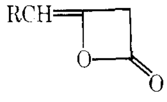
proceeds quite slowly without acid catalyst,[9] its acyl derivatives (**3**) are expected to undergo easily the ethanolysis because of enolization of the acyl group.[11] When the crude **3a**[13] was heated in methanol under reflux, the methanolysis took place smoothly with the evolution of carbon dioxide. After 2 h, the solvent was evaporated and the residue was distilled under reduced pressure to give methyl propionylacetate (**4a**)[5a] in 82% yield from **1**. Various methyl acylacetates (**4b–k**) were similarly synthesized. In the same manner, the ethanolysis of **3** also proceeded readily to give the corresponding ethyl esters (**5a–k**) in good yield. The results are summarized in Table I.

The reactivity of **3** in alcoholysis is comparable to that of diketene,[14] which is known to be susceptible to attack by various nucleophiles such as alcohols[15] and amines[16] to give acetoacetic acid derivatives. Therefore, **3** can be regarded as a synthetic equivalent of mixed diketene **8**, which is usually not available.



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This alcoholysis of **3** was extended to the synthesis of acylacetic acid benzyl and *tert*-butyl esters without any difficulty. A benzene solution of **3** containing 3 equiv of benzyl alcohol or *tert*-butyl alcohol was refluxed for 3 h. After evaporation of the solvent, the residue was distilled to give **6** or **7** in good yield. The results are also summarized in Table I.

Finally, some trichloroethyl esters,[17] which can be hydrolyzed by zinc in acetic acid,[18] were synthesized in fair yield.[19]

$$RCOCH_2CO_2CH_2CCl_3$$

$$\mathbf{9a}, R = CH(CH_3)_2; 67\%$$

$$\mathbf{b}, R = (CH_2)_2CO_2CH_3; 70\%$$

$$\mathbf{c}, R = (CH_2)_2OCH_2CH_3; 67\%$$

Further applications of this simple and versatile synthesis of β-keto esters to some developments of the Carroll reaction,[20] indole synthesis,[21] etc., are currently in progress.

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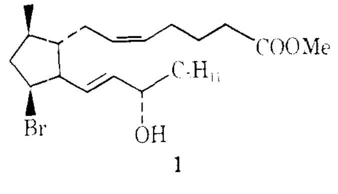
Prostaglandin H_2 Methyl Ester

Summary: Prostaglandin H_2 methyl ester has been prepared in 20–25% yield from $9\beta,11\beta$-dibromo-9,11-dideoxyprostaglandin $F_{2\alpha}$ with silver trifluoroacetate and hydrogen peroxide.

Sir: The prostaglandin endoperoxides PGH_2 and PGG_2 have attracted considerable attention in recent years. These intermediates in prostaglandin biosynthesis play an important role in diverse physiological functions such as blood platelet aggregation,[1–3] and an understanding of the chemistry and pharmacology of these species may well provide new insights into the chemical mechanism of heart attack and stroke.[4] Several different synthetic approaches to the 2,3-dioxabicyclo[2.2.1]heptane system have been reported[5,6] and recently the Upjohn group of Johnson, Nidy, Baczynskyj, and Gorman[7] have reported a synthesis of PGH_2 methyl ester (**2**) in 3% yield from $9\beta,11\beta$-dibromo-9,11-dideoxyprostaglandin $F_{2\alpha}$ methyl ester (**1**). The method reported by Johnson et al.[7] involves reaction of **1** with potassium superoxide[8,9,10] in an S_N2 displacement reaction. Inasmuch as the yields of **2** formed by the superoxide method are low, and prospects for yield improvement are limited,[7] we have sought to develop other methods for carrying out the conversion **1** → **2**. In particular, the potential conversion of **1** to **2** by silver salts and hydrogen



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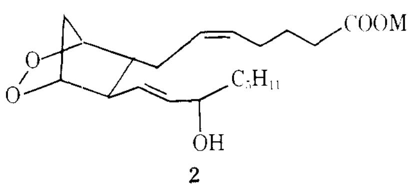

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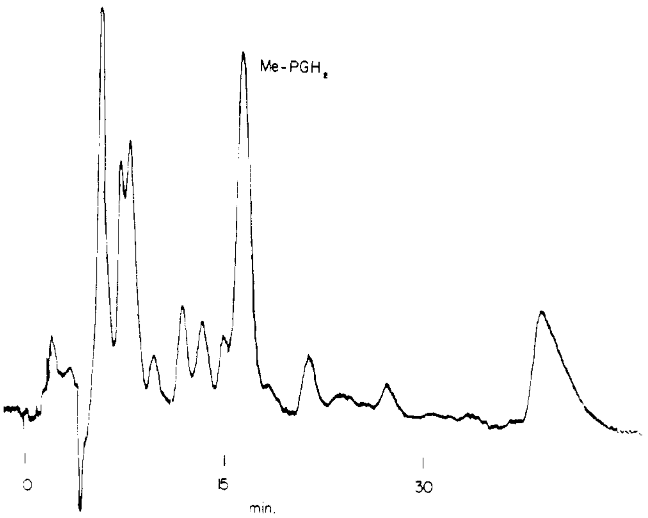

Figure 1. LC trace from reaction mixture of 3.9 mg of **1**, 59 mg of silver trifluoroacetate, and 68 μL of H_2O_2 in 0.5 mL of ether (conditions of chromatography as stated in General Procedure).

peroxide seemed promising, since this method had been used successfully to prepare the model PGH endoperoxide 2,3-dioxabicyclo[2.2.1]heptane from *cis*-1,3-cyclopentane dibromide.[11] We report here the preparation of **2** from **1** by the Ag^+/H_2O_2 method.[11,12] The yields of **2** formed by this method (20–25%) are superior to the superoxide method[7] and this advantage makes the chemical synthesis of **2** or its analogues (including the free acid, PGH_2) synthetically reasonable.

The reaction of **1**[13] with Ag^+/H_2O_2 was carried out under a variety of experimental conditions. Of primary importance in determining the course of reaction of **1** with Ag^+/H_2O_2 was: (1) the silver salt used; (2) the reaction time; and (3) the concentration of Ag^+ and H_2O_2 employed. Preliminary screening reactions (3 mg) were carried out using silver acetate, silver trifluoroacetate, or silver stearate reagents in several organic solvents. Although some **2** may have been produced from the stearate and acetate, by far the best reagent proved to be silver trifluoroacetate/H_2O_2 in diethyl ether. Further, side products appeared to be minimized by using relatively concentrated solutions of silver trifluoroacetate/H_2O_2 and short reaction times. For example, when **1** (7.9 mg/mL) was reacted with silver trifluoroacetate (54 mg/mL) and H_2O_2 (110 μL/mL) in diethyl ether, reaction times of >0.5 h were required for consumption of **1**, and nonpolar compounds were the major products. An increase of the silver reagent to 118 mg/mL and H_2O_2 to 136 μL/mL led to rapid consumption of **1** and, if reaction was terminated after 15 min, a product mixture of which **2** was a significant component.[15]

A major problem encountered in the preparation of PGH_2 methyl ester by the superoxide[7] or silver trifluoroacetate/H_2O_2 methods is the separation of **2** from the complex product mixture. The Upjohn group used preparative TLC, but noted that considerable decomposition of **2** could occur if chromatography was not carried out immediately after application of **2** to the TLC plates.

High-pressure liquid chromatography (LC) is an important separations method, but no reports of PGH_2 purification by LC have appeared. We have been able to greatly simplify the isolation of **2** from the Ag^+/H_2O_2 reaction mixture by LC. A typical LC trace of a crude reaction mixture chromatographed at −11 °C on microporasil (solvent 70:20:10 hexane/EtOAc/THF; refractive index detection) is presented in Figure 1. PGH_2 methyl ester can be readily detected in product mixtures resulting from reaction of as little as 1 mg of dibromide **1**. Thus, quantities of **2** as low as 150 μg can be detected. Although most of our chromatography has been carried out in jacketed columns at −10 °C or colder, we have no evidence that suggests that this low temperature precaution is entirely necessary. In fact, we have carried out LC of pure **2** at room temperature with no apparent decomposition.

The product, **2**, purified by LC was peroxide positive to ferrous thiocyanate reagent,[7] it chromatographed under several different solvent conditions identically with authentic PGH_2 methyl ester,[13] and it was reduced to $PGF_{2\alpha}$ methyl ester with triphenylphosphine.[16]

The sevenfold improvement in the yield of **2** for the Ag^+/H_2O_2 method as compared to the superoxide approach and the easy isolation of PG endoperoxides by LC opens the way for the synthesis of a variety of endoperoxide analogues[17] and makes the parent free acid, PGH_2, potentially available by chemical synthesis.

Silver Trifluoroacetate/H_2O_2 (General Procedure). To 12.4 mg (2.51×10^{-5} mol) of **1** in 1.6 mL of anhydrous ether was added 212 μL of 98% H_2O_2[14] (8.8×10^{-3} mol, 350 equiv) followed by addition of 183 mg of silver trifluoroacetate[18] (8.4×10^{-4} mol, 33 equiv) in one batch to the dibromide–H_2O_2 solution. The mixture was stirred for 15 min at room temperature, during which time a light yellow solid precipitated from solution. The reaction mixture was diluted to 25 mL and washed with 30-mL portions of cold water, cold bicarbonate, and cold water. The ether layer was dried over sodium sulfate at 0 °C and the solvent then removed. LC on a Waters microporasil column (−11 °C) with 70:20:10 hexane (distilled from sodium)/EtOAc (distilled form P_2O_5)/THF (distilled from $LiAlH_4$) with a Waters refractive index detector resulted in a LC trace similar to that shown in Figure 1. Removal of the solvent, first by rotary evaporator at aspirator pressure followed by vacuum pump solvent removal (<0.1 mm for 45 min), resulted in 1.9 mg of **2** (21%), pure by TLC and LC.

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(15) The two major products observed were found at R_f 0.46 and 0.36 (**2**). Minor products were observed at R_f 0.56, 0.38, and 0.25. The R_f of **1** and **2** were 0.50 and 0.36 under these conditions (65:35 EtOAc/hexane; 5 cm × 20 cm × 0.25 mm E. Merck Silica Gel 60F-254 plates).
(16) The tris(trimethylsilyl) ether of $PGF_{2\alpha}$ methyl ester was analyzed by GC-MS and compared to authentic material. Unsilylated $PGF_{2\alpha}$ methyl ester was

also compared to authentic material by TLC (see ref 7).
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