Stereoselective Total Synthesis of Prostaglandin E_1

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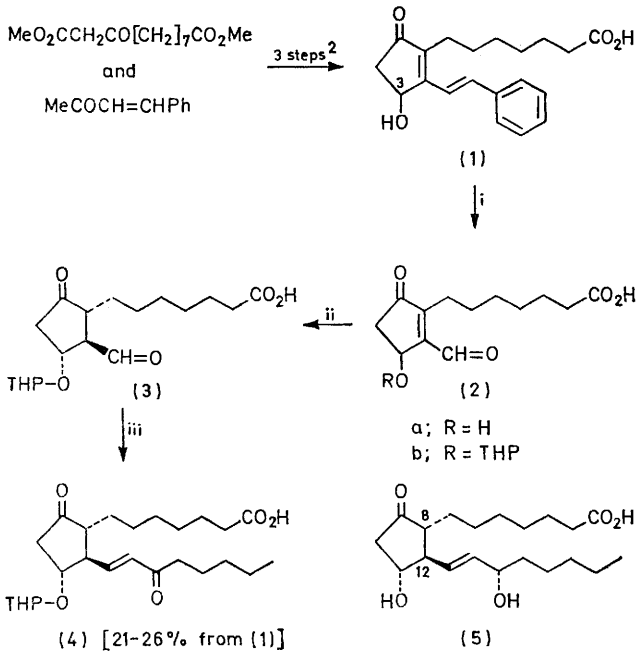
Summary A nine-step stereoselective total synthesis of (±)-PGE_1 (**5**) from benzylideneacetone and dimethyl 3-oxoundecan-1,11-dioate is described.

SEVERAL elegant total syntheses of prostaglandin E_1 [PGE_1 (**5**)] have been published.[1] By expanding our seven-step nonstereoselective synthesis of (±)-$PGF_{1\alpha}$[2] and (±)-dihydro-PGE_1,[3] we have achieved a practical, stereochemically controlled synthesis of PGE_1.

Crude (**2a**), prepared from (**1**) as described earlier,[2] was converted into the tetrahydropyranyl ether (**2b**) and reduced (Cr^{2+}) in aqueous THF at 20° to give (**3**). Without purification, oily (**3**) was condensed with n-hexanoylmethylene(triphenyl)phosphorane in refluxing benzene to give a mixture containing (**4**), which was readily separated by chromatography.† The ratio (**4**) (natural configuration) : 8-*epi*-(**4**) : 8,12-*bisepi*-(**4**) was 70—80 : *ca.* 10 : *ca.* 20. The structure of (**4**) thus obtained [21—26% overall yield‡

† SilicAR CC-4 and 15% EtoAc–benzene. No chromatography was employed in earlier stages.

‡ Not yet optimized.



Reagents: i, a, $NaIO_4$–OsO_4;[2] b, dihydropyran–H^+; ii, $2H(Cr^{2+})$; iii, $C_5H_{11}COC{=}PPh_3$; iv, a, thexyl tetrahydrolimonyl lithium borohydride; b, H_3O^+.

from (**1**)] was confirmed by comparison of its i.r., u.v., and n.m.r. spectra with those of the tetrahydropyranyl ether prepared from (±)-15-dehydro-PGE_1.[2] Reduction of (**4**) with thexyl tetrahydrolimonyl lithium borohydride[4] in THF at −78° took place regioselectively as well as stereoselectively to yield (45—55% after chromatography) the tetrahydropyranyl ethers of PGE_1 and its 15-epimer in the ratio *ca.* 4:1. Hydrolysis of the former afforded (±)-PGE_1 (**5**), m.p. 112–113°, whose n.m.r. spectrum (100 MHz in CD_3OD) was indistinguishable from that of natural PGE_1. While small amounts of the starting material and over-reduced product (mostly $PGF_{1\alpha}$) were obtained, no 9-hydroxy-15-oxo-compound was formed§ on reduction of (**4**) with thexyl tetrahydrolimonyl lithium borohydride.

The key intermediate (**1**) was resolved¶ *via* the (*R*)-(−)-α-methoxyphenylacetic esters, and the (3*R*) isomer ($[\alpha]_D^{25}$ −16·0, 1% in MeOH) was converted as described above into (−)-PGE_1 (**5**), which was indistinguishable from natural PGE_1 in several biological assays and physical properties (100 MHz n.m.r. spectrum in CD_3OD; m.p. 114—114·5°; recrystallized from EtOAc; $[\alpha]_D^{24}$ −53·2, 1% in THF).

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§Rigorously confirmed by comparison of hydrolysis products of crude reduction product with authentic 9α- and 9β-hydroxy-11α-hydroxy-15-oxoprost-13-enoic acids obtained by sodium borohydride reduction of (**4**) followed by hydrolysis.

¶ Carried out by Mr. C. R. Dorn.

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