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# HYDRIDE SHIFT IN THE SOLVOLYSIS OF 5-SUBSTITUTED $PGI_1$ DERIVATIVES

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**Abstract**—Silver ion mediated solvolysis of 5-iodo-$PGI_1$ derivatives as well as the reaction of $PGF_{2\alpha}$ methylester with thallium triacetate in acetic acid were studied with the aid of deuterium isotope labelling. In protic solvents (methanol, acetic acid) high retention (70–90%) of the deuterium label is compatible with a vicinal hydride shift whereas in non-protic solvents (e.g. pyridine) elimination occurs.

In recent papers,[1] G. Kovács and coworkers suggested that the acetolysis of intermediate **1a**, formed in the reacton of $PGF_{2\alpha}$ methyl ester with thallium triacetate (TTA), proceeds with 1,2-hydride shift *via* carbonium ion **3a** stabilized by an overlap with the nonbonding orbital of the neighbouring oxygen and by internal solvation with the $C_{11}$–OH group. A similar sequence of transformations may be assumed in the reaction of 5-iodo-$PGI_1$ derivatives[2] **1b** with silver nitrate in methanol, leading to the 6-methoxy-$PGI_1$ derivatives[3] **4b**.

However, an alternative route proceeding through prostacyclins **5** and **6** could not be excluded with certainty since some results seemed to be compatible both with intermediary formation of prostacyclins and with a hydride shift. Thus, treatment of **1b** with silver acetate in dry acetic acid followed by alkaline work up gave 11,15-diacetyl-6-oxo-$PGF_{1\alpha}$ methyl ester together with a small amount of **5b** and **6b** in a ratio of *ca.* 3:2, which corresponds to the equilibrium composition of these substances.[2] However, in nonprotic solvents (e.g. toluene, DMF, pyridine) the main product formed in the reaction of **1b** with silver acetate was **6b**, illustrating the easy release of $*H^+$ from **2b** under appropriate conditions (**1b** does not react, e.g. with pyridine alone even at reflux temperature and with prolonged reaction time).

The biogenetic formation of prostacyclin[4] **10** from endoperoxide **8** initiated and controlled by enzymatic heterolysis of the peroxide linkage may conceivably follow a path leading to **9**, which after proton loss, gives rise to **10**. This metabolic transformation again seems to support proton release versus hydride shift at least under biogenetic contidions.

## RESULTS AND DISCUSSION

In order to gain decisive evidence for the relevant steps of the reactions concerned, starting from **11**,[5] we have synthetized 6-$^2$H-$PGF_{2\alpha}$ methyl ester **13*** as well as **1b***.

The reaction of **1b*** with 5 equivalents silver nitrate in methanol quenched after 1 min by the addition of excess triethylamine afforded a 1:3 mixture of epimeric methyl ketals **4b*** in quantitative yield. Clean separation of epimers was achieved by chromatography on silica gel using a 4:1 mixture of benzene-ethyl acetate as the eluent. Deacetalization accomplished by AcOH–THF–$H_2O$ (4:5:1) followed by acetylation with acetic anhydride in pyridine furnished the same triacetyl-keto-ester **14** from both epimers of **4b***, demonstrating that epimerism belongs to C-6 methyl ketal structure.

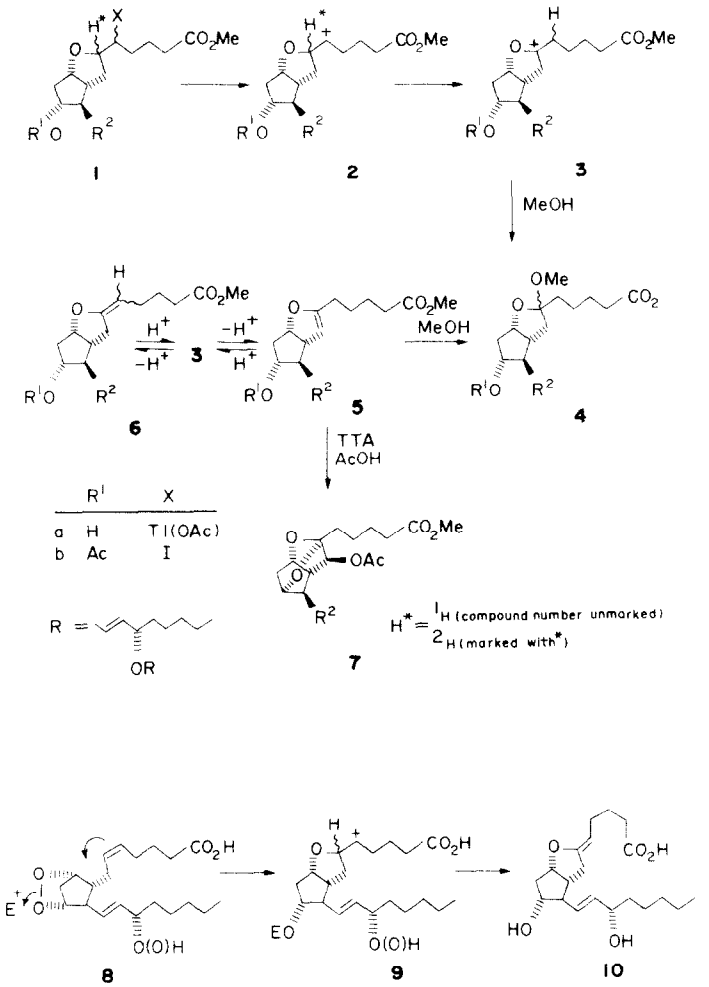
Assignment of the configuration to the epimers of **4b** was made on the basis of the characteristic chemical shift of their H-9 protons.[6] The configuration containing the carboxy-alkyl chain in the *exo*-orientation, *exo*-**4b**, was attributed to the upfield shift of its H-9 proton resonance as compared to that of *endo*-**4b**.

Mass spectrometric fragmentation revealed the retention of 1 deuterium atom per mole in both *exo*- and *endo*-**4b*** located in the carboxy-alkyl chain, reflecting that silver ion induced methanolysis of **1b** proceeds with hydride-shift through stages **2**→**3** (→**5**)→**4**. The possibility that **3** may lose a proton prior to the capture of a nucleophile, resulting in the intervention of **5**, cannot be ruled out rigorously, however, in this case an unusually high degree of regioselectivity of proton release from the ring carbon had to be assumed.

In a solvent less nucleophilic than methanol (e.g. acetic acid), the formation of **5** actually takes place, as is evident from the recovery of small amounts of **5b** and **6b** from **1b** on treatment with silver acetate in acetic acid (*vide supra*).

Evidence for isotope loss due to the intervention of **5a** was observed in the reaction of 6-$^2$H-$PGF_{2\alpha}$ methyl ester **13*** with 2 moles of thallium acetate in acetic acid, affording **7a*** with deuterium content *ca.* 30% lower (0.7 atom/mole) than that of the starting material (1 atom/mole). A reasonable explanation of this finding seems to be that solvolysis of **1a***, formed directly from the starting materials, proceeds with hydride shift via **2a***→**3a***. Deprotonation of **3a*** gives either **5a***, which may be long-lived enough to equilibrate with **6a***, or more probably, **3a*** loses proton in a nonselective manner affording a mixture of **5a*** + **6a***. In both cases partial loss of the isotope label is to be expected.

The reaction of **1b*** with silver acetate in pyridine at 80° afforded a mixture of prostacyclins (**5**:**6** = 1:5). Chromatographic separation gave **5b*** of about 50% lower deuterium content than that of **1b***. The isomeric ratio of prostacyclins corresponds to a pre-equilibrium state starting from **6b**. If formation of **5b** preceded that






of **6b** or even if both **5b** and **6b** were formed from **3b** competitively the amount of **5b** had to exceed that of **6b** since **3b**, an intermediate of the thermolysis of **4b** in HMPA, is known[7] to decompose preferentially to **5b**. Consequently, we conclude that in basic media elimination of proton $*H^+$ from **2*** leading to **6** constitutes a more preferred process than hydride-migration affording **3***. In this case the deuterium content of **5b*** (0.5 atom/mole) originates from repeated by 1-$^2$H-pyridinium acetate and pyridinium acetate while effecting equilibration between **5** and **6**. Direct corroboration of this view was gained from the experiment: treatment of 11,15-diacetyl-$PGI_2$ methyl ester (5,6-*Z*-**6b**) with 1 equivalent 1-$^2$H-pyridinium acetate in pyridine at 80° for 2 h afforded 20% **5b** (corresponding to a mixture of **5b**:**6b** = 1:5, *vide supra*) with $^2$H content *ca.* 0.5 atom/mole. Although the position of deuterium in **5b*** cannot be deduced from MS fragmentation its random distribution over C-5 and C-7 seems to be substantiated by $^1$H-NMR spectroscopy and chemical consideration, thus integration gives *ca.* 20% lower value for H-7 olefinic proton ($\delta = 4.66$) in **5b*** than for that in the unlabelled reference **5b**.

*Results of NMR and mass spectral studies*

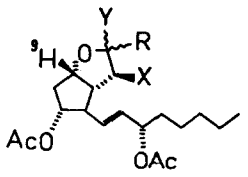
In support of the assignment to *exo* and *endo* configuration of the carboxy-alkyl chain in **4b** epimers, chemical shift data of H-9 proton resonance were measured and compared to those of several related compounds of known absolute configuration. The results summarised in Table 1 indicate a diagnostic value of H-9 shift differences to distinct *exo* and *endo* epimeric pairs of this type of skeleton.

As can be seen the absence of the alkyl group (R=H, No. 15–17) no essential difference in the H-9 shift is caused by the alternate stereochemistry of the Y= OMe substituent, further the rule of upfield shift reflecting an *exo*-oriented alkyl group seems to hold even for derivatives substituted in the heteroring (No. 18–20).

The 70 eV mass spectra of the **4b** epimeric methyl ketals, together with that of their **4b*** analogues derived from **1b***, are presented in Table 2.

Comparison of these spectra as well as these of **5b** and **5b*** leads to the following conclusion. Though no molecular ions appeared in the mass spectra of **4b** and **4b*** epimers, significant difference could be observed between the spectra of the epimeric pairs, and furthermore, these mass spectra characteristically differ from that of **5b**. Above observations are in contrast to the features expected on the basis of the mass spectral behaviour of 6-methoxy-$PGI_1$ methyl ester bis-TMS ether, which was found to give a spectrum identical with prostacycline methyl ester bis-TMS ether.[2] Peaks corresponding to primary fragments from the intact structure of **4b** are:

Table 1.




| No. | R | X | Y | $^9$H exo-R | $^9$H endo-R | solvent |
|---|---|---|---|---|---|---|
| 15. | H | OAc | OMe | 4.73<br>4.50 | 4.66<br>4.45 | $CDCl_3$ |
| 16. | H | Br | OMe | 4.78 | 4.68 | $C_6D_6$ |
| 17. | H | I | OMe | 4.76 | 4.62 | $CDCl_3$ |
| 18. | $-(CH_2)_4-CO_2Me$ | OH | OMe | 4.70 | 4.34 | $C_6D_6$ |
| 19. | " | Cl | OMe | 4.60 | 4.30 | $C_6D_6$ |
| 20. | " | =O | OMe | 4.56 | 4.28 | $C_6D_6$ |
| 21. | $I-CH(CH_2)_3CO_2Me$ | H | H | 4.62 | 4.36 | $CDCl_3$ |
| 22. | $HO-CH(CH_2)_3CO_2Me$ | H | OMe | 4.62<br>4.60 | 4.31<br>4.40 | $C_6D_6$ |
| 23. | $CH_2-I$ | H | H | 4.61 | 4.37 | $CDCl_3$ |
| 4b | $(CH_2)_4CO_2Me$ | H | OMe | 4.57 | 4.42 | $CDCl_3$ |

$(M-31)^+$ (loss of an OMe group), ion $(M-115)^+$ (*m/z* 367,2104, $C_{20}H_{31}O_6$) formed by the loss of the $^{\cdot}C_4H_8COOMe$ chain *via* rupture of the C-6–C-5 bond, which process was found to be stereoselective. The *m/z* 367 ion can lose two acetic acid molecules. These peaks were found to be lacking in the spectrum of **5b**. At the same time, no peaks were observable in the spectra of **4b** and **4b*** at *m/z* 363 and 243 (363–60), which appeared in the spectrum of **5b**. The ion formed corresponds to the loss of $^{\cdot}C_2H_4COOMe$ from the molecular ion of **5b**. Deuterium content for **5b*** was found to low about 50 ± 5 per cent, while for both **4b*** epimers, estimated from the fragment peaks, it corresponded to approximately 80%. In the case of the **4b*** epimers this deuterium atom is parted together with the carbomethoxyalkyl chain, while for **5b*** neither the elimination of $^{\cdot}C_2H_4COOMe$ and $^{\cdot}C_5H_{11}$ radicals, nor the loss of acetic acid molecules affected the labelled atom.

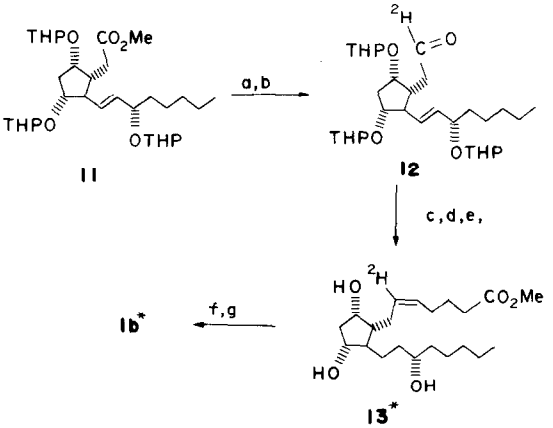
The mass spectra of **7b** and **7b*** again exhibited no molecular peaks, however, by comparison of these spectra the deuterium content of **7b*** was estimated as 60 ± 5%. The main decomposition pathways correspond to the successive elimination of two acetic acid molecules, followed by elimination of either $^{\cdot}C_2H_4COOMe$, $^{\cdot}C_4H_8COOMe$ or $COC_4H_7COOMe$ neutrals, as well as formation of the $COC_4H_8COOMe^+$ ion (*m/z* 143), which gave rise to an ion at *m/z* 111 *via* elimination of a MeOH molecule. In this case the position of the $^2$H atom can be located at the C-4 or C-5 atom of the carbomethoxy-alkyl chain.

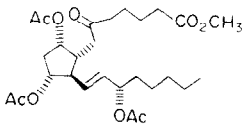


## EXPERIMENTAL

Infrared spectra were recorded on a Spectromom Model 2000 Spectrometer. NMR spectra were recorded on a Varian XL-100-15 Fourier transform instrument with TMS as an internal standard. The mass spectra were taken and the exact mass measurements were carried out using an AEL MS-902 double focusing instrument. Ionizing electron energy of 70 eV and source temperature of 180° were applied. The samples were introduced into the source via a direct probe.

*6-$^2$H-PGF$_{2\alpha}$ methyl ester* **13***. Into a stirred slurry of 100 mg (2.38 mM) lithium tetradeuteroalanate ($^2$H content 99.3 ± 0.3%) in 10 ml dry ether 1.007 g (1.82 mM) **11**[5] in 10 ml ether solution was added dropwise at 0°. After 2 h the reaction was quenched by the





**14**

successive addition of 0.1 ml water, 0.1 ml 4% aqueous NaOH, and 0.3 ml water. After being stirred for 30 minutes the greasy inorganic precipitate was filtered off and washed in portions with 20 ml ether. After evaporation 954 mg clear oil ($R_f$: 0.27 hexane–acetone, 3:1) was obtained, which was then oxidized with 1.5 g pyridinium chlorochromate in 20 ml dichloro-methane containing 1 g sodium acetate at room temperature for 3 h. The reaction mixture was layered on a 8 cm column of silica gel (15 g) and eluted with hexane-ethyl acetate (1:1). Concentration of the appropriate elutes afforded 872 mg (92%) **12** ($R_f$: 0.4, hexane–acetone, 3:1), which was dissolved in 5 ml dry dimethyl-sulfoxide and treated under argon atmosphere with 5 ml 0.5 molar solution of 4-carboxybutyliden triphenylphosphorane sodium salt in dimethyl-sulfoxide. The mixture was stirred at room temperature for 30 min, then poured into 50 ml ice–water, acidified to pH 4 with dilute aqueous sodium hydrogen sulfate and extracted with three 20 ml portions of ether. The ethereal solution was cooled to 0° and under stirring treated dropwise with 25 ml 0.2 molar ethereal solution of diazomethane. The residue obtained by evaporation of the solvent was chromatographed on 50 g silica gel, using 25% acetone–hexane eluent. Fractions collected between 100–160 ml of eluent contained 756 mg tri-tetrahydropyranyl-$PGF_{2\alpha}$ methyl ester ($R_f$: 0.45, hexane–acetone, 3:1) which was dissolved in 20 ml dry methanol and, after the addition of 50 mg pyridinium tosylate, allowed to stand at room temperature for 2 days. The reaction was quenched by the addition of 0.5 ml triethylamine, the solvent removed *in vacuo* and the residue purified by flash chromatography on 40 g silica gel eluted with 33% acetone in hexane to give 428 mg (63.5% based on **11**) **13*** identical to $PGF_{2\alpha}$ methyl ester by TLC and IR. Integration of $^1$H-NMR spectra (70 MHz, in $CDCl_3$) of **13*** gave 3 instead of 4 protons in the vinylic region $\delta_{TMS}$ 5.4–5.6 ppm .Acetylation of **13*** with acetic anhydride in pyridine + 10% 4-dimethylamino-pyridine afforded 9,11,15-triacetyl-6-$^2$H-$PGF_{2\alpha}$ methyl ester ($R_f$: 0.31, hexane–acetone, 3:1) in quantitative yield. MS: *m/z* (I%): 393 (1) M-102; 375 (4) M-120; 344 (5) 393-31; 333 (24) 393-60; 315 (100) 375*-60; 302 (6) 333-31; 284 (12) 315*-31, 262 (10) 333-71, 258 (9), 244 (20), 228 (24), 191 (65).

11,15-*Diacetyl-6-*$^2$*H-5-iodo-PGI*$_1$ *methyl ester* **1b***. The procedure given below is an adaptation of Whittaker's method.[8] To a vigorously stirred solution of 179 mg (0.84 mM) **13*** in 10 ml dry dichloromethane was added 2 ml 5% aqueous sodium hydrogen carbonate, followed by 130 mg (0.512 mM) iodine added in one lot. After 30 min 30 ml ether was added, the phases separated and the organic solution decolorized with dilute aqueous $Na_2S_2O_3$, washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave 216 mg pale yellow oil which was

Table 2. The 70 eV mass spectra† of **4b** epimers, **5b** and their $^2$H labelled analogues

| m/z | exo-4b abund. % | | exo-4b* M-Y abund. % | endo-4b abund. % | endo-4b* abund. % | 5b abund. % | 5b* M-X | 5b* abund. % |
|---|---|---|---|---|---|---|---|---|
| 452 | | | 3 | | 2 | | | |
| 451 | 3 | M-31 | 5 | 2 | 7 | | | 4 |
| 450 | 5 | M-32 | 1 | 7 | 2 | 8 | M | 4 |
| 392 | | | | | 1 | | | |
| 391 | 1 | 451-60 | 10 | 1 | 7 | | | 5 |
| 390 | 12 | 450*-60 | 2 | 8 | 3 | 9 | M-60 | 5 |
| 367 | 18 | M-115 | 19 | 5 | 6 | | | |
| 364 | | | | | | | | 3 |
| 363 | | | | | | 5 | M-87 | 3 |
| 360 | | | | | | | | 2 |
| 359 | | | | | | 6 | 390-31 | 3 |
| 349 | | | 5 | | 4 | | | 4 |
| 348 | 5 | 390*-42 | 1 | 5 | 2 | 8 | 390-42 | 5 |
| 332 | | | 16 | | 12 | | | |
| 331 | 12 | | 100 | 14 | 100 | | | 48 |
| 330 | 100 | 390*-60 | 25 | 100 | 25 | 100 | 390-60 | 52 |
| 307 | 5 | 367*-60 | 5 | 3 | 3 | | | |
| 300 | | | 11 | | 9 | | | 6 |
| 299 | 12 | 330-31 | 2 | 12 | 3 | 13 | 330-31 | 7 |
| 260 | | | 6 | | 11 | | | 8 |
| 259 | 8 | 330*-71 | 3 | 14 | 3 | 16 | 330-71 | 9 |
| 247 | 28 | 307*-60 | 28 | 16 | 10 | | | |
| 243 | 7 | | | 12 | | 8 | | |
| 233 | 5 | | | 7 | | 3 | | |
| 215 | 4 | | | 11 | | 5 | | |
| 208 | 6 | | | 9 | | 5 | | |
| 195 | 13 | | | 22 | | 20 | | |
| 187 | 21 | | | 20 | | 18 | | |

†The abundance values are corrected for naturally occuring heavy isotopes

dissolved in 5 ml dry dichloromethane and treated with 0.3 ml triethylamine, 40 mg 4-dimethylamino-pyridine and 0.2 ml acetic anhydride. After 20 min the mixture was diluted with 30 ml ether and washed subsequently with dilute aqueous sodium hydrogen sulfate, water, 2% aqueous sodium carbonate, and brine. After drying on $MgSO_4$ the solvent was evaporated to leave 243 mg (86% overall yield) **1b*** which was identical to authentic **1b** by tlc and IR. Chromatography on 50 g silica gel (tlc grade) eluted with 25% ethyl acetate in hexane at 1.6 atm pressure afforded *exo*-**1b*** (204 mg). $^1$H-NMR ($CDCl_3$): 5.54 (m, 2H), 5.22 (m, 1H), 4.79 (q, 1H), 4.62 (m, 1H), 3.93 (m, 1H), 3.68 (s, 3H), 2.72–2.26 (m, 5H), 2.06 (s, 3H), 2.03 (s, 3H), 2.0–1.15 (m, 15H), 0.90 (t, 3H) and *endo*-**1b*** (31 mg), $^1$H-NMR ($CDCl_3$): 5.56 (m, 2H), 5.26 (m, 1H), 4.90 (q, 1H), 4.36 (m, 1H), 3.72 (s, 3H), 3.70 (m, 1H), 2.8–2.2 (m, 5H), 2.10 (s, 3H), 2.08 (s, 3H), 2.1–1.15 (m, 15H), 0.96 (t, 3H).

*Solvolysis of* **1b** *induced by* $Ag^+$ *salts*

(a) *$AgNO_3$ in methanol.* Silver nitrate (45 mg, 0.265 mM) was added in one lot into the rapidly stirred solution of *exo*-**1b** (144 mg, 0.249 mM) in 5 ml methanol. The solution became turbid and silver iodide commenced to precipitate immediately. After 15 min stirring, 20 ml ether was added and the mixture filtered. The filtrate was treated with 0.2 ml triethylamine and evaporated under reduced pressure. The residue was chromatographed on 30 g silica gel eluted with 20% ethyl acetate in benzene to give *exo*-**4b** (25 mg, 20.8%); ($R_f$: 0.25, benzene-ethyl acetate, 4:1). $^1$H-NMR ($CDCl_3$): 5.50 (m, 2H), 5.21 (m, 1H), 4.72 (m, 1H), 4.57 (m, 1H), 3.67 (s, 3H), 3.21 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 0.85 (t, 3H), 2.75–1.1 (mm, 20H). MS: (see Table 2.); and *endo*-**4b** (89 mg, 74.2%), ($R_f$: 0.20, benzene-ethyl acetate, 4:1). $^1$H-NMR ($CDCl_3$): 5.45 (m, 2H), 5.16 (m, 1H), 4.85 (q, 1H), 4.42 (m, 1H), 3.65 (s, 3H), 3.10 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 0.83 (t, 3H), 2.6–1.1 (mm, 20H). MS: (see Table 2.)

Reaction of either *endo*-**1b** or *exo-endo* mixture of **1b** proceeded similarly affording the same composition of products with the same yields.

Treatment of **1b*** (*exo-endo* mixture, 54 mg) with 6-fold excess of silver nitrate in 2 ml methanol and quenching the reaction after 1 min by addition of excess triethyl-amine yields *exo*-**4b** (11 mg, 24.4%) and *endo*-**4b** (31 mg, 68.8%). Tlc, IR, $^1$H-NMR properties are identical to those of the unlabelled samples, MS data are given in Table 2. Treatment of either *exo*- or *endo*-**4b** with acetic acid-tetrahydrofurane-water (6:2:2) at room temperature afforded 11,15-diacetyl-6-oxo-$PFG_{1\alpha}$ methyl ester. Subsequent acetylation in dichloromethane with 4-dimethylamino-pyridine (2 equiv) and acetic anhydride (2 equiv) furnished 9,11,15-triacetyl-6-oxo-$PFG_{1\alpha}$ methyl ester **14**, in 92% yield, $R_f$: 0.34 (hexane–ethyl acetate, 1:1), IR (film): 1730, 1720 (shoulder) $cm^{-1}$; $^1$H-NMR: 5.46 (m, 2H), 5.12 (m, 2H), 4.84 (m, 1H), 3.59 (s, 3H), 2.8–2.1 (m, 9H), 2.0 (s, 6H), 1.98 (s, 3H), 1.8–1.0 (m, 13H), 0.86 (t, 3H). $^{13}$C-NMR: 208.5 (C=O), 174.0 ($C=O_2Me$), 170.7, 170.5, 170.3 ($O-C=OCH_3$), 132.4, 131.2 (–CH=CH–), 78.8, 77.2, 75.6 (C–OAc), 51.8 ($CO_2CH_3$).

(b) *AgOAc in acetic acid.* The solution of **1b** (189.1 mg, 0.327 mM) in 1 ml glacial acetic acid was treated with silver acetate (66 mg, 3.95 mM) by stirring at room temperature for 4 h at which time tlc indicated complete consumption of starting material. The reaction was quenched by the addition of excess aqueous saturated $NaHCO_3$ and thoroughly extracted with ether by repeated stirring and decantation. The ethereal solution was washed with brine, dried over $MgSO_4$ and concentrated to leave 150.2 mg clear oil which was subjected to chromatography on 90 g silica gel (tlc grade) column packed in hexane–ethyl acetate 10:1 containing 1% triethylamine. Elution was performed at 2 atm pressure and with a gradient ranging from 10 to 60% ethyl

Table 3. The 70 eV mass spectra† of compounds **7a** and **7b***

| m/z | 7b abund. /%/ | 7b M-X | 7b* abund. /%/ |
|---|---|---|---|
| 436 | | | 1,7 |
| 435 | 3 | M-31 | 1,3 |
| 408 | | | |
| 407 | 1 | M-59 | 0,5 |
| 406 | 2 | M-60 | 1 |
| | | | 1 |
| 365 | | | |
| 364 | 6 | 406-42 | 2,7 |
| | | | 3,3 |
| 347 | | | 15 |
| 346 | 32 | 406-60 | 17 |
| 318 | | | 3 |
| 317 | 6 | M-149 | 3 |
| 303 | | | 7 |
| 302 | 15 | 406-74 | 8 |
| 260 | | | 11 |
| 259 | 25 | 346-87 | 15 |
| 231 | 6 | 346-115 | 6 |
| 209 | 10 | | 11 |
| 204 | 31 | 346-142 | 30 |
| 150 | 50 | | 50 |
| 144 | | | 55 |
| 143 | 100 | | 45 |
| 112 | | | 30 |
| 111 | 70 | 143-32 | 40 |
| 99 | 35 | | 36 |

†The abundance values are corrected for naturally occuring heavy isotopes

acetate in hexane. Concentration of triethylamine (1%) in the eluent was maintained constant during elution. The following fractions were obtained: **5b** (4.6 mg, 3.1%), (*Z,E*-mixture of) **6b** (3.0 mg, 2%), 11,15-diacetyl-6-oxo-$PGF_{2\alpha}$ methyl ester (135 mg, 88.1%).

(c) *AgOAc in pyridine.* To the solution of **1b** (142 mg, 0.245 mM) in 1 ml dry pyridine 50 mg (0.299 mM) silver acetate was added and the mixture immersed with stirring into a pre-heated 80° oil bath for 2 h. After dilution with 30 ml ether, the yellow silver iodide was filtered off and washed several times with ether. The ethereal solution was washed with 2 × 10 ml water, 10 ml brine, dried over $MgSO_4$, concentrated and the residue subjected to chromatography on 80 g tlc grade silica gel, packed in 10% ethyl acetate + 0.1% triethylamine in hexane and eluted with the same mixture at 2 atm pressure to give **5b** (19 mg, 17%) and **6b** (74.5 mg, 76.6%). A similar experiment carried out with **1b*** (110 mg) and AgOAc (35 mg) in pyridine (1 ml) afforded **5b*** (15.4 mg, 18%) and *Z,E*-mixture of **6b** (53 mg, 62%). MS data of **5b** and **5b*** are given in Table 2.

*Equilibration of* 11,15-*diacetyl-PGI*$_2$ *methyl ester* (*5Z*)-**6b**) *with* 1-$^2$*H-pyridinium acetate in pyridine*

Dry pyridine (5 ml) was treated at 0° under argon with 0.3 ml freshly distilled acetic anhydride followed by 0.1 ml tetradeuteromethanol (98% isotopically pure). After 2 h stirring at room temperature the mixture was gradually warmed to 60° and maintained at this temperature for 1 h. Removal of methyl acetate formed was effected by raising the temperature to 80° and blowing off the vapours with an argon stream for 15 min. After cooling to room temperature a 0.5 ml portion was withdrawn and added to the solution of 115 mg (0.255 mM) (*5Z*)-**6b** in 0.5 ml dry pyridine. After 2 h heating at 80° the reaction mixture was worked up and chromatographed as above affording **5b** (23 mg, 20%) and **6b** (68 mg, 59%). The MS fragmentation pattern was indistinguishable from that of **5b*** indicating 50 ± 5 per cent deuterium present in the molecule.

*Reaction of* 6-$^2$*H-PGF*$_{2\alpha}$ *methyl ester* **13*** *with thallium triacetate*

The reaction of 240 mg (0.65 mM) **13*** with 744 mg (1.95 mM) thallium triacetate in 4 ml glacial acetic acid was performed according to the procedure given by G. Kovács and coworkers.[1] Chromatography on 50 g tlc grade silica gel eluted with hexane–acetone (2:1) afforded 52 mg (19%) **7a*** identical by tlc, IR, $^1$H-NMR to the authentic unlabelled compound. For MS measurement **7a*** (40 mg) was converted to **7b*** by acetic anhydride (2 equiv), triethylamine (2 equiv) and 4-dimethylaminopyridine (0.1 equiv) in dichloromethane (10 ml) at ambient temperature (60 min). Usual work-up gave 41 mg (93%) **7b*** (see Table 3.)

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