

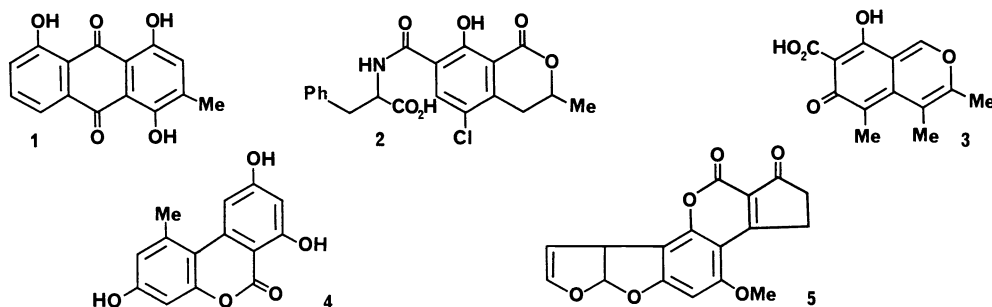
Biomimetic syntheses of aromatic polyketide metabolites

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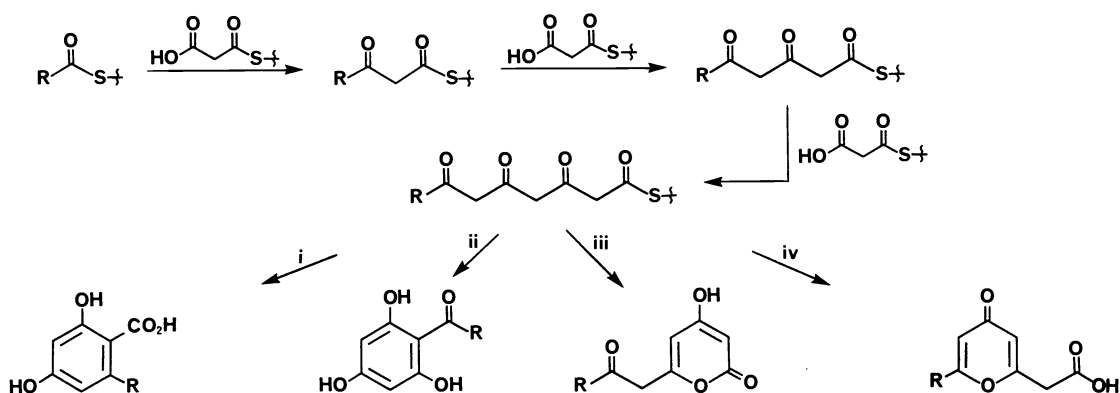
ABSTRACT: Methodology has been developed for synthesis of beta-oligoketo acids and related polycarbonyl compounds. Under appropriate conditions these compounds undergo cyclization reactions to form aromatic products; the cyclizations mimic the processes by which aromatic compounds are formed in nature. Examples include benzene, naphthalene, anthracene, and naphthalene ring systems and a number of heterocyclic structures.

Secondary metabolites are produced by microorganisms by a variety of routes, prominent among them being the polyketide pathway in which aromatic compounds are formed from acetate via oligoketo acids. Examples of aromatic mycotoxins formed by this pathway include islandicin (1), ochratoxin A (2), citrinin (3), alternariol (4), and aflatoxin B₁ (5). Possible existence of the polyketide biosynthetic pathway was first suggested by Collie near the turn of the century (ref. 1), but the idea received little attention until it was revived by Robinson in 1948 (ref. 2). In 1953 Birch and Donovan formulated the polyketide hypothesis essentially as it is understood today (ref. 3). They saw similarities between the pathway to aromatic compounds and the one by which fatty acids are formed from acetate (and malonate) by successive cycles of Claisen condensation, reduction, dehydration and further reduction. They also recognized the key difference, i.e., in the polyketide route the keto groups fail to be reduced so that successive additions of two-carbon units lead to carboxylic acids bearing keto groups at alternating positions along the chain. With increasing chain lengths opportunities arise for a variety of ring closures to occur to form carbocyclic and heterocyclic structures. The pathway to 3,5,7-triketo acids is illustrated in Scheme 1 along with the cyclizations, in this case four, which the acids undergo to give (i) a resorcylic acid via an aldol cyclization between C-2 and C-7, (ii) an acylphloroglucinol by Dieckmann cyclization at C-6, (iii) a 2-pyrone by attack of the carboxyl group on the 5-keto group, and (iv) a 4-pyrone by a dehydration reaction between the C-3 and C-7 carbonyl groups. Many naturally occurring examples of the first three product types are known, but the fourth one has not been observed in monocyclic systems. Carboxylic acids containing longer chains of beta carbonyl groups can undergo an increasing variety of cyclization reactions leading to naphthalenes, anthracenes, naphthacenes and other fused carbocyclics along with numerous complex pyran structures.



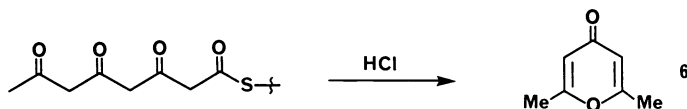
Experimental verification of the polyketide hypothesis has been obtained from feeding studies employing isotopically labelled acetate. Initial studies used ¹⁴C tracers with the site of labelling being analyzed by stepwise degradation (ref. 4). Many of the more recent experiments have used stable isotopes with NMR spectroscopy being used to establish the sites of incorporation. Experiments with double labelled ¹³C-acetate have been particularly instructive for establishing the folding patterns of the polycarbonyl intermediates (refs. 5 and 6).

Scheme 1



In contrast to the success with which the nature and placement of the basic acetate building blocks have been established for the assembly of polyketide-type aromatic metabolites, direct evidence for the intermediacy of polyketo acids has been remarkably difficult to obtain. In only a few cases have enzyme systems been prepared which were capable of forming aromatic structures and in no case has an oligoketo acid precursor of an aromatic ring system been isolated (ref. 7). The difficulties stem in part from the likelihood that the oligoketo acids are always bound to the synthetases via a thiol-ester linkage, but the reactivity of the oligoketo acids themselves complicates or precludes their isolation. In the absence of direct evidence, one of the best experiments has been that of Gatenbeck and coworkers (ref. 8) who isolated the unnatural cyclization product 2,6-dimethyl-4-pyrone (6) when an enzyme system was denatured while in the process of forming an aromatic product (Scheme 2).

Scheme 2

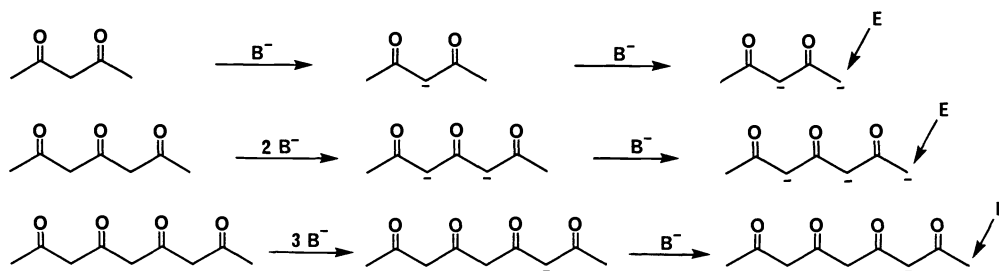


Some years ago we were attracted by the possibility of preparing oligoketo acids. If such compounds could be synthesized, their chemistry could then be studied. It might be possible to achieve biomimetic syntheses of some of the classes of naturally occurring aromatic compounds, if conditions for regioselective cyclizations could be found. These proposals are not without problems, mainly relating to the likelihood that the polyketo compounds would be unstable; intra- and intermolecular aldol condensations might render the compounds too labile to be manipulated. Indeed, Birch and coworkers had unsuccessfully attempted to synthesize a 2,4,6,8,10-pentaketone by an ozonolysis procedure but the product apparently underwent self-condensation (ref. 9).

Our synthetic approach was based on the premise that oligoketo acids would be most stable under two very different sets of conditions. First, since intra- and intermolecular aldol condensations are ionic processes, stability would be maximized in organic solvents of low dielectric constant where ionic species would be poorly stabilized. Moreover, the solvent should be free of acids and bases which could catalyze condensation reactions. Second, oligoketo acids should also be stable under strongly basic conditions where not only would the carboxyl group be ionized but also some or all of the active methylene groups. Probably the compounds would be highly unstable in aqueous solutions, even near neutrality.

The prospect of stability under strongly basic conditions pointed to enolate anion technology as a possible approach for the synthesis of beta-oligoketo acids. 2,4-Pentanedione and other beta-diketones normally undergo condensations with electrophilic reagents at the active methylene position, with the reactions proceeding via the enolate anion or the enol tautomer of the diketone. Upon treatment of the enolate anion with strong bases, such as sodium amide or lithium diisopropylamide (LDA), a further ionization occurs to give a 1,3-bis(enolate anion) (ref. 10). The dianion is much more reactive than the precursor monoanion and its nucleophilicity is observed exclusively at the less stabilized terminal anion. An extension of this principle to trianions of triketones, tetraanions of tetraketones, etc. might provide a route to many of the oligoketo acids (Scheme 3).

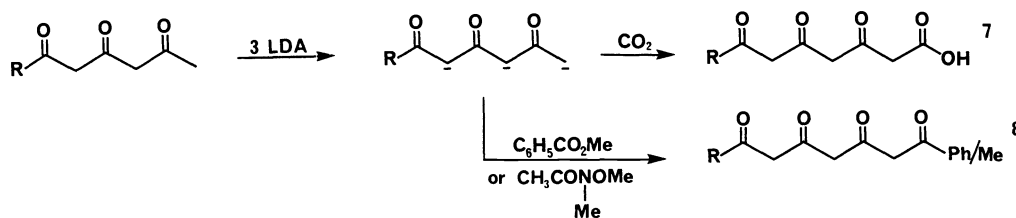
Scheme 3



B^- = strong base; E = electrophile

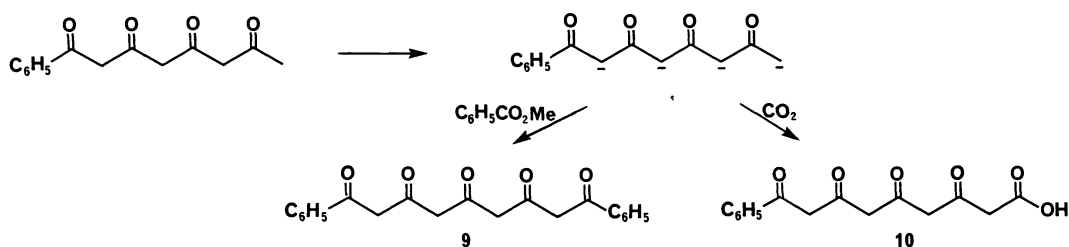
2,4,6-Triketones can be prepared by acylation of 2,4-diketones and by other routes. Our initial investigations of their conversion to trianions involved use of NaNH_2 and KNH_2 in liquid ammonia (refs. 11 and 12). Carboxylation with CO_2 , after replacement of the ammonia with an aprotic solvent, gave the 3,5,7-triketo acids (7, Scheme 4). Yields, however, varied widely; large triketones gave good results but small ones, 2,4,6-heptanetrione in particular, gave very poor yields, apparently because insolubility of the small triketone dianion inhibited formation of the trianion. LDA was found to be more generally useful (refs. 13 and 14). The intermediate dilithium salts did not precipitate and replacement of the solvent was not necessary before addition of the CO_2 . The carboxylic acids are in most cases sufficiently stable that they can be obtained in pure form and stored for long periods at low temperature. Methyl esters of the triketo esters can be formed by careful esterification with diazomethane (refs. 12 and 13). Acylations of triketone trianions can be used to form tetraketones (8). Satisfactory results are obtained with aryl esters (ref. 15) but ethyl acetate and other aliphatic esters fail because ionization of the alpha position predominates over attack on the carbonyl group of the ester. Recently acetylation was accomplished in excellent yield using N-methoxy-N-methylacetamide as the acylating agent (ref. 16).

Scheme 4



Treatment of 2,4,6,8-tetraketones with 4 equivalents of LDA yields tetraanions (Scheme 5). Acylation (with aromatic esters) and carboxylation have given good yields of pentacarbonyl compounds 9 and 10. The pentaanion (11) of a pentaketone and the hexaanion (12) of a hexaketone have been prepared (see below) but the chemistry of these anions has not been studied extensively. The synthetic route to oligocarbonyl compounds, i.e.; tricarbonyl compound \rightarrow tetracarbonyl compound \rightarrow pentacarbonyl compound \rightarrow etc., has serious limitations for synthesis of higher homologs; with the higher members, yields and separations become increasing problems.

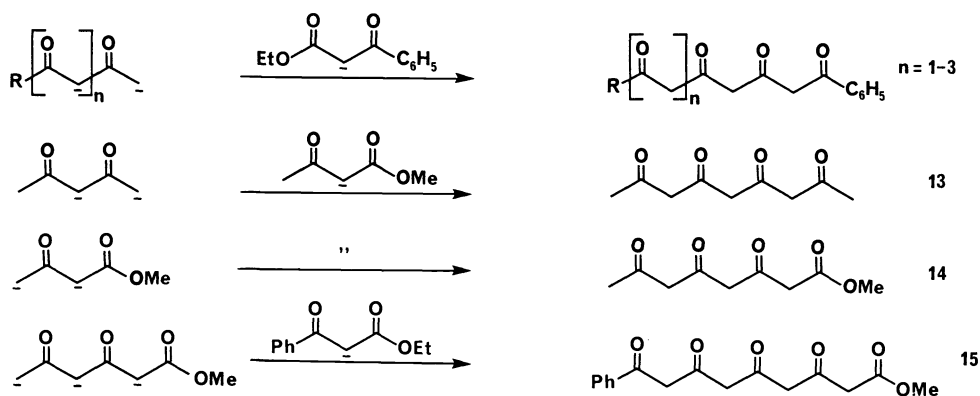
Scheme 5





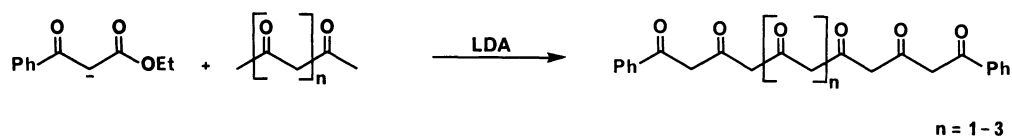
A possible second strategy involves acylation of diketone dianions with keto esters. The addition of carbonyl groups two at a time would shorten the synthesis of higher polycarbonyl compounds. The enolate anion of the keto ester would be used in the condensations because of the susceptibility of the keto group to ionization or to attack by nucleophiles. Thus the enolate anion, in effect, provides protection for the keto group. In THF and the other ethereal solvents commonly used for enolate anion reactions, metal ions are tightly complexed with ionized keto esters and diketones thus minimizing the amount of charge repulsion that must be overcome for a diketone dianion to approach a keto ester monoanion. If convergent processes of this type were successful, one could conceive of extending the strategy to condensations using 3,5-diketo esters (as their dianions) as acylating agents or trianions of triketones as nucleophiles to add three carbonyl groups at a time. Through the use of this strategy (Scheme 6), tetraketones have been prepared by beta-ketoacylation of diketone dianions, a pentaketone from a triketone trianion and a hexaketone from a tetraketone tetraanion (refs. 17 and 18). Electrophilic reactions of methyl acetoacetate anion are of particular value. 2,4,6,8-Nonanetetraone (13) has been prepared in this manner (ref. 17). Methyl acetoacetate can be self-condensed by reaction of the dianion with the monoanion to give methyl tetraacetate (14) (refs. 17 and 19). Beta-ketoacylation of the trianion of methyl triacetate has given a tetraketo ester (15) (ref. 20).

Scheme 6



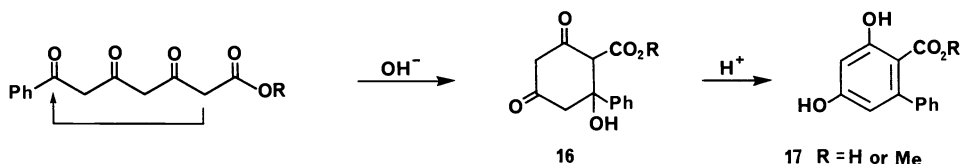
No higher keto acids have been prepared but diaryl hexa-, hepta-, and octaketones have been synthesized by convergent pathways involving bis(beta-ketoacylation) of acetylacetone, 2,4,6-heptanetrione and 2,4,6,8-nonanetetraone with ethyl benzoylacetate (Scheme 7) (ref. 21). The reactions were carried out by "one-pot" processes. Taking the hexaketone as an example, acetylacetone was converted to its dianion by treatment with LDA; two equivalents of the sodium salt of ethyl benzoylacetate were then added. As acylation of the diketone occurred, additional LDA was added to convert the intermediate tetraketone to its tetraanion which condensed with the second equivalent of the keto ester to give the hexaketone in 40% yield. The heptaketone and octaketone were prepared from 2,4,6-heptanetrione and 2,4,6,8-nonanetetraone in yields of 15 and 3%, respectively; the second stages of ketoacylation must involve attack by pentaketone pentaanion 11 and hexaketone hexaanion 12.

Scheme 7



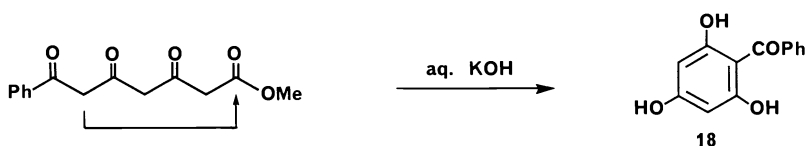
Extensive studies have been made of cyclizations of triketo acids and esters (refs. 12, 13 and 22). The cyclizations model closely the natural pathways; in some cases the conditions that are employed are so mild as to suggest the possibility that the analogous biological reactions may not be under enzymic control. In nature, aldol cyclizations are a major fate of triketo acids giving resorcylic acids and, after decarboxylation, resorcinols. Aldol cyclization of the acids and esters can be effected over a wide range of pH (Scheme 8). Under alkaline conditions non-aromatic cyclization products (16) have been obtained, which dehydrate readily on acidification of the medium to give the resorcylic acids or esters (17). The aldol products of triketo esters are stable enough to isolate but those of triketo acids catalyze their own dehydration.

Scheme 8



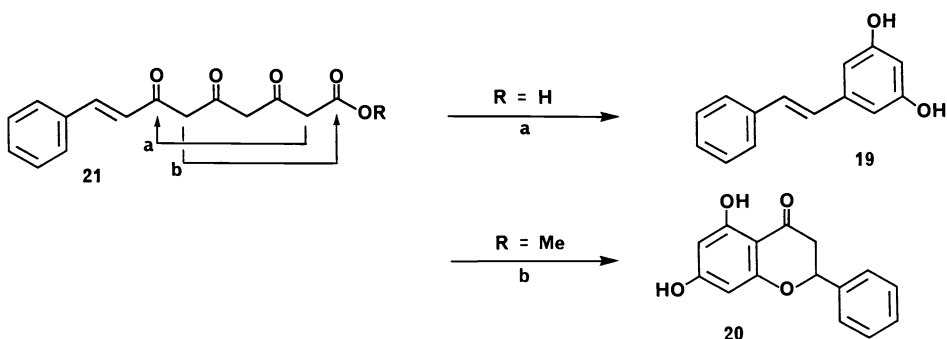
Dieckmann cyclization to give acylphloroglucinols (18) has been observed under strongly basic conditions but only with triketo esters (Scheme 9), since with the acids formation of the carboxylate anion precludes nucleophilic attack on the carboxyl group (refs. 12 and 13). The Dieckmann cyclization is solvent dependent requiring aqueous KOH; ethanolic KOH leads to the resorcyate ester instead.

Scheme 9



Interesting examples of aldol and Dieckmann cyclizations are the syntheses (Scheme 10) of pinosylvin (19) and pinocembrin (20), *co*-metabolites in the heartwood of pine trees (ref. 12). In the formation of 19 from triketo acid 21, cyclization in pH 5.0 buffer was followed by thermal decarboxylation; with 20, Dieckmann cyclization of the ester of 21 in aqueous KOH was followed by conjugate addition of a phenolic hydroxyl group to the double bond to form the heterocyclic ring of the flavanone.

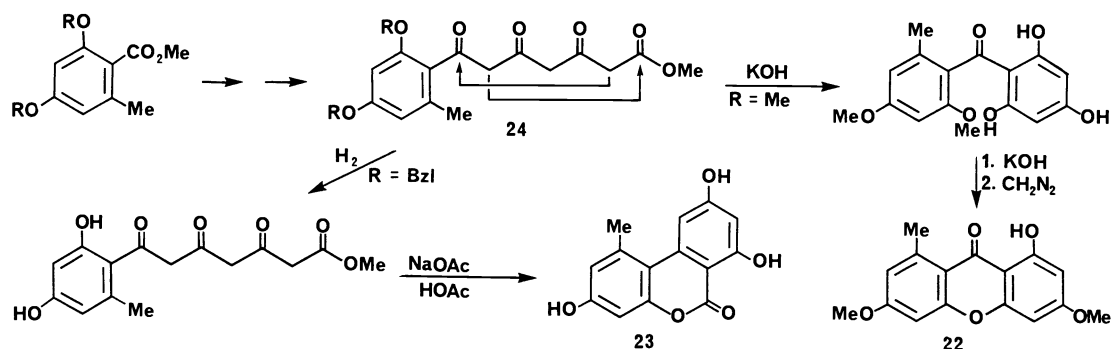
Scheme 10



Lichexanthone (22) and alternariol (23) are heptaacetic acid metabolites that arise by divergent Dieckmann and aldol folding patterns. Both metabolites are tricyclic and contain two benzenoid rings which are not fused together. The compounds can be viewed as having been formed by an aldol condensation between C-8 and C-13, followed, in the formation of 22, by a Dieckmann between C-1 and C-6 and a pyrone ring closure and, in the formation of 23, by an aldol between C-2 and C-7 and a lactonization. The two compounds have been synthesized

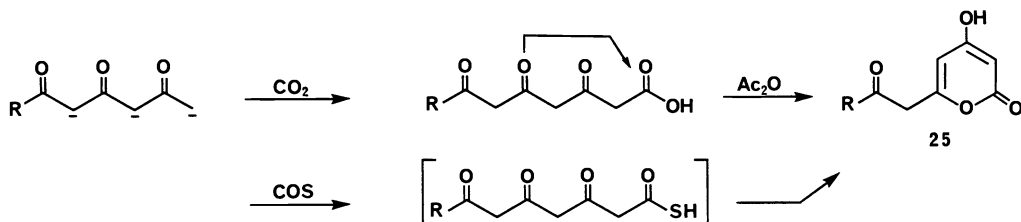
from methyl orsellinate (prepared by cyclization of methyl tetraacetate) by extension of the polyketide chain to form an orcinyltriketo ester and cyclization under appropriate conditions (Scheme 11) (ref. 23). Triketo ester **24** (R = Me), prepared from methyl orsellinate having the phenolic groups protected as methyl ethers, cyclized exclusively by the Dieckmann pathway to give, after methylation, xanthone **22**. Under no circumstances was any product of aldol cyclization observed. Alternariol was synthesized from unprotected triketo ester (**24**, R = H), which had been prepared by hydrogenolysis of bis(benzyl ether) **24** (R = Bzl). Treatment of **24** (R = H) with 1:1 NaOAc/HOAc gave a 52% yield of alternariol. The explanation for the different course taken by the two triketo ester cyclizations is that the 7-keto group in **24** (R = Me) is protected against attack by nucleophiles by the adjacent methyl and methoxyl groups, so that the only cyclization reaction available to it is Dieckmann reaction of C-1 with C-6. With triketo ester **24** (R = H), hydrogen bonding of the ortho hydroxyl group with the 7-keto group holds the keto group in the plane of the aromatic ring making it vulnerable to nucleophilic attack by C-2. In addition, hydrogen-bonding may actually activate the 7-keto group toward nucleophilic attack.

Scheme 11



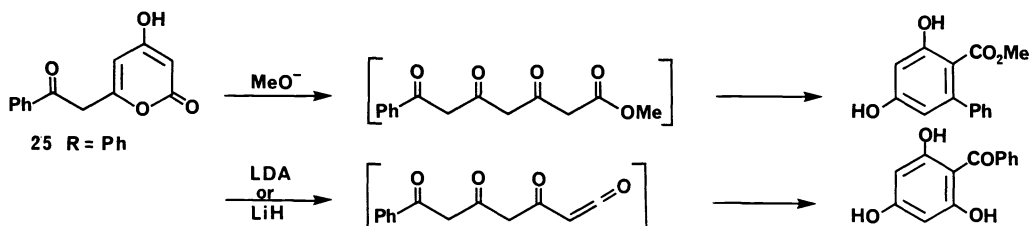
Many 4-hydroxy-2-pyrones have been found in nature. These compounds can be regarded as enol lactones of diketo acids. An important example which reflects the polyketide origin of enol lactones is **25** (R = Me), the lactone of tetraacetic acid (ref. 24). Enol lactones of this type can be synthesized (Scheme 12) by treatment of triketoacids with acetic anhydride or other reagents which activate the carboxyl group (refs. 25 and 26). The triketo thioacids, prepared by treatment of triketoanions with COS, cyclize spontaneously to the enol lactones, a reaction which closely mimics the biological process (ref. 25).

Scheme 12



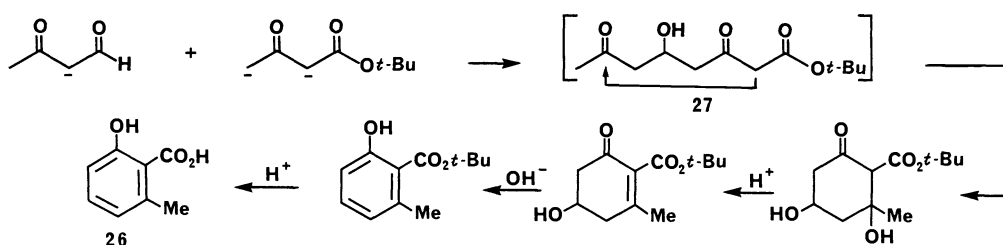
The keto pyrones are useful for synthesis of aldol and Dieckmann type aromatic products and can be regarded as a protected form of the triketo acids. A detailed study has been made of phenacyl pyrone **25** (R = Ph) (Scheme 13) (refs. 27 and 28). Treatment of the pyrone with alcoholic KOH gave the resorcylic ester via opening of the pyrone ring followed by aldol cyclization and dehydration. The triketo ester intermediate could be trapped as a metal chelate by the use of a large excess of methanolic Mg(OMe)₂ or Ca(OMe)₂ to effect the reaction. With only a catalytic amount of Mg(OMe)₂ in an aprotic solvent, i.e., DMF, the pyrone rearranged to the acylphloroglucinol. A preferable procedure for isomerization of the pyrone to **18** involved use of aprotic, non-nucleophilic base systems including LiH and LDA in THF. An excellent synthesis of lichexanthone has been achieved by this method from the lactone of **24** (ref. 23). These rearrangements to phloroglucinol derivatives cannot involve a triketo ester intermediate and a process involving a ketene has been postulated.

Scheme 13



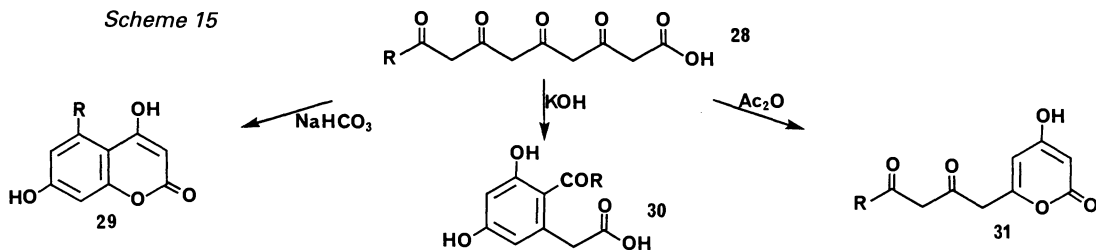
An important polyketide metabolite formed by an aldol pathway is 6-methylsalicylic acid (26, Scheme 14). The compound is an aldol product of a partially reduced form of tetraacetic acid. The condensation of acetoacetaldehyde (as its monoanion) with the dianion of acetoacetic ester gave the 3,7-diketo-5-hydroxy ester (27) which cyclized during isolation; 26 was obtained after two steps of dehydration and hydrolysis of the ester group (ref. 20).

Scheme 14



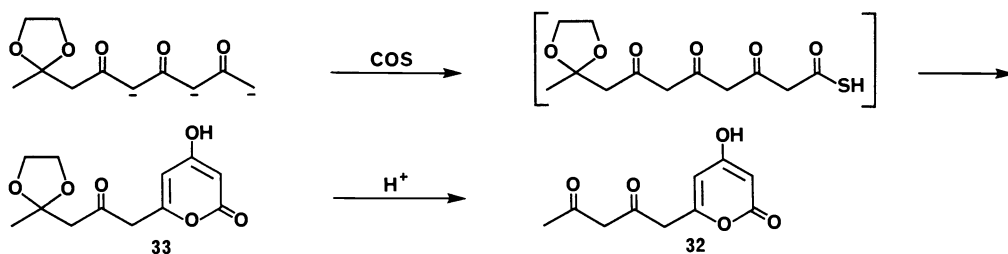
Tetraketo acids have several additional cyclization pathways open to them. Treatment of tetraketo acid 28 (R = Ph) with NaHCO₃ gave aldol cyclization between positions 4 and 9 yielding coumarin 29 via a resorcinol carboxylic acid (Scheme 15) (ref. 15). More strongly basic conditions gave mainly a second aldol product (30) involving attack of the 8-methylene group on the 3-keto group. A third possible aldol cyclization, involving attack of C-2 on C-7, was not observed. Treatment of 28 with acetic anhydride gave enol lactone 31. Reactions of the methyl ester of 28, i.e., 15, were investigated but Dieckmann cyclization was not observed. The regioselectivity observed in the cyclizations of triketo acids is very high; with tetraketo acid 28 additional pathways are possible and decreased selectivity is observed. When 15 was generated by acylation of the trianion of methyl triacetate with the anion of methyl benzoylacetate (see Scheme 6), the tetraketo ester cyclized during workup to coumarin 29 (ref. 29). Acylation of the same trianion with methyl acetoacetate and in situ cyclization led similarly to coumarin 29 (R = Me); no products from alternate cyclization pathways were isolated.

Scheme 15



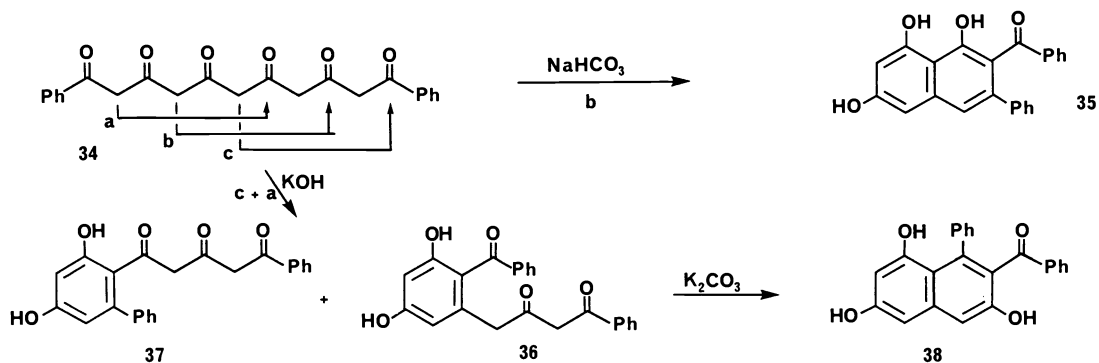
The enol lactone (32) of pentaacetic acid has been prepared by a biomimetic route (ref. 30). Pentaacetic lactone is of interest because it is a minor metabolite of the fungus *Sepedonium chrysospermum* which utilizes pentaacetic acid or the 4-methyl analog of pentaacetic acid to form the tropolone sepedonin. The synthesis of pentaacetic acid itself from tetraketone 13 has not been achieved. The tetraketone, with the 2-carbonyl group protected as the ethylene ketal, was prepared in excellent yield by acylation of acetylacetone dianion with ketal-protected ethyl acetoacetate. Treatment of the protected tetraketone with three equivalents of LDA followed by COS gave the thiol-acid (Scheme 16). Spontaneous cyclization gave enol lactone 33, which was deprotected by treatment with acid to give 32. Scott and coworkers prepared an O-methyl derivative of 32 but were unable to find conditions for deprotecting it (ref. 31).

Scheme 16



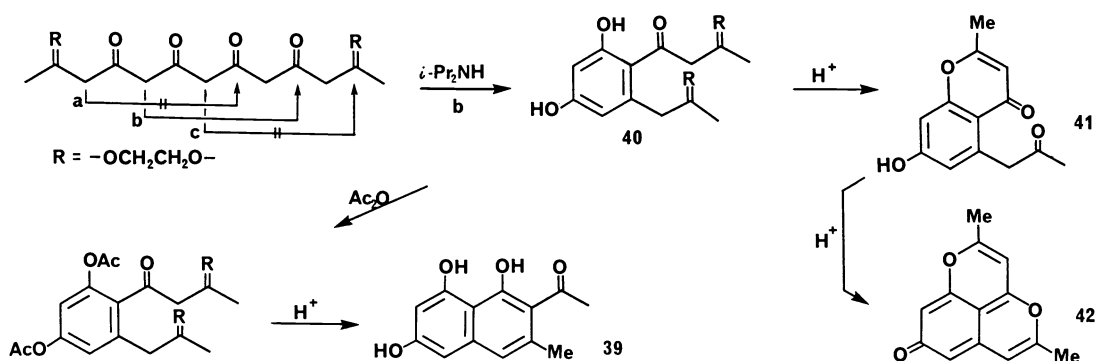
Cyclizations of hexaketone 34 have been investigated (ref. 21). Because of the symmetry of 34, only three aldol processes are possible (Scheme 17). Treatment of 34 with NaHCO₃ or with silica gel caused almost quantitative cyclization to form naphthalenetriol 35, arising by path b, C-4 attacking C-9. The use of aqueous KOH gave resorcinol 36, resulting from path a, C-2 attack on C-7, along with minor quantities of resorcinol (37), derived from path c, C-6 attack on C-11. Further treatment of 36 with K₂CO₃ gave naphthalenetriol 38, isomeric with 35. The formation of naphthalenetriols, such as 35 and 38, requires attack on one of the interior carbonyl groups of the hexaketone in the first stage of cyclization. Cyclization of an aliphatic hexaketone (or hexaketo acid) by path b is required for formation of most of the fused polycyclic metabolites. While cyclization of hexaketone 34 could be controlled to give preferential initial attack at either one of the two interior keto groups, investigations of methyl-terminated pentaketones revealed exclusive attack on the less hindered acetyl termini, i.e., path c. Stockinger and Schmidt have acylated 2,4,6-heptanetrione trianion with 4-methoxy-6-methyl-2-pyrone; the resulting O-methylated hexaketone cyclized *in situ* by an aldol process involving a terminal keto group (ref. 32). Thus it appears unlikely that any aliphatic hexaketone, if prepared, could be cyclized to a naphthalenetriol; moreover, it probably would not be possible to cyclize higher homologs to anthracenes, etc.

Scheme 17



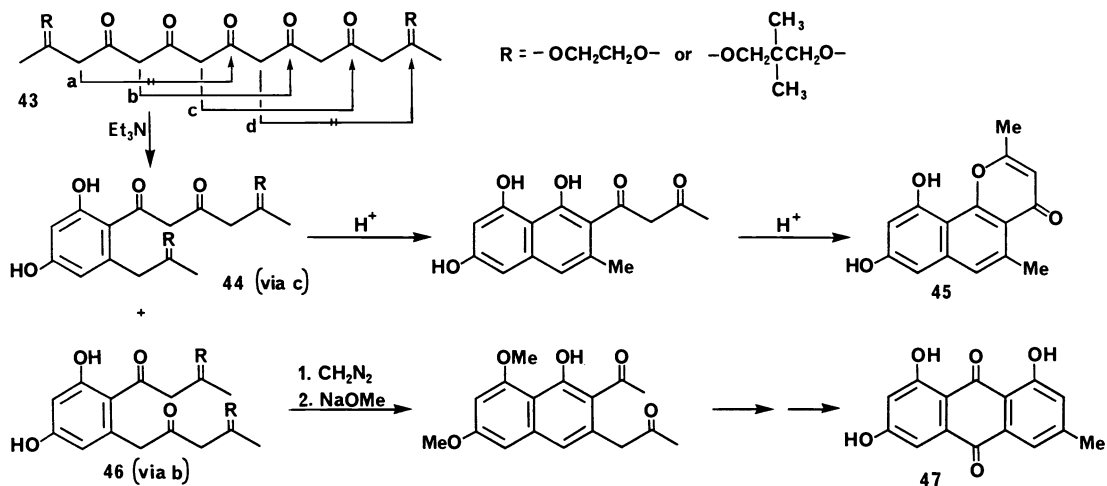
In view of the propensity with which methyl-terminated polyketones cyclize by aldol processes involving the terminal carbonyl groups, a synthetic approach to 6-hydroxymusizin (39) was explored which employed ketal protection of the terminal carbonyl groups to force aldol cyclization by the b route, since ketalization of the 2- and 12-carbonyl groups would block the a and c pathways (Scheme 18) (ref. 18). 2,4,6,8,10,12-Tridecanehexaone with the terminal keto groups protected as ethylene ketals was prepared by sequential acylations of acetylacetone with two equivalents of the ketal-protected ethyl acetoacetate. Treatment of the protected hexaketone with diisopropylamine gave aldol cyclization by the b pathway to form 40. Protection of the phenolic hydroxyl groups by acetylation, followed by removal of the ketals under acidic conditions, gave a second ring closure; removal of the acetate groups gave 39. Acetate protection was essential for formation of the naphthalene ring system; in its absence, chromone 41 formed instead; treatment of 41 with H₂SO₄ gave barakol (42).

Scheme 18



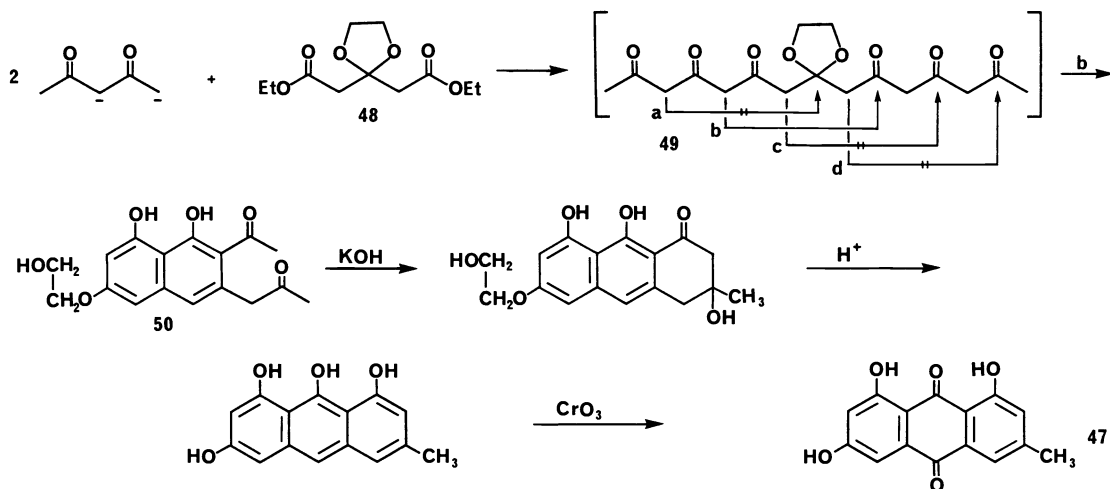
An extension of this strategy to the preparation of derivatives of heptaketones (Scheme 19) involved synthesis of ethylene ketal-protected heptaketone **43** by two-fold acylation of 2,4,6-heptanetrione with ketal-protected ethyl acetoacetate (ref. 18). Treatment of **43** with triethylamine gave 57% of aldol product **44**, derived from attack on the 4-keto group. On deprotection under acidic conditions, **44** cyclized to give eleutherinol (**45**). No more than a trace was observed of the alternative aldol cyclization product (**46**), required for synthesis of anthracene derivatives. The yield of the alternative aldol product was increased slightly by use of the more bulky ketal of 2,2-dimethyl-1,3-propanediol to hinder attack on the 4-keto group. Emodin (**47**) was prepared by protection of the phenolic hydroxyl groups of **46** as methyl ethers prior to removal of the ketals. Closure of the third ring required basic conditions because of the low reactivity of the terminal methyl group. The synthesis of **47** was completed by deprotection and oxidation.

Scheme 19



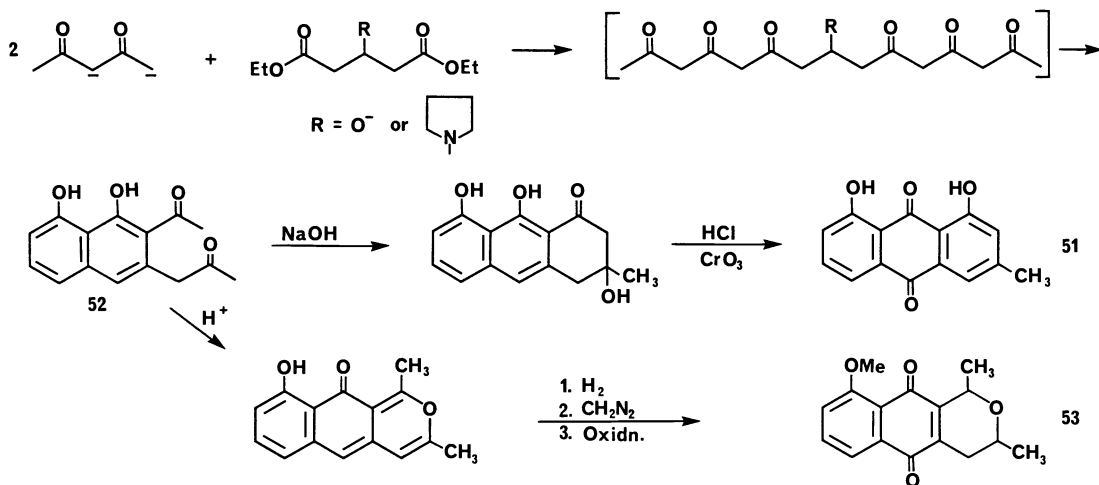
At this point an alternative procedure for synthesis of linearly condensed polycyclic compounds was developed which involved protection of the center carbonyl group rather than the terminal ones (Scheme 20). By this approach only the b cyclization occurs, the other three being suppressed by the ketal group. The approach also provides good synthetic access to the required heptaketone derivatives. Two-fold condensation of a diester containing functionality equivalent to three carbonyl groups (for example, diester **48** having the keto group protected as the ethylene ketal) with the dianion of acetylacetone (ref. 33). This highly convergent route permits seven carbonyl groups to be assembled in a beta array in a single step from small, readily available starting materials. Protected heptaketone **49** was prepared by two-fold reaction of acetylacetone dianion with ketal-protected dimethyl 3-oxoglutarate. In situ cyclization of **49** occurred during work-up to give 39% of naphthalene **50**, which was transformed in high yield to emodin (**47**) by a sequence involving closure of the third ring under basic conditions, dehydration and deprotection under acidic conditions and finally oxidation with CrO_3 to form the anthraquinone.

Scheme 20



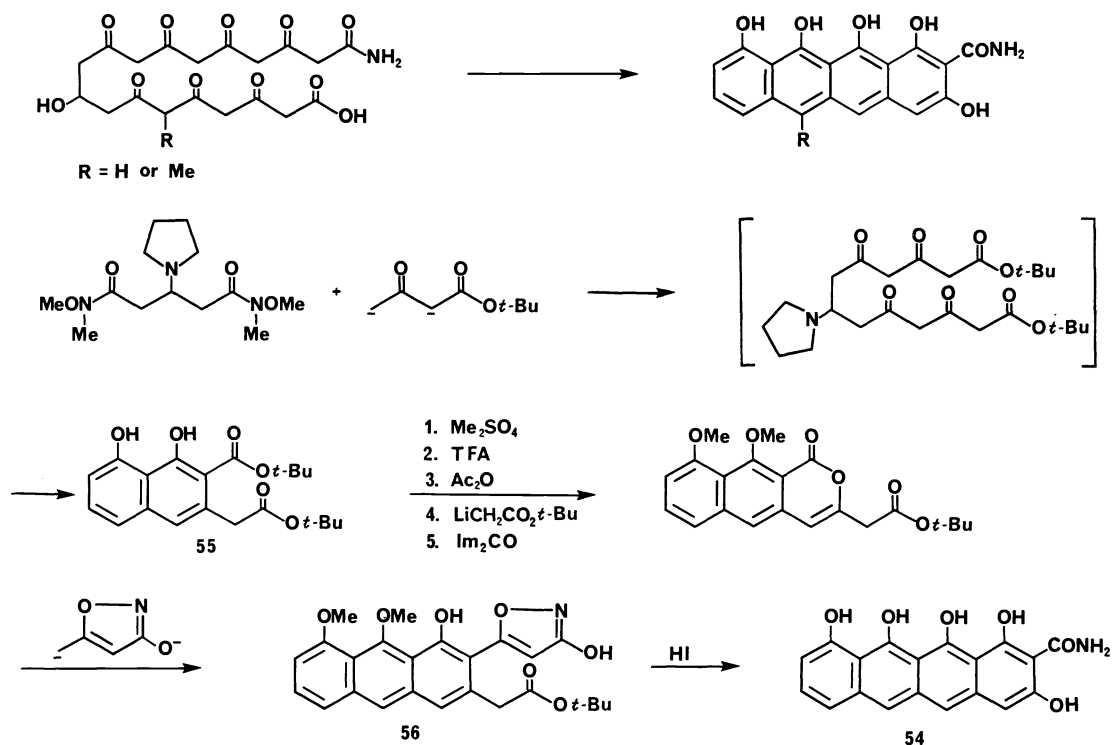
A similar sequence (Scheme 21) based on a glutarate ester bearing either a hydroxyl group or a pyrrolidino group at C-3 yielded chrysophanol (51) via naphthalene 52 (ref. 33). The naphthopyran eleutherin (53) has also been prepared from naphthalene 52 (ref. 34). Whereas alkaline conditions were required to close the third ring in the anthraquinone synthesis, acidic conditions gave a pyran ring. Completion of the synthesis of 53 required reduction of the pyran ring followed by methylation of the terminal hydroxyl group and finally oxidation of the middle ring to the quinone.

Scheme 21

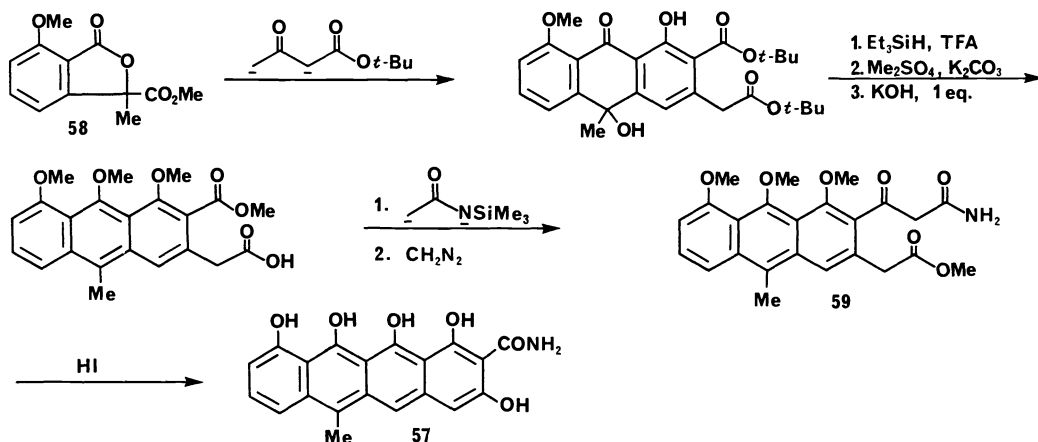


The most complex structures undertaken thus far are the pretetramid precursors of the tetracycline antibiotics, which are derived from an array of ten carbonyl groups including a carboxamide at one end and a carboxyl group at the other. A modification of the approach used for chrysophanol has been employed in the synthesis of pretetramid (54) (ref. 35). Naphthalene diester 55, which contains the elements of seven carbonyl groups, was prepared by a two-fold condensation process using the dianion of tert-butyl acetoacetate. The chain ends have been extended, in one case by two carbonyl groups with an isoxazole dianion and in the other by only one with the anion of tert-butyl acetate to form, after spontaneous closure of a third ring, anthracene 56, a deca-ketide species. The fourth ring closure occurred during reduction and deprotection with HI to give pretetramid (54). 6-Methylpretetramid (57) has been synthesized from homophthalate ester 58 by a related strategy (Scheme 23) (ref. 36). An important feature of the latter synthesis is that it passes through tricyclic protetron 59, similar to the putative biosynthetic precursors of the pretetramids.

Scheme 22



Scheme 23



This paper has concentrated on the studies carried out in the authors' laboratory. Space limitations prevent adequate coverage being given to the work of others. Much of the work carried out by other groups has concentrated on the use of complex pyrones as masked oligoketo acids. Some of those studies were initiated prior to our publication of syntheses of unprotected species. Nevertheless, interesting and useful findings have resulted from their pyrone studies. Of particular note is the work of Scott, Money and coworkers who discovered conditions for cleavage of pyranopyrones and selective reclosure to form resorcyolate and phloroglucinol derivatives. In addition, other strategies have been devised for preparation of oligocarbonyl compounds having some or all of the carbonyl groups protected. Several detailed reviews have been published which discuss other work in this area (refs. 37-39).

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