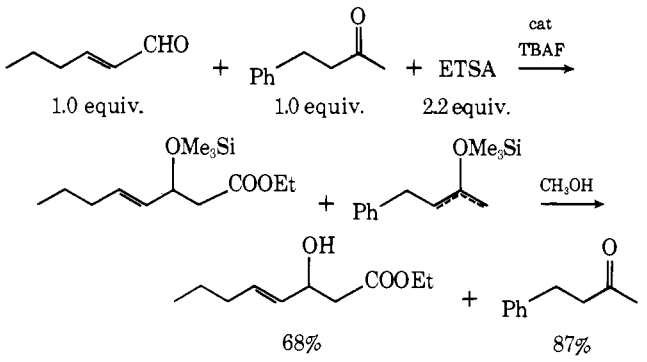
reactive halides are not. Especially aldehydes react with ETSA–TBAF as smoothly as ketones to afford β-trimethylsiloxy ester adducts:[15] for example, *trans*-2-hexenal, benzaldehyde, and β-phenylpropionaldehyde reacted with ETSA at −30° in the presence of a catalytic amount of TBAF to give the corresponding adducts in 82, 76, and 24% yields, respectively. Namely, when this silylation procedure is applied to aldehydes, it offers us a simple and selective way of introducing carboalkoxymethyl groups which discriminate between aldehydes and ketones. The following example illustrates this selectivity.



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(2) (a) G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4462 (1968); (b) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(3) (a) I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97**, 3257 (1975). (b) Quaternary ammonium enolates underwent aldol reactions with aldehydes: unpublished results by the authors and Professor R. Noyori, Nagoya University.

(4) TBAF has been proved to be a relatively weak base. For example, 0.03 equiv of TBAF in THF caused only very slow base-catalyzed reactions of alkyl thiols and diethyl malonate; it catalyzed no condensation between cyclohexanone and benzaldehyde, either: unpublished results. In addition, under the reaction conditions described here, β-trimethylsiloxy esters remained unchanged: cf. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

(5) (a) Neutralization of commercial 10% aqueous tetra-*n*-butylammonium hydroxide with dilute aqueous HF gave TBAF. The bulk of water was removed, and the paste was dried at 90°, 0.5 mm for 15 h. The resulting hygroscopic mass was pulverized and stored over P_2O_5. (b) With KF (0.02 equiv) and dicyclohexyl-18-crown-6 (0.01 equiv) in THF, this catalyzed reaction proceeded well at room temperature, but it took about 1 week for completion.

(6) Trimethylchlorosilane and ethyl bromoacetate reacted in the presence of zinc dust to give ETSA in 70–75% yield, which was practically stable: R. J. Fessenden and J. S. Fessenden, *J. Org. Chem.*, **32**, 3535 (1967).

(7) On silylation of acetoin, the silylation proceeded regiospecifically, and gave none of the isomer, 2,3-bis(trimethylsiloxy)-2-butene (NMR and GLC), while the yield was fair.

(8) Because of some reaction path which may consume fluoride ion, an increased amount of TBAF was required at elevated temperatures in order to obtain a fully equilibrated mixture of a silyl enol ether.

(9) The ratios, **1a**:**2a** = 81:19 and 91:9 were reported by House and Stork, respectively.[2]

(10) The NMR spectrum of the silylated product was completely consistent with the silyl enol ether with a less highly substituted olefinic bond; δ 4.21 (s, 2 H), 5.73 (d, J = 16 Hz, 1 H), 6.36 (br d, J = 16 Hz, 1 H). Treatment of the crude reaction mixture with NBS gave solely the expected bromomethyl ketone in 71% overall yield.

(11) While the reactivity of TBAF rapidly diminishes on exposure to moisture, rapid manipulation in air meets with success.

(12) With 0.003 equiv of TBAF, ketones were silylated in 3 h at ca. 20°.

(13) R. H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974).

(14) On silylation in 1 M CH_3CN, cyclododecanone was silylated in 86% yield.

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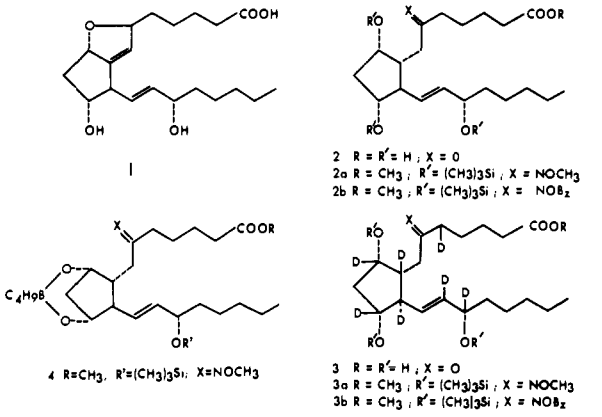
Isolation, Structure, and Biosynthesis of 6-Ketoprostaglandin $F_{1\alpha}$ in the Rat Stomach

Sir:

During our studies of the mechanism of biosynthesis of 6(9)-oxy-11,15-dihydroxyprosta-7,13-dienoic acid (**1**), which was isolated and characterized by us several years ago,[1-3] we discovered the presence of another compound (**2**). This communication deals with evidence supporting its proposed structure i.e., 6-keto-$PGF_{1\alpha}$, evidence arising from biosynthetic studies using as substrates undeuterated as well as 5,6,8,9,11,12,14,15-octatritio-(and octadeuterio)-arachidonic acid and 5,6,8,9,11,12,14,15-octatritio-(and octadeuterio)-15-hydroxy- and -15-hydroperoxyprosta-5,13-dienoate 9,11-cyclic endoperoxide (PGH_2 and PGG_2, respectively).[4-6]

Substrate (100–200 μg) was incubated (10 min, 37°, O_2 atmosphere with arachidonic acid substrate or 2 min with PGG_2 and PGH_2 substrate) with a homogenate (w/v 1/20) of the rat stomach fundus (12 male Wistar rats, 200–250 g) prepared in 0.05 M KH_2PO_4–NaOH buffer (pH 7.4) containing EDTA (20 mM). Incubations were terminated by the addition of water (2 vol) and diethyl ether (10 vol) and the mixture was acidified to pH 3 with 0.5 N HCl. The ether phase was separated, washed to neutrality with water and evaporated under vacuum. The extract was methylated with ethereal diazomethane and the resulting methyl ester was purified by thin layer chromatography (silica gel G/chloroform:methanol:acetic acid:water 90:9:1:0.65 v/v).



The purified TLC zone (R_f 0.45; PGE_2 = 0.43) was only slightly reactive to sodium borohydride or 0.5 N sodium hydroxide in methanol. Both of these reactions convert PGE_2 formed in small amounts during incubation and present in this TLC zone to $PGF_{2\alpha}$ and $PGF_{2\beta}$ and PGB_2, respectively. Compound **2**, however, reacted with methoxylamine hydrochloride (derivative a) and benzylhydroxylamine hydrochloride (derivative b) in pyridine and these derivatives were analyzed as the trimethylsilyl ether derivatives by mass spectrometry.[7] Derivative **2a** (retention time 25.2 carbons; PGE_2 = 23.8, 24.3 carbons—3% SE-30 on Gas Chrom Q, 260°) showed intense fragment ions at *m/e* 629 (M^+), 614 (M − CH_3), 598 (M − OCH_3), 558 (M − C_5H_{11}), 539 (M − $(CH_3)_3SiOH$), 508 (M − (OCH_3 + $(CH_3)_3SiOH$)), 468 (M − (C_5H_{11} + $(CH_3)_3SiOH$)), 449 (M − (2 × $(CH_3)_3SiOH$)), 418 (M − ((2 × 90) + 31)), 378 (M − (C_5H_{11} + (2 × $(CH_3)_3SiOH$ + OCH_3)) 217 ($(CH_3)_3$ Si^+O=CHCH=CHOSi$(CH_3)_3$), 191 ($(CH_3)_3Si$-^+O=CHOSi$(CH_3)_3$), 173 ($(CH_3)_3Si^+O$=CHC_5H_{11}), and 115 (C(1)–C(5) fragment, base peak).[8] The benzylhydroxylamine derivative **2b** (retention time 29.5 carbons first isomer; 29.9 carbons second isomer—3% OV-1 on Gas Chrom Q, 240°) showed fragment ions containing the benzyloxime group (first isomer) observed at *m/e* 690 (M − CH_3), 615

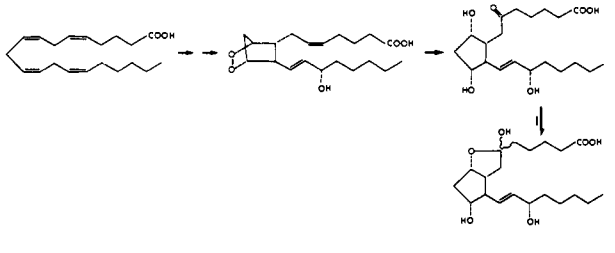
(M − $(CH_3)_3SiOH$), 544 (M − (($(CH_3)_3SiOH$ + C_5H_{11})), 525 (M − (2 × $(CH_3)_3SiOH$)), and 454 (M − (2 × $(CH_3)_3SiOH$ + C_5H_{11})); fragment ions not containing the benzyloxime group were observed at *m/e* 598 (M − C_7H_7O), 508 (M − (C_7H_7O + $(CH_3)_3SiOH$)), 499 (M − (C_7H_7 + (C(1)-C(5) fragment))), 418 (M − (C_7H_7O + (2 × $(CH_3)_3SiOH$))), 413 (M − (C(1)-C(7) fragment) − (2 × CH_3)), 352 (M − ((C(1)-C(7) fragment) + H + $(CH_3)_3SiOH$))), 217, 191, 173, and 115 (base peak above *m/e* 100).

The product derived from PGG_2 had the same R_f value and retention time on gas chromatography. When 5,6,8,9,11,12,14,15-octadeuterioarachidonic acid or PGG_2 was used as substrate, mass spectrometry of the methoxime derivative of the resulting product (**3a**) showed a retention of seven deuterium atoms which were located at positions 5,8,9,11,12,14,15 after comparison of its mass spectrum with that of **2a.** The mass spectrum showed the expected shifts at *m/e* 636 (7 D), 621 (7 D), 606 (7 D), 565 (7 D), 546 (7 D), 545 (6 D), 515 (6 D), 474 (6 D), 455 (6 D), 454 (5 D), 424 (6 D), 419 (6 D), 384 (6 D), 219 (2 D), 192 (1 D), 174 (1 D), and 116 (1 D). The location of the deuterium atoms was further confirmed in the mass spectrum of the benzylhydroxylamine derivative (**3b**). Mass spectral shifts of this compound (first isomer) were observed at *m/e* 697 (7 D), 641 (7 D), 622 (7 D), 621 (6 D), 606 (7 D), 605 (6 D), 550 (6 D), 531 (6 D), 515 (7 D), 505 (6 D), 460 (6 D), 419 (6 D), 219 (2 D), 192 (1 D), 174 (1 D), and 116 (1 D). Similar results were obtained when PGH_2 was used as substrate.

Additional structural support was obtained after catalytic reduction (PtO_2/ethanol) of **2** and **3**. Mass spectra of the hydrogenated derivative of **2a** confirmed the presence of one double bond (M^+ 631). The hydrogenated derivative of **3a** was similarly shifted by two mass units (M^+ 638). The presence of the cis-9,11-dihydroxy function was supported by the formation of a cyclic *n*-butyl boronate (NBB) derivative **4** (retention time 26.6 carbons; $PGF_{2\alpha}$ $MeNBBMe_3Si$ = 25.4 carbons—3% SE-30 on Gas Chrom Q, 240°). Its mass spectrum showed an intense fragmentation pattern characteristic of NBB derivatives of the PGF's[9] namely, *m/e* 551 (M^+), 536 (M − CH_3), 480 (M − C_5H_{11}), and 378 (M − (($(CH_3)_3SiOCHC_5H_{11}$)) [97% intensity]. Other fragment ions in the spectrum included *m/e* 520 (M − OCH_3), 461 (M − (($(CH_3)_3SiOH$)), 449 (M − $C_4H_9BO_2H_2$), 430 (M − (($(CH_3)_3SiOH$ + OCH_3)), 418 (M − ($C_4H_9BO_2H$ + OCH_3)), 187, 173, and 115 (base peak).

These results demonstrate that arachidonic acid is converted in good yield by rat stomach homogenates into 6-keto-$PGF_{1\alpha}$ via the prostaglandin endoperoxide mechanism (see Scheme I). An interesting feature of this compound,

Scheme I. Formation of 6-Keto-$PGF_{1\alpha}$ and Its Lactol Form by the Rat Stomach



which belongs to the prostaglandin "1" series (i.e., PGE_1 and $PGF_{1\alpha}$), is its formation from a substrate of the prostaglandin "2" series (i.e., PGE_2 and $PGF_{2\alpha}$). Since the isolated product is unreactive to sodium borohydride in methanol, yet reacts with methoxylamine hydrochloride, we propose that the keto group at position 6 must be in the lactol form coupled with the hydroxyl group at position 9. Thus the equilibrium between the open and cyclic forms in methanol heavily favors the lactol form. Further work on the origin of the oxygen atom at position 6 is currently in progress.

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(7) All mass spectra were recorded at 70 eV on a Varian MAT CH-5 GC-MS system, an MRC regional facility at the Best Institute, Toronto, operated by Mr. L. Marai.
(8) The mass spectrum of derivative **2a** was identical with that of 6-keto-$PGF_{1\alpha}$ chemically synthesized by Dr. Udo Axen, The Upjohn Co.
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Regioselective Remote Photocyclization. Examples of a Photochemical Macrocyclic Synthesis with Sulfide-Containing Phthalimides[1,2]

Sir:

Certain phthalimides (**1**, *n* = 1-3) possessing a terminal sulfide function in their *N*-alkyl side chain undergo photocyclization to give five- to seven-membered azathiacyclols (**2**, *n* = 1-3), probably by way of Norrish type II reactions.[3] We have now extended this type of reaction to an easy synthesis of medium- to large-sized ring systems on the basis of an unusually regioselective remote photocyclization of the sulfide-containing phthalimides.

A solution of **1a-d** in acetone (10 mM) was irradiated with a 400-W high-pressure mercury lamp in a stream of argon for 1-2 h. As shown in Table I,[4] in most cases mixtures of nine-membered (**2a-d**) and seven-membered ring compounds (**3a-d**) were obtained, with the former as major products, after preparative TLC in moderate direct yields. In a representative example, the structural assignment for **2a** was based on: (i) the presence of the cyclol moiety[5] ((uv 259 nm, ϵ 5200), amide (ir 1655 cm^{-1}), hydroxyl (3240 cm^{-1})) and a methylene (instead of methyl in **1a;** NMR 3.15 ppm, s); (ii) the molecular weight and composition of $C_{14}H_{17}NO_2S$ (mass *m/e* 263; elemental analysis); and finally (iii) by analogy with previous cyclizations[3] of **1** in which the number of methylenes in the side chain (*n*) varied from 1 to 3. The substrates further examined represent a homologous series with side chains varying from *n* = 6 to 12 (**1e-i**).[6] In all examples studied, irradiation afforded mainly the expected ring system, up to 16-membered (**2i**), as a result of C-C bond formation between the imide carbonyl and the terminal methylmercapto group.[7] In some cases (**2d, 3c**) the dehydrated products, such as **4**, were isolated in further support of the postulated cyclol structures. Since it might be suspected that photodimerization has occurred with only the monomer peaks showing in the mass spectra, the molecular weight of, e.g., **2i,** was determined by a vapor pressure method;[8] the value (362) obtained was consistent with that