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SYNTHESIS OF 10,10-DIMETHYLPROSTAGLANDIN E_1[1]

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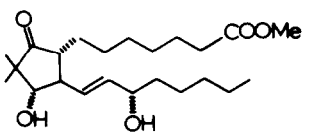
The synthesis of 8-methyl-PGC_2[2] and 12-methyl-PGA_2[3] and -PGE_2[4] has been described recently. Degradation to biological inactive PGB-derivatives is impossible in these compounds.

We now wish to report the synthesis of the 10,10-dimethyl-PGE_1 analog 1, which cannot be deactivated easily by transformation into prostaglandins of the cyclopentenone type and might afford more sustained biological potency.



1

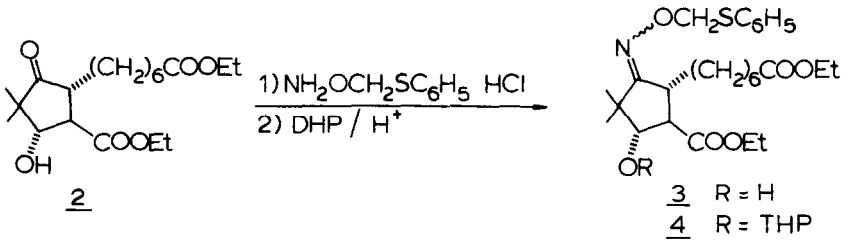
Reaction of the previously described intermediate 2[5] with phenylthiomethoxyamine hydrochloride[6] in pyridine afforded oxime 3 as a 1:1 mixture of syn and anti isomers [ir 3500, 1720, 1570; nmr 7.6 - 7.2 (m, aromatic H), 5.49 and 5.47 (s, $OC\underline{H}_2S$), 3.9 (m, $C\underline{H}OH$)][7]. The alcohol function in 3 was subsequently converted into a tetrahydropyranyl ether (4) with dihydropyran and a catalytic amount of p-toluenesulfonic acid. Reduction of 4 with excess sodium borohydride in ethanol at room temperature produced the C_1-alcohol 5 instead of the desired alcohol 6. Considering selective sodium borohydride reduction of the ester at the ring in related compounds[6,8], this result was rather unexpected. Hydrolysis of the less hindered ester function[9] in 4 with one equivalent of potassium

hydroxide in aqueous ethanol gave potassium salt 7. Subsequent reduction with lithium borohydride in diglyme at 100°C yielded the hydroxy carboxylate 8 which was converted into the methyl ester 9 [32% from 2, ir 3450, 1720, 1570] with methyl iodide in HMPT[10]. Moffatt oxidation of 9 with 1-cyclohexyl-3-(2-morpholineethyl)carbodiimide metho-p-toluenesulfonate[6] gave aldehyde 10. Reaction with the sodium derivative of dimethyl 2-oxoheptylphosphonate and subsequent reduction of the resulting enone 11 [ir 1720, 1690, 1660, 1620, 1580] with zinc borohydride in dimethoxyethane, followed by hydrolysis of the tetrahydropyranyl ether in 12 with acetic acid in aqueous tetrahydrofuran gave a mixture of the C_{15}-epimers 13 [35% from 9; R_f= 0.20 (tlc: SiO_2, ethyl acetate/cyclohexane 1:1); ir 3500, 1720, 1580; nmr 7.5 - 7.1 (m, aromatic H), 5.50 (m, $\underline{H}_{13}$ and $\underline{H}_{14}$), 5.44 and 5.40 (s, $OC\underline{H}_2S$), 4.00 (m, $\underline{H}_{15}$), 3.63 (s, $COOC\underline{H}_3$), 3.34 and 3.30 (d, J= 9.5, H_{11})] and 16 [32% from 9; R_f= 0.25; ir 3500, 1720, 1580; nmr 7.5 - 7.1 (m, aromatic H), 5.55 (m, $\underline{H}_{13}$ and $\underline{H}_{14}$), 5.44 and 5.40 (s, $OC\underline{H}_2S$), 4.08 (m, $\underline{H}_{15}$), 3.63 (s, $COOC\underline{H}_3$), 3.35 and 3.30 (d, J= 10, $\underline{H}_{11}$)] which were separated by column chromatography.

The more polar isomer was tentatively assigned the 15α-configuration (13) by analogy with the chromatographic behaviour of similar derivatives of natural prostaglandins.

Treatment of 13 with HgO, $HgCl_2$ and potassium acetate in acetic acid[6] produced the acetoxymethyl oxime 14 [nmr 5.60 (m, $OC\underline{H}_2O$), 2.04 (s, $COC\underline{H}_3$)]. Hydrolysis with potassium carbonate in aqueous methanol gave the unsubstituted oxime 15 [65% from 13; nmr 5.6 (m, $\underline{H}_{13}$ and $\underline{H}_{14}$), 4.10 (m, $\underline{H}_{15}$)]. Nitrosation[6] of 15 with sodium nitrite in aqueous acetic acid afforded 1 in 40% yield [R_f= 0.37 (SiO_2, ethyl acetate); ir 3500, 1720, 1600; nmr 5.63 (m, $\underline{H}_{13}$ and $\underline{H}_{14}$), 4.16 (m, $\underline{H}_{15}$), 3.65 (s, $COOC\underline{H}_3$), 3.59 (d, J= ca. 8, $\underline{H}_{11}$), 1.11 (s, $C\underline{H}_3$), 0.92 (s, $C\underline{H}_3$), 0.89 (t, J= 7, $C\underline{H}_3$); m/e 378 (M-18)].

Treatment of the oxime 15 with $TiCl_3$[11] for 16 hours at room temperature, however, gave compound 1 in more than 90% yield. The C_{15}-epimer 19 [60% from 16; R_f= 0.47; ir 3500, 1720, 1600; nmr 5.66 (m, $\underline{H}_{13}$ and $\underline{H}_{14}$), 4.16 (m, $\underline{H}_{15}$), 3.65 (s, $COOC\underline{H}_3$), 3.60 (d, J= 8, $\underline{H}_{11}$), 1.12 (s, $C\underline{H}_3$), 0.94 (s, $C\underline{H}_3$), 0.88 (t, J= 7, $C\underline{H}_3$); m/e 378] was prepared via 17 and 18.



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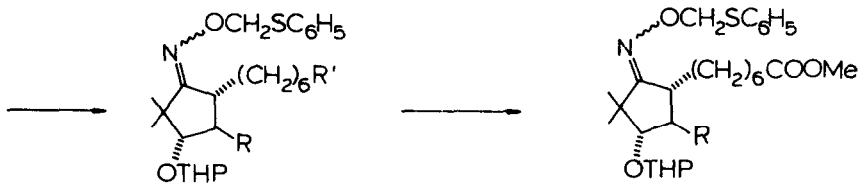
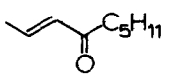
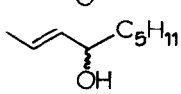
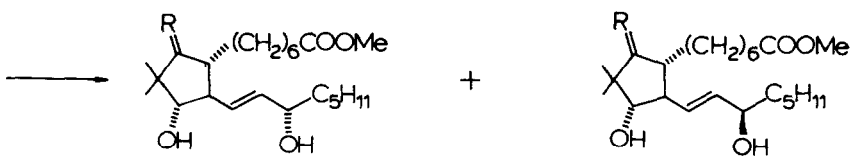
3 R = H
4 R = THP



5 R = COOEt , R'= CH_2OH
6 R = CH_2OH , R'= COOEt
7 R = COOEt , R'= COOK
8 R = CH_2OH , R'= COOK

9 R = CH_2OH
10 R = CHO
11 R = 
12 R = 



13 R = $NOCH_2SC_6H_5$
14 R = $NOCH_2OAc$
15 R = NOH
1 R = O

16 R = $NOCH_2SC_6H_5$
17 R = $NOCH_2OAc$
18 R = NOH
19 R = O

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7. All compounds are racemic. Satisfactory elemental analysis were obtained for key intermediates, ^{1}H-NMR spectra (chemical shifts are reported in ppm on the δ-scale) were obtained on a Varian HA 100 spectrometer in deutero chloroform containing tetramethylsilane as internal reference. IR spectra (cm^{-1}) were obtained in chloroform. Mass spectra were obtained with an AEI MS-9 spectrometer.
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