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SYNTHESIS OF PROSTAGLANDIN D_3

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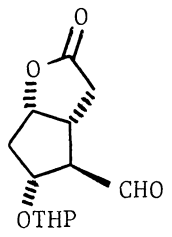
Prostaglandin D_3 has been synthesized from (-)-2-oxa-3-oxo-6-syn-formyl-7-anti-(2-tetrahydropyranyloxy)-cis-bicyclo[3,3,0]octane, a general synthetic intermediate for natural prostaglandins.

The biological activities of PGD_3 (1) have been investigated less than those of PGD_2 and PGD_1. Recently much attention has been focused on the biological activities of 1. Needleman[1] has reported that 1 is more potent and highly specific than PGD_2 in inhibitory effect on platelet aggregation. These facts prompted us a first chemical synthesis of 1 in order to examine its detailed biological activities.

The synthesis of 1 was developed starting with the crucial key intermediate 3,[2] which was prepared by Wittig reaction of the aldehyde 2 with the β-oxido ylide derived from (2S,4Z)-2-hydroxy-4-heptenyltriphenylphosphonium iodide (-78 °C for 5 min then gradually warmed up to -20 °C in 40 min, 38% yield). 3: NMR ($CDCl_3$) δ 5.00-5.65 (4H, m), 4.90 (1H, m), 4.60 (1H, m) 0.90 (3H, t); IR (film) 3430, 1770, 1440, 980 cm^{-1}. The hydroxy function in 3 was protected with a methoxypropyl unit by treatment with 2-methoxypropene to furnish 4 quantitatively. Reduction of the lactone 4 with diisobutylaluminum hydride in toluene at -78 °C afforded the lactol 5 in quantitative yield.

Transformation of 5 into the methyl ester 6 was effected by the following sequence: (1) Wittig reaction with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide in DMSO at 35 °C; (2) selective deprotection of 2-methoxypropyl unit with 0.5 M HCl in THF at 0 °C; and (3) esterification with methyl iodide in the presence of K_2CO_3 in acetone at reflux temperature (overall 56% yield). 6: NMR ($CDCl_3$) δ 5.00-5.75 (6H, m), 4.65 (1H, m), 3.60 (3H, s), 0.95 (3H, t, J=7.5 Hz); IR (film) 3440, 1740 cm^{-1}; MS m/e 348 (M^+-HOTHP). Treatment of the diol 6 with trichloroacetyl chloride and pyridine in dichloromethane at 0 °C for 30 min afforded 7 quantitatively, which was hydrolyzed with p-toluenesulfonic acid in methanol at room temperature to yield the alcohol 8 in 57% yield: NMR ($CDCl_3$) δ 5.00-5.80 (8H, m), 3.95 (1H, m), 3.60 (3H, s), 0.95 (3H, t); IR (film) 3360, 1765, 1740, 1250 cm^{-1}. The benzoate 9 was obtained by treatment of the alcohol 8 with benzoyl chloride and pyridine in dichloromethane quantitatively. Selective hydrolysis of C_9 and C_{15}-trichloroacetyl groups was achieved with K_2CO_3 in methanol at 0 °C for 10 min to give the diol 10 in 93% yield: NMR ($CDCl_3$) δ 7.20-8.10 (5H, m), 4.90-5.70 (7H, m), 3.90-4.40 (2H, m), 3.60 (3H, s), 0.90 (3H, t); IR (film) 3460, 1720, 1605, 1280 cm^{-1}.

The diol 10 was converted quantitatively to the tetrahydropyranyl ether 11 with dihydropyran in the presence of p-toluenesulfonic acid in dichloromethane. Treatment of the resulting tetrahydropyranyl ether 11 with KOH in aqueous ethanol at 45 °C for 2 h produced the hydroxy



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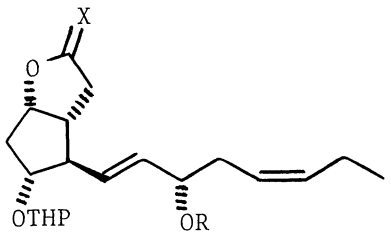
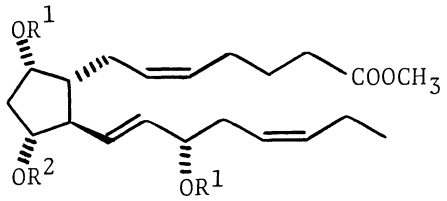
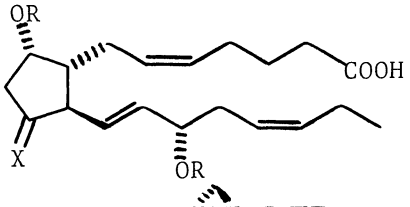


3: X=O, R=H
4: X=O, R=$C(CH_3)_2OCH_3$
5: X=H OH, R=$C(CH_3)_2OCH_3$



	R^1	R^2
6:	H	THP
7:	$COCCl_3$	THP
8:	$COCCl_3$	H
9:	$COCCl_3$	COPh
10:	H	COPh
11:	THP	COPh



12: X=OH H, R=THP
13: X=O, R=THP
1: X=O, R=H

acid 12 in 85% yield: NMR ($CDCl_3$) δ 5.00-6.10 (8H, m, olefinic and hydroxy protons), 4.40-4.80 (2H, m), 0.95 (3H, t); IR (film) 3400, 1740, 1710 cm^{-1}. Two-phase oxidation of 12 with chromic acid[3] provided the ketone 13 in 85% yield, which was hydrolyzed with 65% aqueous acetic acid to the desired PGD_3(1) in 68% yield: $[\alpha]^{25}D$ +9.22° (c 1.09, tetrahydrofuran); R_f 0.24 (chloroform-tetrahydrofuran-acetic acid 10:2:1, silica gel); NMR ($CDCl_3$) δ 4.95-5.80 (9H, m, olefinic and hydroxy protons), 4.49 (1H, m, C_9-H), 4.17 (1H, m, C_{15}-H), 2.84 (1H, dd, J=7, 12 Hz, C_{12}-H), 0.96 (3H, t, J=7.5 Hz, $-CH_3$); IR (film) 3400, 1735, 1715 cm^{-1}; MS m/e 332 (M^+-H_2O), 314 (M^+-2H_2O), 281 ($M^+-C_5H_9$); high-resolution MS calcd for $C_{20}H_{28}O_4$ (M^+-H_2O) m/e 332.19875, found 332.19888. This synthetic PGD_3(1), as well as natural PGD_3,[1c] exhibited the same TLC behavior (several solvent systems with silica gel) as that of PGD_2. Other properties of natural PGD_3 including spectral data have not been reported.

Full biological data will be published in due course.

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References

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