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SYNTHESIS OF NEW ALLENIC PROSTANOIDS[1]

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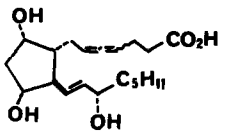
Abstract—New allenic prostanoids **5c, d, 7, 9c,** and **15b** have been prepared by total synthesis. In each case a cuprate-propargylic acetate reaction was used as the key step.

In the light of the biological activities exhibited by a number of allenes,[2,3] the introduction of the propadiene unit in a prostaglandin might be expected to produce a change in its biological effect. In fact, 6,7-dehydro-$PGF_{2\alpha}$ (**1**) has been shown to possess a greater luteolytic activity in various animal species than $PGF_{2\alpha}$.[3] We became interested in



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preparing through the use of organocopper reagents new allenic prostaglandins with the propadiene unit in the upper and lower chains. In this paper we describe the synthesis of allenic prostaglandins **5c, d, 7, 9c** and **15b** which serves to illustrate the applicability as well as some of the limitations of the propargylic alcohol derivative-cuprate synthesis of allenes[4] and the flexibility of the tropolone approach[5e] to modified prostaglandins.

Synthesis of lower chain allenic prostaglandins

The starting material for the synthesis of the lower chain allenic prostaglandins was 2-(6'-carbomethoxyhexyl)-2-cyclopenten-1-one (**2**) (Chart I), readily available from undecylenic acid.[6] Conjugate addition to **2** of nitromethane[5a,7] followed by ozonolysis of the nitronate salt[8] of the resulting nitro compound **3a** provided the known keto aldehyde **3b**.[5] Treatment of aldehyde **3b** with the lithium salt of 3-(2-tetrahydropyranyloxy)-1-octyne then gave alcohol **4a**,[9] which on acetylation afforded the derivative **4b**. In view of the large number of sites in **4b** that could conceivably coordinate with an organocopper reagent and thus, perhaps, adversely influence the course of the reaction, it was gratifying to find that treatment of **4b** with excess lithium dimethylcuprate (LMC) at −78° resulted in the clean formation of the desired 13, 14, 15-allenic prostanoid **5a**.[9] No alkylated material (*e.g.* **5c**, R_1 = THP) could be detected. In contrast, repetition using the free alcohol **4c** in place of the corresponding THP ether **4b** produced a 14% yield of the methylated allene **5c**[9] together with 58% of **5b**.[9] Mild acid hydrolysis of the THP group in **5a** furnished **5b**, which in turn was saponified to afford the free acid, **5d**.

While it has been established that shifting the OH group in certain prostaglandins from carbon 15 to 16, as above, gives rise to a narrower biological profile,[10a] it has also been demonstrated that a number of prostaglandins with the OH group at C-13 in lieu of C-15 retain some of the biological properties typical of the latter.[10b] Thus, aldehyde **3b** was treated with the lithium salt of 3-acetoxy-1-octyne, which resulted in the formation of the hydroxy acetate **6a**[9] (Chart II). In contrast to the aforementioned results, reaction of **6a** with excess LMC furnished in low yield the methylated allenic prostaglandin derivative **7**[9] as the major product. Surprisingly, the corresponding THP derivative **6b** under the same conditions afforded a product tentatively assigned structure **9a**,[9] which was hydrolyzed stepwise to **9c**. This would most likely result from yet another process, *i.e.*, an intramolecular attack on the C-9 carbonyl by an allenic carbanion, as depicted in **8**. There is close precedent for this type of transformation.[11]

Synthesis of upper chain allenic prostaglandins

An intermediate from some of our previous prostaglandin work,[5c,12] the β-keto ester **10**, also proved to be a suitable starting material for the synthesis of the upper chain 5,6,7-allenic prostaglandin **15** (Chart III). This versatile compound **10**, available from tropolone[13] in four steps, can be assigned the expected *trans* configuration on the basis of the coupling constant of 10.5 Hz[14] at 3.17 ppm for the C-8 hydrogen (prostaglandin numbering) and from its recovery unchanged following treatment under equilibrating conditions (AcOK[15] and Al_2O_3[16]). Conversion of keto ester **10** to the key compound, propargylic acetate **13d**, was effected as outlined below.

Among the numerous reducing agents tested for the reduction of keto ester **10**, lithium borohydride in methanol at −78° was found to give the highest proportion of the desired 9α alcohol **11a** (**11a**:**11b**, 85:15 in 95% yield). The identity of the major component **11a** could be readily established

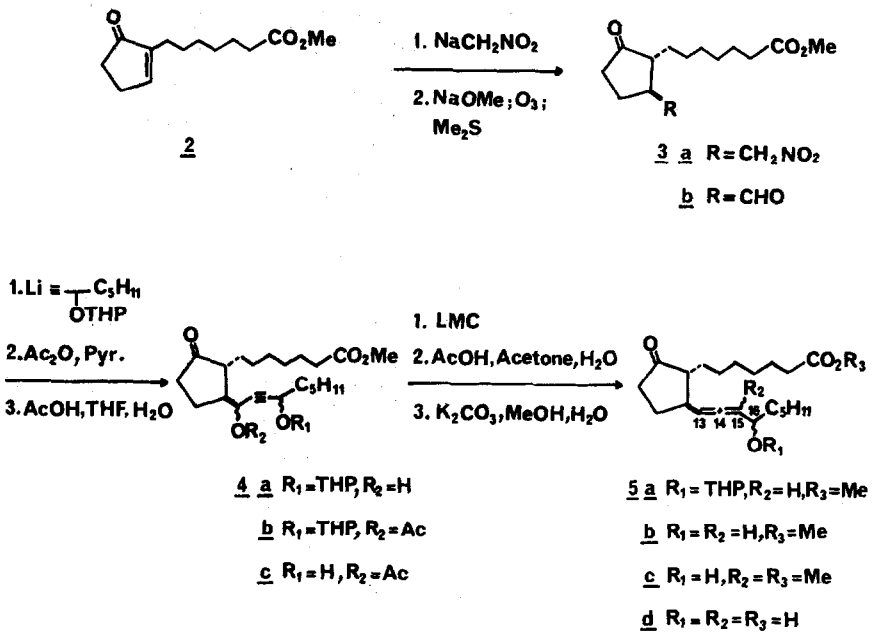


Chart I.

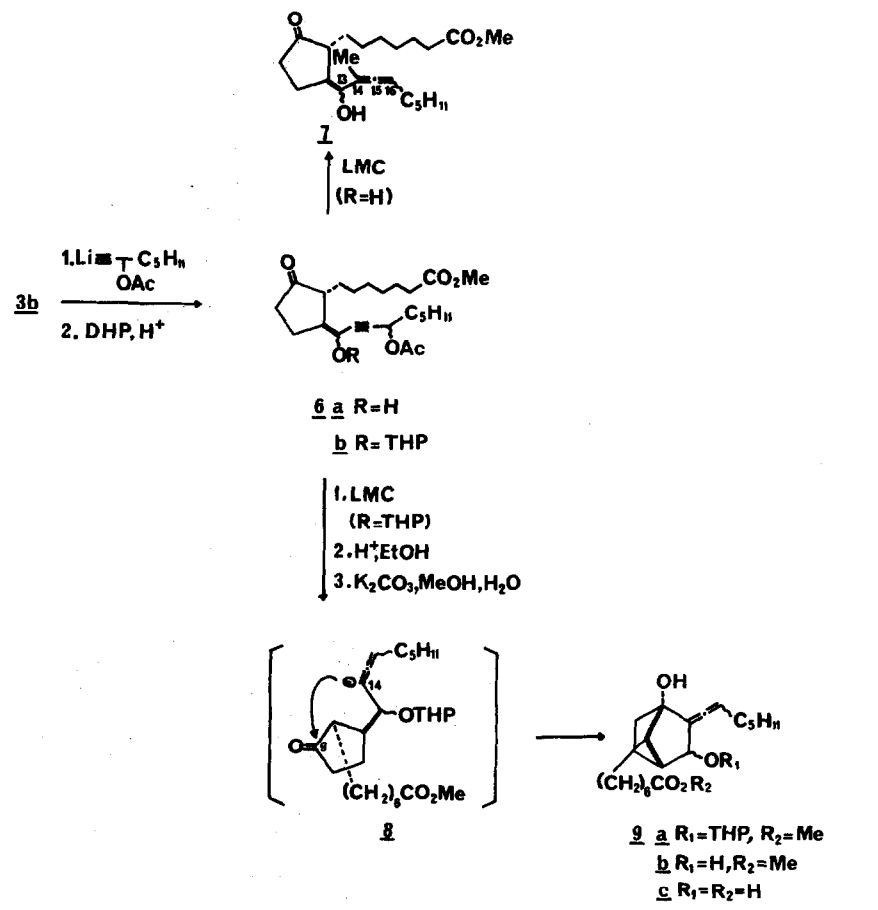


Chart II.

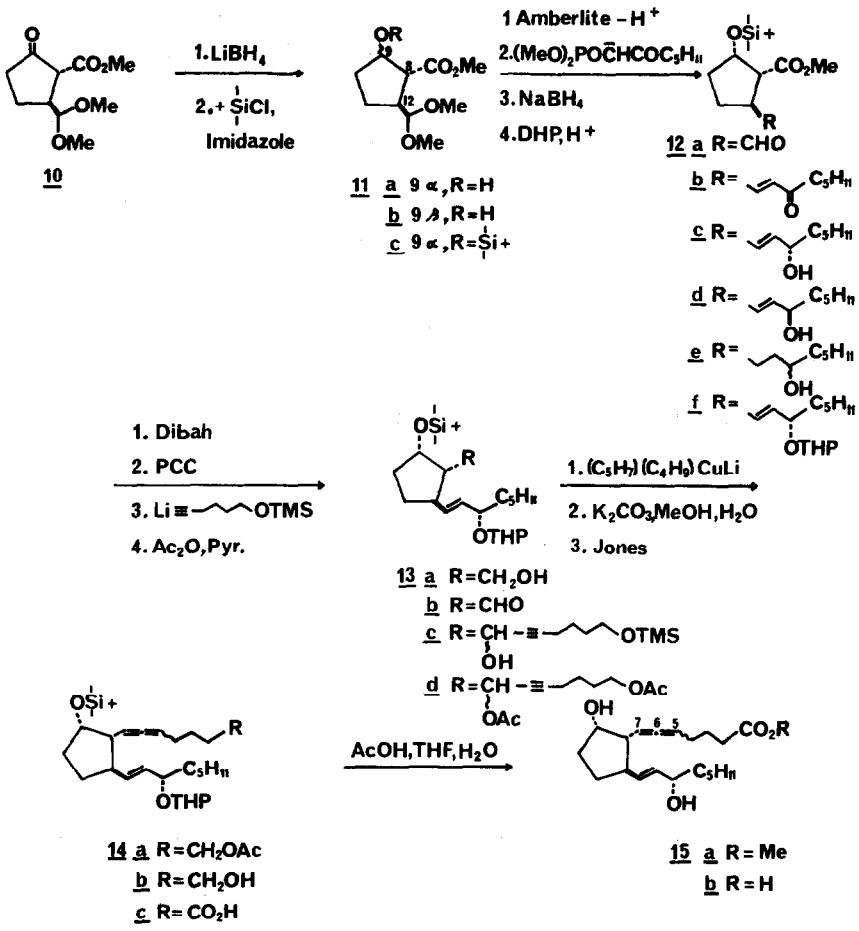


Chart III.

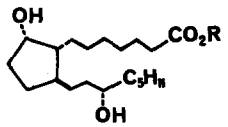
through examination of its 250 MHz NMR spectrum which revealed coupling constants of $J_{8,12} = 9.5$ Hz and $J_{8,9} = 5$ Hz for the three contiguous substituents and through the addition of Eu(fod)$_3$. As is normally observed in the F series, the major 9α isomer **11a**, relative to the 9β epimer **11b**, exhibited a greater mobility on silica gel[17] and also a larger C-9 carbinolic proton downfield chemical shift.[18] Although chromatographic separation of small amounts of these epimeric alcohols could be effected on silica gel, it was far too tedious a separation to attempt on a large scale. A useful technique was developed to alleviate this difficulty which consisted of selective trimethylsilylation of the more reactive minor component **11b** using the convenient reagent trimethylsilyldiethylamine,[19] followed by evaporation of the solvent and simple separation by filtration on silica gel. This method of separation, somewhat similar to the complexation procedure described by Sharpless,[20] allows the more reactive component in the mixture to be readily regenerated and in this case recycled.

The purified alcohol **11a** was transformed to the t-butyldimethylsilyl ether derivative **11c**, which was treated with amberlite IR-120 acid resin to generate the aldehyde **12a** in quantitative yield. Conversion of aldehyde **12a** to the enone **12b** was readily achieved using sodio dimethyl 2-oxoheptylphosphonate, which was followed by reduction with sodium borohydride to produce in 86% yield an *ca* 1:1 mixture of the epimeric allylic alcohols **12c** and **12d** together with 5–8% of the saturated alcohols **12e**, resulting from an initial 1,4-reduction of the enone. The more polar 15α alcohol[17] **12c** was separated from the mixture by silica gel chromatography and then converted to the tetrahydropyranyl ether derivative **12f**.[21] The less polar 15β epimer **12d** could be efficiently recycled through manganese dioxide oxidation, which regenerated enone **12b** in 90% yield.

The conversion of ester **12f** to the aldehyde **13b** was best effected by reduction with diisobutylaluminum hydride followed by oxidation of the resulting alcohol **13a** with pyridinium chlorochromate.[22] The transformation of the aldehyde **13b** to the propargylic alcohol **13c**, was first attempted using the dilithium salt of 5-hexyn-1-ol. Using various solvent systems (Et_2O, THF, DME-HMPA), we were unable to achieve this conversion in over 36% yield. This is in contrast with a previously reported alkynylation of a homologue.[3] However, the lithium salt of the corresponding trimethylsilyl

ether derivative in DME at −78° added smoothly to aldehyde **13b** to afford the propargylic alcohol **13c** as a mixture of diastereomers in 86% yield. Prolonged treatment of **13c** with acetic anhydride in pyridine conveniently yielded the C-7 acetate with attendant reaction at C-1, providing the desired diacetate **13d**.

In the light of published work,[3,4] it was anticipated that the propargylic acetate **13d** could be transformed without difficulty to the desired allene **14a** using LMC. However, application of this method again led to an unexpected result (*vide supra*), producing a complex mixture composed of several products which included alkylated and non-alkylated allenes and acetylenes. In appropriate model systems[23] we examined the effect of changes in the reaction solvent, concentration, time and temperature, and the nature of the C-1 protecting group but were totally unable to bring about any significant improvement in the product distribution. Fortunately, however, we discovered the mixed reagent lithium 1-pentynylbutylcuprate[24] in ether at −78° to be very effective both with model systems and **13d**, very cleanly and rapidly (<6 min) bringing about the conversions to the desired non-alkylated allenes without any evidence for the formation of other allenes or any acetylenes. Thus, the pure allene **14a**[9] could be obtained in 56% yield after silica gel chromatography. The remaining steps in the synthesis, *i.e.*, saponification, Jones oxidation[25], and hydrolysis of the protecting groups, were effected without difficulty and produced the desired 5,6,7-allenic prostanoid **15b**, purified as its methyl ester **15a**. Confirmation of the structural and stereochemical assignments in **15** could be obtained by hydrogenation to the corresponding hexahydro derivative, which was identical in all respects (except for rotation and melting point), both as the methyl ester **16a** and the free acid **16b**, with a sample secured by hydrogenation of 11-deoxy $PGF_{2\alpha}$, obtained from (+)-PGA_2 from *Plexaura homomalla*.[26]



16 a R=Me
b R=H

In summary, a number of new allenic prostaglandins have been obtained by total synthesis. In each case a cuprate reaction with the appropriate propargylic acetate was employed as the key step. While use of this reaction in complex, polyfunctional molecules would still appear to be somewhat unpredictable, conditions were found for successfully effecting the desired conversions to allenes in the upper and lower chains of the prostanoid molecule.

EXPERIMENTAL

Isolation of the products was accomplished by pouring the mixture into water, thoroughly extracting with the specified solvent, washing the combined extracts with 10% HCl aq and/or sat $NaHCO_3$ aq (if required), with water, and then with sat NaCl aq, drying the extracts over anhyd Na_2SO_4 or $MgSO_4$, filtering, and then concentrating under reduced pressure on a Büchi Rotovapor.

IR spectra were obtained using neat liquids between salt plates on a Beckman Acculab 4 spectrophotometer. A Beckman DBT recording spectrophotometer was used for the UV absorption spectra. NMR spectra were determined with a Jeol PMX-60 spectrometer using tetramethylsilane (TMS) as the internal reference. Mass spectra were recorded on a MS-30AEI mass spectrometer generally at 70 eV using a direct insertion probe. M.ps were determined with a Büchi-Tottoli apparatus and are not corrected. Microanalyses were performed by the Central Service of the CNRS, Lyon. Tlc was carried out using Merck $60F_{254}$ (0.25 mm) sheets. For column chromatography, Merck 230–400 mesh silica gel 60 and Mallinckrodt silicic acid silicar CC-4 and CC-7 were used.

3β-Nitromethyl-2α-(6′-carbomethoxyhexyl)-1-cyclopentanone (**3a**)[5a,b]. To a soln of NaOMe in MeOH[from 1.15 g (0.05 g atom) of Na and 20 ml of MeOH] was added 3.20 ml (60 mmol) of nitromethane followed by 8.99 g (40 mmol) of 2-(6′-carbomethyoxyhexyl)-2-cyclopenten-1-one (**2**)[6] in 5 ml of MeOH. The mixture was stirred for 2 hr at 55° and then quenched with 2 ml of AcOH. Isolation of the product with Et_2O followed by column chromatography on silica gel using hexane-EtOAc gave 1.58 g of recovered starting material and 6.06 g (53%) of the adduct **3a**[5a,b]: IR ν_{max} (film) 1730, 1550, 1460, 1440, 1385, 1365, 1200, 1170 cm^{-1}; NMR δ_{TMS} (CCl_4) 4.80–4.18 (m, 2H), 3.58 ppm (s, 3H); mass spectrum *m/e* 255 (M^+—NO), 254 (M^+—OMe), 239 (M^+—NO_2).

3β-Formyl-2α-(6′-carbomethoxyhexyl)-1-cyclopentanone (**3b**)[5]. A 2.25 g (7.89 mmol) sample of **3a** in 10 ml of dry MeOH was treated with 40 ml (8 mmol) of 0.2 M NaOMe in MeOH and stirred for 15 min at 0°. The soln was then cooled to −78° and a stream of O_3-O_2 was bubbled through until the soln turned light blue.[8] After flushing with N_2, 2.5 ml of Me_2S was added at −78°. After standing for 2 hr at −10°, volatiles were removed under reduced pressure and the product was isolated with Et_2O affording 1.93 g (96%) of **3b**[5] as a light yellow oil: IR ν_{max} (film) 2720, 1730, 1460, 1440, 1360, 1170 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 9.80 (d, J = 2 Hz, 1H), 3.64 ppm (s, 3H); mass spectrum m/e 254 (M^+), 226 (M^+—CO), 225 (M^+—CHO), 224 (M^+—CH_2O), 223 (M^+—OMe).

Tetrahydropyranyloxy alcohol **4a**. To lithio 3-(2-tetrahydropyranyloxy)-1-octyne [from 690 mg (3.29 mmol) of 3-(2-tetrahydropyranyloxy)-1-octyne and 2.20 ml (3.30 mmol) of 1.5 M n-BuLi in 7 ml of THF at −20° for 15 min] at −20° under N_2 was added 770 mg (3.03 mmol) of **3a** in 5 ml of THF. After stirring for 45 min, the mixture was poured into sat NH_4Cl aq and the product was isolated with Et_2O. Column chromatography on silica gel using hexane-EtOAc gave 680 mg (48%) of **4a**: IR ν_{max} (film) 3440, 1730, 1460, 1440, 1200, 1160, 1120, 1020, 910, 890, 875 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 4.86 (br s, 1H), 4.64−4.20 (m, 2H), 3.82−3.41 (m, 2H), 3.61 (s, 3H), 0.90 ppm (t, J = 5 Hz, 3H).

Tetrahydropyranyloxy acetate **4b**. A soln of 60 mg (0.13 mmol) of **4a** in 0.5 ml of Ac_2O and 0.5 ml of pyridine was stirred overnight at room temp. MeOH (2 ml) was then added and after stirring for 30 min the product was isolated with Et_2O. Chromatography on silica gel using hexane-EtOAc gave 40 mg (61%) of **4b**: IR ν_{max} (film) 1735, 1460, 1440, 1380, 1230, 1120, 1020, 910, 890, 875 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.50 (br s, 1H), 4.80 (br s, 1H), 4.36 (t, J = 6 Hz, 1H), 3.82–3.26 (m, 2H), 3.61 (s, 3H), 0.90 ppm (t, J = 5 Hz, 3H); mass spectrum *m/e* 405 (M^+—OTHP).

Hydroxy acetate **4c**. A 520 mg (1.03 mmol) sample of

4b was stirred with 20 ml of AcOH—H_2O—THF (1:1:3) at room temp for 27 hr. Following evaporation of the solvents under reduced pressure, the product was isolated with Et_2O and purified by silica gel chromatography affording 390 mg (90%) of **4c**: IR ν_{max} (film) 3480, 1735, 1465, 1445, 1380, 1235, 1025 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.50 (m, 1H), 4.33 (m, 1H), 3.64 (s, 3H), 0.90 ppm (t, J = 5 Hz, 3H).

Tetrahydropyranyloxy allene **5a**. To a stirred suspension of 470 mg (2.47 mmol) of CuI in 6 ml of Et_2O at −20° under N_2 was slowly added 3.29 ml (4.94 mmol) of a 1.5 M soln of MeLi in Et_2O. After cooling to −78°, a soln of 240 mg (0.47 mmol) of **4b** in 3 ml of Et_2O was added. The mixture was stirred for 4 hr and then quenched with MeOH. After stirring for 15 min at −78°, the mixture was poured into NH_4Cl—NH_4OH aq and the product was isolated with Et_2O. Purification of the product by column chromatography on silica gel using hexane-EtOAc gave 120 mg (56%) of **5a**: IR ν_{max} (film) 1960, 1740, 1460, 1440, 1020, 910, 890, 875 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.37–4.80 (m, 2H), 4.70 (br s, 1H), 4.33–3.85 (br m, 1H), 3.85–3.21 (br m, 2H), 3.62 (s, 3H), 0.90 ppm (t, J = 5 Hz, 3H); mass spectrum *m/e* 448 (M^+).

Hydroxy allenes **5b,c,d**. To a −78° ethereal soln of $LiMe_2Cu$ [from 230 mg (1.21 mmol) of CuI and 1.61 ml (2.41 mmol) of 1.5 M ethereal MeLi in 4 ml of Et_2O at −20° under N_2] was added a soln of 80 mg (0.19 mmol) of **4c** in 2 ml of Et_2O. After stirring at −78° for 30 min the reaction was quenched with MeOH and then stirred for an additional 15 min at −78°. The mixture was poured into NH_4Cl—NH_4OH aq and the products were isolated with Et_2O. Purification on silica gel using hexane-EtOAc afforded 40 mg (58%) of **5b** and 10 mg (14%) of **5c**. Allene **5b** could also be obtained from **5a** by hydrolysis in AcOH–H_2O–Me_2CO at room temp. **5b**: IR ν_{max} (film) 3460, 1960, 1735, 1465, 1445, 1175, 1025, 885 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.29 (m, 2H), 4.1 (br m, 1H), 3.62 (s, 3H), 0.92 ppm (t, J = 5 Hz, 3 H); mass spectrum *m/e* 364 (M^+), 347 (M^+–OH), 346 (M^+–H_2O). **5c**: IR ν_{max} (film) 3450, 1960, 1735, 1460, 1440, 1160, 1020 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.10 (m, 1H), 4.12 (m, 1H), 3.60 (s, 3H), 2.40–2.00 (m, 5H), 0.90 ppm (t, J = 5 Hz, 3H); mass spectrum *m/e* 378 (M^+), 361 (M^+–OH), 360 (M^+–H_2O).

A 120 mg (0.33 mmol) sample of **5b** in 60 ml of H_2O–MeOH (2:3) was treated with 1.0 g of K_2CO_3 at room temp for 20 hr to yield 110 mg (95%) of **5d**: IR ν_{max} (film) 3500–2500, 1960, 1740–1705, 1470, 1160, 1030, 880 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.25 (m, 2H), 4.06 (m, 1H), 0.87 ppm (t, J = 5 Hz, 3H).

Hydroxy acetate **6a**. At −110° under N_2, 260 mg (1.55 mmol) of 3-acetoxy-1-octyne in 19.2 ml of 4:1:1 THF–Et_2O-pentane was treated with 1.20 ml (1.56 mmol) of 1.3 M BuLi in hexane. To this soln was added 300 mg (1.18 mmol) of **3b** in 6 ml of THF at −78°. After stirring for 5 hr at −78°, the product was isolated with Et_2O and purified by column chromoatography on silica gel using hexane–EtOAc to give 260 mg (52%) of **6a**: IR ν_{max} (film) 3480, 1735, 1465, 1445, 1380, 1240, 1030 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.18 (t, J = 6 Hz, 1H), 4.39 (br s, 1H), 3.58 (s, 3H), 0.91 ppm (t, J = 5 Hz, 3H).

Tetrahydropyranyloxy acetate **6b**. A soln of 300 mg (0.71 mmol) of **6a** and 100 mg (1.19 mmol) of dihydropyran in 5 ml of dry CH_2Cl_2 containing 20 mg of pyridinium p-toluenesulphonate was stirred for 8 hr. The product was isolated with ether and purified by chromatography on silica gel using hexane-EtOAc to give 260 mg (72%) of **6b**: IR ν_{max} (film) 1740, 1460, 1440, 1370, 1235, 1125, 1020, 910, 890, 870 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.19 (t, J = 6 Hz, 1H), 4.72 (br s, 1H), 4.43 (br s, 1H), 3.95–3.14 (br m, 2H), 3.56 (s, 3H), 1.99 (s, 3H), 0.87 ppm (t, J = 5 Hz, 3H).

Hydroxy allene **7**. To a soln of Me_2CuLi [prepared from 830 mg (4.36 mmol) of CuI and 5.80 ml (8.70 mmol) of 1.5 M ethereal MeLi in 6 ml of Et_2O at −20° under N_2] at −78° was added a soln of 180 mg (0.43 mmol) of **6a** in 2 ml of Et_2O. After stirring at −78° for 2.5 hr, the reaction was quenched with MeOH and then stirred for an additional 15 min at −78°. The reaction was poured into NH_4Cl–NH_4OH aq and the product mixture was isolated with Et_2O. Purification on silica gel using hexane–EtOAc afforded 19 mg (12%) of **7**: IR ν_{max} (film) 3440, 1965, 1735, 1465, 1440, 1200, 1115, 1015 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.50 (m, 1H), 4.43 (m, 1H), 3.59 (s, 3H), 0.88 ppm (t, J = 5 Hz, 3H); mass spectrum *m/e* 378 (M^+).

Bicyclic allene **9c** *via* **9a** *and* **9b**. To 90 mg (0.47 mmol) of CuI in 2 ml of Et_2O at −20° under N_2 was added 0.63 ml (0.95 mmol) of 1.50 M MeLi in Et_2O. The resulting clear soln was cooled to −78° and a soln of 40 mg (0.08 mmol) of **6b** in 2 ml of Et_2O was added. The mixture was stirred for 45 min and then quenched with 1 ml of abs MeOH. After stirring for an additional 15 min at −78°, the mixture was poured into NH_4Cl–NH_4OH aq and the product was isolated with Et_2O. Chromatography of the product on silica gel using hexane–EtOAc afforded 30 mg (86%) of **9a**: IR ν_{max} (film) 3450, 1740, 1465, 1440, 1200, 1120, 1080, 1025, 980, 910, 870, 815 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.33 (br m, 1H), 4.75 (br s, 1H), 4.42 (m, 1H), 3.90–3.13 (br m, 2H), 3.55 (s, 3H), 0.90 ppm (t, J = 5 Hz, 3H); mass spectrum *m/e* 448 (M^+).

Treatment of 220 mg (0.49 mmol) of **9a** with 20 mg of pyridinium *p*-toluenesulphonate in 5 ml of EtOH at 60° for 24 hr followed by isolation of the product with Et_2O and purification on silica gel afforded 120 mg (67%) of **9b**: IR ν_{max} (film) 3310, 1965, 1740, 1470, 1440, 1300, 1200, 1115, 1065 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.50 (m, 1H), 4.50 (m, 1H), 3.60 (s, 3H), 0.90 ppm (t, J = 5 Hz, 3H); mass spectrum *m/e* 364 (M^+), 346 (M^+–H_2O).

A 50 mg (0.14 mmol) sample of **9b** in MeOH (18 ml)–H_2O (12 ml) containing 500 mg of K_2CO_3 was stirred at room temp for 20 hr to yield following isolation with Et_2O 40 mg (83%) of **9c**: IR ν_{max} (film) 3600–2600, 1965, 1710, 1110 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.50 (m, 1H), 4.51 (m, 1H), 0.89 ppm (t, J = 5 Hz, 3H).

3β-Dimethoxymethyl-2α-carbomethoxycyclopentanol **11a,b**. A 118 mg (0.55 mmol) sample of **10**[5c,12] in 8 ml of abs MeOH at −78° under N_2 was treated with 33 mg (1.5 mmol) of $LiBH_4$. After stirring for 10 min the pH of the mixture was adjusted to pH 6 and the products were isolated with Et_2O–ØMe (1:1) to give 113 mg (95%) of a viscous oil. By NMR integration of the CO_2Me groups in the mixture, **11a**:**11b** was found to be *ca* 85:15. The corresponding mixture of acetates (Ac_2O, pyridine) exhibited the some ratio.

A 3.23 g (14.8 mmol) sample of the mixture of alcohols **11a,b** comparable to that described above, in 10 ml of MeCN at 4° under Ar was treated with 3 ml of trimethylsilyldiethylamine.[19] The progress of the reaction was followed by tlc (ØMe–dioxane–AcOH 45:8:2, Rf **11a** = 0.38, R_f **11b** = 0.36). After 25 min, tlc indicated complete silylation of isomer **11b**. The volatile material was evaporated under reduced pressure to furnish 3.8 g, which was filtered on 50 g of silica gel (pretreated with 2 ml of pyridine) using hexane–EtOAc to provide 1.26 g of silylated alcohols and 1.9 g (59%) of pure **11a**: IR ν_{max} 3460, 1730, 1130, 1080, 1060 cm^{-1}; NMR δ_{TMS} ($CDCl_3$, 250 MHz) 4.32 (m, 1H), 4.14 (d, J = 6Hz, 1H), 3.71 (s, 3H), 3.26 (s, 3H), 3.25 (s, 3H), 2.79 (m, 1H), 2.58 (dd, J = 9.5 Hz, 5 Hz, 1H), 2.04–1.48 (m, 4H); mass spectrum *m/e* 218 (M^+), 203 (M^+–Me), 187 (M^+–OMe), 169 (M^+–H_2O–OMe), 75 ($CH(OMe)_2^+$). (Found: C, 55.04; H, 8.68. $C_{10}H_{18}O_5$ requires: C, 55.03; H, 8.31%).

A pure sample of the 9β alcohol **11b** could be secured by partial silylation of a 60:40 mixture of **11a**:**11b** (from reduction of **10** with excess $NaBH_4$ in MeOH at room temp) followed by separation and methanolysis as described below: IR ν_{max} (film) 3460, 1730, 1060 cm^{-1};

NMR δ_{TMS} ($CDCl_3$) 4.12 (m, 2H), 3.68 (s, 3H), 3.28 (s, 6H), 2.9–2.36 (m, 3H), 1.67 ppm (m, 4H).

The above 1.26 g mixture of silylated alcohols in 10 ml of dry MeOH containing a crystal of *p*-TsOH was stirred for 30 min under N_2. Isolation of the products using Et_2O–ØMe (1:1) afforded 750 mg (79%) of a mixture of alcohols. Oxidation of 1.0 g of a comparable mixture was carried out with 0.85 g of pyridinium chlorochromate[22] in 9 ml of CH_2Cl_2 for 3 hr at room temp. Addition of 25 ml of Et_2O to the mixture followed by filtration on florisil with Et_2O afforded 750 mg (76%) of **10**.

t-Butyldimethylsilyl ether **11c**. To a soln of 750 mg of **11a** (3.44 mmol) and 970 mg (14.3 mmol) of imidazole in 8.5 ml of DMF at 38° under N_2 was added 1.035 g (6.87 mmol) of t-butyldimethylsilyl chloride. After stirring for 30 min, the mixture was poured into NaCl aq–hexane and the product was isolated with hexane to afford 1.02 g (89%) of **11c**: IR ν_{max} (film) 1735, 1250, 1120, 1060, 840, 810, 780 cm^{-1}; NMR δ_{TMS} (CCl_4) 4.39 (m, 1H), 4.06 (d, J = 6 Hz, 1H), 3.61 (s, 3H), 3.30 (s, 6H), 2.88–2.42 (m, 2H), 1.82–1.48 (m, 4H), 0.88 (s, 9H), 0.03 ppm (2s, 6H); mass spectrum *m/e* 332 (M^+), 317 (M^+–Me), 301 (M^+–OMe), 275 (M^+–Bu), 75 ($CH(OMe)_2^+$).

Enone **12b** via aldehyde **12a**. A mixture of 1.02 g (3.1 mmol) of **11c** and 9.8 g of amberlite H^+ IR-120 (28–35 mesh) resin in 480 ml of dry Me_2CO was stirred under N_2 for 22 hr. After filtration through a pad of Na_2SO_4 another 9.5 g of the resin was added to the Me_2CO soln and stirring was continued for an additional 17 hr. Filtration and evaporation of the solvent gave a quantitative yield of crude **12a**, which was immediately used below: IR ν_{max} (film) 2720, 1735–1715, 850, 810, 780 cm^{-1}; NMR δ_{TMS} (CCl_4) 9.61 (s, 1H), 4.53 (m, 1H), 3.68 (s, 3H), 3.41–3.0 (m, 2H), 2.10–1.6 (m, 4H), 0.90 (s, 9H), 0.05 ppm (2s, 6H).

To a mixture of sodio dimethyl (2-oxoheptyl)phosphonate in DME [from 134 mg (55–60% dispersion, *ca* 3.2 mmol) of NaH and 790 mg (3.56 mmol) of dimethyl (2-oxoheptyl)phosphonate in 55 ml of DME stirred under N_2 at room temp for 1 hr] at −78° was added 908 mg (3.17 mmol) of **12a** in 15 ml of DME. After stirring overnight at −20°, the temp was allowed to reach room temp over 2 hr. Following the addition at 0° of *ca* 0.2 ml of AcOH, the solvent was evaporated and the resulting oil was filtered over silica gel using CH_2Cl_2 to afford 820 mg (68%) of **12b**: IR ν_{max} (film) 1740, 1670, 1625, 840, 810, 775 cm^{-1}; UV λ_{max} (EtOH) 224 nm (ε = 12,000); NMR δ_{TMS} (CCl_4) 6.63 (dd, J = 8 Hz, 16 Hz, 1H), 6.03 (d, J = 16 Hz, 1H), 4.53 (m, 1H), 3.66 (s, 3H), 0.9 (s, 9H), 0.06 ppm (2s, 6H); mass spectrum *m/e* 367 (M^+–Me), 325 (M^+–Bu).

Allylic alcohols **12c,d** *and saturated alcohol* **12e**. $NaBH_4$ (238 mg, 6.27 mmol) was added to 801 mg (2.10 mmol) of **12b** in 5 ml of MeOH at 10°. After stirring for 10 min the pH of the soln was adjusted to 6 and the products were isolated with Et_2O–ØMe (1:1) and separated by column chromatography on silica gel using hexane–EtOAc to afford 56 mg (7%) of saturated alcohols **12e**: IR ν_{max} (film) 3400, 1740, 1070, 840, 810, 775 cm^{-1}; NMR δ_{TMS} (CCl_4) 4.33 (m, 1H), 3.56 (br s, 4H), 0.90 (s, 9H), 0.03 ppm (2s, 6H); mass spectrum *m/e* 371 (M^+–Me), 355 (M^+–OMe), 329 (M^+–Bu). Further elution afforded 380 mg (47%) of the allylic alcohol **12d** and finally 310 mg (37%) of the desired **12c**: IR ν_{max} (film) 3400, 1740, 1070, 840, 810, 775 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.40 (m, 2H), 4.40 (m, 1H), 3.88 (m, 1H), 3.58 (s, 3H), 0.88 (s, 9H), 0.05 ppm (2s, 6H); mass spectrum *m/e* 366 (M^+–H_2O), 327 (M^+–Bu), 309 (M^+–Bu–H_2O).

The alcohol **12d** could be oxidised back to **12b**: a mixture of 300 mg (0.78 mmol) of **12d** and 1.42 g of MnO_2 in 20 ml of CH_2Cl_2 was stirred at room temp for 4 hr. Filtration of the mixture followed by evaporation of the solvent afforded 270 mg (90%) of **12b**.

Tetrahydropyranyl ether **12f**. To a soln of 619 mg (1.61 mmol) of **12d** and 0.43 ml (4.7 mmol) of dihydropyran in 3 ml of CH_2Cl_2 at room temp under N_2 was added 10 mg of *p*-TsOH in 2 ml of THF. Following tlc indication of the end of the reaction, a small amount of K_2CO_3 and one drop of pyridine were added and the product was isolated with CH_2Cl_2 to afford in quantitative yield the crude **12f**: IR ν_{max} 1740, 1160, 1110, 1070, 1015, 835. 810, 775 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.53–5.20 (m, 2H), 4.50 (m, 2H), 4.08–3.28 (m, 4H), 3.65 (s, 3H), 0.94 (s, 9H), 0.08 ppm (2s, 6H); mass spectrum *m/e* 411 (M^+–Bu).

Aldehyde **13b** *via alcohol* **13a**. A 700 mg (1.50 mmol) sample of **12f** in 6 ml of ØMe under N_2 at −78° was treated with 2.6 ml of a 1.2 M soln of $(i\text{-}Bu)_2AlH$ in ØMe. Following tlc indication of the disappearance of starting material, 0.4 ml of MeOH was added and the soln was warmed to room temp. Isolation of the product with Et_2O afforded in quantitative yield **13a**: IR ν_{max} (film) 3460, 1130, 1110, 1075, 1020, 830, 810, 745 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.30 (m, 2H), 4.85–4.10 (m, 2H), 4.08–3.26 (m, 6H), 0.95 (s, 9H), 0.05 ppm (s, 6H).

Oxidation of 420 mg of **13a** was effected using 450 mg of pyridinium chlorochromate[22] in 4 ml of CH_2Cl_2 under N_2 at room temp for 3 hr. After the addition of 50 ml of Et_2O, the mixture was filtered over florisil to afford 380 mg (91%) of **13b**: IR ν_{max} (film) 2730, 1720, 1255, 1110, 1075, 1020, 835, 810, 775 cm^{-1}; NMR δ_{TMS} (CCl_4) 9.53 (d, J = 3 Hz, 1H), 5.53–5.16 (m, 2H), 4.90–4.33 (m, 2H), 4.15–3.10 (m, 4H), 0.95 (s, 9H), 0.05 ppm (2s, 6H).

Diacetate **13d** *via alcohol* **13c**. The trimethylsilyl ether of 5-hexyn-1-ol (170 mg, 1.0 mmol) [prepared by silylation[19] (*vide supra*) of 5-hexyn-1-ol, which was obtained from 2-hexyn-1-ol by isomerisation[27]] in 3 ml of DME under N_2 at −78° was treated with 0.57 ml of 1.53 M n-BuLi in hexane. After stirring for 10 min, 350 mg (0.80 mmol) of **13b** in 1 ml of DME was added and the resulting soln was stirred at −78° for 30 min. Isolation of the product with Et_2O afforded 420 mg (86%) of **13c**: IR ν_{max} (film) 3460, 1250, 1105, 1020, 870, 840, 775 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.70–5.20 (m, 2H), 4.61–4.45 (m, 1H), 4.46–4.10 (m, 2H), 3.98–3.30 (m, 5H), 0.91 (s, 9H), 0.03 ppm (2s, 6H).

A 380 mg (0.63 mmol) sample of **13c** was acetylated using 1.5 ml of Ac_2O and 4 ml of pyridine at 40° for 16 hr. After addition of ice chips, the product was isolated with Et_2O and purified by silica gel chromatography to afford 290 mg (75%) of **13d**: IR ν_{max} (film) 1740, 1235, 1125, 1020, 835, 810, 775 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.50–5.06 (m, 3H), 4.70–4.46 (m, 1H), 4.36–4.13 (m, 1H) 3.96 (t, J = 6 Hz, 2H), 4.1–3.2 (m, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 0.90 (s, 9H), 0.03 ppm (2s, 6H); mass spectrum *m/e* 478, 419.

Acetoxy·allene **14a**. To an ethereal soln of lithium 1-pentynylbutylcuprate[24] at −78° [from 410 mg (3.14 mmol) of 1-pentynylcopper and 2.06 ml (3.15 mmol) of a 1.53 M hexane soln of n-BuLi in 8 ml of Et_2O at −40° under N_2] was added 230 mg (0.37 mmol) of **13d** in 2 ml of Et_2O. After 6 min, 0.5 ml of MeOH at −78° was added to the mixture which was then poured into ice-NH_4Cl. Isolation of the product with Et_2O and purification on silica gel using hexane–EtOAc afforded 116 mg (56%) of **14a**: IR ν_{max} (film) 1955, 1740, 1240, 1110, 1060, 840, 810, 775 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.40–5.06 (m, 2H), 5.06–4.68 (m, 2H), 4.48 (m, 1H), 4.18–3.06 (m, 4H), 3.86 (t, J = 6.5 Hz, 2H), 1.90 (s, 3H), 0.91 (s, 9H), 0.03 ppm (2s, 6H).

Acid **14c** *via hydroxy allene* **14b**. A soln of 116 mg (0.21 mmol) of **14a** and 110 mg of K_2CO_3 in 28 ml of MeOH–H_2O (3:1) was stirred at room temp for 30 min. Evaporation of the MeOH followed by isolation of the product with Et_2O furnished 103 mg (96%) of **14b**: IR

ν_{max} (film) 3420, 1950, 1250, 1100, 1050, 1015, 830, 800, 770 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.5–5.16 (m, 2H), 5.14–4.76 (m, 2H), 4.58 (m, 1H), 4.25–4.0 (m, 1H), 3.98–3.3 (m, 4H), 3.48 (t, J = 6 Hz, 2H), 0.91 (s, 9H), 0.05 ppm (s, 6H).

To a 324 mg (0.62 mmol) sample of **14b**, comparable to that described above, in 15 ml of Me_2CO at −15° was added over 5 min a slight excess of Jones reagent.[25] After stirring for 40 min at −15°, 2 ml of i-PrOH was added and the product was isolated with Et_2O to afford 291 mg (87%) of **14c**: IR ν_{max} (film) 3600–2400, 1950, 1735, 1705, 1050, 1015, 840, 810, 775 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.46–5.16 (m, 2H), 5.14–4.73 (m, 2H), 4.60 (m, 1H), 4.11 (m, 1H), 3.96–3.13 (m, 4H), 0.95 (s, 9H), 0.07 ppm (s, 6H).

11-Deoxy-6,7-dehydro PGF$_{2\alpha}$ (**15a,b**) *and hexahydro derivatives* **16a,b**. A 290 mg (0.54 mmol) sample of **14c** in 44 ml of AcOH–H_2O–THF (27:9:8) was stirred for 43 hr. The solvents were then evaporated under reduced pressure and the resulting oil was dissolved in Et_2O and treated with an excess of CH_2N_2 to furnish the crude **15a**. Purification of **15a** by silica gel chromatography using hexane–EtOAc afforded 189 mg (99%) of **15a**: IR ν_{max} (film) 3400, 1955, 1730, 1715, 1250, 1040 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.33 (m, 2H), 5.00 (m, 2H), 4.15–3.63 (m, 2H), 3.56 (s, 3H), 0.88 ppm (t, J = 5 Hz, 3H); mass spectrum *m/e* 350 (M^+), 332 (M^+–H_2O), 314 (M^+–$2H_2O$). Hydrogenation (PtO_2, EtOAc, 93%) of **15a** produced the corresponding hexahydro derivative **16a**: IR ν_{max} (film) 3400, 1735, 1720, 1020 cm^{-1}; NMR δ_{TMS} (CCl_4) 4.03 (m, 1H), 3.54 (s, 3H), 3.37 (m, 1H), 2.20 (m, 2H), 0.9 ppm (t, J = 5 Hz, 3H), which was identical in all respects (except for rotation) with an independently prepared sample from (+)-PGA_2.

Hydrolysis of **15a** using K_2CO_3 in aq MeOH afforded the free acid **15b**: IR ν_{max} (film) 3450, 2800–2400, 1955, 1715, 1030, 970, 880 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.30 (m, 2H), 5.00 (m, 3H), 4.16–3.61 (m, 2H), 0.87 ppm (t, J = 5 Hz, 3H). The **16b** (m.p. 95–97°) secured by hydrolysis of **16a** obtained above, was identical in all respects (except for rotation, IR (nujol) and m.p.) with an independently prepared sample from (+)-PGA_2 and with the spectral values in the literature[28]: IR ν_{max} (nujol) 3450, 3300, 2650, 1700, 1015, 955 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 4.16 (m, 1H), 3.90 (s, 3H), 3.60 (m, 1H), 2.3 (m, 2H), 0.87 ppm (t, J = 5 Hz, 3H).

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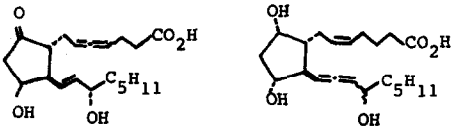

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