and 2.01 (s) [34H], 3.64 (s, 3H), 4.55-5.05 (m, 1H), 6.04 (d, $J_{13,14}$ = 16.5 Hz) and 6.45-7.02 (m) [2H].

Anal. Calcd for $C_{23}H_{40}O_5$: C, 69.66; H, 10.17.
Found: C, 69.62; H, 10.15.

(E)-Methyl 9-Acetoxy-15-hydroxyeicos-13-enoates (IX).- $NaBH_4$ (0.91 g, 0.024 mol) was cooled to -23° under N_2 and dry MeOH was added to obtain a clear solution. Enone VIII (3.15 g, 0.00795 mol) in 50 ml of MeOH was added and the reaction mixture was stirred at -23° for 4.25 hrs. The reaction mixture was poured into 200 ml of brine and extracted with five 100 ml portions of CH_2Cl_2. The organic solution was dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica gel and elution with ether-hexane solutions afforded 2.4 g (76%) of IX; NMR (CCl_4): δ 0.91 (t), 1.06-2.54 (m) and 1.94 (s) [34H], 2.83 (s, 1H), 3.56 (s) and 3.67-4.05 (m) [4H], 4.45-4.95 (m, 1H) and 5.05-5.54 (m, 2H); ir (neat): 3500 (br) and 1740 cm^{-1}.

Anal. Calcd for $C_{23}H_{42}O_5$: C, 69.31; H, 10.62.
Found: C, 69.10; H, 10.49.

(E)-9,15-Dihydroxyeicos-13-enoic Acids (X).- A solution of the ester alcohols IX (1.7 g, 0.0043 mol), MeOH (15 ml), NaOH (0.51 g, 0.0128 mol), and H_2O (7 ml) was stirred at room temperature overnight. The reaction mixture was poured into 130 ml of H_2O and extracted with two 70 ml portions of ether. The aqueous solution was acidified at 0° with conc HCl and extracted with four 100 ml portions of CH_2Cl_2. The organic solution was dried ($MgSO_4$) and concentrated in vacuo, giving a solid. The solid was triturated with an ether-hexane solution and filtration afforded 1.1 g (75%) of X, mp. 75-85°; NMR (DMSO-d_6) δ 0.87 (t) and 5.20-5.55 (m); ir (KBr) 3350 and 1700 (br) cm^{-1}.

Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18.
Found: C, 70.23; H, 10.98.

Chromatography of X on silica gel (elution with hexane and ether-hexane) and subsequent crystallization of the individual fractions afforded two diastereomeric alcohol acids.

Alcohol acid Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18
mp. 77-79° Found: C, 70.28; H, 10.82
NMR (DMSO-d_6): δ 0.87 (t, distorted), 5.22-5.60 (m).

Alcohol acid Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18
mp. 88-90° Found: C, 70.01; H, 11.29
NMR (DMSO-d_6): δ 0.87 (t, distorted), 5.30-5.54 (m).

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