
Communications to the Editor

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SYNTHESIS OF 11-DEOXO-11-METHYLENE-PROSTAGLANDIN D₂ AND ITS DERIVATIVES¹⁾

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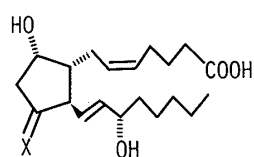
New and stable analogues of prostaglandin D₂, 11-deoxo-11-methylene-PGD₂ (4) and its 9-epi- and 9-deoxy-derivatives (5,6) were synthesized from a suitably protected prostaglandin F_{2α} (PGF_{2α}) (7).

KEYWORDS — PGD₂; 11-deoxo-11-methylene-PGD₂; 11-deoxo-11-methylene-9-epi-PGD₂; 11-deoxo-9-deoxy-11-methylene-PGD₂; PGD₂ stable analogue

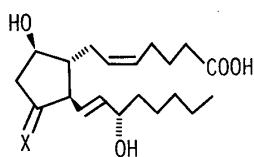
Currently, increasing interest has been focused on the unique features of prostaglandin D₂ (PGD₂, 1) and related compounds because of their inhibition of platelet aggregation,³⁾ antineoplastic activity⁴⁾ and subtle physiological properties.⁵⁾ In spite of these interesting biological profiles, there are relatively few reports concerning the synthesis of their analogues.^{3,6)} In 1983, Bundy and coworkers³⁾ reported the synthesis of some PGD derivatives and their inhibition of platelet aggregation. 9-epi-PGD₂ (2) and 9-deoxy-PGD₂ (3) were found to be more potent than PGD₂ itself. In these analogues, however, the inherent instability of PGD₂ 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 PGE₂ is replaced by a methylene group, is one of the most promising analogues. Accordingly, we planned the synthesis of some PGD₂ analogues and describe herein the synthesis of 11-deoxo-11-methylene-PGD₂ (4) and its 9-epi- and 9-deoxy- derivatives (5,6) with some preliminary biological evaluations.

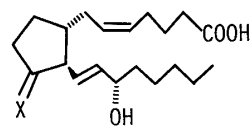
The common intermediate for the synthesis of these compounds was the suitably protected prostaglandin F_{2α} (PGF_{2α}) (7) which could be easily prepared from the lactone (8) in the usual way.⁸⁾ Protection of (7) gave the silyl ether (9) (^tBu(Ph)₂SiCl, imidazole, DMF, 92% yield), which was then converted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



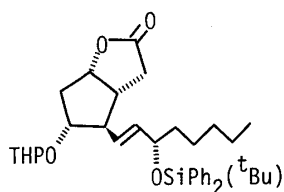
1: X=O
4: X=CH₂



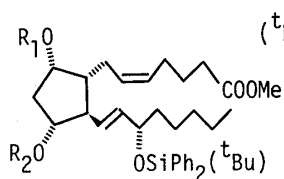
2: X=O
5: X=CH₂



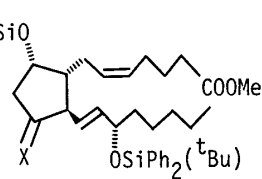
3: X=O
6: X=CH₂



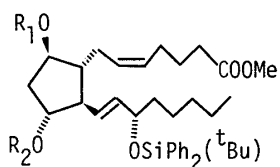
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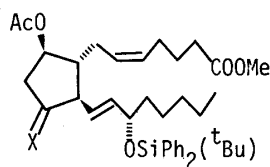
7: R₁=H, R₂=THP
9: R₁=SiPh₂(^tBu), R₂=THP
10: R₁=SiPh₂(^tBu), R₂=H
17: R₁=C(S)OPh, R₂=THP



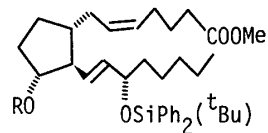
11: X=O
12: X=CH₂



13: R₁=Ac, R₂=THP
14: R₁=Ac, R₂=H



15: X=O
16: X=CH₂



18: R=THP
19: R=H

THP=tetrahydropyran-2-yl

alcohol (10) (AcOH-H₂O-THF, 70°C, 78% yield). PCC-Oxidation of 10 gave the PGD₂ derivative (11),⁹⁾ which was purified by column chromatography over SiO₂ (97.5% yield).

Crucial methylenation of 11 was effected by the addition of Zn-CH₂Br₂-TiCl₄ reagent¹⁰⁾ to a stirred solution of 11 in CH₂Cl₂ at room temperature. After the usual work-up, purification by SiO₂ column chromatography gave the pure methylene compound (12)¹¹⁾ as a yellow oil (54.8% yield).

Deprotection of 12 (ⁿBu₄N⁺F⁻, THF, 25°C, 68% yield) followed by ester hydrolysis (KOH, MeOH, H₂O, 60% yield) furnished the title compound (4)¹²⁾ as a colorless oil.

For the synthesis of the 9-epi-PGD₂ 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 (Et₃N, MeSO₂Cl, CH₂Cl₂, 0°C) followed by reaction with CsOAc and 18-crown-6 in refluxing benzene¹³⁾ afforded the inverted acetate (13) in 74% yield from 7. Cleavage of the THP ether gave the corresponding alcohol (14) in 80% yield (AcOH-H₂O-THF, 70°C), which was subsequently oxidized to the ketone (15)¹⁴⁾ (PCC, CH₂Cl₂, quantitative yield). Methylenation of 15 was conducted as described above to give 16¹⁵⁾ in 47% yield. Sequential deprotection of 16 provided the second analogue, 11-deoxy-11-methylene-9-epi-PGD₂ (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, CH₃CN), which was then treated with excess ⁿBu₃SnH (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-deoxy-11-methylene-PGD₂ (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 50 μg/ml.¹⁹⁾ However, 11-deoxy-11-methylene-PGD₂ (4) could be promising for the production of antibody having a specific affinity to PGD₂ or PGJ₂. 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.
- 3) G.L.Bundy, D.R.Morton, D.C.Peterson, E.E.Nishizawa, and W.L.Miller, J. Med. Chem., **26**, 790 (1983).
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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) $\text{Ph}_3\text{PCH}_2(\text{CH}_2)_3\text{COOH Br}^-$, $t\text{-BuOK}$, benzene, r.t., iii) CH_2N_2 , ether, 75% overall yield.
- 9) 11: IR ν_{max} (neat) cm^{-1} : 2920, 1735, 1105. ^1H -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 ($\text{M}^+ - t\text{Bu}$).
- 10) L.Lombardo, Tetrahedron Lett., **23**, 4293 (1982).
- 11) 12: ^1H -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. ^1H -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: ^1H -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. ^1H -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. ^1H -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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