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15-Fluoro prostaglandin FP agonists: a new class of topical ocular hypotensives

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Abstract—A novel series of 15-fluoro prostaglandins with phenoxy termination of the ω-chain was synthesized and evaluated for binding and functional activation of the prostaglandin FP receptor in vitro and for side effect potential and topical ocular hypotensive efficacy in vivo. Compounds with the 15α-fluoride relative stereochemistry displayed EC_{50} values of $\leqslant 20$ nM, comparable to the value for the endogenous ligand $PGF_{2\alpha}$. Evaluation of selected ester prodrugs of these 15-fluoro prostaglandins in vivo highlighted their generally low propensity to elicit hyperemia or ocular irritation in rabbits and efficacious intraocular pressure-lowering property in monkeys. In particular 13,14-dihydro-15-deoxy-15α-fluoro-16-aryloxy-ω-tetranor-*cis*-Δ^4-$PGF_{2\alpha}$ isopropyl ester (**24**) caused relatively little ocular irritation in rabbits while lowering intraocular pressure in conscious ocular hypertensive monkeys by 39% following a topical ocular dose of 3 μg.

1. Introduction

Glaucoma, a heterogeneous family of optic neuropathies, is one of the leading causes of blindness in the developed world. Elevated intraocular pressure (IOP) is an important risk factor for loss of visual field due to optic nerve damage.[1] Endogenous prostaglandins and their prodrugs, such as $PGF_{2\alpha}$ isopropyl ester, reduce IOP in monkeys and in man, but also cause conjunctival hyperemia, foreign-body sensation, and stinging.[2] Prodrugs of potent, selective prostaglandin FP receptor agonists exhibit similar IOP-lowering potencies and efficacies as their endogenous counterparts but elicit greatly reduced ocular side effects. Three such synthetic prostaglandin analogs-travoprost,[3a] latanoprost,[3b] and bimatoprost[3c]—are the active ingredients of topically active, once-a-day IOP-lowering medications (Fig. 1). Their introduction to clinical practice has revolutionized the treatment of glaucoma.

Our continuing interest in discovering novel structures with prostaglandin FP receptor agonist activity led us to consider the 15-deoxy-15-fluoro (termed 15-fluoro hereinafter) structural motif. The replacement of the carbon 15-hydroxyl group of $PGF_{2\alpha}$ with a fluorine atom should profoundly affect many physicochemical properties of the molecule.[4] The volume occupied by the C–F group (bond distance ~1.38 Å,[5a] F van der Waals radius ~1.47 Å[6]) is smaller than that for the C–O–H array (bond lengths: ~1.43 Å[5b] for a C–O bond and 0.96 Å[5c] for an O–H bond; van der Waals radii: 1.52 Å[6] for O, 1.20 Å[6] for H). Compared to the hydroxyl group the carbon-bound fluorine atom has no hydrogen bond-donating capacity and has a diminished hydrogen

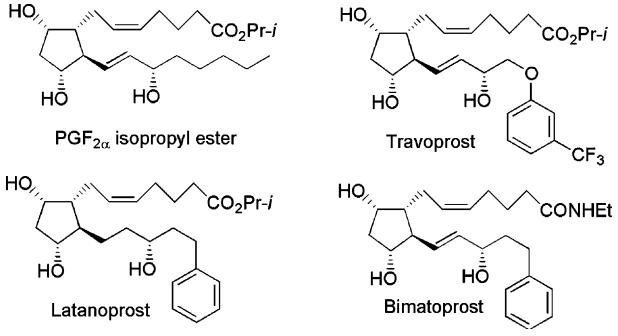

Figure 1.

Keywords: 15-Fluoro prostaglandin; Glaucoma.
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bond-accepting ability, although there is some controversy as to the magnitude of this effect.[7] Due to the greater electronegativity of fluorine compared to oxygen, the fluorinated carbon should be more electronegative than its hydroxylated congener. In a related fashion, the lower energy of the C–F, as compared to the C–O, σ^* orbital can reinforce unusual stereoelectronic-based conformational properties (e.g., the anomeric effect) due to energetically favorable n/σ^* or π/σ^* overlap.[8] Finally, fluorine-for-hydroxyl substitution significantly increases lipophilicity.

Given the structure–activity relationship insight that could be gained by this substitution, there are surprisingly few reports of this motif. This is perhaps due to the belief that hydroxyl substitution at carbon 15 is necessary for potent biological activity.[9] The most systematic studies in the literature are those of Bezuglov et al., who reported the synthesis, ex vivo biological studies, and physicochemical properties of a variety of 15-fluoro analogs of endogenous prostaglandins, including 15-fluoro-$PGF_{2\alpha}$ and 15-fluoro-PGE_2 (Fig. 2).[10]

Based on the effect of 15-fluoro-$PGF_{2\alpha}$ on smooth muscle tone of several organs in rats, hamsters, and guinea pigs, it was theorized that this substitution increased EP receptor affinity.[10c] Interestingly, 15-fluoro PGE_2 itself demonstrated reduced biological activity compared to PGE_2.

We now report the synthesis and pharmacological characterization of a series of 15-fluoro-16-aryloxy-ω-tetranor-$PGF_{2\alpha}$ analogs **I** (Fig. 3).[11,12] Many of these compounds potently activated the prostaglandin FP receptor in vitro, and several effectively lowered IOP in conscious lasered (ocular hypertensive due to trabeculoplasty) monkeys while causing relatively little ocular irritation in rabbits. In particular, phenoxy-terminated congener **24** elicited minimal ocular hyperemic response in rabbits, and a twice-a-day 3 μg dose lowered IOP in monkeys by 39%.

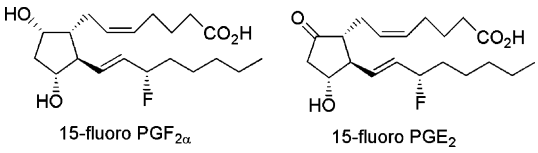


Figure 2.

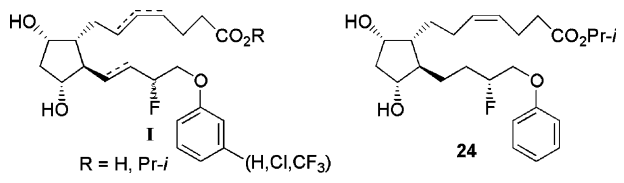


Figure 3.

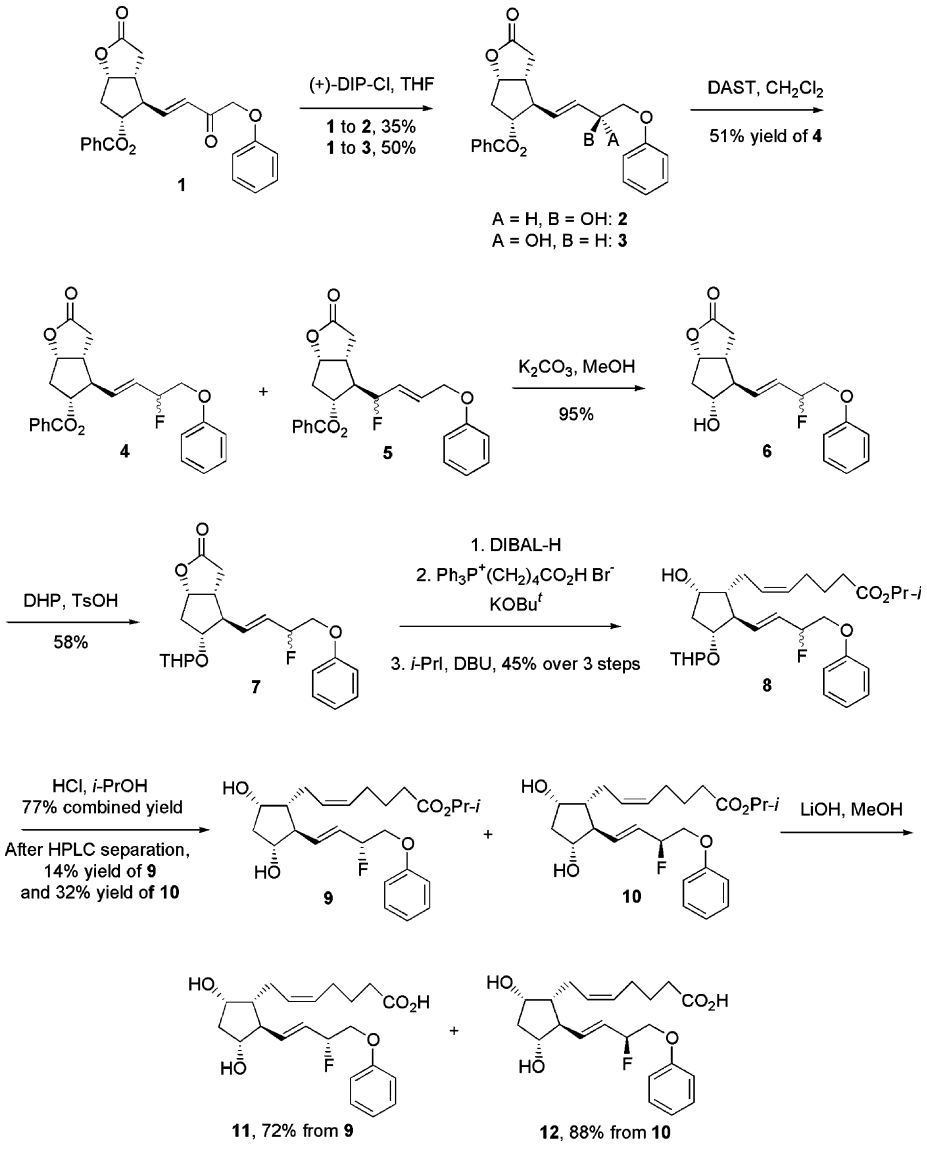
2. Results and discussion

2.1. Chemistry

The syntheses of the 16-phenoxy terminated 15-fluoro compounds are illustrative. Reduction of known enone **1**[13] with (+)-*B*-chlorodiisopinocampheylborane[14] [(+)-DIP-Cl] afforded predominantly the β-alcohol **2** with ~8:1 stereoselectivity; diastereomerically pure **2** was isolated in 35% yield after flash chromatography (Scheme 1). In a complementary fashion, reduction with the antipode (−)-DIP-Cl afforded the diastereomerically pure epimeric α-alcohol **3** in 50% yield after chromatography. Alternatively, carbonyl reduction of **1** with $CeCl_3/NaBH_4$ provided the alcohols **2** and **3** as a ~1:1 mixture. Fluorination of the allyl alcohol functionality with (diethylaminosulfur)trifluoride (DAST) was not stereospecific; using either the diastereomerically pure **2** or the 1:1 mixture **2/3** as the starting material afforded the same mixture of four allylic fluorides **4**–**5**. The lack of stereospecificity in the fluorination implies ionization at carbon 15 to generate the same intermediate from either diastereomeric alcohol, followed by attack of fluoride with retention or inversion at the *ipso*- or β-positions. One diastereomer of **5** and the two diastereo-mers **4** coeluted chromatographically, but were separable from the other diasteromer of **5**. Debenzoylation of the **4**+one diastereomer of **5** mixture provided alcohols **6**, which were separable from the alcohol derived from **5**. The alcohols **6** were then protected as their THP ethers **7**. DIBAL-H reduction of the lactone to the corresponding lactol, followed by Wittig condensation with $Ph_3P{=}CH(CH_2)_4CO_2K$ and esterification of the crude product mixture gave **8**. Deprotection of **8** and HPLC purification afforded the 15α- and 15β-fluoride isopropyl esters **9** and **10**, which were saponified to their corresponding acids **11** and **12** under standard conditions. In this and all subsequent cases, the carbon 15 absolute stereochemistry was tentatively assigned based on the EC_{50} values of the acids in the prostaglandin FP receptor functional assay (see Table 1), the more potent diastereomer being assigned as the 15α-fluoride.[15]

With respect to the 13,14-dihydro series, hydrogenation of β-alcohol **2** followed by DAST fluorination afforded **13** (Scheme 2). In contrast to the allyl alcohol case, DAST fluorination was stereospecific: the same sequence applied to α-alcohol **3** afforded the inverted product **15**. In each case the fluorination product was accompanied by about 20% of an HF elimination by-product, which could be separated by flash chromatography either immediately post-fluorination or at the end of the synthesis. Protecting group interchange, lactone to lactol reduction, α-chain installation/esterification, and deprotection as above afforded 13,14-dihydro-15-fluoro prostaglandin esters **17** and **18**, which were saponified to the acids **19** and **20**.

Synthesis of the 13,14-dihydro-*cis*-Δ^4 congener[16] diverged from **14** (Scheme 3). For convenience, the aforementioned HF elimination contaminant (see above) from the DAST fluorination step was carried forward until HPLC isolation of **24** at the end of the synthesis.

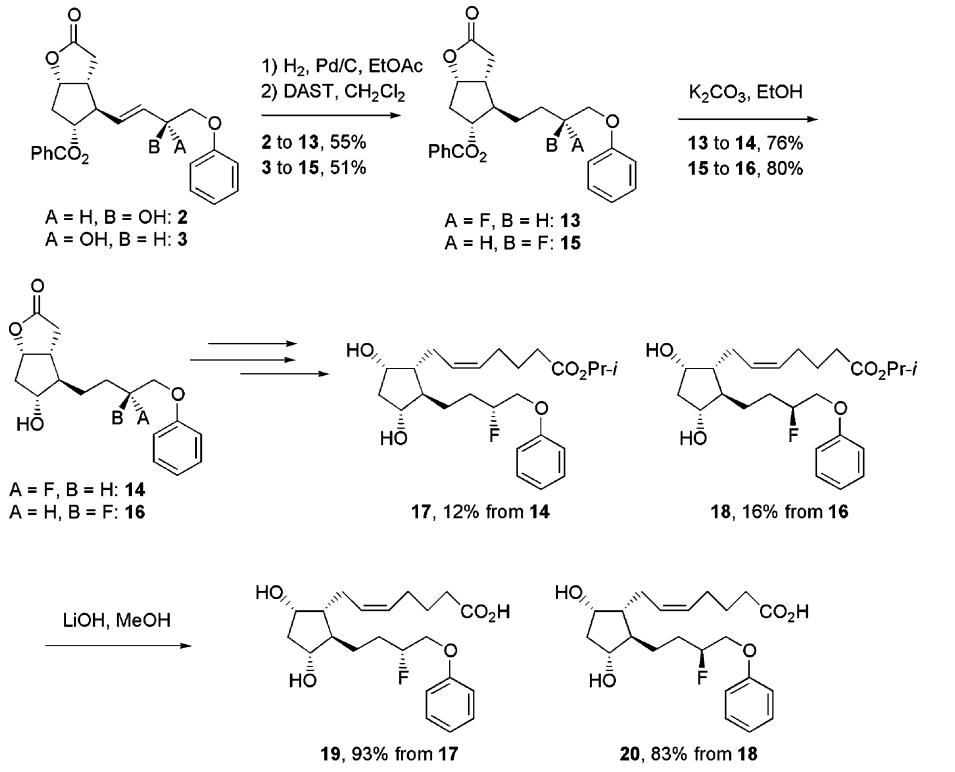


Scheme 1.

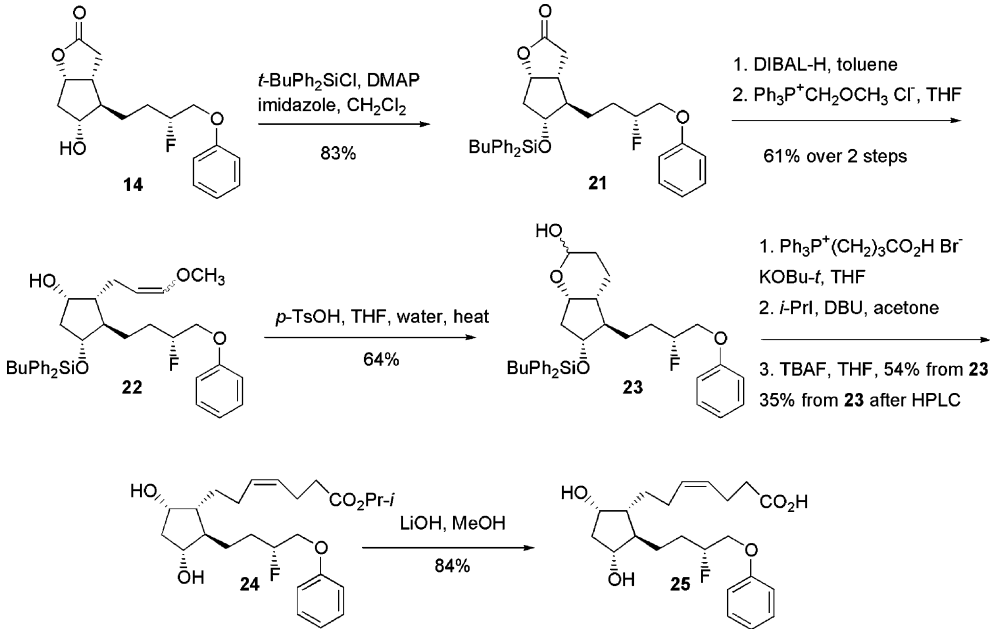
Table 1. FP receptor functional response and binding data

Compound	$K_i \pm$ SEM[a] (nM)	$EC_{50} \pm$ SEM (nM)	Response (%)
11	210 ± 64	4 ± 0.5	104
12	1100 ± 110	96 ± 16	97
19	52 ± 1	10 ± 2	79
20	3900 ± 2200	154 ± 6	65
25	690 ± 140	11 ± 1	81
28	360 ± 27	183 ± 41	91
30	38 ± 12	20 ± 11	64
32	230 ± 23	13 ± 3	85
34	240 ± 130	2 ± 0.5	84
36	182 ± 15	81 ± 10	76
38	160 ± 22	13 ± 5	83
40	3800 ± 160	131 ± 35	44
$PGF_{2\alpha}$	129 ± 12	24.5 ± 0.92	92
Latanoprost acid	92 ± 14	34.4 ± 5.2	75
Cloprostenol	31 ± 2	1 ± 0.04	100
Travoprost acid	52 ± 2	2.7 ± 0.28	100
16-Phenoxy-ω-tetranor-$PGF_{2\alpha}$	22 ± 5	1 ± 0.4	100

[a] SEM = Standard error of the mean.



Scheme 2.



Scheme 3.

Silylation of the C-11 oxygen afforded lactone **21**. Reduction to the lactol using DIBAL-H was followed by Wittig condensation to provide enol ether **22**. Acidic hydrolysis gave homologated lactol **23**, which underwent olefination in the usual manner and TBAF-mediated desilylation to provide **24** as a 96:4 mixture of 4*Z*:4*E* olefin geometrical isomers after HPLC purification. Saponification then afforded **25**.

As a final synthetic note, we were unable to prepare 15-fluoro-$PGF_{2\alpha}$ itself. The immediate post-fluorination product **26**, an allyl alkyl fluoride, largely degraded upon standing over 1–2 days, even in solution at 4 °C (Fig. 4). An odor of H–F could be detected from the degraded sample, and 600 MHz ^{1}H/150 MHz ^{13}C NMR analyses of the crude showed a complex mixture whose components mostly lacked a C–F bond. Interestingly the

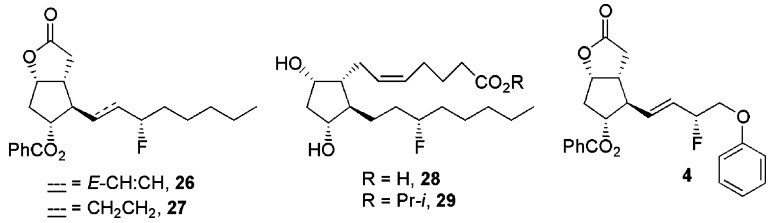


Figure 4.

13,14-dihydro-15-fluoro analog **27**, a dialkyl fluoride, and products synthetically derived from it were stable at room temperature indefinitely. Therefore for comparative biological evaluation we prepared 13,14-dihydro-15-deoxy-15α-fluoro-$PGF_{2\alpha}$ (**28**) and its isopropyl ester (**29**). We currently have no satisfactory explanation for the enhanced stabilities of dialkyl fluorides such as **27** and allyl (phenoxyalkyl) fluorides like **4** over allyl alkyl fluoride **26**.[17]

2.2. Pharmacology

The compounds shown in Figure 5 were evaluated for their binding affinity and functional efficacy at the FP prostaglandin receptor, for side effect potential in the rabbit ocular irritation (ROI) model, for topical ocular potency in the cat pupil diameter (CPD) constriction model, and for IOP lowering in the lasered ocular hypertensive monkey model. The carboxylic acid was used in all in vitro studies since it is believed to be the pharmacologically active form of the compound. The corresponding isopropyl ester prodrugs were used in the in vivo experiments to facilitate corneal penetration and delivery of the carboxylic acid to the aqueous humor.

2.3. In vitro studies

2.3.1. FP receptor functional response and binding. Table 1 summarizes our evaluation of 15-fluoro prostaglandin acids for binding to an FP receptor expressed in bovine corpus luteum (K_i),[18a] and for functional potency (EC_{50} = effective concentration necessary for a compound to attain 50% of its maximal response) and efficacy via stimulation of FP receptor-linked phosphoinositide turnover in Swiss 3T3 mouse fibroblast cells.[18b] The standards $PGF_{2\alpha}$, latanoprost acid, cloprostenol,

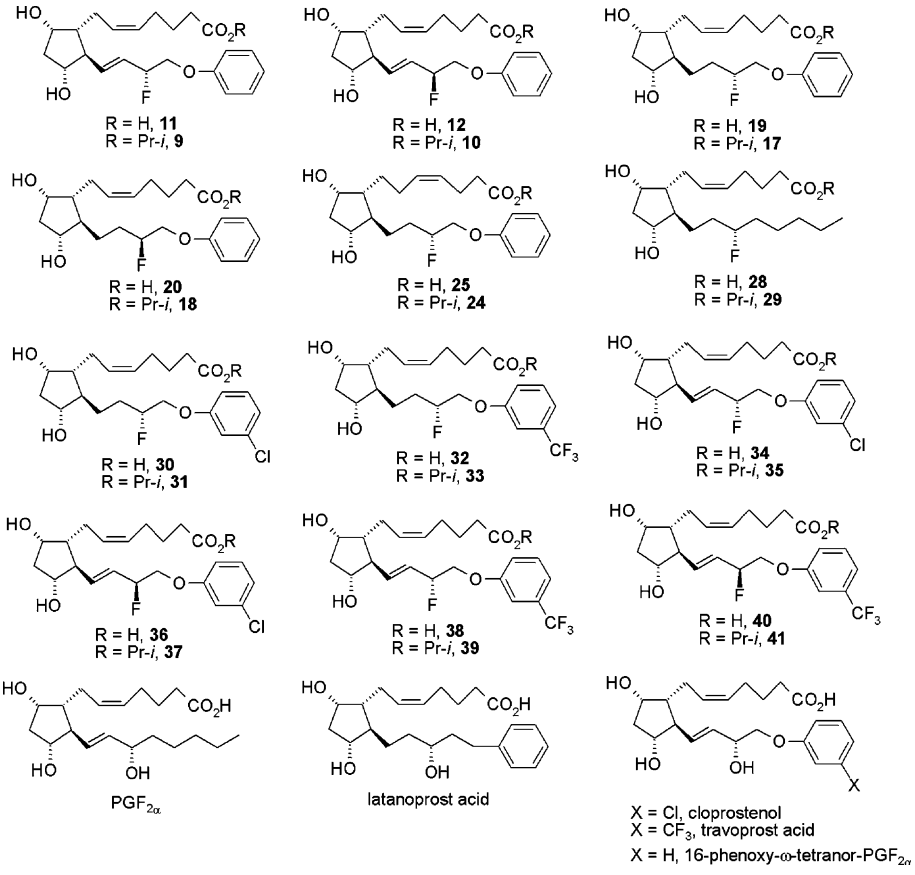


Figure 5. Structure of prostaglandin analogs evaluated in vitro and in vivo.

Table 2. Cat, rabbit, monkey, and lipophilicity data

Ester (corresponding acid)	ROI_{15}[a] (μg)	CPD,[b] ED_5 (μg)	Monkey IOP, % change (dose in μg)	RRI[c]
9 (**11**)	0.3	0.05	—[d]	1.79
10 (**12**)	1	0.5	—	—
17 (**19**)	10	0.2	—	2.41
24 (**25**)	10	0.04	−39% (3)	2.46
31 (**30**)	100	1	−33% (10)	4.13
33 (**32**)	100	10	—	4.96
35 (**34**)	10	0.1	−18% (1)	2.96
37 (**36**)	>100	1	—	—
39 (**38**)	10	1.2	—	3.51
$PGF_{2\alpha}$ isopropyl ester	<0.1	0.03	−38% (1)	1.00
Travoprost	3	0.015	−29% (0.3)	1.16
Latanoprost	1.8	0.13	−27% (3)	1.05
Cloprostenol isopropyl ester	0.3	0.013	−39% (1)	—

[a] ROI_{15} = Dose estimated to produce conjunctival hyperemia in 15% of the tested rabbits over 4 h.
[b] CPD = Cat pupil diameter constriction.
[c] RRI = Relative retention index.
[d] Not tested.

travoprost acid, and 16-phenoxy-ω-tetranor-$PGF_{2\alpha}$ are included for comparison.

2.4. In vivo studies

Conjunctival hyperemia was studied in New Zealand Albino rabbits.[3a] ROI_{15} denotes the dose estimated to produce 15% incidence of hyperemia over the 4 h course of the study. As a preliminary assay of topical ocular potency, the ability of a test compound to constrict the cat pupil over time was measured and is expressed as an ED_5 value,[3a] indicating the dose estimated to produce a 5 unit area (mm h) in a graph of the difference in pupil diameter in the dosed eye versus time. Acute IOP-lowering efficacy was measured in conscious ocular hypertensive cynomolgus monkeys.[3a] These parameters for selected compounds are shown in Table 2.

The high hydrophobicity of prostaglandins in general and these 15-fluoro analogs in particular caused experimental determination of octanol–water partition coefficients to be imprecise and not very useful for comparison purposes. As an alternative, for selected compounds an HPLC-based relative retention index (RRI) was used as a surrogate measure of distribution. Retention times were measured for the compounds on a reverse-phase HPLC column using acetonitrile/pH 3 ammonium phosphate buffer elution. The RRI is defined as the retention time of the test item divided by that for $PGF_{2\alpha}$ isopropyl ester. In general, the higher a compound's RRI value, the more lipophilic it is.

The corresponding data for the standards cloprostenol isopropyl ester, latanoprost, travoprost, and $PGF_{2\alpha}$ isopropyl ester are included in Table 2 for comparison.

The 15-fluoro prostaglandin analogs had approximately 10-fold lower affinity for, while being 2–5-fold less potent for functional activation of the FP receptor as compared to the corresponding 15-hydroxy analogs (**11**, **34**, and **38** vs 16-phenoxy-ω-tetranor-$PGF_{2\alpha}$, cloprostenol, and travoprost acid). The 13,14-dihydro analogs tended to have increased receptor binding affinity but were less potent in the functional assay.

Topical ocular efficacy of a prostaglandin analog depends on its inherent activity, metabolic stability, and bioavailability. To be effective, an ester prodrug must be absorbed and hydrolyzed by ocular tissue and the resulting carboxylic acid delivered to the trabecular meshwork or ciliary muscle, which are the presumed target tissues. In the 15-fluoro series there is neither a strong correlation between FP receptor binding affinity and functional efficacy nor between either in vitro binding affinity or functional efficacy and in vivo efficacy. However within a series of 15α-fluoride ester prodrugs whose acids had similar K_i values (e.g., compounds **11**, **32**, **34**, and **38**, with $K_i = 160–240$ nM), less lipophilic compounds were more potent in the cat pupil diameter assay. Similarly the two 15α-fluoride acids **11** and **34** and the 15-hydroxy compound travoprost acid all had similar functional potency ($EC_{50} = 1–4$ nM), yet for their corresponding isopropyl esters lower lipophilicity afforded higher cat pupil diameter potency.

The *cis*-Δ^4 analog **25** is noteworthy because although it had modest affinity for the FP receptor ($K_i = 690$ nM), it was a fairly potent agonist in the functional assay ($EC_{50} = 11$ nM). The corresponding isopropyl ester **24** was surprisingly potent in the cat pupil diameter assay, while demonstrating good separation between its cat ED_5 (0.04 μg) and ROH_{15} (10 μg) values. The compound was also very effective in lowering IOP in ocular hypertensive monkeys. The *cis*-Δ^4 modification is known to inhibit α-chain metabolism of $PGF_{2\alpha}$ in monkeys.[19] Thus the in vivo efficacy of **24** may be due in part to its enhanced metabolic stability, both in the α-chain due to the Δ^5 to Δ^4 olefin shift and in the ω-chain due to the lack of the 15-hydroxy group.

3. Conclusion

Substitution of a fluorine for the 15-hydroxy group of select prostaglandin FP agonists decreased in vitro

receptor affinity markedly and functional potency less dramatically. As compared to their 15-hydroxy congeners, the 15-fluoro prostaglandin ester prodrugs were less potent but still effective in the cat, and tended to be less hyperemic in the rabbit. Notably compound **24** (13,14-dihydro-15-deoxy-15α-fluoro-16-aryloxy-ω-tetranor-*cis*-Δ^4-$PGF_{2\alpha}$ isopropyl ester) potently constricted the cat pupil, induced minimal hyperemic response in the rabbit, and lowered monkey IOP by 39%. This profile is consistent with other prostaglandin analogs shown to be effective ocular hypotensive agents in humans.

4. Experimental section

4.1. Chemistry general methods

Abbreviations used include: calcd, calculated; DAST (diethylamino)sulfur trifluoride; DBU, 1,8-diazabicylo-[5.4.0]undec-7-ene; DHP, 3,4-dihydro-2*H*-pyran; DMAP, 4-(dimethylamino)pyridine; DIBAL-H, diisobutylaluminum hydride; (+)- and (−)-DIP chloride, (+)- and (−)-*B*-chlorodiisopinocampheylborane; MF, molecular formula; MW, molecular weight; PTFE, poly(terfluoroethylene); *p*-TsOH, *p*-toluenesulfonic acid monohydrate; TBAF, tetra-*n*-butylammonium fluoride. Unless otherwise noted, all ^{1}H NMR and ^{13}C NMR spectra were acquired in $CDCl_3$ solvent. All 200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR spectra were acquired on a Varian Gemini 200 spectrometer. All 600 MHz ^{1}H NMR and 150 MHz ^{13}C NMR spectra were acquired on a Bruker DRX600 spectrometer. For reactions without added water, solvents used were anhydrous grade from Aldrich Chemical Company and were used without further purification. $PGF_{2\alpha}$ and its isopropyl ester and 16-phenoxy-ω-tetranor-$PGF_{2\alpha}$ were purchased from Cayman Chemical Company, Ann Arbor, Michigan, USA, and were used as received. Latanoprost and its acid[20] was synthesized in-house according to published procedures, as were travoprost and its acid and cloprostenol and its isopropyl ester.[21] Unless otherwise stated, all reactions were run under a positive pressure of nitrogen, and all temperatures quoted refer to external temperatures. Concentration refers to removal of solvent in vacuo on a rotary evaporator. Reactions were monitored by TLC on E. Merck Silica Gel 60 F_{254} plates, with visualization by UV light or staining with either ethanolic phosphomolybdic acid or 2% aqueous $KMnO_4$. Column chromatographic purifications were performed under positive air flow using 230–400 mesh silica gel from E.M. Science. Chromatography solvents used were HPLC grade from E.M. Science. Electrospray low resolution mass spectra (ES-LRMS) were acquired on a Finnegan TSQ 46 triple quadrupole mass spectrometer operating in the positive electrospray mode. Matrix-assisted laser desorption ionization low resolution mass spectra (MALDI-LRMS) were acquired on a Voyager RP laser desorption time-of-flight mass spectrometer. High resolution mass spectra (HRMS) were acquired by Analytical Instrument Group, Raleigh, NC; the spectra were acquired using the Fast Atom Bombardment Mode.

4.1.1. [3a*R*,4*R*(1*E*,3*S*),5*R*,6a*S*]-5-Benzoyloxy-4-(3-hydroxy-4-phenoxy-1-buten-1-yl)-hexahydro-2*H*-cyclopenta-[*b*]furan-2-one (2). To a mixture of enone **1**[13] (2.97 g, 7.31 mmol) in THF (25 mL) at 0 °C was added via syringe over 20 min a solution of (+)-DIP chloride (5.0 g, 15.6 mmol) in THF (20 mL). After 90 min the reaction mixture was warmed to room temperature and stirred overnight. Methanol (5 mL) was added, the mixture was stirred for 15 min, and 1 M HCl (75 mL) was added. The solution was extracted with ethyl acetate (3 × 75 mL), dried ($MgSO_4$), filtered, and concentrated, and the residue was dissolved in 100 mL of 1:1 CH_3CN–hexane. The bottom CH_3CN layer was isolated and extracted with hexane (1 × 50 mL), concentrated, and chromatographed on a 15 cm tall × 45 mm diameter silica gel column eluting with 1:1 ethyl acetate–hexane to afford three components; the slowest eluting was a diastereomerically pure ($\geqslant$99:1) sample of alcohol **2** (1.03 g, 35%), the middle eluting was a ~9:1 mixture of **2** and its diastereomeric alcohol **3** (820 mg, 27%), and the fastest eluting was a ~1:1 mixture of **2**:**3** (579 mg, 19%). Spectral data for **2**: ^{13}C NMR (50 MHz): δ 176.36 (C), 166.03 (C), 158.29 (C), 133.37 (CH), 131.14 (CH), 131.00 (CH), 129.65 (CH), 129.57 (CH), 128.54 (CH), 121.39 (CH), 114.60 (CH), 83.28 (CH), 79.03 (CH), 71.56 (CH_2), 70.41 (CH), 54.30 (CH), 42.67 (CH), 37.57 (CH_2), 34.94 (CH_2). MALDI-LRMS, *m*/*z* calcd for $C_{24}H_{24}O_6Na$ [$(M+Na)^+$], 431; found 431.

4.1.2. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-5-Benzoyloxy-4-(3-fluoro-4-phenoxybutenyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (4) and [3a*R*,4*R*(2*E*,1*RS*),5*R*,6a*S*]-5-Benzoyloxy-4-(1-fluoro-4-phenoxy-2-buten-1-yl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (5).

4.1.2.1. Demonstration run. To a solution of **2** (182 mg, 0.45 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C was added dropwise via syringe (diethylamino)sulfur trifluoride (DAST; 110 mg, 0.69 mmol). After 1 h saturated $NaHCO_3$ (3 mL) and ethyl acetate (4 mL) were added, and the mixture was extracted with ethyl acetate (3 × 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on a 7 cm tall × 40 mm diameter silica gel column eluting with 2:1 hexane–ethyl acetate to afford two components. The first to elute, 13.5 mg, was tentatively assigned as a single diastereomer (the olefin geometry was assumed to be *E*) of **5**, the allyl fluoride resulting from formal S_N2' fluorination of the starting material, on the basis of ^{1}H NMR spectral data for this compound (yield = 7%). The ^{1}H NMR spectrum for this compound (200 MHz) showed the proton on the fluorine-containing carbon resonating as a doublet of multiplets between δ = 5.1 and 5.4 ppm with an estimated *J* value of about 50 Hz, and being mostly obscured by the two multiplets due to two oxygenated methine protons resonating between δ = 5.4–5.5 ppm and δ = 5.1–5.2 ppm. Furthermore, the C*H*$_2$OPh protons appeared as a broad singlet between δ = 4.5–4.6 ppm, which was distinct from that for the formal S_N2 fluorination product **4** (vide infra). MALDI-LRMS, calcd for

$C_{24}H_{23}O_5FNa$ [(M+ $Na)^+$], 433; found, 433. The second component to elute, 80.0 mg, was assigned as a mixture of the two diastereomers of the formal S_N2 product **4** and the other diastereomer of **5** (yield = 43%). The proton NMR spectrum (200 MHz) for this three-compound mixture was more complicated than that for the single compound faster-eluting component. However, a key region of the spectrum was between $\delta = 4$–5 ppm. A broad singlet between $\delta = 4.5$–4.6 ppm was likely due to the resonance of the CH_2OPh protons for **5** (vide supra). The appearance of two multiplets, one about $\delta =$ 4.0 ppm and the other about $\delta = 4.1$ ppm, are consistent with resonances due to the individual CH_2OPh for **4**. The integration values indicated a ratio of 3:1 ratio of **4**:one diastereomer of **5**.

Particularly diagnostic for the slower-eluting component was the ^{13}C and DEPT NMR spectra. The first key region of these spectra was that between $\delta = 85$–95 ppm. The appearance of three doublets due to a CH carbon bonded to fluorine ($\delta = 92.16$ ppm, CH, d, $J = 174$ Hz; $\delta = 90.42$ ppm, CH, d, $J = 172$ Hz; $\delta = 90.20$ ppm, CH, d, $J = 174$ Hz) indicate that there were three-fluorinated products. The second key region of the spectra was between $\delta = 65$–70 ppm, with the relevant resonances being at $\delta = 69.44$ ppm (CH_2, d, $J = 24$ Hz) and at $\delta = 66.83$ ppm (CH_2). The third key region was between $\delta = 50$–60 ppm, with resonances at $\delta = 56.98$ ppm (CH, d, $J = 21$ Hz), $\delta = 54.14$ ppm (CH), and $\delta = 54.00$ ppm (CH). HRMS analysis of the slower eluting component exhibited an m/z ratio for M^+ of 410.15283 (calculated for $C_{24}H_{23}O_5F$, 410.152839). These data are most consistent with the assignments in Table 3 below.

4.1.2.2. Synthesis run. To a solution of **2** (2.90 g, 7.11 mmol) in CH_2Cl_2 (45 mL) at −78 °C was added DAST dropwise via syringe (1.71 g, 10.6 mmol). After 5 h the reaction mixture was quenched by the addition of methanol (3 mL), the solution was warmed to room temperature, and saturated $NaHCO_3$ was added (30 mL). The mixture was extracted with CH_2Cl_2 (2 × 75 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on a 20 cm tall × 53 mm diameter silica gel column, 2:1 → 3:2 hexane–ethyl acetate gradient elution, to afford the slower-eluting component described in the demonstration run above, which consisted of a mixture of **4** and one diastereomer of allylically transposed fluoride **5** (1.48 g, 51%).

4.1.3. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-Fluoro-4-phenoxy-butenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (6) and [3a*R*,4*R*(2*E*,1*RS*),5*R*,6a*S*]-4-(1-Fluoro-4-phenoxy-2-buten-1-yl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]-furan-2-one. To a solution of the above mixture of **4** and **5** (830 mg, 2.03 mmol) in methanol (20 mL) was added K_2CO_3 (320 mg, 2.31 mmol). After 1 h the reaction mixture was quenched by the addition of saturated citric acid (25 mL) and the solution was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed on a 23 cm tall × 53 mm diameter silica gel column, 1:1 → 3:2 ethyl acetate–hexane gradient elution.

The first compound to elute was an 82 mg fraction consisting of one diastereomer of the S_N2' fluorination-derived product [3a*R*,4*R*(2*E*,1*RS*),5*R*,6a*S*]-4-(1-fluoro-4-phenoxy-2-buten-1-yl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (yield = 13%). The proton NMR spectrum for this compound (200 MHz) showed the proton on the fluorinated carbon resonating at $\delta = 4.92$ ppm as a doublet of triplets, $J = 5$ Hz and 48 Hz, due to coupling to the protons on the adjacent carbons (the 5 Hz triplet) and to the directly attached fluorine (the 48 Hz doublet). Also, the CH_2OPh protons resonated as a broad singlet about $\delta = 4.58$ ppm.

^{13}C NMR (50 MHz): δ 176.98 (C), 158.08 (C), 129.79 (d, $J = 12$ Hz, CH), 129.49 (CH), 128.25 (d, $J = 19$ Hz, CH), 121.16 (CH), 114.69 (CH), 93.09 (d, $J = 171$ Hz, CH), 84.12 (CH), 73.57 (d, $J = 4$ Hz, CH), 66.87 (CH_2), 58.26 (d, $J = 20$ Hz, CH), 40.89 (CH_2), 39.62 (d, $J = 4$ Hz, CH), 35.81 (CH_2). The appearance of the most downfield CH_2 signal at $\delta = 66.87$ ppm, due to the *C*H_2OPh carbon, as a singlet indicates that a C–F bond was not formed on the adjacent carbon; otherwise a two bond C–F coupling constant would be present. A two-bond C–F doublet with a 20 Hz coupling constant is found instead for a *C*H signal at $\delta = 58.26$ ppm. This is most consistent with an S_N2' fluorination-derived product structural assignment for this compound, as is the presence of two *C*H signals as doublets in the aliphatic region of the spectrum with 4 Hz coupling constants due to three bond C–F couplings: one at $\delta = 73.57$ ppm and one at $\delta = 39.62$ ppm.

The second component to elute was a 593 mg fraction, which was assigned as the S_N2 fluorination-derived product **6** (nominal yield = 95%; there was likely a weighing error as the nominal combined yield exceeds 100%). An inspection of the proton NMR spectrum (200 MHz) for this component showed several key differences to that S_N2' fluorination-derived product from above. First, the appearance of the olefin protons was much sharper. Second, the proton on the fluorinated carbon resonated as a doublet of quartets at $\delta = 5.24$ ppm with $J = 4$ Hz and 50 Hz that is, about 0.3 ppm downfield from the fluorinated C*H* for the S_N2' fluorination-derived product. Third, the CH_2OPh protons resonated as a doublet of multiplets about $\delta = 4.1$ ppm.

Table 3. Selected carbon 13 NMR spectroscopy peaks for compounds **4** and **5**

Compound	Fluorinated carbon resonance	*C*H_2OPh resonance	R_2CHO_2CPh resonance
4, major fluoride diastereomer	$\delta = 90.42$ ppm, d, $J = 172$ Hz	$\delta = 69.44$ ppm, d, $J = 24$ Hz	$\delta = 54.14$ ppm, singlet
4, minor fluoride diastereomer	$\delta = 90.20$ ppm, d, $J = 174$ Hz	$\delta = 69.44$ ppm, d, $J = 24$ Hz	$\delta = 54.00$ ppm, singlet
5, one fluoride diastereomer	$\delta = 92.16$ ppm, d, $J = 174$ Hz	$\delta = 66.83$ ppm, singlet	$\delta = 56.98$ ppm, d, $J = 21$ Hz

The carbon and DEPT NMR spectra for **6** had the following resonances (50 MHz): δ 176.91 (C), 158.27 (C), 134.14 (d, $J = 10$ Hz, CH), 129.61 (CH), 127.55 (d, $J = 18$ Hz, CH), 121.50 (CH), 114.69 (CH), 90.56 (d, $J = 172$ Hz, CH), 82.68 (CH), 76.74 (due to major diastereomer, d, $J = 2$ Hz, CH), 76.65 (due to minor diastereomer, d, $J = 2$ Hz, CH), 69.57 (d, $J = 24$ Hz, CH_2), 56.24 (CH), 42.46 (CH), 40.11 (CH_2), 34.49 (CH_2). Note the appearance of the CH_2OPh carbon as a doublet at $\delta = 69.57$ ppm with $J = 24$ Hz due to 2-carbon C–F coupling, as opposed to its appearance as a singlet in the ^{13}C NMR spectrum for the regioisomeric fluoride (vide supra).

HRMS data for **6**: m/z calcd for $C_{17}H_{20}O_4F$ [$(M+H)^+$], 307.134634; found, 307.134634.

4.1.4. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-Fluoro-4-phenoxybutenyl)-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (7). To a solution of **6** (590 mg, 1.93 mmol) and DHP (202 mg, 2.41 mmol) in CH_2Cl_2 (11 mL) at 0 °C was added *p*-TsOH (73 mg, 0.38 mmol). After 30 min the reaction mixture was quenched by the addition of NEt_3 (110 mg, 1.1 mmol) and concentrated, and the residue was chromatographed on a 14 cm tall × 41 mm diameter silica gel column eluting with 3:2 ethyl acetate–hexane to afford **7** (437 mg, 58%). HRMS, m/z calcd for $C_{22}H_{28}O_5F$ [$(M+H)^+$], 391.192125; found, 391.19213.

4.1.5. (5*Z*,13*E*)-(9*S*,11*R*,15*RS*)-15-Fluoro-9-hydroxy-16-phenoxy-11-(tetrahydropyran-2-yloxy)-17,18,19,20-tetranor-5, 13-prostadienoic acid isopropyl ester (8). To a solution of **7** (426 mg, 1.09 mmol) in THF (9 mL) at −78 °C was added a 1.5 M solution of DIBAL-H in toluene (1.2 mL, 1.8 mmol). After 3 h methanol was added (1 mL) and the solution was warmed to room temperature. Saturated NH_4Cl (3 mL), ether (15 mL), and saturated sodium potassium tartrate (15 mL) were added and the suspension was stirred for 15 min to break the emulsion. The layers were separated, the aqueous phase was extracted with ether (2 × 25 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford the lactol [3a*R*,4*R*(1*E*, 3*RS*), 5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol (406 mg, 93%). MALDI-LRMS, m/z calcd for $C_{22}H_{29}O_5FNa$ [$(M+Na)^+$], 415; found, 415.

To a suspension of $Ph_3P^+(CH_2)_4CO_2HBr^-$ (970 mg, 2.19 mmol) in THF (10 mL) at 0 °C was added a 1 M solution of potassium *t*-butoxide in THF (4.6 mL, 4.6 mmol). After 15 min a solution of the above lactol (426 mg, 1.09 mmol) in THF (10 mL) was added. After 2.5 h the reaction mixture was quenched by the addition of saturated KH_2PO_4 and was warmed to room temperature. The solution was extracted with ethyl acetate (4 × 30 mL), dried (Na_2SO_4), filtered, and concentrated to afford a crude oil.

This oil was dissolved in acetone (15 mL) and cooled to 0 °C. DBU (760 mg, 5.01 mmol) was added, and after 40 min isopropyl iodide was added (850 mg, 5.0 mmol). The reaction mixture was warmed to room temperature and stirred overnight. Saturated KH_2PO_4 (20 mL) was added to quench the reaction mixture, saturated brine (20 mL) was added, and the solution was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on a 10 cm tall × 41 mm diameter silica gel column eluting with 40% ethyl acetate in hexane to afford **8** (236 mg, 45%). HRMS, m/z calcd for $C_{30}H_{44}O_6F$ [$(M+H)^+$], 519.312738; found, 519.31274.

4.1.6. (5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11-Dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-5-prostadienoic acid isopropyl ester (9) and (5*Z*,13*E*)-(9*S*,11*R*,15*S*)-9,11-dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-5-prostadienoic acid isopropyl ester (10). To a solution of THP ether **8**, isopropanol (10 mL), and water (1 mL) was added 12 M HCl (1.5 mL). After 45 min the reaction mixture was quenched by the addition of solid $NaHCO_3$ (2 g), water was added (55 mL), and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the residue was chromatographed on a 25 cm tall × 26 mm diameter silica gel column eluting with 60:35:5 hexane–ethyl acetate–isopropanol to afford the C-15 diastereomer mixture (5*Z*,13*E*)-(9*S*,11*R*,15*RS*)-9,11-dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-5-prostadienoic acid isopropyl ester (146.3 mg, 77%). The individual C-15 diastereomers were separated by normal-phase HPLC on a chiral column to afford **9** (25.9 mg) and **10** (60.5 mg). Compound **9**: ^{13}C NMR (150 MHz): δ 173.43 (C), 158.38 (C), 137.43 (d, $J = 11$ Hz, CH), 129.98 (CH), 129.52 (CH), 128.80 (CH), 125.69 (d, $J = 18$ Hz, CH), 121.30 (CH), 114.68 (CH), 91.00 (d, $J = 170$ Hz, CH), 78.08 (d, $J = 2$ Hz, CH), 73.21 (CH), 69.87 (d, $J = 25$ Hz, CH_2), 67.66 (CH), 56.04 (CH), 50.55 (CH), 42.93 (CH_2), 34.00 (CH_2), 26.63 (CH_2), 25.74 (CH_2), 24.84 (CH_2), 21.82 (CH_3). HRMS, m/z calcd for $C_{25}H_{36}O_5F$ [$(M+H)^+$], 435.254622; found, 435.25460. Compound **10**: ^{13}C NMR (150 MHz): δ 173.45 (C), 158.33 (C), 137.43 (d, $J = 11$ Hz, CH), 129.90 (CH), 129.46 (CH), 128.78 (CH), 125.68 (d, $J = 18$ Hz, CH), 121.23 (CH), 114.64 (CH), 91.00 (d, $J = 170$ Hz, CH), 78.04 (d, $J = 2$ Hz, CH), 73.07 (CH), 69.84 (d, $J = 24$ Hz, CH_2), 67.62 (CH), 55.96 (CH), 50.49 (CH), 42.94 (CH_2), 33.97 (CH_2), 26.57 (CH_2), 25.61 (CH_2), 24.80 (CH_2), 21.76 (CH_3). HRMS, m/z calcd for $C_{25}H_{36}O_5F$ [$(M+H)^+$], 435.254622; found, 435.25464.

4.1.7. (5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11-Dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-5-prostadienoic acid (11). To a solution of **9** (15.8 mg, 0.0364 mmol) in methanol (1.4 mL) was added 0.5 M LiOH (0.33 mL, 0.16 mmol). After stirring 4 d the reaction mixture was quenched by the addition of 0.24 M citric acid (1.9 mL) and was extracted with $CHCl_3$ (3 × 3 mL). The combined organic layers were

washed with water (2×2 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in CH_3CN and filtered through a 0.45 μM nylon syringe filter to remove insoluble material. The filtrate was concentrated to afford **11** (10.3 mg, 72%). ^{13}C NMR (150 MHz): δ 158.39 (C), 137.48 (d, $J = 10$ Hz, CH), 129.88 (CH), 129.56 (CH), 128.99 (CH), 125.82 (CH), 125.82 (d, $J = 18$ Hz, CH), 121.34 (CH), 114.72 (CH), 91.10 (d, $J = 170$ Hz, CH), 78.02 (CH), 73.27 (CH), 69.88 (d, $J = 24$ Hz, CH_2), 55.81 (CH), 50.54 (CH), 42.82 (CH_2), 33.26 (CH_2), 26.43 (CH_2), 25.72 (CH_2), 24.60 (CH_2). HRMS, m/z calcd for $C_{22}H_{30}O_5F$ [(M+H)$^+$], 393.207942; found, 303.20794.

4.1.8. (5*Z*,13*E*)-(9*S*,11*R*,15*S*)-9,11-Dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-5-prostadienoic acid (12). Analogous to the saponification of ester **9** to afford acid **11**, compound **10** (59 mg) was converted to **12** (47 mg) in 88% yield. ^{13}C NMR (150 MHz): δ 178.22 (C), 158.32 (C), 137.31 (d, $J = 11$ Hz, CH), 129.77 (CH), 129.50 (CH), 128.94 (CH), 125.86 (d, $J = 18$ Hz, CH), 121.29 (CH), 114.68 (CH), 91.04 (d, $J = 170$ Hz, CH), 77.87 (CH), 73.09 (CH), 69.84 (d, $J = 24$ Hz, CH_2), 55.59 (CH), 50.28 (CH), 42.76 (CH_2), 33.19 (CH_2), 26.38 (CH_2), 25.57 (CH_2), 24.50 (CH_2). HRMS, m/z calcd for $C_{22}H_{30}O_5F$ [(M+H)$^+$], 393.208311; found, 393.20831.

4.1.9. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-5-Benzoyloxy-4-(3-fluoro-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (13). A suspension of olefin **2** (1.00 g, 2.45 mmol) and 10% w/w Pd/C (100 mg) in ethyl acetate (30 mL) was hydrogenated at atmospheric pressure using a balloon. After 3 d the mixture was filtered through Celite and concentrated to afford [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (998 mg, 99%). ^{13}C NMR (50 MHz): δ 176.86 (C), 166.16 (C), 158.42 (C), 133.33 (CH), 129.68 (CH), 129.60 (CH), 128.56 (CH), 121.34 (CH), 114.57 (CH), 84.58 (CH), 80.42 (CH), 71.98 (CH_2), 70.00 (CH), 53.08 (CH), 43.51 (CH), 37.82 (CH_2), 36.38 (CH_2), 31.14 (CH_2), 29.64 (CH_2). MF for product = $C_{24}H_{26}O_6$, MW = 410. ES-LRMS, peak at $m/z = 428$ [(M+NH_4)$^+$, 100% intensity].

To a solution of the alcohol from the previous step (754 mg, 1.84 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added DAST (512 mg, 3.18 mmol). After 45 min TLC analysis (40% ethyl acetate in hexane eluent) of a saturated $NaHCO_3$-quenched aliquot showed no starting material left and the appearance of two new spots: an $R_f = 0.46$ spot that was not UV active but was visible with phosphomolybdic acid staining, and an $R_f = 0.40$ spot that was UV active but was not visible with phosphomolybdic acid staining. Saturated $NaHCO_3$ was added to the reaction mixture (6 mL), the mixture was warmed to room temperature, the layers were separated, the aqueous phase was extracted with CH_2Cl_2 (2×10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 21 cm tall×26 mm diameter silica gel column eluting with 40% ethyl acetate in hexane to afford two fractions. The first was a 266.5 mg fraction that by TLC analysis was a mixture of the two aforementioned spots, and consisted of a 1.7:1 molar mixture of **13** and an HF elimination by-product (as measured by ^1H NMR spectroscopy). The second was a 259.9 mg fraction that by TLC analysis displayed only the $R_f = 0.40$ spot, and by ^1H NMR and ^{13}C NMR DEPT spectroscopy consisted only of **13**. Total combined yield of fluoride **13** = 430 mg = 57%. ^{13}C NMR DEPT spectrum (50 MHz): δ 133.75 (CH), 130.05 (CH), 129.98 (CH), 128.96 (CH), 121.76 (CH), 115.18 (CH), 115.00 (CH), 91.74 (d, $J = 172$ Hz, CH), 84.76 (CH), 80.35 (CH), 69.73 (d, $J = 24$ Hz, CH_2), 52.77 (CH), 43.94 (CH), 38.14 (CH_2), 36.65 (CH_2), 30.06 (CH_2), 29.37 (d, $J = 27$ Hz, CH_2), 29.06 (d, $J = 4$ Hz, CH_2). MALDI-LRMS, $m/z = 435$, consistent with $C_{24}H_{25}O_5FNa$ [(M+Na)$^+$].

4.1.10. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-(3-Fluoro-4-phenoxybutyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (14). Analogous to the debenzoylation of **4** to alcohol **6**, a 2.5:1 molar mixture of fluoride benzoate **13** and an HF elimination by-product (555 mg) was converted to a mixture of **14** and an HF elimination by-product (316 mg) in 76% yield (calculated as the fluoride). The ^{13}C NMR resonances for **14** were as follows (50 MHz): δ 177.77(C), 158.23 (C), 129.52 (CH), 121.16 (CH), 114.46 (CH), 91.58 (d, $J = 171$ Hz, CH), 84.00 (CH), 77.08 (CH), 69.28 (d, $J = 24$ Hz, CH_2), 53.41 (CH), 42.85 (CH), 40.24 (CH_2), 36.05 (CH_2), 29.38 (d, $J = 20$ Hz, CH_2), 28.03 (CH_2). MF for **14** = $C_{17}H_{21}O_4F$, MW = 308. ES-LRMS, m/z (fragment, intensity): 325.9 [(M+NH_4)$^+$ for **14**, 100%], 308.9 [(M+H)$^+$ for **14**, 43%], 305.9 [(M+NH_4)$^+$ for HF elimination by-product, 28%], 289.0 [(M+H)$^+$ for HF elimination by-product, 15%].

4.1.11. (5*Z*)-(9*S*,11*R*,15*R*)-9,11-Dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-5-prostenoic acid isopropyl ester (17). Analogous to the conversion of alcohol **6** to the THP ether **7**, alcohol **14** (170 mg) was converted to THP ether [3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutyl)-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (140 mg, 70%). MALDI-LRMS, m/z calcd for $C_{22}H_{29}O_5FNa$ (M+Na)$^+$, 415; found, 415.563.

Analogous to the reduction of lactone **7** to the lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol, the above lactone (140 mg) was reduced to the lactol [2*RS*,3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutyl)-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta-[*b*]furan-2-ol (120 mg) in 92% yield. MALDI-LRMS, m/z calcd for $C_{22}H_{31}O_5FNa$ (M+Na)$^+$, 417; found, 417.516.

Analogous to the Wittig reaction/esterification of the lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]-furan-2-ol to **8**, the above lactol (110 mg) was converted to (5*Z*)-(9*S*,11*R*,15*R*)-9-hydroxy-15-fluoro-16-phenoxy-11-

(tetrahydropyran-2-yloxy)-17,18,19,20-tetranor-5-prostenoic acid isopropyl ester (50 mg) in 18% yield in four steps from **14**.

Analogous to the deprotection of THP ether **8** to the diols **9** and **10**, the above THP ether (50 mg) was converted to **17** (29 mg) in 67% yield. ^{13}C NMR (50 MHz): δ 173.4 (C), 158.4 (C), 129.8 (CH), 129.5 (CH), 129.1 (CH), 121.2 (CH), 114.6 (CH), 91.7 (d, $J = 175$ Hz, CH), 78.9 (CH), 74.7 (CH), 69.6 (d, $J = 20$ Hz, CH_2), 67.6 (CH), 52.7 (CH), 51.7 (CH), 42.6 (CH_2), 34.0 (CH_2), 30.4 (CH_2), 28.8 (d, $J = 5$ Hz, CH_2), 26.8 (d, $J = 15$ Hz, CH_2), 24.9 (CH_2), 21.8 (CH_3). HRMS, m/z calcd for $C_{25}H_{38}O_5F$ [(M+H)$^+$], 437.270528; found, 437.27053.

4.1.12. (5*Z*)-(9*S*,11*R*,15*R*)-9,11-Dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-5-prostenoic acid (19). Analogous to the saponification of ester **9** to acid **11**, **17** (8 mg) was converted to **19** (7 mg) in 93% yield. ^{13}C NMR (67.5 MHz): δ 158.5 (C), 129.3 (CH), 129.2 (CH), 129.0 (CH), 120.7 (CH), 114.3 (CH), 91.8 (d, $J = 169$ Hz, CH), 77.0 (CH), 72.3 (CH), 69.6 (d, $J = 20$ Hz, CH_2), 50.6 (CH), 50.1 (CH), 42.6 (CH_2), 33.1 (CH_2), 29.1 (CH_2), 26.2 (d, $J = 20$ Hz, CH_2), 24.8 (CH_2). HRMS, m/z calcd for $C_{22}H_{31}O_5F$ (M^+), 394.215436; found, 394.21542.

4.1.13. [3a*R*,4*R*(1*E*,3*R*),5*R*,6a*S*]-5-Benzoyloxy-4-(3-hydroxy-4-phenoxybutenyl)-hexahydro-2*H*-cyclopenta[*b*]-furan-2-one (3). Analogous to the reduction of enone **1** to β-alcohol **2** with (+)-DIP chloride, enone **1** (3.29 g) was converted to α-alcohol **3** (1.64 g) in 50% yield using (−)-DIP chloride. ^{1}H NMR (600 MHz): δ 7.99 (d, $J = 7$ Hz, 2H), 7.54 (t, $J = 7$ Hz, 1H), 7.43 (t, $J = 8$ Hz, 2H), 7.26 (t, $J = 8$ Hz, 2H), 6.96 (t, $J = 7$ Hz, 1H), 6.85 (d, $J = 8$ Hz, 2H), 5.82 (dd, $J = 16$ Hz, 7 Hz, 1H), 5.73 (dd, $J = 16$ Hz, 5 Hz, 1H), 5.28 (q, $J = 6$ Hz, 1H), 5.05 (t of d, $J = 5$ Hz, 2 Hz, 1H), 4.52–4.50 (br m, 1H), 3.94 (dd, $J = 9$ Hz, 4 Hz, 1H), 3.82 (dd, $J = 9$ Hz, 7 Hz, 1H), 2.86–2.78 (m, 3 H), 2.61–2.55 (m, 1H), 2.51 (d, $J = 16$ Hz, 1H), 2.43 (br s, 1H), 2.28 (dd, $J = 16$ Hz, 4 Hz, 1H). ^{13}C DEPT NMR (150 MHz): δ 133.33 (CH), 131.06 (CH), 130.70 (CH), 129.65 (CH), 129.55 (CH), 128.52 (CH), 121.36 (CH), 114.63 (CH), 83.30 (CH), 79.08 (CH), 71.58 (CH_2), 70.19 (CH), 54.18 (CH), 42.67 (CH), 37.59 (CH_2), 34.94 (CH_2). HRMS, m/z calcd for $C_{24}H_{24}O_6Na$ [(M+Na)], 431.146911; found, 431.14691.

4.1.14. [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-Benzoyloxy-4-(3-fluoro-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (15). Analogous to the hydrogenation of olefin **2** to [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one, **3** (1.59 g) was reduced to [3a*R*,4*R*(3*R*),5*R*,6a*S*]-5-benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (1.60 g) in 100% yield. ^{13}C NMR (50 MHz): δ 176.81 (C), 166.02 (C), 158.40 (C), 133.23 (CH), 129.59 (CH), 129.51 (CH), 128.47 (CH), 121.22 (CH), 114.52 (CH), 84.81 (CH), 80.04 (CH), 71.92 (CH_2), 69.60 (CH), 52.50 (CH), 43.57 (CH), 37.74 (CH_2), 36.23 (CH_2), 30.72 (CH_2), 29.24 (CH_2). HRMS, m/z calcd for $C_{24}H_{26}O_6Na$ [(M+Na)$^+$], 433.162978; found, 433.16296.

Analogous to the conversion of the β-alcohol [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one to the α-fluoride **13**, the above α-alcohol (1.39 g) was converted to a 4:1 molar of **15** and an HF elimination by-product (1.01 g total, 72% calculated as the fluoride). ^{13}C NMR line listing for **15**: (150 MHz): δ 176.54 (C), 166.04 (C), 158.33 (C), 133.29 (CH), 129.64 (CH), 129.54 (CH), 128.52 (CH), 121.39 (CH), 114.62 (CH), 91.45 (d, $J = 171$ Hz, CH), 84.30 (CH), 80.18 (CH), 69.28 (d, $J = 26$ Hz, CH_2), 52.75 (CH), 43.47 (CH), 37.81 (CH_2), 36.23 (CH_2), 29.88 (d, $J = 21$ Hz, CH_2), 28.86 (CH_2). HRMS, m/z calcd for $C_{24}H_{25}O_5FNa$ [(M+Na)$^+$], 435.158817; found, 435.15881.

4.1.15. [3a*R*,4*R*(3*S*),5*R*,6a*S*]-4-(3-Fluoro-4-phenoxybutyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (16). Analogous to the debenzoylation of **4** to alcohol **6**, the above **15**/HF elimination by-product mixture (982 mg calculated as the fluoride) was converted to a mixture of alcohol **16** and an HF elimination by-product (591 mg combined) in 80% yield (calculated as the fluoride). ^{13}C NMR line listing for **16**: (50 MHz): δ 177.43 (C), 158.33 (C), 129.53 (CH), 121.34 (CH), 114.58 (CH), 91.66 (d, $J = 171$ Hz, CH), 83.93 (CH), 77.57 (CH), 69.33 (d, $J = 24$ Hz, CH_2), 53.94 (CH), 43.00 (CH), 40.56 (CH_2), 36.02 (CH_2), 29.81 (d, $J = 21$ Hz, CH_2), 28.38 (d, $J = 4$ Hz, CH_2). HRMS, m/z calcd for $C_{17}H_{22}O_4F$ [(M+H)$^+$], 309.150295; found, 309.15029.

4.1.16. (5*Z*)-(9*S*,11*R*,15*S*)-9,11-Dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-5-prostenoic acid isopropyl ester (18). Analogous to the protection of alcohol **6** as its THP ether **7**, the above **16**/HF elimination by-product mixture (542 mg) was converted to a mixture of its THP ether [3a*R*,4*R*(3*S*),5*R*(2*RS*),6a*S*]-4-(3-fluoro-4-phenoxybutyl)-5-(2-tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one and the corresponding HF elimination by-product (652 mg) in 94% yield (calculated as the fluoride). HRMS, m/z calcd for $C_{22}H_{30}O_5F$ [(M+H)$^+$], 393.207942; found, 393.20794.

Analogous to the reduction of lactone **7** to the corresponding lactol, the above THP ether lactone/HF elimination by-product mixture (641 mg) was converted to the lactol [2*RS*,3a*R*,4*R*(3*S*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutyl)-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol and the corresponding HF elimination by-product (652 mg) in 100% yield (calculated as the fluoride). HRMS, m/z calcd for $C_{22}H_{32}O_5F$ [(M+H)$^+$], 395.223390; found, 395.22339.

Analogous to the conversion of the lactol [3a*R*,4-*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol to the Wittig+esterification product **8**, the above lactol

(643 mg) was converted to a mixture of (5*Z*)-(9*S*,11*R*,15*S*)-15-fluoro-9-hydroxy-16-phenoxy-11-(tetrahydropyran-2-yloxy)-17,18,19,20-tetranor-5-prostenoic acid isopropyl ester and the corresponding HF elimination by-product (430 mg) in 51% yield (calculated as the fluoride). HRMS, *m/z* calcd for $C_{30}H_{45}O_6FNa$ [(M+Na)$^+$], 543.309571; found, 543.30957.

Analogous to the deprotection of THP ether **8** to the alcohols **9** and **10**, the above THP ether/HF elimination compound mixture (420 mg) was treated with HCl/isopropanol to afford a crude deprotection product, which was chromatographed on a 7 cm tall × 41 mm diameter silica gel column eluting with a gradient of 2:3 → 3:2 v:v mixture of ethyl acetate–hexane. Thin layer chromatographic analysis showed that the desired, major product, **18**, eluted with $R_f \sim 0.22$ while the corresponding HF elimination by-product eluted with $R_f \sim 0.26$ (2:3 v:v ethyl acetate–hexane eluent). Two samples were isolated from the column: 53.1 mg of a 97:3 mixture (as measured by 600 MHz proton NMR) of **18**: HF elimination by-product, and 115.6 mg of a 96:4 mixture of the same two compounds (total yield = 168.7 mg = 48% calculated as the fluoride). This sample was further purified by normal-phase HPLC to provide 126.9 mg of **18** without any detectable HF elimination by-product by 600 MHz proton NMR spectroscopy. ^{13}C NMR (150 MHz): δ 173.40 (C), 158.50 (C), 129.87 (CH), 129.58 (CH), 129.22 (CH), 121.31 (CH), 114.72 (CH), 114.72 (CH), 92.16 (d, $J = 171$ Hz, CH), 78.90 (CH), 74.73 (CH), 69.63 (d, $J = 24$ Hz, CH_2), 67.70 (CH), 53.04 (CH), 51.78 (CH), 42.65 (CH_2), 34.11 (CH_2), 30.42 (d, $J = 19$ Hz, CH_2), 29.24 (d, $J = 4$ Hz, CH_2), 27.03 (CH_2), 26.73 (CH_2), 24.99 (CH_2), 21.90 (CH_3). HRMS, *m/z* calcd for $C_{25}H_{38}O_5F$ [(M+H)$^+$], 437.269858; found, 437.26986.

4.1.17. (5*Z*)-(9*S*,11*R*,15*S*)-9,11-Dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-5-prostenoic acid (20). Analogous to the saponification of isopropyl ester **9** to acid **11**, **18** (21 mg) was saponified to give **20** (16 mg) in 83% yield. ^{13}C NMR (150 MHz): δ 178.00 (C), 158.50 (C), 129.58 (CH), 129.47 (CH), 129.26 (CH), 121.21 (CH), 114.61 (CH), 92.06 (d, $J = 171$ Hz, CH), 78.74 (CH), 74.65 (CH), 69.51 (d, $J = 24$ Hz, CH_2), 52.68 (CH), 51.50 (CH), 42.37 (CH_2), 33.00 (CH_2), 30.19 (d, $J = 21$ Hz, CH_2), 29.04 (d, $J = 4$ Hz, CH_2), 26.88 (CH_2), 26.41 (CH_2), 24.49 (CH_2). HRMS, *m/z* calcd for $C_{22}H_{32}O_5F$ [(M+H)$^+$], 395.223759; found, 395.22375.

4.1.18. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-5-(*t*-Butyldiphenylsiloxy)-4-(3-fluoro-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]-furan-2-one (21). To a solution of a mixture of fluoride alcohol **14** and its HF elimination by-product (312 mg, 1.01 mmol calculated as the fluoride), CH_2Cl_2 (10 mL), DMAP (35 mg, 0.29 mmol), and imidazole (109 mg, 1.60 mmol) was added *t*-BuPh_2SiCl (360 mg, 1.31 mmol). After 3 h saturated NaCl was added (10 mL), the layers were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on a 20 cm tall × 26 mm diameter silica gel column eluting with 20% ethyl acetate in hexane to afford pure silyl ether **21** (213 mg, 39% yield), as well as a 65:35 molar mixture (as measured by ^{1}H NMR spectroscopy) of **21** and an HF elimination by-product (246 mg, total = 459 mg = 83% calculated as the fluoride). ^{13}C NMR (50 MHz): δ 177.20 (C), 158.31 (C), 135.95 (CH), 135.91 (CH), 133.47 (CH), 133.35 (C), 129.83 (CH), 129.79 (CH), 129.52 (CH), 127.72 (CH), 127.67 (CH), 121.30 (CH), 114.49 (CH), 91.38 (d, $J = 172$ Hz, CH), 84.30 (CH), 78.53 (CH), 69.17 (d, $J = 24$ Hz, CH_2), 54.98 (CH), 42.92 (CH), 40.17 (CH_2), 36.30 (CH_2), 29.36 (d, $J = 21$ Hz, CH_2), 28.29 (d, $J = 4$ Hz, CH_2), 26.80 (CH_3), 18.93 (C). HRMS, *m/z* calculated for $C_{33}H_{39}O_4SiFNa$ [(M+Na)$^+$], 569.249528; found, 569.24951.

4.1.19. (1*EZ*)-(9*S*,11*R*,15*R*)-11-(*t*-Butyldiphenylsiloxy)-15-fluoro-9-hydroxy-16-phenoxy-3,4,5,6,17,18,19,20-octanor-1-prosten-1-yl methyl ether (22). To a solution of a mixture of **21** and an HF elimination contaminant (645 mg, 1.18 mmol calculated as the fluoride) in toluene (12 mL) at −78 °C was added dropwise a 1.5 M solution of DIBAL-H in toluene (1.8 mL, 2.7 mmol). After 30 min methanol (1 mL) was added and the reaction mixture was warmed to room temperature. Saturated NH_4Cl (5 mL) and sodium potassium tartrate (9 mL) were added, and the mixture was stirred until the emulsion broke (about 20 min). The solution was extracted with ethyl acetate (2 × 25 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on a 10 cm tall × 26 mm diameter silica gel column eluting with 40% ethyl acetate in hexane to afford the lactol [2*RS*,3a*R*,4*R*(3*R*),5*R*,6a*S*]-5-(*t*-butyldiphenylsiloxy)-4-(3-fluoro-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol as a mixture with an HF elimination contaminant (523 mg, 81% nominal yield). HRMS, *m/z* calcd for $C_{33}H_{41}O_4SiFNa$ [(M+Na)$^+$], 571.266039; found, 571.26605.

To a suspension of $Ph_3P^+CH_2OCH_3Cl^-$ (1.05 g, 3.07 mmol) and KOBu^t (1 M in THF, 2.85 mL, 2.85 mmol) in THF (8 mL) at 0 °C was added a solution of the above fluoride lactol/HF elimination by-product mixture (516 mg, 0.94 mmol nominal fluoride) in THF (11 mL). After 15 min saturated KH_2PO_4 (10 mL), saturated NaCl (25 mL), and water (15 mL) were added, the mixture was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on an 18 cm tall × 26 mm diameter silica gel column eluting with 20% ethyl acetate in hexane to afford enol ether **22** as a mixture with an HF elimination by-product (408 mg, 75% yield calculated as the fluoride). HRMS, *m/z* calcd for $C_{35}H_{45}O_4SiFNa$ [(M+Na)$^+$], 599.296403; found, 599.29638.

4.1.20. [2*RS*,4a*R*,5*R*(3*R*),6*R*,7a*S*]-6-(*t*-Butyldiphenylsiloxy)-5-(3-fluoro-4-phenoxybutyl)-octahydro-2*H*-cyclopenta[*b*]pyran-2-ol (23). A solution of a mixture of **22** and an HF elimination contaminant (402 mg,

0.700 mmol nominal fluoride), *p*-TsOH (82 mg, 0.43 mmol), THF (10 mL), and water (1 mL) were heated to 65–70 °C (internal temperature). After 2 h the reaction mixture was cooled to room temperature, saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL) were added, and the mixture was extracted with ethyl acetate (2×30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by chromatography on a 13 cm tall×26 mm diameter silica gel column eluting with a 20%→40% ethyl acetate in hexane gradient to afford lactol fluoride **23** as a mixture with an HF elimination contaminant (254 mg, 64% nominal fluoride yield). HRMS, *m/z* calcd for $C_{34}H_{43}O_4SiFNa$ [(M+Na)$^+$], 585.281036; found, 585.28100.

4.1.21. (4*Z*)-(9*S*,11*R*,15*R*)-9,11-Dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-4-prostenoic acid isopropyl ester (24). Analogous to the conversion of the lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol to the Wittig+esterification product **8**, a mixture of lactol **23** and an HF elimination contaminant (250 mg) was converted to a mixture of (4*Z*)-(9*S*,11*R*,15*R*)-11-(*t*-butyldiphenylsiloxy)-15-fluoro-9-hydroxy-16-phenoxy-17,18,19,20-tetranor-4-prostenoic acid isopropyl ester, its corresponding 15-desfluoro-$\Delta^{14,15}$ olefin, and $Ph_3P^+(CH_2)_3CO_2Pr^iBr^-$ (503 mg total) in >100% nominal yield. HRMS, *m/z* calcd for $C_{41}H_{56}O_5SiF$ [(M+H)$^+$], 675.387994; found, 675.38800.

To a solution of the above impure sample in THF (8 mL) was added a 1 M solution of TBAF in THF (0.85 mL, 0.85 mmol). After 3 h saturated NH_4Cl (20 mL) was added, the mixture was extracted with ethyl acetate (3×20 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on a 16 cm tall×26 mm diameter silica gel column eluting with 60% ethyl acetate in hexane to afford **24** as a 2:1 molar mixture (as measured by ^{13}C NMR spectroscopy) with its corresponding 15-desfluoro-$\Delta^{14,15}$ olefin (103 mg, 54% three-step yield from lactol **23**, calculated as the 15-fluoride). The sample was further purified by HPLC on a chiral AD column eluting with 4:1 hexane–isopropanol to afford the 15-desfluoro-$\Delta^{14,15}$ olefin geometrical isomers (4*Z*,14*EZ*)-(9*S*,11*R*)-9,11-dihydroxy-16-phenoxy-17,18,19,20-tetranor-4,14-prostadienoic acid isopropyl ester as the minor, faster-eluting component (16.8 mg) and the title compound **24** as the major, slower-eluting component (67.3 mg). As measured by ^{13}C NMR spectroscopy, this sample of **24** consisted of a ~94:6 mixture of 4*Z*:4*E* olefin geometrical isomers. ^{13}C NMR (150 MHz): δ 173.02 (C), 158.39 (C), 131.07 (CH), 129.47 (CH), 127.68 (CH), 121.16 (CH), 114.55 (CH), 91.68 (d, J = 171 Hz, CH), 78.54 (CH), 74.14 (CH), 69.58 (d, J = 22 Hz, CH_2), 67.78 (CH), 52.92 (CH), 51.53 (CH), 42.58 (CH_2), 34.42 (CH_2), 30.10 (d, J = 21 Hz, CH_2), 28.79 (CH_2), 28.74 (d, J = 9 Hz, CH_2), 26.02 (CH_2), 22.69 (CH_2), 21.86 (CH_3), 21.79 (CH_3). HRMS, *m/z* calcd for $C_{25}H_{38}O_5F$ [(M+H$^+$)], 437.270740; found, 437.27075.

4.1.22. (4*Z*)-(9*S*,11*R*,15*R*)-9,11-Dihydroxy-15-fluoro-16-phenoxy-17,18,19,20-tetranor-4-prostenoic acid (25). Analogous to the saponification of isopropyl ester **9** to the acid **11**, **24** (34 mg) was converted to **25** (26 mg) in 84% yield as a ~94:6 mixture of 4*Z*:4*E* olefin geometrical isomers. ^{13}C NMR (150 MHz): δ 177.28 (C), 158.42 (C), 131.56 (CH), 129.49 (CH), 128.19 (CH), 127.06 (CH), 121.18 (CH), 114.56 (CH), 91.65 (d, J = 171 Hz, CH), 78.45 (CH), 73.94 (CH), 69.62 (d, J = 22 Hz, CH_2), 52.44 (CH), 51.70 (CH), 42.18 (CH_2), 33.96 (CH_2), 29.96 (d, J = 20 Hz, CH_2), 28.97 (CH_2), 28.97 (CH_2), 28.48 (CH_2), 26.16 (CH_2), 22.80 (CH_2). HRMS, *m/z* calcd for $C_{22}H_{32}O_5F$ [(M+H)$^+$], 395.223759; found, 395.22375.

4.1.23. [3a*R*,4*R*(1*E*,3*R*),5*R*,6a*S*]-5-Benzoyloxy-4-(3-hydroxyoctenyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (42). Analogous to the reduction of enone **1** to β-alcohol **2**, [3a*R*,4*R*(1*E*),5*R*,6a*S*]-5-benzoyloxy-4-(3-oxooctenyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one[13] (7.24 g) was reduced with (+)-DIP chloride to afford β-alcohol **42** (3.78 g; R_f = 0.18, 2:3 ethyl acetate–hexane eluent) in 52% yield, as well as a mixture of **42** with its α(*S*)-alcohol diastereomer (1.08 g; R_f = 0.23, 2:3 ethyl acetate–hexane) in 15% yield. ^{13}C NMR (150 MHz): δ 176.42 (C), 165.95 (C), 136.46 (CH), 133.26 (CH), 129.55 (CH), 129.43 (C), 128.42 (CH), 128.26 (CH), 83.14 (CH), 78.94 (CH), 72.20 (CH), 53.88 (CH), 42.54 (CH), 37.45 (CH_2), 37.20 (CH_2), 34.75 (CH_2), 31.57 (CH_2), 24.91 (CH_2), 22.42 (CH_2), 13.92 (CH_2). HRMS, *m/z* calcd for $C_{22}H_{28}O_5Na$ [(M+Na)$^+$], 395.18346; found, 395.18347.

4.1.24. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-5-Benzoyloxy-4-(3-hydroxyoctyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (43). Analogous to the hydrogenation of olefin **2** to [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-Benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one, **42** (3.72 g) was hydrogenated to afford **43** (3.55 g) in 94% yield. ^{13}C NMR (150 MHz): δ 176.83 (C), 166.09 (C), 123.22 (CH), 129.62 (CH), 128.47 (CH), 84.50 (CH), 80.43 (CH), 71.12 (CH), 52.95 (CH), 43.42 (CH), 37.72 (CH_2), 36.30 (CH_2), 35.79 (CH_2), 35.17 (CH_2), 33.50 (CH_2), 31.77 (CH_2), 29.71 (CH_2), 25.25 (CH_2), 23.45 (CH_2), 22.55 (CH_2), 13.96 (CH_3). HRMS, *m/z* calcd for $C_{22}H_{30}O_5Na$ [(M+Na)$^+$], 397.19923; found, 397.19922.

4.1.25. [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-Benzoyloxy-4-(3-fluorooctyl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (44). Analogous to the fluorination of the alcohol 5-benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta-[*b*]furan-2-one to **13**, alcohol **43** (1.42 g) was fluorinated with DAST and the residue after concentration was chromatographed on a 24 cm tall×53 mm diameter silica gel column eluting with 30% ethyl acetate in hexane to afford **44** (530 mg; R_f = 0.71, 40% ethyl acetate in hexane) as well as a 79:21 (as measured by proton NMR spectroscopy) molar mixture of **44** and an HF elimination by-product (134 mg). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 176.10 (C), 165.98 (C), 133.24 (CH), 129.61 (CH), 128.48 (CH), 93.84 (d, J = 167 Hz, CH), 84.33 (CH),

79.98 (CH), 52,37 (CH), 43.56 (CH), 37.77 (CH_2), 36.20 (CH_2), 35.06 (d, $J = 20$ Hz, CH_2), 32.90 (d, $J = 22$ Hz, CH_2), 31.57 (CH_2), 28.90 (d, $J = 3$ Hz, CH_2), 24.71 (d, $J = 4$ Hz, CH_2), 22.47 (CH_2), 13.92 (CH_3). ES-LRMS, m/z calcd for $C_{22}H_{33}O_4FNa$ [$(M+Na)^+$], 394; found, 394.

4.1.26. [3a*R*,4*R*(3*S*),5*R*,6a*S*]-4-(3-Fluorooctyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (45). Analogous to the debenzoylation of **4** to alcohol **6**, benzoate **44** (520 mg) was converted **45** (248 mg) in 66% yield. ^{1}H NMR (200 MHz; characteristic peaks): δ 4.98 (t of d, $J = 7$ Hz, 2 Hz, 1H), 4.46 (d of m, $J = 47$ Hz for the doublet coupling, 1H), 4.05 (q, $J = 5$ Hz, 1H), 2.75 (d of d, $J = 18$ Hz, 7 Hz, 1H). ^{13}C NMR (50 MHz): δ 177.57 (C), 94.23 (d, $J = 166$ Hz, CH), 84.04 (CH), 77.40 (CH), 53.40 (CH), 43.17 (CH), 40.54 (CH_2), 36.05 (CH_2), 35.02 (CH_2), 33.12 (d, $J = 21$ Hz, CH_2), 31.57 (CH_2), 28.56 (d, $J = 4$ Hz, CH_2), 24.71 (d, $J = 5$ Hz, CH_2), 22.46 (CH_2), 13.91 (CH_3). HRMS, m/z calcd for $C_{15}H_{26}O_3F$ [$(M+H)^+$], 273.18674; found, 273.18673.

4.1.27. [3a*R*,4*R*(3*S*),5*R*,6a*S*]-4-(3-Fluorooctyl)-5-(tetrahydropyran-2-yloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (46). Analogous to the conversion of alcohol **6** to the THP ether **7**, **45** (240 mg) was converted to THP ether **46** (263 mg) in 84% yield. HRMS, m/z calcd for $C_{20}H_{34}O_4F$ [$(M+H)^+$], 357.24383; found, 357.24384.

4.1.28. [3a*R*,4*R*(3*S*),5*R*,6a*S*]-4-(3-Fluorooctyl)-5-(tetrahydropyran-2-yloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-ol (47). Analogous to the reduction of lactone **7** to the lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol, **46** (256 mg) was reduced to lactol **47** (260 mg) in 100% yield. HRMS, m/z calcd for $C_{20}H_{36}O_4F$ [$(M+H)^+$], 341.24867; found, 341.24865.

4.1.29. (5*Z*)-(9*S*,11*R*,15*S*)-15-Fluoro-9-hydroxy-11-(tetrahydropyran-2-yloxy)-5-prostenoic acid isopropyl ester (48). Analogous to the Wittig reaction/esterification of the lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]-furan-2-ol to **8**, lactol **47** (146 mg) was converted to **48** (92 mg) in 46% yield. HRMS, m/z calcd for $C_{28}H_{49}O_5FNa$ [$(M+Na)^+$], 507.34579; found, 507.34579.

4.1.30. (5*Z*)-(9*S*,11*R*,15*S*)-9,11-Dihydroxy-15-fluoro-5-prostenoic acid isopropyl ester (29). Analogous to the deprotection of THP ether **8** to the diols **9** and **10**, THP ether **48** (86 mg) was deprotected with HCl in isopropanol to afford **29** (33 mg) in 47% yield. ^{1}H NMR (600 MHz) (characteristic peaks): δ 5.50–5.42 (m, 1H), 5.41–5.35 (m, 1H), 5.00 (septet, $J = 7$ Hz, 1H), 4.48 (d of m, $J = 49$ Hz for the doublet coupling, 1H), 4.17 (br s, 1H), 3.93 (d, $J = 2$ Hz, 1H), 1.22 (d, $J = 7$ Hz, 6H), 0.89 (t, $J = 7$ Hz, 3H). ^{13}C NMR (150 MHz): δ 173.37 (C), 129.66 (CH), 129.23 (CH), 94.34 (d, $J = 166$ Hz, CH), 78.73 (CH), 74.72 (CH), 67.58 (CH), 52.84 (CH), 51.82 (CH), 42.57 (CH_2), 35.14 (d, $J = 21$ Hz, CH_2), 34.04 (CH_2), 33.68 (d, $J = 21$ Hz, CH_2), 31.65 (CH_2), 29.90 (d, $J = 4$ Hz, CH_2), 26.90 (CH_2), 26.63 (CH_2), 24.91 (CH_2), 24.79 (d, $J = 6$ Hz, CH_2), 22.51 (CH_2), 21.81 (CH_3), 13.94 (CH_3). HRMS, m/z calcd for $C_{23}H_{42}O_4F$ [$(M+H)^+$], 401.30690; found, 401.30689.

4.1.31. (5*Z*)-(9*S*,11*R*,15*S*)-9,11-Dihydroxy-15-fluoro-5-prostenoic acid (28). Analogous to the saponification of ester **9** to acid **11**, isopropyl ester **29** (18 mg) was saponified to provide acid **28** (12 mg) in 74% yield. ^{13}C NMR (150 MHz): δ 177.93 (C), 129.52 (CH), 129.43 (CH), 94.42 (d, $J = 166$ Hz, CH), 78.75 (CH), 74.81 (CH), 52.68 (CH), 51.72 (CH), 42.44 (CH_2), 35.16 (d, $J = 20$ Hz, CH_2), 33.64 (d, $J = 21$ Hz, CH_2), 33.07 (CH_2), 31.67 (CH_2), 29.18 (CH_2), 26.91 (CH_2), 26.47 (CH_2), 24.83 (CH_2), 24.57 (CH_2), 22.53 (CH_2), 13.97 (CH_3). HRMS, m/z calcd for $C_{20}H_{36}O_4F$ [$(M+H)^+$], 359.26007; found, 359.26007.

4.1.32. [3a*R*,4*R*(1*E*,3*S*),5*R*,6a*S*]-5-Benzoyloxy-4-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (49). Analogous to the reduction of enone **1** to β-alcohol **2** with (+)-DIP chloride, the enone [3a*R*,4*R*(1*E*),5*R*,6a*S*]-5-benzoyloxy-4-[4-(3-chlorophenoxy)-3-oxo-1-butenyl]-hexahydro-2*H*-cyclopenta-[*b*]furan-2-one[13] (1.02 g) was reduced with (+)-DIP chloride to afford β-alcohol **49** (502 mg) in 49% yield, as well as a mixture of **49** and the corresponding α-alcohol (254 mg, 23%).

4.1.33. [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-Benzoyloxy-4-[4-(3-chlorophenoxy)-3-hydroxybutyl]-hexahydro-2*H*-cyclopenta[*b*]-furan-2-one (50). Analogous to the hydrogenation of olefin **2** to [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]-furan- 2-one, olefin **49** (500 mg) was hydrogenated to afford **50** (486 mg) in 97% yield.

4.1.34. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-5-Benzoyloxy-4-[4-(3-chlorophenoxy)-3-fluorobutyl]-hexahydro-2*H*-cyclopenta[*b*]-furan-2-one (51). Analogous to the conversion of the β-alcohol [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]-furan-2-one to the α-fluoride **13**, β-alcohol **50** (480 mg) to afford α-fluoride **51** (117 mg, 33%) as well as a mixture of **51** and an HF elimination by-product (44 mg). ^{13}C NMR (50 MHz): δ 176.57 (C), 166.04 (C), 159.03 (C), 134.93 (C), 133.34 (CH), 130.31 (CH), 129.62 (CH), 128.54 (CH), 121.54 (CH), 115.06 (CH), 113.07 (CH), 91.02 (d, $J = 171$ Hz, CH), 84.27 (CH), 79.80 (CH), 69.60 (d, $J = 24$ Hz, CH_2), 52.26 (CH), 43.59 (CH), 36.96 (d, $J = 76$ Hz, CH_2), 29.34 (d, $J = 21$ Hz, CH_2), 28.57 (CH_2).

4.1.35. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-[4-(3-Chlorophenoxy)-3-fluorobutyl]-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (52). Analogous to the debenzoylation of **4** to alcohol **6**, **51** (117 mg) was debenzoylated to afford **52** (60 mg) in 67% yield.

4.1.36. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-[4-(3-Chlorophenoxy)-3-fluorobutyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (53). Analogous to the protection of alcohol **6** as its THP ether **7**, alcohol **52** (59 mg) was protected as its THP ether **53** (59 mg) in 82% yield.

4.1.37. [2*RS*,3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-[4-(3-Chlorophenoxy)-3-fluorobutyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol (54). Analogous to the reduction of lactone **7** to the corresponding lactol, lactone **53** (59 mg) was reduced to lactol **54** (59 mg) in 99% yield.

4.1.38. (5*Z*)-(9*S*,11*R*,15*R*)-16-(3-Chlorophenoxy)-15-fluoro-9-hydroxy-11-(tetrahydropyran-2-yloxy)-17,18,19,20-tetranor-5-prostenoic acid isopropyl ester (55). Analogous to the conversion of the lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol to the Wittig+esterification product **8**, lactol **54** (59 mg) was converted to a sample of olefin **55** contaminated with triphenylphosphine oxide (147 mg total). The sample was used without further purification in the next step.

4.1.39. (5*Z*)-(9*S*,11*R*,15*R*)-16-(3-Chlorophenoxy)-9,11-dihydroxy-15-fluoro-17,18,19,20-tetranor-5-prostenoic acid isopropyl ester (31). Analogous to the deprotection of THP ether **8** to the alcohols **9** and **10**, the above sample of THP ether **55** contaminated with triphenylphosphine oxide (147 mg) was deprotected with HCl/isopropanol to afford **31** (31 mg) in 47% yield from lactol **54**. ^{13}C NMR (50 MHz): δ 173.40 (C), 159.18 (C), 134.90 (C), 130.26 (CH), 129.81 (CH), 129.08 (CH), 121.41 (CH), 115.06 (CH), 113.13 (CH), 91.44 (d, $J = 172$ Hz, CH), 78.65 (CH), 74.61 (CH), 69.91 (d, $J = 23$ Hz, CH_2), 67.63 (CH), 52.57 (CH), 51.72 (CH), 30.05 (d, $J = 21$ Hz, CH_2), 28.86 (CH_2), 28.78 (CH_2), 26.82 (CH_2), 26.63 (CH_2), 24.90 (CH_2), 21.82 (CH_3). MALDI-LRMS, m/z calcd for $C_{25}H_{36}O_5FClNa$ [(M+Na)$^+$], 493; found, 493.

4.1.40. (5*Z*)-(9*S*,11*R*,15*R*)-16-(3-Chlorophenoxy)-9,11-dihydroxy-15-fluoro-17,18,19,20-tetranor-5-prostenoic acid (30). Analogous to the saponification of isopropyl ester **9** to acid **11**, isopropyl ester **31** (16 mg) was converted to a crude sample of the acid **30**. This sample was purified via reverse-phase HPLC using a C18 column eluting with acetonitrile–water–trifluoroacetic acid 60:40:0.02 to afford **30** (3.8 mg, 28%). ^{13}C NMR DEPT spectrum (50 MHz, CD_3OD): δ 171.10 (C), 160.97 (C), 136.63 (CH), 135.84 (C), 131.50 (CH) (CH), 128.69 (CH), 122.03 (CH), 115.95 (CH), 114.18 (CH), 92.94 (d, $J = 171$ Hz, CH), 78.26 (CH), 73.57 (CH), 71.20 (d, $J = 22$ Hz, CH_2), 51.75 (CH), 51.30 (CH), 43.88 (CH_2), 34.33 (CH_2), 30.66 (CH_2), 30.54 (CH_2), 29.17 (CH_2), 27.38 (d, $J = 16$ Hz, CH_2), 26.01 (CH_2). MALDI-LRMS, m/z calcd for $C_{22}H_{30}O_5FClNa$ [(M+Na)$^+$], 451; found, 451.

4.1.41. [3a*R*,4*R*(1*E*,3*S*),5*R*,6a*S*]-5-Benzoyloxy-4-[3-hydroxy-4-(3-(trifluoromethyl)phenoxy)-1-butenyl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (56). Analogous to the reduction of enone **1** to β-alcohol **2** with (+)-DIP chloride, the enone [3a*R*,4*R*(1*E*),5*R*,6a*S*]-5-benzoyloxy-4-[3-oxo-4-(3-(trifluoromethyl)phenoxy)-1-butenyl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one[21] (1.77 g) was reduced with (+)-DIP chloride to provide β-alcohol **56** (624 mg) in 35% yield, as well as a mixture of **56** and the corresponding α-alcohol (681 mg) in 39% yield.

4.1.42. [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-Benzoyloxy-4-[3-hydroxy-4-(3-(trifluoromethyl)phenoxy)-butyl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (57). Analogous to the hydrogenation of olefin **2** to [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one, olefin **56** (600 mg) was hydrogenated to afford **57** (601 mg) in 100% yield.

4.1.43. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-5-Benzoyloxy-4-[3-fluoro-4-(3-(trifluoromethyl)phenoxy)butyl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (58). Analogous to the conversion of the β-alcohol [3a*R*,4*R*(3*S*),5*R*,6a*S*]-5-benzoyloxy-4-(3-hydroxy-4-phenoxybutyl)-hexahydro-2*H*-cyclopenta[*b*]-furan-2-one to the α-fluoride **13**, β-alcohol **57** (600 mg) was reacted with DAST to provide α-fluoride **58** (312 mg) in 50% yield. ^{13}C NMR (50 MHz, peaks not split by CF_3): δ 176.52 (C), 165.65 (C), 158.34 (C), 133.18 (CH), 131.37 (C), 129.99 (CH), 129.47 (CH), 126.36 (CH), 91.10 (d, $J = 172$ Hz, CH), 84.32 (CH), 79.88 (CH), 69.67 (d, $J = 23$ Hz, CH_2), 52.25 (CH), 43.55 (CH), 36.93 (d, $J = 75$ Hz, CH_2), 29.36 (CH_2), 28.71 (d, $J = 11$ Hz, CH_2), 28.41 (CH_2).

4.1.44. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-[3-Fluoro-4-(3-(trifluoromethyl)phenoxy)butyl]-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (59). Analogous to the debenzoylation of **4** to alcohol **6**, **58** (310 mg) was treated with K_2CO_3/MeOH to afford **59** (197 mg) in 82% yield.

4.1.45. [3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-[3-Fluoro-4-(3-(trifluoromethyl)phenoxy)butyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (60). Analogous to the protection of alcohol **6** as its THP ether **7**, alcohol **59** (191 mg) protected as its THP ether afford **60** (224 mg) in 95% yield.

4.1.46. [2*RS*,3a*R*,4*R*(3*R*),5*R*,6a*S*]-4-[3-Fluoro-4-(3-(trifluoromethyl)phenoxy)butyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol (61). Analogous to the reduction of lactone **7** to the corresponding lactol, lactone **60** (220 mg) was reduced to lactol **61** (220 mg) in 100% yield.

4.1.47. (5*Z*)-(9*S*,11*R*,15*R*)-15-Fluoro-9-hydroxy-11-(tetrahydropyran-2-yloxy)-16-[3-(trifluoromethyl)phenoxy]-17,18,19,20-tetranor-5-prostenoic acid isopropyl ester (62). Analogous to the conversion of the lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol to the

Wittig+esterification product **8**, lactol **61** (220 mg) was converted to **62** (147 mg) in 52% yield.

4.1.48. (5*Z*)-(9*S*,11*R*,15*R*)-9,11-Dihydroxy-15-fluoro-16-[3-(trifluoromethyl)phenoxy]-17,18,19,20-tetranor-5-prostenoic acid isopropyl ester (33). Analogous to the deprotection of THP ether **8** to the alcohols **9** and **10**, THP ether **62** (146 mg) was deprotected with HCl/isopropanol to afford **33** (92 mg) in 73% yield. ^{13}C NMR (50 MHz, peaks not split by CF_3): δ 173.44 (C), 155.56 (C), 130.04 (CH), 129.77 (CH), 129.09 (CH), 91.44 (d, $J = 172$ Hz, CH), 78.60 (CH), 74.54 (CH), 69.97 (d, $J = 23$ Hz, CH_2), 67.64 (CH), 52.49 (CH), 51.70 (CH), 42.66 (CH_2), 34.01 (CH_2), 30.01 (d, $J = 21$ Hz, CH_2), 28.84 (CH_2), 28.77 (CH_2), 26.70 (d, $J = 9$ Hz, CH_2), 24.89 (CH_2), 21.79 (CH_3). HRMS, m/z calcd for $C_{26}H_{37}O_5F_4$ [(M+H)$^+$], 505.25706; found, 505.25705.

4.1.49. (5*Z*)-(9*S*,11*R*,1*R*)-9,11-Dihydroxy-15-fluoro-16-[3-(trifluoromethyl)phenoxy]-17,18,19,20-tetranor-5-prostenoic acid (32). Analogous to the saponification of isopropyl ester **9** to acid **11**, isopropyl ester **33** (38 mg) was converted to acid **32** (34 mg) in 99% yield. ^{13}C NMR (50 MHz, peaks not split by CF_3): δ 179.25 (C), 158.45 (C), 129.92 (CH), 129.50 (CH), 129.12 (CH), 91.32 (d, $J = 172$ Hz, CH), 78.47 (CH), 74.54 (CH), 69.84 (d, $J = 23$ Hz, CH_2), 52.15 (CH), 51.40 (CH), 42.34 (CH_2), 33.00 (CH_2), 29.80 (d, $J = 21$ Hz, CH_2), 28.66 (CH_2), 26.66 (CH_2), 26.28 (CH_2), 24.37 (CH_2). HRMS, m/z calcd for $C_{23}H_{31}O_5F_4$ [(M+H)$^+$], 463.210604; found, 463.21060.

4.1.50. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-5-Benzoyloxy-4-[4-(3-chlorophenoxy)-3-fluorobutenyl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (63) and [3a*R*,4*R*(2*E*,1*RS*),5*R*,6a*S*]-5-benzoyloxy-4-[4-(3-chlorophenoxy)-1-fluoro-2-buten-1-yl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (64). Analogous to the fluorination of allyl alcohol **2** to a mixture of the S_N2 and S_N2' fluorinated products **4** and **5**, allyl alcohol **49** (2.29 g) was treated with DAST to afford a crude product, which by TLC analysis (1:1 hexane–ethyl acetate eluent) showed a major spot with $R_f = 0.6$, and a minor spot eluting slightly above $R_f = 0.6$ (ratio of major:minor ca. 9:1). The crude was chromatographed on a 23 cm tall × 53 mm diameter silica gel column eluting with 2:1 hexane–ethyl acetate to afford the major spot, which proton and carbon NMR spectral analysis demonstrated to be a mixture of S_N2 fluorination product **63** and one diastereomer of S_N2' fluorination product **64** (1.63 g total, 71% yield). MS: m/z calcd for $C_{24}H_{22}O_5FClNa$ (M+Na)$^+$, 467.103935; found, 467.10391.

4.1.51. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-[4-(3-Chlorophenoxy)-3-fluorobutenyl]-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]-furan-2-one (65) and [3a*R*,4*R*(2*E*,1*RS*),5*R*,6a*S*]-4-[4-(3-chlorophenoxy)-1-fluoro-2-buten-1-yl]-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (66). Analogous to the debenzoylation of **4** to alcohol **6**, the above mixture of **63** and one diastereomer of **64** (1.60 g) was treated with K_2CO_3/MeOH to afford a crude material, which was chromatographed on a 27 cm tall × 53 mm diameter silica gel column, 1:1 → 3:2 ethyl acetate–hexane gradient elution. The first to elute was a 100 mg fraction consisting of one diastereomer of the S_N2' fluorination product **66** (yield = 8%). The second to elute was an 815 mg fraction consisting of the S_N2 fluorination product **65** (yield = 66%), as a mixture of two diastereomers at the fluorinated carbon. ^{13}C NMR (150 MHz): 176.99 (C), 158.93 (C), 134.83 (C), 134.51 (d, $J = 11$ Hz, CH), 130.32 (CH), 126.85 (d, $J = 18$ Hz, CH), 121.53 (CH), 115.02 (CH), 113.14 (CH), 90.39 (d, $J = 172$ Hz, CH), 82.86 (CH), 76.58 (CH), 69.80 (d, $J = 24$ Hz, CH_2), 56.06 (CH), 42.31 (CH), 39.97 (CH_2), 34.52 (CH_2). HRMS, m/z calcd for $C_{17}H_{19}O_4FCl$ [(M+H)$^+$], 341.095537; found, 341.09555.

4.1.52. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-[4-(3-Chlorophenoxy)-3-fluorobutenyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (67). Analogous to the conversion of alcohol **6** to the THP ether **7**, alcohol **65** (810 mg) was converted to its THP ether **67** (930 mg) in 96% yield. HRMS, m/z calcd for $C_{22}H_{26}O_5FClNa$ [(M+Na)$^+$], 447.135470; found, 447.13546.

4.1.53. (5*Z*,13*E*)-(9*S*,11*R*,15*RS*)-16-(3-Chlorophenoxy)-15-fluoro-9-hydroxy-11-(tetrahydropyran-2-yloxy)-17,18,19,20-tetranor-5,13-prostadienoic acid isopropyl ester (68). Analogous to the reduction of lactone **7** to the corresponding lactol, lactone **67** (925 mg) was reduced with DIBAL-H to afford a crude sample of lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-[4-(3-chlorophenoxy)-3-fluorobutenyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol.

Analogous to the Wittig reaction/esterification of the lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol to **8**, the above sample of lactol was converted to **68** (744 mg) in 59% yield (from lactone **67**). HRMS, m/z calcd for $C_{30}H_{42}O_6FClNa$ [(M+Na)$^+$], 575.266163; found, 575.266163.

4.1.54. (5*Z*,13*E*)-(9*S*,11*R*,15*RS*)-16-(3-Chlorophenoxy)-9,11-dihydroxy-15-fluoro-17,18,19,20-tetranor-5,13-prostadienoic acid isopropyl ester (69). Analogous to the deprotection of THP ether **8** to the diols **9** and **10**, the THP ether **68** (734 mg) was treated with HCl/isopropanol to afford **69** (400 mg) in 64% yield. The individual C-15 diastereomers were separated by HPLC in the next step.

4.1.55. (5*Z*,13*E*)-(9*S*,11*R*,15*R*)-16-(Chlorophenoxy)-9,11-dihydroxy-15-fluoro-17,18,19,20-tetranor-5-prostadienoic acid isopropyl ester (35) and (5*Z*,13*E*)-(9*S*,11*R*,15*S*)-16-(3-chlorophenoxy)-9,11-dihydroxy-15-fluoro-17,18,19, 20-tetranor-5-prostadienoic acid isopropyl ester (37) . The above sample of **69** was purified by normal-phase HPLC on a chiral AD column to afford

15α-fluoride **35** (37 mg) and 15β-fluoride **37** (146 mg). Compound **35**: ^{13}C NMR (150 MHz): δ 173.39 (C), 159.05 (C), 137.66 (d, $J = 10$ Hz, CH), 134.87 (C), 130.24 (CH), 129.95 (CH), 128.71 (CH), 125.31 (d, $J = 19$ Hz, CH), 121.44 (CH), 115.06 (CH), 113.12 (CH), 90.74 (d, $J = 171$ Hz, CH), 78.03 (CH), 73.13 (CH), 70.04 (d, $J = 24$ Hz, CH_2), 67.61 (CH), 55.97 (CH), 50.51 (CH), 42.91 (CH_2), 33.93 (CH_2), 26.56 (CH_2), 25.67 (CH_2), 24.78 (CH_2), 21.76 (CH_3). HRMS, m/z calcd for $C_{25}H_{35}O_5FCl$ [$(M+H)^+$], 469.215774; found, 469.21530. Compound **37**: ^{13}C NMR (150 MHz): δ 173.49 (C), 159.09 (C), 137.73 (d, $J = 11$ Hz, CH), 134.89 (C), 130.27 (CH), 130.00 (CH), 128.76 (CH), 125.38 (d, $J = 18$ Hz, CH), 121.47 (CH), 115.12 (CH), 113.17 (CH), 90.82 (d, $J = 172$ Hz, CH), 78.13 (CH), 73.14 (CH), 70.10 (d, $J = 24$ Hz, CH_2), 67.67 (CH), 56.03 (CH), 50.54 (CH), 43.00 (CH_2), 33.99 (CH_2), 26.61 (CH_2), 25.65 (CH_2), 24.83 (CH_2), 21.80 (CH_3). HRMS, m/z calcd for $C_{25}H_{35}O_5F$ [$(M+H)^+$], 469.215774; found, 469.21573.

4.1.56. (5*Z*,13*E*)-(9*S*,11*R*,15*R*)-16-(3-Chlorophenoxy)-9,11-dihydroxy-15-fluoro-17,18,19,20-tetranor-5,13-prostadienoic acid (34) . Analogous to the saponification of ester **9** to acid **11**, isopropyl ester **35** (23 mg) was converted to acid **34** (17 mg) in 80% yield. ^{13}C NMR (150 MHz): δ 178.30 (C), 159.00 (C), 137.64 (d, $J = 8$ Hz, CH), 134.90 (C), 130.33 (CH), 129.81 (CH), 128.98 (CH), 125.58 (d, $J = 20$ Hz, CH), 121.51 (CH), 115.08 (CH), 113.17 (CH), 90.89 (d, $J = 171$ Hz, CH), 77.94 (CH), 73.20 (CH), 70.07 (d, $J = 24$ Hz, CH_2), 55.77 (CH), 50.37 (CH), 42.77 (CH_2), 32.98 (CH_2), 26.38 (CH_2), 25.66 (CH_2), 24.41 (CH_2). HRMS, m/z calcd for $C_{22}H_{28}O_5FClNa$ [$(M+Na)^+$], 449.15128; found 449.150841.

4.1.57. (5*Z*,13*E*)-(9*S*,11*R*,15*S*)-16-(3-Chlorophenoxy)-9,11-dihydroxy-15-fluoro-17,18,19,20-tetranor-5,13-prostadienoic acid (36). Analogous to the saponification of ester **9** to acid **11**, isopropyl ester **37** (78 mg) was converted to acid **36** (53 mg) in 75% yield. ^{13}C NMR (150 MHz): δ 178.30 (C), 159.00 (C), 137.59 (d, $J = 10$ Hz, CH), 134.90 (C), 130.34 (CH), 129.85 (CH), 128.96 (CH), 125.59 (d, $J = 18$ Hz, CH), 121.50 (CH), 115.10 (CH), 113.19 (CH), 90.91 (d, $J = 171$ Hz, CH), 78.01 (CH), 73.20 (CH), 70.08 (d, $J = 26$ Hz, CH_2), 55.77 (CH), 50.35 (CH), 42.82 (CH_2), 33.06 (CH_2), 26.41 (CH_2), 25.62 (CH_2), 24.46 (CH_2). HRMS, m/z calcd for $C_{22}H_{28}O_5FClNa$ [$(M+Na)^+$], 449.15128; found, 449.15127.

4.1.58. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-5-Benzoyloxy-4-[3-hydroxy-4-(3-(trifluoromethyl)phenoxy)-1-butenyl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (70). To a solution of [3a*R*,4*R*(1*E*),5*R*,6a*S*]-5-benzoyloxy-4-[3-oxo-4-(3-(trifluoromethyl)phenoxy)-1-butenyl]-hexahydro-2*H*-cyclopenta-[*b*]furan-2-one[21] (2.30 g, 4.85 mmol), $CeCl_3 \cdot 7H_2O$ (3.00 g, 8.04 mmol), and methanol (35 mL) at 0 °C was added $NaBH_4$ (230 mg, 6.05 mmol) in six portions over 5 min. After 30 min saturated KH_2PO_4 (30 mL) and water (30 mL) were added and the mixture was warmed to room temperature. The solution was extracted with 3:2 ethyl acetate–hexane (3 × 70 mL), dried ($MgSO_4$), filtered, and concentrated to afford crude **70** (2.62 g, >100% nominal yield). HRMS, m/z calcd for $C_{25}H_{23}O_6F_3Na$ [$(M+Na)^+$], 499.133990; found, 499.13400.

4.1.59. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-5-Benzoyloxy-4-[3-fluoro-4-(3-(trifluoromethyl)phenoxy)-1-butenyl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (71). Analogous to the fluorination of allyl alcohol **2** to a mixture of the S_N2 and S_N2' fluorinated products **4** and **5**, the sample of crude **70** from above (2.62 g nominal, 2.31 g assuming 100% yield in previous step) was treated with DAST to afford S_N2 fluorination product **71** as the major component in a mixture with one diastereomer of the S_N2' fluorination product [3a*R*,4*R*(1*RS*,2*E*),5*R*,6a*S*]-5-benzoyloxy-4-[1-fluoro-4-(3-(trifluoromethyl)phenoxy)-2-buten-1-yl]-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (total = 807 mg, 35% yield calculated as **71**). HRMS, m/z calcd for $C_{25}H_{22}O_5F_4Na$, 501.129842; found, 501.12985.

4.1.60. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-[3-Fluoro-4-(3-(trifluoromethyl)phenoxy)-1-butenyl]-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (72). Analogous to the debenzoylation of **4** to alcohol **6**, **71** (contaminated with its S_N2' fluorination product; 802 mg) was treated with K_2CO_3/MeOH to provide a crude product, which was chromatographed on a 15 cm tall × 40 mm diameter silica gel column eluting with a gradient of 1:1 → 3:2 ethyl acetate–hexane to afford pure **72** as a slower-eluting component (369 mg) in 59% yield, as well as a mixture of **72** with a slightly faster-eluting component (101 mg), this mixture containing approximately 10% of the S_N2' fluorination product. MF of **72** = $C_{18}H_{18}O_4F_4$, MW = 374. ES-LRMS, peaks at $m/z = 392$ [$(M+NH_4)^+$, 100%] and 375 [$(M+H)^+$, 30%].

4.1.61. [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-[3-Fluoro-4-(3-(trifluoromethyl)phenoxy)-1-butenyl]-5-tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (73). Analogous to the conversion of alcohol **6** to the THP ether **7**, alcohol **72** (363 mg) was converted to its THP ether **73** (216 mg) in 49% yield. MF of **73** = $C_{23}H_{26}O_5F_4$, MW = 458. ES-LRMS, peaks at $m/z = 476$ [$(M+NH_4)^+$, 100%], 459 [$(M+H)^+$, 10%].

4.1.62. (5*Z*,13*E*)-(9*S*,11*R*,15*RS*)-15-Fluoro-9-hydroxy-11-(tetrahydropyran-2-yloxy)-16-[3-(trifluoromethyl)phenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid isopropyl ester (74). Analogous to the reduction of lactone **7** to the corresponding lactol, lactone **73** (210 mg) was reduced with DIBAL-H to afford the crude lactol [2*RS*,3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-[3-fluoro-4-(3-trifluoromethyl)phenoxy)-1-butenyl]-5-tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol (180 mg) in 85% yield.

Analogous to the Wittig reaction/esterification of the lactol [3a*R*,4*R*(1*E*,3*RS*),5*R*,6a*S*]-4-(3-fluoro-4-phenoxybutenyl)-5-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-ol to **8**, the above lactol (180 mg) was converted to **74** (122 mg) in 53% yield from the lactol and 45% yield from lactone **73**. MF of **74** = $C_{31}H_{42}O_6F_4$, MW = 586. ES-LRMS, peaks at $m/z = 604$ [$(M+NH_4)^+$, 100%], 586 (M^+, 15%).

4.1.63. (5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11-Dihydroxy-15-fluoro-16-[3-(trifluoromethyl)phenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid isopropyl ester (39) and (5*Z*,13*E*)-(9*S*,11*R*,15*S*)-9,11-dihydroxy-15-fluoro-16-[3-(trifluoromethyl)phenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid isopropyl ester (41). Analogous to the deprotection of THP ether **8** to the diols **9** and **10**, THP ether **74** (115 mg) was treated with HCl/isopropanol to afford the diastereomeric mixture (5*Z*,13*E*)-(9*S*,11*R*,15*RS*)-9,11-dihydroxy-15-fluoro-16-[3-(trifluoromethyl)phenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid isopropyl ester (66 mg) in 66% yield. The diastereomers were separated by HPLC on a chiral AD column eluting with 4:1 hexane–isopropanol to afford the 15α-fluoride **39** (8 mg) and the 15β-fluoride **41** (46 mg). Their spectral properties were as follows:

Compound **39**: ^{13}C NMR (150 MHz, peaks not split by CF_3): δ 173.44 (C), 158.47 (C), 137.78 (d, $J = 10$ Hz, CH), 130.07 (CH), 130.06 (CH), 128.72 (CH), 125.20 (d, $J = 20$ Hz, CH), 90.78 (d, $J = 171$ Hz, CH), 118.06 (CH), 78.12 (d, $J = 2$ Hz, CH), 73.23 (CH), 70.11 (d, $J = 25$ Hz, CH_2), 67.68 (CH), 56.10 (CH), 50.60 (CH), 42.93 (CH_2), 33.94 (CH_2), 26.60 (CH_2), 25.73 (CH_2), 24.80 (CH_2), 21.82 (CH_3), 21.80 (CH_3). HRMS, m/z calcd for $C_{26}H_{34}O_5F_4Na$ [$(M+Na)^+$], 525.223746; found, 525.22326.

Compound **41**: ^{13}C NMR (150 MHz, peaks not split by CF_3): δ 173.51 (C), 158.46 (C), 137.88 (d, $J = 10$ Hz, CH), 130.05 (CH), 130.01 (CH), 128.74 (CH), 125.22 (d, $J = 20$ Hz, CH), 118.14 (CH), 90.86 (d, $J = 171$ Hz, CH), 78.14 (d, $J = 2$ Hz, CH), 73.13 (CH), 70.11 (d, $J = 24$ Hz, CH_2), 67.68 (CH), 56.08 (CH), 50.55 (CH), 42.99 (CH_2), 33.95 (CH_2), 26.59 (CH_2), 25.63 (CH_2), 24.81 (CH_2), 21.79 (CH_3), 21.77 (CH_3). HRMS, m/z calcd for $C_{26}H_{34}O_5F_4Na$ [$(M+Na)^+$], 525.223746; found, 525.22375.

4.1.64. (5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11-Dihydroxy-15-fluoro-16-[3-(trifluoromethyl)phenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid (38). Analogous to the saponification of ester **9** to acid **11**, isopropyl **39** (4.5 mg) was converted to acid **38** (3.8 mg) in 93% yield. ^{13}C NMR (150 MHz, peaks not split by CF_3): δ 177.50 (C), 158.46 (C), 137.68 (d, $J = 10$ Hz, CH), 130.09 (CH), 129.81 (CH), 128.94 (CH), 125.37 (d, $J = 18$ Hz, CH), 118.18 (CH), 90.83 (d, $J = 171$ Hz, CH), 78.07 (CH), 73.29 (CH), 70.11 (d, $J = 25$ Hz, CH_2), 55.97 (CH), 50.50 (CH), 42.82 (CH_2), 32.74 (CH_2), 26.36 (CH_2), 25.71 (CH_2), 24.37 (CH_2). HRMS, m/z calcd for $C_{23}H_{29}O_5F_4$ [$(M+H)^+$], 461.195281; found, 461.19528.

4.1.65. (5*Z*,13*E*)-(9*S*,11*R*,15*S*)-9,11-Dihydroxy-15-fluoro-16-[3-(trifluoromethyl)phenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid (40). Analogous to the saponification of ester **9** to acid **11**, isopropyl **41** (20 mg) was converted to acid **40** (16 mg) in 85% yield. ^{13}C NMR (150 MHz, peaks not split by CF_3): δ 178.19 (C), 158.46 (C), 137.72 (d, $J = 10$ Hz, CH), 130.07 (CH), 129.84 (CH), 128.94 (CH), 125.44 (d, $J = 18$ Hz, CH), 118.16 (CH), 90.89 (d, $J = 171$ Hz, CH), 78.05 (CH), 73.23 (CH), 70.09 (d, $J = 24$ Hz, CH_2), 55.86 (CH), 50.40 (CH), 42.81 (CH_2), 32.93 (CH_2), 26.36 (CH_2), 25.61 (CH_2), 24.41 (CH_2). HRMS, m/z calcd for $C_{23}H_{29}O_5F_4$ [$(M+H)^+$], 461.195281; found, 461.19482.

4.2. Relative retention index measurements

The prostaglandin of interest was dissolved in 1/1 v/v pH 3.0 ammonium phosphate buffer/acetonitrile (hereinafter termed 'mobile phase') to provide a concentration of about 15–20 μg/mL. As reference standard, 5 μL of a 10 mg/mL solution of $PGF_{2\alpha}$ isopropyl ester in ethanol was diluted with 3 mL of mobile phase to afford a concentration of 16.7 μg/mL. The prostaglandin of interest dissolved in mobile phase, the reference standard $PGF_{2\alpha}$ isopropyl ester dissolved in mobile phase, or the mobile phase alone as negative control was injected as a 40 μL aliquot onto a Microsorb-MV ODS reverse-phase 5 μM HPLC column, 4.6 mm internal diameter × 15 cm length, eluting with mobile phase at a rate of 1 mL/min, using a UV detector set at $\lambda = 190$ nM. The relative retention index of a test prostaglandin is defined as the retention time of the test prostaglandin divided by that for the reference standard $PGF_{2\alpha}$ isopropyl ester.

4.3. Biology methods

Binding[18a] and functional activation[18b] of prostaglandin acids to the FP receptor, and rabbit conjunctival hyperemia, cat papillary constriction, and monkey IOP effects[3a] of prostaglandin isopropyl esters, were assayed according to the previously published procedures.

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