Microwave-assisted kinetic resolution of homochiral diols using lipase

Hervé Rouillard, Emmanuel Deau, Lisianne Domon, Jean-René Chérouvrier, Marianne Graber, Valérie Thiéry
Université de La Rochelle
UMR CNRS 7266 Littoral, Environnement et Sociétés (LIENSs)

Aim of the project

Better understanding of the influence of the microwave interaction with enzyme in various conditions :

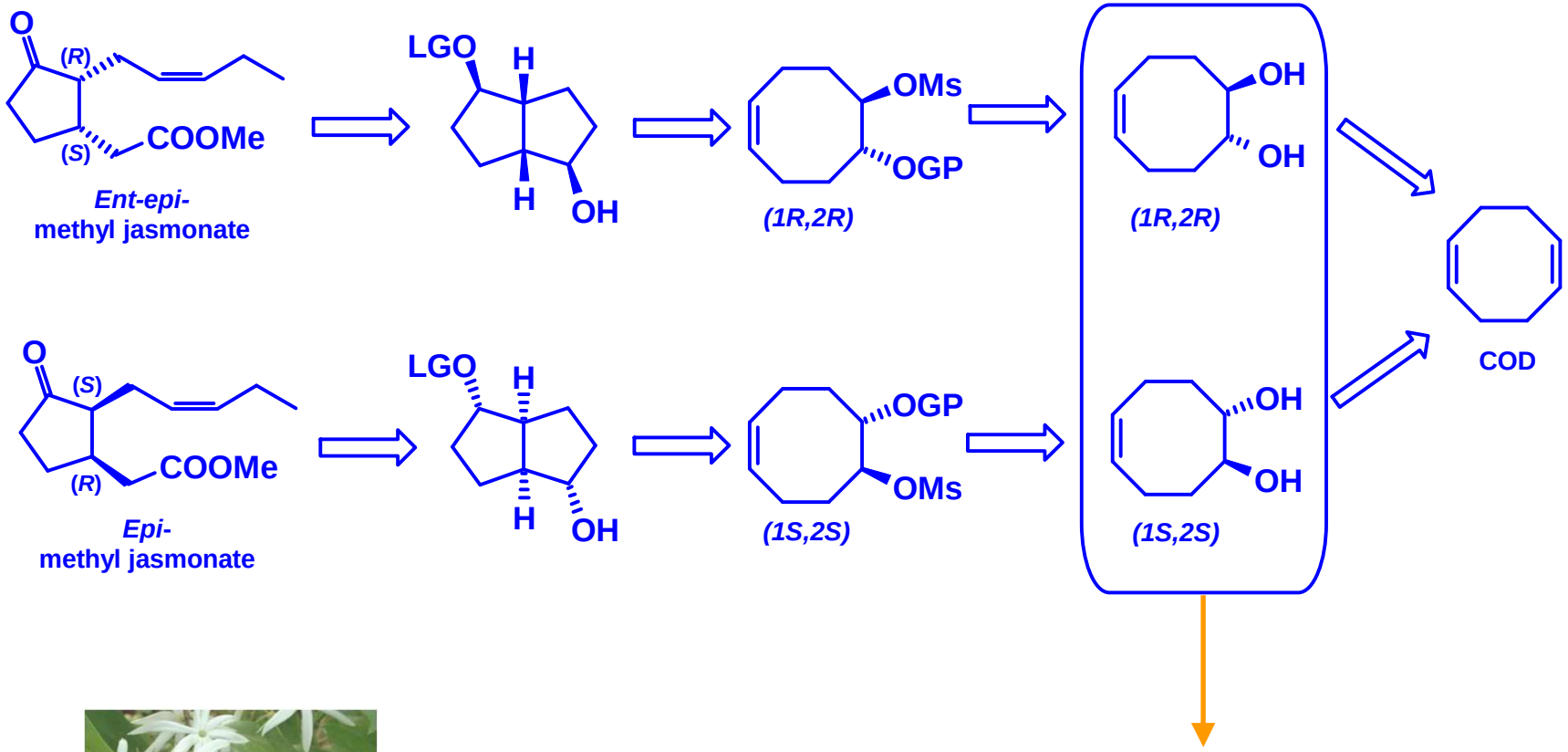
- Aqueous or Non-aqueous medium Solvent free system
- High or Low Temperatures
- Under Pressure or Not

To determine Microwave influence on the enzymatic properties :

Activity	Selectivity
Stability	Reusability

Exploit the irradiation effects on the enzyme activation for the synthesis of interesting compounds

Stereoselective synthesis of methyl jasmonates



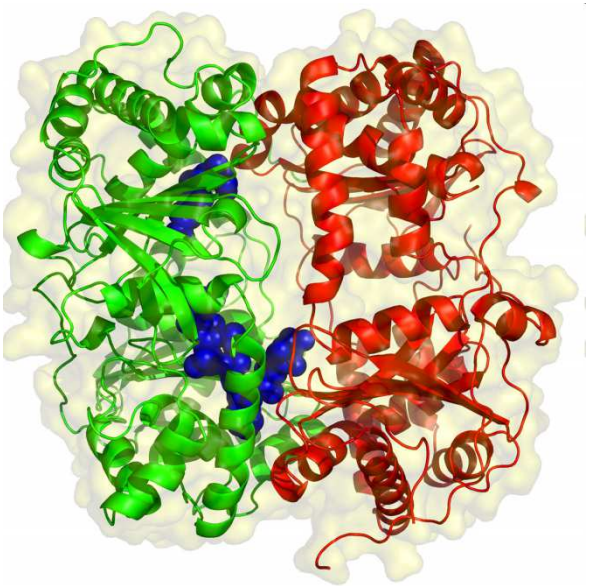
Efficient resolution of homochiral diols

Used as precursor of methyl jasmonates

Enzymes and green chemistry

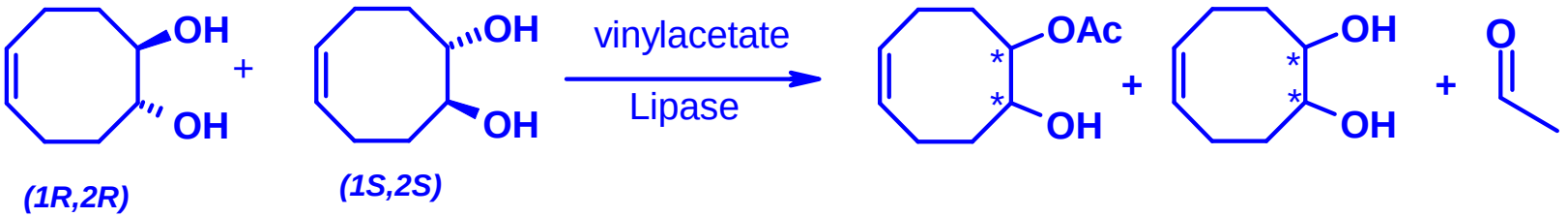
Use of enzymes :

- Chimioselectivity
- Enantioselectivity
- Reusability



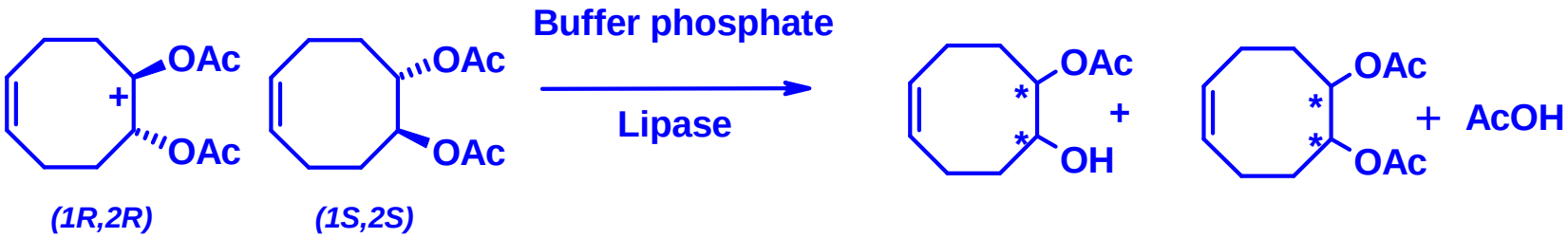
- Efficient catalyst for green chemistry
- The activity/selectivity depend on the reaction conditions

Resolution of rac-diol and rac-diacetate



(1R,2R) *(1S,2S)*

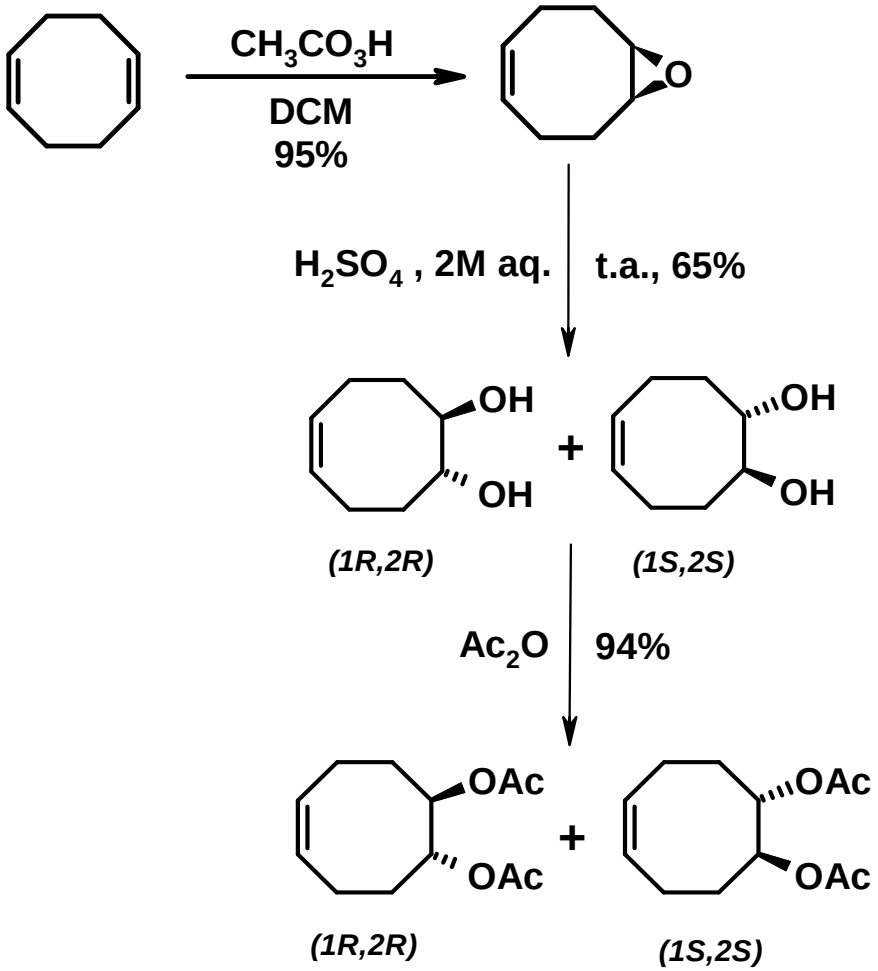
Resolution by acetylation

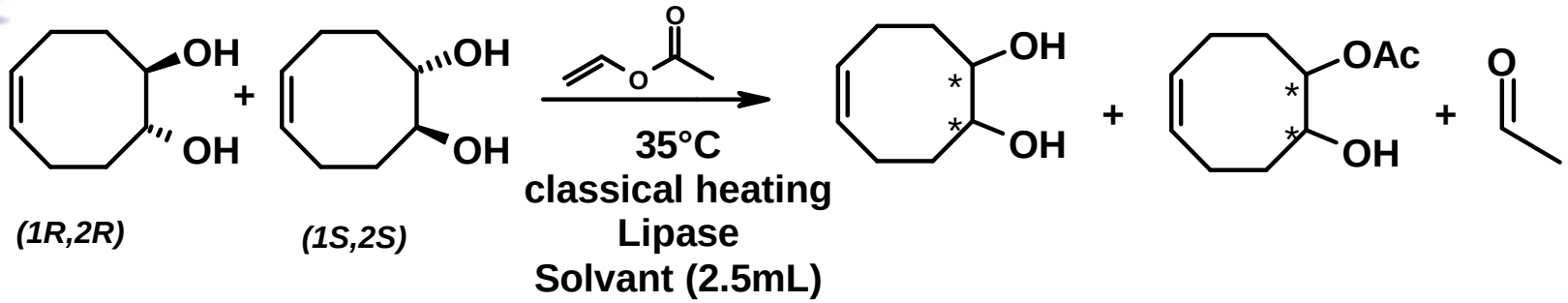


(1R,2R) *(1S,2S)*

Resolution by hydrolysis

Synthesis of rac-diacetate and rac-diols

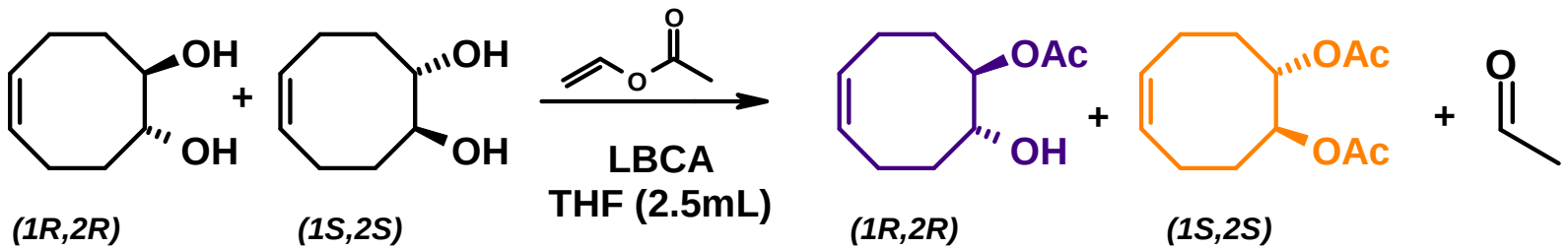




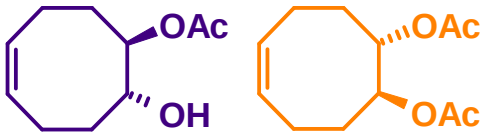
(1R,2R) *(1S,2S)*

Lipase	c (%)	Diol ee (%)	Monoacetate ee (%)
Aspergillus carneus	3	2	50 *(S,S)*
Rhizopus niveus	4	5	38 *(S,S)*
Rhizopus arrhizus	-	-	-
Muccor miehei	-	-	-
Candida cylindracea	-	-	-
Candida antarctica	8	4	50 *(R,R)*
Pseudomonas cepacia	17	12	60 *(S,S)*
Candida antarctica immobilisée (acrylique)	16	9	55 *(R,R)*
Pseudomonas cepacia immobilisée (diatomée)	26	12	57 *(S,S)*

Lipase-catalyzed desymmetrization of rac-diol

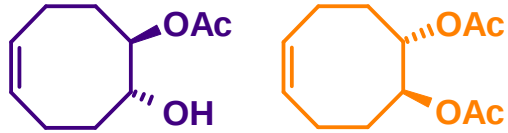


Classical heating versus Microwave irradiation



Temperature (°C)	Time (day)	Yield (%)	ee (%)	Yield (%)	ee (%)
35	22	28	42	6	>99,9
50	7	30	50	**20**	>99,9

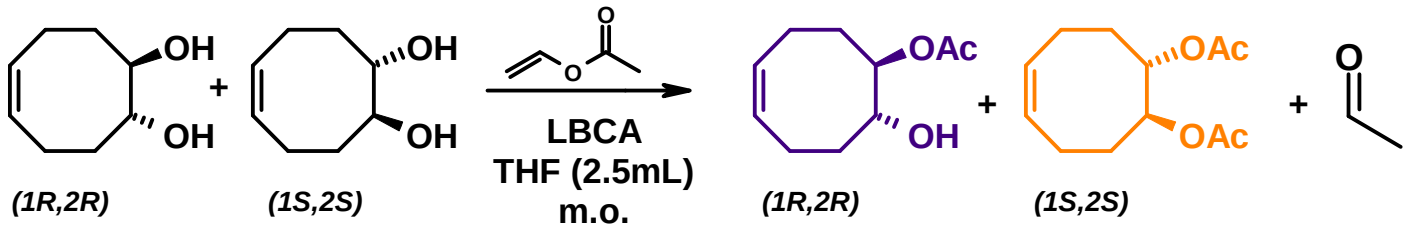
MW open vessel (10W), 14h



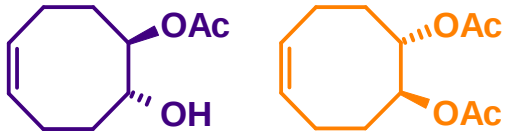
Yield (%)	ee (%)	Yield (%)	ee (%)
58	**55**	**37**	**>99,9**

Optimisation of reaction

Lipase-catalyzed desymmetrization of rac-diol



Influence of temperature

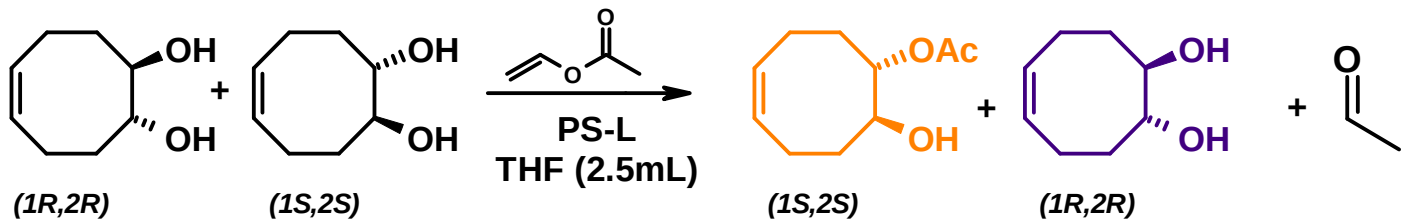


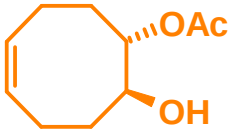
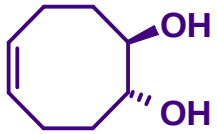
Temperature (°C)	Temps (h)	Yield (%)	ee (%)	Yield (%)	ee (%)
50 (10W)	**14**	**58**	**55**	**37**	**99**
80 (45W)	7	55	57	30	94
100 (syst. fermé, 40W)	7	-	-	-	-
35 (300W)	7	42	67	2	99

Thermal denaturation of enzyme

Diol 51% ee: 50%

Use of free PS

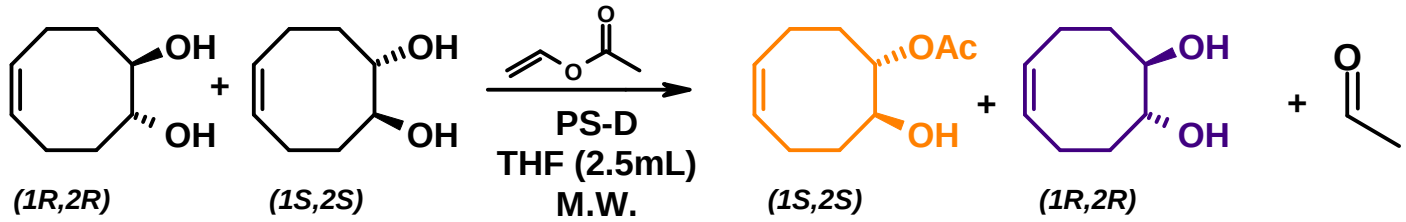


		 (1S,2S)		 (1R,2R)	
Temperature (°C)	**Time (j)**	**Yield (%)**	**ee (%)**	**Yield (%)**	**ee (%)**
35°C	**21**	**55**	**0**	**45**	**0**
55°C	7	47	0	51	0

Good conversion

No selectivity at all !

Use of immobilized PS

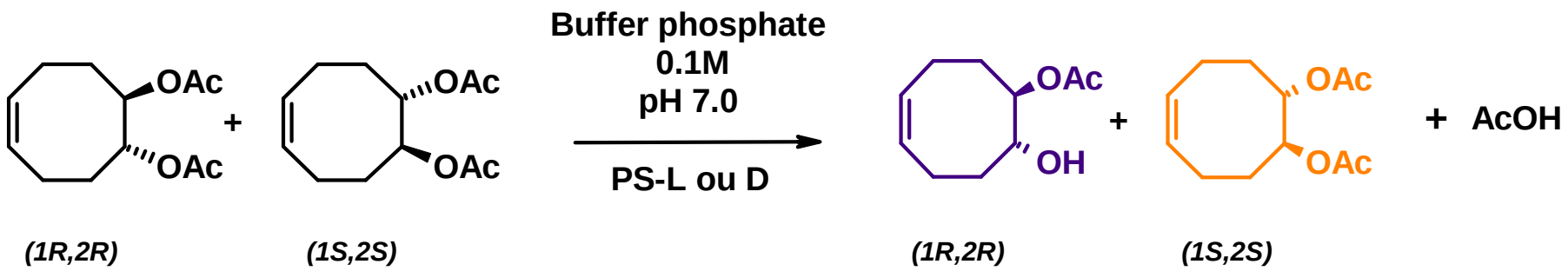


		OAc, OH (1S,2S)		OH, OH (1R,2R)	
Temperature (°C)	**Time (h)**	**Yield (%)**	**ee (%)**	**Yield (%)**	**ee (%)**
50 (15W)	**14**	**41**	**57**	**58**	**35**
80 (35W)	7	12	35	66	5
100 (closed vessel)	7	-	-	-	

Modulation of selectivity

High and fast thermal denaturation

Resolution by hydrolysis under MW irradiation



PS-L	35°C		15j	34%	ee : 99%	ee 99%
PS-L	35°C	(MW)	14h	-		
PS-D	35°C	(MW)	14h	-		-
PS-D	**50°C**	**(15W)**	**14h**	**10%**	**ee 81%**	**90% ee: 28%**

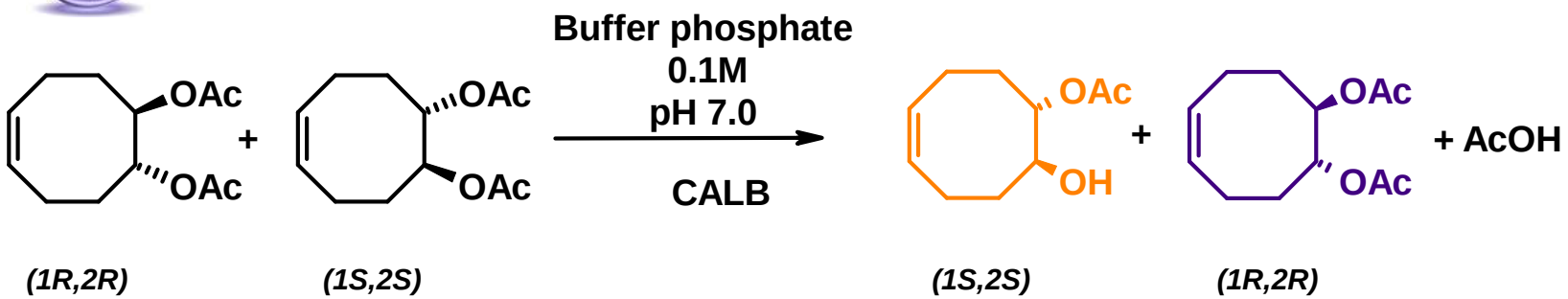
$[\alpha]_D$ = - 5.1°
(c=1.0 $CHCl_3$)

$[\alpha]_D$ = - 21°
(c=1.0 $CHCl_3$)

1rst Enantio-enrichment: 35% ee: 70%

$[\alpha]_D$ = - 52°
(c=1.0 $CHCl_3$)

Resolution by hydrolysis under MW irradiation



35°	4j	17%	ee : 67%	diol: 3%
35°	14h	-		
50° (15W)	**14h**	**20%**	**ee : 97%**	**80% ee 34%**
80°	7-14h	-		

Open vessel (25W) closed vessel (35W)

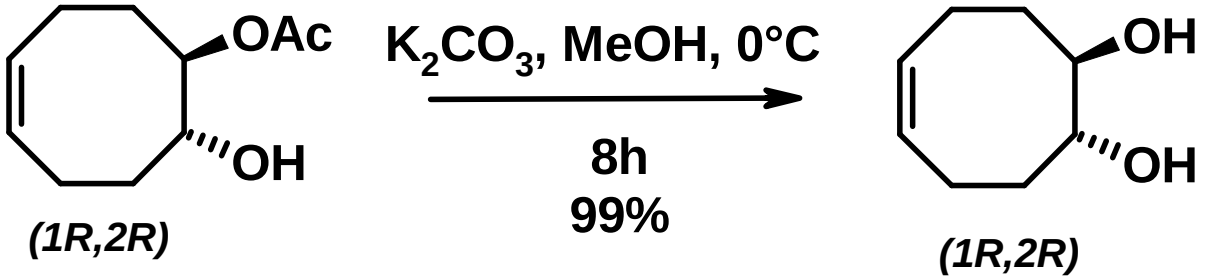
20 %
ee : 97%
$[\alpha]_D$ = + 5,6°
(c=1.0 $CHCl_3$)

80%
ee : 34%
$[\alpha]_D$ = +26°
(c=1.0 $CHCl_3$)

Enantio-enrichment 50°C (15W): 47% ee: 99%

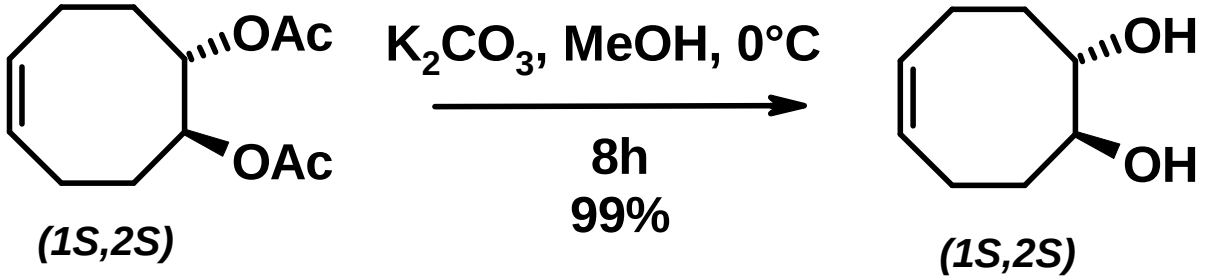
Control of the reaction selectivity by the choose of enzyme

Enantiopure homochiral diols



(1R,2R) *(1R,2R)*

$[\alpha]_D$ = -21°
(c = 1.0 $CHCl_3$)

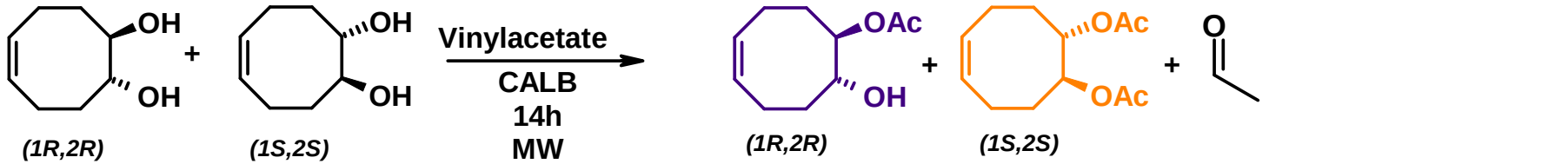


(1S,2S) *(1S,2S)*

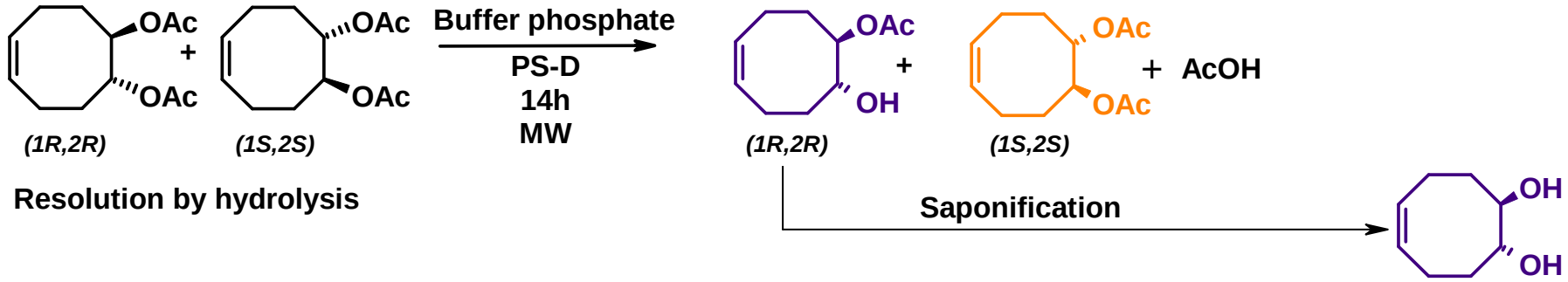
$[\alpha]_D$ = +20.8°
(c = 1.0 $CHCl_3$)

Conclusion

Optimisation d'une résolution enzymatique. Par choix judicieux des conditions :



Diol *(1S,2S)* Yield. 37 % under MW



Resolution by hydrolysis

Diol *(1R,2R)* Yield 20% under MW.


LIENSs
Littoral ENvironnement et Sociétés
cnrs
La Rochelle
UNIVERSITÉ

Thank you