MELDRUM'S ACID IN ORGANIC SYNTHESIS

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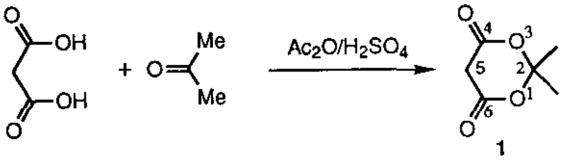
Abstract——The syntheses and reactions of Meldrum's acid derivatives as well as their applications in natural product syntheses reported during 1978-1990 are reviewed.

CONTENTS

1. INTRODUCTION

Meldrum's acid (**1**, 2,2-dimethyl-1,3-dioxane-4,6-dione, isopropylidene malonate), discovered by Meldrum,[1] is a remarkable reagent of versatile reactivities. The susceptibility to electrophilic attack (*via* the anion) at C-5 and nucleophilic attack at C-4 and C-6 along with the unique ring opening reaction makes this reagent tremendously useful in organic synthesis. The chemistry of Meldrum's acid before 1978 has been reviewed by McNab.[2] In this review the new applications of Meldrum's acid in organic synthesis during 1978-1990 is summarized. Meldrum's acid is a white crystalline solid which can be readily prepared in large quantity by the condensation of malonic acid and acetone in acetic anhydride containing catalytic amount of concentrated sulfuric acid.[3]



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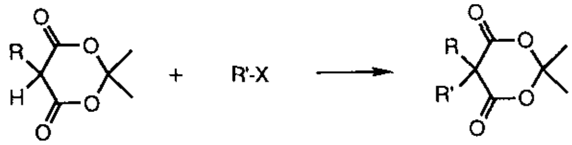
2. 5-ALKYL, ALKENYL, ALKYNYL, AND ARYL MELDRUM'S ACIDS

2.1 *Preparation*

2.1.1 *5-Alkyl Meldrum's Acids*

2.1.1.1. With Alkyl Halides. Meldrum's acid undergoes the expected alkylation reaction with alkyl halides. A number of new reaction conditions have been worked out for the successful alkylation of **1**, which include K_2CO_3 and phase transfer catalysts in $CHCl_3$,[4,5] K_2CO_3 in DMF,[6] triethylamine in DMSO[7] and others.[8]



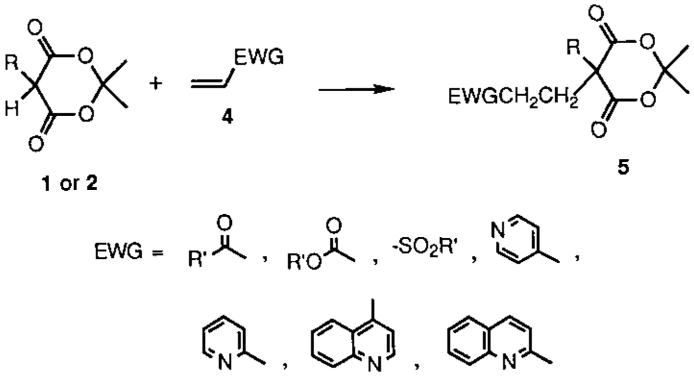
1. R = H
2. R = alkyl, aryl

R' = alkyl
X = Cl, Br, I

3

The alkylation of **1** usually gives symmetrical dialkyl products (**3**, R = R'). Unsymmetrical derivatives (**3**, R ≠ R') could be obtained from the corresponding monoalkyl Meldrum's acid (**2**). Whereas **2** is normally prepared through indirect methods (see section 3.2.1, 3.2.2.2 and 5.2.1). With α-bromoketones Meldrum's acid can be selectively monoalkylated.[9-11]

2.1.1.2. With Electrophilic Olefins. When treated with base Meldrum's acid reacts with electrophilic olefins (**4**) *via* Michael-type addition to afford functionalized alkyl derivatives (**5**). The olefins which have been studied are α,β-unsatuated carbonyl compounds,[12] sulfones,[13] and 2- or 4-vinylpyridines and the analogue quinolines.[14]

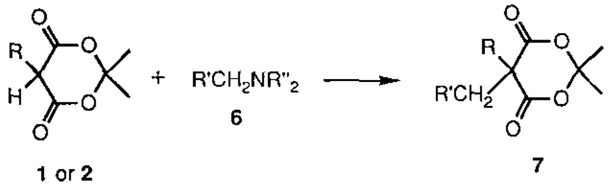


1 or 2

5

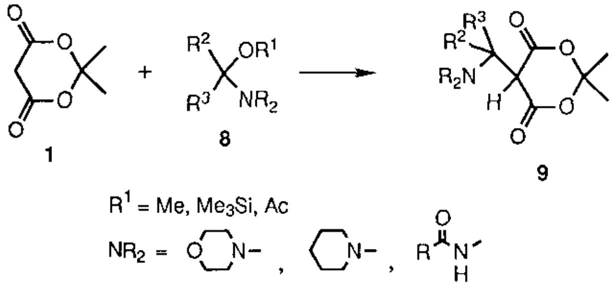
On the other hand, depending upon the reaction conditions **1** undergoes single or double Michael additions to bisvinyl ketones.[15]

2.1.1.3. With Manish Bases. Meldrum's acid (**1**) condenses readily with Mannish bases (**6**) such as those derived from acetone, ferrocene, β-naphthol and indole in the presence of acetic anhydride to give 5-alkylated products (**7**). The mechanism of this reaction may involve the generation of vinyl ketone and subsequent reaction through Michael addition.[16]



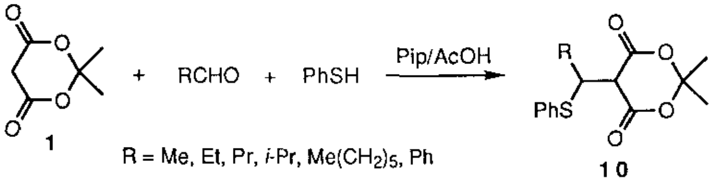
R = Me, Et, Ph, $PhCH_2$, MeCONH
R'= $MeCOCH_2$, ferrocenyl, 3-indolyl, 3-(*N*-methyl)indolyl
R"= Me, Et

2.1.1.4. With O,N-Acetals. Reaction of *O,N*-acetals (**8**) with Meldrum's acid **1** gives 5-(α-amino)alkyl Meldrum's acids (**9**).[17-20]



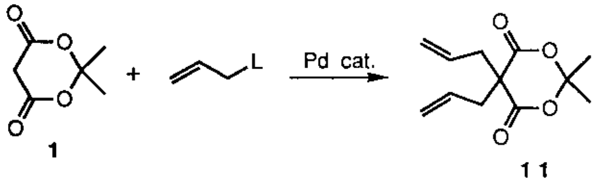
R^1 = Me, Me_3Si, Ac

2.1.1.5. With Aldehydes and Thiols. 5-(α-Thio)alkyl Meldrum's acids (**10**) can be readily prepared by treatment of **1** with aldehydes and thiols in the presence of catalytic amount of piperidium acetate.[21]



R = Me, Et, Pr, *i*-Pr, $Me(CH_2)_5$, Ph

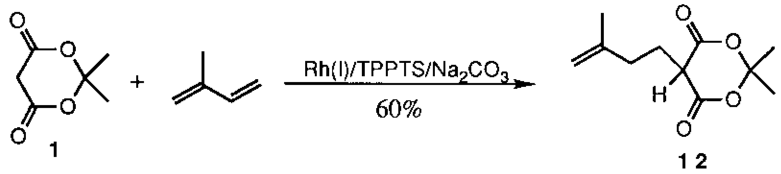
2.1.1.6. With π-Allylpalladium Complexes. Meldrum's acid (**1**) reacts with π-allylpalladium complexes to afford 5-allyl products (**11**).



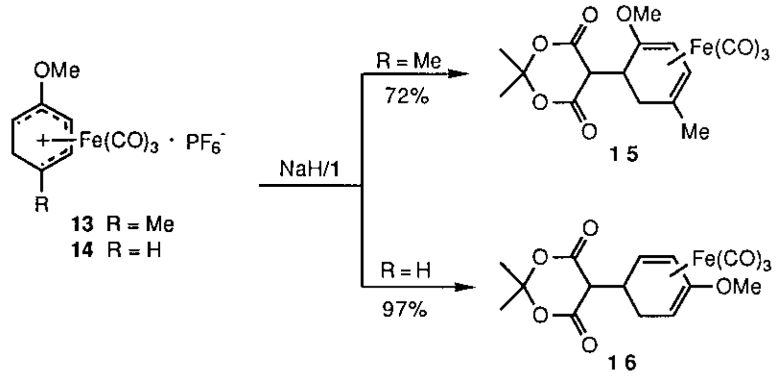
L = AcO-, Cl-, $(RO)_2BO$-
Pd cat. = $Pd(dba)_2$, $Pd(acac)_2$, $Pd(PPh_3)_4$

The palladium catalysts investigated include $Pd(dba)_2$,[22] $Pd(acac)_2$,[23] and $Pd(Ph_3)_4$.[24,25] The allylic substrates used are allyl acetaes,[22,23] allyl chlorides,[25] and allyl borates.[24] 5-Diallyl Meldrum's acid (**11**) is the major or the only product in these reactions.

2.1.1.7. With Isoprene and Rhodium Catalyst. In a recent report the use of isoprene as alkylating reagent was realized. When isoprene was reacted at room temperature with **1** in the presence of rhodium/tris(sodium 3-sulfophenyl)phosphine (TPPTS), the monosubstituted product (**12**) was obtained in 60% isolated yield.[26]



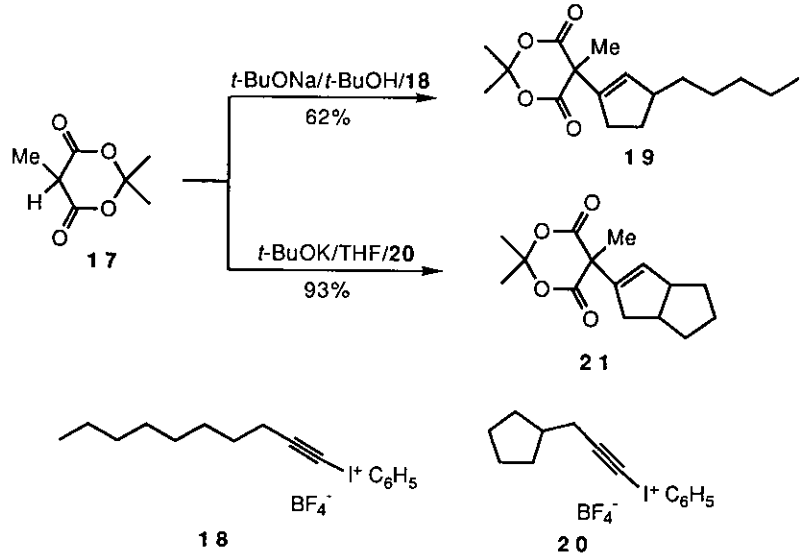
2.1.1.8. With Organoiron Complexes. Organoiron complex such as tricarbonyl(1-5-η-4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate (**13**) reacts with the enolate of **1** to give the monoalkylated product (**15**) in 72% yield. However the non-methylated analogue (**14**) gives rise to product (**16**) in 97% yield. The different regioselectivity can be explained in terms of steric effects.[27]



Scheme 1

2.1.2. 5-Alkenyl Meldrum's Acids

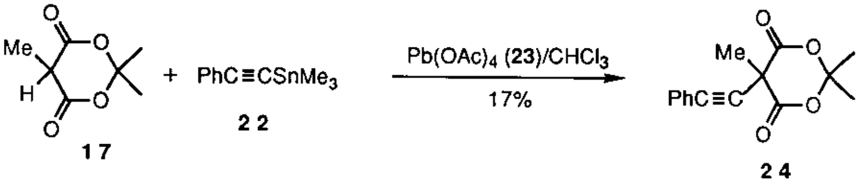
2.1.2.1. With (1-Alkynyl)phenyliodonium Salts. 5-Alkenyl Meldrum's acid has been scarcely investigated. Recently it was found[28] that when (1-decynyl)phenyliodonium tetrafluoroborate (**18**) dissolved in *tert*-butyl alcohol was treated with the enolate generated from 5-methyl Meldrum's acid (**17**) compound (**19**) was obtained in 62% yield. Similarly, **21** was obtained in 93% yield from [1-(3-cyclopentyl)propynyl]phenyliodonium tetrafluoroborate (**20**).



Scheme 2

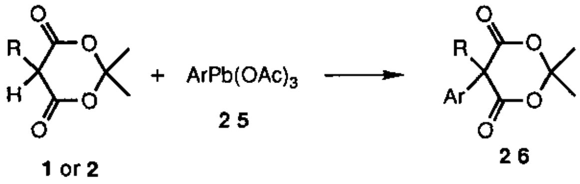
2.1.3. 5-Alkynyl Meldrum's Acid

2.1.3.1. With Trimethyl(phenylethynyl)stannane. Reaction of 5-methyl Meldrum's acid (**17**) with trimethyl(phenylethynyl)stannane (**22**) and lead tetra-acetate (**23**) in chloroform afforded 5-phenylethynyl-5-methyl Meldrum's acid (**24**) in 17% yield. Use of the lithium enolate of **17** and DMSO as solvent did not result in much improvement in the yield of **24** (25%).[29]



2.1.4. 5-Aryl Meldrum's Acids

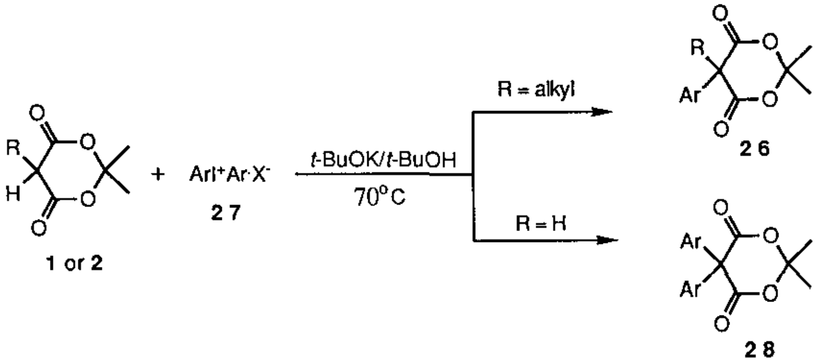
2.1.4.1. With Aryllead Triacetates. As might expected 5-aryl Meldrum's acid (**26**) can not be readily prepared *via* conversional methods. Pinhey and coworkers[30-33] demonstrated that treatment of **1** or **2** with aryllead triacetates (**25**) resulted in formation of 5-aryl derivatives (**26**) in high yields. A variety of 5-aryl Meldrum's acid derivatives (**26**) have been prepared in this way.



1 or **2** **25** **26**

It should be pointed out that 5,5-diaryl Meldrum's acids can only be obtained in poor yields by this method.

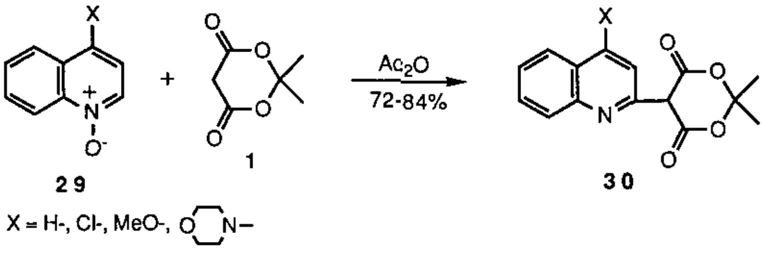
2.1.4.2. With Diaryliodonium Salts. Recently Chen and coworkers[34] presented a convenient synthesis of both 5,5-diaryl and 5-alkyl-5-aryl Meldrum's acid derivatives (**26**) and (**28**). Simple stirring of the potassium salt of **1** or **2** with the appropriate diaryliodonium salts (27) in *tert*-butyl alcohol at 70°C gave after workup and isolation the desired aryl products in good to excellent yields.



1 or **2** **27** **26** **28**

Scheme 3

2.1.4.3. With Quinoline N-Oxides. Reaction of quinoline *N*-oxides (**29**) with **1** in acetic anhydride smoothly occurred to afford the corresponding 5-heteroaryl derivatives (30) in good yield.[35]

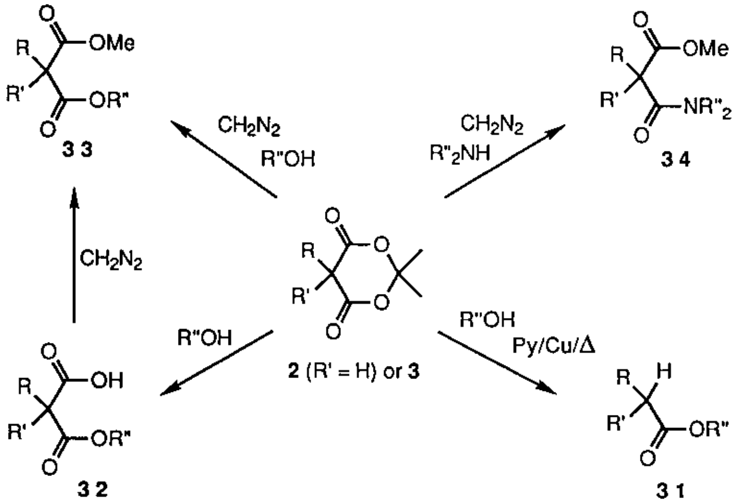


29 **1** **30**

2.2 *Reaction*

2.2.1. Ring Opening Reaction

2.2.1.1. Formation of Carboxylic Esters. In addition to the normal hydrolysis to carboxylic acids, 5-alkyl Meldrum's acids undergo a number of unique reactions that their acyclic analogues can not. Refluxing **2** or **3** with alcohol in pyridine in the presence of copper gives directly the corresponding esters (**31**).[36] Whereas preparation of esters from the acyclic malonates requires two steps involving selective hydrolysis and subsequent decarboxylation or hydrolysis followed by decarboxylation and esterification.

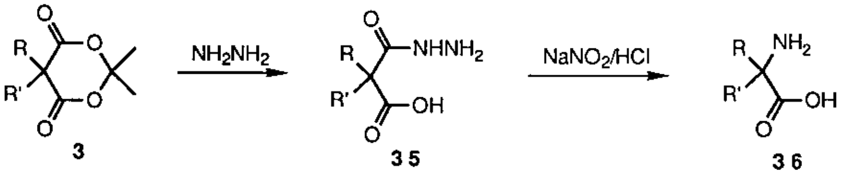


Scheme 4

2.2.1.2. Formation of Malonyl Monoesters. Of interest is the fact that by changing the reaction condition the monoester of malonic acids (**32**) can also be prepared from 5-alkyl Meldrum's acids (Scheme 4).[37-40]

2.2.1.3. Formation of Malonyl Diesters and Malonyl Monoester Amides. The free carboxylic acid of **32** can be esterified using CH_2N_2,[38] or more conveniently by the treatment of **3** with diazomethane in the presence of an alcohol to afford malonyl diesters (**33**). If an amine is used instead of alcohol in this 'one pot' reaction malonyl monoester amide (**34**) is obtained.[41]

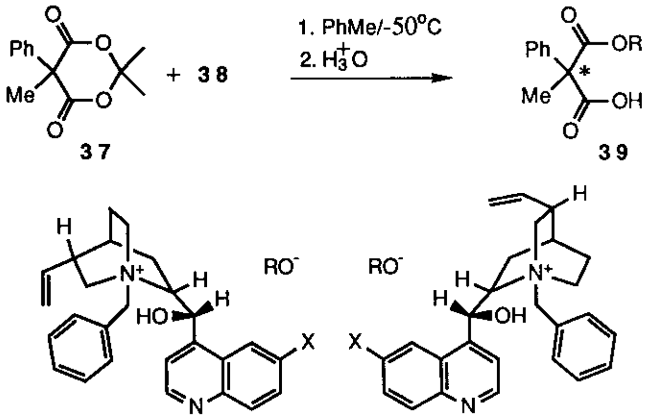
2.2.1.4. Formation of α-Amino Acids. Ring cleavage of 5-alkyl Meldrum's acid (**3**) with hydrazine followed by treatment with sodium nitrite has been applied to the preparation of α-amino acid (**36**).[42]



Scheme 5

2.2.2. Enantioselective Ring Opening Reaction

2.2.2.1. Formation of Optically Active Malonyl Monoesters. Oda and coworkers[43] reported a moderate differentiation of the enantiotopic carbonyl groups of 5-methyl-5-phenyl Meldrum's acid (**37**) by the use of alkoxide anions paired with chiral quaternary ammonium cations derived from cinchona alkaloids (**38**). The yield and the extent of stereoselectivity of the reaction were found to be highly affected by the nature of the reaction medium, polarity of the solvent and the solubility of the nucleophile (**38**). Relatively non-polar and aprotic solvent such as toluene, dimethoxyethane, and tetrahydrofuran were fount to be the preferable solvents from both chemical and optical yields.

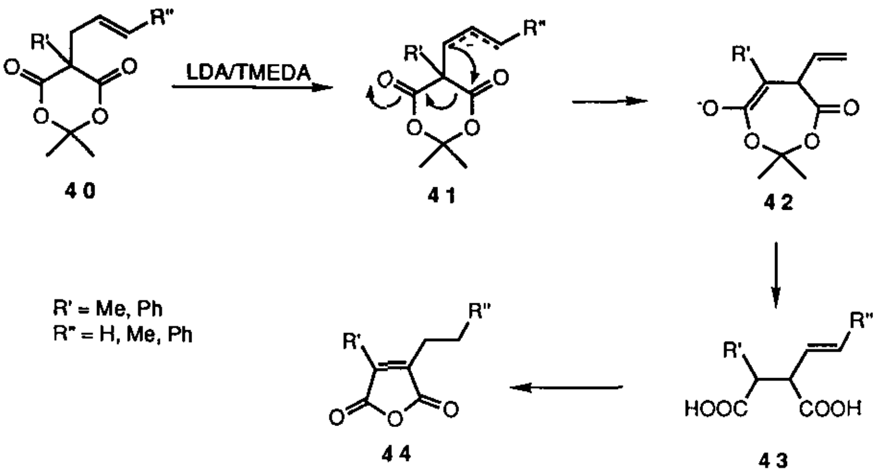


38

R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu
X = H, MeO

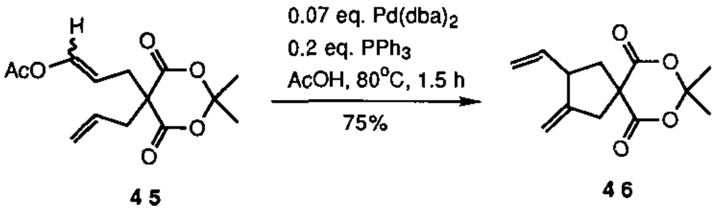
2.2.3. Reactions on the 5-Substituent Groups

2.2.3.1. Reaction of 5-Allyl Meldrum's Acids. A recent study revealed that when treated with LDA in the presence of tetramethylethylenediamine (TMEDA) 5-allyl-5-alkyl Meldrum's acids (**40**) underwent a novel reaction to give 2,3-disubstituted maleic anhydrides (**44**) after work-up and distillation.[44] It appears that the allyl anion (**41**) formed undergoes intramolecular 1,2-carbonyl migration, which can be rationalized in terms of attack of the ester carbonyl by the anion at the latter's α-carbon, followed by C-C bond cleavage to result in ester enolate (**42**), and finally, upon work-up, acid (**43**). Subsequent transformation in which **43** condenses with migration of the double bond to yield the stable maleic anhydride (**44**) takes place during distillation and is not unusual. The acids (**43**) can be isolated in low overall yield (32-46%).



Scheme 6

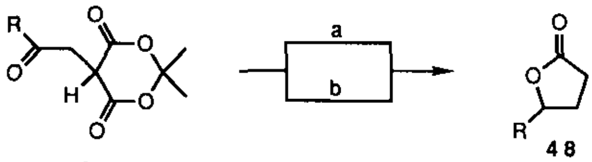
Oppolzer and Gaudin[25] observed that the diene (**45**) underwent catalytic intramolecular palladium-ene reaction when heated with bis(dibenzylideneacetone)palladium [Pd(dba)$_2$] and PPh$_3$ in acetic acid giving the cyclized product (**46**) in 75% yield.



45 **46**

2.2.3.2. Reaction of 5-(Oxyalkyl) Meldrum's Acids. The chemistry of 5-(1-oxyalkyl) Meldrum's acids (5-acyl Meldrum's acids) will be discussed in detail in section 5.

2.2.3.2.1. *5-(2-Oxyalkyl) Meldrum's Acids.* Hydrolysis of 5-(2-oxyalkyl)-Meldrum's acids (**47**) in aqueous acetic acid followed by reduction with sodium borohydride and subsequent cyclization or selective reduction of the ketone functionality followed by thermal cyclization is a convenient method to prepare 4-alkanolides (**48**).[45]

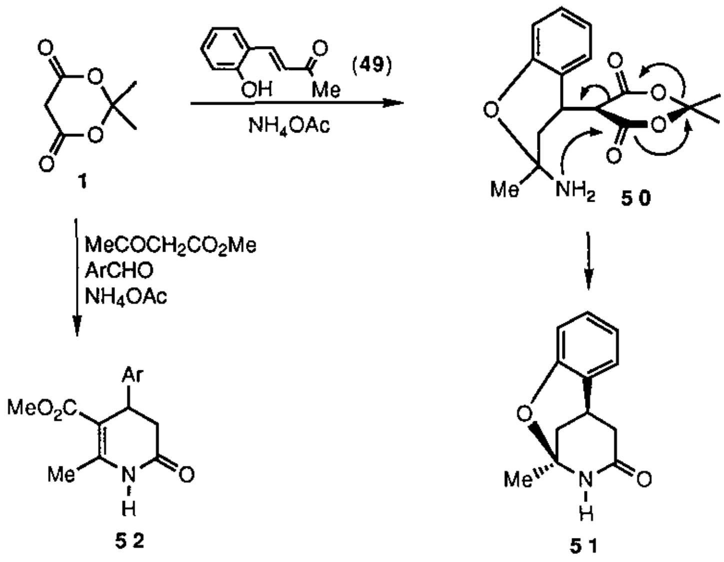


47 **48**

a) 1. aq. HOAc/Δ; 2. NaBH$_4$
b) 1. NaBH$_4$; 2. Δ

Scheme 7

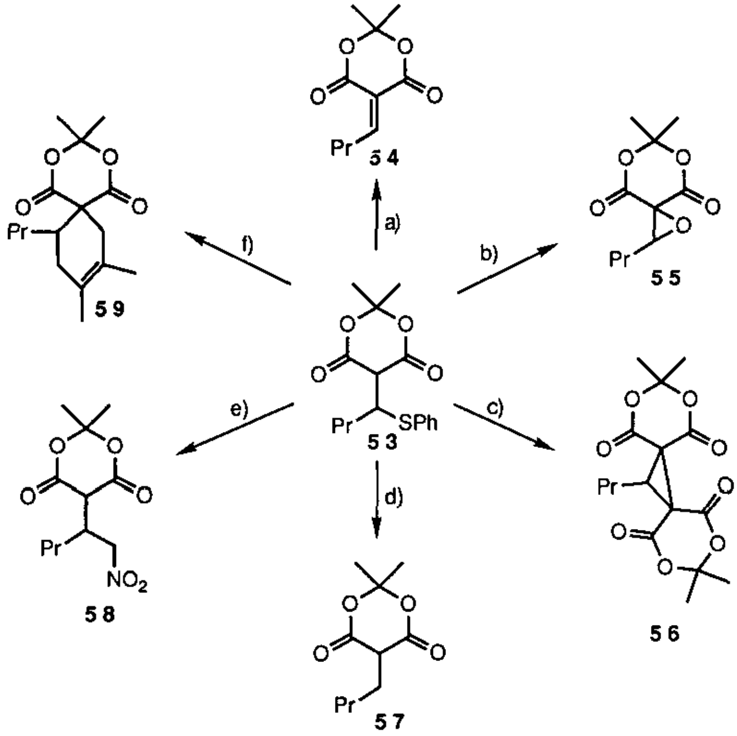
2.2.3.2.2. *5-(3-Oxyalkyl) Meldrum's Acids.* Reaction of **1** with α,β-unsaturated ketones gives 5-(3-oxyalkyl) Meldrum's acids (see section 2.1.1.2). This reaction has been employed in the preparation of heterocyclic compounds. For example, substituted oxygen-bridged tetrahydro-2-pyridone (**51**) was synthesized by the condensation of 4-(2-hydroxyphenyl)but-3-en-2-one (**49**) with **1** in the presence of ammonium acetate in refluxing ethanol.[46] The formation of **51** can be viewed as preceding *via* Michael addition to **49** of the carbanion of **1** and aminal formation of **50**. Nucleophilic attack of the amine nitrogen atom at the dioxanedione ring leads to pyridone ring closure and acetone expulsion to give **51**.



Scheme 8

The reaction has been further utilized in a 'one-pot' fashion to the synthesis of substituted pyridones. Heterocyclization of methyl acetoacetate and benzaldehydes with **1** in the presence of ammonium acetate yields a number of substituted pyridone carboxylates (**52**). In spite of moderate yields, this reaction provides a convenient entry into the chemistry of 3,4-dihydro-2(1*H*)-pyridones due to the availability of the starting components and an easy work-up procedure.

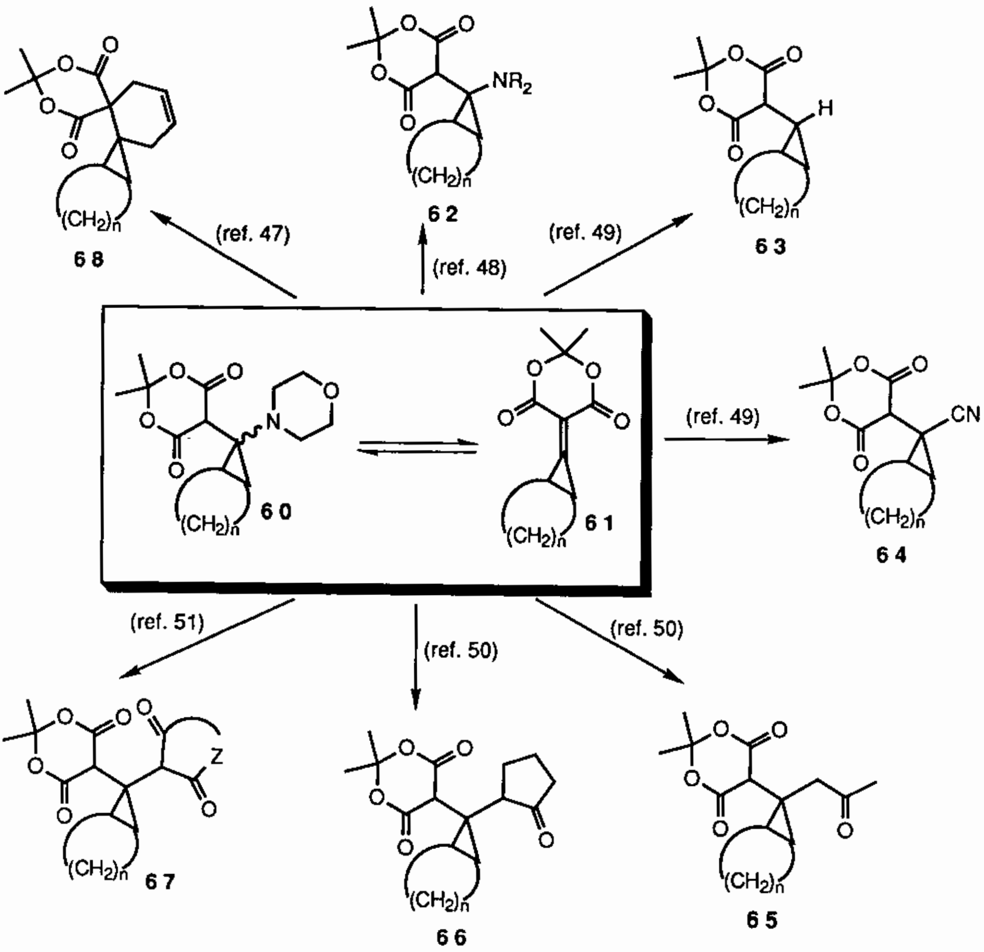
2.2.3.3. *Reaction of 5-(α-Thioalkyl) Meldrum's Acids.* The chemistry of 5-(α-thioalkyl) Meldrum's acids has been studied by Eberle and Lawton.[21] The results are summarized in Scheme 9 using 5-(α-thiobutyl) Meldrum's acid (**53**) as an example. Treatment of **53** with potassium hydroxide in the presence of potassium ferricyanide gives 5-isobutyl Meldrum's acid (**54**). Oxidation with hydrogen peroxide results in the formation of epoxide (**55**). Reaction of **53** with Meldrum's acid (**1**) in the presence of sodium periodate gives cyclopropane derivative (**56**). Reduction with sodium borohydride, on the other hand, affords 5-isobutyl Meldrum's acid (**57**). Treatment of (**53**) with nitromethane using tetrabutylammonium hydroxide as base gives rise a nitro compound (**58**). Diels-Alder reaction also occurs between 5-(α-thiobutyl) Meldrum's acid (**53**) and 2,3-dimethyl-1,3-butadiene, resulting in the formation of cyclohexene derivative (**59**). All the reactions could be rationalized in terms of the formation of **54**.



a) $K_3[Fe(CN)_6]$, KOH; b) H_2O_2; c) **1**, $NaIO_4$; d) $NaBH_4$;
e) $MeNO_2$, Bu_4NOH; f) 2,3-dimethyl-1-3-butadiene

Scheme 9

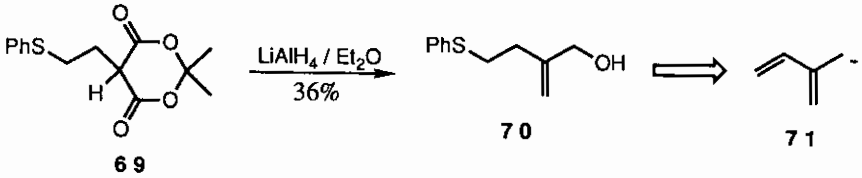
2.2.3.4. Reaction of 5-(α-Aminoalkyl) Meldrum's Acids. The reaction of 5-(α-aminoalkyl) Meldrum's Acids (**60**) has been extensively investigated by Vilsmaier and coworkers. The results are illustrated in Scheme 10. All the reaction could be explained in terms of formation of the intermediate (**61**).



Scheme 10

2.2.4. *Ring Reduction*

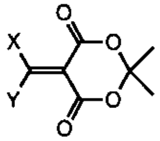
2.2.4.1. With LiAlH$_4$. Reduction of the ring of 5-alkyl Meldrum's acid has also been reported. Treatment of compound (**69**) with lithium aluminium hydride in ether under reflux for 21 h after usual work-up and chromatograghic separation affords the alcohol (**70**) in 36% yield.[52] The alcohol (**70**) could be utilized as the synthetic equivalent to the isoprenyl carbanion (**71**), useful synthon for the construction of some natural terpenes bearing a terminal isoprene unit.



Scheme 11

3. 5-METHYLENE MELDRUM'S ACIDS

The chemistry of another kind of Meldrum's acid derivatives having a general structure (**72**) will be discussed in this section.



7 2

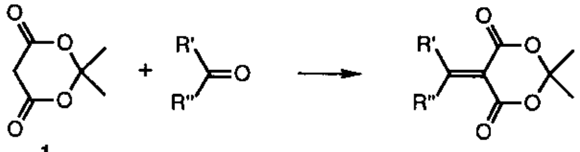
X, Y = H, R, Ar, OR, NR_2, SR

Chart I

3.1 *Preparation*

3.1.1. 5-Alkylidene and Arylidene Meldrum's Acids

The reaction of Meldrum's acid (**1**) with ketones and aldehydes has been discussed in great details by McNab.[2] The reaction was subsequently refined and used to prepare a variety of 5-alkylidene and arylidene Meldrum's acid derivatives (**73**).[2,53-60]



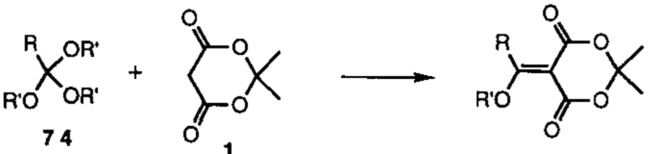
1

7 3

R', R" = H, alkyl, aryl

3.1.2. 5-(α-Heteroatom Substituted)methylene Meldrum's Acids

Orthoformates (**74**) react with **1** to give 5-(α-alkoxy)methylene Meldrum's acids (**75**).[2]

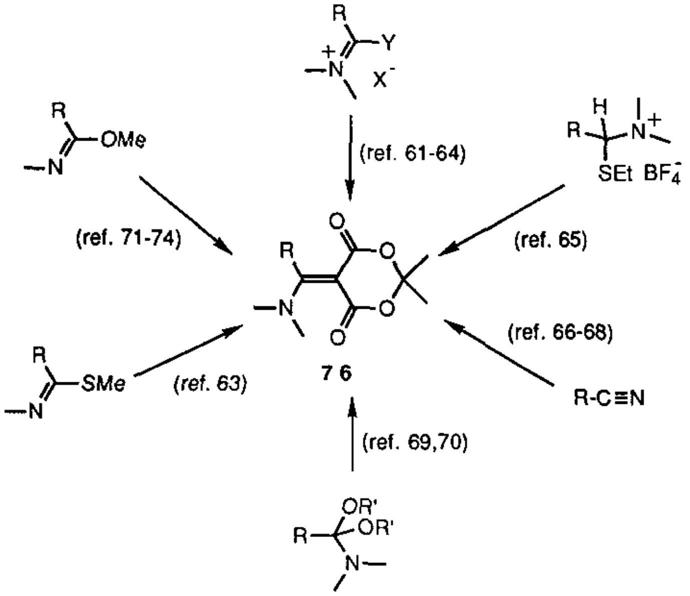


7 4

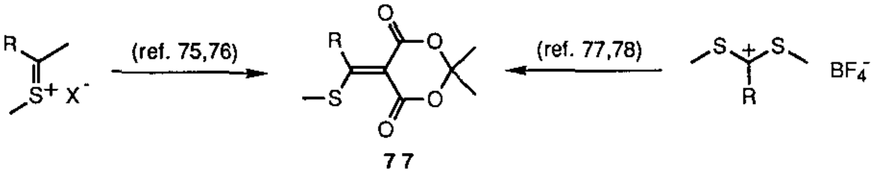
1

7 5

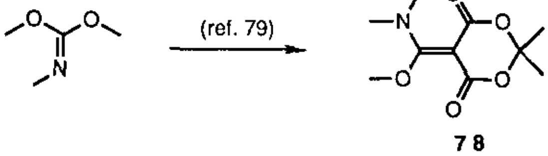
A variety of other 5-(α-heteroatom substituted)methylene Meldrum's acid derivatives have also been prepared. These include 5-(α-amino)methylene Meldrum's acid (**76**) (Scheme 12), 5-(α-thio)methylene Meldrum's acid (**77**) (Scheme 13), 5-(α-amino-α'-oxy)methylene Meldrum's acid (**78**) (Scheme 14), 5-(α-amino-α'-thio)methylene Meldrum's acid (**79**) (Scheme 15) and 5-(α,α'-bisthio)methylene Meldrum's acid (**80**) (Scheme 16).



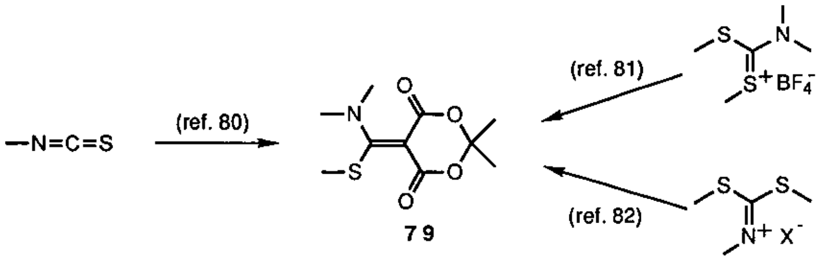
Scheme 12



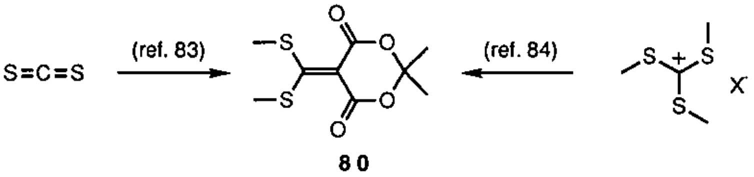
Scheme 13



Scheme 14



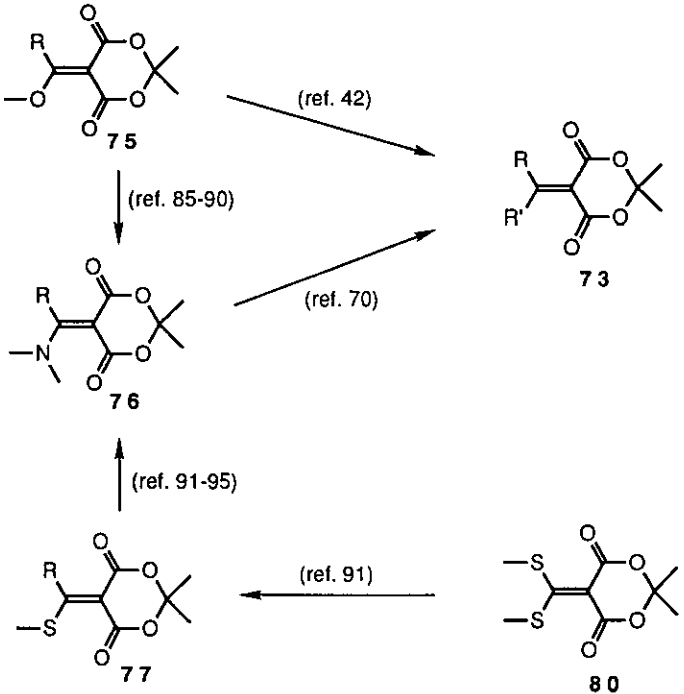
Scheme 15



Scheme 16

3.1.3. Conversions between 5-Methylene Meldrum's Acids

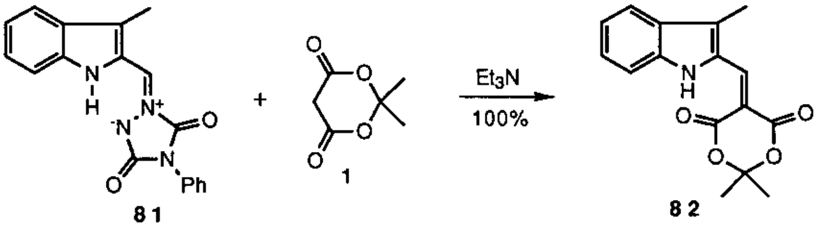
Another general preparation of 5-methylene Meldrum's acids is the conversion between each other (Scheme 17).



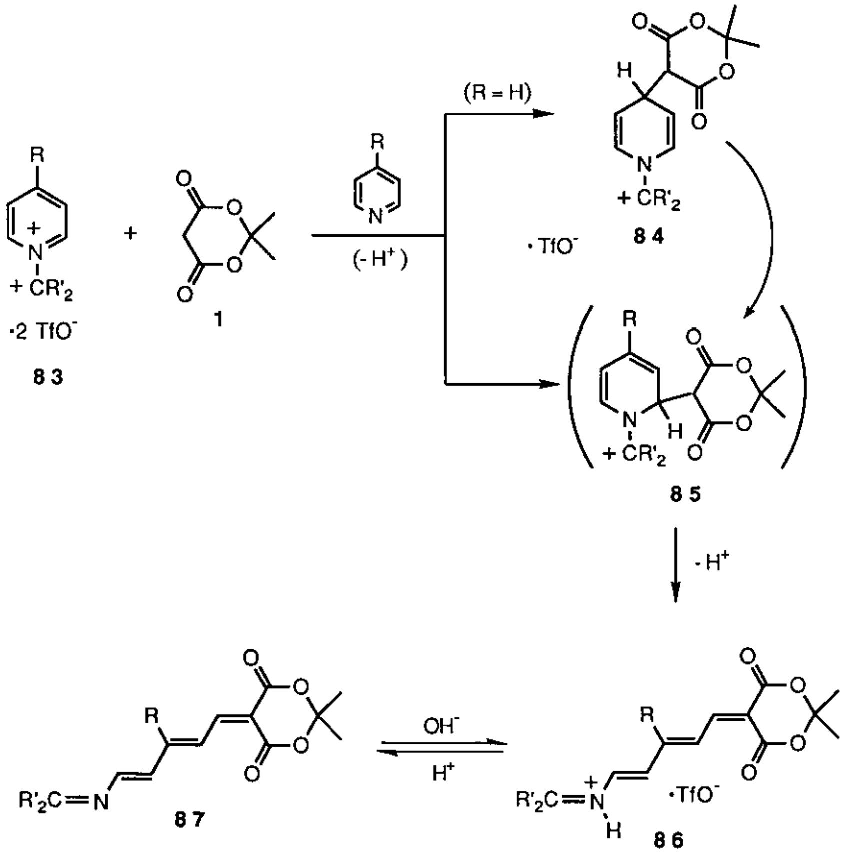
Scheme 17

3.1.4. Miscellaneous

3.1.4.1. With Azomethine Imines. Azomethine imine (**81**) was found to react with **1** to give 5-methylene product (**82**) in quantitative yield.[96,97]

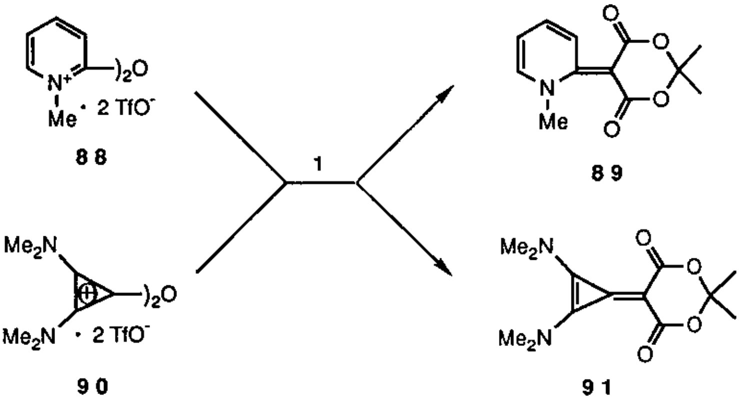


3.1.4.2. With Pyridinium salts. Mass and coworkers[98-100] observed that reaction of the anion of **1** with N-(tetraalkylamidino)pyridinium salts (**83**) leads to the formation of azahexamethine merocyanines (**86**) *via* α-attack at the pyridinium ring followed by ring opening. In some cases, kinetically controlled reactions yield 1,4-dihydropyridines (**84**) which isomerize thermally to give 1,2-dihydropyridines (**85**) which undergo ring opening spontaneously. Neutral dyestuffs (**87**) can be obtained on deprotonation.



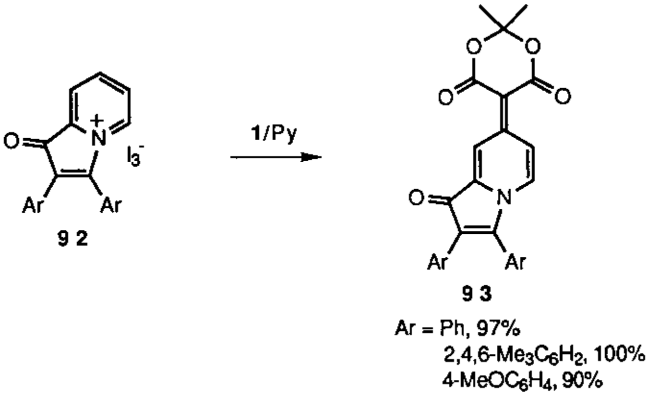
Scheme 18

3.1.4.3. With Dication Ether Salts. When the dication ether salt (**88**) is treated with the anion of **1** 5-methylene Meldrum's acid derivative (**89**) is obtained.[101] Similarly when the dication ether salt (**90**) derived from 2,3-bis(dimethylamino)cyclopropenone was allowed to react with **1**, compound (**91**) was obtained in 42% yield.[102]

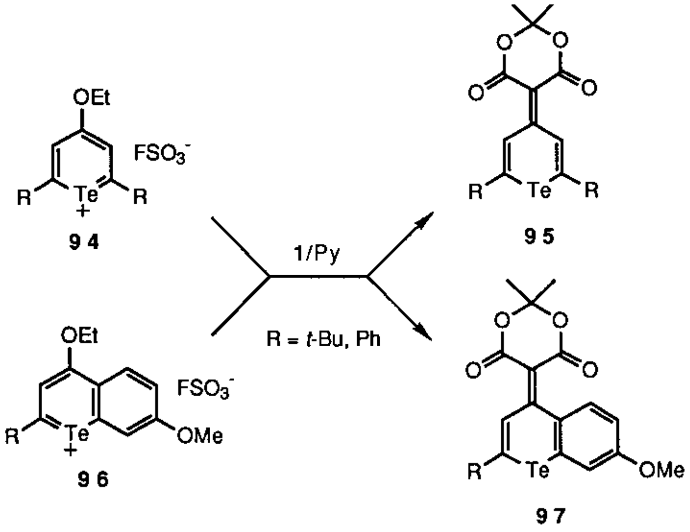


Scheme 19

3.1.4.4. Oxoindolizinium Ions. Oxoindolizinium ions (**92**) react with **1** in the presence of pyridine giving a class of indolizine dyes (**93**) incorporating the 5-methylene Meldrum's acid structural unit.[103]



3.1.4.5. With 4-Ethoxytelluropyrylium Salts. Condensation of **1** with 4-ethoxytelluropyrylium salts (**94**) and 4-ethoxybenzotelluropyrylium salts (**96**) afforded compounds (**95**) and (**97**) respectively.[104]

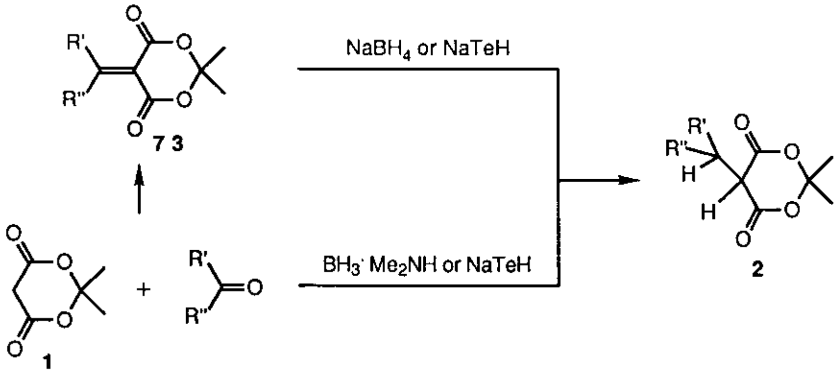


Scheme 20

3.2 *Reaction*

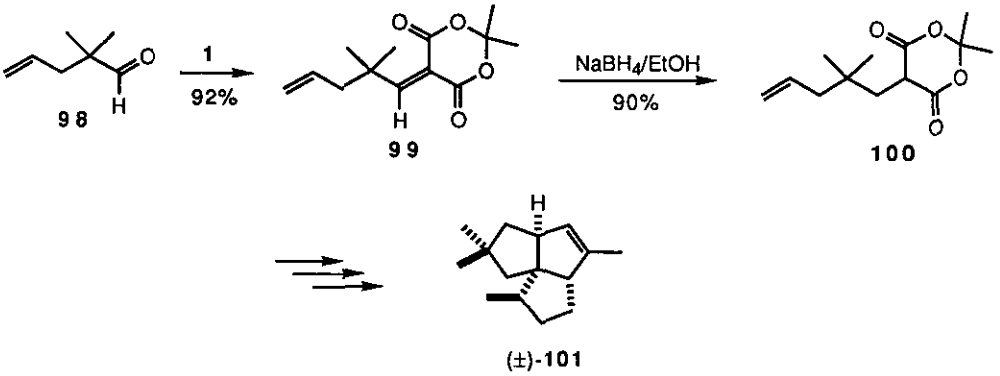
3.2.1 Conjugated Reduction

The conjugated reduction of 5-alkylidene and arylidene Meldrum's acids (**73**) is the way used most often to prepare 5-monoalkyl Meldrum's acids (**2**). The reducing reagent commonly used is sodium borohydride[105] and more recently sodium hydrogentelluride.[106] The monoalkylated products can also be obtained in a 'one pot' fashion if a selective reducing reagents is emploied. For example treating **1** and carbonyl substrates in one pot with borane-dimethylamined[107] or sodium hydrogentelluride[106] readily gives the corresponding 5-monoalkyl Meldrum's acids (**2**).



Scheme 21

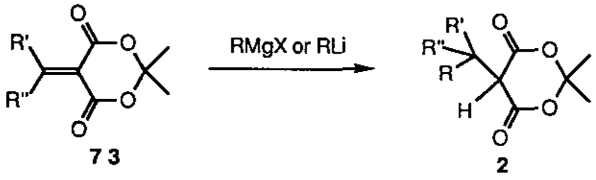
This methodology has been used in the total synthesis of (±)-pentalenene (**101**).[108]



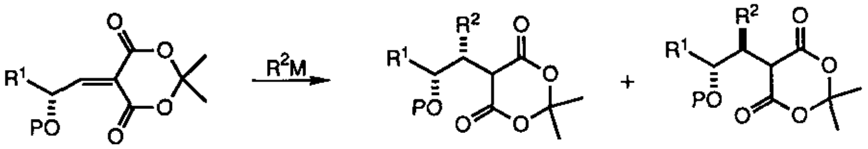
Scheme 22

3.2.2 Conjugated Addition

3.2.2.1. With Grignard and Organolithium Reagents. The conjugated addition of various Grignard and organolithium reagents to 5-alkylidene and arylidene Meldrum's acids (**73**) has been the subject of several investigations.[109-112] In most cases the addition occurs rapidly with or without cuprous salt and the adducts are obtained in high yields. This reaction provides the only opportunity to the preparation of highly β-substituted 5-monoalkyl Meldrum's acids (**2**). The conjugated addition to Meldrum's acid derivatives has some advantages over the acyclic malonate analogues as the latter often offer no reaction or low yield.



More recently, Larcheveque and coworkers[113] investigated the stereochemistry of the conjugated addition of organometallic compounds R^2M (M = Li or MgX) to the protected α-hydroxy Meldrum's acids (**102**) in great detail and found the stereoselectivity of the reaction was highly dependent on the nature of the protecting group; in the case of the MEM group, syn-products (**103**) were obtained almost exclusively with Grignard reagents whereas the use of non-chelating protecting group such as t-BuPh$_2$Si afforded nearly pure anti-compounds (**104**) with organolithium reagents in the presence of 12-crown-4.

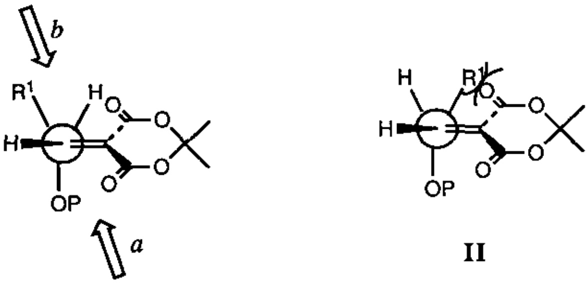


102 a) P = MEM
b) P = t-BuPh$_2$Si

103

104

The diastereoselectivity is interpreted as arising *via* addition to the conformer (I) rather than **II** since the existence of the strong interaction between the carbonyl function and the R^1 group destablizes the conformer (**II**) and favours the conformer (**I**). In the presence of a chelating protective group such as MEM, the approach of the necleophile follows path *a* to give the syn-isomers; in contrast, with a non-chelating group, the addition takes place *via* path *b* leading to the anti-isomers (Chart II).

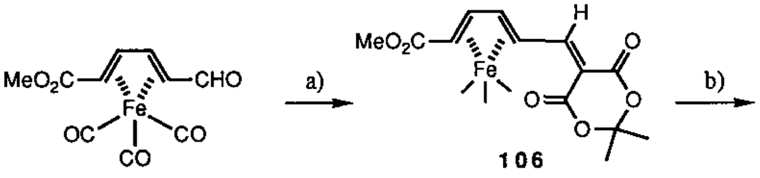


I

II

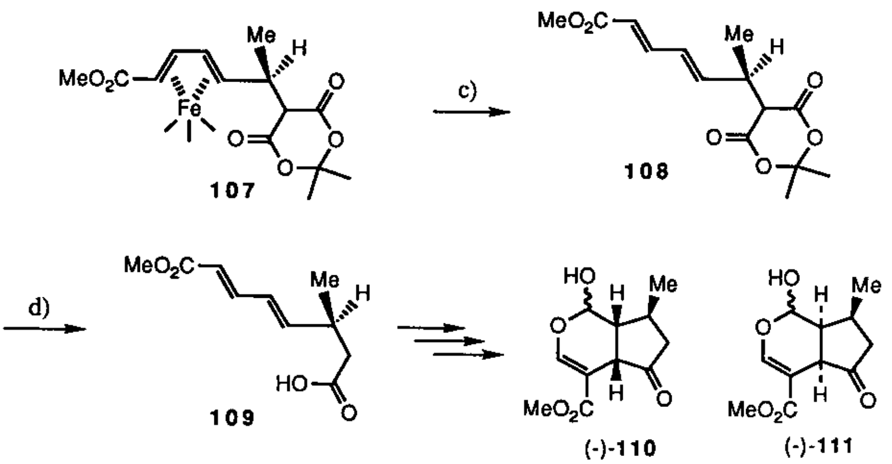
Chart II

Laabassi and Gree[114] have applied the conjugated addition reaction into the total synthesis of (-)-verbenalol (**110**) and (-)-epiverbenalol (**111**) (Scheme 23). The reaction of the chiral aldehyde (**105**) with **1** yielded, quantitatively, the olefin (**106**). Addition of methylmagnesium iodide to **106** was found to highly stereospecifically to give compound (**107**) in 93% yield along with >96% diastereomeric excess. It was confirmed that the reaction occurred by the attack of the Grignard reagent on the face anti to the Fe(CO)$_3$ moiety resulting in an (S)-configuration to the newly formed asymmetric carbon atom. After decomplexation (92% yield) and hydrolysis under mild reaction conditions, the acid (**109**) was obtained which was then transformed into (-)-**110** and (-)-**111** in multisteps.



105

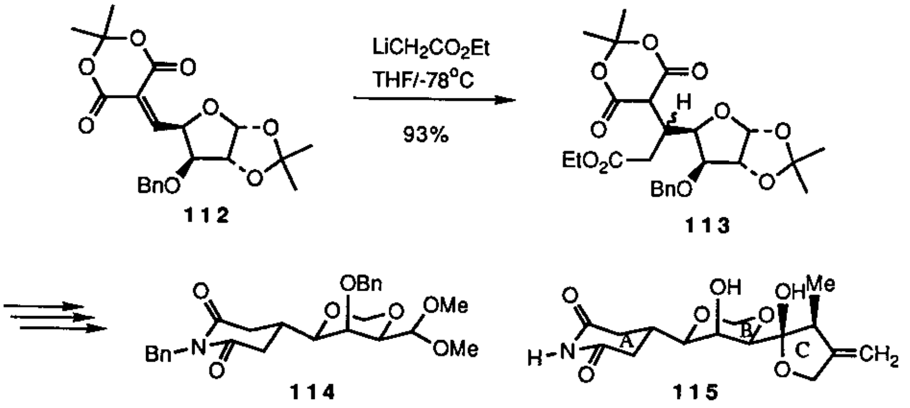
106



a) 1/Py/r.t, 100%; b) MeMgI/THF/-40°C, 93%;
c) $FeCl_3$/MeCN/-15°C, 92%; d) EtC(O)Et/H_2O/Δ, 82%

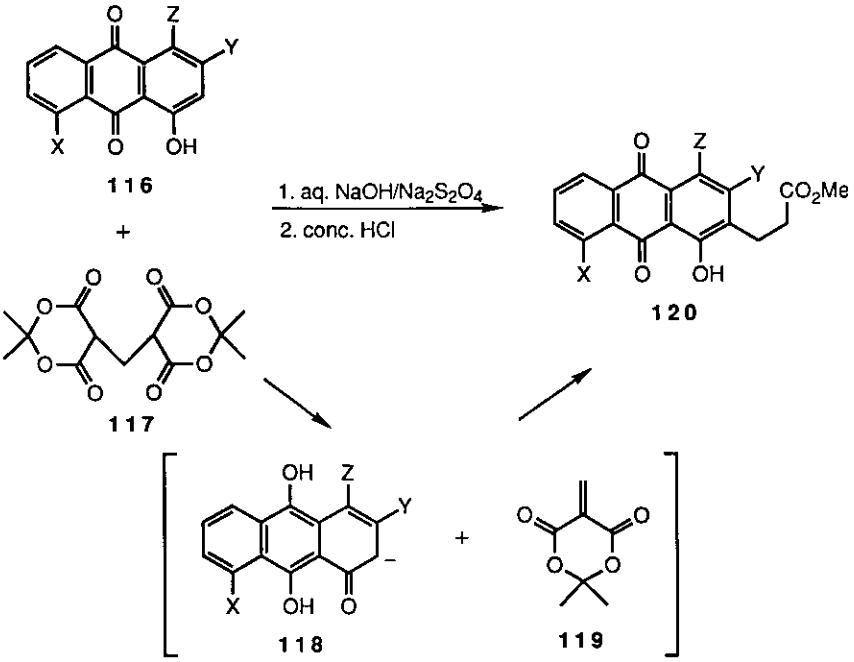
Scheme 23

3.2.2.2. With Enolates. Michael reaction of lithio ethyl acetate with **112** afforded an enantiomeric mixture of the ethyl ester (**113**) in 93% yield. Compound (**113**) was subsequently transformed into **114**, the AB ring moiety of the potent antitumor natural product sesbanimide (**115**). [115]



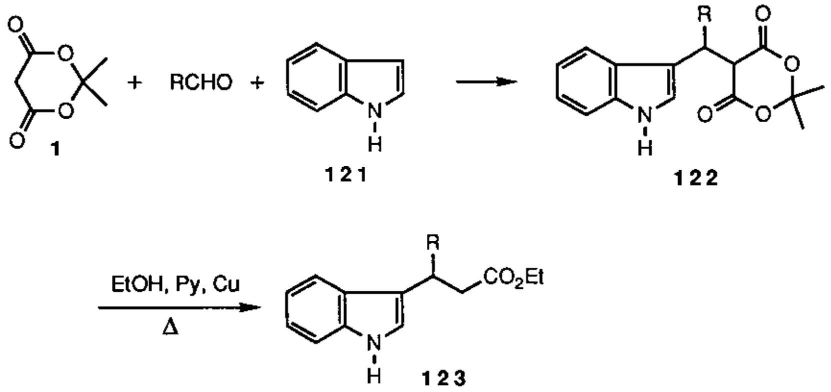
Scheme 24

In the study toward to synthesis of 11-deoxydoxorubicin antitumor antibiotics Mitscher and coworkers[116] found that reaction of leucoanthraquinones (**116**) with diisopropylidene methylenedimalonate (**117**) in aqueous NaOH/$Na_2S_2O_4$ produces β-anthraquinoylpropionate esters (**120**) after decarboxylation and esterification. The reactive components in the process are believed to be **118** and **119**. When heated diisopropylidene methylenedimalonate (**117**) generates **119**.



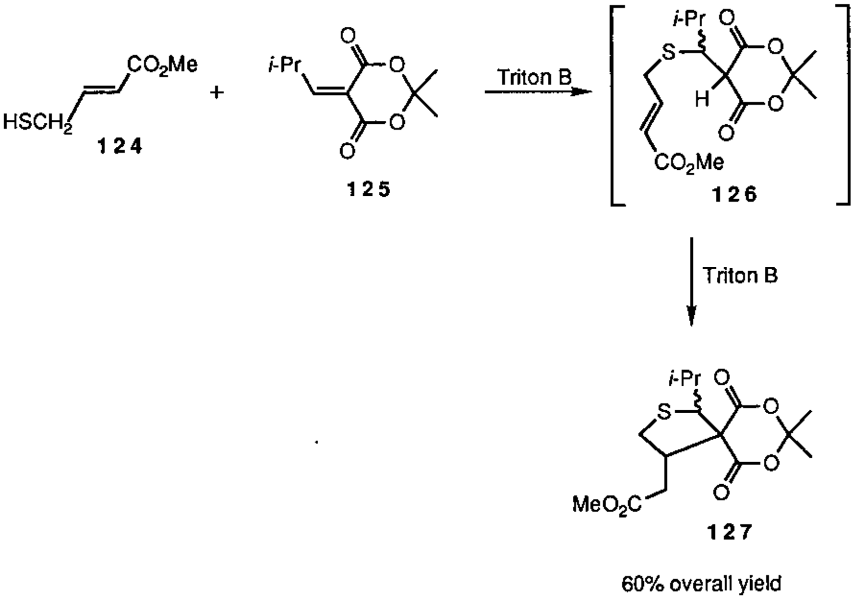
Scheme 25

3.2.2.3. With Indoles. Indole has also been found to be good nucleophile for the conjugated addition reaction affording 3-substituted indoles. As the ease formation of 5-alkylidene Meldrum's acids (**73**) from aldehyde and **1**, the reaction has been developed in 'one-pot' fashion, i.e. warming the mixture of **1**, aldehydes and indole (**121**) readily provides **122**. A number of 3-substituted indoles have been prepared by this convenient mothod.[36,117-120] Refluxing **122** in alcohol in the presence copper powder gives indolepropioic esters (**123**).



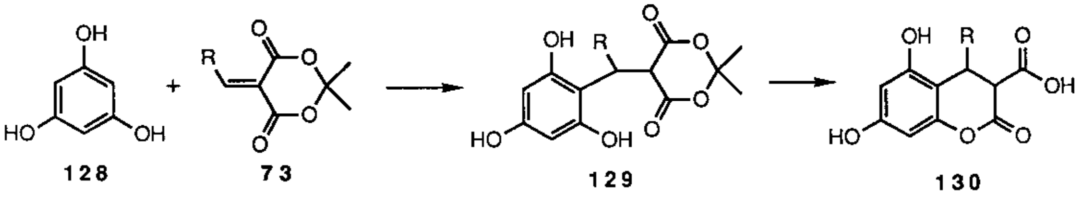
Scheme 26

3.2.2.4. With Methyl 4-Mercaptocrotonate. Methyl 4-mercaptocrotonate (**124**) adds to isobutylidene Meldrum's acid (**125**) in the presence of Triton B as base to give **126** which spontaneously cyclizes to thiolane (**127**) through a second Michael addition.[121]



Scheme 27

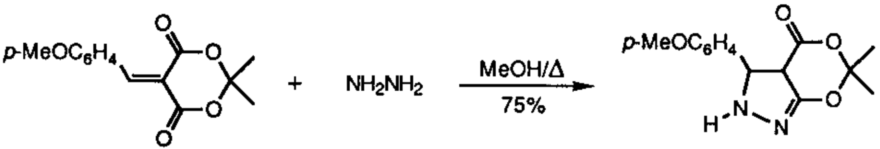
3.2.2.5. With Phloroglucinol. 5-Alkylidene Meldrum's acids (**73**) react with phloroglucinol (**128**) to give **129** which then cyclizes to dihydrocoumarins (**130**).[122]



R = H, Ph, p-HOC_6H_4, p-$AcOC_6H_4$

Scheme 28

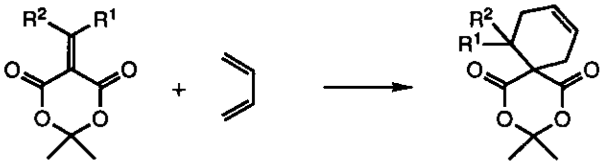
3.2.2.6. With Hydrazine. Refluxing 5-Arylidene Meldrum's acid (**73**) with hydrazine hydrate in methanol for 1.5 h gives the corresponding dioxanopyrazolin (**131**) in 75% isolated yield.[123]



73 **131**

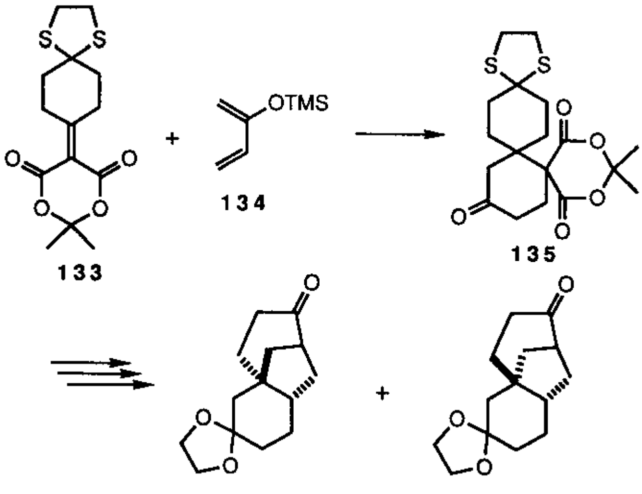
3.2.3 *Cycloaddition reaction.*

3.2.3.1. Diels-Alder Reaction. 5-Alkylidene and arylidene Meldrum's acids (**73**) are good dienophiles.[124-126]

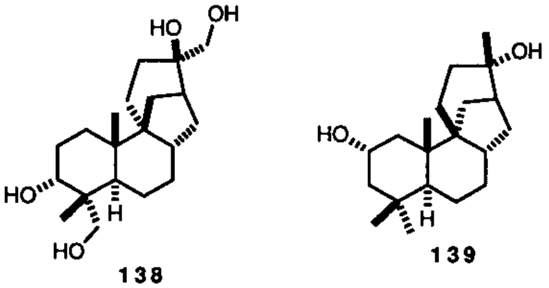


73 **132**

The Diels-Alder reaction has found potential applications in natural product synthesis. For example, Holmes and coworkers[127] prepared polycyclic compound (**136**) and (**137**), promising precursors for the highly biologically active natural product aphidicolin (**138**) and stemodine (**139**) *via* the Diels-Alder reaction of **133** with 2-trimethylsilyloxybuta-1,3-diene (**134**).



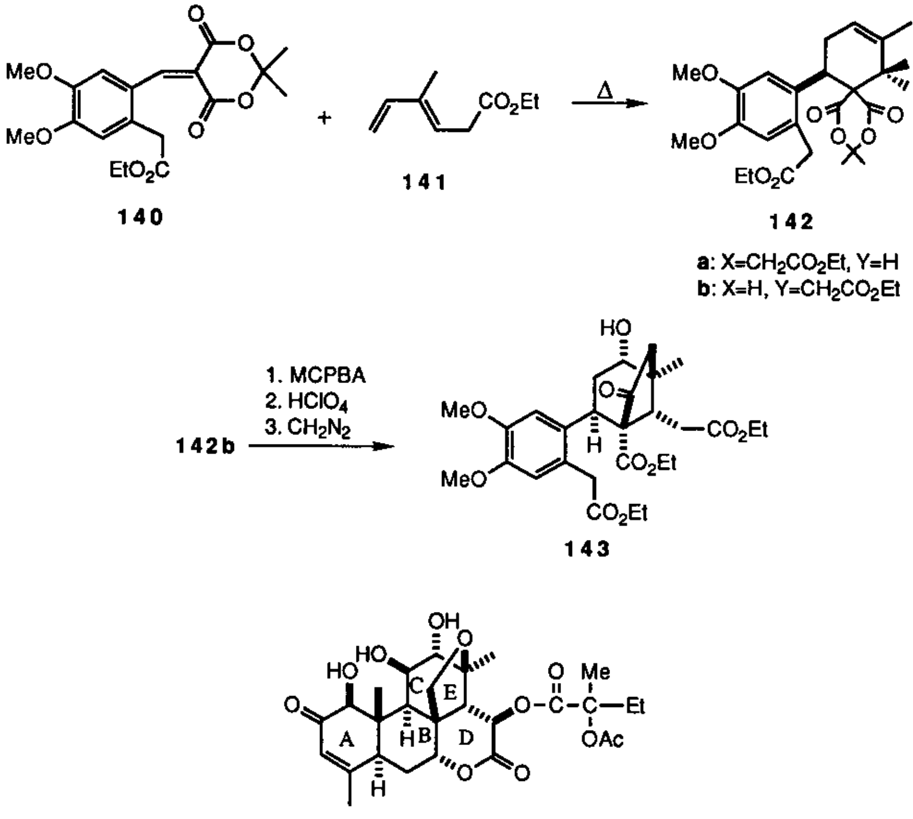
136 **137**



138 **139**

Scheme 29

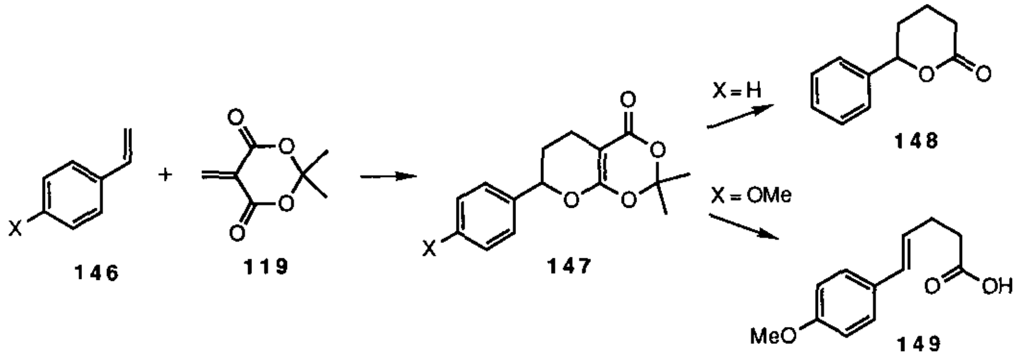
Kraus and Krolski[128] has also applied the Diels-Alder reaction of 5-arylidene Meldrum's acid into the synthesis the ACE ring system of quassimarin (**144**). Cycloaddition of **140** with **141** afforded 84% of **142a** and **142b** in a ratio of 2:5. The adduct (**142b**) separated then was transformed to the intermediate (**143**), the ACE ring system of quassimarin (**144**).



140 **141** **142** **143** **144**

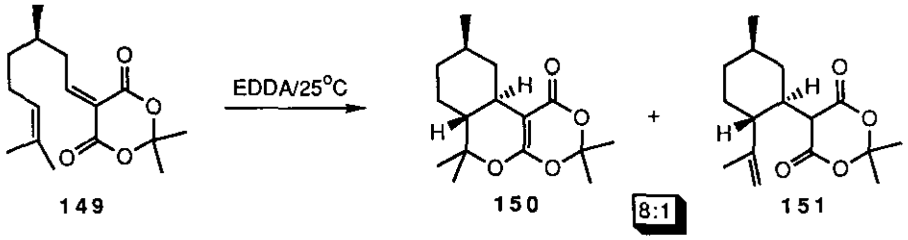
Scheme 30

3.2.3.2. Hetero-Diels-Alder Reaction. 5-Methylene Meldrum's acid (**119**) is not only good dienophiles, but also good oxy-dienes in hetero-Diels-Alder reactions.[129,130] The reaction product (**146**) could be further transformed into δ-lactone (**147**) and γ,δ-unsaturated carboxylic acid (**148**).

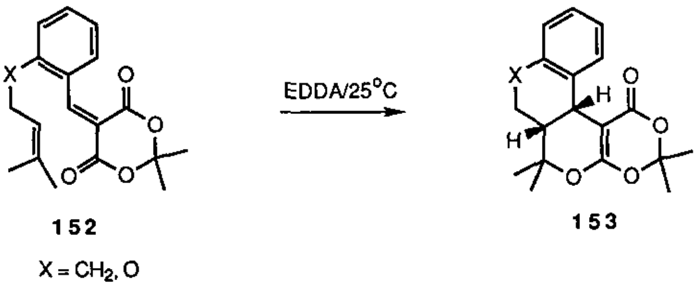


Scheme 31

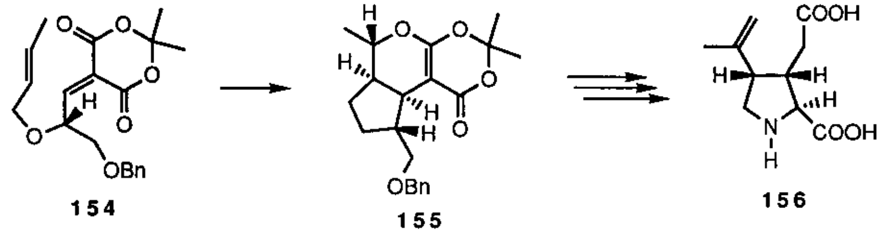
Intramolecular hetero-Diels-Alder reactions have also been a subject of a number of investigations. Reaction of **149** formed *in situ* from citronellal and Meldrum's acid in the presence of ethylenediammonium diacetate (EDDA) at room temperature for 45 min gives the intramolecular hetero-Diels-Alder reaction product (**150**) along with a small amount of the ene product (**151**).[131-133]



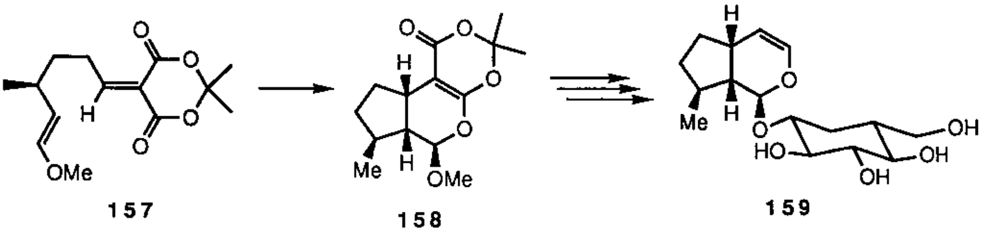
This reaction is extremely highly stereospecific, leading exclusively to the trans-fused dihydropyrans (**150**). However, with substrates like **152**, cis-fused dihydropyrans (**153**) are the exclusive cycloadducts.[134,135]



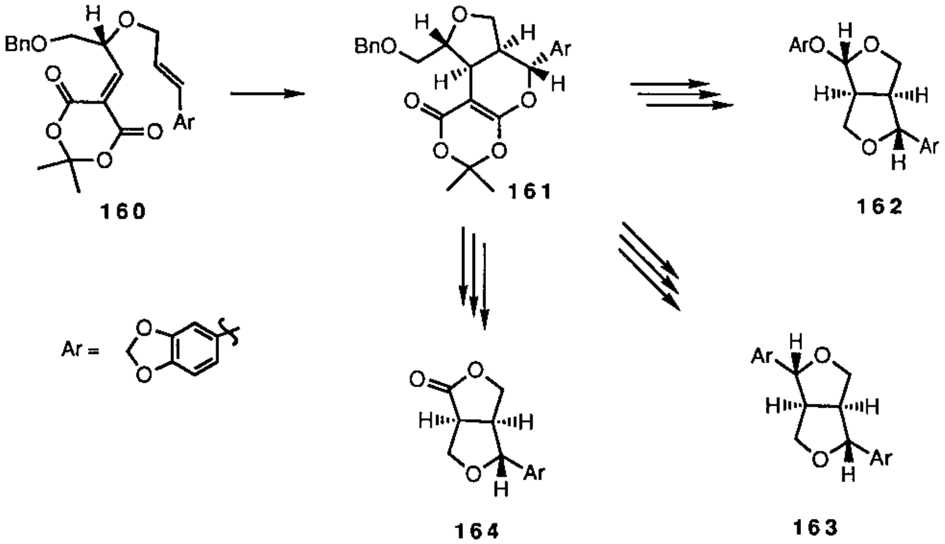
A number of natural products such as (-)-kainic acid (**156**) (Scheme 32),[136] deoxyloganin (**159**) (Scheme 33),[137] furofuran lignans (-)-sesamolin (**162**), (-)-sesamin (**163**), and (-)-acminatolide (**164**) (Scheme 34),[138] and heterosteroids (**167**) (Scheme 35)[139] have been synthesized enantioselectively by using these intramolecular hetero-Diels-Alder reaction as a key step.



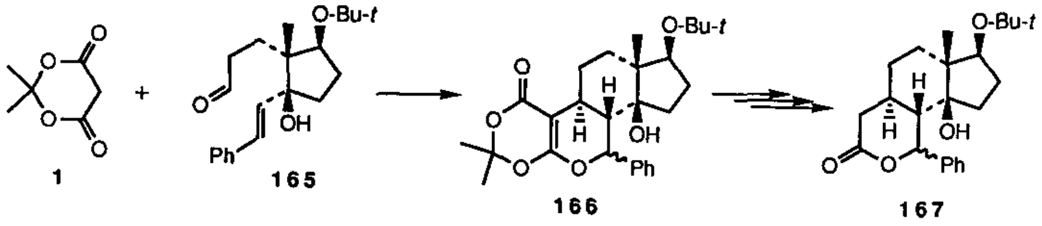
Scheme 32



Scheme 33

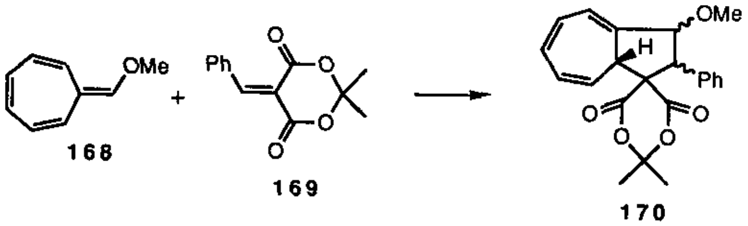


Scheme 34



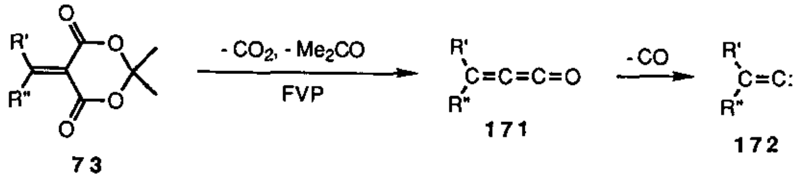
Scheme 35

3.2.3.2. [8+2] Cycloaddition. [8+2] Cycloaddition of 8-methoxyheptafulvene (**168**) with 5-phenylidene Meldrum's acid (**169**) was reported to give compound (**170**).[140]



3.2.4. Pyrolysis

Flash vacuum pyrolysis of **73** has long been known to give methyleneketenes which can afford methylenecarbenes when one molecule of carbon monoxide is lost. A number of extremely reactive methyleneketenes and methylenecarbenes that are difficult to obtain by conventional methods have been prepared and their properties studied.[141-151]



Scheme 36

This technology has made it possible to synthesize and characterize a number of theoretically interesting molecules (see Chart III).

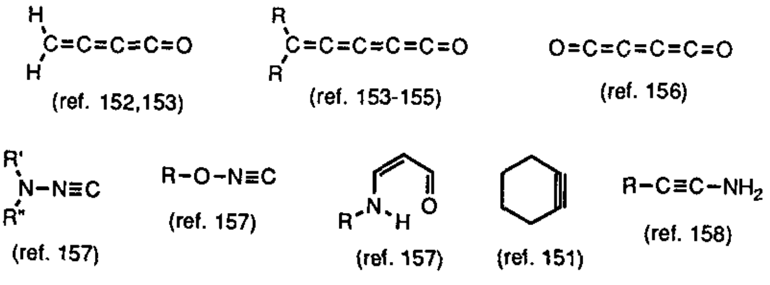


Chart III

More synthetically useful aspect about pyrolysis of 5-methylene Meldrum's acids is that intramolecular reaction may take place when a suitable trapping group is present in the molecule. Depending on the nature of the trapping group the reaction can sometimes occur at much lower temperature. A variety of heterocyclic compounds have been synthesized (see Chart VI).

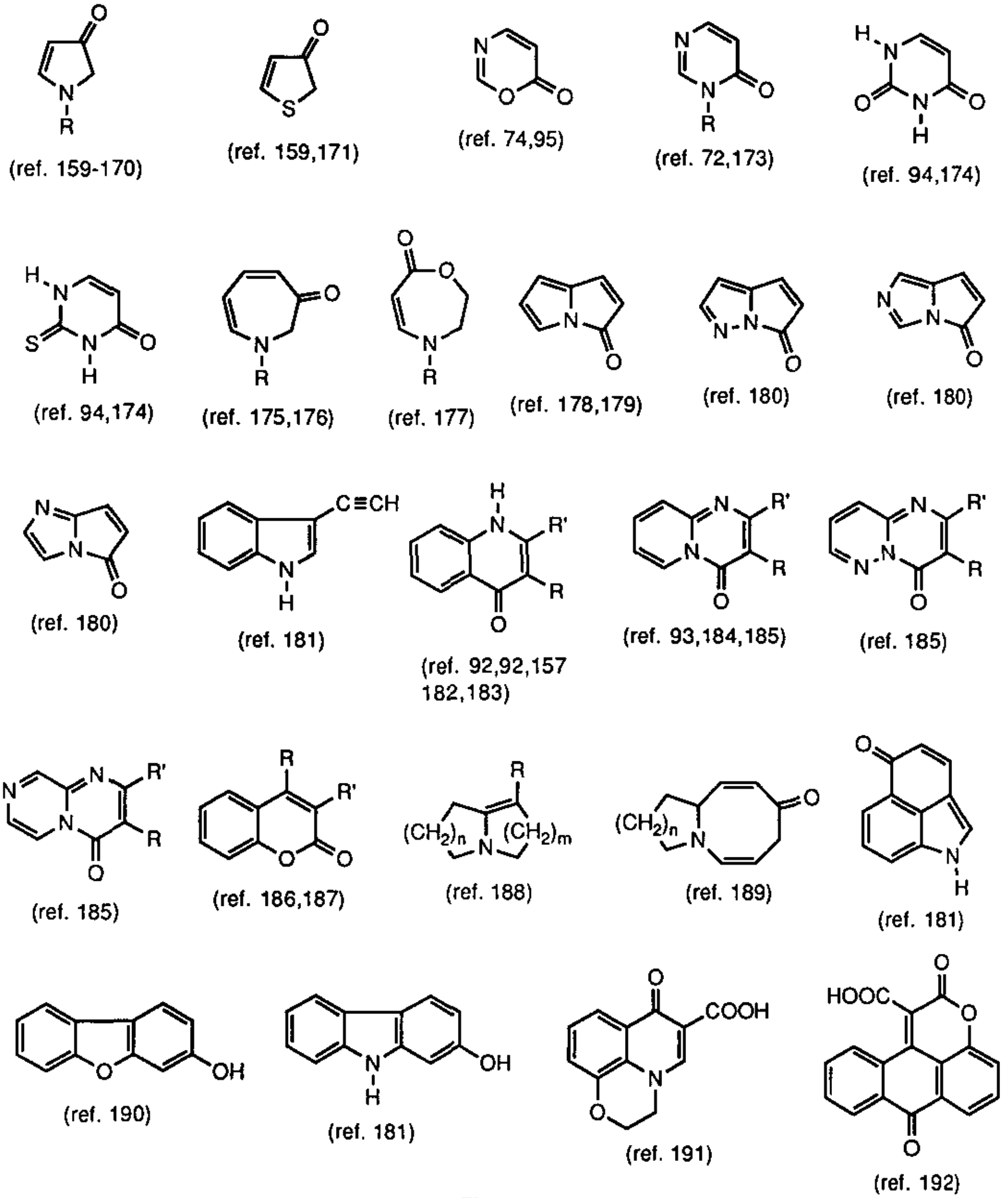
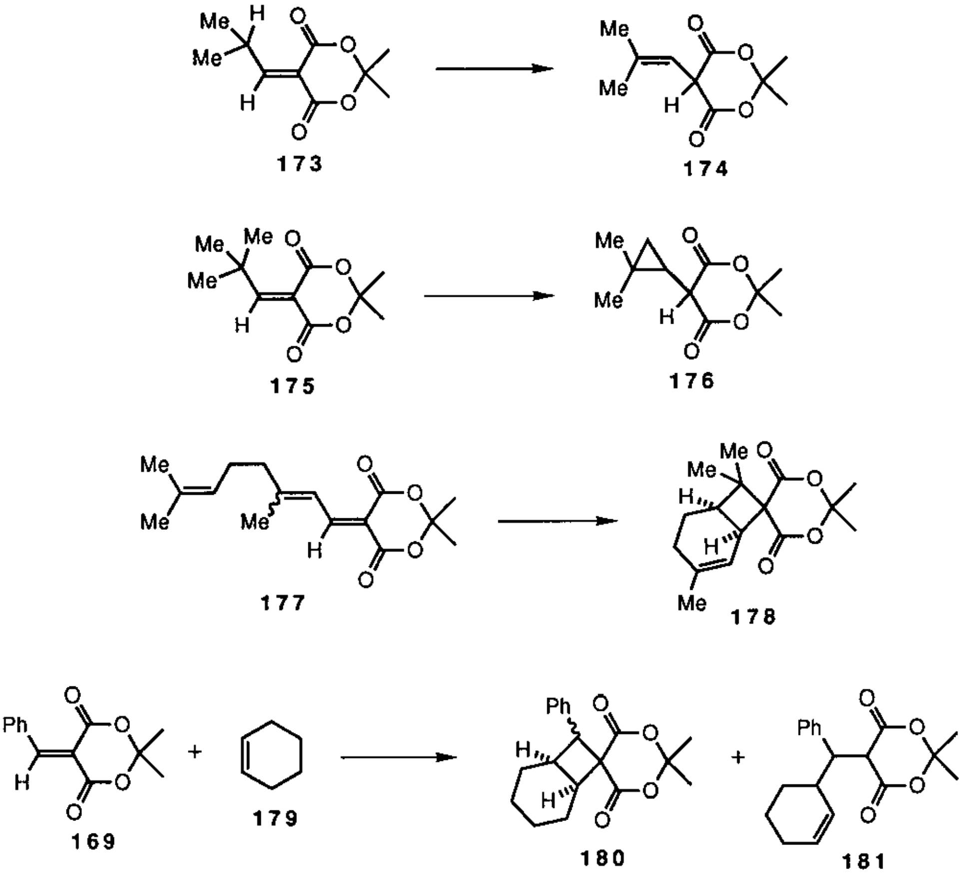


Chart VI

3.2.5. Photoreaction

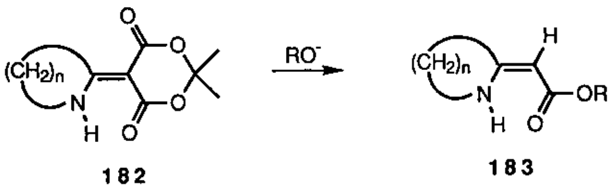
The photochemistry of 5-methylene Meldrum's acid resembles that of α,β-unsaturated esters. Observed reactions include deconjugation (**173** → **174**),[193] β,δ-cyclopropane ring closure (**175** → **176**),[193] and [2+2] cycloaddition (**177** → **178** and **169** → **180**)[193] as well as ene-type addition to olefins (**169** → **181**).[193,194]



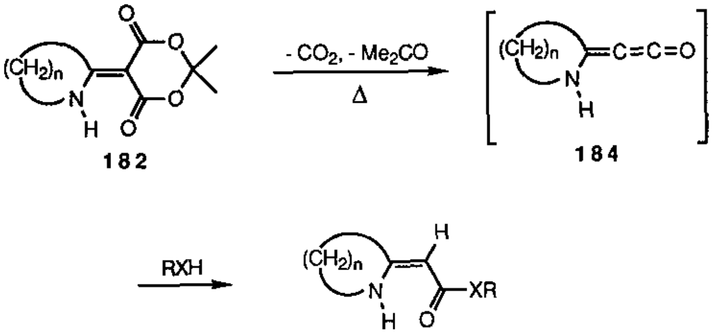
Scheme 37

3.2.6. Ring Opening Reaction

3.2.6.1. Formation of β-Amino-α,β-unsaturated Esters, Thioesters and Amides. When treated with alkoxide **182** can be converted to β-amino-α,β-unsaturated ester (**183**).[61,62,66-68,195-198]



Alternatively, **183** could be obtained by the thermal decomposition of **182** in the presence of an alcohol. When thiol or amine is used instead of alcohol β-amino-α,β-unsaturated thioesters (**183** X = S) or amides (**183** X = NR) were obtained.[199]

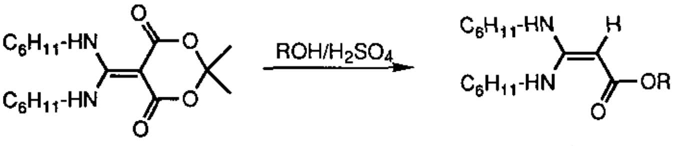


182 **184** **183**

X = O, S, NR

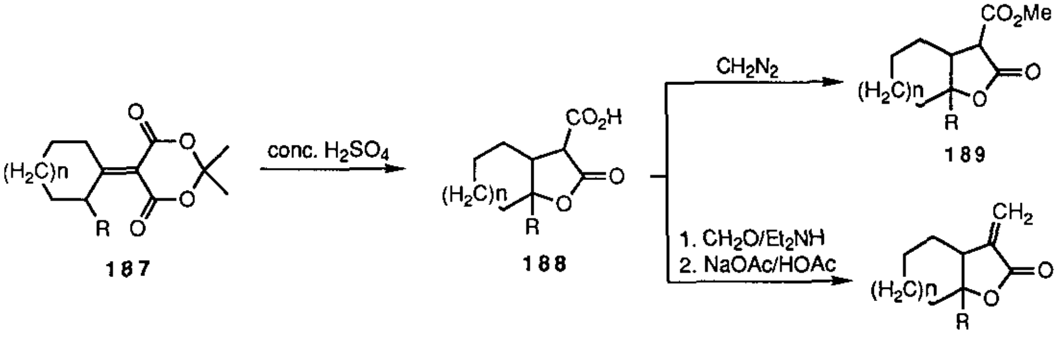
Scheme 38

β-Amino-α,β-unsaturated ester could also be obtained under acidic condition.[200]



185 **186**

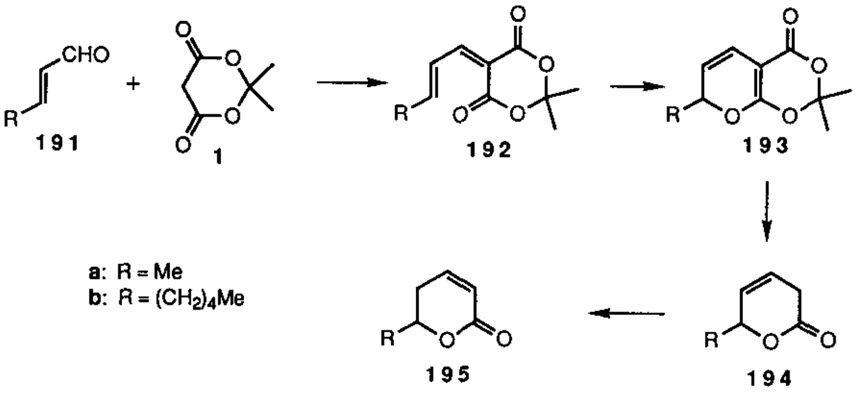
3.2.6.2. *Formation of Lactones.* Campaigne and Beckman[201-203] observed that when treated with concentrated H_2SO_4 5-methylene Meldrum's acids (**187**) could be converted into α-carboxy-γ-lactones (**188**) which were further converted to **189** and **190**.



187 **188** **189** **190**

Scheme 39

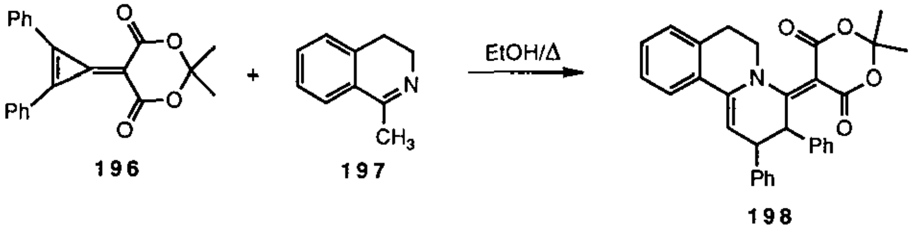
When crotonaldehyde (**191a**) and **1** was allowed to reflux in pyridine and HOAc in the presence of molecular sieves for 48 h (±)-parasorbic acid (**195a**) was obtained in 76% yield after distillation of the product mixture from K_2CO_3 (to isomerize **194** to **195**). Under same reaction conditions (±)-massoilactone (**195b**, dec-2-en-5-olide) was prepared in 59% yield from trans-oct-2-enal (**191b**).[204]



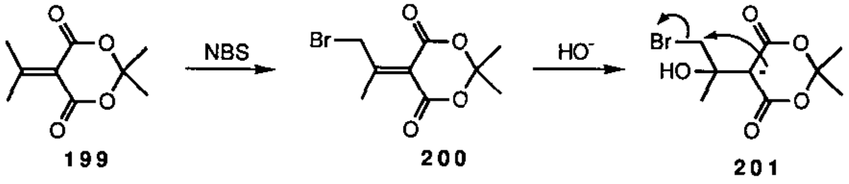
Scheme 40

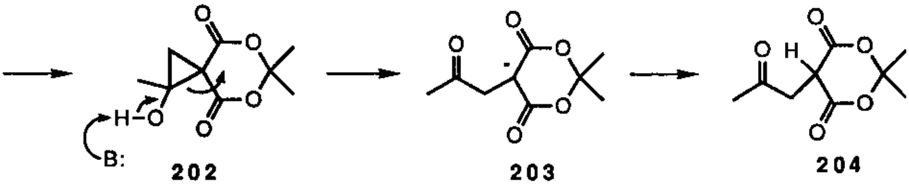
3.2.7. Miscellaneous

Reaction of **196** with 1-methyl-3,4-dihydroquinoline (**197**) gives rise to heterocyclic compound (**198**).[205]



Treatment of an ice-cooled solution of isopropylidene Meldrum's acid (**199**) in CCl_4 with 1.2 equiv. of NBS under irradiation from a 250 watt light bulb over a period of 10 h gave **200** which was treated with K_2CO_3 in aq. THF to afford on workup and recrystallization a single product (**204**) in 67% over all yield based on **199**.[206] The reaction was believed to take place through the intermediates (**201**), (**202**) and (**203**).

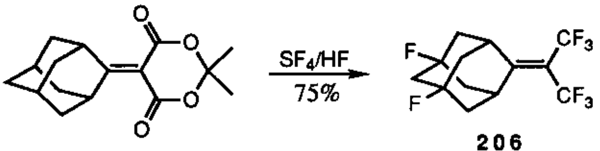




202 **203** **204**

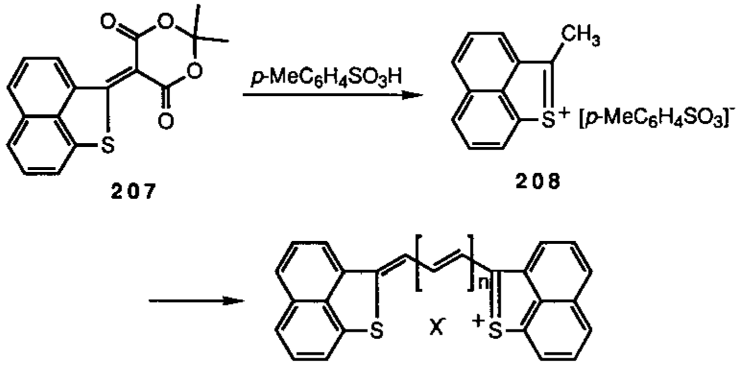
Scheme 41

Treatment of **205** with SF_4 in anhydrous HF gave 75% of **206**.[207]



205 **206**

Reaction of **207** with *p*-toluenesulfonic acid gave methylnaphthothiolium salt (**208**) which can be utilized to prepare symmetrical cyanine dyes (**209**).[75,208]

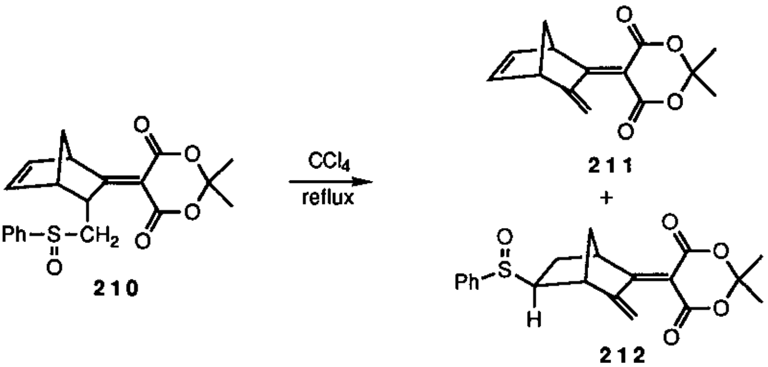


207 **208**

209

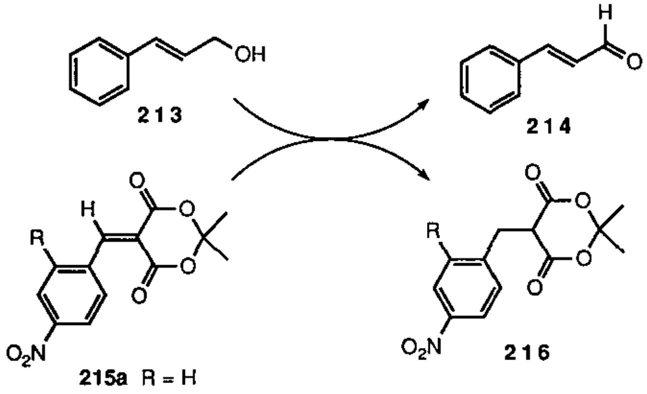
Scheme 42

Refluxing **210** in CCl_4 gave product (**211**) and (**212**), The latter was the re-addition product of benzenesulfenic acid from the initial thermal β-elimination to **211**.[209]



210 **211** **212**

5-(4'-Nitrobenzylidene) Meldrum's acid (**215a**) and 5-(2',4'-dinitrobenzylidene) Meldrum's acid (**215b**) were found to be moderate oxidant to convert cinnamyl alcohol (**213**) to the corresponding aldehyde (**214**).[210]



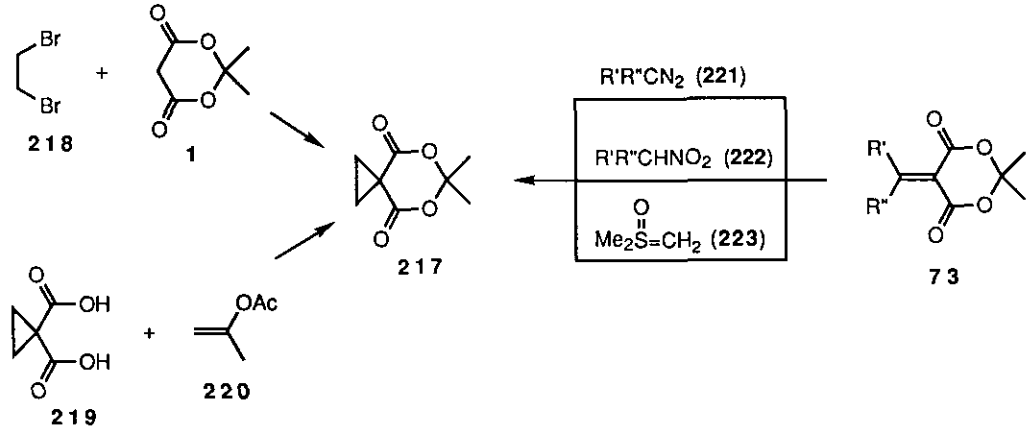
Scheme 43

4. 5-ETHYLENE MELDRUM'S ACIDS

5-Ethylene Meldrum's acids (**217**, 6,6-dimethyl-5,7-dioxaspiro[2,5]octane-4,8-dione) are a special class of 5,5-dialkyl Meldrum's acids. Because of the existence of the three member ring strains the chemical behavior of **217** is very close to 5-methylene Meldrum's acids.

4.1 *Preparation*

Several methods have been developed for the preparation of 5-ethylene Meldrum's acids (**217**). These include the alkylation of Meldrum's acid (**1**) with 1,2-dibromoethane (**218**),[7] the condensation of cyclopropane 1,1-dicarboxylic acid (**219**) with isopropenyl acetate (**220**),[211] the reaction of 5-methylene Meldrum's acid (**73**) with diazo alkane (**221**),[2,212] nitroalkane (**222**),[213] and sulfoxonium ylide (**223**).[212]

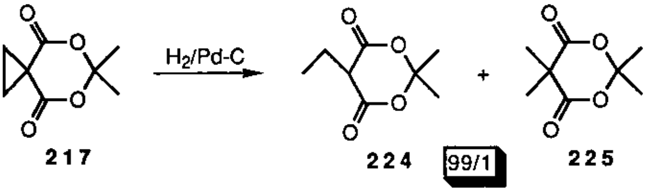


Scheme 44

4.2. *Reaction*

4.1.2. *Hydrogenation*

Hydrogenation of 5-ethylene Meldrum's acid (**217**) gave mainly 5-ethyl Meldrum's acid (**224**) along with trace amount of 5,5-dimethyl Meldrum's acid (**225**).[214]

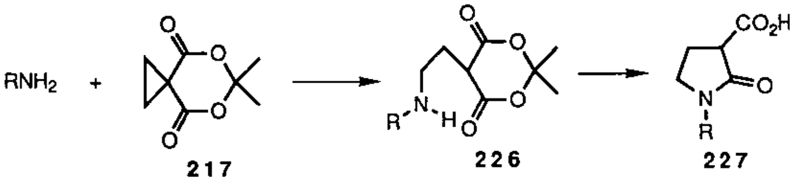


4.2.2. *Homoconjugated Addition (Propane Ring Opening)*

5-Ethylene Meldrum's acid (**217**) is an example of activated electrophilic cyclopropanes.[215] It can undergo homoconjugated addition to a variety of nucleophiles.

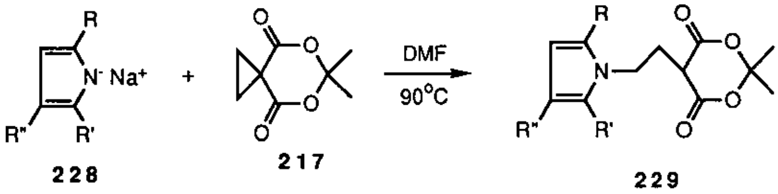
4.2.2.1. *With Nitrogen Nucleophiles.*

4.2.2.1.1. With Amines. Amines readily react with 5-ethylene Meldrum's acid (**217**) resulting in the ring opening of cyclopropane ring to give the intermediate (**226**) which subsequently cyclizes to α-carboxy-γ-lactam (**227**).[211,216]

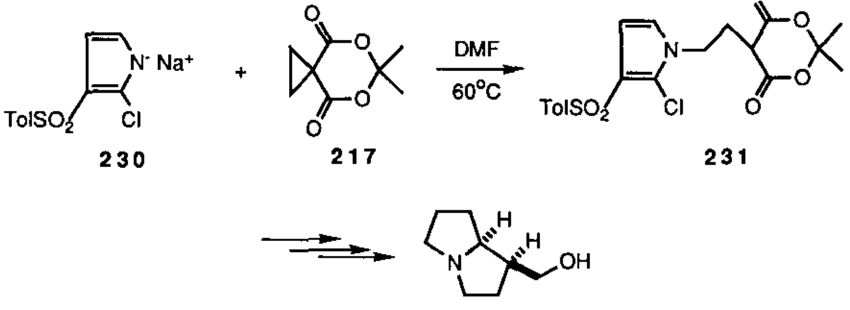


Scheme 45

4.2.2.1.2. With Pyrroles. When the sodium salts of pyrroles (**228**) and 5-methylene Meldrum's acid (**217**) were heated in DMF at 90°C compounds (**229**) were formed.[217]



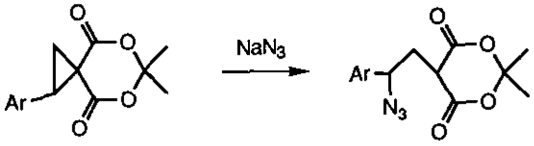
The above reaction has been used in the total synthesis of (+)-isoretronecanol (**232**).[218]



230 **217** **231** **232**

Scheme 46

4.2.2.1.3. With Sodium Azide. Sodium azide reacts with 1-aryl-6,6-dimethyl-5,7-dioxaspiro[2,5]octane-4,8-diones (**233**) to give 5-(2-azido-2-arylethyl) Meldrum's acids (**234**).[212]

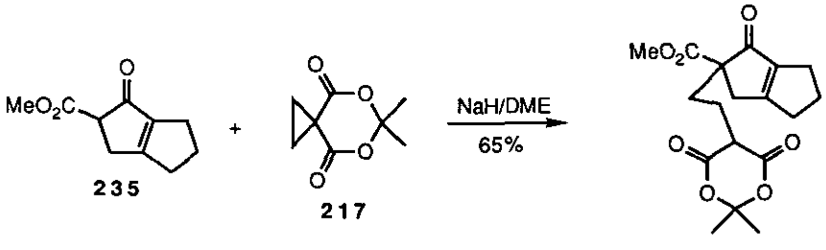


233 **234**

Ar = Ph, p-MeOC$_4$H$_6$, p-NO$_2$C$_4$H$_6$

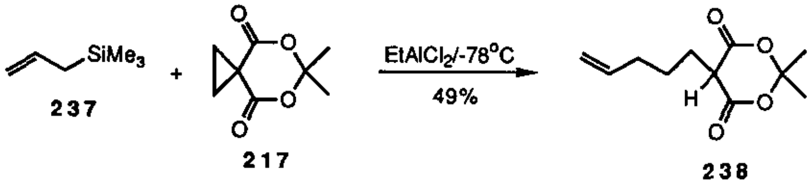
4.2.2.2. With Carbon Nucleophiles

4.2.2.2.1. With Enolate. The sodium enolate of β-keto ester (**235**) reacts smoothly with **217** in DME at room temperature producing the adduct (**236**) in 65% yield.[219,220]



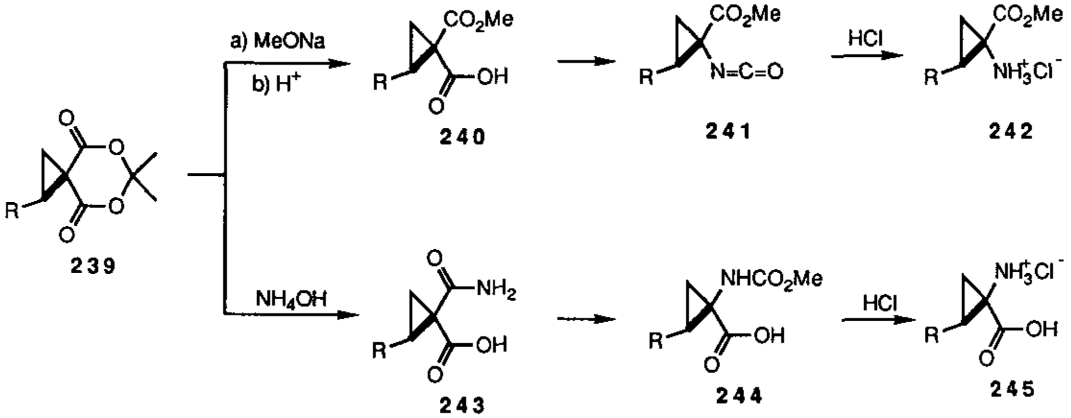
235 **217** **236**

4.2.2.2.2. With Allyltrimethylsilane. Treatment of allyltrimethylsilane (**237**) with **217** in the presence of ethylaluminium dichloride at -78°C afforded the homoconjugated addition product (**238**) in 49% yield.[221]



4.2.3. 1,3-Dioxane-4,6-dione Ring Opening Reaction

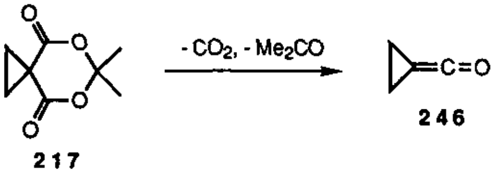
Treatment of 1-aryl(alkyl)-6,6-dimethyl-5,7-dioxaspiro[2,5]octane-4,8-diones (**239**) with sodium methoxide or ammonium hydroxide gave exclusively E-1-methoxy-carboyl-2-aryl-cyclopropanecarboxylic acids (**240**) or Z-1-carbamoyl-2-aryl(alkyl)cyclopropanecarboxylic acids (**243**) respectively. Compounds (**240**) under conditions of Curtius-type reaction, yielded Z-methyl 1-isocyanate-2-arylcyclopropanecarboxylate (**241**), while the derivatives (**243**) could be treated with hypobromite, leading to E-1-methoxycarbonylamino-2-aryl(alkyl)-cyclopropanecarboxylic acids (**244**). Reaction of **241** and **243** with HCl produced the corresponding Z- and E-1-amino-2-aryl(alkyl)cyclopropanecarboxylic acids hydrochlorides (**242**) and (**245**) respectively.^{212}



Scheme 47

4.2.4. Pyrolysis

Pyrolysis of 5-ethylene Meldrum's acid (**217**) was reported to generate ethyleneketene (**246**).^{222}

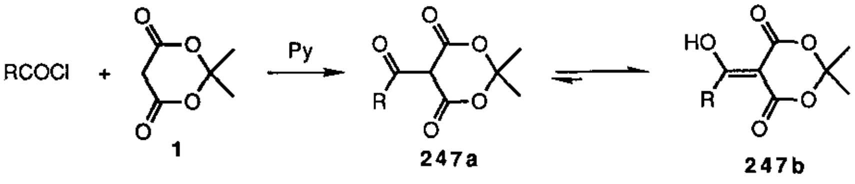


5. 5-ACYL MELDRUM'S ADCIDS

5.1 *Preparation*

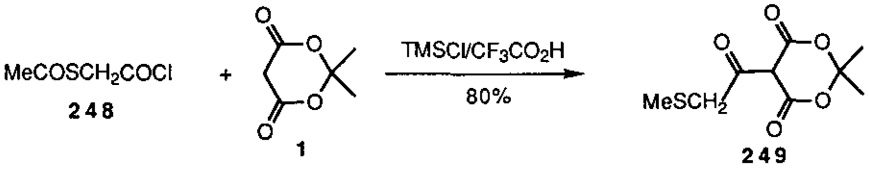
5.1.1. With Acyl Chlorides

In 1978 Yonemitsu and coworkers[223,224] reported for the first time the preparation of 5-acyl Meldrum's acids (**247**). When a dichloromethane solution of **1** was treated with 1.1 equiv. of acyl chloride in the presence of 2 equiv. of pyridine at 0°C for 1 h and then room temperature for 1 h under nitrogen, an acyl Meldrum's acid (**247**) was isolated in almost quantitative yield.



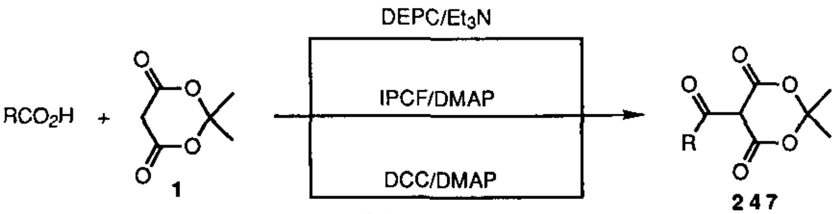
In contrast to alkylation of Meldrum's acid only monoacylation was observed under the reaction conditions. The 5-acyl Meldrum's acid was found to exist exclusively in the enol form (**247b**). Other base such as DMAP can be used instead of pyridine.[225,226]

Acylation of Meldrum's acid with acyl chloride can also be performed under acidic condition. For example reaction of **1** with **248** in CH_2Cl_2 containing TMSCl and CF_3CO_2H at 0°C for 1 h and room temperature for 1 h was reported to give **249** in 80% yield.[227]



5.1.2. With Carboxylic Acids

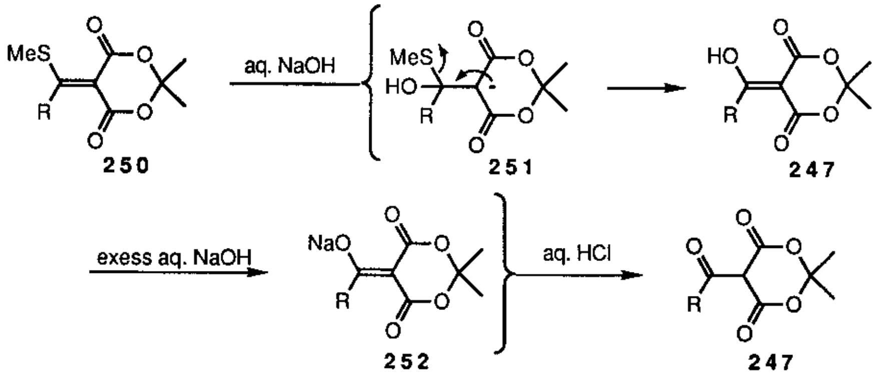
By use of diethyl phosphorocyanidate (DEPC),[228,229] DCC[230] or isopropenyl chloroformate (IPCF)[231] together with base such as triethylamine and DMAP, carboxylic acid can be directly used to acylate Meldrum's acid.



Scheme 48

5.1.3. Basic Hydrolysis of 5-Methylthioalkylidene Meldrum's Acids

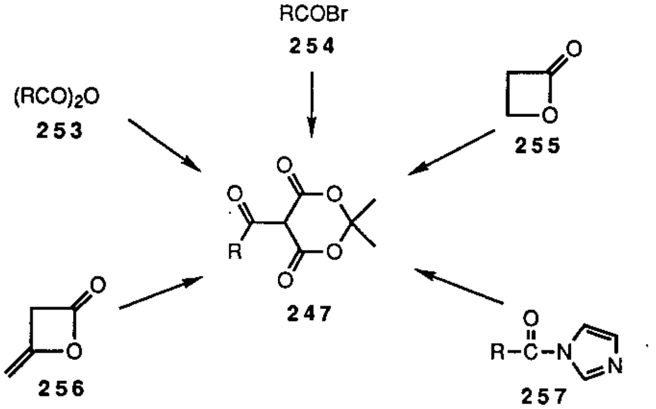
Basic hydrolysis of 5-methylthioalkylidene Meldrum's (**250**) acids is another approach to 5-acyl Meldrum's acid derivatives (**247**).[232] Michael-type addition of hydroxide to **250** generates the intermediate (**251**) which eliminates methyl sulfide anion followed by deprotonation by excess hydroxide to give the thermodynamically stable enolate (**252**). The deriving force for this basic hydrolysis could be the formation of the stable enolate (**252**). Upon acidification the acyl Meldrum's acids (**247**) is regenerated.



Scheme 49

5.1.4. Miscellaneous

Carboxylic anhydride (**253**),[233] acyl bromide (**254**),[234] β-lactone (**255**),[235] diketene (**256**),[236,237] and acyl imidazolide **257**[238] have also been used successfully as acylating reagents.

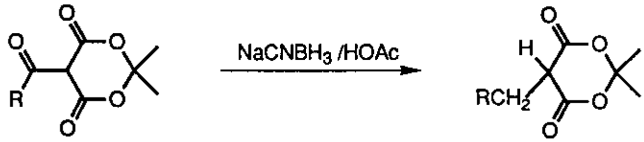


Scheme 50

5.2 Reaction

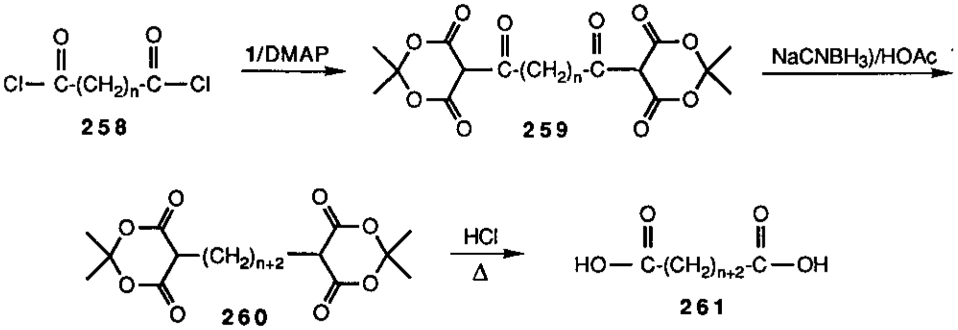
4.2.1. Reduction

Reduction of 5-acyl Meldrum's acids (**247**) with sodium cyanoborohydride[228,239] in acetic acid was reported to give 5-monoalkyl Meldrum's acids (**2**). The reductions take place upon addition of two equiv. of sodium cyanoborohydride to a mixture of the acyl compound (**247**) and acetic acid affording **2** in good to excellent yield. This reductive transformation completes another synthetic method for the preparation of 5-monoalkyl Meldrum's acid.



247 **2**

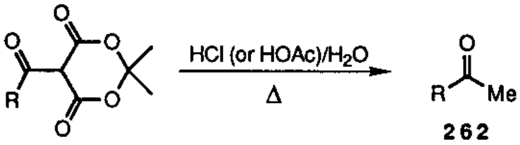
The reaction has been nicely utilized by Obaza and Smith[226] in the homologation of carboxylic acids (Scheme 51).



Scheme 51

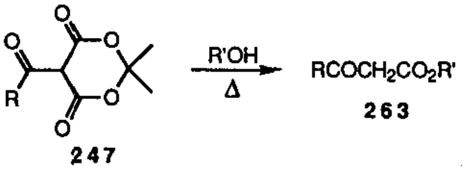
5.2.1 Ring Opening Reactions

5.2.1.1. With Dilute Acids. Refluxing 5-acyl Meldrum's acids (**247**) under in dilute HCl or HOAc causes cleavage of the 1,3-dioxane-4,6-dione ring and subsequent decarboxylation affording methyl ketones (**262**).[240-243] This is a non-organometallic method for the synthesis of methyl ketones from acyl chloride.



247 **262**

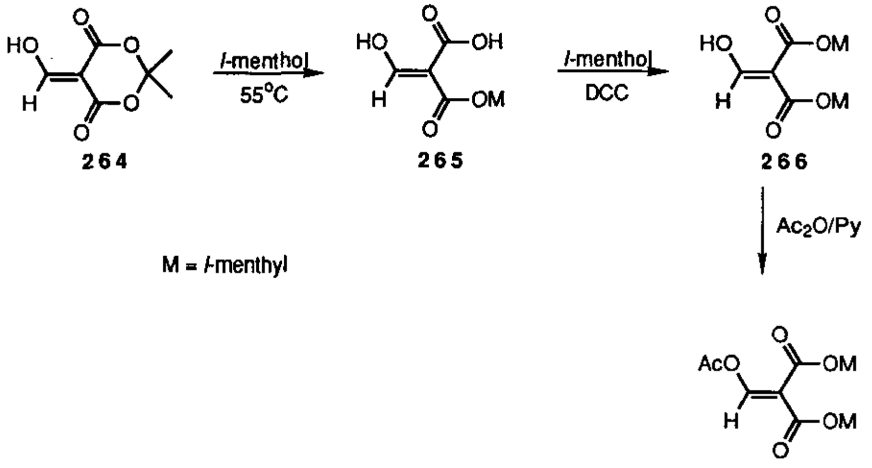
5.2.2.2. With Alcohols. Heating 5-acyl Meldrum's acids (**247**) in the presence of an alcohol is a facile method to prepare β-keto esters (**263**).[223,224,233]



247

This methodology has been extensively used in organic synthesis[2,227,238,244-273] including the total synthesis of a number of natural products such as marine metabolite dysidin[274,275] and cytotoxic cyclic peptides didemnins A and B.[229]

Reaction of 5-formyl Meldrum's acid (**264**) with *l*-menthol in benzene at 55°C for 2 h gave a half ester (**265**) in quantitative yield. In this reaction, prolonged heating or higher temperature resulted in the formation of *l*-menthyl formylacetate. Condensation of **265** with *l*-menthol using DCC gave the diester (**266**) as a crystalline substance, which can be acetylated in a usual manner to give the chiral dienophile (**267**).[276-278]

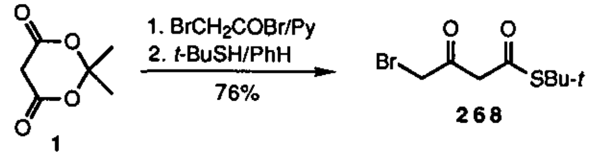


264 **265** **266** **267**

M = *l*-menthyl

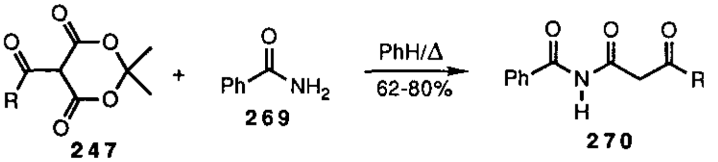
Scheme 52

5.2.2.3. With Thiol. Reaction of 5-acyl Meldrum's acid with thiol has also been reported to give β-keto thioester (**268**).[234]



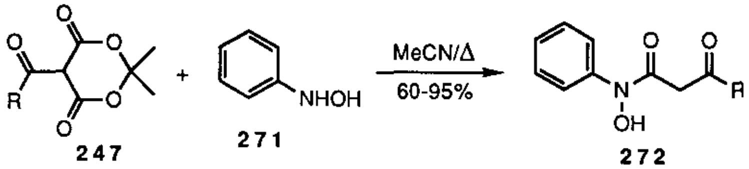
1 **268**

5.2.2.4. With Amides. Ring opening of 5-acyl Meldrum's acids (**247**) with benzamide (**269**) in refluxing benzene gave *N*-acylacetylbenzamides (**270**).[279]



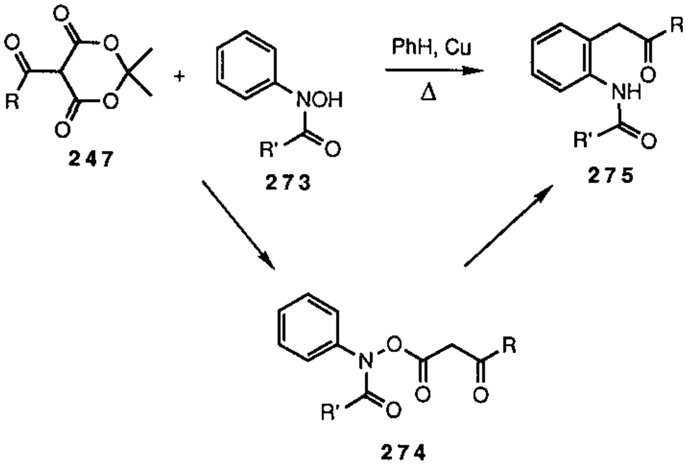
R = Et, *i*-Pr, $BrCH_2$, $PhCH_2$, Ph

5.2.2.5. With Hydroxyamine. Phenylhydroxyamine (**271**) reacts with 5-acyl Meldrum's acids (**247**) in acetonitrile to give *N*-acylacetylphenylhydroxyamines (**272**).[280]



R = Me, Et, *i*-Pr, $X(CH_2)_n$, $PhCH_2$, Ph

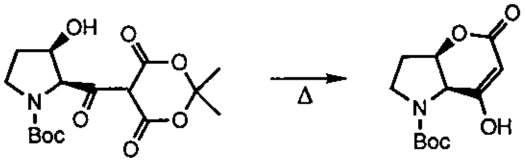
When *N*-acyl phenylhydroxyamines (**273**) were refluxed with 5-acyl Meldrum's acid in benzene in the presence of copper compound (**275**) were obtained.[281] The reaction was believed to proceed through the *O*-acylacetylation intermediate (**274**) which underwent 1-aza-1'-oxa[3,3]sigmatropic rearrangement to **275**.



Scheme 53

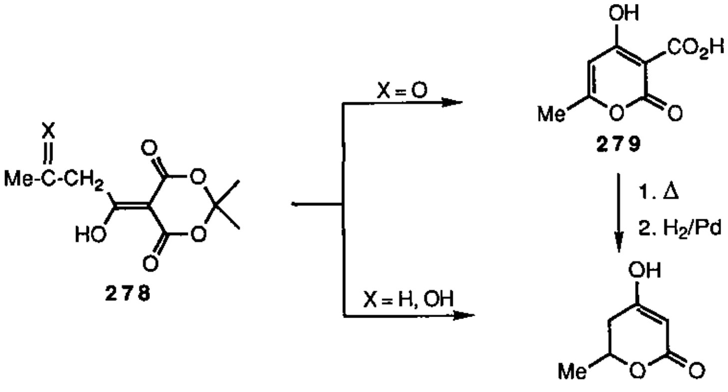
5.2.3. *Intramolecular Ring Opening Reactions*

5.2.3.1. Lactone Formation. When an intra-hydroxy group is present in 5-acyl Meldrum's acid, intramolecular ring opening may occur producing lactones. For example upon heating 5-(β-hydroxy-acyl) Meldrum's acid (**276**) gives lactone (**277**).[235]



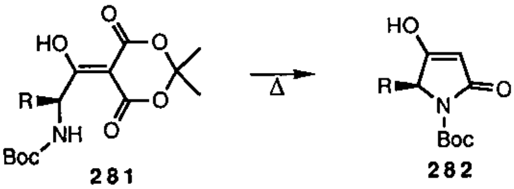
276 **277**

5-(β-Oxoacyl) and 5-(β-hydroxy-acyl) Meldrum's acid (**278**) were found to undergo intra-molecular ring opening reaction also (Scheme 53).[236,237]



Scheme 54

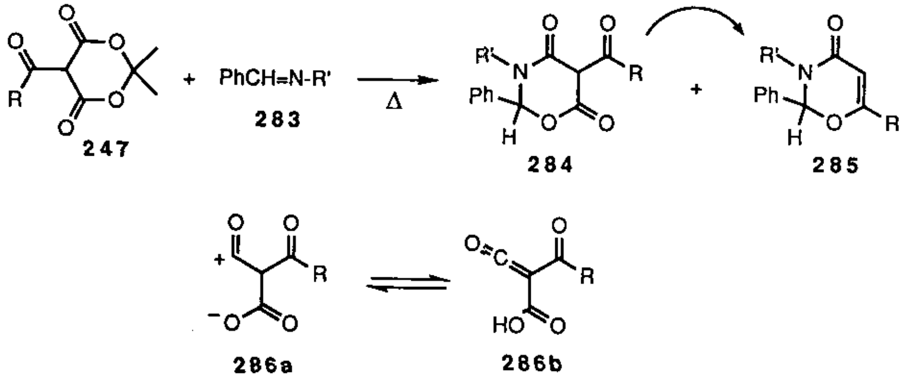
5.2.3.2. Lactam Formation. Similarly when an amino group is present, lactam (**282**) is obtained.[231,282]



281 **282**

5.2.4. Miscellaneous

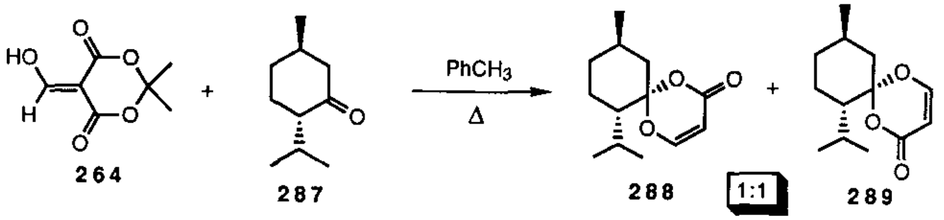
5.2.4.1. With Schiff Bases. Reaction of Schiff bases (**283**) with various 5-acyl Meldrum's acids (**247**) in refluxing benzene caused an exchange reaction of the acetone moiety of acyl Meldrum's acid with the Schiff base moiety through the intermediate acylketenes (**286b**) formed *in situ* from **247** to give 2,3-disubstituted 5-acyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazine-4,6-diones (**284**). The oxazindiones (**284**) could undergo thermal conversion to afford 2,3,6-trisubstituted 2,3-dihydro-1,3-oxazin-4-ones (**285**) in good yield.[283,284]



Scheme 55

Cyclic imino esters and oxazoline underwent similar reactions.[285]

5.2.4.2. With Ketone. Reaction of 5-formyl Meldrum's acid **264** with *l*-menthone **287** in refluxing toluene for 0.5 h gave 27% of **288** and **289**, useful chiral dienophiles.[286]

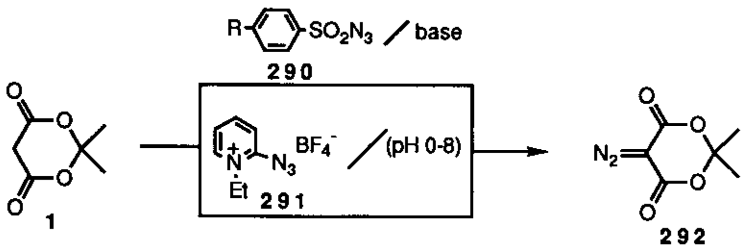


6. 5-HETERO-ATOM SUBSTITUTED MELDRUM'S ACIDS

6.1 *5-Nitrogen Substituted Meldrum's acids*

6.1.1. 5-Diazo Meldrum's acid

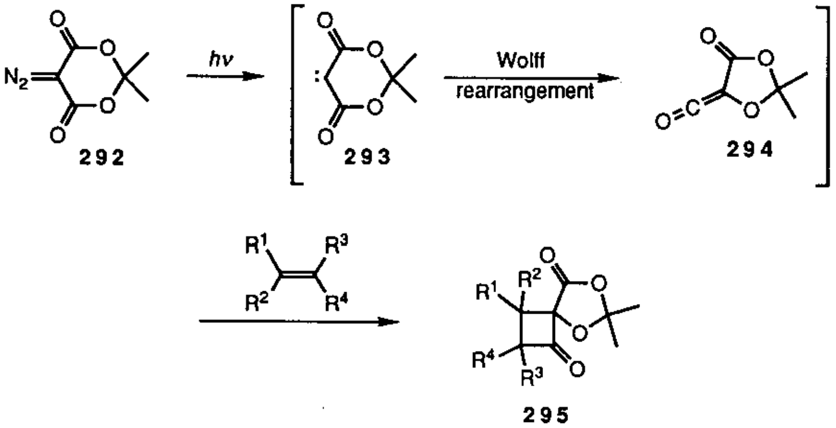
6.1.1.1. Preparation. 5-Diazo Meldrum's acid (**292**) can be readily prepared by direct reaction of Meldrum's acid (**1**) with arylsulfonyl azide (**290**) in the presence of a base.[2,270,287,288] Alternatively it can be obtained under acidic or neutral conditions by using azidinium salts (**291**) as diazo-group transfer reagents.[289,290]



Scheme 56

6.1.1.2. Reaction. Photolysis or thermolysis of 5-diazo Meldrum's acid (**292**) generates "Meldrum's carbene" (**293**) which may undergo Wolff rearrangement to give rise to ketene (**294**).[2,291,292]

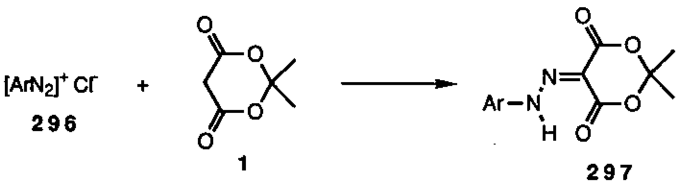
Reaction of **292** with olefin under direct irradiation (253.7 nm) was initially thought to afford spirocyclopropanes.[293,294] However X-ray crystallographic analysis revealed that the product turned to be cyclobutanones (**295**). This result can be rationalized in terms of formation of ketene (**294**) which undergoes a remarkable regio- and stereospecific cycloaddition to olefin to give cyclobutanone (**295**).[295]



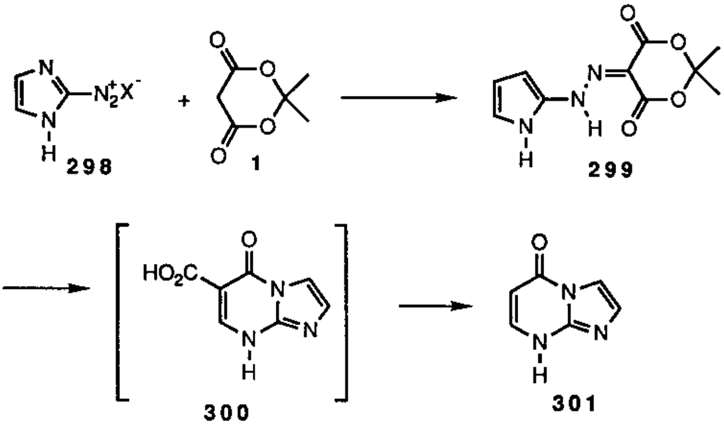
Scheme 57

6.1.2. 5-Hydrazono Meldrum's Acids

6.1.2.1. Preparation. Reaction of Meldrum's acid with (**1**) diazonium salts (**296**) gives 5-hydrazono Meldrum's acids (**297**).[296]



6.1.2.2. Reaction. Coupling between **298** and Meldrum's acid (**1**) occurred instantaneously to give **299** which can cyclizes and decarboxylates to afford product (**301**) in very good overall yield.[297] The whole reaction could be carried in 'one pot' fashion.

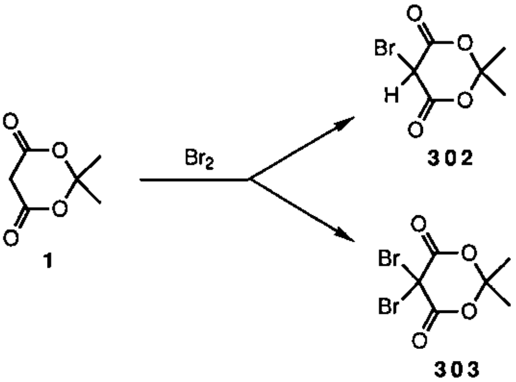


Scheme 58

6.2 *5-Halogen Substituted Meldrum's Acids*

6.2.1 *5-Bromo Meldrum's Acids*

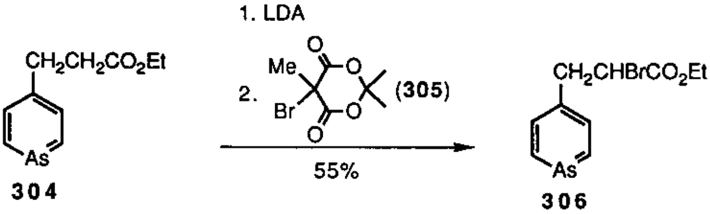
6.2.1.1. Preparation. Both 5-bromo and 5,5-dibromo Meldrum's acids (**302**) and (**303**) can be formed by direct bromonation of MA in the presence of one or two moles of base respectively.[2]



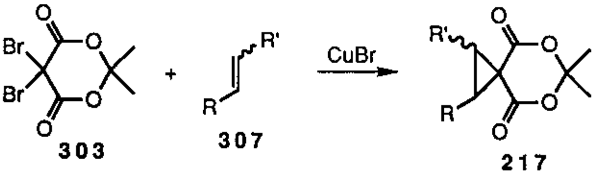
Scheme 59

6.2.1.2. Reactions. 5-Bromo Meldrum's acids were found to be mild and selective brominating reagents.[298-301] For example 4-(2-ethoxycarbonylethyl)arsabenzene (**304**) can be brominated by using 5-methyl-5-bromo

Meldrum's acid (**305**) as brominating reagent to give **306** in 55% yield.[300] Under other brominating conditions the arsabenzene ring suffers.

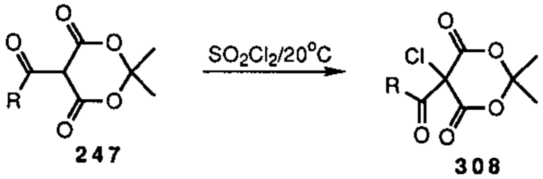


Reaction of 5,5-dibromo Meldrum's acid (**303**) with olefins (**307**) in the presence of CuBr gave 5-ethylene Meldrum's acid derivatives (**217**).[302]

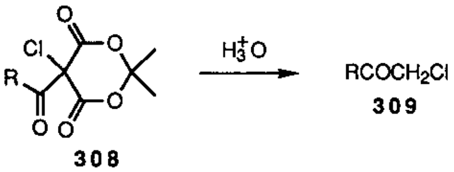


6.2.2. *5-Chloro Meldrum's Acid*

6.2.2.1. Preparation. 5-Acyl Meldrum's acid (**247**) reacts with SO_2Cl_2 to give 5-chloro-5-acyl Meldrum's acid (**308**).[303,304]



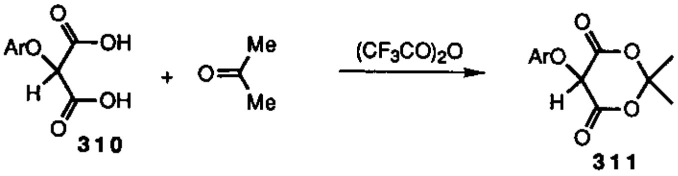
6.2.2.2. Reaction. Hydrolysis of **308** was found to give α-chloro ketone (**309**).[303,304]



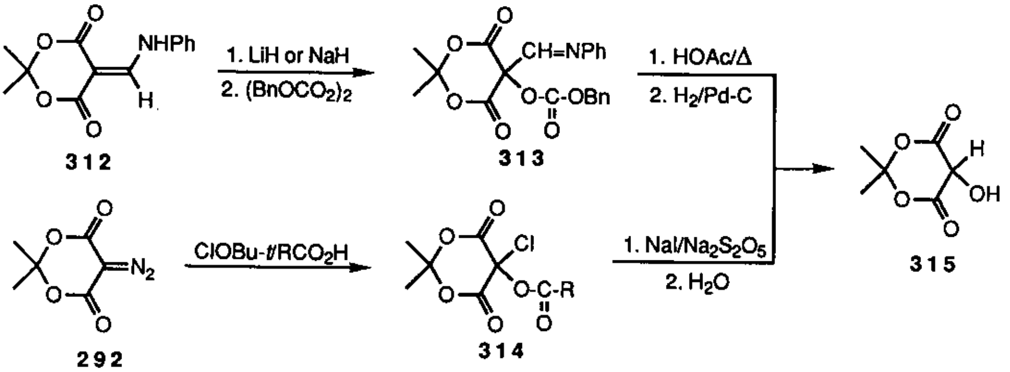
6.3 *5-Oxygen Substituted Meldrum's Acids*

6.3.1. *5-Hydroxy Meldrum's Acids*

6.3.1.1. Preparation. 5-Aryloxy Meldrum's acid (**311**) can be prepared by the reaction of aryloxymalonic acid (**310**) and acetone in trifluoroacetic anhydride.[305]

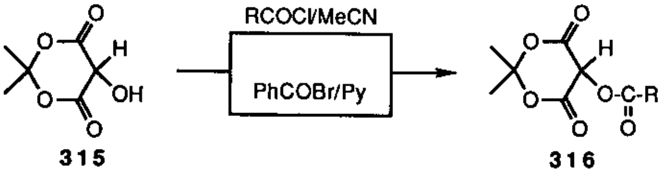


The parent 5-hydroxy Meldrum's acid (**315**) however was prepared later by Schank and coworkers[306,307] according to the following Scheme.



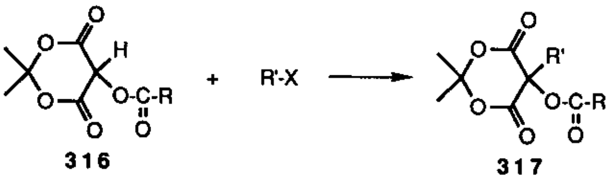
Scheme 60

6.3.1.2. Reaction. 5-Hydroxy Meldrum's acid (**315**) reacts with acyl chloride[306] or bromide[308] to give 5-acyloxy Meldrum's acid (**316**).

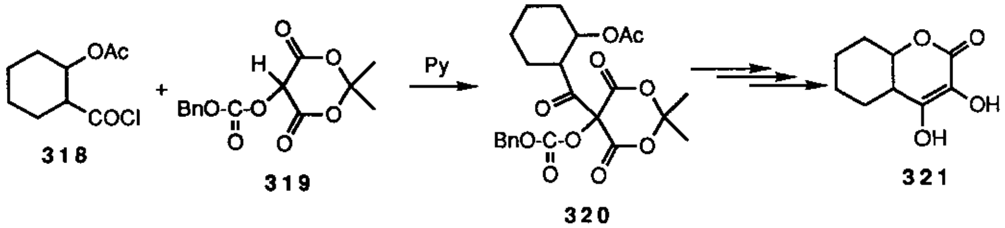


Scheme 61

Like 5-monoalkyl Meldrum's acid 5-acyloxy Meldrum's acid can be further alkylated to give 5-alkyl-5-acyloxy Meldrum's acid (**317**).[308]

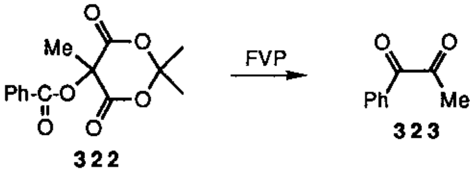


Acylation of 5-acyloxy Meldrum's acid (**316**) has also been reported. For example reaction of the acyl chloride (**318**) with **319** gives product (**320**) which can be subsequently converted to hexahydrobenzopyranone *aci*-reductones (**321**).309



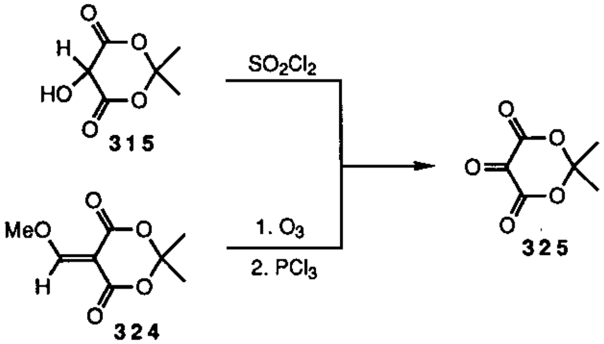
Scheme 62

Flash vacuum pyrolysis of **322** gave 1-phenyl-propane-1,2-dione (**323**).308



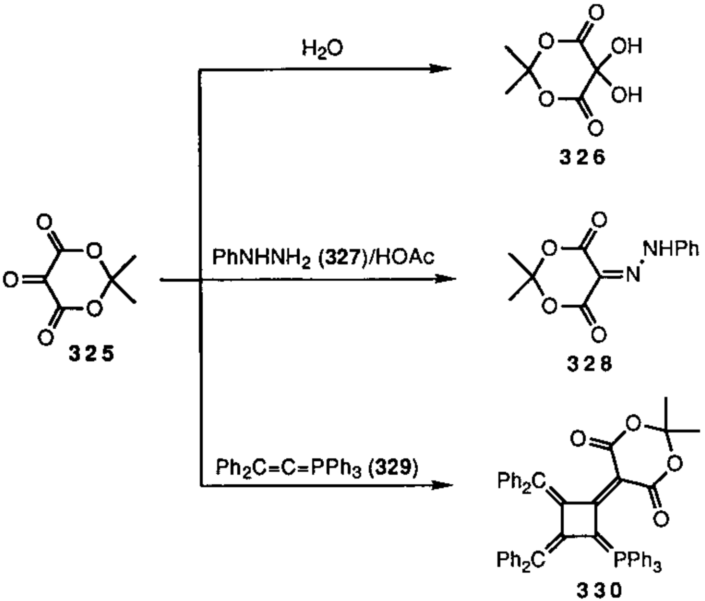
6.3.2. *5-Oxy Meldrum's Acid*

6.3.2.1. Preparation. 5-Oxy Meldrum's acid (**325**) can be prepared by the reaction of 5-hydroxy Meldrum's acid (**315**) with $SO_2Cl_2$306 or by the ozonolysis310 of 5-methoxymethylene Meldrum's acid (**324**).

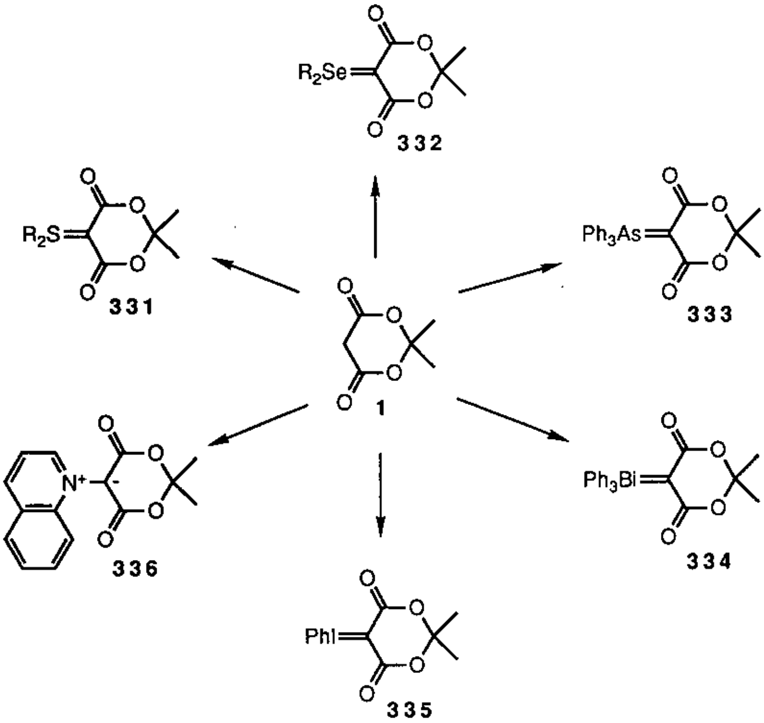


Scheme 63

6.3.2.2. Reaction. Reaction of 5-oxy Meldrum's acid (**325**) with H_2O gave 5,5-dihydroxy Meldrum's acid (**326**) and reaction with phenylhydrazine (**327**) in acidic acid gave **328**.306 More recently it was found that reaction of **325** with cumulated ylide (**329**) afforded **330** in 6.9% yield.311 The structure of **330** was confirmed by an X-ray diffraction study.



Scheme 64



Scheme 65

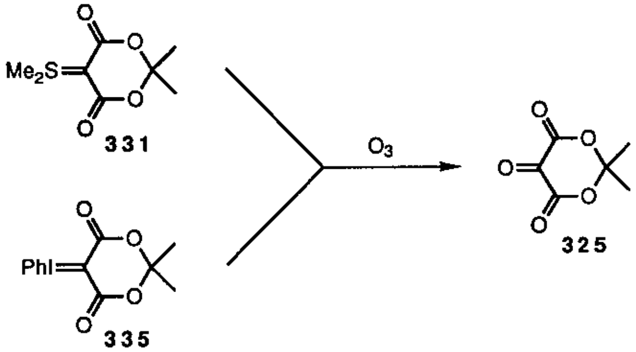
6.4 *Ylides*

6.4.1. Preparation

A number of ylides of Meldrum's acid have been prepared. These include sulfonium (**331**),[2,312,313] selenium (**332**),[2] arsonium (**333**),[2,314] bismuthonium (**334**),[315,316] and iodonium (**335**)[2,317-319] ylides and *N*-ylide (**336**) (Scheme 65)[35]

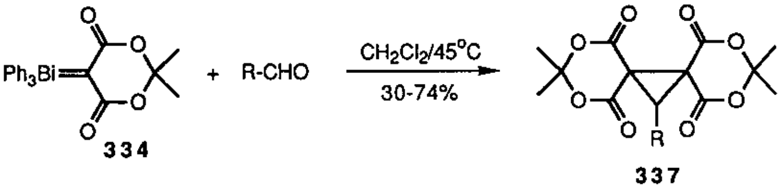
6.4.2. Reaction

Reaction of the sulfonium (**331**)[320] and iodonium (**335**)[319] ylides of Meldrum's acid with ozone gave 5-oxy Meldrum's acid (**325**) in very good yield.

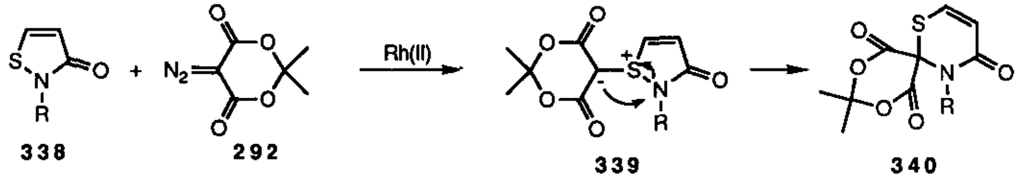


Scheme 66

Reaction of bismuthonium ylide (**334**) with aldehydes gave tetraacylcyclopropanes (**337**) in moderate to good yield.[316] The cyclopropane product (**337**) was believed to arise from a second reaction of **334** with the originally formed normal Wittig reaction product 5-alkylidene Meldrum's acids which in some cases could be isolated.



Refluxing *N*-substituted isothiazol-3-ones (**338**) with 5-diazo Meldrum's acid in the presence of catalytic amount of rhodium(II) acetate in benzene causes ring transformation of **338** to 3,4-dihydro-1,3-thiazin-4(2*H*)-ones (**340**) in high yield.[321] The most likely mechanism for the conversion of **338** to **340** may involve the trapping of a carbene or carbenoid species to form an intermediate sulfonium ylide (**339**), which undergoes ring expansion by a 1,2-shift to give final product (**340**).



R = Et, 74%
R = CO_2Me, 95%

Scheme 67

7. SUMMARY

Since the discovery and especially the correct structure assignment[3] Meldrum's acid has been widely used in organic synthesis. A number of novel reactions associated with the rigid ring structure of Meldrum's acid have been identified which have not been documented in the chemistry of acyclic malonates. On the other hand, however, some seemingly obvious but important transformations such as the 1,3-dioxane-4,6-dione ring opening reaction with carbanion[322] have been surprisingly less studied. It is hoped that this review will stimulate more interest in the development of existing and new applications for Meldrum's acid in organic synthesis.

ACKNOWLEDGEMENT

It is a great pleasure to acknowledge Professors Xiang Huang and Franklin A. Davis for their encouragements.

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Received, 25th December, 1990