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A Highly Convergent Synthesis of Mexiprostil: 16(R) 16-Methoxy 16-Methyl PGE_1 Methyl Ester

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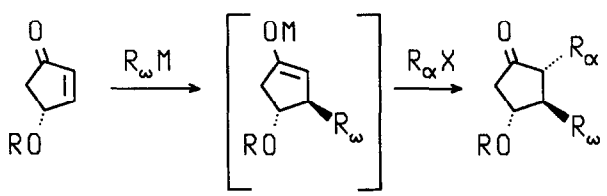
Abstract: The synthesis of optically pure mexiprostil, a PGE_1 analogue, via the three component coupling process, e.g. Michael addition of the appropriate ω-side chain onto enantiomerically pure, protected (R)-4-hydroxy-cyclopentenone, followed by in situ trapping with the α-side chain, is described.

Among the various strategies for prostaglandin synthesis, the three-component coupling process (Scheme 1)[2-5] is one of the best approaches in view of its high degree of convergence and potential for flexibility. The approach involves the conjugate addition of the ω-side chain to a protected 4-hydroxy-2-cyclopentenone and then alkylation of the derived enolate with an appropriate electrophile incorporated in the complete α-side chain.

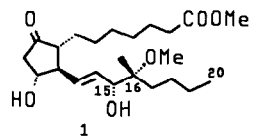
Scheme 1



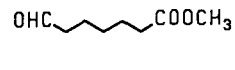
Mexiprostil (**1**, Scheme 2)[6], a Merrell-Dow compound, which has been shown to inhibit gastric acid secretion and to protect the gastric mucosa[7], is singularly well suited, due to its structural analogy to PGE_1, to preparation by this strategy. The aldehyde function in the α-side chain equivalent **2** can be employed for efficient trapping of the intermediate enolate, which alleviates the equilibrium/elimination problem inherent in this process;[2] dehydration and reduction then ensures the correct attachment of the α-side chain.[8]

The required optically active cyclopentenone **3** was prepared from cyclopentadiene.[9] For the prostaglandin-atypical ω-side chain present in mexiprostil (**1**), we relied on the Sharpless oxidation protocol[13] to introduce the correct 15R/16R stereochemistry. Epoxidation of nerol [(-)DET, $Ti(OiPr)_4$, tBuOOH, C_7H_8, -15°C, 15min; nerol, -25°C; -20°C, 3h] gave the epoxide **4a** {bp 95-97°C/0.03torr; $[\alpha]_D$= +15.4°, c= 3.3 ($CHCl_3$)} in 99% chemical yield and in over 70% optical purity [^1H NMR, (+)$Eu(hfc)_3$]. After benzylation (BnBr, KOtBu, THF, 0 to 10°C, 14h), stereo- and regioselectively cleavage (MeOH, Dowex 50, H^+, 25°C, 14h) of the crude epoxide **4b** afforded the methoxy hydroxy derivative **5a**, which has the desired configuration at the C-15 and C-16 functionalities (prostaglandin numbering) required for mexiprostil.

Scheme 2



1



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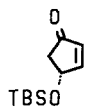

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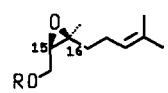
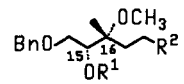
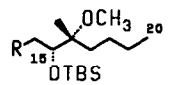


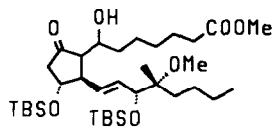
4a R= H
4b R= Bn



5a R^1= H R^2= CH=CMe_2
5b R^1= H R^2= CHO
5c R^1= H R^2= CH=CH_2
5d R^1= TBS R^2= CH=CH_2



6a R= CH_2OH
6b R= CHO
6c R= CH=CBr_2
6d R= C≡CH
6e R= (E) CH=CH$SnBu_3$



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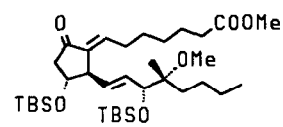

8

For the elaboration of the C-15/C-20 part of the molecule, the propylidene function in **5a** was replaced by a methylene group via a two step sequence: Ozonisation (O_3, MeOH, CH_2Cl_2, -78°C) afforded the hydroxy aldehyde **5b**, isolated as its cyclic hemiacetal; Wittig reaction on the crude ozonised product ($Ph_3PCH_3^+Br^-$, KOtBu, THF, 25°C, 3h) then gave the methylene alcohol **5c** {$[\alpha]_D$= +7.0°, c= 5.3 ($CHCl_3$)} in 52% yield over four steps from epoxide **4b**. Protection of the C-15 alcohol function (**5c** to **5d**; $tBuMe_2SiCl$, imidazole, DMF, 25°C, 48h, 82%)[14] and hydrogenation of the olefin **5d** to **6a** [$Pd(OH)_2$, H_2, EtOAc, 1atm, 25°C, 14h; 98%] completed the synthesis of the C-15/C-20 part in the ω-side chain (41% overall yield from nerol).

In order to prepare the appropriate side chain functionality for the three component coupling process, alcohol **6a** was transformed, via the intermediate ethynyl compound **6d**, into the vinylstannane derivate **6e**, by the following sequence of reactions: Swern oxidation[15] {**6a** to **6b**; DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, 15min; Et_3N, -78 to 25°C} followed by olefination (**6b** to **6c**; CBr_4, CH_2Cl_2, PPh_3, 0 to 25°C, 3h)[16] proceeded in 91% yield over the two steps; treatment of the dibromo olefin **6c** with n-butyl lithium (THF, -78°C, 1h; 25°C, 1h)[16] gave the desired ethynyl derivative **6d** (bp 65-67°C / 0.01torr) in 70% yield; stannyl hydride addition[17] (Bu_3SnH, AIBN, 130°C, 2h, 70%) afforded the target ω-side chain building block **6e** (>90% E isomer, ^1H NMR, J_{HH}= 19.1 Hz).

The organo copper reagent for the attachment of this side chain was prepared from the vinylstannane **6e** by reaction with n-butyl lithium (1 equiv, THF, -78°C, 10min) and then copper (I) iodide (1 equiv) and tri-n-butylphosphine (2.6 equiv, -78°C; -35°C, 5min; -78°C, 1h).[3,18,19] Sequential treatment of the enone **3** with this copper reagent (-78 to -40°C, 1h; -40°C, 5min) and the aldehyde **2**[20] (THF, -78°C, 10min; AcOH, -78 to 25°C) gave a mixture of diastereoisomers of the hydroxy PGE_1 derivative **7** (42%). Dehydration (MsCl, DMAP, CH_2Cl_2, 25°C, 40min)[8] yielded the 11R,12R enone **8** (60% after chromatography: SiO_2, Et_2O / C_6H_{12}, 1/5; $J_{H\text{-}11,H\text{-}12}$= 0 Hz), which on reduction [Bu_3SnH, $(tBuO)_2$, 110°C, 15min; 87% after chromatography: SiO_2, Et_2O/C_6H_{12}, 1/5][8] and deprotection (AcOH, THF, H_2O, 25°C, 48h) afforded the isomerically pure (8R),(11R),(12R), (15R),(16R) target prostaglandin derivative mexiprostil (**1**).

With this highly efficient chemical operation in hand, mexiprostil (**1**) is now available in 20% overall yield and only four steps from the optically pure cyclopentenone derivative **3**.

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19) Under these conditions only the E isomer undergoes transmetallation, see lit. 5
20) Prepared from monomethyl pimelate: 1. $SOCl_2$, 70°C, 2h; 95%; 2. Pd/C, H_2, 2,6-lutidine, THF, 25°C, 15h; 65%; bp 100-110°C/0.05torr

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