

Total Synthesis of ($\pm$)-Prostaglandin I₂ Methyl Ester and ($\pm$)-15-*epi*-Prostaglandin I₂ Methyl Ester

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Summary Prostacyclin (prostaglandin I₂) methyl ester has been prepared; the key step was an aldol reaction between a cyclopentanone enolate and the cyclopentenyl-acetaldehyde derivative (**4**).

PROSTACYCLIN (PGI₂) (**18**) is a naturally occurring compound and a potent inhibitor of blood platelet aggregation.¹ Several methods of synthesis of PGI₂ from prostaglandin F_{2α} 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(OSiMe₂Bu[†])C₈H₁₁]₂ furnished the acid (**3**): the key intermediate (**4**; R=SiMe₂Bu[†]) was prepared from the acid (**3**) in four steps.³

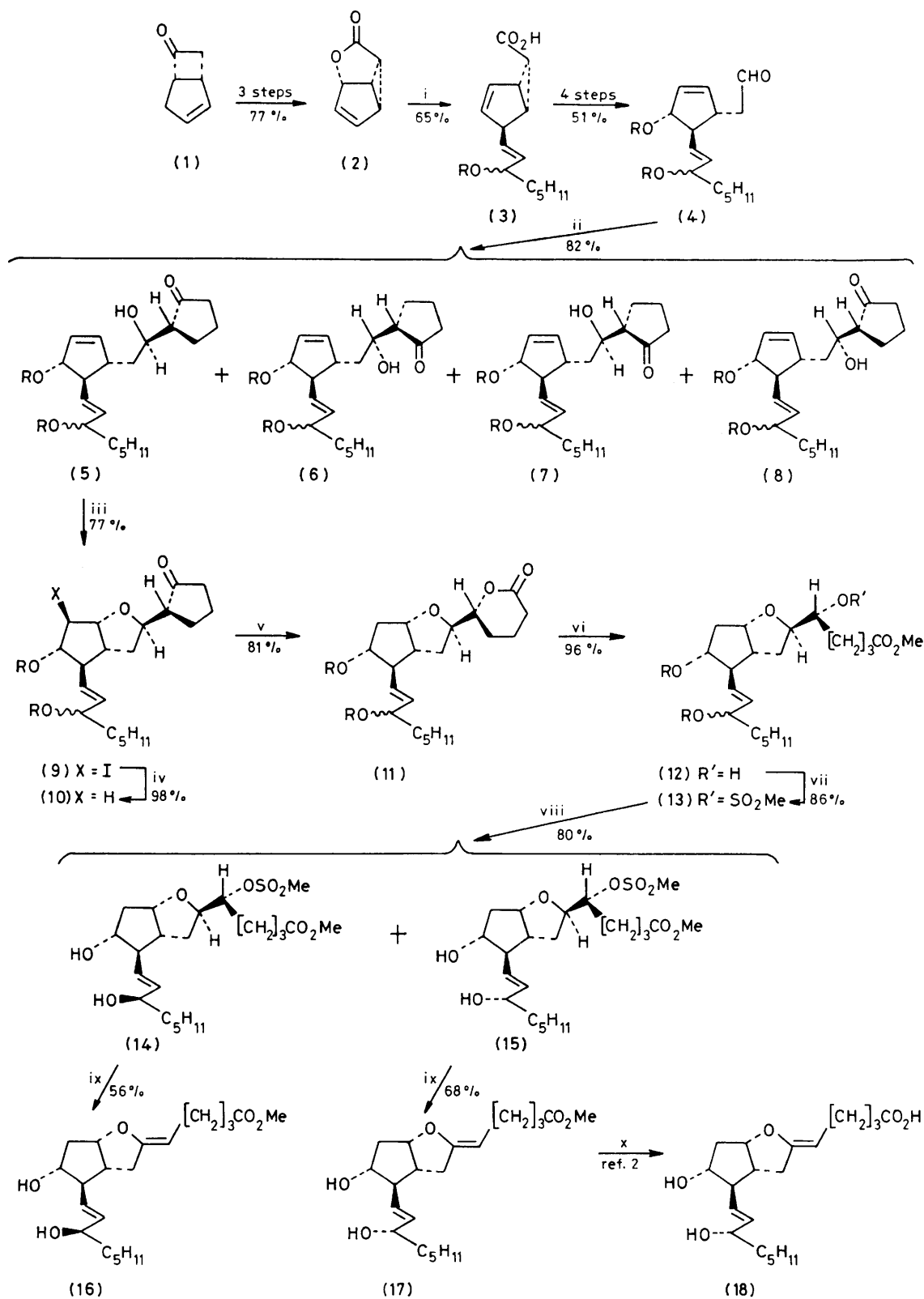
Reaction of the aldehyde (**4**) with the lithium enolate of cyclopentanone gave four products (82% yield). Chromato-

graphy 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 *CHOH* (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 PGI₂.

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 *CHOH* ($\Delta\delta$ = 0.50).



SCHEME. Reagents: i, LiCu[CH=CHCH(OSiMe₂But)₂C₆H₁₁]₂, diethyl ether, -78 °C; ii, CH₂CH₂CH=C(OLi)CH₂; iii, KI₃, H₂O, NaHCO₃, diethyl ether; iv, Bu₃SnH, benzene, heat; v, *m*-ClC₆H₄CO₂H, 0 °C, CH₂Cl₂; vi, K₂CO₃, MeOH; vii, MeSO₂Cl, Et₃N, CH₂Cl₂; viii, MeCO₂H, THF, H₂O; ix, DBU; x, NaOH, H₂O.

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 ($\pm$)-15-*epi*-PGI₂ methyl ester (**16**)⁶ on treatment with neat diazabicycloundecene (DBU). Under similar conditions the diol (**15**) gave ($\pm$)-PGI₂ methyl ester (**17**), which was identical both spectroscopically and biologically to an authentic sample.

PGI₂ methyl ester (**17**) has been readily converted into the corresponding sodium salt and PGI₂.²

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