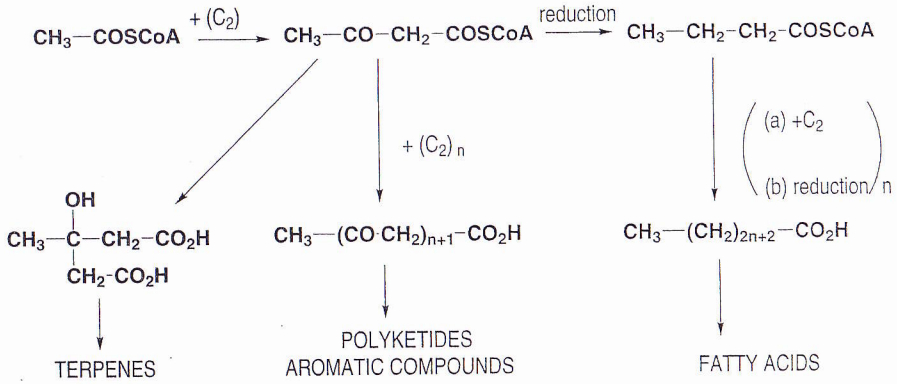
Polyketides

BIOSYNTHETIC GENERALITIES

Acetic acid—in its activated form of acetyl-*S*-coenzyme A—holds a central position in the biosynthesis of a diverse array of complex molecules: a series of Claisen condensations between two-carbon units yields polyketomethylene chains, which lead by reduction to fatty acids, and by further cyclization to many classes of aromatic compounds. A variation, characterized by an aldol condensation, leads, *via* 3-hydroxy-3-methylglutaric acid and mevalonic acid, to the world of terpenes.

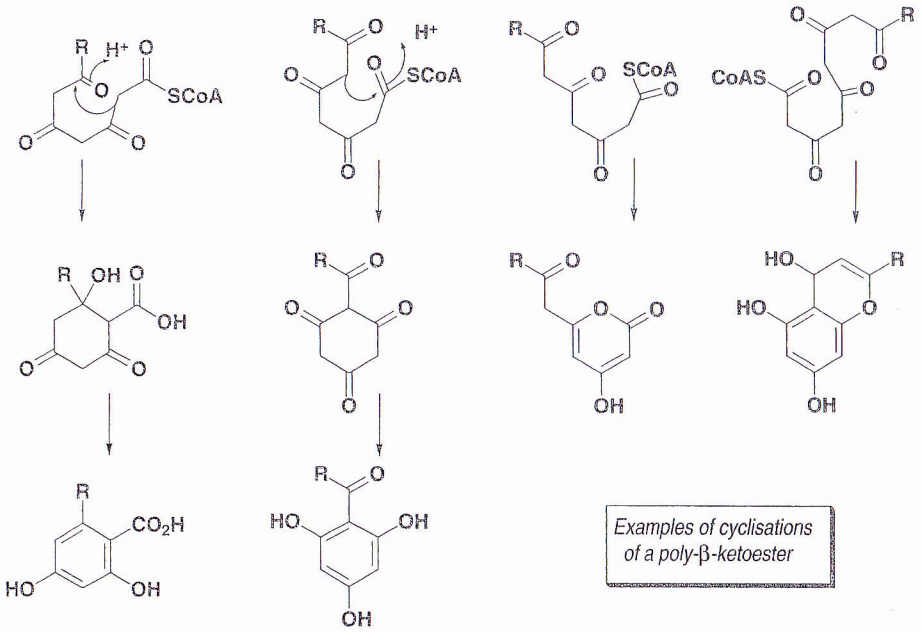


In fact, acetyl-SCoA acts as a starter unit, and it is malonyl-SCoA that adds onto it: a concomitant decarboxylation occurs during the attack on the carbonyl group of acetyl-SCoA, and this makes the malonyl moiety a stronger nucleophile (see fatty acids). This addition of two-carbon units is not—like the formation of fatty acids and their derivatives—preceded by the reduction of the carbonyl function: the result is a poly-β-ketothioester, which is highly reactive because of the simultaneous presence of nucleophilic centers (the methylene groups) and electrophilic centers (the carbonyl groups). It is commonly thought (although the nature of the intermediates remains to be shown) that the poly-β-ketothioester chain is stabilized

either by hydrogen bonding to the enzyme, or by chelation of its enol form with metal ions linked to the enzyme. At this stage, there may be partial reduction of several carbonyl groups, or alkylation of some of them.

The structure of this poly-β-ketothioester makes it highly reactive, and greatly favors intramolecular reactions:

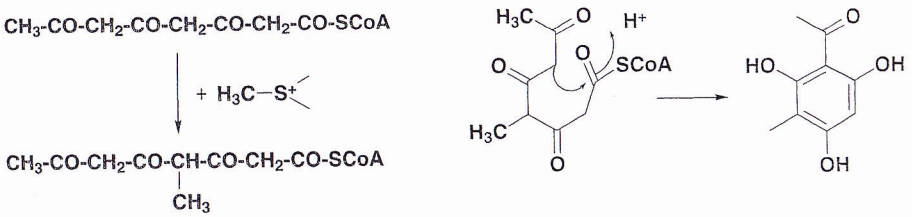
- internal aldol condensation leading to 2,4-dihydroxy-6-alkylbenzoic acids (orsellinic acid and homologs);
- internal Claisen condensation inducing the formation of 1-acyl-2,4,6-trihydroxy-benzene (phloracetophenone and its homologs, the acylphloroglucinols);
- sometimes intramolecular cyclization occurs by lactonization, hence the pyrones. At the same time, aldol condensation may take place, leading to the formation of chromones, isocoumarins, and more.



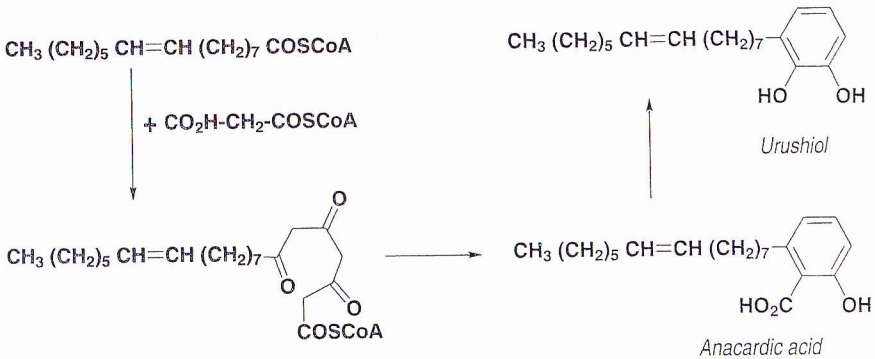
Examples of cyclisations of a poly-β-ketoester

Structural diversity is a direct result of the number of acetate units in the precursor, the mode of cyclization, the identity of the starter*, and the potential secondary transformations: oxidations, reductions, alkylations, rearrangements, ring opening, glycosylation, and so forth.

* The starter is not necessarily acetyl-SCoA. See, for example, the elongation process induced from *p*-coumaroyl-CoA in the case of flavonoids; see also, in the field of antibiotics, the formation of tetracyclines from a nitrogen-containing starter, namely malonamido-SCoA, or, in higher plants, the use by certain Anacardiaceae of unsaturated fatty acids as starters for the biosynthesis of alkenylphenols.



Formation of methylphloracetophenone; its dimerization leads to usnic acid (see generalities)



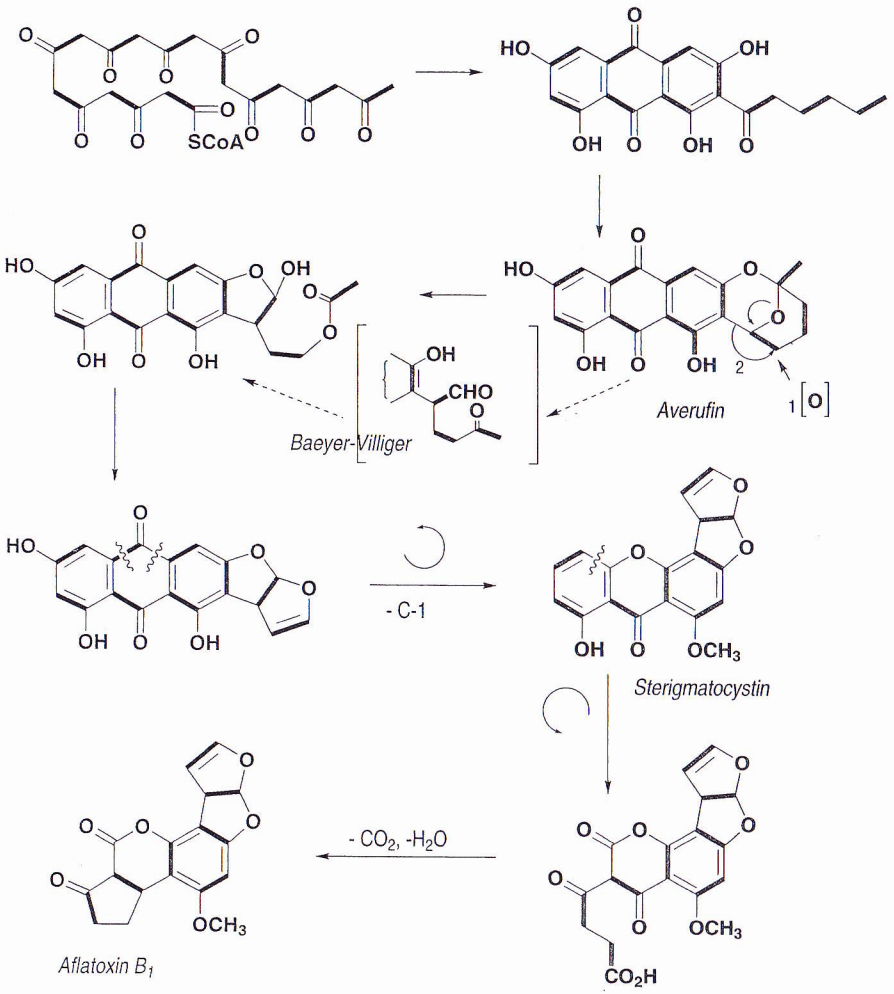
Origin of alkenylphenols in Anacardiaceae: the starter is a fatty acid

The formation of aromatic compounds from poly-β-ketothioesters is particularly common in Bacteria, Lichens, and Fungi: toxins and antibiotics are often elaborated by a process of this type. In higher plants, this pathway only applies to a limited number of compounds, including naphthoquinones, anthraquinones, chromones, and depsides. On the other hand, a common occurrence is that of mixed metabolites, which only partially arise from the metabolism of acetate: flavonoids, xanthones, stilbenoids, terpenophenols of *Cannabis*, certain anthraquinones, and some alkaloids (for example tropanes, harman, and tetrahydroisoquinolines of Cactaceae).

The study of the biosynthesis of "polyketides" is dominated by the massive use of labeling experiments with ^{13}C, a stable isotope whose presence is directly detected, without preliminary degradation, by NMR. Using double-labeled acetate, in other words [1,2-$^{13}C_2$]-acetate, allows the observation of couplings between *adjacent* ^{13}Cs, and therefore the detection of units that are incorporated intact, of bond cleavages, of migrations, and so forth (see specialized works and texts).

BIBLIOGRAPHY

Mann, J. (1987). Secondary Metabolism, 2nd edn., University Press, Oxford.



Biosynthetic origin of a complex polyketide: example of aflatoxin B_1
(mycotoxin elaborated by Aspergillus *sp., see p. 275)*

Note: the boldface bonds represent the acetate units incorporated intact into the structure (double-labeled acetate).

Quinones