BIOGENETIC-TYPE SYNTHESIS OF PHENOLIC COMPOUNDS

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The acyl polymalonate (polyacetate) route[1-3] to naturally occurring phenolic compounds is now supported by a considerable amount of experimental evidence. Detailed descriptions of the historical development of this metabolic pathway have been given in several excellent reviews.[4-6] A brief summary of this major pathway to phenolic compounds is given in Figure 1. This review is concerned with the various attempts which have been made to duplicate, in the laboratory, the final stages of this biosynthetic sequence, *i.e.*, with the synthesis of protected or unprotected β-polyketo esters (**1**) and their cyclization to phenolic compounds of natural type.

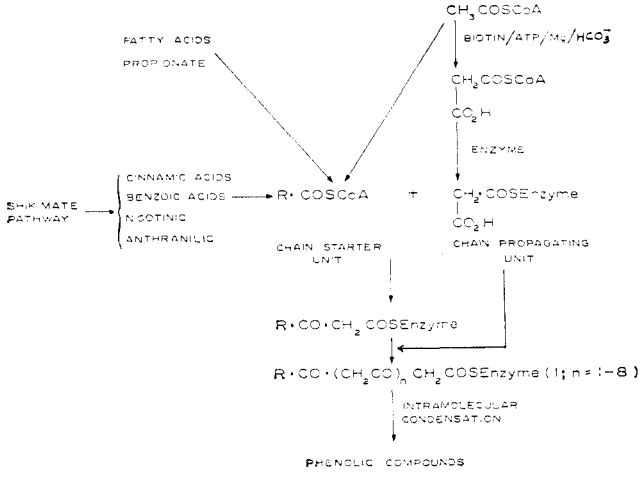


Figure 1.

The early work is due to Collie[7,8] who demonstrated that dehydroacetic acid (**2**, Figure 2), a protected β-triketone, could be converted to orcinol (**5**) by treatment with sodium hydroxide. Orcinol was also obtained by acid-catalyzed cyclization of heptane-2,4,6-trione (**4**) while intermolecular

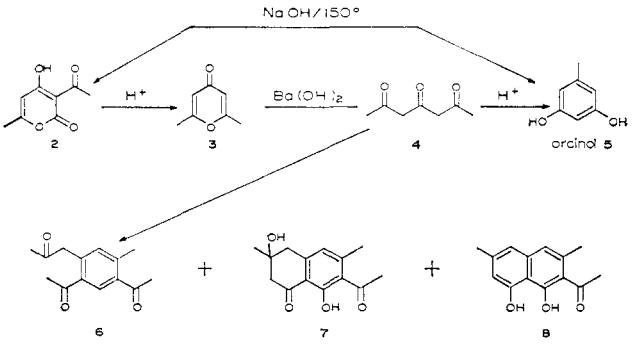


Figure 2.

condensation yielded three aromatic compounds (**6-8**) whose structures have been confirmed by Birch and his coworkers[9] and by Bethel and Maitland.[10] The experimental observations noted above led Collie[1] to suggest that similar reactions occurred in nature, and his statements in this area are regarded as the first enunciation of the polyacetate biosynthetic hypothesis.

More explicit proposals were made by Birch[2] in 1953 and by Robinson[3] in 1955, and these form the basis of the "polyacetate" route to phenolic compounds. Various modifications have been made since then: the importance of malonyl coenzyme A as a chain-propagating unit and the use of other acids besides acetic as chain-initiating units has led to the general term "acyl polymalonate" route (see Figure 1).

During the past decade various reports have appeared which describe the conversion of protected and unprotected β-polyketones and β-polyketo acids to aromatic compounds. These results have shown that to some extent the cyclization–aromatization processes considered to be involved in the acyl polymalonate route can be duplicated in the laboratory. The first of these was reported by Birch and his coworkers[9] and described a biogenetic-type synthesis of dihydropinosylvin (**16**). These results are summarized in Figure 3 and involve base treatment of the γ-pyrone **14** or the corresponding trione **15**. The products obtained, dihydropinosylvin (**16**) and the phenol **17**, are derived by alternative condensation modes of the β-triketone **15**. Unsuccessful attempts to produce pinosylvin (**12**) by treating **10** or **11** with base were also reported. Later work by Birch and his colleagues[11] described a

(1) J. N. Collie, *J. Chem. Soc.*, **91**, 1806 (1907).
(2) A. J. Birch and F. W. Donovan, *Aust. J. Chem.*, **36**, 360 (1953).
(3) R. Robinson, "Structural Relations of Natural Products," Clarendon, Oxford, 1955.
(4) A. J. Birch, *Fortschr. Chem. Org. Naturst.*, **14**, 186 (1957); *Proc. Chem. Soc.*, **3**, (1962); *Science*, **156**, 202 (1967).
(5) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes and Acetogenins," W. A. Benjamin, New York, N. Y., 1964.
(6) J. D. Bu'Lock, "The Biosynthesis of Natural Products," McGraw-Hill, London, 1965.
(7) J. N. Collie and W. S. Meyers, *J. Chem. Soc.*, **63**, 122 (1893).
(8) J. N. Collie, *ibid.*, **63**, 329 (1893).
(9) A. J. Birch, D. W. Cameron, and R. W. Richards, *ibid.*, 4395 (1960).
(10) J. R. Bethel and P. Maitland, *ibid.*, 3751 (1962).
(11) A. J. Birch, F. Fitton, D. C. C. Smith, D. E. Steere, and A. R. Stelfox, *ibid.*, 2209 (1963).

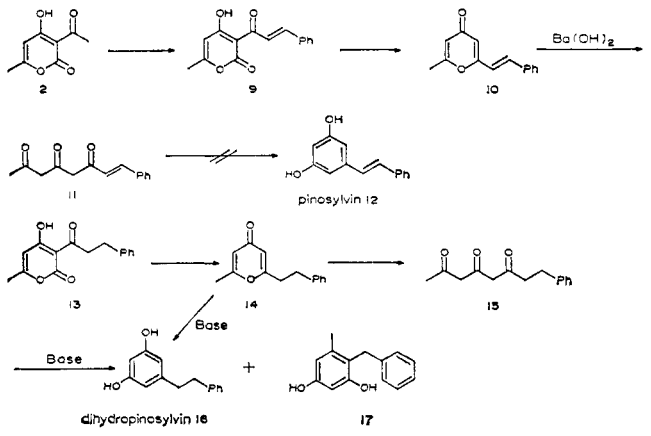


Figure 3.

potentially useful route to β-polyketo acid chains involving ozonolysis of dihydro aromatic compounds (Figure 4). In

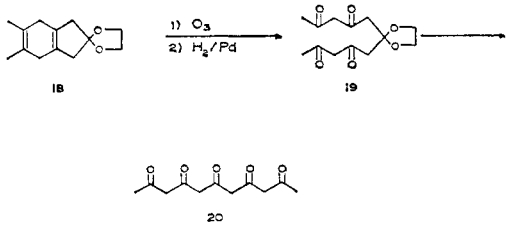


Figure 4.

this way the protected pentaketone **19** was isolated from dihydroindanone ketal (**18**). However, attempts to isolate the pentaketone **20** by a similar route or to convert **19** to phenolic compounds were unsuccessful. The basic idea used by Birch (and indeed by Collie), *i.e.*, to protect the labile polyketone or polyketo acid in the form of a pyrone ring, was adopted by Money, Scott, and their coworkers.[12] In particular, the possibility of using the condensed dipyrone system **21a** (synthesis, Figure 5) as the protected form of a β-triketo acid derivative **22** was fully investigated.

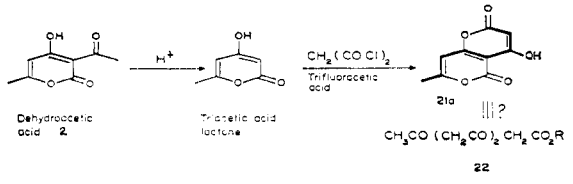


Figure 5.

According to the acyl polymalonate route the cyclization–aromatization reactions of an intermediate β-triketo enzyme bound thiol ester (**1**, $n = 2$; Figure 6) is theoretically capable of producing a large number of phenolic compounds differing widely in structural type. This is made possible by the operation of several variables: these are (a) the nature of the group (R) associated with the chain-initiating unit, RCOS-CoA; (b) the nature of the condensation–aromatization process, *i.e.*, aldol or Claisen; and (c) secondary modifications including alkylation, oxidation, or reduction which may take place before or after the aromatization process. The operation of variables (a) and (b) in a β-triketo ester intermediate are summarized in Figure 6.

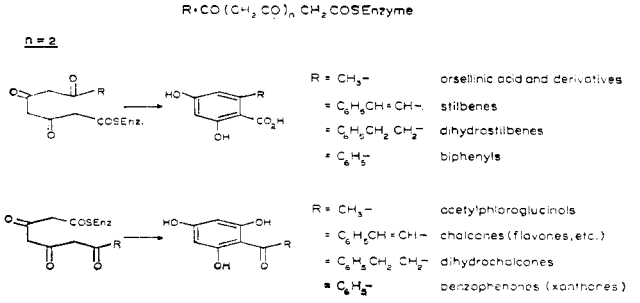


Figure 6.

The results published by Money, Scott, and their colleagues[12–14] have shown that the dipyrone ring system (**21a–d**) can be used effectively as a means of protecting β-triketo ester chains. Thus it was shown that dipyrone **21a** could be converted to phenolic compounds of natural type and that control over the types of phenolic compound obtained could be achieved by appropriate reaction conditions. These results are shown in Figure 7; aqueous or

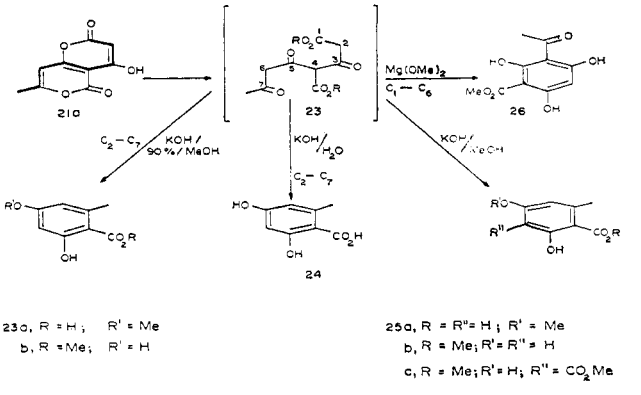


Figure 7.

alcoholic potassium hydroxide treatment gave orsellinic acid and derivatives (**23a,b–25**)[12] by aldol condensation of the intermediate keto diester chain (**23**). In contrast, methanolic magnesium methoxide promoted Claisen condensation and the formation of carbomethoxyphloracetophenone (**26**).[13] Similar results[13,14] were obtained with the dipyrones (**21b–d**). The dipyrone **21b** (Figure 8) is potentially equivalent to the β-triketo ester **27** postulated as an intermediate in the biosynthesis of the flavonoids and natural stilbenes (Fig-

(12) T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright, and A. I. Scott, *Tetrahedron*, **23**, 3435 (1967).

(13) J. L. Douglas and T. Money, *ibid.*, **23**, 3545 (1967).

(14) J. L. Douglas and T. Money, *Can. J. Chem.*, **45**, 1990 (1967).

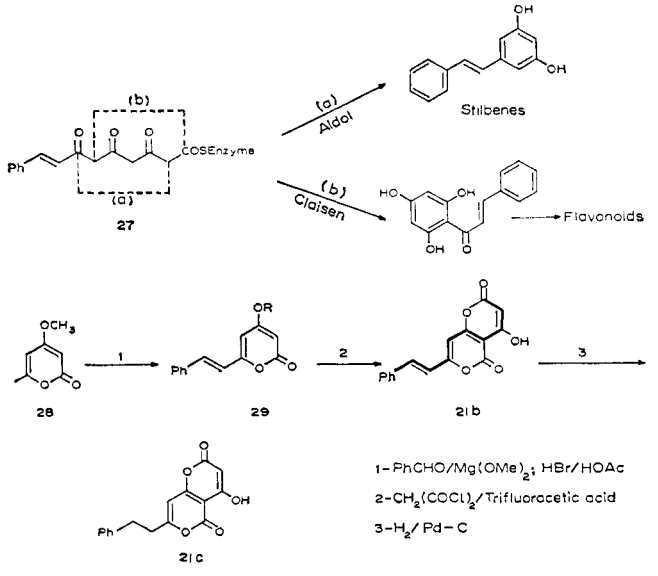


Figure 8.

ure 8). Compounds belonging to these two groups of natural products were obtained when the dipyrone **21b** was treated under the basic conditions described above (Figure 9).[13,15]

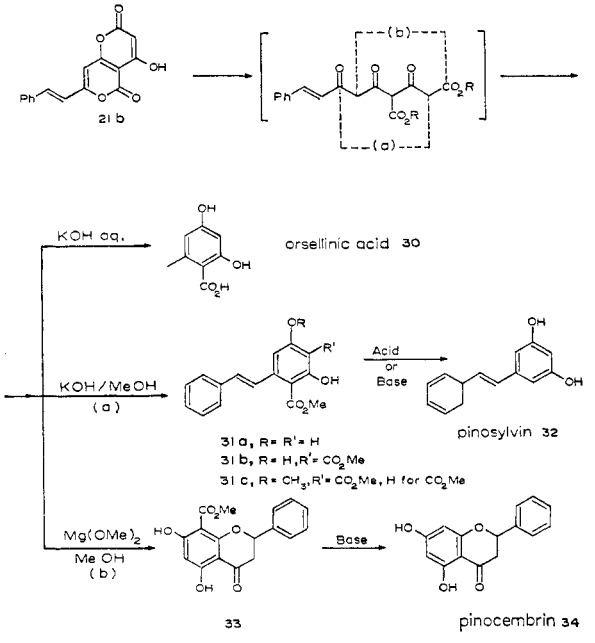


Figure 9.

As before control of this condensation–aromatization process was achieved by choosing the appropriate basic reagent. In predictable fashion these results were extended to include the dipyrones **21c** (Figure 10)[13] and **21d** (Figure 11).[14,15] A summary of the results obtained with the dipyrones **21a–d** are shown in Figure 12 and indicate that a laboratory simulation of the natural cyclization–aromatization processes outlined in Figure 6 can be achieved.

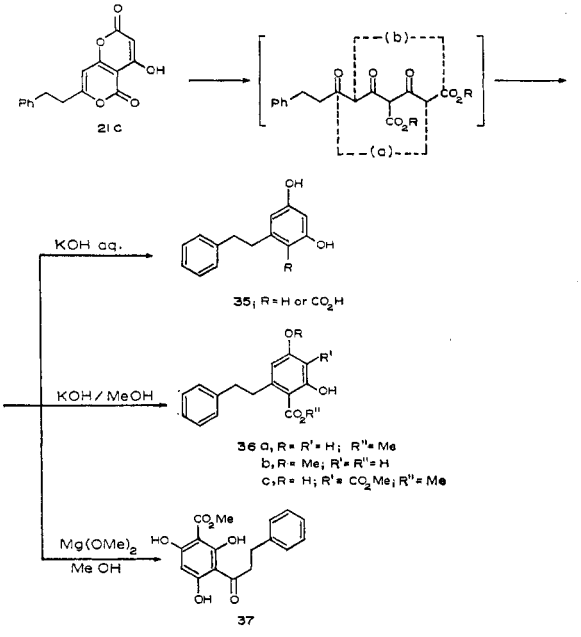


Figure 10.

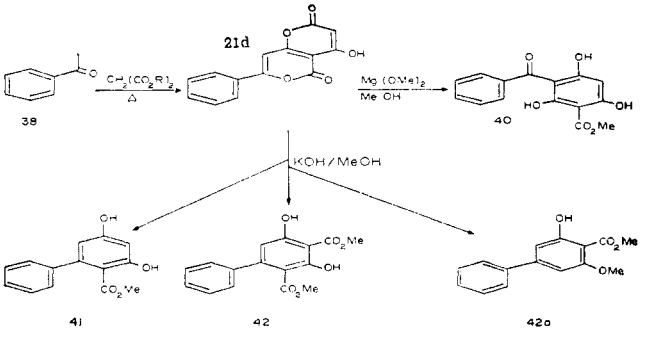


Figure 11.

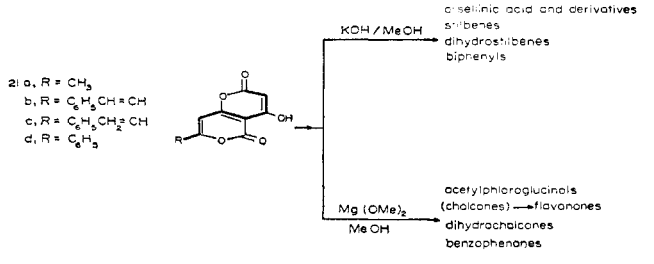


Figure 12.

The directional control exhibited by magnesium methoxide in the reactions described above has not yet been studied in detail.[13] The well-known chelating property of magnesium ions is presumably involved; prior chelation of the dipyrone or chelation of the acyclic intermediate could conceivably reduce the possibility of aldol condensation and allow Claisen condensation to occur. The work of Crombie and his coworkers[16,17] is relevant to this question and further comment on the role of magnesium ions is given in the sequel.

(15) Structures **31c**, **42a**, and **46a** were suggested by T. M. Harris and T. T. Howarth, *Can. J. Chem.*, **64**, 3739 (1968); they correct the previously assigned structures for these compounds in which the carbomethoxy group was in an alternative position *ortho* to the hydroxyl function.

(16) L. Crombie and A. W. G. James, *Chem. Commun.*, 357 (1966).

(17) (a) L. Crombie, D. E. Games, and M. H. Knight, *Tetrahedron Lett.*, 2313 (1964); (b) *J. Chem. Soc. C*, 757, 763, 773 (1967).

The acyl polymalonate hypothesis postulates that β-polyketo enzyme bound thiol esters of variable length act as intermediates in the biosynthesis of phenolic compounds. These intermediates are conveniently represented by the general formula **1**. The work involving dipyrones was con-

$$RCO(CH_2CO)_nCH_2COSEnzyme$$
1

cerned with the laboratory duplication of cyclization processes associated with β-triketo intermediates (*i.e.*, **1**, $n = 2$). A logical extension of this work related to the β-tetraketo intermediate (**1**, $n = 3$) has also been described.[12,18] Biosynthetic theory predicts that a chain length of this size (*i.e.*, **1**, $n = 3$) has three possible cyclization–aromatization modes. These are illustrated in Figure 13, and the natural

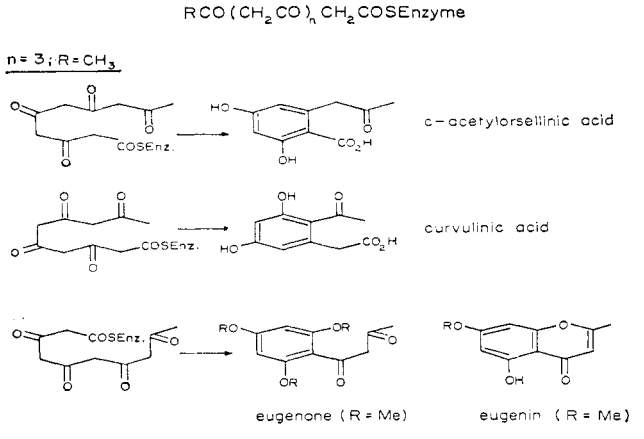


Figure 13.

products shown represent three basic structural types of phenolic compounds which can be obtained by the operation of these reactions. Subsequent results[12,18] (Figure 14)[15] have

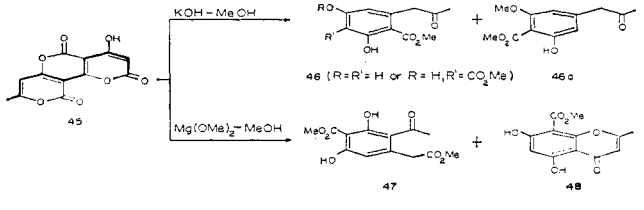
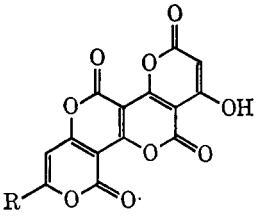


Figure 14.

shown that compounds belonging to each of these structural categories can be obtained when the tripyrone (**45**)[12] (synthesized from dipyrone **21a** by treatment with malonyl chloride in the presence of trifluoroacetic acid) is treated with alcoholic potassium hydroxide or alcoholic magnesium methoxide.

Recent studies have been concerned with attempts to extend the pyrone-protecting concept to higher members of the β-polyketo ester series. In this connection the synthesis of tetrapyrone (**49**)[12] was achieved, but attempts to obtain



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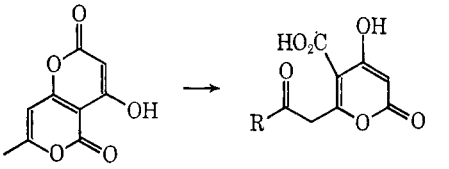
aromatic compounds by the action of base or acid were unsuccessful.[19] Instead evidence was obtained for partial ring opening of the tetrapyrone structure. Selective ring opening of dipyrones has previously been observed[20] (*e.g.*, **21b,c** → **50b,c**) by short treatment with base, and recently an



21b, R = $C_6H_5CH{=}CH$ **50b**, R = $C_6H_5CH{=}CH$
c, R = $C_6H_5CH_2CH_2$ **c**, R = $C_6H_5CH_2CH_2$

application of this phenomenon to the dipyrone **21a** has been used to synthesize tetraacetic acid lactone **51** and convert this *via* the dihydro derivative **52** to 6-methylsalicylic acid (**53**)[21] (Figure 15). Previous to this Bentley and Zwitkowits[22]

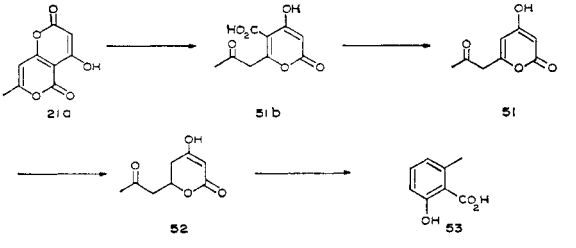


Figure 15.

had demonstrated that tetraacetic acid lactone **51** could be converted to orcinol (**54**), orsellinic acid (**30**), or methyl orsellinate (**55**) using acidic, basic, or neutral conditions (Figure 16).

An alternative way of utilizing pyrone frameworks as a means of obtaining synthetically inaccessible β-polyketo ester chains has also been investigated.[23] One objective of these later studies has been the synthesis of di- and tripyrone structures of the type shown in Figure 17 (**56–58**), since this could provide a reasonably efficient method of producing long-chain β-polyketo esters. Various modifications of these proposals including routes to naphthacenic compounds reminiscent of those involved in tetracycline biosynthesis are also being studied. The basic pyrone units **62** and **63** (Figure

(18) F. W. Comer, T. Money, and A. I. Scott, *Chem. Commun.*, 231 (1967).

(19) F. W. Comer, T. Money, J. J. Ryan, and A. I. Scott, unpublished observations.

(20) J. L. Douglas and T. Money, unpublished observations; J. L. Douglas, Ph.D. Thesis, University of Sussex, 1968, pp 94–96.

(21) H. Guilford, A. I. Scott, D. Skingle, and M. Yalpani, *Chem. Commun.*, 1127 (1968).

(22) R. Bentley and P. M. Zwitkowits, *J. Amer. Chem. Soc.*, **89**, 676 (1967).

(23) J. L. Douglas and T. Money, *Can. J. Chem.*, **46**, 695 (1968).

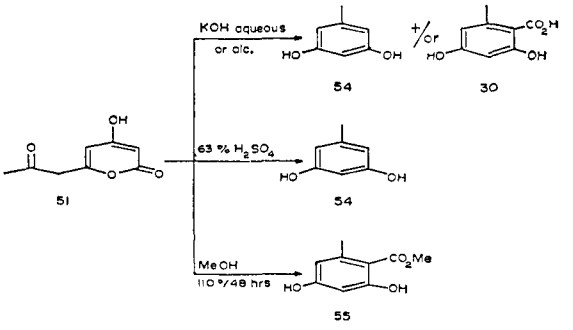


Figure 16.

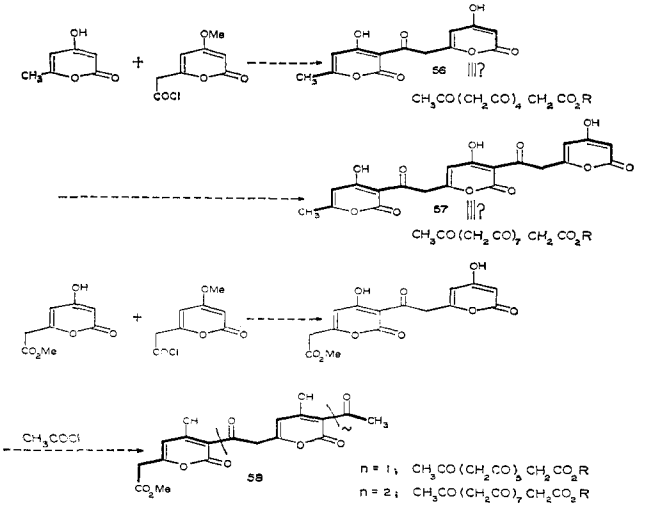


Figure 17.

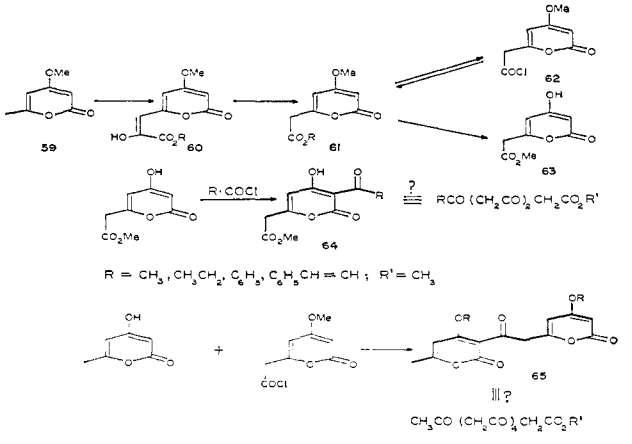


Figure 18.

18) have been synthesized and their chemistry investigated. In particular, acylation studies have provided methods capable of producing the 3-acylpyrones **64** and **65** (R = H) in reasonable yield. Preliminary attempts to convert the 3-acetyl-α-pyrone **64** (R = CH_3) to aromatic compounds of natural type were notably unsuccessful; a variety of acid and basic conditions yielded degradation products **66**, **67**, and **68** (Figure 19). The lack of success in these reactions is also supported by ultraviolet spectral data which indicate

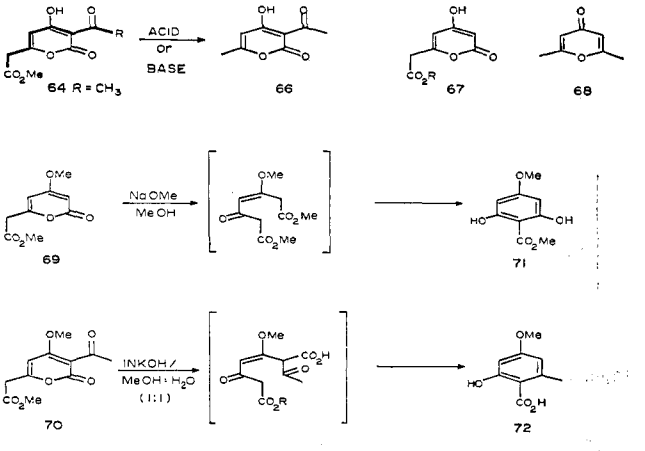


Figure 19.

that the primary effect of base on **64** (R = CH_3) is to produce the corresponding anion and that ring opening is difficult to achieve. In contrast to this, base treatment of the methyl ethers **69** and **70** smoothly converted them to aromatic compounds **71** and **72**.[24] Preliminary results on the effect of basic media on the dipyrone dimethyl ether **65** (R = CH_3) indicate that phenolic compounds corresponding to the cyclization of an intact β-pentaketo ester chain are being formed. A recent report by Scott and his coworkers[25] has shown that the pyrone acid **61** (R = H)[23] can be converted to the keto dipyrone **74** and that treatment of the latter compound with methanolic potassium hydroxide yields the xanthone **75** (Figure 20).

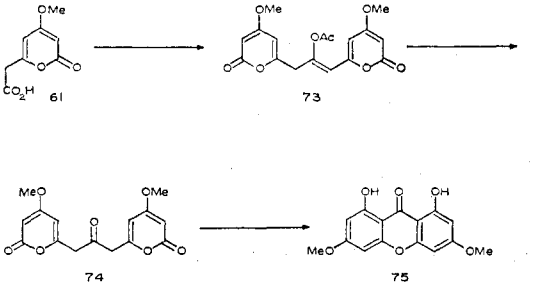


Figure 20.

As part of a detailed investigation[17] into the effect of sodium and magnesium alkoxides on pyrone systems, Crombie and his coworkers have also shown that dipyrones **76** (R = H or CH_2Ph) can be converted to acylphloroglucinols **77** (R = H or CH_2Ph) when treated with *excess* (10 mol) magnesium methoxide.[16] An explanation for the effect of magnesium ions on the mode of cyclization (aldol or Claisen) of the intermediate poly-β-carbonyl systems has been provided.[16] As shown (Figure 21) this involves formation of an intermediate bis chelate (**76b**); aldol condensation is therefore prevented and the alternative Claisen condensation takes place to yield acylphloroglucinols **77** (R = H, CH_2Ph).

(24) C. T. Bedford, J. L. Douglas, B. E. McCarry, and T. Money, *Chem. Commun.*, 1091 (1968).
(25) D. G. Pike, J. J. Ryan, and A. I. Scott, *ibid.*, 629 (1968).

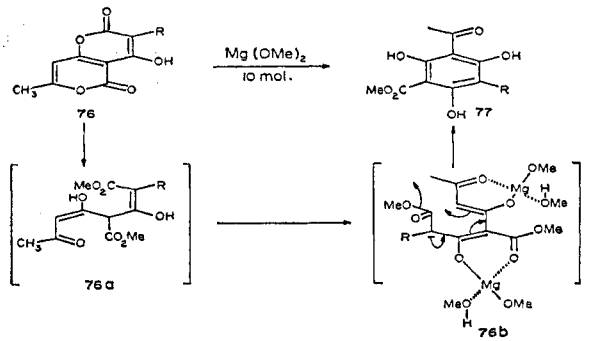


Figure 21.

The effect of magnesium methoxide on monopyrones and straight-chain β-triketones has also been investigated by Crombie and his coworkers.[16,17,26] Dimethyl xanthophanic enol (**78**) and approximately 2 mol of sodium methoxide give **79**, while treatment with magnesium methoxide in limited amount (2 mol) yields compounds **80** and **81** (Figure 22). The

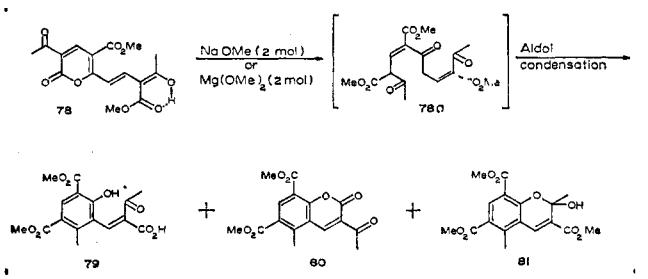


Figure 22.

formation of these products is best explained by aldol condensation of the branched-chain intermediate **78a**. When dimethyl xanthophanic enol (**78**) is treated with an excess of magnesium methoxide (6 mol), the product **82** is formed in 78% yield.

It has been suggested[26] that the formation of **82** involves Claisen condensation of an intermediate having two stable magnesium-containing conjugate chelate rings, **78b** (Figure 23). Recent studies by Crombie and his coworkers[27]

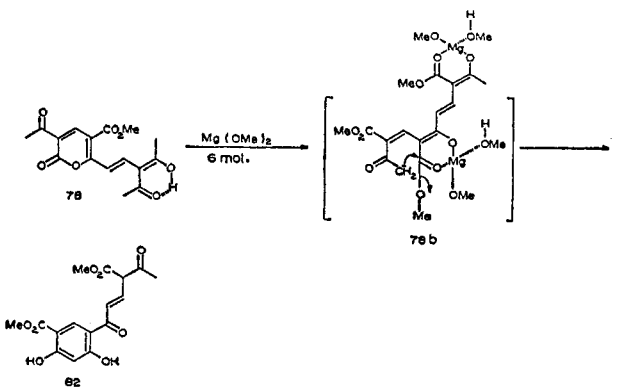
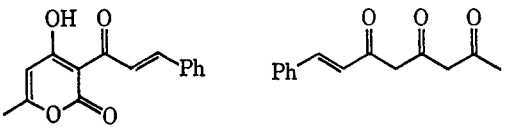


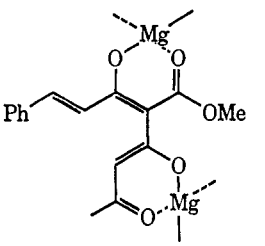
Figure 23.

(26) L. Crombie, D. E. Games, and M. H. Knight, *Chem. Commun.*, 355 (1966).
(27) L. Crombie, M. Eskins, and D. E. Games, *ibid.*, 1015 (1968).

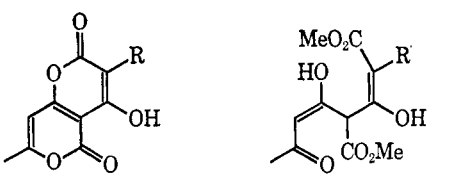
indicate that the nature and composition of the products obtained from xanthophanic enol are dependent upon the concentration of magnesium methoxide. The effect of magnesium methoxide on the monopyrone **83** and the triketone **84** has also been studied, and it was shown[16] that these compounds were resistant to cyclization-aromatization pro-



cesses. It has been suggested that these compounds form chelated intermediates, *e.g.*, **85**, which are geometrically unsuitable for cyclization to aromatic compounds.



The explanation given above (*cf.* Figure 21) for the effect of magnesium ions on the cyclization mode of dipyrones (*e.g.*, **76**, R = H or $C_6H_5CH_2$) requires the presence of a γ-carbomethoxy group in the open-chain intermediate **76a**.



Recent studies[28] indicate that bis chelates (*e.g.*, **85**) are not necessarily involved in those reactions where magnesium ions are exerting control over the mode of cyclization of a β-triketo ester chain. Thus the pyrone **86a** (which cannot form a bis chelate) was converted to the Claisen condensation product **86b** when treated with methanolic magnesium methoxide (Figure 23a). In this reaction a magnesium complex

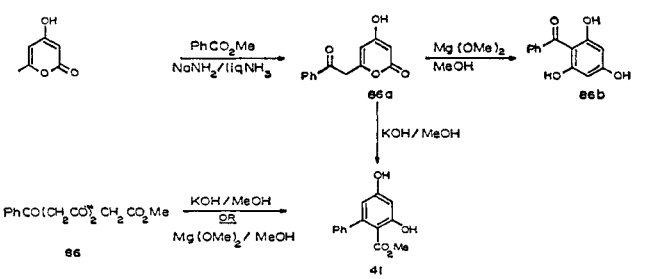


Figure 23a.

of the triketo ester **86** was shown to be an intermediate. Under similar conditions the ester **86** yielded aldol condensa-

(28) T. M. Harris, M. P. Wachter, and G. A. Wiseman, *ibid.*, 177 (1969).

tion product **41** only, and it has been concluded that isomeric magnesium complexes of **86** are involved in these reactions.

The synthesis of unprotected β-polyketo acids or esters has received considerable attention. Of particular significance is the work of Harris and Carney[29] who have developed a synthesis of β-triketo acids **89** and esters from β-triketones **88**. A biogenetically modeled synthesis of β-resorcylic acids **90** was achieved when the triketo acids **89** were treated at room temperature with aqueous buffer (pH 5) (Figure 24).

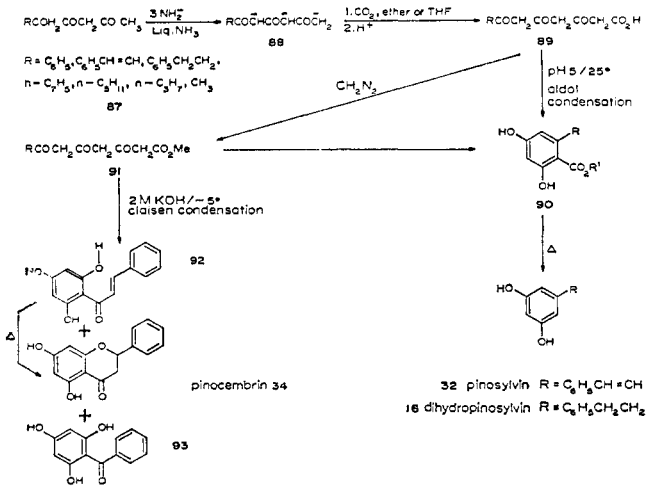
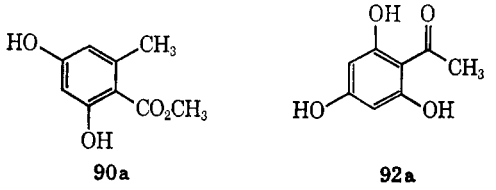


Figure 24.

Enzyme-bound thiol esters of the triketo acids are considered to be intermediates in the biosynthesis of many naturally occurring phenolic compounds: the formation of resorcylic acids **90** (R′ = H) under mild conditions is a laboratory duplication of the aldol condensation processes which could occur in nature. Thermal decarboxylation of **90** (R = C_6H_5-CH=CH, R′ = H or R = $C_6H_5CH_2CH_2$, R′ = H) yielded the natural products, pinosylvin (**32**) and dihydropinosylvin (**16**), respectively. Alternative Claisen condensation of β-triketo ester chain (*e.g.*, **91**) has also been reported by Harris and Carney.[29] Careful esterification of **89** (R = C_6H_5CH=CH or R = C_6H_5) with diazomethane yielded the corresponding esters **91** (R = C_6H_5CH=CH or R = C_6H_5, respectively) which on separate treatment with 2 *M* KOH at −5° provided a mixture of compounds from which benzoylphloroglucinol (**93**), cinnamoylphloroglucinol (**92**), and racemic pinocembrin (**34**) could be isolated; a laboratory duplication of the biosynthetic routes to benzophenones, chalcones, and flavanones had thus been achieved. The formation of acylphloroglucinols from β-triketo esters was highly sensitive to experimental conditions and competitive aldol condensation to resorcylic esters (*e.g.*, **90**, R′ = Me) was dominant in many cases.

The synthetic route to β-triketo acids described above was not successful for tetraacetic acid (3,5,7-trioxooctanoic acid) (**89**, R = CH_3). However, a recent report[30] indicates that the use of lithium diisopropylamide as basic reagent makes possible the synthesis of this acid in reasonable yield. Controlled cyclization of the corresponding ester **91** (R = CH_3) using conditions similar to those described above yielded aldol and Claisen condensation products **90a** and **92a**, respectively.



90a **92a**

Enzyme-bound thiol esters of β-diketo acids are presumably involved in the biosynthesis of the natural 4-hydroxy-2-pyrones. Harris and Harris[31] have reported the synthesis of several diketo acids **94** and their cyclization to 6-substituted 4-hydroxy-2-pyrones (**95**) (Figure 25).

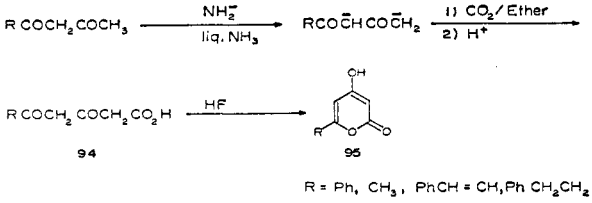


Figure 25.

Recent studies by Harris and Howarth[32] have also shown that a nonaromatic intermediate in the cyclization–aromatization reactions of β-triketo esters can be isolated. Brief treatment of **96** with 0.5 *M* methanolic sodium acetate followed by careful acidification yielded the hydroxy ester **97** and the benzoate **98** (Figure 26). Nonaromatic intermediates

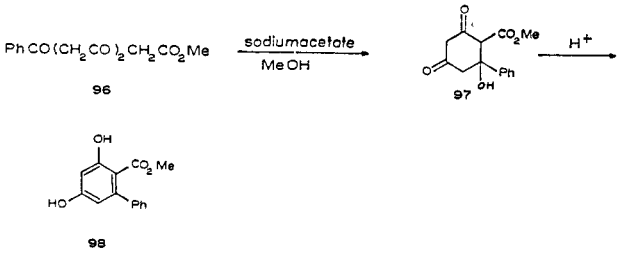


Figure 26.

of the type shown (**97**) were postulated by Birch[33] as possible intermediates in the biosynthesis of acetate-derived phenols. In addition alicyclic intermediates capable of reduction have potential significance in the biosynthesis to 2-hydroxybenzoic acids. For example, 6-methylsalicylic acid (**53**) could be derived by reduction of the intermediate **98** followed by dehydration (Figure 27).

(29) T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, **89**, 6734 (1967); *cf.* K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 4263 (1965).
(30) T. T. Howarth, G. P. Murphy, and T. M. Harris, *J. Amer. Chem. Soc.*, **91**, 517 (1969).
(31) T. M. Harris and C. M. Harris, *J. Org. Chem.*, **31**, 1032 (1966).
(32) T. M. Harris and T. T. Howarth, *Chem. Commun.*, 1253 (1968).
(33) A. J. Birch, *Proc. Chem. Soc.*, 3 (1962).

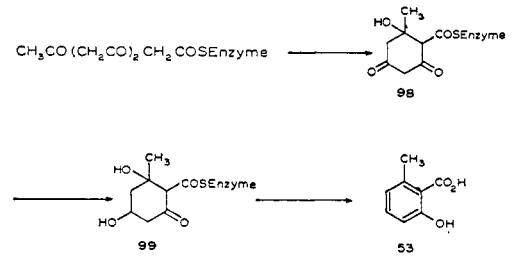


Figure 27.

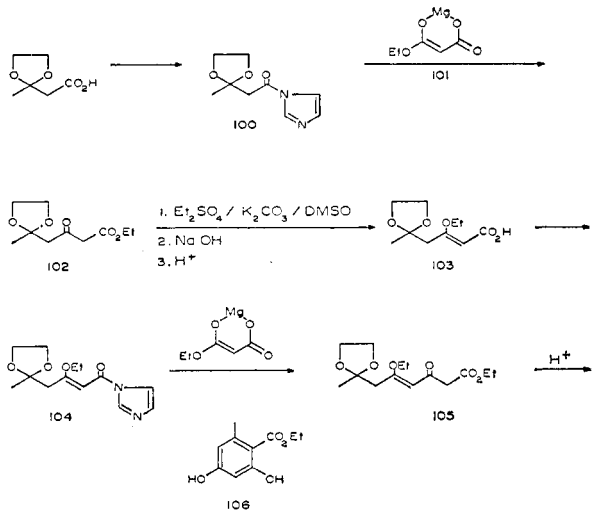


Figure 28.

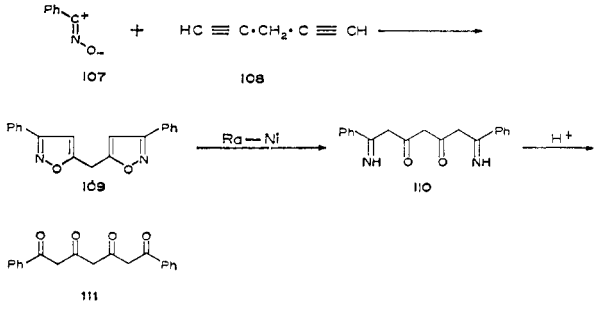


Figure 29.

An elegant synthesis of a protected β-triketo ester chain (**105**) and its subsequent conversion to ethyl orsellinate (**106**) has been reported by Bram.[34] Two interesting features of this synthesis are the use of acylimidazole compounds (*e.g.*, **100**) as intermediates and of monoethyl malonate magnesium chelate (**101**) as a chain-propagating agent (Figure 28).

Casnati and coworkers[35] have synthesized tetra-β-ketones (**111**) by catalytic reduction of bis-isoxazole compounds **109** and subsequent acid hydrolysis of the resulting imino derivatives **110** (Figure 29).

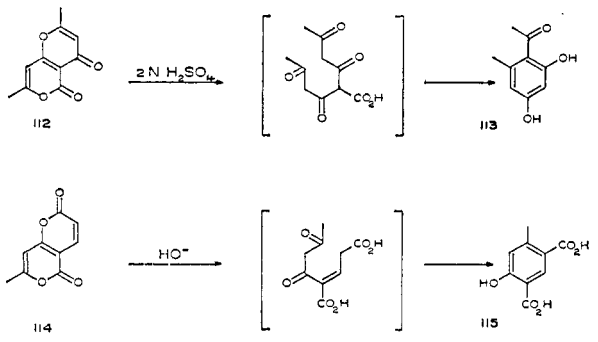


Figure 30.

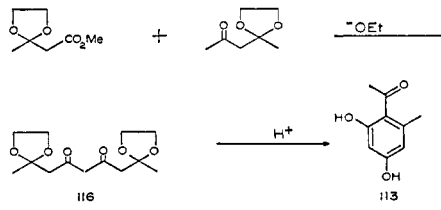


Figure 31.

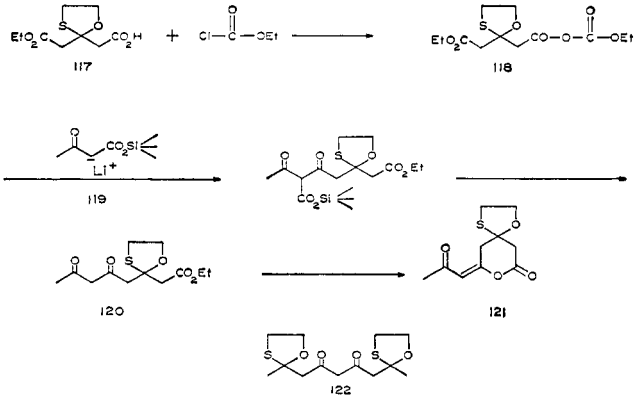


Figure 32.

Other examples of conversion of pyrone derivatives to aromatic compounds have been reported. Treatment of pyronopyrone (**112**) with dilute sulfuric acid gave 2,4-dihydroxy-6-methylacetophenone (**113**)[36] while the desoxy pyronopyrone **114** was converted to the phenolic acid **115** when treated with 10% aqueous sodium hydroxide[37] (Figure 30).

The synthesis of 2,4-dihydroxy-6-methylacetophenone (**113**) from the protected β-tetraketone **116** has also been reported[38] (Figure 31). Schmidt and Schwochau[39] have synthesized protected β-triketo esters **120** and **121** by condensing the mixed anhydride **118** of acetonedicarboxylic acid hemithioketal monoethyl ester (**117**) and ethyl carbonate with the lithium salt of the trimethylsilyl ester of acetoacetic acid (**119**) (Figure 32). Further application of this method provided the protected β-tetraketone **122**.

(34) G. Bram, *Tetrahedron Lett.*, 4069 (1967).
(35) G. Casnati, A. Quilico, A. Ricca, and P. V. Finzi, *ibid.*, 233 (1966).
(36) P. F. Hedgecock, P. F. G. Praill, and A. L. Whitear, *Chem. Ind.* (London), 1268 (1960).
(37) F. C. Cheng and S. F. Tan, *J. Chem. Soc. C*, 543 (1968).
(38) H. Stetter and S. Vestner, *Chem. Ber.*, **97**, 169 (1964).
(39) V. Schmidt and M. Schwochau, *ibid.*, **97**, 1649 (1964); *Tetrahedron Lett.*, 875 (1967); *Monatsh.*, **98**, 1492 (1967).