(0.025 mL, 0.21 mmol) in DMF (2 mL) was added to a solution of the gum in DMF (3 mL), and the solution was allowed to stir at room temperature for 1 h. The solution was poured into H_2O (5 mL) and acidified with 10% HCl. The aqueous solution was extracted with Et_2O (3 × 7 mL), basified with 15% NaOH, and extracted with Et_2O (4 × 8 mL). The combined Et_2O fractions were dried ($MgSO_4$), and the Et_2O was removed under reduced pressure to yield a yellow oil. An ethereal solution of HCl was added to a solution of the oil in absolute EtOH to achieve a pH of 2. The white precipate was collected by filtration, and recrystallization from absolute EtOH/Et_2O yielded 44 mg (52%) of the desired product, mp 174–176 °C.

Binding Studies. The radioligand binding assay was conducted in essentially the same manner as reported earlier.[19,20] Following decapitation, the brains of male Sprague–Dawley rats (ca. 220 g) were removed, placed in 0.9% ice-cold saline, and dissected over ice until the tissue was prepared. Tissues were stored in ice-cold saline for not longer than 1 h and, following blot drying and weighing, were prepared and frozen at −30 °C until used. Freshly dissected or frozen tissue was homogenized in 30 volumes of ice-cold buffer containing 50 mM Tris·HCl (pH 7.4 at 37 °C; pH 8.0 at 4 °C), 0.5 mM Na_2EDTA, and 10 mM $MgSO_4$ and centrifuged at 30000*g* for 15 min. The supernatant was discarded, and the pellet was resuspended and preincubated for 15 min at 37 °C. The pellet was washed twice by centrifugation and resuspension. The final assay buffer contained 50 mM Tris·HCl (pH 7.7), 10 μM pargyline, 0.1% ascorbate, 10 mM $MgSO_4$, and 0.5 mM Na_2EDTA. The 5-HT_{1A} receptor was labeled with 0.1 nM [^{3}H]-8-OH-DPAT (154 Ci/mmol; New England Nuclear) and 4-mg wet weight of rat hippocampal tissue. The presymaptic 5-HT_{1A} site was labeled with 1.0 nM [^{3}H]-8-OH-DPAT in 8 mg/mL wet weight of rat striatal homogenate in assay buffer. In both cases, 8-OH-DPAT (1 μM) was used to determine nonspecific binding. Eleven concentrations of nonradioactive competing drugs were made fresh daily in assay buffer. Following incubation with membranes and radioligand at 37 °C (20 min for hippocampal homogenates and 30 min for striatal homogenates), samples were rapidly filtered over glass fiber filters (Schleicher and Schuell) and were washed with 10 mL of ice-cold 50 mM Tris·HCl buffer. Individual filters were inserted into vials and equilibrated with 5 mL of scintillation fluid (ScintiVerse, Fisher) for 6 h before being counted at 45% efficiency in a Beckman 3801 counter. Results were analyzed by using the program EBDA in order to determine IC_{50}, K_i, and Hill values.

Acknowledgment. This work was supported in part by funds from the A. D. Williams Fund and PHS Grant NS 23523.

Registry No. **2**, 19485-87-1; **3**, 3880-77-1; **3**·HCl, 3880-76-0; **4**, 3902-22-5; **5**, 3902-23-6; **6**, 117145-81-0; **6**·HCl, 117145-90-1; **7**, 117145-82-1; **7**·HCl, 117145-91-2; **8**, 117145-83-2; **8**·HCl, 117145-92-3; **9**, 117145-84-3; **9**·HCl, 117145-93-4; **10**, 117145-85-4; **10**·HCl, 117160-93-7; **11**, 117145-86-5; **11**·HCl, 117145-94-5; **12**, 117145-87-6; **12**·HCl, 117145-95-6; **13**, 117145-88-7; **13**·HCl, 117145-96-7; **14**, 117145-89-8; **14**·HCl, 117145-97-8; $PrNH_2$, 107-10-8; PrNHMe, 627-35-0; $PhCH_2NHMe$, 103-67-3; $Ph(CH_2)_2NH_2$, 64-04-0; $Ph(CH_2)_2NHMe$, 589-08-2; $Ph(CH_2)_3NH_2$, 2038-57-5; $Ph(CH_2)_4NH_2$, 13214-66-9; 8-methoxy-2-tetralone, 5309-19-3; 8-hydroxy-2-tetralone, 53568-05-1.

(19) Lyon, R. A.; Davis, K.; Titeler, M. *Mol. Pharmacol.* **1987**, *31*, 194.
(20) Titeler, M.; Lyon, R. A.; Davis, K. H.; Glennon, R. A. *Biochem. Pharmacol.* **1987**, *36*, 3265.
(21) Cannon, J. G.; Perez, J. A.; Pease, J. P.; Long, J. P.; Flynn, J. R.; Rusterholz, D. B.; Dryer, S. E. *J. Med. Chem.* **1980**, *23*, 745.

Prostaglandin Photoaffinity Probes: Synthesis and Biological Activity of Azide-Substituted 16-Phenoxy- and 17-Phenyl-$PGF_{2\alpha}$ Prostaglandins†

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The development of a prostaglandin $PGF_{2\alpha}$ photoaffinity probe led to the synthesis and biological evaluation of azide-substituted 17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ and 16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ derivatives. Two approaches for the preparation of iodinated versions of these prostaglandins were evaluated: (1) iodination of a phenyl azide bearing an activating hydroxyl group and (2) iodination of an aniline precursor to the phenyl azide group and subsequent conversion of the aniline to the phenyl azide. In the first approach, 17-(4-azido-2-hydroxyphenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$, 16-(5-azido-3-hydroxyphenoxy)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, and 16-(4-azido-2-hydroxyphenoxy)-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ were prepared by using the Corey synthesis, but were biologically inactive presumably as a result of the hydrophilic phenolic hydroxyl group. In the second approach, the iodination of a 17-(4-aminophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ derivative delivered 17-(4-azido-3-iodophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$, which exhibited competitive binding with natural [^{3}H]$PGF_{2\alpha}$ to ovine luteal cells and to plasma membranes of bovine corpora lutea. [^{125}I]-17-(4-Azido-3-iodophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ was utilized in a preliminary photoaffinity cross-linking experiment.

In the course of developing radiolabeled photoaffinity probes[1] for various products of the arachidonic acid cascade,[2] we required a synthesis of aryl azide substituted prostaglandin $F_{2\alpha}$ derivatives[3] **1** (Figure 1). It was anticipated that these probes (PG-ArN_3) would bind the

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.
‡ University of Kentucky.
§ Uniformed Services University of the Health Sciences.
‖ University of Colorado Health Sciences Center.

(1) For excellent reviews on the application of photoactive cross-linking reagents, see: (a) Bayley, H.; Knowles, J. R. *Methods Enzymol.* **1977**, *46*, 69 (1977). (b) Chowdhry, V.; Westheimer, F. H. *Annu. Rev. Biochem.* **1979**, *48*, 293. (c) Bayley, H. *Photogenerated Reagents in Biochemistry and Molecular Biology*; Elsevier: New York, 1983.

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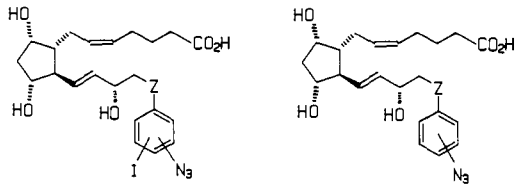
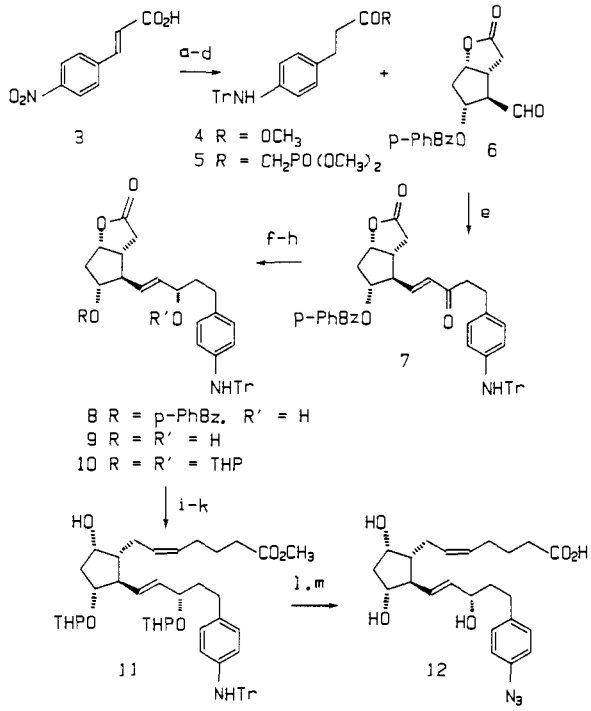


Figure 1.

Scheme I[a]



[a] (a) H_2, Pd–C; (b) HCl, MeOH; (c) TrBr, Py; (d) *n*-BuLi, $MePO(OMe)_2$; (e) NaH; (f) $NaBH_4$, $CeCl_3$; (g) K_2CO_3, MeOH; (h) DHP, PPTS; (i) DIBAL; (j) $Ph_3P{=}CH(CH_2)_3COONa$; (k) CH_2N_2; (l) HOAc, H_2O followed by $NaNO_2$ followed by NaN_3; (m) LiOH.

natural prostaglandin receptor, establish an irreversible cross-link to the receptor on photolysis of the aryl azide,[4]

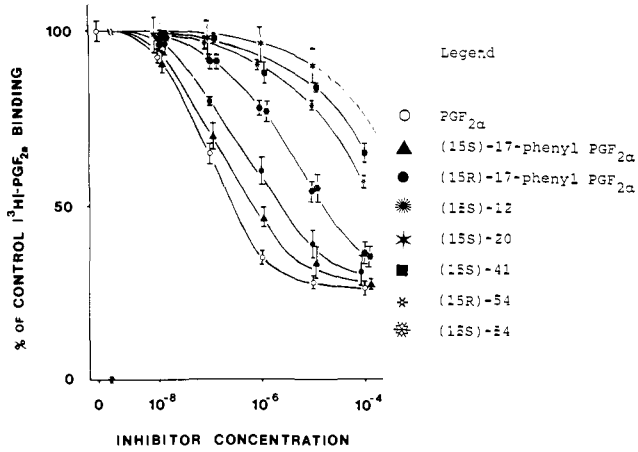
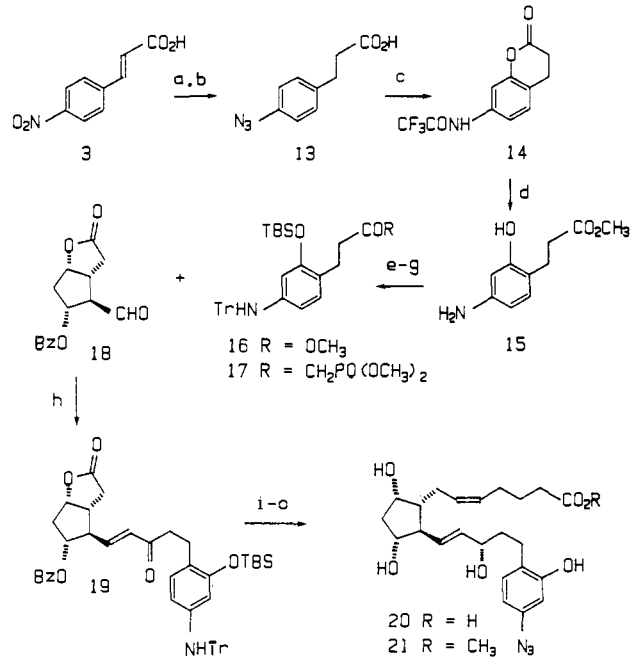


Figure 2. Corpus luteum membrane [^{3}H]$PGF_{2\alpha}$ binding specificity. Bovine corpus luteal membranes were isolated as described in the Experimental Section and used as a source of $PGF_{2\alpha}$ receptors to check competition for [^{3}H]$PGF_{2\alpha}$ binding. The curves shown reflect the ability of analogues to compete for this binding. Data points shown are the mean ± SEM; $n \geq 3$.

Scheme II[a]



[a] (a) H_2, Pd–C; (b) HCl, $NaNO_2$, followed by NaN_3; (c) TFAA, TFA; (d) 6 M HCl, MeOH; (e) TrCl, Py; (f) *t*-$BuMe_2SiCl$, imidazole; (g) *n*-BuLi, $MePO(OMe)_2$; (h) NaH; (i) $NaBH_4$, $CeCl_3$; (j) K_2CO_3, MeOH; (k) DHP, PPTS; (l) DIBAL; (m) $Ph_3P{=}CH(CH_2)_3COONa$; (n) *n*-Bu_4NF; (o) HOAc, H_2O followed by $NaNO_2$ followed by NaN_3.

and permit mapping of the prostaglandin receptor site. In designing suitable probes, we were well aware of the promising biological activity[5] displayed by various 17-phenyl[6] and 16-phenoxy[7] analogues of prostaglandins, and

(2) For recent work in this area, see: (a) Sun, F. F.; Chau, L. Y.; Spur, B.; Corey, E. J.; Lewis, R. A.; Austen, K. F. *J. Biol. Chem.* **1986**, *261*, 8540. (b) Arora, S. K.; Lim, C. T.; Kattelman, E. J.; Le Breton, G. C.; Venton, D. L. National Meeting of the American Chemical Society, Anaheim, CA, September 1986; MEDI 56. (c) Mais, D. E.; Burch, R. M.; Oatis, J. E., Jr.; Knapp, D. R.; Halushka, P. V. *Biochem. Biophys. Res. Commun.* **1986**, *140*, 128. (d) Kattleman, E. J.; Arora, S. K.; Lim, C. T.; Venton, D. L.; Le Breton, G. C. *FEBS Lett.* **1987**, *213*, 179.

(3) For a preliminary account of the synthesis of the (15*S*)-17-(4-azido-2-hydroxyphenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ (**20**), see: Dolence, E. K.; Morita, H.; Watt, D. S.; Fitz, T. A. *Tetrahedron Lett.* **1987**, *28*, 43.

(4) For references to nitrene versus other mechanisms, see: (a) Chapman, O. L. *Pure Appl. Chem.* **1979**, *51*, 331. (b) Iddon, B.; Meth-Cohn, O.; Scriven, E. F. V.; Suschitsky, H.; Gallagher, P. T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 900. (c) Colman, R.; Scriven, E. F. V.; Suschitsky, H.; Thomas, D. R. *Chem. Ind. P.* 1981, 249. (d) Takeuchi, H.; Koyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 202. (e) Nielson, P. E.; Buchardt, O. *Photochem. Photobiol.* **1982**, *35*, 317. (f) Nielson, P. E.; Leick, V.; Buchardt, O. *FEBS Lett.* **1978**, *128*, 17. (g) Mas, M. T.; Wang, J. K.; Hargrave, P. A. *Biochemistry* **1980**, *19*, 648. (h) Staros, J. V. *Trends Biochem. Sci.* **1980**, *5*, 320.

(5) For pertinent papers on the biological activity of 17-phenyl- and 16-phenoxyprostaglandins, see: (a) Miller, W. L.; Weeks, J. R.; Lauderdale, J. W.; Kirton, K. T. *Prostaglandins* **1975**, *9*, 9. (b) Powell, W. S.; Hammarstrom, S.; Samuelsson, B.; Miller, W. L.; Sun, F. F.; Fried, J.; Lin, C. H.; Jarabak, J. *Eur. J. Biochem.* **1975**, *59*, 271. (c) Powell, W. S.; Hammarstrom, S.; Samuelsson, B. *Ibid.* **1975**, *56*, 73. (d) Russell, W. *Prostaglandins* **1975**, *10*, 163. (d) Kimball, F. A.; Lauderdale, J. W.; Nelson, N. A.; Jackson, R. W. *Prostaglandins* **1976**, *12*, 985. (e) Gotze, M. *Monatsh. Verterinarmed.* **1983**, *38*, 415.

as a consequence, we elected to pursue the synthesis of azide-substituted systems **2** of this type as progenitors of the radiolabeled probes **1**. We report the synthesis and biological activity of 17-phenyl and 16-phenoxy prostaglandins bearing azide and iodo groups in the aryl ring including [^{125}I]-17-(4-azido-3-iodophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$, which was used in a preliminary cross-linking experiment.

As shown in Scheme I, we completed a straightforward synthesis of 17-(4-azidophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ (**12**) from 4-nitrocinnamic acid (**3**) by using the Corey synthesis[8] and found that **12** possessed significant biological activity in a competitive assay with [^{3}H]$PGF_{2\alpha}$ as displayed in Figure 2. However, we also required the introduction of an ^{125}I radiolabel[9] of high specific activity in the ultimate photoaffinity probe, and we sought to introduce the radiolabel in the final stages of the synthesis of the probes **1** in order to avoid the problem of carrying "hot" intermediates through a synthetic sequence. Unfortunately, the iodination of **12** or other aryl azide models failed presumably as a consequence of the deactivating effect of the azide group (σ_p = 0.08).[10]

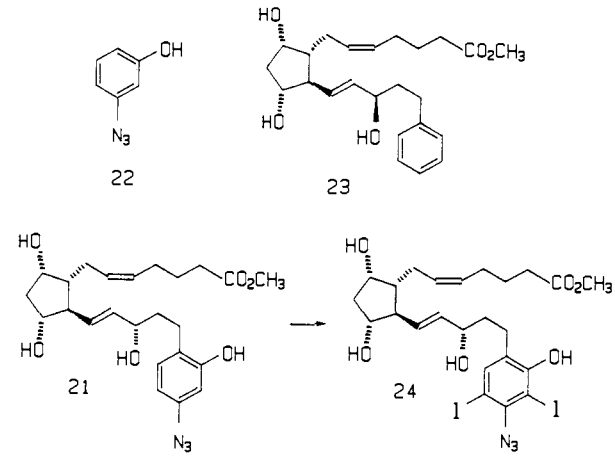


Figure 3.

One attractive plan for circumventing this problem called for the introduction of a hydroxyl group in the aryl azide in order to facilitate radioiodination *under neutral conditions* as the last step in the synthetic sequence,[11] but such a plan introduced another aryl substituent whose impact on biological activity needed to be evaluated. A second plan involved the radioiodination *under acidic conditions* of an aniline precursor to the aryl azide subunit. This plan would require the manipulation of a radioiodinated aniline derivative of high specific activity through several steps in order to secure the radioiodinated aryl azide and the evaluation of the impact of the acidic iodination conditions on the 5*Z* olefin in the "upper" side chain of the $PGF_{2\alpha}$ analogue.

Results

First Approach: Iodination Facilitated by Hydroxyl Substitution. In considering the relative orientation of the hydroxyl and azide groups in the aromatic ring, we initially favored a para orientation of the hydroxyl and azide groups.[12,13] However, we encountered considerable instability in these substituted *p*-azidophenols, an observation that was consistent with the elimination of nitrogen from the *p*-azidophenols to give reactive imino quinones. We concluded that the meta orientation of the hydroxyl and azide groups would be more stable than the para orientation, a fact that we demonstrated was correct in subsequent synthetic work and that led us to prepare exclusively the meta isomers in all subsequent studies.

(6) For leading references to the preparation of various 17-phenylprostaglandins, see: (a) Bundy, G. L.; Lincoln, F. H. *Prostaglandins* **1975**, *9*, 1. (b) Magerlein, B. J.; Bundy, G. L.; Lincoln, F. H.; Youngsdale, G. A. *Ibid.* **1975**, *9*, 5. (c) Johnson, M. R.; Hess, H. J. E.; Schaaf, T. K.; Bindra, J. S. Ger. Pat. 2,353,159, 1975 (*Chem. Abstr.* **1975**, *83*, 58094*p*). (d) Nelson, N. A. U.S. Pat. 3,966,795, 1976; *Chem. Abstr.* **1976**, *85*, 159518*b*. (e) Hayashi, M.; Kori, S.; Takatsuki, M. Ger. Pat. 2,618,663, 1976; *Chem. Abstr.* **1977**, 86, 155245*h*. (f) Hess, H. J. E.; Johnson, M. R.; Bindra, J. S.; Schaaf, T. K. U.S. Pat. 3,971,826, 1976; *Chem. Abstr.* **1977**, *86*, 29427*f*. (g) Nelson, N. A. U.S. Pat. 3,968,144, 1976; *Chem. Abstr.* **1977**, *86*, 29412*x*. (h) Yankee, E. W. U.S. Pat. 3,979,439, 1976; *Chem. Abstr.* **1977**, 86, 5019*y*. (i) Schaaf, T. K.; Bindra, J. S.; Johnson, M. R. U.S. Pat. 3,984,424, 1976; *Chem. Abstr.* **1977**, *86*, 55065*f*. (j) Peterson, D. C. U.S. Pat. 4,142,052, 1979; *Chem. Abstr.* **1979**, 91, 38994*u*.

(7) For leading references to the preparation of various 16-phenoxyprostaglandins, see: (a) Binder, D.; Bowler, J.; Brown, E. D.; Crossley, N. S.; Hutton, J.; Senior, M.; Slater, L.; Wilkinson, P.; Wright, N. C. A. *Prostaglandins* **1974**, *6*, 87. (b) Crossley, N. S. *Ibid.* **1975**, *10*, 5. (c) Grudzinskas, C. V.; Weiss, M. J. Ger. Pat. 2,548,267, 1976; *Chem. Abstr.* **1977**, *86*, 16344*b*. (d) Baumgarth, M.; Orth, D.; Radunz, H. E.; Kraemer, J.; Schliep, H.; Harting, J. Ger. Pat. 2,508,995, 1976; *Chem. Abstr.* **1977**, 86, 43267*k*. (e) Morozowich, W. Ger. Pat. 2,543,775, 1976; *Chem. Abstr.* **1977**, 86, 106034*e*. (f) Nelson, N. A. Ger. Pat. 2,610,718, 1976; *Chem. Abstr.* **1977**, *86*, 139482*c*. (g) Yankee, E. Ger. Pat. 2,719,975, 1977; *Chem. Abstr.* **1978**, *88*, 62048*x*. (h) Hayashi, M.; Kori, S.; Takatsuki, M.; Okada, T. Ger. Pat. 2,637,393, 1977; *Chem. Abstr.* **1977**, *86*, 170943*c*. (i) Bindra, J. S.; Eggler, J. F.; Johnson, M. R.; Schaaf, T. K. U.S. Pat. 4,157,341, 1979; *Chem. Abstr.* **1979**, *91*, 192898*x*. (j) Van Horn, A. R.; Garay, G.; Edwards, J. A. U.S. Pat. 4,178,457, 1979; *Chem. Abstr.* **1980**, *92*, 146339*p*. (k) Bowler, J. Ger. Pat. 2,835,538, 1979; *Chem. Abstr.* **1979**, *91*, 56453*w*. (l) Banerjee, A. K.; Broughton, B. J.; Burton, T. S.; Caton, M. P. L.; Christmas, A. J.; Coffee, E. J. C.; Crowshaw, K.; Hardy, C. J.; Heazell, M. A.; Palfreyman, M. N.; Parker, T.; Saunders, L. C.; Stuttle, K. A. J. *Prostaglandins* **1981**, *22*, 167. (m) Schaaf, T. K.; Johnson, M. R.; Constantine, J. W.; Bindra, J. S.; Hess, H.-J.; Elger, W. *J. Med. Chem.* **1983**, 26, 328. (n) Danilova, N. A.; Miftakhov, M. S.; Lopp, M.; Lille, J.; Tolstikov, G. A. *Dokl. Akad. Nauk* **1983**, *273*, 620. (o) Grudzinskas, C. V.; Weiss, M. J. U.S. Pat. 4,415,746, 1983; *Chem. Abstr.* **1984**, *101*, 23209*t*. (p) Lopp, M.; Lille, J.; Parve, O.; Paju, A.; Narep, M.; Vilimae, T. USSR Pat. 1,211,251, 1986; *Chem. Abstr.* **1986**, *105*, 208671*p*.

(8) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

(9) The need for a radiolabel of high specific activity derives from the uncertainty regarding the small number of receptors and the low efficiency of cross-linking during the photolysis step. The additional need for a radioisotope having a convenient half-life made ^{125}I the radiolabel of choice.

(10) The reported σ values for an azido group suggested that the azide was a weak deactivating group toward electrophilic aromatic substitution: Richie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323.

(11) (a) Kometani, T.; Watt, D. S.; Ji, T. *Tetrahedron Lett.* **1985**, 2043. (b) Kometani, T.; Watt, D. S.; Ji, T.; Fitz, T. *J. Org. Chem.* **1985**, *50*, 5384.

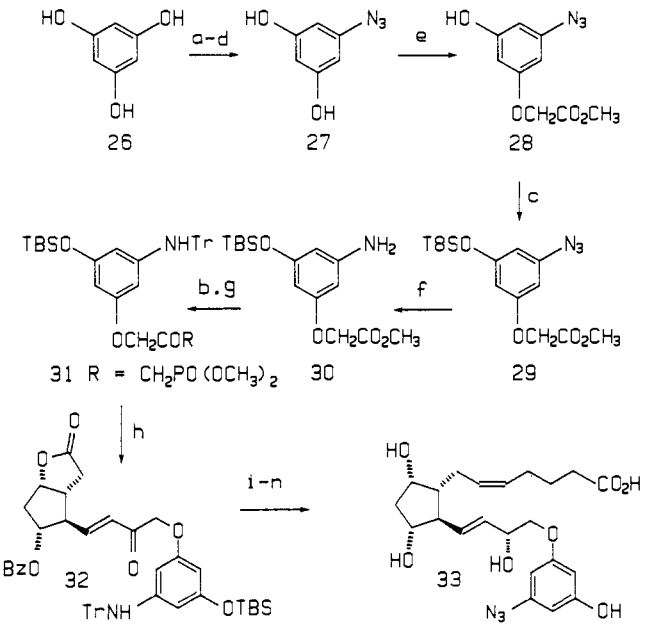
(12) For example, from 6-nitrocoumarin,[13] we prepared 4-(5-azido-2-hydroxyphenyl)-1-(dimethylphosphono)-2-butanone (i) [IR ($CHCl_3$) 3400, 2120, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.15–3.20 (m, 4, CH_2CH_2CO), 3.62 (d, J = 23 Hz, 6, OCH_3), 3.85 (d, J = 12 Hz, 2, $COCH_2PO(OCH_3)_2$), 5.80 (br s, 1, OH), 6.55–6.80 (s, 3, aromatic H)] by using the following sequence: (1) Fe, HCl; (2) MeOH, HCl; (3) H_2, Pt; (4) $NaNO_2$, HCl followed by NaN_3; (5) *n*-BuLi, $MeP(O)(OMe)_2$. Both i and the intermediate, methyl 4-(5-azido-2-hydroxyphenyl)propionate, deteriorated rapidly in a neat state, but the *tert*-butyldimethylsilyl derivative of i was quite stable.

(13) (a) Wheelock, C. E. *J. Am. Chem. Soc.* **1959**, *81*, 1348. (b) Morgan, G. T.; Michlethwait, F. M. G. *J. Chem. Soc.* **1904**, 1230.

In devising a synthesis of a prostaglandin $F_{2\alpha}$ photoaffinity reagent having meta-oriented azide and hydroxyl groups, we examined three routes for the preparation of the putative phosphonate reagent **17**: (1) a route from 7-aminocoumarin,[14] (2) a route from 5-aminosalicylic acid,[15] and (3) a route from 3-(4-azidophenyl)propionic acid.[16] Only the latter approach, which involved a nitrenium ion cyclization,[16] provided a successful route to the phosphonate **17** as shown in Scheme II. The exposure of 3-(4-azidophenyl)propionic acid (**13**) to trifluoroacetic acid led to an intermediate spirolactone, which was trapped with use of trifluoroacetic anhydride to give the trifluoroacetamide **14** in 56% yield, an improvement of the reported yield[16b] of 15%. The treatment of the trifluoroacetamide **14** with 6 M hydrochloric acid in methanol and the protection of the liberated amine with triphenylmethyl (trityl) chloride and the hydroxyl group with *tert*-butyldimethylsilyl (TBS) chloride[17,18] furnished ester **16**. Although the trityl group proved a satisfactory protecting group in many respects, we and others[19] have noted that various tritylamine derivatives persistently retained organic solvents, which complicated obtaining satisfactory combustion analyses despite repeated attempts and which led to the extensive use of exact mass spectral data in characterization. Condensation of **16** with the anion of methyl dimethylphosphonate furnished phosphonate **17**, which, in turn, provided prostaglandin **20**. For purposes of conciseness, only the 15*S* series is shown in Scheme II and described in the Experimental Section. In practice, however, both the 15*S* and 15*R* epimers were prepared in each series since the R_f values and the biological activity[20] of these prostaglandins were used to confirm the C-15 stereochemical assignments. We also prepared methyl ester **21** in order to facilitate purification and characterization and employed lithium hydroxide in order to generate **20**. Enzymatic hydrolysis[21] of 17-phenyl-PGF methyl esters using a porcine lipase was too slow to be practical.

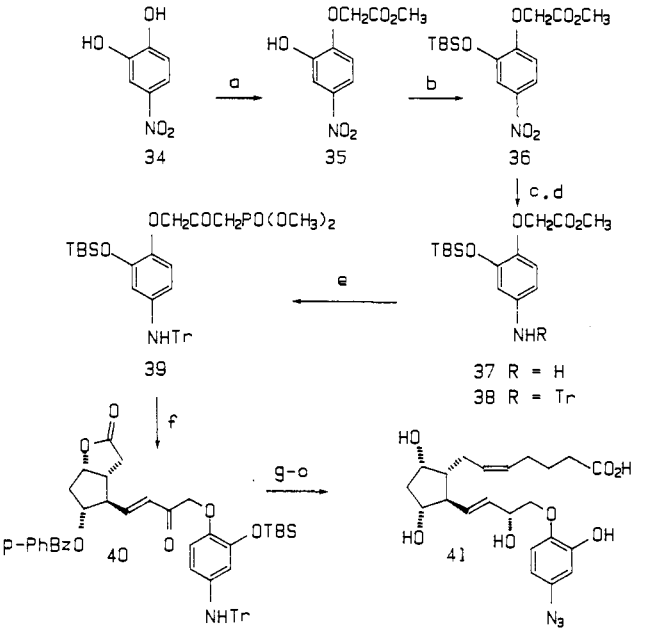
There were two concerns that we needed to address in the iodination of this hydroxyl-substituted prostaglandin analogue. First, since the analogue was an unsymmetrical

Scheme III[a]



[a] (a) NH_3; (b) TrCl, Py; (c) *t*-$BuMe_2SiCl$, imidazole; (d) $NaNO_2$, HCl followed by NaN_3; (e) NaH or Et_3N, $BrCH_2CO_2Me$; (f) H_2, Pd-C or $Zn(BH_4)_2$; (g) *n*-BuLi, $MePO(OMe)_2$; (h) NaH, 18; (i) $NaBH_4$, $CeCl_3$; (j) K_2CO_3, MeOH; (k) DIBAL; (l) $Ph_3P{=}CH(CH_2)_3COONa$; (m) *n*-Bu_4NF; (n) HOAc, H_2O followed by $NaNO_2$ followed by NaN_3.

Scheme IV[a]



[a] (a) Et_3N, $BrCH_2CO_2Me$; (b) *t*-$BuMe_2SiCl$, imidazole; (c) H_2, Pd-C; (d) TrCl, Py; (e) *n*-BuLi, $MePO(OMe)_2$; (f) NaH, 6; (g) $NaBH_4$, $CeCl_3$; (h) K_2CO_3, MeOH; (i) DHP, PPTS; (j) DIBAL; (k) $Ph_3P{=}CH(CH_2)_3COONa$; (l) CH_2N_2; (m) *n*-Bu_4NF; (n) HOAc, H_2O followed by $NaNO_2$ followed by NaN_3; (o) LiOH.

(14) The conversion of 3-aminophenol to 7-aminocoumarin was plagued by low (5%) yields: (a) von Pechmann, *Chem. Ber.* **1884**, *17*, 932. (b) Sethna, S.; Phadke, R. *Org. React.* **1953**, *7*, 1. (c) Gottlieb, H. E.; Alves de Lima, R.; Monache, F. D. *J. Chem. Soc., Perkin Trans. 2* **1979**, *4*, 435.

(15) The desired phosphonate reagent was prepared by treating methyl 4-aminosalicylate with: (1) TrCl, Py; (2) *t*-BuMeSiCl, imidazole; (3) DIBAL; (4) MsCl, Et_3N; (5) *n*-BuLi, $CH_3COCH_2PO(OMe)_2$, but the overall yield of **17** was poor.

(16) (a) Abramovitch, R. A.; Jeyaraman, R. *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: New York, 1984; Chapter 6, p 297. (b) Abramovitch, R. A.; Hawi, A.; Rodrigues, J. A. R.; Trombetta, T. R. *J. Chem. Soc., Chem. Commun.* **1986**, 283. (c) Abramovitch, R. A.; Cooper, M. M.; Jeyaraman, R.; Rusek, G. *Tetrahedron Lett.* **1986**, *27*, 3705.

(17) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(18) The selection of the TBS group was made on the basis of model experiments in which the sequential treatment of 1-[(*tert*-butyldimethylsilyl)oxy]-3-(tritylamino)benzene [IR (KBr) 3440, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6, $Si(CH_3)_2$), 0.90 (s, 9, $SiC(CH_3)_3$), 5.0 (s, 1, NH), 5.8–5.9 (d, 1, aromatic H), 6.1–6.25 (dd, 1, aromatic H), 6.75–6.9 (m, 1, aromatic H), 7.2–7.5 (m, 15, $C(C_6H_5)_3$). Anal. Calcd for $C_{31}H_{35}NSiO_2$: C, 79.95; H, 7.58. Found: C, 79.82; H, 7.64] with 2:1 acetic acid–water at 25 °C, aqueous sodium nitrite, and aqueous sodium azide at 0 °C afforded 3-azidophenol in 67% yield. As an added benefit, these acidic conditions would also be sufficient to hydrolyze tetrahydropyranyl ether (THP) protecting groups that would be present in the final stages of the synthesis.

(19) Verkade, P. E.; Nijon, H.; Tollanaar, F. D.; Van Rij, J. H.; Van Leeuwen, M. *Recl. Trav. Chim. Pays-Bas* **1952**, *71*, 1007. These authors noted a similar, persistent tendency of *N*-tritylamines to retain solvent.

(20) We define "biological activity" as the competitive binding studies shown in Figure 2 and described in the Experimental Section.

(21) (a) Lin, C. H.; Alexander, D. L.; Chidester, C. G.; Gorman, R. R.; Johnson, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1621. (b) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351.

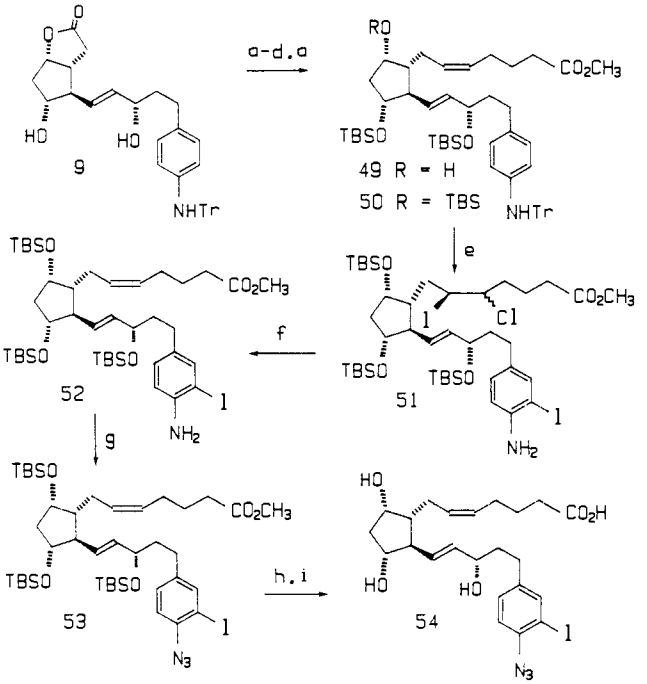
phenol, we anticipated obtaining a mixture of iodinated regioisomers, and in a model study using 3-azidophenol[22] (**22**) (Figure 3), we established that chloramine T (1.2 equiv) and sodium iodide (1.2 equiv) in a *neutral*, buffered acetonitrile solution gave a mixture of 5-azido-2-iodophenol, 3-azido-4-iodophenol, and 5-azido-2,4-diiodophenol. A second concern with regard to the iodoination reaction was the stereochemical integrity of the 5*Z* olefin and the possible interaction of this olefinic bond with the C-9α hydroxyl group.[23] To confirm that no isomerization occurred during iodination, we employed the C-15*R* epimer **23** that possessed C-5 and C-6 vinylic protons which were distinct from the C-13 and C-14 vinylic protons in the ^{1}H NMR spectrum. We demonstrated that the iodination of **22** in the presence of **23** led to the efficient iodination of **22** and the recovery of **23** in 60% yield with unaltered 5*Z* stereochemistry. The iodination of methyl ester **21** using sodium iodide and chloramine T gave a mixture of mono- and dioiodinated $PGF_{2\alpha}$ analogues from which the diiodinated material **24** was isolated in a pure state.

At the same time that these iodination studies were in progress, we evaluated the biological activity of the prostaglandin analogues **12**, **20**, and 17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ (**25**) in a competition assay with natural $PGF_{2\alpha}$. Although the introduction of an azide group into the 17-phenyl moiety had no adverse affect, the introduction of the hydroxyl group diminished the binding efficiency of **20** relative to natural $PGF_{2\alpha}$ itself as shown in Figure 2. Since it was possible that the adverse influence of the hydroxyl group was tied uniquely to the 17-phenyl series, we synthesized analogues in the 16-phenoxy series in order to investigate the generality of this influence of a hydroxyl group on biological activity.

We devised a synthesis of phosphonate **31** and **39** from phloroglucinol (**26**) and 4-nitrocatechol (**34**), respectively, and utilized these phosphonates to obtain 16-phenoxyprostaglandins **33** and **41** as shown in Schemes III and IV. Unfortunately, these 16-phenoxyprostaglandins **33** and **41** were relatively unstable,[24] a fact that complicated obtaining satisfactory combustion and exact mass spectral data. Sufficient material was amassed, however, for biological evaluation, and as in the 17-phenyl series, the hydroxyl group in **33** or **41** again diminished biological activity in competition studies with natural $PGF_{2\alpha}$.

Second Approach: Iodination of 17-(4-Aminophenyl) Intermediates. We focused attention on the synthesis and iodination[25] of an aniline precursor to the aryl azide of 17-phenylprostaglandin $F_{2\alpha}$ analogues. In order to avoid the formation of a prostacyclin type[23] of intermediate and the problem of diastereomers that the standard THP protecting group entailed, we converted diol **8**, which was prepared as shown in Scheme I, to the tris(TBS) derivative **50** as shown in Scheme V. The iodination of **50** under acidic conditions, which were required

Scheme V[a]



[a] (a) *t*-$BuMe_2SiCl$, imidazole; (b) DIBAL; (c) $Ph_3P{=}CH(CH_2)_3COONa$; (d) CH_2N_2; (e) NaI, chloramine T; (f) Zn, HOAc; (g) $NaNO_2$ followed by NaN_3; (h) *n*-Bu_4NF; (i) LiOH.

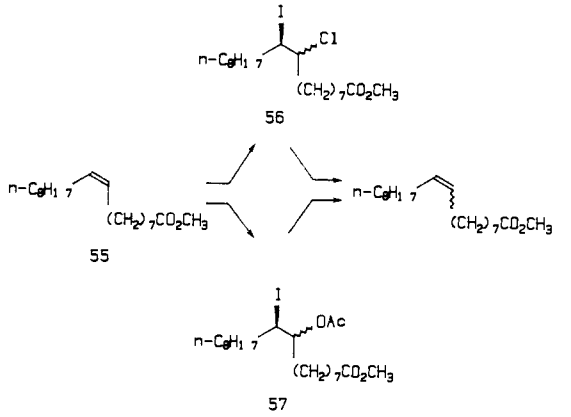


Figure 4.

for successful iodinations of anilines, led to the immediate loss of the acid-sensitive trityl protecting group and the iodination of *both* the aromatic ring and the 5*Z* olefin to give a regio- and diastereomeric mixture of vicinal iodo chlorides, one isomer of which is displayed in Scheme V.

In a related competition study under these same iodination conditions, we noted that the addition of iodine monochloride to the olefinic bond[26] in methyl *cis*-oleate (**55**) was faster than the iodination of the aromatic ring in methyl 3-[4-(tritylamino)phenyl]propionate (**4**). In a further study of the iodination of **55**, we isolated a 4.4:1 ratio of the vicinal iodo chlorides **56** and the iodoacetates **57** (Figure 4).[27] The reduction of the iodo chlorides **56** with zinc in acetic acid gave a 2.6:1 ratio of methyl *cis*- and *trans*-oleate, and the reduction of the iodoacetates **57** gave a 1:2 ratio of the methyl *cis*- and *trans*-oleate. There are

(22) (a) Ugi, T.; Perlinger, H.; Behringer, L. *Chem. Ber.* **1958**, *91*, 2330. (b) Noelting, E.; Michel, O. *Chem. Ber.* **1893**, *26*, 86.

(23) (a) Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mizsak, S. A.; Axen, U. *J. Am. Chem. Soc.* **1977**, *99*, 4182. (b) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *Ibid.* **1978**, *100*, 7690.

(24) The source of this instability was never satisfactorily resolved but appeared to be the consequence of dehydration of the C-15 hydroxyl group. The approximate half-life at 25 °C was 1–2 h.

(25) (a) Bradfield, A. E.; Orton, K. J. P.; Roberts, I. C. *J. Chem. Soc.* **1928**, 782. (b) Heisig, G. B. *J. Am. Chem. Soc.* **1928**, *50*, 139. (c) Berliner, E. *Ibid.* **1956**, *78*, 3632. (d) Sandin, R. B.; Drake, W. V.; Leger, F. *Organic Synthesis*; Wiley: New York, 1943; Collect. Vol. II, p 196.

(26) (a) White, E. P.; Robertson, P. W. *J. Chem. Soc.* **1939**, 1509. (b) Riemschneider, R.; Mau, G. *Chem. Ber.* **1957**, *90*, 2713. (c) Baird, W. C., Jr.; Surridge, J. H.; Buza, M. *J. Org. Chem.* **1971**, *36*, 3324.

(27) Efforts to suppress the formation of **57** by adding tetraethylammonium chloride to the iodination medium were unsuccessful.

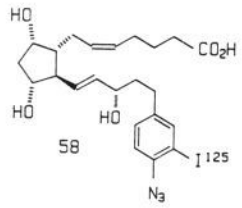


Figure 5.

several implications of these studies for the prostanoid synthesis: (1) the radioiodination of the prostanoid would be "radiochemically wasteful" since a portion of the radiolabel would be lost during the iodination and regeneration of the 5*Z* olefin and (2) the radioiodination and zinc reduction of prostaglandin **50** would afford principally the desired 5*Z* isomer assuming anti addition of iodine monochloride and anti elimination during zinc reduction of the iodo chloride.

To address these issues, we completed a successful synthesis of the desired prostanoid by using the sequence shown in Scheme V: (1) iodination of **50** under acidic conditions, (2) zinc reduction of the iodo chlorides **51**, (3) diazotization, and (4) azide substitution. At this stage, we isolated a 2:1 mixture of the 5*Z* and 5*E* isomers, which were separated by multiple developments on silica gel chromatography to afford **53**. In one case, a 1:1.2 mixture of 5*Z* and 5*E* isomers, respectively, was not separated but was evaluated in the biological screen discussed below, and the mixture displayed the expected reduction in activity compared to the pure 5*Z* isomer. Deprotecting the TBS groups and saponification delivered prostanoid **54**, which retained biological activity as shown in Figure 2.

The synthesis of the radioiodinated analogue presented an additional experimental difficulty: the sodium [^{125}I]-iodide is available as a dilute aqueous solution requiring the use of long reaction times (24 h for the radioiodination versus 2 min for the iodination) in order to effect the radioiodination. A "cold" iodination performed on a milligram scale under dilute conditions that matched those of the radioiodination experiment afforded a 5:1 mixture of the (5*Z*)- and (5*E*)-prostanoids **54**. Application of this same procedure to the radioiodination of **50** led to the desired prostaglandin **58** (Figure 5).

Biological Results. Since large luteal cells from sheep and plasma membranes of bovine corpora lutea have been shown to contain specific and high-affinity receptors[28] for prostaglandin $F_{2\alpha}$, we investigated the binding potencies of the synthetic analogues in two radioreceptor assay systems: (1) membranes prepared from bovine corpora lutea and (2) intact cells from enzymatically dispersed ovine corpora lutea. As shown in Figure 2, we investigated the competitive binding of the synthetic analogues with [^{3}H]$PGF_{2\alpha}$ using membranes from bovine corpora lutea. We noted that the ability of the synthetic analogues to compete with [^{3}H]$PGF_{2\alpha}$ decreased in the following order: (15*S*)-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ > (15*R*)-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ > (15*S*)-17-(4-azidophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ > (15*S*)-17-(4-azido-3-iodophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ > (15*R*)-17-(4-azido-3-iodophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ > (15*S*)-17-(4-azido-2-hydroxyphenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ > (15*R*)-16-(5-azido-3-hydroxyphenoxy)-17,18,19,20-tetranorprostaglandin[33] $F_{2\alpha}$ > (15*R*)-16-(4-azido-2-hydroxyphenoxy)-17,18,19,20-tetranorprostaglandin[33] $F_{2\alpha}$. Observations that the 15α isomers were more active than the 15β isomers were consistent with the analogues binding to a specific receptor. Similar observations were made with the assay system of large luteal cells in which the data were expressed as IC_{50} values (i.e., the concentration of the analogue that decreased the binding of [^{3}H]$PGF_{2\alpha}$ by 50%). The approximate numerical comparison of these analogues in the two assay systems is summarized in Table I. As indicated earlier, it appears that the insertion of a polar phenolic hydroxyl group into either an 17-(4-azidophenyl)- or 16-(3- or 4-azidophenoxy)prostanoid disrupts binding of the $PGF_{2\alpha}$ analogues to a hydrophobic region of the receptor that accepts the nonpolar, natural C-15 *n*-pentyl or the synthetic C-15 β-arylethyl groups. Fortunately, the 17-(4-azidophenyl) analogue **12** and 17-(4-azido-3-iodophenyl) analogue **54** retained sufficient biological activity to warrant preparation of the radioiodinated analogue **58**, which was successfully cross-linked to a single

Table I. Results of Competitive Binding Studies of Synthetic $PGF_{2\alpha}$ Analogues with [^{3}H]$PGF_{2\alpha}$

$PGF_{2\alpha}$ analogues	BCLM[a]	OLC[b]
(15*S*)-$PGF_{2\alpha}$	1.4×10^{-7}	4.3×10^{-8}
(15*S*)-17-phenyl $PGF_{2\alpha}$	2.4×10^{-7} (1.7)	3.2×10^{-8} (0.7)
(15*S*)-17-phenyl $PGF_{2\alpha}$ methyl ester	2.0×10^{-6} (14)	
(15*R*)-17-phenyl $PGF_{2\alpha}$	6.7×10^{-7} (4.8)	7.1×10^{-8} (1.7)
(15*R*)-17-phenyl $PGF_{2\alpha}$ methyl ester	5.0×10^{-5} (360)	
(15*S*)-**12**	7.0×10^{-6} (50)	3.3×10^{-7} (7.7)
(15*S*)-**20**	2.2×10^{-4} (1600)	6.1×10^{-6} (140)
(15*R*)-**33**[c]		1.1×10^{-5} (250)
(15*R*)-**41**[c]	1.2×10^{-4} (860)	
(15*R*)-**54**	6.8×10^{-5} (490)	
(15*S*)-**54**	7.0×10^{-6} (50)	3.5×10^{-7} (8.1)

[a] BCLM = bovine corpus lutea membranes. Data represent the point where displacement of 50% of specific tritiated $PGF_{2\alpha}$ binding occurred. In Figure 2, 26% of the bound tritiated $PGF_{2\alpha}$ cannot be displaced (nonspecific binding), and the midpoint of specific binding occurs at 63% (i.e., 100% − 26% nonspecific = 74% specific binding and midpoint = 100% − (74%/2) = 63%). Numbers in parentheses are values for the relative ratio of the analogue in comparison with $PGF_{2\alpha}$. [b] OLC = ovine luteal cells; data = IC_{50} (M). [c] See footnote 33.

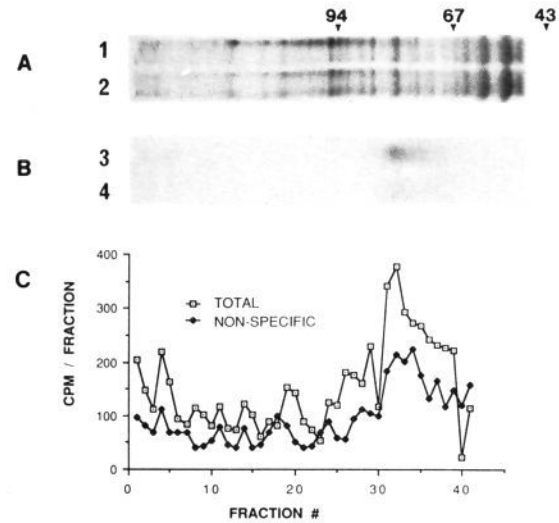


Figure 6. Polyacrylamide gel electrophoresis of [^{125}I]-**58** labeled receptors. Portion A shows the Coomassie stained gel (upper gel lane, total; lower gel lane, nonspecific). Portion B shows the aligned autoradiograms (upper gel lane, total; lower gel lane, nonspecific). Portion C shows the aligned cpm/fraction.

(28) (a) Powell, W. S.; Hammerstrom, S.; Samuelsson, B. *Eur. J. Biochem.* **1975**, *56*, 73. (b) Kimball, F. A.; Lauderdale, J. W. *Prostaglandins* **1975**, *10*, 313. (c) Rao, Ch. V. *Mol. Cell. Endocrinol.* **1976**, *6*, 1.

protein upon photolysis as indicated in Figure 6. The lanes marked 1 and 2 in this figure correspond to the Coomassie blue stained gels for the luteal membranes exposed to both probe 58 and light but without and with $PGF_{2\alpha}$, respectively. The lanes marked 3 and 4 correspond to the autoradiograms of the gels in lanes 1 and 2, respectively, and show specific labeling of a protein (lane 3). The portion of Figure 6 marked C shows the aligned cpm/fraction for the sliced gels from lanes 1 and 2 where the curves marked "total" and "nonspecific" correspond to the cpm/fraction for lanes 1 and 2, respectively. Detailed studies using this prostaglandin photoaffinity probe will be reported in due course.

Experimental Section

Infrared spectra were determined on a Beckman Microlab 600 or Perkin-Elmer 337 spectrometer. The abbreviation TF denotes thin film. NMR spectra were determined on a JEOL 270 MHz, Varian 90 MHz, or XL-200 spectrometer. Mass spectra were determined on VG ZAB spectrometer. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. Column chromatography using Macherey Nagel silica gel 60 is referred to as "chromatography on silica gel", preparative layer chromatography on Macherey Nagel silica gel F254 is referred to as "chromatography on a silica gel plate", chromatography on a Chromatotron (Harrison Research, Palo Alto, CA) using Merck silica gel F254 is referred to as "chromatography on a silica gel disk", chromatography on a medium-pressure liquid chromatograph using Woelm silica gel is referred to as "MPLC", and the drying of an organic phase over anhydrous magnesium sulfate is simply indicated by the phrase "dried".

[^{3}H]$PGF_{2\alpha}$ was purchased from New England Nuclear (Boston, MA) and unlabeled prostaglandins were purchased from Sigma Chemical Co. (St. Louis, MO). Pregnant bovine ovaries were purchased at Litvak Meat Co. (Denver, CO). All other chemicals were of the highest purity commercially available. Purity of synthetic intermediates was established by combustion analysis or by TLC analysis[19] which displayed a single spot on elution in multiple solvent systems.

Experimental details for the compounds appearing in Schemes II–IV and part of Scheme I are in the supplementary material Section.

Preparation of Ovine Corpora Lutea Cells and Assay Procedure. Corpora lutea were harvested from superovulated sheep. Progestogen sponges were inserted vaginally in cycling ewes that were 8–12 days postestrus and were removed 10 days later. Ewes received twice daily injections of FSH (Burns Biotec) (5 mg im first injection and 2.5 mg im remaining injections) beginning 72 h prior to and ending at the time of sponge removal. Most ewes exhibited estrus on the morning following sponge removal. This regimen typically induced 6–18 corpora lutea per animal, and the corpora lutea were removed 8–10 days postovulation.

All manipulations during ovariectomies and corpora luteal dissociation were conducted under aseptic conditions. Corpora lutea were enucleated from ovarian stroma, dissected free of connective tissue, sliced to 2-mm thickness by using a Stadie-Riggs hand-held microtome, and incubated in a shaking water bath at 37 °C in Ca^{2+} and Mg^{2+} free Hanks buffered salt solution containing 0.1% bovine serum albumin (Ca^{2+} and Mg^{2+} free HBSS; pH 7.35) to which was added 0.5% collagenase and 1 mg/mL deoxyribonuclease (4–6 g of tissue/15 mL of solution). After incubation for 45 min, the supernatant containing dispersed cells was harvested from the flasks and replaced with 5 mL of fresh dissociation medium. The remaining tissue was dissociated for an additional 45 min. After this second incubation, essentially all the tissue was dispersed into single cells, and any macroscopically identifiable tissue was discarded. Dispersed cells were washed three times with HBSS–BSA containing 0.1% BSA. The cells were evaluated by microscopic examination, and cell viability was assessed with trypan blue exclusion. Cell preparations were cooled to 4 °C; dimethyl sulfoxide was added to a final concentration of 7.5% by volume; and aliquots containing 10^6 large luteal cells were frozen by using a cell freezer which was programmed to cool cells from 4 °C to −38 °C in 42 min and then from −38 °C to −90 °C in 5 min. Frozen cells were stored in liquid nitrogen until needed. For use in assays, frozen cells were placed in a water bath at 37 °C and gently agitated until thawed. Cells were then placed on ice, pelleted by centrifugation, and resuspended in assay buffer. Viability of thawed large luteal cells was typically 60% as monitored by trypan blue exclusion.

Radioreceptor assays were conducted with glass culture tubes each containing 50 000 large luteal cells, 50 nCi [^{3}H]$PGF_{2\alpha}$ (195 Ci/mmol), and natural $PGF_{2\alpha}$ or a synthetic analogue in 210-μL total volume of assay buffer (HBSS–BSA adjusted to pH 5.75). Incubations were conducted in a gently shaking water bath for 30 min at 30 °C. Incubations were terminated by the addition of 1.5 mL of ice-cold buffer (25 mM Tris, 1 mM calcium chloride, 0.1% BSA, pH 7.35). The resulting solutions were applied individually to Whatman GF/B glass microfilter fibers on a Yeda filtration manifold, and each filter was washed with two 1.5-mL portions of the same cold buffer. Filters containing washed cells were placed in vials containing 10 mL of scintillation fluid (Handiflor), equilibrated for 16 h at 4 °C, and radioactivity was quantified by using a liquid scintillation counter (Tracor Mark III).

Preparation of Bovine Corpora Lutea Membranes and Assay Procedure. Bovine ovaries were collected and immediately stored in crushed ice for transport to the laboratory where corpora lutea were surgically excised from ovaries and homogenized (Virtis homogenizer Model 45, setting 100) twice for 3 min each in 10 volumes of ice-cold homogenization buffer (HB = 10 mM Tris·HCl, pH 7.0, 250 mM sucrose, 1 mM calcium chloride, 0.05% BSA (w/v), 10^{-7} M indomethacin, 1 mM dithiothreitol, 10 μM benzathonium chloride, 60 KalliKrein Inhibitor Units/mL of aprotinin, 100 μg/mL chicken egg white trypsin inhibitor, 1 mM benzamidine, 100 μM leupeptin, 10^{-4} M phenylmethanesulfonyl fluoride, 10^{-5} M pepstatin A, and 1.25 mg/L human placenta α-1 antitrypsin). The crude homogenate was filtered twice with single layer and then once with double-layer cheese cloth and centrifuged (Sorvall RC-5B, rotor HS-4) at 1500 rpm (433g) for 10 min at 4 °C. The supernatant was removed and stored at 0 °C. The pellet was resuspended in 5 volumes of HB, rehomogenized, filtered, and centrifuged as described above. This supernatant was added to the first supernatant, and the resulting homogenate could be stored at −20 °C. Membranes for binding were isolated by centrifugation (Sorvall RC-5B, rotor 55-34) at 12 500 rpm (17339g) for 10 min at 4 °C, removal of the supernatant, addition of new HB (lacking the bovine serum albumin), and swirling of the tube to remove only the top white fluffy coat of the pellet. After this was repeated once, the resulting membranes were resuspended in HB minus the bovine serum albumin at approximately 1–2 mg of protein/mL.

For binding studies, the membranes described above were diluted 1:1 with control, serum-free culture medium[29] and incubated for 90 min (which allowed binding to come to equilibrium[28c] at room temperature on a rotary shaker with 2×10^{-9} M [^{3}H]-$PGF_{2\alpha}$ (150 Ci/mmol) and the test compound. [^{3}H]$PGF_{2\alpha}$ was stored in a dark bottle under a nitrogen atmosphere and at −20 °C. Before addition of the membrane suspension to the tube containing [^{3}H]$PGF_{2\alpha}$, the solvent in which [^{3}H]$PGF_{2\alpha}$ was dissolved was evaporated with a stream of nitrogen gas. Competing compounds were dissolved in several different solvents as described in the Results section. After the 90-min binding period, the reaction was terminated by filtration of the membrane solution through prewashed Whatman GFC fiberglass filters and washing the filters once prior to and twice after filtration with 5 mL of cold 10 mM Tris·HCl buffer (pH 7.0, 0.15 M NaCl). The filters were agitated in scintillation vials with scintillation fluid (New England Nuclear, Aquasol) for at least 24 h prior to counting on a Beckman LS-7500 liquid scintillation counter (^{3}H counting efficiency approximately 48%).

Methyl 3-[4-(Tritylamino)phenyl]propionate (4). To a solution of 4.28 g (25.9 mmol) of 3-(4-aminophenyl)propionic acid[30]

(29) Gerschenson, L. E.; Berliner, J.; Yang, J. J. *Cancer Res.* **1974**, *34*, 2873.
(30) Skinner, W. A.; Gram, H. F.; Mosher, C. W.; Baker, B. R. *J. Am. Chem. Soc.* **1959**, *81*, 4639.

dissolved in 500 mL of anhydrous methanol was bubbled anhydrous hydrogen chloride gas for 5 min. The solution was refluxed for 20 h, concentrated, poured into saturated sodium bicarbonate, and extracted with ethyl acetate. The extracts were washed with brine and dried to afford methyl 3-(4-aminophenyl)propionate.

To a solution of the crude methyl 3-(4-aminophenyl)propionate in 88 mL of anhydrous pyridine was added 9.15 g (28.3 mmol, 1.1 equiv) of trityl bromide. The solution was stirred at 25 °C for 20 h, diluted with ethyl acetate, washed with brine, and dried. The product was chromatographed on silica gel with 1:4 ethyl acetate–hexane to afford 9.24 g (85%) of **4**: IR (KBr) 3400, 1745, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43–2.79 (m, 4, CH_2CH_2), 3.62 (s, 3, OCH_3), 4.94 (s, 1, NH), 6.28 (d, J = 8 Hz, 2, aromatic H), 6.73 (d, J = 8 Hz, 2, aromatic H), 7.15–7.45 (m, 15, $C(C_6H_5)_3$); exact mass spectrum calcd for $C_{29}H_{27}NO_4$ 421.2043, found 421.2043.

1-(Dimethylphosphono)-4-[4-(tritylamino)phenyl]-2-butanone (5). To a solution of 3.49 g (28.2 mmol, 3.3 equiv) of dimethyl methylphosphonate in 56 mL of anhydrous THF at −78 °C was added 17.9 mL (28.2 mmol, 3.3 equiv) of 1.57 M *n*-butyllithium in hexane. The solution was stirred for 30 min at −78 °C to give a cloudy white solution, which was transferred via a double-ended needle to a solution of 3.60 g (8.54 mmol) of **4** in 17.6 mL of anhydrous toluene and 17.6 mL of anhydrous THF at −78 °C to give a red solution. The mixture was stirred at −78 °C for 30 min and quenched with an aqueous methyl acetate solution. The product was extracted with ethyl acetate, washed with brine, and dried. The crude foam was chromatographed on silica gel with ethyl acetate to give 2.42 g (57%) of **5**: IR (KBr) 3340, 1710, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59–2.86 (m, 4, CH_2CH_2), 2.99 (d, J = 23 Hz, 2, $COCH_2PO(OCH_3)_2$), 3.70 (d, J = 11 Hz, 6, OCH_3), 4.95 (s, 1, NH), 6.27 (d, J = 8 Hz, 2, aromatic H), 6.72 (d, J = 8 Hz, 2, aromatic H), 7.07–7.51 (m, 15, $C(C_6H_5)_3$).

Anal. Calcd for $C_{31}H_{32}NO_4P$: C, 72.49; H, 6.28. Found: C, 72.33; H, 6.35.

(−)-3α,5α-Dihydroxy-2β-[5-[4-(tritylamino)phenyl]-3-oxo-*trans*-1-pentenyl]cyclopentane-1α-acetic Acid γ-Lactone 3-(4-Phenylbenzoate) (7). To 29.3 g (0.114 mol) of chromium trioxide–dipyridine complex, 60 g of Celite, and 350 mL of anhydrous dichloromethane at 0 °C under a nitrogen atmosphere was added 4.71 g (13.4 mmol) of Corey lactone 4-phenylbenzoate alcohol[31] in 50 mL of dichloromethane. The mixture was stirred for 20 min at 0 °C and 33.8 g (0.244 mol) of sodium hydrogen sulfate monohydrate was added. The mixture was stirred for an additional 20 min. The slurry was filtered by suction through a bed of Celite covered with anhydrous magnesium sulfate. The filter pad was washed with 200 mL of dichloromethane and 100 mL of anhydrous benzene. The filtrate was concentrated at 30 °C to ca. 50 mL of an amber oil containing aldehyde **6**, which was used immediately in the next reaction.

To 769 mg (16.0 mmol) of 50% sodium hydride in 40 mL of anhydrous 1,2-dimethoxyethane was added dropwise 8.03 g (15.6 mmol) of **5** in 100 mL of 1,2-dimethoxyethane and 20 mL of anhydrous toluene. The resulting cloudy, pale yellow solution was stirred for 30 min at 25 °C. Aldehyde **6** was added to this solution by syringe. The cloudy mixture was stirred for 2 h at 25 °C and diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine and dried. The crude foam was chromatographed on silica gel with 1:1 ethyl acetate–hexane to give 6.38 g (65% based on Corey alcohol) of **7**: IR (KBr) 3400, 1780, 1720, 1680, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.96 (s, 1, NH), 5.02–5.15 (m, 1, C-9β H), 5.24–5.38 (m, 1, C-11β H), 6.18 (d, J = 16 Hz, 1, C-14 vinylic H), 6.27 (d, J = 8 Hz, 2, aromatic H), 6.55–6.79 (m, 3, C-13 vinylic H and aromatic H), 7.11–7.75 (m, 22, $C(C_6H_5)_3$, meta aromatic H of $OCOC_6H_4$, C_6H_5), 8.05 (d, J = 8 Hz, 2, ortho aromatic H of $OCOC_6H_4$); exact mass spectrum (FAB) calcd for $C_{50}H_{43}NO_5$ 737.3143, found 737.3140.

(−)-3α,5α-Dihydroxy-2β-[5-[4-(tritylamino)phenyl]-(3*S*)-3-hydroxy-*trans*-1-pentenyl]cyclopentane-1α-acetic Acid γ-Lactone 3-(4-Phenylbenzoate) (8). To 6.17 g (8.37 mmol) of **7** and 3.12 g (8.37 mmol, 1.0 equiv) of cerium chloride heptahydrate in 100 mL of anhydrous methanol were added slowly 100 mL of anhydrous THF and 317 mg (8.37 mmol, 1.0 equiv) of sodium borohydride.[32] The mixture was stirred for 10 min at 25 °C and poured into ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried. The crude mixture of 15*R* and 15*S* diastereomers (R_f 0.50 for 15*S* and R_f 0.43 for 15*R* in 2:1 ethyl acetate–hexane) was separated by MPLC with 2:1 ethyl acetate–hexane to give 2.91 g (47%) of the 15*S* diastereomer **8**: IR (KBr) 3500, 3420, 1780, 1720, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99–4.13 (m, 1, C-15β H), 4.92 (s, 1, NH), 5.01–5.12 (m, 1, C-9β H), 5.20–5.33 (m, 1, C-11β H), 5.48–5.73 (m, 2, vinylic H), 6.26 (d, J = 8 Hz, 2, aromatic H), 6.68 (d, J = 8 Hz, 2, aromatic H), 7.15–7.73 (m, 22, $C(C_6H_5)_3$, meta aromatic H of $OCOC_6H_4$, C_6H_5), 8.05 (d, J = 8 Hz, 2, ortho aromatic H of $OCOC_6H_4$); exact mass spectrum (FAB) calcd for $C_{50}H_{45}NO_5$ 739.3300, found 739.3297.

The assignment of 15*R* and 15*S* stereochemistry was based originally on R_f values but was subsequently confirmed by the preparation of both the 15*R* and 15*S* prostaglandin analogues in which the 15*S* diastereomer displayed greater biological activity than the 15*R* diastereomer.

(15*S*)-17-[4-(Tritylamino)phenyl]-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester 11,15-Bis(*tert*-butyldimethylsilyl ether) (49). To a solution of 1.04 g (1.86 mmol) of **9** in 20 mL of *N*,*N*-dimethylformamide were added 1.12 g (7.44 mmol) of *tert*-butyldimethylsilyl chloride[17] and 0.63 g (9.30 mmol) of imidazole. The mixture was stirred for 4.5 h at 25 °C, diluted with ethyl acetate, washed with brine, and dried. The residue was chromatographed on silica gel with 1:5 ethyl acetate–hexane to afford 1.24 g (85%) of bis(TBS) lactone: IR (KBr) 3440, 1780, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02–0.08 (m, 12, $Si(CH_3)_2$), 0.90 (s, 18, $SiC(CH_3)_3$), 3.96–4.12 (m, 2, C-11β and C-15β H), 4.92–5.01 (m, 2, NH and C-9β H), 5.37 (dd, J = 8, 15 Hz, 1, vinylic H), 5.53 (dd, J = 6, 15 Hz, 1, vinylic H), 6.30 (d, J = 8 Hz, 2, aromatic H), 6.71 (d, J = 8 Hz, 2, aromatic H), 7.17–7.47 (m, 15, $C(C_6H_5)_3$); exact mass spectrum (FAB) calcd for $C_{49}H_{65}LiNO_4Si_2$ $(M + Li)^+$ 794.4615, found 794.4614.

To 648 mg (0.822 mmol) of bis(TBS) lactone was added 1.26 mL (1.89 mmol, 2.3 equiv) of 1.5 M diisobutylaluminum hydride in toluene at −78 °C to afford the bis(TBS) lactol, which was used immediately in the next reaction. This material was successively treated with 1.82 g (4.11 mmol, 5.0 equiv) of (4-carboxybutyl)-triphenylphosphonium bromide to afford the crude acid, which was treated with an excess of diazomethane. The crude product was chromatographed on silica gel with 1:5 ethyl acetate–hexane to give 434 mg (60%) of **49**: IR (TF) 3510, 3400, 1720, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02–0.07 (m, 12, $Si(CH_3)_2$), 0.89 (s, 18, $SiC(CH_3)_3$), 2.31 (t, J = 8 Hz, 2, C-2 CH_2), 3.67 (s, 3, OCH_3), 3.96–4.20 (m, 3, C-9β, C-11β, and C-15β H), 4.96 (s, 1, NH), 5.27–5.57 (m, 4, vinylic H), 6.31 (d, J = 8 Hz, 2, aromatic H), 6.74 (d, J = 8 Hz, 2, aromatic H), 7.19–7.48 (m, 15, $C(C_6H_5)_3$); exact mass spectrum (FAB) calcd for $C_{55}H_{77}LiNO_5Si_2$ $(M + Li)^+$ 894.5504, found 894.5500.

(15*S*)-17-[4-(Tritylamino)phenyl]-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester 9,11,15-Tris(*tert*-butyldimethylsilyl ether) (50). The procedure described above was repeated with 583 mg (0.656 mmol) of **49**, 297 mg (1.97 mmol, 3.0 equiv) of *tert*-butyldimethylsilyl chloride, 178 mg (2.62 mmol, 4.0 equiv) of imidazole in 8.6 mL of *N*,*N*-dimethylformamide to afford, after chromatography on silica gel with 1:10 ethyl acetate–hexane, 601 mg (91%) of **50**: IR (TF) 3400, 1730, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00–0.06 (m, 18, $Si(CH_3)_2$), 0.86 (s, 9, $SiC(CH_3)_3$), 0.88 (s, 9, $SiC(CH_3)_3$), 0.90 (s, 9, $SiC(CH_3)_3$), 1.25–2.21 (m, 12, CH, CH_2), 2.25 (t, J = 8 Hz, 2, C-2 CH_2), 2.41 (m, 2, C-17 CH_2), 3.65 (s, 3, OCH_3), 3.86 (m, 1, C-9β H), 4.00–4.17 (m, 2, C-11β and C-15β H), 4.95 (s, 1, NH), 5.22–5.60 (m, 4, vinylic H), 6.31 (d, J = 8 Hz, 2, aromatic H), 6.74 (d, J = 8 Hz, 2, aromatic H), 7.18–7.49 (m, 15, $C(C_6H_5)_3$); exact mass spectrum (FAB) calcd for $C_{61}H_{91}LiNO_5Si_3$ $(M + Li)^+$ 1008.6369, found 1008.6366.

(31) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491.

(32) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(33) The 15α epimer has the 15*S* configuration in the 17-phenyl series and the 15*R* configuration in the 16-phenoxy series.

(15*S*)-17-(4-Azido-3-iodophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ Methyl Ester 9,11,15-Tris(*tert*-butyldimethylsilyl ether) (53). To a solution of 151 mg (0.151 mmol) of **50** and 68 mg (0.453 mmol, 1.5 equiv) of sodium iodide in 1.5 mL of glacial acetic acid was added 103 mg (0.435 mmol, 1.5 equiv) of chloramine-T hydrate. The solution was stirred for 2 min at 25 °C and quenched by the addition of 2 mL of 5% sodium thiosulfate solution. Sodium bicarbonate was added to adjust the pH to 9, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried. The iodo chloride **51** was used in the next step without purification.

To a solution of **51** in 0.7 mL of glacial acetic acid was added 99 mg (1.51 mmol) of zinc dust. The solution was stirred for 2.5 h at 25 °C and diluted with water. Sodium bicarbonate was added to adjust the pH to 9, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried. The mixture was chromatographed on silica gel with 1:5 ethyl acetate–hexane to afford 74 mg of crude **52**. This material was successively treated, as described in the preparation of **11**, with 2.4 mL of 9:1 acetic acid–water, 63 mg (0.91 mmol) of sodium nitrite, and 79 mg (1.21 mmol) of sodium azide to afford, after chromatography on silica gel with 1:30 ethyl acetate–hexane, 63 mg (46%) of a 2:1 mixture of C-5 cis and trans olefins. The mixture of cis and trans olefins was separated by MPLC using 1:100 ethyl acetate–hexane to give **53**: IR (TF) 2115, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01–0.07 (m, 18, $Si(CH_3)_2$), 0.85 (s, 9, $SiC(CH_3)_3$), 0.89 (s, 9, $SiC(CH_3)_3$), 0.91 (s, 9, $SiC(CH_3)_3$), 2.23 (t, J = 8 Hz, 2, C-2 CH_2), 2.59 (m, 2, C-17 CH_2), 3.65 (s, 3, OCH_3), 3.86 (m, 1, C-9β H), 4.05–4.22 (m, 2, C-11β and C-15β H), 5.20–5.62 (m, 4, vinylic H), 7.05 (d, J = 8 Hz, 1, aromatic H), 7.19 (dd, J = 2, 8 Hz, 1, aromatic H), 7.61 (d, J = 2 Hz, 1, aromatic H); exact mass spectrum (FAB) calcd for $C_{42}H_{74}ILiN_3O_5Si_3$ $(M + Li)^+$ 918.4145, found 918.4142.

(15*S*)-17-(4-Azido-3-iodophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ (54). A mixture of 12 mg (13.2 μmol) of **53** and 0.26 mL (0.26 mmol, 20 equiv) of 1.0 M tetra-*n*-butylammonium fluoride in THF was stirred for 14 h at 25 °C. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried. The product was chromatographed on silica gel with 1:60 methanol–ethyl acetate to afford 7 mg (93%) of the methyl ester of **54**: IR (TF) 3400, 2115, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (t, J = 8 Hz, 2, C-2 CH_2), 2.46–2.85 (m, 2, C-17 CH_2), 3.67 (s, 3, OCH_3), 3.90–4.28 (m, 3, CHOH), 5.28–5.72 (m, 4, vinylic H), 7.06 (d, J = 8 Hz, 1, aromatic H), 7.24 (dd, J = 2, 8 Hz, 1, aromatic H), 7.64 (d, J = 2 Hz, 1, aromatic H); exact mass spectrum (FAB) calcd for $C_{24}H_{32}ILiN_3O_5$ $(M + Li)^+$ 576.1548, found 576.1547. To 3.6 mg (6.32 μmol) of the methyl ester of **54** was added 0.32 mg (7.58 μmol, 1.2 equiv) of lithium hydroxide monohydrate in 72 μL of THF and 72 μL of water to afford carboxylic acid **54**.

(15*S*)-[^{125}I]-17-(4-Azido-3-iodophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ (58). Investigators wore protective clothing and gloves, and performed radiochemical steps in an appropriate hood. To a solution of 10 mCi (3.97 nmol, 1.4 equiv) of sodium [^{125}I]iodide in 20 μL of 0.1 M sodium hydroxide solution in a screw-capped vial equipped with a rubber septum and a small stirring bar were added 6 μL of glacial acetic acid, 1.4 μg (1.4 nmol) of **50** in 1 μL of glacial acetic acid, and 0.9 μg (3.97 nmol, 1.4 equiv) of chloramine T in 1 μL of water. The solution was stirred for 24 h at 25 °C. The solution was treated as described in the preparation of **52**, with 0.5 mg (7.65 μmol) of zinc dust to afford the ^{125}I-iodinated aniline. The solution was stirred for 2.5 h at 25 °C, diluted with 1 μL of 5% sodium thiosulfate solution, and neutralized with 15 mg (0.18 mmol) of sodium bicarbonate, which was added carefully in small portions. The mixture was extracted several times with ethyl acetate. The combined organic layers were washed with brine and evaporated under a stream of air in an appropriate fume hood.

The procedure described for the preparation of **53** was repeated with 0.8 mg (11.6 μmol) of sodium nitrite, 1.0 mg (15.4 μmol) of sodium azide, and 43 μL of 13:1 acetic acid–water to afford, after HPLC on silica gel with 2:1 dichloromethane–hexane, the ^{125}I-iodinated aryl azide. The product was identified by comparison of TLC (silica gel) R_f values of the ^{125}I-iodinated aryl azide (detection by overlaying radiographic film on the plate) with "cold" **53**.

The procedure described for the preparation of **54** was repeated with 40 μL of 1.0 M tetra-*n*-butylammonium fluoride in THF to afford, after C_{18} reversed-phase HPLC, ^{125}I-iodinated methyl ester of **58** having an R_f value identical with that of the "cold" methyl ester of **58**. The product was treated with 85 μg (2 μmol) of lithium hydroxide monohydrate in 40 μL of 1:1 THF–water, and the reaction mixture was subjected to ion-exchange column chromatography (Amberlite IR-120) with 1:1 THF–water as an eluent to afford **58** having an R_f value identical with that of the "cold" iodinated **54**.

Cross-Linking Experiment in Figure 6 Using [^{125}I]-58. [^{125}I]-**58** was allowed to bind to bovine corpora lutea membranes (with or without unlabeled $PGF_{2\alpha}$ present) for 3 h in the dark and photolyzed. The membranes were washed twice with PBS, solubilized with Laemmli sample buffer, and separated by 6% PAGE. The gel was stained with Coomassie dye, dried, put up for autoradiography, and finally sliced up for counting.

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Registry No. **4**, 117625-23-7; **5**, 117625-24-8; **6**, 38754-71-1; **6** (alcohol), 31752-99-5; **7**, 117625-25-9; **8**, 117625-26-0; **9**, 117625-41-9; **9** (bis TBS ether), 117625-27-1; **9** (bis TBS ether, lactol), 117625-28-2; **10**, 117625-42-0; **10** (lactol), 117625-43-1; **11**, 117625-44-2; **12**, 117625-46-4; **12** (methyl ester), 117625-45-3; (15*R*)-**12**, 117706-87-3; **13**, 103489-31-2; **14**, 103515-26-0; **15**, 110828-47-2; **15** (*N*-CF_3CO deriv), 117625-47-5; **15** (2-methoxy acid), 117625-48-6; **15** (*N*-CPh_3 deriv), 117625-49-7; **16**, 117625-50-0; **17**, 110828-45-0; **18**, 39746-01-5; **18** (alcohol), 39746-00-4; **19**, 110828-48-3; **19** (15*S*-alcohol), 117625-51-1; **19** (15*R*-alcohol), 117706-92-0; **19** (11,15*S*-diol), 117625-52-2; **19** (11,15*S*-diol; bis THP ether), 117625-53-3; **19** (diol; bis THP ether, lactol), 110828-49-4; **20**, 110828-44-9; **20** (11,15-bis THP ether, 2-TBS ether; Ph_3CNH deriv), 117625-54-4; **20** (11,15-bis THP ether; Ph_3CNH analogue), 110828-50-7; (15*R*)-**20**, 117625-86-2; **21**, 117625-55-5; **24**, 117625-56-6; **27**, 51642-28-5; **28**, 114970-03-5; **29**, 117625-57-7; **30**, 117625-58-8; **31**, 117625-60-2; **31** (R = OCH_3), 117625-59-9; **32**, 117625-61-3; **32** (15*R* alcohol), 117625-62-4; **32** (15*S*-alcohol), 117706-93-1; **32** (11,15*R*-diol), 117625-63-5; **32** (11,15-diol, lactol), 117625-64-6; **33**, 117625-66-8; **33** (3-TBS ether, Ph_3CNH analogue), 117625-65-7; (15*S*)-**33**, 117706-88-4; **34**, 3316-09-4; **35**, 117625-67-9; **36**, 117625-68-0; **37**, 117625-69-1; **38**, 117625-70-4; **39**, 117625-71-5; **40**, 117625-72-6; **40** (15*R*-alcohol), 117625-73-7; **40** (11,15*R*-diol), 117625-74-8; **40** (11,15*R*-diol; bis THP ether), 117625-75-9; **40** (11,15-diol; bis THP ether, lactol), 117625-76-0; **41**, 117625-80-6; **41** (methyl ester), 117625-79-3; **41** (11,15-bis THP ether, 2-TBS ether; Ph_3CNH analogue), 117625-77-1; **41** (methyl ester; 11,15-bis THP ether, 2-TBS ether, Ph_3CNH analogue), 117625-78-2; (15*S*)-**41**, 117706-89-5; **49**, 117625-30-6; **49** (acid), 117625-29-3; **50**, 117625-31-7; **51** (isomer 1), 117625-32-8; **51** (isomer 2), 117706-90-8; **51** (isomer 3), 117625-87-3; **51** (isomer 4), 117706-91-9; **52**, 117625-33-9; **52**-^{125}I, 117625-37-3; **53**, 117625-34-0; (5*E*)-**53**, 117706-85-1; **53**-^{125}I, 117625-38-4; **54**, 117625-36-2; **54** (methyl ester), 117625-35-1; (15*R*)-**54**, 117706-86-2; **55**, 112-62-9; (*E*)-**55**, 1937-62-8; (±)-(*R**,*R**)-**56**, 117625-81-7; (±)-(*R**,*S**)-**56**, 117625-88-4; (±)-(*R**,*R**)-**57**, 117625-82-8; (±)-(*R**,*S**)-**57**, 117625-89-5; **58**, 117625-40-8; **58** (methyl ester), 117625-39-5; $H_2NC_6H_4$-4-$(CH_2)_2CO_2H$, 2393-17-1; $H_2NC_6H_4$-4-$(CH_2)_2COOMe$, 35418-07-6; $MePO(OMe)_2$, 756-79-6; $Ph_3P^+(CH_2)_4CO_2H$ Br^-, 17814-85-6; $BrCH_2CO_2Me$, 96-32-2; (15*S*)-$PGF_{2\alpha}$, 551-11-1; (15*S*)-17-phenyl $PGF_{2\alpha}$, 55582-75-7; (15*S*)-17-phenyl $PGF_{2\alpha}$ methyl ester, 117625-83-9; (15*R*)-17-phenyl $PGF_{2\alpha}$, 117625-84-0; (15*R*)-17-phenyl $PGF_{2\alpha}$ methyl ester, 117625-85-1.

Supplementary Material Available: Experimental section for compounds appearing in Figure 4, Schemes II–IV and part of Scheme I (28 pages). Ordering information is given on any current masthead page.