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SYNTHESIS OF BIS-HOMO-PROSTAGLANDINS[1]

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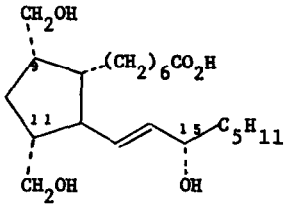
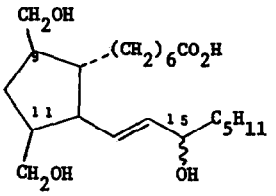
The wide spectrum of biological activity of the prostaglandins has prompted a search for more specific agents and antagonists among analogs of the natural compounds. We report here a synthesis of DL 9,11-bis-homo-prostaglandin F_1 (1)[2] and the isomer (2) with inverted stereochemistry at positions 9 and 11, by a route which defines the stereochemistry of the four cyclopentane substituents at an early stage.

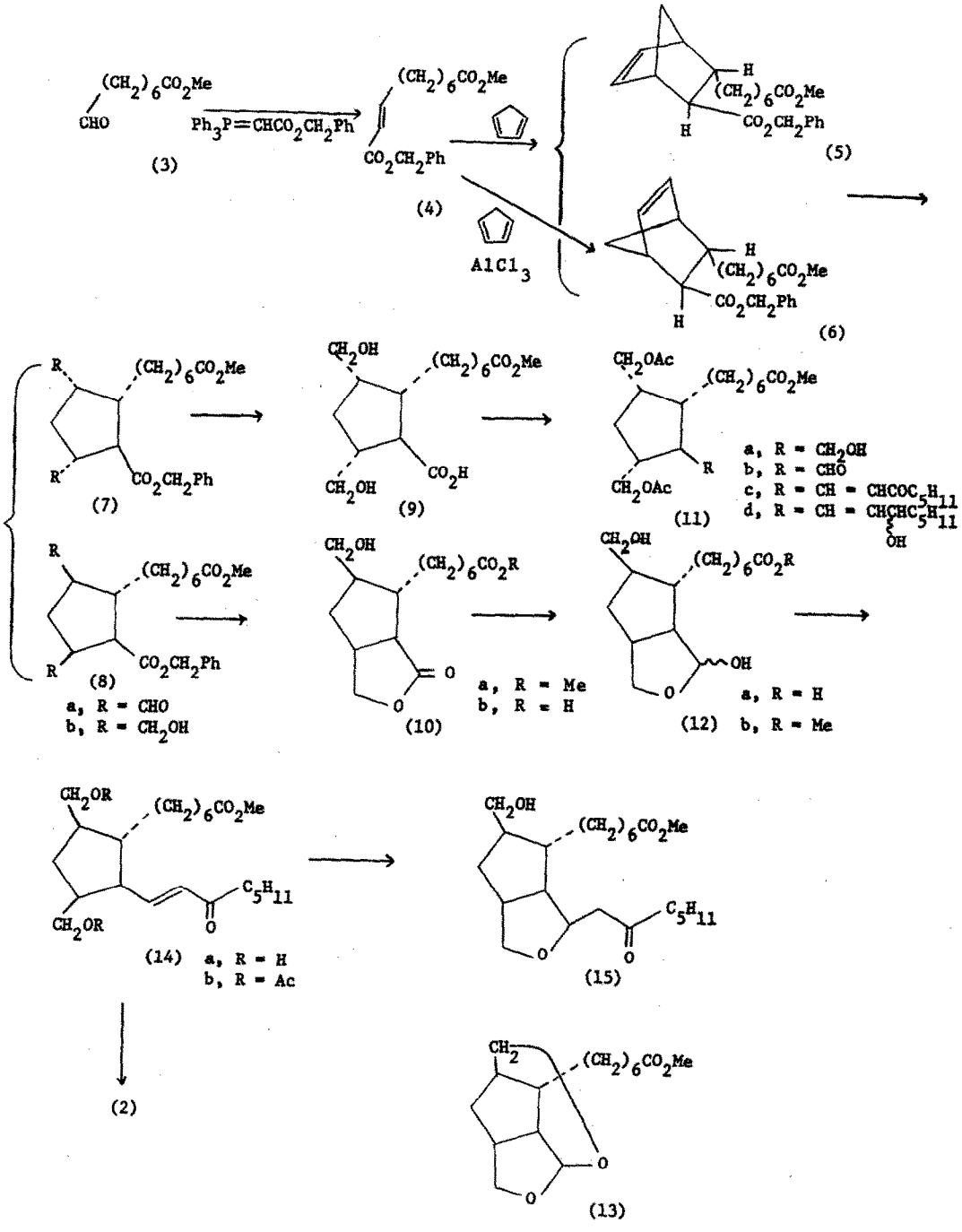


(1)



(2)

Reaction of 7-carbomethoxyheptaldehyde (3)[3] with carbobenzyloxymethylidene triphenylphosphorane gave the unsaturated diester (4) [57%; oil; trans/cis 9/1 by GLC; ν_{max} 1720, 1650 cm^{-1}; m/e 304 (M^+)].[5,6] A Diels-Alder condensation[7] of (4) with cyclopentadiene under reflux formed the bicyclic esters (5) [a sample separated by TLC had ν_{max} (film) 1730 cm^{-1}; m/e 305 ($M-C_5H_5$)] and (6) [ν_{max} (film) 1735 cm^{-1}; m/e 370 (M^+), 305 ($M-C_5H_5$)]. This mixture was oxidized[8] with osmium tetroxide and sodium periodate in aqueous tetrahydrofuran, forming the mixture [ν_{max} 1730 (sh), 1720 cm^{-1}] of dialdehydes (7a) and (8a) which was reduced with sodium borohydride in methanol-ethyl acetate to a mixture containing the dihydroxy esters (7b) [ν_{max} (film) 3310, 1720 cm^{-1}] and (8b) [ν_{max} (film) 3310, 1720 cm^{-1}], separable by TLC, together with the product of base catalyzed cyclization (10a). Hydrogenation of this mixture with palladium charcoal catalyst in ethanol cleaved the benzyl groups, the resulting lactone (10a) [ν_{max} 3410, 1765, 1725 cm^{-1}; m/e 299 (M+1), 298 (M^+)] and acid (9) [ν_{max} 3310, 1715 cm^{-1}; m/e 298 ($M-H_2O$)] were then readily


(CH2)6CO2Me
CHO
Ph3P=CHCO2CH2Ph
(3)
CO2CH2Ph
(4)
AlCl3
H
H
CO2CH2Ph
(5)
(6)
R
R
CO2CH2Ph
(7)
CH2OH
CO2H
(9)
CH2OAc
CH2OAc
(11)
a, R = CH2OH
b, R = CHO
c, R = CH = CHCOC5H11
d, R = CH = CHCHC5H11
OH
(8)
a, R = CHO
b, R = CH2OH
CO2R
O
(10)
a, R = Me
b, R = H
OH
(12)
a, R = H
b, R = Me
CH2OR
C5H11
(14)
a, R = H
b, R = Ac
(2)
(15)
CH2
(13)

separated by partition between sodium bicarbonate solution and ether. The acid (9), prepared in 35% overall yield from (3) includes the correct relative stereochemistry of the natural prostaglandins at the four substituents on the cyclopentane ring while the lactone (10) has inverted stereochemistry at two positions.

The two hydroxyl groups of the acid (9) were protected by acetylation (acetic anhydride-pyridine) and the carboxyl group converted to hydroxymethyl by reduction[9] of the mixed ethyl carbonic anhydride with sodium borohydride in methanol-ethyl acetate forming the alcohol (11a) [ν_{max} 3370 cm^{-1}; m/e 248 (M-2HOAc-H_2O)]. Oxidation of (11a) with chromium trioxide pyridine complex in dichloromethane led to the aldehyde (11b). The remaining steps in the synthesis were completed by established procedures;[10] reaction with the sodio derivative of dimethyl 2-oxoheptyl phosphonate and reduction of the resulting enone (11c) [m/e 420.2859 (M-HOAc, calc. 420.2873)] with zinc borohydride to the racemic 15α and 15β bis-homo-prostaglandin esters (11d) [m/e 411 (M-C_5H_{11}), 404 (M-HOAc-H_2O)]. The more polar (TLC, silica) isomer is tentatively assigned the 15α stereochemistry by analogy with the chromatographic behavior of the esters of the natural prostaglandins. Hydrolysis of the separated epimers (11d) with potassium hydroxide in methanol gave the required DL-15α-bis-homo-prostaglandin F_1 (1) [11% from (9); m.p. 95°; ν_{max} 3310, 1705 cm^{-1}], which was weakly active in smooth muscle relaxation assays,[11] and the inactive 15β epimer [15% from (9); gum].

For the synthesis of the isomeric bis-homo-prostaglandin (2), the required adduct (6) was formed as the sole product of a Diels-Alder reaction of the unsaturated ester (4) with cyclopentadiene in benzene catalyzed by aluminum chloride (0.5 mol). Conversion of (6) to (8a) and (8b) as described above followed by basic hydrolysis and acidification gave the lactone (10b) [33% from (3)]. Reduction with diisobutyl aluminum hydride in tetrahydrofuran formed the lactol (12a) [m/e 264 (M-2H_2O)]. Under strongly acidic work-up conditions this was rapidly converted into the ether (13)[12][δ5.33 ppm (d, J 6 Hz, OCHO)]. The ester (12b) was formed from the acid (12a) with diazomethane and reacted with the sodio derivative of dimethyl 2-oxoheptyl phosphonate in dimethylformamide, presumably forming the enone (14a) although the isolated product proved to be (15) [ν_{max} 1720 cm^{-1}; m/e 378 (M-H_2O)] resulting from the conjugate addition of a hydroxyl group to the enone system. Acetylation of (15) by heating under reflux with acetic anhydride containing trifluoroacetic acid produced (14b) [n.m.r. 6.04 ppm (d,J 16 Hz, trans olefin); m/e 480 (M^+)] in which the required enone system is regenerated. Reduction of (14b) with zinc borohydride, separation of the 15-epimers by column chromatography on silica gel and hydrolysis of ester

groups gave the DL 9β,11β,9,11-bis-homo-prostaglandins F_1 (2) [2% from (10b); gum; ν_{max} 3335, 1715 cm^{-1}] and [0.2% from (10b); gum; ν_{max} 3330, 1710 cm^{-1}].

REFERENCES AND FOOTNOTES

[1] Contribution No. 415 from the Syntex Institute of Organic Chemistry. Studies on Prostaglandins No. 12.

[2] Only one isomer of DL pairs is shown in the diagram.

[3] Prepared in quantitative yield by oxidation of 7-carbomethoxyheptanol[4] with chromium trioxide Pyridine complex.

[4] E. Schauenstein and H. Esterbauer, Fette, Siefen, Anstrichm., 70, 4 (1968).

[5] Except where noted otherwise, i.r. spectra were taken in $CHCl_3$ and n.m.r. spectra in $CDCl_3$. The n.m.r. spectra were consistent with the assigned structures. Satisfactory C and H analyses were obtained for (1), all other compounds were non-crystalline.

[6] We wish to thank Dr. L. Throop, Dr. L. Tokés and Dr. M. Maddox for the determination of physical data.

[7] Similar Diels-Alder condensations have been described by J. Katsube, H. Shimomura and M. Matsui, Agr. Biol. Chem., 35, 1828 (1971), and by P. Wlodawer, B. Samuelsson, S. M. Albonico and E. J. Corey, J. Amer. Chem. Soc., 93, 2815 (1971). We wish to thank Dr. Corey for providing details of this reaction prior to publication.

[8] R. Pappo, D. S. Allen, R. U. Lemieux and W. S. Johnson, J. Org. Chem., 21, 478 (1956).

[9] K. Ishizumi, K. Koga and S. Yamada, Chem. Pharm. Bull., 16, 492 (1968).

[10] E. J. Corey, N. M. Weinshenker, T. K. Schaaf and W. Huber, J. Amer. Chem. Soc., 91, 5675 (1969).

[11] We wish to thank Dr. A. Roszkowski for this data.

[12] The absence of hydroxyl groups in this compound is supported by the low polarity on TLC and by the i.r. spectrum which lacks absorption in the 3300 cm^{-1} region.