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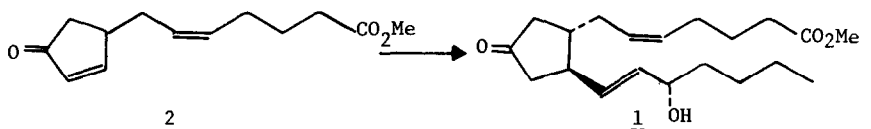
PREPARATION OF METHYL 10-OXO-15S-HYDROXYPROSTA-5E,13Z-DIENOATE

Henry C. Arndt*, Cynthia Rajani

Miles Laboratories, Inc., P.O.Box 40, Elkhart, indiana 46514

Abstract. The synthesis of methyl 10-oxo-15S-hydroxyprosta-5E,13Z-dienoate is described.

Despite the prodigious amount of research related to the natural prostaglandins and their analogs, little work has appeared concerning the synthesis of 10-oxoprostaglandins 1 [1]. Our synthetic goal was to prepare a series of 10-oxoprostanoids to evaluate their biological activity. A logical approach to this problem was to prepare a common cyclopentenone precursor 2 and utilize a copper (I) mediated conjugate addition to introduce the lower side chain (C_{13}-C_{20}) as has been done by Sih[2] and the Syntex group[3].

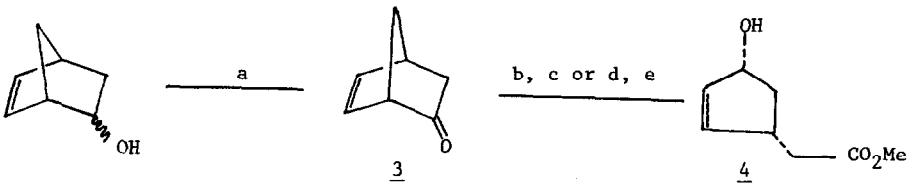


2 1

We report here the synthesis of methyl 10-oxo-15S-hydroxyprosta-5E,13Z-dienoate 1.

5-Norbornen-1-ol, selected as the starting material, was oxidized to 5-norbornen-2-one 3 by either the Collins[4] or Pfitzner-Moffatt[5] procedures. Conversion of 3 to hydroxy-ester 4 was achieved by Baeyer-Villiger oxidation-esterification (MCPBA/$NaHCO_3$/CH_2Cl_2, MeOH/5% KOH[6] or 30% H_2O_2/NaOH/Ether, CH_2N_2/Ether[7]) in 41% overall yield. 4 was transformed into aldehyde 5 by first protecting the hydroxyl group ($C_2H_5OC_2H_3$/$POCl_3$/Ether[8]) and then ester reduction (DIBAH/CH_2Cl_2/-78°C[9]). Reaction of 5 with 4-carboxybutyltriphenylphosphorane in dry DMSO[10], followed by acid hydrolysis of the protecting group (3N HCl/THF) gave a 62% yield of hydroxyacid 6. Esterification of 6 with diazomethane gave hydroxyester 7 which upon oxidation with Collins reagent[4] afforded 2 in 92% yield. Reaction of 2 with vinyl cuprate 8 [11], followed by acid hydrolysis of the C-15 protecting group (HOAc/H_2O/THF) afforded the desired 10-oxoprostanoid 1 in a 64% yield as a 1:1 mixture of diastereomers. The side chains are assumed to be trans since the organocopper species should approach the reaction site from the sterically least hindered face[14].

Acknowledgement. We wish to thank Dr. Loretta Grezzo for obtaining ^{13}C NMR data on 2 and Dr. James Kinsinger for the mass spectral analysis.



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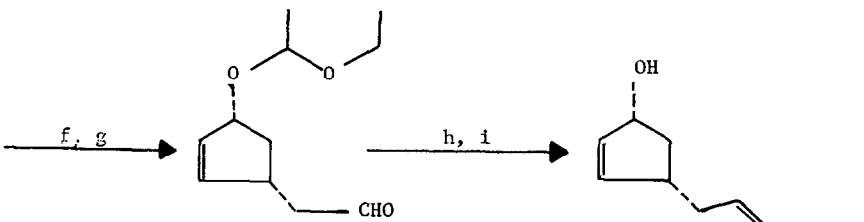
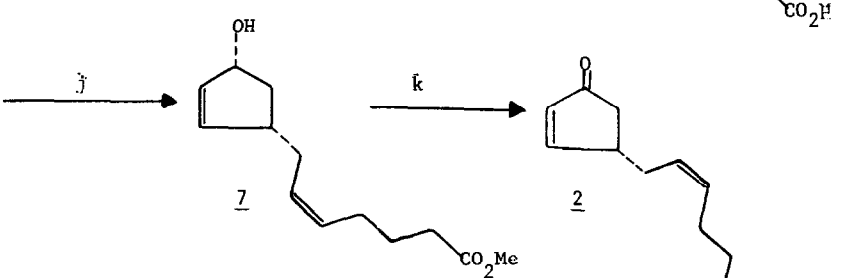
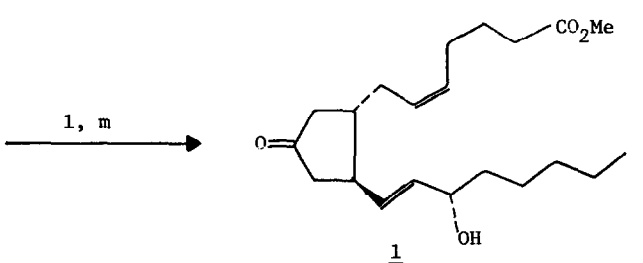


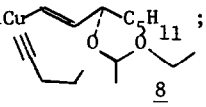
5 6



7 2



1

a) $CrO_3 \cdot PYR_2/CH_2Cl_2$ or DMSO/DCC/PYR·TFA; b) MCPBA/$NaHCO_3/CH_2Cl_2$; c) 5% KOH/MeOH or d) 30% H_2O_2/NaOH/Ether/H_2O; e) CH_2N_2/Ether; f) $C_2H_5OC_2H_3/POCl_3$/Ether; g) DIBAH/CH_2Cl_2; h) $(C_6H_5)_3PCH(CH_2)_3CO_2^-$/DMSO; i) 3N HCl/THF; j) CH_2N_2/Ether; k) $CrO_3 \cdot PYR_2/CH_2Cl_2$; l) LiCu  ; m) HOAc/THF/H_2O

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12. 2: IR($CHCl_3$) 1745 and 1724 cm^{-1}; PMR $\delta^{TMS}_{CCl_4}$ 1.2-3.1 (11H, m), 3.58 (3H, s), 5.3-5.6 (2H, m), 6.1 (1H, dd, J=2, 6 Hz), and 7.6 ppm(1H, dd, J=2, 6 Hz); CMR $\delta^{TMS}_{CDCl_3}$ 24.35, 26.33, 31.63, 33.01, 40.14, 126.66, 130.95, 133.77, 167.17, 173.35, and 209.01 ppm; MS m/e(70 ev) 222 (M^+), 141, and 82.

Diastereomer I: Rf 0.64 (1:1 v/v Hex/EtOAc); IR (CCl_4) 3540, 2950, and 1750 cm^{-1}; PMR $\delta^{TMS}_{CCl_4}$ 0.8-2.8 (25H, m), 3.70 (3H, s), 4.10 (1H, m), and 5.3-5.8 (4H, m); CMR $\delta^{TMS}_{CDCl_3}$ 13.98, 22.63, 24.84, 25.10, 26.73, 30.43, 31.80, 33.36, 37.52, 43.12, 44.16, 45.33, 45.46, 51.50, 72.51, 127.72, 130.52, 131.75, 135.33, 174.02, and 216.55 ppm; MS m/e (70ev) 350 (M^+).

Diastereomer II: Rf 0.56 (1:1 v/v Hex/EtOAc); IR (CCl_4) 3540, 2950, and 1750 cm^{-1}; PMR $\delta^{TMS}_{CDCl_3}$ 0.8-2.8 (25H,m), 3.70 (3H, s), 4.08 (1H, m), and 5.3-5.8 (4H, m); CMR $\delta^{TMS}_{CDCl_3}$ 13.98, 22.63, 24.78, 25.17, 26.73, 30.34, 31.80, 33.43, 37.46, 42.99, 44.16, 45.26, 45.46, 51.44, 72.51, 127.66, 130.52, 131.69, 135.20, 173.89, and 216.88 ppm; MS m/e (70 ev) 350 (M^+).

13. All intermediates gave satisfactory NMR, IR, and MS analysis.

14. See references 2a and 2b for similar observations in prostaglandin synthesis.

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