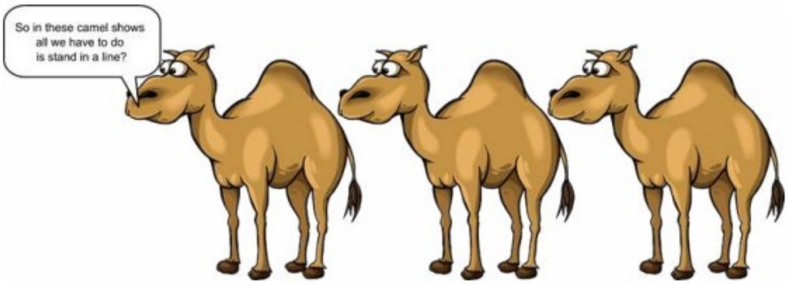
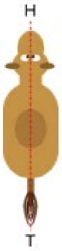
1. Stereocamelstry

A nighttime camel show in the UAE

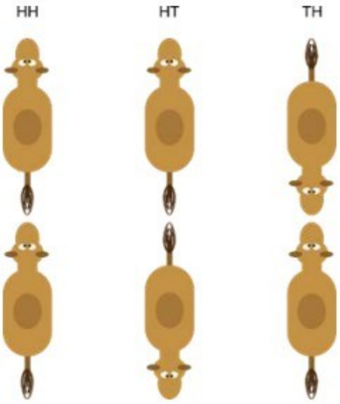
The UAE is well known for its camel shows, where camels stand in a line one after another and don’t really do anything else. This arrangement of camels is called a train of camels, or a caravan of camels, and the camels are tied head to tail. This is the most convenient way of arranging camels when moving across the desert.



For this problem we shall approximate a normal camel as having a plane of symmetry along its body; its left side is the same as its right side. However, the two ends of a camel are different; a camel has a head end (H) and a tail end (T).



Colin was trying to tie lots of camels up into trains of camels that were two camels long, but was a bit forgetful and didn’t think to look at which way around the camels were when he was tying them up. This resulted in three different arrangements of camels in the train being possible.

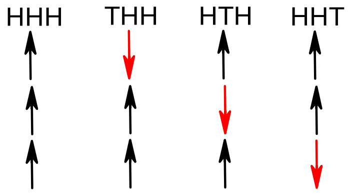


The three arrangements possible when viewed from overhead are shown above. We could call these three arrangements HH, HT, and TH respectively, based on whether the head or the tail of the camel comes first as we look from top to bottom. We might at first think that there is a fourth possible arrangement of camels (TT).

However, this arrangement is not unique. If we were to view the TT arrangement from the other end, it is the same as HH.
This question requires you to draw various arrangements of camels. If your artistic skills have deserted you somewhat, then you may approximate a camel to something simpler in your drawings such as an arrow. It is important to remember though that camels are three dimensional objects.

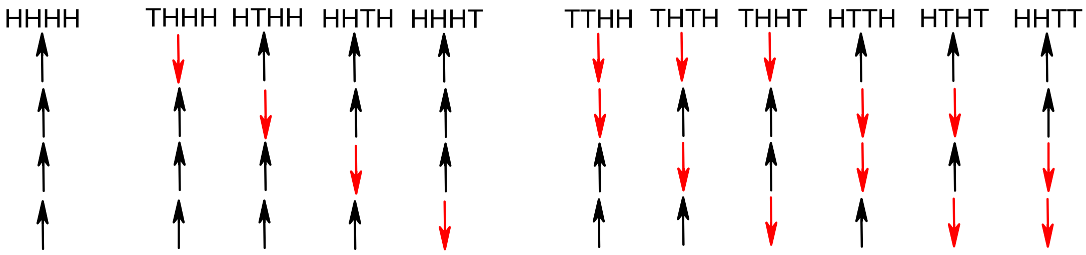
(a) Draw all possible arrangements of camels in a camel train that is three camels long.

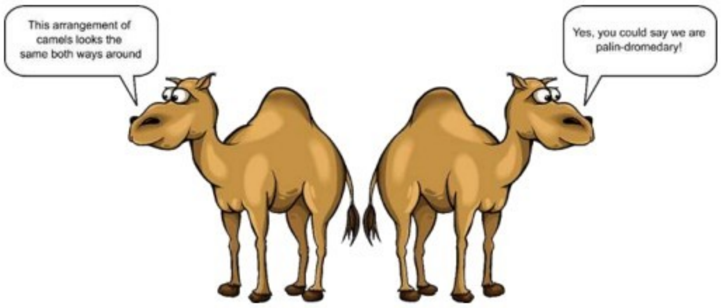
--(a) Risposta
Vi sono solo 4 possibili disposizioni distinguibili.
Se si rovesciano due cammelli si ottengono posizioni già viste rovesciandone uno solo.



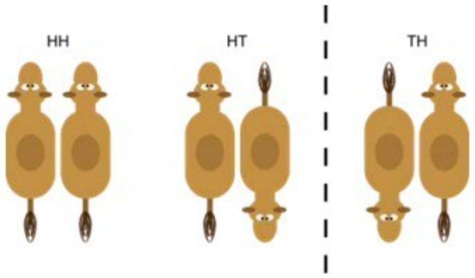
(b) Draw all possible arrangements of camels in a camel train that is four camels long.

--(b) Risposta
Vi è una sola sistemazioni con 4 cammelli orientati verso l’alto.
Vi sono 4 sistemazioni con 1 cammello orientato in direzione opposta.
Vi sono 6 sistemazioni con due cammelli in direzione opposta.
Se si capovolgono 3 cammelli si ottengono sistemazioni già viste capovolgendo 1 cammello, e così con 4 cammelli orientati in basso si ottiene la stessa sistemazione di 4 cammelli orientati verso l’alto.
In totale sono possibili 11 disposizioni diverse.





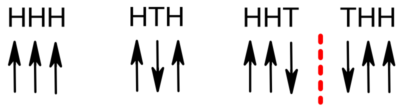
When camels are tied up for the night, they are sometimes arranged side by side. Let’s first consider a parking arrangement where two camels are side by side.
Again, Colin was a bit forgetful and didn’t pay attention to which way round he was tying the camels. There are three possible side by side arrangements of two camels.



When viewed from overhead, and described going left to right, we can call these arrangements HH, HT, and TH respectively. Again, we might think there is a fourth possible arrangement of camels (TT), but this is the same as HH if viewed from the other side. The HT and TH arrangements are also interesting, as they are chiral arrangements of camels. Even though an individual camel is achiral, these two arrangements of camels are chiral overall, and they are enantiomers of each other.

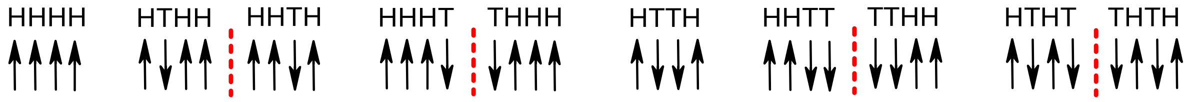
(c) Draw all possible arrangements of camels when three camels are tied side by side, indicating which arrangements are achiral and which arrangements are chiral.

–(c) Risposta
Ci sono 4 possibili disposizioni, due di queste sono una coppia di enantiomeri (HHT e THH), mentre le altre due disposizioni sono achirali perchè hanno un piano di simmetria interno (HHH e HTH).

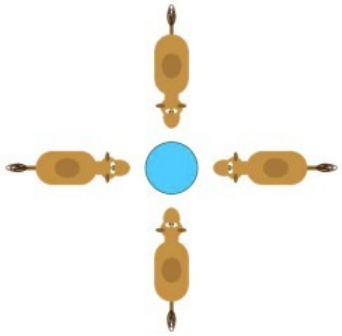


(d) Draw all possible arrangements of camels when four camels are tied side by side, indicating which arrangements are achiral and which arrangements are chiral.

–(d) Risposta
Ci sono 10 possibili disposizioni, 8 di queste formano 4 coppie di enantiomeri (HTHH e HHTH; HHHT e THHH; HHTT e TTHH; HTHT e THTH), mentre le altre due disposizioni sono achirali perchè hanno un piano di simmetria interno (HHHH e HTTH).



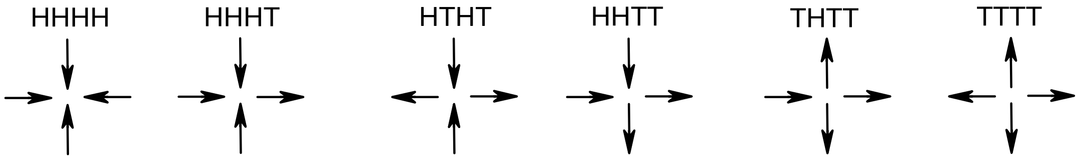
Although camels are famous for going for long periods without water, they do sometimes need to drink. A particular well has space for four camels to stand around it and drink water. To do this, the camels should be arranged around the well as shown.



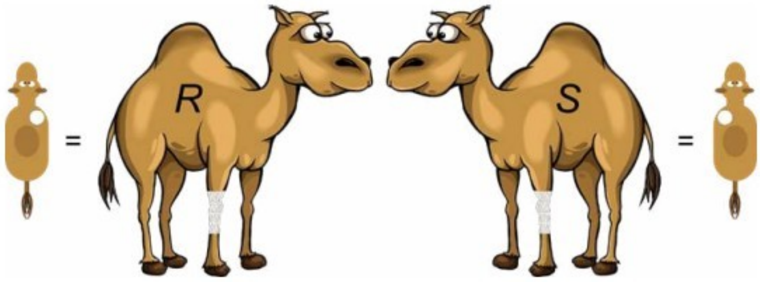
However, Colin was forgetful again and did not pay attention to which was the head end, and which was the tail end, when tying them up.

(e) Draw all possible arrangements of camels around the well, indicating which arrangements are achiral and which arrangements are chiral.

–(e) Risposta
Ci sono 6 possibili disposizioni. Dato che tutte contengono un piano di simmetria (perpendicolare al terreno), non ci sono arrangiamenti chirali.

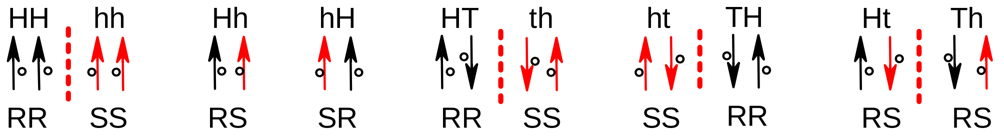


Carrying people across the desert is an arduous task for camels. Camels bend their front legs to sit down when carrying a rider and sometimes this leads to them injuring a leg. An individual camel who has injured one leg is no longer achiral and becomes a chiral camel. We will call chiral camels who have injured their front right leg as R camels and camels who have injured their front left leg as S camels.

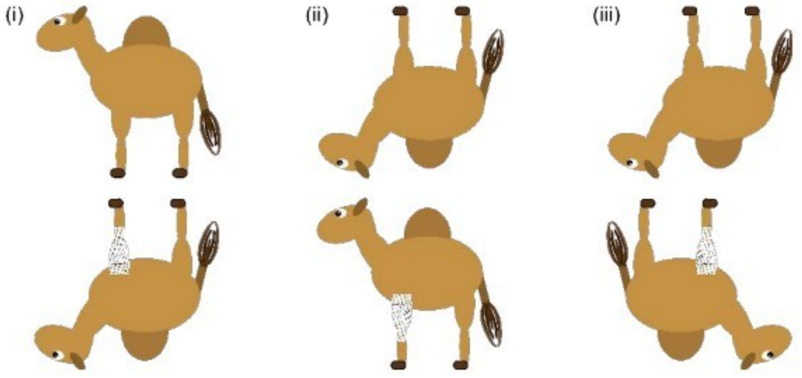


(f) Draw all possible arrangements of camels when two chiral camels are tied side by side, indicating which arrangements are achiral and which arrangements are chiral. Assume camels were picked randomly from a herd containing both R and S camels and then were parked randomly with no attention paid to which way around they were parked.

-(f) Risposta
Le tre diverse disposizioni di due cammelli affiancati diventano 10 se i cammelli possono essere R o S.
Qui sotto sono indicati con H e T maiuscole i cammelli R (neri), con h e t minuscole i cammelli S (rossi).
La zampa malata è mostrata con un cerchietto.
Queste 10 disposizioni si possono organizzare in 5 coppie.
Quattro di queste coppie sono formate da arrangiamenti chirali e quindi sono coppie di enantiomeri speculari (lo specchio è mostrato con un tratteggio).
Solo la seconda coppia contiene arrangiamenti achirali (3 e 4). Gli arrangiamenti 3 e 4 sono achirali perchè contengono un piano di simmetria. Sono sovrapponibili alla propria immagine speculare.



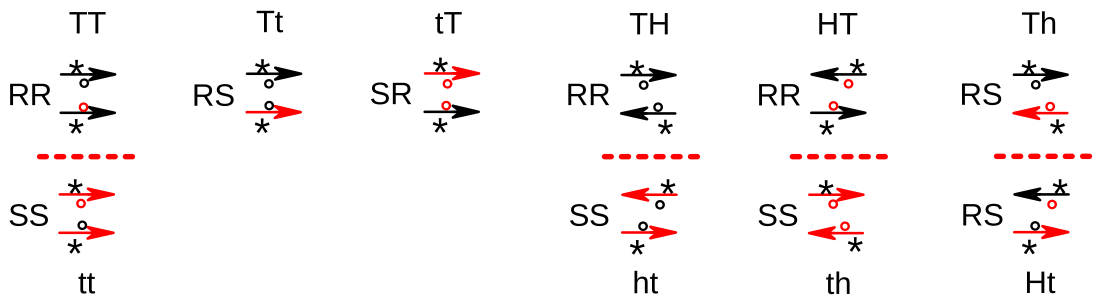
Fortunately, the UAE have just opened a Care Centre for Chiral Camels. To maximise efficiency, Carol the surgeon operates on two camels at once. The camels are lying down during their operation and there are three possible operation layouts: (i) feet-to-feet, (ii) hump-to-hump, and (iii) feet-to-hump. Note in the cartoon below only the top leg is visible.



(g) Draw all possible arrangements of two chiral camels on the operating table in a feet-to-feet layout, indicating which arrangements are achiral and which arrangements are chiral. Just consider the position of the two camels relative to each other.

–(g) Risposta

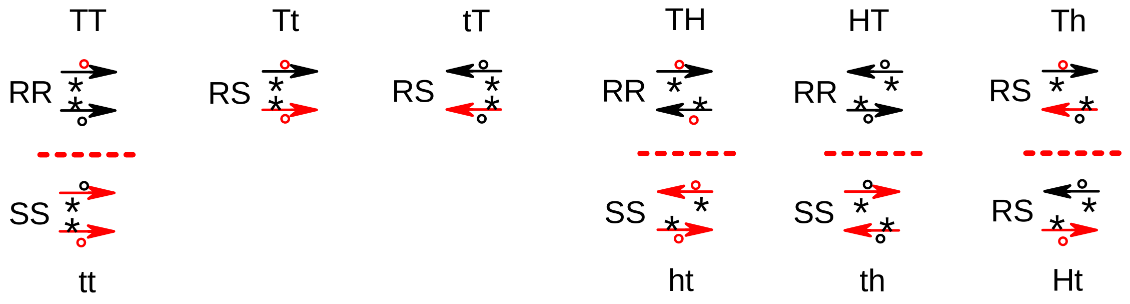
Ci sono 10 diverse disposizioni di coppie di cammelli sdraiati piedi contro piedi.
Qui sotto sono indicati con H e T maiuscole i cammelli R (neri), con h e t minuscole i cammelli S (rossi).
La zampa malata è mostrata con un cerchietto nero se è visibile dall'alto, con un cerchietto rosso se non è visibile dall'alto. L'asterisco indica la posizione della gobba che qui è sempre esterna alla coppia.
Otto di queste disposizioni sono state organizzate in 4 coppie formate da arrangiamenti chirali e quindi sono coppie di enantiomeri speculari.
Solo due arrangiamenti sono achirali. Gli arrangiamenti 3 e 4 sono achirali perchè contengono un piano di simmetria. Ciascuno di loro è sovrapponibile alla propria immagine speculare.



(h) Draw all possible arrangements of two chiral camels on the operating table in a hump-to-hump layout, indicating which arrangements are achiral and which arrangements are chiral. Just consider the position of the two camels relative to each other.

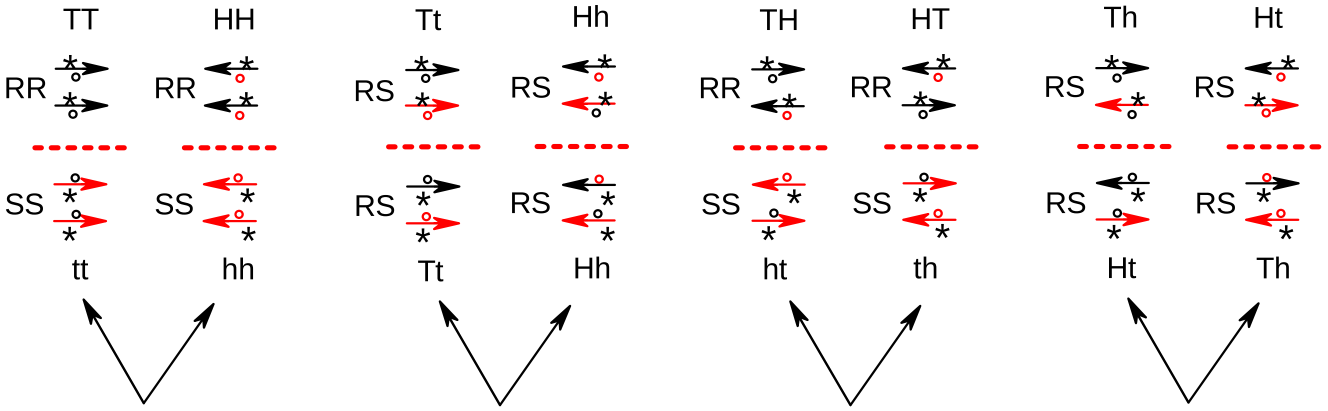
–(h) Risposta

Ci sono 10 diverse disposizioni di coppie di cammelli sdraiati gobba contro gobba.
Qui sotto sono indicati con H e T maiuscole i cammelli R (neri), con h e t minuscole i cammelli S (rossi).
La zampa malata è mostrata con un cerchietto nero se è visibile dall'alto, con un cerchietto rosso se non è visibile dall'alto. L'asterisco indica la posizione della gobba che qui è sempre all'interno della coppia.
Otto di queste disposizioni sono state organizzate in 4 coppie formate da arrangiamenti chirali e quindi sono coppie di enantiomeri speculari.
Solo due arrangiamenti sono achirali. Gli arrangiamenti 3 e 4 sono achirali perchè contengono un piano di simmetria. Ciascuno di loro è sovrapponibile alla propria immagine speculare.



(i) Draw all possible arrangements of two chiral camels on the operating table in a feet-to-hump layout, indicating which arrangements are achiral and which arrangements are chiral. Just consider the position of the two camels relative to each other.
No camels were harmed in the making of this question.

–(i) Risposta
Ci sono 16 diverse disposizioni di coppie di cammelli sdraiati piedi contro gobba.
Qui sotto sono indicati con H e T maiuscole i cammelli R (neri), con h e t minuscole i cammelli S (rossi).
La zampa malata è mostrata con un cerchietto nero se è visibile dall'alto, con un cerchietto rosso se non è visibile dall'alto.
L'asterisco indica la posizione della gobba che qui è per entrambi i cammelli diretta da un lato o dal lato opposto.
Nella disposizione piedi contro gobba ogni disposizione può essere appoggiata sul tavolo operatorio su un lato (ad esempio con la gamba malata rivolta in alto) oppure appoggiata sul lato opposto (con la gamba malata rivolta in basso) ottenendo disposizioni diverse perchè manca la simmetria interna che si aveva disponendo i cammelli in modo simmetrico (piedi contro piedi o gobba contro gobba).
Le 16 disposizioni sono tutte chirali e si possono organizzare in 8 coppie di enantiomeri speculari.



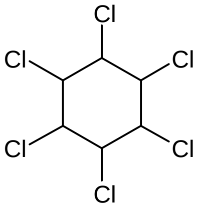
Soluzione proposta da Mauro Tonellato

2. Mirror, mirror plane on the wall, who's the deadliest of them all?

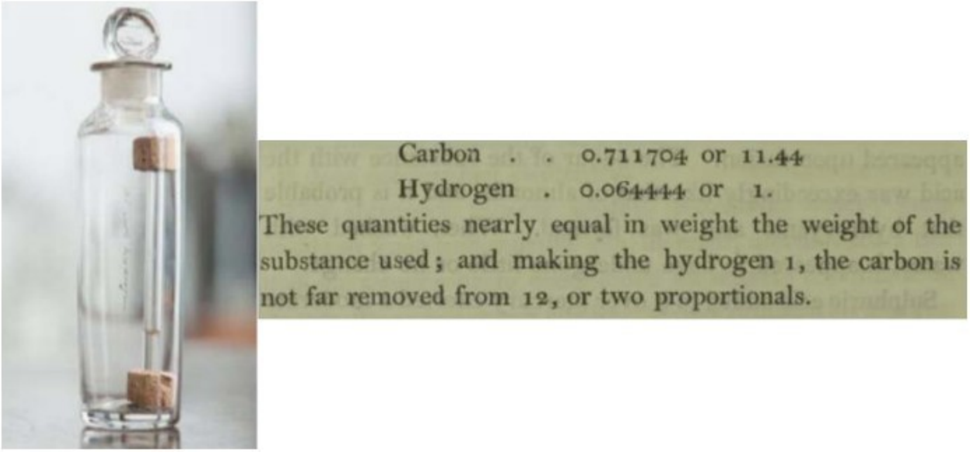
In the fairy tale Snow White, the evil queen looks at her reflection in the mirror and asks, "Mirror mirror on the wall, who is the fairest one of all?" The queen assumes she sees her exact self in the mirror; however, this is not always true. The reflection of a chiral object in a mirror gives its enantiomer. Sadly, for us chemists, this book from 1812 does not specify whether the queen was a chiral object or not.

Some compounds are formed as mixtures of many isomers, some of which are chiral, and some are not. Different isomers often have different chemical properties including how toxic they are. This is problematic if the synthesis leads to a mixture of isomers, but not all isomers are useful.

2025 is the 200th anniversary of the discovery of one of these compounds, 1,2,3,4,5,6-hexachlorocyclohexane (**HCH**), where many isomers turned out to be very toxic.



In 1825, British scientist Michael Faraday reported the discovery of benzene, which he had extracted from products of the pyrolysis of sperm oil. Through a series of meticulous experiments, he identified the accurate mass percentage of carbon and hydrogen in benzene. However, due to the concept of "proportionals" in use in science at the time, Faraday called this molecule the "bi-carburet of hydrogen" as 11.44 was close to 12, which was two "proportionals" of carbon.

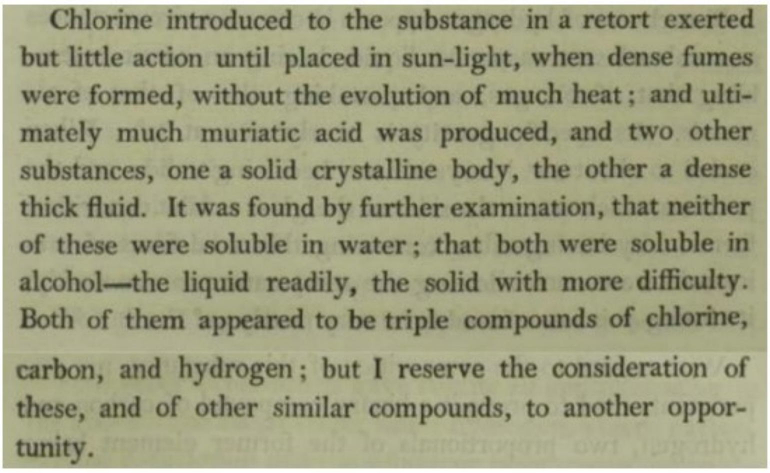


Carbon . . 0.711704 or 11.44
Hydrogen . 0.064444 or 1.

These quantities nearly equal in weight the weight of the substance used; and making the hydrogen 1, the carbon is not far removed from 12, or two proportionals.

Figure 1: Left. Faraday's sample of the bi-carburet of hydrogen which is kept at the Royal Institution. Right. Faraday's determination of the mass percentages in benzene.

Faraday also reported the reaction of benzene with various other chemicals including chlorine gas.



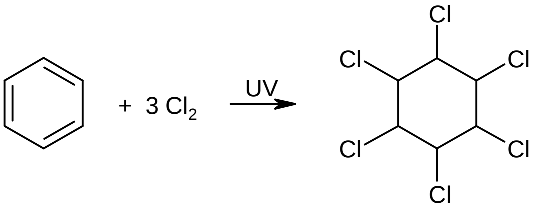
Chlorine introduced to the substance in a retort exerted but little action until placed in sun-light, when dense fumes were formed, without the evolution of much heat; and ultimately much muriatic acid was produced, and two other substances, one a solid crystalline body, the other a dense thick fluid. It was found by further examination, that neither of these were soluble in water; that both were soluble in alcohol—the liquid readily, the solid with more difficulty. Both of them appeared to be triple compounds of chlorine, carbon, and hydrogen; but I reserve the consideration of these, and of other similar compounds, to another opportunity.

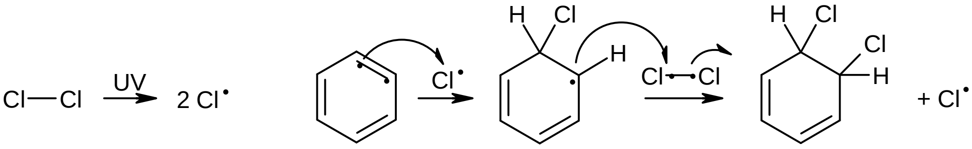
Figure 2: Faraday's description of the reaction of benzene and chlorine under sunlight.

Several different equations could be written to describe his observations, likely due to the presence of impurities in the sample. However, the "solid crystalline body" produced was the first synthesis of **HCH**. Faraday correctly deduced that this compound contained carbon, hydrogen, and chlorine, but was unable to identify it further or know that it contained a mixture of isomers.
A modern synthesis of **HCH** involves the treatment of benzene with chlorine gas under UV light. The reaction is a free-radical addition.

(a) Write an equation for this reaction.

-(a) Risposta

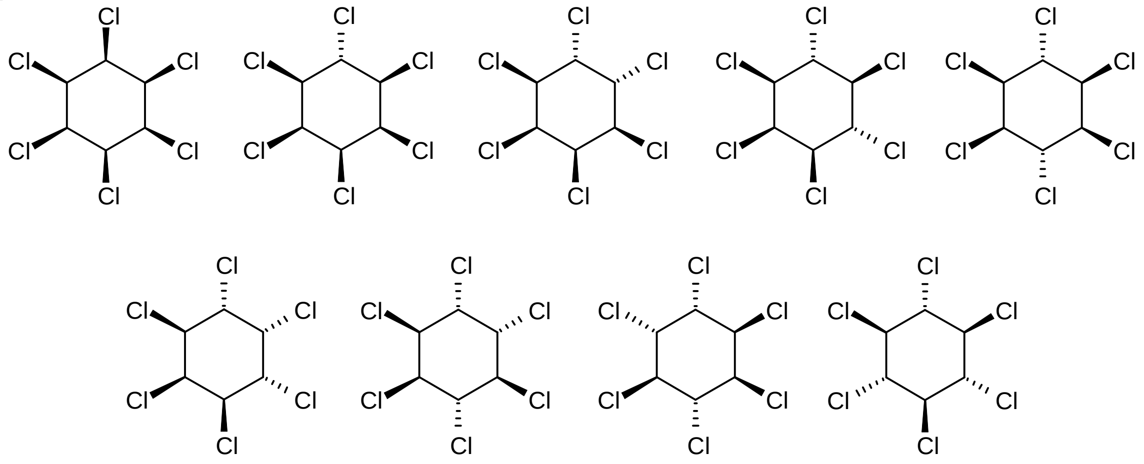




HCH exists as nine stereoisomers. For the purposes of parts (b) and (c) consider the cyclohexane ring to be flat.

(b) Draw all the stereoisomers of **HCH**.

–(b) Risposta



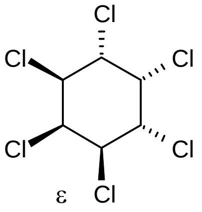
The nine stereoisomers of HCH are named with the following Greek letters.

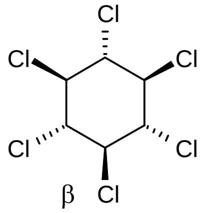
α+	α–	β
γ	δ	ε
ζ	η	θ

(c) Using the following clues, as far as possible, **assign** the Greek letters to each of the isomers.

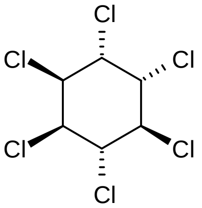
1 - The β and ε isomers contain centres of inversion.
2 - The ζ isomer is not an epimer of the α+ isomer.
3 - The θ isomer is an epimer of the η isomer.
4 - The γ isomer has more planes of symmetry than the δ isomer.
5 - The η isomer does not possess a plane of symmetry through any of the atoms.
6 - The + and – refer to dextrorotatory and levorotatory respectively.
7 - The β isomer has by far the lowest chemical reactivity.

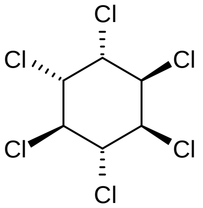
–(c) Risposta


ε

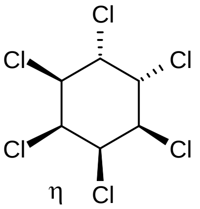

β

(1) Questi due sono i soli isomeri che contengono un centro di inversione.
(7) La seconda molecola è di gran lunga l'isomero più stabile perchè può avere tutti gli atomi di cloro in posizione equatoriale dato che sono diretti in direzioni opposte, uno verso l'alto e il successivo verso il basso.
Il primo isomero quindi è ε, il secondo è β, il più stabile.

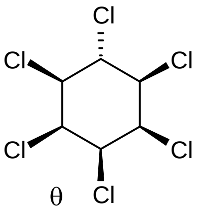


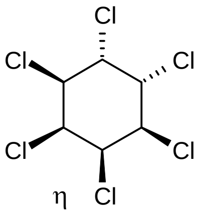


(6) Questi due isomeri sono una coppia di enantiomeri, quindi sono gli isomeri α+ e α–.

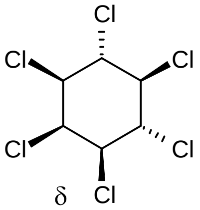

η

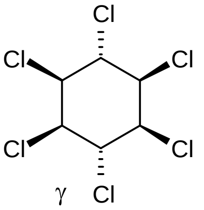
(5) Questo è il solo isomero che non possiede un piano di simmetria che attraversi i suoi atomi di cloro (ha un piano di simmetria che taglia la molecola nel centro di un legame C-C).
Quindi questo è l'isomero η.


θ

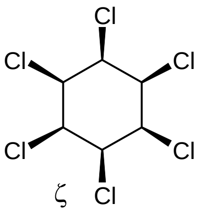

η

(3) Il primo di questi due isomeri è θ perchè è l'epimero di η sul C-2, cioè ha tutti i centri stereogenici uguali all'altro fuorchè uno, quello sul C-2.


δ


γ

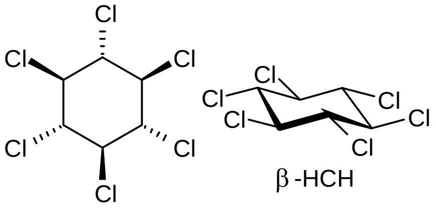
(4) Questi due sono gli isomeri δ e γ.
L'isomero γ è il secondo perchè ha più piani di simmetria.
Entrambi hanno un piano di simmetria che passa per gli atomi di cloro, ma il secondo ha anche un altro piano (orizzontale) che taglia i legami C-C centrali.


ζ

(2) Questo è l'isomero ζ che non è epimero dell'isomero α+. Infatti, i due isomeri hanno tre atomi di cloro con configurazione invertita e non uno solo.

(d) Explain why the β isomer has by far the lowest chemical reactivity.

-(d) Risposta



L’isomero β **HCH** è mostrato qui a fianco con la conformazione a barca. Si vede che tutti gli atomi di cloro si trovano nella posizione equatoriale grazie al fatto che sono diretti, alternativamente, uno verso l’alto e il successivo verso il basso.
La molecola con sostituenti in posizione equatoriale è più stabile perchè ha meno ingombro sterico che invece sorge con i sostituenti in posizione assiale, chiamato ingombro 1,3 diassiale.

Many years later, the mixture of isomers of **HCH** was found to have potent insecticidal activity. Dutch chemist Teunis van der Linden was the first to isolate and describe γ-**HCH** in 1912 and this isomer was named “lindane” after him. By 1942, it was realised that lindane (γ-**HCH**) was the isomer responsible for the potency of the insecticide and γ-**HCH** went on sale as a seed treatment in 1949 called Mergamma A, which contained 1% mercury and 20% lindane. The mercury was removed later for safety reasons, but lindane products remained on sale for over 50 years.

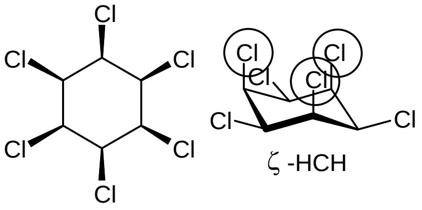
Whilst the γ-isomer of **HCH** was available in >98% purity by this point, this was achieved through purification; the synthesis of **HCH** always gave a complex mixture composed of 65-70% α-**HCH**, 7-10% β-**HCH**, 14-15% γ-**HCH**, 7% δ-**HCH**, 1-2% ε-**HCH**, and 1-2% of the other isomers. Once separated, the remaining isomers were dumped creating huge chemical waste problems.

Figure 3: Mountains of the useless isomers of HCH which were dumped as waste in places such as Eastern Europe (left) and France (right).

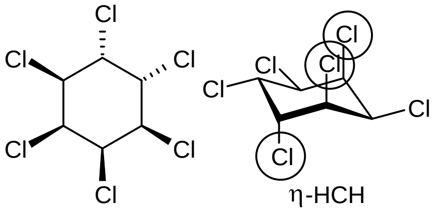
(e) Suggest why very little of the ζ-**HCH**, η-**HCH**, and θ-**HCH** isomers are formed during synthesis.

-(e) Risposta

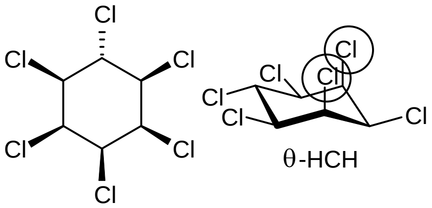
Nella reazione radicalica i due atomi di cloro di Cl_2 si legano all’anello in tempi diversi, e si legano preferenzialmente nella posizione più favorevole, quella che crea meno ingombro sterico.



L’isomero ζ-**HCH**, possiede tre atomi di cloro in posizione assiale tutti disposti dallo stesso lato della molecola e quindi creano un forte ingombro sterico 1,3 diassiale. La molecola è molto instabile.



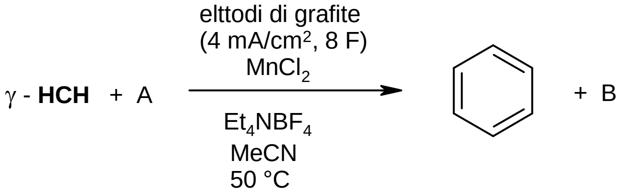
L’isomero η-**HCH**, ha tre atomi di cloro in posizione assiale due su un lato della molecola e uno sul lato opposto. Quindi creano un certo ingombro sterico 1,3 diassiale. La molecola è instabile.



L’isomero θ-**HCH**, ha due atomi di cloro in posizione assiale dallo stesso lato della molecola. Quindi creano un certo ingombro sterico 1,3 diassiale. La molecola è instabile.

Over time the toxicity of γ-**HCH** itself became apparent. The γ-isomer is now classified by the World Health Organisation as acutely toxic. Prolonged exposure leads to various symptoms including headaches, dizziness, seizures, convulsions, and even death in extreme cases. An international ban on the use of γ-HCH in agriculture came into effect in 2009. The α-HCH and β-HCH isomers, which were dumped as chemical waste, proved to be even more toxic. All isomers show long term persistence in the environment and hence still cause problems today.

In 2021, a research team led by Swiss chemist Bill Morandi developed a new way to clean up HCH waste through electrolysis. His reaction reverses the reaction performed two centuries earlier by Faraday, as γ-HCH is converted back to benzene. However, rather than produce toxic chlorine gas, the chlorine atoms are transferred to another readily available non-cyclic alkene starting material A, giving chloroalkane B as a by-product. This makes the transformation overall redox neutral. This process is highly synthetically useful as it removes toxic HCH waste and produces two valuable chemical products: benzene and chloroalkane B.



The mass spectrum of compound B gave the following ions: m/z 238.125 (100.0%); 239.128 (13.0%); 240.122 (63.9%); 241.125 (8.3%); 242.119 (10.2%); 243.122 (1.3%). Percentages listed show the relative amounts with the most intense peak set at 100%.

(f) Determine the formula for B.

-(f) Risposta

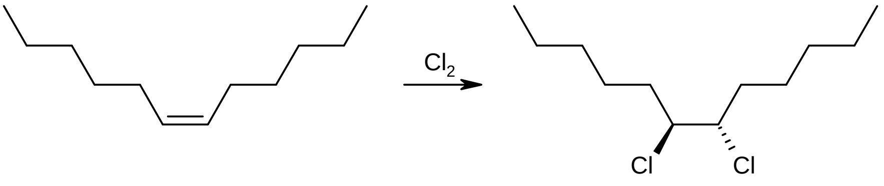
Il cloro esiste come combinazione di due isotopi ^{35}Cl e ^{37}Cl che si trovano in rapporto 3:1.
La variabilità della massa della molecola è influenzata anche dalla presenza di ^{13}C oltre a ^{12}C e di ^{2}H oltre a ^{1}H. Questi isotopi hanno però un'abbondanza molto minore, circa 1:100.
La presenza di ^{37}Cl al posto di ^{35}Cl fa aumentare il PM di due unità, quindi nella molecola B ci sono due atomi di cloro perchè i PM variano da 238 (^{35}Cl-^{35}Cl) a 240 (^{35}Cl-^{37}Cl) a 242 (^{37}Cl-^{37}Cl).
Le abbondanze relative prevedibili sono:
(^{35}Cl-^{35}Cl) = 0,75 · 0,75 = 0,56 → 100%
(^{35}Cl-^{37}Cl) = 0,75 · 0,25 + 0,25 · 0,75 = 0,37 → 66%
(^{37}Cl-^{37}Cl) = 0,25 · 0,25 = 0,062 → 11%
Queste percentuali sono in accordo coi dati sperimentali (100%, 63,4%, 10,2%).
Il PM senza i due atomi di cloro diventa: 238 – 70 = 168. Quindi la molecola contiene 168/14 = 12 CH_2.
La formula bruta della molecola **B** è: $C_{12}H_{24}Cl_2$.

Compound B is produced as a racemic mixture of two enantiomers. As this process was designed to potentially be run on a large scale, compound A was chosen to be as simple/cheap as possible.

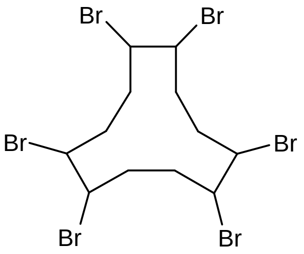
(g) Propose structures for compounds A and B.

(g) Risposta

La formula bruta della molecola **B** ($C_{12}H_{24}Cl_2$) ci dice che si tratta di una molecola priva di insaturazioni infatti, sostituendo i due atomi di cloro con due atomi di idrogeno, si ottiene $C_{12}H_{26}$ cioè la formula di un alcano C_nH_{2n+2}. (26 = 12 + 12 + 2). La molecola A è un alchene che, reagendo con Cl_2, forma un dicloroderivato. Dato che la reazione forma una coppia di enantiomeri, l'alchene deve essere simmetrico e deve avere configurazione cis, dato che l'alogenazione del doppio legame è una addizione anti. La molecola A, quindi è (6Z)-dodec-6-ene e la molecola B è (6R,7R) o (6S,7S)-6,7-diclorododecano.



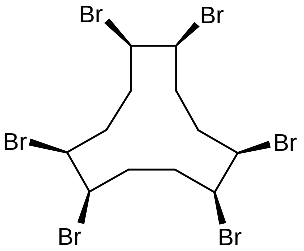
(6Z)-dodec-6-ene (6S,7S)-6,7-diclorododecano



The compound 1,2,5,6,9,10-hexabromocyclododecane (**HBCD**) has a lot of structural similarity to **HCH**. It also exists as multiple different stereoisomers; many of which are produced during its synthesis.
Dubai is famous for skyscrapers and high-rise buildings. Although not an issue in the UAE, many tall buildings in colder climates use polystyrene foam for thermal insulation. This insulation is very flammable, and due to the fire risks in tall buildings, flame retardants are put on this polystyrene foam. **HBCD** is used as one such flame retardant.

(h) Draw all the stereoisomers of HBCD, indicating which ones are chiral and which ones are achiral.

–(h) Risposta
Le specie achirali hanno un piano di simmetria nella molecola.



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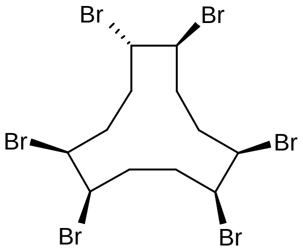

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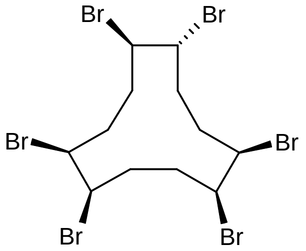

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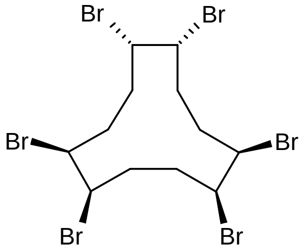

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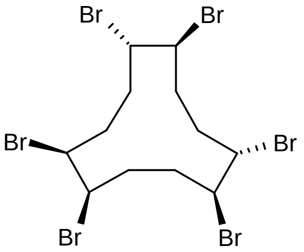

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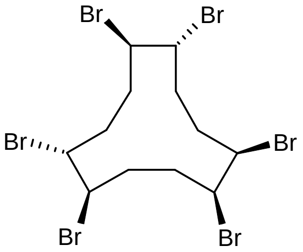

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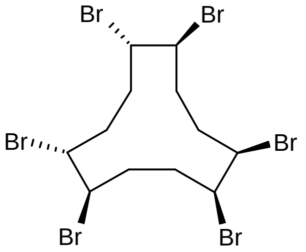

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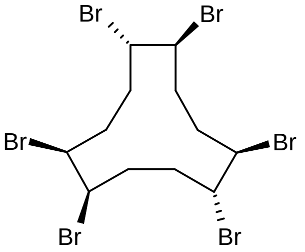

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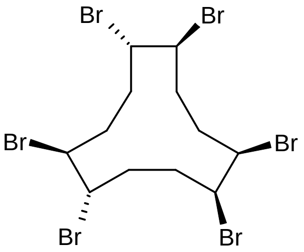

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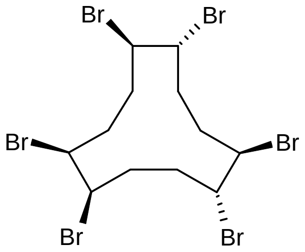

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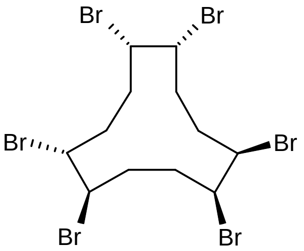

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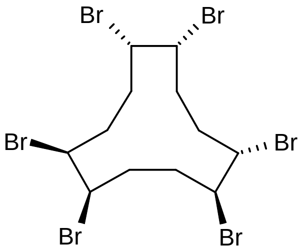

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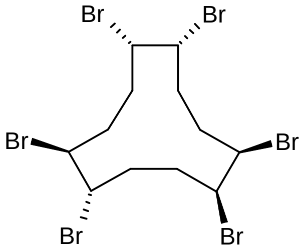

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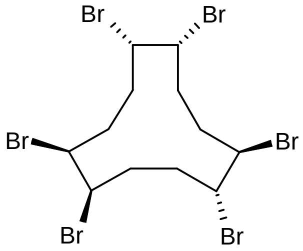

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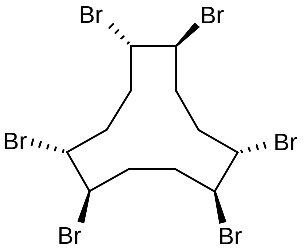

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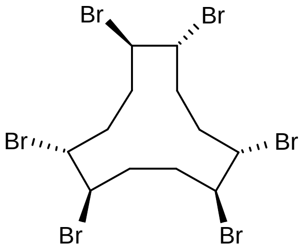

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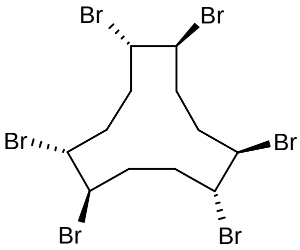

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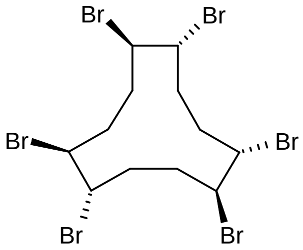


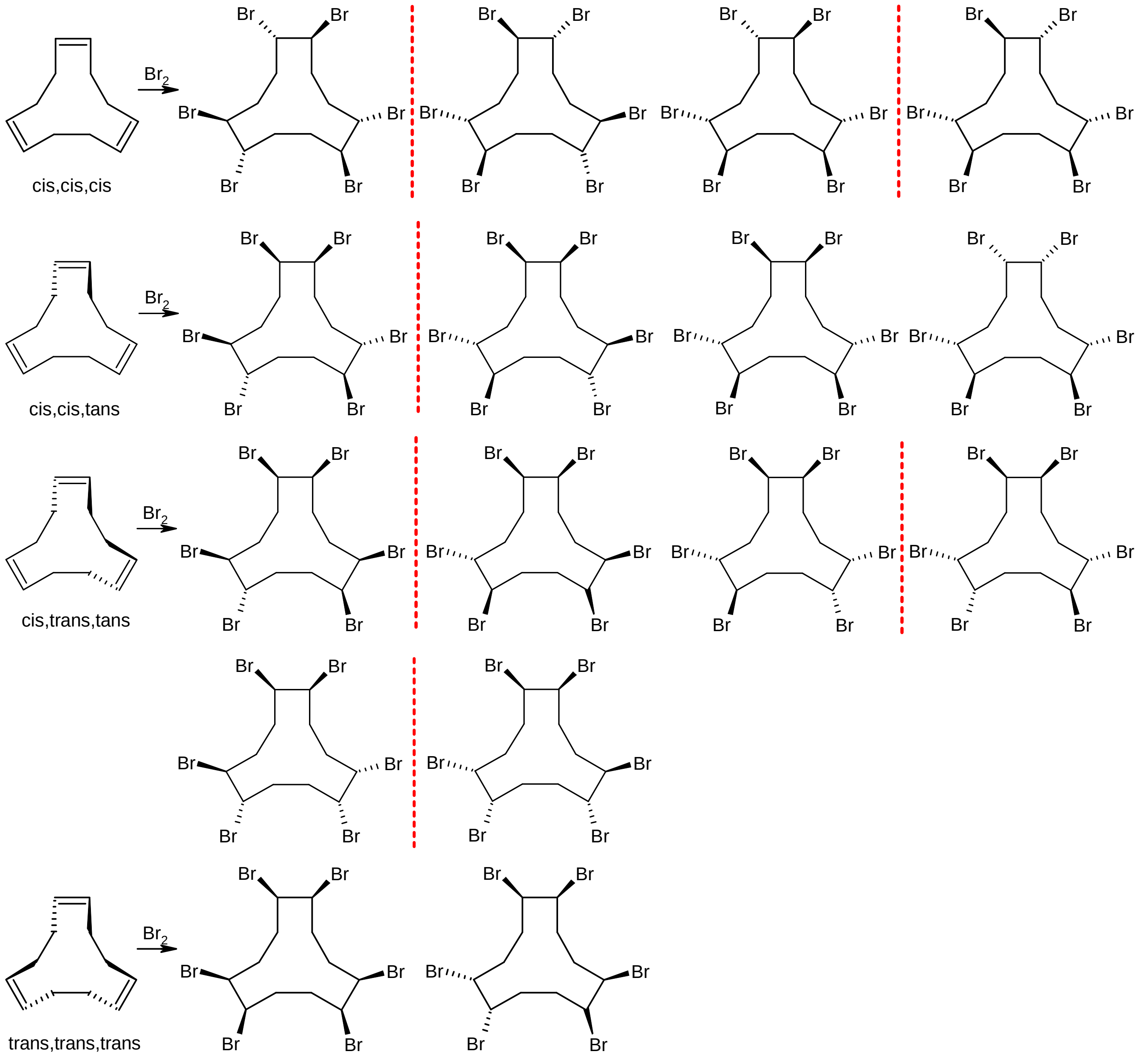
ch.

HBCD is also now known to have significant toxicity problems and be long lived in the environment. Assessing overall toxicity is complicated because the different isomers have different toxicities and break down at different rates.

Unlike **HCH**, the **HBCD** commercial product is used as a mixture of isomers. **HBCD** is produced from the bromination of cyclododeca-1,5,9-triene. Four isomers of cyclododeca-1,5,9-triene are possible:
(i) all-cis; (ii) cis,cis,trans; (iii) cis,trans,trans; and (iv) all-trans.

(i) Assuming the standard mechanism of alkene bromination, **determine** which **HBCD** isomers are produced from each of the four possible starting materials.

–(i) Risposta



(j) Given the commercial **HBCD** product is quoted as containing “three major diastereoisomers”, **is it possible to determine** which isomer of cyclododeca-1,5,9-triene is used as the starting material for the commercial synthesis?

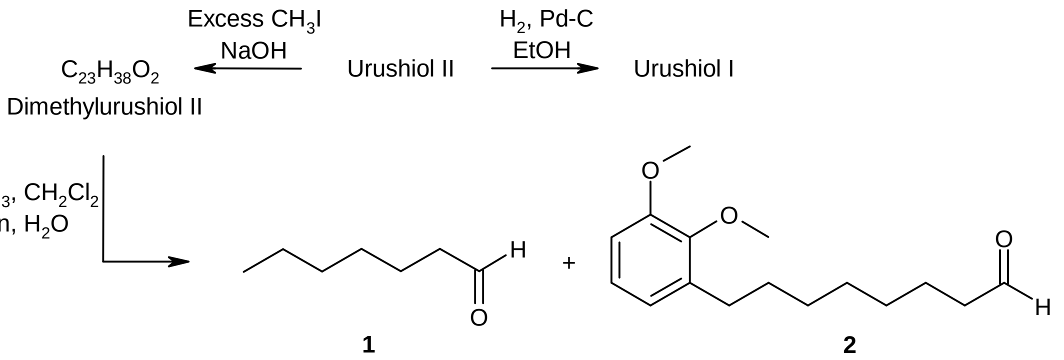
–(j) Risposta

I trieni che formano tre diversi diastereoisomeri **BHCD** sono solo due: l’isomero cis,cis,trans e il cis,trans,trans. L’isomero cis,cis,trans, però, forma composti più stabili che hanno solo 4 atomi di bromo rivolti dallo stesso lato della molecola **BHCD**. Mentre l’isomero cis,trans,trans forma una molecola con 5 Br dallo stesso lato.

Soluzione proposta da Mauro Tonellato

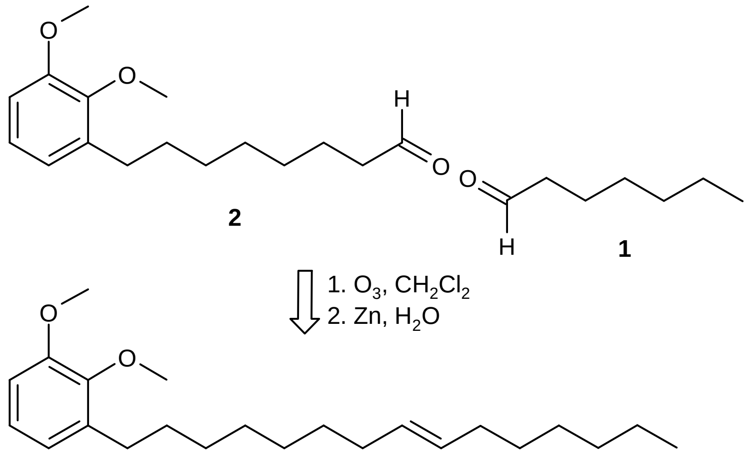
3. Urushiols

Urushiols are compounds that cause skin irritation. They are the active compounds in gypsum and poison oak that cause skin rash. Some chemical modifications of Urushiols I and II are shown below.



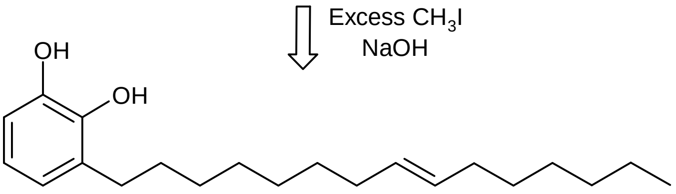
(a) Draw the structures of Urushiol I, Urushiol II, and dimethylurushiol II.

–(a) Risposta
La reazione che forma i composti 1 e 2 è un’ozonolisi seguita da un trattamento leggermente riducente che spezza la molecola di partenza sui doppi legami formando aldeidi o chetoni.
Riunendo con una retrosintesi i due frammenti attraverso i due legami C=O si ottiene la molecola di partenza.



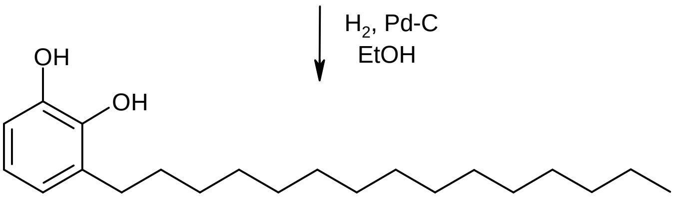
Dimethylurushiol II $C_{23}H_{38}O_2$

Il trattamento con NaOH trasforma un fenolo in fenato. Questo è più nucleofilo e può essere alchilato sull’ossigeno con una reazione SN2 con CH_3I formando un etere metilico.
La retrosintesi restituisce i due OH fenolici liberi dell’Urushinolo II.



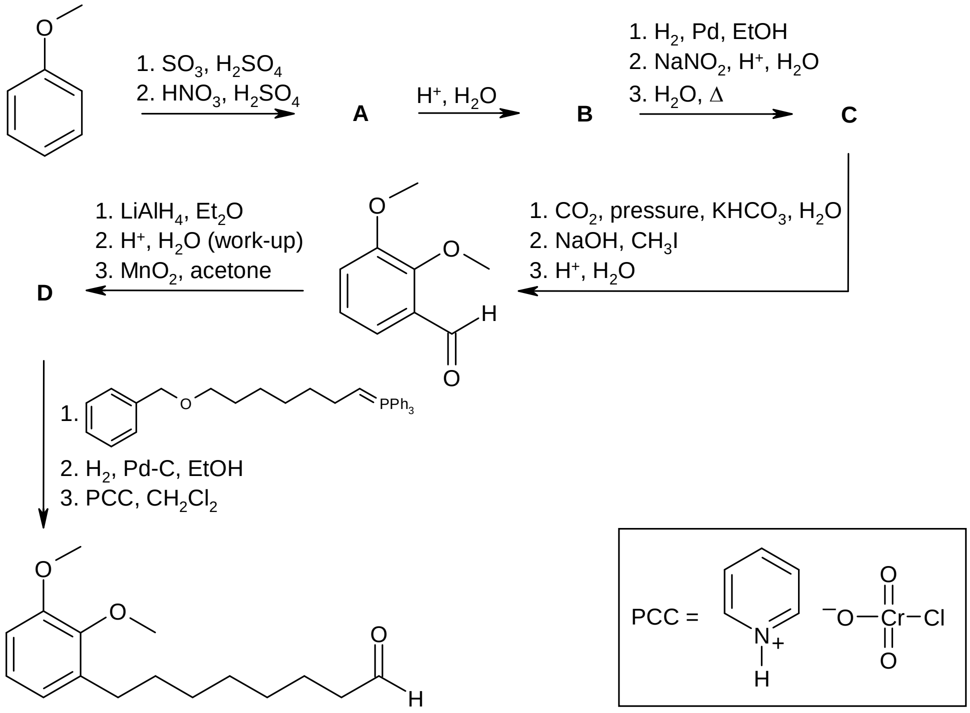
Urushiol II $C_{21}H_{34}O_2$

Il doppio legame dell’Urushinolo II può essere ridotto ad alcano con una idrogenazione catalitica.



Urushiol I $C_{21}H_{36}O_2$

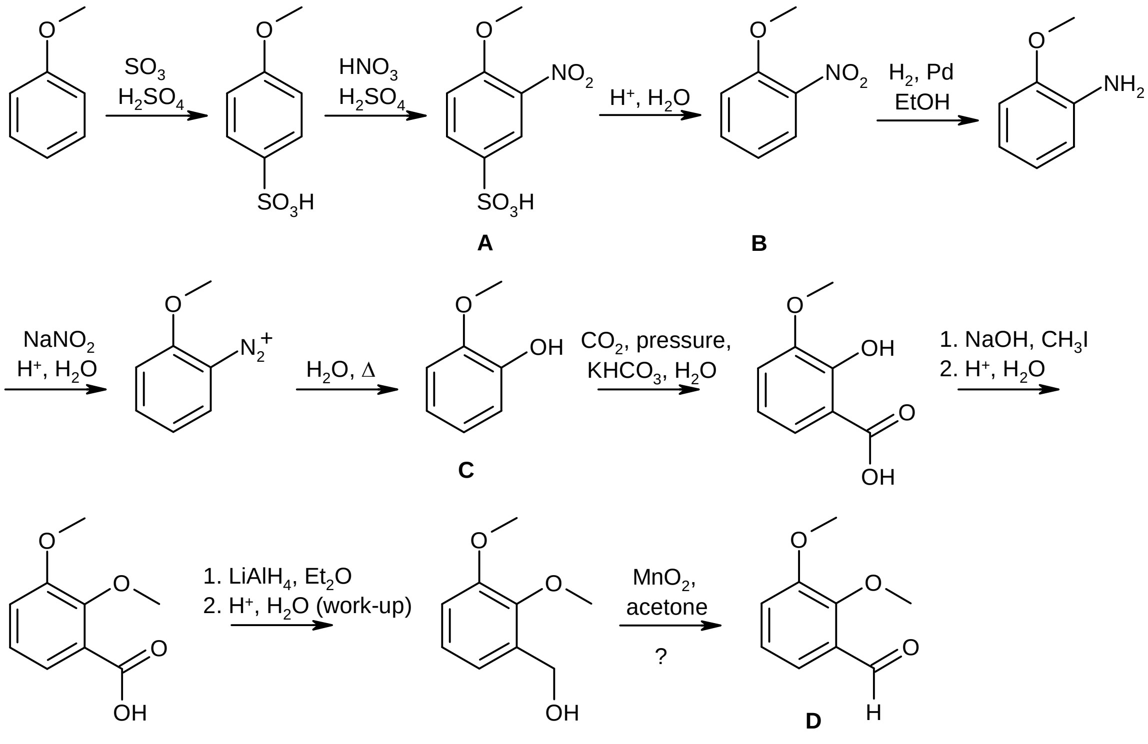
The synthesis of compound **2** is shown below.



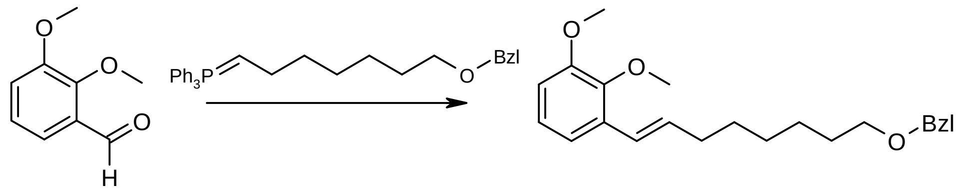
2

(b) Draw the structures of A-D.

–(b) Risposta



La reazione successiva è una reazione di Wittig che usa un'ilide di fosforo per unire la nuova catena formando un doppio legame C=C. La reazione di Wittig fa reagire l'ilide di fosforo con un composto carbonilico, un'aldeide o un chetone.

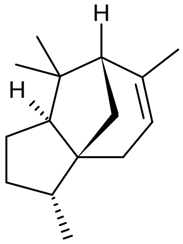


Qui ci deve essere l'aldeide (benzaldeide) solo così la nuova catena può contenere 7+1 = 8 atomi di carbonio.

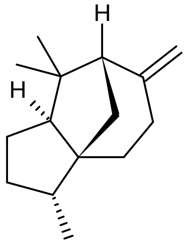
Soluzione proposta da Mauro Tonellato

4. Cedrene

Sesquiterpenes are a class of organic structures that contain three isoprene units and often have the molecular formula $C_{15}H_{24}$. Cedrene is one such compound that is found in the essential oil of cedar. There are two types of cedrene, α and β, which differ in the position of the double bond.



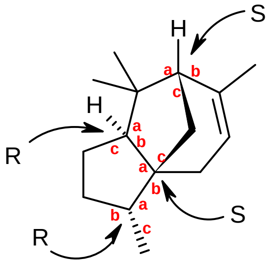
α-Cedrene



β-Cedrene

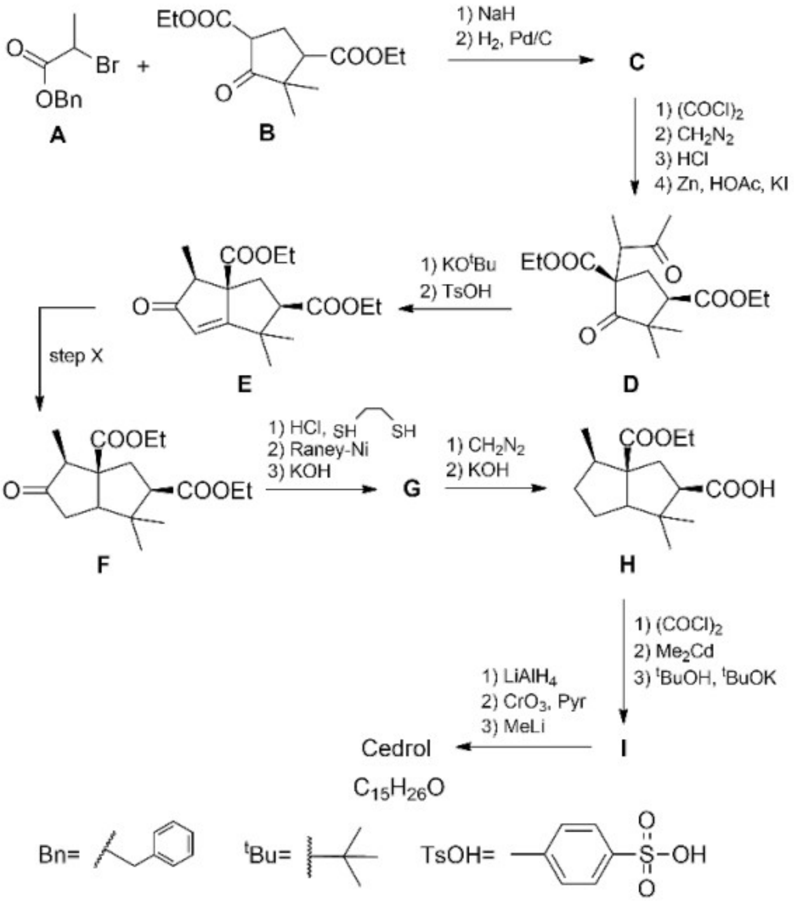
(a) Circle the stereocentres in α-cedrene and assign them as R or S.

–(a) Risposta



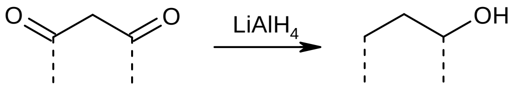
There are various ways to synthesise cedrene. In this exercise we look at two of these methods.
In 1955 Stork et al. used an eight step synthesis to make cedrol, a precursor to cedrene. It is possible to convert cedrol to cedrene by adding a sulfate salt. The synthesis of cedrene starts from compounds A and B.

Method 1: Synthesis of α-cedrene by Stork et al. (1955)

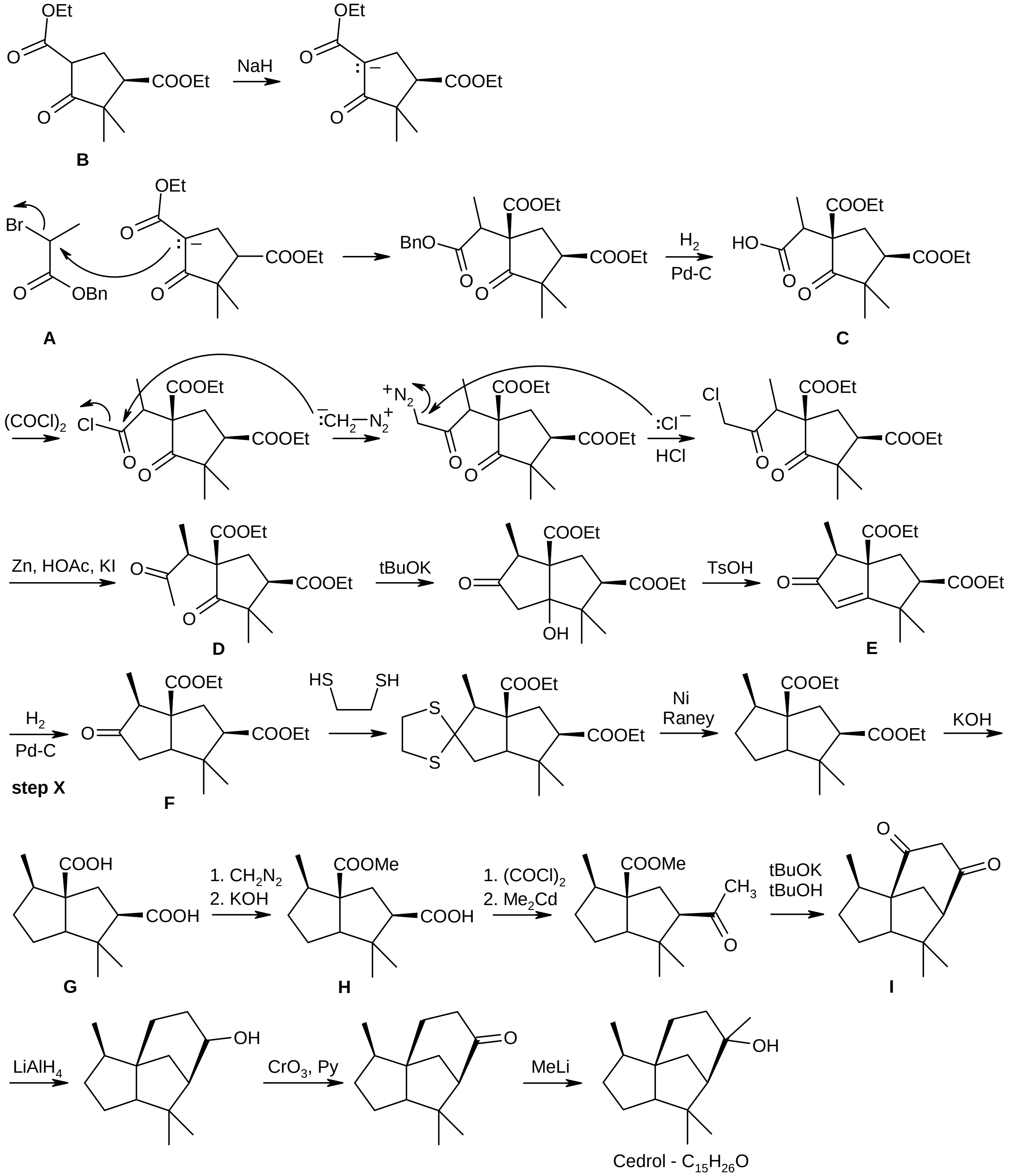


Additional hints:

- Pyr = pyridine;
- $(COCl)_2$ works similar to $SOCl_2$;
- CrO_3, Pyr converts alcohols to ketones;
- Organocadmium reagents work similar to Grignard reagents;
- Cedrol can be converted to cedrene via an elimination reaction in which water is removed;
- $LiAlH_4$ performs a reaction similar to the one shown below.



(b) Draw the structures of C, G, I, and cedrol. You do not need to show stereochemistry.



(c) Tick which reagent(s) would be suitable for step X.

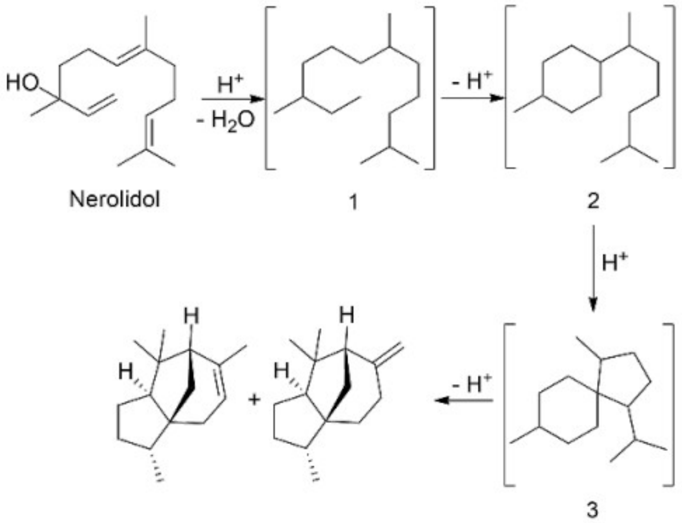
☐ Li, NH_3 ☐ $LiAlH_4$ ☐ H_2 , Pd/C ☐ HNO_3 ☐ H_2SO_4

–(c) Risposta

Come è mostrato nello schema precedente, il passaggio X è una riduzione di un doppio legame C=C ad alcano e si realizza con H_2 e Pd-C

Method 2: Cyclisation of nerolidol

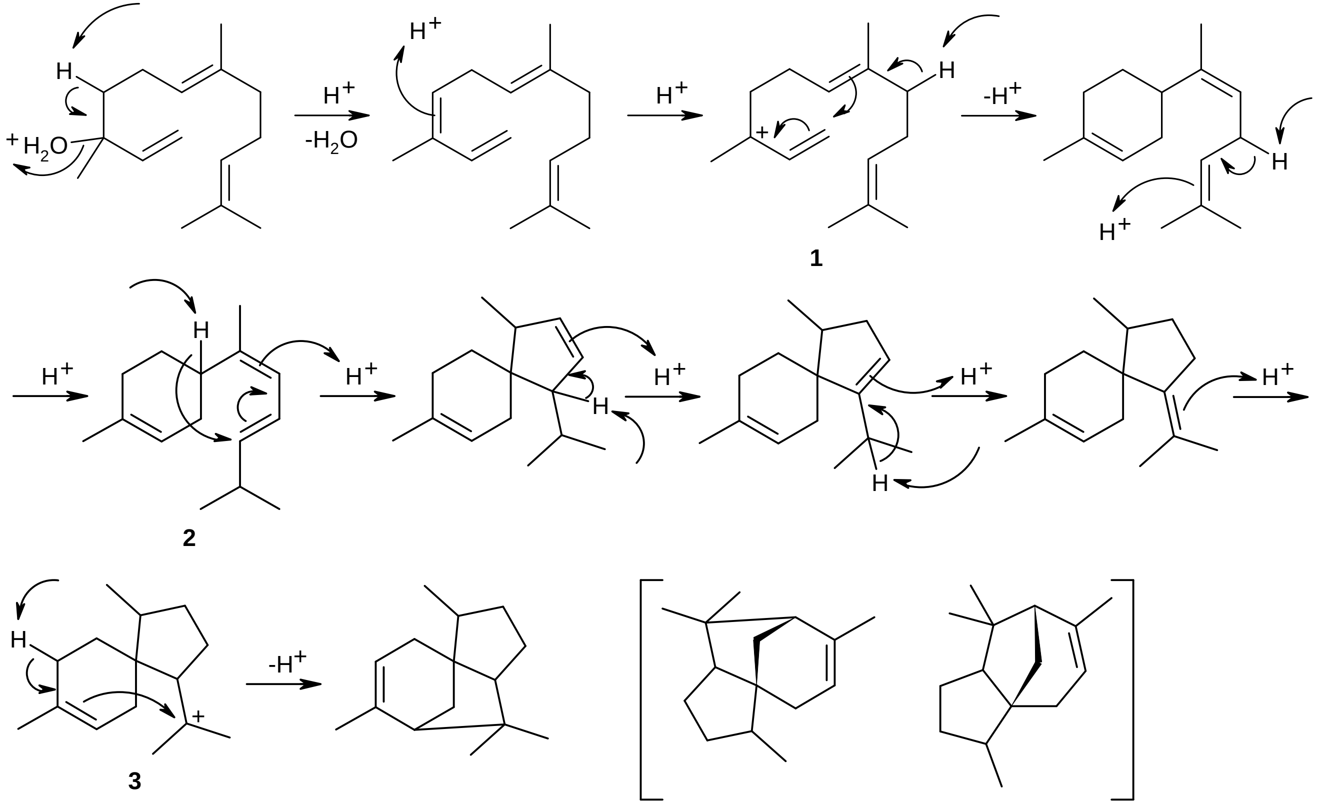
It is also possible to isomerise the structure of nerolidol to both α-, and β-cedrene by adding acid. This will remove the alcohol group and start a cyclisation reaction. The conversion takes place via multiple intermediate structures. Incomplete structures of three of these intermediates are shown.



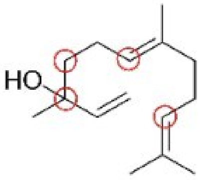
Intermediates 1 and 3 are charged. Intermediate 2 is neutral.

(d) Complete the structure of intermediates 1, 2, and 3 by adding double bonds and charges in the correct places.

–(d) Risposta

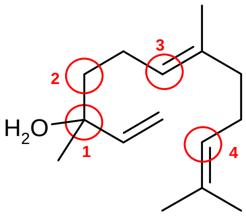


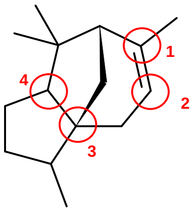
Four carbon atoms are circled in nerolidol. Through understanding the mechanism we can determine where these four carbon atoms end up in cedrine.



(e) Circle the four corresponding carbon atoms in cedrene (α or β) which were circled in nerolidol.

–(e) Risposta



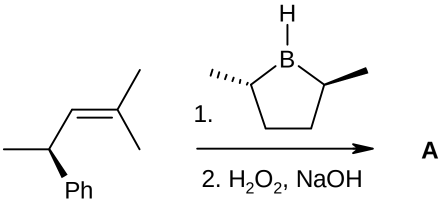


Soluzione proposta da Mauro Tonellato

5. Stereochemical models

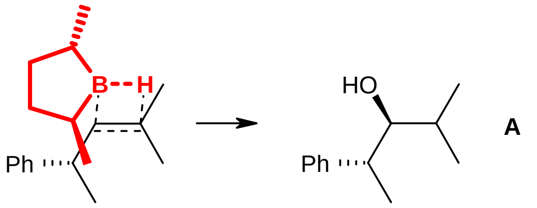
Stereochemistry is abundant in the natural world, with most molecular building blocks of life being chiral. While the origin of homochirality is still a subject of much debate, there is no doubt about the importance of stereochemistry in biological systems. The famous thalidomide tragedy occurred due to one stereoisomer having therapeutic effects while the other stereoisomer was teratogenic. Since then, synthetic chemists have focussed efforts on developing methods to make molecules in a stereoselective way. In this question, we will explore different aspects of stereochemical control.

One of the simplest ways to perform a stereoselective reaction is through the use of a chiral reagent.

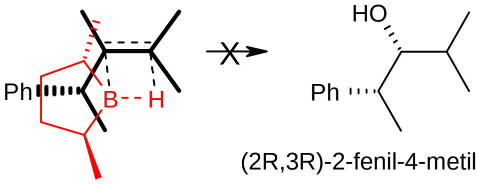


(a) By considering the transition state for the hydroboration reaction across the double bond, **draw** the structure of the major stereoisomer **A**.

–(a) Risposta



(2R,3S)-2-fenil-4-metilpentan-3-olo

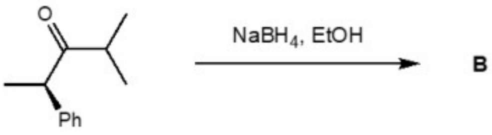


(2R,3R)-2-fenil-4-metilpentan-3-olo

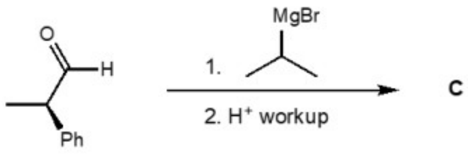
Nello stato di transizione qui a fianco, il borano è sopra il piano dell’alchene. L’anello del borano ha un sostituente che si allontana dal sostituente sul doppio legame.
Nello stato di transizione qui sotto, invece, il borano è sotto il piano dell’alchene. Il sostituente dell’alchene e dell’anello del borano si avvicinano tra loro.
Quindi il borano, a causa dell’ingombro sterico, non è libero di affacciarsi ad entrambe le facce dell’alchene e si forma solo uno dei due alcoli possibili, quello mostrato sopra che ha configurazione S sul carbonio che regge l’OH.

Instead of using a chiral reagent, the presence of a stereocentre nearby can also help to control the stereochemical outcome of a reaction. Imagine you want to synthesise product A starting from a carbonyl group. You could come up with two methods to do this (Reaction B and Reaction C).

Reaction **B**:



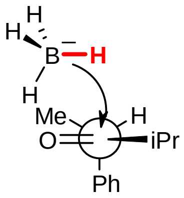
Reaction **C**:

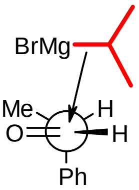


The stereochemical outcome of the reactions can be predicted using the Felkin-Anh model.

(b) For each reaction, **draw** a Newman projection showing the ideal approach of the nucleophile. Use the labels =O, –H, –Ph, –Me and –iPr. Show the structure of the nucleophile in full.

–(b) Risposta





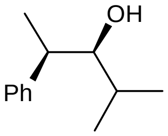
La proiezione di Newman va disegnata in modo che il carbonio del carbonile sia vicino a noi e il carbonio chirale in alfa sia lontano e abbia il sostituente più ingombrante (Ph) rivolto in basso. Il carbonile va posto in posizione sfalsata (orizzontale) con l'ossigeno rivolto verso il gruppo a medio ingombro (Me), in questo modo il sostituente del carbonile (iPr) è rivolto verso il gruppo a minore ingombro (H).

Nella reazione **B** il nucleofilo è lo ione idruro di BH_4^- che attacca il carbonio del carbonile mentre il boro si lega all'ossigeno. Il BH_4^- si avvicina più facilmente dall'alto al piano del carbonile, come mostrato in figura, dove l'ingombro sterico è minore.

Nella reazione **C**, l'idrogeno dell'aldeide è diretto verso il gruppo a minor ingombro sterico (H) anche se non c'è ingombro sterico tra i due idrogeni. Questo trova giustificazione nel fatto che l'attacco del nucleofilo al carbonile non avviene perpendicolarmente, ma è inclinato perchè l'orbitale LUMO del carbonile (π di antilegame) è formato da due lobi, il lobo sul carbonio si allontana dall'ossigeno e costringe il nucleofilo ad attaccare un po' da sotto e quindi l'attacco avviene più facilmente dalla parte meno ingombrata (H). Nella reazione **C** il nucleofilo è il gruppo isopropilico che, come carbanione, attacca il carbonio del carbonile mentre $MgBr^+$ si lega all'ossigeno. Il reattivo di Grignard si avvicina più facilmente dall'alto al piano del carbonile dove l'ingombro sterico è minore.

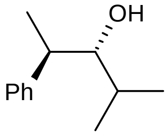
(c) Draw the structures of compounds B and C, indicating the stereochemistry clearly.

–(c) Risposta



B

(2R,3S)-2-fenil-4-metilpentan-3-olo



C

(2R,3R)-2-fenil-4-metilpentan-3-olo

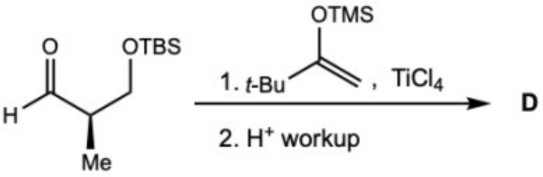
(d) Which reaction should you use to synthesise product **A**?

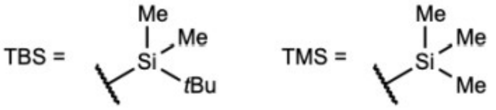
☐ **B** ☐ **C** ☐ Either **B** or **C** ☐ Neither **B** nor **C**

–(d) Risposta

La reazione **B** forma l'alcol (2R,3S)-2-fenil-4-metilpentan-3-olo che è identico al composto **A**.

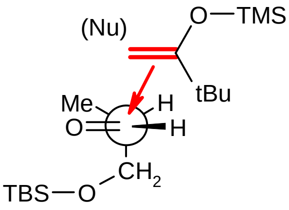
Often, the stereochemical outcome can be influenced by a small change in the reagent. Let's predict the stereoselectivity of the following reaction using the Felkin-Anh model:





(e) Draw a Newman projection showing the ideal approach of the nucleophile.
Use the labels =O, –H, –Me, –CH_2OTBS and Nu.

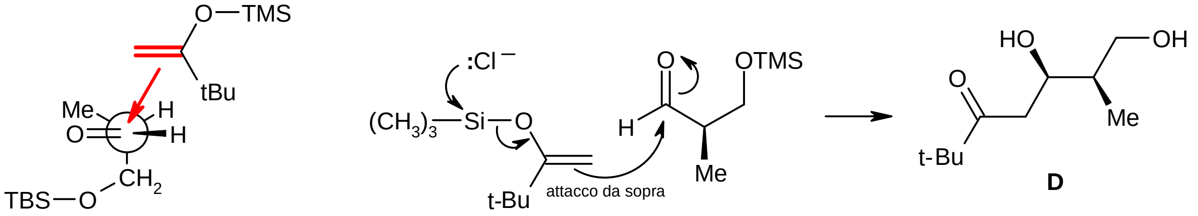
–(e) Risposta



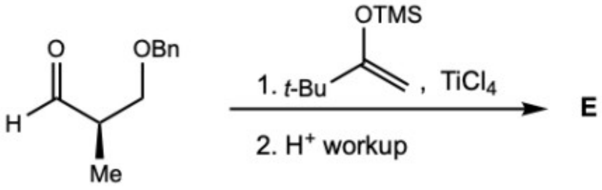
Il sostituente OTBS è il gruppo protettore dell'alcol. E' particolarmente ingombrante anche per la presenza del gruppo terzbutilico. L'ossigeno dell'alcol così protetto non è in grado di legarsi al titanio del $TiCl_3$ e non è in grado di formare complessi chelati con l'ossigeno del carbonile. Dato che l'ossigeno dell'alcol non interagisce con carbonile, il gruppo CH_2OTBS si comporta come semplice gruppo ingombrante e va posto in basso nella proiezione di Newman. L'attacco del nucleofilo avviene dal lato meno ingombrato, in anti rispetto al CH_2OTBS.

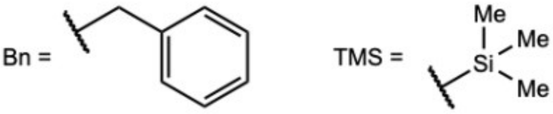
(f) Draw the structure of compound **D**, indicating the stereochemistry clearly.

–(f) Risposta



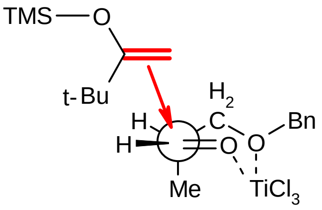
The stereochemical outcome of the reaction can be changed by using a different alcohol protecting group.





(g) Draw a diagram of the transition state in this reaction. Hint: It involves the formation of a six-membered ring adopting a half-chair conformation.

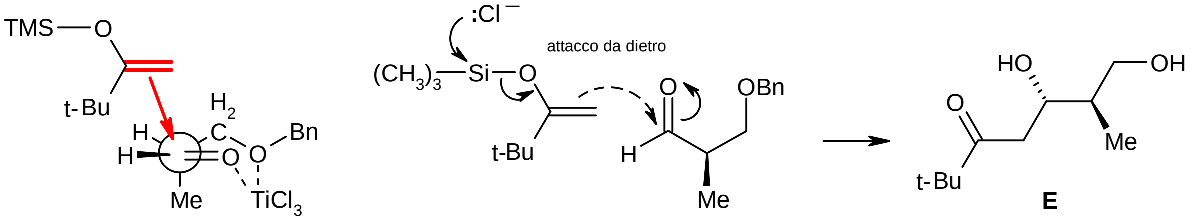
–(g) Risposta



Il gruppo benzilico che protegge l'ossigeno è meno ingombrante stericamente del CH_2OTBS (che ha un gruppo terzbutilico legato al silicio). In queste condizioni si può formare un intermedio chelato nel quale i due ossigeni (basi di Lewis) sono legati al $TiCl_3$ (acido di Lewis). Questo costringe l'ossigeno del carbonile a restare vicino al sostituente più ingombrante (CH_2OBn), mentre di solito è vicino al sostituente di medio ingombro (Me). L'attacco del nucleofilo avviene dal lato meno ingombrato, in anti rispetto al metile (e non al CH_2OBn).
La reazione ha un'orientazione opposta a quella vista sopra e viene detta anti-Felkin.

(h) Draw the structure of compound **E**, indicating the stereochemistry clearly.

–(h) Risposta

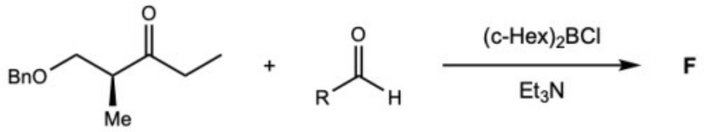


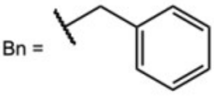
(i) Why does the Felkin-Anh model not predict the correct stereoisomer in this example?

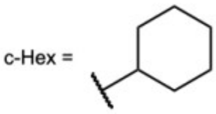
–(i) Risposta

La formazione del legame chelato del $TiCl_3$ con i due ossigeni mantiene l'ossigeno del carbonile vicino al gruppo ingombrante CH_2OBn, mentre il modello di Felkin lo pone vicino al gruppo di medio ingombro (Me).

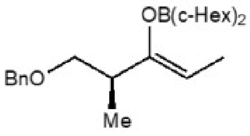
Six-membered rings are highly favoured thermodynamically, and many organic reactions go through transition states that involve six-membered rings. One example is the aldol reaction, which goes through a six-membered ring Zimmerman-Traxler transition state.





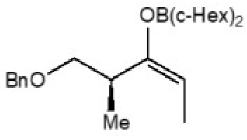


(j) Determine the geometry of the boron enolate formed.



(Z) - enolate

a.

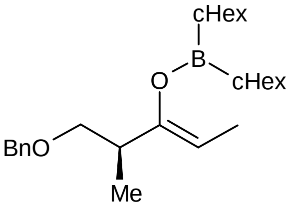


(E) - enolate

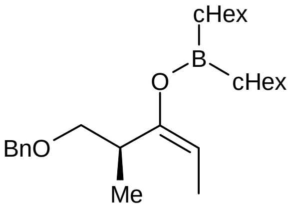
b.

–(j) Risposta

L’ingombro sterico dei due anelli di cicloesano legati al boro favorisce la configurazione (E) nella quale il metile sul doppio legame dell’enolato si avvicina al metile in alfa e si trova in posizione anti rispetto all’ossigeno.



(Z)

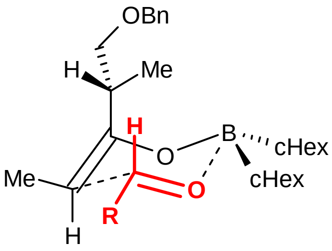


(E) più stabile

(k) Using the Zimmerman-Traxler model, **draw** the arrangement of the reactants as they come together to form the six-membered ring transition state in the reaction to form **F**.

Hint: The stereocentre next to an alkene favours a geometry with the smallest group (H in this case) eclipsing the double bond. This is known as the Houk model.

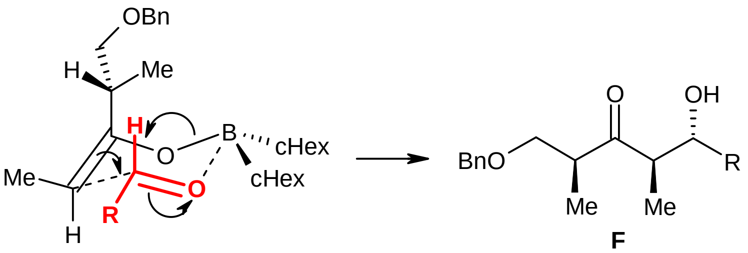
–(k) Risposta



Dato che il metile è in posizione anti rispetto all’ossigeno dell’enolato, si trova in posizione equatoriale nell’anello a 6. La posizione più stabile per il gruppo R dell’aldeide è anche questa equatoriale (in posizione assiale c’è ingombro sterico 1,3 diassiale con il resto della catena).

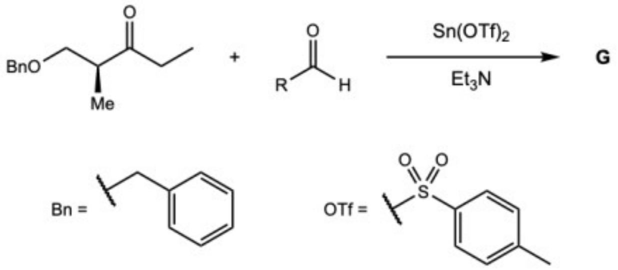
(l) Draw the structure of compound **F**, indicating the stereochemistry clearly.

–(l) Risposta



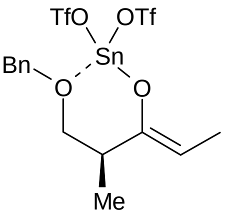
F

Once again, changing the reaction conditions can lead to the formation of a different stereoisomer.

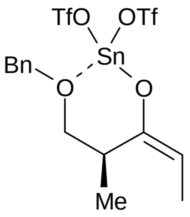


(m) Using the Zimmerman-Traxler model, **draw** the arrangement of the reactants as they come together to form the six-membered ring transition state in the reaction to form **G**.
Hint: Carefully consider the geometry of the enolate. You should have two six-membered rings in this transition state.

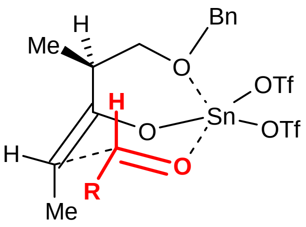
–(m) Risposta
Lo stagno legato all’ossigeno dell’intermedio enolato può coordinare anche l’ossigeno del secondo gruppo alcolico protetto come etere benzilico. Questo toglie l’ingombro sterico dalla parte destra della molecola e così è più stabile la configurazione (Z) del doppio legame dell’enolato (mentre prima era più stabile la configurazione (E)).
Il gruppo metile sul doppio legame dell’enolato si trova in posizione *sin* rispetto all’ossigeno e quindi si trova in posizione assiale nell’anello a 6. Il gruppo R dell’aldeide è più stabile in posizione equatoriale.



(Z) più stabile

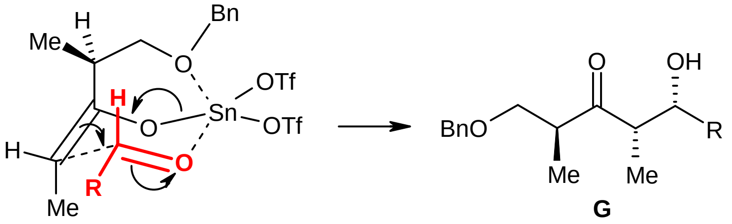


(E)



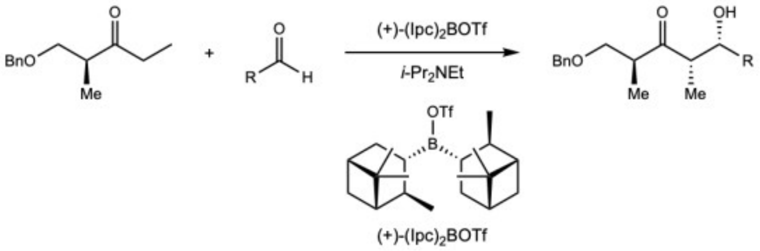
(n) Draw the structure of **G**, indicating the stereochemistry clearly.

–(n) Risposta
Il metile in alfa è orientato in modo opposto a prima.



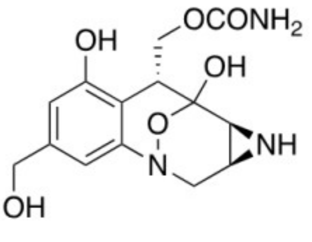
In fact, using a chiral reagent, yet another stereoisomer can be formed selectively.

Rationalising the stereoselectivity of this reaction is beyond the syllabus of IChO2025 and left as a challenge to the enthusiastic student!



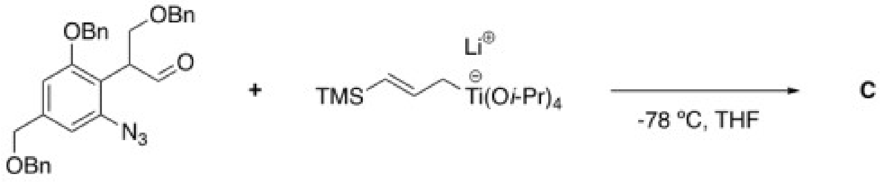
Soluzione proposta da Mauro Tonellato

6. Stereocontrol in the synthesis of FR66979



FR66979

FR66979 was isolated from the bacterium Streptomyces sandaensis in 1987. It was first identified as a promising antibiotic, but subsequently found to also possess potent antitumour activity by forming interstrand cross-links in duplex DNA. In this question, we will examine the total synthesis of FR66979 completed in 2002 by Ciufolini and co-workers.



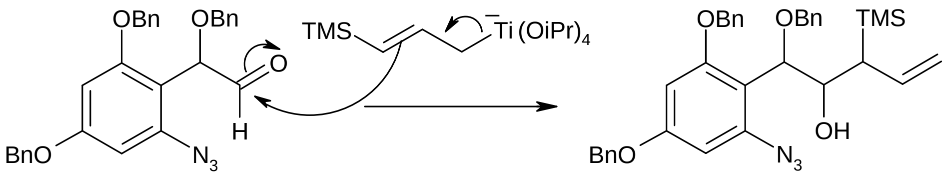
A **B**

The first step in the synthesis involved the coupling of aldehyde **A** with organometallic species **B** to form **C**.

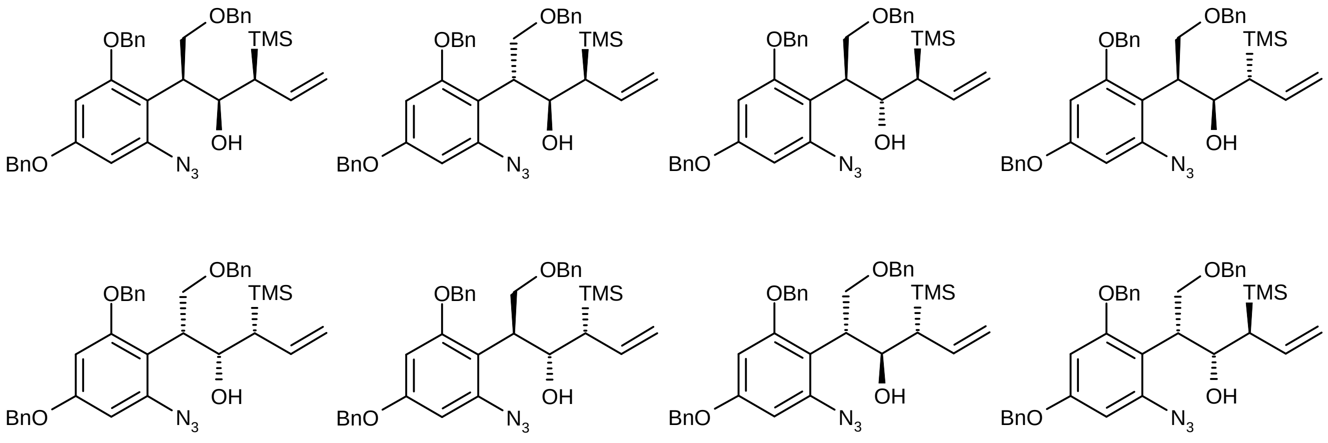
(a) Draw all the possible stereoisomers of **C**.

–(a) Risposta

In questa reazione l'attacco nucleofilo è fatto dal carbonio terminale del gruppo allilico che ha una maggiore carica negativa perchè è legato al silicio (poco elettronegativo).



La molecola C ha tre centri stereogenici e quindi ci possono essere 2^3 = 8 diversi stereoisomeri.

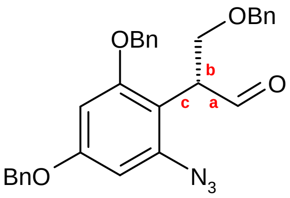


From what you have learnt in the previous question, not all the possible stereoisomers will be formed in equal amounts. Consider the reaction between (R)-**A** and **B**.

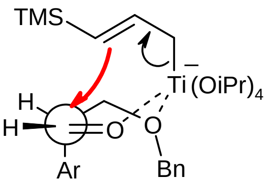
(b) Draw a Newman projection showing the ideal approach of the nucleophile in this reaction. Use the labels =O, –H, –Ar, –CH_2OBn, and Nu.

–(b) Risposta

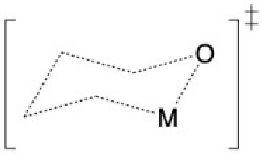
Qui sotto è mostrata la molecola con configurazione R sul carbonio in alfa. La configurazione è R con il gruppo che sprofonda sotto il foglio perchè la priorità maggiore (a) va al gruppo aldeidico mentre in C andava al CH_2OBn. Nella proiezione di Newman questo carbonio è posto lontano da noi. Il titanio si coordina con l'ossigeno del carbonile e con quello in beta (OBn) formando un anello a 6 termini che tiene vicini i due ossigeni. Nella posizione in basso si trova il gruppo ingombrante (Ar). L'attacco del nucleofilo al carbonile avviene da sopra, il lato meno ingombrato.



(R)-A

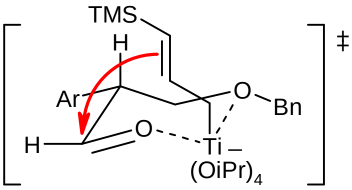


(c) Referencing your answer to part (b), **draw** the arrangement of the reactants as they come together to form the six-membered ring transition state in the reaction to form **C** following the template below. Clearly show the orientation of the stereocentre, using the same labels as in part (b). Edit the dotted lines to show the correct bond orders and add substituents as necessary



–(c) Risposta

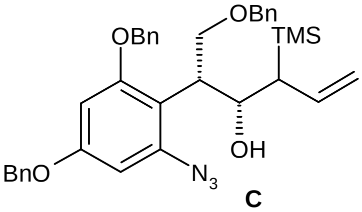
Il gruppo alchilico del composto organometallico è legato al titanio che a sua volta è coordinato ai due atomi di ossigeno. L'attacco nucleofilo al carbonile avviene dall'alto, il lato meno ingombrato stericamente.



(d) Draw the structure of compound **C** showing all stereochemistry.

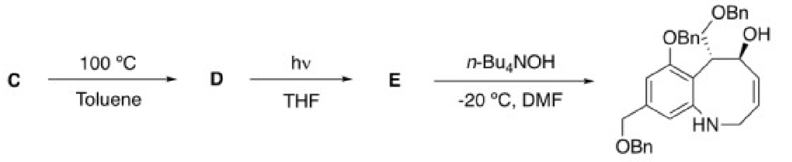
–(d) Risposta

Si forma prevalentemente il composto che ha configurazione (S,S), il composto **C**.



C

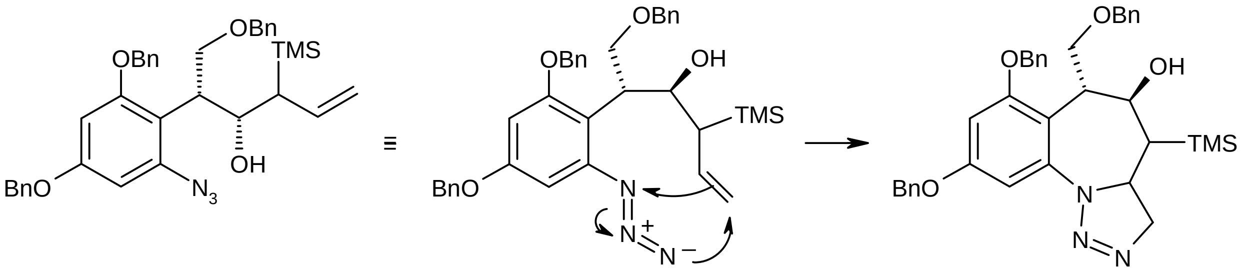
Compound **C** was further transformed into compound **D** by heating in toluene. Brief photolysis of **D** yielded **E**, which can undergo fragmentation to form **F**.
Hint: Nitrogen gas evolved during the photolysis of **D** to form **E**. **D** contained a fivemembered ring while **E** contained a three-membered ring.



F

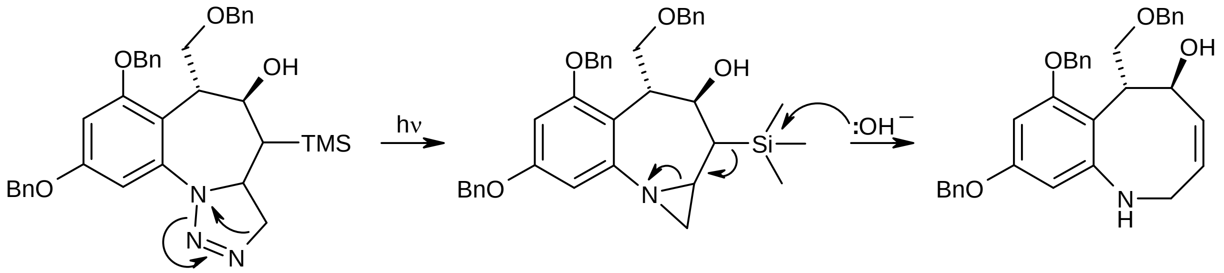
(e) Draw the structures of **D** and **E**. You do not need to indicate stereochemistry.

–(e) Risposta
La prima reazione è una cicloaddizione del gruppo azide al doppio legame che forma un anello triazolico a cinque termini (**D**).



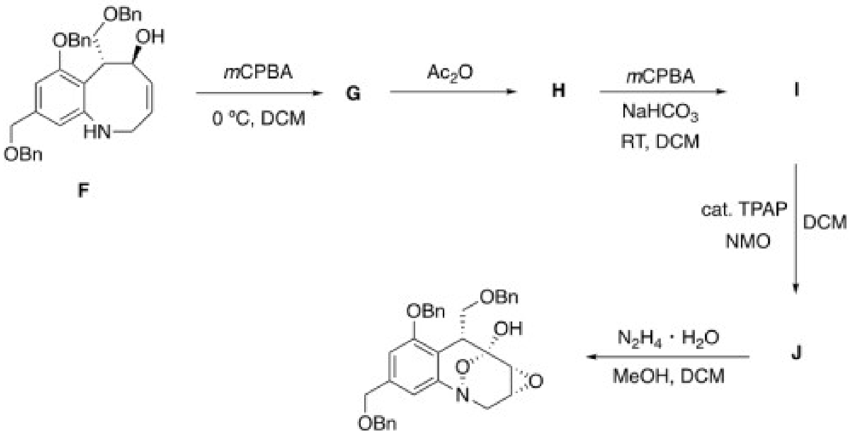
C C D

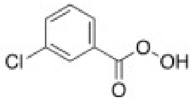
La seconda reazione espelle N_2 per formare un anello a tre termini (**E**). Infine lo sblocco del trimetilsilano forma un nuovo doppio legame e apre l'anello a tre termini formando un nuovo anello a 8 termini (**F**).



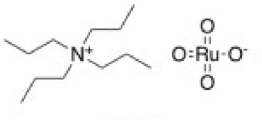
D E F

The next series of steps allowed the formation of the bridged bicyclic ring scaffold.

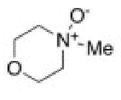




*m*CPBA



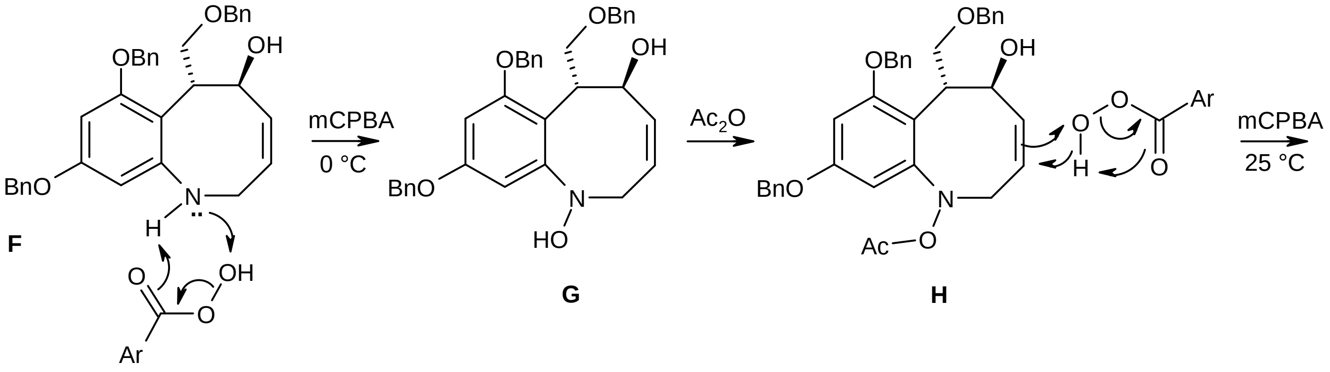
TPAP



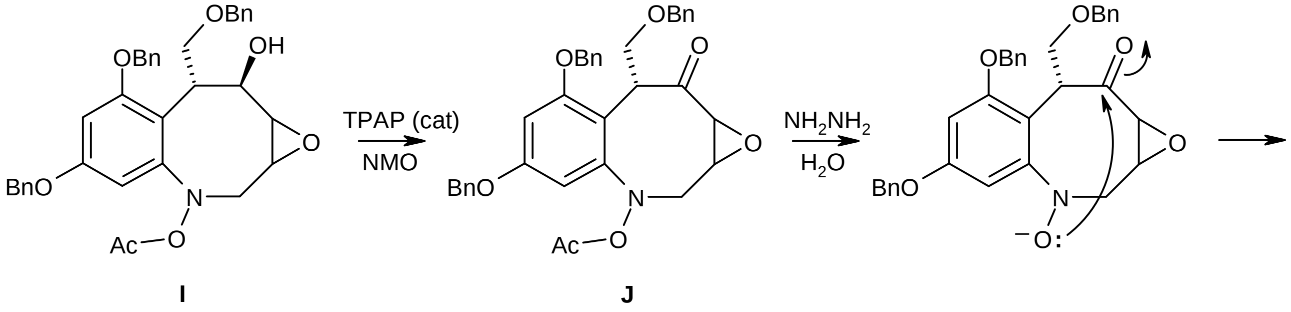
NMO

(f) Draw the structures of compounds **G**, **H**, **I**, and **J**. You do not need to indicate stereochemistry.
Hint: cat. TPAP/NMO works similarly to pyridinium chlorochromate (PCC).

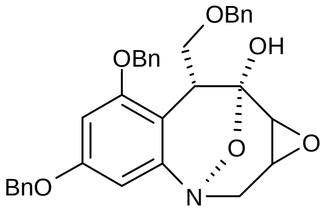
–(f) Risposta
La prima ossidazione on acido metacloroperossibenzoico (mCPBA) avviene a 0 °C e ossida l'ammina a idrossilammina (**G**). Questa viene poi protetta come estere acetico. (**H**).



La seconda ossidazione con mCPBA avviene a 25 °C e forma un epossido sul doppio legame (**I**).
L'ossidazione successiva è fatta con quantità catalitiche di tetrossido di rutenio che viene riossidato da NMO (N-metilmolfolina-N-ossido) e così si ossida l'alcol a chetone (**J**).



Il trattamento con idrazina idrolizza l'estere acetico e libera l'OH dell'idrossilammina che si deprotona in gran parte dato che è leggermente acido.
Questo favorisce la reazione di ciclizzazione che forma il semiacetale ciclico finale.

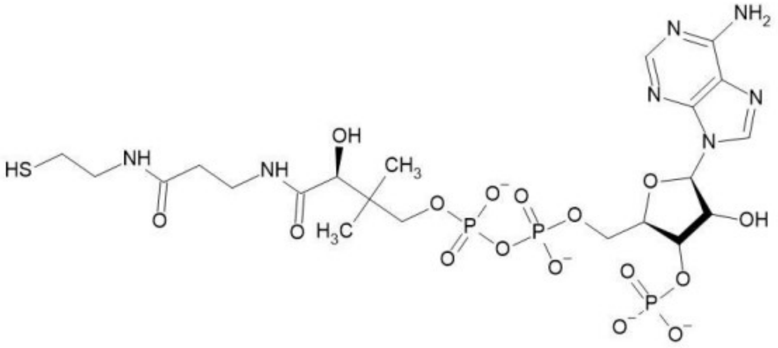


Soluzione proposta da Mauro Tonellato

7. Coenzyme A and anaplerotic reactions

Glycolysis is one of the most important catabolic transformations. It affords pyruvate, which is further subjected to oxidative decarboxylation under aerobic conditions entering the tricarboxylic acid (TCA) cycle in the form of acetyl-coenzyme A (CoA), which reacts with oxaloacetate to produce citrate.

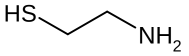
CoA is composed of three blocks, which are residues of phosphorylated ADP, pantothenic acid (vitamin B5), and thioethanolamine:

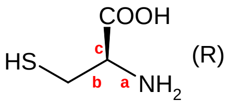


During CoA biosynthesis, vitamin B5 is modified from both sides.

(a) Suggest the canonical amino acid **X1**, from which the thioethanolamine residue originates. **Draw** the structure of the L-isomer of **X1** with stereochemical details. What is the absolute configuration (R or S) of the stereocentre?

–(a) Risposta





L-cisteina

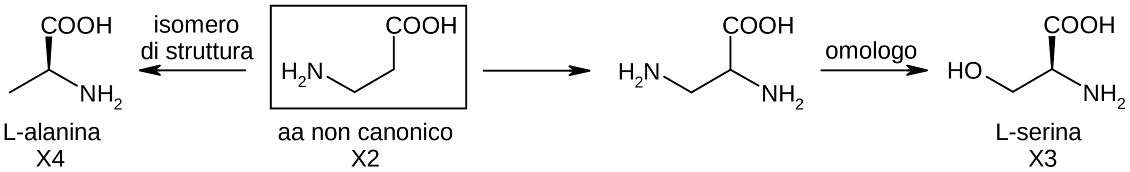
X1

La tioetanolammina è facilmente correlabile alla L-cisteina che ha una configurazione (R) sul carbonio alfa (e non S come gli altri AA) perchè la catena laterale ha la priorità sul carbossile a causa dello zolfo.

Vitamin B5 is produced in most bacteria by combination of pantoate and a noncanonical amino acid **X**2, which is a nearest homologue of the canonical amino acid **X3** and a structural isomer of the canonical amino acid **X4**.

(b) Draw the structures of **X2-X4** and pantoate.

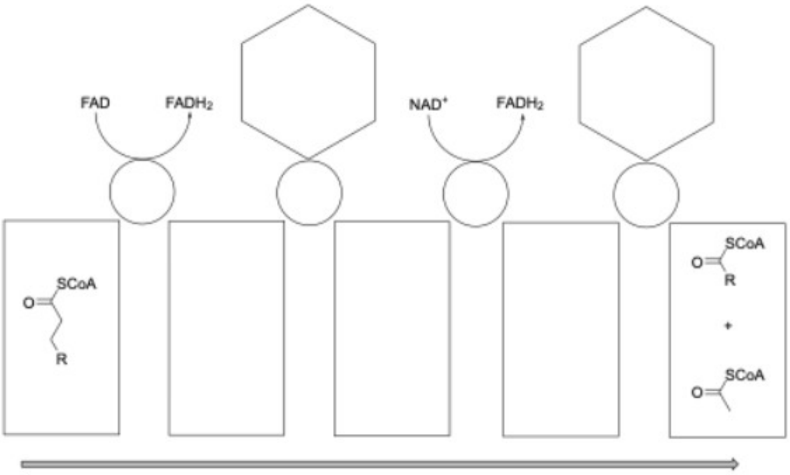
–(b) Risposta



CoA is a universal carrier of acyl groups in numerous metabolic processes including degradation and biosynthesis of fatty acids. The β-oxidation of fatty acids takes place in the mitochondrial matrix through a series of four reactions collectively referred to as β-oxidation. This process is named for the successive oxidations occurring at the β-carbon, which lead to the stepwise removal of two carbon atoms from the carboxyl end of the fatty acyl-CoA molecule. Four enzymes are involved in this process and their functions are shown in the table.

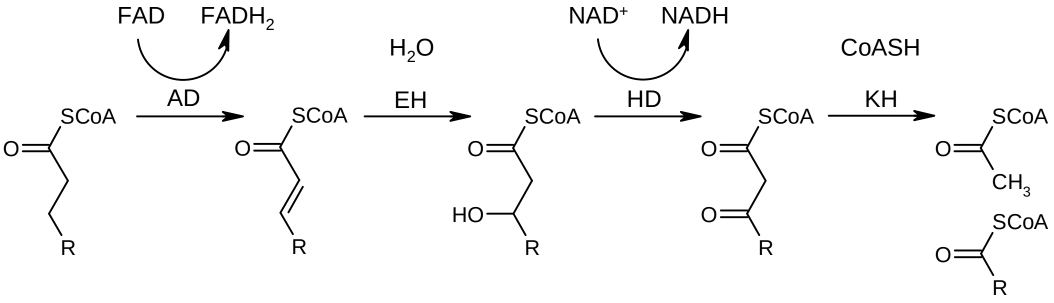
Abbreviation	Name	Function
EH	Enoyl-CoA Hydratase	Forms a β-hydroxyl carbonyl (aldol) from an α, β-unsaturated carbonyl
KH	β-ketothiolase	Cleaves the bond between the α and β-carbons in a β-ketothioester
HD	3-L-hydroxyacyl-CoA Dehydrogenase	Oxidises a hydroxyl group to a carbonyl group
AD	Acyl-CoA Dehydrogenase	Removes hydrogen atoms from the α and β positions of a carbonyl to form an α, β-unsaturated carbonyl

The process of the β-oxidation of fatty acids is shown underneath with blanks.



(c) Fill in the circles with the abbreviations of the enzymes needed. Each enzyme should be used once.
(d) Draw in the hexagons the structure(s) of the substrate(s) needed by the enzyme at each point.
(e) Complete the rectangles with the structures of the intermediates.

–(c)(d)(e) Risposta



Recently CoA was found to play an important protective role in preserving a particular functional group in various enzymes from irreversible oxidation. This reaction is referred to as CoAlation.

(f) From the following functional groups, **choose** the most probable one that is being protected:
–OH –C=O –COOH –C(O)NH_2 –NH_2 -NH-C$(NH_2)_2^+$ –SH -S-CH_3

–(f) Risposta
Il gruppo funzionale che può essere ossidato facilmente è il gruppo tiolico della cisteina (-SH). La reazione con CoASH forma un disolfuro relativamente stabile (Cys-S-S-CoA) (ma legato in modo reversibile) che protegge dall'ossidazione per esempio da H_2O_2.

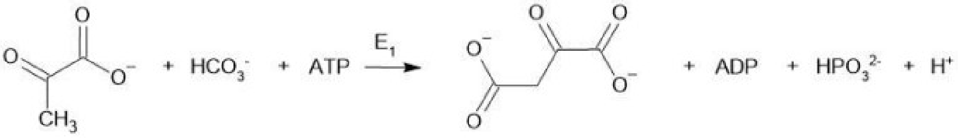
During the periods of rest, organisms synthesise various important molecules including storage compounds, mostly using TCA cycle intermediates as starting substrates, thus depleting the pool of cycle intermediates. As a result, glycolytic overproduction of pyruvate and phosphoenolpyruvate as well as that of acetyl-CoA is observed when energy is required again. This happens because of a diminished concentration of oxaloacetate, which slows down the initial reaction of the TCA cycle.
Most organisms can overcome this potentially dangerous situation due to four different reactions catalysed by enzymes E1-E4 belonging to three different classes.

Enzymes catalyse diverse reactions and can be grouped into six classes:

i) **Oxidoreductases** – Oxidation/reduction reactions.
ii) **Transferases** – Transfer of a methyl-, acyl-, amino- or phosphate group from one substance to another; kinases forming a subclass catalyse the transfer of phosphate group(s) from high-energy phosphorylated species to accepting substrate(s).
iii) **Hydrolases** – Hydrolytic formation of two products from a substrate.
iv) **Lyases** – Non-hydrolytic addition or removal of groups from substrates, with C-C, C-N, C-O, or C-S bonds cleavage in the latter case.

v) **Isomerases** – Intramolecular rearrangement.
vi) **Ligases** – Joining together two molecules by formation of new C-O, C-S, C-N, or CC bonds with simultaneous breakdown of ATP.
Hint: enzymes catalyse both forward and reverse reactions.

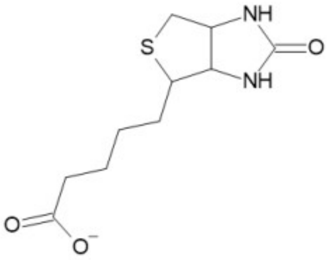
A very important reaction occurring in mammalian livers and kidneys is catalysed by **E1** :



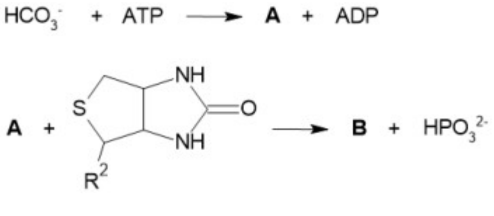
(g) What class does E1 belong to?

–(g) Risposta
In questa reazione si forma ossalacetato con la creazione di un nuovo legame C-C per attacco del CH_3 in alfa dell’acido piruvico al carbonio del bicarbonato con idrolisi di una molecola di ATP. L’enzima **E1** è una ligasi.

Biotin (see below) covalently bound to a lysine (Lys) residue is the co-factor found in the active site of **E1** . The reaction develops in two subsites, one being responsible for the biotin carboxylation (Scheme 1) and the other for CO_2 attachment to pyruvate.



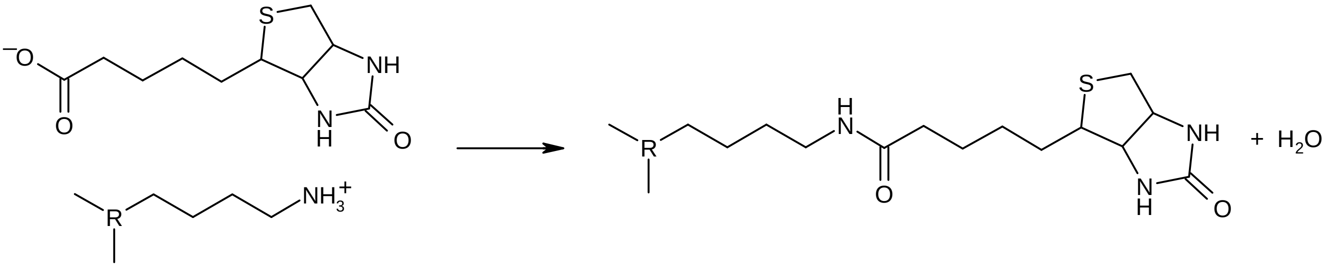
Biotin



Scheme 1

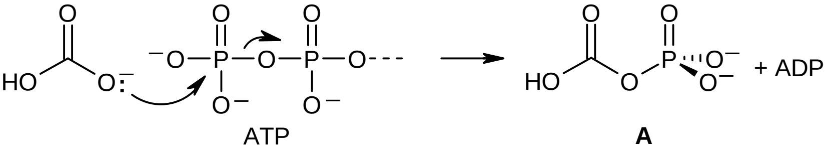
(h) Write the reaction between biotin and the Lys residue (show the latter as R^1-$(CH_2)_4$-NH_3^+).

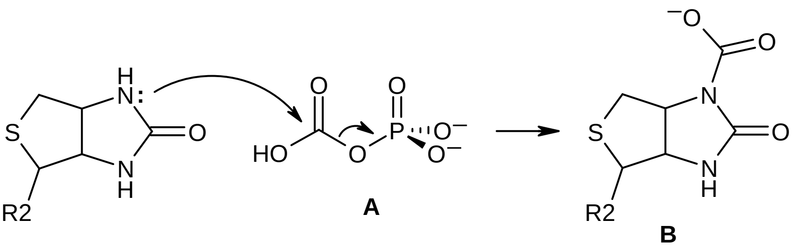
–(h) Risposta



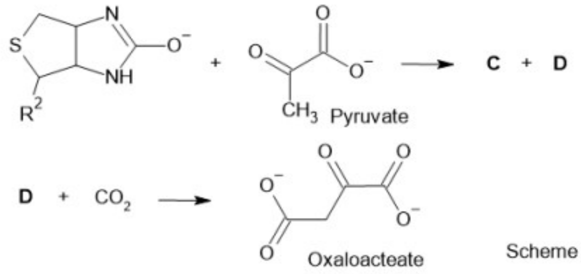
(i) Draw the activated intermediate **A** and biotin residue with the product of addition of carbon dioxide, **B**. Show the biotin residue as in Scheme 1.

–(i) Risposta





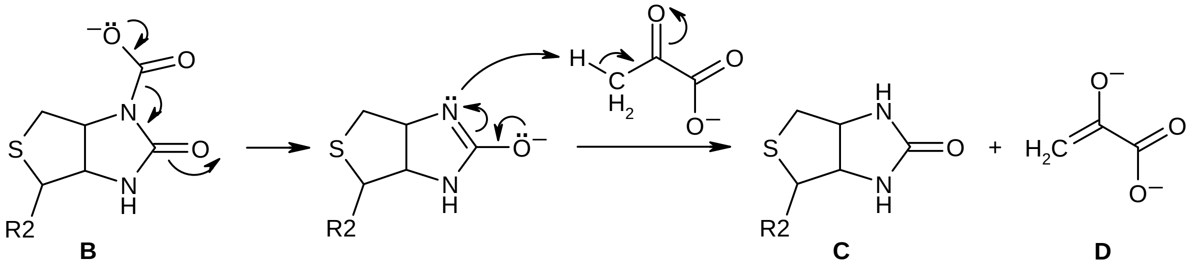
After being transferred to the second subunit, CO_2 leaves the biotin residue, the enol form of which further activates pyruvate by removing one of its protons to facilitate its reaction with CO_2 (Scheme 2):

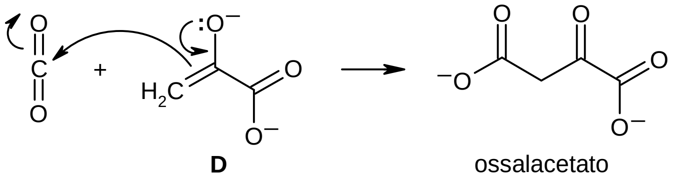


Scheme 2

(j) Draw the structures of **C** and **D**.

–(j) Risposta
La forma enolica della biotina, che ha perso CO_2, strappa un H^+ sul carbonio in alfa dell'acido piruvico che viene trasformato in enolato (**D**). Questa è una forma reattiva che reagisce con CO_2 per formare ossalacetato.

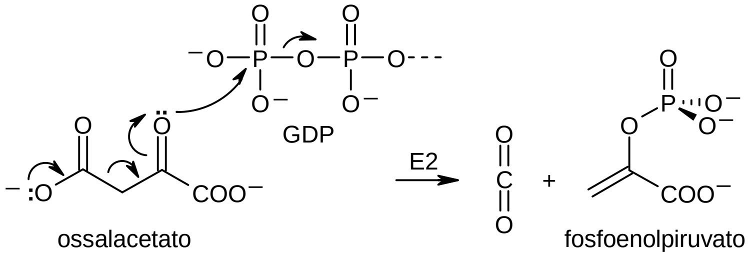




E2 catalyses a reversible reaction which involves (along with other reaction participants) GTP, oxaloacetate, and phosphoenolpyruvate, the latter containing nearly twice as much energy as in ATP.

(k) Write down the **E2** catalysed reaction.

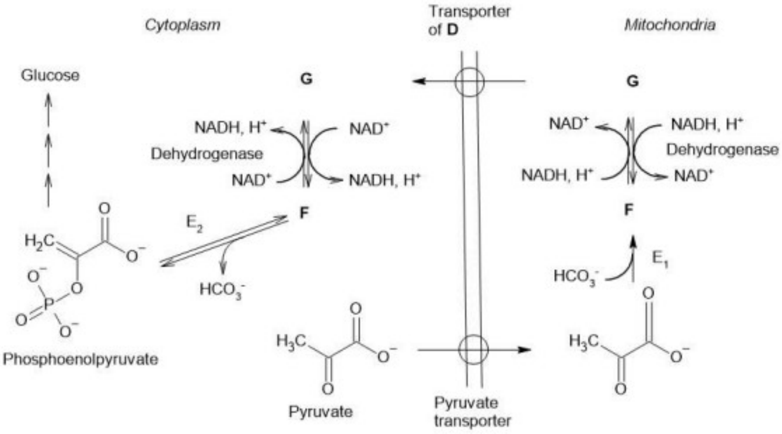
–(k) Risposta
Per descrivere questa reazione bisogna considerare lo schema che viene dato più avanti.



(l) What class does E2 belong to?

–(l) Risposta
Dato che la decarbossilazione rompe un legame C-C e inoltre si rompe GTP, l'enzima **E2** è una ligasi.

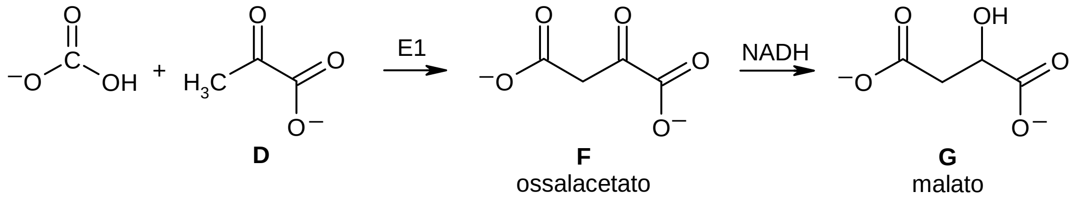
E2 plays an important role in the process of gluconeogenesis where it catalyses one of the bypass steps given in Scheme 3 (phosphorylated nucleosides and inorganic phosphate are not shown).



Scheme 3

(m) Draw the structures of **F** and **G**.

–(m) Risposta

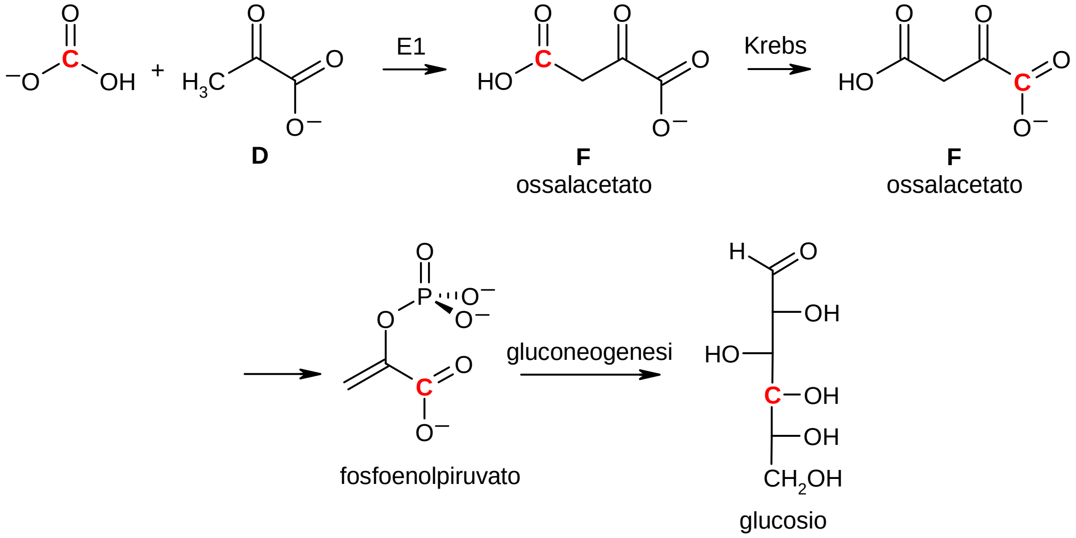


CO_2 (in the form of the hydrogencarbonate anion) is attached to pyruvate in mitochondria and is released as a result of decomposition of **F** in the cytoplasm. Studies show that this is the same species. Thus, one should not expect any label in newly formed glucose if $^{14}CO_2$ enters the carboxylation reaction instead of $^{12}CO_2$. However, some trace amount of labelled glucose is detected in actual experiments with $^{14}CO_2$.

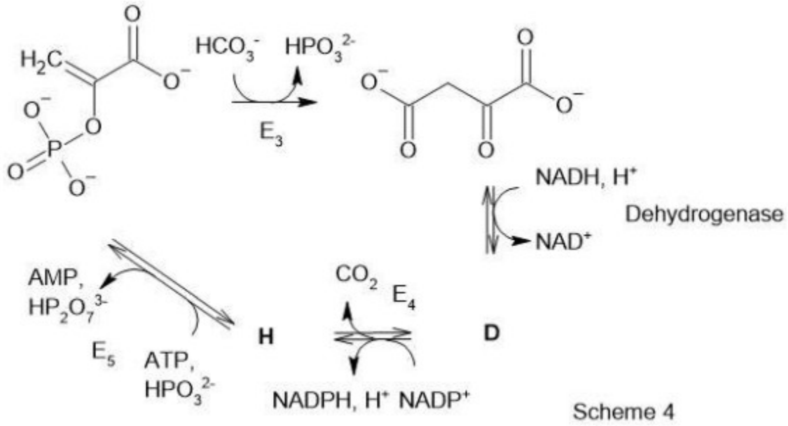
(n) Explain the reason for this. Hint. Some substances are intermediates of several metabolic pathways.

–(n) Risposta

L’ossalacetato che entra nel ciclo di Krebs viene rigenerato alla fine del ciclo e il ^{14}C (qui mostrato in rosso) che inizialmente era nel COOH terminale (C-4) può trovarsi nel COOH iniziale (C-1). In questo modo, se l’ossalacetato esce dai mitocondri (come malato **G**), forma un fosfoenolpiruvato che ha il carbossile marcato ^{14}C. Questo, nella gluconeogenesi, introduce il ^{14}C nella catena del glucosio (nel C-3 o nel C-4)



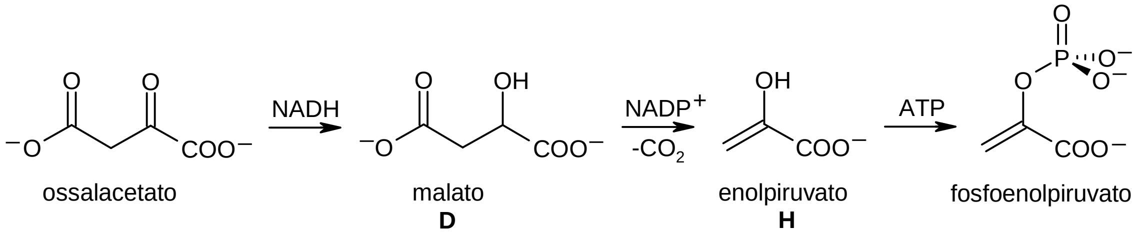
E3 and **E4** are involved in the metabolic cycle found in some plants (Scheme 4).



Scheme 4

(o) Draw the structure of **H**.

–(o) Risposta



(p) What class(es) do **E3** and **E4** belong to?

–(p) Risposta
L’enzima **E3** forma un nuovo legame C-C, ma coinvolge ATP, quindi **E3** è una liasi (non ligasi che rompe ATP)
L’enzima **E4** prima ossida il malato ad ossalacetato con NADP$^+$ e quindi è una ossidoriduttasi. Poi decarbossila l’ossalacetato senza coinvolgere ATP, quindi è anche una liasi.

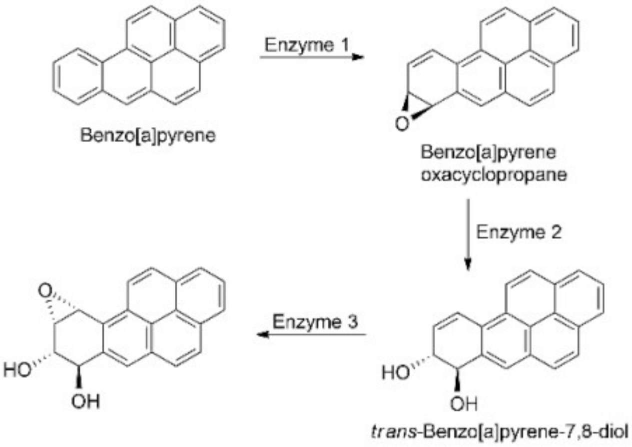
(q) Identify the kinase(s) in Scheme 4 (if any) and suggest the name of the enzyme(s).

–(q) Risposta
L’enzima **E5** è una chinasi perchè fosforila l’ossigeno dell’enolpiruvato. Il suo nome potrebbe essere: enolpiruvato-fosfoenolpiruvato chinasi.

Soluzione proposta da Mauro Tonellato

8. Why smoking is deadly

People who smoke have an increased chance of getting lung cancer; there are multiple reasons for this. One of these reasons is the molecule benzo[a]pyrene that is released upon burning certain substances in a cigarette. When this is inhaled, it is enzymatically converted to another molecule that reacts with DNA. This disturbance of the DNA can eventually lead to cancer. The enzymatic reaction pathway is shown below.



This is an enzymatic conversion in which a reactive metabolite is formed.

(a) Which enzyme class do enzymes 1, 2 and 3 belong to? **Assign** Enzyme 1, Enzyme 2, and Enzyme 3 to one of the classes given below. Hint: The enzyme classes are discussed in previous problems.

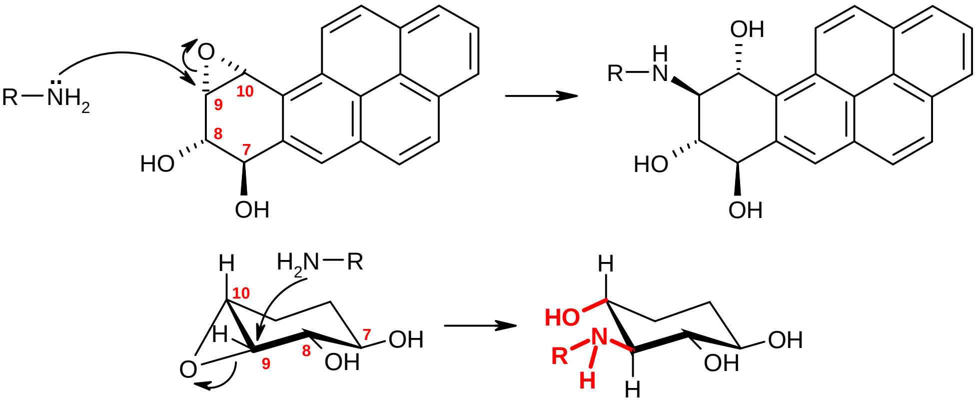
Ligase
Isomerase
Oxidase
Transferase
Hydrolase

–(a) Risposta
Gli enzimi E1 ed E3 ossidano un doppio legame formando un epossido, quindi sono ossidasi.
L'enzima E2 apre l'anello epossidico con addizione di acqua, quindi è un idrolasi.

The final product reacts with amine groups that are present in DNA. In this reaction the amine group attacks on the least hindered side.

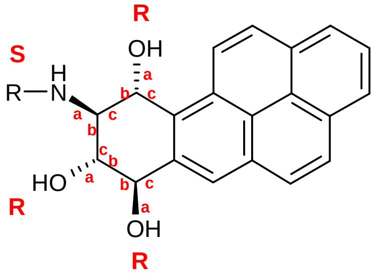
(b) Show how the final product in the pathway above can react with this amine group. Use R-NH_2 to represent the amine group present in DNA.

–(b) Risposta
Il gruppo amminico attacca l'epossido sul C-9 perchè così tutti i sostituenti si vengono a trovare in posizione equatoriale. L'attacco sulla posizione 10 avrebbe posto i due nuovi sostituenti in posizione assiale.



(c) Determine the absolute stereochemistry of all of the stereocentres in the product of the conversion above and assign them as R or S.

–(c) Risposta

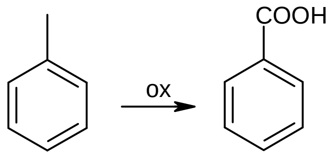


I quattro stereocentri hanno configurazione (7R,8R,9S,10R).
Le prime 3 priorità attorno ad ogni carbonio stereogenico sono state indicate con le lettere a, b, c.

This mechanism also works for benzene. Therefore benzene is also carcinogenic. Toluene (methylbenzene), however, is not carcinogenic.

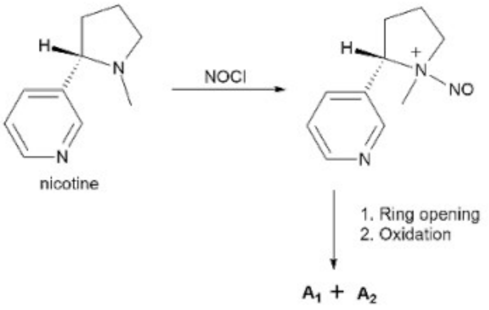
(d) Draw the structure of the product obtained by oxidation of toluene.

–(d) Risposta



Il toluene può essere ossidato con facilità formando acido benzoico che è solubile in acqua e può essere espulso.

It has been known for years that smoking can cause cancer and now it is also known why. The number of people who smoke remains quite high. This is due to the addictive compound nicotine. This compound causes the synthesis of dopamine, which gives the feeling of joy. The absence of nicotine causes stress. Nicotine is not only a compound that causes the above to happen. It is a known ‘tumour enhancing’ compound. Nicotine can also react to form two compounds that are both carcinogenic. This happens in the following way:

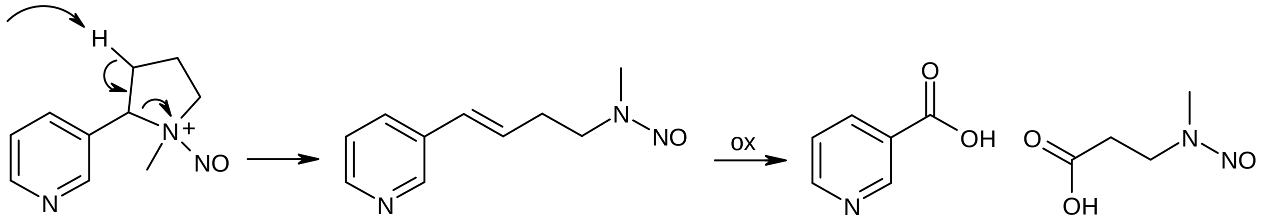


Both A_1 and A_2 show bands around 1700 cm^{-1} in the IR spectrum

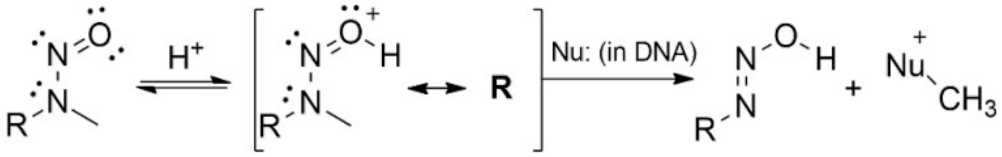
(e) Draw the structural formulae of **A1** and **A2**.

–(e) Risposta

Dopo l’apertura del secondo anello si ottiene un composto con un doppio legame coniugato con l’anello piridinico. L’ossidazione di questo composto porta a due molecole solubili in acqua che possono essere eliminate. La prima di queste non contiene il gruppo NO (mentre più sotto si dice che entrambe contengono NO). D’altra parte la tossicità dello ione nitrosonio NO^+ è ben nota. Questo, però, non deriva dalla nicotina ma dallo ione nitrito usato come conservante alimentare.

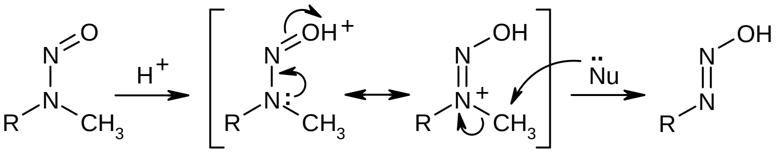


The carcinogenic effect is due to the NO group that is present in both products. Under acidic conditions, in tumour cells, the following happens:

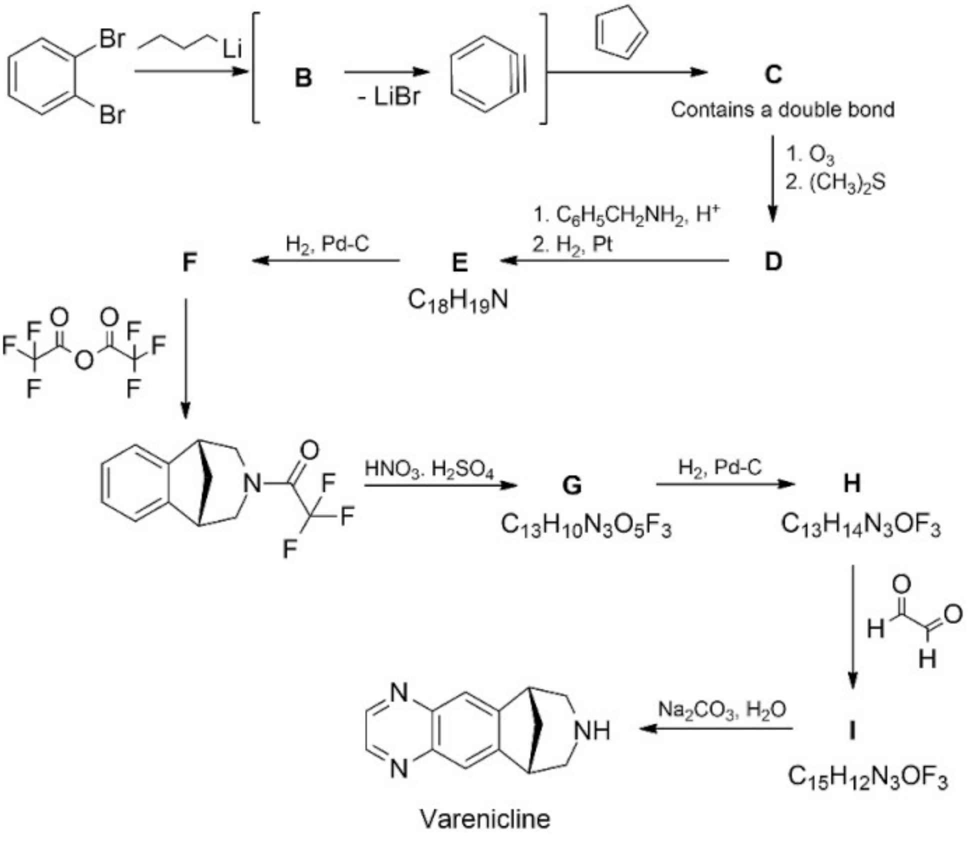


(f) Draw the missing resonance form denoted "**R**" in the scheme above. All atoms in the structure follow the octet rule.

–(f) Risposta



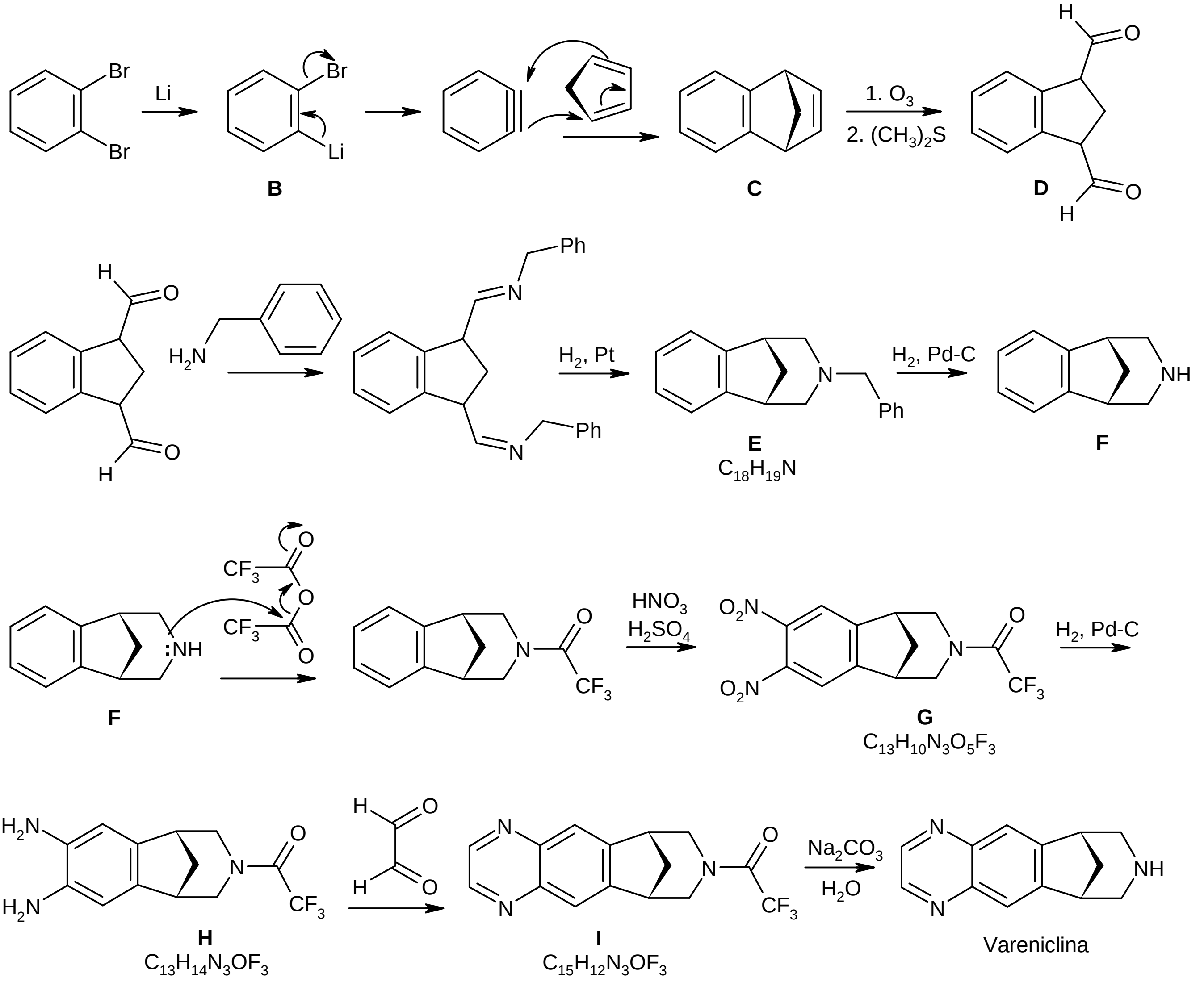
Because nicotine was used in lots of methods to quit smoking, an alternative had to be found. An alternative is the compound varenicline, that was released on the market in 2006 under the name Chantix. This compound has the same effect as nicotine, but is not as addictive. This means less dopamine is released in comparison with nicotine. This makes it easier to quit smoking. The incomplete synthesis of varenicline is shown below.



(g) Draw the structures of compounds **B-I**

–(g) Risposta

Forse il 1° reattivo è Li e non BuLi come indicato nel diagramma precedente.



B

C

D

E
$C_{18}H_{19}N$

F

F

G
$C_{13}H_{10}N_3O_5F_3$

H
$C_{13}H_{14}N_3OF_3$

I
$C_{15}H_{12}N_3OF_3$

Vareniclina

Soluzione proposta da Mauro Tonellato