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Kojic acid in organic synthesis

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Abstract: The reactions of kojic acid in organic synthesis are reviewed. The aim of this review is to cover the literature up to the end of 2014, showing the distribution of publications involving kojic acid chemistry in the synthesis of various pyrone containing compounds, pyridine and pyridone heterocycles, and also other organic compounds. First, introductory text about the preparation, biological, and industrial applications, and the chemical properties of kojic acid is given. Then its uses in organic synthesis are presented considering the reaction type.

Key words: Kojic acid, pyrone, pyridone, organic synthesis

1. Introduction

Kojic acid (KA), 5-hydroxy-2-(hydroxymethy1)-4*H*-pyran-4-one, is produced from carbohydrate sources, especially glucose, through multistep enzymatic reactions.[1] KA can be also produced by fungi during aerobic fermentation using various substrates such as sucrose, glucose, xylose, and arabinose.[2,3] Industrially, KA was produced by *Aspergillus* species in aerobic fermentation. Saito discovered KA in the mycelia of *Aspergillus oryzae* grown on steamed rice in 1907 and then its structure was established in 1924 by Yabuta. In 1930, KA was obtained from *D*-glucose by chemical synthesis.[4] Due to the importance of KA in industry, the production of KA is increasing and a considerable amount of research has been devoted to the biosynthesis of KA, and numerous publications have dealt with its chemical and biological properties. KA has a wide range of applications in the cosmetic, medicine, food, agriculture, and chemical industries. In the cosmetic industry, KA is a natural skin whitening agent[5,6] that prevents ultraviolet radiation and inhibits tyrosinase activities,[7,8] which cause pigmentation. In the medical field, KA has been reported as a potential antibacterial,[9] antimicrobial,[10] antileukemic,[11] and antifungal[12,13] agent. In the food industry, KA is used as an agent to prevent undesirable melanosis (blackening) of agricultural products such as vegetables, fruits, and crustaceans during storage.[14] KA also exhibits the action of a polyphenol oxidase (PPO) enzyme when these products are exposed to oxygen.[15] In the chemical industry, KA can be used as an analytical tool for the determination of cations, since the reaction of KA with a trace of Fe^{3+} ions can form a deep red complex.[16] In addition, KA can be converted to comenic acid, which is an important intermediate for the preparation of maltol and its derivatives. Finally, KA is widely used in agriculture as a chelating agent and insecticide activator.[17]

KA, with the molecular formula $C_6H_6O_4$, is a monocyclic pyrone consisting of a carbon ring with two double bonds (Figure) that can be found in the form of nearly odorless white crystals or pale yellow crystalline

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powder. The hydroxyl group at position C_5 shows a weakly acidic characteristic. KA is a polyfunctional heterocycle, with several important reaction centers, incorporated in many types of reactions, involving addition, alkylation, acylation, oxidation, ring opening, and nucleophilic and electrophilic substitution reactions. Although there are some reviews about biological properties,[18,19] and one old book chapter[20] on very limited chemical properties of KA, to the best of our knowledge, there are no comprehensive reviews or book chapters on the reactions of KA in organic synthesis. Moreover, there is a growing number of published papers on the reactions of KA in organic synthesis. We have recently published two review articles on the synthesis of heterocyclic compounds,[21,22] and in continuing our works on pyrone chemistry,[23–25] we decided to write a review on the application of KA in organic chemistry. The aim of this review is to cover the literature up to the end of 2014, showing the distribution of publications involving all types of reactions of KA, such as synthesis of pyridine and pyridone derivatives, aldol, Mannich, Michael addition, multicomponent, diazo coupling, Claisen rearrangement, cycloaddition, cross-coupling, Wittig, and ring-opening reactions, and substitution at enolic OH and hydroxylmethyl involving protections, and metal complexation.

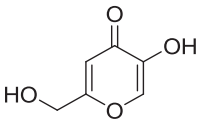
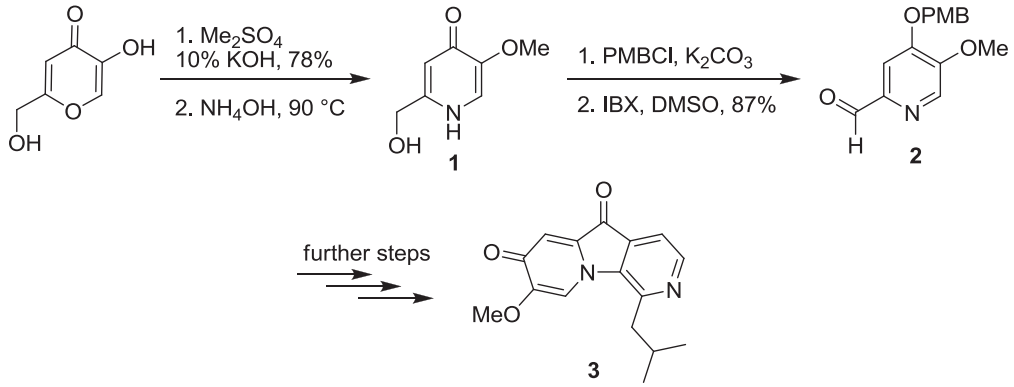


Figure. The structure of KA.

2. Reactions of kojic acid

2.1. Synthesis of pyridones and pyridines

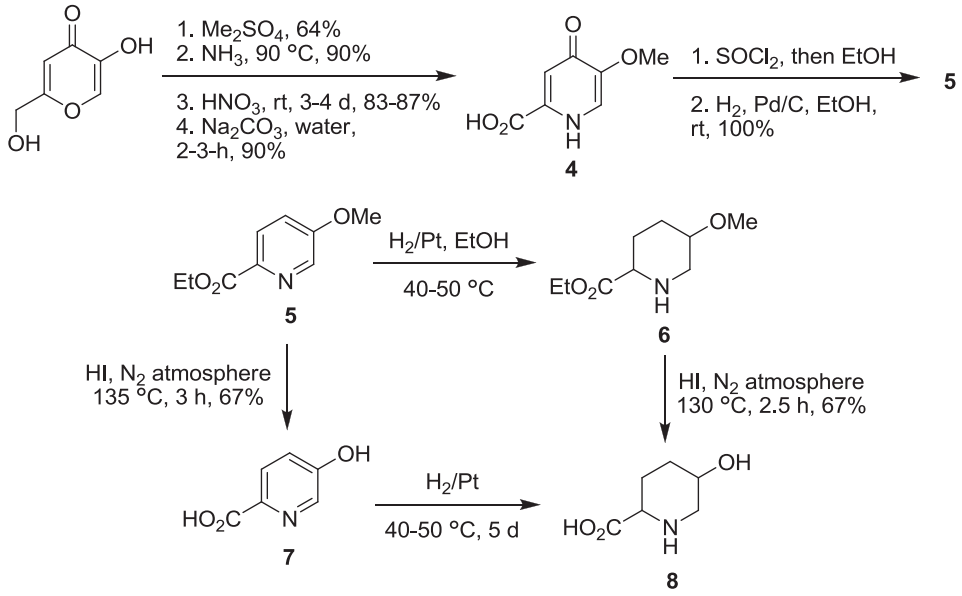
O'Malley et al.[26] reported the synthesis of pyridine-2-carbaldehyde **2** starting from KA in four steps. Methylation of KA using Me_2SO_4 in the presence of KOH and then heating with NH_4OH at 90 °C afforded pyridone **1**. Pyridine-2-carbaldehyde **2** was prepared from the reaction of pyridone **1** with *p*-methoxybenzyl chloride (PMBCl) and then by oxidation with *O*-iodoxybenzoic acid (IBX) in DMSO. The obtained pyridine-2-carbaldehyde **2** was transformed into pterocellin A **3**, which exhibited anticancer activity (Scheme 1).



Scheme 1.

5-Hydroxypipecolic acid **8**, a natural substances found in *Rhapis/Iabellifannis* (Rhapisercelsa, Acacia-species), Rhodesian teak (Baikiaeaplurijuga), and in the pericarp of edible dates (Phoenixdactyli/era), was synthesized from KA in a sequence of reactions as outlined in Scheme 2. Reaction of KA with Me_2SO_4 and then with 22% aqueous NH_3 at 90 °C for 2–3 h, followed by oxidation using HNO_3 at room temperature for 3–4

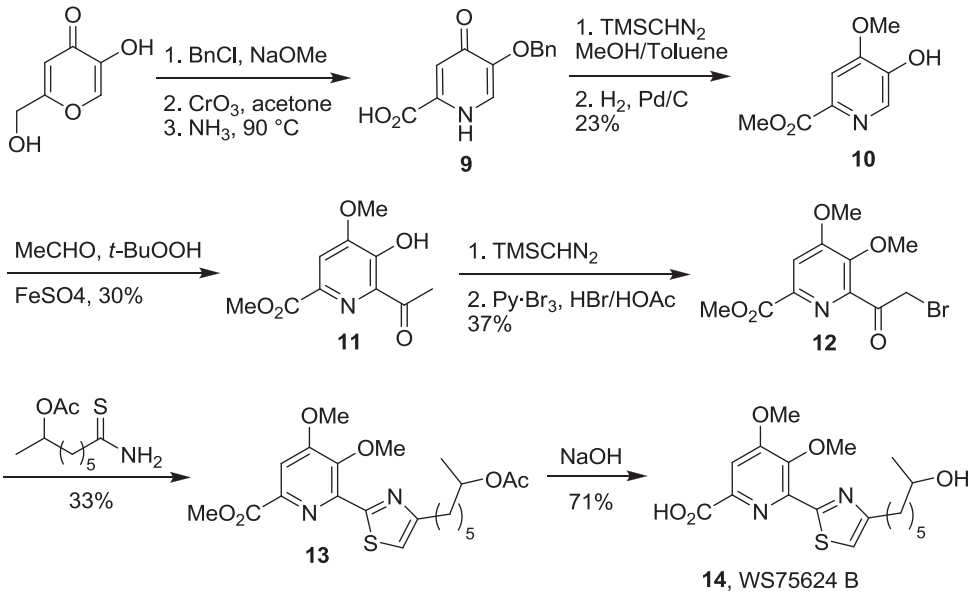
days and then treatment of the obtained product with Na_2CO_3 in water for 2–3 h, gave 5-methoxy-4-pyridone-2-carboxylic acid **4** in 90% yield. By reaction of **4** with $SOCl_2$ under reflux conditions for 5 h continued by reduction with H_2 in the presence of Pd/C at room temperature, ethyl 5-methoxypyridine-2-carboxylate **5** was obtained quantitatively, which was converted to **6** and **7** by treatment with H_2/Pt in EtOH at 40–50 °C and HI under N_2 atmosphere at 135 °C for 3 h, respectively. 5-Hydroxypipecolic acid **8** was obtained from **6** by treatment with HI under N_2 atmosphere at 130 °C for 2.5 h or from **7** through reduction with H_2/Pt at 40–50 °C.[27]



Scheme 2.

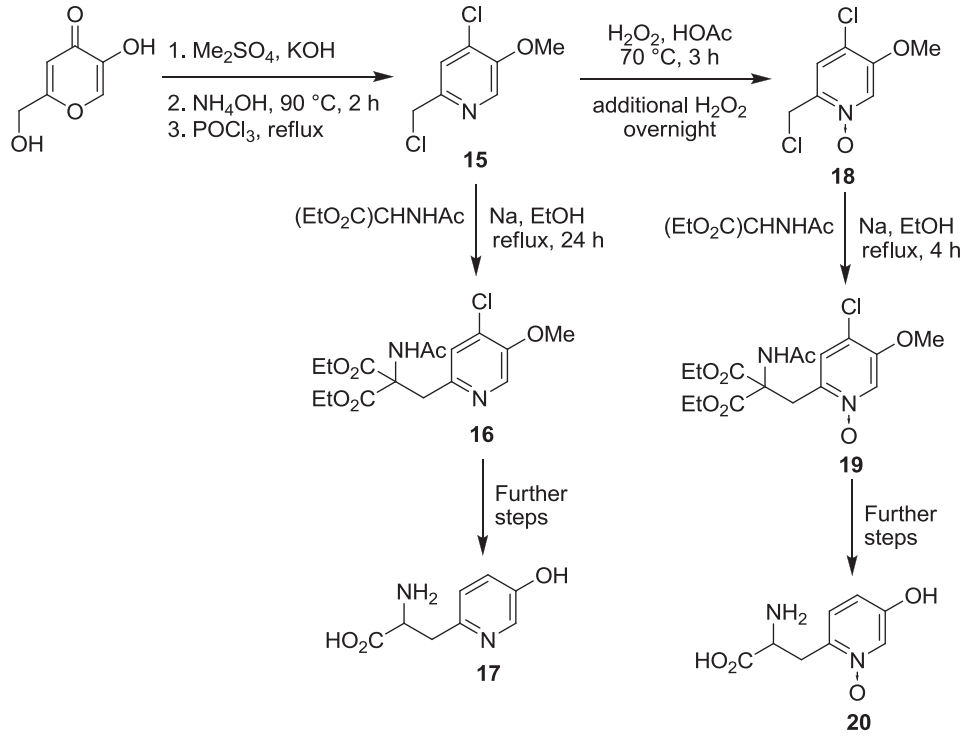
Stangeland et al.[28] described the total synthesis of WS75624 B **14**, which is a potent endothelin converting enzyme (ECE) inhibitor and potential antihypertensive agent.[29] This compound was synthesized from KA in ten steps. By protection of enolic OH with BnCl in the presence of NaOMe in MeOH (70% yield) and then oxidation of the hydroxymethyl group to carboxylic acid with Jones reagent in acetone (63% yield), followed by reaction with concentrated NH_4OH in a sealed flask at 90 °C, pyridone **9** was obtained quantitatively for the last step. Pyridine carboxylate **10** was obtained in 23% yield by methylation of both the carboxyl and phenolic OH with trimethylsilyldiazomethane ($TMSCHN_2$) in MeOH/toluene, followed by deprotecting of the benzyl ether moiety with Pd/C in MeOH. By treatment of compound **10** with acetaldehyde in the presence of *t*-BuOOH and $FeSO_4$, compound **11** was obtained in 97% yield, according Patt and Massa's synthesis.[30] Compound **11** was converted to WS75624 B **14** in further steps through compounds **12** and **13** as outlined in Scheme 3. WS75624 A was also synthesized in a similar procedure.

Norton et al.[31,32] reported the synthesis of 5-hydroxy-2-pyridine-DL-alanine **17**, a potent competitive antagonist of tyrosine in *Leuconostocdeztranicum 8086* and a moderately active growth inhibitor of *Escherichia coli 9723*, and *β*-(5-hydroxy-2-pyridyl 1-oxide)-DL-alanine **20**, analogues of tyrosine, through a sequence of reactions starting from KA. Reaction of KA with Me_2SO_4 in the presence of KOH solution and then treatment with concentrated NH_4OH in a stainless steel bomb at 90 °C for 2 h, followed by reaction with $POCl_3$ under reflux conditions, gave 4-chloro-2-chloromethyl-5-methoxypyridine **15**. Diethyl 2-acetamido-2-(4-chloro-5-methoxy-2-pyridinemethyl) malonate **16** was obtained from the reaction of **15** with ethyl acetamide malonate



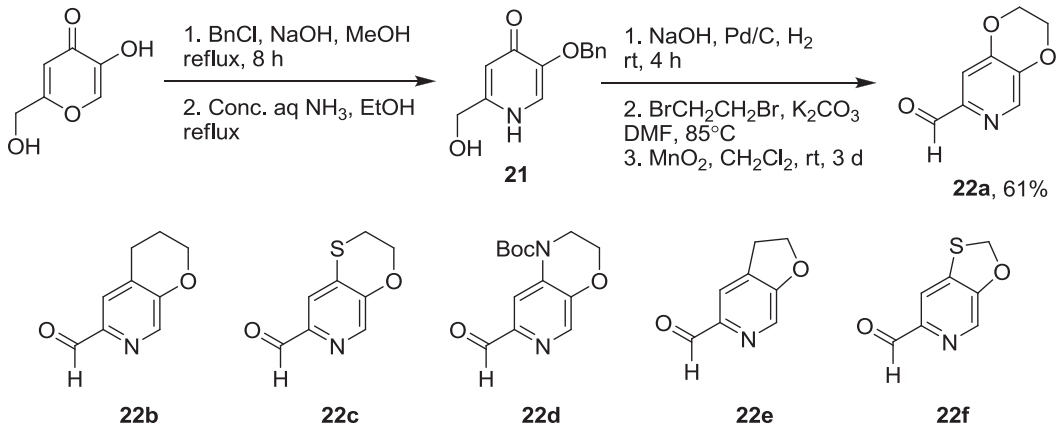
Scheme 3.

in the presence of Na/EtOH under reflux conditions for 24 h, which was converted to **17** in further steps as shown in Scheme 4. In addition, the pyridine N-oxide, β-(5-hydroxy-2-pyridyl 1-oxide)-DL-alanine **20**, was synthesized by oxidation of **15** with H_2O_2 in glacial AcOH at 70 °C for 3 h, to afford 4-chloro-2-chloromethyl-5-methoxypyridine 1-oxide **18**, which by treatment with ethyl acetamide malonate led to product **19** under reaction conditions similar to those mentioned above (Scheme 4).



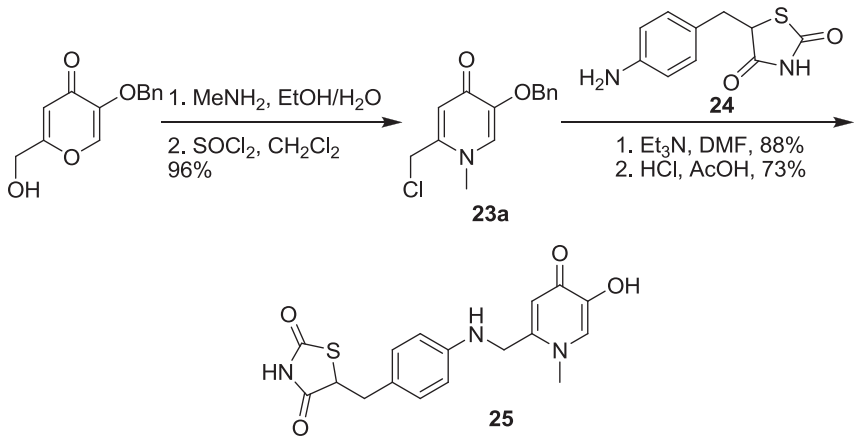
Scheme 4.

Barfoot et al.[33] synthesized pyridyl analogues of 2,3-dihydro-1,4-benzodioxin-6-carbaldehydes as a key intermediates for antibacterial medicinal chemistry. 2,3-Dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carbaldehyde **22a** was prepared by treatment of KA with BnCl in the presence of NaOH in MeOH at reflux for 8 h and then reaction with NH_3 in EtOH under reflux conditions to give pyridone **21**, followed by deprotection and cyclization with 1,2-dibromoethane in the presence of K_2CO_3 in DMF at 85 °C and oxidation using of MnO_2 in CH_2Cl_2 at room temperature for 3 days. Moreover, pyridines **22b**–**f** were synthesized by a similar procedure (Scheme 5).



Scheme 5.

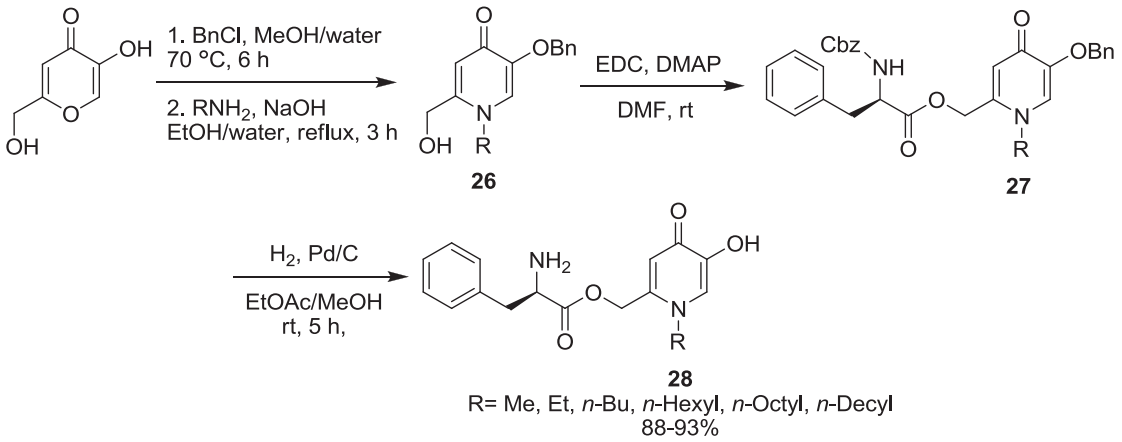
By reaction of Bn-protected KA with $MeNH_2$ in EtOH/water, followed by treatment with $SOCl_2$ in CH_2Cl_2, pyridinone **23a** was obtained in good yield. Reaction of pyridinone **23a** and amine **24** was carried out in DMF in the presence of Et_3N and the obtained product was deprotected using HCl and AcOH to give hydroxy pyridinone **25** in 73% yield (Scheme 6). The complexing ability of **25** with VO^{2+} and its biological activity were also investigated.[34]



Scheme 6.

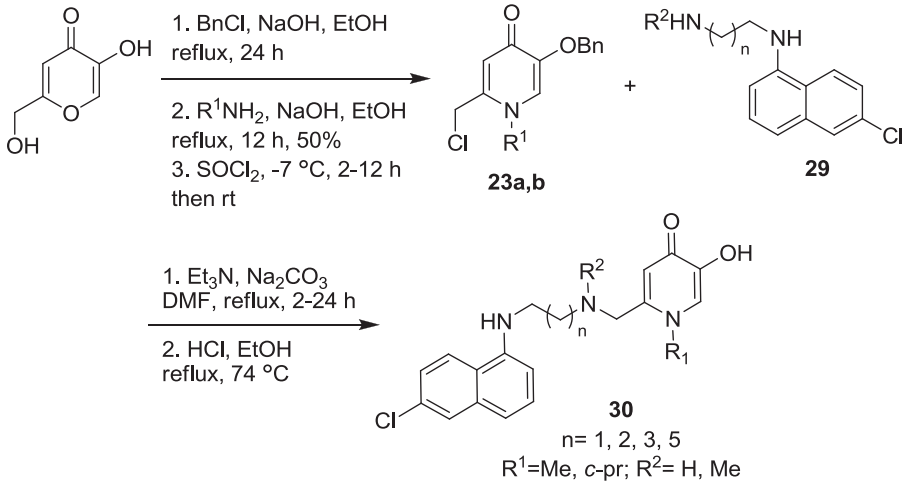
Li et al.[35] reported the synthesis of hydroxypyridinone and L-phenylalanine conjugates as potential tyrosinase inhibitors from KA. Firstly, protection of the OH group of KA with BnCl in MeOH/water at 70 °C for 6 h, followed by treatment with alkyl amines in EtOH/water in the presence of NaOH at reflux for 3 h, gave

pyridone **26** in 72%–85% yields. Coupling of the resulting pyridone **26** with Cbz-L-phenylalanine by ester bond formation in the presence of EDC and DMAP in DMF at room temperature led to **27**, which after deprotection of the benzyl and Cbz groups in the presence of H_2/Pd/C in EtOAc/water (1/1) at room temperature for 5 h converted to the desired product **28** in 88%–93% yields (Scheme 7).



Scheme 7.

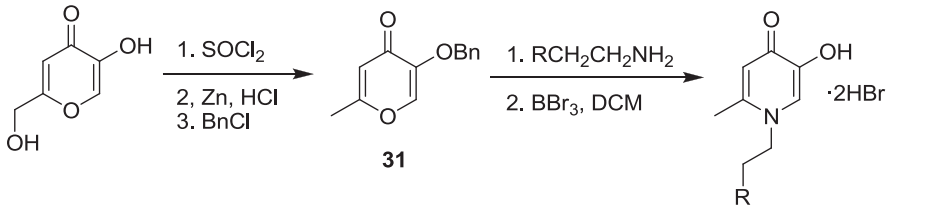
Chemoselective protection of enolic OH of KA with BnCl in the presence of NaOH in EtOH under reflux conditions for 24 h, followed by reaction with $MeNH_2$ or c-$PrNH_2$ in EtOH and then chlorination using neat $SOCl_2$, afforded the intermediates **23a,b**. Treatment of **23a,b** with N-(7-chloro-4-quinolinyl)diaminoalkane **29** in the presence of Na_2CO_3 and Et_3N in DMF under reflux conditions for 2–24 h, followed by deprotection with HCl at 74 °C gave aminochloroquinoline–pyridone hybrids **30** that exhibited β-hematin inhibition and antiplasmodial activity against drug resistant (K1) and sensitive (3D7) strains of plasmodium falciparum (Scheme 8).[36]



Scheme 8.

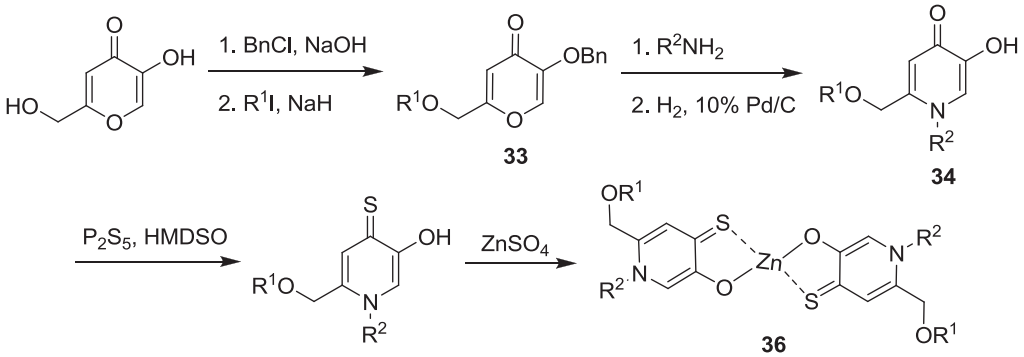
A series of 1,2,5-trisubstituted 4(1H)-pyridinone derivatives **32** were reported by Öztürk et al.[37,38] through reaction of KA with amines in EtOH. Treatment of KA with $SOCl_2$ and then reduction with Zn/HCl, followed by the protection of OH with BnCl afforded 4-pyrone derivative **31**. Pyridinone derivatives **32**, with

high analgesic and anti-inflammatory activities, were produced in 50%–72% yields by reaction of **31** with amines continued by deprotection with BBr_3 in DCM (Scheme 9).[39–41] Furthermore, synthesis of N-aryl-γ-pyridones starting from KA was reported.[42]



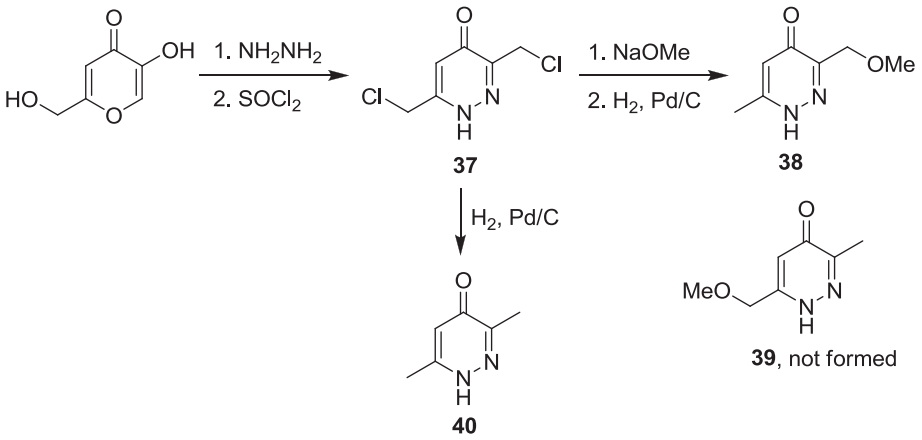
Scheme 9.

Sakurai et al.[43] described the synthesis of pyridine-4-thiones **35** from KA in five steps. The OH group of KA at the C-5 position was protected by reaction with BnCl in the presence of NaOH, followed by treatment with alkyl iodides in the presence of NaH to give the O-alkylated products **33**. Addition of amines to O,O'-disubstituted KAs and then debenzylation with 10% Pd/C as a catalyst under an H_2 atmosphere gave pyridinones **34**. By treatment of the resulting 5-hydroxy-4(1H)-pyridinones **34** with P_2S_5 in the presence of hexamethyldisiloxane (HMDSO), the C=O bond was converted into C=S. Reaction of two equimolar amounts of **35** with $ZnSO_4$ afforded the corresponding zinc complexes, **36**, which exhibited antidiabetic and antimetabolicsyndrome effects in animals (Scheme 10).



Scheme 10.

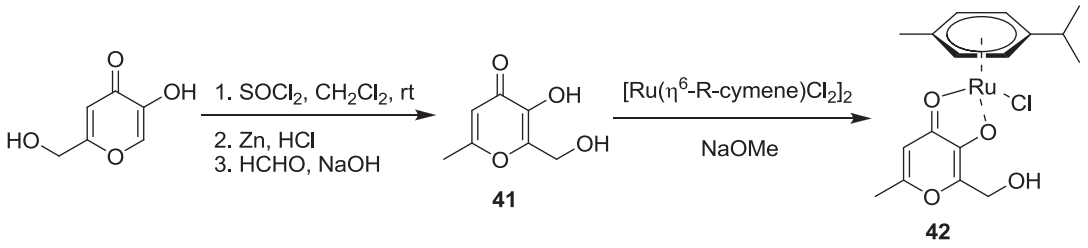
The reaction of KA with hydrazine was investigated by Thomas et al. and 4-oxo-1,4-dihydropyridazine was obtained. As shown in Scheme 11, KA in reaction with hydrazine and then $SOCl_2$ was converted to dihydropyridazine **37** in 45% yield. Reduction of compound **37** with H_2 in the presence of Pd/C afforded product **40.** Moreover, compound **37** in treatment with NaOMe in MeOH and then reduction with H_2/Pd/C gave dihydropyridazine **38**, while the isomer **39** was not produced.[44–47]



Scheme 11.

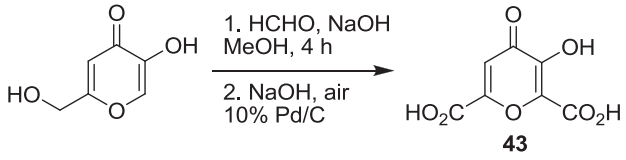
2.2. Aldol reaction

Maltol-derived ruthenium–cymene complex **42** with tumor inhibiting properties was reported by Kandioller et al.[48] in 2009. As shown in Scheme 12, aldol product **41** was synthesized in three steps from KA. Reaction of KA with $SOCl_2$ in CH_2Cl_2 at room temperature and then reduction with Zn/HCl in water at 75 °C, followed by treatment with formaldehyde under alkaline conditions gave aldol product **41** in 70% yield. The corresponding Ru^{II} complex **42** was obtained in good yields (81%) by reaction of **41** and bis[dichlorido(η^6-*p*-cyachyungtrenungmene)ruthenium(II)] using NaOMe in MeOH for 5–18 h.



Scheme 12.

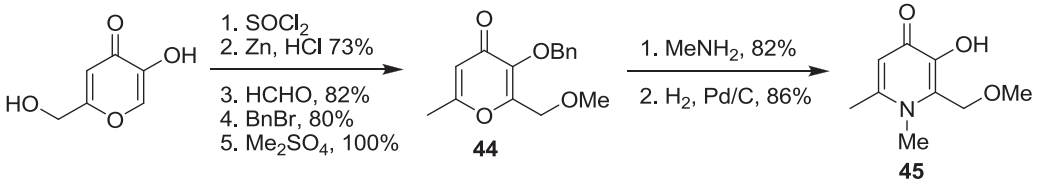
Poppy acid, 3-hydroxy-4-oxo-4*H*-pyran-2,6-dicarboxylic acid **43**, was prepared in 30% yield by subjecting KA to formaldehyde in the presence of NaOH in MeOH/water mixture for 4 h, followed by oxidation with air in the presence of NaOH and Pd/C (Scheme 13).[49]



Scheme 13.

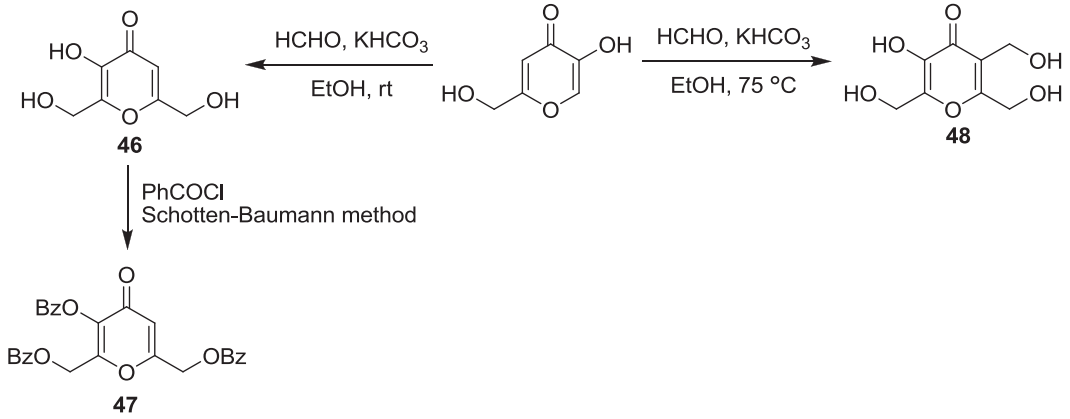
Liu et al.[50] synthesized 2-substituted- 3-hydroxypyridin-4-ones **45** starting from KA and evaluated the inhibitory activity of the corresponding iron-containing metalloenzyme. By reaction of KA with $SOCl_2$, followed by reduction using Zn/HCl and then treatment with formaldehyde, aldol product was obtained, which was transformed into compound **44** by protection of enolic OH with BnBr, and CH_2OH moiety with Me_2SO_4.

Pyridinone **45** was obtained in 82% yield when **44** was treated with $MeNH_2$, followed by deprotection using H_2 in the presence of Pd/C (Scheme 14).



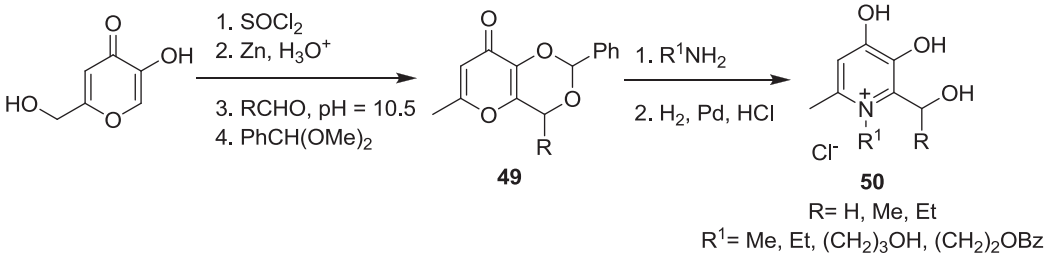
Scheme 14.

Treatment of a mixture of KA in absolute EtOH with paraformaldehyde in the presence of either $KHCO_3$ or anhydrous K_2CO_3 at room temperature afforded 3-hydroxy-2,6-bis(hydroxymethyl)-4*H*-pyran-4-one **46**, which in the reaction with benzoyl chloride via the Schotten–Baumann method, yielded (5-hydroxy-4-oxo-4*H*-pyran-2,3,6-triyl)tris(methylene) tribenzoate **47**. When a mixture of KA with paraformaldehyde in absolute EtOH was heated at 75 °C in the presence of $KHCO_3$ for 17 h, 3-hydroxy-2,5,6-tris(hydroxymethyl)-4*H*-pyran-4-one **48** was produced (Scheme 15).[51] Hydroxyl methylation of KA was also reported.[52]



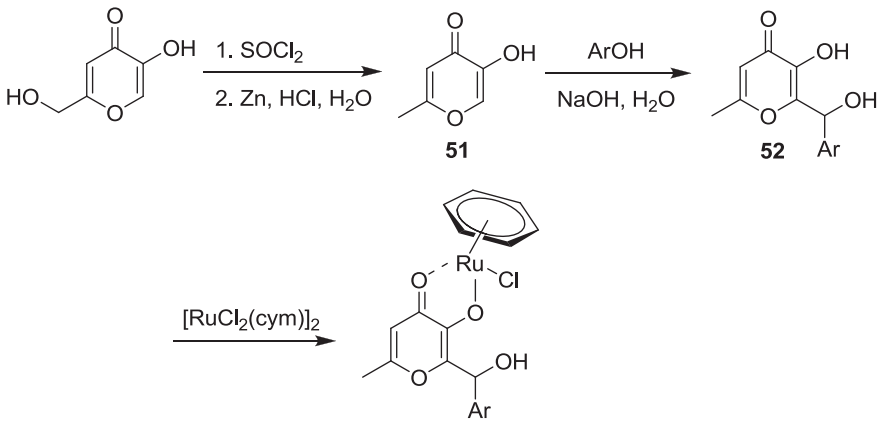
Scheme 15.

The synthesis of 2-(1-hydroxyalkyl)-3-hydroxypyridin-4-ones **50**, as 4-hydroxypyridinium ions, was reported by Liu et al.[53] starting from KA in six steps. Compounds **49** were produced by treatment of KA with $SOCl_2$ and then Zn in acidic solution, followed by the aldol condensation with aliphatic aldehydes under alkaline aqueous conditions and then protection with benzaldehyde dimethylacetal in DMF in the presence of a catalytic amount of *p*-TSA. Treatment of **49** with primary amines and then deprotection with H_2 in the presence of Pd and HCl gave the desired product **50** in 73%–87.5% yields (Scheme 16).



Scheme 16.

Kandioller et al.[54] described the synthesis of Ru(II)-p-cymene complexes **53**, which exhibit anticancer activity against human tumor cell lines. The precursor allomaltol **51** was prepared from KA by reaction with $SOCl_2$, followed by reduction with Zn under acidic conditions. Then allomaltol **51** was treated with substituted benzaldehydes in the presence of NaOH in water to give aldol products **52** in 64%–91% yields. Complexes **53** were obtained in 54%-73% from the reaction of **52** with bis[dichloride(η^6-p-cymene)ruthenium(II)] in the presence of NaOMe in MeOH (Scheme 17). A similar aldol reaction of **51** with formaldehyde was also reported.[55]

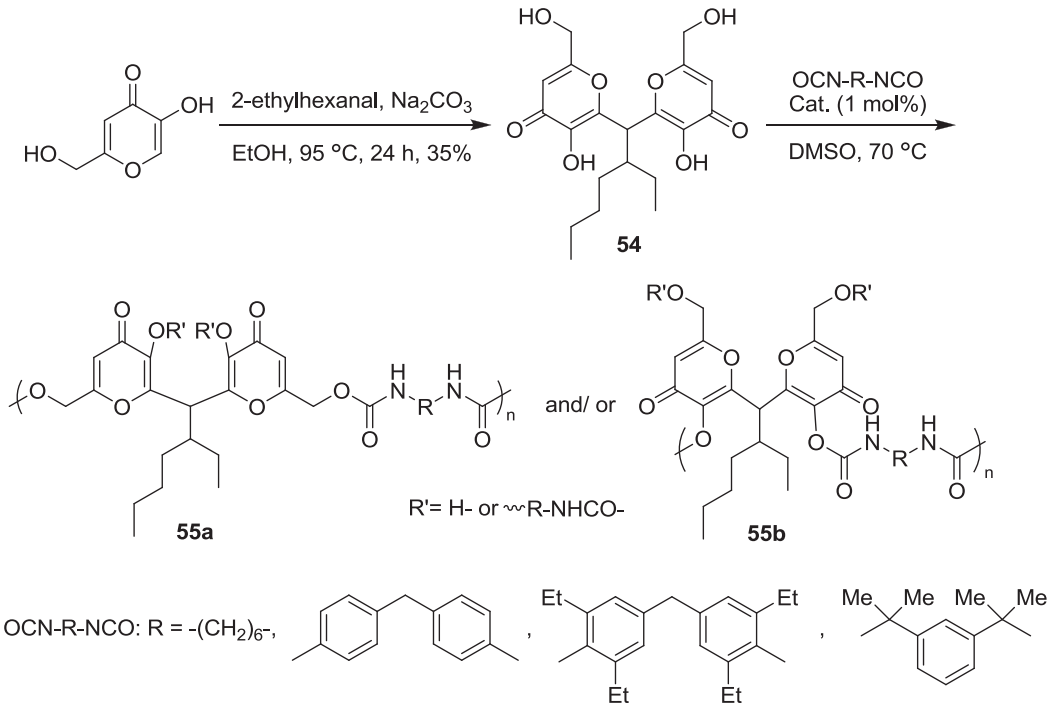


Scheme 17.

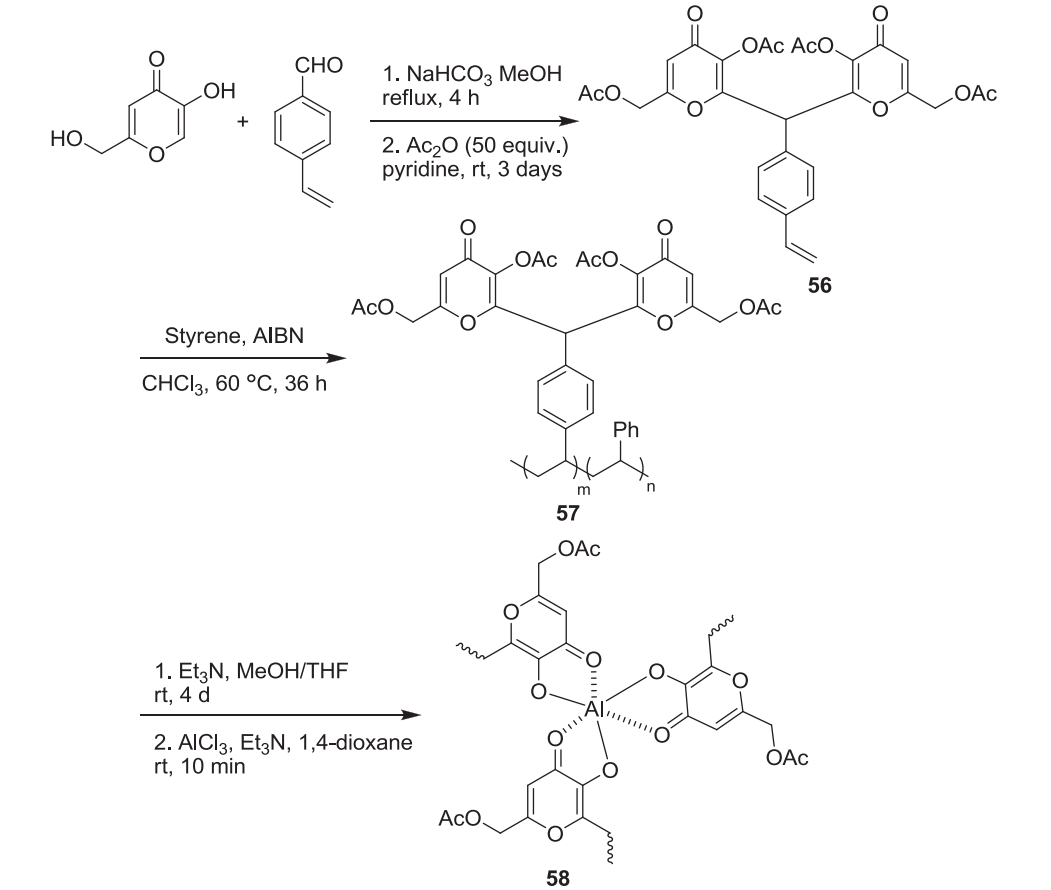
Ochiai et al.[56] synthesized polyurethane containing KA moiety **55** in the main chain and investigated the Fe(III)-complexation ability of the hydroxyl group of KA. The aldol product **54** was prepared in 35% yield by stirring KA with 2-ethylhexanal in the presence of Na_2CO_3 in EtOH at 95 °C for 24 h. Polymerization of KA dimer **54** with diisocyanates in the presence of catalyst in DMSO under heating at 70 °C and N_2 atmosphere for 24 h led to polymers **55a, b** in 26%–71% yields. Ratios of the polymers **55a**/**55b** are outlined in Scheme 18. Metal-complexation ability of the polyurethane-bearing KA structure was examined by mixing a DMSO solution of the polyurethane **55** and $FeCl_3$. There are also other reports on the synthesis of KA dimers similar to **54** from aldol reaction of KA with various aldehydes.[57,58]

Synthesis and radical polymerization of styrene derivative containing KA moieties **56** was reported by Tomita et al.[59] p-Formyl styrene was reacted with 2 equiv. KA in the presence of Na_2CO_3 in MeOH under N_2 atmosphere at reflux for 4 h and then protected with acetic anhydride in pyridine at room temperature to afford styrene derivative **56** in 90% yield. Radical copolymerization of **56** with styrene was conducted using AIBN under heating at 60 °C for 36 h, in which copolymer **57** was obtained in 83% yield. Deacetylation of copolymer **57** was carried out using Et_3N in MeOH/THF at room temperature for 4 h, which underwent complexation with $AlCl_3$ in the presence of Et_3N in 1,4-dioxan to **58** (Scheme 19). Other metal complexing polymers containing KA moiety were reported by Davies et al. in 1959.[60]

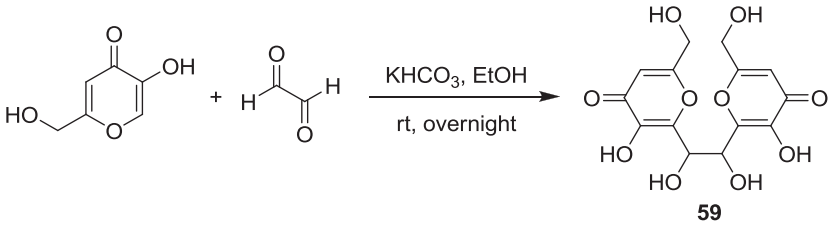
In addition to common aldehydes, glyoxal was also investigated in the aldol reaction, in which a solution of KA and glyoxal in EtOH was stirred at room temperature overnight, and 1,2-bis-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-ethylene glycol **59** was obtained in good yield (Scheme 20).[61]



Scheme 18.

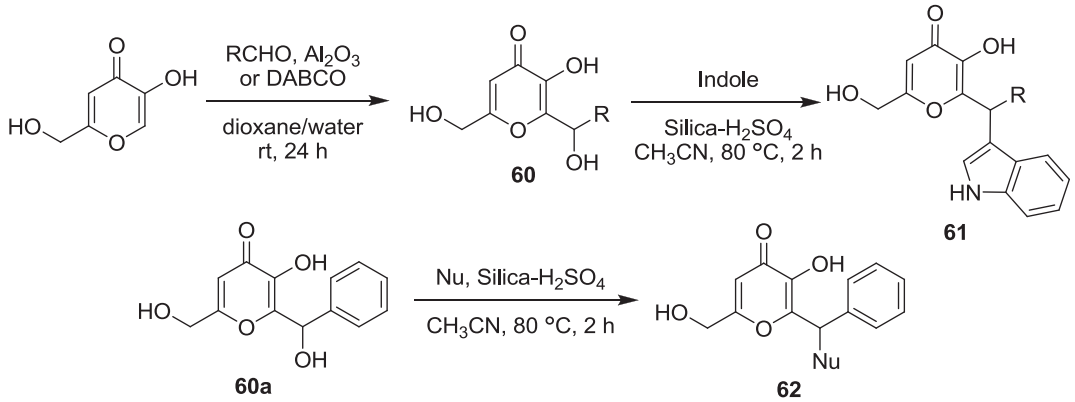


Scheme 19.



Scheme 20.

The aldol reaction of KA with aromatic and aliphatic aldehydes was performed using alumina as a base in dioxane/water (1/1) at room temperature for 24 h, and the desired products **60** were achieved in 83%–98% yields.[62] Moreover, treatment of KA (1 mmol) with aldehydes (1.2 mmol) in the presence of DABCO under reaction conditions similar to those mentioned above, followed by treatment with indole (1.5 equiv.) in the presence of silica-H_2SO_4 as a catalyst in CH_3CN at 80 °C for 2 h, gave indol-KA conjugates **61** as active insulin mimics in 86%–98% yields. Nucleophilic substitution of aldol product **60a** to **62** was performed with various substituted indoles and other nucleophiles under similar reaction condition (Scheme 21).[63] Sadeghi et al. reported one-pot synthesis of 2-substituted aryl(indolyl)KA derivatives **61** from the reaction of KA with aromatic aldehydes and indole using FAU zeolite nanoparticles[64] and kaolin/Ag nanocomposite[65] as catalyst under solvent-free conditions. Furthermore, 2-substituted aryl(indolyl)KA derivatives **61** were obtained in good yields and high selectivity from the three-component reaction of aldehyde, indole, and KA in the presence of catalytic amounts of $InCl_3$[66] and *p*-TSA[67] under solvent-free conditions.

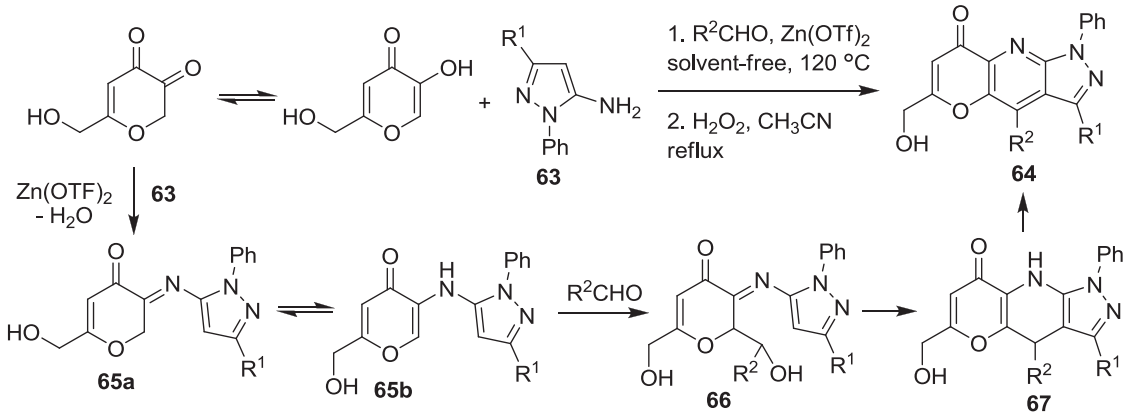


61: R= C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2,5-$(MeO)_2C_6H_3$, 2,3-$(MeO)_2C_6H_3$, 2-naphthyl, *n*-Bu, *n*-Oct; 83-98%
62: Nu= (2-Ph, 5-MeO, 5-CN, *N*-Methyl, *N*-Pentyl, *N*-Bn)-3-indolyl, C_6H_5S, 4-$MeOC_6H_4S$, 4-HOC_6H_4, 5-Me-2-thienyl, 3-Benzothienyl, 2-pyrolyl; 85-94%.

Scheme 21.

One-pot three-component synthesis of pyrano[3,2-*b*]pyrazolo[4,3-*e*]pyridin-8(1*H*)-ones **64** was described by Safaei et al.[68] by heating KA (1 mmol), 1,3-diphenyl-1*H*-pyrazol-5-amine **63** (1 mmol), and an aldehyde (1 mmol) in the presence of $Zn(OTf)_2$ at 120 °C under solvent-free conditions for 1 h, followed by treatment with H_2O_2 (30 mol%) in CH_3CN under reflux conditions for 30 min in 82%–96% yields (Scheme 22). The proposed reaction mechanism for the formation of **64** involves the condensation of 1*H*-pyrazol-5-amine **63** with the keto tautomer of KA, and then nucleophilic attack of enamine intermediate **65b** to the aldehyde that

produced intermediate **66**, which converted to compound **67** by intramolecular cyclization and dehydration. Finally, oxidative aromatization of intermediate **67** gave the corresponding product **64**.

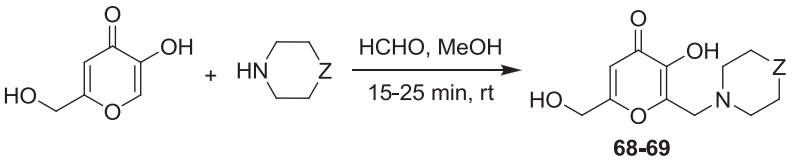


64: R^1 = Me, Ph; R^2 = XC_6H_4 (X= H, 4-Cl, 4-Br, 4-Me, 4-*i*-Pr, 4-MeO, 4-BnO, 4-Ph, 4-CN, 3-NO_2, 3-Cl, 3-Br, 3-PhO), 3,4-$(MeO)_2C_6H_3$, 1-naphtyl, 2-thienyl, *n*-pr; 82-96%.

Scheme 22.

2.3. Mannich reaction

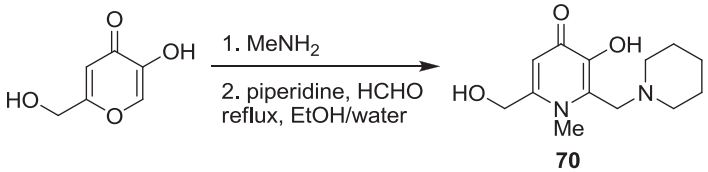
Aytemir et al.[69–71] described the Mannich reaction of piperazine derivatives, formaldehyde, and KA in 2010, as outlined in Scheme 23. The reactions were carried out in MeOH at room temperature, and Mannich bases **68** were obtained in 50%–86% yields. Anticonvulsant activities of **68** were investigated and all compounds exhibited anticonvulsant activities. In another investigation, treatment of KA with 37% formalin and piperidine derivatives in similar reaction conditions afforded Mannich products **69** in 58%–96% yields (Scheme 23). Aytemir et al. also reported similar synthesis of other Mannich bases from KA.[72,73]



68: Z = NR: R= X-C_6H_4 (X= H, 4-Ac, 3-NO_2, 3-CF_3, 2-F, 4-F, 2-OMe, 3-OMe, 2-Cl, 3-Cl, 4-Cl), 2-pyridyl, 2-pyrimidyl, Ac, Boc; 50-86%.
69: Z = C(Ar)Y: Y = OH, CN, Ac; Ar = 4-XC_6H_4 (X = H, Cl, Br); 58-96%.

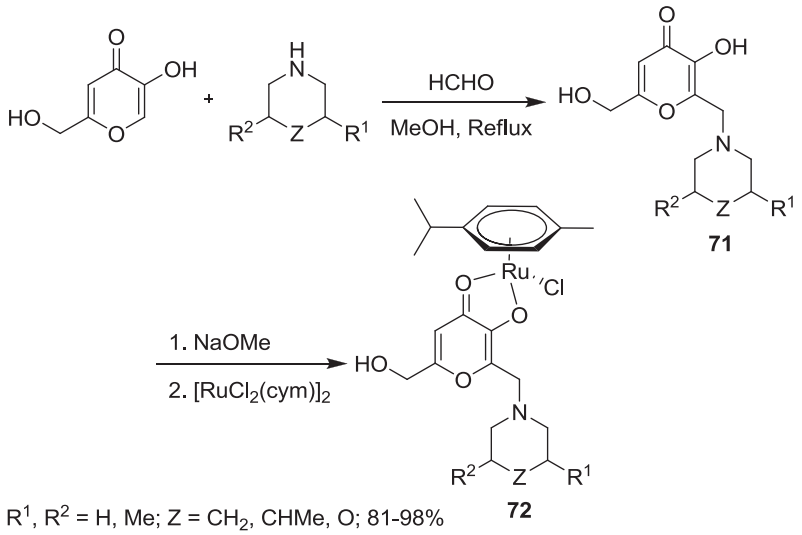
Scheme 23.

Reaction of KA with methylamine, followed by treatment with formaldehyde (37% aqueous solution) and piperidine under reflux conditions in EtOH for 24 h under a Mannich reaction gave 3-hydroxy-6-hydroxymethyl-l-methyl-2-piperidinomethyl-4(1*H*)-pyridinone **70** in 47% yield (Scheme 24), which acts as a bidentate ligand with high affinity for metal ions in high oxidation state.[74]



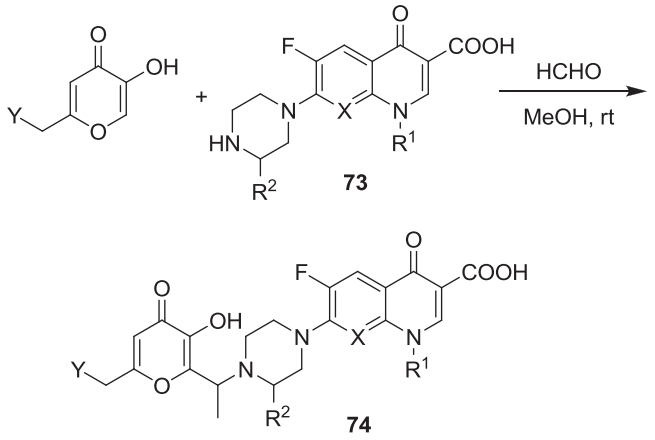
Scheme 24.

Mannich reactions between KA, cyclic secondary amines, and 35% formaldehyde solution were performed in MeOH under reflux conditions and Mannich adducts **71** were obtained in 25%–94% yields. Stirring the obtained Mannich adducts **71** (2 equiv.) and bis[dichlorido(η^6-*p*-cymene)ruthenium(II)] in the presence of NaOMe in MeOH/CH_2Cl_2 at room temperature for 18 h afforded complexes **72** in 81%–98% yields (Scheme 25), which exhibited anticancer and antitumor activities.[75]



Scheme 25.

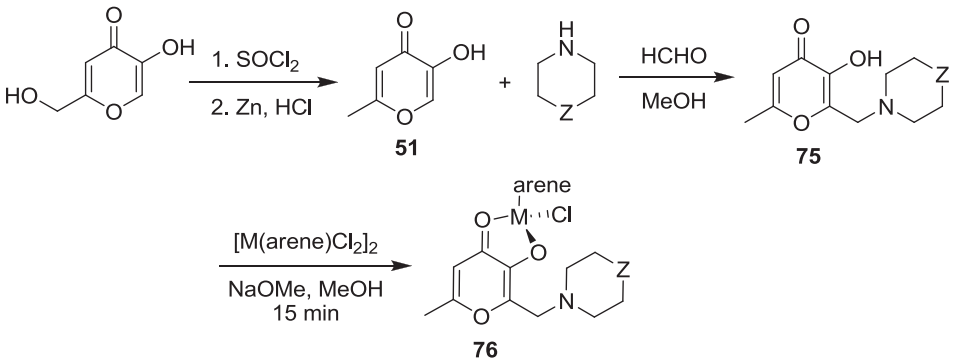
Furthermore, a Mannich-type reaction of KA derivatives, 7-piperazinylquinolones **73**, and 37% formalin solution was carried out in MeOH at room temperature for 48–72 h to give Mannich bases **74** in 20%–90% yields (Scheme 26). The obtained Mannich adducts exhibited antibacterial activity.[76]



Scheme 26.

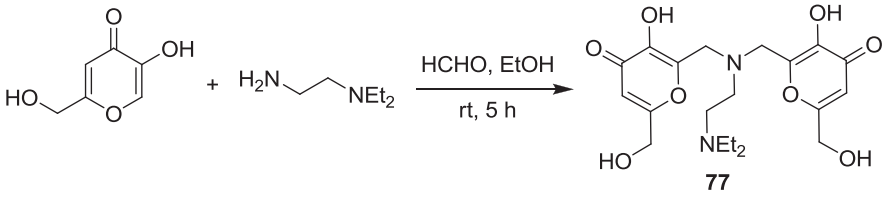
Treatment of KA with $SOCl_2$ continued by reduction with Zn/HCl gave allomaltol **51**, which was reacted with cyclic secondary amines and formaldehyde in MeOH to produce Mannich adducts **75** in 73%–92% yields. The complexation properties of the obtained Mannich adducts **75** were investigated by subjecting

with $[M(arene)Cl_2]_2$ in the presence of NaOMe in MeOH for 15 min under argon atmosphere, which led to pyrone-based organometallic complexes **76** in 50%–73% yields (Scheme 27). Among the prepared complexes, Ru(II or III) complex exhibited moderate activity in CH1 cells.[77]



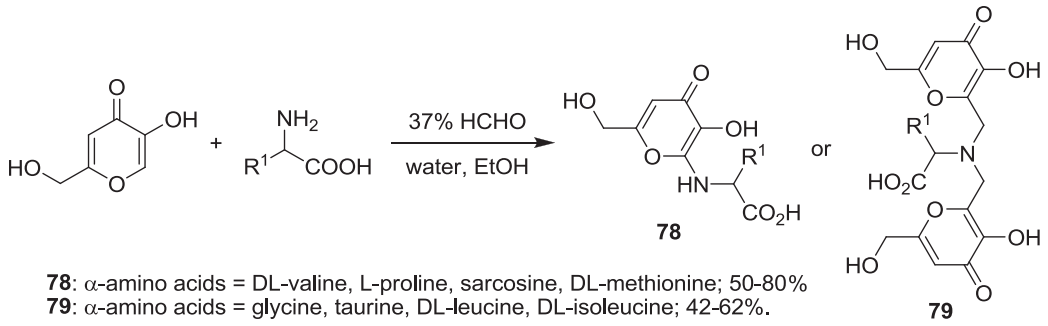
Scheme 27.

Nurchi et al.[78] described a Mannich-type reaction of KA, formaldehyde, and *N*,*N*-diethylethylenediamine by dropwise addition of a solution of *N*,*N*-diethylethylenediamine and aqueous formaldehyde (36%) (2.2 equiv.) in EtOH to a solution of KA (2 equiv.) in EtOH and stirring at room temperature for 5 h, leading to 6,6′-[2-(diethylamino)ethylazanediyl]bis(methylene)bis[5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one] **77** as a potential therapeutic iron chelating agent in 67% yield (Scheme 28). A Mannich-type reaction of KA, formaldehyde, and other amines such as methyl amine, benzyl amine, and piperazine was reported by Toso et al. in 2013.[79,80]



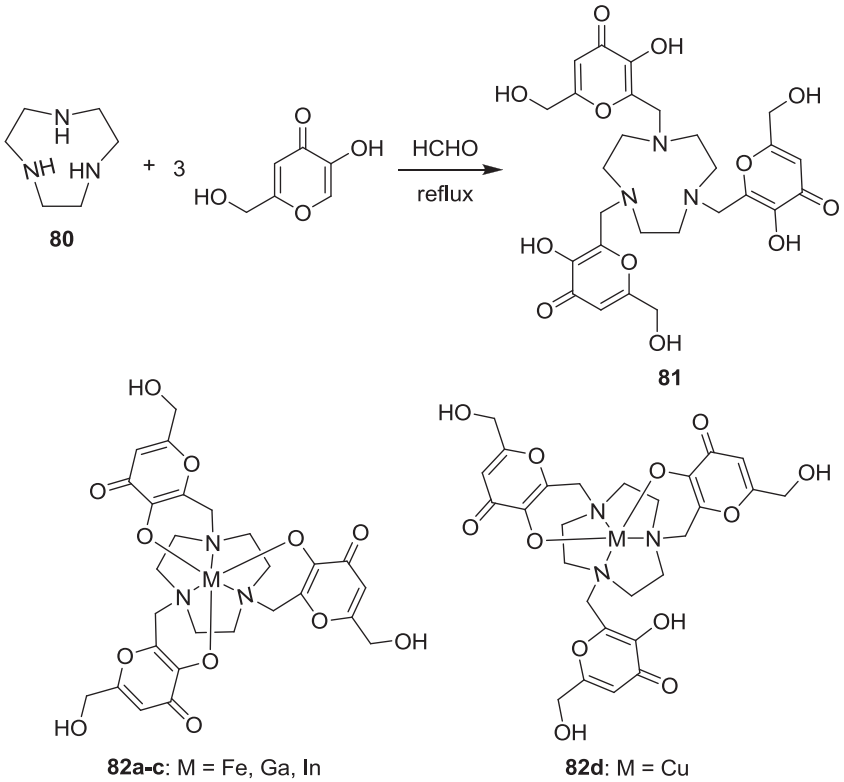
Scheme 28.

A Mannich-type reaction of KA with amino acids and formaldehyde was reported by O'Brien et al.;[81] it is not as simple as the reaction with other types of amines because of variations in the structure and solubility characteristics of amino acids. The reaction of KA with several amino acids was carried out in the presence of 37% formaldehyde in water/EtOH. In the case of glycine, taurine, DL-leucine, and DL-isoleucine, both hydrogen atoms of amines were replaced, and bis-Mannich adducts **79** were produced, while only one hydrogen atom of amines can be replaced by KA in the case of sarcosine, DL-valine, DL-methionine, and L-proline to give Mannich-adducts **78** (Scheme 29). However, reactions with L-asparic acid, L-asparagine, L-glutamic acid, L-glutamine, DL-phenyl alanine, and DL-tyrosine did not occur. In addition, O'Brien et al.[82] in 1960 showed that the reaction of KA with secondary amines such as dimethyl and diethyl amine, pyrolidine, morpholine, piperidine, *N*-methylpiperazine, and 1,2,3,4-tetrahydroquinoline afforded a product similar to **78**, but the reaction with lauryl and stearyl amines gave bis-Mannich adducts, similar to **79**.



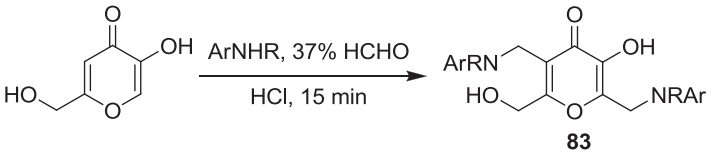
Scheme 29.

The multicomponent reaction of 1,4,7-triazacyclononane **80** and KA (3 equiv.) with excess amount of formaldehyde (30% aqueous solution) was carried out in EtOH under reflux conditions for 20 h, leading to $6,6',6''$-(1,4,7-triazonane-1,4,7-triyl)tris(methylene)tris[5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one] **81** in 54% yield, which underwent complexation with metal salts to produce complexes **82** in 35%–61% yields (Scheme 30).[83]



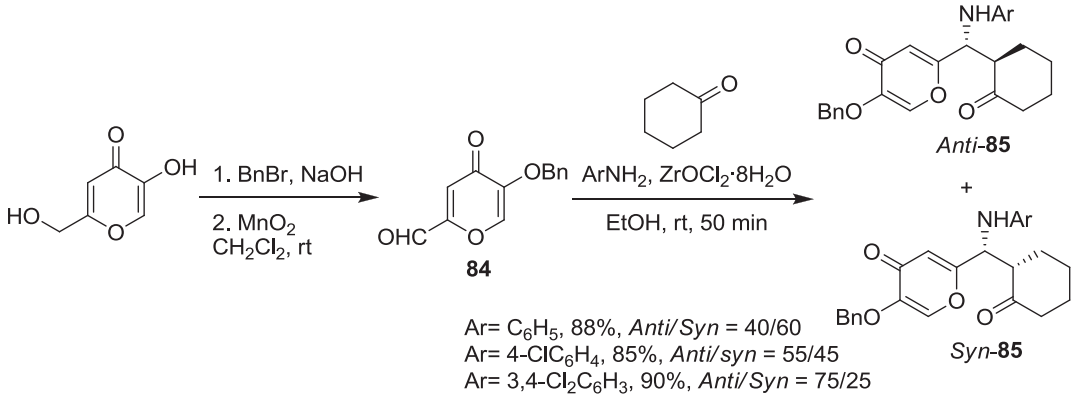
Scheme 30.

The multicomponent Mannich-type reaction of KA, aryl amines, and 37% formalin in the presence of concentrated HCl was reported under heating conditions for 15 min. As shown in Scheme 31, reactions occurred at both C-3 and C-6 positions, leading to **83** in good yields.[84]



Scheme 31.

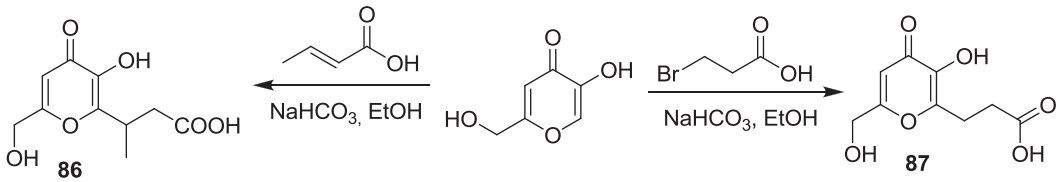
5-(Benzyloxy)-4-oxo-4*H*-pyran-2-carbaldehyde (*O*-protected comenic aldehyde) **84** was synthesized by protection of KA with benzyl bromide in the presence of NaOH, followed by oxidation with MnO_2 in CH_2Cl_2 at room temperature according to the literature[85] and used in a three-component direct Mannich-type reaction with different anilines and cyclohexanone using $ZrOCl_2 \cdot 8H_2O$ as catalyst in EtOH at room temperature over 50 min to give Mannich adducts **85** in high yields with moderate stereoselectivity (Scheme 32).[86]



Scheme 32.

2.4. Conjugate addition

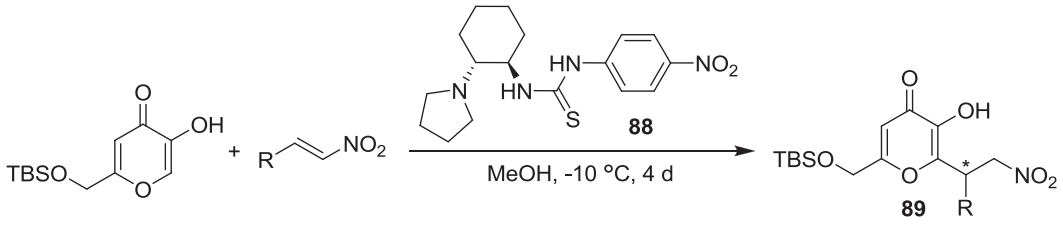
By stirring crotonic acid with KA in the presence of $NaHCO_3$ in absolute EtOH under reflux conditions for 20 h, conjugate addition occurred at the C-6 position of KA and gave 3-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)butanoic acid **86**. On the other hand, refluxing ethanolic solution of β-bromopropionic acid with KA in the presence of $NaHCO_3$ for 5 h afforded 3-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)propanoic acid **87** via an alkylation reaction (Scheme 33).[87]



Scheme 33.

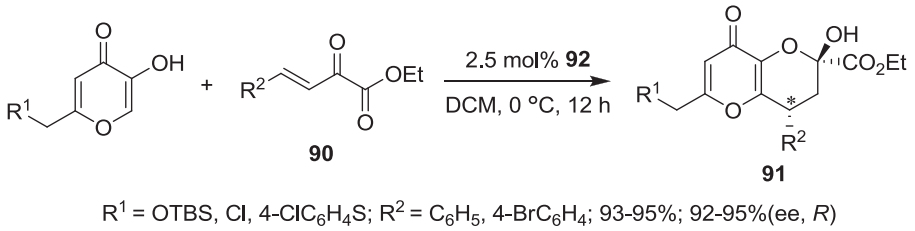
Wang et al.[88] developed an enantioselective Michael addition of a KA derivative to nitro olefins using bifunctional chiral thiourea–tertiary amine **88** as catalyst. Reactions were conducted by stirring a solution of KA derivative and nitro olefins in MeOH in the presence of **88** (0.1 equiv.) at -10 °C for 4 days to obtain products **89** in 58%–99% yields and good enantioselectivities (Scheme 34). Moreover, Subba Reddy et al.[89] reported a

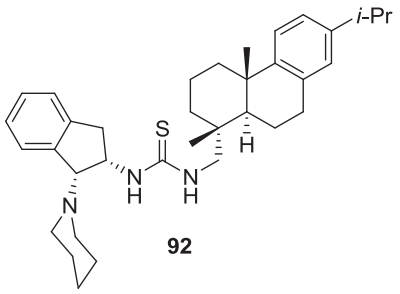
similar approach using cinchonine-derived sugar thioureas in 2014, in which the corresponding Michael adducts exhibited promising cytotoxicity against various cancer cell lines.



Scheme 34.

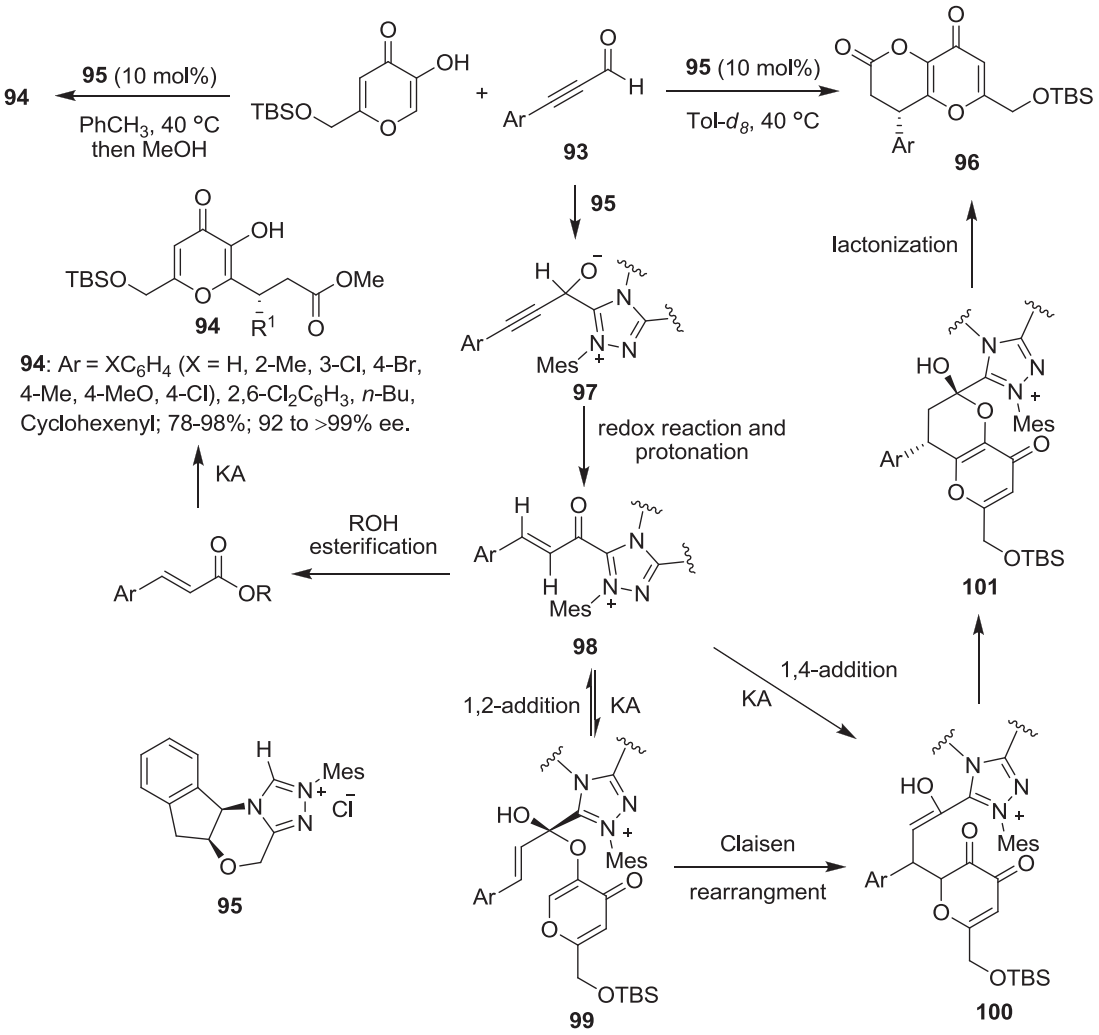
Michael addition/hemiketalization reaction of KA derivatives and (*E*)-ethyl-2-oxo-4-phenylbut-3-enoate **90** was catalyzed with **92** in DCM at 0 °C for 12 h, and products **91** were obtained in excellent yields, with high enantioselectivity, up to 95% ee (Scheme 35).[90]





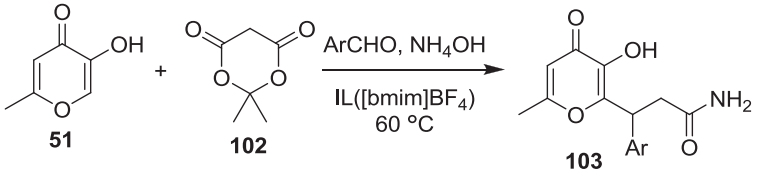
Scheme 35

Enantioselective reaction of KA derivatives with ynals **93** catalyzed by *N*-heterocyclic carbenes **95** was described by Kaeobamrung et al.[91] Reactions were carried out using *N*-mesityl substituted precatalyst **95** in toluene at 40 °C, which led to unstable dihydropyranones that converted to products **94** in good yields and high enantioselectivity when stirred in MeOH for 6 h. The reaction did not occur without triazolium salt. As outlined in Scheme 36, the proposed reaction mechanism involves in situ generation of intermediate **97** by addition of NHC to aldehyde moiety, followed by a redox reaction and then protonation to give **98**, which underwent 1,2- or 1,4-addition with KA to give intermediates **99** or **100**, respectively; however, hemiacetal **99** transformed into **100** via Claisen rearrangement. Tautomerization with subsequent acetalization of compound **100** afforded **101**, which gave pyrano-pyrane derivatives **96** by lactonization, along with removal of triazolium salt.[92–95] There is another similar report in the literature.[96]



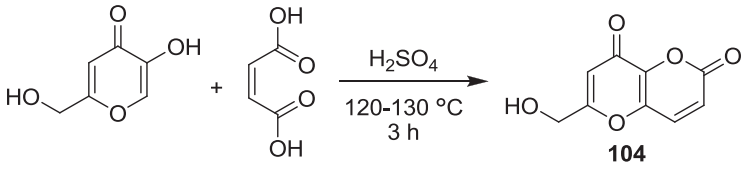
Scheme 36.

The four-component condensation reaction of aromatic aldehydes, allomaltol **51**, Meldrum's acid, and NH_4OAc (2 equiv.) was accomplished in ionic liquid [bmim]BF_4 at 60 °C, and 3-(3-hydroxy-6-methyl-4-oxo-4*H*-pyran-2-yl)-3-phenylpropanamides **103** were produced in 65%–92% yields (Scheme 37).[97]



Scheme 37.

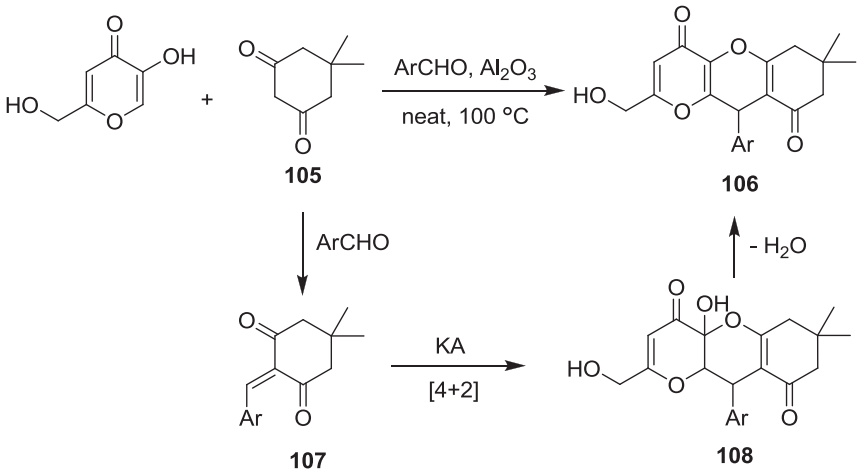
Synthesis of 2-hydroxymethylpyrano[3,2-*b*]pyran-4,6-dione **104** was achieved from the reaction of KA with maleic acid (1 equiv.) catalyzed by H_2SO_4 at 120–130 °C for 3 h in 69% yield (Scheme 38). The reaction occurred by conjugate addition of KA to maleic acid, followed by lactonization and decarboxylation.[98]



Scheme 38.

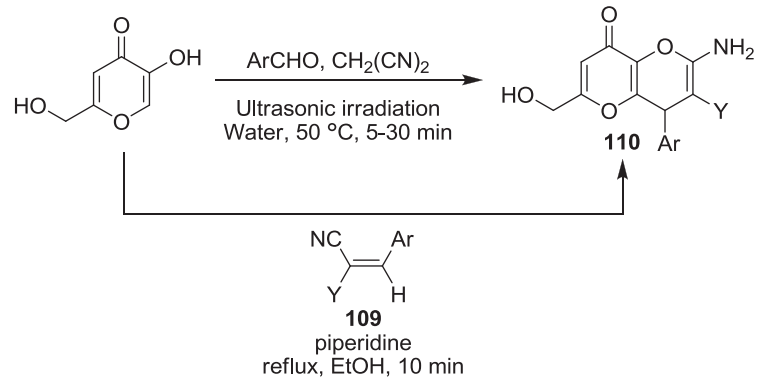
2.5. Multicomponent reactions

An alumina-catalyzed three-component reaction of KA, aldehydes, and dimedone **105** was conducted under solvent-free conditions at 100 °C, and 2-(hydroxymethyl)-7,7-dimethyl-10-phenyl-7,8-dihydropyrano[3,2-*b*]chromene-4,9(6*H*,10*H*)-diones **106** were obtained in short time and high yields. The possible mechanism for this reaction involves a domino Knoevenagel-hetero-Diels–Alder reaction intermediate **107** and then dehydration of in situ generated tricyclic hemiacetal intermediate **108** (Scheme 39). With aliphatic aldehydes no reaction occurred.[99] A three-component reaction of KA, aldehyde, and 1,3-diones was also performed by $InCl_3$[100] and CAN[101] as catalyst under solvent-free conditions.



Scheme 39.

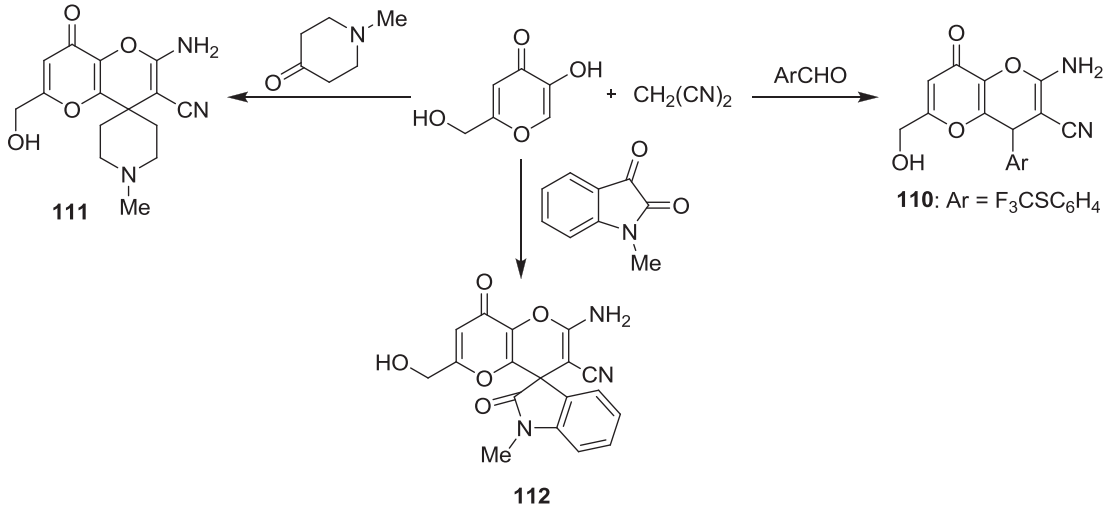
The three-component reaction of KA, malononitrile, and aromatic aldehydes was described by Banitaba in 2013. Reactions were carried out by ultrasound irradiation of a mixture of malononitrile, benzaldehyde (1 equiv.), and KA (1 equiv.) in water in an ultrasonic bath at 50 °C to produce 2-amino-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives **110** in 35%–88% yields.[102] Moreover, Piao et al. reported the synthesis of amino-substituted 4*H*,8*H*-pyrano[3,2-*b*]pyran-4-ones **110** in high yields from the reaction of KA with substituted benzylidene malononitriles **109**, which exhibited nonpeptide human immunodeficiency virus (HIV) protease inhibitory activity. The reaction was carried out by treatment of KA with benzylidene malononitriles **109** in the presence of piperidine in EtOH under reflux conditions for 10 min (Scheme 40).[103]



[103] Y = CN; Ar = XC_6H_4 (X = H, 2-F, 2-Cl, 3-F, 3-Me, 3-Br, 4-F), 2,4-$Cl_2C_6H_3$, 3,5-$(MeO)_2C_6H_3$, 3-Pyridyl, 4-Pyridyl, 2-Furyl, 2-Thienyl; 88-98%
[102] R= CN, CO_2Et, CO_2Me; Ar = XC_6H_5 (X = H, 4-Me, 4-MeO, 4-Cl), 1-Naphthyl, 2-Naphthyl; 84-99%.

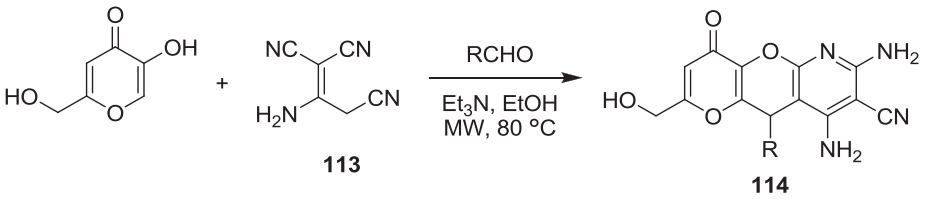
Scheme 40.

Shestopalov et al.[104] reported the synthesis of dihydropyrano[3,2-*b*]pyran-4-ones **110**–**112**, analogues of human immunodeficiency virus (HIV) protease inhibitors, starting from KA. Reactions were performed by refluxing ethanolic solution of KA, malononitrile (1 equiv.), and *p*-trifluoromethylthiobenzaldehyde, *N*-methylpiperidin-4-one, and *N*-methylisatine (1 equiv.) in the presence of Et_3N for 15 min, leading to 4,8-dihydropyrano[3,2-*b*]pyran-4-ones **110**–**112** in 97%, 83%, and 89% yields, respectively (Scheme 41). Moreover, a multicomponent reaction of KA, isatin, and malononitrile or ethyl cyanoacetate catalyzed with DABCO-functionalized mesoporous SBA-15 was reported by Azimi et al. in 2014.[105]



Scheme 41.

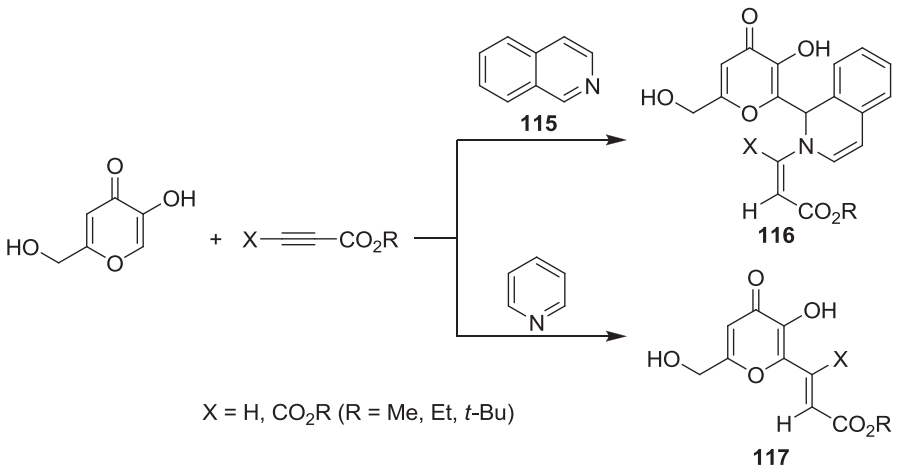
Tu et al.[106] synthesized pyrano[2′,3′:5,6]pyrano[2,3-*b*]pyridines **114** via three-component bicyclization of KA, aldehydes, and 2-aminoprop-1-ene-1,1,3-tricarbonitrile **113**. Reactions were carried out by heating a mixture of KA, aldehydes (1 equiv.), and 2-aminoprop-1-ene-1,1,3-tricarbonitrile **113** (1 equiv.) in EtOH in the presence of Et_3N at 80 °C under microwave irradiation for 16 min, and corresponding pyrano[2′,3′:5,6]pyrano[2,3-*b*]pyridines **114** were obtained in 44%–84% yields (Scheme 42).



R = XC_6H_4 (X = H, 2-Cl, 4-Cl, 4-F, 4-Br, 4-NO_2, 4-Me, 4-MeO, 4-Me_2N, 2-MeO, 3-formyl), YC_6H_3 (Y = 3,4-Cl_2, 2,3-Cl_2, 2,4-Cl_2, 3,4-Me_2, 2,3-$(MeO)_2$, 3,4-$(MeO)_2$, 3-NO_2-4-HO, 3,4-$(HO)_2$, 2-Br-5-Cl), ZC_6H_2 (Z = 3,4,5-$(MeO)_3$, 6-Br-3-HO-4-MeO), 2-thienyl, 3-Br-2-thienyl, 2-pyridyl, Bn, *n*-Bu; 74-84%.

Scheme 42.

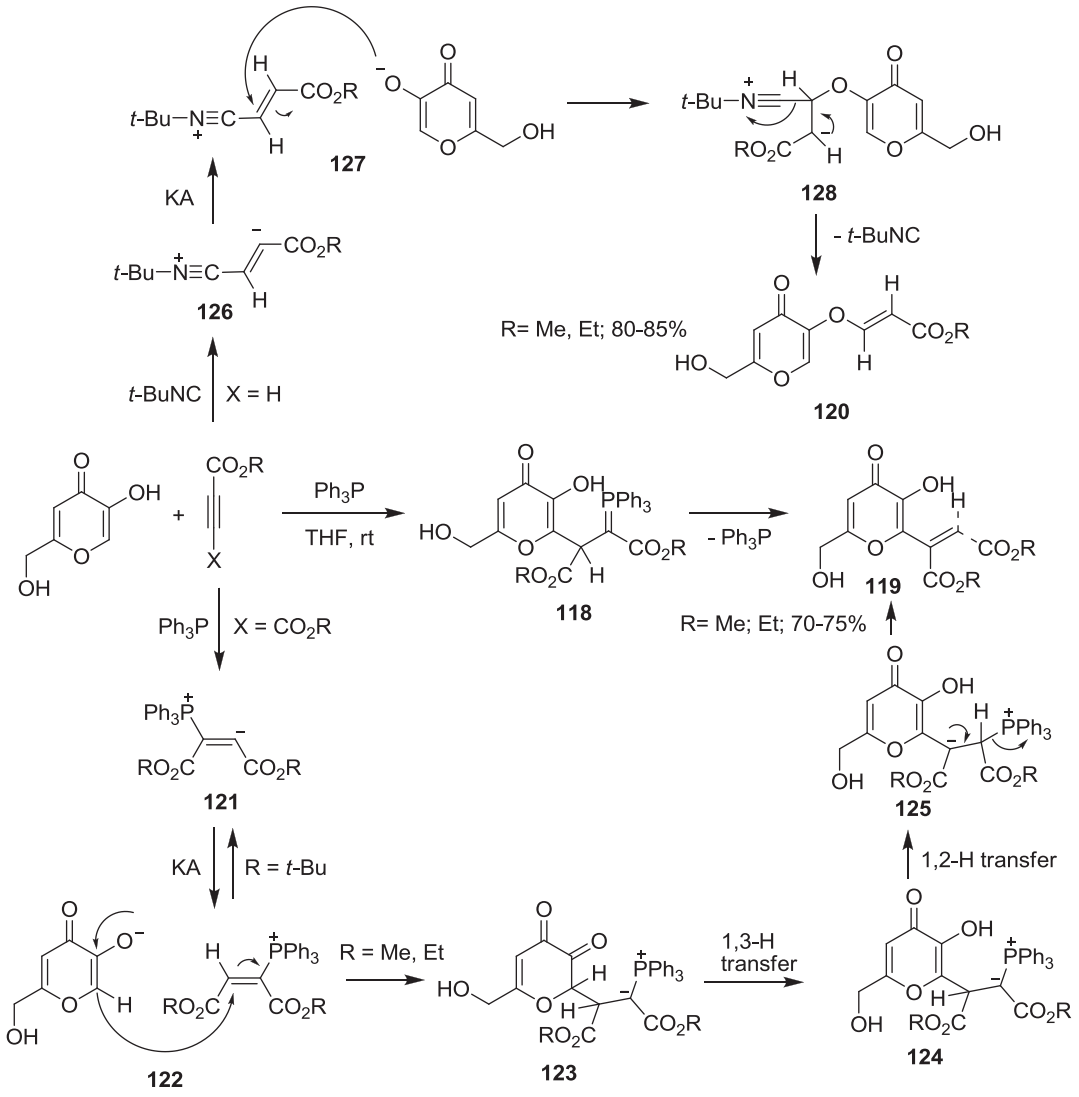
Treatment of KA (2 mmol) with acetylenic esters (2 mmol) and isoquinoline **115** (2 mmol) in THF afforded 1,2-dihydroisoquinoline derivatives **116** in 58%–80% yields that showed moderate to good antibacterial activity. In the case of dialkyl acetylenedicarboxylates, the reaction mixture was stirred at room temperature for 2 h, while with alkyl acetylenecarboxylates, reactions were carried out at 60 °C for 7–8 h. However, *C*-vinylated products of KA **117** were obtained from the reaction of KA with acetylenic esters and pyridine instead of isoquinoline under reaction conditions similar to those mentioned above (Scheme 43).[107]



X = H, CO_2R (R = Me, Et, *t*-Bu)

Scheme 43.

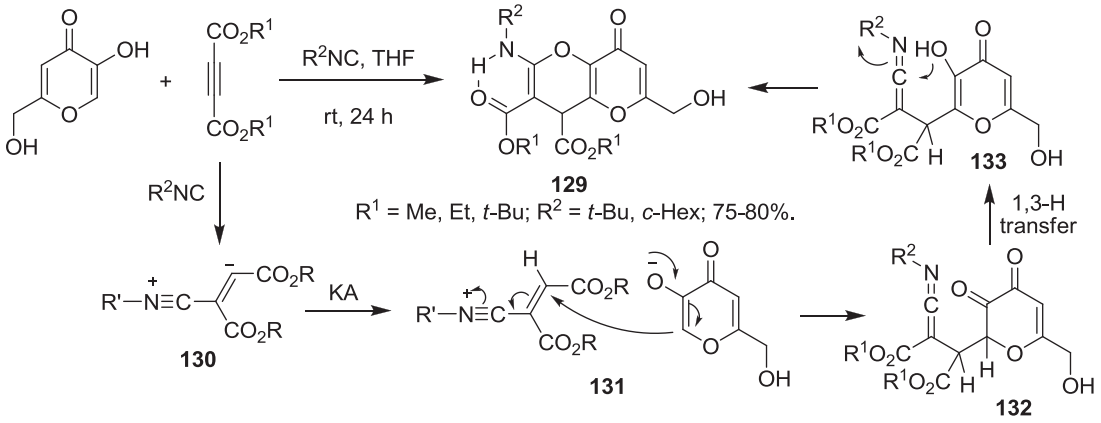
Regioselective vinylation of KA was performed using acetylenic esters in the presence of Ph_3P or *tert*-butylisocyanide, in which *C*- or *O*-vinylated KA derivatives **119** or **120** were obtained. The reaction of KA with dialkyl acetylenedicarboxylates was carried out in the presence of Ph_3P in THF at room temperature and *C*-alkylation **119** was achieved in a regioselective manner. However, the reaction of KA with alkyl propiolate in the presence of *tert*-butylisocyanide in THF at room temperature gave *O*-alkylated KA regioselectively. A possible reaction mechanism of *C*-vinylation of KA involves nucleophilic addition of Ph_3P to the dialkyl acetylenedicarboxylates **121** and subsequent protonation by KA to give intermediate **122**. The resulting enolate from KA attacked **122** via the*C*-atom to produce intermediate **123**, which was converted to final *C*-vinylated product **119** in two steps by proton transferring, followed by removal of Ph_3P intermediates **125**. Moreover, nucleophilic addition of *tert*-butylisocyanide to the acetylenic ester **126** with subsequent protonation by KA yielded positively charged intermediate **127**, which was attacked by the negative oxygen atom of KA enolate to generate intermediate **128**, which was transformed into *O*-vinylated KA derivatives **120** by removing the *tert*-butylisocyanide molecule (Scheme 44).[108]



Scheme 44.

Functionalized 4,8-dihydropyrano[3,2-*b*]-pyran-4-ones **129** were synthesized in 75%–80% yields from the three-component reaction of KA, alkyl isocyanides, and dialkyl acetylenedicarboxylates in THF at room temperature for 24 h. In the proposed reaction mechanism, nucleophilic addition of alkyl isocyanide to dialkyl acetylenedicarboxylate led to zwitterion **130**, which underwent protonation by KA to give intermediate **131**. Attack of the KA anion on **131** and then 1,3-proton transfer of **132** to **133** with subsequent cyclization gave dihydropyrano[3,2-*b*]-pyran-4-ones **129** (Scheme 45).[109]

Shahrisa et al.[110] described the Ugi four-component reaction of *O*-protected comenic aldehyde, isocyanides, carboxylic acids, and amines in the absence of any catalyst. Stirring a mixture of *O*-protected comenic aldehyde (0.5 mmol), amines (0.5 mmol), carboxylic acid (0.5 mmol), and isocyanide (0.6 mmol) in MeOH at room temperature for 2 h gave bis-carboxamide derivatives of KA **134** in 71%–88% yields (Scheme 46). The obtained Ugi products **134** showed considerable cytotoxic potential, especially in the HL-60 cell line. *O*-protected comenic aldehyde was obtained from KA by benzylation of enolic OH, followed by oxidation of the hydroxymethyl moiety with active MnO_2.[111]



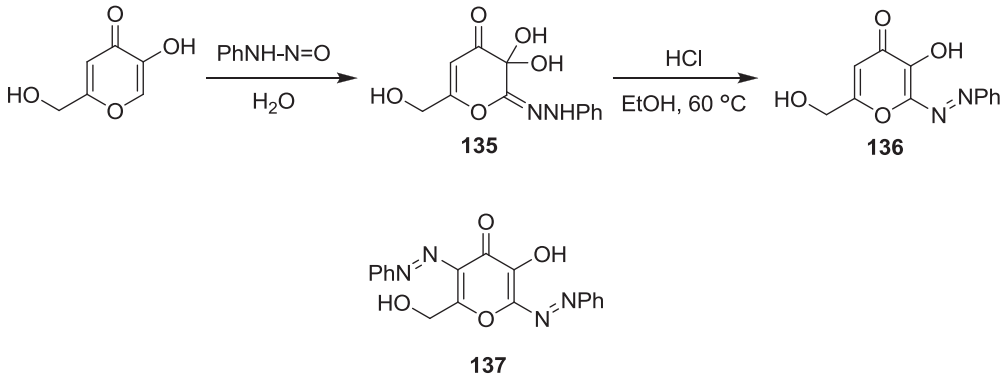
Scheme 45.

R = *c*-Hex, *t*-Bu; $Ar^1 = XC_6H_4$ (X = H, 2-Cl); $Ar^2 = 4\text{-}XC_6H_5$ (X = H, 4-Me, 4-*n*-Bu, 4-MeO, 4-Cl); 71-88%.

Scheme 46.

2.6. Diazo coupling

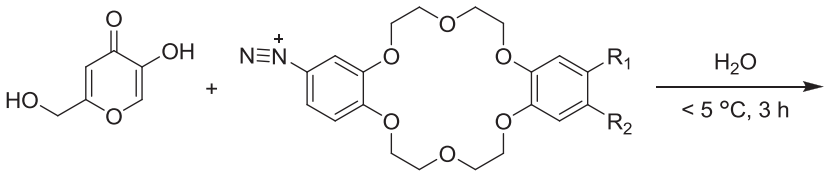
By treatment of KA (0.01 mol) with phenyldiazonium oxide hydrate (1 equiv.) in water in the presence of 5% NaOH at 0 °C, 4-oxo-3,3-dihydroxy-6-hydroxymethyl-2,3-dihydropyran-2-phenylhydrazone **135** was obtained in 75% yield. Refluxing of crude hydrazone **135** in EtOH in the presence of HCl for 15 min gave 3-hydroxy-6-(hydroxymethyl)-2-(phenyldiazenyl)-4*H*-pyran-4-one **136** in 54% yield (Scheme 47). In addition, 3-hydroxy-6-(hydroxymethyl)-2,5-bis(phenyldiazenyl)-4*H*-pyran-4-one **137** was obtained in 45% yield from the reaction of phenyldiazohydrate with KA using 5% NaOH in water.[112]



Scheme 47.

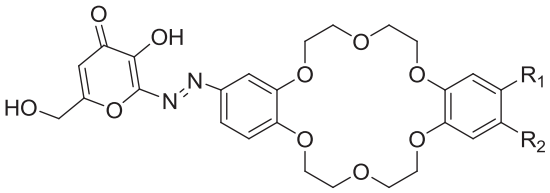
Kuznetsov et al.[113,114] prepared dibenzo-18-crown-6 derivatives having KA fragment **139**, potential double ionophores, from the diazo-coupling reaction of diazonium salt **138** with KA in water. The mixture

of reaction was stirred for 3 h below 5 °C, and 4'-(6-azo-5-hydroxy-2-hydroxymethyl-γ-pyronyl)dibenzo-18-crown-6s **139** were obtained in 66%–74% yields (Scheme 48). Diazonium salts **138** were prepared from the reaction of corresponding amines with $NaNO_2$/HCl in water.[115]



138

$R^1 = R^2 = H$; $R^1 = H$, $R^2 = N_2^+$; $R^1 = N_2^+$, $R^2 = H$

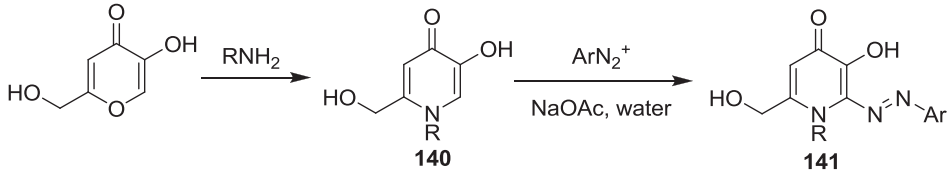


139

$R^1 = R^2 = H$; $R^1 = H$, R^2 = N=N-kojyl; R^1 = N=N-kojyl, $R^2 = H$

Scheme 48.

6-Arylazo-substituted-5-hydroxy-2-hydroxymethyl-4-pyridones **141** were prepared from the reaction of 5-hydroxy-2-hydroxymethyl-4-pyridone **140**, derived from the action of amines on KA, with aryldiazonium salts in the presence of NaOAc in water for 2 h, in 21%–83% yields (Scheme 49).[116]



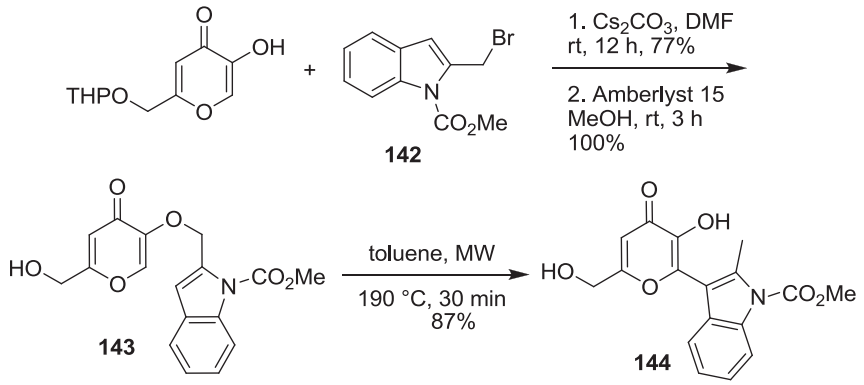
140 **141**

R= H, Me; Ar = XC_6H_4 (X = H, 3-Cl, 4-Cl, 4-Br)

Scheme 49.

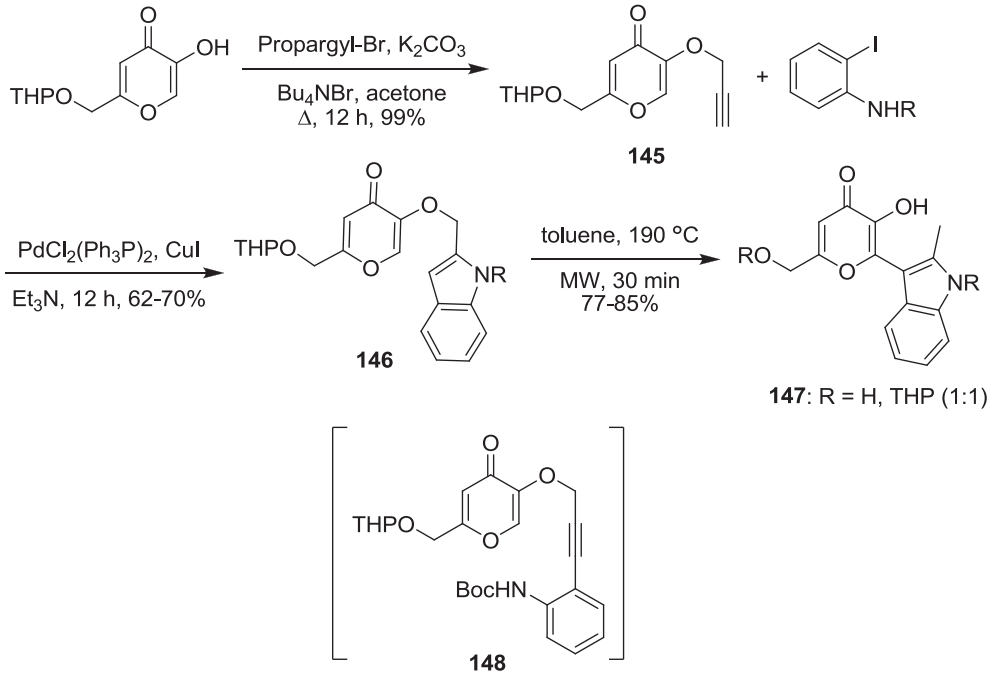
2.7. Claisen rearrangement

Xiong et al.[117] reported the preparation of (indolyl)KA **144** as antidiabetes agents. Protection of hydroxymethyl moiety of KA with THP followed by treatment with **142** in the presence of Cs_2CO_3 at room temperature for 12 h and then with Amberlyst 15 at room temperature for 3 h in MeOH gave **143** quantitatively for the last step. Claisen rearrangement of **143** in toluene at 190 °C for 30 min yielded (indolyl)KA **144** in 87% yield (Scheme 50). In another report, (indolyl)KA derivatives were obtained via Claisen rearrangement using of $Zn(OTf)_2$ as a catalyst under microwave irradiation.[118]



Scheme 50.

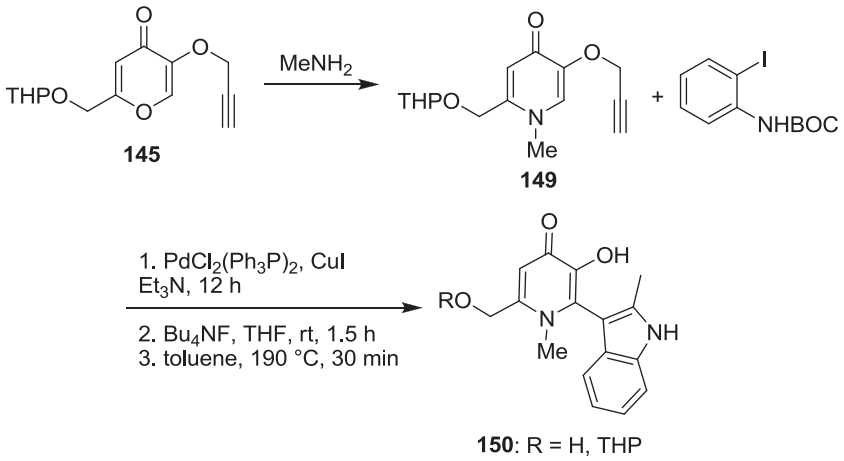
Furthermore, indol-substitute KA **147** was synthesized via Claisen rearrangement of **146**, obtained in 70% yield from the Sonogashira reaction of **145** with *O*-iodoaniline sulfonamide in the presence of $PdCl_2(Ph_3P)_2$/CuI as catalyst. Compound **145** was prepared by treatment of KA with propargyl bromide in the presence of K_2CO_3 and Bu_4NBr in acetone, in 99% yield. Claisen rearrangement of **146** was conducted by MW irradiation in toluene at 190 °C for 30 min, in 85% yield. In the similar procedure, coupling of **145** with *N*-Bociodoaniline in the presence of $PdCl_2(Ph_3P)_2$/CuI and Et_3N produced **148** in 62% yield. Cyclization of **148** was performed by treatment with Bu_4NF in THF at room temperature for 1.5 h to afford (indolyl)methyl kojate **146** in 90% yield, which was converted to (indolyl)KA **147** when heated in toluene for 30 min as outlined in Scheme 51.



Scheme 51.

The synthesis of indole substituted pyridinone **150** was achieved from Sonogashira coupling and Claisen rearrangement of pyridinone **149** and *N*-Boc-protected *o*-iodoaniline. Pyridinone **149** was synthesized in three steps starting from KA by protecting hydroxymethyl moiety of KA with THP and then reacting with propargyl bromide to give compound **145**, followed by treatment with $MeNH_2$ under acidic conditions. The reaction of

149 with ***N***-Bociodoaniline in the presence of $PdCl_2(Ph_3P)_2$ and CuI as catalyst in Et_3N for 12 h, followed by treatment with Bu_4NF in THF at room temperature for 1.5 h, and then heating in toluene at 190 °C for 30 min gave indolyl KA derivatives **150** in good yield (Scheme 52).

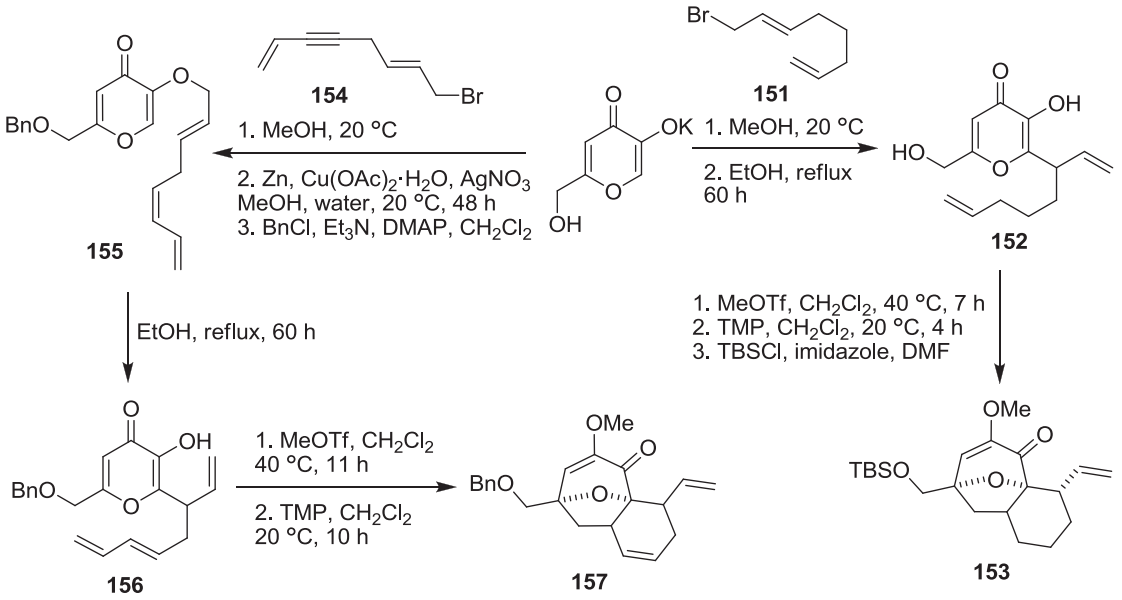


Scheme 52.

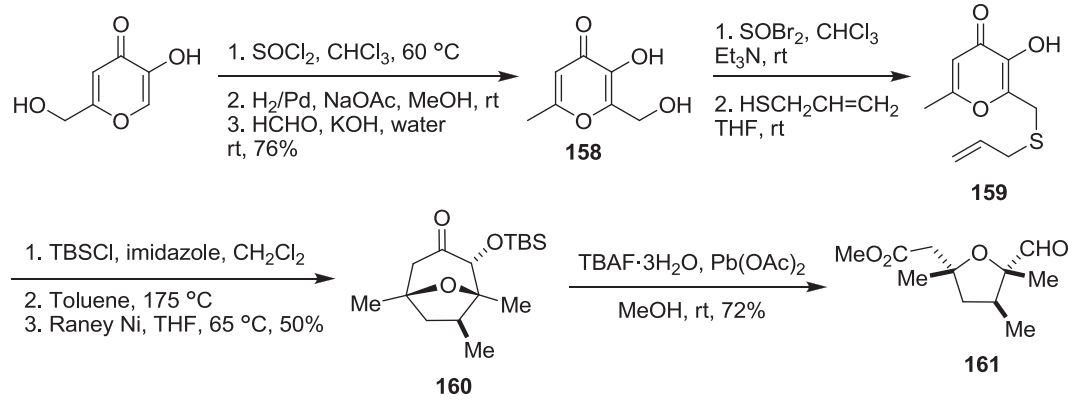
2.8. Cycloadditions

In 1991, Wender et al.[119] synthesized the precursors of tiglianes, daphnanes, and ingenanes, as highly potent tumor promoters, via [5 + 4] cycloaddition reaction starting from KA. The synthesis of pyrone **152** was achieved in 90% yield from the reaction of potassium kojate and bromide **151** in MeOH at 20 °C, followed by Claisen rearrangement in EtOH under reflux condition for 60 h. Compound **152** was converted to **153** in three steps, by reaction with MeOTf in CH_2Cl_2 and then by treatment with 2,2,6,6-tetramethylpiperidine (TMP) in CH_2Cl_2, followed by treatment with TBSCl in the presence of imidazole in DMF. Moreover, treatment of potassium kojate with bromide **154** and then reduction with $Zn/Cu(OAc)_2{\cdot}H_2O$ in the presence of $AgNO_3$ in $MeOH/H_2O$ at 20 °C, followed by the reaction with BnCl in the presence of Et_3N and DMAP in CH_2Cl_2 afforded diene **155** in 72% yield. Compound **155** was converted to **156** by refluxing in EtOH for 60 h (Claisen rearrangement). Finally **157a** and **157b** were produced via [5 + 4] cycloaddition reaction by stirring **156** with MeOTf in CH_2Cl_2 at 40 °C for 11 h, followed by treatment with TMP in CH_2Cl_2 at 20 °C for 10 h (Scheme 53).

The reaction of KA with $SOCl_2$ in $CHCl_3$ at 60 °C and then reduction with H_2/Pd in the presence of NaOAc in MeOH at room temperature, followed by aldol condensation with formaldehyde using KOH in H_2O at room temperature, afforded compound **158** in 76% yield. In continuation, compound **158** was converted to compound **159** by treatment with $SOBr_2$ in the presence of Et_3N in $CHCl_3$ at room temperature and then allyl mercaptane in THF at room temperature. Compound **159** underwent protection using TBSCl in the presence of imidazole in CH_2Cl_2, and then regio- and stereoselective [5 + 2] cycloaddition when heated in toluene at 170 °C, to give the corresponding cycloadduct, which was transformed into compound **160** in 50% yield, by reductive desulfurization using Raney Ni in THF at room temperature. Tetrahydrofuran **161** was obtained in 72% yield by desilylation of **160** with $TBAF{\cdot}3H_2O$ and then oxidative cleavage of the C—C bond with $Pb(OAc)_4$ in MeOH at room temperature (Scheme 54).[120,121] There is another similar multistep approach for the construction of tetrahydrofuran starting from KA.[122]



Scheme 53.

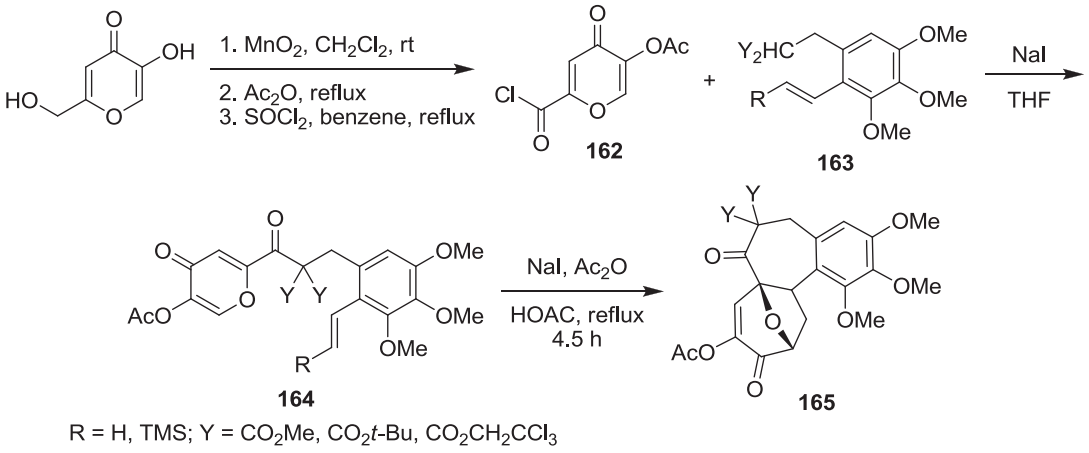


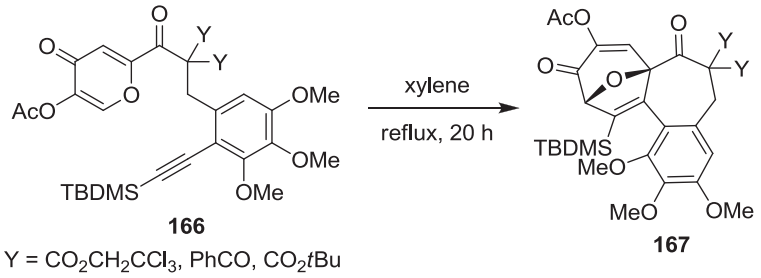
Scheme 54.

McBride et al.[123,124] reported intramolecular cycloaddition of KA derivatives **164**, by refluxing a mixture of **164** and NaI in Ac_2O and HOAc for 4.5 h, to give cycloadduct **165**. Compounds **164** were prepared by acylation of **163** with KA derived acyl chloride **162** in the presence of NaI in THF. Acyl chloride **162** was obtained from comenic acid in two steps, by protection of enolic OH with Ac_2O and then reaction with $SOCl_2$ in benzene at reflux. Similarly, cycloaddition of alkyne **166** in xylene under reflux conditions for 20 h afforded the desired product **167** (Scheme 55). As shown in Scheme 56, compounds **169** and **171** were obtained by heating of KA derivatives **168** in xylene at 140 °C and refluxing of **170** in the presence of *p*-TSA and trimethylorthoformate in MeOH for 12 h, respectively.

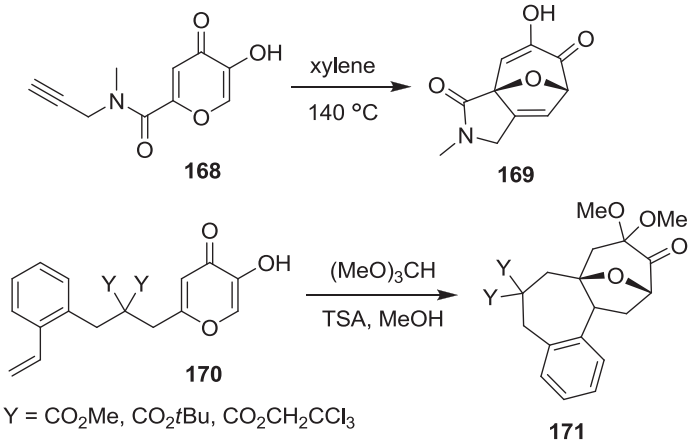
Very recently, synthesis of functionalized cyclohepta[*b*]indoles **175** was reported by Mei et al.[125] via [5+2] cycloaddition reactions. Firstly, treatment of chloromethyl derivative **172** with diethyl 2-[(1-methyl-1*H*-indol-3-yl)methyl]malonate **173** in the presence of NaH and TBAI in THF at 0 °C afforded indole KA derivatives **174** in 56%–82% yields. Then the intramolecular [5+2] cycloaddition reaction between methoxy

oxidopyrylium ylide, in situ generated by reaction of **174** with MeOTf in DCM at 40 °C for 12 h, and indole moiety was conducted by addition of CsF in a mixture of DCM/DMF at 25 °C for 7 h, to give functionalized cyclohepta[*b*]indoles **175** in 43%–85% yields (Scheme 57).



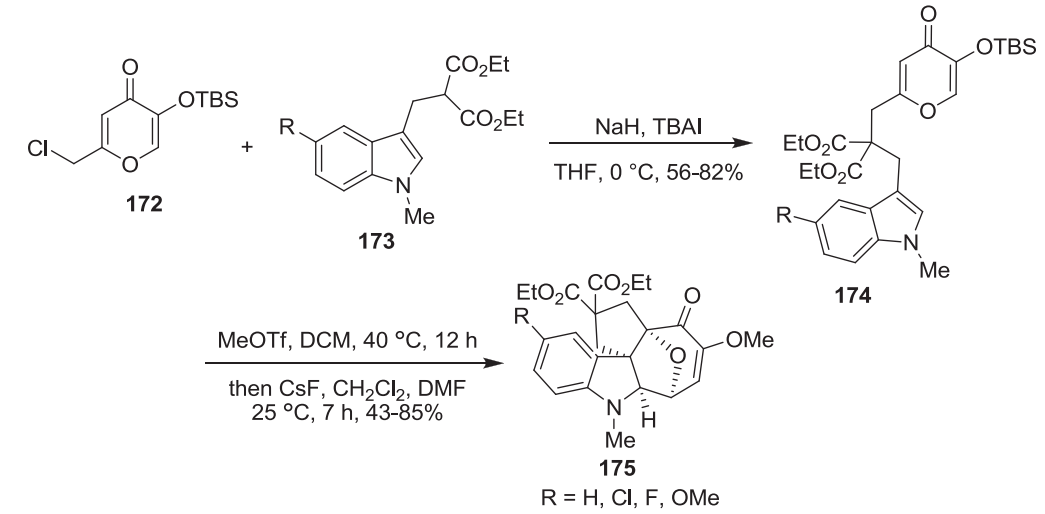


Scheme 55.

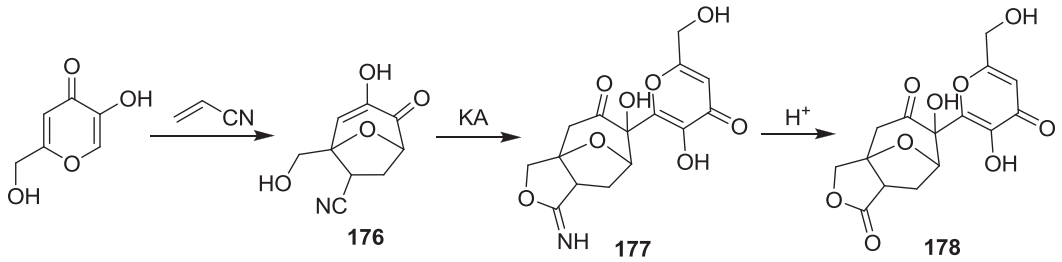


Scheme 56.

Volkmann et al.[126] reported an ionic [4 + 2] cyclization of KA with acrylonitrile as outlined in Scheme 58. Intermediate **176** was obtained in situ and converted to **177** in the reaction with the second molecule of KA. Compound **177** transformed into compound **178** in acidic conditions.



Scheme 57.



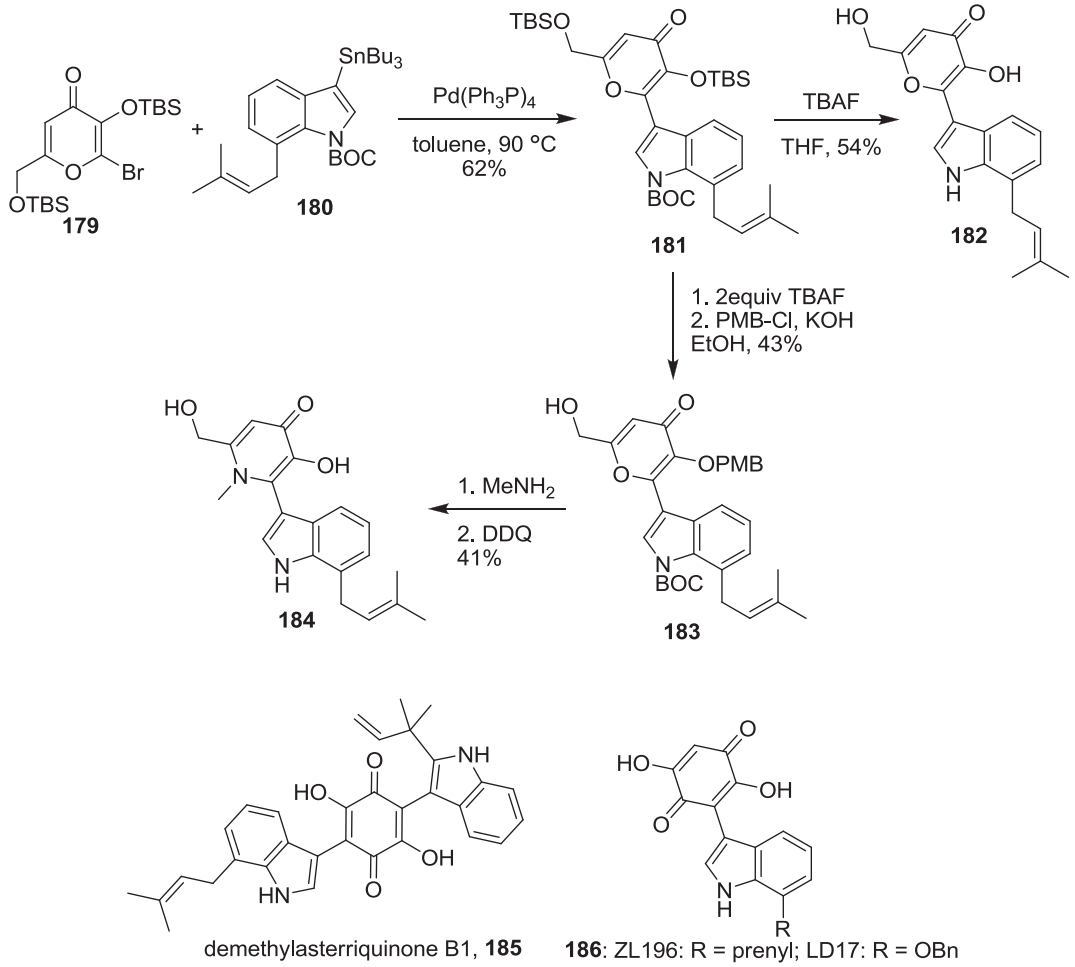
Scheme 58.

2.9. Cross coupling reactions

Compounds **182** and **184**, candidates for quinone replacement in demethylasterriquinone B1 **185**, ZL196 **186a,** and LD17 **186b** as insulin mimic with oral activity in mouse models of diabetes, were prepared via Stille coupling reaction of stannane **180** and 2-bromoKA derivative **179**, as shown in Scheme 59. The reaction was performed using $Pd(Ph_3P)_4$ as catalyst in toluene at 90 °C and product **181** was obtained in 62% yield. Deprotection of *O*-silyl and *N*-Boc groups with excess fluoride ions in THF gave product **182** in 54% yield. In addition, deprotection of *O*-silyl groups and then selective protection of the enol **181** with PMB-Cl afforded **183** in 43% yield, which was converted to **184** in 41% yield, by treatment with methylamine, along with removal of the *N*-Boc group, followed by deprotection of the PMB group.[127]

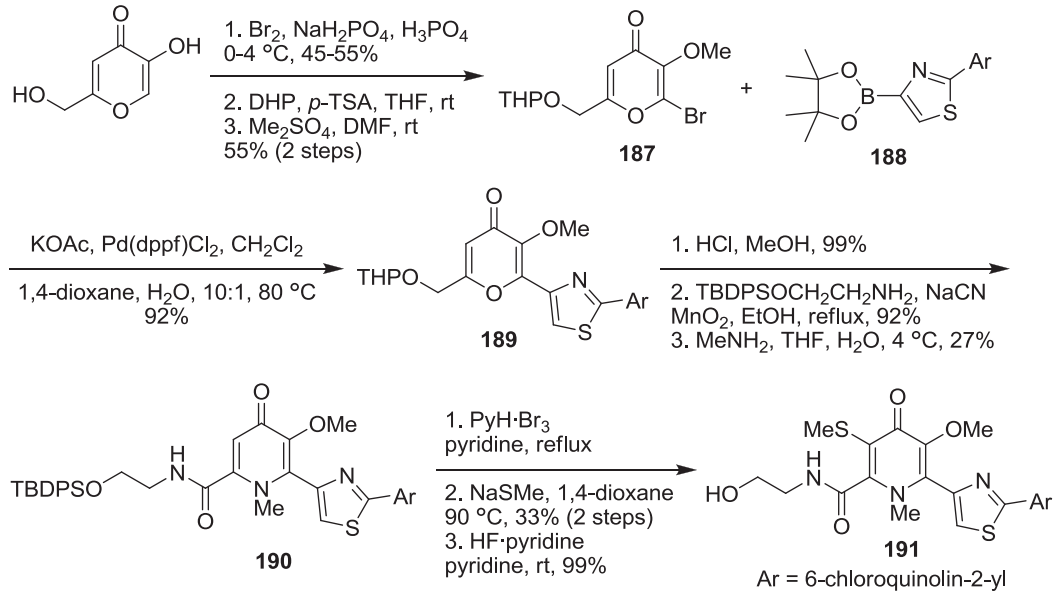
The total synthesis of lodopyridone **191**, an inhibitor of human quinone reductase 2 (NQO2, QR2), was recently described by George et al.[128] starting from KA. 6-Bromo KA derivative **187** was prepared by adding a solution of bromine and NaH_2PO_4 in water to a solution of KA in H_3PO_4 at 0 °C and stirring for 72 h at 4 °C, in 45%–55% yield, which was converted to **187** in 55%, by protection with DHP in the presence of *p*-TSA in THF at room temperature and then with Me_2SO_4 in DMF at room temperature. Compound **187** was treated with **188** in the presence of bis(diphenylphosphino)ferrocene palladium dichloride in 1,4-dioxane/water at 80 °C to give **189** in 92% yield. Deprotection of compound **189** in methanolic HCl solution, followed by treatment with *tert*-butyldiphenylsiloxyethanamine in the presence of NaCN and MnO_2 in EtOH at reflux, and then by treatment with $MeNH_2$ in THF/water at 4 °C gave pyridone **190** in 27% yield for three steps. Finally, lodopyridone **191** was obtained by the reaction of **190** with pyridinium tribromide in pyridine under

reflux conditions and then treatment with NaSMe in dioxane at 90 °C, followed by deprotection of TBDPS group by using hydrogen fluoride pyridine complex in pyridine at room temperature in 99% yield, for the last step (Scheme 60).

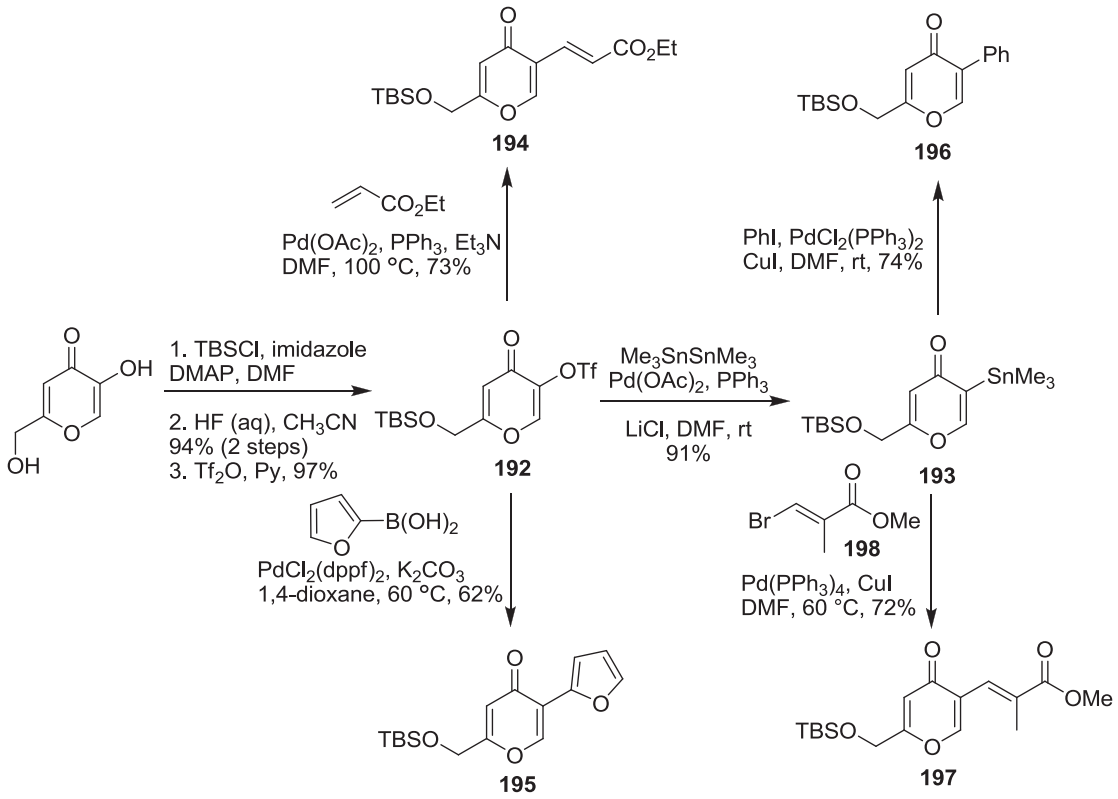


Scheme 59.

Tomoyukikamino et al.[129] reported Heck and Suzuki reactions of the triflate derivative of KA **192** as outlined in Scheme 61. KA was converted to triflate **192** by protection of the hydroxymethyl group using TBSCl in the presence of imidazole in DMAP/DMF, and then treatment with Tf_2O in pyridine. Triflate **192** transformed into stannane **193** in 91% yield by the reaction with $Me_3SnSnMe_3$ in the presence of $Pd(OAc)_2$, Ph_3P, and LiCl in DMF at room temperature. The Suzuki reaction of triflate **192** with furyl-$B(OH)_2$ in the presence of $PdCl_2(dppf)_2$ and K_2CO_3 in dioxane at 60 °C and the Heck reaction of **192** with ethyl acrylate using $Pd(OAc)_2/PPh_3$ and Et_3N at 100 °C in DMF gave **195** and **194** in 62% and 73% yields, respectively. In addition, the Stille coupling of stannane **193** with iodobenzene in the presence of $PdCl_2(PPh_3)_2$/CuI in DMF at room temperature and β-bromo-methacrylate **198** using $Pd(PPh_3)_4$/CuI in DMF at 0 °C yielded **196** and **197**, in 74% and 72% yields, respectively.

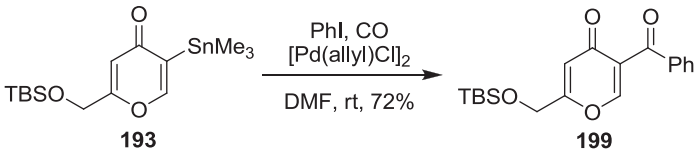


Scheme 60.



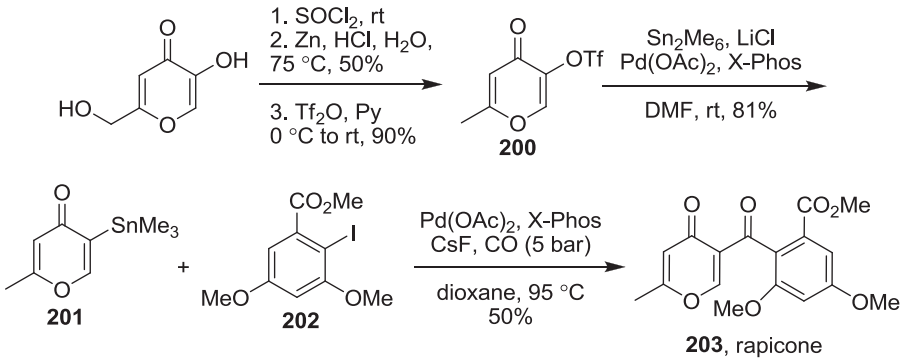
Scheme 61.

Furthermore, $[Pd(allyl)Cl]_2$ catalyzed carbonylation of stannane **193** with PhI and CO in DMF at room temperature led to 5-benzoyl-4-pyrone **199** in 72% yield (Scheme 62).



Scheme 62.

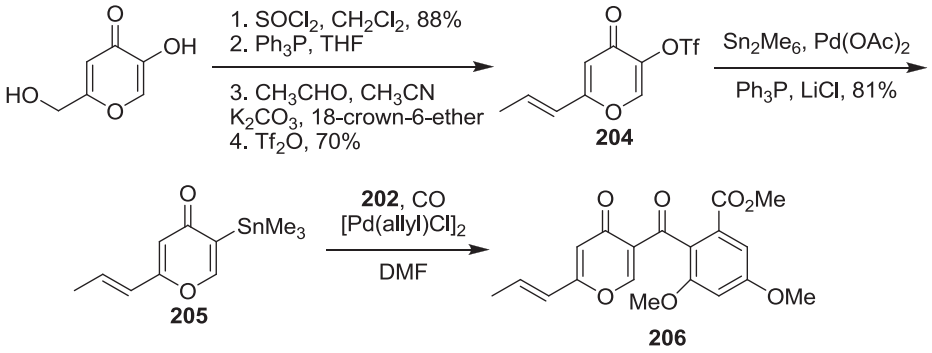
Rapicone **203**, with HIV integrase inhibitory, plant growth reduction, and antifungal activities, was synthesized from KA in several steps as shown in Scheme 63. The reaction of KA with $SOCl_2$ at room temperature and then reduction with Zn/HCl in water at 75 °C gave allomaltol in 50% yields over 2 steps, which was protected with Tf_2O in the presence of pyridine at 0 °C to room temperature to give **200** in 90% yield. Protected allomaltol **200** transformed into **201** in 81% yield by direct stannylation with hexamethylditin in the presence of LiCl and $Pd(OAc)_2$/X-Phos catalyst in DMF at room temperature. Carbonylative Stille cross-coupling of **201** with **202** using $Pd(OAc)_2$/X-Phos and CsF as additive in dioxane at 95 °C produced rapicone **203** in 50% yield.[130]



Scheme 63.

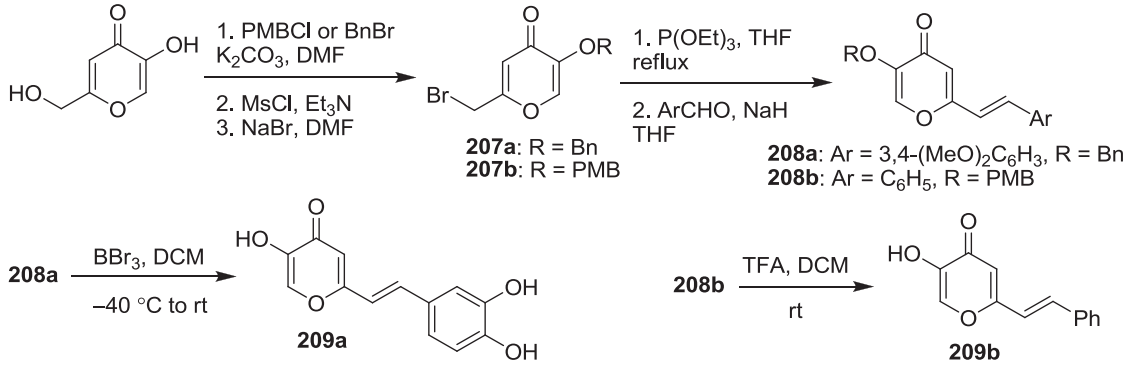
2.10. Wittig reaction

Synthesis of funicone analogue **206**, a compound with cytostatic and antiproliferative properties, was investigated by Manzo et al.[131] in 2012. A solution of KA and $SOCl_2$ in CH_2Cl_2 was stirred at room temperature overnight to give chloro-KA in 88% yield, which was treated with Ph_3P in THF at 67 °C for 4 days, followed by treatment with acetaldehyde in CH_3CN in the presence of K_2CO_3 and dicyclohexyl-18-crown-6, leading to a Wittig product. By addition of Tf_2O to the reaction mixture, Wittig product **204** was obtained in 70% yield, which was transformed into product **205** in 81% yield when reacted with $Pd(OAc)_2$, hexamethylditin, Ph_3P, and LiCl in DMF at room temperature for 21 h. Stille carbonylative coupling between stannane derivative **205** and iodobenzo precursor **202** in CO atmosphere in the presence of allylpalladium(II) chloride dimer as catalyst in DMF at room temperature for 1 day resulted in the formation of deoxyfunicone **206** in 33% yield (Scheme 64).



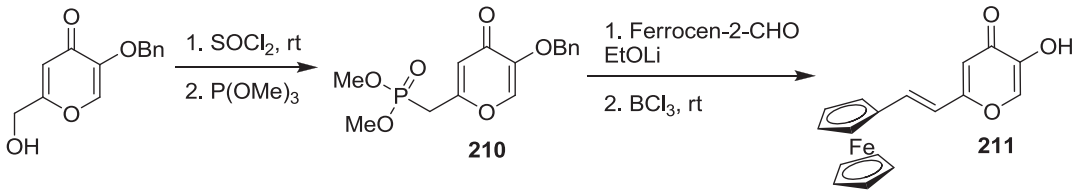
Scheme 64.

Chen et al.[132] reported the preparation of a class of KA derivatives **209**, which exhibit antiproliferative activity against Hella cells in chelated form with Cu(II). KA was converted to **207a** or **207b** in 92% or 87% yield by protection using PMBCl or BnBr in the presence of K_2CO_3 in DMF, respectively, followed by treatment with MsCl in the presence of Et_3N and then NaBr in DMF. Compounds **208a** and **208b** were obtained from the Arbuzov reaction of **207a** and **207b** with $P(OEt)_3$ in THF at reflux, followed by the Horner–Emmons reaction with benzaldehyde in the presence of NaH in THF in 58% and 64% yields, respectively. Deprotection of **208a** with BBr_3 in DCM at -40 °C to room temperature and **208b** with TFA in DCM at room temperature afforded the final products **209a** and **209b** in 63% and 55% yields, respectively (Scheme 65).



Scheme 65.

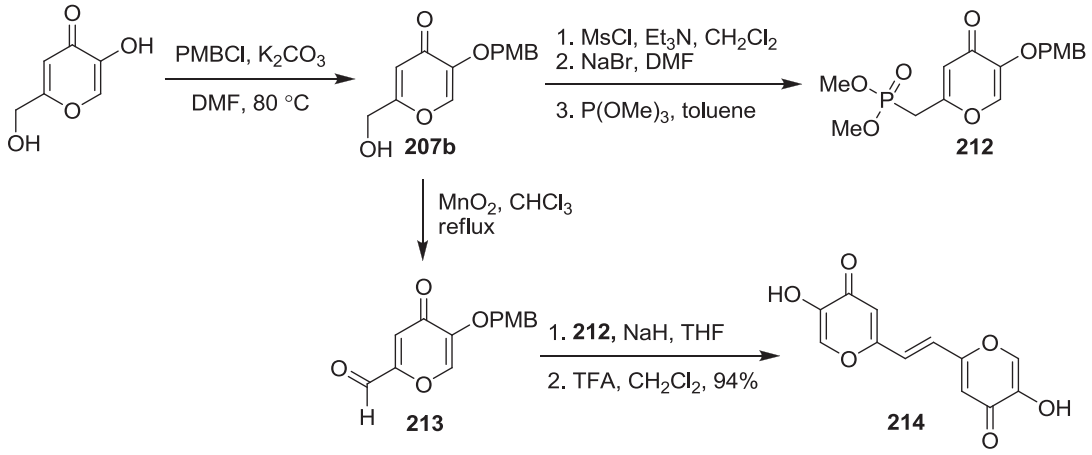
The reaction of *O*-protected KA with $SOCl_2$ at room temperature, followed by treatment with $P(OMe)_3$ gave phosphonate **210**. Reactions of **210** with ferrocene carboxaldehyde in the presence of EtOLi under Wittig–Horner conditions and then deprotection using BCl_3 at room temperature led to ferrocene-containing compound **211** in 70% yield, which is sensitive to Fe^{3+} (Scheme 66).[133]



Scheme 66.

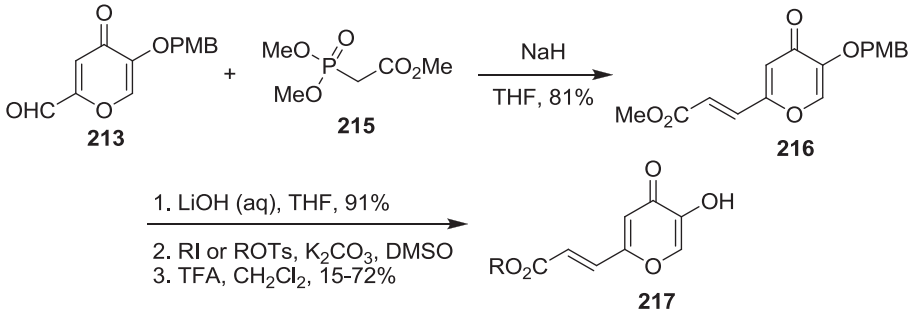
Lee et al.[134] reported KA derivative **214**, possessing melanin synthesis and tyrosinase inhibitory activity, by joining two pyrone rings via Horner–Emmons reaction of phosphonate **212** with aldehyde **213** in the presence

of NaH in THF at room temperature for 1 h. Comenic aldehyde **213** was produced by protection of enolic OH with PMB-Cl in the presence of K_2CO_3 in DMF at 80 °C to **207b**, followed by oxidation with MnO_2 in $CHCl_3$ under reflux conditions, and phosphonate **212** was obtained from protection of KA as above, followed by the reaction with MsCl in the presence of Et_3N in CH_2Cl_2 and NaBr in DMF and then with $P(OMe)_3$ in toluene (Scheme 67).



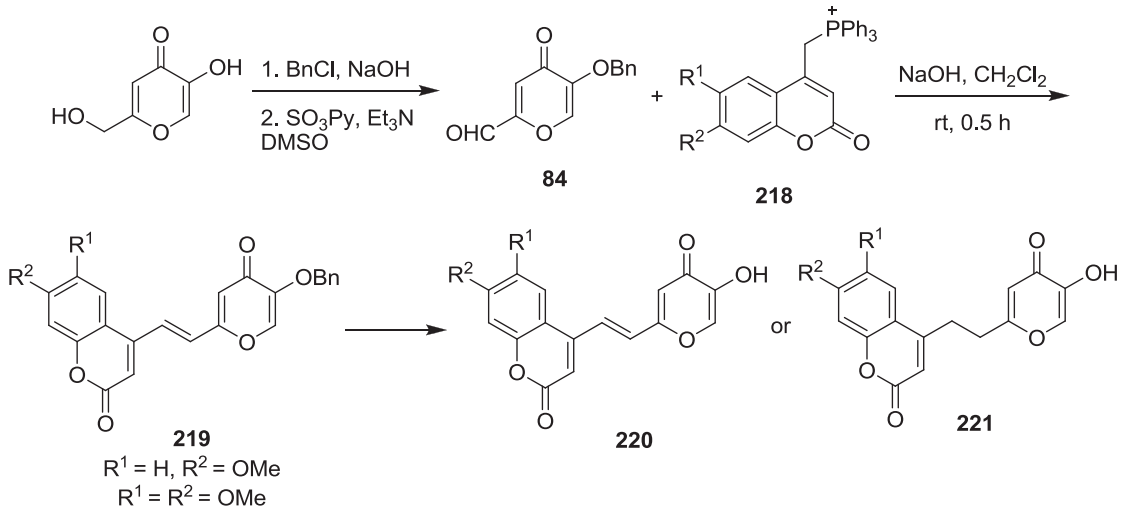
Scheme 67.

The Horner–Emmons reaction of aldehyde **213** was also performed with phosphonate **215** by NaH in THF, and methyl ester **216** was obtained in 81% yield. Hydrolysis of ester moiety with LiOH in aqueous THF followed by alkylation with alkyl iodides in the presence of K_2CO_3 as a base in DMSO and then deprotection of the PMB group using trifluoroacetic acid (TFA) in CH_2Cl_2 afforded products **217**, as a tyrosinase inhibitor, in 15%–72% yields (Scheme 68).[135] Aldehyde **213** was obtained by protection of KA with PMB-Cl continued by oxidation with MnO_2.



Scheme 68.

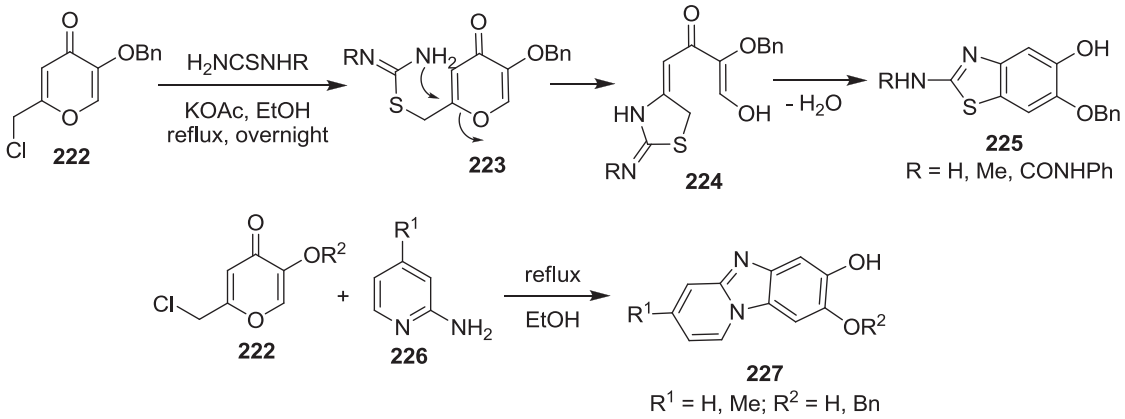
Ma et al.[136] reported the synthesis of 2-aryl substituted pyrones **220** and **221** from KA. As shown in Scheme 69, benzoylation of KA followed by selective oxidation with sulfur trioxide pyridine complex in DMSO afforded 6-formyl-3-benzyloxypyran-4(1*H*)-one **84**, which converted to products **219** in 32%–38% yield by Wittig reaction with phosphonium salt **218** in the presence of NaOH in CH_2Cl_2 at room temperature for 0.5 h. Deprotection of product **219** using BCl_3 in CH_2Cl_2 at room temperature for 5 h afforded products **220** in 67%–70% yields. Deprotection of **219** with catalytic hydrogenation using H_2/Pd/C for 5 h yielded product **221** in 32% yield.



Scheme 69.

2.11. Ring opening reactions

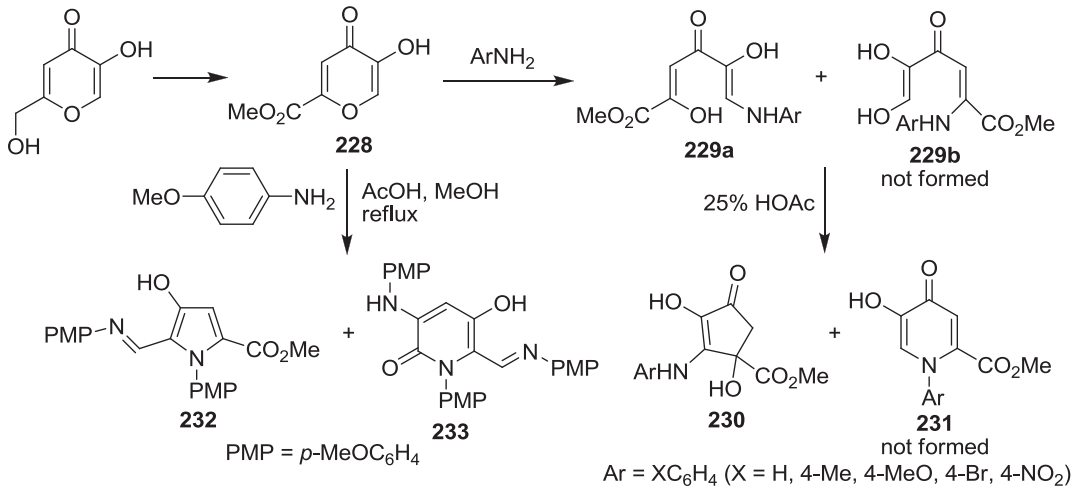
The chloromethyl derivative of KA was a versatile intermediate to yield benzothiazoles **225** and pyrido[l,2-*a*]benzimidazoles **227** in the reaction with thiourea and 2-aminopyridine **226**, via ring opening of KA, respectively. The chloromethyl pyrone **222** was heated with thiourea derivatives in the presence of KOAc in EtOH at 110 °C overnight and benzothiazoles **225** were obtained in 74%–93% yields. The proposed mechanism for this conversion involves the nucleophilic substitution of Cl with thiourea through the *S*-atom to give intermediate **223**, which underwent intramolecular conjugate addition of nitrogen to α-carbon of KA and thereby opening the pyrone ring, yielding the intermediate **224**. Final benzothiazols **225** were obtained by the cyclodehydration of **224**. The reaction of **222** with 2-aminopyridins **226** in EtOH at reflux for 24 h gave the pyrido[l,2-*a*]benzimidazoles **227a,b** in 20% and 25% yields, respectively. Hydrolysis of **227a,b** in concentrated HCl produced dihydroxyl compounds **227c,d** in 17%–25% yields (Scheme 70).[137]



Scheme 70.

By stirring equimolar amounts of 5-hydroxy-2-methoxycarbonyl-4-pyrone **228** and aromatic amines in AcOH or MeOH at 75–80 °C for 20–60 min, 3-arylamino-2,4-dihydroxy-4-methoxycarbonyl-2-cyclopenten-1-ones **230** were obtained in 42%–73% yields. Reactions proceeded by conjugate addition of amine to pyrone,

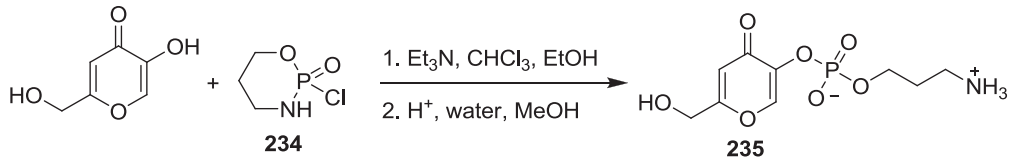
followed by ring opening to intermediate **229a**, which underwent cyclization to **230**. As shown in Scheme 71, 4-pyridone **231** was not formed. On the other hand, the reaction of methyl comenate **228** with 3.5 equiv. of 4-anisidine in HOAc/MeOH under reflux conditions for 2 h led to a mixture of pyrrole **232** and pyridone **233**.[138,139]



Scheme 71.

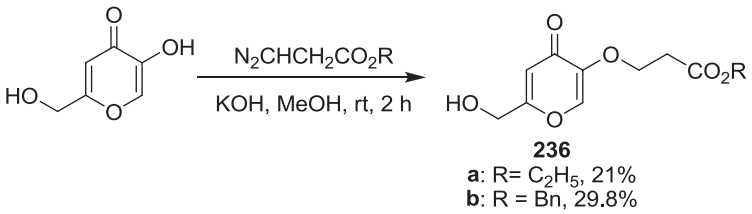
2.12. Reactions in enolic OH

5-[(3-Aminopropyl)phosphinooxy]-2-(hydroxymethyl)-4*H*-pyran-4-one **235** was prepared in 98% yield from the reaction of KA with 2-chloro-[1,3,2]oxazaphosphinane 2-oxide **234** in the presence of Et_3N as an organic base in $CHCl_3$/EtOH at room temperature for 12 h, continued by hydrolysis in acidic conditions in aqueous MeOH (Scheme 72). The obtained kojyl-APPA **235** exhibited a tyrosinase inhibition effect (30%) in vivo, but not in vitro.[140]



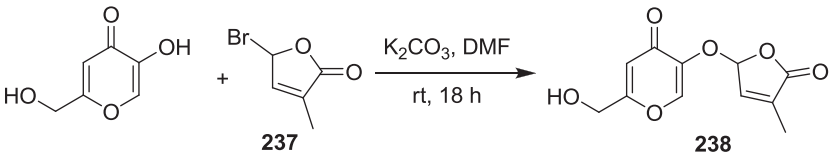
Scheme 72.

Reaction of KA with ethyl and benzyl β-diazopropionates in the presence of KOH in MeOH at room temperature for 2 h produced ethyl β-(2-hydroxymethyl-4-pyrone-5-oxy)-propionate **236a** and benzyl β-(2-hydroxyrnethyl-4-pyrone-5-oxy)-propionate **236b** in 21% and 29.8% yields, respectively (Scheme 73).[141]



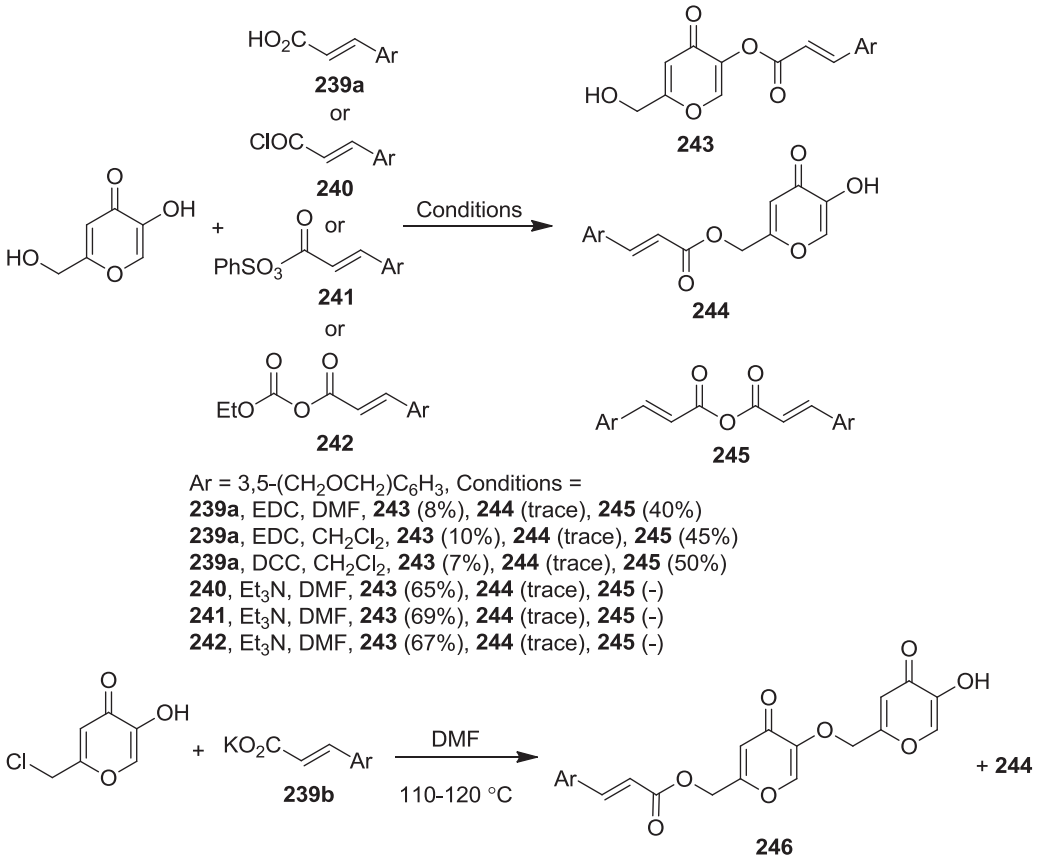
Scheme 73.

O-Alkylation of enolic OH was conducted by stirring a mixture of KA and bromo butenolides **237** in the presence of anhydrous K_2CO_3 in dry DMF at room temperature for 18 h, and product **238**, germination stimulants for seeds of parasitic weeds, was obtained in 36.6% yield (Scheme 74).[142]



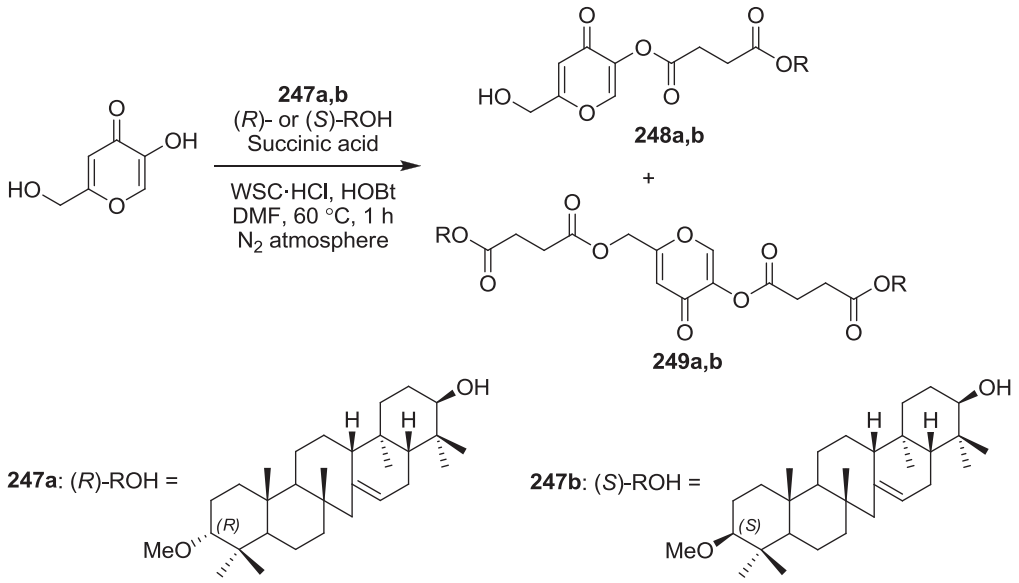
Scheme 74.

In 2012, Cho et al.[143] reported cinnamate derivatives of KA **243** and **244** that act as depigmenting agents. Reaction of KA with 3,4-(methylenedioxy)cinnamoyl chloride **240** was performed in the presence of Et_3N (1.1 equiv.) in DMF at room temperature and compound **243** was obtained in 65% yield. Treatment of KA with **241** or **242** in the presence of Et_3N in DMF gave **243** in 65% yield. The reaction of KA with 3,4-(methylenedioxy)cinnamic acid **239a** in the presence of EDC and DCC led to the formation of anhydride of cinnamic acid **245**, whereas compound **244** was not obtained. Moreover, side product **246** was obtained besides product **244** when chloro KA was treated with potassium salt of 3,4-(methylenedioxy)cinnamic acid **239b** in DMF at 110–120 °C (Scheme 75).



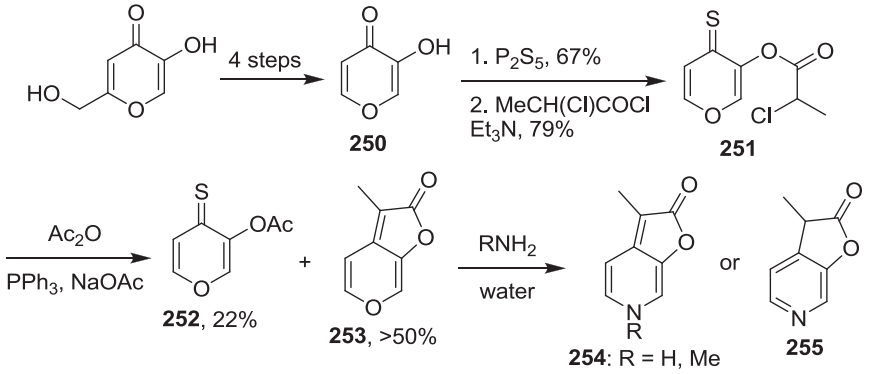
Scheme 75.

Stirring 3a-methoxyserrat-14-en-21b-ol **247a** or 3b-methoxyserrat-14-en-21b-ol **247b** linked to succinic acid with an equimolar amount of KA in the presence of EDC·HCl and 1-hydroxybenzotriazole (HOBt) in DMF at 60 °C for 1 h under N_2 atmosphere produced conjugates **248a** or **248b** in 17% or 40% yields, respectively. Conjugates **249a** and **249b** were also obtained in 30% and 19% yields, from 2 molecules of **247a** and **247b** linked to succinic acid with one molecule of KA under conditions similar to those mentioned for **248a** and **248b** (Scheme 76). Conjugates **248** and **249** act as anti-HIV agents.[144]



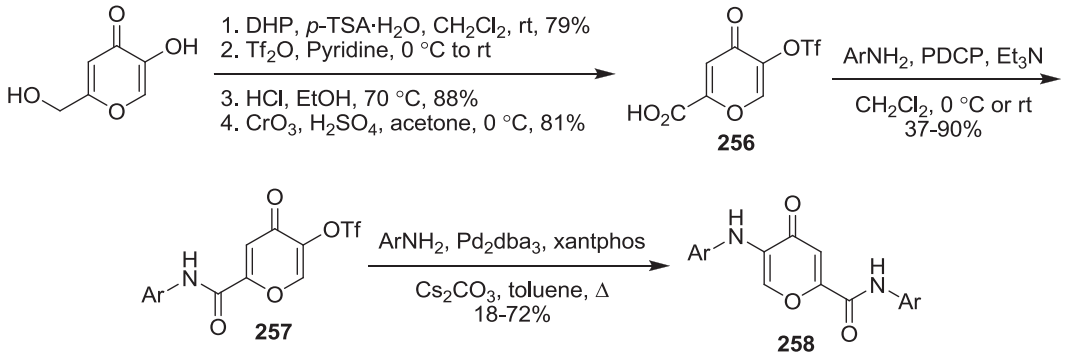
Scheme 76.

Preparation of 2*H*-furo[2,3-*c*]pyran-2-one derivatives **253** and evaluation of their germination-promoting activity were reported by Flematti et al.[145] As shown in Scheme 77, butenolides **253** were obtained from KA in 7 steps. Treatment of **250** with P_2S_5 followed by the reaction with 2-chloropropionylchloride in the presence of Me_3N afforded ester **251** in 79% yield. Heating **251** in Ac_2O in the presence of Ph_3P and NaOAc under reflux conditions gave **253** in 50% yield along with **252** in 22% yield. Furthermore, by heating butenolides **253** in concentrated NH_4OH and aqueous methylamine solution, the expected pyridine **255** and *N*-methyl-pyridone **254** were obtained in 10% and 14% yields, respectively.



Scheme 77.

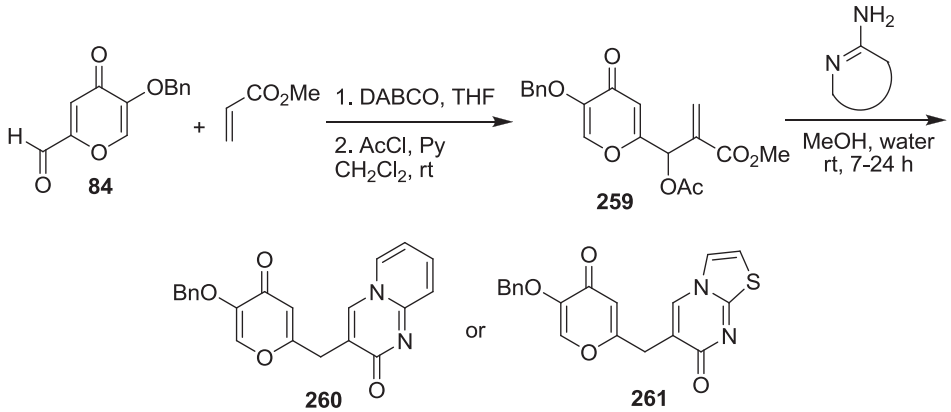
A series of 5-arylamino-4*H*-pyran-4-ones **258** were prepared using a palladium-catalyzed amination reaction with triflates **257** as key intermediates. Selective protection of the primary alcohol function of KA by 3,4-dihydro-2*H*-pyran in the presence of *p*-TSA as a catalyst in CH_2Cl_2 at room temperature and then protection of enolic OH with Tf_2O in pyridine at 0 °C to room temperature, followed by deprotection of THP moiety under acidic conditions in EtOH at 70 °C and oxidation with Jones reagent in acetone at 0 °C gave carboxylic acid **256** in 81% yield. The reaction of **256** with anilines in the presence of PDCP and Et_3N in CH_2Cl_2 at 0 °C to room temperature afforded carboxamides **257** in 37%–90% yields. 5-Arylamino-4*H*-pyran-4-ones **258** were obtained in 18%–72% yields from a Buchwald–Hartwig-type amination reaction of the triflates **257** with arylamines catalyzed with Pd_2dba_3, xantphos, and Cs_2CO_3 in toluene (Scheme 78).[146] Moreover, 5-amido-3-hydroxy-4-pyrones[147] and 2-amido-3-hydroxy-4-pyrones, and other 6-amido-3-hydroxy-4-pyrones,[148,149] as inhibitors of matrix metalloproteinases, were reported.



Scheme 78.

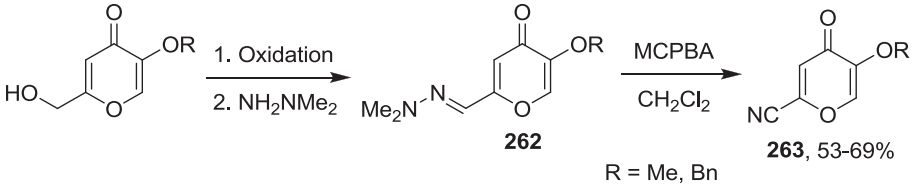
2.13. Reactions at hydroxymethyl moiety

Shahrisa et al.[150] synthesized fused pyrimidone derivatives containing KA skeleton **260** and **261**. The Baylis–Hillman reaction of comenic aldehyde **84**, derived from KA, with methyl acrylate using DABCO in THF followed by the reaction with AcCl and pyridine in CH_2Cl_2 at room temperature produced **259** in 67% yield. Fused pyrimidines **260** and **261** were obtained in 76% and 74% yields from the reaction of **259** with 2-aminopyridine and 2-aminothiazole in water/MeOH at room temperature, respectively (Scheme 79).



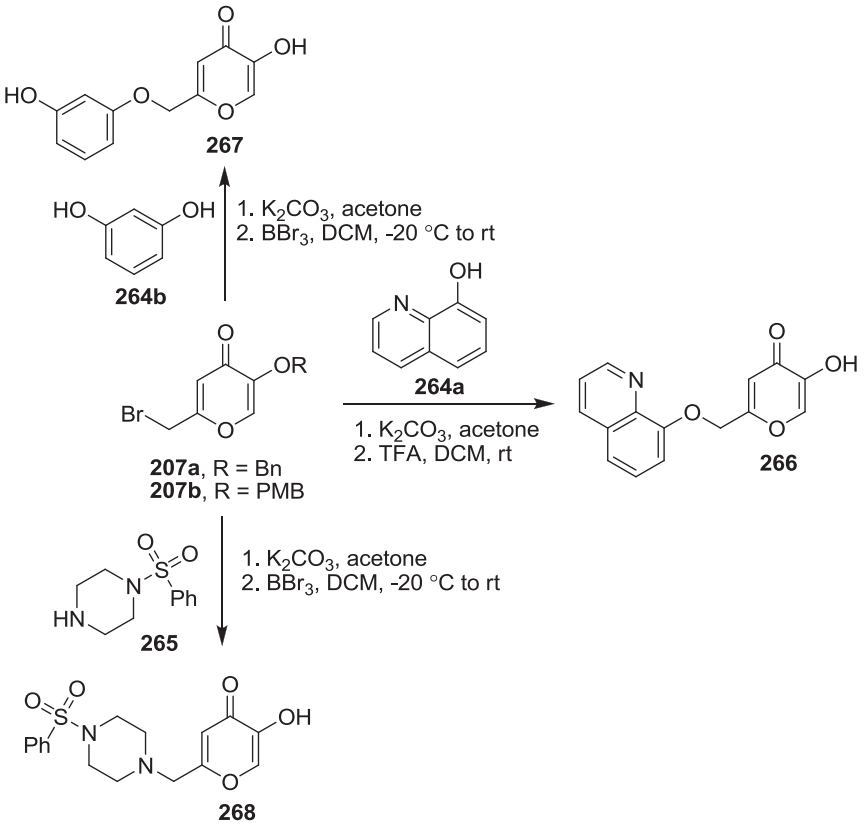
Scheme 79.

N,N-Dimethylhydrazones **262** were obtained from the reaction of KA with MnO_2 in CH_2Cl_2, followed by the reaction with N,N-dimethylhydrazine in the presence of catalatic amount of p-TSA in toluene at reflux for 4 h. Stirring of hydrazones **262** with MCPBA in CH_2Cl_2 at –15 to 20 °C for 24 h gave nitriles **263** in 53%–69% yields (Scheme 80).[151]



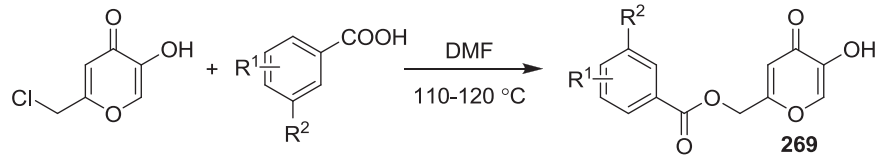
Scheme 80.

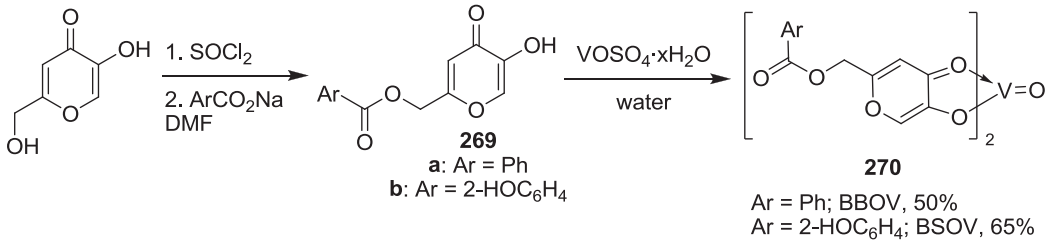
Chen et al.[152] reported the preparation of a class of KA derivatives **266**–**268**, which exhibit antiproliferative activity against Hella cells in chelated form with Cu(II). Bromides **207b** and **207a** were reacted with 8-hydroxyquinoline **264a** and resorcinol **264b** in the presence of K_2CO_3 in acetone and then underwent deprotection with TFA and BBr_3 in DCM to give **266** and **267** in 72% and 46% yields, respectively. Moreover, treatment of compound **207a** with arylsulfonylpiperazine **265** in the presence of K_2CO_3 in DMF, followed by deprotection using BBr_3 in DCM, afforded product **268** in 86% yield (Scheme 81). In 2003, Kadokawa et al.[153] synthesized two KA derivatives containing phenolic hydroxy groups, like **267**. The reactions were carried out by treatment of chloro KA **222** with phenol derivatives in the presence of K_2CO_3 in DMF at room temperature, followed by subsequent deprotection, leading to corresponding products in 24.8% and 56.6% yields, respectively.



Scheme 81.

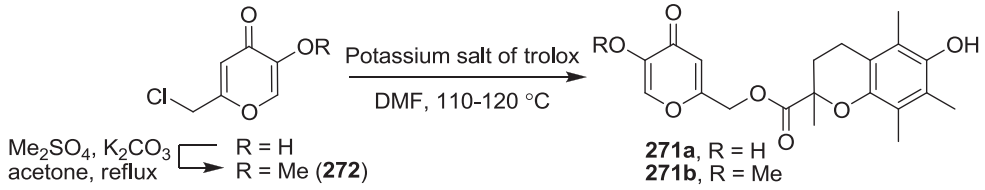
Benzoate esters of KA **269** were synthesized and their tyrosinase inhibitory activity and depigmenting activity were evaluated. Treatment of KA with thionyl chloride in DMF at room temperature, followed by reaction with potassium salts of benzoic acids in DMF at 110–120 °C, gave benzoate derivatives **269** in good yields.[154,155] Furthermore, treatment of chloro KA with sodium benzoate and sodium salicylate gave (5-hydroxy-4-oxo-4*H*-pyran-2yl)methyl benzoate **269a** and (5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl 2-hydroxybenzoate **269b** in 75% and 80% yields, respectively. [Bis-(5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl benzoatato] oxovanadium (BBOV) and bis[(5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl 2-hydroxybenzoatato] oxovanadium (BSOV) **270**, as potent hypoglycemic and great potential antidiabetic agents, were obtained from the reaction of **269** with vanadyl sulfate by heating at 70 °C for 12 h, in 50% and 65% yields, respectively (Scheme 82).[156,157]





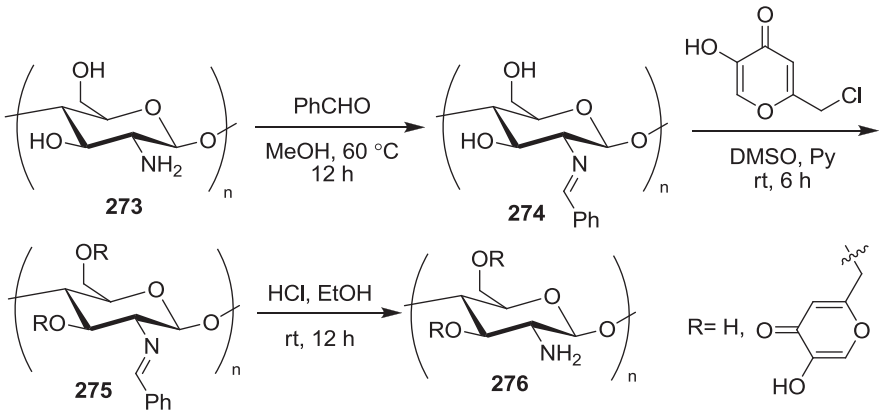
Scheme 82.

Ahn et al.[158] reported KA derivatives containing trolox moiety **271a** and **271b** that exhibited potent tyrosinase inhibitory activity and radical scavenging activity. Reaction of KA with $SOCl_2$ in DMF at room temperature, followed by treatment with potassium salts of trolox in DMF at 110–120 °C, gave the corresponding ester **271a**. In addition, **272** was obtained from the reaction of chloro KA with Me_2SO_4 in the presence of K_2CO_3 in acetone under reflux conditions, which transformed into **271b** under the same conditions for **271a** (Scheme 83).



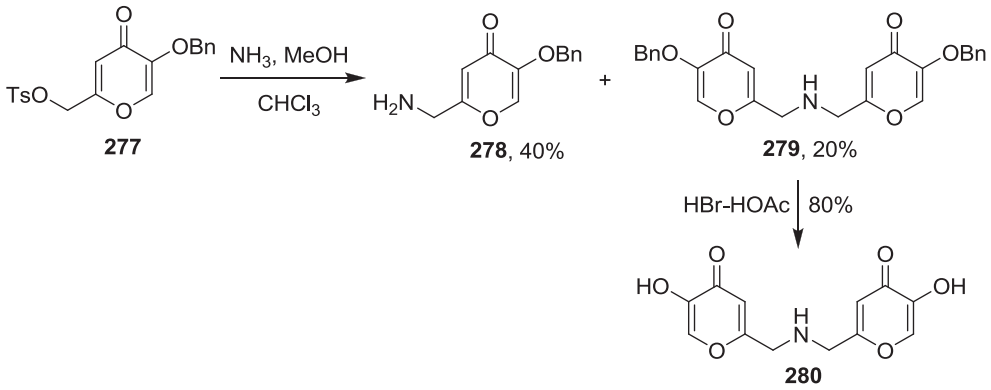
Scheme 83.

Liu et al.[159] prepared the water-soluble chitosan oligosaccharide (COS) derivative **276**, by treatment of **273** with benzaldehyde in MeOH at 60 °C for 12 h to give **274** and then by treatment with chloro KA in DMSO in the presence of pyridine at room temperature for 6 h leading to **275**, followed by deprotection with HCl at room temperature for 12 h (Scheme 84). The synthesized **276** showed more antibacterial activity than the chitosan oligosaccharide **273**.



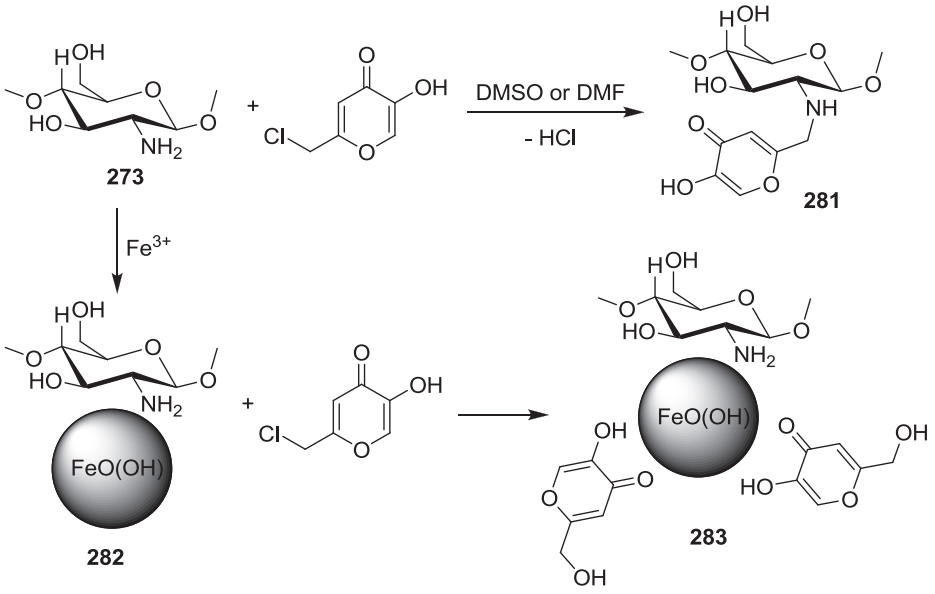
Scheme 84.

Atkinson et al.[160] synthesized kojic amines **278** that are skeletal muscle relaxants and partial agonists in chick spinal cord neurons. The reaction of KA derivative **277** with NH_3 in $MeOH/CHCl_3$ afforded kojic amine **278** in 40% yield and dimer **279** in 20% yield. Dikojic amine **279** was deprotected in the presence of HBr-HOAc to give compound **280** in 80% yield (Scheme 85). Moreover, kojic amine **278** was obtained in 81% yield from reaction of chloro KA with NaN_3 in DMF, followed by reduction with HBr-HOAc-phenol.



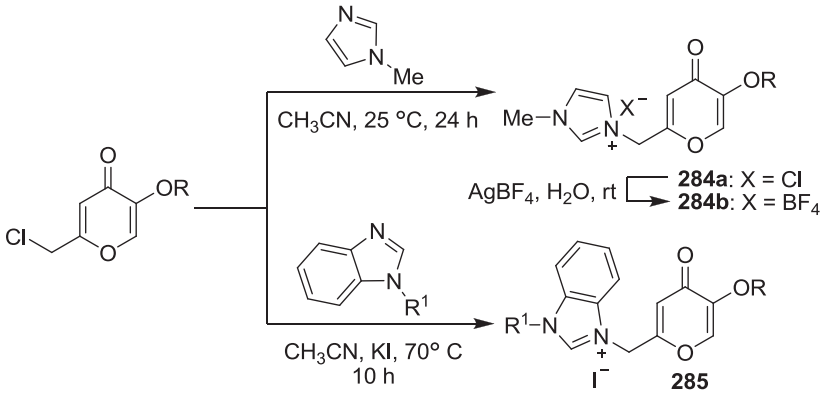
Scheme 85.

KA–chitosan conjugate **281**, an interesting compound for some applications in the food, cosmetics, and pharmacy industries, was synthesized from treatment of KA with chitosan in two different approaches: (a) covalent binding of chloro KA to chitosan via free amino groups, and (b) complexation of KA with iron(III) bound to chitosan as nanoparticles of subcolloidal FeO(OH). In the first way, chloro KA was reacted with chitosan **273** in DMSO or DMF at room temperature for 7 days to produce chit/koj **281** in 7%–27% yields. In the second way KA was attached to polysaccharide via FeO(OH) nanoparticles. Chitosan–FeO(OH) composite **282** was formed by the reaction of chitosan with $FeCl_3$, and then KA was chelated to peripheral iron(III) cations of the FeO(OH) particles bounded to chitosan **283** (Scheme 86).[161] In addition, KA–polymer-based magnetic nanocomposites, such as KA–chitosan–iron oxide nanoparticles, and KA–polyethylene glycol–iron oxide nanoparticles, were synthesized in 2014 for medical applications.[162]



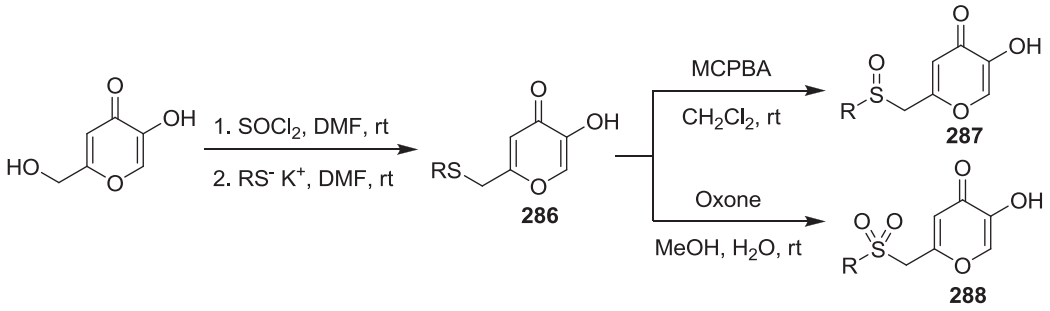
Scheme 86.

Ghasemi et al.[163] reported a series of imidazolium and benzimidazolium salts of KA derivatives **284** and **285**, which were used to synthesize functionalized *N*-heterocyclic carbenes and ionic liquids. Treatment of chloromethyl KA derivatives with *N*-methylimidazole in CH_3CN at 25 °C for 24 h or *N*-alkylbenzimidazoles in the presence of KI at 70 °C for 10 h afforded imidazolium salts **284a** or benzimidazolium salts **285** in 83%–88% or 68%–90% yields, respectively. In addition, anion exchange reactions of imidazolium salts **284a** with $AgBF_4$ in water at room temperature led to salts **284b** as new ionic liquids (Scheme 87).



Scheme 87.

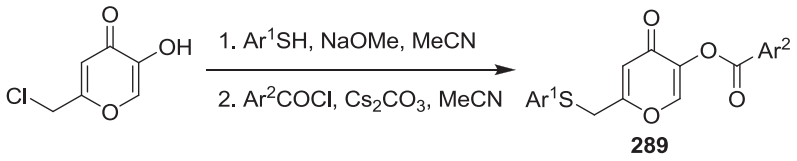
Rho et al.[164,165] synthesized derivatives of KA containing thioether **286**, sulfoxide **287**, and sulfone **288** linkages and evaluated their tyrosinase inhibitory and anti-inflammatory activities. Treatment of KA with $SOCl_2$ in DMF at room temperature, followed by the reaction with potassium salts of thiols in DMF at room temperature, gave kojyl thioether derivatives **286**. Sulfoxide derivatives **287** were achieved from the reaction of kojyl thioether derivatives **286** with MCPBA in CH_2Cl_2 at room temperature. Furthermore, kojyl thioether derivatives **286** were transformed into sulfones **288** by oxidation with oxone in a MeOH/water mixture at room temperature (Scheme 88).



286: R= Et, *n*-Pr, *n*-Bu, *n*-Pent, *n*-Hex, *n*-Hept, *n*-Oct, *c*-Hex, C_6H_5, 4-HOC_6H_4, 4-$MeOC_6H_4$
287-288: R= *n*-Pr, *n*-Hex, *c*-Hex, C_6H_5, 4-HOC_6H_4, 4-$MeOC_6H_4$

Scheme 88.

4-Oxo-6-[(pyrimidin-2-ylthio)methyl]-4*H*-pyran-3-yl 4-nitrobenzoate **289**, as a functional antagonist of the apelin (APJ) receptor, was prepared from the reaction of KA with $SOCl_2$ continued by treatment with RSH in the presence of NaOMe in CH_3CN and then the reaction with an acid chloride in the presence of CS_2CO_3 in CH_3CN (Scheme 89).[166]

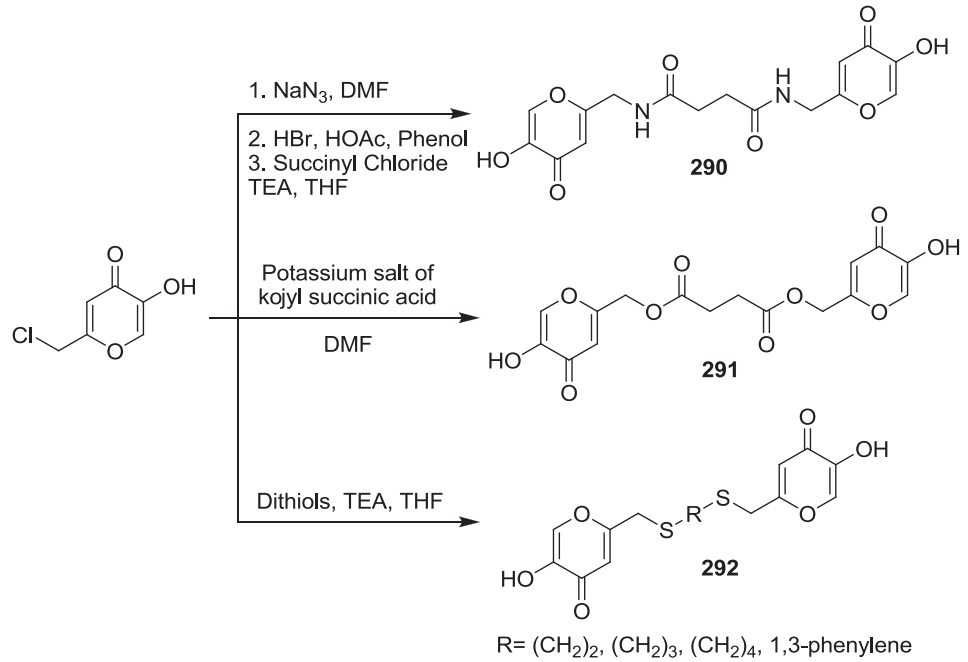


Ar^1 = XC_6H_4 (X = H, 4-F, 4-MeO, 4-F_3CO, 4-Cl, 4-Me), 2-pyrimidyl, 4-Me-2-pyrimidyl, 4,6-Me_2-2-pyrimidyl; Ar^2 = XC_6H_4 (X = H, 3-NO_2, 4-Cl, 4-NO_2, 4-CN, 4-CF_3, 4-Br, 4-Me, 4-OMe, 4-OEt, 4-O*i*-Pr, 4-O*n*-Bu, 4-*t*-Bu, 4-F, 4-SO_2NMe_2, 4-$SO_2N(CH_2)_4$, 4-Ph, 4-SO_2NEt_2, 4-$SO_2N(CH_2)_5$, 4-$SO_2N(CH_2CH_2)_2O$), YC_6H_3 (Y = 3,4-Me_2, 2-NO_2-5-Cl, 2-Cl-5-NO_2, 2-Me-3-NO_2, 2-NO_2-4,5-$(OMe)_2$, 3-NO_2-4-Cl, 3-NO_2-4-Cl,

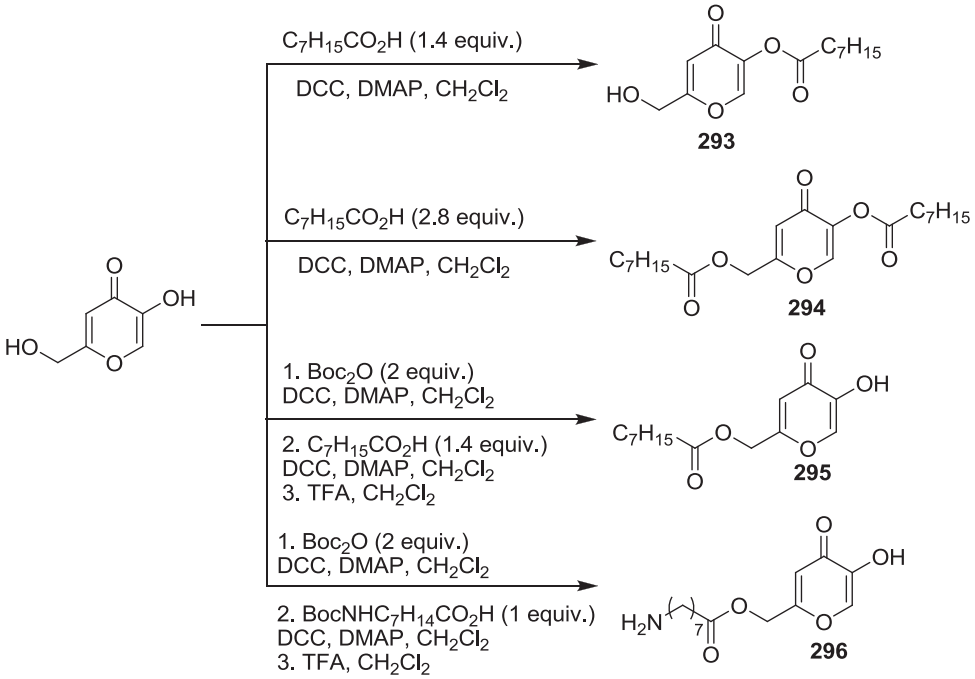
Scheme 89.

Rho et al.[167] demonstrated KA derivatives **290**–**292** having two molecules of KA connected by various linkages such as ester, amide, and thioether. Treatment of kojyl chloride with NaN_3 in DMF and then with HBr·HOAC in phenol continued by the reaction with succinyl chloride in the presence of Et_3N in THF at room temperature for 1 h afforded product **290** in 91% yield. Compound **291** was prepared in 83% yield by reaction of kojyl chloride with potassium salt of kojyl succinic acid in DMF at 110 °C for 4 h. As outlined in Scheme 90, stirring of kojiyl chloride with dithiols in the presence of Et_3N in THF at room temperature for 10 h gave the desired products **292** in good yields. In another report, a tetradentate chelator for Fe(III), Al(III), Cu(II), and Zn(II) metal ions was prepared by the reaction of KA with succinimide in the presence of TsCl or MsCl.[168] Hudecova et al. described azidometalkojates from KA and evaluated their biological activity.[169]

Treatment of KA with caprylic acid (1.4 equiv.) for 12 h or caprylic acid (2.8 equiv.) for 36 h in DMAP/DCC/CH_2Cl_2 at room temperature afforded KA octanoates **293** or **294** in 76% or 83% yields, respectively. In addition, KA octanoates **295** and **296** were obtained from the reaction of KA with di-*tert*-butyl-dicarbonate, followed by treatment with caprylic acid and *N*-BOC-aminoundecanoic acid under reaction conditions similar to those above and then deprotection using TFA in CH_2Cl_2 in 60% and 35% yields, respectively (Scheme 91).[170]

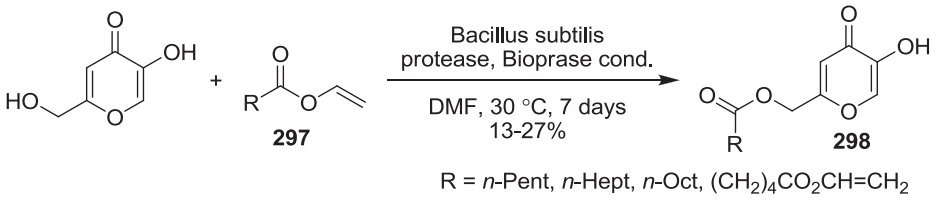


Scheme 90.



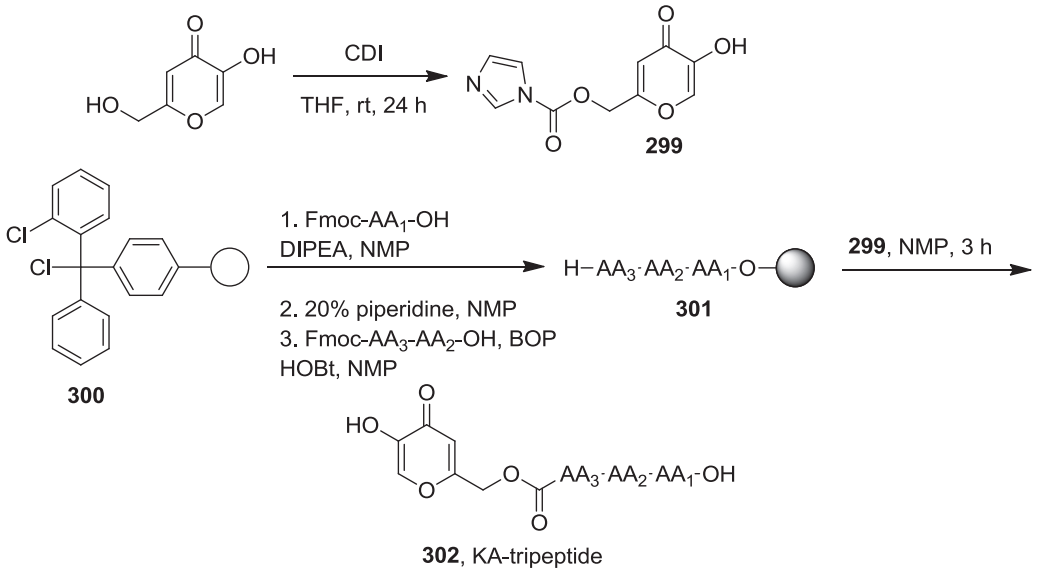
Scheme 91.

Raku et al.[171] reported regioselective synthesis of KA esters **298** by *Bacillus subtilis* protease as outlined in Scheme 92. By addition of *B. subtilis* protease to a mixture of KA and vinyl ester **297** in DMF and stirring at 30 °C for 7 days, *O*-vinyladaipoyl KA **298** was obtained in 25% yield. Other compounds **298** were obtained in a similar procedure from the reaction of KA with vinylhexanoate, vinyl octanoate, and vinyl decanoate in 25%, 27%, and 13% yields, respectively.



Scheme 92.

Solid-phase synthesis of KA-tripeptides **302**, exhibiting tyrosinase inhibitory activities, was reported by Kim et al.[172] starting from KA. Treatment of KA with carbonyl diimidazile (CDI) in THF at room temperature for 24 h afforded activated KA **299** in 70% yield. On the other hand, the tripeptides were assembled on 2-chlorotrityl chloride (CTC) resin **300** using solid-phase Fmoc chemistry. *N*-Fmoc-amino acid was quantitatively introduced to the resin using DIPEA in NMP and then the general procedure of benzotriazole-1-yloxy-tris(dimethylamino)-phosphoniumhexafluorophosphate (BOP)-mediated coupling method gave resin-bound tripeptides **301**, which then reacted with activated KA **299**. After the final cleavage, KA-tripeptides **302** were obtained in 49%–95% yields (Scheme 93). KA–tripeptide amide as a tyrosinase inhibitor was also synthesized in a similar procedure by Noh et al.[173]

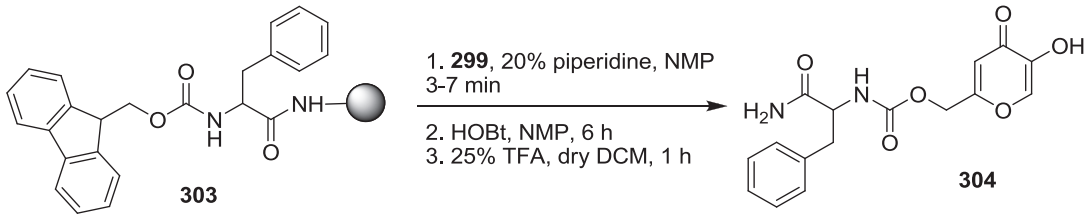


Scheme 93.

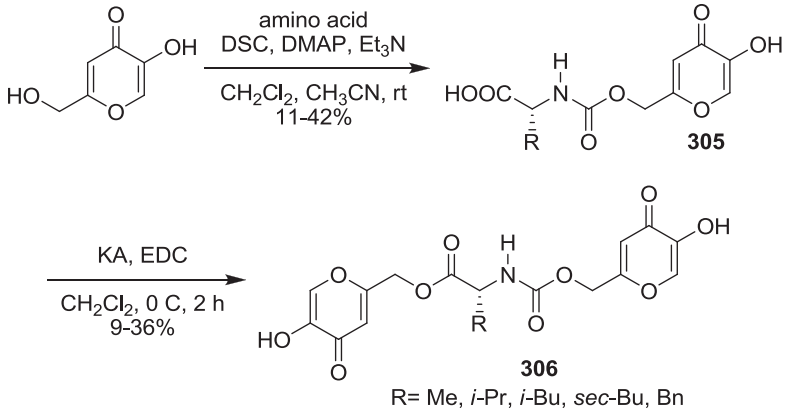
Kwak et al.[174] described the synthesis of KA–phenylalanine amide **304**, which exhibited an excellent tyrosinase inhibitory activity, from KA. Treatment of KA with CDI in dry THF for 24 h gave KA 7-imidazolide **299** in 78% yield, which was transformed into **303** in several steps by reaction with **303** as outlined in Scheme 94. In addition, complexation of **304** with $CuCl_2$ and $Zn(OAc)_2$ was developed. In 2011, Kwak et al.[175] synthesized KA–amino acid amides and their metal complexes, and investigated their tyrosinase inhibitor activity.

N-Kojic-amino acid **305** and *N*-kojic-amino acid-kojate **306** derivatives were prepared from KA. The reaction of KA with amino acids was carried out using *N*,*N*′-disuccinimidyl carbonate and 4-dimethylaminopyridine and Et_3N in a mixture of CH_2Cl_2/CH_3CN (1/1) at room temperature, and *N*-kojic-amino acid derivatives **305** were obtained in 11%–42% yields. By stirring *N*-kojic-amino acid derivatives **305** with KA in the presence

of EDC in CH_2Cl_2 at 0 °C for 2 h, *N*-kojic-amino acid-kojiate derivatives **306** were achieved in 9%–36% yields (Scheme 95).[176]



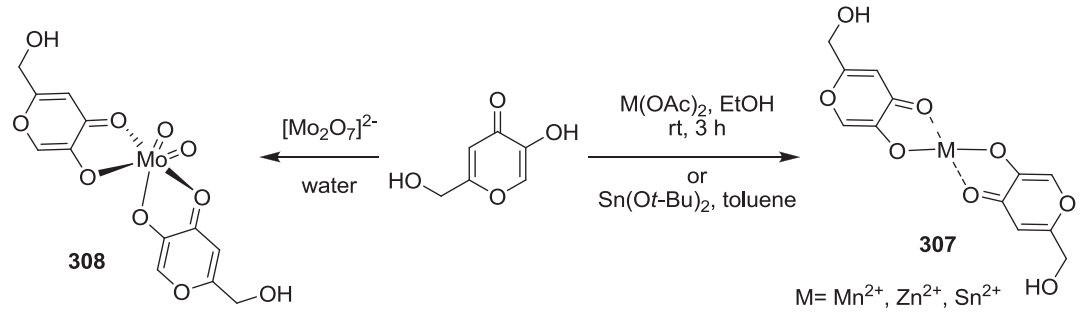
Scheme 94.



Scheme 95.

2.14. Metal complexation

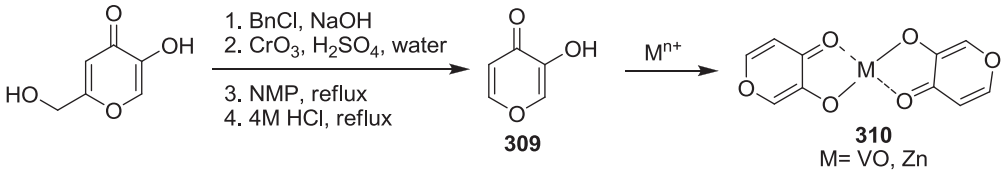
KA was used for the preparation of Mn, Zn, and Sn complexes **307**. Complexation of KA with $Mn(OAc)_2 \cdot 4H_2O$ or $Zn(OAc)_2 \cdot 2H_2O$ in EtOH at room temperature and $Sn(Ot\text{-}Bu)_2$ in toluene gave **307a**, **307b**, and **307c** in 50%, 82%, and 45% yields (Scheme 96), respectively, which exhibited potential radioprotective activity.[177,178] Lord et al.[179] synthesized complexes of molybdenum involving KA moiety **308** that were effective in lowering blood glucose and free fatty acid levels. $MoO_2(ka)_2$ **308** was prepared in 36% yield from addition of aqueous solution of KA to a stirred suspension of molybdic acid in water.



Scheme 96.

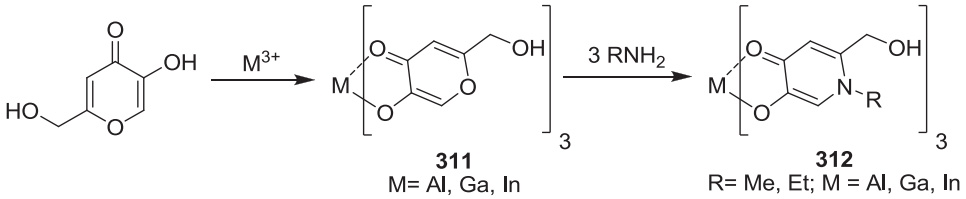
Protection of the enolic OH-group of KA with BnCl followed by the reaction with CrO_3 and then refluxing in NMP gave *O*-protected 3-HP, which was deprotected by refluxing in 4 M HCl to give **309**. Treatment of **309**

with VO or Zn afforded VO or Zn complexes that showed insulin-mimetic activity (Scheme 97).[180,181] Other antidiabetic VO^{2+} complexes containing KA ligand were also described.[182]



Scheme 97.

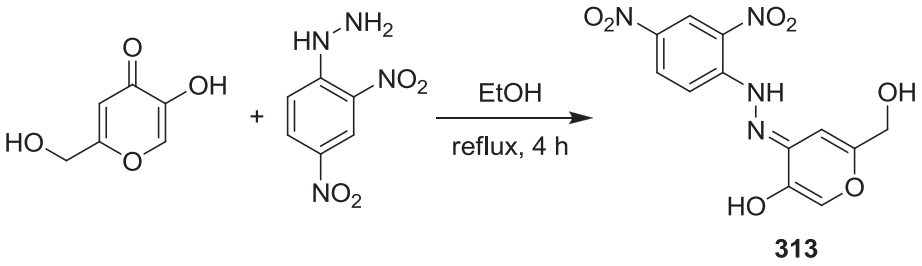
N-substituted tris(6-hydroxymethyl-3-hydroxy-4-pyridinonato)complexes of Al(III), Ga(III), and In(III) **312** were synthesized in good yield. First, the metal pyrone complexes **311** were formed in situ and then reacted with primary amines to give appropriate 3-hydroxy-4-pyridinone complexes **312** in 21%–63% yields under pH 4–9 (Scheme 98).[183] Moreover, other complexes of KA with various metal ions have been reported.[60,184–195]



Scheme 98.

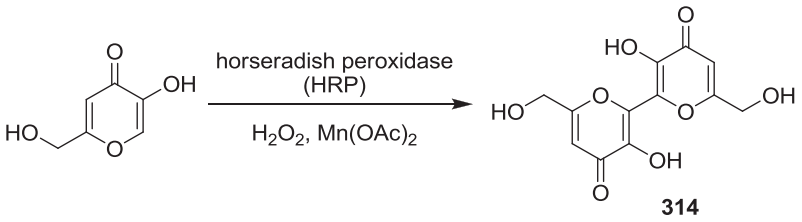
2.15. Miscellaneous reactions

4-[2-(2,4-Dinitro-phenyl)hydrazono]-6-(hydroxymethyl)-4*H*-pyran-3-ol **313** was obtained in 85% yield, from heating a solution of 2,4-dinitrophenylhydrazine and KA in EtOH under reflux for 4 h (Scheme 99). **313** is a new probe for water analysis that acts as a selective colorimetric probe for the determination of Cu^{2+} ions at trace level.[196]



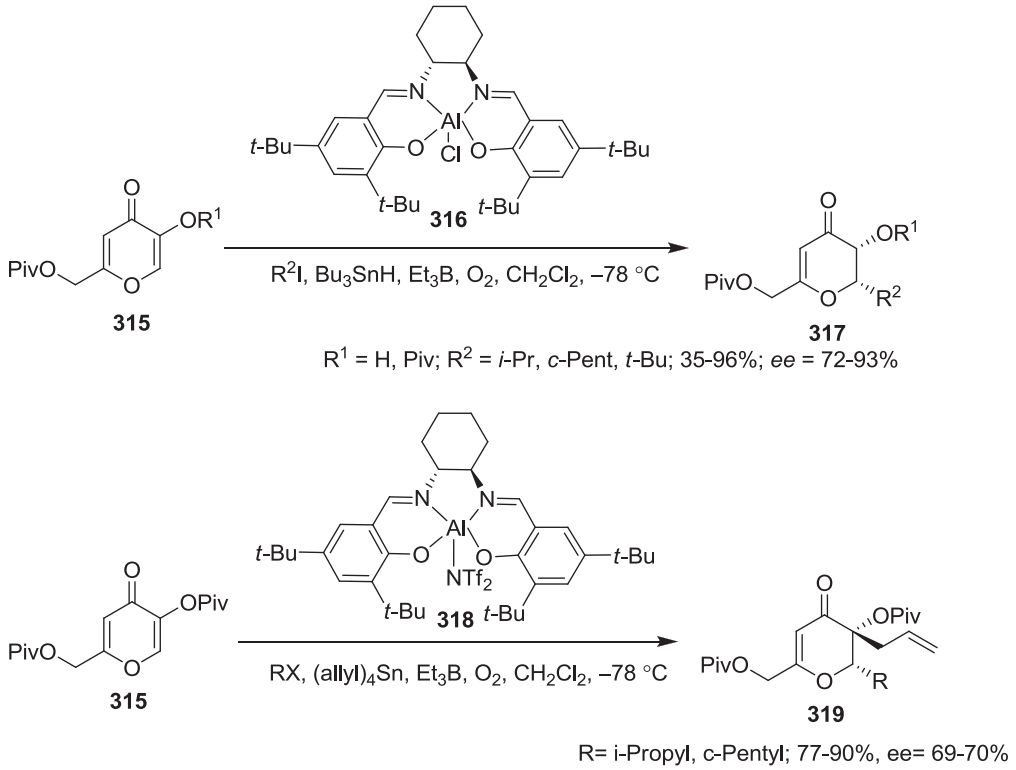
Scheme 99.

Bastidas et al.[197] reported the oxidation of KA catalyzed by H_2O_2 in the presence of horseradish peroxidase (HRP) and $Mn(OAc)_2$, leading to 6,6′-bis[5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one] **314** in low yield. Urzúa et al.[198] also oxidized KA to **314** by manganese peroxidase (MnP) from *Ceriporiopsis subvermispora* in the absence of H_2O_2 (Scheme 100).



Scheme 100.

Sibi et al.[199] described the conversion of pyrones **315** to pyrans **317**, a structural unit present in compounds with significant biological activity. Enantioselective radical additions to pyrones **315** were carried out in the presence of 30 mol% of **316** as a catalyst and RI using Bu_3SnH, Et_3B, and O_2 in CH_2Cl_2 at −78 °C, and pyrans **317** were produced in 35%–98% yields, with excellent diastereoselectivity (99:1), and moderate *ee* (72%–93%). Compounds **319** were also obtained by the reaction of **315** with allyltin in the presence of **318** as a catalyst and Et_3B and O_2 in CH_2Cl_2 at −78 °C in 77%–90% yields (Scheme 101).



Scheme 101.

Other reactions of KA are also reported in the literature, such as acylation and benzoylation,[200−205] cyanoethylation,[206] esterification,[207−216] methylation,[217,218] mesylation of KA,[219] bromination,[220] thiocyanation,[221] cyanidation,[222] glucosylation of KA,[223,224] reaction of KA with acrylonitrile and acrylic ester,[225,226] diethyl malonate,[227] *s*-butyl mercaptan,[228] glucose pentaacetate,[229] ethyl levulinate[230] and nucleophilic substitution reactions,[231] formation of KA diacetate,[232] Betti reaction of KA,[233] synthesis of selenocyanato derivatives of KA,[234] oxidation of the side chain in KA,[235] and Hoesch reaction of KA.[236]

3. Conclusion

We have presented an overview of the use of kojic acid in organic synthesis. The organic transformations of kojic acid were presented in order of the type of reaction. Thanks to the poly-functionality of kojic acid with different reactivity, such as carbonyl group, enol moiety, primary alcohol functional group, diene, and also aromatic characters, kojic acid was incorporated in various types of reactions, including aldol, Mannich, diazo coupling, conjugate addition, Claisen, and cycloaddition reactions. The synthesis of pyridone and pyridine heterocycles is one of the most important reactions of kojic acid. Moreover, there are some reactions at primary alcoholic moiety, such as halogenation, and oxidation, followed by other transformations. Although the synthesis of variety types of compounds and complexes through different one- or multistep kojic acid reactions are presented, the future evolution of other methodologies promises the synthesis of new organic compounds that were previously thought to be inaccessible.

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