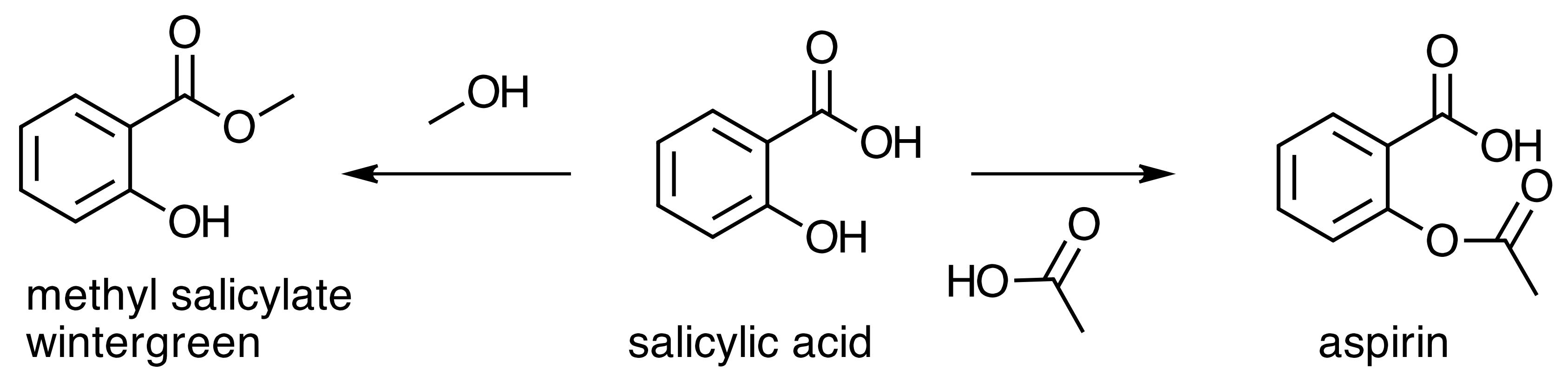
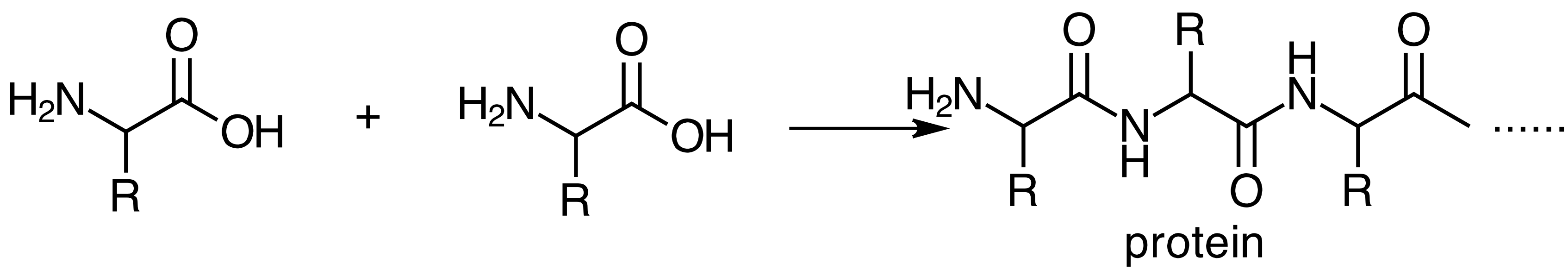
Objective 12. Apply nucleophilic addition and elimination concepts to nucleophilic acyl substitution reactions of acids and derivatives (focus on esters and amides)

Skills: Draw structure
ID structural features and reactive sites (alpha C, beta C, LG, etc.)
ID Nu^- and E^+
use curved arrows to show bonds breaking and forming
show delocalized electrons with resonance structures.

Key ideas:
Nucleophilic acyl substitution is similar to Nucleophilic addition.
Both have Td intermediate.
No LG in Nu addition vs. LG in Nucleophilic acyl sub.

A Lot of Nucleophilic Acyl Substitution Reactions

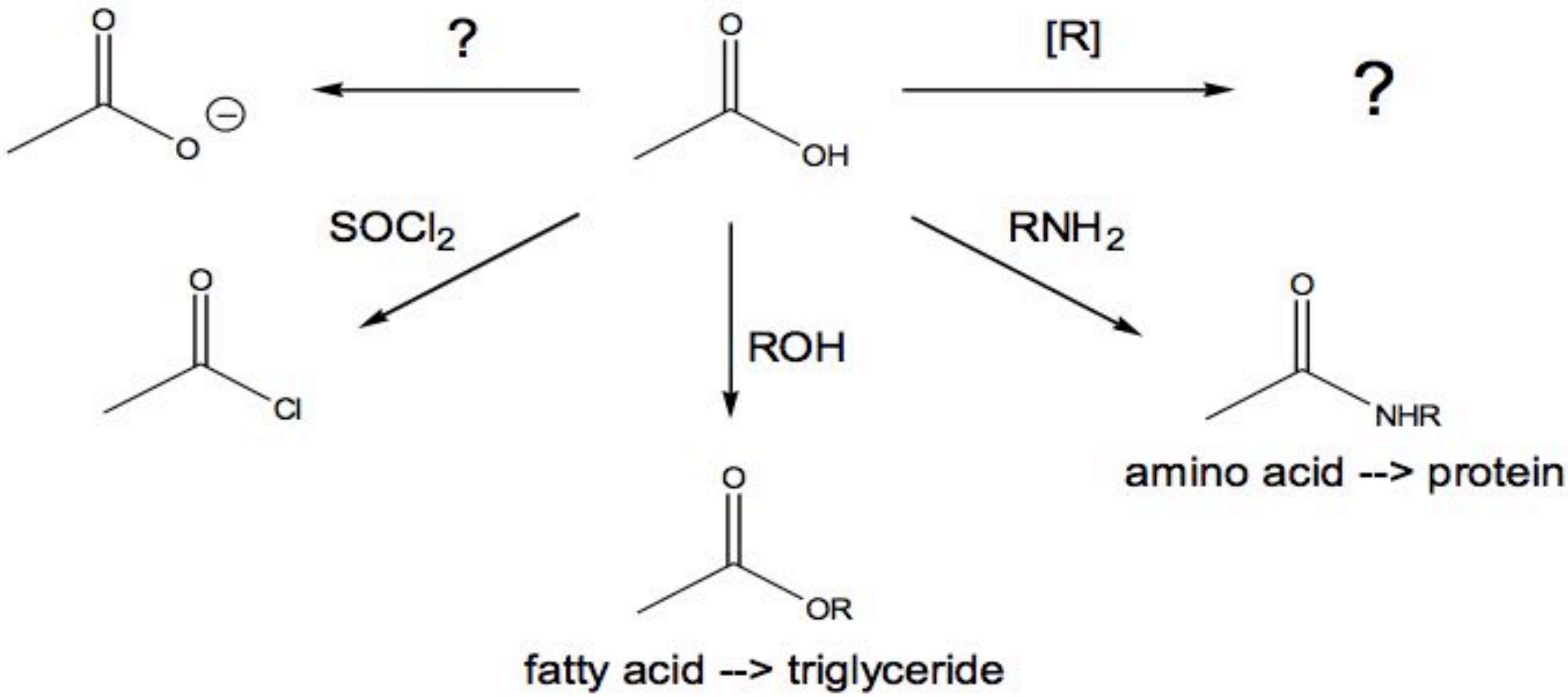




Objective: Predict product of reactions of acids

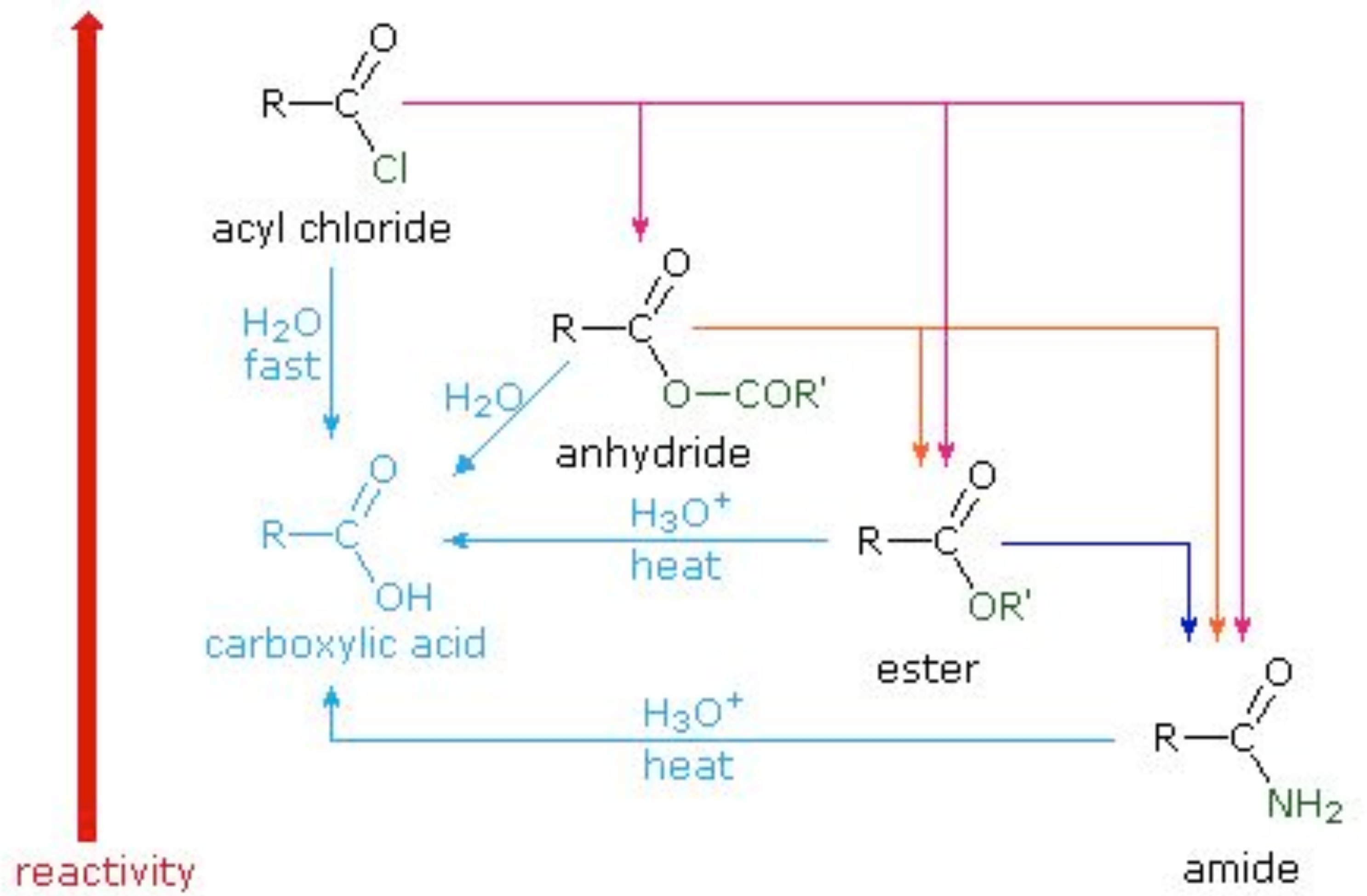
Acids React To Form A Variety of Functional Groups

Acid-Base and Nucleophilic Acyl Substitution



1. What do 4 of the 5 reactants have in common? ($Nu:^-$, E^+)
What atom in the acid reacts?
What is the reaction type? (acid-base, addition, elimination, substitution)
What is the intermediate formed in each reaction?
2. What are acyl chlorides used for? (see Ch. 19)

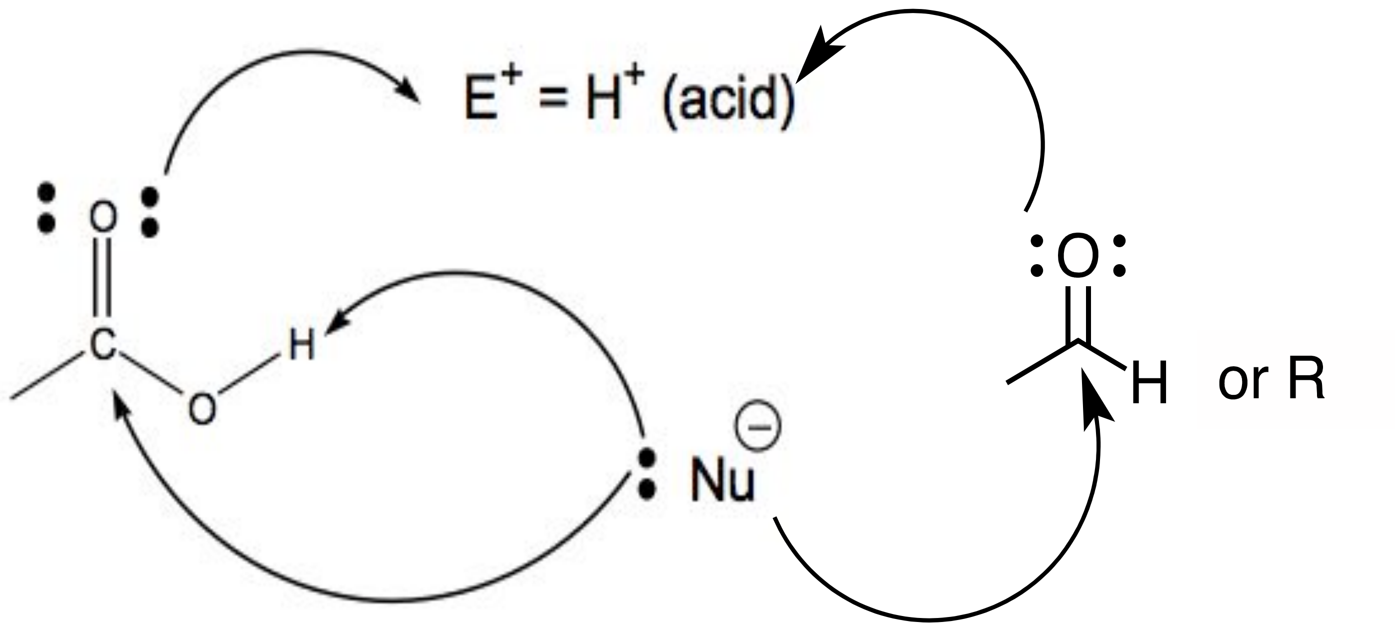
Acids and Acid Derivatives Can Be Converted From One to Another (Nu:$^-$ Acyl Substitution at carbonyl C (E^+))



Reference: Virtual Textbook of Organic Chemistry
http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/crbacid2.htm#react

Carbonyl Carbon is ***Electrophilic*** ==> reacts w/ ***Nucleophiles***.

Lone pair on O is ***Nu:⁻*** ==> reacts with ***Electrophiles*** (H^+).



At which atom will the Nu:⁻ react first?

(i) Carbonyl carbon

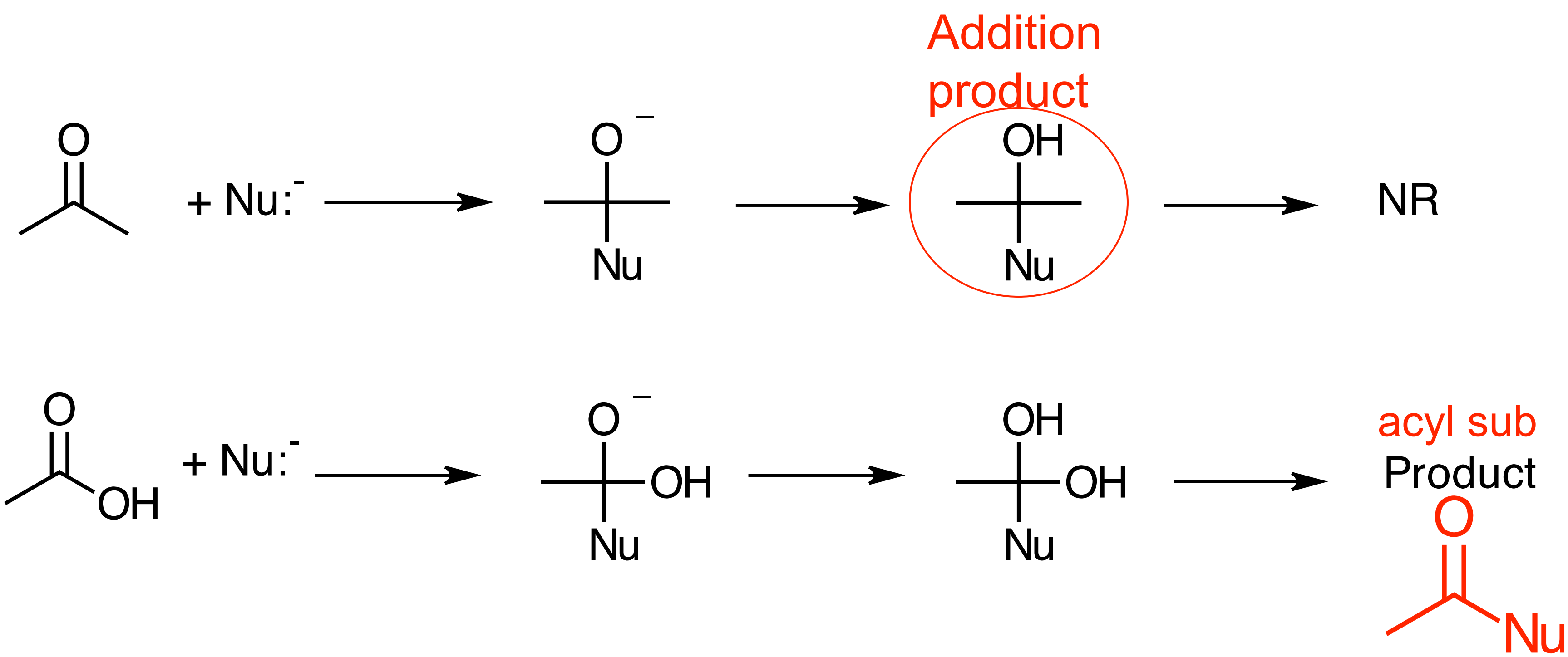
(ii) H bonded to O

Which carbonyl carbon is more reactive (*electrophilic*)?

(iii) On acid

(iv) On aldehyde/ketone

Compare a Nu:⁻ addition to Nu:⁻ acyl substitution



Can use an acid catalyst.

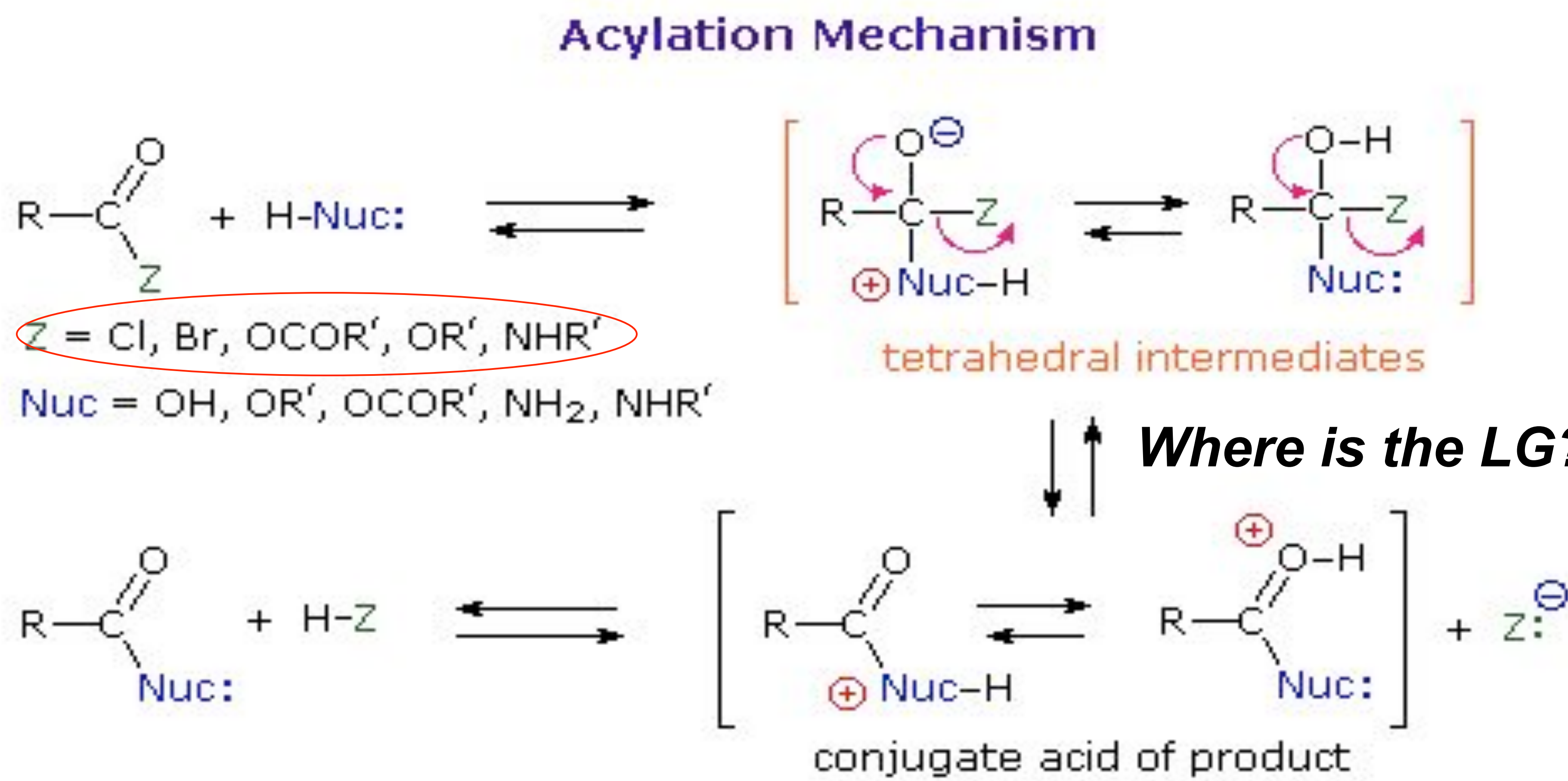
Why does Nu:⁻ addition not make a C=O bond?

Why does Nu:⁻ acyl substitution make a C=O bond?

Hint: Leaving Group

Nucleophilic Acyl Substitution Involves A ***Tetrahedral Intermediate***

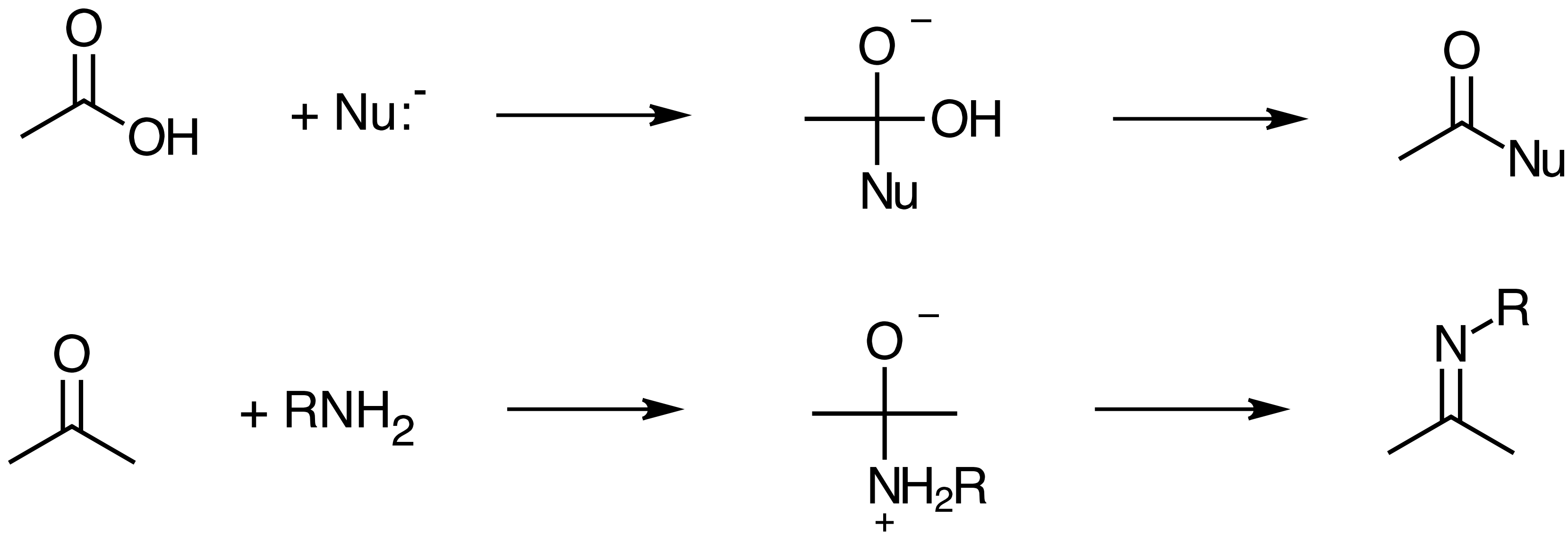
How is *nucleophilic acyl substitution* reaction similar to a *nucleophilic addition* reaction of aldehydes and ketones?



Where is the LG?

Reference: Virtual Textbook of Organic Chemistry
http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/crbacid2.htm#react

Compare imine formation to Nu:$^-$ acyl substitution



How are these two reactions similar?

Objective: Describe Nu: acyl substitution mechanism

Nucleophilic Acyl Substitution (Nu:$^-$ subs for OH) involves a ***Tetrahedral Intermediate***

E.g., Nu:$^-$ = ROH   (Acid -----> Ester)

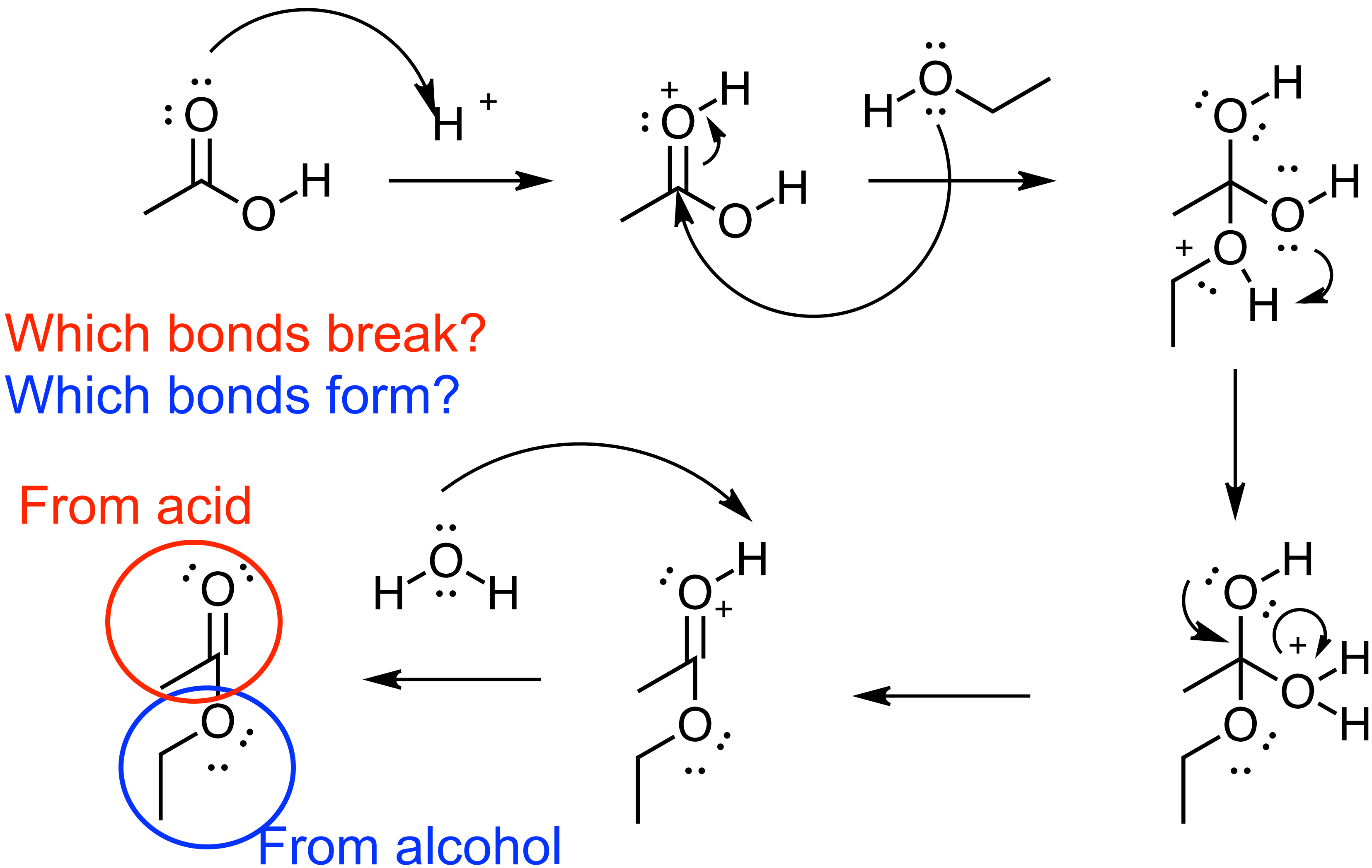
RCOOH + ROH -- H^+ catalyst --> RCOOR + H_2O

Describe the mechanism of ester formation.

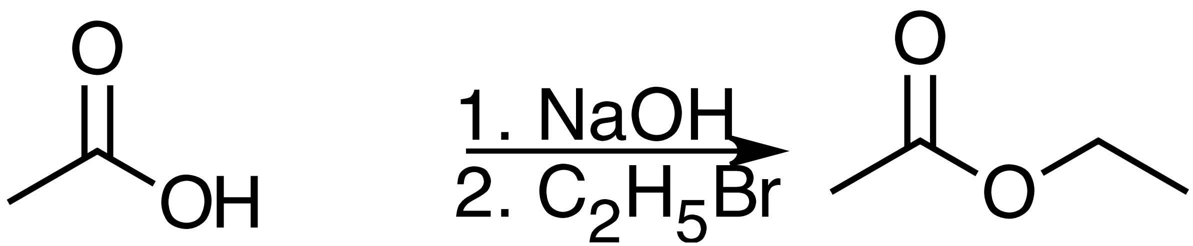
<u>Objective</u>: Describe Nu: acyl substitution mechanism

Nucleophilic Acyl Substitution (Nu:$^-$ subs for OH) involves a ***Tetrahedral Intermediate***

RCOOH + ROH -- H^+ catalyst --> RCOOR + H_2O



Another way to convert an Acid ----> Ester



Is this a Nucleophilic Acyl Substitution reaction?
Use curved arrows to show the mechanism.

Application: Aging Spirits in 6 days instead of 20 years

http://www.wired.com/2015/04/lost-spirits/

http://www.lostspirits.net/

"… *the more complex part of the barrel aging process is esterification, which is when alcohol and phenol or weak acids bond together. The result of this reaction is the creation of medium- and long-chain esters, which are responsible for the flavors and aromas of honey, floral elements, and nutty notes—the classic character of a nicely aged spirit.*"

Aging Spirits: pineapple (ethyl butanoate) takes years to form in an oak barrel depending on storage conditions.
http://www.wired.com/2015/04/lost-spirits/

ethanol + butanoic acid ---> ethyl butanoate + ____

(also called butyric acid)

Draw the structure of each reactant and product.

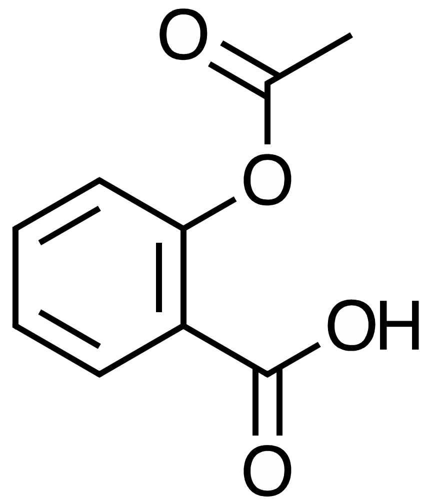
Acid + Alcohol → Ester + water

Which bonds break?

Which bonds form?

Aspirin is a common OTC pain reliever.
How would you synthesize aspirin?
Hint: use an alcohol and acid.
Which bonds break? Which bonds form?

ROH + R’COOH →

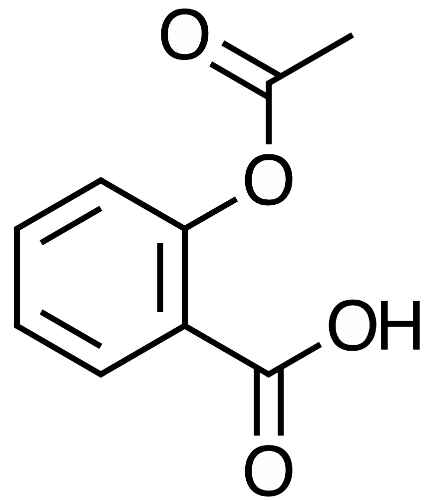


aspirin

Acid + Alcohol → Ester + water

Aspirin undergoes a hydrolysis reaction to form salicylic acid. Draw the structure of salicylic acid and the other product of aspirin hydrolysis.

ROH + R’COOH ⟵



aspirin

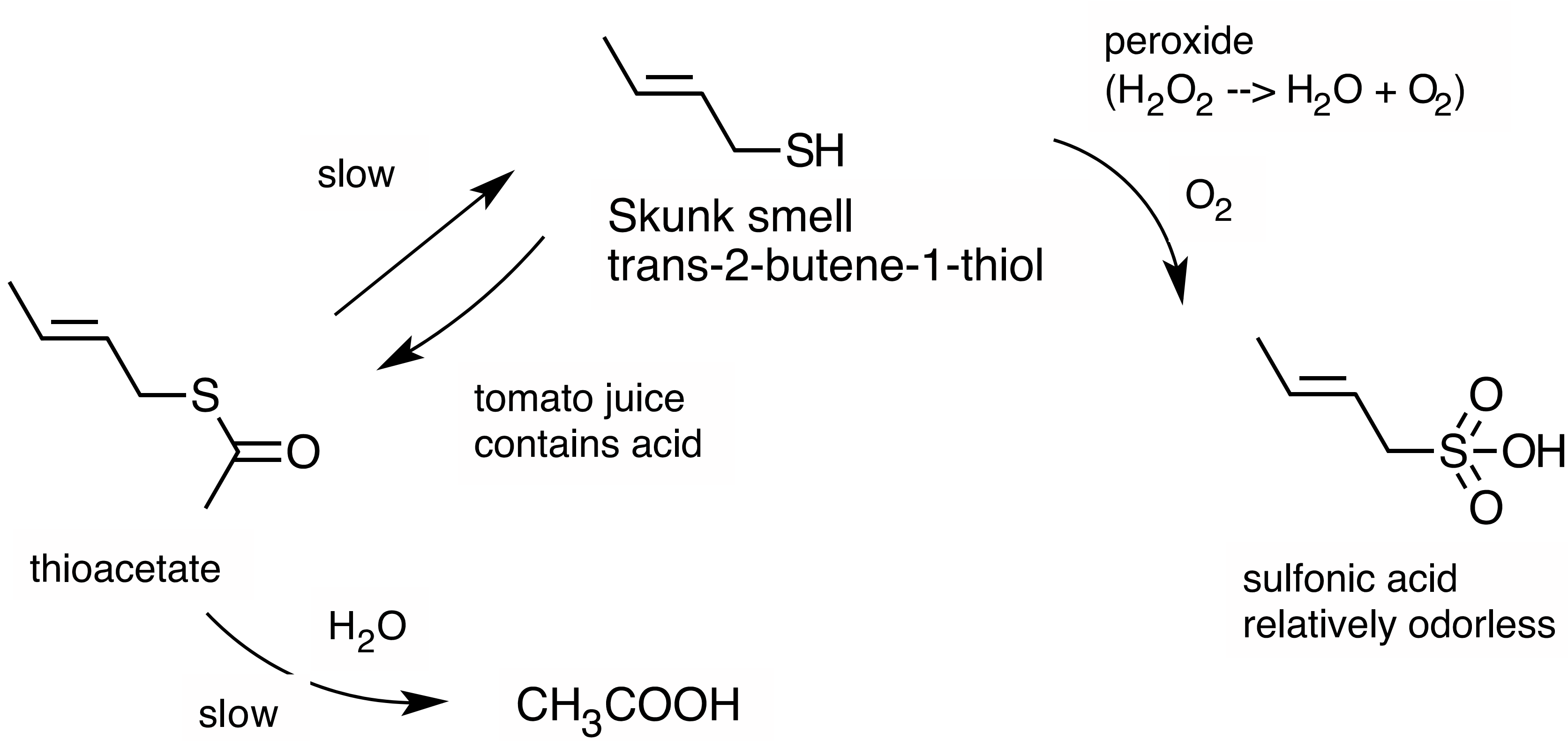
Reversible Reaction!

Acid + Alcohol <==> Ester + water

Note: aspirin metabolizes in our body to form salicylic acid.
In general: ester hydrolysis is a metabolism reaction.

Sprayed by a Skunk!

Should I use tomato juice or hydrogen peroxide?

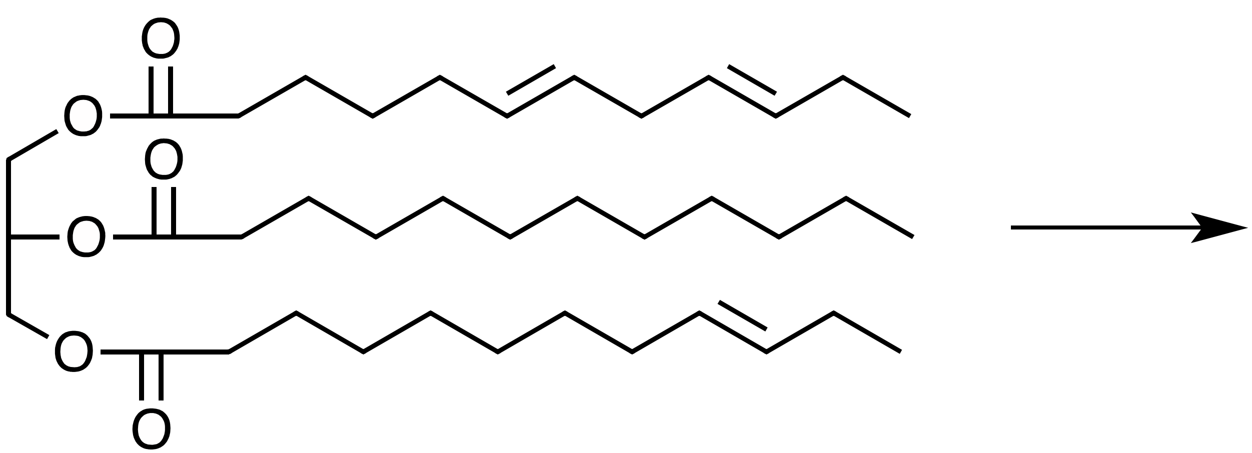


Unsaturated fats, especially polyunsaturated fats, go ***rancid***

Three pathways: http://en.wikipedia.org/wiki/Rancidification

1. Microbial
2. Oxidative - the double bonds of an unsaturated fatty acid can undergo cleavage, releasing volatile aldehydes and ketones.
3. Hydrolytic - ester hydrolysis

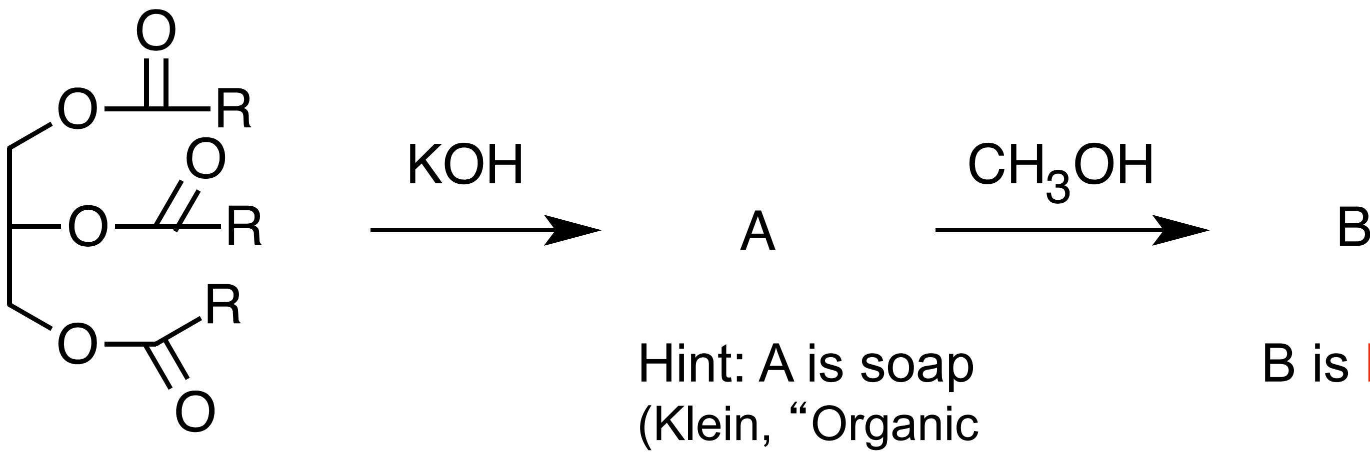
    triglyceride (ester) --> ROH + 3 RCOOH



Which chain is unsaturated? Polyunsaturated?

Is the same acid formed when this triglyceride hydrolyzes?

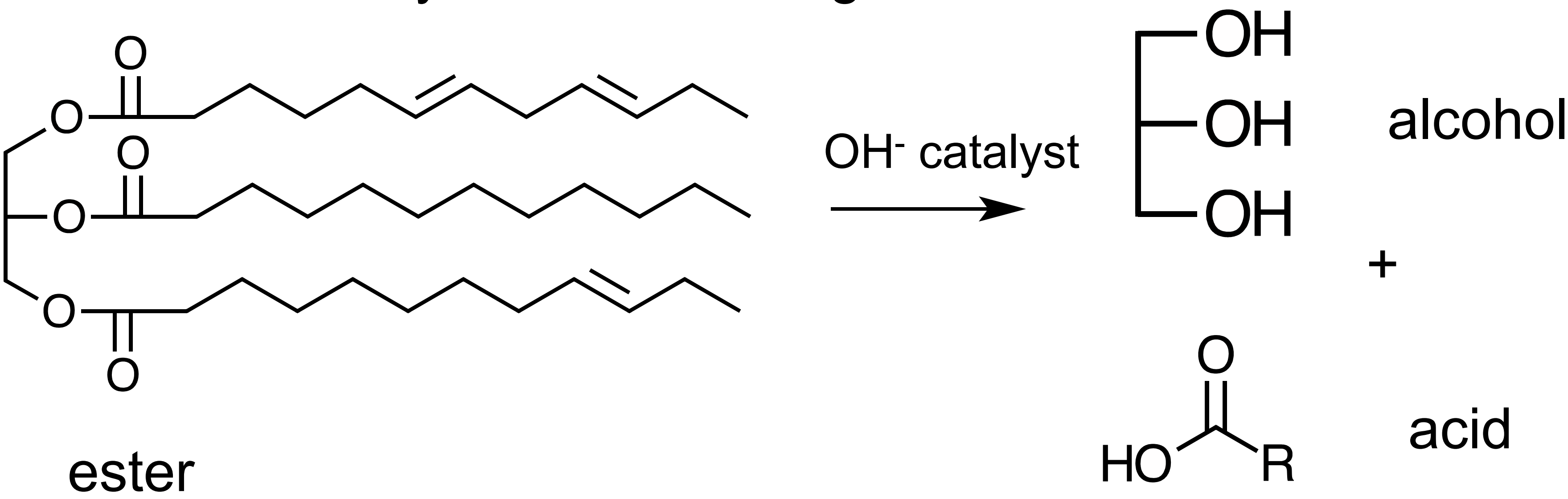
Predict the product:

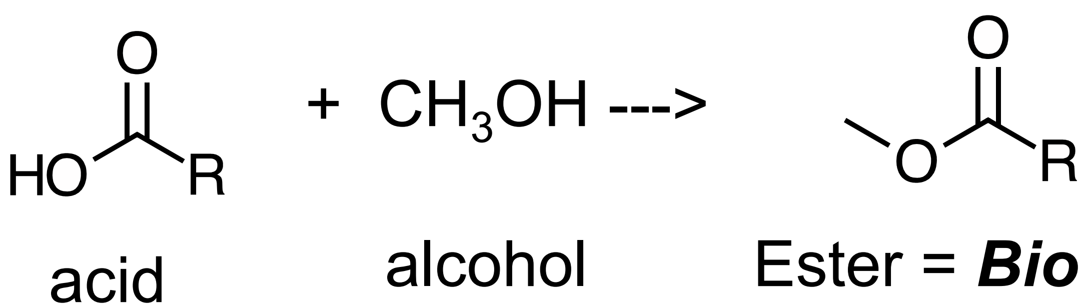


Hint: A is soap
(Klein, "Organic
Chemistry", p. 1002)

B is biodiesel

Biodiesel synthesis from vegetable oil





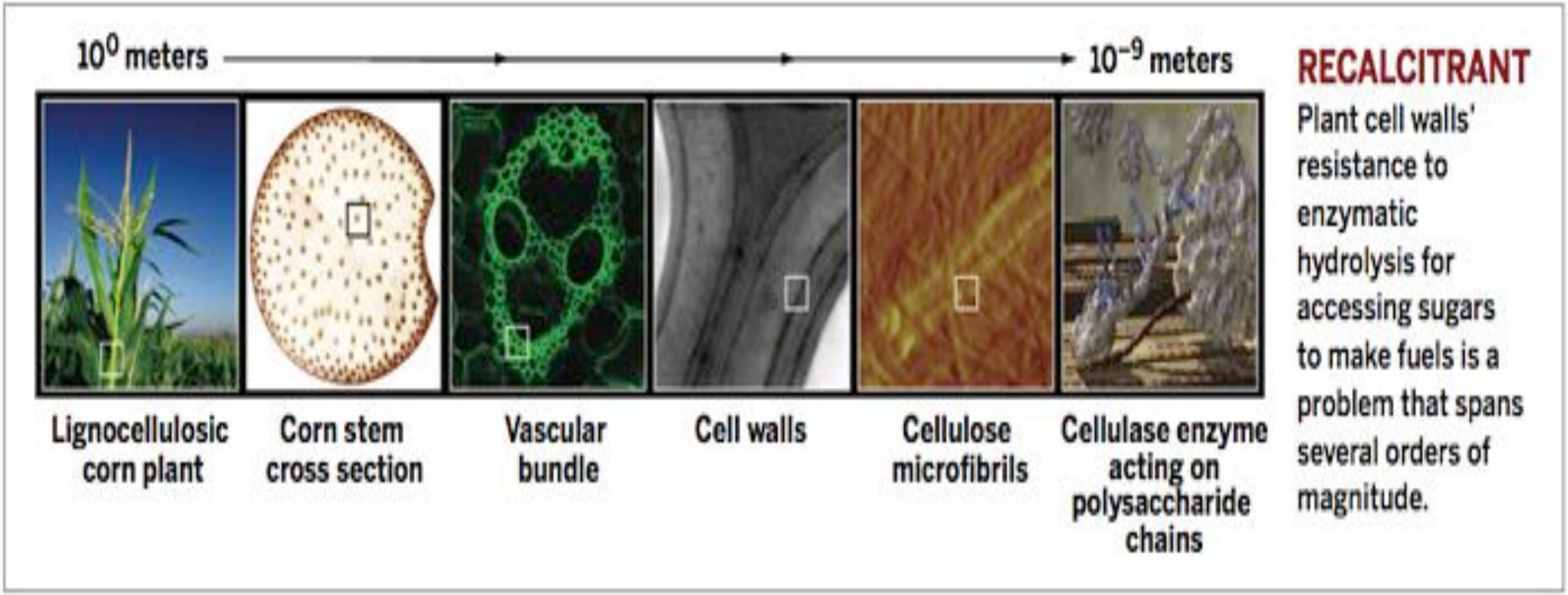
Ester = ***Biodiesel***

FAMEs = fatty acid methyl esters

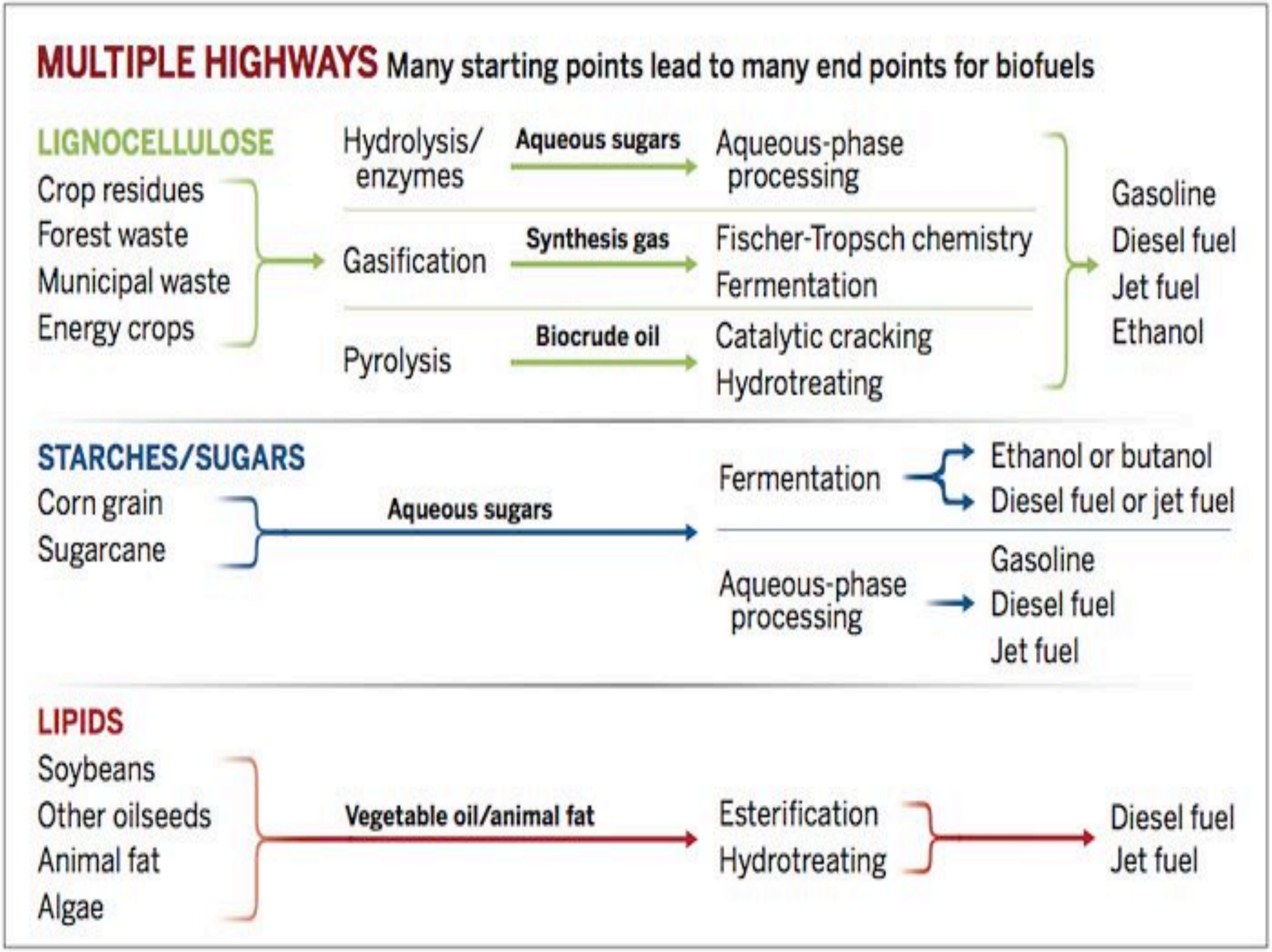
Analyze by: IR - check for ?

GC - FAMEs. Which fatty acid type has the higher b.p.?

CEN, 2/14/11, p. 11 "Race To The Pump: Biofuel technologies vie to provide a sustainable supply of transportation fuels."



CEN, 2/14/11, p. 11 "Biofuel Technologies"



2nd generation

1st generation

3rd generation

See also CEN, 8/15/11, p. 10 "Biofuels Policy"

Biodiesel ***Cetane Number*** measures Combustion Quality of fuel during compression ignition (CEN, 6/13/11, p. 30)

Fuel	Cetane Number
US biodiesel from soybean oil	47
Europe biodiesel from rapeseed and canola oil	54

* ***More efficient***

Difference in cetane number is due to number of C=C bonds

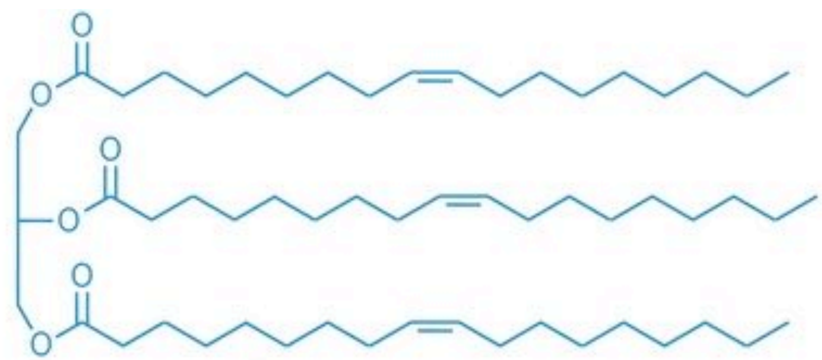
4.2 million barrels of oil (CEN, 10/28/13, p. 19)

= Deepwater Horizon spilled into GOM in 2010.

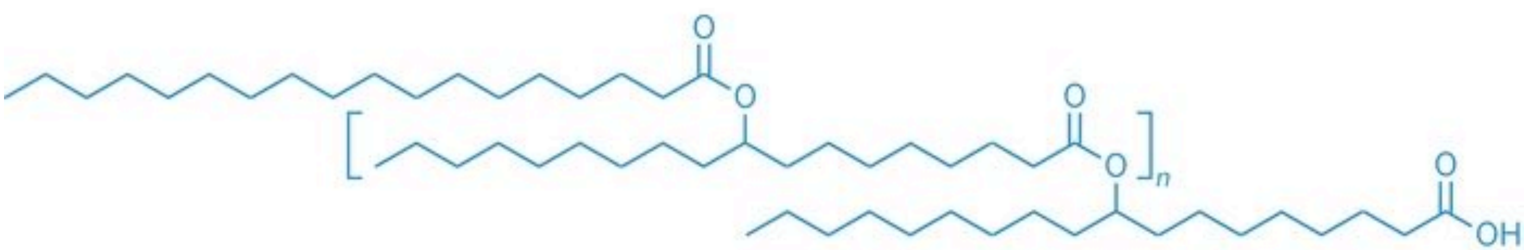
= used motor oil dumped into environment in U.S. each year.

Takes months for organisms to break down.

Motor Oil from (environmentally friendly) Vegetable Oil?



High-oleic vegetable oil



Estolide

How would you convert vegetable oil to estolide?

http://cen.acs.org/articles/90/i12/Old-Plastics-Fresh-Dirt.html

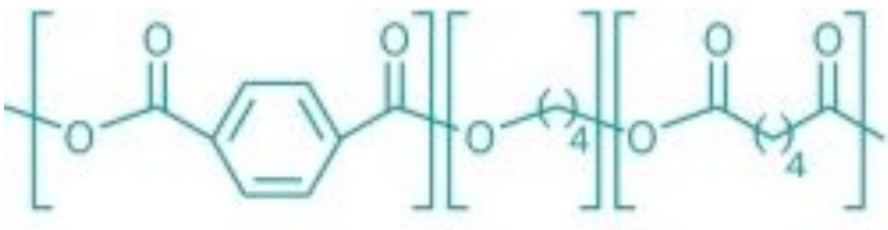
3/19/12, CEN, p. 12 “Old Plastics, Fresh Dirt”

2010: 250 million tons of trash generated by Americans:

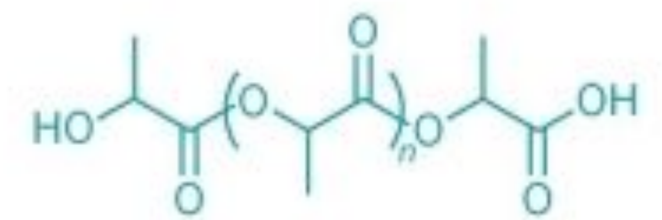
Plastics = 12%, Food waste and yard trimmings = 27%

Only a handful of polymers are biodegradable in a matter of months.

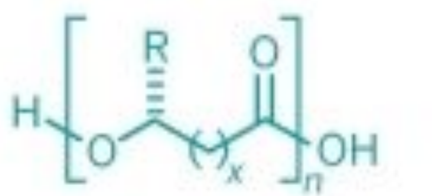
Compostable Plastics biodegrade in a specific environment in a relatively short period of time.



BASF's Ecoflex (copolyester)



NatureWorks' Ingeo (polylactic acid)

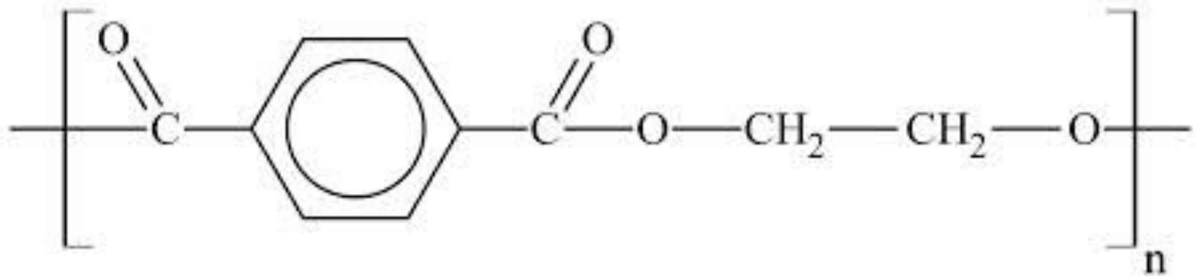


Polyhydroxyalkanoate

Biodegradable (consumed by bacteria as food) polymers:

- have bonds that are readily **hydrolyzed**, e.g., esters are particularly vulnerable to esterases (enzymes).
- are highly aliphatic (need flexible molecular chains for esterases to attack).
- are water permeable.

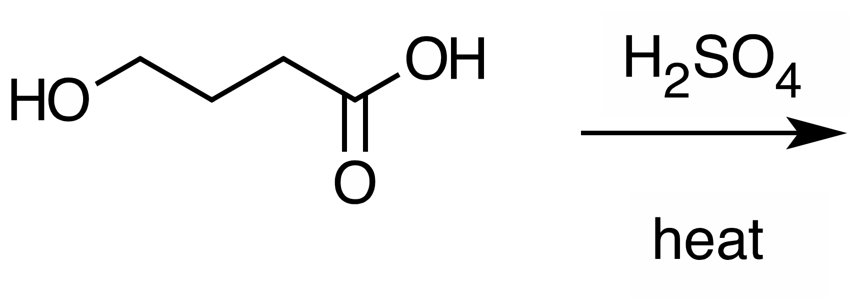
Polyethylene terephthalate (PET) is the world's most popular polyester.

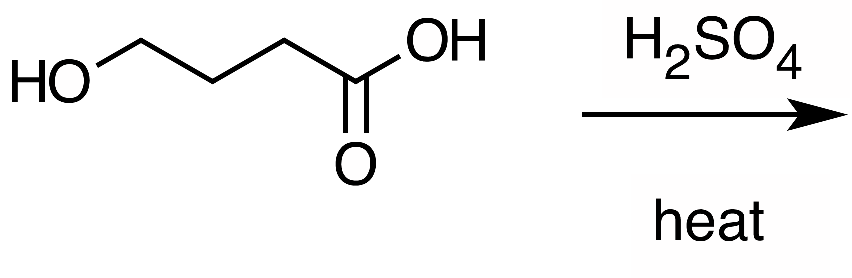


http://www.ehow.com/info_8609097_uses-polyethylene-terephthalate.html

Why is PET **not** biodegradable?

Predict the product:

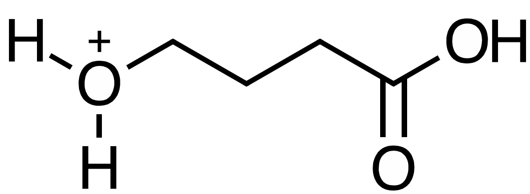


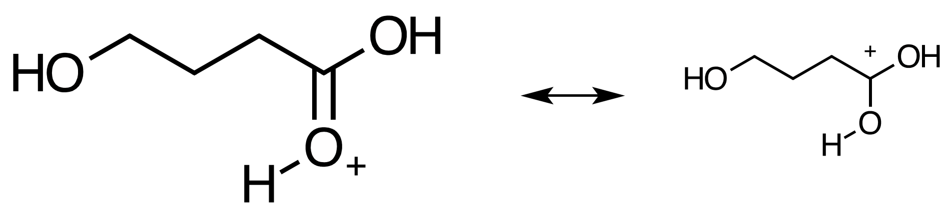


Possibilities:

H_2SO_4 reacts with -OH

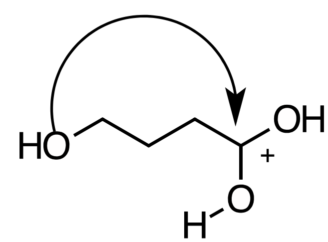
H_2SO_4 reacts with O=C



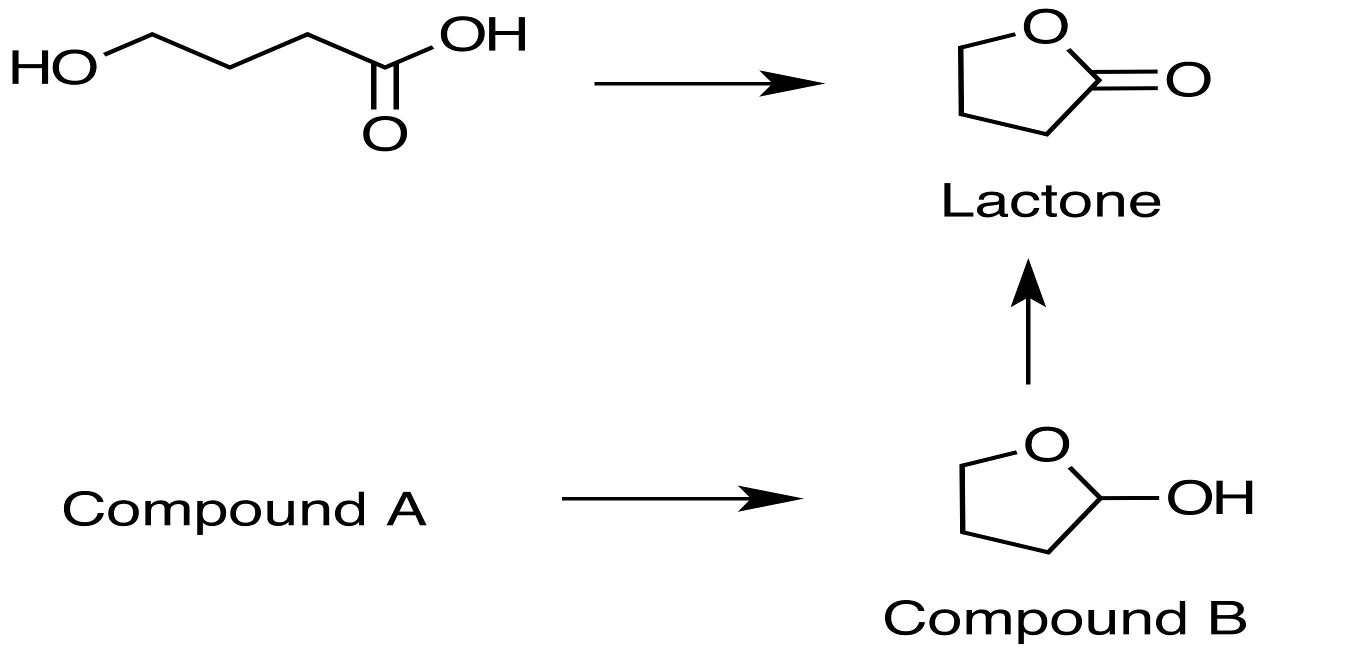


Now what?

Now what?



A compound that contains -COOH and -OH can form a 5 or 6 sided ***Lactone*** ring (Intramolecular Cyclic Ester Formation).

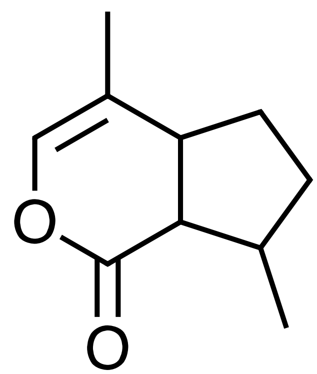


1. What is Compound A? (Hint: What functional group is in B?)
   (Hint 2: starts with H)

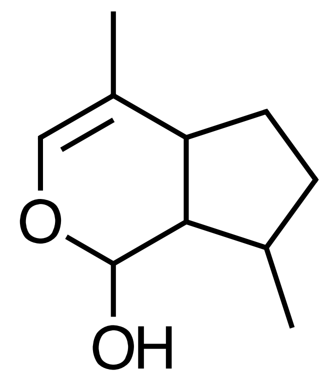
2. How is Compound B converted to lactone?

More Lactones

ACS Reactions video: Catnip plant makes aphid pheromones



nepetalactone

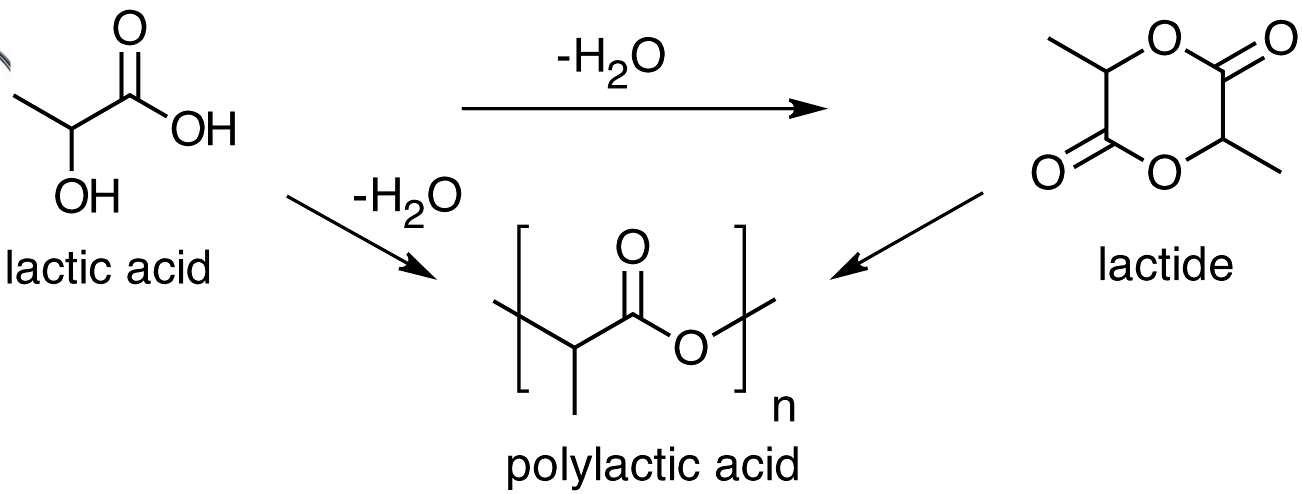


nepetalactol

Terpenoids

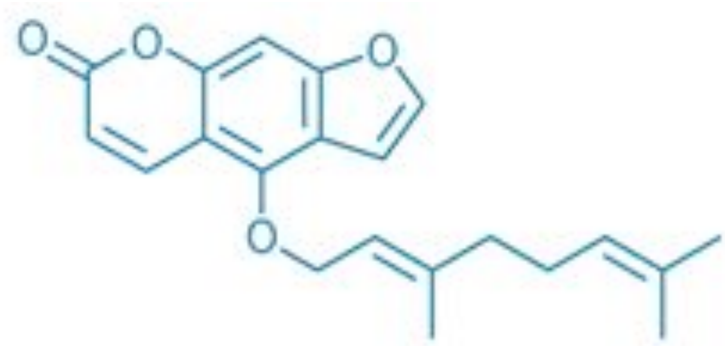
1. What are the hydrolysis products of nepetalactone?
2. What functional group is in nepetalactol? What reactants would you use to make this compound?

3D printer filament:
PLA (polylactic acid)



How is PLA made from lactic acid? Use curved arrows to show how bonds break and form.
How is lactide made from lactic acid?
How is PLA made from lactide?

Some Foods interfere with drug activity



Bergamottin

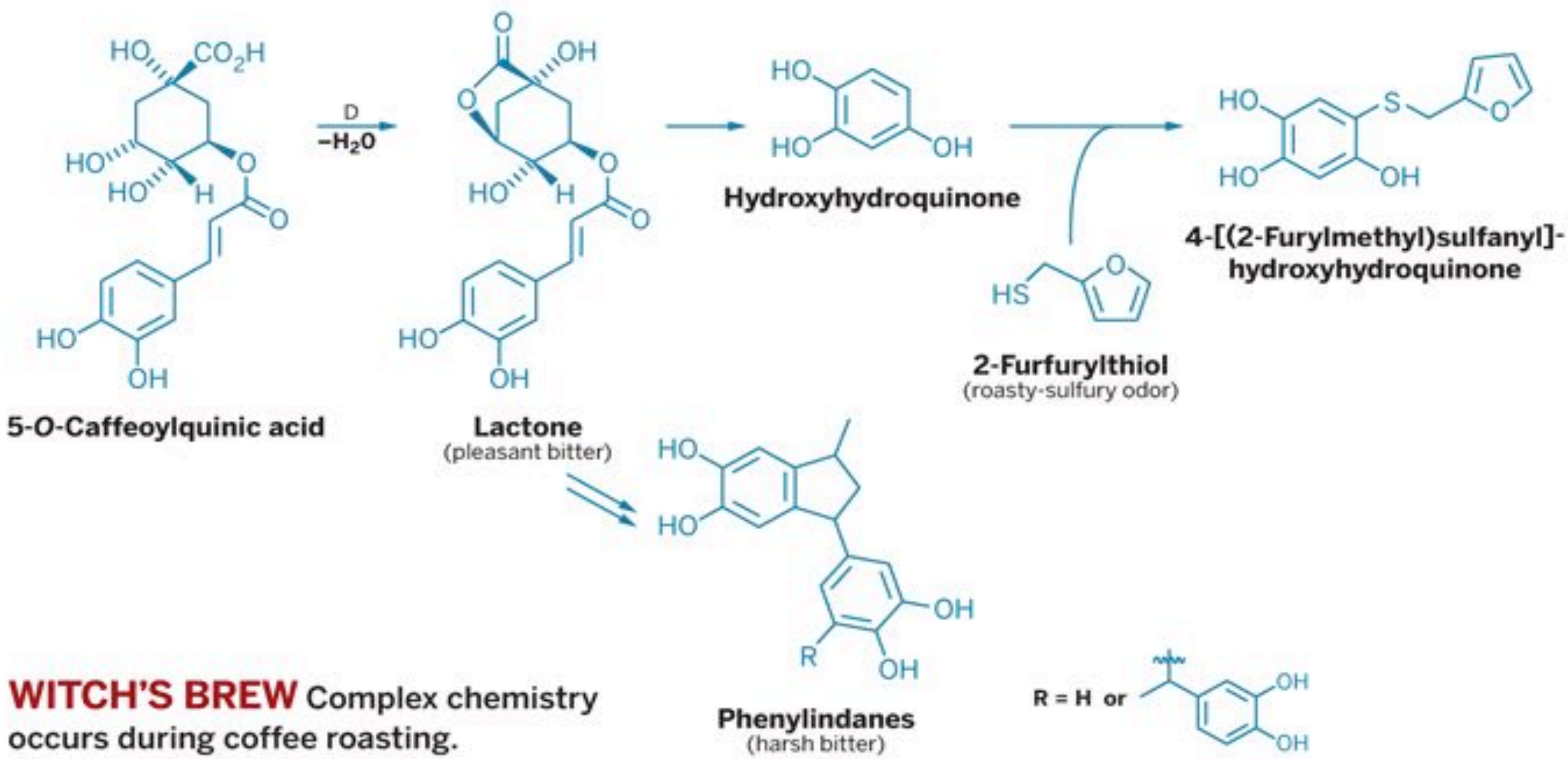
Found in grapefruit juice, which inactivates a cytochrome P450 enzyme.

ID the functional groups.

http://cen.acs.org/articles/88/i39/Foods-Drugs-Collide.html

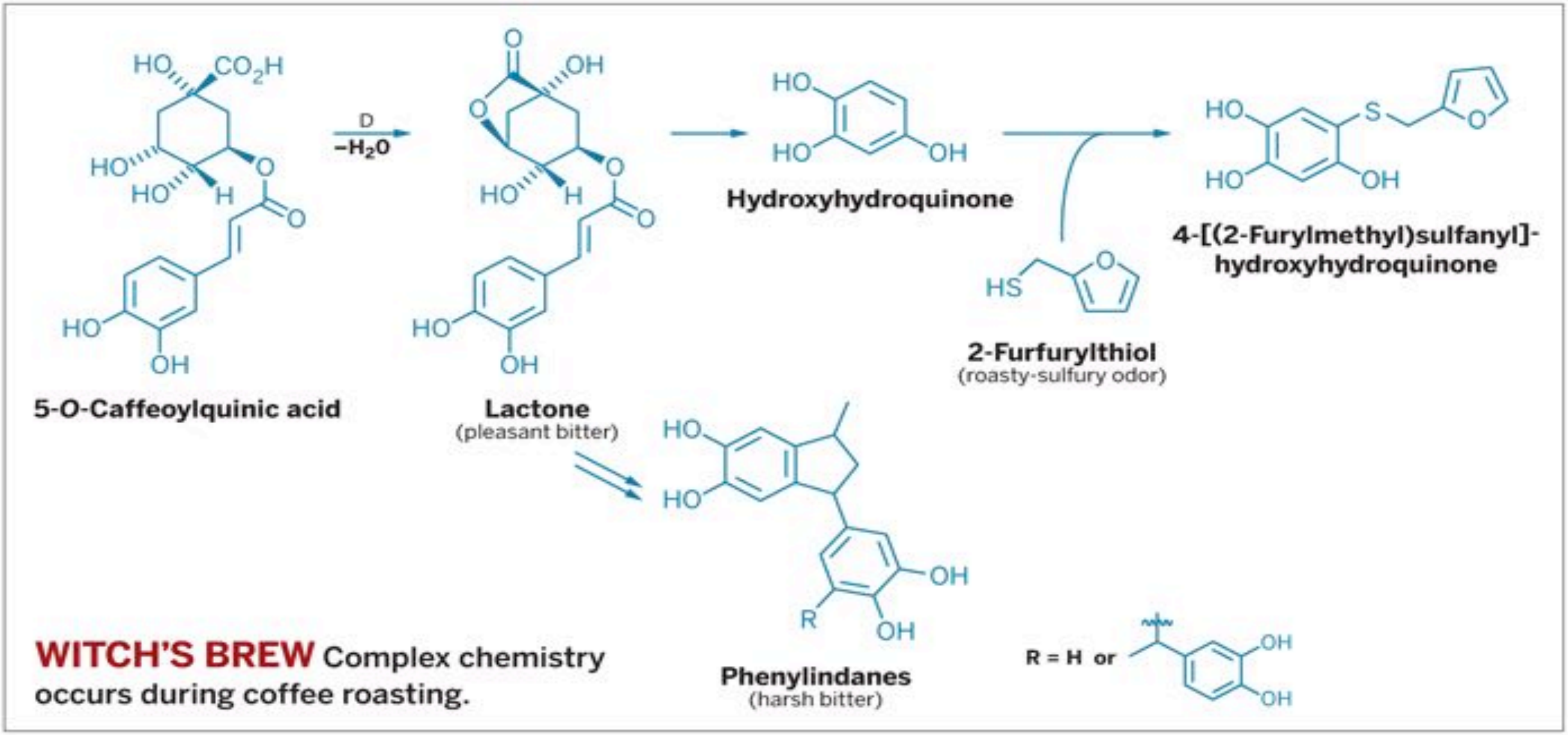
Coffee flavor affected by roasting, cooling, and storage (CEN, 9/17/07, p. 32)

Raw green coffee seeds, or beans, are removed from bright red coffee berries, then dried and roasted. Beans are typically roasted for eight to 12 minutes and ultimately reach a temperature of 210–225 °C. "The final roasting temperature influences not only the quality and quantity of aroma compounds that give coffee its enticing character but also the correct ratio between bitter and acid flavor,"



WITCH'S BREW Complex chemistry occurs during coffee roasting.

Coffee flavor affected by roasting, cooling, and storage (CEN, 9/17/07, p. 32)

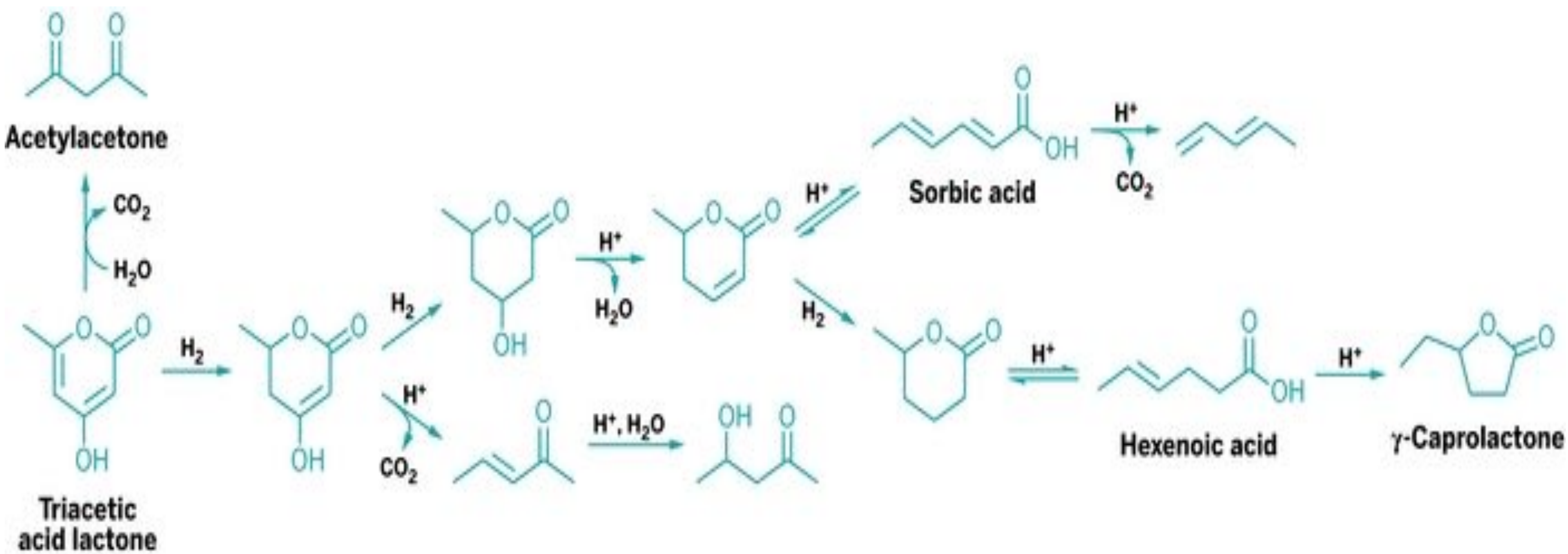


Use curved arrows to show how the Lactone (cyclic ester) is produced in the 1st step.

http://cen.acs.org/articles/90/i32/Teaming-Biobased-Chemicals.html

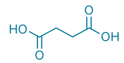
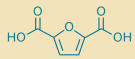
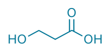
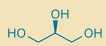
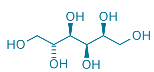
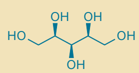
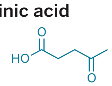
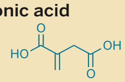
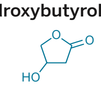
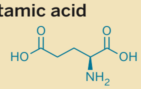
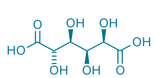
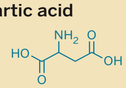
8/6/12, CEN, p. 37 Biobased Chemicals

Triacetic acid lactone may serve as a new "platform" to produce a range of biobased chemicals.



Where Are They Now?

In 2004, the Energy Department identified a set of biomass-derived compounds best suited to replace petroleum-derived chemicals.

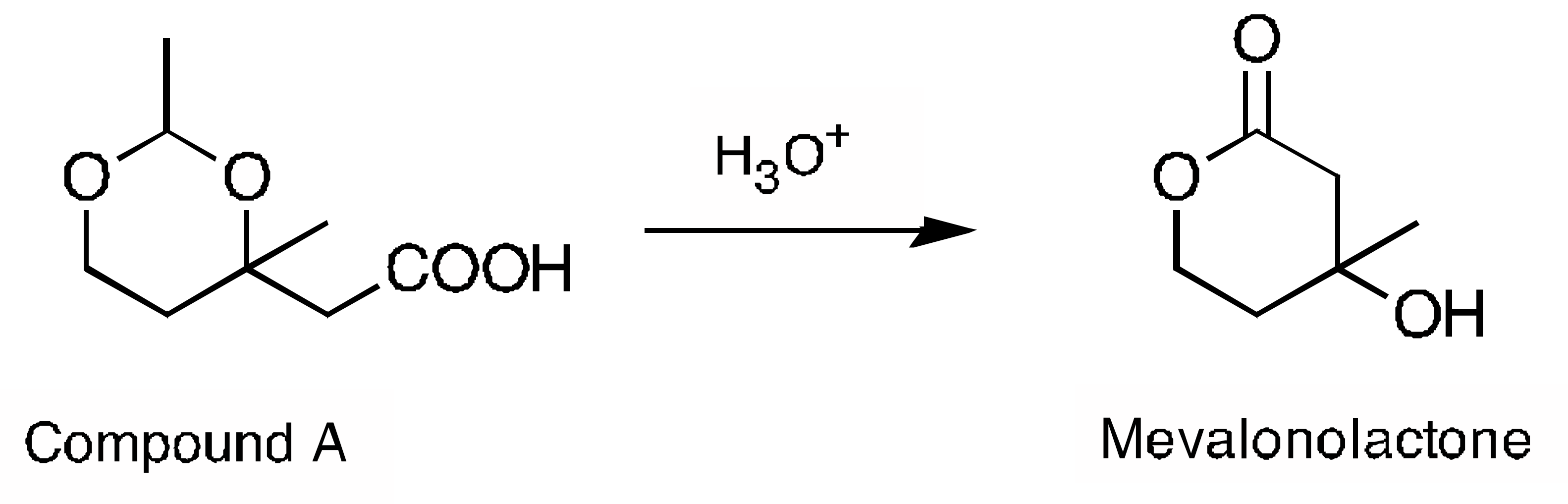
DOE's Top 15	Source	Downstream chemicals and materials	Key uses and products	Commercial biobased products		Bio-scorecard grade[a]
				Now	Likely in 10 years	
Succinic acid (plus fumaric and malic acids) 	Bacterial fermentation of glucose, chemical oxidation of 1,4-butanediol	1,4-Butanediol, tetrahydrofuran, γ-butyrolactone, maleic anhydride, pyrrolidones	Solvents, polyesters, polyurethanes, nylon, food and beverage acidity control, fabrics, inks and paints, much more	Yes	Yes	A
2,5-Furandicarboxylic acid 	Chemical dehydration of glucose, oxidation of 5-hydroxymethylfurfural	2,5-Dihydroxymethylfuran, 2,5-bis(aminomethyl)tetrahydrofuran	Polyethylene terephthalate analogs, polyamides such as nylon, plastic bottles and containers, fabrics, carpet fiber	Coming soon	Yes	B
3-Hydroxypropionic acid 	Bacterial fermentation of glycerol or glucose	1,3-Propanediol, acrylic acid, methyl acrylate, acrylamide	Polytrimethylene terephthalate, acrylate polymers, carpet fiber, paints and adhesives, superabsorbent polymers for diapers, contact lenses	No	Yes	B
Glycerol 	Chemical or enzymatic transesterification of vegetable oils	Propylene glycol, ethylene glycol, 1,3-propanediol, glyceric acid, lactic acid, acetol, acrolein, epichlorohydrin	Polyesters, butanol, soaps, cosmetics, foods and beverages, antifreeze/deicing fluids, pharmaceuticals, coatings, carpet fiber	Yes	Yes	B
Sorbitol 	Hydrogenation of glucose from corn syrup, bacterial fermentation (under development)	Isosorbide, propylene glycol, ethylene glycol, glycerol, lactic acid, alkanes	Sweeteners, mouthwash and toothpaste, sugar-free chewing gum, polyethylene terephthalate analogs, fuel ingredients, antifreeze/deicing fluids, water treatment	Yes	Yes	B
Xylitol (plus arabinitol) 	Hydrogenation of xylose, extraction from lignocellulose, bacterial fermentation (under development)	Propylene glycol, ethylene glycol, glycerol, xylaric acid, furfural	Sweeteners, sugar-free chewing gum, cough drops and medicines, antifreeze/deicing fluids, new polyesters	Yes	Yes	C
Levulinic acid 	Acid-catalyzed dehydration of sugars	2-Methyltetrahydrofuran, γ-valerolactone, 1,4-pentanediol, acetylacrylic acid, diphenolic acid, caprolactam, adiponitrile, pyrrolidones	Fuel ingredients, solvents, acrylate polymers, BPA-free polycarbonates, polyesters, polyamides, pharmaceuticals, herbicides, plastic bottles and containers	No	Maybe	C
Itaconic acid 	Fungal fermentation of glucose	4-Methyl-γ-butyrolactone, 3-methyltetrahydrofuran, pyrrolidones	Styrene-butadiene copolymers, polyitaconic acid, rubber, plastics, paper and architectural coatings	No	Maybe	C−
3-Hydroxybutyrolactone 	Multistep chemical synthesis from starch	3-Hydroxytetrahydrofuran, acrylate-lactone, 3-aminotetrahydrofuran	Solvents, synthetic intermediates for pharmaceuticals, polyurethane fiber analogs, new polymers	No	Maybe	C−
Glutamic acid 	Bacterial fermentation of glucose	1,5-Pentanediol, glutaric acid, 5-amino-1-butanol	Polyesters, nylon analogs, glutamate flavor enhancers, fabrics, plastics	No	Maybe	D+
Glucaric acid 	Oxidation of starch or glucose by nitric acid or bleach	Lactones, polyhydroxypolyamides, adipic acid	Solvents, nylon analogs, branched polyesters, fabrics, plastics, detergents	No	Maybe	D
Aspartic acid 	Enzymatic amination of fumaric acid, fermentation route (under development)	2-Amino-1,4-butanediol, 3-aminotetrahydrofuran, aspartic anhydride, amino-γ-butyrolactone	Aspartame, polyaspartate, sweeteners, chelating agents for water treatment, superabsorbent polymers for diapers	No	No	D−

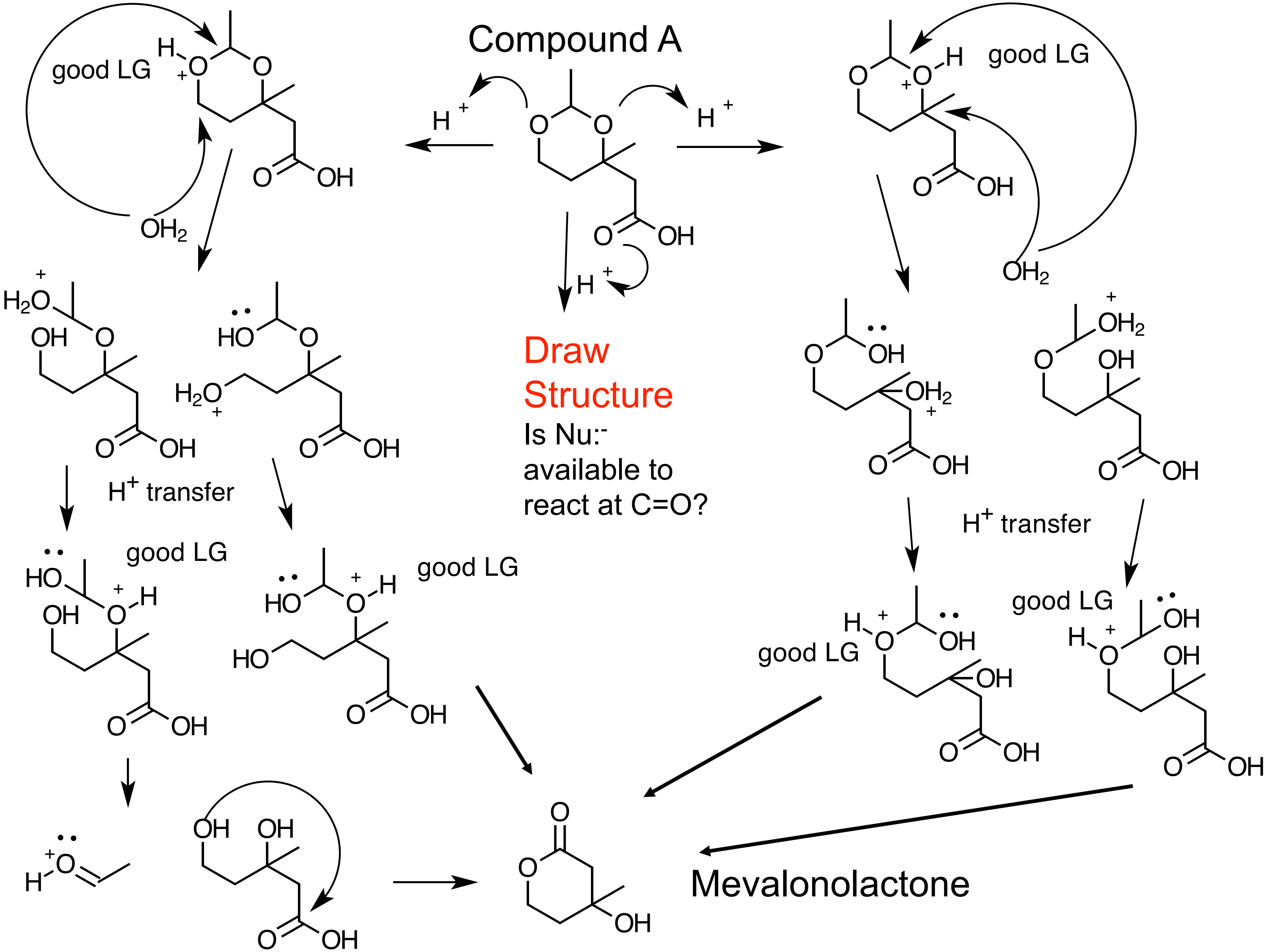
NOTE: Other platform chemicals that are doing well or poised to do well as feedstock chemicals: ethanol, butanediols, acetic acid, acrylic acid, adipic acid, lactic acid, farnesene, *p*-xylene, isobutanol, fatty acid esters, isoprene, furfurals, γ-valerolactone, triacetic acid lactone, and isosorbide. **a** Scorecard grade based on assessments by biobased chemicals experts and compiled by C&EN: **A** = being commercialized, **B** = significant activity, **C** = actively pursued by researchers, **D** = limited activity, **F** = no activity.

SOURCES: Government and industry reports, company information

http://cen.acs.org/articles/92/i43/Biobased-Polymers.html

Mevalonolactone is an intermediate in the biosynthesis of terpenes and steroids.
On standing in dilute aqueous acid, Compound A is smoothly converted to Mevalonolactone. Suggest a reasonable mechanism for this reaction. For each step, use curved arrow to show bonds breaking and forming. What other organic product is formed?





Compound A
Draw
Structure
Is Nu:⁻
available to
react at C=O?
good LG
H⁺ transfer
good LG
good LG
H⁺ transfer
good LG
good LG
good LG
Mevalonolactone