

BICYCLIC COMPOUNDS STRUCTURALLY RELATED TO DEHYDROACETIC ACID AND TRIACETIC ACID LACTONE

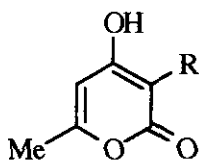
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Abstract- The preparation and reactivity of bicyclic compounds derived from dehydroacetic acid and triacetic acid lactone are reviewed.

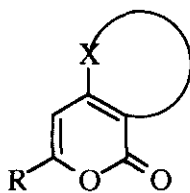
INTRODUCTION

Dehydroacetic acid (1a) and triacetic acid lactone (1b) are important pyrones and we have reviewed recently their chemistry.¹ However, bicyclic compounds derived from pyrones (1) were not systematically covered. We want now to fill this gap in a selective rather than comprehensive manner. The present review covers general structures (2) (A series) and (3) (B series) in which X is a heteroatom and R is a non-aromatic radical. Natural products pertaining to these families were fully covered in our previous review.¹ Therefore, only those reported since July 1990 are included here.

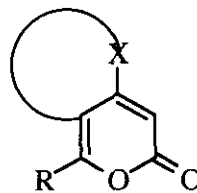


1a: R = COMe

1b: R = H



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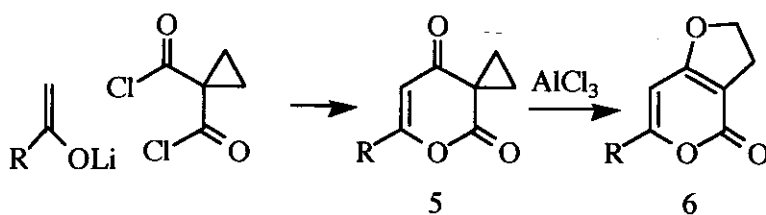
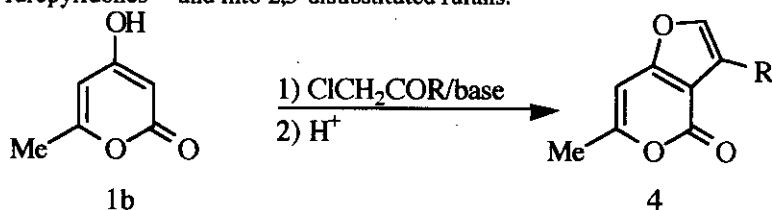


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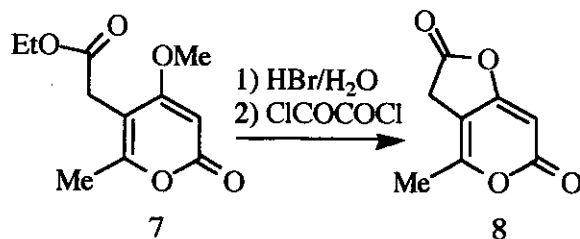
Compounds (2) are abundant and easily accessible from monopyrones (1) or related by appropriate modification at C-3 and C-4. However, structures (3) are less abundant and more easily prepared by constructing the pyrone ring from precursors already possessing the second heterocyclic ring and suitable substituents such as CH_2COOH and -CO-R . The present review is organized according to a) the size of the second ring; b) the heteroatom or heteroatoms in the second ring; and c) the oxidation level of the second ring within each type of heteroatom.

PYRONES FUSED TO A FIVE-MEMBERED RING

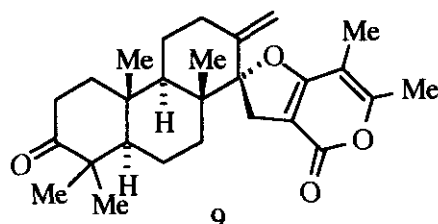
Fuopyranones. Fuopyran-4-ones (4) (A series) have been prepared by reaction of 1b with halogeno ketones followed by acid-induced cyclization of the intermediate ethers.^{2,3} A preparation of dihydro compounds (6) required the rearrangement of cyclopropyl derivatives (5).⁴ Other less general preparation requiring the construction of the pyrone ring on a suitably substituted furan derivative has been reported.⁵ Compounds (4) can be converted into fuopyridones^{2,5} and into 2,3-disubstituted furans.³



Hydrolysis of pyrone (7) followed by cyclization of the resulting hydroxyacid led to dihydrofuopyran-2,6-dione (8) (B Series).⁶

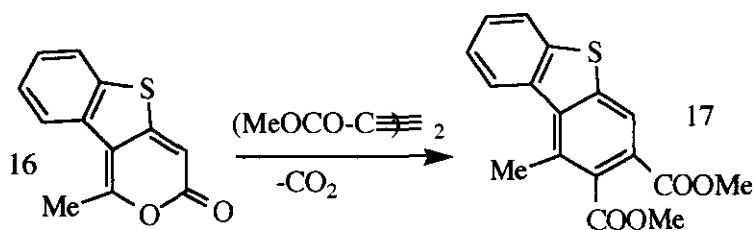
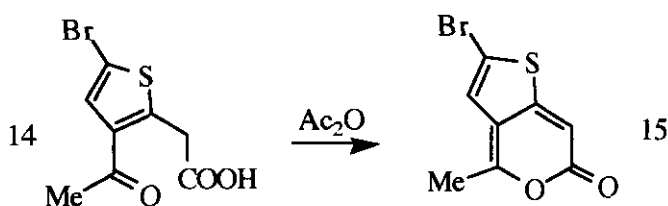
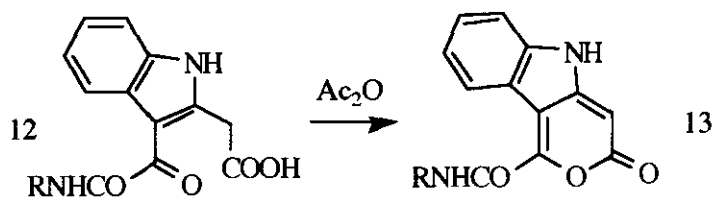
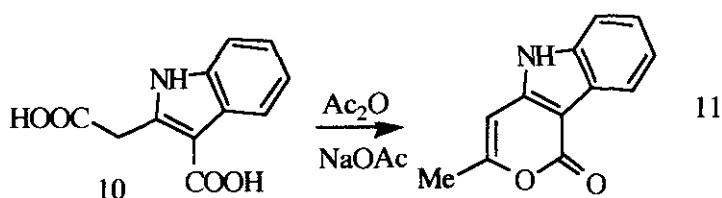


A natural product, lygodinolide (9) has been isolated from *Lygodium flexuosum*.⁷

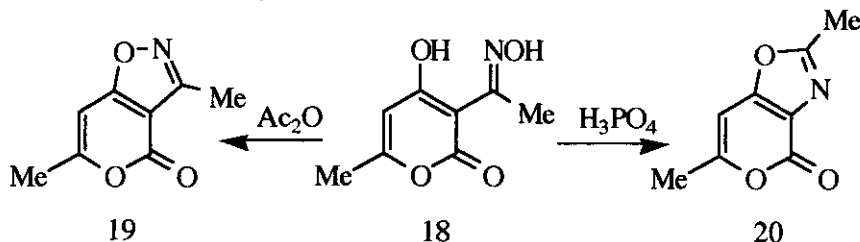


Pyranoindolones and Thienopyranones. Pyranoindol-5-one (11) (A series) has been prepared by one-pot acetylation of diacid (10) or its anhydride, decarboxylation and cyclization.^{8,9}

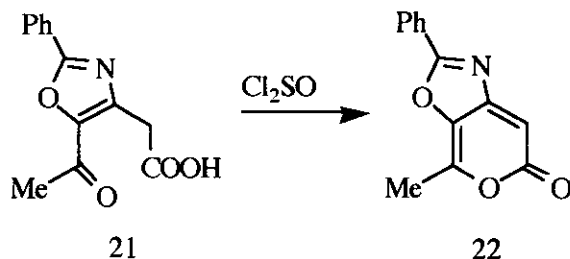
Pyranoindol-3-ones (13)^{10,11,12} and thienopyran-3-ones (15)¹³ (B series) have been prepared by pyrone building from indoles (12) and thiophenes such as 14. Benzothiophenes have also been fused to the pyrone ring in the same way.¹⁴ Both pyranoindolones and thienopyranones of the B series are active in inter and intramolecular Diels-Alder reactions leading to benzene derivatives, as indicated in the transformation of 16 into 17.^{11,14}



Pyranooxazolones and Pyranoisoxazolones. The same precursor, dehydroacetic acid oxime (18) has been transformed into both pyranoisoxazolone (19)^{15,16} and pyranooxazolone (20)¹⁷ (A series). The last reaction is a Beckmann rearrangement followed by cyclization of the amide intermediate.



A representative of the B series is compound (22), prepared from 21 by lactonization.¹⁸ Double bond C7-C8 of 22 was selectively hydrogenated in a step of a synthesis of 4-deoxy-D,L-daunosamine.¹⁸



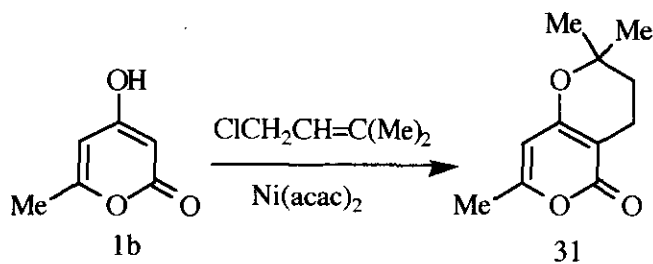
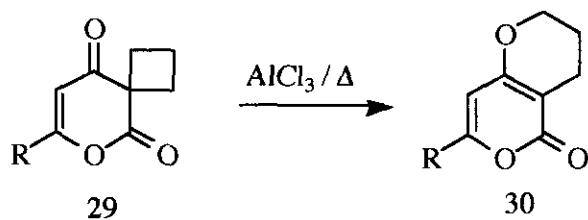
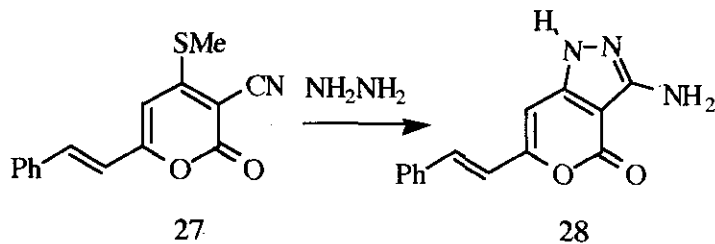
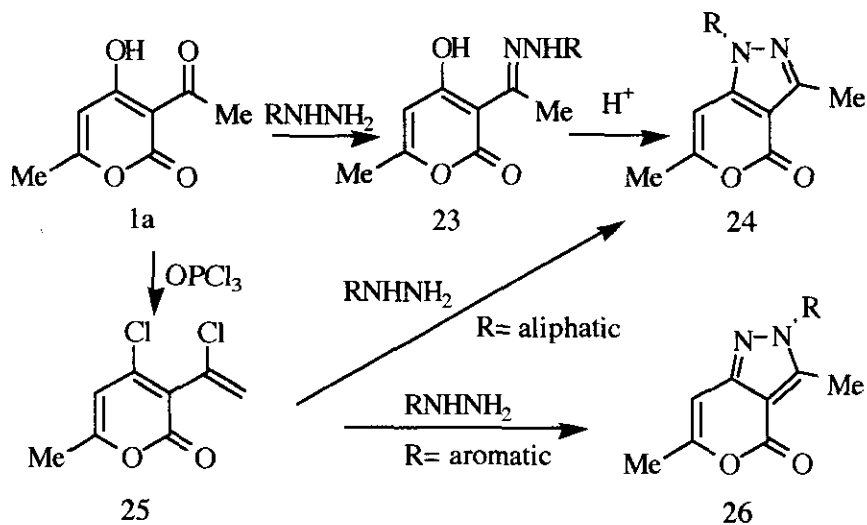
Pyranopyrazolones. Both alkyl and arylhydrazones (23) of dehydroacetic acid cyclize under acidic conditions to afford pyranopyrazol-4-ones (24)^{19,20} (A series). Control of regioselectivity in the cyclization step was achieved through dichloropyrone (25). It reacted with aliphatic hydrazines producing compounds (24), whereas aromatic hydrazines gave rise to the isomeric pyranopyrazol-4-ones (26).¹⁹ A different approach is exemplified by the reaction of sulfide (27) with hydrazine to give pyranopyrazolone (28).²¹ Some products initially believed to pertain to the A series²² were later shown to have structures beyond the scope of this review.²³

PYRONES FUSED TO A SIX-MEMBERED RING

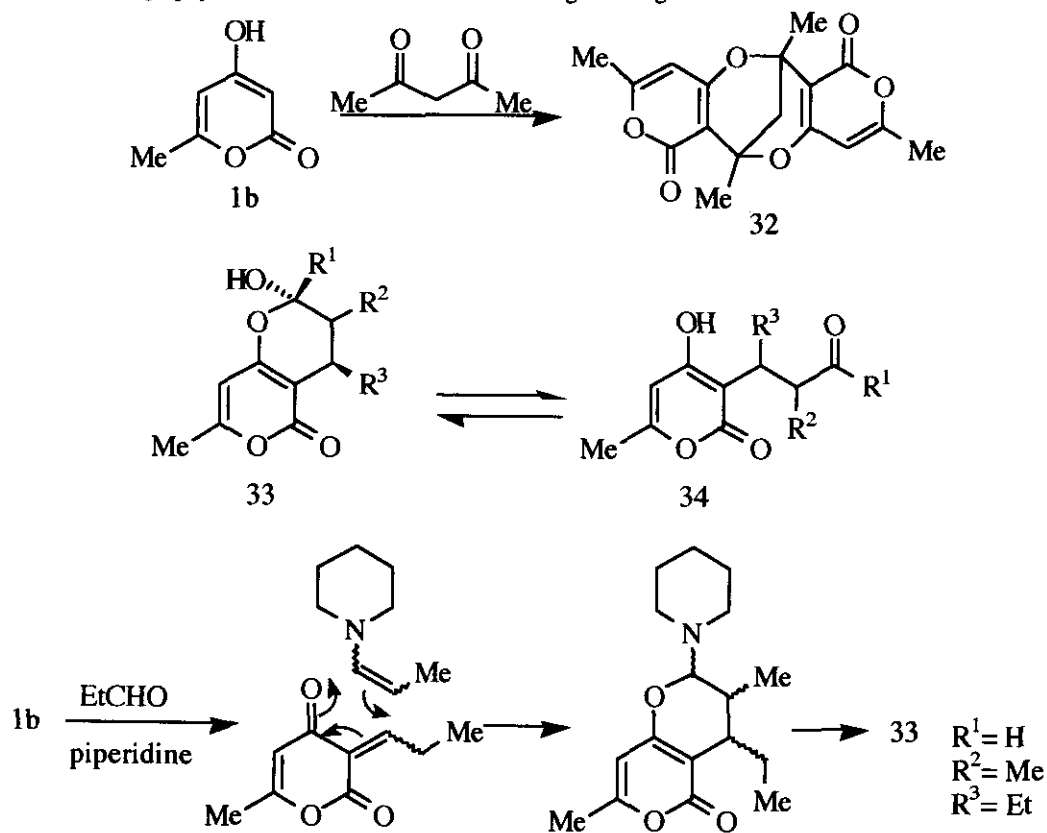
This is by far the most represented group of compounds covered in this review. The most abundant compounds in this chapter are pyrones fused to a second pyrane ring and pertaining to the A series.

Dihydropyranopyranones. Dihydropyranopyran-5-ones (30) (A series) have been prepared by rearrangement of cyclobutyl derivatives (29)⁴ in a similar way as mentioned earlier for furopyranones (6). Alkylation of 1b with 1-

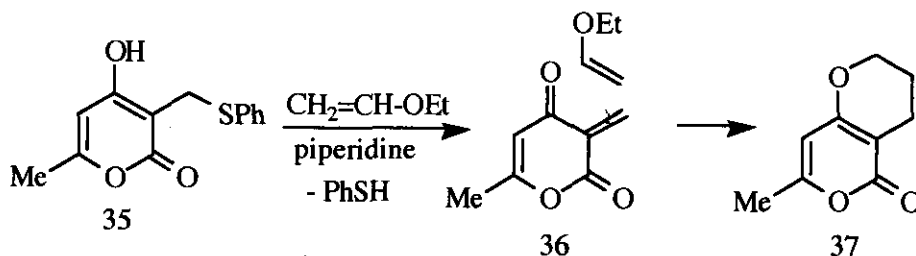
chloro-3-methyl-2-butene under $\text{Ni}(\text{acac})_2$ catalysis led to the cyclized compound (31).²⁴ Related cyclizations from 4-hydroxy-2-pyrone derivatives bearing allylic and homoallylic chains at C-3 have been reported.^{25,26,27}



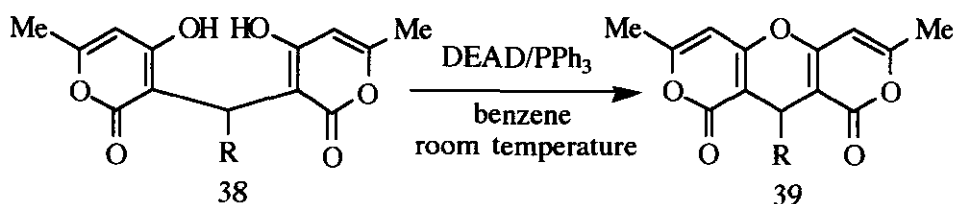
Hydroxy and Alkoxydihydropyranopyranones. Compound (32) was prepared by condensation of 1b with pentane-2,4-dione.²⁸ Hemiketals (33) ($R^2 = H$), which are in equilibrium with the open chain keto forms 34, were obtained by alkylation of 1b with free Mannich bases of several ketones²⁹ or by C-3 Michael addition to α,β -unsaturated ketones.³⁰ The reaction of 1b with propanal and piperidine afforded 33 ($R^1 = H$, $R^2 = Me$, $R^3 = Et$) after chromatography of the crude reaction mixture through silica gel.³¹



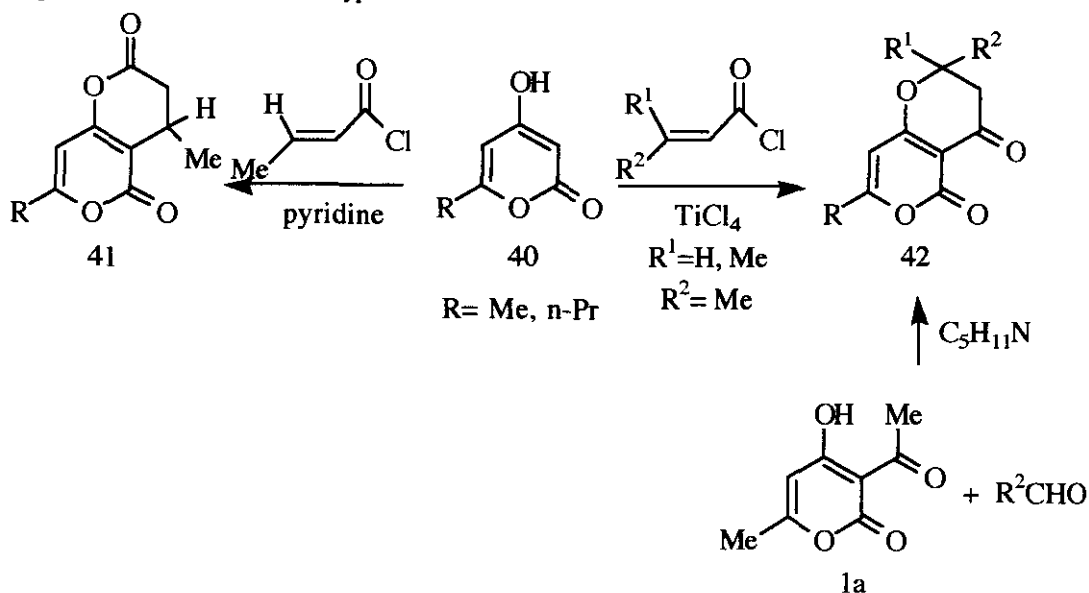
2-Ethoxypyranopyran-5-one (37) was formed by treatment of pyrone (35) with piperidine in refluxing ethyl vinyl ether, presumably through a Diels-Alder reaction of intermediate quinonemethide (36) generated *in situ*.³¹



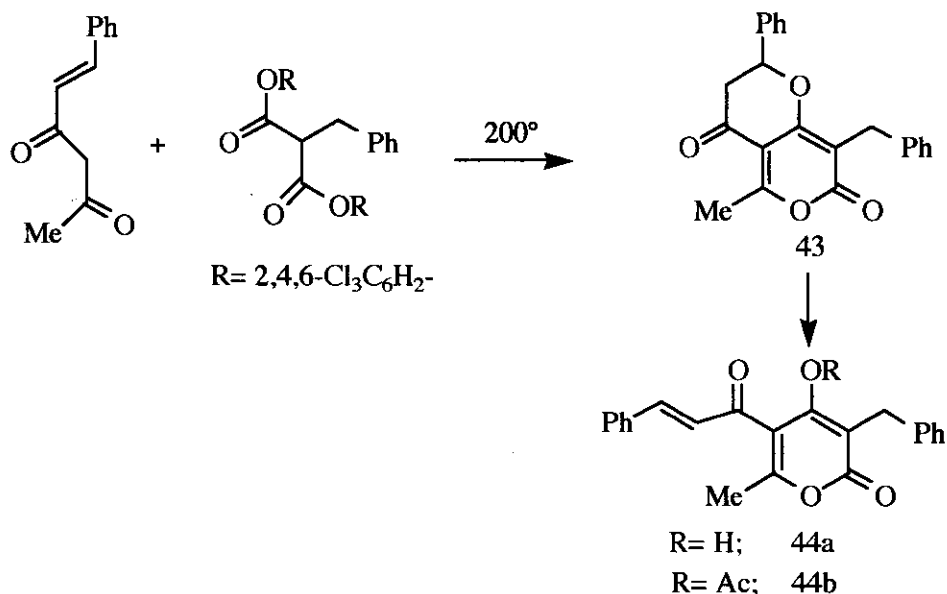
Pyranopyranones. The 3,6,9-trioxanthracenes (39) have been prepared from 38 by Mitsunobu dehydration.³² Similar pyranodipyrane structures were obtained by condensation of 1b with ethyl propiolate in the presence of Triton B as catalyst. The mechanism involves successive Michael additions of two molecules of nucleophile to one of acetylenic ester, followed by cyclization.^{33,34}



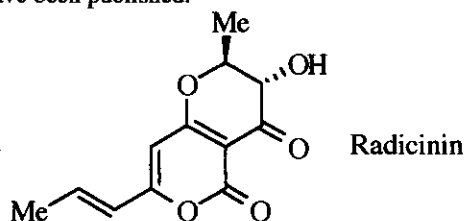
Dihydropyranopyrandiones. Treatment of 6-alkyl-4-hydroxy-2-pyrones (40) with α,β -unsaturated acid chlorides led to pyranopyran-2,5-diones (41) (A series) or the isomeric pyranopyran-4,5-diones (42) (A series) depending on the reaction conditions.³⁵⁻³⁷ By refluxing the mixture in anhydrous pyridine, compound (41) was formed via the *O*-acyl derivative. The use of TiCl_4 or trifluoroacetic acid promoted the rearrangement to the C-3 acyl derivative and subsequent cyclization to 42. However, both isomers were obtained in the reaction of 1b with 3-methyl-2-butenoyl chloride,³⁶ thus indicating some influence of the acid chloride structure. Analogous mixtures are formed by using saturated β -chloro acid chlorides in refluxing pyridine.³⁵ Another synthetic approach to compounds (42) ($\text{R}^1 = \text{H}$) is based upon the base-catalyzed aldol condensation of 1a with aliphatic aldehydes and subsequent intermolecular Michael-type reaction.^{38,39}



The reactions of cinnamoylacetone with trichlorophenylmalonates at 200°C gave pyranopyran-4,7-diones such as 43 (B series), which is converted to 44a by thermal rearrangement at 230°C and to 44b by treatment with acetic anhydride.⁴⁰

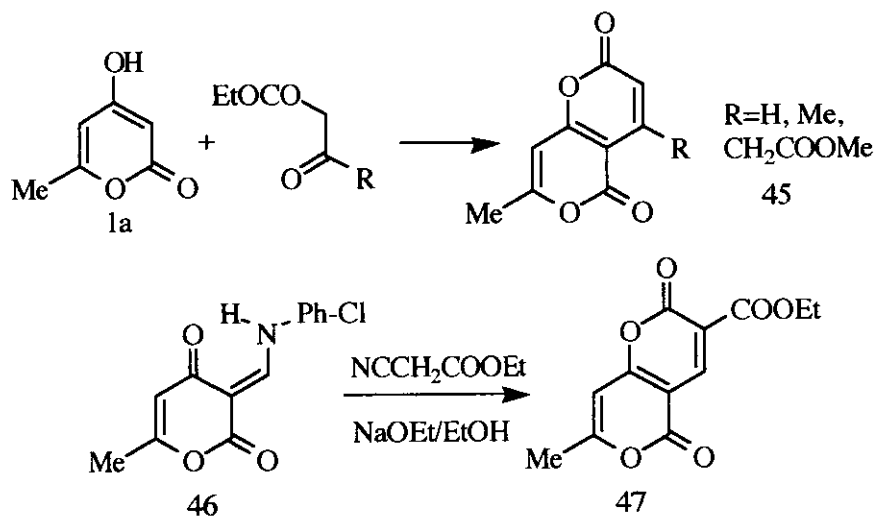


2,5-Dioxopyranopyranes and 4,5-Dioxopyranopyranes. Efforts directed to the preparation of these structures and others related with different oxidation levels at the second ring were triggered in the late sixties and early seventies by the interest arisen by a natural product, radicinin, and related molecules.^{35,41} The synthesis³⁵ and the biosynthesis⁴¹ of radicinin have been published.

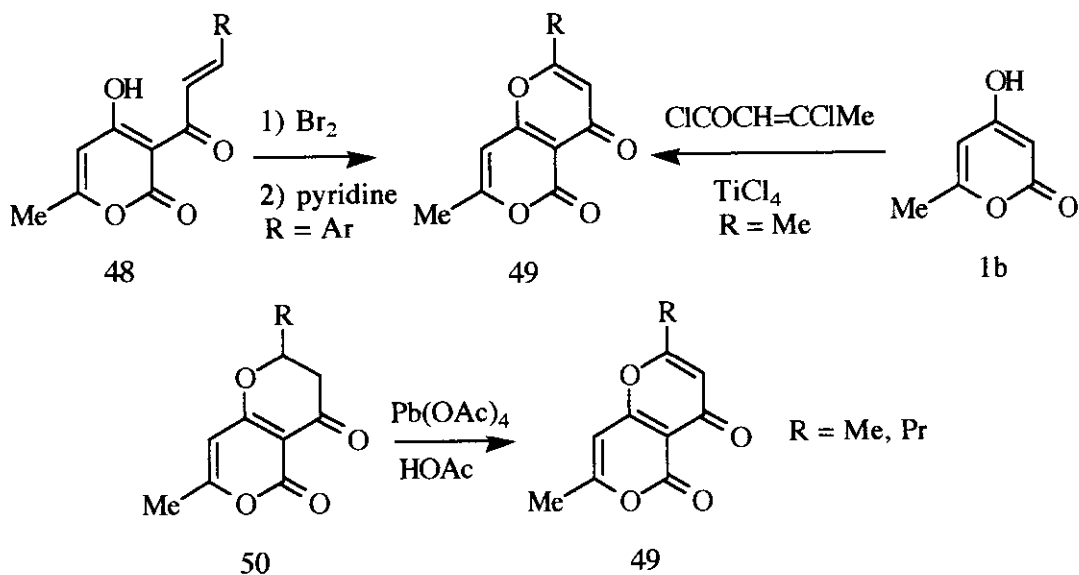


Product (45) (R = Me) is the so called Fleischmann pyrone, first reported in 1907.⁴² It was obtained by acid-promoted condensation of three equivalents of ethyl acetoacetate.⁴² A wrong structure was assigned to Fleischmann pyrone but it was later corrected.⁴³ The best method to prepare structures (45) is the pyridine-promoted condensation of 1a with β -keto esters.⁴⁴ Malic acid is a synthetic equivalent of formylacetic acid and its condensation with 1a produces (45, R = H).⁴⁵ Acetylenes have also been used for condensations with 1a since they have the appropriate oxidation level.³⁴ Other approaches to 2,5-dioxopyranopyranes require starting materials bearing already carbon atoms linked at C-3 as in the reaction of the formylpyrone equivalent (46) with

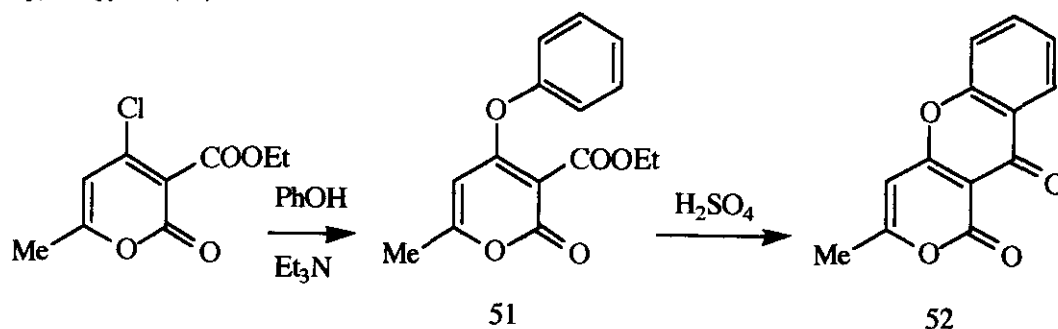
ethyl cyanoacetate to afford compound (47).⁴⁶ The condensations of 3-acyl-4-hydroxy-2-pyrones with sodium carboxylates and carboxylic anhydrides gave mixtures of different pyranopyrones.⁴⁷



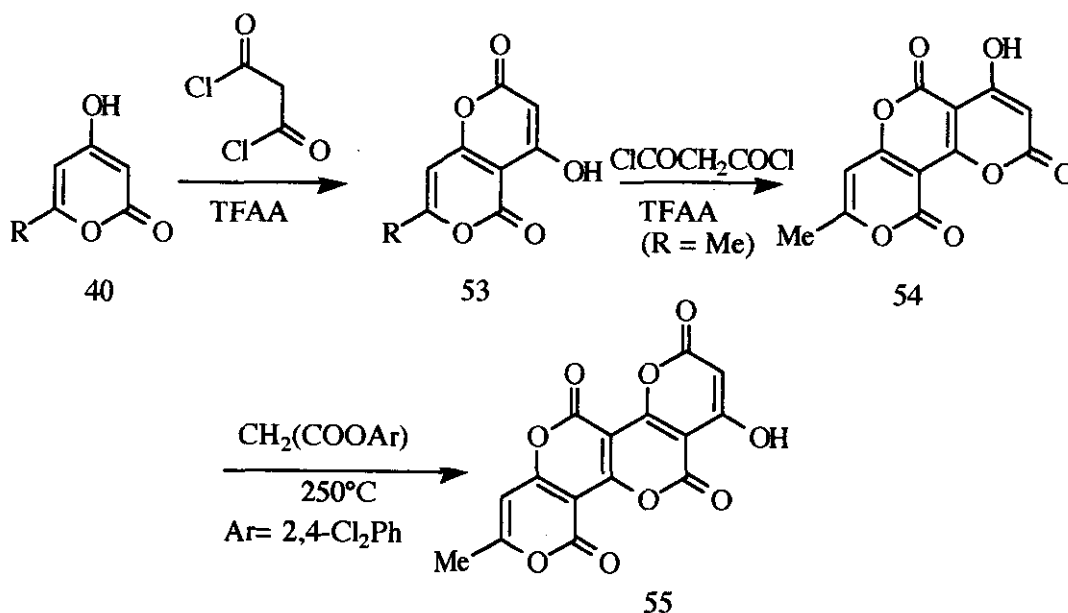
The reactions of dehydroacetic acid (1a) with aromatic aldehydes gave pyrones (48) that upon treatment with bromine followed by refluxing pyridine produced 4,5-dioxypyranopyranes (49) with an aromatic substituent at C-2.^{48,49} The thermodynamically controlled reaction of 3-chlorobutenoic acid chloride with 1b afforded 49 (R = Me).⁵⁰ Compounds (49) (R = Me, Pr) were prepared by lead tetraacetate oxidation of 50.³⁷



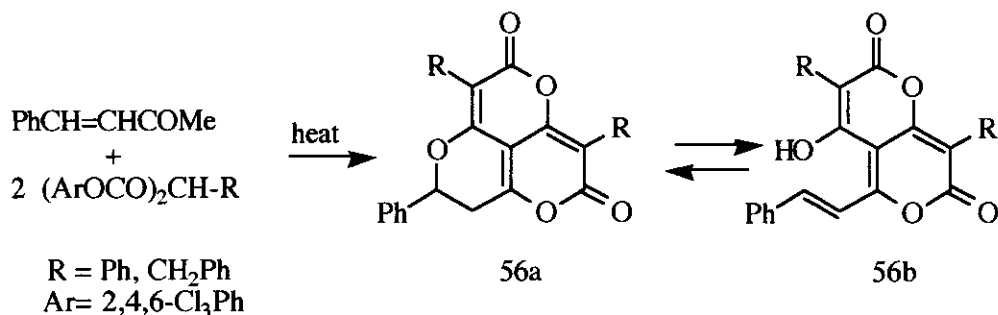
A completely different approach is exemplified by the acid-promoted cyclization of phenyl ether (51) into 4,5-dioxopyranopyrane (52).⁵¹



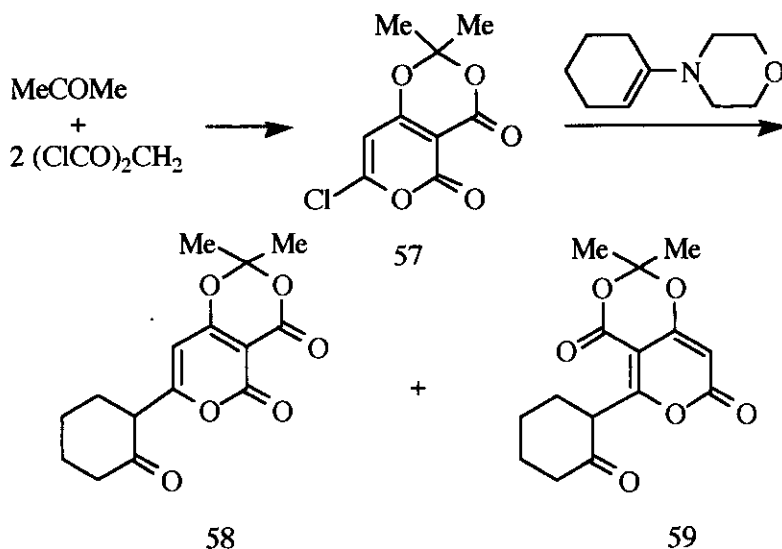
4-Hydroxy-2,5-dioxopyranopyranes. The interest on these type of molecules arose in the late sixties and early seventies in connection with biomimetic studies of conversion of poly- β -keto esters and related structures into aromatic compounds.^{1,52,53} 4-Hydroxy-2,5-dioxopyranopyranes can be prepared by condensation of 6-alkyl-4-hydroxy-2-pyrones (40) with malonic acid derivatives, such as the dichloride,^{52,54-56} bis-(2,4-dichlorophenyl) esters,^{52,57-59} and Meldrum acid.⁶⁰ The pyrone (53) (R = Me), formed in the reaction of 1b with malonyl dichloride, reacted in the same way to afford the tripyrone (54), that reacted further with bis-(2,4-dichlorophenyl) malonate to give tetrapyrone (55).⁵² These polypyrones are synthetic analogues of poly- β -ketoesters, suitable for biomimetic conversions into polyphenols.



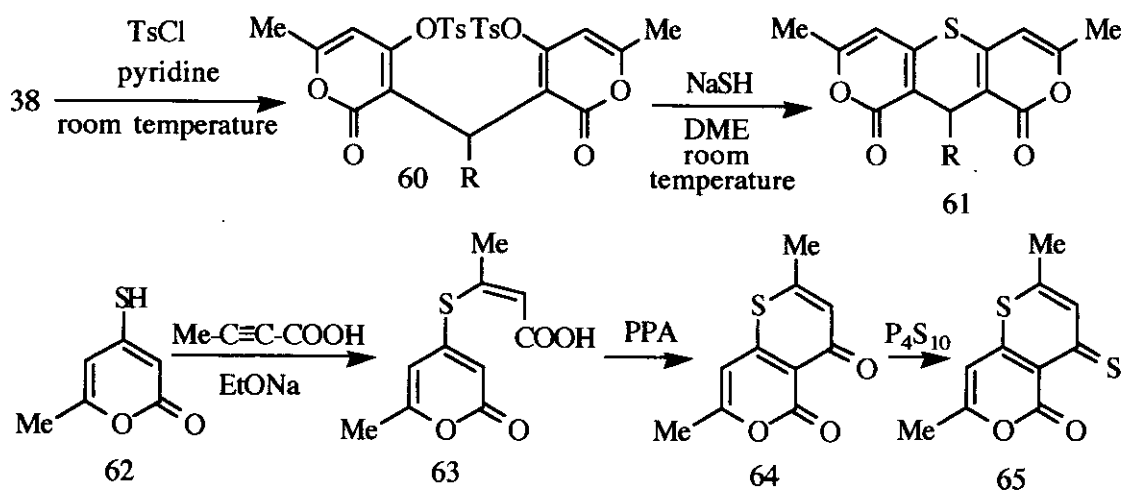
Dipyrones (**56**) pertaining to the B series have been formed in the reactions of benzylideneacetone with two equivalents of substituted bis-(2,4,6-trichlorophenyl) malonates.⁴⁰



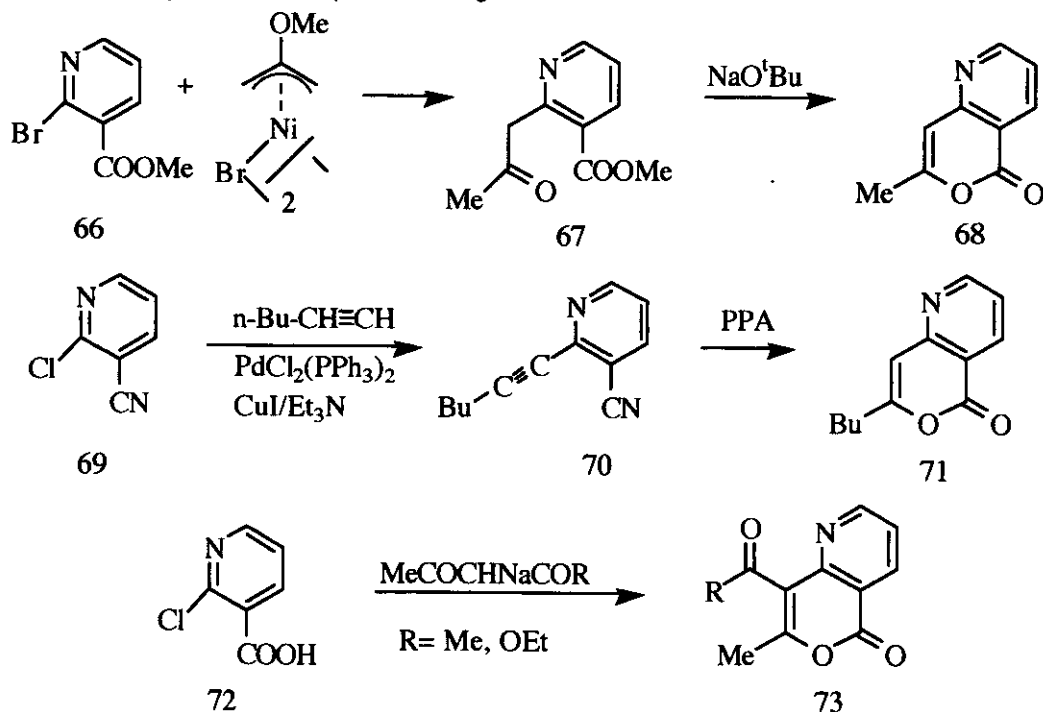
Pyrones fused to rings possessing more than one oxygen atom. The reaction of acetone with two equivalents of malonyl dichloride gave the chloropyrone (**57**), which upon reaction with 1-morpholinocyclohexene afforded a mixture of bicyclic pyrones (**58**) and (**59**). The second one results from a rearrangement and is a representative compound of the B series.⁶¹



Pyrones fused to rings possessing one sulfur atom. The 3,6-dioxo-9-thianthracene ring system (**61**) (A series) (sulfur analogue of **39**) has also been synthesized from bispyrones (**38**) by treating the *p*-toluenesulfonates (**60**) with anhydrous sodium hydrosulfide.³² Polyphosphoric acid induced cyclization of thioethers (**63**), prepared by Michael addition of **62** to 2-butyric acid, led to thiino[3,2-*c*]pyran-4,5-dione (**64**) which was converted to 4-thioxothiino[3,2-*c*]pyran-5-one (**65**) by treatment with P₄S₁₀.⁶²

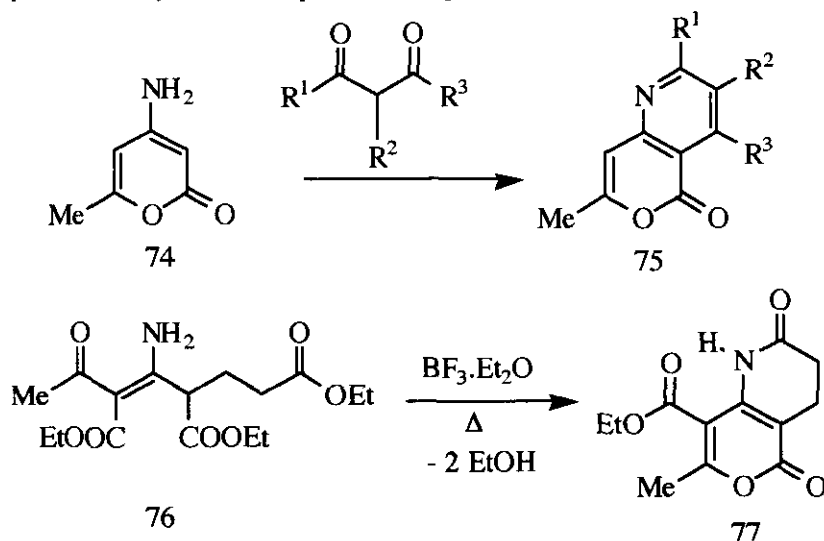


Pyranopyridines. Several preparations of pyrano[4,3-*b*]pyridine systems (A series) involve the construction of the pyrone ring on a suitably substituted pyridine derivative. Thus, cyclization of 67 under basic conditions gave 68, compound (67) being prepared from 2-bromo-3-methoxycarbonylpyridine (66) and a π -allylnickel complex.⁶³ Palladium-mediated coupling of 2-chloro-3-cyanopyridine (69) with 1-hexyne, followed by acid-induced cyclization of the resulting cyanoalkyne (70) afforded 71.⁶⁴ The reactions of 2-chloronicotinic acid (72) with sodium salts of β -diketones and β -keto esters gave 73.⁶⁵

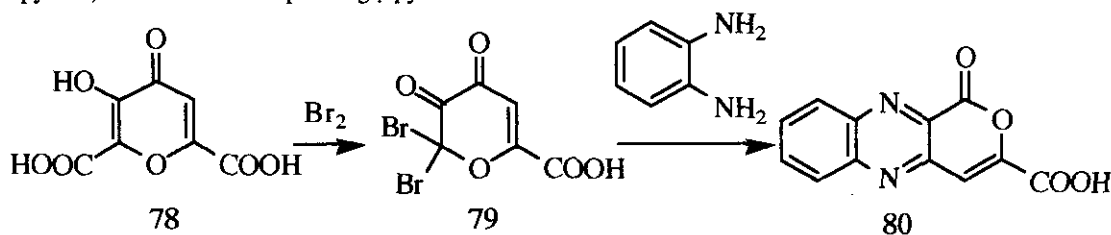


A different approach, that requires the construction of the pyridine ring, is based on the reaction of the 4-amino-6-methyl-2-pyrone (74) with β -dicarbonyl compounds to afford pyrano[4,3-*b*]pyridines (75) differently substituted on the pyridine ring.⁶⁶

Lewis acid-catalyzed thermal cyclization of open chain compound (76) gave the bicyclic lactam (77).⁶⁷



Pyranopyrazines and Pyranopyrimidines. Dibromocomenic acid (79) formed by reaction of meconic acid (78) with bromine, reacted with *o*-phenylenediamine to give 1-oxopyrano[3,4-*b*]quinoxaline-3-carboxylic acid (80) (α -pyrone) and not the corresponding γ -pyrone.⁶⁸

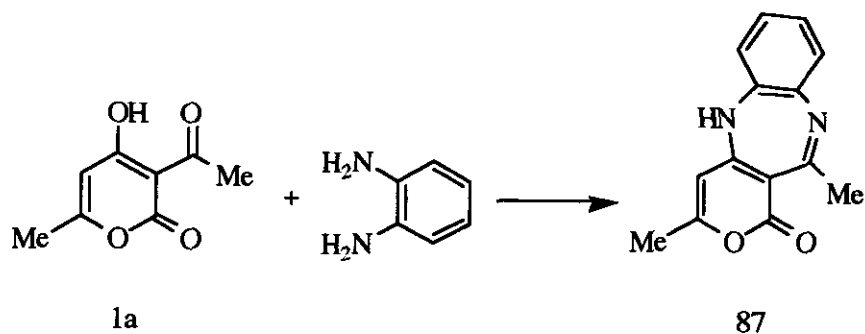
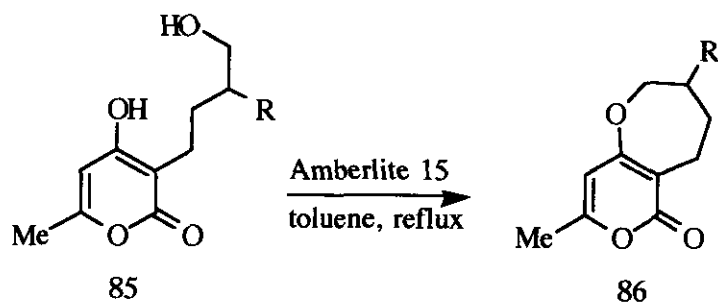
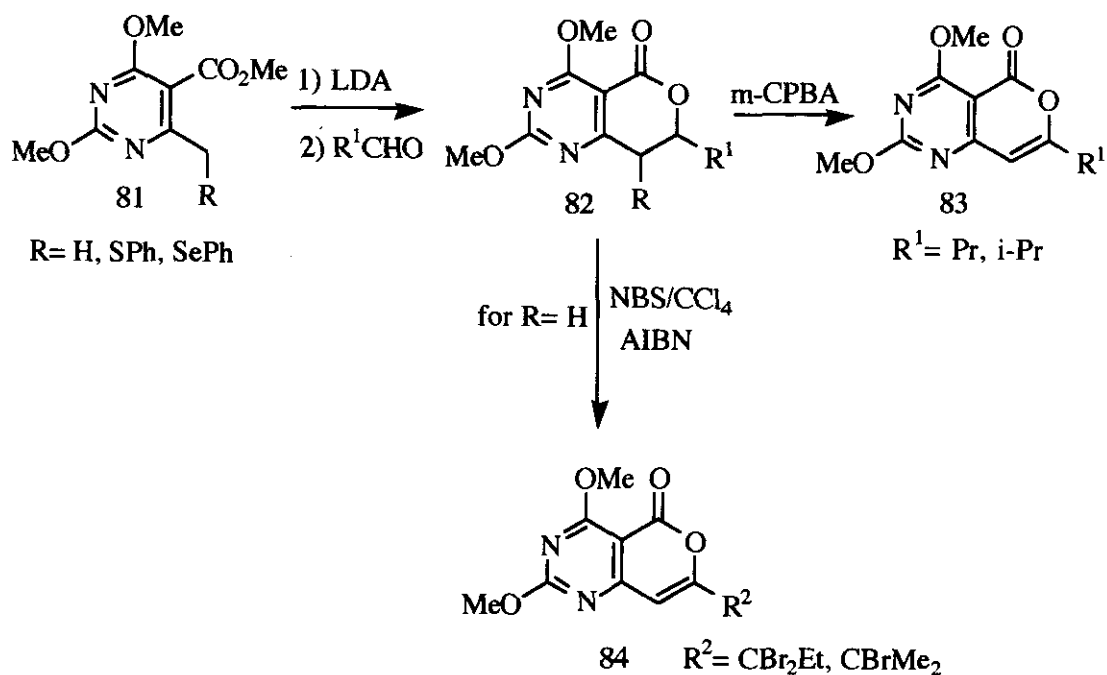


Preparations of 5-oxopyrano[4,3-*d*]pyrimidines (83) and (84) starting from pyrimidines (81) (R= SPh, SePh, H) and aldehydes have been described. This involves treatment of sulfur or selenium containing intermediates (82) (R= SPh, SePh) under oxidative elimination conditions or allylic bromination (for 82, R= H) and subsequent dehydrobromination.⁶⁹

PYRONES FUSED TO A SEVEN-MEMBERED RING

Treatment of 85 with Amberlite-15 gives the seven membered ring compound (86).⁷⁰

The reaction of dehydroacetic acid (1a) with *o*-phenylenediamine produced compound (87).⁷¹



ACKNOWLEDGEMENT

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