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SYNTHESIS OF RING MODIFIED PROSTAGLANDINS

JEAN-PIERRE DEPRÉS, ANDREW E. GREENE* and PIERRE CRABBÉ†

Laboratoire de Chimie Organique, C.E.R.M.O., Université Scientifique et Médicale, 38041 Grenoble, France

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Abstract—The total syntheses of the ring modified prostaglandins **8**, **12**, **16**, **18**, **20**, and **22** are described.

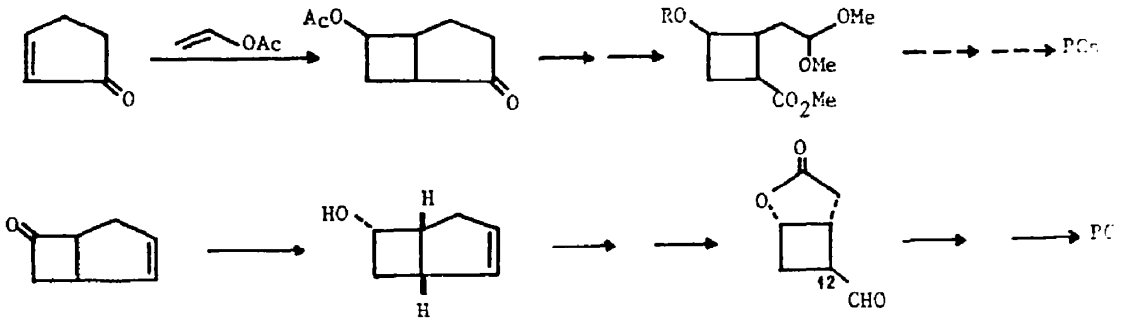
In spite of the numerous modifications of the prostaglandin skeleton that had already been carried out, at the inception of our work directed toward the synthesis of 11-nor $PGF_{2\alpha}$ and 11-nor PGE_2 no 4-membered ring prostaglandin analogs had been reported. The synthesis of 11-nor PGE_2 was of interest not only because little was known about the effect of ring size on biological activity but also due to the expected ease of effecting various alterations of the reactive cyclobutanone, which would produce additional novel prostaglandin derivatives. In this paper, a full report is given of our synthesis of 11-nor $PGF_{2\alpha}$, 11-nor PGE_2, and the lactone, lactam, and cyclopentanone ring expansion products obtained from 11-nor PGE_2. In addition, the detailed synthesis of another group of 4-membered ring analogs, β-lactam prostaglandins, is presented.[1-3]

Synthesis of cyclobutane prostaglandins 11-*nor* $PGF_{2\alpha}$ *and* 11-*nor* PGE_2

In our initial synthetic approach, we had envisaged the transformation of the photoadduct from vinyl acetate and cyclopentenone to an intermediate which could be, in principle, elaborated to give the desired cyclobutane prostaglandin analogs (Scheme 1).[4] Although we met with some success during the early stages of the synthesis, the generally mediocre yields and lack of adequate selectivity led us to examine an alternative, which is outlined in Scheme 2. The known bicyclo[3.2.0]heptenone was readily available through dechlorination of the cycloaddition product obtained from dichloroketene and cyclopentadiene.[5] It was expected, owing to the folded nature of this bicyclic ketone, that reduction of the keto group would by highly stereoselective and provide the corresponding *endo*-alcohol. This, in turn, through double bond cleavage, lactonization, and modification of the function at C-12 (prostaglandin numbering) could give the key "Corey-type lactone" intermediate, expected to be readily convertible to the desired prostaglandin analogs.[6]

L-Selectride reduction of the bicyclic ketone **2b**, obtained from cyclopentadiene in 80% yield,[5] was, in fact, completely stereoselective and afforded the *endo* alcohol **3** in 80% yield (Chart 1). Other hydride reagents such as sodium borohydride, lithium aluminum hydride, and lithium tri-*t*-butoxyaluminum hydride were less selective in this reduction, generating significant amounts of the corresponding *exo*-alcohol. The stereochemical assignments were readily made by comparison of the relative shifts of the olefinic protons in the presence of $Eu(fod)_3$. Confirmation was obtained in the next step in which the *endo*-alcohol **3** was smoothly converted to the crystalline lactone acid **4a** by ozonolysis followed by treatment with hydrogen peroxide-formic acid (88% yield). The intermediate hydroxy diacid suffered spontaneous lactonization under the reaction conditions.

Sodium borohydride or zinc borohydride reduction of the mixed anhydride[7] obtained from the lactone acid **4a** gave at best a 25% yield of the desired lactone alcohol **4b**. Part of the reason for the low yield in this reaction probably can be ascribed to the unusually polar nature of the product, which made its isolation, in practice, somewhat difficult. Fortunately, however, borane in THF effected the selective reduction[8] of the lactone acid and provided the lactone alcohol **4b**, easily isolated in 74% yield. Oxidation of **4b** with pyridinium chlorochromate (PCC)[9] then engendered the sensitive lactone aldehyde **4c**.



†Present address: Department of Chemistry, 123 Chemistry Building, University of Missouri, Columbia, Mo. 65211, U.S.A.

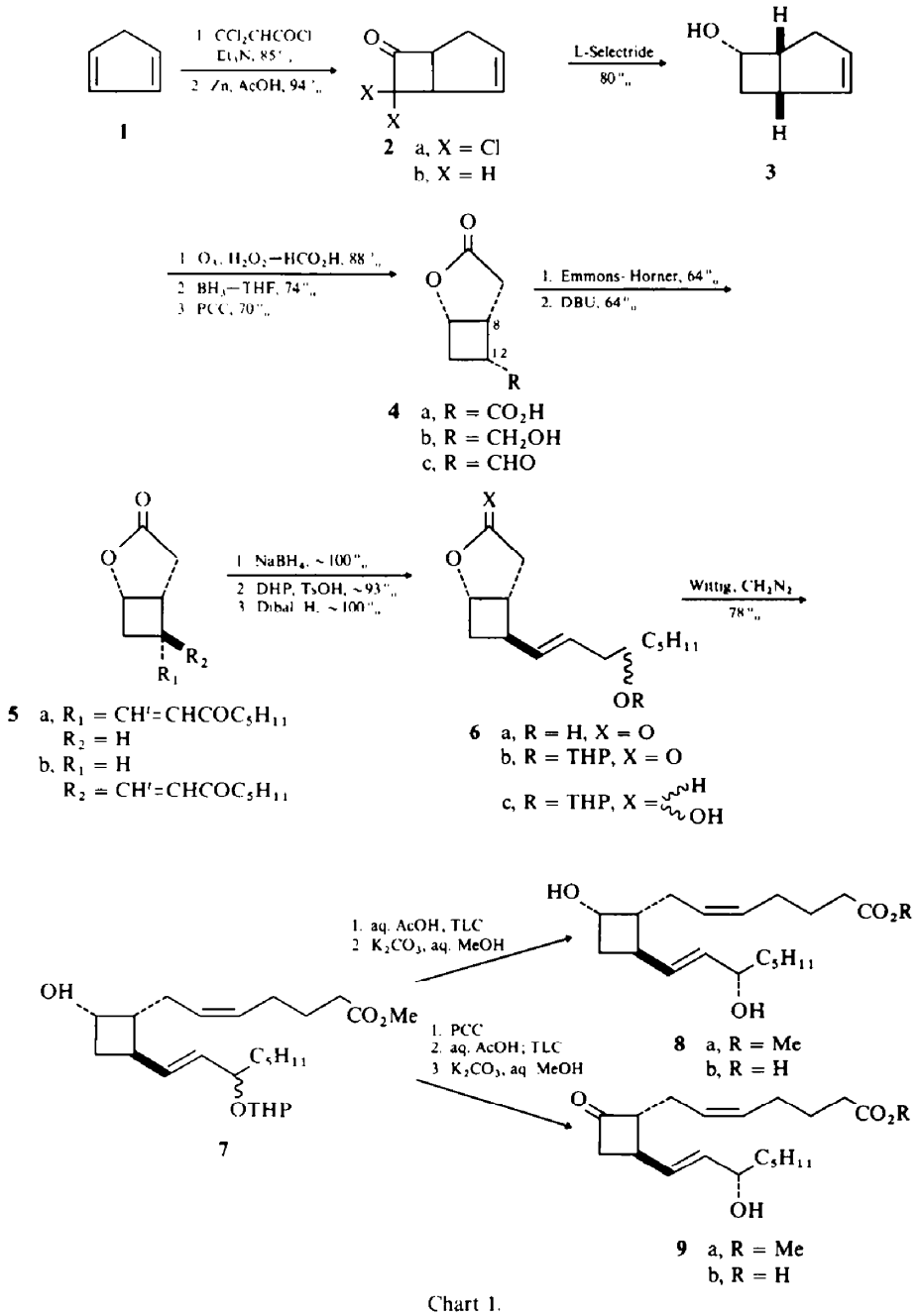


Chart 1.

We had hoped to isomerize aldehyde **4c** in order to obtain the C-8, C-12 trans relationship found in most natural prostaglandins. However, the requisite epimerization at C-12 proved not to be feasible at this stage due to the instability of the material. Attempted isomerization using diazabicycloundecene (DBU) under the reaction conditions previously used for effecting a similar epimerization[10] led to almost total destruction of the aldehyde function. However, during the next step in the synthesis, the Emmons Horner reaction of **4c** with the sodium salt of dimethyl 2-oxoheptylphosphonate.[11] we noted attendant partial equilibration[12] (**5a**:**5b**, 80:20, 64% yield) and found that it could be completed by using DBU in methylene chloride. This produced a readily separated 9 to 1 mixture of the trans and cis derivatives **5b**, **5a** in 64% yield.

For the most part, the methodology used to complete the synthesis had been worked out previously.[6,13] Sodium borohydride reduction of enone **5b** in methanol gave quantitatively an inseparable mixture of diastereomeric allylic alcohols **6a**, which were converted to the corresponding tetrahydropyranyl ethers **6b**. Treatment of **6b** with diisobutylaluminum hydride produced the mixture of lactols **6c**, readily transformed with excess Wittig reagent, prepared from (4-carboxybutyl)triphenylphosphonium bromide and dimsylpotassium, and

diazomethane to the prostanoic acid derivatives **7**. It should be pointed out that dimsylpotassium (DMSO, KH,[14] 25°, < 5 min) is not only easier to generate than the more commonly employed dimsylsodium (DMSO, NaH, 70°, *ca* 1 hr), but, in our hands, also appears to give better reproducibility in this and related reactions.

The tetrahydropyranyl ethers **7** were next hydrolyzed with aqueous acetic acid to yield the C-15 epimeric alcohols, which, fortunately, could now be separated. The α-configuration was assigned[15] to the more polar (SiO_2) isomer (**8a**), which on hydrolysis produced the novel prostaglandin analog 11-nor $PGF_{2\alpha}$ (**8b**). The new cyclobutanone prostaglandin derivative 11-nor PGE_2 (**9b**), could also be obtained in good yield from the tetrahydropyranyl ethers **7** by pyridinium chlorochromate oxidation,[9] followed by acetolysis, chromatographic separation and ester hydrolysis. While 11-nor $PGF_{2\alpha}$ was rather stable to storage, 11-nor PGE_2 was found to undergo significant decomposition at 0° over a relatively short period. It was, however, sufficiently stable to permit several ring expansion reactions to be successfully carried out.

Ring expansion reactions of 11-*nor* PGE_2

It had been anticipated, because of the ring strain in 11-nor PGE_2, that several ring expansion reactions might be readily achieved, which would produce interesting, previously unreported prostaglandin analogs.

The conversion of 11-nor PGE_2 (**9b**) to the γ-lactone **10b** with hydrogen peroxide in aqueous acetic acid at 0° was selective and high yielding (Chart 2). The product (as its methyl ester **10a**) was chromatographically homogeneous; its NMR spectrum showed a two proton multiplet at 4.05 ppm (for the C-8 and C-15 protons), supporting the assignment of the expected[16,17] structure **10** for the lactone.[18]

Similarly, treatment of 11-nor PGE_2 methyl ester (**9a**) in methylene chloride at 0° with an excess of O-mesitylenesulfonylhydroxylamine followed by passage of the reaction mixture through basic alumina[19] gave selectively the crystalline γ-lactam prostaglandin **11a** in 80% yield.[17,20] The 250 MHz NMR spectrum of **11a** showed a one proton multiplet at 3.4 ppm, indicating a structure for the γ-lactam analogous to that of the γ-lactone **10**. Hydrolysis of **11a** produced the free acid **11b**.[21]

The diazomethane ring expansion of 11-nor PGE_2, as expected,[22] proved to be less regioselective affording a separable *ca.* 1:2 mixture of 11-dexosy PGE_2 methyl ester (**13a**) and the new 10-oxo analog **12a** (66% yield, uncorrected), together with 29% of recovered starting material. The minor product, 11-desoxy PGE_2 methyl ester, was identified by comparison with an independently prepared sample from PGA_2.[4a] The major product, **12a**, on hydrolysis gave the free acid **12b**.[17] The relative cleanliness of this ring expansion coupled with the surprising paucity in the literature of reactions of diazomethane with cyclobutanones[22] encouraged us to look at other examples of this reaction, which led to a synthetically useful procedure for the synthesis of cyclopentanone derivatives.[23]

β-Lactam prostaglandins

We next considered the synthesis of another group of 4-membered ring analogs, the β-lactam prostaglandins. While the number of monocyclic β-lactams that exhibit important biological effects is limited,[24] the fact that several aza prostaglandins had been found to possess significant activities[20] prompted us to undertake the synthesis of the β-lactam prostaglandin analogs.

An ideal starting material for their synthesis appeared to be the azetidinones **15a,b**,[25] readily available through the cycloaddition of chlorosulfonyl isocyanate with butadiene and isoprene, respectively, followed by mild reduction.[26] The prostaglandin upper side chain, in principle, could be joined to **15** by a C or N

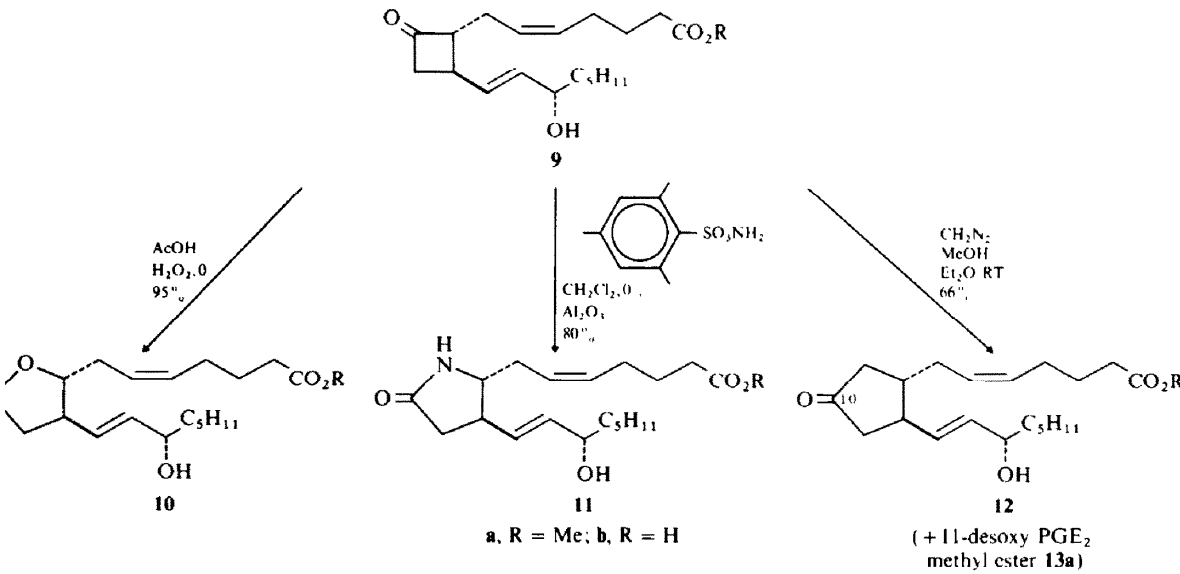


Chart 2.

alkylation reaction; the lower chain might be introduced via an aldehyde function derived from the vinyl group.[27]

It was found that the lactams **15a** and **15b** could be efficiently N-alkylated[28] with ethyl 7-iodoheptanoate in DMSO through the use of dimsylpotassium to afford the lactam esters **16a** (76% yield) and **16b** (92% yield) (Chart 3). The ozonolysis of **16a** and of **16b** in methylene chloride-methanol gave, in each case, after treatment with dimethyl sulfide the corresponding hemiacetal (and, perhaps, some hydrate); no aldehyde could be detected by NMR or IR.[29] By using an excess of the sodio derivative of dimethyl 2-oxoheptylphosphonate, however, these hemiacetals readily produced the desired enones **17a** and **17b** in 60% and 70% yields, respectively.

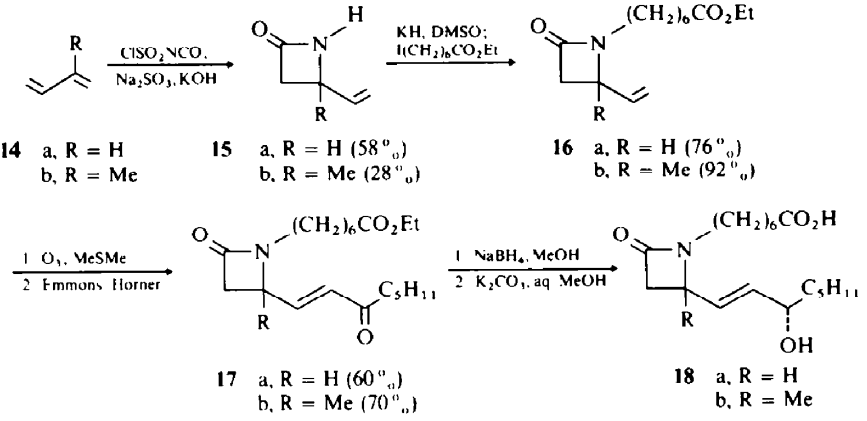
Sodium borohydride reduction of enones **17a** and **17b** in methanol at 0 gave in both cases an easily separated *ca* 3:2 mixture of the C-15 α and β-alcohols in 85% yield. The α-configuration was assigned to the more abundant (more polar) isomers.[15] Hydrolysis of the α-alcohol esters with aqueous methanolic potassium carbonate then produced in high yield the new prostaglandin derivatives, 8-aza-11-nor PGE_2 (**18a**) and 8-aza-12-methyl-11-nor PGE_2 (**18b**).

Durst *et al.*[30] had shown that 1,3-unsubstituted azetidinones are cleanly converted with 2 equivalents of n-butyllithium in THF to the corresponding 1,3-dilithio salts, which react with various electrophiles selectively at the 3-position. As an approach to 10-aza-11-nor PGE_2 (**22**), direct introduction of the upper side chain by this technique using ethyl 7-iodoheptanoate was initially attempted, but was unsuccessful due to competing reactions. However, with 1-bromo-7-trimethylsilyloxyheptane C-alkylation was readily achieved and, after brief exposure of the silyl ether to aqueous acid, the lactam alcohol **19** was obtained in 63% yield (Chart 4). Oxidation of the primary alcohol was carried out with Jones reagent, and the resultant acid was treated with diazomethane to give the lactam ester **20** in 66% yield. The 2 Hz coupling constant for the C-8 and C-12 protons in **20** confirmed the expected[30] trans orientation of the side chains.

Ozonolysis of **20** followed by reduction again produced a hemiacetal, which was transformed to enone **21** with excess Emmons-Horner reagent in 58% overall yield. Sodium borohydride reduction of the keto group in **21** yielded a readily separated mixture of C-15 alcohols, with a slight excess of the less polar β-isomer.[15] The more polar α-isomer produced upon saponification the β-lactam prostaglandin derivative 10-aza-11-nor PGE_2 (**22**).[31]

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



14 a, R = H; b, R = Me

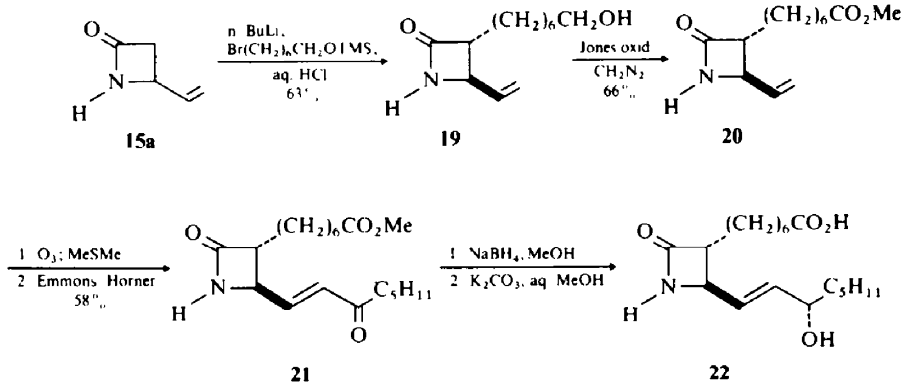
15 a, R = H (58%); b, R = Me (28%)

16 a, R = H (76%); b, R = Me (92%)

17 a, R = H (60%); b, R = Me (70%)

18 a, R = H; b, R = Me

Chart 3



15a

19

20

21

22

Chart 4.

$MgSO_4$, and then filtering and concentrating the solution under reduced pressure on a Büchi Rotovapor.

Solvents were redistilled prior to use. Hexane, pentane, and CH_2Cl_2 were distilled from $CaCl_2$, DMSO and HMPA were distilled under vacuum from CaH_2 and Et_2O, THF and DME were distilled from LAH.

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 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 or 70–230 mesh silica gel 60 was employed.

7,7-Dichlorobicyclo [3.2.0] *hept-2-ene* (**2a**).[5] To a rapidly stirred soln of 270 ml (3.28 mol) freshly distilled cyclopentadiene in 700 ml hexane was simultaneously added at 26–30° over 5 hr a soln of 142 g (0.96 mol) dichloroacetyl chloride in 400 ml hexane and a soln of 101 g Et_3N in 400 ml hexane. After the addition, the reaction was stirred for an additional 4 hr. The mixture was then treated with ice-H_2O and the organic phase was washed successively with 5% HCl aq, sat $NaHCO_3$ aq, and sat NaCl aq, dried over anhyd Na_2SO_4 and concentrated. Distillation of the resultant oil afforded 145 g (85%) of **2a**: b.p. 47–48° (0.5 mm); IR ν_{max} (film) 1805, 1608 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.86 (m, 2 H), 4.06 (m, 2 H), 2.66 ppm (m, 2 H).

Bicyclo[3.2.0]*hept-2-en-6-one* (**2b**).[5] To a stirred suspension of 11 g Zn powder in 15 ml AcOH at room temp was added dropwise 5 g of **2a** in 5 ml AcOH. After the addition, the mixture was heated at 70° for 40 min. The product was isolated with ether and distilled to give 2.85 g (94%) of **2b**: b.p. 55–56° (13 mm); IR ν_{max} (film) 1778, 1605 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.85 (br s, 2 H), 4.0–3.6 (m, 1 H), 3.6–3.0 (m, 2 H), 2.9–2.4 ppm (m, 3 H).

Bicyclo[3.2.0]*hept-2-en-6-ol* (**3**). To a 1 M soln of L-Selectride (280 ml) at −78° under N_2 was added dropwise over 50 min a soln of 30 g **2b** in 120 ml THF. After being stirred for 2 hr at −78°, the soln was allowed to warm to 0° and then treated dropwise with a 3 M soln of NaOH (120 ml), followed by 30% H_2O_2 aq (120 ml). After an additional 2 hr at 0°, the product was isolated with ether and distilled to give 24.5 g (80%) of pure *endo*-alcohol **3**: b.p. 76° (12 mm); IR ν_{max} (film) 3330, 3050 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.8 (br s, 2 H), 4.4 (m, 1 H), 3.3–1.2 ppm (m, 7 H); mass spectrum *m/e* 111 ($M^+ + 1$), 110 (M^+). (Found: C, 76.27; H, 9.13. $C_7H_{10}O$ requires: C, 76.32; H, 9.15%).

Treatment of **2b** with an excess of LAH in THF at −78° afforded a chromatographically separable 85:15 mixture of the *endo*- and *exo*-alcohols in 79% yield. *Exo*-alcohol: IR ν_{max} (film) 3320, 3050 cm^{-1}, NMR δ_{TMS} ($CDCl_3$) 5.9–5.6 (m, 2 H), 4.0 (dt, J = 4 Hz, 7 Hz, 1 H), 3.4–1.8 ppm (m, 7 H). The olefinic protons of the *endo*-alcohol were further displaced than those of the *exo* alcohol in the presence of $Eu(fod)_3$.

Lactone acid **4a**. A soln of 1.5 g (1.4 mmol) of **3** in 15 ml MeOH was treated with O_3 at −78° until the soln turned blue. After removal of the excess ozone with N_2, the solvent was evaporated at room temp under reduced pressure. The residue was then refluxed 30 min with 4.6 ml 30% H_2O_2 aq and 9.6 ml 90% HCO_2H (exothermic!). After evaporation of the solvents 2.10 g of **4a** (m.p. 53–58°) was obtained as a yellow solid: m.p. 86–87° (Et_2O–pentane); IR ν_{max} (KBr) 3150, 1775, 1725 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 4.95 (m, 1 H), 3.8–3.0 (m, 2 H), 3.0–2.4 ppm (m, 4 H). (Found: C, 53.71; H, 5.29. $C_7H_8O_4$ requires: C, 53.84; H, 5.16%).

A 312 mg sample of **4a** was esterified by using CH_2N_2 in EtOAc–Et_2O. Purification of the ester by SiO_2 chromatography using 4:6 EtOAc-hexane afforded 300 mg (88%): IR ν_{max} (film) 1775, 1730 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 4.95 (m, 1 H), 3.7 (s, 3 H), 3.70–2.90 (m, 2 H), 2.90–2.20 ppm (m, 4 H); mass spectrum *m/e* 171 ($M^+ + 1$), 139 (M^+ − OMe) (Found: C, 56.46; H, 6.07. $C_8H_{10}O_4$ requires: C, 56.46; H, 5.92%).

Lactone alcohol **4b**. To a soln of 1.56 g (1 mmol) crude **4a** in 10 ml of THF at 0° under N_2 was added dropwise 10.5 ml of a 1 M soln of BH_3 in THF. After 30 min, 20 ml MeOH was added to the soln, which was then stirred at room temp for 2 hr. Evaporation of the solvents followed by chromatography of the residue on florisil using 7:3 EtOAc–hexane gave 0.92 g (74%) of **4b**. IR ν_{max} (film) 3450, 1770 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.0 ppm (m, 1 H). (Found: C, 58.86; H, 7.18. $C_7H_{10}O_3$ requires: C, 59.14; H, 7.09%).

Lactone aldehyde **4c**. A mixture of 4.30 g (20 mmol) pyridinium chlorochromate[9] and 1.42 g (10 mmol) of **4b** in 100 ml CH_2Cl_2 was stirred for 2.5 hr and then filtered over florisil using 1:1 Et_2O–EtOAc to give 0.98 g (70%) of **4c**, used immediately below: IR ν_{max} (film) 2850, 2740, 1775, 1720 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 9.70 (br s, 1 H), 5.0 ppm (m, 1 H).

Lactone enones **5a** *and* **5b**. To a soln of sodio dimethyl (2-oxoheptyl)phosphonate in DME [obtained by addition of 1.52 g (6.85 mmol) of dimethyl (2-oxoheptyl)phosphonate in 20 ml DME to 300 mg (6.9 mmol) of 55% NaH dispersion in 90 ml DME at room temp under N_2] was rapidly added at −78° a soln of 870 mg (6.2 mmol) of **4c** in 15 ml DME. After 14 hr at −10° and 1 hr at room temp, the mixture was treated with a few drops of AcOH and then concentrated. Purification of the residue by silica gel chromatography provided 185 mg of the *trans*-isomer **5b** and 750 mg of the *cis*-isomer **5a** (64% combined yield). Enone lactone **5b**: IR ν_{max} (film) 1775, 1670, 1625 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 6.85 (dd, J = 6.5 Hz, 16 Hz, 1 H), 6.0 (d, J = 16 Hz, 1 H), 4.95 ppm (m, 1 H); UV λ_{max} (EtOH) 226 nm (ε = 11,300); mass spectrum *m/e* 237 ($M^+ + 1$), 236 (M^+). (Found: C, 70.80; H, 8.32. $C_{14}H_{20}O_3$ requires: C, 71.11; H, 8.38%). Enone lactone **5a**: IR ν_{max} (film) 1775, 1670, 1630 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 6.75 (dd, J = 5.5 Hz, 16 Hz, 1 H), 6.0 (d, J = 16 Hz, 1 H), 4.90 ppm (m, 1 H); UV λ_{max} (EtOH) 227; mass spectrum *m/e* 237 ($M^+ + 1$), 236 (M^+).

Equilibration of a 420 mg (1.8 mmol) sample of the isomer **5a** was carried out by using 300 mg 1,5-diazabicyclo-[5.4.0]undec-5-ene (DBU) in 20 ml CH_2Cl_2 at room temp for 15 hr. After being washed once with 5% HCl aq, the CH_2Cl_2 soln was dried and concentrated and the resulting oil was purified by silica gel chromatography using 1:4 EtOAc–hexane to provide 242 mg (58%) of **5b** and 25 mg (6%) of **5a**. The isomer **5b** could also be obtained in 47% overall yield by equilibration of the crude product mixture from the Emmons–Horner reaction followed by purification on silica gel.

Lactols **6c** *via allylic alcohols* **6a** *and tetrahydropyranyl ethers* **6b**. Sodium borohydride (140 mg, 3.7 mmol) was added to a stirred soln of 800 mg (3.4 mmol) of **5b** in 50 ml MeOH at 0°. After 10 min, the mixture was diluted with 150 ml Et_2O and 30 ml ØMe, and treated with 15 ml of sat NaH_2PO_4 aq. Product isolation in the usual fashion gave 810 mg of an inseparable mixture of allylic alcohols **6a**: IR ν_{max} (film) 3440, 1775 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.60 (q, 2 H), 4.90 (m, 1 H), 4.06 ppm (m, 1 H).

A soln of 730 mg (3.1 mmol) of alcohols **6a**, 0.4 ml of dihydropyran, and 1.8 ml of TsOH–THF (from 50 mg TsOH in 10 ml THF) in 9 ml of CH_2Cl_2 was stirred at room temp for 1.5 hr. Two drops of pyridine were then added, the solvents were evaporated, and the product mixture was purified by rapid filtration over florisil using 1:9 EtOAc–hexane to afford 916 mg (93%) of **6b**: IR ν_{max} (film) 1775 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.8–5.2 ppm (m, 2 H).

To a soln of 935 mg (2.9 mmol) of **6b** in 30 ml ØMe at −60° was added 4 ml of a 1.2 M soln of diisobutylaluminum hydride in ØMe. After 15 min, 1 ml of MeOH was added to the soln which was then stirred at room temp for 20 min. After dilution with 100 ml of Et_2O, the mixture was washed three times with sat NaCl aq, dried over Na_2SO_4, filtered, and concentrated to give 940 mg of **6c**, used directly below: IR ν_{max} (film) 3420 cm^{-1}.

11-Nor PGF$_{2\alpha}$ (**8b**) *via tetrahydropyranyl ethers* **7** *and 11-nor PGF$_{2\alpha}$ methyl ester* (**8a**). To a soln of 3.72 g (8.4 mmol) of (4-carboxybutyl)triphenylphosphonium bromide in 6 ml DMSO under N_2 at 10° was slowly added 11 ml of a DMSO soln of dimsylpotassium [from 3.84 g (20 mmol) of 22.5% KH in oil and 12 ml DMSO, N_2, room temp]. To the resultant red soln was added 940 mg (2.9 mmol) of **6c** in 6 ml of DMSO. After being stirred for 14 hr, the mixture was poured into ice-H_2O which was then extracted three times with 60 ml of 1:1 Et_2O EtOAc. The aqueous phase was acidified with oxalic acid to pH 2–3, and was then extracted four times with 100 ml of 1:1 Et_2O–pentane. Following the usual treatment, the combined Et_2O–pentane was concentrated to give 1.27 g of crude acid. Esterification of the acid with CH_2N_2 in ether gave 0.99 g of crude **7**, 0.50 g of which afforded after purification on florisil using 15:85 EtOAc hexane 0.48 g (78%) of pure **7**: IR ν_{max} (film) 3420, 1740 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.7–5.2 (m, 4H), 3.70 ppm (s, 3H).

A 368 mg (0.87 mmol) sample of **7** was treated with 25 ml of 7:3 AcOH–H_2O for 5 hr. The soln was then concentrated under reduced pressure and the products were separated by silica gel chromatography using EtOAc hexane to yield 88 mg of the less polar 15 βOH isomer, 90 mg of the more polar 15αOH isomer **8a**[15] and 40 mg of a mixture of 15α,βOH (74% combined yield). Isomer **8a**: IR ν_{max} (film) 3400, 1737, 1720 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.75–5.15 (m, 4H), 4.60–4.25 (m, 1H), 4.25–3.85 (m, 1H), 3.68 ppm (s, 3H); mass spectrum *m/e* 338 (M^+). (Found: C, 70.63; H, 10.15. $C_{20}H_{34}O_4$ requires: C, 70.97; H, 10.13%).

The free acid **8b** was obtained quantitatively by stirring 6 mg of **8a** at room temp for 24 hr in 6 ml of 6:4 MeOH–H_2O in the presence of 50 mg of K_2CO_3, followed by the usual product isolation: IR ν_{max} (film) 3400, 3020, 2660, 1720 cm^{-1}; NMR δ_{TMS} ($CDCl_3$–D_2O) 5.50 (m, 4H), 4.40 (m, 1H), 4.05 ppm (m, 1H).

11-Nor PGE$_2$ (**9b**) *via 11-nor PGE$_2$ methyl ester* (**9a**). A 660 mg (1.56 mmol) sample of **7** and 470 mg (2.18 mmol) of pyridinium chlorochromate[9] in 25 ml CH_2Cl_2 were stirred for 1 hr. After the addition of 60 ml Et_2O, the mixture was filtered over florisil to afford 550 mg (84%) of the cyclobutanone: IR ν_{max} (film) 1780, 1740 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.6–5.2 (m, 4H), 3.60 ppm (s, 3H).

A 202 mg (0.48 mmol) sample of this material was treated with 15 ml of 7:3 AcOH–H_2O for 5 hr. The soln was then concentrated under reduced pressure and the products were separated by silica gel chromatography using EtOAc–hexane to give 37 mg of the less polar C-15 βOH isomer, 30 mg of the more polar α-isomer **9a**[15] and 27 mg of a mixture of the α and β isomers (58% combined yield): Isomer **9a**: IR ν_{max} (film) 3450, 3020, 1780, 1740 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.90–5.35 (2 pseudo t, 4H), 4.10 (m, 1H), 3.70 ppm (s, 3H); mass spectrum *m/e* 336 (M^+). (Found: C, 70.91; H, 9.89. $C_{20}H_{32}O_4$ requires: C, 71.39; H, 9.59%).

The free acid **9b** was obtained in quantitative yield by stirring 30 mg of **9a** in 10 ml of 6:4 MeOH–H_2O in the presence of 100 mg of K_2CO_3 at room temp, followed by the usual product isolation: IR ν_{max} (film) 3400, 3020, 2600, 1780, 1715 cm^{-1}; NMR δ_{TMS} ($CDCl_3$–D_2O) 5.75 (pseudo t, 2H), 5.45 (pseudo t, 2H), 4.15 ppm (m, 1H).

Lactone acid **10b** *and lactone ester* **10a**. To a soln of 24 mg (0.07 mmol) of **9b** dissolved in 1 ml of 9:1 AcOH–H_2O at 0° was added 1 drop of 30% H_2O_2 aq. After being stirred overnight at 0–5°, the mixture was worked up in the usual manner to give 25 mg of **10b**. IR ν_{max} (film) 3300, 2600, 1730 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.75–5.45 (m, 4H), 4.40–4.00 ppm (m, 2H).

Esterification of 25 mg of **10b** with CH_2N_2 in Et_2O gave after purification by silica gel chromatography using 3:10 EtOAc hexane 18 mg of **10a**: IR ν_{max} (film) 3450, 1775, 1740 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.70–5.35 (m, 4H), 4.25–3.85 (m, 2H), 3.62 ppm (s, 3H); mass spectrum *m/e* 352.2240 (M^+). Calc. for $C_{21}H_{32}O_4$: 352.2250.

Lactam ester **11a** *and lactam acid* **11b**. O-mesitylenesulfonylhydroxylamine[19] (70 mg, 0.3 mmol) was added to a soln of 56 mg (0.18 mmol) of **9a** in 1 ml of CH_2Cl_2 at 0°. After 30 min, the solvent was evaporated and the residue was dissolved in 1 ml of ØH. Rapid filtration of this soln through 4 g of basic alumina (act I), eluting with MeOH, gave 67 mg of crude **11a**, which was further purified on florisil using EtOAc–hexane to give 46 mg (80%) of **11a**: m.p. 76–77° (Et_2O–pentane); IR ν_{max} (KBr) 3250, 1735, 1685 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 6.30 (br s, 1H), 5.75–5.30 (m, 4H), 4.30–3.90 (m, 1H), 3.70 (s, 3H), 3.40 ppm (m, 1H); mass spectrum *m/e* 351 (M^+). (Found: C, 68.43; H, 9.28; N, 4.14. $C_{20}H_{33}NO_4$ requires: C, 68.34; H, 9.46; N, 3.99%).

The free acid **11b** was obtained in 97% yield by stirring 130 mg of **11a** in 25 ml of 6:4 MeOH–H_2O in the presence of 300 mg of K_2CO_3 for 20 hr at room temp., followed by the usual isolation: IR ν_{max} 3260, 2600, 1700, 1685 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 7.15 (br s, 1H), 5.70–5.30 (m, 4H), 4.25–3.90 (m, 1H), 3.40 ppm (m, 1H).

Cyclopentanone ester **12a** *and cyclopentanone acid* **12b**. A soln of 220 mg (0.65 mmol) of **9a** in 4 ml of MeOH at −15° was treated with 16 ml of an *ca* 1.2 M soln of CH_2N_2 in Et_2O. The soln was stirred for 70 min at room temp, after which a few drops of AcOH were added, followed by evaporation of the solvent. Separation of the products by silica gel chromatography using 8:92 EtOAc ØH gave, in order of elution, 63 mg of **9a**, 29 mg of **13a**, 42 mg of a mixture of **12a** and **13a**, and 80 mg of **12a** (yield 66%; 93% based on consumed **9a**). Cyclopentanone **13a** was identified as 11-desoxy PGE_2 methyl ester through spectral and chromatographic comparison with an authentic sample.[4a] Cyclopentanone **12a**: IR ν_{max} (film) 3450, 1738 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.55–5.20 (m, 4H), 4.20–3.80 (m, 1H), 3.60 ppm (s, 3H); mass spectrum *m/e* 350.2452 (M^+) Calc. for $C_{21}H_{34}O_4$: 350.2457.

The free acid **12b** was obtained in quantitative yield by stirring 17 mg of **12a** in 10 ml of 6:4 MeOH–H_2O in the presence of 100 mg of K_2CO_3 for 20 hr at room temp, followed by the usual product isolation: IR ν_{max} (film) 3360, 2660, 1740, 1710 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.60–5.20 (m, 4H), 4.25–3.90 ppm (m, 1H).

4-Vinylazetidin-2-one (**15a**).[25,26] A soln of 11 g (68 mmol) of $ClSO_2NCO$ in 40 ml Et_2O was added over 30 min to an excess of 1,3-butadiene (condensed from 2.5 l, 0.11 mol) in 60 ml Et_2O at −63° under N_2. The resulting soln was stirred at reflux (CO_2-acetone condenser) for one week, after which it was added slowly to a stirred mixture of 100 ml 20% Na_2SO_3 aq and 50 ml Et_2O at 0°. An aqueous soln of 10% KOH was then added until pH 8–9 and the mixture was stirred for 14 hr at 0–5°. The usual workup afforded 3.82 g (58%) of **15a** (*ca* 95% pure) which could be further purified by filtration over florisil using 3:1 EtOAc–hexane: IR ν_{max} (film) 3260, 3090, 1750 cm^{-1}, NMR δ_{TMS} (CCl_4) 7.42 (br s, 1H), 6.20–4.90 (m, 3H), 4.16–3.86 (m, 1H), 3.30–2.35 ppm (m, 2H).

4-Methyl-4-vinylazetidin-2-one (**15b**).[25,26] To a soln of 2.5 g (36.7 mmol) of isoprene in 20 ml Et_2O at −65° under N_2 was slowly added 5 g (35.3 mmol) of $ClSO_2NCO$. After being stirred at −10° for 3 hr, the mixture was processed as above to give 1.1 g (28%) of **15b** (*ca* 95% pure), which could be further purified by filtration over florisil: IR ν_{max} (film) 3480, 3270, 3090, 1750 cm^{-1}; NMR δ_{TMS} (CCl_4) 7.42 (br s, 1H), 6.25–4.90 (m, 3H), 2.70 (d, J = 1.5 Hz, 2H), 1.50 ppm (s, 3H).

Lactam ester **16a**.[28] To a soln of 97 mg (1 mmol) of **15a** in 15 ml DMSO at 10° under N_2 was added 1.2 ml of a soln of dimsylpotassium in DMSO (from 2 g of 22.5% KH in oil and 10 ml of DMSO). After 10 min, the resultant red soln was treated with 568 mg (2 mmol) of ethyl 7-iodoheptanoate (obtained from the bromide by using NaI in acetone) in 2 ml DMSO. After being stirred for 2 hr, the mixture was poured into ice-H_2O. Isolation of the crude product with 1:1 Et_2O–pentane followed by purification by chromatography on silica gel using EtOAc-hexane yielded 230 mg ethyl 7-iodoheptanoate and 193 mg (76%) of **16a**: IR ν_{max} 1750 cm^{-1}; NMR δ_{TMS} (CCl_4) 6.00–4.98 (m, 3H), 4.00 (q, J = 7 Hz, 2H), 4.00–3.70 (m, 1H), 2.96 (t, J = 6 Hz, 2H), 2.18

(t, J = 6 Hz, 2 H), 1.22 ppm (t, J = 7 Hz, 3 H); mass spectrum *m/e* 254 (M^+ + 1), 253 (M^+).

Lactam ester **16b**. To a soln of 222 mg (2 mmol) of **15b** in 5 ml of DMSO under N_2 was added 0.5 g of 22.5% KH in oil. The resultant red soln was stirred for 15 min after which 1.23 g (4 mmol) ethyl 7-iodoheptanoate in 4 ml DMSO was added. After being stirred for 2 hr, the mixture was poured into ice H_2O–Et_2O. Isolation of the crude product with 1:1 Et_2O pentane followed by purification by chromatography on silica gel using EtOAc–hexane gave 580 mg ethyl 7-iodoheptanoate and 490 mg (92%) of **16b**: IR ν_{max} 1750 cm^{-1}; NMR δ_{TMS} (CCl_4) 6.10–5.00 (m, 3 H), 4.00 (q, J = 7 Hz, 2 H), 2.95 (t, J = 6 Hz, 2 H), 2.68 (s, 2 H), 2.20 (t, J = 6.5 Hz, 2 H), 1.45 (s, 3 H), 1.23 ppm (t, J = 7 Hz, 3 H); mass spectrum *m/e* 267 (M^+). (Found: C, 66.88; H, 9.77; N, 5.54. $C_{15}H_{25}O_3N$ requires: C, 67.38; H, 9.43; N, 5.24%).

Lactam enone **17a**. A stream of O_3 O_2 was passed through a stirred soln of 506 mg (2 mmol) of **16a** in 15 ml 3:7 MeOH CH_2Cl_2 at −78° until blue. The excess ozone was removed with N_2 and the soln was treated at −78° with 1 ml MeSMe. After the soln was stirred for 3 hr at room temp, the solvents were evaporated to provide 693 mg of a mixture, used below, of the crude hemiacetal and DMSO: IR ν_{max} (film) 3320, 1750, 1735 cm^{-1}; NMR δ_{TMS} (CCl_4) 4.66–4.30 (m, 1 H), 4.00 (q, J = 7 Hz, 2 H), 3.30 and 3.27 (2s, ~3H), 1.22 ppm (t, J = 7 Hz, 3 H).

To a suspension of 262 mg (6 mmol) of 55% NaH in oil in 80 ml of DME at room temp under N_2 was added 1.40 g (6.3 mmol) of dimethyl (2-oxoheptyl)phosphonate. After being stirred for 1 hr, the mixture was cooled to −78° and the crude hemiacetal, obtained above, was rapidly added in 10 ml DMF. After being stirred at −10° for 1/4 hr, 5° for 1.5 hr, and room temp for 0.5 hr, the mixture was treated with 14 drops AcOH and then filtered through silica gel using CH_2Cl_2. Further purification on silica gel using 7:13 EtOAc–hexane gave 428 mg (60%) of **17a**: IR ν_{max} (film) 1755, 1735, 1700, 1675, 1655, 1635 cm^{-1}; NMR δ_{TMS} (CCl_4) 6.58 (dd, J = 7.5 Hz, 16 Hz, 1 H), 6.14 (d, J = 16 Hz, 1 H), 4.00 (m, q, J = 7 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H), 0.90 ppm (t, J = 5 Hz, 3 H); UV λ_{max} (EtOH) 220 nm (ε = 12,300); mass spectrum *m/e* 352 (M^+ + 1), 351 (M^+).

Lactam enone **17b**. Ozonolysis of 300 mg (1.12 mmol) of **16b**, carried out as with **16a**, gave 420 mg of a mixture, used below, of the crude hemiacetal and DMSO: IR ν_{max} (film) 3350, 1735 cm^{-1}; NMR δ_{TMS} (CCl_4) 4.50 and 4.34 (2s, 1 H), 4.00 (q, J = 7 Hz, 2 H), 3.30 and 3.27 (2s, 3 H), 1.33 (s, 3 H), 1.22 ppm (t, J = 7 Hz, 3 H).

A 375 mg sample of the above crude hemiacetal was treated as in the synthesis of **17a** to give 255 mg (70%) of **17b**: IR ν_{max} (film) 1755, 1740, 1700, 1675, 1655, 1630 cm^{-1}, NMR δ_{TMS} (CCl_4) 6.64 (d, J = 16 Hz, 1 H), 6.02 (d, J = 16 Hz, 1 H), 4.00 (q, J = 7 Hz, 2 H), 2.77 (s, 2 H), 1.53 (s, 3 H), 1.20 (t, J = 7 Hz, 3 H), 0.90 ppm (t, J = 5 Hz, 3 H); UV λ_{max} (EtOH) 219 nm (ε = 8,500); mass spectrum *m/e* 366 (M^+ + 1), 365 (M^+).

8-Aza-11-nor PGE$_1$ (**18a**). A 456 mg (1.3 mmol) sample of **17a** in 15 ml MeOH at 0° was treated with 50 mg $NaBH_4$. After being stirred for 10 min, the mixture was diluted with 150 ml Et_2O, 30 ml ØMe, and 10 ml sat NaH_2PO_4 aq, and then processed as usual to afford a mixture of alcohols. Separation of the mixture by silica gel chromatography using EtOAc–hexane gave 161 mg of the less polar C-15β OH and 213 mg of the more polar α-isomer[15] and 26 mg of a mixture of the α,β-isomers (87% yield). The C-15α alcohol: IR ν_{max} (film) 3420, 1735 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.76–5.50 (m, 2 H), 4.00 (q, J = 7 Hz, 2 H), 3.98 (m, 2 H), 1.22 ppm (t, J = 7 Hz, 3 H); mass spectrum *m/e* 335.2469 (M^+ − 18). Calc. for $C_{20}H_{33}O_3N$: 335.2460.

Hydrolysis of a 140 mg (0.4 mmol) sample of the above C-15α alcohol ester was carried out in 25 ml of 6:4 MeOH–H_2O in the presence of 400 mg of K_2CO_3 for 20 hr to give 105 mg (81%) of **18a**: IR ν_{max} (film) 3400, 1735 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.76–5.54 (m, 2 H), 4.30–3.80 (m, 2 H), 3.05 (t, J = 6 Hz, 2 H), 2.27 (t, J = 7 Hz, 2 H), 0.88 ppm (t, J = 4 Hz, 3 H).

8-Aza-12-methyl-11-nor PGE$_1$ (**18b**). The reduction of 183 mg (0.5 mmol) of **17b** with 20 mg $NaBH_4$ was carried out as above to give, following silica gel chromatography, 51 mg of the less polar C-15β alcohol, 83 mg of the more polar α-isomer,[15] and 22 mg of a mixture of the α,β-isomers (85% yield). The C-15α alcohol: IR ν_{max} (film) 3420, 1735 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.62 (br s, 2 H), 4.02 (t, J = 7 Hz, 2 H), 3.96 (m, 1 H), 1.47 (s, 3 H), 1.22 ppm (t, J = 7 Hz, 3 H); mass spectrum *m/e* 368 (M^+ + 1), 367 (M^+). (Found: C, 68.37; H, 10.09; N, 3.68; $C_{21}H_{37}O_4N$ requires: C, 68.63; H, 10.15; N, 3.81%)

Hydrolysis of 64 mg (0.17 mmol) of the above C-15α alcohol ester was carried out in 15 ml of 6:4 MeOH–H_2O in the presence of 200 mg K_2CO_3 to give 59 mg (100%) of **18b**: IR ν_{max} (film) 3400, 1730 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 5.66 (br s, 2 H), 4.24–3.90 (m, 1 H), 3.0 (t, J = 6 Hz, 2 H), 2.77 (s, 2 H), 2.27 (t, J = 7 Hz, 2 H), 1.48 (s, 3 H), 0.88 ppm (t, J = 4 Hz, 3 H).

Lactam alcohol **19**. To a soln of 388 mg (4.0 mmol) of **15a** in 15 ml THF at 0° under N_2 was added 5.6 ml (8.4 mmol) of a 1.5 M soln of nBuLi in hexane. After being stirred for 1 hr at 0°, the mixture was treated with 1.06 g (4 mmol) of 1-bromo-7-trimethylsilyloxyheptane (obtained in 91% yield by reduction of ethyl 7-bromoheptanoate with BH_3 in THF at reflux followed by silylation of the resultant bromo alcohol with trimethylsilyldiethylamine in MeCN) in 8 ml of THF. After 30 min, the mixture was poured into H_2O–ice–Et_2O. The Et_2O phase (150 ml) was separated and stirred with 30 ml 5% HCl aq for 30 min. The Et_2O phase was then worked up as usual and the crude product was purified by silica gel chromatography using 11:9 EtOAc-hexane to afford 533 (63%) of **19**: IR ν_{max} (film) 3300, 1750 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 6.72 (br s, 1 H), 6.15–4.95 (m, 3 H), 3.86–3.36 (m, 3 H), 2.76 ppm (br s, 2 H); mass spectrum *m/e* (chemical ionization) 212 (M^+ + 1).

Lactam ester **20**. To a soln of 253 mg (1.20 mmol) of **19** in 25 ml acetone at −10° was slowly added a slight excess Jones reagent (45 drops). After the addition of 2 ml isopropyl alcohol, the mixture was filtered and the product was isolated with Et_2O to give 196 mg crude acid. The acid was esterified with CH_2N_2 in Et_2O and the resultant ester was purified by silica gel chromatography using 3:7 EtOAc-hexane to give 190 mg (66%) of **20**: IR ν_{max} (film) 3280, 1750, 1740 cm^{-1}; NMR δ_{TMS} (CCl_4) 7.25 (br s, 1 H), 6.18–4.90 (m, 3 H), 3.66 (dd, J = 2 Hz, 6 Hz, 1 H), 3.56 ppm (s, 3 H); mass spectrum *m/e* 239 (M^+). (Found: C, 64.87; H, 8.72; N, 5.66 $C_{13}H_{21}O_3N$ requires: C, 65.24; H, 8.85; N, 5.85%).

Lactam enone **21**. Ozonolysis of 239 mg (1.0 mmol) of **20** was carried out as above and furnished 350 mg of a mixture, used below, of the crude hemiacetal and DMSO: IR ν_{max} (film) 3300, 1750, 1740 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 6.30 (br s, 1 H), 4.48 and 4.40 (2s, 1 H), 3.62 (s, 3 H), 3.36 and 3.34 ppm (2s, 3 H).

The Emmons-Horner reaction was carried out with the above 350 mg sample as before to provide after purification by silica gel chromatography using 7:13 EtOAc–hexane 188 mg (58%) of **21**: IR ν_{max} (film) 3300, 1760, 1740, 1700, 1670, 1630 cm^{-1}, NMR δ_{TMS} (CCl_4) 7.15 (br s, 1 H), 6.68 (dd, J = 6 Hz, 16 Hz, 1 H), 6.14 (d, J = 16 Hz, 1 H), 3.88 (dd, J = 2 Hz, 6 Hz, 1 H), 3.55 (s, 3 H), 0.88 ppm (t, J = 5 Hz, 3 H); UV λ_{max} (EtOH) 226 nm (ε = 13,800); mass spectrum *m/e* 294 (M^+ − HNCO).

10-Aza-11-nor PGE$_1$ (**22**). The reduction of 197 mg (0.58 mmol) of **21** was effected in 8 ml MeOH with 28 mg $NaBH_4$ to give following silica gel chromatography using EtOAc–hexane 65 mg of the less polar C-15β alcohol, 48 mg of the more polar α-isomer[15] and 27 mg of a mixture of α- and β-isomers (70% yield). The C-15α alcohol: IR ν_{max} (film) 3300, 1740 cm^{-1}; NMR δ_{TMS} ($CDCl_3$) 6.30 (br s, 1 H), 5.80–5.60 (m, 2 H), 4.05 (m, 1 H), 3.72 (dd, J = 2 Hz, 6 Hz, 1 H), 3.60 ppm (s, 3 H); mass spectrum *m/e* 321 (M^+ − H_2O).

Hydrolysis of a 44 mg (0.13 mmol) sample of the above C-15α alcohol ester was carried out in 10 ml 6:4 MeOH–H_2O in presence of 140 mg K_2CO_3 to give 34 mg (81%) of **22**: IR ν_{max}

(film) 3300, 2660, 1740 cm $^{-1}$; NMR δ_{TMS} ($CDCl_3$) 6.55 (br s, 1 H), 5.80–5.60 (m, 2 H), 4.25–3.90 (m, 1 H), 3.90–3.64 (m, 1 H), 3.00–2.66 (m, 1 H), 2.30 (t, J = 7 Hz, 2 H), 0.88 ppm (t, J = 5 Hz, 3 H).

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[31]The β-lactams **18a** and **22** (free acids and methyl esters) were independently synthesized by the Hoechst group[3c] and shown to possess weak spasmogenic activity compared with PGA_2 on the Wistar rat stomach strip and in high doses (about 10 mg/kg) some ulcer-protecting activity in the rat. We thank Drs W. Bartmann and G. Beck for communicating to us this information.