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A SHORT WAY TO PROSTACYCLIN[1]

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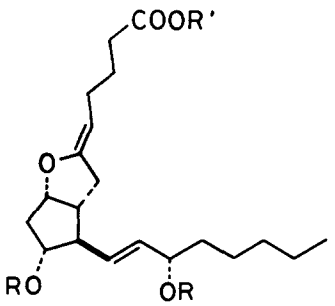
Summary: A facile, stereospecific preparation of prostacyclin has been accomplished starting from a 5,6-dehydroprostaglandin $F_{2\alpha}$ derivative.

The highly convergent entry to prostaglandins (PGs) developed in our laboratories has now set the stage for the general synthesis of various naturally occurring compounds and analogues.[1] Prostacyclin (PGI_2, 1) possessing diverse biological activities is known to be the most potent natural inhibitor of blood platelet aggregation and a powerful vasodilator.[2] We here describe a very short synthesis of this important compound.[3,4]

The success relies heavily on the stereospecificity of the reductive demercuration of vinylic mercury compounds. While reaction of alkylmercury salts of type RHgX with sodium borohydride or related reducing agents generates free alkyl radicals,[5,6] the reaction of the vinylic substrates proceeds via non-radical mechanism, resulting in removal of the mercury moiety with retention of configuration.[6] Therefore, the intramolecular oxymercuration of an acetylenic alcohol in a 5-exo-dig manner[7] followed by reductive demercuration should allow stereospecific construction of a (Z)-2-alkylidenetetrahydrofuran structure.

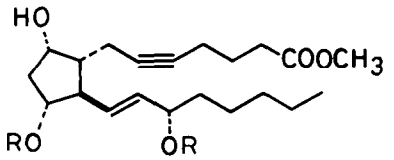
In practice, efficiency of the transformation is highly influenced by the substitution pattern of the substrates and reaction conditions.[8] Fortunately, we have found that the chiral acetylenic



1, R = R' = H

2, R = H; R' = CH_3

3, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = CH_3



4, R = $Si(CH_3)_2$-*t*-C_4H_9

alcohol 4,[1] prepared in four steps from (R)-4-t-butyldimethylsiloxy-2-cyclopentenone using the tandem organocopper conjugate addition/aldol reaction[9] as a key procedure, is convertible to a PGI_2 derivative by a single-pot process. To a THF solution of 4 was added slowly a mixture of mercury(II) trifluoroacetate and triethylamine (1.1 equiv each) in THF at -78 °C. After stirring of the mixture at this temperature for 1 h, a 1 N methanolic sodium methoxide solution containig 5 equiv of sodium borohydride was added rapidly, and the resulting mixture was maintained at -78 °C for 1 h. Aqueous workup followed by chromatography on a Florisil column using a 200:5:1 mixture of hexane, ethyl acetate, and triethylamine as eluant[10] afforded the cyclization product 3 (67% yield), $[\alpha]_D^{21}$ +28.8° (c 0.4, $CHCl_3$), and unreacted 4 (30%). The ^1H NMR spectrum of 3 was superimposable on that of authentic material,[11] and no evidence was provided for the formation of any stereo- or positional isomers of the 5Z alkenyl ether.[12] Deblocking of 3 by commercial tetrabutylammonium fluoride (8 equiv) in THF (15 °C, 15 h) gave PGI_2 methyl ester (2) (74% yield), mp 35 °C, $[\alpha]_D^{20}$ +79.8° (c 0.27, $CHCl_3$),[13] identical with authentic specimen as judged by comparison of the spectral properties (IR, ^1H and ^{13}C NMR) and thin-layer chromatographic behavior. Alkaline hydrolysis of the methyl ester 2 leads to PGI_2 (1).[3d]

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12. When the oxymercuration/demercuration process was conducted at 0 °C in the absence of triethylamine, the Δ^6-isomer (a double-bond positional isomer) was obtained exclusively.
13. Reported values;[3d] mp 30--33 °C; $[\alpha]_D^{25}$ +78° (c 0.8820, $CHCl_3$).

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