1.10 Type I Modular PKS

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1.10.1 Introduction to Polyketides

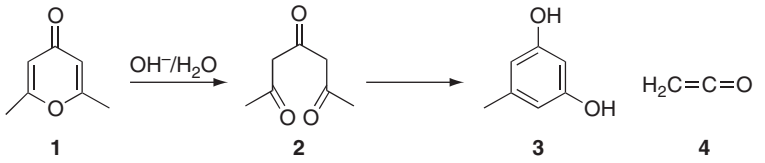
1.10.1.1 Development of the Biosynthetic Theory

The term polyketide (PK) was coined more than 100 years ago by the organic chemist J. Collie to describe a class of aromatic molecules produced synthetically while studying pyrones.[1] For example, in **Scheme 1**, on treatment with aqueous sodium hydroxide, the pyrone (**1**) was converted into the phenolic compound, orcinol (**3**). Collie rightly proposed that the triketone (**2**) was an intermediate. He also noted that the substitution pattern of hydroxyl groups on alternate carbons of the aromatic ring of orcinol was characteristic of many phenolic natural products.[2] He therefore proposed that such β-polyketones might be produced in living cells as biosynthetic precursors of phenolic natural products with a 1,3 pattern of hydroxyl groups. He also noted that the proposed polyketone intermediates could be hypothetically considered as polymers of ketene (**4**). He therefore coined the term PK for both the polyketones and the derived phenolic natural products.

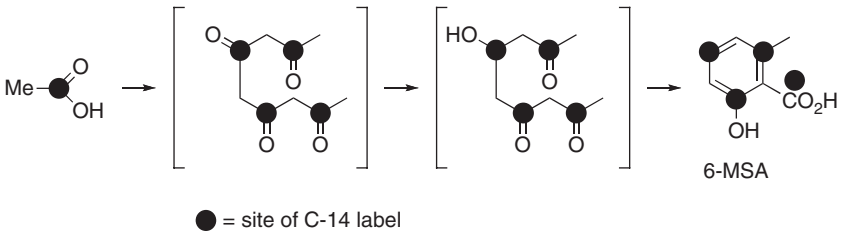
With these biosynthetic speculations, Collie was well in advance of his contemporaries. His ideas failed to achieve the impact they deserved. They and the term PK therefore became buried in the literature for more than 50 years.

In the mid-1950s, Birch independently had essentially the same idea.[3] By this time much more was known about the molecules and chemical processes occurring in living cells, and so Birch was able to extend the proposal with the suggestion that the proposed polyketones might arise in nature by condensation of acetate units. Unaware of the term PK, some natural product chemists coined the term acetogenin for these classes of natural products (See Chapters 2.04, 2.07, 2.17, 2.19, 3.03, 3.06, 3.08).

Working in the 1950s, Birch also had a key technical advantage over Collie in that radiotracer elements including carbon-14 had become commercially available. He therefore was able to test his acetate hypothesis by feeding labeled acetic acid to cells of a fungus that produce 6-methylsalicylic acid (6-MSA).[3] The resulting natural product molecules were isotopically labeled as shown in **Scheme 2** in the manner predicted by Birch's acetate hypothesis, thereby vindicating the biosynthetic proposal. Birch went on to justify his hypothesis with many other phenolic systems.



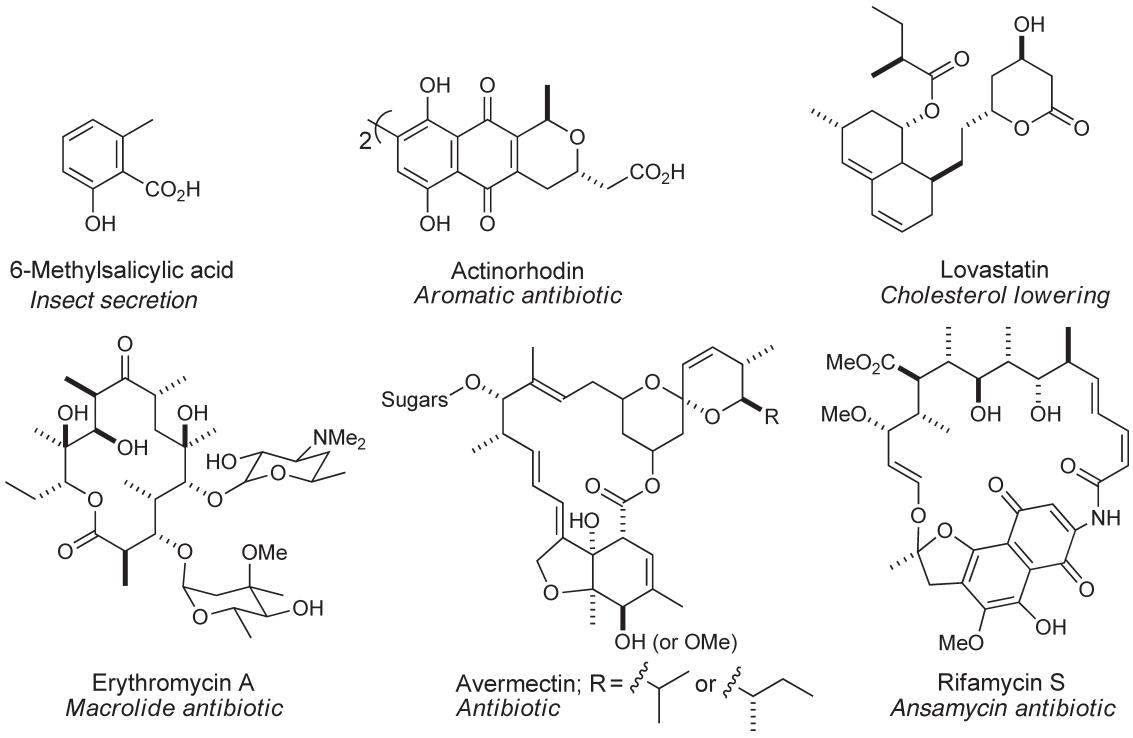
Scheme 1 Collie's chemical studies of polyketones and polyketides.



Scheme 2 Biosynthetic study of 6-MSA biosynthesis.[3]

Later, when Collie's pioneering contributions were rediscovered, the research community had to choose what to call this class of acetate-derived natural products. Both terms, acetogenin and PK, had their adherents for a while, but in the end PK gained universal acceptance.

Since the middle of the last century, there has been a vigorous search for new natural products and as a result, the number and diversity of PK structures has rapidly increased.[4–11] Some high-profile compounds are shown in **Scheme 3**. As can be seen, some are aromatic compounds whereas others are aliphatic. Collie would have been surprised to see the latter included under his chosen heading, but with the benefit of further knowledge accumulated over half a century, Birch was able to produce a unified hypothesis, which accounted for the genesis of both types of PK. He based his ideas partly on mechanistic reasoning and partly on analogy



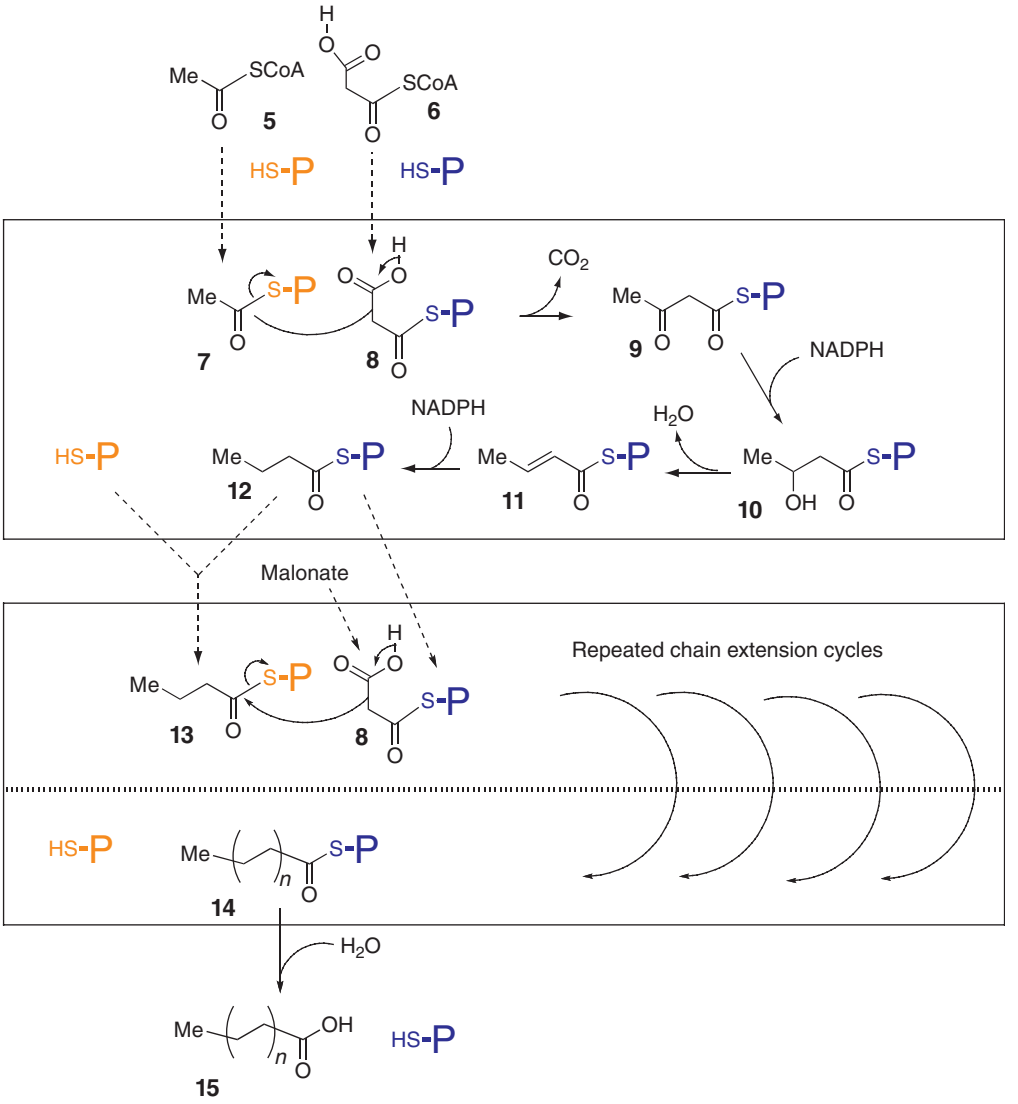
Scheme 3 Polyketide structures.

with new knowledge of fatty acid biosynthesis. The relationship between fatty acid biosynthesis and that of PKs continues to influence thinking in the PK field to this day, so it is appropriate to give a brief account of the biosynthetic reactions used in fatty acid biosynthesis.

1.10.2 Fatty Acid Biosynthesis – Reactions and Enzymes

1.10.2.1 Synthetic Operations

Saturated fatty acids such as stearic acid are produced by repeated condensation of units of acetate to give a chain of the requisite length. The detailed steps are shown in **Scheme 4**. On mechanistic grounds, it is not surprising that the carboxyl groups of reacting acyl units are derivatized as thioesters using active thiol groups at the active sites of the participating ketosynthase (KS) enzymes and acyl carrier proteins (ACPs). This derivatization activates the carbonyl toward nucleophilic attack, and so helps to stabilize enolate anion derivatives where they occur in the



Scheme 4 The interactions between proteins and intermediates during the successive cycles of chain extension in fatty acid biosynthesis.