Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester: Potential Antiglaucoma Agents

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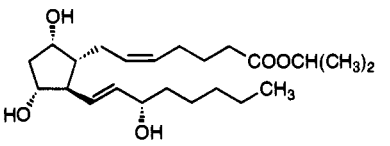
The 15*R* and 15*S* epimers of a series of phenyl substituted analogs of 17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropyl ester [(15*S*)-**3**] have been synthesized. The intraocular pressure (IOP) lowering effects and potential side effects of these novel derivatives have been studied in cats and rabbits. In addition, the effects of selected analogues on IOP have been studied in monkeys. Furthermore, we have hydrolyzed some of the isopropyl esters and assessed the ability of the resulting carboxylic acids to contract the cat iris sphincter muscle in vitro. In general, the 15*S*-derivatives were more active than the 15*R*-epimers. Derivatives substituted with an acetyl group in the benzene ring appeared to have a better side effect profile as compared to (15*S*)-**3**. Furthermore, substitution with an aromatic moiety had a dramatic effect on the activity in that the resulting compounds reduced IOP in cats but had little effect on the pupil diameter. Thus, the activity profile of (15*S*)-**3** may be changed by the introduction of substituents in the benzene ring.

Introduction

It is well-known that prostaglandins reduce the intraocular pressure (IOP) in animals as well as humans.[1,4] Prostaglandins could thus be used therapeutically for the treatment of glaucoma, and the topic has recently been reviewed.[5] Of particular interest is the ability of prostaglandin derivatives to increase uveoscleral outflow of aqueous humor since this is a new principle for reducing IOP.[6–8] Unfortunately most prostaglandins such as $PGF_{2\alpha}$ isopropyl ester (**1**), in addition to reducing IOP, also cause irritation and conjunctival hyperemia, thus limiting their therapeutic potential.[9–11] The narrow therapeutic index of **1** has provided impetus for the synthesis and pharmacological characterization of prostaglandin analogues with better separation between ocular side effects and the IOP-lowering effect. These efforts have resulted in the identification of PhXA41 (Latanoprost; (15*R*)-**2**)[12,13] as a potent and selective potential antiglaucoma agent.[14] In humans, (15*R*)-**2** has been reported to be efficacious in ameliorating the increased IOP in ocular hypertension, and open-angle glaucoma.[5] Furthermore, the side-effect profile of (15*R*)-**2** appears to be acceptable, and the separation between the ability to lower IOP and irritation as well as conjunctival hyperemia is much larger in (15*R*)-**2** than in **1**.

In a preliminary communication,[15] we described the facile syntheses of some phenyl-substituted analogs of the potent IOP-lowering agent (15*S*)-**3**.[12,13] We now present a full and extended report of that study. A number of substituents have been introduced in the phenyl group of 15*S*- and 15*R*-epimers related to **3**. The IOP reducing effect and side effects of these new derivatives have been studied in cats and rabbits (Tables 1 and 2). In addition, the effects of selected analogs on IOP in the eye of monkeys have been assessed (Table 3) and the ability of some hydrolyzed esters to contract the cat iris sphincter muscle has been studied in vitro (Table 4).



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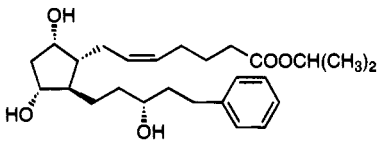
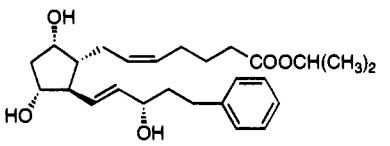


(15*R*)-**2**



(15*S*)-**3**

Chemistry

Aryl halides may be converted into a variety of derivatives by palladium-catalyzed cross couplings, reactions which do not require protective groups and which do not normally affect existing stereochemistry. Since we aimed to prepare an array of derivatives, the stereochemically well-defined 3- and 4-bromophenyl derivatives (15*S*)- and (15*R*)-**11** were identified as key intermediates in the present study. By use of the synthetic sequence described in Scheme 1[15] we prepared gram amounts of the required bromides. The assignment of the stereochemistry at C15 was made on the basis of the outcome of the stereoselective Li selectride[16] reduction of the C15 carbonyl in related systems which predominantly forms the 15*S*-epimer.[17] This assignment is also consistent with the observation that the natural prostaglandins are the less polar epimers.[18]

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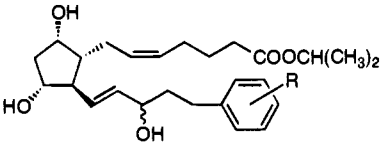
Table 1. Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester: Ocular Effects in the Cat



compd	R	dose (μg/eye)	I_{max}[a] (mmHg)	I_{ABC}[b]	P_{max}[c] (mm)	P_{ABC}[d]	irr[e] (arbitrary units)
(15*S*)-**3**	H	1.0	2.7 ± 1.0*	36.9 ± 12.0*	−9.7 ± 0.3***	−126.3 ± 6.3***	0
(15*R*)-**3**	H	1.0	−0.5 ± 0.2	0.3 ± 4.8	−5.7 ± 0.6***	−50.5 ± 7.8**	0
(15*S*)-**11a**	3-Br	1.0	−1.0 ± 0.5	−12.9 ± 6.4	−6.3 ± 0.4***	−99.3 ± 6.8***	0.2 ± 0.2
		3.0	−2.7 ± 1.1	−42.5 ± 16.8	−6.8 ± 0.2***	−125.0 ± 4.1***	0.3 ± 0.2
		10.0	−3.3 ± 0.7*	−49.0 ± 13.5*	−6.7 ± 0.6***	−138.0 ± 7.6***	0.2 ± 0.1
(15*R*)-**11a**	3-Br	1.0	1.2 ± 0.2***	0.2 ± 12.2	−3.8 ± 0.5***	−50.3 ± 8.6**	0
		3.0	−2.0 ± 0.9	−6.2 ± 6.4	−5.3 ± 0.8***	−71.0 ± 8.1***	0
(15*S*)-**11b**	4-Br	1.0	0.3 ± 0.2	3.4 ± 8.0	−1.5 ± 0.2**	−18.1 ± 2.4***	0
		10.0	−3.0 ± 0.9*	−25.0 ± 9.4*	−6.0 ± 0.4***	−80.0 ± 5.6***	0.3 ± 0.1
(15*R*)-**11b**	4-Br	1.0	−1.0 ± 0.7	−14.0 ± 9.0	−2.2 ± 0.7*	−27.0 ± 6.9*	0.5 ± 0.4
		3.0	−2.0 ± 0.3**	−17.0 ± 5.7*	−0.7 ± 0.6	−2.2 ± 4.0	0.2 ± 0.2
		10.0	−2.0 ± 0.4*	−10.0 ± 6.4	−2.3 ± 0.4**	−23.0 ± 3.7**	0
(15*S*)-**12a**	3-Me	1.0	−1.0 ± 0.9	−17.0 ± 15.7	−6.8 ± 0.8**	−85.0 ± 11.5**	0.3 ± 0.2
		3.0	1.2 ± 1.0	8.0 ± 10.4	−8.3 ± 0.3***	−122.0 ± 9.0***	0.1 ± 0.1
		10.0	2.3 ± 1.4	14.1 ± 16.2	−8.8 ± 0.7***	−149.0 ± 12.0***	0
(15*R*)-**12a**	3-Me	1.0	−0.3 ± 0.6	−1.8 ± 6.8	−1.5 ± 0.3**	−13.3 ± 4.3*	0.1 ± 0.1
(15*S*)-**12b**	4-Me	1.0	−1.0 ± 1.1	−4.3 ± 11.7	−3.5 ± 0.6**	−46.0 ± 10.1**	0.2 ± 0.1
		3.0	−1.3 ± 0.7	−28.0 ± 10.7*	−6.0 ± 0.5***	−73.0 ± 7.3**	0
(15*R*)-**12b**	4-Me	3.0	−1.8 ± 0.9	−10.8 ± 10.3	−0.2 ± 0.2	−0.2 ± 0.3	0
(15*S*)-**13a**	3-COMe	1.0	0.7 ± 1.5	7.1 ± 18.7	−1.8 ± 0.3**	−30.0 ± 7.8*	1.3 ± 0.3
(15*R*)-**13a**	3-COMe	1.0	−4.0 ± 1.8	−43.3 ± 24.3	−0.6 ± 0.3	1.2 ± 2.2	0.3 ± 0.1
		3.0	−2.6 ± 0.7**	−23.8 ± 2.9***	−0.7 ± 0.3*	−1.4 ± 0.6	0.1 ± 0.1
(15*S*)-**13b**	4-COMe	1.0	−0.3 ± 0.2	−4.3 ± 3.7	0.2 ± 0.2	1.4 ± 1.4	0
(15*R*)-**13b**	4-COMe	1.0	−1.8 ± 1.7	−17.9 ± 8.5	−0.2 ± 0.2	0.2 ± 2.4	0
(15*S*)-**14a**	3-Ph	1.0	−4.0 ± 0.8**	−30.0 ± 7.4*	−0.3 ± 0.3	2.3 ± 5.8	0.1 ± 0.1
(15*R*)-**14a**	3-Ph	1.0	−1.5 ± 0.4*	−23.5 ± 13.0	0.5 ± 0.2	6.5 ± 3.5	0
(15*S*)-**14b**	4-Ph	1.0	−1.0 ± 0.8	−10.1 ± 6.2	−1.5 ± 0.4*	−18.3 ± 4.7*	0.8 ± 0.3
		3.0	−6.0 ± 0.8***	−99.3 ± 10.9***	−0.8 ± 0.4	−4.9 ± 1.8*	1.6 ± 0.2
(15*R*)-**14b**	4-Ph	1.0	−1.0 ± 0.4*	−8.3 ± 6.4	0.5 ± 0.2	1.8 ± 0.8	0
		10.0	−0.3 ± 0.3	−2.0 ± 4.0	−0.8 ± 0.3*	−3.8 ± 2.3	0.4 ± 0.1
(15*S*)-**15a**	3-(2-furanyl)	3.0	0.8 ± 0.5	9.8 ± 12.9	−0.3 ± 0.6	−2.5 ± 3.0	0.1 ± 0.1
(15*R*)-**15a**	3-(2-furanyl)	3.0	−1.2 ± 0.7	−8.0 ± 6.7	−0.3 ± 0.2	−5.7 ± 2.6	0.4 ± 0.2
(15*S*)-**15b**	4-(2-furanyl)	3.0	−5.0 ± 0.7***	−76.1 ± 20.2**	−0.6 ± 0.5	−6.0 ± 6.1	0.6 ± 0.3
(15*R*)-**15b**	4-(2-furanyl)	3.0	2.5 ± 2.4	−25.8 ± 31.6	−1.5 ± 0.4*	−10.6 ± 2.7*	0.2 ± 0.2
(15*S*)-**16a**	3-(3-furanyl)	3.0	−3.0 ± 1.8	−24.4 ± 23.3	−1.3 ± 0.6	−9.3 ± 3.3*	0.5 ± 0.4
(15*R*)-**16a**	3-(3-furanyl)	3.0	−3.0 ± 1.7	−16.3 ± 28.3	−1.3 ± 0.6	−13.0 ± 6.2	0
(15*S*)-**16b**	4-(3-furanyl)	3.0	−3.0 ± 0.8*	−50.1 ± 13.2*	−0.3 ± 0.2	−1.3 ± 1.1	0.3 ± 0.1
(15*R*)-**16b**	4-(3-furanyl)	3.0	−3.4 ± 1.5	−11.0 ± 23.1	−0.6 ± 0.4	−2.1 ± 5.2	0.4 ± 0.1
(15*S*)-**17a**	3-(2-thienyl)	1.0	−3.0 ± 1.0*	−40.0 ± 14.8*	−1.5 ± 0.3**	−9.2 ± 4.3	0.1 ± 0.1
		3.0	−1.2 ± 0.5	−10.3 ± 7.3	−3.5 ± 0.5***	−28.0 ± 7.8*	0.3 ± 0.2
(15*R*)-**17a**	3-(2-thienyl)	1.0	2.2 ± 0.7*	12.8 ± 15.5	−1.3 ± 0.4*	−12.4 ± 2.9**	0.3 ± 0.3
(15*S*)-**17b**	4-(2-thienyl)	1.0	−4.2 ± 1.4*	−84.0 ± 19.6**	−0.9 ± 0.3*	−2.2 ± 4.5	0.4 ± 0.2
(15*R*)-**17b**	4-(2-thienyl)	3.0	−1.3 ± 1.1	4.2 ± 23.7	0	0	0.2 ± 0.1
(15*S*)-**18a**	3-(3-thienyl)	1.0	−1.1 ± 1.1	−21.0 ± 9.4	−1.0 ± 0.2**	−1.7 ± 1.8	0.1 ± 0.1
(15*R*)-**18a**	3-(3-thienyl)	1.0	1.7 ± 1.4	16.0 ± 14.5	−1.0 ± 0.3*	−14.0 ± 4.5*	0.1 ± 0.1
(15*S*)-**18b**	4-(3-thienyl)	1.0	−4.0 ± 0.6**	−63.2 ± 14.1**	−1.0 ± 0	−3.3 ± 1.4	0.2 ± 0.1
		3.0	−5.0 ± 0.4***	−66.0 ± 8.4***	−1.2 ± 0.2***	−9.2 ± 2.4*	0.6 ± 0.2
(15*R*)-**18b**	4-(3-thienyl)	1.0	−0.3 ± 0.3	−3.1 ± 6.1	−0.7 ± 0.2*	−1.8 ± 2.6	0

[a] The maximal difference in IOP between treated and control eyes. [b] The mean area between curves for IOP measured in treated and control eyes, compare Figure 2. [c] The maximal difference in pupil diameter between treated and control eyes. [d] The mean area between curves for measurements of pupil diameter in treated and control eyes according to Figure 2. [e] The mean ocular irritation in the treated eyes. An arbitrary scale from 0 to 3 was used, 0 indicating absence of irritation and 3 complete closure of the lids. Statistics: matched pair *t* test *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ ($n = 6$).

Palladium-catalyzed couplings with trimethyltin[19] or with the appropriate arylboronic acids[20] afforded the desired methyl- or aryl-substituted derivatives, respectively. In addition, an acetyl group was introduced by a Heck reaction using butyl vinyl ether as the olefin[21] followed by hydrolysis of the resulting enol ether (Scheme 2).

In analogy with the strategy described above, we also prepared the *o*-halophenyl derivatives as precursors of the corresponding aryl-, methyl-, and acetyl-substituted derivatives. However, attempts to perform the palladium-catalyzed couplings with *ortho*-substituted substrates consistently produced major products resulting from intramolecular cyclizations.[22]

A series of carboxylic acids were prepared by hydrolysis of the corresponding isopropyl esters for in vitro studies (see Table 4).

The compounds tested were purified to homogeneity by preparative HPLC. Physical data are presented in the Experimental Section.

Pharmacological Results and Discussion

The compounds were used as isopropyl esters in the in vivo experiments, and they were tested for IOP-

Table 2. Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester: Ability To Induce Hyperemia in the Rabbit

compd	dose (μg/eye)	H_{max}[a]	H_{ABC}[b]
(15*S*)-**3**	0.5	1.5 ± 0.3***	−4.0 ± 0.5**
(15*R*)-**3**	0.5	1.7 ± 0.2***	2.9 ± 0.6*
(15*S*)-**11a**	0.5	1.5 ± 0.2***	4.8 ± 0.6***
(15*R*)-**11a**	0.5	1.2 ± 0.2***	2.0 ± 0.3***
(15*S*)-**11b**	0.1	1.1 ± 0.2**	2.2 ± 0.4**
	0.5	0.5 ± 0.2*	1.2 ± 0.6
(15*R*)-**11b**	0.1	0.2 ± 0.2	0.3 ± 0.4
	0.5	0.7 ± 0.2*	0.6 ± 0.7
(15*S*)-**12a**	0.5	1.6 ± 0.2***	4.9 ± 1.0**
(15*R*)-**12a**	0.5	0.2 ± 0.2	−0.1 ± 0.4
(15*S*)-**12b**	0.5	1.5 ± 0.3**	4.4 ± 1.1**
(15*R*)-**12b**	0.5	0.2 ± 0.2	−0.2 ± 0.3
(15*S*)-**13a**	0.5	−0.1 ± 0.1	0.0 ± 0.5
(15*R*)-**13a**	0.5	−0.3 ± 0.2	−0.7 ± 0.6
(15*S*)-**13b**	0.5	−0.2 ± 0.2	−0.5 ± 0.5
(15*R*)-**13b**	0.5	−0.2 ± 0.1	−0.3 ± 0.3
(15*S*)-**14a**	0.5	0.9 ± 0.2**	1.9 ± 0.5*
(15*R*)-**14a**	0.5	0.7 ± 0.1**	2.2 ± 0.6*
(15*S*)-**14b**	0.1	0.2 ± 0.2	0.2 ± 0.5
	0.5	0.4 ± 0.2*	1.2 ± 1.0
(15*R*)-**14b**	0.5	0.5 ± 0.2*	0.7 ± 0.5
(15*S*)-**15a**	0.5	0.3 ± 0.1*	0.3 ± 0.3
(15*R*)-**15a**	0.5	0.3 ± 0.1	0.4 ± 0.3
(15*S*)-**15b**	0.5	−0.1 ± 0.2	−0.2 ± 0.4
(15*R*)-**15b**	0.5	0.5 ± 0.2*	1.0 ± 0.3*
(15*S*)-**16a**	0.5	0.5 ± 0.2*	1.3 ± 0.6
(15*R*)-**16a**	0.5	0.5 ± 0.1*	1.6 ± 0.5*
(15*S*)-**16b**	0.5	0.2 ± 0.2	0.3 ± 0.5
(15*R*)-**16b**	0.5	−0.3 ± 0.1	−0.7 ± 0.5
(15*S*)-**17a**	0.5	0.9 ± 0.2*	2.6 ± 0.8*
(15*R*)-**17a**	0.5	0.2 ± 0.1	0.1 ± 0.2
(15*S*)-**17b**	0.5	0.3 ± 0.2	0.0 ± 0.4
(15*R*)-**17b**	0.5	0.3 ± 0.3	0.3 ± 0.1
(15*S*)-**18a**	0.5	1.3 ± 0.1***	2.9 ± 0.4***
(15*R*)-**18a**	0.5	−0.3 ± 0.3	−0.8 ± 0.6
(15*S*)-**18b**	0.5	0.3 ± 0.2	0.8 ± 0.2*
(15*R*)-**18b**	0.5	−0.2 ± 0.2	−0.1 ± 0.5

[a] The maximal difference in hyperemia between treated and control eyes. A semiquantitative evaluation using an arbitrary scale of 11 steps from 0 to 5 (0 = totally pale conjunctiva, 1 = vessels normal, 2 = mild hyperemia, 3 = moderate hyperemia, 4 = severe hyperemia, 5 = severe hyperemia with chemosis). [b] The mean area between curves for hyperemia measurements in treated and control eyes, compare Figure 2. Statistics: matched pair *t* test *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ ($n = 6$).

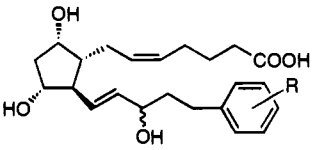
Table 3. Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester: Ocular Effects in the Monkey

compd	dose (μg/eye)	I_{max}[a] (mmHg)	I_{ABC}[b]
(15*S*)-**3**	1.0	−3.3 ± 0.8**	−5.8 ± 1.4**
	3.0	−2.9 ± 1.0	−5.9 ± 3.7
(15*S*)-**11a**	3.0	−2.0 ± 1.0	−6.5 ± 3.7
(15*R*)-**11a**	3.0	−1.4 ± 0.5	−6.0 ± 2.3*
(15*S*)-**11b**	3.0	−1.0 ± 0.7	−1.3 ± 2.8
(15*S*)-**12a**	1.0	−2.5 ± 0.7*	−3.6 ± 3.0
	3.0	−0.6 ± 0.2*	−0.1 ± 1.0
(15*S*)-**12b**	3.0	−1.6 ± 0.4*	−3.8 ± 1.6
	10.0	−1.5 ± 0.6	−3.5 ± 2.7
(15*S*)-**13a**	3.0	−2.8 ± 0.8*	−12.3 ± 1.9**
(15*S*)-**13b**	3.0	−2.3 ± 0.8*	−10.0 ± 3.1*
(15*S*)-**14b**	3.0	0.8 ± 0.2*	3.0 ± 0.8*
	10.0	1.4 ± 0.3**	6.1 ± 1.5*
(15*S*)-**15b**	3.0	0.3 ± 0.2	0.5 ± 0.8
(15*S*)-**17b**	3.0	1.5 ± 0.6*	6.5 ± 2.3*

[a] The maximal difference in IOP between treated and control eyes. [b] The mean area between curves for IOP measured in treated and control eyes, compare Figure 2. Statistics: matched pair *t* test *$p < 0.05$; **$p < 0.01$ ($n = 6$).

reducing effect, miotic (pupillary constrictive) effect, ocular irritative effect, and conjunctival hyperemic effect as recently described.[12] The effect on IOP and pupil diameter as well as the ocular irritative effect were tested in cats, and the effect on conjunctival hyperemia was tested in rabbits (Tables 1 and 2). In addition selected analogues were tested for IOP-reducing effect in cynomolgus monkeys (Table 3). The effect of some of the analogues on FP receptors was investigated using isolated cat iris sphincter muscle in organ baths (Table 4 and Figure 1). This tissue expresses predominantly FP receptors.[23] The analogues for these experiments were hydrolyzed and tested as carboxylic acids.

Table 4. Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$: Ability To Contract Cat Iris Sphincter Muscle in Vitro



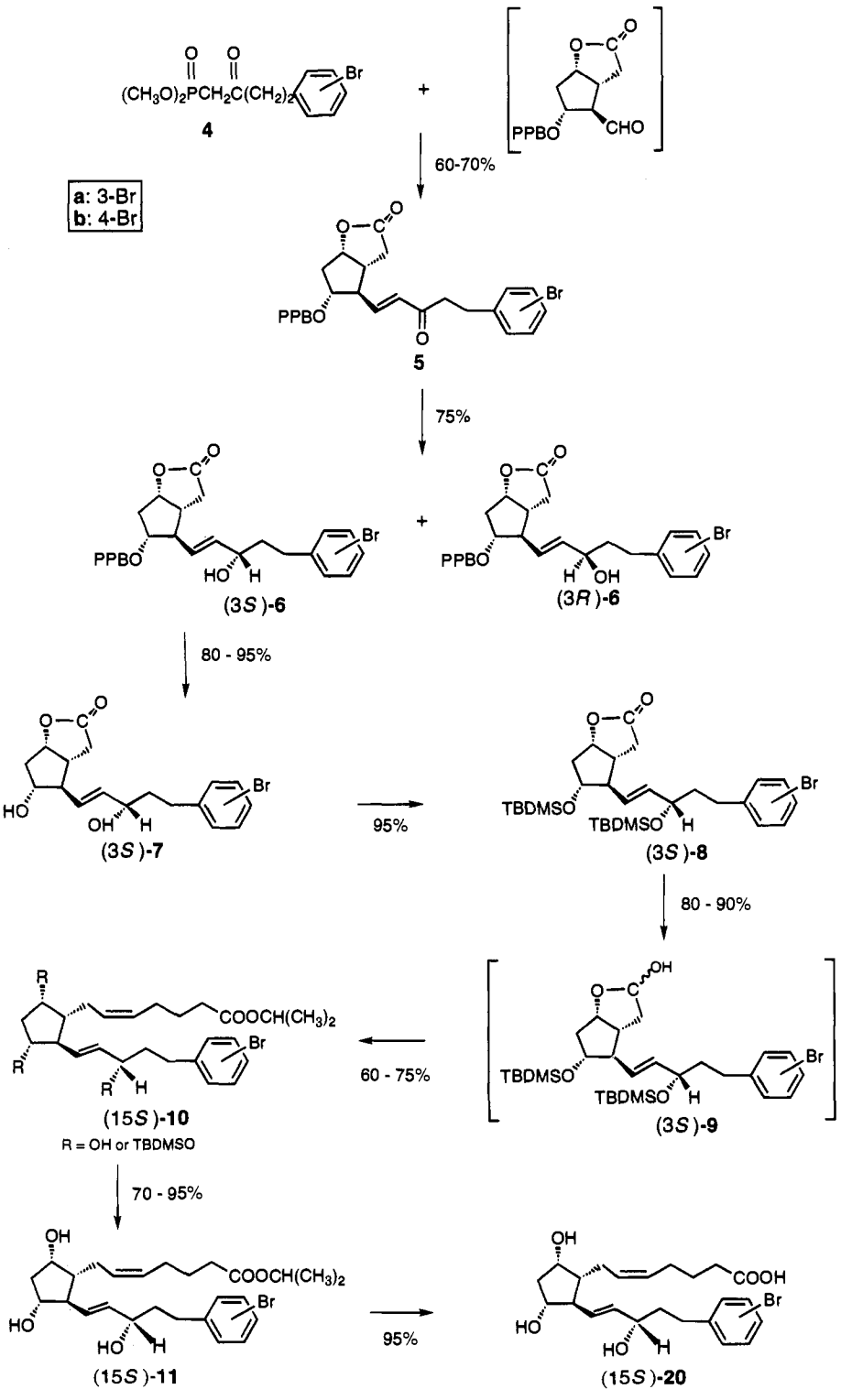
compd	R	EC_{50}[a,b] (M)
17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$		$7.1 \times 10^{-10} \pm 3 \times 10^{-11}$
(15*S*)-**20a**	3-Br	$4.9 \times 10^{-9} \pm 6 \times 10^{-10}$
(15*R*)-**20a**	3-Br	$3.3 \times 10^{-8} \pm 4 \times 10^{-9}$
(15*S*)-**20b**	4-Br	$3.5 \times 10^{-8} \pm 2 \times 10^{-9}$
(15*R*)-**20b**	4-Br	$2.1 \times 10^{-6} \pm 7 \times 10^{-8}$
(15*S*)-**21a**	3-Me	$4.3 \times 10^{-9} \pm 2 \times 10^{-10}$
(15*S*)-**21b**	4-Me	$4.0 \times 10^{-8} \pm 3 \times 10^{-9}$
(15*S*)-**22b**	4-Ph	$1.9 \times 10^{-6} \pm 2 \times 10^{-7}$
(15*R*)-**22b**	4-Ph	$1.0 \times 10^{-4} \pm 2 \times 10^{-6}$

[a] Concentration giving a half-maximal contraction of the cat iris sphincter muscle. [b] The EC_{50} value of $PGF_{2\alpha}$ is 6.7×10^{-9} M.

In humans, **1** is a potent ocular hypotensive, but it also causes side effects such as irritation and conjunctival hyperemia.[5] In cats, **1** also constricts the pupil. Substitution of carbons 18−20 of $PGF_{2\alpha}$ with a ring structure, e.g., a phenyl ring, has been shown to improve the side-effect profile in the eye.[12,13] Whereas (15*S*)-**3** is a poor ocular hypotensive agent in cats, it effectively reduces IOP in primates.[12,13] This compound also exhibits a marked and dose-dependent miotic effect in the cat. For comparison, the effects of the (15*S*)-**3** in the different test systems have been included in Tables 1−4. Both the 15*S* and 15*R* epimers of all compounds have been tested. In general, the 15*R* epimers exert a weaker biological activity than the 15*S* epimers (Tables 1−4).

Introduction of bromine [(15*S*)- and (15*R*)-**11a**)] or a methyl group [(15*S*)- and (15*R*)-**12a**)] into the *meta* position of the benzene ring resulted in compounds which produced a somewhat decreased miotic response in the cat (Table 1) but gave similar effects on the conjunctival hyperemic response as compared to the reference compounds [(15*S*)-**3** and (15*R*)-**3**] (Tables 1 and 2). These bromo- and methyl-substituted compounds had no or weak IOP-reducing effects in cats but reduced IOP in monkeys (Table 3). Shifting the bromo [(15*S*)- and (15*R*)-**11b**)] or methyl substituent [(15*S*)- and (15*R*)-**12b**)] to the *para* position in the benzene ring further reduced the activity of the compounds (Tables 1−4). However, the 4-methyl-substituted compound still caused some IOP reduction in monkeys (Table 3) as well as some conjunctival hyperemia (Table 2). Thus, it appears that bromo or methyl substitution in the *meta* or *para* position of the benzene ring tends to reduce the activity of (15*S*)-**3** and that substitution in the *para* position seems to cause a larger loss in biologic activity than *meta* substitution.

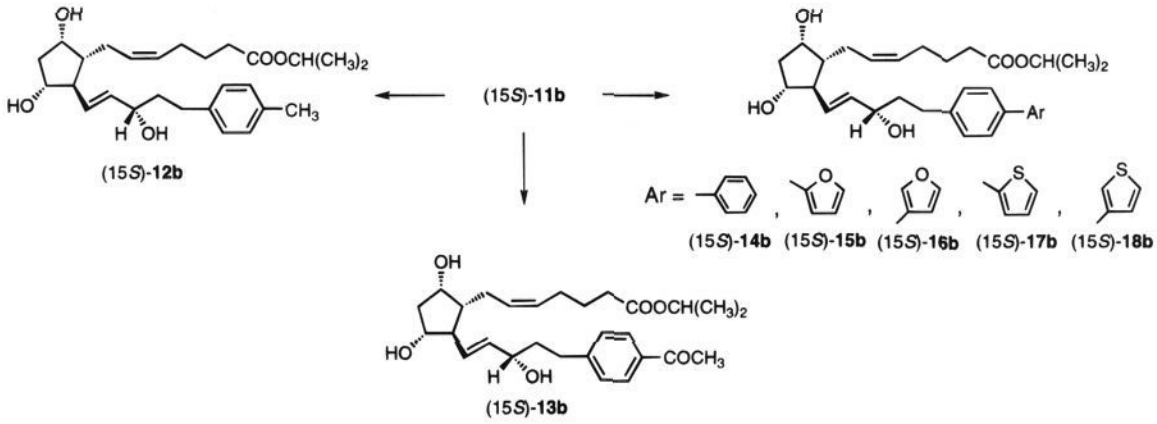
Scheme 1



Introduction of an acetyl group in the *meta* [(15*S*)- and (15*R*)-**13a**] or *para* position [(15*S*)- and (15*R*)-**13b**] of the benzene ring dramatically reduced the miotic effect in cats (Table 1). Furthermore, these analogs had no or only a weak IOP-reducing effect in cats, but (15*S*)-**13a** and (15*S*)-**13b** significantly reduced IOP in monkeys (Table 3). Interestingly, these acetyl-substituted compounds caused no conjunctival hyperemia or ocular irritation. Thus, *meta* or *para* substitution in the benzene ring with an acetyl group appears to reduce the activity on FP receptors as indicated by the weak constrictive effect on the pupil in cats. These analogs may have an improved side-effect profile compared to that of (15*S*)-**3**.

Attachment of a phenyl, furanyl, or thienyl ring to the benzene ring resulted in a most unexpected feature, as these analogues lost practically all of their miotic effect but retained some of the IOP-reducing effect of **1** in the cat. As discussed above, **1** causes miosis and reduces IOP in cats, whereas (15*S*)-**3** causes miosis but has no or a very weak effect on IOP in cats. However, the compounds with phenyl, furanyl, or thienyl groups attached to the benzene ring caused no or little miosis, but several of them reduced IOP in cats. Furthermore,

Scheme 2



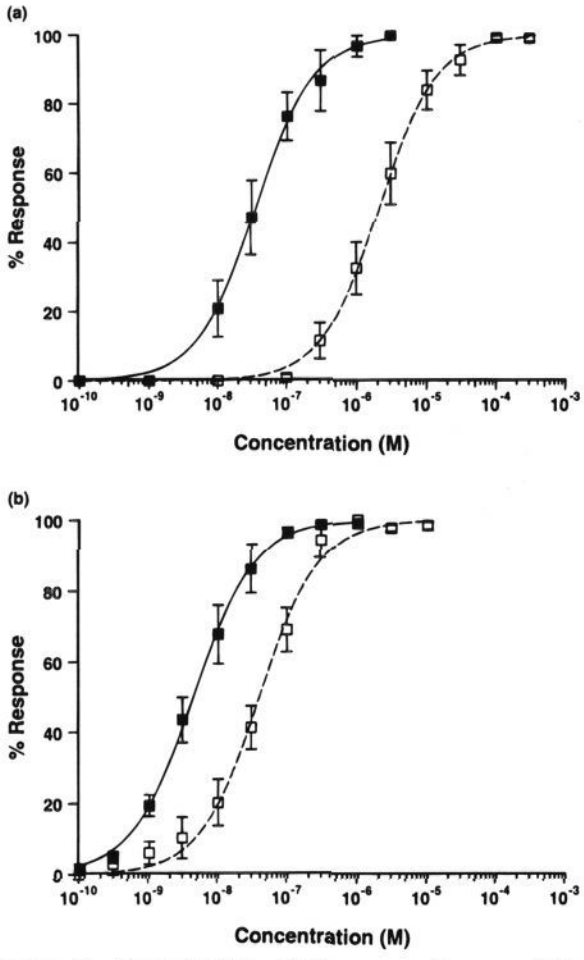


Figure 1. Concentration–effect curves after cumulative dosing of (a) (15*S*)-**20b** (solid line) and (15*R*)-**20b** (dotted line, and (b) (15*S*)-**21a** (solid line) and (15*S*)-**21b** (dotted line) on cat iridial sphincter muscles in vitro. Each point represents the mean value obtained from four different preparations, and bars indicate SEM. The curves were fitted to the data using the logistic sigmoid function. The estimated EC_{50} values are shown in Table 4.

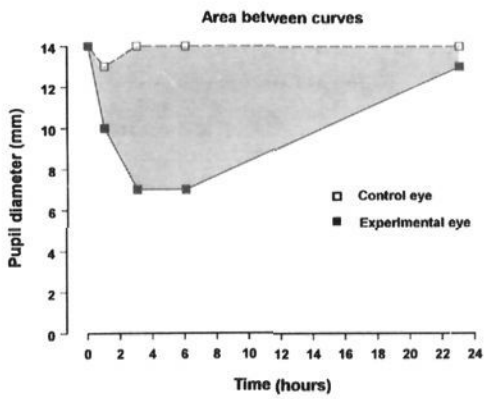


Figure 2. The effect on pupil diameter after single topical treatment (1 μg) in one eye and vehicle solution in the contralateral eye. The duration of the response was estimated from the area between curves (ABC, shaded area). This area was calculated as the area under the response versus time curve for the experimental eye (filled squares, solid line) minus the area under the corresponding response curve for the contralateral control eye (open squares, broken line) for each animal.

most of these analogues caused no or minimal irritation and only mild conjunctival hyperemia (Tables 1 and 2).

It seems that *para* substitution in the benzene ring with an aromatic moiety is particularly advantageous for obtaining IOP-reducing effect in cats. Thus, 4-phenyl [(15*S*)-**14b**), 4-(2-furanyl) [(15*S*)-**15b**)], 4-(3-furanyl) [(15*S*)-**16b**)], 4-(2-thienyl) [(15*S*)-**17b**)], and 4-(3-thienyl) [(15*S*)-**18b**)] substitution significantly reduced IOP in cats with 3–6 mmHg. In general, these compounds exerted very little miotic or irritant effects. However, the 4-phenyl-substituted compound seemed somewhat irritating. Furthermore, these compounds induced no significant conjunctival hyperemia (Table 2). It would appear that there is no major difference between analogues in which furanyl or thienyl groups are attached to the benzene ring via *C-2* or *C-3*, respectively (Table 1). Although these analogues of **1** significantly reduced IOP in cats, they did not appear to reduce IOP in monkeys (Table 3). The reason for this remains unknown until the exact prostanoid receptor profiles of these new analogues have been determined. Our results thus indicate that the receptor profile of compounds carrying an aromatic *para* substituent on the benzene ring is changed as compared to that of (15*S*)-**3**. This is unexpected since it is well-known that the receptor profile of naturally occurring prostaglandins is predominantly determined by the substituents in the cyclopentane ring.

The effect of some of the analogues on the isolated cat iris sphincter muscle, a tissue expressing predominantly FP receptors, is presented in Table 4 and Figure 1. Three clear-cut features can be observed: Firstly, all 15*R*-epimers were less potent and exhibited higher

EC_{50} values than the 15*S*-epimers, usually 1–2 orders of magnitude higher. Secondly, any substitution in the benzene ring of (15*S*)-**3** resulted in a compound with higher EC_{50} value than that of the original compound. Thirdly, the *p*-phenyl-substituted derivatives [(15*S*)- and (15*R*)-**22b**)] and possibly the other corresponding ring-substituted analogues exhibit markedly increased EC_{50} values, which would explain the absence of miosis in vivo.

In conclusion, the in vivo pharmacology data indicate that the receptor profile of (15*S*)-**3** can be changed substantially by appropriate substitutions in the benzene ring. In particular the acetyl-substituted derivatives may be important leads in this respect since they seem to cause minimal irritation and conjunctival hyperemia with retained IOP-reducing effect in primates.

Experimental Section

Chemistry. General Comments. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^1H and ^{13}C NMR spectra were recorded on a JEOL EX270 at 270.05 and 67.8 MHz, respectively, or a Varian UNITY 500 spectrometer at 499.84 and 125.70 MHz, respectively. The NMR spectra were referenced to internal tetramethylsilane and recorded in $CDCl_3$, unless otherwise noted. ^{31}P NMR spectra were recorded on a JEOL EX270 spectrometer and referenced to external phosphoric acid. All spectra were in accordance with assigned structures. Optical rotations were obtained on a Perkin-Elmer Model 241 polarimeter. Flash chromatography was carried out using Merck silica gel 60, 200–400 mesh. Thin-layer chromatography (TLC) was carried out using precoated silica gel F-254 plates (thickness 0.25 mm). Chromatographic spots were visualized by UV and/or spraying with an aqueous solution of 3% copper acetate and 15% phosphoric acid, or an aqueous solution of 2% $KMnO_4$, followed by heating. Preparative HPLC (straight phase) was performed with a Gilson liquid chromatograph (column, silica gel, 21.4 × 250 mm, stainless steel; mobile phase, 5–10% ethanol in *n*-hexane; flow rate, 15 mL/min; detection, 210 nm). Analytical HPLC (reversed phase) was performed with a Shimadzu liquid chromatograph (column, Nucleosil C_{18}, 7 μm, 250 × 4 mm, stainless steel; thermostated to 60 °C; mobile phase, phosphate buffer (pH 2.5)/acetonitrile gradient; flow rate, 1.8 mL/min; detection, 200 nm). Analytical HPLC (straight phase) were performed with a Merck-Hitachi liquid chromatograph (column, silica gel Waters Radial-Pak, 80 × 10 mm; mobile phase, 6% ethanol in *n*-hexane; flow rate, 1.2 mL/min; detection, 210 nm). Elemental analyses were performed by Mikro kemi AB, Uppsala, and were within 0.4% of the calculated values.

Dimethyl [4-(4-Bromophenyl)-2-oxobutyl]phosphonate (4b). Dimethyl (2-oxopropyl)phosphonate (25.0 g, 150 mmol) was added to a stirred suspension of sodium hydride (80%, 4.7 g, 158 mmol) (washed with *n*-pentane to remove mineral oil) in THF (200 mL) under nitrogen.[24] The mixture was mechanically stirred for 1 h at room temperature and then cooled to 0 °C. *n*-Butyllithium (2.5 M in *n*-hexane, 72 mL, 181 mmol) was added dropwise, and the mixture was stirred for 30 min at 0 °C. *p*-Bromobenzyl bromide (41.4 g, 166 mmol) was dissolved in THF (100 mL) and added dropwise to the reaction mixture. After being stirred at room temperature for 2 h, the reaction mixture was poured into ice water and acidified with 1 M aqueous HCl to pH 4. The product was extracted with EtOAc (100 mL). The organic layer was washed with brine (2 × 300 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (EtOAc/acetone, 1:1), which furnished 21.1 g (42%) of **4b** as a yellow oil: TLC R_f = 0.38 (EtOAc/acetone, 1:1); ^1H NMR δ 2.90 (4H, m, $COCH_2CH_2Ar$), 2.94 and 3.20 (2H, two s, $POCH_2$), 3.73 and 3.77 (6H, two s, CH_3O), 7.0–7.4 (4H, two d, Ar); ^{13}C NMR δ 28.7 (s, CH_2CH_2Ar), 40.2 and 42.8 (d, $POCH_2CO$), 45.08 (s, CH_2CH_2Ar), 53.01 and 53.10 (d, CH_3O), 119.86, 130.14 (2C), 131.43 (2C), 139.49 (Ar), 200.34 and 200.45 (d, CH_2COCH_2); ^{31}P NMR δ 22.44. Anal. ($C_{12}H_{16}BrO_4P$) C, H.

Dimethyl [4-(3-Bromophenyl)-2-oxobutyl]phosphonate (4a). Compound **4a** was prepared from dimethyl (2-oxopropyl)phosphonate and *m*-bromobenzyl bromide by the above method in 52% yield as a yellow oil: TLC R_f = 0.40 (EtOAc/acetone, 1:1); ^1H NMR δ 2.91 (4H, m, $COCH_2CH_2Ar$), 3.04 and 3.13 (2H, two s, $POCH_2$), 3.73 and 3.77 (6H, two s, CH_3O), 7.1–7.4 (4H, m, Ar); ^{13}C NMR δ 28.86 (s, CH_2CH_2Ar), 40.56 and 42.44 (d, $POCH_2CO$), 45.05 (s, CH_2CH_2Ar), 53.04 and 53.13 (d, CH_3O), 122.44, 127.17, 129.29, 130.02, 131.43, 142.91 (Ar), 200.41 and 200.50 (d, CH_2COCH_2); ^{31}P NMR δ 22.43. Anal. ($C_{12}H_{16}BrO_4P$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[3-Oxo-5-(4-bromophenyl)-1-(*E*)-pentenyl]-7-[(4-phenylbenzoyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one (5b). Compound **4b** (23.1 g, 69 mmol) was added to a stirred suspension of sodium hydride (1.8 g, 60 mmol) (washed with *n*-pentane to remove mineral oil) in dimethoxyethane (200 mL).[25] The mixture was mechanically stirred for 2 h under nitrogen. The sodium salt of the acyl phosphonate was obtained as a white precipitate. The reaction mixture was cooled to −5 °C with an ice/acetone bath and the crude (1*S*,5*R*,6*R*,7*R*)-6-formyl-7-[(4-phenylbenzoyl)oxy]-2-oxabicyclo-[3.3.0]octan-3-one[18,26] (20 g, 58 mmol) was added dropwise. The mixture was stirred for 3 h at room temperature, followed by acidification with glacial acetic acid. The crude product was extracted with EtOAc (100 mL), washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (gradient system: toluene to toluene/EtOAc, 1:5), which gave 19.3 g (60%) of **5b** as a yellow oil: TLC R_f = 0.52 (EtOAc/toluene, 2:1); $[\alpha]^{23}_D$ = −114.7° (*c* 1.0, CH_3CN); ^1H NMR δ 2.1–3.0 (m, 10H), 5.09 (1H, m, $CHOC(O)CH_2$), 5.31 (1H, q, $CHOC(O)Ar$), 6.21 (1H, d, $CH{=}CHC(O)$), 6.67 (1H, dd, $CH{=}CHC(O)$), 7.05–8.1 (13H, m, Ar); ^{13}C NMR δ 29.11, 34.81, 37.73, 41.99, 42.52 (methylene and methine), 54.02 ($CHCH{=}CH$), 78.37 ($CHOC(O)Ar$), 83.01 ($CHOC(O)CH_2$), 119.9, 127.10, 127.16, 127.83, 128.19, 128.86, 130.11, 130.70, 131.16, 131.34, 131.43, 139.66, 139.81, 143.16, 146.11 (Ar and CH=CH), 165.59 ($ArC(O)O$), 175.63 ($COC(O)CH_2$), 197.97 ($CH{=}CHC(O)$). Anal. ($C_{31}H_{27}BrO_5$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[3-Oxo-5-(3-bromophenyl)-1(*E*)-pentenyl]-7-[(4-phenylbenzoyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one (5a). Compound **5a** was prepared from **4a** and (1*S*,5*R*,6*R*,7*R*)-6-formyl-7-[(4-phenylbenzoyl)oxy]-2-oxabicyclo-[3.3.0]octan-3-one[18,26] by the above method in 70% yield as a yellow oil: TLC R_f = 0.57 (EtOAc/toluene, 2:1); $[\alpha]^{23}_D$ = −111.8° (*c* 1.0, CH_3CN); ^1H NMR δ 2.1–2.9 (10H, m), 5.09 (1H, m, $CHOC(O)CH_2$), 5.32 (1H, q, $CHOC(O)Ar$), 6.22 (1H, d, $CH{=}CHC(O)$), 6.69 (1H, dd, $CH{=}CHC(O)$), 7.10–8.07 (13H, m, Ar); ^{13}C NMR δ 29.42, 34.94, 37.86, 42.00, 42.61 (methylene and methine), 54.12 ($CHCH{=}CH$), 78.50 ($CHOC(O)Ar$), 83.14 ($CHOC(O)CH_2$), 122.31, 127.15, 127.20, 127.26, 128.29, 128.96, 129.31, 130.09, 130.21, 131.29, 131.44, 139.76, 143.32, 146.21 (Ar and CH=CH), 165.72 ($ArC(O)O$), 175.79 ($COC(O)CH_2$), 197.98 ($CH{=}CHC(O)$). Anal. ($C_{31}H_{27}BrO_5$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*S*)-3-Hydroxy-5-(4-bromophenyl)-1(*E*)-pentenyl]-7-[(4-phenylbenzoyl)oxy]-2-oxabicyclo-[3.3.0]octan-3-one [(3*S*)-6b] and (1*S*,5*R*,6*R*,7*R*)-6-[(3*R*)-3-Hydroxy-5-(4-bromophenyl)-1(*E*)-pentenyl]-7-[(4-phenylbenzoyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one [(3*R*)-6b]. A solution of **5b** (5.6 g, 12 mmol) and cerium chloride heptahydrate (1.3 g, 3.5 mmol) in $MeOH/CH_2Cl_2$, 2:1 (30 mL), was cooled to −78 °C under nitrogen. Sodium borohydride (0.26 g, 6.9 mmol) was added in small portions to the stirred reaction mixture during a period of 1 h.[27] After being stirred at −78 °C for 2 h, the reaction mixture was acidified with 1 M aqueous HCl to pH 4 and concentrated. The crude product was extracted with EtOAc (50 mL), washed with brine (2 × 20 mL) and 3% aqueous citric acid (2 × 20 mL), dried (Na_2SO_4), and concentrated. The residue consisted of a diastereomeric mixture of (3*S*)-**6b** and (3*R*)-**6b** (α and β isomers). Analytical HPLC (straight phase) showed that the diasteriomeric relationship was 53:47 α:β. The isomers were separated by flash chromatography (gradient system: CH_2Cl_2 to CH_2Cl_2/EtOAc, 1:5). Crystallization from CH_2Cl_2/*n*-hexane furnished 2.7 g of (3*S*)-**6b** (41%) and 2.0 g of (3*R*)-**6b** (32%).

(3*S*)-**6b:** TLC R_f = 0.39 (CH_2Cl_2/EtOAc 1:2); mp 122–124 °C; $[\alpha]^{23}_D$ = −93.2° (*c* 1.0, CH_3CN); ^1H NMR δ 1.6–2.9 (10H, m), 4.07 (1H, broad m, CH=CHC*H*(OH)), 5.04 (1H, broad m, C*H*OC(O)CH_2), 5.24 (1H, broad m, C*H*OC(O)Ar), 5.65 (2H, qq, C*H*=C*H*), 7.01–8.1 (13H, m, Ar); ^{13}C NMR δ 30.89, 34.82, 37.50, 38.40, 42.66 (5 methylene and methine carbons), 53.99 (*C*HCH=CH), 71.12 (CH=CH*C*H(OH)), 78.87 (*C*HOC(O)Ar), 83.14 (*C*HOC(O)CH_2), 119.62, 127.18, 127.27, 128.12, 128.26, 128.78, 128.96, 130.15, 131.44, 135.95, 139.76, 140.52, 146.1 (Ar and CH=CH), 165.94 (Ar*C*(O)O), 176.35 (*C*OC(O)CH_2). Anal. ($C_{31}H_{29}BrO_5$) C, H.

(3*R*)-**6b:** TLC R_f = 0.31 (CH_2Cl_2/EtOAc, 1:2); mp 130.5–131 °C; $[\alpha]^{23}_D$ = −124.4° (*c* 1.1, CH_3CN); ^1H NMR δ 1.6–2.9 (10H, m), 4.09 (1H, broad m, CH=CHC*H*(OH)), 5.05 (1H, broad m, C*H*OC(O)CH_2), 5.27 (1H, broad m, C*H*OC(O)Ar), 5.64 (2H, qq, C*H*=C*H*), 6.69–8.1 (13H, m, Ar); ^{13}C NMR δ 30.98, 34.75, 37.48, 38.47, 42.62 (5 methylene and methine carbons), 54.05 (*C*HCH=CH), 71.44 (CH=CH*C*H(OH)), 78.72 (*C*HOC(O)Ar), 83.05 (*C*HOC(O)CH_2), 119.6, 127.18, 127.27, 128.08, 128.26, 128.98, 129.05, 130.13, 131.41, 136.19, 139.75, 140.46, 146.1 (Ar and CH=CH), 165.89 (Ar*C*(O)O), 176.35 (*C*OC(O)CH_2). Anal. ($C_{31}H_{29}BrO_5$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*S*)-5-(3-Bromophenyl)-3-hydroxy-1(*E*)-pentenyl]-7-[(4-phenylbenzoyl)oxy]-2-oxabicyclo-[3.3.0]octan-3-one [(3*S*)-6a] and (1*S*,5*R*,6*R*,7*R*)-6-[(3*R*)-5-(3-Bromophenyl)-3-hydroxy-1(*E*)-pentenyl]-7-[(4-phenylbenzoyl)oxy]-2-oxa-bicyclo[3.3.0]octan-3-one [(3*R*)-6a]. Compounds (3*S*)-**6a** and (3*R*)-**6a** were prepared from **5a** by the above method. Separation by flash chromatography (gradient system: CH_2Cl_2 to CH_2Cl_2/EtOAc, 1:5) and crystallization from CH_2Cl_2/*n*-hexane furnished the α isomer (3*S*)-**6a** in 39% yield. The β isomer (3*R*)-**6a** was purified by additional flash chromatography (gradient system: CH_2Cl_2 to CH_2Cl_2/EtOAc, 1:5) and was obtained in 20% yield as an oil.

(3*S*)-**6a:** TLC R_f = 0.72 (CH_2Cl_2/EtOAc, 1:2); mp 125–125.5 °C; $[\alpha]^{23}_D$ = −87.3° (*c* 1.0, CH_3CN); ^1H NMR δ 1.76–2.88 (10H, m), 4.11 (1H, broad m, CH=CHC*H*(OH)), 5.04 (1H, broad m, C*H*OC(O)CH_2), 5.26 (1H, broad m, C*H*OC(O)Ar), 5.64 (2H, qq, C*H*=C*H*), 7.06–8.06 (13H, m, Ar); ^{13}C NMR δ 31.17, 34.91, 37.56, 38.35, 42.73 (5 methylene and methine carbons), 54.09 (*C*HCH=CH), 71.08 (CH=CH*C*H(OH)), 79.03 (*C*HOC(O)Ar), 83.26 (*C*HOC(O)CH_2), 122.3, 127.09, 127.18, 127.26, 128.26, 128.87, 128.96, 129.02, 129.98, 130.15, 131.47, 135.95, 139.91, 139.80, 144.05, 146.07 (Ar and CH=CH), 165.95 (Ar*C*(O)O, 176.41 (*C*OC(O)CH_2). Anal. ($C_{31}H_{29}BrO_5$) C, H.

(3*R*)-**6a:** TLC R_f = 0.62 (Ch_2Cl_2/EtOAc, 1:2); $[\alpha]^{23}_D$ = −106.9° (*c* 0.82, CH_3CN); ^1H NMR δ 1.64–2.89 (10H, m), 4.12 (1H, broad m, CH=CHC*H*(OH)), 5.07 (1H, broad m, C*H*OC(O)CH_2), 5.27 (1H, broad m, C*H*OC(O)Ar), 5.64 (2H, qq, C*H*=C*H*), 7.01–8.06 (13H, m, Ar); ^{13}C NMR δ 31.13, 34.73, 37.40, 38.30, 42.53 (5 methylene and methine carbons), 53.96 (*C*HCH=CH), 71.23 (CH=CH*C*H(OH)), 78.76 (*C*HOC(O)Ar), 83.08 (*C*HOC(O)CH_2), 122.31, 126.97, 127.09, 127.17, 128.00, 128.16, 128.86, 128.90, 129.87, 130.06, 131.34, 135.99, 139.66, 143.88, 145.97 (Ar and CH=CH), 165.83 (Ar*C*(O)O), 176.40 (*C*OC(O)CH_2). Anal. ($C_{31}H_{29}BrO_5{\cdot}^1/_2H_2O$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*S*)-5-(4-Bromophenyl)-3-hydroxy-1(*E*)-pentenyl]-7-hydroxy-2-hydroxy-2-oxabicyclo[3.3.0]-octan-3-one [(3*S*)-7b]. A mixture of (3*S*)-**6b** (9.8 g, 17 mmol) and powdered K_2CO_3 (1.4 g, 10 mmol) in MeOH (40 mL) was stirred at room temperature for 7 h. The reaction mixture was treated with ice and acidified with 1 M aqueous HCl to pH 4. The product was extracted with EtOAc, washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography (gradient system: CH_2Cl_2 to EtOAc), which afforded 6.5 g (98%) of (3*S*)-**7b**: TLC R_f = 0.12 (EtOAc); mp 124–124.5 °C; $[\alpha]^{23}_D$ = +1.1° (*c* 1.0, CH_3CN); ^1H NMR δ 1.6–3.1 (10H, m), 3.91 (1H, broad m, CH_2CH(OH)CH), 4.04 (1H, broad m, CH=CHC*H*(OH)), 4.89 (1H, app sext, C*H*OC(O)CH_2), 5.43 (1H, dd, C*H*=CHCH(OH)), 5.62 (1H, dd, CH=C*H*CH(OH)), 7.06 and 7.40 (4H, two d, Ar); ^{13}C NMR δ 31.14, 34.12, 38.43, 39.78, 42.42 (5 methylene and methine carbons), 56.08 (*C*HCH=CH), 71.75 (CH_2CH(OH)CH), 77.23 (CH=CH*C*H(OH)), 82.46 (*C*HOC(O)CH_2), 119.66, 130.20, 130.44, 131.48, 136.40, 140.54 (Ar and CH=CH), 176.89 (O*C*(O)CH_2). Anal. ($C_{18}H_{21}BrO_4$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*R*)-5-(4-Bromophenyl)-3-hydroxy-1(*E*)-pentenyl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one [(3*R*)-7b]. Compound (3*R*)-**7b** was prepared from (3*R*)-**6b** by the above method in 84% yield: TLC R_f = 0.18 (EtOAc); mp 98–100 °C; $[\alpha]^{23}_D$ = −18.8° (*c* 0.96, CH_3CN); ^1H NMR δ 1.6–2.9 (10H, m), 3.98 (1H, broad m, CH_2CH(OH)CH), 4.08 (1H, broad m, CH=CHC*H*(OH)), 4.91 (1H, app sext, C*H*OC(O)CH_2), 5.50 (1H, dd, C*H*=CHCH(OH)), 5.66 (1H, dd, CH=C*H*CH(OH)), 7.07 and 7.40 (4H, two d, Ar); ^{13}C NMR δ 31.12, 34.48, 38.49, 39.99, 42.53 (5 methylene and methine carbons), 56.03 (*C*HCH=CH), 71.14 (CH_2CH(OH)CH), 77.25 (CH=CH*C*H(OH)), 82.77 (*C*HOC(O)CH_2), 119.66, 129.36, 130.22, 131.48, 136.01, 140.59 (Ar and CH=CH), 177.03 (O*C*(O)CH_2). Anal. ($C_{18}H_{21}BrO_4$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*S*)-5-(3-Bromophenyl)-3-hydroxy-1(*E*)-pentenyl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one [(3*S*)-7a]. Compound (3*S*)-**7a** was obtained from (3*S*)-**6a** by the above method in 89% yield as a yellow oil: TLC R_f = 0.33 (EtOAc); $[\alpha]^{23}_D$ = −4.0° (c 1.2, CH_3CN); ^1H NMR δ 1.7–2.75 (10H, m), 3.89 (1H, broad m, CH_2CH(OH)CH), 4.02 (1H, broad m, CH=CHC*H*(OH)), 4.88 (1H, app sext, C*H*OC(O)CH_2), 5.41 (1H, dd, C*H*=CHCH(OH)), 5.66 (1H, dd, CH=C*H*CH(OH)), 7.11–7.33 (4H, m, Ar); ^{13}C NMR δ 31.40, 34.21, 38.29, 39.78, 42.38 (5 methylene and methine carbons), 56.10 (*C*HCH=CH), 71.81 (CH_2CH(OH)CH), 76.43 (CH=CH*C*H(OH)), 82.62 (*C*HOC(O)CH_2), 122.42, 127.18, 129.04, 130.07, 130.77, 131.53, 136.29, 144.11 (Ar and CH=CH), 177.14 (O*C*(O)CH_2). Anal. ($C_{18}H_{21}BrO_4$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*R*)-5-(3-Bromophenyl)-3-hydroxy-1(*E*)-pentenyl]-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one [(3*R*)-7a]. Compound (3*R*)-**7a** was obtained from (3*R*)-**6a** by the above method in 78% yield as a yellow oil: TLC R_f = 0.26 (EtOAc); $[\alpha]^{23}_D$ = −17.3° (*c* 1.8, CH_3CN); ^1H NMR δ 1.6–2.8 (10H, m), 3.99 (1H, broad m, CH_2CH(OH)CH), 4.10 (1H, broad m, CH=CHC*H*(OH)), 4.92 (1H, app sext, C*H*OC(O)CH_2), 5.51 (1H, dd, C*H*=CHCH(OH)), 5.65 (1H, dd, CH=C*H*CH(OH)), 7.10–7.34 (4H, m, Ar); ^{13}C NMR δ 31.28, 34.48, 38.21, 39.78, 42.32 (5 methylene and methine carbons), 55.76 (*C*HCH=CH), 70.85 (CH_2CH(OH)CH), 76.52 (CH=CH*C*H(OH)), 82.96 (*C*HOC(O)CH_2), 122.30, 127.09, 128.91, 129.28, 129.95, 131.40, 135.59, 144.08 (Ar and CH=CH), 177.44 (O*C*(O)CH_2). Anal. ($C_{18}H_{21}BrO_4{\cdot}^1/_2H_2O$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*S*)-5-(4-Bromophenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1(*E*)-pentenyl]-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one [(3*S*)-8b]. *tert*-Butyldimethylsilane (4.9 g, 33 mmol) was added to a solution of (3*S*)-**7b** (4.1 g, 11 mmol), triethylamine (4.5 mL, 33 mmol), and (dimethylamino)pyridine (0.13 g, 1.1 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred for 3 days at room temperature and then washed with 5% aqueous $NaHCO_3$ (2 × 10 mL), 3% aqueous citric acid (2 × 10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_2) and concentrated. The residue was purified by flash chromatography (ether/petroleum ether, 1:1), which furnished 6.3 g (84%) of (3*S*)-**8b** as a crystalline product: TLC R_f = 0.72 (EtOAc/CH_2Cl_2, 2:1); mp 93–95 °C; $[\alpha]^{23}_D$ = −8.3° (*c* 1.0, CH_3CN); ^1H NMR δ 0.3 (12H, m, $Si(CH_3)_2C(CH_3)_3$), 0.89 (18H, m, $Si(CH_3)_2C(CH_3)_3$), 1.6–2.6 (10H, m), 3.98 (1H, app q, CH_2CH(OSi)CH), 4.11 (1H, app q, CH=CHC*H*(OSi), 4.96 (1H, app sext, C*H*OC(O)CH_2), 5.40 (1H, dd, C*H*=CHCH(OSi)), 5.52 (1H, dd, CH=C*H*CH(OSi)), 7.02 and 7.38 (4H, two d, Ar); ^{13}C NMR d −4.88, −4.84, −4.29, −3.71, −0.13, 17.84, 18.07, 25.51, 25.56, 25.72, 30.88, 34.89, 39.76, 40.49, 42.13, 56.58, 72.05, 77.92, 83.24, 119.29, 128.97, 129.95 (2C), 131.24 (2C), 135.08, 141.03, 176.84. Anal. ($C_{30}H_{49}BrO_4Si_2$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*R*)-5-(4-Bromophenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1(*E*)-pentenyl]-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one [(3*R*)-8b]. Compound (3*R*)-**8b** was obtained from (3*R*)-**7b** by the above method in 98% yield as a yellow oil: TLC R_f = 0.70 (EtOAc/CH_2Cl_2, 2:1); $[\alpha]^{23}_D$ = −17.1° (*c* 1.0, CH_3CN); ^1H NMR δ −0.15 to 0.1 (12H, m, $Si(CH_3)_2C(CH_3)_3$), 0.79 (18H, m, $Si(CH_3)_2C(CH_3)_3$), 1.6–2.7 (10H, m), 3.83 (1H, app q, CH_2CH(OSi)CH), 4.02 (1H, app q, CH=CHC*H*(OSi), 4.82 (1H, app sext,

C*H*OC(O)CH_2), 5.28 (1H, dd, C*H*=CHCH(OSi)), 5.43 (1H, dd, CH=C*H*CH(OSi)), 6.93 and 7.29 (4H, two d, Ar); ^{13}C NMR δ −4.57, −4.03, −3.51, 0.07, 18.04, 18.27, 25.73, 25.76, 25.94, 30.90, 34.87, 39.85, 40.79, 42.04, 56.58, 72.52, 77.59, 83.12, 119.49, 129.25, 130.16 (2C), 131.46 (2C), 135.66, 141.25, 177.03. Anal. ($C_{30}H_{49}BrO_4Si_2$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*S*)-5-(3-Bromophenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1(*E*)-pentenyl]-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one [(3*S*)-8a]. Compound (3*S*)-**8a** was obtained from (3*S*)-**7a** by the above method in 98% yield: TLC R_f = 0.78 (EtOAc/CH_2Cl_2, 2:1); mp 72−74 °C; $[\alpha]^{23}_D$ = −9.8° (*c* 1.2, CH_3CN); ^{1}H NMR δ −0.15 to 0.1 (12H, m, Si(C*H*$_3$)$_2$C(C*H*$_3$)$_3$), 0.85 (18H, m, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 1.74−2.79 (10H, m), 3.98 (1H, app q, CH_2CH(OSi)CH), 4.53 (1H, app q, CH=CHC*H*(OSi), 4.95 (1H, app sext, C*H*OC(O)CH_2), 5.41 (1H, dd, C*H*=CHCH(OSi)), 5.50 (1H, dd, CH=C*H*CH(OSi)), 7.09−7.32 (4H, m, Ar); ^{13}C NMR δ −4.63, −4.53, −4.11, −3.42, 18.09, 18.29, 25.83, 25.97, 31.34, 35.17, 39.84, 40.75, 42.38, 56.83, 72.31, 78.21, 83.46, 127.06, 128.96, 129.34, 130.01, 131.50, 135.26, 144.67, 176.96. Anal. ($C_{30}H_{49}BrO_4Si_2$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*R*)-5-(3-Bromophenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1(*E*)-pentenyl]-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-one [(3*R*)-8a]. Compound (3*R*)-**8a** was obtained from (3*R*)-**7a** by the above method in 98% yield as a yellow oil: TLC R_f = 0.72 (EtOAc/CH_2Cl_2, 2:1); $[\alpha]^{23}_D$ = −16.9° (*c* 1.1, CH_3CN); ^{1}H NMR δ 0.03 (12H, m, Si(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.90 (18H, m, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 1.62−2.77 (10H, m), 3.93 (1H, app q, CH_2CH(OSi)CH), 4.11 (1H, app q, CH=CHC*H*(OSi), 4.92 (1H, app sext, C*H*OC(O)CH_2), 5.40 (1H, dd, C*H*=CHCH(OSi)), 5.49 (1H, dd, CH=C*H*CH(OSi)), 7.06−7.30 (4H, m, Ar); ^{13}C NMR δ −4.93, −4.70, −4.66, −4.14, −3.62, 17.92, 18.17, 25.61, 25.66, 25.83, 31.03, 34.80, 39.61, 40.67, 41.93, 56.50, 72.37, 77.72, 83.05, 122.34, 126.96, 128.81, 129.19, 129.87, 131.37, 135.48, 144.55, 176.93. Anal. ($C_{30}H_{49}BrO_4Si_2$) C, H.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*S*)-5-(4-Bromophenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1(*E*)-pentenyl]-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-ol [(3*S*)-9b]. Diisobutylaluminum hydride (20 w/w in toluene, 5.0 mL, 7.1 mmol) was added to a solution of (3*S*)-**8b** (3.6 g, 5.9 mmol) in THF (40 mL), kept at −78 °C, under nitrogen.[28] The reaction mixture was stirred vigorously at −78 °C until TLC indicated that all lactone had been consumed (about 4 h). The reaction mixture was treated with MeOH (20 mL) and was stirred overnight while being allowed to warm to room temperature. The precipitate was filtered off, and the THF was evaporated. The residue was dissolved in CH_2Cl_2 (40 mL), washed with brine (20 mL), dried (Na_2SO_4), and concentrated, furnishing 2.7 g (76%) of (3*S*)-**9b** as a yellow oil, which is a mixture of diastereomers: TLC R_f = 0.61 (EtOAc/*n*-hexane, 1:1), ^{1}H NMR δ 0−0.1 (12H, m, OSi (C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.89 (18H, d, OSi-(CH$_3$)$_2$C(C*H*$_3$)$_3$), 1.6−2.9 (10H, m), 3.86, 3.98, 4.12, 4.62, 4.83 (app q, q, m, m, d respectively), 5.38−5.59 (2H, m, C*H*=C*H*), 7.03 and 7.39 (4H, two d, Ar); ^{13}C NMR δ −4.13 to −4.78 (5 peaks), 18.00, 18.20, 25.80, 25.88, 31.05, 39.10, 40.02, 40.43, 40.93, 43.20, 44.71, 46.72, 56.26, 57.25, 72.38, 72.55, 78.60, 80.18, 80.29, 84.27, 100.02, 101.26, 119.33, 119.37, 130.08, 130.28, 131.18, 131.34, 133.58, 134.21, 141.31, 141.36.

(1*S*,5*R*,6*R*,7*R*)-6-[(3*R*)-5-(4-Bromophenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1(*E*)-pentenyl]-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-ol [(3*R*)-9b]. Compound (3*R*)-**9b** was prepared from (3*R*)-**8b** by the above method in 91% yield as a mixture of diastereomers: TLC R_f = 0.55 (EtOAc/*n*-hexane, 1:1).

(1*S*,5*R*,6*R*,7*R*)-6-[(3*S*)-5-(3-Bromophenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1(*E*)-pentenyl]-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-ol [(3*S*)-9a]. Compound (3*S*)-**9a** was prepared from (3*S*)-**8a** by the above method in 84% yield as a mixture of diastereomers: TLC R_f = 0.62 (EtOAc/*n*-hexane, 1:1).

(1*S*,5*R*,6*R*,7*R*)-6-[(3*R*)-5-(3-Bromophenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1(*E*)-pentenyl]-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.0]octan-3-ol [(3*R*)-9a]. Compound (3*R*)-**9a** was prepared from (3*R*)-**8a** by the above method in 84% yield as a mixture of diastereomers. TLC R_f = 0.56 (EtOAc/*n*-hexane, 1:1).

9,11- and 11,15-Bis[(*tert*-butyldimethylsilyl)oxy]-17-(4-bromophenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-10b]. Step 1. Potassium *tert*-butoxide (2.7 g, 24 mmol) was added to a suspension of 4-carboxybutyltriphenylphosphonium bromide (5.7 g, 13 mmol) in THF (10 mL/g of lactol) at 0 °C (ice bath) under nitrogen.[29] After being stirred at 0 °C for 10 min and at room temperature for 10 min, the reaction mixture had turned to a deep orange color. A solution of (3*S*)-**9b** (2.6 g, 4.3 mmol) in THF (20 mL) was added dropwise. After being stirred for 20 min, the reaction mixture was acidified with 10% aqueous citric acid to pH 4, extracted with ether (20 mL), dried (Na_2SO_4), and concentrated. During the reaction, silyl group migration was detected by TLC. On the basis of previous findings,[30] it may be assumed that the silyl group on the 11-hydroxy substituent migrated to the 9-hydroxy group. The crude acid was used in the next step without further purification. TLC R_f = 0.36 and 0.46 (EtOAc/*n*-hexane, 1:1).

Step 2. A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[31] (3.9 g, 26 mmol) in acetone (4 mL) was added to a stirred solution of the above crude acid in acetone (20 mL). The reaction mixture was stirred for 10 min, and a solution of 2-iodopropane (3.6 g, 21 mmol), in acetone (3 mL), was added. After being stirred at room temperature overnight, the mixture was concentrated and extracted with EtOAc. The organic layer was washed with 3% aqueous citric acid (2 × 10 mL), 5% aqueous $NaHCO_3$ (2 × 10 mL), and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (ether/petroleum ether, 1:10), which furnished 2.2 g (71%) of (3*S*)-**10b** as a slightly yellow oil. The product is a mixture of isomers in which the silyl protecting groups have migrated partially: TLC R_f = 0.52 and 0.60 (ether/petroleum ether, 1:1); ^{13}C NMR δ −4.88, −4.81, −4.63, −4.20, 17.79, 18.15, 21.80, 24.89, 25.73, 25.82, 26.54, 26.60, 30.98, 34.05, 40.09, 42.89, 51.66, 56.34, 61.30, 72.44, 74.48, 79.84, 119.32, 129.29, 129.33, 130.01 (2C), 131.30, 131.54, 133.73, 141.28, 173.10. Anal. ($C_{38}H_{65}BrO_5Si_2$) C, H.

9,11- and 11,15-Bis[(*tert*-butyldimethylsilyl)oxy]-17-(4-bromophenyl)-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-10b]. This mixture was prepared from (15*R*)-**9b** by the above method. After purification by flash chromatography (ether/petroleum ether, 1:10), (15*R*)-**10b** was obtained in 70% yield as a slightly yellow oil: TLC R_f = 0.55 and 0.57 (ether/petroleum ether, 1:1); ^{13}C NMR δ −5.08, −4.73, −4.38, −4.08, 17.99, 18.23, 21.86, 24.84, 25.86, 25.88, 26.19, 26.84, 31.02, 34.17, 40.04, 43.35, 51.51, 56.72, 67.39, 72.74, 74.70, 79.14, 119.33, 129.31 (2C), 130.13 (2C), 131.33 (2C), 132.05, 134.03, 141.40, 173.08. Anal. ($C_{38}H_{65}BrO_5Si_2$) C, H.

9,11- and 11,15-Bis[(*tert*-butyldimethylsilyl)oxy]-17-(3-bromophenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-10a]. This mixture was prepared from (15*S*)-**9a** by the above method. After purification by flash chromatography (ether/petroleum ether, 1:10), (15*S*)-**10a** was afforded in 97% yield as a slightly yellow oil: TLC R_f = 0.52 and 0.60 (ether/petroleum ether, 1:1). Anal. ($C_{38}H_{65}BrO_5Si_2$) C, H.

9,11- and 11,15-Bis[(*tert*-butyldimethylsilyl)oxy]-17-(3-bromophenyl)-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-10a]. This mixture was prepared from (15*R*)-**9a** by the above method. After purification by flash chromatography (ether/petroleum ether, 1:10), (15*R*)-**10a** was afforded in 54% yield as a slightly yellow oil: TLC R_f = 0.62 and 0.65 (ether/petroleum ether, 1:1). Anal. ($C_{38}H_{65}BrO_5Si_2$) C, H.

17-(4-Bromophenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-11b)]. Tetrabutylammonium fluoride (1 M in THF, 7.5 mL, 7.7 mmol) was added to a stirred solution of (15*S*)-**10b** (2.2 g, 3.0 mmol) in THF (5 mL) under nitrogen. The deprotection was complete after the mixture was stirred for 24 h and 1 equiv of tetrabutylammonium fluoride (TLC) was added. $CHCl_3$ (10 mL) was added to the reaction mixture, and the organic layer was washed with brine (5 mL) and 5% aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography (gradient system: $CHCl_3$ to $CHCl_3$/acetone, 4:1), which furnished 1.1 g (71%) of an oily product. Analytical HPLC

(reversed phase) showed that the product contained about 5% of the *trans* isomer (from the Wittig reaction); 150 mg of the oil was purified by preparative HPLC (straight phase). This gave 65 mg of isomerically pure (15*S*)-**11b**: TLC R_f = 0.12 (EtOAc); $[\alpha]^{23}_D$ = +25.9° (*c* 1.0, CH_3CN); mp 59–61 °C; ^1H NMR δ 1.22 (6H, d, $OCH(CH_3)_2$, J = 6.20), 1.51 (1H, app sept, H_8), 1.65 (2H, app quint, H_3, J = 7.02), 1.75 (2H, m, $H_{10\beta}$ and H_{16a}), 1.85 (1H, m, H_{16b}), 2.05 (3H, m, H_4 and H_{7a}), 2.20 (1H, m, $H_{10\alpha}$), 2.25 (3H, m, H_{7b} and H_2), 2.35 (1H, ddd, H_{12}), 2.62–2.70 (2H, m, H_{17a} and H_{17b}), 3.95 (1H, broad m, H_{11}), 4.10 (1H, ddd, H_{15}, J = 6.5, 6.5), 4.185 (1H, broad m, H_9), 4.98 (1H, sept, $OCH(CH_3)_2$, J = 6.20), 5.38 (1H, m, H_5), 5.42 (1H, m, H_6), 5.52 (1H, dd, H_{13}), 5.605 (1H, dd, H_{14}), 7.07 (2H, d, $H_{2'}$, J = 8.4), 7.39 (2H, d, $H_{3'}$, J = 8.4); ^{13}C NMR δ 21.84 ($OCH(CH_3)_2$), 24.88 (C_3), 25.62 (C_7), 26.64 (C_4), 31.21 (C_{17}), 34.02 (C_2), 38.60 (C_{16}), 42.96 (C_{10}), 50.60 (C_8), 55.88 (C_{12}), 67.71 ($OCH(CH_3)_2$), 71.83 (C_{15}), 73.01 (C_9), 78.21 (C_{11}), 119.53 ($C_{4'}$) 128.91 (C_6), 129.86 (C_5), 130.18 ($C_{2'}$), 131.40 ($C_{3'}$), 132.88 (C_{13}), 134.60 (C_{14}), 140.84 ($C_{1'}$), 173.42 (C_1); analytical HPLC (reversed phase) 97.6 area %. Anal. ($C_{26}H_{37}BrO_5$) C, H.

17-(4-Bromophenyl)-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-11b)]. Compound (15*R*)-**11b** was prepared from (15*R*)-**10b** by the above method. After purification by flash chromatography (gradient system: $CHCl_3$ to $CHCl_3$/acetone, 4:1), the product was obtained as an oil in 79% yield (1.1 g). Analytical HPLC (reversed phase) showed that the product contained about 5% of the *trans* isomer. A total of 120 mg of the oil was purified by preparative HPLC (straight phase), affording 68 mg of isomerically pure (15*R*)-**11b** as an oil: TLC R_f = 0.23 (EtOAc); $[\alpha]^{23}_D$ = +16.9° (*c* 1.0, CH_3CN); ^1H NMR δ 1.22 (6H, d, $OCH(CH_3)_2$, J = 6.20), 1.49 (1H, app sept, H_8) 1.65 (2H, app quint, H_3, J = 7.02), 1.76 (1H, m, H_{16a}), 1.77 (1H, m, $H_{10\beta}$), 1.84 (1H, m, H_{16b}), 2.07 (2H, dt, H_4), 2.11 (1H, m, $H_{10\alpha}$), 2.14 (1H, m, H_{7a}), 2.24 (3H, m, H_{7b} and H_2), 2.33 (1H, ddd, H_{12}), 2.62–2.69 (2H, m, H_{17a} and H_{17b}), 3.93 (1H, broad m, H_{11}), 4.08 (1H, ddd, H_{15}, J = 6.5, 6.5), 4.19 (1H, broad m, H_9), 5.00 (1H, sept, $OCH(CH_3)_2$, J = 6.20), 5.38 (1H, m, H_5), 5.43 (1H, m, H_6), 5.52 (1H, dd, H_{13}), 5.61 (1H, dd, H_{14}), 7.06 (2H, d, $H_{2'}$, J = 8.4), 7.37 (2H, d, $H_{3'}$, J = 8.4); ^{13}C NMR δ 21.84 ($OCH(CH_3)_2$), 24.84 (C_3), 25.59 (C_7), 26.57 (C_4), 31.17 (C_{17}), 33.95 (C_2), 38.54 (C_{16}), 43.01 (C_{10}), 50.83 (C_8), 55.88 (C_{12}), 67.75 ($OCH(CH_3)_2$), 71.58 (C_{15}), 73.09 (C_9), 78.30 (C_{11}), 119.48 ($C_{4'}$), 128.98 (C_6), 129.77 (C_5), 130.19 ($C_{2'}$), 131.36 ($C_{3'}$), 132.48 (C_{13}), 134.54 (C_{14}), 140.88 ($C_{1'}$), 173.53 (C_1); analytical HPLC (reversed phase) 98.4 area %. Anal. ($C_{26}H_{37}BrO_5 \cdot {}^1/_2H_2O$) C, H.

17-(3-Bromophenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-11a]. Compound (15*S*)-**11a** was prepared from (15*S*)-**10a** by the above method. After purification by flash chromatography (gradient system: $CHCl_3$ to $CHCl_3$/acetone, 4:1), the product was obtained as an oil in 95% yield (3.7 g). Analytical HPLC (reversed phase) showed that the product contained about 5% of the *trans* isomer; 100 mg was purified by preparative HPLC (straight phase), affording 67 mg of isomerically pure (15*S*)-**11a** as an oil: TLC R_f = 0.14 (EtOAc); $[\alpha]^{23}_D$ = +28.0° (*c* 1.0, CH_3CN); ^1H NMR δ 1.21 (6H, d, $OCH(CH_3)_2$), 1.49 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.73 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, H_{16}, $H_{10\alpha}$), 2.25 (2H, app t, H_2), 2.68 (2H, m, H_{17}), 3.91 (1H, broad m, H_{11}), 4.06 (1H, app q, H_{15}), 4.16 (1H, broad m, H_9), 4.99 (1H, sept, $OCH(CH_3)_2$), 5.38 and 5.42 (2H, m, H_5 and H_6), 5.48 (1H, dd, H_{13}), 5.60 (1H, dd, H_{14}), 7.12–7.34 (4H, Ar); ^{13}C NMR δ 21.92 ($OCH(CH_3)_2$), 24.94 (C_3), 25.53 (C_7), 26.70 (C_4), 31.56 (C_{17}), 34.11 (C_2), 38.52 (C_{16}), 42.91 (C_{10}), 50.23 (C_8), 55.71 (C_{12}), 67.79 ($OCH(CH_3)_2$), 72.08 (C_{15}), 72.66 (C_9), 77.87 (C_{11}), 122.47, 127.20, 129.03, 130.01, 131.58, 144.40 (Ar), 129.00 (C_6), 129.90 (C_5), 133.38 (C_{13}), 135.04 (C_{14}), 173.63 (C_1); analytical HPLC (reversed phase) 99.3 area %. Anal. ($C_{26}H_{37}BrO_5 \cdot {}^1/_2H_2O$) C, H.

17-(3-Bromophenyl)-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-11a]. Compound (15*R*)-**11a** was prepared from (15*R*)-**10a** by the above method. After purification by flash chromatography (gradient system: $CHCl_3$ to $CHCl_3$/acetone, 4:1) the product was obtained as an oil in 93% yield (1.8 g). Analytical HPLC (reversed phase) showed that the product contained about 5% of the *trans* isomer; 150 mg was purified by preparative HPLC (straight phase), affording 130 mg of isomerically pure (15*R*)-**11a** as an oil: TLC R_f = 0.25 (EtOAc); $[\alpha]^{23}_D$ = +18.9° (*c* 1.2, CH_3CN); ^1H NMR δ 1.21 (6H, d, $OCH(CH_3)_2$), 1.48 (1H, app sept, H_8), 1.65 (2H, app quint, H_3), 1.76 (1H, m, $H_{10\beta}$), 1.75–2.4 (8H, m, H_{12}, H_7, H_4, H_{16}, $H_{10\alpha}$), 2.26 (2H, app t, H_2), 2.69 (2H, m, H_{17}), 3.94 (1H, broad m, H_{11}), 4.08 (1H, app q, H_{15}), 4.16 (1H, broad m, H_9), 4.98 (1H, sept, $OCH(CH_3)_2$), 5.37 and 5.43 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.62 (1H, dd, H_{14}), 7.12–7.35 (4H, Ar); ^{13}C NMR δ 21.87 ($OCH(CH_3)_2$), 24.85 (C_3), 25.52 (C_7), 26.59 (C_4), 31.48 (C_{17}), 33.99 (C_2), 38.45 (C_{16}), 42.98 (C_{10}), 50.68 (C_8), 55.63 (C_{12}), 67.82 ($OCH(CH_3)_2$), 71.38 (C_{15}), 72.87 (C_9), 78.08 (C_{11}), 122.41, 127.19, 129.11, 129.96, 131.55, 144.43 (Ar), 128.92 (C_6), 129.73 (C_5), 132.35 (C_{13}), 134.59 (C_{14}), 173.71 (C_1); analytical HPLC (reversed phase) 99.0 area %. Anal. ($C_{26}H_{37}BrO_5 \cdot {}^1/_2H_2O$) C, H.

17-(4-Methylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-12b]. A solution of triethylamine (0.2 mL) in DMF (0.8 mL) was added to a mixture of (15*S*)-**11b** (159 mg, 0.31 mmol, containing 5% of the *trans* isomer), palladium(II) acetate (1.4 mg, 2 mol %), and tri-o-tolylphosphine (7.6 mg, 8 mol %) in a 5 mL vial. Tetramethylsilane (0.13 mL, 0.93 mmol) was added, the vial was tightly sealed, and the mixture was stirred at 100 °C for 8 h.[19] Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*S*)-**11b** had been consumed (t_R = 15.73 min), and a new peak had appeared at t_R = 15.24 min. The reaction mixture was extracted with EtOAc (2 mL), washed with brine (2 mL) and 3% aqueous citric acid (2 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (EtOAc), which furnished 64 mg (46%) of (15*S*)-**12b** contained about 5% of the *trans* isomer. Preparative HPLC (straight phase) affording 51 mg of isomerically pure (15*S*)-**12b**: TLC R_f = 0.15 (EtOAc); $[\alpha]^{23}_D$ = +33.9° (*c* 1.1, CH_3CN); ^1H NMR δ 1.21 (6H, d, $OCH(CH_3)_2$), 1.47 (1H, app sept, H_8), 1.65 (2H, app quint, H_3), 1.7–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.75 (1H, m, $H_{10\beta}$), 2.27 (2H, app t, H_2), 2.31 (3H, s, $ArCH_3$), 2.67 (2H, m, H_{17}), 3.90 (1H, broad m, H_{11}), 4.07 (1H, app q, H_{15}), 4.14 (1H, broad m, H_9), 4.98 (1H, sept, $OCH(CH_3)_2$), 5.36 (1H, m, H_5), 5.40 (1H, m, H_6), 5.46 (1H, dd, H_{13}), 5.60 (1H, dd, H_{14}), 7.08 (4H, app s, $H_{2'}$ and $H_{3'}$); ^{13}C NMR δ 21.05 ($ArCH_3$), 21.90 ($OCH(CH_3)_2$), 24.93 (C_3), 25.50 (C_7), 26.68 (C_4), 31.43 (C_{17}), 34.10 (C_2), 38.92 (C_{16}), 42.87 (C_{10}), 50.20 (C_8), 55.69 (C_{12}), 67.73 ($OCH(CH_3)_2$), 72.36 (C_{15}), 72.62 (C_9), 77.81 (C_{11}), 128.36 (2C), 129.10 (2C), 135.27, 138.85 (Ar), 129.07 (C_6), 129.80 (C_5), 133.20 (C_{13}), 135.27 (C_{14}), 173.58 (C_1); analytical HPLC (reversed phase) 99.5 area %. Anal. ($C_{27}H_{40}O_5 \cdot {}^1/_2H_2O$) C, H.

15β-Hydroxy-17-(4-methylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-12b]. Compound (15*R*)-**12b** was prepared from (15*R*)-**11b** (80 mg, 0.16 mmol, containing about 5% of the *trans* isomer) by the above method. The reaction was monitored by analytical HPLC (straight phase, 6% ethanol in *n*-hexane), and after the mixture was stirred at 100 °C overnight, the peak due to (15*R*)-**11b** (t_R = 15.53 min) had disappeared and a new peak had appeared at t_R = 15.01 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 66 mg (94%) of (15*R*)-**12b** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 13 mg of isomerically pure (15*R*)-**12b** as an oil: TLC R_f = 0.24 (EtOAc); $[\alpha]^{23}_D$ = +19.9° (*c* 0.99, CH_3CN); ^1H NMR δ 1.22 (6H, d, $OCH(CH_3)_2$), 1.52 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.80 (1H, m, $H_{10\beta}$), 2.27 (2H, app t, H_2), 2.31 (3H, s, $ArCH_3$), 2.68 (2H, m, H_{17}), 3.95 (1H, broad m, H_{11}), 4.10 (1H, app q, H_{15}), 4.19 (1H, broad m, H_9), 5.00 (1H, sept, $OCH(CH_3)_2$), 5.39 and 5.43 (2H m, H_5 and H_6), 5.51 (1H, dd, H_{13}), 5.63 (1H, dd, H_{14}), 7.09 (4H, app s, $H_{2'}$ and $H_{3'}$); ^{13}C NMR δ 20.97 ($ArCH_3$), 21.83 ($OCH(CH_3)_2$), 24.80 (C_3), 25.57 (C_7), 26.54 (C_4), 31.30 (C_{17}), 33.91 (C_2), 38.88 (C_{16}), 42.89 (C_{10}), 50.84 (C_8), 55.96 (C_{12}), 67.73 ($OCH(CH_3)_2$), 71.84 (C_{15}), 73.14 (C_9), 78.36 (C_{11}), 128.30 (2C), 129.03 (2C), 135.23, 138.77 (Ar), 129.03 (C_6), 129.78 (C_5), 132.24 (C_{13}), 134.70 (C_{14}), 173.57 (C_1); analytical HPLC (reversed phase) 97.7 area %. Anal. ($C_{27}H_{40}O_5 \cdot {}^1/_4H_2O$) C, H.

17-(3-Methylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-12a]. Compound (15*S*)-**12a** was prepared from

(15*S*)-11**a** (198 mg, 0.39 mmol, containing about 5% of the *trans* isomer) by the above method. The reaction was monitored by analytical HPLC (straight phase), and after the mixture was stirred at 100 °C overnight, the peak due to (15*S*)-11**a** (t_R = 15.58 min) had disappeared and a new peak had appeared at t_R = 14.88 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 146 mg (84%) of (15*S*)-**12a** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 43 mg of isomerically pure (15*S*)-**12a** as an oil: TLC R_f = 0.18 (EtOAc); $[\alpha]^{23}_D$ = +31.9° (*c* 0.97, CH_3CN); ^1H NMR δ 1.21 (6H, d, OCH(CH_3)$_2$), 1.49 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.7–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.76 (1H, m, $H_{10\beta}$), 2.25 (2H, app t, H_2), 2.33 (3H, s, ArCH_3), 2.65 (2H, m, H_{17}), 3.92 (1H, broad m, H_{11}), 4.09 (1H, app q, H_{15}), 4.16 (1H, broad m, H_9), 4.98 (1H, sept, OCH(CH_3)$_2$), 5.37 (1H, m, H_5), 5.42 (1H, m, H_6), 5.48 (1H, dd, H_{13}), 5.48 (1H, dd, H_{14}), 6.98–7.19 (4H, m, Ar); ^{13}C NMR δ 21.38 (ArCH_3), 21.82 (OCH(CH_3)$_2$), 24.84 (C_3), 25.48 (C_7), 26.60 (C_4), 31.74 (C_{17}), 34.00 (C_2), 38.78 (C_{16}), 42.80 (C_{10}), 50.27 (C_8), 55.71 (C_{12}), 67.66 (OCH(CH_3)$_2$), 72.25 (C_{15}), 72.70 (C_9), 77.89 (C_{11}), 125.40, 126.53, 128.25, 129.23, 137.88, 141.82 (Ar), 128.96 (C_6), 129.78 (C_5), 132.99 (C_{13}), 135.02 (C_{14}), 173.49 (C_1); analytical HPLC (reversed phase) 97.4 area %. Anal. ($C_{27}H_{40}O_5$) C, H.

15β-Hydroxy-17-(3-methylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-12a]. Compound (15*R*)-**12a** was prepared from (15*R*)-11**a** (147 mg, 0.29 mmol, containing about 5% of the *trans* isomer) by the above method. After the mixture was stirred at 100 °C overnight, analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that the peak due to (15*R*)-11**a** (t_R = 15.13 min) had disappeared and a new peak had appeared at t_R = 14.61 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 96 mg (75%) of (15*R*)-**12a** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 23 mg of isomerically pure (15*R*)-**12a** as an oil: TLC R_f = 0.23 (EtOAc); $[\alpha]^{23}_D$ = +21.9° (*c* 0.86, CH_3CN); ^1H NMR δ 1.22 (6H, d, OCH(CH_3)$_2$), 1.53 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.80 (1H, m, $H_{10\beta}$), 2.27 (2H, app t, H_2), 2.33 (3H, s, ArCH(3), 2.67 (2H, m, H_{17}), 3.95 (1H, broad m, H_{11}), 4.12 (1H, app q, H_{15}), 4.20 (1H, broad m, H_9), 5.00 (1H, sept, OCH(CH_3)$_2$), 5.39 and 5.43 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.63 (1H, dd, H_{14}), 6.99–7.20 (4H, m, Ar); ^{13}C NMR δ 21.38 (ArCH_3), 21.83 (OCH(CH_3)$_2$), 24.81 (C_3), 25.60 (C_7), 26.56 (C_4), 31.69 (C_{17}), 33.91 (C_2), 38.83 (C_{16}), 42.92 (C_{10}), 50.87 (C_8), 56.03 (C_{12}), 67.73 (OCH(CH_3)$_2$), 71.92 (C_{15}), 73.20 (C_9), 78.42 (C_{11}), 125.43, 126.54, 128.26, 129.26, 137.91, 141.82 (Ar), 129.01 (C_6), 129.83 (C_5), 132.30 (C_{13}), 134.71 (C_{14}), 173.55 (C_1); analytical HPLC (reversed phase) 98.7 area %. Anal. ($C_{27}H_{40}O_5 \cdot {}^1/_2H_2O$) C, H.

17-(4-Acetylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-13b]. Butyl vinyl ether (0.50 mL, 3.90 mmol) was added to a stirred suspension of (15*S*)-11**b** (199 mg, 0.39 mmol, containing about 5% of the *trans* isomer), thallium(II) acetate (111 mg, 0.42 mmol), palladium(II) acetate (4.4 mg, 5 mol%), 1,3-bis(diphenylphosphino)propane (8.8 mg, 5.5 mol %), and triethylamine (0.22 mL, 1.6 mmol) in DMF (0.8 mL).[21] The reaction mixture was flushed with nitrogen, sealed, and stirred at 100 °C. After 1 day, acidic workup (see below) was done on an aliquot from the reaction mixture. Monitoring with analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that a new peak at t_R = 33.1 min had appeared with 40 area% relative to (15*S*)-11**b** (t_R = 15.73 min). The reaction mixture was treated with additional butyl vinyl ether (0.39 mmol), palladium(II) acetate (2 mol %), and 1,3-bis(diphenylphosphino)propane (2.2 mol %), flushed with nitrogen, sealed, and stirred at 100 °C. This procedure was repeated until all starting material was consumed (about 3 days). THF was added (0.8 mL), and the reaction mixture was treated with 10% aqueous HCl (0.2 mL). After being stirred for 30 min, the mixture was extracted with EtOAc, washed with brine (2 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (EtOAc), which furnished 85 mg (46%) of (15*S*)-**13b** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 12 mg of isomerically pure (15*S*)-**13b** as a slightly yellow oil: TLC R_f = 0.10 (EtOAc); $[\alpha]^{23}_D$ = +30.5° (*c* 1.2, CH_3CN); ^1H NMR δ 1.21 (6H, d, OCH(CH_3)$_2$), 1.50 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.75–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.77 (1H, m, $H_{10\beta}$), 2.26 (2H, app t, H_2), 2.58 (3H, s, ArCOCH_3), 2.77 (2H, m, H_{17}), 3.93 (1H, broad m, H_{11}), 4.06 (1H, app q, H_{15}), 4.17 (1H, broad m, H_9), 4.98 (1H, sept, OCH(CH_3)$_2$), 5.38 and 5.42 (2H, m, H_5 and H_6), 5.51 (1H, dd, H_{13}), 5.62 (1H, dd, H_{14}), 7.28 (2H, d, $H_{2'}$), 7.88 (2H, d, $H_{3'}$); ^{13}C NMR δ 21.81 (OCH(CH_3)$_2$), 24.83 (C_3), 25.48 (C_7), 26.54 (ArCOCH_3), 26.58 (C_4), 31.83 (C_{17}), 33.97 (C_2), 38.29 (C_{16}), 42.87 (C_{10}), 50.36 (C_8), 55.74 (C_{12}), 67.71 (OCH(CH_3)$_2$), 71.93 (C_{15}), 72.78 (C_9), 78.00 (C_{11}), 128.56 (2C), 128.63 (2C), 135.04, 147.84 (Ar), 128.92 (C_6), 129.83 (C_5), 133.13 (C_{13}), 134.72 (C_{14}), 173.51 (C_1), 197.89 (ArCOCH$_3$); analytical HPLC (reversed phase) 98.7 area %. Anal. ($C_{28}H_{40}O_6$) C, H.

15β-Hydroxy-17-(4-acetylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-13b]. Compound (15*R*)-**13b** was prepared from (15*R*)-11**b** (129 mg, 0.25 mmol, containing 5% of the *trans* isomer) by the above method. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that a new chromatographic peak had appeared at t_R = 34.78 min. Flash chromatography (EtOAc) furnished 52 mg (43%) of (15*R*)-**13b** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 29 mg of isomerically pure (15*R*)-**13b** as an oil: TLC R_f = 0.16 (EtOAc); $[\alpha]^{23}_D$ = +18.9° (*c* 1.3, CH_3CN); ^1H NMR δ 1.22 (6H, d, OCH(CH_3)$_2$), 1.51 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.80 (1H, m, $H_{10\beta}$), 2.27 (2H, app t, H_2), 2.59 (3H, s, ArCOCH_3), 2.77 (2H, m, H_{17}), 3.95 (1H, broad m, H_{11}), 4.10 (1H, app q, H_{15}), 4.20 (1H, broad m, H_9), 4.99 (1H, sept, OCH(CH_3)$_2$), 5.38 and 5.44 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.64 (1H, dd, H_{14}), 7.29 (2H, d, $H_{2'}$), 7.88 (2H, d, $H_{3'}$); ^{13}C NMR δ 21.80 (OCH(CH_3)$_2$), 24.77 (C_3), 25.51 (C_7), 26.51 (ArCOCH_3), 26.54 (C_4), 31.79 (C_{17}), 33.88 (C_2), 38.28 (C_{16}), 42.97 (C_{10}), 50.84 (C_8), 55.90 (C_{12}), 67.74 (OCH(CH_3)$_2$), 71.63 (C_{15}), 73.05 (C_9), 78.29 (C_{11}), 128.53 (2C), 128.66 (2C), 135.00, 147.91 (Ar), 128.99 (C_6), 129.76 (C_5), 132.61 (C_{13}), 134.48 (C_{14}), 173.59 (C_1), 197.92 (ArCOCH$_3$); analytical HPLC (reversed phase) 99.5 area %. Anal. ($C_{28}H_{40}O_6$) C, H.

17-(3-Acetylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-13a]. Compound (15*S*)-**13a** was prepared from (15*S*)-11**a** (130 mg, 0.25 mmol, containing 5% of the *trans* isomer) by the above method. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that a new peak had appeared at t_R = 33.76 min. Flash chromatography (EtOAc) furnished 56 mg (47%) of (15*S*)-**13a** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 27 mg of isomerically pure (15*S*)-**13a** as an oil: TLC R_f = 0.09 (EtOAc); $[\alpha]^{23}_D$ = +29.1° (*c* 0.91, CH_3CN); ^1H NMR δ 1.21 (6H, d, OCH(CH_3)$_2$), 1.51 (1H, app sept, H_8), 1.65 (2H, app quint, H_3), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.76 (1H, m, $H_{10\beta}$), 2.25 (2H, app t, H_2), 2.60 (3H, s, ArCOCH_3), 2.75 (2H, m, H_{17}), 3.93 (1H, broad m, H_{11}), 4.09 (1H, app q, H_{15}), 4.17 (1H, broad m, H_9), 4.98 (1H, sept, OCH(CH_3)$_2$), 5.37 and 5.42 (2H, m, H_5 and H_6), 5.50 (1H, dd, H_{13}), 5.62 (1H, dd, H_{14}), 7.37–7.80 (4H, m, Ar); ^{13}C NMR δ 21.80 (OCH(CH_3)$_2$), 24.82 (C_3), 25.46 (C_7), 26.57 (ArCOCH_3), 26.69 (C_4), 31.65 (C_{17}), 33.97 (C_2), 38.58 (C_{16}), 42.81 (C_{10}), 50.19 (C_8), 55.64 (C_{12}), 67.66 (OCH(CH_3)$_2$), 71.96 (C_{15}), 72.63 (C_9), 77.85 (C_{11}), 126.09, 128.13, 128.58, 133.20, 137.19, 142.51 (Ar), 128.95 (C_6), 129.77 (C_5), 133.33 (C_{13}), 134.84 (C_{14}), 173.49 (C_1), 198.47 (ArCOCH$_3$); analytical HPLC (reversed phase) 98.5 area %. Anal. ($C_{28}H_{40}O_6$) C, H.

15β-Hydroxy-17-(3-acetylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-13a]. Compound (15*R*)-**13a** was prepared from (15*R*)-11**a** (157 mg, 0.31 mmol, containing 5% of the *trans* isomer) by the above method. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that a new peak had appeared at t_R = 34.89 min. Flash chromatography (EtOAc) furnished 65 mg (45%) of (15*R*)-**13a** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 49 mg of isomerically pure (15*R*)-**13a** as an oil: TLC R_f = 0.16 (EtOAc); $[\alpha]^{23}_D$ = +22.3° (*c* 0.83, CH_3CN); ^1H NMR δ 1.22 (6H, d, OCH(CH_3)$_2$), 1.51 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.77 (1H, m, $H_{10\beta}$), 2.27 (2H, app t, H_2), 2.60 (3H, s, ArCOCH_3), 2.77 (2H, m, H_{17}), 3.96 (1H, broad m, H_{11}), 4.10 (1H, app q,

H_{15}), 4.20 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH_3)$_2$), 5.38 and 5.44 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.64 (1H, dd, H_{14}), 7.35–7.81 (4H, m, Ar); ^{13}C NMR δ 21.82 (OCH(*C*H_3)$_2$), 24.79 (C_3), 25.54 (C_7), 26.52 (ArCO*C*H_3), 26.69 (C_4), 31.62 (C_{17}), 33.89 (C_2), 38.55 (C_{16}), 42.98 (C_{10}), 50.84 (C_8), 55.94 (C_{12}), 67.74 (O*C*H(CH_3)$_2$), 71.73 (C_{15}), 73.08 (C_9), 78.32 (C_{11}), 126.10, 128.19, 128.59, 132.73, 137.20, 142.51 (Ar), 129.00 (C_6), 129.79 (C_5), 133.35 (C_{13}), 134.55 (C_{14}), 173.58 (C_1), 198.48 (Ar*C*OCH$_3$); analytical HPLC (reversed phase) 99.5 area %. Anal. ($C_{28}H_{40}O_6$) C, H.

17-(4-Phenylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-14b]. An aqueous solution of 2 M Na_2CO_3 (0.42 mL, 0.84 mmol) was added to a stirred mixture of (15*S*)-**11b** (143 mg, 0.19 mmol, containing 5% of the trans isomer), tetrakis(triphenylphosphine)palladium(0) (11 mg, 3 mol %), and phenylboronic acid (85.5 mg, 0.70 mmol) in dimethoxyethane.[20] The reaction mixture was refluxed at 95 °C under nitrogen for 12 h. TLC indicated that some of the 9- and 11-hydroxyl groups had complexed with the excess of phenylboronic acid. The dimethoxyethane was evaporated, and the residue was dissolved in THF (2 mL). The reaction mixture was treated with H_2O_2 (about 20 drops from a pasteur pipette) and was stirred for 20 min (TLC showed that the 9,11-hydroxyl deprotection was complete). EtOAc was added (5 mL), and the organic layer was washed with brine (5 mL) and 3% aqueous citric acid (5 mL), dried ($MgSO_4$), and concentrated. The obtained oily product was purified by flash chromatography (EtOAc), furnishing 69 mg (72%) of (15*S*)-**14b** as an oil. The product was separated from the *trans* isomer with preparative HPLC (straight phase) which afforded 37 mg of isomerically pure (15*S*)-**14b**: TLC R_f = 0.11 (EtOAc); mp 79–83 °C; $[\alpha]^{23}_D$ = +32.1° (*c* 0.67, CH_3CN); ^{1}H NMR δ 1.21 (6H, d, OCH(C*H*$_3$)$_2$), 1.52 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.77 (1H, m, $H_{10\beta}$), 2.26 (2H, app t, H_2), 2.65–2.70 (2H, m, H_{17a} and H_{17b}), 3.96 (1H, broad m, H_{11}), 4.13 (1H, app q, H_{15}), 4.18 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH_3)$_2$), 5.38 (1H, m, H_5), 5.42 (1H, m, H_6), 5.52 (1H, dd, H_{13}), 5.63 (1H, dd, H_{14}), 7.20–7.60 (9H, m, Ar); ^{13}C NMR δ 21.83 (OCH(*C*H_3)$_2$), 24.89 (C_3), 25.59 (C_7), 26.63 (C_4), 31.46 (C_{17}), 34.03 (C_2), 38.76 (C_{16}), 42.89 (C_{10}), 50.47 (C_8), 55.85 (C_{12}), 67.71 (O*C*H(CH_3)$_2$), 72.13 (C_{15}), 72.92 (C_9), 78.11 (C_{11}), 126.97 (2C), 127.02 (2C), 127.13 (2C), 128.71 (2C), 128.86 (2C), 138.83, 141.04 (Ar) 128.98 (C_6), 129.86 (C_5), 132.95 (C_{13}), 134.88 (C_{14}), 173.51 (C_1); analytical HPLC (reversed phase) 98.8 area %. Anal. ($C_{32}H_{42}O_5 \cdot {}^1/_2H_2O$) C, H.

15β-Hydroxy-17-(4-phenylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-14b]. Compound (15*R*)-**11b** was prepared from (15*R*)-**11b** (136 mg, 0.27 mmol, containing 5% of the *trans* isomer) by the above method. Purification by flash chromatography (EtOAc) furnished 63 mg (67%) of (15*R*)-**14b**, containing about 5% of the *trans* isomer. Prepared HPLC (straight phase) furnished 42 mg of isomerically pure (15*R*)-**14b** as an oil: TLC R_f = 0.22 (EtOAc); $[\alpha]^{23}_D$ = +14.7° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.21 (6H, d, OCH(C*H*$_3$)$_2$), 1.52 (1H, app sept, H_8), 1.67 (2H, app quint, H_3), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.78 (1H, m, $H_{10\beta}$), 2.27 (2H, app t, H_2), 2.7–2.85 (2H, m, H_{17a} and H_{17b}), 3.96 (1H, broad m, H_{11}), 4.13 (1H, app q, H_{15}), 4.19 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH_3)$_2$), 5.38 (1H, m, H_5), 5.43 (1H, m, H_6), 5.55 (1H, dd, H_{13}), 5.64 (1H, dd, H_{14}), 7.20–7.60 (9H, m, Ar); ^{13}C NMR δ 21.94 (OCH(*C*H_3)$_2$), 24.96 (C_3), 25.74 (C_7), 26.70 (C_4), 31.52 (C_{17}), 34.06 (C_2), 38.85 (C_{16}), 43.08 (C_{10}), 50.94 (C_8), 56.05 (C_{12}), 67.84 (O*C*H(CH_3)$_2$), 71.90 (C_{15}), 73.24 (C_9), 78.47 (C_{11}), 127.06 (2C), 127.18 (2C), 128.78 (2C), 128.96 (2C), 129.13 (2C), 138.88, 141.13 (Ar), 128.96 (C_6), 129.89 (C_5), 132.46 (C_{13}), 134.77 (C_{14}), 173.63 (C_1); analytical HPLC (reversed phase) 97.9 area %. Anal. ($C_{32}H_{42}O_5$) C, H.

17-(3-Phenylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-14a]. Compound (15*S*)-**14a** was prepared from (15*S*)-**11a** (164 mg, 0.32 mmol, containing about 5% of the *trans* isomer) by the above method. Purification by flash chromatography (EtOAc) provided (15*S*)-**14a** in yield of 81% (131 mg). The product contained about 5% of the *trans* isomer. Preparative HPLC (straight phase) furnished 52% of isomerically pure (15*S*)-**14a** as a slightly yellow oil: TLC R_f = 0.15 (EtOAc); $[\alpha]^{23}_D$ = +29.1° (*c* 0.87, CH_3CN); ^{1}H NMR δ 1.19 (6H, d, OCH(C*H*$_3$)$_2$), 1.46 (1H, app sept, H_8), 1.67 (2H, app quint, H_3), 1.7–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.73 (1H, m, $H_{10\beta}$), 2.22 (2H, app t, H_2), 2.75 (2H, m, H_{17}), 3.89 (1H, broad m, H_{11}), 4.12 (2H, m, H_{15} and H_9), 4.96 (1H, sept, OC*H*(CH_3)$_2$), 5.35 and 5.42 (2H, m, H_5 and H_6), 5.47 (1H, dd, H_{13}), 5.62 (1H, dd, H_{14}), 7.16–7.59 (9H, m, Ar); ^{13}C NMR δ 21.78 (OCH(*C*H_3)$_2$), 24.81 (C_3), 25.39 (C_7), 26.57 (C_4), 31.90 (C_{17}), 33.97 (C_2), 38.74 (C_{16}), 42.76 (C_{10}), 50.01 (C_8), 55.54 (C_{12}), 67.64 (O*C*H(CH_3)$_2$), 72.26 (C_{15}), 72.44 (C_9), 77.64 (C_{11}), 124.66, 127.11 (2C), 127.15, 127.29, 127.36, 128.66 (2C), 128.75, 141.21, 141.24, 142.39 (Ar), 128.97 (C_6), 129.71 (C_5), 133.23 (C_{13}), 135.17 (C_{14}), 173.50 (C_1); analytical HPLC (reversed phase) 99.5 area %. Anal. ($C_{32}H_{42}O_5$) C, H.

15β-Hydroxy-17-(3-phenylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-14a]. Compound (15*R*)-**14a** was prepared from (15*R*)-**11a** (122 mg, 0.24 mmol, containing about 5% of the *trans* isomer) by the above method. Purification by flash chromatography (EtOAc) afforded 79 mg (65%) of (15*R*)-**14a** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) furnished 49 mg of isomerically pure (15*R*)-**14a** as an oil: TLC R_f = 0.25 (EtOAc); $[\alpha]^{23}_D$ = +18.0° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.21 (6H, d, OCH(C*H*$_3$)$_2$), 1.49 (1H, app sept, H_8), 1.64 (2H, app quint, H_3), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 1.78 (1H, m, $H_{10\beta}$), 2.25 (2H, app t, H_2), 2.77 (2H, m, H_{17a} and H_{17b}), 3.94 (1H, broad m, H_{11}), 4.13 (2H, app q, H_{15}), 4.17 (1H, broad m, H_9), 4.98 (1H, sept, OC*H*(CH_3)$_2$), 5.37 and 5.44 (2H, m, H_5 and H_6), 5.54 (1H, dd, H_{13}), 5.65 (1H, dd, H_{14}), 7.17–7.60 (9H, m, Ar); ^{13}C NMR δ 21.78 (OCH(*C*H_3)$_2$), 24.77 (C_3), 25.51 (C_7), 26.51 (C_4), 31.85 (C_{17}), 33.89 (C_2), 38.75 (C_{16}), 42.87 (C_{10}), 50.71 (C_8), 55.75 (C_{12}), 67.71 (O*C*H(CH_3)$_2$), 71.64 (C_{15}), 72.96 (C_9), 78.17 (C_{11}), 124.65, 127.10 (2C), 127.14, 127.32, 127.37, 128.65 (2C), 128.74, 141.21, 141.24, 142.42 (Ar) 129.04 (C_6), 129.68 (C_5), 132.23 (C_{13}), 134.64 (C_{14}), 173.58 (C_1); analytical HPLC (reversed phase) 96.4 area %. Anal. ($C_{32}H_{42}O_5$) C, H.

17-[4-(2-Furanyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-15b]. Compound (15*S*)-**15b** was prepared from (15*S*)-**11b** (120 mg, 0.24 mmol, containing about 5% of the *trans* isomer) and 2-furanylboronic acid[32] (66 mg, 0.59 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*S*)-**11b** had been consumed (t_R = 15.73 min) and a new peak had appeared at t_R = 17.37 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 90 mg (77%) of (15*S*)-**15b**, containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 47 mg of isomerically pure (15*S*)-**15b**: TLC R_f = 0.14 (EtOAc); mp 93–94 °C; $[\alpha]^{23}_D$ = +35.4° (*c* 0.83, CH_3CN); ^{1}H NMR δ 1.20 (6H, d, OCH(C*H*$_3$)$_2$), 1.48 (1H, app sept, H_8), 1.65 (2H, app quint, H_3), 1.74 (1H, m, $H_{10\beta}$), 1.75–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.25 (2H, app t, H_2), 2.69 (2H, m, H_{17}), 3.91 (1H, broad m, H_{11}), 4.08 (1H, app q, H_{15}), 4.14 (1H, broad m, H_9), 4.98 (1H, sept, OC*H*(CH_3)$_2$), 5.37 and 5.42 (2H, m, H_5 and H_6), 5.47 (1H, dd, H_{13}), 5.61 (1H, dd, H_{14}), 6.45 (1H, dd, ArCCH-C*H*CHO), 6.59 (1H, d, ArCCHCHC*H*O), 7.20 (2H, m, $H_{2'}$), 7.44 (1H, d, ArCC*H*CHCHO), 7.58 (2H, d, $H_{3'}$); ^{13}C NMR δ 21.79 (OCH(*C*H_3)$_2$), 24.84 (C_3), 25.43 (C_7), 26.59 (C_4), 31.54 (C_{17}), 34.00 (C_2), 38.55 (C_{16}), 42.79 (C_{10}), 50.14 (C_8), 55.62 (C_{12}), 67.66 (O*C*H(CH_3)$_2$), 72.15 (C_{15}), 72.57 (C_9), 77.77 (C_{11}), 104.34, 111.53, 123.83 (2C), 128.62, 128.71 (2C), 141.13, 141.70, 154.02 (Ar and Ar*C*CHCHCHO), 128.95 (C_6), 129.76 (C_5), 133.16 (C_{13}), 135.05 (C_{14}), 173.50 (C_1); analytical HPLC (reversed phase) 98.8 area %. Anal. ($C_{30}H_{40}O_6$) C, H.

17-[4-(2-Furanyl)phenyl]-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-15b]. Compound (15*R*)-**15b** was prepared from (15*R*)-**11b** (160 mg, 0.32 mmol, containing about 5% of the *trans* isomer) and 2-furanylboronic acid (88 mg, 0.78 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*R*)-**11b** had been consumed (t_R = 15.53 min), and a new peak had appeared at t_R = 16.92 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 140 mg (90%) of (15*R*)-**15b**, containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded

58 mg of isomerically pure (15*R*)-**15b** as a slightly yellow oil: TLC R_f = 0.26 (EtOAc); $[\alpha]^{23}_D$ = +18.3° (*c* 0.88, CH_3CN); ^1H NMR δ 1.22 (6H, d, OCH(C*H*$_3$)$_2$), 1.51 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.80 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.27 (2H, app t, H_2), 2.72 (2H, m, H_{17}), 3.96 (1H, broad m, H_{11}), 4.13 (1H, app q, H_{15}), 4.19 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH$_3$)$_2$), 5.38 and 5.43 (2H, m, H_5 and H_6), 5.51 (1H, dd, H_{13}), 5.64 (1H, dd, H_{14}), 6.45 (1H, dd, ArCCHC*H*CHO), 6.60 (1H, d, ArCCHCHC*H*O), 7.22 (2H, m, $H_{2'}$), 7.45 (1H, d, ArCC*H*CHCHO), 7.58 (2H, d, $H_{3'}$); ^{13}C NMR δ 21.82 (OCH(*C*H$_3$)$_2$), 24.82 (C_3), 25.61 (C_7), 26.56 (C_4), 31.52 (C_{17}), 33.93 (C_2), 38.62 (C_{16}), 42.97 (C_{10}), 50.85 (C_8), 55.94 (C_{12}), 67.73 (O*C*H(CH$_3$)$_2$), 71.75 (C_{15}), 73.15 (C_9), 78.37 (C_{11}), 104.35, 111.53, 123.86 (2C), 128.66, 128.77 (2C), 141.19, 141.72, 154.09 (Ar and Ar*C*C*H*C*H*C*H*O), 129.04 (C_6), 129.79 (C_5), 132.42 (C_{13}), 134.64 (C_{14}), 173.54 (C_1); analytical HPLC (reversed phase) 99.2 area %. Anal. ($C_{30}H_{40}O_6 \cdot {}^1/_2H_2O$) C, H.

17-[3-(2-Furanyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-15a]. Compound (15*S*)-**15a** was prepared from (15*S*)-**11a** (121 mg, 0.24 mmol, containing about 5% of the *trans* isomer) and 2-furanylboronic acid (66 mg, 0.59 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*S*)-**11a** had been consumed (t_R = 15.58 min) and a new peak had appeared at t_R = 17.32. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 90 mg (76%) of (15*S*)-**15a**, containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 61 mg of isomerically pure (15*S*)-**15a** as an oil: TLC R_f = 0.16 (EtOAc); $[\alpha]^{23}_D$ = +29.0° (*c* 1.0, CH_3CN); ^1H NMR δ 1.20 (6H, d, OCH(C*H*$_3$)$_2$), 1.46 (1H, app sept, H_8), 1.64 (2H, app quint, H_3), 1.72 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.22 (2H, app t, H_2), 2.70 (2H, m, H_{17}), 3.96 (1H, broad m, H_{11}), 4.08 and 4.12 (2H, m, H_{15} and H_9), 4.96 (1H, sept, OC*H*(CH$_3$)$_2$), 5.36 and 5.41 (2H, m, H_5 and H_6), 5.44 (1H, dd, H_{13}), 5.61 (1H, dd, H_{14}), 6.45 (1H, dd, ArCCHC*H*CHO), 6.62 (1H, d, ArCCHCHC*H*O), 7.07–7.51 (4H, m, Ar), 7.44 (1H, d, ArCC*H*CHCHO); ^{13}C NMR δ 21.74 (OCH(*C*H$_3$)$_2$), 24.79 (C_3), 25.33 (C_7), 26.54 (C_4), 31.80 (C_{17}), 33.97 (C_2), 38.57 (C_{16}), 42.72 (C_{10}), 49.83 (C_8), 55.41 (C_{12}), 67.59 (O*C*H(CH$_3$)$_2$), 72.25 (C_{15}), 72.25 (C_9), 77.47 (C_{11}), 104.84, 111.55, 121.34, 123.76, 127.47, 128.65, 130.82, 141.85, 142.33, 153.98 (Ar and Ar*C*C*H*C*H*C*H*O), 128.97 (C_6), 129.63 (C_5), 133.37 (C_{13}), 135.24 (C_{14}), 173.48 (C_1); analytical HPLC (reversed phase) 99.7 area %. Anal. ($C_{30}H_{40}O_6 \cdot {}^1/_4H_2O$) C, H.

17-[3-(2-Furanyl)phenyl]-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-15a]. Compound (15*R*)-**15a** was prepared from (15*R*)-**11a** (156 mg, 0.31 mmol, containing about 5% of the *trans* isomer) and 2-furanylboronic acid (86 mg, 0.77 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*R*)-**11a** had been consumed (t_R = 15.13 min) and a new peak had appeared at t_R = 16.91 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc) furnishing 115 mg (76%) of (15*R*)-**15a**, containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 52 mg of isomerically pure (15*R*)-**15a** as an oil: TLC R_f = 0.24 (EtOAc); $[\alpha]^{23}_D$ = +19.6° (*c* 1.0, CH_3CN); ^1H NMR δ 1.21 (6H, d, OCH(C*H*$_3$)$_2$), 1.50 (1H, app sept, H_8), 1.65 (2H, app quint, H_3), 1.78 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.26 (2H, app t, H_2), 2.77 (2H, m, H_{17}), 3.96 (1H, broad m, H_{11}), 4.12 (1H, app q, H_{15}), 4.18 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH$_3$)$_2$), 5.38 and 5.43 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.64 (1H, dd, H_{14}), 6.46 (1H, dd, ArCCHC*H*CHO), 6.63 (1H, d, ArCCHCHC*H*O), 7.09–7.52 (4H, m, Ar), 7.45 (1H, d, ArCC*H*CHCHO); ^{13}C NMR δ 21.81 (OCH(*C*H$_3$)2), 24.79 (C_3), 25.55 (C_7), 26.53 (C_4), 31.79 (C_{17}), 33.90 (C_2), 38.63 (C_{16}), 42.89 (C_{10}), 50.79 (C_8), 55.87 (C_{12}), 67.74 (O*C*H(CH$_3$)$_2$), 71.72 (C_{15}), 73.07 (C_9), 78.27 (C_{11}), 104.88, 111.58, 121.39, 123.83, 127.53, 128.69, 130.87, 141.90, 142.34, 154.02 (Ar and Ar*C*C*H*C*H*C*HO), 129.03 (C_6), 129.74 (C_5), 132.37 (C_{13}), 134.63 (C_{14}), 173.59 (C_1); analytical HPLC (reversed phase) 98.0 area %. Anal. ($C_{30}H_{40}O_6$) C, H.

17-[4-(3-Furanyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-16b]. Compound (15*S*)-**16b** was prepared from (15*S*)-**11b** (119 mg, 0.24 mmol, containing about 5% of the *trans* isomer) and 3-furanylboronic acid[32] (65 mg, 0.58 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, TLC indicated some complexation between the excess of 3-furanylboronic acid and the 9,11-hydroxyl groups. Deprotection was done as above. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*S*)-**11b** had been consumed (t_R = 15.73 min), and a new peak had appeared at t_R = 17.29 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 72 mg (61%) of (15*S*)-**16b** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 58 mg of isomerically pure (15*S*)-**16b**: TLC R_f = 0.13 (EtOAc); mp = 89–92 °C; $[\alpha]^{23}_D$ = +31.9° (*c* 1.0, CH_3CN); ^1H NMR δ 1.20 (6H, d, OCH(C*H*$_3$)$_2$), 1.48 (1H, app sept, H_8), 1.65 (2H, app quint, H_3), 1.73 (1H, m, $H_{10\beta}$), 1.75–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.25 (2H, app t, H_2), 2.69 (2H, m, H_{17}), 3.91 (1H, broad m, H_{11}), 4.09 (1H, app q, H_{15}), 4.15 (1H, broad m, H_9), 4.98 (1H, sept, OC*H*(CH$_3$)$_2$), 5.38 and 5.43 (2H, m, H_5 and H_6), 5.48 (1H, dd, H_{13}), 5.63 (1H, dd, H_{14}), 6.68 (1H, dd, ArCHC-C*H*CHO), 7.19 (2H, d, $H_{2'}$), 7.39 (2H, d, $H_{3'}$), 7.46 (1H, dd, ArCHCCHC*H*O), 7.70 (1H, dd, ArC*H*CCHCHO); ^{13}C NMR δ 21.80 (OCH(*C*H$_3$)$_2$), 24.84 (C_3), 25.42 (C_7), 26.59 (C_4), 31.47 (C_{17}), 34.00 (C_2), 38.65 (C_{16}), 42.79 (C_{10}), 50.12 (C_8), 55.61 (C_{12}), 67.66 (O*C*H(CH$_3$)$_2$), 72.19 (C_{15}), 72.53 (C_9), 77.75 (C_{11}), 108.80, 125.85 (2C), 126.24, 128.84 (2C), 129.94, 138.17, 140.72, 143.52 (Ar and Ar*C*C*H*C*H*C*HO), 128.96 (C_6), 129.75 (C_5), 133.16 (C_{13}), 135.10 (C_{14}), 173.50 (C_1); analytical HPLC (reversed phase) 96.4 area %. Anal. ($C_{30}H_{40}O_6 \cdot {}^1/_2H_2O$) C, H.

17-[4-(3-Furanyl)phenyl]-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-16b]. Compound (15*R*)-**16b** was prepared from (15*R*)-**11b** (95 mg, 0.19 mmol, containing about 5% of the *trans* isomer) and 3-furanylboronic acid (53 mg, 0.47 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, TLC indicated some complexation between the excess of 3-furanylboronic acid and the 9,11-hydroxyl groups. Deprotection was done as above. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*R*)-**11b** had been consumed (t_R = 15.53 min) and a new peak had appeared at t_R = 16.85 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 86 mg (93%) of (15*R*)-**16b** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 42 mg of isomerically pure (15*R*)-**16b** as an oil: TLC R_f = 0.26 (EtOAc); $[\alpha]^{23}_D$ = +17.0° (*c* 1.1, CH_3CN); ^1H NMR δ 1.22 (6H, d, OCH(C*H*$_3$)$_2$), 1.51 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.80 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.27 (2H, app t, H_2), 2.71 (2H, m, H_{17}), 3.96 (1H, broad m, H_{11}), 4.14 (1H, app q, H_{15}), 4.19 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH$_3$)$_2$), 5.38 and 5.43 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.64 (1H, dd, H_{14}), 6.68 (1H, app q, ArCHCC*H*CHO), 7.21 (2H, d, $H_{2'}$), 7.40 (2H, d, $H_{3'}$), 7.46 (1H, app t, ArCHCCHC*H*O), 7.70 (1H, m, ArC*H*CCHCHO); ^{13}C NMR δ 21.81 (OCH(*C*H$_3$)$_2$), 24.79 (C_3), 25.54 (C_7), 26.53 (C_4), 31.43 (C_{17}), 33.90 (C_2), 38.68 (C_{16}), 42.92 (C_{10}), 50.82 (C_8), 55.91 (C_{12}), 67.74 (O*C*H(CH$_3$)$_2$), 71.75 (C_{15}), 73.09 (C_9), 78.32 (C_{11}), 108.80, 125.85 (2C), 126.25, 128.87 (2C), 129.95, 138.17, 140.74, 143.53 (Ar and Ar*C*C*H*C*H*C*HO), 129.01 (C_6), 129.77 (C_5), 132.35 (C_{13}), 134.64 (C_{14}), 173.57 (C_1); analytical HPLC (reversed phase) 99.6 area %. Anal. ($C_{30}H_{40}O_6 \cdot {}^1/_2H_2O$) C, H.

17-[3-(3-Furanyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-16a]. Compound (15*S*)-**16a** was prepared from (15*S*)-**11a** (108 mg, 0.21 mmol, containing about 5% of the *trans* isomer) and 3-furanylboronic acid (59 mg, 0.53 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, analytical HPLC (straight phase) showed that the (15*S*)-**11a** had been consumed (t_R = 15.58 min) and a new peak had appeared at t_R = 17.34 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 79 mg (75%) of (15*S*)-**16a** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 44 mg of isomerically pure (15*S*)-**16a** as an oil: TLC R_f = 0.15 (EtOAc); $[\alpha]^{23}_D$ = +26.2° (*c* 1.0, CH_3CN); ^1H NMR δ 1.20 (6H, d, OCH(C*H*$_3$)$_2$), 1.48 (1H, app sept, H_8), 1.64 (2H, app quint, H_3), 1.73 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.24 (2H, app t, H_2), 2.70 (2H, m, H_{17}),

3.91 (1H, broad m, H_{11}), 4.10 (2H, m, H_{15} and H_9), 4.97 (1H, sept, OC*H*(CH_3)$_2$), 5.37 and 5.41 (2H, m, H_5 and H_6), 5.47 (1H, dd, H_{13}), 5.62 (1H, dd, H_{14}), 6.69 (1H, dd, ArCHCC*H*CHO), 7.08–7.32 (4H, m, Ar), 7.46 (1H, dd, ArCHCCHC*H*O), 7.72 (1H, dd, ArC*H*CCHCHO); ^{13}C NMR δ 21.78 (OCH(CH_3)$_2$), 24.82 (C_3), 25.41 (C_7), 26.58 (C_4), 31.82 (C_{17}), 33.98 (C_2), 38.71 (C_{16}), 42.79 (C_{10}), 50.14 (C_8), 55.59 (C_{12}), 67.66 (O*C*H(CH_3)$_2$), 72.20 (C_{15}), 72.54 (C_9), 77.76 (C_{11}), 108.83, 123.40, 125.96, 126.42, 127.11, 128.81, 132.39, 138.44, 142.46, 143.56 (Ar and Ar*C*C*H*C*H*CHO), 128.95 (C_6), 129.77 (C_5), 133.13 (C_{13}), 135.08 (C_{14}), 173.51 (C_1); analytical HPLC (reversed phase) 98.2 area %. Anal. ($C_{30}H_{40}O_6$·H_2O) C, H.

17-[3-(3-Furanyl)phenyl]-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-16a]. The compound (15*R*)-**16a** was prepared from (15*R*)-**11a** (156 mg, 0.31 mmol, containing about 5% of the *trans* isomer) and 3-furanylboronic acid (85 mg, 0.76 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, TLC indicated some complexation between the excess of 3-furanylboronic acid and the 9,11-hydroxyl groups. Deprotection was done as above. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*R*)-**11a** had been consumed (t_R = 15.13 min) and a new peak had appeared at t_R = 16.89 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 68 mg (45%) of (15*R*)-**16a** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 11 mg of isomerically pure (15*R*)-**16a** as an oil: TLC R_f = 0.28 (EtOAc); $[\alpha]^{23}_D$ = +20.6° (*c* 1.1, CH_3CN); ^{1}H NMR δ 1.22 (6H, d, OCH(C*H*$_3$)$_2$), 1.52 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.80 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.27 (2H, app t, H_2), 2.74 (2H, m, H_{17}), 3.96 (1H, broad m, H_{11}), 4.12 (1H, app q, H_{15}), 4.19 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH_3)$_2$), 5.38 and 5.43 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.64 (1H, dd, H_{14}), 6.69 (1H, dd, ArCHCC*H*CHO), 7.10–7.33 (4H, m, Ar), 7.47 (1H, dd, ArCHCCHC*H*O), 7.73 (1H, dd, ArC*H*CCHCHO); ^{13}C NMR δ 21.82 (OCH(*C*H$_3$)$_2$), 24.80 (C_3), 25.57 (C_7), 26.54 (C_4), 31.79 (C_{17}), 33.89 (C_2), 38.74 (C_{16}), 42.93 (C_{10}), 50.85 (C_8), 55.98 (C_{12}), 67.73 (O*C*H(CH_3)$_2$), 71.82 (C_{15}), 73.14 (C_9), 78.37 (C_{11}), 108.84, 123.41, 126.02, 126.45, 127.15, 128.82, 132.42, 138.44, 142.48, 143.58 (Ar and Ar*C*C*H*C*H*CHO), 129.00 (C_6), 129.79 (C_5), 132.42 (C_{13}), 134.66 (C_{14}), 173.57 (C_1); analytical HPLC (reversed phase) 97.4 area %. Anal. ($C_{30}H_{40}O_6$·H_2O) C, H.

17-[4-(2-Thienyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-17b]. Compound (15*S*)-**17b** was prepared from (15*S*)-**11b** (79 mg, 0.16 mmol, containing about 5% of the *trans* isomer) and 2-thienylboronic acid[32] (50 mg, 0.39 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*S*)-**11b** had been consumed (t_R = 15.73 min) and a new peak had appeared at t_R = 16.63 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 68 mg (85%) of (15*S*)-**17b**, containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 26 mg of isomerically pure (15*S*)-**17b**: TLC R_f = 0.15 (EtOAc); mp 93–94 °C; $[\alpha]^{23}_D$ = +30.0° (*c* 0.82, CH_3CN); ^{1}H NMR δ 1.21 (6H, d, OCH(C*H*$_3$)$_2$), 1.52 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.79 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.26 (2H, app t, H_2), 2.72 (2H, m, H_{17}), 3.96 (1H, broad m, H_{11}), 4.12 (1H, app q, H_{15}), 4.18 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH_3)$_2$), 5.38 and 5.43 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.63 (1H, dd, H_{14}), 7.05–7.54 (7H, m, Ar and ArCC*H*C*H*C*H*S); ^{13}C NMR δ 21.83 (OCH(*C*H$_3$)$_2$), 24.85 (C_3), 25.58 (C_7), 26.61 (C_4), 31.47 (C_{17}), 33.98 (C_2), 38.64 (C_{16}), 42.87 (C_{10}), 50.56 (C_8), 55.88 (C_{12}), 67.70 (O*C*H(CH_3)$_2$), 71.99 (C_{15}), 72.99 (C_9), 78.19 (C_{11}), 122.66, 124.37, 125.97 (2C), 127.92, 128.94 (2C), 129.86, 132.09, 141.29, 144.39 (Ar and Ar*C*C*H*C*H*CHS), 128.94 (C_6), 129.86 (C_5), 132.85 (C_{13}), 134.71 (C_{14}), 173.50 (C_1); analytical HPLC (reversed phase) 98.0 area %. Anal. ($C_{30}H_{40}O_6$·$^1/_2H_2O$) C, H.

15β-Hydroxy-17-[4-(2-thienyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-17b]. Compound (15*R*)-**17b** was prepared from (15*R*)-**11b** (93 mg, 0.18 mmol, containing about 5% of the *trans* isomer) and 2-thienylboronic acid (57 mg, 0.45 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*R*)-**11b** had been consumed (t_R = 15.53 min) and a new peak had appeared at t_R = 16.23 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 86 mg (92%) of (15*R*)-**17b** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 66 mg of isomerically pure (15*R*)-**17b** as an oil: TLC R_f = 0.25 (EtOAc); $[\alpha]^{23}_D$ = +14.6° (*c* 0.95, CH_3CN); ^{1}H NMR δ 1.22 (6H, d, OCH(C*H*$_3$)$_2$), 1.51 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.79 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.27 (2H, app t, H_2), 2.71 (2H, m, H_{17}), 3.95 (1H, broad m, H_{11}), 4.11 (1H, app q, H_{15}), 4.18 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH_3)$_2$), 5.38 and 5.43 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.64 (1H, dd, H_{14}), 7.04–7.54 (7H, m, Ar and ArCC*H*C*H*C*H*S); ^{13}C NMR δ 21.80 (OCH(*C*H$_3$)$_2$), 24.79 (C_3), 25.54 (C_7), 26.52 (C_4), 31.41 (C_{17}), 33.90 (C_2), 38.58 (C_{16}), 42.91 (C_{10}), 50.79 (C_8), 55.86 (C_{12}), 67.73 (O*C*H(CH_3)$_2$), 71.67 (C_{15}), 73.06 (C_9), 78.28 (C_{11}), 122.62, 124.33, 125.92 (2C), 127.91, 128.94 (2C), 132.02, 141.35, 144.38 (Ar and Ar*C*C*H*C*H*CHS), 129.02 (C_6), 129.74 (C_5), 132.35 (C_{13}), 134.62 (C_{14}), 173.58 (C_1); analytical HPLC (reversed phase) 99.3 area %. Anal. ($C_{30}H_{40}O_6$) C, H.

17-[3-(2-Thienyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-17a]. Compound (15*S*)-**17a** was prepared from (15*S*)-**11a** (109 mg, 0.21 mmol, containing about 5% of the *trans* isomer) and 2-thienylboronic acid (58 mg, 0.46 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*S*)-**11a** had been consumed (t_R = 15.58 min) and a new peak had appeared at t_R = 16.35 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 99 mg (90%) of (15*S*)-**17a** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 32 mg of isomerically pure (15*S*)-**17a** as an oil: TLC R_f = 0.15 (EtOAc); $[\alpha]^{23}_D$ = +30.0° (*c* 0.92, CH_3CN); ^{1}H NMR δ 1.20 (6H, d, OCH(C*H*$_3$)$_2$), 1.51 (1H, app sept, H_8), 1.65 (2H, app quint, H_3), 1.78 (1H, m, $H_{10\beta}$), 1.75–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.25 (2H, app t, H_2), 2.72 (2H, m, H_{17}), 3.94 (1H, broad m, H_{11}), 4.12 (1H, app q, partly obscured by H_9, H_{15}), 4.17 (1H, broad m, H_9), 4.98 (1H, sept, OC*H*(CH_3)$_2$), 5.38 and 5.42 (2H, m, H_5 and H_6), 5.51 (1H, dd, H_{13}), 5.63 (1H, dd, H_{14}), 7.05–7.44 (7H, m, Ar and ArCC*H*C*H*C*H*S); ^{13}C NMR δ 21.81 (OCH(*C*H$_3$)$_2$), 24.84 (C_3), 25.54 (C_7), 26.60 (C_4), 31.79 (C_{17}), 33.98 (C_2), 38.68 (C_{16}), 42.82 (C_{10}), 50.36 (C_8), 55.76 (C_{12}), 67.68 (O*C*H(CH_3)$_2$), 72.08 (C_{15}), 72.82 (C_9), 78.01 (C_{11}), 122.99, 123.53, 124.66, 126.07, 127.63, 127.93, 128.96, 134.86, 142.58, 144.46 (Ar and Ar*C*C*H*C*H*CHS), 128.91 (C_6), 129.82 (C_5), 133.02 (C_{13}), 134.40 (C_{14}), 173.50 (C_1); analytical HPLC (reversed phase) 96.2 area %. Anal. ($C_{30}H_{40}O_6$·$^1/_4H_2O$) C, H.

15β-Hydroxy-17-[3-(2-thienyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-17a]. Compound (15*R*)-**17a** was prepared from (15*R*)-**11a** (150 mg, 0.29 mmol, containing about 5% of the *trans* isomer) and 2-thienylboronic acid (113 mg, 0.88 mmol) by the above method. After the mixture was reflux at 95 °C overnight, analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*R*)-**11b** had been consumed (t_R = 15.13 min) and a new peak at t_R = 16.02 min had appeared. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 97 mg (65%) of (15*R*)-**17a**, containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 65 mg of isomerically pure (15*R*)-**17a** as an oil: TLC R_f = 0.18 (EtOAc); $[\alpha]^{23}_D$ = +17.2° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.21 (6H, d, OCH(C*H*$_3$)$_2$), 1.51 (1H, app sept, H_8), 1.65 (2H, app quint, H_3), 1.79 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.26 (2H, app t, H_2), 2.74 (2H, m, H_{17}), 3.95 (1H, broad m, H_{11}), 4.13 (1H, broad m, H_{15}), 4.17 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH_3)$_2$), 5.38 and 5.43 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.65 (1H, dd, H_{14}), 7.05–7.45 (7H, m, Ar and ArCC*H*C*H*C*H*S); ^{13}C NMR δ 21.81 (OCH(*C*H$_3$)$_2$), 24.79 (C_3), 25.55 (C_7), 26.53 (C_4), 31.74 (C_{17}), 33.90 (C_2), 38.65 (C_{16}), 42.91 (C_{10}), 50.79 (C_8), 55.87 (C_{12}), 67.73 (O*C*H(CH_3)$_2$), 71.71 (C_{15}), 73.07 (C_9), 78.28 (C_{11}), 122.98, 123.50, 124.64, 126.08, 127.65, 127.92, 128.88, 134.37, 142.61, 144.46 (Ar and Ar*C*C*H*C*H*CHS), 129.03 (C_6), 129.74 (C_5), 132.39 (C_{13}), 134.62 (C_{14}), 173.58 (C_1);

analytical HPLC (reversed phase) 99.5 area %. Anal. ($C_{30}H_{40}O_6$) C, H.

17-[4-(3-Thienyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-18b]. Compound (15*S*)-**18b** was prepared from (15*S*)-**11b** (99 mg, 0.19 mmol, containing about 5% of the *trans* isomer) and 3-thienylboronic acid[32] (62 mg, 0.48 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, TLC indicated some complexation between the excess of 3-thienylboronic acid and the 9,11-hydroxyl groups. Deprotection was done as above. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*S*)-**11b** had been consumed (t_R = 15.73 min) and a new peak had appeared at t_R = 16.97 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 63 mg (64%) of (15*S*)-**18b** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 31 mg of isomerically pure (15*S*)-**18b**: TLC R_f = 0.14 (EtOAc); mp 88–89 °C; $[\alpha]^{23}_D$ = +37.1° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.21 (6H, d, OCH(C*H*$_3$)$_2$), 1.51 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.7–2.4 (9H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, $H_{10\beta}$, H_{16}), 2.26 (2H, app t, H_2), 2.71 (2H, m, H_{17}), 3.95 (1H, broad m, H_{11}), 4.12 (1H, broad m, H_{15}), 4.17 (1H, broad m, H_9), 4.98 (1H, sept, OC*H*(CH$_3$)$_2$), 5.38 and 5.43 (2H, m, H_5 and H_6), 5.51 (1H, dd, H_{13}), 5.63 (1H, dd, H_{14}), 7.22 (2H, d, $H_{2'}$), 7.38 (3H, m, ArC*H*CC*H*C*H*S), 7.51 (2H, d, $H_{3'}$); ^{13}C NMR δ 21.82 (OCH(*C*H$_3$)$_2$), 24.84 (C_3), 25.54 (C_7), 26.60 (C_4), 31.46 (C_{17}), 33.99 (C_2), 38.68 (C_{16}), 42.85 (C_{10}), 50.44 (C_8), 55.81 (C_{12}), 67.69 (O*C*H(CH$_3$)$_2$), 72.08 (C_{15}), 72.88 (C_9), 78.08 (C_{11}), 119.75, 126.06, 126.26, 126.43 (2C), 128.85 (2C), 132.91, 140.84, 142.18 (Ar and ArC*H*CC*H*CHS), 128.95 (C_6), 129.83 (C_5), 133.51 (C_{13}), 134.83 (C_{14}), 173.49 (C_1); analytical HPLC (reversed phase) 98.8 area %. Anal. ($C_{30}H_{40}O_6$) C, H.

15β-Hydroxy-17-[4-(3-thienyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-18b]. Compound (15*R*)-**18b** was prepared from (15*R*)-**11b** (117 mg, 0.23 mmol, containing about 5% of the *trans* isomer) and 3-thienylboronic acid (74 mg, 0.58 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, TLC indicated some complexation between the excess of 3-thienylboronic acid and the 9,11-hydroxyl groups. Deprotection was done as above. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*R*)-**11b** had been consumed (t_R = 15.53 min) and a new peak had appeared at t_R = 16.26 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 73 mg (62%) of (15*R*)-**18b** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 50 mg of isomerically pure (15*R*)-**18b** as a white solid: TLC R_f = 0.23 (EtOAc); $[\alpha]^{23}_D$ = +15.5° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.22 (6H, d, OCH(C*H*$_3$)$_2$), 1.52 (1H, app sept, H_8), 1.66 (2H, app quint, H_3), 1.7–2.4 (9H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, $H_{10\beta}$, H_{16}), 2.27 (2H, app t, H_2), 2.73 (2H, m, H_{17}), 3.96 (1H, broad m, H_{11}), 4.14 (1H, broad m, H_{15}), 4.19 (1H, broad m, H_9), 4.99 (1H, sept, OC*H*(CH$_3$)$_2$), 5.39 and 5.44 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.65 (1H, dd, H_{14}), 7.23 (2H, d, $H_{2'}$), 7.37–7.42 (3H, m, ArC*H*CC*H*C*H*S), 7.51 (2H, d, $H_{3'}$); ^{13}C NMR δ 21.83 (OCH(*C*H$_3$)$_2$), 24.81 (C_3), 25.57 (C_7), 26.54 (C_4), 31.42 (C_{17}), 33.91 (C_2), 38.67 (C_{16}), 42.94 (C_{10}), 50.85 (C_8), 55.96 (C_{12}), 67.74 (O*C*H(CH$_3$)$_2$), 71.80 (C_{15}), 73.14 (C_9), 78.86 (C_{11}), 119.75, 126.07, 126.27, 126.42 (2C), 128.89 (2C), 132.38, 140.89, 142.19 (Ar and ArC*H*CC*H*CHS), 129.02 (C_6), 129.79 (C_5), 133.49 (C_{13}), 134.66 (C_{14}), 173.57 (C_1); analytical HPLC (reversed phase) 99.2 area %. Anal. ($C_{30}H_{40}O_6$) C, H.

17-[3-(3-Thienyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*S*)-18a]. Compound (15*S*)-**18a** was prepared from (15*S*)-**11a** (106 mg, 0.21 mmol, containing about 5% of the *trans* isomer) and 3-thienylboronic acid (66 mg, 0.52 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, TLC indicated some complexation between the excess of 3-thienylboronic acid and the 9,11-hydroxyl groups. Deprotection was done as above. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that (15*S*)-**11a** had been consumed (t_R = 15.58 min) and a new peak had appeared at t_R = 16.41 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 80 mg (75%) of (15*S*)-**18a** containing about 5% of the *trans* isomer. Separation with preparative HPLC (straight phase) afforded 38 mg of isomerically pure (15*S*)-**18a** as an oil: TLC R_f = 0.22 (EtOAc); $[\alpha]^{23}_D$ = +26.9° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.20 (6H, d, OCH(C*H*$_3$)$_2$), 1.48 (1H, app sept, H_8), 1.64 (2H, app quint, H_3), 1.73 (1H, m, $H_{10\beta}$), 1.75–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.24 (2H, app t, H_2), 2.73 (2H, m, H_{17}), 3.91 (1H, broad m, H_{11}), 4.12 (2H, broad m, H_{15} and H_9), 4.97 (1H, sept, OC*H*(CH$_3$)$_2$), 5.36 and 5.41 (2H, m, H_5 and H_6), 5.48 (1H, dd, H_{13}), 5.62 (1H, dd, H_{14}), 7.11–7.43 (7H, m, Ar and ArC*H*CC*H*C*H*S); ^{13}C NMR δ 21.80 (OCH(*C*H$_3$)$_2$), 24.83 (C_3), 25.43 (C_7), 26.59 (C_4), 31.86 (C_{17}), 33.98 (C_2), 38.74 (C_{16}), 42.80 (C_{10}), 50.19 (C_8), 55.64 (C_{12}), 67.66 (O*C*H(CH$_3$)$_2$), 72.17 (C_{15}), 72.62 (C_9), 77.82 (C_{11}), 120.18, 124.00, 126.09, 126.34, 126.59, 127.26, 128.81, 135.87, 142.36, 142.44 (Ar and ArC*H*CC*H*C*H*S), 128.97 (C_6), 129.78 (C_5), 133.09 (C_{13}), 135.05 (C_{14}), 173.50 (C_1); analytical HPLC (reversed phase) 98.7 area %. Anal. ($C_{30}H_{40}O_6$) C, H.

15β-Hydroxy-17-[3-(3-thienyl)phenyl]-18,19,20-trinor-PGF$_{2\alpha}$ Isopropyl Ester [(15*R*)-18a]. Compound (15*R*)-**18a** was prepared from (15*R*)-**11a** (156 mg, 0.31 mmol, containing about 5% of the *trans* isomer) and 3-thienylboronic acid (118 mg, 0.92 mmol) by the above method. After the mixture was refluxed at 95 °C overnight, TLC indicated some complexation between the excess of 3-thienylboronic acid and the 9,11-hydroxyl groups. Deprotection was done as above. Analytical HPLC (straight phase, 6% ethanol in *n*-hexane) showed that the (15*R*)-**11a** had been consumed (t_R = 15.13 min) and a new peak had appeared at t_R = 16.18 min. The workup was done as above, and the residue was purified by flash chromatography (EtOAc), furnishing 77 mg (49%) of (15*R*)-**18a** containing about 5% of the *trans* isomer. Preparative HPLC (straight phase) afforded 54 mg of isomerically pure (15*R*)-**18a** as an oil: TLC R_f = 0.20 (EtOAc); $[\alpha]^{23}_D$ = +17.9° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.21 (6H, d, OCH(C*H*$_3$)$_2$), 1.49 (1H, app sept, H_8), 1.65 (2H, app quint, H_3), 1.79 (1H, m, $H_{10\beta}$), 1.8–2.4 (8H, m, H_{12}, H_7, H_4, $H_{10\alpha}$, H_{16}), 2.26 (2H, app t, H_2), 2.76 (2H, m, H_{17}), 3.94 (1H, broad m, H_{11}), 4.17 (2H, broad m, H_{15} and H_9), 4.98 (1H, sept, OC*H*(CH$_3$)$_2$), 5.37 and 5.43 (2H, m, H_5 and H_6), 5.52 (1H, dd, H_{13}), 5.65 (1H, dd, H_{14}), 7.12–7.44 (7H, m, Ar and ArC*H*CC*H*C*H*S); ^{13}C NMR δ 21.80 (OCH(*C*H$_3$)$_2$), 24.78 (C_3), 25.52 (C_7), 26.51 (C_4), 31.82 (C_{17}), 33.90 (C_2), 38.73 (C_{16}), 42.89 (C_{10}), 50.75 (C_8), 55.81 (C_{12}), 67.73 (O*C*H(CH$_3$)$_2$), 71.68 (C_{15}), 73.00 (C_9), 78.22 (C_{11}), 120.17, 123.98, 126.08, 126.33, 126.61, 127.27, 128.80, 135.85, 142.35, 142.46 (Ar and ArC*H*CC*H*C*H*S), 129.03 (C_6), 129.71 (C_5), 132.28 (C_{13}), 134.64 (C_{14}), 173.58 (C_1); analytical HPLC (reversed phase) 97.3 area %. Anal. ($C_{30}H_{40}O_6 \cdot {}^1/_2H_2O$) C, H.

17-(3-Bromophenyl)-18,19,20-trinor-PGF$_{2\alpha}$ [(15*S*)-20a]. An aqueous solution of sodium hydroxide (60 μL, 2 M) was added to a stirred solution of (15*S*)-**11a** (24 mg, 0.047 mmol) in ethanol (99.6%, 2 mL). The hydrolysis was complete after stirring at room temperature for 2 days and the addition of 1 equiv of sodium hydroxide (TLC). Toluene (10 mL) was added to the reaction mixture, and the organic layer was extracted with 5% aqueous $NaHCOH_3$ (10 mL). The aqueous layer was acidified with 1 M aqueous HCl, and the acid was isolated by extraction with EtOAc (3 × 10 mL). The organic layers were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated to give 16 mg (75%) of (15*S*)-**20a** as an oil: $[\alpha]^{23}_D$ = 39.1° (*c* 1.1, CH_3CN); ^{1}H NMR δ 1.47 (1H, m, H_8), 1.66 (H, m, H_3), 1.7–1.9 (3H, m, H_{16}, $H_{10\beta}$), 2.05–2.4 (8H, m, H_7, H_4, H_2, H_{12}, $H_{10\alpha}$), 2.64 (2H, m, H_{17}), 3.92 (1H, broad m, H_{11}), 4.09 (1H, app q, H_{15}), 4.15 (1H, broad m, H_9), 5.34–5.59 (4H, m, H_5, H_6, H_{13} and H_{14}), 7.11 (2H, m, Ar), 7.30 (2H, m, Ar); ^{13}C NMR δ 24.38 (C_3), 25.21 (C_7), 26.24 (C_4), 31.44 (C_{17}), 32.86 (C_2), 38.17 (C_{16}), 42.70 (C_{10}), 50.03 (C_8), 55.25 (C_{12}), 72.14 (C_{15}), 72.42 (C_9), 77.20 (C_{11}), 122.39, 127.11, 128.94, 129.95, 131.47, 144.24 (Ar), 129.07 (C_6), 129.68 (C_5), 133.18 (C_{13}), 134.64 (C_{14}), 177.66 (C_1); analytical HPLC (reversed phase) 98.2 area %.

17-(3-Bromophenyl)-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ [(15*R*)-20a]: yield 81%; $[\alpha]^{23}_D$ = 15.7° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.43 (1H, m, H_8), 1.62 (2H, m, H_3), 1.78 (1H, m, $H_{10\beta}$, partly obscured by H_{16}), 1.85 (2H, m, H_{16}, partly obscured by $H_{10\beta}$), 2.10 (2H, m, H_4, partly obscured by H_7), 2.18 (2H, m, H_7, partly obscured by H_4 and $H_{10\alpha}$), 2.21 (1H, m, $H_{10\alpha}$, partly obscured by H_7), 2.33 (2H, m, H_2, partly obscured by H_{12}), 2.36 (1H, m, H_{12}, partly obscured by H_2), 2.68 (2H, m, H_{17}), 3.94

(1H, broad m, H_{11}), 4.10 (1H, app q, H_{15}), 4.17 (1H, broad m, H_9), 5.39 (1H, m, H_5), 5.52 (2H, m, H_6 and H_{13}), 5.63 (1H, m, H_{14}), 7.11 (2H, m, Ar), 7.31 (2H, m, Ar); ^{13}C NMR δ 24.38 (C_3), 24.94 (C_7), 26.11 (C_4), 31.37 (C_{17}), 32.70 (C_2), 38.23 (C_{16}), 42.92 (C_{10}), 50.74 (C_8), 55.41 (C_{12}), 71.84 (C_{15}), 72.48 (C_9), 77.21 (C_{11}), 122.37, 127.12, 128.92, 129.94, 131.48, 144.20 (Ar), 128.98 (C_6), 129.62 (C_5), 132.74 (C_{13}), 134.26 (C_{14}), 177.36 (C_1); analytical HPLC (reversed phase) 95.2 area %, largest impurity was estimated to 1.8 area %.

17-(4-Bromophenyl)-18,19,20-trinor-PGF$_{2\alpha}$ [(15*S*)-20b]: yield 81%; $[\alpha]^{23}_D$ = +30.9° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.45 (1H, m, H_8), 1.63–1.9 (5H, m, H_3, $H_{10\beta}$, H_{16a}, H_{16b}), 2.04–2.3 (8H, m, H_7, H_4, H_2, H_{12}, $H_{10\alpha}$), 2.61 (2H, m, H_{17}), 3.89 (1H, broad m, H_{11}), 4.10 (2H, broad m, H_{15} and H_9), 5.2–5.6 (4H, m, H_5, H_6, H_{13} and H_{14}), 7.03 (2H, d, Ar), 7.36 (2H, d, Ar); ^{13}C NMR δ 24.54 (C_3), 25.36 (C_7), 26.41 (C_4), 31.29 (C_{17}), 33.07 (C_2), 38.38 (C_{16}), 42.85 (C_{10}), 50.09 (C_8), 55.32 (C_{12}), 72.28 (C_{15}), 72.46 (C_9), 77.74 (C_{11}), 119.64, 130.30 (2C), 131.50 (2C), 140.90 (Ar), 129.19 (C_6), 129.75 (C_5), 133.31 (C_{13}), 134.83 (C_{14}), 177.63 (C_1). Analytical HPLC (reversed phase): 98.7 area %.

17-(4-Bromophenyl)-15β-hydroxy-18,19,20-trinor-PGF$_{2\alpha}$ [(15*R*)-20b]: yield 94%; $[\alpha]^{23}_D$ = +13.9° (*c* 1.0, CH_3CN); ^{1}H NMR δ 1.43 (1H, m, H_8), 1.64–1.85 (5H, m, H_3, $H_{10\beta}$, H_{16a}, H_{16b}), 2.05–2.4 (8H, m, H_7, H_4, H_2, H_{12}, $H_{10\alpha}$), 2.63 (2H, m, H_{17}), 3.92 (1H, broad m, H_{11}), 4.10 (2H, broad m, H_{15} and H_9), 5.3–5.6 (4H, m, H_5, H_6, H_{13} and H_{14}), 7.04 (2H, d, Ar), 7.36 (2H, d, Ar); ^{13}C NMR δ 24.51 (C_3), 25.12 (C_7), 26.26 (C_4), 31.20 (C_{17}), 32.86 (C_2), 38.44 (C_{16}), 43.05 (C_{10}), 50.85 (C_8), 55.52 (C_{12}), 71.93 (C_{15}), 72.63 (C_9), 77.83 (C_{11}), 119.61, 130.30 (2C), 131.47 (2C), 140.84 (Ar), 129.07 (C_6), 129.69 (C_5), 132.78 (C_{13}), 134.36 (C_{14}), 177.31 (C_1); analytical HPLC (reversed phase) 97.7 area %.

17-(3-Methylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ [(15*S*)-21a]: yield 95%; $[\alpha]^{23}_D$ = +31.7° (*c* 1.7, CH_3CN); ^{1}H NMR δ 1.45 (1H, m, H_8), 1.63 (2H, m, H_3), 1.72 (1H, m, $H_{10\beta}$), 1.78 (1H, m, H_{16a}), 1.89 (1H, m, H_{16b}), 2.05–2.35 (11H, m, H_7, H_4, H_2, C*H*$_3$, H_{12}, $H_{10\alpha}$), 2.64 (2H, m, H_{17}), 3.91 (1H, broad m, H_{11}), 4.12 (2H, broad m, H_{15} and H_9), 5.35–5.62 (4H, m, H_5, H_6, H_{13} and H_{14}), 6.99 (3H, m, Ar), 7.15 (1H, m, Ar); ^{13}C NMR δ 21.46 (Ar*C*H$_3$), 24.50 (C_3), 25.29 (C_7), 26.35 (C_4), 31.81 (C_{17}), 33.02 (C_2), 38.57 (C_{16}), 42.77 (C_{10}), 50.12 (C_8), 55.33 (C_{12}), 72.45 (C_{15}), 72.53 (C_9), 77.30 (C_{11}), 125.48, 126.63, 128.34, 129.31, 137.96, 141.86 (Ar), 129.21 (C_6), 129.70 (C_5), 133.13 (C_{13}), 134.92 (C_{14}), 177.74 (C_1); analytical HPLC (reversed phase) 97.0 area %.

17-(4-Methylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ [(15*S*)-21b]: yield 83%; $[\alpha]^{23}_D$ = +34.5° (*c* 0.78, CH_3CN); ^{1}H NMR (MeOD) δ 1.48 (1H, app sept, H_8), 1.59 (3H, m, H_3 and $H_{10\beta}$), 1.74 (1H, m, H_{16a}), 1.82 (1H, m, H_{16b}), 2.05 (2H, app q, H_4), 2.18 (1H, m, H_7), 2.20 (2H, app t, H_2), 2.26 (4H, m, and s, H_{12} and ArC*H*$_3$), 2.34 (1H, m, $H_{10\alpha}$), 2.61 (2H, app t, H_{17}), 3.83 (1H, broad m, H_{11}), 4.03 (1H, app q, H_{15}), 4.10 (1H, broad m, H_9), 5.33 (1H, m, H_5), 5.48 (1H, app q, H_{13}), 5.52 (1H, m, H_6), 5.56 (1H, app q, H_{14}), 7.01 (4H, app s, (Ar); ^{13}C NMR (MeOD) δ 21.04 (Ar*C*H$_3$), 26.04 (C_7), 26.30 (C_3), 27.67 (C_4 and C_{17}), 32.45 (C_2), 40.46 (C_{16}), 44.31 (C_{10}), 50.84 (C_8), 56.13 (C_{12}), 72.21 (C_{15}), 73.19 (C_9), 77.84 (C_{11}), 129.27 (2C), 129.95 (2C), 136.24, 140.25 (Ar), 130.19 (C_6), 130.44 (C_5), 134.35 (C_{13}), 136.20 (C_{14}), 177.50 (C_1); analytical HPLC (reversed phase) 97.7 area %.

17-(4-Phenylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ [(15*S*)-22b]: yield 82%; $[\alpha]^{23}_D$ = +37.9° (*c* 0.82, CH_3CN); ^{1}H NMR δ 1.45 (1H, m, H_8), 1.6–2.4 (13H, m, H_3, $H_{10\beta}$, H_{16}, H_7, H_4, H_2, H_{12}, $H_{10\alpha}$), 2.70 (2H, m, H_{17}), 3.90 (1H, broad m, H_{11}), 4.12 (2H, broad m, H_{15} and H_9), 5.3–5.6 (4H, m, H_5, H_6, H_{13} and H_{14}), 7.21–7.56 (9H, m, Ar); ^{13}C NMR δ 24.57 (C_3), 25.36 (C_7), 26.38 (C_4), 31.52 (C_{17}), 33.04 (C_2), 38.56 (C_{16}), 42.88 (C_{10}), 50.18 (C_8), 55.37 (C_{12}), 72.49 (C_{15} and C_9), 77.74 (C_{11}), 127.03 (2C), 127.18 (3C), 128.78 (2C), 128.93 (3C), 141.07 (2C) (Ar), 129.25 (C_6), 129.75 (C_5), 133.19 (C_{13}), 134.88 (C_{14}), 177.52 (C_1); analytical HPLC (reversed phase) 97.7 area %.

15β-Hydroxy-17-(4-phenylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ [(15*R*)-22b]: yield 88%; $[\alpha]^{23}_D$ = +11.6° (*c* 1.4, CH_3CN); ^{1}H NMR δ 1.43 (1H, m, H_8), 1.6–1.9 (5H, m, H_3, $H_{10\beta}$, H_{16a}, H_{16b}), 2.05–2.4 (8H, m, H_7, H_4, H_2, H_{12}, $H_{10\alpha}$), 2.73 (2H, m, H_{17}), 3.95 (1H, broad m, H_{11}), 4.16 (2H, broad m, H_{15} and H_9), 5.3–5.6 (4H, m, H_5, H_6, H_{13} and H_{14}), 7.23–7.58 (9H, m, Ar); ^{13}C NMR δ 24.57 (C_3), 25.18 (C_7), 26.26 (C_4), 31.46 (C_{17}), 32.83 (C_2), 38.67 (C_{16}), 43.11 (C_{10}), 51.02 (C_8), 55.75 (C_{12}), 72.28 (C_{15}), 72.78 (C_9), 77.97 (C_{11}), 127.03 (3C), 127.12, 127.18 (2C), 128.81, 128.96 (2C), 138.89, 141.02, 141.07 (Ar), 129.13 (C_6), 129.75 (C_5), 132.87 (C_{13}), 134.45 (C_{14}), 177.16 (C_1); analytical HPLC (reversed phase) 96.6 area %.

Pharmacology. Intraocular Pressure, Pupil Diameter, and Irritation in the Cat Eye. Domestic female cats, weighing 2–3 kg and specially trained for intraocular pressure (IOP) measurements, were used. One eye of each animal was topically treated with the drug dissolved in a vehicle containing 0.9% sodium chloride and 0.5% polysorbate 80 (drop size 20 μL), and the contralateral eye received the vehicle solution. IOP was measured using a pneumatonometer (Digilab Modular One, Bio-Rad) under local anaesthesia with oxibuprocain. The horizontal diameter of the pupil was measured with a millimeter ruler under constant illumination conditions (10 lux). Measurements of IOP and pupil diameter were performed before drug treatment and 1, 3, 6, and 23 h after treatment. The ocular irritation was evaluated from the behaviour of the animals, in particular the degree of lid closure during the first hour after drug treatment. An arbitrary scale from 0 to 3 was used, 0 indicating absence of irritation and 3 complete closure of the lids.

Intraocular Pressure in the Monkey Eye. Cynomolgus monkeys specially trained for IOP measurements were used. The animals were sedated with ketamine (2–3 mg/kg of body weight) for transportation from the animal housing facility to the laboratory and placed in specially disigned chairs. Oxibuprocain was used for local anaesthesia. IOP was measured with a pneumatonometer (Digilab Modular One) calibrated for monkey eyes. The drug dissolved in a vehicle containing 0.9% sodium chloride, and 0.5% polysorbate 80 was applied to one eye (drop size 10 μL), and the contralateral eye received the vehicle solution. Measurements were performed before treatment and 1, 2, 4, and 6 h after treatment.

Conjunctival Hyperemia in the Rabbit. Albino rabbits (New Zealand White, 2–3 kg) were used for evaluation of conjuntival hyperemia. One eye of each animal was topically treated with the drug dissolved in a vehicle containing 0.9% sodium chloride and 0.5% polysorbate 80 (drop size 30 μL), and the contralateral eye received the vehicle solution. Color photographs of the drug-treated and control eyes were taken using a camera equipped with a Medical Nikkor lens (magnification 2×) before treatment and 1, 2, 3, and 4 h after treatment. The photos were used for semi quantitative evaluation of conjunctival hyperemia using an arbitrary scale of 11 steps from 0 to 5 (0 = totally pale conjunctiva, 1 = vessels normal, 2 = mild hyperemia, 3 = moderate hyperemia, 4 = severe hyperemia, 5 = severe hyperemia with chemosis).

Contraction of Cat Iris Sphincter in Vitro. Functional receptor studies were performed using iris sphincter muscles from cat eyes. The iris sphincter muscles were prepared, cut in halfs, and suspended in modified Kreb's solution in thermostated (37 °C) tissue baths airated with 95% O_2 and 5% CO_2. The composition (mmol/L) of the physiological solution was 133 NaCl, 16.1 $NaHCO_3$, 4.7 KCl, 2.4 $CaCl_2$, 1.4 NaH_2PO_4, 1.0 $MgCl_2$, and 7.8 glucose. The bath fluid also contained indomethacin (2.8×10^{-6} mol/L), atropin (10^{-7} mol/L), and propranolol (10^{-6} mol/L). A resting tension of 150 mg was applied, and after an equibrating period of at least 30 min, the contractile force was measured after cumulative dosing of prostaglandin analogues. The interval between doses was approximately 5–10 min, which was the time required to reach a stable level of contraction. Force transducers for measurement of isometric contraction (Grass FT30C) connected to a polygraph (Grass Model 7) were used for registration of the response. For each tissue sample the maximal response was normalized to 100%. The mean response from four different preparations was calculated, and concentration–effect curves

were fitted to the data using the following equation:

$$\text{Resp} = \frac{100}{1 + (10^{\log E}/10^{\log C})^D}$$

Resp = response in percent, $\log E = \log(EC_{50})$, $\log C$ = log concentration, D = Hill coefficient.

Statistics. Results are given as arithmetic means ± standard error of the mean. Statistical analysis was performed using Student's t test for matched pairs.

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