Total Synthesis of 12-Methylprostaglandin A_2

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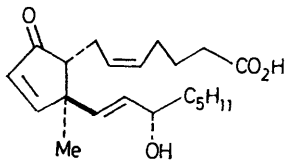
Summary An efficient synthesis of 12-methylprostaglandin A_2 from norbornadiene is described.

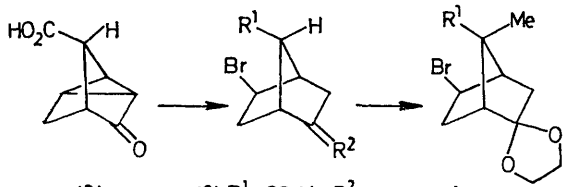
THE conversion of prostaglandin A_2(PGA_2) *via* PGC_2[1] into PGB_2 in mammalian blood constitutes one pathway for deactivation of PGA_2. In an attempt to block this mode of deactivation and produce compounds with more sustained biological potency, we have developed a synthesis of 12-methylprostaglandin A_2(12-$MePGA_2$),[2] a compound which is structurally protected against deactivation by transformation to the more stable, biologically inactive PGB_2 series. We now report the synthesis of 12-$MePGA_2$ (**1**) which is based on observations[3] that the readily available bicyclo-[2,2,1]heptane derivative (**4**)[3,4] undergoes an efficient,

highly stereoselective (>95%) alkylation with methyl iodide providing access to compound (**5**).



(1)

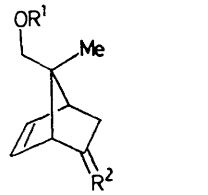
Treatment of the cyclopropyl keto acid (**2**), available in large quantities from the reaction of norbornadiene with 1·0 equiv. of paraformaldehyde in formic acid containing a trace of H_2SO_4 followed by Jones oxidation,[4] with refluxing 48% hydrobromic acid–acetic acid (1 : 1) for 1·5 h produced a bromo acid [4b] which was immediately esterified with diazomethane to afford the ester (**3**) (92%). Acetalization [2-ethyl-2-methyl-1,3-dioxalan–benzene–TsOH (18 h)] of (**3**) gave a 95% yield of the pure bromo acetal (**4**). Alkylation of the ester enolate (lithium di-isopropylamide–tetrahydrofuran at −78 °C) derived from (**4**) with methyl iodide [−78 °C (2 h)— −40 °C (2 h)] resulted in an 80% yield of chromatographically pure methyl ester (**5**).



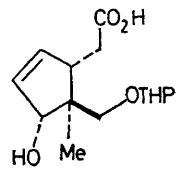
(2) (3) $R^1 = CO_2Me$, R^2=O (4) $R^1 = CO_2Me$, R^2=-O[CH_2]$_2$O- (5) $R^1 = CO_2Me$ (6) $R^1 = CH_2OH$

Reduction of (**5**) with $LiAlH_4$ in refluxing anhydrous ether to the alcohol (**6**), followed by dehydrobromination with 1,5-diazabicyclo[5,4,0]undec-5-ene in refluxing benzene (72 h) gave (**7**), τ 3·9 (m, 2H), in 92% overall yield from (**5**). Deacetalization (30% acetic acid, 90 °C, 2·5 h) of compound (**7**) afforded a 95% yield of the bicyclo[2,2,1]-heptenone derivative (**8**), ν_{max} 1742 cm^{-1}, which was converted into the tetrahydropyranyl (THP) derivative (**9**) (81%) using dihydropyran (1·2 equiv) in methylene chloride containing toluene-*p*-sulphonic acid (0·1 equiv). Baeyer–Villiger oxidation[5] of (**9**) with 30% H_2O_2 and NaOH in aqueous MeOH (1 : 1) at 0 °C for 16 h afforded the hydroxy carboxylic acid (**10**), ν_{max} 3400 and 1720 cm^{-1}, in 89% yield. The hydroxy acid could be converted directly in high yield into the butyrolactone (**11**) [ν_{max} 1768 cm^{-1}; τ 4·12 (m, 2H), 4·54 (d, 1H), 6·60 (s, 2H), and 8·95 (s, 3H)] upon treatment with toluene-*p*-sulphonic acid in MeOH or stepwise *via* (**13**) using BF_3–Et_2O in methylene chloride (0 °C) followed by treatment with toluene-*p*-sulphonic acid in MeOH.

Using synthetic methodology developed previously for the synthesis of natural prostaglandins, the aldehyde (**12**) was converted into 12-MePGA_2. Collins oxidation[6] of (**11**) provided (**12**) which upon treatment[7] with the sodio derivative of dimethyl 2-oxoheptylphosphonate[8] in dry dimethoxyethane produced stereospecifically the *trans*-enone lactone (**14**) [68% overall from (**11**)], reduction ($NaBH_4$–EtOH; low temperatures) of which gave in near quantitative yield a 1 : 1 mixture of epimeric alcohols (**15**) which was used without



(7) R^1=H, R^2=-O[CH_2]$_2$O- (8) R^1=H, R^2=O (9) R^1=THP, R^2=O



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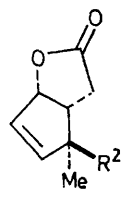
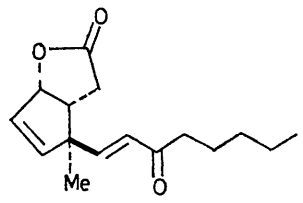


(11) R^2= CH_2OH (12) R^2= CHO (13) R^2= CH_2OTHP



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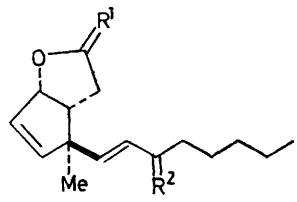
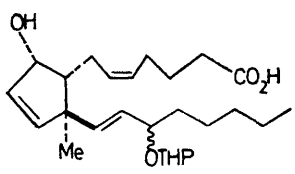


(15) R^1=O; R^2=H, OH (16) R^1=H,OH; R^2=H,OTHP



(17)

separation. Tetrahydropyranylation and reduction (Bu^i_2-AlH; toluene; −78 °C) produced the hemiacetal (**16**), condensation of which with the Wittig reagent[9] derived from $Ph_3P^+CH_2[CH_2]_3CO_2H$ and $MeSOCH_2^-Na^+$ gave the hydroxy carboxylic acid (**17**), 74% overall yield from (**15**). Collins oxidation and removal of the tetrahydropyranyl group under acidic conditions gave a 1 : 1 mixture of 12-Me PGA_2 and its C-15 epimer (71%) which were separated by preparative t.l.c.

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