CHIRALITA'

Una molecola è chirale quando non è sovrapponibile alla sua immagine speculare

Immagine speculare = entità distinta

Chiralità: proprietà PSEUDOSCALARE

Resta invariata con un'operazione di simmetria del I ordine

Cambia di segno con un'operazione di simmetria del II ordine

Forme Enantiomorfe:

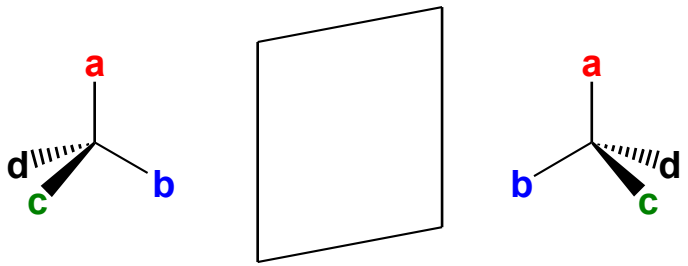
due forme non sovrapponibili di una struttura chirale

STRUTTURA ACHIRALE

Struttura sovrapponibile alla sua immagine speculare

Nel gruppi puntuale deve comparire almeno un elemento di simmetria del II ordine

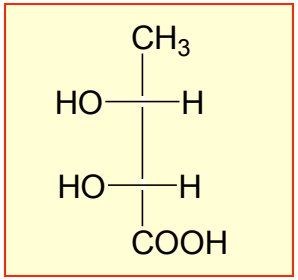
Consideriamo due modelli enantiomorfi:



- Stessa composizione chimica
- Stessa connettività
- Le strutture possono essere scambiate da un'isometria (riflessione)
- Sono isometriche (identiche per forma e dimensione)
- Possono anche essere definite isomere (fatte delle stesse parti)

Due isomeri enantiomorfi sono detti enantiomeri

Relazioni di Isomeria

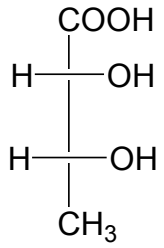


Due strutture isomere sono isometriche?

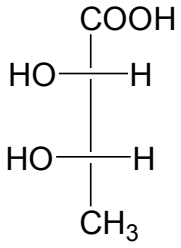
SI

Sono correlate da un'isometria del primo ordine?

SI → **omomeri**



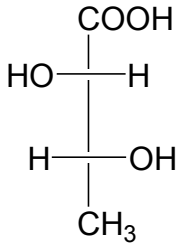
NO → **enantiomeri**



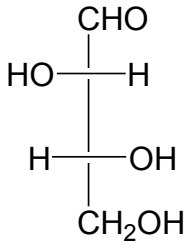
NO

Hanno la stessa costituzione?

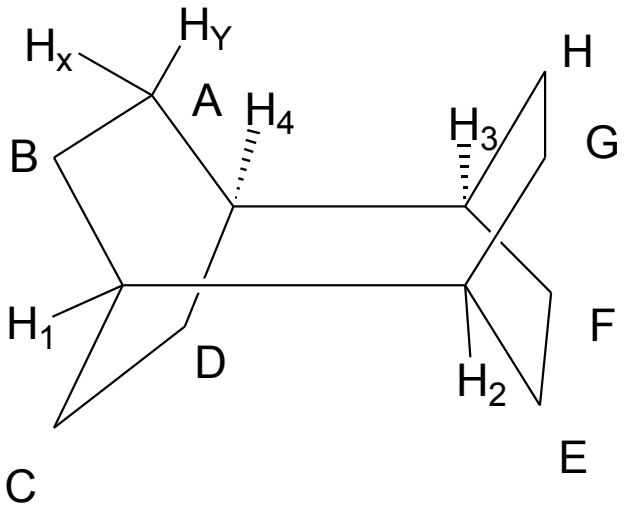
SI → **diastereoisomeri**



NO → **isomeri costituzionali**



Relazioni di Topicità



D_{2h}

$3C_2$, σ_h, 2σ, i

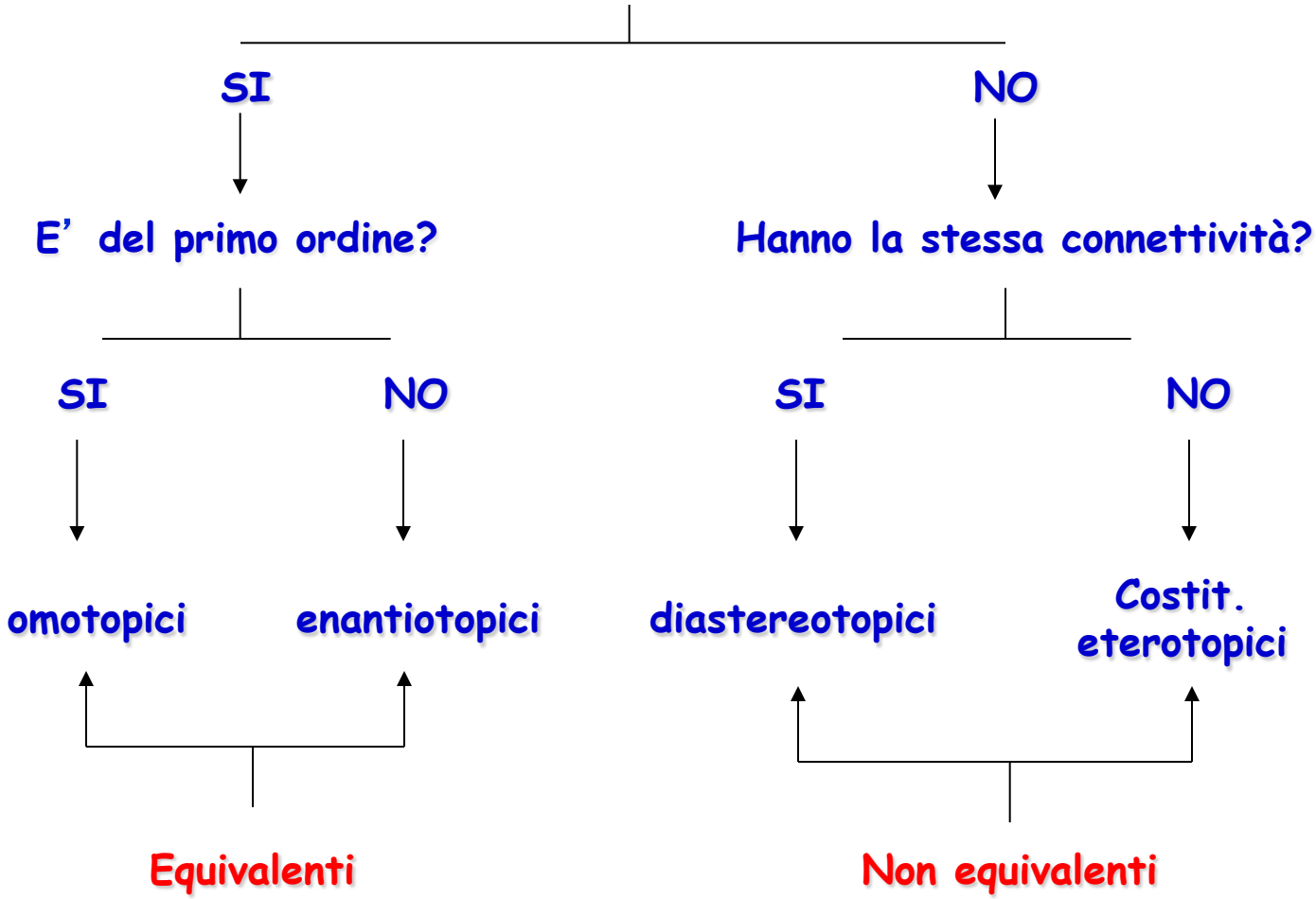
^{1}H NMR

1 segnale per CH (4)
1 segnale per CH_x (8)
1 segnale per CH_y (8)

^{13}C NMR

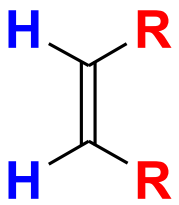
1 segnale per CH (4)
1 segnale per CH_2 (8)

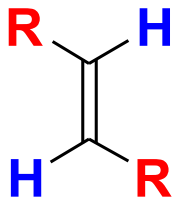
Relazioni di Topicità

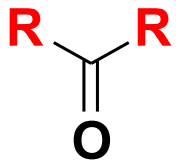


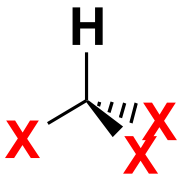
Gruppi Omotopici

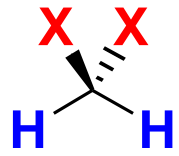
Devono essere presenti assi C_n (n>1) – no C_1, S_1, S_2

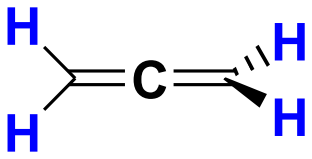


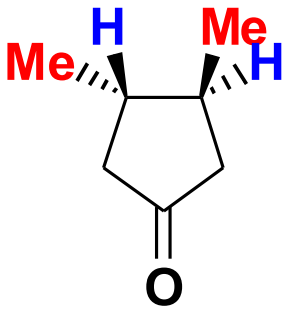


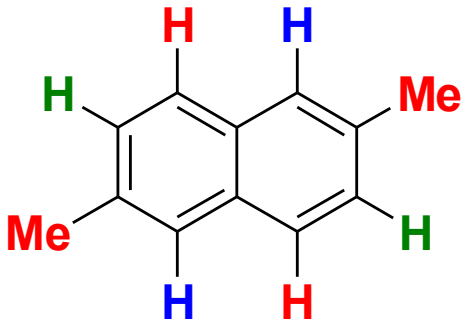






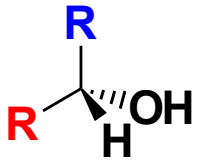


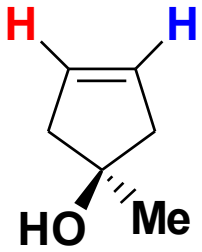


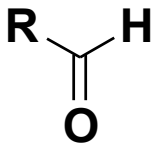


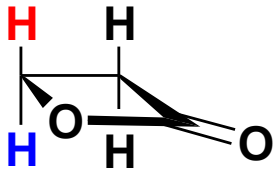
Gruppi Enantiotopici

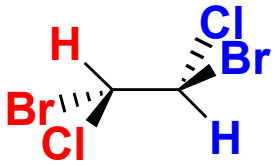
Devono essere presenti elementi di simmetria del II ordine

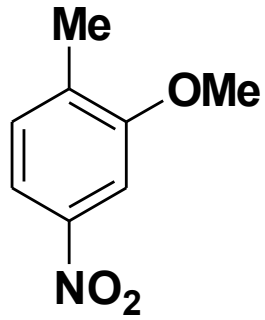


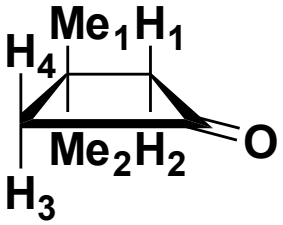


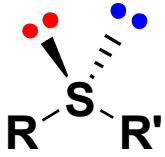


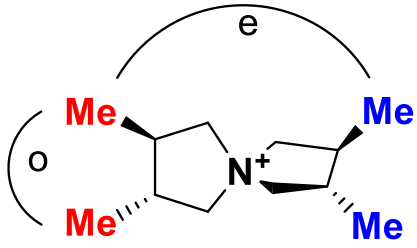






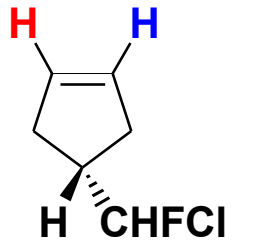


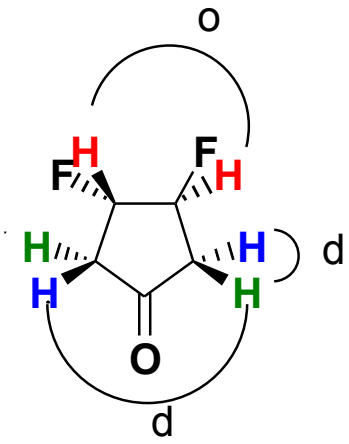


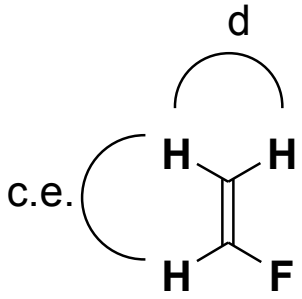


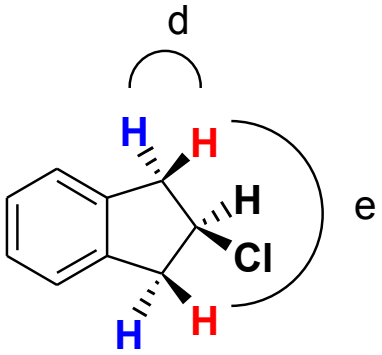
Gruppi Diastereotopici

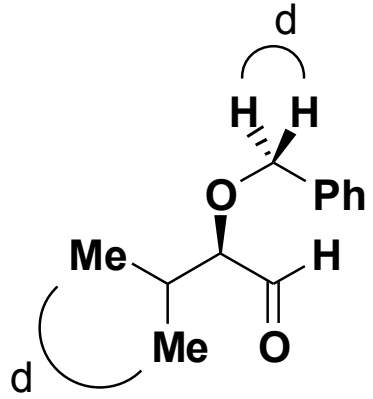
Comprendono tutti i gruppi puntuali

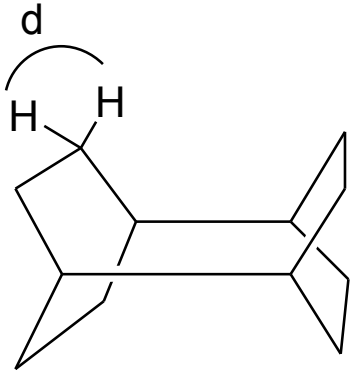






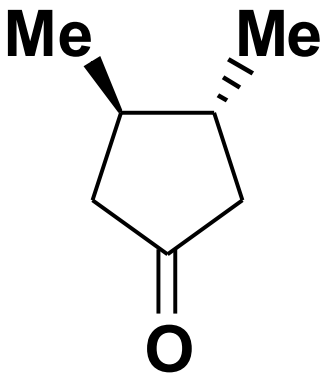


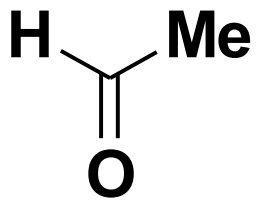


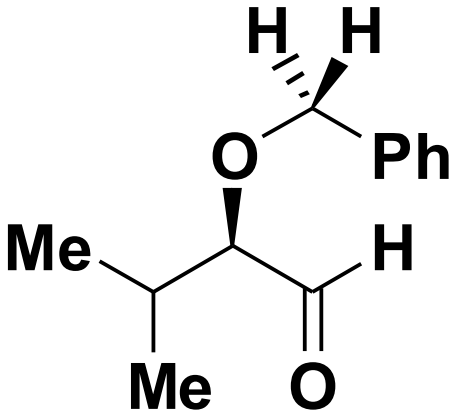


Intorno di Molecole

Carbonili







Topicità relativa	Criterio di simmetria	Gruppi puntuali non compatibili
Omotopicità	C_n $(1<n<\infty)$	$C_{\infty v}$, C_1, C_s, C_i
Enantiotopicità	S_n	$C_{\infty v}$, $D_{\infty h}$ e gruppi chirali
Diastereotopicità	Non sono scambiati da alcun elemento	$C_{\infty v}$, $D_{\infty h}$

ATOMI, GRUPPI, FACCE, SPAZI CHIROTOPICI

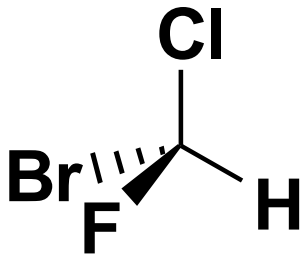
CHIROTOPICO: ogni punto (atomo, segmento, parte, gruppo) di una molecola che risiede in un intorno chirale.

ACHIROTOPICO: ogni punto (atomo, segmento, parte, gruppo) di una molecola che giace in un intorno achirale.

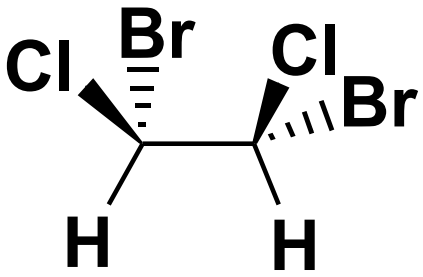
In una molecola chirale tutti i punti sono chirotopici, in una achirale almeno un punto deve essere achirotopico

LA CHIRALITA' E' UNA PROPRIETA' PERVASIVA

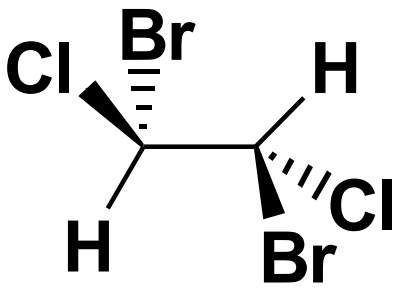
PUNTI CHIROTOPICI/ACHIROTOPICI



C_1



C_s



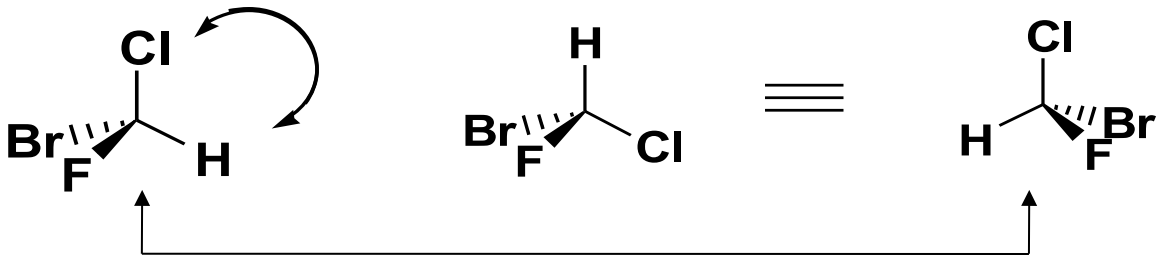
C_i

Come possiamo riconoscere la CHIROTOPICITA' di un punto di una molecola?

Basandoci sul fatto che esso giaccia o meno su un elemento di simmetria del II ordine

MOLECOLE PLANARI: ACHIROTOPICHE

GRUPPI ENANTIOTOPICI: CHIROTOPICI



Una permutazione di due leganti all'atomo di carbonio della struttura originale ha generato una struttura non coincidente con l'originale e da essa distinguibile

Non è un isomero costituzionale, ha le stesse connettività ma diversa disposizione nello spazio

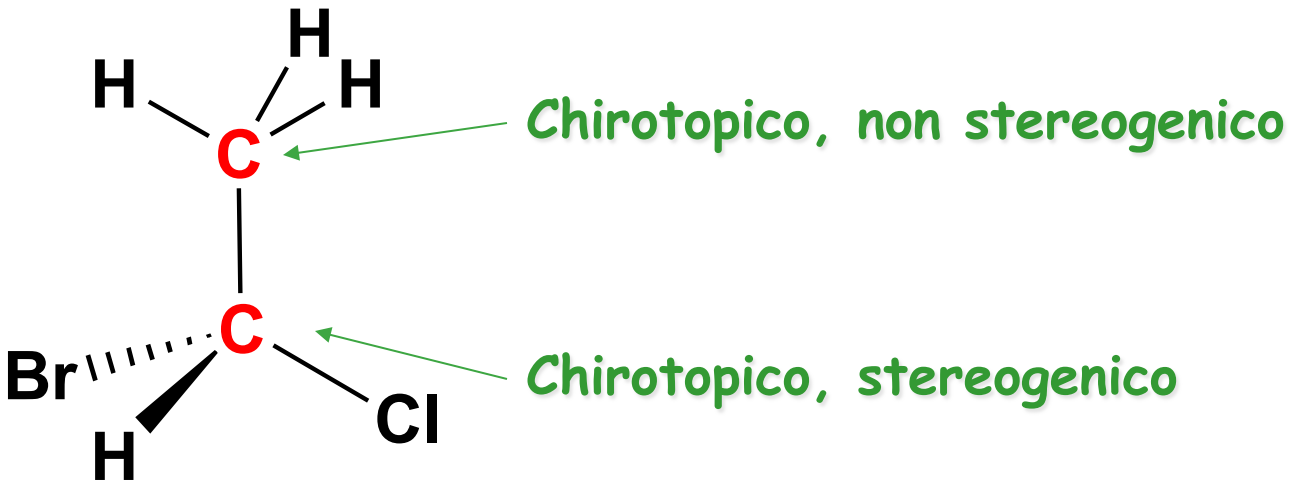
ENANTIOMERI O DIASTREOISOMERI

STEREOISOMERI

isomeri per disposizione spaziale

UNITA' STEREOGENICA

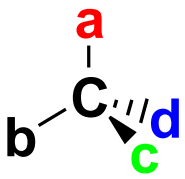
E' una struttura semplice per la quale una permutazione di leganti trasforma la struttura in un suo stereoisomero



CHIRALITA' deriva dalla struttura e dalla geometria di una molecola

STEREOGENICITA' deriva dalla costituzione molecolare e dalla permutazione di leganti

STEREOCENTRI O CENTRI STEREOGENICI

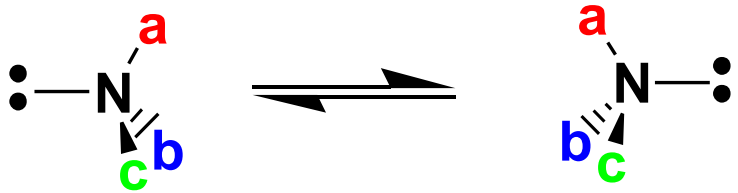


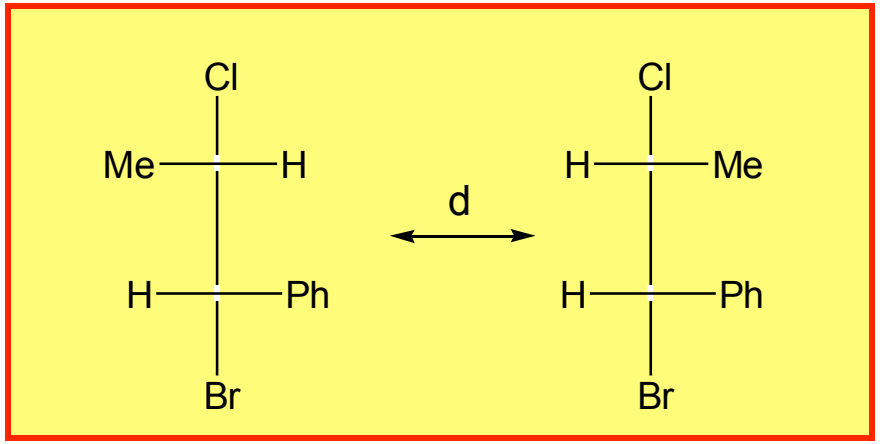
Atomi di carbonio tetrasostituiti in maniera diversa

Altri elementi che possono essere stereocentri:

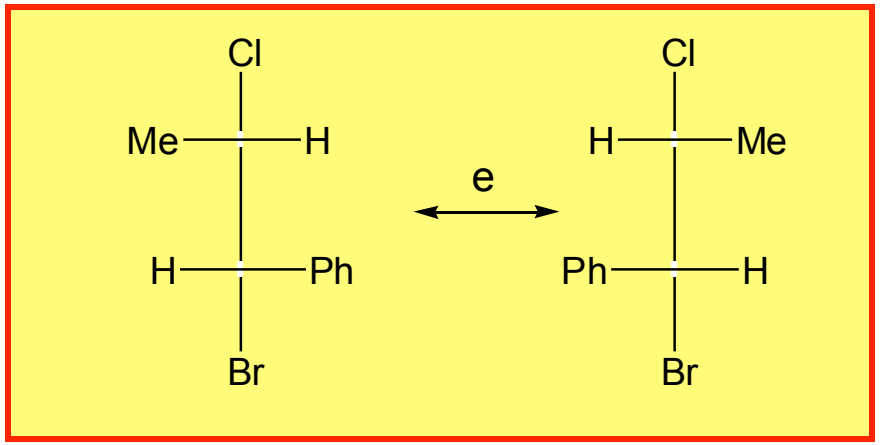
Si, Ge, Sn, Pb tetrasostituiti

N, P, As, Sb, S, Se trisostituiti





EPIMERI



In presenza di n stereocentri:

2^n STEREOISOMERI

Una molecola *meso* è una molecola in cui è presente un piano di simmetria che correla i carboni con quattro sostituenti diversi

Struttura *meso* è uno stereoisomero achirale di un set di stereoisomeri che ne contiene di chirali

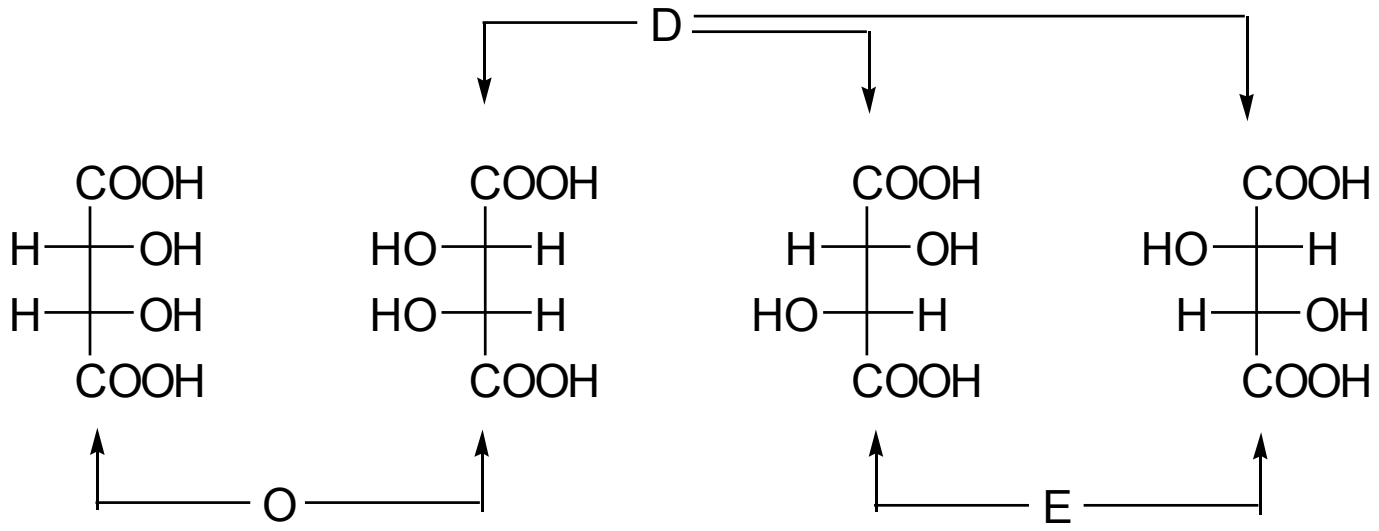
2^{n-1}

n dispari

$2^{n-1} + 2^{(n-2)/2}$

n pari

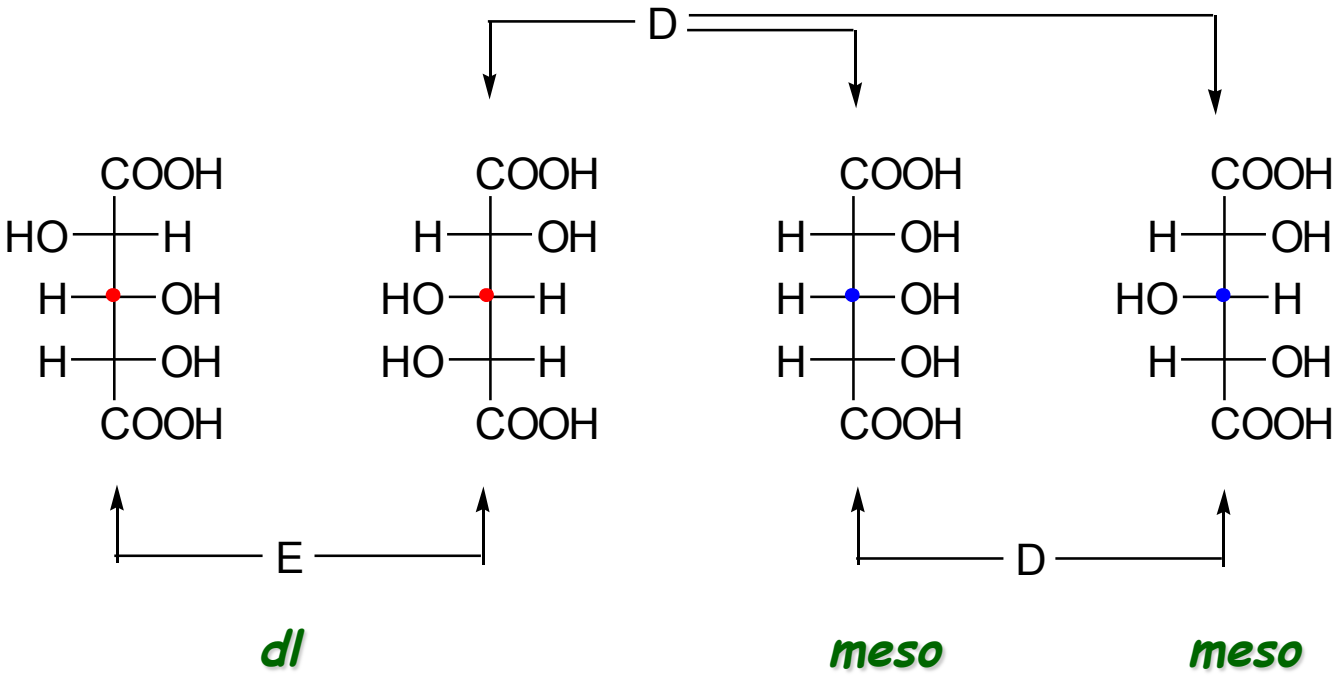
ACIDO TARTARICO



meso ***dl***

Due stereocentri – tre stereoisomeri

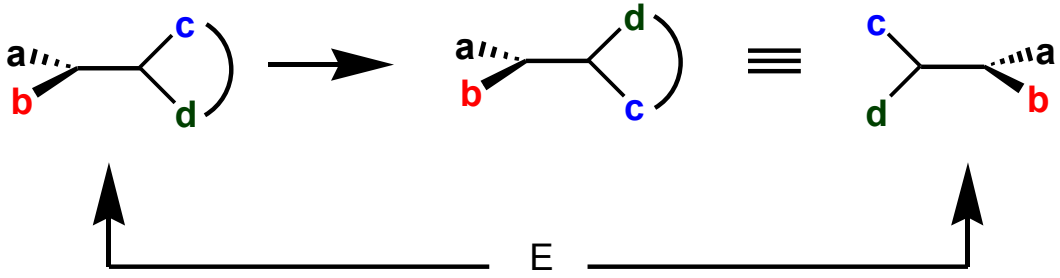
ACIDO TRIIDROSSIGLUTARICO

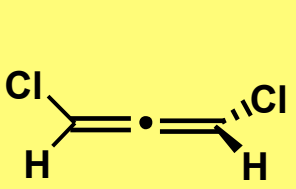


Tre stereocentri – quattro stereoisomeri

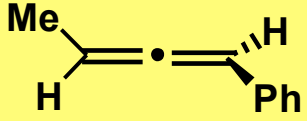
- chirotopico, non stereogenico
- achirotopico, stereogenico

ALTRI ELEMENTI STEREOGENICI

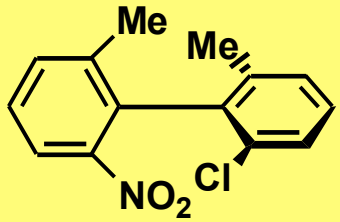




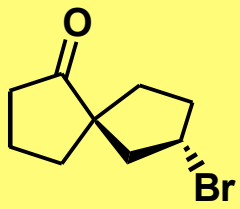
C_2



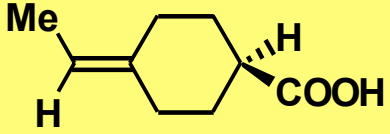
C_1



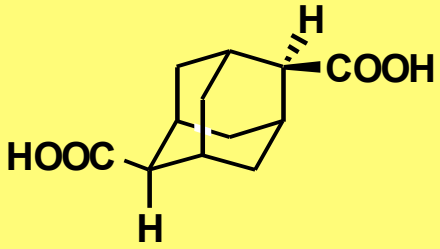
C_1



C_1

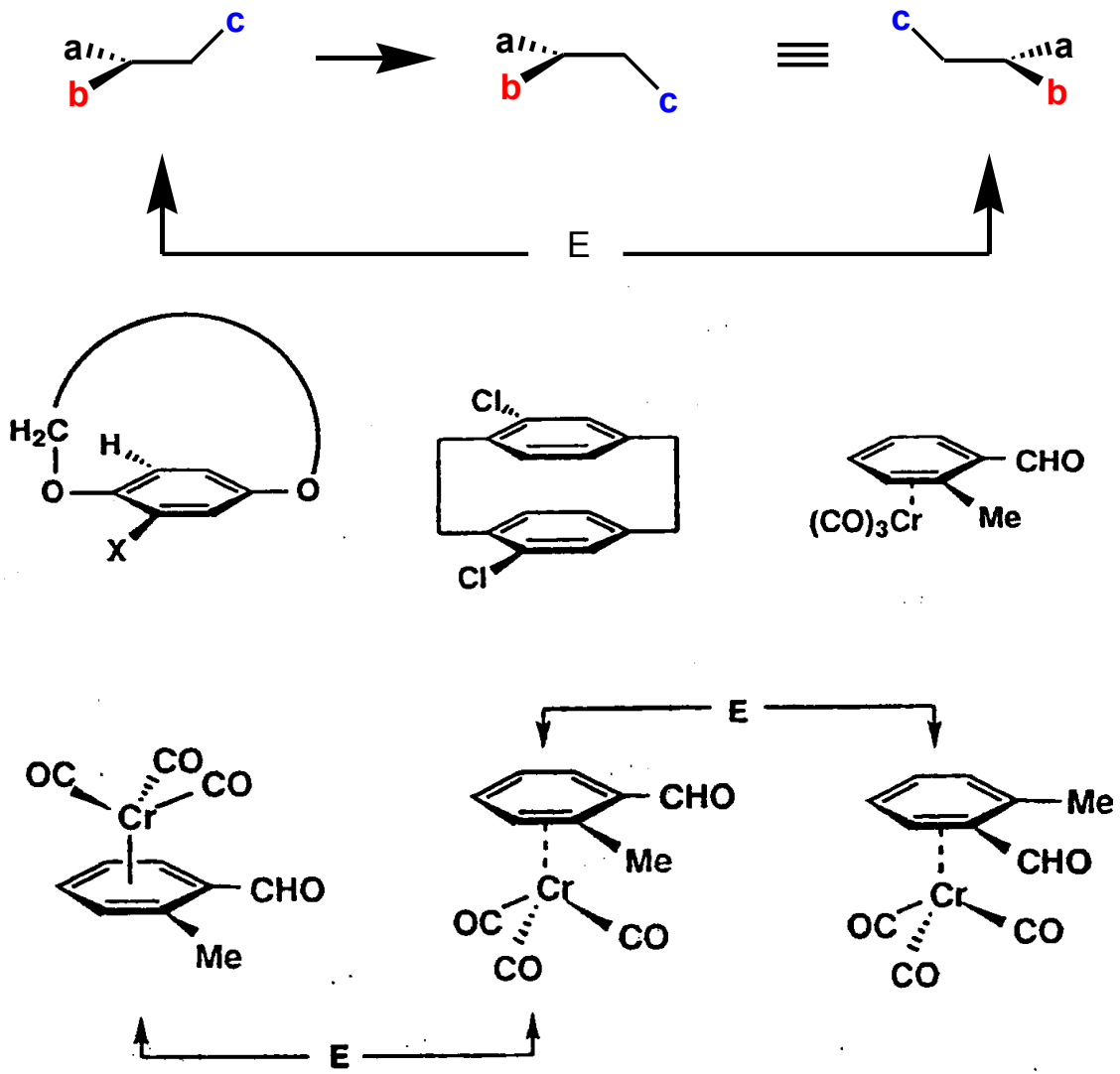


C_1



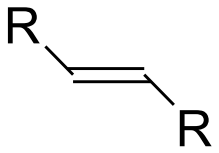
C_2

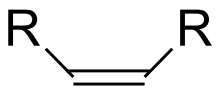
ALTRI ELEMENTI STEREOGENICI



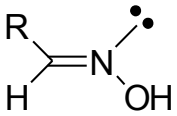
ELEMENTI STEREOGENICI

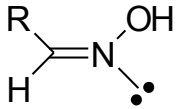
che generano solo diastereoisomeri



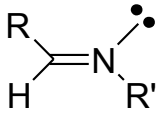


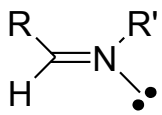
Alcheni



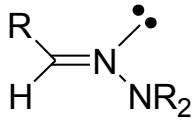


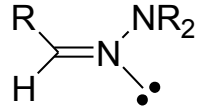
Ossime



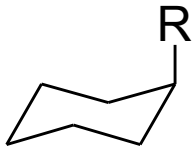


Immine





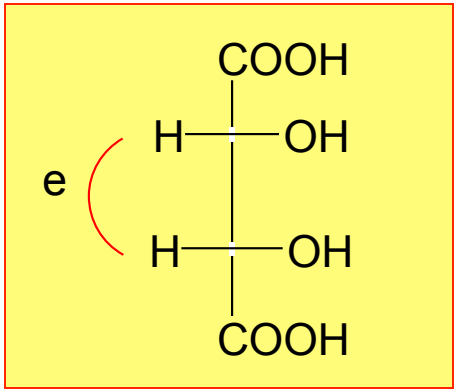
Idrazoni

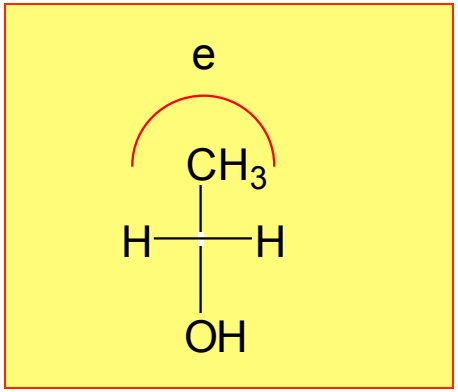


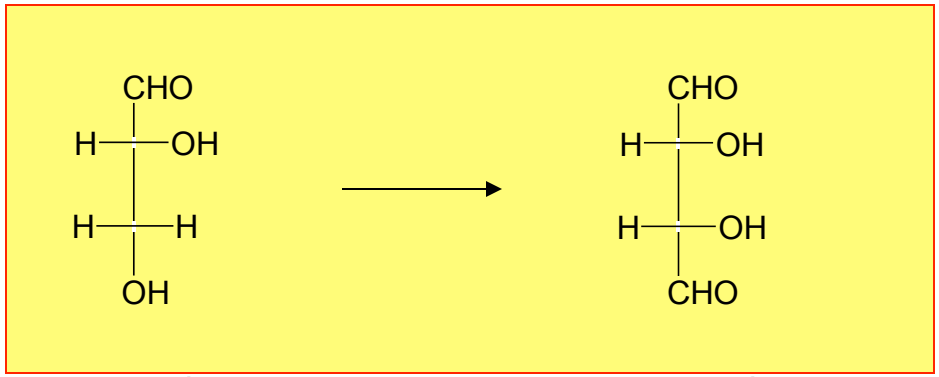
Cicloesani sostituiti

PROCHIRALITA' E PROSTEREOGENICITA'

La prochiralità è la proprietà di una struttura achirale di diventare chirale se uno dei suoi leganti viene sostituito da uno nuovo (secondo Hanson)







(pro)^p-CHIRALE (Mislow e Siegel)

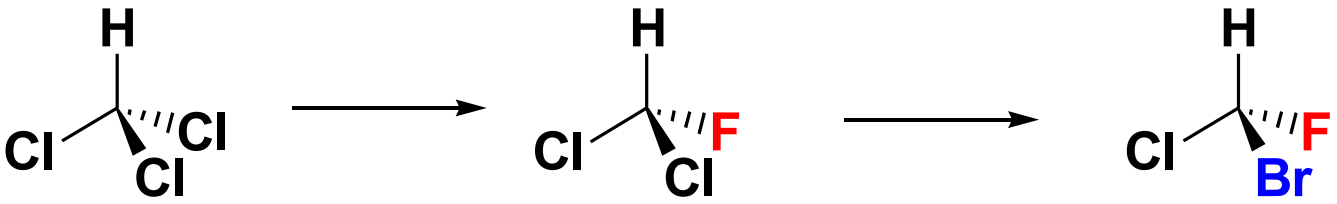
(pro)^p-Chirale (con p=1,2,3) è ogni oggetto finito achirale che può essere desimmetrizzato a dare un oggetto chirale con un numero massimo p di sostituzioni di un suo punto diverso dal primo

Le sostituzioni sono mirate alla distruzione degli elementi di simmetria del II ordine

C_s, C_i, S_{2n}	(pro)^1-chirale
C_{nh}, C_{nv}	(pro)^2-chirale
D_{nd}, D_{nh}, solidi platonici	(pro)^3-chirali

$(pro)^2$-chirale

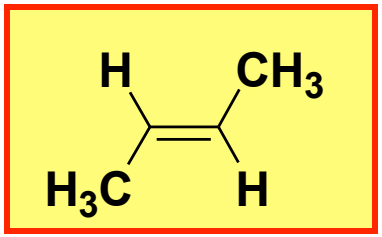
$(pro)^2$ $(pro)^1$



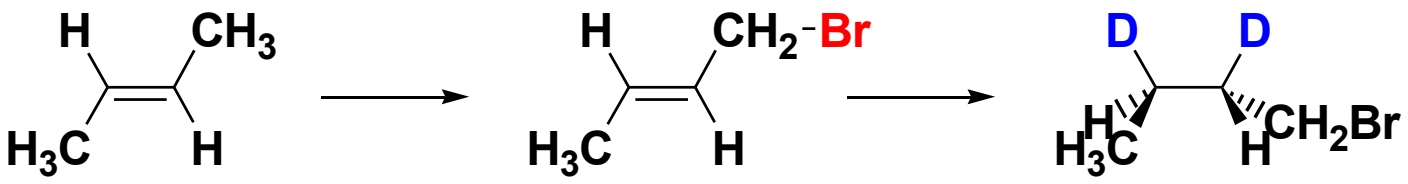
C_{3v} C_s C_1

$C_3 + 3\sigma_v$ σ C_1

$(pro)^2$-chirale

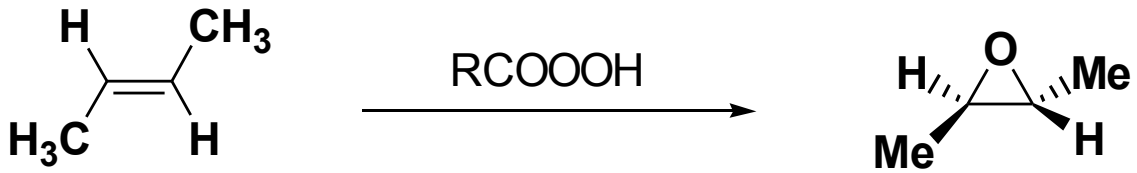


$(pro)^2$ $(pro)^1$



C_{2h} C_s C_1

$C_2 + \sigma_h + i$ σ C_1

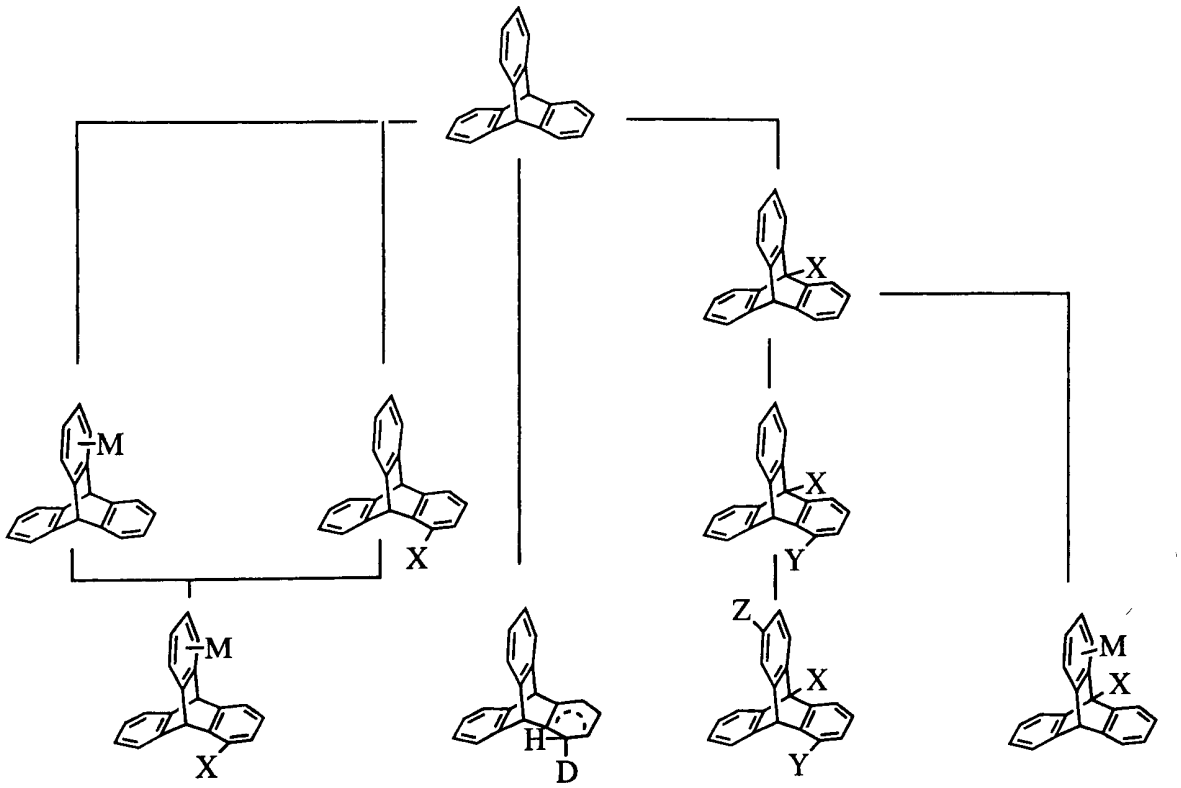


C_{2h} C_2

$C_2 + \sigma_h + i$ C_2

Prochirality according to Mislow & Siegel

Any finite, achiral object that can be desymmetrized into a chiral object by <u>at most</u> p stepwise replacements of a point by a differently labeled one is defined $(pro)^p$-chiral (p =1, 2, 3), and $(pro)^p$-chirality is the corresponding property. $(Pro)^0$-chiral is chiral (*JACS* **1984**,*106*, 3319).



p

3

2

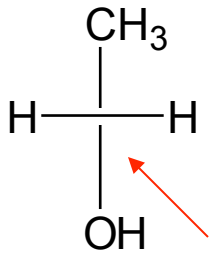
1

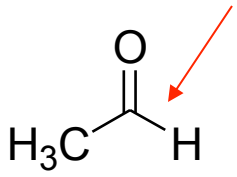
0

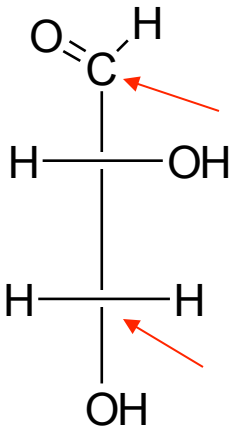
Any productive desymmetrization step must occurr outside a symmetry element of the 2nd order. At least one of these elements must disappear upon each desymmetrization step. The maximum number of productive steps defines the p level of $(pro)^p$-chirality. For triptycene p = 3

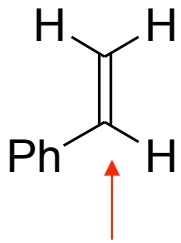
Unita' Prostereogeniche

Una struttura che può venire convertita in unità stereogenica per opportuna sostituzione di un suo legante

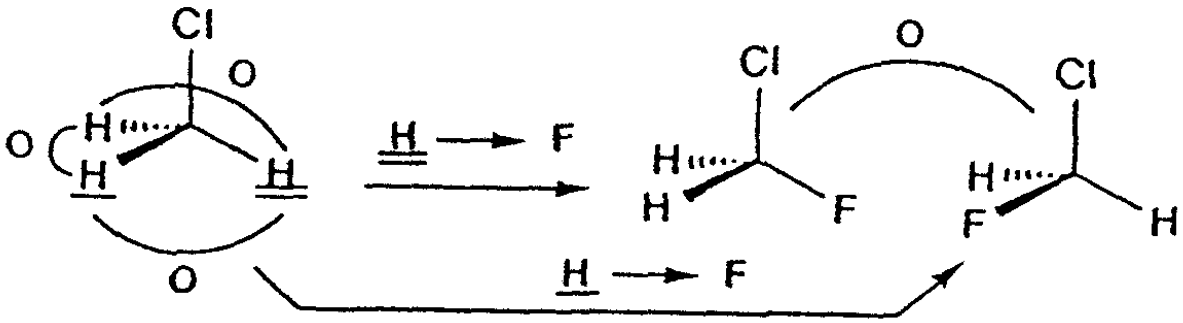








Gruppi Omotopici

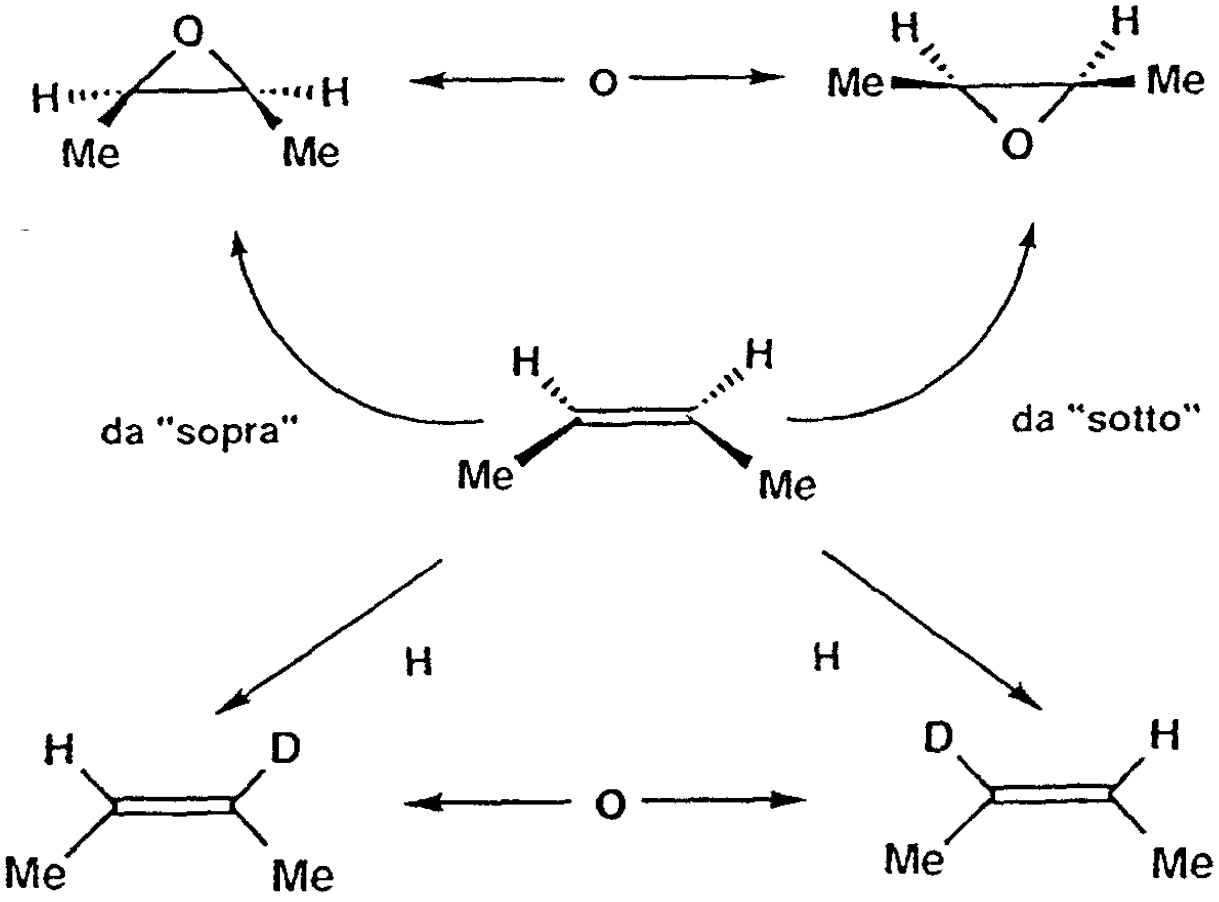


La sostituzione non genera isomeri

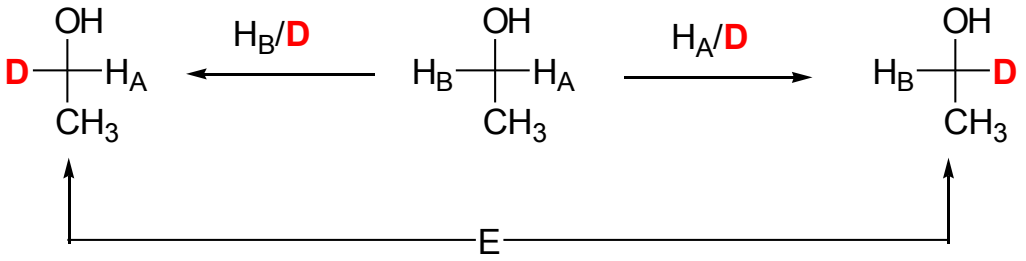
Non cambia il livello di stereogenicità

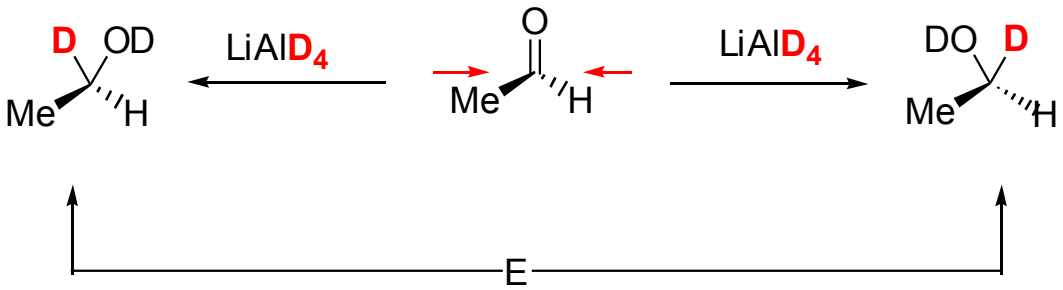
Si abbassa semplicemente la simmetria della molecola

Gruppi Omotopici



Gruppi Enantiotopici

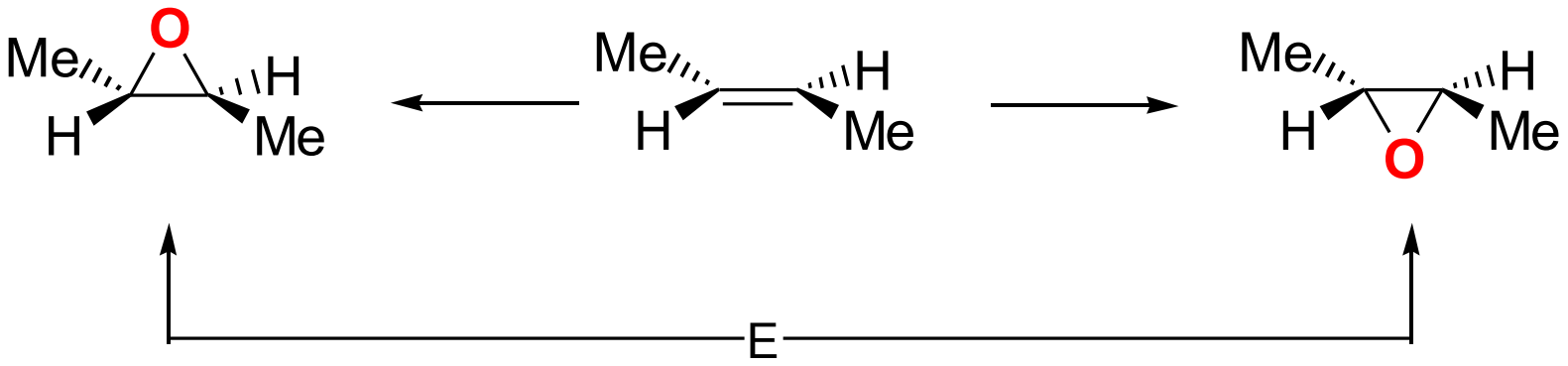


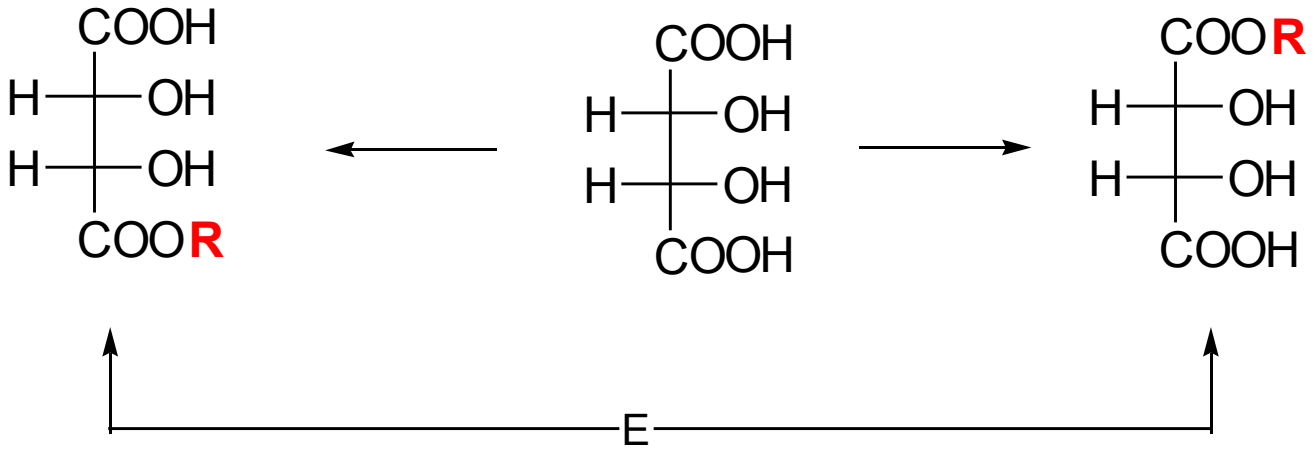


La sostituzione genera enantiomeri

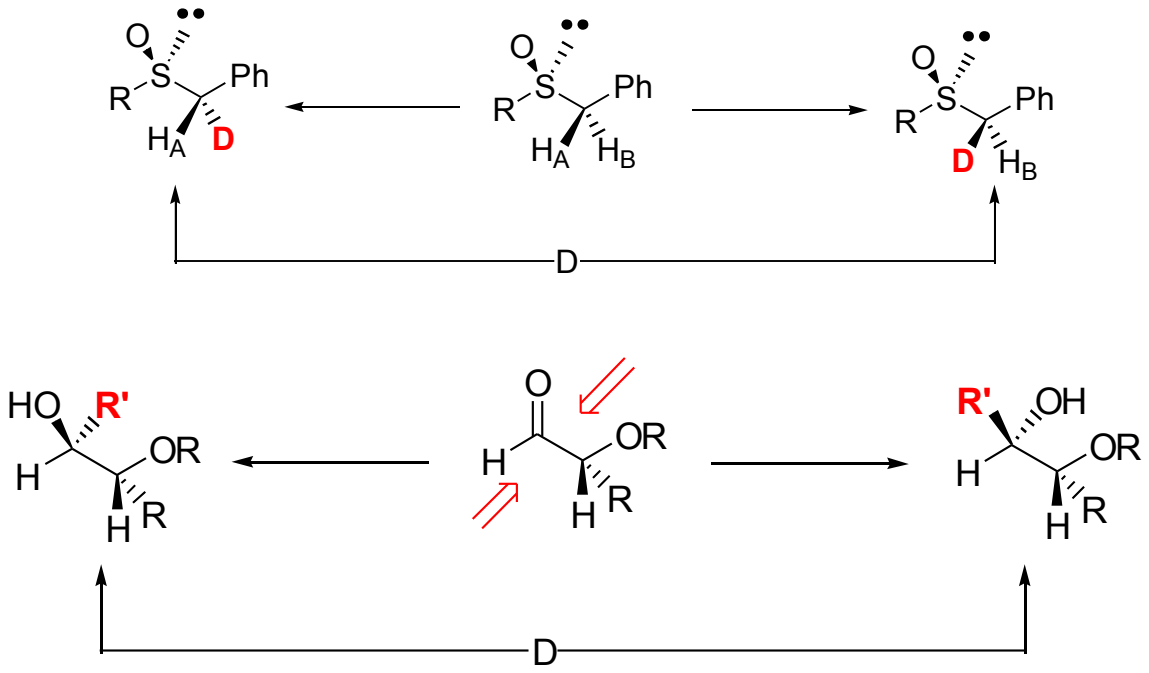
Trasforma unità prostereogeniche in stereogeniche

Gruppi Enantiotopici





Gruppi Diastereotopici

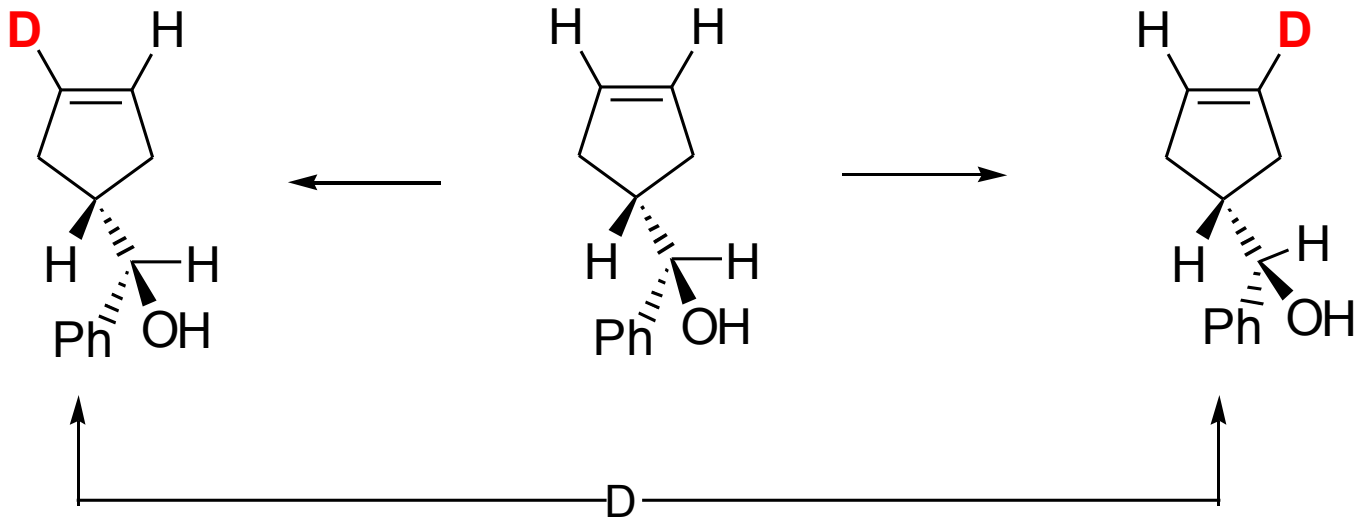


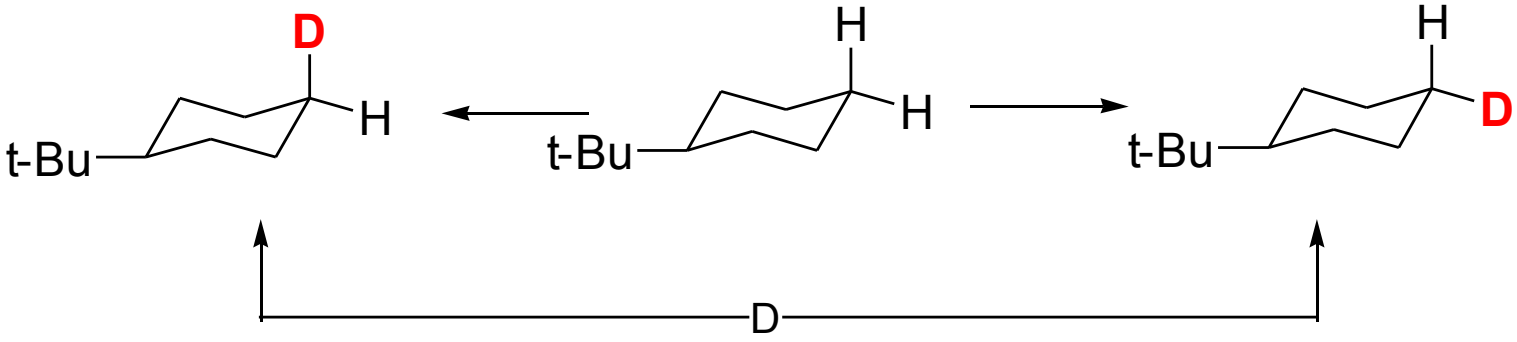
La sostituzione genera diastereoisomeri

Trasforma unità prostereogeniche in stereogeniche

Se possibile abbassa la simmetria del sistema

Gruppi Diastereotopici





Configurazione

(Mislow, 1965)

Posizione relativa degli atomi nello spazio cha caratterizza un particolare stereoisomero

Enantiomeri: configurazione opposta
Diastereoisomeri: configurazione diversa

Conformazione

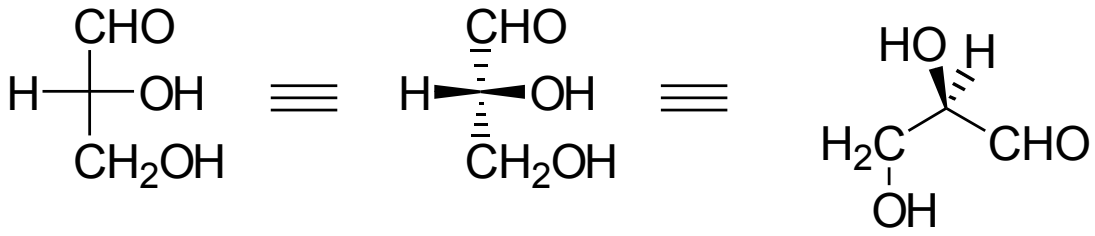
(Mislow, 1965)

Particolare geometria di una molecola che dipende da certi valori di lunghezza di legame e di angoli, semplici o diedri, fra i legami

Infinite conformazioni all'interno di una determinata configurazione

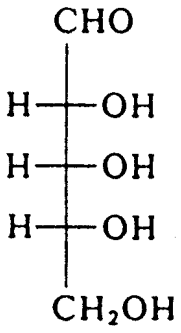
CONVENZIONE DI FISHER

Convenzione arbitraria

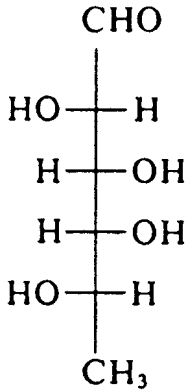


(+)-D-GLICERALDEIDE

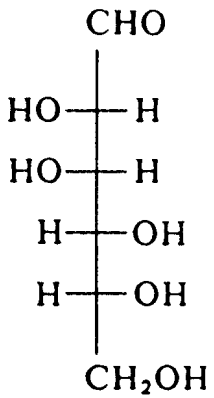
utilizzata per gli zuccheri e amminoacidi



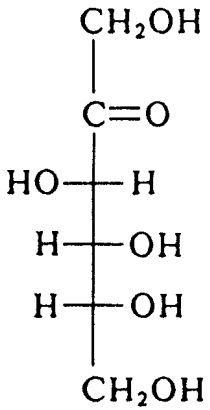
D-ribose



L-fucose

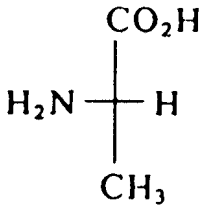


D-mannose

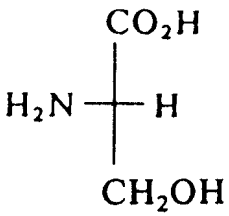


D-fructose

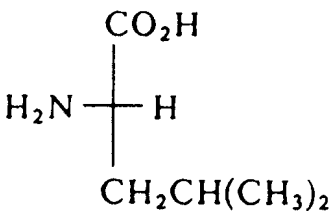
All of the amino acids found in proteins have the L-configuration as illustrated for alanine, serine, and leucine.



L-alanine



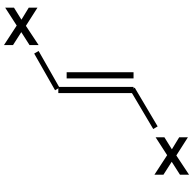
L-serine



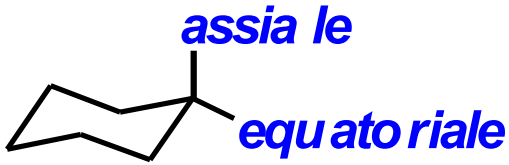
L-leucine

Descrittori di Configurazione di Unità Stereogeniche

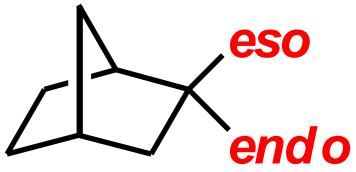
Unità stereogeniche per le quali scambio di legante genera diastereoisomeri



trans, E



cis, Z



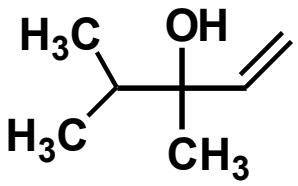
Descrittori di Configurazione di Unità Stereogeniche

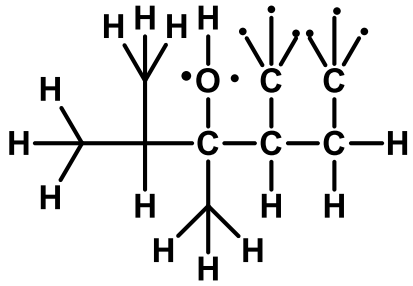
Unità stereogeniche per le quali scambio di legante genera enantiomeri

REGOLE CIP, 1951 (CIP = Chan, Ingold e Prelog)

1. Identificazione di quali e quanti elementi stereogenici sono presenti
2. Costruzione del grafico ramificato intorno agli elementi stereogenici che rappresenti la connettività degli atomi legati all'elemento.
3. Determinare in base alle regole le priorità dei leganti
4. Attribuire alla configurazione l'appropriato descrittore sulla base delle priorità facendo riferimento ad uno standard esterno arbitrario

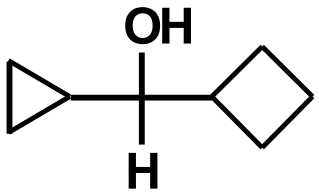
Grafico Ramificato

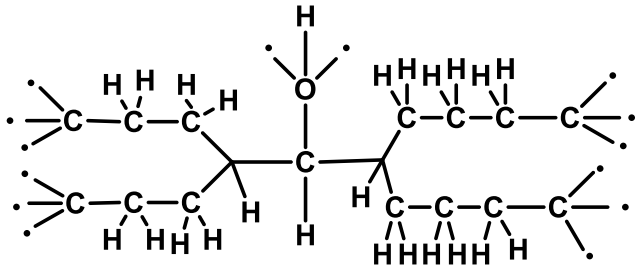




4-metil-1-penten-3-olo

- = atomo fantasma



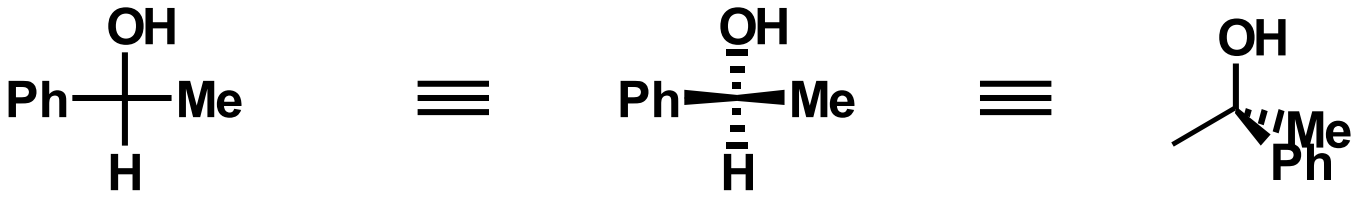


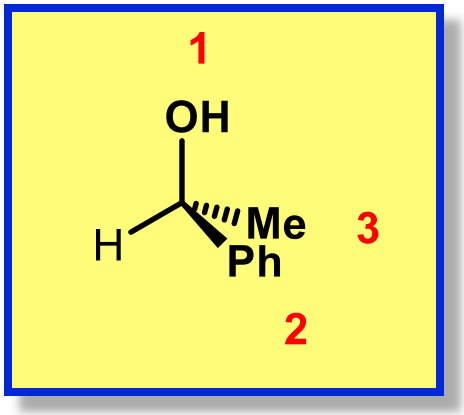
Ciclopropil ciclobutil carbinolo

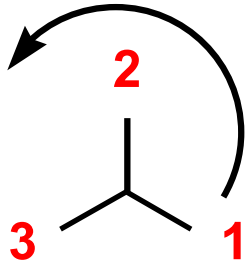
Sottoregole REGOLE CIP

1. Atomi a numero atomico maggiore precedono atomi a numero atomico minore
2. Atomi a numero di massa maggiore precedono atomi a numero di massa minore
3. Doppi legami cis precedono doppi legami trans
4. Se nei leganti ci sono degli stereocentri quelli R precedono quelli S. Se ci sono più stereocentri: RR > SS; RS > SR.

Descrittori di Configurazione di Centri Stereogenici



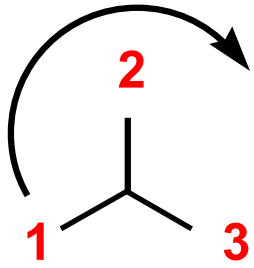




Antiorario

S

sinistrus

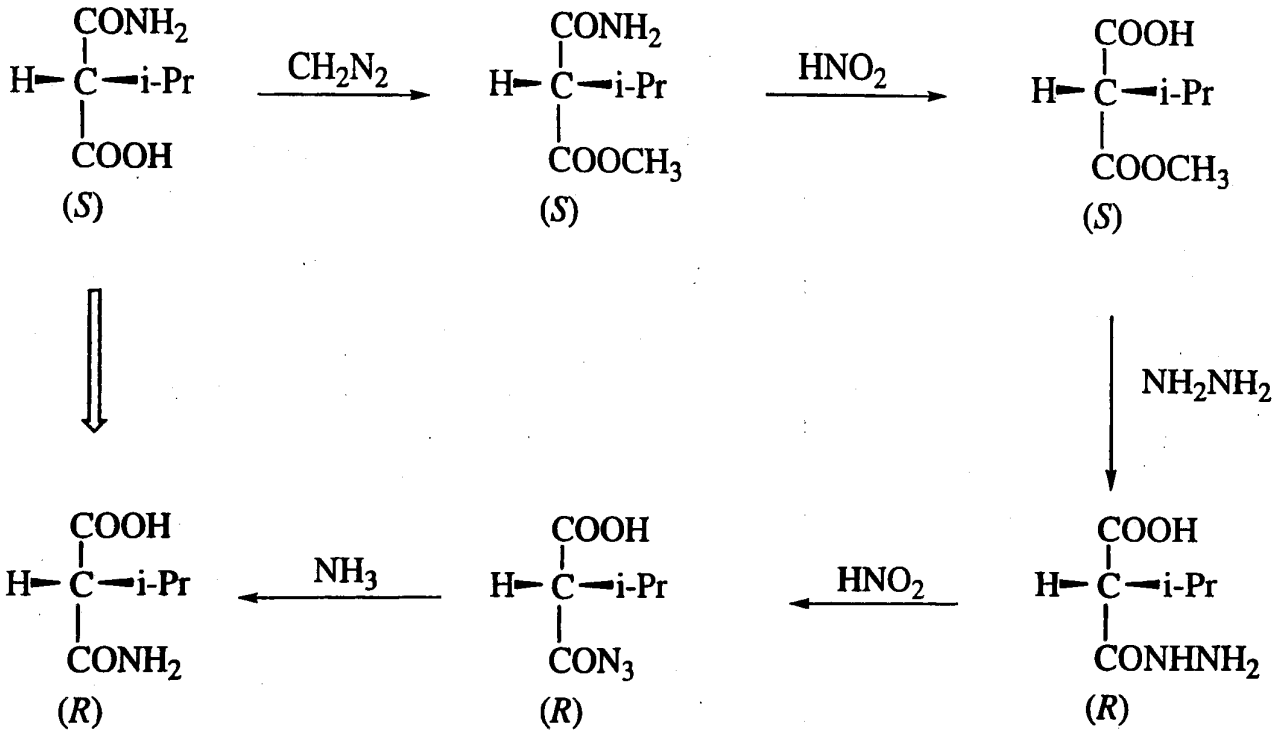


Orario

R

rectus

CIP stereodescriptors do not describe chirality

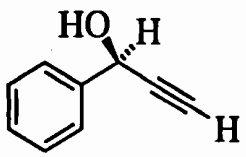


E. Fischer, *Ber.d.D.Chem.Gesellsch.* **1914**, *47*, 3181

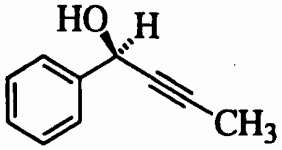
On passing from (+)- to (-)-isopropylmalonamic acid the ligands at the stereogenic center maintain their relative "position". Still the stereodescriptor changes from (*S*) to (*R*).

Chirality and stereogenicity are different properties of the molecule

Also Cahn, Ingold, and Prelog strongly and "authoritatively" contributed to the confusion between chirality and stereogenicity. They entitled their 1966 paper on the CIP rules: "Specification of Molecular Chirality", as if the stereochemical descriptors *R* and *S* (and the like) were intended to describe chirality rather than stereogenicity. Obviously, the symbols *R* and *S* solely describe the relative disposition of ligands around a stereogenic unit. The chirality of the molecular ensemble does not depend on the ligands' "priority" or "sequence order", but exclusively on the absence of symmetry. Indeed, chiral molecules sharing the same disposition of structurally similar ligands around structurally identical units can have different CIP descriptors, as in:

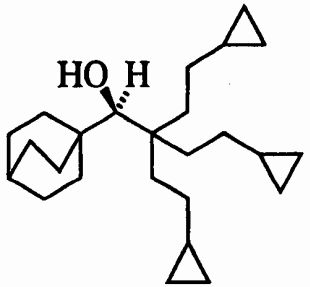


(*S*)



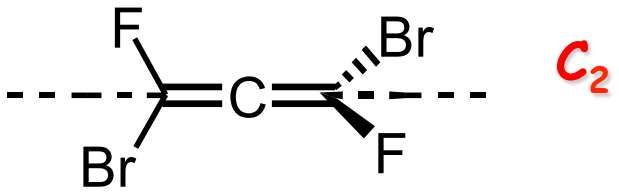
(*R*)

In addition chiral structures do exist to which the *R/S* symbols cannot be assigned:

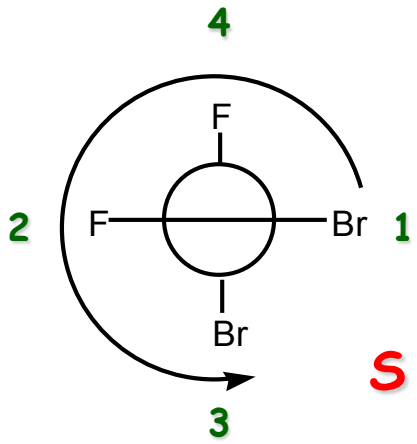


Descrittori di Configurazione di Altri Elementi Stereogenici

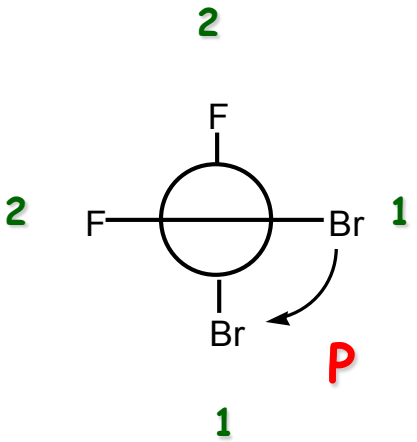
Alleni (R,S o M,P)



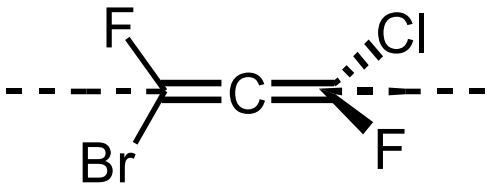
C_2



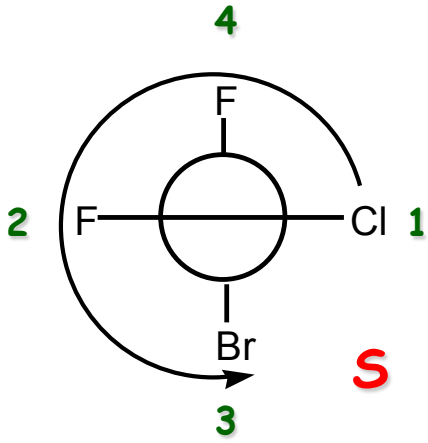
S



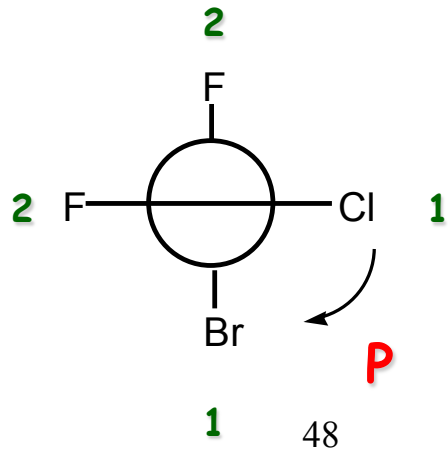
P



C_1



S

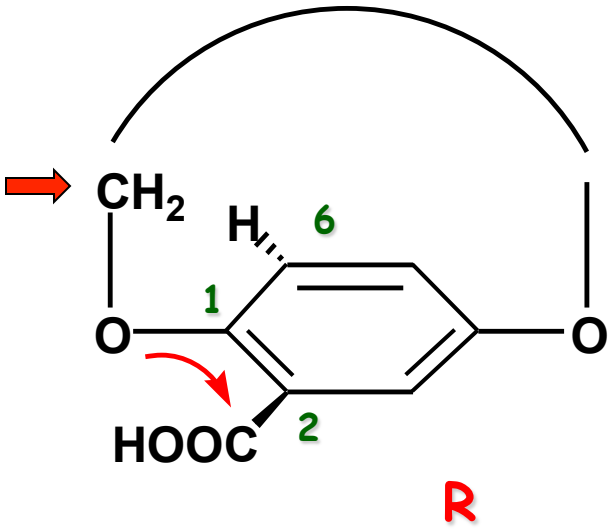


P

Descrittori di Configurazione di Altri Elementi Stereogenici

Composti ad ansa

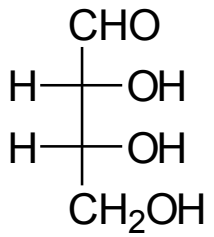
Atomo pilota



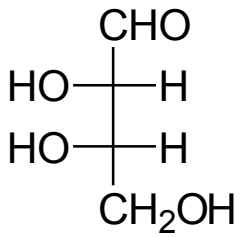
C(1) – C(2) – COOH > C(1) – C(6) – H

DESCRITTORI DI CONFIGURAZIONE RELATIVA

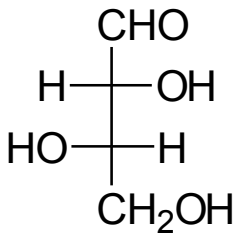
treo e eritro



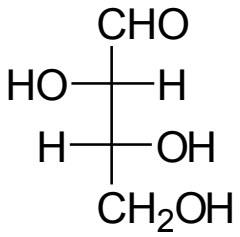
D-ERITROSIO



L-ERITROSIO



L-TROSIO



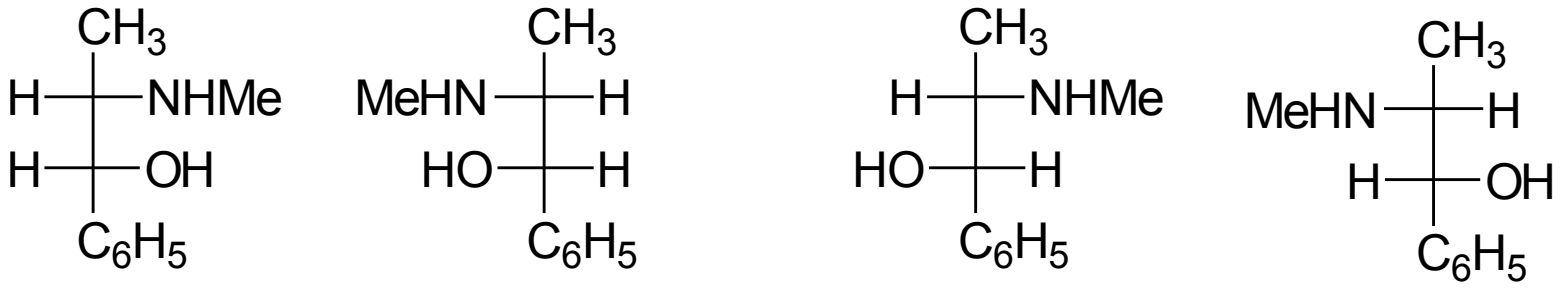
D-TROSIO

eritro

treo

DESCRITTORI DI CONFIGURAZIONE RELATIVA

efedrina



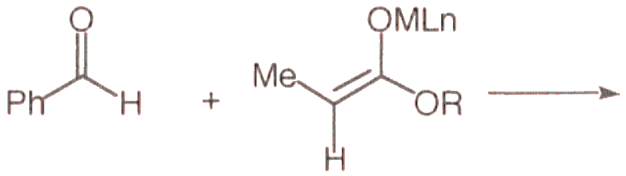
Simile a

D-ERITROSIO L-ERITROSIO L-TROSIO D-TROSIO

eritro **treo**

CONVENZIONE IUPAC

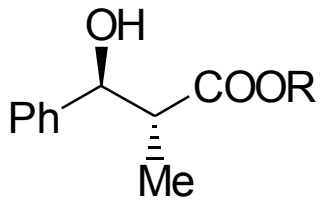
Si definiscono le configurazioni relative dei singoli stereocentri

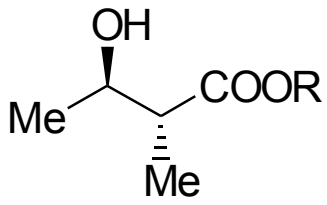


2R,3R ⟷ (**e**) **2S,3S** ⟷ (**d**) **2S,3R** ⟷ (**e**) **2R,3S**

Se abbiamo molecole raceme possiamo indicarle come:

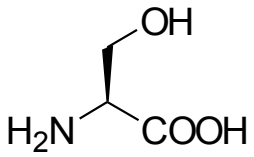
(RR/SS) – (RS/SR) o (R*,R*) – (R*,S*)

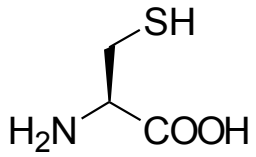




(R*,S*) **(R*,R*)**

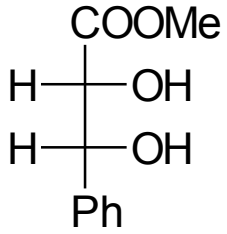
Notazioni diverse – stessa serie sterica!



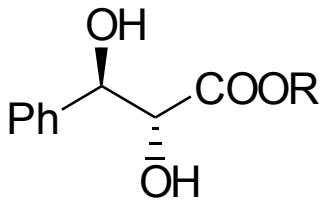


(S)-serina **(R)-cisteina**

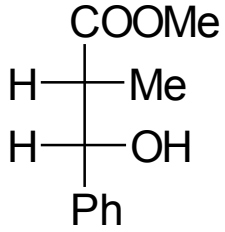
CONVENZIONE IUPAC – nomenclatura carboidrati



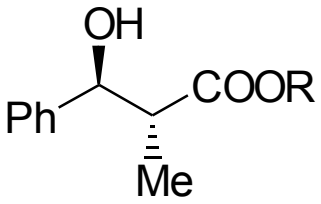
≡



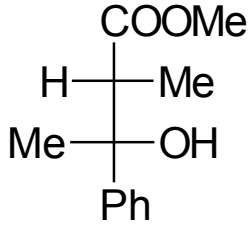
eritro



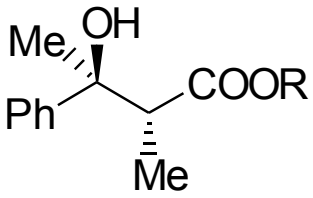
≡



(R*,S*)-eritro



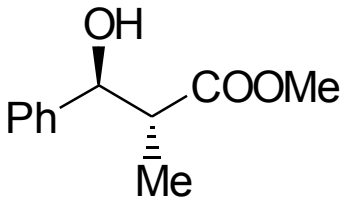
≡



eritro o treo?

Regola di Prelog e Seebach (1982)

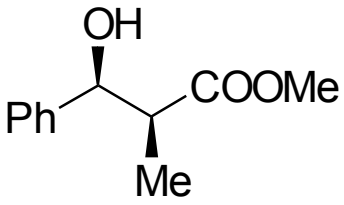
l (like)



R*,S*

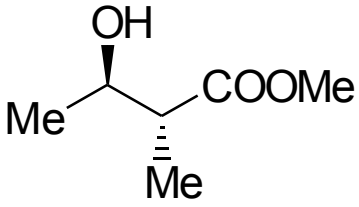
u
CONFIG. OPPOSTA

u (unlike)



S*,S*

l
CONFIG. UGUALE

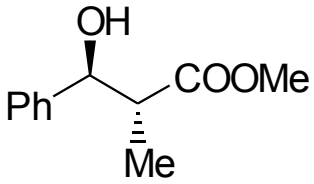


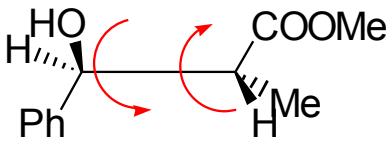
l R*,R*

Regola di Carey e Kuehne (1982)

PARF
priorità antiriflessiva

PREF
Priorità riflessiva

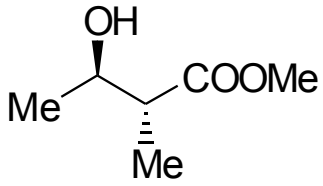


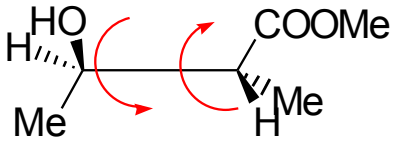


COOMe>Me>H

OH>Ph>H

PARF





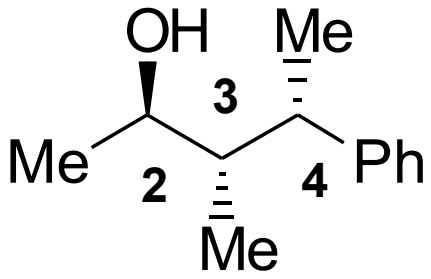
COOMe>Me>H

OH>Me>H

PARF

Notazioni uguali per la stessa serie sterica

Regola di Carey e Kuehne



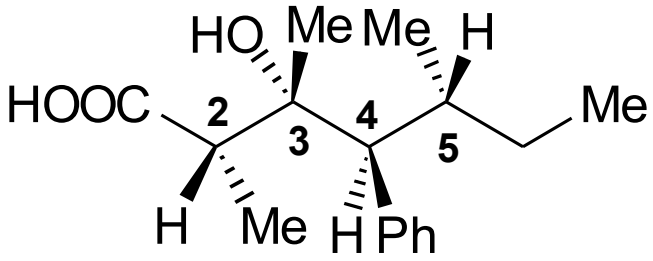
2,3-PARF-3,4-PREF

- Nessun vantaggio rispetto alle regole CIP
- non si risale facilmente al corretto steroisomero
- non vengono definiti tutti gli stereocentri

Regola di BREWSTER (1986)

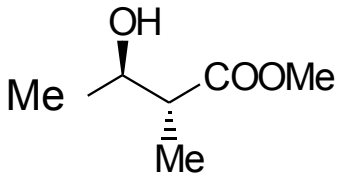
(Carey e Kuehne + Prelog)

1. Numerare la coppia di stereocentri interesse
2. Mettere un riferimento esterno per risalire alla stereochimica assoluta

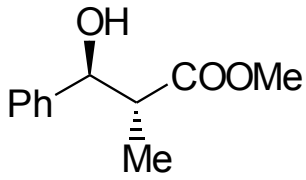


2S, 3R, 4S, 5R (IUPAC, nota la configurazione assoluta)
2S*, 3R*, 4S*, 5R* (IUPAC, nota la configurazione relativa)
u,u,u (Prelog)
2,3-PREF-3,4-PREF-4,5-PREF (Carey/Kuelne)
2S (2ref, 3u,4l,5u) (Bruester)

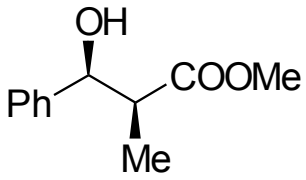
METODO di MASAMUNE (1980)



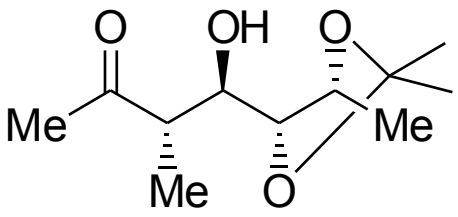
anti



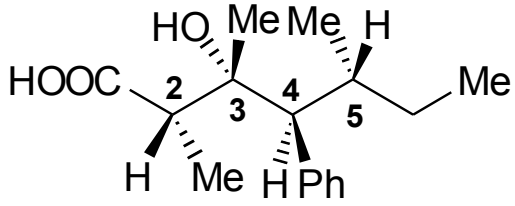
anti



syn

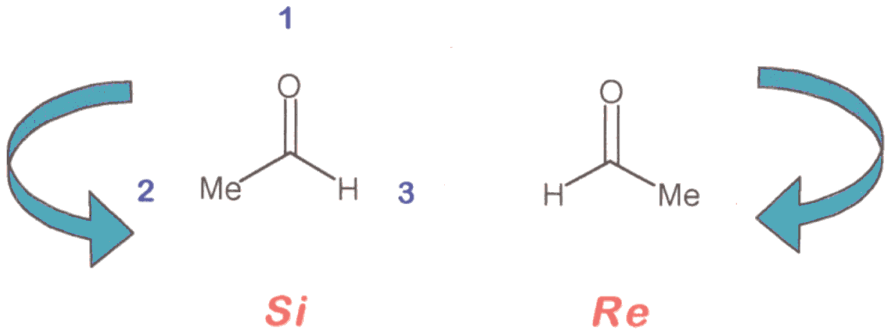


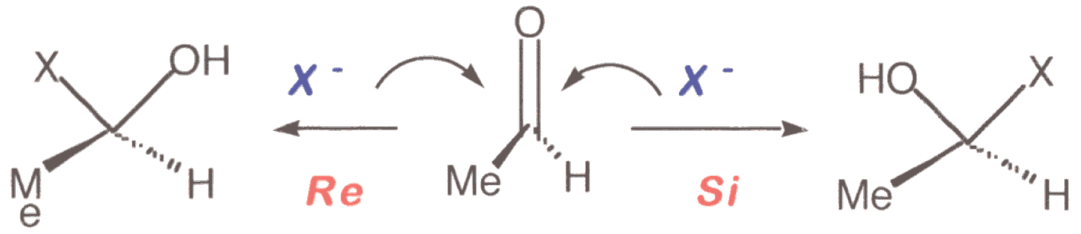
2,3-anti-3,4-anti-4,5-syn
2,4-syn//3,5-anti



2S 2,3-syn-3,4-anti-4,5-anti
2,4-anti//3,5-syn

DESCRITTORI DI UNITA' PROSTEREOGENICHE

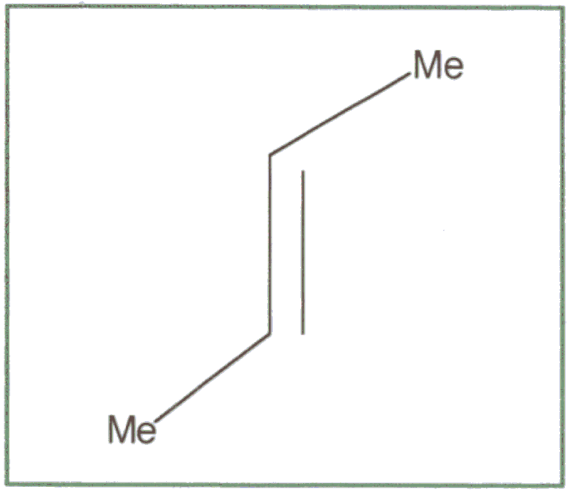


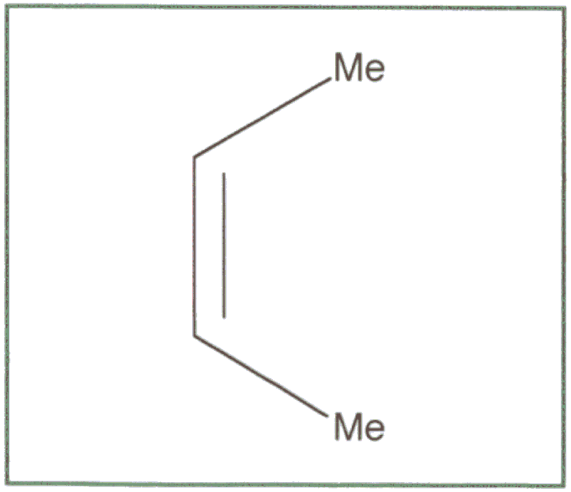


X = D (*R*)
X= Ph (*S*)

X = D (*S*)
X= Ph (*R*)

ALCHENI





Facce: enatiotopiche

Superiore: *Si/Si* lk
Inferiore: *Re/Re* lk

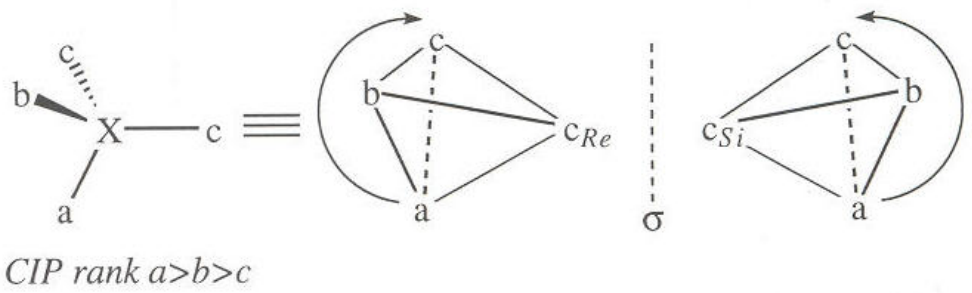
Facce: omotopiche

Superiore: *Si/Re* ul
Inferiore: *Re/Si* ul

Descrizione di unità prostereogeniche - *Re/Si* vs pro-*R* e pro-*S*

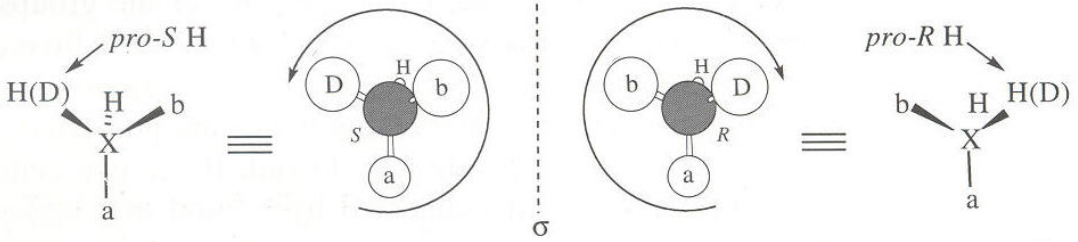
Nel caso di sostituenti enantio o diastereotopici si possono usare i due seguenti descrittori:

Re/Si



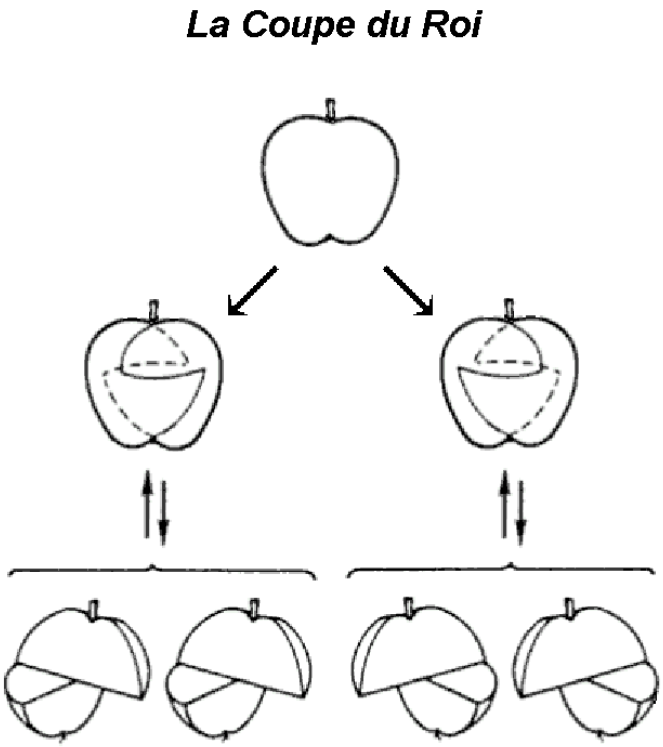
CIP rank a>b>c

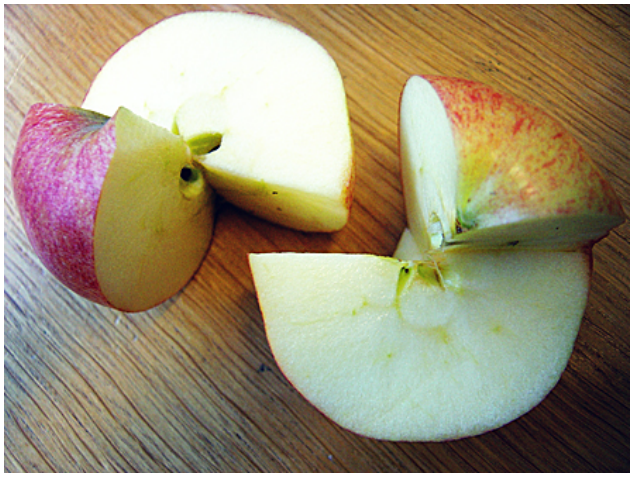
pro-R e pro-S



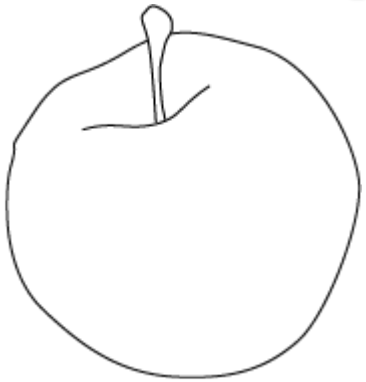
Utilizzata principalmente dai biochimici

Le Coupe du Roi (il taglio del Re)



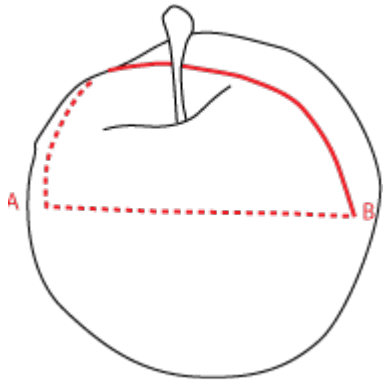


1



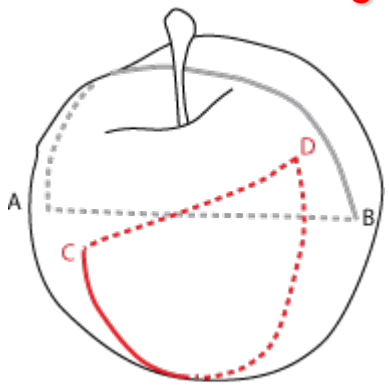
Place the apple in front of you, top up, as if you'd just naturally place it on a surface as seen in this picture. Also, make sure you have a small knife ready.

2



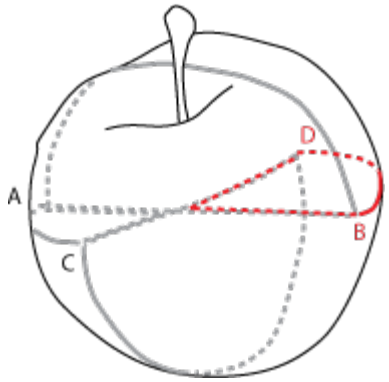
First, you cut your apple halfways through as shown in this picture. You will thus create a cut that will start at the top and end halfways into the apple. I have labelled the end points of that cut A and B, as you will have to locate those later for further cuts.

3



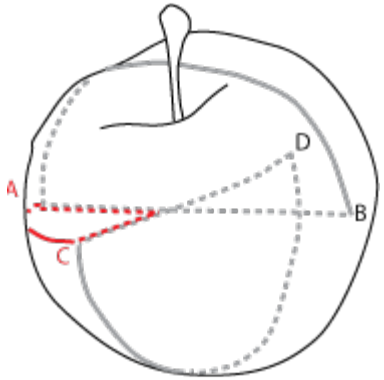
Now you will cut your apple from the bottom, perpendicularly to the first cut - as shown on this picture. In other words, you'll slice that apple halfways through from the other side, and at a right angle to the first cut. The end points of this cut are labelled C and D for later reference

5



The last cut will be another horizontal quarter slice, now connecting end points B and D, as seen in this picture

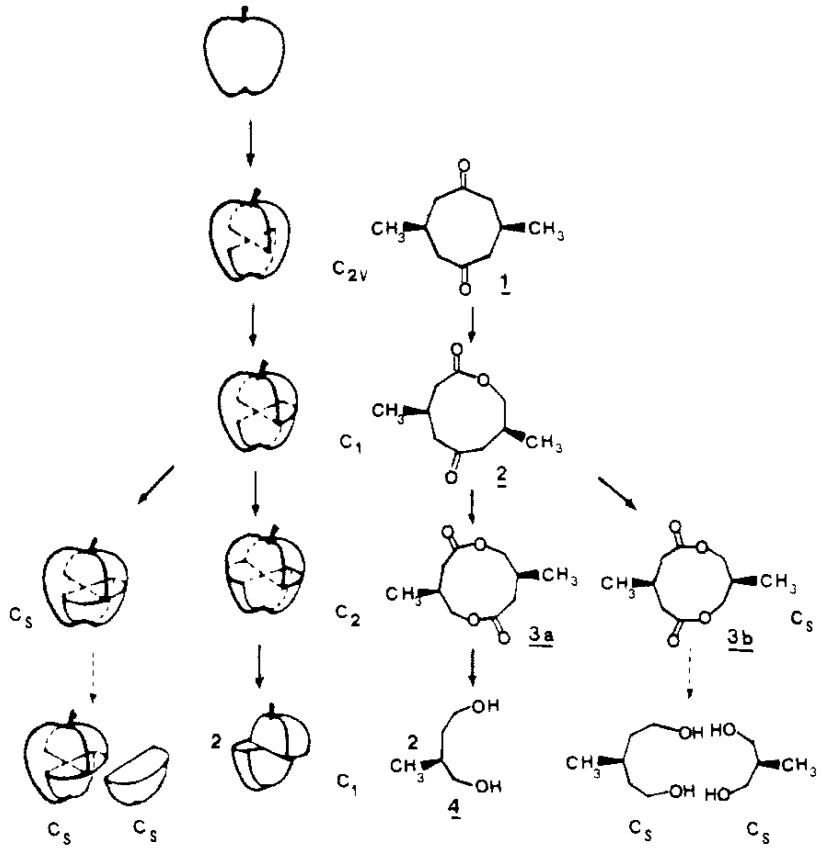
4

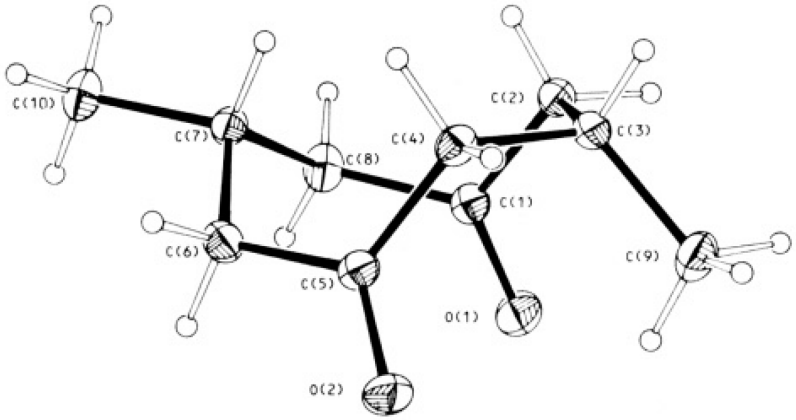


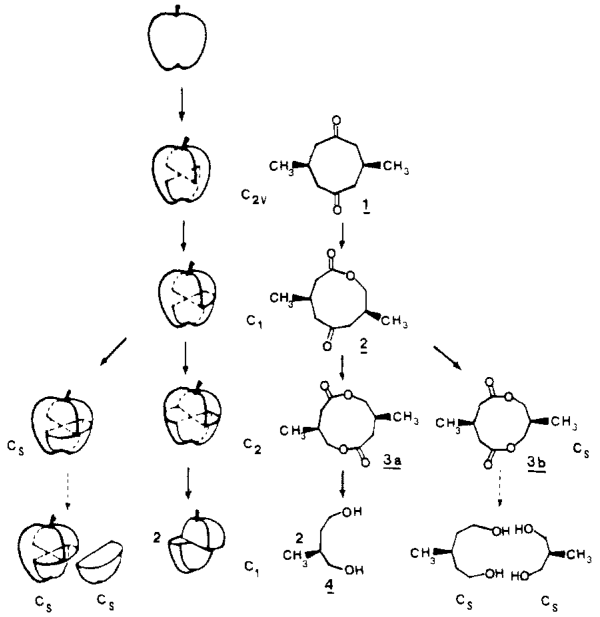
Now you have to slice a horizontal quarter cut, connecting end points A and C

Bisection of an Achiral Molecule into Homochiral Halves: The First Chemical Analogue of "La Coupe du Rei"

Mauro Cinquini, Franco Cozzi, * Franco Sannicolò* and Angelo Sironi *J. Am. Chem. Soc.* **1988,** *110,* 4363-4364





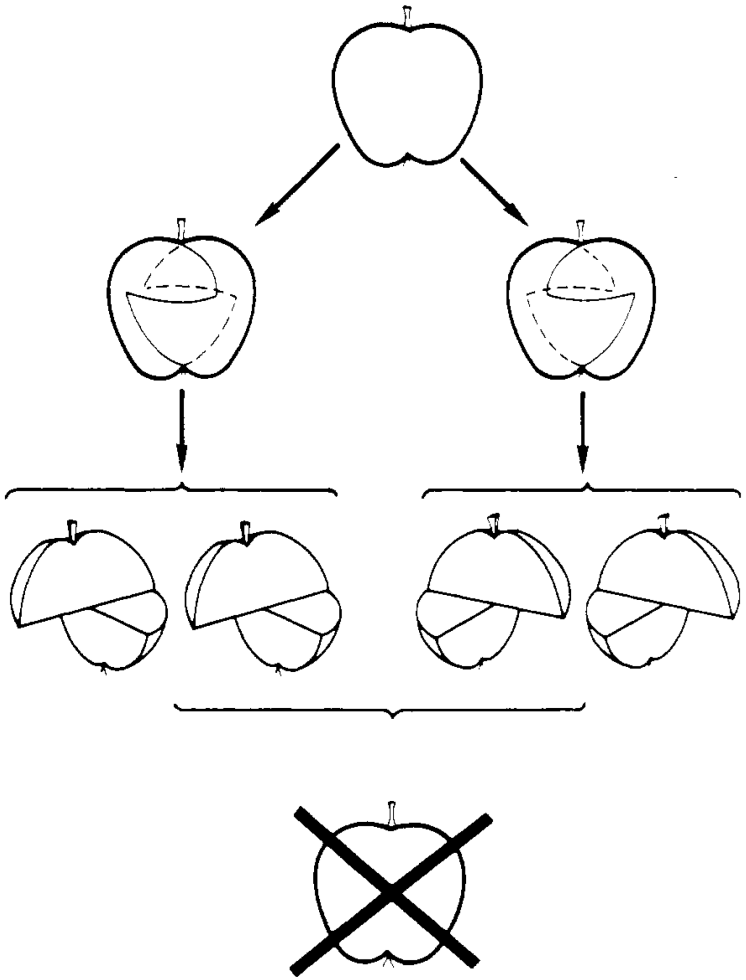


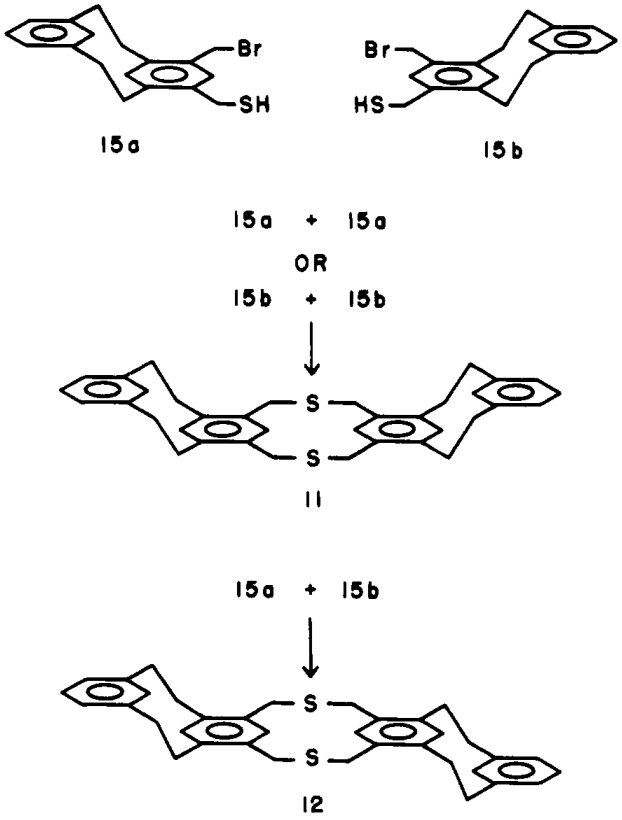
Compound **1** (C_{2v} on the appropriate time scale) was prepared following the described procedure,[10] and its structure unambiguously determined by X-ray analysis[11] (Figure 1). Trifluoroperoxyacetic acid[12] promoted oxidation of **1**, carried out in the presence of an excess of anhydrous Na_2HPO_4,[13] gave, in 82% yield, racemic *cis*-4,8-dimethyloxacyclononane-2,6-dione (**2**) (deliquescent solid at room temperature), that has C_1 symmetry. A second Baeyer–Villiger reaction, performed on **2** with a large excess of the same peroxy acid, afforded pure *cis*-4,9-dimethyl-1,6-dioxacyclodecane-2,7-dione (**3a**) (mp 110 °C) in 12% yield and its constitutional isomer **3b** (3% yield), which could not be isolated free of **2**.[14] The structural assignment resided on inspection of high-field NMR spectra. For instance, **3a** (C_2 symmetry) features a doublet in the ^{1}H NMR methyl region (two doublets observed for C_s symmetry **3b**) and only five different signals in the ^{13}C spectrum (seven signals observed for **3b**). The final bisection was achieved by $LiAlH_4$ reduction of **3a** in refluxing diethyl ether to give C_1 symmetry 2-methyl-1,4-butanediol (**4**) in quantitative yield. This compound was identical with an authentic sample of **4**.

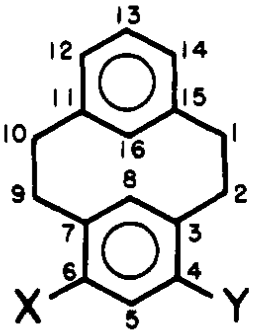
In order to obtain diol **4** in optically active form, lactone **2** was kinetically resolved by pig liver esterase promoted hydrolysis to afford (−)-**2**, $[\alpha]^{22}_D$ −8.7 (*c* 1, $CHCl_3$), which was shown to be ⩾90% enantiomerically pure. Referred to the apple model, this operation corresponds to performing the first horizontal cut on a large number of apples in a random way and discarding almost all the homochiral apples of one sort. Oxidation of (−)-**2** gave dilactone (−)-**3a**: mp 106 °C; $[\alpha]^{22}_D$ −31.0 (*c* 0.8, $CHCl_3$). Finally, reduction of (−)-**3a** afforded (−)-(*S*)-**4**, $[\alpha]^{22}_D$ −13.0 (*c* 0.46, MeOH), which was 90% optically pure by comparison with

La Coupe du Roi and Its Relevance to Stereochemistry. Combination of Two Homochiral Molecules To Give an Achiral Product

Kurt Mislow* et al. *J. Am. Chem. SOC.* 1983, *105,* 1419-1426







$$13 \xrightarrow[92\%]{\text{1. NaOAc}\ \text{2. KOH}} 17 \xrightarrow[50\%]{\text{1. } MnO_2\ \text{2. } Ag_2O} (\pm)\text{-}18 \xrightarrow[55\%]{\text{quinine}} (+)\text{-}18$$

$$\xrightarrow[69\%]{\text{1. } PBr_3\ \text{2. } CH_3OH} (+)\text{-}19 \xrightarrow[92\%]{KSCN} (+)\text{-}20 \xrightarrow[99\%]{LiAlH_4} (+)\text{-}21 \xrightarrow[94\%]{PBr_3} (+)\text{-}15$$

13, X = Y = CH_2Br
14, X = Y = CH_2SH
15, X = CH_2SH; Y = CH_2Br
16, X = Y = CH_3
17, X = Y = CH_2OH
18, X = CH_2OH; Y = CO_2H
19, X = CH_2Br; Y = CO_2CH_3
20, X = CH_2SCN; Y = CO_2CH_3
21, X = CH_2SH; Y = CH_2OH

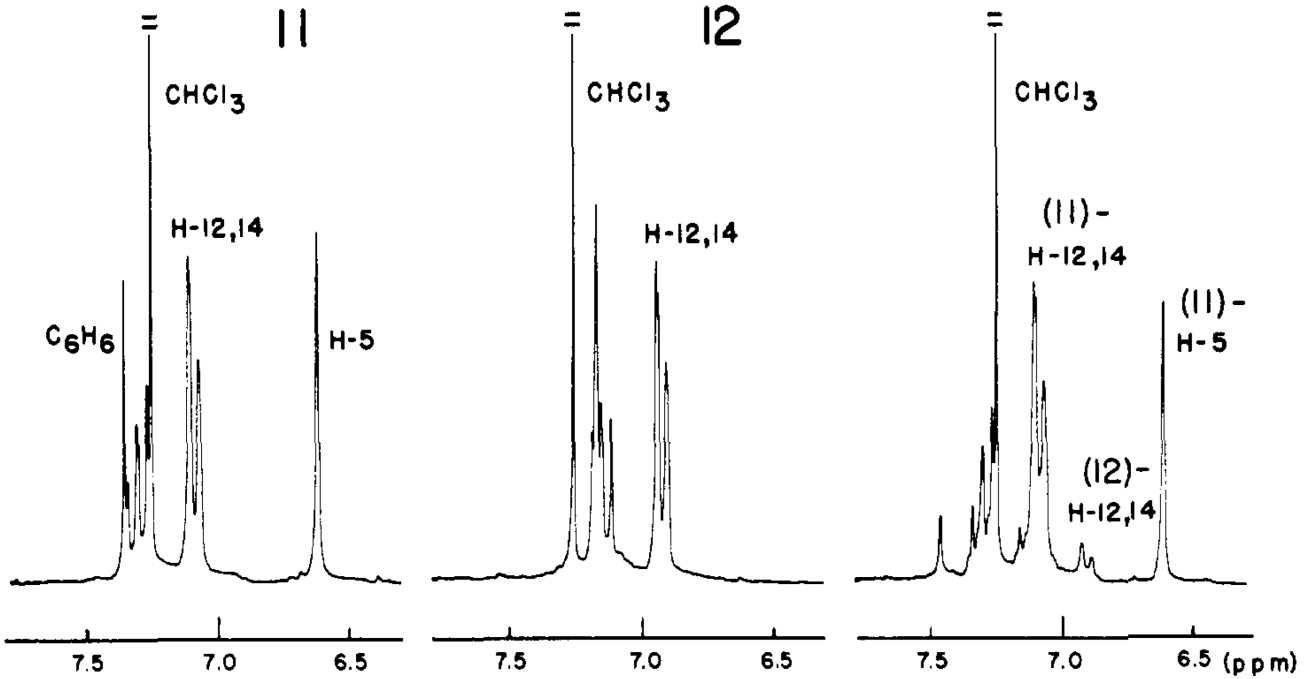


Figure 6. 200-MHz ^1H NMR spectra of the low-field aromatic region of dimers **11** (left) and **12** (center) and of the dimer mixture obtained from 90% enantiomerically pure (+)-**15** (right).