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E- OR Z-SELECTIVE WITTIG REACTIONS IN THE SYNTHESIS OF THE CARBACYCLIN ILOPROST

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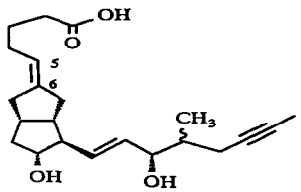
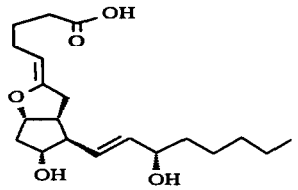
Summary: Wittig reaction of ketones **3** with 4-carboxybutyltriphenyl-phosphonium bromide generates the exocyclic 5,6 double bond of *iloprost* (**1**) *in E/Z ratios between 35:65 and 90:10 depending on substituents and reaction conditions.*

Iloprost (**1**) is a stable analogue of the natural prostacyclin **2**. It has the same biological profile and shows promise in the treatment of arterial occlusive disease [1,2].



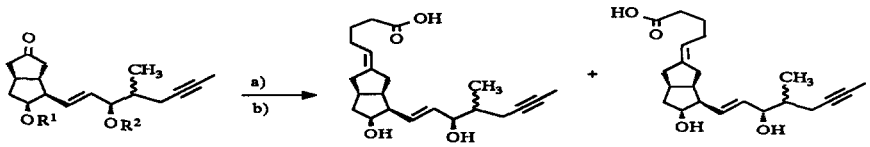
1 iloprost



2 prostacyclin

A major problem in the synthesis of iloprost (**1**) and other carbacyclins is the stereoselective generation of the trisubstituted exocyclic 5,6 double bond (prostaglandine numbering). The original Wittig routes gave both isomers in essentially equal amounts [3]. There are attempts to introduce or generate this E double bond stereospecific by different methods, this often includes longer sequences, incomplete conversions and reduced overall yields [4]. The stereospecific 1,4-hydrogenation of a 1,3 diene leads to a partial hydrogenation of the lower side chain [4a]. Protodesilylation of an allyl silane is highly stereoselective, but generation of its precursor is not [4d]. 3-Oxa-carbacyclins have been prepared in a stereoselective manner via chiral phosphonoacetates [5].

The Wittig reaction can be an effective method for the synthesis of carbon carbon double bonds. Conversion of ketones are normally less selective than with aldehydes, which react with salt-free ylides to give predominantly cis olefins, and with stabilized ylides to produce trans olefins [6].



3 → (a), (b) → **1** E-iloprost + **4** Z-iloprost

a) $Ph_3P^+(CH_2)_4CO_2H\ Br^-/KOtBu$ b) deprotection if R^1,R^2 not H

*In optimizing the E/Z stereoselectivity of the Wittig reaction of **3** with 4-carboxybutyltriphenyl-phosphonium bromide we checked the influence of the 11 and 15 substituents R^1 and R^2, solvent effects and further reaction conditions. The results are given in table 1.*

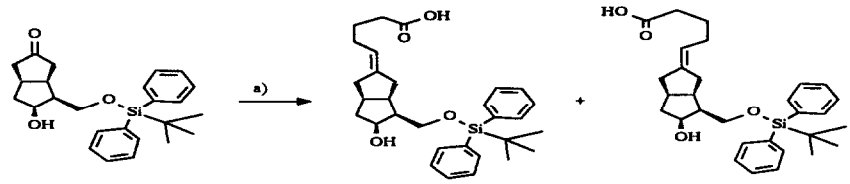
Table 1: Conversion of ketones **3** into E-iloprost (**1**) and Z-iloprost (**4**)

entry	ketone	R^1 in **3**	R^2 in **3** [a]	ratio 1:4 [b]	Solvent[c]
1	3a	THP	THP	60 : 40	DMSO/THF
2	3b	H	THP	67 : 33	"
3	3c	TBDMS	TBDMS	78 : 22	"
4	3c	TBDMS	TBDMS	80 : 22	DME/rt
5	3d	TBDMS	H	38 : 62	DMSO/THF
6	3e	H	TBDMS	76 : 24	"
7	3f	TBDPS	TBDPS	72 : 28	"
8	3g	TBDPS	H	35 : 65	"
9	3h	H	TBDPS	75 : 25	"
10	3i	H	H	75 : 25	"
11	3i	H	H	82 : 18	DME/rt
12	3i	H	H	85 : 15	DME/0°C
13	3i	H	H	90 : 10	DME/0°C[d]

a) THP = tetrahydropyranyl-; TBDMS = tert-butyl-dimethylsilyl-; TBDPS= tert-butyl-diphenylsilyl-; b) all ketones gave complete conversion; c) the solvent is DMSO/THF 2:1 (20°C); the E/Z ratios were determined by HPLC after cleaving the protecting groups [7,8,9]; d) entry 13: 10 eq Wittig reagent were used (entry 1-12: 3 eq).

Ketone **3c** with two TBDMS protecting groups gave generally a better selectivity than the di-THP-ketone **3a** . The 11 monosilylated ketones **3d** and **3g** gave more of the Z isomer **4**. Steric hindrance can influence the attack of the phosphorous ylide and might inverse selectivity. In contrast the 15 mono-protected ketones **3e** and **3h** and the unsubstituted ketone **3i** gave more of the desired E isomer **1**. The best result was obtained with diolketone **3i** in dimethoxyethane (DME) as solvent at 0°C (entry 12) and gave an E/Z ratio of 85:15. (isolated yield of both isomers >90%). Using 10 equivalents of Wittig reagent with ketone **3i** in dimethoxyethane as solvent gave the isomers **1** and **4** in a 90:10 ratio. It seems that the stereocontrol is induced by the polar carboxylate end group of the Wittig reagent and steric effects of the lower side chain. Other bases than potassium tert-butylate (LiHMDS,NaHMDS and KHMDS) gave comparable results. The isomers **1** and **4** can be separated readily by chromatography on LiChrosorb, Sorbax or spherical Kromasil silica gel with hexane-isopropanol as eluent [10]. The configuration of the 5,6-double bond in **1** has been determined by ^{13}C-NMR shifts using two dimensional techniques [11].

In checking the E/Z selectivity of a bicyclooctanone system in the absence of the lower side chain we tested the reaction of the ketone **5** with a 13 TBDPS substituent in the Wittig reaction. A steric hindered group might lead to the desired isomer **E-6**. In effect reaction of ketone **5** with a 13 TBDPS ether group and 11 hydroxy function gave the isomers **E-6** and **Z-6** in a 88:12 ratio. The result shows, that the E/Z-stereoselectivity of the Wittig reaction is dependent on subtle changes in substrate and solvent.



5 **E-6** **Z-6**

a) $PH_3P^+(CH_2)_4CO_2H\ Br^-$ / KOtBu/DME/0°C E-6/Z-6 = 88 : 12

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[7] The E/Z ratio was determined by reversed phase HPLC (UV-detection at 205 nm) after cleavage of the substituents [8a] from the crude mixture and compared with authentic material. The R/S-configuration at C-16 is 1:1.

[8] a) Silyl ethers are cleaved with tetrabutylammonium fluoride in THF, the THP ethers with acetic acid/water/THF 3:2:1. b) The starting materials are prepared by using common methods. The ketones 3c,d,e,g,h are prepared by treating ketone 3i [lit.3h] in DMF as solvent with 1.2 eq imidazole and 1.2 eq TBDMS-Cl or TBDPS-Cl at 40°C. Aqueous workup and chromatography of the crude mixture with hexane / ethyl acetate as eluent on silica gel gave a first fraction of disilylated compound 3c/3f, the next fraction is the 11 monosilylated ketone 3d/3g, the third fraction is the 15 monosilylated silyl ether 3e/3h all in nearly equal amounts.

[9] A typical procedure is as following: Under nitrogen at 0°C 3 mmol 4-carboxy-butyltriphenyl-phosphonium bromide in 10 ml dimethoxyethane is stirred with 6.6 mmol potassium tert-butoxide for 30 min, treated with 1 mmol ketone 3i in 1 ml THF and stirred for 2 h. The mixture is acidified with 50% citric acid in water and the product extracted with ethyl acetate. The 1/4 ratio is 85:15 (see entry 12 in table 1).

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