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Polyketide Biosynthesis
Review

All polyketides use malonyl-CoA (= acetate) and methyl malonyl-CoA (propionyl) as building blocks.
Sometimes unusual building blocks are incorporated at the "loading" or "initiation" module.

Type I, non-iterative PK pathways have one "module" dedicated for each acetate unit.
Each module has KS, AT and ACP functions, plus KR, DH, and/orER depending on
keto, hydroxyl, alkene or aliphatic functionality
macrolides, polyenes, polyethers are typical products

Type II, iterative "aromatic" PK pathways have one minimal module KS, KSb or CLF (same thing) and ACP
that constructs the entire polyketide chain
bketo chains are extremely reactive and can enolize to form cyclization products.
Spontaneous cyclization products occur, but presumably the KR, ARO and CYC enzymes control the regioselectivity
In the process of cyclization the polyketide chain cleaves itself from the thioester linkage (i.e. see novobiocin)
Additional hydroxylation, oxidation steps can occur, but not discussed in class

Type III "chalcone synthases" are similar to type II but do not utilize an ACP domain;
instead utilize Co-A tethered substrates and intermediates.
Did not discuss, will return to when discuss flavonoids

Type I iterative
Utilizes what looks like a standard type I enzyme module: KSATDHKRACP all on same polypeptide, but this
single module is used for all acetate units.
Some products are aromatic (salicylate in yeast) or very unusual (enediynes)

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Saccharide Biosynthesis
Deoxy sugar biosynthesis

Chem Rev 2000, 100, 4465.

Carbohydrates are critical for activity of antibiotics.

Provide recognition elements
Polyketide and NRP products are typically derivatized with "unusual" saccharides

How are these sugars made?
How are they attached to the product?

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Saccharide Biosynthesis
Deoxy sugar biosynthesis

Chem Rev 2000 100 4615
Ann Rev Biochem 2002 71 701

1. Different deoxygenation states of sugars (major modifcation)
2. Addition of Amines
3. Addition of carbons
4. Epimerization of carbon centers

Typically deoxygenation occurs in a specific order and in certain patterns

3,6 dideoxy

2,6 dideoxy

4,6 dideoxy

All deoxy sugars start from NDP-Glucose

Start with oxidation of 4 and deoxygenation of 6

Many steps utilize the PLP/PMP cofactor in unusual ways.

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Saccharide Biosynthesis
Deoxy sugar biosynthesis

Glycosyltransferases

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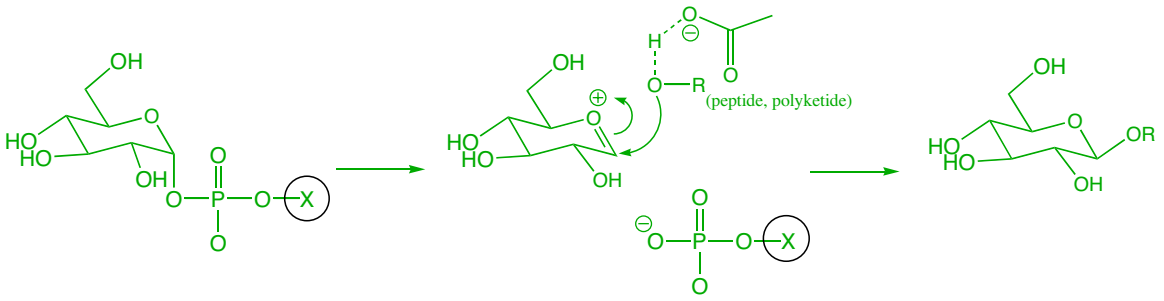

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Koeller, Kathryn M., and Chi-Huey Wong. Schemes 2 and 5 in “Synthesis of Complex Carbohydrates and Glycoconjugates: Enzyme-Based and Programmable One-Pot Strategies.” *Chem Rev* 100 (2000): 4465 – 4494.

Walsh, Christopher. *Enzymatic Reaction Mechanisms*. San Francisco, CA: W.H. Freeman Company, 1979, pp.778-781. ISBN: 0716700700.

He, Xuemei, Gautam Agnihotri, and Hung-wen Liu. Structures 3-6, Scheme 2, and Scheme 1 in “Novel Enzymatic Mechanisms in Carbohydrate Metabolism.” *Chem Rev* 100 (2000): 4615 – 4662.

He, Xuemei, and Hung-wen Liu. Schemes 5, 6, 8, 9, 11, 14, 17, 16, and 7 in “Formation Of Unusual Sugars: Mechanistic Studies and Biosynthetic Applications.” *Ann Rev Biochem* 71 (2002): 701-754.

Chen, Huawei et al. Scheme 1 in “Deoxysugars in glycopeptide antibiotics: Enzymatic synthesis of TDP-L-epivancosamine in chloroeremomycin biosynthesis.” *PNAS* 97 (2000): 11942-11947.

Ünligil, Ulug M., and James M. Rini. Figure 4b in “Glycosyltransferase structure and mechanism.” *Curr Opin Struc Biol* 10 (2000): 510-517.

Mulichak, Anne M et al. Figure 1 in “Structure of the TDP-epi-vancosaminyltransferase GtfA from the chloroeremomycin biosynthetic pathway.” *PNAS* 100 (2003): 9238-9243.

Losey, Heather C. et al. Figures 1 and 4 in “Incorporation of Glucose Analogs by GtfE and GtfD from the Vancomycin Biosynthetic Pathway to Generate Variant Glycopeptides.” *Chem Biol* 9 (2002): 1305-1314.

Zhao, Lishan et al. Schemes 1 and 2 in “Engineering a Methymycin/Pikromycin-Calicheamicin Hybrid: Construction of Two New Macrolides Carrying a Designed Sugar Moiety.” *JACS* 121 (1999): 9881.

Hoffmeister, Dirk et al. Structures 1 and 2 in “The C-Glycosyltransferase UrdGT2 Is Unselective toward - and -Configured Nucleotide-Bound Rhodinoses.” *JACS* 125 (2003): 4678 – 4679.