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Prostaglandin phosphonic acids through homolytic halodecarboxylation of prostaglandins F_{1α} and F_{2α}

Andrew S. Kende,^{a,*} Jared B. J. Milbank,^a Frank H. Ebetino^b and Mitchell A. deLong^b

^aDepartment of Chemistry, University of Rochester, Rochester, NY 14627, USA

^bProcter and Gamble Pharmaceuticals, Mason, OH 45040, USA

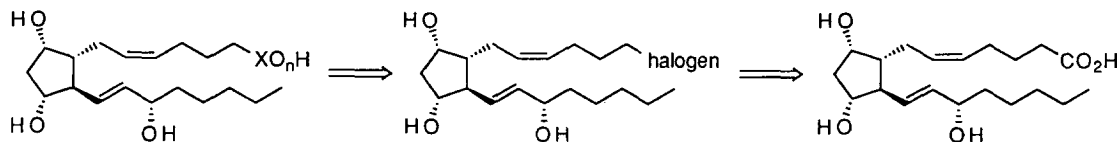
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Abstract

Phosphonic acid derivatives of prostaglandins F_{1α} and F_{2α} were prepared through Arbuzov reaction of 2-decarboxy-2-iodoprostaglandin intermediates. The intermediate iodo compounds, which are potentially valuable for the synthesis of other analogs, were obtained from the parent prostaglandins by Barton's modification of the Hunsdiecker reaction. © 1999 Elsevier Science Ltd. All rights reserved.

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The wide range of biological interactions of prostaglandins has prompted much synthetic effort directed both towards the prostaglandins themselves and towards analogs of them.¹ One underrepresented class of analogs is that in which the carboxylic acid is replaced with heteroatom acids.² We considered that a 2-decarboxy-2-haloprostaglandin, a heretofore undisclosed class of prostaglandin, could act as an intermediate for the synthesis of such compounds, and that intermediates of this type could be obtained from prostaglandins themselves by halodecarboxylation; i.e., Hunsdiecker reaction (Scheme 1). Overall, this would allow quick access to a variety of new prostaglandin derivatives without recourse to de novo synthesis.

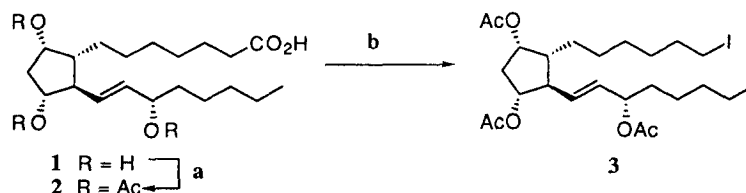


Scheme 1.

The harshness of the classical Hunsdiecker reaction³ would probably limit its use on prostaglandins. However, Barton has introduced a much milder method in which a carboxylic–thiohydroxamic mixed anhydride is homolyzed and undergoes decarboxylation to give an alkyl radical which abstracts halide

* Corresponding author.

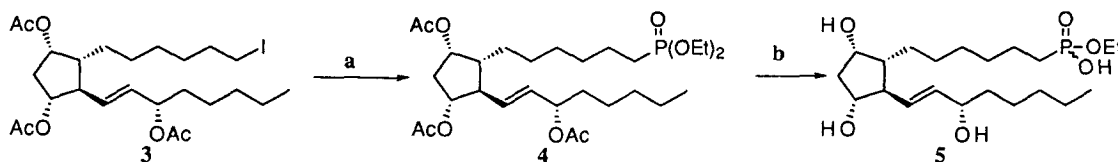
from a donor, often the solvent.⁴ Although this is a mild method, we initially selected prostaglandin F_{1α} (**1**)⁵ because it is one of the more robust prostaglandins and lacks a double bond on the *alpha*-side chain on which a radical will be generated. Additionally, because the carboxylic–thiohydroxamic anhydride is generally prepared by treatment of an acid chloride with a salt of *N*-hydroxypyridine-2-thione, we elected to acetylate the alcohols (Scheme 2).



Scheme 2. (a) 30 equiv. Ac₂O, 35 equiv. Et₃N, cat. DMAP, CH₂Cl₂, rt 8 h; then sat. aq. Na₂CO₃, 1 h, 97%; (b) (COCl)₂, cat. DMF, CH₂Cl₂; then CF₃CH₂I, cat. DMAP, the sodium salt of *N*-hydroxypyridine-2-thione, CH₂Cl₂, hv, reflux, 56%

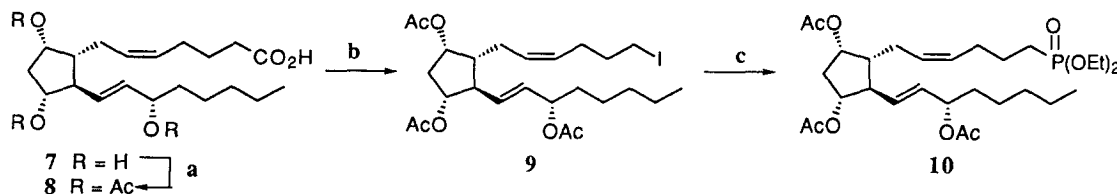
In terms of propensity of displacement, the alkyl iodide would be most desirable. Unfortunately, iodides are the halides obtained in lowest yield by Barton's procedure. Indeed, when prostaglandin F_{1α} triacetate (**2**) was treated by Barton's best procedure for formation of iodides (iodoform as iodine radical source and cyclohexene as solvent and trap for I₂ formed) a complex mixture resulted. More recently, Eaton has advocated the use of trifluoroiodoethane as the source of iodide radical.⁶ Under his conditions, including in situ formation of the carboxylic–thiohydroxamic anhydride,⁶ prostaglandin F_{1α} triacetate gave iodo-norprostaglandin **3**⁷ in 56% yield after chromatography.

With a halo-norprostaglandin in hand, we elected to produce a phosphonic acid derivative, since this would be readily obtainable from the Arbuzov reaction⁸ and in the only reported case of a prostaglandin phosphonate,^{2b} the phosphorus ester was not subsequently deprotected. Thus, iodo-norprostaglandin **3** was heated at reflux with a 100-fold excess of triethyl phosphite to give diethylphosphonate **4**.⁹ The phosphorus ester of diethylphosphonate **4** was then hydrolyzed under basic conditions with concomitant deprotection of the alcohols to give monoethyl phosphonate **5**¹⁰ (Scheme 3).



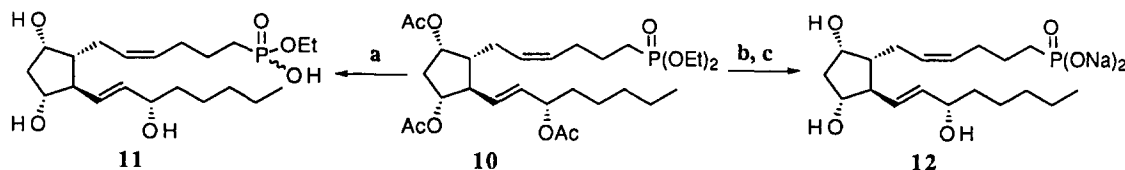
Scheme 3. (a) 100 equiv. P(OEt)₃, reflux, 4 h, 91%; (b) 100 equiv. 2.5 M aq. NaOH, EtOH, reflux, 5 h, 73%

Having successfully prepared a prostaglandin F_{1α} analog, we turned to prostaglandin F_{2α} (**7**). In this case there is a potentially problematic alkene in the side chain; however, a cyclization would require a 4-*exo trig* or 5-*endo trig* process, neither of which is favored. In the event, prostaglandin F_{2α} triacetate (**8**) gave the corresponding iodo-norprostaglandin **9**¹¹ in 64% yield (Scheme 4).



Scheme 4. (a) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt 8 h; then sat. aq. Na₂CO₃, 1 h, 99%; (b) (COCl)₂, DMF, CH₂Cl₂; then CF₃CH₂I, DMAP, sodium salt of *N*-hydroxypyridine-2-thione, CH₂Cl₂, hv, reflux, 64%; (c) 100 equiv. P(OEt)₃, reflux, 4 h, 82%

As in the previous case, iodo-norprostaglandin **9** was converted into diethyl phosphonate **10**¹² then deprotected under basic conditions to give pure monoethyl phosphonate **11**.¹³ Alternatively, we attempted to doubly deprotect the phosphorus ester of diethyl phosphonate **10** with bromotrimethylsilane,¹⁴ which required subsequent removal of the acetate protecting groups (Scheme 5). Unfortunately, the sodium phosphonate produced by this method (**12**) was only about 75% pure and was difficult to purify.



Scheme 5. (a) 100 equiv. NaOH, EtOH–water, reflux, 5 h, 73%; (b) TMSBr, rt 14 h; (c) 5.5 equiv. NaOH, MeOH–water, rt 22 h

Overall, we have demonstrated that natural prostaglandins can be converted rapidly into 2-decarboxy-2-phosphonic acid derivatives through protected 2-iodo-2-decarboxy intermediates obtainable by Barton's modification of the Hunsdiecker reaction. The 2-haloprostaglandins could be widely useful in the synthesis of diverse novel prostaglandins.

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- Compound **3**: Oxalyl chloride (60 μ L, 0.69 mmol) was added to a solution of **2** (44.5 mg, 92 μ mol) and DMF (0.08 μ L) in CH_2Cl_2 (0.3 mL). The mixture was allowed to stand at room temperature for 1 h, and was then concentrated. The residue was taken up in CH_2Cl_2 (0.2 mL). Meanwhile, a mixture of the sodium salt of *N*-hydroxypyridine-2-thione (15 mg, 0.10 mmol), DMAP (1.0 mg, 8.2 μ mol), CH_2Cl_2 (0.4 mL), and $\text{CF}_3\text{CH}_2\text{I}$ (0.10 mL, 1.0 mmol) under argon was brought to reflux by irradiation with a 250 W General Electric floodlamp. The solution of acid chloride was added to this second mixture over 5 min, and irradiation was continued for a further 25 min. The mixture was purified directly by preparative TLC (SiO_2 , 20% ethyl acetate/hexane) to give compound **3** (29 mg, 56%). ^1H NMR (CDCl_3 , 300 MHz) 5.45–5.54 (m, 2H), 5.21 (tdd, $J=6.5, 5.0, 1.5$ Hz, 1H), 5.14 (t, $J=4.7$ Hz, 1H), 4.86 (ddd, $J=8.8, 7.8, 4.4$ Hz, 1H), 3.17 (t, $J=7.0$ Hz, 2H), 2.45–2.58 (m, 2H), 2.06, 2.04, 2.01 (3 \times s, 3H each), 1.79 (quin, $J=7.1$ Hz, 2H), 1.59–1.67 (m, 4H), 1.2–1.40 (m, 14H), 0.87 (t, $J=6.7$ Hz, 3H). ^{13}C NMR 170.6, 170.5, 170.2, 132.5, 131.3, 77.8, 74.13, 74.05, 52.1, 47.1, 39.0, 34.3, 33.3, 31.5, 30.2, 28.6, 27.3, 26.8, 24.7, 22.5, 21.3, 21.1, 21.0, 14.0, 7.0. Found (FAB) MNa^+ : 587.1835; $\text{C}_{25}\text{H}_{41}\text{IO}_8$ requires MNa^+ : 587.1846.
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- Compound **4**: ^1H NMR (CDCl_3 , 300 MHz) 5.43–5.53 (m, 2H), 5.20 (tdd, $J=6.6, 3.9, 1.6$ Hz, 1H), 5.12 (t, $J=4.7$ Hz, 1H), 4.85 (ddd, $J=8.8, 7.6, 4.4$ Hz, 1H), 4.00–4.14 (m, 4H), 2.43–2.57 (m, 2H), 2.05, 2.03, 2.00 (3 \times s, 3H each), 1.48–1.73 (m, 8H), 1.30 (t, $J=7.0$ Hz, 6H), 1.20–1.35 (m, 14H), 0.86 (t, $J=6.7$ Hz, 3H). ^{13}C NMR 170.6, 170.4, 170.2, 132.5, 131.3, 77.8, 74.1, 74.0, 61.4 (d, $J=8$ Hz), 52.1, 47.1, 38.9, 34.2, 31.4, 30.4 (d, $J=17$ Hz), 29.3, 27.4, 26.9, 25.6 (d, $J=142$ Hz), 24.7, 22.5, 22.4, 21.3, 21.1, 21.0, 16.4 (d, $J=3$ Hz), 13.9. ^{31}P NMR 33.1. Found (FAB) MNa^+ : 597.3164; $\text{C}_{29}\text{H}_{51}\text{O}_9\text{P}$ requires MNa^+ : 597.3168.
- Compound **5**: ^1H NMR (CDCl_3 , 300 MHz) 5.52 (dd, $J=15.2, 7.3$ Hz, 1H), 5.42 (dd, $J=15.2, 8.7$ Hz, 1H), 4.60 (br s, 4H), 4.15 (br tr, 1H), 4.01–4.12 (m, 3H), 3.86–3.93 (m, 1H), 2.20–2.37 (m, 2H), 1.55–1.78 (m, 8H), 1.21–1.50 (m, 14H), 1.32 (t, $J=7.1$ Hz, 3H), 0.88 (t, $J=6.8$ Hz, 3H). ^{13}C NMR 135.0, 133.3, 77.8, 73.2, 72.6, 61.1 (d, $J=7$ Hz), 55.9, 49.8, 42.9, 37.0,

- 31.7, 29.9 (d, $J=16$ Hz), 29.1, 27.4, 27.3, 25.7 (d, $J=142$ Hz), 25.3, 22.7, 21.9 (d, $J=4$ Hz), 16.3 (d, $J=6$ Hz), 14.0. ^{31}P NMR 35.0. Found (FAB) MNa^+ : 443.2548; $\text{C}_{21}\text{H}_{41}\text{O}_6\text{P}$ requires MNa^+ : 443.2538.
11. Compound **9**: ^1H NMR (CDCl_3 , 300 MHz) 5.50–5.58 (m, 2H), 5.27–5.40 (m, 2H), 5.18–5.25 (m, 1H), 5.09 (t, $J=4.6$ Hz, 1H), 4.88 (ddd, $J=8.9, 7.6, 4.4$ Hz, 1H), 3.17 (td, $J=6.9, 2.0$ Hz, 2H), 2.48–2.61 (m, 2H), 2.11–2.19 (m, 4H), 2.07, 2.04, 2.01 (3×s, 3H each), 1.85 (quin.d, $J=6.8, 2.1$ Hz, 2H), 1.51–1.74 (m, 4H), 1.23–1.32 (m, 6H), 0.87 (t, $J=6.7$ Hz, 3H). ^{13}C NMR 170.5, 170.4, 170.2, 132.1, 131.5, 128.8, 128.5, 77.7, 74.2, 74.0, 51.0, 47.5, 38.9, 34.3, 33.0, 31.5, 27.8, 25.0, 24.8, 22.5, 21.29, 21.27, 21.0, 14.0, 6.5. Found (FAB) MNa^+ : 585.1700; $\text{C}_{25}\text{H}_{39}\text{IO}_6$ requires MNa^+ : 585.1689.
12. Compound **10**: ^1H NMR (CDCl_3 , 300 MHz) 5.47–5.54 (m, 2H), 5.28–5.37 (m, 2H), 5.20 (tdd, $J=6.8, 3.8, 1.4$ Hz, 1H), 5.06 (t, $J=4.5$ Hz, 1H), 4.86 (ddd, $J=8.8, 7.5, 4.4$ Hz, 1H), 4.00–4.13 (m, 4H), 2.46–2.58 (m, 2H), 2.05–2.21 (m, 4H), 2.04, 2.03, 2.00 (3×s, 3H each), 1.47–1.74 (m, 8H), 1.10 (t, $J=7.1$ Hz, 6H), 1.11–1.23 (m, 6H), 0.86 (t, $J=6.8$ Hz, 3H). ^{13}C NMR 170.5, 170.3, 170.2, 132.0, 131.5, 129.6, 128.1, 77.7, 74.2, 73.9, 61.4 (d, $J=7$ Hz), 51.8, 47.3, 38.9, 34.2, 31.4, 27.8 (d, $J=18$ Hz), 25.2 (d, $J=141$ Hz), 24.9, 24.7, 22.4, 22.3 (d, $J=5$ Hz), 21.2, 21.1, 21.0, 16.4 (d, $J=6$ Hz), 13.9. ^{31}P NMR 32.7. Found (FAB) MNa^+ : 595.3027; $\text{C}_{29}\text{H}_{49}\text{O}_9\text{P}$ requires MNa^+ : 595.3012.
13. Compound **11**: ^1H NMR (CDCl_3 , 300 MHz) 5.55 (dd, $J=15.2, 7.3$ Hz, 1H), 5.44 (dd, 15.2, 8.8 Hz, 1H), 5.29–5.46 (m, 2H), 5.15 (br s, 4H), 4.04–4.14 (m, 4H), 3.86–3.96 (m, 1H), 2.22–2.40 (m, 4H), 1.89–2.16 (m, 2H), 1.55–1.81 (m, 6H), 1.40–1.51 (m, 2H), 1.32 (t, $J=7.1$ Hz, 3H), 1.25–1.36 (m, 6H), 0.88 (t, $J=6.6$ Hz, 3H). ^{13}C NMR 135.4, 133.0, 129.6, 129.2, 77.5, 73.2, 72.3, 61.1 (d, $J=7$ Hz), 55.3, 49.9, 42.8, 36.9, 31.7, 29.7 (br), 27.5 (d, $J=14$ Hz), 25.4, 25.3, 25.1 (d, $J=142$ Hz), 22.4 (d, $J=4$ Hz), 16.3 (d, $J=6$ Hz), 14.0. ^{31}P NMR 34.2. Found (FAB) MNa^+ : 441.2381; $\text{C}_{21}\text{H}_{39}\text{O}_6\text{P}$ requires MNa^+ : 441.2382.
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