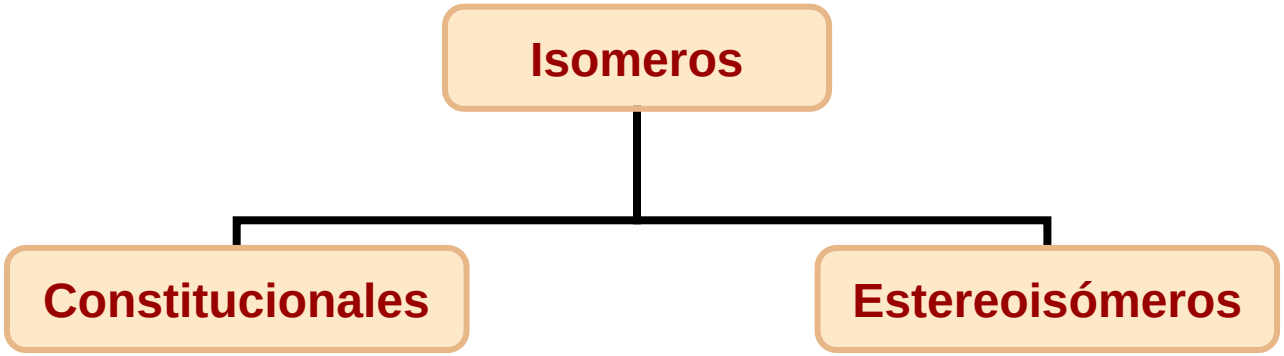
Tema 3
Estereoquímica

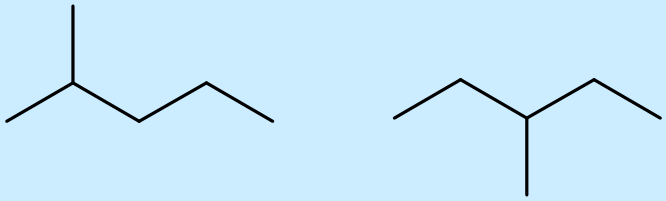
Introducción. Concepto de quiralidad. Centros estereogénicos. Atomos de carbono asimétricos. Enantiomería. Relación entre enantiomería y actividad óptica. Especificación de la configuración absoluta. Moléculas con más de un centro estereogénico. Diastereómeros. Formas meso.

Introducción

La **estereoquímica** estudia la estructura tridimensional de una molécula.

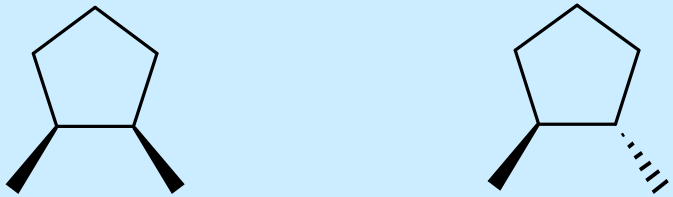


Fórmula molecular: C_6H_{14}



2-metilpentano **3-metilpentano**

Fórmula molecular: C_7H_{14}

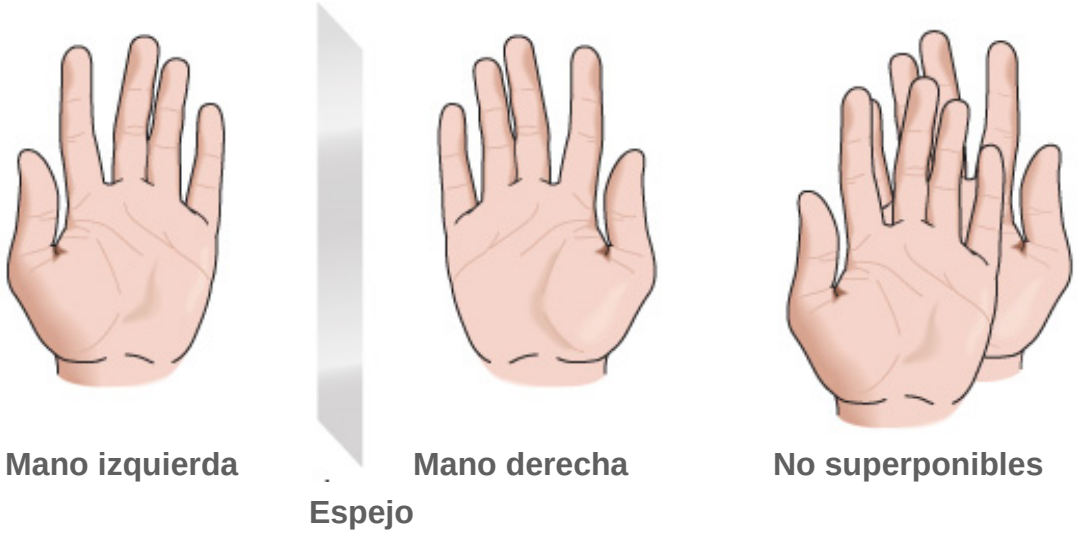


***cis*-1,2-dimetilciclopentano** ***trans*-1,2-dimetilciclopentano**

Quiralidad

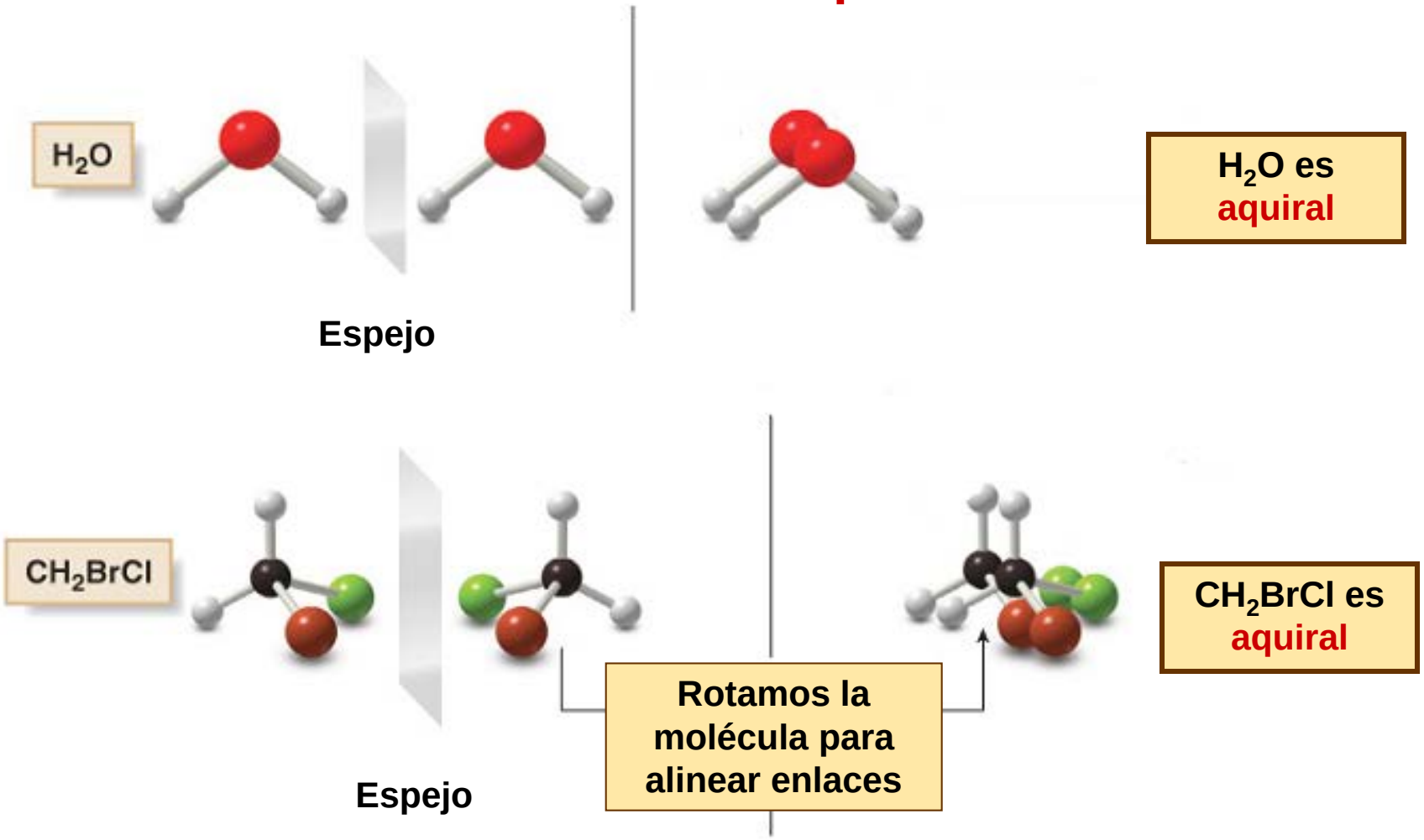
Quiralidad ⇨ **Cheir (χειρ)** ⇨ **Mano**

Objetos y moléculas quirales y aquirales



Una molécula (u objeto) que no es superponible con su imagen especular se dice que es **QUIRAL**

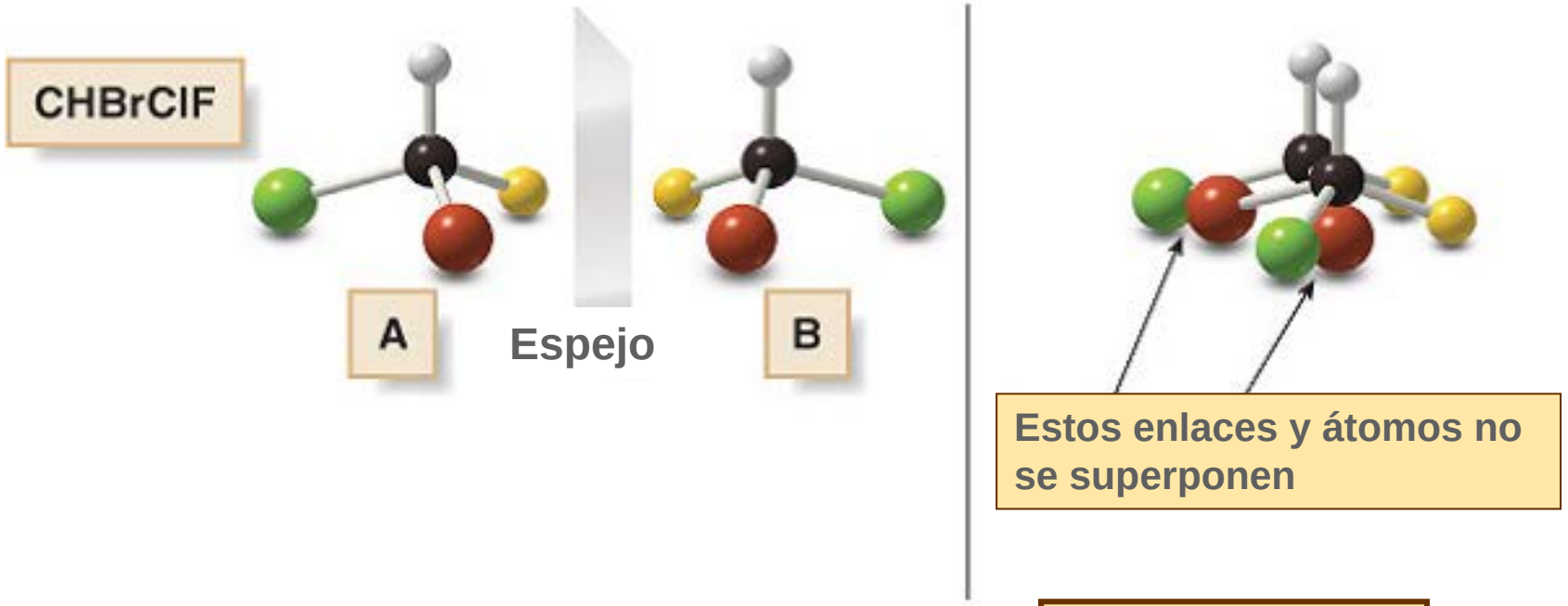
Moléculas aquirales



Una molécula (u objeto) que es superponible con su imagen especular se dice que es **AQUIRAL**

Centros estereogénicos

- **carbono asimétrico**
- **centro estereogénico**



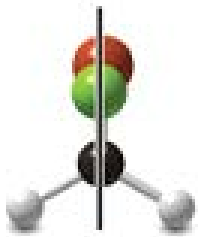
CHBrClF es quiral

Una molécula (u objeto) que no es superponible con su imagen especular se dice que es **QUIRAL**

- **Elementos de simetría**: **plano de simetría**

Alineamos los enlaces C-Cl y C-Br en cada molécula

CH_2BrCl	$CHBrClF$
Plano de simetría	No tiene plano de simetría

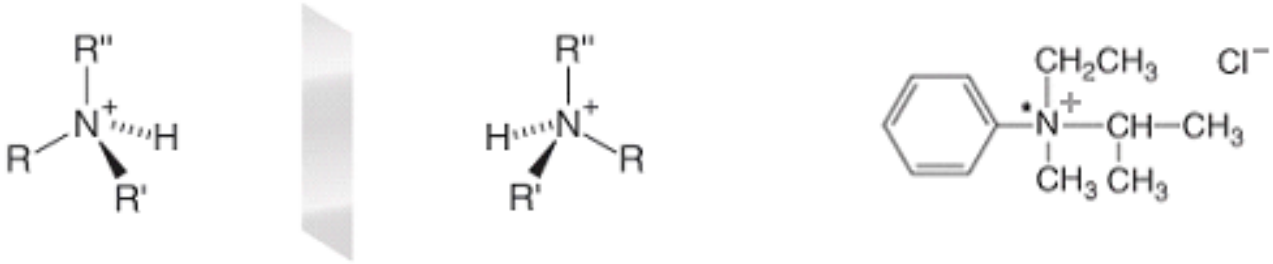


CH_2BrCl es aquiral

$CHBrClF$ es quiral

Moléculas con centros estereogénicos diferentes al carbono

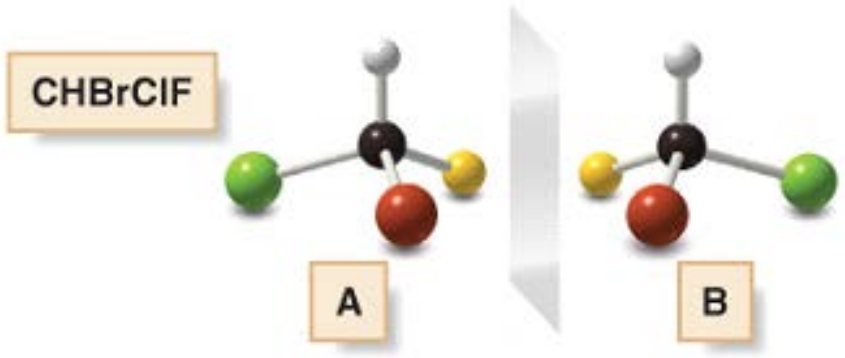
- S, N, P, S



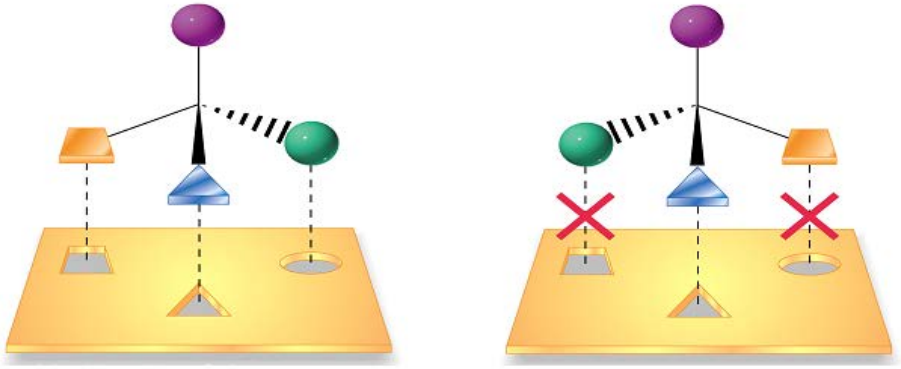
cloruro de etilfenilisopropilamonio

Una molécula con **UN centro estereogénico** será siempre quiral

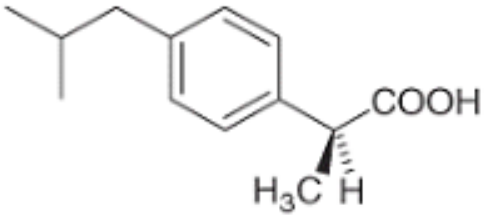
- **Enantiómeros**: estereoisómeros que son imagen especular uno de otro.
- Los enantiómeros poseen la misma **constitución** pero diferente **configuración**.
- La **configuración** es la disposición de sus átomos en el espacio,



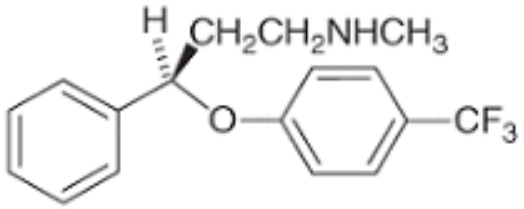
Importancia biológica de la existencia de enantiómeros



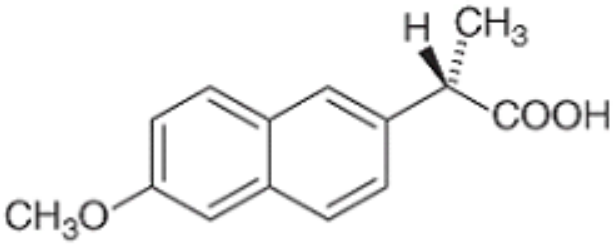
Ejemplos en compuestos naturales y fármacos



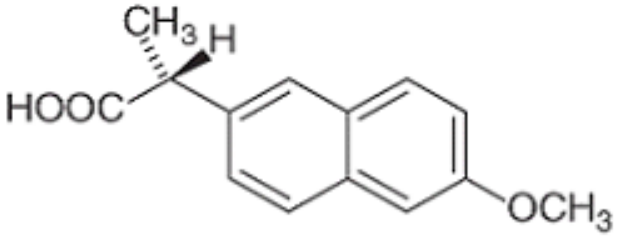
***(S)*-Ibuprofeno**
(antiinflamatorio)



***(R)*-Fluoxetina**
(antidepresivo)



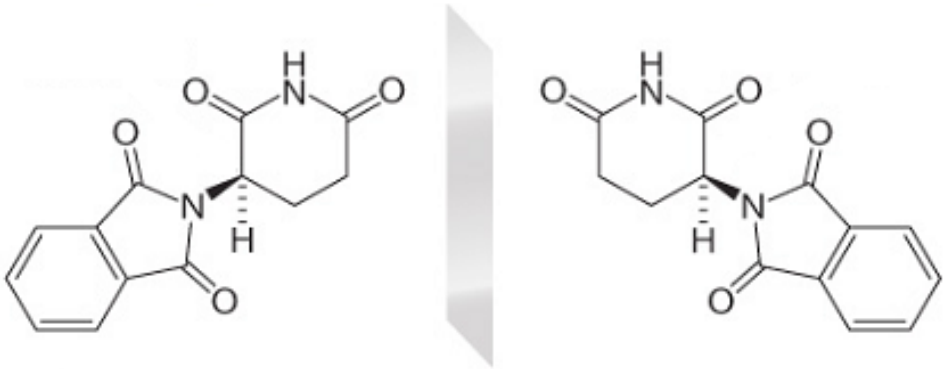
***(S)*-Naproxeno**
(antiinflamatorio)



***(R)*-Naproxeno**
(tóxico hepático)

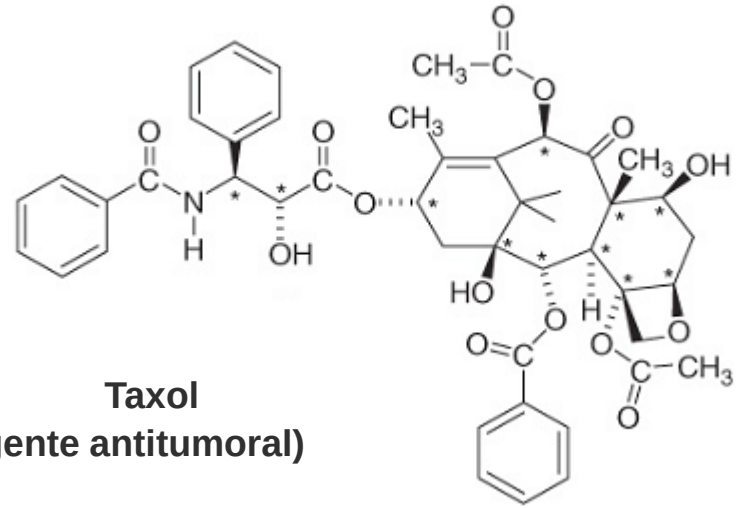
Ejemplos en compuestos naturales y fármacos

Talidomida



***(R)*-Talidomida**
(antiemético, sedante)

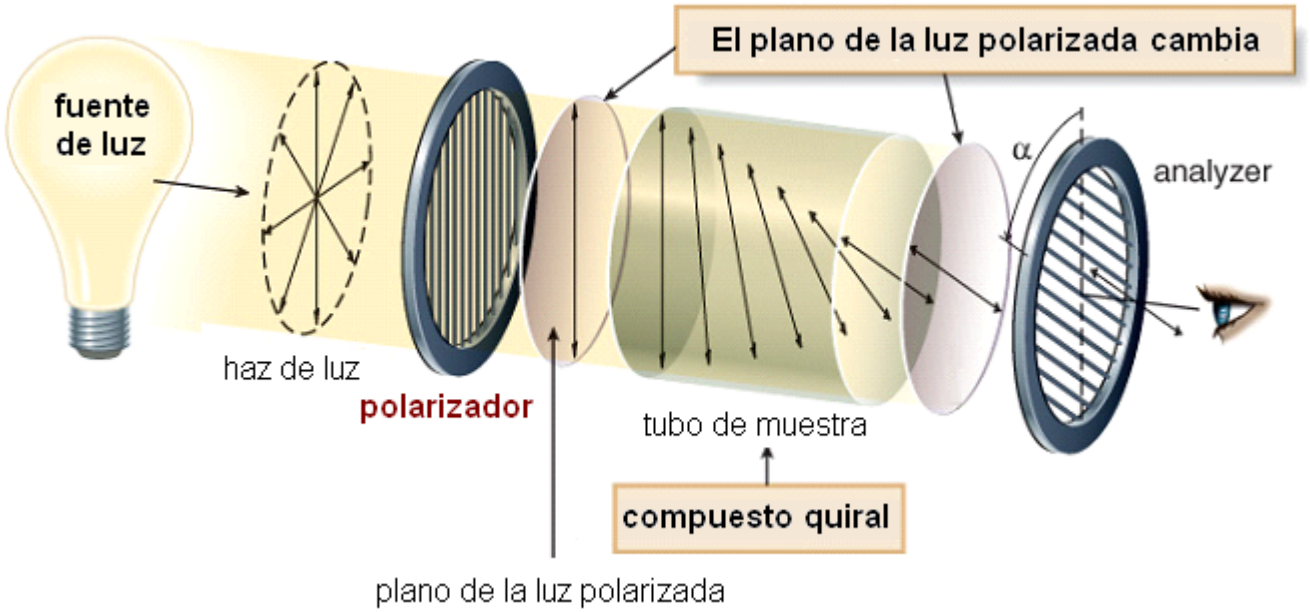
***(S)*-Talidomida**
(teratógeno)



Taxol
(agente antitumoral)

Actividad óptica

- **La luz polarizada**
- El **polarímetro**.
- Compuestos **ópticamente activos**.



- Si la rotación es hacia la derecha la sustancia es **dextrógira** o **dextrorrotatoria** (***d***) y a α se le asigna un valor (+). Si la rotación es hacia la izquierda la sustancia es **levógira** o **levorrotatoria** (***l***) y a α se le asigna un valor (-).

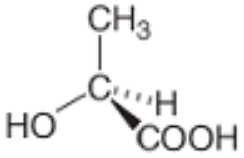
- Dos enantiómeros: enantiómero **A**: + 5° enantiómero **B**: – 5°

- Mezcla al 50% o **racémico**. Un **racémico es ópticamente inactivo.**

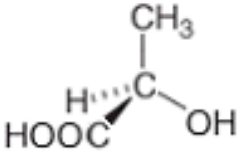
Rotación específica [α] es una constante física estandarizada

$$\text{Rotación específica} = [\alpha]_D^{25\,^oC} = \frac{\alpha}{l \times c}$$

α = rotación observada
l = longitud del tubo de muestra en dm
c = concentración de la muestra en g/ml



ac. (*S*)-(+)-láctico
$[\alpha]_D^{25}$ +3.8º



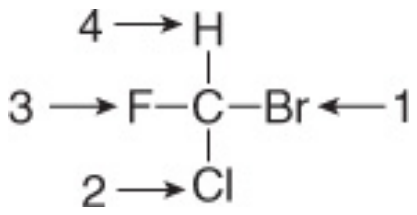
ac. (*R*)-(-)-láctico
$[\alpha]_D^{25}$ -3.8º

Nomenclatura de la configuración absoluta de un centro estereogénico

- Paso [1] Ordene los cuatro átomos unidos al centro

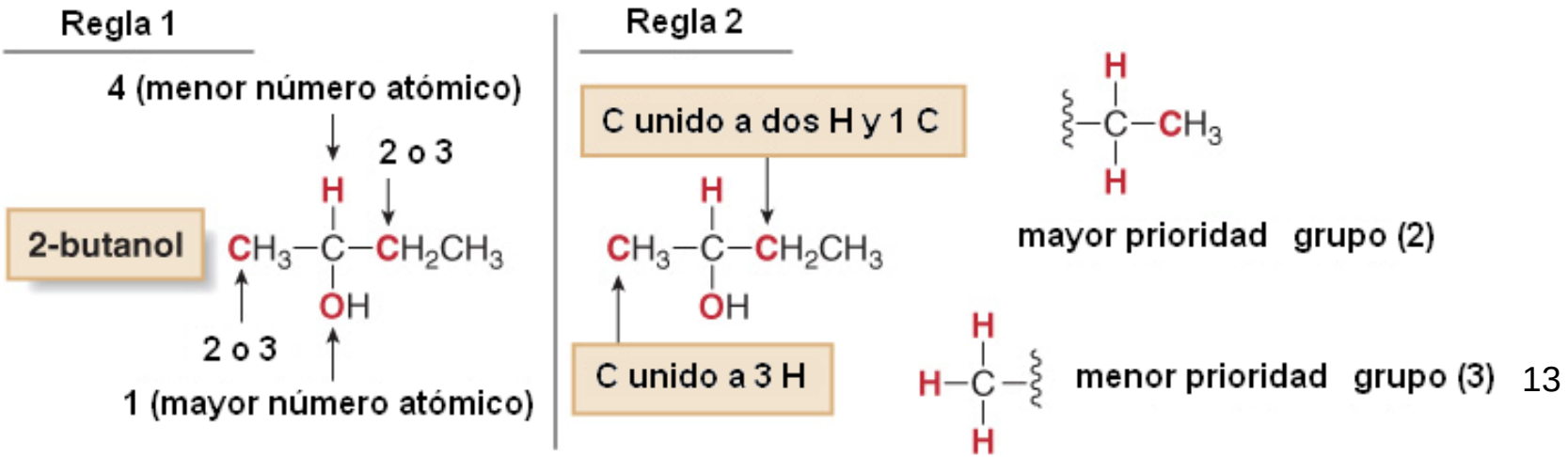
REGLAS de Cahn-Ingold-Prelog

1. Tiene prioridad el átomo con mayor número atómico (si se trata de isótopos el de masa superior)



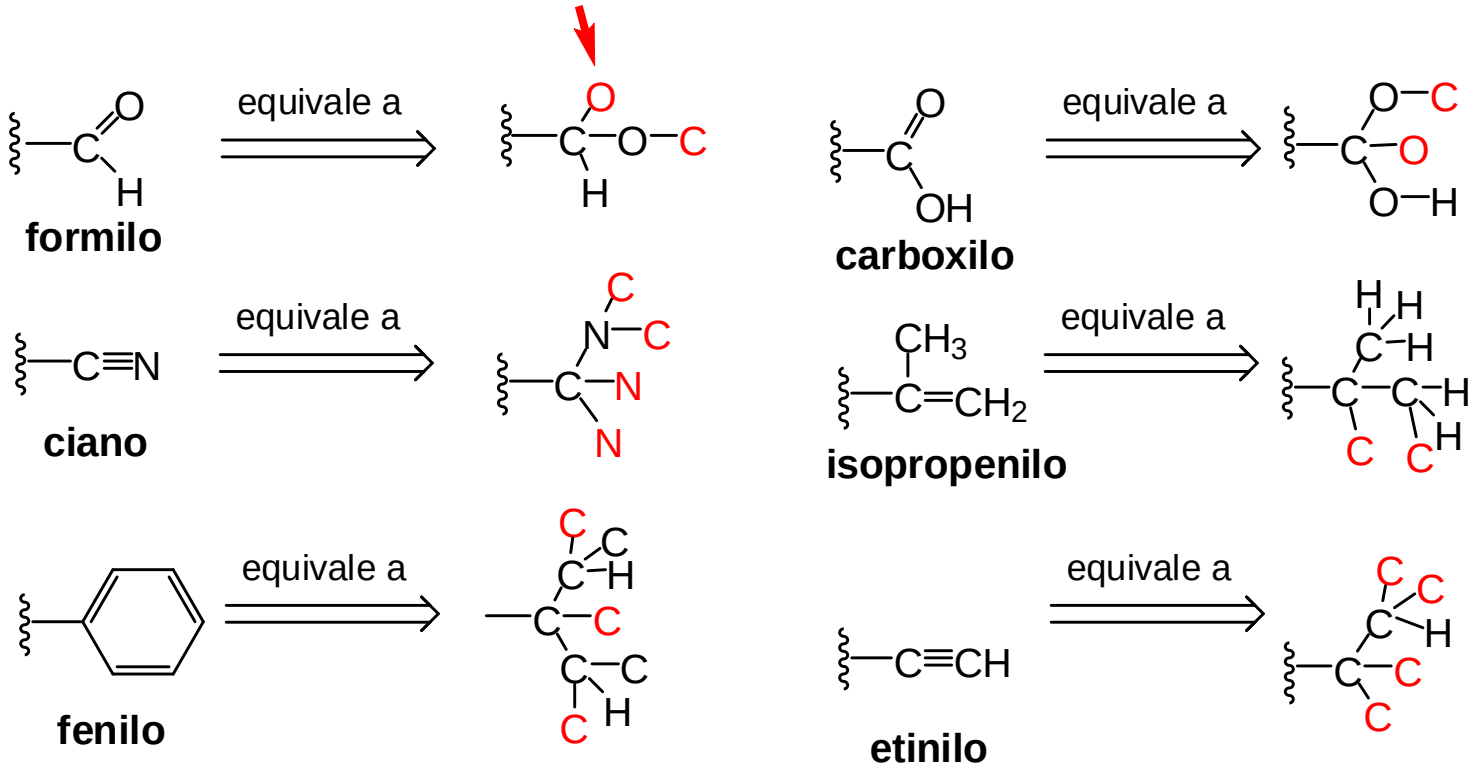
Isótopo	Masa atómica	Prioridad
T (tritio)	3 (1 protón + 2 neutrones)	**1**
D (deuterio)	2 (1 protón + 1 neutrón)	**2**
H (hidrógeno)	1 (1 protón)	**3**

2. Si dos átomos unidos al centro estereogénico son idénticos, la prioridad se asigna considerando el número atómico de los átomos unidos a ellos.



3. Un enlace múltiple, doble o triple, se considera como dos o tres enlaces sencillos con átomos idénticos.

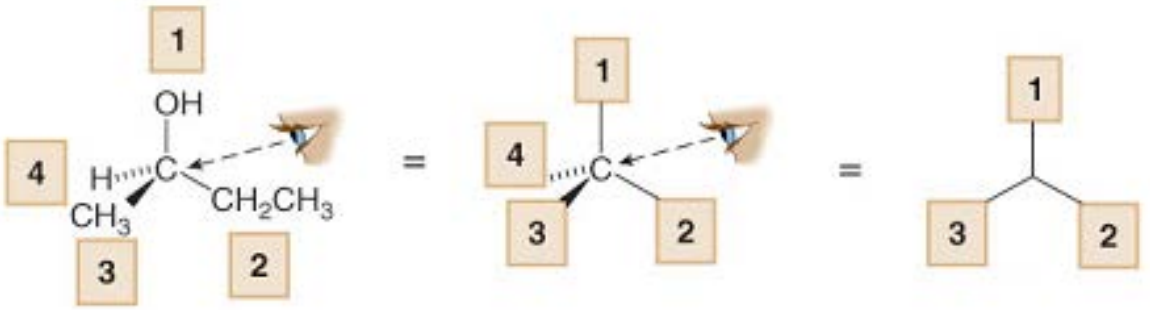
(en rojo para indicar que está repetido y que por ahí no se puede seguir la secuencia)



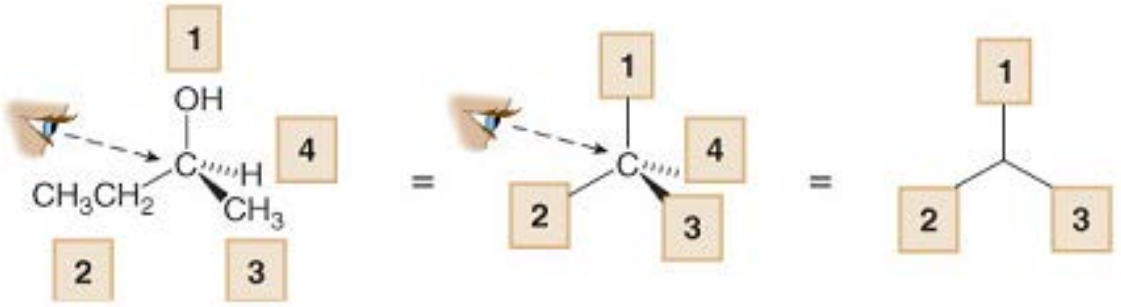
carboxilo > formilo > ciano > fenilo > etinilo > isopropenilo

Paso [2] Oriente la molécula con el grupo de menor prioridad (4) lo más alejado del observador (hacia atrás) y vea la orientación de los tres grupos restantes

Enantiómero A



Enantiómero B

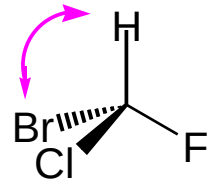


Paso [3] Se traza un círculo que vaya 1⟶ 2 ⟶ 3.

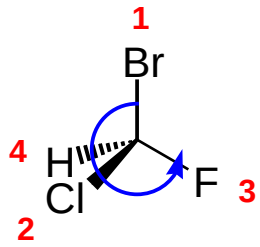
- Si sigue el sentido de las agujas del reloj: configuración ***R*** *(Rectus)*
- Si sigue el sentido opuesto a las agujas del reloj: configuración ***S*** *(Sinister)*

Otros ejemplos:

_R_-bromoclorofluormetano

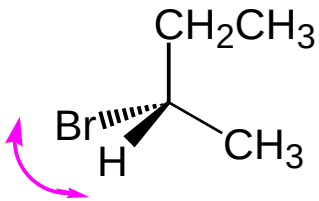


un cambio

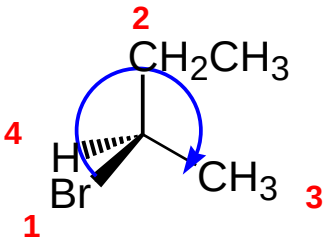


S

_S_-2-bromobutano

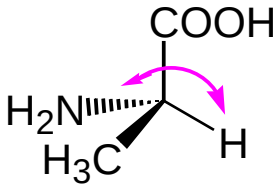


un cambio

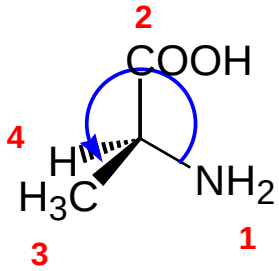


R

ac. _R_-2-aminopropanoico



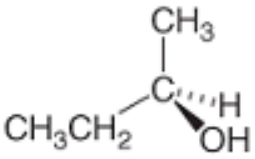
un cambio



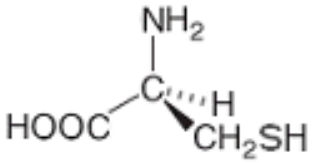
S

El intercambio de dos grupos en una molécula que tenga un único centro estereogénico, la convierte en su enantiómero.

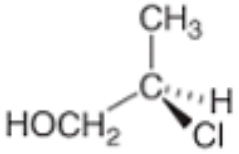
El signo es independiente de la configuración.
Es una medida experimental.



(*R*)-(-)-2-butanol
$[\alpha]_D^{25}$ -13.5º



(*R*)-(+)-cisteína
$[\alpha]_D^{23}$ +5.2º

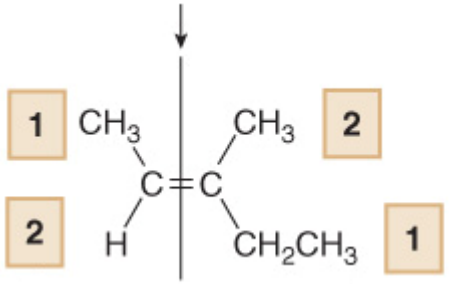


(*R*)-(-)-2-cloro-1-propanol
$[\alpha]_D^{19}$ -17.5º

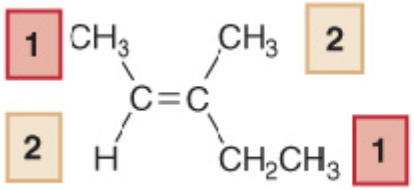
El carácter **dextrógiro** o **levógiro** de un compuesto es independiente de que su configuración sea ***R*** o ***S***, (**D** o **L**)
Es una medida experimental que no se puede predecir.

Las reglas de C-I-P aplicadas a alquenos. Nomenclatura *Z*-*E*

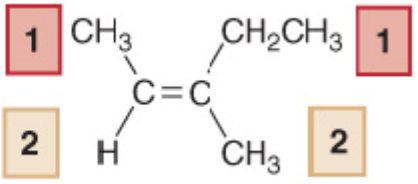
- La nomenclatura ***cis,trans*** no es adecuada en muchos casos
- Se asigna la prioridad a los grupos unidos a a cada carbono del doble enlace usando las reglas de Cahn-Ingold-Prelog



- Grupos de mayor prioridad hacia el mismo lado, ***Z*** (por *zusammen*)
- Grupos de mayor prioridad en lados opuestos, ***E*** (por *entgegen*)



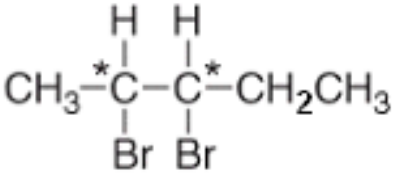
(*E*)-3-metil-2-penteno

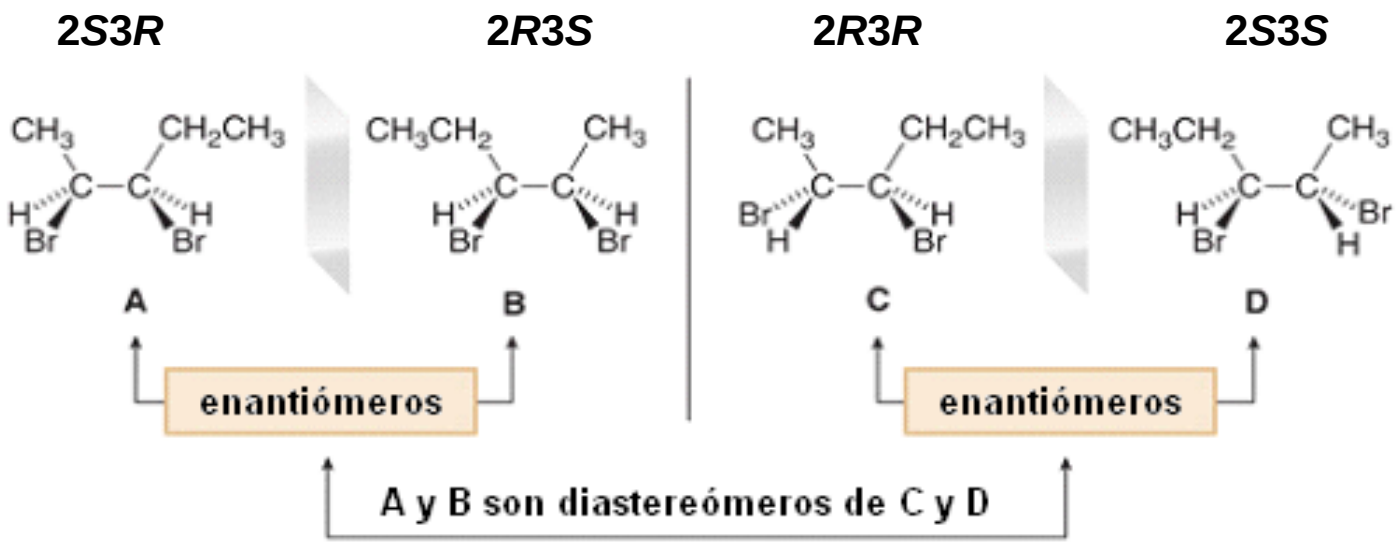


(*Z*)-3-metil-2-penteno

Moléculas con dos centros estereogénicos

- Con *n* centros estereogénicos, el número máximo de estereoisómeros es 2^n.
- El 2,3-dibromopentano

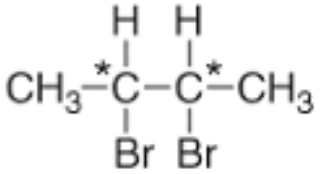


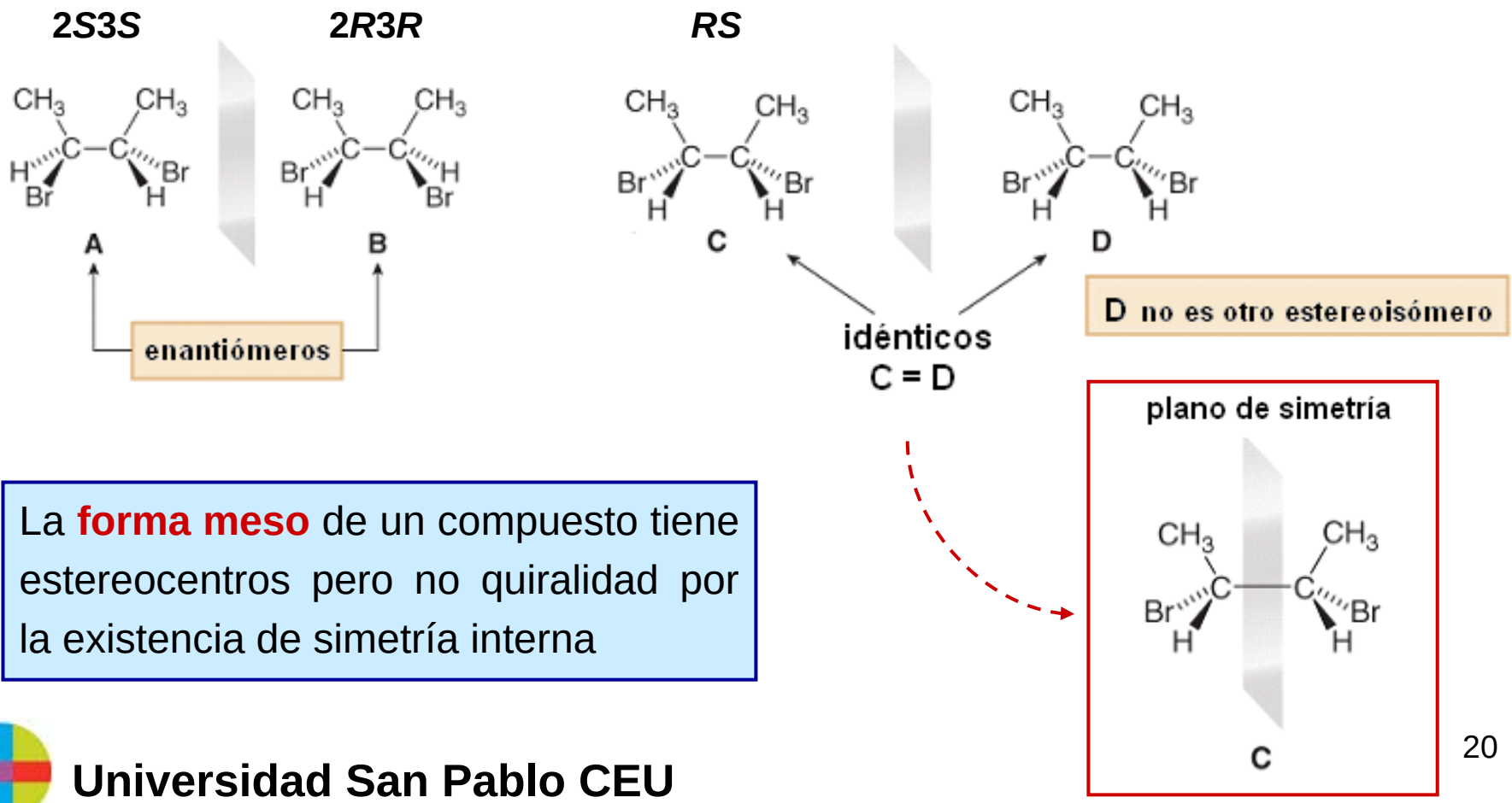


Los **diastereómeros** son estereoisómeros que **NO** son imágenes especulares

Moléculas con dos centros estereogénicos. Formas meso

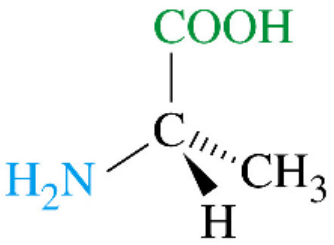
- El 2,3-dibromobutano



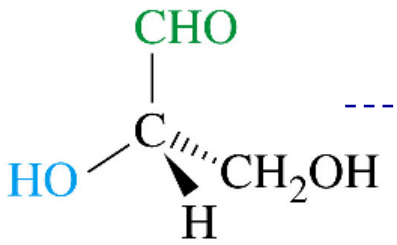


La **forma meso** de un compuesto tiene estereocentros pero no quiralidad por la existencia de simetría interna

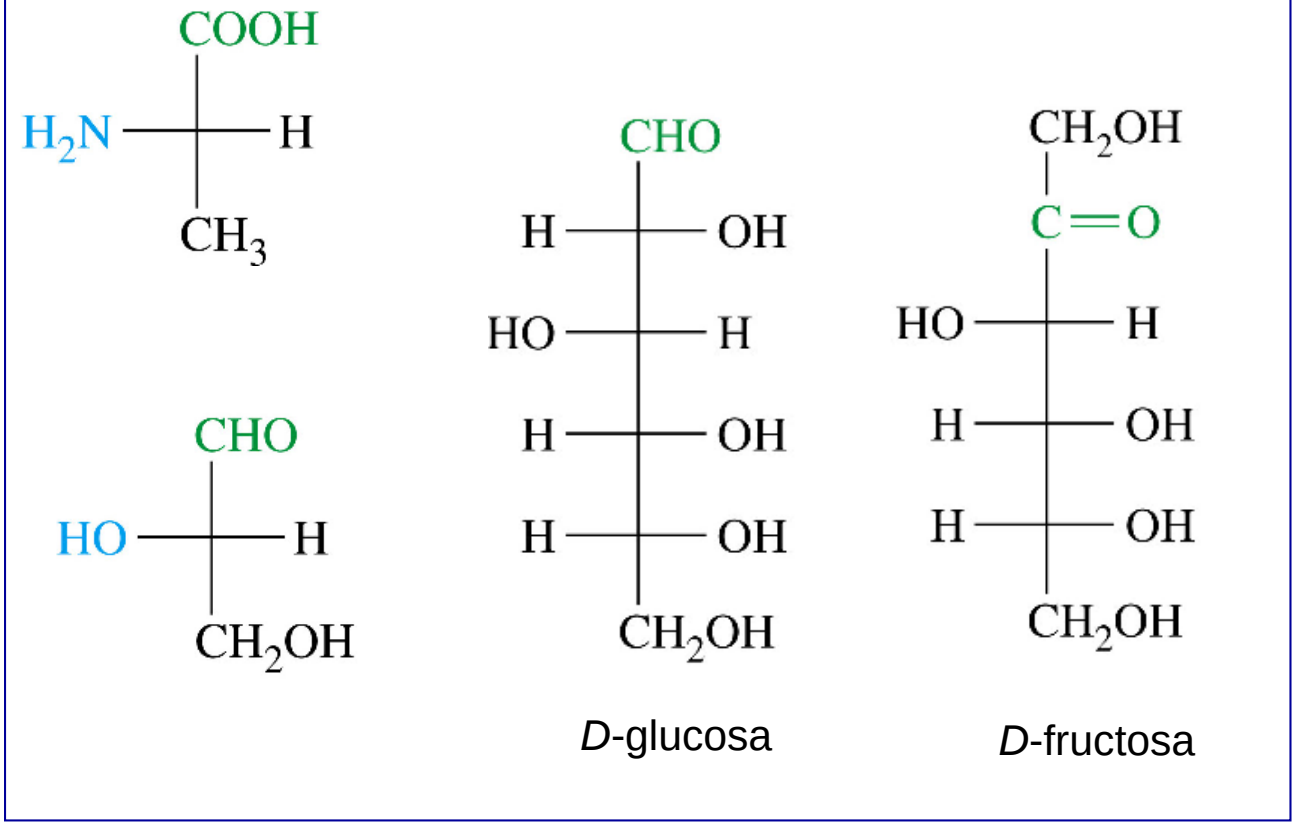
Proyecciones de Fischer



S-alanina
(*L*-alanina)



S-gliceraldehido
(*L*-(-)-gliceraldehido)

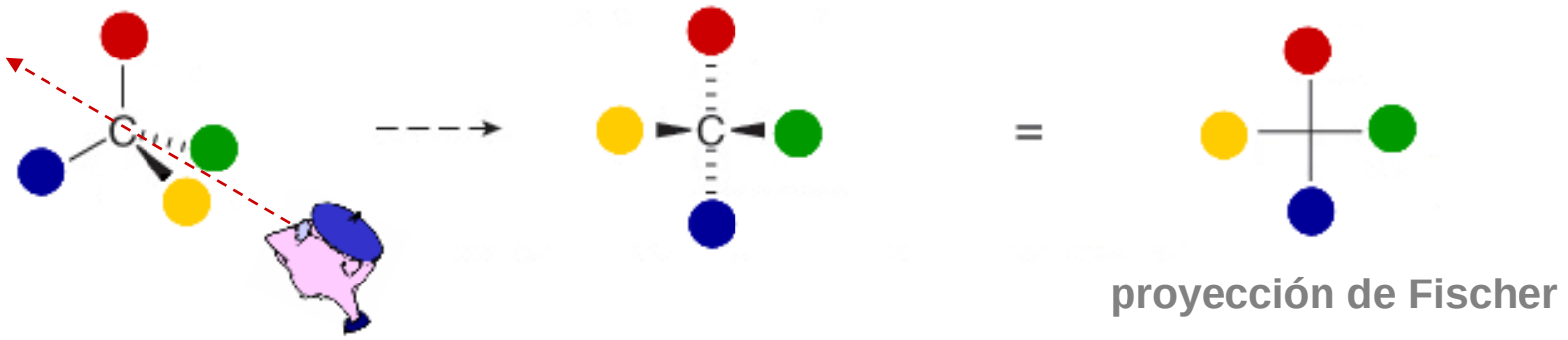


D-glucosa

D-fructosa

Proyecciones de Fischer

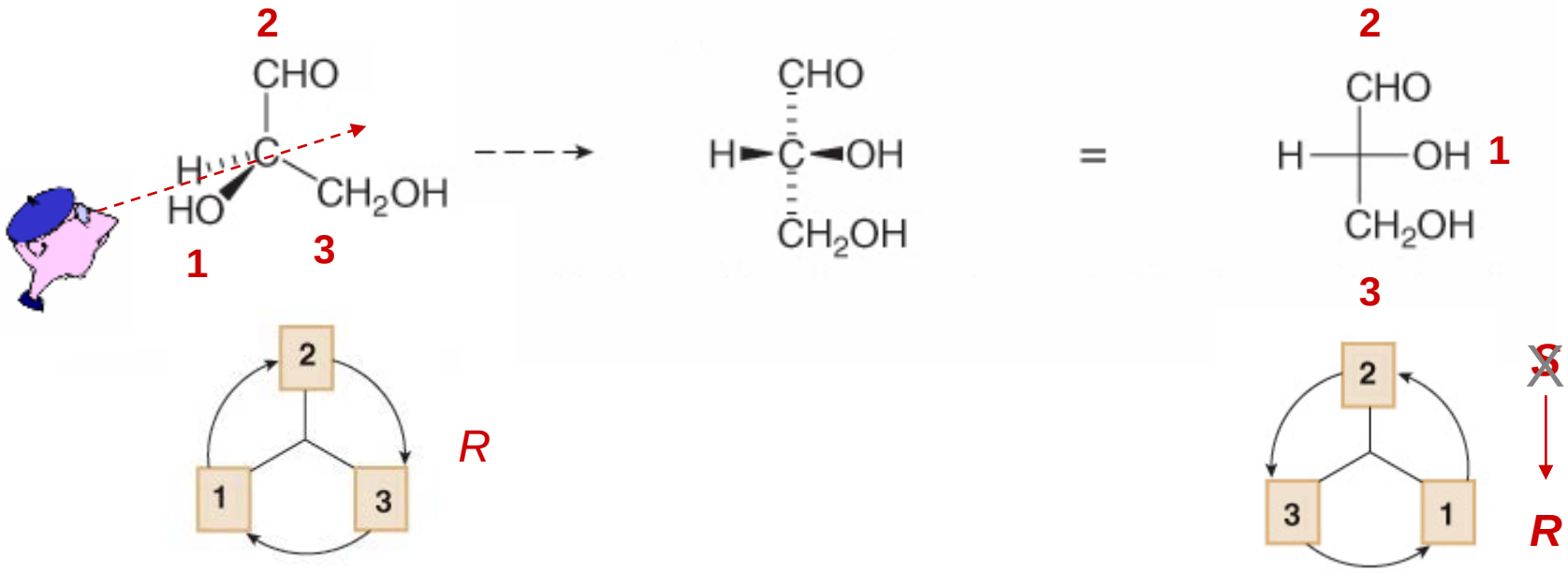
1. El observador se sitúa entre los enlaces que quedan hacia fuera y hacia dentro del plano del papel.
2. Se dibuja una cruz.
3. En la línea horizontal se ponen los grupos que están situados fuera del plano..
4. En la línea vertical se colocan los grupos que están en los enlaces que están en el plano.



proyección de Fischer

Proyecciones de Fischer

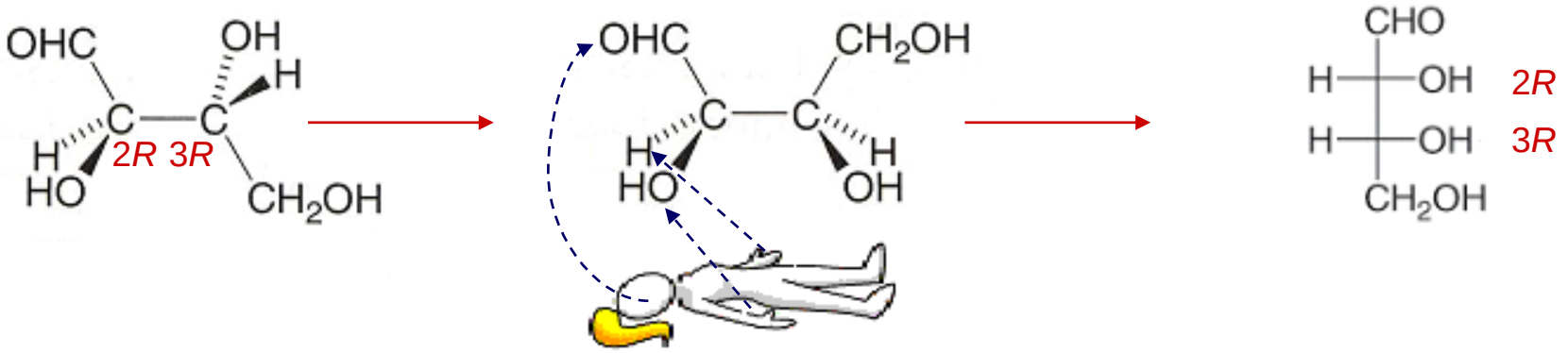
5. En la proyección de Fischer el grupo con mayor estado de oxidación se sitúa en el extremo superior (CH_3 > CH_2OH > CHO > COOH).
6. Para asignar la configuración *R* o *S* se aplican las reglas habituales. Si el grupo de menor prioridad está situado en la línea vertical la asignación *R* o *S* es directa, si está en horizontal es la contraria a la que se obtiene.



configuración absoluta: *R*-gliceraldehido

Proyecciones de Fischer

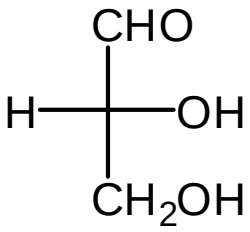
7. Para pasar a proyección de Fischer una molécula con varios centros estereogénicos primero hay que eclipsar todos los enlaces.



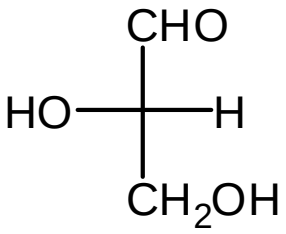
enlaces alternados **enlaces eclipsados** **Proyección de Fisher**

configuración absoluta: 2*R*3*R*

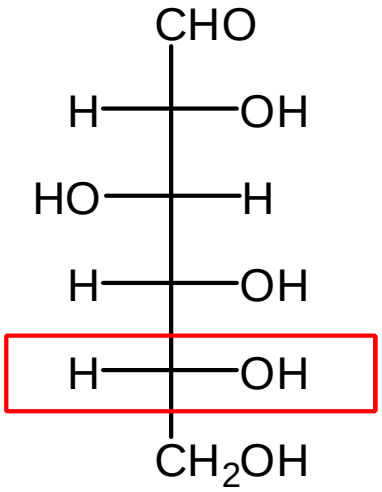
Nomenclatura D y L



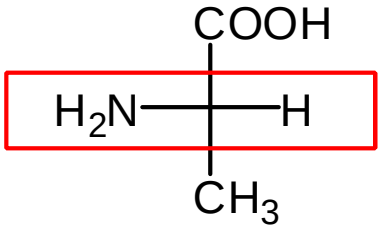
D-(+)-Gliceraldehído



L-(-)-Gliceraldehído



D-Glucosa



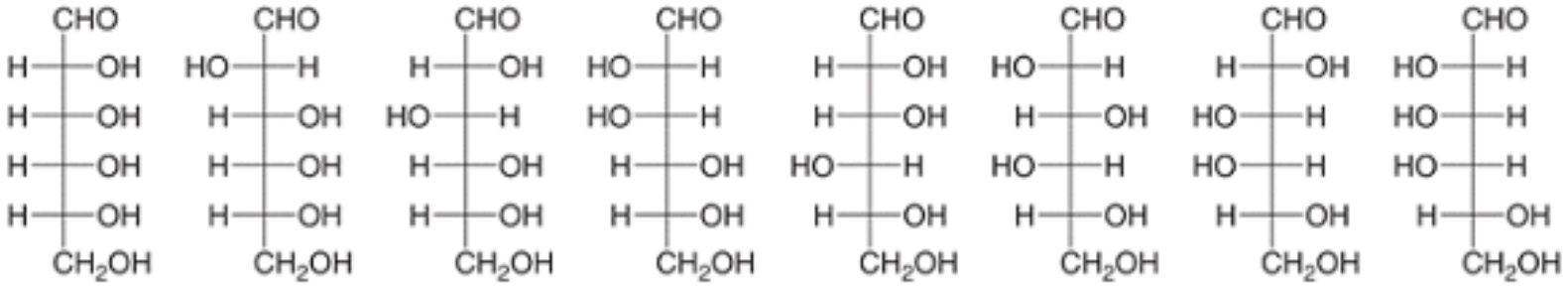
L-Alanina

!!Los términos D y L no tienen nada que ver con dextrógiro y levógiro!!

Moléculas con tres o más centros estereogénicos

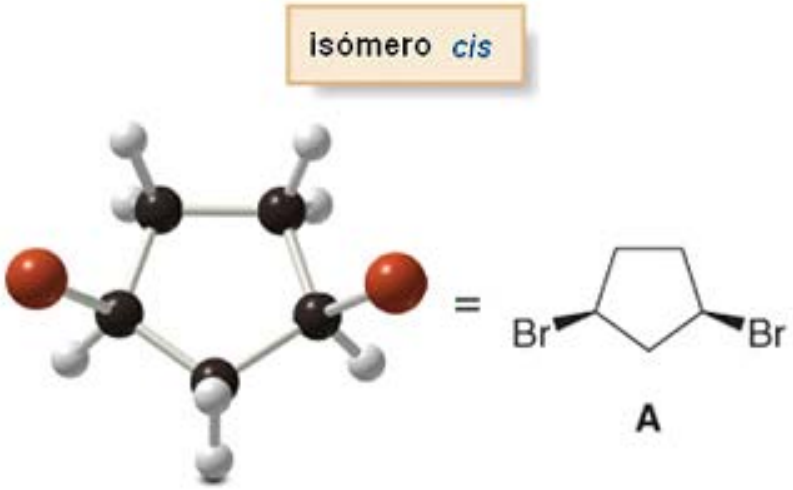
Hexosas: $2^4 = 16$ posibles estereoisómeros

Hexosas de la serie D

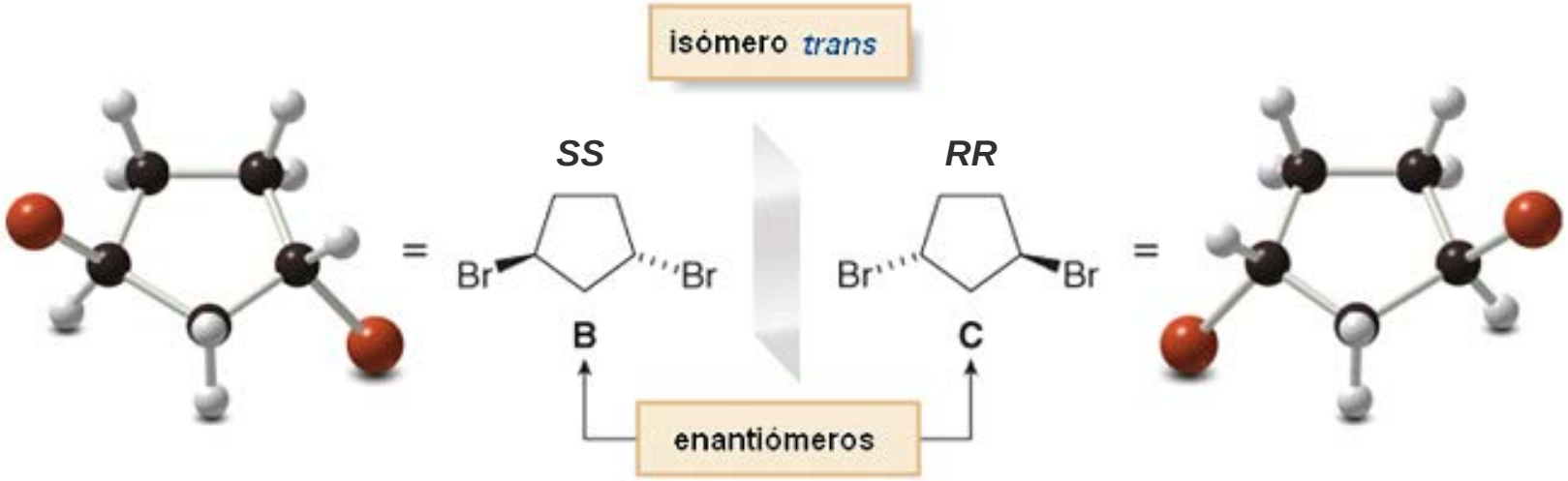


Epímeros: moléculas que sólo difieren en la configuración de un estereocentro

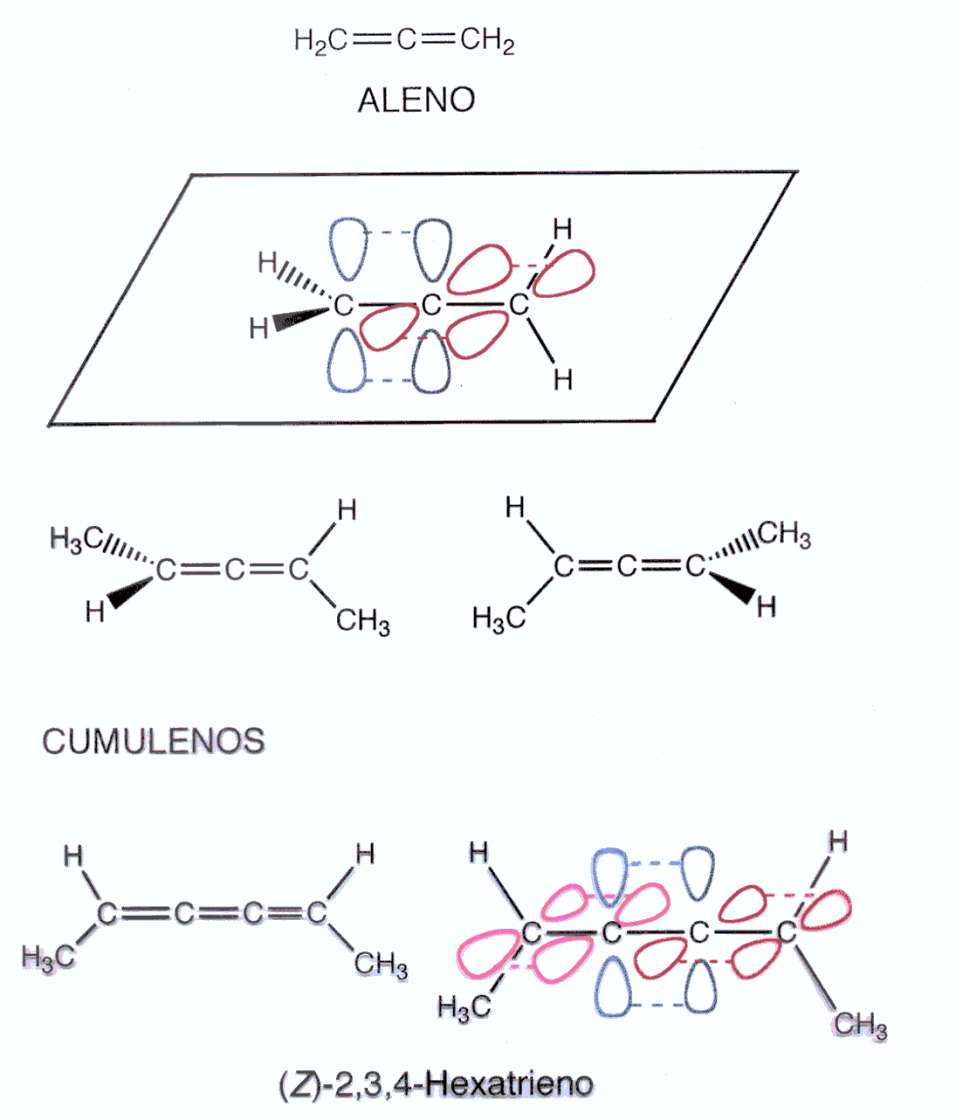
Estereoquímica de Cicloalcanos



***RS* (forma meso)**



Moléculas quirales sin centros estereogénicos: alenos



Isómeros

Compuestos distintos con la misma fórmula molecular

Isómeros constitucionales

Se diferencian en el orden en que sus átomos están conectados entre sí

Estereoisómeros

Idéntica conexión de enlaces. Se diferencian en la forma en que se disponen sus átomos en el espacio

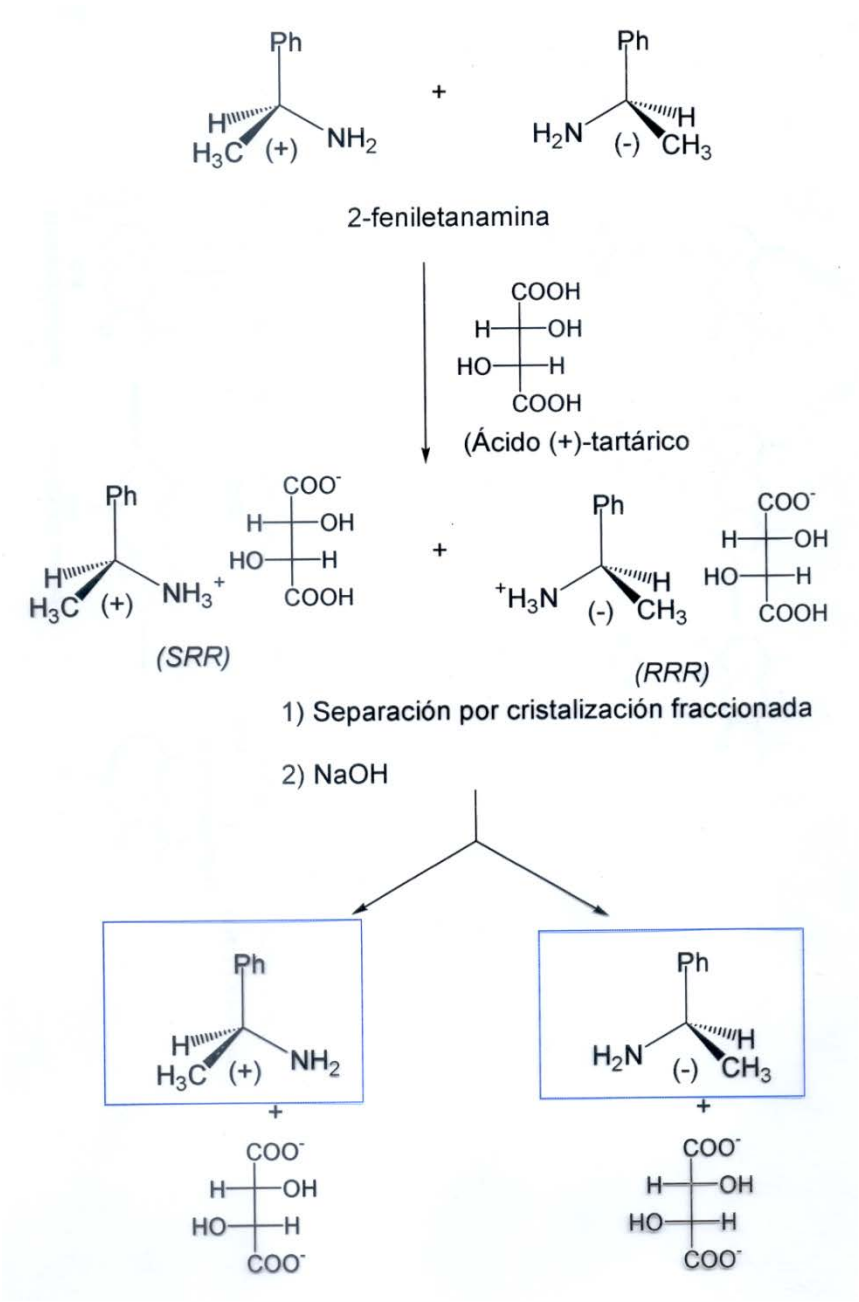
Enantiómeros

Estereoisómeros que son imagen especular

Diastereómeros

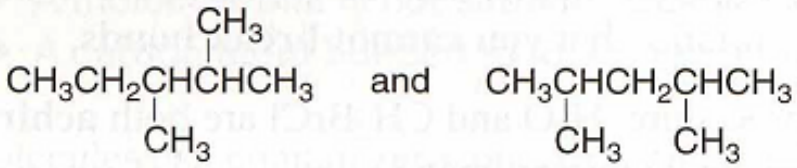
Estereoisómeros que **NO** son imagen especular

Resolución de racémicos



Ejercicios de Autoevaluación

1 Classify each pair of compounds as constitutional isomers or stereoisomers.

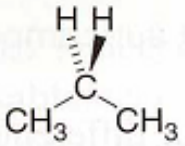
a. 

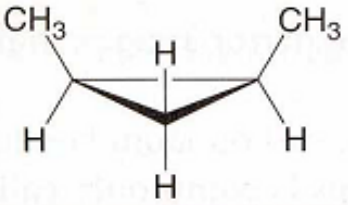
b. 

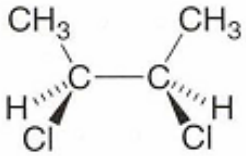
c. 

d. 

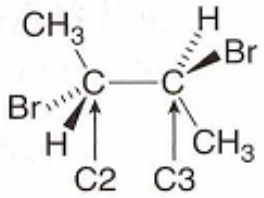
2 Draw in the plane of symmetry for each molecule.

a. 

b. 

c. 

3 A molecule is achiral if it has a plane of symmetry in *any* conformation. The given conformation of 2,3-dibromobutane does not have a plane of symmetry, but rotation around the C2–C3 bond forms a conformation that does have a plane of symmetry. Draw this conformation.

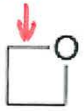
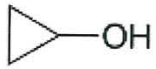


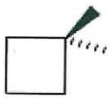
Ejercicios de Autoevaluación

1 Classify each pair of compounds as constitutional isomers or stereoisomers.

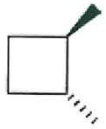
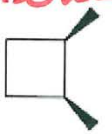
a. $CH_3CH_2CH(CH_3)CHCH_3$ and $CH_3CH(CH_3)CH_2CH(CH_3)CH_3$

Constitucional

b.  and 

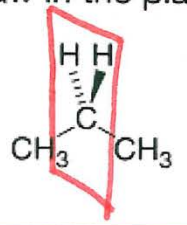
c.  and 

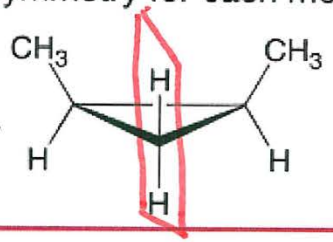
constitucional

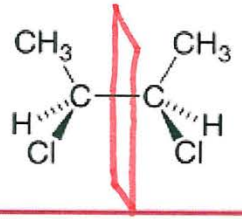
d.  and 

estereoisómeros

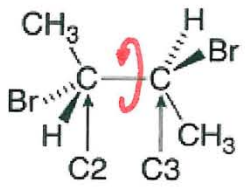
2 Draw in the plane of symmetry for each molecule.

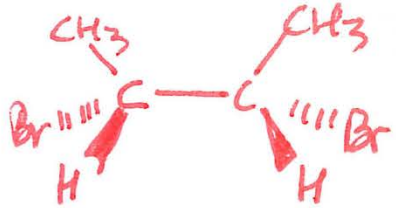
a. 

b. 

c. 

3 A molecule is achiral if it has a plane of symmetry in *any* conformation. The given conformation of 2,3-dibromobutane does not have a plane of symmetry, but rotation around the C2–C3 bond forms a conformation that does have a plane of symmetry. Draw this conformation.





4 Label any stereogenic center in the given molecules. (Some compounds contain no stereogenic centers.)

a. $CH_3CH_2CH(Cl)CH_2CH_3$

b. $(CH_3)_3CH$

c. $CH_3CH(OH)CH{=}CH_2$

d. $CH_3CH_2CH_2OH$

e. $(CH_3)_2CHCH_2CH_2CH(CH_3)CH_2CH_3$

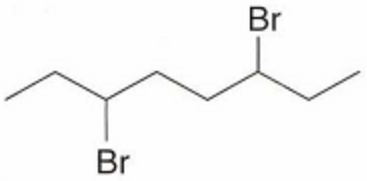
f. $CH_3CH_2CH(CH_3)CH_2CH_2CH_3$

5 Label the stereogenic centers in each molecule. Compounds may have one or more stereogenic centers.

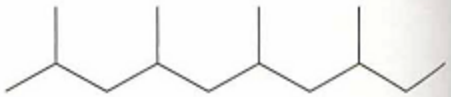
a. $CH_3CH_2CH_2CH(OH)CH_3$

b. $(CH_3)_2CHCH_2CH(NH_2)COOH$

c.

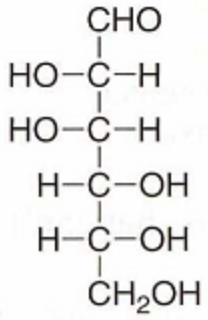


d.



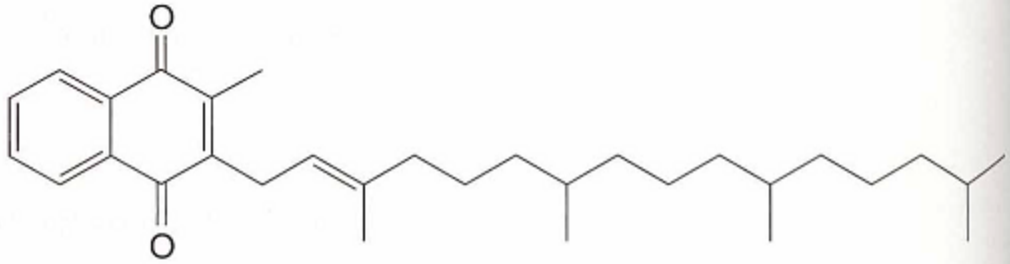
6 Label the stereogenic centers in each biomolecule.

a.



mannose
(a simple carbohydrate)

b.



vitamin K_1

4 Label any stereogenic center in the given molecules. (Some compounds contain no stereogenic centers.)

a. $CH_3CH_2CH(Cl)CH_2CH_3$

b. $(CH_3)_3CH$

c. $CH_3CH(OH)CH=CH_2$

d. $CH_3CH_2CH_2OH$

e. $(CH_3)_2CHCH_2CH_2CH(CH_3)CH_2CH_3$

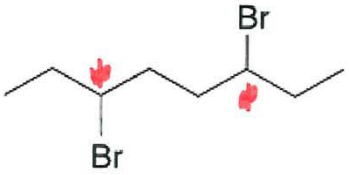
f. $CH_3CH_2CH(CH_3)CH_2CH_2CH_3$

5 Label the stereogenic centers in each molecule. Compounds may have one or more stereogenic centers.

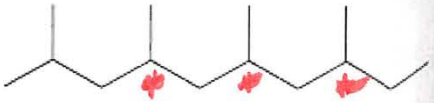
a. $CH_3CH_2CH_2CH(OH)CH_3$

b. $(CH_3)_2CHCH_2CH(NH_2)COOH$

c.

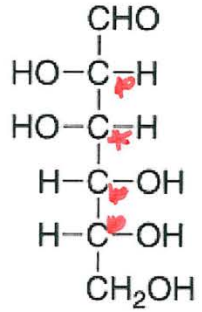


d.



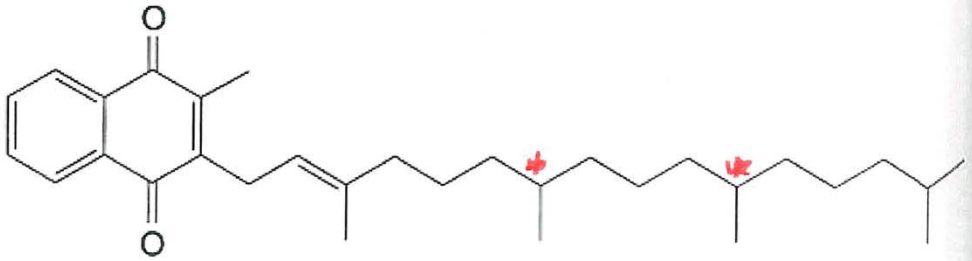
6 Label the stereogenic centers in each biomolecule.

a.



mannose
(a simple carbohydrate)

b.



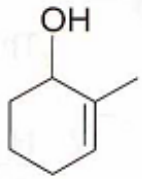
vitamin K_1

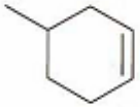
Universidad San Pablo CEU

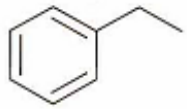
7 Locate the stereogenic center in each compound and draw both enantiomers.

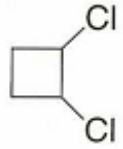
a. $CH_3CH(Cl)CH_2CH_3$ b. $CH_3CH_2CH(OH)CH_2OH$

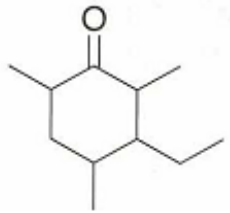
8 Label the stereogenic centers in each compound. A molecule may have zero, one, or more stereogenic centers.

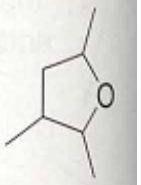
a. 

b. 

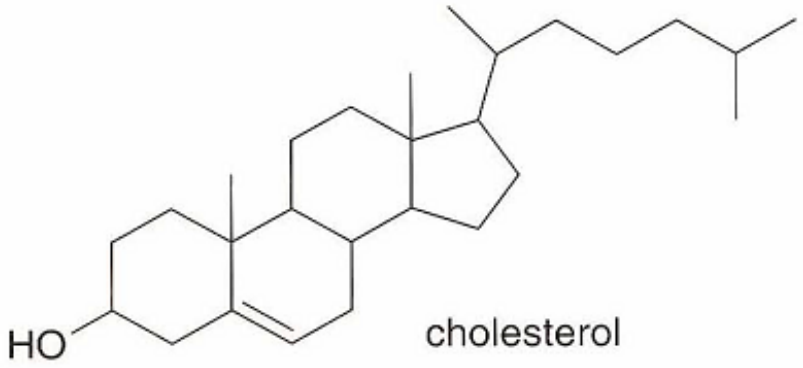
c. 

d. 

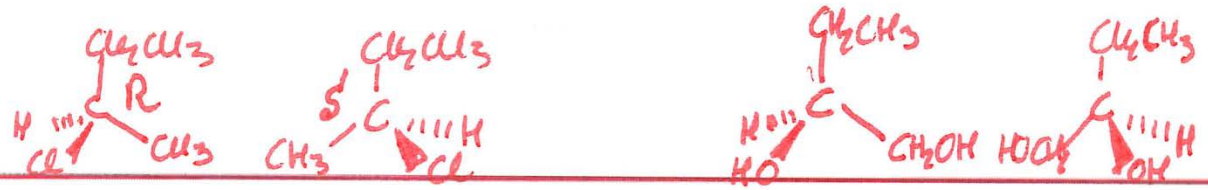
e. 

f. 

9 Label the eight stereogenic centers in the biomolecule cholesterol.



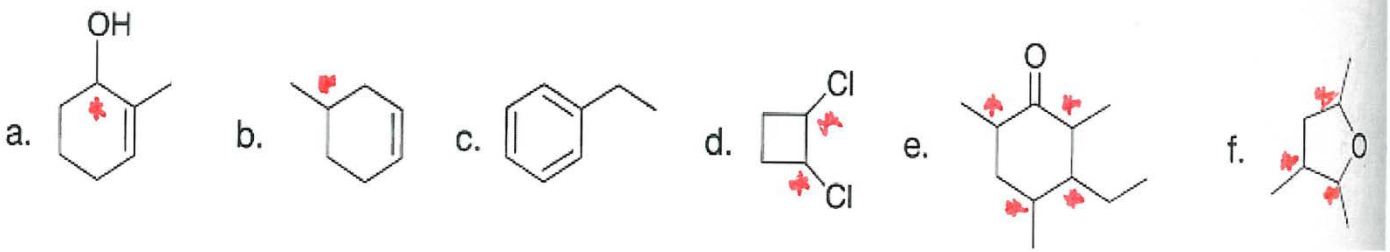
cholesterol



7 Locate the stereogenic center in each compound and draw both enantiomers.

a. $CH_3CH(Cl)CH_2CH_3$ b. $CH_3CH_2CH(OH)CH_2OH$

8 Label the stereogenic centers in each compound. A molecule may have zero, one, or more stereogenic centers.



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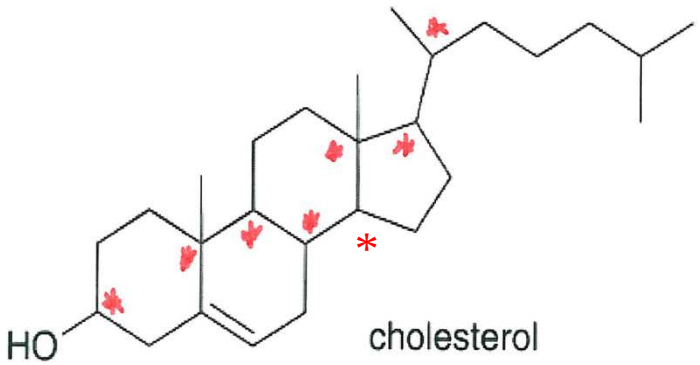
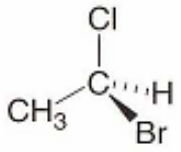
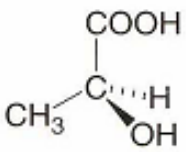
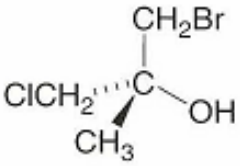


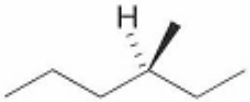
cholesterol

10 Label each compound as *R* or *S*.

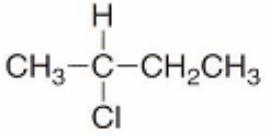
a. 

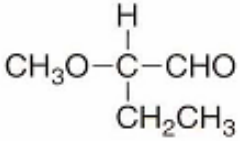
b. 

c. 

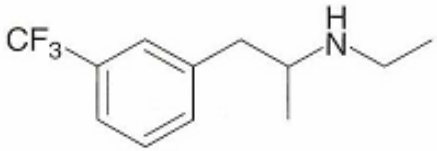
d. 

11 Draw the two enantiomers of each compound and label them as *R* or *S*.

a. 

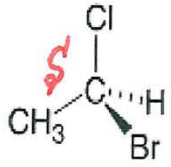
b. 

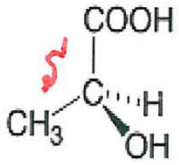
12 Draw both enantiomers of fenfluramine, one component of the appetite suppressant Fen–Phen. The *S* enantiomer was sold independently under the name dexfenfluramine. Which enantiomer is dexfenfluramine? (Fen–Phen was withdrawn from the market in 1997, after it was shown to damage heart valves in some patients.)

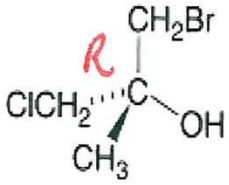


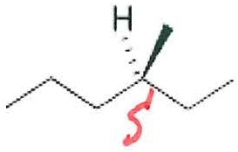
fenfluramine

10 Label each compound as *R* or *S*.

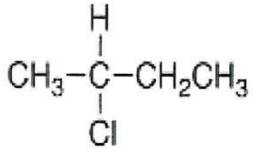
a. 

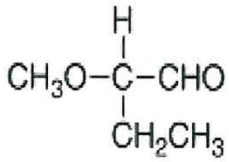
b. 

c. 

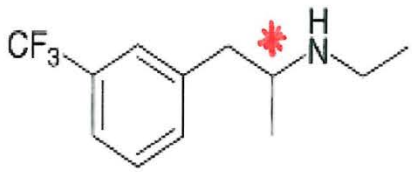
d. 

11 Draw the two enantiomers of each compound and label them as *R* or *S*.

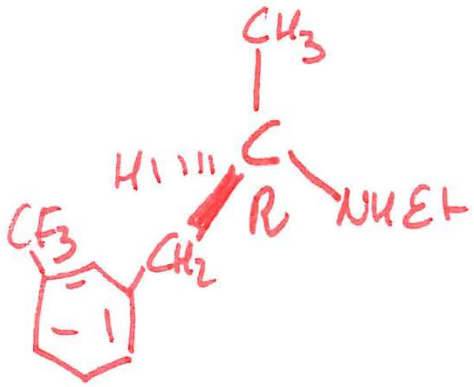
a. 

b. 

12 Draw both enantiomers of fenfluramine, one component of the appetite suppressant Fen–Phen. The *S* enantiomer was sold independently under the name dexfenfluramine. Which enantiomer is dexfenfluramine? (Fen–Phen was withdrawn from the market in 1997, after it was shown to damage heart valves in some patients.)



fenfluramine

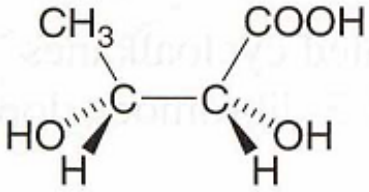


13 What is the maximum number of stereoisomers possible for a compound with three stereogenic centers? What is the maximum number of stereoisomers for a compound like cholesterol (Problem 5.11) with eight stereogenic centers?

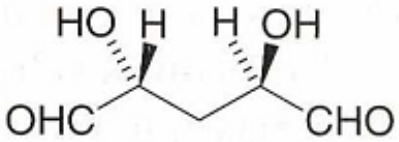
14 Label the two stereogenic centers in each compound and draw all possible stereoisomers: (a) $CH_3CH_2CH(Cl)CH(OH)CH_2CH_3$; (b) $CH_3CH(Br)CH_2CH(Cl)CH_3$

15 Draw the enantiomer and one diastereomer for each compound.

a.

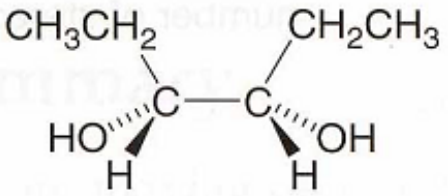


b.

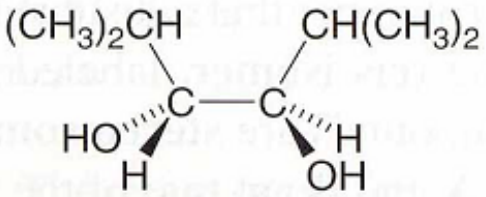


16 Which compounds are meso compounds?

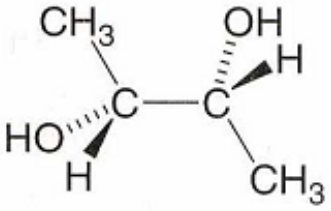
a.



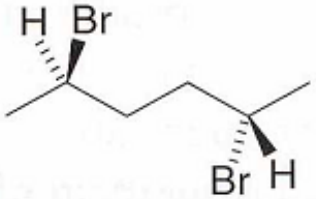
b.



c.



d.



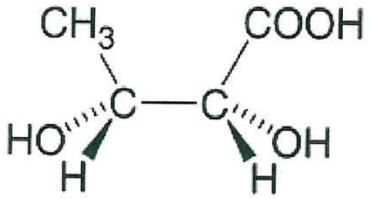
13 What is the maximum number of stereoisomers possible for a compound with three stereogenic centers? What is the maximum number of stereoisomers for a compound like cholesterol (Problem 5.11) with eight stereogenic centers? 8

$2^8 =$

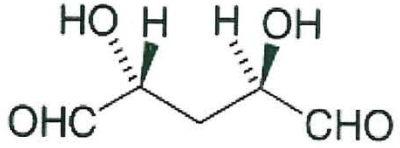
14 Label the two stereogenic centers in each compound and draw all possible stereoisomers: (a) $CH_3CH_2CH(Cl)CH(OH)CH_2CH_3$; (b) $CH_3CH(Br)CH_2CH(Cl)CH_3$

15 Draw the enantiomer and one diastereomer for each compound.

a.

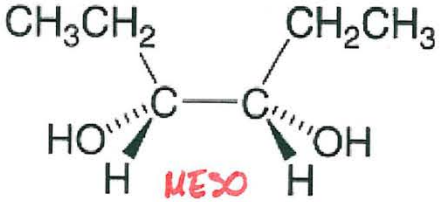


b.



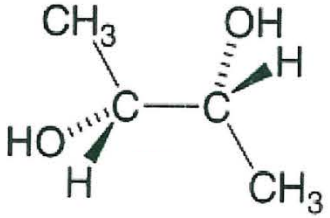
16 Which compounds are meso compounds?

a.

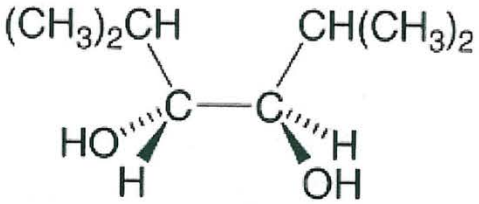


MESO

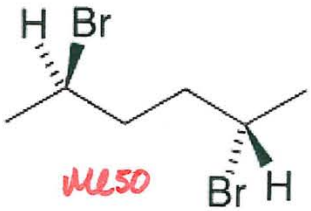
c.



b.



d.



MESO

17 If the two stereogenic centers of a compound are *R,S* in configuration, what are the *R,S* assignments for its enantiomer and two diastereomers?

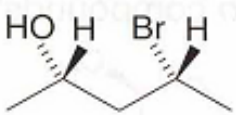
18 Without drawing out the structures, label each pair of compounds as enantiomers or diastereomers.

a. (2*R*,3*S*)-2,3-hexanediol and (2*R*,3*R*)-2,3-hexanediol

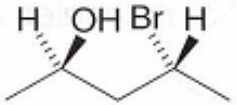
b. (2*R*,3*R*)-2,3-hexanediol and (2*S*,3*S*)-2,3-hexanediol

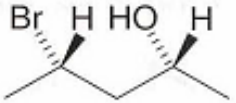
c. (2*R*,3*S*,4*R*)-2,3,4-hexanetriol and (2*S*,3*R*,4*R*)-2,3,4-hexanetriol

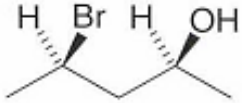
19 How is each compound related to **A?** Is it an enantiomer, diastereomer, or identical?

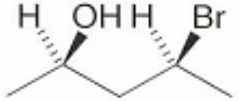


A

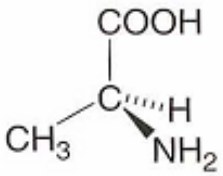
a. 

b. 

c. 

d. 

20 The amino acid (*S*)-alanine has the physical characteristics listed under the structure.



(*S*)-alanine
[α] = +8.5°
mp = 297 °C

a. What is the melting point of (*R*)-alanine?

b. What is the melting point of a racemic mixture of (*R*)- and (*S*)-alanine?

c. What is the observed rotation of (*R*)-alanine, recorded under the same conditions as the reported rotation of (*S*)-alanine?

d. What is the observed rotation of a racemic mixture of (*R*)- and (*S*)-alanin

e. Label each of the following as optically active or inactive: a solution of pure (*S*)-alanine; an equal mixture of (*R*)- and (*S*)-alanine; a solution that contains 75% (*S*)- and 25% (*R*)-alanine.

S,R

17 If the two stereogenic centers of a compound are *R,S* in configuration, what are the *R,S* assignments for its enantiomer and two diastereomers? → RR, SS

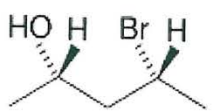
18 Without drawing out the structures, label each pair of compounds as enantiomers or diastereomers.

a. (2*R*,3*S*)-2,3-hexanediol and (2*R*,3*R*)-2,3-hexanediol diast

b. (2*R*,3*R*)-2,3-hexanediol and (2*S*,3*S*)-2,3-hexanediol enant

c. (2*R*,3*S*,4*R*)-2,3,4-hexanetriol and (2*S*,3*R*,4*R*)-2,3,4-hexanetriol diast

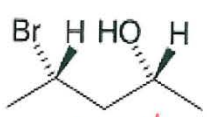
19 How is each compound related to **A?** Is it an enantiomer, diastereomer, or identical?



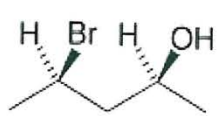
A

a. 

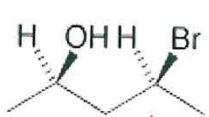
Diast

b. 

enant

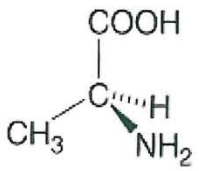
c. 

identico

d. 

enant.

20 The amino acid (*S*)-alanine has the physical characteristics listed under the structure.



(*S*)-alanine
[α] = +8.5°
mp = 297 °C

a. What is the melting point of (*R*)-alanine? 297°C

b. What is the melting point of a racemic mixture of (*R*)- and (*S*)-alanine? Menor

c. What is the observed rotation of (*R*)-alanine, recorded under the same conditions as the reported rotation of (*S*)-alanine? −8.5°

d. What is the observed rotation of a racemic mixture of (*R*)- and (*S*)-alanin 0°

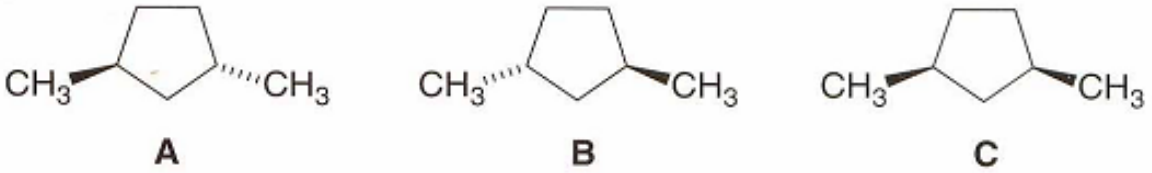
e. Label each of the following as optically active or inactive: a solution of pure (*S*)-alanine; an equal mixture of (*R*)- and (*S*)-alanine; a solution that contains 75% (*S*)- and 25% (*R*)-alanine.

activa

activa +4,25°

no activa

21 Compare the physical properties of the three stereoisomers of 1,3-dimethylcyclopentane.



A **B** **C**

three stereoisomers of 1,3-dimethylcyclopentane

a. How do the boiling points of **A** and **B** compare? What about **A** and **C**?
b. Characterize a solution of each of the following as optically active or optically inactive: pure **A;** pure **B;** pure **C;** an equal mixture of **A** and **B;** an equal mixture of **A** and **C.**
c. A reaction forms a 1:1:1 mixture of **A, B,** and **C.** If this mixture is distilled, how many fractions would be obtained? Which fractions would be optically active and which would be optically inactive?