

# Synthesis and antiviral activity of prostaglandin-J<sub>1</sub> methyl ester

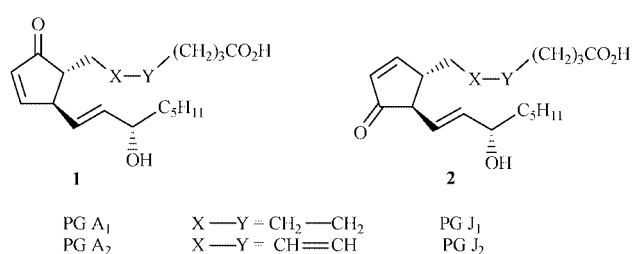
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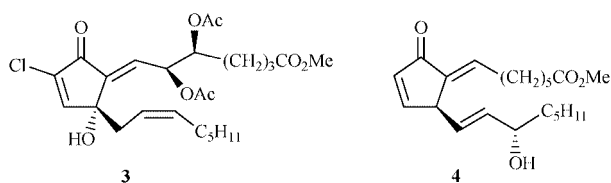
A prostaglandin-F<sub>1α</sub> methyl ester derivative (**12**) possessing three different protecting groups on the hydroxy units was prepared so as to allow selective removal of the group attached to the 11-OH group. Compound (**12**) was converted into prostaglandin-J<sub>1</sub> methyl ester (**16**) in two steps (77% overall yield). Prostaglandin-J<sub>1</sub> methyl ester showed potent activity against Sendai virus.



The synthesis of prostaglandins was investigated in many academic and industrial laboratories in the 1970's.<sup>1</sup> Much of this research was aimed at the preparation of prostaglandins D, E, F, I and analogues, due to the multi-faceted biological activity of these natural products. At that time, less attention was paid to the synthesis of the cyclopentenone prostaglandins PG-A's (**1**) and PG-J's (**2**).

While, in general, chemical instability and biological side effects prevented the vast majority of prostaglandins and analogues (prostanoids) being used in the clinic, nevertheless several prostaglandin-E and -F mimetics found medical applications as antithrombotic, abortifacient, antihypertensive and antiulcer agents.<sup>2</sup>

A marked elevation of interest in the cyclopentenone prostaglandins was generated by the isolation of the punaglandins (**3**) and the discovery that these compounds, as well as closely-related compounds such as  $\Delta^7$ -prostaglandin-A<sub>1</sub> methyl ester (**4**), displayed antitumour properties and may control adipogenesis and osteogenesis.<sup>3</sup>

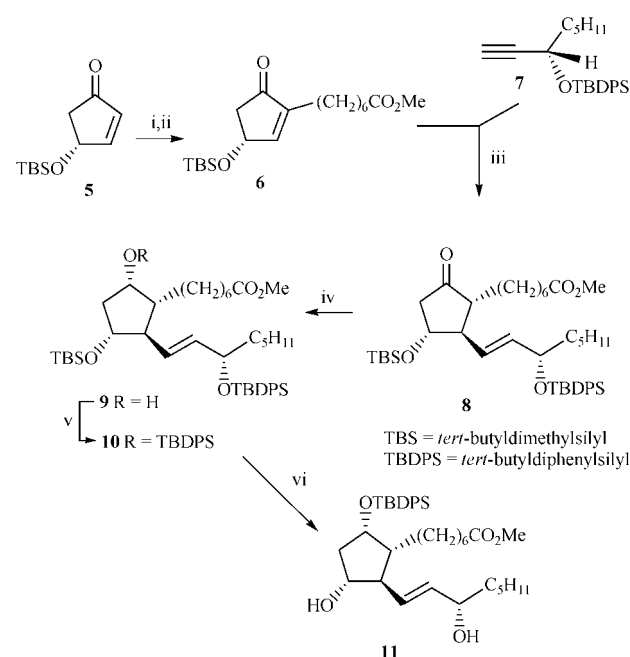


Recently, Santoro *et al.* reported potent antiviral activities of prostaglandins-A<sub>1</sub>, -A<sub>2</sub> and -J<sub>2</sub>.<sup>4</sup> The wide-ranging antiviral activity of the natural cyclopentenone prostaglandins was attributed to two factors. First prostaglandins of the A- and J-series induce the synthesis of cytoprotective heat-shock proteins *via* activation of the heat shock transcription factor (HSF) type 1. Secondly, the same compounds down-regulate transcription factors NF-kappa B (NF-kB), known to be involved in the transcription of viral DNA.

It had been shown that antiviral activity increased in the order PG-A<sub>2</sub> < PG-A<sub>1</sub> < PG-J<sub>2</sub> (Table 1). It had also been shown that formation of the methyl ester did not ameliorate

biological activity. Hence we set out to prepare PG-J<sub>1</sub> methyl ester, a compound that has not been prepared previously, to our knowledge.

Thus the enone (*R*)-(**5**) was converted into the ketoester (*R*)-(**6**) using the methodology developed by Johnson and co-workers (Scheme 1).<sup>5</sup> Treatment of enone (**6**) with protected

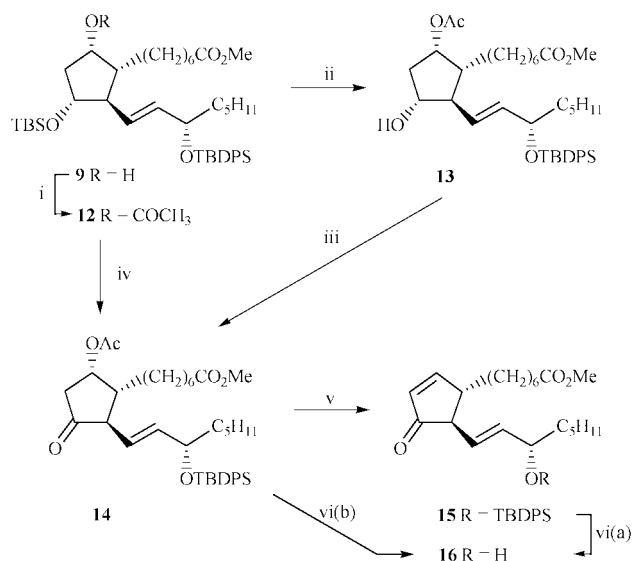


**Scheme 1** Reagents and conditions: i) I<sub>2</sub>, pyridine-CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 97%; ii) H<sub>2</sub>C=CH-(CH<sub>2</sub>)<sub>4</sub>CO<sub>2</sub>Me, 9-BBN-H, Cs<sub>2</sub>CO<sub>3</sub>, (dppf)PdCl<sub>2</sub> (cat.), H<sub>2</sub>O, THF-DMF, 0 °C, 74%; iii) Cp<sub>2</sub>Zr(H)Cl, (7), MeLi, CuCN, THF-ether, -78 °C, 73%; iv) L-Selectride®, THF, -78 °C, 85%; v) TBDPSCl, imidazole, DMF, 86%; vi) MeOH-CCl<sub>4</sub> (1 : 1), sonic bath, 91%.

(*S*)-octyn-3-ol (**7**) (prepared by enzyme-catalysed transesterification of racemic oct-1-yn-3-ol followed by silylation) gave the coupled product (**8**) in 73% yield.<sup>6</sup> Stereoselective reduction of the ketone moiety (using L-Selectride®) gave the alcohol (**9**) which when protected as the *tert*-butyldiphenylsilyl ether afforded the fully protected triol (**10**).

Attempts to cleave the TBS-ether linkage in compounds (**10**) selectively, using a variety of reagents, were unsuccessful.<sup>7</sup> However, sonication of compound (**10**) in a 1 : 1 mixture of methanol and carbon tetrachloride<sup>8</sup> furnished the mono-silylated compound (**11**) in 91% yield. Unfortunately regio-selective *O*-silylation of the latter compound could not be accomplished; treatment of the diol (**11**) with one equivalent of *tert*-butyldiphenylchlorosilane and imidazole in DMF gave equal amounts of 11- and 15-silylated products in 93% yield.

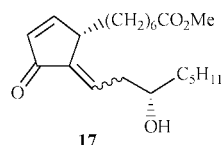
We surmised that the root-cause of the problem resulting in the lack of selective deprotection of the trisilylated compound (**10**) was the bulk of the TBDPS unit attached to the oxygen atom at C-9. Therefore the di-silyl compound (**9**) was converted into the acetate (**12**) (Scheme 2). Subsequent treatment of (**12**)



**Scheme 2** Reagents and conditions: i)  $\text{Ac}_2\text{O}$ , DMAP, pyridine, 92%; ii)  $\text{CH}_3\text{CO}_2\text{H}$ –THF– $\text{H}_2\text{O}$  (3:1:1), 48 h, room temp., 79%; iii) Dess–Martin reagent,  $\text{CH}_2\text{Cl}_2$ , room temp., 89%; iv) Jones' reagent, KF, acetone, 0 °C, 87%; v)  $\text{NaHCO}_3$ , MeOH, room temp., 82%; vi) aq. HF (40% w/w),  $\text{CH}_3\text{CN}$ , –20 °C, (a): 77% yield, (b): 88% yield.

with a mixture of acetic acid, THF and water gave compound (13) (79%) as the only identifiable product. Oxidation of this compound with Dess–Martin periodinane<sup>9</sup> gave the PG- $\text{D}_1$  derivative (14) in 89% yield. Alternatively, oxidation of diester (12) with KF in Jones' reagent ( $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ )<sup>10</sup> provided the  $\beta$ -acetoxyketone (14) directly in 87% yield. Thereafter treatment of the  $\beta$ -acetoxyketone with sodium hydrogen carbonate in methanol afforded the desired cyclopentenone (15) in 82% yield.

Attempted desilylation of the enone (15) with *tert*-butoxide in DMF<sup>11</sup> or with tetra-*n*-butylammonium fluoride buffered with acetic acid<sup>12</sup> led to the formation of PG- $\text{J}_1$  methyl ester (16) together with the inseparable isomeric compound (17).



However treatment of the enone (15) with 40% aqueous hydrogen fluoride in acetonitrile at –20 °C gave the desired product (16) cleanly in 77% yield. Gratifyingly, when the acetate (14) was reacted under the same conditions, PG- $\text{J}_1$  methyl ester (16) was obtained as the sole product in 88% yield.

In the biological tests PG- $\text{J}_1$  methyl ester showed potent, sub-micromolar activity against Sendai 37RC virus (Table 1). The mechanism of action is unlikely to be specific to Sendai virus; related studies into the antiviral activity of various prostaglandin analogues are on-going and will be reported shortly.

**Table 1** Activity of some prostaglandins against Sendai virus

Compound	Activity $\text{ID}_{50}$ ( $\mu\text{M}$ ) <sup>a</sup>
PG- $\text{A}_2$	3.0
PG- $\text{A}_1$	1.5
PG- $\text{J}_2$	1.0
PG- $\text{J}_1$ methyl ester	0.5

<sup>a</sup>  $\text{ID}_{50}$ : concentration of test compound necessary to reduce virus load by 50%.

## Experimental

### (13E,15S)-15-Hydroxy-11-oxoprostano-9,13-dien-1-oic acid methyl ester (16)<sup>†</sup>

A degassed (argon) solution of compound (14) (17 mg) in anhydrous acetonitrile (1.7 ml) was cooled to –20 °C and treated with an aqueous solution of hydrofluoric acid (40% w/w, 0.22 ml). After stirring for 9 h at –20 °C, ethyl acetate (10 ml) and sodium hydrogen carbonate (8% aqueous solution, 30 ml) were added. The organic layer was separated and the aqueous solution washed with ethyl acetate (15 ml). The combined organic extracts were washed with sodium hydrogen carbonate (8% aqueous solution, 2 × 20 ml). The aqueous extracts were back-extracted with ethyl acetate (2 × 20 ml). The organic extracts were combined and dried ( $\text{MgSO}_4$ ). Filtration and evaporation of the solvent gave a crude product which was purified by chromatography over silica [eluent ethyl acetate in hexane (2:3)] to give the title compound (16) (8.1 mg, 88%) as a colourless oil.  $\nu_{\text{max}}$  (neat) 3590, 1730, 1700, 1585  $\text{cm}^{-1}$ .  $[\alpha]_{\text{D}}^{25}$  91.4 (*c* 0.7,  $\text{CHCl}_3$ ).  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 0.88 (3H, t, *J* 7.0,  $\text{CH}_2\text{CH}_3$ ), 1.18–1.66 (19H, m, 9 ×  $\text{CH}_2$  and OH), 2.31 (2H, t, *J* 7.5,  $\text{CH}_2\text{CO}$ ), 2.62 (1H, dd, *J* 2.75 and 7.1, H-12), 2.75 (1H, m, H-8), 3.67 (3H, s,  $\text{OCH}_3$ ), 4.10 (1H, dt, *J* 6.5 and 6.5, H-15), 5.57 (1H, dd, *J* 7.1 and 15.4, H-13), 5.69 (1H, dd, *J* 6.5 and 15.4, H-14), 6.14 (1H, dd, *J* 2.2 and 5.6, H-10), 7.59 (1H, dd, *J* 2.2 and 5.6, H-9).  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 13.95 ( $\text{CH}_3$ ), 22.57, 24.79, 25.06, 27.21, 28.91, 29.23, 31.72, 33.95, 33.96, 37.07 (all  $\text{CH}_2$ ), 48.22 ( $\text{OCH}_3$ ), 51.45, 55.23, 72.67, 127.14, 132.49, 136.93, 166.71 (all CH), 174.20, 208.88 (C=O). Found (CI): ( $\text{M} + \text{NH}_4$ )<sup>+</sup> 368.27930.  $\text{C}_{21}\text{H}_{38}\text{NO}_4$  requires  $\text{M}^+$  368.28008.

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## Notes and references

<sup>†</sup> The IUPAC name for 16 is methyl 7-[(1E,3S)-oct-1-enyl]-4-oxocyclopent-2-en-1-yl]heptanoate.

- S. M. Roberts and F. Scheinmann, *New Synthetic Routes to Prostaglandins and Thromboxanes*, Academic Press, London, 1982.
- P. W. Collins and S. W. Djuric, *Chem. Rev.*, 1993, **93**, 1533.
- M. A. Tius, H. Hu, J. K. Kawakami and J. Busch-Petersen, *J. Org. Chem.*, 1998, **63**, 5971.
- M. G. Santoro, *Trends Microbiol.*, 1997, **5**, 276; A. Rossi, G. Elia and M. G. Santoro, *Proc. Natl. Acad. Sci. U.S.A.*, 1997, **94**, 746; M. G. Santoro, *Leukotrienes*, 1998, 95; A. Rossi, G. Elia and M. G. Santoro, *J. Biol. Chem.*, 1998, **273**, 1; A. De Marco, A. Caratolli, C. Rozera, D. Fortini, C. Giorgi, G. Belardo, C. Amici and M. G. Santoro, *Eur. J. Biochem.*, 1998, **256**, 334.
- C. R. Johnson and M. P. Braun, *J. Am. Chem. Soc.*, 1993, **115**, 11014; C. R. Johnson, J. P. Adams, M. P. Braun, C. B. B. Senanayake, P. M. Wovkulichand, M. R. Uskokovic, *Tetrahedron Lett.*, 1992, **33**, 917.
- M. Schlosser and J. Hartmann, *Angew. Chem., Int. Ed. Engl.*, 1973, **85**, 544; B. H. Lipshutz, in *Organometallics in Synthesis - A Manual*, ed. M. Schlosser, Wiley and Sons, New York, 1994, p. 319.
- Conditions reported to cleave TBS ethers in the presence of TBDPS ethers include  $\text{CH}_3\text{CO}_2\text{H}$ –THF– $\text{H}_2\text{O}$  (3:1:1);  $^t\text{BuOK}$ –DMF;  $\text{HCl}$  (2 M)–THF;  $\text{LiCl}$ – $\text{H}_2\text{O}$ –DMF. All these methods failed to desilylate selectively in the case of compound (10).
- A. S.-Y. Lee, H.-C. Yeh, M.-K. Yeh and M.-H. Tsai, *J. Chin. Chem. Soc. (Taipei)*, 1995, **42**, 919.
- D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277.
- A. J. Pearson, Y.-S. Lai, W. Lu and A. A. Pinkerton, *J. Org. Chem.*, 1989, **54**, 3882; H.-J. Liu and I.-S. Han, *Synth. Commun.*, 1985, **12**, 759.
- C. Negron, F. Vasquez and G. Calderon, *Synth. Commun.*, 1998, **28**, 3021.
- C. M. Hayward, D. Yohannes and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1993, **115**, 9346; A. B. Smith III, S. Y. Chen, F. C. Nelson, J. M. Reichert and B. A. Salvatore, *J. Am. Chem. Soc.*, 1997, **119**, 10935.