A STEREOSELECTIVE STUDY OF ALFAPROSTOL OMEGA CHAIN SYNTHESIS - APPLICATION POSSIBILITIES IN THE SYNTHESIS OF INTERMEDIATES

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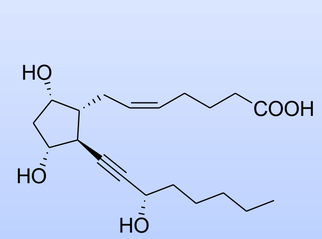
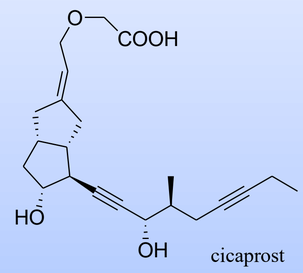
Introduction:

13,14-Dehydro prostaglandin derivatives are special derivates of prostglandins which present allylic alcohol moiety at position 13-14 of their skeleton, 13,14-dehydro PG derivatives present a triple bond at the referred position:



Alfaprostol = 13,14-dehydroPGF$_{2\alpha}$

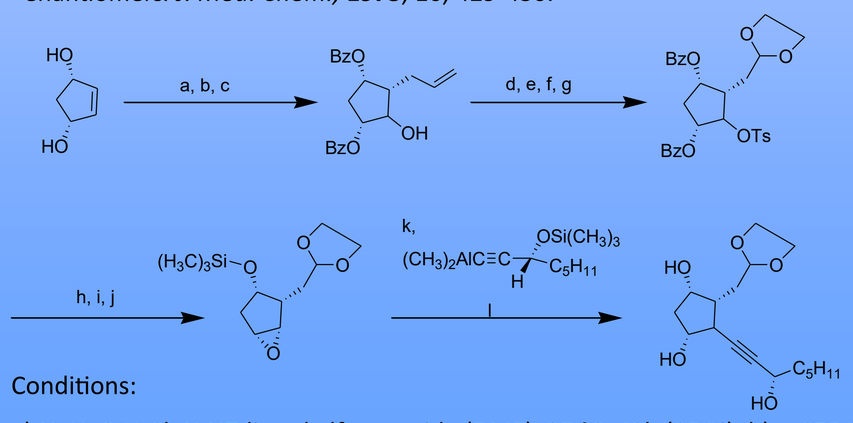


cicaprost

First synthesis to 13,14-dehydro PG:

A Fried to key intermediates:

Fried, J.; Lin, C.H., Synthesis and biological effects of 13-dehydro derivatives of natural prostaglandins $F_{2\alpha}$ and E_2 and their 15-epi enantiomers. *J. Med. Chem.,* **1973**, 16, 429-430.

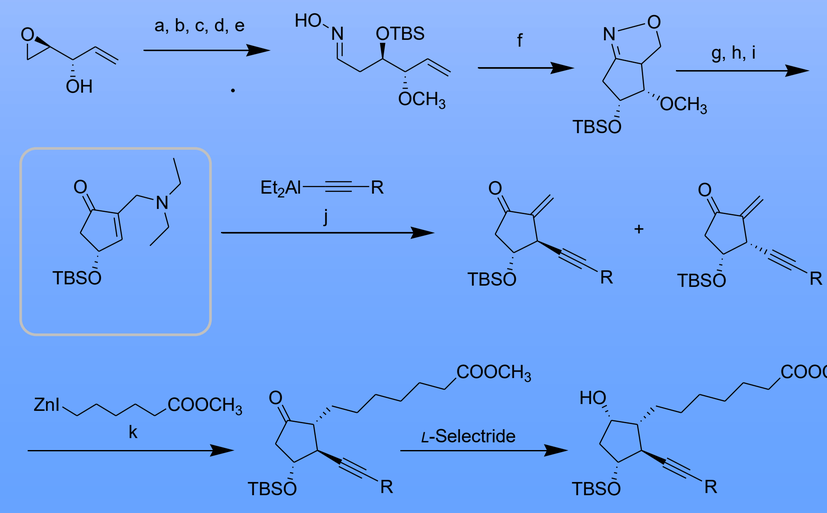


Conditions:

a) NaH, C_7H_7Cl, N,N‑dimethylformamide (DMF), 25 °C, 48h (95 %); b) *m*CPBA, CCl_4, 25 °C, 100h (73 %), c) $(CH_2{=}CHCH_2)_2CuLi$, ether, 2h (95 %); d) Ts-Cl, pyridine, 25 °C, 48h (95 %); e) O_3 stream, DCM, –78 °C; f) Zn, CH_3COOH, 25 °C; g) ethylene glycol, $C_4H_{10}BF_3O$, benzene, (92 %, 3 steps); h) H_2, 10% Pd/C, ethanol, CH_3COOH, CH_3COOK; i) KOH, MeOH, 25 °C, 2h (75 %, 2 steps); j) $(CH_3)_3SiCl$, Et_3N; k) toluene, 40 °C, 2h; l) K_2CO_3, 25 °C, 4h (26 % mixture of LIII and opposite configuration in the chiral center of the cyclopentane ring).

Several approaches were suggested e.g. Satto´s group strategy :

Yoshino, Y.; Okamoto, S.; Sato, F., Highly efficient synthesis of 13-dehydroprostaglandins by 1,4-addition reaction of alkynyl ω side-chain unit onto cyclopentenone framework. J. Org. Chem., 1991, 56, 3205-3207

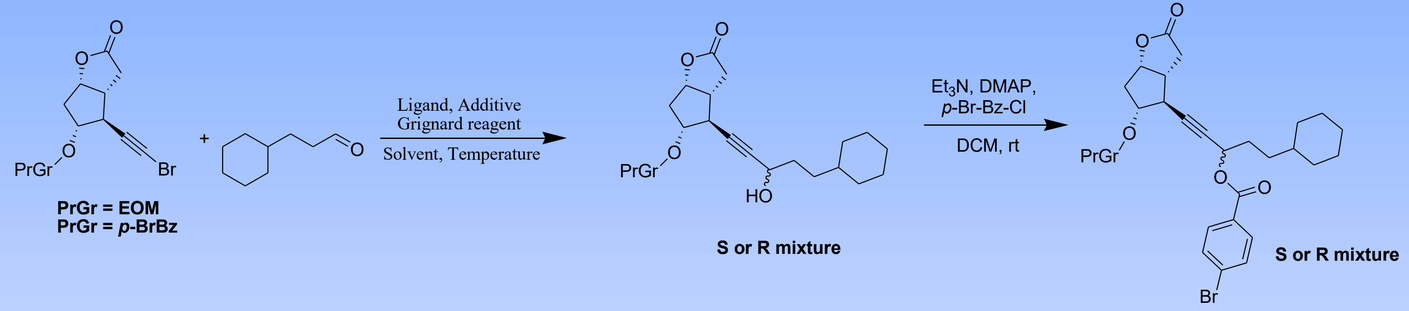


Conditions:

Satto´s group strategy to 13,14-dehydroPG derivatives synthesis. Reagents: a) NaH, CH_3I, THF, 0 °C, 2h. b) KCN, CH_3COOH, MeOH, 40 °C, 3-6h; c) TBS-Cl, imidazole, DMF, rt, 10h; d) DIBAL, hexane, Et_2O, –20 °C, 30 min; e) $HONH_2{\cdot}HCl$, pyridine, DCM, rt, 4h; f) NaOCl, DCM, rt, 4h; g) 10% Pd/C, H_2, $B(OH)_3$, THF, H_2O, rt, 2-4h; h) CH_3SO_2Cl, Et_3N, DCM, 0 °C, 40 min (from a to h 53 % yield); i) Et_2NH, THF, rt, 12h (95 %); j) benzene, rt, (82 % to **LXI** and 14 % to **LXII**); k) CuCN·2LiCl, Me_3SiCl, THF, –78 °C to rt (78 %).

Each of the suggestions represents different synthetic challenges however in the context of our study just the introduction of the triple bond were considered.

Stereoselective study of the new formed propargyl alcohol connection:



Number of experiment	Starting material	Solvent	Ligand (eq[a])	Grignard reagent	Additive (eq[a])	Temperature (°C)	*S/R* Ratio (35)[c]	*S/R* Ratio (29 or 36)[c]
1	**11**	THF	(-)NME (2)	*i*-PrMgCl	-	–78	-	50:50
2	**11**	THF	(-)NME (2)	*i*-PrMgCl	-	–78	-	50:50
24	**24a**	THF	(*R*)-BINOL (1)	*i*-PrMgCl	-	–78	64:36	63:34
25	**24a**	THF	(*R*)-BINOL (4)	*i*-PrMgCl	Ti(*i*OPro)$_4$ (2)	–78	82:18	82:18

Results:

It was proved that we are able to prepare key intermediate of alfaprostol with excess of desired epimer. On the other hand, this experimental approach, can be marked as „Blind technological approach“. For the technogical approach we will study another approach which will be more stereoselective.

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