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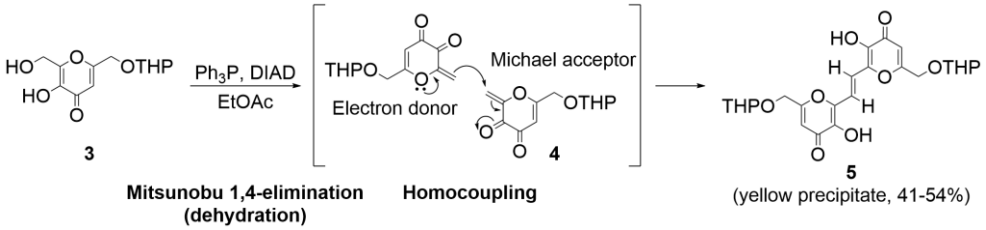
Graphical abstract



Highlights

• Mitsunobu dehydration of a kojic acid analog with a hydroxymethyl group on the C-6 carbon yields the homocoupling product.

• The dimerization, the so-called “Mitsunobu homocoupling,” may occur *via* generation of a quinone methide-like intermediate.

• Presumably, the enol ether moiety of the intermediate acts as an electron donor and attacks another molecule.

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Abstract

In this study, we attempted to carry out the Mitsunobu 1,4-elimination using the kojic acid analog **3**, which carries a hydroxymethyl group on C-6 introduced by aldol condensation, to obtain an effective Michael acceptor **4**. To the ethyl acetate solution of **3** and Ph_3P, diisopropyl azodicarboxylate was added quickly at 0 °C, resulting in the immediate generation of a yellow precipitate. NMR, mass spectrometry, and X-ray crystal structure analyses allowed to identify the precipitate as a diastereomeric/racemic mixture of dimeric compounds of **4**. The dimerization reaction was hypothesized to occur through two major steps: (i) intramolecular dehydration of **3** by Mitsunobu reagents and (ii) homocoupling of the dehydration product **4** to form a new *trans*-carbon–carbon double bond. Presumably, the enol ether moiety of **4** acts as an electron donor and immediately attacks to the α,β-unsaturated carbonyl group of another molecule via a reaction that can be dubbed "Mitsunobu homocoupling."

Keywords: Kojic Acid; Mitsunobu Reaction; Homocoupling; Quinone Methide; Michael Acceptor

1. Introduction

Kojic acid (5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one, KA, Fig. 1) is a natural compound synthesized by several species of fungi, such as those belonging to the *Aspergillus* genus.[1] KA displays inhibitory effect against tyrosinase, which is a key enzyme in the synthesis of melanin in melanocytes.[2] Therefore, KA has been used as a skin whitening agent in the cosmetic industry.[3]

(Fig. 1)

KA has an enolic property between C-5 and C-6 carbons, so it can react with various aldehydes by way of an aldol condensation, so that the corresponding 1-hydroxyalkyl groups are introduced at the C-6 carbon. For example, Ferard and co-workers observed the aldol condensations of KA or 5-hydroxy-2-[(tetrahydropyranyloxy)methyl]-4-pyrone (**2**) with formaldehyde in basic aqueous conditions.[4] Ellis *et al*. also reported the hydroxymethylation of 3-hydroxy-6-methyl-4*H*-pyran-4-one (allomaltol) in the same conditions.[5] On the other hand, Sharma and others demonstrated that the best base for the aldol condensations of KA with both aromatic or aliphatic aldehydes is 1,4-diazabicyclo[2.2.2]octane (DABCO) in dioxane–H_2O (1:1) as solvent.[6]

The Mitsunobu reaction is a versatile approach to the nucleophilic substitution of primary or secondary hydroxyl groups with nucleophiles using a triaryl or trialkyl phosphine, such as triphenylphosphine (Ph_3P) or tributylphosphine (*n*-Bu_3P), and a dialkyl azodicarboxylate, such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD).[7,8] A possible main pathway for the Mitsunobu substitution of hydroxyl groups goes as follows: (i) formation of betaine reacted Ph_3P with a dialkyl azodicarboxylate, (ii) deprotonation of the nucleophile by betaine to enhance the nucleophilicity of the former, (iii) and an S_N2 reaction between the alkoxyphosphonium ion generated by reacting the protonated betaine with the alcohol and the deprotonated nucleophile.[8] On the other hand, some reports have been published whereby a Mitsunobu 1,2-elimination reaction had occurred in the absence of a nucleophile. For example, Olpp *et al*. achieved the *anti*-selective 1,2-dehydration of γ-(α-hydroxyalkyl)butenolides under Mitsunobu reaction condition.[9] Yadav and co-workers also reported the observation of a Mitsunobu *anti*-dehydration reaction that yielded a dienone.[10] Furthermore, Chen and Leu demonstrated the unique 1,2-elimination reaction between 2-(butylthio)ethanthionyl and hydroxy moieties from γ,δ-alkynyl alcohols using Ph_3P and DIAD.[11] In addition, Mulzer *et al*. reported a Mitsunobu 1,4-elimination-like reaction consisting of the decarboxylative dehydration of the *threo*-β-hydroxy acid analogs achieved by treatment with Ph_3P and DEAD, leading to the formation of the corresponding (*Z*)-olefins.[12]

In this study, we attempted to carry out the Mitsunobu 1,4-elimination using the KA analog 3-hydroxy-2-(hydroxymethyl)-6-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-4*H*-pyran-4-one (**3**), which carries a hydroxymethyl group on the C-6 carbon (Scheme 1). Generally, an enolic hydroxy group of KA is acidic (pKa = 7.9–8.0).[13] Therefore, we considered that the enolic hydroxy group of **3** could be preferentially deprotonated, and the additional primary hydroxy moiety could be modified with Ph_3P

as a removing group under the Mitsunobu reaction condition. In fact, formation of the hydroxy anion was expected to favor the 1,4-elimination, which would generate the 2-methylene-2*H*-pyran-3,4-dione **4**, a quinone methide-like species that would act as an effective Michael acceptor (Scheme 1). Contrary to our expectations, however, an unprecedented dimerization of **3** with dehydration occurred preferentially under the Mitsunobu reaction conditions. In the current study, we also investigated the unique dimerization mechanism of **3**.

(Scheme 1)

2. Results and discussion

2.1. Mitsunobu 1,4-elimination of the KA analog 3

The primary hydroxy group of KA was selectively protected with the tetrahydropyranyl (THP) group implementing the previously described method.[14] An additional hydroxymethyl moiety was introduced at the C-6 carbon of **2** *via* an aldol condensation with formaldehyde under basic conditions.[4] A Mitsunobu 1,4-elimination of the diol **3** was then attempted to try and obtain the quinone methide-like **4**. For this purpose, to a CH_2Cl_2 solution of **3** and Ph_3P (1.2 equiv), was added a DIAD solution (40% in toluene, 1.2 equiv) at 0 °C, and the resulting mixture was stirred for 1 h at room temperature. The mixture was then concentrated *in vacuo* and ethyl acetate (EtOAc) was added to the residue thus obtained. A yellow precipitate was generated, which was also insoluble in water; it was isolated by filtration. The ^{1}H NMR spectrum of the yellow precipitate was similar to that of **2**, expect for the resonance signal due to H-6, which appeared at 7.86 ppm (Fig. 2). On the other hand, the ^{13}C NMR spectrum of the obtained product was characterized by the presence of 12 different resonance signals (see experimental section). Furthermore, the molecular formula of the yellow precipitate was estimated to be $C_{24}H_{28}O_{10}$ based on results from high-resolution electrospray ionization mass spectrometry (ESI–HRMS) analysis. This molecular formula is characterized by twice as many C, H, and O atoms as compound **4**. Therefore, it was thought that the obtained precipitate was a dimeric compound of **4** and that it was similar to **2**. In Fig. 3 is depicted the predicted structure of the said dimer(s), **5**. However, the compound **5** should be a diastereomeric/racemic mixture because the substrate **3** has a racemic THP-protecting group. Nevertheless, ^{1}H and ^{13}C NMR spectrometry data indicated the obtained yellow precipitate to be a single and symmetric molecule. In order to determine the structure of the yellow compound, a crystal structure analysis was attempted after the racemic THP groups of **5** were removed under acidic conditions. However, the deprotected derivative of **5** was insoluble in water and various organic solvents (i.e., $CHCl_3$, CH_2Cl_2, EtOAc, MeOH, and EtOH) and only slightly soluble in dimethyl sulfoxide (DMSO). Thus, no sufficient amounts of high-quality crystalline material were obtained to perform X-ray crystal structure analysis. Notably, however, the deprotected derivative of **5** was readily dissolved in a basic water solution. Evidence thus suggested that the compound had an acidic, KA-like structure. In fact, ^{1}H NMR spectrum of this compound was

also similar to the spectrum of KA (see experimental section).

(Figure 2)

(Figure 3)

Fortunately, the yellow precipitate **5** could be recrystallized from $CHCl_3$. Therefore, an X-ray crystal structure analysis of the obtained crystalline material was carried out. In Fig. 4 is reported the crystal structure of the yellow precipitate **5**. Although it was a disordered structure over three states of the racemic (*R*,*R*- or *S*,*S*-) and the meso (*S*,*R*-) compounds, the evidence pointed to a dimeric structure with a *trans*-configuration, as expected. Furthermore, both two carbonyl groups and the conjugated triene were found to be arranged linearly. Both the racemic and meso dimers are symmetric, and two THP groups of these compounds are far from the *trans*-type olefin moiety. Therefore, the two diastereomers of **5** were assumed to be indistinguishable by ^{1}H and ^{13}C NMR spectrometry. Notably, reaction of the diol **3** with 1.3 equiv of DIAD and Ph_3P in CH_2Cl_2 produced **5** as a precipitate after addition of EtOAc in 32–43% yield. On the other hand, it was difficult to purify the remaining dimers **5** in the filtrate, which included various byproducts, by silica gel chromatography. In order to improve the yield of this reaction, EtOAc was used as a solvent instead of CH_2Cl_2, because the dimers **5** displayed poor solubility in EtOAc. In these conditions, a yellow precipitate was generated immediately after addition of the solution of DIAD to the solution of **3** and Ph_3P, and the dimers **5** were readily isolated by filtration (54% yield). Based on the thin-layer chromatography (TLC) analyses performed on the filtrates, most of the dimers **5** had been removed from the reaction mixture. The effect of changing the dosages of the Mitsunobu reagents (DIAD and Ph_3P) from 1.1 to 1.6 equiv was also examined. The yield of **5** as a precipitate remained within the 41–54% range. In particular, when 1.3 or 1.4 equiv of the Mitsunobu reagents were utilized, a tendency to high yields (>50%) was detected. By contrast, the yield of **5** was affected by the rate of the addition of the DIAD solution. In the typical Mitsunobu reaction, DEAD or DIAD solutions are added to the reaction mixture slowly, so as to limit byproduct formation. In the present case, however, the yield of **5** decreased substantially (to 19–24%) when the DIAD solutions (1.3–1.4 equiv) were slowly added dropwise to the solution of **3** and Ph_3P. Probably, in the case of the slow addition of the DIAD solution, the dehydrated and extremely unstable compound **4**, which is quickly generated, would have the opportunity to engage in side-reactions, instead of yielding the dimerization product.

(Figure 4)

2.2. A possible dimerization mechanism of compound 3 under the Mitsunobu condition

Next, we have evaluated the mechanism through which the dimers **5** were generated from compound **3** under the Mitsunobu reaction conditions. The dehydrated compound **4** is expected to be produced as a result of the Mitsunobu 1,4-elimination, because the obtained dimers **5** have a newly formed carbon–carbon double bond. The quinone methide-like compound **4** could be regarded as an effective

Michael acceptor, because the 1,4-adducts of **4** with the nucleophiles could return to the stable aromatic structures. For example, Honda *et al*. reported that the proton-transfer-induced photocleavage reaction of 2-acetoxy-3-biphenylmethanol in MeOH gave 2-methoxy-3-biphenylmethanol *via* the production of a quinone methide intermediate form.[15]

On the other hand, the oxygen atom on the dihydropyran ring of **4** would act as an electron donor, so compound **4** would also behave as a nucleophile. A proposed dimeric mechanism is illustrated in Scheme 2. Although compound **4** has two enol ether moieties, the nucleophilicity of the C-5 carbon of **4** is thought to be reduced by the electron-withdrawing effect of the neighboring carbonyl group. In addition, the C-5 carbon of **4** is sterically hindered compared with the methylene moiety on the C-2 carbon. Thus, the enol ether moiety of **4** characterized by the lower steric hindrance would act as an electron donor and attack to the α,β-unsaturated carbonyl group of another molecule. After the intramolecular proton rearrangements of the dimeric intermediates, a *trans*-type double bond would be formed, and two vinyl alcohol moieties would be reproduced.

(Scheme 2)

The yield of a substitution product obtained using a weak nucleophile (pKa > 11) is known to be quite low under normal Mitsunobu conditions, because betaine is unable to deprotonate the nucleophile substantially.[8] In addition, a hydrazide adduct is mainly generated no nucleophiles are utilized in the Mitsunobu reaction. For example, Brown and co-workers reported the direct substitution of the allylic alcohol group by the reduced azodicarboxylate under nucleophile-excluded Mitsunobu conditions.[16] Frank and Roush showed that substantial amounts of the hydrazide coupling byproduct were produced in the Mitsunobu macrocyclization between an allylic hydroxy moiety and a carboxylate group.[17] Therefore, in the present system, significant amounts of the hydrazide adduct may have been generated in competition with the dimerization process of **4**. In order to confirm the existence of the hydrazide coupling byproduct **7**, ESI-MS analysis of the filtrate obtained after separating the dimers **5** (51% yield) was carried out (Fig. 5). Contrary to expectations, no significant peak attributable to the protonated (or Na^+-adducted) molecular ion peak of the hydrazide adduct **7** (calcd for $C_{20}H_{31}N_2O_3$, 443.2 or $C_{20}H_{30}N_2O_3Na$, 465.2) was observed. On the other hand, the substrate **3** was detected based on TLC analysis of the filtrate. In order to determine the amount of remaining substrate **3**, a chromatographic separation was carried out. It was difficult to separate the substrate **3** from the residue of the filtrate, therefore, **3** was isolated in mixture with Ph_3PO. Based on ^1H NMR analysis, the percentage of the unreacted **3** was estimated to be about 12% of the initial amount.

(Figure 5)

Next, we ascertained whether a group endowed with steric hindrance located on the terminal alkene carbon could inhibit the proposed dimerization reaction. A 1-hydroxypropyl moiety was introduced at the C-6 carbon of **2** *via* an aldol condensation with 1-propanal in the presence of DABCO.[6] The same

Mitsunobu reaction (solvent: EtOAc) was tried using the aldol condensation product **8** as substrate (Scheme 3). Contrary to the case of **3**, no precipitate was observed after addition of DIAD to the mixed solution of **8** and Ph_3P. After removing the solvent, a chromatographic separation of the main product was tried. Separation of the main product from the byproduct Ph_3PO was difficult to achieve; therefore, the yield of the product could not be accurately determined. The ^1H NMR and MS analyses indicated that the main products of the reaction were probably hydrazide adducts **10** (>50%, diastereomeric/racemic mixture). The steric hindrance around the methylene moiety of **9** by the existence of the ethyl group is thought to suppress the dimerization reaction. Interestingly, the hydrazide adducts **10** were observed to be the main reaction product, although no significant amount of the corresponding adduct **7** was observed when **3** was used as substrate of the Mitsunobu reaction. In the latter reaction, the nucleophilicity of **4** is predicted to be higher than that of the DIAD reductant, so that the dimer(s) **5** would be generated preferentially over adduct **7**.

(Scheme 3)

2.3. Mitsunobu dimerization of other kojic acid analogs

We attempted the Mitsunobu dimerization reaction using another KA analog, *tert*-butyl ((5-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)methyl)carbamate (**15**) as substrate, which is characterized by the presence of a bulky and achiral *tert*-butyloxycarbonyl (Boc) group. The synthesis of the *N*-Boc-KA analog **15** was accomplished in five steps starting from KA (Scheme 4). A primary hydroxy group of KA was substituted with a chloro group, which was subsequently substituted with an azide moiety.[18] A Staudinger reaction between Ph_3P and the kojic azide **12**, followed by hydrolysis and acidification, provided the kojic amine HCl salt **13** in 68% yield. In the case of the amino protection of **13** using Boc_2O and triethylamine in CH_2Cl_2, the *N*,*O*-diBoc-compound was mainly produced rather than the desired *N*-Boc-compound **14**. Therefore, the selective protection of the amino group of **13** was implemented according to the literature's method, which consists of an *N*-Boc protection of 4-hydroxybenzylammonium bromide.[19] When the HCl salt **13** was made to react with Boc_2O (1.1 equiv) in a methanolic suspension of $NaHCO_3$, a small amount of *N*,*O*-diBoc-compound was also observed to be produced by TLC analysis. However, the diBoc-byproduct was hydrolyzed to the *N*-Boc-compound **14** following additional treatment with 1 M NaOH solution;[20] notably, **14** was obtained in 68% yield. A hydroxymethyl moiety was introduced on the C-6 carbon of **14** implementing the same aldol reaction described above (yield: 76%).

(Scheme 4)

The obtained compound **15** exhibited low solubility in EtOAc, so the Mitsunobu dimerization reaction of **15** was carried out at room temperature. A yellow precipitate was generated also in this reaction, and the reaction product was also presumed to be the dimeric compound **16** based on the

results of ^{1}H NMR and MS analyses (yield: 51–57%). No X-ray crystal structure analysis of **16** was carried out, because **16** was insoluble with various organic solvents (i.e., $CHCl_3$, CH_2Cl_2, EtOAc, MeOH, and EtOH) and hardly soluble in DMSO. The cluster ion peak at *m/z* 1035.4 ($[2M+Na]^+$) was observed beside the molecular ion peak at *m/z* 529.2 ($[M+Na]^+$) by the ESI–MS pattern of the DMSO solution of **16** (Fig. 6). On the other hand, this signal diminished greatly in intensity in the case of the deprotected compound **17** (analyzed in H_2O). Probably, compound **16** forms an aggregate in DMSO by intermolecular π-π stacking interaction.

(Figure 6)

We also tried the Mitsunobu dimerization reaction using the KA analog, 3-hydroxy-2-(hydroxymethyl)-6-((prop-2-ynyloxy)methyl)-4*H*-pyran-4-one (**21**). This compound has a propargyl moiety which facilitates to introduce various functional groups by click reaction. The synthesis of the alkynyl compound **21** was accomplished in four steps from KA (Scheme 5). Firstly, selective protection of the enolic hydroxy group of KA was carried out using 4-methoxybenzyl chloride (PMBCl) in the presence of K_2CO_3 according to the previous report.[21] Subsequent treatment of **18** with two equimolar amounts of sodium hydride and 3-bromo-1-propyne provided the propargyl ether **19** in 61% yield. The PMB group of **19** was removed by the treatment with trifluoroacetic acid (TFA). A hydroxymethyl moiety was introduced on the C-6 carbon of **20** by the same aldol reaction described above (77%). The obtained compound **21** also showed a low solubility in EtOAc. Therefore, the Mitsunobu dimerization reaction of **21** was also carried out at room temperature. Orange precipitate was generated in this reaction, and the ^{1}H NMR spectrum of the reaction product **22** was similar to those of compounds **5** and **16** (Supplementary material: S3, S11 and S16). However, the ESI–HRMS analysis of **22** showed the unknown ion peak at *m/z* 645.2 between the molecular ion peak of the dimerized product **22** (*m/z* 407.1, $[M+Na]^+$) and the cluster ion peak (*m/z* 791.1, $[2M+Na]^+$, Fig. 7). From the ^{1}H and ^{13}C NMR analyses, the obtained product was a single and symmetric molecule as well as compounds **5** and **16** (Supplementary material: S16 and S17). Probably, the unidentified ion appeared at *m/z* 645.2 would be a cluster ion of one molecule (M) and its fragment ion ($[M–123]^+$, or $[M–146+Na]^+$), although the structure of the fragment is unknown. Therefore, the obtained product **22** is the dimeric compound as well as compounds **5** and **16** (yields: 41–47%). The obtained **22** was also hardly soluble in various organic solvents (i.e., $CHCl_3$, CH_2Cl_2, EtOAc, MeOH, and EtOH), except for DMSO. It is thought that the poor solubilities of these achiral dimeric products **16** and **22** are due to the strong intermolecular π-π stacking. As both two dimeric products are symmetric molecules, there is no effectual method to determine the configurations of the newly formed carbon-carbon double bonds of them except for X-ray crystal structure analysis. However, the configurations of the olefin moieties of both two compounds are expected to be a *trans*-configuration because a *trans*-type double bond would be generated preferentially during the expected intramolecular proton rearrangements of

the dimeric intermediates (Scheme 2). Furthermore, the resulting planar structures are advantageous to construct the strong intermolecular π-π stacking. It is thought that more bulky moiety than the THP-protected group, for example, 1-adamantyl group, is needed for the substrate to enhance the solubility of the resulting dimeric compounds and to obtain the high-quality crystalline materials.

(Scheme 5)

(Figure 7)

3. Conclusions

We attempted to perform a Mitsunobu 1,4-elimination reaction using the KA analog **3** as substrate, which is characterized by a hydroxymethyl moiety on the C-6 carbon; however, we were unable to isolate the desired quinone methide-like product **4**. Alternatively, we identified a novel one-pot dimerization reaction starting from the diol **3** occurring under the Mitsunobu reaction conditions. This unique reaction is likely to go through two major steps: (i) intramolecular dehydration of **3** by the Mitsunobu reagents, and (ii) homocoupling of the dehydration product **4** to form a new *trans*-carbon–carbon double bond. Therefore, this reaction can be defined as a "Mitsunobu homocoupling". Purification of the Mitsunobu reaction products from the reaction mixture, including the two main byproducts, phosphine oxides and dialkylhydrazine 1,2-dicarboxylates, is generally hard to achieve. However, implementation of the hereby developed synthetic approach readily afforded the dimeric products as a precipitate, upon selection of a suitable solvent. Although the reaction yields were not high, our findings are of interest for the unique, transient-metal-free homocoupling reaction under mild conditions.

4. Experimental

All materials were obtained commercially (guaranteed reagent grade) and used without further purification. CH_2Cl_2 was distilled from CaH_2 under nitrogen gas atmosphere before use. Super dehydrated EtOAc and tetrahydrofuran (THF) were purchased from Fujifilm Wako Chemicals. Column chromatography was performed on silica gel (Wakogel® C-300, Fujifilm Wako Chemicals). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANS 300N spectrometer.

4.1. 3-Hydroxy-2-(hydroxymethyl)-6-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-4*H*-pyran-4-one (3).

The aldol reaction of 5-hydroxy-2-[(tetrahydropyranyloxy)methyl]-4-pyrone (**2**)[14] with a formaldehyde was carried out referring to Farard's method.[4] Briefly, sodium hydroxide (550 mg, 13.8 mmol) was dissolved with distilled water (20 mL). To the just prepared sodium hydroxide solution was added compound **2** (3.00 g, 13.3 mmol). The pH value of the solution thus obtained was adjusted

to 10.5 using 1 M NaOH and 1 M HCl. A solution of 37% formaldehyde (1.1 mL, 1.1 equiv) was then added slowly to the reaction solution, and the mixture thus obtained was stirred overnight at room temperature. The resulting mixture was neutralized with 1 M HCl and then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. To the organic layer was then added *n*-hexane, which prompted the precipitation of a crystalline solid, which was recrystallized from an EtOAc–*n*-hexane to afford **3** (1.97 g, 58%) as a colorless solid; mp 71 °C; IR (KBr) 3383, 3251, 1658, 1620, 1584, 1231, 1143 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 6.55 (s, 1 H), 4.74 (t, J = 3.4 Hz, 1 H), 4.71 (s, 2 H), 4.57 (dd, J = 0.57, 14.7 Hz, 1 H), 4.39 (d, J = 0.57, 14.7 Hz, 1 H), 3.77-3.89 (m, 1 H), 3.51-3.61 (m, 1 H), 1.47-1.95 (m, 6 H); HRMS (ESI) calcd for $C_{12}H_{16}O_6Na$, $[M+Na]^+$ 279.0845; found, 279.0852.

4.2. (*E*)-6,6'-(Ethene-1,2-diyl)bis(5-hydroxy-2-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-pyran-4-one) (5)

To a stirred solution of **3** (400 mg, 1.56 mmol) and Ph_3P (532 mg, 1.3 equiv) in dry EtOAc (20 mL), diisopropyl azodicarboxylate (40% in toluene, 1.03 g, 1.3 equiv) was added quickly under N_2 atmosphere at 0 °C. Upon addition, the color of the solution changed from pale brown to dark brown, and a yellow precipitate was immediately generated. After completing the addition of DIAD, the reaction mixture was stirred for 1 h at room temperature. The mentioned yellow residue was then collected by filtration and was washed with EtOAc until the filtrate was colorless. The residue was dried under reduced pressure to yield the dimeric compounds **5** (202 mg, 54%); mp 325 °C (decomp.); IR (KBr) 3220, 1645, 1618, 1584, 1441, 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 7.32 (s, 2 H), 6.56 (s, 2 H), 4.78 (t, 2 H, J = 3.0 Hz), 4.66 (dd, 2 H, J = 0.8, 14.9 Hz), 4.47 (dd, 2 H, J = 0.5, 14.9 Hz), 3.81-3.95 (m, 2 H), 3.55-3.67 (m, 2 H), 1.51-1.95 (m, 12 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 137.9, 163.7, 144.8, 143.5, 118.1, 111.0, 98.2, 64.7, 61.7, 30.3, 25.2, 19.1; HRMS (ESI) calcd for $C_{24}H_{28}O_{10}Na$, $[M+Na]^+$ 499.1580; found, 499.1577.

4.3. (*E*)-6,6'-(Ethene-1,2-diyl)bis(5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one) (6)

The dimers **5** (200 mg, 0.42 mmol) were dissolved in 60 mL of the mixed solvent $CHCl_3$–MeOH (2:1); subsequently, conc. hydrochloric acid (125 μL) was added to the obtained solution. The resulting mixture was stirred for 1 h at room temperature. It was then concentrated under reduced pressure, and the resulting residue was dispersed in CH_2Cl_2 and filtered. The yellow solid thus isolated was washed with CH_2Cl_2 and dried to give **6** (129 mg, quantitative); mp 314 °C (decomp.); IR (KBr) 3160, 1646, 1625, 1582, 1444, 1252, 1089 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6); δ 9.97 (brs, 2 H), 7.27 (s, 2 H), 6.35 (s, 2 H), 5.78 (t, J = 6.0 Hz, 2 H), 4.39 (d, J = 6.0 Hz, 4 H), the spectrum was similar to that of KA expect for the resonance signal due to H-6 (7.27 ppm) [lit.[22] (KA in DMSO-d_6); δ 9.06 (s, 1 H, OH), 8.02 (s, 1 H, H-6), 6.33 (s, 1 H, H-3), 5.67 (s, 1 H, OH), 4.28 (s, 2 H, -CH_2-)]; HRMS (ESI) calcd

for $C_{14}H_{12}O_8Na$, $[M+Na]^+$ 331.0430; found, 331.0435.

4.4. 3-Hydroxy-2-(1-hydroxypropyl)-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-pyran-4-one (8)

The aldol reaction of **2** with 1-propanal was carried out referring to the published literature.[6] Briefly, to a mixture of **2** (1.85 g, 8.18 mmol) and 1-propanal (704 μL, 1.2 equiv) in dioxane:H_2O (1:1, 20 mL), DABCO (1.10 g, 1.2 equiv) was added, and the resulting mixture was stirred at room temperature for 2 days. Saturated saline was then added to the reaction mixture, and the resulting mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography using *n*-hexane–EtOAc (1:5) as eluent, and it was recrystallized from EtOAc–*n*-hexane to afford **8** as a colorless solid (1.20 g, 52%); mp 86 °C: IR (KBr) 3275, 2937, 1653, 1623, 1593, 1457, 1365, 1208, 969 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.54 (s, 1 H), 4.85 (t, *J* = 7.2 Hz, 1 H), 4.73 (dd, *J* = 3.4, 7.0 Hz, 1 H), 4.56 (dd, *J* = 0.76, 14.7 Hz, 1 H), 4.39 (dd, *J* = 0.56, 14.7 Hz, 1 H), 3.77-3.89 (m, 1 H), 3.51-3.61 (m, 1 H), 2.63 (brs, 1 H), 1.49-1.99 (m, 8 H), 0.99 (t, *J* = 7.4 Hz, 3 H); HRMS (ESI) calcd for $C_{14}H_{20}O_6Na$, $[M+Na]^+$ 307.1158; found, 307.1162.

4.5. Diisopropyl 1-(1-(3-hydroxy-4-oxo-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-pyran-2-yl)propyl)hydrazine-1,2-dicarboxylate (10)

The Mitsunobu reaction was carried out as described for the preparation of the dimers **5**, using **7** (222 mg, 0.78 mmol), Ph_3P (287 mg, 1.4 equiv) and DIAD (40% in toluene, 552 mg, 1.4 equiv) in dry EtOAc (10 mL). After stirring the reaction solution for 1 h at room temperature, the solvent was removed by rotary evaporation. Diethyl ether was then added to the residue, and the resulting mixture was cooled in and ice-bath. After removing the large precipitate of Ph_3PO by filtration, the organic layer was concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography ($CHCl_3$, then $CHCl_3$:MeOH = 30:1, as eluents) to afford the hydrazide adducts **10** (diastereomeric/racemic mixture) as a pearl yellow oil (182 mg, 50%); IR (NaCl) 3280, 1714, 1630, 1112, 1037 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.78 (brs, 1 H), 6.66 (brs, 1 H), 6.48 (d, *J* = 9.3 Hz, 1 H), 5.20-5.44 (m, 1 H), 4.85-5.08 (m, 2 H), 4.66-4.75 (m, 1 H), 4.52 (dd, *J* = 5.5, 14.4 Hz, 1 H), 4.39 (t, *J* = 14.4 Hz, 1 H), 3.77-3.89 (m, 1 H), 3.51-3.61 (m, 1 H), 1.48-2.08 (m, 8 H), 1.10-1.42 (m, 12 H), 1.02 (t, *J* = 7.2 Hz, 3 H); HRMS (ESI) calcd for $C_{22}H_{34}N_2O_9Na$, $[M+Na]^+$ 493.2162; found, 493.2163.

4.6. 2-(Aminomethyl)-5-hydroxy-4*H*-pyran-4-one hydrochloride (13)

To a stirred solution of 2-(azidomethyl)-5-hydroxy-4*H*-pyran-4-one **12**[18] (3.60 g, 21.5 mmol) in dry THF (50 mL), Ph_3P (8.48 g, 1.5 equiv) was added slowly at 0 °C. The mixture thus obtained was stirred for 10 min at 0 °C. H_2O (1.92 mL) was then added dropwise to the resulting solution, which

was stirred overnight at 55 °C. The solution was concentrated under reduced pressure and then acidified with 1 M HCl (60 mL). The water layer was then extracted several times with CH_2Cl_2 to remove the byproduct Ph_3PO. The water layer was concentrated under reduced pressure, and the solid thus obtained was recrystallized from H_2O–ethanol to afford **13** (2.48 g, 65%) as a brown solid; mp 222 °C (decomp.); IR (KBr) 3252, 3069, 3019, 1655, 1627, 1592, 1552, 1526, 1449, 1387, 1217, 934, 897, 876, 768 cm^{-1}; ^{1}H-NMR (300 MHz, D_2O) δ: 8.16 (s, 1 H), 6.68 (s, 1 H), 4.22 (s, 2 H); HRMS (ESI) calcd for $C_6H_8NO_3$, $[M-Cl]^+$ 142.0504; found, 142.0487.

4.7. *tert*-Butyl ((5-hydroxy-4-oxo-4*H*-pyran-2-yl)methyl)carbamate (14)

Boc protection of the amino group of **13** was carried out according to the *N*-Boc protection method of 4-hydroxybenzylammonium bromide.[19] Briefly, the HCl salt **13** (400 mg, 2.25 mmol) was suspended in dry MeOH (20 mL) and then $NaHCO_3$ (757 mg, 4 equiv) was subsequently added to the suspension. Boc_2O (540 mg, 1.1 equiv) was added to the mixture, and the resulting mixture was stirred overnight at room temperature. 1 M NaOH (22.5 mL, 10 equiv) was added to the resulting solution to hydrolyze the carbonate byproduct.[20] After stirring for 1 h at room temperature, the pH of the mixture was adjusted to 4–5 using 1 M HCl; the mixture was then extracted with EtOAc. Subsequently, the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was crystallized by adding *n*-hexane to it, and recrystallized from $CHCl_3$–*n*-hexane to afford **14** (372 mg, 68%) as a colorless solid; mp 113 °C; IR (KBr) 3385, 3279, 1688, 1650, 1625, 1600, 1587, 1520, 1464, 1392, 1368, 1270, 1216, 1170, 940, 927, 884, 727 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.82 (s, 1 H), 6.43 (s, 1 H), 5.04 (brs, 1 H), 4.19 (d, J = 6.0 Hz, 2 H), 1.74 (brs, 1 H), 1.46 (s, 9 H); HRMS (ESI) calcd for $C_{11}H_{15}NO_5Na$, $[M+Na]^+$ 264.0848; found, 264.0855.

4.8. *tert*-Butyl ((5-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl)methyl)carbamate (15)

NaOH (105 mg, 2.63 mmol) was dissolved with distilled water (6 mL), and compound **14** (600 mg, 2.49 mmol) was added to the solution thus obtained. The pH of the resulting solution was adjusted to 10.5 using 1 M NaOH and 1 M HCl. A solution of 37% formaldehyde (238 µL, 1.3 equiv) was added slowly to the solution, and the obtained mixture was stirred overnight at room temperature. The resulting mixture was acidified with 1 M HCl and then extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was purified by silica gel chromatography using first $CHCl_3$–MeOH (10:1) and then $CHCl_3$–MeOH (8:1) as eluents; it was then recrystallized from $CHCl_3$–*n*-hexane to afford the aldol adduct **15** (516 mg, 76%) as a colorless solid; mp 144 °C; IR (KBr) 3330, 1684, 1618, 1591, 1532, 1286, 1235, 1162, 1011, 963, 864, 763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 6.39 (s, 1 H), 5.14 (brs, 1 H), 4.69 (s, 1 H), 4.20 (d, J = 6.1 Hz, 2 H), 1.67 (brs, 2 H), 1.46 (s, 9 H); HRMS (ESI) calcd for $C_{12}H_{17}NO_6Na$, $[M+Na]^+$ 294.0954; found, 294.0954.

4.9. Di-*tert*-butyl ((ethene-1,2-diylbis(5-hydroxy-4-oxo-4*H*-pyran-6,2-diyl))bis(methylene))(*E*)-dicarbamate (16)

To a stirred solution of **15** (100 mg, 0.369 mmol) and Ph_3P (126 mg, 1.3 equiv) in dry EtOAc (5 mL), DIAD (40% in toluene, 242 mg, 1.3 equiv) was added quickly under N_2 atmosphere at room temperature. The mixture thus obtained was then stirred for 1 h at room temperature; a yellow precipitate appeared as a result, which was collected by filtration. The precipitate was washed with EtOAc and dried to give the dimeric compound **16** (53 mg, 57%); mp 255 °C (decomp.); IR (KBr) 3365, 3189, 1689, 1639, 1624, 1592, 1518, 1442, 1241, 1168, 983, 951, 774 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6); δ, 10.02 (brs, 2 H, exchanged with D_2O), 7.58 (t, J = 5.9 Hz, 2 H, exchanged with D_2O), 7.27 (s, 2 H), 6.20 (s, 2 H), 4.08 (d, J = 5.9 Hz, 2 H), 1.40 (s, 18 H); HRMS (ESI) calcd for $C_{24}H_{30}N_2O_{10}Na$, $[M+Na]^+$ 529.1798; found, 529.1787.

4.10. (*E*)-6,6'-(Ethene-1,2-diyl)bis(2-(aminomethyl)-5-hydroxy-4*H*-pyran-4-one) dihydrochloride (17)

The dimeric compound **16** (40 mg, 0.079 mmol) was suspended in H_2O–MeOH (1:1, 10 mL), and a 4 M solution of HCl (0.8 mL) was added to the said suspension. The mixture thus obtained was stirred for 4 days at room temperature. It was subsequently concentrated and dried to yield **17** (28 mg, 93%) as a yellow solid; mp 262 °C (decomp.); IR (KBr) 3189, 3064, 3034, 1647, 1620, 1585, 1505, 1469, 1442, 1369, 1340, 1246, 959, 773 cm^{-1}; ^1H NMR (300 MHz, D_2O); δ 7.57 (s, 2 H), 6.66 (s, 2 H), 4.29 (s, 4 H); HRMS (ESI) calcd for $C_{14}H_{15}N_2O_6$, $[M-2HCl+H]^+$ 307.0930; found, 307.0928.

4.11. 5-((4-Methoxybenzyl)oxy)-2-((prop-2-yn-1-yloxy)methyl)-4*H*-pyran-4-one (19)

To a stirred solution of 2-(Hydroxymethyl)-5-(4-methoxybenzyloxy)-4*H*-pyran-4-one **18**[21] (300 mg, 1.14 mmol) in dry DMF (15 mL), a suspension of sodium hydride (60% dispersion, washed with *n*-hexane before use, 92 mg, 2 equiv) in dry DMF (6 mL) was added at 0 °C. The mixture was stirred for 30 minutes under N_2 atmosphere at 0 °C. 3-Bromo-1-propyne (273 mg, 2 equiv) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. The solvent was concentrated under reduced pressure, and then 1 M citric acid was added to the residue. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography using $CHCl_3$ as eluents to afford **19** as a blown oil (210 mg, 61%); IR (NaCl) 2116, 1651, 1613, 1515, 1250 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ: 7.52 (s, 1 H), 7.30 (d, J = 8.7 Hz, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 6.47 (s, 1 H), 5.01 (s, 2 H), 4.37 (s, 2 H), 4.23 (d, J = 2.5 Hz, 2 H), 3.80 (s, 3 H), 2.50 (t, J = 2.5 Hz, 1 H); HRMS (ESI) calcd for $C_{17}H_{16}O_5Na$, $[M+Na]^+$ 323.0895; found, 323.0912.

4.12. 5-Hydroxy-2-((prop-2-yn-1-yloxy)methyl)-4*H*-pyran-4-one (20)

To a stirred solution of **19** (155 mg, 0.516 mmol) in dry CH_2Cl_2 (1.8 mL), TFA (302 µL, 10 equiv) was added at room temperature. The resulting mixture was stirred for 2 h at room temperature. The solvent and excess TFA were removed under reduced pressure and the residue was purified by silica gel chromatography using first $CHCl_3$ and then $CHCl_3$–MeOH (20:1) as eluents to afford **20** as a pale blown solid (64 mg, 69%); mp 91 °C; IR (KBr) 3230, 2115, 1657, 1630 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.85 (s, 1 H), 6.56 (s, 1 H), 4.44 (s, 2 H), 4.27 (d, J = 2.5 Hz, 2 H), 2.53 (t, J = 2.5 Hz, 1 H); HRMS (ESI) calcd for $C_9H_8O_4Na$, $[M+Na]^+$ 203.0320; found, 203.0318.

4.13. 3-Hydroxy-2-(hydroxymethyl)-6-((prop-2-ynyloxy)methyl)-4*H*-pyran-4-one (21).

Sodium hydroxide (23 mg, 0.57 mmol) was dissolved with distilled water (3 mL). Compound **20** (101 mg, 0.56 mmol) was added to the solution and dissolved. The pH value of the mixture was adjusted to 10.5 using 1 M NaOH and 1 M HCl solutions. A solution of 37% formaldehyde (0.17 mL) was added to the mixture and stirred overnight at room temperature. The resulting mixture was neutralized with 1 M HCl and then extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography using $CHCl_3$–MeOH (10:1) as eluents to give **21** (91 mg, 77%) as a pale blown solid; mp 101 °C; IR (KBr) 3265, 2114, 1656, 1620, 1578, 1334, 1122 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 9.12 (brs, 1 H), 6.37 (s, 1 H), 5.42 (brs, 1 H), 4.41 (d, *J* = 2.2 Hz, 2 H), 4.39 (s, 2 H), 4.26 (d, J = 2.4 Hz, 2 H), 3.56 (t, J = 2.4 Hz, 1 H); HRMS (ESI) calcd for $C_{10}H_{10}O_5Na$, $[M+Na]^+$ 233.0426; found, 233.0432.

4.14. (*E*)-6,6'-(Ethene-1,2-diyl)bis(5-hydroxy-2-((prop-2-yn-1-yloxy)methyl)-4*H*-pyran-4-one) (22)

To a stirred solution of **21** (30.0 mg, 0.143 mmol) and Ph_3P (52.5 mg, 1.4 eq) in dry EtOAc (1.8 mL), DIAD (40% in toluene, 101 mg, 1.4 equiv) was added quickly under N_2 atmosphere at room temperature. The mixture was stirred for 1 h at room temperature and the precipitate was collected by filtration. The orange precipitate was washed with EtOAc and dried to give the dimeric compound **22** (12.8 mg, 47%); mp 197 °C (decomp.); IR (KBr) 3228, 2117, 1645, 1618, 1583, 1246, 1119 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6); δ, 10.12 (brs, 2 H), 7.25 (s, 2 H), 6.41 (s, 2 H), 4.49 (s, 4 H), 4.29 (d, *J* = 2.5 Hz, 4 H), 3.54 (t, *J* = 2.5 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.5, 162.4, 144.5, 143.2, 117.9, 111.2, 79.6, 78.2, 67.1, 57.8; HRMS (ESI) calcd for $C_{20}H_{16}O_8Na$, $[M+Na]^+$ 407.0743; found, 407.0750.

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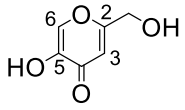

Figure 1. Structure of kojic acid (KA).

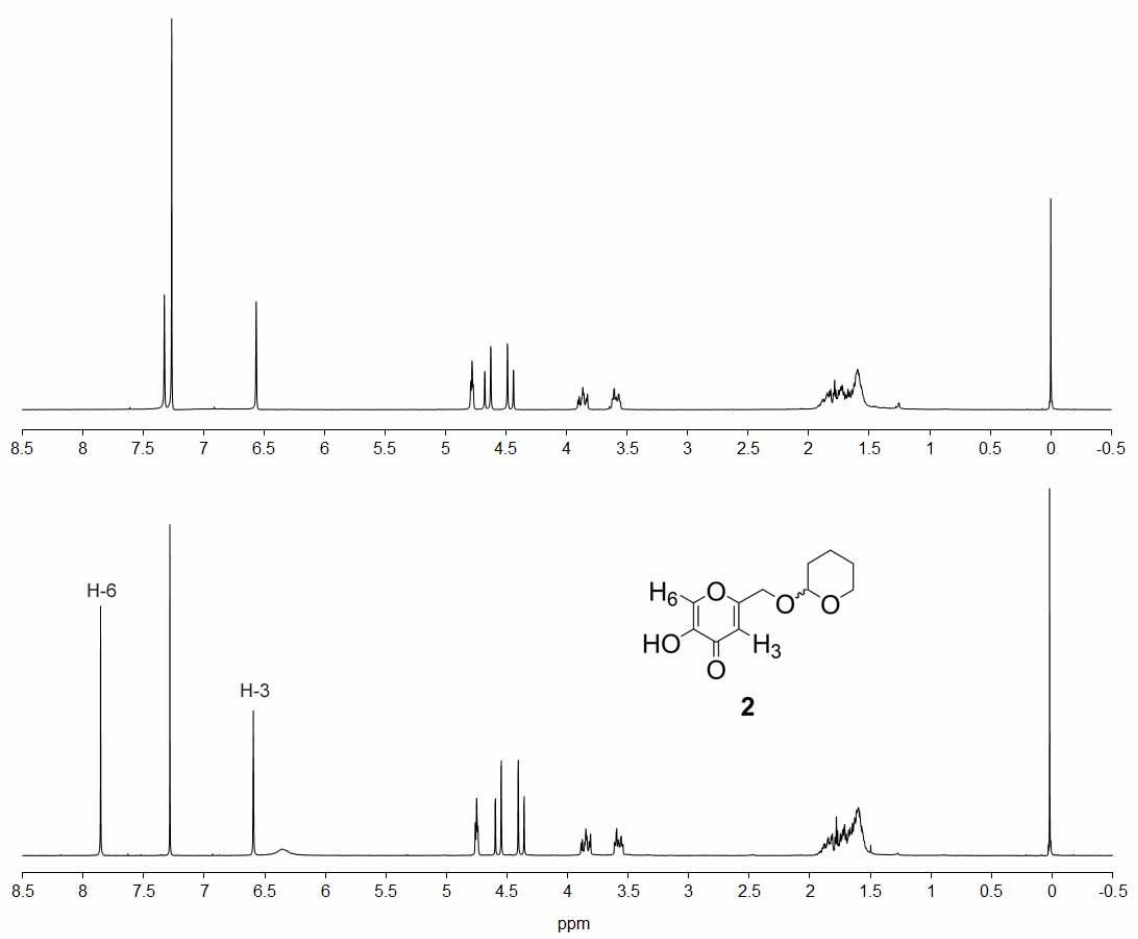

Figure 2. ^{1}H NMR spectra of the Mitsunobu elimination product (upper panel) and the tetrahydropyranyl (THP)-protected derivative of kojic acid (**2**, lower panel) in $CDCl_3$.

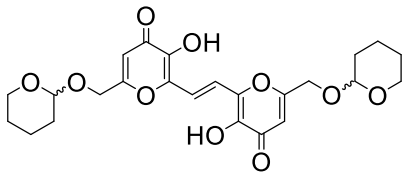

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Figure 3. Predicted structures (diastereomeric/racemic mixture) of the Mitsunobu elimination products.

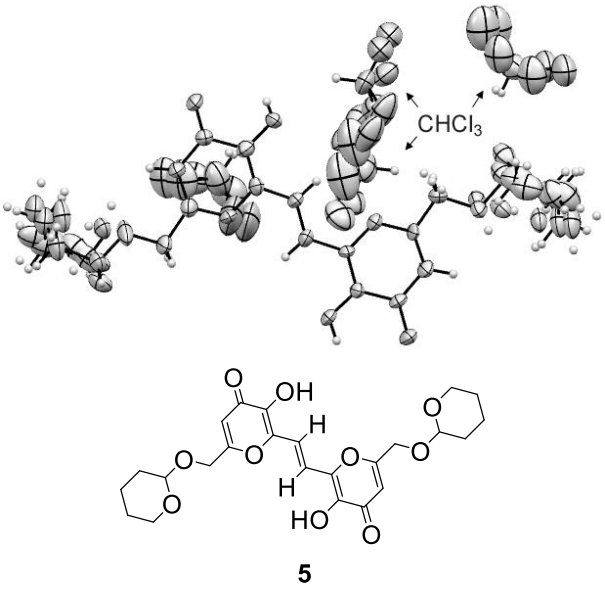

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Figure 4. X-ray diffraction-determined crystal structure of products **5** obtained by the Mitsunobu elimination reaction of **3**.

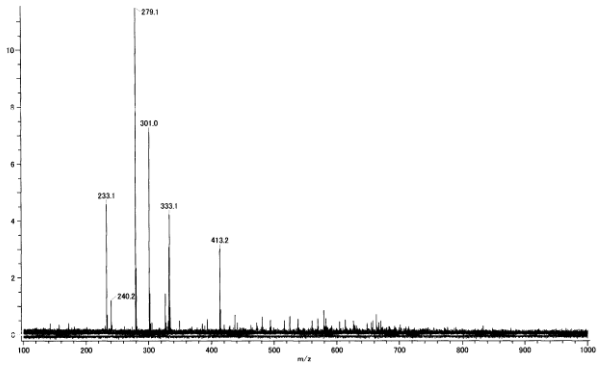


Figure 5. Electrospray ionization mass spectrum of the residue obtained after removing the dimers **5** by filtration. The solvent was removed, and the sample was prepared by dissolving the obtained residue in MeOH. The peaks at m/z 301.1 and 333.1 were ascribed to the Na^+ adducts of Ph_3PO or Ph_3PO with MeOH. The peak at m/z 279.1 was ascribed to the H^+ adducts of Ph_3PO or the Na^+ adduct of unreacted **3**.

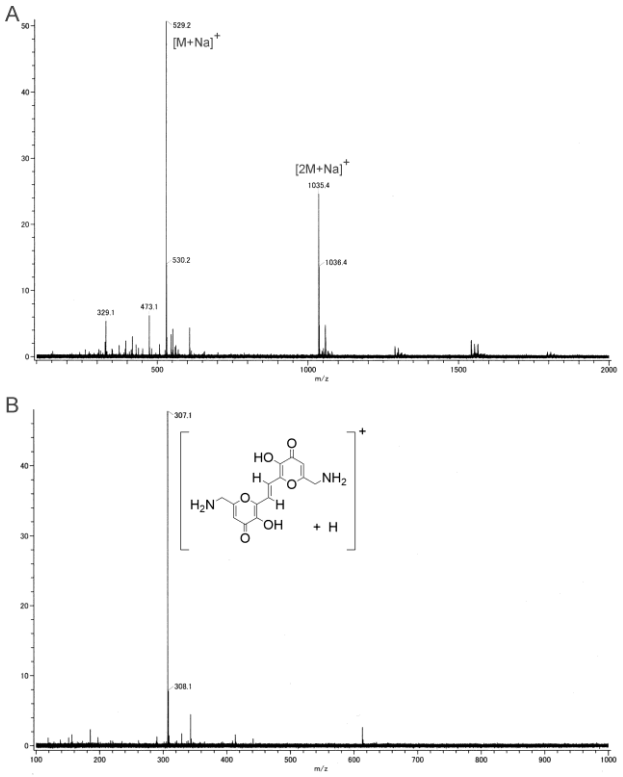


Figure 6. Electrospray ionization mass spectra of compound **16** (A, dissolved in DMSO) and compound **17** (B, dissolved in H_2O).

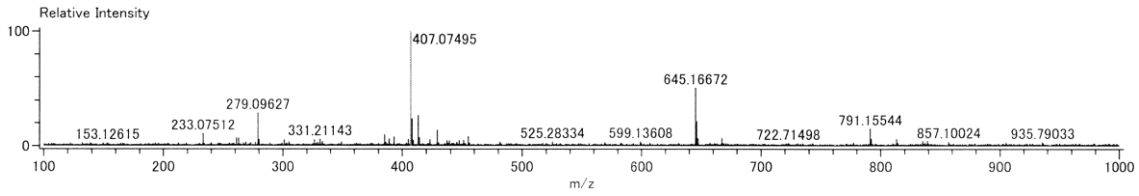
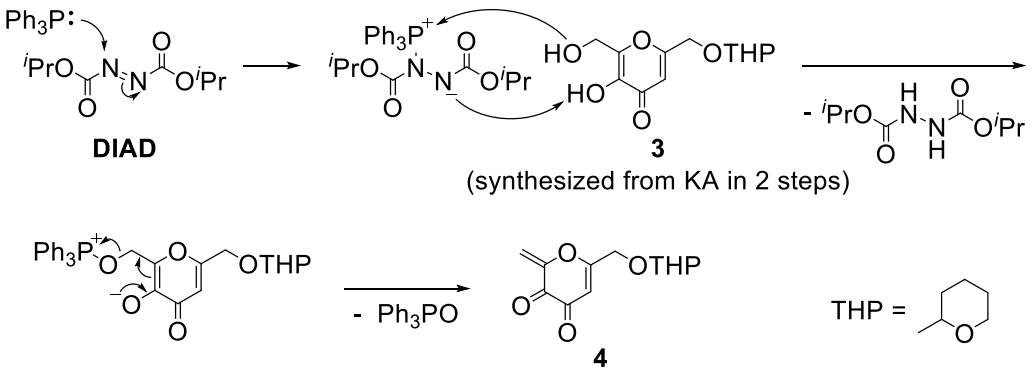
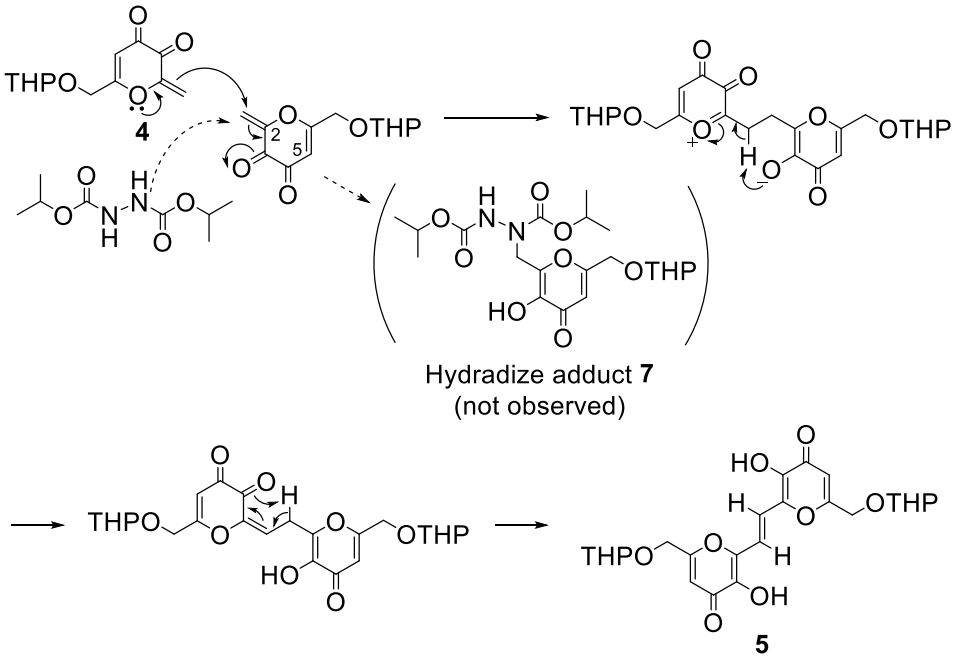


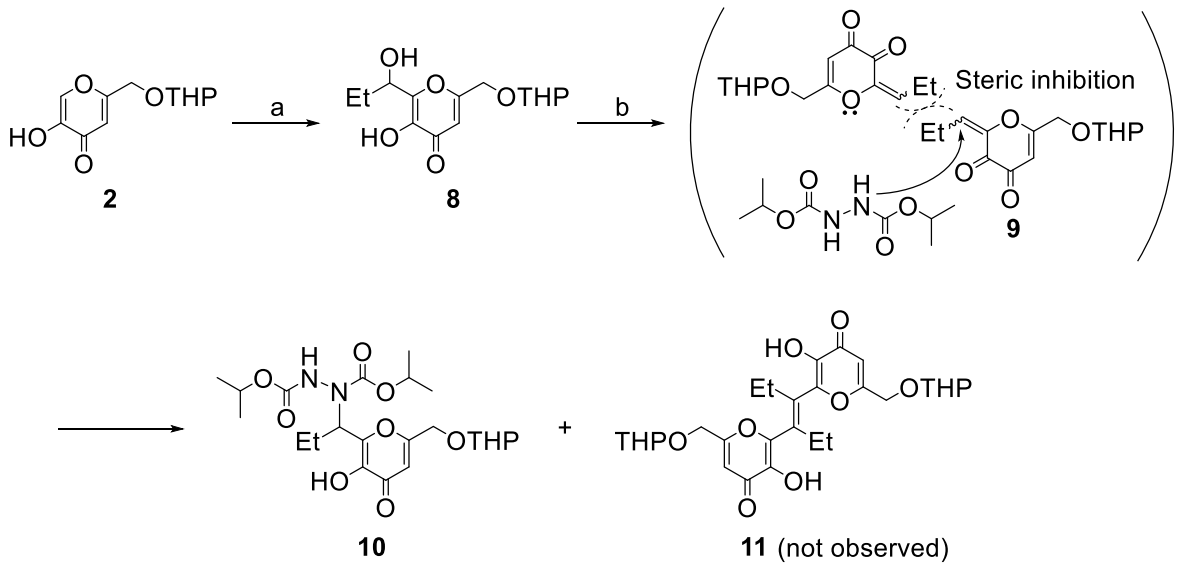
Figure 7. High-resolution electrospray ionization mass spectrum of compound **22**.



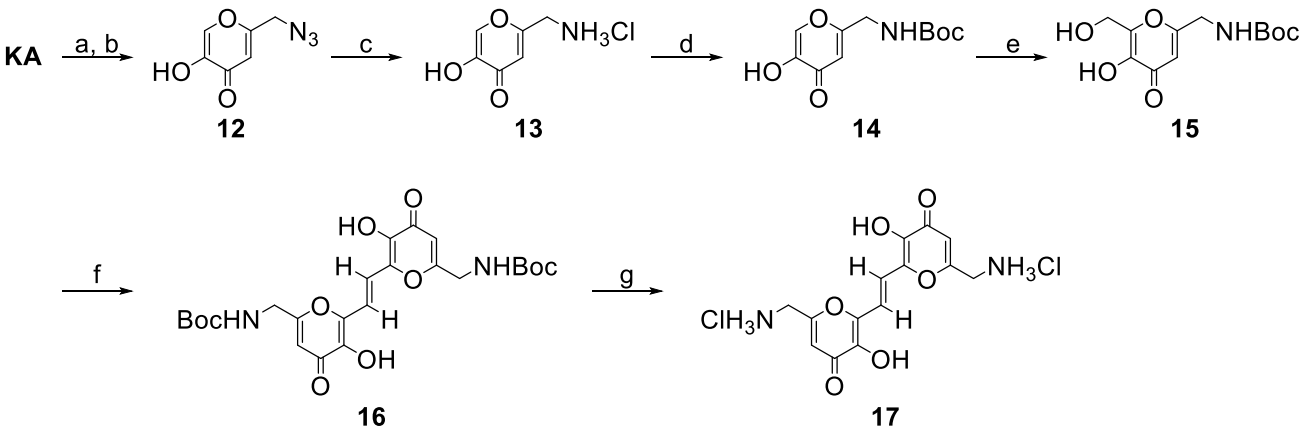
Scheme 1. Proposed mechanism of the Mitsunobu 1,4-elimination of KA analog **3**.



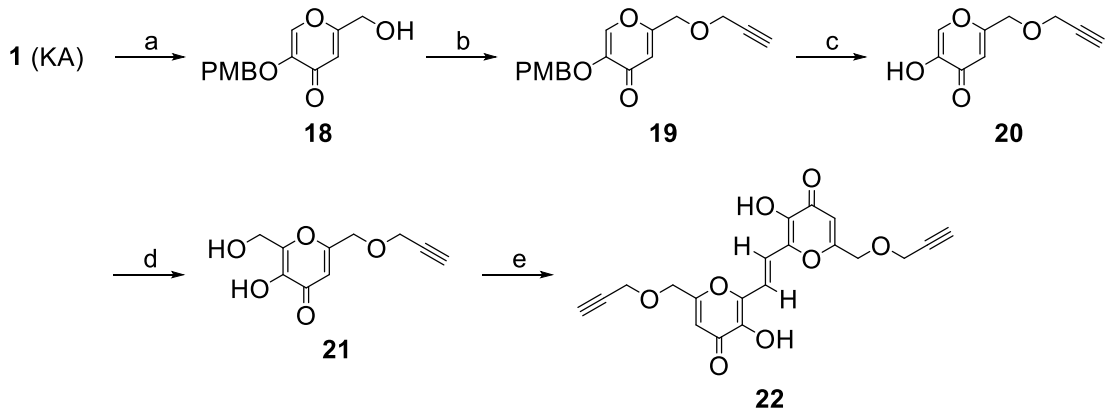
Scheme 2. Predicted mechanism of the dimerization of **4** generated by the Mitsunobu 1,4-elimination of **3**.



Scheme 3. Reagents and conditions: (a) 1-Propanal, DABCO, 1,4-dioxane–H_2O (1:1), rt, 2 days, 52%; (b) Ph_3P (1.4 equiv), DIAD (1.4 equiv), EtOAc, 0 °C, 1 h, >50%.



Scheme 4. Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, rt, overnight, 73%; (b) NaN_3, DMF, rt, 55%; (c) 1) Ph_3P, THF–H_2O, 4 h, 55 °C; 2) acidified with 1 M HCl, then washed with CH_2Cl_2, 65%; (d) 1) Boc_2O, $NaHCO_3$, MeOH, overnight, rt; 2) 1 M NaOH (10 eq), 1 h, rt, 68%; (e) NaOH, HCHO, H_2O, rt, overnight, 76%; (f) Ph_3P (1.3 equiv), DIAD (1.3 equiv), EtOAc, rt, 1 h, 51−57%; (g) 4 M HCl, H_2O–MeOH, rt, 4 days, 93%.



Scheme 5. Reagents and conditions: (a) PMBCl, K_2CO_3, DMF, 50 °C, 2 h, 77%; (b) NaH, DMF, 0 °C, then 3-Bromo-1-propyne, 0 °C to rt, 2 h, 61%; (c) TFA, CH_2Cl_2, rt, 2 h, 69%; (d) NaOH, HCHO, H_2O, overnight, rt, 77%; (e) Ph_3P, DIAD, EtOAc, rt, 1 h, 41−47%.