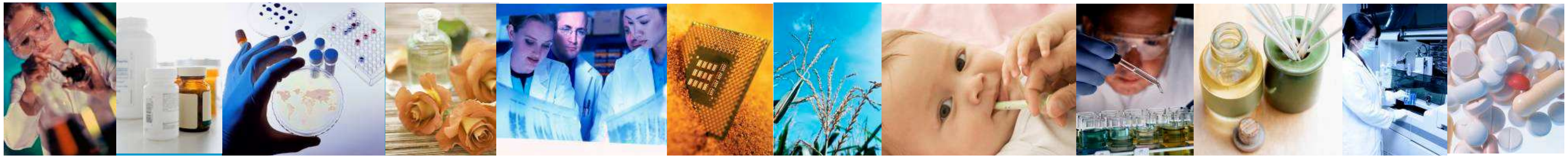
Enzymes for Green Solutions

in fine Chemicals



'Green Chemistry' applied in
'PCAS-Biosolution'

- Basics -

June 26, 2008

Gérard Guillamot
R&D Director , PCAS Group

1998 . 2008 : 10 ans d'Innovation @ Protéus

Summary

- PCAS & PCAS-Bio profiles
  - In House examples
- How biocatalysis can be a major contributor to green solutions in Fine Chemicals
  - In House examples
- Uncommon examples of Biocatalysis from recent litterature

Key Figures

- 1050 Employees
- 185,3 Millions € of net sales
- 103 persons in R&D (35 Ph.D.)
- 8 Manufacturing plants: France (6), Finland(1) & Canada(1)
- 700m³ production capacity with 350m³ under cGMP
- 4 cGMP sites systematically audited by regulatory agencies (FDA, AFSSAPS…)

Core Business activities

? Pharmaceutical actives « API » & intermediates division

- Non-exclusive molecules
- Key Intermediates within cGMP guidelines
- Early Intermediates, out of cGMP guidelines

? Fine chemicals and performances division

- Fragrance-Flavours-Cosmetics sector
- Imaging, electronics & new technologies chemicals
- Additives for performance chemicals

Enzymes for Green Solutions in fine Chemicals

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The initial interest for 'Biocatalysis': 20 years ago

? 1987 : A. Klibanov, Enzymes in organic 'Solvents'

? 1993 : An enzyme to lead to a '-pril' Intermediate

? 1998 : First contact with PROTEUS

? 2001 : PCAS-Finland integrated University expertise

(Lisa Karnerva who did her post-doctorate under Klibanov)

? 2005 : Discussions for mutual interests : PCAS-PROTEUS

? 2006 : Set of the 'PCAS-Biosolution' joint-venture

? 2007 : Start with the first identified targets

? 2008 : First results delivery at Industrial scale

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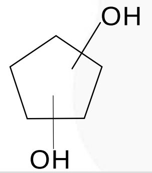
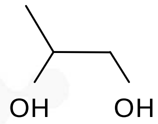
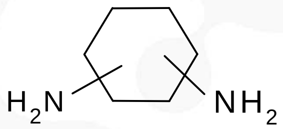
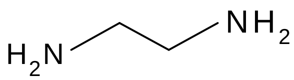
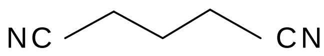
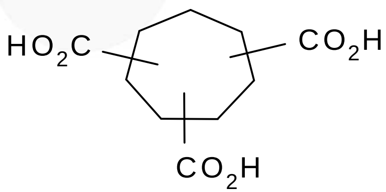
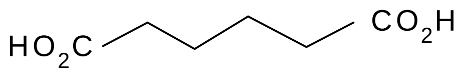
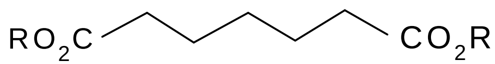
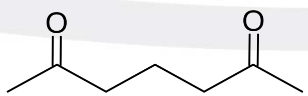
- Regio-selectivity from basic building blocks to very complex structures

- Avoid multiple protection-deprotection steps
  - Diols, Triols & Polyols (Sugars derivatives)
  - Diamines & Polyamines
  - Diacids & Polyacids
  - Dinitriles
  - Diesters & Polyesters
  - Diketones
  - Dialdehydes

Enzymes for Green Solutions in fine Chemicals

PCAS Biosolution

☞ *Regioselectivity advantages*

		Diol
		Di-amine
		Di-nitrile
		Di or tri -acids
		Di-esters
		Di-ketone

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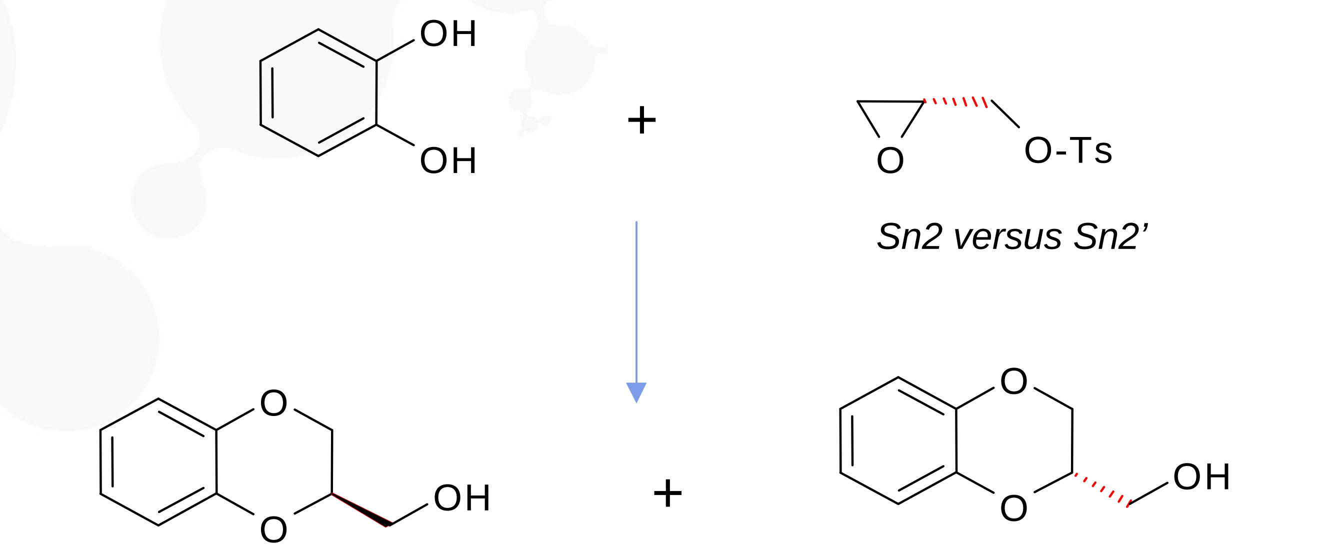
working from nature's imagination
www.pcasbiosolution.com

Enzymes for Green Solutions in fine Chemicals

PCAS Biosolution

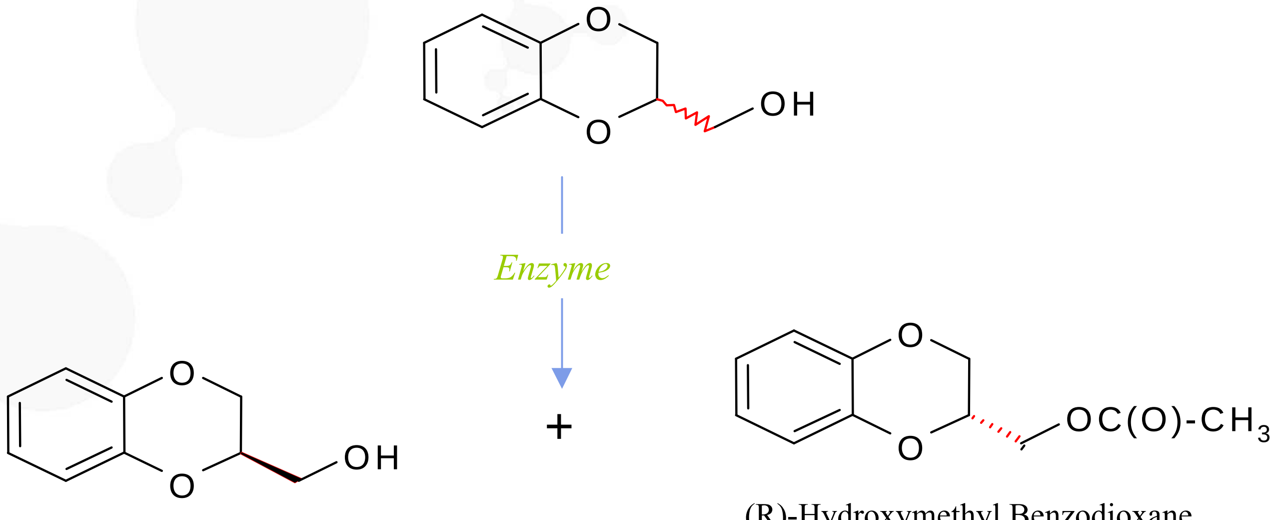
☞ ***Regioselectivity: 'Chiral-Chemistry' using Chiral building blocks***



(S)-Hydroxymethyl benzodioxane

(R)-Hydroxymethyl benzodioxane

☞ *Enantioselectivity: 'Chiral-Chemistry' using Biocatalysis*

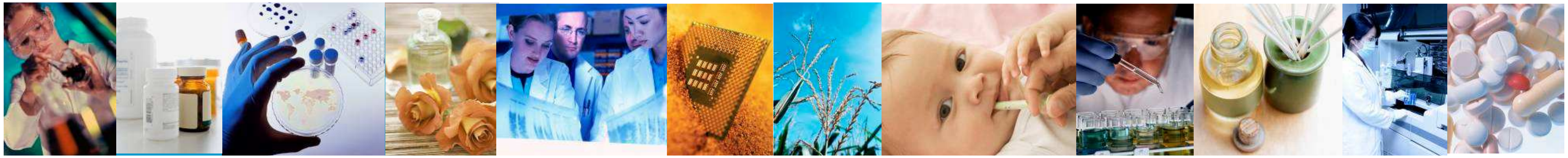


(S)-Hydroxymethyl Benzodioxane
→ 50%

(R)-Hydroxymethyl Benzodioxane
→ 50 %

☞ *Today, 100% could achievable through ADH reduction on the aldehyde*

Enzymes for Green Solutions in fine Chemicals



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Enzymes for Green Solutions in fine Chemicals

↳ To prevent 'wastes' production

- ? Increase both selectivities & conversions rates
- ? Build 'convergent' synthetic routes
- ? Favor the atom economy solutions
- ? Use the existing natural chiral pool

↳ To maximize the amount of starting material used in the final product : « Maximise atom economy »

- ? Avoid protection-deprotection steps
- ? Avoid chiral auxilaries except when recycle is done
- ? Avoid Stoëchiometric reagents
- ? Promote 'Catalytic' solutions

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Enzymes for Green Solutions in fine Chemicals

- To design safer Chemicals and Products (reagents/solvents/starting materials) that will respect Environnement

? Avoid solvent use or promote recycling

? Use safer solvents & Reactions conditions

? Promote biological solutions for waste treatment

? Avoid toxic reagents (Heavy metals and derivatives)

? Promote bio- & chemio-catalytic systems

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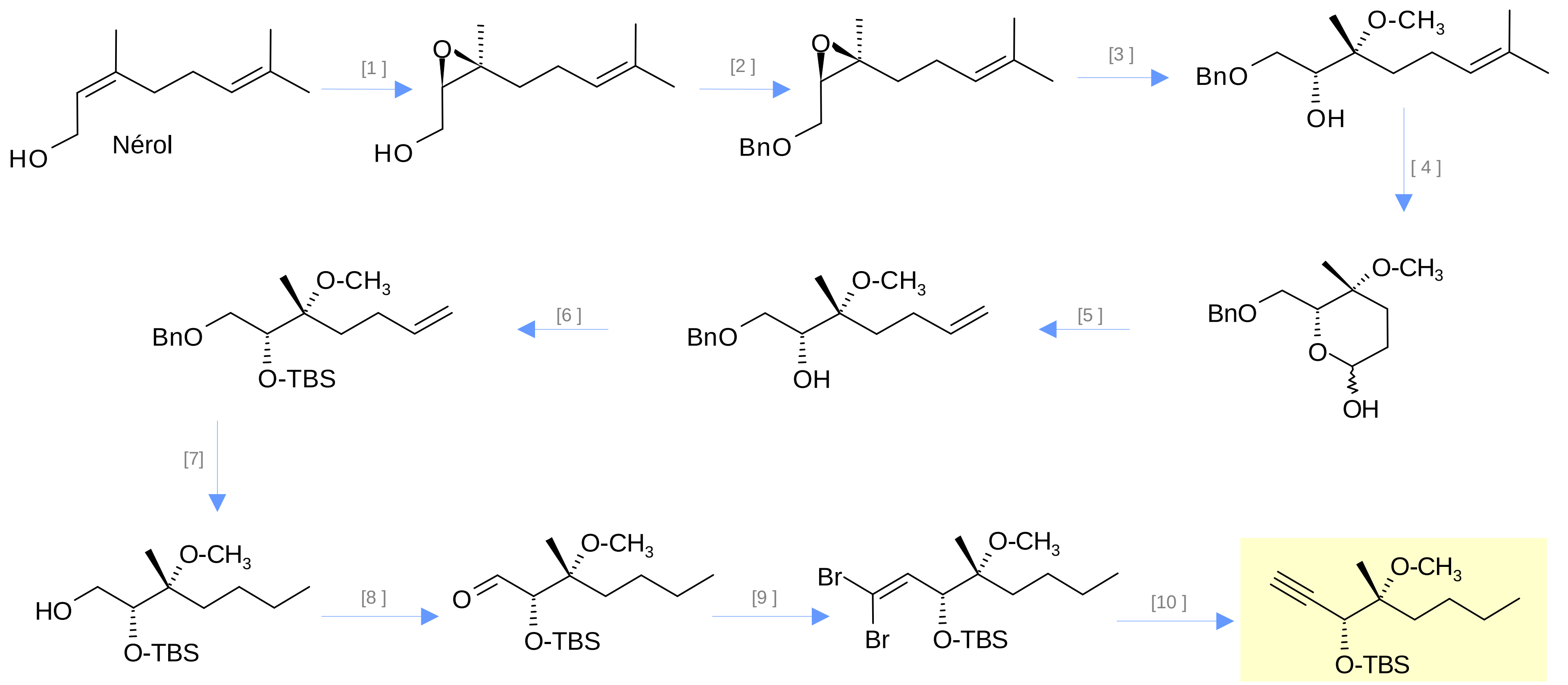
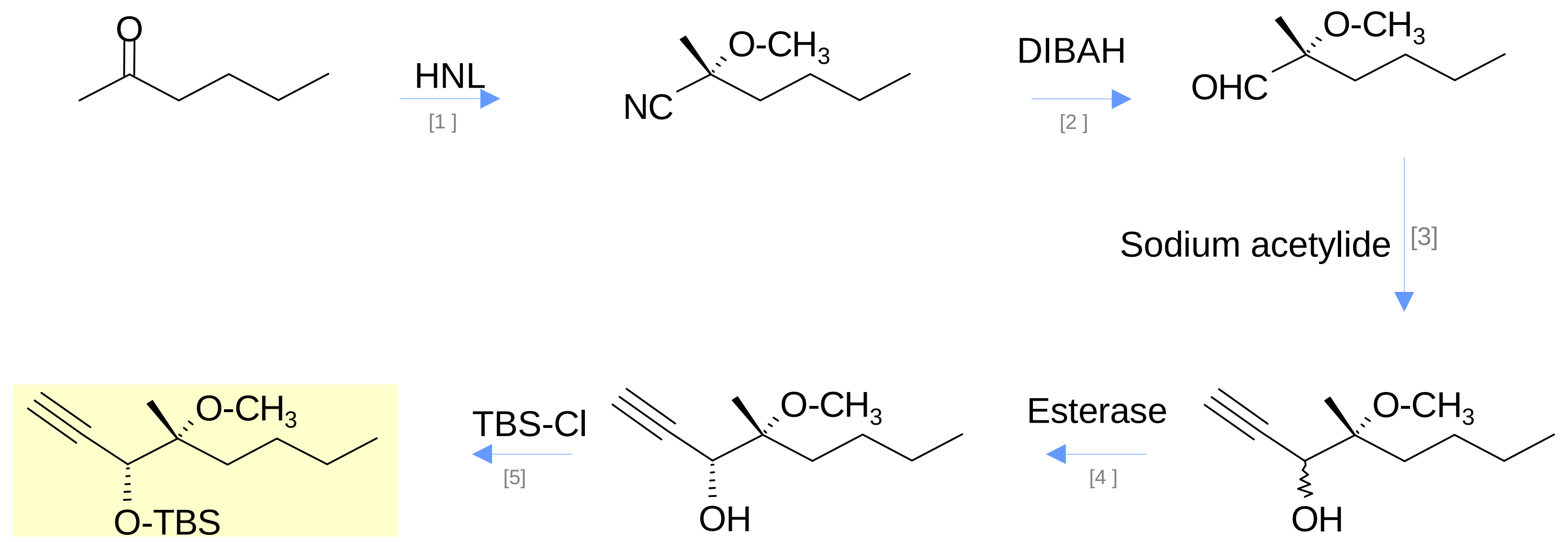
Case # 1: Lower side chain of a Prostaglandin
Chemical route / L. Van Hijfte : 10 steps



Prostaglandine side chain

Case # 1: Lower side-chain of a Prostaglandine

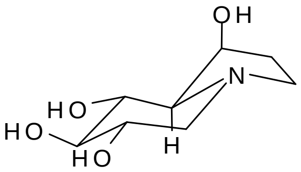
New route Proposal /G. Guillamot: 5 steps (Chemo-biocatalyse)



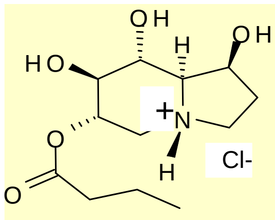
Prostaglandine Side Chain

☞ *Expected savings: 50% on costs*

Case # 2: Celgosivir (5 steps)



Dream: 1 step / Enzyme



To increase Energy efficiency

? 19° Century : Energetic barrier to allow 'chemicals' to react is overcome by heating up the mixture

? 20° Century : Energetic barrier is transferred to very energetic reagents and chemical catalysts and we have now to cool down to keep the reaction under control

? 21° Century : Energetic barrier is lowered by using more efficient catalytic systems, either Chemicals or Biologics ones (Enzymes...)

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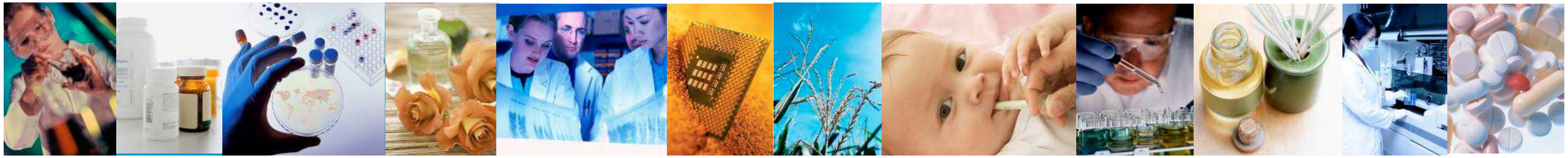

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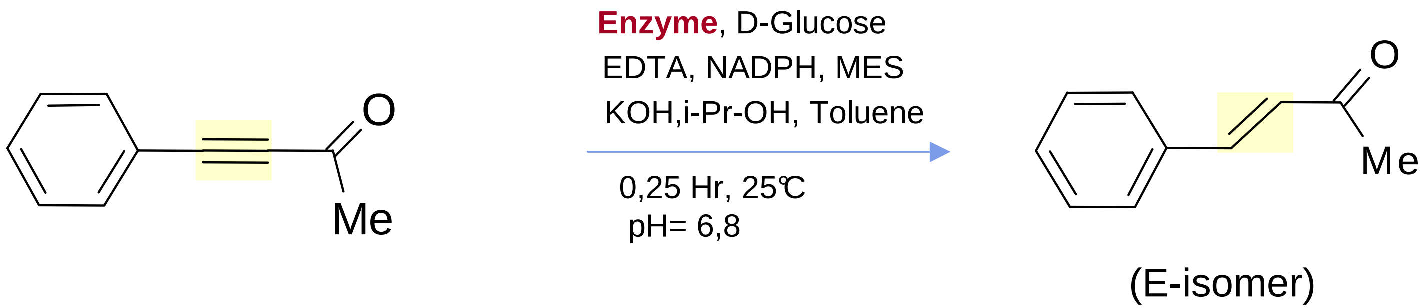
Unusual 'Biocatalytic' methods complementing Chemical tools

- Bioconversion examples -

- Bioconversion examples -

Carbon-Carbon Triple Bond Reduction

☞ **Stereospecific Alkyne reduction-Novel activity of old yellow enzymes**



Muller A, Sturmer R, Hauer B, Rosche B. Univ New S Wales, Sch Biotechn & Biomol Sci, Sydney, Australia
ANGEW CHEM INT ED 46 (18), 3316-3318 (**2007**)

The final product is the saturated product but the kinetic of the reaction allows isolation of this unsaturated E-isomer

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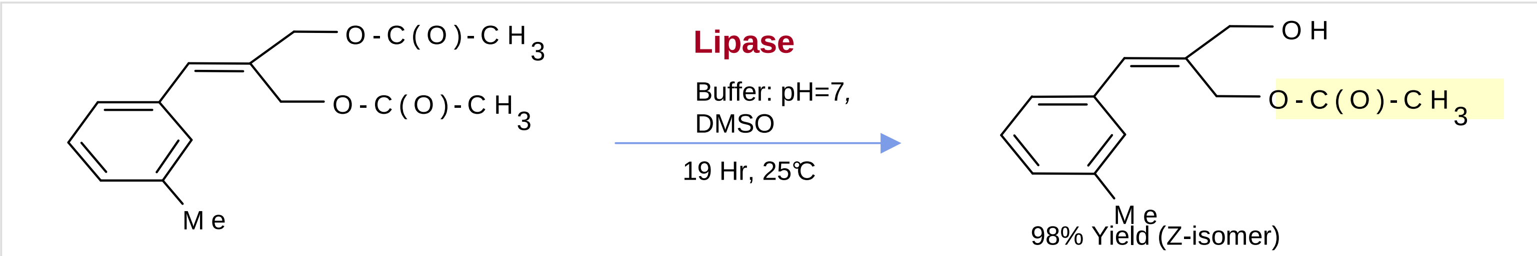
- Bioconversion examples -

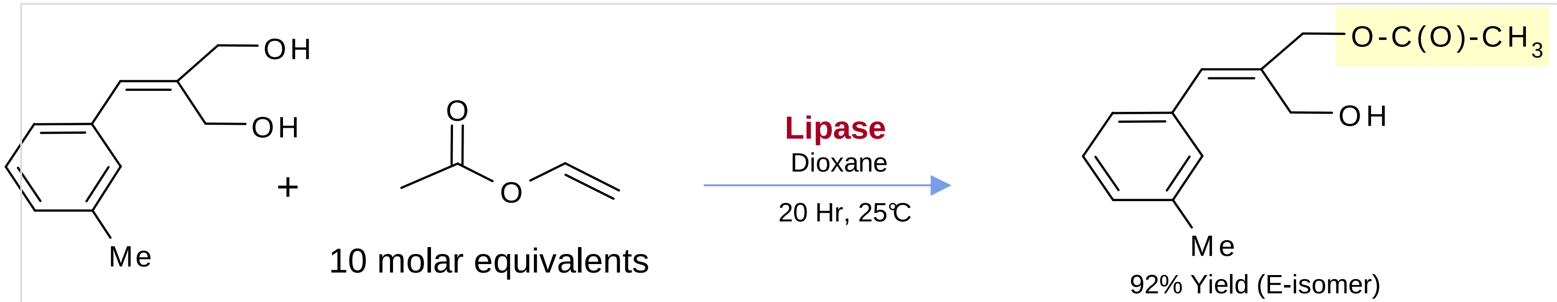
Separation of the E or Z-geometric isomers on a double bound

☞ Highly regioselective hydrolysis of substituted 2-Benzylidene-1,3 propylene diacetates using Porcine pancreas lipase"



Miura T, Kawashima Y, Umetsu S, Kanamori D, Tsuyama N, Jyo Y,Murakami Y, Imai N. Chiba Inst Sci, Fac Pharm, Japan . CHEM LETT 36(6), 814-815 **(2007)**

? Regiospecific acetylation of substituted alpha,alpha'-Benzylidene-dimethanols with vinylacetate using Porcine pancreas lipase



Miura T, Kawashima Y, Takahashi M,Murakami Y, Imai N. Chiba Inst Sci, Fac Pharm, Japan, SYN COMMUN 37 (18), 3105-3109 (**2007**)

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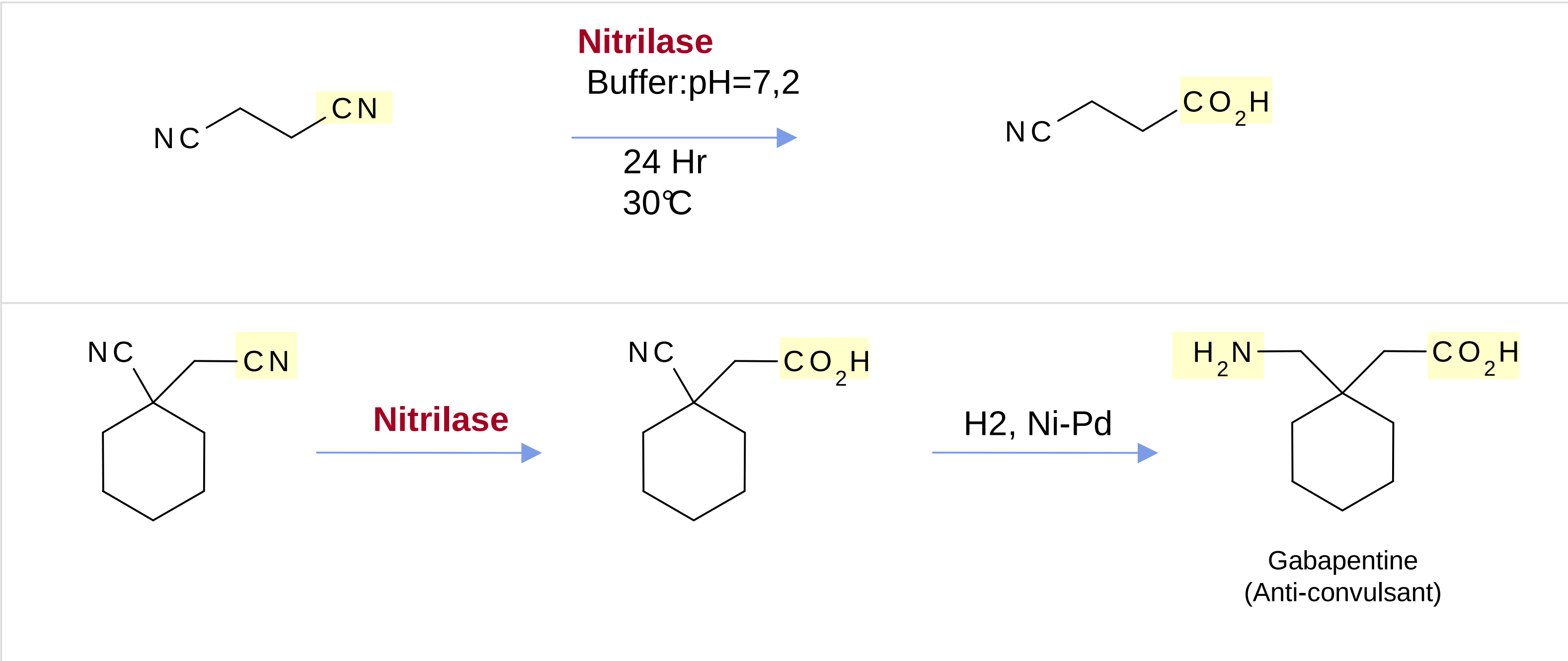
- Bioconversion examples -

Regioselectivity between 'Nitriles functions'

☞ Nitrilase-catalyzed selective hydrolysis of dinitriles and green access to the cyanocarboxylic acids of pharmaceutical importance



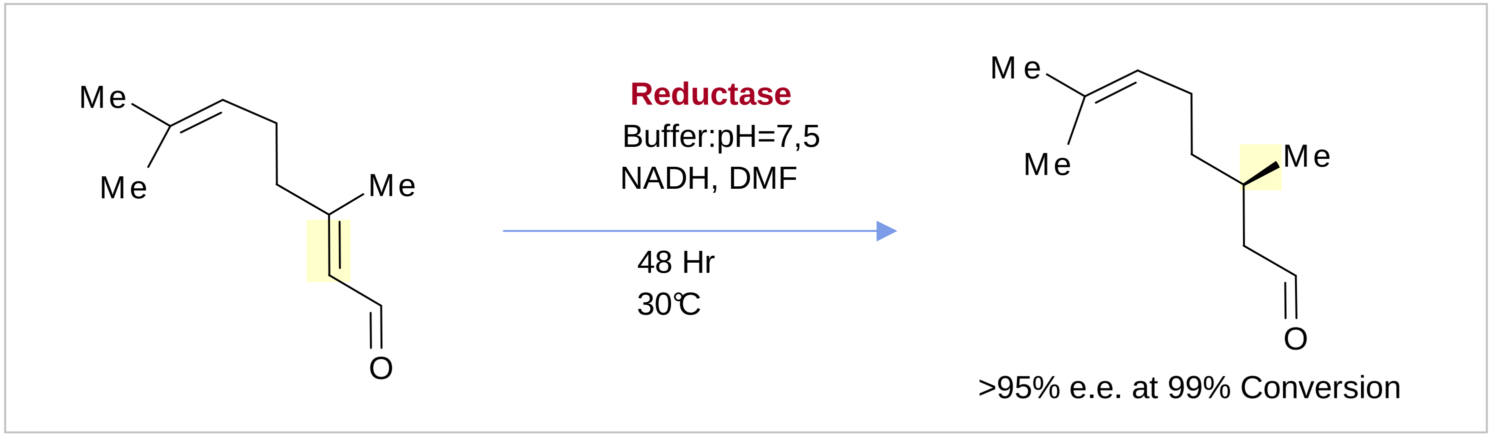
Zhu D, Muherjee C, Biehl ER, Hua L. So Methodist Univ., Dallas, USA . ADV. SYNTH CATAL 3495 (10), 1667-1670 (**2007**)

- Bioconversion examples -

Combination of Regio-& Stereo-selectivity in one step

☞ Asymmetric Bioreduction of activated alkenes using cloned ‘ 12 oxophytodienoate reductase isoenzymes OPR-1 and OPR-3 from Lycopersicon-esculentum (Tomato)

Fragrance field



Hall M, Stueckler C, Kroutil W, Macheroux P, Faber K. Graz Univ. Dept Chem.Organ. & Bioorgan., Austria
ANGEW CHEM INT ED 46(21), 3934-3937 (**2007**)

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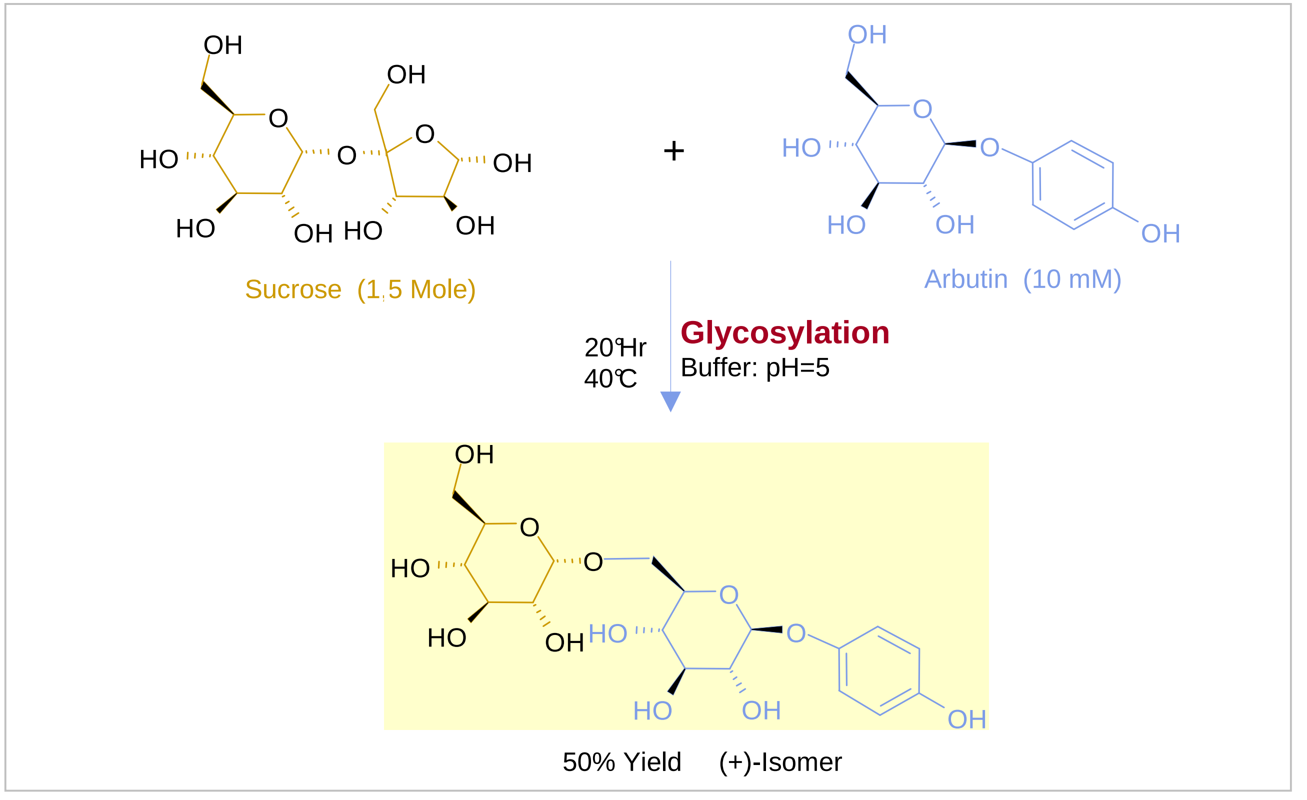
- Bioconversion examples -

☞ A simple and efficient one-step, regioselective, enzymatic glucosylation of Arbutin by alpha-glucosidase



Milosavic N B, Prodanovic R M, Jankov R M. Univ Belgrade, Serbia. Tetrahedron Letters 48(40),7222-7224 (**2007**)

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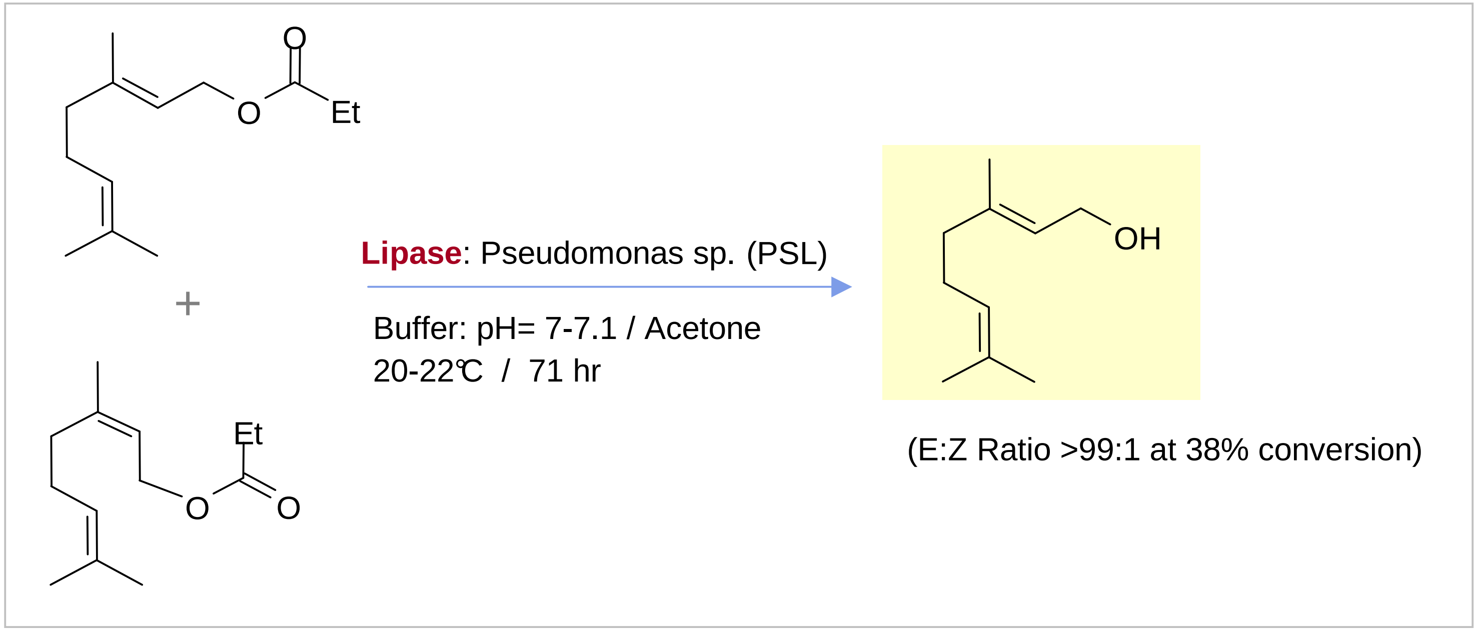
☞ Lipase-catalyzed separation of geometrical-Isomers- « Geraniol-Nerol »

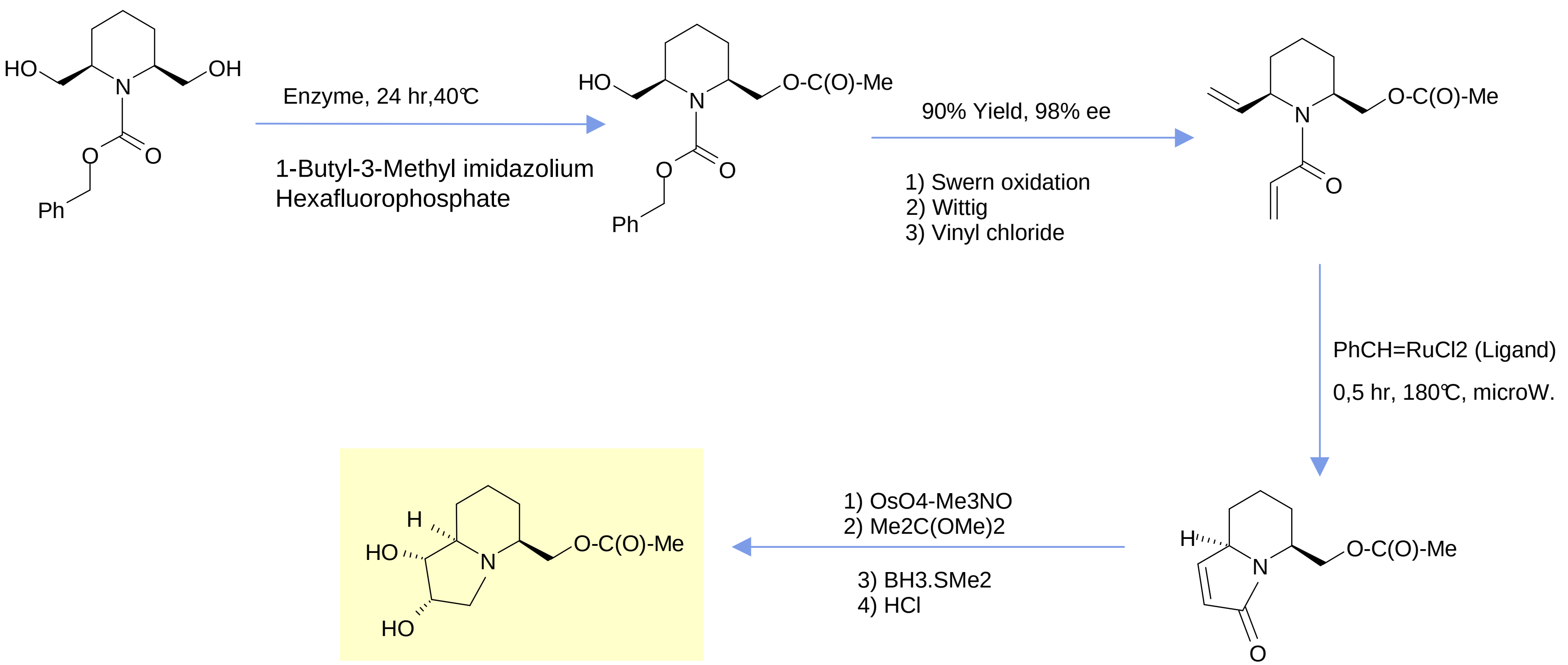
Fragrance field



Gupta P., Taneja S. C., Shah B.A., Sethi V.K. Qazi G.N.CHEM LETT 36(9), 1110-1111 (**2007**)

New methodologies Impact on the complex molecules elaboration

☞ A Chemoenzymatic-RCM Strategy for enantioselective synthesis…



Lesma G., Colombo A., Landoni N., Sacchetti A.,Silvani A. Tetrahedron Asymmetry 18(16), 1948-54 (2007)

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« Nature has more imagination than our dreams »

- Ten years ago, both Biology and Chemistry were still used to copy Nature - That was when Proteus was born

- Today, by combining Chemistry and Biology, your dreams will meet our "sense of art" and expertise - we can deliver success in Science.

Join Proteus & PCAS-Biosolution, you will meet our Biodiversity World »»»»

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Enzymes for Green Solutions

in fine Chemicals

What else !

Thank you

Gérard Guillamot
R&D Director , PCAS Group

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Who else !