**What is a Polyphenol?**

**Definition #1**
- Water Soluble (even minimally)
- 500-4000 Da
- >12 phenolic hydroxy groups
- 5-7 aromatic rings/100 Da

- definitions are likely narrow due to necessity of fields
- nitrogen may be incorporated to DAHP in shikimate pathway or prior to transformations "allowed" for cannonical polyphenols

**Definition #2**
- The term "polyphenol" should be used to define compounds exclusively derived from the shikimate/phenylpropanoid and/or the polyketide pathway, featuring more than one phenolic unit and deprived of nitrogen-based functions.

Quideau, "Why bother with polyphenols?", Groupe Polyphenols.

**The Basics:**
- contain multiple phenolic moieties
- secondary metabolites of plants, fungi, bacteria, and archaean
- thought to be ubiquitous in plants
- may contain furans, pyrones, biaryls, aryl ethers, pyrans, dioxins, spiro, benzopyrans, O- or C-glycosides
- exist as definable monomers and oligomers, as well as heterogeneous oligomers/polymers

**Biological Significance (Plants):**
- signalling molecules in ripening
- allelopathic agents: modulate other plants' growth
- phytoalexins: antimicrobial activity (bacterial, fungal, viral, and parasitic)
- hardening of non-vegetative tissues
- herbivore deterrent: taste and astringent properties
- inhibit rot
- flame retardant properties
- UV protection
- variety of pigments
- 1-25% of dry plant weight (species dependent)

**Biological Significance (Humans):**
- Antioxidant properties - no FDA recognition (no MOA, no biomarkers, heterogeneity)
- possible "anti-nutrients": bind metals and enzymes
- Tastes: bitterness/astringency (higher polymer = more astrigent/less bitter)
- source of therapeutically effective molecules

**Properties:**
- OXIDATION
- OXIDATION
- chelate metal ions
- precipitate/bind proteins
- fluorescent/autofluorescent
- facile ionization
- generally water soluble

**Uses:**
- tanning of leather
- dyes for non-synthetic fibers
- green chemistry feedstocks
- resins, paints, polymers, surfactants, friction linings, wood preservatives, glues (particle board)

**Topics Covered In This Meeting:**
Ellagitannins (hydrolyzable tannins)
Oligostilbenoids
Lignans
Various polyphenolic ethers
Anthraquinone natural products
Polyphenolic peptides (Non-Ribosomal Flavanoids)
Lignin Degradation (brief)

**Topics Not Covered:**
- polyphenolic alkaloids
- polyphenols with isolated phenolic components
- tetracyclines (G.M. - Lin, 2005)

**Shikimate Pathway**

Pathway only present in plants, fungi, bacteria, and archaean
- produces the major components/monomers (in blue) of most polyphenols
- various alkylations, oxidations and reductions may take place prior to incorporation
Ellagitannins: (hydrolyzable tannins)

- biosynthesized from pentagalloyl glucose, then oxidations and esterifications
- tellimagrandins I and II are the most basic members
- high concentration in fruits
- immunomodulatory: immunosuppressive and tumor necrosis
- no therapeutic use to date

**Tellimagrandin I**

1. TFA, H₂O
2. Ac₂O, Pyr.
3. KOH-Bu, H₂O


**O-permethyl tellimagrandin I**


**Tellimagrandin II**

1. Pb(OAc)₃, pyr.
2. H₂, Pd/C


**Coriariin A**


Oligostilbenoids:
- resveratrol isolated from 72 different plant sources across the world
- oxidative dimerization via enzymes
- observed as diverse, structurally complex dimers, trimers, dimers of dimer, and oligomers
- high concentration in red wines and dark fruits (almost absent in white wine)
- extremely diverse biological activities observed
- often serve as antifungals for the producer organisms
- "French Paradox" - Can diets high in oligostilbenoids counter the effects of a diet high in fat and cholesterol?

Polyphenols


**Lignans:**
- not to be confused with Lignin
- biosynthesized by the oxidative dimerization of cinnamic alcohols
- co-nutrients with dietary fiber: high in wheats, rye, flax, strawberries, broccoli
- 0.3% wt/wt of flax seed
- antioxidants and anti-inflammatory in human health
- antibiotics for plant health
- often inhibit topoisomerase

**Polyphenols**

Snyder, Nature 2011, 461.
**Polyphenols**

**Anthraquinone Natural Products**
- polyketide-derived natural products
- not all are deprived of nitrogen (tetracyclines)
- often cytotoxic - topoisomerase I and II inhibitors
- diversity in oxygenation, O-methylation, glycosides, and cyclization regiochemistry

**The Marschalk Reaction**

**Polyphenolic Ethers**
- generally refers to compounds that contain an Ar-O-Ar linkage, but has also referred to compounds containing aryl ethers not included directly in other polyphenol classes
- arise from various biosynthetic pathways and precursors
- due to diversity, little coherent biological activity among group
- caviularin represents unique natural product: chirality derived completely from atropisomerism
**Polyphenols**

1. NaBH₄, PhMe, Δ
2. PPTS, neopentyl glycol, PhMe, Δ

**Harrowven, Angew. Chem. Int. Ed. 2005, 3699.**

2. DCC, DMAP, DMF

**DCC, DMAP, DMF, 1300°C**

- **cavicularin**
  - (+) proto-deiodination

3. TMSN₃H₂, AIBN, PhMe, Δ

4. PPTS, aq. acetone

**Hermann catalyst, NaOAc, Toluene**

**DIBAL, X = O, Y = H**

5. TiCl₄, Mg, THF, arene

6. DIBAL, X = O, Y = H

7. TiCl₄, Mg, THF, arene

8. DIBAL, X = O, Y = H

9. TiCl₄, Mg, THF, arene

10. DIBAL, X = O, Y = H

11. TiCl₄, Mg, THF, arene

12. DIBAL, X = O, Y = H

13. TiCl₄, Mg, THF, arene

14. DIBAL, X = O, Y = H

**Beaudry, Angew. Chem. Int. Ed. 2014, 10500.**

15. TsNHNH₂, NaHCO₃, p-Tol

16. NaNO₂, AcOH, H₂O

17. NaH₂PO₄, PhH

18. 4, BBr₃

19. BrNMe₂Cl₂

20. NaNO₂, AcOH, H₂O

21. NaH₂PO₄, PhH

22. (TMS)SiH, AIBN, NaH₂PO₄, PhH

23. BBr₃

24. PhMe, Δ

25. NaOAc

26. (62%)

27. DCC, HOBr, 5

28. NaH₂SO₄, PhMe/H₂O (pH 8)


**Polyphenolic Peptides:**

- not included are non-interacting phenols
- generally isolated from fungi or bacteria
- Non-ribosomally derived polypeptides
- show a broad range of activities; antibacterial, antifungal, anti-parasitic, cytotoxic
- built of tyrosine and modified aromatic amino acids
- generally modified (halogenation/ P450 [O])

**after NRPS module**

- **Arilomycin A**

- **Biphenomycin A**

- **RP-66453**

- **Biphenomycin A**

- **desoxy-Biphenomycin A**
  - (biphenomycin A also prepared)

**Suzuki, Angew. Chem. Int. Ed. 2013, 10472**

**Schmidt, Synthesis 1992, 1025.**

**Kreufer, Org. Process Res. Dev. 2011, 1348.**

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**Polyphenols**

Toward RP-66453

For strategies in the synthesis of Vancomycin see *Classics in Total Synthesis II.*

**Flavanoids:**
- Biosynthesized from cinnamic acid and 3 malonyl additions
- Almost all -OH patterns/cis and trans observed naturally
- Flavanoids: 3-OH
- Flavonoids: ketone at C4
- Present in tea, wine, fruits, cocoa
  (8x more in apple than wine per serving)
- No supported beneficial health effects
- Lawsuits and FDA cautionary warnings due to false claims

**Recently In Polyphenol Synthesis**
- Mallotojaponin C and 14 analogs prepared this way
  - >60% yield in all coupling reactions
  - All analogs tested against *P. falciparum*, *T. brucei*, and *T. brucei* farnesyl transferase

For details, see Cariou and Dubois, Org. Lett. 2016, 708.
Lignin Degradation
- 170 billion metric tons of lignocellulose in commercial stream per year
  (20 to 40% is lignin)
- Can make up to 25% of dry plant mass
- very little use for it - currently only 5% used (low-value materials)
- high yielding, selective, low cost degradation process would be very attractive
- has possibility of providing “renewable” chemical feedstocks
- Challenges: relatively unreactive moieties, enormous chemical diversity for a substance with one name

Survey of Top Procedures to Date

<table>
<thead>
<tr>
<th>Method</th>
<th>Reagents</th>
<th>Temperature (°C)</th>
<th>Pressure (MPa)</th>
<th>Main Products</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>Acid</td>
<td>formic acid 10 wt%, EtOH 81 wt%</td>
<td>380</td>
<td>25</td>
<td>methoxyphenols, catechols, phenols</td>
<td>2.9</td>
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<tr>
<td></td>
<td></td>
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<td>1.5</td>
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<td></td>
<td>2.0</td>
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<tr>
<td>Base</td>
<td>2 wt% NaOH</td>
<td>350</td>
<td>25</td>
<td>syringol, hydroxy acetophenone, guaiacol</td>
<td>4.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td>Metal Cat.</td>
<td>Pt/C (4 wt%), formic acid (16 wt%), EtOH (80 wt%)</td>
<td>350</td>
<td>-</td>
<td>4-propylguaiacol, 4-methylguaiacol</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>5.0</td>
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<tr>
<td>Ionic Liquid</td>
<td>Mn(NO₃)₂</td>
<td>100</td>
<td>8.4</td>
<td>2,6-methoxyl-1,4-benzoquinone</td>
<td>11.5</td>
</tr>
<tr>
<td>Supercritical Fluid</td>
<td>water</td>
<td>300</td>
<td>25</td>
<td>catechols, phenol, cresols</td>
<td>28</td>
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Zhang, Chem. Rev. 2015, 11559.
