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Review

4-Hydroxy-2-pyrones: Synthesis, Natural Products, and Application

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Abstract: 4-Hydroxy-2-pyrones are of interest as potential biorenewable molecules for a sustainable transition from biomass feedstock to valuable chemical products. This review focuses on the methodologies for the synthesis of 4-hydroxy-2-pyrones published over the last 20 years. These pyrones as polyketides are widespread in Nature and possess versatile bioactivity that makes them an attractive target for synthesis and modification. Biosynthetic paths of the pyrones are actively developed and used as biotechnological approaches for the construction of natural and unnatural polysubstituted 4-hydroxy-2-pyrones. The major synthetical methods are biomimetic and are based on the cyclization of tricarbonyl compounds. Novel chemical methods of de novo synthesis based on alkyne cyclizations using transition metal complexes and ketene transformations allow for straightforward access to 4-hydroxy-2-pyrones and have been applied for the construction of natural products. Possible directions for further pyrone ring modification are discussed.

Keywords: 2-pyrone; 4-pyrone; 4-hydroxy-2-pyrone; triacetic acid lactone; polyketide; cyclization; ketene; ketoacetylene; biological activity; natural products

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1. Introduction

2-Pyrones are an important class of heterocyclic compounds of interest as valuable reagents in organic synthesis and an essential pharmacophore in many biologically active products [1–10]. Among them, 4-hydroxy-2-pyrones occupy a special place because these molecules are both polyketide structures and pyrans [3,5–8] (Figure 1). These substances can exist in two tautomeric forms, namely, 4-hydroxy-2-pyrone and 2-hydroxy-4-pyrone. The former is a major tautomer as the result of effective conjugation. This structural feature makes a wide range of synthesis methods available for their synthesis that are typical for both 2-pyrones and 4-pyrones and that were not covered in recent reviews [1,4].

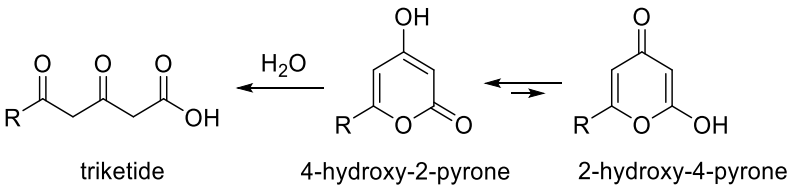


Figure 1. Structural features of 4-hydroxy-2-pyrones.

4-Hydroxy-2-pyrones are polyfunctional molecules that bear several electrophilic and nucleophilic centers that determine their application in organic synthesis. These heterocycles are attractive building blocks for the preparation of biologically important pyran structures, aromatics, polymers, azaheterocycles and acyclic structures via ring-opening transformations or pyran ring modifications [11–21]. Two molecules that receive the most attention are triacetic acid lactone (4-hydroxy-6-methyl-2*H*-pyran-2-one) [11] and dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one) [12,13], which are already

produced industrially and show high reactivity. Additionally, triacetic acid lactone is considered a bioprivileged molecule and a potential platform molecule because it can be prepared from carbohydrates using biological methods [22]. This approach allows for the sustainable preparation of valuable chemicals and end products based on renewable carbon sources [23]. Numerous other 4-hydroxy-2-pyrones are also produced using polyketidases [6] and can lead to various structures that can also be attributed to bioprivileged molecules. Thus, the development of the synthesis of 4-hydroxy-2-pyrones as a renewable feedstock for the chemical industry is a serious task for sustainable chemistry.

The 4-hydroxy-2-pyrone fragment provides these molecules with promising and diverse biological and physical properties [1,5–9]. The main strategy and feature of the search for new bioactive substances includes their isolation from natural sources. Plenty of 4-hydroxy-2-pyrones have been described as varying in the nature and complexity of their substituents, number and position to which they are attached. These pyrones were found in bacteria, microbes, plants, insects, fungi and animals [1–10] and are involved in many types of biological processes, such as defense against other organisms and as signaling function [1,5–9], as well as representing key intermediates for biochemical transformations of complex natural molecules [6].

The wide distribution of 4-hydroxy-2-pyrones as secondary metabolites and diverse biological activity makes them an attractive target for synthesis and the design of new bioactive compounds. At the same time, the major methods of preparation are isolation from natural sources and the use of biotechnologies. This review describes modern general and effective synthetic methods for the construction of 4-hydroxy-2-pyrones, including natural products.

2. Synthetic Strategies

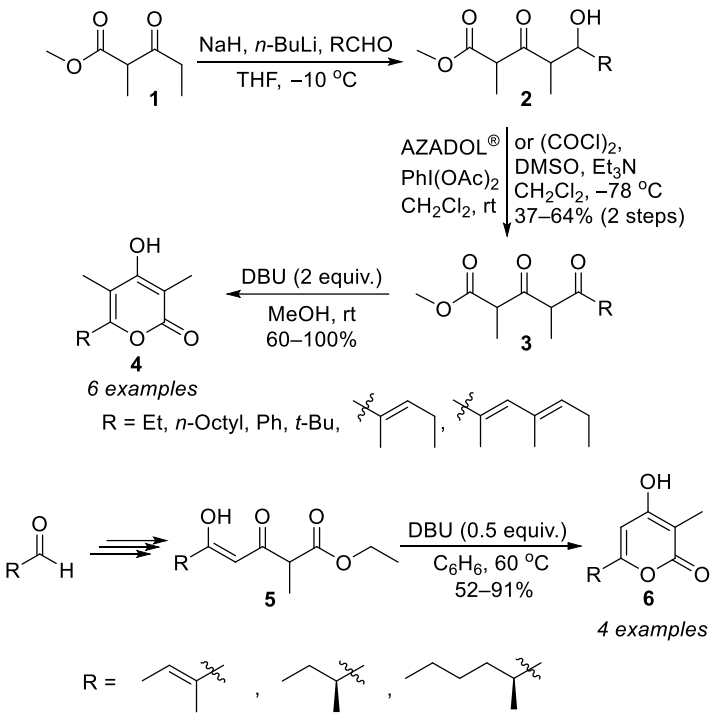
2.1. Cyclization of 1,3,5-Tricarbonyl Compounds Derived from Acetoacetic Esters

The most common method for the synthesis of 4-hydroxy-2-pyrones is the cyclization of 1,3,5-tricarbonyl compounds or their protected derivatives [24–31]. This method can be considered as a biomimetic strategy because the same processes occur under the action of polyketide synthases in Nature [6]. The general approach is based on a condensation reaction of acetoacetic esters with aldehydes at the C-4 position in the presence of sodium hydride and/or *n*-BuLi with subsequent oxidation. For example, the corresponding ester **1** gives the corresponding products **2**, which lead to the diketoesters **3** with the use of AZADOL® (2-azaadamantan-2-ol) and $PhI(OAc)_2$ in dichloromethane (Scheme 1). The DBU-catalyzed cyclization in polar and non-polar solvents produces 4-hydroxy-2-pyrones **4** in 60–100% yields [24,29]. This method allows for the use of various derivatives of acetoacetic ester, which bear the Me, Et, *n*-Pr, *n*-Bu groups at the C-2 position, and aldehydes. However, 2-methylacetoacetic ester is most often used because a few natural compounds based on 3-methyl-4-hydroxy-2-pyrones. Using this approach, the α-pyrones **6** are also synthesized, some of which possess a chiral center in the side chain [29]. It should be noted that the cyclization of 4-acyl-acetoacetate **5** is carried out in the presence of catalytic DBU (Scheme 1).

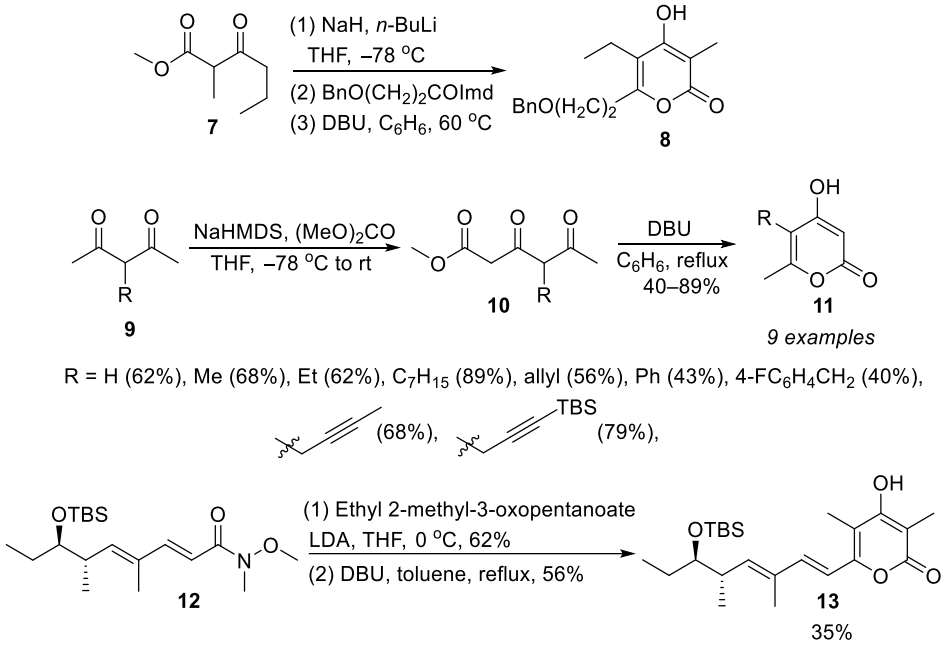
There are examples in the literature of the direct preparation of tricarbonyl compounds based on Claisen condensation of substituted acetoacetic ester in the presence of strong basics, such as LDA [27,32], *n*-BuLi [30], LiHMDS [25] or NaHMDS [33]. The use of an active derivative of carboxylic acid, such as 2-methylmalonyl chloride [25], $BnO(CH_2)_2COImd$ (Imd = imidazolyl) [27], dimethyl carbonate [33] and Weinreb amide **12** [32] (Scheme 2), lead to the corresponding tricarbonyl compounds. The subsequent cyclization in the presence of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) gives pyrones **8**, **11** and **13**, respectively. Several works [30,34] describe the use of carbon dioxide as a carboxylation reagent in the presence of acetic anhydride.

DBU is the most popular promoter for the cyclization of tricarbonyl compounds, and also the catalysis of MeONa [26], PTSA [25], PPA [35] and Ac_2O [34] is applied for the preparation of 4-hydroxy-2-pyrones. Although the majority of the methods are

based on the lactonization of the methyl esters, the ethyl esters can also be used for the cyclization [25,27,29]. The cyclization of 4-acyl-acetoacetates has been applied in the synthesis of natural compounds and biologically important products or their precursors, such as cyercene A [31], phenoxan [27], gulypyrone A [29], verticipyrone [26], salinipyrone A [32], sesquicillin A [36] and subglutinol A [37].



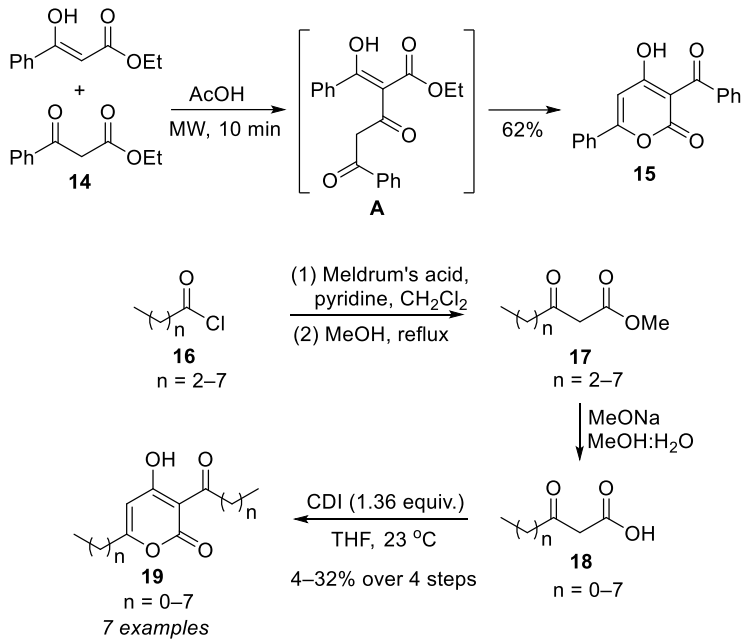
Scheme 1. Preparation of 4-hydroxy-2-pyrones from aldehydes and acetoacetic ester derivatives.



Scheme 2. The preparation of 4-hydroxy-2-pyrones based on Claisen condensation.

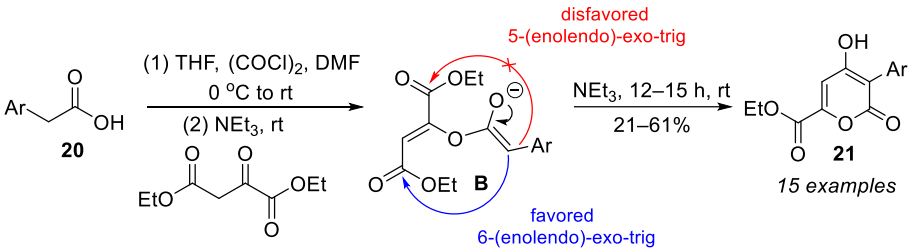
A classical self-condensation of ketoesters first described for the synthesis of dehydroacetic acid [38] was revised recently with the use of modern techniques and reagents. Thus, product **15** is prepared from ethyl benzoylacetate (**14**) via microwave excitation in

acetic acid in 62% yield (Scheme 3) [39]. Tetracarbonyl compound **A** is a possible intermediate in the reaction, which is formed via the Claisen condensation. The self-condensation of β-ketoacids **18**, which are obtained via acylation of Meldrum's acid with acyl chlorides **16** and the subsequent hydrolysis of esters **18**, makes it possible to obtain 3-acyl-substituted 4-hydroxy-2-pyrones **19** in low-to-moderate yields over four steps. Carbonyldiimidazole (CDI) is used for the promotion of both the Claisen condensation and the subsequent cyclization in THF at room temperature (Scheme 3) [40].



Scheme 3. Preparation of 4-hydroxy-2-pyrones **15**, **19** from ketoesters via the self-condensation reaction.

The *one-pot* synthesis of a wide range of 3-aryl-4-hydroxy-2-pyrones **21** was achieved by Dhage et al. [41]. Diethyl oxaloacetate undergoes *O*-acylation with arylacetyl chlorides, which is generated in situ from arylacetic acids **20**, followed by base-catalyzed intramolecular Claisen condensation (Scheme 4). Both ester groups can be attacked during the cyclization of intermediate **B**, and competition between the formation of pyrone and furan systems occurs. However, a more favorable 6-*exo-trig* cyclization directs the process toward the formation of the pyrone ring.

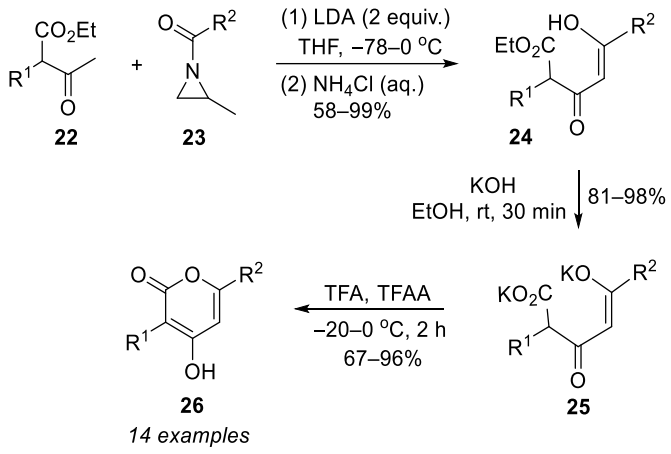


Ar = Ph (61%), 2-FC_6H_4 (42%), 4-FC_6H_4 (45%), 2-ClC_6H_4 (38%), 2,4-$Cl_2C_6H_3$ (21%), 4-ClC_6H_4 (30%), 4-BrC_6H_4 (57%), 2-MeC_6H_4 (42%), 3-MeC_6H_4 (48%), 4-MeC_6H_4 (51%), 2-$MeOC_6H_4$ (39%), 3-$MeOC_6H_4$ (40%), 4-$MeOC_6H_4$ (45%), 2-methylbenzoate (30%), 2-naphthyl (36%)

Scheme 4. One-pot preparation of 4-hydroxy-2-pyrones **21** from 2-arylacetic acids.

Schmidt and co-authors showed that the acylation of esters **22** proceeds with aziridines **23** to form tricarbonyl compounds **24**. Diketones **24** give salts **25** under treatment with KOH. The potassium salts of 5-hydroxy-3-oxopent-4-enoic acids **25,** which are a stable equivalent of diketoacids and cyclized to the corresponding 2-pyrones **26** at low temperatures in the medium of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) in 67–96%

yields [42] (Scheme 5). This approach is effective enough, and the total yield of 6-phenyl-4-hydroxy-2-pyrone is 57% for three steps.

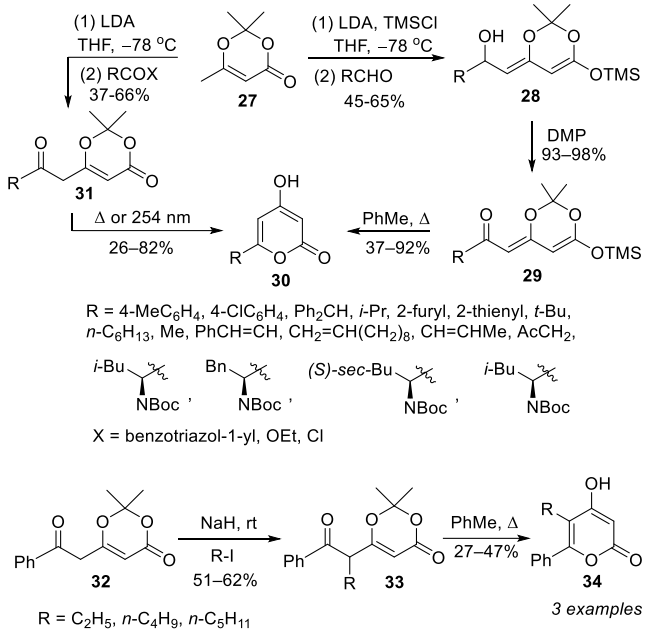


R^1 = H, C_6H_{13}, prenyl;
R^2 = 2-furyl, 3-furyl, Et, *n*-Pr, *i*-Pr, *t*-Bu, Ph, 3,4,5-$(MeO)_2C_6H_2$, 3,4-$(MeO)_2C_6H_3$, 3-pyridyl, 4-pyridyl, 2-thienyl, C_7H_{15}, $C_{15}H_{35}$

Scheme 5. Preparation of 4-hydroxy-2-pyrones **26** from the potassium salts **25**.

2.2. Recyclization of Acetals

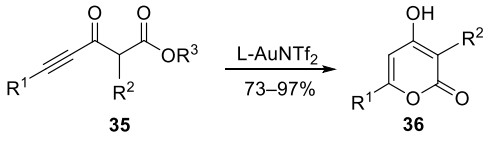
Synthetic equivalents of dicarbonyl compounds can also be used for the preparation of pyrones. Diketene acetone adduct **27** is enolized via deprotonation with lithium diisopropylamide (LDA) in the presence of trimethylsilyl chloride, followed by a Mukaiyama condensation with aldehydes to form silyl dienol ether **28**. Subsequent oxidation with Dess–Martin reagent (DMP) leads to the desired ketones **29** [26,43–47] (Scheme 6). Compounds **29** undergo cyclization to pyrones **30** under reflux in toluene. The use of acid chlorides, esters and other carbonyls with good leaving groups allows for the direct formation of oxo derivatives **31**, thus reducing the number of stages. The alkylation of derivative **32** with alkyl iodides gives substituted ketones **33**, which are similarly cyclized under heating to pyrones **34**.



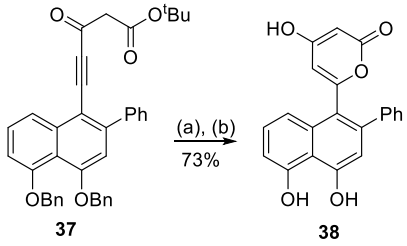
Scheme 6. Synthesis of 4-hydroxy-2-pyrones via recyclization of acetals.

2.3. Cyclization of Acetylenic 1,3-Dicarbonyl Compounds in the Presence of Gold Complexes

Fürnster and colleagues actively utilized gold(I) catalysis for the synthesis of 3,6-disubstituted 4-hydroxy-2-pyrones **36** from acetylenic diketones **35** [48–50] (Scheme 7). The alkyl part of the ester group (R^3) is critical for the transformation with *t*-Bu and CH_2CH_2TMS gives the best results due to the facile elimination of the corresponding alkene. The scope of the method is exceptionally broad, including bicyclic and macrocyclic products. The conditions are quite robust and allow for variation in the solvent and the phosphine ligand. The synthesis of wailupemycin G (**38**) was shown to be a typical representative and is based on the cylclization of alkyne **37** [49]. This method is also applied for the preparation of various natural products, such as neurymenolide A, orevactaene, DMDA-pateamine A, radicinol, hispidine, phellinin A [49] and violapyrone C [51].



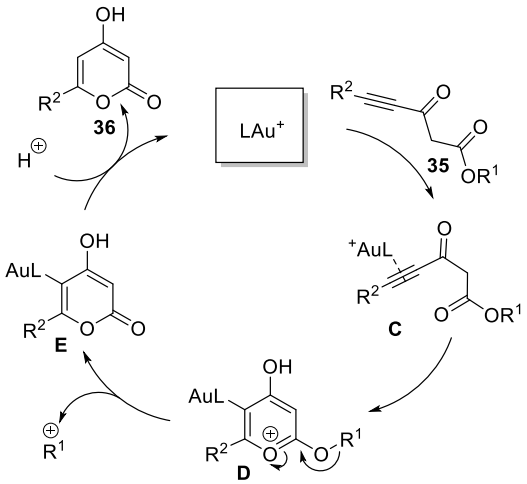
R^1 = alkyl, alkenyl, aryl, allyl;
R^2 = alkyl, alkenyl, halogen;
R^3 = *t*-Bu, $CH_2CH_2SiMe_3$



(a) [(XPhos)AuNTf$_2$] (5 mol%), MeNO$_2$ (78%);
(b) H_2, Pd/C, EtOAc (94%)

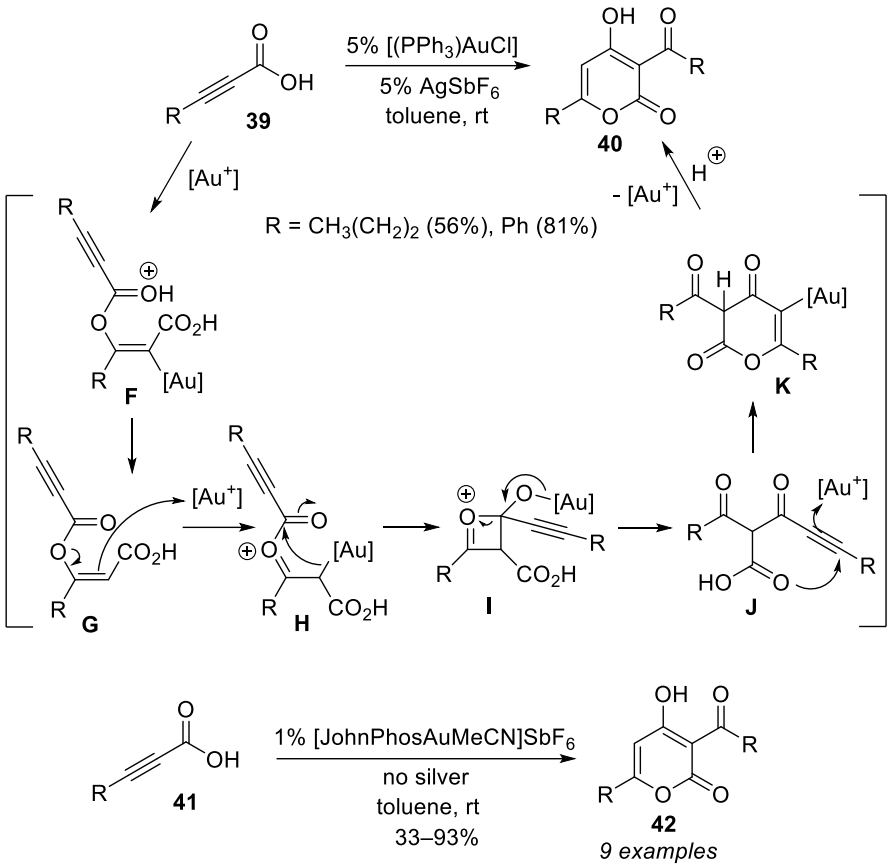
Scheme 7. Cyclization of acetylenic 1,3-dicarbonyl compounds.

The catalytic cycle starts with the coordination of the gold-based carbophilic catalyst, which is primarily coordinated at the triple bond to form the π-complex **C**. The next step includes the intramolecular attack of the oxygen atom on the π-complex that leads to the favorable 6-*endo-dig* cyclization and the formation of an intermediate **D**. The heterolysis of the O–R bond and subsequent protonation gives 4-hydroxy-2-pyrone **36** and the release of the catalyst (Scheme 8).



Scheme 8. Proposed mechanism of cyclization of alkynyl ketoesters **35** to 4-hydroxy-2-pyrones **36** under the action of gold salts.

Schreiber et al. showed that 4-hydroxy-2-pyrones **40** can be obtained via the self-condensation of acetylenecarboxylic acids **39** with the use of a gold-based catalyst [52]. The reaction is carried out in the presence of 5% chloro(triphenylphosphine)gold(I) and 5% silver hexafluoroantimonate(V) in toluene at room temperature. However, only 6-phenyl- (81%) and 6-propyl-(56%) 4-hydroxy-2-pyrone are synthesized in this way (Scheme 9). Later, Ghosh and co-workers [53] showed the activity of other gold catalysts with the best result using the JohnPhos ligand, which promotes the transformation of compounds **41** with no silver additive. The scope of this reaction includes aromatic and aliphatic derivatives, and the yields of pyrones **42** range from 33% to 93%. Using this approach, pseudopyronine A is obtained in a 24% total yield over four stages.



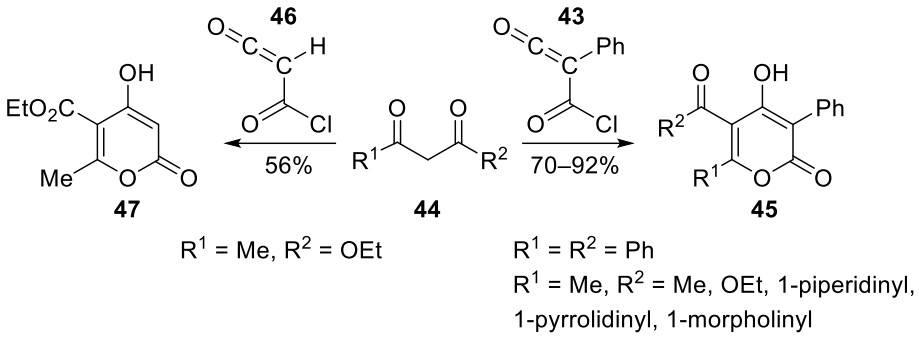
Scheme 9. Direct preparation of 4-hydroxy-2-pyrones **40** and **42** from acetylenecarboxylic acids.

2.4. Syntheses Based on Ketenes

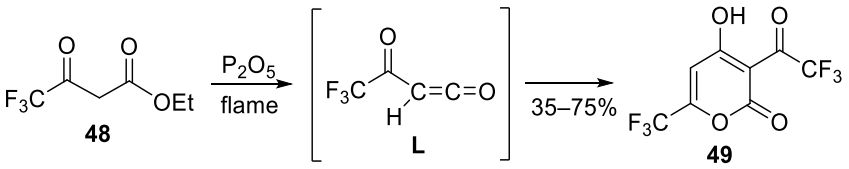
[4+2]-Cyclization reactions with ketenes are involved less often in the synthesis of 2-pyrones [1]. However, several new examples appeared in recent years. 5-Carbomethoxy-4-hydroxy-6-methyl-2*H*-pyran-2-one is obtained from malonyl chloride and methyl acetoacetate in a 58% yield [54]. Similarly, the reaction of stable ketenes **43** and **46** with dicarbonyl compounds **44** afforded 4-hydroxy-2-pyrones **45** and **47** in good yields (Scheme 10) [55,56]. The reaction scope includes only the available symmetrical diketones and acetoacetic acid derivatives **44**. The ketenes are easily obtained from corresponding acid chlorides in situ.

It was also demonstrated [57] that CF_3-substituted ester **48** gives hexafluorodehydroacetic acid **49** in 41% yield under heating with a flame burner in the presence of phosphorus(V) oxide (Scheme 11). A proposed mechanism of the reaction includes the formation of ketene **L**, which then dimerizes. Recently, our group [58] repeated this synthesis and showed that the method is difficult to reproduce, and the yields of hexafluorodehydroacetic

acid **49** are in the range of 35–75%. The molecule can be considered an important building block for the synthesis of fluorine-containing molecules [58].

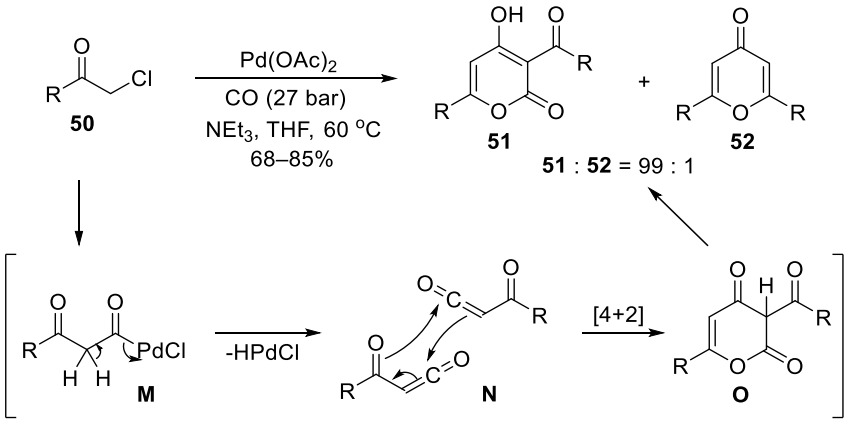


Scheme 10. Reactions of chloroformylketenes with dicarbonyl compounds.



Scheme 11. The synthesis of hexafluorodehydroacetic acid **49**.

A simple and direct method for the preparation of 3-acyl-4-hydroxy-2-pyrones **51** was described by Perrone et al. [59]. The carbonylation of α-chloroketones **50** under the action of a palladium catalyst and triethylamine in tetrahydrofuran [59] gives 3-alkanoyl- and 3-aroyl-substituted 2-pyrones **51** in high yields (Scheme 12). The byproducts are 4-pyrones **52**, but their amount is minimized to 1% in optimal conditions with the use of palladium(II) acetate at 60 °C. The reaction is tolerant of various alkyl and aryl substituents. The authors suggested that the formation of acylketene **N** occurs through the cleavage of palladium from the product of the carbonylation (intermediate **M**). The last step is the [4+2]-cycloaddition of the ketene **N** to give target 2-pyrone **51**.

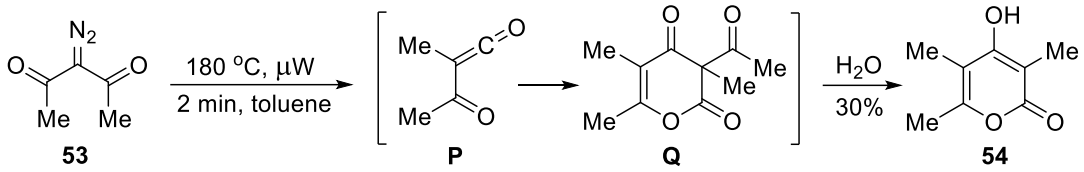


R = Ph (75%), 4-MeC$_6$H$_4$ (75%), 4-MeOC$_6$H$_4$ (68%), 2-BrC$_6$H$_4$ (71%), 4-ClC$_6$H$_4$ (75%), 2-furyl (78%), Me (85%), *t*-Bu (82%)

Scheme 12. Formation of 2-pyrones **51** from α-chloroacetophenones **50**.

Recently, Castilio et al. showed that 3-diazoacetylacetone **53** transforms to 4-hydroxy-2-pyrone **54** [60], which is an important intermediate in the synthesis of natural compounds [26,61]. Diazoacetylacetone (**53**) is heated to 180 °C under microwave irradiation in toluene for two minutes, and pyrone **54** crystallizes out of the reaction medium in a total

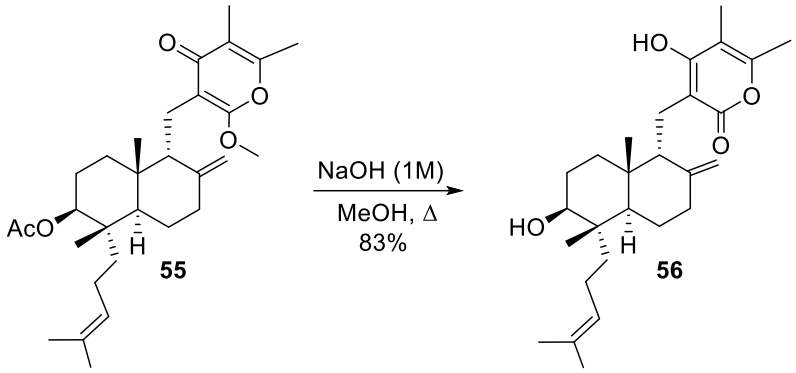
yield of 30%. It is most likely formed as the result of the hydrolysis of the non-isolated intermediate **Q**, which is the dimer of acetyl ketene **P** (Scheme 13).



Scheme 13. Phe preparation of 4-hydroxy-2-pyrone **54** based on diazoacetylacetone (**53**).

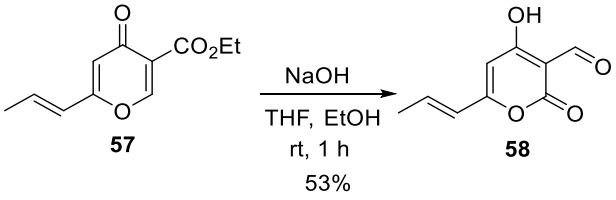
2.5. Pyrone Fragment Modification

2-Cyano-4-pyrones can be considered as a synthetic equivalent of 4-hydroxy-2-pyrones via ring-opening transformations and elimination of HCN; however, their direct conversion has never been described. The substitution occurs selectively only upon treatment with amines and hydrazines [62,63]. On the other hand, the transformation of MeO-substituted γ-pyrones under the action of alkali is a general method for the synthesis of 4-hydroxy-2-pyrones (Scheme 14). This approach was used by Kato's group in the synthesis of (+)-sesquicillin A. (−)-Nalanthalide (**55**) was heated under basic conditions (1 M NaOH) leading to γ-pyrone hydrolysis and removal of acetyl protection in the non-pyrone fragment, as a result, deacetylated sesquicillin A (**56**) was prepared in 83% yield [37].



Scheme 14. Hydrolysis of 2-methoxy-γ-pyrone **55** in the synthesis of deacetylated (+)-sesquicillin A (**56**).

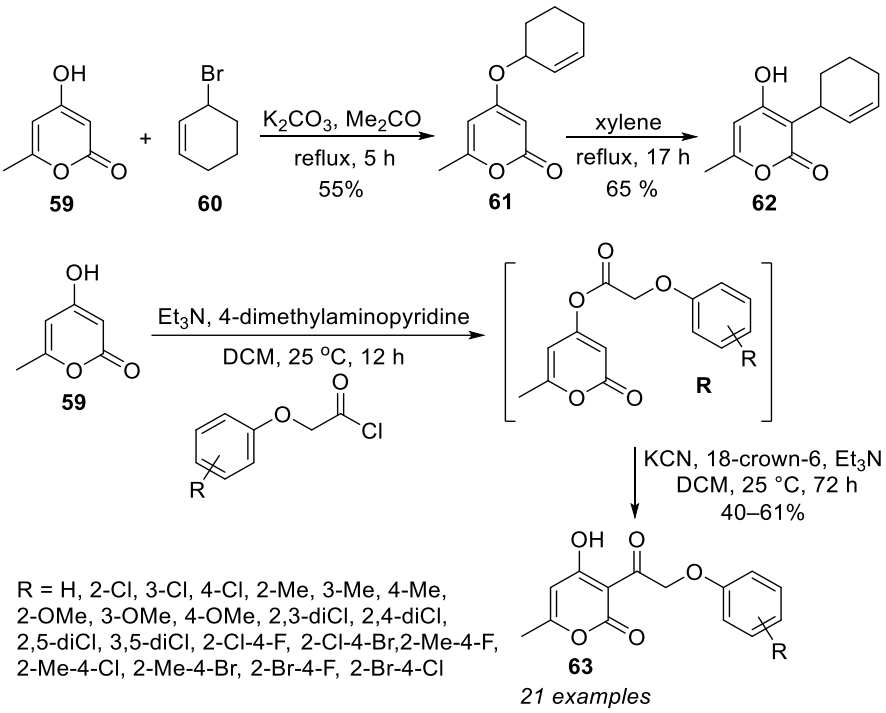
Another approach is based on an ANRORC reaction of 3-carbethoxy-substituted 4-pyrones under the action of a base. Although this reaction was described only in two works [64,65], it provides access to difficult-to-find 3-formyl-4-hydroxy-2-pyrones. Very recently, it was observed that the reaction of 4-oxo-4*H*-pyran-3-carboxylate **57** with NaOH proceeded selectively and led to 4-hydroxy-2-pyrone **58** in 53% yield. This transformation presumably occurs through a conjugate nucleophilic addition at the C-2 position of the γ-pyrone ring, followed by pyrone ring opening and then ring closure to produce the stable anion of **58** (Scheme 15).



Scheme 15. Recyclization of 4-oxo-4*H*-pyran-3-carboxylate **57**.

The reaction of triacetic acid lactone (**59**) with 3-bromocyclohexene **60** in acetone in the presence of potassium carbonate leads to compound **61**, which can undergo a Claisen rearrangement under heating in xylene to give the corresponding 3-cyclohexenyl-substituted

4-hydroxy-2-pyrones **62** (Scheme 16) [66]. Another approach for the modification of the pyrone ring is based on the Fries reaction. Acylation of **59** with phenoxyacetyl chloride leads to O-acylation products **R**, which are treated without isolation with potassium cyanide in DCM. These pyrones undergo rearrangement to produce 6-methyl-4-hydroxy-3-(2-phenoxyacetyl)-2-pyrones **63** in 41–60% yields [67].



Scheme 16. Preparation of 3-cyclohexenyl-4-hydroxy-2-pyrone and 3-acyl derivatives of triacetic acid lactone (**59**).

Methods for the modification of triacetic acid lactone and dehydroacetic acid are widely used, which make it possible to obtain 4-hydroxy-2-pyrones [11,13,68]. These reactions include the electrophilic substitution method common to pyrones for the functionalization of positions 3 and 5 of the pyrone ring. For example, bromination or iodination reactions, Michael reactions, acylation and alkylation of the ring, modification of side substituents [11,13,68] and selective palladium-catalyzed carbofunctionalization [69]. In many total syntheses of natural products, the modification of the methyl group located at the C-6 position of the pyrone ring is a convenient strategy via condensation reactions [1,11].

Dealkylation and deacylation reactions are often used for the preparation of 4-hydroxy-2-pyrones because the methods of side substituent modification and the introduction of additional groups to the pyrone ring are accompanied by the protection of the hydroxyl group at the C-4 position. For debenzylation, general methods for removing this group are applied, such as hydrogen on palladium or sodium borohydride [29,70]. The cleavage of the methoxymethyl group is achieved with the use of trifluoroacetic acid [71,72]. The methyl group is deprotected via sequential treatment with hydrogen bromide in acetic acid and sodium hydroxide or trimethylsilyl iodide in chloroform and then with sulfuric acid [37,73]. The 2,2,2-trimethylacetyl and acetyl group is cleaved by a base, for example, DBU in methanol at 0 °C [74] or sodium hydroxide in tetrahydrofuran [37].

3. Natural 4-hydroxy-2-pyrones and Their Applications

Several 4-hydroxy-2-pyrones, which have their own names, include the five main classes of 4-hydroxy-2-pyrones, but we cannot cover this rapidly developing area and all observed metabolites bearing the 4-hydroxy-2-pyrone moiety in this review [3,7,8,75]. The known natural 4-hydroxy-2-pyrones can be classified according to the nature of the substituents and positions of substitution at the pyran ring. The first class includes the

simplest 6-substituted 4-hydroxy-4-pyrones bearing alkyl, styryl and aromatic substituents (Figure 2). A feature of these molecules is the presence of the free C-3 position, which can be modified and leads to several new 4-hydroxy-2-pyrones [11]. The simplest natural 4-hydroxy-2-pyrones are triacetic acid lactone and tetracetic acid lactone, which were first isolated in 1967 from *Penicillium stipitatum*. These substances were important for understanding the pathways the polyketide formation in nature [76,77] and stimulated the development of the synthesis of lactone from carbohydrates [22]. Another simple 6-alkyl-4-hydroxy-2-pyrone, namely, fistupyrone (4-hydroxy-6-isovaleryl-2-pyrone), is produced by *Streptomyces* and demonstrates inhibition of the infection of *Alternaria brassicicola* in the leaves of seedlings of Chinese cabbage [78]. Among this series of compounds, hispidin, which is 6-styryl-4-hydroxy-2-pyrone, bears the catechol fragment and can be distinguished as a low molecular compound with valuable biological activities, such as anti-oxidative, anti-inflammatory, cytotoxic, anti-platelet aggregation, anti-diabetic, anti-dementia and anti-viral effects [79,80]. This pyrone was isolated for the first time from *Inonotus hispidus* fungi in 1889 and was later found in various fungi used in traditional medicine [79]. Furthermore, hispidin contains a conjugated system as a natural yellow-brown pigment and can be used for dyeing [81]. Hydroxylation at the C-3 position occurs in luminescent mushrooms *Neonothopanus nambi*, leading to fungal luciferin ((*E*)-6-(3,4-dihydroxystyryl)-3,4-dihydroxy-2*H*-pyran-2-one) [82]. This process is followed by light emission. Also, hispidin and bisnoryangonin undergo transformations in mushrooms to give a large and diverse range of biogenerated styrylpyrones, which have a role similar to that of flavonoids in plants [80]. Several products of the dimerization or oligomerization are connected with modifications of the C-3 position and include substituted 6-styryl-4-hydroxy-2-pyrones, such as fasciculines A and B, phelligridins B and I, phelligridimer A, phaeolschidins A–E and pinillidine [80,83]. Moreover, the oxidized structures at the benzene ring isolated from micro-organisms as metabolites of the fruiting bodies of *Hyrnenochaete mougestii* (Poriales) are hymenoquinone and leucohymenoquinone (Figure 2) [7].

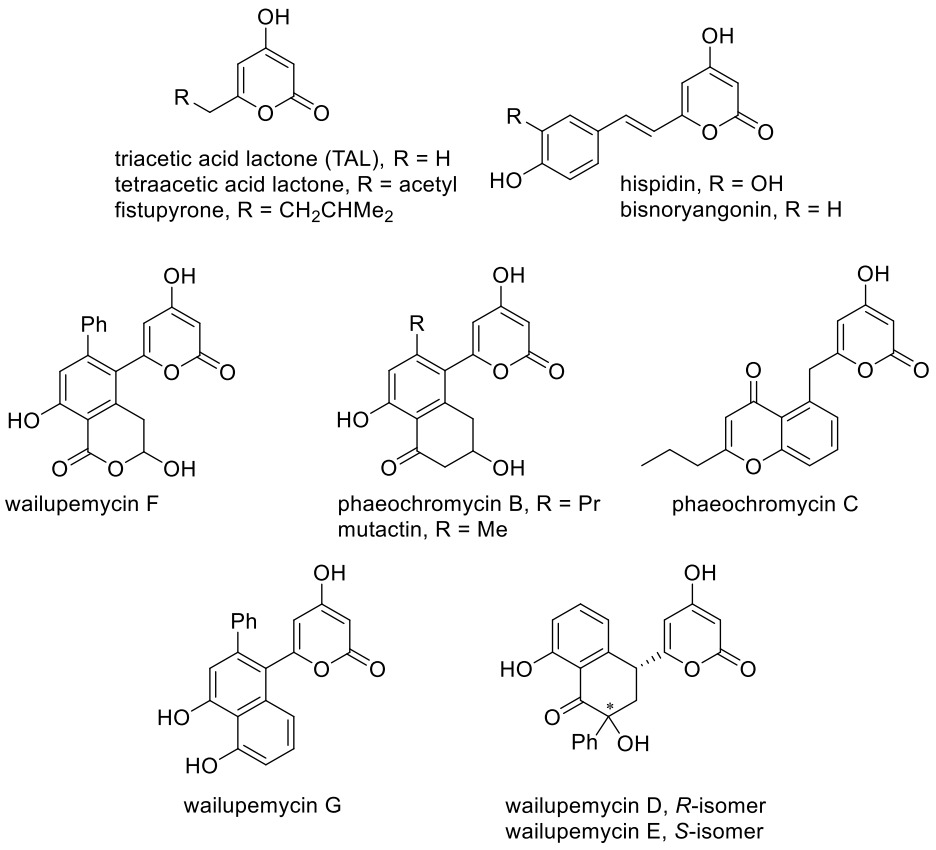


Figure 2. The main representatives of 6-substituted 4-hydroxy-2-pyrones.

An aromatic substituent at the C-6 position occurs in such structures, as wailupemicines, phaeochromycins and mutactin. Wailupemicines are a metabolism product of *Streptomyces maritimus*, which was found at Wailupe Beach Park along the southeast coast of Oahu (Hawaii), and are of interest as new α-glucosidase inhibitors [84]. Phaeochromycins were isolated from an actinomycete *Streptomyces phaeochromogenes* and demonstrate anti-inflammatory activity [85].

The most common class of natural 4-hydroxy-2-pyrones includes 3-alkyl-substituted molecules, which contain alkyl and alkenyl substituents at the C-6 position and less often substituents at the C-5 position (Figure 3). A large class includes germicidins A–J as important representatives of 3,6-dialkyl-substituted 4-hydroxy-2-pyrones [86]. These compounds are natural antibiotics that were isolated from *Streptomyces bacteria* and are responsible for spore germination via inhibition of porcine Na^+/K^+-activated ATPase [87]. Related molecules are violapyrones A–F, which bear the methyl substituent at the C-3 position and a long aliphatic substituent at the C-6 position [88]. They are secondary metabolites of *Streptomyces violascens* and demonstrate modest antibacterial activity. Another feature of alkylated 4-pyrones is that they can perform signaling functions [89]. It was reported that photopyrones A–H act as signaling molecules in the cell–cell communication system of the entomopathogenic bacterium *Photorhabdus luminescens* via the inhibition of quorum sensing. Pseudopyronines A,B bearing long alkyl substituents at the C-3 and C-6 positions isolated from different *Pseudomonas* strains have antibacterial properties, especially against mycobacteria [9,90]. It is known that 3-methyl-6-alkyl-4-hydroxy-2-pyrones are included in the *M. tuberculosis* cell wall as permeability regulators. Pseudopyronines, which are similar to these compounds, selectively disrupt the membrane and inhibit the growth of *M. tuberculosis* by blocking its fatty acid biosynthesis pathway [90].

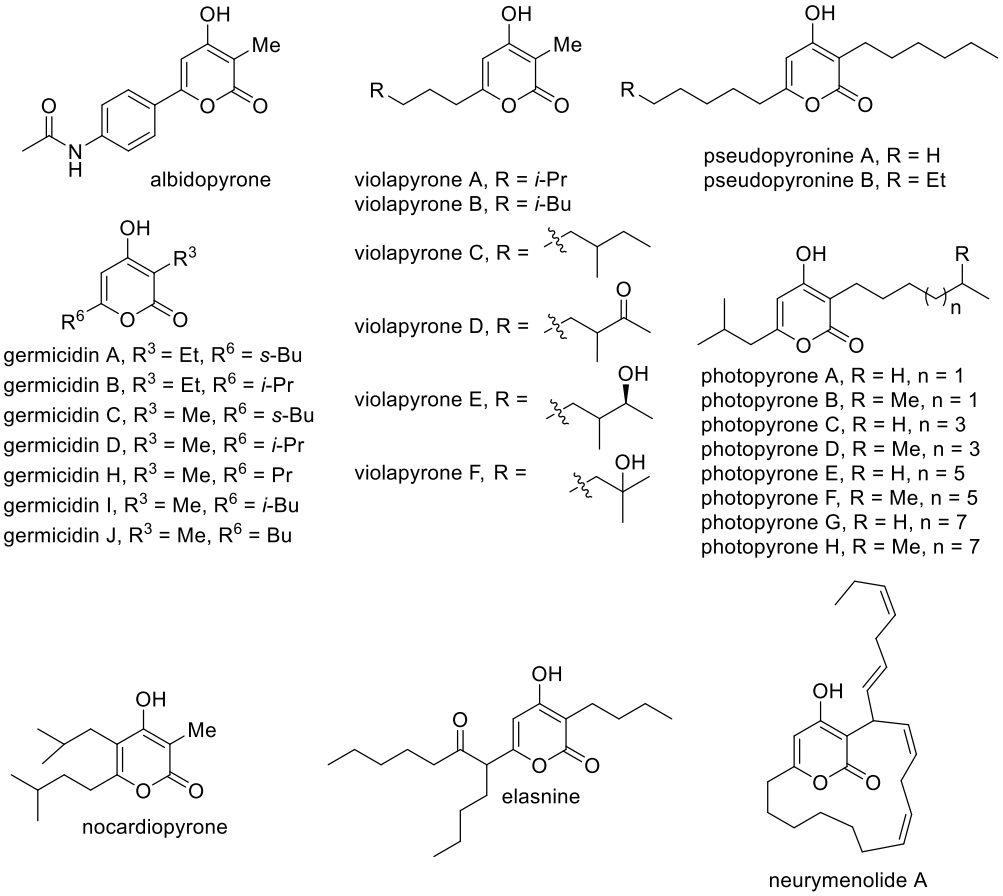


Figure 3. The main representatives of 3-alkyl-substituted 4-hydroxy-2-pyrones.

Elasnine contains branched alkyl substituents that are modified by a carbonyl group. It is interesting as an effective and selective inhibitor of human sputum (leukocyte) elastase, which is implicated in many inflammatory disease states [7]. Also, elasnine can be used in controlling marine biofilms and displays feasibility and advantages when used as a signal molecule to develop eco-friendly technologies. Elasnine's action is connected with disturbing the regulation of the ATP-binding cassette transport system and the bacterial secretion system [91]. The marine-pyrone macrolide neurymenolide A contains the 4-hydroxy-2-pyrone moiety, which was previously isolated from the Fijian red macroalga, namely, *Neurymenia fraxinifolia*, and characterized as an antibacterial agent against antibiotic-resistant strains [92]. It was observed that neurymenolide A significantly delays the in vivo polymerization of tubulin to form microtubules and bipolar mitotic spindles at the prophase–metaphase transition. A feature of albidopyrone is the presence of an aromatic substituent at the C-6 position, and it demonstrates a moderate inhibitory activity against protein-tyrosin phosphatase B, which is the major negative regulator of insulin signaling [93]. Nocardiopyrone contains a completely alkyl-substituted pyrone ring and was isolated from the marine microorganism *Nocardiopsis* [94].

Although natural 4-hydroxy-2-pyrones are usually polyacetates, some polypropionates were found in mollusks, fungi and bacteria [95]. Fusaripyrone A and exiguapyrone were isolated from the mollusks *Haminoea* and contain an unusually long chain and form via a regular condensation process starting with propionyl-CoA and continuing with elongation of C3 units up to the linear C30-polypropionates after cyclization [96]. These compounds can play the role of chemical markers for these marine organisms [95]. Nipyrones A and B were isolated from a marine sponge-derived fungus *Aspergillus niger* and exhibit moderate antibacterial efficacy against four pathogenic bacteria [97]. Salinipyrones A and B were isolated from the marine-derived bacterium *Salinispora pacifica*. These metabolites are by-products of the PKS system, which is associated with the rosamicin macrolide antibiotics [32,98]. A related molecule, namely, capsulactone, was isolated from an endophytic fungus *Penicillium capsulatum* obtained from the leaves of *Panax notoginseng* and demonstrated weak antibacterial activity (Figure 4) [99].

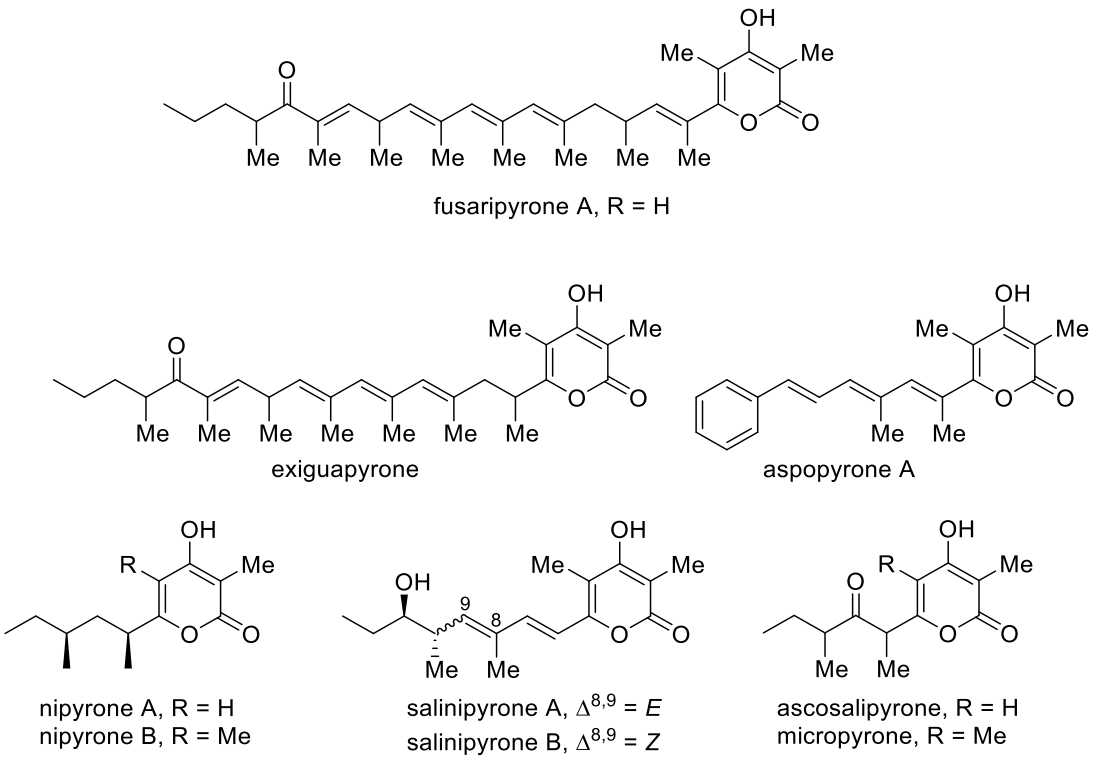


Figure 4. The major representatives of 3-alkyl-substituted 4-hydroxy-2-pyrones as polypropionate polyketides.

The structurally similar micropyrone and ascosalipyrone [100] contain the carbonyl group and were isolated from *Helichrysum italicum* ssp. *microphyllum* and the endophytic and obligate marine fungus *Ascochyta salicorniae* of the green alga *Ulva* sp., respectively. Bioassay-guided investigation of Okinawan plant-associated fungus *Aspergillus* sp. led to the isolation of aspopyrone A [101], which exhibited significant protein tyrosine phosphatase 1B (PTP1B) and T-cell PTP inhibitory activities.

A separate group includes 3-acyl-4-hydroxy-2-pyrones (Figure 5). This class of compounds stands out due to its biological properties. The simplest of this series, namely, dehydroacetic acid, is used as a food preservative (E265) and in cosmetics due to its antibacterial and fungicidal properties [68]. A structurally similar 6-methyl-4-hydroxy-2-pyrone, namely, pogostone, which was isolated from patchouli oil, inhibits both Gram-negative and Gram-positive bacteria and demonstrates anti-cancer activities [102]. Furthermore, pogostone can be used as a repellent and insecticide [103]. Csypyrones B are 3-acetyl-α-pyrone compounds bearing the carboxylic acid side chain as the result of oxidation of the corresponding alkyl substituent and were isolated from the fungus *Aspergillus oryzae* [104].

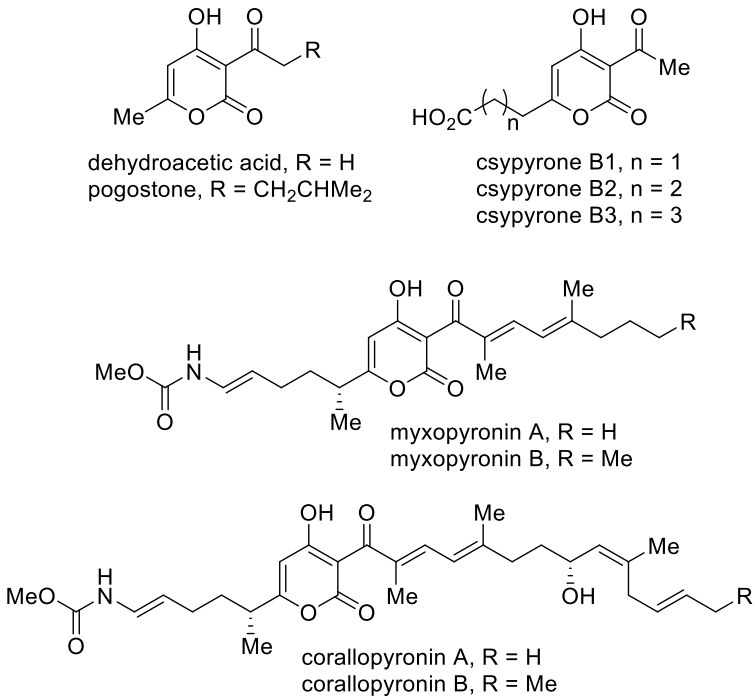


Figure 5. The major representatives of 3-acyl-4-hydroxy-2-pyrones.

Mixopyronins and corallopyronins are functionalized *N*-alkenylcarbamate 3-acyl-4-hydroxy-2-pyrones bearing chiral centers. These molecules are promising natural antibiotics produced by the terrestrial bacterium *Myxococcus fulvus* Mx f50 and possess antibacterial activity against Gram-positive and Gram-negative pathogens [105]. The pyrones are rare inhibitors of the bacterial RNA polymerase (RNAP) "switch region" as non-competitive inhibitors with rifampicin. RNAP is a highly conserved protein, which makes the possible application of these molecules in medical practice important. From the point of view of biological activity and the possibility of biotechnological production, special attention is focused on corallopyronin A as an antibiotic undergoing preclinical studies [106].

A few 4-hydroxy-2-pyrone conjugates are known to have carbohydrates and terpenes, which are attracted to the C-3 position of the pyrone ring (Figure 6). Such structures exhibit a wide spectrum of biological activity and are an attractive target for total synthesis. Carbohydrate derivatives, namely, fusapyrone and deoxyfusapyrone, were isolated from *Fusarium semitectum* [8,107–109]. These compounds show considerable antifungal activity (*Botrytis cinerea*, *Aspergillus parasiticus* and *Penicillium brevi-compactum*) [109]. Epipyrone A (Orevactaene) is a polyene pigment isolated from *Epicoccum nigrum* with broad-spectrum

antifungal activity [110,111]. Moreover, this molecule interferes with the RNA binding activity of the regulatory protein Rev in human immunodeficiency virus type I; demonstrates anti-microbial activity; and displays inhibitory activities against cytopathic effect of influenza A virus (H1N1) and NF-κB-dependent gene expression, cysteine and serine proteases [110].

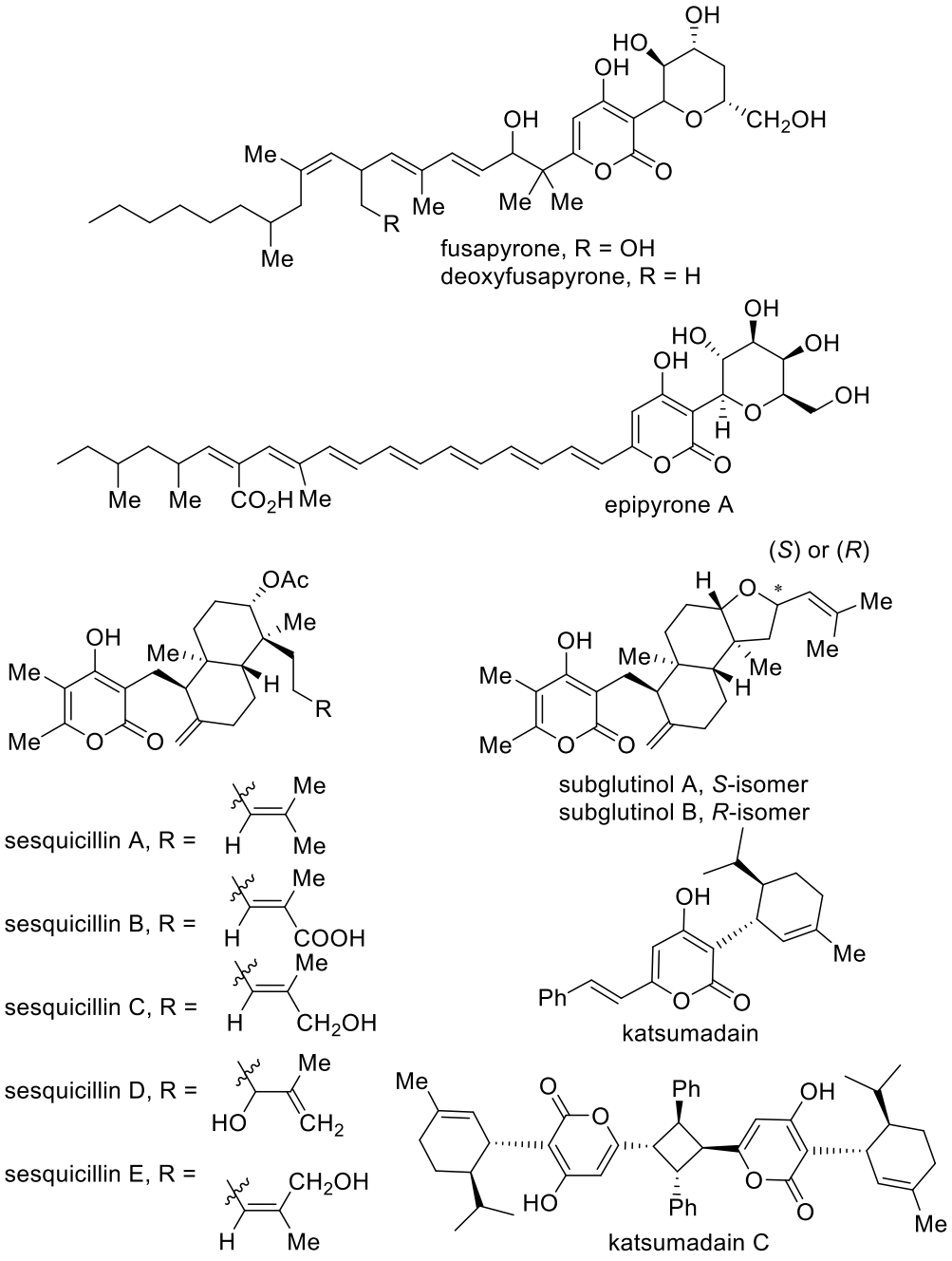


Figure 6. The major representatives of conjugates based on 4-hydroxy-2-pyrones.

A large class of pyrano-diterpene conjugates includes sesquicillins A–E [112], which were isolated from the fungi *Albophoma*. Sesquicillins are insecticides and cytotoxic molecules showing moderate inhibitory activity against the growth of *Artemia salina* (brine shrimps) and Jurkat cells.

Another meroterpenoid, namely, subglutinol A, is a natural product isolated from *Fusarium subglutinans*, which is an endophytic fungus from the vine *Tripterygium wilfordii* [113]. This compound demonstrated multimodal immune-suppressive effects on

activated T cells in vitro. These results suggest the potential of subglutinol as a novel therapeutic for inflammatory diseases. Katsumadain C bears a four-membered cycle and is isolated from *Alpinia katsumadain*. This molecule is a product of katsumadain dimerization and is used as an anti-emetic and stomachic agent [74]. Various pyrones bearing a terpene fragment, such as sartorypyrones [114,115], aszonapyrones [114,116] and metarhizin A [117], are also isolated and of interest as biologically important compounds.

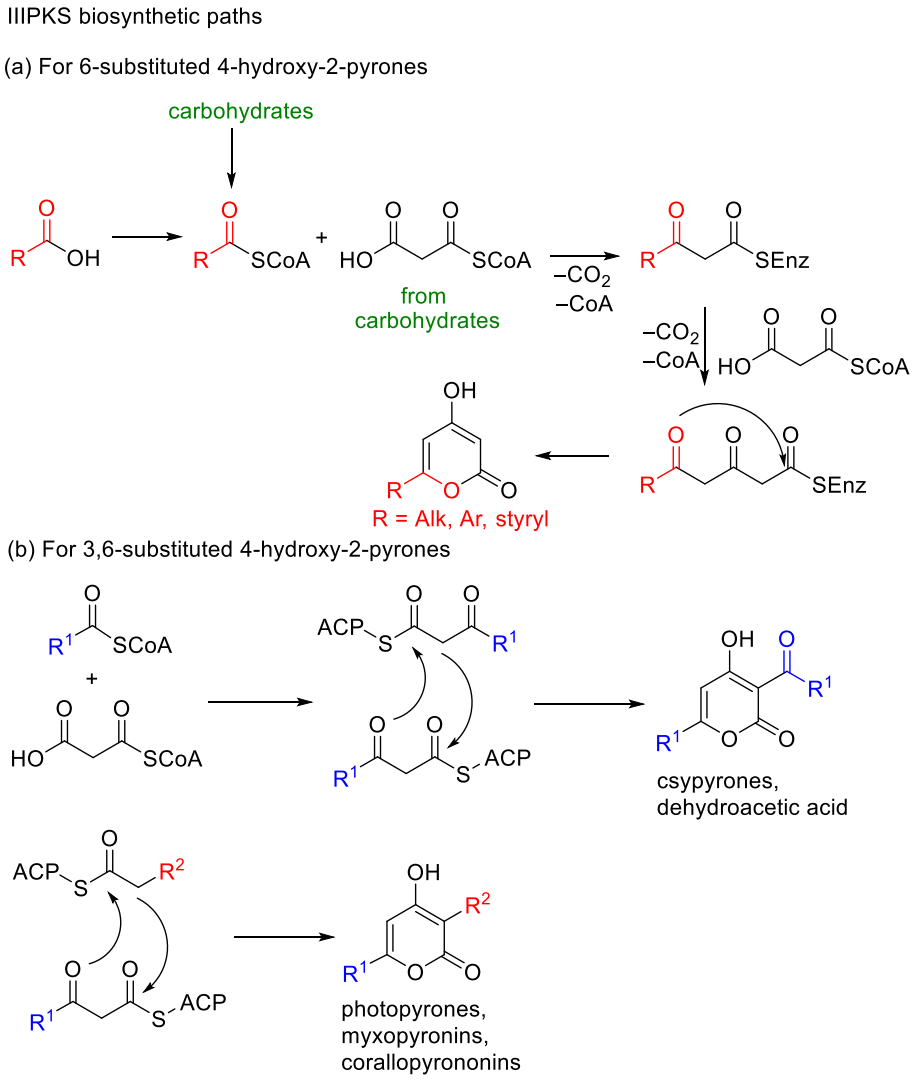
4. Biosynthesis and Biotechnological Methods for the Preparation of 4-Hydroxy-2-pyrones

Polyketides are a large class of biomolecules assembled by repeating Claisen-condensations between an activated acylstarter unit and malonyl-CoA-derived extender units [76,118–120]. In Nature, the synthesis of 4-hydroxy-2-pyrones is catalyzed by polyketidases (PKS), which give chain elongation using structural fragments, such as acetyl-CoA, propyl-CoA, malonyl-CoA and methylmalonyl-CoA, as well as other derivatives of carboxylic acids (Scheme 17) [6]. The majority of this family of 4-hydroxy-2-pyrones is found to be biosynthesized by type III polyketide synthases (PKSs), which provide a two-step process, including two condensation processes and intramolecular cyclization. III PKS systems were described in plants, fungi and bacteria. In contrast to I PKS and II PKS, III PKS acts independently of the acyl carrier protein (ACP), and acyl CoA is used directly as a substrate (Scheme 17). Although usually 4-hydroxy-2-pyrones as triketides are isolated as by-products in the biosynthesis of complex polyketides [98], in some cases, special pyrone synthases, which are a kind of polyketide synthase III, are able to control the final length of a polyketide and responsible for the selective lactonization [121]. Another important biosynthetic pathway is characteristic of natural 3,6-disubstituted 4-hydroxy-2-pyrones, such as csypyrones, photopyrones, myxopyronins, corallopyrononins and dehydroacetic acid, and is based on the intermolecular cyclization of two acyl carrier protein (ACP)-tethered β-ketoacyl intermediates or β-ketoacyl-ACP with acyl-ACP [6,120]. This unique process is non-decarboxilative and catalyzed by a special type of ketidases, which are also related to III polyketidases.

For 6-substituted aromatic 4-hydroxy-2-pyrones, such as wailupemicines, II polyketidase is an enzyme for synthesis [121]. The involvement of various enzymes in the process makes it possible to carry out the modification of side substituents, methylation of the pyrone ring, reduction and glycosylation, which ensures the diversity of these pyrones [71,122,123].

The wide distribution of 4-hydroxy-2-pyrones in Nature, the presence of well-functioning biosynthetic pathways based on polyketide synthases and the application of the pyrones as important reagents stimulate the development of biotechnological methods. Advances in synthetic biology and metabolic engineering allow for the improvement of production efficiency, both using microorganisms and in vitro methods [124]. In addition, in some cases, the synthesis of pharmaceutically attractive pyrones by chemical approaches is rather complicated due to the large number of steps [106]. Important features of biotechnological methods are enzymatic cascade formation of many C–C and C–O bonds; high stereoselectivity; and the use of available compounds as starting molecules, such as glucose or simple carboxylic acids. In the literature, most attention is paid to biotechnological methods for the microbial production of triacetic acid lactone as an effective process. This molecule is constructed via 2-pyrone synthase catalysis from one acetyl-CoA and two malonyl-CoA, which are obtained from glucose [22]. These approaches allow for the transition from carbohydrates to valuable products based on biological and chemical methods. At the same time, special attention in the literature is paid to the synthesis of natural 4-hydroxy-2-pyrones, such as hispidin [125] and corallopyronin A [106,126], because it is practically important from the point of view of further application. PKSs allow for different fragments of carboxylic acids to be involved in the reactions. Also, biological methods were applied for the construction of unnatural 4-hydroxy-2-pyrones using different carboxylic acids as a starter [127–129].

In contrast to PKSs, the recently reported thiolase-based polyketide biosynthesis can directly use acetyl-CoA as the extender unit to form various 6-substituted 4-hydroxy-2-pyrones via a nondecarboxylative Claisen condensation, enabling the product synthesis at maximum energy and carbon efficiency [124].



Scheme 17. General approach for the synthesis of 4-hydroxy-2-pyrones catalyzed by polyketide synthetases.

Biotechnological methods have some drawbacks associated with the isolation of the required 4-hydroxy-2-pyrones because in most cases, the desired pyrones are not isolated in a pure form. Also, the use of bioengineering methods is difficult for chemists and these pyrones are hard to access in sufficient quantities for further study and application in organic synthesis. But given the rapid development of these areas, these problems can be solved, which is important from the point of view of sustainable chemistry.

5. Summary

Thus, the main strategies have been demonstrated for the construction of 4-hydroxy-2-pyrones via de novo synthesis or pyran modification. Although the isolation of new pyrones from natural sources is still an urgent task, a wide range of strategies is actively being developed for the application of 4-hydroxy-2-pyrones in the synthesis of biologically important and natural compounds. Since these pyrones are hidden tricarbonyl structures, the most popular are biomimetic methods that are based on the cyclization of tricarbonyl

compounds and their derivatives. The most accessible approaches are based on the self-condensation of dicarbonyl compounds without the use of organometallic compounds but demonstrate a very limited scope. At the same time, a search is underway for new methods related to both the construction of the carbon skeleton and selective cyclization. Among them, a special place is occupied by approaches that are based on catalysis by transition metals. The use of acetylenes makes it possible to easily create new C-C bonds and carry out subsequent selective gold-catalyzed cyclization, which has found wide application in the total synthesis of natural pyrones. In contrast to other 2-pyrones, methods based on [4+2]-cyclization of ketenes for the construction of acyl-substituted 4-hydroxy-2-pyrones are actively applied. Despite the development of de novo synthesis methods, the modification of readily available and reactive 4-hydroxy-2-pyrones, such as triacetic acid lactone and dehydracetic acid, are widespread for the preparation of the pyrones. A special group of methods includes biotechnological approaches that allow for the one-step construction of complex pyrone structures from simple and accessible molecules. In general, although 4-hydroxy-2-pyrones are attractive objects for the creation of new bioactive compounds, the methods of preparation are rather limited, which does not allow for the synthetic potential to be fully revealed and requires lengthy synthetic procedures for the construction of the target molecule. We hope that this review will stimulate the development of the chemistry of 4-hydroxy-2-pyrones, both in terms of the search for efficient synthetic methods and convenient methods for their further transformations and modifications, as well as joint approaches based on biotechnology and organic synthesis. After all, this can lead to low-cost and effective methods for the creation of valuable chemical products based on biomass feedstock or readily accessible starting reagents.

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