An Asymmetric Approach to the Synthesis of 12-Methylprostaglandins

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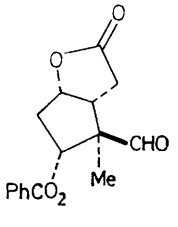
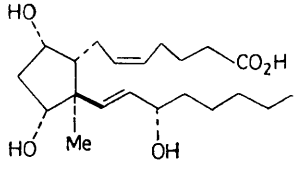
Summary An asymmetric route from the well known triketone (**3**) to the key intermediate aldehyde (**1**) for construction of 12-methylprostaglandins is described.

THE stable aldehyde (**1**) represents a key intermediate in the synthesis of 12-methylprostaglandins and related compounds. Recently the aldehyde (**1**) has been employed in the total synthesis of 12-methylprostaglandin $F_{2\alpha}$ (12-methyl $PGF_{2\alpha}$) (**2**).[1] However, the preparation and transformation of the aldehyde (**1**) into 12-methyl $PGF_{2\alpha}$ (**2**) is based on

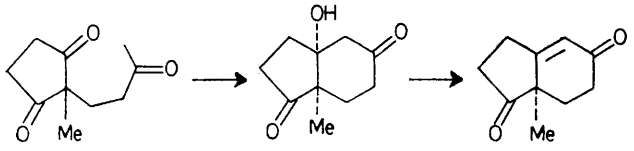


(1)

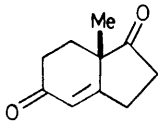


(2)

racemic materials and depends on resolution at an early stage.[2] We now report an asymmetric approach to the aldehyde (**1**) which is based on the catalytic asymmetric cyclization of the triketone (**3**) to the aldol (**4**) followed by β-elimination to the enedione (**5**).[3] The antipode of the enedione (**5**), namely compound (A), has previously been



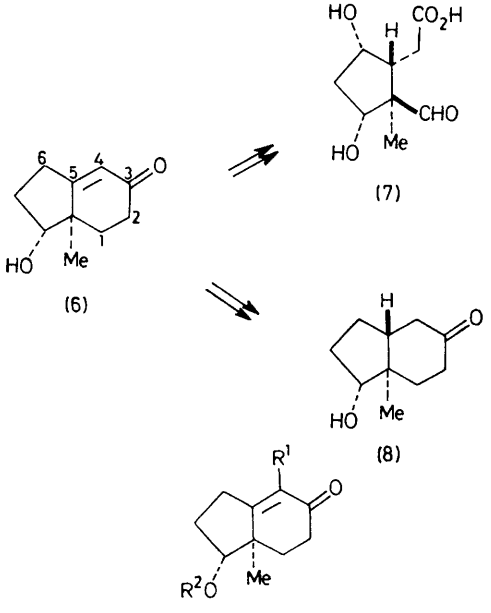
(3) (4) (5)



(A)

prepared optically pure from (**3**) employing L-proline and represents an important starting material for steroid total synthesis.[3,4]

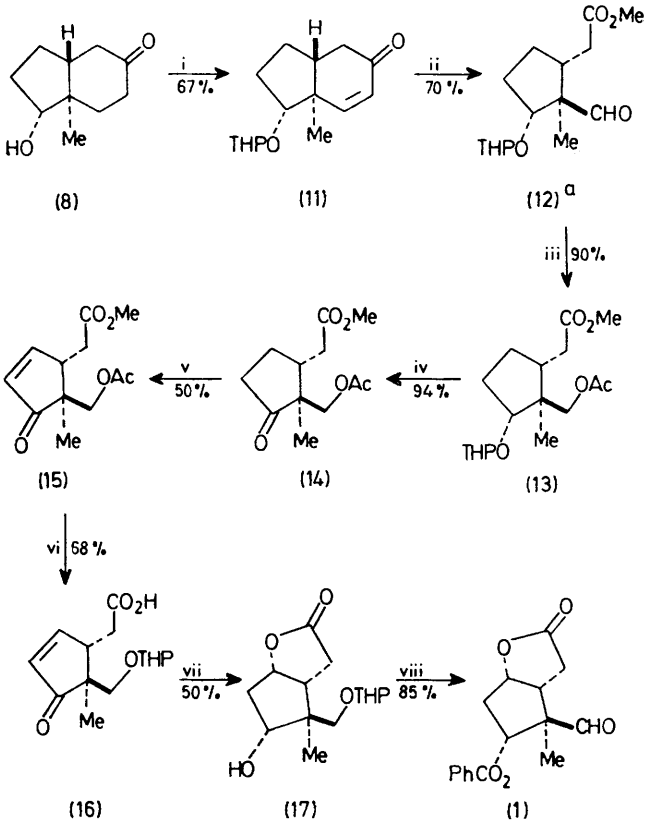
The starting triketone[5] was cyclized with a catalytic amount of D-proline in dimethylformamide (DMF) (as described in the literature with L-proline).[4] The resultant aldol (**4**) was dehydrated employing toluene-*p*-sulphonic acid in refluxing benzene. A 72% yield of the enedione (**5**) was obtained with 96% optical purity. Reduction[6] of (**5**) with lithium tri-t-butoxyaluminium hydride in tetrahydrofuran (THF) at 0 °C gave stereospecifically the alcohol (**6**).



(6) (7) (8)

(9) R^1 = H, R^2 = But
(10) R^1 = CO_2H; R^2 = But

In principle if one could introduce an α-hydroxy function at C-6 in compound (**6**) and a β-hydrogen at C-5, the four chiral centres of the five-membered ring nucleus of 12-methyl $PGF_{2\alpha}$ (**2**) would be established and all that would remain is the abstraction of C-2 so as to convert C-1 into an aldehyde function and C-3 into a carboxylic acid function [*cf.* (**6**)→(**7**)]. Unfortunately we were unsuccessful in our attempts to create the correct stereochemistry at both C-5 and C-6 stereospecifically. We therefore turned our attention to the construction of the *trans*-hydrindanone (**8**), which after extraction of C-2 would at some point in the synthesis require functionalization at C-6.



(8) (11) (12)[a] (13) (14) (15) (16) (17) (1)

SCHEME. Reagents: i, (a) $PhN^+Me_3Br_3^-$, THF, 25 °C, (b) DHP, $POCl_3$, CH_2Cl_2, 0 °C, (c) Li_2CO_3, DMA, 125 °C; ii, (a) OsO_4, Py, (b) IO_4^-, MeOH–H_2O, (c) CH_2N_2 (see ref. 11); iii, (a) BH_4^-, MeOH, (b) Ac_2O, Py; iv, (a) TsOH, MeOH, (b) CrO_3·2Py; v, (a) $PhN^+Me_3Br_3^-$, THF, (b) DBU, PhH; vi, (a) K_2CO_3, MeOH, (b) DHP, TsOH, CH_2Cl_2, (c) OH^-, MeOH; vii, (a) TsOH, PhH, (b) BH_4^-, EtOH; viii, (a) PhCOCl, Py, (b) H^+, MeOH, (c) CrO_3·Py. (DHP = dihydropyran; DMA = dimethylacetamide; Py = pyridine; Ts = *p*-Me·C_6H_4·SO_2^-; DBU = 1,5-diazabicyclo[5.4.0]-undec-5-ene.)

[a] Using standard synthetic methodology, (**12**) was converted into 9-deoxy-12-methylprostaglandin $F_{2\alpha}$.

Treatment of (**6**) with isobutene in phosphoric acid containing BF_3–Et_2O[7] gave (**9**) in 95% yield. Direct carbonation[8] of (**9**) with methyl methoxymagnesium carbonate[9] in DMF gave the keto acid (**10**) in 54% yield. Hydrogenation[10] (H_2, 10% Pd on $BaSO_4$, 0 °C) followed by treatment with THF–2NHCl (1:1) gave the ketone (**8**). The conversion of (**8**) into the aldehyde (**1**), identical in all respects with an authentic sample prepared by an alternative route,[1] is outlined in the Scheme.

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