Synthesis of Prostaglandin-E_2 and Prostaglandin-C_2 from 5-*endo*,7-*anti*-Disubstituted Bicyclo[2.2.1]heptan-2-ones

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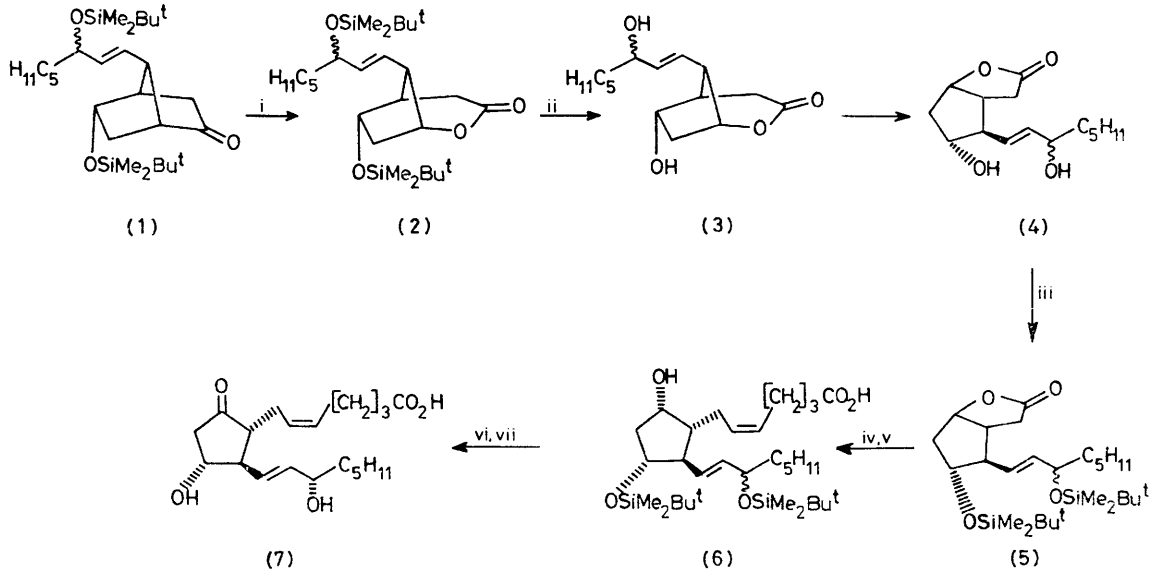
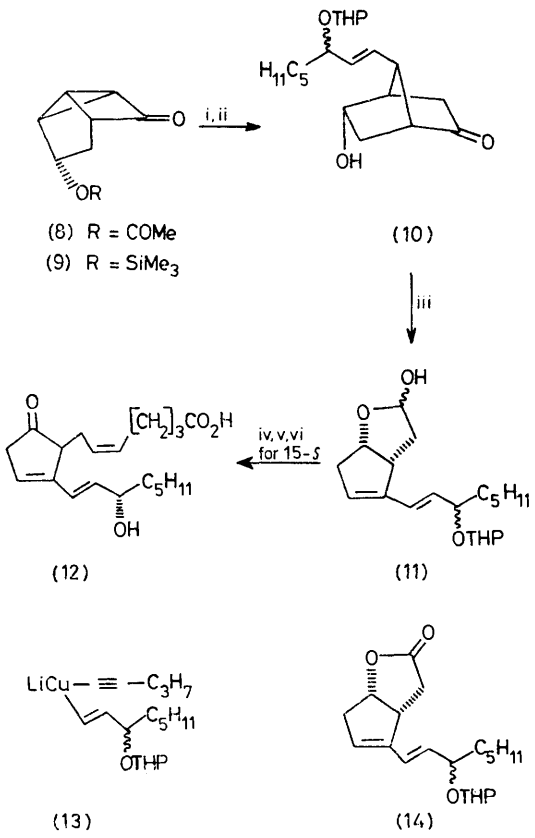
Summary The known bis(silyloxy)bicycloheptanone (**1**) has been converted into prostaglandin-E_2 (**7**) in seven steps, and the readily prepared mono-protected dihydroxyketone (**10**) has been photoisomerised to the known prostaglandin-C_2 precursor (**11**).

WE have described the synthesis of prostaglandin-$F_{2\alpha}$[1] and 9α-methoxy-9-deoxyprostaglandin-C_2[2] from readily available 5-*endo*,7-*anti*-disubstituted bicyclo[2.2.1]heptan-2-ones. Herein we describe synthetic routes to prostaglandin-E_2 (PG-E_2) (**7**) and prostaglandin-C_2 (PG-C_2) (**12**) from similarly substituted norbornanones thus illustrating the versatility of our synthetic scheme.

The bicycloheptanone (**1**) was oxidised to the 2-oxabicyclo[3.2.1]octan-3-one (**2**) using peracetic acid (Scheme 1).[1] Treatment of the lactone (**2**) with tetrabutylammonium



SCHEME 1. Reagents: i, $MeCO_3H$; ii, $Bu_4N^+F^-$; iii, Me_2Bu^tSiCl, $HCONMe_2$, imidazole; iv, Bu^i_2AlH; v, $Ph_3PCH[CH_2]_3CO_2^-$; vi, Jones oxidation; vii, H^+, chromatography.



SCHEME 2. Reagents: i, (**13**); ii, H^+; iii, *hν*, MeOH, $NaHCO_3$; iv, $Ph_3PCH[CH_2]_3\ CO_2^-$; v, Collins oxidation; vi, $MeCO_2H$, H_2O, tetrahydrofuran. THP = tetrahydropyranyl.

fluoride initially led to desilylation and formation of the dihydroxy-δ-lactone (**3**), which spontaneously rearranged to the γ-lactone (**4**) under the reaction conditions. Silylation of the lactone (**4**) gave the 2-oxabicyclo[3.3.0]octan-3-one (**5**) [70% from (**2**) after chromatography]. Reduction of the lactone (**5**) to the corresponding lactol, followed by reaction with the requisite Wittig reagent gave the disilylated PG-$F_{2\alpha}$ derivative (**6**) which was converted into PG-E_2 (**7**) by oxidation and acid-catalysed deprotection as described previously.[3]

Homoconjugate addition of the cuprate reagent (**13**) to the 3-*endo*-acetoxytricycloheptan-6-one[4] (**8**) furnished, after deacetylation *in situ*, the 5-*endo*-hydroxynorbornanone (**10**) (Scheme 2). The same hydroxyketone was prepared by reaction of the mixed cuprate reagent (**13**) with the trimethylsilyloxyketone (**9**), desilylation occurring during the work-up (aq. HCl). Photolysis of the ketone (**10**) in methanol containing a trace of sodium hydrogen carbonate caused the expected[5] isomerization to the lactol (**11**) (65%) which was oxidised to the more stable lactone (**14**) [λ_{max} (MeOH) 228, 234, and 242 nm; ν_{max} ($CHCl_3$) 1770 cm^{-1}; δ ($CDCl_3$) *inter alia* 6·25 (1H, d, *J* 13 Hz)][6] for the purpose of full characterization. In this way, the lactol (**11**) was obtained as a mixture of diastereomers (15*R* and 15*S*-prostaglandin numbering) one of which (15*S*) has been converted into PG-C_2 in three steps.[6,7] We are presently engaged in the use of the appropriate chiral cuprate reagent to avoid the formation of the biologically less active 15-*epi*-prostaglandin.

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