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# Upgraded Production of a Hydroxylactone Anhydrosugar by Cellulose Pyrolysis and its Application in the Synthesis of Biologically Active Compounds

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*Biorefinery I, ECI Conference Chania (Crete), Greece September 27-October 2, 2015*

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**Ines Mancini, Andrea Defant, Federico Dosi,**



UNIVERSITY  
OF TRENTO - Italy

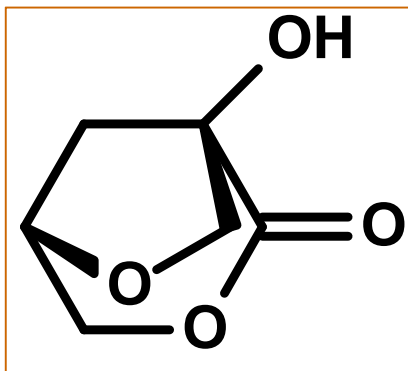
**Danilo Malferrari, Daniele Fabbri**



Alma Mater Studiorum  
Università di Bologna-Italy

**Funding: ENAM project, 2013-2015**  
Provincia Autonoma di Trento,  
CNR, Naples  
Inst. Composite Biomedical Materials

# LAC: a building block from biomass

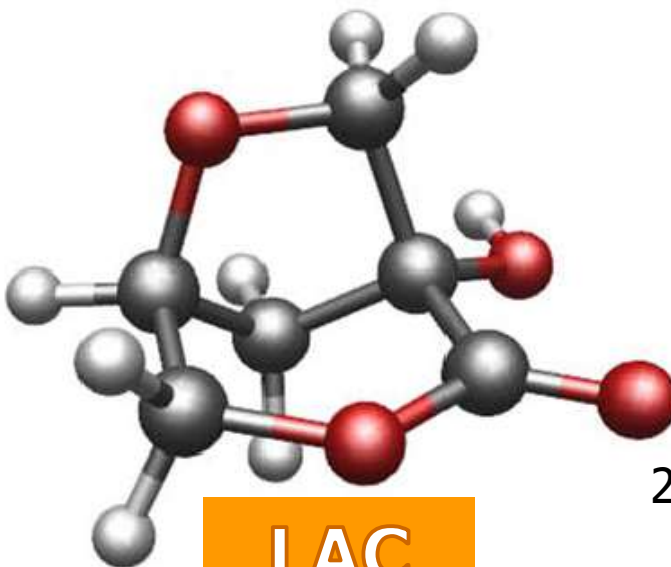


**DERIVABLE  
from CELLULOSE**

1989: Discovered by  
Forneaux *et al* from  
pyrolysis of cellulose with  
 $ZnCl_2$  -  
Mechanism proposed.

R.H.Furneaux et al., *J.Chem.Soc.* 1988, 1, 49

**CHIRAL**



**LAC**

**Functional groups  
HYDROXYLACTONE**

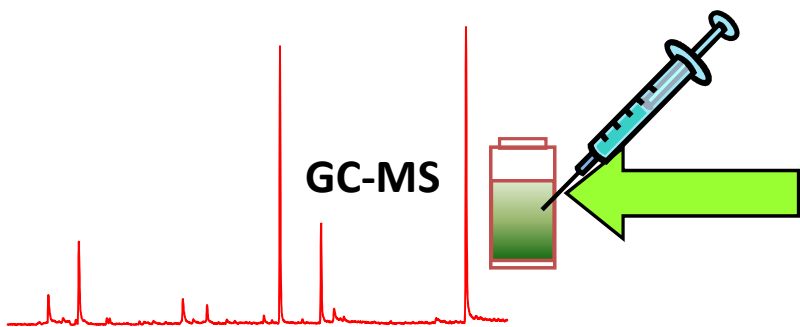
**C6 MONOMER**

2007: Re-discovered from  
pyrolysis of cellulose  
with nanopowders  
metal oxide  
( $Al_3(TiO_4)_2$ )

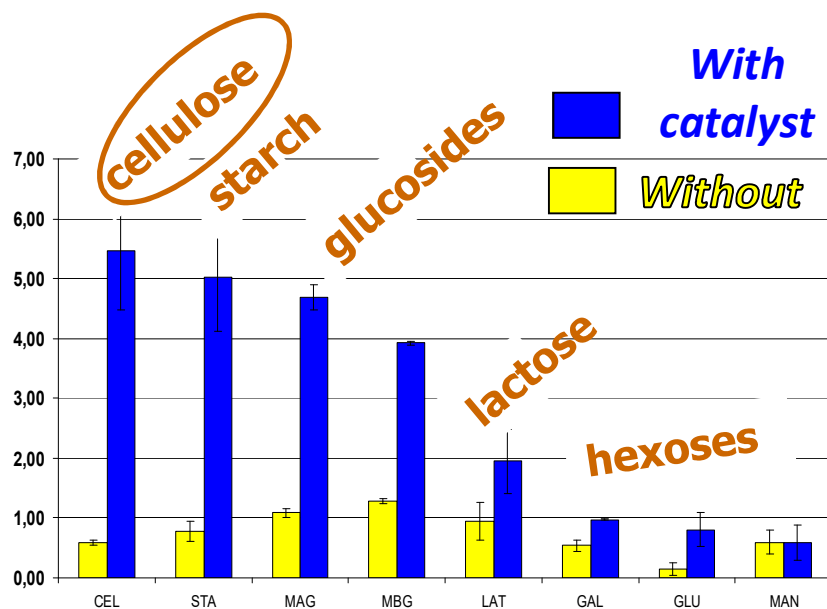
D.Fabbri et al. *Green Chem.* 2007, 9, 1374

# The role of analytical pyrolysis

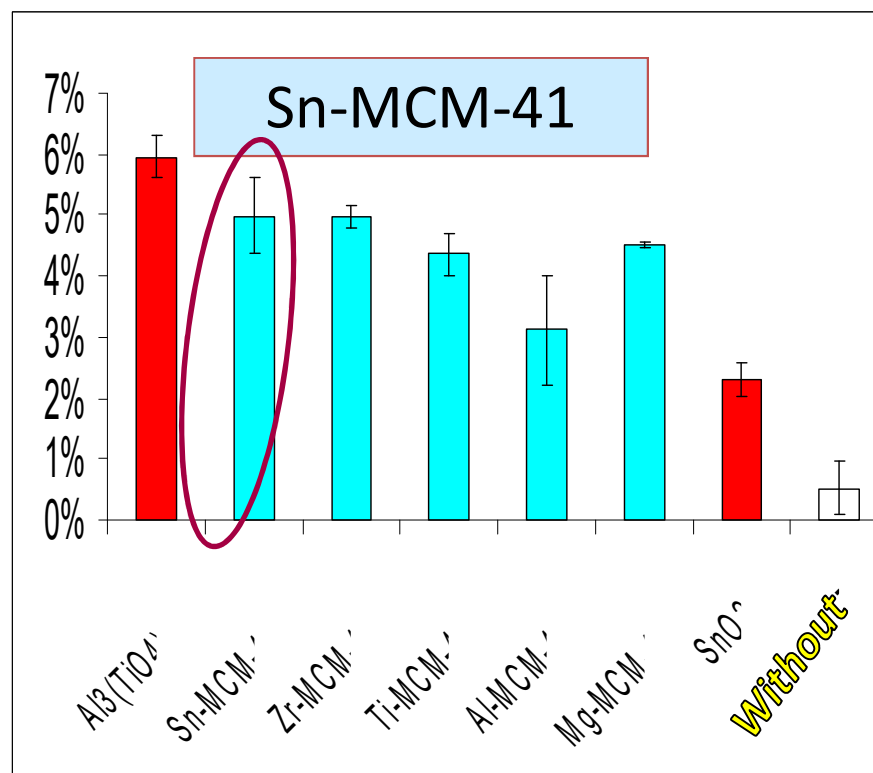
## Preliminary screening



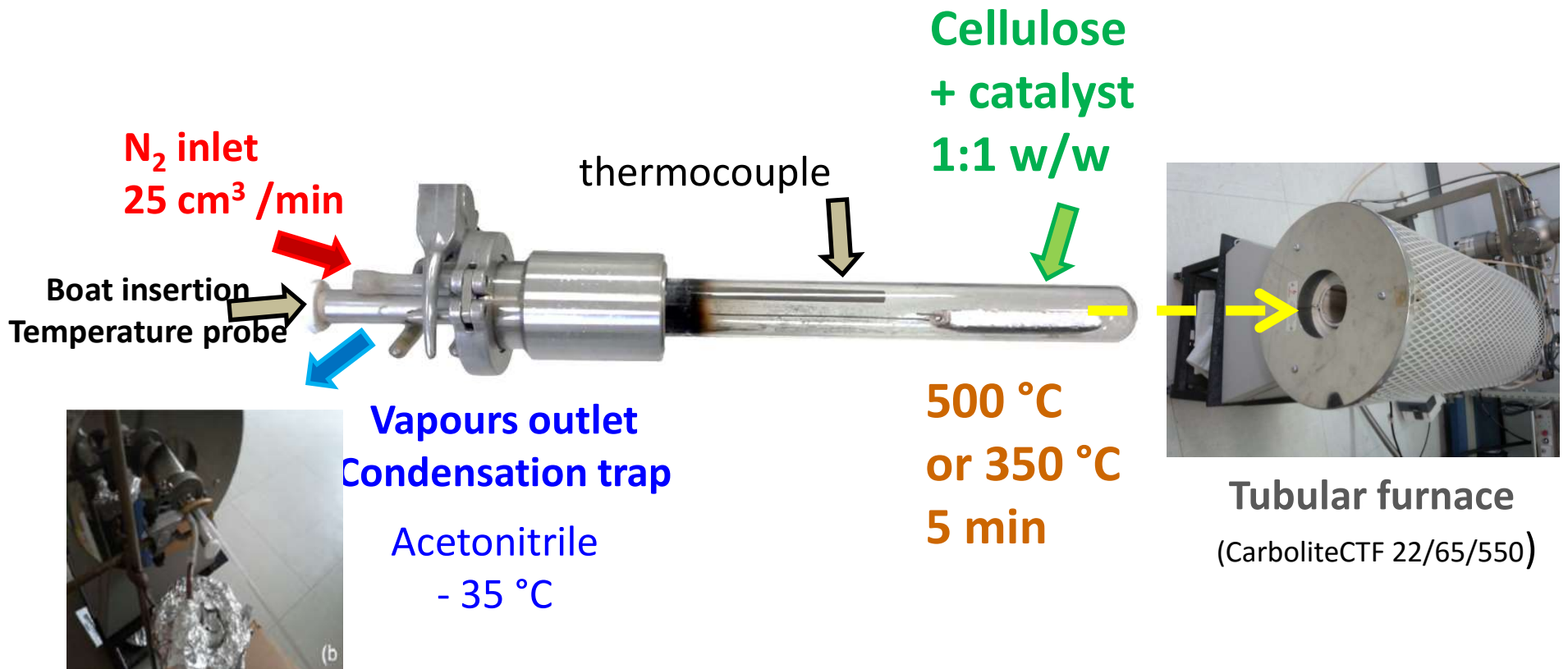
LAC yields



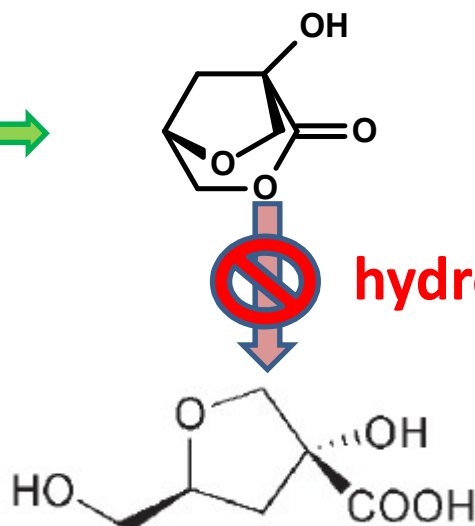
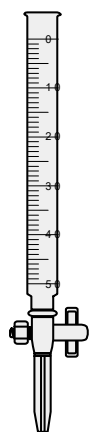
C.Torri et al. JAAP 2009, 84, 25



# Scale-up: bench pyrolyser



# LAC purification Liquid chromatography



pure LAC  
is a liquid

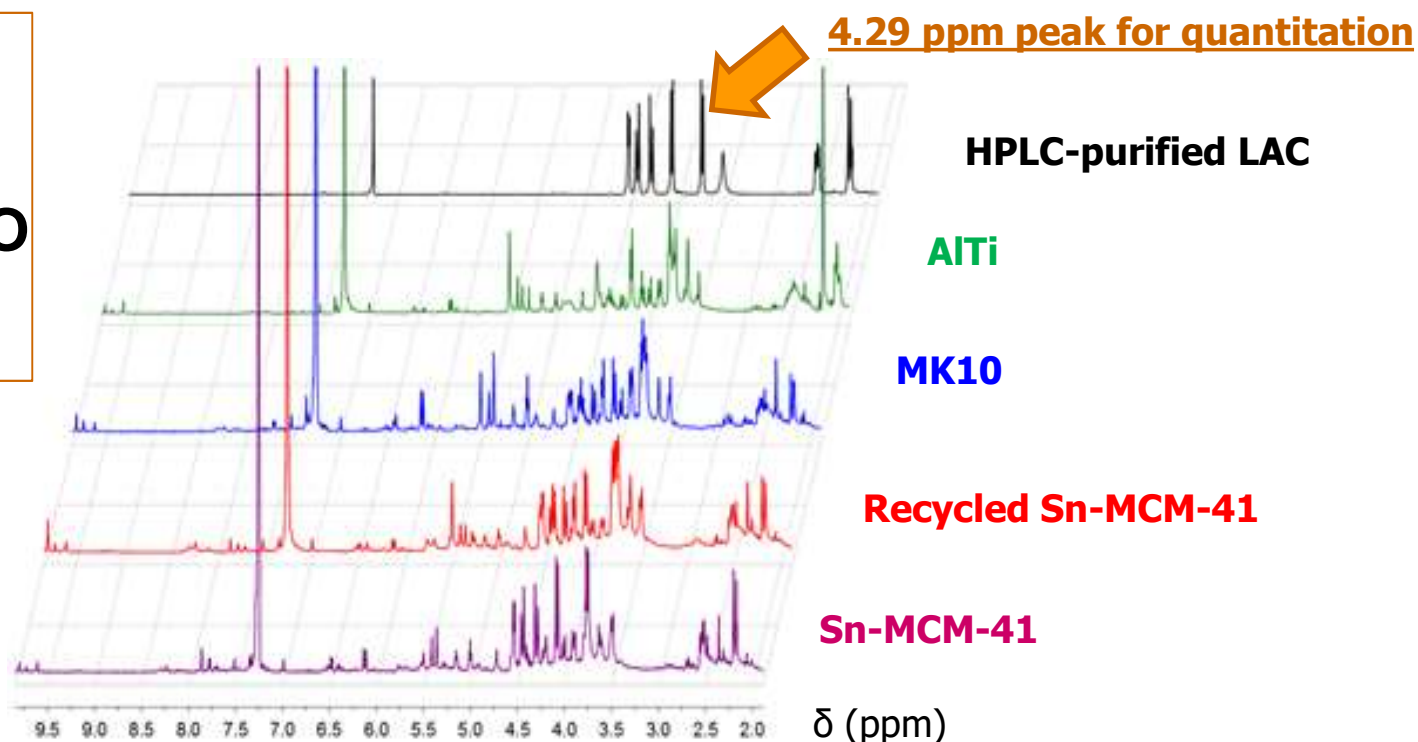
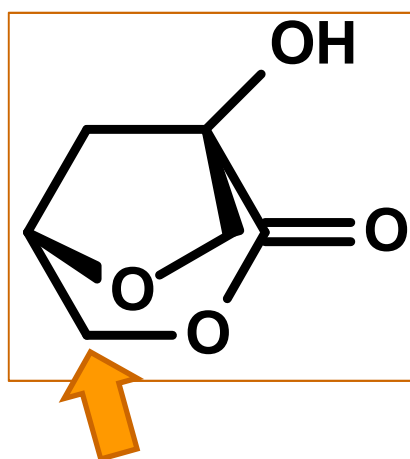
## ➤ Observed weakness

- Polar Silica gel its acidity down-grade LAC → rapid chromatography
- Normal cyano phase allowed a major recovery → expensive
- Non-polar reversed phase, water as co-eluent → hydrolysis of lactone

## ➤ Final conditions for gram-scale purification

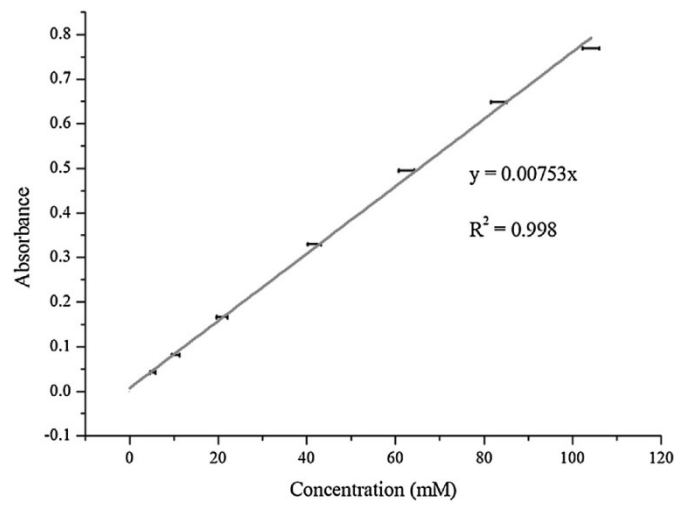
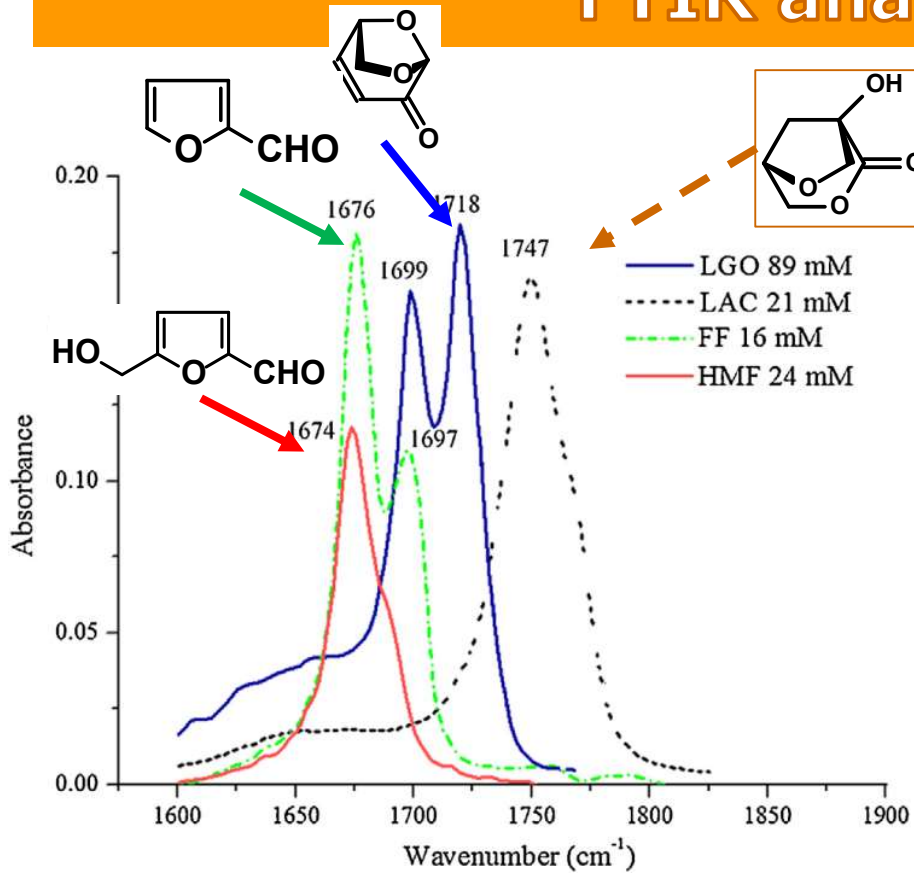
Column LC (silica gel, hexane /EtOAc gradient elution) of the soluble portion from dichloromethane suspension of bio-oil and further purification by filtration on active charcoal.

# Quantitation of LAC in bio-oil by NMR analysis



<sup>1</sup>H NMR spectrum ( $1.5 \text{ mg mL}^{-1}$  in  $\text{CDCl}_3$ , 400 MHz) of pure LAC and bio-oil samples from cellulose pyrolysis in the presence of the indicated catalysts.

# Quantitation of LAC in bio-oil by FTIR analysis



## Carbonyl C=O region

Levoglucosenone,
Furaldehyde,  
Hydroxymethylfuraldehyde,
LAC

FTIR Calibration curve for LAC quantification, at  $c = 2 \div 104$  mM.



## LAC yields from Sn-MCM-41

Catalyst	LAC concentration (wt.%)		Yield of LAC from cellulose (wt.% ±0.1%)
	<sup>1</sup> HNMR	FT-IR	
Sn-MCM-41	27.6 ± 0.4	28.1 ± 0.3 (27.0 ± 0.3)	7.6
Recycled Sn-MCM-41	26.8 ± 0.5	27.3 ± 0.3 (25.4 ± 0.3)	7.3

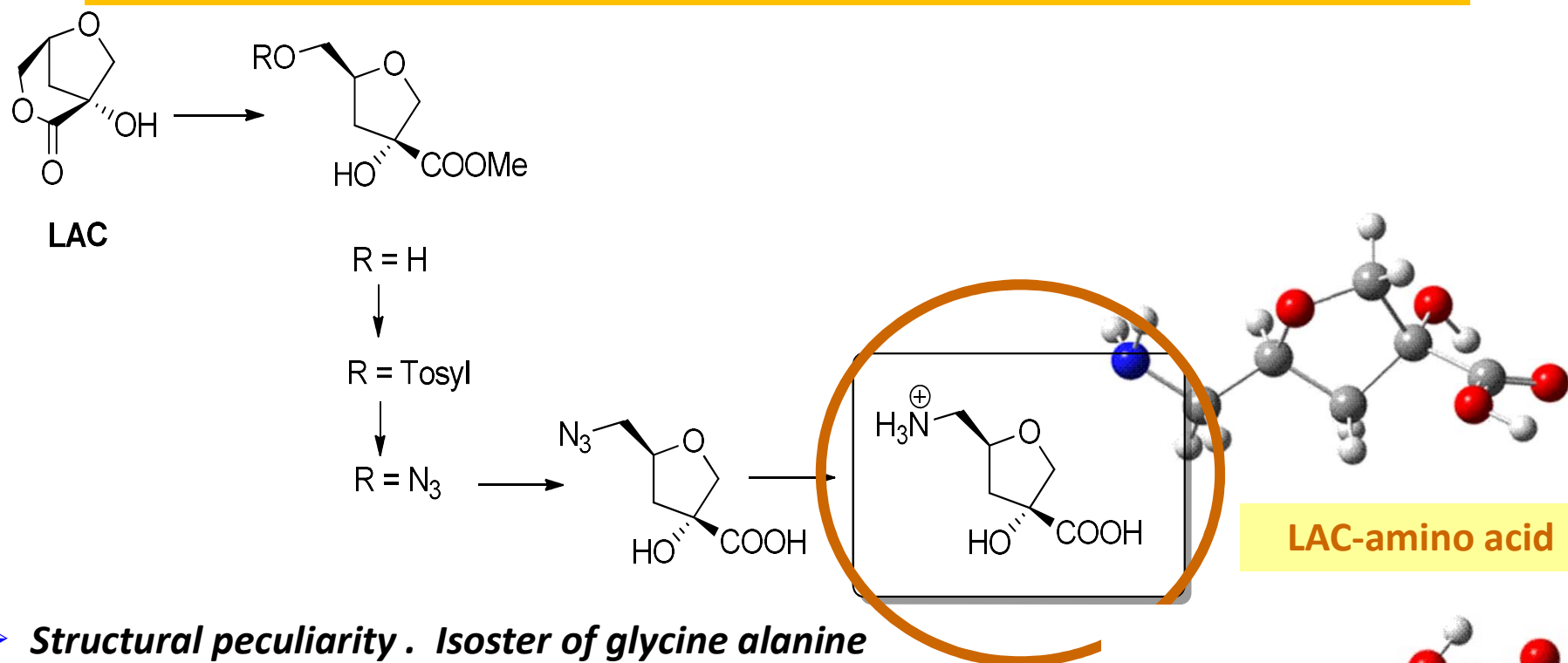
## LAC yields from montmorillonite

Catalyst			Yield of LAC from cellulose (wt.% $\pm 0.1\%$ )
	Pyrolysis T	FT-IR LAC conc. Wt%	
<b>MK10</b>	<b>500 °C</b>	<b>18.6 <math>\pm</math> 0.2</b>	<b>4.8</b>
<b>MK10</b>	<b>350 °C</b>	<b>24.1 <math>\pm</math> 0.3</b>	<b>-</b>

Industrially available, low cost, regenerable

# LAC derivatives

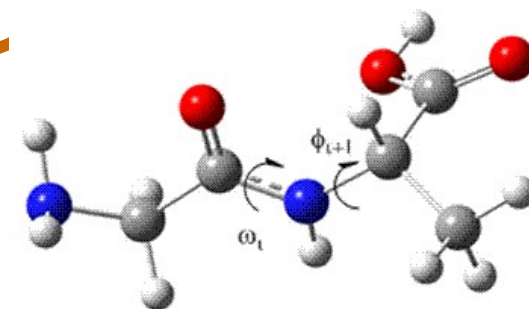
## Synthesis of a new amino acid



➤ **Structural peculiarity . Isoster of glycine alanine**

It is comparable to H-Gly-Ala-OH dipeptide, with the peculiarity of assuming a restricted conformation.

Replacement for the Gly-Ala residue in a peptide sequence can be interesting in peptidomimetics studies .



Glycine-Alanine

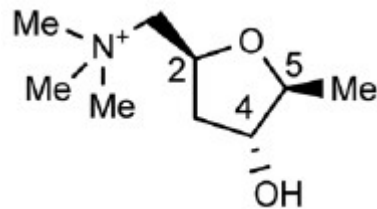
# its similarity with muscarine

*Amanita muscaria*



It.wikipedia.org

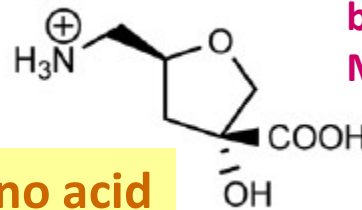
muscarine



## Muscarinic receptors

Muscarine is an agonist of the acetylcholine neurotransmitter due its binding with muscarinic receptors  $M_1$ - $M_5$ .

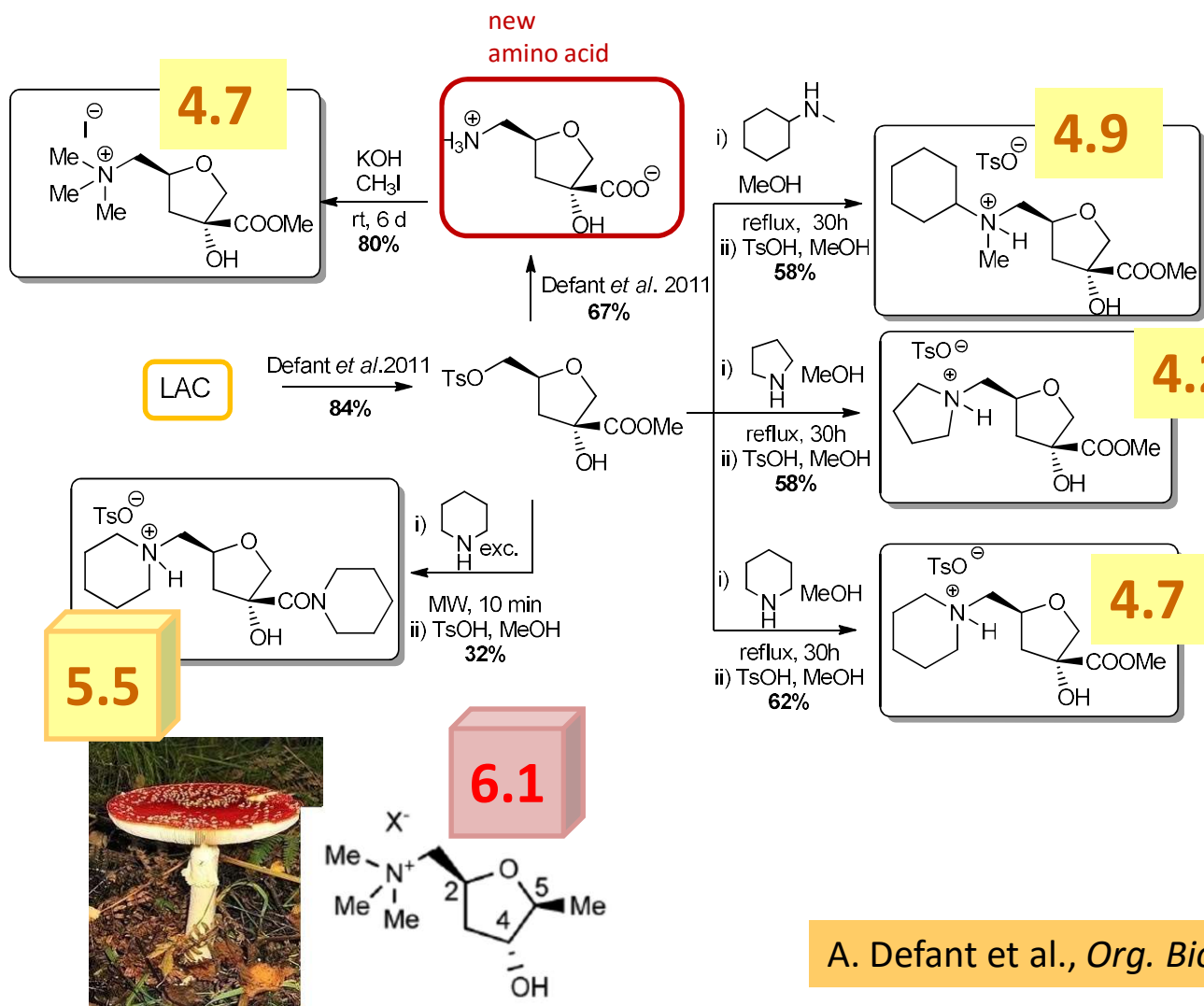
LAC-amino acid



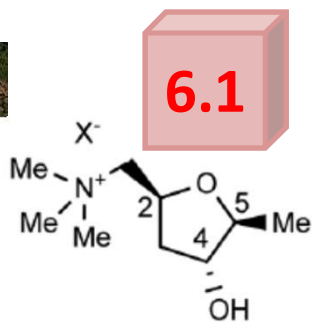
The LAC-derived aminoacid has a strong structural similarity with the alkaloid muscarine.

Compounds mimicking muscarine activity are of interest in drug design in order to achieve new selective agents in the therapeutic treatment of various disease (Alzheimer's, glaucoma).

# Synthesis and activity of muscarin-like compounds

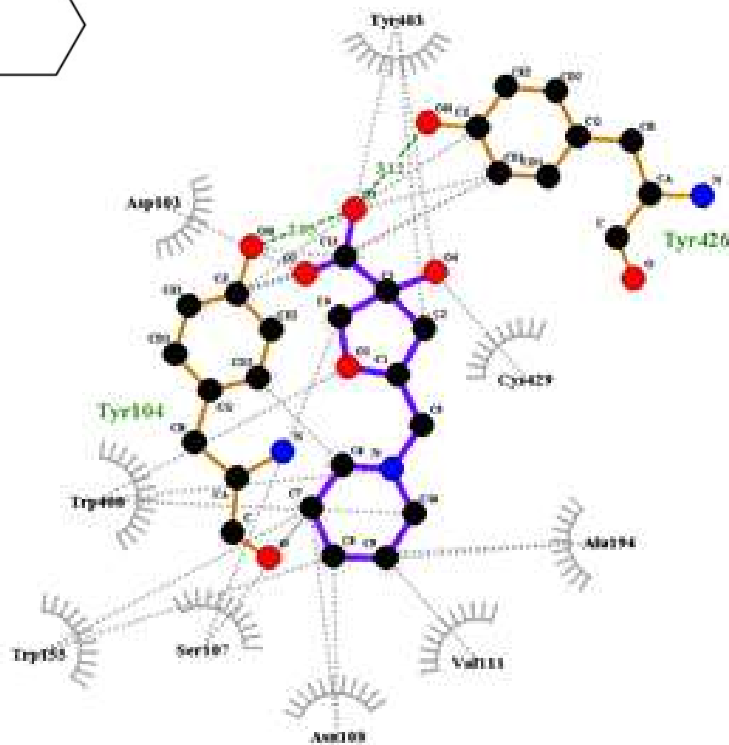
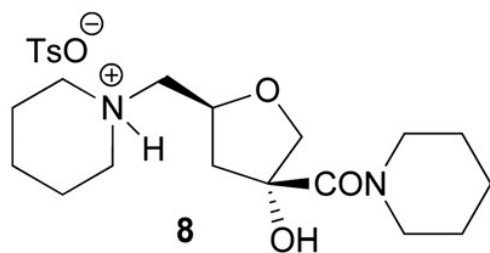


**X.X**  
**Binding data with**  
**receptor**  
**M2**  
**(cardiac function)**



A. Defant et al., *Org. Biomol. Chem.* **2015**, *13*, 6291.

# LAC-muscarinic interaction with hM2 receptor



Docking calculation of the complex between the most experimentally active compounds with hM<sub>2</sub> subtype (3UON PDB.file): view of the interactions in the receptor site.