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Towards a Large Scale Preparation of Mexiprostil#1

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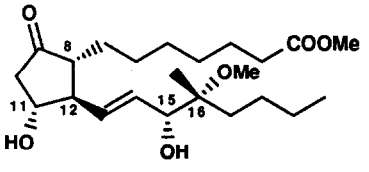
Abstract: The enantioselective synthesis of mexiprostil (16R-16-methoxy-16-methyl PGE_1 methyl ester) is described. The assembly of the prostaglandin framework has been accomplished by the three component coupling process, via consecutive linking of the ω and α-sidechain to unsubstituted (R)-4-hydroxy-2-cyclopentenone, and alternatively by a conjugate addition of the ω-side chain to a (R)-4-hydroxy-2-cyclopentenone in which the α-side chain is already incorporated. The required lower side chain building block is prepared enantioselectively from nerol utilising the Sharpless epoxidation reaction.

Introduction

The broad spectrum of biological activities displayed by prostaglandins has led to a considerable synthetic effort in this field[3,4,5]. A wide variety of analogues were prepared, with the objective to discover new, therapeutically useful agents.

Mexiprostil (**1**), a PGE_1 derivative developed by Merrell Dow[6], has been shown to inhibit gastric acid secretion and to protect the gastric mucosa[7]. The compound is presently under development in phase II clinical trials and rather large quantities of the drug are required.



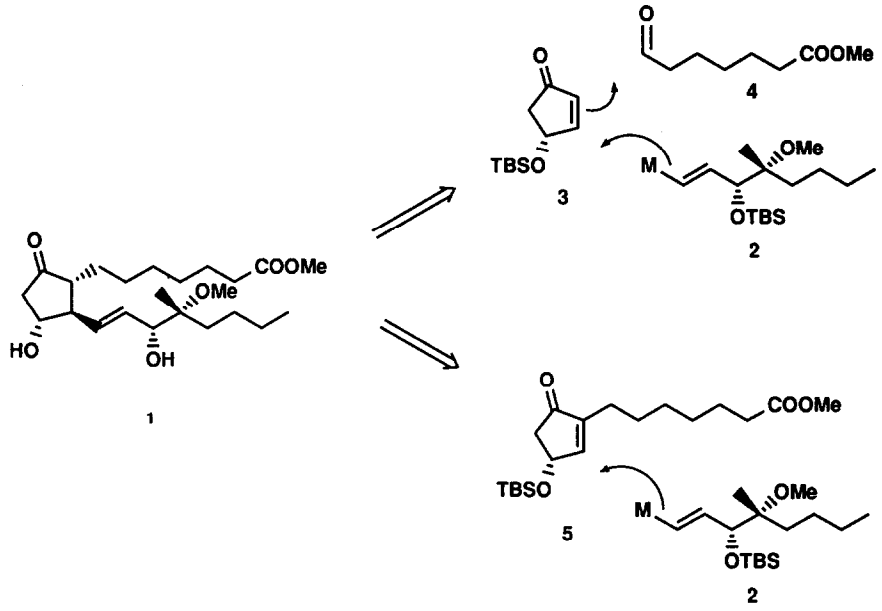
1 ; MEXIPROSTIL

Mexiprostil (**1**) is prepared in a 15-step linear sequence, starting from Corey lactone in 3-5 % overall yield. Scaling up this route proved to be very difficult. To ensure the further development of the drug, a new synthesis had to be developed, which allows for large scale preparation.

#Dedicated to the memory of Dr. Fritz Gerhart.

Among the various strategies for prostaglandin synthesis, the three-component coupling reaction[4] was considered most suitable for our purpose. In view of its convergency and flexibility, the approach seemed to be especially promising for its scale-up potential. In the context of the synthesis of mexiprostil (**1**), this pathway implies the conjugate addition of the metallated ω-side chain precursor **2** to the cyclopentenone derivative **3**, followed by *in situ* trapping of the derived enolate species with aldehyde **4**. This protocol circumvents the equilibrium / elimination problem inherent to this coupling reaction[4].

The process has a high degree of stereoselectivity. The required R-stereochemistry at C_{12} is induced by the spacial positioning of the protected hydroxy function at C_{11} (PG-numbering) in the enone **3**. The ω-side chain then eventually directs the incoming aldehyde **4** in the enolate-trapping reaction to the α-face, such affording the (R)-configuration at C_8. As the configuration at C_{11} directly and indirectly determines the stereochemical outcome of the complete reaction sequence, it is of utmost importance to use optically pure (R)-enone **3** as starting material.



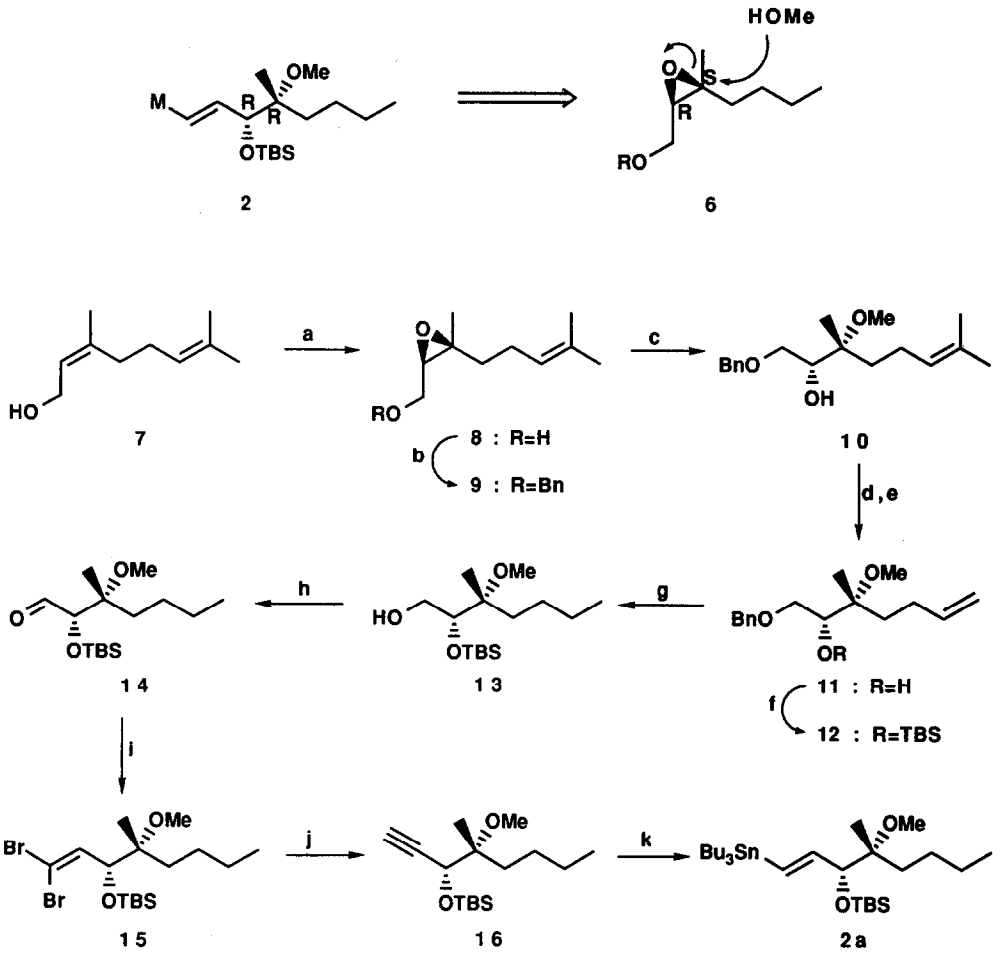
Conjugate addition of the nucleophilic ω-side chain building block **2** to a protected derivative of optically pure (4R)-2-(6-carboxymethylhexyl)-4-hydroxy-2-cyclopenten-1-one (**5**) may be considered as an alternative to the three-component coupling reaction[5]. However, the elaborous preparation of optically pure (R)-**5** rendered this two-component coupling reaction initially less attractive for scale up purposes.

Results and Discussion:

Preparation of the ω-side chain precursor 2 . The optically active siloxy cyclopentenone **3** and the aldehyde **4** are available in various ways[8,9]. Our main concern was the design of the synthesis of the prostaglandin atypical ω-side chain, with as main problem the control of the stereogenic centers at C_{15} and C_{16}. In our approach we relied on the Sharpless oxidation protocol[10] to obtain an epoxide, which upon regio- and stereoselective acid

catalyzed opening in methanol was expected to furnish both the desired (15R)-hydroxy and (16R)-methoxy functions[11].

Retrosynthetically, the (15R,16R)-configuration of the side chain **2** requires a (15R,16S)-configurated epoxide **6**, which may derive from Sharpless epoxidation of an allylic alcohol with (Z)-geometry using (D)-diethyl tartrate as chiral ligand. Eventually then, the commercially available monoterpene nerol (**7**) proved to be a convenient starting material.



Reagents : a: D(-)DET, $Ti(OiPr)_4$, t.BuOOH, CH_2Cl_2, -20°C (95%) ; b: BnBr, KOt.Bu, THF, 0°C ; c : MeOH, DOWEX 50 (H^+), rt (82%) ; d : O_3, Ph_3P, CH_2Cl_2, MeOH, -78°C ; e: Ph_3PCH_3Br, KOt.Bu, THF, rt (91%) ; f : TBSCl, imidazole, DMF, rt (82%); g : H_2, 1atm, 20% $Pd(OH)_2/C$, EtOAc, rt (93%) ; h : DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, -78°C ; i : Ph_3P, CBr_4, CH_2Cl_2, rt (91%) ; j : Mg, THF, reflux (82%) ; k : Bu_3SnH, AIBN, 130°C (70%)

Scheme 1 : Synthesis of the ω-side chain precursor

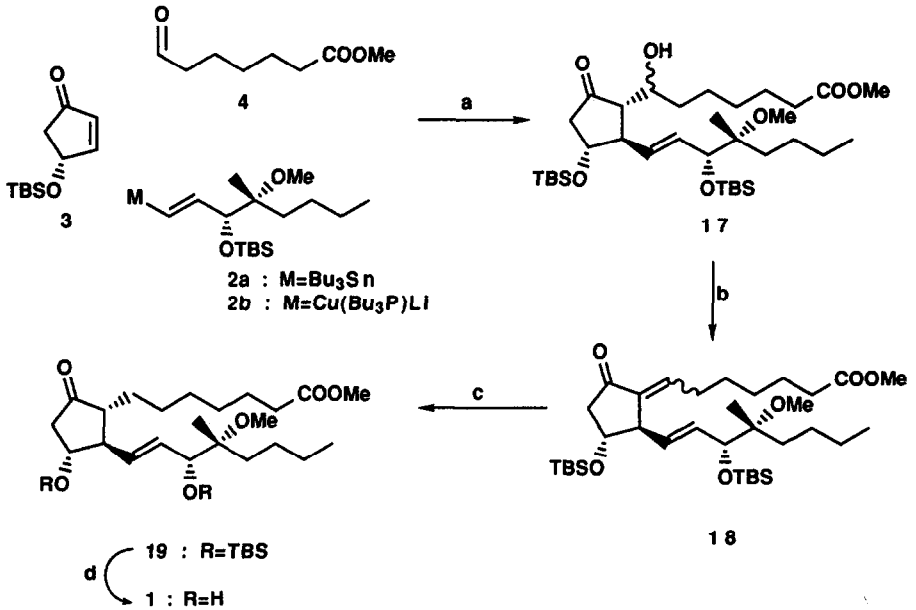
"Catalytic" Sharpless epoxidation of nerol (**7**) gave the epoxide **8** in over 95% chemical yield and with 70 - 80% e.e. The alcohol **8** was transformed into the benzyl ether **9**, which was stirred in methanol in the presence of

an acid catalyst [Dowex 50 (H^+)], to afford the (16R)-methoxy (15R)-hydroxy derivative **10** with high stereo- and regioselectivity[11].

In order to obtain the correct side chain length, the propylidene function had to be replaced by a methylene group. Ozonolysis of alcohol **10** at -78°C, followed by treatment with triphenylphosphine, gave a crude hemiacetal, which, treated with methyl triphenylphosphonium bromide and potassium *tert.*butoxide in tetrahydrofuran, afforded the methylene derivative **11**. The alcohol **11** was converted to the silyl ether **12**[12], whereafter catalytic hydrogenation over Pearlman's catalyst in ethylacetate removed the benzyl group and reduced the double bond to furnish alcohol **13**.

This completes the assembly of the C_{15} - C_{20} part in the ω-side chain, and the transformation of the primary alcohol function into the metallated vinyl species **2** was due next. Swern oxidation[13] of alcohol **13** gave the aldehyde **14**, which, treated with carbontetrabromide and triphenylphosphine in dichloromethane, afforded the dibromo olefin **15**[14] (91% over two steps). The debrominative rearrangement of **15** to the alkyne **16** can be performed using *n.*butyl lithium in tetrahydrofuran at -78°C[14]. However, more practically, magnesium metal in tetrahydrofuran at reflux temperature, as recently reported by us[15], also converted the dibromo alkene **15** to the acetylene **16** very efficiently. Finally, AIBN initiated stannyl hydride addition[16] on the alkyne **16** at 130°C proceeded with 90% (E)-selectivity, to afford the required target ω-side chain **2**.

The three-component coupling reaction. Having the required three building blocks in hand, we next explored the coupling reaction in the synthetic context of mexiprostil (**1**).



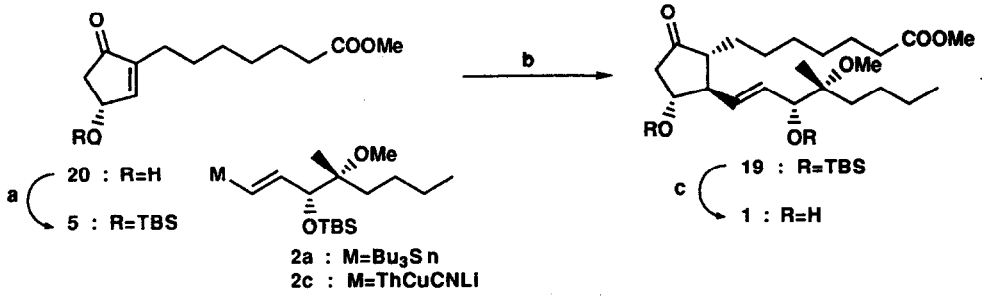
Reagents : a : **2a**, n.BuLi, Bu_3P, CuI, then **3**, then **4**, -78°C (50%) ; b : MsCl, DMAP, CH_2Cl_2, rt (60%) ; c : Bu_3SnH, $(t.BuO)_2$, 110°C (90%) ; d : HOAc, H_2O, THF, rt (50%).

Scheme 2 : The three component coupling reaction

The vinylstannane **2a** was treated with *n*.butyl lithium in tetrahydrofuran at -78°C[17], followed by the addition of copper(I)iodide and tri-*n*.butyl phosphine, to afford the organo copper reagent **2b**[4a,e]. Sequential treatment of the enone **3** with this copper reagent at -40°C and then aldehyde **4** at -78°C gave a mixture of diastereomers of the hydroxy PGE_1 derivative **17**. It is essential to trap the intermediate enolate with the aldehyde **4** at low temperature, and to quench the reaction with acetic acid, also at -78°C, in order to avoid elimination of the C_{11}-siloxy group, wich leads to PGA-type derivatives[4]. The attack of the anion species **2b** was found to occur from the β-face, opposite to the bulky C_{11} *tert*.butyldimethylsiloxy substituent, thus establishing the required (12R)-configuration.

The C_7-hydroxyl group was removed via a dehydration / reduction sequence. Treatment of alcohol **17** with mesyl chloride and dimethylamino pyridine in dichloromethane at room temperature yielded the enone **18** in 60% yield[4e,18]. The reduction of the enone was efficiently accomplished with tri-*n*.butyl stannane and di-*tert*.butyl peroxide at 110°C[18], affording the bis-protected mexiprostil derivative **19**. Attempts to reduce the enone function with zinc in isopropanol and acetic acid[4c] were unsuccessfull. Finally, deprotection of **19** with acetic acid in aqueous tetrahydrofuran afforded, after column chromatography[21], the optically pure target (8R,11R,12R,15R,16R)-prostaglandin derivative mexiprostil (**1**), in all respects identical to the material obtained from the earlier synthesis[6].

The two component coupling reaction[5]: During the course of this investigation, the optically pure enone **20** became commercially available[19]. This then offered the opportunity to shorten further our new synthesis of mexiprostil (**1**). The silylether **5**[19], obtained from the alcohol **20** using a standard silylation procedure[9] (*tert*.butyldimethylsilyl chloride, imidazole, dimethylformamide), reacted with the copper derivative **2b**, to afford stereospecifically the protected prostaglandin derivative **19**, albeit in only 23% yield (50% starting material recovered). The low conversion is attributed to the decreased reactivity of the more substituted enone **5** compared to cyclopentenone **3**. However, when the cyclopentenone **5** was treated instead with the mixed higher order cuprate **2c**[20] in tetrahydrofuran at -50°C, the prostanoic acid derivative **19** was formed stereospecifically in a satisfying 65% yield. As discussed above for the three-component coupling reaction, the stereochemical outcome of the transformation is determined by the steric environment of the protected hydroxyl function at C_{11}. As described, acid hydrolysis of **19**, followed by chromatographic purification[21], gave pure mexiprostil (**1**), with over 98% enantiomeric purity.



Reagents : a : TBSCl, imidazole, DMF, rt (95%) ; b : **2a**, n.BuLi, ThCu(CN)Li, THF, then **5**, -78°C (65%) ; c : HOAc, H_2O, THF, rt (50%).

Scheme 3 : The two component coupling reaction.

In summary, we here describe two alternative, new enantioselective syntheses of mexiprostil (**1**), which will facilitate the preparation of large quantities of the drug for further clinical testing[22].

The overall sequence has a high degree of convergency and enantioselectivity. Both stereogenic centers C_{15} and C_{16} of the prostaglandin atypical side chain **2** were obtained in 70 - 80% e.e. using the Sharpless epoxidation protocoll. Addition of this side chain to the >98% enantiomerically pure cyclopentenones **3** and **5** respectively, followed by chromatography[21], gives optically pure mexiprostil (**1**).

Experimental

All reactions carried out at room temperature were at or near 20°C. Melting points are uncorrected. Solvents were dried or distilled before use. Unless otherwise stated, all reactions were carried out under an inert atmosphere of nitrogen or argon with stirring. During workup, solvents were removed *in vacuo* with a rotatory evaporator.

Proton magnetic resonance spectra were recorded on samples dissolved in $CDCl_3$ on either a varian-EM 390 NMR spectrometer (90 MHz) or a Bruker instrument (360 MHz). Chemical shifts are reported in δ units, parts per million (ppm) relative to tetramethyl silane as internal standard. IR spectra were recorded on a Perkin-Elmer IR-577 or IR-277 spectrometer. MS spectra were recorded on a Ribermag R10-10 or Finnigan TSQ GC/MS/MS spectrometer. Elemental analysis were performed on a Carlo Erba Elemental Analyzer-1106. Thin layer chromatography (TLC) utilized silica gel precoated onto glass plates (E. Merck silica gel 60F-254).

(2R,3S)2,3-epoxy-3,7-dimethyl-6-octene-1-ol (8). A 2 liter 3-necked flask is fitted with an overhead mechanical stirrer, a thermometer and a pressure equalizing addition funnel. Activated crushed 3Å molecular sieves (15 g) are brought in the flask, and the set up is dried under vacuum while heating with a heat gun. The flask is purged with nitrogen. Dry CH_2Cl_2 (600 mL, dried over activated mol sieves) is introduced and the mixture is cooled to -15°C, utilizing a glycol/water : 4/6 mixture-dry ice cooling bath or a cryocool apparatus. D-(-)-Diethyltartrate (77.8 mmol, 13.3 mL), titanium tetraisopropylate (58.3 mmol, 17.3 mL) and t.butyl hydroperoxide (583 mmol, 194 mL of a 3 M solution in toluene) are added sequentially. The mixture is agitated for 30 minutes at -15°C, and the temperature is lowered to -25°C. Nerol (389 mmol, 68.5 mL) is added over a period of 30 minutes with vigorous stirring. The reaction mixture is kept for 3 h at -20°C. The cooling bath is removed, and the reaction mixture is allowed to warm to 0°C, at which moment water (340 mL) is added in one portion. After 15 min, an aqueous solution of NaOH and NaCl (72 mL of a solution prepared by adding 5 g NaCl to a solution of 30 g NaOH in 90 mL of water) is added. A sudden phase separation occurs, and the stirrring is stopped immediately. The mixture is transferred to an extraction funnel and the CH_2Cl_2 layer is removed. The water layer is extracted with CH_2Cl_2 (3 x 300 mL). Emulsions are broken by adding 15 mL of MeOH, while gentle stirring with a glass bar. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Distillation (66-68°C, 0.1 Torr) affords 65.7 g (99%) of the desired epoxide **8** : $[\alpha]_D$ = +15.4° (c = 3.3, $CHCl_3$); TLC Rf (hexane/ether : 7/3) 0.20; ^{1}H NMR δ 1.29 (s, 3H, 3-CH_3), 1.55-1.80 (m, 2H, 4-H), 1.57 (s, 3H, 7-CH_3), 2.25 (m, 2H, 5-H), 2.64 (br s, 1H, OH), 2.91 (dd, 1H, J=5Hz,6Hz, 2-H), 3.64 (m, 2H, 1-H), 5.03 (br t, 1H, J=7Hz, 6-H).

Acylation was carried out on a 10 mg scale by using an excess of acetic anhydride and triethylamine and a catalytic amount of 4-(dimethylamino) pyridine in 100 µL of CH_2Cl_2. Analysis by the shift reagent Eu(III)(hfc)$_3$ indicated an optical purity of 70%.

(2R,3R)-1-benzyloxy-3-methoxy-3,7-dimethyl-6-octene-2-ol (10). To a solution of the alcohol **8** (386 mmol, 65.7 g) in dry THF (400 mL), cooled in an ice-salt bath, is added benzyl bromide (463 mmol, 72.6 g), followed by the portionwise addition of potassium t.butoxide (463 mmol, 52 g), so that the temperature is kept below 10°C. The cooling bath is removed and the mixture is stirred overnight at room temperature. NEt_3 (15 mL) is added and the mixture is stirred for an additional 24 h. THF is then evaporated, the residue is taken up in ether and the organic phase is washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The benzyl ether **9** is used without purification in the next step : TLC Rf (hexane/ether : 80/20) 0.60; ^{1}H NMR δ 1.28 (s, 3H, 3-CH_3), 1.50-1.80 (m, 2H, 4-H), 1.57 (s, 3H, 7-CH_3), 1.65 (s, 3H, 7-CH_3), 2.20 (m, 2H, 5-H), 2.95 (t, 1H, J=6.0Hz, 2-H), 3.47 (dd, 1H, J=6.0Hz,16.4Hz, 1-H), 3.65 (dd, 1H, J=6.0Hz, 16.4Hz, 1-H), 4.55 (s, 2H, $PhCH_2$), 5.06 (br t, 1H, J=7.0Hz, 6-H), 7.30 (s, 5H, Ph).

To a solution of the crude benzyl ether **9** (120 g, approx 386 mmol) in MeOH (1 L) is added prewashed Dowex 50 (H^+, 6 g). The mixture is stirred overnight at room temperarure. TLC (petroleumether/EtOAc : 8/2) indicates an uncomplete reaction. Dowex 50 (H^+, 3 g) is added, and the reaction mixture is stirred for an additional 24 h at room temperature. The resin is filtered off and is washed with CH_2Cl_2. The organic solution after addition of a trace K_2CO_3 is kept without purification for the next step. A small sample was concentrated in vacuo, and purified by column chromatography (silica gel, petroleum ether/EtOAc : 80/20) to afford an analytical

pure sample of the alcohol **10** : TLC Rf (hexane/ether : 6/4) 0.42; IR (neat) 3420, 2880, 1440, 1070, 730, 695 cm^{-1}; ^1H NMR δ 1.10 (s, 3H, 3-CH_3), 1.50-1.80 (m, 2H, 4-H), 1.58 (s, 3H, 7-CH_3), 1.66 (s, 3H, 7-CH_3), 2.0 (m, 2H, 5-H), 2.55 (br s, 1H, OH), 3.20 (s, 3H, OCH_3), 3.40-3.65 (m, 2H, 1-H), 3.85 (br dd, 1H, J=3.0Hz,8.0Hz, 2-H), 4.55 (s, 2H, $PhCH_2$), 5.06 (br t, 1H, J=7.0Hz, 6-H), 7.30 (s, 5H, Ph); MS m/z 310(MNH_4^+, 100), 293(MH^+, 80); Anal. calculated for $C_{18}H_{28}O_3$: C, 73.92; H, 9.66; Found : C, 73.79; H, 9.51.

(2R,3R)-1-benzyloxy-3-methoxy-3-methyl-6-heptene-2-ol (11). A 2 L 3-necked flask, fitted with a thermometer and a gas bubbler, is loaded with a solution of the alcohol **10** (98 mmol) in a MeOH/CH_2Cl_2 : 1/1 mixture (750 mL). The reaction mixture is cooled in a dry ice-acetone bath (internal temperature approximately -60°C), and ozone is bubbled through the solution. The mixture is stirred with a magnetic stirrer. Ozone bubbling is continued till the solution turns blue. A few drops of Me_2S are added so that the blue color disappears (reduction of excess ozone). Ph_3P (100 mmol, 26.3 g) is added in one portion and the cooling bath is removed. The mixture is allowed to warm slowly to room temperature and the stirring is continued for 1 h. The solvent is removed in vacuo. Finally, traces of MeOH are removed by addition and evaporation of toluene (2 times 100 mL). The residue is taken up in anhydrous THF, and the product is used as such in the next reaction (the reaction was repeated twice more to convert all of the alcohol **10**).

A dry 4 liter 3-necked flask, fitted with a thermometer, mechanical stirrer and addition funnel, is loaded with Ph_3PCH_3Br (588 mmol, 210 g, dried overnight at 80°C under vacuum). The system is purged with nitrogen. Anhydrous THF (600 mL) is introduced, the reaction mixture is cooled in a crushed ice-water bath, and KOt.Bu (784 mmol, 88 g) is added, to give a bright yellow solution. The cooling bath is removed, and a solution of the lactol (approx 386 mmol, crude from previous reaction) in THF (400 mL) is added dropwise over 0.5h via the addition funnel. The mixture is stirred for 3 h at room temperature. The reaction mixture is then cooled in an ice-water bath, and 800 mL of a saturated aqueous NH_4Cl solution is added. The mixture is extracted with EtOAc. The organic phase is washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. Petroleum ether is added to the residue to precipitate the Ph_3PO, which is removed by filtration. The filtrate is concentrated in vacuo to afford the alkene **11** as an oil. The product is purified by filtration through a path of silica gel, eluting succesively with petroleum ether/EtOAc : 95/5 (to rinse off the Ph_3P) and then with petroleum ether/EtOAc : 70/30 to afford the reaction product **11** (60 g, 60%) as a yellow oil after concentration in vacuo : TLC Rf (hexane/ether : 60/40) 0.40; $[\alpha]_D^{20}$ +7.0 ($CHCl_3$, c=5.3); IR (neat) 3440, 2920, 1640, 1440, 1070, 730 cm^{-1}; ^1H NMR (360 MHz) δ 1.10 (s, 3H, 3-CH_3), 1.61 (m, 2H, 5-H), 2.08 (m, 2H, 4-H), 2.60 (d, 1H, J=2.4 Hz, OH), 3.22 (s, 3H, OCH_3), 3.48 (dd, 1H, J=9.8Hz,8.0Hz, 1-H), 3.60 (dd, 1H, J=9.8Hz,3.2Hz, 1-H), 3.88 (ddd, 1H, J=2.4Hz,3.2Hz,8.0Hz, 2-H), 4.54 (d, 1H, J=11.9Hz, $PhCH_2$), 4.60 (d, 1H, J=11.9Hz, $PhCH_2$), 4.94 (ddd, 1H, J=1.3Hz,1.8Hz,10.1Hz, cis 7-H), 5.01 (dt, J=1.7Hz,17.1Hz, trans 7-H), 5.81 (ddt, J=10.1Hz,17.1Hz,6.6Hz, 6-H), 7.26-7.37 (m, 5H, Ph); MS m/z 282 (MNH_4^+, 80), 265 (MH^+, 100); Anal. calculated for $C_{16}H_{24}O_3$: C, 72.68; H, 9.16; Found : C, 72.57; H, 9.06.

(2R,3R)-1-benzyloxy-2-t.butyl dimethylsiloxy-3-methoxy-3-methyl-6-heptene (12). To a solution of the alcohol **11** (194 mmol, 51.4 g) in anhydrous DMF (500 mL) at room temperature under nitrogen, is added imidazole (388 mmol, 46.4 g) followed by t.butyl dimethylsilyl chloride (291 mmol, 44 g). The mixture is stirred for 2 d. The DMF is removed under reduced pressure, water (1 L) is added and the mixture is extracted with ether (2 x 500 mL). The combined organic fractions are washed with 1 N HCl, then saturated aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the solvent is evaporated in vacuo. The residue is filtered through a short path of silica gel, first eluting with petroleum ether to remove the siloxanes, then with petroleum ether/EtOAc : 9/1 to collect the silyl ether **12** (60.6 g, 82.3%) : TLC Rf (hexane/EtOAc : 9/1) 0.65; IR (neat) 2952, 2928, 2856, 1641, 1471, 1460, 1250, 1110, 835, 777 cm^{-1}; ^1H NMR δ 0.08 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, t.Bu), 1.14 (s, 3H, 3-CH_3), 1.40-1.80 (m, 2H, 4-H), 1.80-2.25 (m, 2H, 5-H), 3.22 (s, 3H, OCH_3), 3.25-3.90 (m, 3H, 1-H and 2-H), 4.50 (s, 2H, $PhCH_2$), 4.89 (br d, 1H, J=10Hz, cis 7-H), 4.94 (br d, 1H, J=17Hz, trans 7-H), 5.83 (m, 1H, 6-H), 7.30 (s, 5H, Ph); MS m/z 396 (MNH_4^+, 100), 379 (MH^+, 83).

(2R,3R)-2-t.butyl dimethylsiloxy-3-methoxy-3-methyl-1-heptanol (13). A solution of **12** (159 mmol, 60 g) and 20% $Pd(OH)_2$ on carbon[23] (6 g) in EtOAc (600 mL) is hydrogenated at 1 atm overnight. The reaction is monitored by TLC. The catalyst is removed by filtration through a short path of celite. The filtrate is concentrated in vacuo and the residue is filtered through a short path of silica gel, eluting with petroleum ether/EtOAc : 8/2, to afford 43 g (93%) of the alcohol **13** : TLC Rf(hexane/EtOAc : 9/1) 0.28; IR (neat) 3390, 2860, 1450, 1245, 1070, 830, 770 cm^{-1}; ^1H NMR δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, t.Bu), 0.8-1.8 (m, 9H, n.Bu), 2.67 (br s, 1H, OH), 3.21 (s, 3H, OCH_3), 3.5-3.8 (m, 3H, 1-H and 2-H); MS m/z 308 (MNH_4^+, 100), 291 (MH^+, 70); Anal. calculated for $C_{15}H_{34}O_3Si$: C, 62.00; H, 11.80; O, 16.53; Found : C, 61.80; H, 11.81; O, 16.66.

(2R,3R)-2-t.butyl dimethylsiloxy-3-methoxy-3-methyl-heptanaldehyde (14). A solution of the alcohol **13** (148 mmol, 43 g) and DMSO (296 mmol, 21.5 mL) in dry CH_2Cl_2 (750 mL) under nitrogen is

cooled in a dry ice-acetone bath. Oxalyl chloride (192 mmol, 16.1 mL) is added dropwise. During the addition, gas evolution occurs. The mixture is stirred for 15 min, and NEt_3 (666 mmol, 88 mL) is added in one portion (a white solid precipitates). The cooling bath is removed to allow the mixture to warm to room temperature. Ether (2 L) is added, and water is added to dissolve the precipitate. The organic phase is separated and washed with 1 N HCl, saturated aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the mixture is concentrated in vacuo. The residue is taken up in a small amount of toluene and is concentrated in vacuo again. The aldehyde **14** is used without purification in the next reaction : TLC Rf (hexane/EtOAc : 96/4) 0.25; ^1H NMR δ 0.05 (s, 6H, $Si(CH_3)_2$), 0.92 (s, 9H, t.Bu), 0.8-1.8 (m, 9H, n.Bu), 1.20 (s, 3H, 3-CH_3), 3.28 (s, 3H, OCH_3), 3.88 (d, 1H, J=2.5Hz, 2-H), 9.69 (d, 1H, J=2.5Hz, CHO).

(3R,4R)-1,1-dibromo-3-t.butyl dimethylsiloxy-4-methoxy-4-methyl-1-octene (15). To a solution of CBr_4 (296 mmol, 98.3 g) in anhydrous CH_2Cl_2 (250 mL), cooled in an ice-water bath and under nitrogen, is added dropwise a solution of Ph_3P (592 mmol, 155 g) in anhydrous CH_2Cl_2. The solution turns orange-red. After 10 min the cooling bath is removed and the aldehyde **14** (approx 148 mmol, crude from previous reaction) in anhydrous CH_2Cl_2 (100 mL) is added dropwise. The mixture is stirred at room temperature for 3 h. The reaction is cooled at -20°C, and NEt_3 (636 mmol, 88 mL) is added, followed by the very slow addition of water (300 mL). A precipitate is formed, which is dissolved with water (2 L). The water layer is extracted with CH_2Cl_2. The organic phase is washed with 1 N HCl, saturated aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the mixture is concentrated in vacuo. The residue is triturated with petroleum ether to precipitate Ph_3PO, which is filtered off. The filtrate is concentrated in vacuo, and the residue is purified by filtration through a short path of silica gel, eluting with petroleum ether/EtOAc : 9/1 to afford 60 g (91 % yield) of the desired vinyl dibromide **15** : TLC Rf (hexane/EtOAc : 97/3) 0.60; IR (neat) 2956, 2858, 1611, 1462, 1463, 1252, 1083, 868, 837, 777 cm^{-1}; ^1H NMR δ 0.11 (s, 6H, $Si(CH_3)_2$), 0.92 (s, 9H, t.Bu), 0.8-1.8 (m, 9H, n.Bu), 1.18 (s, 3H, 4-CH_3), 3.33 (s, 3H, OCH_3), 4.24 (d, 1H, J=9Hz, 3-H), 6.57 (d, 1H, J=9Hz, 2-H); MS m/z 460, 462, 464 (MNH_4^+), 443, 445, 447 (MH^+), 411, 413, 415 (MH^+-MeOH, 100).

(3R,4R)-3-t.butyl dimethylsiloxy-4-methoxy-4-methyl-1-octyne (16). Magnesium turnings (175 mmol, 4.2 g) in anhydrous THF (50 mL) are activated with a trace of I_2. A solution of the vinyl dibromide **15** (135 mmol, 60 g) in anhydrous THF (600 mL) is added at such a rate that a gentle reflux is maintained. The stirring is continued at room temperature for 2 h. Ether is added, the organic layer is washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo (the reaction can also be worked up by precipitating the $MgBr_2$ with pentane, followed by a filtration through a plug of silica gel). The obtained oil is distilled using a small Vigreux column (66-68°C, 0.01 Torr) to yield 31.4 g (82%) of the alkyne **16** : Rf (hexane/EtOAc : 97/3) 0.50; IR (neat) 2880, 1450, 1250, 1070, 830, 770 cm^{-1}; ^1H NMR δ 0.11 (s, 3H, $Si(CH_3)$), 0.15 (s, 3H, $Si(CH_3)$), 0.92 (s, 9H, t.Bu), 0.8-1.8 (m, 9H, n. Bu), 1.18 (s, 3H, 4-CH_3), 2.38 (d, 1H, J=2Hz, 1-H), 3.26 (s, 3H, OCH_3), 4.30 (d, 1H, J=2Hz, 3-H); ^{13}C NMR δ -4.57 (CH_3, TBS), -3.93 (CH_3, TBS), 14.73 (C_8), 18.77 ($\underline{C}(CH_3)_3$), 19.51 (C_4), 24.02 (C_7), 26.07 (C_6), 26.43 ($C(\underline{C}H_3)_3$), 34.56 (C_5), 51.11 (OCH_3), 69.33 (C_3), 74.23 (C_4), 79.62 (C_2), 84.29 (C_1); MS m/z 302 (MNH_4^+, 3), 164 (100); Anal. calculated for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34; Found : C, 67.21; H, 11.69.

E-(3R,4R)-3-t.butyl dimethylsiloxy-4-methoxy-4-methyl-1-tributylstannyl-1-octene (2a). A mixture of the alkyne **16** (20 mmol, 5.7 g), Bu_3SnH (30 mmol, 8.7 g) and AIBN (40 mg) is heated under nitrogen atmosphere for 2 h at 130°C. The mixture is allowed to cool to room temperature. Purification of the vinyl tin derivative **2a** is achieved through chromatography (silica gel, eluant : hexane) to afford 8.1 g (70%) of **2a** : TLC Rf (hexane) 0.17; IR (neat) 2880, 1450, 1250, 1070, 830, 770 cm^{-1}; ^1H NMR (360 MHz) δ 0.00 (s, 3H, $SiCH_3$), 0.3 (s, 3H, $SiCH_3$), 0.90 (br s, 21 H, t.Bu and 4xCH_3 of n.Bu), 1.06 (s, 3H, 4-CH_3), 1.25-1.65 (m 24H, CH_2's), 3.25 (s, 3H, OCH_3), 3.98 (dd, 1H, J=0.7Hz,6.2Hz, 3-H), 5.98 (dd, 1H, J=6.2Hz,19.1Hz, 2-H), 6.12 (dd, 1H, J=0.7Hz,19.1Hz, 1-H); MS m/z 577 (MH^+, ^{120}Sn (10 sattelite peaks due to the different isotopes from Sn), 20); 594 (MNH_4^+, 7)

(8R,11R,12R,15R,16R)-11,15-di t.butyl dimethylsiloxy-7-hydroxy-16-methyl-16-methoxy-9-oxo-prost-13-en-1-oic acid, methyl ester (17). To a solution of the vinyl tin derivative **2a** (0.87 mmol, 0.5 g) in THF (2 mL) under nitrogen at -78°C is added n.butyl lithium (0.87 mmol, 0.55 mL, 1.6 M in hexane) and stirring is continued for 10 minutes, before a precooled (-78°C) solution of CuI (0.9 mmol, 0.17 g) and $n.Bu_3P$ (2.27 mmol, 0.46 g) in THF (2 mL) is added. The mixture is allowed to warm to -35°C during 5 min, cooled again to -78°C and stirred for 1 h. A solution of (4R)-4-t.butyl dimethylsiloxy-2-cyclopentene-1-one (**3**, 0.9 mmol, 0.19 g) in THF (1 mL) is added, and the mixture is allowed to warm over a 1 h period to -40°C. After stirring at -40°C for 5min, the reaction mixture is cooled again to -78°C and a solution of methyl 7-oxo-heptanoate (1.07 mmol, 0.17 g) in THF (1 mL) is added. Stirring is continued for 10 min at -78°C before AcOH (80 µL) is added. The mixture is allowed to warm to room temperature, poured into ether and water is added. The layers are separated, the aqueous layer is extracted once more with ether and the combined organic layers are washed with water and brine. The organic layer is dried over $MgSO_4$ and flash evaporated. A filtration through a

short path of silica gel permits removal of non polar impurities (eluant ether/hexane : 1/5); the desired compound **17**, eluted off using as eluant ether/hexane : 1/1, is used as such in the next step : TLC Rf(hexane/EtOAc : 2/1) 0.23; IR (neat) 3450, 2920, 2860, 1735, 1630, 1250, 830, 770 cm^{-1}; ^1H NMR δ 0.05 (s, 12H, 2xSi$(CH_3)_2$), 0.90 (br s, 21H, 20-H and 2xt.Bu), 1.02 (s, 3H, 16-CH_3), 3.17 (s, 3H, OCH_3), 3.65 (s, 3H, $COOCH_3$), 3.76-4.22 (m, 3H, 7,11,15-H), 5.55 (m, 2H, 13,14-H), other protons : undefined m between 1 and 3 ppm.; MS m/z 657 (MH^+, 20), 674 (MNH_4^+, 70), 176 (100)

(8R,11R,12R,15R,16R)-11,15-di t.butyl dimethylsiloxy-16-methyl-16methoxy-9-oxo-prost-7,13-dien-1-oic acid, methyl ester (18). To a solution of **17** (0.32 mmol, 0.21 g) in CH_2Cl_2 (1.6 mL) is added MsCl (0.9 mmol, 0.1 g) and 4-dimethylamino pyridine (1.6 mmol, 0.2 g). The mixture is stirred for 40 min, poured into CH_2Cl_2 (100 mL) and water is added. The layers are separated, the aqueous layer extracted once more with CH_2Cl_2 and the combined organic layers are washed with water and brine. The organic layer is dried over $MgSO_4$ and concentrated in vacuo, to afford crude **18**. Purification by chromatography (silica gel, eluant ether/hexane : 1/5) gave 123 mg (60%) of pure **18** : TLC Rf (hexane/EtOAc : 2/1) 0.48; IR (neat) 2880, 1735, 1715, 1645, 1250, 1070, 830, 770 cm^{-1}; ^1H NMR δ 0.05 (s, 12H, 2xSi$(CH_3)_2$), 0.90 (br s, 21H, 20-H and 2xt.Bu), 1.03 (s, 3H, 16-CH_3), 3.19 (s, 3H, OCH_3), 3.46 (m, 1H, 12-H), 3.64 (s, 3H, $COOCH_3$), 3.98 (br d, 1H, J=6Hz, 15-H), 4.19 (m, 1H, 11-H), 5.51 (m, 2H, 13,14-H), 6.70 (br t, 1H, J=7Hz, 7-H), (other protons : undefined m between 1.1 and 2.5 ppm); MS m/z 656 (MNH_4^+, 100).

(8R,11R,12R,15R,16R)-11,15-di t.butyl dimethylsiloxy-16-methyl-16-methoxy-9-oxo-prost-13-en-1-oic acid, methyl ester (19). A mixture of **18** (0.14 mmol, 90 mg), n.Bu_3SnH (0.7 mmol, 205 mg) and t.butyl peroxide (2 mg) is heated for 15 min to 110°C (bath temperature). The reaction mixture is allowed to warm to room temperature and then chromatographed on silica gel (eluant ether/hexane : 1/5) to give the protected mexiprostil derivative **19** : Rf (hexane/EtOAc : 9/1) 0.30 ; IR (neat) 2880, 1735, 1250, 1070, 830, 770 cm^{-1}; ^1H NMR (360 MHz) δ 0.03 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.08 (s, 6H, Si$(CH_3)_2$), 0.90 (s, 9H, t.Bu), 0.92 (s, 9H, t.Bu) (the 20-CH_3 signal is hidden under the signals of the t.Bu's), 1.07 (s, 3H, 16-CH_3), 1.2-1.7 (m, 16H, CH_2's), 1.96 (dt, 1H, $J_{H8,H12}$=10.1Hz, $J_{H8,H7}$=5Hz, 8-H), 2.18 (dd, 1H, $J_{H10a,H10b}$=18.2Hz, $J_{H10a,H11}$=7.5Hz, 10a-H), 2.28 (t, 2H, J=7.4Hz, 2-H), 2.52 (ddt, 1H, 12-H; simplifies to dd upon irradiation at 5.63 ppm (vinylic protons), J_{H8H12}=10.1Hz, J_{H11H12}=7.1Hz; simplifies to dt upon irradiation at 4.10 ppm (11-H), $J_{H8,H12}$=10.1Hz, $J_{H12,H13}$=3Hz, $J_{H12,H14}$=3Hz), 2.62 (ddd, 1H, $J_{H10aH10b}$=18.2Hz, $J_{H10bH11}$=6.8Hz, J_{H10bH8}=1Hz, 10b-H), 3.24 (s, 3H, OCH_3), 3.68 (s, 3H, $COOCH_3$), 4.05 (dd, 1H, J=1.3Hz,3.5Hz, 15-H), 4.10 (apparent q, 1H, J=7Hz, 11-H), 5.63 (m, 2H, 13,14-H); MS m/z 658 (MNH_4^+, 100); Anal. calculated for $C_{35}H_{68}O_6Si_2$: C, 65.56; H, 10.70; O, 14.98; Found : C, 65.43; H, 10.61; O, 15.02.

(R)-4-t.butyl dimethylsiloxy-2-(6-carbomethoxyhexyl)-cyclopent-2-enone (5). A solution of (R)-4-hydroxy-2-(6-carbomethoxyhexyl)-cyclopent-2-enone (**20**, 5.6 mmol, 1.34 g), t.butyl dimethylsilyl chloride (11.2 mmol, 1.69 g) and imidazole (11.7 mmol, 0.8 g) in DMF is stirred at room temperature under nitrogen atmosphere for 30 min. The reaction mixture is diluted with petroleum ether, and the organic layer is washed with 1N aqueous HCl, water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. Column chromatographic purification (silica gel, EtOAc/petroleum ether : 5/95) gives 1.88 g (95 %) of pure **5** : TLC Rf (hexane/EtOAc : 9/1) 0.25 ; ^1H NMR δ 0.12 (s, 6H, Si$(CH_3)_2$), 0.91 (s, 9H, t.Bu), 1.20-1.80 (m, 10H, 1'-5'-H), 2.18 (t, 2H, J=6Hz, 6'-H), 2.19 (dd, 1H, J=18Hz,2.5Hz, 5-H), 2.75 (dd, 1H, J=18Hz,6Hz, 5-H), 3.62 (s, 3H, $COOCH_3$), 4.85 (m, 1H, 4-H), 6.98 (m, 1H, 3-H).

(8R,11R,12R,15R,16R)-11,15-di t.butyl dimethylsiloxy-16-methyl-16-methoxy-9-oxo-prost-13-en-1-oic acid, methyl ester (19). A solution of the tributyltin derivative **2a** (0.82 mmol, 470 mg) in THF (1 mL) at -78°C under nitrogen atmosphere is treated with n.BuLi (0.82 mmol, 0.55 mL, 1.5 M in hexane). The solution is stirred for 15 minutes at -78°C, and a solution of ThCuCNLi in THF[20] (1.05 mmol, 5.25 mL, 0.2M) is added. The solution is stirred for 30 min at -78°C, and a solution of the enone **5** (0.75 mmol, 267 mg) in THF (2 mL) is added. The mixture is stirred for 30 min at -78°C and the reaction is quenched with 10 mL of a 10% saturated aqueous NH_4OH in saturated aqueous NH_4Cl solution. The cooling bath is removed to allow the mixture to warm to room temperature. The organic layer is diluted with petroleum ether (20 mL), the blue aqueous layer is removed and the organic layer is washed with brine and dried over $MgSO_4$. Column chromatographic purification (silica gel, EtOAc/petroleum ether : 5/95) gives 310 mg (65% yield) of the desired bis protected mexiprostil derivative **19**, identical to the material prepared above.

(8R,11R,12R,15R,16R)11,15-dihydroxy-16-methyl-16-methoxy-9-oxo-prost-13-en-1-oic acid, methyl ester (1, mexiprostil). A solution of **19** (0.07 mmol, 45 mg) in a HOAc/H_2O/THF : 3/1/1 (0.5 mL) mixture is stirred for 48 h at room temperature. Water (5 mL) is added, and the mixture is neutralized with solid K_2CO_3. The aqueous layer is extracted with ether (3 x 10 mL), the combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Column chromatographic purification

(silica gel, 2% MeOH in EtOAc) gives 2 mg (8%) of the (15S,16S) isomer[6] (TLC Rf (EtOAc) 0.28) and 12 mg (50 %) of mexiprostil : TLC Rf (EtOAc) 0.20; $[\alpha]_D^{20}$ (c=1.0, $CHCl_3$) -50.3; mp (hexane) 44-45°C; IR ($CHCl_3$) 3550, 3390, 2880, 1735 cm^{-1}; ^1H NMR (360 MHz) δ 0.91 (br t, 3H, J=6.8Hz, 20-H), 1.08 (s, 3H, 16-CH_3), 1.30-1.85 (m, 16H, CH_2's), 2.00 (dt, 1H, $J_{H8,H12}$=11.6Hz, $J_{H8,H7}$=6.1Hz, 8-H), 2.23 (dd, 1H, $J_{H10a,H10b}$=18.5Hz, $J_{H10a,H11}$=9.4Hz, 10a-H), 2.28 (t, 2H, J=7.6Hz, 2-H), 2.37 (ddt, 1H, 12-H; simplifies to dd upon irradiation at 5.67 (vinylic protons), $J_{H8,H12}$=11.6Hz, $J_{H11,H12}$=8.6Hz; simplifies to dt upon irradiation at 2.00 ppm (8-H), $J_{H11,H12}$=8.6Hz, $J_{H12,H13}$=3Hz,, 28, 945 $J_{H12,H14}$=3Hz), 2.74 (ddd, 1H, $J_{H10a,H10b}$=18.5Hz, $J_{H10b,H11}$=7.5Hz, $J_{H10b,H8}$=1Hz, 10b-H), 2.89 (br s, 1H, OH), 3.05 (br s, 1H, OH), 3.25 (s, 3H, OCH_3), 3.68 (s, 3H, $COOCH_3$), 4.06 (apparent q, 1H, J=8.3Hz, 11-H), 4.12 (dd, J=3Hz,6Hz, 1H, 15-H; simplifies to s upon irradiation at 5.67 ppm (vinylic protons)), 5.67 (m, 2H, 13,14-H); MS m/z 430 (MNH_4^+, 100); Anal. calcd for $C_{23}H_{40}O_6$: C, 66.96; H, 9.77; Found : C, 67.28; H, 9.98.

References

1. For a preliminary report of this work : Kolb, M.; Van Hijfte, L.; Ireland R. E. *Tetrahedron Lett.* **1988**, *29*, 6769.
2. Present address : Marion Merrell Dow Research Institute, Cincinnati Center, 22110 E. Galbraith Road, Cincinatti, Ohio 43215, U.S.A..
3. Bindra, J.S. in *The Total Synthesis of Natural Products*, J. Apsimon, Ed., New York, 1981 ; Bindra, J.S. and Bindra, R. *Prostaglandin Synthesis*, Ac. Press, New York, 1977 ; Roberts, S.M.; Scheinmann,F. *New Synthetic Routes to Prostaglandins and Thromboxanes*, Ac. Press, New York, 1982
4. a) Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron*, **1990**, *46*, 4809 ; b) Noyori, R. *Chemistry in Britain* **1989**, 883 ; c) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847 ; d) Johnson, C.R.; Penning, T.D. *J. Am. Chem. Soc.* **1988**, *110*, 4726 ; e) Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299.
5. a) Kluge, A.F.; Untch, K.G.; Fried, J.H. *J. Am. Chem. Soc.* **1972**, *94*, 9256 ; b) Sih, C.J.; Salomon, R.G.; Price, P.; Peruzzotti, G.; Sood, R. *Chem. Comm.* **1972**, 240 ; c) Sih, C.J.; Salomon, R.G.; Price, P.; Sood, R.; Peruzzotti, G. *J. Am. Chem. Soc.* **1975**, *97*, 857 ; d) Floyd, M.B.; Weiss, M.J. *Prostaglandins*, **1973**, *3*, 921 ; e) Collins, P.W. *Med. Res. Rev.* **1990**, *10*, 149; f) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.
6. Guzzi, U.; Giabatti, R. U.S. Pat. 4.547.521, Oct. 15, 1985 (*Chem. Abstr.* **1981**, *94*, 120966g) ; Guzzi, U.; Giabati, R.; Pandora, G.; Battaglia, F.; Cellentani, M.; Depaoli, A.; Galliani, G.; Schiatti, P.; Spira, G. *J. Med. Chem.* **1986**, *29*, 1826 ; Pelizzi, G.; Ciabatti, R.; Padova, R.; Tarzia, G. *Prostaglandins* **1988**, *35*, 639.
7. Petrillo, M.; Lazzaroni, M.; Fucella, L.; Sassella, D.; Porro, G.B. *Hepatogastroenterol.* **1987**, *34*, 117.
8. See refs 4a, 4c and 4d. We have prepared the optically pure cyclopentenone following the procedure described by prof. Schneider : Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875.
9. See ref 4e. Methyl 7-oxo-heptanoate can be prepared from monomethyl pimelate : see ref 1.
10. Hanson, R.M.; Sharpless, K.B. *J. Org. Chem.* **1986**, *51*, 1922.
11. Hanson, R.M. *Tetrahedron Lett.* **1984**, *25*, 3783.
12. Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
13. Manensco, M.J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480
14. Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.* **1972**, 3769.
15. Van Hijfte, L.; Kolb, M.; Witz, P. *Tetrahedron Lett.* **1989**, *30*, 3655.
16. Corey, E.J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hawada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.
17. Under these conditions only the E isomer undergoes transmetalation : see ref 4d.
18. Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1383.
19. Commercially available from the Sumitomo Chemical Company, Ltd., Osaka, Japan. The corresponding silyl ether can be obtained from the Nissan Chemical Industries Ltd., Chiyoda-Ku, Tokyo, Japan.
20. Lipshutz, B.H. *Synthesis* **1987**, 325 ; Lipshutz, B.H.; Koerner, M.; Parker, D.A. *Tetrahedron Lett.* **1987**, *28*, 945.
21. At this stage, the (8R,11R,12R,15S,16S) isomer[6], derived from coupling of the minor (15S,16S)-ω-side chain enantiomer with the enantiomerically pure cyclopentenone, was separated from mexiprostil.
22. During the preparation of this manuscript, G. Guillamot (MMD Chemical Development, Société Chimique Grévis, Avenue de la Paix, 78520 Limay, France) has succesfully scaled up the synthesis and has prepared a batch of 580 g of mexiprostil, using the 2 component coupling approach.
23. Purchased from the Aldrich Chemical Co. See Pearlman, W.M. *Tetrahedron Lett.* **1967**, 1663.