CARBOHYDE
REVOLUTION OF
CYCLODEXTRINS

# Cyclodextrins

## *Synthetic strategies*

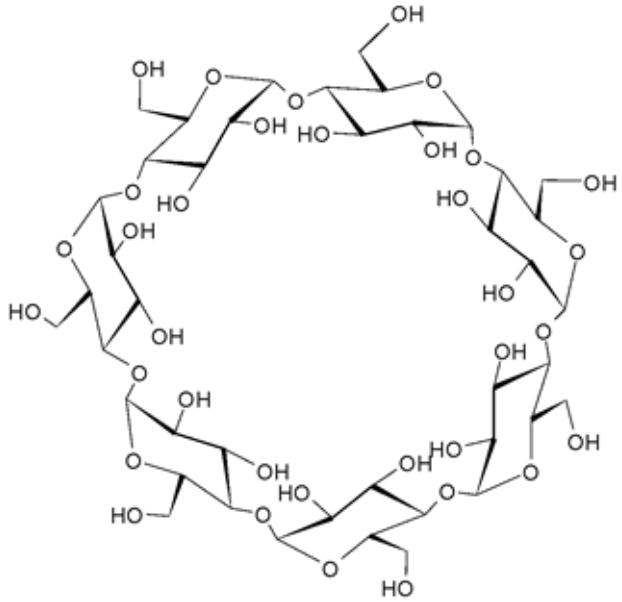
# Why modify cyclodextrins?

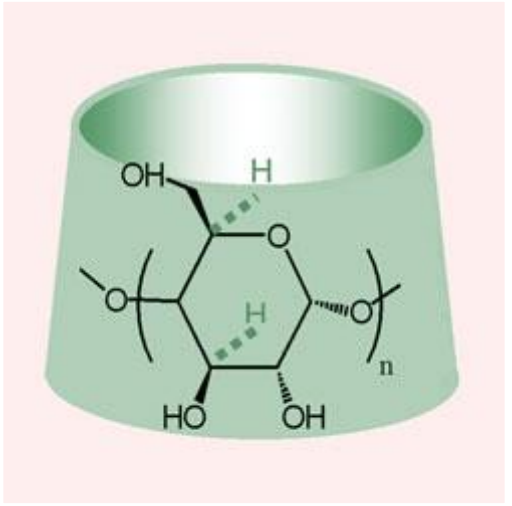
- Solubility improvement of the CD (and its complexes) in desired solvent, usually in water;

- better fit and/or association between the CD and its guest, with concomitant stabilization of the guest by changing its reactivity;

- more appropriate mimic of a binding site (e.g., in enzyme modeling) via attachment of specific groups; or

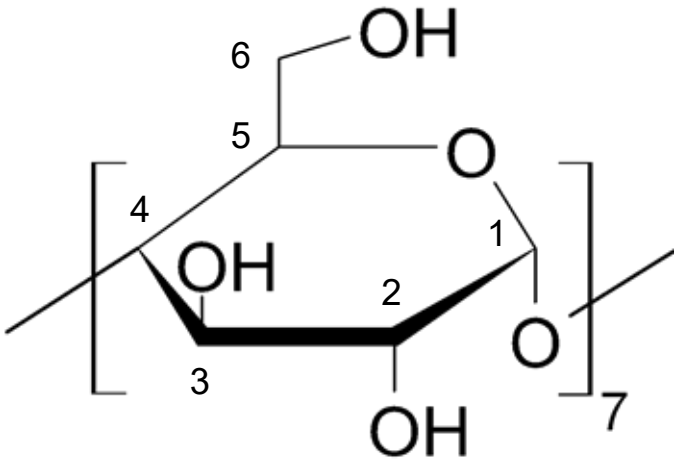
- formation of insoluble or immobilized CD-containing structures, polymers (e.g., for chromatographic purposes).





# Characteristics of the Hydroxyl Groups

**Less acidic, most nucleophilic**

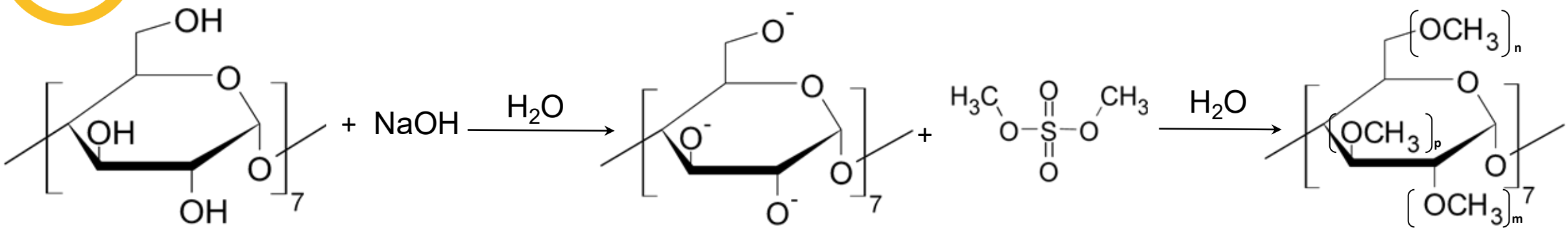



**More acidic, less nucleophilic**

**Most acidic, more nucleophilic**

C1= anomeric carbon
C6= methylene unit (-CH2-)
C2= easy accessible
C3= most hindered, difficult to modify
C4, C5= not inolved in reaction

# Random Alkylation




Regioselective with appropriate base

Degree of substitution can be controlled

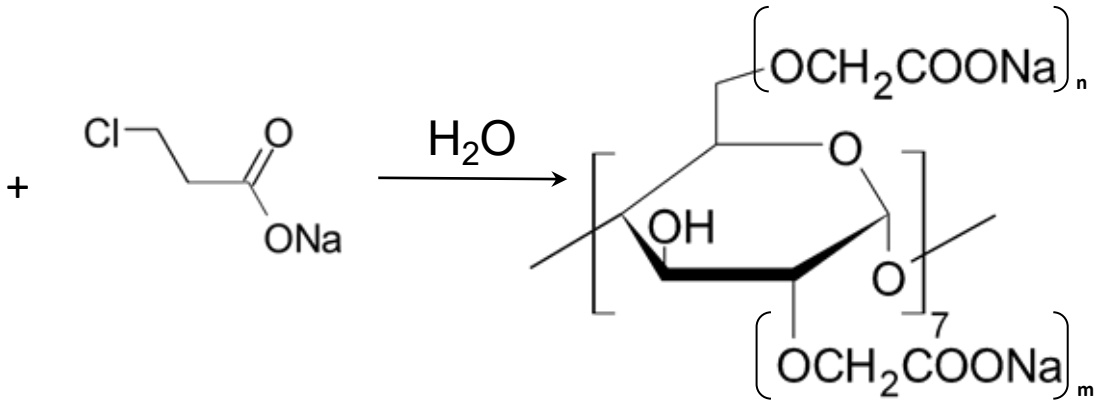
Substitution pattern: O(2)>>O(6)/O(3)

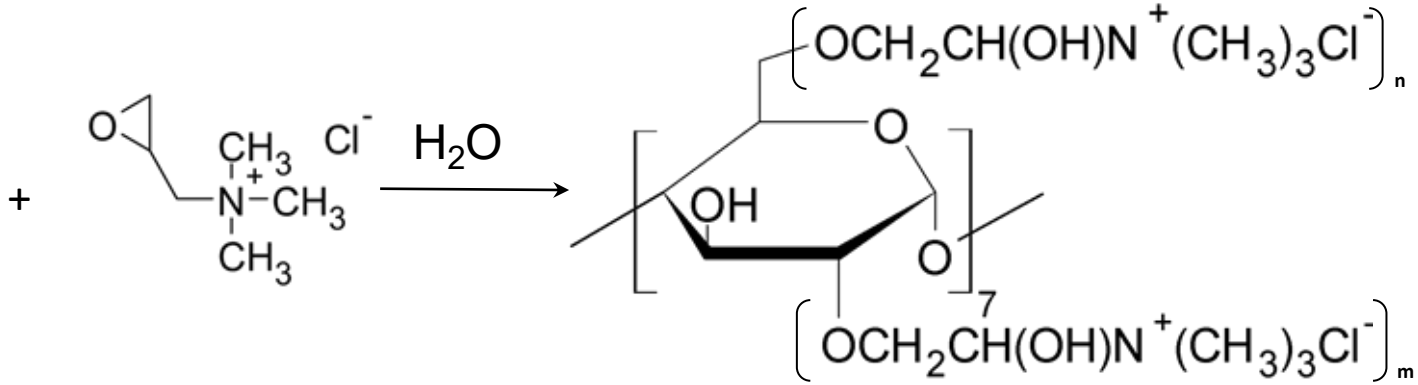
The longer alkyl chain the more 2,6-O-selective.

High solubility in water and organic solvents.

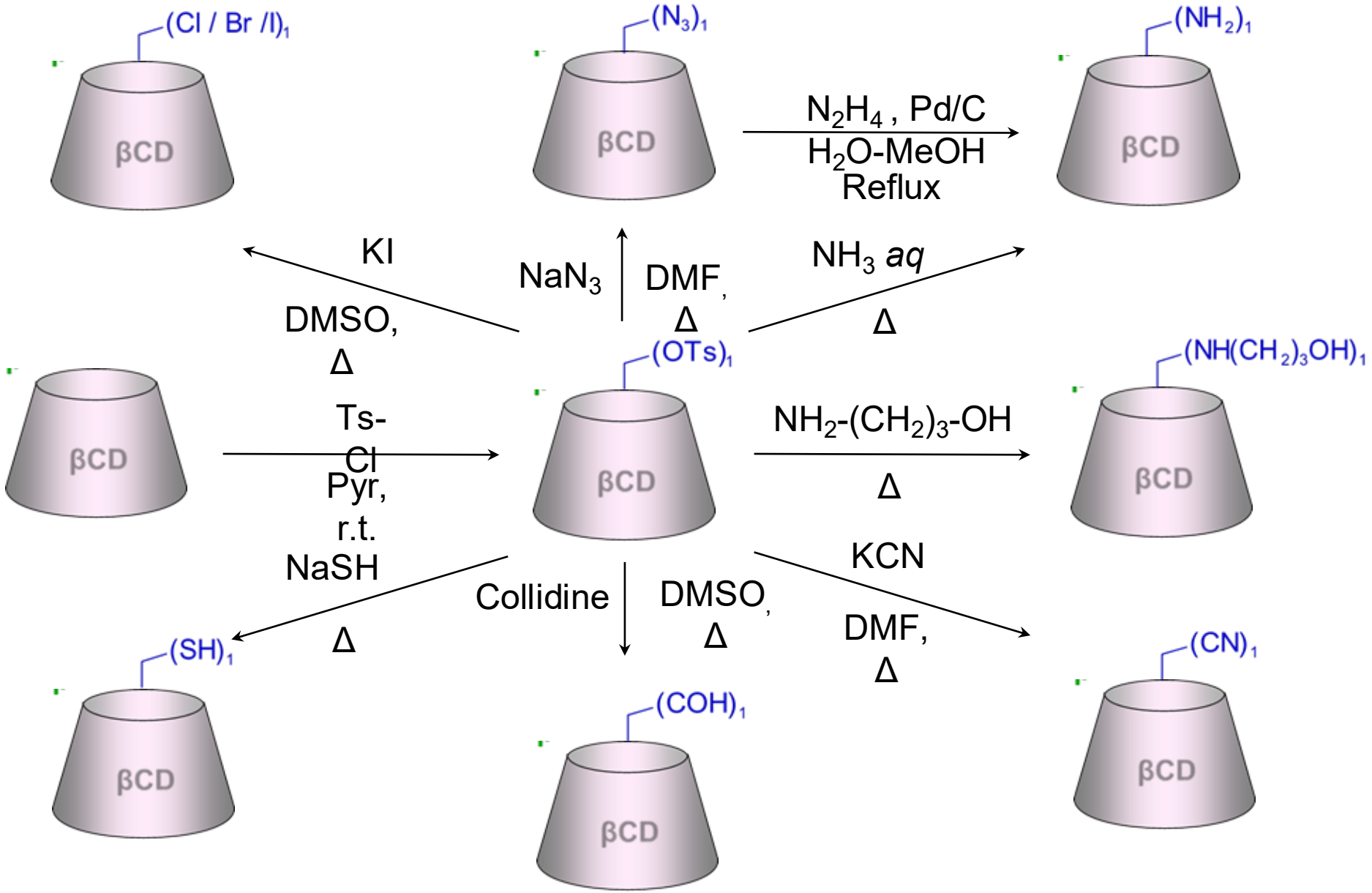
Per-substituion difficult in water

5-1000 kg scale production.

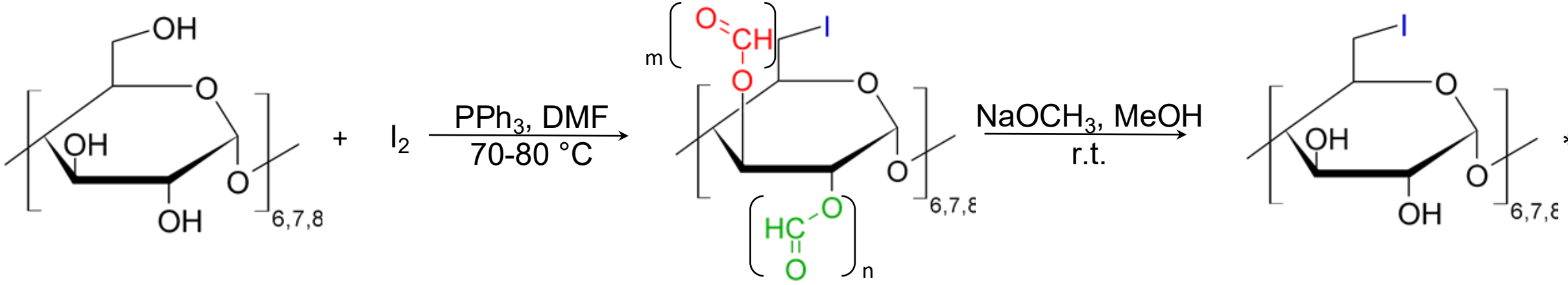


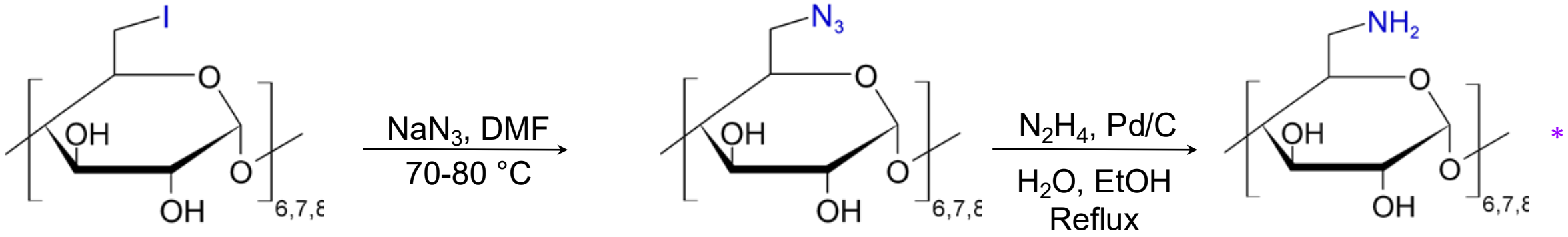



# Mono-6-Tosyl-βCD, a Key Intermediate



# Per-6-Halogen-CDs, Versatile Compounds



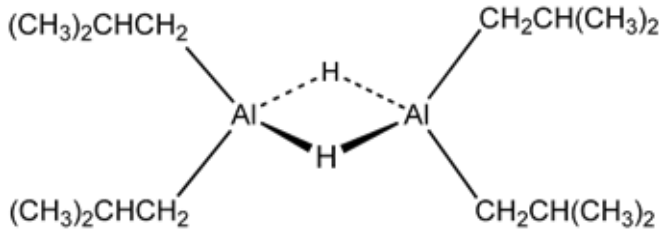





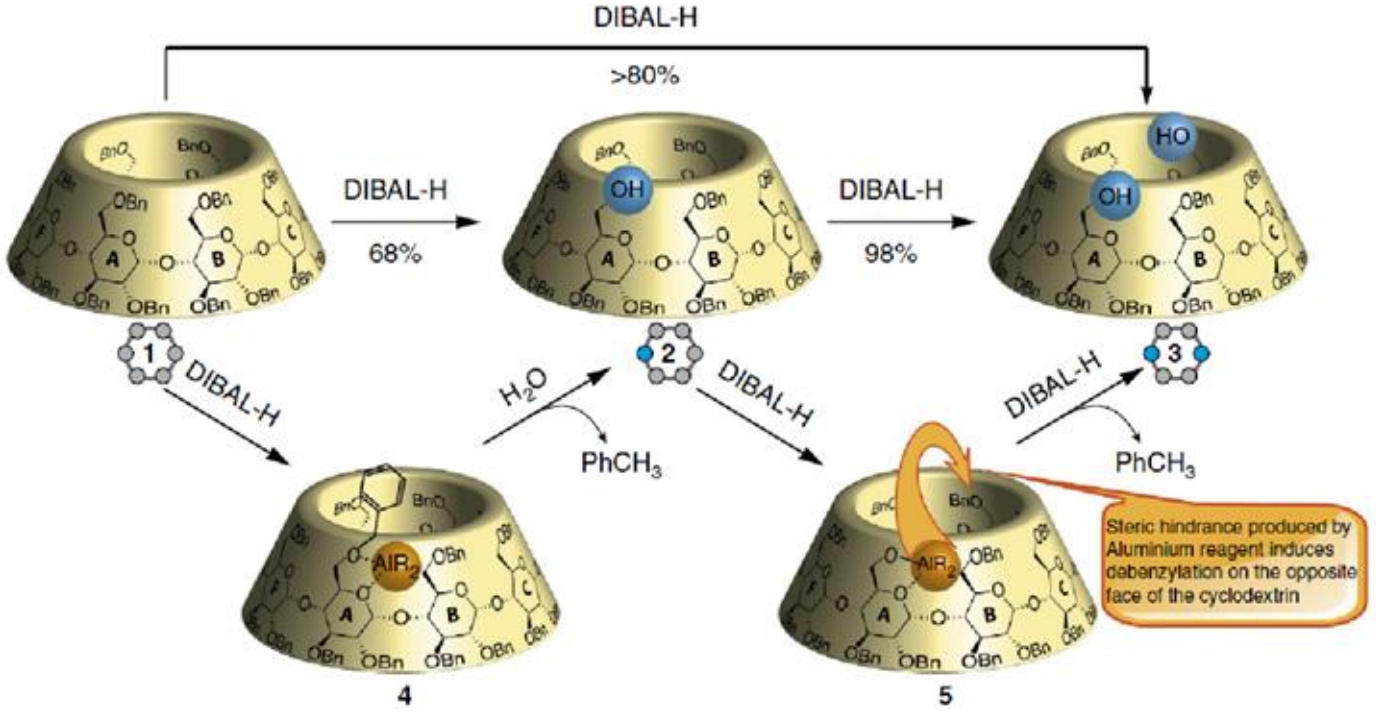
* Ashton P. R., Stoddart J. F. et al., J. Org. Chem., 60, 3898, 1995

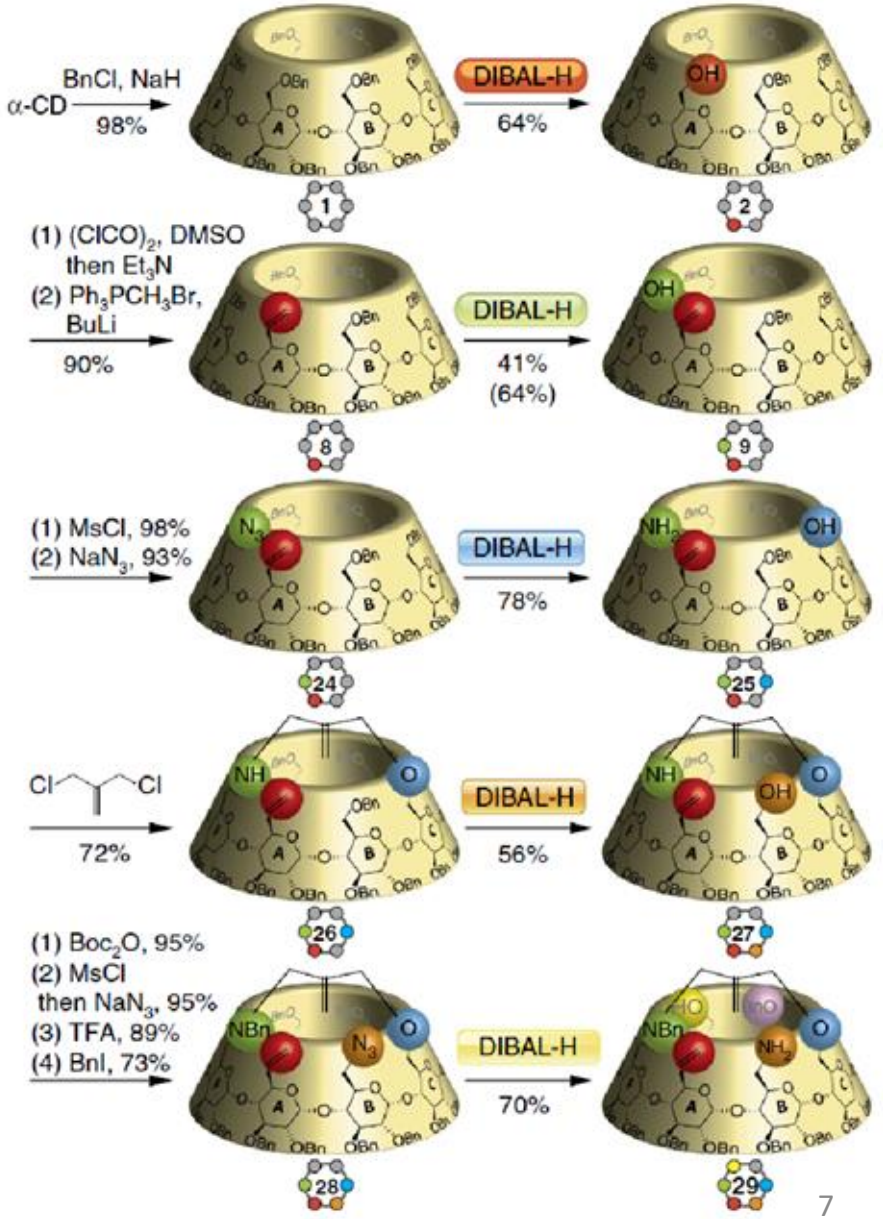
* Jicsinszky L., Iványi R., Carbohydr. Polym., 45, 139-145, 2001

# Per-6-Hetero-Substituted CDs
# The Magic of DIBALH



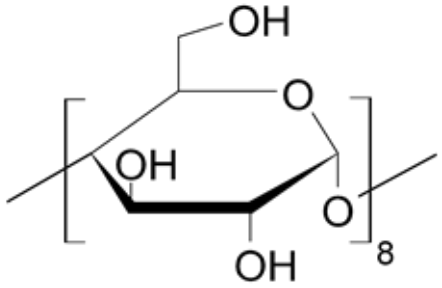

**Diisobutylaluminium hydride**



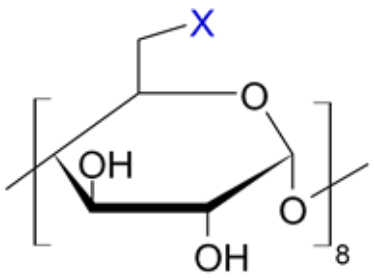



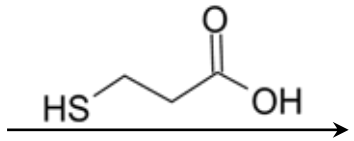

Sollogoub M. et al., Nature Communication, 5, 5354, 2014

# Synthetic Strategies for Sugammadex

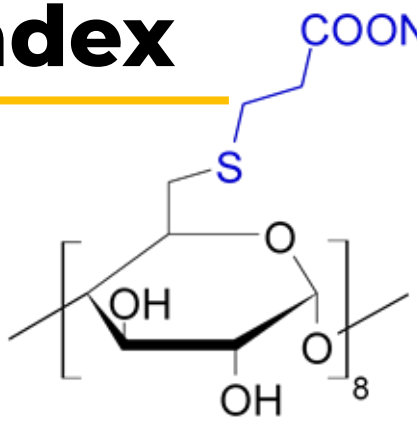


$PPh_3$, $X_2$, DMF
70-75 °C, 14 h

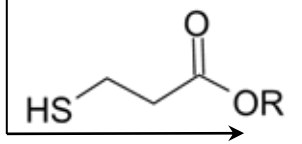




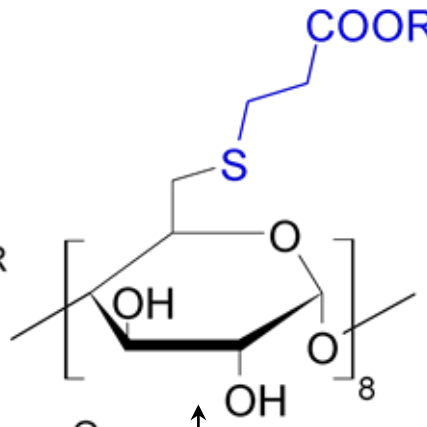
Base1, DMF,
65-70 °C, 14 h



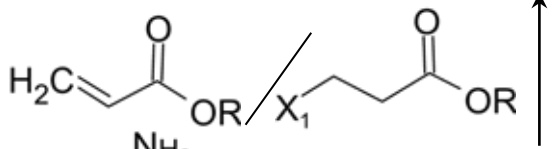
X = Br, I
$X_1$ =Br, I, Cl
Base1 = NaH, NaOR
Base2 = organic or inorganic base
R = alkyl group



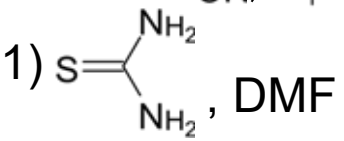
Base2, DMF



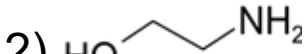
$NaOH$, $H_2O$
20-25 °C, 20 h



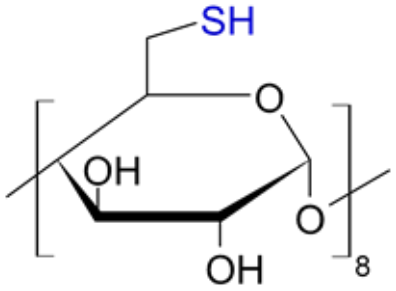
Base2, DMF
65 °C, 12 h



1) , DMF
65 °C, 3 days

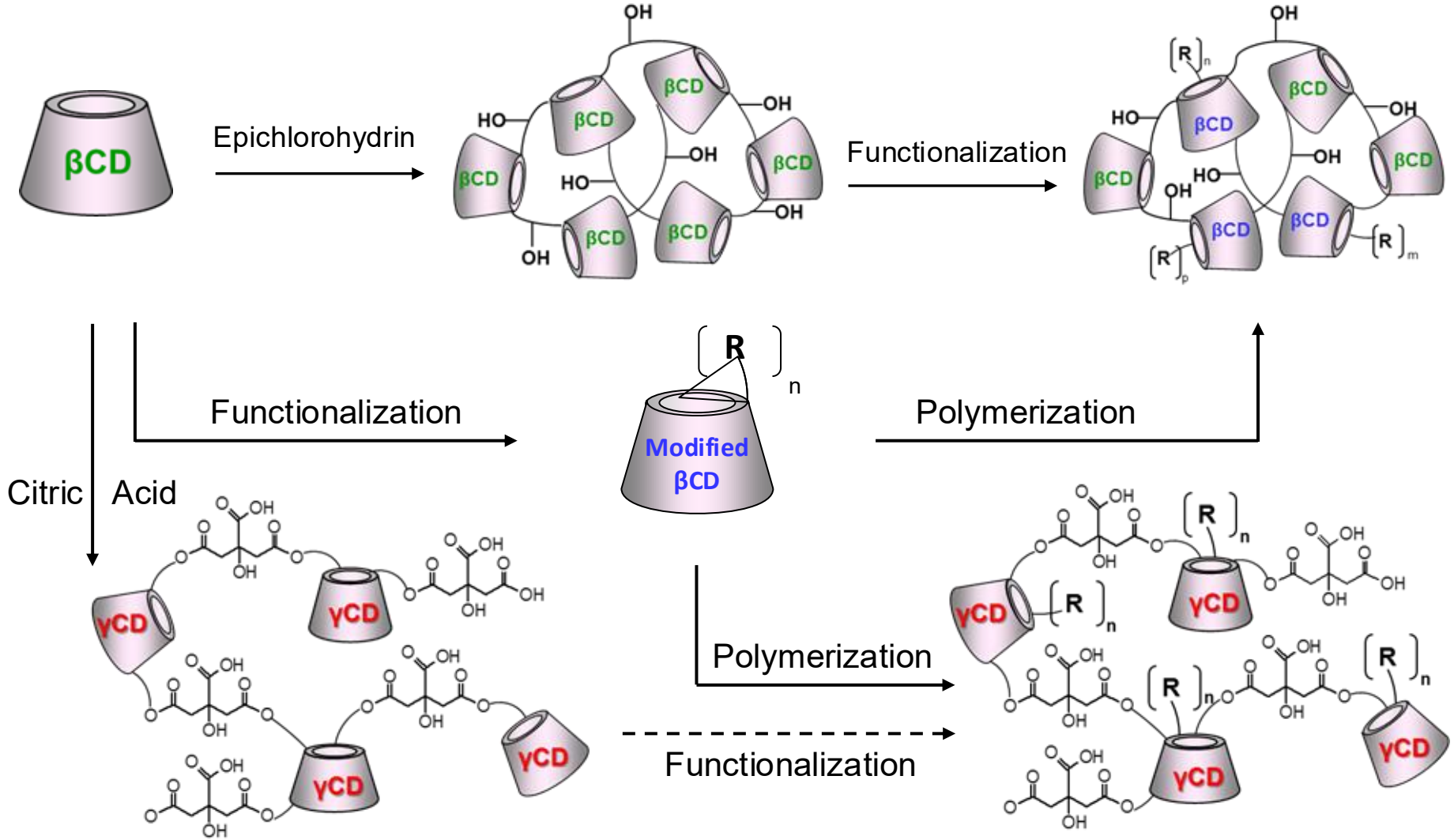


2)
65 °C, 2 h



Adam J. M. et al., J. Med. Chem., 45, 1806-1816, 2002

# Cyclodextrin polymers



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# For any questions:

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