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Prostaglandin phosphonic acids through homolytic halodecarboxylation of prostaglandins $F_{1\alpha}$ and $F_{2\alpha}$

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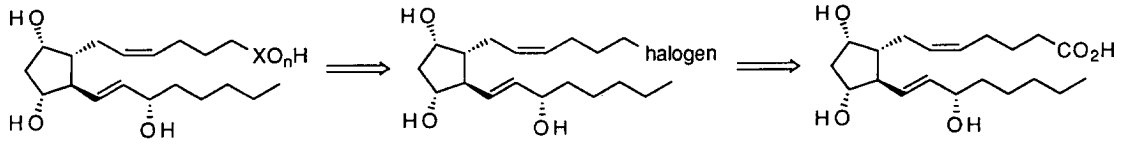
Abstract

Phosphonic acid derivatives of prostaglandins $F_{1\alpha}$ and $F_{2\alpha}$ 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.

Keywords: prostanoids; phosphonic acids; phosphonic acid derivatives; Barton–Hunsdiecker reaction; Arbuzov reaction.

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 reaction[3] 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

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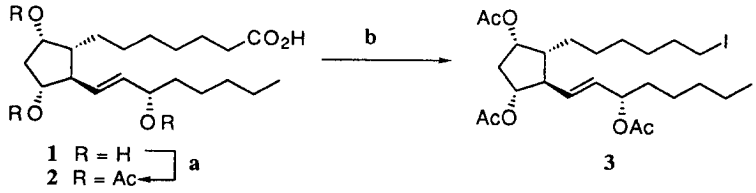
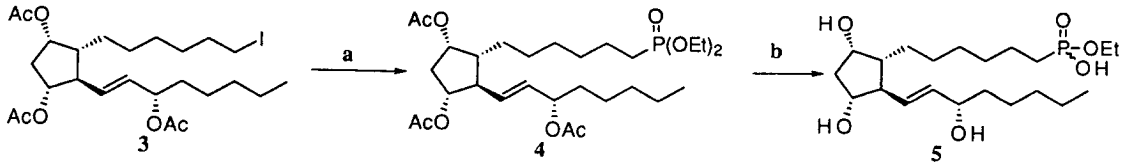
from a donor, often the solvent.[4] Although this is a mild method, we initially selected prostaglandin $F_{1\alpha}$ (**1**)[5] because it is one of the more robust prostaglandins and lacks a double bond on the *alpha*-side chain on which a radical will be generated. Additionally, because the carboxylic–thiohydroxamic 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. Ac_2O, 35 equiv. Et_3N, cat. DMAP, CH_2Cl_2, rt 8 h; then sat. aq. Na_2CO_3, 1 h, 97%; (b) $(COCl)_2$, cat. DMF, CH_2Cl_2; then CF_3CH_2I, cat. DMAP, the sodium salt of *N*-hydroxypyridine-2-thione, CH_2Cl_2, hν, reflux, 56%

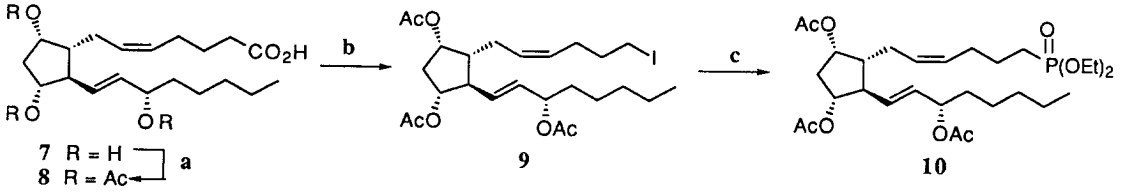
In terms of propensity of displacement, the alkyl iodide would be most desirable. Unfortunately, iodides are the halides obtained in lowest yield by Barton's procedure. Indeed, when prostaglandin $F_{1\alpha}$ triacetate (**2**) was treated by Barton's best procedure for formation of iodides (iodoform as iodine radical source and cyclohexene as solvent and trap for I_2 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 $F_{1\alpha}$ 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 reaction[8] 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).



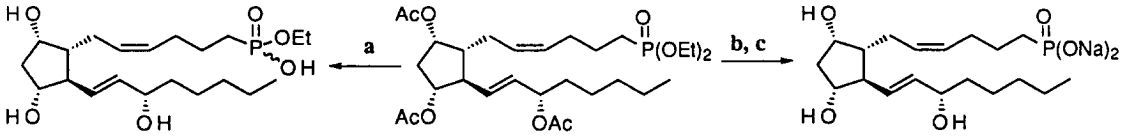
Scheme 3. (a) 100 equiv. $P(OEt)_3$, reflux, 4 h, 91%; (b) 100 equiv. 2.5 M aq. NaOH, EtOH, reflux, 5 h, 73%

Having successfully prepared a prostaglandin $F_{1\alpha}$ analog, we turned to prostaglandin $F_{2\alpha}$ (**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 $F_{2\alpha}$ triacetate (**8**) gave the corresponding iodo-norprostaglandin **9**[11] in 64% yield (Scheme 4).



Scheme 4. (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt 8 h; then sat. aq. Na_2CO_3, 1 h, 99%; (b) $(COCl)_2$, DMF, CH_2Cl_2; then CF_3CH_2I, DMAP, sodium salt of *N*-hydroxypyridine-2-thione, CH_2Cl_2, hν, 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.



11 **10** **12**

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.

References

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7. Compound **3**: Oxalyl chloride (60 μL, 0.69 mmol) was added to a solution of **2** (44.5 mg, 92 μmol) and DMF (0.08 μL) 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 μmol), CH_2Cl_2 (0.4 mL), and CF_3CH_2I (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%). ^{1}H 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×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; $C_{25}H_{41}IO_8$ requires MNa^+: 587.1846.
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9. Compound **4**: ^{1}H 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×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; $C_{29}H_{51}O_9P$ requires MNa^+: 597.3168.
10. Compound **5**: ^{1}H 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; $C_{21}H_{41}O_6P$ requires MNa^+: 443.2538.

11. Compound **9**: ^{1}H 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; $C_{25}H_{39}IO_6$ requires MNa^+: 585.1689.
12. Compound **10**: ^{1}H 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; $C_{29}H_{49}O_9P$ requires MNa^+: 595.3012.
13. Compound **11**: ^{1}H 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; $C_{21}H_{39}O_6P$ requires MNa^+: 441.2382.
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