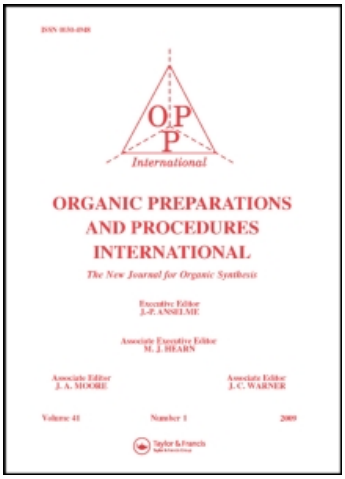

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Pavel F. Vlad[a]; Miron Z. Krimer[a]
[a] Academy of Sciences of Moldova, Institute of Chemistry, Kishinev, Republic of MOLDOVA

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Pavel F. Vlad* and Miron Z. Krimer

Institute of Chemistry, Academy of Sciences of Moldova
MD-2028 Kishinev, Republic of MOLDOVA

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INTRODUCTION

On-going challenges of organic chemistry have spurred the development and improvement of synthetic methods and stimulated the search for new reagents which would provide milder reaction conditions and higher selectivity; among such reagents are substituted glutaconic (2-pentenedioic) acids and their esters. Although known since the last century, most of these compounds remained unexploited for many years. Only during the last decades did they begin to attract attention as convenient and accessible synthons offering a simple and efficient approach to a broad spectrum of organic compounds. As a result, the chemistry of glutaconic acids and their derivatives has been developed. Although a wealth of publications have appeared, to the best of our knowledge, they have not been surveyed yet.

The present review covers mostly publications on preparation and usage of glutaconates that appeared during the last 15-20 years. Although some of the earlier important works are referred to, it is hardly possible to discuss all aspects of glutaconate chemistry in a single review. We had to limit ourselves to the material on the preparation and properties of representative derivatives of glutaconates, which are currently in wide use in synthesis. Thus, 3-methylglutaconates are undoubtedly the most important and versatile synthetic intermediates and that is why more than half of the present review is devoted to the detailed discussion of the specific preparative methods, reactivity patterns and synthetic applications of these compounds. Other important glutaconates include such derivatives as the 2-, 4-methyl, 2,3- and 4,4-dimethyl, 2,3,4-trimethyl, 2-keto, 3-nitro, 4-diazo and 3-chloroglutaconates, selected as examples illustrative of the peculiarities of chemical properties of these systems and of novel options for preparative utilization of glutaconate moieties. In this article we considered it appropriate not to include 3-arylglutaconates.[1,2]

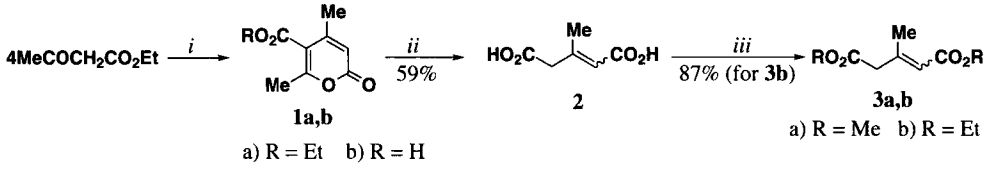
We use the nomenclature according to which the positions are specified by Arabic numerals, i.e., positions 2 and 3 in glutaconic acids stand for vinylic carbons and position 4 corresponds to the allylic carbon. Such an approach avoids the confusion caused by the older nomenclature where the positions of the substituents were indicated by Greek letters, the letter "α" denoting a substituent at the allylic carbon atom.

I. 3-METHYLGLUTACONIC ACID AND ITS ESTERS

A. Preparation

1. From Ethyl Isodehydroacetate

Dimethyl and diethyl 3-methylglutaconates (**3a** and **3b**), the compounds most frequently used in syntheses, are prepared (yields > 80%) by the cleavage of ethyl isodehydroacetate **1a** with alkali (with subsequent esterification) or with sodium alkoxides.[3-6] Compound **1a** itself is prepared by self-condensation of ethyl acetoacetate catalyzed by hydrogen chloride[5] or conc. sulfuric acid.[7a,b] With hydrogen chloride, the yield of **1a** amounts to 63%, but this procedure is cumbersome and time-consuming (it takes about two weeks). Conc. H_2SO_4 is a better catalyst. The reaction is carried out with 3-4 fold molar excess of the acid for 5-6 days at RT. The reaction product consists of a mixture of **1a** (36%) and isodehydroacetic acid (**1b**, 27%). It was found[8] that a two-fold decrease of both acid quantity and reaction time gave **1a** as the only reaction product, albeit in only 47% yield. Although acid **1b** can be readily transformed into compound **1a**,[9] it was established recently[10] that acid **1b** on reaction with 50% aqueous potassium hydroxide is converted in nearly quantitative yield into 3-methylglutaconic acid **2**. This result made it possible to work out a practical method for the preparation of **3b**.[10] Namely, a mixture of ester **1a** and acid **1b**, formed on condensation of ethyl acetoacetate in the presence of sulfuric acid, is treated with a 50% aqueous-methanolic solution of potassium hydroxide. The resulting **2** is then transformed into ester **3b** by refluxing with absolute ethanol and conc. sulfuric acid in 87% yield (44% overall yield) (*Scheme 1*). This more convenient protocol has also been used in the synthesis of 3-(2,4,6-$^{13}C_3$)-methylglutaconic acid, useful for quantification of acid **2** in some biological systems.[11]

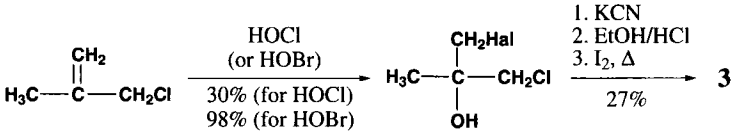


i) conc.H_2SO_4, 10-15° to r.t., 120 h ii) 1. 50% KOH/H_2O-MeOH, 10° to r.t., 1 h. 2. conc. HCl to pH 1, 10-15° iii) conc. H_2SO_4/ROH, reflux, 5 h

Scheme 1

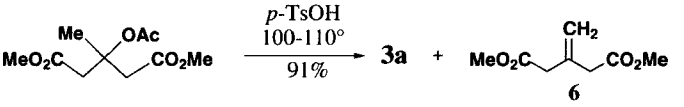
2. Other Methods

There are several other methods for preparing esters **3a** and **3b**. Thus, starting from methallyl chloride and HOCl (or HOBr), ester **3b** was prepared in three steps (*Eq. 1*).[3]



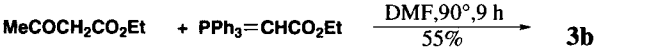
(1)

Deacylation of dimethyl 3-acetoxy-3-methylglutaconate by *p*-TsOH gives a mixture of **3a** and its isomer **6** in a 3:2 ratio in high yield. Though the yield of this mixture was high, attempts to separate it were not made (*Eq. 2*).[13]



(2)

The one-step conversion of ethyl acetoacetate into ester **3b** according to *Eqs. 3* and *4* was also reported.[14-16] Ester **3b** was obtained also in one step from the reaction of ethyl (dimethylsulfuranylidene)acetate **7** (for its preparation see ref. 17) with ethyl crotonate (*Eq. 5*)[18a,b] in good yield; however compound **7** is unstable at RT.



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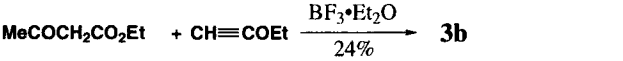

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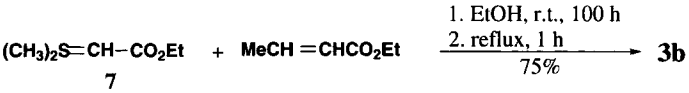
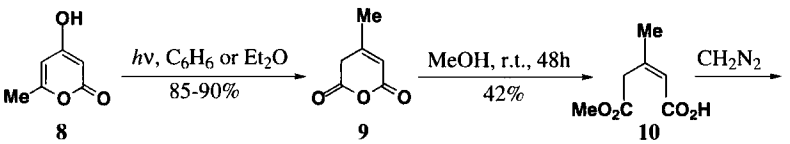


(5)

All the above-mentioned methods of preparing esters **3a** and **3b** and acid **2** lead to ~ 1:1 mixtures of (*E*)- and (*Z*)-isomers which can be easily identified by their ^{1}H NMR spectra.[19] The pure (*E*)-form of **2** was prepared by isomerization of the crude acid **2** obtained upon alkaline cleavage of **1a** with HCl.[19] Its (*Z*)-isomer may be obtained from the same mixture of **2** upon UV irradiation in the presence of iodine[19] or simply by recrystallization from benzene.[16] An entirely different route for the preparation of the (*Z*)-ester **3a** is shown in *Eq. 6*.[20]



(6)

The photolysis of triacetic acid lactone **8** in dry benzene or ether leads to the formation of 3-methylglutaconic acid anhydride **9** (for its preparation see also refs. 7,21). The methanolysis of the latter affords monoester **10**, which is then converted into (*Z*)-ester **3a** by treatment with diazomethane.

Recently,[15] a convenient procedure for the preparation of (*E*)- and (*Z*)-acids **2** has been developed, which is based on stirring 6:4 mixture of (*E*)- and (*Z*)-acids **2** with 0.5 equiv. of acetic anhydride in dry benzene (45-50°, 12h); both (*Z*)-acid (totally) and its (*E*)-isomer (partially) are transformed into the soluble anhydride **9**, leaving pure (*E*)-acid as an insoluble solid (*ca* 40%). The hydrolysis of **9** with 1 equiv. of 10% aqueous NaOH at RT gives pure (*Z*)-acid, but its treatment with 2 equiv. of aqueous NaOH at 100° affords a 6:4 mixture of (*E*)- and (*Z*)-isomers of **2**, from which addi-

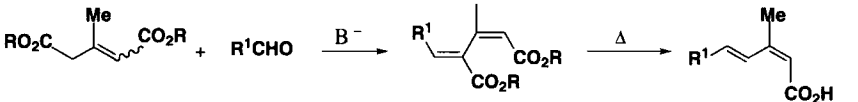
tional amounts of the (*E*)-acid could be isolated as before. This procedure seems to be the method of choice for preparation of either one of the isomers of acid **2** at the expense of the other.

It should be mentioned, however (*vide infra*), that in the most synthetically important reactions of esters **3a** and **3b** with aldehydes and ketones, the isomeric composition does not influence the nature of the products formed.

B. Reactions

1. Condensation with Aldehydes

The most important structural feature of dialkyl 3-methylglutaconates is the activated methylene group at C4. The condensation of glutaconates with aldehydes is one of the most valuable and thoroughly investigated reactions. It is carried out in basic medium and leads to 4-alkylidene (or 4-arylidene)-3-methylglutaconic acids **12**[4,22,36] possessing (2*Z*,4*E*)-configuration.[25-27,36,37] Decarboxylation of **12** upon thermolysis is accompanied by isomerization at the remote double bond to afford (2*Z*,4*E*)-3-methyl-2,4-dienoic acids **13** [4,22,35-40] (*Eq. 7*). This reaction first mentioned at the beginning



3a,b **11** (R = Na or K) **12** (R = H) **13** (7)

of the century[41] remained unexploited for many years.[42] Its systematic investigation started only in the mid-1950s. The most important results obtained so far are discussed in the next section.

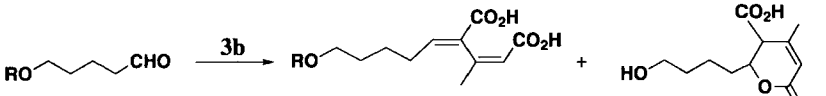
a) Scope

Either **3a**[4,23,27,38,43] or **3b**,[4,26,29-32,39,44] as well as mixed esters,[27,33-36,38] anhydride **9**[43,44] or even **1a**[24a,b] may serve as the substrates for reaction with aldehydes. (*Z*)- or (*E*)-configuration at the double bond of **3a** or **3b** does not seem to substantially alter reactivity and the course of the reaction. In fact, as was shown by Cawley,[4] nearly the same yields of the adduct **12** (R^1 = PhCH=CH-) are produced by condensing (*E*)-cinnamaldehyde with individual isomers of ester **3a**.

Condensation was accomplished with aromatic,[4,23,27,33,42b] saturated,[4,24,29-31,38] α,β-unsaturated[22a,26,27,32,39,44] and heterocyclic[4,35,36,42b] aldehydes. Although sodium[24b,28,30,31,35,36,38] and potassium[4,24a,26,27,29,32-34,38] hydroxides were the main condensation reagents, sodium methoxide[45] and pyridine[38] have also been employed. Methanol was the solvent of choice.[4,24a,b,26,27,29-31,33-35,37] There are several protocols for carring out the reaction. According to one[22,28-32,39,44] of these, the methanolic or aqueous-methanolic solution of the basic agent (1.0-1.5 equiv.) is added to the solution of substrates at 0-5° and the mixture is allowed to stand for 1h at RT to complete the condensation; then an additional ~3 equiv. of base are added and the mixture is refluxed for 1h. Another procedure consists in adding all of the amount of the basic agent at once at ambient temperature and allowing the mixture then to stand at the same temperature for 6-24h,[23,24a] or heating at reflux for 1h.[24b,33-35,38] With α,β-conjugated aldehydes, the reaction is conducted at -10° to -20° for 1h and the mixture allowed to stand for 5-6 additional days at 0° to 5° [4,26,27,39,42b]

The reaction results in the formation of dipotassium or disodium salts **11** which precipitate. They are collected, dissolved in water and acidified, giving acids **12** which usually also precipitate and are purified by recrystallization. Although the yields of diacids **12** varied greately, in most cases they are high (≥70%) for aliphatic, aromatic and some heterocyclic[36] aldehydes. Only *o*- and *p*-hydroxy benzaldehydes and their acetates do not undergo this reaction, whereas *m*-hydroxy benzaldehyde gives the corresponding diacid **12** in 92% yield.[4] For α,β-unsaturated aldehydes the yields of diacids **12** are lower and vary broadly. Thus, for example, cinnamaldehyde gives diacid **12** (R^1 = PhCH=CH-) in 52% yield, senecialdehyde[26] and α-methylcinnamaldehyde[27] afford diacids **12** in yields of 30 and 10%, respectively, but crotonaldehyde gives only resinous products.[4]

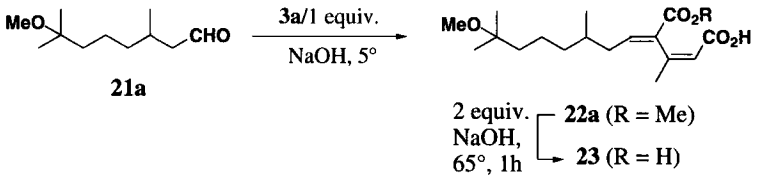
As was pointed out above, the reaction is stereospecific and its products mostly are (2*Z*,4*E*)-4-alkylidene (or 4-arylidene)-3-methylglutaconic acids **12** (*Eq. 7*). However there are cases when the condensation products were carboxy-δ-lactones **14** (R = H)[24a,b,31,36] or their mixtures with acids **12**.[24a,31] Wiley and Ellert[24a] attempted to correlate the nature of the products obtained with the structure of the starting aldehydes. They have found that, on acidification of the condensation products of aliphatic aldehydes, mixtures of compounds **12** and **14** (R = H) are formed; aldehydes with short and branched chains gave mostly diacid **12,** and those with long and unbranched chains giving carboxy-δ-lactones **14**. In the case of aromatic and α,β-unsaturated aldehydes,[4,26-28,32] exclusive formation of diacids was observed. Though these data are in agreement with the finding of other authors,[28-30,32-34] apparently there is no simple and strict relationship between the structure of the aldehydes and those of the reaction products. For example,[31] reaction of 5-hydroxypentanal **15** with glutaconates **3b** gave a mixture of diacid **16** and carboxylactone **17** in which the latter predominated whereas, under the same conditions, 5-(isopropoxy)pentanal **18** afforded exclusively diacid **19** in ~ 90% yield (*Eq. 8*). Evidently, the nature of reaction products depends not only on aldehyde structure but also on reaction conditions. Clearly, more work in these areas is needed.



15 (R = H) **16** (R = H) **17** (8)
18 (R = *i*-Pr) **19** (R = *i*-Pr)

Unlike esters **12** (R = Me or Et), the diacids **12** often turned out to be unstable and cyclized easily into mixtures of lactones **14** and **20**. ^{1}H NMR investigation has shown[38] in the case of diacid **23** that the formation of lactone **20** (R = H, R^1 = $MeOC(Me)_2(CH_2)_3CH(Me)\text{-}CH_2CH_2$) is the reaction product. On mild basic treatment, or on TLC on SiO_2, this lactone is readily converted to isomer **14** (R = H, R^1= $MeOC(Me)_2(CH_2)_3CH(Me)\text{-}CH_2CH_2$). A number of important features concerning the mechanism of the reaction were revealed in the excellent and comprehensive study by Henrick *et al.*[38] In particular, they demonstrated that the condensation of aldehyde **21a** with ester **3a** in the presence of

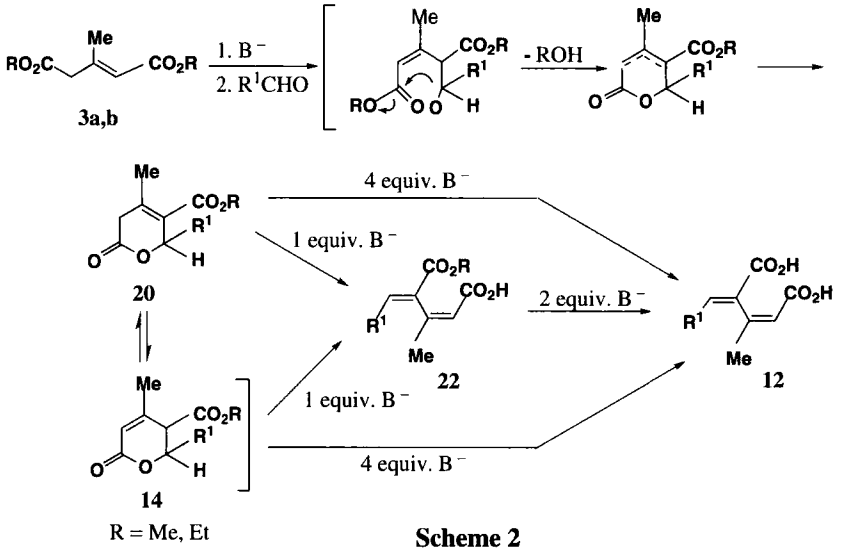
NaOH gives monoester **22a** (see also ref. 4), which on further NaOH treatment is converted into diacid **23** (95% yield, 96% purity) (*Eq. 9*). The fact that monoester **22a** is the precursor of diacid **23**



(9)

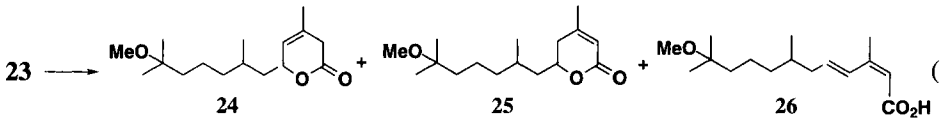
suggests that δ-lactones **14** or **20** (R = Me, R^1 = $MeOC(Me)_2(CH_2)_3CH(Me)CH_2CH_2$) are intermediates in this reaction.

In light of these data, the condensation of aldehydes with 3-methylglutaconates **3a** and **3b** may be depicted as shown in *Scheme 2*.



Scheme 2

As was already pointed out (*Eq. 7*), diacids **12** undergo decarboxylation on heating with organic bases regio- and stereoselectively with the elimination of 4-carboxy group and inversion of configuration at C4, yielding (2*Z*,4*E*)-dienoic monoacids **13**; the mechanism of decarboxylation reaction was not studied. The following bases have been used most often for decarboxylation: pyridine,[4,29,34,38] a mixture of pyridine and piperidine,[32] 2,4-lutidine,[28] quinoline[23] and particularly 2,4-lutidine in the presence of copper acetate.[4,22-24,26,27,32,39] However, Henrick *et al.*[38] demonstrated that copper acetate exerted little influence on the results by carrying out the decarboxylation of diacid **23** by heating in toluene in the presence of 10% 2,4-lutidine only. Under these conditions, a mixture of compounds **24, 25** and **26** is formed, in which lactone **24** predominates (*Eq. 10*). In this case decarboxylation proceeded easily, but the subsequent isomerization of lactone **24** into alkoxy lactone **25** and the opening of the lactone ring resulting in monoacid **26** were slow and incomplete. In conformity



24 25 26 (10)

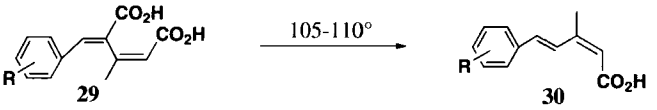
with the data,[46,47] these two processes occurred more easily in the presence of alcoholic sodium alkoxides, and decarboxylation could be carried out more efficiently in two steps. Diacid **21** is initially heated in toluene at 100° in the presence of 2,4-lutidine (0.1 equiv.) until the elimination of CO_2 ceases, prior to addition of MeONa in MeOH (1.1 equiv.), and then heating for 1h at 70°. In this way, (2*Z*,4*E*)-monoacid **26** of high purity was prepared in better than 90% yield. This decarboxylation protocol was also successfully applied to a number of other diacids.[30,31]

Decarboxylation of 5-(pyridin-3-yl)- and 5-(*N*-methylindol-3-yl)-3-methyl 2,4-pentadienoic acids **27a,b** was studied (*Eq. 11*).[35,36,40] For these acids, the use of organic bases such as pyridine

27 a,b a) R^1 = pyridin-3-yl b) N-methylindol-3-yl **28 a,b** (11)

proved to be ineffective. Thus, for example, diacid **27b** on heating in pyridine gave only 14% of monoacid **28b**. It was further shown, however, that the disodium salts of diacids **27** readily undergo decarboxylation in the mixture DMSO-CH_3COOH to give monoacids **28** in good yields. Thus, for example, the disodium salt of diacid **27a** was transformed, under the given conditions, into monoacid **28a** in a yield of 87%.

There is a need for more detailed studies of the relationship between the ease of decarboxylation of diacids **12** and their structures. The decarboxylation of a series of 5-phenylsubstituted diacids **29** to the respective monoacids **30** in pyridine was studied by Popa *et al.*[34] (*Eq. 12* and Table 1). These



29 **30** (12

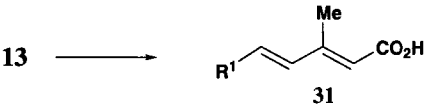
TABLE 1. Decarboxylation of 5-Phenyl-2,4-pentadienoic acids **29**[34]

Acid **29**	R	Reaction time (min)	Yield **30** (%)
a	H	100	93.8
b	4-Cl	40	97.3
c	4-Br	40	95.2
d	2,4-$(MeO)_2$	240	91.8
e	3,4-$(MeO)_2$	225	92.2
f	Me_2N	spontaneous	35[a]

a) Data from ref. 23. The overall yield of 2 step transformation.

data suggest that the elimination of CO_2 takes place more readily with decreasing of electron density on the carbon atom adjacent to the carboxy group, as is obviously the case with compounds **29b,c.** On the other hand, the reaction proceeds considerably more slowly with diacids **29d,e** with electron-releasing substituents in the aromatic ring [2,4-$(OMe)_2$, 3,4-$(OMe)_2$]. At the same time, it was established[4,23] that on condensation of *p*-dimethylaminobenzaldehyde with glutaconate **3a**, the corresponding intermediate diacid **29** (R = *p*-NMe_2) decarboxylates spontaneously.

Another important aspect of the condensation reaction of aldehydes with dialkyl 3-methylglutaconates is the subsequent isomerization of (2*Z*,4*E*)-acids **13**, formed upon decarboxylating diacids **12**, into the (2*E*,4*E*)-acids **31**, many of which are of practical importance (*vide infra*) (*Eq. 13*).



(13

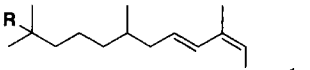
The most widely used agents to accomplish isomerization have been: iodine in boiling benzene or UV light,[23,27,44] or iodine in benzene–ether at RT or reflux (Table 2).[22,28,39,44] For a series of 5-phenylsubstituted acids **13,** the yield of (2*E*,4*E*)-acids was shown to depend on the nature of substituents in the aromatic ring. Thus, for example, isomerization of acid **13** (R^1 = Ph) by iodine in ether or benzene gives only 50% of acid **31** (R^1 = Ph),[23] while acid **13** [R^1 = 4-(MeO)C_6H_4] under similar conditions is completely isomerized into the corresponding (2*E*,4*E*)-acid. At the same time,

TABLE 2. Isomerization of (2*Z*,2*E*)-Acids **13** to (2*E*,4*E*)-Acids **31**

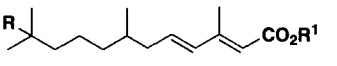
R^1	Yield (%)	Method	Products (%)		Ref.
			13	**31**	
C_6H_5	50	$I_2/Et_2O/C_6H_6$			23*
$C_6H_5CH{=}CH$	80	——"——			
3,4-$CH_2O_2C_6H_4$	84	$I_2/C_6H_6/h\nu$			
3,4-$(MeO)_2C_6H_3$	25	——"——			
4-$MeOC_6H_4$	84	$I_2/Et_2O/C_6H_6$		100	28
2,4,6-$Me_3C_6H_2$	72	——"——	15	85	
2,3,6-Me_3-4-$MeOC_6H$	78	——"——	7	93	
C_6H_5	94	KOH/DMSO	10	90	40
3-Py	83	——"——	4	96	
4-BrC_6H_4	75	C_6H_5SH	5	95	33
4-ClC_6H_4	87	——"——	3	97	
4-FC_6H_4	83	——"——	5	95	
$MeOC(Me)_2(CH_2)_5$	97	——"——	35	65	30
$Me_2C{=}CH(CH_2)_4$	95	——"——	35	65	
$Me_2CHO(CH_2)_4$	98	——"——	25	75	31
$HO(CH_2)_4$	98	——"——	25	75	

a) The ration of isomers not given

(2*Z*,4*E*)-5-(2,4,6-trimethylphenyl) acid **13** [R^1 = 2,4,6$(CH_3)_3C_6H_2$] and (2Z,4E)-5-(2,3,6-trimethyl-4-methoxyphenyl) acid **13** [R^1 = 2,3,6-$(CH_3)_3$-4-(MeO)-C_6H] give the mixture of (2*E*,4*E*)-**31** and (2*Z*,4*E*)-**13** isomers in ratios 85:15 and 97:7, respectively. Kuchkova *et al.*[40] carried out the isomerization using powdered KOH in anhydrous DMSO at 135-145°. Under these conditions (2*Z*,4*E*)-5-(pyridin-3-yl)-2,4-pentadienoic acid was converted into the (2*E*,4*E*)-isomer in 83% yield. The isomerization of acids **32a,b** and esters **32c-e** was thoroughly studied by Henrick's group[38] who tested a large number of inorganic and organic compounds (Al_2S_3, Na_2S, LiSCN, KF, $RuCl_3 \cdot 3H_2O$, alkoxides, butadiene sulfone, thiobenzoic, thioglycolic and triacetic S-acids, diphenyl disulfide and sulfur) as isomerization agents. It turned out that such reagents as $(PhS)_2$ and thioacetic S-acid do indeed bring about the isomerization of acids **32a,b**, whereas sulfur, EtONa, Na_2S and $RuCl_3 \cdot 3H_2O$ isomerized esters **32c-e**, with the formation of equilibrated mixtures containing 65% of (2*E*,4*E*)-isomers **33** and



32 a-e



33 a-e

a) R = R^1 = H b) R^1 = MeO, R = H c) R^1 = MeO, R = Et d) R^1 = MeO, R = *i*-Pr e) R = H, R^1 = Me

35% of (2*Z*,4E)-isomers **32**. However, a substantial amount (20-30%) of these reagents was needed, and the reaction required prolonged heating (4-48 hours) at elevated temperatures (115-130°). The best catalyst to establish equilibrium on isomerization is thiophenol. Thus, heating acid **32a** with 0.5-1% of thiophenol without solvent for 1-2h at 100° gave a 95% yield of a mixture, containing 35% of acid **32a** and 65% of acid **33a**. Reaction probably proceeds by the reversible addition of the thermally generated thiophenyl radicals to the 2,3-double bond of acid **32.** Neither UV irradiation nor the use of AIBN are necessary. Moreover, it should be pointed out[48] that the UV light causes isomerization of (2*Z*,4*E*)-3-methyl-5-phenyl-2,4-pentadienoic acids not only at the 2,3-double bond, but also at the 4,5-double bond, giving mixtures of all four possible isomers. Similar results were obtained in the thiophenol induced isomerization of acid **32b** and esters **32c-e**. Later this isomerization protocol was also successfully employed for isomerizing a number of other (2*Z*,4*E*)- pentadienoic acids and esters (Table 2).[30,31,33]

Henrick *et al.*[38] have also proposed a convenient method for the isolation of pure (2*E*,4*E*)-acids **33** from their mixtures with acids **32** by precipitation as the ammonium salts with dry ammonia in ether, hexane or methylene chloride (see also refs. 30, 31 and 33). The regenerated (2*Z*,4*E*)-acids may be completely converted into (2*E*,4*E*)-isomers by repeated isomerization.

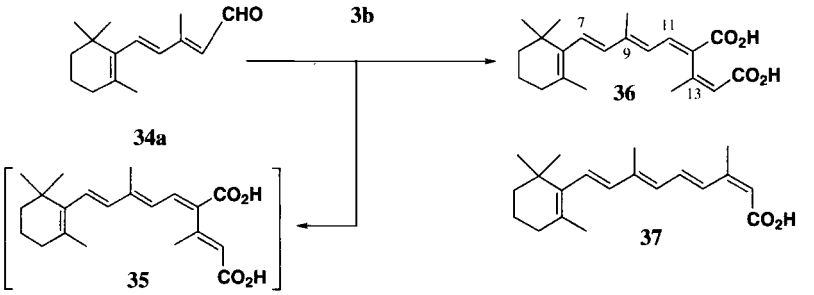
Thus, the condensation of aldehydes with dialkyl 3-methylglutaconates may serve as a general, preparatively convenient, simple and efficient stereoselective method of prenylation, with production of (2*E*,4*E*)- and (2*Z*,4*E*)-3-methyl-2,4-dienoic acids and esters. This "glutaconate method"[38] is especially valuable for the synthesis of terpenoids and their analogs and has a number of advantages over other known general methods, for instance, the Reformatsky and Wittig reactions.[4,47,49-53]

b) Synthetic Uses

This section present a concise account of compound types synthesized from glutaconates.

i) Synthesis of Vitamin A and Retinoids

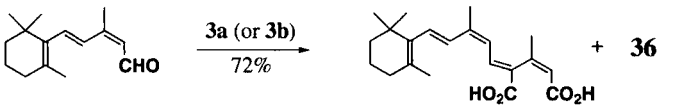
The condensation of aldehydes with 3-methylglutaconates **3a** and **3b** turned out to be particularly rewarding in the synthesis of such biologically active natural compounds as vitamin A, retinoic acid and related substances. Most of these syntheses are based on the transformation of 12-carboxyretinoic acids obtained from (9*E*)-β-ionylideneacetaldehyde (**34a**). The results of early work in this area were contradictory and confusing.[23,55] For example, the structure of (9*E*,11*E*,13*E*)-12-carboxyretinoic acid (**35**) was assigned without sufficient evidence to the product of the condensation of (9*E*)-aldehyde **34a** and glutaconates **3b**. It was assumed that the conversion of dicarboxylic acid **35** into (13*Z*)-retinoic acid **37** by selective decarboxylation is accompanied by the inversion of configuration of the double bond not only at C11, but also at C13 (*Eq. 14*).



(14

Later, Lewin and coworkers[44] carried out a more detailed study of the structures of 12-carboxyretinoic acids prepared according to Robeson *et al.*[22] and to Petrov and Stephenson.[54] A reinvestigation of Robeson's[22] work on the condensation of (9*E*)-aldehyde **34a** with glutaconate **3b** revealed that the resulting dicarboxylic acid has in fact the (*Z*)-configuration at C13 and is consequently (9*E*,11*E*,13*Z*)-12-carboxyretinoic acid (**36**). Similar results were obtained by replacing **3b** by **3a**.

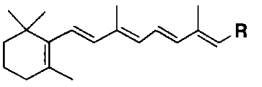
It was possible to prepare (9*Z*,11*E*,13*Z*)-12-carboxyretinoic acid (**38**) as a 1:1 mixture with its (9*E*,11*E*,13*Z*)-isomer **36** upon condensing the (9*Z*)-isomer of β-ionylideneacetaldehyde **34b** with glutaconates **3a** or **3b**[31] (*Eq. 15*). Under basic catalysis, dicarboxylic acid **38** is prone to isomerization at C9, giving rise to diacid **36** which is stable in basic media.[44]



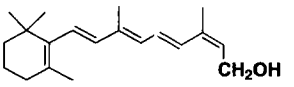
34b 38

(15

Polyachenko *et al.*[32] have reinvestigated decarboxylation of diacid **36** under the same conditions[22] and confirmed the formation of (13*Z*)-retinoic (neoretinoic) acid **37** (54% yield). This acid was isomerized by iodine[22] into all-*trans* natural retinoic acid **39a**. Lithium aluminium hydride reduction of acids **39a** and **37** led to vitamin A **39b** and neovitamin A **39c,** respectively. A mixture of (9*Z*,*E*)-

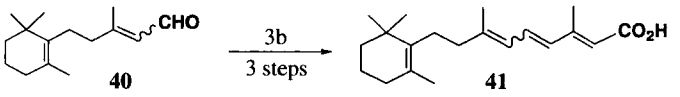


39 a, R = CO_2H
39 b, R = CH_2OH



39c

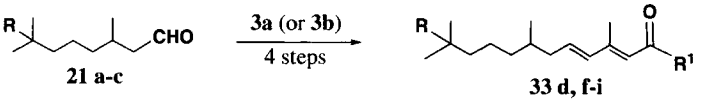
isomers of 7,8-dihydroretinoic acids **41** was obtained under standard conditions from (9*Z*,*E*)-7,8-dihydro-β-ionylideneacetaldehyde (**40**) and **3b** (*Eq. 16*).[39]



40 **41** (16)

ii) Synthesis of Juvenoids

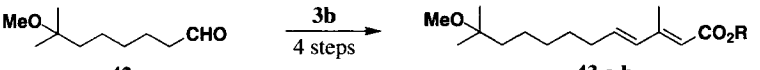
The condensation of aldehydes with glutaconates **3a** and **3b** was also employed for the preparation of a number of juvenoids. Thus, Henrick *et al.*[38] prepared one of the most active juvenoids - methoprene **33d** and its analog **33f** starting from commercialy available aldehyde **21a**. In the same way, hydroprene **33g** and kinoprene **33h** were obtained from aldehyde **21b**, and hydroprene hydroxy analog **33i** from aldehyde **21c** (*Eq. 17*). The methods of preparation of these compounds have been



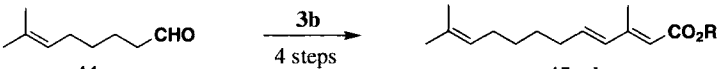
21 a-c **33 d, f-i** (17)

a) R = OMe b) R = H c) R = OH d) R = OMe, R^1 = $OCHMe_2$ f) R = OMe, R^1 = SEt
g) R = H, R^1 = OEt h) R = H, R^1 = $OCH_2C{\equiv}CH$ i) R = OH, R^1= OEt

patented.[55] The methoprene analogs of the related structures **43a,b** and **45a,b** without the methyl group at C7 were synthesized[30] in reactions starting with methoxyaldehyde **42** and 7-methyl-6-octenal (**44**), respectively (*Eq. 18* and *19*).

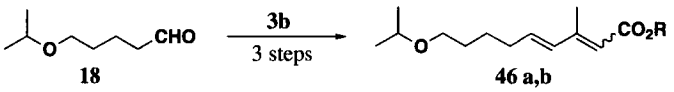


42 **43 a,b** (18)
a) R = Me b) R= $CHMe_2$



44 **45 a,b** (19)
a) R = Me b) R= $CHMe_2$

Similarly the oxa-analogs of juvenile hormones **46a-c**, as ~ 3:1 mixtures of (2*E*,4*E*)- and (2*Z*,4*E*)-isomers, were prepared from 7-methyl-6-oxaoctanal (**18**) and **3b** (*Eq. 20*).[31]



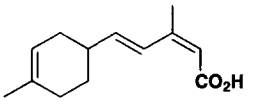
18 46 a,b (20)

a) R = Me b) R = $CHMe_2$ c) R = $CH_2C_6H_5$ d) R = $CH_2C{\equiv}CH$

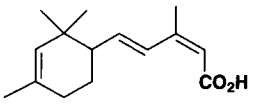
iii) Synthesis of Abscisic Acid Analogs

The important regulatory function of abscisic acid in plants stimulated the synthesis of a great number of related compounds in order to investigate structure-activity correlations.[56] As a result, a number of active analogs have been found, for example, (2*E*,4*E*)-3-methyl-5-(*p*-chlorophenyl)[51]- and (2*Z*,4*E*)-3-methyl-5-(2,4,6-trimethylcyclohexane-2-yl)[57]-pentadienoic acids, which differ from abscisic acid by the structure of their cyclic moieties.

Later publications have appeared dealing with the glutaconate method as the most convenient route for the stereoselective synthesis of (2*Z*,4*E*)-and (2*E*,4*E*)-5-substituted 3-methylpentadienoic acids. For example, the search for new plant growth regulators led to the synthesis of (2*Z*,4*E*)-acids **47a** and **47b** from the methyl homologs of 3-cyclohexene-1-carboxaldehyde.[29]

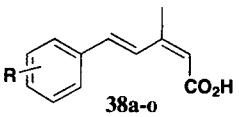


47a

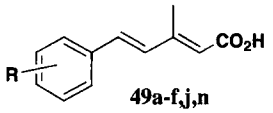


47b

Such aromatic analogs of abscisic acid as **48a-o** and **49a-f,j,n** have also been prepared.[23,24a,27,33,34,58] A number of these syntheses were patented.[33]



38a-o

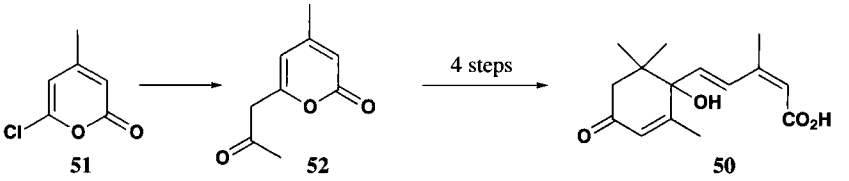


49a-f,j,n

a) R = H b) R = 4-Cl c) R = 4-Br d) R = 2,4-$(NO_2)_2$ e) R = 3,4-$(NO)_2$ f) R = 4-F
g) R = 2-Cl h) R = 2,6-Cl_2 i) R = 3-NO_2 j) R = 4-MeO k) R = OH
l) R = 2-OCOMe m) R = 4-OCOMe n) R = 2,4,6-Me_3 p) R = 2,3,6-Me_3-4-MeO

Heteroanalogs of abscisic acid, (2*Z*,4*E*)-5-(pyridin-3-yl)pentadienoic acid (**28a**), its (2*E*,4*E*)-isomer and (2*Z*,4*E*)-5-(1-methylindol-3-yl)pentadienoic acid (**28b**)[35,36,40] were also prepared and tested for biological activity, and it was found that acid **28b** has strong antitranspiration activity.

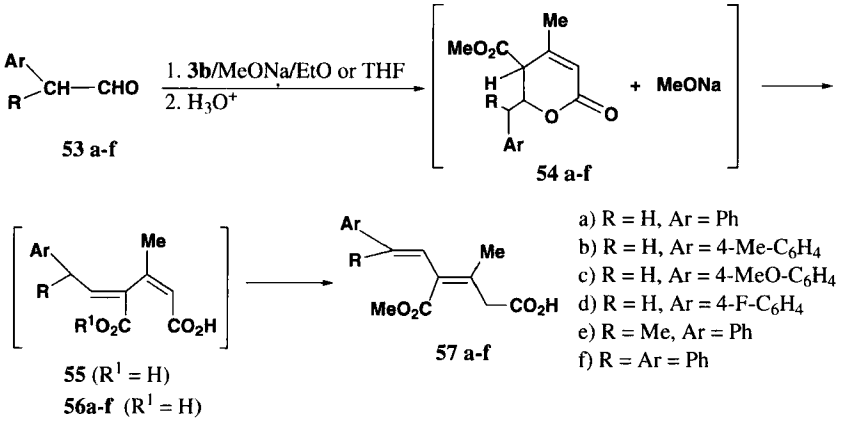
Recently[15] a stereospecific synthesis of (±)-abscisic acid **50** has been accomplished. It was found that upon treatment (see sec. A) with acetyl chloride or thionyl chloride, only the (*E*)-isomer of **2** afforded 6-chloro-4-methylpyran-2-one (**51,** 70%), while the (*Z*)-isomer of **2** yielded anhydride **9**. With acetyl chloride, the mixture of **2** produced in turn a mixture of chloropyranone **51** and anhydride **9,** separable by distillation (see also ref. 57). The reaction of compound **51** with sodio-*t*-butyl acetoacetate, followed by acid-catalyzed cleavage of the ester group gave 4-methyl-6-(2'-oxopropyl)pyran-2-one (**52,**78%), from which (±)-abscisic acid **50** was obtained in four steps (*Eq.* 21).



(21)

iv) Synthesis of 6-Aryl-3,5-hexadienoic Acids

Surprising results have recently been obtained [45] on condensation of **3b** with phenylacetaldehyde derivatives **53a-f**. It was expected that this reaction, as a particular case of the glutaconate method, would lead to the respective 4-carboxy-3-methyl-5-benzylpenta-2,4-dienoic acids **55**. However, the reaction products proved to be (3*Z*,5*E*)-6-aryl-4-carbomethoxy-3-methylhexadienoic acids **57a-f**. The condensation was carried out in the presence of MeONa and the yields of acids **57** ranged from 65% to 85%. Stereospecificity of formation of these acids can be easily accounted for by assuming an initial formation of lactones **54a-f** (*Scheme 2*) followed by the opening of the latter by MeONa to give first non-conjugated dienoic adducts **55,56a-f** and finally more stable products **57a-f** (*Eq. 22*). It should be mentioned that these acids are used as intermediates in the synthesis of some antibiotics produced by basidomycetes.[60,61]



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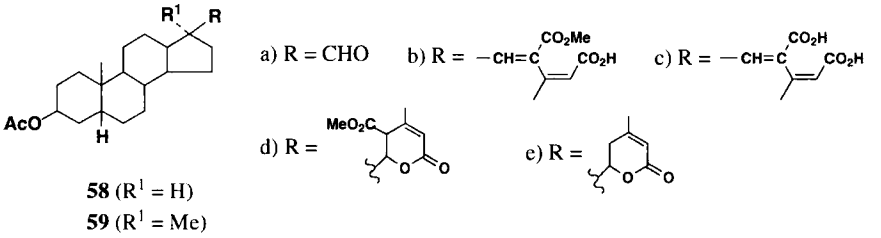
v) Introduction of the Lactone Moiety into a Withanolide Precursor

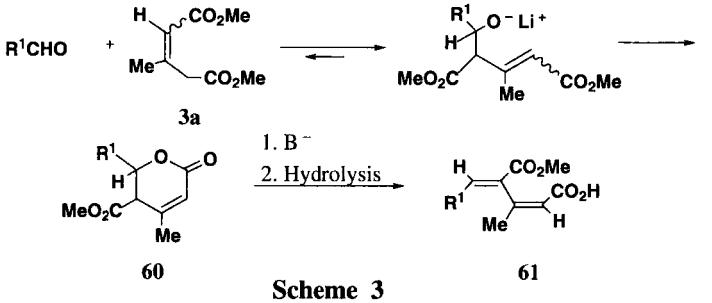
The use of the glutaconate method was elaborated into a simple route to construct the α,β-unsaturated side-chain δ-lactone fragment of a classical withanolide precursor of the structures **58e** and **59e**.[24b]



Condensation of steroidal aldehydes **58a** and **59a** with ester **1a** in the presence of 4 equiv. of NaOH in dry methanol proceeds smoothly to give insoluble salts of half-esters **58b** and **59b** (yield 75%). Upon the decarboxylation of these half-esters, lactones **58d** and **59d** were isolated in 41% yields. When 2 more equiv. of aqueous NaOH were added and the reaction mixture was heated (65°C,1h), diacids **58c** and **59c** were obtained which on subsequent decarboxylation afforded lactones **58e** and **59e** in 30% yield.

vi) Synthesis of 5,6-Dihydro-(2H)-pyran-2-ones

It was stated above that 4-arylidene-3-methylglutaconic acids **12**, formed at the first step of glutaconate synthesis, in some cases are further transformed into the respective 4-carboxy-δ-lactones **14** (R = H). These lactones, being typical representatives of 5,6-dihydro-α-pyrones, are of some interest as potentially biologically active compounds.[62] Recently[63] a direct method has been elaborated for the preparation of lactones **60** by reaction of aldehydes with **3a** in basic medium. The conditions should be selected in such a way as to exclude the opening of the lactone ring[62] and formation of undesirable hemiesters **61** (*Scheme 3*). This goal was accomplished under the conditions indicated in



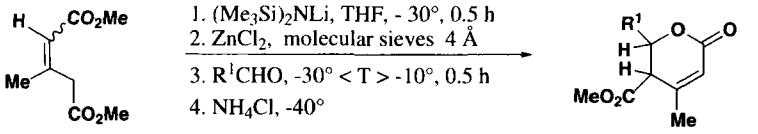
60 **61**

Scheme 3

Eq. 23. For lactone **60a,** prepared from benzaldehyde, the yield was only 31%, but lactones **60b-g** were obtained from the corresponding saturated aldehydes in good yields. In most cases lactones **60a-g** are formed as mixtures of diastereoisomers in which *cis*-isomers predominate (Table 3). These mixtures can be separated chromatographically.

TABLE 3. Preparation of Lactones **60**[63]

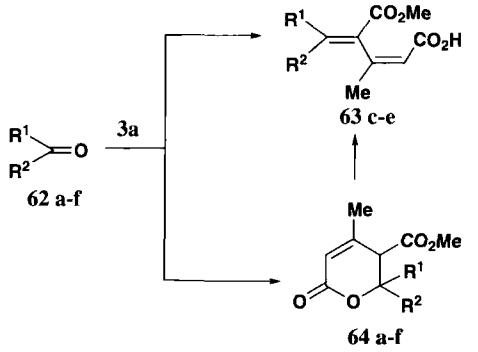
Lactone **60**	Yield (%)	*% cis*	*% trans*
R^1 = a: Ph	31	0	100
b: Me	50	75	25
c: $(CH_2)_2CH_3$	90	70	30
d: $(CH_2)_6CH_3$	80	85	15
e: CH_2Ph	65	100	0
f: $CH(CH_3)_2$	80	80	20
g: $C(CH_3)_3$	90	0	100



3a — 60 a-g (23)

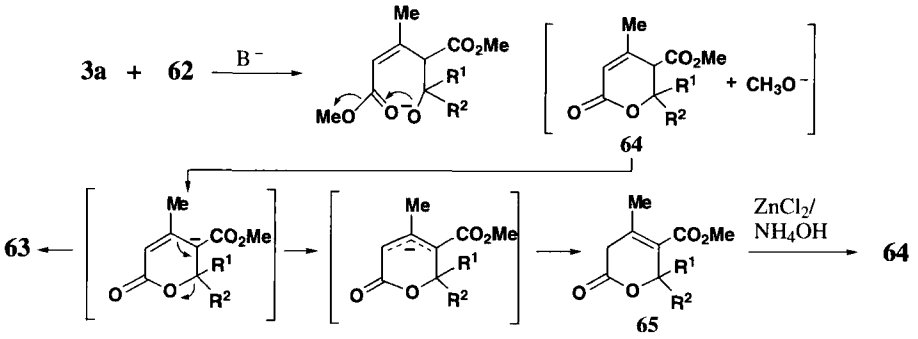
2. Condensation with Ketones

Strange as it may seem, for a long time ketones were not used as carbonyl components in the reactions with 3-methylglutaconates. It is only in 1988 that such a condensation was performed.[64] Thus, **3a** was shown to react with ketones **62a-f** (*Eq. 24*) in the presence of sodium methoxide or with LDA in the presence of TMEDA, giving the monoesters of dicarboxylic acids **63c-e** (yields 60-70%).



a) $R^1 = R^2 = Me$
b) $R^1 = R^2 = Et$
c) $R^1 + R^2 = -(CH_2)_4-$
d) $R^1 + R^2 = -(CH_2)_5-$
e) $R^1 + R^2 = -(CH_2)_6-$
f) $R^1 + R^2 = -(CH_2)_2CH(n\text{-}C_4H_9)(CH_2)_2-$ (24)

The formation of monoesters **63** revealed that, just as in the case of condensation of **3a** with aldehydes (*Schemes 2* and *3*), the intermediates in this reaction are δ-lactones **64a-f** (*Scheme 4*). This conclusion is supported by the fact that, on treatment with MeONa, lactone **64d** gave monoester **63d** in 83%



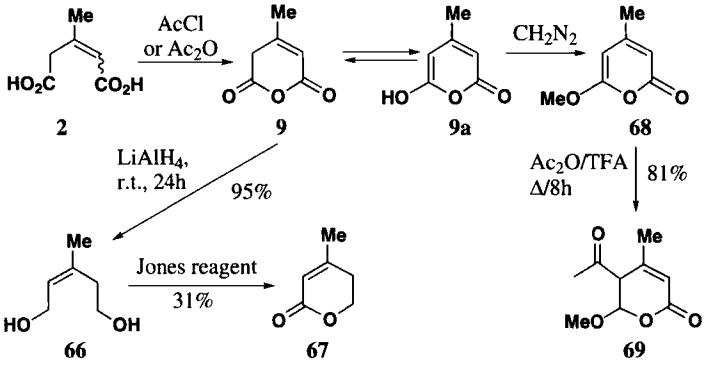
Scheme 4

yield. If the reaction is carried out with LDA in THF–HMPT or with NaH in THF, then lactones (dihydropyranones) **65** are formed; unfortunately, yields were not reported. When the reaction is conducted in the presence of $ZnCl_2$, it leads to lactones **64,** albeit in yields ranging from 19-40% with

LDA to 15% with NaH (only the yields for **64c** were given). Lactones **65** are quantitatively isomerized into lactones **64** by $ZnCl_2$-NH_4OH in diethyl ether. The reverse transformation of **64** to **65** takes place on deprotonation and subsequent kinetically-controlled protonation of intermediate anions.

3. Preparation of Anhydromevalonolactone and Substituted Anthraquinones

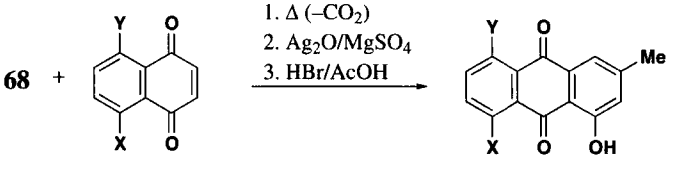
Cyclodehydration of **2** using AcCl (see sec. A) or Ac_2O[65] leads to 3- methylglutaconic anhydride **9** which was used in a simple synthesis of anhydromevalonolactone **67**, an important and versatile intermediate in the preparation of natural products.[66,67a,b] Anhydride **9** was reduced by $LiAlH_4$ into diol **66,** which after Jones oxidation afforded anhydromevalonolactone **67** (*Eq. 25*).



(25)

The utilization of 2-pyrans as dienes in the Diels-Alder reaction provided a general route to anthracycline antibiotics[68] and other natural compounds of the anthraquinone series. Some of the 2-pyrans used for these purposes have been synthesized from acid **2**. Thus, 3-methylglutaconic anhydride **9** which is in an equilibrium with tautomeric form **9a** (see also ref. 70) on methylation with diazomethane gives 2-pyrone **68** (overall yield from **2** is 30%) which served as the diene component in reactions with a number of naphthoquinone dienophiles in the syntheses of anthraquinone antibiotics.[69,70]

For example, reaction of pyrone **68** with naphthoquinone **70a** and subsequent oxidation and demethylation afford in a regiospecific manner the natural product pachybasin **71a** (64% yield). Similarly, juglone **70** was converted into chrysophanol **71b** (62% yield), and naphthazarin **70c** into helmintosporin **71c** (38% yield) (*Eq. 26*).



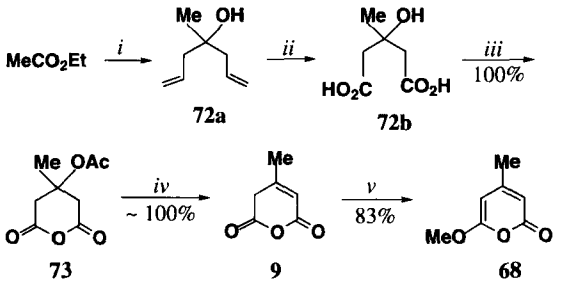
70 a-c **71 a-c**

a) X = Y = H b) X = OH, Y = H c) X = Y = OH

(26)

The Friedel-Crafts acetylation of 2-pyrone **68** afforded 5-acetyl pyrone **69** (*Eq. 25*), which readily and regiospecifically reacted with naphthoquinone dienophiles to yield natural anthracycline compounds.[70,71]

An alternative route to pyrone **68**, suitable for the introduction of an isotopic label, has been reported by Ahmed *et al.*[72] (*Scheme 5*). In this synthesis ethyl acetate was converted by



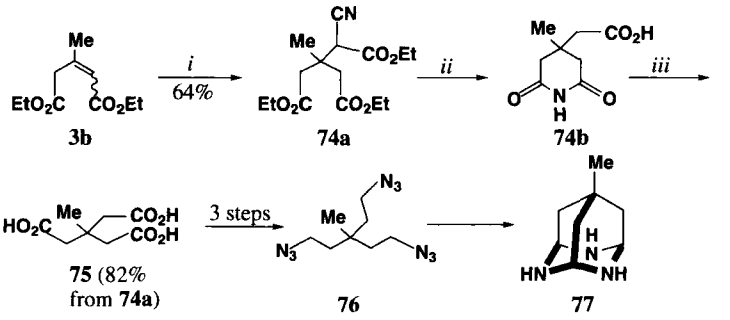
i) CH_2=$CHCH_2Br$, Mg, ether-THF (1:1) *ii)* O_3, CH_2Cl_2–CH_3CO_2H (10:1)
iii) AcCl, 60°,2h *iv)* $Me_2C_6H_4$, reflux, 20h *v)* CH_2N_2

Scheme 5

Grignard reaction with allylmagnesium bromide into hydroxydiene **72a,** which gives on oxidation with ozone diacid **72b**. Reaction of the latter with acetyl chloride gave anhydride **73** which upon pyrolysis was transformed into anhydride **9** which upon treatment with diazomethane furnished the required pyrone **68**.

4. Synthesis of 2,4,9-Triazaadamantane

2,4,9-Triazaadamantane **77**[73] was synthesized from **3b** according to *Scheme 6*. The key intermediate, 1,1,1-ethanetriacetic acid **75,** was converted in three steps into triazide **76**, which upon photolysis or pyrolysis was transformed into the target 2,4,9-triazaadamantane **77**.

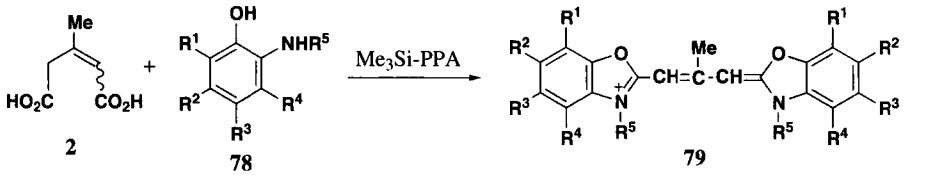


i) NCCHNaCO_2Et *ii*) 1. H^+ 2. Δ (–CO_2) *iii*) HCl

Scheme 6

5. Synthesis of Benzoxazole Derivatives

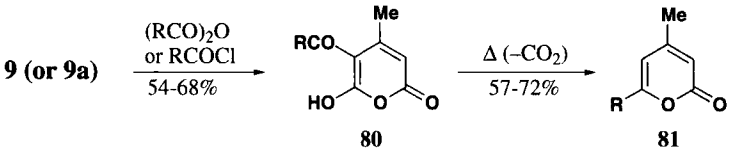
Condensation of **2** with *o*-aminophenols **78** or their salts in the presence of trimethylsilyl polyphosphate affords compounds **79** which have been patented as photosensitizers (*Eq. 27*).[74]



(27)

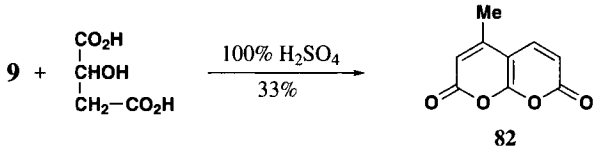
6. Synthesis of Dialkylpyran-2-ones and Pyranopyrandiones

3-Methylglutaconic anhydride **9** was used[21] for the synthesis of 4,6-dialkyl-2-pyrones **81**. Acylation of anhydride **9** with carboxylic acid anhydrides or chloroanhydrides in pyridine yielded 4-methyl-5-acyl-6-hydroxy-2-pyrones **80** which on heating underwent decarboxylation to give compounds **81** (*Eq. 28*).



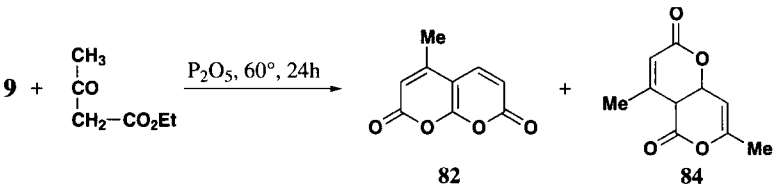
(28)

Anhydride **9** served also as a starting compound for the preparation of a number of pyranopyrandiones.[75] Pechmann condensation of anhydride **9** with (±)-malic acid in 100% H_2SO_4 gave 4-methyl-2*H*,7*H*-pyrano-[2,3-*b*]pyran-2,7-dione (**82**) (*Eq. 29*).



(29)

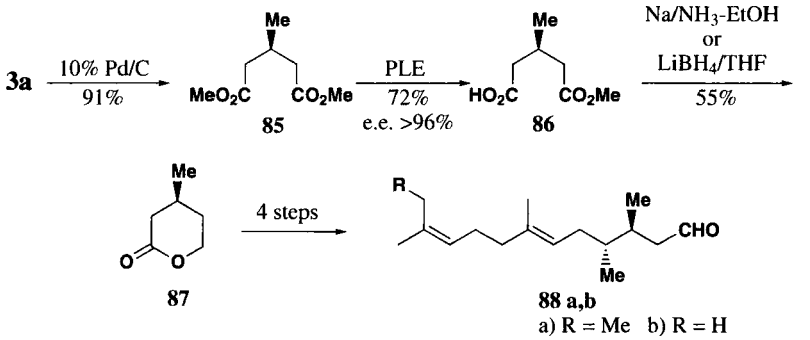
Anhydride **9** reacted with ethyl acetoacetate in the presence of P_2O_5 to give a mixture of the Pechmann condensation product, 4,5-dimethyl-2*H*,7*H*-pyrano[2,3-*b*]pyran-2,7-dione (**83**) (22 % yield), with the product of the Simonis reaction, 4,7-dimethyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (**84**) (19% yield) (*Eq. 30*).[76]



(30)

7. Preparation of (3S)-Methyl Valerolactone

Glutaconate **3a** was employed in the synthesis of (3*S*)-methyl valerolactone **87,** a key chiral intermediate for the preparation of (+)-faranal **88a**, the trail pheromone of Pharaoh's ant, and its congener (+)-13-norfaranal **88b.**[77] Ester **3a** was catalytically hydrogenated to 3-methylglutaconate **85**, which was in turn enantioselectively hydrolyzed with pig liver esterase (PLE) to afford the (R)-monoester **86**. The latter was selectively reduced with sodium in NH_3-EtOH or $LiBH_4$ in THF into the desired (3*S*)-methyl valerolactone **87** (*Eq. 31*).



(31)

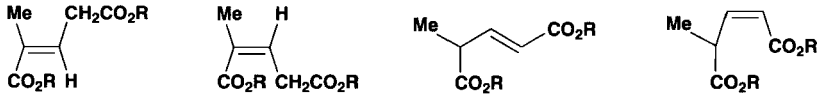
II. OTHER ALKYL- AND HETEROSUBSTITUTED GLUTACONIC ACIDS AND THEIR ESTERS

The data concerning other alkylsubstituted glutaconates are much more limited. Nevertheless the facts available so far show that they are of interest as synthetic precursors to valuable substances. The dialkyl substituted glutaconates and the related derivatives have been the most widely and successfully used for these purposes.

A. Di- and Trialkylglutaconates

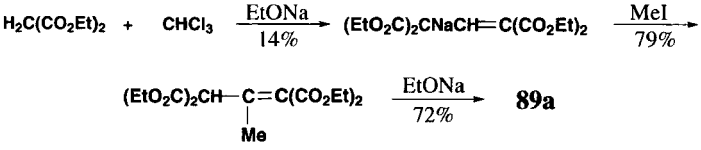
1. Dialkyl 2- and 4-Methylglutaconates

2-Methylglutaconic acids **89a**, **90a** and their ethyl esters **89b**, **90b**, as well as 4-methylglutaconic acids **91a**, **92a** and their ethyl esters **91b**, **92b** (in earlier publications these compounds were named γ-and α-methylglutaconic acids and their esters) are the closest analogs of 3-methylglutaconates.[78] Compounds **89-92** differ by position or configuration of the double bond and they can easily undergo isomerizations. An unambigous determination of their structure was far from simple. This question is discussed in detail by Kagan[79] who has characterized all the four possible isomeric esters **89b-92b** and studied their mutual transformations under acidic and base catalysis, thermolysis



a) R = H b) R = Et

and photolysis. The reexamination of some of the reported methods for the preparation of these esters revealed that the compounds, to which the structure of 4-methyl substituted glutaconates **91**, **92** had been ascribed, are in fact the (*E*)-2-methylsubstituted derivatives **89**, **90** (*Eq. 32* and *Scheme 7*).



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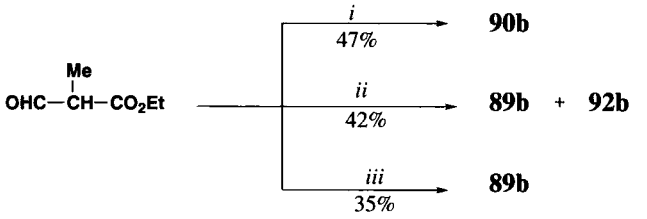


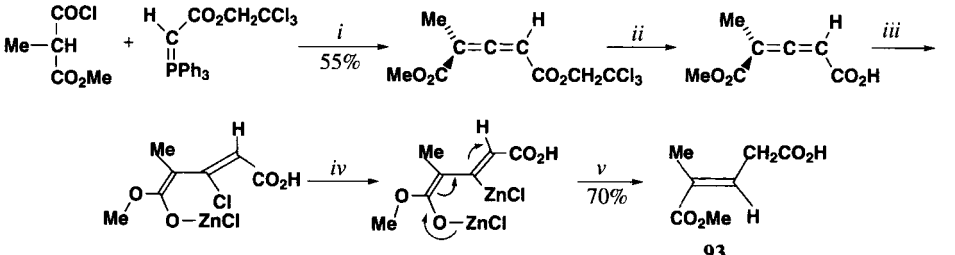
i) 1. $H_2C(CO_2H)_2$ 2.Py,100°, 2h *ii)* $Ph_3PCH_2CO_2Et$, r.t., 48h *iii)* 1. $H_2C(CO_2Et)_2$ 2. Py,100°,8h

Scheme 7

The Wittig reaction is the method of choice for regioselective introduction of a carbon-carbon double bond. However, on condensation of ethyl 2-formylpropionate with (carbethoxy)methylenetriphenyl phosphorane, an equimolar mixture of (*E*)-2-methyl- and (*Z*)-4-methylsubstituted esters **89b** and **92b** was obtained, but not the 4-methylsubstituted esters **91b** and **92b** as might have been expected.

In the presence of an acidic catalyst, (*E*)-2-methylglutaconic acid **89a** isomerizes to (*Z*)-2-methylglutaconic acid **90a**, but under basic catalysis, along with isomerization, tautomeric transformations take place, thus forming (*E*)-4-methylglutaconic acid **91a**. For example, (*E*)-2-methylglutaconic acid **89a** under the influence of H_2SO_4 or FSO_3H is converted into a mixture (29:71) of starting compound **89a** and (*Z*)-2-methylglutaconic acid **90a**. Under basic catalysis (KOH), the same acid **89a** gave in 75% yield the mixture (5:1) of acids **89a** and **90a** and 25% of (*E*)-4-methylglutaconic acid **91a**. Under photolysis both isomerization and tautomerization occur; for example, diethyl (*E*)-2-methylglutaconate **89b** affords a mixture of methyl esters (*Z*)-**90b** (46%), (*E*)-**91b** (5%), (*Z*)-**92b** (2%) with the starting compound **89b** (47%). Similar results were obtained upon $RhCl_3$-catalyzed thermal isomerization of acid **89a** or ester **89b**, and also of ethyl 2-methyleneglutarate. In other words, 4-methylglutaconic acids **91a**, **92a** or their esters **91b**, **92b** can not be prepared in pure form. The results of Kagan *at al.*[79] are thus of importance because they confirm the structures of the these compounds.

A complex, multistep synthesis of a hemiester of (*E*)-2-methylglutaconic acid **93** was carried out by Nader *et al.*[80] Its essence is clear from *Scheme 8*.

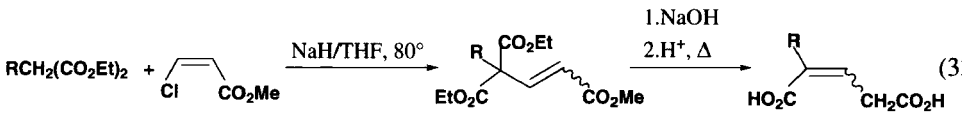


i) Et_3N *ii)* Zn/HOAc *iii)* $ZnCl_2$ *iv)* Zn *v)* HCl

Scheme 8

Monomethyl esters of (*E*)-2-isopropyl- and (*E*)-2-*tert*-butylglutaconic acids were prepared in a similar way. The CCl_3CH_2-protecting group was used in addition to the *tert*-butyl group in this synthesis. Another work[81] improved the known method[78] of preparing the mixture of (*E*,*Z*)-2-substi-

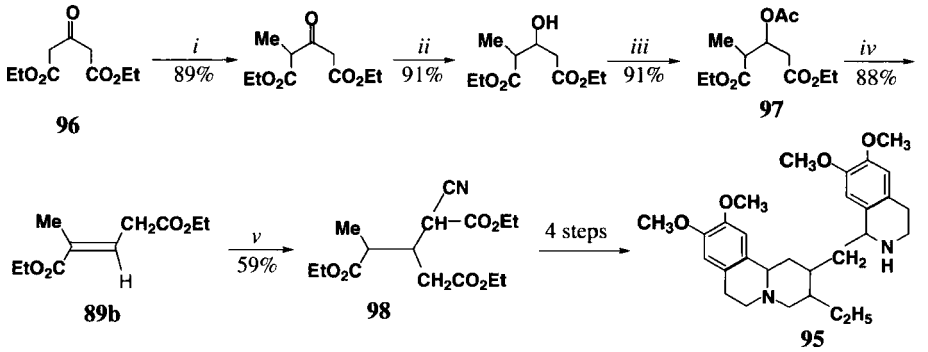
tuted glutaconic acids **94** starting from malonic esters and methyl (*Z*)-2-chloroacrylate (*Eq. 33*). This method was also used to obtain 3-*n*-butyl-**94a** (96% yield)-, 2-phenyl-**94b,** 2-(1-naphthylmethyl)-**94c,** 2-(2-naphthylmethyl)-**94d** (46% yield)-glutaconic acids. However, there were no attempts made to prepare 2-methylglutaconic acid by this procedure.[81]



(33)

a) R = *n*-Bu b) R = Ph c) R = CH_2(1-Np) d) R = CH_2(2-Np) **94a-d**

A synthesis of 8-methylemetine **95** has been described,[82] which required preparation of 2-methyl-3-(cyanocarbethoxymethyl)glutarate **98** as a key intermediate. The latter was prepared from ethyl acetonedicarboxylate **96** *via* a sequence shown in *Scheme 9*. The authors assumed that, on

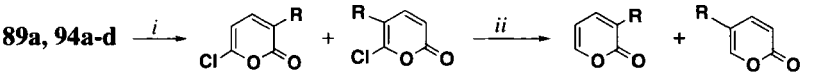


i) MeI/NaOEt *ii)*Ni/Re *iii)* Ac_2O *iv)* KOAc *v)* $NCCH_2CO_2Et$

Scheme 9

deacetylation of diethyl 2-methyl-3-acetyloxyglutarate **97,** diethyl 4-methylglutaconate is formed. However, taking into account the above results,[79] it may be reasoned that these workers[82] in fact obtained diethyl (*E*)-2-methylglutaconate **89b**, or its mixture with diethyl (*Z*)-2-methyl- **90b** or (*Z*)-4-methyl- **92b**-glutaconates.

2-Alkylsubstituted glutaconic acids **89a** and **94** were used to obtain 3- and 5-alkylsubstituted 6-chloropyran-2-ones **99** and **100**. According to Kagan *et al.*,[79] the treatment of (*E*)-2-methylglutaconic acid **89a** with an excess of acetyl chloride leads to the mixture of chloropyran-2-ones **99** and **100** (*Scheme 10*). Similar results were obtained by Boulanger and Katzenellenbogen[81] and by Weis and Winkler.[83] It was found that in this reaction, $SOCl_2$ and PCl_5 are more effective than AcCl, and



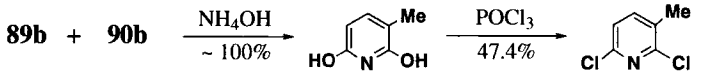
i) AcCl *ii*) Zn/AcOH

a) R = *n*-Bu b) R = Ph c) R = CH_2(1-Np) d) R = CH_2(2-Np)

Scheme 10

also that PBr_5 allows one to obtain the corresponding 6-bromopyran-2-ones.[81] The mixture of 6-chloropyranones **99** and **100** was separated chromatographically and pyranones **99b,d** and **100b** were reduced by Zn in AcOH to the respective 3- and 5-alkylpyran-2-ones **101b,d** and **102b**. Pyran-2-ones **99-102** have been tested as possible inhibitors of α-chymotrypsin. It was found out that 6-chloro-3-(2-naphthylmethyl)pyran-2-one (**97d**) rapidly deactivates this enzyme.

It was also shown[84] that the mixture of diethyl (*E,Z*)-2-methylglutaconates **89b** and **90b** reacts with aqueous ammonia with the formation of 2,6-dihydroxy-3-methylpyridine (**103a**); the latter gives 2,6-dichloro-3-methylpyridine (**103b**) on treatment with $POCl_3$ (*Eq. 34*). Some works[85,86] describe the formation of esters **89b-92b** as by-products.

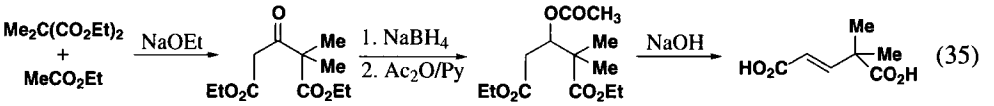


(34)

103a **103b**

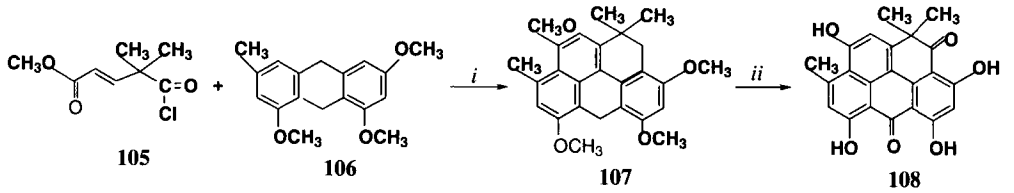
2. 4,4-Dimethylglutaconic Acid

(*E*)-4,4-Dimethylglutaconic acid **104** was prepared in low yield (17%) from diethyl dimethylmalonate and ethyl acetate[87] (*Eq. 35*). Photoaddition of ethyl propiolate to ethyl isobutyrate[88] gave a mixture (1.25 : 1) of diethyl esters of (*E*)- acid **104** and its (*Z*)-isomer in low yield (6%).



(35)

Acyl chloride **105**, prepared from the hemiester of (*E*)-4,4-dimethylglutaconic acid **110,** was involved into the five-step synthesis[89] of antibiotic resistomycin **108** (*Scheme 11*). The key step

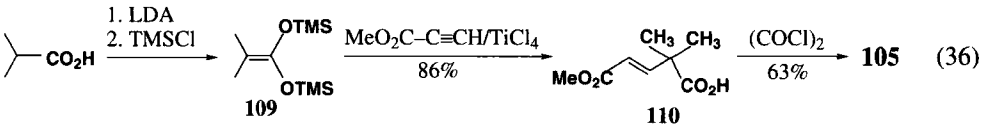


i) 1. $CH_3SO_3H/ClCH_2CH_2Cl$ 2. CF_3SO_3H/CF_3COOH 3. CH_3OH quench *ii*) 1. RuO_4 2. Py•HCl

Scheme 11

of this synthesis was the preparation of benzopyrene **107** through the reaction of acyl chloride **105** with anthracene derivative **106**.

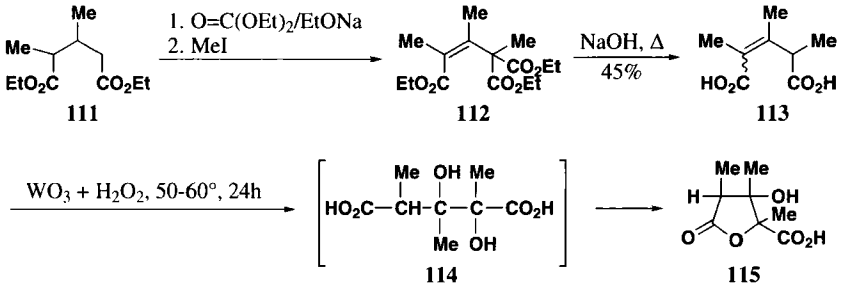
The precursor of acyl chloride **105,** hemiester **110**, was synthesized from methyl propiolate and ketene acetal **109**[88] and converted into **105** according to *Eq. 36*.



(36)

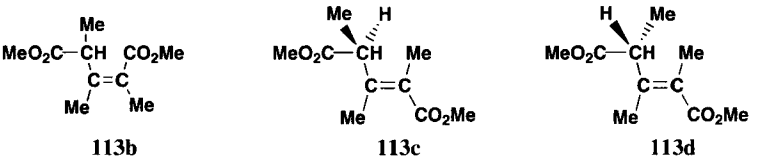
3. 2,3-Dimethyl- and 2,3,4-Trimethylglutaconic Acids

2,3,4-Trimethylglutaconic acid **113a** was obtained[91] from diethyl 2,3-dimethylglutaconate **111**, prepared[92] in turn by carbethoxylation of **1a** with subsequent methylation. Adams *et al.*[91] observed that the reaction product **111** is often contaminated with **3b** which is difficult to separate by conventional procedures. Pure 2,3-dimethylglutaconic acid was obtained (61% yield) by recrystallization of the saponified reaction product. For the introduction of the third methyl group into **111**, the latter was treated with ethyl carbonate in the presence of NaOEt and the resulting enolate alkylated *in situ* with methyl iodide. The reaction product, diethyl 2,3,4-trimethyl-4-carbethoxyglutaconate **112,** was hydrolyzed by sodium hydroxide and decarboxylated, giving the target acid **113a** as a mixture of (*E*)- and (*Z*)-isomers (*Eq. 37*). This mixture was used[91] for the synthesis of racemic monocrotalic acid **115**, a degradation product of pyrrolizidine alkaloid monocrotaline. To this end, the mixture of acids **113a** was hydroxylated with pertungstic acid into 2,3,4-trimethyl-2,3-dihydroglutaric acid **114** which on



(37)

lactonization led to a mixture of diastereomers of monocrotalic acid **115**. All the eight stereoisomers of monocrotalic acid **113** were synthesized[93] by *cis*-hydroxylation of methyl esters **113b-d** with $KMnO_4$.



B. Heterosubstituted glutaconates

2. Dialkyl 2-Oxoglutaconates

Diethyl 2-ketoglutaconate **117b** was obtained[94] in a very low yield (2%) from the oxidation of diethylglutaconate **116b** with SeO_2. A more efficient oxidant for this reaction is molecular oxygen in the presence of active carbon.[95] For example, dimethyl glutaconate **116a** gave dimethyl-2-oxoglutaconate **117a** in 53% yield (*Eq. 38*). Another way to ester **117a** was elaborated by Corey and Tramontano,[96] who started from methyl-2-oxoglutarate **118a**. On treatment with bromine the latter

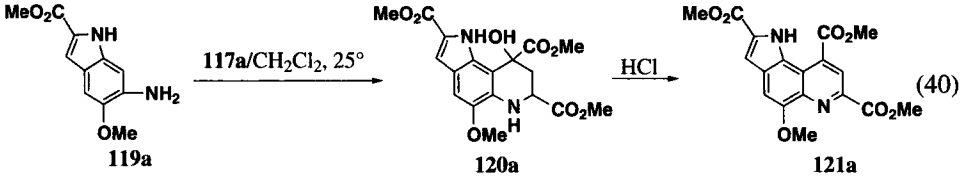
(38)

a) R = Me b) R = Et

was converted into α-bromoketone **118b** which smoothly eliminated HBr with Et_3N and gave the target ester **117a** (97% yield from compound **118a**) (*Eq. 39*).

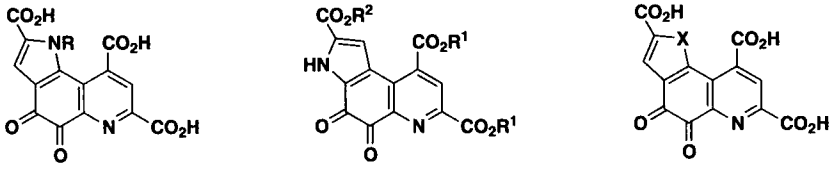
(39)

Corey and Tramontano[96] used this ester in the synthesis of compound **121a**, a precursor of methoxatin **122a**, the coenzyme of a dehydrogenase from methylotrophic bacteria *(Eq. 40).*



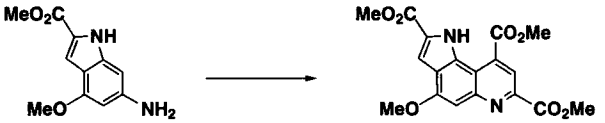
(40)

Aminoindole **119a** smoothly adds to glutaconate **117a**, giving piperidinol **120**; dehydration and dehydrogenation of the latter affords tricyclic product **121a** (90%). This approach was also explored[97] in the synthesis of coenzyme **122a** itself and its derivatives **122b,c** as well as azaisomers **122d,e,**[98a] furo-**122f**- and thieno-**122g**-analogs.[98b]



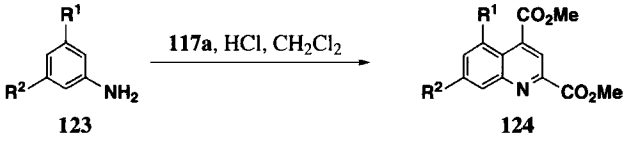
a) R = H b) R = Me c) R = $PhCH_2$ d) $R^1 = R^2$ = Me e) R^1 = Me, R^2 = Et, f) X = O g) X = S

MacKenzie *et al.*[99a,b] used the same protocol for the annelation of methoxyaminoindole **119b** with glutaconate **117a** and obtained tricyclic pyrroloquinoline **121b** (*Eq. 41*), converted further into methoxatin **122a**.



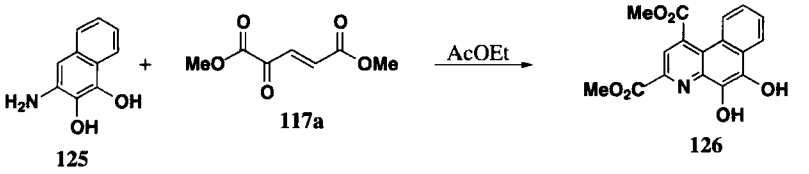
(41)

The method of Corey and Tramontano was used also in the synthesis of 2,4-disubstituted quinolines **124** from anilines **123** and ester **117a** (*Eq. 42*). These quinolines were further transformed into *cis*- and *trans*-2-carboxy-1,2,3,4-tetrahydroquinoline derivatives of biological interest.[100]



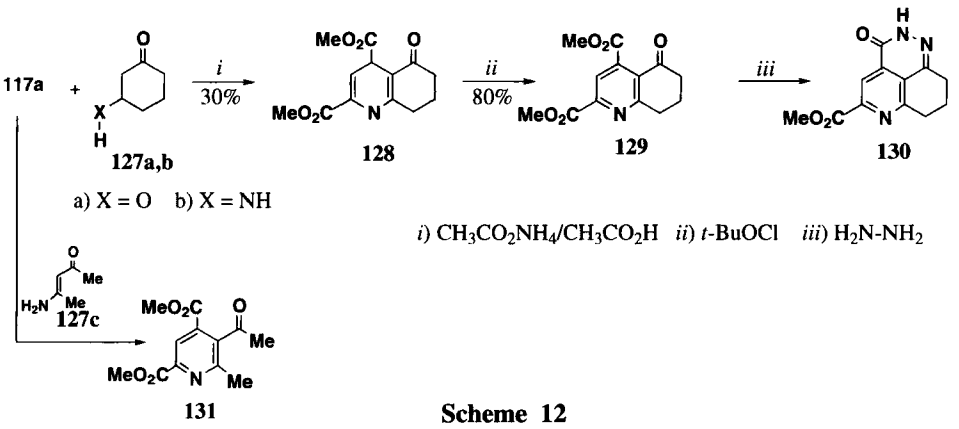
123 124 (42)

Recently,[101] in order to understand the role of the specific functional groups of methoxatin in the chelation of metal ions, new analogs of methoxatin were synthesized from benzoquinoline **126**, prepared from ester **117a** and aminodihydroxynaphthalene **125** (*Eq. 43*).



125 117a 126 (43)

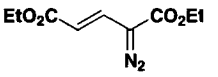
Compounds with a novel 2,3,7-triazaphenalene ring system, of interest as potential pharmacophores, were also described.[102] The condensation of cyclohexane-1,3-dione **127a** and glutaconate **117a** led to hexahydroquinoline **128.** Replacement of β-diketone **127a** by aminoketone **127b** made it possible to avoid the use of ammonium acetate and to obtain directly hexahydroquinoline **128** in 46% yield. Oxidation of the latter compound with *t*-BuOCl gives tetrahydroquinoline **129** which yields 2,3,7-triazaphenalene **130** on treatment with hydrazine (*Scheme 12*). Another illustration of this route involves the hyghly substituted pyridine **131** obtained (85% yield) from glutaconate **117a** and enamine **127c**.



Scheme 12

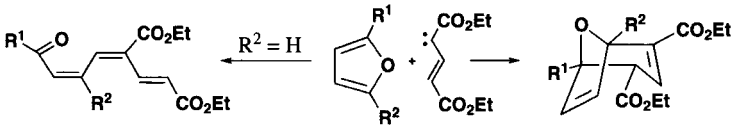
2. Diethyl (E)-4-Diazo-2-pentenedioate

Diethyl (*E*)-4-diazo-2-pentenedioate (**132**) was obtained by diazotization of diethylglutaconate **116b**. The diazo transfer was performed by using *p*-(*n*-dodecyl)- and *p*-acetamidobenzenesulfonyl azides in the presence of triethylamine. The yields of 4-diazoester **132** were 94% and 84% respectively.[103,104] The reaction is



132

stereospecific and independent of the isomer composition of glutaconate **116b**, always leading to the more stable (*E*)-isomer **132**. This diazoester **132** decomposes under the influence of rhodium(II) acetate catalyst, giving a vinylcarbenoid, which reacts with furans. Two types of compounds can be obtained depending on the furan structure.[103,105] 2,5-Disubstituted furans give exclusively the products of [3+4]cycloaddition, *endo*-adducts **133a** (*Eq. 44*), whereas monosubstituted furans give mainly

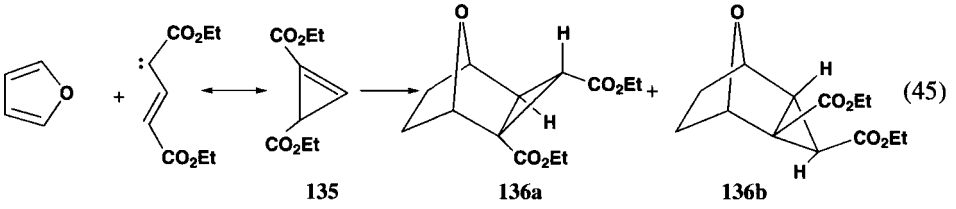


(44)

134 **133a**

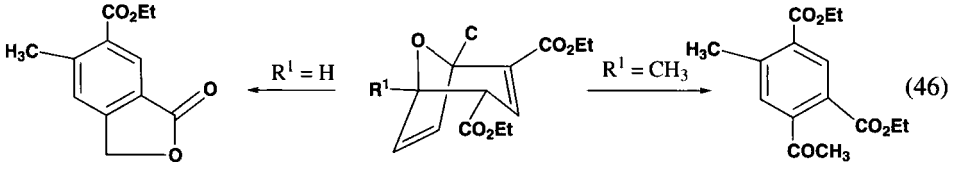
trienes **134**. Davies *et al.*[106] established that the mechanism of stereospecific formation of *endo*-adducts of structure **133** involves [3+4]cycloaddition of rhodium(II) acetate-stabilized vinylcarbenoids and dienes, which should proceed *via* a tandem cyclopropanation–Cope rearrangement process.

The reaction proceeds differently[105] upon irradiating diazoester **132** with UV light without a catalyst. In this case a mixture of adducts **136a** and **136b** (2:1), is formed as a result of the [4+2]cycloaddition of cyclopropene **135** to furan (*Eq. 45*). Davies *et al.*[105] attempted to obtain tropones and tropolones by ring opening of adducts **133b,c**, but the reaction products turned out to be polysubstituted aromatic compounds **137a,b** (*Eq. 46*).



(45)

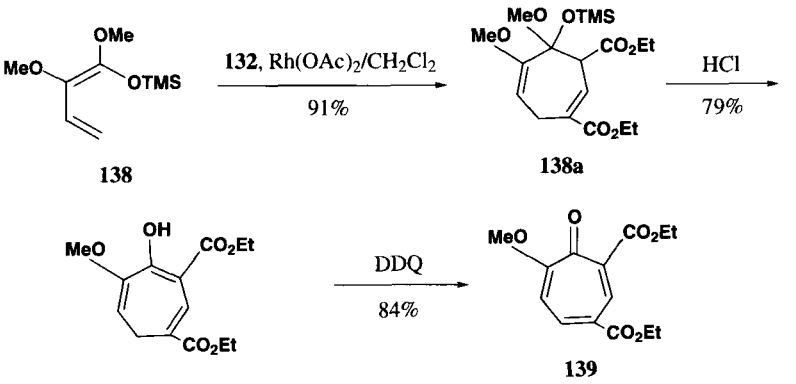
135 **136a** **136b**



(46)

137a **133b,c** b) $R^1 = H$ c) $R^1 = CH_3$ **137b**

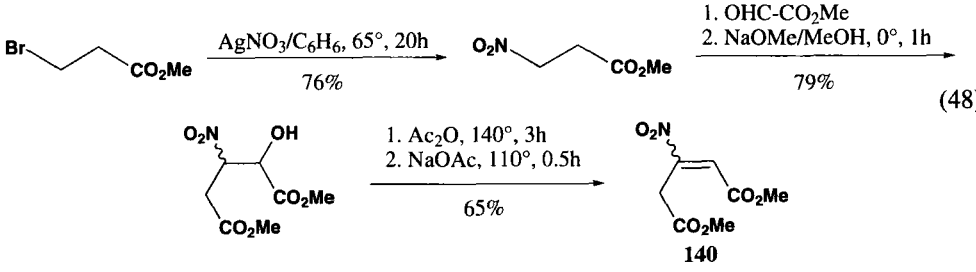
Vinylcarbenoids formed by the rhodium(II)-catalyzed decomposition of diazoester **132** react regioselectively with oxygenated dienes to give cycloheptadienes.[107] The latter are readily hydrolyzed and oxidized, and thus a general and direct route to highly functionalized tropolones was elaborated. For example, rhodium(II) acetate-catalyzed decomposition of **132** in the presence of 1,2-dimethoxy-1-(trimethylsiloxy)butadiene (**138**) gave adduct **138a**, which was easily converted into tropolone **139** (*Eq. 47*).



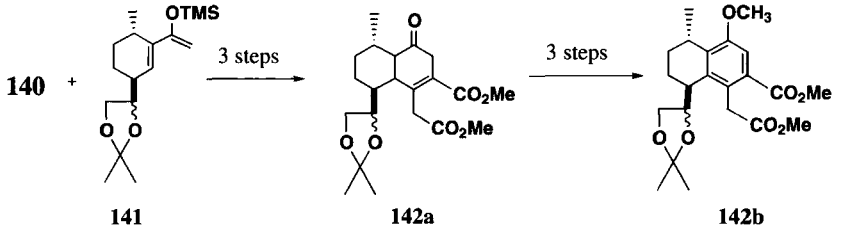
(47)

3. Dimethyl (E)-3-Nitroglutaconate

Recently a general approach to the synthesis of pseudopterosins[108] (a family of polar lipid metabolites isolated from a sea whip of genus *Pseudopterogorgia*) has been elaborated. Dimethyl (*E*)-3-nitroglutaconate **140** which serves as one of the starting compounds, was synthesized according to *Eq. 48*, starting from methyl β-bromopropionate.[108] The Diels-Alder reaction of diester **140** with diene **141** followed by the hydrolysis of the addition product and elimination of the nitro group afforded a mixture of diastereomeric ketoesters **142a,** which was converted in three steps into compound **142b**, an intermediate in the synthesis of pseudopterosin analogs (*Eq. 49*).



(48)



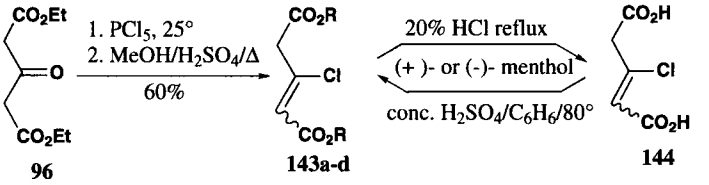
(49)

III. 3-CHLOROGLUTACONIC ACID AND ITS ESTERS

A. Preparation

Among the halogenated derivatives of glutaconic acids, 3-chloroglutaconic acid and its esters have found the widest application in synthesis. Dimethyl 3-chloroglutaconate **143a** was obtained as a mixture of (*E,Z*)-isomers (6:1) on chlorination of diethyl acetonedicarboxylate **96** with

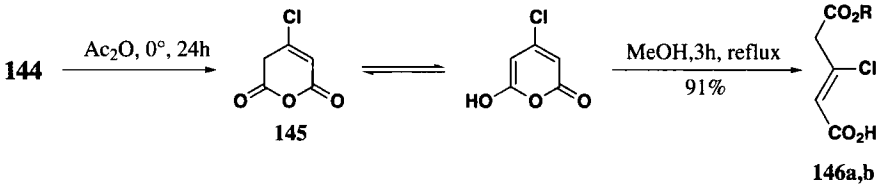
PCl_5 according to Ingold's method (*Eq. 50*).[109a,b] Aso *et al.*[110] prepared optically active 3-chloroglutaconates **143c,d** by esterification of 3-chloroglutaconic acid **144** with (+)- and (-)-menthols also as a



(50)

a) R = Me b) R = Et c) R = (+)-menthyl d) R = (-)-menthyl

6:1 mixture of (*E,Z*)-isomers. Nakamura[111] obtained diethyl 3-chloroglutaconate **143b** as a 10:1 mixture of (*E,Z*)-isomers. Acid **144,** on treatment with Ac_2O, gave anhydride **145,** the methanolysis of which led to the monomethyl ester of (*E*)-3-chloro-4-methoxycarbonylbuten-2-oic acid (**146a**), formed as a single isomer[112] (*Eq. 51*). Moreover, methanol attacks the unconjugated carbonyl group, so there is a complete analogy with 3-methylglutaconic anhydride (see sec. A). Note that Jung and



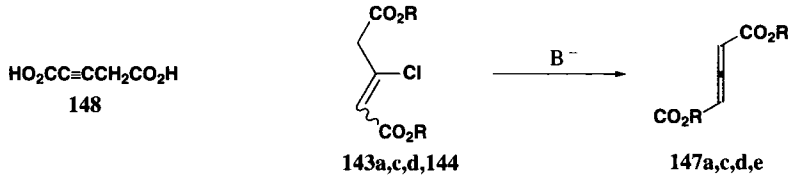
(51)

coworkers[113] reported the formation of a mixture of isomeric monoethyl esters **146b** upon hydrolysis of diethyl ester **143b**, to be used in preparation of acid **144**.

B. Synthetic Uses

1. Preparation of Allene-1,3-dicarboxylic Acids and Their Derivatives

The application of **144** and its ester **143a** to the synthesis of allenedicarboxylic acids and their derivatives is well known. The parent 2,3-pentadiene-1,5-dioic acid **147e** is formed upon dehydrochlorinating **144** with potassium hydroxide[114] in almost quantitative yield, and uncontaminated with "glutimic" acid **148**. The corresponding dimethyl ester **147a** was prepared in 64% yield by dehydrochlorination of dimethyl 3-chloroglutaconate **143a** with Et_3N (*Eq. 52*).[109a] Similarly, esters **147c,d**

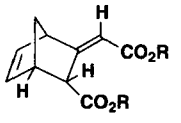


(52)

a) R = Me c) R = (+)-menthyl d) R = (-)-menthyl e) R = H

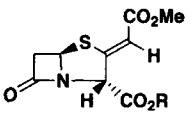
were prepared from optically active menthyl esters **143c,d.**[110] A number of mixed esters of allenedicarboxylic acids, synthesized from the respective 3-chloroglutaconates, were used for the preparation

of bi- and tricyclic compounds **149-152** which are intermediates in the synthesis of more complex biologically active compounds.[110,112,115,116]

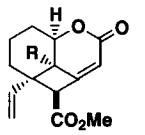


149

a) R = (+)- menthyl b) R = (-)-menthyl

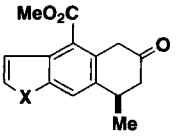


150a,b



151a,b

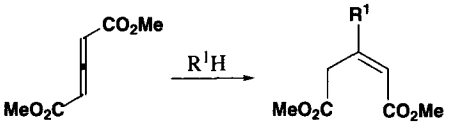
a) R = H b) R = Me



152a,b

a) X = O b) X = S

It should be also mentioned that dimethyl allenedicarboxylate **147a** gives stable adducts with a number of alcohols and amines, namely dimethyl esters of 3-substituted glutaconic acids **153a-h** (*Eq. 53*).[117] The product resulting from the addition of cyclohexylamine is a mixture (4:1) of (*Z*)- and (*E*)-isomers, but all other 3-substituted glutaconates **153** have the (*E*)-configuration. Hence,



(53)

147a **153a-h**

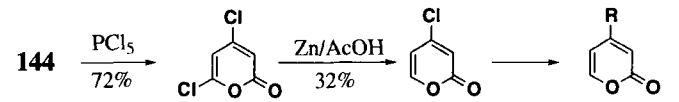
a) R^1 = MeO b) R^1 = EtO c) R^1 = *i*-PrO d) R^1 = OPO(OEt) e) R^1 = NEt_2

f) R^1 =  g) R^1 =  h) R^1 = C_6H_{11}

3-chloroglutaconates may be used for the stereospecific preparation of a number of 3-substituted glutaconates, using the respective esters of 2,3-pentadiene-1,5-dioic acid.

2. Synthesis of Substituted (2H)-Pyran-2-ones

With PCl_5, acid **144** gives 4,6-dichloro-2*H*-pyran-2-one (**154**), which upon reduction affords 4-chloro-2*H*-pyran-2-one (**155**). The latter was used as a starting material for the synthesis of 4-substituted pyran-2-ones **156a-d** (*Eq. 54*).[118]



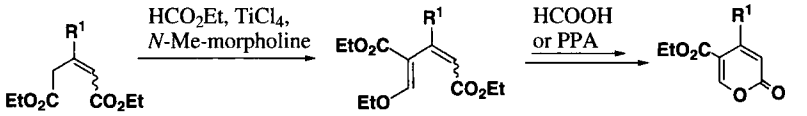
(54)

154 **155** **156a-d**

a) R= SO_2CH_3 [CH_3SO_2Na, 58%] b) R=SCH_2Ph [$PhCH_2SH/K_2CO_3$, 50%],
c) R=OPh [PhONa, 40%] d) R=$N(CH_2)_4$ [$HN(CH_2)_4$, 15%]

A method for the preparation of 4-substituted 5-carbethoxypyran-2-ones **158** was also developed.[119] 4-Chloro-5-carbethoxy-2*H*-pyran-2-one (**158**, R^1 = Cl) was synthesized from diethyl 3-chloroglutaconate and ethyl formate, which reacted in the presence of $TiCl_4$ and *N*-methylmorpholine, to give compound **157** (R^1 = Cl) (70% yield). Subsequent reaction of **157** (R^1 = Cl) with HCO_2H or PPA afforded pyrone **158** (R^1 = Cl) in 31% and 57% yield, respectively. This method appears to be general (*Eq. 55*) and involves the following glutaconates (the yields of **157** and **158** and the cyclizing

reagent are indicated in the Table 4).

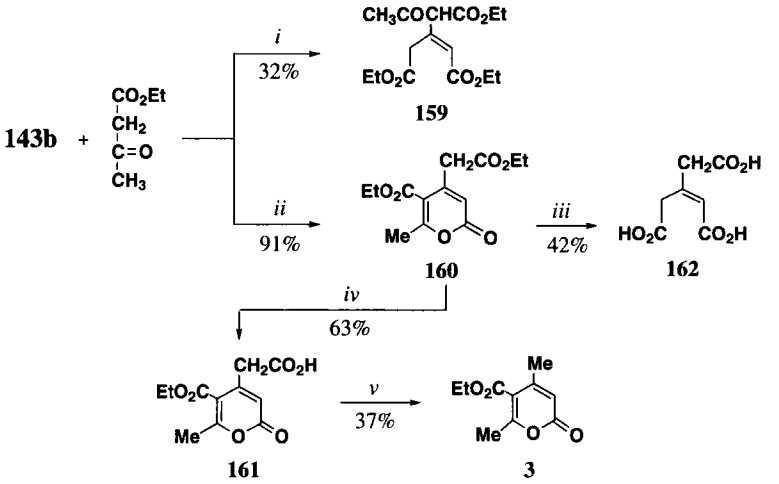


153 b,i-p 157 b,i-p 158 b,i-p (55)

TABLE 4. Preparation of Pyranones **157**

153	R^1	Cyclization agents	Yield (%) **157**	Yield (%) **158**
b)	EtO	PPA	52	58.7
i)	*n*-Bu	HCOOH	50	96.5
k)	H	HCOOH	72 (*E*:*Z* = 6:1)	26.9 from (*Z*) 35.7 from (*E*)
l)	F	PPA	76.9	28
m)	$PhCH_2S$	HCOOH	94	68.7
n)	CH_2SO_2	PPA	60.9	26.3
o)	EtOCO	HCOOH	45	54
p)	Ph	HCOOH	47	60

The reaction of glutaconate **143b** with sodium ethyl acetoacetate in anhydrous ethanol gave 3-(1-acetyl-1-carbethoxy)methylglutaconic acid **159** (*Scheme 13*).[120] Replacemet of ethanol by benzene led 6-methyl-5-carbethoxy-4-carbethoxymethylpyrone-2 (**160**). The acid-catalyzed hydrolysis of compound **160** resulted in the acid **161,** which underwent decarboxylation upon heating with

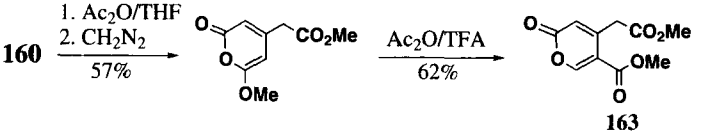


i) Na/EtOH *ii)* NaH/C_6H_6 *iii)* NaOH *iv)* 50% H_2SO_4 or HCl *v)* Cu bronze, 230-240°, 0.5 h

Scheme 13

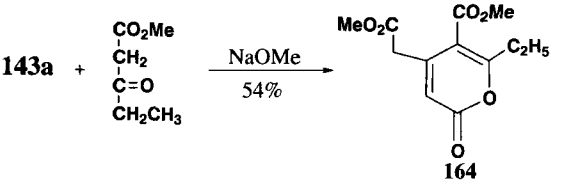
copper bronze to afford **1a**. If the hydrolysis of pyrone **160** is carried out with dilute aqueous NaOH,

the product is 3-carboxymethyl glutaconic acid **162** (*Scheme 13*).[121] This acid was employed in the synthesis of pyrone **163** (*Eq. 56*), a convenient synthon for the preparation of some antibiotics of the anthracycline group[70,71] (*cf.* sec. A).



(56)

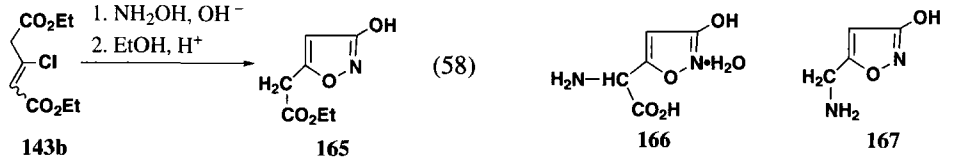
Methyl 6-ethyl-5-(methoxycarbonyl)-2-oxo-2*H*-pyran-4-acetate (**164**) was involved as the key intermediate in one of the approaches to the synthesis of antibiotic aklavione. This intermediate was obtained by condensation of dimethyl 3-chloroglutaconate **143a** with methyl 3-oxopentanoate (*Eq. 57*).[122a,b]



(57)

3. Synthesis of Isoxazoles

Diethyl (*Z*)- and (*E*)-3-chloroglutaconates **143b** interact with hydroxylamine in a strongly alkaline medium, and after esterification furnish ester **165** in 60% and 53% yields respectively (*Eq. 58*).[123] This isoxazole was used as a starting material for the synthesis of *d,l*-ibotenic acid **166** and

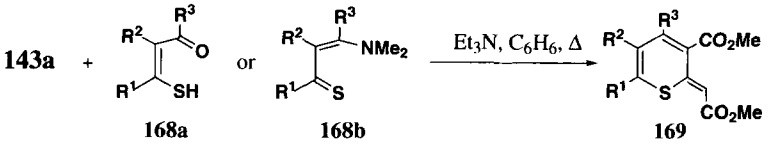


(58)

muscimol **167**, biologically active compounds, isolated from some *Amanita* mushrooms, which act on the central nervous system; *d,l*-ibotenic acid also exhibits pesticide properties.

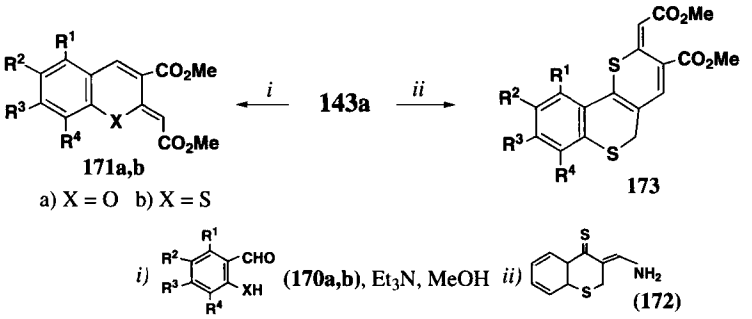
4. Preparation of Substituted Thiopyrans, Benzothiopyrans and Benzopyrans

Base-catalyzed cyclocondensation of dimethyl 3-chloroglutaconate **143a** with mercapto ketones of general formula **168a** or with enamino thioketones **168b** affords 2-[(alkoxycarbonyl)-methylene]-2*H*-thiopyran-3-carboxylates **169** in 70-80% yields (*Eq. 59*). Compounds **169** are useful



(59)

intermediates in the preparation of polymethylene dye-stuffs.[124a,b] In a similar way, the cyclocondensation of substituted salicylic **170a** or thiosalicylic **170b** aldehydes with dimethyl 3-chloroglutaconate affords benzopyran **171a** or thiobenzopyran **171b** respectively, patented as dyes and photographic sensitizers.[125a,b,126] From 3-dimethylaminomethylene thiochroman-4-thione (**172**), a more complex heterocyclic compound **173** was prepared (*Scheme 14*).[127]



Scheme 14

IV. CONCLUSIONS

The data examined in this review show that over the last 15-20 years, substituted glutaconic acids and their derivatives have found a number of useful applications in organic synthesis. Nevertheless, their synthetic potential has not been fully explored, and much more work is needed. This is convincingly confirmed by the results obtained recently on the synthesis of 4-substituted 2-fluoroglutaconates, an important class of intermediates for the preparation of biologically active compounds.[128] Further, the important reactions of glutaconates with ketones have not been fully investigated.

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