Total Synthesis of (±)-Prostaglandin I_2 Methyl Ester and (±)-15-epi-Prostaglandin I_2 Methyl Ester

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Summary Prostacyclin (prostaglandin I_2) methyl ester has been prepared; the key step was an aldol reaction between a cyclopentanone enolate and the cyclopentenylacetaldehyde derivative (**4**).

PROSTACYCLIN (PGI_2) (**18**) is a naturally occurring compound and a potent inhibitor of blood platelet aggregation.[1] Several methods of synthesis of PGI_2 from prostaglandin $F_{2\alpha}$ have been reported previously.[2] Now we disclose a *de novo* preparation (Scheme) of this important prostaglandin.

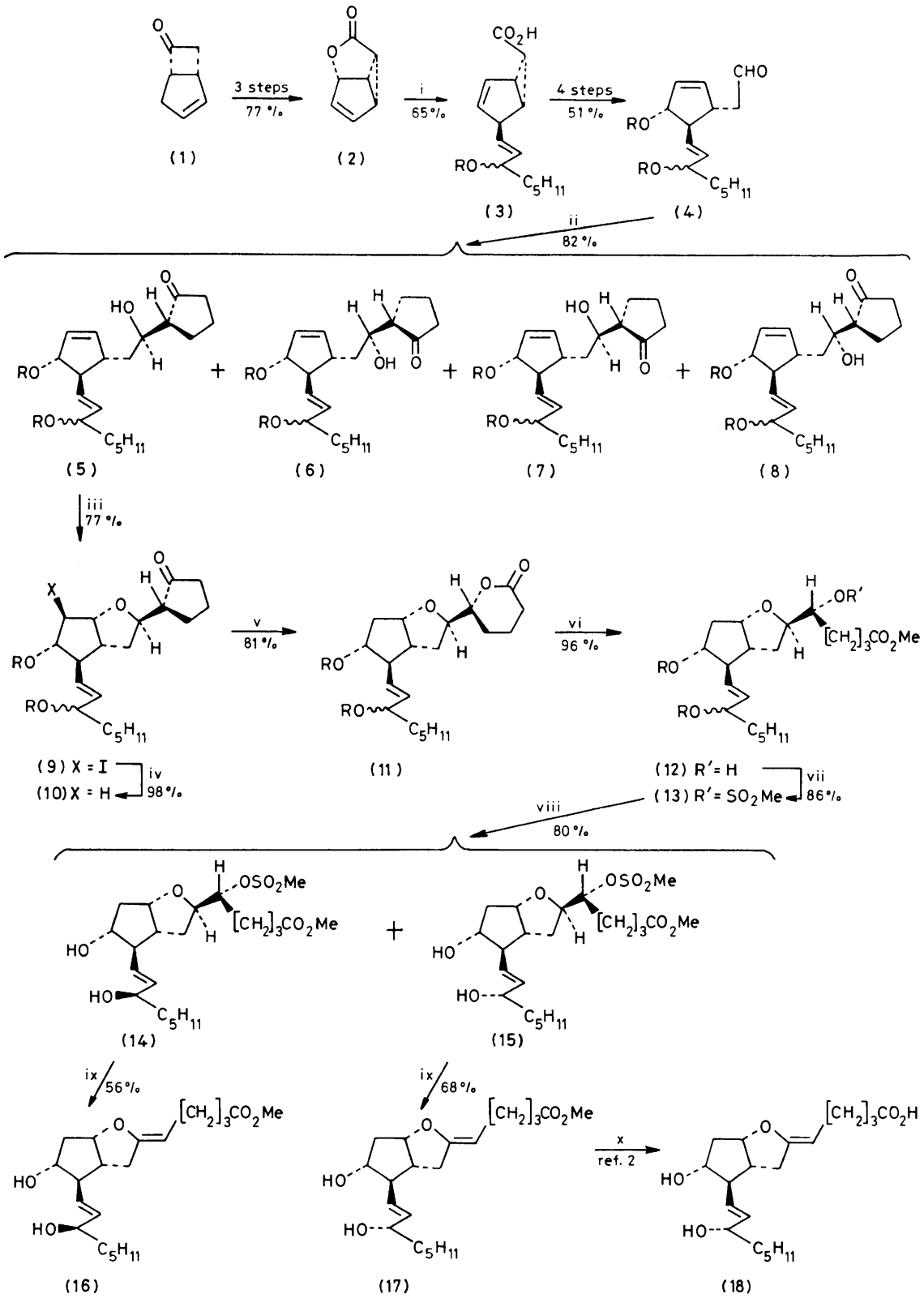
The readily available bicyclic ketone (**1**) was converted into the oxatricyclo-octanone (**2**) in high yield. Reaction of (**2**) with $LiCu[CH{=}CHCH(OSiMe_2Bu^t)C_5H_{11}]_2$ furnished the acid (**3**): the key intermediate (**4**; $R{=}SiMe_2Bu^t$) was prepared from the acid (**3**) in four steps.[3]

Reaction of the aldehyde (**4**) with the lithium enolate of cyclopentanone gave four products (82% yield). Chromatography over silica using 5% ethyl acetate in dichloromethane as eluant effected separation of products (I) (R_F 0·76), (II) (R_F 0·72), (III) (R_F 0·42), and (IV) (R_F 0·32) in the ratio 10 : 25 : 1 : 5. The stereochemistry at the newly formed chiral centres was elucidated by high resolution ^1H n.m.r. spectroscopy. Compounds (I) and (II) were judged to be the *threo* adducts (**5**) and (**6**) since the signal from the proton C*H*OH (δ 3·84, 3·76, respectively) was observed at a significantly higher field than the corresponding signal from the isomers (III) and (IV) (δ 4·27, 4·20, respectively).† Coupling constant data were in accord with these assignments.[4]

Thus the two major products (70% isolated yield) from the aldol reaction possess the correct stereochemistry for conversion into PGI_2.

The least polar aldol product (I), underwent iodoetherification readily [indicating that (I) was the (*R*,*R*) isomer (**5**)][5]

† The *threo*- and *erythro*-adducts derived from cyclopentanone enolate and benzaldehyde showed a similar disparity in the chemical shifts of the proton C*H*OH ($\Delta\delta = 0{\cdot}50$).



R = $SiMe_2Bu^t$

SCHEME. *Reagents:* i, $LiCu[CH{=}CHCH(OSiMe_2Bu^t)C_5H_{11}]_2$, diethyl ether, −78 °C; ii, $CH_2CH_2CH{=}C(OLi)CH_2$; iii, KI_3, H_2O, $NaHCO_3$, diethyl ether; iv, Bu^n_3SnH, benzene, heat; v, *m*-$ClC_6H_4CO_3H$, 0 °C, CH_2Cl_2; vi, K_2CO_3, MeOH; vii, $MeSO_2Cl$, Et_3N, CH_2Cl_2; viii, $MeCO_2H$, THF, H_2O; ix, DBU; x, NaOH, H_2O.

to give the ketone (**9**). Deiodination was accomplished in high yield using tri-n-butyltin hydride, and the product (**10**) reacted with peracid regiospecifically to give the required lactone (**11**). Cleavage of the lactone ring using potassium carbonate in methanol gave the ester (**12**) which on conversion of the free hydroxy- into a methanesulphonyl group furnished (**13**). Desilylation of (**13**) using aqueous acetic acid in tetrahydrofuran (THF) and chromatography afforded equal amounts of the 15-epimeric diols (**14**) and (**15**). The former compound gave (±)-15-epi-PGI_2 methyl ester (**16**)[6] on treatment with neat diazabicycloundecene (DBU). Under similar conditions the diol (**15**) gave (±)-PGI_2 methyl ester (**17**), which was identical both spectroscopically and biologically to an authentic sample.

PGI_2 methyl ester (**17**) has been readily converted into the corresponding sodium salt and PGI_2.[2]

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