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C-8-QUATERNARY PROSTAGLANDIN ANALOGS

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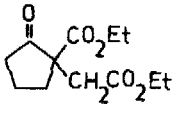
Abstract: A simple and convenient synthesis of the title compounds is presented.

As part of our synthetic work on prostaglandin chemistry we wish to report the preparation of certain 11-deoxy-C(8)-quaternary prostanoids wherein both side-chains are located at the same carbon atom of the cyclopentane ring[1]. Despite the enormous number of prostaglandin analogs which has been synthesized over the past few years, only some papers deal with C(8)-substituted compounds[2] with special biological activity.

Our primary goal was to prepare spirolactone 5 from which all prostaglandin congeners presented here can be derived via standard procedures.



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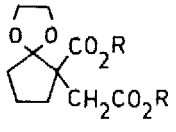
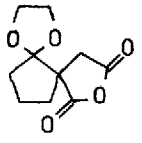


2 R=C_2H_5

3 R=H



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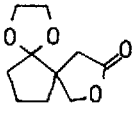

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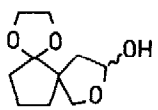
Alkylation of 2-carbethoxycyclopentanone with ethyl bromoacetate[3] gave

diester 1 [*bp. 123-126/1 mmHg; 70%*], which was converted to ketal 2 [*bp. 116-118/1 mmHg: 90%*] with ethylene glycol in benzene solution in the usual manner. Hydrolysis of 2 with 4N aqueous NaOH [*100°, 24 h.*], acidification [*1:1 HCl*] and extraction with ethyl acetate gave the dicarboxylic acid 3 [*mp. 139-41°; 83%*] which can be easily converted to the desired acid anhydride 4 [*mp. 79-80°; NMR*[4] *3.98(4H), 2.6-3.3(2H), 1.7-2.55(6H); 90%*] with equimolar amount of dicyclohexylcarbodiimide [*ether, room temp., 3 h*]. The regiospecific reduction of unsymmetrical anhydride[5] 4 was performed with $NaBH_4$, yielding exclusively spirolactone 5 [*oil; ir 1778 cm^{-1}; NMR 4.01-4.41(2H), 3.97(4H), 2.29-2.81(2H), 1.79(6H); R_f 0.43(a)*[6]*; 60%*] and some unidentified over-reduced product [*methanol, 0°, 2 h.*].



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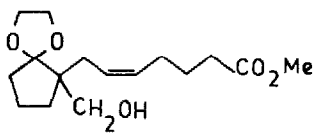

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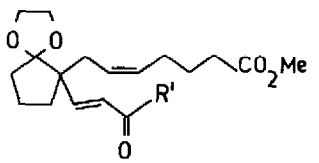
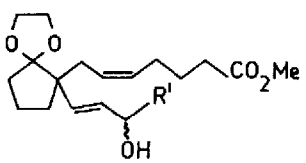


8 R'=C_5H_{11} 9 R'=C_6H_{13}

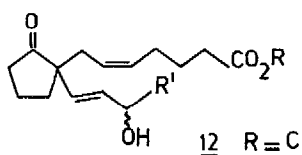
Reduction of 5 with i-Bu_2AlH [*toluene, -60°, 3 h.*] gave lactol 6 [R_f *0.17 (a); ir 3408 cm^{-1}; 80%*], which was treated with the Wittig reagent derived from (4-carboxybutyl) triphenylphosphonium bromide [*DMSO, NaH, room. temp., 12 h.*] to yield, after esterification with CH_2N_2, the hydroxy-ester 7 [*oil; ir 3540, 3005, 1748 cm^{-1}; R_f 0.56(a); 50%*]. Collins oxidation of 7 followed by the Wittig-Horner reaction with 2-oxoheptylidine-dimethylphosphonate provided enone 8 [*ir 1738, 1670, 1623 cm^{-1}; NMR 6.08-6.86(2H, dd, J=16 Hz), 5.32(2H, m), 3.93 (4H, b.s.), 3.67(3H, s.), 0.90(3H, t.); R_f 0.65(c); 60%*]. By similar reactions the homolog 9 could also be prepared [R_f *0.56(d); 56%*]. With the corresponding triphenyl or tributylphosphoranes the same reaction was unsuccessful.



10 R'=C_5H_{11}

11 R'=C_6H_{13}

a: less polar b: more polar



12 R=CH_3 R'=C_5H_{11}

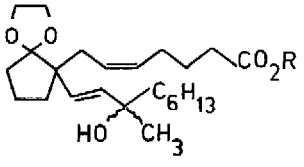
13 R=H R'=C_5H_{11}

14 R=CH_3 R'=C_6H_{13}

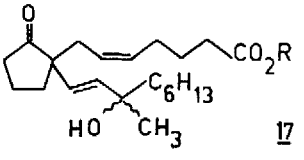
15 R=H R'=C_6H_{13}

Isomeric alcohols 10a [*oil; ir 3450, 1738 cm^{-1}; R_f 0.66(c)*], 10b [R_f *0.53 (c)*] and 11a [*oil; ir 3480, 1740 cm^{-1}; R_f 0.68(c)*], 11b [R_f *0.60(c)*] formed in

quantitative yield by the reduction of 8 and 9 [*$NaBH_4$ in methanol, 0°*] were separated by silica gel column chromatography. The less polar fractions [10a *and* 11a] were treated successively with AcOH-H_2O-THF 20:10:3 [*40°, 2 h.*] and 5% aqueous NaOH-CH_3OH 1:1 to yield 12 [R_f *0.53(e); 94%*], 13 [R_f *0.42(e); NMR 6.08 (2H), 5.15-5.80(4H), 4.1(1H) 76%*] and 14 [R_f *0.45(e); ir 3480, 1755 cm^{-1}; 87%*] 15 [R_f *0.65(e); NMR 5.15-5.7(4H, m), 4.09 (1H, m), 0.83(3H, s);* ^{13}C *NMR 134.04, 131.57, 72.77, 33.78, 25.32; 83%*], respectively.



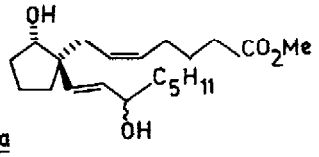
16 R=CH_3



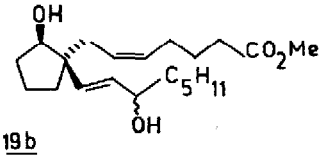
17 R=CH_3

18 R=H

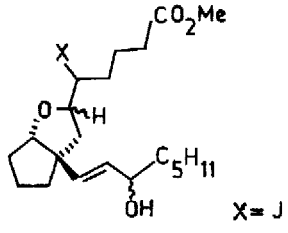
The **conjugated ketone** 9 can be easily converted to the 15-methyl derivative 16 [*ir 3475, 3005, 1740 cm^{-1}; NMR 5.52-5.62(2H, q), 5.34(2H, m), 3.90(4H, m), 3.67(3H, s), 1.25(3H, s), 0.88(3H, s); R_f 0.43(f); 88.5%*] by an equivalent amount of CH_3MgI [*ether, room temp., reverse addition*]. After deprotection and hydrolysis 17 [*ir 3475, 3005, 1745, 1740 cm^{-1}; R_f 0.55(f); 70%*] and 18 [*ir 3440, 3005, 1731, 1710 cm^{-1}; NMR 5.2-5.65(4H, m), 4.93(2H, s), 1.22 (3H, s), 0.88(3H, s); R_f 0.55(e); 80%*] respectively were formed, as a mixture of stereoisomers at C-15.



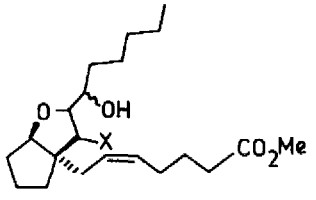
19a



19b



20 X= J



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For the preparation of F-type analogs, 12 was reduced with $NaBH_4$ [*methanol, 0°*] and the diastereoisomeric alcohols were separated by column chromatography on silica gel: 19a [R_f *0.52(e)*] and 19b [R_f *0.36(e); ir 3425, 1740 cm^{-1}; NMR 5.68(2H, m), 5.42(2H, m), 4.13(1H, q), 3.8(1H.b.t.), 3.66(3H, s), 1.88(2H, s)*].

The structures assigned to 19a and 19b were confirmed by chemical transformation. Each of the alcohols was subjected to halocyclization by Whittaker's[7] method resulting **in the iodo** ethers 20 [R_f *0.28(f); NMR 5.87(1H), 5.81(1H),5.49*

(1H), 4.15(2H), 4.2(1H), 3.85(1H), J_{13-14}=15 Hz; ^{13}C NMR 137.47, 136.26(C-14), 129.90, 130.64(C-13), 90.39(C-6), 82.60(C-9), 73.04(C-15); 58%] as the C-6 epimeric mixture and 21 *[R_f 0.68(f); NMR 5.50(2H), 4.25(1H), 4.2(2H), 3.85(1H), J_{5-6}=10.5-11 Hz; ^{13}C NMR 72.54(C-15), 58.33(C-8); 67%]* as apparently the sole isomer.

Pharmacological studies revealed that compounds 13 and 15 specifically inhibit contractions produced by $PGF_{2\alpha}$ on isolated mouse and rat uteri. An antagonistic effect on myometrial motility, in situ, was also observed during infusion of $PGF_{2\alpha}$ and compound 15 to anesthetized rats. These data and the complete block of endotoxin-induced abortion following pretreatment of the mice with compound 15, indicate that some C-8-quaternary-prostanoids can be regarded as active prostaglandin antagonists in the uterus.

References and notes

1. A similar synthesis was presented on a slide by Prof.H.Vorbrüggen at the "Symposium on the Chemistry and Biochemistry of Prostanoids" held at the University of Salford, jul 10-14, 1978.
2. T.Toru, et al., Tetrahedron Letters, 4087 (1976).; E.J.Corey, H.S.Sachdev, J.Am.Chem.Soc., 95, 8483 (1973); S.Kurozumi, et al., Tetrahedron Letters, 4091 (1976); W.Bartmann, et al., Tetrahedron Letters, 3879 (1976).
3. A.Barco, S.Benetti, G.P.Pollini, Synthesis, 353 (1974).
4. NMR spectra were taken on Varian XL-100 instrument in $CDCl_3$ solution using Me_4Si as internal standard (δ, ppm).
5. J.J.Bloomfield, S.L.Lee, J.Am.Chem.Soc., 32, 3919 (1967).
6. Eluents: Ph-EtOAc 3:1 (*a*); Ph-EtOAc-MeOH 5:1:0.5 (*b*); n-Hexan-EtOAc 1:1 (*c*); n-Hexan-EtOAc 3:1 (*d*);n-Hexan-EtOAc-AcOH 5:5:0.1 (*e*); n-Hexan-EtOAc 2:1 (*f*).
7. N.Whittaker, Tetrahedron Letters, 2805 (1977).

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