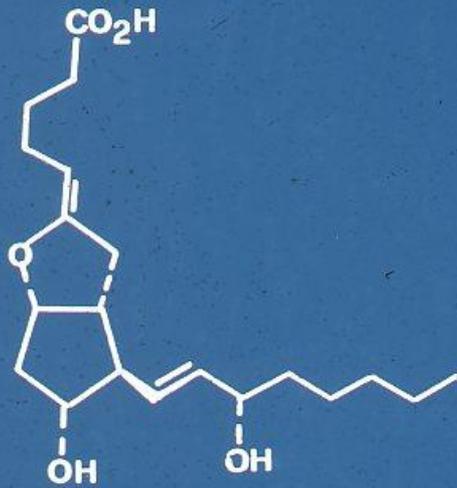
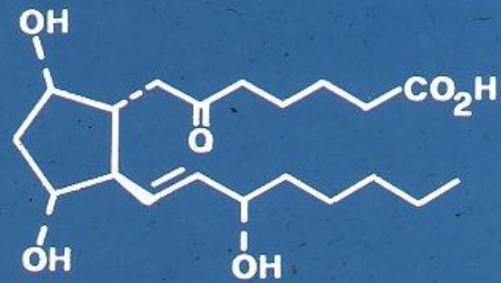
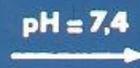


**Strategie nella sintesi di analoghi delle  
prostacicline e nella sintesi totale dei  
leucotrieni**

**V Scuola di chimica farmaceutica  
Urbino, Settembre 1985**

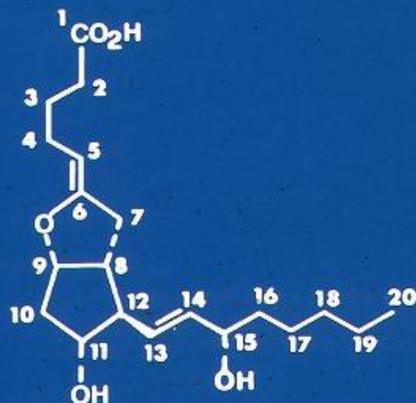


PGI<sub>2</sub>



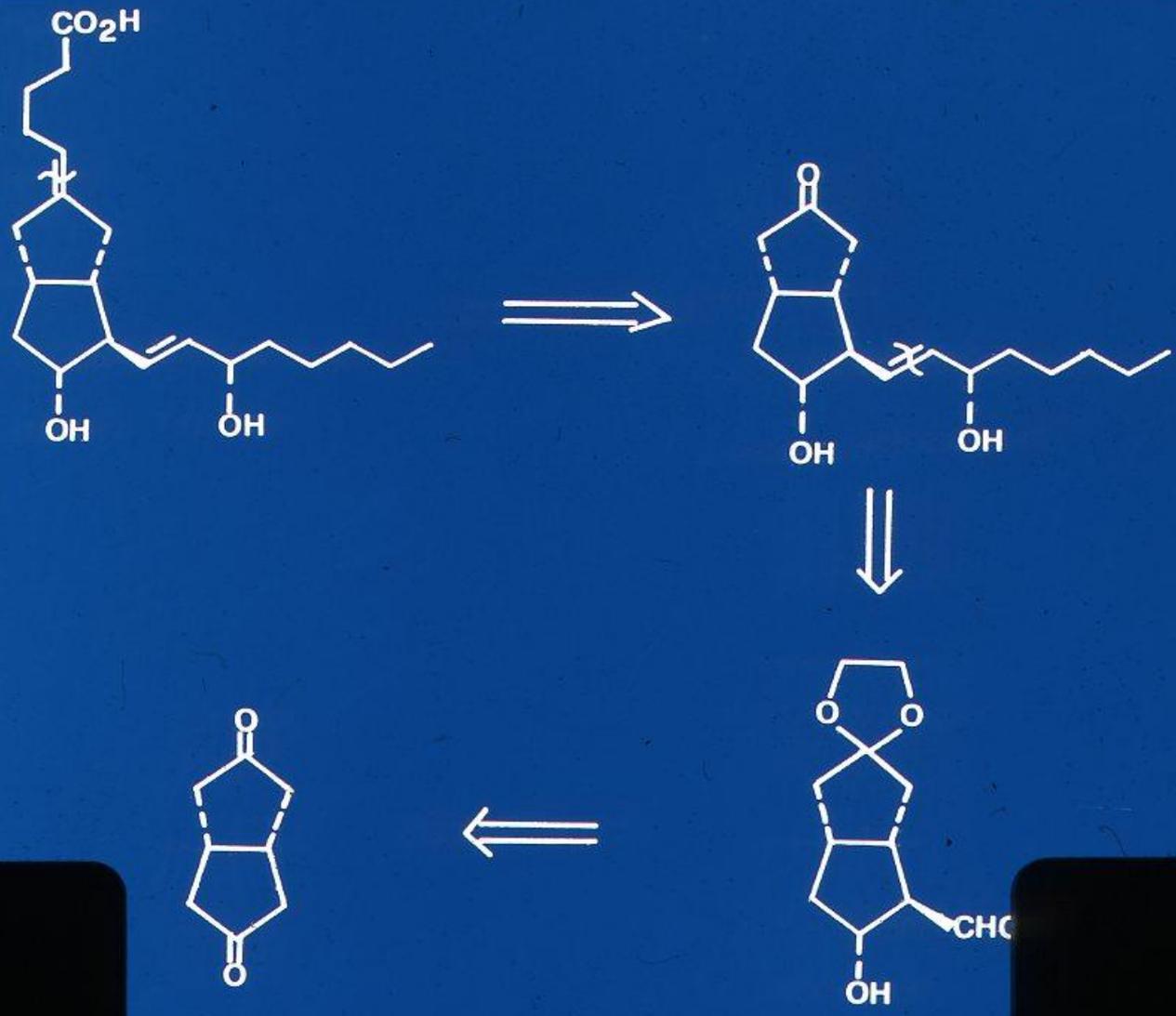
6-cheto-PGF<sub>1α</sub>

Analoghi stabili della prostaciclina PGI<sub>2</sub> (Rif. 2-4)

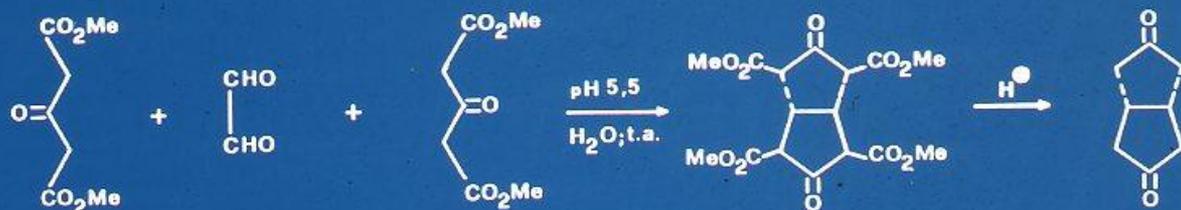


- a) Sostituzione atomo di O in posizione C<sub>9</sub> con atomi di S, N, CH<sub>2</sub>.
- b) Spostamento del doppio legame esociclico 5-eso in posizione 6-endo e 7-endo.
- c) Introduzione in posizione 5 di un ciano gruppo, di un gruppo tiofenilico.
- d) Saturazione del doppio legame esociclico 5-eso.
- e) Ossidazione del C<sub>5</sub> in gruppo carbonilico.
- f) Sostituzione del nucleo tetraidrofuranico con altri eterocicli pentatomici ed esatomici (es. pirrolo, pirazolo, tiazolo, piridazina).
- g) Modificazioni della parte alchilica della catena  $\omega$

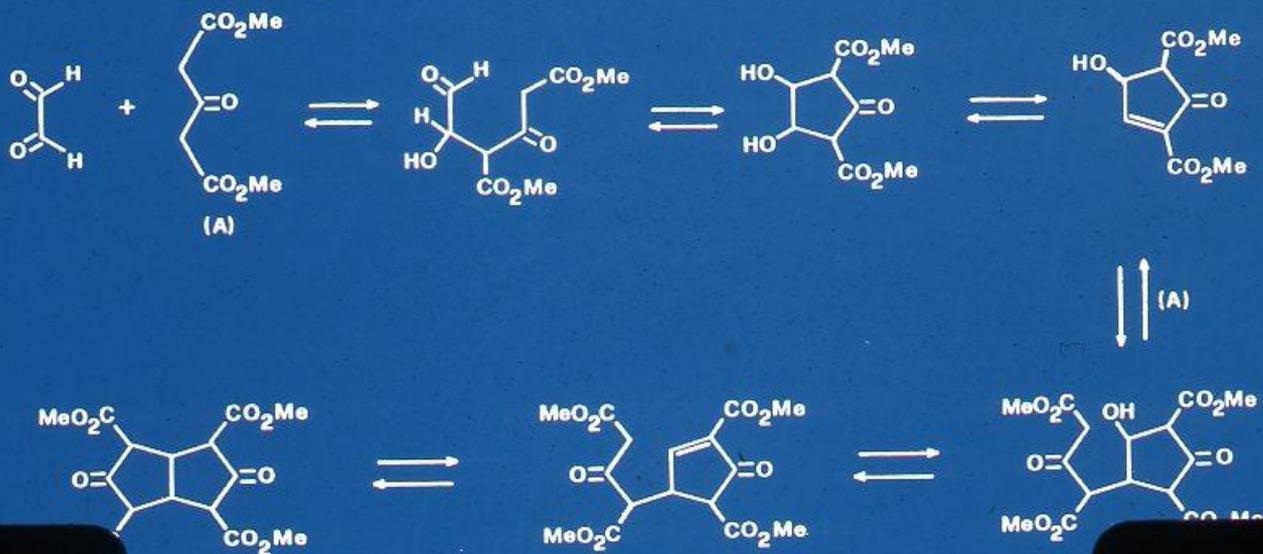
Analisi retrosintetica della carba-PGI<sub>2</sub>



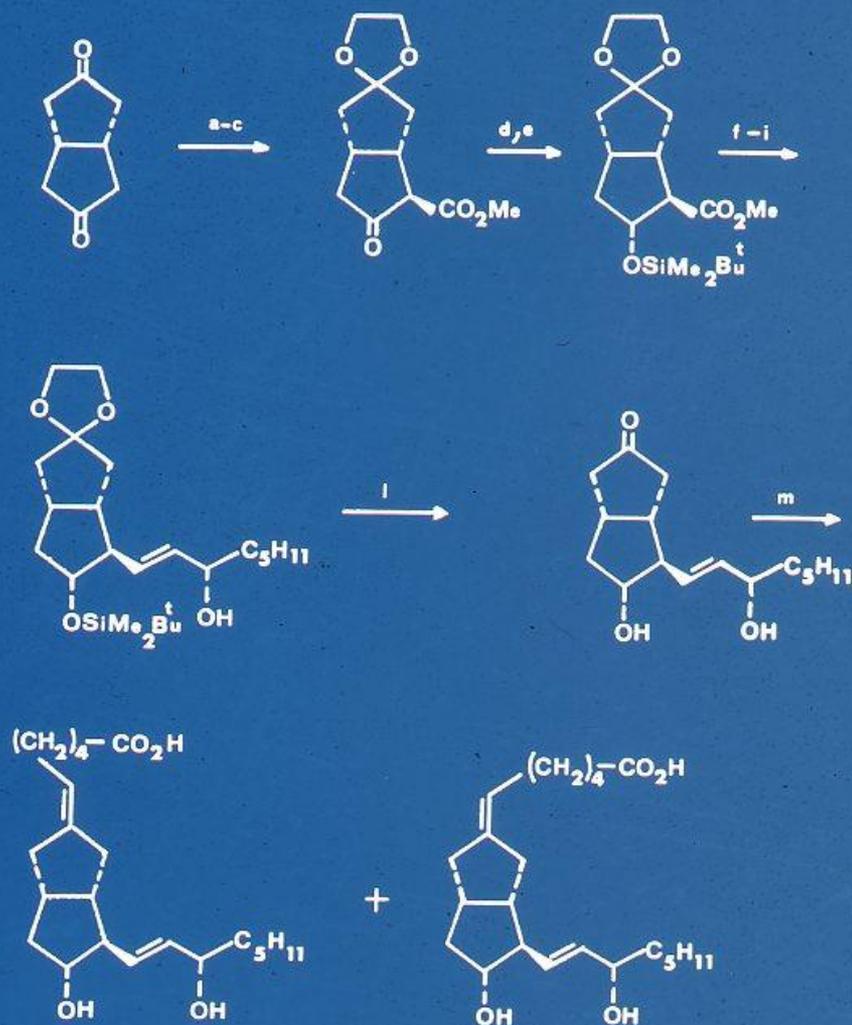
Preparazione del cis-biciclo[3.3.0]ottano



Meccanismo:

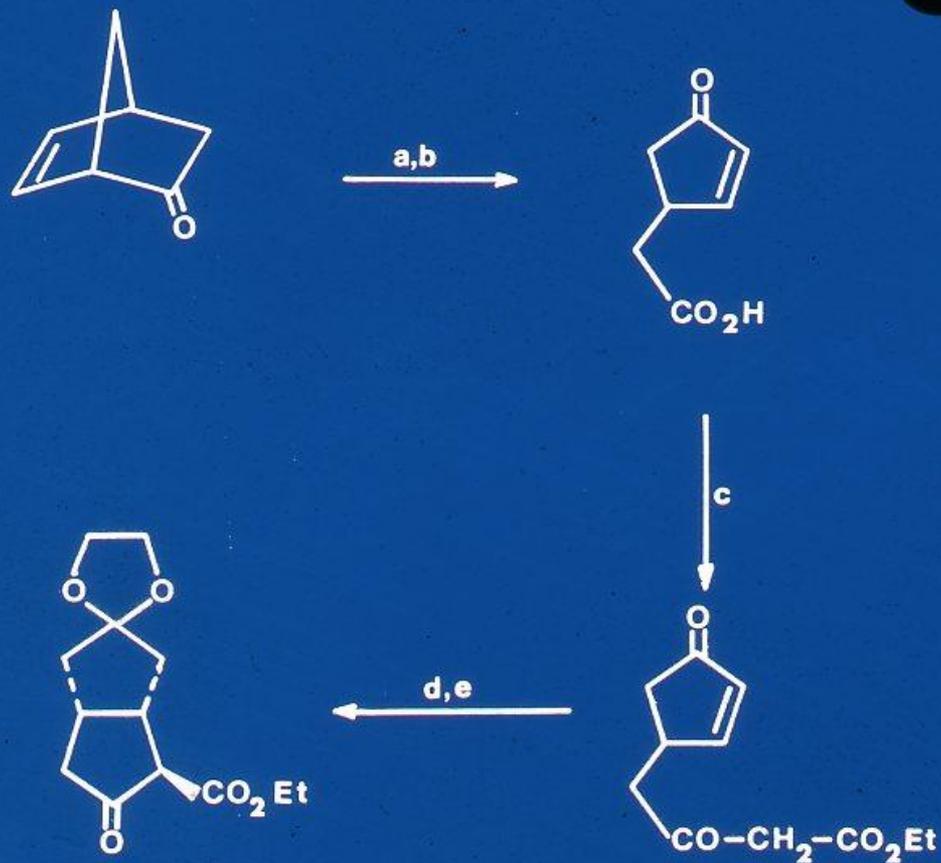


Sintesi di Gandolfi-Nicolaou della 9-carba-PGI<sub>2</sub> (Rif. 6-7)



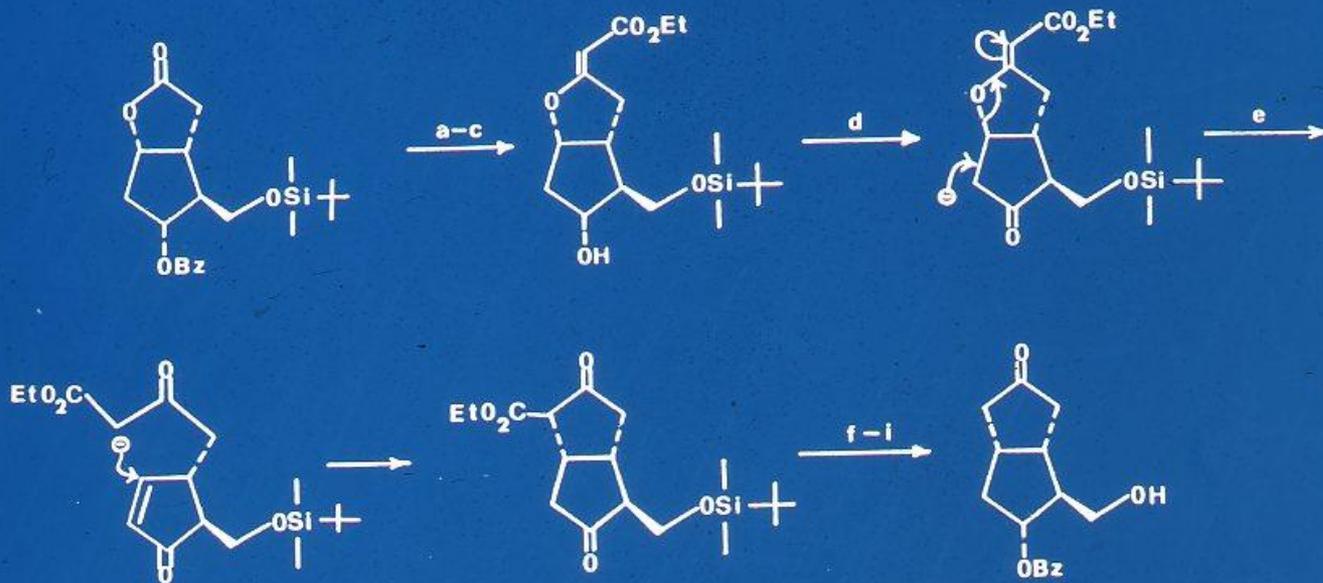
Reagenti: a)  $(\text{CH}_2\text{OH})_2$ , pTsOH; b)  $\text{H}^+$ ,  $\text{H}_2\text{O}$ ; c) NaH,  $(\text{MeO})_2\text{CO}$ ; d)  $\text{NaBH}_4$ , EtOH,  $-45^\circ\text{C}$ ; e)  $\text{Bu}^t\text{Me}_2\text{SiCl}$ , Imidazolo; f)  $\text{Bu}^i\text{AlH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; g) Piridinio clorocromato; h)  $(\text{MeO})_2\text{P}(\text{o})\text{CH}_2\text{COC}_5\text{H}_{11}$ , NaH; i)  $\text{Zn}(\text{BH}_4)_2$ , ( $\alpha$ : $\beta$ =1:1); l) AcOH-THF- $\text{H}_2\text{O}$ ,  $45^\circ\text{C}$ ; m)  $\text{Ph}_3\text{P}-\text{CH}(\text{CH}_2)_3\text{CO}_2\text{Na}$ , (6 eq.), DMSO, E:Z=1:1.

Sintesi del bicyclo [3.3.0] ottano attraverso reazione di Michael intramolecolare (Rif. 8)



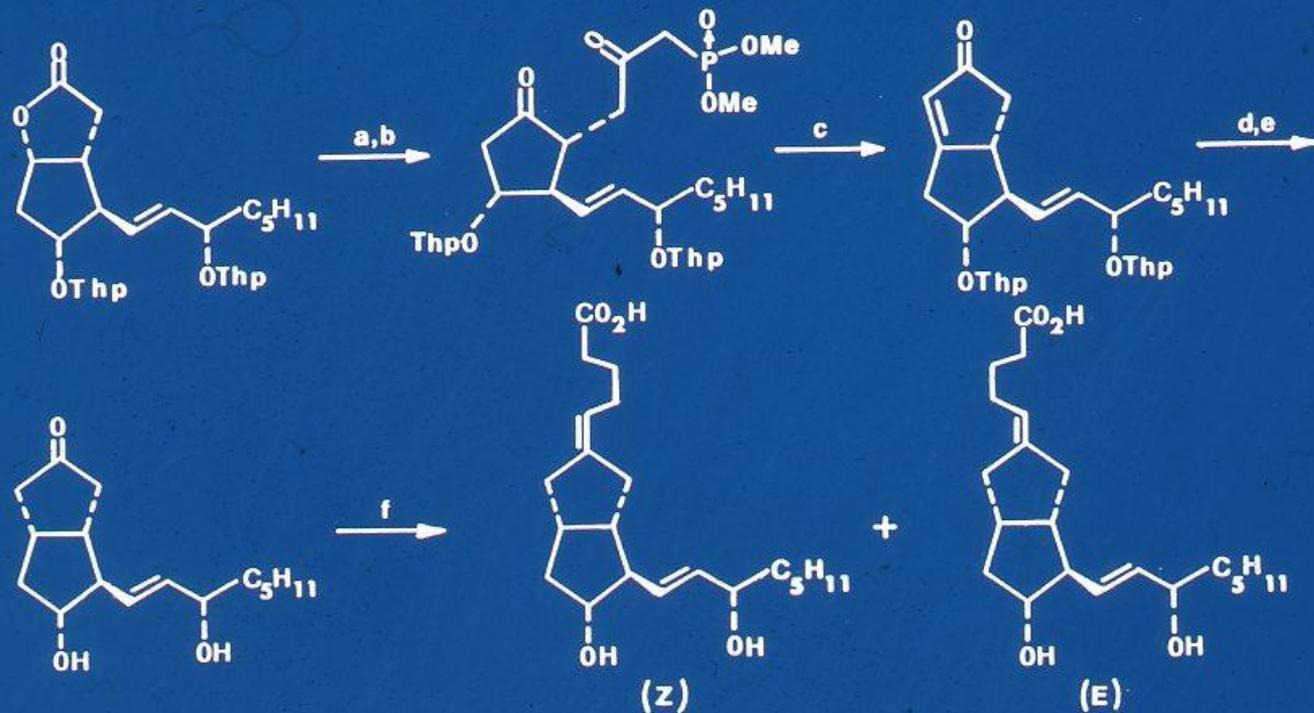
Reagenti: a)  $\text{H}_2\text{O}_2$ , NaOH; b)  $\text{CrO}_3$ ,  $\text{H}_3\text{O}^+$ ,  $-30^\circ\text{C}$ ; c)  $(\text{Im})_2\text{CO}$ ,  $\text{Mg}(\text{OEt})_2$ ,  $\text{HO}_2\text{C}-\text{CH}_2-\text{CO}_2\text{Et}$ ; d)  $\text{K}_2\text{CO}_3$ , EtOH, T.amb.; e) MED, pTsOH.

Sintesi della 9-carba-PGI<sub>2</sub> secondo Vorbrüggen (Rif. 10)



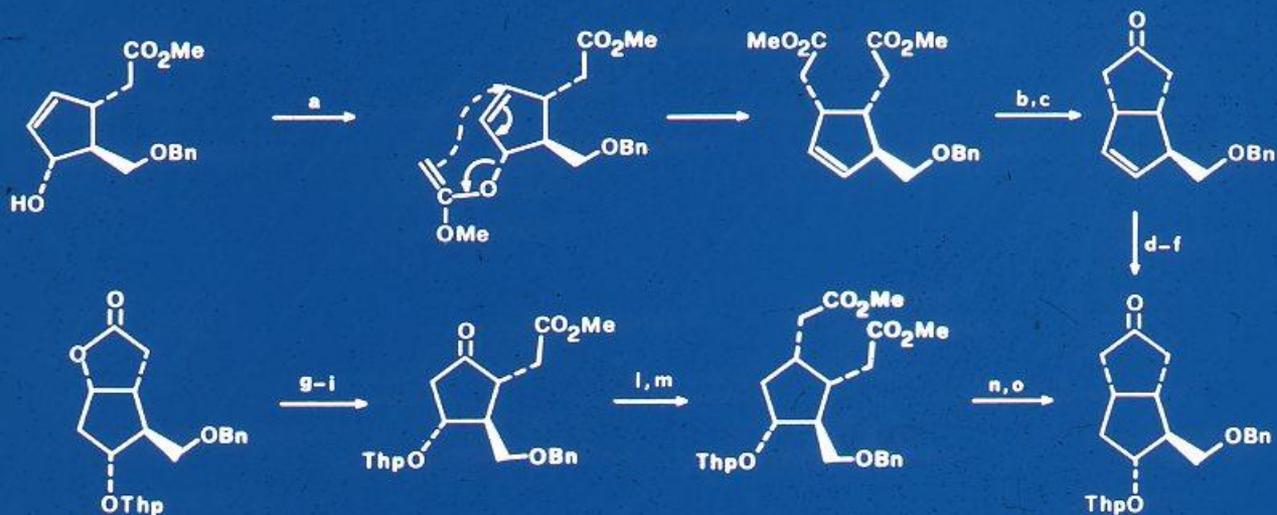
Reagenti: a) LiCH<sub>2</sub>CO<sub>2</sub>Et, THF, -70°C; b) pTsOH, C<sub>6</sub>H<sub>6</sub>; c) K<sub>2</sub>CO<sub>3</sub>, MeOH; d) CrO<sub>3</sub>·2Py; e) DBM, THF, 0°C; f) NaBH<sub>4</sub>, MeOH; g) DABCO, 110°C; h) PhCOCl, 0°C; i) AcOH/H<sub>2</sub>O/THF.

Sintesi di Aristoff della 9-carba-PGI<sub>2</sub> (Rif. 9)



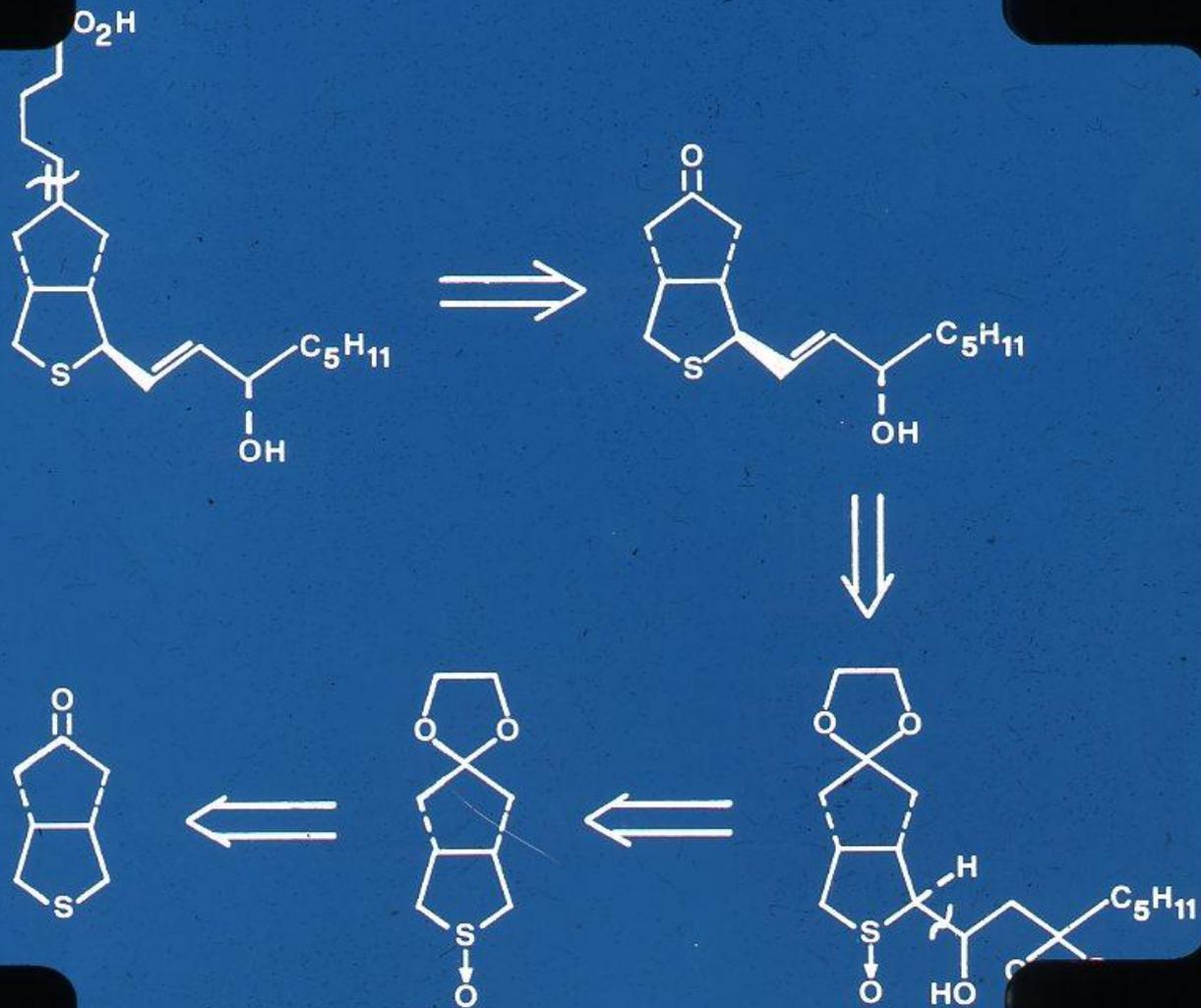
Reagenti: a)  $\text{LiCH}_2\text{P}(\text{O})(\text{OMe})_2$ , THF,  $-78^\circ\text{C}$ ; b)  $\text{CrO}_3 \cdot 2\text{Py}$ ,  $\text{CH}_2\text{Cl}_2$ ; c)  $\text{K}_2\text{CO}_3$ , Crown 18-6, toluene,  $\Delta$ ;  
 d)  $\text{Et}_3\text{NH}^+\text{HCO}_2^-$ , 5% C/Pd, toluene; e)  $\text{AcOH}/\text{H}_2\text{O}/\text{THF}$ ; f)  $\text{Ph}_3\text{P}=\text{CH}(\text{CH}_2)_4\text{CO}_2\text{Na}$ , DMSO, (6 eq.).

Sintesi di Hayashi della 9-carba-PGI<sub>2</sub> (Rif. 11)

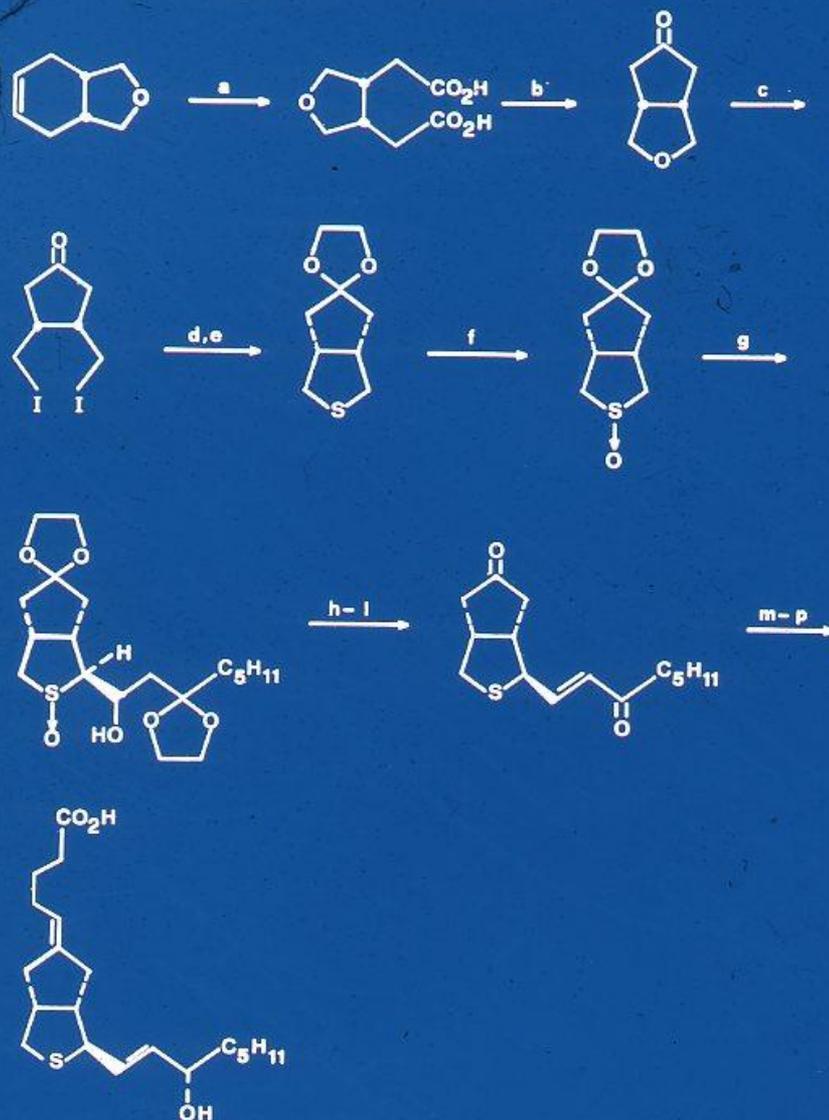


Reagenti: a)  $(EtO)_3C-CH_3$ ,  $140^\circ C$ ; b)  $KOBu^t$ ,  $C_6H_6$ ; c)  $DMSO$ ,  $NaCl$ ,  $\Delta$ ; d)  $NBS$ ,  $DMSO$ ,  $H_2O$ ; e)  $Bu_3SnH$ ,  $AIBN$ ,  $C_6H_6$ ,  $h\nu$ ; f)  $DHP$ ,  $H^+$ ; g)  $NaOH$ ; h)  $CH_2N_2$ ; i) Piridinio clorocromato; l)  $Ph_3P=CH-CO_2Me$ ; m)  $H_2$ ,  $Pd/C$ ; n)  $KOBu^t$ ,  $75^\circ C$ ,  $C_6H_6$ ; o)  $HMPT$ ,  $\Delta$ .

Analisi retrosintetica della 9-carba-11-tia-prostaciclina

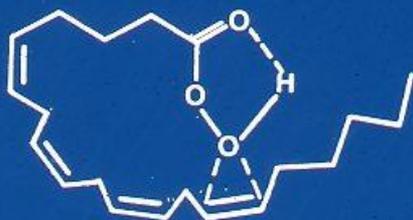
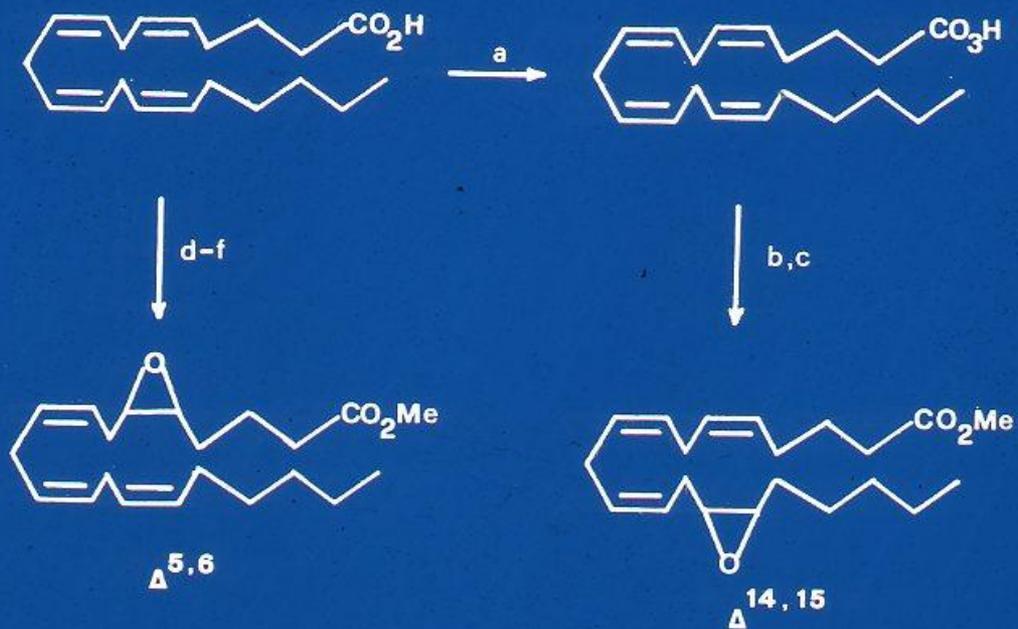


Sintesi della 9-carba-11-tiaprostaciclina (Rif. 12-14)



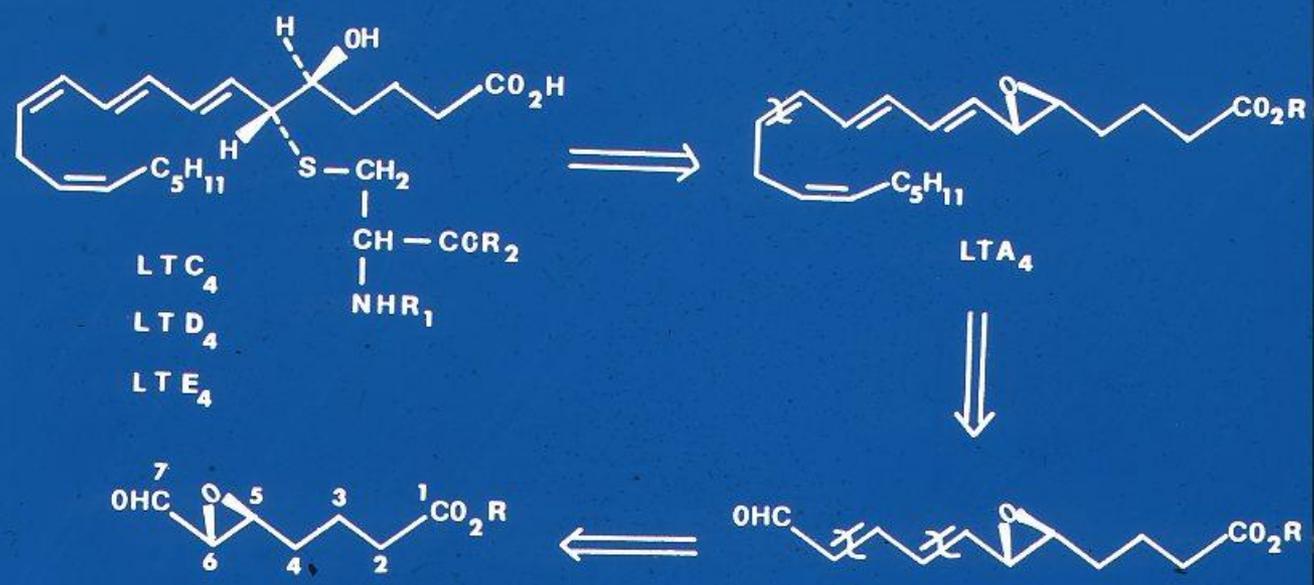
Reagenti: a)  $O_3$ ,  $-78^\circ C$ ;  $HCO_2H-H_2O_2$ ; b)  $Ba(OH)_2$ , Fe; c) HI 67%; d) NED, pTsOH;  
 e)  $Na_2S$ ; f)  $NaIO_4$ ; g) R-CHO, LDA,  $-78^\circ C$ ; h)  $B_2H_6$ ; i) AcOH/ $H_2O$ ; l)  
 $H_2SO_4$  20%; m) NED, pTsOH; n)  $NaBH_4$ ; o)  $H_2SO_4$  dil.; p) Wittig.

Sintesi degli epossidi  $\Delta^{14,15}$  e  $\Delta^{5,6}$  (Rif. 18)

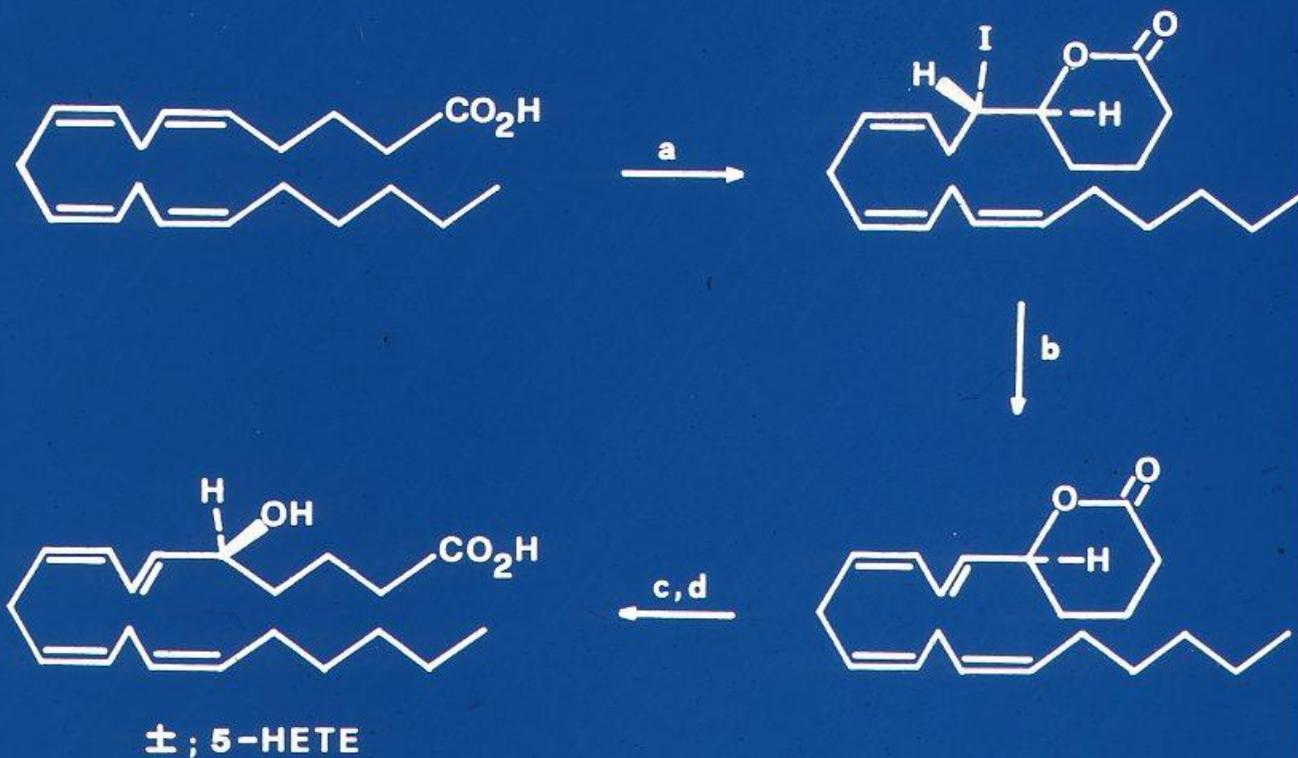


Reagenti: a)  $(\text{Im})_2\text{CO}$ ,  $\text{H}_2\text{O}_2$ ; b) T.A.; c)  $\text{CH}_2\text{N}_2$ ; d)  $\text{KI}_3$ ,  $\text{OH}^-$ ; e)  $\text{LiOH}$ ; f)  $\text{CH}_2\text{N}_2$

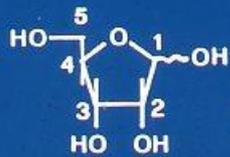
Analisi retrosintetica dei leucotrieni



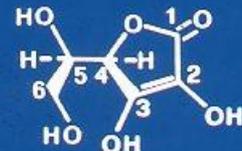
Sintesi di 5-HETE (Rif. 20)



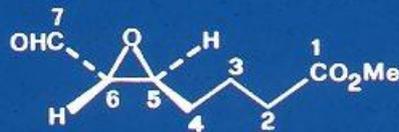
Reagenti: a)  $\text{KI}_3$ ,  $\text{OH}^-$ ; b) DBU; c) TEA, MeOH; d) LiOH



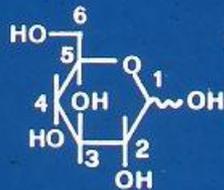
D-RIBOSIO



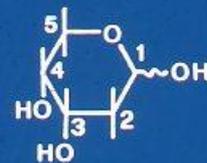
ACIDO D-ARABOASCORBICO



(5S,6R)

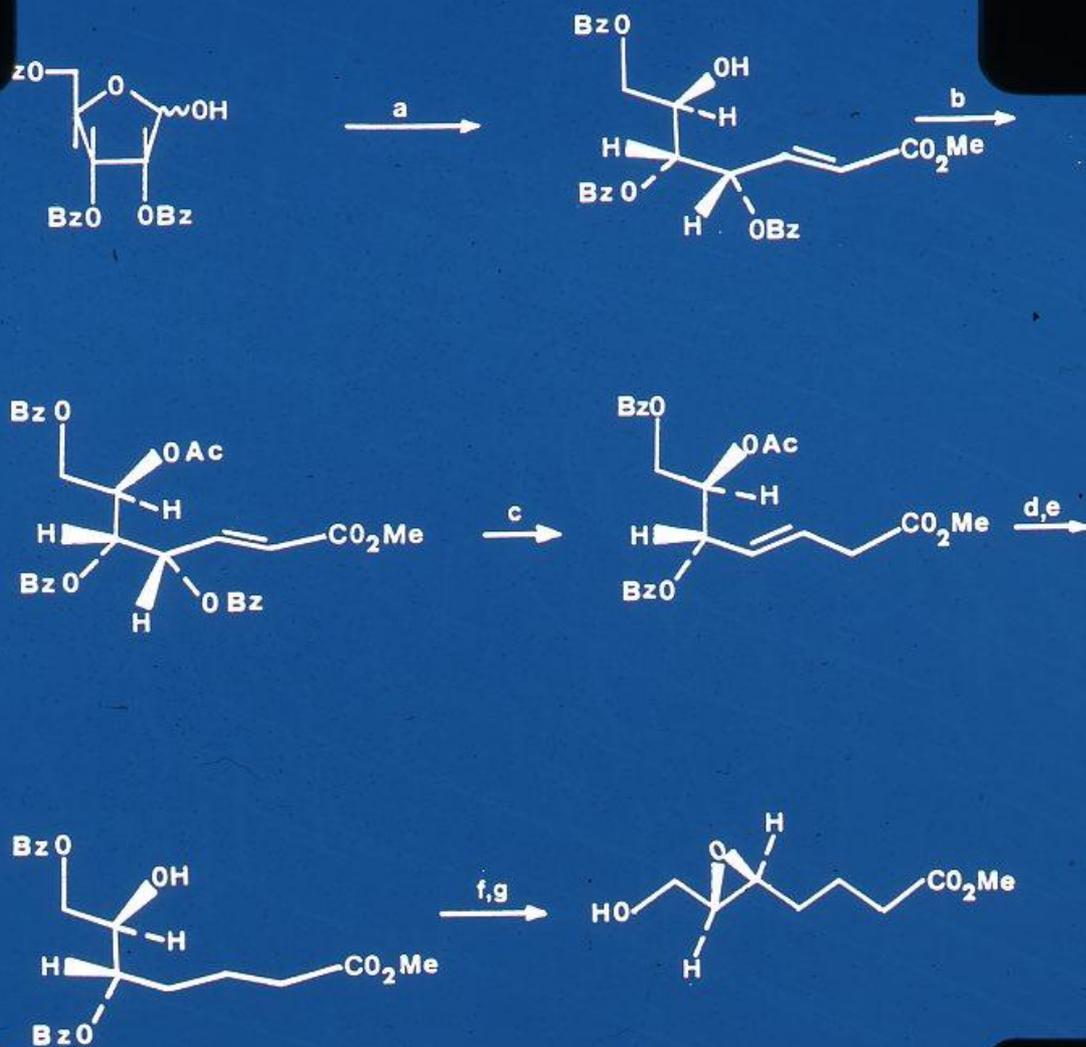


D-GLUCOSIO



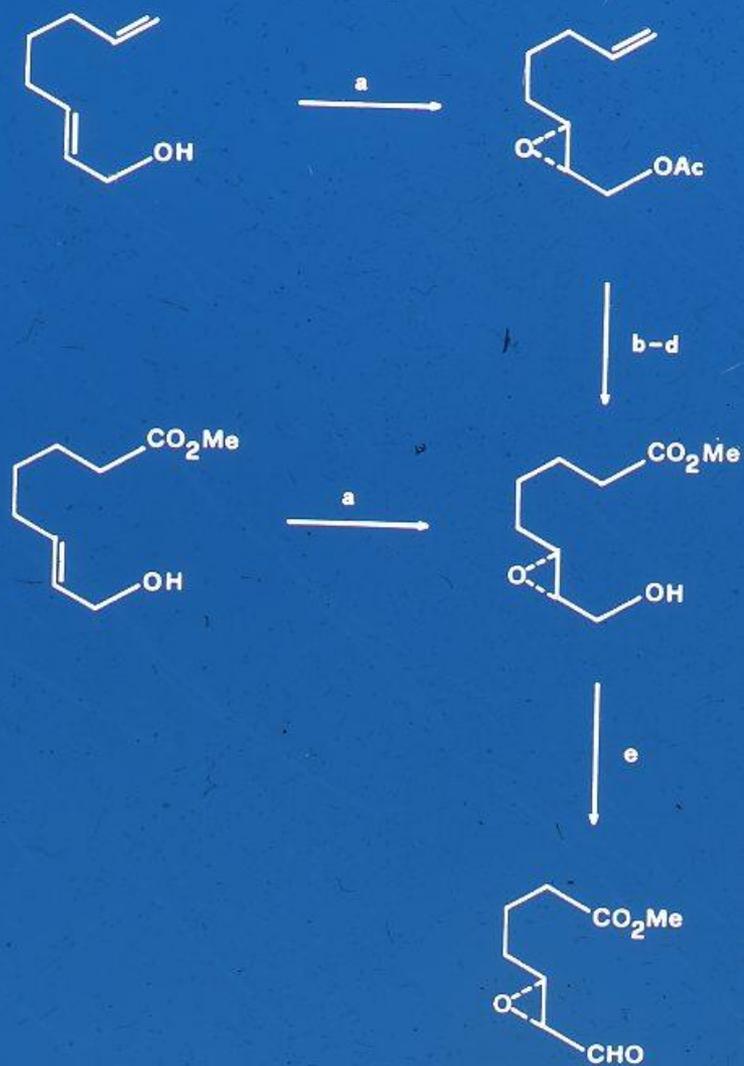
2-DESOSSI-D-RIBOSIO

Sintesi enantiospecifica di Corey del LTA<sub>4</sub> (Rif.24)



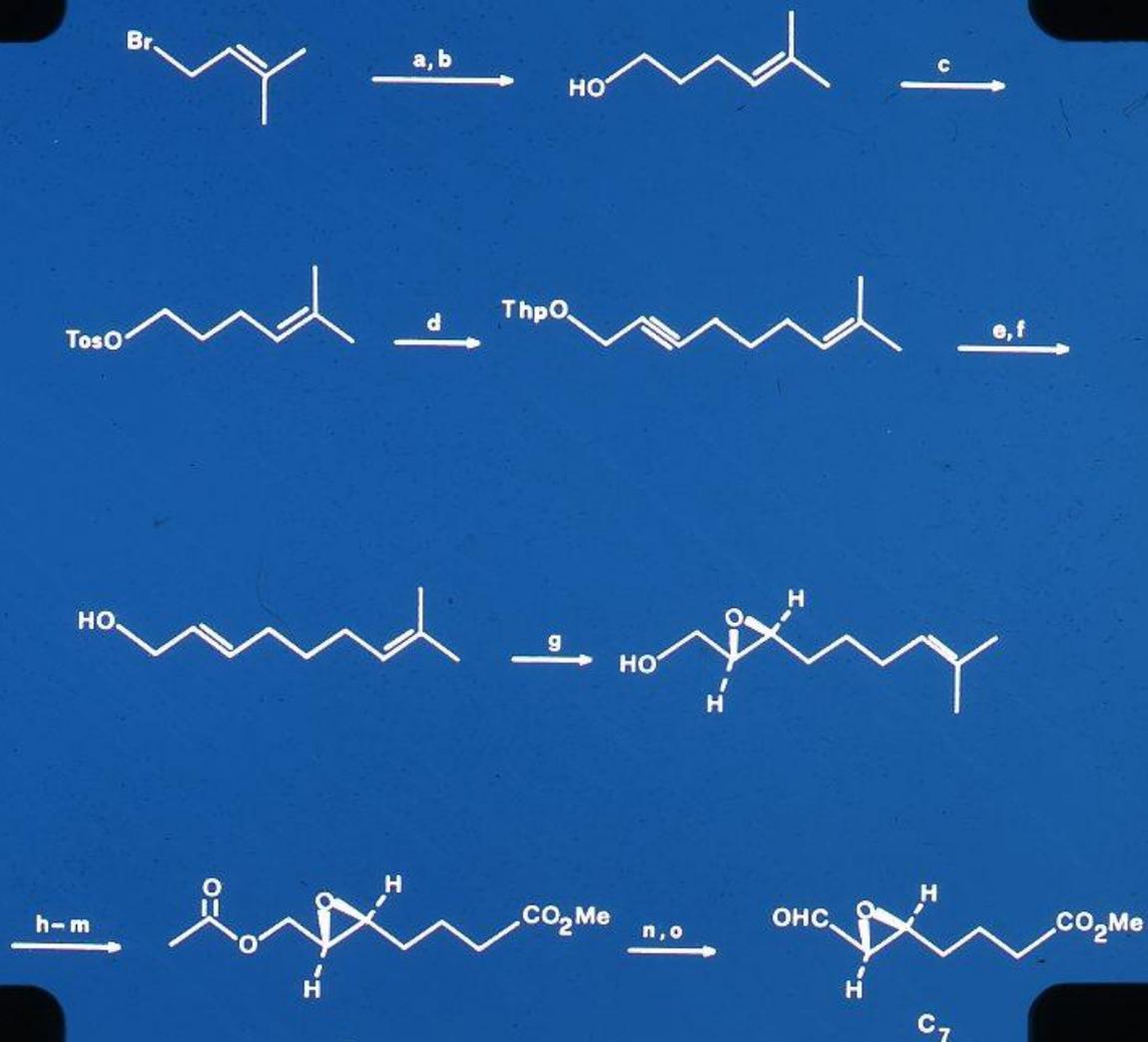
Reagenti: a)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ ; b)  $\text{Ac}_2\text{O}$ ; c) Zn amalgama; d)  $\text{H}_2$ , Pd/C 10%;  
 e) HCl, MeOH; f) TosCl, Py; g)  $\text{K}_2\text{CO}_3$ , MeOH.

Sintesi di Sharpless della trans-epossi-aldeide C<sub>7</sub> (Rif. 21)



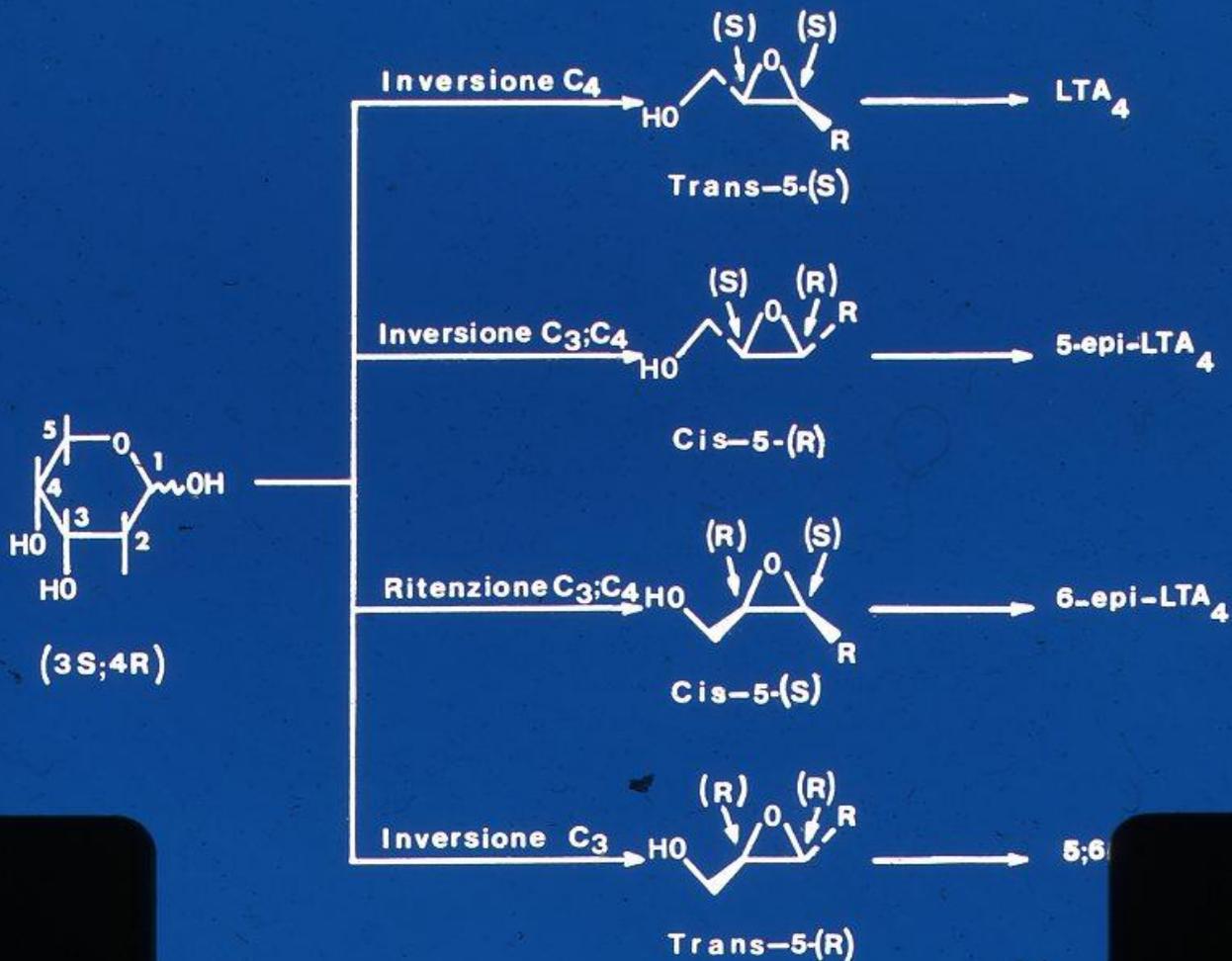
Reagenti: a)  $\text{Ti}(\text{OPr}^i)_4$ ,  $t\text{-BuO}_2\text{H}$ , (+)-DET; b)  $\text{IO}_4^-$ ,  $\text{RuCl}_3$ ; c)  $\text{CH}_2\text{N}_2$ ;  
 d)  $\text{K}_2\text{CO}_3$ , MeOH; e)  $\text{CrO}_3 \cdot 2\text{Py}$ .

Sintesi di Corey della trans epossialdeide C<sub>7</sub> (Rif. 22)

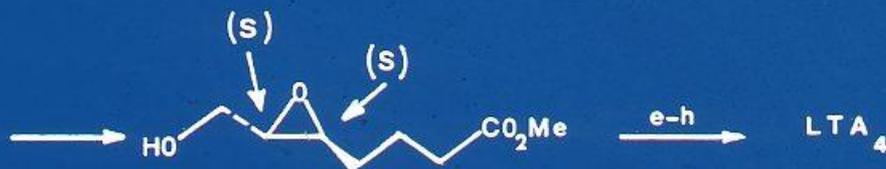
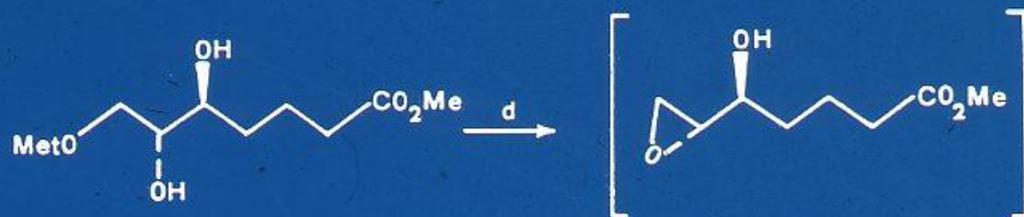
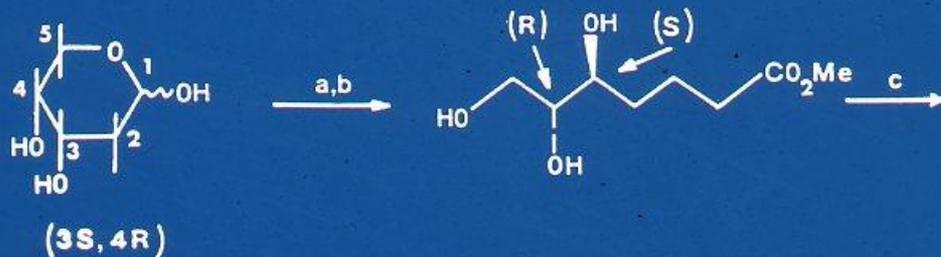


Reagenti: a)  $\text{LiCH}_2\text{CO}_2\text{Bu}^t$ ; b)  $\text{LiAlH}_4$ ; c)  $\text{Tos-Cl, Py}$ ; d)  $\text{LiC}\equiv\text{CCH}_2\text{OThp}$ ; e)  $\text{H}_3\text{O}^+$ ; f)  $\text{LiAlH}_4$ ; g)  $\text{Ti}(\text{OPr}^i)_4, \text{BuO}_2\text{H}, (+)\text{-DET}$ ; h)  $\text{Ac}_2\text{O-Py}$ ; i)  $\text{O}_3$ ; l)  $\text{CrO}_3, \text{H}^+$ ; m)  $\text{CH}_2\text{N}_2$ ; n)  $\text{K}_2\text{CO}_3$ ; o)  $(\text{CrO}_3 \cdot 2\text{Py})$ .

stereochimiche tra 2-Desossi-D-Ribosio e gli isomeri ottici  
(Rif. 17)



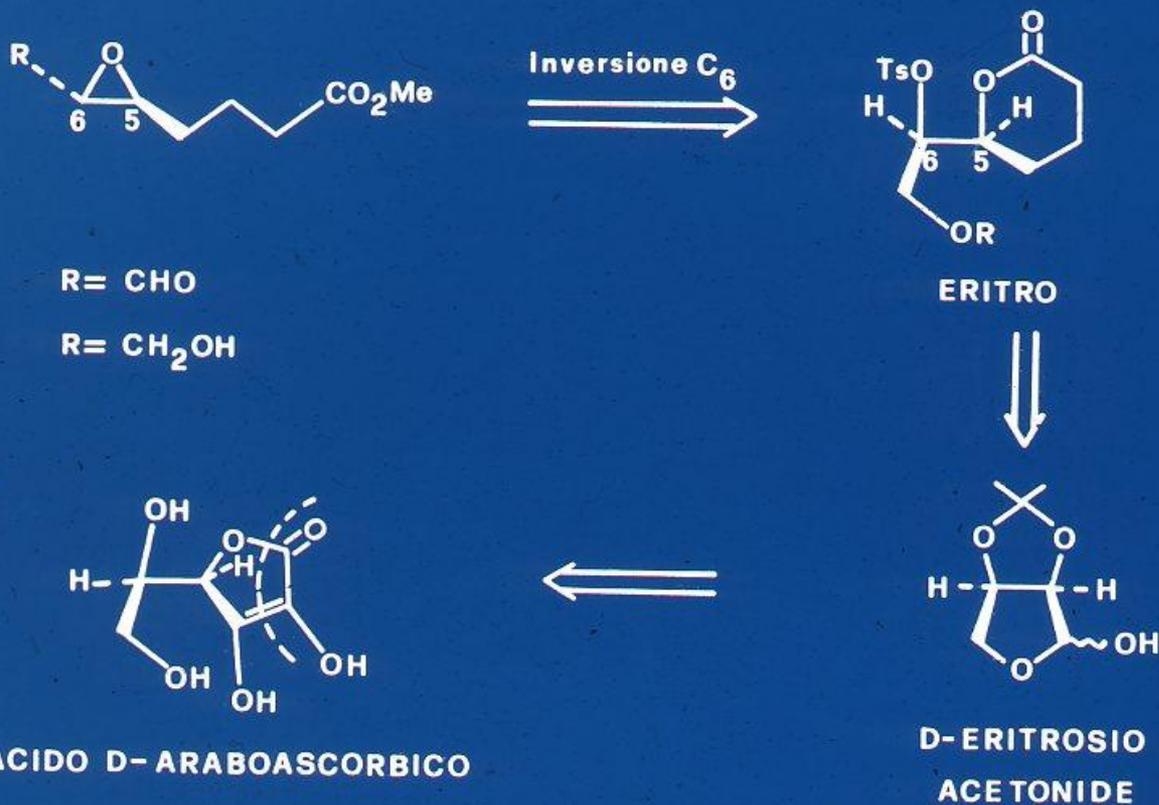
Sintesi di Rokack del  $LTA_4$  (Rif.25,26)



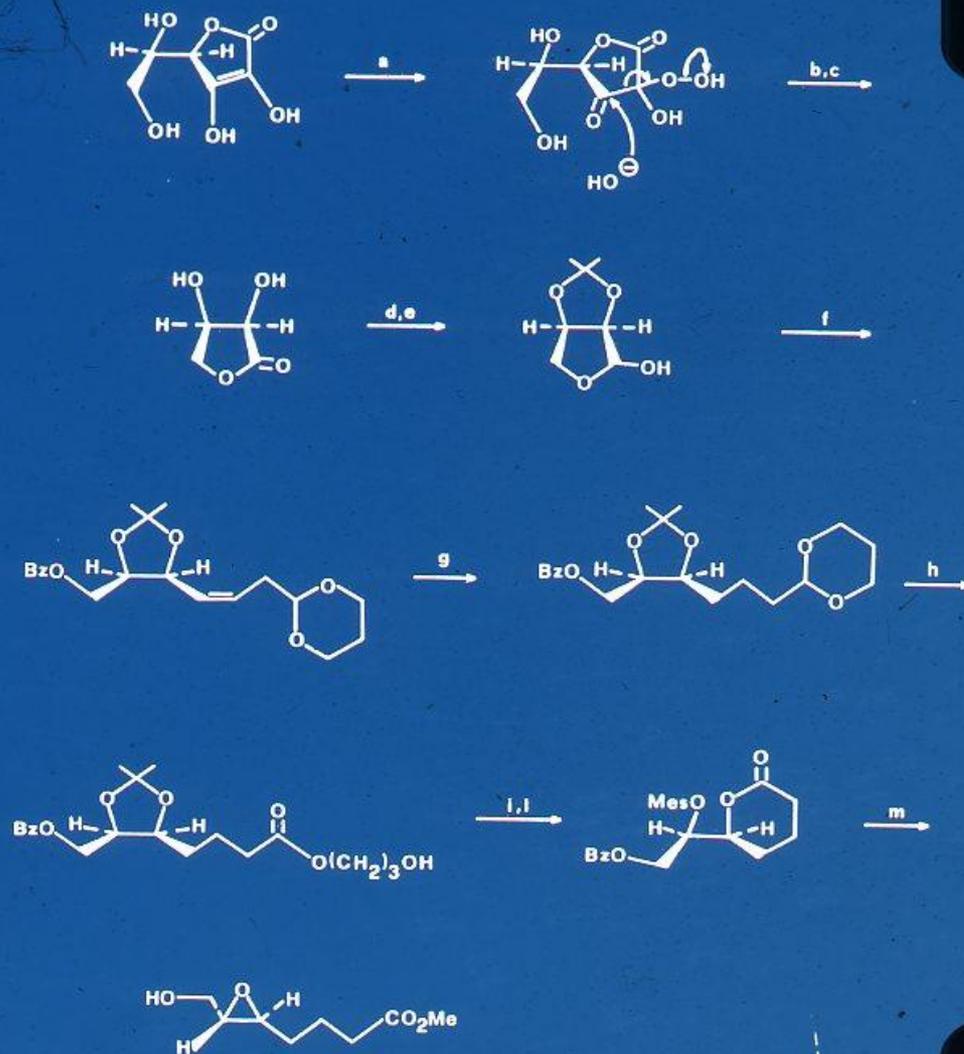
reagenti: a)  $Ph_3P=CHCO_2Me$ ; b)  $H_2$ , Pd/C; c)  $MeI$ ; d)  $MeONa$ ; e) Collins;

f)  $Ph_3P=CH-CHO$ ; g)  $Ph_3P=CH-CHO$ ; h)  $Ph_3P=CHCH_2CH=CH-C_5H_{11}$

Retrosintesi della epossialdeide C<sub>7</sub> secondo Cohen (Rif.23)

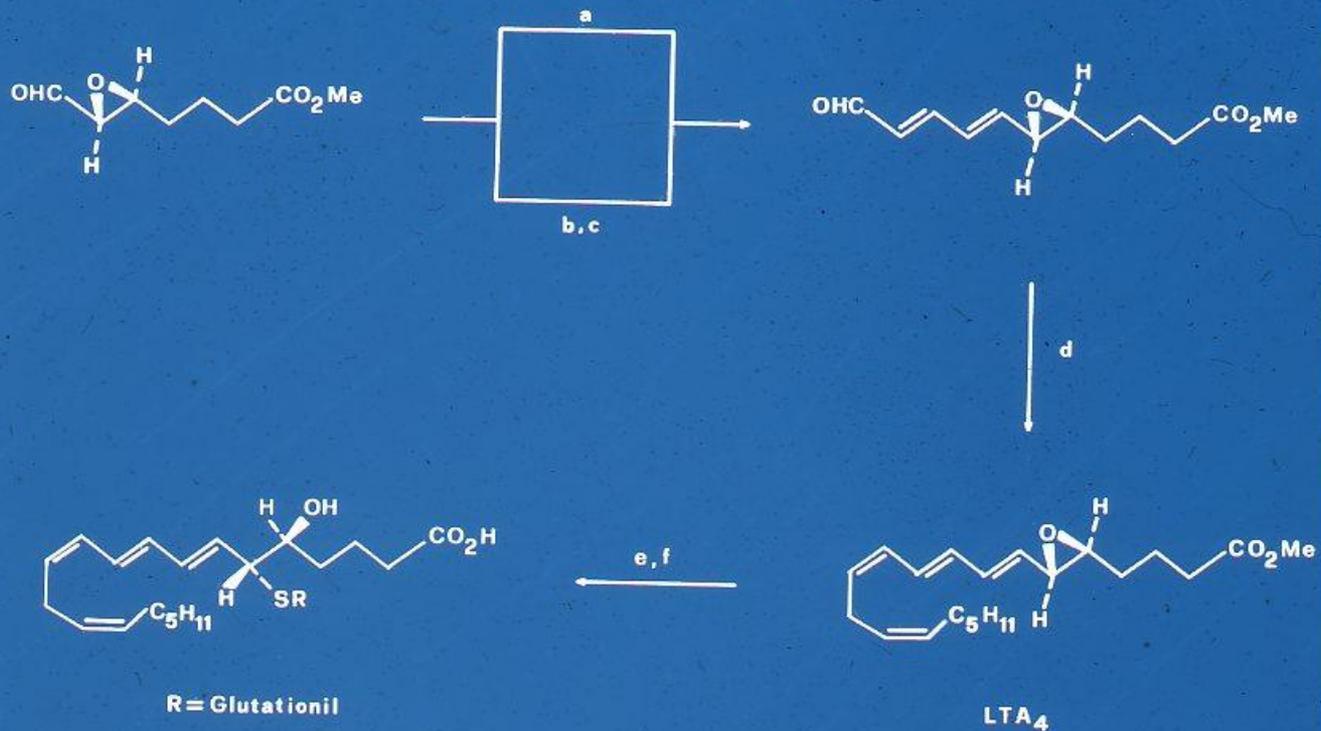


Sintesi di Cohen di LTC<sub>4</sub> (Rif, 23)



Reagenti: a)  $\text{H}_2\text{O}_2, \text{Na}_2\text{CO}_3$ ; b)  $-(\text{CO}_2\text{Na})_2$ ; c)  $\text{HCl}$ ; d)  $(\text{CH}_3)_2\text{C}(\text{OMe})_2$ , pTsOH;  
 e) DIBAL,  $-78^\circ\text{C}$ ; f) Wittig; g)  $\text{H}_2$ , Pt; h)  $\text{O}_3$ ; i)  $\text{CF}_3\text{CO}_2\text{H}-\text{H}_2\text{O}$ ;  
 l) Mes-Cl, TEA; m)  $\text{K}_2\text{CO}_3$ , MeOH.

Sintesi enantiospecifica di  $LTA_4$  ed  $LTC_4$  di Corey (Rif. 19)



Reagenti: a)  $LiCH=CH-CH=CHOEt$ ; b)  $Ph_3P=CH-CHO$ ; c)  $Ph_3P=CH-CHO$ ; d)  $Ph_3P=CHCH_2\overset{Z}{CH=CH}-C_5H_{11}$ ,  $BuLi$ ; e) glutatione,  $E_3N$ ; f)  $K_2CO_3$ ,  $H_2O$ ,  $MeOH$ .