Communications to the Editor

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SYNTHESIS OF 11-DEOXO-11-METHYLENE-PROSTAGLANDIN D_2 AND ITS DERIVATIVES[1)]

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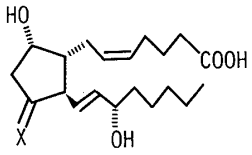
New and stable analogues of prostaglandin D_2, 11-deoxo-11-methylene-PGD_2 (4) and its 9-epi- and 9-deoxy-derivatives (5,6) were synthesized from a suitably protected prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (7).

KEYWORDS — PGD_2; 11-deoxo-11-methylene-PGD_2; 11-deoxo-11-methylene-9-epi-PGD_2; 11-deoxo-9-deoxy-11-methylene-PGD_2; PGD_2 stable analogue

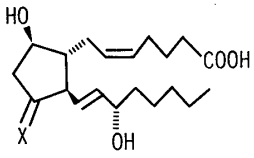
Currently, increasing interest has been focused on the unique features of prostaglandin D_2 (PGD_2, 1) and related compounds because of their inhibition of platelet aggregation,[3)] antineoplastic activity[4)] and subtle physiological properties.[5)] In spite of these interesting biological profiles, there are relatively few reports concerning the synthesis of their analogues.[3,6)] In 1983, Bundy and coworkers[3)] reported the synthesis of some PGD derivatives and their inhibition of platelet aggregation. 9-epi-PGD_2 (2) and 9-deoxy-PGD_2 (3) were found to be more potent than PGD_2 itself. In these analogues, however, the inherent instability of PGD_2 is left unsettled.

On the other hand, in the E series of prostaglandin, its methylene analogue,[7)] in which the carbonyl oxygen in the 9-position in PGE_2 is replaced by a methylene group, is one of the most promising analogues. Accordingly, we planned the synthesis of some PGD_2 analogues and describe herein the synthesis of 11-deoxo-11-methylene-PGD_2 (4) and its 9-epi- and 9-deoxy- derivatives (5,6) with some preliminary biological evaluations.

The common intermediate for the synthesis of these compounds was the suitably protected prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (7) which could be easily prepared from the lactone (8) in the usual way.[8)] Protection of (7) gave the silyl ether (9) ($^tBu(Ph)_2SiCl$, imidazole, DMF, 92% yield), which was then converted to the 11-



1: X=O
4: X=CH_2



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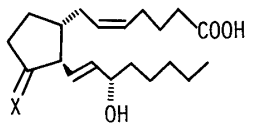

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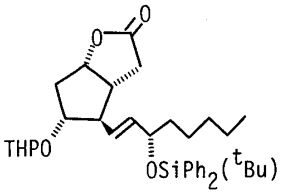

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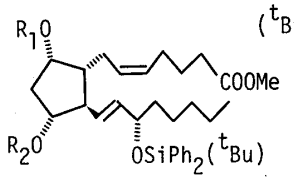
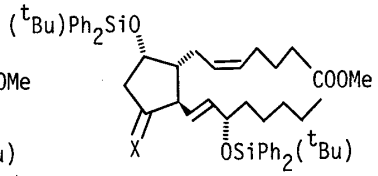
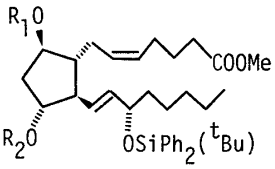


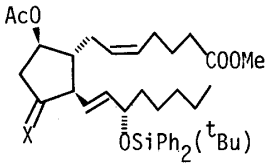
7: R_1=H, R_2=THP
9: R_1=$SiPh_2(^tBu)$, R_2=THP
10: R_1=$SiPh_2(^tBu)$, R_2=H
17: R_1=C(S)OPh, R_2=THP



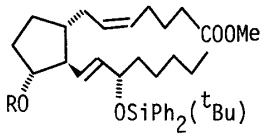
11: X=O
12: X=CH_2



13: R_1=Ac, R_2=THP
14: R_1=Ac, R_2=H



15: X=O
16: X=CH_2



18: R=THP
19: R=H

THP=tetrahydropyran-2-yl

alcohol (10) (AcOH-H_2O-THF, 70°C, 78% yield). PCC-Oxidation of 10 gave the PGD_2 derivative (11),[9] which was purified by column chromatography over SiO_2 (97.5% yield).

Crucial methylenation of 11 was effected by the addition of Zn-CH_2Br_2-$TiCl_4$ reagent[10] to a stirred solution of 11 in CH_2Cl_2 at room temperature. After the usual work-up, purification by SiO_2 column chromatography gave the pure methylene compound (12)[11] as a yellow oil (54.8% yield).

Deprotection of 12 ($^nBu_4N^+F^-$, THF, 25°C, 68% yield) followed by ester hydrolysis (KOH, MeOH, H_2O, 60% yield) furnished the title compound (4)[12] as a colorless oil.

For the synthesis of the 9-epi-PGD_2 derivative (5), the inversion of the 9α-alcohol in 7 to the β-configuration was effectively carried out using a method we developed recently.[13] The mesylation of 7 (Et_3N, $MeSO_2Cl$, CH_2Cl_2, 0°C) followed by reaction with CsOAc and 18-crown-6 in refluxing benzene[13] afforded the inverted acetate (13) in 74% yield from 7. Cleavage of the THP ether gave the corresponding alcohol (14) in 80% yield (AcOH-H_2O-THF, 70°C), which was subsequently oxidized to the ketone (15)[14] (PCC, CH_2Cl_2, quantitative yield). Methylenation of 15 was conducted as described above to give 16[15] in 47% yield. Sequential deprotection of 16 provided the second analogue, 11-deoxy-11-methylene-9-epi-PGD_2 (5),[16] in 27% yield from 16 as a colorless oil.

For the synthesis of the third target (6), the 9α-alcohol (7) was converted to the 9α-thionocarbonate (17) (PhOC(S)Cl, DMAP, CH_3CN), which was then treated with excess $^nBu_3SnH$ (AIBN, toluene, reflux, 0.5 h) to give the 9-deoxy compound (18)[17] in 73% yield from 7. Through the same sequence of reactions (9→4) shown above, 18 was successfully transformed to 9-deoxy-11-deoxo-11-methylene-PGD_2 (6)[18] via the alcohol (19) in 37% overall yield from 18.

To our disappointment, none of the compounds described here potently inhibited platelet aggregation or distinctively inhibited L5178Y cell growth in concentrations up to 50μg/ml.[19] However, 11-deoxo-11-methylene-PGD_2 (4) could be promising for the production of antibody having a specific affinity to PGD_2 or PGJ_2. This is currently under investigation in this course.

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REFERENCES AND NOTES

1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.
2) Visiting scientist in 1984 from Yamasa Shoyu Ltd., Choshi, Chiba, Japan.
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6) For example, see M.Hayashi and T.Tanouchi, J. Org. Chem., 38, 2115 (1973); S.M.Ali, M.A.W.Finch, S.M.Roberts and R.F.Newton, J. Chem. Soc., Chem. Commun., 1979, 679.
7) For example, see F.A.Kimball, G.L.Bundy, A.Roberts, and J.R.Weeks, Prostaglandins, 17, 657 (1979).
8) i) DIBALH, toluene, -78°C, ii) $Ph_3PCH_2(CH_2)_3COOH\ Br^-$, t-BuOK, benzene, r.t., iii) CH_2N_2, ether, 75% overall yield.
9) 11: IR, ν_{max}(neat) cm^{-1}: 2920, 1735, 1105. ^{1}H-NMR($CDCl_3$) δ(ppm): 7.79-7.22 (m, 2OH), 5.68, 5.06 (m, 4H), 4.44 (m, 1H), 4.11 (q, 1H, J=7 Hz), 3.61 (s, 3H), 2.79 (dd, 1H, J=7 & 12 Hz). MS (m/z): 785 ($M^+-{}^tBu$).
10) L.Lombardo, Tetrahedron Lett., 23, 4293 (1982).
11) 12: ^{1}H-NMR($CDCl_3$) δ(ppm): 7.79-7.22 (m, 2OH), 5.68-5.03 (m, 4H), 4.78, 4.70 (each s, 2H, methylene), 4.28-4.06 (m, 2H), 3.64 (s, 3H), 2.98 (m, 1H).
12) 4: IR ν_{max}(neat) cm^{-1}: 3380, 2930, 1705. ^{1}H-NMR($CDCl_3$) δ(ppm): 5.63-5.37 (m, 4H), 4.98, 4.85 (each s, 2H, methylene), 4.27 (t, 1H, J=4 Hz), 4.20 (q, 1H, J=7 Hz), 2.87 (dd, 1H, J=7 & 12 Hz).
13) Y.Torisawa, H.Okabe, and S.Ikegami, Chem. Lett., 1984, 1555.
14) 15: IR ν_{max}(neat) cm^{-1}: 2930, 1935, 1240.
15) 16: ^{1}H-NMR($CDCl_3$) δ(ppm): 5.51-5.17 (m, 4H), 4.83, 4.59 (each s, 2H).
16) 5: IR ν_{max}(neat) cm^{-1}: 3350, 2930, 1705. ^{1}H-NMR($CDCl_3$) δ(ppm): 5.63-5.41 (m, 4H), 4.92, 4.78 (each s, 2H), 3.94 (q, 1H, J=8 Hz), 2.65 (m, 1H).
17) 18: IR ν_{max}(neat) cm^{-1}: 2920, 1730, 1105.
18) 6: IR ν_{max}(neat) cm^{-1}: 3350, 2930, 1705. ^{1}H-NMR($CDCl_3$) δ(ppm): 5.59-5.35 (m, 4H), 4.88-4.73 (each s, 2H), 4.19 (q, 1H, J=8 Hz).
19) Biological assay was carried out by H.Machida and Y.Watanabe at Yamasa Shoyu Ltd.

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