Synthesis of Prostaglandins III:[1] Efficient and Practical Synthesis of Antisecretory Prostaglandin Enprostil

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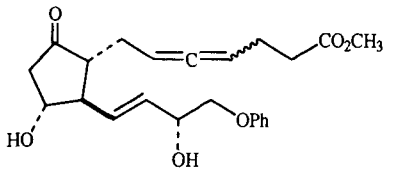
An efficient and practical 8-step synthesis of enprostil (**1**) starting from the lactone **2** has been developed. The propargylic acetate **5** was prepared from the lactol **3** by the reaction with ethynylmagnesium bromide followed by acetylation. Propargylic acetate **5** was converted into enprostil (**1**) via the introduction of an allene moity by reaction with a Grignard reagent in the presence of a CuI · $P(OEt)_3$ complex.

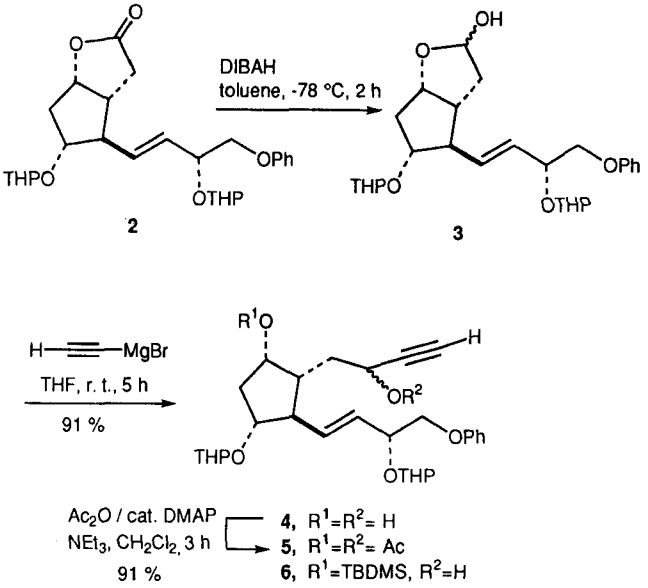
The prostaglandins of the E-series occur naturally in most mammalian cells and exhibit powerful gastric antisecretory activity.[2] However, the therapeutic use of these compounds is limited due to their exceedingly rapid metabolism and chemical instability. Many PGE analogs have been synthesized to overcome these disadvantages. Among them, enprostil (**1**), the C-4 allenic 16-phenoxy-17,18,19,20-tetranor PGE analog, is a potent, orally active gastric antisecretory agent with an exceptionally long duration of action.[3] Since its development, a number of synthetic methods for **1** have been reported.[4-6]



Enprostil (1)

One of the synthetic problems with enprostil is the formation of the allene moiety in an efficient manner. In previous reports, the allenyl group was introduced by the reaction of a propargylic ester with lithium dimethylcuprate[4] or by using an orthoester Claisen rearrangement of a propargylic alcohol intermediate.[5] The reaction of a propargylic acetate with organocopper reagents is one of the most popular methods for the synthesis of a protonated allene.[7] However, the specific formation of a protonated allene from a propargylic ester is sensitive to various factors depending on the kind of propargylic ester or ether, the cuprate reagent, reaction temperature, workup conditions, etc.[8] Therefore, careful experiments are required for the introduction of protonated allenes since the possibilities for the formation of alkylated allene and alkylated acetylene exist.[9] The reported synthesis of Cooper and his co-workers[5] required a 7-step sequence for the synthesis of propargylic alcohol **6**, a key intermediate for orthoester Claisen rearrangement from the known lactone[10] **2** in 38.2% overall yield, necessitating differentiation of the hydroxy groups at C-6 and C-9 (PG numbering).

We describe herein a simple and short synthesis of **1** starting with the known lactone **2**. The basic strategy of this synthesis involves efficient ring opening of lactol **3** with ethynylmagnesium bromide and convenient formation of the allenyl group with concomitant three-carbon homologation (Scheme 1).

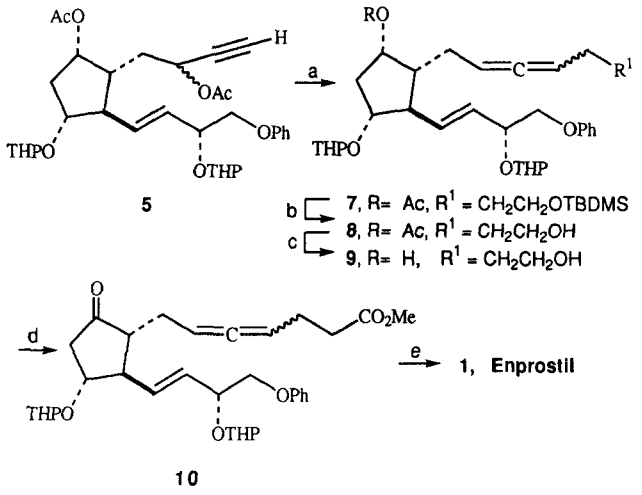


Scheme 1

Lactone **2** was reduced with diisobutylaluminum hydride in toluene at − 78 °C to the lactol **3**, which was sufficiently pure to be used without purification. Although the reaction of γ-lactones with metal alkylacetylides have been reported in literature,[11] the reaction of γ-lactols with ethynylmagnesium halides were unexpectedly little known. We intended to simplify the overall synthetic route to enprostil by the direct reaction of the lactol with a metal acetylide, since our synthetic strategy need not differentiate hydroxy group at C-6 and C-9 (PG numbering). The crude lactol **3** was transformed smoothly into the propargylic alcohol **4** by the treatment with ethynylmagnesium bromide solution (0.5 M in THF) in THF at 0 °C in 91% overall yield from the lactone **2**. The propargylic alcohol **4** was di-acetylated to afford the propargylic acetate **5** with acetic anhydride and triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) in 91% yield.

With the required propargylic acetate **5** in hand, the next step is the formation of the allenyl group with concomitant three-carbon homologation (Scheme 2). The reaction of propargylic acetate **5** with 3-*tert*-butyldimethylsilyloxypropylmagnesium bromide and a catalytic amount of CuI · $P(OEt)_3$ at − 40 °C in THF afforded cleanly the allenic acetate **7** with the three-carbon homologation in 76% yield. Removal of the silyl group and acetyl group in **7** with tetrabutylammonium fluoride (TBAF) and methanolic potassium carbonate, respectively, gave the diol **9** in 98% yield. The diol **9** was transformed to keto ester **10** by consecutive oxidation with pyridinium dichromate (PDC)/CH_2Cl_2 and PDC/MeOH/DMF in 55%

yield. The second oxidation step is notable because it provides direct esterification without necessitating the use of explosive diazomethane. Finally, treatment of **10** with acetic acid/H_2O/THF (19:11:3) afforded enprostil in 67% yield, whose spectroscopic properties were in accord with those described in the literature.[3,4]



Reagents and conditions: a, $TBDMSOCH_2CH_2CH_2MgBr$, CuI·$P(OEt)_3$, THF, -40°C (76%); b, TBAF, THF, rt; c, K_2CO_3, MeOH, rt (98%); d, i, PDC/CH_2Cl_2, rt, ii, PDC, MeOH, DMF, rt (55%); e, AcOH-H_2O-THF, 40°C (67%).

Scheme 2

In conclusion, a short and practical synthesis of the antisecretory prostaglandin enprostil **(1)** has been developed. The synthetic pathway was shortened by direct reaction of lactol **3** with ethynylmagnesium bromide to afford a propargylic alcohol **4**. The concomitant three-carbon homologation and allene formation were accomplished by the reaction of propargylic acetate **5** with a cuprate-based Grignard reagent. The whole synthesis comprises 8 steps from lactone **2** and proceeds in ca. 23% overall yield.

IR spectra were recorded on a Analect FX-6160 FT-IR spectrometer. NMR spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer with $CDCl_3$ as solvent and tetramethylsilane as internal standard. Mass spectra were recorded on a HP 5988A GC-Mass spectrometer by electron impact method (EI) at 70 eV. THF was distilled from Na/benzophenone immediately prior to use. CH_2Cl_2 and toluene were distilled from NaH. DMF was distilled from CaH_2. Flash column chromatography was performed using E. Merck Kieselgel 60 (230–400 mesh) silica gel.

1-{5α-Hydroxy-2β-[(*E*)-4-phenoxy-3α-tetrahydropyran-2-yloxy-1-butenyl]-3α-tetrahydropyran-2-yloxycyclopent-1α-yl}but-3-yn-2-ol (4):

To a solution of lactone **2** (730 mg, 1.54 mmol) in toluene (1.5 mL) was added a solution of diisobutylaluminum hydride (1.70 mL, 1 M solution in toluene) dropwise over 5 min at −78 °C. The reaction mixture was stirred for 2 h at the same temperature and treated dropwise with MeOH (2 mL) and water (2 mL). The mixture was diluted with Et_2O (40 mL) and the resulting precipitate was filtered off. The organic solution was dried ($MgSO_4$) and evaporated to dryness to afford 730 mg of lactol **3** (ca. 100%). The crude lactol was used in next step without further purification.

To a solution of above lactol **3** (103 mg, 0.21 mmol) in THF (0.6 mL) was added a solution of ethynylmagnesium bromide (2.65 mL, 0.5 M solution in THF) dropwise at 0 °C. The reaction was allowed to reach r.t. and stirred further for 5 h. After cooling to 0 °C, the mixture was treated with sat. aq NH_4Cl (1 mL) and partitioned between Et_2O (20 mL) and water (10 mL). The ethereal solution was washed with sat. aq NaCl, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (50% petroleum ether in EtOAc) to afford propargylic alcohol **4** (99 mg, 91%) as an oil.

IR (neat): ν = 3294, 2936, 2870, 1497, 1454 cm^{-1}.

^1H NMR: δ = 6.87–7.32 (m, 5H), 5.46–5.85 (m, 2H), 4.42–5.00 (m, 4H), 3.70–4.39 (m, 6H), 3.42–3.57 (m, 2H), 2.42–2.50 (m, 1H).

3α,β-Acetoxy-4-{5α-acetoxy-2β-[(*E*)-4-phenoxy-3α-tetrahydropyran-2-yloxy-1-butenyl]-3α-tetrahydropyran-2-yloxycyclopent-1α-yl}but-1-yne (5):

A solution of propargylic alcohol **4** (99 °C, 0.119 mmol), Et_3N (139 mg, 1.37 mol), Ac_2O (139 mg, 1.32 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (2 mL) was stirred at r.t. for 3 h. The mixture was concentrated and purified by flash column chromatography (20% EtOAc in hexane) to afford propargylic acetate (**5**, 106 mg, 91%) as an oil.

IR (neat): ν = 2936, 2859, 1742, 1601, 1244 cm^{-1}.

^1H NMR: δ = 6.86–7.40 (m, 5H), 5.58–5.85 (m, 2H), 5.10–5.48 (m, 2H), 4.50–5.00 (m, 3H), 3.77–4.20 (m, 5H), 3.41–3.55 (m, 2H), 2.37–2.46 (m, 1H), 2.02, 2.05, 2.06 and 2.07 (four s, 6H), 1.95–2.15 (m, 6H).

1-{5α-Acetoxy-2β-[(*E*)-4-phenoxy-3α-tetrahydropyran-2-yloxy-1-butenyl]-3α-tetrahydropyran-2-yloxycyclopent-1α-yl}-7-*tert*-butyldimethylsilyloxyhepta-2,3-diene (7):

A solution of 3-*tert*-butyldimethylsilyloxypropylmagnesium bromide [prepared from 3-*tert*-butyldimethylsilyloxypropyl bromide (0.5 g, 1.98 mmol) and magnesium (72 mg, 2.96 mg atom) in THF (10 mL)] was added dropwise to a solution of propargylic acetate **6** (102 mg, 0.17 mmol) and CuI · $P(OEt)_3$ (62 mg, 0.174 mmol) in THF (5 mL) at −40 °C over 5 min. The mixture was allowed to warm to 0 °C and further stirred for 2 h. After cooling to 0 °C, the mixture was treated with a mixture of aq NH_3 (2 parts) and sat. aq NH_4Cl (10 mL). The aqueous phase was washed with Et_2O (20 mL × 2), and the combined organic phase was washed with a mixture of aq NH_3/NH_4Cl (10 mL × 2) and then dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (15% EtOAc in petroleum ether) to afford allenic acetate **7** (92 mg, 76%) as an oil.

IR (neat): ν = 2944, 2853, 1962, 1738, 1599, 1375 cm^{-1}.

^1H NMR: δ = 6.88–7.53 (m, 5H), 5.50–5.82 (m, 2H), 4.86–5.25 (m, 3H), 4.48–4.83 (m, 3H), 3.32–4.18 (m, 9H), 2.07 and 2.08 (2 s, 3H), 0.86 (s, 9H).

7-{5α-Hydroxy-2β-[(*E*)-4-phenoxy-3α-tetrahydropyran-2-yloxy-1-butenyl]-3α-tetrahydropyran-2-yloxycyclopent-1α-yl}-hepta-4,5-dien-1-ol (9):

To a solution of **7** (63 mg, 0.09 mmol) in THF (0.5 mL) was added a solution of TBAF (108 µL, 0.108 mmol, 1 M solution in THF) and stirred at r.t. for 3 h. The mixture was evaporated to afford crude **8**, which was used without purification. For identification, the crude **8** was purified by flash column chromatography (50% EtOAc in hexane).

IR (neat): ν = 3233, 2940, 2870, 1962, 1736, 1599, 1246 cm^{-1}.

^1H NMR: δ = 6.86–7.31 (m, 5H), 5.55–5.72 (m, 2H), 5.03–5.15 (m, 3H), 4.49–4.63 (m, 3H), 3.79–4.11 (m, 5H), 3.60–3.68 (m, 2H), 3.45–3.52 (m, 2H), 2.04 (s, 3H).

The crude **8** was diluted with MeOH (0.5 mL) and treated with anhydr. K_2CO_3 (14 mg, 0.107 mmol) and stirred for 5 h. The mixture was concentrated and purified by flash column chromatography (67% EtOAc in hexane) to afford diol **9** (48 mg, 98%) as an oil.

IR (neat): ν = 3440, 2932, 2871, 1961, 1597, 1449, 1385, 1346, 1246, 1203 1129, 1073, 977 cm^{-1}.

^1H NMR: δ = 6.88–7.30 (m, 5H), 5.47–5.77 (m, 2H), 4.93–5.19 (m, 2H), 4.66–4.80 (m, 2H), 4.56–4.58 (m, 1H), 3.84–4.24 (m, 6H), 3.61–3.77 (m, 2H), 3.43–3.52 (m, 2H).

Methyl 11α,15α-Bis(tetrahydropyran-2-yloxy)-16-phenoxy-9-oxo-17,18,19,20-tetranorprosta-4,5,13(*E*)-trienoate (10):
To a solution of diol **9** (26 mg, 0.048 mmol) in CH_2Cl_2 (1 mL) was added pyridinium dichromate (PDC, 72 mg, 0.191 mmol) and the mixture was stirred for 24 h. The mixture was diluted with Et_2O (10 mL) and the resulting precipitate was filtered through Florisil and washed several times with Et_2O. The combined organic solution was concentrated to afford a crude 9-keto aldehyde. The crude 9-keto aldehyde was dissolved in MeOH (50 μL) and DMF (300 μL) and treated with PDC (100 mg, 0.265 mmol). After stirring for 24 h, the mixture was diluted with Et_2O (10 mL) and the resulting precipitate was filtered off through Florisil and washed several times with Et_2O. The combined organic filtrate was dried ($MgSO_4$) and concentrated to afford a keto ester **10** (15 mg, 55%) as an oil.

IR (neat): ν = 2924, 2855, 1965, 1741, 1597, 1495 cm^{-1}.

^1H NMR: δ = 6-87–7.27 (m, 5H), 5.53–5.80 (m, 2H), 4.93–5.18 (m, 2H), 4.69–4.82 (m, 2H), 4.52–4.58 (m, 1H), 3.82–4.24 (m, 5H), 3.66 (s, 3H).

Methyl 11α,15α-Dihydroxy-16-phenoxy-9-oxo-17,18,19,20-tetranorprosta-4,5,13(*E*)-trienoate (1) (Enprostil):
A solution of **10** (21 mg, 0.037 mmol) in AcOH (19 mL), water (11 mL), and THF (3 mL) was stirred at 40 °C for 14 h. The mixture was concentrated in vacuo and purified by flash column chromatography (50% EtOAc in hexane) to afford enprostil **(1)** (10 mg, 67%) as an oil.

IR (neat): ν = 3300, 2925, 2857, 1963, 1740, 1596, 1494, 1455 cm^{-1}.

^1H NMR δ = 6.91–7.33 (m, 5H), 5.79–5.83 (m, 2H), 5.07–5.14 (m, 2H), 4.57–4.60 (m, 1H), 3.92–4.20 (m, 3H), 3.66 (s, 3H).

^{13}C NMR: δ = 213.40, 213.61 (C9), 204.72, 204.80 (C5), 173.54 (C1), 158.39 (C17), 132.98, 133.07 (C14), 131.94 (C13), 129.5, 129.68 (C19), 121.36, 121.49 (C20), 114.51, 114.60 (C18), 90.20, 90.27 (C4), 88.74 (C6), 71.83, 72.01 (C11), 71.62 (C16), 70.76 (C15), 54.15, 54.20 (C12), 53.28, 53.42 (C8), 51.64, 51.67 (OCH_3), 46.06 (C10), 33.11, 33.26 (C2), 26.76 (C7), 23.74, 23.85 (C3).

MS (EI, 60 eV): m/z = 382 ($M^+ - H_2O$), 275, 221, 195, 169, 145, 131, 115, 91, 77 (base peak), 65, 39.

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