Synthesis of β-C-glycosidic ketones from unprotected sugars and their use in aldol condensations

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Rodrigues, F.; Canac, Y.; Lubineau, A. A Convenient, One-Step, Synthesis of β-C-Glycosidic Ketones in Aqueous Media. *Chem. Commun.* **2000,** 2049-2050.

De Winter, T.M.; Petitjean, L.; Erythropel, H.C.; Moreau, M.: Hitce, J.; Coish, P.; Zimmerman, J.B.; Anastas, P.T. Greener Methodology: An Aldol Condensation of an Unprotected C-Glycoside with Solid Base Catalysts. *ACS Sustainable Chem.* **2018,** 6, 7810-7817.

What are Glycosides?

Pharmaceutical Industry

Chemical Industry

Photos courtesy of Jon Chiaramonte

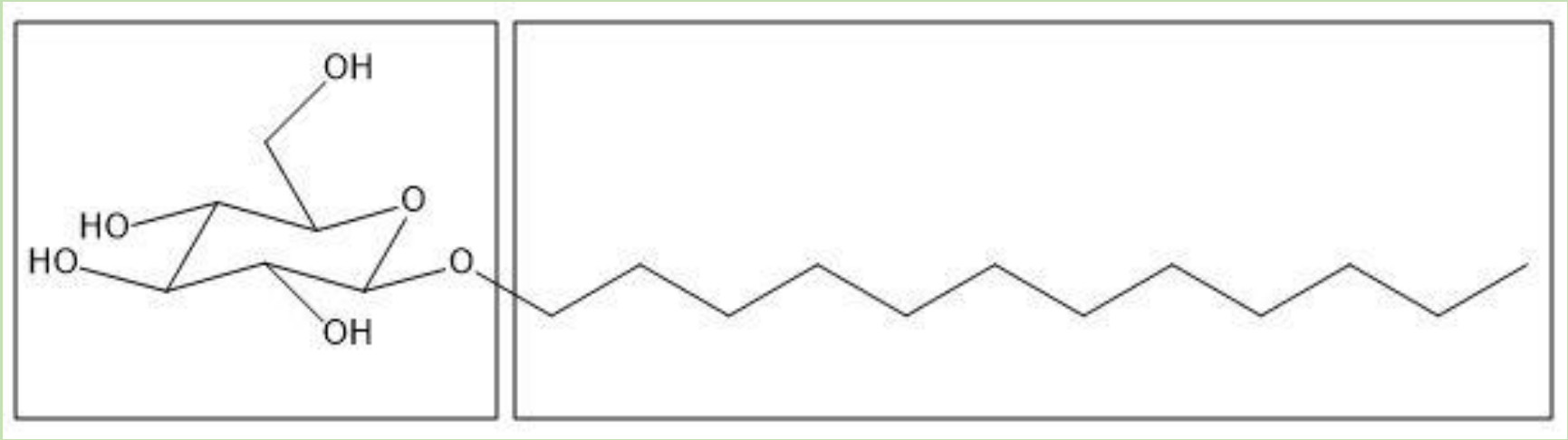
What are Glycosides?

- A glycoside is a molecule in which a sugar is bonded to another chemical functional group via a glycosidic linkage.

- Glycosidic linkages can be formed through either oxygen, nitrogen, sulfur or carbon atoms.

Lauryl Glucoside

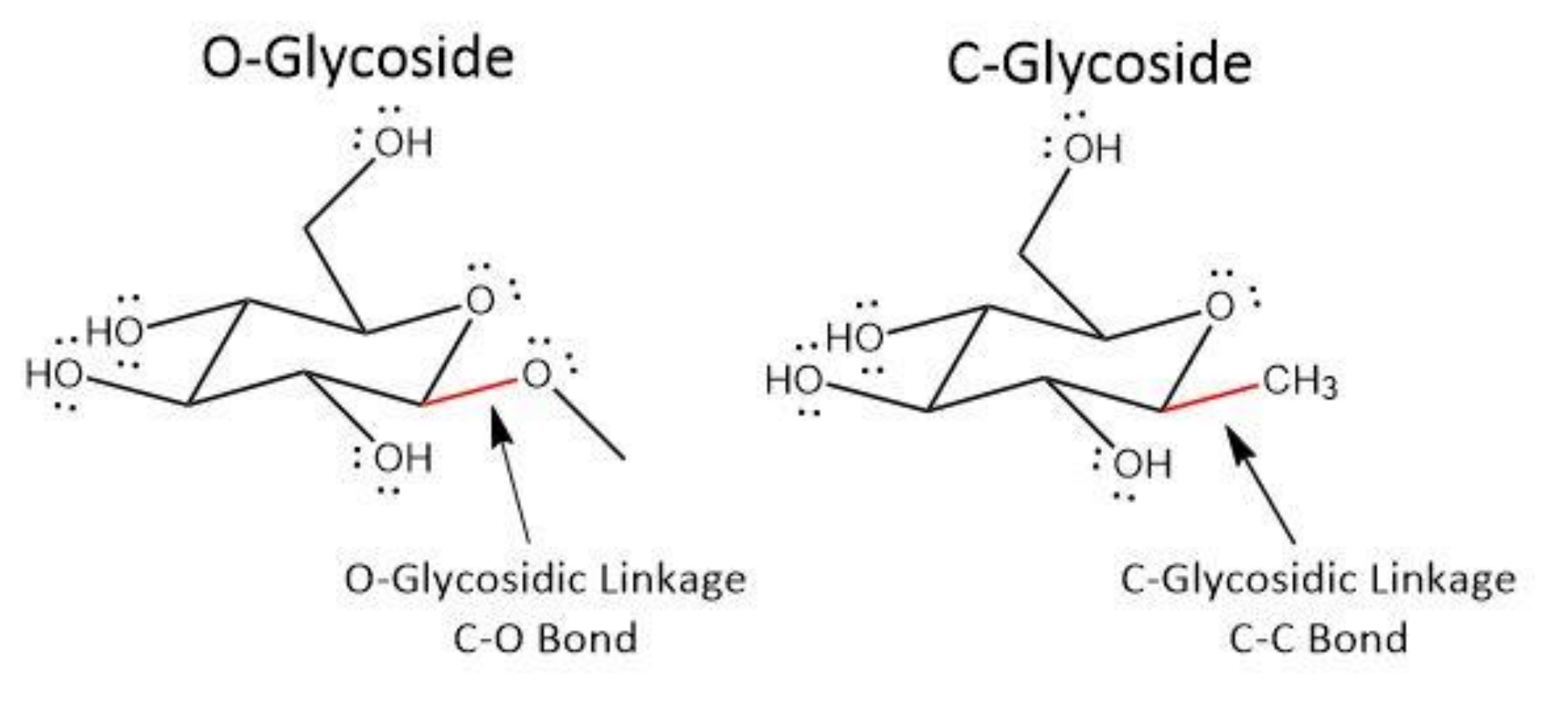
Glycone



Aglycone

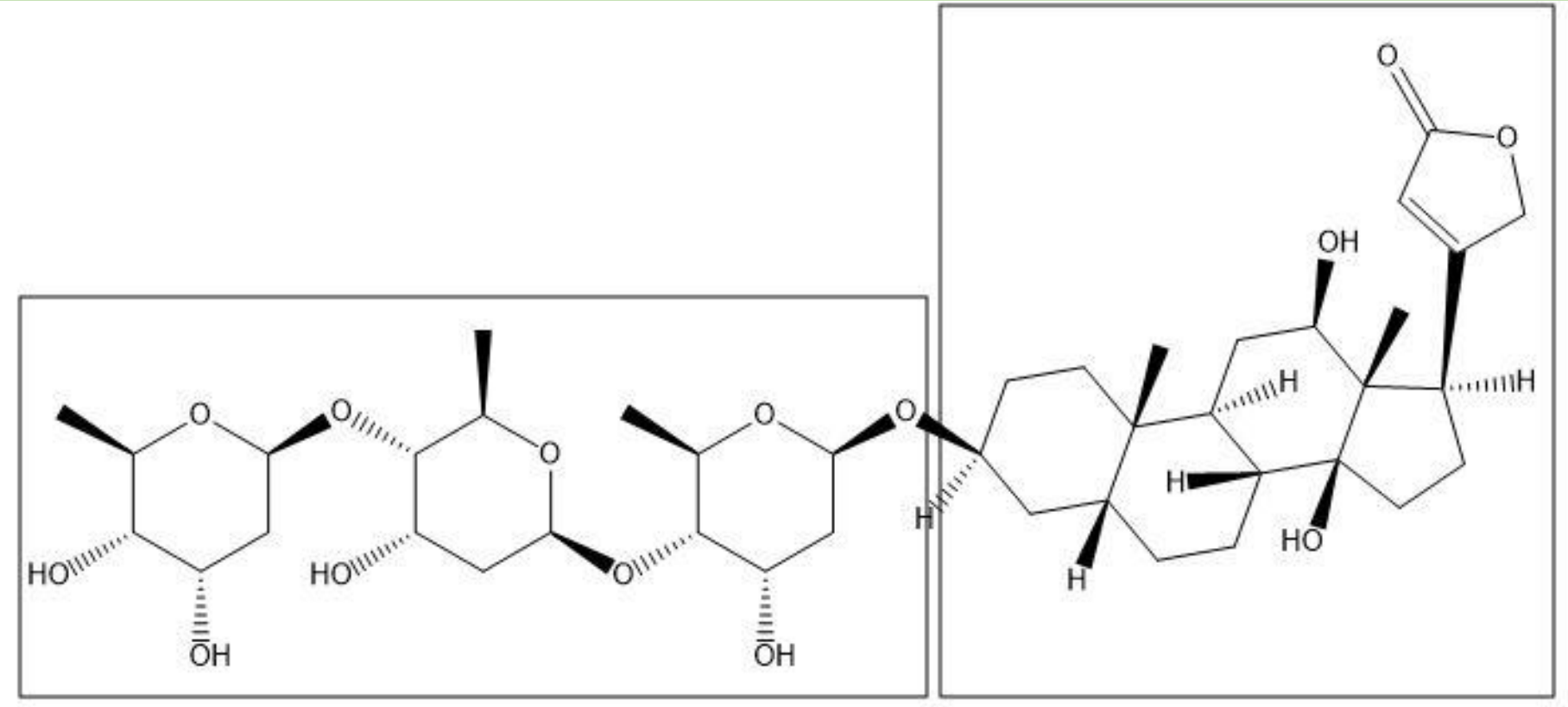
Sugar (Glucose) + Some other functional group (in this case an alkane)

What are Glycosides?



Uses of Glycosides - Drugs

- Digoxin – a cardiac glycoside medication
- Digoxin is an O-glycoside



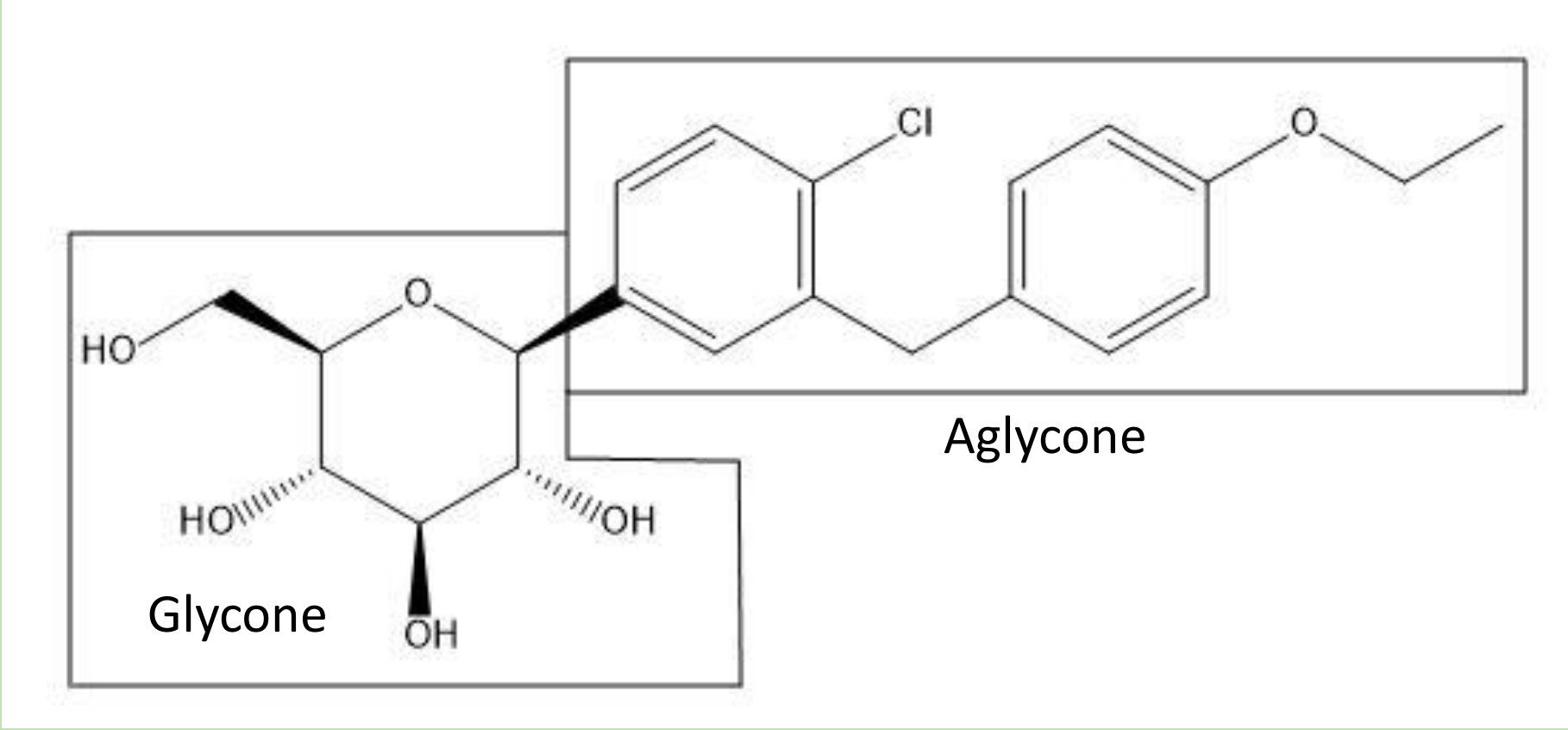
Glycone

Aglycone

Uses of Glycosides - Drugs

- Dapagliflozin – a SGLT2 enzyme inhibitor used to treat diabetes

- Dapagliflozin is a C-glycoside



Surfactants

How Soap Is Made…

Saponification of Triglycerides Produces Fatty Acid Salts

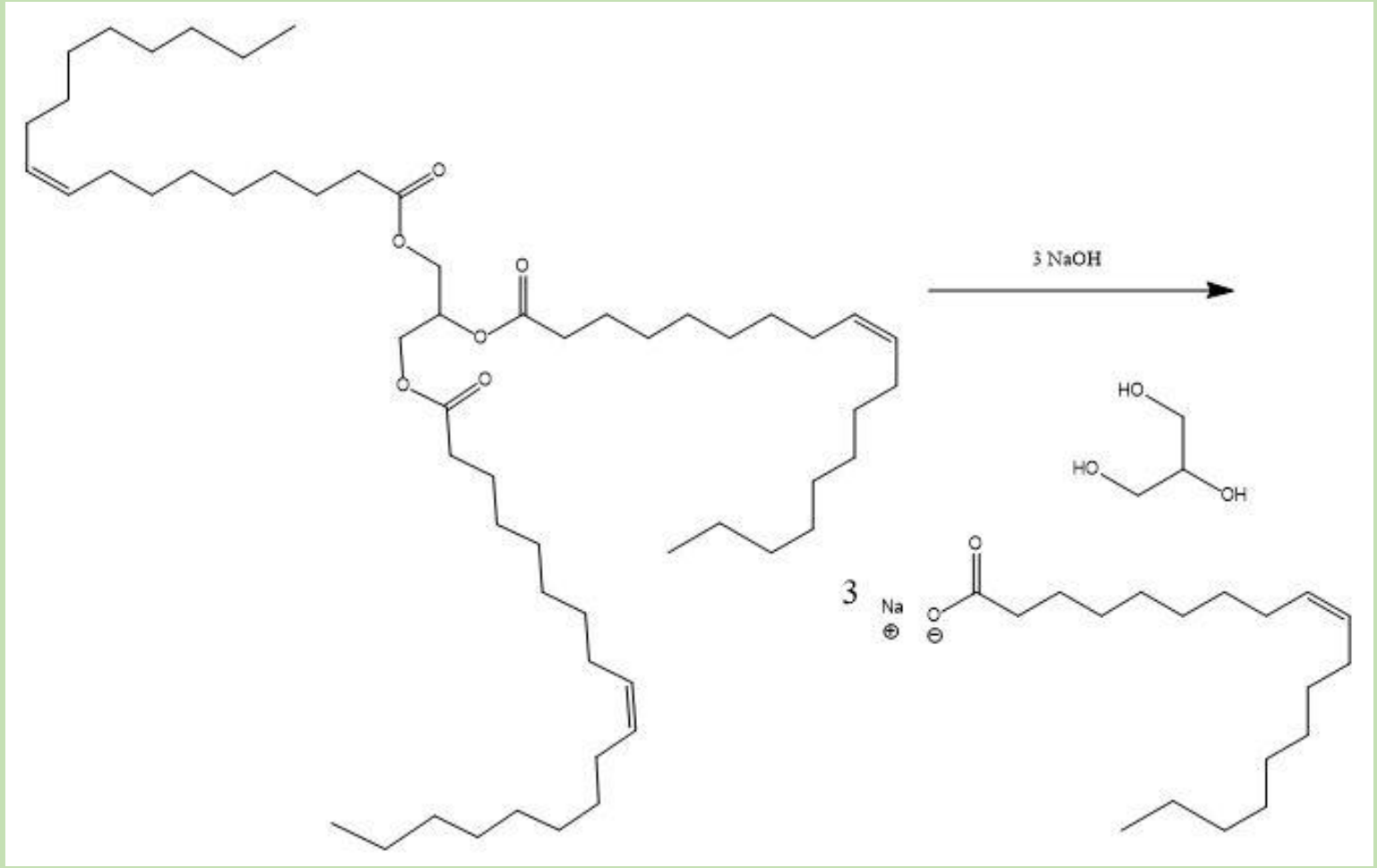
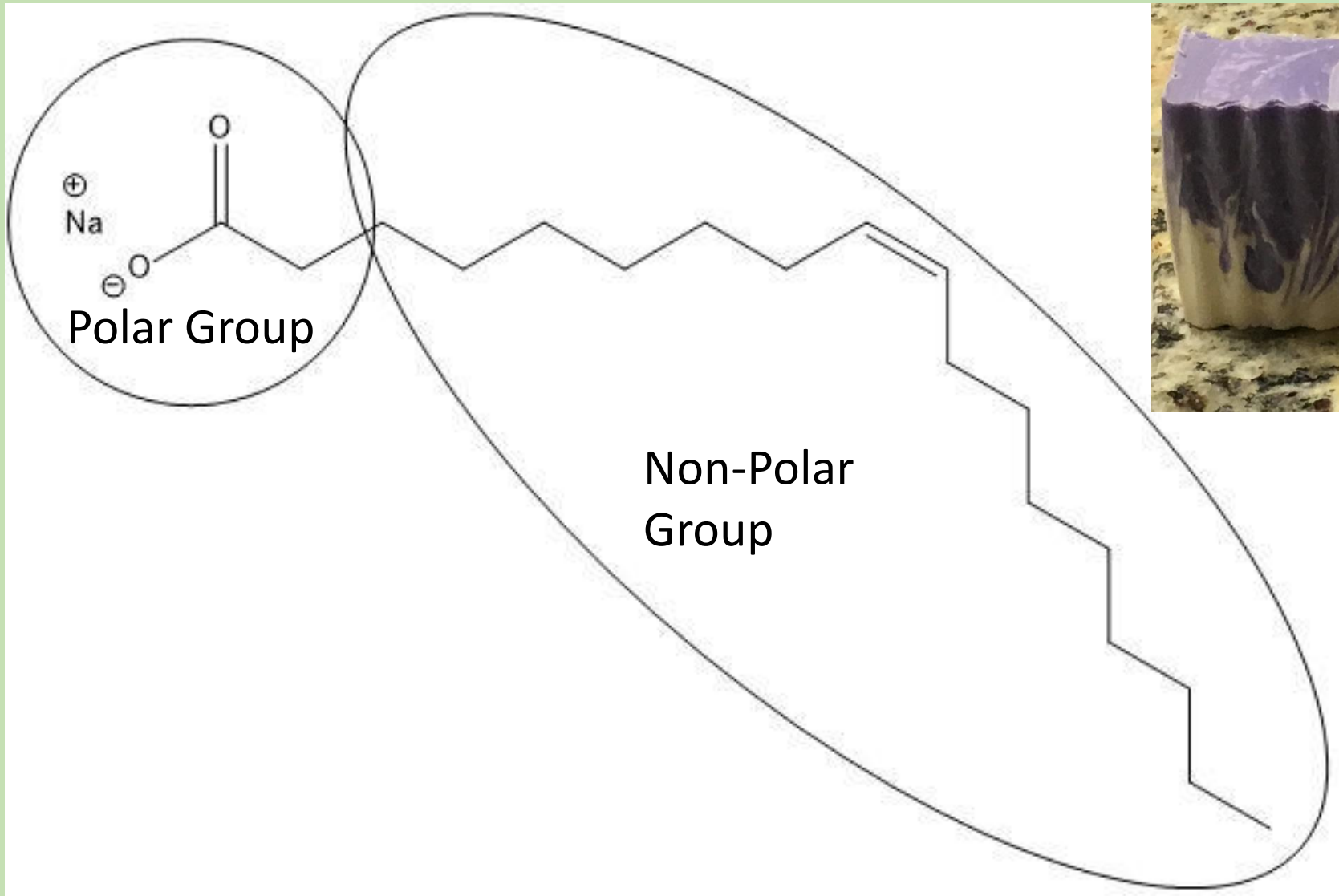


Photo courtesy of Jon Chiaramonte

Surfactants



Photos courtesy of Jon Chiaramonte

Surfactants

Micelle

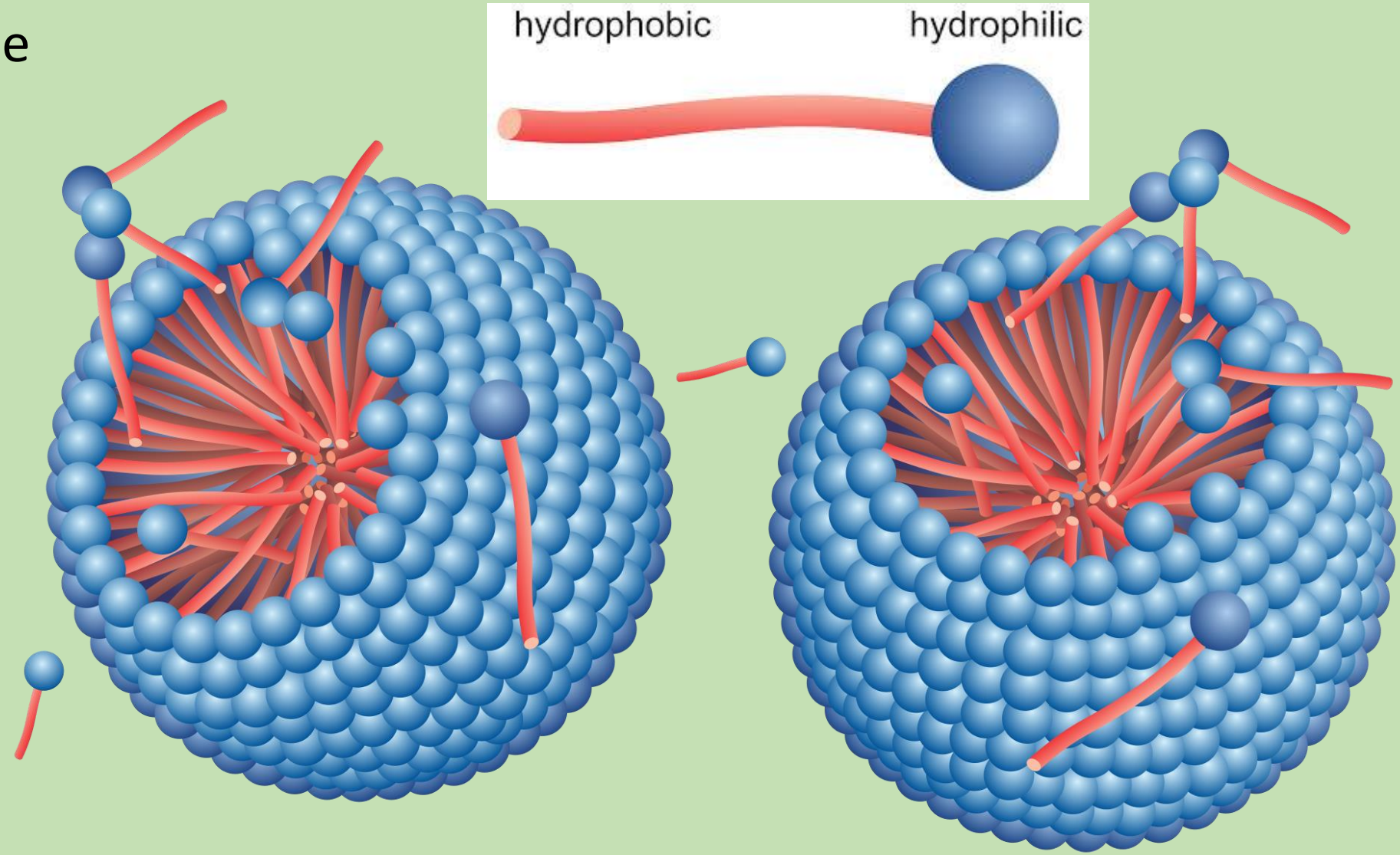
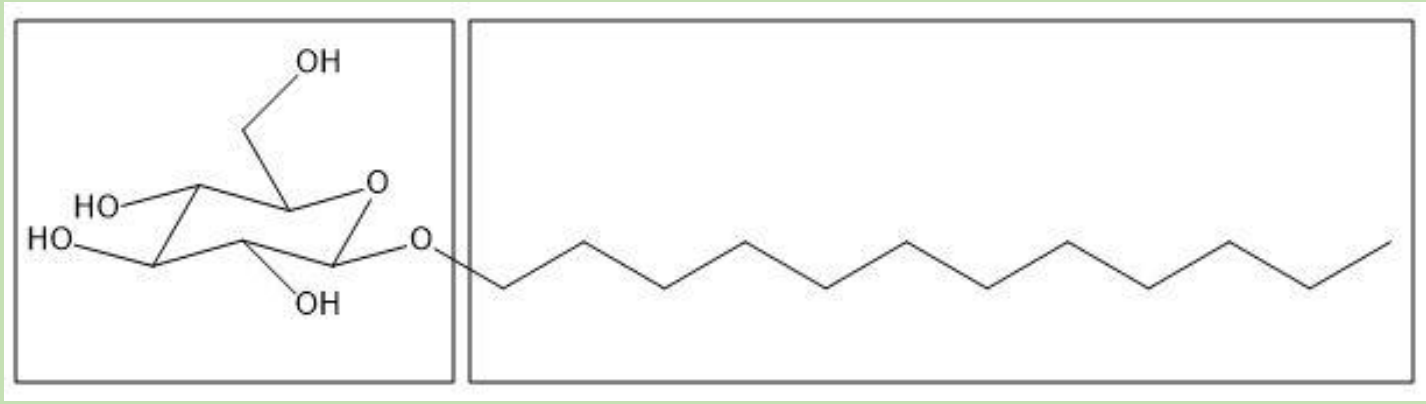


Image Courtesy of Dataphysics: Understanding Interfaces

Surfactants

- Glycosides can serve as surfactants

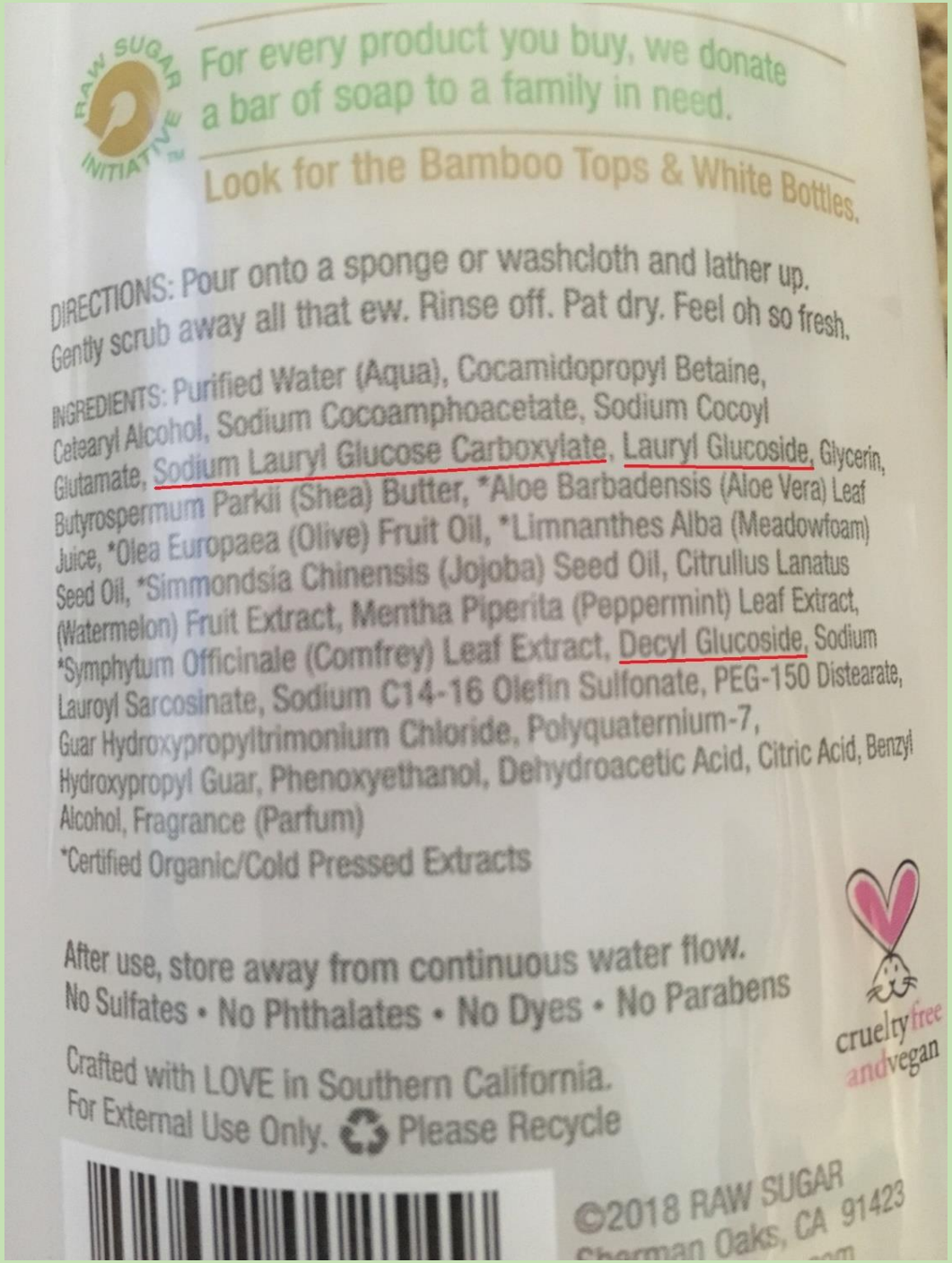
Lauryl Glucoside – an O-linked glycoside



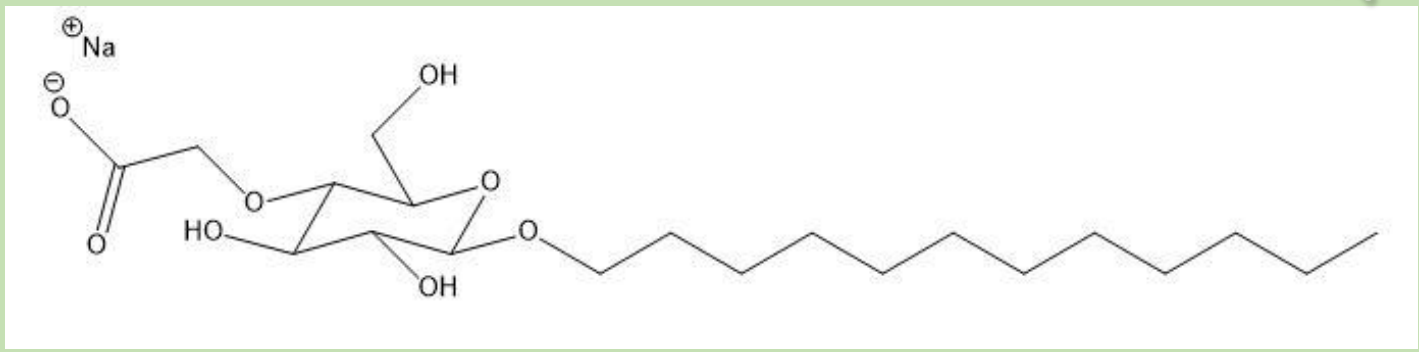
Polar Group

Non-Polar Group

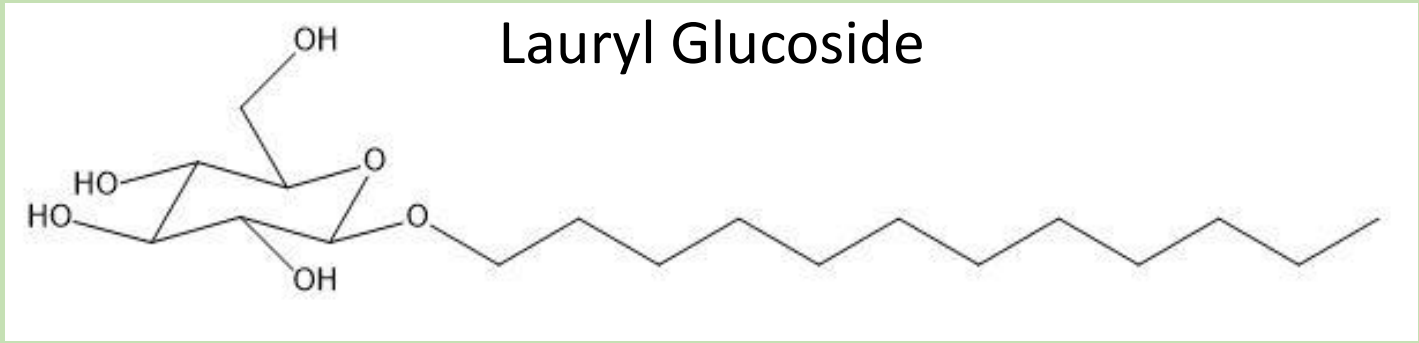
Photo courtesy of Jon Chiaramonte



Sodium Lauryl Glucose Carboxylate



Lauryl Glucoside



Decyl Glucoside

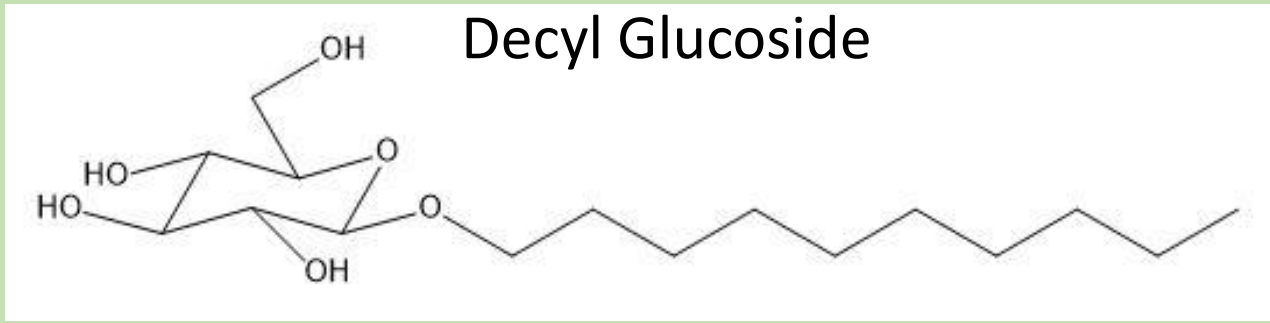
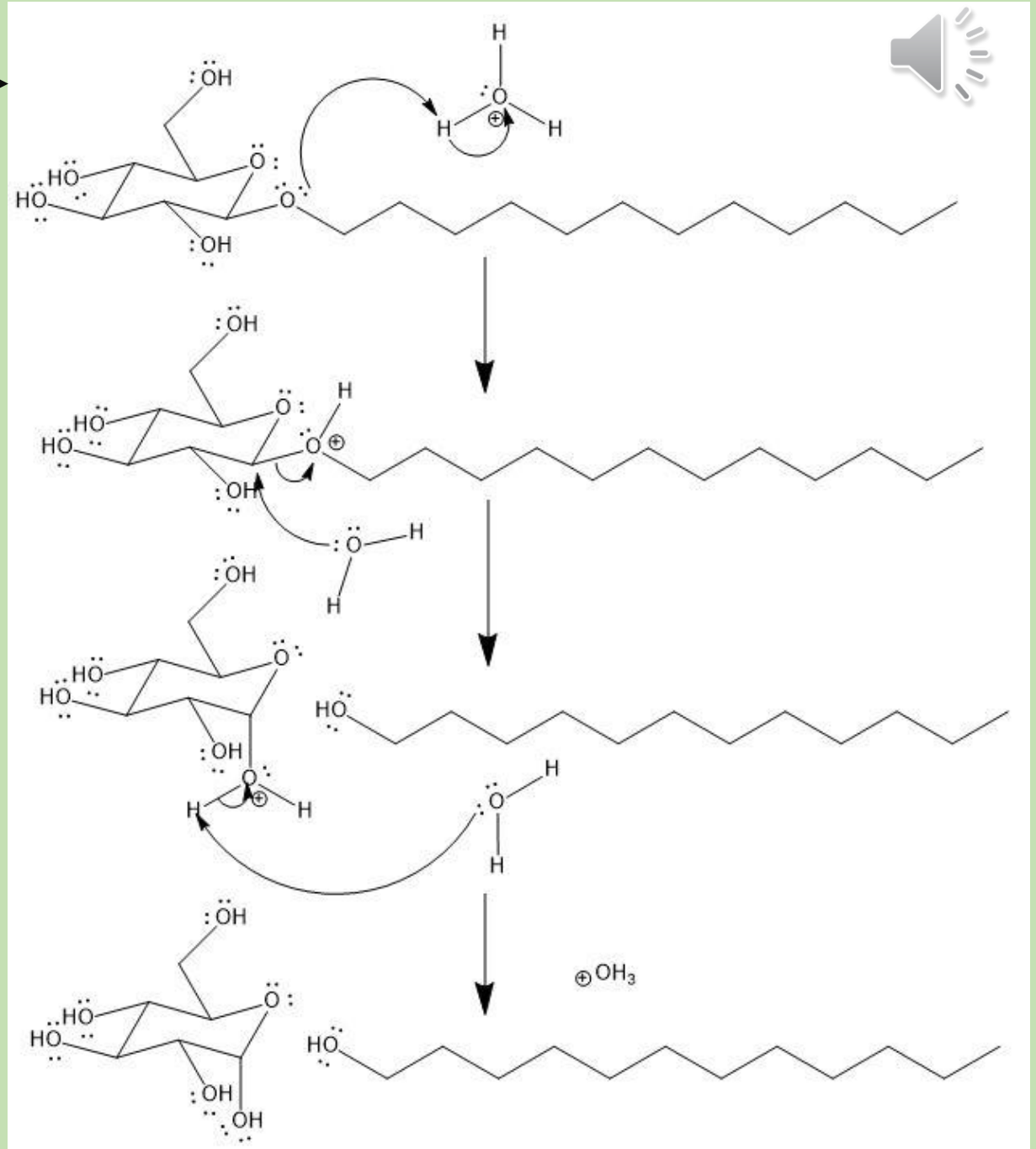


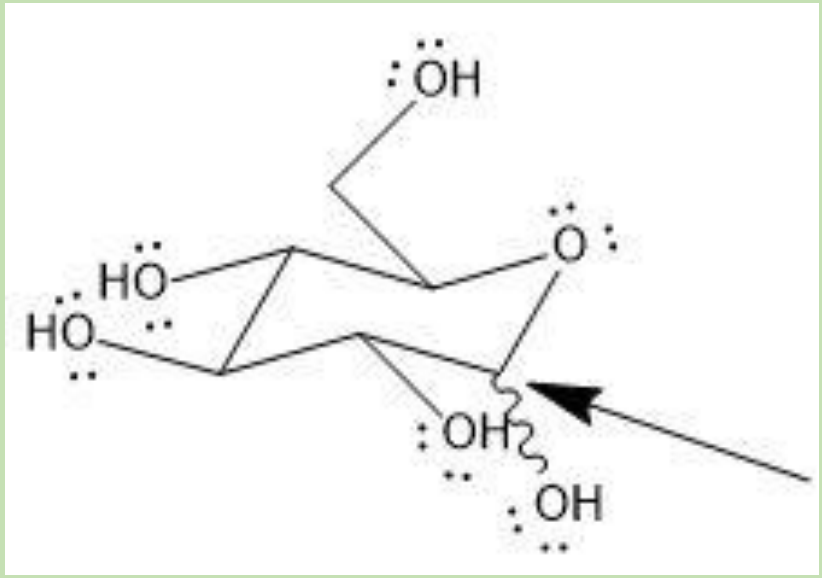
Photo coutesy of Jon Chiaramonte

Acid Hydrolysis of an O-glycoside.

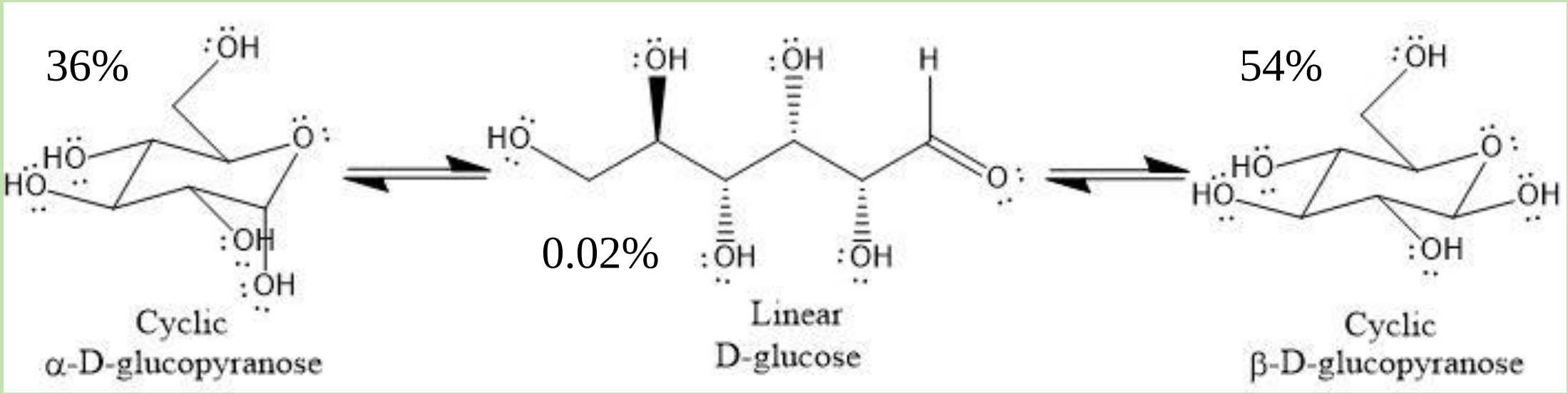


- The main difference between C-glycosides and other glycosides is in chemical reactivity.
- O-,N- or S-glycosides are susceptible to acid hydrolysis.
- C-glycosides are resistant to hydrolysis.

Synthesis of C-Glycosides

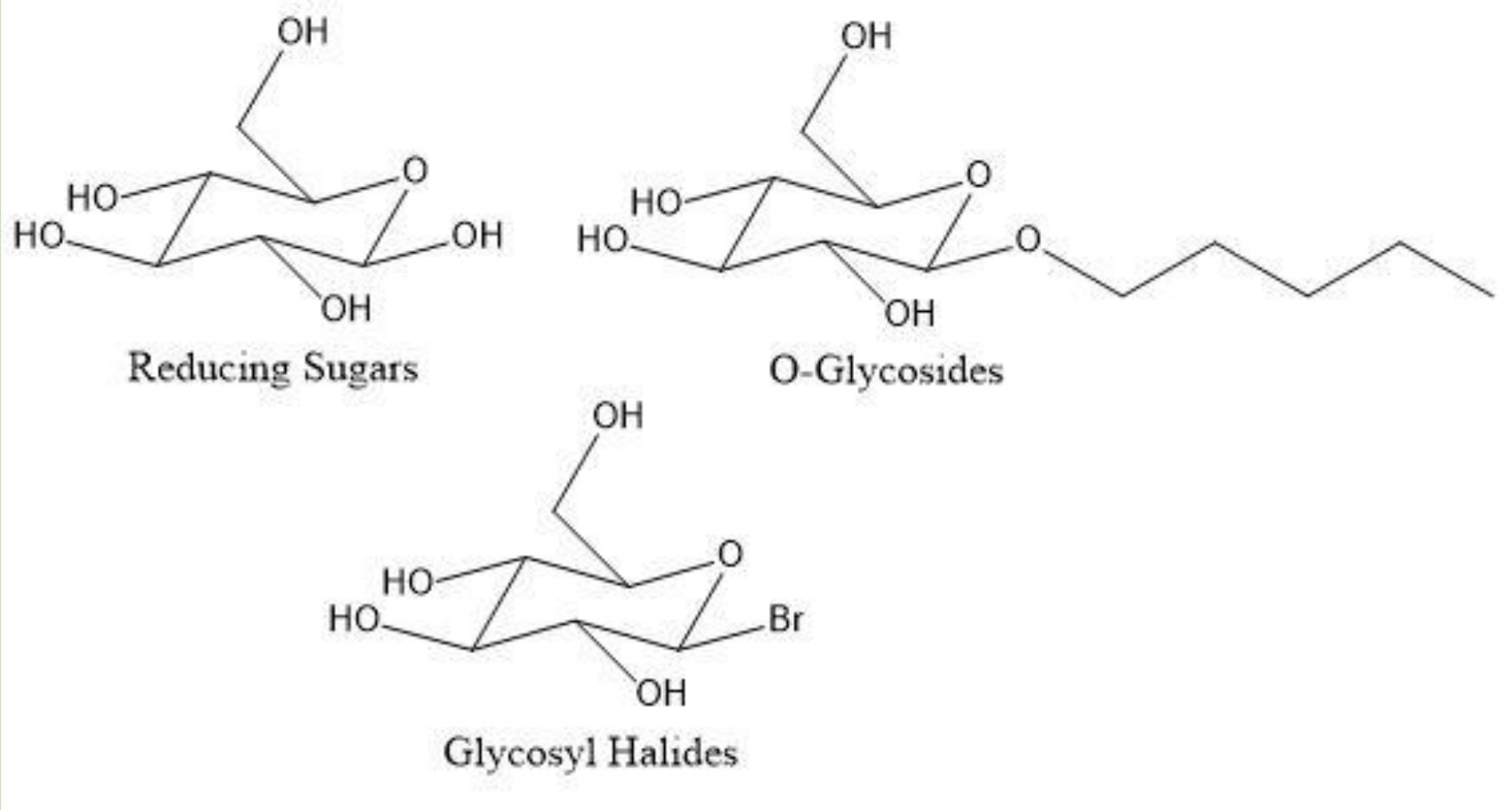


- The anomeric carbon is naturally electrophilic.
- Acetal carbons are electrophilic due to the two electronegative oxygen atoms connected to it.
- The oxygen atoms inductively withdraw electron density from the carbon atom.



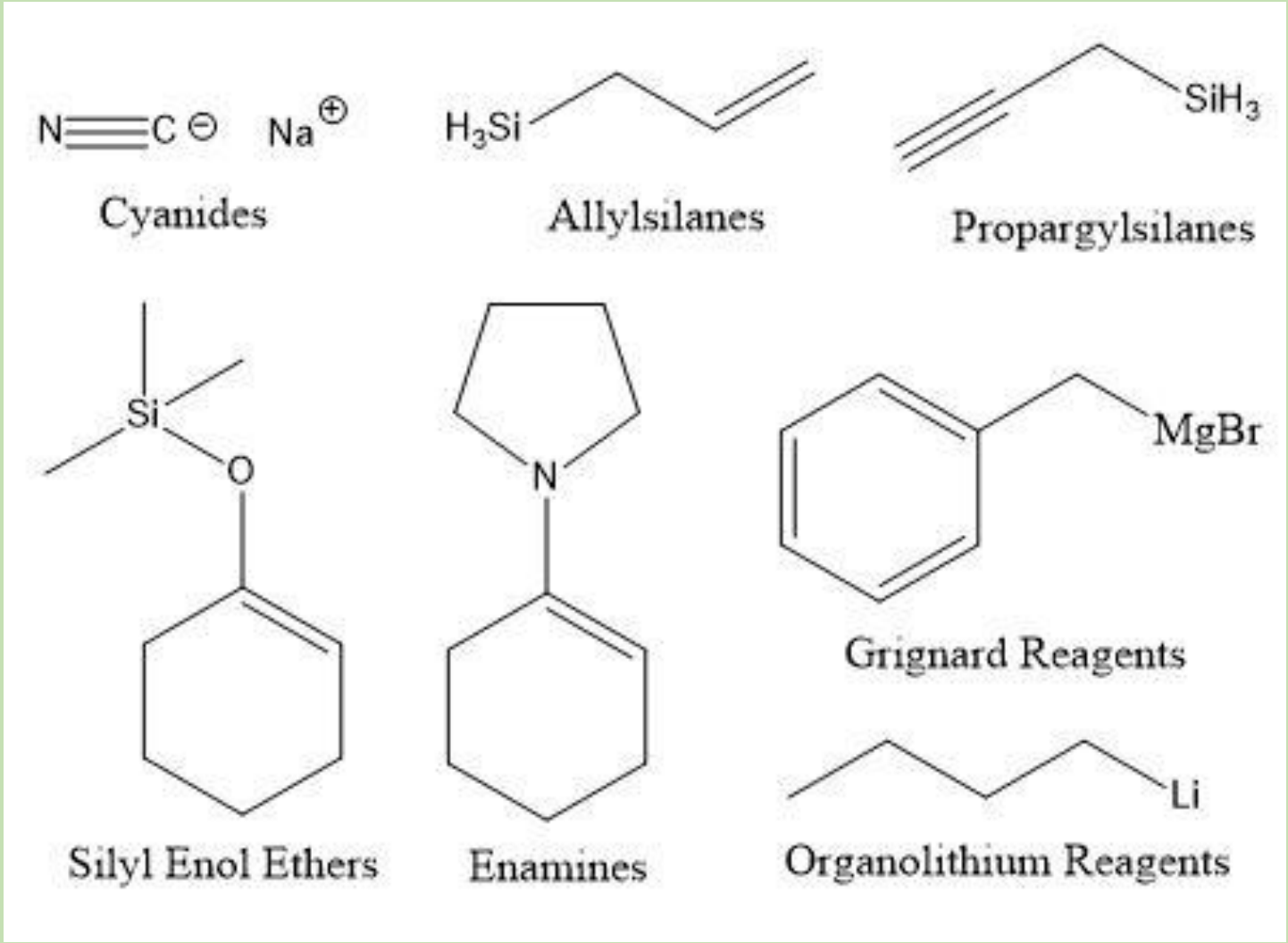
Synthesis of C-Glycosides

Typical electrophiles include:



Synthesis of C-Glycosides

Typical nucleophiles include:



Typical C-glycoside syntheses involving protecting groups.

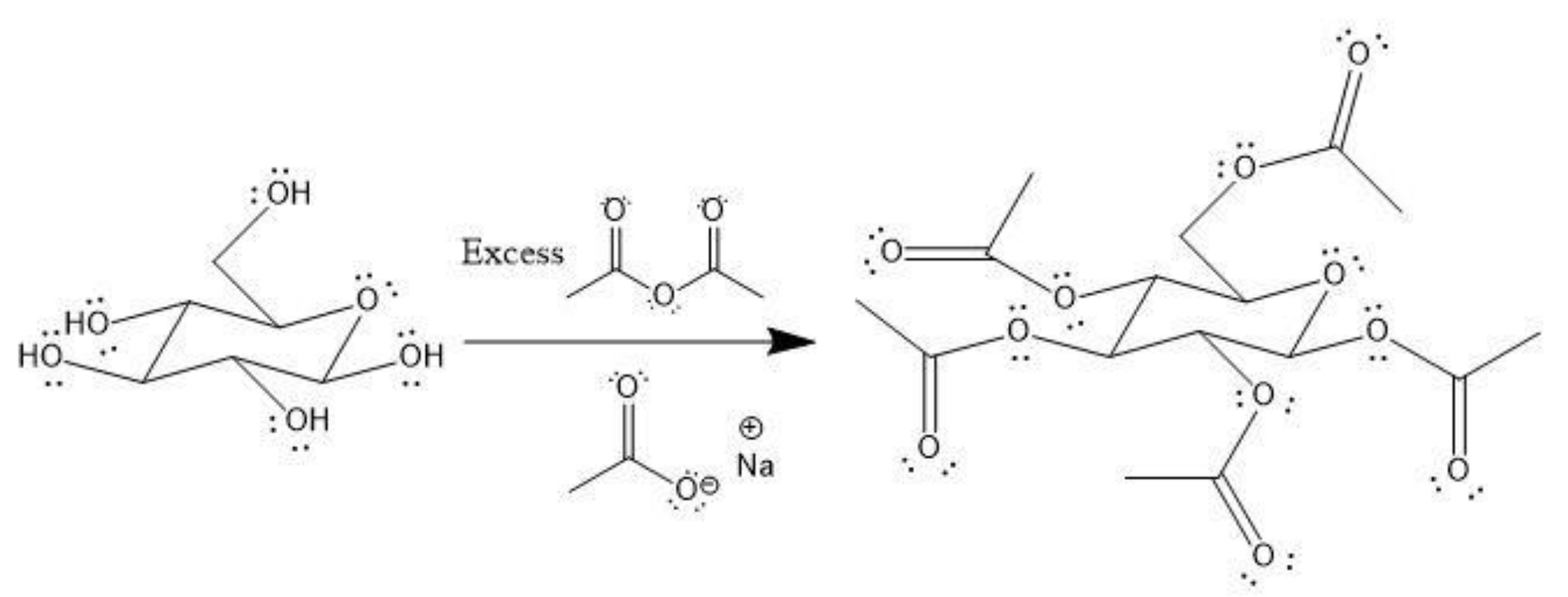
1. Protection

2. Alkylation

3. Deprotection

Typical C-glycoside syntheses involving protecting groups.

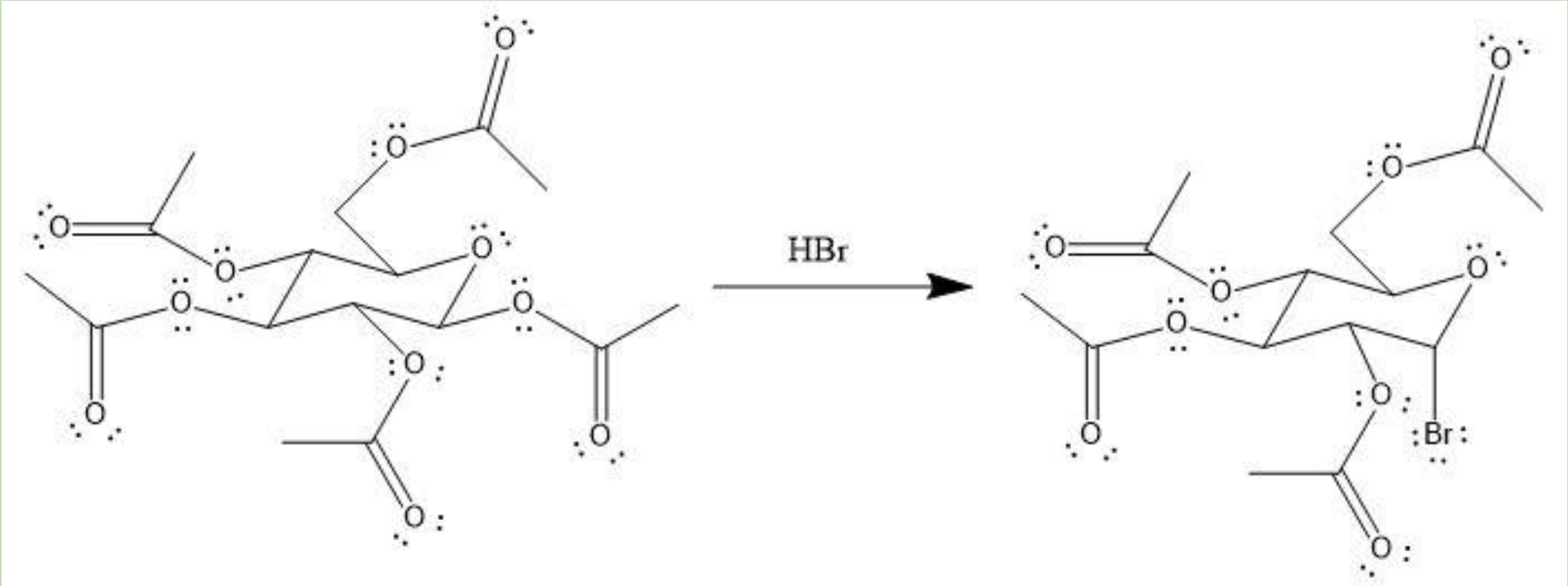
Protection



Vogel, A. I. *A Textbook of Practical Organic Chemistry Including Qualitative Organic Analysis,* 3rd ed.; Longman, 1956.

Typical C-glycoside syntheses involving protecting groups.

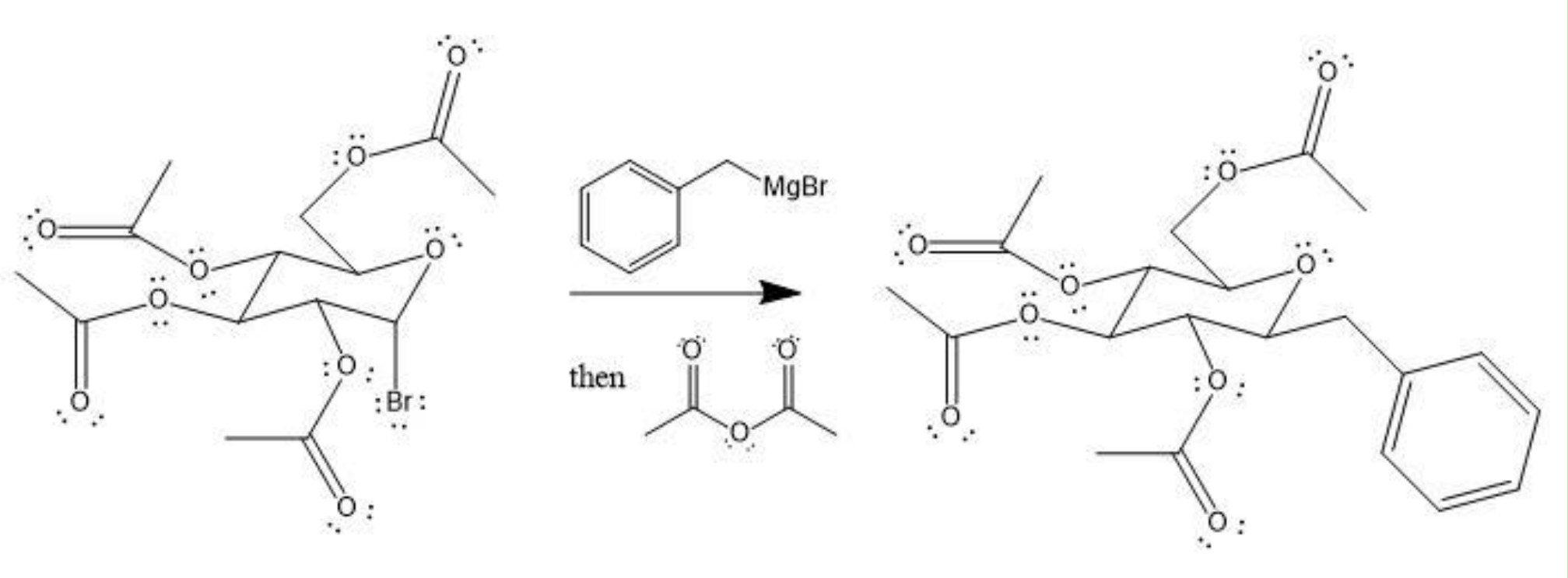
Bromination



Tojino, M.; Hirose, Y.; Mizuno, M. Convenient Synthesis of Glycosyl Bromide from 1-O-Acetyl Sugars by Photo-Irradiative Phase-Vanishing Reaction of Molecular Bromine. *Tetrahedron Letters.* **2013,** 54, 52, 7124-7126.

Typical C-glycoside syntheses involving protecting groups.

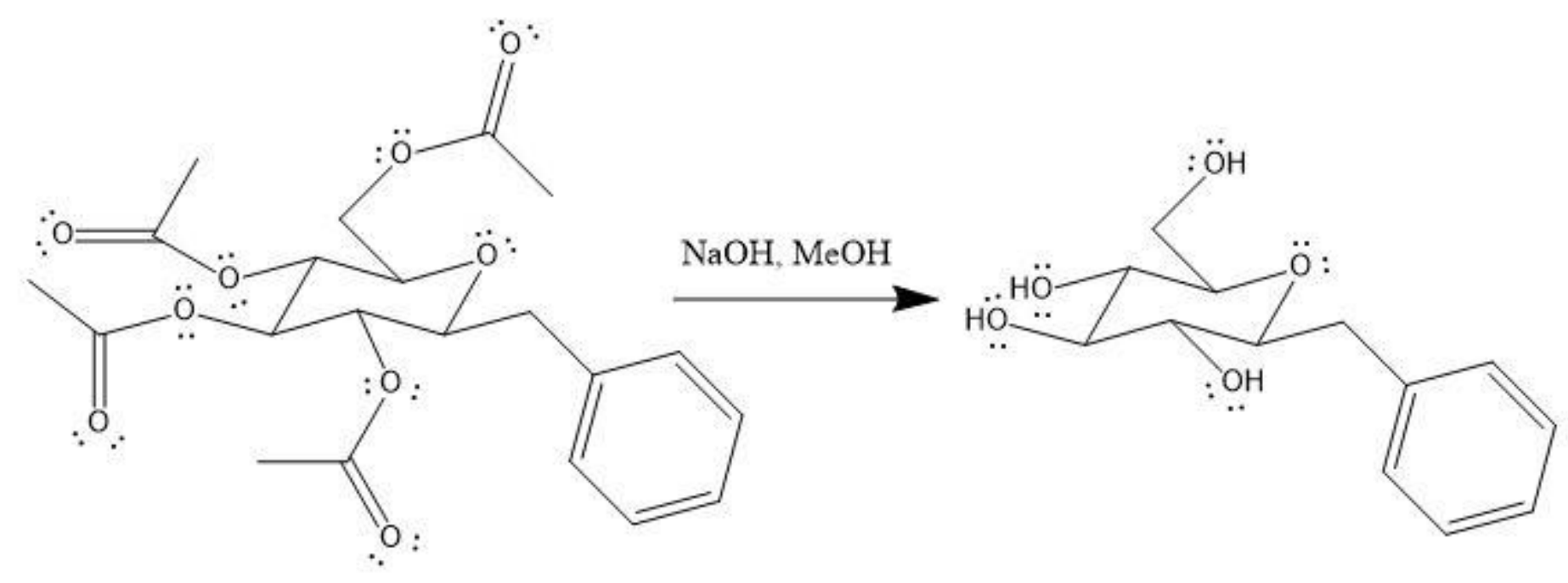
Alkylation using a Grignard Reagent



Postema, M. *C-Glycoside Synthesis,* 1st ed.; CRC Press, 1995.

Typical C-glycoside syntheses involving protecting groups.

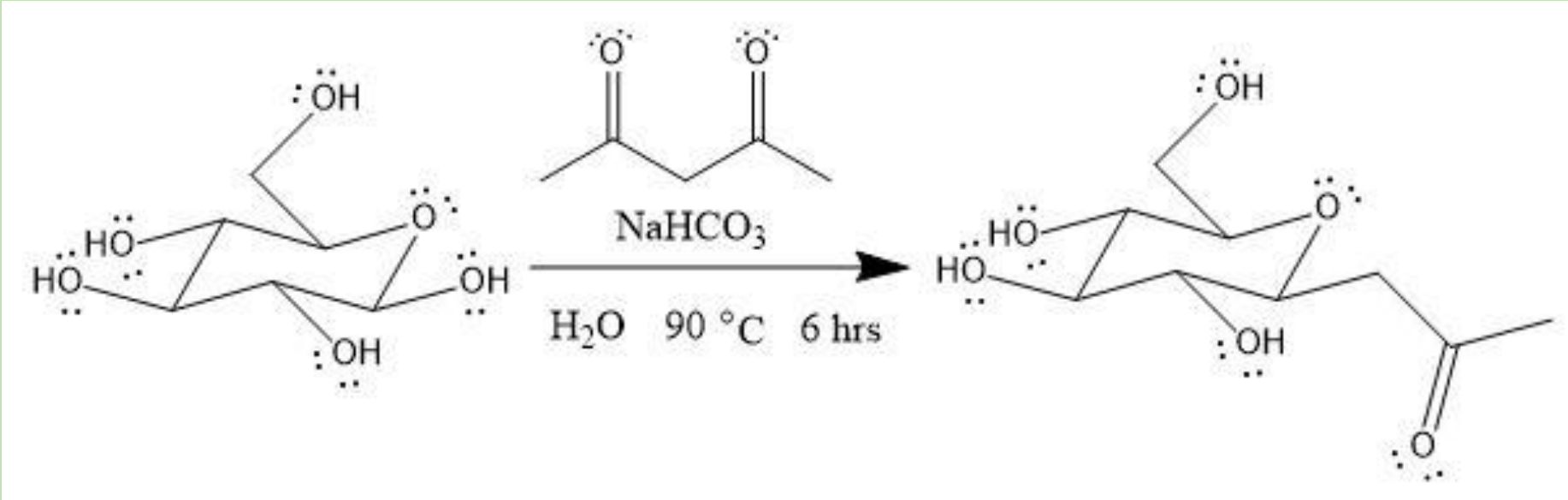
Deprotection



Can a simpler method of synthesis be devised?

- A method without the use of protecting groups?
- A method that is efficient, in one step?
- A method that is environmentally sustainable?

C-glycoside synthesis without protecting groups



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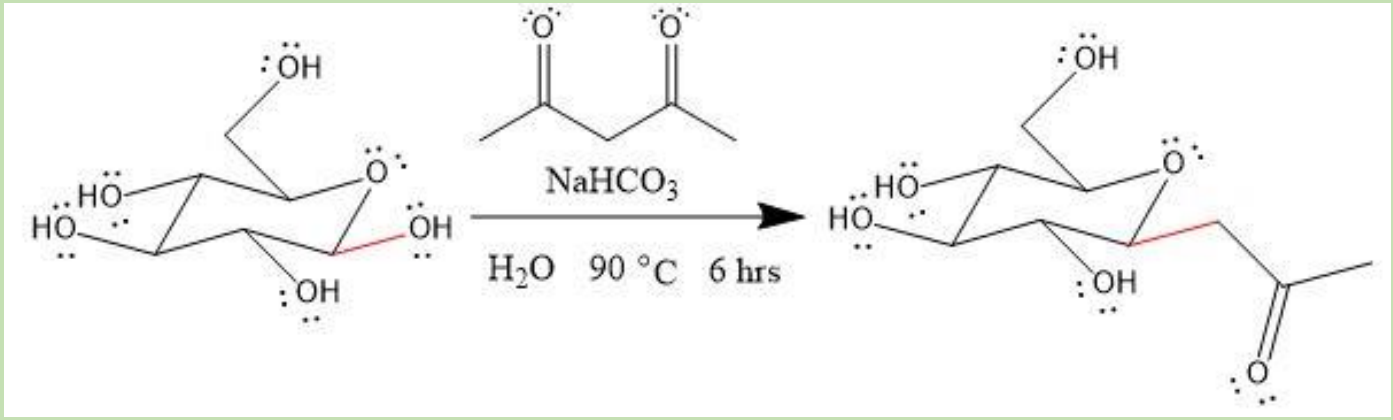
C-glycoside synthesis without protecting groups



- Functional group transformation… Changes a hemiacetal into an ether
- Forms a carbon-carbon bond

Rodrigues, F.; Canac, Y.; Lubineau, A. A Convenient, One-Step, Synthesis of β-C-Glycosidic Ketones in Aqueous Media. *Chem. Commun.* **2000,** 2049-2050.

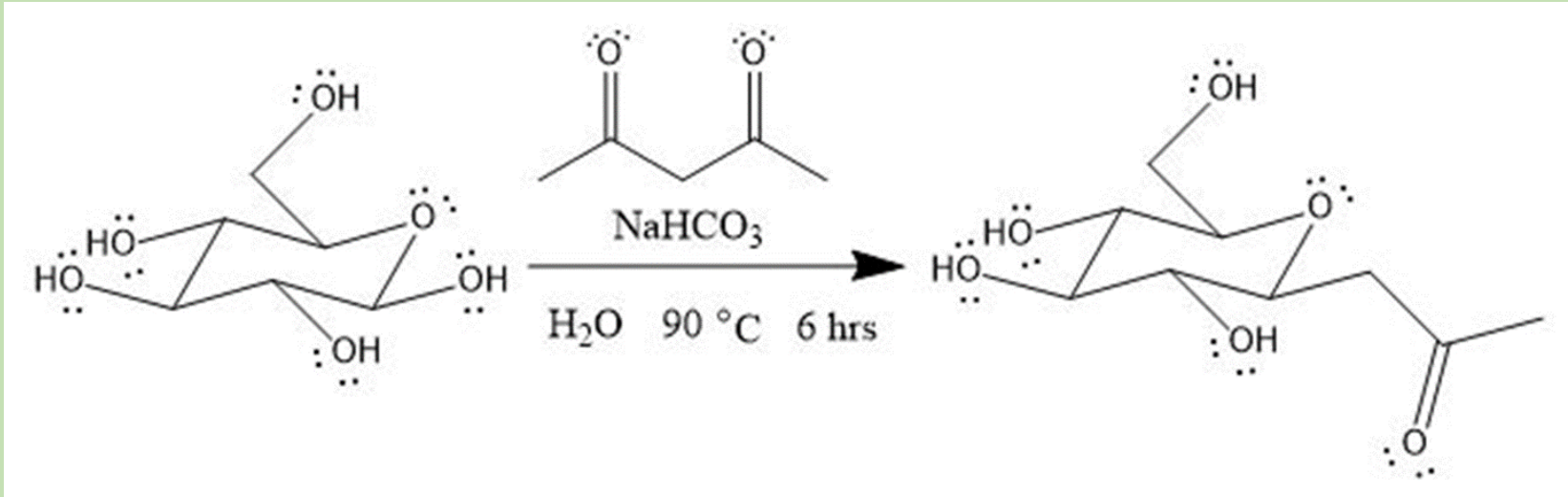
Results for the Synthesis of β-C-Glycosidic Ketone

Substrates	Conditions	Stereoselectivity	Total Yield
D-Glucose	6 hrs, 90 °C	100% β	96%
D-Mannose	12 hrs, 90 °C	100% β	95%
D-Cellobiose	12 hrs, 90 °C	100% β	93%

- Stereochemistry at the anomeric carbon was determined using ^{1}H and ^{13}C NMR Spectroscopy
- Products were purified with either crystallization [from MeOH : Diethyl ether, 1 : 1] or flash chromatography [Ethyl acetate : Isopropyl alcohol : Water, 8 : 1 : 1]
- Yields displayed are isolated product yields

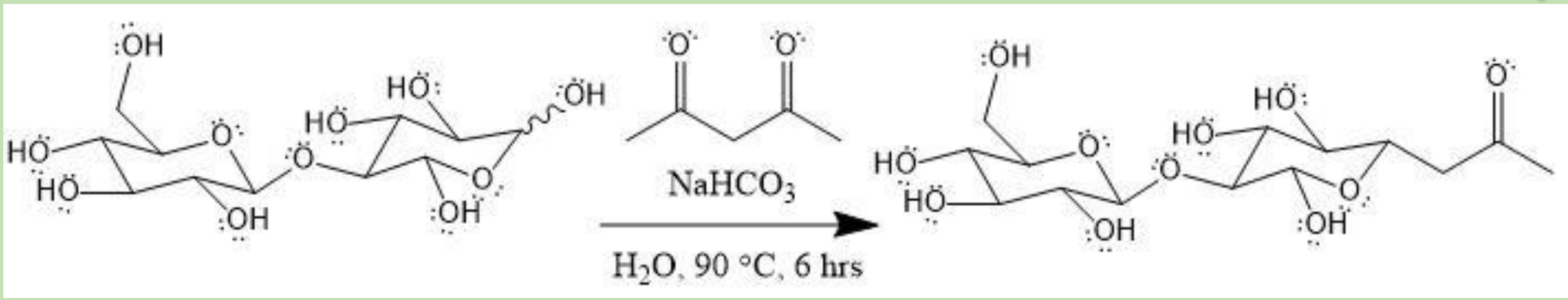
Rodrigues, F.; Canac, Y.; Lubineau, A. A Convenient, One-Step, Synthesis of β-C-Glycosidic Ketones in Aqueous Media. *Chem. Commun.* **2000,** 2049-2050.

My Results



- Product was crystallized from a 50:50 mix of methanol and ether.
- Isolated Yield: 8.8%

My Results



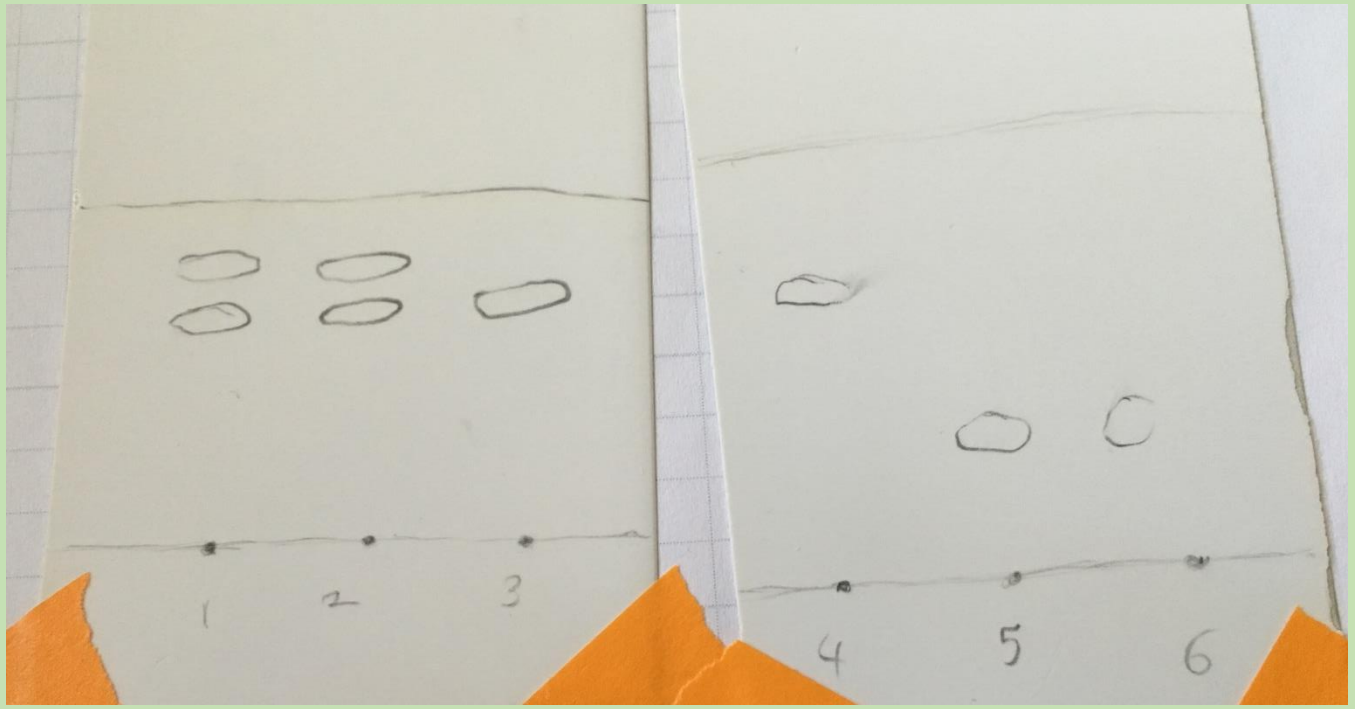
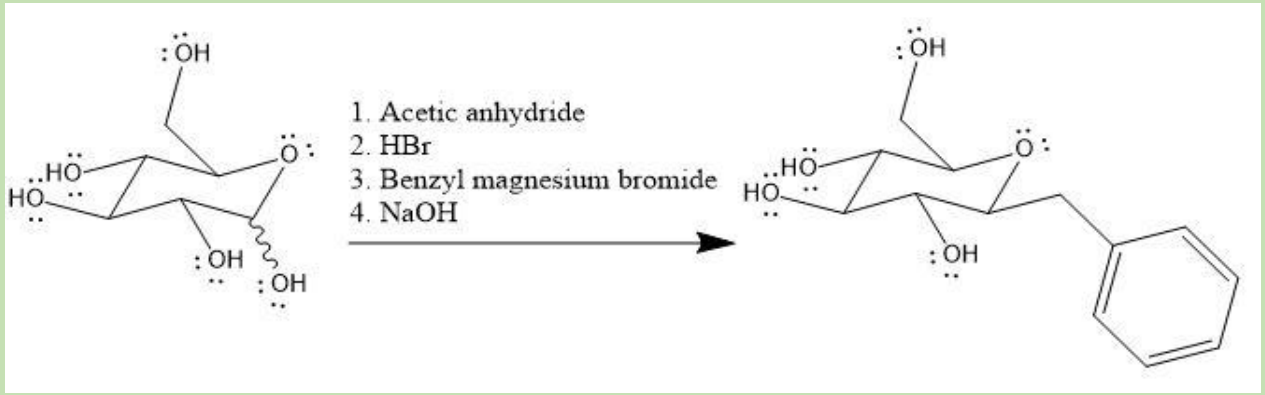
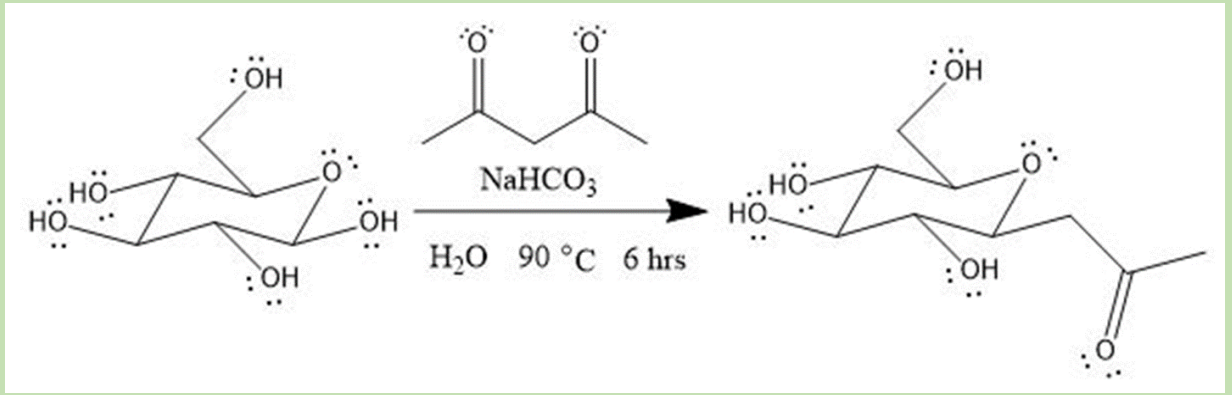


Photo courtesy of Jon Chiaramonte

Green Chemistry Principles

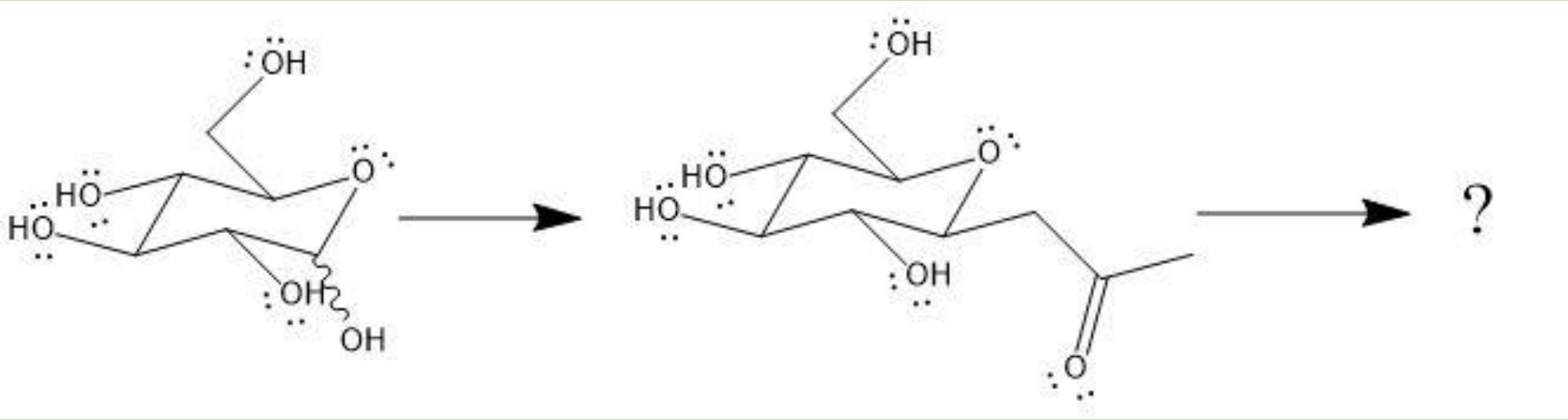


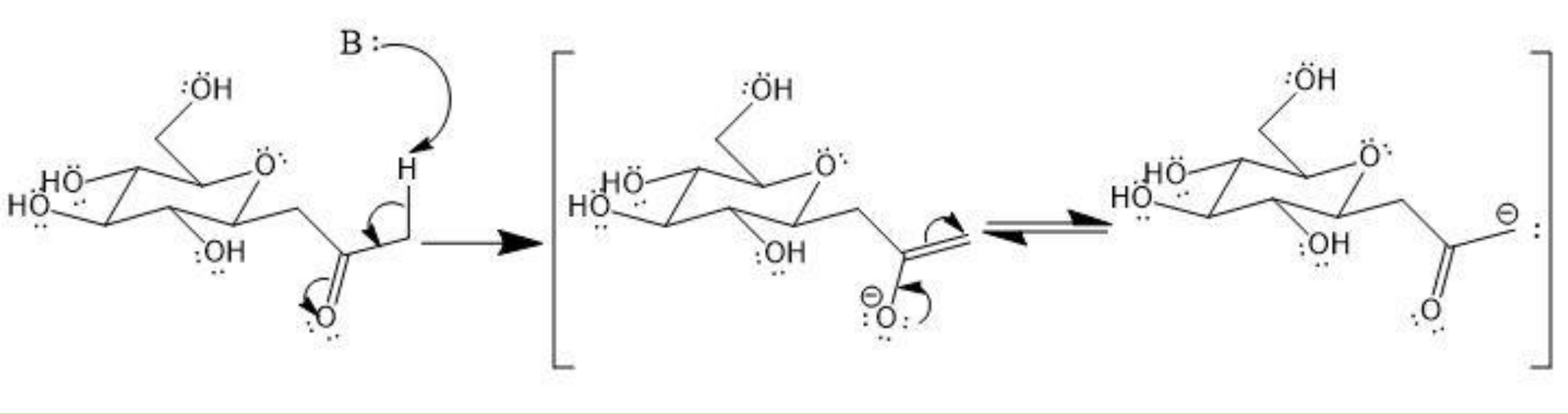


- Many steps, inefficient
- Low atom economy
- Requires many different hazardous reagents
- A dangerous synthesis to perform
- Creates a lot of waste products

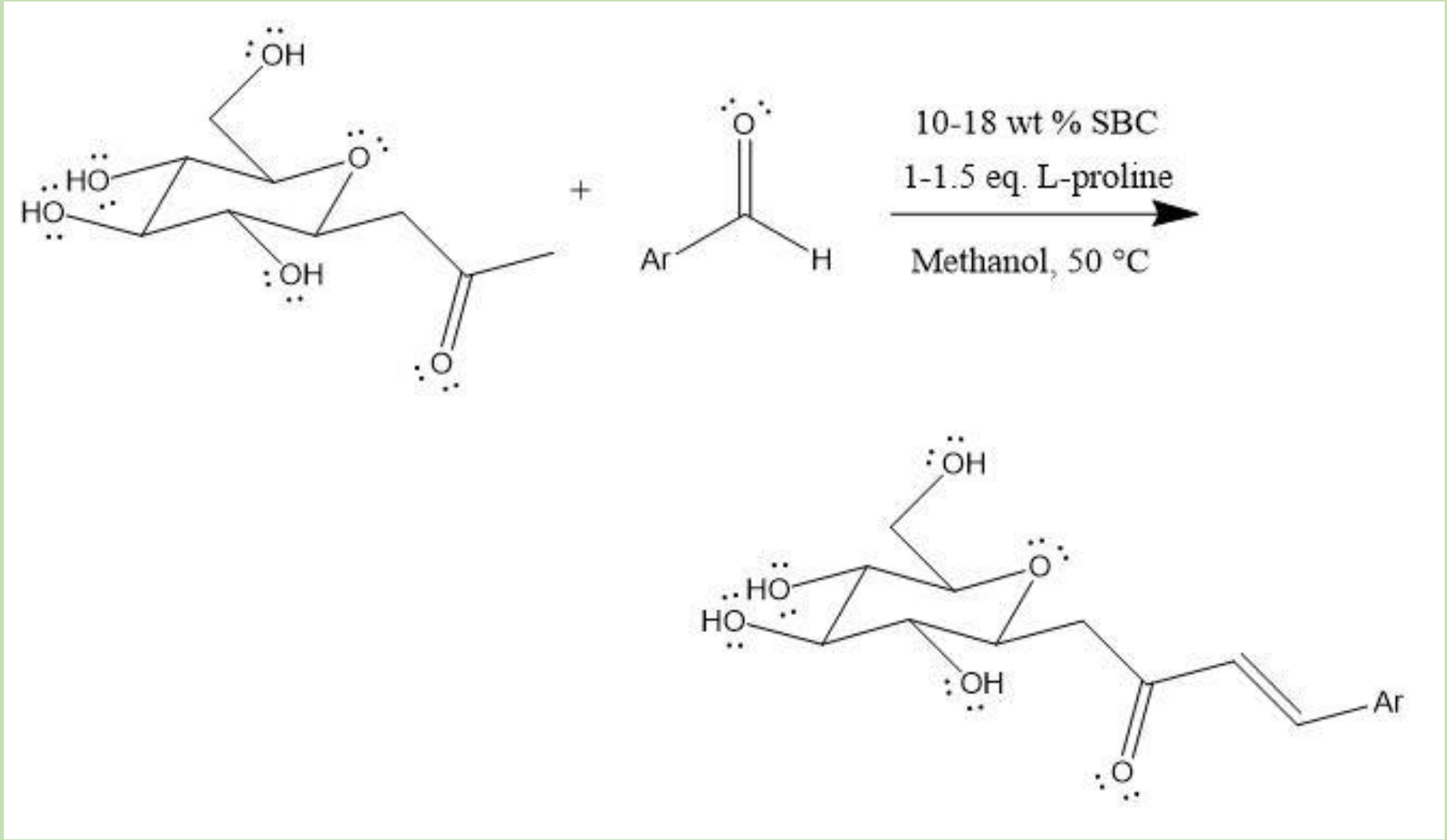
- One step, efficient.
- High atom economy
- Uses less hazardous reagents
- A safer synthesis to perform
- Limited waste products

What can we do with our product now?





Aldol condensation with unprotected β-C-glycosidic ketone



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Base Catalysts

MgO – Magnesium Oxide

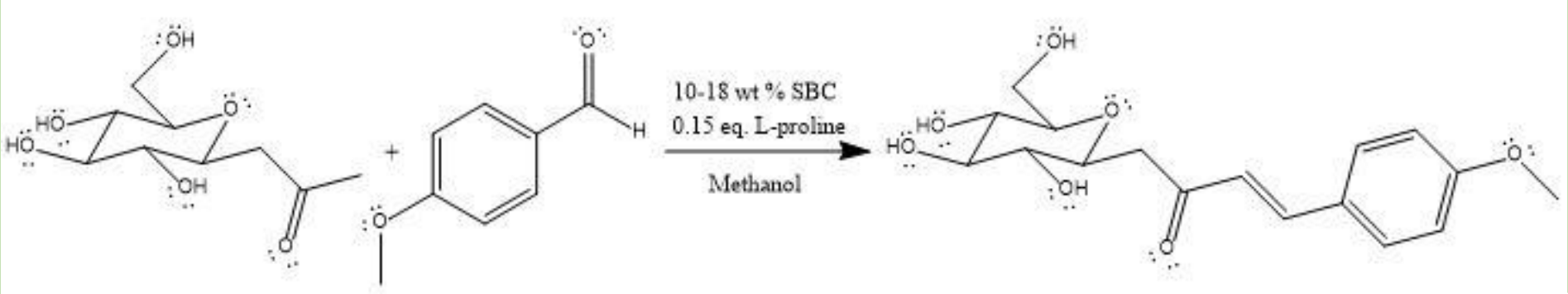
CaO – Calcium Oxide

$Mg_6Al_2CO_3(OH)_{16} \cdot 4H_2O$ - Hydrotalcite

Hydrotalcite can be activated which produces a porous metal oxide (PMO)

$Mg_6Al_2CO_3(OH)_{16} \cdot 4H_2O \longrightarrow MgO\text{-}Al_2O_3$ (PMO)

Reaction Times for Different Solid Base Catalysts



Conditions used:

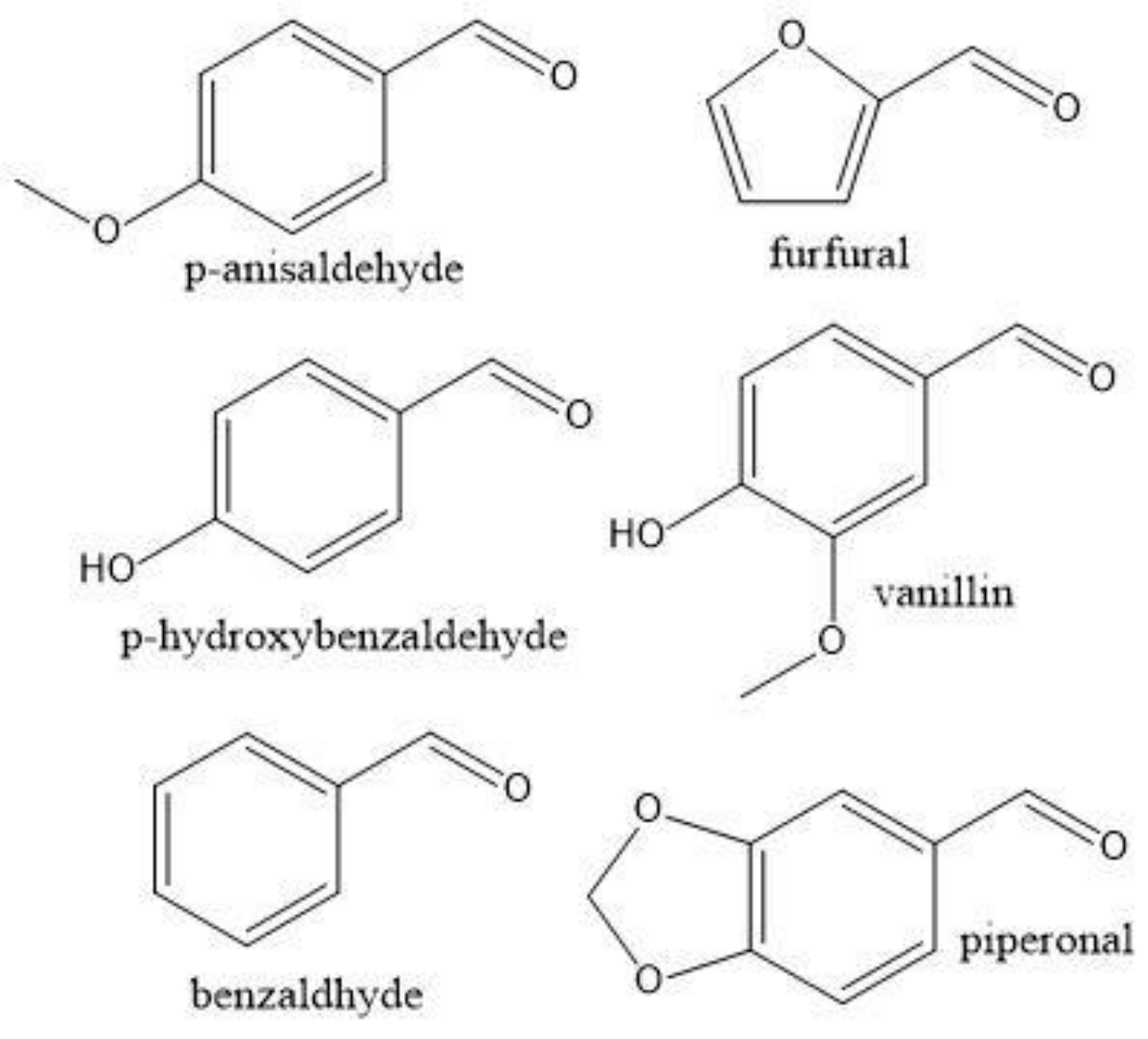
- 10-18 wt % solid base catalyst (SBC)
- 0.15 eq. of L-proline
- Methanol solvent

Solid Base Catalyst	Time (at room temp)	Yield by NMR
MgO	9 days	>95%
CaO	9 days	54%
HT	9 days	76%
PMO	9 days	93%

Solid Base Catalyst	Time (at 50 °C)	Yield by NMR
MgO	2 days	>95%
CaO	3 days	77%
HT	≈ 1 day	>95%
PMO	≈ 1 day	>95%

De Winter, T.M.; Petitjean, L.; Erythropel, H.C.; Moreau, M.: Hitce, J.; Coish, P.; Zimmerman, J.B.; Anastas, P.T. Greener Methodology: An Aldol Condensation of an Unprotected C-Glycoside with Solid Base Catalysts. *ACS Sustainable Chem.* **2018,** 6, 7810-7817.

Reaction Times for Different Aromatic Aldehydes

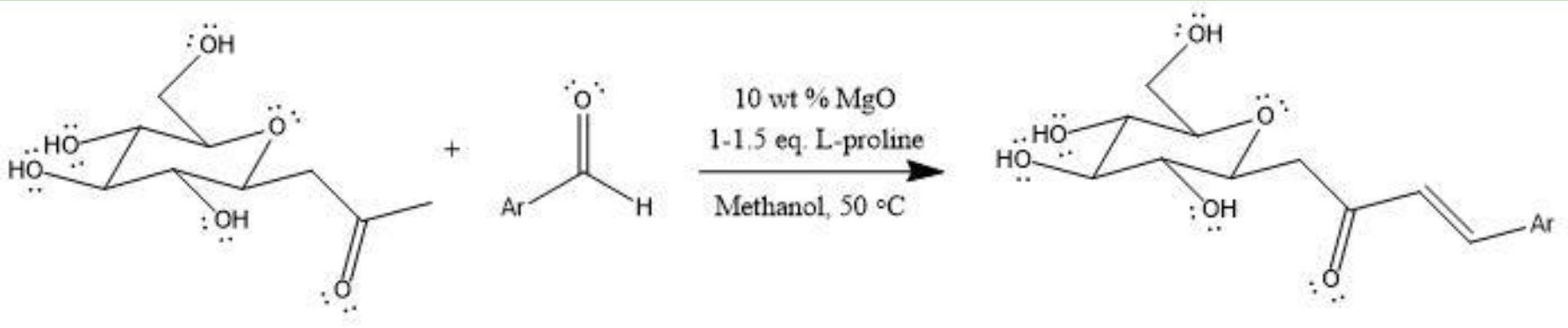


Reaction Conditions:

- 10 wt % MgO and 1-1.5 eq. L-proline
- Methanol solvent.
- Reaction held at 50 °C

De Winter, T.M.; Petitjean, L.; Erythropel, H.C.; Moreau, M.: Hitce, J.; Coish, P.; Zimmerman, J.B.; Anastas, P.T. Greener Methodology: An Aldol Condensation of an Unprotected C-Glycoside with Solid Base Catalysts. *ACS Sustainable Chem.* **2018,** 6, 7810-7817.

Reaction Times for Different Aromatic Aldehydes



Aldehyde	Time	NMR Yield
p-anisaldehyde	16 hrs	>95%
P-hydroxybenzaldehyde	26 hrs	
benzaldehyde	6.5 hrs	
furfural	15 hrs	
vanillin	21 hrs	
piperonal	15 hrs	

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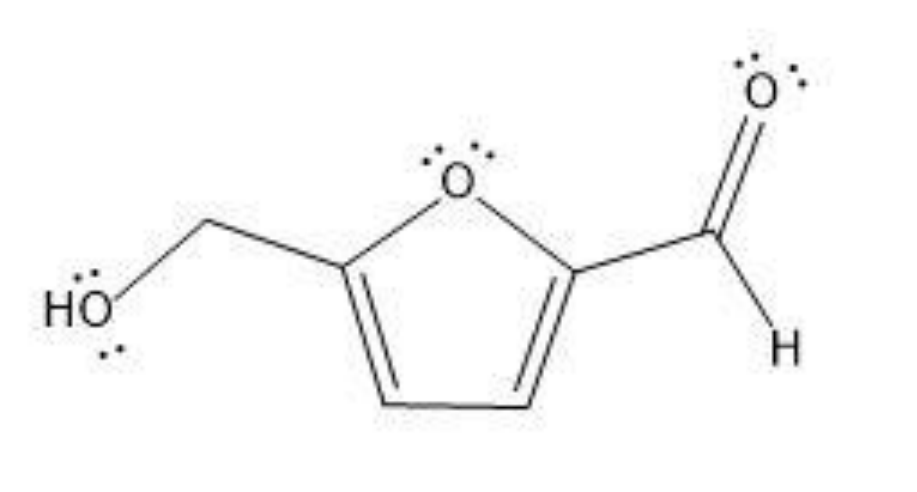
Green Chemistry Prinicples

- Efficient synthesis in one step
- Solid base catalysts are reuseable.
- Uses a green solvent - methanol
- Protecting groups not required
- A safe synthesis to perform
- Low energy consumption

Future Work

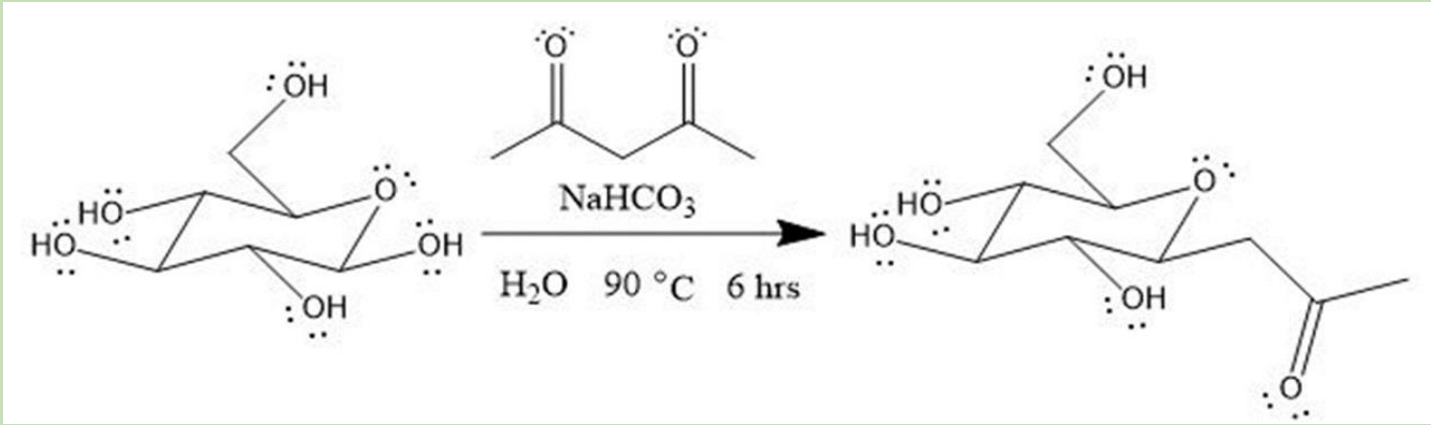
- Testing the β-C-glycosidic ketone synthesis with other reducing sugars
- Performing the aldol condensation with other aldehydes
- We wanted to test the aldol condensation with hydroxymethylfurfural but the Coronavirus pandemic prevented us from doing so.

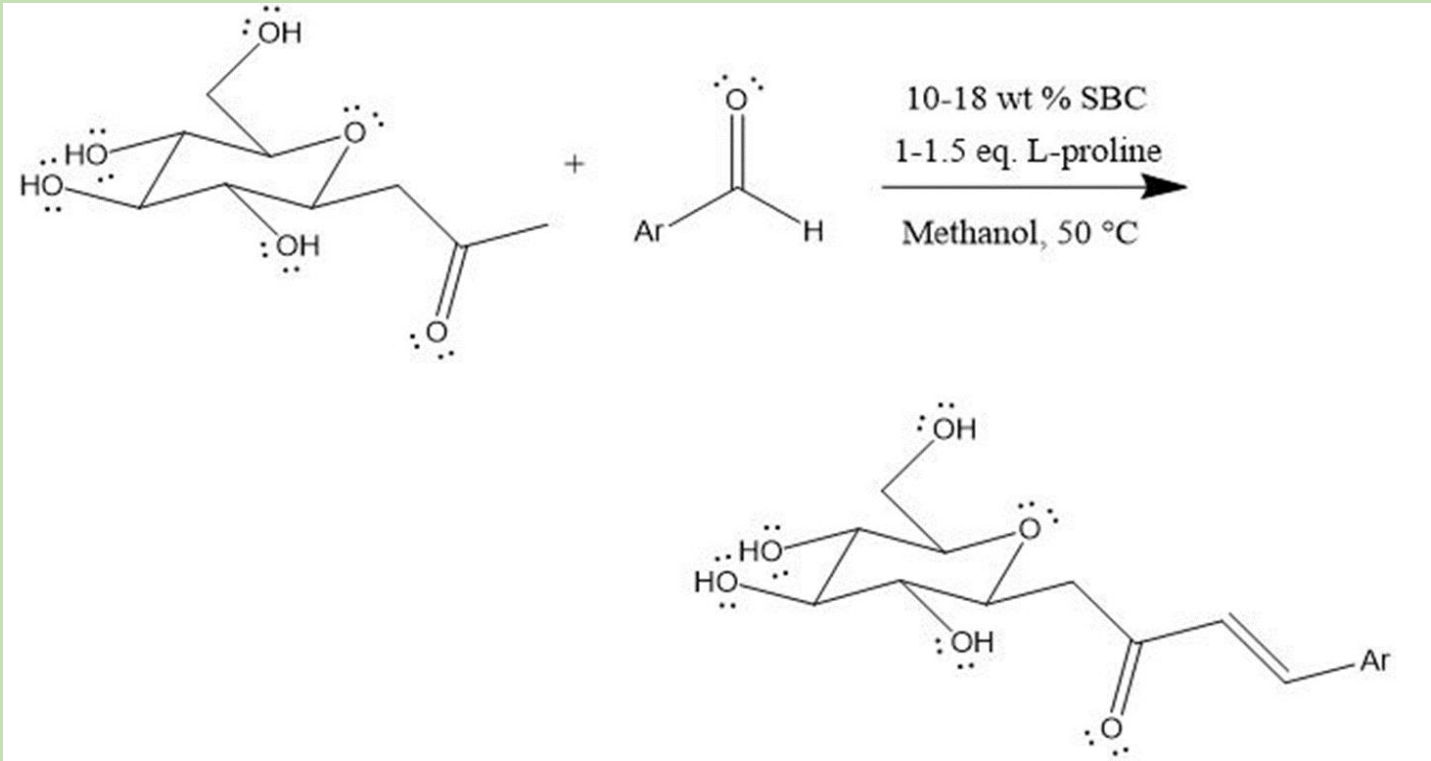


Hydroxymethylfurfural

- Hydroxymethylfurfural is produced from acid catalyzed dehydration of six carbon sugars.

Conclusions





Acknowledgements

Special Thanks to Dr. Kovacs

and Grand Valley State University