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SYNTHESIS OF A CHEMICALLY AND METABOLICALLY STABLE AND BIOLOGICALLY POTENT PGD_2-ANALOGUE

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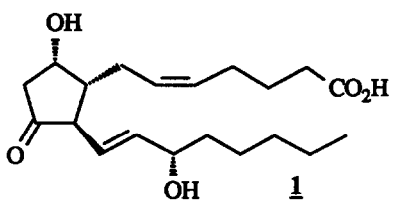
Abstract - The metabolic labile α-chain of the PGD_2-analogue 2 (ZK 110841) can be stabilized by introduction of an β-oxygen-atom resulting in 3 (ZK 118182), which has a much higher and longer lasting biological activity on oral application in rats. The synthetic methodology for the synthesis of 3-oxa-Z-$\Delta^{5,6}$-prostaglandins will be discussed.

Prostaglandin D_2 (PGD_2) 1 is the major cyclooxygenase product in the central nervous system[1] and can induce sleep in the brain[2]. PGD_2, which is also synthesized by platelets, is furthermore a very strong vasodilator and inhibitor of blood-platelet aggregation[3] and exerts these effects through a distinct receptor different from the prostacyclin (PGI_2) and prostaglandin E_1 receptors.

Since PGD_2 contains a β-hydroxy-ketone moiety it is a very labile compound. Therefore we[4] and others[5] have synthesized stable analogues such as 2 (ZK 110841), which mimics the activity of the natural PGD_2 in biological profile and potency[4].

To improve the metabolic stability of 2 while preserving its high intrinsic activity we introduced an oxygen-atom at position 3 to inhibit the β-oxidation of the α-side chain.

In this communication we describe the synthesis of the 3-oxa-PGD_2-analogue 3 (ZK 118182) using a reaction sequence which might be generally useful for preparing prostaglandins with a 3-oxa-Z-$\Delta^{5,6}$-α-side chain. The major problem in this synthesis is a two carbon elongation by a **Wittig-Horner** reaction to give an Z-α,β-unsaturated ester, which has then to be converted into the α-side chain.



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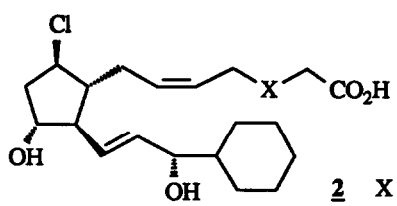
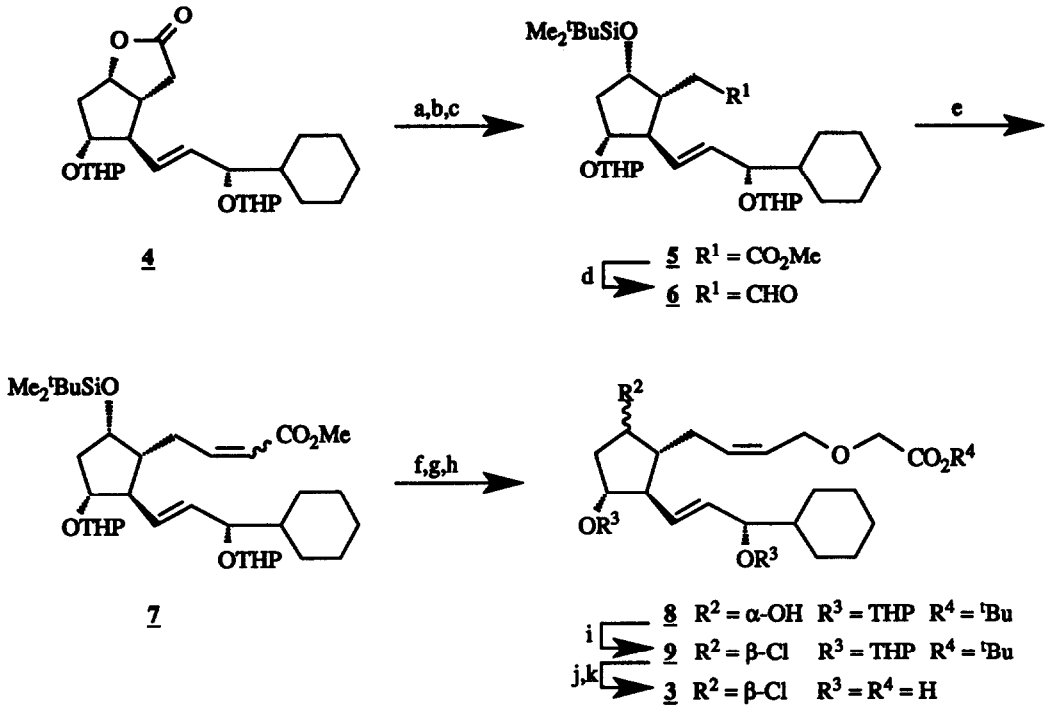


2 X = CH_2
3 X = O

Saponification of the lactone 4[6] with sodium hydroxide afforded after reaction with methyl iodide and tert.-butyldimethylsilylchloride the silylether 5, which was reduced selectively with DIBAH in 79% yield to the aldehyde 6[7]. For the subsequent Z-selective **Wittig-Horner** reaction of 6 we studied the methods of Breuer[8] and Still[9].



a) NaOH / MeOH 24°C 22h, b) MeI / DMSO / THF 24°C 16h, c) imid. / $Me_2{}^tBuSiCl$ / DMF 24°C 4h, d) DIBAH / toluene -70°C 2h, e) 11 / $KN(SiMe_3)_2$ / 18-crown-6 -70°C 30min, f) DIBAH / toluene -70°C to -20°C 2h, g) $BrCH_2CO_2{}^tBu$ / 25% NaOH / Bu_4NHSO_4 / toluene 24°C 15h, j) HOAc / H_2O / THF = 65 / 35 / 10 24°C 18h, k) LiOH / MeOH 24°C 16h

Under the conditions of Breuer (see table 1, entry 1) the cyclic phosphonate 10 converted 6 in only 75% yield to the α,β-unsaturated esters 7[10], containing predominantly the undesired E-isomer, whereas an Z/E-ratio of 9:1 could be achieved employing the bis(trifluoroethyl)-phosphonate 11 (entry 3) according to Still[9].

On using a normal phosphonate like 12 with butyllithium (entry 5) or with the base of the Still system (entry 4) 6 gave a 1:9 mixture of Z,E-7, whereas Still described a Z/E-ratio of 8:1 in a reaction of 12 with n-octanal under the conditions of entry 4. We obtained however the predominant formation of the desired Z-isomer when we used the Breuer phosphonate 10 in combination with the Still base $KN(SiMe_3)_2$/18-crown-6 (entry 2).

In summary we found that the Still conditions gives generally the best Z/E-ratio. But even the cyclic phosphonate 10 will produce a good Z-selectivity on using a base system having minimally complexing counterions like $KN(SiMe_3)$/18-crown-6.

The 9:1 mixture of Z,E-7 could not be completely separated due to the diastereomers of the 11,15-tetrahydropyranylethers. However, after DIBAH reduction of 7 followed by etherification under phase-transfer-condition with tert.-butylbromoacetate[11] and desilylation, the small amount of the undesired

Table 1: Reactions of 6 with $(R^5O)_2P(O)-CH_2CO_2Me$

entry*	phosphonate	R^5	base	Z / E-ratio**	yield
1	10		BuLi	1:3	75%
2	10		$KN(SiMe_3)_2$ / 18-crown-6	7:3	89%
3	11	CF_3CH_2	$KN(SiMe_3)_2$ / 18-crown-6	9:1	95%
4	12	Me	$KN(SiMe_3)_2$ / 18-crown-6	1:9	90%
5	12	Me	BuLi	1:9	85%

* all reactions were carried out at -70°C in THF as solvent ** measured by integration of the ^{1}H-NMR-signals of the β-hydrogens of the unsaturated ester-moiety in 7

E-8[12] could be completely removed by chromatography (SiO_2, n-hexane / 0 - 60% ethyl acetate). Tosylation of alcohol Z-8[12] and subsequent reaction with tetrabutylammonium chloride furnished the 9-β-chloro compound 9[13] containing only traces of the $\Delta^{8,9}$-unsaturated by-product. After removal of the 11,15-protecting groups we were able to separate the pure 9-β-chloro compound from the $\Delta^{8,9}$-olefin[14] by chromatography (SiO_2, toluene / 0 - 15% isopropanol). Saponification with lithium hydroxide furnished finally 3 (ZK 118182)[15].

3 showed the same potency as 2 in the PGD_2-receptor binding test (competition factor = 0.5; PGD_2 = 1) but had a much higher and longer blood pressure lowering activity on oral application in rats than the PGD_2-analogue 2[16].

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6) 4 was obtained from the optically active Corey aldehyde by Wittig-Horner reaction, followed by reduction with $NaBH_4$, saponification of the 11-benzoate and tetrahydropyranylation using standard methodology, see: B.J. Magerlein, D.W. DuCharme, W.E. Magee, W.L. Miller, A. Robert, J.R. Weeks

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7) IR (neat): 2710, 1725 cm^{-1}, NMR ($CDCl_3$): 0.0 - 0.07 (6H, m, $SiMe_2$), 0.88 (9H, s, Si^tBu), 3.35 - 3.53 (2H), 3.68 - 4.04 (4H, m, 2·OCHO$\underline{CH_2}$, H-9β, H-11β), 4.23 (1H, m, H-15β), 4.58 - 4.77 (2H, m, 2·O$\underline{CH}OCH_2$), 5.26 - 5.65 (2H, m, H-13, H-14), 9.79 (1H, s, br., $\underline{CH}O$).

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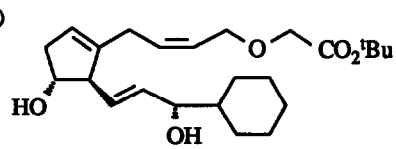
10) the data from E- and Z-7 are from special THP-ether-isomer chromatography-fractions
E-7: IR (neat): 1727, 1658 cm^{-1}, NMR (CD_2Cl_2): 0.0 - 0.12 (6H, m, $SiMe_2$), 0.85 - 0.95 (9H, s, Si^tBu), 3.40, 3.60 - 4.22 (7H, m, 2·OCHO$\underline{CH_2}$, H-9β, H-11β, H-15β), 3.68 (3H, s, CO_2Me), 4.55 - 4.75 (2H, m, 2·O$\underline{CH}OCH_2$), 5.24 - 5.62 (2H, m, H-13, H-14), 5.78 / 5.79 (1H, dt, J = 16.5 + 1.5 Hz, H-5), 6.96 / 6.97 (1H, dt, J = 16.5 + 7.5 Hz, H-6)
Z-7: IR (neat): 1725, 1645 cm^{-1}, NMR (CD_2Cl_2): 0.0-0.10 (6H, m, $SiMe_2$), 0.88 (9H, s, Si^tBu), 2.73 / 2.76 (2H, dd, br., J = 7.5 + 7.5 Hz, H-7), 3.66 (3H, s, CO_2Me), 3.32 - 3.50 (2H), 3.62 - 4.05 (4H, m, 2·OCHO$\underline{CH_2}$, H-9β, H-11β), 4.16 (1H, m, H-15β), 4.59 - 4.76 (2H, m, 2·O$\underline{CH}OCH_2$), 5.30 - 5.65 (2H, m, H-13, H-14), 5.72 / 5.73 (1H, d, br., J = 11.5 Hz, H-5), 6.31 / 6.32 (1H, dt, J = 11.5 + 7.5 Hz, H-6).

11) W. Skuballa, E. Schillinger, C.-St. Stürzebecher, H. Vorbrüggen *J. Med. Chem.* 29, 313 (1986).

12) E-8: IR (neat): 1750, 1735 cm^{-1}, NMR(CD_2Cl_2): 1.48 (9H, s, $CO_2{}^tBu$), 3.33 - 3.50 (2H), 3.82 (2H, m, 2·OCHO$\underline{CH_2}$), 3.72 / 3.73 (1H, dd, J = 7.5 + 7.5 Hz, H-15β), 3.90 (2H, s, H-2), 3.97 (2H, d, J = 6.5 Hz, H-4), 4.03 (1H, m, H-11β), 4.12 (1H, m, H-9β), 4.60 - 4.73 (2H, m, 2·O$\underline{CH}OCH_2$), 5.28 - 5.35 (1H), 5.49 - 5.54 (1H, m, H-13, H-14), 5.61 (1H, dt, J = 15 + 6 Hz, H-6), 5.76 (1H, dt, J = 15 + 6.5 Hz, H-5)
Z-8: IR (neat): 1750, 1735 cm^{-1}, NMR (CD_2Cl_2): 1.51 (9H, s, $CO_2{}^tBu$), 3.33 - 3.52 (2H), 3.83 (2H, m, 2·OCHO$\underline{CH_2}$), 3.74 (1H, m, H-15β), 3.94 / 3.95 (2H, s, H-2), 3.90 - 4.15 (3H, m, H-4, H-11β), 4.20 - 4.33 (1H, m, H-9β), 4.60 - 4.74 (2H, m, 2·O$\underline{CH}CH_2$), 5.32 - 5.60 (2H, m, H-13, H-14), 5.64 (2H, m, H-5, H-6).

13) $[\alpha]_D^{22}$ = -10.6° (c = 0.46 in $CHCl_3$), IR (neat): 3400 (br.), 1745, 1735 cm^{-1}, NMR (benzene-d^6): 0.58 (2H, s, br., 11-OH, 15-OH), 1.34 (9H, s, $CO_2{}^tBu$), 3.69 (1H, dd, J = 6.5 + 6.5 Hz, H-15β), 3.84 (2H, s, H-2), 3.80 - 3.95 (1H, m, H-9α), 3.95 (1H, ddd, J = 7 + 7 + 7 Hz, H-11β), 4.08 (2H, d, br., J = 5 Hz, H-4), 5.31 (1H, dd, J = 8.5 + 15.5 Hz, H-13), 5.4 - 5.6 (1H, m, H-6), 5.53 (1H, dd, J = 7.5 + 15.5 Hz, H-14), 5.72 (1H, dt, J = 11.5 + 5 Hz, H-5).

14) 

IR ($CHCl_3$): 3610, 3440 (br.), 1743 cm^{-1}, NMR ($CDCl_3$): 1.48 1.48 (9H, s, $CO_2{}^tBu$), 3.03 (1H, d, br., J = 8.5 Hz, H-12α), 3.81 (1H, dd, J = 6.5 + 6.5Hz, H-15β), 3.93 (2H, s, H-2), 4.11 (2H, d, J = 5 Hz, H-4), 4.16 (1H, m, H-11β), 5.39 (1H, s, br., H-9), 5.43 (1H, dd, J = 8.5 + 15.5 Hz, H-13), 5.56 (1H, dd, J = 7 + 15.5 Hz, H-14), 5.68 (2H, m, H-5, H-6).

15) $[\alpha]_D^{22}$ = -12.6° (c = 0.44 in $CHCl_3$), IR (neat): 3400 (br.), 1735 cm^{-1}, NMR (benzene-d^6): 3.75 (1H, dd, J = 7 + 7 Hz, H-15β), 3.85 (2H, s, H-2), 3.70 - 4.10 (4H, m, H-4, H-9α, H-11β), 5.44 (1H, dd, J = 8.5 + 15.5 Hz, H-13), 5.55 (2H, m, H-5, H-6), 5.65 (1H, dd, J = 7.5 + 15.5 Hz, H-14).

16) B.-G. Schulz, R. Beckmann, B. Müller, G. Schröder, B. Maaß, K.-H. Thierauch, B. Buchmann, P.F.J. Verhallen, W. Fröhlich to be presented on the 7th International Conference on Prostaglandins and related Compounds, Florence, May 28 - June 1 (1990).

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