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# Challenges and opportunities in the synthesis of biologically relevant flavonoids and their glycosides

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Covering: 2015 to 2025

Natural product synthesis is key to unravel the roles and functions of complex biological molecules and drive innovations in drug discovery, agrochemicals, and materials sciences. Flavonoids are ubiquitous plant secondary metabolites with a C(6)–C(3)–C(6) benzo-γ-pyrone carbon skeleton, and they encompass a vast family of derivatives that play essential roles in UV protection, flower pigmentation, auxin transport, and defense against environmental stress. Flavonoid biosynthesis yields a diverse array of compounds, including flavones, anthocyanins, and proanthocyanidins, whose stability and bioactivity are often enhanced by post-translational modifications such as glycosylation and methylation. Flavonoids are known for their potent antioxidant properties and thus play a critical role in neutralizing reactive oxygen species and preserving cellular redox balance. Beyond their antioxidant activity, these phytochemicals exhibit a wide range of biological effects, including antibacterial, antiviral, anti inflammatory, and anticancer activities, highlighting their significant therapeutic potential. Due to their structural complexity and pharmacological promise, the total synthesis of flavonoids and their glycosylated analogues has garnered considerable research interest. This review aims to provide an overview of the recent advances in the total synthesis of flavonoid glycosides and their derivatives over the last decade. We selected twenty exemplary examples to illustrate key synthetic strategies while discussing their natural sources, therapeutic applications, and structure–activity relationship (SAR) studies that helped elucidate specific functional groups that are important for their pharmacological properties. We hope we can provide a current perspective on the recent advancements in flavonoid chemistry and their significance in the development of novel therapeutic agents for a range of diseases.

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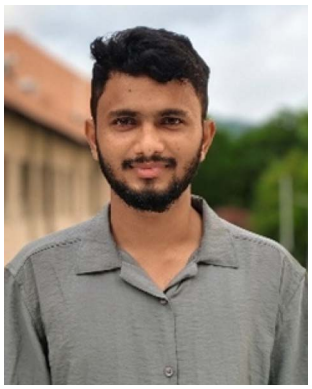

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# 1. Introduction

## 1.1. Background

Flavonoids are a diverse group of polyhydroxylated phenolic compounds characterized by a benzo-γ-pyrone structure and are widely found throughout the plant kingdom, especially in the seeds, leaves, bark, and flowers of plants, and they are also linked to the production of colors.[1–3] Both flavonoid and their glycosides exhibit broad inhibitory activities against diseases like cancer, diabetes, and cardiovascular and neurological disorders, with their protective effects in biological systems attributed to their ability to transfer electrons to free radicals, chelate metal catalysts, activate antioxidant enzymes, reduce alpha-tocopherol radicals, and inhibit oxidases.[4–8] Dietary flavonoids, which feature distinct hydroxy, methoxy, and glycosidic functional groups and include A- and B-ring conjugation, predominantly exist in food as 3-*O*-glycosides and polymers, which undergo hydroxylation, methylation, sulfation, or glucuronidation during metabolism. Interestingly, flavonoid moieties found in wine have been shown to exert potent antioxidant activity by inhibiting the oxidation of human low-density lipoproteins *in vitro* and also by reducing thrombosis, which is a major cause of death from coronary disease.[9,10] During the fermentation of green tea leaves to produce black tea, flavanols oxidize and polymerize into tannins and a complex blend of polyphenolic compounds, which are responsible for the distinctive color and flavor of black tea.[11–13] One of the major components found in black tea is procyanidins, composed of (+)-catechin and (−)-epicatechin monomers, and they stand out as key dietary elements and contribute to the rich flavor of grape seeds, apples, and cocoa.[14,15]

Building on the 2014 review from Yu and co-workers, which discussed glycosylation reactions in the synthesis of flavonoid glycosides,[16] as well as the significant contribution of Liu in 2020 to flavonoid chemistry,[17] we aim to provide an updated overview of recent synthetic advances in the total synthesis of this very important class of natural products. Key seminal examples will be discussed to highlight the key challenges in the field, emerging strategies and developments, and current limitations. In particular, twenty case studies were selected not as exemplary targets *per se*, but as representative platforms that expose recurring synthetic bottlenecks and decision points, including the regioselective functionalisation of the flavone A- and B-rings, strategic timing of *O- vs. C*-glycosylation, late-stage oxidation and dearomatisation challenges, and the chemoselective manipulation of densely functionalised phenolic systems.

# 2. Classification of flavonoids

Flavonoids present a C(6)–C(3)–C(6) carbon skeleton structure that consists of at least two aromatic rings, called A and B, linked by a three-carbon chain that can form a heterocyclic ring containing oxygen, called ring C, with ring A (Fig. 1). Generally, flavonoids are divided into flavones, flavonols, flavanones, flavanols, isoflavones, leucoanthocyanidins, anthocyanidins, and chalcones based on the oxidation level of the central pyran C-ring.[18] The subclasses are determined by minor structural variations, including the absence of ring C, the position of the bond between ring B and ring C, the degree of unsaturation, and ring C oxidation.

## 2.1. Flavanols

A highly complex class of polyphenol monomers, flavanols have an extra hydroxy group in the C-3 position and lack a C2–C3

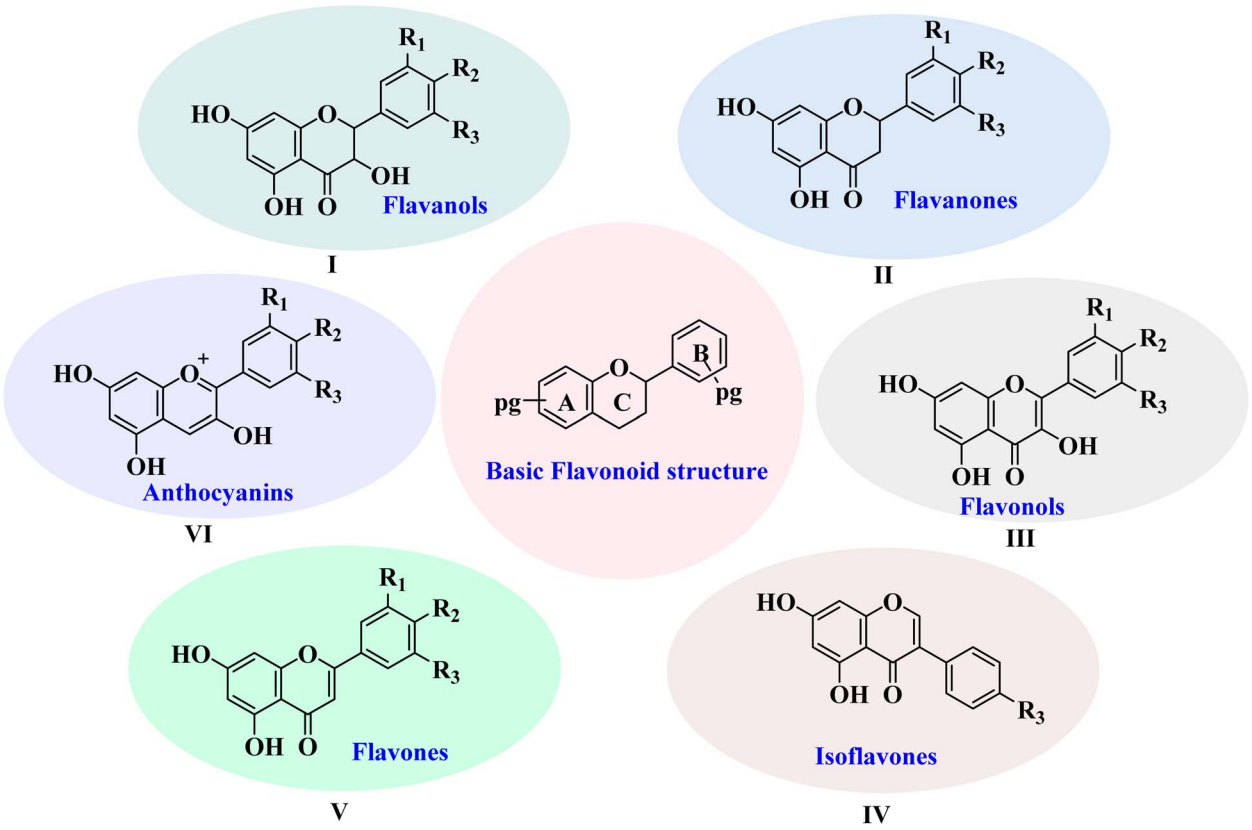



Fig. 1 Classification of plant flavonoids.

double bond; they include polymeric procyanidins, also referred to as condensed tannins, and monomeric flavan-3-ols, such as epicatechin, gallo-catechin, and catechin (Fig. 1-I). The primary sources of flavanols are fruit and their derivatives, such as fruit juices and jams. In addition, this group can be found in cereals, apples, kiwis, cocoa, red wine, and tea.[19,20] Except for broad beans and lentils, they are virtually nonexistent in vegetables and legumes. Flavanols are also present in fruit and vegetable peels and seeds, but since these components are frequently eliminated during processing or eating, their consumption is likewise restricted. Flavanols primarily exert health benefits through their metabolic products, with phase-II and microbial metabolites entering systemic circulation and promoting nitric oxide (NO) release, which supports vascular health. By promoting NO-mediated vascular repair, long-term ingestion of foods that are high in flavanols enhances endothelial function and helps avoid cardiovascular illnesses, with advantages even for smokers.[21,22]

### 2.2. Flavanones

Dihydroflavones (Fig. 1-II) known as flavanones, are structurally different from other flavonoids due to their unique saturation of the C ring,[23] notable lack of a double bond between the C2–C3 positions[24] and the presence of hydroxy groups at the C5 and C7 positions, along with hydroxy or methoxy groups located at C-3′ or C-4′ positions (Fig. 1).[25] Flavanones are widely distributed across approximately 42 major families, with Compositae, Leguminosae, Rutaceae containing the highest amounts.[26] Although flavanones are present in all parts of a plant, including the bark, branches, leaves, roots, flowers, and fruits, they are most abundant in the peel of citrus fruits rather than in the meaty inside.[27–29] Because of their high occurrence and health benefits, naringenin (5,7,4′-trihydroxyflavanone) and hesperetin (4′-methoxy-5,7,3′-trihydroxyflavanone)—flavanones present in common foods including tomatoes and citrus fruits (lemon, orange, lime, and tangelo)—are of special interest. Without altering liver histology, these substances, which are found as both aglycones and glycosides, aid in thyroid function restoration.[30] Additionally, naringenin has been suggested to strengthen the immune system, bolster antioxidant enzymes to protect organs from oxidative damage, and control intestinal inflammation by lowering nitrate and nitrite levels and preventing the creation of pro-inflammatory cytokines.[31]

### 2.3. Flavonols

Distinguished by their unique substitutions on the A- and B-rings, flavonols (also referred to as 3-hydroxy flavones) are connected by a flexible three-carbon chain (Fig. 1-III).[32] Predominantly observed in epidermal cells, it acts as nature's shield by protecting DNA from the harmful effects of UV radiation due to the hydroxy groups placed at the C-5 and C-7 positions on the A-ring.[33] The significance of flavonols concerning their biological activities and antioxidant properties makes them one of the most studied subgroups of flavonoids. This class of polyphenolic

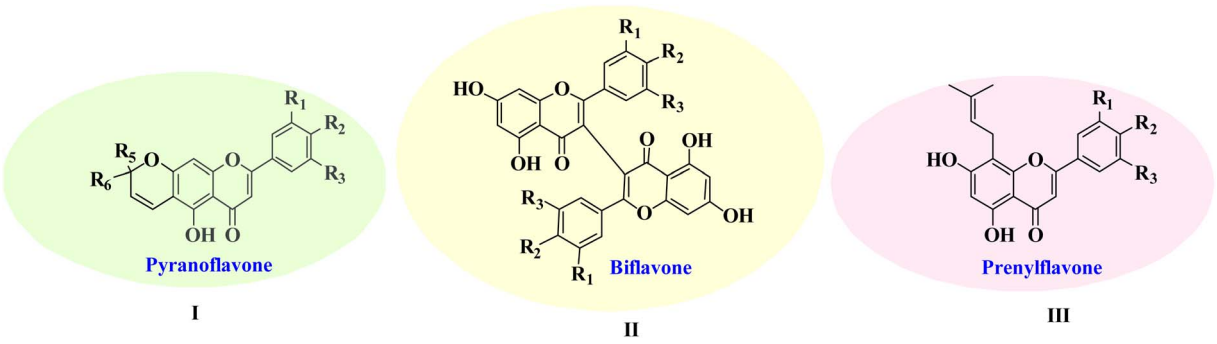



Fig. 2 Structures of various flavonoid derivatives.

phytochemicals is abundant in frequently eaten fruits, like apples and grape berries, vibrant vegetables, such as red lettuce, broccoli, tomato, and onion, as well as plant-based beverages.[34,35] Drinks like red wine, black tea, and green tea are important sources of flavonols, in addition to fruits and vegetables. Among the main flavonols, myricetin, kaempferol, and quercetin can be identified. Celebrated for their antioxidant, cardioprotective, antibacterial, antiviral, and anticancer properties,[36] dietary flavonols have been shown to significantly reduce the risk of gastric cancer, especially in women and smokers.[37] They also improve enzymatic and non-enzymatic antioxidant defenses, such as those modulated by quercetin, to combat reactive oxygen species (ROS) mediated liver cancer.[38]

### 2.4. Isoflavones

A unique and significant subclass of flavonoid compounds is isoflavones. The 3-phenylchromen skeleton is made up of these structures, which are chemically derived from the 2-phenylchromen skeleton through an aryl-migration mechanism (Fig. 1-IV).[39,40] The majority of isoflavones are found in legumes, particularly soy. However, their presence has also been reported in split peas, chickpeas, black beans, lima beans, clover sprouts, and sunflower seeds. Genistein and daidzein are the two main isoflavones found in the human diet, among a total of twelve soybean isoflavones.[41] They are found in four related chemical structures: aglycones, 7-*O*-glucosides, 6′-*O*-acetylglucosides, and 6′-*O*-malonylglucosides. This type of flavonoid acts as a potential antioxidant, which can lower the risk of cancer and prevent free radical damage to DNA.[42]

### 2.5. Flavones

One of the biggest and most varied groups of flavonoids, flavones are mostly found as 7-*O*-glycosides and are based on the 4H-chromen-4-one backbone with a phenyl group at the C-2 position (Fig. 1-V).[43,44] The two main flavones, luteolin and apigenin, are present in a wide variety of foods. While luteolin graces broccoli, celery, carrots, parsley, onion leaves, cabbages, peppers, chrysanthemum flowers, and apple skins, apigenin makes its mark in seasonings, onions, wheat sprouts, tea, oranges, and chamomile.[45] The apigenin group, which includes substances like vitexin, isovitexin, rhoifolin, schaftoside and apiin, is well known for its strong anti-inflammatory and free radical scavenging properties.[46,47] It also protects pancreatic cells and lessens the loss of antioxidant enzymes in disorders such as cancer, heart disease, and neuroinflammation.[48]

### 2.6. Anthocyanidins

Anthocyanidins, a class of phytochemicals, are natural water-soluble plant vacuolar pigments responsible for the stunning spectrum of blue, red, purple, and orange hues that grace many fruits, flowers, vegetables, as well as various delicious food products made from them.[49] There are more than 650 distinct anthocyanidins that have been identified and documented in the literature.[50] This class of flavonoids is predominant in teas, honey, cereals, fruits, vegetables, nuts, olive oil, and cocoa.[51] The structural basis of anthocyanidins is the flavylium or 2-phenylbenzopyrilium cation, which has hydroxyl and methoxy groups positioned at various points in the basic structure of flavonoids (Fig. 1-VI). Anthocyanidins have also been observed in the aglycone form of anthocyanins. The stability of anthocyanins (glycosylated anthocyanidins), which are extremely reactive and unstable substances, is affected by several variables, including pH, temperature, light, oxygen, enzymes, other flavonoids, proteins, and metal ions. As the pH rises, these compounds are converted into blue quinoidal bases (pH 2–4), colorless hemiketals, and finally pale-yellow chalcones, which can break down into phenolic acids (pH 5–6). They are most stable as red-colored flavylium cations in acidic environments (pH 1–3).[52–54]

### 2.7. Other flavonoid derivatives

Flavonoids are undergoing rapid developments in the field of molecular science, influenced by the moieties that bind to them. These modifications cause them to transform into fascinating and biologically active new forms, such as pyranoflavones, biflavones, and prenyl flavanones.

**2.7.1. Pyranoflavones.** A specific category of flavonoids that have a pyran group is called pyranoflavones (Fig. 2-I). The synthesis of these compounds has been the subject of a recent study in order to investigate their potential as selective inhibitors of cytochrome P450 enzymes, specifically cytochrome P450 1A1, P450 1A2, and cytochrome P450 B1, which are implicated in the bioactivation of polycyclic aromatic hydrocarbons like procarcinogens.[55,56] The findings revealed that cytochrome P450 1A2 is strongly inhibited by the α-naphthoflavone-like

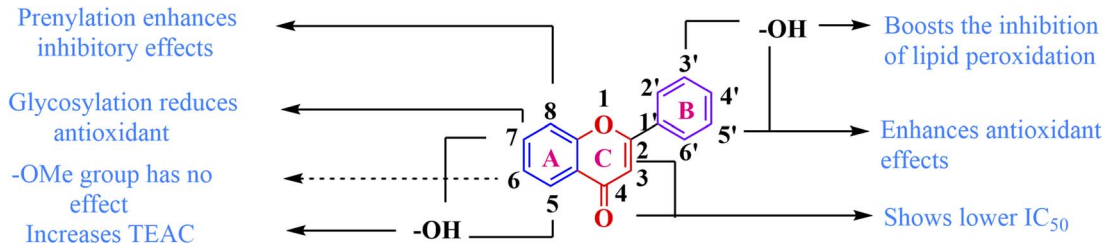



Fig. 3 Structure-activity relationship of flavonoids towards therapeutic applications.

derivatives 7,8-pyranoflavone (78 PF) and 5-hydroxy-7,8-pyranoflavone (5H78 PF), with $IC_{50}$ values of 0.059 and 0.014 μM, respectively, while P450 1A1 is weakly inhibited. However, cytochrome P450 1A1 is more strongly inhibited by the β-naphthoflavone-like derivatives 5,6-pyranoflavone (56 PF) and 6,5-pyranoflavone (65 PF) ($IC_{50}$ values of 0.32 and 0.15 μM) than P450 1A2 ($IC_{50}$ values of 1.13 and 0.76 μM).[57]

**2.7.2. Biflavones.** Angiosperms, bryophytes, ferns, and gymnosperms naturally contain biflavones, which comprise two monoflavonoid residues. Biflavones are dimeric flavonoids composed of two flavonoid units connected by a C–C or C–O–C bond, typically between the C-6 and C-8 positions (Fig. 2-II).[58] They can have free or methylated hydroxyl groups and are substituted at the 5-, 7- and 4′-positions. Flavone–flavone and flavanone–flavanone dimers make up the majority of this subclass's members.[59] Various other factors, including the kind of monomeric flavonoid (flavones, flavanones, and flavonols), the substituents on their monomers (usually hydroxy or methoxy groups), and the interflavonoid bond between the units, contribute to the structural diversity of these biflavones.[60,61] Regardless of the bioactivity associated with each monomeric unit, some of these biflavones have been shown to exhibit improved biological activities.[62]

**2.7.3. Prenyl flavanones.** Prenylated flavonoids, which combine a lipophilic prenyl side chain with a flavonoid skeleton, are a significant class of polyphenolic compounds (Fig. 2-III). The most prevalent subclass of prenylated flavonoids is prenylated flavonones, whereas the rarest is prenylated flavanols. On flavonoids, *C*-prenylation occurs far more frequently than *O*-prenylation. Prenylation makes flavonoids more lipophilic, improving their interaction with target proteins and increasing their affinity for biological membranes.[63]

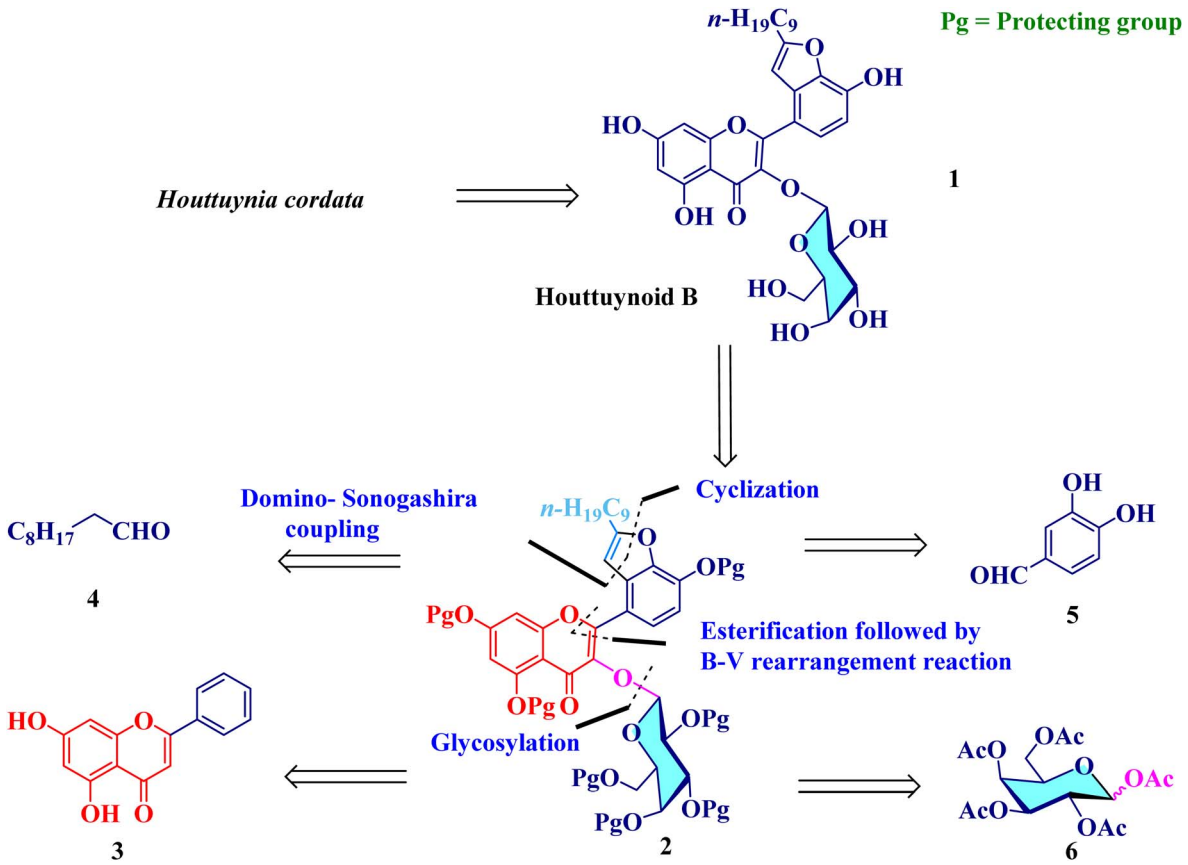
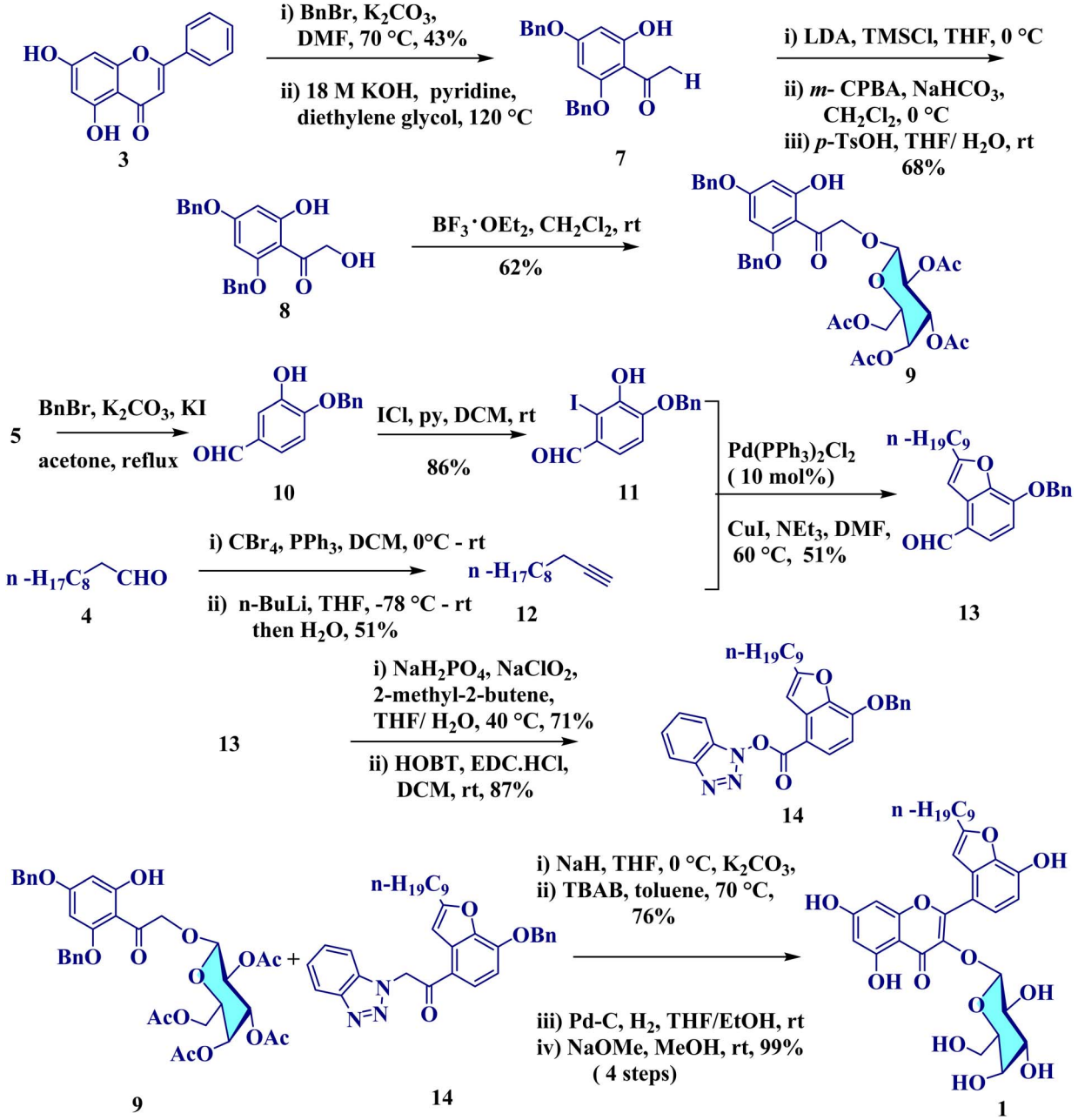



Fig. 4 Convergent strategy for the total synthesis of houttuynoid B.

### 2.8. Biological activity

Flavonoids are primarily known for their antioxidant properties, which are attributed to the presence of a large number of phenolic hydroxy groups that act as hydrogen-donating radical scavengers.[64,65] These compounds are also known for their health benefits as anti-inflammatory,[66] antiulcer, antiviral,[67] antifungal,[68] anticancer,[69] antiallergic,[70] and antidiabetic[71] agents in addition to exhibiting some cytotoxic effects, among others.[72] It is believed that the hydroxyl group of the B-ring on the flavan (Fig. 3) nucleus plays a critical role in the scavenging of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by donating both a hydrogen atom and an electron to hydroxyl, peroxyl, and peroxynitrite radicals. Additionally, the presence of a catechol group at the 3′- and 4′-positions on the B-ring significantly boosts the inhibition of lipid peroxidation.[73] The 5-OH group enhances antioxidant effects and explains the higher Trolox equivalent antioxidant capacity (TEAC) and peroxynitrite scavenging of genistein, while the 5,7-dihydroxy arrangement increases TEAC, but methylation of the 6-OH group does not alter lipid peroxidation inhibition. Furthermore, the A-ring hydroxylation's impact on antioxidant activity is less significant compared to that of the B-ring.[74] In a microsomal system, flavonoids containing a 2–3 double bond conjugated with a 4-carbonyl group exhibit lower $IC_{50}$ values compared to those with saturated heterocycles. The reduction of this double bond reduces the antiperoxidative phenomenon, as the




Scheme 1 Forward synthesis of houttuynoid B (Schmalz, 2016).[90]

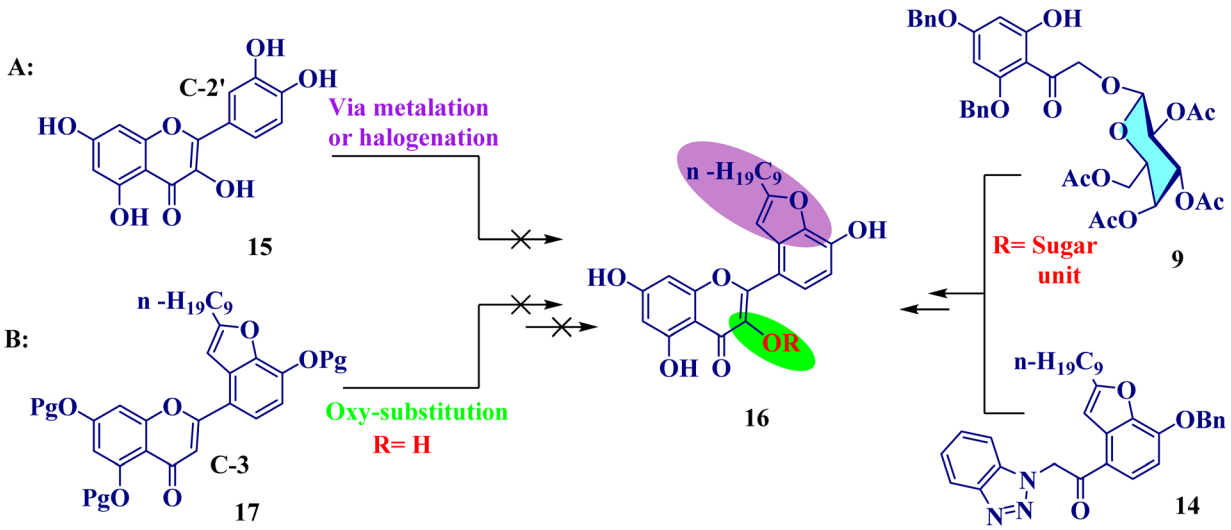



Fig. 5 Lessons from the total synthesis of houttuynoid B.

resonance conjugation between the A and B rings *via* the unsaturated carbonyl moiety enhances the stabilization of flavonoid radicals.[75] Glycosylation on the A-ring of flavonoids reduces antioxidant activity more than glycosylation at the 3-position. Whereas the glycosylation in rat mitochondria at the 7-position has been shown to weaken antioxidant activity. However, no difference was found between 3- and 7-glucosides of quercetin in phospholipid bilayers.[76,77] The existence of the 3-OH group preserves the coplanarity and conjugation with the B-ring through intramolecular hydrogen bonding, which is essential for effective radical scavenging ability.[78] Quercetin is a highly effective peroxyl radical scavenger, with its *O*-methylated and *O*-glycosylated derivatives showing reduced potency, likely due to steric hindrance from the *O*-methylation that disrupts molecular planarity and diminishes antioxidant activity.[79] Prenylation of flavonoids at positions 3, 6, and 8

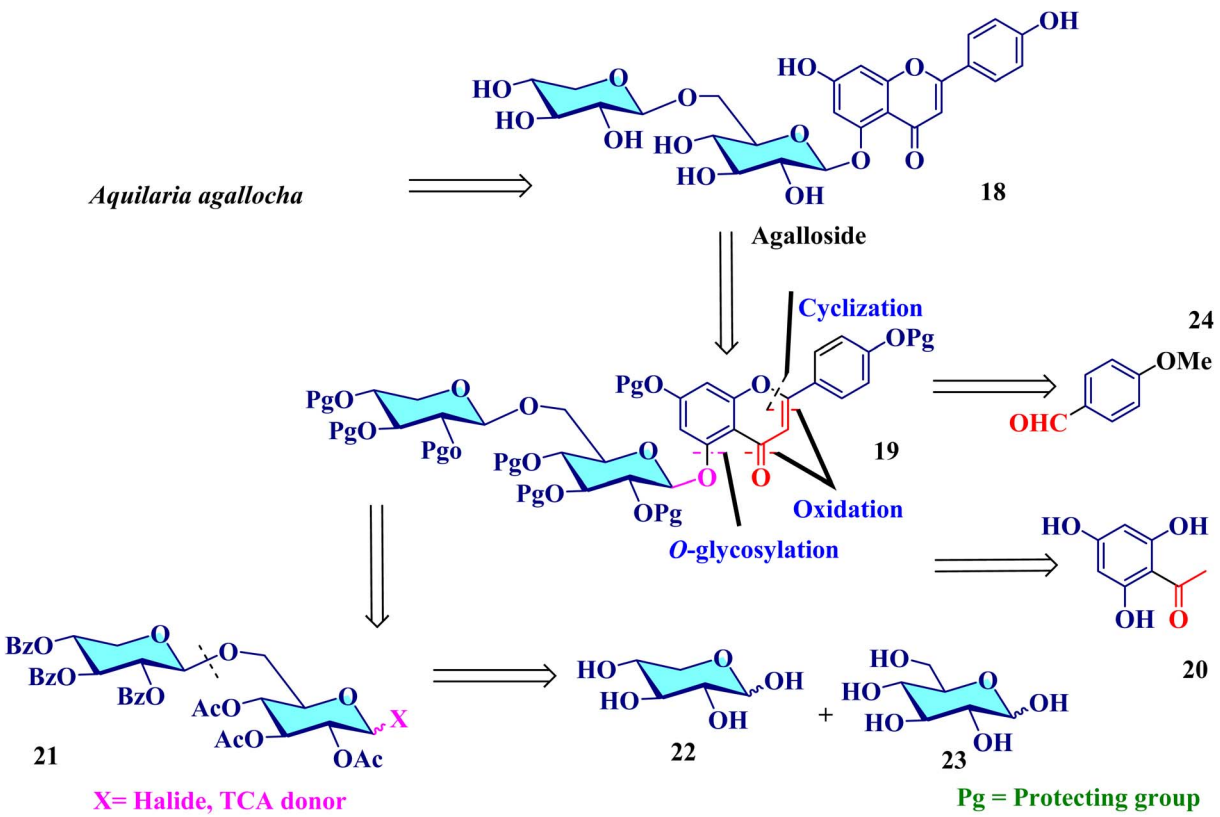
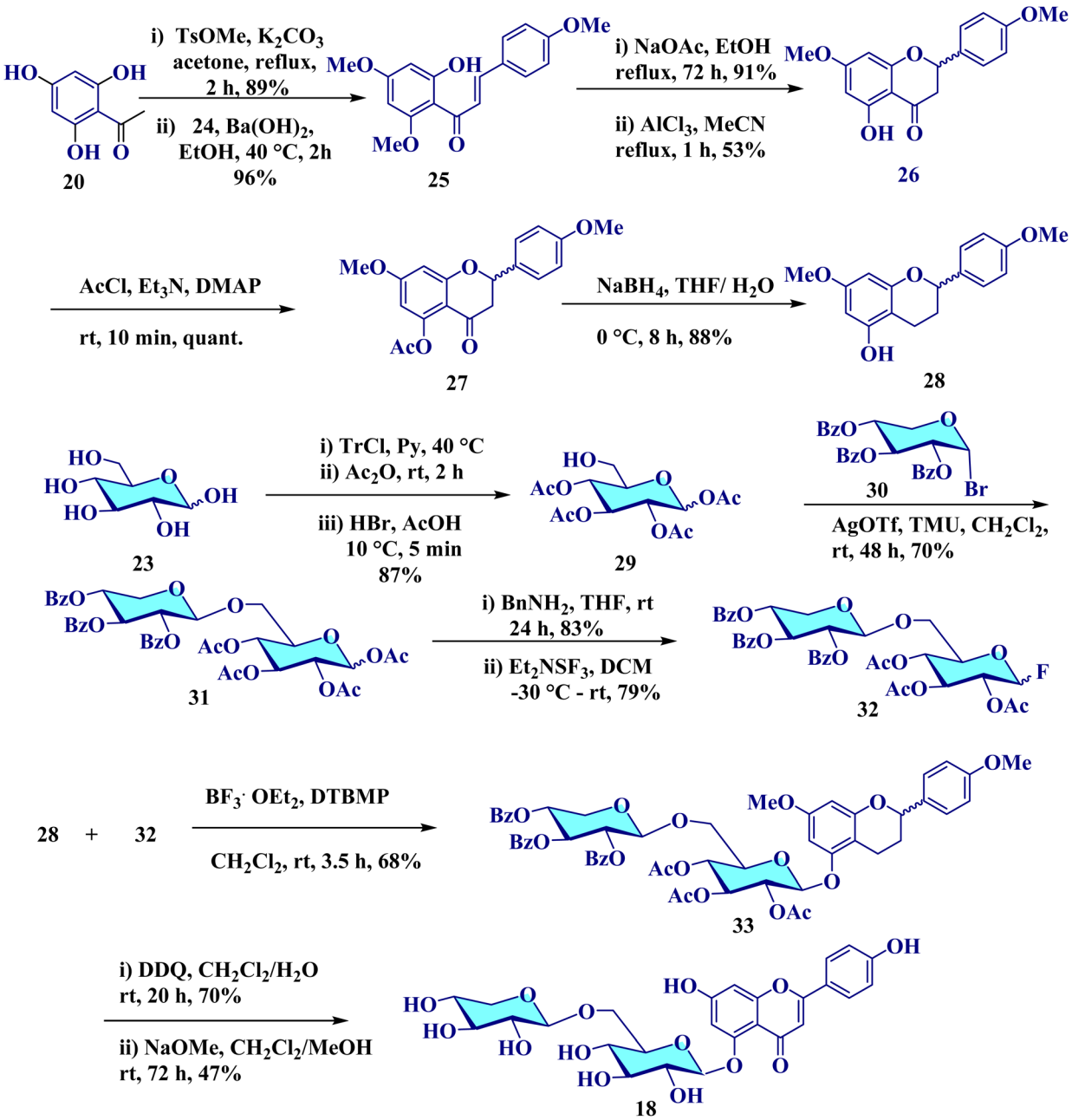



Fig. 6 Conversion strategy for the synthesis of agalloside.




Scheme 2 Forward synthesis of agalloside (Arai and Ishibashi, 2017).[107]

enhances their inhibitory effects against various enzymatic processes, including tyrosinase, melanin biosynthesis, alpha-glucosidase, and mitogen-activated protein kinase (MAPK) pathways, as seen with luteolin, apigenin, quercetin, genistein, and chalcone.[63,80–82]

## 3. Total synthesis of flavonoid *O*-glycosides

Flavonoids are characterized by a six-membered ring in the C6–C3–C6 carbon skeleton, which will be highlighted in this research. The coupling between a hydroxyl group of a flavonoid aglycone and the anomeric carbon of a sugar moiety will generate an *O*-linkage to form flavonoid *O*-glycosides.[83,84] Flavonoid *O*-glycosides are generally more stable than their corresponding aglycone under physiological conditions, but can be hydrolyzed under acidic environments or by the action of enzymes. This stability is attributed to the presence of the glycosidic bond, which protects the flavonoid core from oxidation and degradation. Although 5-, 8-, and 4′-*O*-glycosides have also been found in some exceptional cases, flavonoid glycosides are more commonly present as 3- or 7-*O*-glycosides.[85] Because of the steric barrier and decreased ability for electron delocalization, *O*-glycosylation at the C-7, C-3, and C-4′ sites reduces the

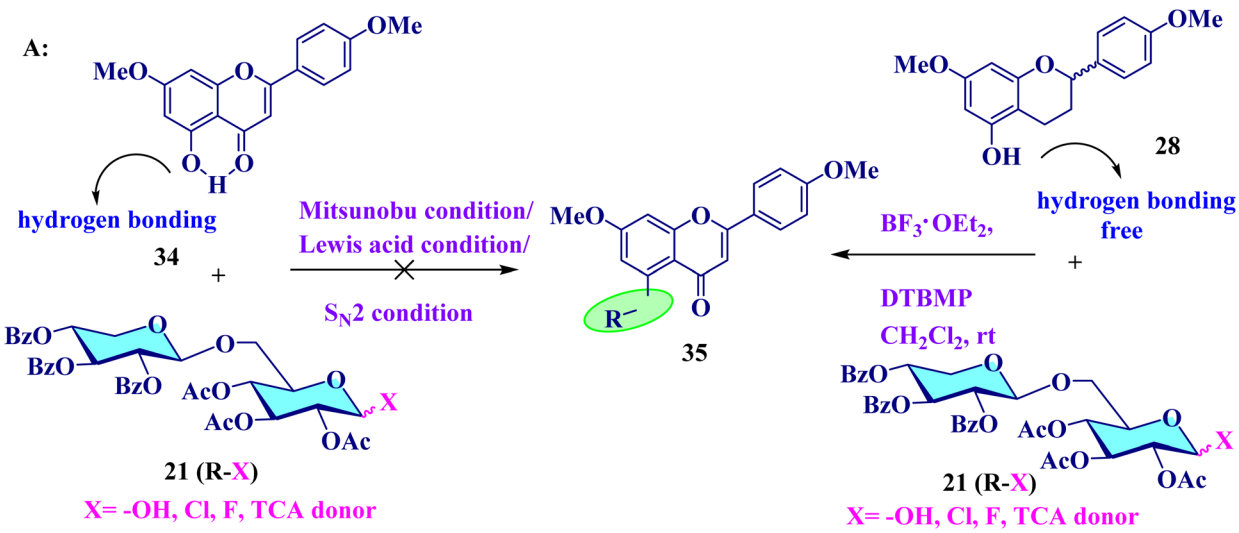



Fig. 7 Lessons from the total synthesis of agalloside.

radical scavenging action of flavanones.[86–88] These natural products are found in many plants, where they support interspecies communication as well as growth and development. Flavonoid *O*-glycosides also have a wide range of protective effects on humans, such as antibacterial, anticancer, and radical-scavenging capabilities.[89]

### 3.1. Synthesis of houttuynoid B

**3.1.1. Synthetic approach.** In 2016, the Schmalz group achieved the first total synthesis of houttuynoid B,[90] an antiviral agent that suppresses the herpes simplex virus with $IC_{50}$ values of 57.7 μM.[91,92] This compound was isolated by the Yao group from the tree *Houttuynia cordata* in 2012.[93,94] The target molecule **1** was generated *via* the Baker–Venkataraman rearrangement[95] and cyclization from the intermediate ester, containing the appropriate sugar scaffold, which is formed by esterification with the intermediate having a furan ring **14** and an acetophenone scaffold **9**. Compound **9** was obtained from chrysin **3** *via* retro-aldol degradation and alpha oxidation, followed by glycosylation. Similarly, compound **12** was obtained from 3,4-dihydroxybenzaldehyde **5** by Sonogashira coupling, Corey–Fuchs reaction, and domino Sonogashira coupling/5-*endo*-dig-cyclization. Although a normal ester is suitable for the esterification of compound **9**, a stable HOBT-activated ester of compound **14** was produced for easier handling (Fig. 4).

**3.1.2. Synthetic route.** Based on their retrosynthetic study, the group started by synthesizing aromatic scaffold **13**, which serves as the building block for benzofurans. By treating 3,4-dihydroxybenzaldehyde **5** with benzyl bromide, KI, and $K_2CO_3$ in acetone, the known intermediate 4-benzyl-3,4-dihydroxybenzaldehyde **10** was generated, which was then treated with iodine monochloride and pyridine in DCM to yield **11**. Separately, 1-undecyne **12** was prepared from decanal **4** in two steps under Corey–Fuchs conditions using $CBr_4$, $PPh_3$ in DCM at 0 °C[96,97] and *n*-butyllithium in THF at −78 °C, followed by the addition of water. The benzofuran **13** was produced by a domino Sonogashira coupling between iodo-phenol **11** and alkyne **12** using $Pd(PPh_3)_2Cl_2$, CuI, and $NEt_3$ in DMF at 60 °C. The Pinnick oxidation of benzofuran **13** with $NaH_2PO_4$, $NaClO_2$, and 2-methyl-2-butane in THF/$H_2O$ produced the carboxylic acid intermediate,[98] which was then transformed into the HOBT-activated ester **14** by the reaction with HOBT and EDC HCl in DCM. Compound **9**,[99] the second building block, was created from chrysin **3** by first double *O*-benzylation with BnBr and $K_2CO_3$ and then retro-aldol degradation with 18 M KOH and pyridine in ethylene glycol at 120 °C, and alpha oxidation, resulting in the hydroxylated product **7**.[100] $BF_3$ $OEt_2$ was used to glycosylate alcohol **7** with peracetylated β-galactose **6**, resulting in the galactose derivative **9**.[101] Under Steglich conditions, the ester intermediate was produced in 76% yield through the esterification of **9** and **13** in the presence of NaH using THF as solvent.[102] By using *in situ* cyclization and Baker–Venkataraman rearrangement with $K_2CO_3$, TBAF, and toluene at 70 °C, this ester was transformed into the chromenone intermediate.[103] Ultimately, benzyl ethers were finally eliminated by Pd/C, $H_2$ in THF/EtOH, and the sugar moiety was deprotected with NaOMe in MeOH to get the natural product Houttuynoid B **1** (Scheme 1).

**3.1.3. Strategies and lessons learned from the synthesis.** Their approach is intriguing since they formed the glycosyl derivative **9** and then produced an intermediate ester. Their previous study revealed that metalation or halogenation could not be used to achieve regioselective functionalization of quercetin derivatives **15** at C-2′, and that the benzofuran moiety's electron-donating effect was the reason behind the failure of attempts to introduce an oxy-substituent at C-3 in the intermediate of type **17** (Fig. 5).[104–106]

### 3.2. Agalloside

**3.2.1. Synthetic strategy.** In 2017, Arai and Ishibashi's group embarked on an intricate journey to synthesize Agalloside **18**,[107] a compound that activates neural stem cell differentiation,[108] by leveraging the direct *O*-glycosylation of the corresponding flavan with a disaccharide **21** (Fig. 6). This

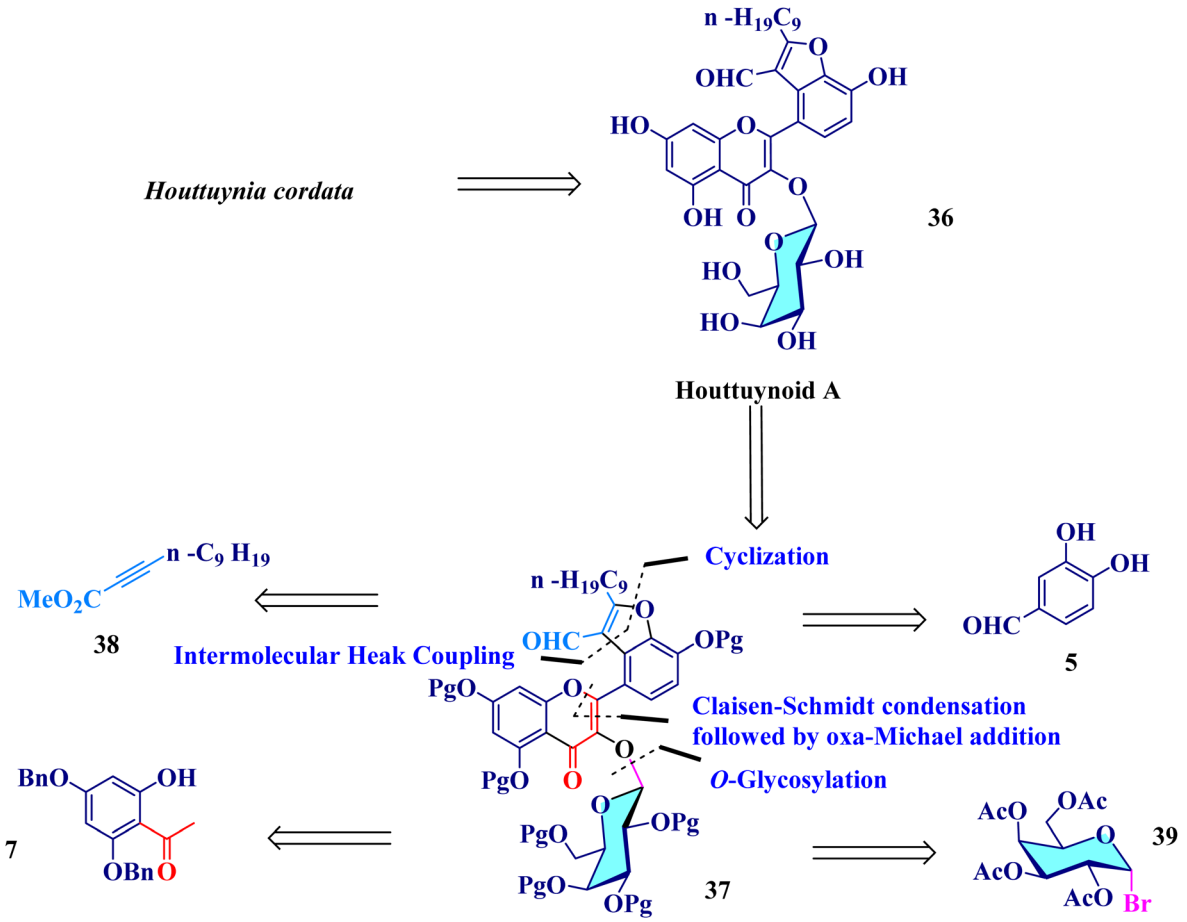



Fig. 8 Conversion strategy for the total synthesis of houttuynoid A.

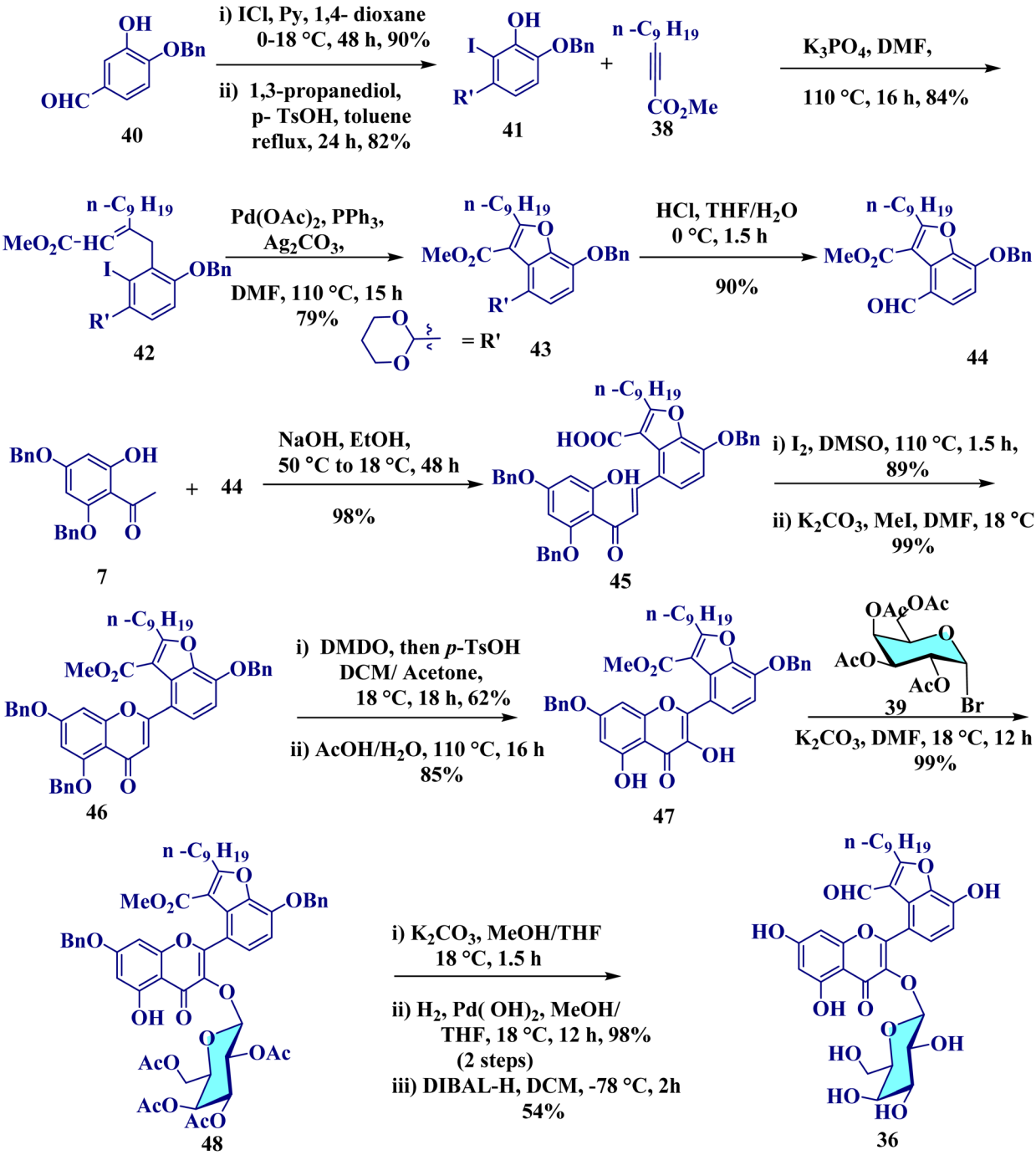
naturally occurring substance had been isolated by the same research group in 2016 from *Aquilaria agallocha*.[109,110] The crucial process consisted of selectively choosing the flavan unit for the glycosylation instead of the flavonoid unit for glycosylating disaccharide **21**. The sophisticated synthesis of the flavan unit began with 2,4,6-trihydroxyacetophenone **20** and proceeded *via* a series of methylation, chalcone production, cyclization catalyzed by NaOAc/EtOH, selective demethylation by $AlCl_3$, acylation, and reduction of the carbonyl moiety.

**3.2.2. Synthetic route.** The synthesis of glycosyl donors began with the protection of glucose **23** and xylose **22**, where glucose's 6-hydroxy group was protected as the trityl ether with trityl chloride and pyridine at 40 °C, followed by acetylation of the remaining hydroxyl groups with acetic anhydride and removal of the trityl group in HBr/AcOH to yield compound **29**.[111] Then, the xylose donor **30** was crafted by protecting all hydroxyl groups with benzoyl groups, and selectively removing the anomeric –OBz with HBr/AcOH to unveil a perbenzoylated xylose with an anomeric bromide. Starting with chalcone **25**, a Michael reaction in the presence of NaOMe in ethanol medium yielded the cyclized product **26**, which was subsequently used to deprotect the 5-OMe group using $AlCl_3$, followed by acetylation and reduction of the carbonyl group in **27** with $NaBH_4$ in $THF/H_2O$ to produce the desired flavan **28**. The *O*-glycosylation of flavan **28** with glycosyl fluoride **32**, catalyzed by $BF_3$ $OEt_2$ and 4 equiv. of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in DCM, proceeded efficiently in just 3.5 hours, yielding 5-*O*-glycoside **33** in 68% yield.[112] Subsequently, oxidation of **33** with DDQ in $DCM/H_2O$ medium and complete deprotection with NaOMe/MeOH afforded the target molecule, Agalloside **18** (Scheme 2).

**3.2.3. Strategies and lessons learned from the synthesis.** Due to strong hydrogen bonding between the 5-OH and carbonyl group, attempts to glycosylate flavone **34** with the synthesized disaccharide donors **21** under Mitsunobu,[113] Lewis acid,[111,114] and $S_N2$ conditions[115] did not result in the production of *O*-glycosides (Fig. 7). Furthermore, under $BF_3{\cdot}OEt_2$ and DTBMP conditions, the glycosylation of flavan **28** with glycosyl fluoride produced an inseparable combination of 5-*O*-glycoside and 6-*C*-glycoside with yields of 38% and 22%, respectively. After that, the glycosyl donor to flavan ratio was increased to 2 : 1, and the amount of DTBMP was raised to 4 equiv. to enhance the formation of the desired *O*-glycoside with a short reaction time of 3.5 h.

### 3.3. Houttuynoid A

**3.3.1. Synthetic strategy.** Houttuynoid A, isolated from *Houttuynia cordata* in 2013 by the Yao group,[116] was synthesized




Scheme 3 Forward synthesis of houttuynoid A (Gao and Sun, 2018).[117]

in 2018 by Sun and Gao's group;[117] the compound was shown to inhibit herpes simplex virus type 1 (HSV-1) multiplication and prevent lesions in a mouse model.[93,118,119] This compound demonstrated wide antiviral activity against α-herpesviruses such as varicella zoster and herpes simplex virus type 2 (HSV-2), and it also rendered HSV-1 inactive by preventing viral membrane fusion. With an $IC_{50}$ value of 23.5 μM, its effectiveness against the herpes simplex virus was associated with the aldehyde group at the C-2″ position.[93,120] The target molecule is synthesized from the corresponding flavone intermediate by means of functional group interconversions and *O*-glycosylation with **39** at the C-3 position (Fig. 8). The flavone is created by oxidizing chalcone and adding by oxa-Michael reaction, then protecting the C-2 hydroxycarbonyl group. In this procedure, compound **7** is subjected to a Claisen–Schmidt condensation with benzofuran aldehyde scaffold to form the corresponding chalcone, which is also synthesized from commercially available 3,4-dihydroxybenzaldehyde **5** with concomitant selective protection and intermolecular Heck reaction with **38**.

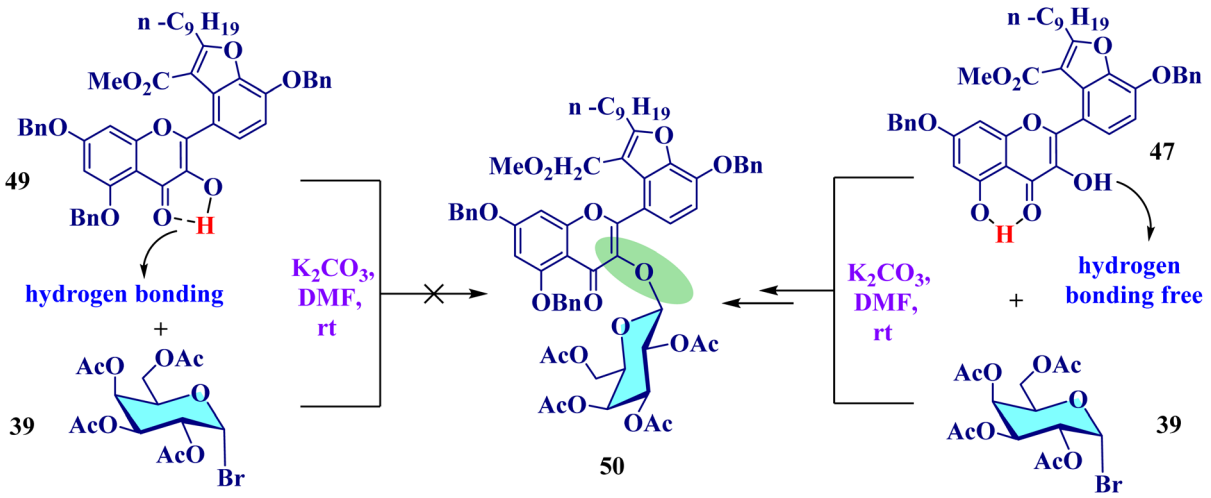



Fig. 9 Lessons from the total synthesis of houttuynoid A.

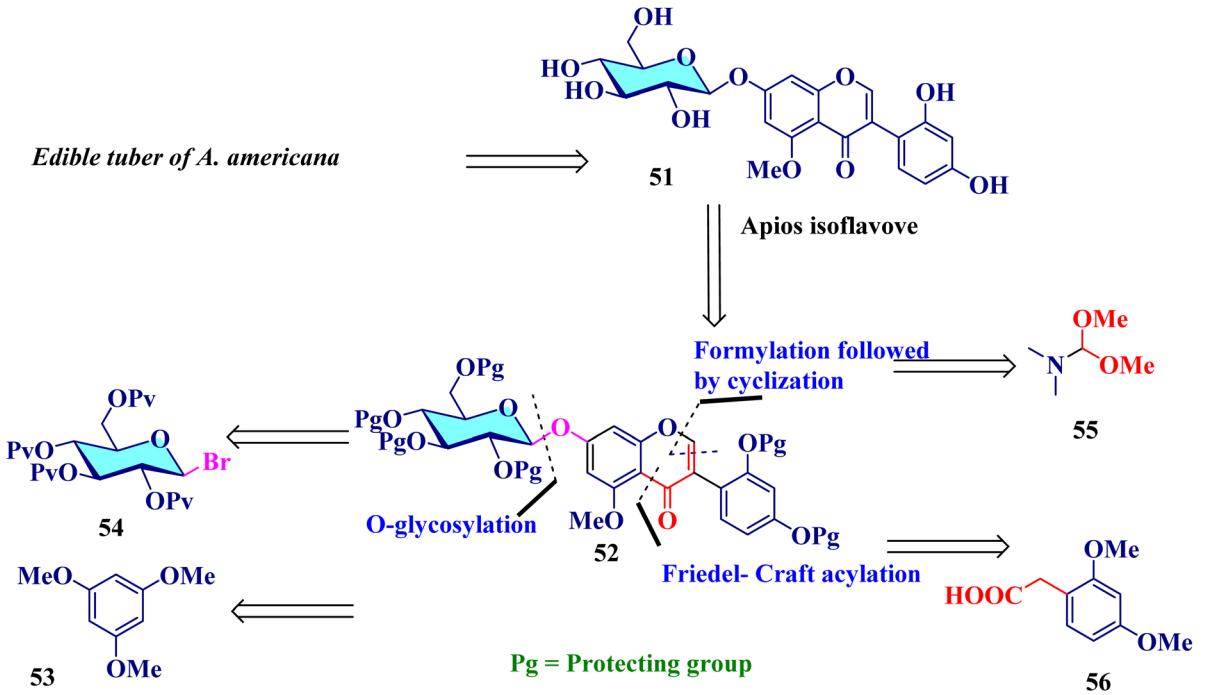
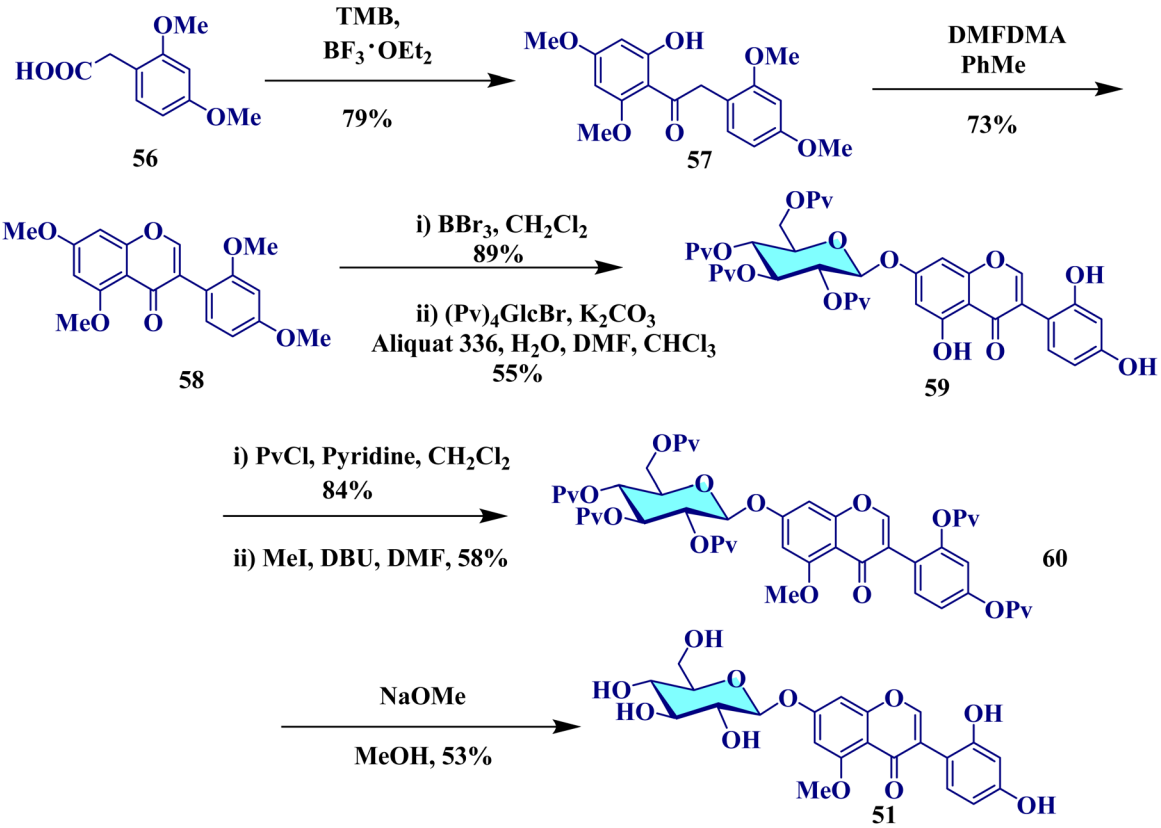



Fig. 10 Conversion strategy for the total synthesis of apios isoflavone.

**3.3.2. Synthetic route.** According to their retrosynthetic analysis, the para-hydroxy group of 3,4-dihydrobenzaldehyde **5** was first regioselectively benzylated with BnBr, KI, and $K_2CO_3$ in acetone at 60 °C, resulting in the formation of compound **40** in 76% yield.[121] The treatment of this benzaldehyde with iodine monochloride in 1,4-dioxne resulted in a 90% yield of the iodinated compound, after which the formyl group was protected as acetal **41** using 1,3-propanediol, *p*-TsOH/toluene in two consecutive steps before the conjugate addition of phenol **41** to methyl dodec-2-ynoate **38** in DMF at 110 °C to produce aryl ether **42** with 84% yield.[122–125] Using an intramolecular Heck reaction, compound **42** could be used to generate the benzofuran skeleton **43** with 79% yield,[126] and the hydrolysis of the 1,3-dioxanyl group with HCl in moist THF produced the critical intermediate **44** with a 90% yield. Through the Claisen–Schmidt condensation of compound **7** and aldehyde **44**, with NaOH/EtOH, compound **44** was transformed into chalcone **45**, which, in turn, was converted into 4H-chromen-4-one derivative **46** with 89% yield using $I_2$/DMSO cyclization at 110 °C.[127,128] Prior to oxidation at C-3, the hydroxycarboxyl group at C-2 was methylated with MeI/$K_2CO_3$. A 62% yield of 3-hydroxyflavone **47** was achieved by treating compound **46** with in situ-generated DMDO, followed by TsOH-mediated rearrangement and the selective deprotection of the 5-benzyloxy group *via* refluxing in




Scheme 4 Forward synthesis of apios isoflavone (Nihei, 2019).[132]

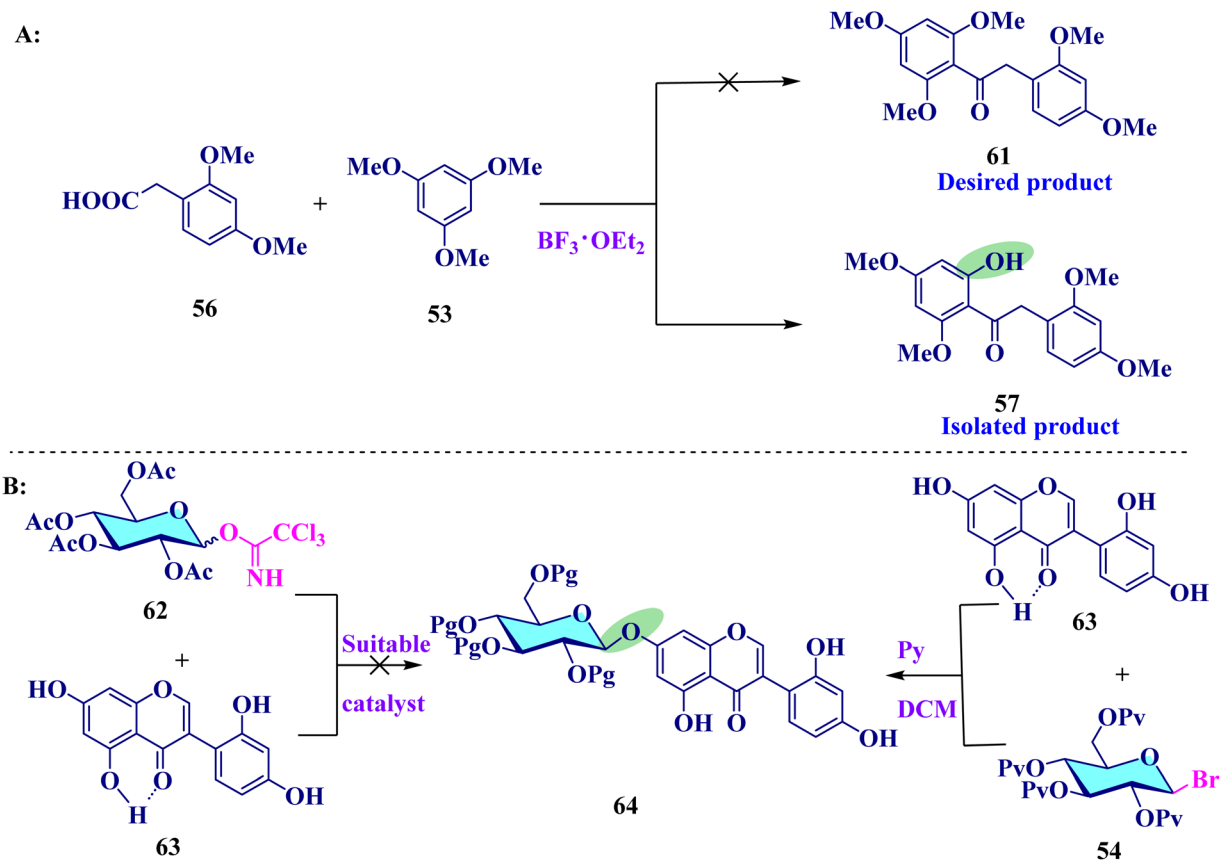



Fig. 11 Lesson from the total synthesis of apios isoflavone. (A) Abnormal Friedel–Crafts reaction; (B) unsuccessful glycosylation.

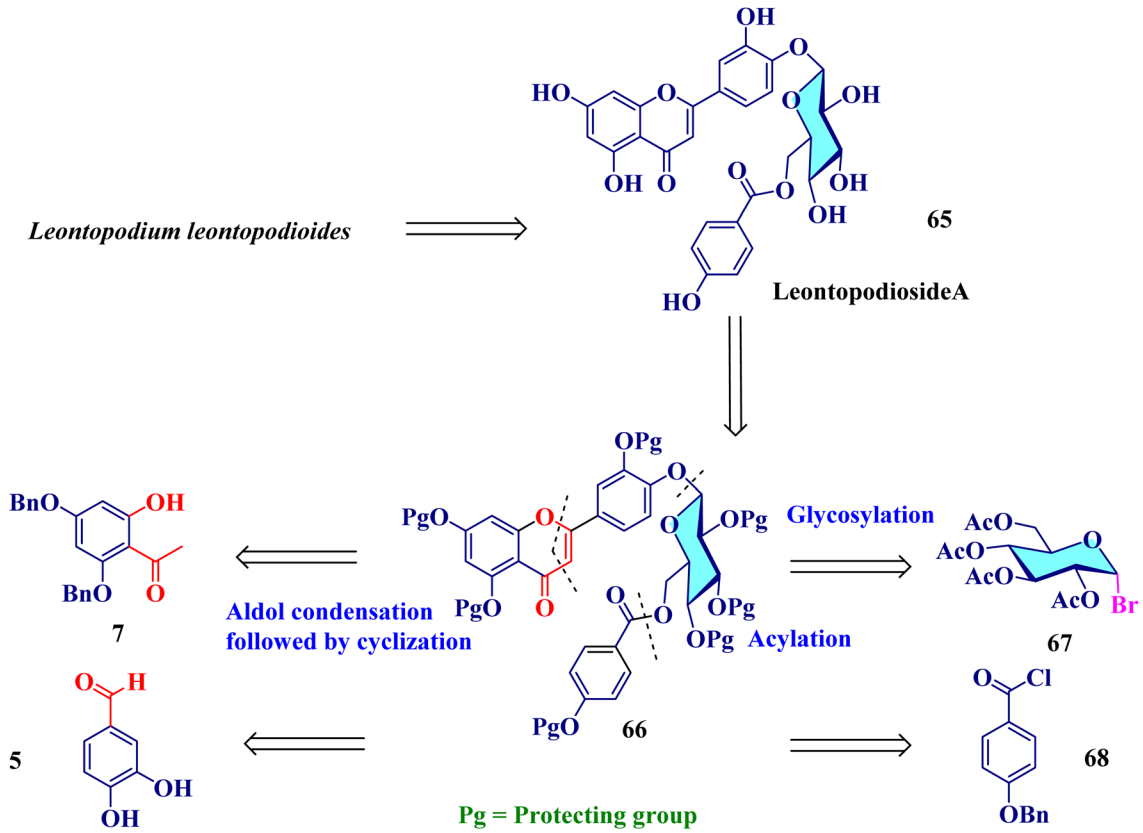
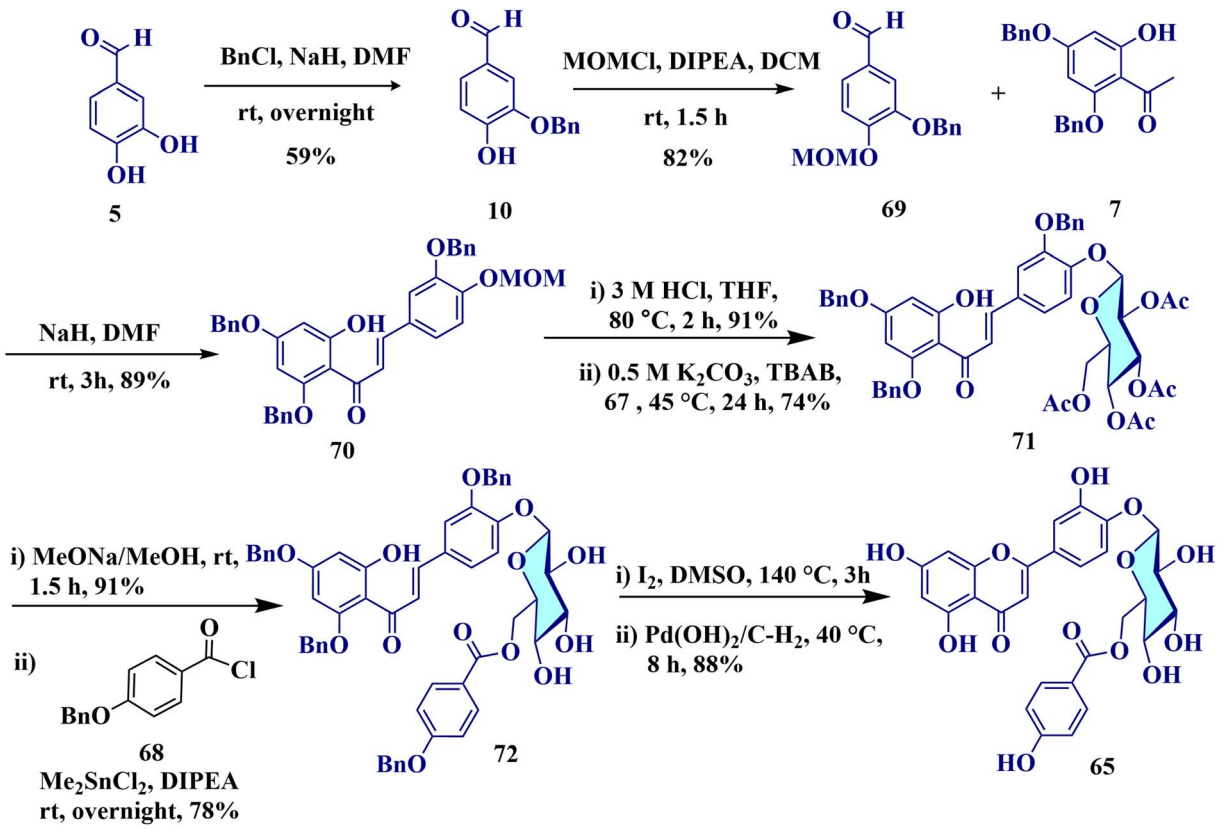



Fig. 12 Conversion strategy for the total synthesis of leontopodioside A.




Scheme 5 Forward synthesis of leontopodioside A (Ding and Li, 2020).[146]

$HOAc/H_2O$.[129,130] Chromenone **48** was quantitatively generated *via* glycosylation of **47** with compound **39** in the presence of $K_2CO_3$/DMF.[131] The acetyl and benzyl protecting groups of compound **48** were removed using conventional hydrolysis with $K_2CO_3$, MeOH/THF, and hydrogenation with $H_2$, $Pd(OH)_2$ in MeOH/THF, respectively. Ultimately, a 54% reduction in the yield of target Houttuynoid A **36** was observed after exposure of the ester intermediate to DIBAL-H (Scheme 3).

**3.3.3. Strategies and lessons learned from this synthesis.** In this synthesis, several attempts to glycosylate compound **49** with the glycosyl donor **39** were unsuccessful (Fig. 9). This was attributed to hydrogen bonding between the C-4 carbonyl group and the 3-hydroxyl group, which rendered the 3-OH group unavailable towards nucleophilic attack. Therefore, the C-5 benzyl group was first debenzylated using $AcOH/H_2O$ at 110 °C to resolve the encountered issue.

### 3.4. Apios isoflavones

**3.4.1. Synthetic strategy.** In 2019, Nihei and co-workers embarked on the remarkable total synthesis of apios isoflavones,[132] which are potent and hydrophilic tyrosinase inhibitors extracted from the edible tuber of *A. americana* by the Shindo group in 2013.[133–136] To unlock novel inhibitors, the synthesis of target molecule **51** was ingeniously designed, culminating in a global transesterification of compound **52** (Fig. 10). This key intermediate **52** was crafted *via* selective acylation of 2′-OH and 4′-OH positions using PvCl and pyridine, followed by precise methylation at the C-5 position of the flavone intermediate. Notably, the isoflavone intermediate was synthesized through the selective glycosylation of the isoflavone scaffold and compound **54**, with the isoflavone part itself being obtained through a masterful Friedel–Crafts reaction and Bischler–Napieralski-type cyclization using compound **56** and trimethoxybenzene **53**.

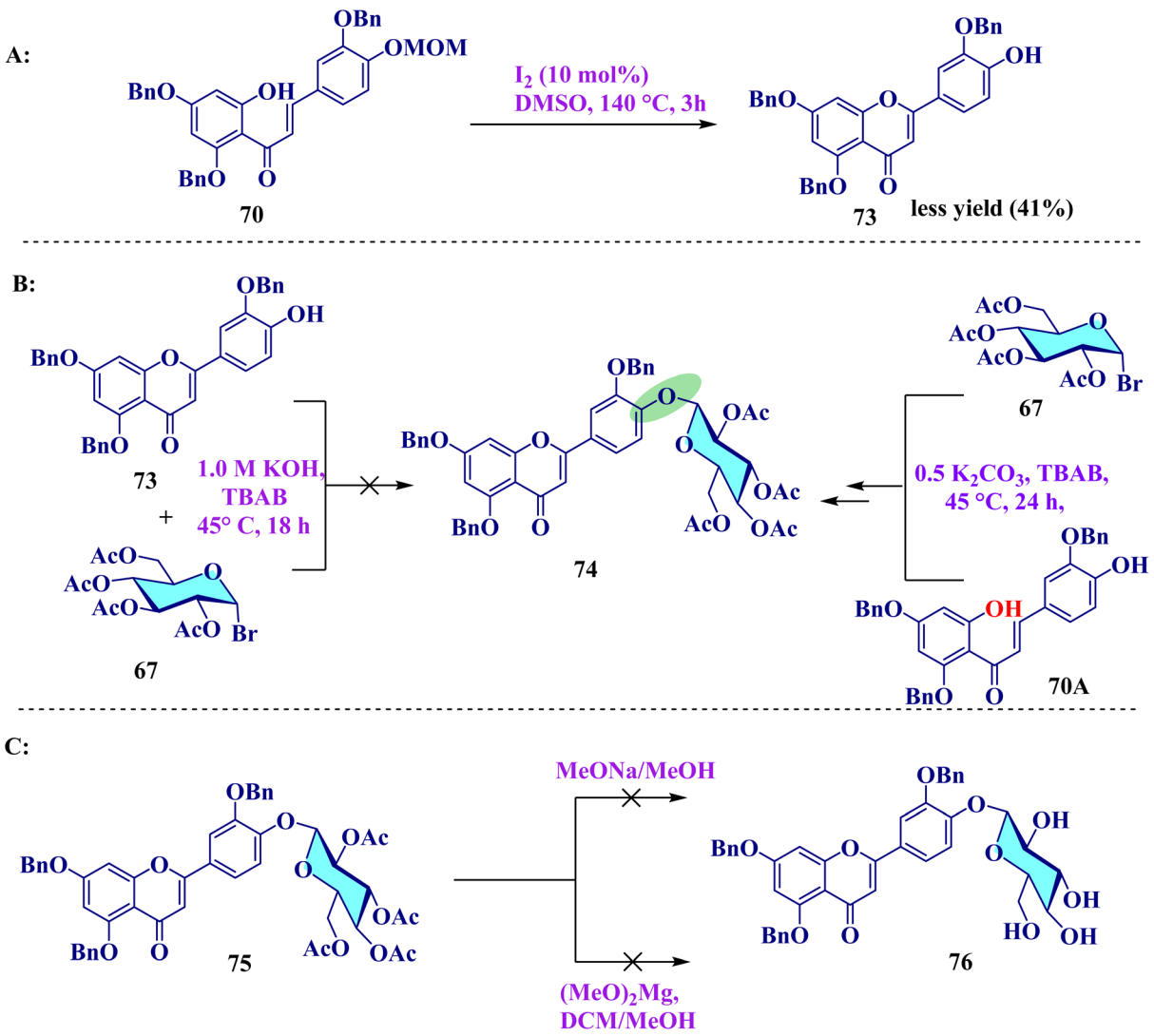



Fig. 13 Lessons from the total synthesis of leontopodioside A. (A) Unexpected deprotection of the MOM group; (B) unsuccessful glycosylation of flavone; (C) unsolved deacetylation.

**3.4.2. Synthetic route.** The forward synthesis, inspired by the retrosynthetic analysis, began with a masterful Friedel–Crafts reaction between 1,3,5-trimethoxybenzene **53** and carboxylic acid **56** at 70 °C using $BF_3$ $OEt_2$ as a Lewis acid to form phenyl ketone **57** with 79% yield.[137,138] The exquisitely methylated isoflavone **58** was obtained in 73% using a Bischler–Napieralski-type cyclization of **56** with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA).[139] Then, employing $BBr_3$, a high-yielding ether cleavage of **58** was performed, converting it into an isoflavone intermediate in an amazing 89% yield.[140] In the presence of a phase transfer catalyst, the glycosyl donor 2,3,5,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide, $(Pv)_4GlcBr$, **54** proved essential in achieving the selective glycosylation of that intermediate because of its resilience to basic environments, resulting in compound **59** with 84% yield.[141,142] The final product **51** was obtained by the protection of 2′- and 4′-OH groups with -Pv groups in the presence of PvCl/Py using DCM as a solvent, methylation with DBU and MeI, forming compound **60**, followed by transesterification with NaOMe (Scheme 4).

**3.4.3. Strategies and lessons learned from this synthesis.** A crucial observation in this synthesis was that during the Friedel–Crafts reaction, fully methylated product **61** was not identified by TLC due to the preferential deprotection of the 2′-OMe group, most likely resulting from Lewis acid coordination between the carbonyl and 2′-OMe groups (Fig. 11). Furthermore, only 30% of compound **58** was produced during its synthesis, along with a number of unknown side products, suggesting problems with DMF and $BF_3 \cdot OEt_2$ and methanesulfonyl chloride.[143] Ultimately, the process became even more sluggish when 2,3,4,6-tetra-*O*-acetyl-α-D-glycosyl trichloroacetimidate **62** was used as a glucosyl donor for the Schmidt glycosylation of compound **64**.[144,145]

### 3.5. Leontopodioside A

**3.5.1. Synthetic strategy.** In 2020, Li's group synthesized leontopodioside A,[146] a potent α-glucosidase inhibitor with an $IC_{50}$ of 55.6 ± 1.9 μM, significantly lower than that of acarbose ($IC_{50}$ = 626.3 ± 25.8 μM), which had been isolated from *Leontopodium leontopodioides* by Xie's group in 2016.[147–149] They employed a convergent synthetic strategy, connecting the aglycone intermediate **11** with the sugar unit **67** (Fig. 12). The aglycone was synthesized *via* aldol condensation of protected compounds **5** and **7** using a strong base, starting from commercially available 3,4-dihydroxybenzaldehyde **5**. Similarly, the introduction of the ester linkage at the primary –OH group is achieved by selectively reacting the glucose unit with benzyl-protected 4-hydroxybenzoyl chloride **68**, following the formation of the glycosyl bond with the flavone unit.

**3.5.2. Synthetic route.** The synthesis started with 3,4-dihydroxybenzaldehyde **5**, which underwent benzyl chloride and NaH treatment in DMF to regioselectively create the 3-*O*-benzyl product **10** in 59% yield, as per the retrosynthetic analysis.[150] The methoxymethyl (MOM) group was used to

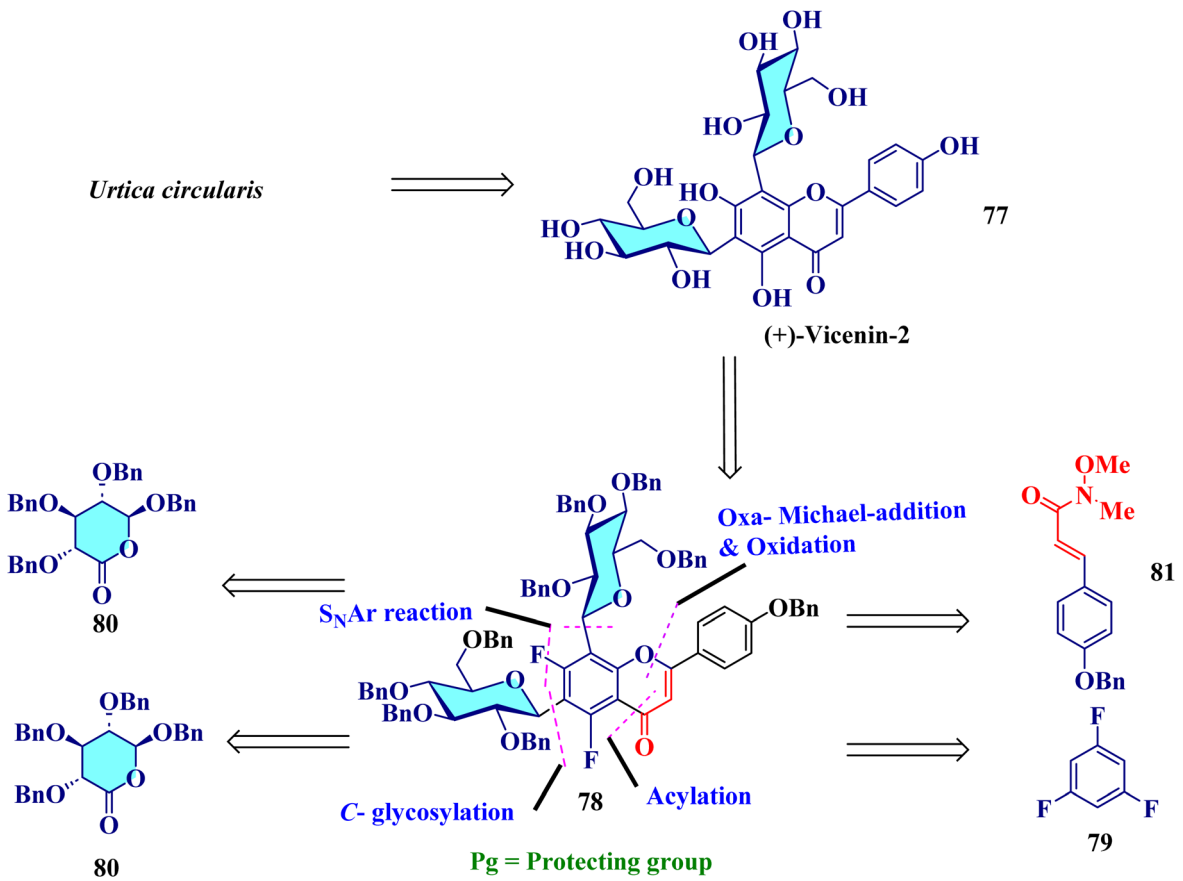
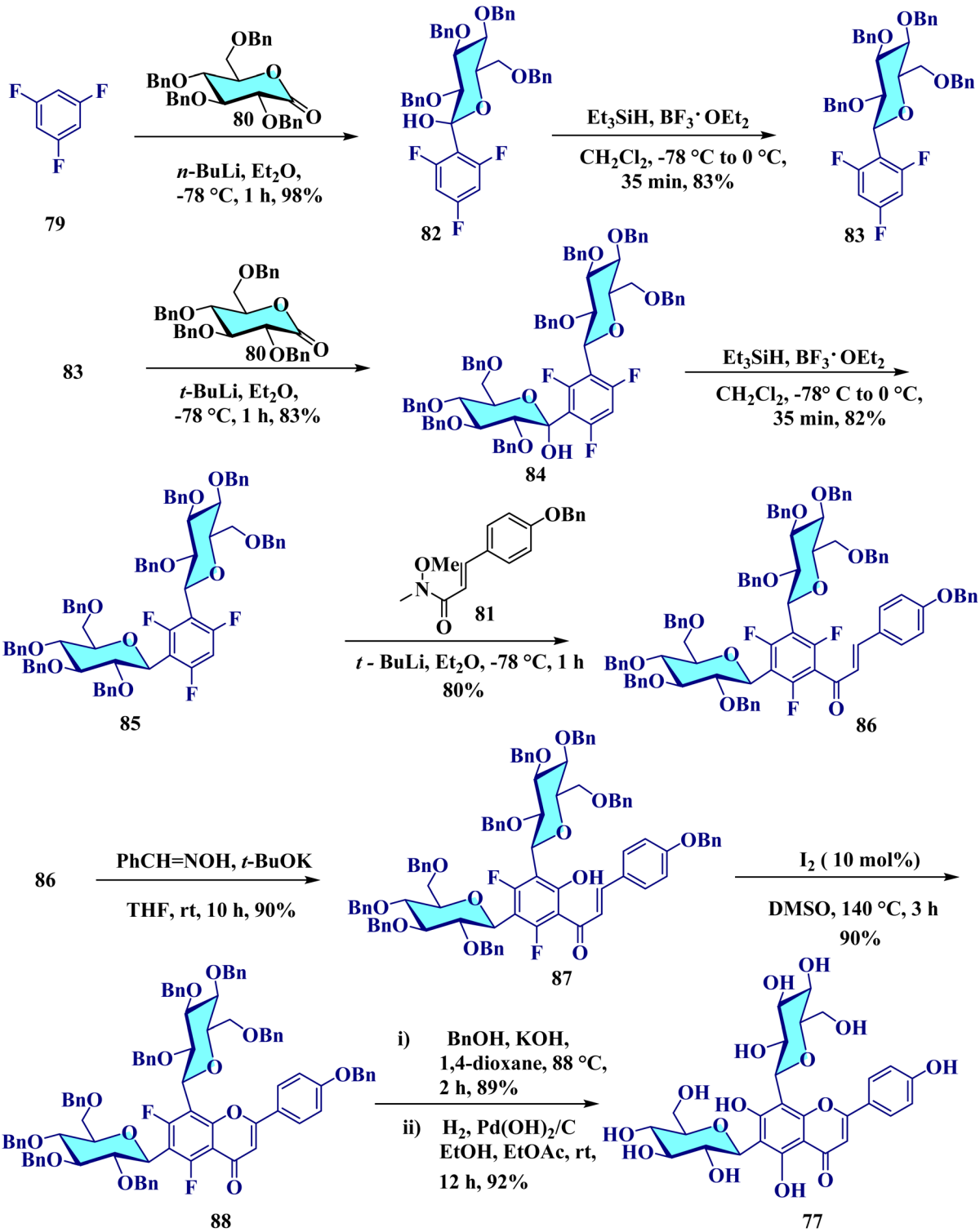



Fig. 14 Conversion strategy for the total synthesis of (+)-vicenin-2.




Scheme 6 Forward synthesis of (+)-vicenin-2 (Ohmori and Suzuki, 2016).[166]

preserve the remaining free phenolic –OH group in compound **10** using DCM and DIPEA as a base. Compound **70** was obtained *via* aldol condensation of compound **69** and 7 in the presence of NaH. It was then deprotected with 3 M HCl in THF under reflux for 2 h, resulting in 91% yield of the chalcone aglycone. After this, the required glycosylated compound **71** was generated in 74% yield by phase-transfer glycosylation with glycosyl donor **67** and 0.5 M $K_2CO_3$ at 45 °C.[151] After employing a MeONa/MeOH system to deprotect the acyl group, glucoside **71** was *O*-6 acylated with benzyl-protected 4-hydroxybenzoyl chloride **68** and DIPEA/$Me_2SnCl_2$ to produce compound **72**. Compound **65**, leontodioside A,

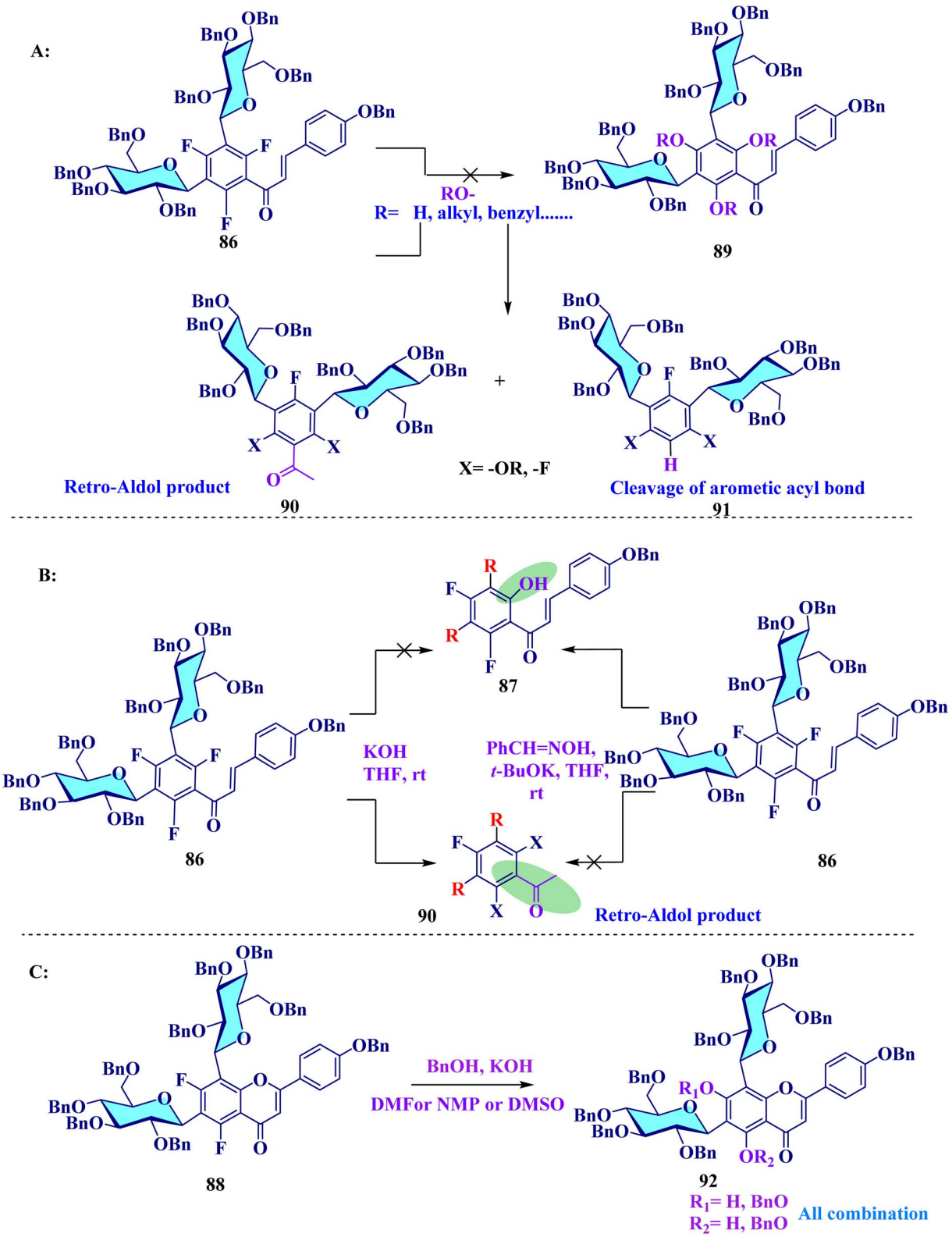



Fig. 15 Lesson from the total synthesis of (+)-vicenin-2. (A) Unsuccessful $S_NAr$ reaction; (B) regioselective defluorination; (C) random debenzylation.

was generated in 88% yield by cyclization with $I_2$/DMSO[152] with final deprotection using hydrogen and $Pd(OH)_2/C$ (Scheme 5).

**3.5.3. Strategies and lessons learned from this synthesis.** In this paper, the authors encountered significant challenges in optimizing the yield of the target molecule. Their first approach

involved cyclizing the chalcone to obtain the flavone, followed by the introduction of the sugar unit **67** (Fig. 13). However, only 41% of the flavone was produced, mostly because of the elimination of the -MOM group. Therefore, they changed their synthetic strategy, concentrating on glycosylating the chalcone. The phase-transfer glycosylation procedure was hindered by the use of 1.0 M KOH as a base, even though $K_2CO_3$ was used to execute glycosylation between compounds **73** and **67**. Furthermore, the typical MeONa/MeOH system did not deprotect the acyl groups on compound **75**, and attempts to utilize $(MeO)_2Mg$ as a moderate base in DCM/MeOH were similarly unsuccessful, underscoring the instability of the flavonoid ring.[153]

## 4. Total synthesis of flavonoid *C*-glycosides

*C*-Glycosylated flavonoids are an intriguing class of chemicals that are present in many different plants. They are oxygen-rich heterocycles that are stable compared to the flavonoid *O*-glycoside due to the presence of more acid, base, or enzymatic hydrolysis-resistant covalent C–C bonds,[154,155] and they are formed when the sugar moiety's anomeric carbon is joined to the carbon of the flavonoid aglycone skeleton by a *C*-glycosidic bond.[156] As siderophores, antibiotics, antioxidants, and even insect attractants or feeding deterrents, flavonoid *C*-glycosides found in various plants, microbes, and insects have a variety of vital functions in nature.[157] Flavone *C*-glycosides, which are abundant in major cereal crops, including maize, wheat, and rice, are noteworthy for their resistance to hydrolysis, which guarantees both their biological activity in plants and their nutritional value.[158] Curiously, research has demonstrated that *C*-glycosylation in the A-ring can lower antioxidant activity; this impact may be related to the intrinsic characteristics of the sugar rather than the removal of a hydroxyl group.[73] The improved enzymatic and chemical stability of these *C*-glycosides suggests their potential for developing small-molecule inhibitors targeting glycoside metabolism and cell-surface recognition.[159,160]

### 4.1. (+)-Vicenin-2

**4.1.1. Synthetic strategy of (+)-vicenin-2.** In 2016, Ohmori and Suzuki efficiently synthesized (+)-vicenin-2, a bis-*C*-glycosyl apigenin, extracted by Ferraro's group in 2011 from the Argentinean native herb *Urtica circularis*[161] and used as anticancer,[162] antidiabetic,[163] anti-inflammatory[164] and antioxidant[165] agents, utilizing 1,3,5-trifluorobenzenes as a starting material.[166] They leveraged two distinct reactions of fluorobenzenes, namely, *ortho*-lithiation and nucleophilic aromatic substitution ($S_NAr$), to modify the structure. By substituting oxygenated functional groups for fluorine atoms on the A-ring *via* $S_NAr$, the flavone C-ring was created through an intramolecular oxa-Michael addition, followed by oxidation. Aryl anion attacks on carbonyl derivatives were used to gradually add the sugar lactone units **80** and the cinnamoyl-group-containing compound **81** (Fig. 14).

**4.1.2. Synthetic route for (+)-vicenin-2.** The synthesis started with compound **79**, which was lithiated with $^n$BuLi in a diethyl ether medium, and hemiketal **82** was quantitatively generated through a reaction with lactone **80**.[167] Compound **82**

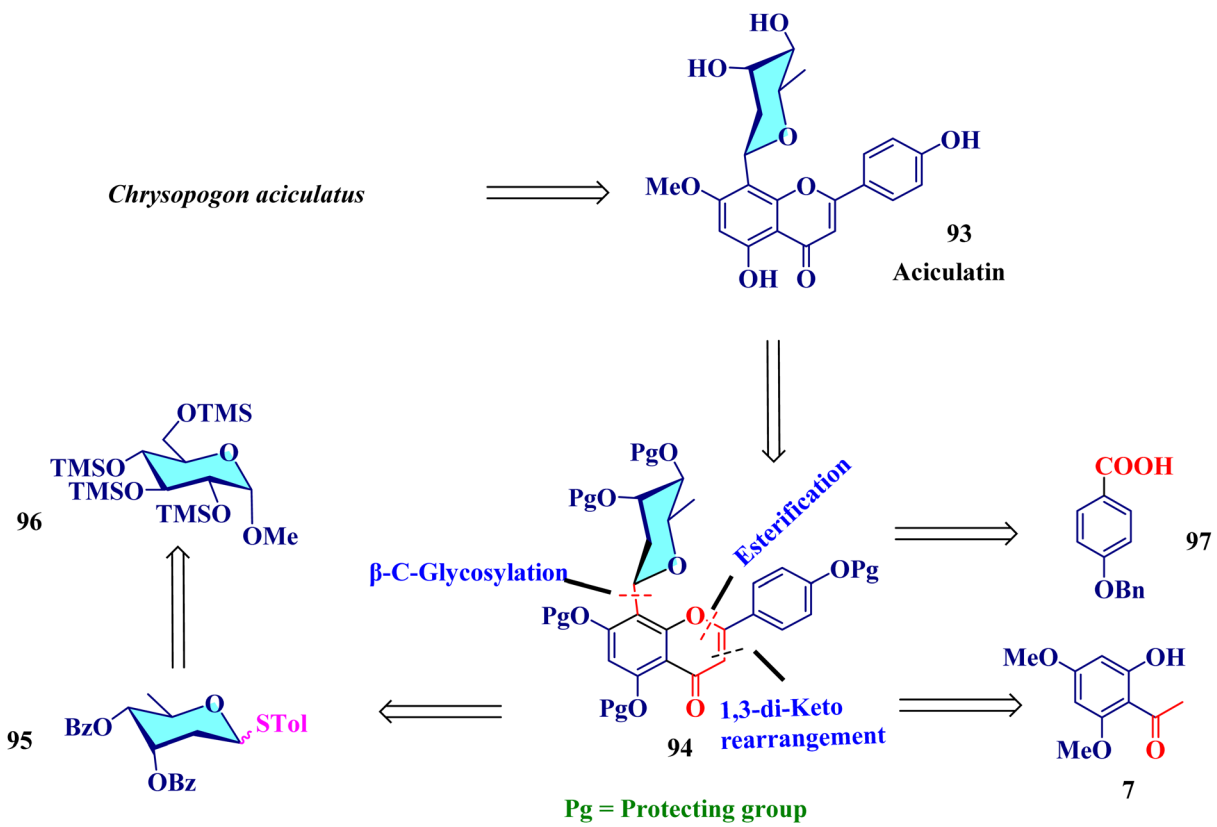
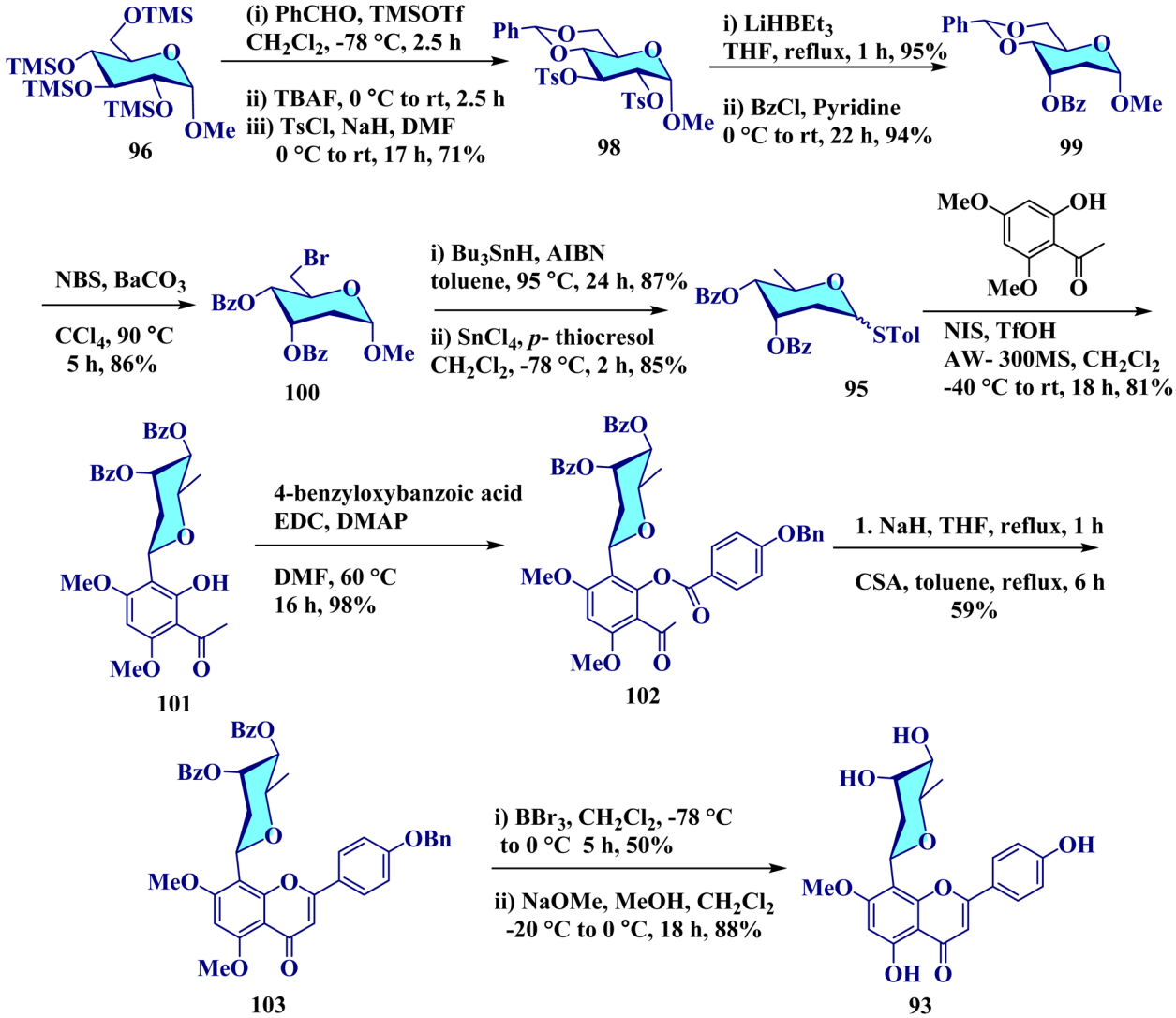



Fig. 16 Convergent strategy for the total synthesis of aciculatin.




Scheme 7 Forward synthesis of aciculatin (Lee, 2016).[177]

was reduced with triethylsilane and $BF_3 \cdot OEt_2$ in DCM to give mono-β-*C*-glycoside **83** in 83% yield.[168] Similarly, lactol **84** was produced by lithiating *C*-glycosyl trifluorobenzene **83** with $^t$BuLi and then reacting with lactone **80**. Compound **84** was then reduced under similar conditions to produce bis-β-*C*-glycoside **85** in 82% yield. The crucial intermediate **86** was obtained in 80% yield through the deprotonation of **85** with $^t$BuLi using $Et_2O$ solvent at −78 °C and subsequent reaction with α,β-unsaturated Weinreb amide **81**.[169] Vicenin 2 was produced in 92% yield through the last transformations, which included the substitution of a hydroxy group for fluorine of compound **86** with $^t$BuOK and benzaldoxime in THF,[170] the production of chromanone using $I_2$/DMSO cyclization of compound **87**,[171] replacement of C-5 and C-7 fluorine atoms of compound **88** with BnOH/KOH in 1,4-dioxane at 88 °C (ref. 172) and hydrogenolysis in the presence of $H_2/Pd(OH)_2/C$ (Scheme 6).

**4.1.3. Strategies and lessons learned from the synthesis of (+)-vicenin-2.** After compound **86** was obtained, attempts to substitute hydroxy or alkoxy groups for all fluorine atoms failed, and no trisubstituted compound **89** was produced (Fig. 15).[173] Byproducts **90** and **91** were produced as a result of the severe circumstances, causing retro-aldol condensation and/or cleavage of the C(4)–C(10) bond. Therefore, the C-5 fluorine atom was first replaced with the hydroxy group, and 90% of the phenol **87** was formed when **86** reacted with benzaldoxime in THF at room temperature. By treating flavone **88** with KOH and benzyl alcohol in 1,4-dioxane at 88 °C, the remaining fluorines were substituted with benzyl alkoxide, resulting in a fully benzoxylated compound in 89% yield.[172] However, ether cleavage at C(4′), C(5′), and C(7) occurred when dipolar aprotic solvents like DMF, NMP, or DMSO were utilized in the presence of the same chemical environment, resulting in the undesirable mono- and di-phenolic compounds **92**. Similarly, retro-aldol condensation of **86** occurred in the absence of benzaldoxime by reaction with KOH in THF at rt to form **90** instead of **87**.

### 4.2. Acicullatin

**4.2.1. Synthetic strategy.** Acicullatin, a potent anti-inflammatory[174] and anti-cancer[175] agent isolated from *Chrysopogon aciculatus* by Carte's group in 1991,[175,176] was synthesized by Lee's group in 2016 based on a retrosynthetic scheme that starts with β-D-digitoxopyranosylflavone **95** and proceeds through a sequence of functional group modifications (Fig. 16).[177] In the beginning, using a one-pot process including protection and functional group transformations, methyl 2,3,4,6-tetra-*O*-trimethylsilyl-alpha-glucopyranoside **96** is converted into the crucial digitoxosyl donor intermediate. Then the β-C-digitoxosyl derivative is anticipated to be produced by glycosylation of an electron-rich phenol acceptor **7** with the digitoxyl donor through an *O*-to-*C* Fries-type rearrangement. The following stages involve the esterification of β-D-digitoxopyranosyl phenol and –OBn protected acid **97**, which is then converted into the flavone through a Beker–Venkataraman rearrangement and cyclohydration reaction with CSA.

**4.2.2. Synthetic route.** Starting with methyl 2,3,4,6-tetra-*O*-trimethylsilyl-α-D-glucopyranoside **96**, thiodigitoxoside **95** was synthesized. In a one-pot reaction, methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucopyranoside **98** was produced from compound **96** with an extraordinary 71% yield.[178] Compound **99** (methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-α-ribohexopyranoside) was produced in 94% when glucoside **98** was reduced with lithium triethylborohydride ($LiBEt_3$) in THF *via* the involvement of the α-D-allo-2,3-epoxide intermediate and selective ring opening and further benzoylation of the 3-axial hydroxy group of the intermediate formed in this reaction with BzCl in pyridine.[179] Fully protected digitoxoside **100** was obtained in 86% yield through the NBS-mediated fragmentation of 4,6-benzylideneacetal using the Hanessian–Hullar reaction in $CCl_4$ at 90 °C.[180,181] After that, reductive debromination with $Bu_3SnH$ and AIBN in toluene at 90 °C, and subsequent *p*-thiocresol and $SnCl_4$ were used to convert compound **100** into the desired 3,4-di-*O*-benzoylthio-digitoxide **95**, yielding 85% product.[182] Then, with the help of digitoxin derivative **95** and NIS/TfOH, the electron-rich phenol **7** was glycosylated, yielding β-D-digitoxopyranoside **101** with strong regio- and stereo-selectivity (81% yield).[183] The hydroxy-*C*-glycosyl product was likely produced *via* an *in situ* O-to-C Fries-type rearrangement. Using EDC, β-*C*-digitoxoside **101** was esterified with 4-benzyloxybenzoic acid **97**, resulting in 98% yield of ester **102**. This ester was rearranged by the Baker and Venkataraman rearrangement using NaH as a reagent to produce a 1,3-diketone, which was subsequently cyclodehydrated by CSA to form flavone **103**.[184,185] The monomethoxy *C*-glycosyl compound **93** was finally generated *via* $BBr_3$/DCM mediated de-*O*-methylation and then

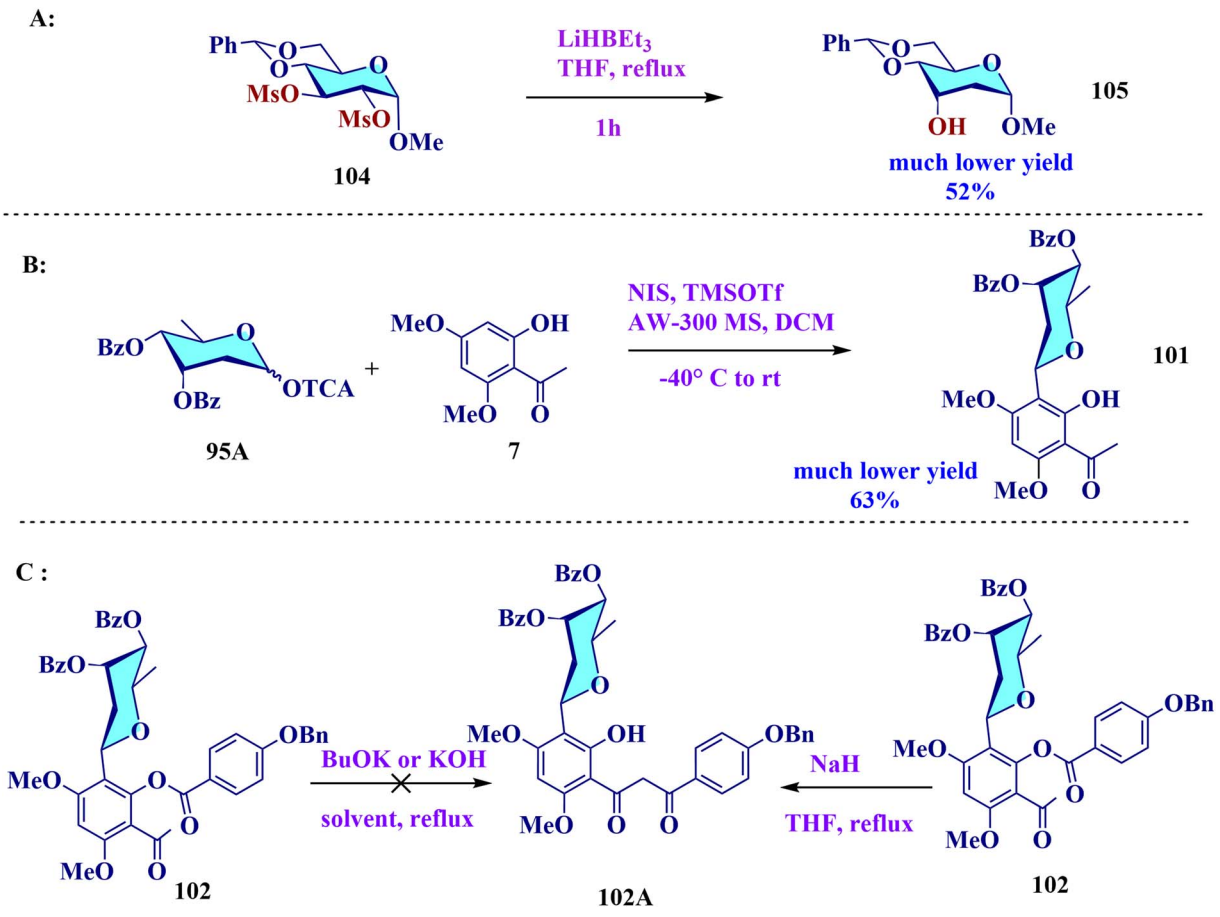



Fig. 17 Lesson from the total synthesis of aciculatin. (A) Unsuccessful reductive cleavage; (B) low-yielding *C*-glycosylation; (C) re-optimisation for B–V rearrangement.

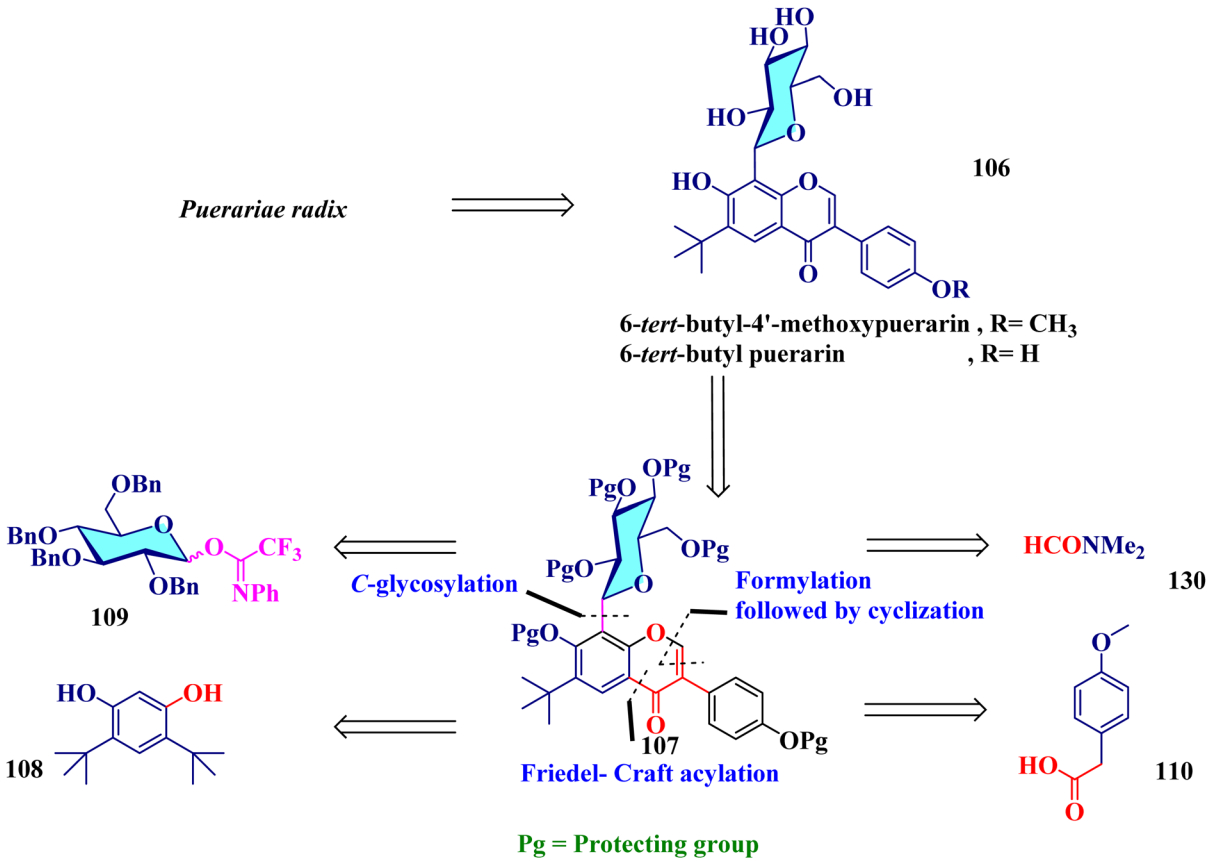



Fig. 18 Convergent strategy for the total synthesis of 6-*tert*-butyl-4′-methoxypuerarin and 6-*tert*-butyl puerarin.

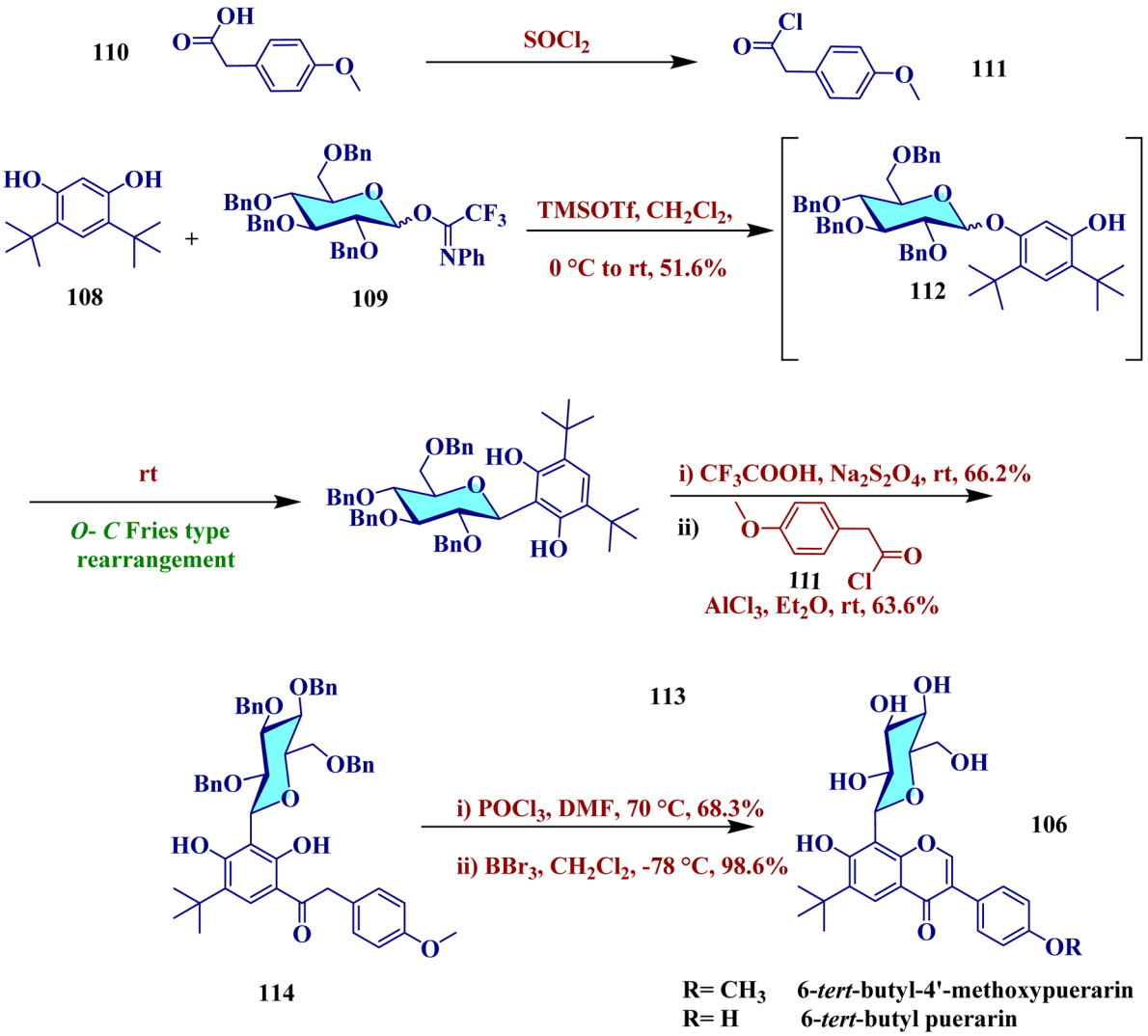
de-*O*-benzoylation of flavone **103** with NaOMe/MeOH, DCM to yield aciculatin in 88% yield (Scheme 7).[186]

**4.2.3. Strategies and lessons learned from this synthesis.** Numerous issues with the entire synthesis were observed, including a 52% lower yield for the reductive cleavage of methyl-4,6-*O*-benzylidene-2,3-di-*O*-mesyl-α-D-glucopyranoside with lithium triethylborohydride (Fig. 17). Therefore, the synthesis was continued with the tosyl-protected compound **98**. Additionally, employing the 3,4-di-*O*-benzoyldigitoxosyl imidate donor **95A** with a catalytic quantity of TMSOTf resulted in a low yield of just 63% of compound **101**, highlighting that TfOH is the optimal choice for achieving the best yield in this *C*-glycosylation process. Then, purification was made more difficult by the development of two significant byproducts when $^{t}$BuOK or KOH was used as a base in the 1,3-diketone formation reaction using the Beker–Venkataraman rearrangement. However, the utilization of NaH as a base in this process provides satisfactory results. In this particular case, the selective demethylation of flavone **103**, using the $BBr_3{\cdot}SMe_2$ complex, produces the desired compound with an unsatisfactory yield of 42%, which inspires us to pursue this process with $BBr_3$ in DCM medium.

### 4.3. 6-*Tert*-butyl puerarin and 6-*tert*-butyl-4′-methoxypuerarin

**4.3.1. Synthetic strategy.** The isoflavone *C*-glycosides from *Pueraria radix*[187] show strong anti-myocardial ischemic action[188] and are more resistant to hydrolysis in acidic gastric juices than *O*-glycosides and aglycones; they exhibit various biological activities like radio-protectivity,[189] colony-stimulating[190] and antidiabetic effect, and derivatives such as 6-*tert*-butylpurrarin and 6-*tert*-butyl-4′-methoxy-puerarin have been synthesized to enhance the efficacy and concentration of puerarin by preventing its metabolism in the liver.[191] Therefore, in 2017, Peng, Gao, and Wang pioneered a green synthesis of 6-*tert*-butyl-puerarin and 6-*tert*-butyl-4′-methoxypuerarin *via* a streamlined deoxybenzoin route.[192] Starting with compound **108**, they employed an *O*- to *C*-glycoside rearrangement, followed by de-*tert*-butylation to create 2-*C*-β-D-glucopyranoside **114** (Fig. 18). This compound was reacted with thionyl chloride, producing a deoxyenzoin intermediate, which was then cyclized in DMF using $POCl_3$/DMF to form the desired flavone structure. Finally, debenzylation and demethylation were performed to yield the target compounds.

**4.3.2. Synthetic route.** They began the synthesis with compound **108**, which was reacted with 2,3,4,6-tetra-*O*-benzyl-glucopyranosyl trifluoroacetamide **109** to form 2-*C*-β-D-glucopyranoside **113** *via* *O*- to *C*-glycoside rearrangement with TMSOTf in DCM medium.[193,194] The *tert*-butyl group was then removed in the presence of trifluoroacetic acid at room temperature for 1.5 h,[195] and the intermediate was reacted with 4-methoxyphenylacetyl chloride **111**, synthesized from the corresponding acid with thionyl chloride **110** at room temperature,[196] to yield deoxybenzoin **114** with 63.6% isolated product.




Scheme 8 Forward synthesis of 6-*tert*-butyl-4′-methoxypuerarin and 6-*tert*-butyl puerarin (Peng, Gao, and Wang, 2017).[192]

Treatment of **114** with $POCl_3$/DMF gave glucosylisoflavone in 68.3% yield,[197] and subsequent temperature-controlled debenzylation (at −78 °C) and demethylation (−10 °C) with $BBr_3$/DCM yielded the final compound 6-*tert*-butyl-4′-methoxy-puerarin and 6-*tert*-butylpurrarin in 95.5% and 98.6% yield, respectively (Scheme 8).[198–200]

**4.3.3. Strategies and lessons learned from the synthesis.** Their attempt to react 1-(5-*tert*-butyl-2,4-dihydroxyphenyl)-2-(4-methoxypenyl)-ethenone **115** with 2,3,4,6-tetra-*O*-benzyl-glucopyranosyl trifluoroacetimidate **109** was unsuccessful because the phenol acceptor's electron-withdrawing acyl group decreased the reactivity and prevented the production of *C*-glycoside (Fig. 19). Several attempts to de-*tert*-butylate β-*C*-glycoside **113** with solutions such as HBr,[201] TfOH,[202] $AlCl_3$/toluene,[203] $AlCl_3$/DCM,[204] $AlCl_3$/toluene and nitromethane,[205] and sulfuric acid/toluene were unsuccessful. Furthermore, subsequent attempts to cyclize deoxybenzoin **114** using DMF, morpholine, and triethyl orthoformate at 140 °C destroyed the sugar ring, and debenzylation of **119** using 10% Pd–C also failed due to olefin reduction and produced compound **120**.[206]

## 4.4. Carambolaflavone A (1)

**4.4.1. Synthetic strategy.** In 2018, the Du and Sun group achieved a remarkable enantioselective total synthesis of the hypoglycemic drug carambolaflavone A, which was extracted from the leaves of *Averrhoa carambola* in 2005 by Chou's group.[207–209] Carambolaflavone A is used to treat diabetes mellitus, which is synthesized using a masterfully designed convergent strategy (Fig. 20).[210] Central to their approach was the construction of a crucial *C*-glycosidic linkage, seamlessly connecting a flavone subunit derived from monobenzyl-protected 2,4,6-trihydroxyacetophenone **123**, derived from dimethoxymethylated 2,4,6-trihydroxyacetophenone **124**. By leveraging the thermodynamically favored Suzuki *O* → *C* glycoside rearrangement[211] with a perbenzylated L-fucopyranosyl acetate donor **126**, derived from 1,2:3,4-di-*O*-isopropyllidine-α-fucopyranose **127**, they elegantly assembled the flavone scaffold through a sophisticated sequence of esterification with 4-(benzyloxy) benzoic acid **125**, Baker–Venkataraman rearrangement, and acid-catalyzed cyclization.

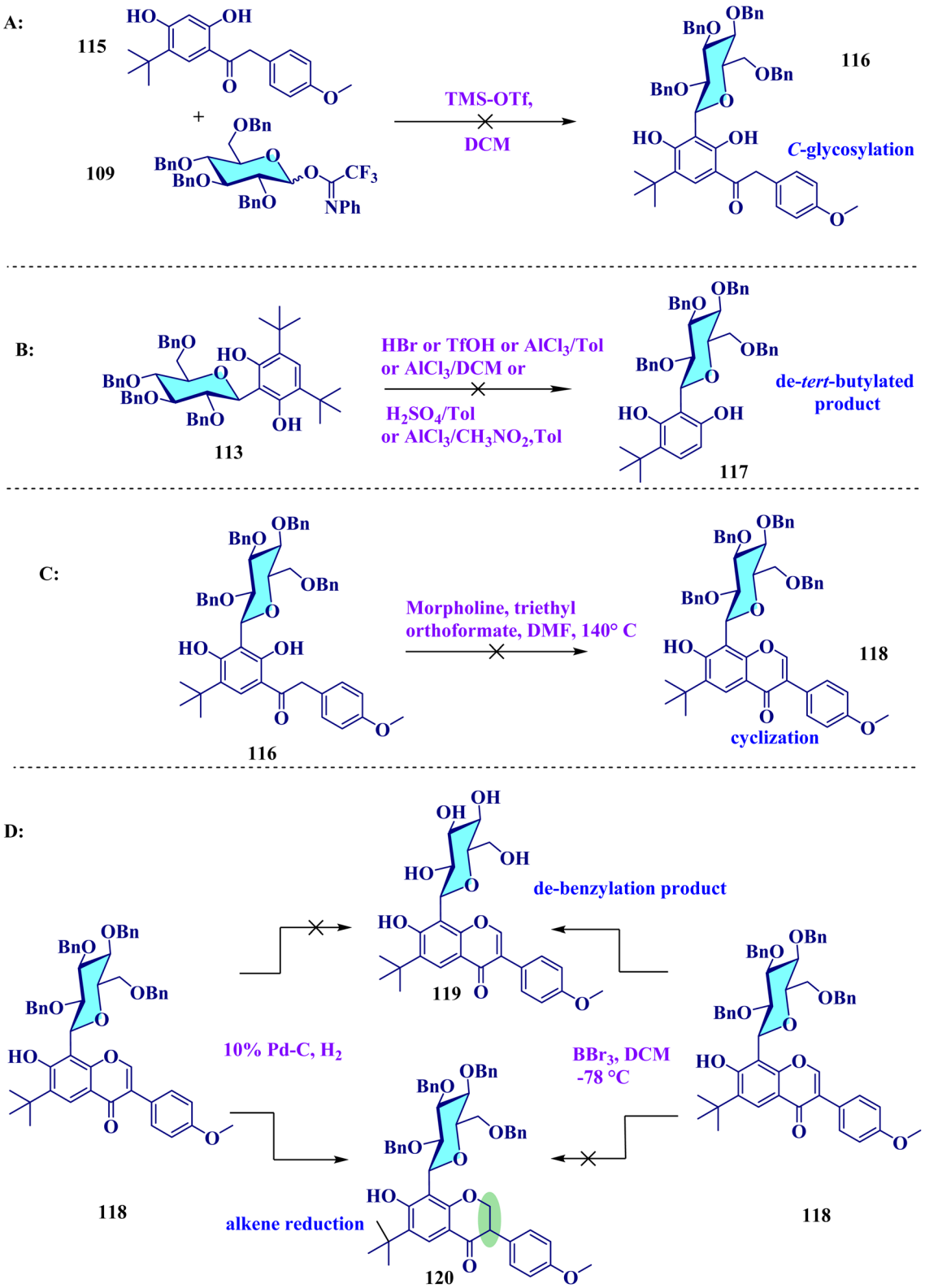



Fig. 19 Lessons from the synthesis of 6-*tert*-butyl-4′-methoxypuerarin and 6-*tert*-butyl puerarin. (A) Unsuccessful *C*-glycosylation; (B) failed de-*tert*-butylation; (C) issue with cyclization reaction; (D) uncontrolled reduction.

**4.4.2. Synthetic route.** The synthesis began with the protection of the 6-OH group of dimethoxymethylated 2,4,6-trihydroxyacetophenone **124** using a 2-naphthylmethyl group (Nap) in the presence of $K_2CO_3$/DMF, yielding the mono-naphthylated compound **128** in 94%. Subsequent selective removal of the methoxymethyl groups with 3 M HCl in MeOH

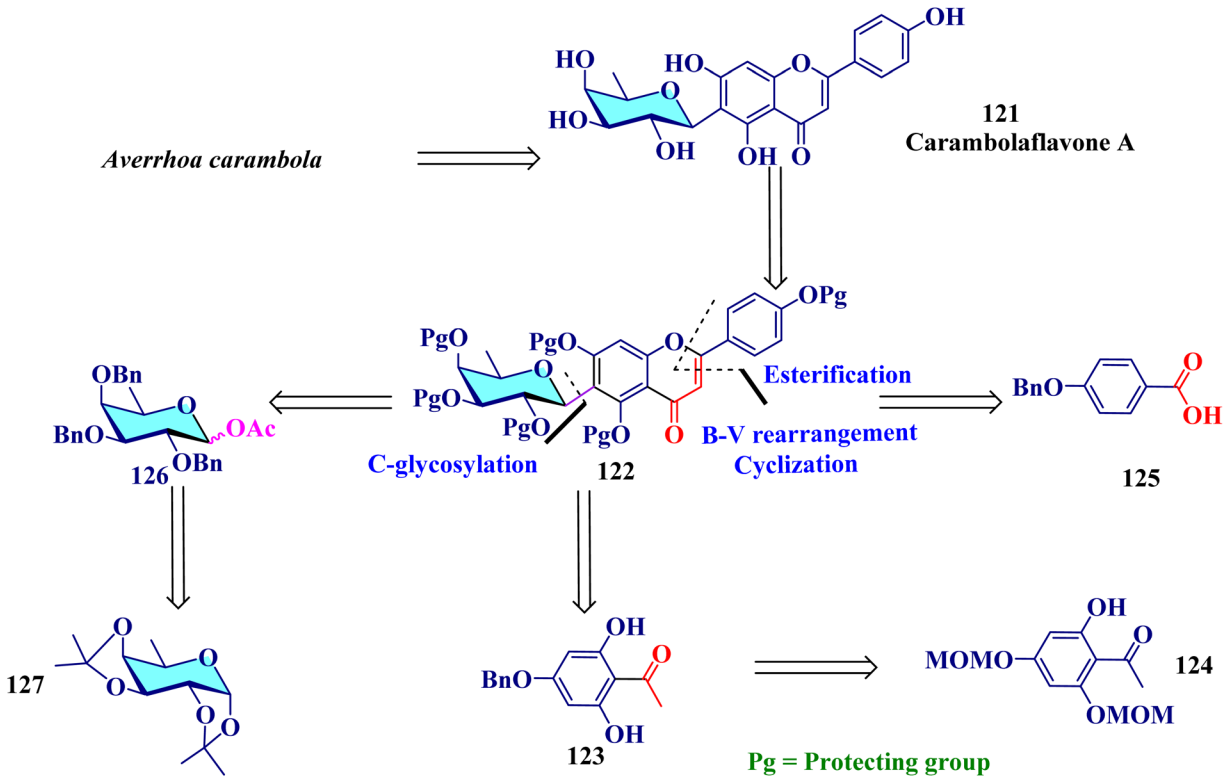


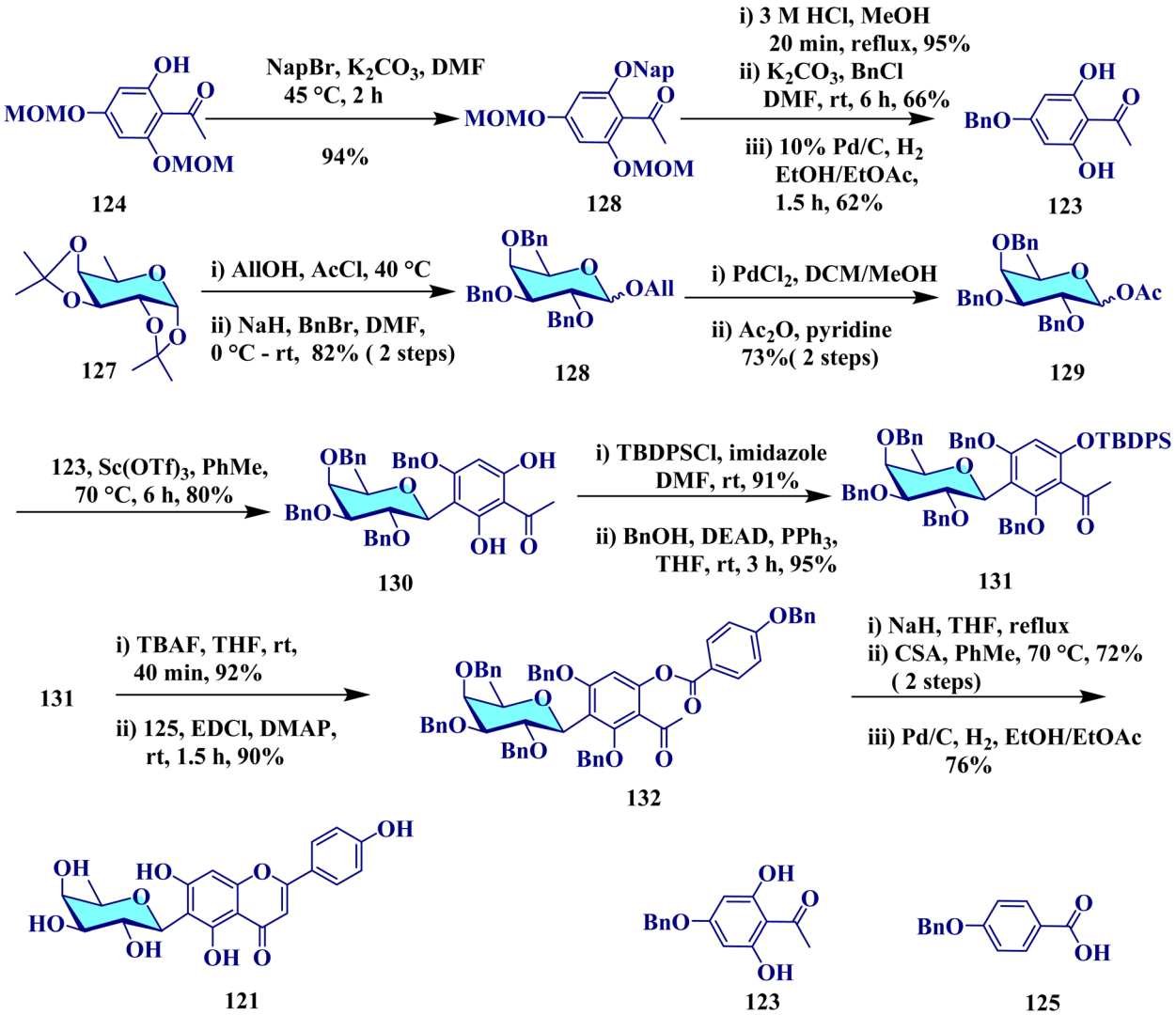

Fig. 20 Convergent strategy for the total synthesis of carambolaflavone A.

afforded a diol intermediate, which, after regioselective benzylation under mild conditions with $K_2CO_3$ and BnCl in DMF and controlled hydrogenolysis removing the Nap group selectively, provided the desired monobenzylated acetophenone **123** in 62% yield.[212] Using $Sc(OTf)_3$ in dry toluene at 70 °C, the critical *C*-glycosidic linkage was formed after obtaining the main acceptor **126**, yielding *C*-glycoside **130** with great effectiveness.[213–215] They synthesized perbenzylated fucosyl intermediate **126** starting from fucose diacetone **127**. First, they carried out a glycosylation reaction between fucose diacetone and allyl alcohol in the presence of a catalytic amount of acyl chloride. The product was then benzylated using BnBr and NaH in DMF, yielding the allyl-protected perbenzylated D-fucosyl donor **128**. Subsequent deallylation using $PdCl_2$/MeOH, followed by acylation with acetic acid in pyridine, gave the desired intermediate **126**.[216,217] Based on NMR spectroscopic analysis, atropisomer formation of the reported compound was caused by the inclusion of a *tert*-butyldiphenylsilyl (TBDPS) group in intermediate **130**. The flavone scaffold was eventually produced by tetrabutylammonium fluoride (TBAF)-mediated TBDPS removal to obtain compound **131** in 92% yield after Mitsunobu protection of compound **130** with BnOH, DEAD, and $PPh_3$ in THF (95%), followed by dehydrative esterification of the intermediate with EDCl, DMAP in DMF,[218] Baker–Venkataraman rearrangement in the presence of NaH in THF medium, and CSA mediated cyclization (2 steps, 61%). Hydrogenolysis by Pd/C and $H_2$ in EtOH/EtOAc of perbenzylated intermediate **132** was used to achieve universal deprotection and produce carambolaflavone A **121** (Scheme 9).

**4.4.3. Strategies and lessons learned from this synthesis.** While synthesizing the target molecule **121**, when the same procedure was followed for the synthesis of carambolaflavone A with perbenzylated L-fucosyl acetate donor **133**, a product with identical NMR spectra but an opposite optical rotation value was obtained, indicating that the enantiomer of authentic **121** was produced and that the originally proposed structure of **121** was misassigned (Fig. 21). Additionally, the coupling of monobenzylated acetophenone **123** with perbenzylated L-fucosyl acetate under Suzuki's conditions[219] (0.2 equiv. $Sc(OTf)_3$) in dry DCM yielded only 25% of the desired β-*C*-glycoside, alongside 30% α-*C*-glycoside and 22% α-*O*-glycoside. Although switching to toluene provided a broader tunable temperature range, the yield was not improved under these conditions. Increasing the reaction temperature proved effective in suppressing *O*-glycoside formation, and raising the $Sc(OTf)_3$ amount from 0.2 to 0.5 equiv. increased the β-*C*-glycoside yield to 78%. Further optimization, including the removal of 4 Å MS, led to a clean conversion to the desired product with a high yield of 94% under the final optimal conditions of 0.2 equiv. of $Sc(OTf)_3$ in dry toluene at 70 °C.[220]

### 4.5. Schaftoside

**4.5.1. Synthetic strategy.** The total synthesis of schaftoside, found in the leaves of sugarcane,[221] was started in 2021 by Liu and Du's group[222] to investigate its anti-obesity, anti-diabetic, hepatoprotective, and antiallergenic effects.[223–225] Although the synthesis strategy comprised severing the apigenin A-ring at the 6-*C*-β-D-glucopyranoside and 8-*C*-α-L-arabinopyranoside linkages, they strategically selected (±)-naringenin as the starting




Scheme 9 Forward synthesis of carambolaflavone A (Du and Sun, 2018).[207]

material due to its electron-rich aromatic ring, which facilitated *C*-glycosylation at the C-6 position of the flavone moiety. After introducing the sugar units onto the naringenin derivative **138**, they converted it to apigenin derivatives through a two-step process (Fig. 22). This process involved the two consecutive oxidations of *C*-glycosylflavan. Lewis acid-promoted *O*-to-*C* fries-type rearrangement was used to achieve regio- and stereoselective *C*-glycosylation between flavan, which is strategically derived from flavanone **138**, and the peracetylglycosyl trichloroacetimidates **137** and **139**, which were actually synthesized from D-glucose and L-arabinose.

**4.5.2. Synthetic route.** According to the retrosynthetic analysis, the synthesis of key *C*-glycosyl flavan **142** started with (±)-naringenin. Before acetylating the 5-OH and 4″-OH groups with acyl chloride in the presence of pyridine to produce the diacetate flavone intermediate with a 70% yield, regioselective silyl protection of (±)-naringenin **138** with TBSCl in the presence of triethylamine/THF occurred at the 7-OH group due to its higher acidity. After removing the carbonyl group at C-4 by reduction with sodium borohydride in THF-$H_2O$ to obtain compound electron-rich flavan **140**.[226] Compound 6-*C*-β-D-glucopyranosyl flavan **141** was produced by *C*-glycosylation of flavan **140** with glucosyl donor **137** and a catalytic amount of TMSOTf at −15 °C. The TBS group was then selectively removed to yield a phenolic intermediate by the reaction of **141** with HF Py. Following a second glycosylation with donor **139** and TMSOTf to yield 6-*C*-β-D-glucopyranosyl-8-*C*-α-L-arabinopyranosyl flavan **142**, the latter was then bis-benzylated in the presence of benzyl bromide and $K_2CO_3$ base in DMF medium and oxidized twice, first with CAN and then with PDC, to form di-*C*-glycosylflavanone **143**.[227,228] Finally, hydrogenolysis of **143** with 10% Pd/C and $H_2$, followed by acetylation, produced compound **144**, which, in turn, cyclized with $I_2$/DMSO for the synthesis of the required flavone.[229] Global deacetylation of the intermediate flavone with MeOH/MeONa yielded the target compound, schaftoside **135**, in 89% yield (Scheme 10).

**4.5.3. Strategies and lessons learned from this synthesis.** Their strategy is unique as they first synthesized the target

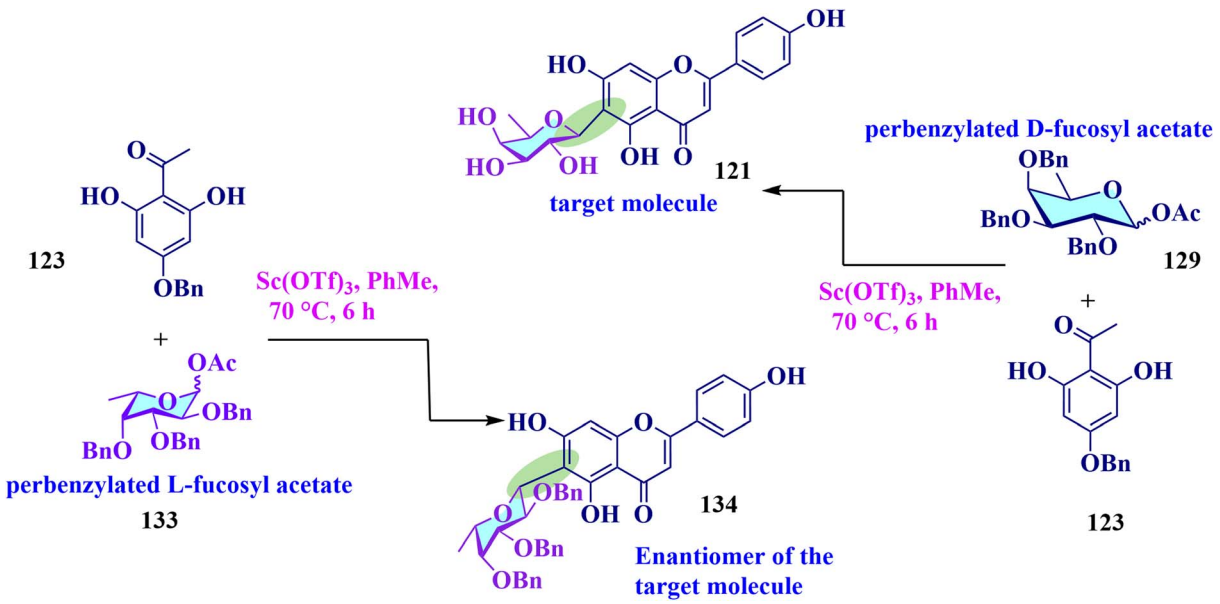



Fig. 21 Lessons from the total synthesis of carambolaflavone A.

molecule by modifying the core structure, recognizing that the apigenin derivative is less susceptible to *C*-glycosylation due to the electron-withdrawing effect of the C-4 carbonyl group and strong hydrogen bonding between the 5-OH and C-4, prompting a shift towards the forward synthesis. The oxidative dehydrogenation of *C*-glycosylflavan **142** proved challenging, with direct oxidation attempts failing and producing undesired benzoquinone byproducts (Fig. 23).[230] Protecting the phenolic hydroxyl groups with benzyl groups using $K_2CO_3$ allowed the reaction to proceed. However, one-pot oxidation method with cerium(IV) ammonium nitrate and peracetylated *C*-glycosylflavan **145** yielded the product **146** in less than 30% yield, likely due to reduced reactivity from electron-withdrawing acyl groups.

### 4.6. Carambolaflavone A (2)

**4.6.1. Synthetic strategy.** The Simpson group initiated stereoselective *C*-aryl glycosylation with bismuth triflate in 2022

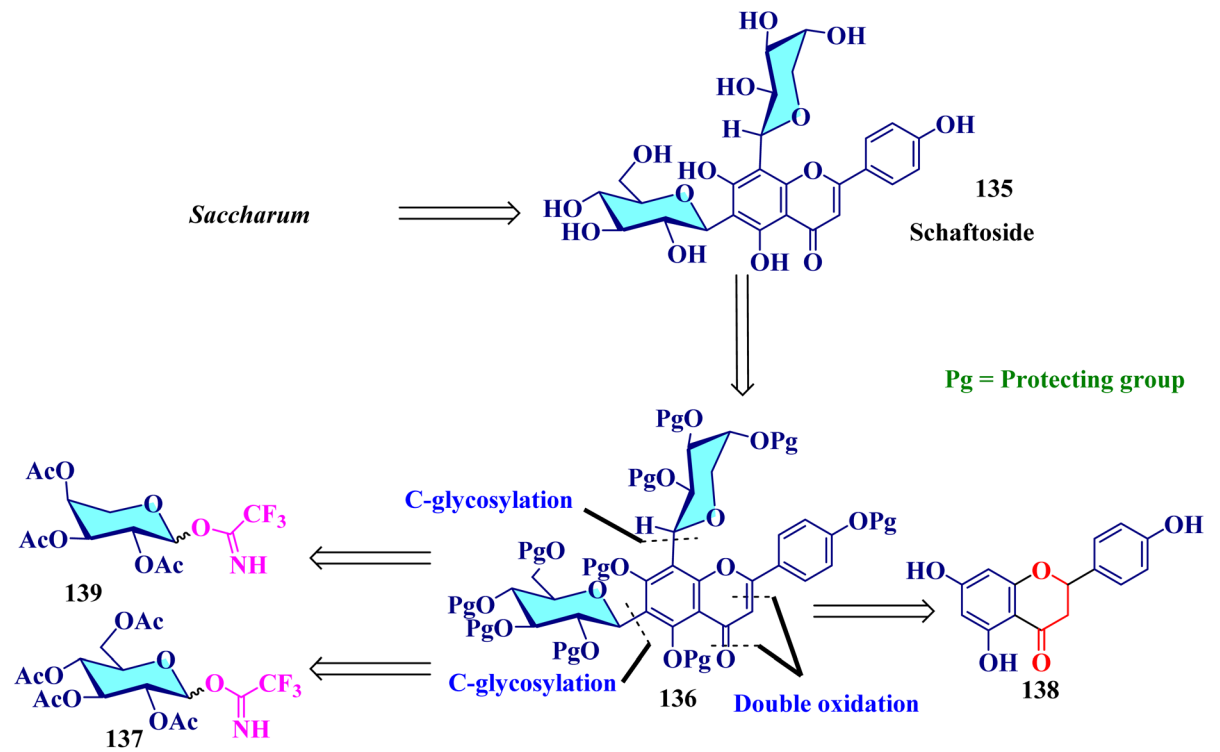
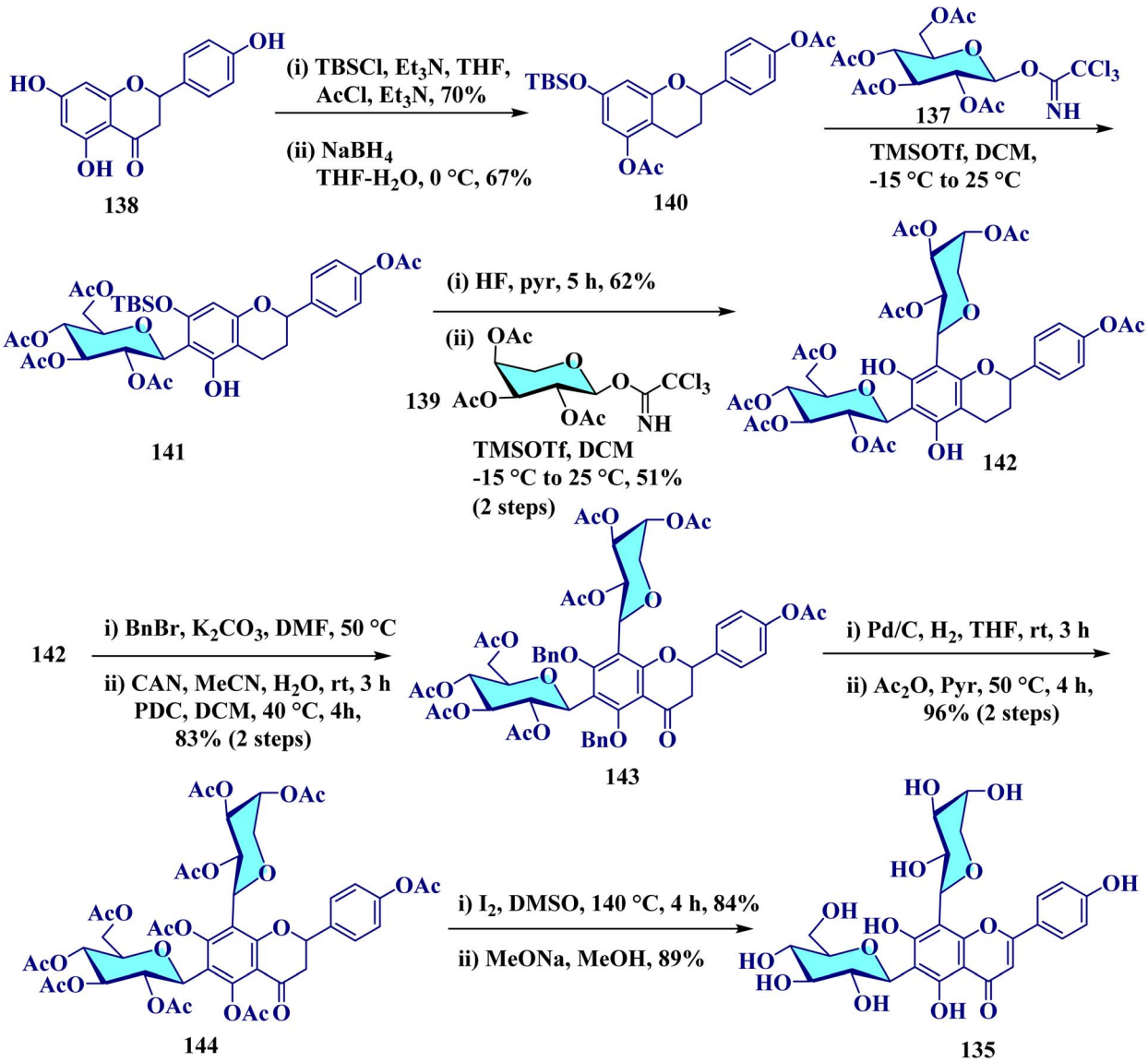



Fig. 22 Convergent strategy for the total synthesis of schaftoside.




Scheme 10 Forward synthesis of schaftoside (Liu, 2021).[222]

to synthesize carambolaflavone A,[231] a possible lead for anti-hyperglycemic medications, which was extracted from leaves of *Averrhoa carambola* in 2005 by Chou's group.[209,232] They wanted to build (+)-carambolaflavone A by *C*-glycosylating the protected flavan derivative **149** and D-fucose derivative **148** because breakdown occurs when flavones are directly *C*-glycosylated (Fig. 24). Flavan derivative **149** was produced from (±)-naringenin, and compound **148** was made from commercially available D-galactose **147** *via* a couple of concomitant protection–deprotection reactions.

**4.6.2. Synthetic route.** According to the retrosynthetic strategy, compound **149**, reacting with anhydrous $K_2CO_3$ and benzyl bromide in acetone at 23 °C to 56 °C for 12 hours, produced the monobenzylated intermediate, which was acylated with acetyl chloride in pyridine to produce diacetate intermediate **150** in two steps with a 69% yield. In dioxane and $H_2O$, diacetate **150** was reduced with $NaBH_4$ to obtain protected flavan derivative **151** as a racemic mixture in 91% yield. Diisopropylidene derivative **152** was formed in 93% yield by reacting D-(+)-galactose **147** with $ZnCl_2$, acetone, and a catalytic amount of $H_2SO_4$. In two processes, the main alcohol of **152** was transformed into an iodide intermediate with the reaction of $I_2$, imidazole/$PPh_3$ in toluene, and then the fucose derivative **153** was produced by hydrogenolysis with $H_2$, $Pd(OH)_2$, and $Et_3N$ in MeOH with 93% yield. After heating the glucose derivative **153** in AcOH to produce the tetraol, it was then benzylated with BnBr and NaH in DMF, to yield the tetrabenzyl derivative **154** in 75% yield.[233] After compound **154** was treated with $H_2SO_4$ and AcOH to create a hemiacetal, benzoyl chloride was added, and over the course of two stages, compound **154** produced fucose derivative **148** in a 63% yield. Bismuth triflate catalyzed *C*-aryl glycosylation of racemic flavan derivative **151** and glycosyl donor **148** in the presence of DCM solvent, resulting in a 76% yield of compound **155**.[234] In two phases, compound **155**

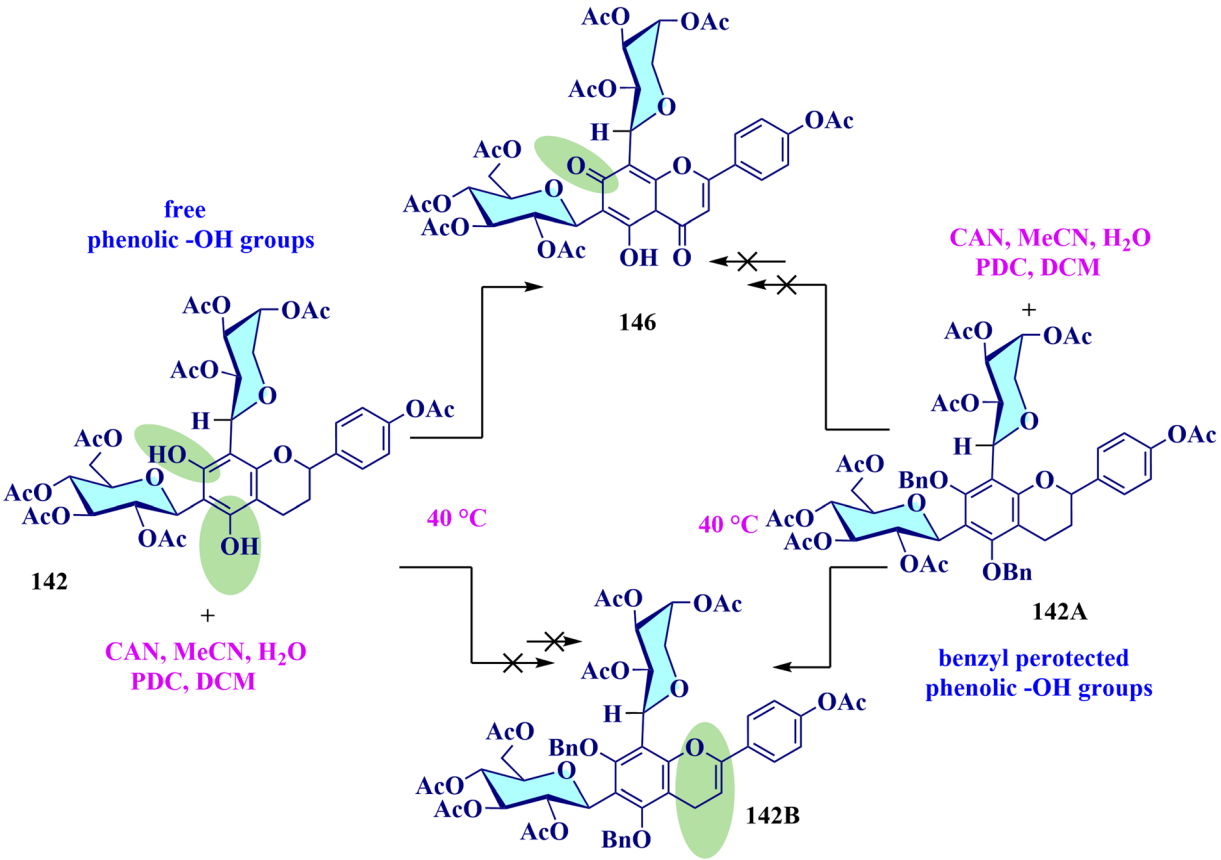



Fig. 23 Lessons from the total synthesis of schaftoside.

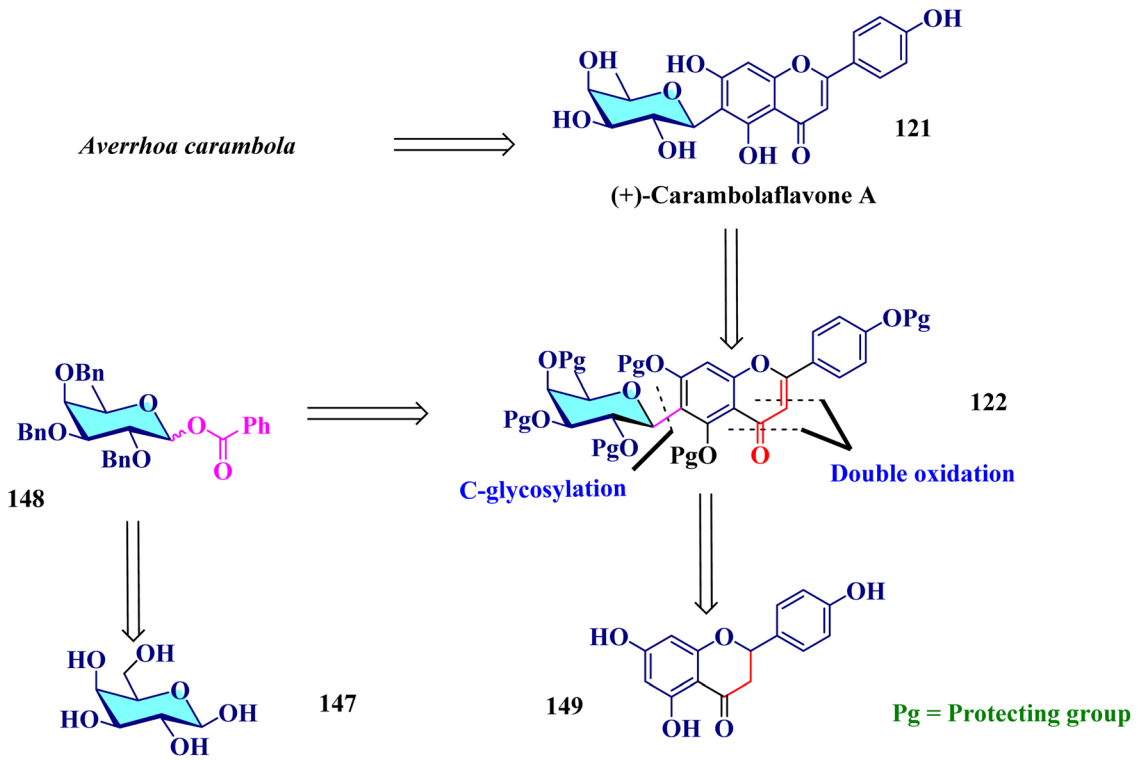
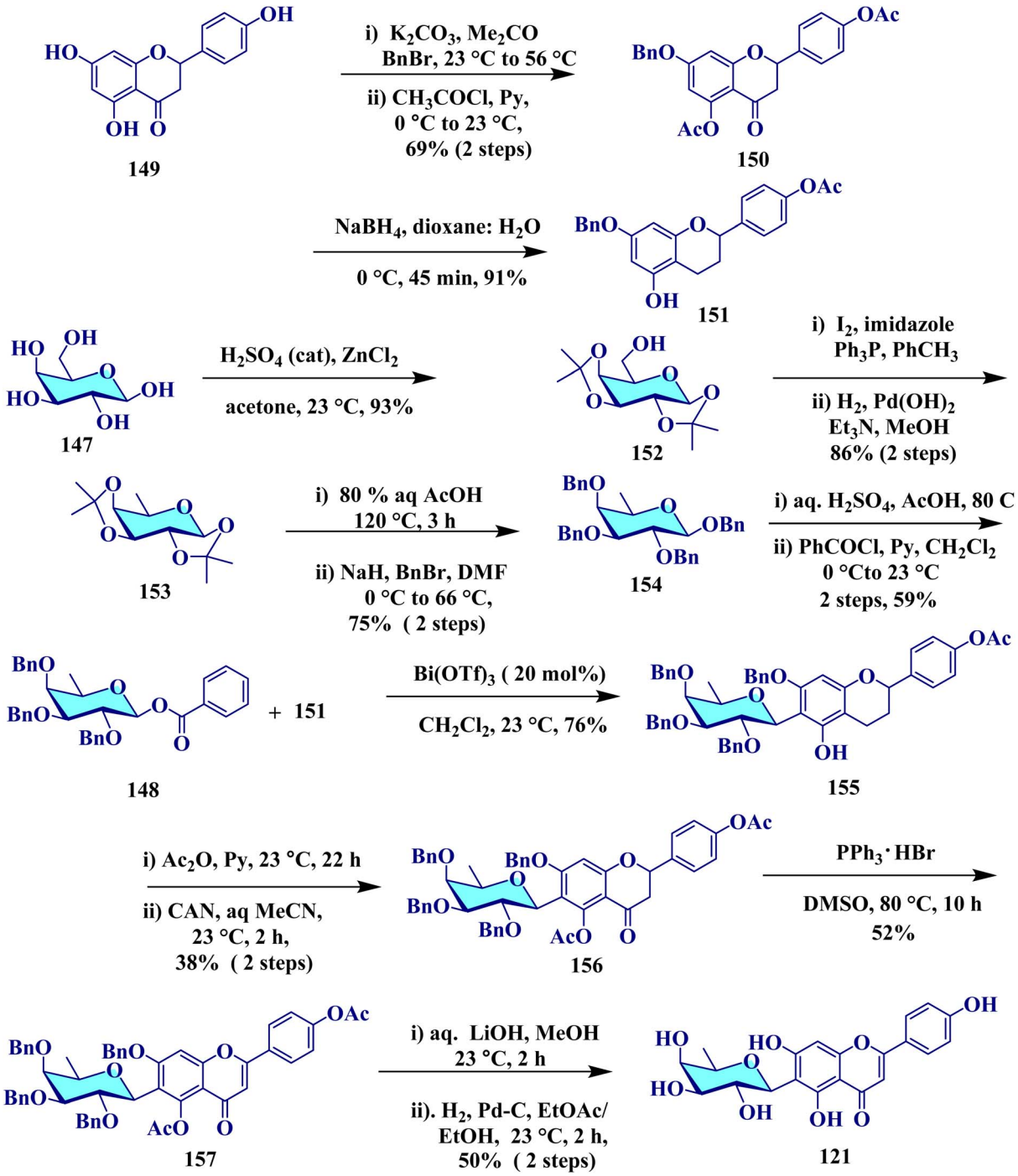



Fig. 24 Convergent strategy for the total synthesis of (+)-carambolaflavone A.




Scheme 11 Forward synthesis of carambolaflavone A (Simpson, 2022).[231]

underwent acetylation with $Ac_2O$/Py and oxidation with ceric ammonium nitrate in MeCN to give flavanone derivative **156** in 38% yield.[112] Protected flavone **157** was produced in 52% yield by brominating and dehydrogenating flavanone **156** in the presence of $PPh_3 \cdot HBr$ in DMSO for 10 hours at 80 °C. Ultimately, flavone **157** was deprotected by saponification with LiOH in MeOH and hydrogenolysis with $H_2$/Pd–C in EtOAc-EtOH, producing synthetic (+)-carambolaflavone A in 50% yield (Scheme 11).[235]

**4.6.3. Strategies and lessons learned from this synthesis.** Direct *C*-glycosylation of flavone derivatives frequently results in degradation of the starting material; Oyama and Kondo already tackled this issue using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) and $BF_3$ $OEt_2$. Although $Sc(OTf)_3$ has been utilized for this purpose in the past, $Bi(OTf)_3$, a nontoxic and affordable Lewis acid, was used in this study for the first time as an effective catalyst for the *C*-glycosylation of flavan derivatives **151**, utilizing acetate or benzoate derivatives to achieve a higher yield (Fig. 25).

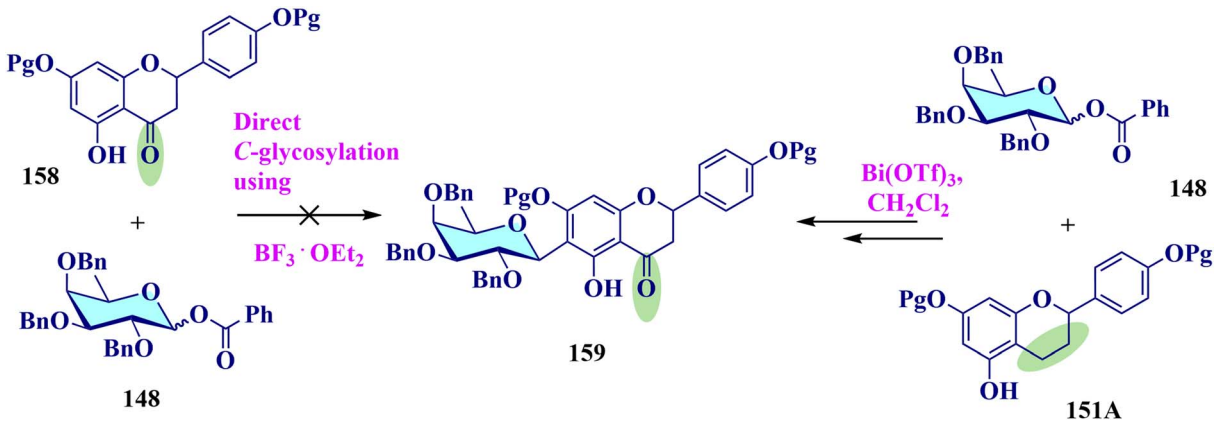



Fig. 25 Lessons from the total synthesis of carambolaflavone A (2).

Also, using a racemic flavan derivative and a small excess of acetate glycosyl donor, different metal triflates were used to study the *C*-aryl glycosylation processes in DCM at 23 °C. In the case of $Sc(OTf)_3$, 39% of β-*C*-aryl glycoside **155** was formed, but $Fe(OTf)_3$ yielded significantly smaller amounts of the desired product. Other catalysts, such as $Dy(OTf)_3$, $Cu(OTf)_2$, and $Zn(OTf)_2$, on the other hand, did not yield any product and instead recovered the starting material. Using benzoate derivatives as the glycosyl donor and $Bi(OTf)_3$ as a catalyst produced the highest yield of the flavan derivative **151** (76%). Electron-donating or electron-withdrawing groups on the phenyl ring of the benzoate glycosyl donor **148**, however, reduced the reactivity.

## 5. Total synthesis of flavonoid derivatives

Pyranoflavones, biflavones, and prenylated flavones are three fascinating families into which flavonoid derivatives are intriguingly divided. Flavonoid derivatives with a pyran group are called pyranoflavonoids, whereas bioflavonoids are dimeric substances made up of two monoflavonoid residues joined by C–C or C–O–C bonds. Flavone–flavone and flavanone–flavanone dimers are examples of these molecules, which may have free or methylated hydroxyl groups and frequently have substitutions at the 5-, 7-, and 4′-positions. Prenylated flavonones are the most prevalent subclass of prenylated flavonoids, which are also significant due to their lipophilic prenyl side chain. These types of flavonoids are praised for their many physiological functions, including their potent anti-inflammatory and anti-cancer properties, antioxidant protection, and prevention of atherosclerosis.[236,237]

### 5.1. Sophoflavescenol

**5.1.1. Synthetic strategy.** Sophoflavescenol, a prenylated flavonoid with strong inhibitory activity against HL-60, LLC, and A549 tumor cells,[238] was synthesized by the Wang group in

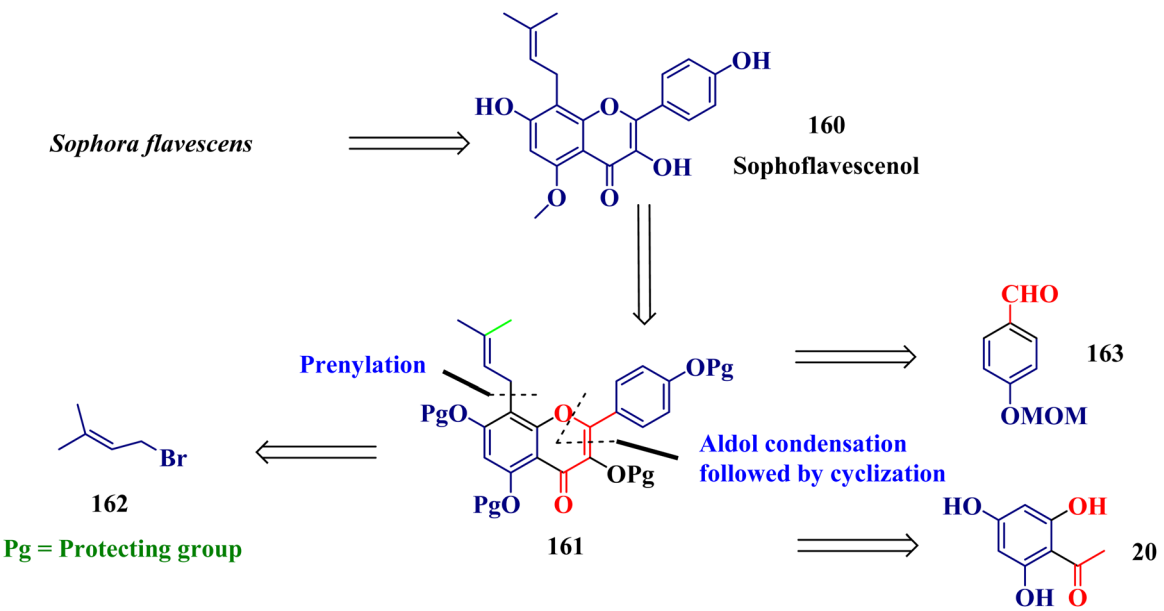
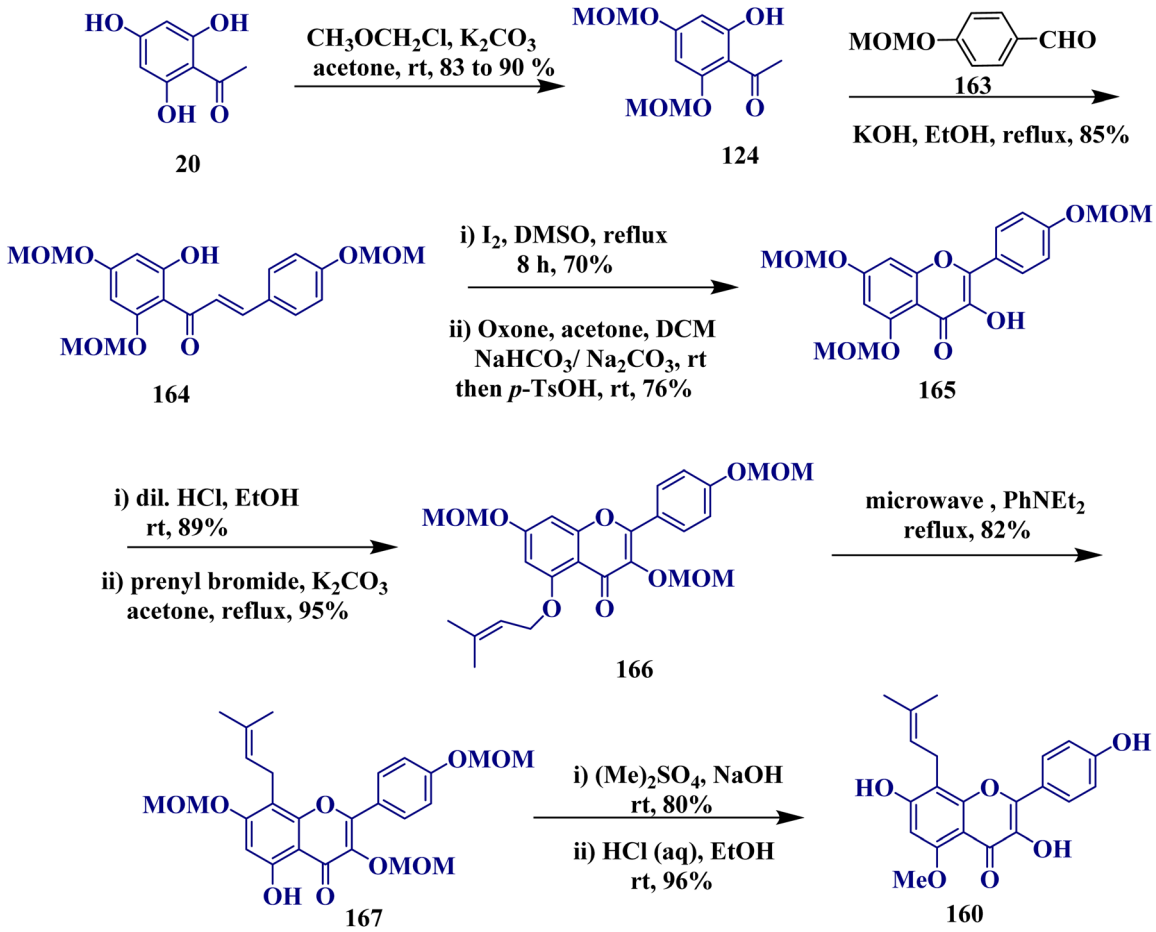



Fig. 26 Convergent strategy for the total synthesis of sophoflavescenol.




Scheme 12 Forward synthesis of sophoflavescenol (Wang, 2015).[239]

2015, after being extracted from *Sophora flavescens* by the Lee group in 2002.[239–241] It is the most selective CGMP phosphodiesterase 5 inhibitor ($IC_{50}$: 0.013 μM), making it a promising therapeutic option for erectile dysfunction.[241] To convert a 5-*O*-prenylflavonoid into the required 8-prenylated structure, their synthesis involved a regioselective, microwave-assisted Claisen rearrangement, beginning with commercially available 2,4,6-trihydroxyacetophenone **20** and MOM-protected 4-hydroxybenzaldehyde **163** (Fig. 26).

**5.1.2. Synthetic route.** Starting from commercially available 2,4,6-trihydroxyacetophenone **20**, the base-stable and acid-labile MOM-protected 2-hydroxyacetophenone compound **124** was produced by reaction with MOM-Cl and $K_2CO_3$ using acetone as solvent. Then, a base-catalyzed aldol condensation reaction of compound **124** with MOM-protected 4-hydroxybenzaldehyde **163** using KOH in ethanol was performed to produce chalcone **164**. The $I_2$/DMSO catalyzed cyclization of chalcone **164** was performed to obtain a flavone intermediate, on which the 3-OH group was installed by treatment with DMDO/acetone, generated *in situ* from oxone and acetone, followed by the opening of the resulting epoxide with catalytic *p*-TsOH to yield the flavanol **165**.[242] Selective deprotection and prenylation of 5-MOM with dilute HCl and prenyl bromide/$K_2CO_3$ in acetone were consecutively performed to obtain the *O*-prenylated compound **166**. Microwave-assisted Claisen rearrangement was performed to obtain the *C*-prenylated product **167** from **166** with 82% yield. The target natural sophoflavscenol **160** was synthesized by introducing methyl functionality at the 5-OH position, followed by the deprotection of all MOM groups with HCl and EtOH in 96% yield (Scheme 12).

**5.1.3. Strategies and lessons learned from this synthesis.** A major regioselectivity issue was highlighted by the fact that the ortho-rearranged product was obtained in 70% yield, with just 15% of the targeted para rearrangement product, when the usual heating approach was used for the Claisen-rearrangement of *O*-prenylated precursor **166** in *N*,*N*-diethylaniline at 190 °C (Fig. 27). This restriction was successfully overcome by microwave-assisted synthesis by preferentially producing the para rearrangement product with an astounding 82% yield under the same conditions.

### 5.2. I3, II8-biapigenin and idiculuflavone A

**5.2.1. Synthetic strategy.** In 2017, the group of Lu and Yu initiated the first total synthesis of two naturally occurring unsymmetrical bioflavonoids: I3, II8-biapigenin, which was extracted from *Hypericum perforatum* L. by the Holzl group in 2006,[243,244] and ridiculuflavone A, whose biological studies

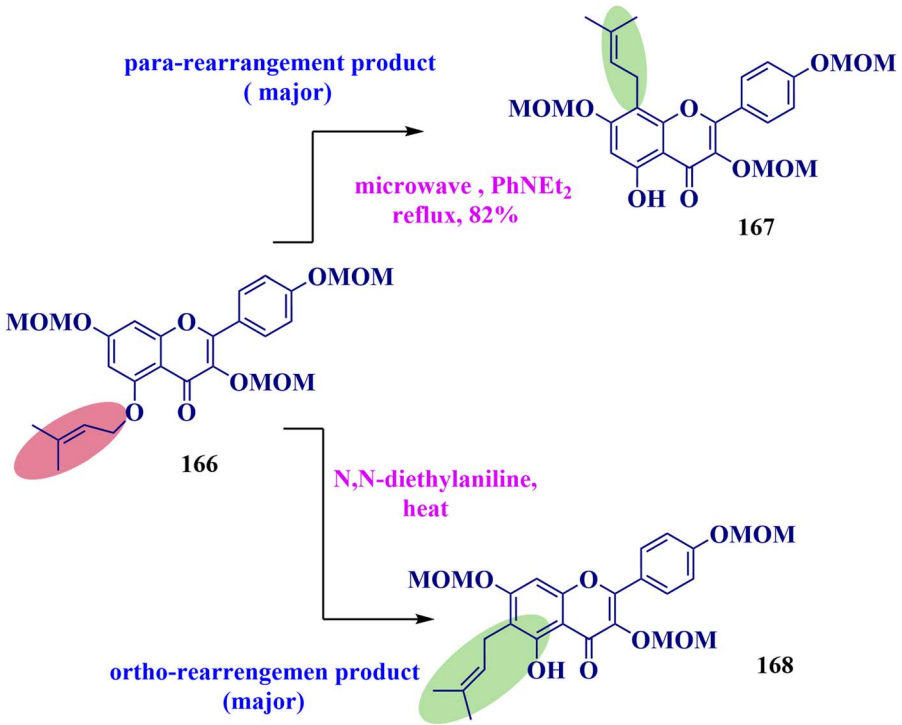



Fig. 27 Lessons from the total synthesis of sophoflavescenol.

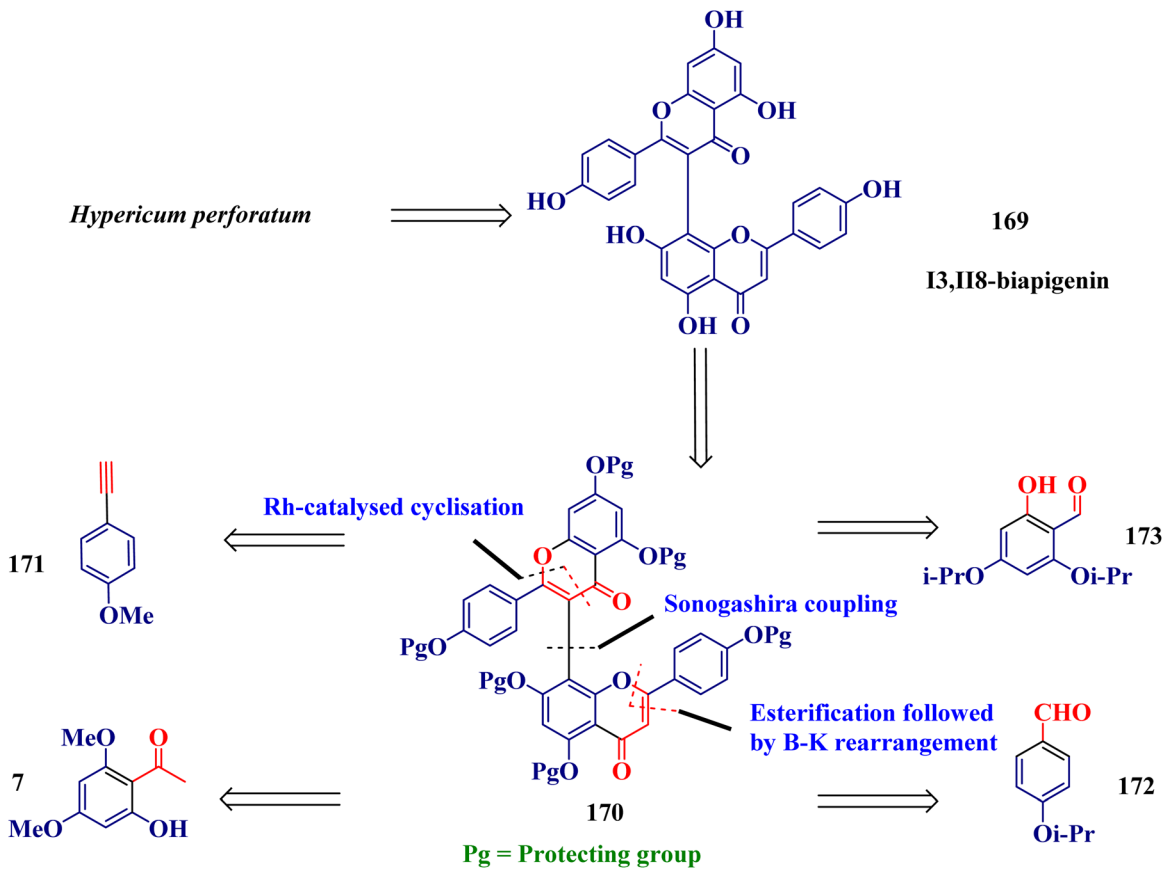
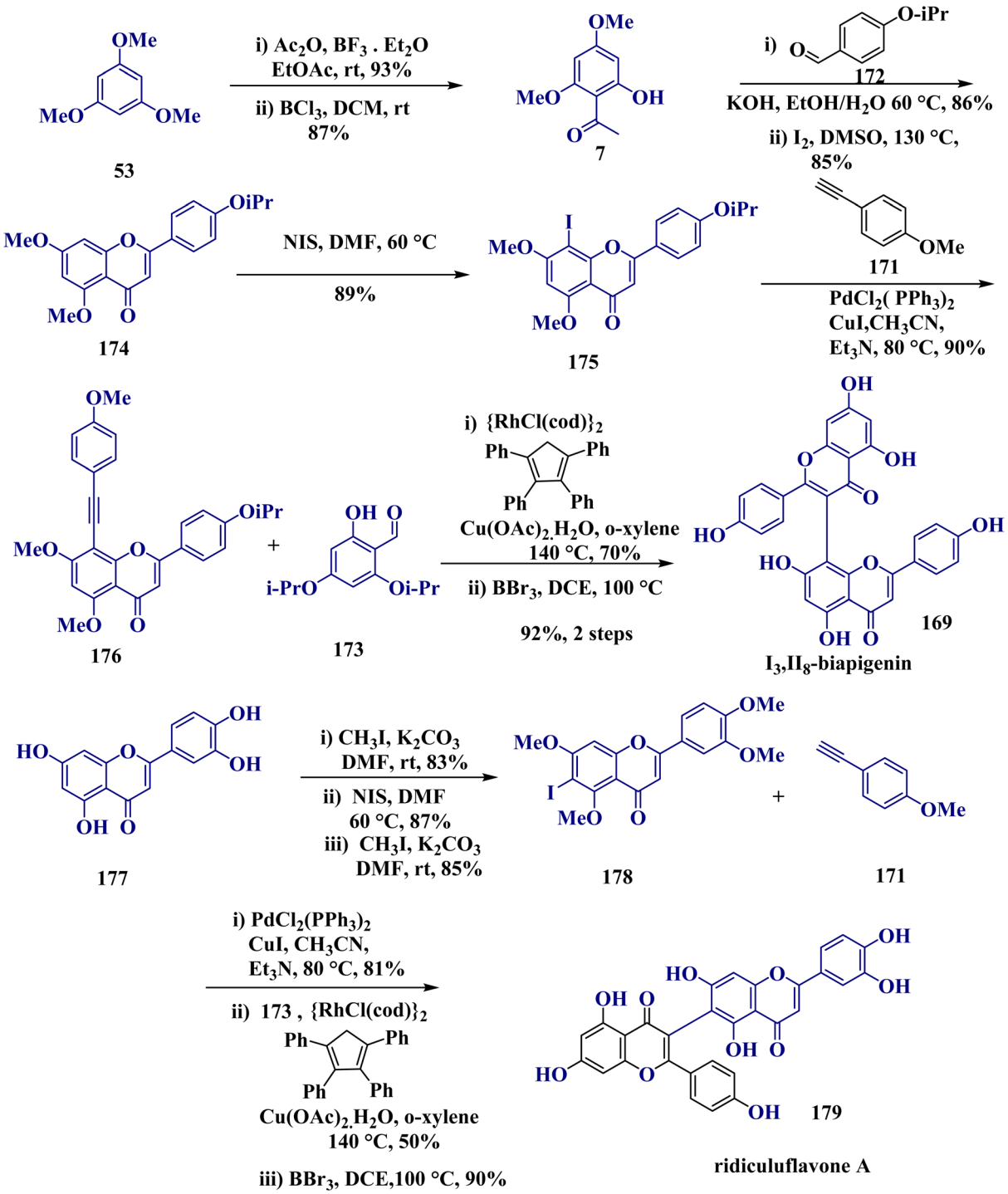



Fig. 28 Convergent strategy for the total synthesis of I3, II8-biapigenin.




Scheme 13 Forward synthesis of I3, II8-biapigenin.

remain unpublished. I3, II8-biapigenin exhibits various biological activities, including antidepressant,[245] α-estrogen and benzodiazepine receptor inhibitor,[246] as well as anti-cancer,[247] anti-inflammatory,[248] and neuroprotective properties.[249] The synthesis involved a rhodium-catalyzed oxidative coupling between the corresponding alkyne intermediates and aldehyde **173** as a key step (Fig. 28).[236] In this synthesis, the key alkyne intermediates were elegantly crafted through a Sonogashira reaction, coupling the iodo-derivative of corresponding flavone components with 1-ethynyl-4-methoxybenzene **171**. By selectively inserting iodine at the C-8 or C-6 position using NIS in DMF, they produced the required iodo-intermediates. The corresponding flavones can then be synthesized through the standard $I_2$/DMSO cyclization of the chalcone products.

**5.2.2. Synthetic route.** According to retrosynthesis analysis, the key intermediate **175** was derived from 1,3,5-

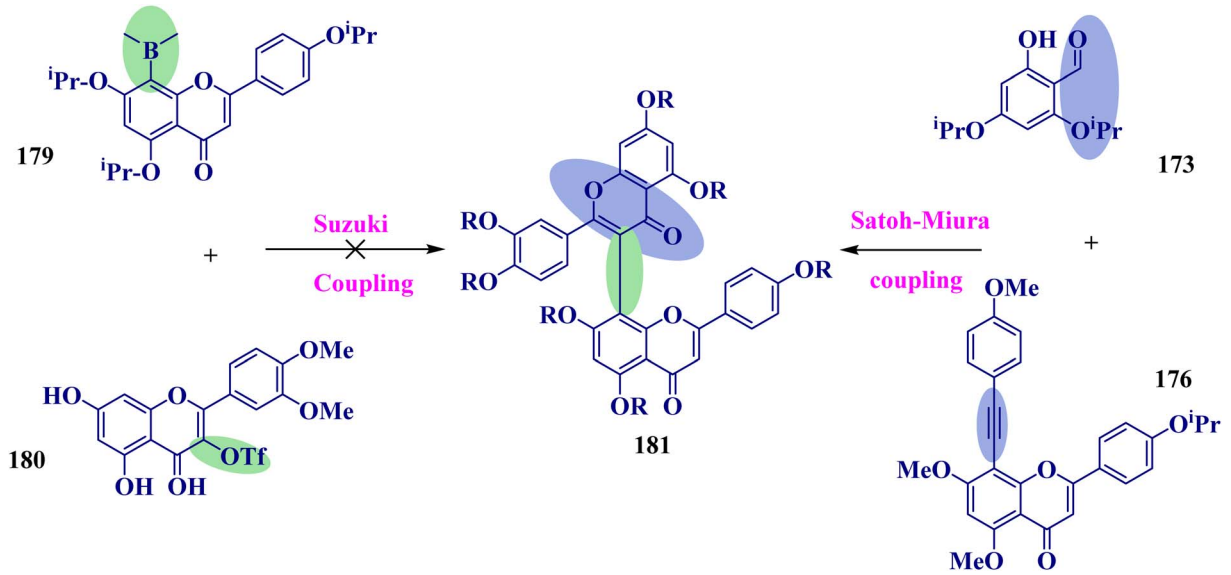



Fig. 29 Lesson from the total synthesis of I3, II8-biapigenin.

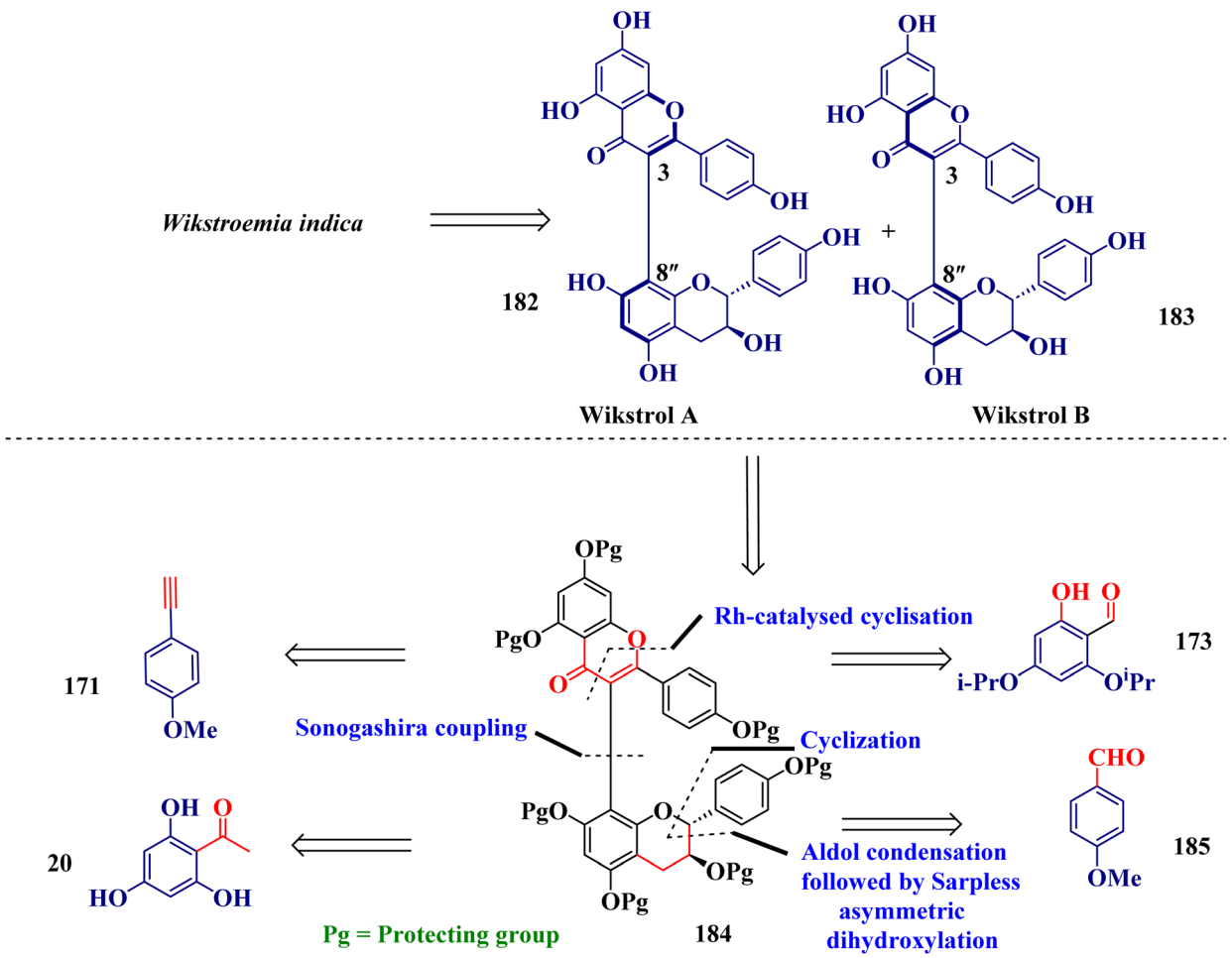
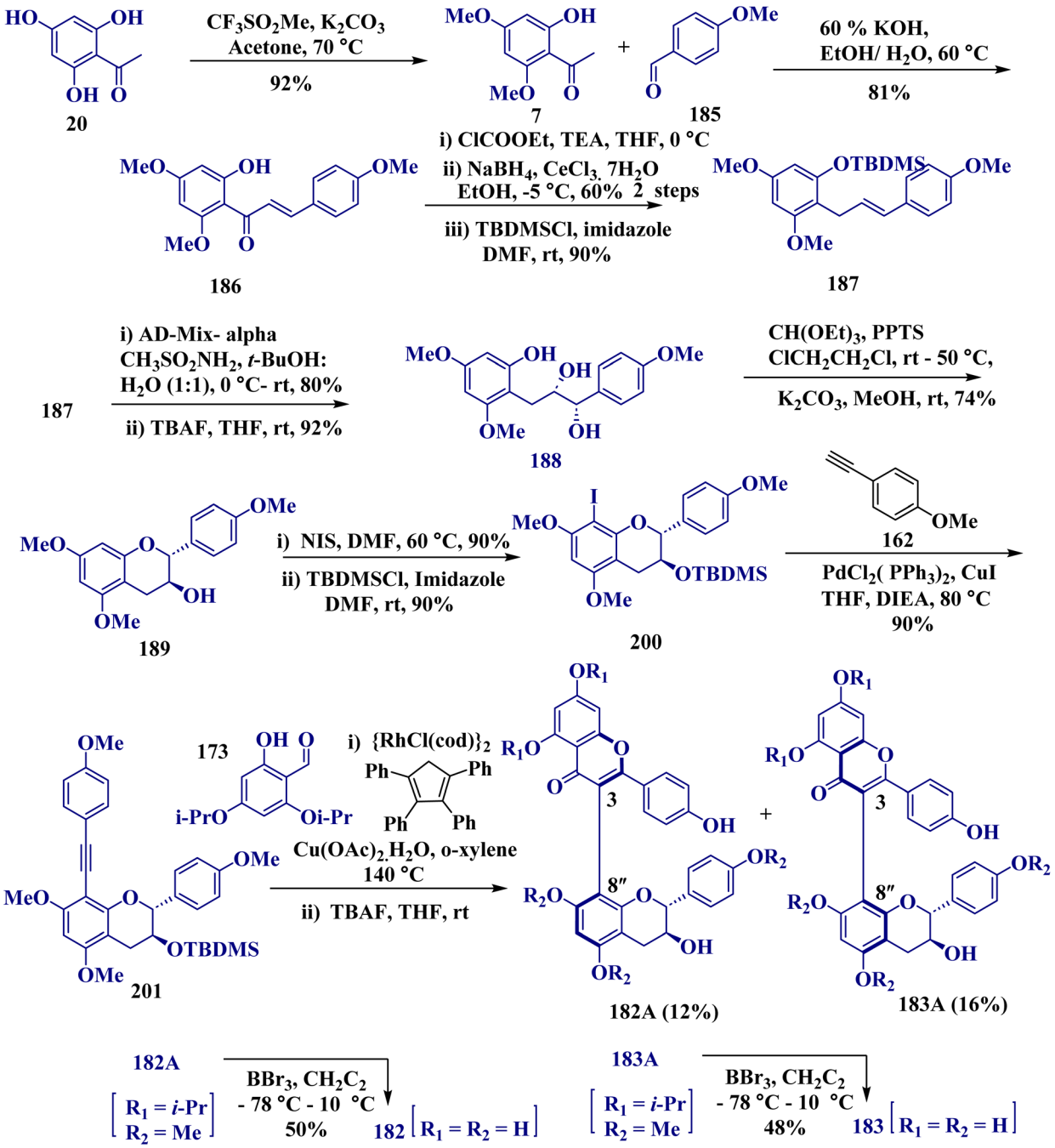



Fig. 30 Convergent strategy for the total synthesis of wikstrol A and wikstrol B.




Scheme 14 Forward synthesis of wikstral A and wikstral B (Zhang and Yu, 2019).[258]

trimethoxybenzene **53**, which was converted into compound **7** through acetylation with $BF_3 \cdot OEt_2$ and acetic anhydride in an ethyl acetate medium, followed by selective demethylation using $BCl_3$ in DCM with 87% yield. Then the synthesis proceeded with an aldol condensation between **7** and **172** under basic conditions (KOH, $EtOH/H_2O$), forming chalcone, which underwent $I_2$/DMSO-mediated cyclization to form the required flavone **174**. Subsequent regioselective iodination with NIS in DMF yielded **175** in 89% yield,[250] followed by a high-yielding Sonogashira coupling reaction between **175** and 1-ethynyl-4-methoxybenzene **171** in the presence of $PdCl_2(PPh_3)_2$, CuI, $CH_3CN$ and $Et_3N$, resulting in **176** with a 90% yield. After successfully synthesizing compound **176**, a rhodium-catalyzed oxidative coupling with **173** produced the desired product in 70% yield,[251] which, upon complete deprotection with $BBr_3$ at 100 °C, afforded the target biflavonoid **169**. Employing a comparable method, compound **179** was adeptly produced. They again started the synthesis from luteolin **177**, which involved methylation with MeI and $K_2CO_3$, regioselective iodination using NIS of the alkyne compound and again methylation using MeI, followed by Sonogashira coupling with compound **171** and rhodium-catalyzed oxidative coupling with

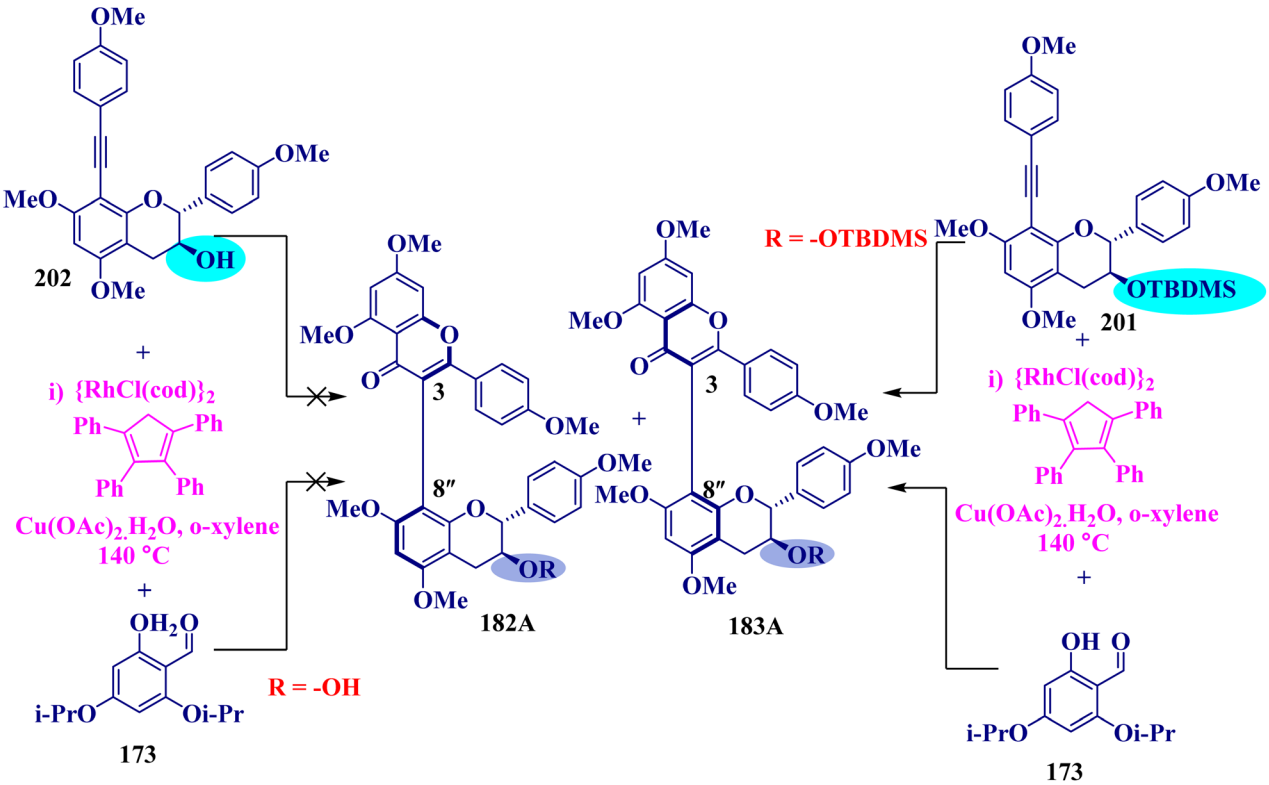



Fig. 31 Lessons from the total synthesis of wikstral A and wikstral B.

the previously utilized reagents, resulting in an intermediate, which, upon demethylation with $BBr_3$, yielded **179** in an impressive 90% yield (Scheme 13).

**5.2.3. Strategies and lessons learned from this synthesis.** Their previous work showed that apigenin with isopropyl-protecting groups has high solubility in organic solvents, which is important in any organic process.[252] This resulted in the cyclization alkyne precursor being synthesized from 1,3,5-trimethoxybenzene **53** after an isopropoxy group was purposefully kept at the 4′-position.[253,254] The failure of the Suzuki coupling attempts to create compound **181** with triflate **180** and borate **179** was probably caused by the ortho-substituents' steric hindrance, which prevented transmetallation and reductive elimination (Fig. 29). The M+H peak in mass spectrometry showed that Satoh and Miura's rhodium-catalyzed oxidative coupling[255] produced the intended product, but the yield was too low to pursue the pathway for the forward synthesis. However, by substituting a methyl group for the isopropyl group, these problems were fixed in this process.

### 5.3. Wikstrol A and wikstrol B

**5.3.1. Synthetic strategy.** Wikstrol A and B, two diastereomers with interflavonyl linkages, were first isolated from the root of *Wikstroemia sikokiana* by the Baba group in 1994,[256] and later found in *Wikstroemia indica*.[257] Their first total synthesis was achieved by the Yu group in 2019.[258] Wikstrol A demonstrated inhibitory activity against aldose reductase[259] and NO production,[260] but the bioactivity of wikstrol B has not yet been reported. The retro-synthesis of the target compounds was masterfully executed using a conversion strategy, featuring a rhodium-catalyzed cyclization[255] and deprotection of salicylaldehyde derivative **173** and the corresponding flavane (Fig. 30). The synthesis of flavane involved a sophisticated Sonogashira coupling between compound **185** and the corresponding iodo derivative. Remarkably, the iodo derivative was produced by cyclization and regioselective iodination of an intermediate diol, which was created *via* aldol condensation, reduction, and Sharpless asymmetric dihydroxylation using compounds **7** and **187**.

**5.3.2. Synthetic route.** The forward synthesis was initiated by converting 2,4,6-trihydroxyacetophenone **20** into its dimethyl ether **7** using $CF_3SO_2Me$ and $K_2CO_3$ in an acetone medium at 70 °C, which then underwent aldol condensation with 4-methoxybenzaldehyde **185** in 60% KOH, EtOH/$H_2O$ to produce chalcone **186** in an impressive 81% yield. Using ClCOOEt and TEA in THF, the hydroxy group of compound **186** was first protected. It was then reduced and deprotected in a single step using $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ in EtOH at −5 °C. Finally, a reaction with TBDMSCl and imidazole produced the protected intermediate **187**. Compound **188** was expertly created by Sharpless asymmetric dihydroxylation using AD-Mix-α and $CH_3SO_2NH_2$ in 1 : 1 $^t$BuOH : $H_2O$, and, consecutively, the -TBDMS group was removed with TBAF/THF. The catechin derivative **189** was produced in 74% yield by hydrolyzing and cyclizing the product under the influence of acid, PPTS, and $CH(OEt)_3$ in DCE medium.[261,262] Compound **200** was obtained by regioselective iodination of **189** with NIS in DMF and protection

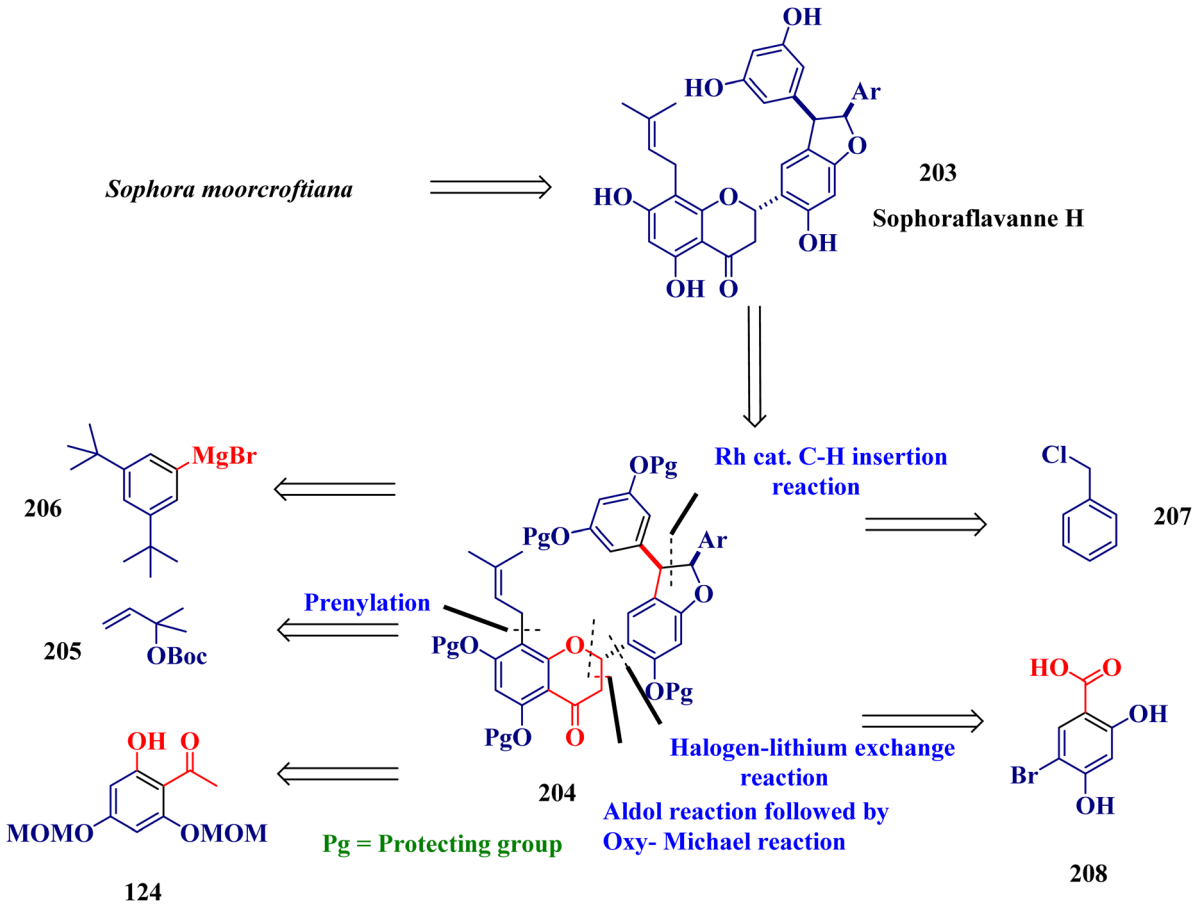



Fig. 32 Convergent strategy for the total synthesis of sophoraflavanone H.

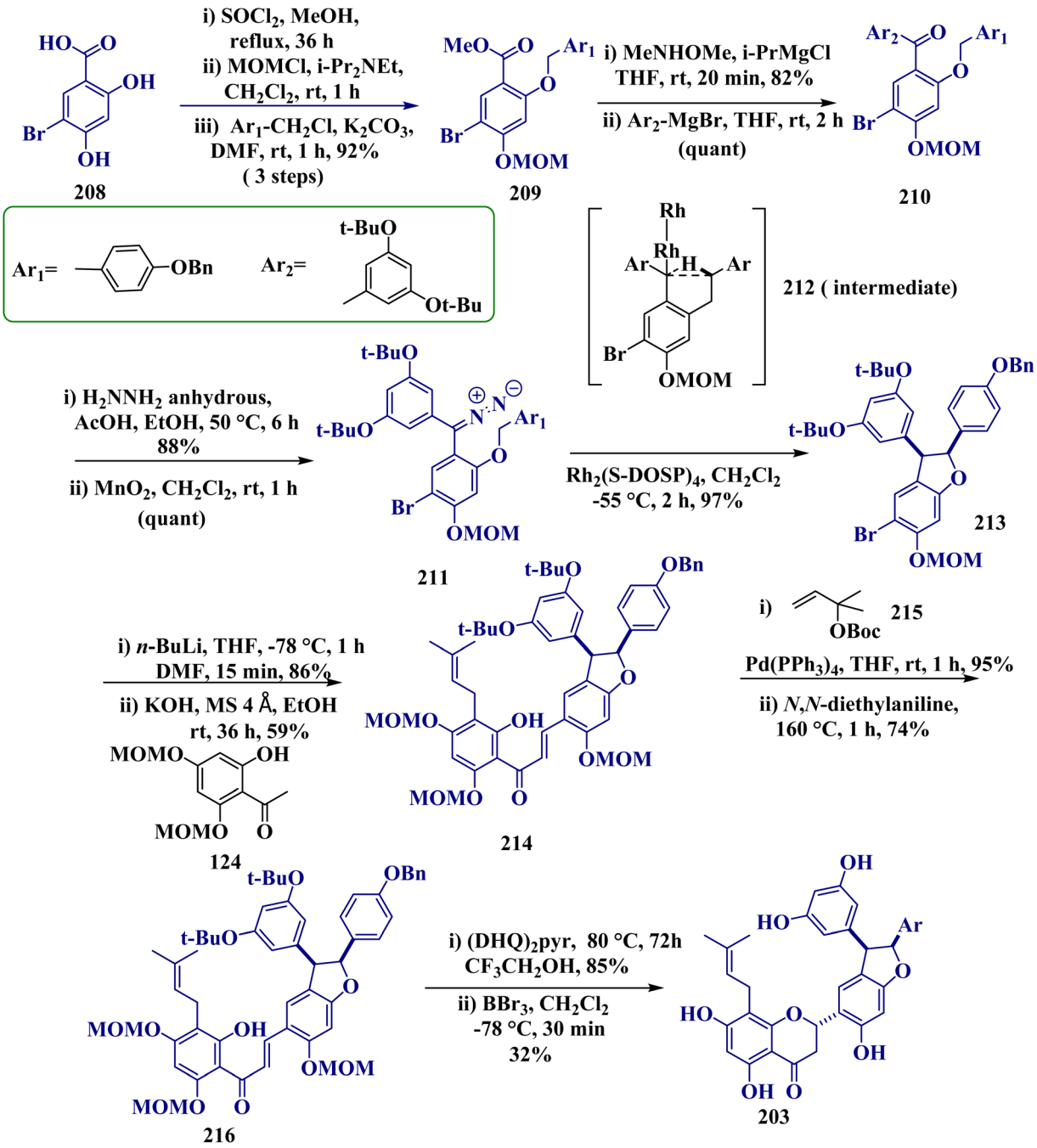
with TBDMSCl in imidazole. This compound then underwent Sonogashira coupling with 1-ethynyl-4-methoxybenzene **162** in the presence of $PdCl_2(PPh_3)_2$, CuI, DIEA, and THF, yielding the crucial intermediate **201** in an impressive 90% yield. Ultimately, compounds **182** and **183** in 50% and 48% yields, respectively, were produced by the oxidative coupling of **201** with **173** mediated by $RhCl(cod)_2$ catalyst and $Cu(OAc)_2 \cdot H_2O$ in *o*-xylene medium, followed by removal of the silyl group with TBAF and dealkylation with $BBr_3$ (Scheme 14).[251]

**5.3.3. Strategies and lessons learned from this synthesis.** The synthesis proceeded smoothly overall, but complications arose when attempting to synthesize protected target compounds with isopropyl-protected hydroxyl groups. By using diisopropyl ether **164** as a cyclization precursor with compound **183**, no intended product was produced, likely because the free hydroxyl group of compound **184** coordinated with the rhodium catalyst, impeding the reaction (Fig. 31). Therefore, they protected the hydroxy group and the TBDMS group to solve the problem.

## 5.4. Sophoraflavanone H

**5.4.1. Synthetic strategy.** In 2020, the Kan group succeeded for the first time in synthesizing sophoraflavanone H, which had been isolated in 1991 by the Komatsu group from *Sophora moorcroftiana*.[263,264] This type of polyphenol compound, which combines prenyl flavanone and 2,3-dihydrobenzofuran lignin moieties, is lethal to human oral carcinoma cells and has antibacterial action against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF).[265] Their synthesis approach to the target compound comprised the formation of flavanone molecules by a crucial oxy-Michael reaction of the corresponding chalcone synthesized from compound **124** and the formation of the 2,3-diaryl-2,3-dihydrobenzofuran ring *via* C–H insertion mediated by a rhodium carbenoid (Fig. 32).[266] Strategically, compound **208** is used as the key starting material to gradually introduce the flavanone ring.

**5.4.2. Synthetic route.** According to their retrosynthesis analysis, they synthesized the dihydrobenzofuran moiety by first selectively protecting the three hydroxyl groups in 5-bromo-2,4-dihydroxybenzoic acid **208** as a methyl ester and then selectively incorporating a MOM group at OH-4, leaving OH-2 unprotected because of its hydrogen bonding with the ester carbonyl group. After that, $K_2CO_3$ in DMF was used to benzylate the residual OH-2, resulting in compound **209**.[267] By using magnesium amide to facilitate ester exchange to a Weinreb amide and then reacting with aryl Grignard reagent **206**, diaryl ketone **210** was created from **209**.[169,268] Treatment of **210** with anhydrous hydrazine in acetic acid/ethanol at 50 °C for 5 h and subsequent $MnO_2$ oxidation in DCM produced unstable diaryl diazomethane **211**, which underwent a smooth Rh-catalysed




Scheme 15 Forward synthesis of sophoraflavanone H (Kan, 2020).[264]

C–H insertion at −55 °C without purification, yielding *cis*-dihydrobenzofuran **213**.[269,270] Following halogen–lithium exchange and DMF treatment, the benzaldehyde derivative of **213** was utilized for aldol condensation reaction with acetophenone **124** to form chalcone **214**,[150] which then underwent reverse prenylation in the reaction with compound **215** in the presence of $Pd(PPh_3)_4$/THF and Claisen rearrangement in presence of *N*,*N*-diethylaniline solvent at 160 °C,[271] cyclization with $(DHQ)_2Pyr$ catalyst,[272] and deprotection with $BBr_3$ in DCM at −78 °C to yield the desired product **203** (Scheme 15).

**5.4.3. Strategies and lessons learned from this synthesis.** During the synthesis of the methylated *cis*-dihydrobenzofuran **220**, they found considerable difficulties in removing the methyl ether. As a result, they boldly substituted *tert*-butyl ether **216**, which maintained the exceptional enantioselectivity they had previously discovered (Fig. 33).[273] Furthermore, efforts to reduce the flavone ring *via* a β-diketone intermediate failed because different reduction techniques, such as hydrogenolysis, one-electron reduction, and hydride reduction, had undesirable results, and the Sajiki's protocol[274] caused unwanted cleavage of the benzyl O-7 bond in dihydrobenzofuran, yielding **219** instead.[275]

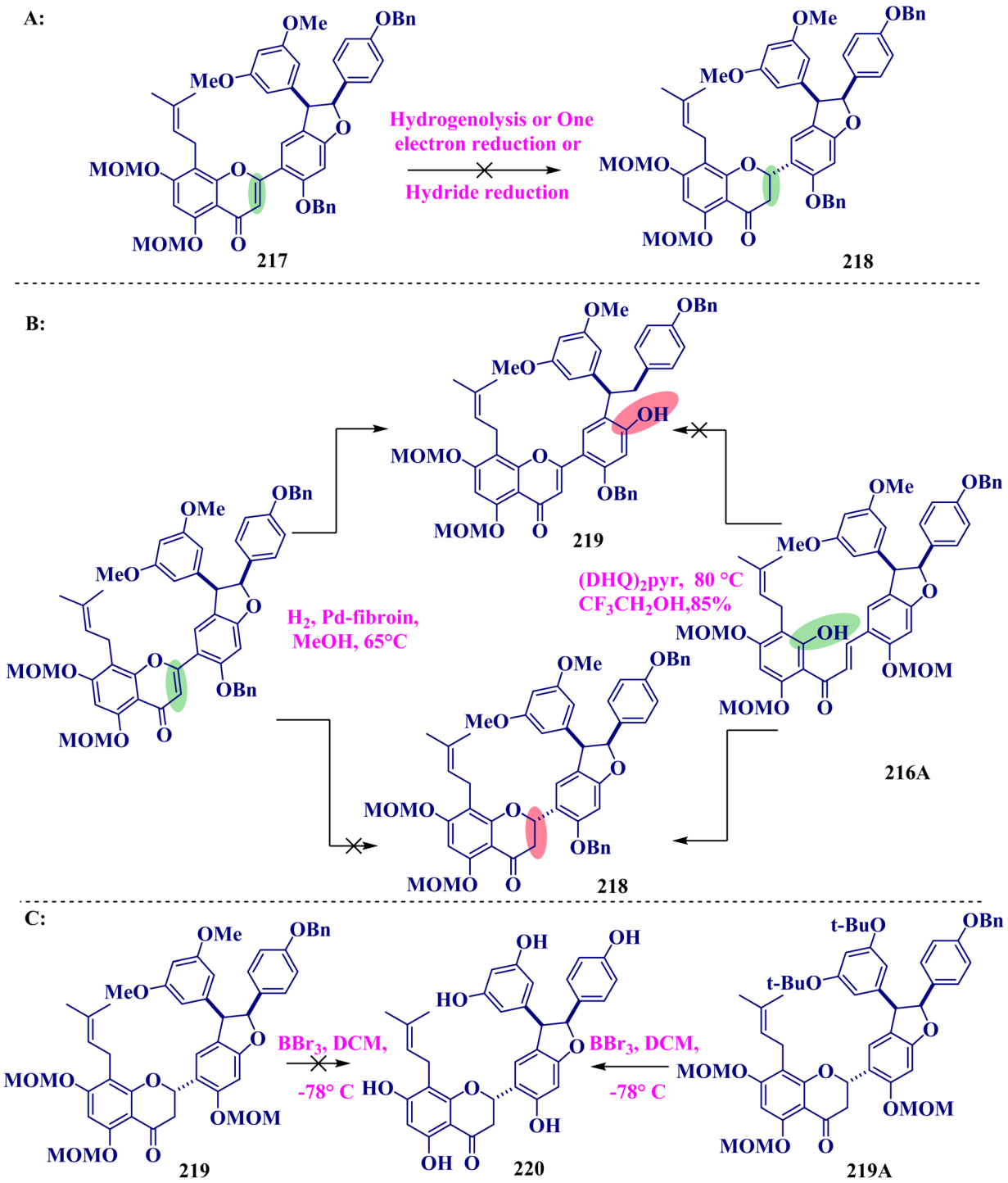



Fig. 33 Lessons from the total synthesis of sophoraflavanone H. (A) Unsuccessful chemoselective reduction; (B) unwanted hydrogenolysis; (C) functional group-dependent deprotection.

### 5.5. Neocyclomorusin

**5.5.1. Synthetic strategy.** In 2022, Shi synthesised neocyclomorusin **221**, originally extracted from plants of the Moraceae family by the Fukai group in 2005,[276,277] a potent antimicrobial agent[278] with cytotoxicity,[279] β-secretase[280] and cholinesterase-inhibiting effect,[281] along with anti-inflammatory activity.[282] Their synthesis begins with the formation of compound **222** *via* a base-catalyzed intramolecular $S_N2$ reaction on an epoxide, which is synthesized from the epoxidation of prenylated flavone **223** (Fig. 34). Flavone **223** is derived from the alkylation of β-diketone, obtained from protected hydroxybenzoic acid **224** and hydroxyacetophenone **20**, utilizing the BK–VK rearrangement reaction, with 1-bromo-3-methyl-2-butene, followed by cyclization. In this particular

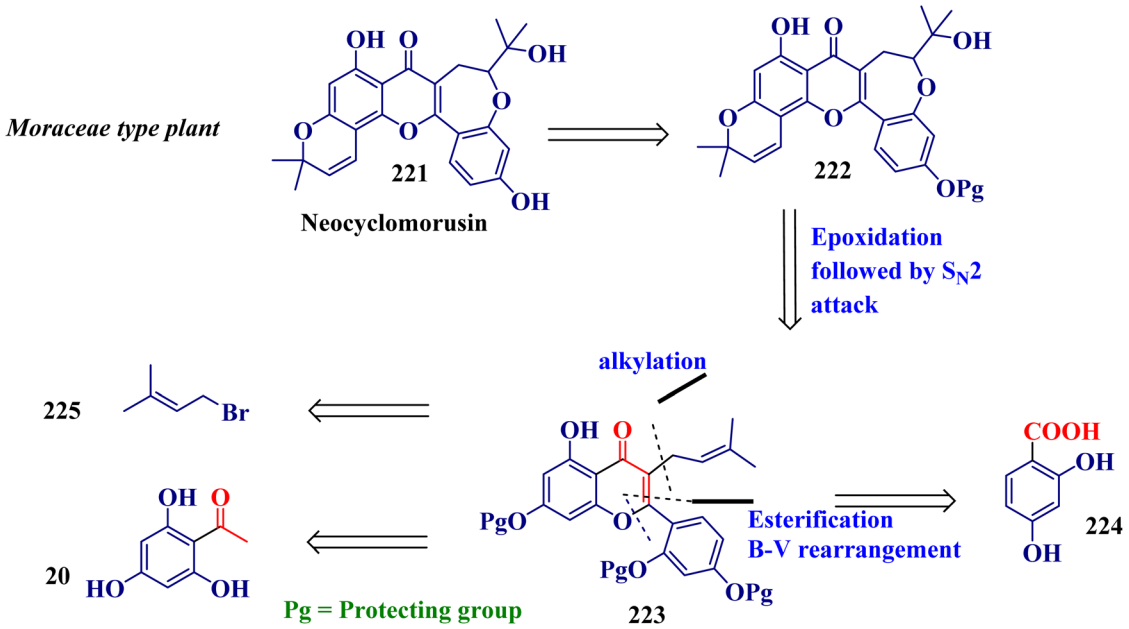



Fig. 34 Convergent strategy for the total synthesis of neocyclomorusin.

case, the intermediate **20** originates from *m*-trihydroxybenzene through a Friedel–Crafts reaction with acetyl chloride.

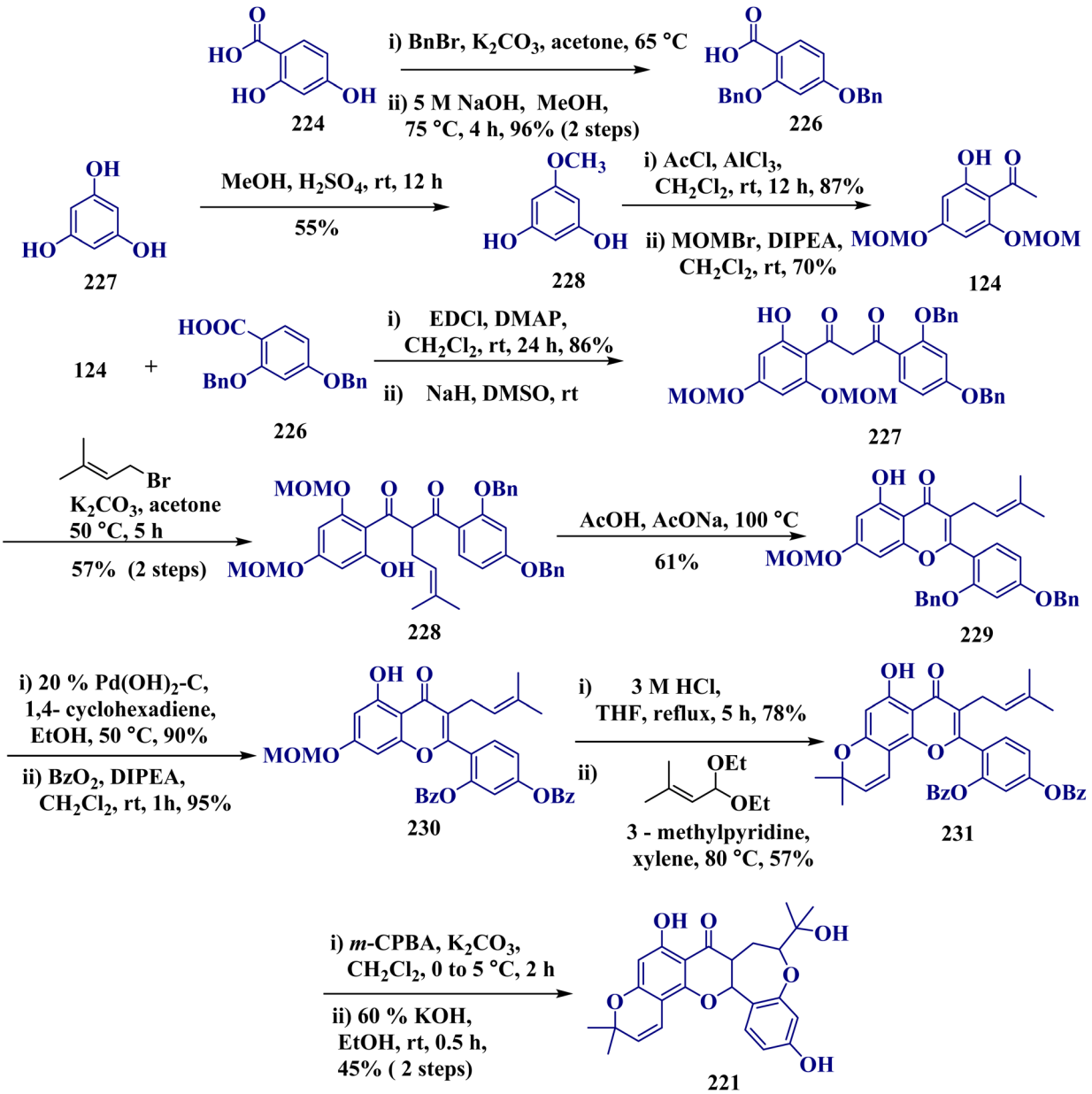
**5.5.2. Synthetic route.** The Shi group's total synthesis of neocyclomorusin **221** commenced with the selective methylation and Friedel–Crafts reaction of the starting material *m*-trihydroxybenzene **227**, first with MeOH in $H_2SO_4$ and then with AcCl/$AlCl_3$ in DCM, consecutively.[283] The product formed in the reaction sequence was then protected with methoxymethyl bromide (MOMBr) in the presence of DIPEA, producing **124** in an excellent 80% yield, and when 2,4-dihydroxybenzoic acid **224** was benzylated with BnBr in the presence of $K_2CO_3$/acetone at 65 °C and hydrolyzed with 5 mol $L^{-1}$ NaOMe/MeOH, 2,4-bis(benzyloxy)benzoic acid **226** was produced in 96% yield.[284] Carboxylic acid **226** and compound **124** were coupled in the presence of EDCI/DMAP in DCM to form an ester, which then underwent a BK-VK rearrangement in the presence of NaH/DMSO to provide β-diketone **227**.[285–287] It was then further alkylated with 3,3-dimethylallyl bromide using acetone as a solvent and $K_2CO_3$ as a base to make compound **228**, and, lastly, it underwent a sophisticated NaOAc/AcOH-mediated cyclization to yield **229** in 90% yield. In the end, the benzyl group of the flavone **229** was removed by a debenzylation reaction using $Pd(OH)_2$–C in 1,4-cyclohexadiene/EtOH, and the free hydroxy group was again protected with a benzoyl moiety.[288] This resulted in compound **230** being deprotected with dilute HCl, forming a crucial intermediate in 78% yield, which, with 1,1-diethoxy-3-methyl-2-butene, produced compound **231** in a selective aldol-type condensation.[289] Finally, a simple epoxidation of compound **231** with *m*-CPBA in DCM and a facile treatment with 60% KOH of the intermediate were conducted to obtain neocyclomorusin **221** in 41% yield (Scheme 16).

**5.5.3. Strategies and lessons learned from this synthesis.** While synthesizing the target compound, they also followed the synthetic path, having the methyl protection in place of the –MOM group. However, the removal of the methyl group from compound **235** is highly difficult using $BBr_3$, $AlCl_3$, HBr, or pyridinium hydrohalide. The instability of the isopentenyl double bond, however, prevented attempts to deprotect compound **232** with HCl/$CH_3COOH$ and other acids, such as $AlCl_3$ and trifluoroacetic acid, from succeeding (Fig. 35).[290,291] During the synthesis, the deprotection of the benzyl group from compound **229** was required. However, significant side-chain alkene reduction occurred even under mild hydrogenolysis conditions (Pd–C/$H_2$, Pd-$(OH)_2$/$H_2$, Pd–C/$HCOONH_4$), complicating the synthesis. Hence, the issue was resolved by using 20% $Pd(OH)_2$–C with 1,4-cyclohexadiene in EtOH medium.

### 5.6. Kuwanons A and B

**5.6.1. Synthetic strategy.** In 2023, Xu, Liao, and Lu synthesized Kuwanons A and B,[292] two prenylated flavone isomers with antimicrobial properties, which had been extracted from the root bark of the *Morus alba* L. tree in 1997 by the Katayanagi group.[293–300] These substances are made from a common prenylated flavone core containing model substrate **239** (Fig. 36). The synthesis of compound **239**, as usual, commenced with a β-diketone, obtained *via* the Baker–Venkataraman rearrangement, which was itself derived from a selective protection and esterification of commercially available 2,4-dihydroxybenzoic acid **240** and 1-(2,4,6-trihydroxyphenyl)-ethan-1-one **20**, followed by a strategic acid-catalyzed cyclization to complete the transformation.

**5.6.2. Synthetic route.** The synthesis started with the esterification of compound **224** using MeOH and concentrated $H_2SO_4$ to afford the methyl ester,[301] which was selectively alkylated with 3-chloro-3-methylbut-1-yne **240** to form compound **241**. Subsequent heating in DMF at 175 °C provided cyclized compound **242** in 85% yield, followed by benzyl protection of the C-2 phenol and hydrolysis to yield intermediate **243** in 95%




Scheme 16 Forward synthesis of neocyclomorusin (Shi, 2022).[276]

yield. After synthesizing MOM-protected acetophenone **124** from 1-(2,4,6-trihydroxyphenyl)-ethan-1-one by reacting with MOMBr in DCM using DIPEA, esterification with compound **243** in the presence of EDCl/DMAP in DCM led to the formation of an ester, which underwent a NaH-promoted Baker–Venkataraman (Bk–Vk) rearrangement to produce 1,3-diketone **244**. Subsequent alkylation produced compound **245**, and cyclization with AcONa/AcOH at 100 °C resulted in the desired product **246** in 71% yield, with the concomitant removal of the C-5 MOM group during the final cyclization step.[302,303] Following the formation of compound **246**, the benzyl group was removed using excess 1-dodecantiol and NaOMe in DMF at 120 °C, giving the target compounds **247** and **248** in 35% and 55% yield, respectively.[304] Compounds **247** and **248** were then refluxed with 3 N HCl/EtOH to produce kuwanon B and kuwanon A in the final step (Scheme 17).

**5.6.3. Strategies and lessons learned from this synthesis.** Cyclization attempts with compound **245** using various reported conditions, including $H_2SO_4$/AcOH,[291,305] $H_2SO_4$/EtOH,[306] $CuCl_2$/TMSCl,[284] and CSA,[207] led only to complex mixtures without yielding the desired cyclic product, likely due to the instability of MOM and isopentenyl groups under strong acidic conditions (Fig. 37). Therefore, the weak acidic mixture of AcOH/AcONa was successfully employed for the cyclization.[307] Additionally, compound **246** was decomposed when attempts were made to remove both the benzyl and MOM groups in a single step using $BBr_3$, $AlCl_3$, 48% HBr(aq.), and $CF_3COOH$. Subsequent attempts to debenzylate **246** with Pd–C/$HCOONH_4$,

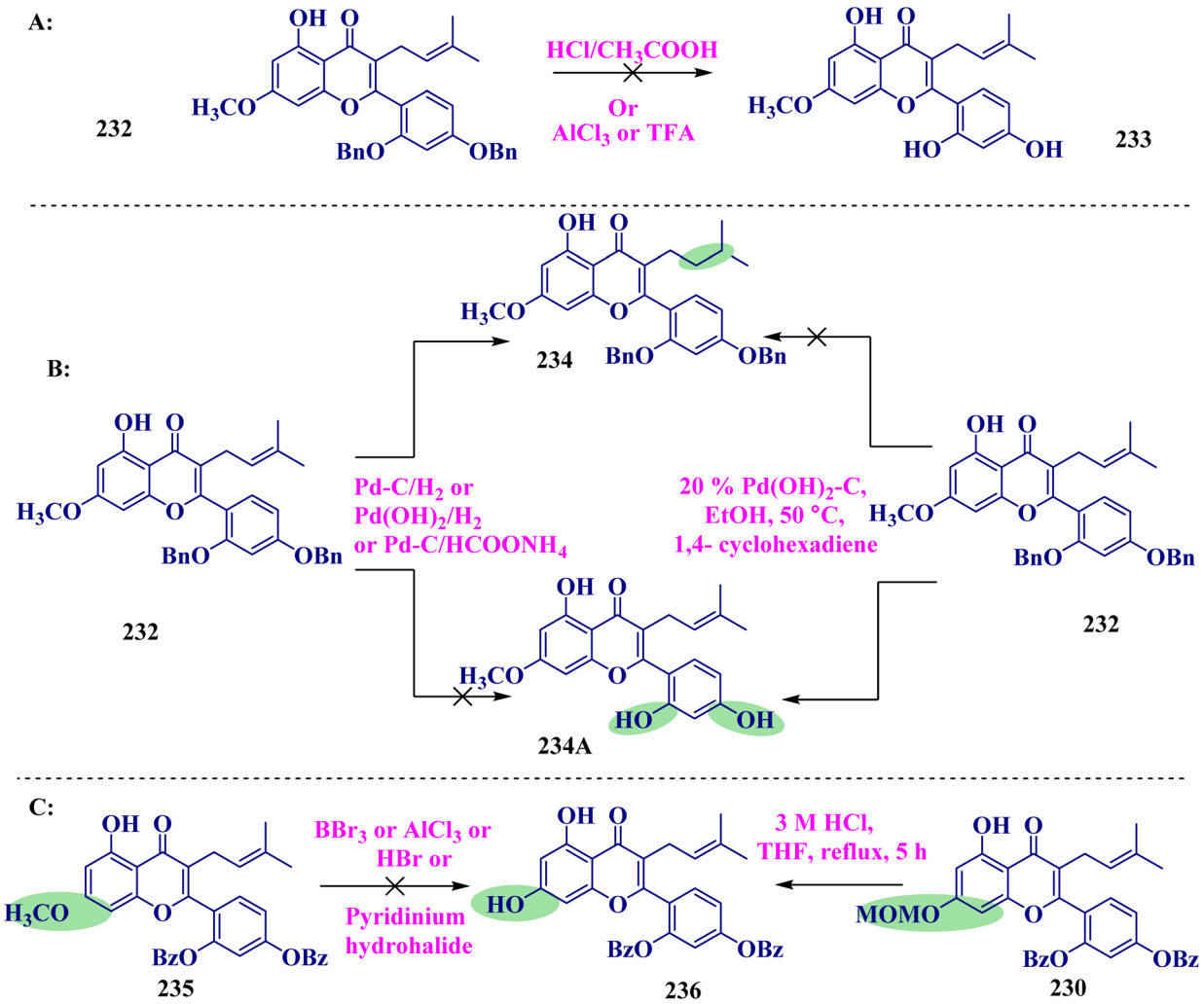



Fig. 35 Lessons from the total synthesis of neocyclomorusin. (A) Unsuccessful debenzylation; (B) regio-selective reduction; (C) chemo-selective de-etherification.

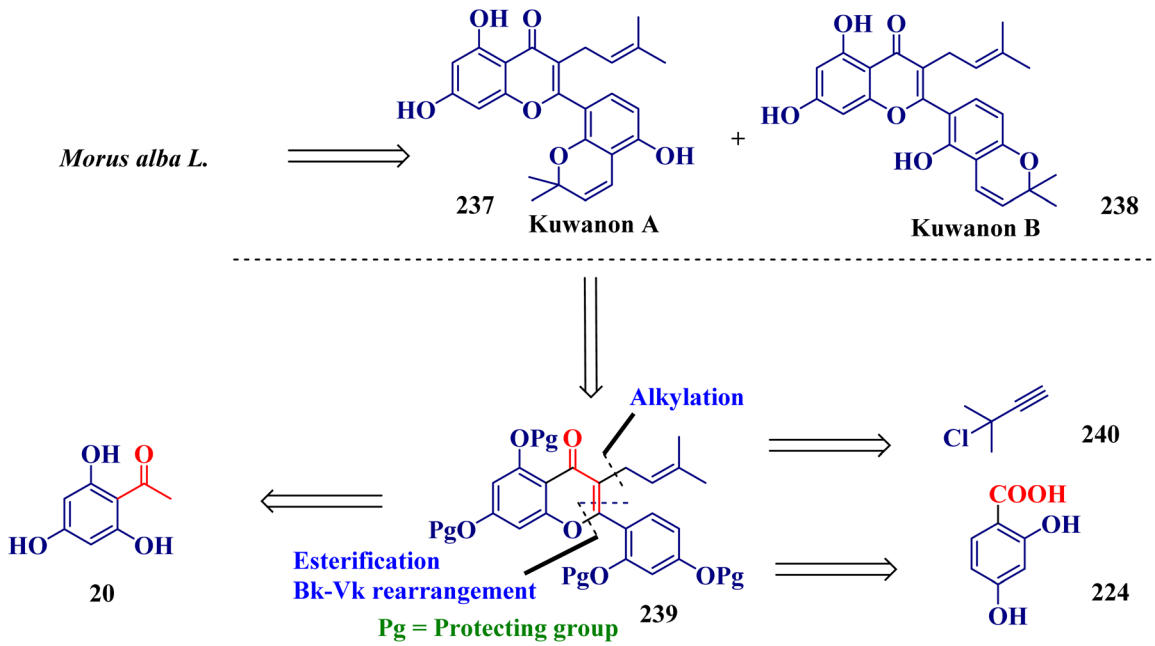
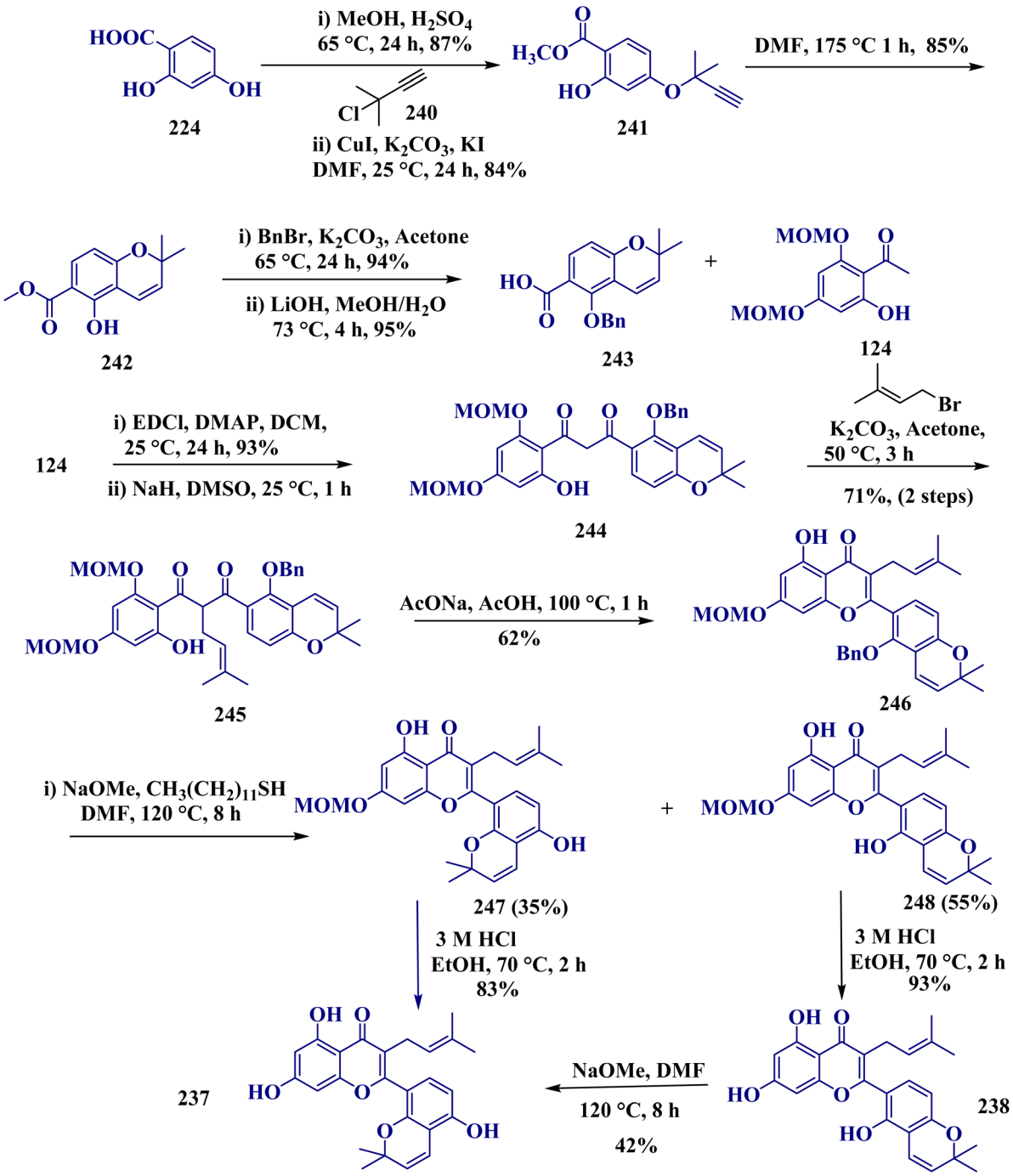



Fig. 36 Convergent strategy for the total synthesis of kuwanon A and kuwanon B.




Scheme 17 Forward synthesis of kuwanon A and kuwanon B (Xu, Liao and Lu, 2023).[292]

Pd–C/HCOOH, or $Pd(OH)_2$–C/cyclohexadiene resulted in a significant alkene reduction. Hence, highly nucleophilic dodecane-1-thiol in the presence of freshly prepared NaOMe was used for the debenzylation.

### 5.7. Pongaflavone

**5.7.1. Synthetic strategy.** Pongaflavone, a secondary metabolite isolated from the root of the tree *Pongamia pinnata* L.,[308,309] was synthesized by He and the Dong group in 2023.[310] It exhibits notable cytotoxicity against M156 and HepG2 cell lines ($IC_{50}$ values of 0.5 ± 0.08 μM),[311] antimycobacterial activity against *Mycobacterium tuberculosis* H37Ra (MIC: 15 μg $mL^{-1}$),[312] and significant inhibition of LPS-induced NO release in BV-2 microglial cells (IC50; 15.2 ± 5.4 μM).[313,314] The compound was successfully synthesized in 2023 by the Dong group with an impressive yield under considerably mild conditions.[310] The key pyran ring structural components are easily integrated through a Claisen rearrangement and cyclization with 3-chloro-3-methylbut-1-yne **240** (Fig. 38). Through a base-catalyzed aldol

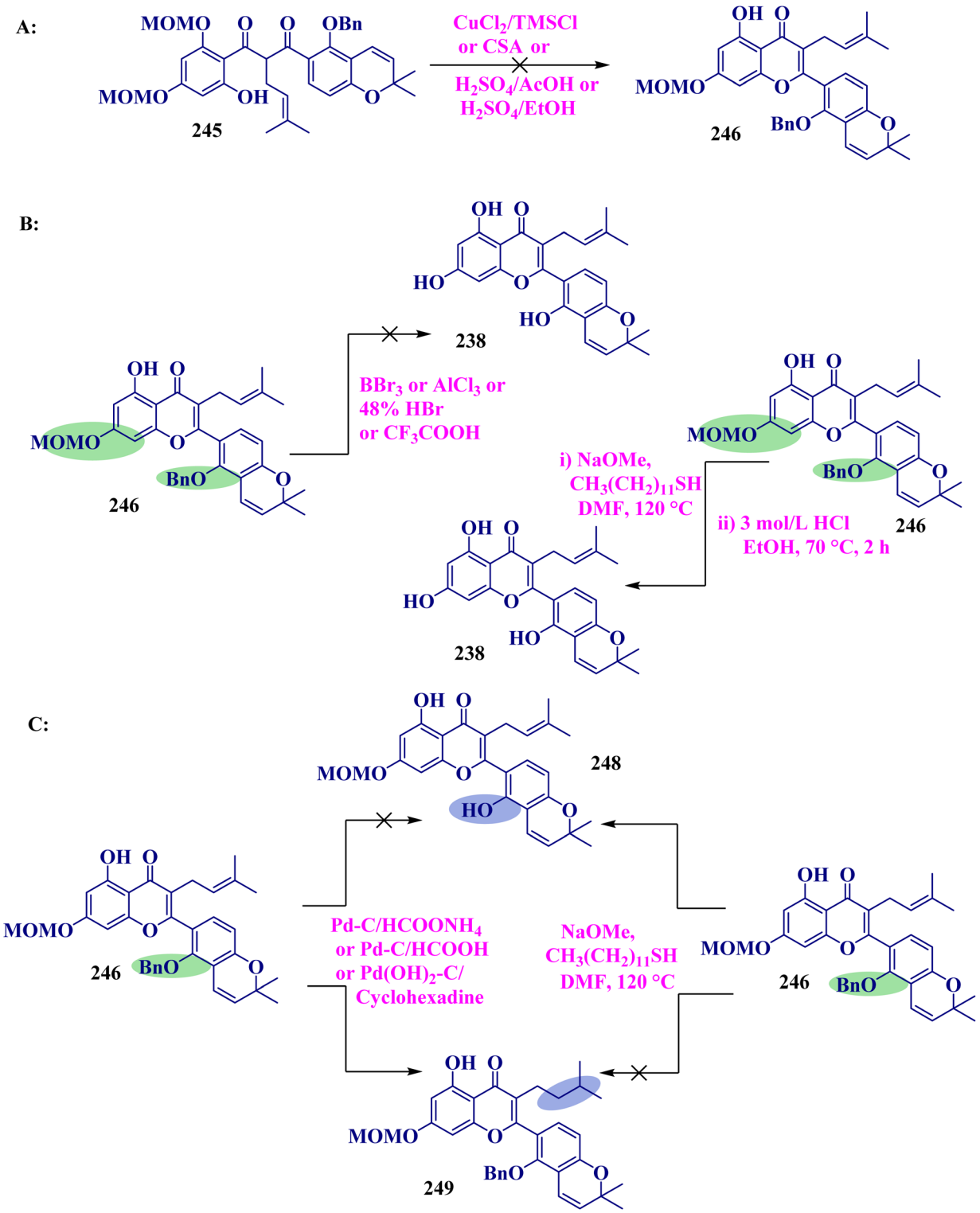



Fig. 37 Lessons from the total synthesis of kuwanon A and kuwanon B. (A) Deprotection cyclization; (B) regioselective deprotection; (C) mild debenzylation.

condensation between compound **252** and benzaldehyde **253**, the target molecule's flavone part was elegantly constructed, paving the way for chalcone cyclization under AFO reaction conditions.

**5.7.2. Synthetic route.** The total synthesis of pongaflavone started with the synthesis of compound **250**, starting with the selective protection of the 4-hydroxyl group of compound **252** with the methoxymethyl (-MOM) group in the presence of

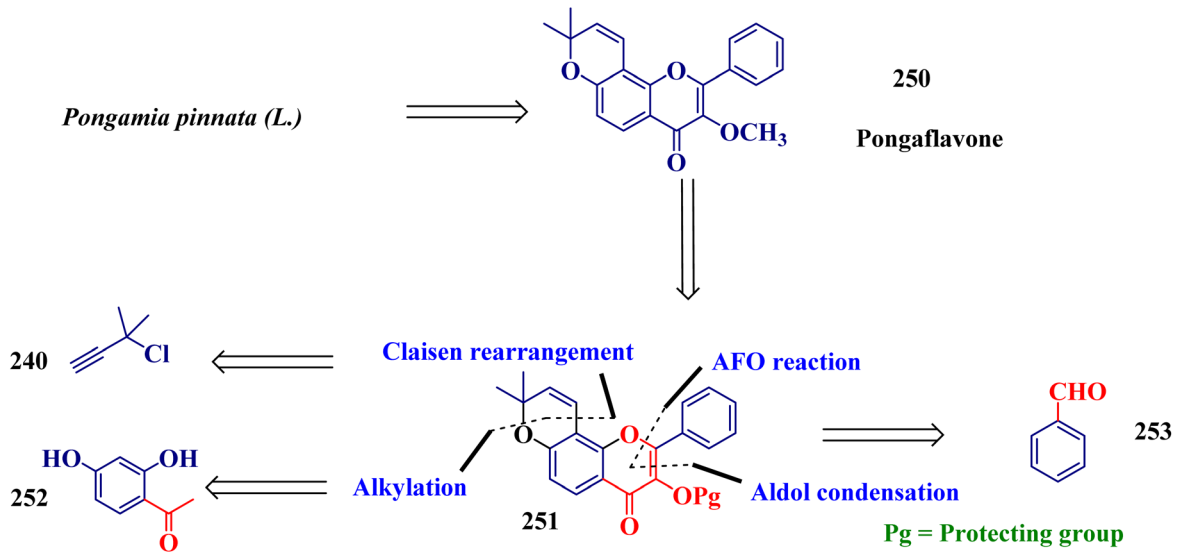
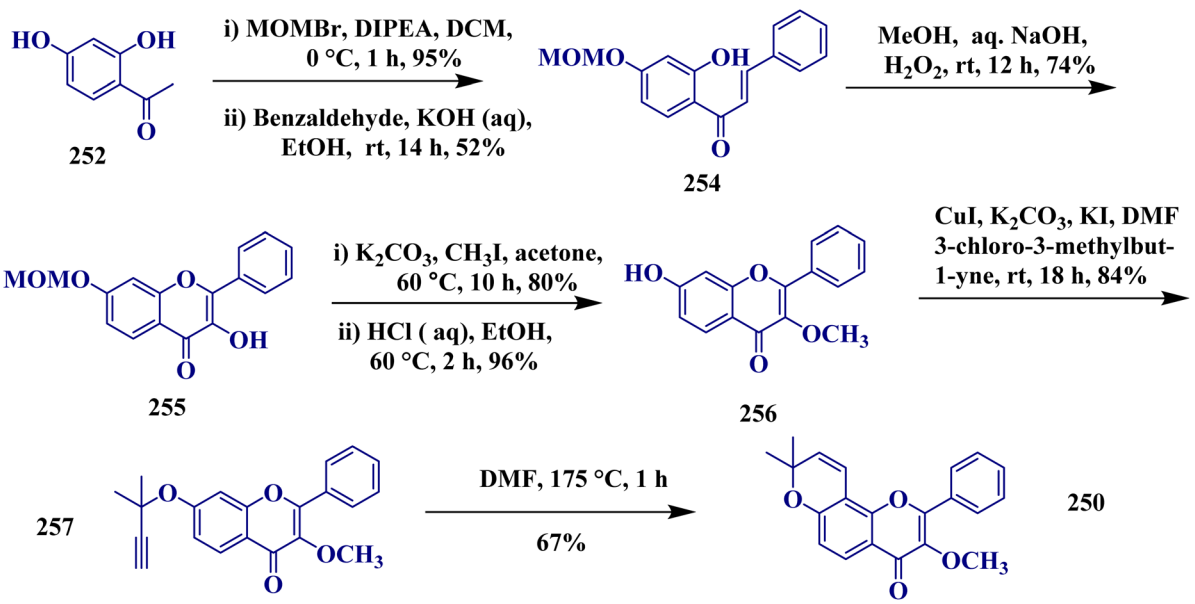



Fig. 38 Convergent strategy for the total synthesis of pongaflavone.

DIPEA using DCM as solvent at 0 °C,[237] followed by KOH-catalyzed aldol condensation with benzaldehyde to give chalcone **254**.[315] AFO reaction was used to perform the oxidative cyclization of chalcone **254** with NaOH and $H_2O_2$ in MeOH. The resultant flavone intermediate **255** was methylated with methyl iodide in the presence of $K_2CO_3$, and the –MOM group was deprotected with aq. HCl at 60 °C to yield compound **256.** Alkylation of compound **256** was done with 3-chloro-3-methylbut-1-yne **240** in the presence of KI with $K_2CO_3$ and CuI catalyst to produce compound **257**,[316] which was then subjected to Claisen rearrangement/cyclization in DMF at 175 °C to successfully synthesize pongaflavone **250** (Scheme 18).

**5.7.3. Strategies and lessons learned from this synthesis.** After the successful synthesis of intermediate **258** *via* the Bk–Vk reaction, followed by cyclization,[317] the DMDO-mediated oxidation step failed to afford compound **259** (Fig. 39). This is probably because of the instability of the olefin between C-3″ and C-4″ of compound **258** under strong oxidants (DMDO).[318] The attempt to synthesize compound **259** by the AFO route also failed, most likely because the olefin's electron cloud density at C-3″/4″ was higher than that at the C-alpha/beta double bond. This made the olefin more susceptible to oxidation by peroxide ($H_2O_2$), which produced a variety of byproducts. Based on these results, it was concluded that to obtain the target compound, the flavonol framework in pongaflavone **250** must be constructed before the dihydropyran ring is installed at C-7/C-8 positions.




Scheme 18 Forward synthesis of pongaflavone (Dong, 2023).[310]

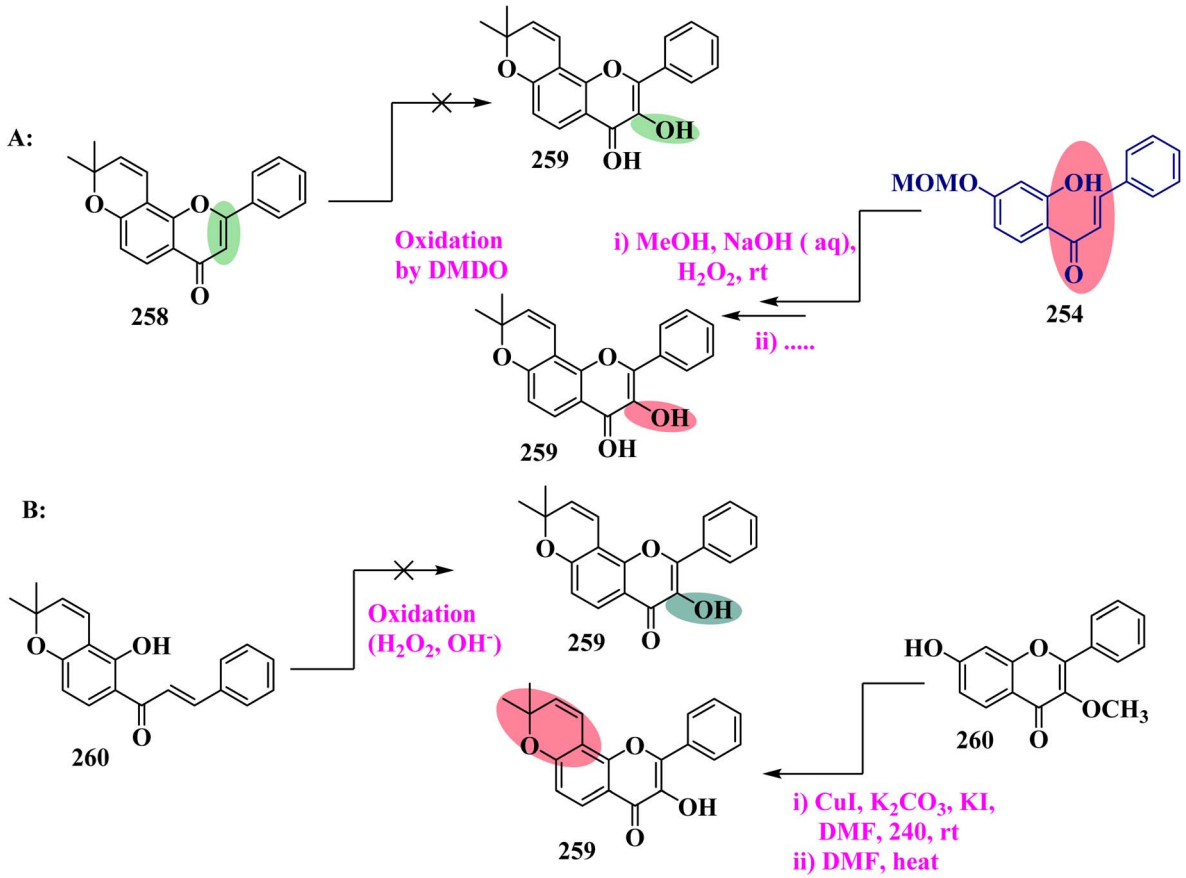



Fig. 39 Lessons from the total synthesis of pongaflavone. (A) Chemoselective oxidation of flavone olefin; (B) oxidative cyclization of chalcone.

### 5.8. Lupinifolin

**5.8.1. Synthetic strategy.** In 2024, the synthesis of lupinifolin, extracted from a plant belonging to the family of Fabaceae by the Sutthivaiyakit group in 2009,[319,320] was initiated by Xu's group from compound **262** (Fig. 40).[237] It exhibits remarkable potential as an antibacterial agent[321–323] and demonstrates

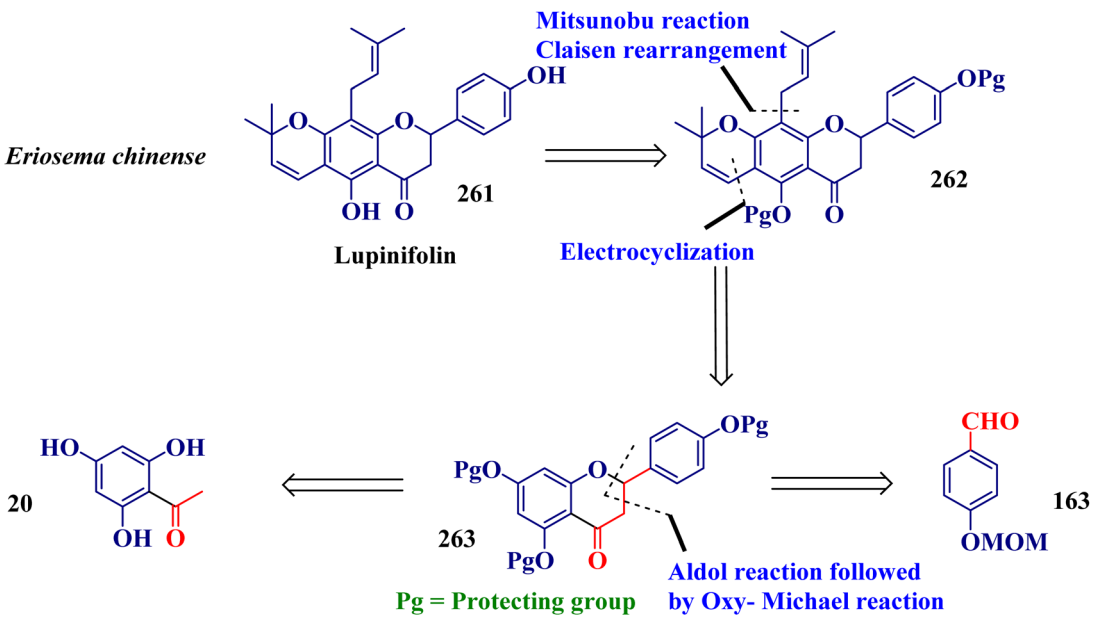
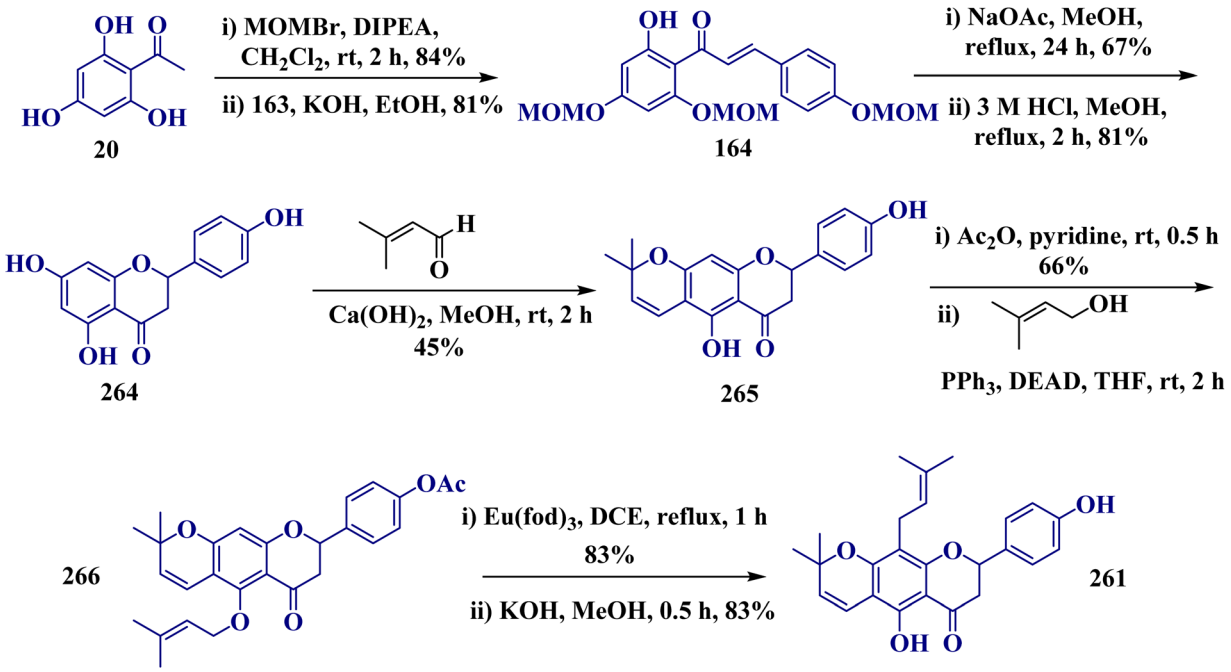



Fig. 40 Convergent strategy for the total synthesis of lupinifolin.




Scheme 19 Forward synthesis of lupinifolin (Xu, 2024).[237]

strong inhibition of biofilm formation in multidrug-resistant (MDR) enterococcal bacteria.[324] The construction of compound **262**, having a prenylated flavanone core, was achieved through Mitsunobu reaction, followed by a *para*-Claisen/Cope rearrangement, and an electrocyclization (to make the pyrane ring) starting from compound **263**. By using a chalcone, which is prepared using aldol condensation with commercially available 2,4,6-trihydroxy acetophenone monohydrate **20** and benzaldehyde **163**, in an oxy-Michael reaction, compound **263** was synthesized.

**5.8.2. Synthetic route.** The synthesis began with 2,4,6-trihydroacetophenone **20**, which was protected using methoxymethyl bromide (MOM-Br) and DIPEA in dry DCM to yield the 2,4-di-MOM protected intermediate in 84% yield, which then undergoes a base-catalyzed aldol condensation with MOM-protected *p*-hydroxybenzaldehyde **163**, resulting in a 95% yield of chalcone **121**.[302,325] Through careful optimization, chalcone **164** was cyclized using sodium acetate, yielding a 67% equilibrium of product, which, after removing the –MOM groups with diluted HCl, transformed into compound **264** with an impressive 88% yield.[237,326–328] Treating **264** with 3-methyl-2-

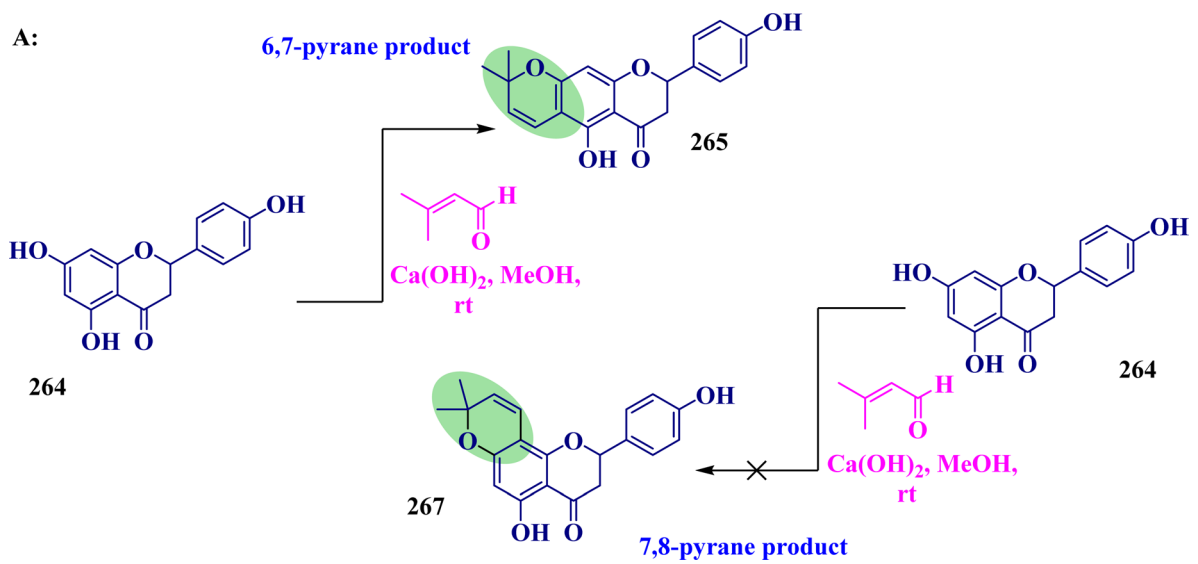



Fig. 41 Lessons from the total synthesis of lupinifolin. (A) Regioselective pyrane adduct formation.

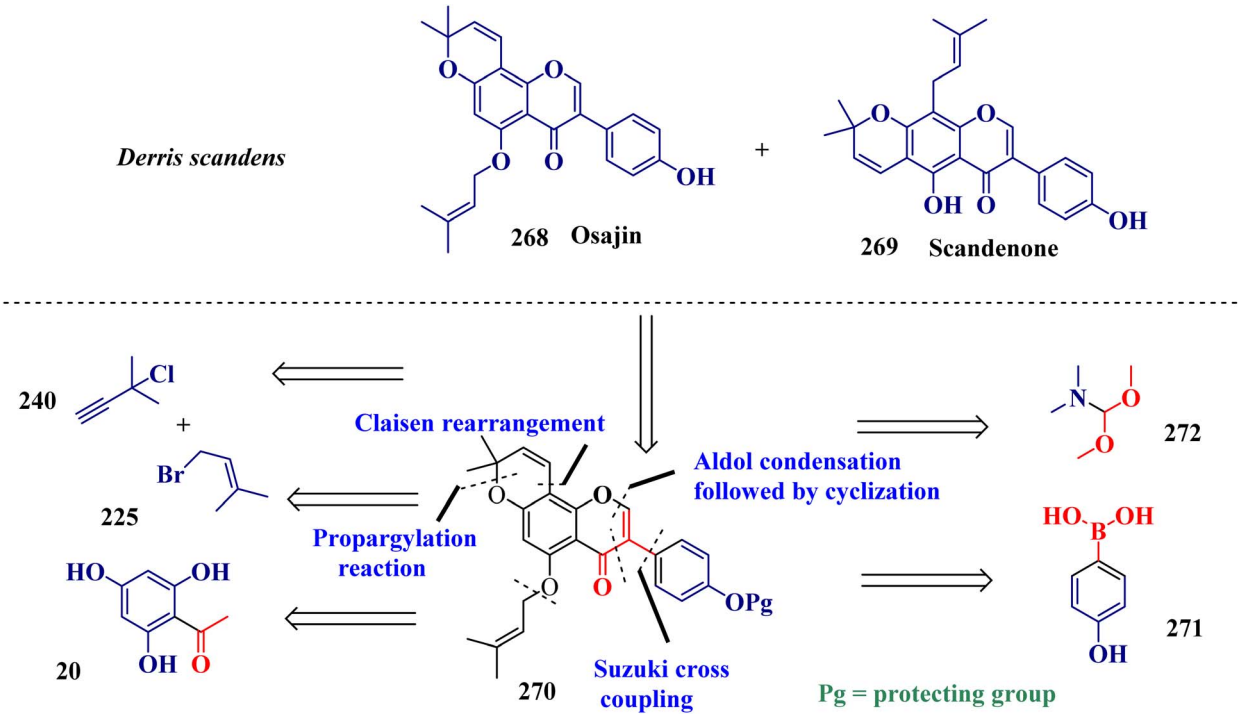



Fig. 42 Convergent strategy for the total synthesis of osajin and scandenone.

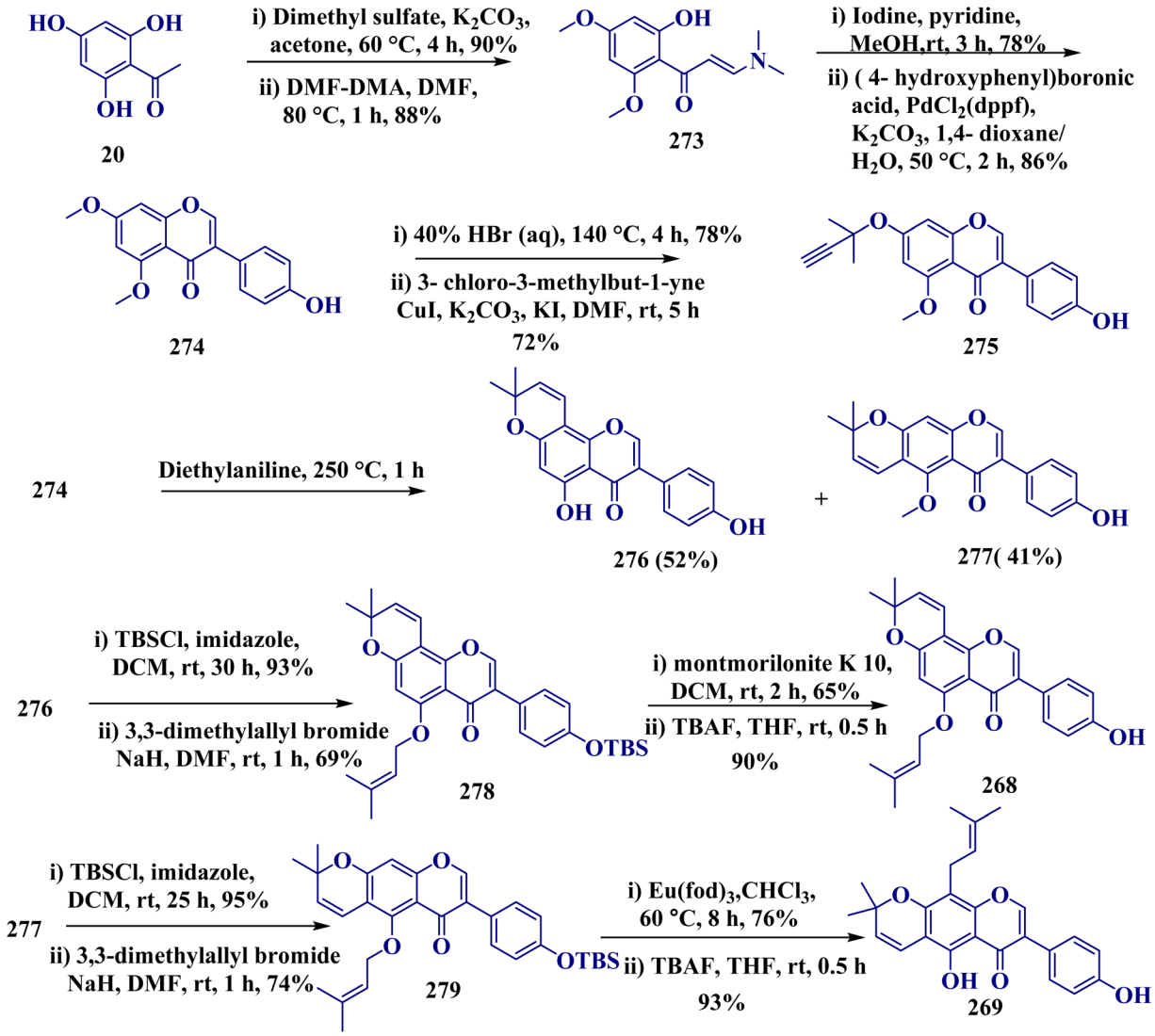
butenal and $Ca(OH)_2$/MeOH, 6,7-pyran, adduct **265** was synthesized in 45% yield. Finally, under Mitsunobu conditions using DEAD and $PPh_3$ in THF, compound **266** was formed by coupling **265** with 3-methylbut-2-en-1-ol. In the presence of $Eu(fod)_3$, compound **266** underwent a para-rearrangement and concomitant hydrolysis using KOH/MeOH, yielding lupinifolin **261** with an impressive yield (Scheme 19).[329]

**5.8.3. Strategies and lessons learned from this synthesis.** The 6,7-pyrane adduct **265** was the only product obtained by treating molecule **264** with 3-methyl-2-butenal and $Ca(OH)_2$/MeOH in this synthesis, demonstrating remarkable selectivity (Fig. 41). Interestingly, despite the apparent structural similarities between these sites in flavanone **264**, no 7,8-cyclized product appeared, demonstrating a remarkable degree of reaction specificity.[330–332]

### 5.9. Osajin and scandenone

**5.9.1. Synthetic strategy.** In 2024, Zhao and Jin achieved the synthesis of two remarkable natural flavonoid compounds, osajin and scandenone,[315] which are known for their potent abilities to inhibit the proliferation of various cancer cells and exhibit significant anti-inflammatory properties.[333,334] The compounds were isolated from the tree, *Derris scandens*, by Babu in 2010.[335] Targeting the C-7 hydroxy group of molecules **270**, which acts as a common intermediary for both natural products, the compounds were produced by chemoselective propargylation (Fig. 42). Compound **270**'s sequential reactions resulted from an intramolecular cyclization and nucleophilic substitution reaction concomitant with aromatic Claisen rearrangement at 250 °C, which led to the formation of the desired natural products. The intermediate **270** was produced by Suzuki cross-coupling reactions, aldol condensation, intramolecular iodoetherification, and elimination using 1-(2,4,6-trihydroxyphenyl)-ethan-1-one **20**, 1,1-dimethoxy-*N*,*N*-dimethylmethanamine **272**, and 4-hydroxyphenyl boronic acid **271**.

**5.9.2. Synthetic route.** In order to create the compounds, the free hydroxyl group of **20** was protected with a methyl group using acetone, dimethyl sulfate, and $K_2CO_3$, and the intermediate was subsequently reacted with **272** in DMF at 80 °C to produce compound **273** in 88% yield. Compound **273** and $I_2$, pyridine, and MeOH underwent an addition reaction to produce the iodo-derivative of the cyclized flavone intermediate. Then, using $PdCl_2$(dppf) as a catalyst in 1,4-dioxane/$H_2O$ at 50 °C, with an 86% yield, this intermediate underwent a Suzuki cross-coupling reaction with (4-hydroxyphenyl) boronic acid **271** to form the main tricyclic core containing compound **274**.[336] Treatment of compound **274** with 40% aqueous HBr in refluxing water, followed by chemoselective propargylation of the C-7 hydroxy group, produced compound **275** in 72% yield. With yields of 52% and 41%, respectively, compounds **276** and **277** were produced by cyclization of **275** in the presence of diethylaniline at 250 °C for 1 h.[337] In the two processes, compound **278** was produced with 64% yield by reacting compound **276** with TBSCl and imidazole in DCM medium to protect its more reactive C4′-hydroxy group with the TBS group and subsequent nucleophilic substitution reaction with 3,3-dimethylallyl bromide in DMF in the presence of NaH as a base. Compound **278** underwent Claisen rearrangement when it was treated with montmorillonite $K_{10}$




Scheme 20 Forward synthesis of osajin and scandenone (Zhao and Jin, 2024).[315]

in DCM, and further deprotection of the intermediate with TBAF in THF gave the target compound **268** in an excellent 90% yield. TBS-protected compound **277** was prenylated with **225** and NaH in DMF to produce compound **279** in 74% yield. The rearrangement product was then produced in 76% yield by reacting with $Eu(fod)_3$ in $CHCl_3$ at 60 °C for 8 h. Natural product **269** was obtained in 93% yield after the 4-OH group of the rearrangement intermediate was deprotected with TBAF in THF (Scheme 20).

**5.9.3. Strategies and lessons learned from this synthesis.** Initially, the reaction yielded only 20% to 36% of the cyclized flavone intermediate's iodo derivative. However, the yield increased after the addition of one equivalent of pyridine. The Suzuki cross-coupling reaction between the same iodo intermediate and **271** under normal conditions $Pd(OAc)_2$/MeOH/$NaCO_3$, yielded only 40% of product **274**, with minimal improvement from changes in solvents and bases like $Pd(OAc)_2$/DMF/$K_2CO_3$ and $Pd(PPh_3)_4$/DMF/$K_2CO_3$ at different temperatures; however, increasing the temperature to 50 °C improved the yield to 60%.[338,339]

## 6. Conclusion

On account of the diverse biological activities and therapeutic potential of flavonoids, much effort has been devoted to their total synthesis within the last few decades. Here, we have highlighted synthetic efforts for twenty distinct flavonoid analogues of high biomedical importance (Fig. 43). We have described the synthetic routes to access them, including the challenges and limitations of current approaches. In this exceptionally elegant synthesis of flavonoid molecules, the pivotal benzo-γ-pyrone ring core was exquisitely constructed *via* an aldol condensation between an acetophenone moiety and an aldehyde scaffold, yielding the chalcone intermediate, which then cyclized efficiently in the presence of iodine to produce the flavone. Alternatively, the benzo-γ-pyrone ring core was

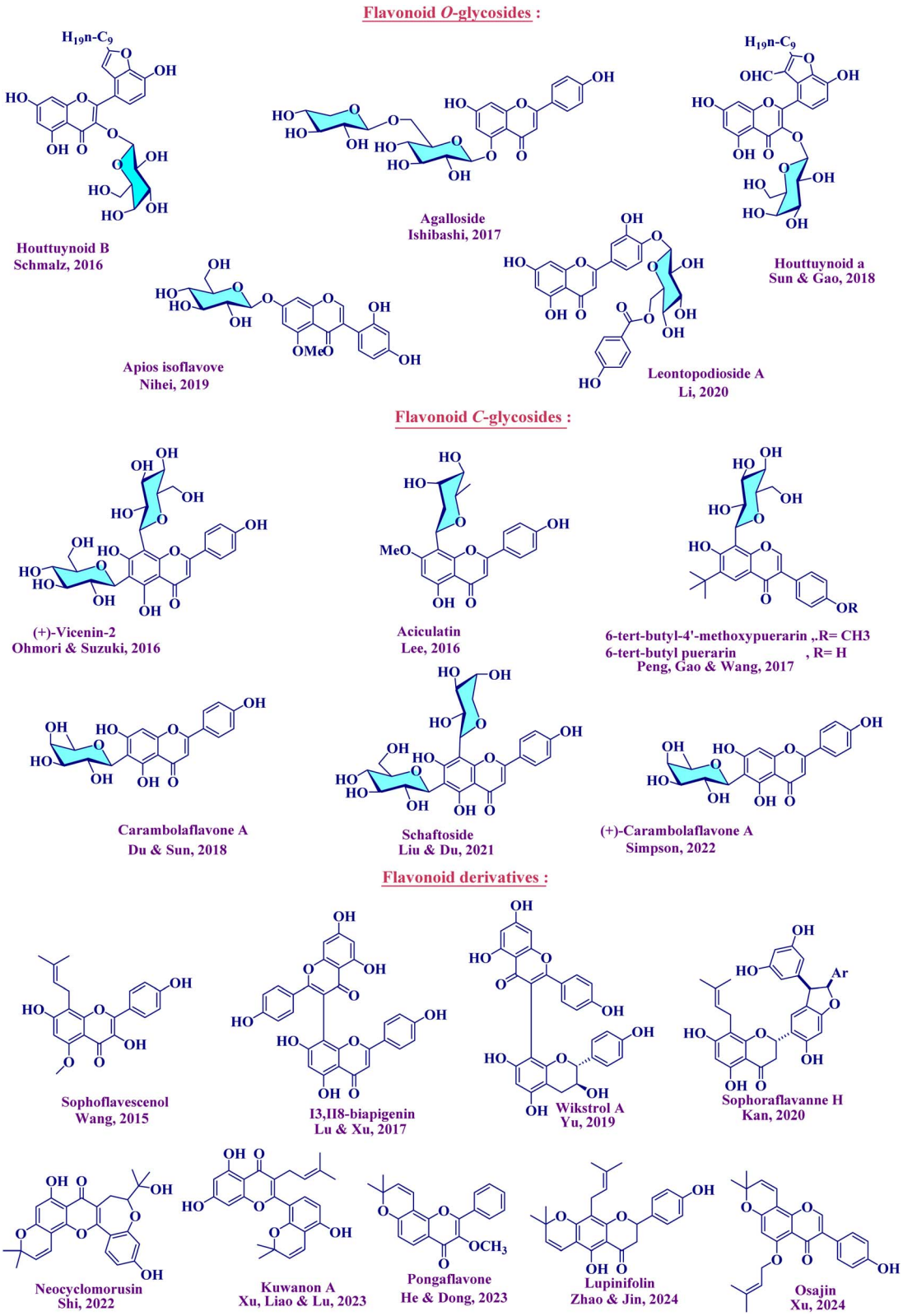



Fig. 43 Summary of flavonoids and their glycosides.

ingeniously synthesized from a 1,3-diketone intermediate, itself derived through a Baker–Venkataraman rearrangement of a 2-hydroxy-protected acetophenone ester, followed by cyclization in the presence of acid. For highly intricate structures, an extraordinary Rh-catalyzed cyclization of alkynes with protected aldehydes was masterfully employed. The creation of *O*- or *C*-glycosyl derivatives of these flavone frameworks unfolds through an enchanting coupling between the flavone core and

a meticulously selected glycosyl acceptor, orchestrated under the influence of a masterfully chosen catalyst.

During the synthesis of flavonoid-type natural products, several significant challenges remain to be addressed:

1. Regioselective functionalization of the B-ring of the quercetin nucleus, particularly for the construction of benzofuran moieties, continues to be a formidable challenge (from the synthesis of houttuynoid B).

2. The development of efficient glycosyl donors and suitable activated catalysts remains necessary for the synthesis of phenolic glycosides in the presence of a flavone enone moiety (from the synthesis of agalloside, houttuynoid A, *etc*).

3. Functionalization of the chalcone scaffold to access flavone cores bearing electron-withdrawing groups is particularly challenging due to the predominance of retro-aldol pathways under such conditions (from the synthesis of vicenin-2).

4. Achieving regioselective oxidation of the benzopyran core from the synthesis of flavone-type molecules from the flavan core, while retaining free phenolic hydroxyl groups, remains difficult (from the synthesis of schaftoside).

5. Rhodium-catalysed cross-coupling reactions involving unprotected hydroxy flavones are still inefficient, limiting the development of more atom-economical methodologies, as the synthesis of biflavones faces severe obstacles in other Pd-catalysed conventional cross-coupling reactions (from the synthesis of wikstral A and B).

6. Chemoselective reduction of the flavone enone moiety remains insufficiently developed. Moreover, the stereoselective synthesis of the flavanone core from chalcone precursors using modern synthetic approaches is highly desirable to overcome the current limitations (from the synthesis of sophoraflavanone H).

7. The synthesis of flavanol cores from flavones predominantly relies on oxone-mediated oxidation; however, this approach is highly functional-group dependent. Alternatively, the AFO reaction of chalcones to flavanols often leads to the undesired formation of the aurone framework (from the synthesis of pongaflavone).

The total synthesis of flavonoid-type natural compounds represents a fascinating frontier, offering vast potential for groundbreaking innovations, despite its numerous challenges, with the diversity of yet unidentified molecules. The synthesis of these complex flavanol molecules has led to the development of new catalysts, reagents, and reactions with the potential to transform the field of natural product synthesis. We hope this review will encourage synthetic chemists to further develop innovative methodologies that will advance the frontiers of natural product synthesis and address its intrinsic challenges.

## 7. Conflicts of interest

There are no conflicts to declare.

## 8. Data availability

The data that support the findings of this study are available in the published research articles.

## 9. Acknowledgements

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