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SYNTHESIS OF POLYKETIDE-TYPE AROMATIC NATURAL PRODUCTS BY BIOGENETICALLY MODELED ROUTES

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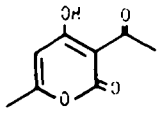
Many of the aromatic compounds found in nature arise from acetate via poly-β-carbonyl intermediates. The pathway by which the so-called polyketide natural products are formed was first grasped by Collie near the turn of the century,[1] but his pioneering ideas concerning biosynthesis had little impact on other chemists because suitable methods for the study of biochemical pathways were not then available. He was, however, able to construct some rather crude chemical models of the aromatization processes. Assessments of the significance of his work are complicated by a misconception which he held concerning the structure of one of his key compounds, dehydroacetic acid (1). Collie erroneously concluded that the compound was the enol lactone (2) of 3,5,7-trioxooctanoic acid and it remained for others to demonstrate that the compound was actually the lactone of a branched triketo acid.[2]



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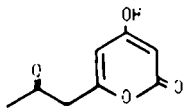

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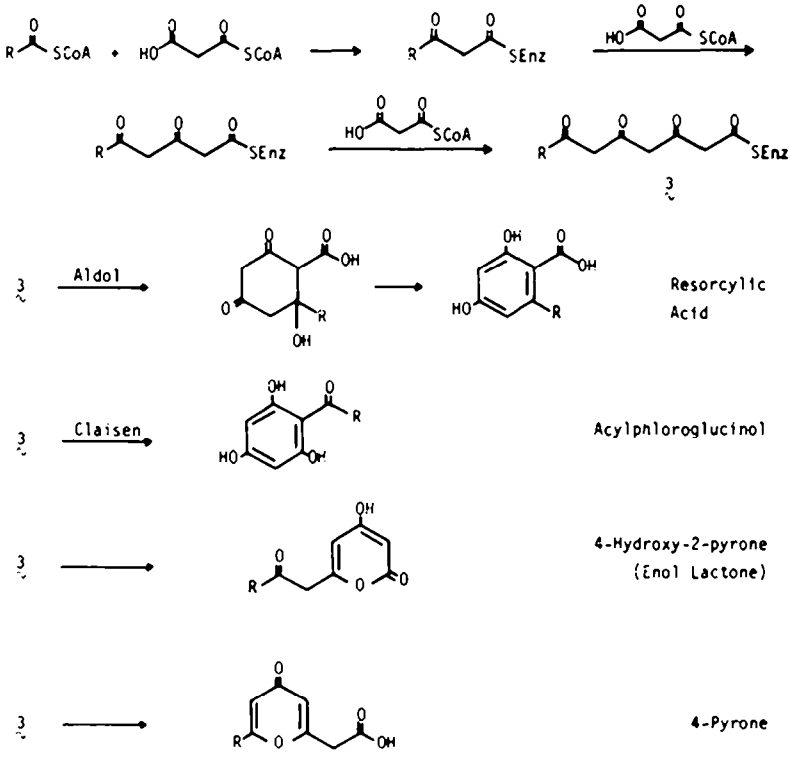
Renewed interest in the biosynthesis of polyketide compounds occurred in 1948 when Robinson revived Collie's ideas[3] and a few years later when Birch formulated the polyketide hypothesis essentially in the form in which it is accepted today.[4] The current conception[5] (Scheme 1) of the biosynthesis of polyketide metabolites is that coenzyme A esters of acetic acid or other carboxylic acids condense with malonyl coenzyme A to give the thiol esters of β-keto acids, which in turn undergo further Claisen-type condensations with malonyl coen-



Scheme 1.

zyme A to give thiol esters of 3,5-diketo acids, 3,5,7-triketo acids, etc. The polyketo acids can undergo a variety of intramolecular condensations to give aromatic and heteroaromatic systems. Carbocyclic systems can be formed by aldol and Claisen (Dieckmann) cyclizations. Other ring closures can give 4-hydroxy-2-pyrones (enol lactones) and 4-pyrones.

The polycarbonyl compounds can undergo a variety of modifications prior to cyclization. Examples include reduction of keto groups to alcohols, and reaction of methylene positions with electrophiles, particularly with alkylating agents. After cyclization other transformations can occur including changes of oxidation state, alkylation, halogenation and even cleavage of the aromatic nucleus. In cases where the polycarbonyl chain is long enough, multiple ring systems can be formed. Many fused polycyclic compounds are known including some where one or more rings are heterocyclic. Polyketide pathways are apparently limited to polycarbonyl compounds of no more than approximately ten carbonyl groups but this is enough to permit construction of tetracyclic systems. Larger acetate-derived aromatic natural products are known but these would appear to arise by oxidative coupling of smaller pre-formed aromatic structures.

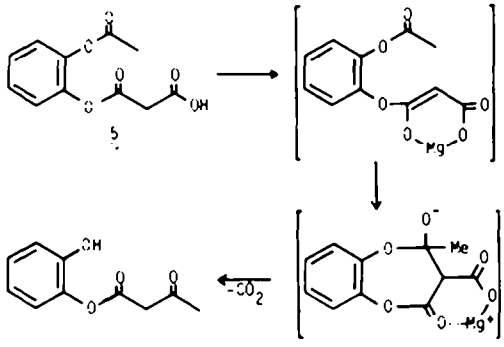
The first *in vivo* experimental support for the polyketide hypothesis was obtained by Birch *et al.*, who demonstrated that acetate could serve as a precursor in the biosynthesis of 6-methylsalicylic acid (**4**) by *Penicillium griseofulvum* and specifically that 1-^{14}C acetate labeled the four sites in **4** as predicted by the polyketide hypothesis (Scheme 2).[6] Numerous supporting studies have been carried out with other natural products of apparent polyketide origin.[7] On the other hand, no direct confirmation of the intermediary role of polycarbonyl compounds has been obtained although the body of indirect evidence, including differential labeling with acetate and malonate and the isolation of polyketide fragments from aborted biosyntheses,[7] is such that little doubt remains that polycarbonyl compounds are intermediates in the formation of many aromatic natural products.

Further evidence for the role of polycarbonyl compounds in the biosynthesis of aromatic compounds has come from the model studies described in this review.[8] While the proviso must be emphasized that studies of chemical models can prove nothing about biochemical mechanisms and pathways, in the present case the model studies provide strong general support for the putative pathways in that the polycarbonyl compounds in many cases undergo the postulated cyclizations without enzymic catalysis.

In favorable cases biogenetically modeled syntheses of aromatic metabolites rival non-biogenetic routes for preparation of these compounds. The comparison is aided by the fact that conventional routes for substitution on aromatic rings are cumbersome for many polyketide metabolites. The dominant feature of these compounds is the presence of multiple hydroxyl groups arranged on alternating positions around the aromatic rings; however, reliable synthetic methods are scarce for direct introduction of hydroxyl groups into aromatic rings, particularly at positions *meta* to other hydroxyl groups.

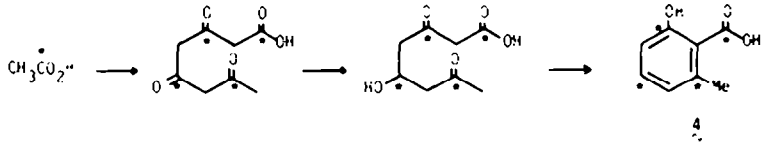
There are three areas in which the study of models might improve our understanding of the biosynthesis of polyketide-type aromatic metabolites. One of them is the process by which polycarbonyl chains are assembled, a second is the regiocontrol of competing cyclization reactions, and the final one is the process by which aromatic metabolites with hydroxyl deletions are formed. These compounds lack one or more of the hydroxyl groups predicted by biogenetic theory.

The first area has received little attention, a noteworthy exception being a model of the initial acylation step recently described by Scott *et al.*[9] Their model (Scheme 3) is an acetate-malonate diester (**5**) of catechol which is converted by base to the acetoacetate ester with concommitant loss of CO_2. The transformation requires Mg^{2+} ion and has been shown to be intramolecular. The applicability of this model to subsequent acylation steps is not known. No other acylation models have been reported.



Scheme 3.

The most heavily studied area has been the control of competing cyclization reactions. With triketo esters the competition is between aldol and Claisen cyclization and to a lesser extent the formation of oxygen heterocycles. Higher polycarbonyl compounds are capable of two or more different aldol condensations to give isomeric products. Compounds containing at least five carbonyl groups can undergo further cyclization to give naphthalenes and other polycyclic compounds. Much effort has been devoted to regiospecific aldol cyclizations; in many cases these reactions have been undertaken with specific natural products as the goals. This review of these cyclization reactions has been organized on the basis of size of the polycarbonyl precursors. The examples surveyed range from readily available compounds containing two or three carbonyl groups to relatively inaccessible ones containing seven to nine. Some of the cyclization reactions have questionable biological rele-

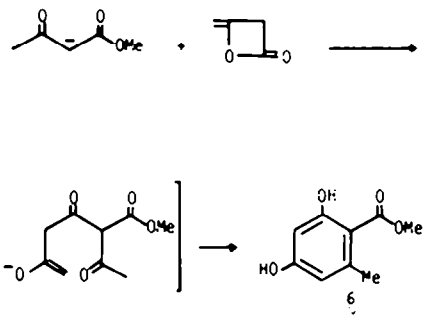


Scheme 2

vance whereas others closely mimic the natural processes.

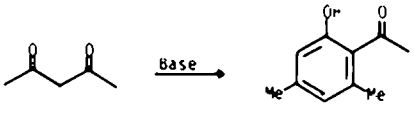
DICARBONYL COMPOUNDS

Many methods are known for the synthesis of malonates, β-keto esters and β-diketones and others are still being developed but none of them will be reviewed here. Dicarbonyl compounds cannot undergo intramolecular reactions to give aromatic and heteroaromatic compounds but they can form these ring systems by intermolecular condensations. The formation of dehydroacetic acid by the self-condensation of ethyl acetoacetate is a prime example of such a condensation.[1,2] A proposal by Robinson[3] that orsellinic acid arises by the self-condensation of acetoacetate has not been borne out by biosynthetic experiments but Kato and Hozumi have recently observed a similar reaction, namely the formation of methyl orsellinate (**6**) by the condensation of methyl acetoacetate with ketene dimer.[10] The reaction has been proposed to involve a branched triketo ester as an undetected intermediate (Scheme 4).



Scheme 4

Acetylacetone undergoes self-condensation in refluxing aqueous sodium hydroxide to give 2,4-dimethyl-6-hydroxyacetophenone (Scheme 5).[11] The use of non-nucleophilic bases should lead to improved yields and wider applicability of this reaction. Phloroglucinol, although found in nature, is probably not a direct product of polyketide biosynthesis but rather results from degradations of more complex polyketide metabolites. A synthesis of phloroglucinol by trimerization of diethyl malonate has been reported.[12]

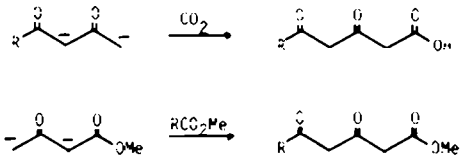


Scheme 5.

TRICARBONYL COMPOUNDS

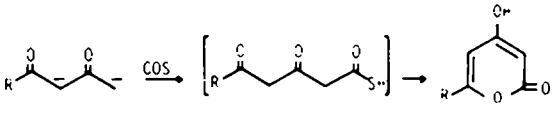
3,5-Diketo acids and their esters can be prepared by hydrolysis or alcoholysis of triacetic lactone and other 4-hydroxy-2-pyrones;[1,13] both the esters and the acids are relatively stable at room temperature. 4-Hydroxy-2-pyrones have been prepared by a number of routes, the most important being deacylation of dehydroacetic acid derivatives which in turn are prepared by self-condensation of β-keto esters.[14] A recent report of the direct transformation of dehydroacetic acid to methyl 3,5-dioxohexanoate[15] indicates that initial deacylation of 3-acyl-4-hydroxy-2-pyrones is not actually necessary. 4-Hydroxy-2-pyrones having complex substituents at the 6 position are also available from electrophilic condensations of the dianion of triacetic lactone[16] or the monoanion of its methyl ether.[17]

Alternatives to the cleavage of pyrones are the carboxylation of the dianions of acetylacetone and other β-diketones[18] and acylations of the dianion of acetoacetic ester (Scheme 6).[19] Alkylation of the trianion of ethyl 3,5-dioxohexanoate is potentially another route to 6 substituted diketo esters; although the trianion has been acylated,[20] alkylation reactions have not been reported.



Scheme 6.

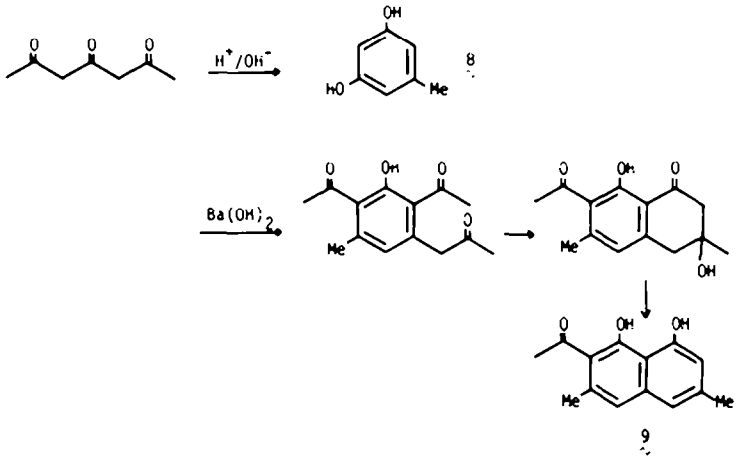
A number of enol lactones of 3,5-diketo acids (4-hydroxy-2-pyrones) are found in nature and probably arise by cyclizations of CoA or enzyme-bound thiol esters of the diketo acids. The laboratory cyclization of 3,5-diketo acids to give pyrones has been effected by acid catalysts and by acetic anhydride.[18] One route of particular note is the spontaneous cyclization of a 3,5-diketo thiolacid (Scheme 7);[21] this reaction is a very close model for the putative biosynthetic route. The thiolacid was prepared by treatment of the dianion of the β-diketone with carbonyl sulfide. A low yield synthesis of phloroglucinol from the acid chloride of 3,5-dioxohexanoic acid has been reported;[22] no other examples of this cyclization reaction have been observed.



Scheme 7.

2,4,6-Triketones can be obtained from dehydroacetic acid and other 6-substituted 3 - acyl - 4 - hydroxy - 2 - pyrones via ring cleavage, decarboxylation, and recyclization under acidic conditions to give 4-pyrones, which can then be converted to the triketone by hydrolysis with $Ba(OH)_2$.[1,2,23] Dehydroacetic acid derivatives can be prepared by acylation of 4-hydroxy-2-pyrones[14] and by electrophilic substitution reactions at the 6-methyl and acetyl-methyl positions of dehydroacetic acid, the latter reactions involving anionic intermediates.[24] Direct routes to triketones involve acylation of dianions of β-diketones[25] and alkylation and other condensations of trianions of 2,4,6-triketones.[26]

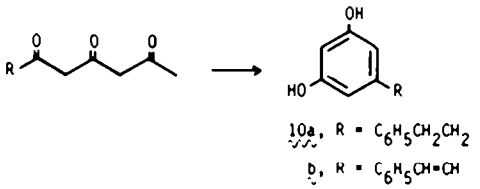
Collie's early studies of 2,4,6-heptanetrione played a central role in his formulation of the polyketide theory and laid the groundwork for our present understanding of the chemistry of polycarbonyl compounds. He found that this triketone cyclized in acid or under strongly basic conditions to give orcinol **8**. He also observed a gradual self-condensation under mildly basic conditions to give naphthalenediol **9**. The transformation required three consecutive aldol condensations for which two intermediate cyclization products have been isolated (Scheme 8). Reinvestigation of the self-condensation



Scheme 8.

reaction by Bethell and Maitland[27] and by Birch *et al.*[28] led to more concrete evidence for Collie's proposed structures.

Birch has explored extensions of the orcinol-type cyclization of triketones (Scheme 9). Treatment of 8-phenyl - 2,4,6 - octanetrione with strong base gave a low yield of dihydropinosylvin (**10a**) but similar treatment of the corresponding unsaturated triketone failed to give pinosylvin (**10b**).[30] Birch concluded that triketones are but poor analogues of triketo acids because the terminal methyl group is not reactive enough; the acids, if they had been available, would have cyclized much more satisfactorily to the corresponding resorcylic acids.

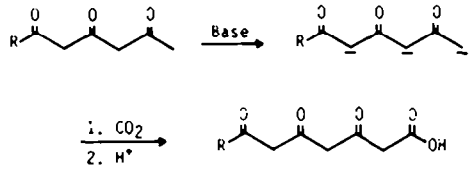


10a, R = $C_6H_5CH_2CH_2$

b, R = $C_6H_5CH{=}CH$

Scheme 9.

obtained with these compounds in the liquid ammonia system.



R	$NaNH_2$	KNH_2	LiN^iPr_2
C_6H_5	46%		82%
$C_6H_5CH{=}CH$	52%		
$C_6H_5CH_2CH_2$	16%	57%	
n-C_7H_{15}	>2%	30%	
n-C_5H_{11}		16%	44%
n-C_3H_7		>5%	28%
C_2H_5			42%
CH_3		trace	47%

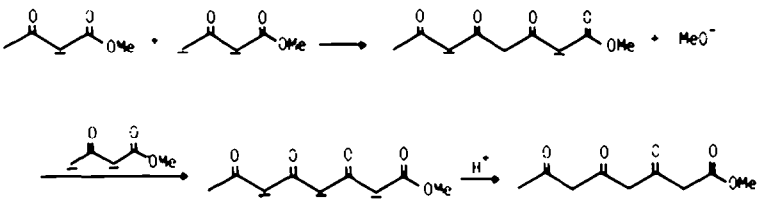
Scheme 10.

TETRACARBONYL COMPOUNDS

Some of the most prominent examples of polyketide biosynthesis involve the formation of monocyclic compounds from 3,5,7-triketo acids. Tetracarbonyl compounds, both free and masked, have been studied extensively because they are the smallest polycarbonyl systems that can provide reasonable models of biological systems. The investigation of unprotected 3,5,7-triketo acids has centered in the authors' laboratory. Triketo acids have been synthesized by carboxylation of trianions of 2,4,6-triketones (Scheme 10). Initial studies employed the trisodio and tripotassio salts formed in liquid ammonia by treatment of the triketones with alkali amides and then carboxylated in ether with CO_2.[21,26,29] Later studies showed lithium diisopropylamide in THF to be a superior base for the ionization process.[30] The base is soluble in THF and carboxylation can be carried out without removal of diisopropylamine, thus permitting the ionization-carboxylation to be done in a single solvent. Satisfactory yields were obtained for the carboxylation of 2,4,6-heptanetrione and other small triketones with the latter system; poor results had been

The triketo acids, although subject to thermal decarboxylation and facile cyclization, are sufficiently stable to permit isolation, purification and storage of the crystalline examples if suitable precautions are taken. 3,5,7-Trioxooctanoic acid (tetraacetic acid) is one of the most difficult to handle because of aldol cyclization but analytically pure samples of the compound have been produced by chromatography and recrystallization.[30] NMR spectra indicate that the triketo acids exist in solution as mixtures of enol forms with enolization of the 4- and 6-methylene groups predominating.

Methyl esters of the triketo acids can be prepared in good yields from the triketo acids by treatment with CH_2N_2, if care is exercised to use only a stoichiometric amount of the reagent.[29,30] The triketo acids are not sufficiently stable to permit acid-catalyzed esterification with methanol. A second route to methyl 3,5,7-trioxooctanoate involves acylation of the dianion of methyl acetoacetate with the monoionized form of the ester (Scheme 11).[19,20] The mechanism of the reaction is not known but seems likely to involve attack of one anion on the other, although the involvement of a ketene inter-



Scheme 11.

mediate is not excluded. Elimination of methoxide from monoionized keto ester would give acetylketene. The stoichiometry of the acylation reaction requires two equivalents of dianion per monoanion of keto ester but since monoanion is generated from dianion in the course of the condensation the reaction is carried out most efficiently using the dianion plus only a *catalytic amount* of the monoanion.

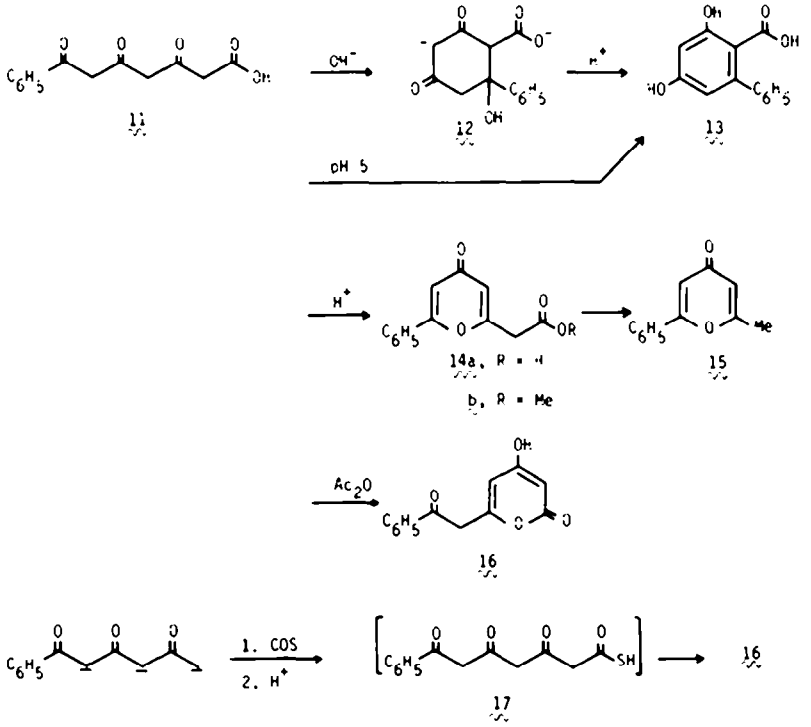
The triketo acids are in theory capable of undergoing four dehydrative cyclization reactions (see Scheme 1); the products of three of these reactions, i.e. resorcylic acids, acylphloroglucinols, and enol lactones, have been found in nature but the natural occurrence of polyketide-derived 4-pyrones is in doubt. Cyclization reactions leading to all four of these ring systems have been observed with triketo acid and ester model systems.

The chemistry of 7-phenyl-3,5,7-trioxoheptanoic acid (**11**) has received the most detailed study (Scheme 12).[21,29,31] Aldol cyclization of **11** occurs in aqueous or alcoholic solution over a pH range from 4 to strong base. The undehydrated aldol cyclization product (**12**) can be observed in basic solution but it dehydrates rapidly in acid to give the resorcylic acid. The NMR spectrum of the aldol product indicates that the cyclization is stereospecific but the relative configuration is not known. The cyclization also shows a high degree of regiospecificity; the resorcylic acid (**13**) has been isolated in 86% yield from a cyclization reaction carried out at pH 5; other cyclization products were not observed.

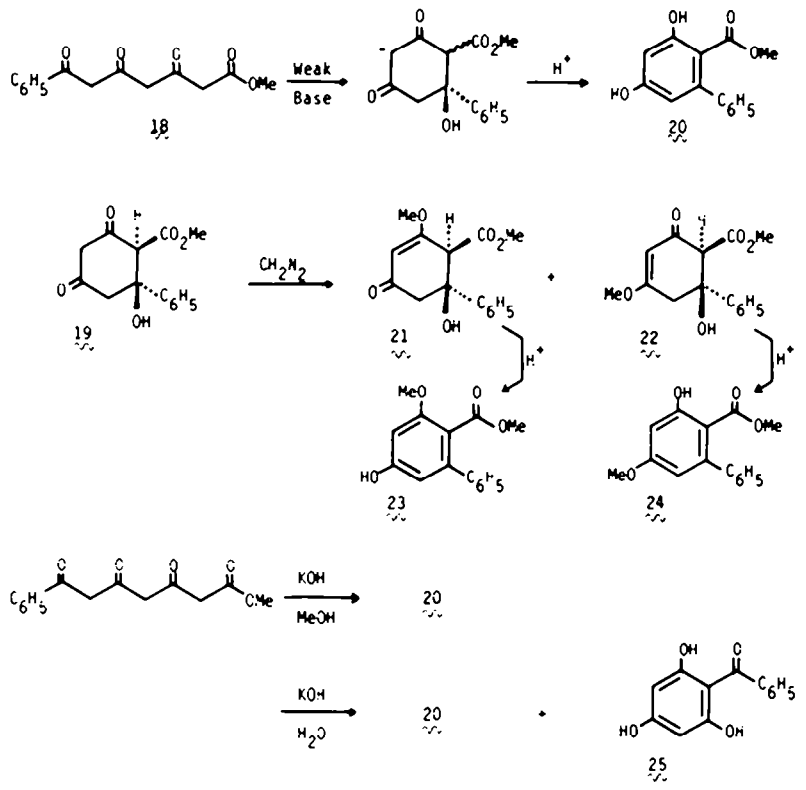
Treatment of the triketo acid with anhydrous, liquid HF gave pyrone-acid **14a** which decarboxylated readily to give the parent 4-pyrone (**15**). Methanolic HCl converted the triketo acid to pyrone ester **14b**. Treatment of the triketo acid with acetic anhydride gave enol lactone **16**. The enol lactone was also formed by a spontaneous cyclization of triketo thiolacid **17**, a reaction which almost certainly bears a close resemblance to the natural process. Thiolacid **17** had been prepared by treatment of the trianion of 1-phenyl-1,3,5-hexanetrione with carbonyl sulfide.[21]

Claisen cyclization has not been observed with the phenyl triketo acid or with other triketo acids but this is not surprising when one considers the fact that the carboxyl group will be fully ionized under conditions needed to remove a proton from the 6-methylene position. The possibility that acylphloroglucinols could be formed under acidic conditions cannot be excluded but the ease with which oxygen heterocycles are formed in acid makes the prospects poor that acid-catalyzed C-acylation can be realized. The shortcomings of the triketo acids for base-catalyzed Claisen-type cyclizations are circumvented with the corresponding esters.

The methyl ester (**18**) of 7-phenyl-3,5,7-trioxoheptanoic acid has received the most study (Scheme 13).[29] Under



Scheme 12.



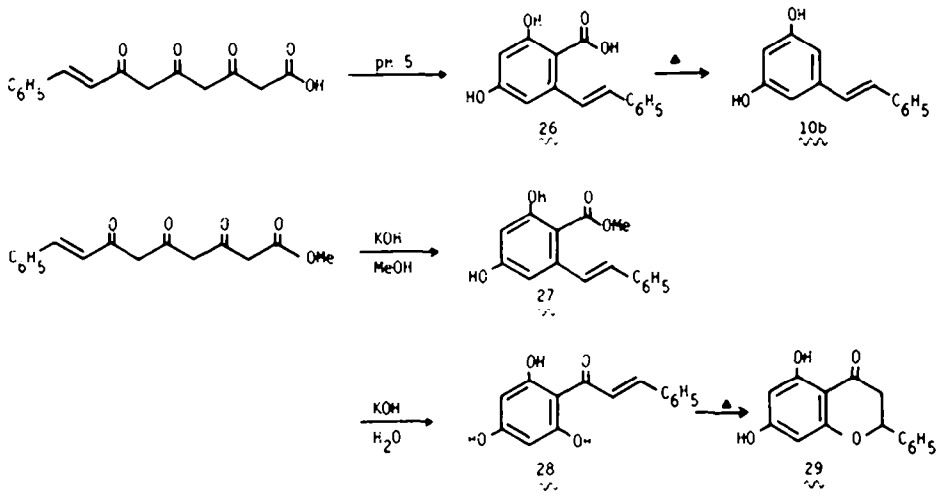
Scheme 13.

most conditions the principal mode of ring closure with **18** is the aldol cyclization also. In weakly basic solution aldol cyclization occurs without dehydration of the products.[31] NMR studies indicate that cyclization is not stereospecific. The major stereoisomer has been isolated by careful neutralization of the reaction mixture and has been identified as the one in which the phenyl and carbomethoxyl groups are *trans*. Equilibration of the stereoisomers occurs in basic solution by a mechanism involving ionization of the proton alpha to the carbomethoxy groups rather than by a retro-aldol reaction. Resorcylate ester **20** can be prepared in high yield by treatment of the aldol adducts with acid or directly from triketo ester by incubation in pH 5 buffer. Aldol adduct **19** can be methylated with CH_2N_2 to give a mixture of the 2- and 4-enol ethers (**21** and **22**); these compounds, as well, aromatize readily on acid-treatment to give esters **23** and **24**. It is noteworthy that prior to this work Birch had suggested that non-aromatized aldol adducts of this type might be sufficiently stable that dehydration *in vivo* would have to be mediated by enzymes and that these intermediates could be branch points in the metabolic pathway, i.e. the stage at which reductions of carbonyl groups and other transformations occur prior to aromatization.[4]

Strongly basic cyclization conditions were studied with the hope that the dianion or trianion of triketo ester **18** might undergo different reactions than the monoanion. Methanolic KOH gave essentially the same results as milder conditions; ester **20** being obtained in excellent yield after acidification of the reaction mixture (Scheme 13).[29] Little or no hydrolysis of the ester group occurred under the reaction conditions. Aqueous KOH was also investigated and gave the surprising result that the major product was benzoylphoroglucinol (**25**) arising from a Claisen cyclization; the other product was the resorcylate ester. The reaction gave a 2:1 mixture of the products from which **25** was isolated in 47% yield. No adequate explanation for the effect of solvent on the regioselection process has yet been found.

Metal ions almost certainly play a major role in the biological cyclization reactions, but attempts to alter the cyclization pathways of the phenyl triketo ester using $Mg(OH)_2$, $Mg(OMe)_2$ and buffer containing Mg^{2+} ion have all been disappointing.[29] Aldol cyclization was the only ring closure observed when Mg^{2+} was present. The principal effect of Mg^{2+} ion was to stabilize the triketo ester against cyclization. This stabilization may be due in part to the fact that a chelate involving the 2 position cannot undergo Claisen cyclization, one involving the 6 position cannot undergo aldol cyclization and one involving the 4 position cannot under either cyclization, but a major factor must be the insolubility of the chelates.

In a followup of Birch's earlier attempted synthesis of pinosylvin (**10b**) from the styryl triketone (Scheme 9), the corresponding triketo acid was prepared in the authors' laboratory by carboxylation of the triketone.[29] In pH 5 buffer the acid underwent facile aldol cyclization to give 88% of pinosylvic acid (**26**) from which **10b** was obtained by thermal decarboxylation (Scheme 14). The methyl ester of of the styryl triketo acid, prepared by treatment of the acid with CH_2N_2, cyclized to resorcylic ester **27** (69%) in methanolic KOH but aqueous KOH gave 82% of the Claisen product, cinnamoylphloroglucinol (**28**), which on heating cyclized further to give the flavanone, pinocembrin (**29**). The formation of both pinosylvin and pinocembrin is significant. These two metabolites occur



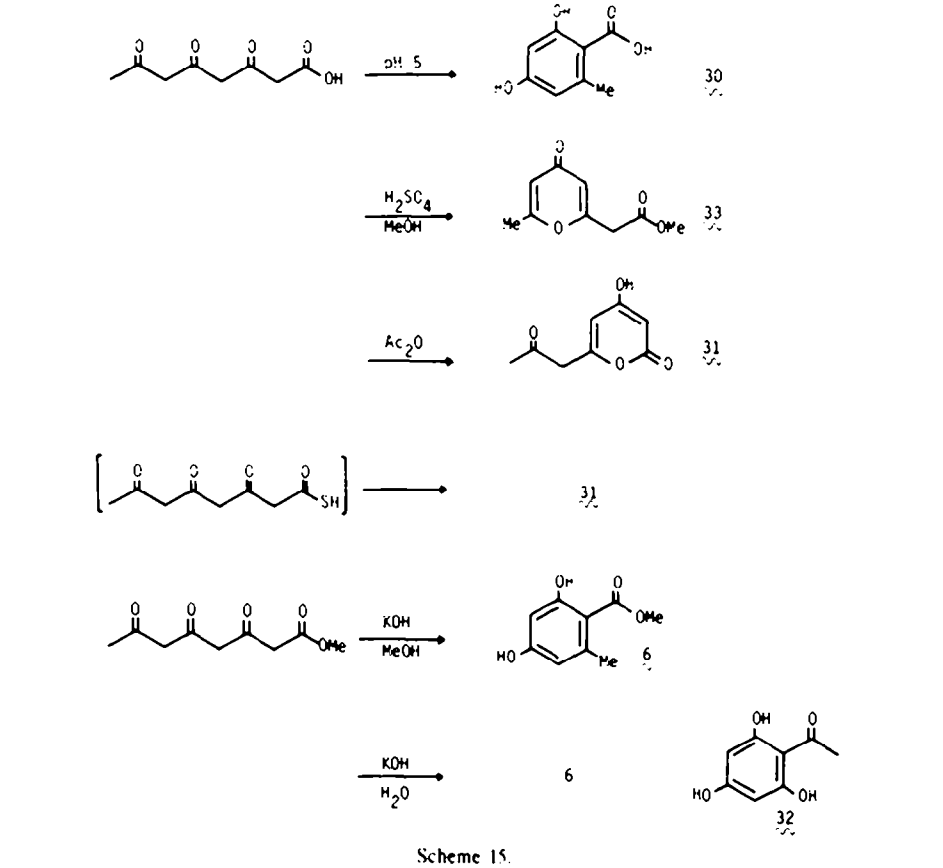
Scheme 14.

together in the heartwood of pine trees and were one of the major cases cited by Birch in his formulation of the polyketide hypothesis.[4]

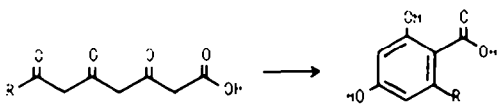
Another important case is tetraacetic acid (Scheme 15),[30] which undergoes an extremely facile aldol cyclization to give orsellinic acid (**30**). Tetraacetic lactone (**31**) was formed from the acid by treatment with acetic anhydride (66%) and also by a spontaneous cyclization of the triketo thiolacid. The methyl ester of tetraacetic acid gave methyl orsellinate (**6**) (50%) in methanolic NaOAc and a mixture of methyl orsellinate (13%) and the Claisen product, 2,4,6-trihydroxyacetophenone (**32**) (39%) in aqueous KOH. The last of the four possible cyclization products, the 4-pyrone **33** was obtained in 50% yield by treatment of tetraacetic acid with methanolic H_2SO_4.

Aldol cyclizations of several other triketo acids have been used for synthesis of the corresponding resorcylic acids (see following page).[29,30]

Both the 3- and the 5-methyl derivatives of orsellinic acid are naturally occurring and probably arise by methylation at a stage prior to aromatization. The carboxylation of 3-methyl-2,4,6-heptanetrione was investigated to see whether anion formation and carboxylation might be regiospecific (Scheme 16).[30] Selec-



Scheme 15.



R

$C_6H_5CH_2CH_2$

n-C_7H_{15}

n-C_5H_{11}

n-C_3H_7

C_2H_5

tivity was not observed; the mixture of triketo acids was cyclized without isolation to give equal quantities of the methylorsellinic acids.

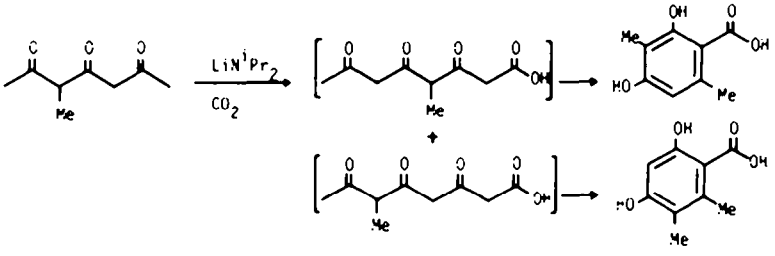
Among the derivatives of triketo acids in which one or more of the carbonyl groups have been protected, the least protected case is the 3-enol ether (**34**) of methyl 7-phenyl-3,5,7-trioxoheptanoate, which was one of the products formed from the triketo acid by treatment with excess CH_2N_2. The enol ether in actuality provides no protection at all since both aldol and Claisen cyclizations can still occur (Scheme 17). In the presence of methanolic NaOAc, **34** underwent aldol cyclization. The main product (72%) was the stereoisomer (**35**) of **21** which had been prepared by another route (see Scheme 13).[11] Treatment of **35** with acid gave aromatic ester **23**. A pH 9.5 buffer converted **34** into a mixture of **23** (34%) and Claisen product, cotoin (**36**) (12%). These cyclization reactions have been proposed as models of the biosynthesis of phenolic ethers.[12] Although many phenolic ethers arise in nature by alkylation of the parent phenols, others may arise by alkylation of precursors of the aromatic systems.

Stockinger and Schmidt have recently reported formation of the 4-methyl ether (**37**) of *tert*-butyl orsellinate (~50%) by a condensation of the anion of *tert*-butyl acetate with 6-methyl-4-methoxy-2-pyrone (Scheme 18).[13] The reaction probably involved the 5-enol ether (**38**) of *tert*-butyl 3,5,7-trioxooctanoate as an intermediate but the compound was not isolated.

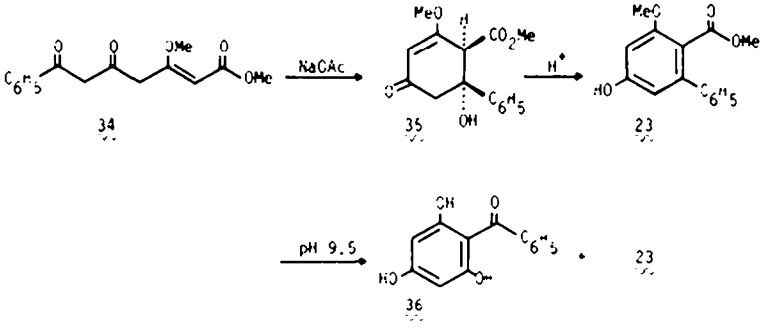
Schmidt and Schwochau have prepared ethyl 3,5,7-trioxooctanoate (**39**) protected at the 3 position with an ethylene hemithioketal (Scheme 19).[14] They have also prepared the corresponding derivative (**40**) of tetraacetic lactone.[14] Exploitation of this sequence for the synthesis of orsellinic acid and other natural products has not yet been reported.

Griffin and Staunton have prepared the dimethyl ether of methyl orsellinate by the condensation of a pyrylium ion (**41**) with an enolate anion (Scheme 20).[15] Intermediates were not isolated but the reaction is presumed to proceed via a bis(enol ether) (**42**) of the triketo ester. A noteworthy feature of the reaction is the presence of the phosphonate group which ensured regiospecificity for the cyclization reaction. The condensation reaction went in good yield (65%). Pyrylium ion **41** will undoubtedly find future uses as a triketone synthon. Of equal value is the scheme of using phosphonate anions to direct cyclizations.

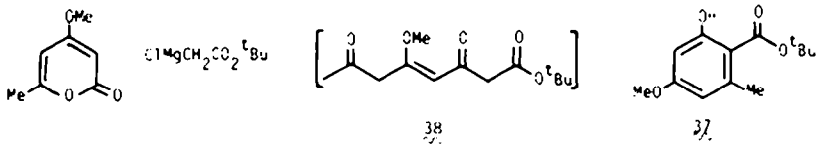
Bram has prepared ethyl 3,5,7-trioxooctanoate (**43**) with the 5- and 7-keto groups protected as the enol ether



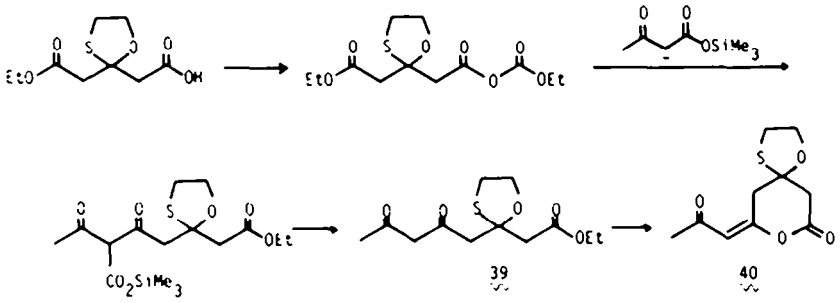
Scheme 16.



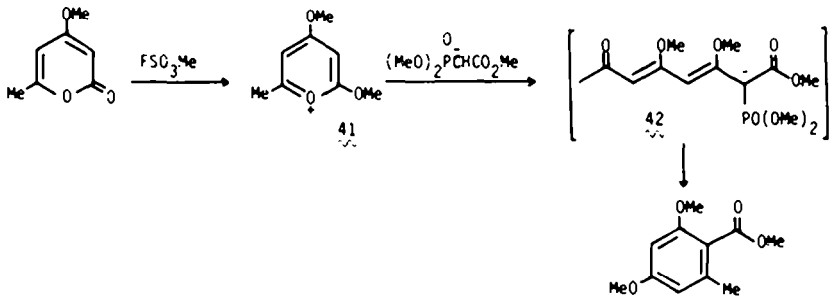
Scheme 17.



Scheme 18.



Scheme 19.

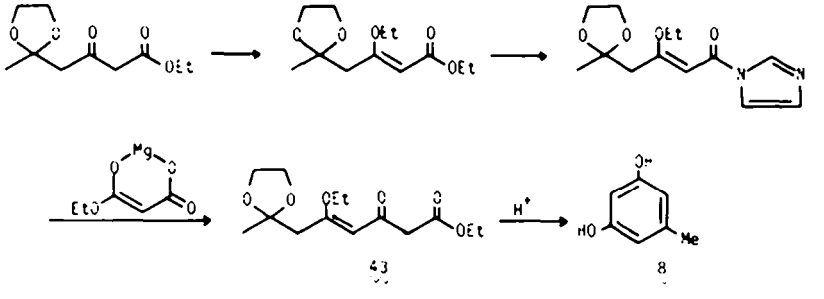


Scheme 20.

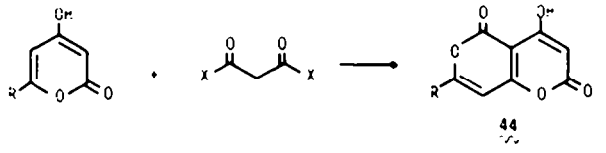
and the ketal, respectively (Scheme 21).[16] During the course of deprotection, aldol cyclization, hydrolysis of the ester, and decarboxylation occurred to give orcinol (**8**) as the isolated product. Bram's synthesis of protected triketo ester **43** as well as the preparation of **39** by Schmidt and Schwochau[14] employ interesting intermediates which should find applications in the synthesis of other more complex polycarbonyl compounds.

Scott and Money have used complex pyrones as masked polycarbonyl compounds.[17] Pyranopyrandiones **44** are protected equivalents of triketo acids having an extra carboxyl group at the 4 position on the keto acid chain which is used to protect the 7-carbonyl group. Members of this class of pyranopyrandiones are prepared by condensations of readily available 4-hydroxy-2-pyrones with malonate derivatives (Scheme 22).[17,18] Under basic conditions the pyranopyrandiones undergo cleavage of the two lactone rings to give acyclic intermediates which can undergo recyclization reactions to give aromatic compounds. The acyclic intermediates cannot be isolated because the vigorous conditions required to cleave the lactone linkages bring about rapid recyclizations.

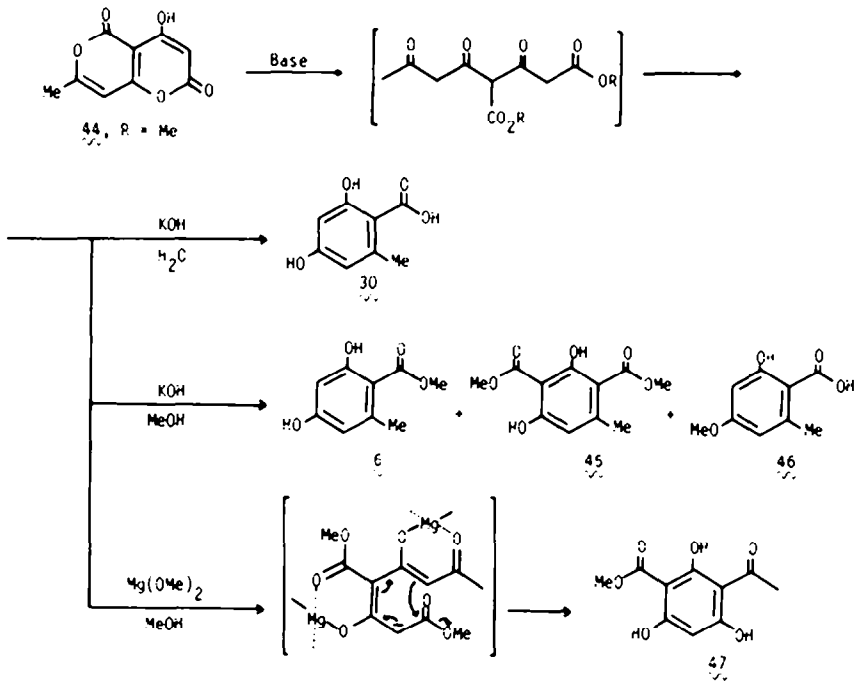
The pyranopyrandione equivalent to tetraacetic acid (**44**, R = Me) when treated with aqueous KOH underwent ring-opening and aldol-type recyclization to give orsellinic acid (**30**) (6%) as the only benzenoid product (Scheme 23).[17] Methanolic KOH gave 18% of methyl orsellinate (**6**) along with 5% of diester **45** which retains the "extra" carboxyl group and 10% of acid **46**. In methanolic KOH retention of the "extra" carboxyl group can occur because cleavage of the lactone ring gives an ester rather than an acid; diacylacetic acids decarboxylate readily but the esters are more stable.



Scheme 21.



Scheme 22.

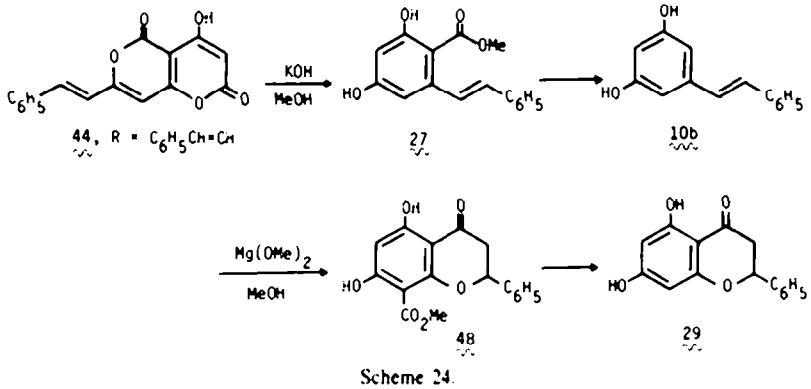


Scheme 23.

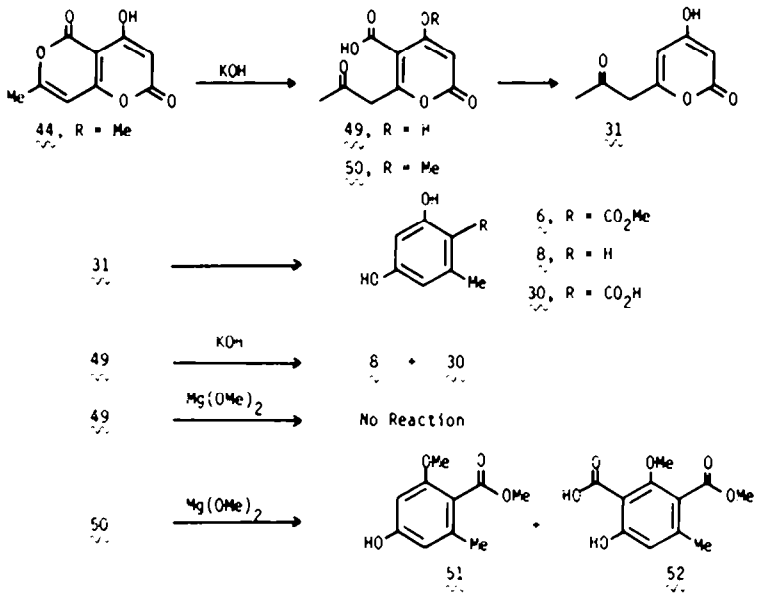
The use of methanolic $Mg(OMe)_2$ with **44** (R = Me) led to the formation of a Claisen product, phloroglucinol **47**, in 8.5% yield (Scheme 23). Although the yield was low, the result is of interest from a mechanistic point of view in relation to our own observation that Mg^{2+} ion will not catalyze Claisen cyclizations of triketo esters. Crombie and James have put forth the suggestion that the Mg^{2+} effect with pyranopyrandiones involves chelation of two Mg^{2+} ions by keto ester sites in the acyclic intermediate, thus holding the molecules in a conformation from which Claisen but not aldol cyclization can occur.[39] The failure of $Mg(OMe)_2$ to bring about Claisen cyclization of simple triketo esters is a consequence of the absence of the second chelation site; i.e. the one involving the "extra" carboxyl group. With simple triketo esters chelation of two Mg^{2+} ions gives linear structures which are incapable of either cyclization reaction.

Three additional pyranopyrandiones (**44**, R = C_6H_5, $C_6H_5CH_2CH_2$ and $C_6H_5CH{=}CH$) have been investigated and have given results which are qualitatively the same as those obtained with the methyl compound.[17,40] The reactions of the styryl compound are of particular interest (Scheme 24); treatment with methanolic KOH gave methyl pinosylvate (**27**) by an aldol cyclization, whereas methanolic $Mg(OMe)_2$ gave flavanone **48** by a Claisen cyclization. Subsequent transformations of **27** and **48** gave pinosylvin (**10b**) and pinocembrin (**29**), respectively.

The two lactone rings of the pyranopyrandiones are not of equal stability; using the methyl compound (**44**, R = Me) Scott's group achieved a partial hydrolysis to give pyrone-acid **49**, from which tetraacetic lactone (**31**) could be obtained by decarboxylation (Scheme 25).[41] The latter step has been a troublesome one[42] and the synthesis was subsequently improved by use of the methyl ether (**50**) of **49**.[43] Because of the importance of tetraacetic lactone, two other syntheses have been reported[44] in addition to this one and the previously described triketo acid cyclization.[30] Bentley and Zwitkowits found that tetraacetic lactone undergoes facile transformations to aldol products.[44] Aqueous acid or base gives orsellinic acid (**30**) and/or orcinol (**8**). Reaction with methanol at 110° gave methyl orsellinate. Pyrone-acid **49** on treatment with KOH gave aldol products **30** and **8** but failed to react with $Mg(OMe)_2$.[43] Methyl ether **50** reacted with $Mg(OMe)_2$ but gave mainly aldol products **51** and **52**.[45]



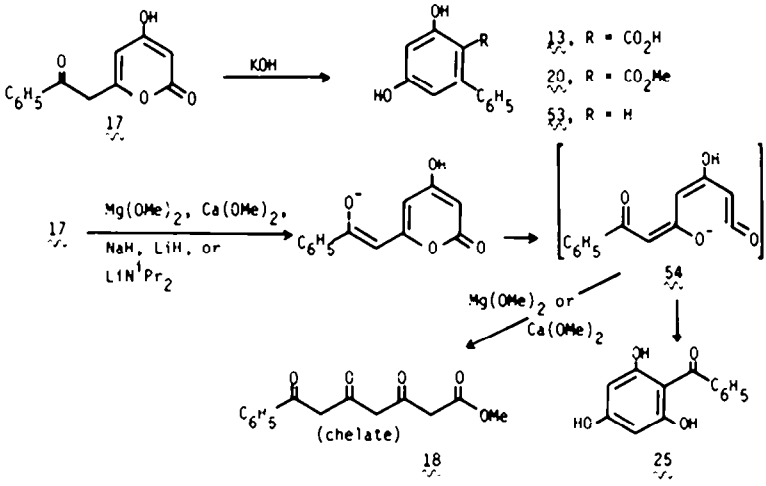
Scheme 24.



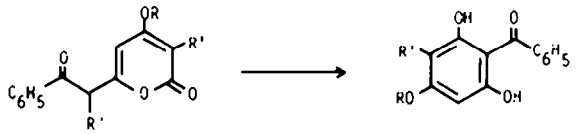
Scheme 25.

The reaction of phenacyl pyrone **17** has been investigated both by Scott[41,41] and by the authors (Scheme 26).[47] With aqueous KOH hydrolysis to the triketo acid followed by aldol cyclization gave low yields of resorcylic acid **13** and resorcinol **53**. Better results were obtained with methanolic KOH; resorcylic ester **20** was obtained in 55–67% yield along with a minor product tentatively identified as phloroglucinol **25** derived from Claisen cyclization. In neither case was the acyclic intermediate detected, pyrone cleavage being much slower than recyclization. With $Mg(OMe)_2$ as the base the reaction gave 44% of phloroglucinol **25** and 15% of resorcylic ester **20** along with a trace of triketo ester **18**. A large excess of $Mg(OMe)_2$ or $Ca(OMe)_2$ gave **18** (58%). For the synthesis of phloroglucinol **25** from **17** an excellent yield (87%) could be obtained with 0.27 equiv of $Mg(OMe)_2$ in hot dimethylformamide. Equally good results were obtained with LiH in tetrahydrofuran, $LiN(^iPr)_2$, and other non-nucleophilic bases. These results indicate that triketo ester **18** is not an intermediate in the formation of phloroglucinol **25**. Ketene **54** has been proposed in its place, with triketo ester **18** only being formed when **54** is intercepted by methanol or methoxide ion. A ketene intermediate may also be involved in the Mg^{2+}-directed reactions of pyranopyrandiones **44** but this question has not been studied. Moreover, nothing is known about the mechanistic details of enzymic formation of acylphloroglucinols; these reactions may also involve ketene intermediates.

Cleavage-recyclization reactions have been investigated with four derivatives (**55–58**) of pyrone **17** (Scheme 27).[47] Methyl ether **55** on treatment with LiH gave 89% of Claisen product **36** and C-methyl derivative **56** gave 54% of Claisen product **59**. The methyl group on **56** blocks aromatization of aldol products; treatment of **56** with methanolic KOH apparently caused Claisen cyclization to occur instead but the resultant acylphloroglucinol was not isolated and only cleavage products (benzoic acid and 2-methylphloroglucinol) were found. C-Methyl derivative **57** can not give an aromatic Claisen product; no aldol or Claisen products were obtained from treatment of **57** with $Mg(OMe)_2$, $Ca(OMe)_2$ or



Scheme 26.



55, R = Me, R' = R'' = H
56, R = H, R' = Me, R'' = H
57, R = R' = H, R'' = Me
58, R = H, R' = $COCH_3$, R'' = H

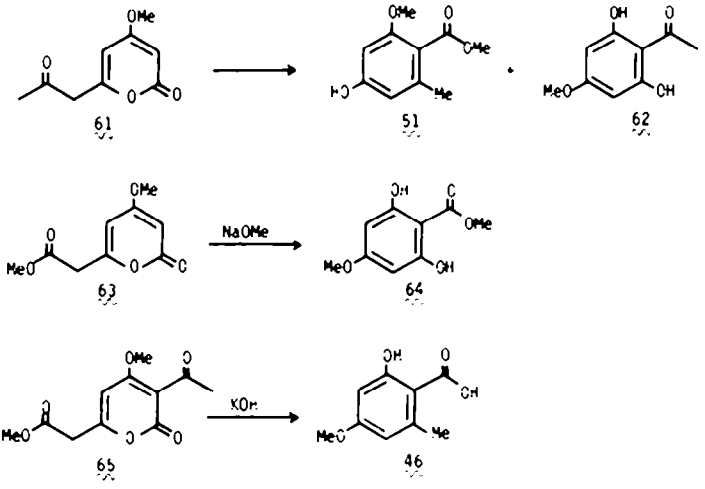
20, R = R' = H
36, R = Me, R' = H
59, R = H, R' = Me
60, R = H, R' = $COCH_3$

Scheme 27.

KOMe. Acetyl derivative **58** lost the acetyl group in the course of cleavage and recyclization to give resorcylate ester **20** when treated with methanolic KOH and phloroglucinol **25** when treated with $Mg(OMe)_2$. With LiH, however, the acetyl group was retained and phloroglucinol **60** was obtained.

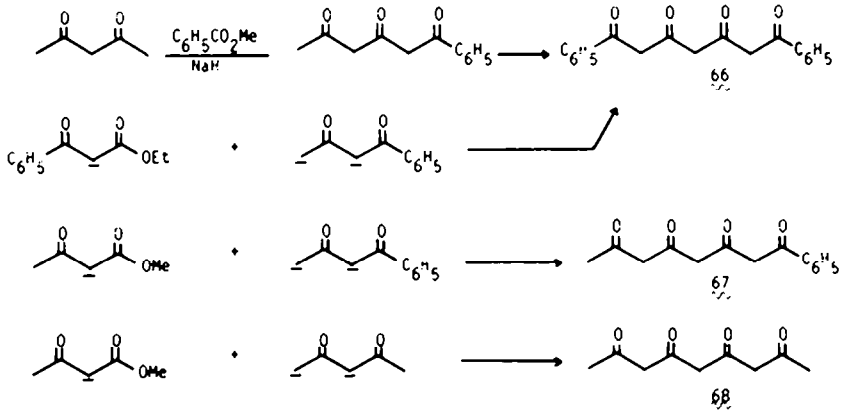
The methyl ether of tetraacetic lactone (**61**) has been converted to aldol product **51** and to Claisen product **62**, but the conditions for these reactions were not reported (Scheme 28).[45,46] Money has observed the formation of a Claisen product (**64**) from pyrone-ester **63** but with pyrone-ester **65** only a degraded aldol product (**46**) was obtained.[48] For both these reactions the presence of the methyl ether was crucial; the corresponding hydroxy compounds gave no benzenoid products under a variety of conditions.

A tetraketone was the first unprotected 1,3,5,7-tetracarbonyl compound to be prepared. In 1963, Hauser's group prepared diphenyl tetraketone **66** by acylating both methyl groups of acetylacetone with methyl benzoate in the presence of NaH and also by a single acylation of 1-phenyl-1,3,5-hexanetrione (Scheme 29).[49] The alkali amides, lithium diisopropylamide in particular, were later found to be superior for the acylation of triketones.[26,50] The unanticipated stability of tetraketone **66** provided the impetus for further study of unprotected polycarbonyl compounds. Acylations of triketones have been limited to introduction of aroyl groups; trianions of



61, 51, 62, 63, 64, 65, 46

Scheme 28.



66, 67, 68

Scheme 29.

triketones apparently are too basic to permit acylations with aliphatic esters.

A second route to tetraketones which was developed in the authors' laboratory, can be used for preparation of aliphatic tetraketones.[37] β-Diketone dianions can be acylated by β-keto esters to give linear tetraketones if the acidic methylene group of the β-keto ester is first ionized (Scheme 29). Acylation occurs in spite of the deactivation of the ester resulting from delocalization of negative charge. The condensation reaction is limited to diketone dianions and other highly nucleophilic anions and is believed to involve attack of the dianion on the keto ester monoanion as opposed to elimination of alkoxide from the keto ester followed by nucleophilic attack on the resulting acylketene. This condensation reaction has been used to prepare diphenyl, phenyl methyl and dimethyl tetraketones **66–68** in yields of 30–51%.

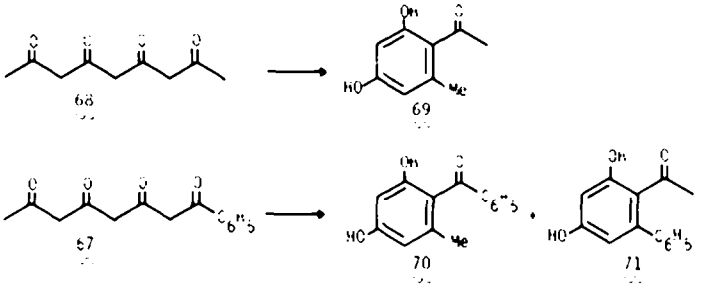
Cyclization reactions of diphenyl tetraketone **66** have not been studied although aldol cyclization should occur in base. Dimethyl tetraketone **68** undergoes aldol cyclization to form resorcinol **69** so readily that isolation of the tetraketone is difficult (Scheme 30).[40] Phenyl methyl tetraketone **67** has intermediate reactivity. With **67** two aldol cyclizations are possible; base treatment gives mainly (62%) resorcinol **70** resulting from nucleophilic attack at the less sterically hindered acetyl carbonyl group along with 7% of isomeric resorcinol **71**.[40] No method has been found by which this regioselectivity can be reversed.

Numerous masked or partially masked tetraketones have been synthesized and studied. Protected forms of dimethyl tetraketone **68** include 2-ketal **72**,[37] 2,8-bisketal **73**,[37] 2,8-bisenamine **74**,[44] acetylenic ketone **75**,[37] 2,8-bis-(hemithioketal) **76**[44] and pyrones **77–79**.[37,43,36] Treatment of **73**,[37] **74**,[44] **75**[37] and **78**[36] with acid has given resorcinol **69**; treatment of **77** with base has failed to give aromatic products[41] but **79** was converted to resorcinol **69**.[37] Pyrone **80**, equivalent to tetraketone **67**, failed to give a phenolic product with base but was converted to resorcinol **70** by acid.[24,41]

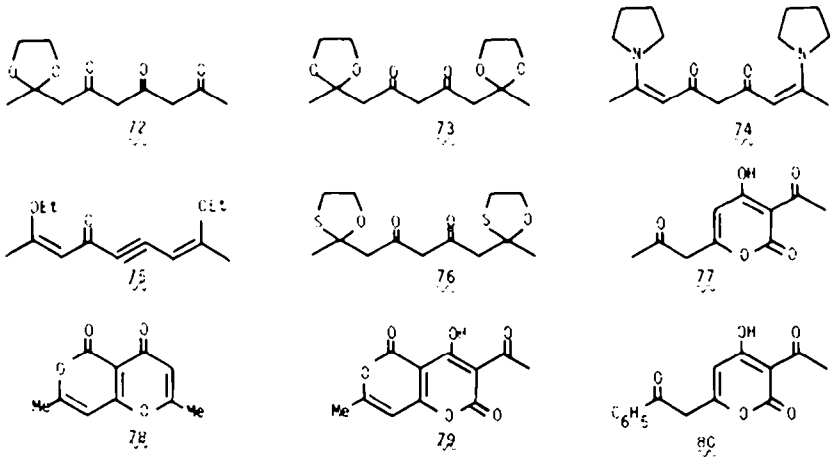
Italian workers have studied several bis-isoxazoles equivalent to phenyl and methyl terminated tetraketones.[37] Hydrogenolysis of the bis-isoxazoles gives keto imines which cyclize under acidic conditions to resorcinol derivatives. Examples analogous to tetraketones **66–68** have been reported. A 4:1 mixture of resorcinols **70** and **71** was obtained from bis-isoxazole **81** (Scheme 31). Bis-isoxazole **81** has also been converted into diketoisoxazole **82** by partial hydrogenolysis and hydrolysis. Hydrogenolysis-cyclization of **82** gave resorcinol **71** exclusively, illustrating the directive effect of the imine group. This highly significant finding has not yet been applied to the synthesis of polycyclic systems but could be of substantial value for establishing regiospecificity of aldol cyclizations with higher polycarbonyl compounds.

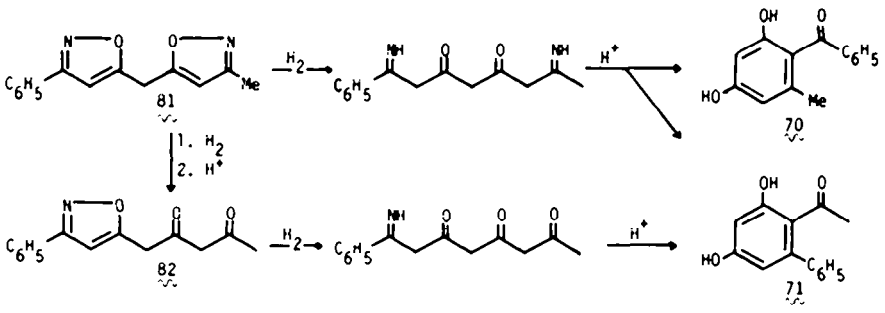
PENTACARBONYL COMPOUNDS

With increasing chain lengths, the number of possible cyclization products rises rapidly. A pentaketo acid can undergo 3 aldol, a Claisen, and additional heterocyclic ring closures and some of the initial cyclization products can undergo further cyclization reactions. Natural examples of many of the resulting ring systems are known. Phenyl-terminated tetraketo acid **83** is the only unprotected tetraketo acid to have been prepared.[40] Treatment of phenyl methyl tetraketone **67** with excess lithium diisopropylamide gave a polyanion presumed to be the tetraanion, carboxylation of which gave **83** in 56%



Scheme 30.





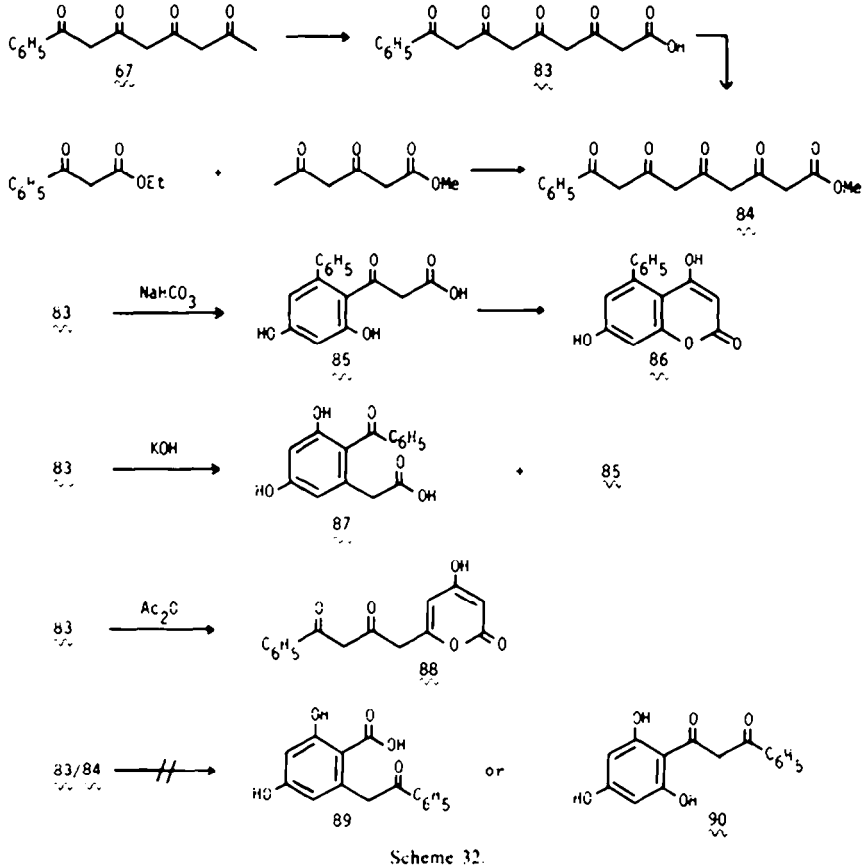
Scheme 31.

yield (Scheme 32). The corresponding methyl ester (**84**) has been prepared by treatment of **83** with CH_2N_2 and also by a condensation (60%) between the trianion of methyl 3,5-dioxohexanoate and the monoanion of ethyl benzoylacetate.[20]

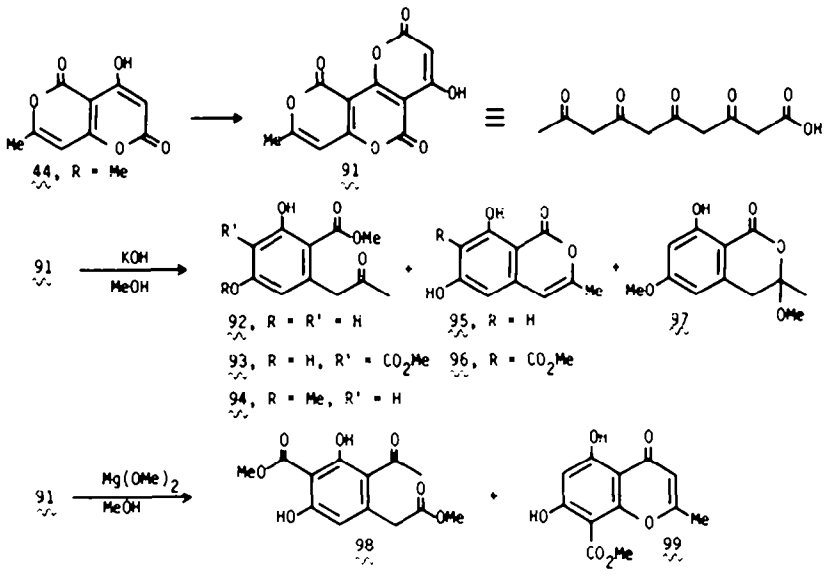
On treatment with aqueous $NaHCO_3$, **83** gave mainly (84%) unstable resorcinol **85** which cyclized further to give coumarin **86** (Scheme 32).[20] Weakly acidic conditions gave the same result. With aqueous KOH, **85** became a minor product, the principal one (67%) being isomer **87**. Methyl ester **84** showed essentially the same reactivity profile. Neither the third aldol product (**89**) nor the Claisen product (**90**) were detected. Tetraketone **83** was converted to the enol lactone (**88**) by treatment with acetic anhydride. The reactions of **88** have not been explored but non-nucleophilic bases might well yield **90** or the related flavone via a ketene intermediate.

Money and Scott have extended their studies of fused pyran derivatives to masked pentaacetic acid (Scheme 33).[17,18] Dipyranopyrantrione **91**, prepared by the condensation of pyranopyrandione **44** (R = Me) with malonyl chloride, gave on treatment with methanolic KOH, products **92–97** resulting from aldol cyclization of pentaketide acyclic intermediates. This result is of considerable interest because **92–97** all arise by the aldol cyclization which had not been observed with unprotected triketo acid **83** or ester **84**. With methanolic $Mg(OMe)_2$, **91** gave a second aldol product, resorcinol **98**, and a Claisen product, chromone **99**. Chain cleavage was a serious problem in both reactions and several aromatic products were obtained which resulted from partial degradation of the polyketide chain. Total yields of identifiable products did not exceed 15%.

Stockinger and Schmidt have recently described the condensation of the methyl ether of triacetic lactone with the dianion of ethyl acetoacetate to give coumarin **101a** in 39% yield; the 7-enol ether **100a** of ethyl pentaacetate is thought to be an intermediate in the reaction (Scheme



Scheme 32.

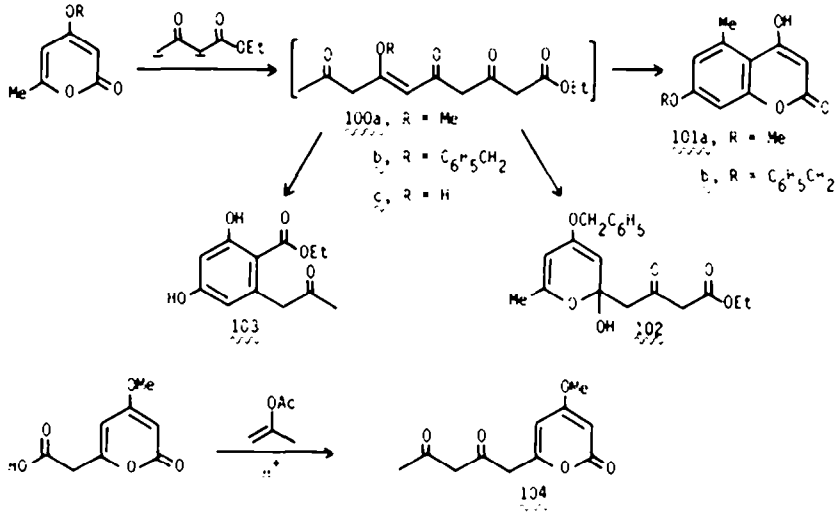


Scheme 33.

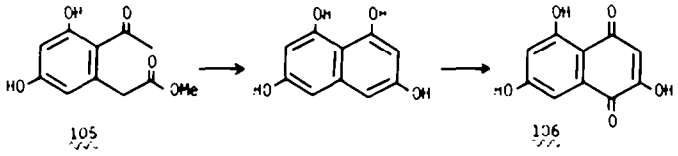
34).[33] Repetition of the reaction with the benzyl ether of triacetic lactone gave 17% of benzyl homolog **101b** along with 20% of heterocycle **102** which is the hemiketal of the acyclic intermediate **100b**. Protection of the hydroxyl group of triacetic lactone is not essential for the condensation to occur. Unprotected triacetic lactone, as its lithium salt, reacted with the dianion of ethyl acetoacetate to give resorcylate ester **103** derived from ethyl pentaacetate by a different aldol cyclization. This alteration in the cyclization pathway is noteworthy; the unprotected tetraketo ester cyclized by the pathway followed by dipyranopyrandione **91** rather than that followed by phenyl triketo acid **83**. Scott has described the preparation of the enol lactone (**104**) of 3-O-methylated pentaacetic acid,[49] but rearrangements to benzenoid compounds have not been explored.

A tetraketo ester is the smallest polycarbonyl system that can form a naphthalene derivative. Although such a cyclization of a pentacarbonyl array has not been performed, Baker and Bycroft have carried out the final step, converting methyl curvulinate (**105**) to flaviolin (**106**) by cyclization to 1,3,6,8-naphthalenetetraol followed by oxidation (Scheme 35).[50]

Unprotected diphenyl pentaketone **107** has been prepared in our laboratory by benzoylation of tetraketone **67** (19%) and by a two-stage benzoylation of 2,4,6-hep-



Scheme 34.



Scheme 35.

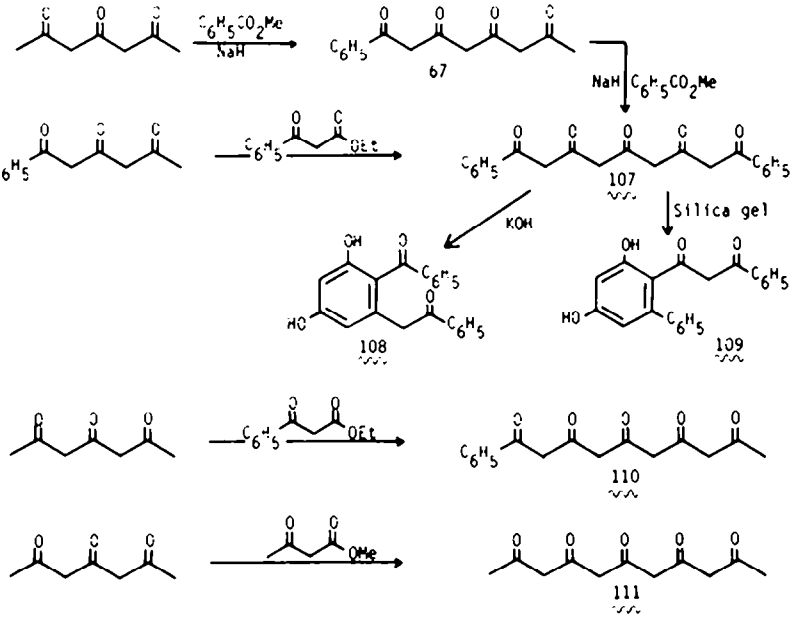
tanetrione (20%) (Scheme 36).[60] The compound has also been synthesized (41%) by acylation of 1-phenyl-1,3,5-hexanetrione with ethyl benzoylacetate.[61] Cyclizations of **107** have been investigated; aqueous KOH gives 53% of one aldol product (**108**)[60] while activated silica gel has given 73% of another (**109**).[61] Phenyl methyl and dimethyl pentaketones **110** and **111** have been prepared by condensations of 2,4,6-heptanetrione with ethyl benzoylacetate and methyl acetoacetate, respectively.[61]

Stockinger and Schmidt have used the condensation of the dianion of acetylacetone with the methyl ether of triacetic lactone to prepare flavone **112** in 15% yield (Scheme 37).[13] The intermediate pentaketone monoenol ether was not isolated.

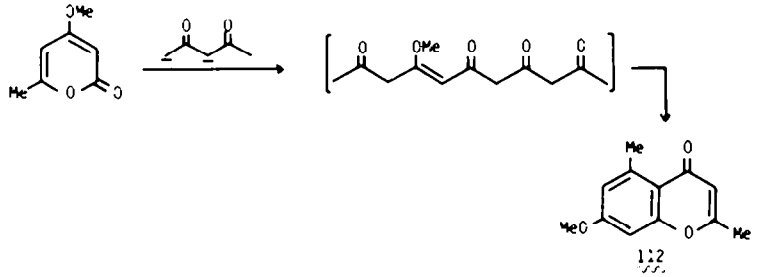
In a pioneering effort to synthesize polycarbonyl compounds, Birch and coworkers examined the ozonolysis of dihydroindene **113**, which had been prepared by a Birch reduction of the corresponding benzenoid compound (Scheme 38).[62] They failed to isolate the expected 6-ketalized pentaketone **114** or cyclization products thereof; however the approach warrants further study using newer methods for carrying out the oxidation and isolating the product.[62a] In all likelihood, removal of the ketal would not be possible prior to cyclization of **114**, but its presence would be advantageous in some cases.

HEXACARBONYL COMPOUNDS

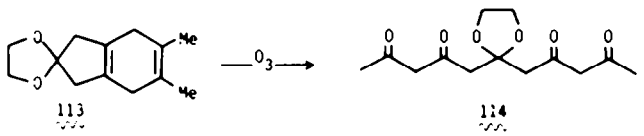
No unprotected pentacarbonyl compounds have been prepared yet, although a dipyrone (**115**)[17] and a tripyranopyrantetraone (**116**)[17] have been reported which are formally equivalent to hexaacetic acid (Scheme 39). Reactions of **116** have been studied but no benzenoid or naphthalenoid products have been obtained. Two of the pyrone rings in **116** are resistant to hydrolysis and dipyrone **117** has been obtained from the reaction of **116** with KOH. Chain cleavage occurs under conditions required to open the remaining rings. Cleavage of polycarbonyl chains occurs more readily than opening of isolated 4-hydroxy-2-pyrones by base. This finding places a definite limit on the applicability of the fused pyrone approach to the synthesis of polycyclic phenols.



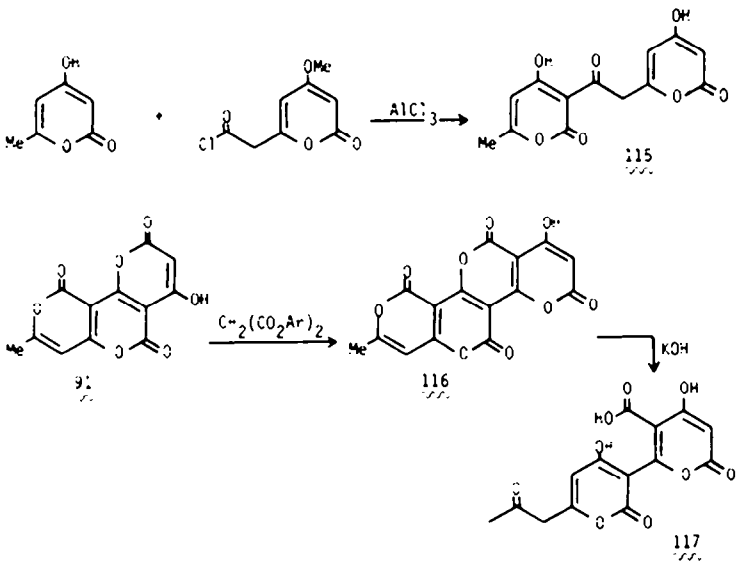
Scheme 36.



Scheme 37.



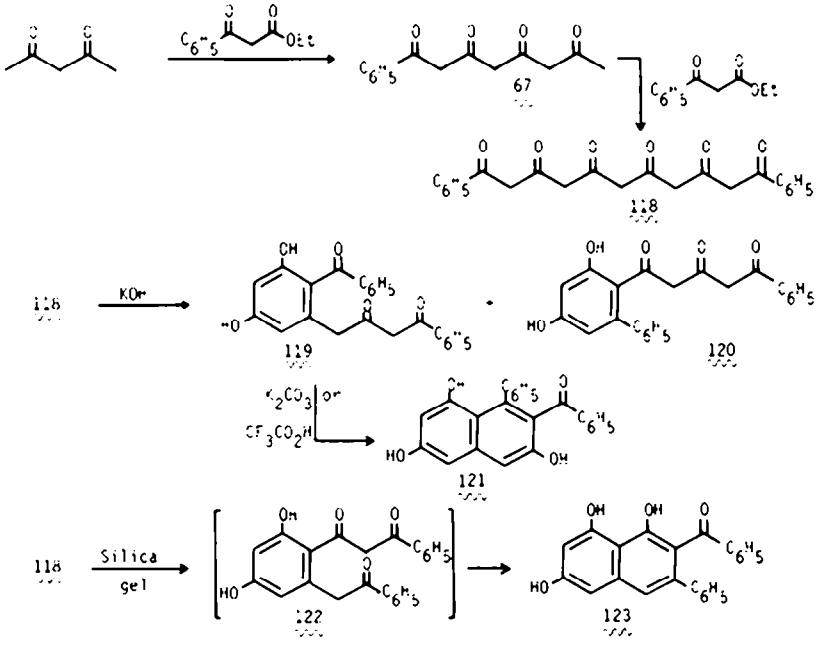
Scheme 38.



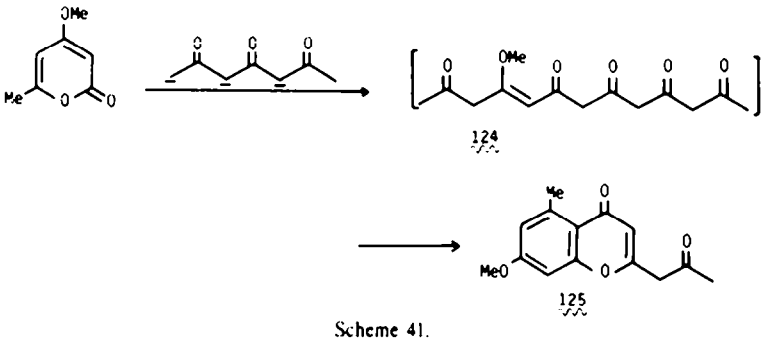
Scheme 39.

One unprotected hexaketone has been synthesized. The preparation, which was carried out in the authors' laboratory, involved acylation of tetraketone **67** with ethyl benzoylacetate by a polyanion procedure and gave diphenyl hexaketone **118** in 19% yield.[61] Hexaketone **118** was also prepared by a convergent procedure involving sequential condensations of two equivalents of ethyl benzoylacetate with acetylacetone in a "one-pot" procedure to give 40% of **118** (Scheme 40). The hexaketone is formally capable of many cyclization reactions. Considering only carbocyclic processes, **118** could undergo three initial aldol cyclizations; secondary cyclizations could give four isomeric naphthalenetriols. In spite of the many pathways open to the molecule, a high degree of regiospecificity was observed in the cyclization reactions. Treatment of **118** with aqueous KOH gave mainly (70%) resorcinol **119** with minor quantities of the isomeric resorcinol **120** and the related cyclic hemiketal being formed. Further treatment of **119** with K_2CO_3 or with CF_3CO_2H gave naphthalenetriol **121**. On the other hand, treatment of **118** with pH 8 silica gel gave isomeric naphthalenetriol **123** in high yield. The pattern of aldol cyclizations in the latter case is the same as in the aphid metabolite 6-hydroxymusizin. During the formation of **123** the precursor, resorcinol **122**, was not observed.

Stockinger and Schmidt, extending the approach they employed for tetra- and pentacarbonyl systems (see Schemes 18 and 34), have condensed the methyl ether of triacetic lactone with the trianion of 2,4,6-heptanetrione to give 19% of chromone **125**, derived from hexaketone enol ether **124** (Scheme 41).[11]



Scheme 40



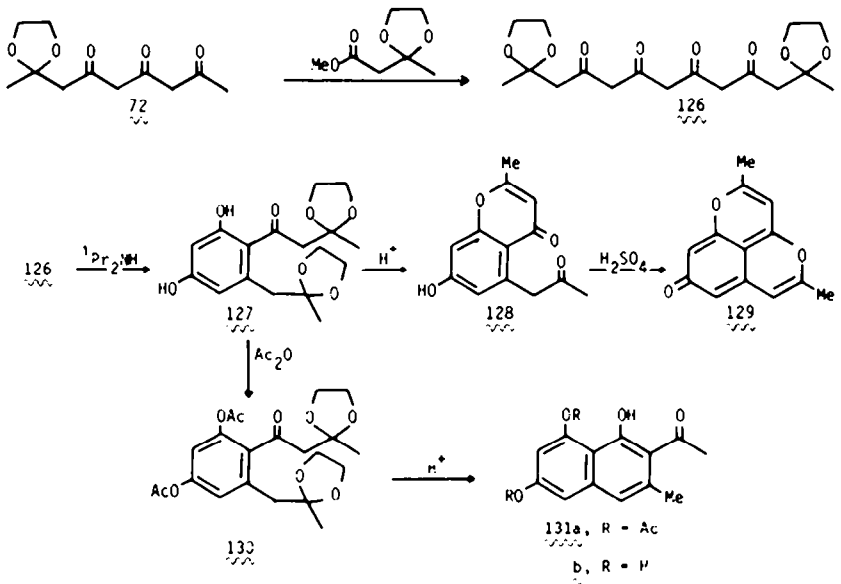
Scheme 41.

Many of the polyketide metabolites arise by reaction sequences in which the initial aldol cyclization of a polycarbonyl compound occurs at one of the central carbonyl groups. In fact, for formation of naphthalene, anthracene, and naphthacene compounds, initial aldol attack must occur at internal carbonyl groups. The propensity of methyl-terminated polycarbonyl chains to undergo cyclization reactions involving nucleophilic attack on the terminal keto group led us to investigate the derivative (**126**) of dimethyl hexaketone which has both of the terminal keto groups protected as ketals (Scheme 42).[52] The preparation of **126** involved a Claisen condensation of ketal-protected methyl acetoacetate with the trianion of monoketal-protected tetraketone **72**. Whereas the unprotected hexaketone would have had available to it four discrete aldol cyclizations of which the cyclization involving positions 2 and 7 would be expected to predominate, doubly protected hexaketone **126** would have only one, the 4:9 condensation. Treatment of **126** with diisopropylamine gave 80% of the expected resorcinol **127**. Removal of the ketal groups by treatment with acid caused concommitant cyclization to the naturally occurring chromone **128** (87%); further treatment of **128** with H_2SO_4 gave the tricyclic metabolite barakol (**129**) in 80% yield. Chromone formation during deprotection of the keto groups could be avoided by prior acetylation of the phenolic groups. With diacetyl derivative **130**, acid treatment gave the triketone which immediately underwent aldol cyclization to give naphthalene **131a** (55%). Saponification of the acetate esters gave 6-hydroxymusizin (**131b**).

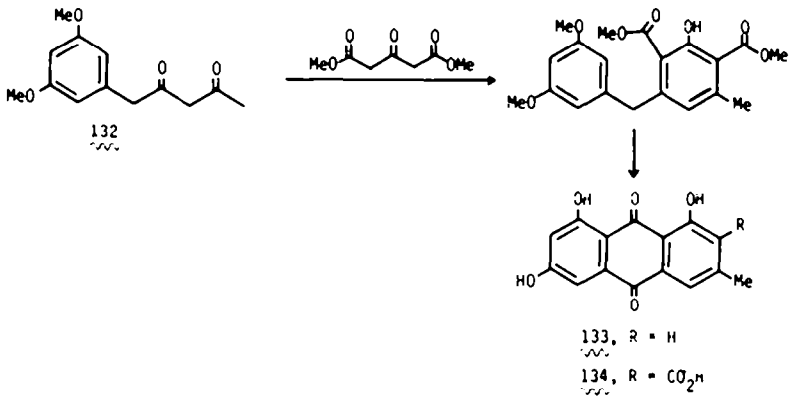
HEPTACARBONYL COMPOUNDS

Hexaketo acids and heptaketones are sufficiently large arrays of carbonyl groups to permit construction of tricyclic compounds. The tricyclic polyketide natural products are very numerous and represent a fruitful area for study, but the size of the polycarbonyl system has been a major stumbling block. As an alternative to using a heptaketone Mühlemann has used a two-chain approach for a biogenetically inspired synthesis of emodin (**133**) (Scheme 43).[64,65] The condensation of diketone **132** with dimethyl 3-oxoglutarate gave a benzylisophthalate ester. Completion of the synthesis involved closing the middle ring by a Friedel–Crafts procedure. Steglich and Reininger later extended the method to the synthesis of endocrocin (**134**).[66]

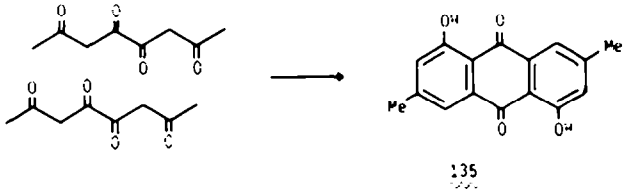
Another two-chain synthesis was used recently by Balenovic and Poje for the preparation of an anthraquinone; 2,4,5,7-octanetetraone underwent self-condensation to give anthraquinone **135** (Scheme 44).[67] It should be noted that neither the tetraketone nor the anthraquinone has the normal polyketide placement of substituents. Intermolecular condensations of polyketones do not usually occur if intramolecular condensations are possible. Nevertheless, intermolecular con-



Scheme 42.



Scheme 43.



Scheme 44.

densation competes successfully in this case because high reactivity of the 4 and 5 carbonyl groups in the tetraketone favors an initial 3:4' condensation between two molecules over five-membered ring formation by an internal 2:6 condensation.

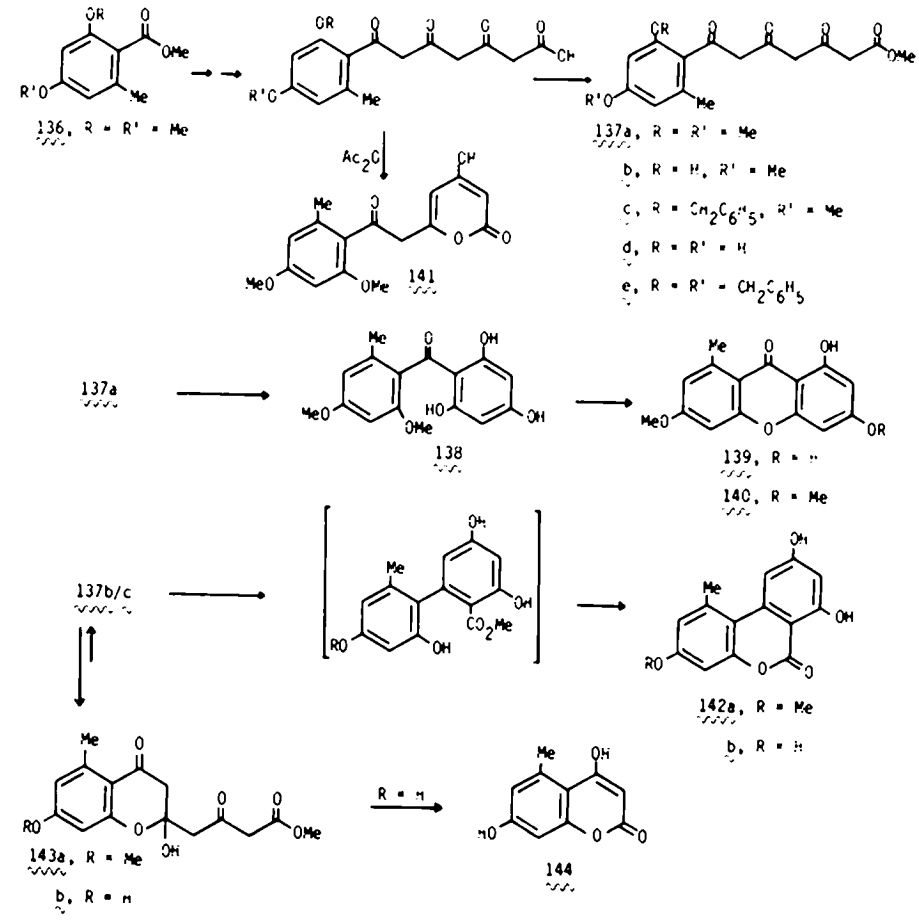
In the absence of heptacarbonyl compounds, another approach which is applicable in some cases involves stepwise construction of the polycarbonyl chain, i.e. building up a short chain, cyclizing it, then adding the rest of the carbonyl groups and carrying out the remaining cyclizations.[62a] This type of approach is particularly well suited for the synthesis of alternariol (**142b**) and lichexanthone (**140**) in which the benzene rings are not fused together. Orsellinic acid, (**30**), prepared from tetraacetic acid, was the starting point for syntheses of **140** and **142b** in the authors' laboratory.[62a] The ester of **30** having the hydroxyl groups protected as methyl ethers (**136**) was used to prepare aryl triketo ester **137a** (Scheme 45). Alternariol is formally derived from ester **137a** by an aldol cyclization and lichexanthone by a Claisen. Treatment of ester **137a** with KOH gave xanthone **139** via benzophenone **138**; lichexanthone (**140**) was prepared from **139** by methylation with CH_2N_2. No reaction conditions were found by which the aldol cyclization would occur; steric hindrance to nucleophilic attack on the 7 carbonyl group is believed to account for the failure in this case of the normally facile aldol cyclization of a triketo ester. A more efficient route to benzophenone **138** and xanthone **139** involved rearrangement of enol lactone **141**, which had been prepared by treatment of the corresponding triketo acid with Ac_2O. Treatment of **141** with LiH gave 87% of benzophenone **138** which cyclized to **139** with hot KOH.

In a second experiment the homologous triketo ester (**137b**) having a hydroxyl group rather than a methoxyl in the *ortho* position on the aromatic ring was prepared by hydrogenolysis of benzyl ether **137c**; **137b** cyclized reversibly to hemiketal **143a**. Treatment of **143a** with NaOAc brought about re-opening of the hemiketal ring, aldol cyclization of the triketo ester and finally lactonization to give 64% of methyl ether **142a** from which alternariol (**142b**) was obtained by demethylation with HI. The *ortho* hydroxyl group of **137b** is believed to activate the 7-keto group to nucleophilic attack by holding it in the plane of the aromatic ring. In yet another experiment hemiketal **143b** of unprotected triketo ester **137d**, prepared by hydrogenolysis of dibenzyl ether **137e**, was treated with NaOAc. Ring-opening and recyclization gave alternariol directly but chain cleavage to give coumarin **144** was a major side reaction. A 52% yield of alternariol was obtained with 1:1 HOAc/NaOAc as the reaction catalyst.

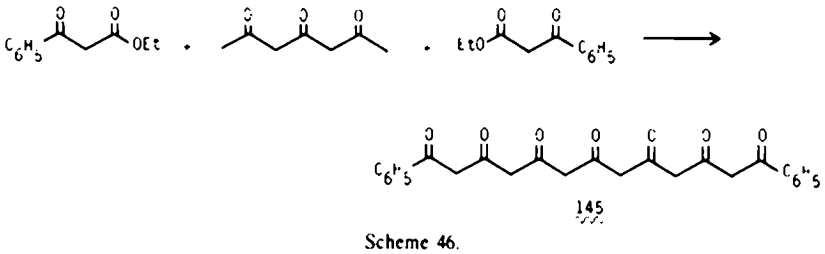
No unprotected hexaketo acids have been synthesized but one heptaketone (**145**) has been prepared in our laboratory by a two-fold acylation of 2,4,6-heptanetrione with ethyl benzoylacetate (Scheme 46).[63] Heptaketone **145** was isolated in 15% yield. Cyclization reactions of **145** have not been investigated but it should be noted that on account of the phenyl termini the carbonyl chain is not long enough for synthesis of anthracene derivatives.

Scott has investigated pyrone analogues of heptacarbonyl compounds. His first model, tetrapyranopyranpentaone **146** was abandoned on account of a poor yield observed in the synthesis of **146** and disappointing results which had been obtained with the lower homolog, tripyranopyrantetraone **116**.[41] Bis-pyrone **148** proved to be more attractive even though it is actually a protected pentaketo dicarboxylic acid instead of a hexaketo acid. The synthesis of **148** involved decarboxylative dimerization of pyrone-acid **147** with acetic anhydride. Treatment of **148** with methanolic KOH gave xanthone **149** in 15% yield (Scheme 47).[59,60] A heptacarbonyl compound may be a transient intermediate in the rearrangement but the regiospecificity of the reaction is more readily accounted for by the pyrone rings opening and recyclizing one at a time. The use of LiH or other non-nucleophilic bases might well improve the yield of the reaction sequence.

We have been able to extend the approach used for



Scheme 45.

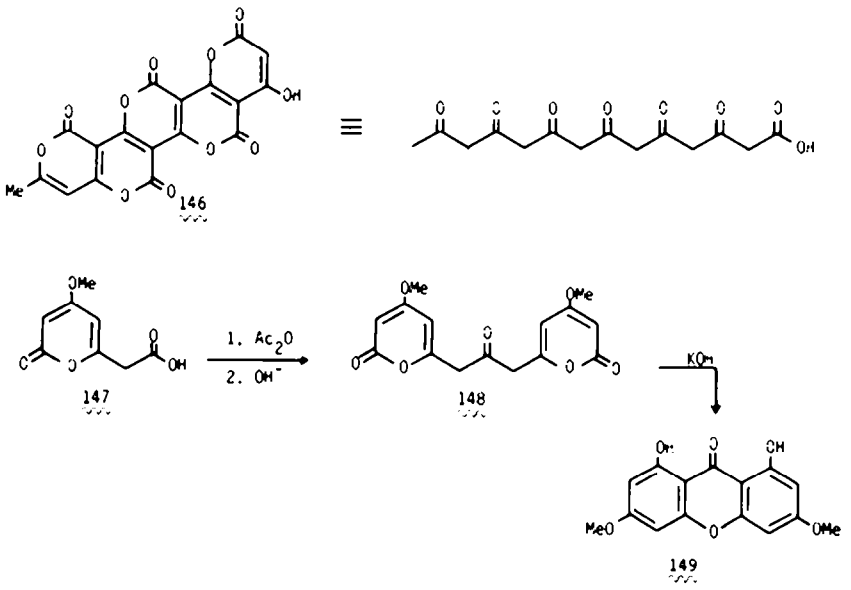


Scheme 46.

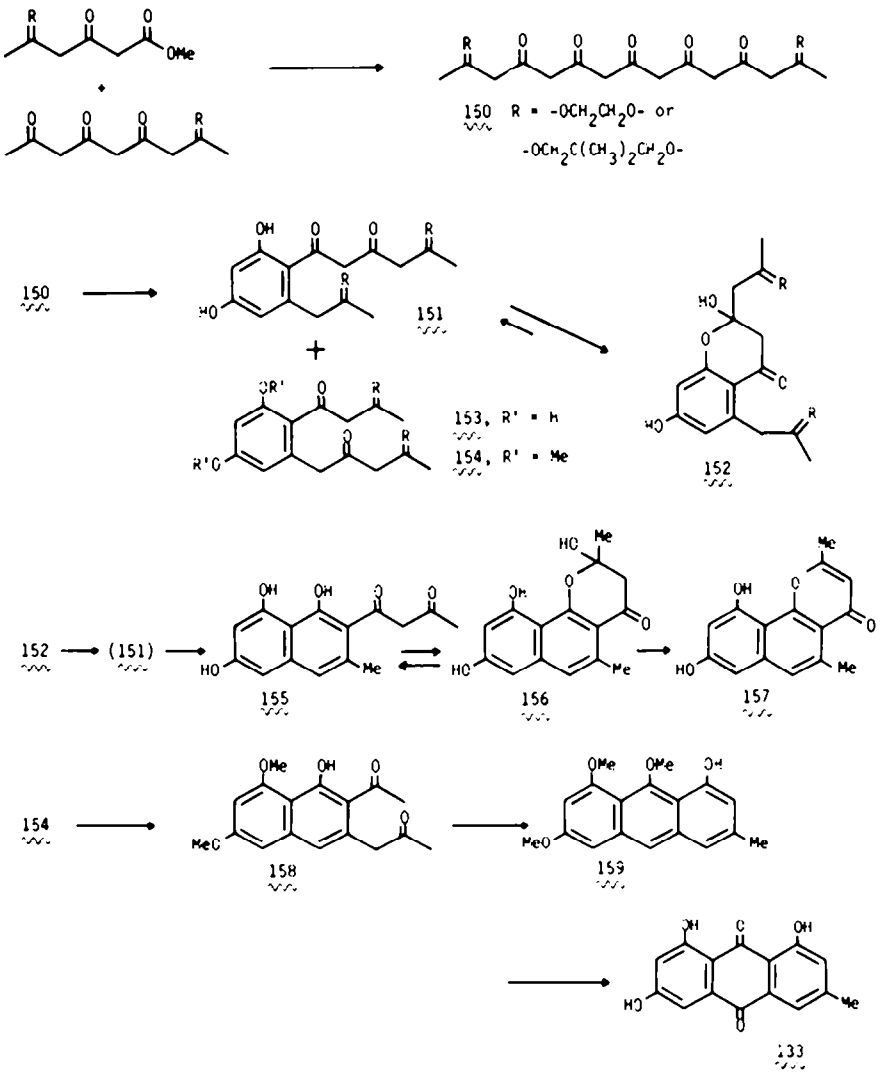
synthesis of 6-hydroxymusizin (**131b**) and barakol (**129**), i.e. cyclization of a polyketone with terminal groups protected, to the synthesis of eleutherinol (**157**), for which a terminally protected heptaketone would be required. Polyketone **150** (R = OCH_2CH_2O) was prepared by acylation of protected tetraketone **72** with 5 ketal-protected methyl 3,5-dioxohexanoate (Scheme 48).[52] Treatment of **150** (R = OCH_2CH_2O) with triethylamine gave 57% of resorcinol **151**, which had the correct structure for synthesis of **157**, along with 3% of isomeric resorcinol **153** (isolated as dimethyl ether **154**). Resorcinol **151** existed predominantly as cyclic hemiketal **152** but treatment with acid reopened the hemiketal ring, removed the ketal protective groups and brought about aldol cyclization to give naphthalene **155** which existed in equilibrium with cyclic hemiketal **156**. Further acid treatment (CF_3CO_2H) of this mixture brought about dehydration to give eleutherinol in 20% yield (based on **152**).

The minor product of the aldol cyclization of **150** (R = OCH_2CH_2O) has the correct cyclization pattern for synthesis of emodin but was formed in too low yield for a practicable synthesis. More favorable conditions for the cyclization of **150** (R = OCH_2CH_2O) could not be found but some improvement was obtained by using a more bulky protective group on the terminal carbonyl groups of **150** since the desired cyclization involved the 6-keto group rather than the 4.[52] Using ketal groups derived from 2,2-dimethyl-1,3-propanediol, the ratio of 6 to 4 attack improved slightly, cyclization products **154** and **152** [R = $OCH_2C(CH_3)_2CH_2O$] being isolated in yields of 10 and 54%, respectively (Scheme 48). Emodin (**133**) was synthesized from **154** by closure of the second ring by NaOMe and removal of the ketal groups by HCl to give **158**, protection of the new phenolic OH group by methylation and closure of the third ring by NaOMe to give **159** and finally removal of the O-methyl groups by HI and oxidation of the resulting anthrone by CrO_3. A 20% yield was obtained for the six-step sequence.

From these studies it can be concluded that poly-



Scheme 47.



Scheme 48.

carbonyl chains will show a tendency to undergo cyclization reactions involving the terminal keto groups. Diphenyl hexaketone (**118**) is an exception to this generalization because the reactivity of the terminal keto groups is reduced by the phenyl substituents. For the synthesis of 6-hydroxymusizin and barakol, the terminal keto groups of the hexaketone had to be blocked to avoid orcinol-type cyclization products. With terminally protected heptaketone the preferred site of attack becomes the 4-keto group. Thus terminal protection has only very limited value for synthesis of anthracene derivatives.

A superior strategy for directing aldol cyclizations of the heptaketone toward anthracene derivatives involves protection of the middle, i.e. 8, keto group rather than the terminal ones. With the 8 position derivatized all aldol cyclizations other than that between the 6 and 11 positions become impossible or unlikely. The subsequent cyclizations, as already demonstrated, occur in the desired fashion to give the anthracene nucleus. The protected heptaketone (**161**) was prepared by two-fold nucleophilic attack of acetylacetone dianion on ketal-protected diethyl 3-oxoglutarate (**160**) but was unstable undergoing cyclization during work-up to give naphthalene **163** in an overall 39% yield (Scheme 49).[70] With careful treatment intermediate **162** could be isolated. Closure of the third ring was brought about (94%) by treatment of **163** with methanolic KOH. Aldol adduct **164** was dehydrated quantitatively by pyridine or HCl and the hydroxyethyl group was removed by HI in HOAc to give emodin anthrone (**165**) in 78% yield. Oxidation of **165** with CrO_3 gave 70% of emodin (**133**).

The ease and specificity of this sequence is noteworthy; isomeric cyclization products were not detected. Apparently the 8-ketal group not only blocked unwanted initial cyclization reactions but also promoted the desired 6:11 ring closure. A possible explanation for the facilitation of cyclization is that the ketal blocks enolization involving the 7 and 9 methylene groups so that free rotation can occur around C–C bonds 6, 7, 8 and 9. The bulkiness of the ketal group favors conformations in which the two triketone fragments of **161** are close together. The factors governing the second and third cyclizations are not known.

OCTACARBONYL COMPOUNDS

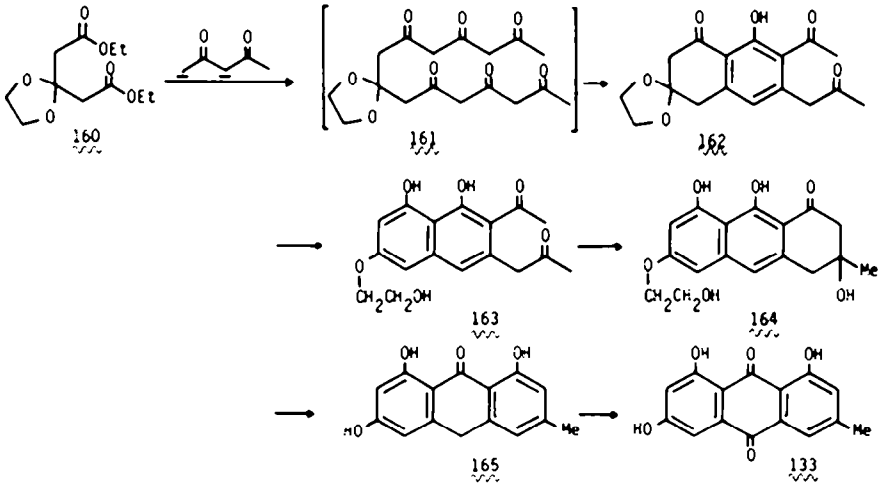
The only member of this class to have been prepared is octaketone **166** which was prepared in low yield by two-fold acylation of 2,4,6,8-nonanetetraone (**68**) with ethyl benzoylacetate (Scheme 50).[61] Cyclization reactions have not been studied.

NONACARBONYL COMPOUNDS

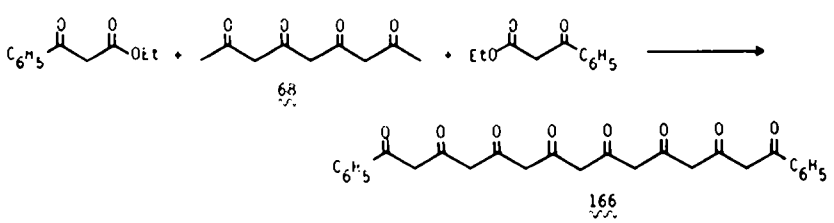
Bis(pyranopyrandione) **168** has been studied by Scott as a potential precursor for anthracenes.[59] It is, in fact, short only one carbonyl group of the chain length needed for preparation of a naphthacene. The preparation of **168** involved decarboxylative dimerization of acid **167** by acetic anhydride (Scheme 51). Previous studies of simple pyranopyrandiones had shown that mild basic conditions would selectively hydrolyze **168** to triketone **169** for which only one aldol cyclization is possible, the one which could lead to anthracene **171**. Treatment of **168** with NaOH brought about the anticipated cleavages and aldol cyclization to give resorcinol **170**, but suitable conditions for conversion of **170** to **171** could not be found.

REDUCED β-POLYCARBONYL COMPOUNDS

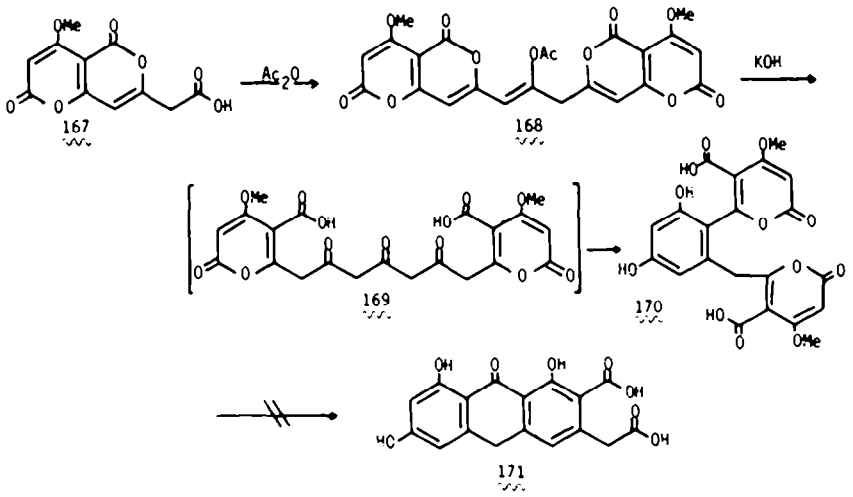
The final topic to be considered in this review is the formation of aromatic metabolites in which one or more of the anticipated hydroxyl groups are absent. This sub-



Scheme 49.



Scheme 50.



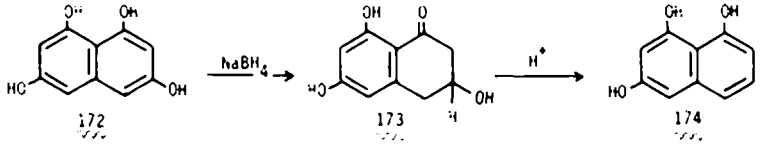
Scheme 51.

ject takes on special significance because several of the key polyketide metabolites, 6-methylsalicylic acid (**4**), chrysophanol (**193**) and pretetramide (**199**), are examples of this group. Deletion of a hydroxyl group comes about by a reduction process; in some cases reduction occurs prior to aromatization,[6] while in others it occurs after.[71] Bycroft and coworkers have described a simple model for the latter involving reduction of 1,3,6,8-naphthalenetetraol (**172**) by $NaBH_4$ to give scytalone (**173**) which dehydrates readily in acid to give 1,3,8-naphthalenetriol (Scheme 52).[72]

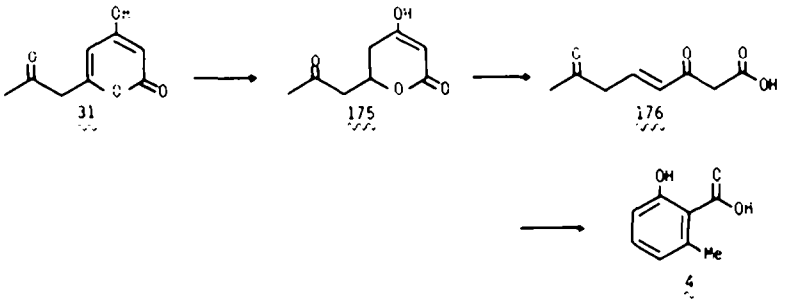
In cases where reduction occurs prior to aromatization, the polyketonic intermediate will have a keto group replaced by a hydroxyl group or by a double bond. Polycarbonyl compounds containing these modifications are more difficult to prepare and to isolate than compounds containing perfectly regular chains. The extent of the problem can be seen in the fact that heptene-2,6-dione has not yet been synthesized.[73] Nevertheless, several excellent models have been described for the formation of aromatic compounds with hydroxyl deletions.

6-Methylsalicylic acid (**4**) requires for its preparation 5-hydroxy-3,7-dioxooctanoic acid or equivalent species. Scott *et al.* have described a clever approach to **4** involving partial reduction of tetraacetic lactone (**31**) (Scheme 53).[41,43] Dihydropyrone **175** on treatment with base underwent ring opening to give an anion of 3,7-dioxooctenoic acid (**176**), which could be isolated by cautious acidification but cyclized readily in base to give **4** in 28% overall yield.

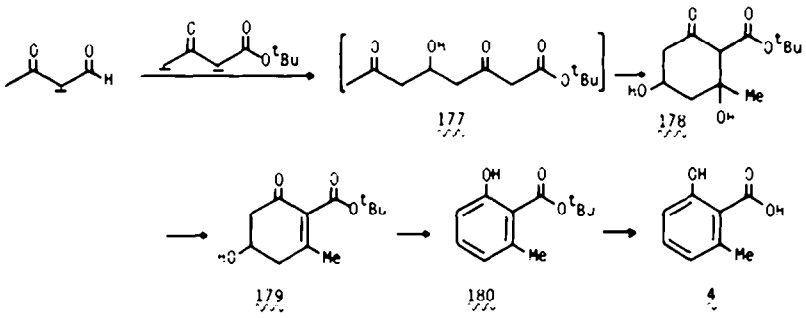
Another approach to 6-methylsalicylic acid which was developed in our laboratory involves nucleophilic attack of the dianion of *tert*-butyl acetoacetate on the monoanion of formylacetone (Scheme 54).[20] The condensation gave 64% of a mixture of stereoisomers of the undehydrated aldol cyclization product **178** of hydroxydiketo ester **177**. Dehydration of **178** in two stages gave esters **179** and **180**. Removal of the *tert*-butyl group from **179** by HCl gave 6-methylsalicylic acid (**4**). A 40% yield was obtained for the conversion of **178** to **4** when the sequence was carried out without isolation of intermediates. The stability of intermediates **178** and **179** shows that enzymes may be required to catalyze the individual biosynthetic steps. It should be noted that aldol-type polyketide metabolites arise via chiral inter-



Scheme 52.



Scheme 53.



Scheme 54.

mediates even though the starting materials, i.e. acetate and malonate, are not chiral nor, in general, are the metabolites.

Scott and coworkers have investigated a bis-pyrone (**181**) equivalent to a reduced pentaketo diacid.[59] Treatment of **181** with methanolic KOH gave three aldol type coumarin derivatives (**182–184**), one of which on treatment with NaOMe gave a naphthalene derivative (**185**) by a second aldol cyclization (Scheme 55). The result provides an interesting contrast with unreduced bis-pyrone **148** which underwent two consecutive Claisen cyclizations to yield a xanthone.

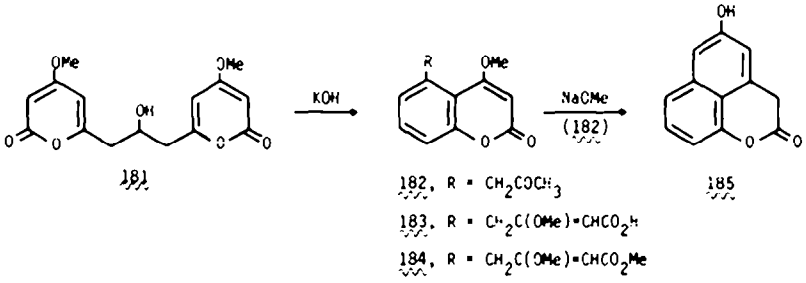
Several other pyrone studies have been reported but the results bear a more distant relationship to the biosynthesis of natural products. Cheng and Tan have described the cleavage-recyclization of pyranopyrandione **186**.[74] Crombie and coworkers have described extensive studies of xanthophanic and glaucophanic enols **187** and **188** which rearrange with basic reagents to give benzenoid products.[75] They have observed that with large excesses of $Mg(OMe)_2$ the products are formed by Claisen cyclizations whereas with smaller amounts of $Mg(OMe)_2$ the products are formed by aldol cyclizations. The change of pathway has been accounted for on the basis of chelation controlled cyclizations.

Syntheses of chrysophanol (**193**) and eleutherin (**196**) have been achieved in the authors' laboratory using a modification of the approach that had been successful for emodin (Scheme 56). Treatment of diester **189** with acetylacetone dianion gave naphthalene **191** in 24% yield. Neither aminohexaketone **190** nor other intermediates were detected. The final ring closure by NaOH (88%) followed by dehydration by HCl (96%) gave chrysophanol anthrone (**192**) which was oxidized to chrysophanol (**193**) by CrO_3 (74%).[70] Under acidic conditions **191** cyclized to naphthopyran **194** from which eleutherin (**196**) was synthesized by reduction with H_2 and Pd/C, methylation of **195a** by CH_2N_2 and oxidation of **195b** with Fremy's salt.[76]

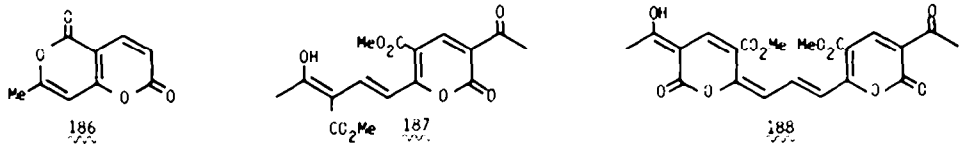
Pretetramide (**199**) is one of the most interesting and challenging of the polyketide metabolites that remains to be synthesized by a biogenetically modeled route. A decacarbonyl compound could be required for its preparation. Key features of pretetramide are deletion of one of the phenolic hydroxyl groups and the involvement of two carboxylate termini, or more precisely a carboxylic ester and a carboxamide. To date no decacarbonyl compounds or masked decacarbonyl compounds have been synthesized. However, one important model experiment has been carried out by McCormick *et al.* at Lederle Laboratories.[77] In their studies of mutants of the tetracycline-producing microorganism they found two tricyclic metabolites (**197** and **198**) which, although not biogenetic precursors of tetracyclic compounds, would undergo closure of the fourth ring on treatment with HI to give pretetramide (**199**) and 6-methylpretetramide (**200**), respectively (Scheme 57).

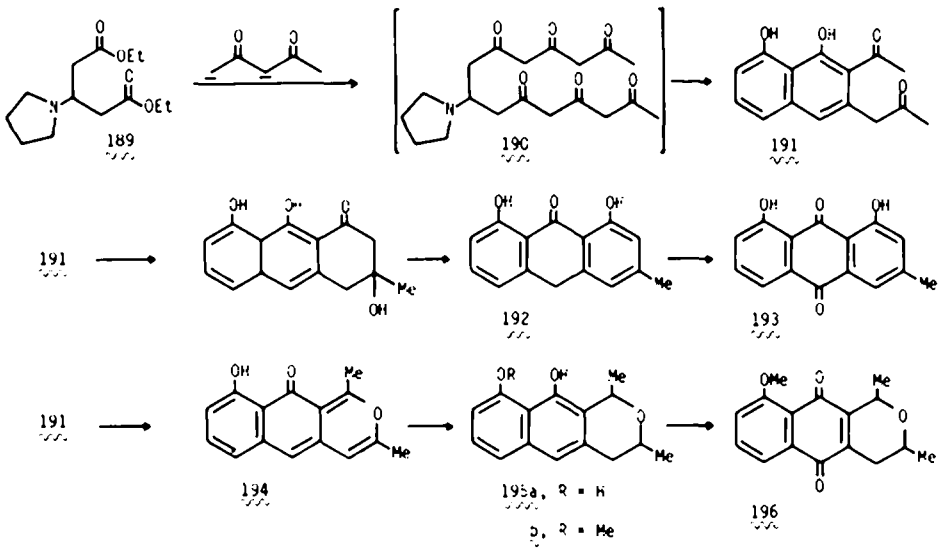
SUMMARY

In view of the successes which have been seen with mono-, di-, and tricyclic natural products, further work directed toward syntheses of pretetramide and other target molecules can clearly be expected. Much remains to be learned about the mechanisms of reactions and about the factors that control cyclizations. Many classes of polyketide metabolites have not yet been synthesized.

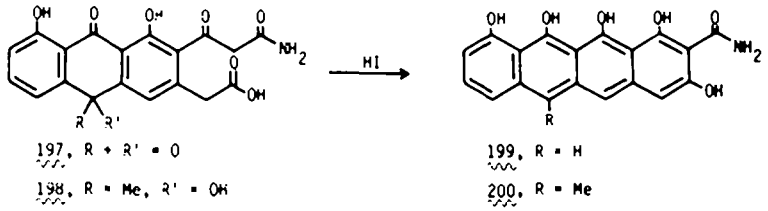


Scheme 55.





Scheme 56.



Scheme 57.

One area where much more study is needed is the synthesis of polycarbonyl compounds themselves by biogenetically modeled routes. Scott's synthesis[9] of acetoacetate provides a useful start but the stepwise preparation of long carbonyl chains remains a challenging problem.

A second area of importance is the effect of metal ions on cyclization reactions. Metallic cation effects play an important role in controlling Claisen versus aldol cyclization in the synthesis of benzenoid compounds although the relevance of these observations to biosynthesis of benzenoid compounds can be questioned. It seems likely that metal chelates play a greater role in the biosynthesis of polycyclic compounds. For example, in the formation of anthracenes, chelation would hold the polycarbonyl chain in configurations that would favor linear fusion of rings. Recent work by Glick and Lintvedt on the structure of metal chelates of polycarbonyl compounds[78] serves as a first step to understanding the effect of metal ions in such systems.

A third area which will undoubtedly see future acivity is the preparation of undecarboxylated aldol-type polycyclic metabolites. Although all of the metabolites arise from polyketo acids, in many cases the carboxyl group is lost in the course of or after cyclization. 6-Hydroxymusizin, barakol, emodin, eleutherinol, chrysophanol and eleutherin are examples of the decarboxylated group and represent some of the most successful of the polycyclic biogenetic-type syntheses. Other compounds, such as endocrocin (**134**) and pyrromycinones (e.g. **200**) retain the carboxyl group. The latter compounds will be more difficult to synthesize in part because general methods for the synthesis of the higher polyketo acids are not available but mainly because the absence of end-to-end symmetry of the polycarbonyl compounds doubles the number of possible cyclization products.

The high yields obtained in the best of the biogenetic-type syntheses raises the hope that this esthetically pleasing route to natural products can in selected cases have practical value and can provide commercially attractive routes to antibiotics and other natural products of economic importance by total synthesis or by synthesis of key biosynthetic intermediates which would then be transformed to the ultimate product by microorganisms.

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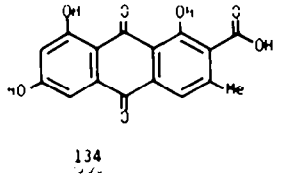
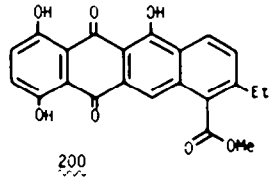


134



200

REFERENCES

[1]J. N. Collie, *J. Chem. Soc.* **59**, 179 (1891); **59**, 607 (1891); **63**, 329 (1893); **91**, 1806 (1907); *Proc. Chem. Soc. (London)* **23**, 230 (1907); J. N. Collie and W. S. Myers, *J. Chem. Soc.* **63**, 122 (1893); J. N. Collie and B. D. Steele, *Ibid.* **77**, 961 (1900).

[2]F. Feist, *Liebig's Ann. Chem.* **257**, 253 (1890); C. F. Rassweiler and R. Adams, *J. Am. Chem. Soc.* **46**, 2758 (1924).

[3]R. Robinson, *J. Roy. Soc. Arts* **96**, 795 (1948); see also R. Robinson, *The Structural Relations of National Products*. Clarendon Press, Oxford (1955).

[4]A. J. Birch and F. W. Donovan, *Austral. J. Chem.* **6**, 360 (1953); A. J. Birch, *Fortschr. Chem. Org. Naturst.* **14**, 186 (1957); A. J. Birch, *Proc. Chem. Soc. (London)* 3 (1962).

[5]See J. H. Richards and J. B. Hendrickson, *The Biosynthesis of Steroids, Terpenes and Acetogenins*. W. A. Benjamin, New York (1964); J. D. Bu'Lock, *The Biosynthesis of Natural Products*. McGraw-Hill, London (1965); R. J. Light, *J. Agr. Food Chem.* **18**, 260 (1970).

[6]A. J. Birch, R. A. Massy-Westropp, R. W. Rickards and H. Smith, *Austral. J. Chem.* **8**, 539 (1955); see also P. Dimroth, H. Walter and F. Lynen, *Eur. J. Biochem.* **13**, 98 (1970).

[7]S. Gatenbeck, P. O. Eriksson and Y. Hansson, *Acta Chem. Scand.* **23**, 699 (1969); T. M. Harris, C. M. Harris and R. J. Light, *Biochim. Biophys. Acta* **121**, 420 (1966); S. W. Tanenbaum, S. Nakajima and G. Marx, *Biotech. Bioengineering* **11**, 1135 (1969).

[8]For other reviews, see T. Money, *Chem. Rev.* **70**, 553 (1970); T. M. Harris, C. M. Harris and K. B. Hindley, *Fortschr. Chem. Org. Naturst.* **31**, 217 (1974).

[9]A. I. Scott, C. S. Wiesner, S. Yoo and S.-K. Chung, *J. Am. Chem. Soc.* **97**, 6277 (1975).

[10]T. Kato and T. Hozumi, *Chem. Pharm. Bull. (Tokyo)* **20**, 1574 (1972).

[11]A. Heikel, *Suomen Kemistilehti* **8B**, 33 (1935) [*Chem. Abstr.* **30**, 437 (1936)]; see also J. H. Clark and J. M. Miller, *Tetrahedron Letters* 139 (1977) and H. Takeshita, *Ibid.* 1657 (1977).

[12]A. Baeyer, *Ber. Dtsch. Chem. Ges.* **18**, 3454 (1885).

[13]F. Sproxton, *J. Chem. Soc.* **89**, 1186 (1906); K. Balenovic and D. Sunko, *Monatsh. Chem.* **79**, 1 (1948); R. F. Witter and E. Stotz, *J. Biol. Chem.* **176**, 485 (1948); W. B. Mors, O. R. Gottlieb and C. Djerassi, *J. Am. Chem. Soc.* **79**, 4507 (1957).

[14]F. Arndt, B. Eistert, H. Scholz and E. Aron, *Ber. Dtsch. Chem. Ges.* **69**, 2373 (1936); F. Kögl and C. A. Salemink, *Rec. Trav. Chim. Pays-Bas* **71**, 779 (1952) and **74**, 221 (1955).

[15]J. G. Batelaan, *Synth. Commun.* **6**, 81 (1976).

[16]M. P. Wachter and T. M. Harris, *Tetrahedron* **26**, 1685 (1970).

[17]J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.* 502 (1960); J. L. Douglas and T. Money, *Can. J. Chem.* **46**, 695 (1968).

[18]C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.* **80**, 6360 (1958); T. M. Harris and C. M. Harris, *J. Org. Chem.* **31**, 1032 (1966); T. M. Harris and C. S. Combs, Jr., *Ibid.* **33**, 2399 (1968).

[19]J. F. Wolfe, T. M. Harris and C. R. Hauser, *J. Org. Chem.* **29**, 3249 (1964); S. N. Huckin and L. Weiler, *Tetrahedron Letters* 2405 (1972); S. N. Huckin and L. Weiler, *Can. J. Chem.* **52**, 1343 (1974).

[20]T. M. Harris, T. P. Murray, C. M. Harris and M. Gumulka, *J. Chem. Soc. Chem. Commun.* 362 (1974).

[21]T. M. Harris and C. M. Harris, *Tetrahedron* **25**, 2687 (1969).

[22]T. Komninos, *Bull. Soc. Chim. Fr.* [iv] **23**, 449 (1918).

[23]S. S. Deshapande, Y. V. Dingankar and D. N. Kopil, *J. Indian. Chem. Soc.* **11**, 595 (1934); K. Balenovic and R. Munk, *Arkiv. Kem.* **18**, 41 (1946) [*Chem. Abstr.* **42**, 2926 (1948)].

[24]R. H. Wiley, C. H. Jarboe and H. G. Ellert, *J. Am. Chem. Soc.* **77**, 5102 (1955); T. M. Harris and C. M. Harris, *Chem. Commun* 699 (1966); T. M. Harris, C. M. Harris and M. P. Wachter, *Tetrahedron* **24**, 6897 (1968).

[25]R. J. Light and C. R. Hauser, *J. Org. Chem.* **25**, 538 (1960); F. B. Kirby, T. M. Harris and C. R. Hauser, *Ibid.* **28**, 2266 (1963); S. D. Work and C. R. Hauser, *Ibid.* **28**, 725 (1963); M. L. Miles, T. M. Harris and C. R. Hauser, *Ibid.* **30**, 1007 (1965); P. J. Wittek, K. B. Hindley and T. M. Harris, *Ibid.* **38**, 896 (1973).

[26]K. G. Hampton, T. M. Harris, C. M. Harris and C. R. Hauser, *J. Org. Chem.* **30**, 4263 (1965).

[27]J. R. Bethell and P. Maitland, *J. Chem. Soc.* 3751 (1962).

[28]A. J. Birch, D. W. Cameron and R. W. Rickards, *Ibid.* 4395 (1960).

[29]T. M. Harris and R. L. Carney, *J. Am. Chem. Soc.* **88**, 2053 (1966); **88**, 5686 (1966), and **89**, 6734 (1967).

[30]T. T. Howarth, G. P. Murphy and T. M. Harris, *Ibid.* **91**, 517 (1969); T. M. Harris, G. P. Murphy and A. J. Poje, *Ibid.* **98**, 7733 (1976).

[31]T. T. Howarth and T. M. Harris, *Ibid.* **93**, 2506 (1971).

[32]T. M. Harris, T. T. Howarth and R. L. Carney, *Ibid.* **93**, 2511 (1971).

[33]H. Stockinger and U. Schmidt, *Liebigs Ann. Chem.* 1617 (1976).

[34]U. Schmidt and M. Schwochau, *Monatsh. Chem.* **98**, 1492 (1967).

[35]D. A. Griffin and J. Staunton, *J. Chem. Soc. Chem. Commun.* 675 (1975).

[36]G. Bram, *Tetrahedron Letters* 4069 (1967).

[37]T. Money, I. H. Qureshi, G. B. Webster and A. I. Scott, *J. Am. Chem. Soc.* **87**, 3004 (1965); T. Money, J. L. Douglas and A. I. Scott, *Ibid.* **88**, 624 (1966); T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright and A. I. Scott, *Tetrahedron* 3435 (1967); J. L. Douglas and T. Money, *Can. J. Chem.* **45**, 1990 (1967) and *Tetrahedron* **23**, 3545 (1967).

[38]E. Ziegler and H. Junek, *Monatsh. Chem.* **89**, 323 (1958); C. Goetschel and C. Mentzer, *Bull. Soc. Chim. Fr.* 365 (1962).

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

[40]For a discussion of the pathway by which aldol products are formed and reassignment of the structure of one of them, see T. T. Howarth and T. M. Harris, *Can. J. Chem.* **46**, 3739 (1968).

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

[42]J. Carnduff, J. A. Miller, B. R. Stockdale, J. Larkin, D. C. Nonhebel and H. C. S. Wood, *J. Chem. Soc. Perkin I* 692 (1972).

[43]A. I. Scott, H. Guilford, J. J. Ryan and D. Skingle, *Tetrahedron* **27**, 3025 (1971).

[44]R. Bentley and P. M. Zwitkowits, *J. Am. Chem. Soc.* **89**, 676 (1967).

[45]A. I. Scott, H. Guilford and D. Skingle, *Tetrahedron* **27**, 3039 (1971).

[46]S. Yamamura, K. Kato and Y. Hirata, *Chem. Commun.* 1580 (1968) and *J. Chem. Soc. C* 2461 (1969); J. L. Bloomer, S. M. H. Zaidi, J. T. Strupczewski, C. S. Brosz and L. A. Gudzyk, *J. Org. Chem.* **39**, 3615 (1974).

[47]T. M. Harris, M. P. Wachter and G. A. Wiseman, *Chem. Commun.* 177 (1969); T. M. Harris and M. P. Wachter, *Tetrahedron* **26**, 5255 (1970).

[48]C. T. Bedford, J. L. Douglas, B. E. McCarry and T. Money, *Chem. Commun.* 1091 (1968).

[49]M. L. Miles, T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.* **85**, 3884 (1963).

[50]T. M. Harris and G. P. Murphy, *Ibid.* **93**, 6708 (1971); G. P. Murphy, Dissertation, Vanderbilt University (1971).

[51]T. P. Murray and T. M. Harris, *J. Am. Chem. Soc.* **94**, 8253 (1972).

[52]T. M. Harris and P. J. Wittek, *Ibid.* **97**, 3270 (1975).

[53]H. Stetter and S. Vestner, *Chem. Ber.* **97**, 169 (1964).

[54]J. F. Stephen and E. Marcus, *J. Org. Chem.* **35**, 258 (1970).

[55]H. Zak and U. Schmidt, *Chem. Ber.* **106**, 3652 (1973).

[56]P. F. G. Prail and A. L. Whitear, *Proc Chem. Soc. (London)* 112 (1961).

[57]G. Casnati, A. Quilico, A. Ricca and P. Vita-Finzi, *Chim. et Ind.* **47**, 993 (1965) [*Chem. Abstr.* **64**, 8068 (1966)]; *Tetrahedron Letters* 233 (1966); *Gazz. Chim. Ital.* **96**, 1064 (1966) [*Chem. Abstr.* **66**, 37811 (1967)]; S. Auricchio, S. Morrocchi and A. Ricca, *Tetrahedron Letters* 2793 (1974).

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

[59]A. I. Scott, D. G. Pike, J. J. Ryan and H. Guilford, *Tetrahedron* **27**, 3051 (1971).

[60]P. M. Baker and B. W. Bycroft, *Chem. Commun.* 71 (1968).

[61]P. J. Wittek, Vanderbilt University, Dissertation (1975).

[62]A. J. Birch, P. Fitton, D. C. C. Smith, D. E. Steere and A. R. Stelfox, *J. Chem. Soc.* 2209 (1963).

[62a]For recent results, see C. Kirkemo, Oregon State University, Dissertation (1976).
[63]P. J. Wittek and T. M. Harris, *J. Am. Chem. Soc.* **95**, 6865 (1973).
[64]Mühlemann, *Pharm. Acta Helv.* **26**, 195 (1951) [*Chem. Abstr.* **46**, 8078 (1952)].
[65]For a newer synthesis of diketone **132**, see J. D. White, J. B. Bremner, M. J. Dimsdale and R. L. Garcea, *J. Am. Chem. Soc.* **93**, 281 (1971).
[66]W. Steglich and W. Reininger, *Chem. Commun.* 178 (1970).
[67]K. Balenovic and M. Poje, *Tetrahedron Letters* 3427 (1975).
[67a]For another excellent example, see F. M. Hauser and R. Rhee, *J. Am. Chem. Soc.* **99**, 4533 (1977).
[68]J. V. Hay and T. M. Harris, *J. Chem. Soc. Chem. Commun.* 953 (1972); T. M. Harris and J. V. Hay, *J. Am. Chem. Soc.* **99**, 1631 (1977).
[69]D. G. Pike, J. J. Ryan and A. I. Scott, *Chem. Commun.* 629 (1968).
[70]T. M. Harris, A. D. Webb, C. M. Harris, P. J. Wittek and T. P. Murray, *J. Am. Chem. Soc.* **98**, 6065 (1976).
[71]U. Sankawa, Y. Ebizuka and S. Shibata, *Tetrahedron Letters* 2125 (1973).
[72]B. W. Bycroft, M. M. Cashyap and T. K. Leung, *J. Chem. Soc. Chem. Commun.* 443 (1974).
[73]5-Oxohexenoic acid has, however, been synthesized; C. M. Harris and T. M. Harris, *J. Org. Chem* **36**, 2181 (1971).
[74]F. C. Cheng and S. F. Tan, *J. Chem. Soc. C* 543 (1968).
[75]L. Crombie, D. E. Games and M. H. Knight, *Tetrahedron Letters* 2313 (1964); *Chem. Commun* 355 (1966); *J. Chem. Soc. C* 757, 763, 773 and 777 (1967); L. Crombie, M. Eskins and D. E. Games, *Chem. Commun.* 1015 (1968).
[76]A. D. Webb and T. M. Harris, *Tetrahedron Letters* 2069 (1977).
[77]J. R. D. McCormick, In *Biogenesis of Antibiotic Substances* (Edited by Z. Vanek and Z. Hostalek), p. 73. Czechoslovak Academy of Sciences, Prague (1965); J. R. D. McCormick and E. R. Jensen, *J. Am. Chem. Soc.* **90**, 7126 (1968); J. R. D. McCormick, E. R. Jensen, N. H. Arnold, H. S. Corey, U. H. Joachim, S. Johnson, P. A. Miller and N. O. Sjolander, *Ibid.* **90**, 7127 (1968).
[78]M. D. Glick, R. L. Lintvedt, T. J. Anderson and J. L. Mack, *Inorg. Chem.* **15**, 2258 (1976) and earlier papers