Synthesis and Biological Activity of α-Methylene-γ-butyrolactones

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Dedicated to Dr. Wilhelm A. Schuhler on the occasion of his 70th birthday

α-Methylene-γ-butyrolactones [dihydro-3-methylene-2(3H)furanes] constitute an important group of natural products and possess wide-ranging biological activities. Progress in the synthesis of the heterocycle and the classification of the synthetic methods are not only of practical interest, but also fundamentally important as a current example for the construction of an unusual 1,4-functionality distance and an α-substituted acrylic ester moiety which is susceptible to nucleophilic attack.

1. Introduction

The α-methylene-γ-butyrolactone ring is an integral building block of many natural products, especially the sesquiterpene lactones, which exhibit interesting biological properties. In a book published in 1973, ca. 200 representatives of this class of compounds together with their 1H-NMR spectra and other physical data were listed; 6 years later there were already ca. 90016. Since then the number of these compounds has risen further: a Chemical Abstracts Online Search with projection shows that at present at least 2000—3000 α-methylene-γ-butyrolactones, mainly of the sesquiterpene type, are known. Since the current number of structurally elucidated natural products has been estimated to be only between 25 000 and 30 00021, α-methylene-γ-lactones represent (with approx. 10%) a major class of known natural products. α-Methylene-γ-butyrolactones have been dealt with in a series of articles2a-d, which quickly appeared following the first review by Grieco3 in 1975. After a description of the biological activities it is our purpose to present the various conceptions for the synthesis of the heterocycle and to describe recently developed syntheses.

2. Biosynthesis

The biosynthesis of the sesquiterpenoid α-methylene-γ-butyrolactones is fairly simple1,3. The compounds are derived from trans,trans-farnesyl pyrophosphate, which first cyclizes to give the strained cyclodecadiene skeleton of germacradiene (or germacratriene) and then reacts further intramolecularly to form a perhydroazulene system (e.g., guaiane and pseudoguaiane) or a decalin system (e.g., eudesmane). The sequence of oxidation steps is less well understood. In accord with Scheme 1, the lactone moiety, which is indicated by the suffix "olide", is cis- or trans-fused to a six-, seven-, or ten-membered ring. Further rearrangements and oxidative modifications give rise to the structural diversity of these compounds.

Many plants which belong to the large, species-rich family of the Compositae16,21 (composites) contain sesquiterpene lactones as characteristic constituents. These compounds are colorless, lipophilic, often bitter-tasting, and are mainly present in the leaf tissue, where they can constitute up to 5% of the dry weight. The closer two species are related to each other, the smaller is the difference between the distribution of these terpenes. In addition to morphology, i.e., the comparison of external plant form, chemotaxonomy, in which secondary plant metabolites are identified and compared, has established itself as a method for the botanical classification of plants and for the clarifica-
tion of evolutionary problems (sesquiterpene lactones as chemotaxonomic markers).}

3. Important Biological Activities

\(\alpha\)-Methylene sesquiterpene lactones show cytotoxic, antitumoral, and bactericidal properties. Other representatives cause an allergenic contact dermatitis or affect plants by inhibition of growth. There are already several studies on the relationship between biological activity and structure. As has been shown, \(\alpha\)-methylene-\(\gamma\)-butyrolactones must be looked upon as alkylating agents which are biologically active because they undergo a Michael reaction with biological nucleophiles such as L-cysteine or thiol-containing enzymes (Enz-SH).

\[
\text{TS-Enz + Enz-SH} \rightarrow \text{S-Enz}
\]

It is probable that these lactones inhibit the incorporation of selected amino acids into proteins, i.e., they inhibit the metabolism at the cellular level, but do not alkylate DNA.

Presumably, the residual molecule and its lipophilicity also determine the specificity and the site of the activity.

3.1. Antitumoral and Cytotoxic Activity

A large number of active sesquiterpene lactones, including vernolepin, aromaticin, and elephantopin, have been isolated from plant extracts which show tumor-inhibiting activity (Scheme 2).

It has been shown that almost all known cytotoxic sesquiterpene lactones possess an \(\alpha,\beta\)-unsaturated lactone structure, and that the conjugated double bond must be exocyclic. A cyclopentenone or an additional \(\alpha\)-methylene lactone moiety enhances the cytotoxic activity; hydroxy groups can also cause an enhancement. The high cytotoxicity of the sesquiterpene lactones is probably due to the inhibition of DNA synthesis and/or transcription. Howev-er, protein synthesis, also, is partially impaired. It should be mentioned, however, that at present there is no sesquiterpene cytostatic which is used clinically, apparently because of the relatively high toxicity of the compounds. Attempts to increase the activity by chemical modification have, so far, been unsuccessful.

3.2. Allergenic Activity

Many people suffer from an allergic contact dermatitis (ACD) which is caused by contact with plants or their chemical constituents. Sesquiterpene lactones, which are sometimes present in the pollen, can cause this allergic contact dermatitis—even when carried by the wind. The presence of an \(\alpha\)-methylene butyrolactone moiety is a sufficient requirement for the allergenic activity. For example, parthenin, present in *Parthenium hysterophoros*, is a primary allergen of this widespread and unusually aggressive pioneer plant. The allergy thus caused represents a serious dermatological problem in India and her neighboring countries.

Perfume oils extracted from the costus root (*Saussurea lappa*) or from the laurel (*Laurus nobilis*), cultivated since antiquity, can also cause a dermatitis due to the germacranelide costunolide present in both mixtures. In order to obtain a perfume free from allergens, one passes the raw oil through a column containing a nucleophile on a solid support, e.g., \(\beta\)-aminoethyl-poly styrene. Thus, the allergen is bound to the nucleophilic. Finally, even simple acrylic esters, such as those used in the printing trade and in other industries, can cause occupational dermatitis.

With respect to the pathogenesis of ACD, it is assumed that the \(\alpha\)-methylene lactone becomes bonded to a skin protein via a Michael reaction, thus forming an antigen which causes the sensitization of the lymphocytes. In view of the widespread occurrence of ACD, further research efforts can be expected in this area.

3.3. Phytotoxic and Antimicrobial Activities

In addition to the cytotoxic and allergenic activities described, phytotoxic activities are shown by a number of sesquiterpene lactones. Thus, heliangin, a germacranolide of the tuberous sunflower (*Helianthus tuberosus L.*, also called topinambur or Jerusalem artichoke), and vernolepin, from *Vernonia hymenolepis*, cause plant growth inhibition. Xanthatin is also used in the regulation of plant growth (Scheme 4).

According to Hager, \(\alpha\)-methylene sesquiterpene lactones can attack an SH-group of the auxin-receptor complex; upon binding of the growth hormone auxin to its protein receptor the SH-group is set free. As a result of this
sulfur bond, the lactone effects the irreversible inhibition of plant growth. The \( \alpha \)-methylene lactones present in the common sunflower (Helianthus annuus L.) appear to be stress metabolites, i.e., they are formed, e.g., during attack by pests, during periods of dryness or overexposure to sunlight and heat, and probably act mainly as chemical defenses against pests, especially microorganisms \[24c1\]. This fascinating plant, originating in the USA and Mexico, is mainly cultivated at present in the USSR and in Eastern Europe. It is, after the soybean, the second most important oil-producing plant in the world (annual world production in 1982 more than 16 million metric tons of sunflower seeds) \[24d1\].

Other \( \alpha \)-methylene-\( \gamma \)-butyrolactones show bactericidal, fungicidal, and anthelminthic activities \[25\]. Helenalin \[26a1\] and eremanthin \[26h1\] are shown here as representatives of such compounds (Scheme 5).

Recently, Picman et al. were able to show that sesquiterpene lactones such as parthenin and alantolactone, which are present in the sunflower, also play a role in the defense of plants against insects \[27a-e\] and even against herbivorous mammals \[27d\]. Similarly, euponin, which has been isolated from the leaves of Eupatorium japonicum, inhibits the development of the fruit fly (Drosophila melanogaster) at the egg stage and thus protects the plant from insect attack \[27e\] (Scheme 6).

Not only highly functionalized, complex sesquiterpene lactones but also simple representatives have been studied for their biological activity. Several years ago, two compounds with fungicidal properties were isolated from tulip bulbs and identified \[28\]. Tulipalin A is the simplest \( \alpha \)-methylene-\( \gamma \)-butyrolactone possible (Chemical Abstracts Name: dihydro-3-methylene-2(3H)furanone). The 4-hydroxy derivative, i.e., tulipalin B, is present in nature as the (S)-enantiomer (Scheme 7). It appears certain that \( \alpha \)-methylene-\( \gamma \)-butyrolactones, due to their high and selective antibiotic activities, afford important protection to plants. In the course of evolution, this fact, together with the outstanding adaptive and reproductive capabilities of the Compositae, has contributed to a selective advantage in the survival of this plant family and also to its broad distribution over all continents with the exception of Antarctica.

Thus, \( \alpha \)-methylene-\( \gamma \)-butyrolactones can serve as a model in the search for biological activity. The structurally related five-membered-ring \( \alpha \)-methylene ketones pleurotellol and pleurotellic acid have been found in fungi and show antibiotic activity \[29\] (Scheme 8).

In view of the similarity of the ester group to the \( \text{P(O)(OR)} \), group as \( \pi \)-acceptor (compare also the Horner-Wittig reaction), a corresponding modification of the lactone is of interest. As Beneza et al. \[30\] were able to demonstrate, the biological activity changes: cyclic phosphonates (Scheme 10) show no allergenic activity and only a very low cytotoxicity.

Because of their broad range of biological activities and their interesting structural features, \( \alpha \)-methylene-\( \gamma \)-butyrolactones present a scientific challenge which is reflected in an increasing number of investigations and syntheses of these heterocycles.
4. Syntheses of \( \alpha \)-Methylene-\( \gamma \)-butyrolactones

Two main problems dominate the synthesis of these lactones:

1. The construction of the unusual 1,4-functionality distance in the acrylic precursor of the heterocycle. This fundamental synthetic problem, which also appears in the synthesis of simpler five-membered heterocycles such as the furans, pyrroles, and thiophenes as well as their saturated derivatives, can be solved, among other methods, by "umpolung" \(^\text{43}^*\), e.g., the combination \( a^2+d^2 \), where the \( d^2 \) component is frequently an enolate and the \( a^2 \) component an epoxide (umpolung). The combination \( a^2+d^2 \) is also feasible: in an efficient synthesis the \( d^3 \) building block (umpolung) is also an \( a^3d^3 \) component (cf. Section 4.3).

\[
\begin{align*}
\text{HO} & \quad \text{HO} \quad \text{O} \quad \text{CO}_2\text{Me} \\
\text{a}^2 & \quad \text{d}^2
\end{align*}
\]

2. The construction of the nucleophile-sensitive \( \alpha \)-acrylic ester moiety.

The presence of additional oxygen-containing functionality and the stereochemistry of the residual carbocyclic portion of the molecule increase the appeal of the naturally-occurring sesquiterpene lactones as a synthetic goal. However, the total syntheses of these complex compounds and the elegant work already carried out have recently been described comprehensively in a book by Heathcock \textit{et al.}\(^\text{43}^*\) and will remain largely neglected here. Instead, we will concentrate on the methods of synthesis of the simple, key five-membered-ring. Insofar as meaningful, we will use the retrosynthetic approach both for the classification and the mechanistic interpretation of the large number of synthetic methods. Thus, the organization of the article is predetermined (cf. Scheme 11).

Scheme 11.

If the molecule is dissected as outlined in Sections 4.1—4.4, the educt can be regarded as a functionalized acrylic ester.

The direct \( \alpha \)-functionalization of acrylic compounds via the \( \alpha \)-anion is only of limited use due to the pronounced tendency of acrylic esters to polymerize under basic conditions\(^\text{525}^*\). For this reason, the detour via masked acrylic esters is often chosen, since these are generally easier to functionalize.

\[
\begin{align*}
\text{CO}_2\text{Me} & \rightarrow \text{CO}_2\text{Me} \\
\text{R} & \rightarrow \text{R}
\end{align*}
\]

The problem of polymerization of \( \alpha \)-acrylic esters can be circumvented in different ways. On the one hand, the reactivity of the carbonyl group can be masked by conversion of the ester group or the aldehyde group into an ortho ester or an acetal, respectively.

\[
\begin{align*}
\text{CO}_2\text{R} & \rightarrow \text{C(OR)}_3 \\
\text{CHO} & \rightarrow \text{CH(OR)}_2
\end{align*}
\]

On the other hand, it is possible to mask the CC double bond, e.g., by adding groups in the \( \alpha \)- and \( \beta \)-positions that are capable of undergoing elimination (Scheme 12). Masking is also possible by reversible cycloaddition (see Section 4.8).

Scheme 12. \( X \) = groups capable of elimination.

4.1. Cyclization of 4-Hydroxy-2-methylenebutanoic Acids

Dissection:

This dissection reduces the synthesis to the preparation of a homoallyl alcohol, the methylene group of which must also be part of an acrylic acid or a masked acrylic acid. Marino \textit{et al.}\(^\text{36a,b,43}^*\) used the diethyl acetal of acrolein as acrylic acid equivalent and allowed it to react as the cuprate (\( d^2 \) building block) with epoxides (\( a^3a^2 \) building block) (Scheme 13). The two isomeric alcohols formed contain the desired 1,4-functionality distance or vinylous 1,4-distance and can be cyclized to trans- and cis-fused \( \alpha \)-methylene lactones 1a and 1b, respectively, following oxidation to their respective acids. As a \( d^2 \) component for the reaction with epoxides, dimethyl sodiomalonate has been used, also; subsequent decarboxylationative methylenation (cf. Section 4.7) gives the \( \alpha \)-methylene lactone\(^\text{43}^*\).
After masking of the double bond, acrylic compounds can also be functionalized. This can be accomplished by introducing a phenylseleno group via the dianion of 2-phenylselenopropionic acid according to Petagnani and Ferraz[38] or of a trimethylsilyl group according to Fleming et al.[38] (Scheme 14). After cyclization, both groups can be eliminated with regeneration of the double bond. However, in the case of the silicon compound a bromination is necessary; the selenide, which only needs to be oxidized to the selenoxide, is especially useful, because intramolecular elimination is spontaneous. In both reactions the trans-lactone 2 is formed.

Functionalized allylsilanes appear as intermediates in the syntheses described by Fujita et al.[41] and Sakurai et al.[42] also. The key step in Fujita’s (Scheme 17) work is a desilylating oxidation of an allylsilane to give an α,β-unsaturated aldehyde. This was achieved in a novel way, using iodosylbenzene, which was activated by coordination with a Lewis acid. In contrast to the oxidation of an allylsilane with m-chloroperbenzoic acid, which proceeds with allyl inversion (intermediate formation of the epoxide), the formation of 4 and 4a proceeds with allyl retention. In the case of oxidation giving 4 and 4a, an S2' attack on the electron-rich allylsilane is followed by an intramolecular 3,2-shift. Sakurai et al.[42] allowed the trimethylsilyl ester 5 to react with an acetal and obtained by dealkylation the α-methylene-γ-butyrolactone (Scheme 17).
The combined homoallylic alcohol-allylic alcohol such as 4, formed in the reaction sequence of Itoh\(^{40}\) (Scheme 16), is an intermediate in many other synthetic routes since the selective oxidation with MnO\(_2\) yields a cyclizable compound and therefore offers convenient access to the desired lactones. Thus, in the work of Pinnick et al.\(^{42b1}\) (Scheme 18) the protected isopulegol 6b is converted into the epoxide 7b, which in the presence of the strong base LiNEt\(_2\) undergoes a regioselective E2 reaction to give the allylic alcohol. The further oxidation of the \(\alpha,\beta\)-unsaturated aldehyde, formed by reaction of the alcohol with MnO\(_2\), to give the \(\alpha,\beta\)-unsaturated carboxylic acid is not trivial, nor is the oxidation of other allylic alcohols to their carboxylic acids. Recently, inexpensive NaClO\(_2\) has been recommended for this oxidation, also in the presence of sensitive functional groups.

With MnO\(_2\), the epimeric diol 8 is directly converted via the cyclic hemiacetal into cis-p-menthenolide\(^{42b}\). Thus, cyclization to the cis-fused lactone proceeds more easily than to the trans-fused isomer.

In the route described by Kozikowski et al.\(^{43a2}\) (Scheme 19) an isoxazoline, formed by cycloaddition, is reductively opened and the exo-methylene double bond is then formed by a Wittig reaction. Again, cleavage of the tetrahydropropynyl (THP) ether and oxidation with MnO\(_2\) affords the \(\alpha\)-methylene lactone.

N-substituted methacrylamides can be used as synthetic equivalents of the hypothetical \(\alpha'd'd'\) methacrylic acid since they are more easily deprotonated and alkylated than acrylic esters. This method, developed in 1980, was used by three different research groups in the synthesis of \(\alpha\)-substituted acrylamides\(^{47}\) and of \(\alpha\)-methylene lactones\(^{48,44a}\) (Scheme 22). These syntheses proceed via the dianions 10b and 11, which polymerize less easily, probably because the amide nitrogen chelates a lithium ion and the reactivity of the carbonyl group is simultaneously reduced by electron delocalization. Trapping with ketones yields the cyclizable homoallylic alcohols (cf. also Section 4.3, i.e. the umpolung of \((Z)\)-2-bromomethyl-2-alkenoic esters to give \(\alpha'd'd'\) components).

An interesting \(\alpha'd'd'\) building block is the readily accessible, doubly activated triethyl 2-propene-1,1,2-triacrylate, as shown recently by Dowd et al.\(^{49e}\). For this compound even catalytic amounts of potassium bicarbonate suffice for deprotonation and for bringing about the nucleophilic addition to formaldehyde. After decarboxylation of the crude lactone diester with hydrochloric acid, the crystalline \(\beta\)-carboxylic acid of \(\alpha\)-methylene-\(\gamma\)-butyrolactone is obtained in 54% overall yield. Alternatively, butadiene-2,3-dicarboxylic acid has been converted smoothly into bromomethyl-itaconic acid, which in turn cyclizes

2,3-\(\text{O-Isopropylidenglyceraldehyde}\)—a chiral building block which has been used a great deal recently and has perhaps also become something like a vogue compound\(^{43e1}\)—was homologated in several steps to 9 and then cyclized to tulipalin B using acid catalysis\(^{43c1}\) (Scheme 20).

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\[ \text{Scheme 18. (a) m-Chloroperoxybenzoic acid (CPBA). (b) LiNEt}, \quad \text{–78°C-RT.} \quad \text{(c) 1) Desilylation, 2) DCC, pyridine (77%); or 1) MeW}, \quad \text{CHCl}_3, \quad \text{A, 2) Distillation.} \]

\[ \text{Scheme 19. (a) 1) H}_2, \quad \text{Raney nickel, 2) H}_2C=\text{PPh}_3. \quad \text{(b) i) TolOH}, \quad \text{MeOH (OTHP—OH), 2) MnO}_2, \quad \text{CH}_2\text{Cl}_2.} \]

\[ \text{Scheme 20. (a) 5 steps. (b) 1 NHCl.} \]

\[ \text{Scheme 21. (a) 1) KH, 2) LiAlH}_4, \quad \text{(b) 1) MnO}_2, \quad \text{C}_6\text{H}_6, \quad \text{2) CF}_3\text{CO}_{2}\text{H, 3) PrOH, NaOH. (c) CrO}_3, \quad \text{pyridine, CH}_2\text{Cl}_2 (\text{Collins oxidation).} \]

\[ \text{Scheme 22. (a) 1) KH, 2) LiAlH}_4, \quad \text{(b) 1) } \text{MnO}_2, \quad \text{C}_6\text{H}_6, \quad \text{2) CF}_3\text{CO}_{2}\text{H, 3) PrOH, NaOH. (c) CrO}_3, \quad \text{pyridine, CH}_2\text{Cl}_2 (\text{Collins oxidation).} \]

Scheme 22. (a) 2 BuLi/N,N,N',N'-tetramethylenediamine (TMEDA)/THF, -70 - 20°C 1 h. (b) Ph2CO. (c) Xylene, reflux, 3 d. (d) KOrBu/BuLi. (e) 1) R=CO, 2) H2O. (f) 10\% HCl. 

spontaneously to the same lactone in neutral or basic conditions[469] (Scheme 23).

\[
\begin{align*}
\text{CO}_2\text{H} & \xrightarrow{\text{a})} \text{CO}_2\text{Et} \\
\text{HO} & \xrightarrow{\text{b})} \text{CO}_2\text{Et} \\
\text{CO}_2\text{H} & \xrightarrow{\text{c})} \text{HO} \\
\text{Br} & \xrightarrow{\text{d})} \text{HO}
\end{align*}
\]

m.p. = 105-107°C

m.p. = 118-120°C

Scheme 23. a) 35\% CH3O, catalytic amounts KHCO3, 65°C, 25 min. b) 20\% HCl. c) HBr/\text{AcOH} (1 mol). d) neutral or basic solvent.

4.2. Cyclization of 2-Methylene-4-pentenoic Acids

Dissection:

Raucher et al.[150] used the Claisen ortho ester rearrangement, which leads directly to the desired arrangement of carboxyl group and terminal CC double bond, i.e., to the γ,δ-unsaturated carboxylic acid or 4-pentenoic acid; cyclization was accomplished via seleno-lactonization. Oxidation of the selenium group and spontaneous elimination gave the α-methylene group and—thanks to the second phenylselenide group—another double bond (Scheme 24).

By analogy with the synthesis described by Raucher et al.[150], Still et al.[193] had previously started from an allylic alcohol and used a Claisen triethylsilylketene acetal rearrangement, i.e., the Ireland variant, for the synthesis of a functionalized acrylic ester, which was converted into the desired frullanolide in two steps in 30\% total yield (Scheme 25).

Mechanistically related is the one-pot reaction recently described by Yatele[520] for the synthesis of α-methylene-γ,δ-unsaturated esters. An allylic alcohol is again used as starting material, which is transformed in three steps into a cyclizable 2-methylene-4-pentenoic acid (Scheme 26):

1. nucleophilic substitution at the activated vinylic carbon atom,
2. Claisen ester enolate rearrangement, and
3. sulfoxide elimination to introduce the double bond.

\[
\begin{align*}
\text{HO} & \xrightarrow{\text{a})} \text{PhSeC} \xrightarrow{\text{b})} \text{PhSeC} \\
\text{HO} & \xrightarrow{\text{c})} \text{PhSeC} \\
\text{Br} & \xrightarrow{\text{d})} \text{PhSeC}
\end{align*}
\]

m.p. = 105-107°C

m.p. = 118-120°C

Scheme 26.

4.3. Metal-Promoted Reaction of Aldehydes and Ketones with a'a'a' Components

Dissection:

In this method (Scheme 30), developed by Dreiding et al.\textsuperscript{[58,59]} and U. Schmidt et al.\textsuperscript{[60]}, a (Z)-2-bromomethyl-2-alkenoic ester (a'a'a' building block) is treated with zinc to give an a'd'd' intermediate with umpolung. The combination with the a' aldehyde takes place with allylic shift and yields an intermediate alkoide, which cyclizes spontaneously to the \(\alpha\)-methylene lactone. The Dreiding-Schmidt reaction, which is also incorrectly called a Reformatsky synthesis (in which d' enolate esters, but not d components are used), has been very useful in the synthesis of monocyclic and spiro-\(\alpha\)-methylene lactones\textsuperscript{[61]}.
Perhaps the most important building blocks in the synthesis of \( \gamma \)-monosubstituted and \( \gamma,\gamma \)-disubstituted \( \alpha \)-methylene-\( \gamma \)-butyrolactones are the \( 2-(\text{bromomethyl}) \)acrylic ester 13a and the ethyl ester 13b.

\[
13a: R = \text{Me} \\
13b: R = \text{Et} \\
13c: R = \text{H}
\]

Recently, the synthesis of 13a in three steps (50% yield) and that of 13b in two steps (30% yield) have been described. 2-(Bromomethyl)acrylic acid 13c is also available commercially. Starting from 13b, Benesta et al.\cite{65a} reported the synthesis of more than thirty lactones, some of which are structurally quite complex (Scheme 34).

\[
R \rightarrow O + 13b \xrightarrow{a) \text{Zn/THF, 2) dil. HCl}} \text{COzMe}
\]

Scheme 34. (a) 1) Zn/THF, 2) dil. HCl.

Heindel et al.\cite{66a}, Lee et al.\cite{66b}, and Cassady et al.\cite{67a} (Scheme 35) proceeded similarly; Cassady et al. also obtained bislactones\cite{67a}, i.e., double haptens, from dialdehydes by using the corresponding one-pot reaction\cite{65b}.

\[
\text{CHO} + \xrightarrow{\text{DABCO}} \text{COzMe} \xrightarrow{a) \text{Zn/THF, 2) dil. H}_2\text{SO}_4, 0^\circ \text{C.}} \text{COzMe}
\]

Scheme 35. (a) 1) Zn/THF, 2) dil. H\(_2\)SO\(_4\), 0\(^\circ\)C.

A synthetic difficulty in the metal-promoted cyclization to give bicyclic \( \alpha \)-methylene lactones has been in the synthesis of the functionalized methacrylic acid as starting material.

Starting from the ortho ester 14, Dreiding et al.\cite{64a} synthesized the ortho ester 15 of 2-bromoaacrylic acid in several steps. 15 was metalated with \( \text{n} \)-butyllithium to give the corresponding lithium compound, i.e., a d\(^2\)-acrylic ester. After trapping of the lithium compound with aldehydes, the hydroxy ester was rearranged to the substituted allyl bromides 16 (Scheme 36).

\[
\text{CHO} \xrightarrow{\text{NaH, } \text{MeSMe}} \xrightarrow{\text{Br}} 14 \xrightarrow{a) 30\%} 15 \xrightarrow{b) 82\%} 16
\]

Scheme 36. (a) 1) KO\( \text{Bu} \), 2) Br\(_2\), CuO. 3) KOH, Et\( \text{O} \). (b) 1) BuLi, 2) CH\(_2\)\( \text{CHO} \). (c) H\( \text{SO}_4\). (d) NBS/Me\(_2\)S.

The synthesis of the allylic sulfur compound used by Semmelhack et al.\cite{68b} as a \( \alpha,\alpha \)-t precursor, also requires several steps and is not \((Z)\)-selective. The last step, the conversion of the allylic sulfide into the bromide, is not very simple either (Scheme 37).

In connection with the synthesis of a wide range of allyl alcohols and their precursors, which are further functionalized on the central carbon atom\cite{69}, we have prepared the necessary \( \alpha,\alpha,\alpha \)^{-} coupling reagents (the allylic bromides 18) in excellent yields by DABCO (diazabicycl0[2.2.2]octane)-catalyzed coupling of acrylic esters and aldehydes to 17 and subsequent bromanination accompanied by allylic rearrangement\cite{70-72} (Scheme 38).

The reaction of \( 2-(\text{hydroxy} \alpha \text{-alkyl}) \)acrylates 17 with \( \text{N} \)-bromosuccinimide/dimethyl sulfoxide yields regioselectively \((S,\text{S}^{\prime})\) reaction and stereoselectively \((Z)\)-2-(bromomethyl)-2-alkenoic esters 18 irrespective of the group R\cite{70-72}. Metal-induced coupling of 18 with carbonyl compounds allows ready access to \( \beta \)-substituted \( \alpha \)-methylene lactones (compare 19). Another advantage of this approach is that parent acrylic ester can be \( \alpha \)-functionalized without loss of material, much additional functionality being tolerated. Esoteric acrylic acid building blocks and organometallic conditions are unnecessary. The selective coupling of a ketoaldehyde, e.g., 6-oxoheptanal, with an
acrylic ester in the presence of DABCO is also possible; the less reactive ketone group need not be masked, e.g. by ketalization. After bromination with NBS/Me2S, which entails clean allylic rearrangement, a cyclizable molecule is obtained[731 (Scheme 39).

Scheme 39.

In addition to these compounds, other a'd3 components—as already described in Section 4.1—have been used in the cyclization: the allylsilane 5 and the dianions 10 and 11. The allylic bromoester method offers the advantages of a simple synthesis, a high degree of convergence, mild reaction conditions, and compatibility with other functionality. At least for many of the structurally more simple a-methylene-γ-butyrolactones, this is the method of choice.

4.4. Insertion of the Oxygen via Baeyer-Villiger Oxidation of 2-Methylenecyclobutanones

Dissection:

There are only a few examples of the synthesis of α-methylene lactones via the Baeyer-Villiger oxidation.

The syntheses of Hassner et al.[741 and Roberts et al.[751 will be presented here. As shown in Scheme 40, this approach begins with a [2+2]-cycloaddition of chloro- and bromoketenes to reactive double bonds to form a functionalized cyclobutanone. Baeyer-Villiger oxidation with exclusive migration of the bridgehead carbon atom and subsequent elimination of hydrogen halide yields the desired lactone.

In following the fate of the three carbon atoms of the chloroketone one may see that these are incorporated into the product as the desired acrylic moiety. In the example given here, the total yield of α-methylene lactone—starting from the haloketene precursor—is 20%. It remains to be seen whether this route can be developed preparatively. A limitation of the cycloaddition route is that only cis-fused lactones result (cf. also Section 4.8).

Grieco et al.[761 also used a Baeyer-Villiger oxidation to construct a γ-lactone and subsequently incorporated the α-methylene group by reaction of the enolate with formaldehyde (see Section 4.7) (Scheme 41).

Scheme 41. (a) 1) Cl2CHCOCl, 2) Zn/CH3CO2H, (b) 1) Ketal formation, 2) BH3/THF, NaOH/H2O2, (c) 1) 10% HCl, 2) HOAc/30% H2O2, (d) α-Methylation.

4.5. Introduction of the Carbonyl Oxygen by Oxidation of 3-Methylenetetrahydrofurans

Dissection:

This very simple method, which could also be of biosynthetic interest, has only been described recently. Starting from dihydrocarvone, Brocksom and Ferreira[771 synthesized monoterpenoid α-methylene-γ-butyrolactones (Scheme 42). After an interesting oxidative cyclization using lead tetraacetate to give the furan derivative (compare also the Barton reaction), the exo-methylene group is formed by selenoxide elimination. Finally, the carbonyl oxygen is introduced, in analogy to the method of Dauben et al.[781, by Collins oxidation with CrO3-2pyridine. It remains to be seen whether other oxidizing agents will bring about an improvement in yield.
4.6. Insertion of a Carbonyl Group into Functionalized Homoallylic Alcohols

Dissection:

This synthesis can be realized using reactions taken from the organic chemist’s “box of magic tricks”, namely by

a) transition-metal-catalyzed carbonylation of a vinylly-substituted homoallylic alcohol and
b) use of the Shapiro reaction.

a) In recent years the intramolecular version of the transition-metal-catalyzed carbonylation described by Corey and Hegedus has been used increasingly for the synthesis of α-methylene lactones. Zero-valent transition metal compounds, usually of nickel or palladium, function as catalysts and reagents. Scheme 43 shows the proposed mechanism of the nickel-induced reaction, in which 3-bromohomoallylic alcohols have been employed as starting compounds. Recently, Ban et al. have also used the more reactive 3-iodohomoallylic alcohols.

Scheme 43. Representative of other syntheses are those of Trost et al. and Stille et al., described here. Trost et al. joined a functionalized allylsilane to a carbonyl compound to obtain the functionalized homoallylic alcohol which is necessary for the insertion of the carbonyl group. The tricyclic spiro-α-methylene lactone is formed stereoselectively and in high yield (Scheme 44).

Scheme 44. (a) TiCl₄, CH₂Cl₂, -70°C. (b) 1.5 [(Ph₃P₂)Ni(CO)₃], Et₃N, THF, reflux.

The Grignard reagent prepared from 2-bromo-3-(trimethylsilyl)propene 21 can also be combined with epoxides to establish the desired 1,4-distance of functional groups (cf. Section 4.1) and added to α,β-unsaturated enones in Michael fashion using CuI catalysis, cyclopentane precursors being formed. The possibility of storing the carbamation reactivity of 2-bromo-3-(trimethylsilyl)propene while selectively activating the allylsilane (with TiCl₄), and subsequently metalating the bromide (with magnesium) makes 21 a valuable equivalent for the hypothetical dianion 22 (cf. also the conversion of 3 into 4).

Stille et al. reacted a vinylic Grignard compound (a ‘d’’ ethylene building block) with epoxides (a’a² components) and thus obtained the desired homoallylic alcohol. Electrophilic substitution of the trimethylsilyl group by bromine yielded the 3-bromohomoallylic alcohol required for the carbonylating cyclization (Scheme 45).

Scheme 45. (a) CuI, THF, Et₂O, 2) H₂. (b) 1) Br₂/CH₂Cl₂ -78°C, 2) NaOMe/MeOH. (c) 1) CO, [Pd(PPh₃)₄], 2) CH₂CN, K₂CO₃.

Carbonylnickel plays an interesting double role in the synthesis of (+)-frullanolide (Semmelhack et al., Scheme 46).

Scheme 46. (a) 4 steps. (b) 2 steps. (c) [Ni(CO)₄], C₆H₆, 65°C.

The allylic system in 24 can first be activated as π-allylnickel complex (M = Ni) and cyclized with the aldehyde function to give 26 (potentially a cis/trans mixture). In the next step, tetracarbonylnickel functions as carboxylating reagent to form the α-methylene lactone (Scheme 47).

Scheme 47.
Experimentally, a very high selectivity is observed for the formation of a cis-fused lactone as well as for the syn-orientation of the lactone with respect to the angular methyl group (cf. 23). The reason for these stereochemical results is not yet clear.

A variant of the transition-metal-catalyzed cyclization was recently presented by a French research group 21. In this reaction, CO is not inserted and cyclized using Pd-catalysis. Instead, the homoallyl alcohol is esterified with phosgene as C1 building block to give the chloroformate, which is then cyclized to give the α-methylene lactone (Scheme 48).

A fundamental result of Reppe chemistry is the synthesis of acrylic esters by nickel-catalyzed carbonylation of acetylene 9 (Scheme 49).

As Norton et al. were able to show, this reaction can also be intramolecularized by treating a homopropargyl alcohol with CO in the presence of catalytic PdCl2/SnCl2 and a tertiary phosphane 10 (Scheme 50).

The reaction proceeds under comparatively mild conditions. In a model experiment for establishing the functionality in the BC ring, Heathcock et al. 11 converted the trans-homopropargyl alcohol 27 into the trans-fused lactone 28 (Scheme 51). Although the yield is low (21%), the α-methylene lactone is formed directly in this way, and the normally chosen α-methylenation of a γ-lactone precursor (cf. Section 4.7) is not necessary.

b) A further variant is the insertion of CO, according to Barrett et al., via the Shapiro reaction, in which CO2 functions as CO building block 24 (Scheme 52).

The dianion from the activated hydrazone of acetone is allowed to react with ketones. As usual, elimination of nitrogen yields a vinyl anion (cf. also 22), which after trapping by carbon dioxide (carboxylation instead of carbonylation) is cyclized to the α-methylene lactone. This reaction sequence requires strongly basic conditions, which are not always tolerated by highly functionalized molecules.

4.7. α-Methylenation of 2-Oxotetrahydrofurans

Dissection:

The later incorporation of the α-methylene group into a preformed lactone has been used for many years in the synthesis of α-methylene lactones. Since the various methods have also been reviewed, only variations and new methods will be mentioned here.

For the incorporation of the α-methylene moiety, a functionalized C1 building block is usually introduced and the double bond is formed by subsequent elimination (Route 1). However, the introduction of a leaving group α to the carbonyl group, when the methyl group is already present, is also known (Route 2). In this case, elimination results in the exocyclic double bond, although the endocyclic double bond can also be formed 24-26 (Scheme 53).
In order to avoid the formation of the endocyclic double bond, one introduces the leaving group advantageously to the carbonyl group (Route 1).

Two methods are used most frequently at present:
1. The lactone is converted into the enolate and subsequently trapped with formaldehyde to give the hydroxymethyl derivative. Alternatively, the anion is trapped with formic esters and reduced to give the hydroxymethyl derivative. After conversion of the hydroxyl group into a tosylate or mesylate group, elimination is easily carried out with a base.

As almost arbitrary examples the synthesis of (±)-bigelovin by Grieco et al.[73] (Scheme 54) and of (±)-damsin by Vanderwalle et al.[90] and Kretchmer et al.[99] (Scheme 55) are shown here.

Other sesquiterpene lactones which have been obtained via α-methylation are, e.g., (±)-ambrosin, (±)-psilos-tachyin C[80], as well as (±)-eriolanin and (±)-eriolangin[100]. This methodology, which was developed by Grieco et al.[101], has also been applied to other representatives of the guaianolides (which have been investigated much less than the pseudoguaianolides), including, inter alia, (±)-compressanolide and (±)-estafiatin (Vanderwalle et al.[100]).

2. Another valuable method for introducing the α-methylene group uses the –NR₃ group as leaving group. This can be introduced by trapping of the enolate of the lactone with dimethyl(methylene)ammonium salts. After quaternization of the nitrogen, elimination affords the double bond[102-105] (Scheme 56).

The synthesis of (±)-eriolitin by Schlessinger et al.[106] and that of vernolepin by Isobe et al.[100] were carried out similarly. The incorporation of the α-methylene group by reductive amination of an α-carboxy lactone with CH₂O/
(Scheme 59) suggests that the specific deuteration of the methylene position should be feasible by reduction of the vinylogous carbamate with diisobutylaluminum deuteride (DAI/Bu₂).

Sulfur and especially selenium may also serve as leaving groups. The following synthesis, in which sulfur is incorporated exocyclically in the β-position (Route 1) was described by Paterson and Fleming (Scheme 60). The sulfur, following its oxidation to the sulfoxide, is removed as usual in a pericyclic reaction by heating (Scheme 60).

![Scheme 60](image)

The incorporation of the phenylseleno group via electrophilic diphenyl diselenide and its elimination to give the double bond were steps in the synthesis of estafiatin (Scheme 61).

![Scheme 61](image)

It has been known for several years that α-methylene lactones can be synthesized via a Wittig reaction, but this reaction has only been employed in specific cases (Scheme 62).

![Scheme 62](image)

Fraser-Reid et al. and Nair et al. have shown that chiral α-methylene lactones can be obtained from the chiral pool using a Wittig reaction (Scheme 63).

![Scheme 63](image)

4.8. Other Methods

Synthetic methods which have not been considered in Scheme 2 will be dealt with in this section. These involve pericyclic reactions and rearrangements:

a) The cycloaddition of nitrones to olefins (Diels-Alder reaction with inverse electron demand) described by Eschenmoser et al. was further studied by Riediker and Graf. As already mentioned (see Section 4.4), the cycloaddition route is limited in its applicability insofar as only cis-fused lactone rings can be prepared (Scheme 64).

![Scheme 64](image)

b) The Diels-Alder reaction can be used for the protection of the CC double bond of acrylic ester as cycloadduct. After the deprotonation with lithium disopropylamide (LDA), the S₅,2 reaction with propylene oxide gives the desired 1,4-functionality distance and then the spirolactone is formed. In the final step, the protecting group is cleaved off by cycloreversion (Scheme 65).

![Scheme 65](image)

c) A third route to synthesize α-methylene lactones is the cyclopropane rearrangement developed by Hudrlik et al. All the atoms of the product are already present in the cyclopropane educt 29. The cyclopropylmethyl-homoallyl rearrangement is facilitated by S₅,1-like conditions (Scheme 66). In the case of the formation of the bicyclic lactone 30 the two rings are cis-fused (Scheme 67).

![Scheme 66](image)
Recent examples have been described by Hiyama et al.\textsuperscript{[120]} and Hudrlik et al.\textsuperscript{[121]} The remarkably sensitive tulipalin A is formed in 43\% yield under almost neutral, anhydrous conditions\textsuperscript{[120]}.

\[
\begin{align*}
\text{CO}_2\text{Me} & \xrightleftharpoons{\text{MeSi}l, 43\%} \text{Tulipalin A} \\
\text{OH} & \xrightarrow{\text{CrO}_3, \text{pyridine}, \text{CH}_2\text{Cl}_2, 60\%} \text{O}_3
\end{align*}
\]

Scheme 67.

\(\text{O}_3\)

D) The formation of CC bonds can also be brought about by carbon radicals, and this approach has become a popular field of research in recent years. Carbon-centered radicals react with electron-rich and electron-deficient \(\pi\)-systems under neutral conditions. Thus, compounds with numerous further potential reaction centers are employable without the need for protecting groups. One example is the cyclization of a propargyl ether to a secondary carbon radical. This radical is formed by single electron transfer (SET) from catalytic amounts of cobaloxime\(1\), which is cyclically regenerated from cobaloxime\(2\). The last step, i.e. the oxidation of the 3-methylenetetrahydrofuran to the lactone, is still preparatively difficult (Scheme 68).

\[
\begin{align*}
\text{CH} & \xrightarrow{\text{Cobaloxime (1)}} \text{O}_3 \\
\text{CH} & \xrightarrow{\text{Cobaloxime (II)}} \text{O}_3
\end{align*}
\]

Scheme 68. (a) \(\text{HC}≡\text{C─CH}_2\text{OH}, \text{NBS}, -30^\circ \text{C} \rightarrow \text{RT}\). (b) \(\varepsilon^\circ (\text{Br}^\circ)\). (c) Solvent-H. (d) \(\text{CrO}_3, \text{pyridine}, \text{CH}_2\text{Cl}_2\).

One other route starts from functionalized bisallyl ether \(31\), which, once again, is prepared with NBS and an excess of allyl alcohol at low temperature, probably via an ionic intermediate. The generation of the vinyl radical from \(31\) takes place under normal conditions. Although \(31\) carries different types of labile hydrogen atoms (allylic and one acetal hydrogen), the cyclization proceeds in respectable yield (60–65\%). Jones oxidation furnishes the desired lactone \(30\)\textsuperscript{[124]} (Scheme 69).

\[
\begin{align*}
\text{BuO} & \xrightarrow{\text{Bu}_3\text{SnH, 2,2'-azobisisobutyronitrile (AIBN), C}_2\text{H}_6, 60-65\%} \text{Br} \\
\text{BuO} & \xrightarrow{\text{Bu}_3\text{SnH, 2,2'-azobisisobutyronitrile (AIBN), C}_2\text{H}_6, 60-65\%} \text{O}_3
\end{align*}
\]

Scheme 69. (a) \(\text{Bu}_3\text{SnH, 2,2'-azobisisobutyronitrile (AIBN), C}_2\text{H}_6\). (b) Jones oxidation.

Besides 2-cyclohexenol, other allylic alcohols can be used for the reaction with the allenyl ether.

The various radical reactions illustrate that new synthetic methods must go through the trials of practical application and total synthesis. Conversely, it is clear that such an important class of heterocycles as the \(\alpha\)-methylene-\(\gamma\)-butyrolactones mobilizes the whole arsenal of synthetic methods which are at our disposal.

5. Outlook

Kupchan’s discovery in 1970 of the cytotoxic activity of the sesquiterpene lactones was the green light for a rapid development, which is continuing today and proceeding in various directions. The isolation and identification of many additional representatives, especially by Bohlmann et al.\textsuperscript{[125]}, the total syntheses, and the discovery of a broad spectrum of biological activities followed. At the same time the lactones functioned as a lead in the search for analogues and attention was focussed also on completely different constituents of the Compositae, as well as on their pharmaceutical and economic uses. Of the many new and ingenious methods that have been published on the preparation of the \(\alpha\)-methylene-\(\gamma\)-butyrolactone moiety, a large number are of academic interest only. The most commonly used methods include:

1. oxidative cyclization of crossed allylic-homoallylic alcohols (Section 4.1),

2. halogeno-lactonization and seleno-lactonization of 2-methylene-4-pentenoic acids (Section 4.2),

3. metal-promoted cyclization of \(a'\)\(a''\) components with carbonyl compounds (Section 4.3),

4. transition-metal-catalyzed carbonylation of 3-bromo- and 3-iodo homoallylic alcohols (Section 4.6);

5. \(\alpha\)-methyleneation of preformed \(\gamma\)-butyrolactones (Section 4.7).

The investigations carried out in this sector have enriched heterocyclic chemistry, terpene synthesis, and, at the same time, contributed to the development of new synthetic methods.

The future offers a wide choice for interdisciplinary efforts regarding the use of \(\alpha\)-methylene-\(\gamma\)-butyrolactones in the fields of organic chemistry, biology, immunology, medicine, and pharmacology.

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