Synthesis of (±)-Prostaglandin I_2 Methyl Ester and its 15-Epimer from 2-(Cyclopent-2-enyl)-1-(2-oxocyclopentyl)ethanol Derivatives

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The *threo*-2-(cyclopent-2-enyl)-1-(2-oxocyclopentyl)ethanol derivatives (2) and (3) have been converted into (±)-prostaglandin I_2 methyl ester and its 15-epimer. The route involved halogenoetherification, hydrodehalogenation, Baeyer–Villiger oxidation, and methanolysis, to give the 5-hydroxyprostaglandin I_1 derivatives (17) and (18). These hydroxy esters were mesylated, the 11- and 15-hydroxy groups were deprotected, and the resulting 15-epimeric alcohols were separated. The final elimination, accomplished by means of neat 1,8-diazabicyclo[5.4.0]undec-7-ene, gave the required Δ^5-olefin with a high degree of regioselectivity, and was stereospecifically *trans*, giving the required *Z*-configuration (25).

We have reported in a preliminary communication [1] that one of the four products of the aldol reaction between the aldehyde (1) and cyclopentanone enolate [2] can be converted into the important natural product prostacyclin (prostaglandin I_2).[3] In principle, it should be possible to obtain prostacyclin from both the *threo*-aldol products (2) and (3) by this route. However, although the (5*R*,6*R*)-compound † (2) underwent iodocyclisation cleanly, though slowly, to give the required iodo ether (4), the (5*S*,6*S*)-isomer (3) failed to react either under similar conditions or at higher temperature.

In an analogous iodocyclisation, *en route* to PGI_1 analogues, a difference in rate between the stereoisomers (7) and (10) was attributed to steric interference between an alkyl chain and the cyclopentane ring in the transition state leading to cyclisation of the isomer (7).[4] Evidently the effective bulk of the cyclopentanone ring is sufficient to inhibit the iodocyclisation of one stereoisomer (3) altogether. Initial attempts to overcome the resistance of isomer (3) to cyclisation by the use of sources of the more reactive bromonium ion [5] [*N*-bromosuccinimide, bromine, *N*,*N*′-dibromodimethylhydantoin (DBDMH)], met with limited success. Thus, although isomer (2) gave the bromo ether (5) rapidly, only with the last reagent were fair yields of the bromo ether (8) obtained from isomer (3), accompanied by large amounts of the dibromo compound (11).‡ Acceptable results were obtained, however, with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TABCO) (12).[6] This compound presumably reacts with the double bond to give a bromonium/carbenium ion intermediate, and the bulky, non-nucleophilic 2,4,6-tribromophenolate ion, which does not compete with intramolecular attack by the hydroxy group. Even in this case, a small amount of the dibromo compound (11) was obtained, possibly owing to the liberation of traces of free bromine.

All of the halogeno ethers (4), (5), and (8) were almost quantitatively hydrodehalogenated by tributyltin hydride, to give the corresponding intermediates (6) and (9).

The next stage of the synthesis required the Baeyer–Villiger oxidation of the cyclopentanones (6) and (9) to give the lactones (13) and (14), respectively. It was expected that the Baeyer–Villiger reaction would proceed with the required regioselectivity since, in general, oxygen is inserted between the carbonyl group and the more substituted α-carbon atom.[7]

It was also hoped that the double bonds would be sufficiently shielded by the t-butyldimethylsilyloxy groups to avoid epoxidation. Under carefully controlled conditions, both expectations were largely realised. The stereoisomer (6) gave the required lactone (13) in 81% yield with only 14% of the epoxy lactone (15), while the other *threo*-isomer (9) gave the required lactone (14) in 83% yield, and epoxidised by-product (16), *ca.* 10%.

Ring opening of the lactones (13) and (14) by potassium carbonate in methanol gave the hydroxy esters (17) and (18), respectively, without complications. The hydroxy esters were then treated with methanesulphonyl chloride and triethylamine to give the mesyl derivatives (19) and (20), respectively.

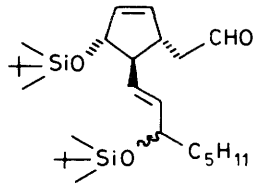
Of the various methods available for deprotection of the hydroxy groups, treatment with aqueous acetic acid in tetrahydrofuran (THF) was found to be the cleanest. It proved possible at this stage to separate the 15-epimeric products, *viz.* (21) and (22) [derived from (19)], and (23) and (24) [derived from (20)].

Although the stereochemistry of the mesylates (21)—(24) was correct for the formation of the required *Z*-geometry at Δ^5, (25), by *trans* elimination, there existed the possibility of an alternative elimination pathway to give the unwanted Δ^4-isomers (26). It was hoped that the inductive effect of the ring oxygen atom, with possible anchimeric assistance from the 11-hydroxy group in the case of (21) and (22), would favour the removal of the proton at C-6 (*cf.* ref. 8). Other groups have observed the desired regioselectivity in analogous elimination reactions, and have noted that the choice of base was critical.[9] We chose to use 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) since prostacyclin is known to be stable to this base, it could be removed by washing with water, and it has been used for analogous eliminations.

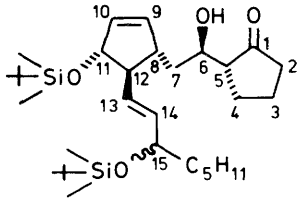
The mesylate (21) was heated at 60 °C in neat DBU, to give (±)-prostacyclin methyl ester (25) in 68% yield accompanied by only *ca.* 9% of the Δ^4-isomer (26); the 15-epimer (22) behaved very similarly, to give (±)-15-*epi*-prostacyclin methyl ester (27). The other pair of mesylates (23) and (24) each gave rather more of the undesired isomers (26), possibly because of the lack of anchimeric assistance by the 11-OH group, but isomer (23) still gave (±)-prostacyclin methyl ester in 61% yield.

Almost all of the intermediates in our synthesis of (±)-prostacyclin methyl ester were oils, whose identities were

† Prostaglandin-type numbering.
‡ The stereochemistry of the dibromo compound at C-9 and C-10 has not been proved, but that shown in structure (11) seems most likely.



(1)



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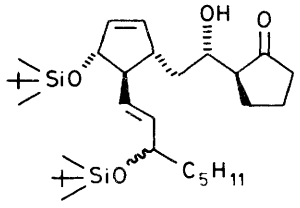

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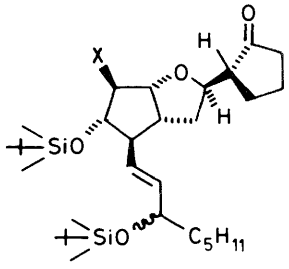
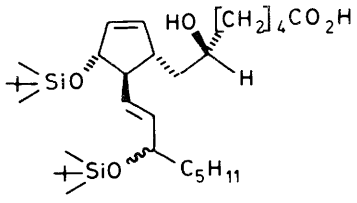
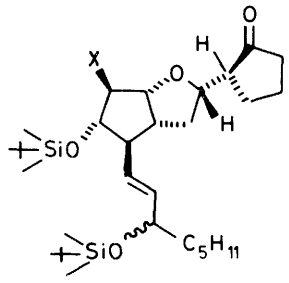


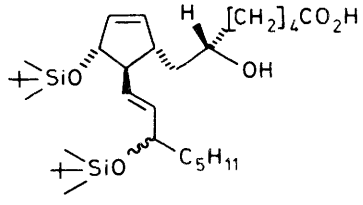
(4) X = I
(5) X = Br
(6) X = H



(7)



(8) X = Br
(9) X = H



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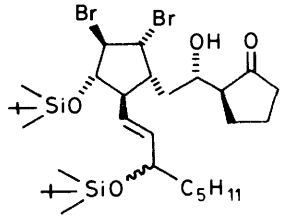
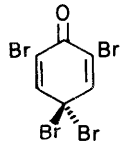
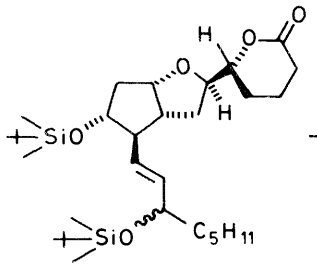


(11)



(12)

established by n.m.r. and mass spectrometry. The final products again had the expected n.m.r. spectra and molecular ions, and the identity of (±)-PGI_2 methyl ester was confirmed by bioassay. Our racemic specimen showed half the activity of



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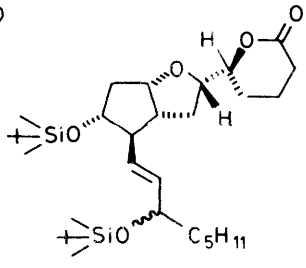

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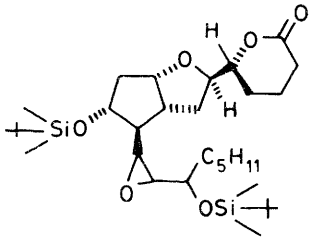

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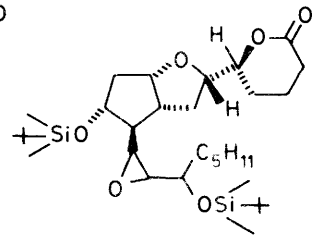


(16)

natural optically active prostacyclin methyl ester in inhibiting blood platelet aggregation induced by collagen.[10] In accord with previous reports,[11] the 15-epimer was inactive.

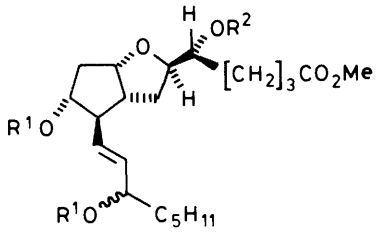
Prostacyclin methyl ester has been converted into prostacyclin and prostacyclin sodium salt.[9]

Experimental

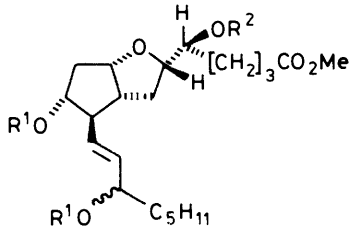
Details of the spectroscopic and chromatographic methods used, and of the preparation of compounds (2) and (3), are given in ref. 2. Yields of products are based on starting materials consumed.

Halogenocyclisation of 2-[4-*t*-*Butyldimethylsilyloxy*-5-(3-*t*-*butyldimethylsilyloxyoct*-1-*enyl*)*cyclopent*-2-*enyl*]-1-(2-*oxocyclopentyl*)*ethanols* (2) *and* (3).—(a) The (±)-(5*R*,6*R*)-*threo*-ketol (2) (140 mg, 0.248 mmol) was dissolved in diethyl ether (3.5 ml) and 8% aqueous sodium hydrogen carbonate (3.5 ml) was added. To the stirred mixture was added potassium iodide (163 mg, 0.97 mmol) and iodine (90 mg, 0.36 mmol), and the mixture was stirred for a further 6 d. Saturated aqueous solutions of sodium chloride (50 ml) and sodium sulphite (50 ml) were added. The mixture was extracted with diethyl ether (3 × 50 ml) and the combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue, an oil, was subjected to short-path column chromatography. Elution with 2% ethyl acetate–light petroleum gave (i) starting material (39 mg recovery) and (ii) 7-endo-*t*-*butyldimethylsilyloxy*-6-exo-(3-*t*-*butyldimethylsilyloxyoct*-1-*enyl*)-3-exo-[(1R)-2-*oxocyclopentyl*]-8-exo-*iodo*-cis-2-*oxabicyclo*[3.3.0]*octane* (4) (95 mg, 77%), $\nu_{max.}$ 1 725 cm^{-1}; δ 0 (12 H, m, 2 × $SiMe_2$), 0.7—2.9 (40 H, m), 3.8—4.5 (4 H, m, 3-, 7-, 8-, and 3′-H), 4.7 (1 H, m, 1-H), and 5.35—5.6 (2 H, m, 1′- and 2′-H) [Found: *m*/*z* 633.2291 $(M - 57)^+$. $C_{32}H_{59}IO_4Si_2$ requires $(M - C_4H_9)$, *m*/*z* 633.2292].

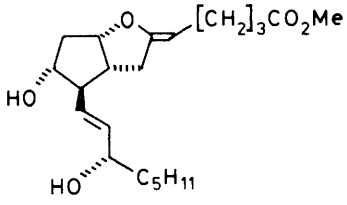
(b) To a stirred solution of the (±)-(5*S*,6*S*)-ketol (3) (0.246 g, 0.437 mmol) in dry dichloromethane (25 ml) was added anhydrous potassium carbonate (0.06 g, 0.437 mmol), together with DBDMH (0.175 g, 0.611 mmol), and the mixture was stirred for 150 min. Dichloromethane (25 ml) was added, and the solution was washed in turn with saturated aqueous



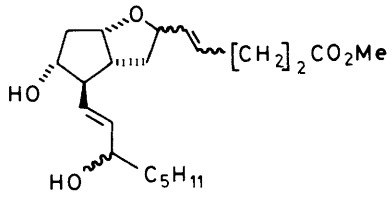
(17) $R^1 = SiBu^tMe_2$, $R^2 = H$
(19) $R^1 = SiBu^tMe_2$, $R^2 = SO_2Me$
(21) (15*S*), $R^1 = H$, $R^2 = SO_2Me$
(22) (15*R*), $R^1 = H$, $R^2 = SO_2Me$



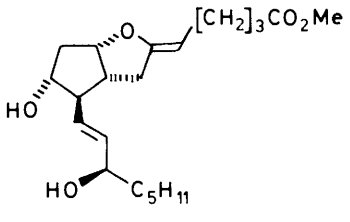
(18) $R^1 = SiBu^tMe_2$, $R^2 = H$
(20) $R^1 = SiBu^tMe_2$, $R^2 = SO_2Me$
(23) (15*S*), $R^1 = H$, $R^2 = SO_2Me$
(24) (15*R*), $R^1 = H$, $R^2 = SO_2Me$



(25)



(26)



(27)

sodium hydrogen carbonate (30 ml) and water (30 ml). The combined aqueous fractions were extracted with diethyl ether (2 × 30 ml). The combined organic fractions were dried ($MgSO_4$), filtered, and evaporated to give an oily yellow residue. This was subjected to medium-pressure column chromatography. Elution with 2% ethyl acetate-light petroleum gave (i) the *bromo ether* (8) (0.158 g, 57%) as an oil, R_F 0.46 (10% ethyl acetate–light petroleum); $\nu_{max.}$ 1 725 cm^{-1}; δ 0.1 (12 H, s, 2 × $SiMe_2$), 0.7—0.9 (21 H, m, 7 × Me), 1.1—2.6 (19 H, m), 3.7—3.9 (2 H, m, 7- and 3′-H), 4.0 (1 H, m, 8-H), 4.07 (1 H, m, 3-H), 4.27 (4.27 (1 H, q, 1-H), 5.35 (1 H, m, 1′-H), and 5.45 (1 H, m, 2′-H) [Found: *m/z* 585.2426 $(M - 57)^+$. $C_{28}N_{50}BrO_4Si_2$ requires $(M - 57)$, *m/z* 585.2429] and (ii) the *dibromo compound* (11) (42.7 mg), oil, R_F 0.31; $\nu_{max.}$ 3 400 and 1 725 cm^{-1}; δ 0.1 (12 H, m, 2 × $SiMe_2$), 0.8—1.0 (21 H, m, 7 × Me), 1.2—2.6 (19 H,) 3.8 (1 H, m, 1-H), 3.95—4.5 (5 H, m, 2′-, 3′-, 4′-, 3″-H, and OH), and 5.5 (2 H, m, 1″ and 2″-H) [Found: *m/z* 665.1688 $(M - 57)^+$. $C_{28}H_{51}Br_2O_4Si_2$ requires $(M - 57)$, *m/z* 665.1691].

A similar experiment on the (5*R*,6*R*)-ketol (2), but with a reaction time of 3 h, gave a starting material (38% recovery), and the *bromo ether* (5) (76%), R_F 0.46; $\nu_{max.}$ 2 900 and 1 725 cm^{-1}; δ 0.1 (12 H, s, 2 × $SiMe_2$), 0.9 (21 H, m, 7 × Me), 1.0—2.6 (19 H, m), 3.8 (2 H, m, 7- and 8-H), 4.05 (1 H, m, 3′-H), 4.2 (1 H, td, *J* 7.0 and 2.5 Hz, 3-H), 4.5 (1 H, dd, *J* 5.0 2.5 Hz, 1-H), and 5.35—5.6 (2 H, m, 1′- and 2′-H) [Found: *m/z* 585.2426 $(M - 57)^+$. $C_{28}H_{50}BrO_4Si_2$ requires $(M - 57)$, *m/z*, 585.2429].

(c) To a solution of the (±)-(5*S*,6*S*)-*threo*-ketol (3) (54 mg) in dry dichloromethane (10 ml) was added TABCO (39 mg). The mixture was stirred at room temperature for 18 h. Dichloromethane (40 ml) was added, and the organic phase was washed in turn with 2M-sodium hydroxide (2 × 30 ml) and water (40 ml). The combined aqueous layers were extracted with dichloromethane (30 ml). The combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the resulting yellow gum (silica; 2% ethyl acetate in light petroleum) gave the bromo ether (8) (45 mg, 73%) and the dibromo compound (11) (6.8 mg, 10%).

A similar experiment on the (5*R*,6*R*)-ketol (2) gave the bromo ether (5) (87%).

Hydrodehalogenation of the Halogeno Ethers (4) *and* (8).—(a) To a solution of the iodo ether (4) (0.47 g, 0.68 mmol) in dry benzene (100 ml) containing a crystal of azobisisobutyronitrile was added a solution of tri-n-butyltin hydride (0.297 g, 1.02 mmol) in dry ethanol (15 ml). The solution was heated under reflux for 45 min. The organic solvents were evaporated and the oily residue was dissolved in diethyl ether (50 ml) and the mixture was stirred with saturated aqueous potassium fluoride (20 ml) for 2 min in order to remove the tin residues. Filtration gave an organic phase which was washed with water (2 × 50 ml). The combined aqueous layers were extracted with diethyl ether (2 × 30 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give a residue which was subjected to short-path column chromatography (eluant 2% EtOAc in light petroleum) to afford 7-endo-*t-butyldimethylsilyloxy*-6-exo-(3-*t-butyldimethylsilyloxyoct*-1-*enyl*)-3-exo-[(1R)-2-*oxocyclopentyl*)]-cis-2-*oxabicyclo*[3.3.0]*octane* (6) (0.372 g, 98%) as an oil, $\nu_{max.}$ 1 735 cm^{-1}; R_F 0.87 (30% EtOAc–light petroleum); δ 0 (12 H, m, 2 × $SiMe_2$), 0.7—1.0 (21 H, m, 7 × Me), 1.0—3.0 (21 H, m), 3.65 (1 H, m, 7-H), 3.85—4.5 (3 H, m, 1-, 3-, and 3′-H), and 5.35—5.6 (2 H, m, 1′- and 2′-H) [Found: *m/z* 507.3322 $(M - 57)^+$. $C_{32}H_{60}O_4Si_2$ requires $(M - C_4H_9)$, *m/z* 507.3323].

(b) A similar experiment on the bromo ether (8) gave the 3-endo-[(1*S*)-2-*oxocyclopentyl*] *isomer* (9) (99%), R_F 0.86; $\nu_{max.}$ 1 725 cm^{-1}; δ 0.1 (12 H, s, 2 × $SiMe_2$), 0.7—1.0 (21 H, m, 7 × Me), 1.1—2.7 (21 H, m), 3.55—3.8 (1 H, m, 7-H), 3.85—4.3 (3 H, m, 1-, 3-, and 3′-H), and 5.3—5.55 (2 H, m, 1′- and 2′-H) [Found: *m/z*, 507.3321 $(M - 57)^+$. $C_{32}H_{60}O_4Si_2$ requires $(M - 57)$, *m/z* 507.3323].

Baeyer–Villiger Oxidations.—(*a*) The ketone (6) (0.716 g, 1.27 mmol), *m*-chloroperbenzoic acid (0.308 g, 1.4 mmol), sodium hydrogen carbonate (0.292 g, 3.7 mmol), and dry dichloromethane (80 ml) were stirred together for 5 h at 0 °C and set aside for a further 19 h at 0 °C. A saturated solution of sodium hydrogen carbonate (200 ml) was added and the aqueous layer was separated and extracted with dichloromethane (4 × 100 ml). The organic layers were washed with water (2 × 100 ml), dried, and evaporated to give a yellow oil. Short-path column chromatography (eluant 5% EtOAc–light petroleum) gave (i) starting material (0.148 g recovery), (ii) 7-endo-*t-butyldimethylsilyloxy*-6-exo-(3-*t-butyldimethylsilyl-oxyoct*-1-*enyl*)-3-exo[(1R)-6-*oxotetrahydropyran*-2-*yl*]-cis-2-*oxabicyclo*[3.3.0]*octane* (13) (0.474 g, 81%), $\nu_{max.}$ 1 735 cm^{-1}; R_F 0.60 (30% ethyl acetate–light petroleum); δ 0.0 (12 H, m, 2 × $SiMe_2$), 0.7—1.0 (21 H, m, 7 × Me), 1.0—2.7 (20 H, m), 3.8 (1 H, m, 7-H), 3.9—4.55 (4 H, m, 1-, 3-, 2′-, and 3″-H), and 5.3—5.5 (2 H, m, 1″- and 2″-H) [Found: *m/z*, 523.3270 $(M - 57)^+$. $C_{32}H_{60}O_5Si_2$ requires $(M - C_4H_9)$, *m/z* 523.3272], and (iii) 7-endo-*t-butyldimethylsilyloxy*-6-endo-3-*t-butyldimethylsilyloxy*-1,2-*epoxyoctyl*)-3-exo-[(1R)-6-*oxotetrahydropyran*-2-*yl*]-cis-2-*oxabicyclo*[3.3.0]*octane* (15) (0.081 g, 14%), $\nu_{max.}$ 1 735 cm^{-1}; R_F 0.47 (30% EtOAc–light petroleum); δ 0.0 (12 H, m, 2 × $SiMe_2$), 0.7—2.9 (41 H, m), 3.2—4.7 (7 H, m, 1-, 3-, 7-, 1′-, 2′-, 3′-, and 1″-H) [Found: *m/z*, 539.3188 $(M - 57)^+$. $C_{32}N_{60}O_6Si_2$ requires $(M - C_4H_9)$, *m/z* 539.3221].

(*b*) A similar experiment on the ketone (9) (71 mg), but with a reaction temperature of 0 °C for 20 min and −20 °C for 72 h, gave (i) starting material (29% recovery), (ii) the *lactone* (14 (43.2 mg, 83%), R_F 0.21 (10% ethyl acetate–light petroleum); $\nu_{max.}$ 1 725 cm^{-1}; δ 0.1 (12 H, m, 2 × $SiMe_2$), 0.8—0.95 (21 H, m, 7 × Me), 1.1—1.3 (8 H, m), 1.35—2.7 (12 H, m), 3.8 (1 H, m, 3-H), 3.9 (1 H, m, 3″-H), 4.0 (1 H, m, 7-H), 4.25 (H, m, 1-H), 4.4 (1 H, m, 2′-H), and 5.3—5.55 (2 H, m, 1″- and 2″-H) [Found: *m/z*, 523.3290 $(M - 57)^+$. $C_{32}H_{60}O_5Si_2$ requires $(M - C_4H_9)$, *m/z* 523.3272], and (iii) the *epoxy lactone* (16) (5.1 mg, 10%), R_F 0.17; $\nu_{max.}$ 1 725 cm^{-1}; δ 0.1 (12 H, s, 2 × $SiMe_2$), 0.9 (21 H, m, 7 × Me), 1.1—3.0 (20 H, m), and 3.25—4.65 (7 H, m) [Found: *m/z*, 539.3223 $(M - 57)^+$. $C_{32}H_{60}O_6Si_2$ requires $(M - C_4H_9)$, *m/z* 539.3221].

Methanolysis of the Lactones.—(*a*) To a stirred solution of the lactone (13) (0.205 g, 0.353 mmol) in dry methanol (7 ml) was added anhydrous potassium carbonate (0.13 g, 0.942 mmol). The mixture was stirred for 15 min at room temperature and then water (70 ml) was added. The mixture was extracted with chloroform (4 × 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give the methyl ester (17) (0.207 g, 96%) as an oil, $\nu_{max.}$ 3 450 and 1 737 cm^{-1}; R_F 0.7 (30% EtOAc–light petroleum; δ * 0.0 (12 H, s, 2 × $SiMe_2$), 0.7—1.0 (21 H, m, 7 × Me), 1.0—2.7 (20 H, m), 2.8—4.1 (8 H, m, 5-, 6-, 11-, and 15-H, OH, and OMe), 4.3 (1 H, m, 9-H), and 5.3—5.6 (2 H, m, 13- and 14-H).

(*b*) A similar experiment on the isomeric lactone (14) gave the *methyl ester* (18) (92%), R_F 0.83 (60%) ethyl acetate–light petroleum); $\nu_{max.}$ 3 400 and 1 725 cm^{-1}; δ * 0.1 (12 H, m, 2 × $SiMe_2$), 0.9 (21 H, 7 × Me), 1.15—1.4 (8 H, m), 1.4—2.6 (6 H, m), 3.45—3.6 (1 H, m, 5-H), 3.7 (3 H, s, OMe), 3.75—4.3 (4 H, m, 6-, 9-, 11-, and 15-H), and 5.3—5.55 (2 H, m, 13- and 14-H) [Found: *m/z*, 555.3537 $(M - 57)^+$. $C_{33}H_{64}O_6Si_2$ requires $(M - C_4H_9)$, *m/z* 555.3534].

Mesylation.—(*a*) To the hydroxy ester (17) (0.207 g, 0.343 mmol) in dry dichloromethane (8 ml) at 0 °C was added triethylamine (0.206 g, 2.06 mmol). The solution was stirred and mesyl chloride (0.243 g, 2.06 mmol) was slowly added during 2 min. The solution was stirred for 15 min and then more dichloromethane (50 ml) was added. The mixture was washed in turn with water (20 ml), 2M-hydrochloric acid (20 ml), saturated sodium hydrogen carbonate (20 ml), and saturated sodium chloride (20 ml). The aqueous layers were combined and extracted with dichloromethane (4 × 30 ml). The combined organic layers were dried and evaporated to leave a residue (0.4 g). Purification by short-path column chromatography (eluant 10% EtOAc–light petroleum) gave the *mesylate* (19) 0.02 g, 86%) as an oil, $\nu_{max.}$ 1 730 cm^{-1}; R_F 0.34 (15% EtOAc–light petroleum); δ * 0.0 (12 H, s, 2 × $SiMe_2$), 0.7 − 1.0 (21 H, m, 7 × Me), 3.1 (3 H, s, OSO_2Me), 3.7 (3 H, s, CO_2Me), 3.75—4.3 (3 H, m, 6-, 11-, and 15-H), 4.3—4.75 (2 H, m, 5- and 9-H), and 5.3—5.6 (2 H, m, 13- and 14-H) [Found: *m/z*, 595.4212 $(M - 95)^+$. $C_{35}H_{69}O_{11}SSi_2$ requires $(M - MeSO_3)$, *m/z* 595.4211].

(*b*) The hydroxy ester (18) similarly gave the *mesylate* (20) (61%), R_F 0.78 (30% EtOAc–light petroleum); δ (inter alia) 3.1 (3 H, s, OSO_2Me) and 3.7 (CO_2Me) [Found (c.i.m.s.): $(M + NH_4)^+$, 708.4324. $C_{35}H_{69}O_{11}SSi_2$ requires $(M + NH_4)$, *m/z* 708.4360].

Desilylation.—(*a*) The mesylate (19) (0.2 g, 0.29 mmol) was added to a mixture of glacial acetic acid (4.5 ml), THF (1.5 ml), and water (1.5 ml) and the mixture was stirred at room temperature for 19 h. A saturated solution of sodium hydrogen carbonate (20 ml) was added and the solution was neutralized with solid sodium hydrogen carbonate. The mixture was extracted with dichloromethane (4 × 15 ml) and diethyl ether (2 × 15 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give an oil. Short-path column chromatography (eluant 50% EtOAc–light petroleum) gave (i) (±)-(5R)- *mesyloxy*-(6S)-*prostaglandin* I_1 *methyl ester* (22) (53 mg, 40%), m.p. 89—92 °C; $\nu_{max.}$ 3 360 and 1 730 cm^{-1}; R_F 0.21 (EtOAc); δ * 0.9 (3 H, m, 20-H_3), 1.1—2.3 (19 H, m), 2.3—2.5 (3 H, m, 10-H_2 and 12-H), 3.12 (3 H, s, SMe), 3.68 (3 H, s, OMe), 3.8 (1 H, td, *J* 8 and 7 Hz, 11-H), 4.12—4.16 (2 H, m, 6- and 15-H), 4.52 (1 H, td, *J* 7 and 4.5 Hz, 9-H), 4.6 (1 H, q, *J* 6.5 Hz, 5-H), 5.55 (1 H, dd, *J* 15.5 and 8 Hz, 13-H), and 5.65 (1 H, dd, *J* 15.5 and 6 Hz, 14-H) [Found: *m/z*, 426.2075 $(M - 36)^+$. $C_{22}H_{38}O_8S$ requires $(M - 2H_2O)$, *m/z* 426.2074] and (ii) its 15-*epimer* (21) (53 mg, 40%), an oil, R_F 0.29 (EtOAc), with i.r., n.m.r., and m.s. indistinguishable from its epimer except for small differences in the coupling constants for the olefinic protons: δ 5.54 (1 H, dd, *J* 15.5 and 7.5 Hz, 13-H) and 5.66 (1 H, dd, *J* 15.5 and 6.5 Hz, 14-H).

(*b*) The mesylate (20) similarly gave (i) (±)-(5S)-*mesyloxy*-(6R)-*prostaglandin* I_1 *methyl ester* (24) (43%), R_F 0.38 (EtOAc); $\nu_{max.}$ 3 400 and 1 730 cm^{-1}; δ * 0.9 (3 H, m, 20-H_3), 1.2—2.5 (20 H, m), 3.1 (3 H, s, SMe), 3.7 (O-Me), 3.75—4.7 (5 H, m), and 5.4—5.7 (2 H, m, 13- and 14-H) [Found (c.i.m.s.) $(M + NH_4)^+$, 480.2648. $(C_{22}H_{38}O_8S_6 + NH_4)^+$ requires *m/z*, 480.2631], and (ii) its 15-*epimer* (23), (43%), R_F 0.28; with i.r., n.m.r., and m.s. indistinguishable from its epimer except for the n.m.r. signals for the olefinic protons: δ 5.54 (1 H, dd, *J* 15.5 and 6.0 Hz, 13-H) and 5.65 (1 H, dd, *J* 15.5 and 6.5 Hz, 14-H).

(±)-*Prostaglandin* I_2 *Methyl Ester.*—(*a*) A mixture of the mesylate (22) (48 mg) and DBU (1.75 g) was heated at 65 °C under argon for 20 h. Diethyl ether (30 ml) was added and the mixture was washed with ice-cold water (4 × 5 ml). The organic layer was dried ($MgSO_4$ with the addition of a few drops of triethylamine) and evaporated to give an oil (50 mg). Short-path column chromatography over silica [eluant EtOAc–cyclohexane–triethylamine (100 : 100 : 3)] gave (i) starting material (7 mg recovery), R_F 0.24 (EtOAc), (ii) (±)-

* Prostaglandin numbering used here.

prostaglandin I_2 methyl ester (25) (22 mg, 68%), R_F 0.33 (EtOAc); $\nu_{max.}$ (1% $CHCl_3$ solution) 3 605, 1 730, 1 695, and 975 cm^{-1}; δ * 0.9 (3 H, m, 20-H_3), 1.0—1.4 (6 H, m), 1.52 (2 H, m, 16-H_2), 1.7 (2 H, m, 3-H_2), 1.78 (1 H, ddd, *J* 15, 7.5, and 2.5 Hz, 10-H *exo* or *endo*), 2.0—2.15 (3 H, m, 12-H and 4-H_2), 2.2—2.4 (4 H, m, 2-H_2, 8-H, and 7-H *endo* or *exo*), 2.5 (1 H, m, 10-H *endo* or *exo*), 2.62 (1 H, m, 7-H *exo* or *endo*), 3.68 (3 H, s, OMe), 3.85 (1 H, q, *J* 8 Hz, 11-H), 4.17 (1 H, q, *J* 6.5 Hz, 15-H), 4.16 (1 H, td, *J* 7.5 and 2 Hz, 5-H), 4.6 (1 H, td, *J* 6 and 2.5 Hz, 9-H), 5.48 (1 H, dd, *J* 15 and 8 Hz, 13-H), and 5.6 (1 H, dd, *J* 15 and 6.5 Hz, 14-H); *m/z* 366 M^+, 348 $(M - H_2O)^+$, 335 $(M - CH_3O)^+$, 279 $(M - CH_2CH_2COOMe)^+$, and 265 $(M - [CH_2]_3CO_2Me)^+$ [Found: $(M + 1)^+$, 367.2537. Calc. for $C_{21}H_{34}O_5$: *m/z* 367.2484], and (iii) *trans*-Δ⁴-(6*S*)-prostaglandin I_1 methyl ester [*trans*-(26)] (3 mg, 9%), R_F 0.21 (EtOAc); $\nu_{max.}$ (1% $CHCl_3$ solution) 3 450, 1 735, and 975 cm^{-1}; δ * 0.89 (3 H, m, 20-H_3), 1.1—1.9 (12 H, m), 2.08 (1 H, q, *J* 9 Hz, 12-H), 2.3—2.5 (5 H, m, 2- and 3-H_2, 10-H *exo* or *endo*), 3.67 (3 H, s, OMe), 3.74 (1 H, m, 11-H), 4.09 (1 H, q, *J* 6 Hz, 15-H), 4.4 (2 H, m, 6- and 9-H), 5.41 (1 H, dd, *J* 15.5 and 7 Hz, 5-H), 5.52 (1 H, dd, *J* 15.5 and 8.5 Hz, 13-H), 5.62 (1 H, dd, *J* 15.5 and 6 Hz, 14-H), and 5.74 (1 H, dt, *J* 15.5 and 3.5 Hz, 4-H) [Found: (c.i.m.s.) $(M + NH_4)^+$, 384.2727; $(M + NH_4 - H_2O)^+$, 366.2603; $(M + H - H_2O)^+$, 349.2364. Calc. for $C_{21}H_{34}O_5$ (*M*): *m/z* 384.2750, 366.2644, and 349.2379 respectively.

(b) A similar experiment on the mesylate (24) gave (i) (±)-prostaglandin I_2 methyl ester (72%) with properties identical with those described above and (ii) a mixture comprising (analysis by n.m.r.) *trans*-Δ⁴-(5*S*,6*R*)-prostaglandin I_2 methyl ester (10%) and starting material.

(±)-15-epi-*Prostaglandin* I_2 *Methyl Ester*.—(a) A mixture of the mesylate (21) (9.0 mg) and DBU (0.7 g) was heated at 60 °C under nitrogen for 20 h. Diethyl ether (25 ml) was added and the mixture was washed with water (2 × 5 ml). The organic layer was dried ($MgSO_4$ with the addition of a few drops of triethylamine) and evaporated to give an oil (11 mg). Short-path column chromatography over silica [eluant EtOAc–light petroleum–triethylamine (50 : 20 : 1)] gave (±)-15-*epi*-PGI_2 methyl ester (27) (4 mg, 56%) as an oil, R_F 0.46 (EtOAc); $\nu_{max.}$ (1% $CHCl_3$ solution) 3 600, 1 730, and 970 cm^{-1}; δ * 0.9 (3 H, m, 20-H_3), 1.0—1.4 (6 H, m), 1.53 (2 H, m, 16-H_2), 1.7 (2 H, m, 3-H_2), 1.83 (1 H, ddd, *J* 15, 7.5, and 2.5 Hz, 10-H *exo* or *endo*), 2.09—2.14 (3 H, m, 12-H and 4-H_2), 2.25—2.4 (4 H, m, 2-H_2, 7-H *endo* or *exo*, and 8-H), 2.48 (1 H, m, 10-H *endo* or *exo*), 2.65 (1 H, m, 7-H *exo* or *endo*), 3.67 (3 H, s, OMe), 3.89 (1 H, q, *J* 8 Hz, 11-H), 4.11 (1 H, q, *J* 6 Hz, 15-H), 4.16 (1 H, td, *J* 7.5 and 1.5 Hz, 5-H), 4.62 (1 H, td, *J* 6 and 2.5 Hz, 9-H), 5.55 (1 H, dd, *J* 15.5 and 7.5 Hz, 13-H), and 5.65 (1 H, dd, *J* 15.5 and 5.5 Hz, 14-H); *m/z* 366 $(M)^+$, 348 $(M - H_2O)^+$, 335 $(M - CH_3O)^+$, 279 $(M - CH_2CH_2CO_2Me)^+$, and 265 $(M - [CH_2]_3CO_2Me)^+$ [Found: $(M + 1)^+$ 367.2467. Calc. for $C_{21}H_{34}O_5$: *m/z* 367.2484]. T.l.c. of the crude product showed spots attributed to starting material (R_F 0.33) and, probably, the 15-*epi*-Δ⁴-isomer (26) (R_F 0.31) as well as the main product.

(b) A similar experiment on the mesylate (23) gave (i) (±)-15-*epi*-prostaglandin I_2 methyl ester (61%), with properties identical with those described above, and (ii) a mixture of the 15-*epi*-Δ⁴-isomer (26) (12%) and starting material.

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