Saccharide Biosynthesis

Deoxy sugar biosynthesis review
Amination requires the presence of a keto group; otherwise timing not specified.

Desosimine --> erythromycin
Attachment of carbon
1. If a single methyl group is attached, SAM is cofactor, and a nucleophilic site on the sugar is required enzyme will help generate enolate

Attachment of carbon
2. If a 2-carbon group is attached, pyruvate is the source. Pyruvate acts as a nucleophile (with the help of TPP cofactor) and an electrophilic site on the sugar - i.e. a carbonyl carbon - is required
Shikimate Pathway

Normally used in synthesis of aromatic amino acid

Branch points from a primary metabolic pathway to make a variety of natural products

1. phenyl-glycine amino acids $\rightarrow$ vancomycin $\rightarrow$ comparison (incorporated peptide products) PKS

2. amino shikimate $\rightarrow$ rifamycin $\rightarrow$ PK product

3. cyclohexyl CoA $\rightarrow$ avermectins $\rightarrow$ incorporated into a PK product

4. coumaryl CoA derivatives for flavonoid biosynthesis $\rightarrow$ starting materials
transfer plant genes to e. coli
+ express S.A. in e.coli

28g/L

14% yield based glucose
starting material

another technique
culture presence of a solid
ion exchange resin

based compounds accumulate
Knock out transporter = leave shik. acid
in media outside cell --> 52g/L 18% yield

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Please see Scheme 1a in JACS 123 (2001): 10173-10172.
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Please see: Hubbard, Brian K., and Christopher T. Walsh.
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Please see: Hubbard, Brian K., and Christopher T. Walsh.
Figure 6 in “Vancomycin Assembly: Nature’s Way.” *Angew Chem Intl Ed* 42 (2004): 730-765.
Shikimate Pathway

Vancomycin

Chorismate (Shikimate) Pathway

PKS-type Pathway

Orf 1 → Orf 21 → Orf 22 → Orf 17

Orf 27 → Orf 28 → Orf 30 → Orf 29

Shikimate Pathway

Shikimate Pathway

Prephenate → p-Hydroxyphenylpyruvate → L-p-Hydroxymandelate → p-Hydroxybenzoylformate → L-p-Hydroxyphenylglycine

Orf 1 (Prephenate Deh.) → Orf 21 (HmaS) → Orf 22 (Hmo) → Orf 17 (HpgT)

Shikimate Pathway
Ansa macrolides: incorporation of amino shikimate

Rifamycin W

Mitomycin

Naphthomycin

Geldanamycin

Rifamycin W → Proansamycin X

Ansatrienin A
Shikimate Pathway
Amino Derivatives

enzymes of amino shik. require amine moiety for recognition
Fig. 2. Proposed pathway for AHBA biosynthesis. AminoDHS, 5-aminoo analog of 3-dehydroshikimic acid; aminoDAHP, 3,4-dideoxy-4-amino-o-arabino-heptulosonic acid 7-phosphate; PEP, phosphoenolpyruvic acid; aminoDHQ, 5-deoxy-5-amino-3-dehydroquinic acid.

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from PNAS(2003) 100, 9774-9778
Shikimate Pathway
Cyclohexyl-CoA

Rapamycin
(Ascomycin, FK506)

Ansatrienin A
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Please see Figure 2 in *J Indus Microbiol Biotech* 20 (1998): 299-303.
Shikimate Pathway
Adding on a cyclohexyl starter unit

Antiparasitic agents

Avermectin
S. avermitilis

Doramectin
S. collinus

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Please see Figure 3 in *Nature Biotech* 18 (2000): 980-983.
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Please see Figure 1 in *J Indus Microbiol Biotech* 30 (2003): 456-461.
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Shikimate Pathway
Coumarin

L-Tyrosine → NovH → NovJ/K → NovO

Novobiocin → 4-hydroxy-3-amino coumarin

Coumarin --> PKS | shik.

Amino coumarin
Shikimate Pathway

Deoxy sugar biosynthesis

polyketide starter units

polyketide starter units

non-ribosomal peptide biosynthesis

flavonoids

Tyr, Phe