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Ligand-Controlled Palladium-Catalyzed Intramolecular Reactions of Phenyl-Substituted Prostaglandin $F_{2\alpha}$ Analogues.

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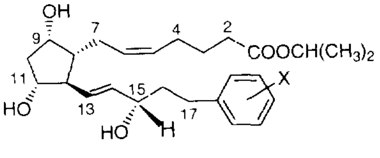
Abstract: Palladium catalyzed intramolecular cyclizations of the 15*R* and 15*S* epimers of 17-(2-iodophenyl)-18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropylester [(15*R*)-**5** and (15*S*)-**5**, respectively] produce a complex mixture of products including various tetrahydronaphthol derivatives and related ketones. The products have been isolated and structurally determined and mechanisms that rationalize their formation are discussed. The cyclizations can be controlled to selectively provide predominantly one or two cyclized products by the appropriate choice of phosphine ligand.

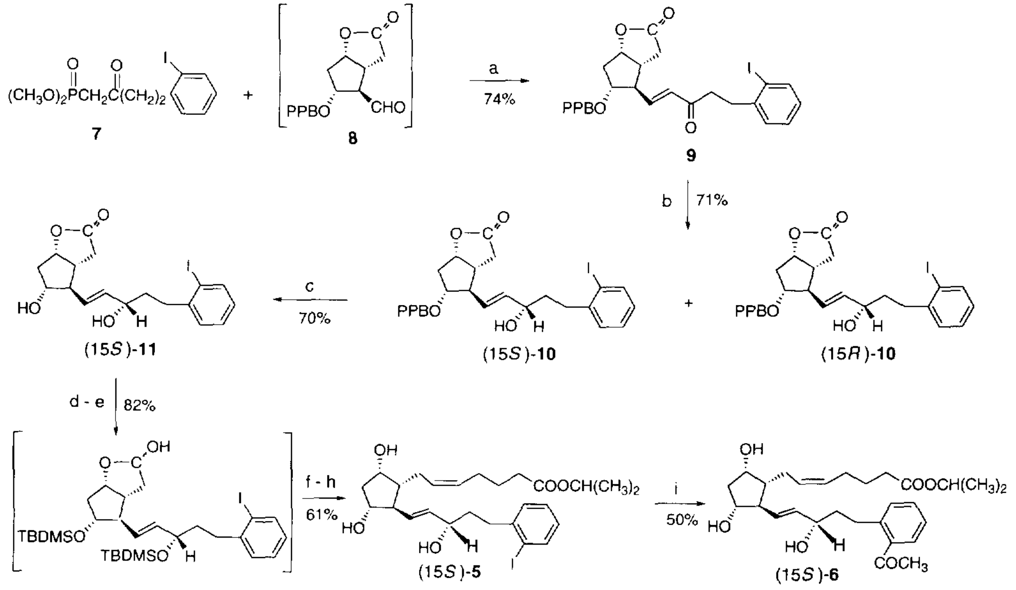
Ongoing studies in our laboratory focus on exploring the relation between antiglaucoma activity and the structure of the ω-chain of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) isopropylester analogues.[1,2] A practical strategy used for the synthesis of a variety of derivatives of 17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropylester is based on medium scale preparation of analogues with aromatic halide substituents that can be conveniently converted into an array of substituents by palladium catalyzed methods;[3,4] e.g., Heck reaction[5] of the 3- and 4-bromophenyl analogues **1** and **2** with butyl vinyl ether[6] and hydrolysis of the resulting enol ethers afford the corresponding acetyl derivatives **3** and **4**, respectively, in good yields. These palladium-catalyzed reactions are chemoselective and we have not observed disturbing side reactions involving the labile allylic alcohol functionality.[3,4]



1: X = 3-Br
2: X = 4-Br
3: X = 3-$COCH_3$
4: X = 4-$COCH_3$

The corresponding coupling reaction with the 2-iodophenyl analogue (15*S*)-**5** was less facile (Scheme 1). Because of competing intramolecular cyclization reactions, the yield of the 2-acetylphenyl derivative (15*S*)-**6** was very low (5%, HPLC) when standard conditions were employed. The yield of (15*S*)-**6** could be improved to about 50 %, however, by use of butyl vinyl ether as solvent.

In the present study, we have determined the structures of the products obtained by the palladium-catalyzed intramolecular cyclization[7] of the epimeric (15*S*)-**5** and (15*R*)-**5**, respectively, rationalized their formation in mechanistic terms, and studied how the product distribution is directed by use of various phosphine ligands.

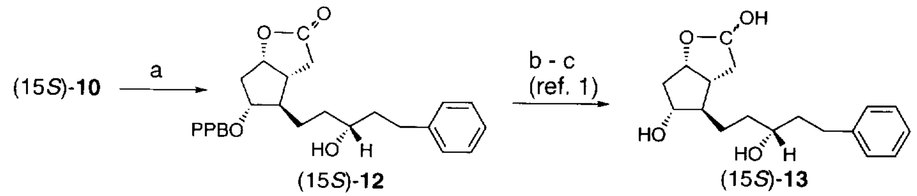


Scheme 1. (a) NaH/DME; (b) Li-Selectride/THF, -120 °C; (c) K_2CO_3/MeOH; (d) TBDMS, Et_3N, DMAP/CH_2Cl_2; (e) DIBAL/THF, -78 °C; (f) KOtBu, $Ph_3P(CH_2)_4COOH$/THF, 0 °C; (g) DBU, $ICH(CH_3)_2$/acetone; (h) TBAF/THF; (i) $Pd(OAc)_2$, DPPP, TlOAc, Et_3N/butyl vinyl ether:DMF (10:1).

RESULTS AND DISCUSSION

Synthesis of (15S)-5 and (15R)-5

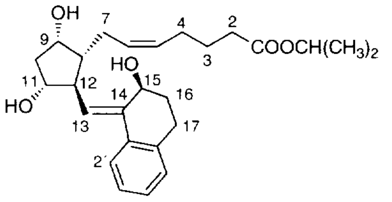
The target compounds were prepared by a synthetic sequence (Scheme 1) which is analogous to that used previously for the preparation of **1** and **2**.[3,4] The assignment of the stereochemistry at C15 was initially based on the well-documented difference in polarity between the 15*S* and 15*R* epimers and the more powerful biological actions of the 15*S*-epimers.[8] The stereochemistry of C15 was unamibiguously established by chemical correlation of (15*S*)-**10** with (15*R*)-**13**[1] (Scheme 2), the structure of which has been confirmed by X-ray crystallography.[9]



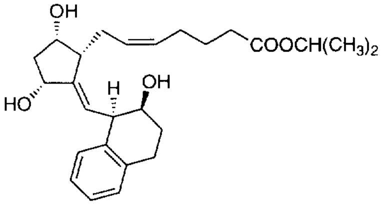
Scheme 2. (a) H_2, Pd/C, 1 M NaOH/ EtOH; (b) K_2CO_3/ MeOH; (c) DIBAL/ THF, -78 °C.

Structural Assignment of Products Generated in the Cyclization Reactions

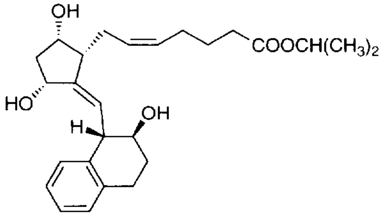
The palladium-catalyzed cyclizations of (15*S*)-**5** afforded a complex mixture of products including the tetrahydronaphthols (15*S*)-**14**, (15*S*)-**15**, and (15*S*)-**16** and a 1:1 mixture of C14 epimeric ketones (**17**).[10] The epimer (15*R*)-**5** could form the same mixture of ketones (**17**) but gave three different tetrahydronaphthols [(15*R*)-**14**, (15*R*)-**15**, and (15*R*)-**16**]. Although the epimeric ketones (**17a** and **17b**) were separated, the configuration at C14 could not be assigned unambiguously. The relative stereochemistries of the other products were deduced on the basis of NMR spectroscopic data.



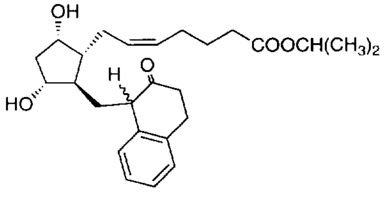
(15*S*)-**14**



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



(15*S*)-**16**



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The *Z* stereochemistry of the 1,2,3,4-tetrahydronaphth-1-ylidene derivatives (15*S*)-**14** and (15*R*)-**14** was readily established by NOE-difference spectroscopy since C11-H and C2'-H showed a NOE upon irradiation of C13-H (d 5.9 and 6.1 ppm, respectively) (Figure 1). The assignment of the configuration at C15 of (15*S*)-**14** and (15*R*)-**14** was based on the assumption that the stereochemistry of the starting material is retained in the product.

The *E* stereochemistry of the C12-C13 double bond of (15*S*)-**15** and (15*R*)-**15** was established by observation of a strong NOE between C11-H and C13-H (Figure 1). In contrast, no NOE was observed between C11-H and C13-H in the Z isomer (15*R*)-**16**.

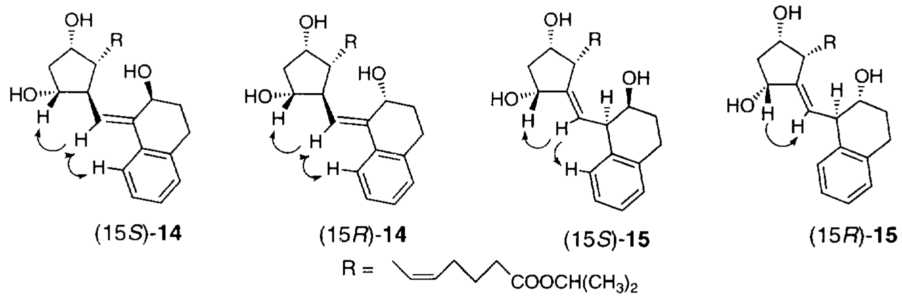


Figure 1. Observed NOEs used for stereochemical assignment.

The *trans* relationship between the substituents in the tetrahydronaphthalene ring of (15*R*)-**15** and (15*S*)-**16** was indicated by the fairly large vicinal coupling constants between C14-H and C15-H which are consistent with a coupling between pseudoaxial hydrogens. The pseudoaxial disposition of C15-H was further corroborated by the large $J_{15,16'}$(Table 1). The coupling $J_{14,15}$ is considerably smaller in the *cis* substituted (15*S*)-**15** and (15*R*)-**16** (Table 1). Furthermore, the small couplings from C15-H to the C16-hydrogens indicate that the C15-hydrogen is pseudoequatorially dispositioned.

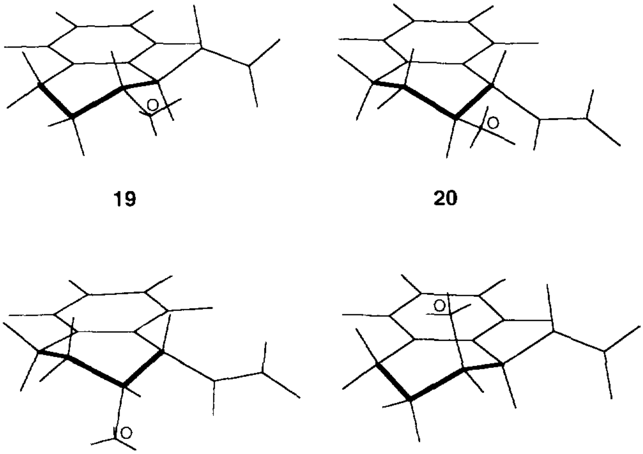
Table 1. Vicinal coupling constants used for stereo-chemical assignments.[a]

compound	$J_{14,15}$	$J_{15,16'}$	$J_{15,16''}$
(15*R*)-**15**	8.6	10.1	3.4
(15*S*)-**16**	7.9	10.1	3.1
(15*R*)-**16**	4.6	7.9	3.1
(15*S*)-**15**	3.9	6.7	2.7

[a] Values are given in Hz.

In order to facilitate the assignment of relative configurations in the tetrahydronaphthalene derivatives possessing two stereogenic centra, we performed MM2 calculations on model compounds of (15*S*)-**15**, (15*R*)-**15**, (15*S*)-**16**, and (15*R*)-**16** (**18** - **21**, respectively; Figure 2). In the minimum-energy conformations of *trans* derivatives **19** (a model for (15*R*)-**15**) and **20** (a model for (15*S*)-**16**) the cyclohexene ring preferentially adopted half-chair conformations with dipseudoequatorial substituents. These conformations were energetically favoured by 1.04 and 1.05 kcal/mol over conformations with dipseudoaxial substituents. The *cis*-derivatives **18** (a model for (15*S*)-**15**) and **21** (a model for (15*R*)-**16**) preferred conformations in which the cyclohexene ring adopted a half chair and in which the hydroxyl group was pseudoaxially dispositioned. Conformations with a pseudoequatorial hydroxyl group were considerably higher in energy ($\Delta E_s > 0.24$ kcal/mol).

Thus, there is a congruence between the results from the MM2 calculations on the model compounds and the conclusions drawn from coupling constant data. This provides further support for the structural assignments. However, since the NMR-data only provide evidence for relative configurations, the configuration of C15 has to be assumed to be identical to that of the starting material.



19 **20**

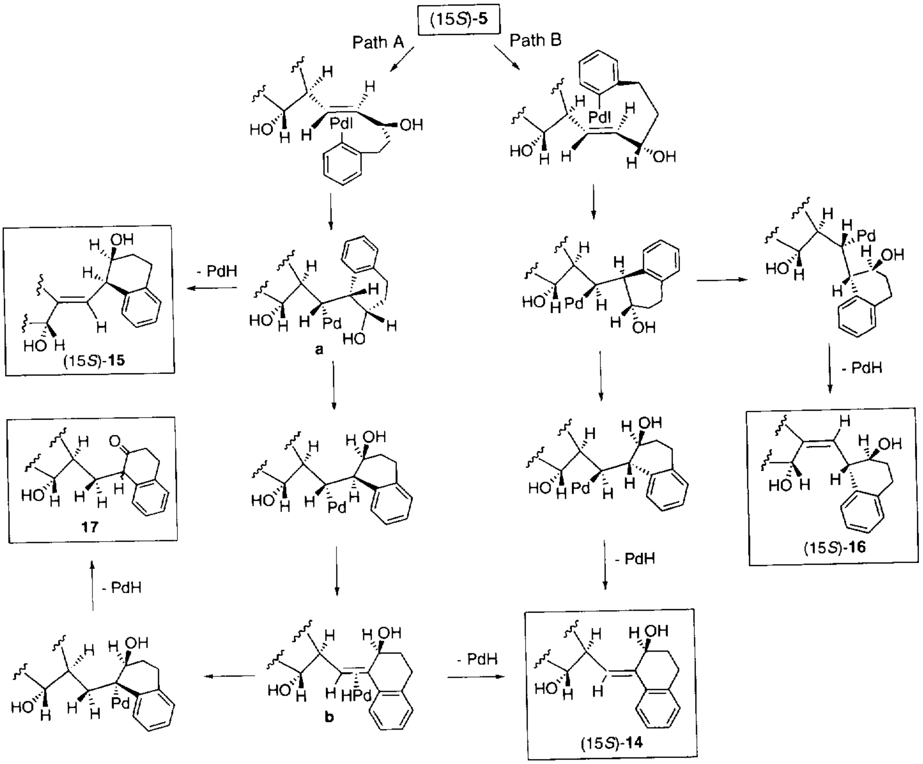
21 **18**

Figure 2. Stereoscopic representation of MM2-derived minimum-energy conformations of model compounds of (15*S*)-**15** (**18**), (15*R*)-**15** (**19**), (15*S*)-**16** (**20**), and (15*R*)-**16** (**21**).

Mechanism of the Cyclization Reaction

A mechanistic rationale for the formation of the various products in the intramolecular ring closure reaction is given in Scheme 3; Oxidative addition of (15*S*)-**5** to the palladium catalyst generates a palladium species that is able to form two different π complexes depending on which face of the double bond that is approached (Path A and B, respectively). *Syn* addition of the palladium and the aryl moiety to the double bond occurs via an exo-trig rather than an endo-trig process, thus forming a new six-membered ring.[11] A number of *syn* eliminations and *syn* readditions of PdH[5] account for the stereochemistries of all products observed. In Path A, the initial addition product (**a**; Scheme 3) has the possibility to eliminate PdH in two directions thus forming (15*S*)-**14** or (15*S*)-**15**. Alternatively, the π complex formed by PdH elimination from the initial addition product may form ketone **17** (or the corresponding enol) by readdition and elimination of PdH. Reaction along Path B leads to (15*S*)-**16** and to (15*S*)-**14** which can also be formed via Path A.

The product mixture resulting from the intramolecular cyclization of (15*R*)-**5** is rationalized by an identical series of mechanistic steps. It should be noted that the three isomeric alcohols formed from (15*R*)-**5** are C15 epimers of those formed from (15*S*)-**5**.



Scheme 3

Effects of Phosphine ligands

The intramolecular cyclizations of (15*S*)-**5** and (15*R*)-**5** were performed in acetonitrile using triethylamine as the base and various phosphine ligand-containing palladium catalysts (Table 2 and 3). The reactions were complete after 6 h at 100 °C (HPLC-analysis). In contrast, when no phosphine ligand was present (entry 9, Table 2), only small amounts of products were formed.

The product distribution resulting from the use of different phoshine ligands (PPh_3, P(o-tolyl)$_3$, 1,1-bis(diphenylphosphino)methane (DPPM), 1,2-bis(diphenylphosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP) and 1,1'-bis(diphenylphosphino)ferrocene (DPPF)) in the intramolecular cyclizations of (15*S*)- and (15*R*)-**5** are shown in Table 2 and 3, respectively.

The initial syn-addition in (15*S*)-**5** appears to have occured according to pathway A when P(o-tolyl)$_3$ was used as ligand because no (15*S*)-**16** was formed. The palladium adduct specifically eliminated PdH towards the tetrahydronaphthalene ring (C13-C14 double bond) resulting in (15*S*)-**14** as one major product. An almost equal amount of ketone **17** was formed, presumably from the intermediate (**b**; Scheme 3) leading to (15*S*)-**14**, via readdition and elimination of PdH.

Table 2. Palladium-Catalyzed Intramolecular Coupling of (15*S*)-**5**.[a]

entry	catalyst	yield (%)[b]			
		(15*S*)-**14**	(15*S*)-**15**	(15*S*)-**16**	**17**
1	$Pd(OAc)_2/P(o\text{-tolyl})_3$	53			47
2	$Pd(PPh_3)_4$	1	50	46	
3	$Pd(OAc)_2$/DPPM	47	41	12	
4	$Pd(OAc)_2$/DPPE	80	20		
5	$Pd(OAc)_2$/DPPP	62	38		
6	$Pd(OAc)_2$/DPPF	19	59		3
7	$PdCl_2$(DPPF)	17	39	20	16
8	$PdCl_2(PP_3)_2$	10	50	31	6
9	$Pd_2(dba)_3$[c]	13			20

[a] 1 equiv of (15*S*)-**5**, 2 equiv of triethylamine, 0.05 equiv of catalyst and 0.11 equiv of ligand, stirred in CH_3CN at 100 °C for 6 h. [b] Based on HPLC analyses, detection at 210 nm. [c] 67% of (15*S*)-**5** was recovered.

Table 3. Palladium-Catalyzed Intramolecular Coupling of (15*R*)-**5**.[a]

entry	catalyst	yield (%)[b]			
		(15*S*)-**14**	(15*S*)-**15**	(15*S*)-**16**	**17**
1	$Pd(OAc)_2/P(o\text{-tolyl})_3$	83	1		5
2	$Pd(PPh_3)_4$	5	65	24	
3	$Pd(OAc)_2$/DPPE	87	1		7
4	$Pd(OAc)_2$/DPPP	86	8		1

[a] 1 equiv of (15*R*)-**5**, 2 equiv of triethylamine, 0.05 equiv of catalyst and 0.11 equiv of ligand, stirred in CH_3CN at 100 °C for 6 h. [b] Based on HPLC analyses, detection at 210 nm.

When PPh_3 was used as the ligand, a completely different product distribution was observed (Table 2, entry 2). No formation of ketone **17** was observed and only a small amount of (15*S*)-**14** was formed. Instead, two new alcohols, (15*S*)-**15** and (15*S*)-**16**, were generated in about equal amounts.

Although there is a preference for cylization of (15*R*)-**5** along Path A in the presence of $Pd(PPh_3)_4$, the mechanistic reasoning used for the cyclization of the 15*S*-epimer may be applied also in this case. The difference in product distribution between the cyclization of the two epimers is probably due to different interactions of the intermediates with the C11 hydroxyl group (cf. ref. 12).

When strongly chelating bidentate ligands were used,[13] (entries 3-5, Table 2), cyclizations of (15*S*)-**5** produced mainly (15*S*)-**14** and (15*S*)-**15**. The use of bidentate ligands in the cyclization of (15*R*)-**5** apparently proceeded along Path B, (15*R*)-**14** being the major product.

In conclusion, the palladium-catalyzed cyclizations described herein can be controlled to selectively provide predominantly one or two out of several possible products by the appropriate choice of phosphine ligand.

EXPERIMENTAL SECTION[4]

Preparative HPLC was performed using a silica gel column (21.4 x 250 mm); mobile phase: 3-7% of ethanol in n-hexane; flow rate: 14 mL/min; detection: 220 nm. All the palladium-catalyzed reactions were carried out in 25 mL, heavy-walled, and thin-necked Pyrex tubes, sealed with a screw cap fitted with a Teflon gasket.

Dimethyl-4-(2-iodophenyl)-2-oxobutylphosphonate (7). Dimethyl(2-oxopropyl)phosphonate (24 g, 144 mmol) was added to a stirred suspension of NaH (80%, 4.5 g, 151 mmol), (washed with n-pentane to remove mineral oil), in THF (200 mL) under N_2.[14] The mixture was mechanically stirred for 1 h at room temperature, and then cooled to 0 °C. n-BuLi (2.5 M in n-hexane, 69 mL, 173 mmol) was added dropwise, and the mixture was stirred for 30 minutes at 0 °C. 2-Iodobenzyl chloride (40 g, 158 mmol) was dissolved in THF (25 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), washed with brine (2 x 100 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (EtOAc/aceton 1:1) which furnished 39 g (64%) of **7** as an oil. TLC R_f = 0.41 (EtOAc/aceton 1:1); ^1H NMR (CD_3Cl) δ 2.97 (4H, m), 3.07 and 3.15 (2H, d), 3.75 and 3.79 (6H, d), 6.89 (1H, m), 7.25 (2H, m), 7.79 (1H, d); ^{13}C NMR (CD_3Cl) δ 34.3 (s), 40.4 and 42.3 (d), 43.9 (s), 52.9 and 53.0 (d), 100.1, 128.1, 128.4, 129.8, 139.4, 143.0, 200.3 and 200.4 (d); ^{31}P NMR ($CDCl_3$) δ 22.92. Anal. Calcd for $C_{12}H_{16}IO_4P$: C, 37.7; H, 4.2. Found: C, 38.1; H, 4.3.

(1S,5R,6R,7R)-6-[3-Oxo-5-(2-iodophenyl)-1-(E)-pentenyl]-7-(4-phenylbenzoyloxy)-2-oxabicyclo-[3.3.0]octane-3-one (9). Compound **7** (28 g, 75 mmol) was added to a stirred suspension of NaH (80%, 2.0 g, 65 mmol) (washed with n-pentane to remove mineral oil), in dimethoxyethane (200 mL).[15] The mixture was mechanically stirred for 2 h under N_2. The sodium salt of the acylphosphonate was obtained as a white precipitate. The reaction mixture was cooled to -5 °C and the crude aldehyde (1*S*,5*R*,6*R*,7*R*)-6-formyl-7-[4-phenylbenzoyloxy]-2-oxabicyclo[3.3.0]octane-3-one (**8**)[8a,16] (22 g, 62 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 ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (gradient system: toluen to EtOAc/toluen 5:1) which furnished 28 g (74%) of **9**. TLC R_f = 0.59; $[\alpha]^D{}_{23}$ = -105.3° (c 1.1, CH_3CN); ^1H NMR ($CDCl_3$) δ 2.1 - 3.1 (10H, m), 5.08 (1H, m), 5.30 (1H, broad quart), 6.22 (1H, d, J = 15.8), 6.71 (1H, dd, J = 15.8, 7.5), 6.80 - 8.06 (13H, m); ^{13}C NMR ($CDCl_3$) δ 34.9, 35.1, 37.8, 40.8, 42.5, 54.1, 78.5, 83.2, 100.2, 127.2 (2C), 127.3 (2C), 128.2, 128.2, 128.3, 128.6, 129.0 (2C), 129.8, 130.2 (2C), 139.5, 139.8, 143.3, 146.2, 131.3, 143.3, 165.7, 175.9, 198.2. Anal. Cald for $C_{31}H_{27}IO_5$: C, 61.4; H, 4.5. Found: C, 61.5; H, 4.5.

(1S,5R,6R,7R)-6-[(3S)-3-Hydroxy-5-(2-iodophenyl)-1-(E)-pentenyl]-7-(4-phenylbenzoyloxy)-2-oxabicyclo[3.3.0]octane-3-one [(15S)-10] and (1S,5R,6R,7R)-6-[(3R)-3-Hydroxy-5-(2-iodophenyl)-1-(E)-pentenyl]-7-(4-phenylbenzoyloxy)-2-oxa-bicyclo[3.3.0]octane-3-one [(15R)-10]. Cold litium *tri*-sec-butylborohydride (1M in THF, 27 mL, 27 mmol) was slowly added to a solution of **9** (28 g, 46 mmol) in THF cooled to -120 °C, (slurry of n-pentane and liquid N_2), under N_2.[17] After being stirred for 1 h at -120 °C, additional litium *tri*-sec-butylborohydride (10 mmol) was added, and the mixture was stirred for 30 minutes. The reaction mixture was acidified with 1 M aqueous HCl and was allowed to warm to room temperature. The product was extracted with EtOAc (50 mL), washed with brine (2 x 50 mL), 3% aqueous citric acid (2 x 50 mL), dried ($MgSO_4$) and concentrated. The obtained product was a diastereomeric mixture of (15*S*)-**10** and (15*R*)-**10** (α and β isomers). Analytical HPLC showed that the α:β relationship was 69:31. The isomers were separated and purified by repeated flash chromatography (gradient system: CH_2Cl_2 to EtOAc/CH_2Cl_2 1:5), which furnished 14.0 g (50%) of (15*S*)-**10** and 6.0 g of (15*R*)-**10** (21%).

(15S)-10: TLC R_f = 0.48 (EtOAc/CH_2Cl_2 2:1); $[\alpha]^D{}_{23}$ = -83.4° (c 1.0, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.6 - 3.0 (10H, m), 4.19 (1H, broad m), 5.06 (1H, broad m), 5.28 (1H, broad quart), 5.70 (2H, m), 6.80 - 8.06 (13H, m); ^{13}C NMR ($CDCl_3$) δ 35.0, 36.5, 37.4, 37.6, 42.7, 54.1, 71.4, 79.1, 83.3, 100.6, 127.2 (2C), 127.3 (2C), 127.9, 128.2, 128.2, 128.5, 128.9, 128.9 (2C), 129.4, 130.2 (2C), 135.8, 139.5, 139.8, 144.2, 146.0, 166.0, 176.5. Anal. Calcd for $C_{31}H_{29}IO_5$: C, 61.2; H, 4.8. Found: C, 61.1; H, 5.1.

(15R)-10: TLC R_f = 0.40 (EtOAc/CH_2Cl_2 2:1); $[\alpha]^D{}_{23}$ = -62.6° (c 1.1, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.6 - 3.0 (10H, m), 4.16 (1H, broad m), 5.08 (1H, broad m), 5.28 (1H, broad quart), 5.71 (2H, m), 6.8 - 8.1 (13H, m); ^{13}C NMR ($CDCl_3$) δ 34.9, 36.5, 37.4, 37.5, 42.6, 54.0, 71.4, 79.0, 83.2, 100.5, 127.1 (2C), 127.2 (2C), 127.8, 128.2, 128.4, 128.4, 128.9 (2C), 128.9, 129.9, 130.1 (2C), 135.8, 139.4, 139.8, 144.1, 146.0, 165.8, 176.4. Anal. Calcd for $C_{31}H_{29}IO_5$: C, 61.2; H, 4.8. Found: C, 60.9; H, 4.9.

(1S,5R,6R,7R)-6-[(3S)-3-Hydroxy-5-(2-iodophenyl)-1-(E)-pentenyl]-7-hydroxy-2-oxabicyclo-[3.3.0]octane-3-one [(15S)-11]. A mixture of (15*S*)-**10** (12 g, 19 mmol) and powdered K_2CO_3 (1.6 g, 11 mmol) in MeOH (50 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 x 40 mL), dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (gradient system: EtOAc to EtOAc/aceton 1:3), which afforded 5.7 g (70%) of (15*S*)-**11** as an oil. TLC R_f = 0.18 (EtOAc); $[\alpha]^{23}{}_D$ = -9.4° (c 1.1, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.82 (2H, m), 1.90 (1H, m), 2.25 (1H, m), 2.43 (1H, dd), 2.55 (2H, m), 2.72 (3H, m), 3.92 (1H, broad), 4.12 (1H, broad m), 4.88 (1H, app broad sextet), 5.48 (1H, dd), 5.66 (1H, dd), 6.88 (1H, m), 7.24 (2H, m), 7.79 (1H, d); ^{13}C NMR ($CDCl_3$) δ 34.2, 36.8, 37.3, 39.7, 42.4, 56.2, 72.1, 76.4, 82.5, 100.7, 128.0, 128.5, 129.4, 130.8, 136.3, 139.5, 144.2, 177.2. Anal. Calcd for $C_{18}H_{21}IO_4 \cdot 1/2\ H_2O$: C, 49.4; H, 5.3. Found: C, 49.2; H, 5.1.

(1S,5R,6R,7R)-6-[(3R)-3-Hydroxy-5-(2-iodophenyl)-1-(E)-pentenyl]-7-hydroxy-2-oxabicyclo-[3.3.0]octane-3-one [(15R)-11]. Compound (15*R*)-**11** was prepared from (15*R*)-**10** by the above method in 80% yield as an oil. TLC R_f = 0.22 (EtOAc); $[\alpha]^{23}{}_D$ = -10.1° (c 0.93, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.81 (2H, app quart), 1.96 (1H, m), 2.31 - 2.83 (7H, m), 3.99 (1H, broad m), 4.19 (1H, broad m), 4.91 (1H, app broad sext), 5.56 (1H, dd), 5.70 (1H, dd), 6.89 (1H, m), 7.25 (2H, m), 7.80 (1H, d); ^{13}C NMR ($CDCl_3$) δ 34.5, 36.6, 37.3, 39.9, 42.5, 56.0, 71.2, 76.5, 82.7, 100.5, 127.9, 128.4, 129.3, 129.4, 135.7, 139.4, 144.1, 177.1. Anal. Calcd for $C_{18}H_{21}IO_4$: C, 50.5; H, 4.9. Found: C, 50.8; H, 5.2.

17-(2-Iodophenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropylester [(15S)-5]. *tert*-Butyldimethylsilyl chloride (6.0 g, 40 mmol) was added to a solution of (15*S*)-**11** (5.7 g, 13 mmol), triethylamine (5.6 mL, 40 mmol) and dimethylaminopyridine (0.16 g, 1.3 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred for 2 days at room temperature, and then washed with brine (20 mL), 3% aqueous citric acid (2 x 20 mL) and 5% aqueous $NaHCO_3$ (2 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The resulting product was purified by flash chromatography (ether/petroleum ether 1:1) which furnished 7.6 g of the hydroxyl protected product. The product was dissolved in THF (40 mL) and diisobutylaluminiumhydride (20 w/w in toluene, 9.2 mL, 13 mmol) was added at -78 °C, under N_2.[18] The reaction mixture was stirred vigorously at -78 °C until TLC monitoring indicated that all lactone had been consumed (6 h). The reaction mixture was treated with MeOH (20 mL) and was stirred over night while the temperature was 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 (2 x 20 mL), dried ($MgSO_4$) and concentrated, to furnish 7.2 g (82%) of (1*S*,5*R*,6*R*,7*R*)-6-[(3*S*)-5-(2-iodophenyl)-3-(*tert*-butyldimethylsilyloxy)-1-(*E*)-pentenyl]-7-(*tert*-butyldimethylsilyloxy)-2-oxabicyclo[3.3.0]octane-3-ol as an oil, which is a mixture of diastereomers. TLC R_f = 0.55 (EtOAc/n-hexane 1:1).

Potasium-*tert*-butoxide (5.3 g, 48 mmol) was added to a suspension of 4-carboxybutyl triphenylphosphonium bromide (11.3 g, 25 mmol) in THF (60 mL) at 0 °C under N_2.[19] After being stirred at 0 °C for 10 minutes, and at room temperature for 10 minutes, the reaction mixture had turned to a deep orange colour. A solution of the above lactol (5.6 g, 8.5 mmol) in THF (25 mL), was added dropwise. After being stirred for 20 minutes the reaction mixture was treated with ice and acidified with 10% aqueous citric acid to pH 4, extracted with ether (30 mL), dried ($MgSO_4$) and concentrated. During the reaction, silyl group migration was detected by TLC. On the basis of previous findings,[20] it was assumed that the silyl group on the 11-hydroxy substituent migrated to the 9-hydroxy substituent. The crude acid was used in the next step without further purification. TLC R_f = 0.46 and 0.50 (EtOAc/n-hexane 1:1).

A solution of 1,8-Diazobicyclo[5.4.0]undec-7-ene (DBU)[21] (9.0 mL, 60 mmol), in acetone (10 mL), was added to a stirred solution of the above crude acide in aceton (40 mL). The reaction mixture was stirred for 10 minutes, and a solution of 2-iodopropane (5.0 mL, 50 mmol) in aceton (8 mL) was added. After being stirred at room temperature over night, the mixture was concentrated and extracted with EtOAc. The organic layer was washed with 3% aqueous citric acid (2 x 20 mL), 5% aqueous $NaHCO_3$ (2 x 20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (ether/petroleum ether 1:10), which furnished 5.1 g (65%) of the product as a mixture of isomers in which the silyl protecting groups have partially migrated. TLC R_f = 0.21 and 0.34 (ether/petroleum ether 1:3). The deprotection was carried out by adding tetrabutylammonium fluoride (1 M in THF, 19 mL, 19 mmol) to a stirred solution of the product in THF (50 mL), under N_2. The deprotection was complete after 48 h, and addition of 2 equivalents of tetrabutylammonium fluoride (TLC). $CHCl_3$ (20 mL) was added to the reaction mixture and the organic layer was washed with brine (20 mL), 5% aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (gradient system: chloroform to chloroform/aceton 4:1), which furnished 2.9 g (61%) of an oily product. Analytical HPLC showed that the product contained about 3% of the trans isomer (from the Wittig reaction). 70 mg of the oil was purified by preparative HPLC, which furnished 58 mg of isomerically pure (15*S*)-**5** as an oil. TLC $R_f = 0.19$ (EtOAc); $[\alpha]^{23}_D = +17.34°$ (c 0.94, CH_3CN); ^1H NMR (CD_3OD) δ 1.19 (6H, d, *J* = 6.40), 1.49 (1H, m), 1.57 (2H, app quint, *J* = 7.32), 1.60 (1H, m), 1.75 and 1.80 (2H, m), 2.05 (2H, app broad quart), 2.16 (2H, app t, *J* = 7.32), 2.19 (2H, m), 2.30 (1H, m), 2.35 (1H, m), 2.77 (2H, m), 3.84 (1H, m), 4.08 (2H, m), 4.91 (1H, sept, *J* =6.40), 5.31 (1H, m), 5.51 (1H, m), 5.53 (1H, dd), 5.61 (1H, dd), 6.88 (1H, m), 7.27 (2H, m), 7.79 (1H, d); ^{13}C NMR (CD_3OD) δ 22.1, 26.0, 26.4, 27.7, 34.9, 38.1, 38.9, 44.3, 50.8, 56.1, 68.9, 72.2, 73.4, 77.8, 100.8, 128.9, 129.6, 130.1, 130.5, 130.6, 134.8, 136.0, 140.7, 146.0, 175.0. Anal. Calcd for $C_{26}H_{37}IO_5$: C, 56.1; H, 6.7. Found: C, 56.3; H, 6.9.

15β-Hydroxy-17-(2-iodophenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropylester [(15R)-5]. Compound (15*R*)-**5** was prepared from (15*R*)-**11** by the above method in 63% yield as an oil. TLC $R_f = 0.26$ (EtOAc); $[\alpha]^{23}_D = +16.4°$ (c 0.42, CH_3CN); ^1H NMR (CD_3OD) δ 1.21 (6H, d, *J* = 6.10), 1.52 (1H, m), 1.62 (3H, m), 1.79 (2H, m), 2.09 (2H, app broad quart, *J* = 7.3), 2.21 (2H, m, H_7), 2.23 (2H, app t, *J* = 7.32), 2.32 (1H, m), 2.34 (1H, m), 2.80 (2H, m), 3.87 (1H, m), 4.12 (2H, m), 4.94 (1H, sept, *J* =6.10), 5.33 (1H, m), 5.52 (1H, m), 5.59 (1H, dd), 5.66 (1H, dd), 6.89 (1H, m), 7.29 (2H, m), 7.80 (1H, d); ^{13}C NMR (CD_3OD) δ 22.1, 26.1, 26.4, 27.7, 35.0, 37.8, 39.0, 44.4, 51.0, 55.8, 69.0, 72.3, 72.6, 77.9, 100.8, 128.8, 129.5, 130.1, 130.6, 130.6, 133.5, 135.7, 140.6, 146.2, 175.1. Anal. Calcd for $C_{26}H_{37}IO_5$: C, 56.1; H, 6.7. Found: C, 55.9; H, 6.3.

17-(2-Acetylphenyl)-18,19,20-trinor-PGF$_{2\alpha}$ Isopropylester [(15S)-6]. Compound (15*S*)-**5** (132 mg, 0.24 mmol) was added to a stirred solution of $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), DPPP (11 mg, 0.026 mmol) and TlOAc (69 mg, 0.26 mmol) in butyl vinyl ether/DMF 10:1 (1.5 mL).[6] Triethylamine (0.066 mL, 0.47 mmol) was added and the reaction mixture was flushed with N_2, sealed and stirred at 100 °C over night. The reaction mixture was allowed to reach room temperature, diluted with THF (1 mL) and acidified with 10% aqueous HCl. After being stirred for 30 minutes the mixture was extracted with EtOAc (5 mL), washed with brine (5 mL), 5% aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$) and concentrated. The product is a mixture of compound (15*S*)-**6**, (15*S*)-**14** and (15*S*)-**15** 67:25:8 (HPLC analyses). Separation by flash chromatography (EtOAc) furnished 56 mg (50%) of (15*S*)-**6** and 18 mg of a mixture of (15*S*)-**14** and (15*S*)-**15**. 25 mg of (15*S*)-**6** was purified by preparative HPLC, which furnished 13 mg of isomerically pure (15*S*)-**6** as an oil. TLC $R_f = 0.15$ (EtOAc); $[\alpha]^{23}_D = +23.0°$ (c 0.62, CH_3CN); ^1H NMR δ 1.21 (6H, d), 1.54 (1H, m), 1.66 (2H, app quint), 1.78 (1H, m), 1.83 (3H, m), 2.0-2.4 (5H, m), 2.26 (2H, app t), 2.60 (3H, m), 2.93 (2H, m), 3.98 (1H, m), 4.15 (2H, m), 4.99 (1H, sept), 5.39 (2H, m), 5.55 (1H, dd), 5.67 (1H, dd), 7.30 (1H, m), 7.41 (2H, m), 7.69 (1H, d); ^{13}C NMR (CD_3OD) δ 22.8, 24.9, 25.5, 26.6, 29.5, 29.8, 34.0, 39.3, 42.7, 50.4, 55.8, 67.6, 71.3, 72.8, 77.9, 125.9, 129.6, 131.5, 131.6, 137.4, 142.4, 129.1, 129.7, 131.8, 134.7, 173.4, 202.6. Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.2; H, 8.5. Found: C, 71.2; H, 8.1.

General Procedure for the Intramolecular Palladium-Catalyzed reactions

A mixture of (15*S*)-**5** (20 mg, 0.036 mmol), $Pd(OAc)_2$ (0.4 mg, 5 mol%) and ligand (11 mol%), or $Pd(PPh_3)_4$ (2.1 mg, 5 mol%), was dissolved in CH_3CN (0.6 mL). Triethylamine (10 mL, 0.072 mmol) was added and the mixture was stirred under N_2 at 100 °C for 6 h. EtOAc (2 mL) was added and the organic layer was washed with brine (2 mL), 3% aqueous citric acid (2 x 2 mL), dried ($MgSO_4$) and concentrated. The product distribution was evaluated by analytical HPLC analyses of the crude reaction mixture and is given in Table 2 and 3. Physical data of the products are given in Table 4.

Table 4. Physical data of compounds **14-17**.

compound	R_f[a]	$[\alpha]^D$, deg[b]	t_R, min[c]
(15*S*)-**14**	0.30	+126.9	16
(15*R*)-**14**	0.20	+36.5	12
(15*S*)-**15**	0.18	-47.8	24
(15*R*)-**15**	0.17	-33.7	23
(15*S*)-**16**	0.39	+71.2	16
(15*R*)-**16**	0.30	+100.8	15
17[d]	0.47		12

[a] SiO_2, EtOAc. [b] CH_3CN, c 1.0. [c] Merck-Hitachi liquid chromatograph, column; silica gel Waters Radial-Pak 80 x 10 mm, mobile phase; 6% of ethanol in n-hexane, flow rate; 1.2 mL/min, detection 210 nm. [d] Mixture of diastereomers 1:1.

Cyclization of (15S)-5 using Pd(OAc)$_2$/P(o-tolyl)$_3$. Preparation of Isopropyl [1R-[1α(Z),2β(1Z,2S*),3α,5α]]-7-[2-[(3,4-Dihydro-2-hydroxy-1(2H)-naphthylidene)methyl]-3,5-dihydroxy-cyclopentyl]-5-heptenoat [(15S)-14] and Isopropyl [1R-[1α(Z),2β(1RS*),3a,5a]]-7-[3,5-Dihydroxy-2-[(1,2,3,4-tetrahydro-2-oxo-1-naphthyl)methyl]cyclopentyl]-5-heptenoat (17). Intramolecular coupling of 26 mg of (15*S*)-**5** using P(o-tolyl)$_3$ as ligand, afforded a mixture of (15*S*)-**14** and **17**. The mixture was separated by flash chromatography (EtOAc) which furnished 9.8 mg (48%) of **17** and 7.5 mg (37%) of (15*S*)-**14**. Analytical samples were obtained by preparative HPLC using 5% of ethanol in n-hexane as eluent for (15*S*)-**14** (t_R = 89 min), and 4% of ethanol in n-hexane as eluent for **17**, flow rate; 10 mL/min. Compound **17** was a 1:1 mixture of isomers (**17a** and **17b**) with t_R = 69 min and t_R = 84 min.

(15S)-14: ^{1}H NMR (CD_3OD) δ 1.19 (6H, d, *J* = 6.3), 1.59 (1H, m), 1.63 (2H, H_3, app quint, *J* = 7.7), 1.64 (1H, m), 1.91 (1H, m, *J* = 15.0, 11.0, 5.0, 4.6), 2.07 (1H, m), 2.10 (2H, m), 2.24 (2H, app t, *J* = 7.7), 2.28 (2H, m), 2.44 (1H, ddd, *J* = 15.0, 7.6, 6.0), 2.68 (1H, m, *J* = 15.3, 11.0, 5.2), 3.01 (1H, ddd, *J* = 10.1, 10.0, 7.4), 3.12 (1H, m, *J* = 15.3, 4.6, 3.0), 3.84 (1H, ddd, *J* = 10.0, 8.0, 6.0), 4.14 (1H, ddd, *J* = 7.6, 6.9, 1.9), 4.92 (1H, sept, *J* = 6.3), 5.12 (1H, dd, *J* = 5.0, 3.0), 5.36 (1H, m), 5.58 (1H, m), 5.87 (1H, d, *J* = 10.1), 7.09 (3H, m), 7.58 (1H, m); ^{13}C NMR (CD_3OD) δ 22.1, 25.3, 26.1, 26.4, 27.6, 31.7, 35.0, 44.7, 51.3, 52.2, 65.2, 68.9, 72.2, 78.5, 125.4, 127.0, 127.8, 129.6, 135.7, 137.5, 130.0, 130.8, 130.9, 139.8, 175.1. Anal. Calcd for $C_{26}H_{36}O_5 \cdot 1/2\ H_2O$: C, 71.4; H, 8.5. Found: C, 71.6; H, 8.2.

17a: ^{1}H NMR ($CDCl_3$) δ 1.21 (6H, d), 1.36 (1H, m,), 1.58 (1H m), 1.66 (2H, app t), 1.77 (1H, m), 1.93 (1H, m), 2.08 (3H, m), 2.26 (2H, app t), 2.15 (1H, m), 2.29 (1H, m,), 2.55 (1H, m), 2.74 (1H, m), 3.05 (1H, m), 3.23 (1H, m), 3.68 (1H, dd), 4.10 (1H, broad m), 4.17 (1H, broad m), 4.97 (1H, sept), 5.38 (2H, m), 7.15-7.27 (4H, m); ^{13}C NMR ($CDCl_3$) δ 21.8, 24.9, 26.6, 26.6, 27.7, 34.0, 37.5, 42.1, 50.6, 52.3, 52.8, 67.5, 74.5, 77.7, 127.0, 127.2, 127.6, 128.1, 136.0, 137.6, 129.1, 129.7, 173.2, 213.9.

17b: ^1H NMR ($CDCl_3$) δ 1.21 (6H, d), 1.37 (1H, m,), 1.64 (2H, app quint), 1.70 (1H, m), 1.77 (1H, m), 1.85 (1H, m,), 1.90 (4H, m), 2.10 (1H, m), 2.23 (2H, app t), 2.28 (1H, m,), 2.50 (1H, m), 2.68 (1H, m), 3.02 (1H, m), 3.18 (1H, m), 3.58 (1H, m), 4.01 (1H, broad m), 4.13 (1H, broad m), 4.98 (1H, sept), 5.33 (2H, m), 7.23 (4H, m); ^{13}C NMR ($CDCl_3$) δ 21.8, 24.8, 26.4, 26.7, 27.5, 34.0, 36.2, 37.5, 42.3, 50.6, 52.3, 53.6, 67.5, 74.8, 78.6, 126.9, 126.9, 127.9, 129.0, 136.3, 136.7, 128.7, 129.8, 173.3, 213.8.

Cyclization of (15S)-5 using Pd(OAc)$_2$/DPPE. Preparation of (15S)-14 and Isopropyl [1R-[1α(Z),2E(1R*,2S*),3α,5α]]-7-[3,5-Dihydroxy-2-[(1,2,3,4-tetrahydro-2-hydroxy-1-naphthyl)-methylene]cyclopentyl]-5-heptenoat [(15S)-15]. Intramolecular coupling of 16.5 mg of (15*S*)-**5** using DPPE as ligand afforded, after purification by flash chromatography (EtOAc), a mixture of (15*S*)-**15** and (15*S*)-**14** (8 mg, 63%). Analytical samples were obtained by preparative HPLC using 7% of ethanol in n-hexane as eluent; (15*S*)-**15** (t_R = 102 min) and (15*S*)-**14** (t_R = 68 min).

(15S)-15: ^1H NMR (CD_3OD) δ 1.20 (6H, d, *J* = 6.1), 1.56 (2H, app quint, *J* = 7.6), 1.81 (1H, ddd, *J* = 13.1, 9.0, 6.1), 1.92 (1H, m), 1.99 (1H, m), 2.03 (2H, m), 2.12 (2H, app t, *J* = 7.6), 2.27 (1H, ddd, *J* = 13.1, 6.7, 6.6), 2.38 (1H, m), 2.55 (1H, m), 2.76 (1H, m), 2.82 (1H, m), 3.04 (1H, ddd, *J* = 16.1, 8.85, 6.4), 3.75 (1H, dd, *J* = 10.4, 3.9), 4.08 (1H, ddd, *J* = 6.7, 3.9, 2.7), 4.15 (1H, ddd, *J* = 9.0, 6.7, 6.7), 4.41 (1H, dd, *J* = 6.6, 6.1), 4.91 (1H, sept, *J* = 6.1), 5.30 (1H, m), 5.68 (1H, m), 5.74 (1H, d, *J* = 10.4), 7.08 (3H, m), 7.27 (1H, m); ^{13}C NMR (CD_3OD) δ 22.1, 26.1, 26.6, 27.7, 28.1, 30.1, 35.0, 41.3, 45.9, 46.8, 68.9, 70.4, 73.1, 74.2, 126.7, 127.1, 129.5, 130.6, 136.9, 138.4, 129.9, 130.1, 131.6, 149.4, 175.0. Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.9; H, 8.5. Found: C, 72.6; H, 8.4.

Cyclization of (15S)-5 using Pd(PPh$_3$)$_4$. Preparation of Isopropyl [1R-[1α(Z),2Z-(1S*,2S*),3α,5α]]-7-[3,5-Dihydroxy-2-[(1,2,3,4-tetrahydro-2-hydroxy-1-naphthyl)methylene]-cyclopentyl]-5-heptenoat [(15S)-16] and (15S)-15. Intramolecular coupling of 29 mg of (15*S*)-**5** using $Pd(PPh_3)_4$ as catalyst, afforded a mixture of (15*S*)-**16** and (15*S*)-**15**. Separation by flash chromatography (EtOAc) furnished 5.7 mg (25%) of (15*S*)-**16** and 6.7 mg (30%) of (15*S*)-**15**. Analytical samples were obtained by preparative HPLC using 5% of ethanol in n-hexane as eluent for (15*S*)-**16** (t_R = 85 min) and 7% of ethanol in n-hexane as eluent for (15*S*)-**15** (t_R = 102 min).

(15S)-16: ^1H NMR (CD_3OD) δ 1.18 (6H, d, *J* = 6.4), 1.60 (2H, app quint, *J* = 7.5), 1.81 (1H, m, *J* = 16.2, 12.8, 10.1, 6.1), 1.94 (1H, ddd, *J* = 14.0, 3.3, 2.4), 2.01 (1H, ddd, *J* = 14.0, 7.1, 4.0), 2.10 (2H, m), 2.11 (1H, m), 2.21 (2H, app t, *J* = 7.5), 2.38 (2H, m), 2.42 (1H, m), 2.82 (1H, m), 2.90 (1H, m), 3.69 (1H, ddd, *J* = 10.1, 7.9, 3.05), 3.89 (1H, dd, *J* = 9.0, 7.9), 4.22 (1H, ddd, *J* = 7.1, 3.3, 2.4), 4.87 (1H, broad d), 4.92 (1H, sept, *J* = 6.4), 5.34 (1H, m), 5.37 (1H, m), 5.57 (1H, m), 7.02 (3H, m), 7.34 (1H, m); ^{13}C NMR (CD_3OD) δ 22.1, 26.0, 27.5, 27.6, 28.7, 31.3, 34.9, 43.4, 49.1, 50.9, 68.9, 72.6, 72.9, 74.2, 126.7, 126.9, 129.2, 131.2, 136.6, 138.7, 130.3, 130.7, 130.7, 149.4, 175.1. Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.9; H, 8.5. Found: C, 73.1; H, 8.3.

Cyclization of (15R)-5 using $Pd(OAc)_2/P(o\text{-}tolyl)_3$. Preparation of Isopropyl [1R-[1α(Z),2β-(1Z,2R*),3α,5α]]-7-[2-[(3,4-Dihydro-2-hydroxy-1(2H)-naphthylidene)methyl]-3,5-dihydroxycyclopentyl]-5-heptenoat [(15R)-14] and 17. Intramolecular coupling of 34 mg of (15*R*)-**5** using $P(o\text{-}tolyl)_3$ as ligand, afforded a mixture of (15*R*)-**14** and **17**. Separation by flash chromatography (EtOAc) gave 16.5 mg (63%) of (15*R*)-**14** and 1.8 mg (6%) of **17**. The fractions of (15*R*)-**14** also contained small amounts of (15*R*)-**15** (analytical HPLC, see Table 3). Analytical samples of (15*R*)-**14** was obtained by preparative HPLC using 3% of ethanol in n-hexane as eluent (t_R = 110 min).

(15R)-14: ^1H NMR (CD_3OD) δ 1.16 (6H, d, J = 6.4), 1.58 (2H, app quint, J = 7.3), 1.67 (1H, m), 1.69 (1H, m), 1.78 (1H, m, J = 12.5, 8.2, 4.5, 3.35), 2.03 (2H, m), 2.08 (1H, m), 2.10 (1H, m), 2.20 (2H, app t, J = 7.32), 2.24 (1H, m), 2.50 (1H, ddd, J = 14.6, 8.5, 6.1), 2.605 (1H, ddd, J = 15.9, 8.2, 4.6), 2.97 (1H, ddd, J = 11.3, 10.2, 8.2), 3.03 (1H, ddd, J = 15.9, 12.2, 4.5), 3.87 (1H, ddd, J = 8.5, 8.2, 5.8), 4.16 (1H, m), 4.89 (1H, sept, J = 6.4), 4.92 (1H, dd, J = 3.8, 3.35), 5.31 (1H, m), 5.51 (1H, m), 6.07 (1H, d, J = 10.2), 7.11 (3H, m), 7.64 (1H, m); ^{13}C NMR (CD_3OD) δ 22.1, 25.6, 26.0, 26.7, 27.6, 30.9, 34.9, 44.6, 51.3, 52.0, 65.0, 68.9, 72.4, 76.6, 124.9, 127.2, 127.8, 129.5, 135.0, 138.1, 130.1, 130.4, 131.5, 139.8, 174.9. Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.9; H, 8.5. Found: C, 72.8; H, 8.5.

Cyclization of (15R)-5 using $Pd(OAc)_2$/DPPE. Preparation of (15R)-14 and 17. Intramolecular coupling of 43 mg of (15*R*)-**5** using DPPE as ligand afforded a mixture of (15*R*)-**14** and **17**. Separation by flash chromatography (EtOAc) furnished 22 mg (66%) of (15*R*)-**14** and 3.4 mg (10%) of **17**.

Cyclization of (15R)-5 using $Pd(PPh_3)_4$. Preparation of Isopropyl [1R-[1α(Z),2E-(1R*,2R*),3α,5α]]-7-[3,5-Dihydroxy-2-[(1,2,3,4-tetrahydro-2-hydroxy-1-naphthyl)methylene]-cyclopentyl]-5-heptenoat [(15R)-15] and Isopropyl [1R-[1α(Z),2Z(1S*,2R*),3α,5α]]-7-[3,5-Dihydroxy-2-[(1,2,3,4-tetrahydro-2-hydroxy-1-naphthyl)methylene]-cyclopentyl]-5-heptenoat [(15R)-16]. Intramolecular coupling of 135 mg of (15*R*)-**5** using $Pd(PPh_3)_4$ as catalyst, afforded a mixture of (15*R*)-**15** and (15*R*)-**16**. Separation by flash chromatography (EtOAc) furnished 70 mg (67%) of (15*R*)-**15** and 18 mg (17%) of (15*R*)-**16**. The fractions of (15*R*)-**15** also contained small amounts of (15*R*)-**14** (analytical HPLC, see Table 3). Analytical samples were obtained by preparative HPLC using 7% of ethanol in n-hexane as eluent for (15*R*)-**15** (t_R = 120 min) and and 4.5% of ethanol in n-hexane as eluent for (15*R*)-**16** (t_R = 74 min).

(15R)-15: ^1H NMR (CD_3OD) δ 1.20 (6H, d, J = 6.4), 1.56 (2H, app quint, J = 7.6), 1.81 (1H, m), 1.83 (1H, m), 2.03 (2H, app quart, J = 7.6), 2.10 (2H, app t, J = 7.6), 2.12 (1H, m), 2.28 (1H, ddd, J = 13.1, 6.7, 6.4), 2.39 (1H, m), 2.54 (1H, m), 2.90 (1H, m), 2.90 (2H, m), 3.56 (1H, dd, J = 10.0, 8.6), 3.63 (1H, ddd, J = 10.1, 8.6, 3.4), 4.17 (1H, ddd, J = 8.8, 8.8, 6.4), 4.41 (1H, ddd, J = 6.7, 5.8, 1.2), 4.92 (1H, sept, J = 6.4), 5.28 (1H, m), 5.745 (1H, ddd, J = 10.0, 1.5, 1.2), 5.67 (1H, m), 7.08 (3H, m), 7.30 (1H, m); ^{13}C NMR (CD_3OD) δ 22.1, 26.1, 27.7, 28.3, 29.0, 31.9, 35.0, 41.4, 46.9, 49.7, 68.9, 72.7, 73.0, 74.3, 126.7, 127.2, 129.4, 130.4, 136.8, 138.4, 129.8, 130.7, 131.6, 150.8, 175.0. Anal. Calcd for $C_{26}H_{36}O_5 \cdot 1/2\ H_2O$: C, 71.4; H, 8.5. Found: C, 71.6; H, 8.2.

(15R)-16: ^{1}H NMR (CD_3OD) δ 1.18 (6H, two d, *J* = 6.4), 1.59 (2H, app quint, *J* = 7.3), 1.87 - 2.02 (4H, m), 2.06 (2H, m), 2.21 (2H, app t, *J* = 7.3), 2.33 (2H, m,), 2.41 (1H, m), 2.82 (1H, m), 3.02 (1H, m), 4.09 (1H, ddd, *J* = 7.9, 4.6, 3.05), 4.15 (1H, dd, *J* = 10.1, 4.6), 4.20 (1H, app quart), 4.83 (1H, m), 4.90 (1H, sept, *J* = 6.4), 5.34 (1H, m), 5.54 (1H, m), 5.61 (1H, ddd, *J* = 10.1, 2.1, 1.8), 7.05 (3H, m), 7.32 (1H, m); ^{13}C NMR (CD_3OD) δ 22.1, 26.0, 27.5, 27.6, 27.7, 29.2, 34.9, 43.5, 45.6, 50.9, 68.9, 70.7, 72.3, 74.1, 126.7, 126.9, 129.4, 131.4, 136.4, 139.1, 129.0, 130.2, 130.7, 148.5, 175.1. Anal. Calcd for $C_{26}H_{36}O_5 \cdot 1/2\ H_2O$: C, 71.4; H, 8.5. Found: C, 71.1; H, 8.0.

Chemical correlation of (15S)-10 with (1S,5R,6R,7R)-6-[(3R)-3-Hydroxy-5-phenyl-1-pentyl]-7-(4-phenylbensoyloxy)-2-oxabicyclo[3.3.0]octane-3-one (15R)-12.[1] A solution of (15*S*)-**10** (39.3 mg, 0.064 mg) in ethanol (2 mL) was added to a suspension of 10% Pd/C (7.1 mg) in 1 M aqueous NaOH (0.4 mL). The mixture was stirred under hydrogen atmosphere for 6 h, and then quenched with 1 M aqueous HCl. The catalyst was removed by filtration through a Celite pad. The product was extracted with EtOAc (10 mL), washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (CH_2Cl_2/EtOAc 5:1), which afforded 18.2 mg (58%) of (15*R*)-**12** as an oil. All physical data were in accordance with those reported on (15*R*)-**12**.[1]

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REFERENCES AND NOTES

1. Resul, B.; Stjernschantz, J.; No, K.; Liljebris, C.; Selén, G.; Astin, M.; Karlsson, M.; Bito, L. Z. *J. Med. Chem.* **1993**, 36, 243-248.
2. Stjernschantz, J.; Resul, B. *Drugs Future.* **1992**, 17, 691-704.
3. Liljebris, C.; Resul, B.; Hacksell, U. *Bioorg. Med. Chem. Lett.* **1993**, 3, 241-244.
4. Liljebris, C.; Selén, G.; Resul, B.; Stjernschantz, J.; Hacksell, U. *J. Med. Chem.* **1995**, 38, 289-304.
5. For general reviews see: (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, **1985**. (b) Heck, R. F. *Org. React.* **1982**, 27, 345-390. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 2379-2411. (d) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, 28, 2-7.
6. (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Tetrahedron Lett.* **1991**, 32, 1753-1756. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, 57, 1481-1486.
7. For related intramolecular Heck reactions of aryl halids possessing an allylic alcohol moiety, see: (a) Gaudin, J-M. *Tetrahedron Lett.* **1991**, 32, 6113-6116. (b) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org Chem.* **1983**, 48, 3894-3900.

8. (a) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, 93, 1491-1493. (b) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, 94, 8616-8618.
9. Resul, B. Unpublished data.
10. For convenience, we use the prostaglandin numbering system in the running text. Correct nomenclature can be found in the Experimental Section.
11. 6-Exo-trig cyclizations are usually preferred over 7-endo-trig cyclizations, see for example ref. 7a and: Grigg, R.; Stridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, 46, 4003-4018, and references cited therein.
12. (a) Hacksell, U.; Kalinkoski, H. T.; Barofsky, D. F.; Daves D. *Acta Chem. Scan.* **1985**, 39, 469-476. (b) Arcadi, A.; Bernocchi, E.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1991**, 47, 1525-1540. (c) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, 33, 4859-4862. (d) Ono, K.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1994**, 35, 4133-4136. (e) Hosokawa, T.; Sugafujji, T.; Yamanaka, T.; Murahashi, S-I. *J. Organomet. Chem.* **1994**, 470, 253-255. (f) Larhed, M.; Andersson, C-M.; Hallberg, A. *Tetrahedron* **1994**, 285-303.
13. For controlled regioselectivity with bidentate phosphine ligands, see ref. 6 and: (a) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santi, R. *J. Org. Chem.* 1991, 56, 5796-5800. (b) Carfagna, C.; Musco, A.; Sallese, G.; Santi, R.; Fiorani, T. *J. Org. Chem.* **1991**, 56, 261-263.
14. Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, 95, 3071-3072.
15. (a) Wadsworth, W.; Emmons, W. *J. Am. Chem. Soc.* **1961**, 83, 1733. (b) Horner, L.; Hoffmann, H.; Wippel H. G. *Chem. Ber.* **1958**, 61-64.
16. Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, 87, 5661-5670.
17. Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, 94, 7159-7161.
18. Wilson, K. E.; Seidner, R. T. *J. Chem. Soc. Chem. Comm.* **1970**, 213-214.
19. For a review see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 89, 863-927.
20. Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1979**, 20, 1865.
21. (a) Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591-598. (b) Rao, C. G. *Org. Prep. Proc. Int.* **1980**, 12, 225-228.

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