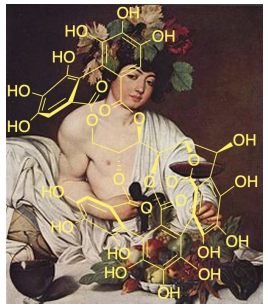

Les Ellagitannins
Des Polyphénols Bioactifs du Bois de Chêne au Vin

Stéphane Quideau, Ph.D., Prof.
Membre Sénior de l'IUF
Université de Bordeaux
Institut des Sciences Moléculaires (UMR-CNRS 5255)
Talence, France

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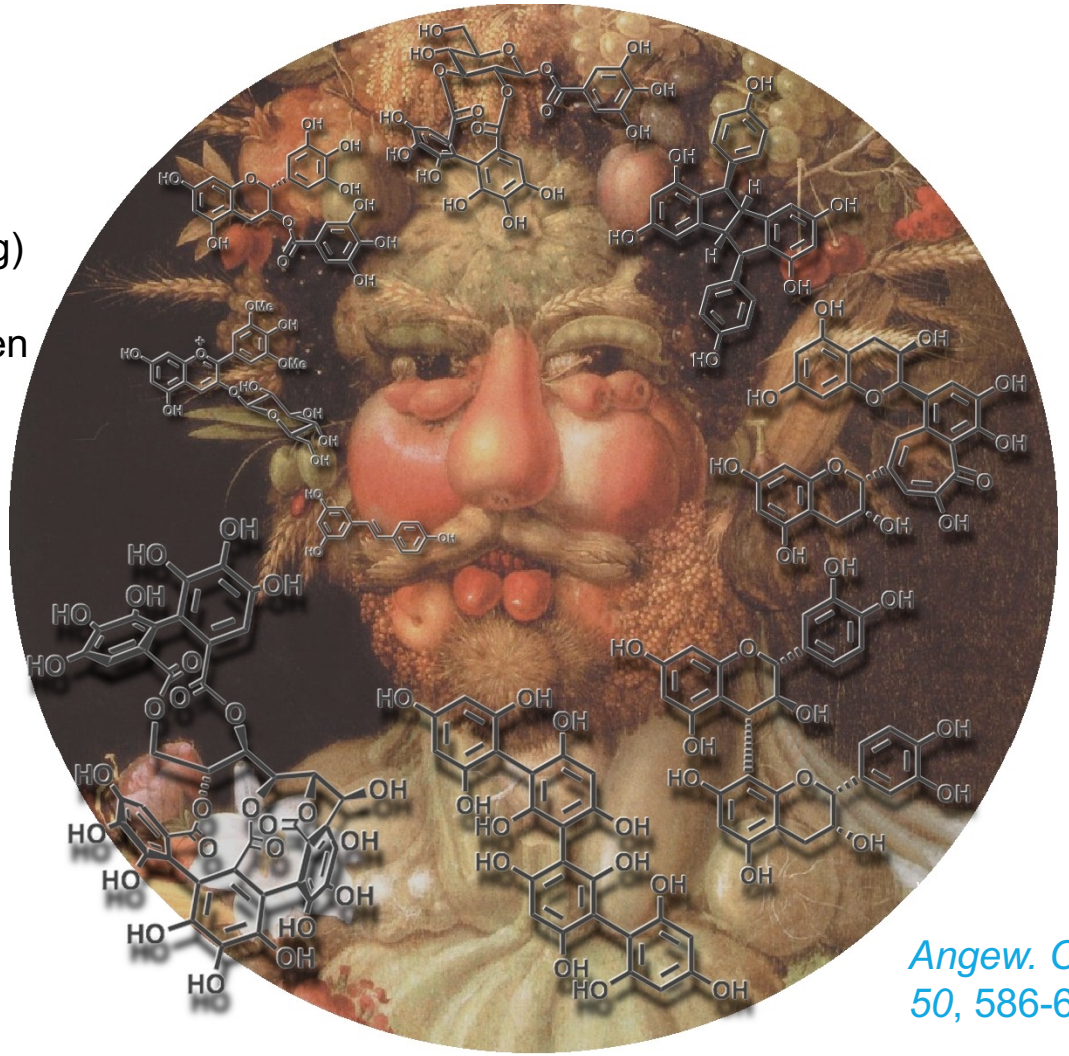
Stéphane Quideau, Ph.D., Prof.

Plant Polyphenols
Natural Products with a Thousand of Virtues

Painting by Giuseppe Arcimboldo (1527-1593) representing a portrait of Rudolf II (Holy Roman Emperor, House of Habsburg) as Vertumnus (roman god of seasons, plant growth, garden and fruit trees) and made entirely of fruits, vegetables and flowers.



Angew. Chem. Int. Ed. **2011**, *50*, 586-621

(Our) Definition: Polyphenols are plant secondary metabolites derived exclusively from the shikimate-derived phenylpropanoid and/or the polyketide pathway, featuring more than one phenolic ring and deprived of any nitrogen-based functional group in their most basic structural expressions.

A variety of structural classes

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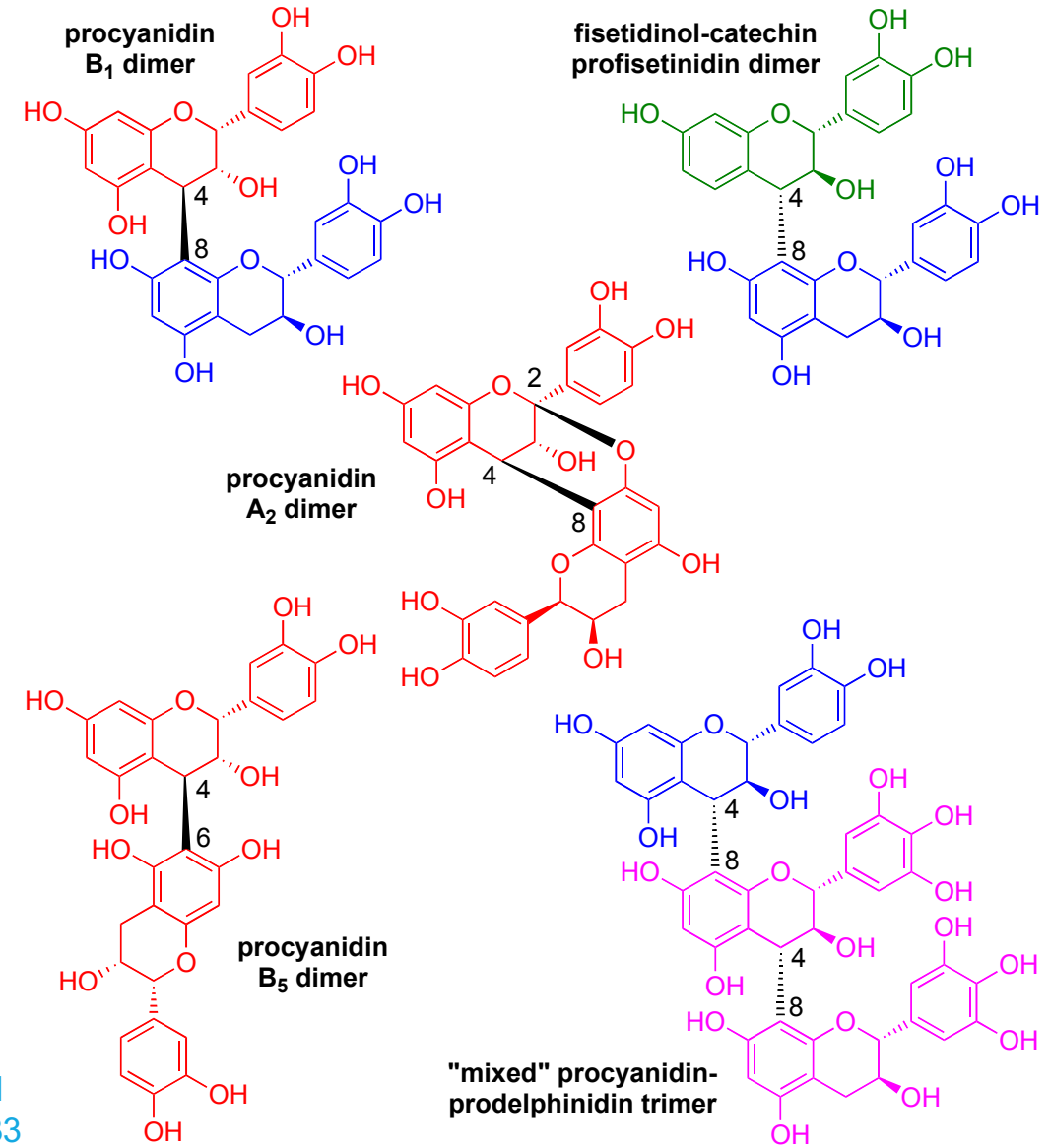
Proanthocyanidins (syn. condensed tannins)

Proanthocyanidins, such as procyanidins, prodelphinidins and profisetinidins, are derived from the oligo/polymerization of flavan-3-ol units such as epicatechin, catechin, fisetinidol and gallocatechin.

These flavan-3-ol units are linked principally through their 4 and 8 positions. Oligomers containing two to five or six units are water soluble. Higher oligomers and polymers are insoluble.

Procyanidins and prodelphinidins are the most commonly found types of proanthocyanidins.

These polyphenols occur in both dicotyledonous and monocotyledonous angiosperms (flowering plants) and are of universal occurrence in gymnosperms and pteridophytes.



Ferreira, D.; Slade, D. *Nat. Prod. Rep.* **2002**, *19*, 517-541
Ferreira, D.; Bekker, R. *Nat. Prod. Rep.* **1996**, *13*, 411-433

Flavo/flavanoids

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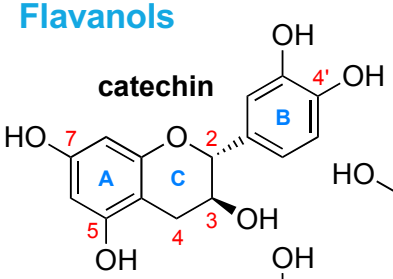
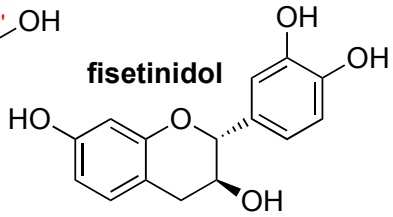
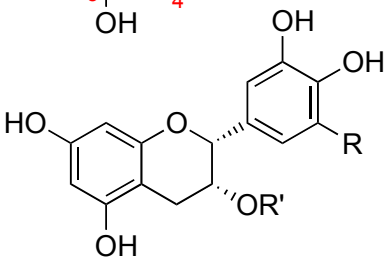
Many other simpler plant phenolics can be defined as “true” plant polyphenols as long as they feature at least two phenolic moieties in agreement with our (bio)chemically based definition of plant polyphenols. Among those are the numerous (more than 8000 structures) flavo/flavanoids, which are all derived from the phenylpropanoid/polyketide hybrid biosynthetic pathway.

Flavanols

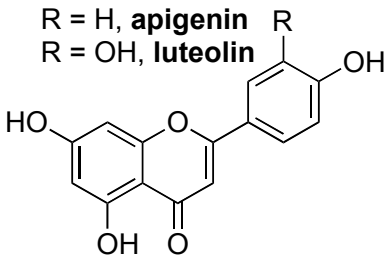




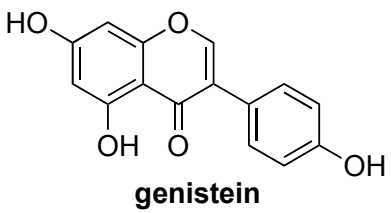


R = R' = H, **epicatechin** (EC)
R = OH, R' = H, **epigallocatechin** (EGC)
R = H, R' = galloyl, **epicatechin gallate** (ECG)
R = OH, R' = galloyl, **epigallocatechin gallate** (EGCG)

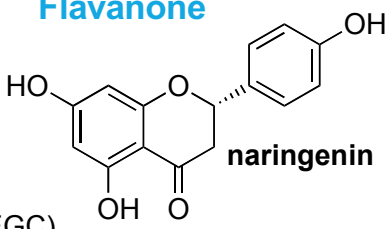
Flavones



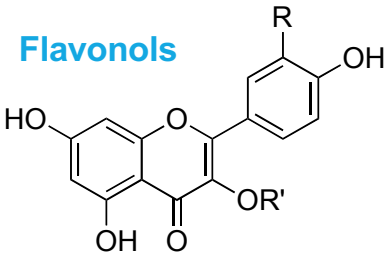
Isoflavone



Flavanone

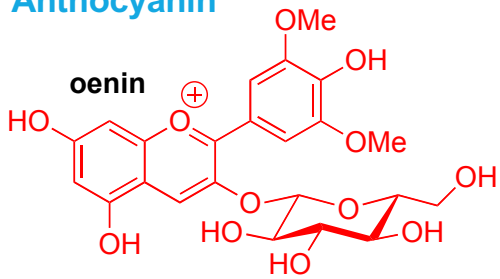


Flavonols

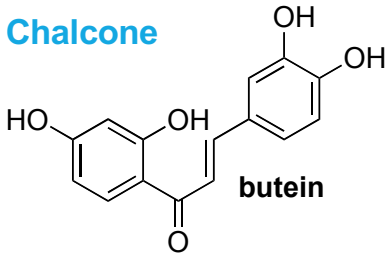


R = R' = H, **kaempferol**
R = OH, R' = H, **quercetin**
R = OH, R' = α-L-Rha-1,6-β-D-Glc, **rutin**

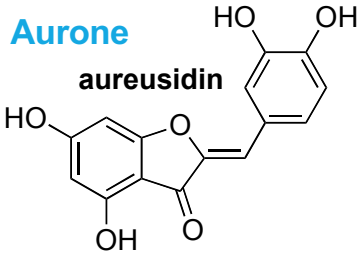
Anthocyanin



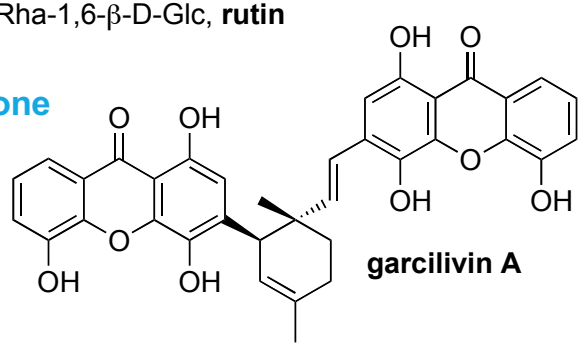
Chalcone



Aurone



Xanthone



Andersen, Ø. M.; Markham, K. R. *Flavonoids – Chemistry, Biochemistry and Applications*. CRC/Taylor & Francis: Boca Raton, **2006**

Phlorotannins

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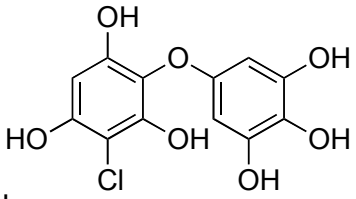
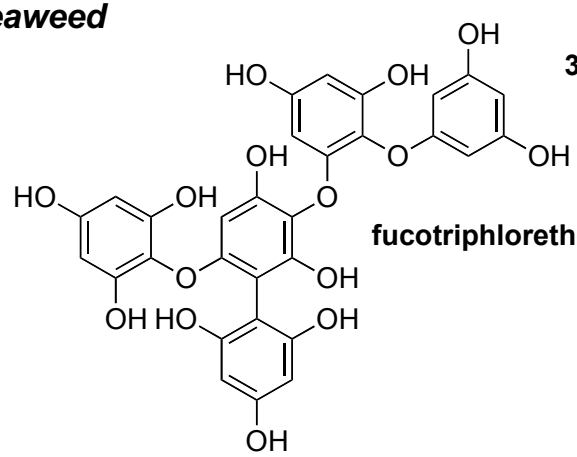
These polyphenols are isolated from several genera of red and brown algae.

Their building unit is phloroglucinol (1,3-5-trihydroxybenzene). The oligomerization of this simple phenol by oxidative coupling processes leads to various structures featuring C–C biaryl and C–O diaryl ether bonds.

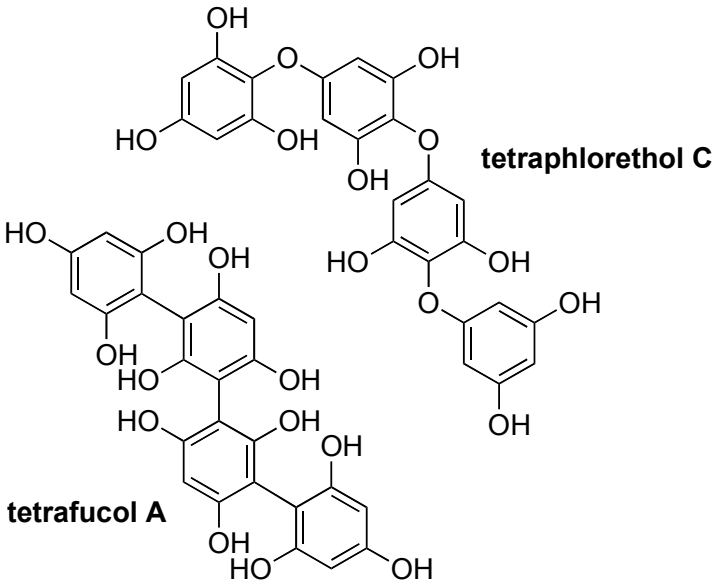
Cystophora retroflex
a brown seaweed



3[A]chlorobifuhalol



fucotriphlorethol H



tetraphlorethol C

tetrafucol A

Sailler, B.; Glombitza, K. *Phytochemistry* **1999**, *50*, 869-881
Stern, J. L.; Hagerman, A. E.; Steinberg, P. D.; Mason, P. K. *J. Chem. Ecol.* **1996**, *22*, 1877-1899

Polyhydroxystilbenoids

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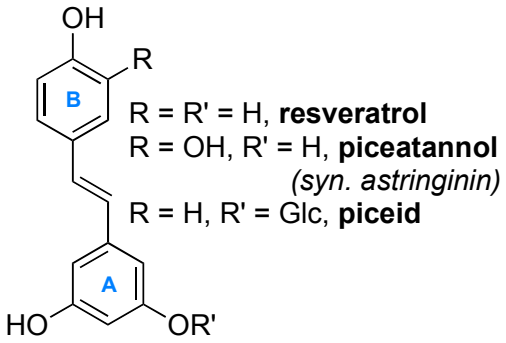
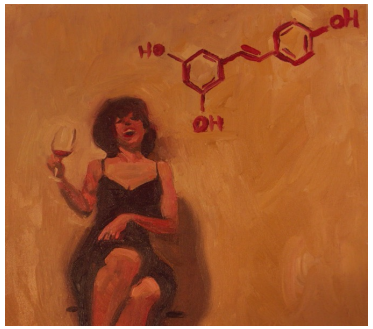
The hybrid phenylpropanoid/polyketide metabolic pathway also leads to another important class of polyphenolic substances, the **polyhydroxystilbenes**. The most famous example of which is without a doubt the phytoalexin ***trans*-resveratrol** (3,5,4'-trihydroxy-*trans*-stilbene). In recent years, this compound has been the focus of much scientific attention and media exposure – **« resveratrol buzz »** – following its biological evaluation as a cancer chemopreventing agent and as an activator of « longevity » proteins called sirtuins, and because of its presence in **red wine**.

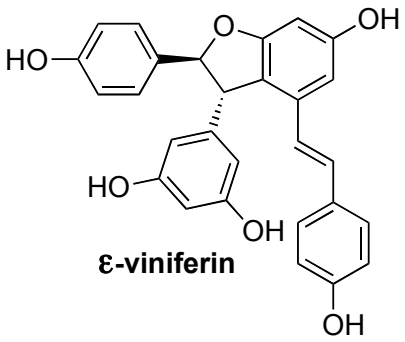
Phenolic oxidative coupling reactions initiate other chemical transformations leading to numerous resveratrol-derived derivatives.



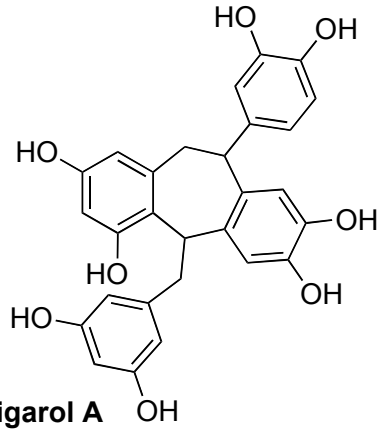
R = R' = H, **resveratrol**
R = OH, R' = H, **piceatannol**
(syn. astringinin)
R = H, R' = Glc, **piceid**



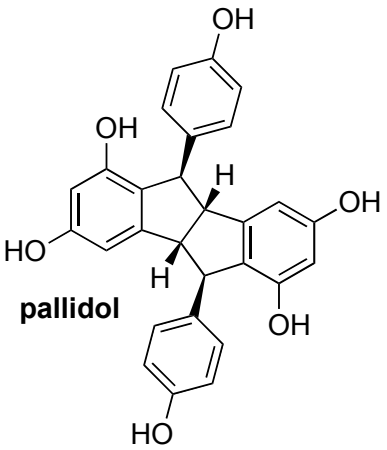
I Know God Loves Me Because He Created Resveratrol (by the American artist Tracy Villa Carrera)



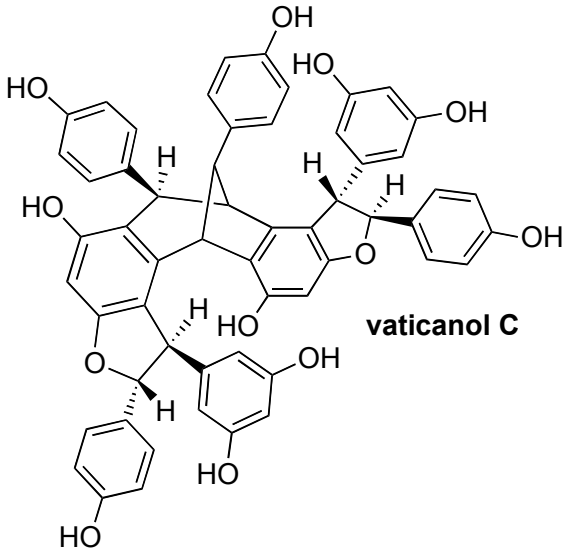
ε-viniferin



cassigarol A
(unassigned stereochemistry)



pallidol



vaticanol C

Lin, M.; Yao, C.-S. Natural Oligostilbenes. In: *Studies in Natural Products Chemistry, Vol. 33*, Atta-ur-Rahman (Ed.); Elsevier: Amsterdam, **2006**, pp. 601-644
Nicotra, S. *et al. Tetrahedron* **2004**, *60*, 595-600

Gallo- and Ellagitannins (hydrolyzable tannins)

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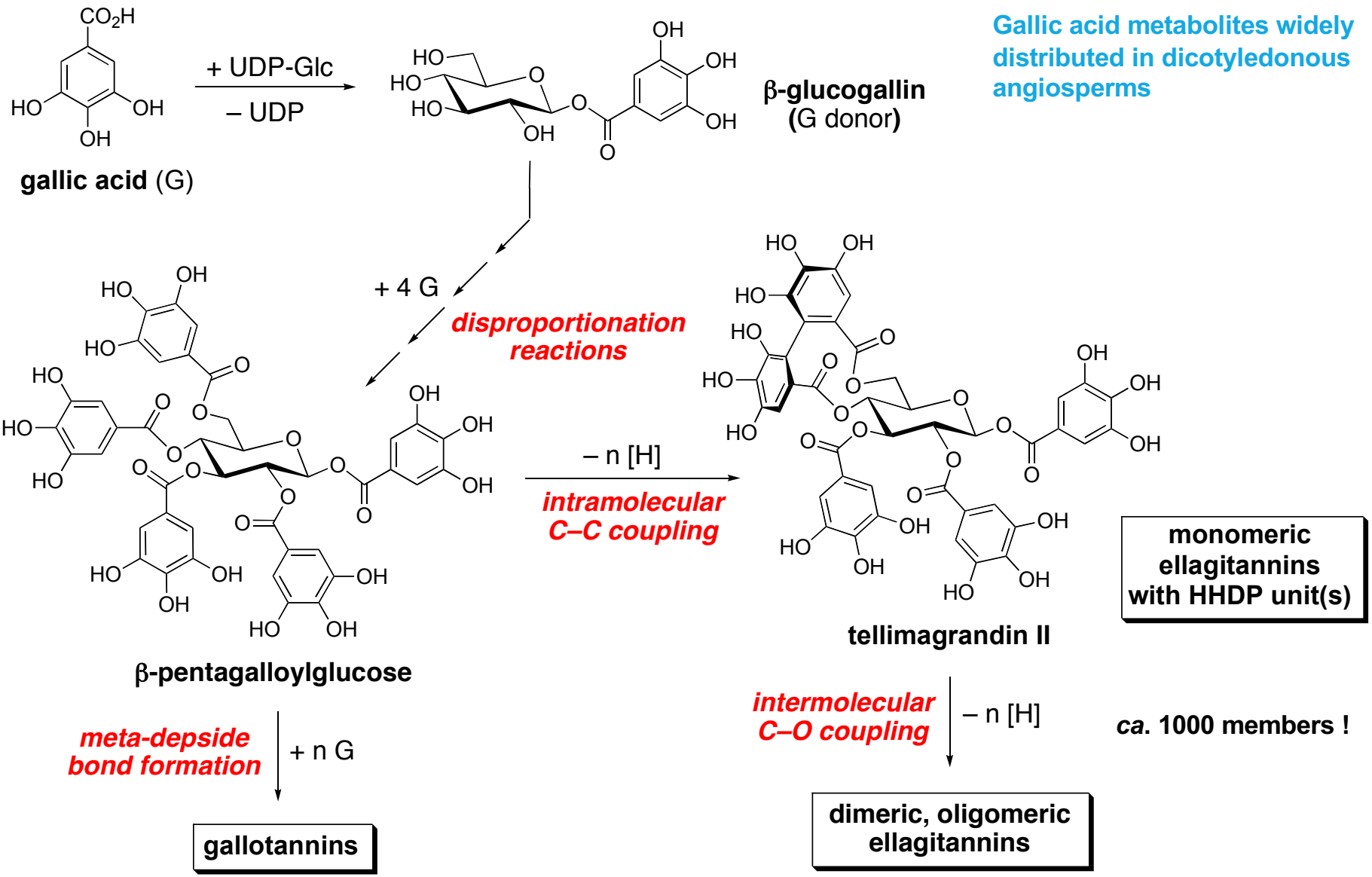

Haslam, E. *Prog. Chem. Org. Nat. Prod.* **1982**, *41*, 1-46
Niemetz, R.; Gross, G. G. Phytochemistry **2001**, *58*, 657-661
Haslam, E.; Cai, Y. *Nat. Prod. Rep.* **1994**, *11*, 41-66
Quideau, S.; Feldman, K. S. *Chem. Rev.* **1996**, *96*, 475-503

Gallotannins

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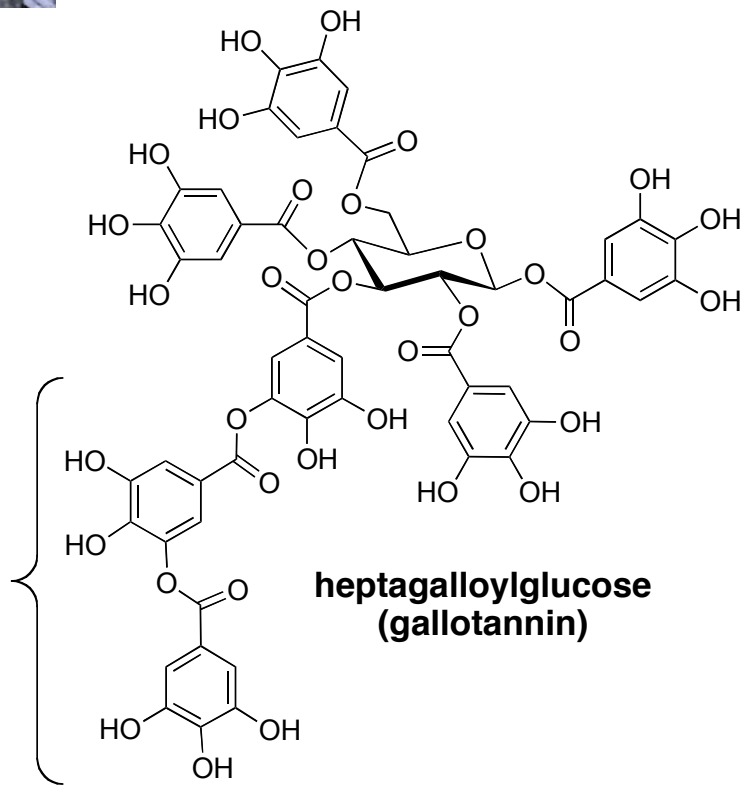
Sumac gallnuts

Oak gallnuts

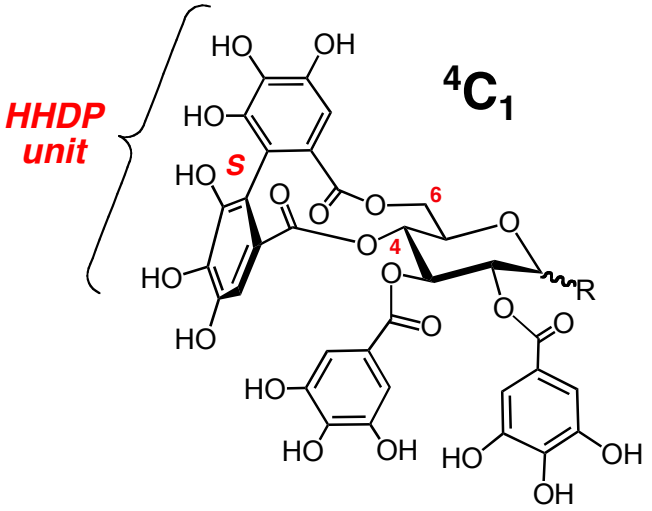


meta-depsidically linked galloyl units

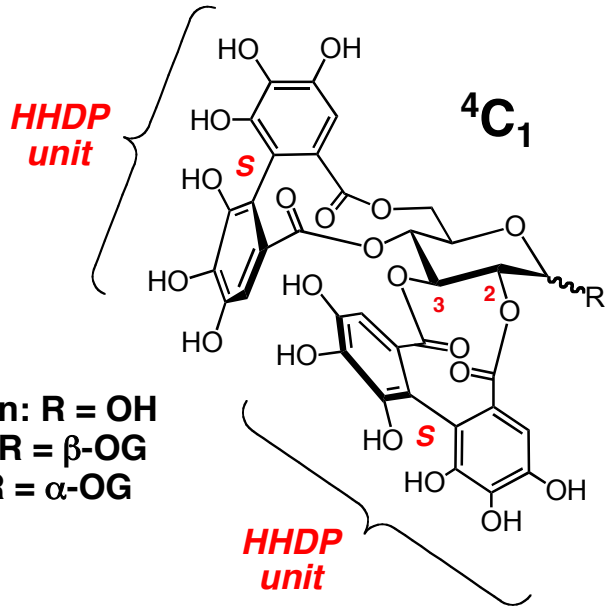
heptagalloylglucose (gallotannin)

Leather tanning in Morocco (Fes)

Monomeric Ellagitannins



tellimagrandin I: R = OH
tellimagrandin II: R = β-OG



pedunculagin: R = OH
casuarictin: R = β-OG
potentillin: R = α-OG

Why bother with plant polyphenols ?

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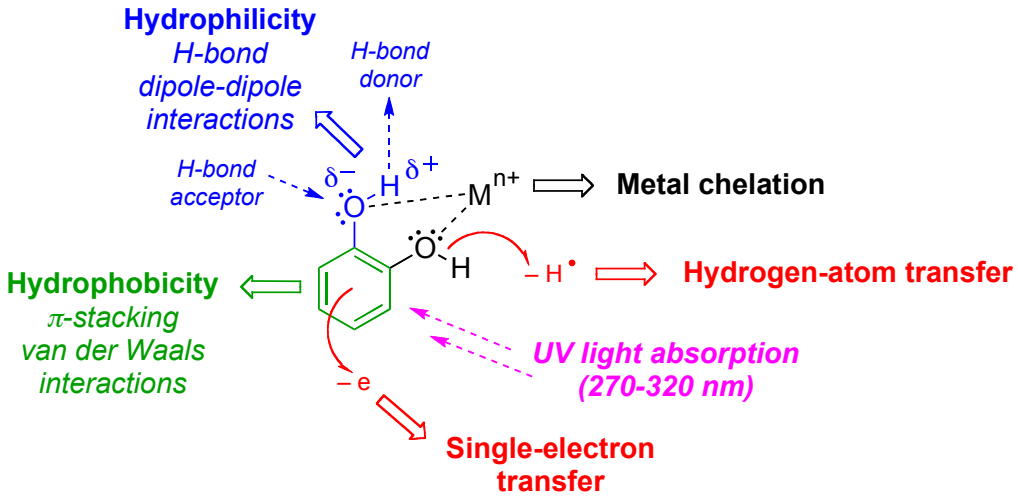
Plant polyphenols exhibit a wide range of bio-physicochemical properties. They are consequently very versatile in their actions as ***specialized metabolites*** and have been shown to play diverse functional roles in **plant resistance**, from protection against animal herbivores and microbial pathogens to **protection against solar radiation**, in **plant nutrition**, **reproduction** and **growth**.

Courtesy from Prof. Vincenzo Lattanzio

Present in many fruits and vegetables, they do impact the nutritional and organoleptic qualities of foods, feeds and beverages derived from these plant products…

… and are often claimed to act as natural (and dietary) chemopreventive agents against age-related cardiovascular, cancer and neurodegenerative human diseases, as well as metabolic disorders such as diabetes.

The origin of the impressive panoply of biological effects that have been attributed to various plant polyphenols acting, for example, as **antifeeding**, **antibiotic**, **antiviral**, **antitumor**, **anti-inflammatory**, **antifibrillogenic**, and **antioxidant agents**, as well as **UV light screens**, can be tracked down to the inherent fundamental physicochemical properties of the phenolic functional group…



hydrophobic nature of its **planar aromatic nucleus**, combined with the **hydrophilic** character of its **polar hydroxy substituent**, render the phenol function **amphiphilic**, thus capable of both **hydrophobic (*e.g.*, π-stacking) interactions** and **hydrogen bond formations with proteins**

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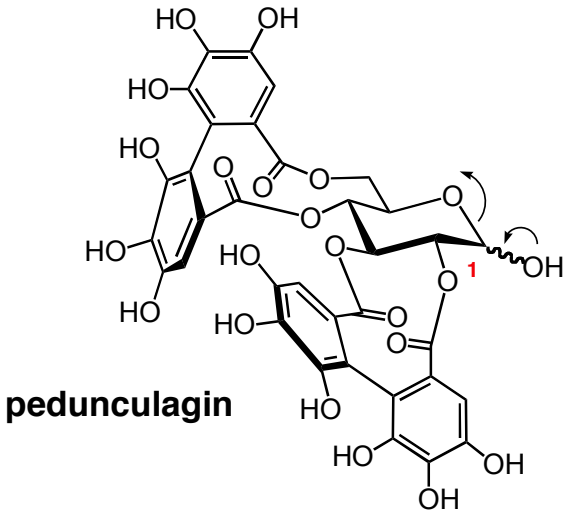
C-Glucosidic Ellagitannins

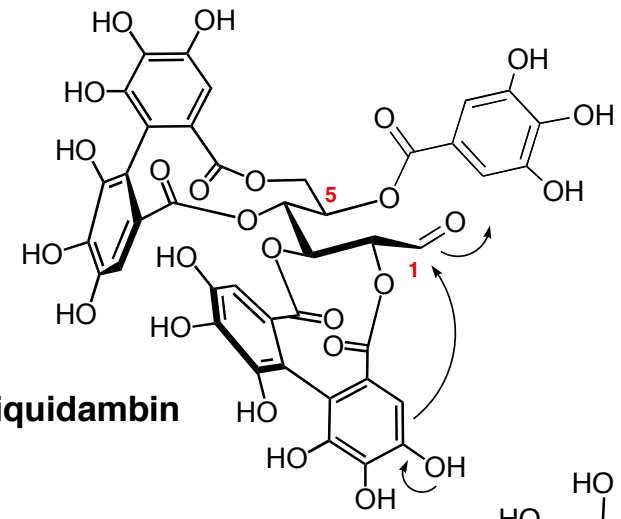
In some plant species, an opening of the glucopyranose ring occurs, which is followed by an intramolecular *C*-glycosylation and further oxidative coupling leading to nonahydroxytriphenoyl (**NHTP**)-bearing ellagitannins.



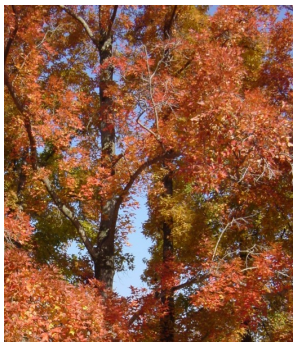
pedunculagin

glucopyranose ring opening

5-O-galloylation

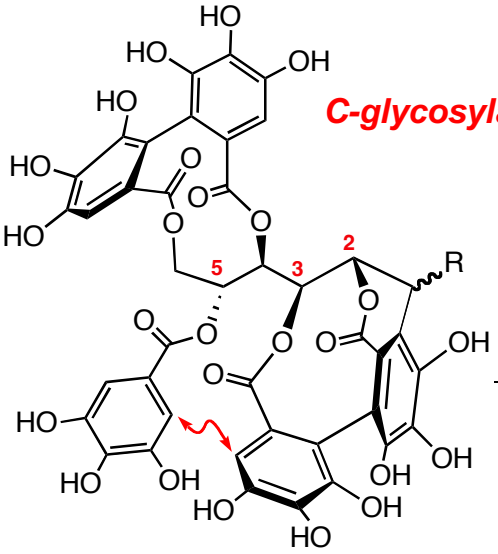


liquidambin



Liquidambar formosana (Hamamelidaceae)

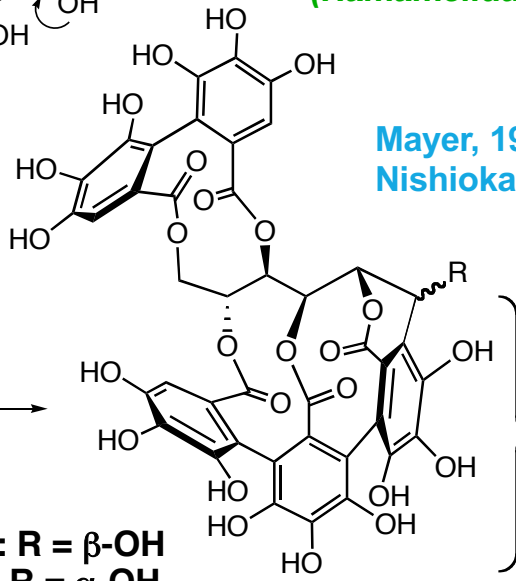
C-glycosylation



stachyurin: R = β-OH
casuarinin: R = α-OH

Mayer, 1971
Nishioka, 1990

oxidative coupling



NHTP unit

vescalagin: R = β-OH
castalagin: R = α-OH

Hatano *et al.*, *Phytochemistry* **1986**, *25*, 2787-2789
Okuda *et al.*, *Phytochemistry* **1987**, *26*, 2053-2055

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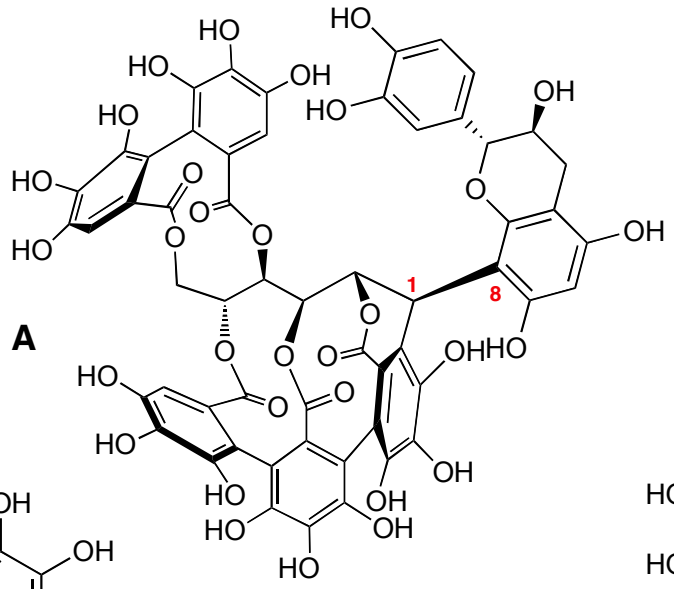
Flavano-ellagitannins

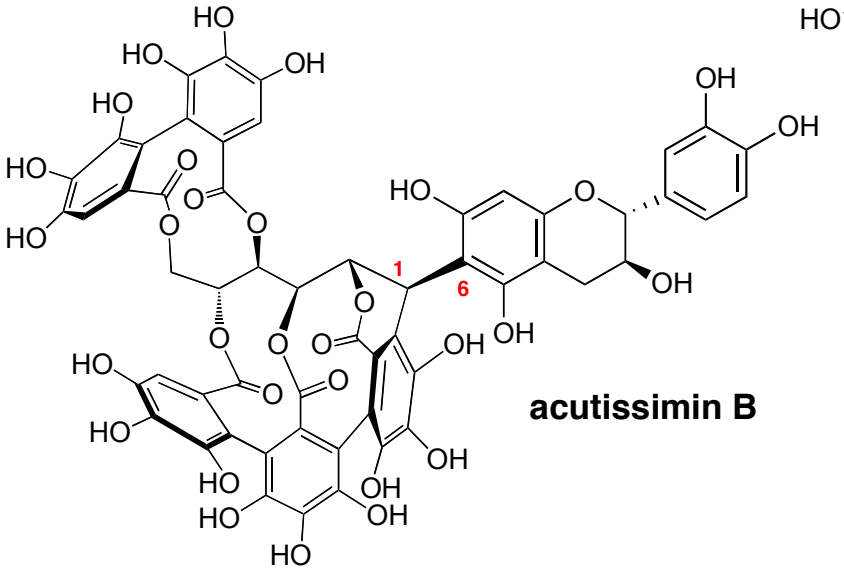
Ishimaru, Nonaka & Nishioka, *Chem. Pharm. Bull.*, **1987**, *35*, 602-610

Bark of Quercus acutissima (Fagaceae)

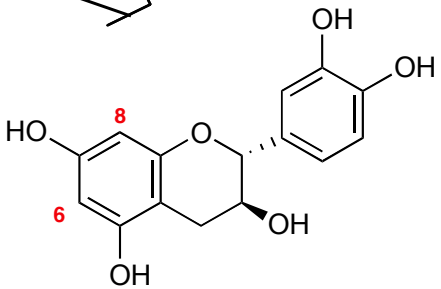
acutissimin A



acutissimin B

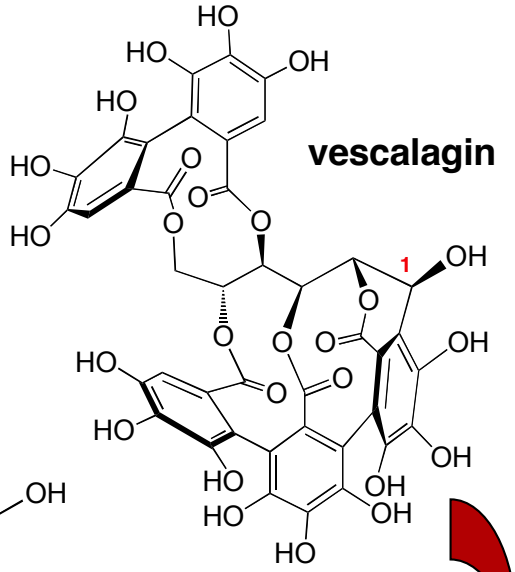


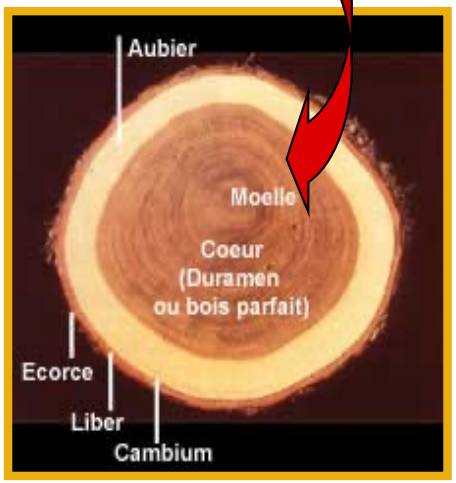
+

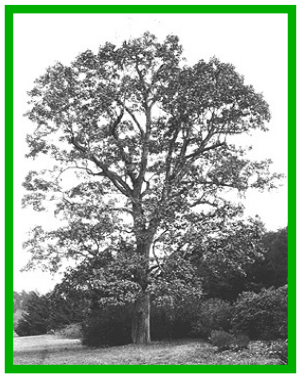


catechin

vescalagin







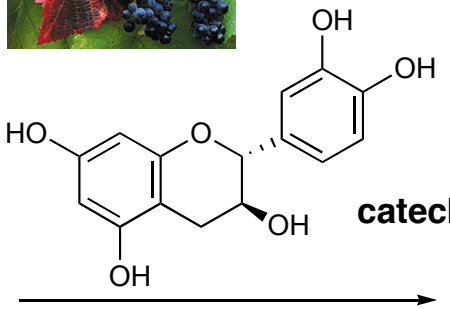
Quercus alba

Quercus petraea

Quercus robur



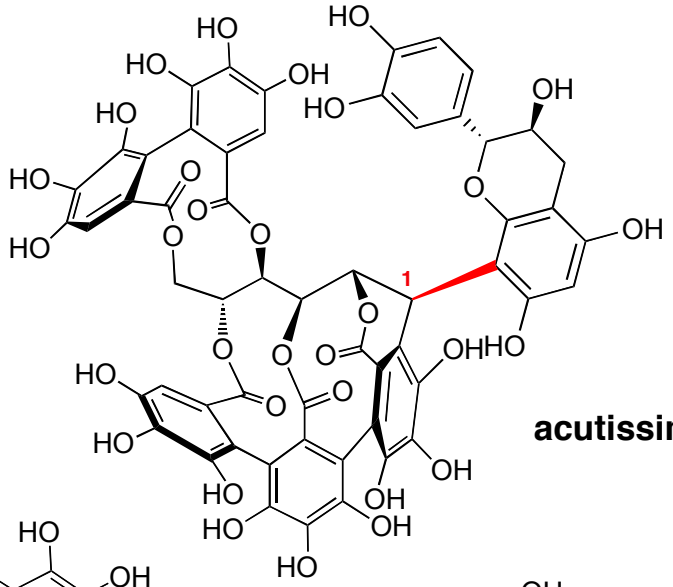

vescalagin



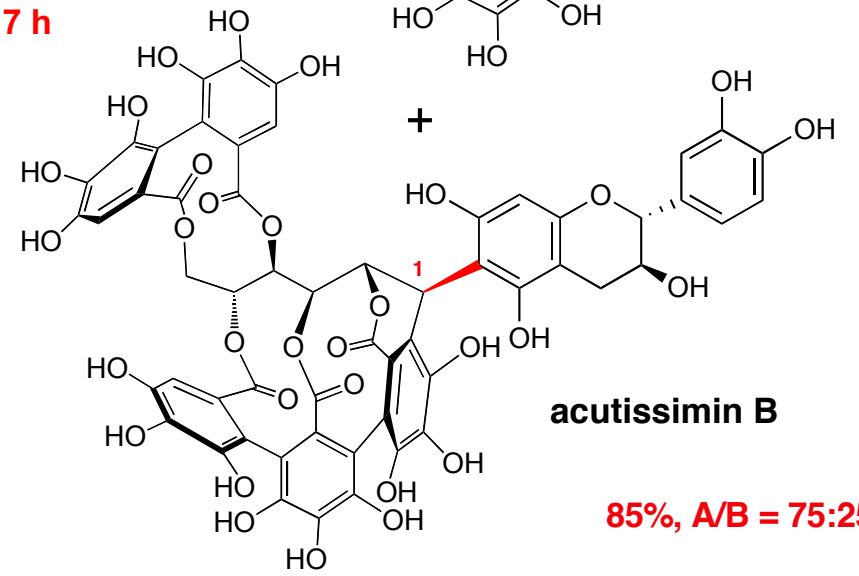
catechin

$+ H^+, - H_2O$

THF/TFA, 60 °C, 7 h



acutissimin A



acutissimin B

retention of configuration at C-1 !

85%, A/B = 75:25

Angew. Chem. Int. Ed. **2003**, *42*, 6012-6014

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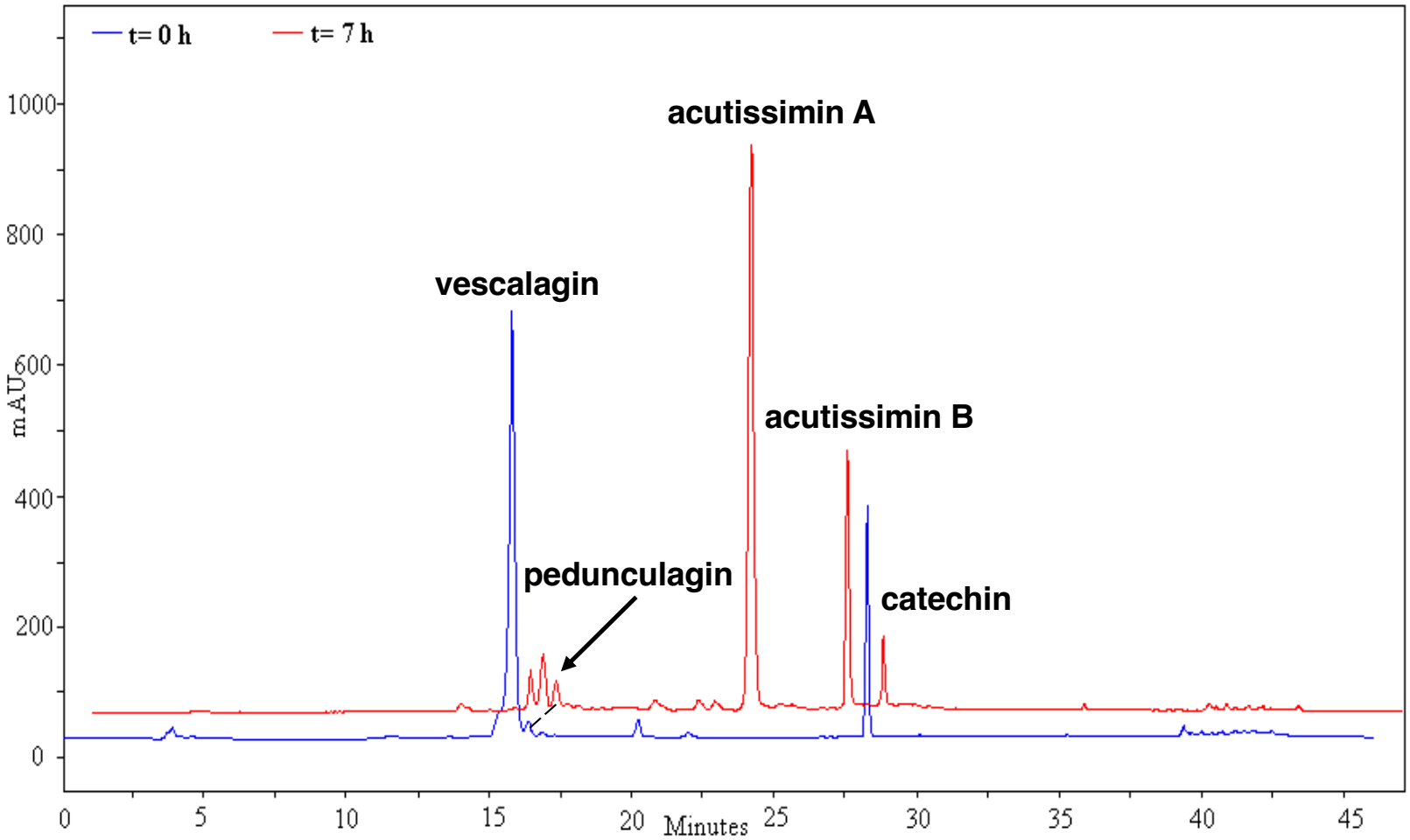
Stéphane Quideau, Ph.D., Prof.

HPLC Monitoring of Acutissimins Formation in an Acidic Organic Solution

(THF, 1% TFA, 60 °C)

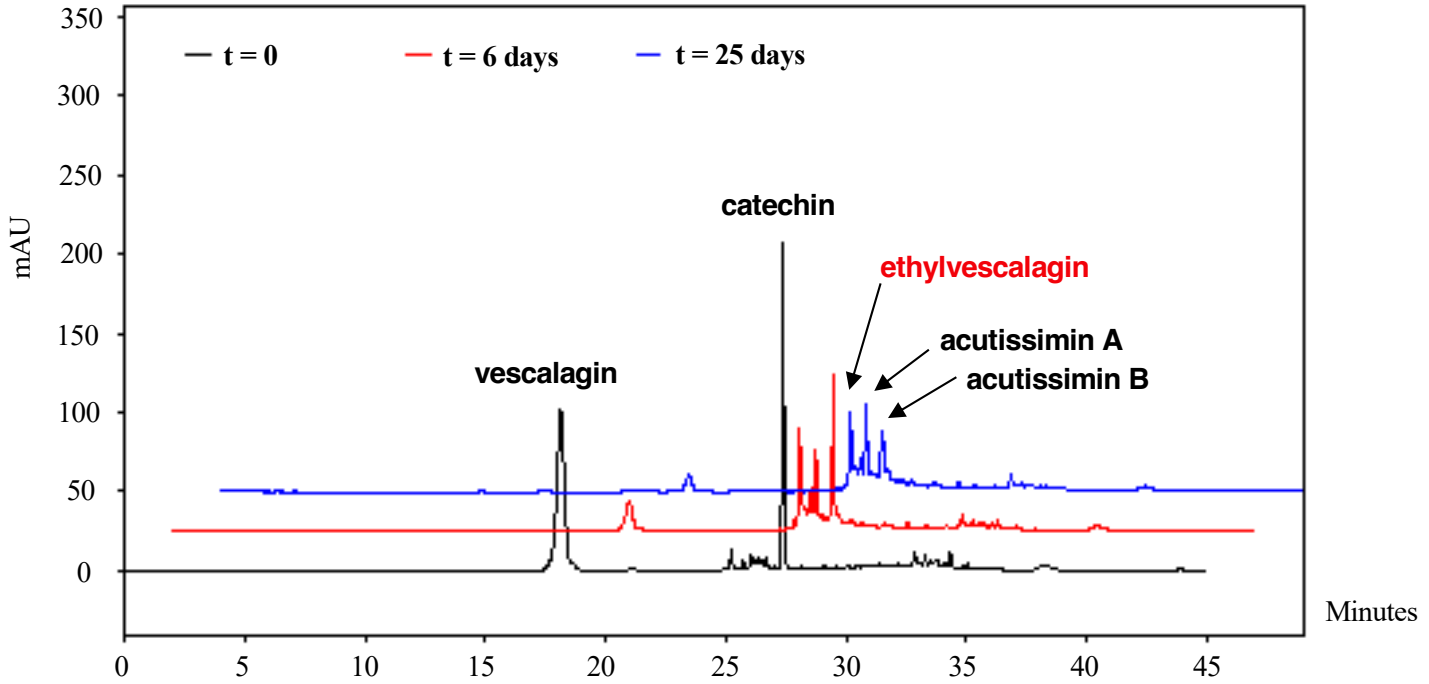


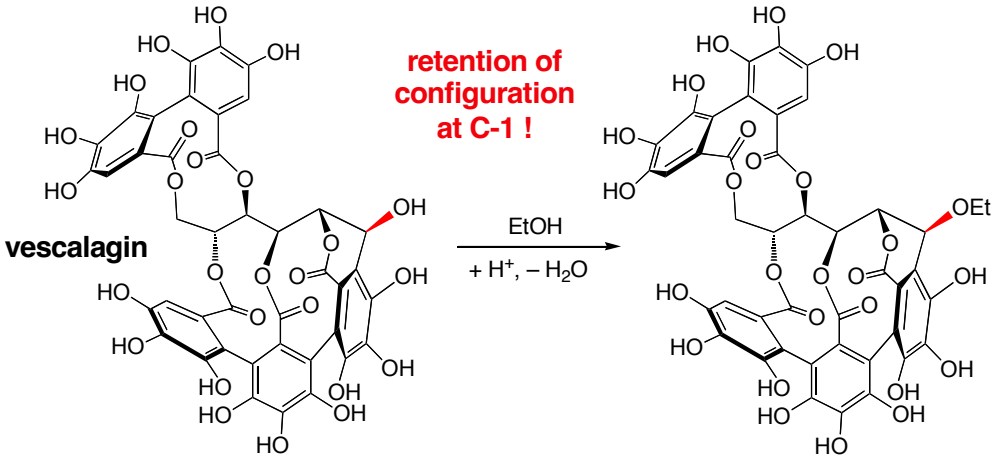
université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.

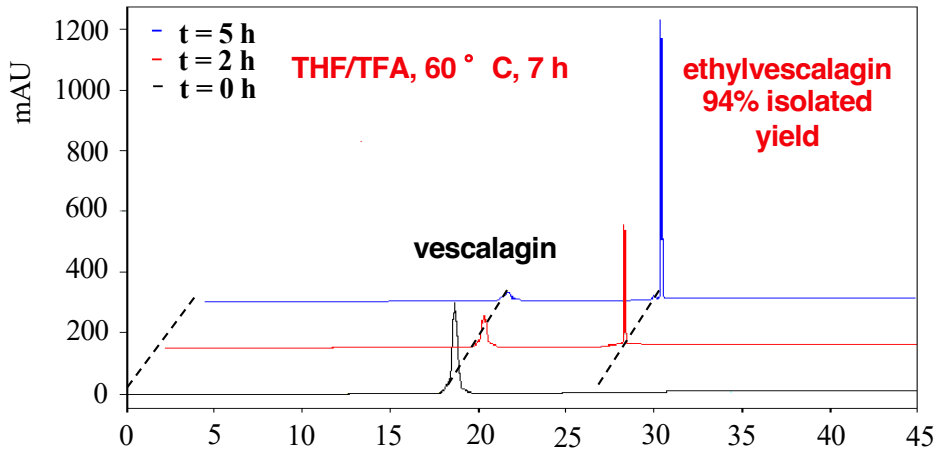
HPLC Monitoring of Acutissimins Formation in a Wine Model Solution

(12% aq. EtOH, 5g/l tartaric acid, pH 3.2)

Chem. Eur. J. **2005**, *11*, 6503-6513







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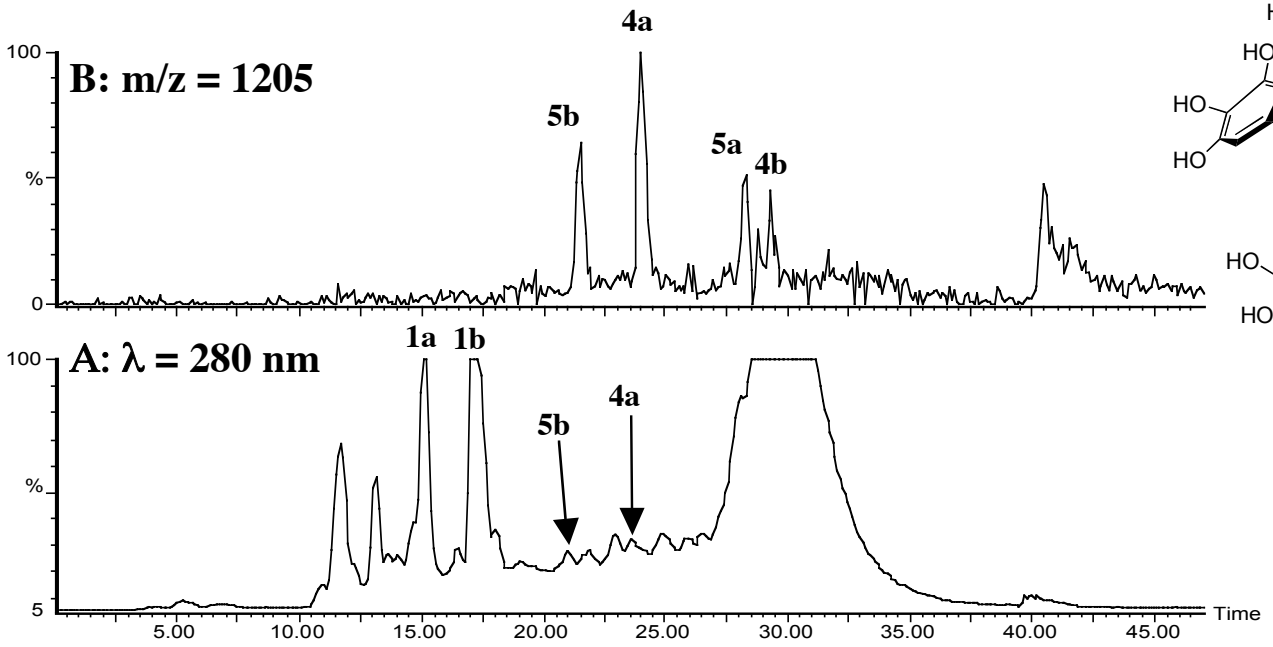
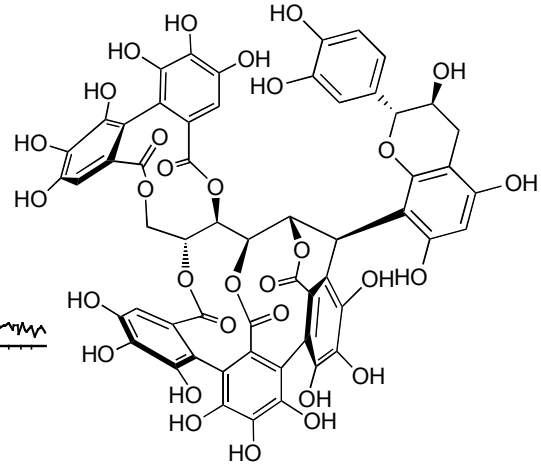
Identification and Quantification of "Acutissimins" in Red Wine Aged in Oak Barrels





MM = 1206 D

HPLC-ESI-MS profiles of a partially purified sample of red wine aged in oak barrels for 18 months :

A: UV detection at 280 nm
B: selective ion trace chromatogram (m/z = 1205, negative mode)

1a: vescalagin (2 mg/L), 1b: castalagin (8 mg/L)
4a: acutissimin A (0.4 mg/L), 4b: acutissimin B (0.28 mg/L)
5a: epiacutissimin A (0.30 mg/L), 5b: epiacutissimin B (0.35 mg/L)

Angew. Chem. Int. Ed. **2003**, *42*, 6012-6014
J. Agric. Food Chem. **2006**, *54*, 7349-7354

Inhibition of Human DNA Topoisomerase II

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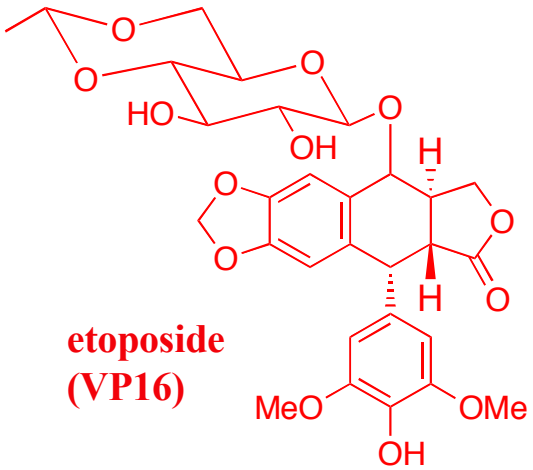
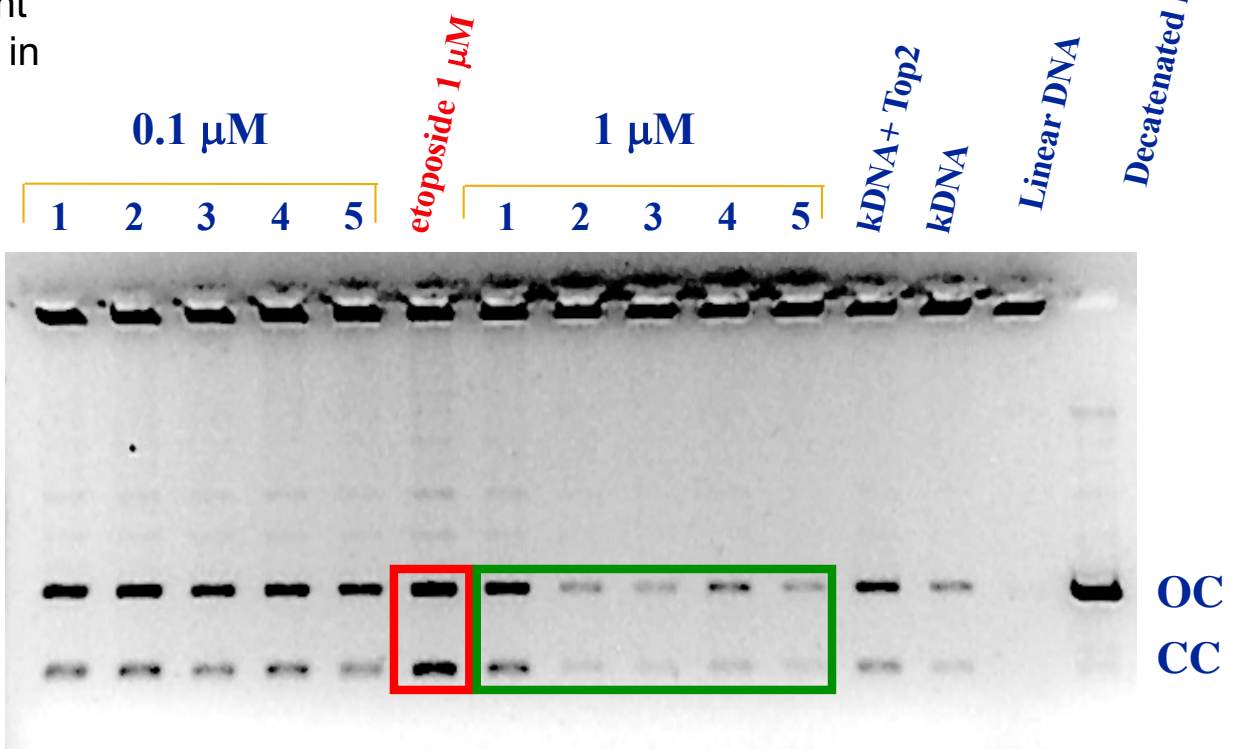
Stéphane Quideau, Ph.D., Prof.

C-glucosidic ellagitannins and their hybrids found and formed during the aging of wines in oak barrels are potent inhibitors of top2, an enzyme targeted in current anticancer chemotherapeutic strategies !

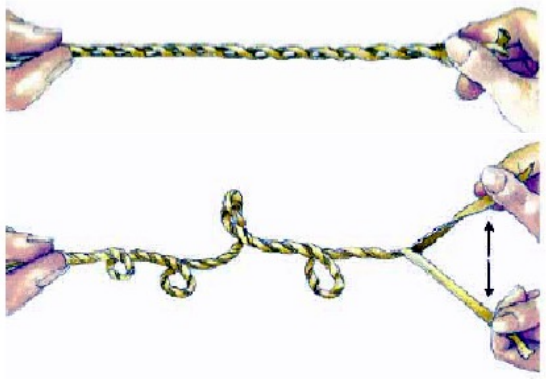
See: Kashiwada *et al.*, *J. Pharm. Sci.* **1993**, *82*, 487-492



etoposide (VP16)



Chem. Eur. J. **2005**, *11*, 6503-6513
Mol. Pharmacol. **2012**, *82*, 134-141
Patent WO2007/003741-A2

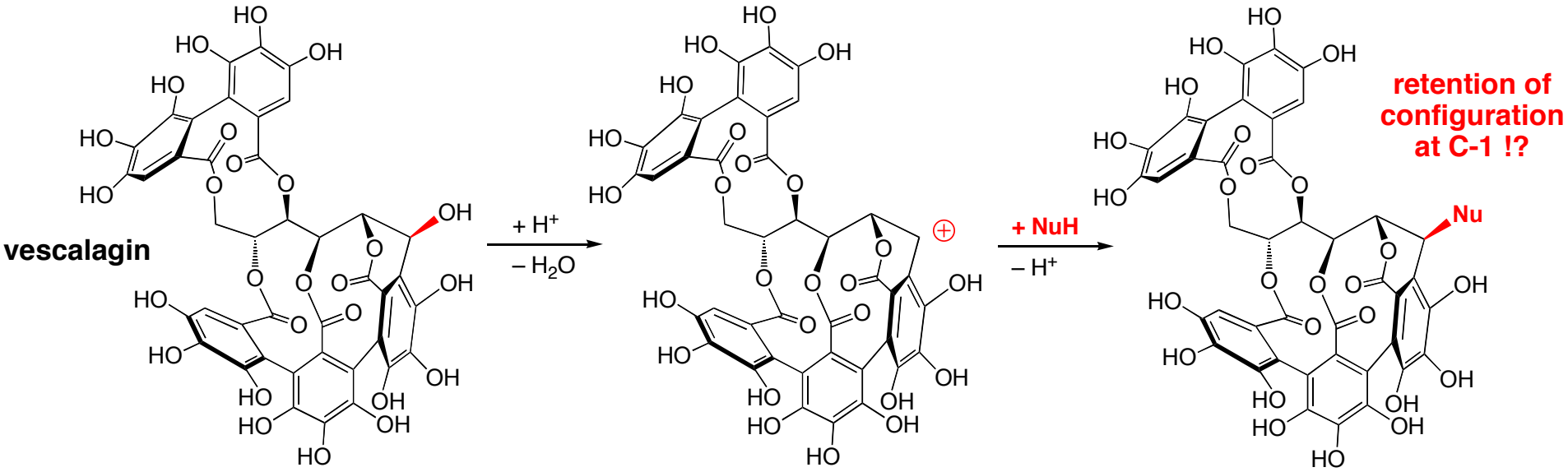


	1 µM	10 µM
etoposide	**3.7**	**6.5**
ethylvescaline	49.3	66.2
acutissimin A	89.2	96.3
acutissimin B	78.8	94.5
epiacutissimin A	72.6	83.3
epiacutissimin B	74.3	97.5
vescalin	**95.5**	**100 !!!**
vescalene	78.8	97.3

Michael Jourdes

université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.

How does it work ? Simply by an Acid-catalyzed S_N1-type Reaction ! This Mechanism is General…



a stable benzylic cation !

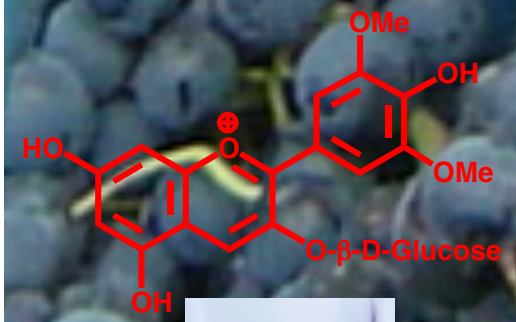
NuH :

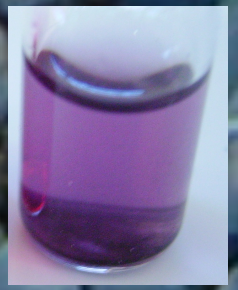
catechin via its carbon 8 or 6	⟹	acutissimin A and B
epicatechin via its carbon 8 or 6	⟹	epiacutissimin A and B
ethanol	⟹	β-1-*O*-ethylvescalagin
any NuH species !	⟹	other vescalagin derivatives…

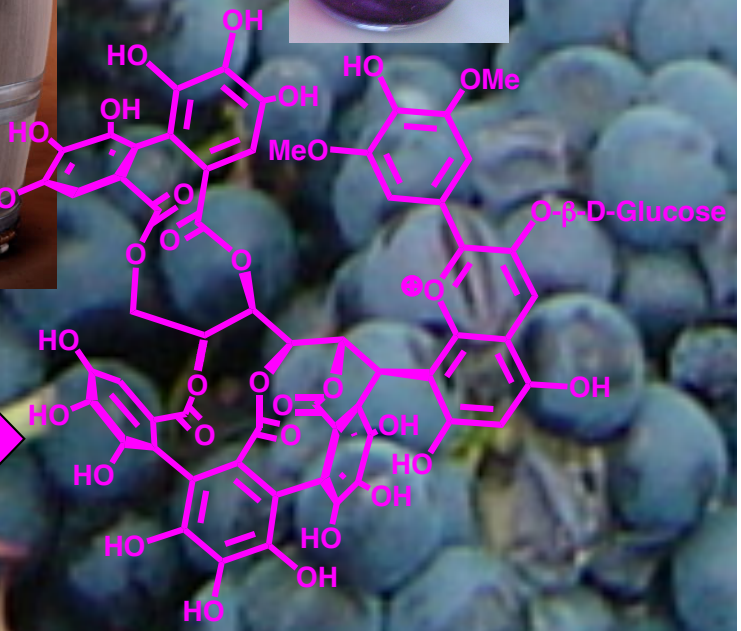
Angew. Chem. Int. Ed. **2003**, *42*, 6012-6014
Chem. Eur. J. **2005**, *11*, 6503-6513

When wine meets oak…

e Quideau, Ph.D., Prof.



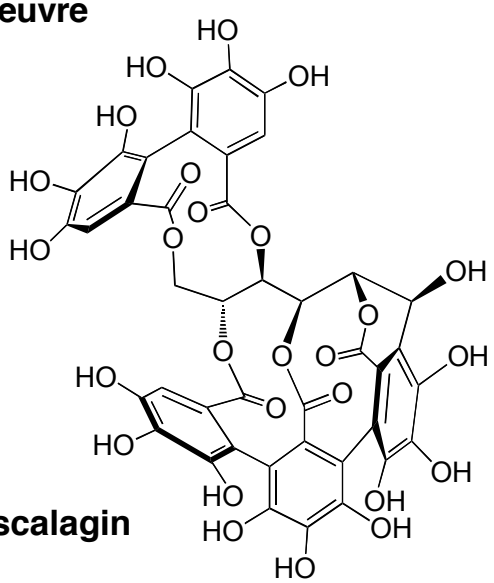




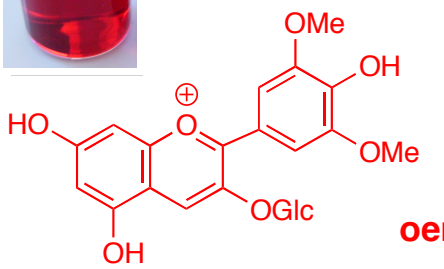
Hemisynthesis of a Novel Anthocyano-Ellagitannin Pigment

université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.

Dorothée Lefeuvre

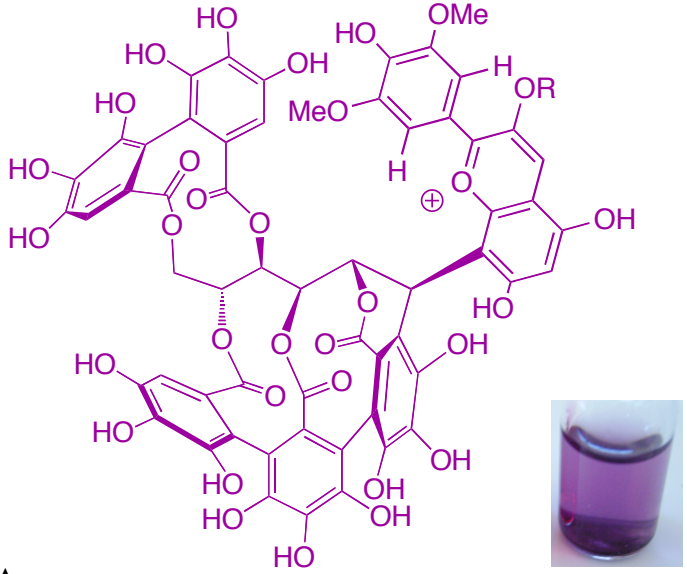


vescalagin



oenin

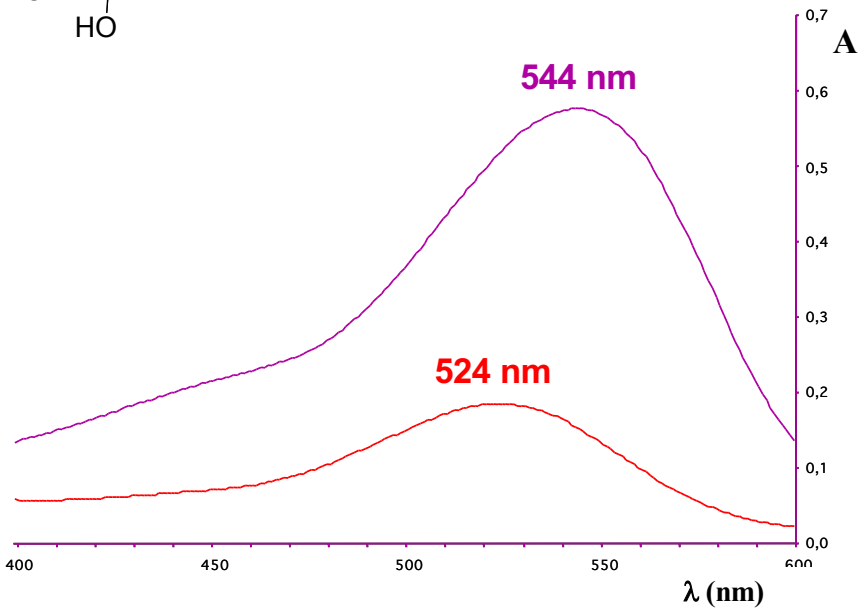
+ H^+, – H_2O



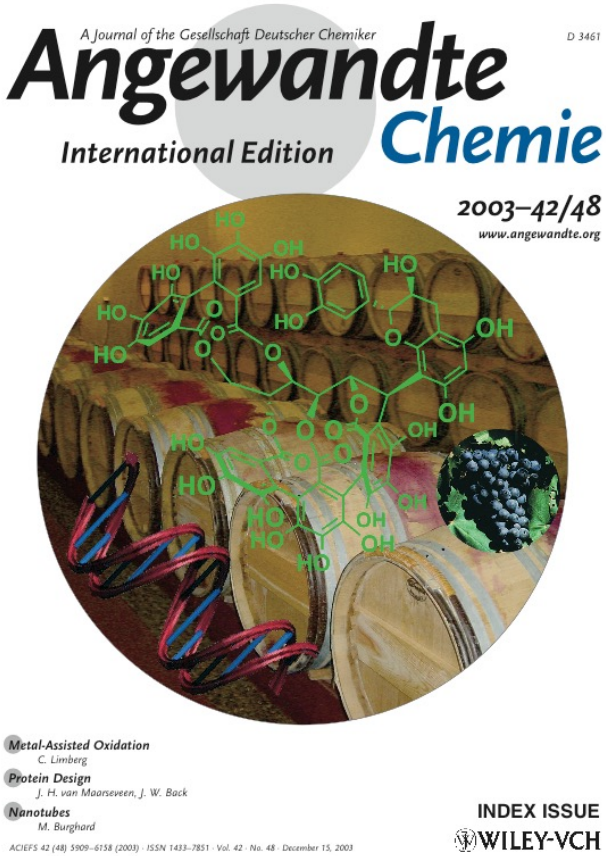
oenin-8-*C*-vescalagin

3% isolated by semi-prep HPLC

Rémi Jacquet



Chem. Eur. J. **2005**, *11*, 6503-6513
Eur. J. Org. Chem. **2010**, 55-63



Angew. Chem. Int. Ed. **2003**, *42*, 6012-6014

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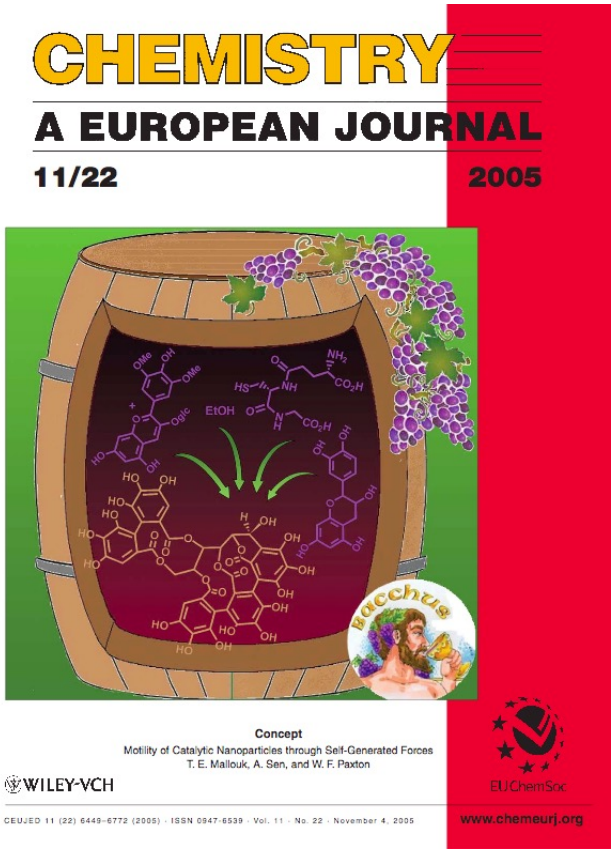
Eur. J. Org. Chem. **2009**, 1–204



Chem. Eur. J. **2005**, *11*, 6503-6513

Eur. J. Org. Chem. **2010**, 55-63

See also:
Borman, S. Anticancer Agents Found in Aged Wine. *Chemical & Engineering News*, **2005**, *October 31*, 36

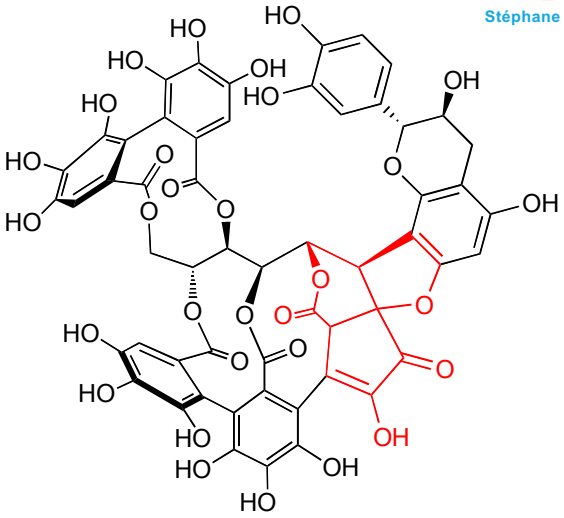
In his 2010 EurJOC editorial, Haymo Ross suggested:

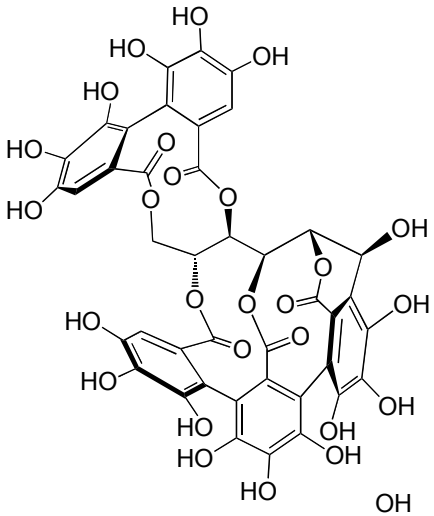
« Let's raise a glass of fine Bordeaux (instead of Champagne) to the New Year 2010! »

The Secrets of Bacchus…

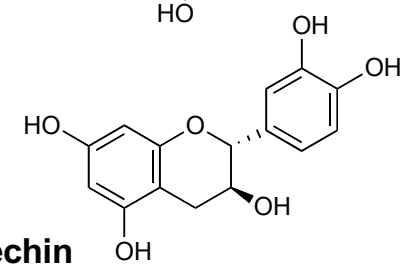
université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.

Something Else Is Going On…

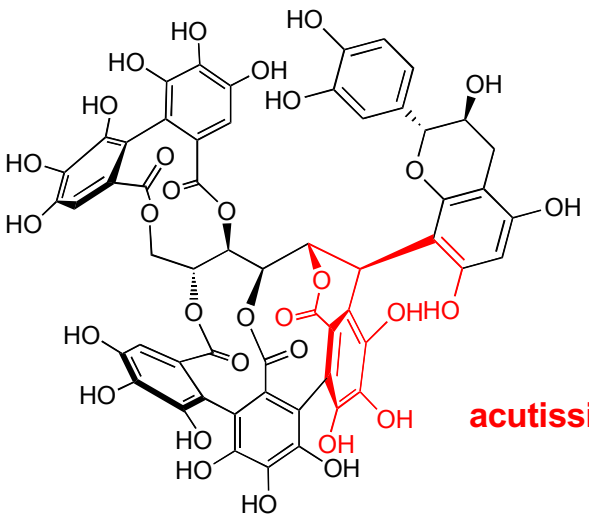




vescalagin



catechin



acutissimin A

O_2, H_2O

mongolicain A

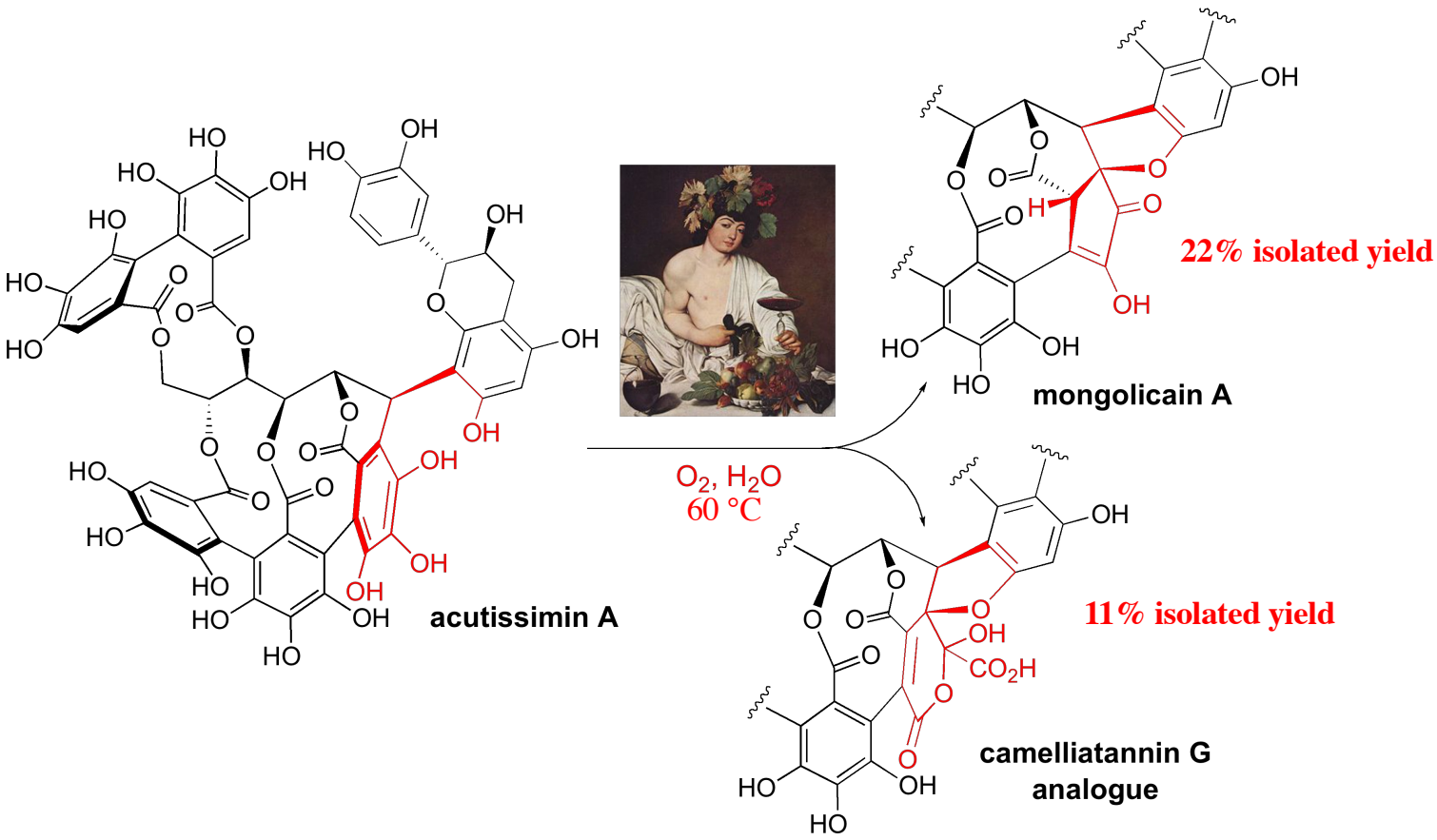
Quercus mongolica Jap. Mizunara

Quercus acutissima Jap. Kunugi

université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.

Remarkable Biomimetic Chemoselective Aerobic Oxidation of Oak Found-in-Wine Flavano-Ellagitannins

When chemistry is run under the auspices of Bacchus…

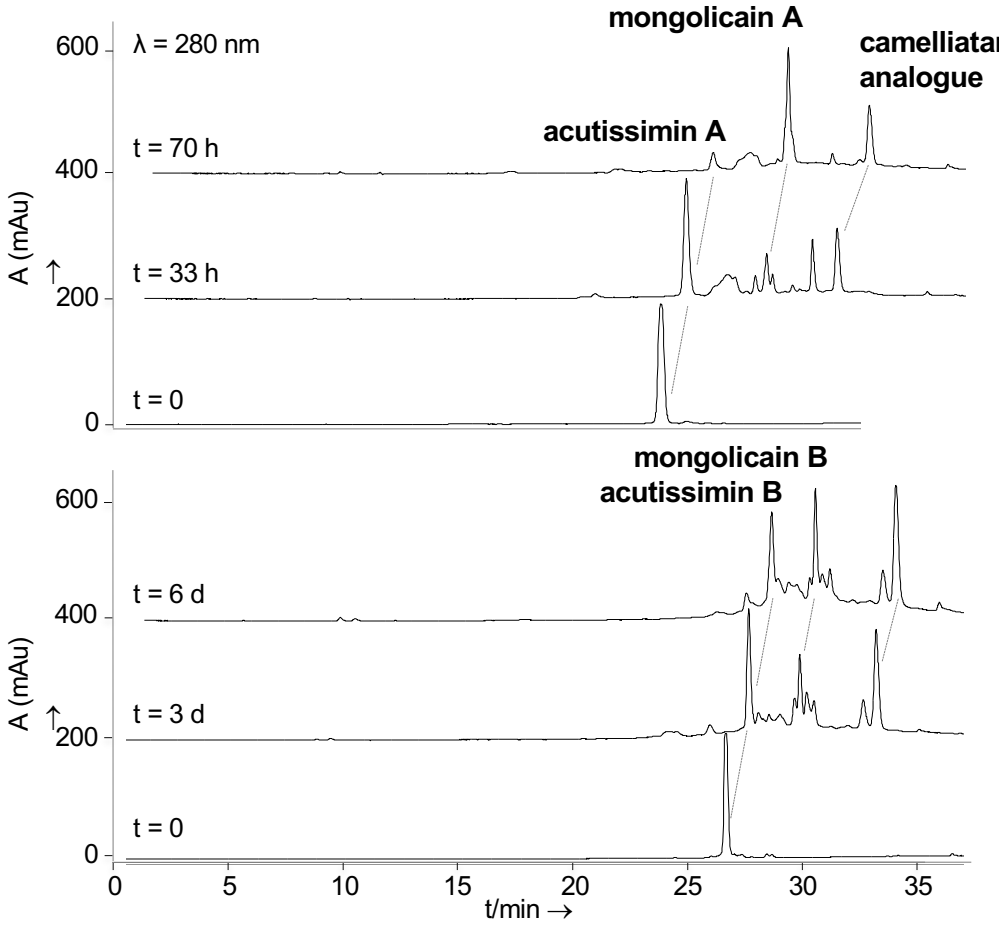


Angew. Chem. Int. Ed. **2013**, *52*, 11530-11533

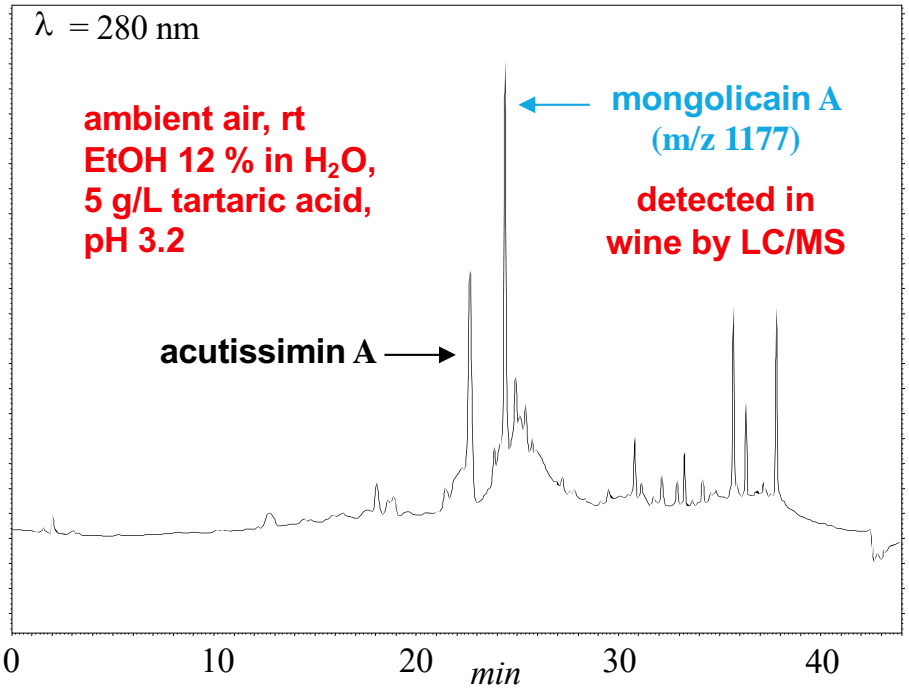
HPLC Monitoring of the Aerobic Oxidation of Acutissimins into Mongolicains and Camelliatannin G Analogues

[H_2O, O_2 (air), 60 °C]

université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.



Emilie Petit



Angew. Chem. Int. Ed. **2013**, *52*, 11530-11533

université de BORDEAUX
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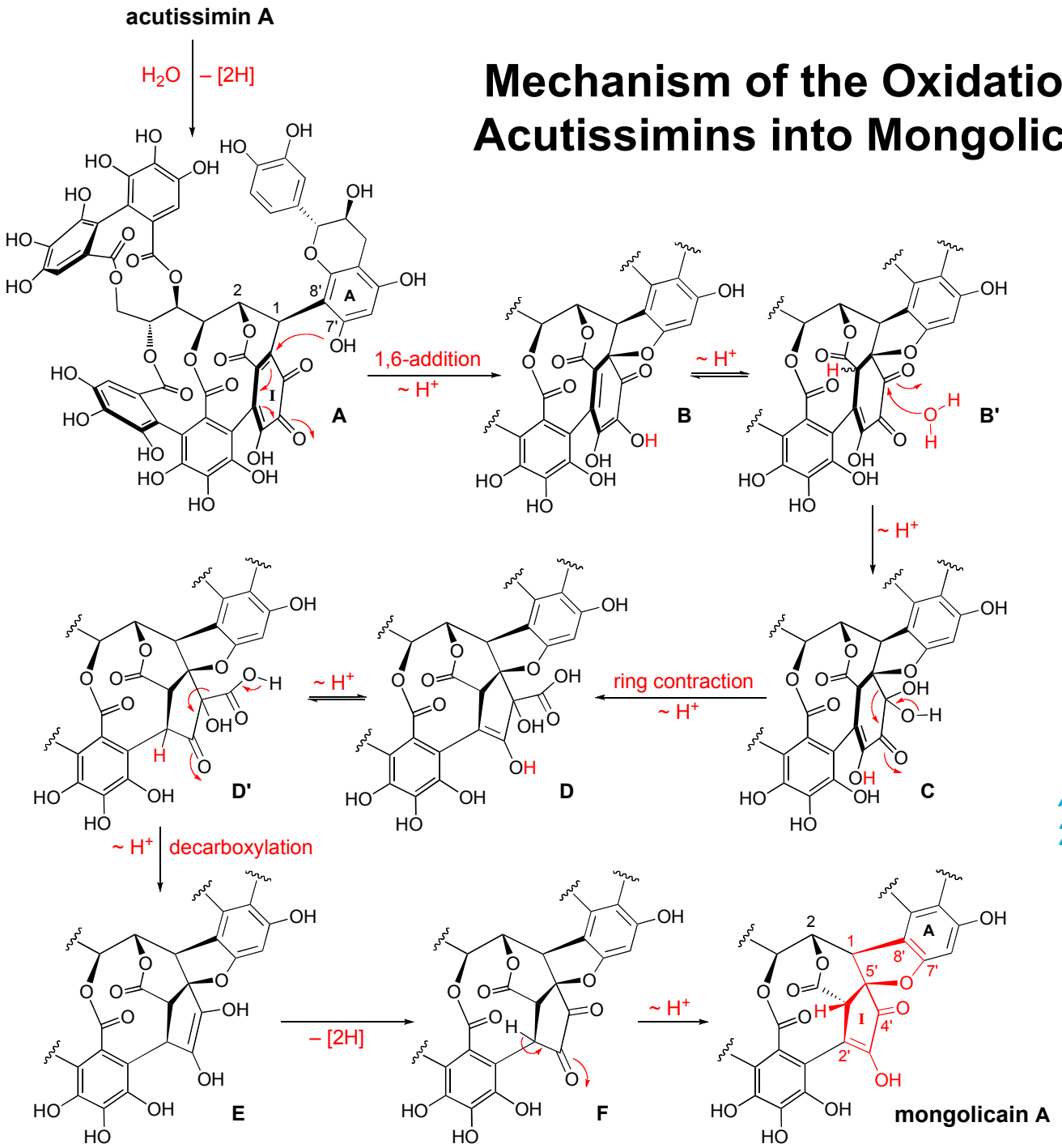
Mechanism of the Oxidation of Acutissimins into Mongolicains



Angew. Chem. Int. Ed.
2013, *52*, 11530-11533

Vescalagin selectively binds filamentous actin in cellulo…

université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.

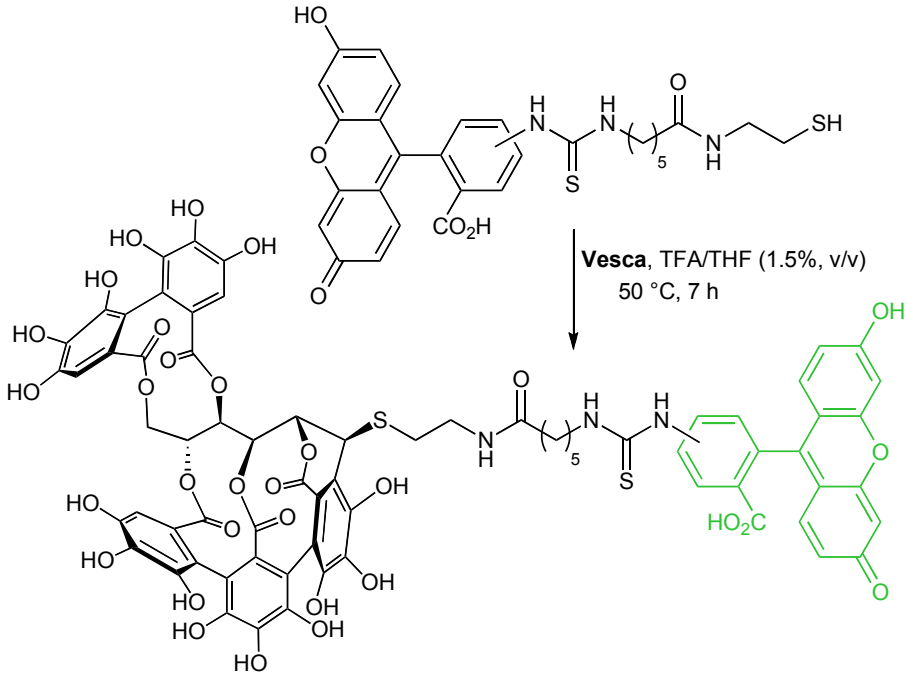
BAE cells transfected with actin-GFP

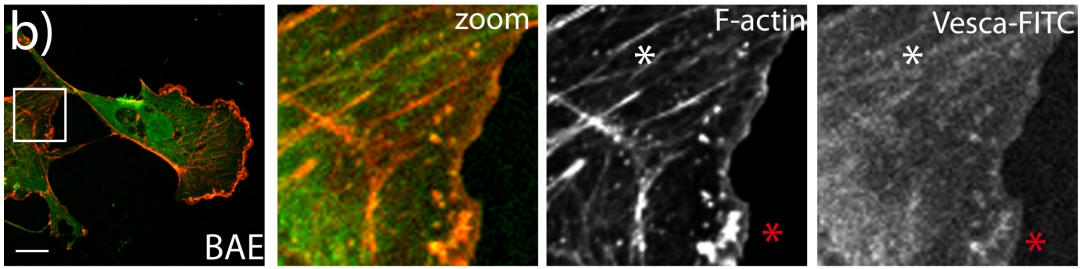
Control :

- Stack of 32 images
- 1 image every 37,87 sec.
- field approx 180 X 180 µm.

Actin-568 in G buffer actin
+
Vescalagin 100 µM

- Stack of 20 images
- 1 image every 37,439 sec.
- field approx 29 X 29 µm.

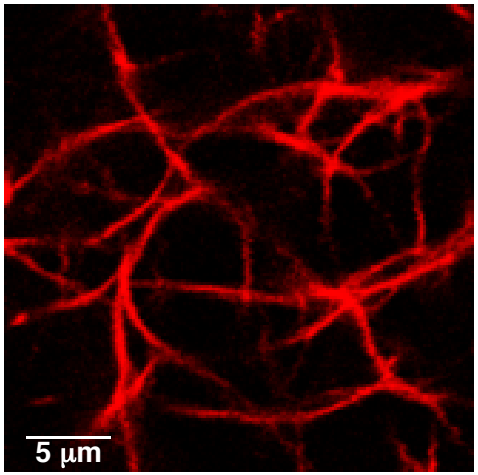




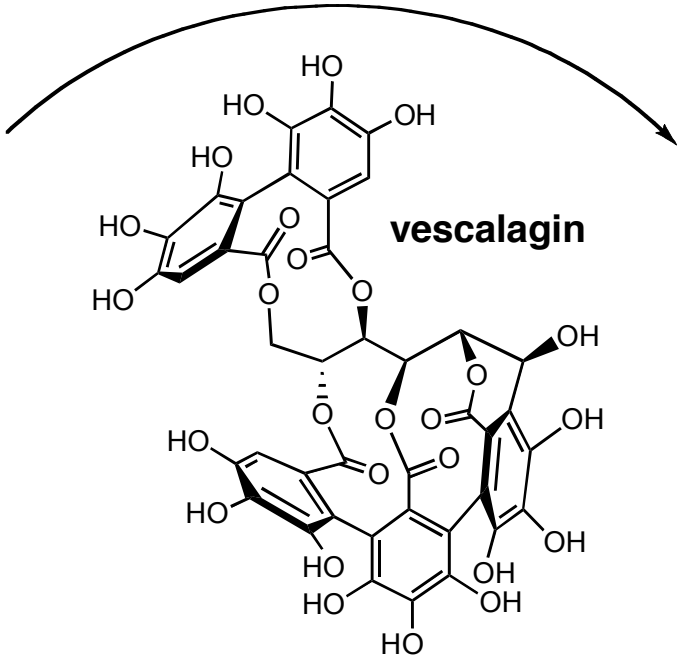
… and winds it into fibrillar aggregates !

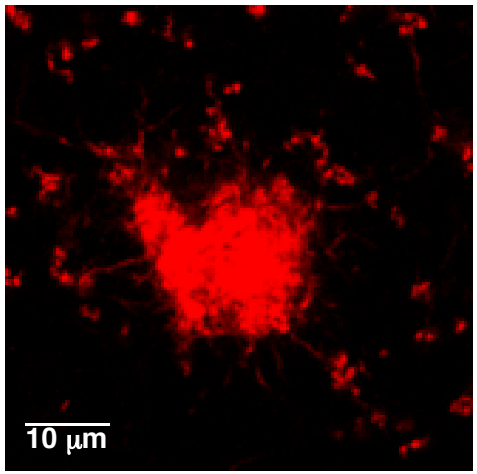
Angew. Chem. Int. Ed. **2011**, *50*, 5099-5104
Patent EP11305186

Vescalagin: a New Anti-Actin Agent !



F-actin
in vitro





BAE cells transfected with actin-GFP

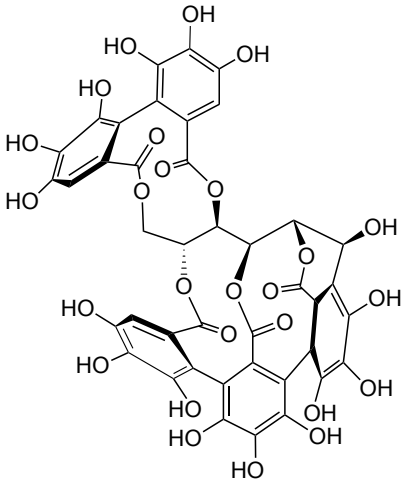
Control :

- Stack of 48 images
- 1 image every 37,75 sec.
- field approx 128 X 128 µm.

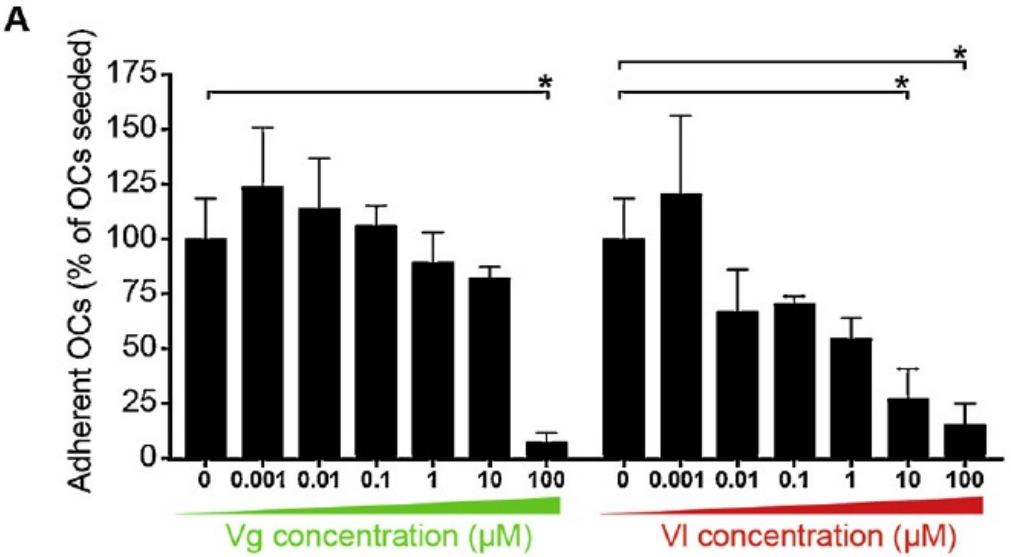
Angew. Chem. Int. Ed. **2011**, *50*, 5099-5104
Patent EP11305186

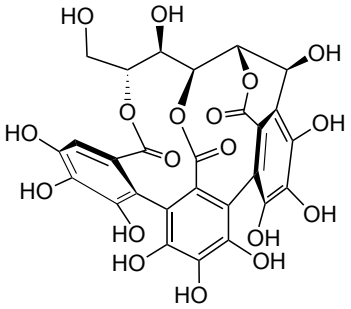
Vescalagin and vescalin disturb *de novo* osteoclast (OC) adhesion and inhibit matrix resorption activity without affecting OC survival…

université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.

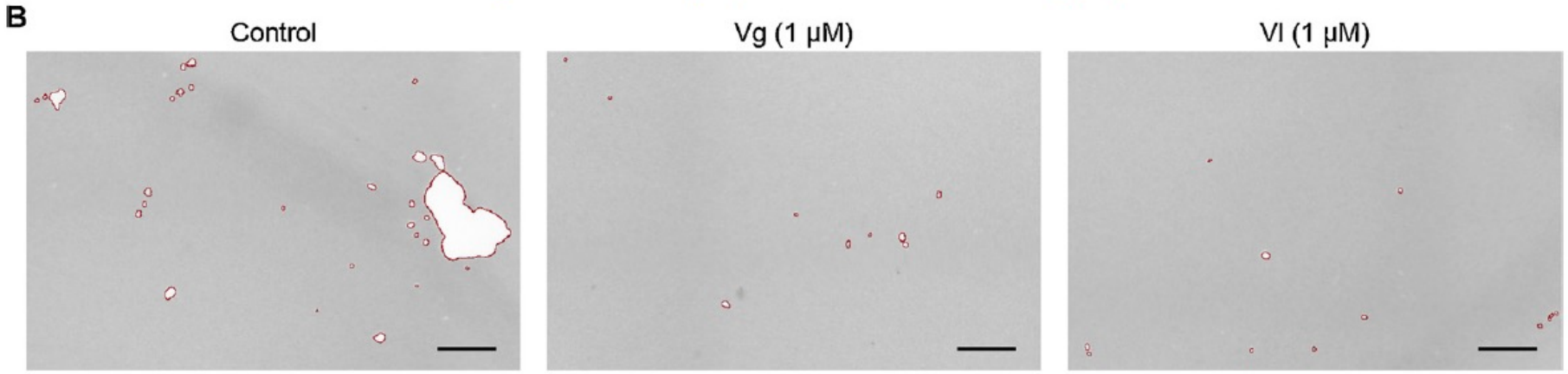


Vescalagin (Vg)





Vescalin (Vl)



Micrographs showing the bone-mimicking mineralized matrix (grey) after OC resorption in the presence of control, 1 µM Vg or 1 µM Vl. The red line contours the extent of the degraded (absent) mineralized matrix. Scale bar = 100 µm.

with Elisabeth Génot,
Eur. J. Cell Biol. **201**8, 97, 533-545

Natural Products

DOI: 10.1002/anie.201000044

Plant Polyphenols: Chemical Properties, Biological Activities, and Synthesis**

Stéphane Quideau, Denis Deffieux, Céline Douat-Casassus, and Laurent Pouységu*

Keywords:
antioxidants · biological activity · natural products · polyphenols · total synthesis

Dedicated to Professor Edwin Haslam

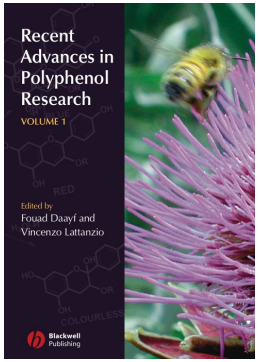
Angew. Chem. Int. Ed. **2011**, *50*, 586-621

université de BORDEAUX

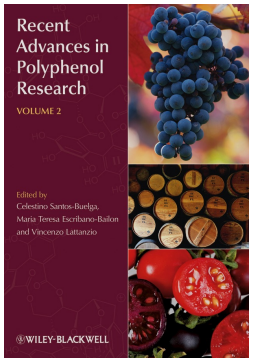
Stéphane Quideau, Ph.D., Prof.

groupe polyphénols

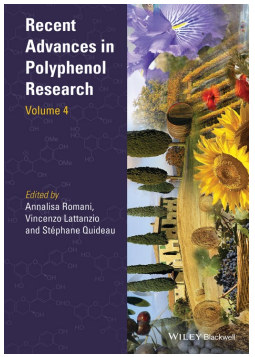
Recent Advances in Polyphenol Research



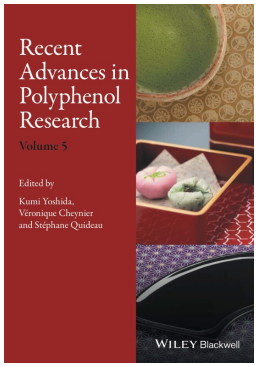
Vol. 1



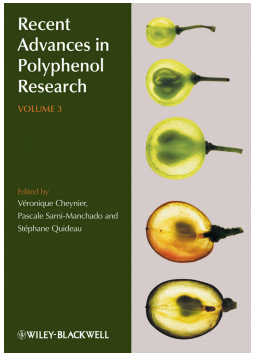
Vol. 2



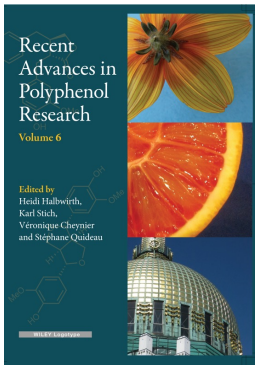
Vol. 4



Vol. 5



Vol. 3



Vol. 6

Released in 2009 !

université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.

Chemistry and Biology of
Ellagitannins
An Underestimated Class of
Bioactive Plant Polyphenols

This book is the first of its kind to focus on the chemistry and biology of ellagitannins, a special class of naturally occurring polyphenols that have so far not received the attention they deserve. These polyphenolic substances are found in many plants, including numerous food sources. They exhibit unique structural features and express remarkable biological activities, but have yet to attract the general interest of the pharmaceutical industry. This is surprising considering that ellagitannins have been identified as active principles in traditional Asian medicines.

The principal aim of this book is to set the record straight. Most, if not all, worldwide experts in each aspect of the chemistry and biology of this underestimated class of natural products have contributed to this book. Beginning with a foreword written by one of the pioneers in modern polyphenol research, Professor Edwin Haslam, it covers topics such as the structural determination and natural occurrence of ellagitannins, the most up-to-date knowledge of their biosynthesis, the current state of the art of their total chemical synthesis, their main physicochemical properties and principal biological activities, their presence in food and beverages, and their related health effects. This book will be useful not only to scientists involved in natural product research, but also to lecturers and their students as a source of key references and/or a textbook.

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ISBN-13 978-981-279-740-7
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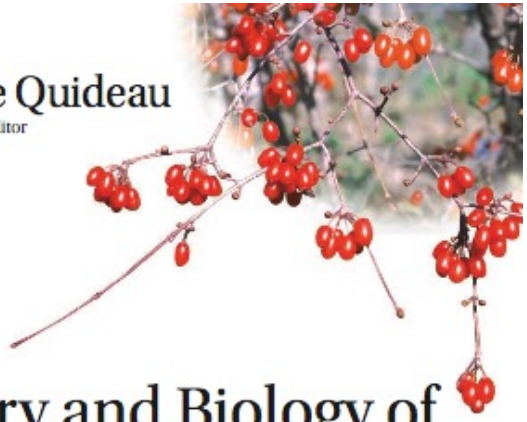
Chemistry and Biology of Ellagitannins
An Underestimated Class of Bioactive Plant Polyphenols

Quideau

Stéphane Quideau
Editor



Chemistry and Biology of
Ellagitannins
An Underestimated Class of
Bioactive Plant Polyphenols

World Scientific

université de BORDEAUX
Stéphane Quideau, Ph.D., Prof.

Tetrahedron Symposium-in-Print
Chemistry in the Vine and Wine Sciences

Preface. In *Chemistry in the Vine and Wine Sciences*, Quideau, S., Snyder, S. A., Eds; Tetrahedron Symposium-in-Print, *Tetrahedron*, **2015**, *71*, 2969-2970.

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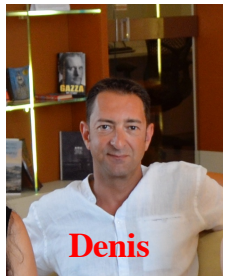

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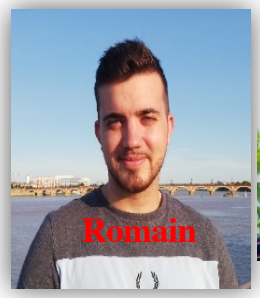
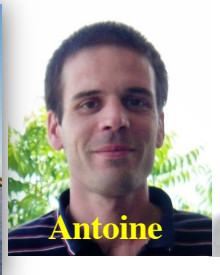


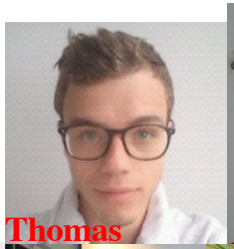


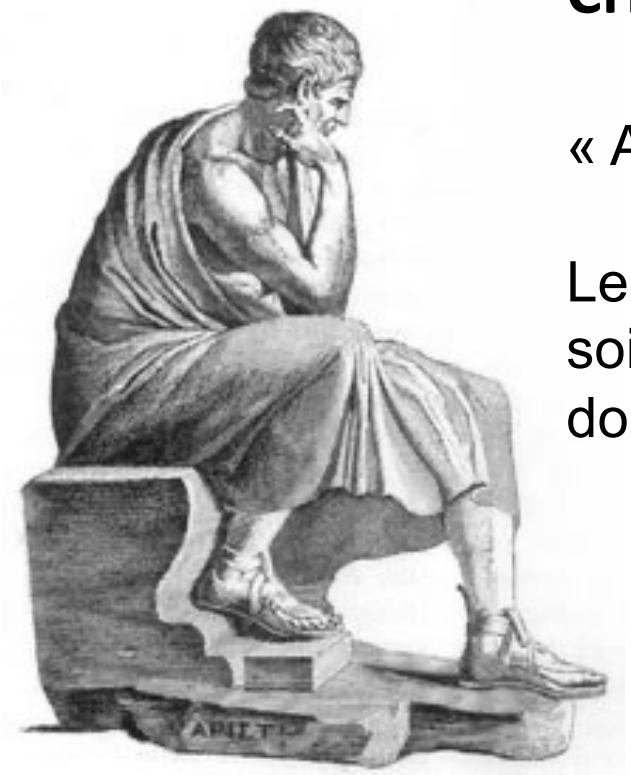
The Polyphenolists

The Kempf's

http://squideau-lab.fr

The Syniodanists





Critique du Relativisme de Protagoras

« Au sujet de la vérité…

Le même vin, soit parce qu'il aura changé lui-même, soit parce que notre corps aura changé, pourra paraître doux à tel moment, et, à tel autre moment, non-doux. »

Aristote, *Métaphysique,*
trad. Jean Tricot 1933, t. 1, Γ, 5, p. 146
(Librairie Philosophique J. Vrin, 1991)