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Total synthesis of isoflavonoids

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Covering: 2012 to 2024

Isoflavonoids are phenolic compounds with wide structural diversity and a plethora of biological activities. Owing to their structural variation and potential health-promoting and other benefits, they have been targeted for synthesis. Herein, we review the synthesis of natural isoflavonoids belonging to different classes that include isoflavones, isoflavanones, isoflavans, isoflavenes, pterocarpans, rotenoids, coumaronochromones, and coumestans. The synthetic methodologies employed and advancements in synthetic strategies are highlighted.

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1. Introduction

Isoflavonoids are a class of flavonoids that possess a 3-phenylchroman skeleton, which is derived from a 1,2-aryl migration during the biosynthesis of flavonoids.[1] Isoflavonoids occur mainly in the Leguminosae family,[1–4] however, there is a limited number of isoflavonoids that have been identified from non-leguminous plants.[5,6] Despite their limited distribution, isoflavonoids have large structural variation and are divided into subclasses that include isoflavones, isoflavanones, isoflavans, pterocarpans, rotenoids, 3-arylcoumarins, coumaronochromones, coumestans, and others depending on the oxidation state of the chroman ring and the presence of

additional heterocyclic rings.[1,7,8] Structural diversity also arises from the substitution patterns and the structural modifications that include hydroxylation,[2,3] methylation,[2,3] prenylation,[3,9] glycosylation,[3,4,10,11] and oligomerisation.[3,4,12–15]

In the plant kingdom, isoflavonoids act as phytoalexins that offer protection to plants against microorganisms.[5,16] Apart from interaction with microorganisms, isoflavonoids have been reported to exhibit biological activities with potential health-promoting benefits to humans.[8,17–21] These include oestrogenic,[22,23] anti-inflammatory,[24] anti-microbial,[17,24–26] vasorelaxation,[27] antiarthritic,[28] cardioprotective,[29] neuroprotective,[20] antiviral,[30] immunosuppressive,[31,32] osteoprotective,[33] chemoprotective and antiproliferative activities.[34–36] Examples of bioactive isoflavonoids are shown in Fig. 1. They comprise of a *C*-glucosylated isoflavone, puerarin (**1**);[18,20,37] prenylated isoflavans, eryzerin C (**2**);[38,39] a pterocarpan, (+)-(6a*S*,11a*S*)-2,3,9-trimethoxypterocarpan [(+)-**3**];[40,41] a rotenoid, amorphispironone B (**4**);[34] a pyranocoumarochromone, hirtellanine A (**5**);[31,32] and a coumestan, psoralidin (**6**).[33,42,43]

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Owing to their important biological activities, the synthesis of isoflavonoids and their derivatives has been of interest to researchers.[32,37,41,44–47] Several synthetic strategies have been developed for the different classes and applied to the synthesis of natural isoflavonoids. The methods range from classical condensations and rearrangements,[43,48–54] to metal-catalysed cross-coupling reactions of pre-functionalised precursors[55–61] and transformations facilitated by direct C–H activation amongst others.[62–64] In this review, the synthesis of natural isoflavonoids belonging to different subclasses is discussed. The main focus is on reports published from 2012 to 2024. The sections are divided based on the subclasses of isoflavonoids and further (where permissible) based on methodologies that include conventional and newly developed methods. For chiral isoflavonoids that include isoflavanones, isoflavans, pterocarpans and rotenoids, recent studies on syntheses of racemic mixtures, as well as stereoselective syntheses encompassing the use of chiral pool building blocks,[65–67] metal-catalysed reactions in the presence of chiral ligands,[68,69] organocatalysed stereoselective syntheses,[70–75] and stereoselective hydrogenation and hydrogen transfer are discussed.[76–79]

2. Synthesis of isoflavones

Traditionally, isoflavones are synthesised from 2-hydroxyphenyl benzyl ketone (2-hydroxydeoxybenzoin) and chalcone precursors.[49,53] The construction of isoflavones from 2-hydroxydeoxybenzoins requires the incorporation of an additional carbon unit to afford a $C_6C_3C_6$ skeleton. This is achieved by formylation or acylation at the benzylic position and consequent *O*-cyclisation.[49,50,53] The synthesis of isoflavones from chalcones follows a biomimetic sequence that involves oxidative rearrangement of the B-ring aryl group to the 3 position.[53] Depending on the reaction conditions, this often leads to the formation of α-formyldeoxybenzoins or α-acetaldeoxybenzoins as intermediates, which undergo ring-closure with the hydroxy group on the phenyl A-ring to afford isoflavones.[48,51,52] The syntheses of

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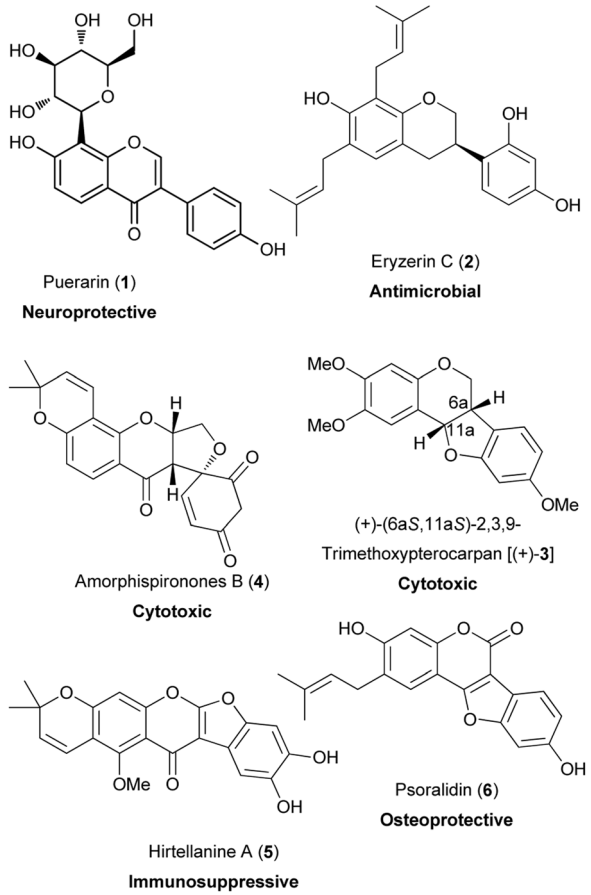
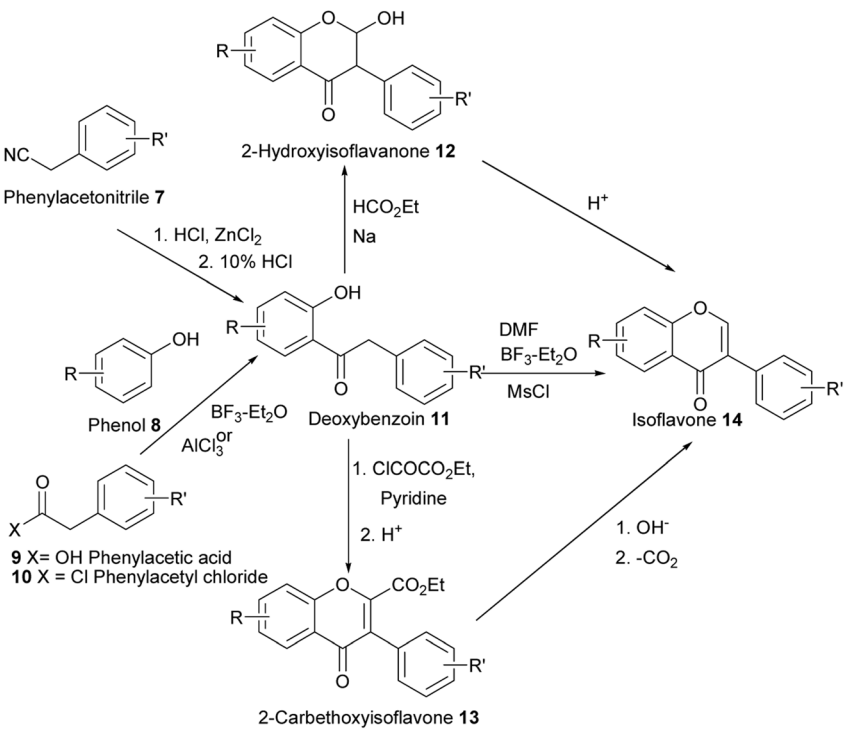


Fig. 1 Examples of bioactive isoflavonoids.

isoflavones from the deoxybenzoin and chalcone precursors were carried out as early as the 1920s and the 1950s and the methods continue to be modified and applied to the synthesis of natural isoflavones.[53,80–84] Modified deoxybenzoin-based methodologies developed lately involve Pd(II)-catalysed oxidative cyclisation of α-methylenedeoxybenzoins,[85] and CuI-catalysed intramolecular cyclisation of 2-bromo-α-formyldeoxybenzoins.[60,61] Other recent synthetic strategies for isoflavones include oxidation of isoflavenes obtained by ring-closing metathesis,[86] tandem demethylation and ring/opening cyclisation of methoxybenzoylbenzofurans,[87] and metal-catalysed cross-coupling reactions of functionalised chromones that encompass the Suzuki–Miyaura,[55,56,88] the Negishi cross-coupling,[57,58] and the Stille cross-coupling reactions.[59,89] Very recently, new methods that involve direct arylation of 2-hydroxyenaminoketones for the synthesis of isoflavones have been developed.[90–93]

2.1. Deoxybenzoin route

2.1.1 Simple isoflavones. Several natural isoflavones have been synthesised by the deoxybenzoin route. The deoxybenzoin intermediates **11** can be accessed by reactions of phenols **8** with phenylacetonitriles **7** followed by hydrolysis.[94,95] Alternatively, the benzyl ketones can be synthesised by Friedel–Crafts acylation of phenols **8** with phenylacetic acids **9** or acyl chlorides **10**.[80,96–98] Deoxybenzoins **11** can be converted into isoflavones **14** by treatment with reagents containing activated units that include ethyl formate, ethyl orthoformate,[53] *N*,*N*-dimethylformamide (DMF),[80,96] *N*,*N*-dimethylformamide dimethyl acetal (DMF–DMA)[98,99] and bis(dimethylamino)-*t*-

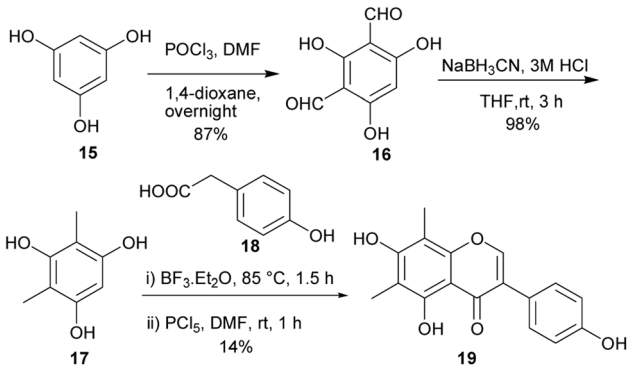


Scheme 1 Synthesis of isoflavones from deoxybenzoin intermediates.

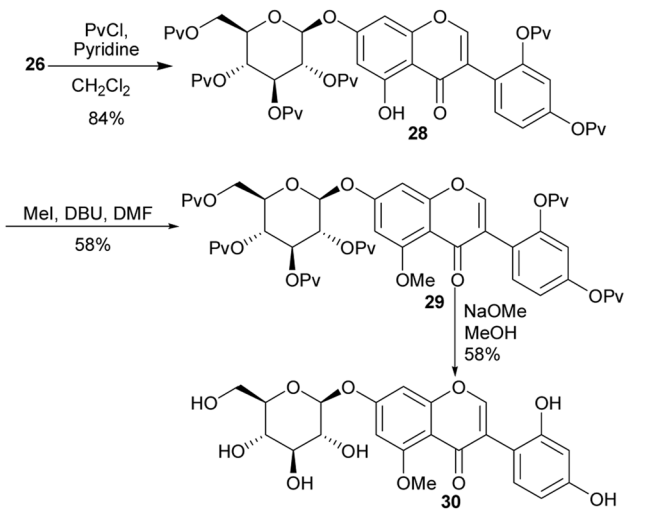
butoxymethane [HC[N(CH$_3$)$_2$]$_2$O-^{t}Bu].[97] Using ethyl formate in the presence of sodium metal first converts the deoxybenzoins **11** into 2-hydroxyisoflavanone intermediates **12**, which upon dehydration form the requisite isoflavones **14**.[53] Treatment of **11** with ethyl oxalyl chloride in pyridine affords the intermediates **13** and subsequently isoflavones **14** upon hydrolysis and decarboxylation.[53] A depiction of the synthesis of isoflavones by the deoxybenzoin route is shown in Scheme 1.

6,8-Dimethylgenistein (**19**), an isoflavone with a fully substituted A-ring was isolated from *Henriettella fascicularis*.[100] It showed a stronger binding affinity to estrogen receptor β than estrogen receptor α and moderate antiestrogenic activity with cultured Ishikawa cells.[100] This compound was synthesised by two independent synthetic routes (the deoxybenzoin route and the Suzuki–Miyaura coupling reaction).[80] Following the deoxybenzoin route, the synthesis was initiated by formylation of phloroglucinol (**15**) to give compound **16**, which was reduced to give the dimethylated phloroglucinol **17**. $BF_3 \cdot Et_2O$-mediated coupling of **17** with 4-hydroxyphenylacetic acid (**18**) followed by treatment of the resulting benzyl ketone with PCl_5/DMF gave 6,8-dimethylgenistein (**19**) in a 14% yield (Scheme 2).[80]

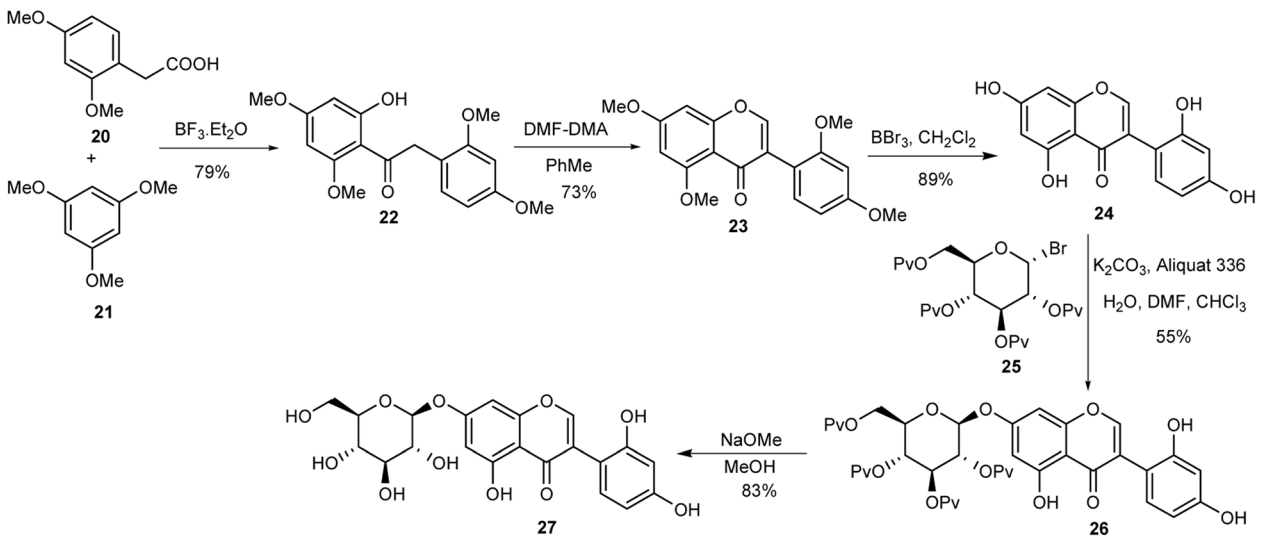
2.1.2 Glucosylated isoflavones. *O*-Glucosylated isoflavones **27** and **30** together with their aglycone derivatives from *Apios americana* were synthesised for the first time by Asebi and co-workers.[98,101] The synthesis of the compounds featured acylation of trimethoxybenzene **21** with dimethoxyphenylacetic acid **20** to give a mono-demethylated deoxybenzoin **22** in a 79% yield, Scheme 3. Condensation of the benzyl ketone **22** with DMF–DMA gave an isoflavone **23**,[99] which was demethylated with BBr_3 to give aglycone precursor **24**. Selective phase-transfer *O*-glucosylation of **24** using 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide [(Pv)$_4$GlcBr] in the presence of aliquat 336 and K_2CO_3 gave compound **26**,[102] from which 7-β-D-glucopyranosyloxy-2′-hydroxygenistein (**27**) was accessed by deprotection of the pivaloyl groups, Scheme 3. The synthesis of 7-β-D-glucopyranosyloxy-2′-hydroxy-5-*O*-methylgenistein (**30**) was accomplished by the pivaloyl protection of the 2′- and 4′-hydroxy groups of **26** followed by methylation of the 5-hydroxy group of



Scheme 2 Synthesis of 6,8-dimethylgenistein (**19**).



Scheme 4 Synthesis of isoflavone glucoside **30**.



Scheme 3 Synthesis of isoflavone glucoside **27**.

28 to afford isoflavone **29**, and finally cleavage of all the pivaloyl protecting groups under basic conditions (Scheme 4).[98]

Puerarin (**1**) is a *C*-glucosylated isoflavone isolated from *Pueraria lobata* (Willd.).[103] It has many important biological activities that include antioxidant, antihyperglycemic, anti-inflammatory and neuroprotective effects.[20,104–106] The first synthesis of puerarin (**1**) was reported by Lee and co-workers.[37] The synthesis involved the coupling of aryllithium species with pyranolactone for the *C*-glucosylation and oxidative rearrangement of a chalcone for isoflavone formation.[37] In 2018, Zhou and colleagues synthesised puerarin (**1**) by coupling alkyl-substituted resorcinol **31** with glucosyl trifluoroacetimidate **32** to afford *C*-glucoside **34** in a 46.2% yield. Removal of the *tert*-butyl group followed by oxidation of the resulting diarylethene **35** gave deoxybenzoin **36**.[107] Modified Vilsmeier–Haack formylation and debenzylation gave the isoflavone **37** and the targeted puerarin (**1**), respectively (Scheme 5).[107,108]

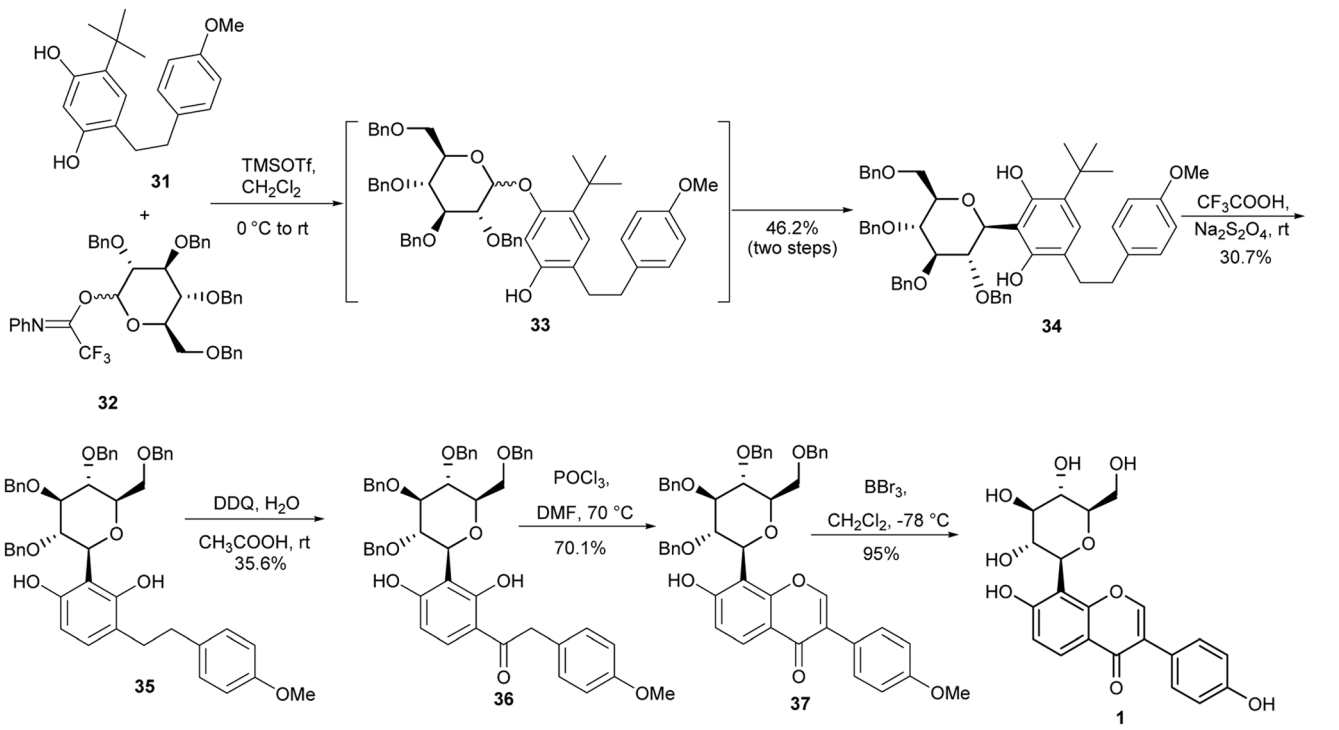
Although the deoxybenzoin route avoids the use of toxic TTN(III) that was utilised by Lee and colleagues for the synthesis of puerarin (**1**),[37,107] the synthesis in Scheme 4 gave comparatively low yields of the *C*-glucosylated precursor **34**. Also, the *t*-butyl deprotection and oxidation steps leading to the deoxybenzoin intermediate **36** were low yielding.[107]

Although synthesis of isoflavones by the deoxybenzoin route was first reported almost 100 years ago,[109] the method is still utilised for the synthesis of natural isoflavones that include simple isoflavones, glucosylated isoflavones and prenylated isoflavones.[80,94,97,98,107] The main advantage of the method is that the deoxybenzoin precursors can be synthesised from non-protected phenylacetic acids and phenols, thereby eliminating the protection and deprotection steps.[80,94] However, the formation of deoxybenzoin and their conversion into isoflavones provide relatively low yields of the products depending on the reaction conditions and substituents present.[80,97] Moreover, the harsh acidic conditions employed necessitate the installation of sensitive substituents such as prenyl groups upon the complete construction of the isoflavone core structure and in several steps.[94]

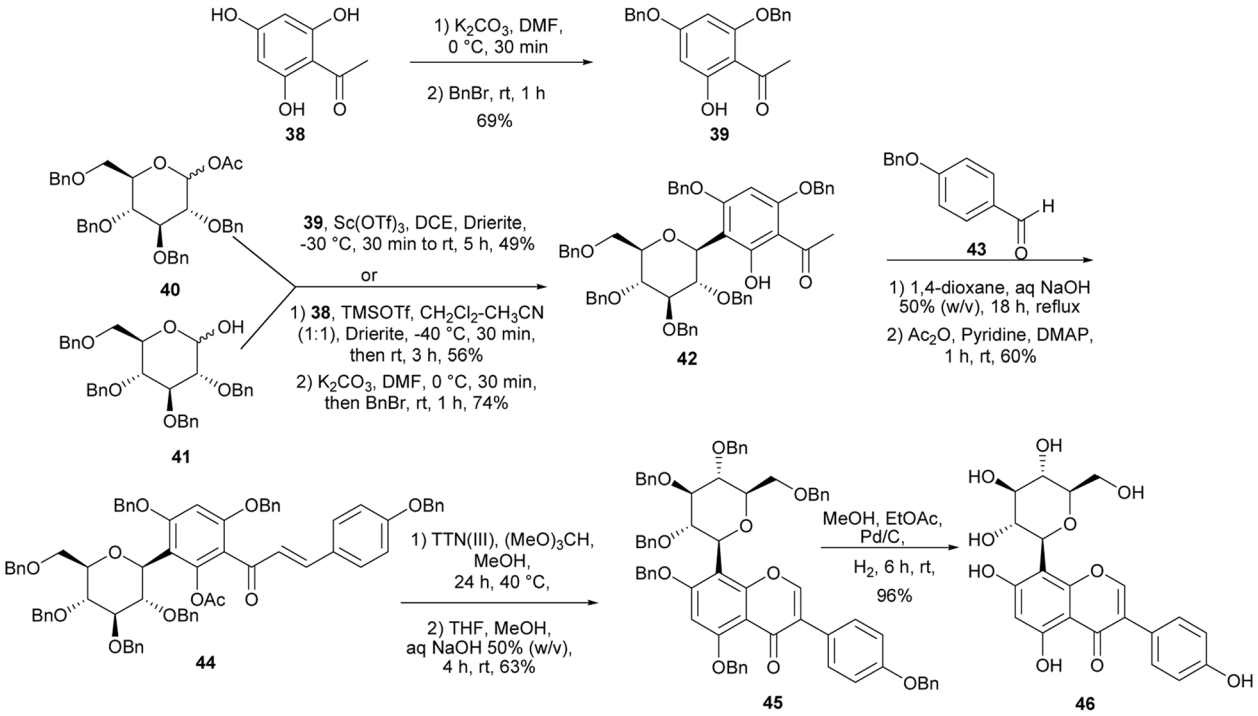
2.2. Oxidative rearrangement of chalcones

Unlike deoxybenzoins, chalcones can be readily prepared by a Claisen–Schmidt condensation of readily available benzylaldehydes and acetophenones. Earlier protocols utilised thallium nitrate [TTN(III)] and thallium acetate [$Tl(OAc)_3$] to facilitate oxidative rearrangement of chalcones.[52,53] Hypervalent iodine reagents that include phenyliodine(III) bis(trifluoroacetate), (diacetoxyiodo)benzene/*p*-toluenesulfonic acid, [hydroxy(tosyloxy)iodo]benzene and [bis(trifluoroacetoxy)iodo]benzene are other reagents that have been developed to facilitate the aryl migration.[53,82,110]

2.2.1 Glycosylated isoflavones. 8-β-D-Glucopyranosylgenistein **46** was identified as a major constituent of the extract of *Genista tenera* with anti-hyperglycemic activity.[111] Jesus and colleagues synthesised this compound and conducted further antidiabetic activity studies.[81] The synthesis is shown in Schemes 6. The first step entailed preparation of the *C*-glucosylated acetophenone **42**. This was accomplished in 49% yield by $Sc(OTf)_3$-catalysed reaction of 2,4-dibenzyloxy-6-hydroxyacetophenone (**39**) with perbenzylglucosyl acetate **40**. Alternatively, compound **42** could be synthesised by TMSOTf-



Scheme 5 Synthesis of puerarin (**1**).



Scheme 6 Synthesis of 8-β-D-glucopyranosylgenistein (**46**).

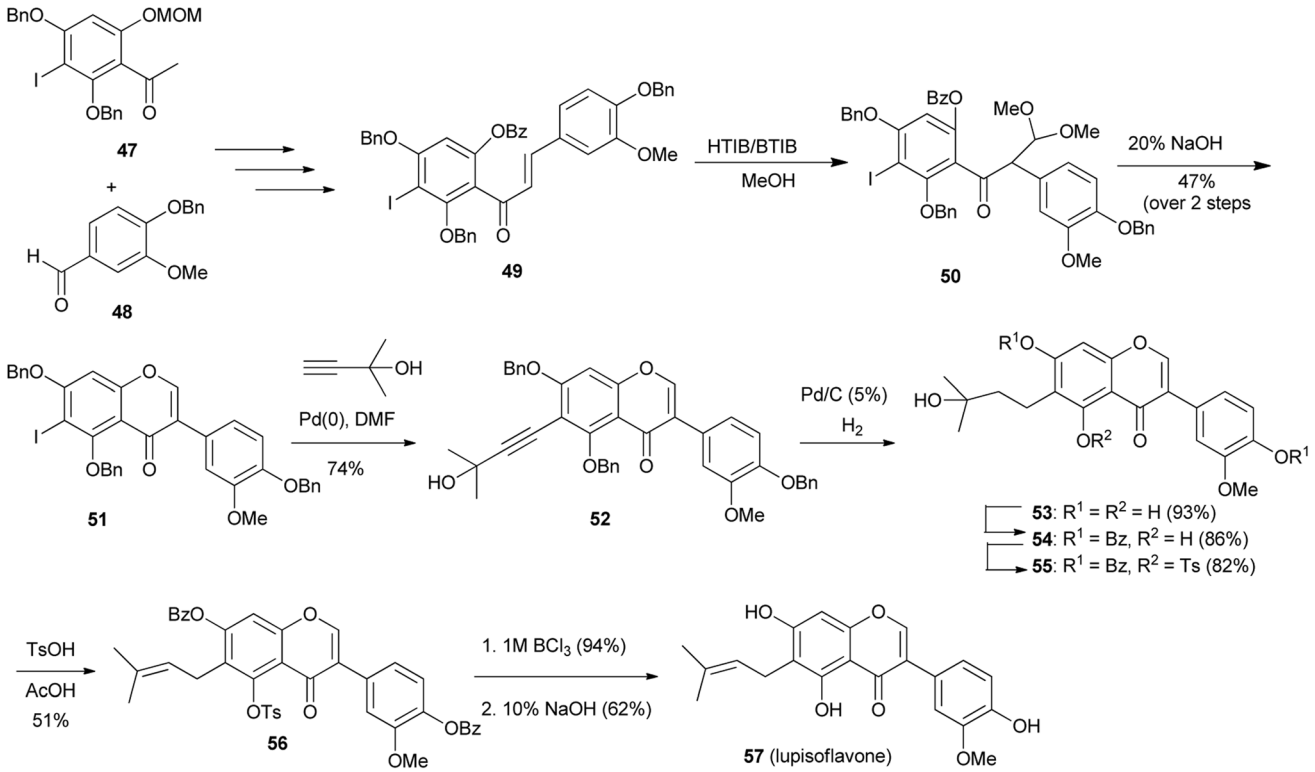
catalysed reaction of phloroacetophenone (**38**) with glucosylating agent **41** followed by dibenzylation. Aldol condensation of **42** and benzyladehyde **43** gave a chalcone **44**, which underwent rearrangement into isoflavone **45** upon oxidation with TTN(III). Finally, debenzylation of **44** gave 8-β-D-glucopyranosylgenistein (**46**).[81]

2.2.2 Prenylated isoflavones. Several prenylated isoflavones and pyranoisoflavones have been synthesised by oxidative rearrangement of chalcones.[82–84,112,113] Owing to the sensitivity of the prenyl side chain to highly oxidative and acidic conditions employed, the complete installation of the prenyl group has been conducted in the late stages of the synthesis, upon complete construction of the isoflavone core structure.[82–84] Some examples of prenylisoflavones and dimethylpyranoisoflavones that were synthesised by oxidative rearrangement of chalcones are wighteone,[82] derrubone,[82] lupisoflavone,[82,83] erysubin F, other *Erythrina* isoflavones[84] and barbigerone.[113]

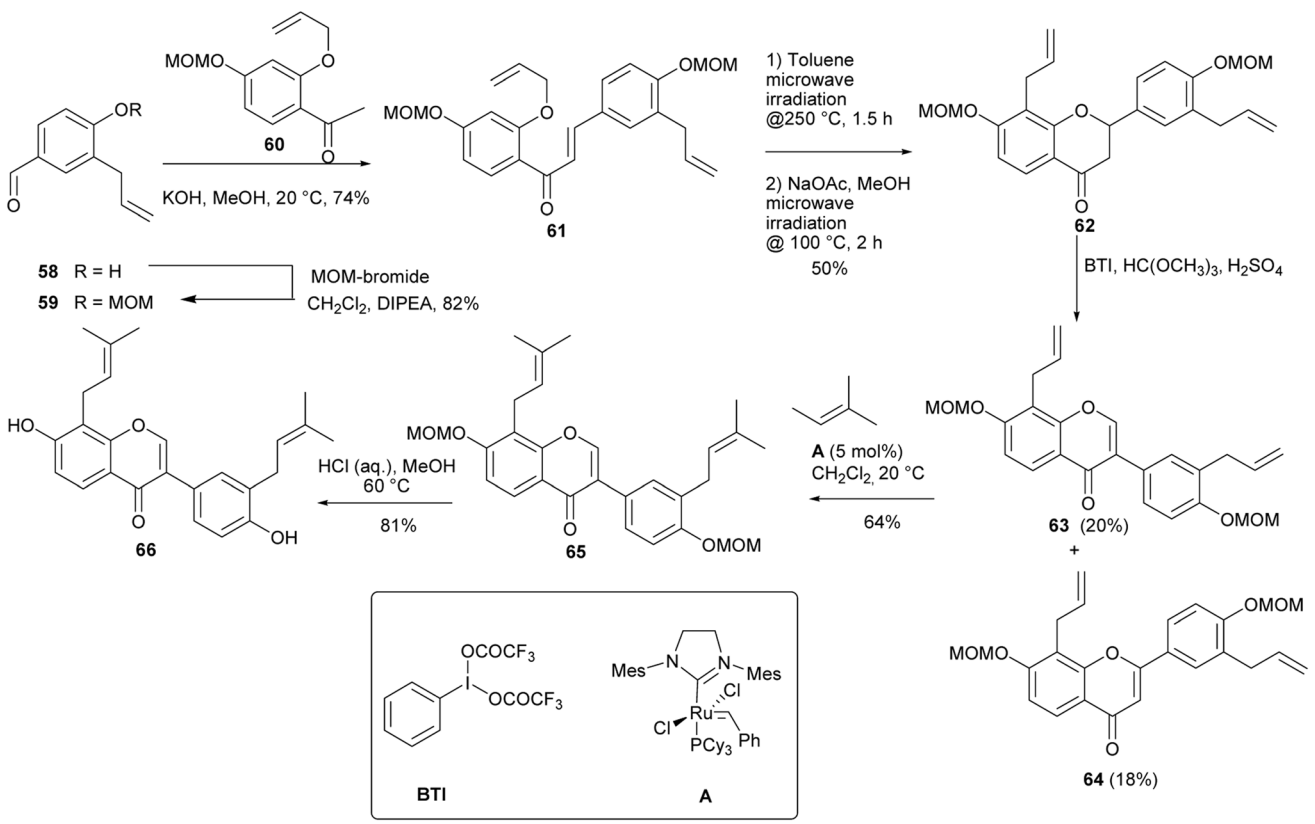
Lupisoflavone (**57**), the antifungal prenylisoflavone from *Lupinus albus*[114] was synthesised by Hossain and colleagues together with other prenylisoflavones.[82,83] Initially they utilised microwave irradiation in several key steps, which led to higher yields and shorter reaction times.[82] The synthesis of lupisoflavone (**57**) under conventional conditions was reported in 2012.[83] As shown in Scheme 7, benzoylchalcone **49**, obtained in a sequence of steps from iodoacetophenone **47** and benzaldehyde **48**, underwent oxidative rearrangement upon treatment with a mixture of [hydroxyl(toxyloxy)iodo]benzene (HTIB) and [bis(trifluoroacetoxy)iodo]benzene (BTIB) to afford acetal intermediate **50**. *O*-Cyclisation of acetal **50** under basic conditions gave 6-iodoisoflavone **51**. Sonogashira coupling of **51** with 2-methyl-3-butyn-2-ol followed by reduction of the alkynylisoflavone **52** gave **53**. Sequential protection of phenolic groups with benzoyl and tosyl groups and subsequent dehydration of the 2-hydroxybutyl group gave a mixture of 6-prenylisoflavone **56** and the regioisomer, 6-(3-methyl-3-butenyl) isoflavone. Finally, lupisoflavone (**57**) was obtained by successive deprotection of tosyl and benzoyl groups.[83]

Several prenylated isoflavones from the genus *Erythrina* have been synthesised by Kwesiga and colleagues by 2,3-oxidative aryl migration of flavanones obtained from chalcones.[84,112] These included a diprenylated isoflavone erysubin F (**66**). The synthesis of erysubin F (**66**) was initiated by MOM protection of allylbenzaldehyde **58** followed by Claisen–Schmidt condensation of the resulting **59** with *O*-allylacetophenone **60** to afford chalcone **61** in 74% yield. Claisen rearrangement and *O*-cyclisation gave flavanone **62** in 50% yield, which upon treatment with BTI and trimethylorthoformate gave isoflavone **63** in 20% yield, together with flavone **64** in 18% yield. Double cross-coupling metathesis of bisallylisoflavone **63** with 2-methyl-2-butene using the second-generation Grubbs catalyst **A** rendered bisprenylated isoflavone **65**, which was deprotected to give erysubin F (**66**), Scheme 8.[84]

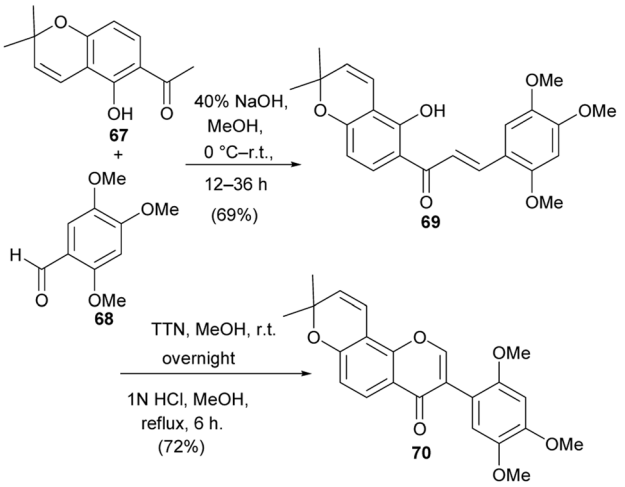
Barbigerone (**70**) is a pyranoisoflavone that was first isolated from *Tephrosia barbigera*.[115] It has also been identified from other sources, especially from the *Millettia* genus.[116,117] It has been determined to exhibit biological activities that include antiparasitic activity,[118] cytotoxicity against several cancer cells including MDR cells[119,120] and anti-inflammatory activities.[113] The synthesis of barbigerone has been reported by several groups.[113,121] The synthesis by Wei and colleagues proceeded *via* condensation of pyranoacetophenone **67** with benzaldehyde **68** to give chalcone **69**. Oxidative migration of the



Scheme 7 Synthesis of lupisoflavone (**57**).



Scheme 8 Synthesis of erysubin F (**66**).



Scheme 9 Synthesis of barbigerone (70).

trimethoxybenzene ring in the presence of TTN(III) gave an acetal intermediate, which underwent oxycyclisation to afford barbigerone **70**, Scheme 9.[113]

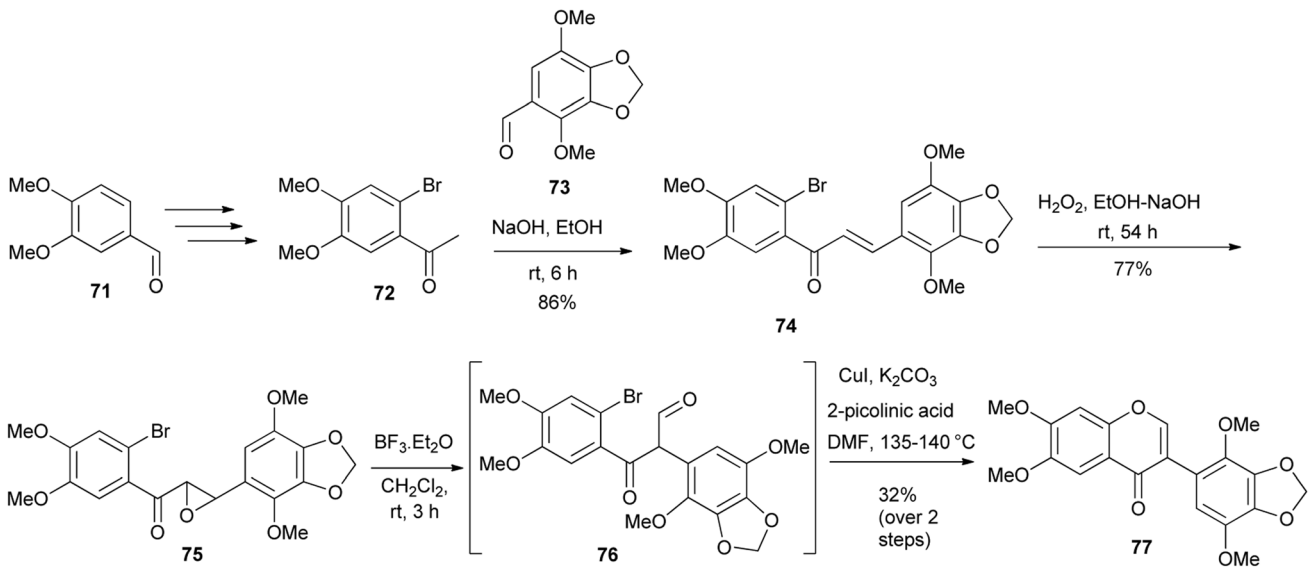
Despite the continued application of the oxidative rearrangement of chalcones for the synthesis of isoflavones, the high cost, toxicity and adverse environmental effects of thallium reagents make the method unattractive.[82] Environmentally friendly and less toxic hypervalent iodine reagents have been developed to facilitate the aryl shift.[53,110] The challenge with these reagents is inconsistencies in product yields. Some studies reported moderate to high yields of isoflavones obtained by oxidative rearrangement of hypervalent iodine reagents, while other studies reported low to moderate yields. The low yields result from the formation of other untargeted products including benzofurans and flavones.[53,84,110] Moreover, like the deoxybenzoin route, the incorporation of the prenyl groups is restricted to the late-stages of the synthesis due to the oxidative reaction conditions that are incompatible with such substituents. This can pose challenges in controlling the regioselectivity and therefore, necessitate the attachment of such groups in multiple steps.[84,112]

2.3. Modified deoxybenzoin and chalcone routes

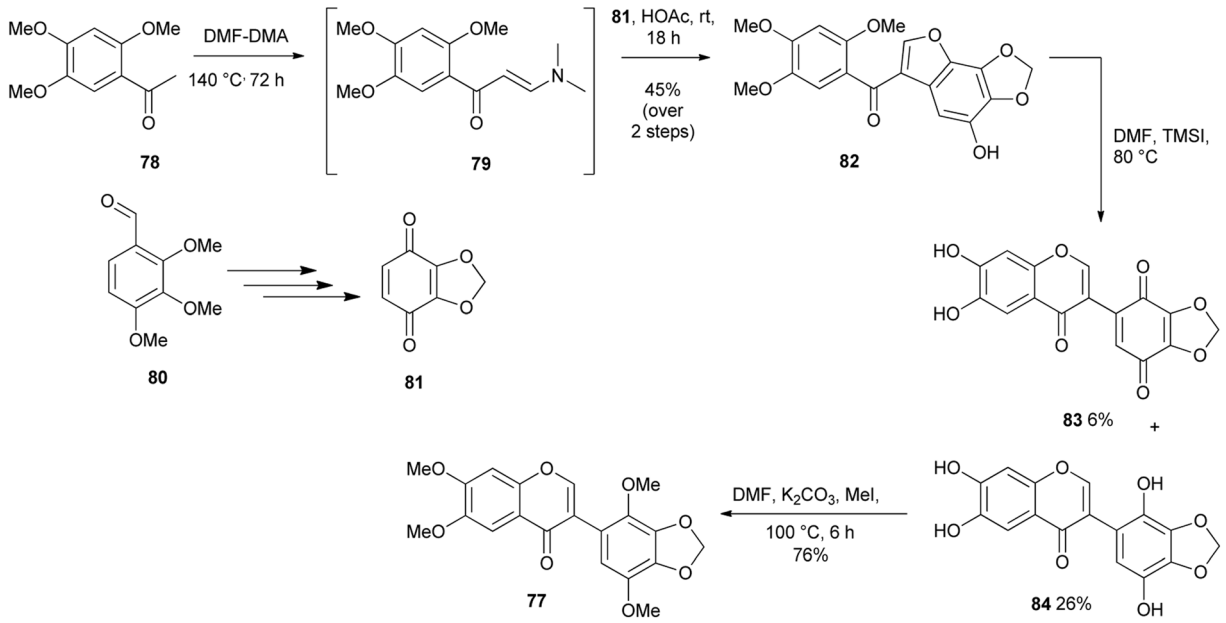
A modified deoxybenzoin route that involved CuI-catalysed intramolecular cyclisation of α-formylated 2-bromodeoxybenzoin was reported by Zhu's group in 2011.[60] Later (2016) Semenov and colleagues synthesised a potential anti-cancer compound, glaziovianin A (77) and several derivatives from 3-(2-bromophenyl)-3-oxopropanal intermediates using Zhu's conditions.[60,61] However, the α-formyldeoxybenzoin precursors in Semenov's synthesis were prepared by rearrangement of epoxychalcones.[48,122] As illustrated in Scheme 10, the synthesis of glaziovianin A (77) commenced with the preparation of bromoacetophenone **72** and benzaldehyde **73**, from plant metabolites, methyleugenol and apiol, respectively. Condensation of **72** and **73** gave chalcone **74**, which was converted into epoxide **75**. Treatment of epoxide **75** with $BF_3 \cdot OEt_2$ and subsequent CuI-mediated cyclisation of the resulting bromodiarylketoaldehyde **76** gave glaziovianin A (77).[61]

2.4. Transformation of methoxybenzoylbenzofurans into isoflavones

Kunyane and colleagues reported the unexpected conversion of methoxybenzoylbenzofurans into isoflavones through a one-pot sequence that involved demethylation and oxycyclisation, resulting in furan ring-opening and chromone ring-formation.[87] A series of isoflavone derivatives were prepared by demethylation of 2′-methoxybenzoylbenzofurans. The method was further applied to the synthesis of glaziovianin A (77), Scheme 11. The synthesis was initiated by the preparation of benzoquinone **81** from trimethoxybenzaldehyde **80**. Condensation of



Scheme 10 Synthesis of glaziovianin A (77) by Semenov and colleagues.[61]



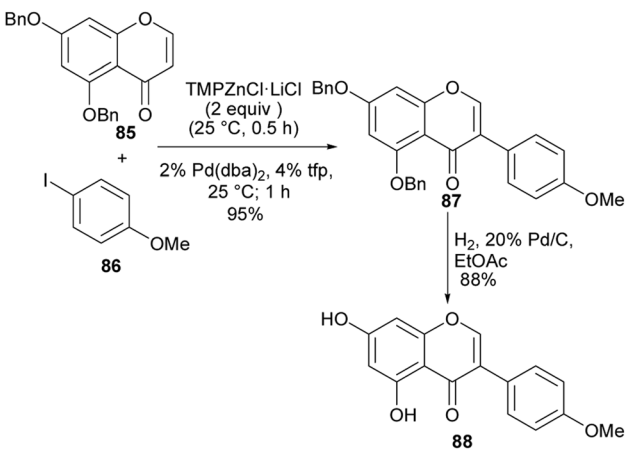
Scheme 11 Synthesis of glaziovianin A (77).

acetophenone **78** with DMF–DMA and subsequent coupling of the resulting enaminone intermediate **79** with benzoquinone **81** under acidic conditions gave 2′-methoxybenzoylbenzofuran **82** in 45% yield. Demethylation with TMSI gave a separable mixture of isoflavone **84** and isoflavone quinone **83.** Methylation of the isoflavone **84** gave the targeted compound **77**, Scheme 11.

2.5. Functionalised chromones

Metal-catalysed cross-coupling reactions of C-3 functionalised chromones have been employed successfully for the synthesis of isoflavones. Access to functionalised chromone coupling partners could be attained from enaminone precursors or by direct C-3 metalation or halogenation of chromones.[57,123,124] Metal-catalysed cross-coupling reactions such as the Suzuki–Miyaura reaction,[55,56,88] the Negishi and Stille cross-coupling reactions utilise the 3-halogenated or metallated chromone precursors for the synthesis of isoflavones.[55–59,89] In other instances, triarylbismuths have also been employed as coupling partners for chromonetriflates.[125] In comparison to the Suzuki–Miyaura reaction, studies on the synthesis of isoflavones by the Negishi and Stille reactions are still limited.

2.5.1 Negishi cross-coupling reaction. Klier and colleagues reported regioselective metalation of chromones and quinolones leading to C-2 zincated chromones upon treatment with $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$, whereas chromone-3-zinc chlorides were obtained with TMPZnCl·LiCl in the absence of $MgCl_2$.[57] Isoflavone derivatives could be synthesised by Pd-catalysed Negishi cross-coupling of aryl iodides or aryl bromides with the C-3 zincated chromones. As shown in Scheme 12, the natural compound biochanin A (**88**) was synthesised by treatment of chromone **85** with TMPZnCl·LiCl followed by Pd-catalysed coupling with *p*-methoxyphenyl iodide **86** and debenzylation of **87**. The isoflavones **87** and biochanin A (**88**)

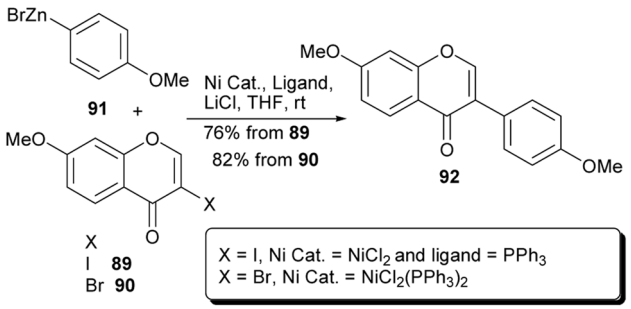


Scheme 12 Synthesis of biochanin A (**88**) by Negishi cross-coupling reaction.

were obtained in 95% and 88% yields, respectively (Scheme 12).[57]

On the other hand, Zhang and colleagues prepared a series of isoflavones at room temperature by nickel-catalysed Negishi coupling of halochromones with arylzinc bromides in the presence of LiCl, as an additive.[58] Under these conditions, the natural compound 7,4′-dimethoxyisoflavone (**92**)[126] was synthesised in 76–82% yield by coupling of 3-iodochromone **89** or 3-bromochromone **90** with 4-methoxyphenylzinc bromide (**91**), Scheme 13.[58]

2.5.2 Stille cross-coupling reactions. Chang and co-workers synthesised isoflavones by Pd-catalysed Stille coupling of 3-bromochromones with arylbutylstannanes. The employed conditions were tolerant to air and water and several isoflavone derivatives could be synthesised in good yields including daidzein (**94**). Coupling of 3-bromo-7-methoxychromone **90**

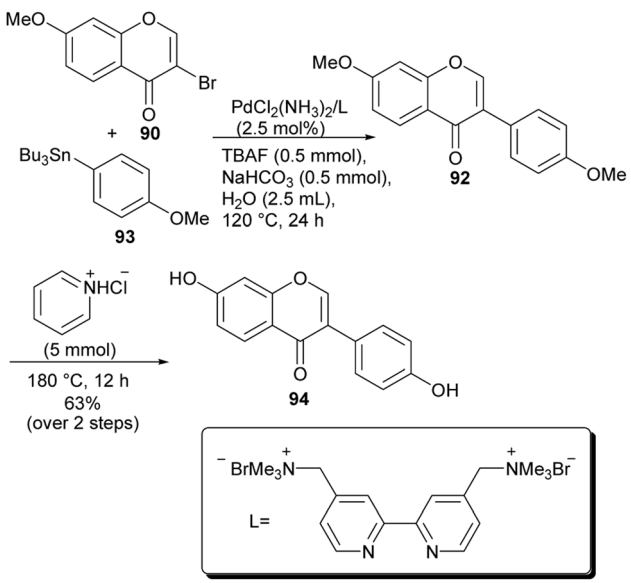


Scheme 13 Synthesis of 7,4′-dimethoxyisoflavone (**92**) by Negishi cross-coupling reaction.

with arylstannane **93** in the presence of $PdCl_2(NH_3)_2$/2,2′-ammonium bipyridyl catalytic system and TBAF gave dimethoxyisoflavone **92**, which was demethylated with pyridine hydrochloride to afford daidzein (**94**) in 63% yield, Scheme 14.[59]

2.5.3 Suzuki–Miyaura coupling reaction

2.5.3.1 Simple isoflavones. Alternative to the deoxybenzoin route, Jung and colleagues also synthesised 6,8-dimethylgenistein (**19**) and isosideroxylin (**101**) by the Suzuki–Miyaura reaction, Scheme 15.[80] This necessitated further functionalisation of the dimethylphloroglucinol **17** into 3-iodochromone **98**. To achieve this, compound **17** was converted into trimethyl ether **95**, which was acylated to render acetophenone **96**. The reaction of acetophenone **96** with DMF–DMA followed by iodine-mediated cyclisation of the resulting enaminoketone **97** gave 3-iodochromone **98**. The Suzuki–Miyaura cross-coupling reaction of the 3-iodochromone **98** with 4-hydroxyphenylboronic acid (**99**) and subsequent demethylation with BBr_3 gave dimethylgenistein (**19**). Selective demethylation of **100** with BCl_3 rendered isosideroxylin (**101**), Scheme 15.[80]

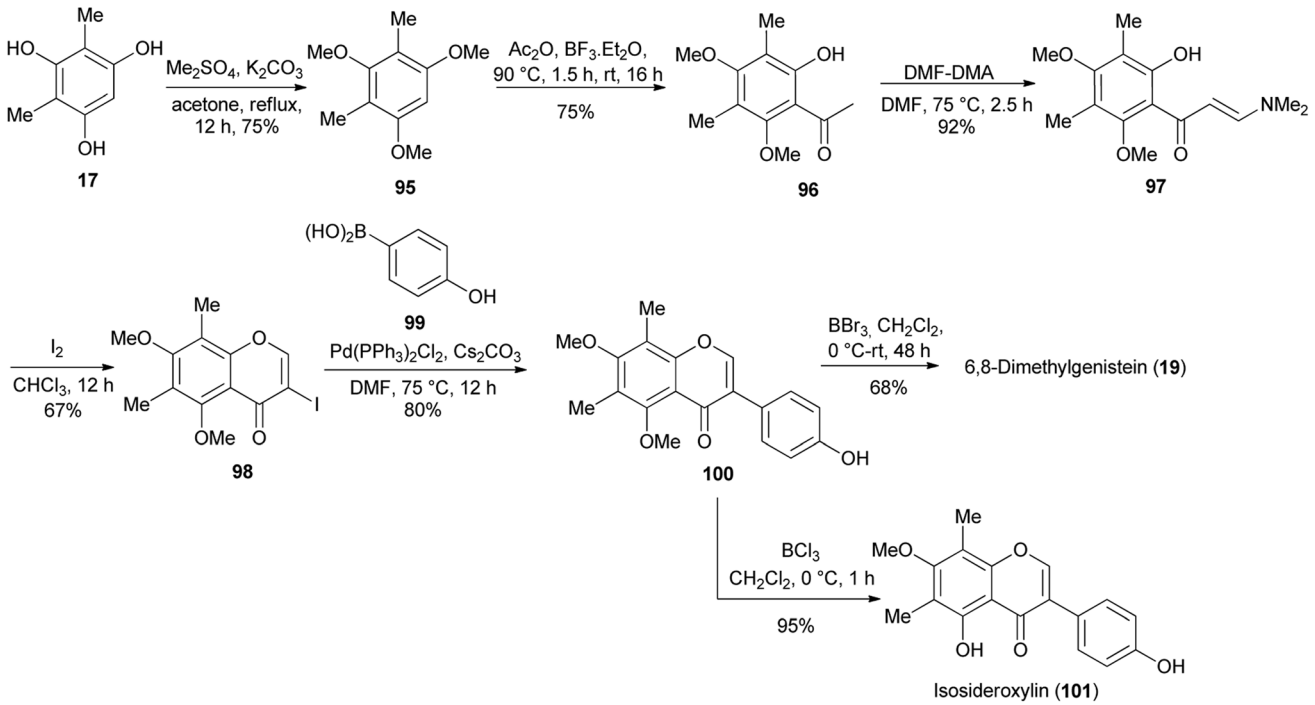


Scheme 14 Synthesis of daidzein (**94**) by Stille cross-coupling reactions.

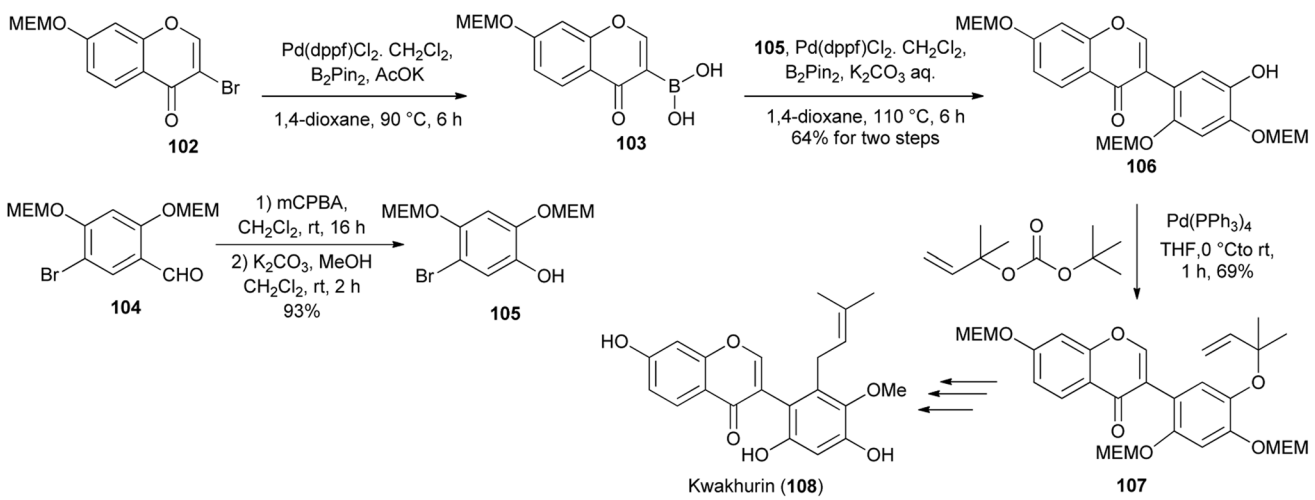
2.5.3.2 Prenylated isoflavones. Isoflavones bearing prenyl substituents or their long-chain derivatives such as geranylated analogues, as well as those with dimethylpyran and furan ring systems that originated from *O*-cyclisation of prenyl groups have been conveniently synthesised by the Suzuki–Miyaura reaction.[44,88,127,128] Several strategies were employed for the introduction of the prenyl side chains, which include direct *C*-prenylation using prenylbromide,[129] *O*-prenylation followed by Claisen rearrangement[129,130] and allylation followed by cross-coupling metathesis.[128,129] The dimethylpyran scaffold is often assembled by condensation of phenolic rings of the isoflavones with prenal or by *O*-propargylation followed by sigmatropic rearrangements.[44,88,131]

Kwakhurin (**108**), a B-ring prenylated isoflavone isolated from *Pueraria mirifica* was determined to exhibit moderate estrogenic activity.[132] It was first synthesised by Ito and colleagues in 2005 [133] and a modified synthesis route was disclosed by Tsuji and co-workers in 2020.[130] As illustrated in Scheme 16, the synthesis entailed coupling of bromophenol **105** (synthesised from aldehyde **104**) with boronic acid **103** that was obtained from 3-bromochromone **102** to give isoflavone **106**. Pd-catalysed *O*-allylation followed by Claisen rearrangement of the resulting 1,1-dimethylallyl ether **107**, methylation and desilylation gave kwakhurin (**108**), Scheme 16.[130,133]

4′-*O*-Methylgrynullarin (**124**) was isolated from *Derris scandens* flowers together with other structurally related compounds,[134] glyurallin B (**126**),[135] isoangustone A (**128**)[136] and lupalbigenin (**130**).[134,137] The compounds **124**, **128**, and **130** were determined to exhibit preferential cytotoxicity against pancreatic cancer cell lines.[134] The synthesis of 4′-*O*-methylgrynullarin (**124**) and related compounds **126**, **128**, and **130** was reported by Okada and colleagues.[129] The key step involved the Suzuki–Miyaura coupling of the prenylboronate esters **120**, **121**, and **122** with prenyl-3-iodochromones **112** and **114** (Schemes 17 and 18). Three strategies were followed for early-stage *C*-prenylation, *viz.* cross-coupling metathesis, *O*-prenylation followed by Claisen rearrangement and direct *C*-prenylation using prenylbromide.[129] As shown in Scheme 17, the C-6 dimethylallyliodochromone precursor **112** was prepared by *O*-prenylation of acetophenone **109** followed by Claisen rearrangement of **110** and condensation of the resulting prenylacetophenone **111** with DMF–DMA and iodine-mediated cyclisation. Alternatively, the C-8 prenyl group on the iodochromone **114** was introduced by cross-coupling metathesis of 2-methyl-2-butene with allylchromone **113** prepared from acetophenone **109**. The boronate precursors **120**, **121**, and **122** were synthesised by direct *C*-prenylation of bromophenols **115** and **116**, followed by alkylation or silylation of the hydroxy groups to afford bromobenzenes **117**, **118**, and **119** and finally Pd-catalysed cross coupling with bis(pinacolato)diboron $(Bpin)_2$, Scheme 17.[129] The Suzuki–Miyaura coupling reaction of 3-iodochromone **114** with boronate esters **120** and **121**, followed by MOM deprotection gave methylgrynullarin (**124**) and glyurallin B (**126**), respectively. Isoangustone A (**128**) and lupalbigenin (**130**) were synthesised by the Pd-cross coupling reaction of iodochromone **112** with boronate esters **122** and **121**, respectively, followed by removal of the MOM and silyl protecting groups, Scheme 18.[129]



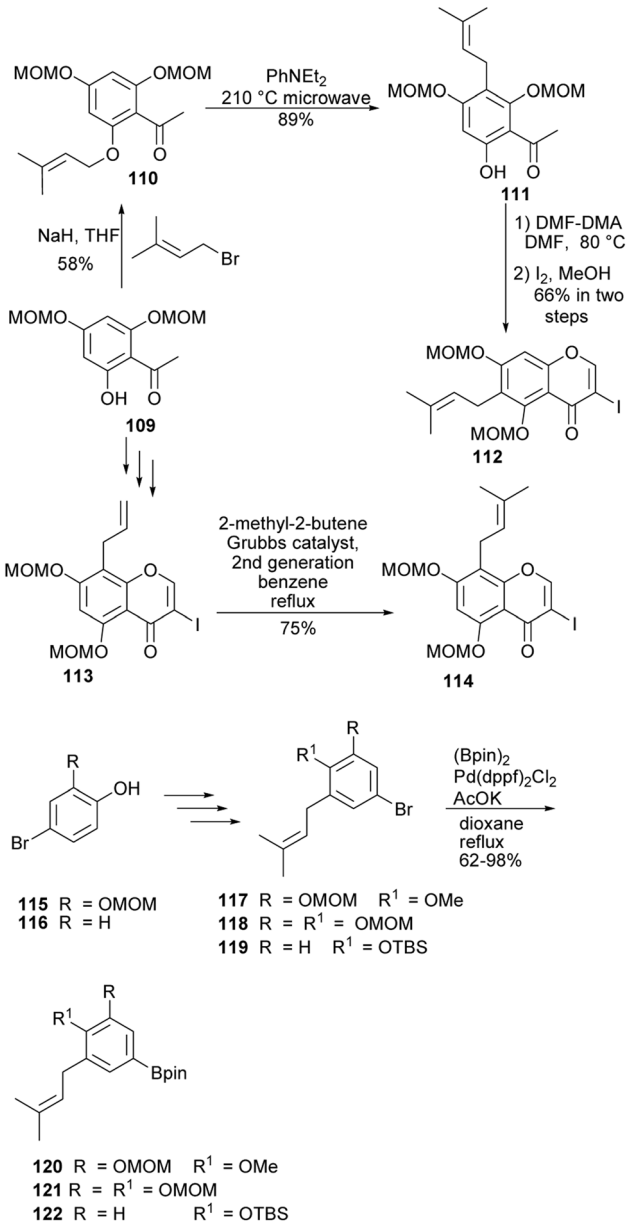
Scheme 15 Synthesis of 6,8-dimethylgenistein (**19**) and isosideroxylin (**101**).



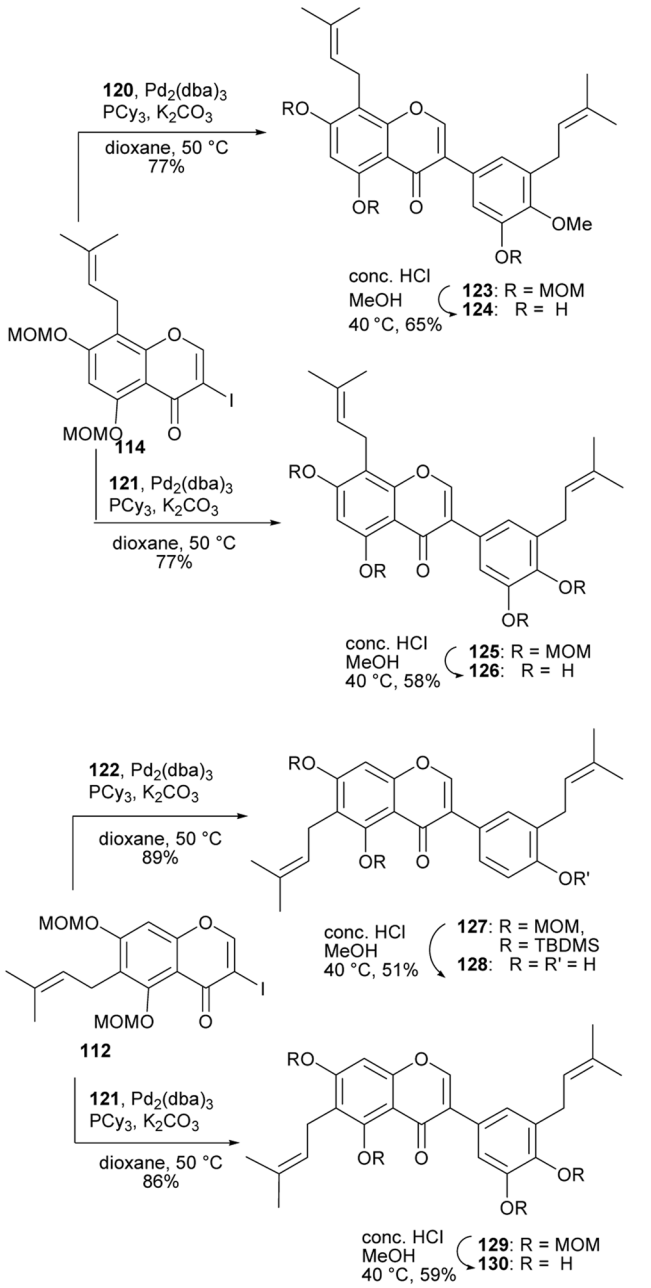
Scheme 16 Synthesis of kwakhurin (**108**) by Tsuji and co-workers.[130]

Cudraisoflavone J (**134**), a neuroprotective isoflavone bearing a 3-hydroxy-2,2-dimethyldihydropyran scaffold was isolated together with other structurally related compounds from the fruits of *Cudrania tricuspidata* (Carr.) Bur. (Moraceae).[138] The synthesis of *rac*-cudraisoflavone J (**134**) was reported by Lee's group.[139] As illustrated in Scheme 19, the synthesis was initiated by the preparation of dimethyldihydropyranoacetophenone **131** obtained from phloroacetophenone (**38**) by primary steps that involved MOM protection, *O*-prenylation, Claisen rearrangement, and oxidative cyclisation. Compound **131** was converted into 3-iodochromone **132** by a modified Gammill procedure.[123] The Suzuki coupling of **132** with *p*-methoxyphenylboronic acid followed by MOM deprotection of the resulting isoflavone **133** gave *rac*-cudraisoflavone J (**134**).[139] In addition to synthesis of the racemate, the group conducted stereoselective synthesis of *R* and *S* cudraisoflavone J enantiomers using Sharpless asymmetric dihydroxylation for induction of stereochemistry. Moreover, kinetic resolution was also employed to afford the *R* and *S* enantiomers, and Mosher's ester method was used to confirm the absolute configuration of the compounds.[139]

Scandenone (**142**) and osajin (**140**) are isoflavones that possess a dimethylpyran scaffold and a 3,3-dimethylallyl side chain in the A-ring. The compounds have been isolated from different sources that include *Derris*, *Flemingia*, *Millettia*, and



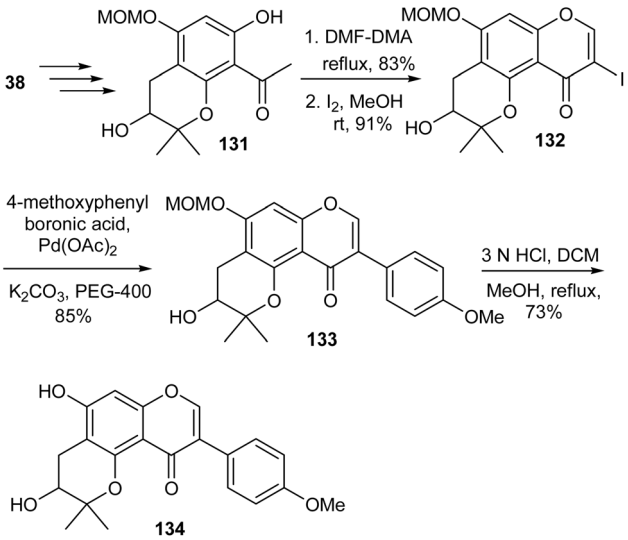
Scheme 17 Syntheses of 3-iodochromones and boronate ester precursors.



Scheme 18 Total synthesis of isoflavones **124**, **126**, **128**, and **130**.

Tephrosia genera and from non-leguminous families.[5,140–144] They have been reported to exhibit cytotoxicity against different cancer cells,[35,142] and nitric oxide production inhibition.[145] The synthesis of scandenone (**142**) and osajin (**140**) involved the Suzuki–Miyaura coupling reaction as the key step for the construction of genistein (**135**), followed by *O*-propargylation and Harfenist–Thom rearrangement of **136** to afford the dimethylpyranoisoflavones **137** and **138**.[146] TBDMS protection of **137** and **138** followed by *O*-prenylation and sigmatropic rearrangement gave isoflavones **139** and **141**, respectively, from which osajin (**140**) and scandenone (**142**) were obtained upon TBDMS deprotection, Scheme 20.[131] Several derivatives were also synthesised from compounds **140** and **142** and evaluated for anti-inflammatory activity.[131]

A furanoisoflavone with potential anti-obesity activity from *Crotalaria albida*, crotadihydrofuran C (**153**), was synthesised by Sun and coworkers.[147,148] As shown in Scheme 21, the synthesis was accomplished by coupling of 3-iodochromone **151** and furanylboronate ester **150** to afford the isoflavone **152**, which was demethylated to give crotadihydrofuran C (**153**). The 5-boronate ester **150** was in turn prepared in a sequence of steps that entailed the conversion of a dimethoxybenzaldehyde **143** into *rac*-2,3-dihydro-2-carboxy-4-methoxybenzofuran (**144**). The *rac*-**144** was resolved into *R* and *S* enantiomers by coordination with enantiomers of α-methylbenzylamine (α-MBA), followed by hydrolysis. Amide coupling of the (*S*)-**146a** gave **147**, which was selectively brominated to afford **148** in a sequence of steps that



Scheme 19 Total synthesis of (±)-cudraisoflavone J (**134**).

involved blocking the *para*-position by iodination, followed by bromination, methylation with methylmagnesium bromide, and concurrent deiodination. Finally, Wittig reaction of **148** and Pd-catalysed coupling of the resulting **149** with bis(pinacolato) diboron gave the boronate ester **150**, Scheme 21.[148]

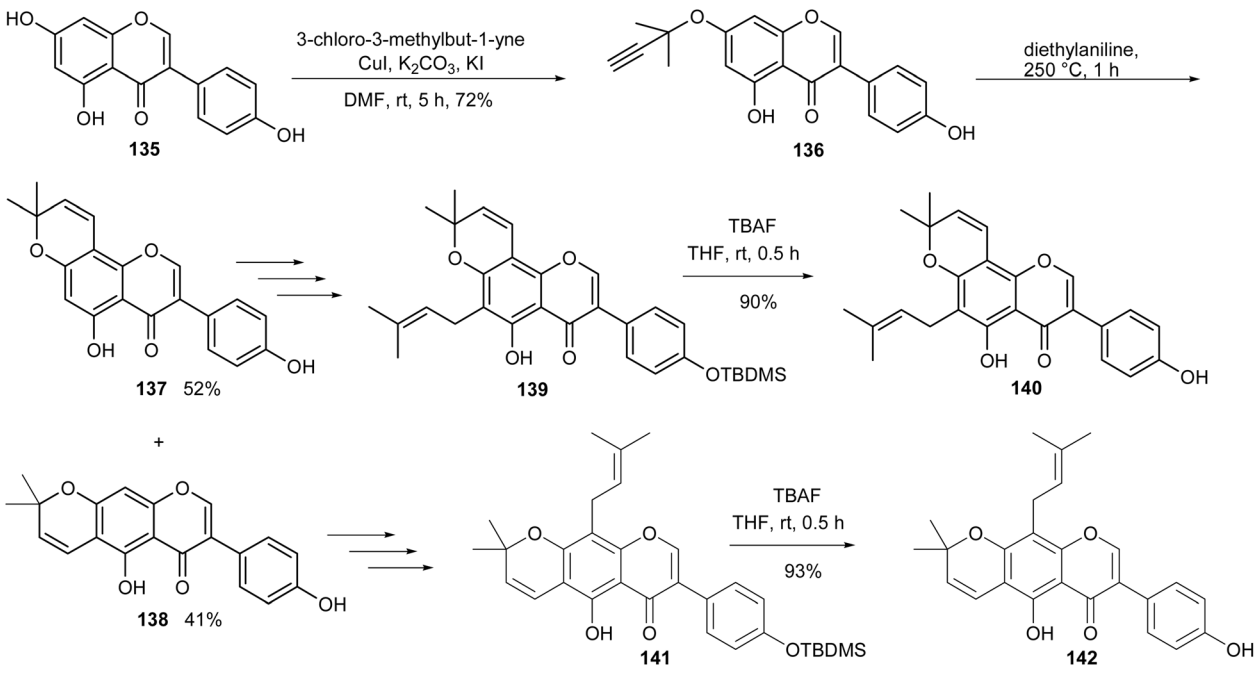
In other instances, the Suzuki–Miyaura reaction was used for the installation of substituents to the isoflavones nuclei.[149] Geranylated isoflavones from *Lespedeza homoloba* and *Dalbergia paniculata*, lespedezols E1 (**160**) and 8-geranyl-7-*O*-methylbiochanin A (**161**), respectively,[150,151] were synthesised from genistein **135**, Scheme 22. Alkylation with methyl iodide or MOMCl followed by iodination gave iodinated isoflavones **156** and **157**. The Suzuki–Miyaura coupling of 8-iodoisoflavones **156** and **157** with geranyl boronate ester and subsequent MOM deprotection or selective demethylation of **158** and **159** gave the compounds **160** and **161**.[149]

2.6. Direct arylation of 2-hydroxyenaminoketones

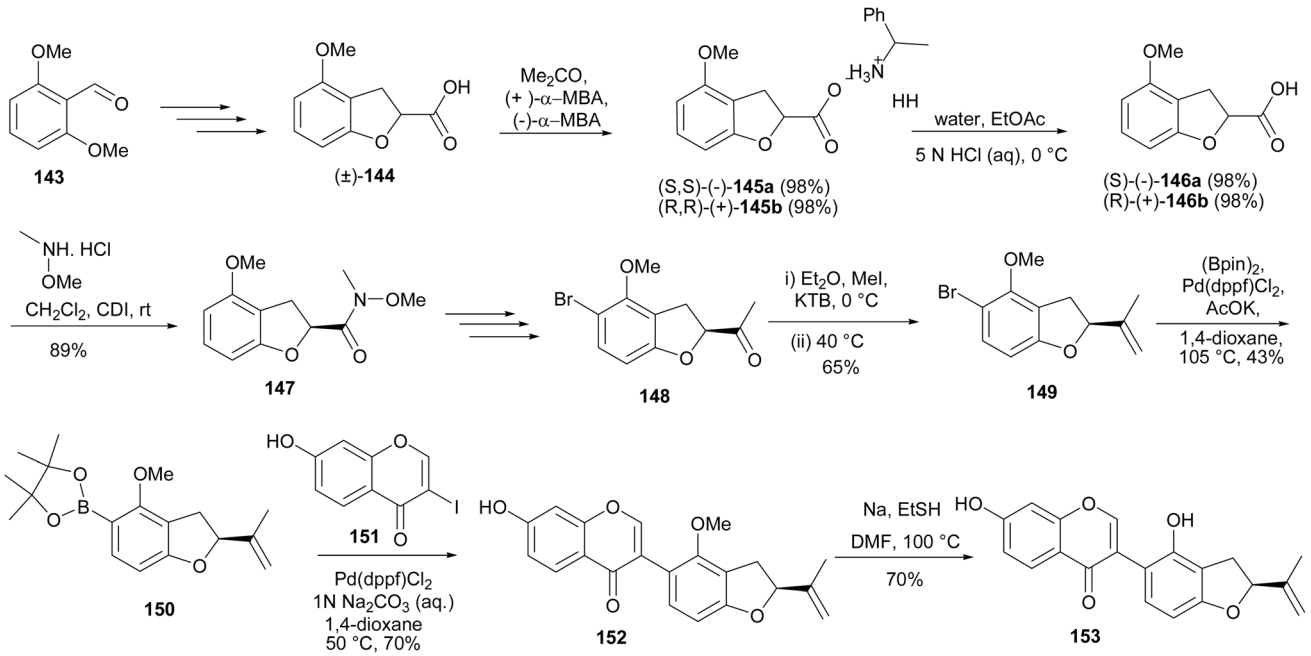
More recently, different research groups have developed methods for the synthesis of isoflavones by direct arylation of 2-hydroxyenaminoketones.[90–93] These provide an advantage of eliminating the pre-functionalisation steps required in metal-catalysed C–C forming reactions that utilise functionalised chromones as precursors. However, the applications of most of the newly developed methodologies involving direct transformation of enaminones are yet to be demonstrated in the synthesis of natural isoflavones.

Wan and colleagues developed a method for direct arylation of 2-hydroxyenaminomes with boronic acids in the presence of Pd catalyst, benzoyl peroxide (BPO) and catalytic KI.[90] The reaction proceeded through the momentary formation of 3-iodochromone and *in situ* arylation. Several C-3 arylated derivatives were synthesised including the natural isoflavone daidzein (**94**). Coupling of enaminone **162** with boronic acid **163** under established conditions gave the isoflavone **92**, which was demethylated to afford daidzein (**94**), Scheme 23.[90]

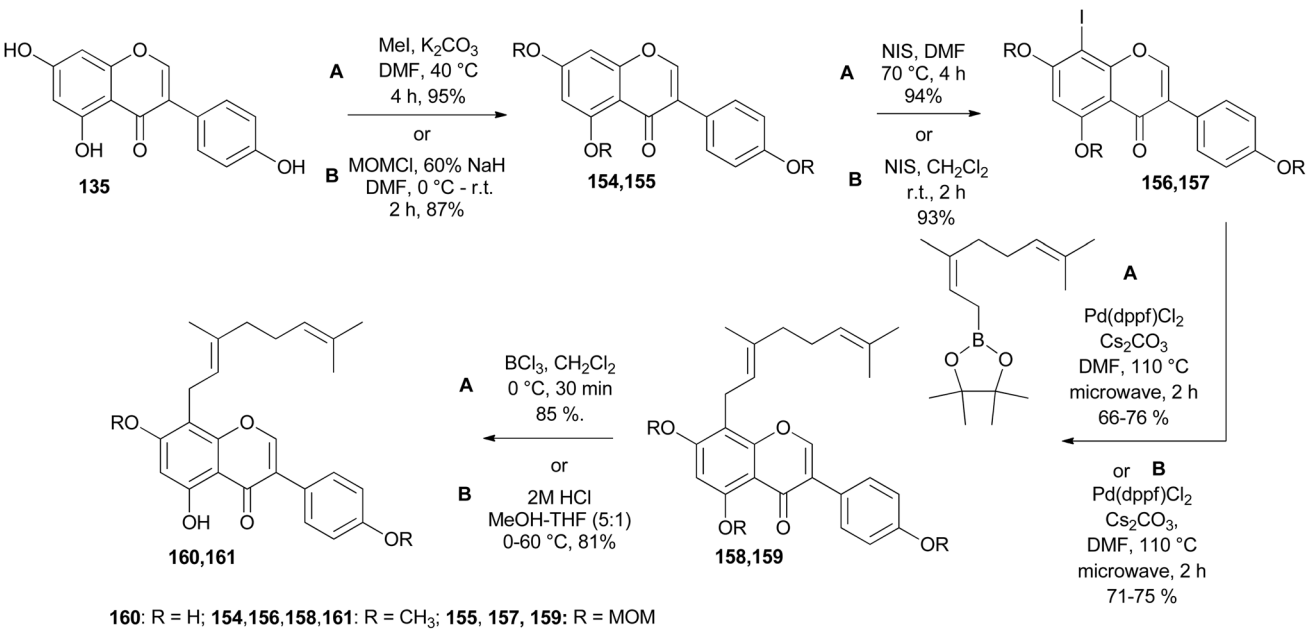
Although many new synthetic strategies have been developed for isoflavones, their application has been demonstrated mainly in the synthesis of simple isoflavones. Isoflavones with additional substituents such as glycosyl and prenyl units continue to be synthesised by well-established protocols that include the deoxybenzoin route, oxidative rearrangement of chalcones, and the Suzuki–Miyaura reaction. As already mentioned, both the chalcone and deoxybenzoin routes use



Scheme 20 Total synthesis of scandenone (**142**) and osajin (**140**).

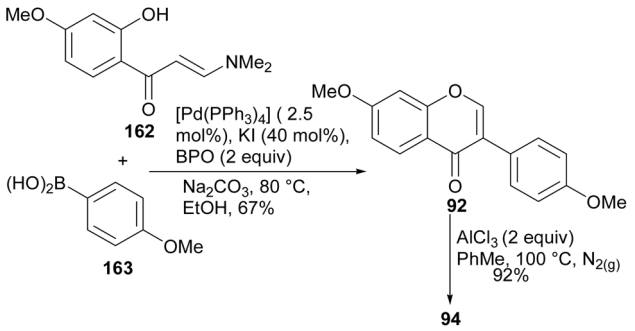


Scheme 21 Total synthesis of crotadihydrofuran C (**153**).



Scheme 22 Total synthesis of lespedezol E1 (**160**) and 8-geranyl-7-*O*-methylbiochanin A (**161**).

harsh conditions that necessitate the installation of sensitive groups in the late stages of the synthesis. The Suzuki–Miyauara reaction on the other hand makes use of benign reaction conditions that enable incorporation of such substituents in the early stages of the synthesis. Moreover, a variety of boronic acids are available commercially that enable the ease of synthesis of simple isoflavones and derivatives. The main disadvantage of the Suzuki–Miyaura reaction and other chromone-based metal-catalysed reactions is that they require pre-derivatisation of the chromones and the coupling partners. These increase the number of synthetic steps. Moreover, since the added atoms are eliminated during the cross-coupling reactions, these methodologies are not atom-economic. The methods also utilise transition metals to catalyse the reactions, which are often expensive. In a recent study, isoflavones were synthesised by demethylation and concomitant cyclisation of methoxybenzoylbenzofuran intermediates, prepared by conjugate addition of 2-methoxyenaminoketones with benzoquinones.



Scheme 23 Synthesis of daidzein (**94**) by direct arylation of 2-hydroxyenaminone.

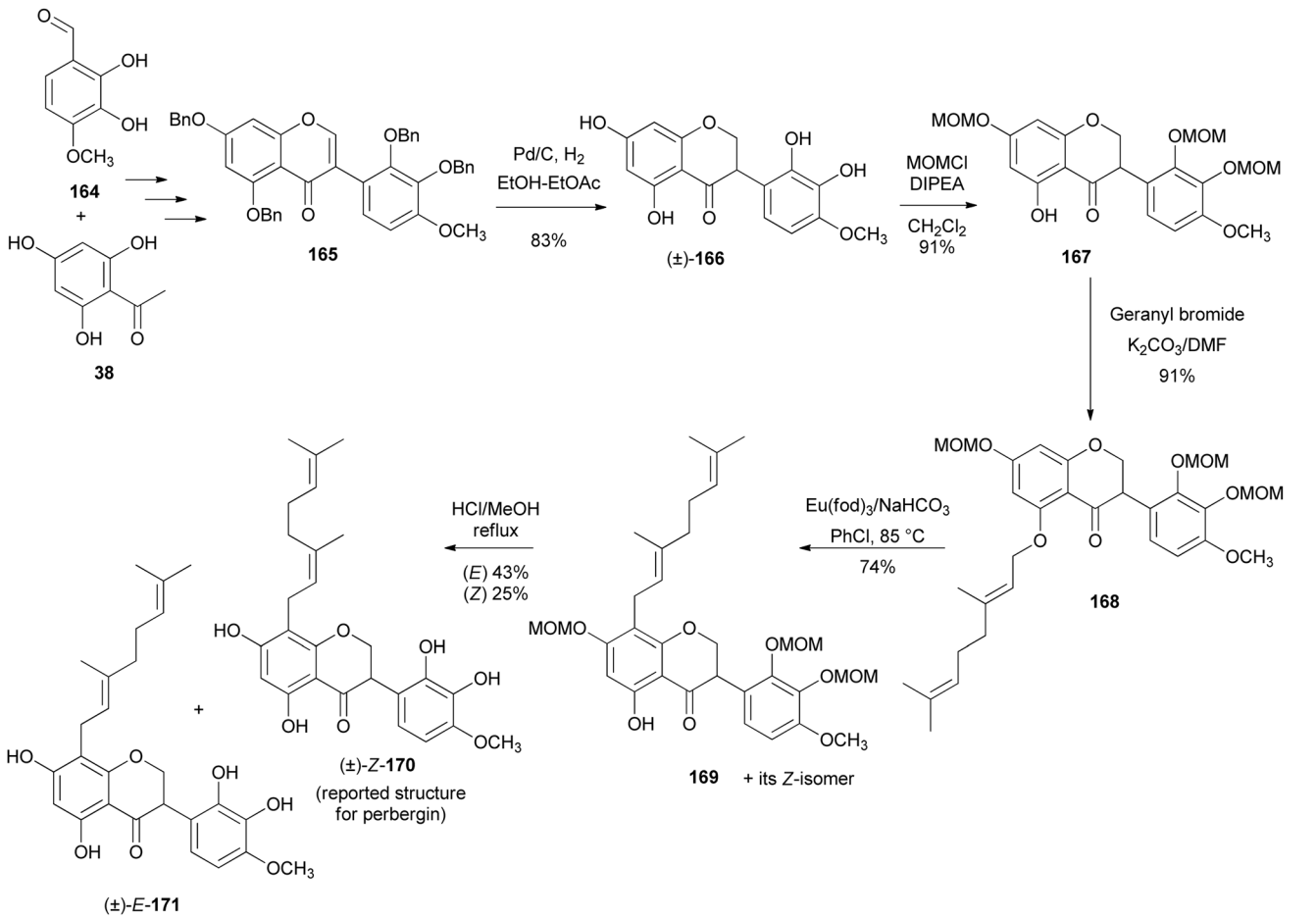
Although there was no pre-functionalisation of the coupling partners, the method could be improved by optimising the conditions for direct synthesis of isoflavones from 2-hydroxyenaminoketones and benzoquinones. This will eliminate the demethylation step and avoid the use of the toxic BBr_3 or volatile TMSI. The synthesis of isoflavones by direct arylation of 2-hydroxyenaminoketones presents an advancement in the synthesis of isoflavones. Therefore, it is encouraged that the scope of these reactions be extended to the synthesis of natural isoflavones.

3. Synthesis of isoflavanones and isoflavans

3.1. Synthesis of racemates

Isoflavanones and isoflavans have been synthesised in racemic form and stereoselectively. Different synthetic strategies were followed for the synthesis of racemates. These included hydrogenation of isoflavones or isoflavenes,[152–154] reaction of deoxybenzoin with paraformaldehyde and diethylamine,[155,156] [3 + 2]-annulation of chromenes with 1,4-benzoquinones followed by reduction of the resulting pterocarpans to afford isoflavans, and finally oxidation of the isoflavans to isoflavanones.[157]

3.1.1 Isoflavanones. Almabruk *et al.* synthesised proposed [(±)-*Z*-**171**] and its isomer [(±)-*E*-**170**] over nine steps.[152] The key steps involved the synthesis of isoflavanone (±)-**166** and C-8 geranylation. The isoflavanone (±)-**166** was prepared by reduction of the isoflavone **165**, which was synthesised starting from commercially available 2,3-dihydroxy-4-methoxybenzylaldehyde (**164**) and trihydroxyacetophenone **38**.[152] Selective MOM protection of the isoflavanone (±)-**166** gave compound **167** (91%), which upon *O*-geranylation under mild conditions afforded compound **168** in good yield (91%) (Scheme 24). The first attempted *p*-Claisen–Cope rearrangement of the *O*-geranyl group leading to *C*-geranylated products proved impossible, but



Scheme 24 Synthesis of proposed perbergin [(±)-*Z*-**170**] and its isomer [(±)-*E*-**171**].

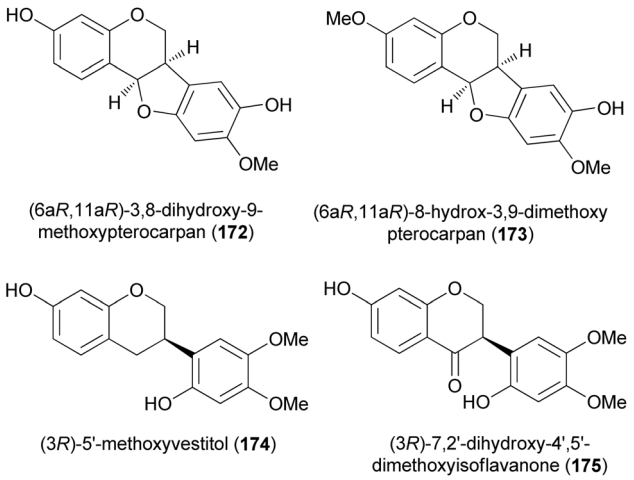
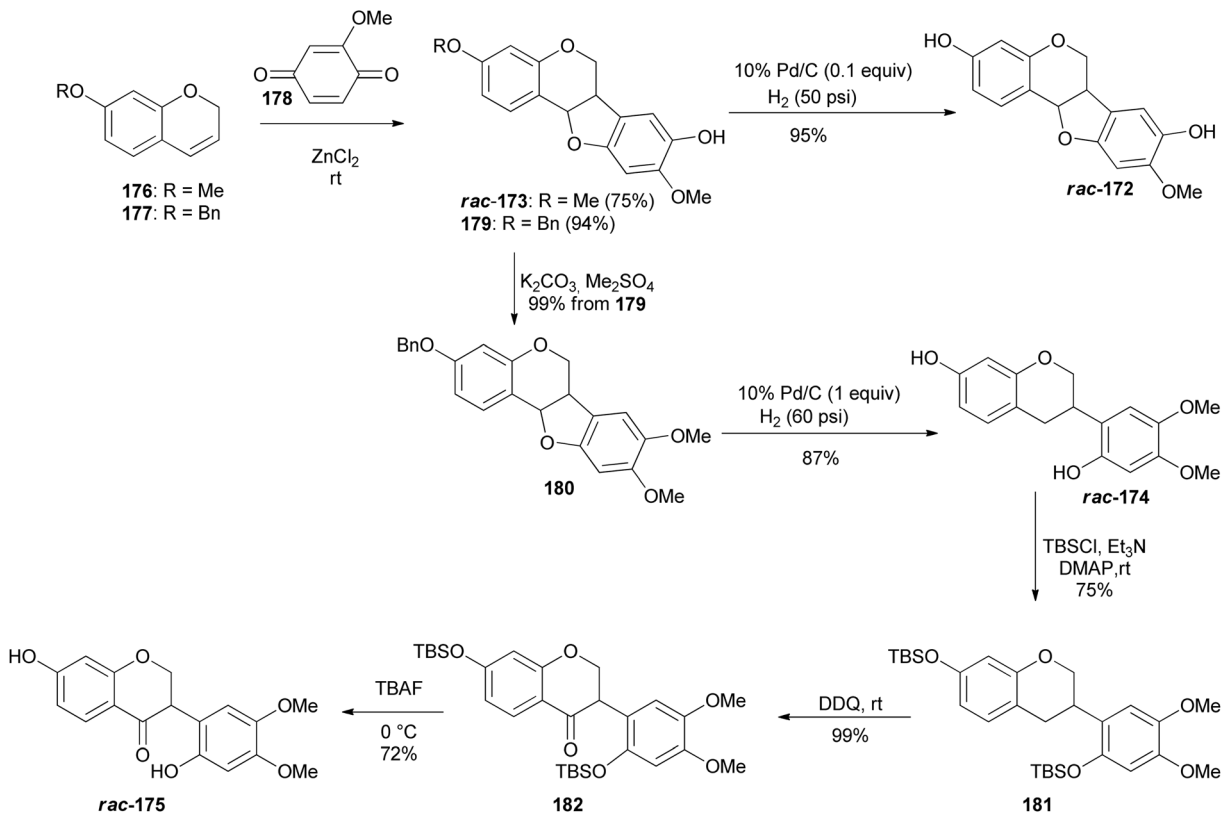


Fig. 2 Naturally occurring pterocarpans, isoflavan, and isoflavanone.

instead resulted in cleavage of the geranyl side chain. This was remedied by employing modified conditions reported by Zhang's group utilising the europium catalyst $Eu(fod)_3$ in the presence of $NaHCO_3$,[158] resulting in an *E*- and a *Z*-geranylated isoflavanone **169** in 74% yield. Following failure to separate the isoflavanone **169** isomers by HPLC using a chiral-phase column, deprotection of **169** in MeOH under reflux in the presence of 3 N aqueous HCl followed by separation using chiral-phase HPLC (Chiralcel OD-R column) afforded pure (±)-*E*-**171** (43%) and (±)-*Z*-**170** (25%), as well as a mono-MOM-protected intermediate (20%) (Scheme 24).[152] Analysis and comparison of the NMR data of the synthesised perbergin [(±)-*Z*-**170**] with those of the isolated compound[159] prompted structural revision of the isolated compound to that of a C-6 geranylated isoflavanone.[152] The synthesised isoperbergins were evaluated for antibacterial activity. They showed good activity against *Rhodococcus fascians*, *Mycobacterium smegmatis*, and *Staphylococcus aureus*, but not against the Gram-negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*.[152]

D. K. Singh *et al.* recently synthesised racemic pterocarpans and isoflavanones isolated from *Dalbergia oliveri* using a $ZnCl_2$-mediated [3 + 2]-annulation and reductive ring cleavage/reoxidation as key steps. This marked the first total synthesis of **172**, **174**, and **175** which would pave the way for more biological studies among these compounds (Fig. 2).[157] Chromenes **176** and **177** were reacted with 2-methoxy-1,4-benzoquinone (**178**) in the presence of $ZnCl_2$ at room temperature to afford the corresponding pterocarpans **173** and **179** in good yields (Scheme 25). The $ZnCl_2$ catalyst was preferred over known catalysts like $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ by Engler *et al.*[160] for the same transformation because of ease of manipulation. Pterocarpan **179** was debenzylated using Pd/C catalyst in the presence of hydrogen gas to give *rac*-**172** in a 95% yield. The racemic isoflavan **174** was then synthesised from **179** by methylation of the phenolic group first using Me_2SO_4 to give **180** in 99% yield, followed by reductive cleavage of the benzylic position of **180** with a large amount of Pd/C to render isoflavan **174** in 87% yield (Scheme 25). The benzylic position of isoflavan **174** could not be

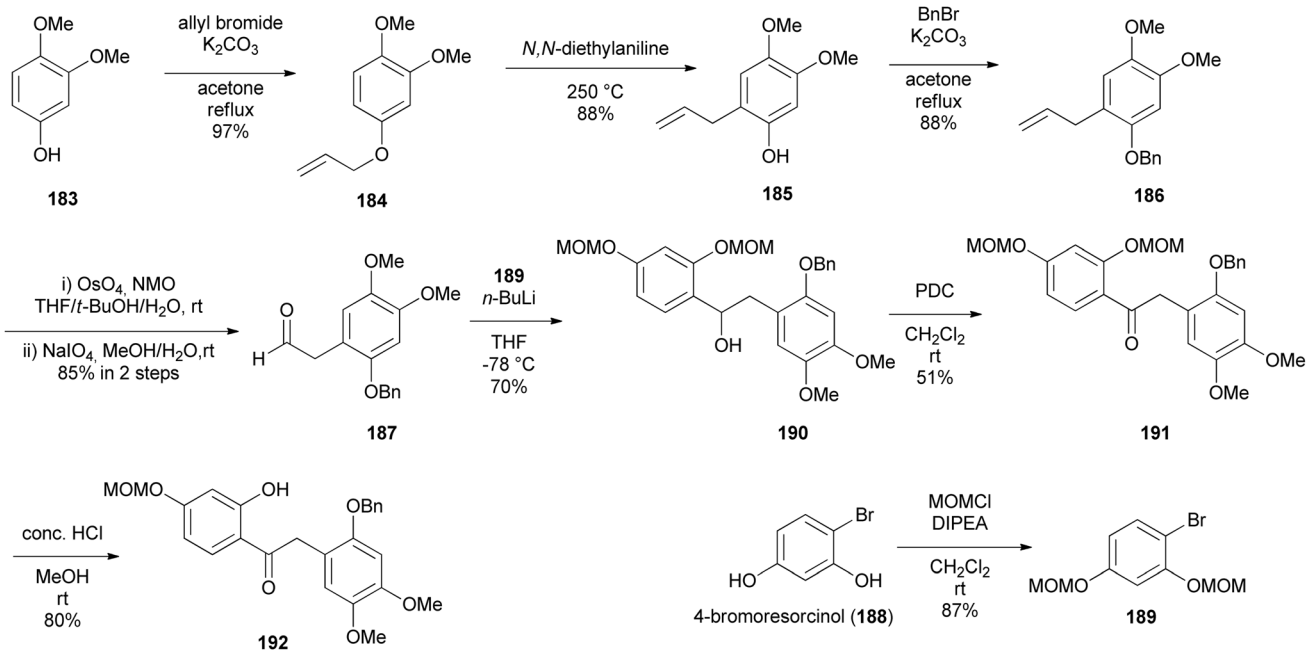


Scheme 25 $ZnCl_2$-mediated [3 + 2]-annulation.

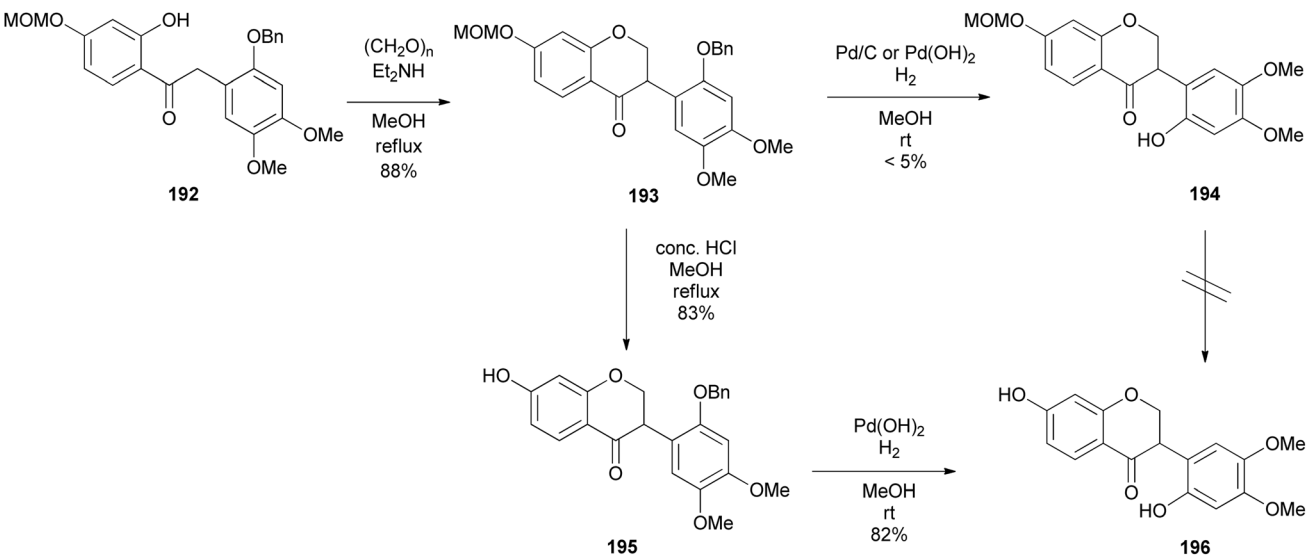
oxidised under several oxidation conditions. Protection of the two hydroxy groups of **174** with TBSCl furnished **181** in a 75% yield, followed by exposure of **181** to DDQ to afford **182**, and finally desillylation of **182** with TBAF gave *rac*-**175** as a pale yellow amorphous solid in a 72% yield.[157]

T. Kim *et al.* (2022) reported the synthesis of a phytoestrogen, 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (**196**) in a gram scale over 11 steps.[156] Large quantities of isoflavone **196** made it possible to do further biological studies, although the route was longer as compared to the sophisticated synthesis of isoflavanone **196** by Singh *et al.* (2018) with low yields.[157] The synthesis followed the deoxybenzoin route. However, the deoxybenzoin intermediate **191** was prepared in a sequence of steps that differ from the traditional method involving acylation of phenylacetic acids with phenols.[156]

The preparation of key intermediate deoxybenzoin **192** was paramount to accessing the isoflavone scaffold **193** (Scheme 27). 1-Allyl-2-(benzyloxy)-4,5-dimethoxybenzene (**186**) was synthesised by allylation of commercially available 3,4-dimethoxyphenol (**183**) to afford *O*-allyl-substituted phenol **184** in 97% yield, followed by Claisen rearrangement in *N*,*N*-diethylaniline exclusively fashioning *C*-allylated phenol **185** in 88% yield, which was then protected to give benzyl ether **186** in 88% yield. Dihydroxylation followed by oxidative cleavage of the



Scheme 26 Preparation of key intermediate deoxybenzoin **192**.

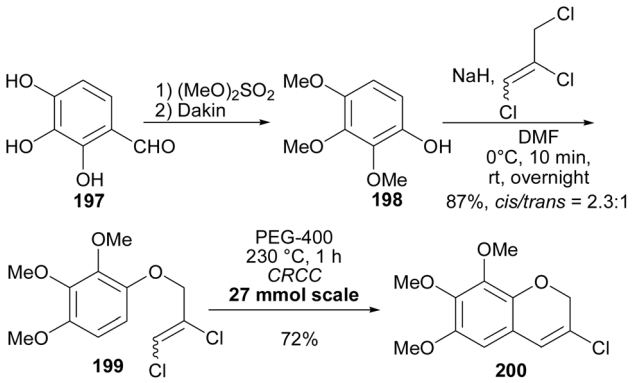


Scheme 27 Completion of 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (**196**) synthesis.

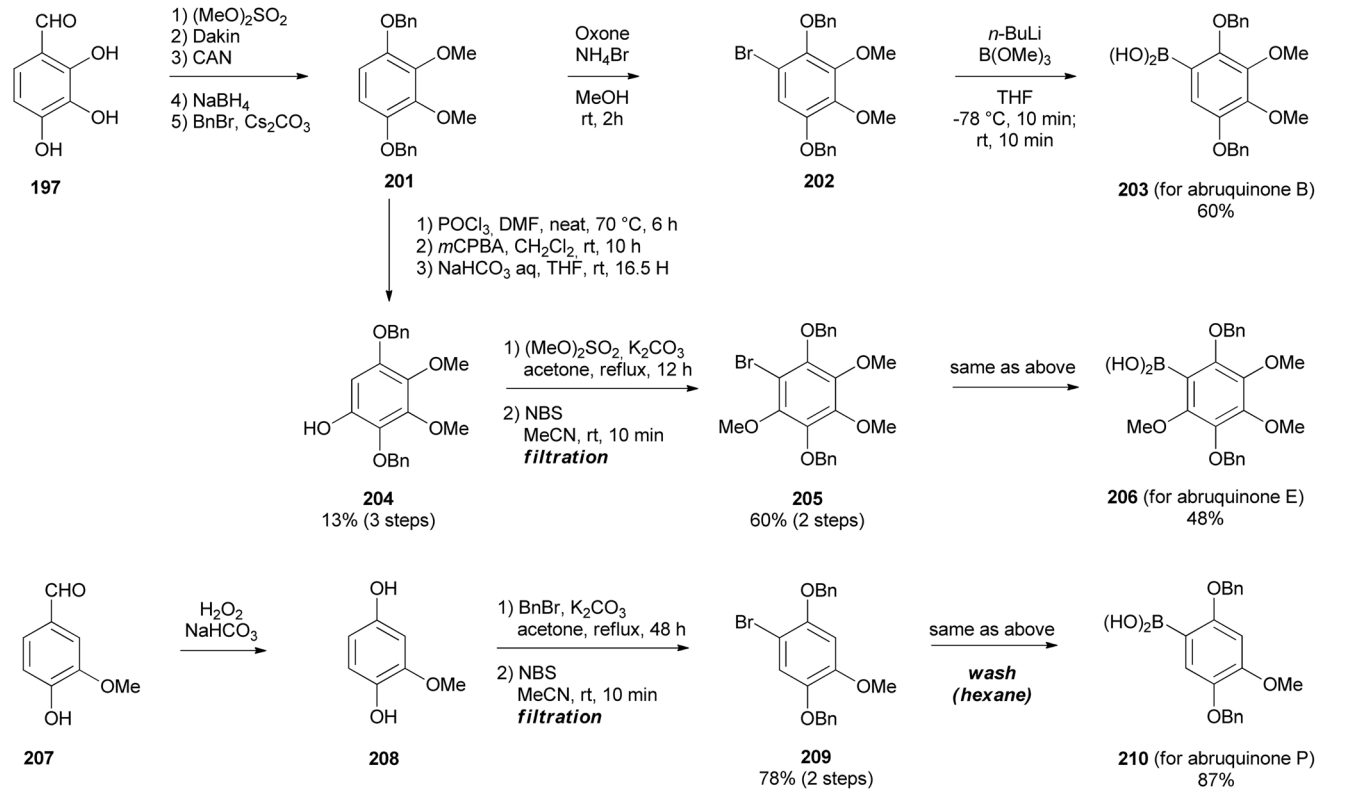
olefinic function of benzyl ether **186** gave phenylacetaldehyde **187** in 85% yield. Aryl bromide **189** was lithiated followed by a spontaneous nucleophilic addition to the acetaldehyde **187** giving benzyl alcohol **190** in 70% yield, which was oxidised by pyridinium dichromate (PDC) affording deoxybenzoin **191** in 51% yield, subsequently followed by selective MOM deprotection in deoxybenzoin **191** finally affording benzylketone **192** in 80% yield. To construct the isoflavanone nucleus, the efficient and scalable approach developed by Gouda *et al.* was used.[155] It is important to note that aryl bromide **189** was obtained in good yields (87%) by protecting 4-bromoresorcinol (**188**) with the MOM group. Isoflavanone **193** was synthesised in 88% yield on a multi-gram scale by refluxing 2-hydroxyketone **192** in paraformaldehyde and Et_2NH in MeOH (Scheme 26). Finally, successive deprotection of the MOM and Bn protecting groups in **193** gave isoflavanone **196** in 82% yield over two-steps. Reversing the sequence of deprotection failed to give the targeted compound **196** (Scheme 27).

3.1.2 Isoflavans. Kang and colleagues utilised 3-chlorochromenes[153,154,161] as intermediates for the divergent synthesis of several natural isoflavans[153] and isoflavanquinones, abruquinones B, E, and P (**217**, **218**, and **219**).[154] The synthesis of the 3-chloro-6,7,8-trimethoxy-2*H*-chromene **200** and aryl boronic acids needed in divergent Suzuki–Miyaura coupling reactions to form isoflavene derivatives is shown in Schemes 28 and 29. They began by synthesising 2,3,4-trimethoxyphenol **198** starting with commercially available 2,3,4-trihydroxyybenzaldehyde (**197**).[162,163] This was followed by alkylation of phenol **198** with 1,2,3-trichloropropene (1 : 0.8 mixtures of *cis*- and *trans*-isomers) to give aryl 2,3-dichloroallyl ether **199** in 87% yield as a 2.3 : 1 mixture of *cis*- and *trans*-isomers. Lastly, compound **200** was synthesised in 72% yield in a Claisen-rearrangement–cyclisation cascade (CRCC) by heating **199** in polyethylene glycol 400 (PEG-400) at 230 °C for 1 h (Scheme 28),[154] which was an improvement compared to the yields obtained in their previous study.[153]

Having synthesised the 3-chlorochromene **199** precursor, the next step was to prepare arylboronic acids **203**, **206**, and **210** (Scheme 29). The arylboronic acid **203** was synthesised by converting 2,3,4-trihydroxybenzaldehyde (**197**) to compound **202** over six steps.[164,165] Subsequently, compound **202** was



Scheme 28 Synthesis of 3-chloro-2*H*-chromene **200**.



Scheme 29 Synthesis of arylboronic acids **203**, **206**, and **210**.

reacted with $B(OMe)_3$ and *n*-BuLi to yield arylboronic acid **203** in 60% yield. The phenylboronic acid **206** was synthesised from **201** by Vilsmeier–Haack formylation followed by Dakin oxidation to give phenol **204**, in low yields (13%). Methylation, bromination (68% in two steps), and borylation of phenol **204** afforded arylboronic acid **206** (48%). Borylation of **202** and **205** succeeded by pre-addition of $B(OMe)_3$ before *n*-BuLi. The phenylboronic acid **210** was obtained by Dakin oxidation of vanillin (**207**) to give compound **208**,[164] which was benzylated and brominated to give highly crystalline bromobenzene **209** in 60% yield over two steps and finally, borylation of **209** gave arylboronic acid **210** in 87% yield, Scheme 29.[154]

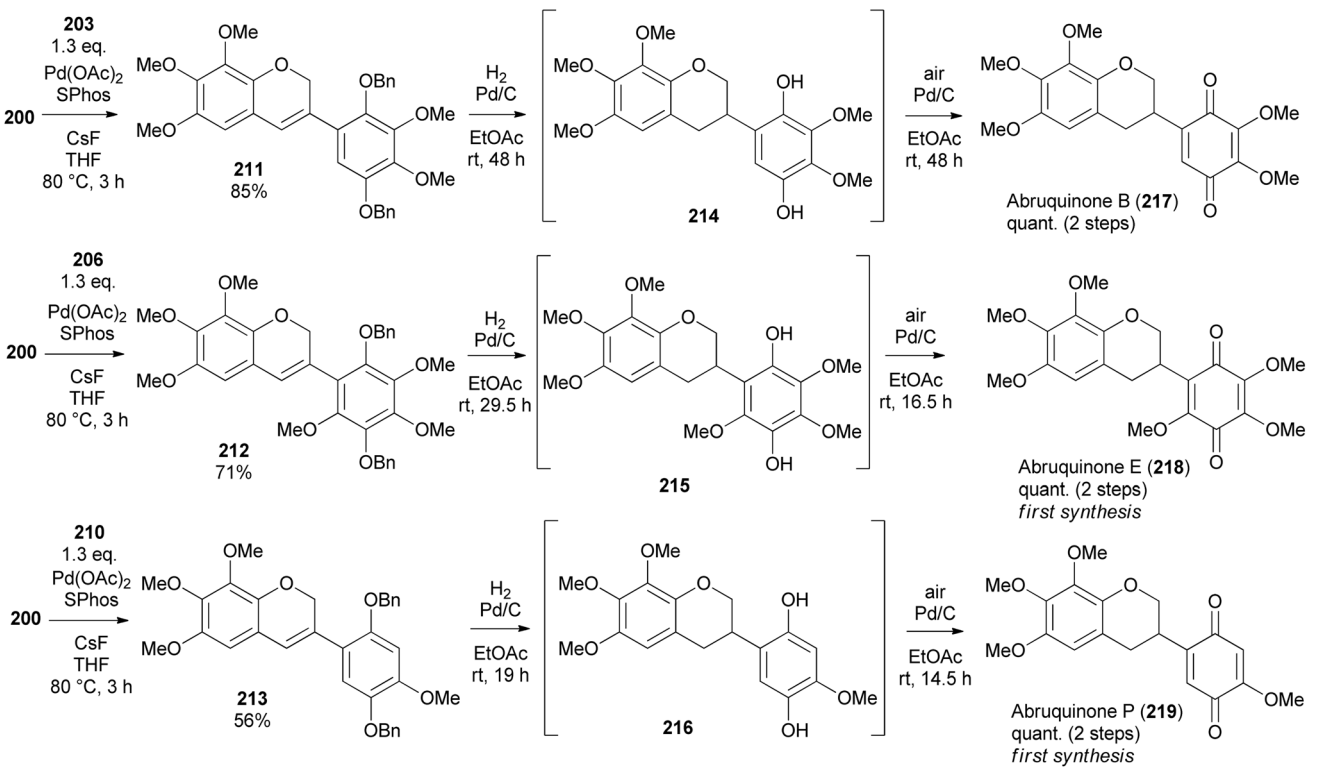
The Suzuki–Miyaura coupling of 3-chloro-2*H*-chromene **200** and arylboronic acids **203**, **206**, and **210** using SPhos ligand and $Pd(OAc)_2$ proceeded successfully giving isoflavene derivatives **211**, **212**, and **213** in 85, 71, and 56% yield, respectively (Scheme 30).[153] Reduction and debenzylation of **211**, **212**, and **213** were carried out under H_2 with Pd/C catalyst affording hydroquinone intermediates **214**, **215** and **216**, which were subsequently exposed to Pd/C in the presence of air to give isoflavanquinone racemates, abruquinones B, E, and P (**217**, **218**, and **219**) quantitatively.

3.2. Stereoselective synthesis

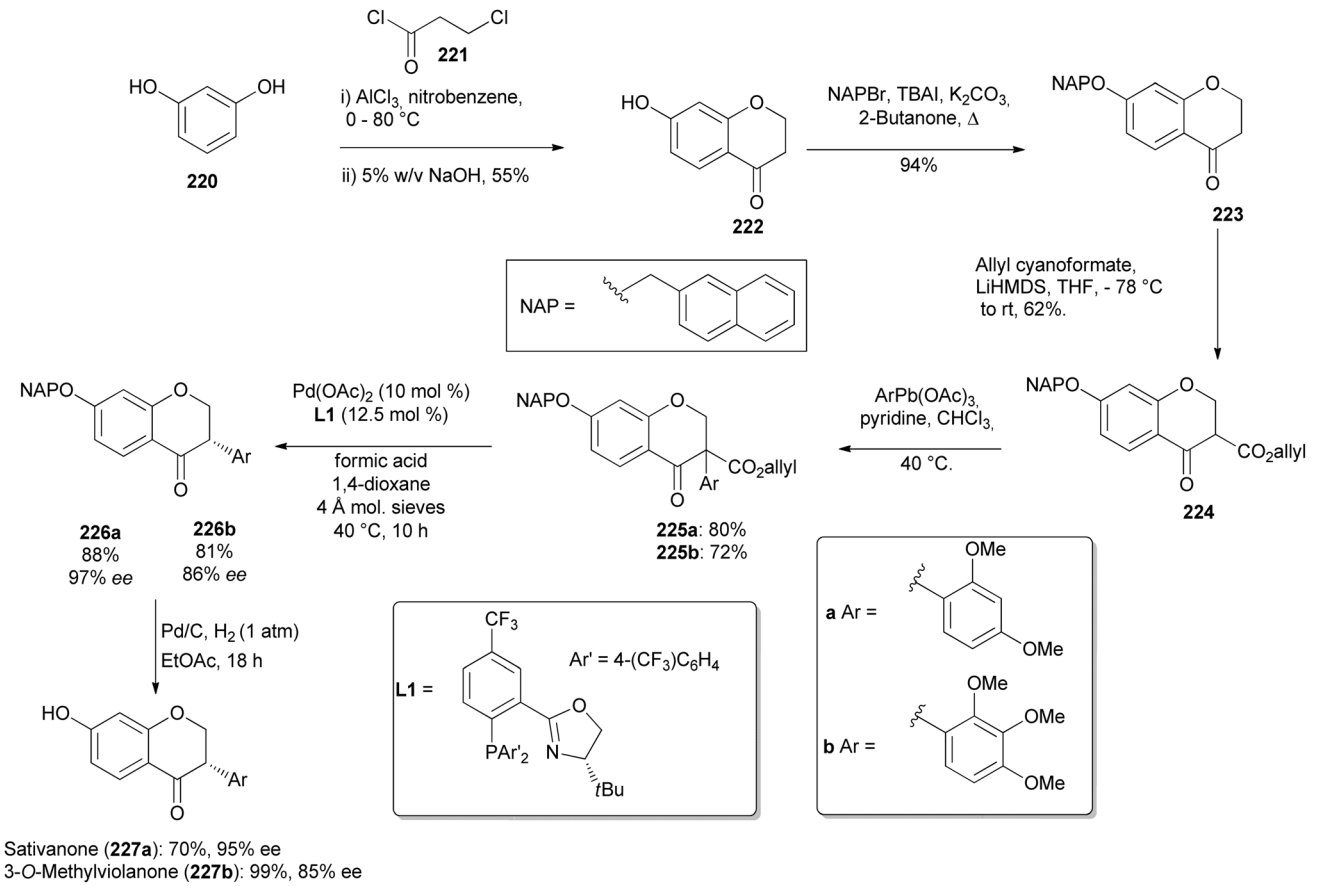
Several strategies have been employed for stereoselective syntheses of isoflavanones and isoflavans. These include stereoselective hydrogenation and stereoselective transfer hydrogenation promoted by palladium, ruthenium, and iridium catalysts.[76–78] Pd-catalysed decarboxylative stereoselective protonation[68] and organo-catalysed stereoselective syntheses of isoflavanones and isoflavans have also been reported.[70,74,166] Earlier conventional studies utilised chiral auxiliaries and reagents.[167–170]

3.2.1 Isoflavanones. Doran *et al.* synthesised the 7-hydroxyisoflavanones including sativanone (**227a**) and 3-*O*-methylviolanone (**227b**) by Pd-catalysed decarboxylative stereoselective protonation[68] starting from chromanone carboxylate.[68,171] They synthesised isoflavanone precursors **225a** and **225b** by lead-mediated arylations of allyl-β-keto ester **224** in yields of 80 and 72%, respectively. To begin, a Friedel–Crafts acylation and cyclisation of resorcinol **220** and 3-chloropropionyl chloride (**221**) gave 7-hydroxychroman-4-one **222** in 55% yield, followed by 2-naphthylmethyl (NAP) protection to afford **223** in 94% yield and subsequent acylation with allyl cyanoformate to give **224** in 94% yield (Scheme 31). The isoflavanone precursors **225a** and **225b** were reacted in the decarboxylative stereoselective protonation reaction with the (S)-$(CF_3)_3$-*t*-Bu-PHOX ligand to give compounds **226a** and **226b** in 88 to 81% isolated yields and 97 to 81% ee (Scheme 31). The NAP group was removed to yield the natural compounds sativanone (**227a**) and 3-*O*-methylviolanone (**227b**) without erosion of enantiomeric excess by stirring the protected isoflavanones **226a** and **227b** overnight with Pd/C (10%) in ethyl acetate under hydrogen (1 atm), Scheme 31.[68]

Iwai and colleagues were the first to synthesise natural product isodarparvinol B (**233**) using an intramolecular benzoin reaction as a key step in the presence of N-heterocyclic carbene (NHC) catalyst.[70] This took advantage of C–C bond formation *via*



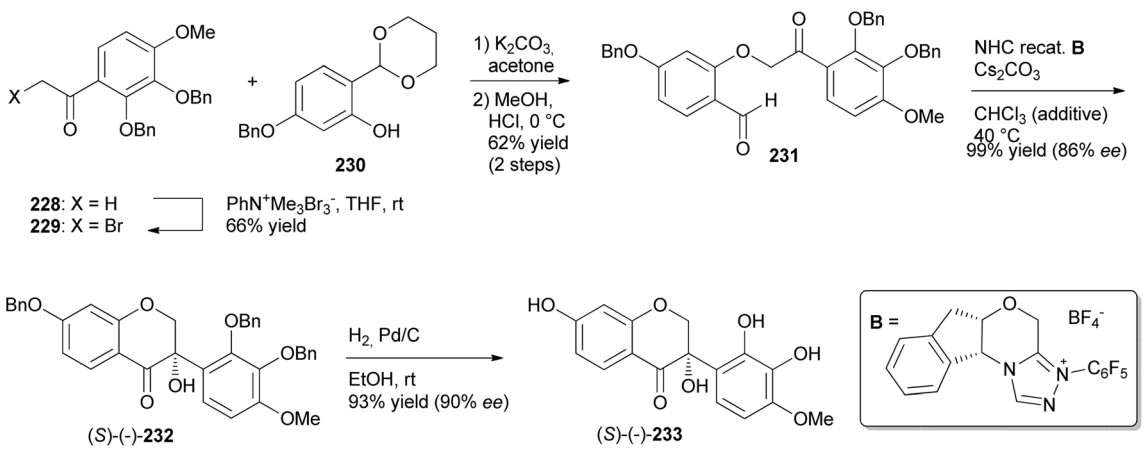
Scheme 30 Total synthesis of abruquinones B, E, and P.



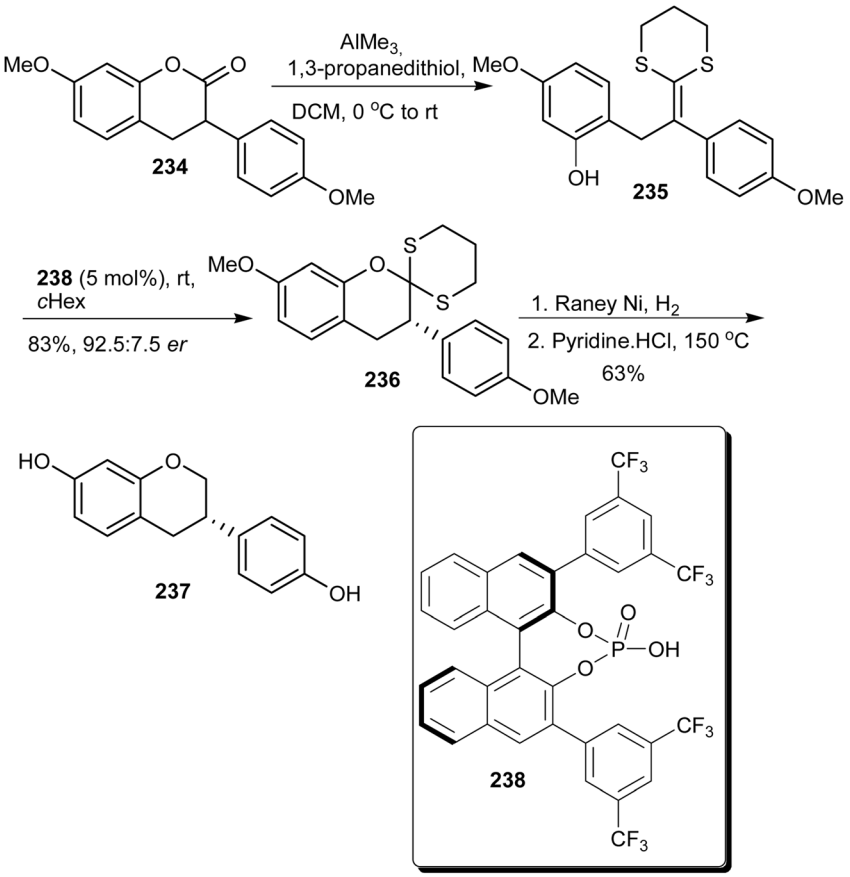
Scheme 31 First stereoselective synthesis of sativanone (**227a**) and the first synthesis of 3-*O*-methylviolanone (**227b**).

polarity inversion of the formyl group into acetyl anion equivalent and high enantioselectivity of NHCs.[73] Ketone **228** was α-brominated with phenyltrimethylammonium tribromide to give α-bromoketone **229** in 66% yield. Compound **230** was *O*-alkylated with α-bromoketone **229** in a Williamson ether synthesis reaction, followed by deprotection of the acetal group, to afford aldehyde **231** in 62% yield. Aldehyde **231** was exposed to the NHC-catalysed intramolecular benzoin reaction to furnish optically active 4-chromanone **232** in 99% yield with 86% ee. Finally, hydrogenation of **232** gave (−)-**233** in 93% yield with 90% ee (38% total yield from starting material) (Scheme 32).[70] When the NHC-catalysed intramolecular benzoin reaction was conducted in THF in the previous study, a racemic mixture was obtained.[166]

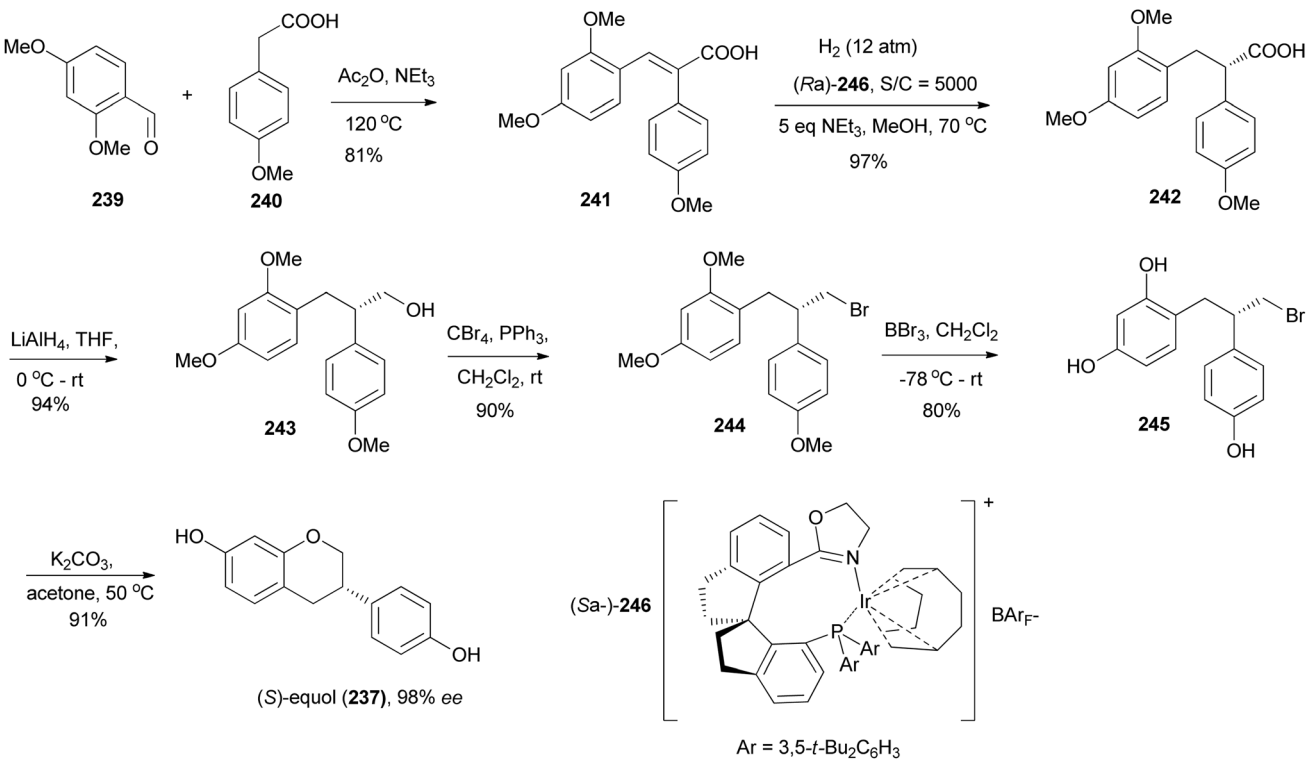
3.2.2 Isoflavans. One of the well-studied isoflavan compounds is equol, a metabolite of the soy isoflavone,



Scheme 32 Total synthesis of (−)-isodarparvinol B [(−)-**233**].



Scheme 33 Synthesis of (*S*)-equol (**237**) using chiral phosphoric acid.

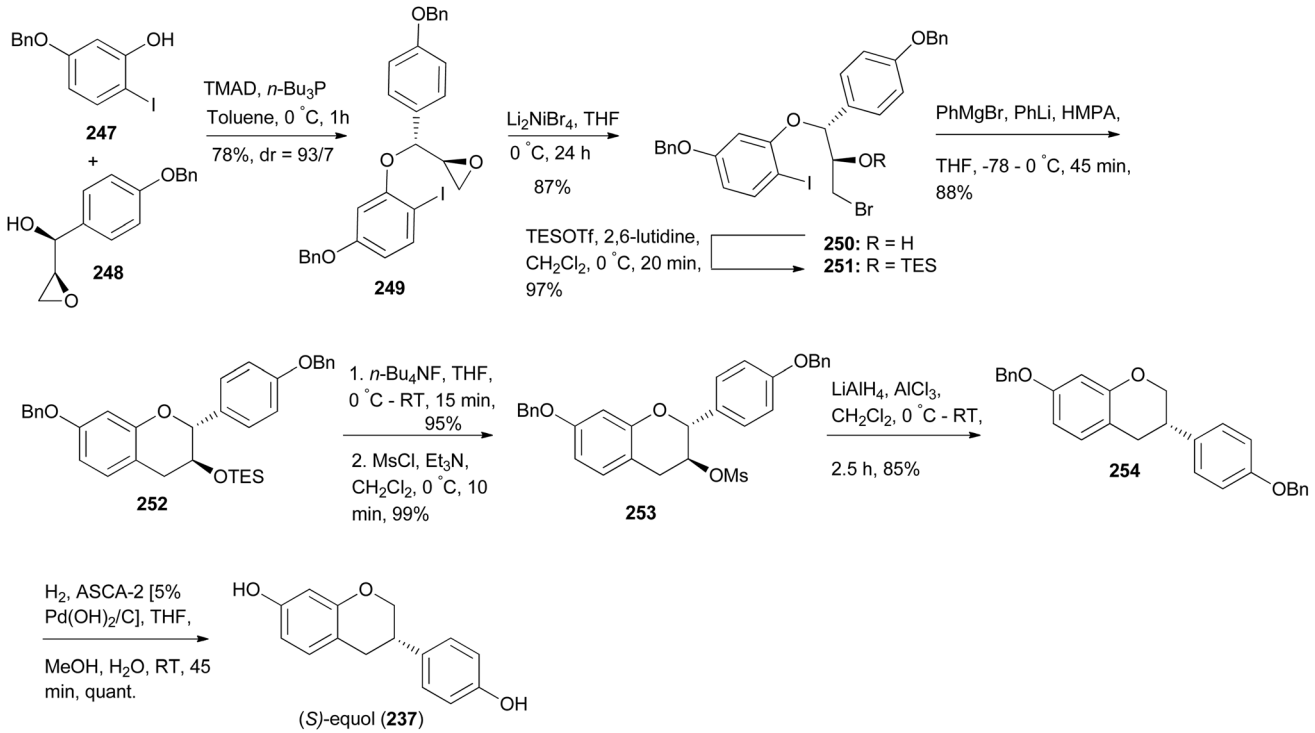


Scheme 34 Synthesis of (*S*)-equol (**237**) by stereoselective hydrogenation using iridium catalyst.

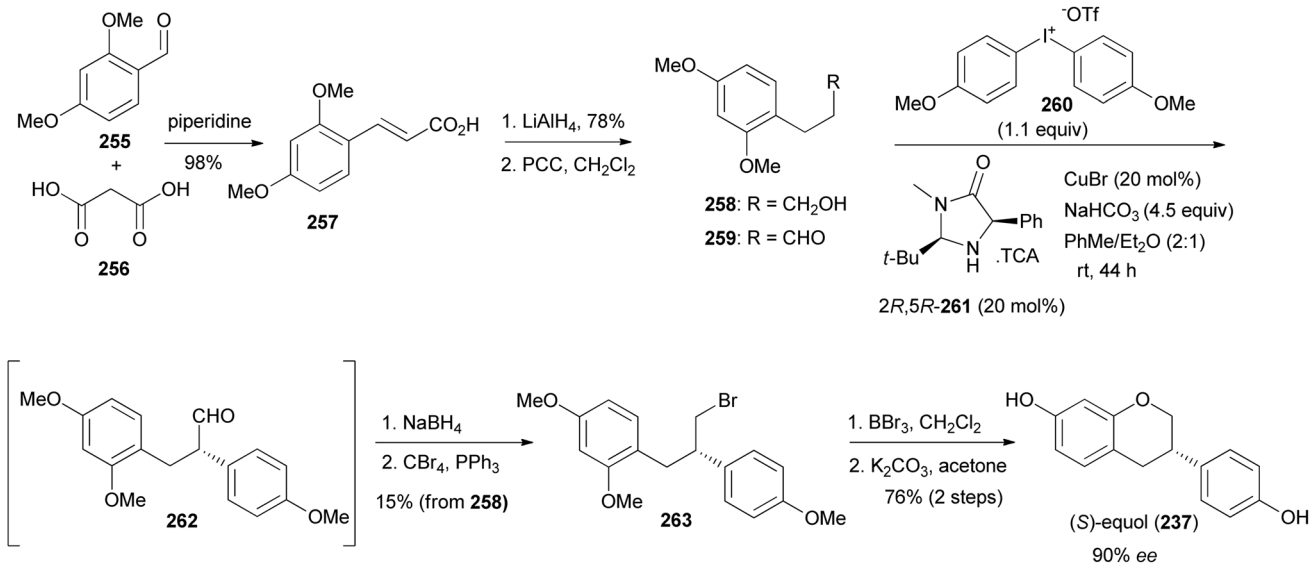
daidzein (**94**). Equol was first identified from the horse urine.[172] It has been reported to exhibit many biological activities, particularly oestrogenic activity.[173,174] Therefore, its synthesis has been of interest to researchers. Several studies report the stereoselective synthesis of the natural enantiomer (*S*)-equol (**237**)[74,77–79,169,170,175–178] and there are limited studies that include the synthesis of the non-natural enantiomer (*R*)-equol.[75,179,180]

Lee and List developed a method for deracemisation of 3-arylcoumarins using chiral phosphoric acids.[74] The method could be applied to afford enantioenriched 3-arylcoumarins and 3-arylchromans. Following this, (*S*)-equol (**237**) was synthesised by conversion of racemic 3-arylcoumarin **234** into ketene dithioacetal **235**, which upon protonation in the presence of chiral phosphoric acid **238** afforded enantioenriched coumarin dithioacetal **236** in 83% yield and 92.5 er. Reduction of **236** and demethylation afforded (*S*)-equol (**237**), Scheme 33.[74]

Yang and colleagues synthesised (*S*)-equol (**237**) from a chiral 2,3-diarylpropionic acid **242**, obtained by stereoselective



Scheme 35 Synthesis of (*S*)-equol **237** by 1,2-aryl migration of a 3-methanesulfonylflavan **253**.



Scheme 36 Synthesis of (*S*)-equol (**237**) from enantioenriched diarylpropanal.

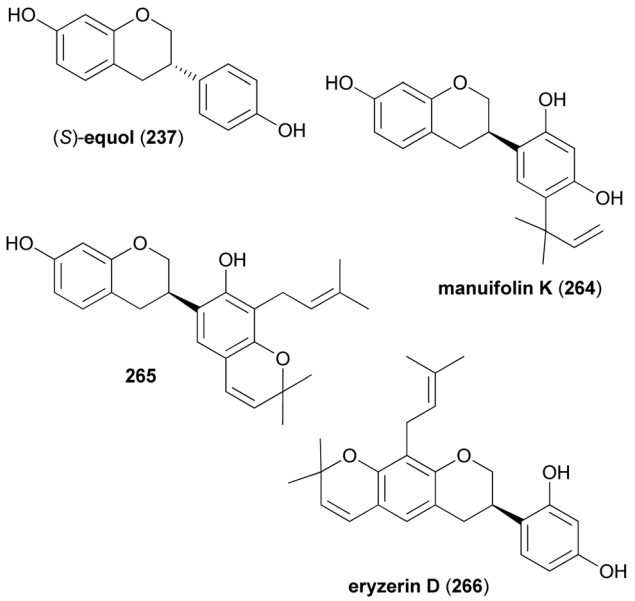


Fig. 3 Target isoflavonoids.

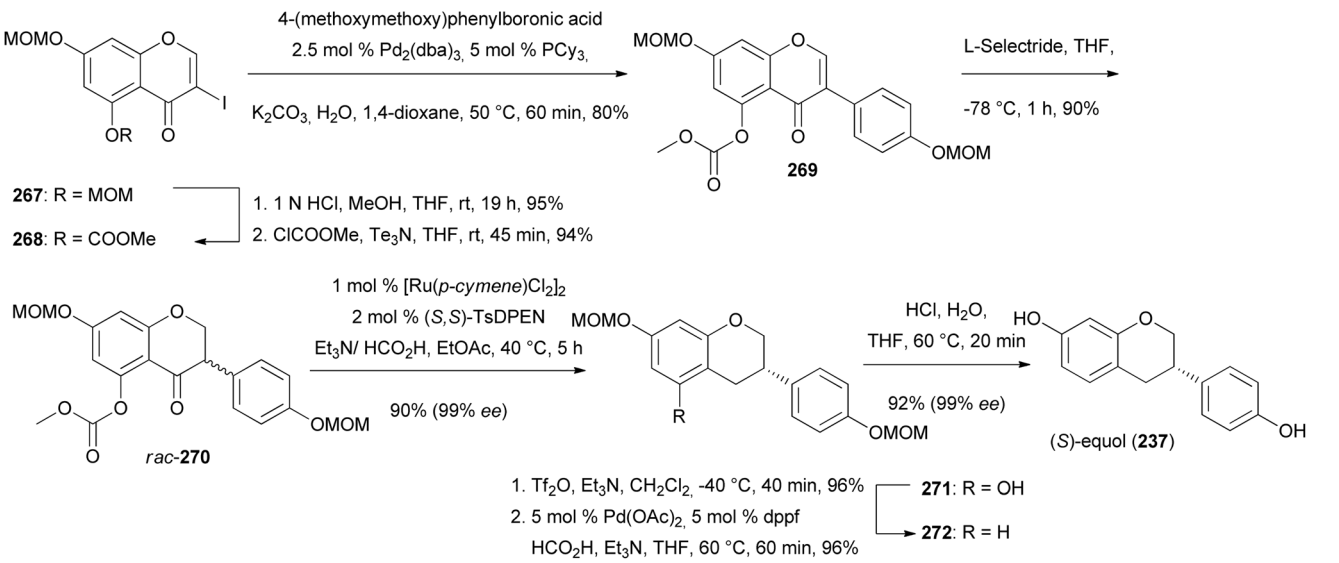
hydrogenation of cinnamic acid **241** in the presence of a chiral iridium catalyst (R_a)-**246**. Reduction of the carboxylic acid group of **242** gave an alcohol **243**, which was converted into alkylbromide **244**. Demethylation of **244** and subsequent *O*-cyclisation of **245** gave (*S*)-equol (**237**) in 91% yield and 98% ee, Scheme 34.[79]

Nakamura and colleagues synthesised (*S*)-equol (**237**) by a strategy that involved 1,2-aryl migration of 3-methanesulfonylflavans as the key step.[175] The synthesis was initiated by Mitsunobu reaction of iodophenol **247** with chiral epoxyalcohol **248** to afford a diaryl ether **249**. Bromination of oxirane **249** gave an alkylbromide **250** in 87% yield and its epimer. Bromohydrin **250** was converted into a TES ether **251**, which was assembled into an isoflavan **252** upon treatment with Ph_3MgLi. Conversion of **252** into mesylate **253** followed by 1,2-aryl shift facilitated by AlH_3 afforded isoflavan **254**, which upon debenzylation gave (*S*)-equol (**237**), Scheme 35.[175]

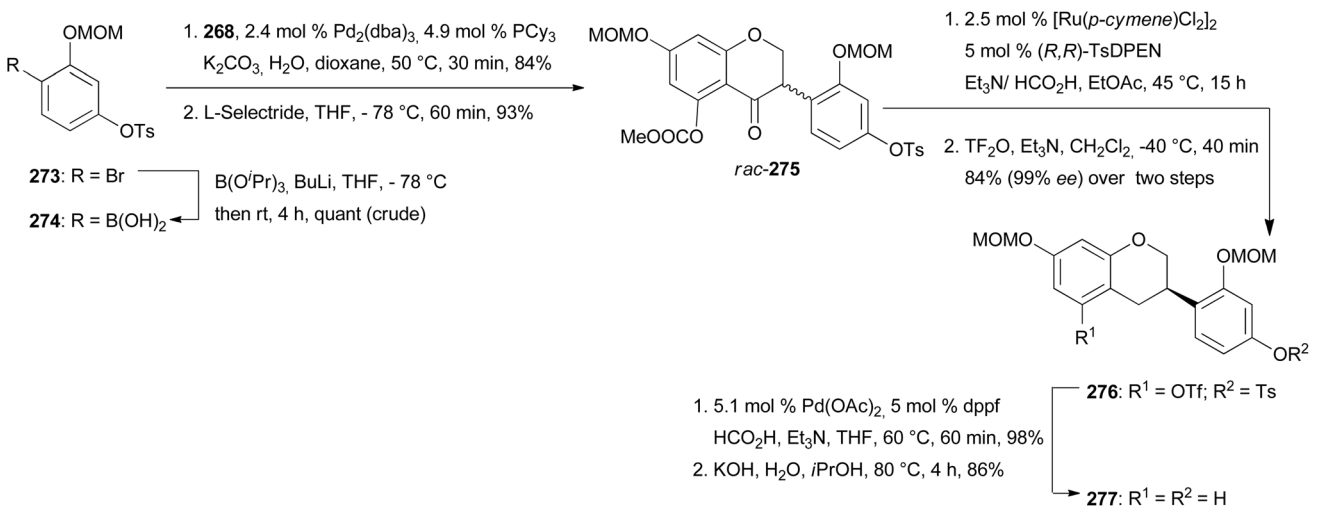
Uemura and colleagues synthesised (*S*)-equol (**237**) from enantioenriched diphenylpropanal **262**.[75] The diphenylpropanal (*S*)-**262** was prepared by stereoselective α-arylation of phenylpropanal **259** with diaryliodotriflate **260** in the presence of a chiral phenylimidazolidin-4-one catalyst (2*R*,5*R*) **261** and CuBr.[181,182] Compound **259** was in turn synthesised by oxidation of the alcohol **258**, obtained from cinnamic acid **257**. Reduction of the aldehyde **262** and bromination of the resulting alcohol gave bromodiphenylpropane **263**. Demethylation and oxycyclisation rendered (*S*)-equol (**237**) in 76% yield over two steps and 90% ee (Scheme 36). The same protocol was followed for the synthesis of (*R*)-equol from **259**, using phenylimidazolidin-4-one catalyst (2*S*,5*S*) **261**.[75]

Keßberg *et al.* stereoselectively synthesised isoflavans (*S*)-equol (**237**), manuifolin K (**264**), **265** and eryzerin D (**266**) by key steps involving ruthenium-catalysed stereoselective transfer hydrogenation of racemic isoflavanone precursors and Pd-catalysed deoxygenation (Fig. 3).[77] The synthesis of (*S*)-equol (**237**) started with chemoselective deprotection of the 5-*O*-MOM moiety of chromone **267**, followed by acylation of the phenol with methyl chloroformate to give vinyl iodide **268** in 94% yield (Scheme 37). The Suzuki coupling of **268** with 4-(methoxymethoxy)phenylboronic acid followed by conjugate reduction of **269** resulted in isoflavanone *rac*-**270**. The stereoselective transfer hydrogenation/deoxygenation cascade using ruthenium catalyst at low catalyst loading first gave (*S*)-**271** in 90% yield with 99% ee. The free hydroxy group was removed reductively by treatment of compound **271** with triflic anhydride followed by palladium-catalysed deoxygenation to afford product **272** in 96% yield over two steps. Finally, hydrolysis of the acetal moieties of **272** gave (*S*)-equol (**237**) in 92% yield with 99% ee.

The syntheses of manuifolin K (**264**) and isoflavan **265** commenced by coupling of chromone **268** with boronic acid **274**



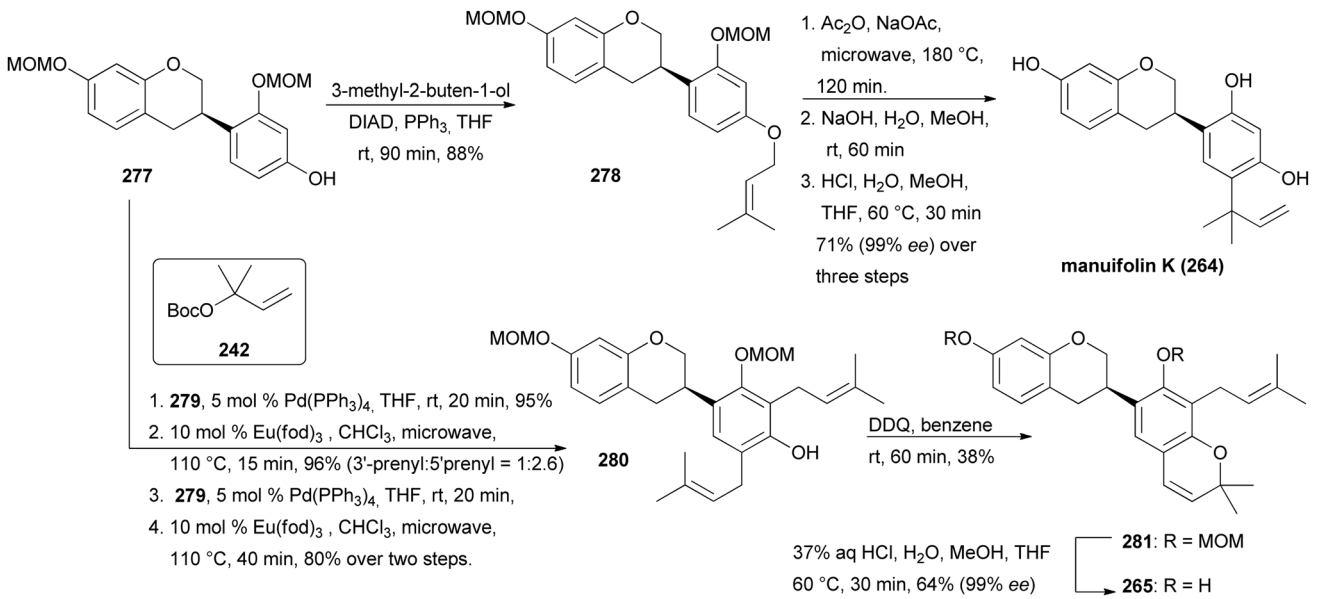
Scheme 37 Synthesis of (*S*)-equol (**237**).



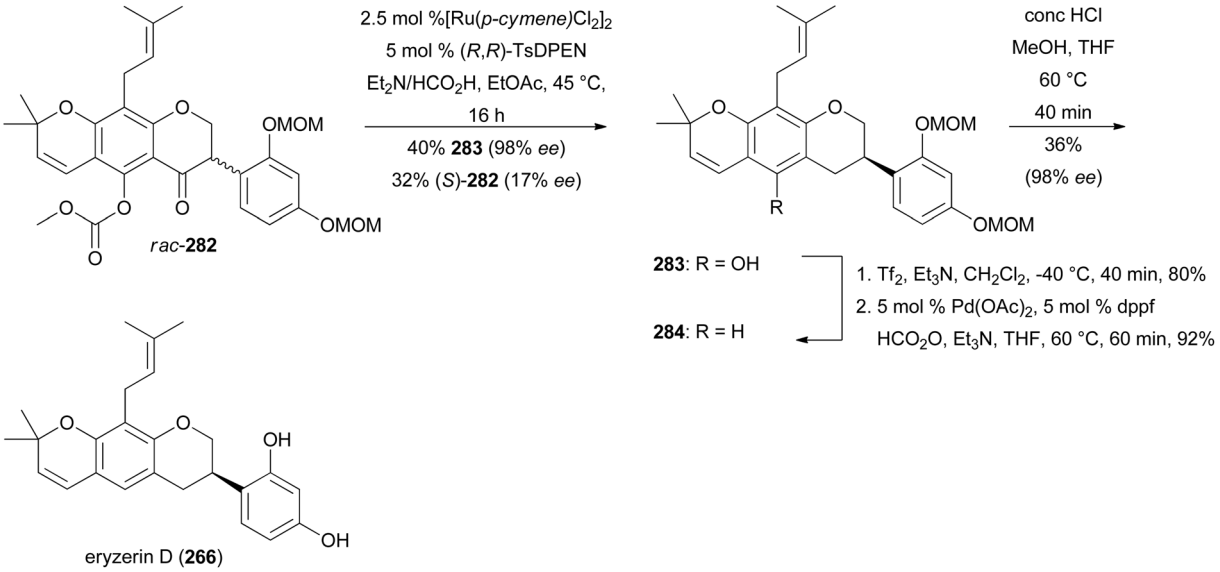
Scheme 38 Synthesis of isoflavan **277**.

and subsequent treatment of the intermediate with L-selectride to give ATH substrate *rac*-**275** in 93% yield (Scheme 38). The domino ATH reaction of *rac*-**275** was achieved at a slightly higher catalyst loading followed by treatment with triflic anhydride giving enantiopure isoflavan **276** in 84% yield with 99% ee over two steps. Lastly, deoxygenation at C-5 and removal of the tosylate group furnished product **277**. *O*-Prenylation of isoflavan **277** under Mitsunobu conditions gave prenyl ether **278** in 88% yield. Lastly, Claisen rearrangement in acetic anhydride and cleavage of the acetyl and MOM groups gave manuifolin K (**264**) in 71% with 99% ee (Scheme 39). The isoflavan **265** was synthesised from compound **277** in six steps. The prenyl groups were installed by a Tsuji–Trost allylation with allylic carbonate in 95% yield and subsequent europium-catalysed rearrangement, favouring the 5′-position over the 3′-position due to steric constraints. Both regioisomers were transformed to **280** in 80% yield using the same two-step protocol. Benzopyran **281** was synthesised in 38% yield through oxidative cyclisation of **280** using DDQ. Finally, acid-promoted deprotection furnished the target compound **265** in 68% yield with 99% ee.[77] Comparison of the analytical data of the synthesised isoflavan **265** with those of the isolated compound revealed a mismatch between the data sets,[183] which revealed that Jang and colleagues had isolated eryzerin D (**266**) instead.[77,183]

To complete the synthesis of eryzerin D (**266**) an enantioselective reduction of the highly functionalised isoflavanone *rac*-**282** was conducted, which yielded 40% of the unstable compound (*R*)-**283** with 98% ee. Compound (*R*)-**283** was immediately treated with triflic anhydride and subsequently deoxygenated to give isoflavan **284** in 86% yield over two steps.



Scheme 39 Synthesis of isoflavans **264** and **265**.



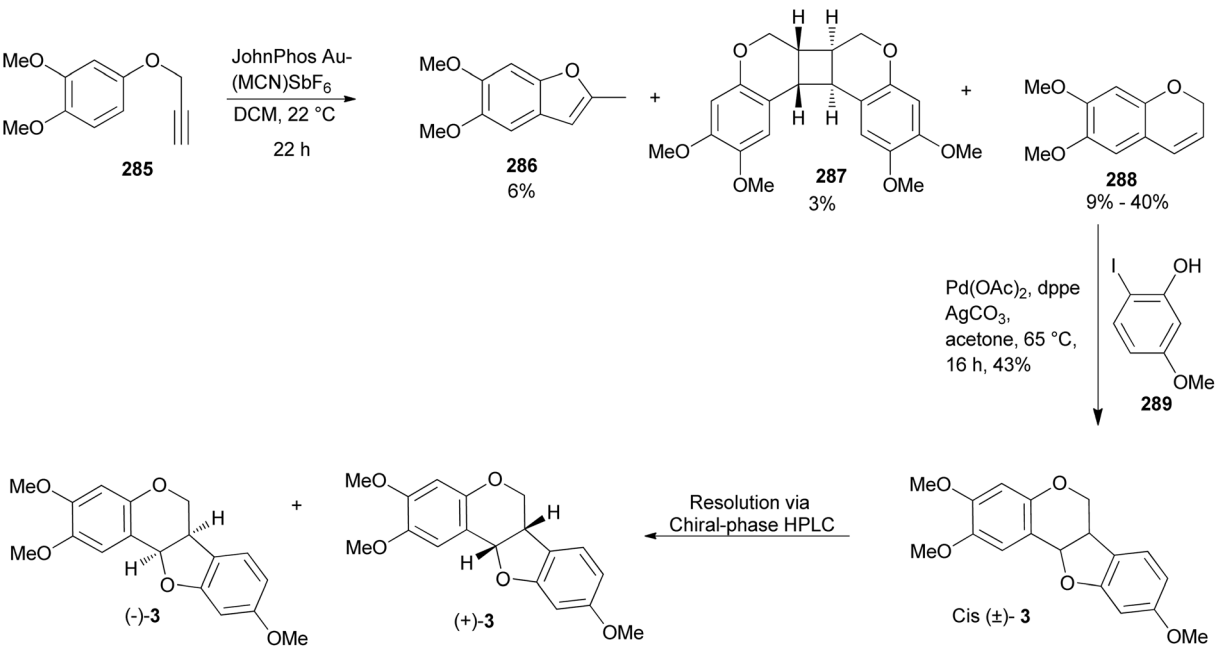
Scheme 40 Synthesis of eryzerin D (**266**).

The removal of MOM groups gave eryzerin D (**266**) in 38% yield with 98% ee (Scheme 40).[77] The NMR and MS data of the synthesised eryzerin D (**266**) matched those reported for the isolated compound,[38,183] and its configuration was determined to be *R* based on ECD data.[77] It is noteworthy that *rac*-**282** was synthesised in several steps from chromone **267**.[184]

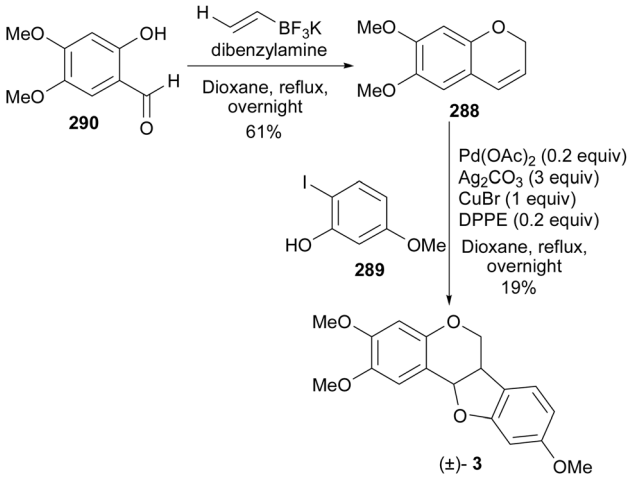
4. Synthesis of pterocarpans

A detailed review on pterocarpans was published in 2013 (ref. 185) and other recent reviews included sections on the synthesis of pterocarpans.[76,186] Therefore, the syntheses of pterocarpans not included in these reviews will be discussed. They include: the synthesis of 2,3,9-trimethoxypterocarpan by Mizoroki–Heck oxyarylation reaction,[41] total synthesis of neorautenol and shinpterocarpin,[187] and the stereoselective total synthesis of stachyodin A.[67]

A pterocarpan, (+)-(6a*S*,11a*S*)-2,3,9-trimethoxypterocarpan [(+)-**3**] was isolated from the indigenous Brazilian tree *Platymiscium floribundum* Vogel. (Fabaceae) and the compound showed high cytotoxic activity against leukemia (HL-60 and CEM), breast (MCF-7), colon (HCT-8), and skin (B16) cancer cell-lines with IC_{50} values ranging from 0.1 to 2.9 μg mL^{-1}.[40] To provide additional material for further studies, Farias *et al.* completed the total



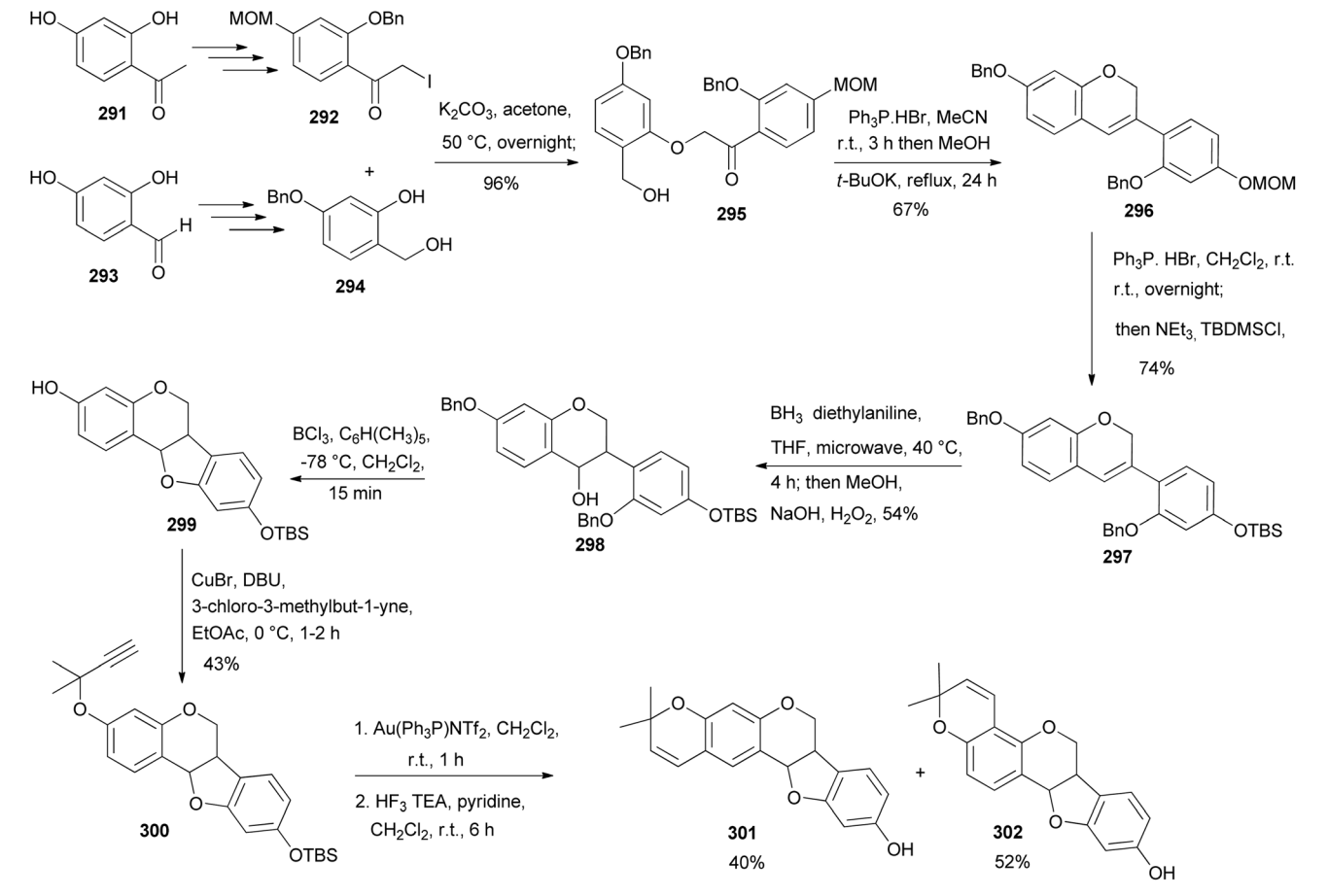
Scheme 41 Synthesis of (±)-2,3,9-trimethoxypterocarpan [(±)-**3**] and its resolution into enantiomers.



Scheme 42 Synthesis of the racemic 2,3,9-trimethoxypterocarpan [(±)-**3**].

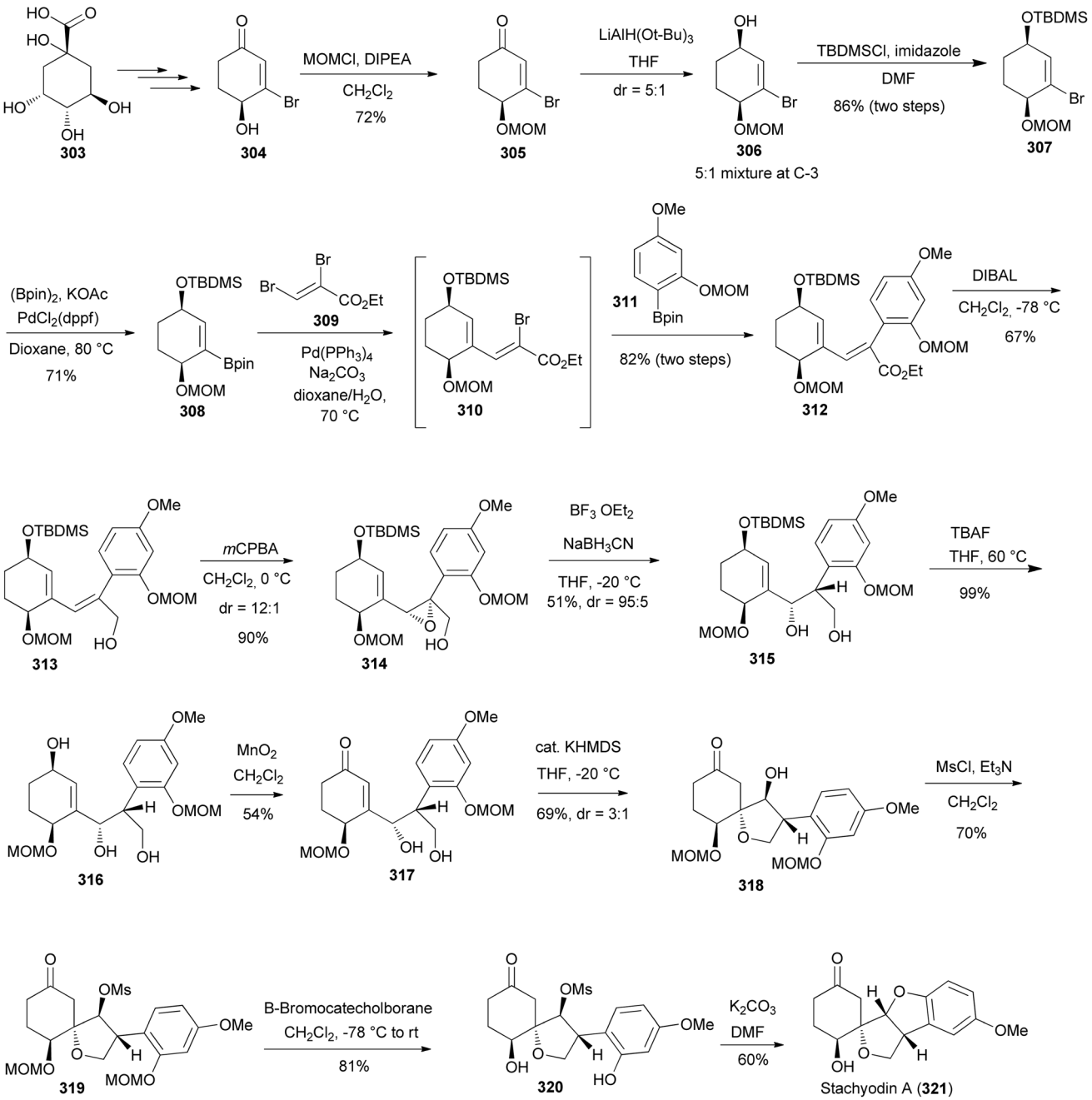
synthesis of the racemic compound (±)-**3** in 2020 and resolved it into its enantiomers, (+)- and (−)-2,3,9-trimethoxypterocarpans [(+)-**3** and (−)-**3**].[41] (−)-(6a*R*,11a*R*)-2,3,9-Trimethoxypterocarpan [(−)-**3**] is also a natural compound that was isolated from *Fusarium solani* infected *Pisum sativum* Linn. (Fabaceae).[188] They started their synthesis by alkylation of the 3,4-dimethoxyphenol with propargyl bromide to obtain the aryl propargyl ether **285** in a 90% yield. Initially, the gold(I)-catalysed intramolecular cyclisation reaction of the aryl propargyl ether **285** afforded a mixture of benzofuran **286** (6%), chromene **288** (9%), and a [2 + 2] dimer **287** (3%), Scheme 41. The chromene **288** could be synthesised in moderate yields (40%) by changing the reaction conditions.[86] Finally, the (±)-2,3,9-trimethoxypterocarpan [(±)-**3**] was synthesized in a 43% yield by Mizoroki–Heck oxyarylation of chromene **288** and 2-iodophenol **289**. The racemic mixture was resolved into separate enantiomers using semi-preparative HPLC that was equipped with a chiral-phase column. The synthesised (±)-2,3,9-trimethoxypterocarpan [(±)-**3**] and enantiomers (+)-**3** and (−)-**3** were evaluated for antiproliferative effects against HL-60, HCT-116, OVCAR-8, and SF-295 tumor cell lines. The enantiomer (+)-**3** was determined to be the most active, particularly against OVCAR-8, while the racemic mixture (±)-**3** and the levorotatory enantiomer (−)-**3** were less active.[41]

It is noteworthy that Kakuda *et al.* reported the synthesis of chromene **288** in a 61% yield from the salicylaldehyde **290** while utilising the Petasis boronic acid-Mannich reaction.[189] However, by subjecting the chromene **288** to the Mizoroki–Heck oxyarylation conditions [$Pd(OAc)_2$ (0.2 equiv.), Ag_2CO_3 (3.0 equiv.), CuBr (1.0 equiv.), and DPPE (0.2 equiv.)] the racemic 2,3,9-trimethoxypterocarpan [(±)-**3**] was obtained in 19% yield (Scheme 42).[189]



Scheme 43 Total syntheses of neorautenol (**301**) and shinpterocarpin (**302**).

Neorautenol (**301**) and shinpterocarpin (**302**) are pyranopterocarpans which were first isolated from *Neorautanenia edulis* and *Glycyrrhiza glabra* L., respectively.[190,191] The first synthesis of racemic pterocarpans neorautenol (**301**) and shinpterocarpin (**302**) together with their derivatives was conducted by Huang *et al.*[187] This was followed by evaluation of their antitumour properties towards a panel of cancer cells. They were synthesised by a modified version of the method described by Erhardt's group.[192,193] The synthesis of **301** and **302** proceeded *via* an intramolecular Wittig reaction of **295** that gave the highly sought-after isoflavene intermediate **296,** Scheme 43. The precursor **295** was synthesised starting from 2,4-dihydroxyacetophenone (**291**) that was chemo-selectively protected with MOM and benzyl groups, followed by iodination using Selectfluor and molecular iodine to afford the α-iodoketone **292.** In a parallel synthesis to the α-iodoketone **292,** 2,4-dihydroxybenzaldehyde (**293**) was chemoselectively protected and reduced with $NaBH_4$ to afford benzyl alcohol **294** that served as the coupling partner to α-iodoketone **292.** The union of **292** and **294** under basic conditions gave the α-phenoxyketone **295** in excellent yields. The cyclisation of **295** afforded isoflavene **296** which was subsequently silyl protected *in situ via* MOM deprotection with mild acid to produce **297.** Compound **297** was subjected to the hydroboration–oxidation of the



Scheme 44 Stereoselective total synthesis of stachyodin A (**321**).

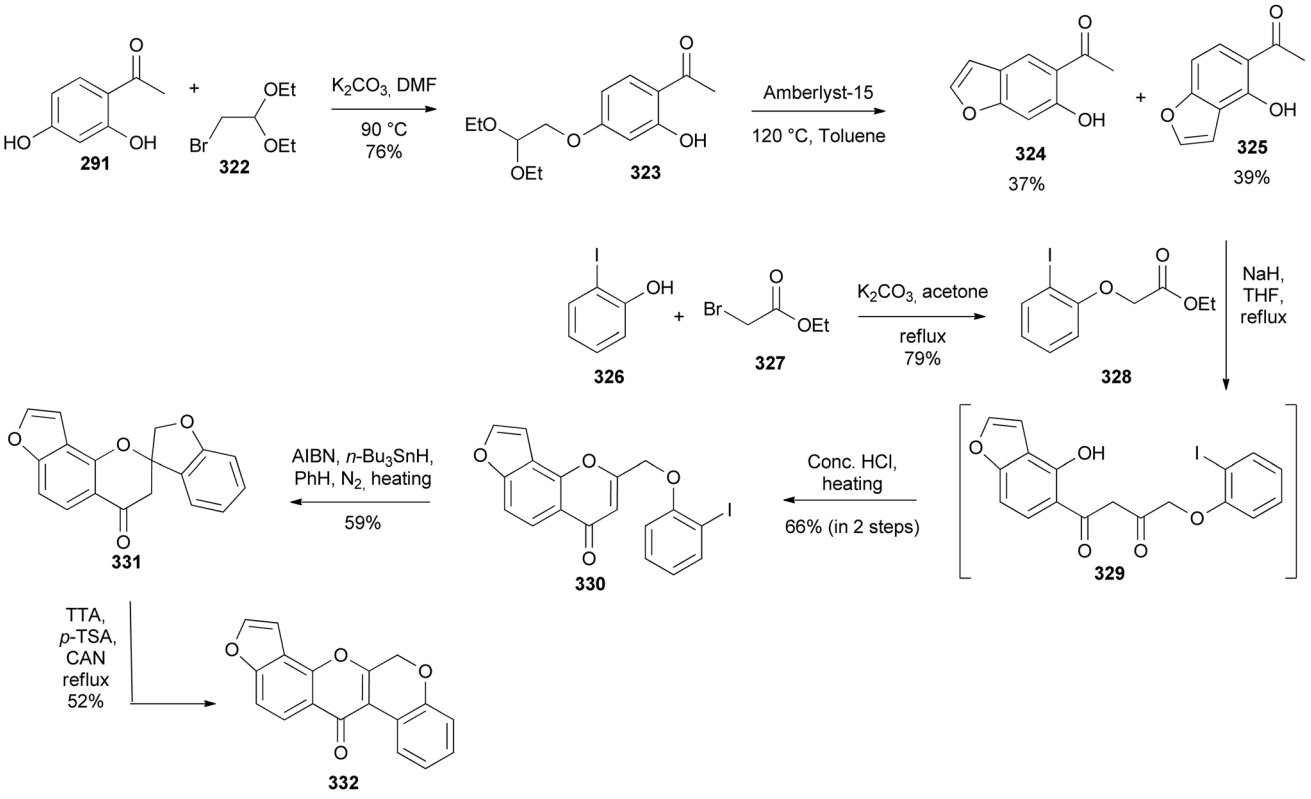
chromene double bond, which favoured the anti-Markovnikov product **298** due to the steric presence of the phenyl ring at C-3 of isoflavene **297**. Treatment of **298** with boron trichloride furnished pterocarpan **299** that was alkylated with 3-chloro-3-methylbut-1-yne to produce **300**. The cyclisation of **300** under gold(I) catalysis gave two 2,2-dimethyl-2*H*-chromene regioisomers in a ratio of 4 : 5, which upon desilyllation afforded racemic neorautenol (**301**) and shinpterocarpin (**302**), Scheme 43.[187]

Stachyodin A (**321**), a pterocarpan derivative with an unusual spirotetrahydrofuran ring was isolated from the roots of *Indigofera stachyodes* Lindl. (Papilionoideae).[194] Kawamoto *et al.* reported the first total synthesis of racemic **321** in 2021 and in the subsequent year developed its stereoselective total synthesis.[67,195] The stereoselective total synthesis was accomplished in 14 steps from a known precursor **304** that was readily prepared from the chiral pool building block, (−)-quinic acid (**303**) (Scheme 44).[67] The synthesis was initiated by instituting the MOM protecting group to a carbinol group of **304** to give the MOM ether **305**. The reduction of the MOM ether **305** with $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF afforded **306** as a 5 : 1 diastereomeric ratio at C-3. The subsequent treatment of **306** with TBDMSCl in the presence of a mild base (imidazole) also afforded **307** as a mixture of diastereoisomers with a ratio of 5 : 1 at C-3. Compound **307** was transformed into the pinacolato borane intermediate **308** through the Suzuki coupling reaction. It is noteworthy that **308** and its coupling partner **309** serve as crucial intermediates towards achieving the stereoselective total synthesis of stachyodin B. The aryl borane **311** was prepared in three steps starting from 1-hydroxy-3-methoxybenzene.[195] Therefore, the one-pot three-component Suzuki coupling reaction of pinacolato borane **308**, dibromide **309**, and aryl borane **311** was undertaken to render **312** through the intermediate **310**. The reaction was conducted at elevated temperatures in the presence of Na_2CO_3 while utilising $Pd(PPh_3)_4$ as a catalyst to obtain **312** in 82% yield. Upon successfully achieving the synthesis of **312** the focus shifted to the synthesis of an optically active enone **317**. The treatment of **312** with DIBAL gave allyl alcohol **313**, which upon stereoselective epoxidation with mCPBA afforded **314**. The subsequent reductive opening at the benzylic position afforded the diol **315** in 51% yields. Desilylation of **315** with TBAF gave the secondary alcohol **316**, which was selectively oxidized with MnO_2 to furnish the requisite enone **317** in a 54% yield. Treatment of **317** with KHDMS afforded compound **318** through a 1,4-intramolecular dehydration reaction. Mesylation of **318** with MsCl in the presence of Et_3N produced **319**. MOM deprotection with catechol borane gave **320**. The intramolecular cyclisation of **320** following the S_N2 inversion strategy in the presence of K_2CO_3 afforded stachyodin A (**321**) in a 60% yield after purification (Scheme 39). The specific rotation of **321** matched that of the reported natural compound.[67]

5. Synthesis of rotenoids

5.1. Synthesis of dehydrorotenoids

Kurapati and colleagues synthesised pongarotene (**332**), an antimicrobial dehydrorotenoid isolated from *Pongamia pinnata*



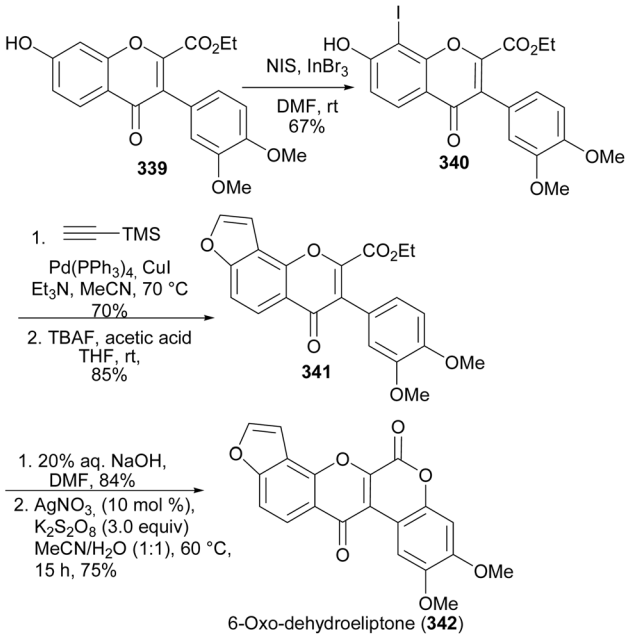
Scheme 45 Synthesis of pongarotene (**332**).

(L.) Pierre.[46,196] The synthesis featured oxidative aryl rearrangement of a spirocyclic flavanone. It commenced by selective alkylation of dihydroxyacetophenone **291** with bromoacetal **322** followed by cyclisation of **323** to give the targeted angular benzofuranyl ketone **325** in 39% yield together with a linear benzofuran **324** in 37% yield (Scheme 45). Condensation of acetophenone **325** with phenoxyacetate **328** obtained from the reaction of iodophenol **326** with bromoacetate **327** gave **329**, which was converted into a chromone **330** by treatment with concentrated HCl. The radical-initiated cyclisation of **330** gave a spirocyclic flavanone **331**, which underwent 1,2-aryl migration upon treatment with *in situ*-generated thallium(III) *p*-tosylate to give pongarotene (**332**) (Scheme 45).[46]

Boonsombat and colleagues developed a method for the synthesis of oxodehydrorotenoid by silver-catalysed intramolecular lactonisation of isoflavone-2-carboxylic acids.[197] The method was applied to the first total syntheses of stemonone (**338**), 6-oxodehydroelliptone (**342**), 6-oxo-6a,12a-dehydrodeguelin (**349**), and rotenonone (**346**). The synthesis of stemonone (**338**) commenced by preparation of isoflavone-2-ethylcarboxylate **335** by Houben–Hoesch reaction of phloroglucinol (**15**) and phenylacetonitrile **333** to give **334** that was subsequently converted to **335** following Baker's reaction.[50,198] Methylation of **335** and hydrolysis of the resulting isoflavone **336** rendered **337**. Direct lactonisation of **337** using $AgNO_3$ and $K_2S_2O_8$ optimised conditions gave stemonone (**338**) (Scheme 46).[197]

6-Oxodehydroelliptone (**342**) was synthesised from isoflavone-2-ethylcarboxylate **339** by a sequence of steps that involved iodination to give 8-iodoisoflavone **340**, followed by Sonogashira coupling annulation with trimethylsilylacetylene and TMS deprotection to give the furanoisoflavone **341** (Scheme 47). Cleavage of the ester and silver-catalysed intramolecular esterification of the aryl C_{sp^2}–H carbon and the carboxylic group gave 6-oxodehydroelliptone (**342**).

The two final oxodehydrorotenoids, 6-oxo-6a,12a-dehydrodeguelin (**349**) and rotenonone (**346**) were synthesised from **339** (Scheme 48) *via* hydrolysis of dimethylpyranoisoflavone **347** and furanoisoflavone **344** and subsequent

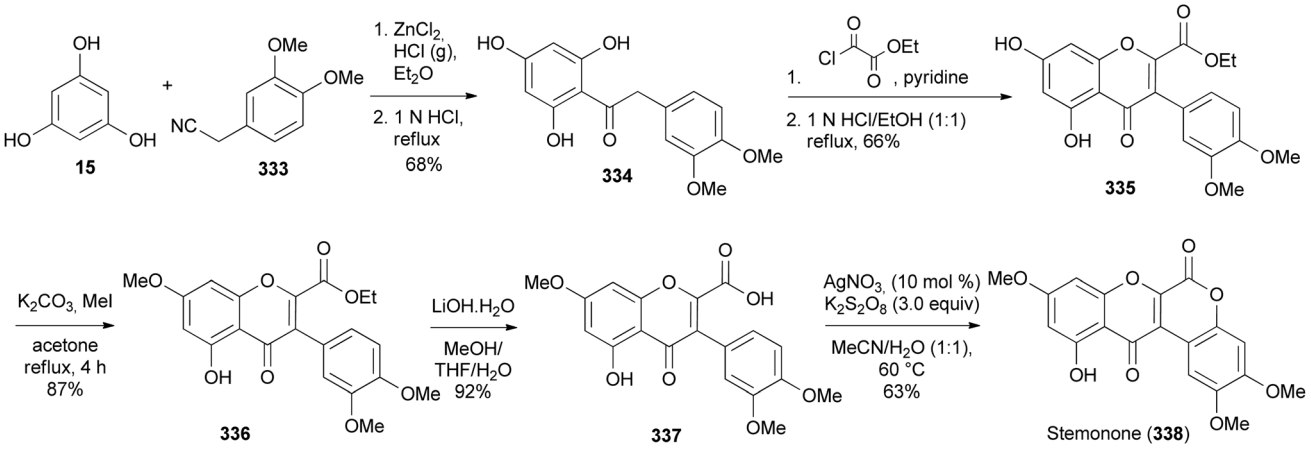


Scheme 47 Total synthesis of 6-oxodehydroelliptone (**342**).

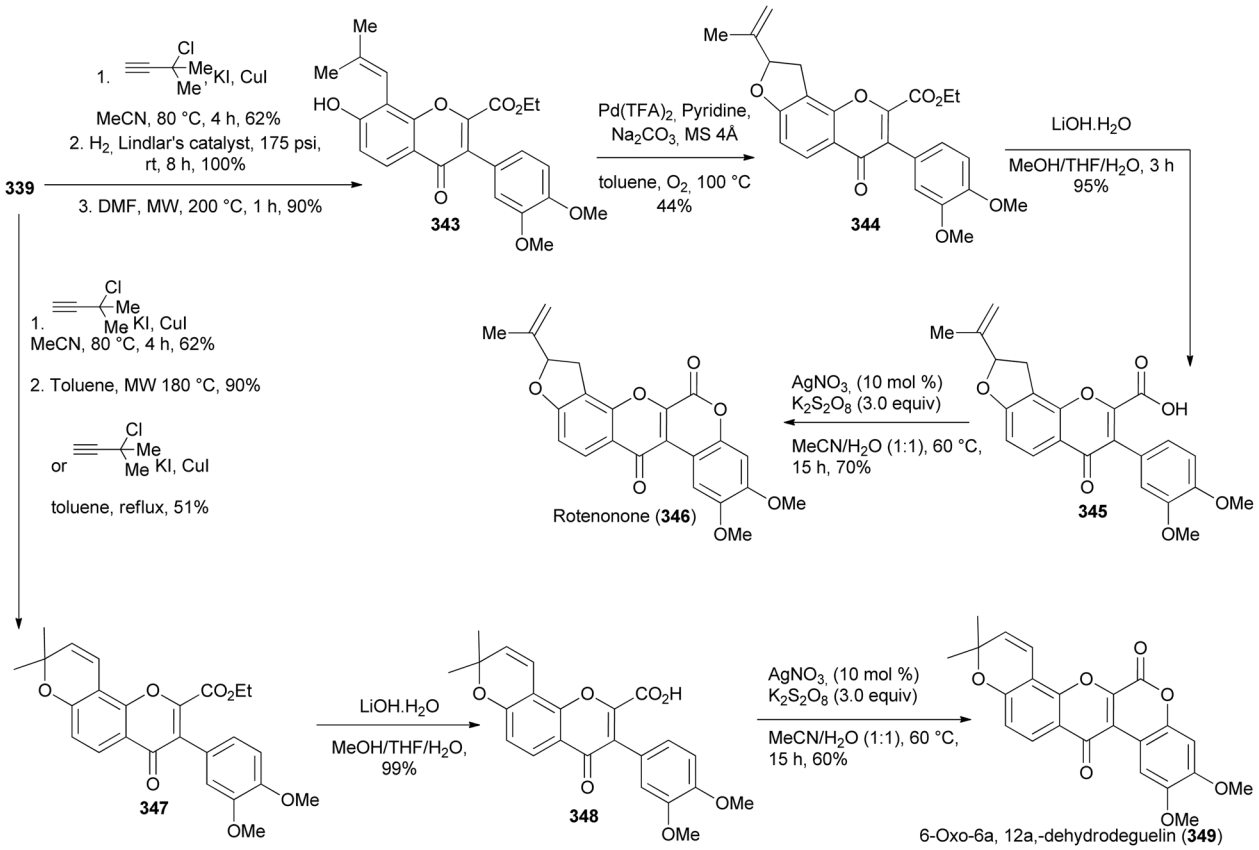
lactonisation of **348** and **345**, respectively. The requisite dimethylpyran scaffold in **347** was constructed by *O*-propagylation of **339** followed by microwave-assisted cyclisation at 180 °C to give **347**. Alternatively, **347** could be prepared in one step by treatment of **339** with dimethylpropargyl chloride under reflux (Scheme 48). The furan ring in **344** was prepared by Heck coupling reaction of the prenylated isoflavone **343**, which was in turn synthesised by *O*-propagylation, reduction, and Claisen rearrangement, Scheme 48.[197]

5.2. Synthesis of rotenoids

Rotenoids including deguelin, tephrosin, and rotenone have attracted the interest of researchers due to their biological activities that include pesticidal, insecticidal, and anticancer activities.[8,69,71] Several synthesis routes have been reported for these compounds.[47,66,69,71,199–203]

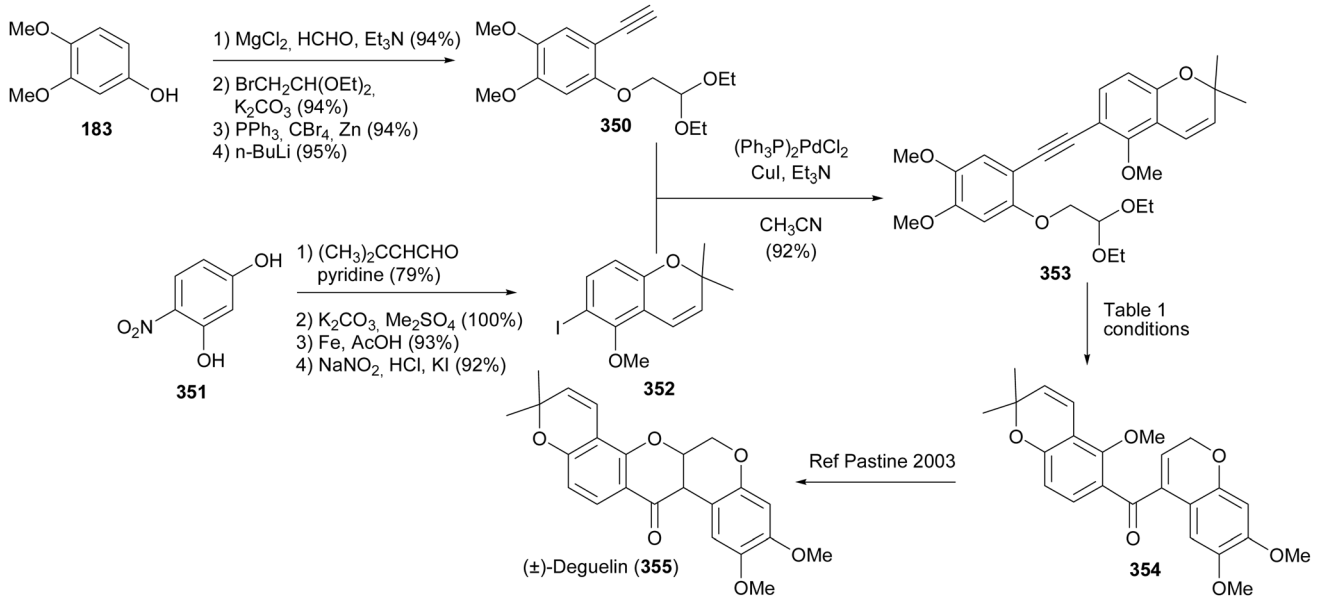


Scheme 46 The total synthesis of stemonone (**338**).

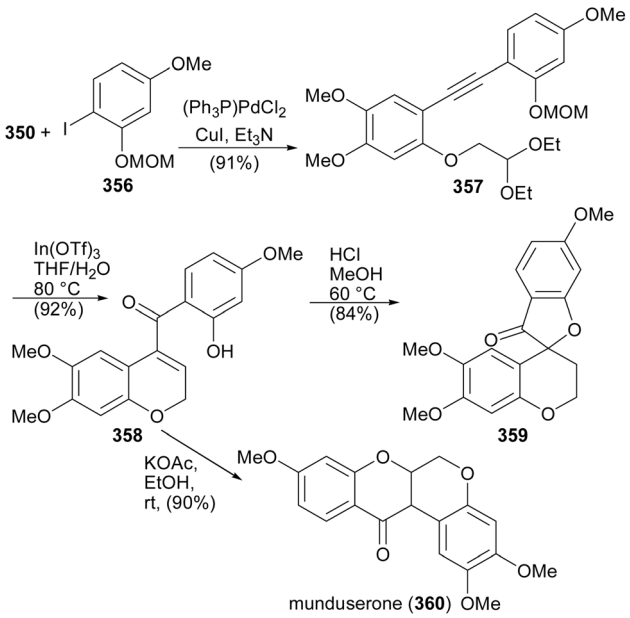


Scheme 48 Total syntheses of rotenonone (**346**) and 6-oxo-6a,12a-dehydrodeguelin (**349**).

Nayak and Kim synthesised (±)-deguelin (**355**) and (±)-munduserone (**360**) by utilising benzoylchromenes as key intermediates (Schemes 49 and 50).[47] The successful approach to the synthesis of (±)-deguelin (**355**) involved Sonogashira coupling of alkyne **350** with iodochromene **352** to give a diarylalkyne **353**. Different conditions were evaluated for the intramolecular alkyne carbonyl metathesis of **353** leading to acyldichromene **354**. Good yields of **354** were obtained when $In(OTf)_3$, $Sc(OTf)_3$, or $Yb(OTf)_3$ were used as catalysts (Table 1). Compound **354** could be converted into



Scheme 49 Synthesis of (±)-deguelin (**355**).



Scheme 50 Total synthesis of munduserone (**360**).

(±)-deguelin (**355**) following the protocol of Pastine and Sames.[204]

Munduserone (**360**) was synthesised by the Sonogashira coupling of phenylethyne **350** with iodobenzene **356** to give diphenylacetylene **357**. The intramolecular alkyne carbonyl metathesis of **357** using $In(OTf)_3$ rendered **358**, which was converted into munduserone (**360**) by conjugate addition under basic conditions. An attempt to cyclise **358** under acidic conditions led to the formation of spirocycle **359**.

Xu and colleagues synthesised deguelin (**355**) and tephrosin (**365**) in racemic form through a protecting-group-free strategy starting from commercially available chromanone **361** and chromenecarbaldehyde **363**.[200] Conversion of **361** into iodochromene **362** followed by coupling of **362** with chromenecarbaldehyde **363** and oxidation gave a bischromene **364**. Base-catalysed oxa-Michael addition of **364** gave deguelin (**355**), which was converted into tephrosin (**365**) by Cu-catalysed hydroxylation with molecular oxygen (Scheme 51).[200,205]

5.3. Stereoselective synthesis

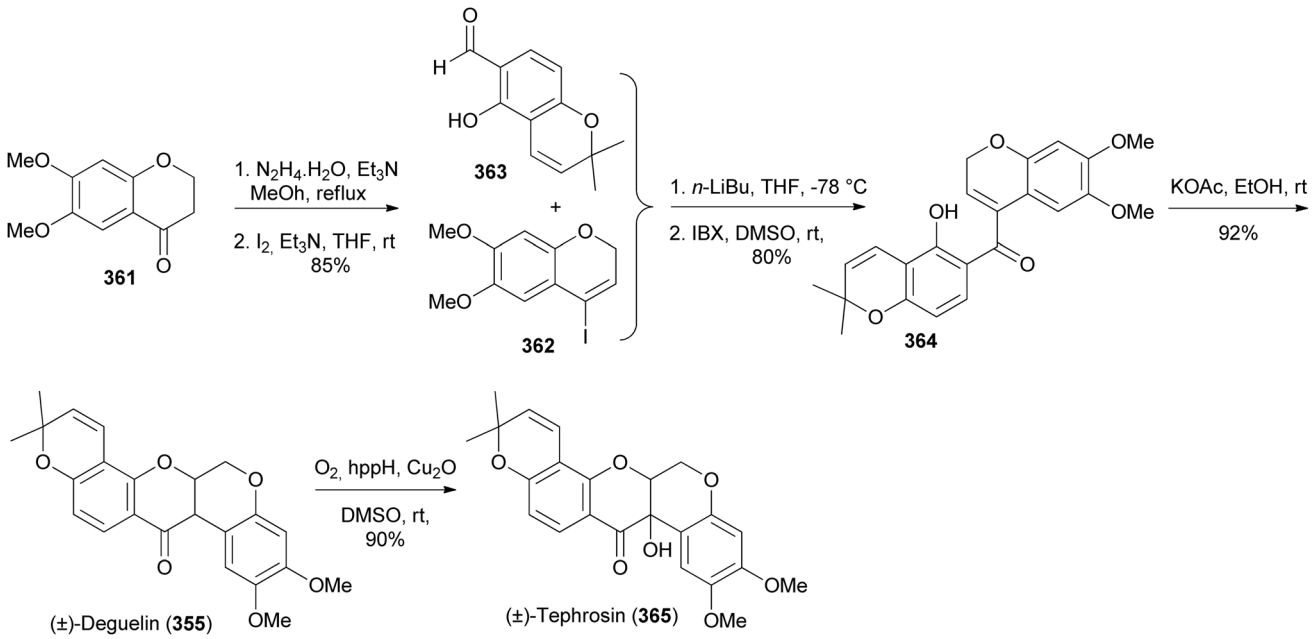
Several methods have been employed for the stereoselective synthesis of rotenoids. These include organocatalysed enantioselective synthesis,[71,72] metal-catalysed reactions using chiral ligands,[69] induction of configuration by Sharpless asymmetric hydroxylation,[202,206] the use of chiral starting materials,[65,66,203] and semisynthetic strategies starting from readily available enantiopure rotenoids.[201,207]

5.3.1 Organocatalysed stereoselective synthesis. Farmer and colleagues synthesised two enantiomers of deguelin by a thiourea-catalysed enantioselective cyclisation strategy.[71] The synthesis was initiated by preparation of ketoesters **367** and **369** starting from 2,4-dihydroxyacetophenone (**291**) and 2,4-dihydroxymethyl benzoate (**368**), respectively (Scheme 52). The coupling partner, 2-phenoxyacetaldehyde **366** was synthesised from the reaction of 3,4-dimethoxyphenol (**183**) with 2-bromodimethoxyethane followed by deprotection of the resulting acetal under mild conditions using Amberlyst-15 resin. Attempts to couple the ketoester **367** with the acetaldehyde **366** led to poor yields of **371**. Therefore, phenoxyethylmorpholine **370** was coupled to the oxopropanoate **367** leading to **371** in 26% yields. The low yields were attributed to cyclisation, leading to racemic chromanone. Stereoselective oxa-Michael addition facilitated by chiral thiourea catalysts **373** and **374** and subsequent decarboxylation gave the enantioenriched chromanones **372** in 85 : 15 and 84 : 16 er from **373** and **374**, respectively (Scheme 52). An alternative strategy was designed for the direct conversion of **367** or **369** into **372** and better yields and enantiomeric excess were obtained from **369** after optimisation of the conditions. Therefore, the complete synthesis of the deguelin enantiomers was carried out using chromanone **372** obtained from **369** in one pot. As illustrated for the synthesis of (−)-deguelin [(−)-**355**] in Scheme 53, the chromanone enantiomer (−)-**372** obtained using **373** as a catalyst was converted into a TBDMS-protected enol ether **375**, which upon oxyarylation using Snider's procedure[208] gave (−)-deguelin [(−)-**355**] in 25% yield (Scheme 53). The deguelin enantiomers were evaluated for antiproliferative activity against PC-3 (prostate), MCF-7 (breast), HepG2 (liver) and Jurkat (leukemia) cells. Both compounds showed potent inhibitory activities and

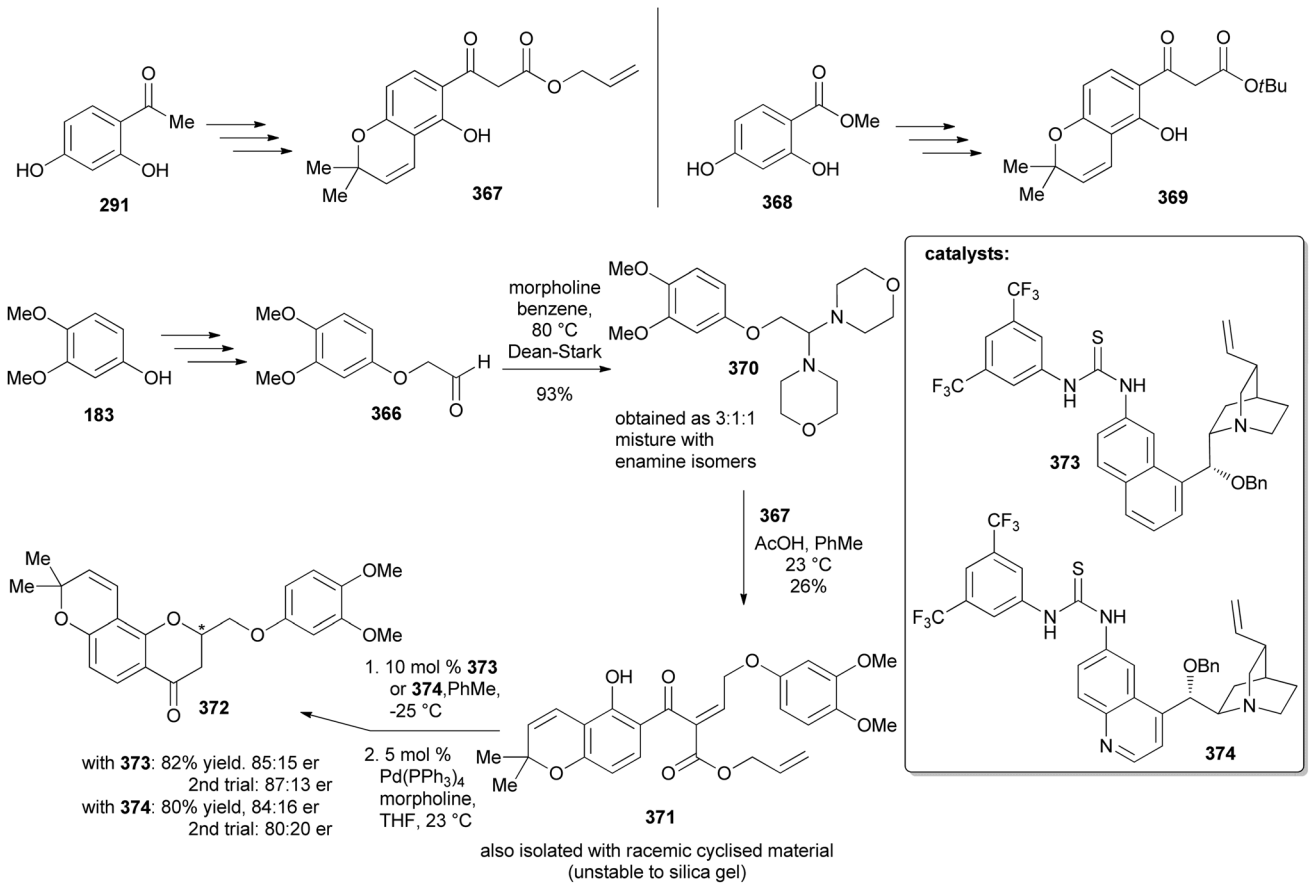
Table 1 Conditions for conversion of **353** into **354** [a]

Entry	Catalyst (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	HCO_2H	[c]	100	12	nr
2	$InCl_3$ (1.0)	THF/H_2O (4 : 1)	80	12	nr
3	TFA·HCl	DCM	80	16	[d]
4	$FeCl_3$ (1.0)	THF/H_2O (4 : 1)	80	16	[d]
5	$In(OTf)_3$ (1.0)	THF/H_2O (4 : 1)	80	12	94
6	$In(OTf)_3$ (0.4)	THF/H_2O (4 : 1)	80	36	93.5
7	$In(OTf)_3$ (0.2)	THF/H_2O (4 : 1)	80	48	84.6
8	$Cu(OTf)_3$ (0.4)	THF/H_2O (4 : 1)	80	36	34
9	$Sc(OTf)_3$ (0.4)	THF/H_2O (4 : 1)	80	36	83
10	$Yb(OTf)_3$ (0.4)	THF/H_2O (4 : 1)	80	36	82

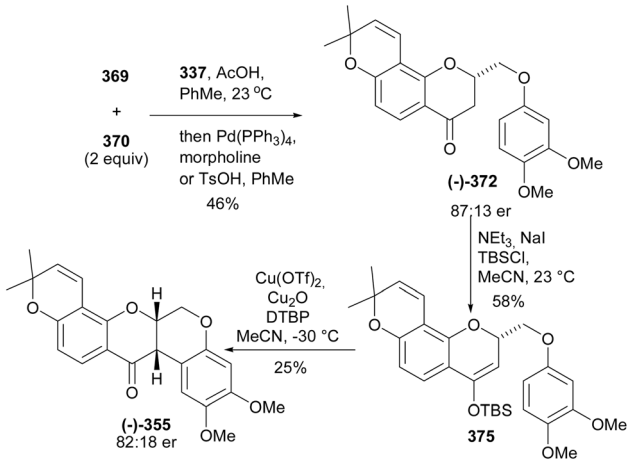
[a] A mixture of **354** (0.1 mmol) and catalyst in solvent (1 mL) was heated at the temperature indicated above. [b] Isolated yield (%). [c] HCO_2H was used as solvent. [d] A complex mixture.



Scheme 51 Total syntheses of (±)-deguelin (355) and (±)-tephrosin (365).



Scheme 52 Synthesis of enantioenriched chromanone precursors 372.



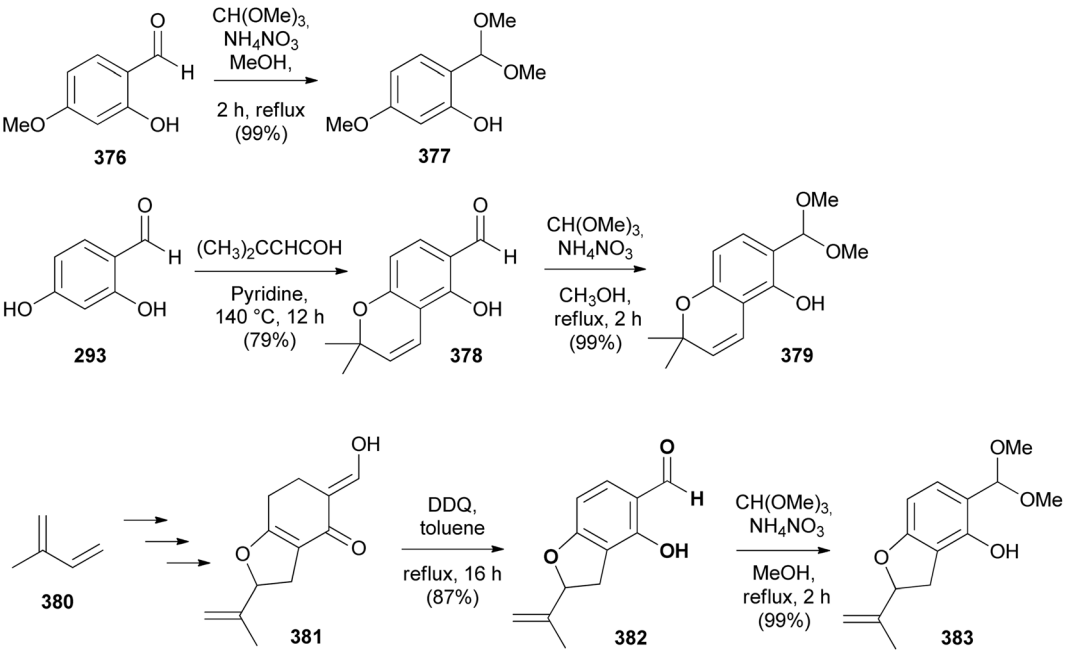
Scheme 53 Complete synthesis of (−)-deguelin [(−)-**355**].

(+)-deguelin inhibited the growth of the MCF-7 and HepG2 cell lines more effectively than the natural enantiomer (−)-deguelin [(−)-**355**] (IC_{50} = 4.64 ± 1.33 μM and 0.90 ± 0.29 μM, for (+)-deguelin; and 10.59 ± 1.38 μM and 2.95 ± 1.19 μM, for (−)-deguelin, respectively).

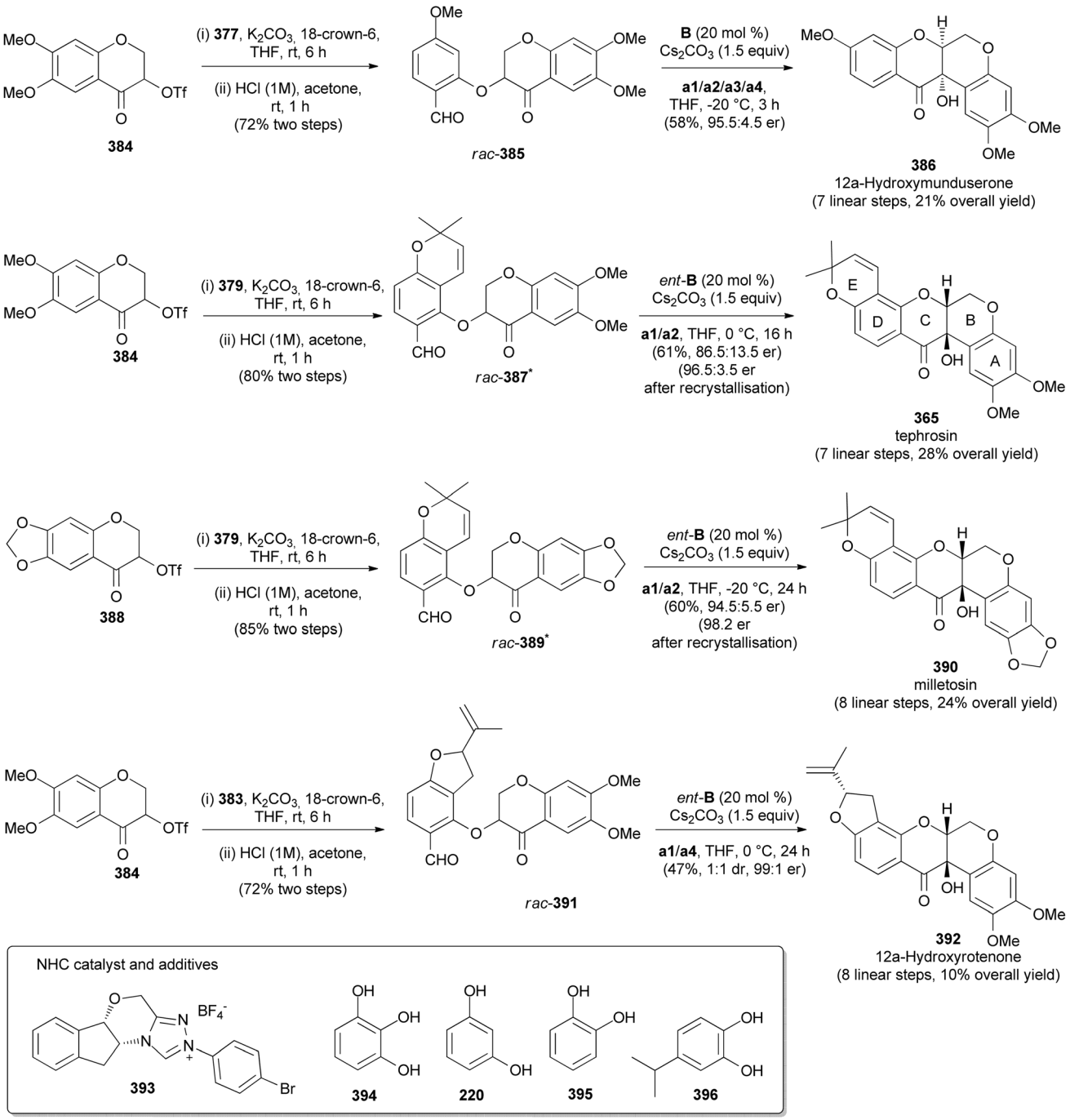
Fang's group reported the stereoselective total synthesis of several rotenoids, including 12a-hydroxymunduserone (**386**), tephrosin (**365**), milletosin (**390**), and 12a-hydroxyrotenone (**392**) by N-heterocyclic carbene (NHC) catalysis with dynamic kinetic resolution.[72] Taking advantage of the similarity of the substitution patterns in the A and D rings, all the compounds were synthesised by a combination of dimethylacetals **377**, **379**, and **383** and chromanone-3-triflates **384** and **388** (Schemes 54 and 55). Compounds **377**, **379**, and **383** were prepared by acetyl protection of **376**, **378** and **382**, respectively. Compound **378** was in turn synthesised by condensation of 2,4-dihydroxybenzaldehyde (**293**) with prenal, while **382** was obtained by aromatisation of enol **381**, prepared in a sequence of steps from isoprene **380** (Scheme 54). Coupling of chromanones and phenols **377** and **384**; **379** and **384**; **379** and **388**; and **383** and **384** followed by deprotection gave racemic aryl ethers **385**, **387**, **389**, and **391**, respectively, which upon treatment with $CsCO_3$ in the presence of chiral NHC catalyst **393** rendered **386**, **365**, **390**, and **392**, respectively with good enantiomeric excess (Scheme 55). Compound **392** was obtained together with its diastereoisomer. In addition, deguelin (**355**) and rotenone (**406**) could be synthesised from tephrosin (**365**) and 12a-hydroxyrotenone (**392**), respectively, following the established procedures.[72]

5.3.2 Chiral ligands. In 2017, De Koning's group reported the stereoselective total synthesis of rotenone (**406**) and the synthesis of munduserone in racemic form. The chiral dihydrobenzofuran **398**, prepared by Pd-catalysed oxyarylation of **397** in the presence of the *R*,*R*′-Trost ligand **399** was used as a key building block for the stereoselective synthesis of rotenone (**406**), Scheme 56.[69,209] The benzofuran **398** was converted into aldehyde **400** and methylated to give **401**. A coupling of **401** with **285** gave alkyne **402**, which was oxidised to give **403**. Pt-catalysed hydroarylation and subsequent demethylation of **404** rendered **405**. The final step involved intramolecular conjugate addition to give rotenone (**406**) and its quasi-enantiomer **407**, which were separable (Scheme 57).

5.3.3 Chiral pool strategy. Ohmori and Suzuki's group reported the stereoselective total syntheses of (−)-rotenone [(−)-**406**] and (−)-dalpanol [(−)-**429**] that featured 1,2-aryl migration and triple S_NAr *O*-cyclisation for the construction of the furanyl E-ring and two fused pyranyl C- and B-ring systems with the requisite stereogenicity.[66] The synthesis was initiated by preparation of the chiral benzofuranyl unit **412**, by

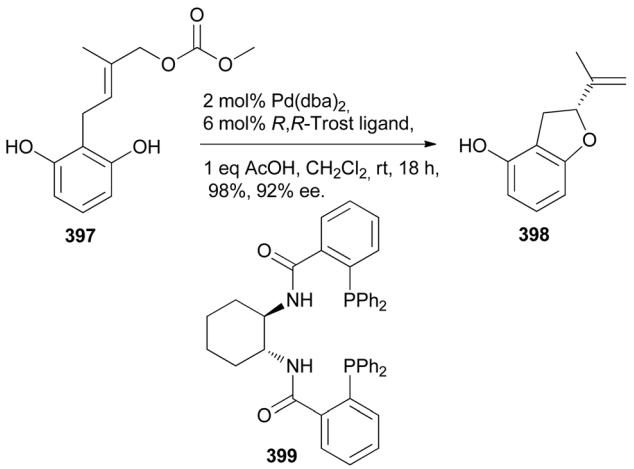


Scheme 54 Synthesis of acetal precursors **377**, **379**, and **383**.



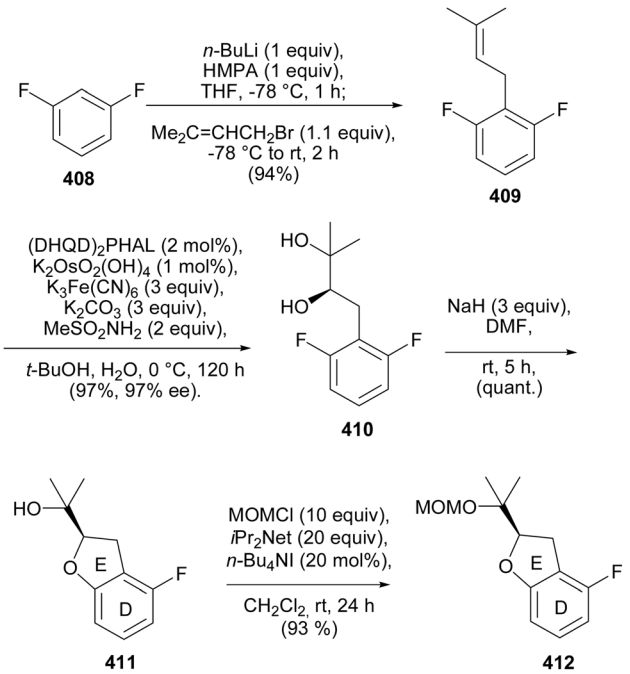
Scheme 55 NHC-catalysed stereoselective synthesis of rotenoids.

prenylation of difluorobenzene **408** to afford **409**, followed by asymmetric Sharpless dihydroxylation[210] and nucleophilic aromatic substitution of the resulting (*R*)-diol **410** to give the benzofuran **411**, which was protected with a MOM group (Scheme 58). The reaction of the lithiated species of **412** with chiral epoxy amide **413** gave **414**. Bromine–lithium exchange of **415** and nucleophilic addition to **414** rendered a diaryl epoxy alcohol **416**. A $BF_3 \cdot OEt_2$-catalysed 1,2-aryl shift followed by reduction and protection of the diol **418** gave **419**. However, **418** was the untargeted intermediate that resulted from the migration of the benzofuranyl (DE) ring instead of the A-ring (Scheme 59). As a result, the sequence of assembly of substrates was altered as shown in Scheme 60. Coupling of epoxy amide **413** with the lithiated **415** gave **420**, which was reacted with the lithium reagent of **412** to give epoxy alcohol **421**. A 1,2-aryl shift followed by reduction gave diol **422** as a single isomer, confirmed by extensive NMR data analysis. The final steps involved diol protection, TBS deprotection, and oxycyclisation to give **423**, **424**, and **425**, respectively. The oxycyclisation conditions are shown in Table 2. Acetal deprotection



Scheme 56 Stereoselective synthesis of the dihydrobenzofuran **398** moiety.

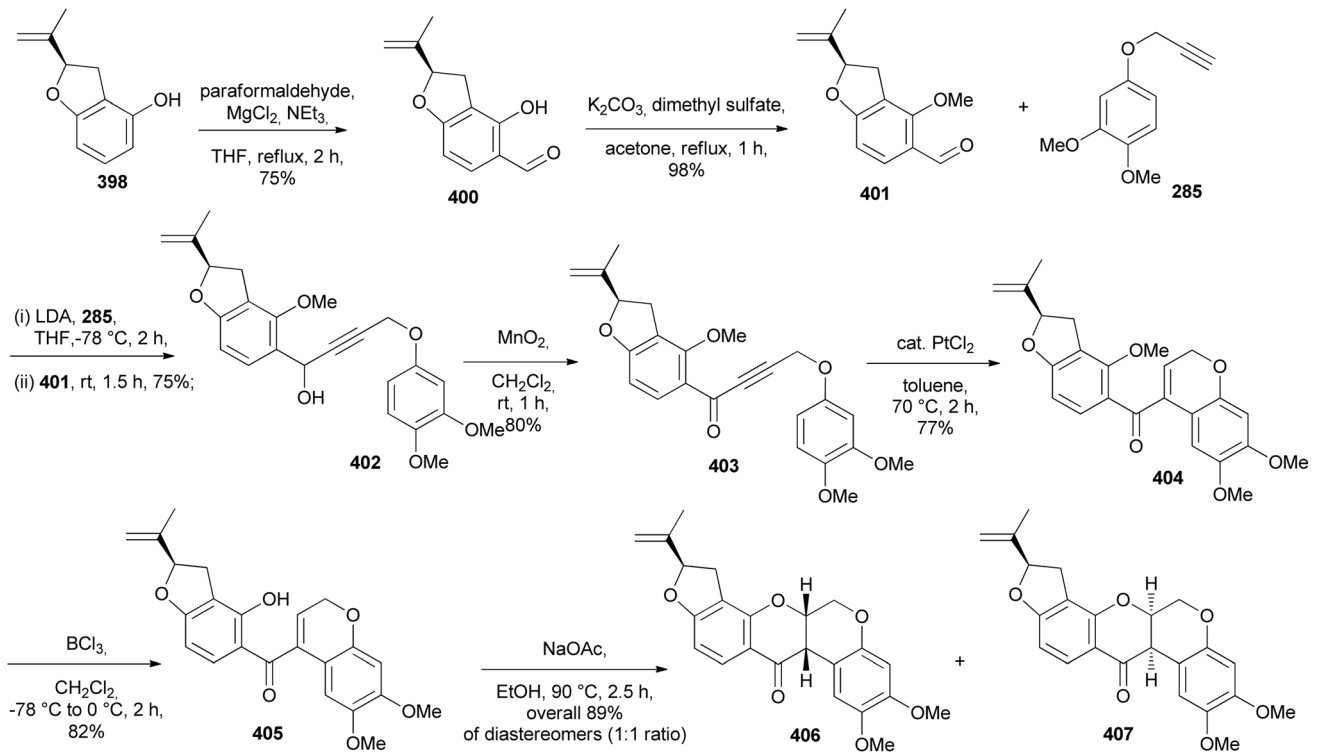
of **425** and subsequent *O*-cyclisation of the resulting **426** gave **427**. Cleavage of the MPM group of **427** followed by oxidation and MOM deprotection gave (−)-dalpanol [(−)-**429**], which was dehydrated to give (−)-rotenone [(−)-**406**] (Scheme 61).[66]



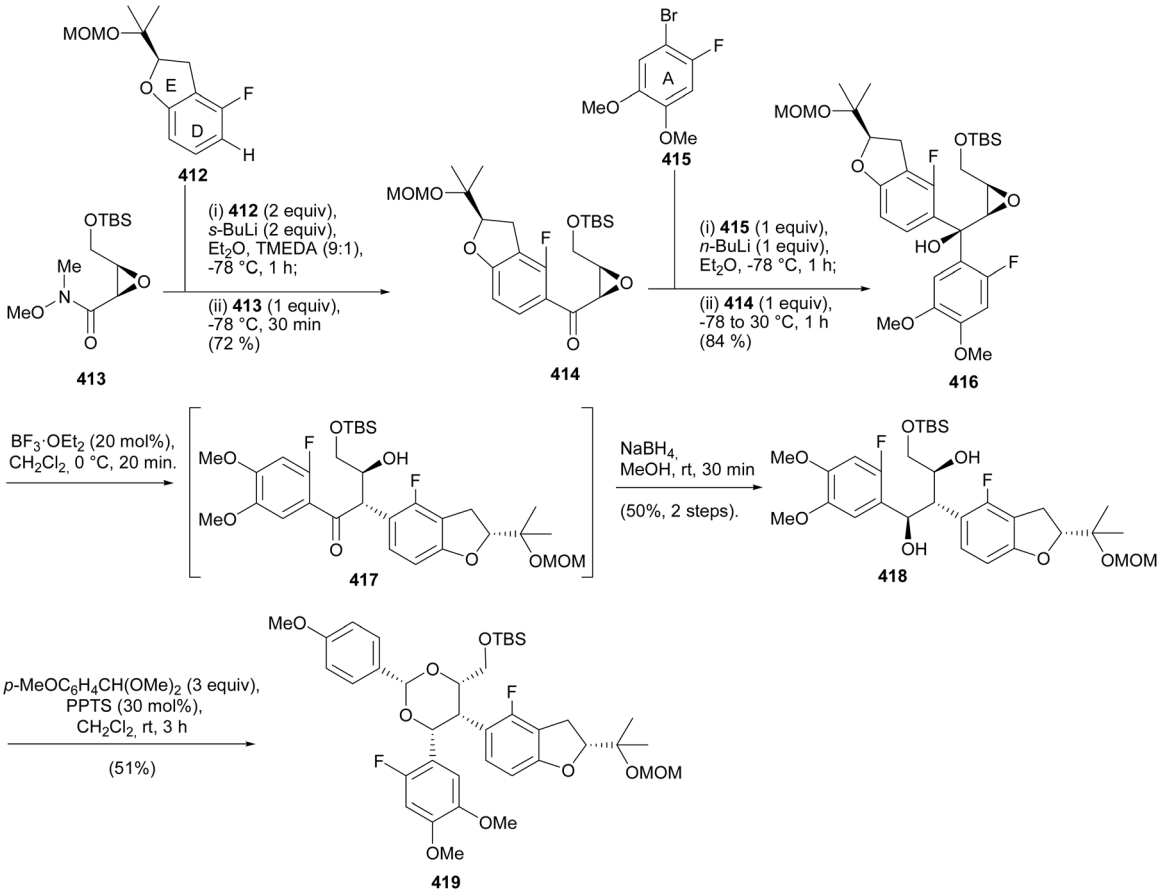
Scheme 58 Synthesis of the DE-ring fragment **412**.

6. Synthesis of coumaronochromones

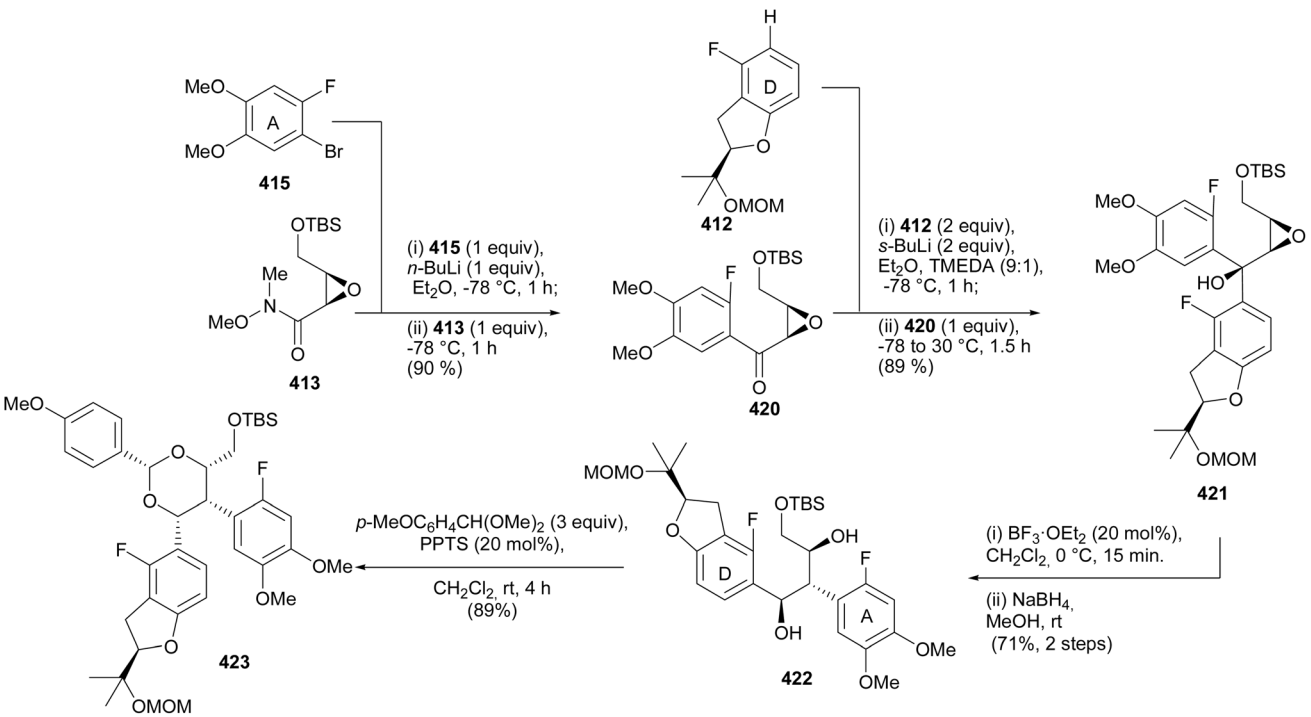
Coumaronochromones constitute a rare subclass of isoflavonoids.[3] They have been determined to exhibit biological activities that include anti-HIV,[211] immunosuppressive,[212] cytotoxicity against cancer cells[213] and anti-neuroinflammatory.[214] A few synthetic strategies have been developed for coumaronochromones[62,215–218] and the most widely employed procedure involves oxidative cyclisation of 2′-hydroxyisoflavones.[217–221]



Scheme 57 Synthesis of rotenone (**406**).



Scheme 59 Synthesis of the epoxy alcohol **416** and the first attempted 1,2-shift-reduction sequence.



Scheme 60 Synthesis of the epoxy alcohol **421** from altered sequence of precursors and 1,2-aryl migration.

Table 2 Conditions for the conversion of 424 into 425

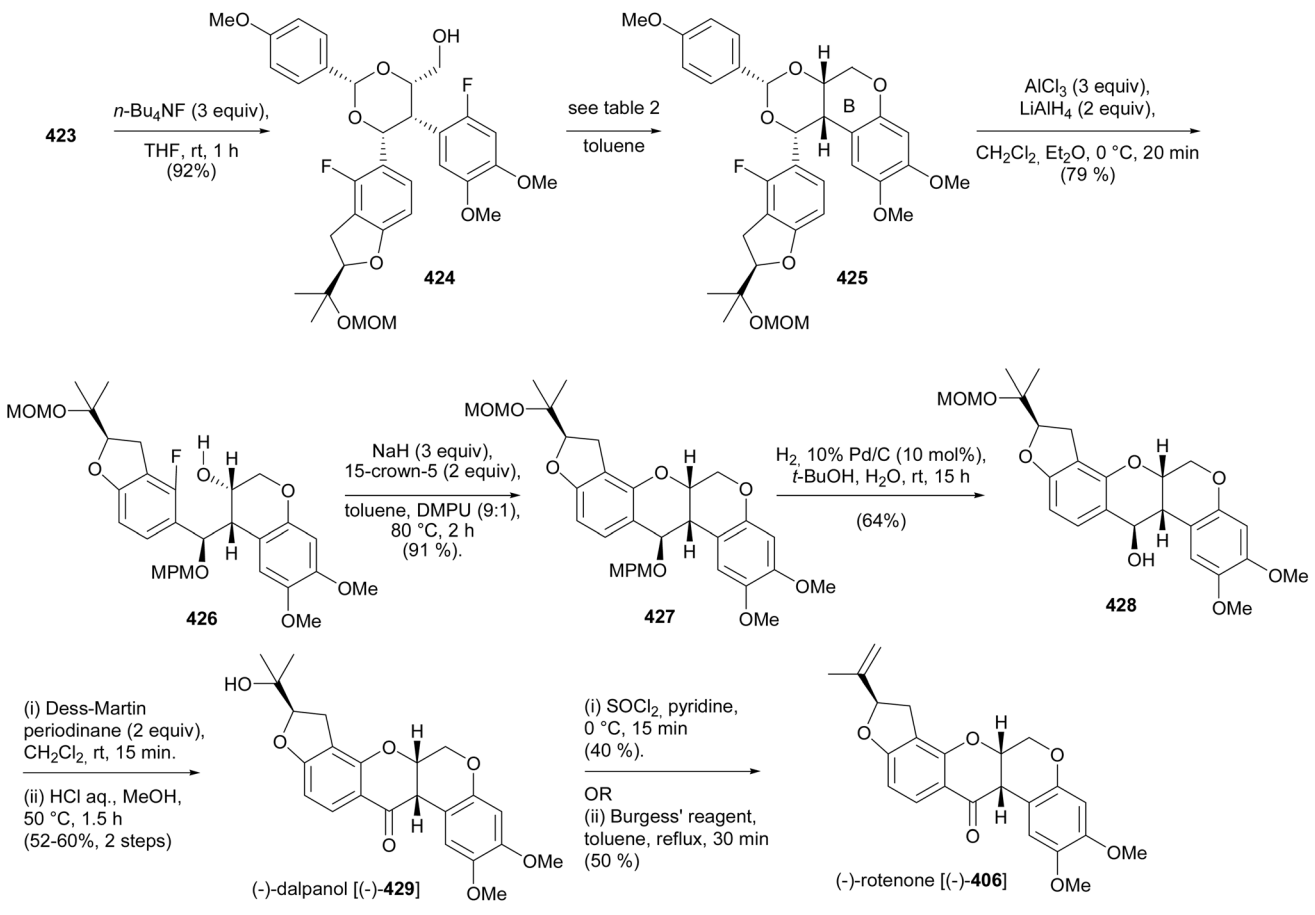
Run	Base	Additive	Temperature	Yield of 425
1	KH	18-Crown-6, DMPU	80 °C	46% (8%)[a]
2	*t*-BuOK	_	Reflux	12% (52%)[a]
3	*t*-BuOK	$Ni(cod)_2$,[b] PCy_3[c]	Reflux	86%

[a] Recovery of 424. [b] 10 mol%. [c] 30 mol%.

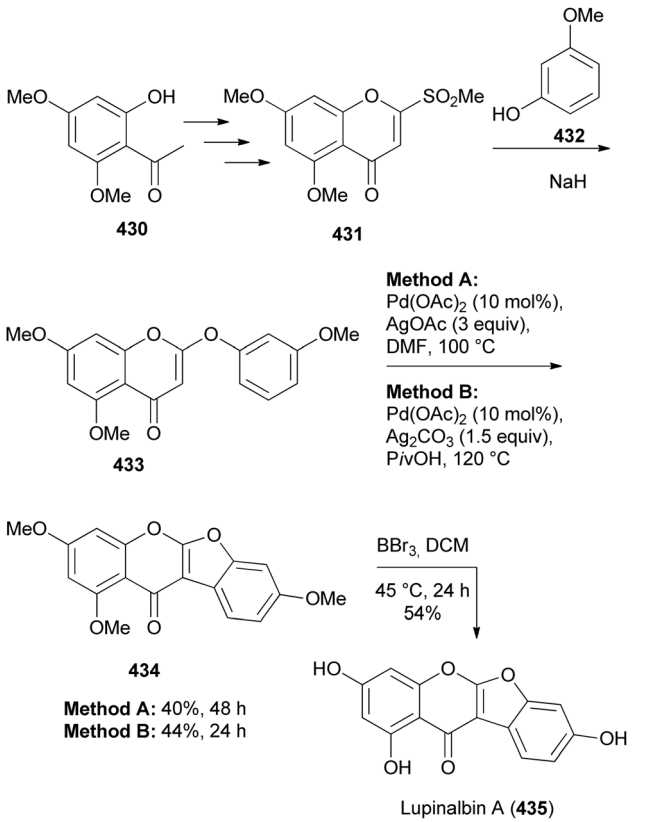
Recently, Gu and co-workers developed a method for the synthesis of coumaronochromones by direct oxidative double C–H activation of 2-phenoxychromones using palladium catalyst and silver oxidants.[62] The application of the method was demonstrated in the synthesis of a natural coumaronochromone, lupinalbin A (435). Cross dehydrogenative coupling of phenoxychromone 433 using $Pd(OAc)_2$ with AgOAc or Ag_2CO_3 gave trimethoxycoumaronochromone 434 in 40–44% yield, which was demethylated using BBr_3 to give lupinalbin A (435) in 54% yield (Scheme 62). The phenoxychromone 433 was prepared by displacement of the sulfonyl group in 2-methylsulfonyl-4*H*-4-chromenone 431 by 3-methoxyphenol (432), which was in turn synthesised from 2-hydroxyacetophenone 430.[62,222]

Lee and co-workers isolated a coumaronochromone, antiboeravinone Y (441) with antisepsis properties from *Abronia nana* suspension cultures.[221] The structure of 441 was confirmed by synthesis that involved the preparation of isoflavone 439 by the Suzuki–Miyaura reaction of chromone 437 with boronic acid 438, demethylation and oxidative cyclisation of the 2′-hydroxyisoflavone 440 with DDQ (Scheme 63). The oxidative cyclisation step was however low-yielding.[221]

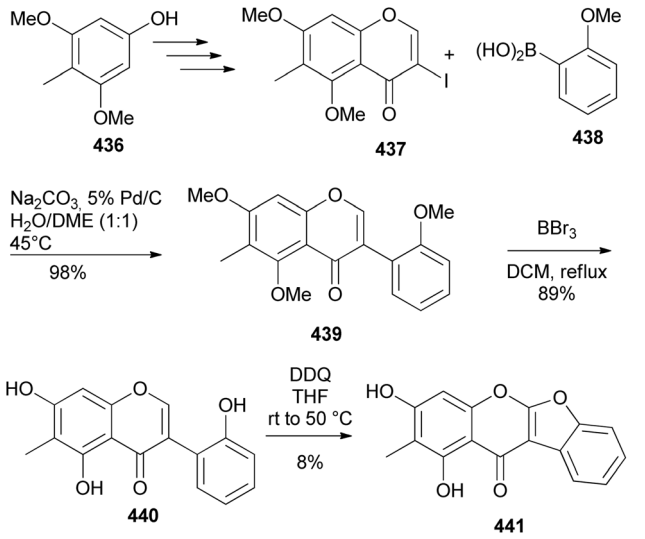
Hirtellanine A (5) was isolated from *Campylotropis hirtella* (Franch.).[212] It strongly inhibited proliferation of concanavalin A-induced T-cells (IC_{50} = 0.92 μM) and lipopolysaccharide-induced B-cell splenocytes (IC_{50} = 0.06 μM), and showed low cytotoxicity on splenic lymphocytes (CC_{50} = 3.03 μM).[212] The synthesis of hirtellanine A (5) was reported by Zheng and Shen in 2010.[32] The first synthesis involved the Suzuki–Miyaura reaction for the construction of the isoflavone, followed by oxidative deprotection to give an isoflavonequinone, and acid-mediated *O*-cyclisation.[32] Another synthesis route, based on the deoxybenzoin intermediate was reported in 2013.[45] Paramount to the total synthesis, was regioselective installation of the dimethylpyran scaffold that was achieved by *O*-allylation of isoflavone 442 to give 443 followed by Claisen rearrangement to afford pyranoisoflavone 444. Several conditions were screened for the Claisen rearrangement, and optimum conditions that



Scheme 61 Stereoselective total synthesis of (−)-rotenone [(−)-406] and (−)-dalpanol [(−)-429].



Scheme 62 Synthesis of lupinalbin A (**435**).



Scheme 63 Confirmation of the structure of antiboeravinone Y (**441**).

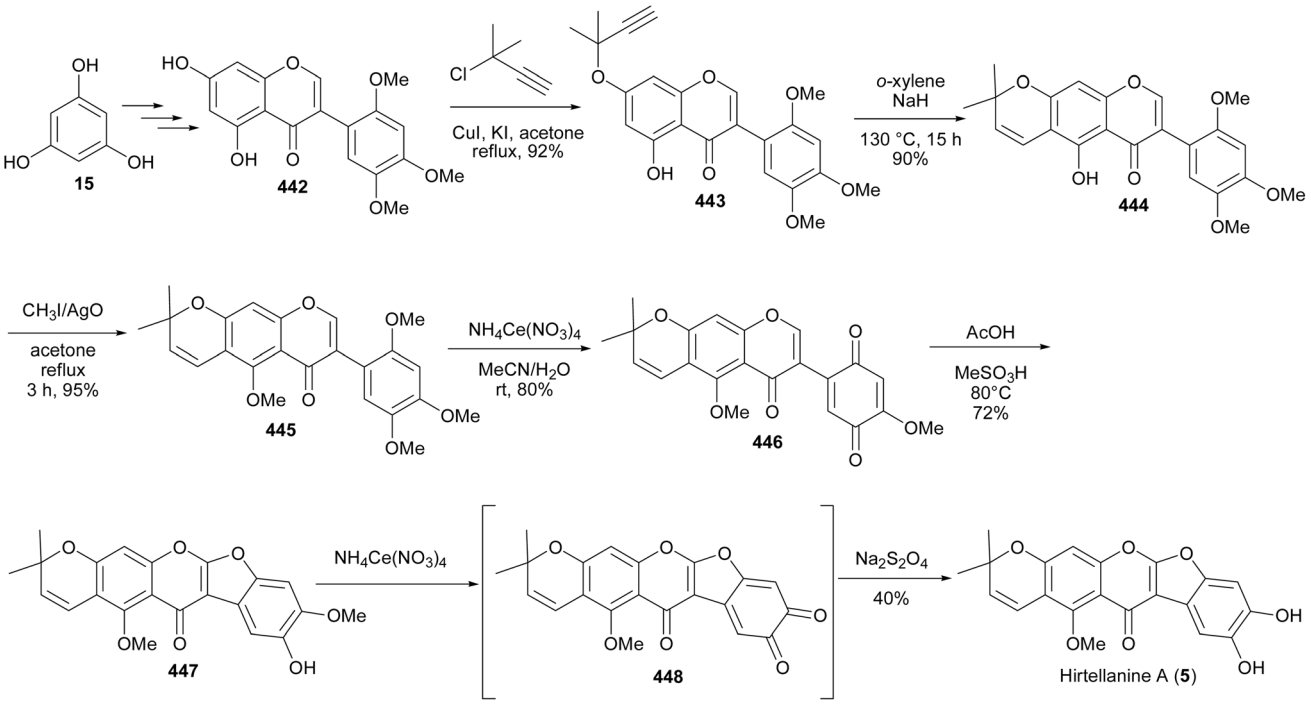
yielded the linear chromene isomer **444** in excellent yields were when xylene was used with NaH as a base at 130 °C. Methylation of the 5-hydroxy group followed by oxidative demethylation of **445** using CAN afforded an isoflavonequinone **446**, which was cyclised under acidic conditions to give the coumaronochromone **447**. The last steps involved the second oxidative deprotection and reduction to give the target compound, hirtellanine A (**5**), Scheme 64.[45]

7. Synthesis of isoflavenes and 3-arylcoumarins

Isoflavenes are synthesised by strategies that include ring-closing metathesis,[223,224] conjugate addition of phenyllithium to chromenesulphones followed by elimination of sulphonyl benzene,[225] reduction of 2-morpholinoisoflav-3-ene precursors,[226] and Suzuki–Miyaura coupling of halochromenes with boronic acids,[161] they serve as synthetic precursors to other isoflavonoid compounds that include 3-arylcoumarins, isoflavans, pterocarpans, and complex isoflavonoids.[153,161,224]

The 3-arylcoumarin, santalin AC (**453**) and isoflavene-bearing condensed derivatives, santalins and santarubins were synthesised by Strych and colleagues.[227,228] Santalins and santarubins are chemical entities that belong to the red sandalwood (*Pterocarpus santalinus* tree and related species). They were first isolated by Pelletier in the early 1800's and due to their complex structures, their structural elucidation remained an unfinished quest.[227–232] In the early 1970's, studies towards the elucidation of santalins and santarubins attracted attention as the structures for santalin A (**449**) and B (**450**) were proposed. The structural elucidation of compounds **449** and **450** was later established by Arnone *et al.* in 1975.[232] Although the structures of santalins A (**449**), B (**450**) and santarubins A (**451**), B (**452**) share a similar core (Fig. 4), they have different hydroxylation, methylation, oxidation, and substitution patterns and these features made it impossible for many years to properly elucidate the structures of these compounds. For example, the phenyl substituent at C-5 for santalin A (**449**) bears the resorcinol substitution pattern and the phenyl substituent at C-5 for santarubin A (**451**) features the catechol substitution pattern. Interestingly, a contrasting substitution pattern of the benzyl substituent is observed for both structures at C-6.[233] The structural assignments of these compounds were made possible by improving the sensitivity of the NMR and X-ray crystallography machines. In 1995, Kinjo *et al.* isolated and elucidated the structures of a simple isoflavonoid santalin AC (**453**), which is a coumarin and that of a yellow pigment santalin Y (**454**), which is a rather complex structure from red sandalwood, Fig. 4.[234]

The advent of santalin AC (**453**) and santalin Y (**454**) made it possible to propose the biosynthetic route for santalins and santarubins. The proposed biosynthetic route places the isoflavylium as the central core structure for obtaining the santalins and santarubins.[227,234] Satalin Y (**454**) is a racemic natural product that exhibits a unique [6,6,6,5]-oxafenestrane framework that is comprised of a catechol ring as well as pyrogallol and resorcinol moieties that are partially methylated. Following the synthesis of santalins A (**449**), B (**450**), and santarubins A (**451**), B (**452**),[227] Strych *et al.* reported a biomimetic total synthesis of santalin Y (**454**).[228] The synthesis started by first preparing the isoflavylium **463** and anhydrobase base **464** in seven and eight linear steps from malic acid (**456**) and 1,2,4-triacetoxybenzene (**455**) (Scheme 65). Thus, the union of **455**



Scheme 64 Total synthesis of hirtellanine A (**5**).

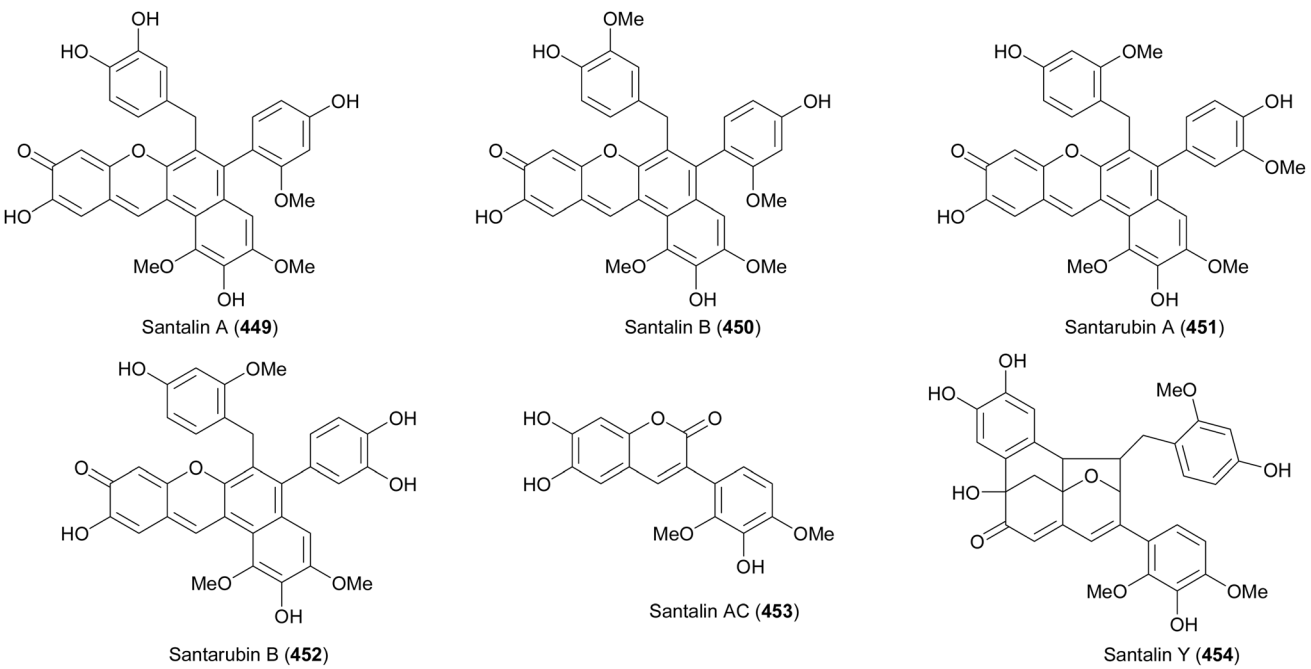
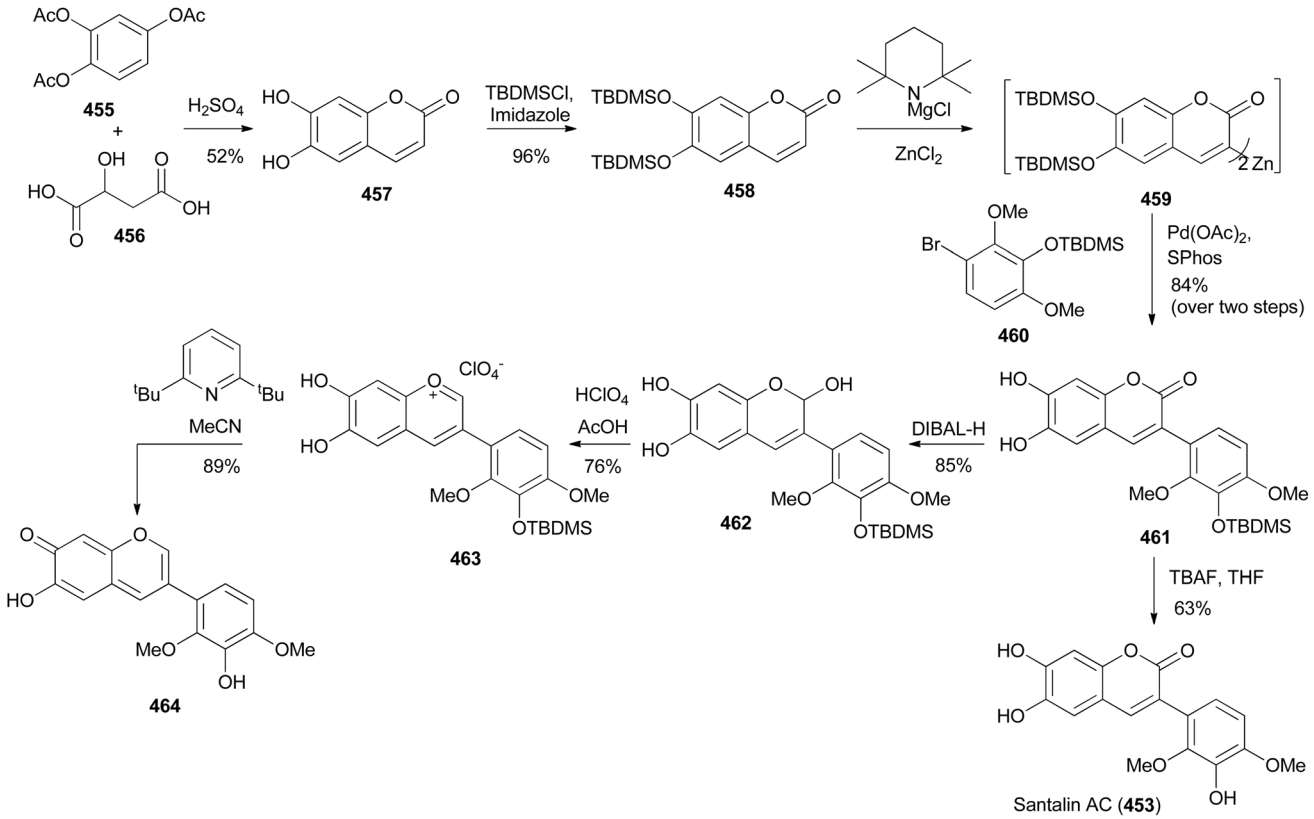
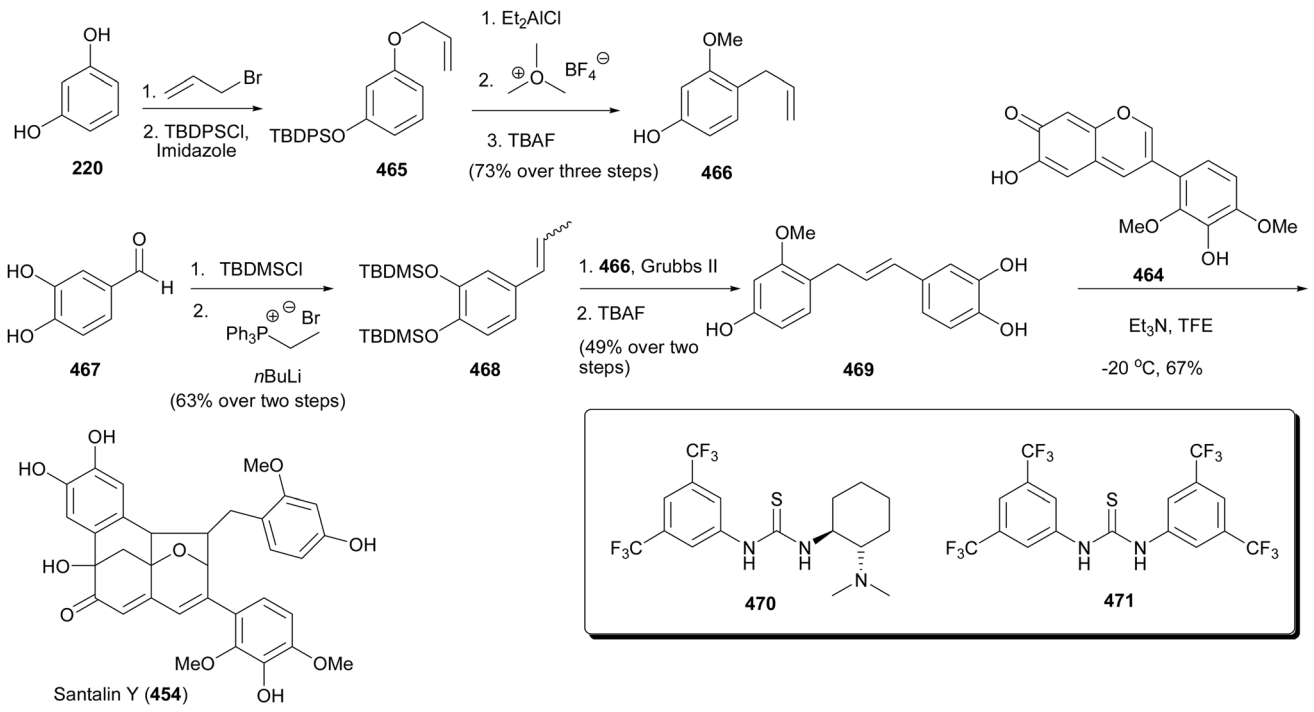


Fig. 4 Structures for santalins and santarubins.

and **456** under acid-catalysed conditions gave coumarin **457** (52%), which was subsequently subjected to TBDMS protection to afford compound **458** in 96% yield. The key step utilised to synthesise **463** and **464** was the zinc-mediated Negishi-coupling reaction developed by the group of Prof. Knochel.[57,227,228,235] Therefore, the zincation of **458** delivered intermediate **459** that was subjected to Negishi-cross coupling reaction with aryl bromide **460** to afford the isoflavonoid derivative **461.** The silyl deprotection of isoflavonoids **461** gave access to santalin AC (**453**). Reduction of **461** with DIBAL-H afforded lactol **462** and subsequent protonation and dehydration of lactol **462** using acetic acid and perchloric acid rendered isoflavylium **463** in a 76% yield. Finally, the deprotonation of **463** with non-nucleophilic base afforded anhydrobase **464.**



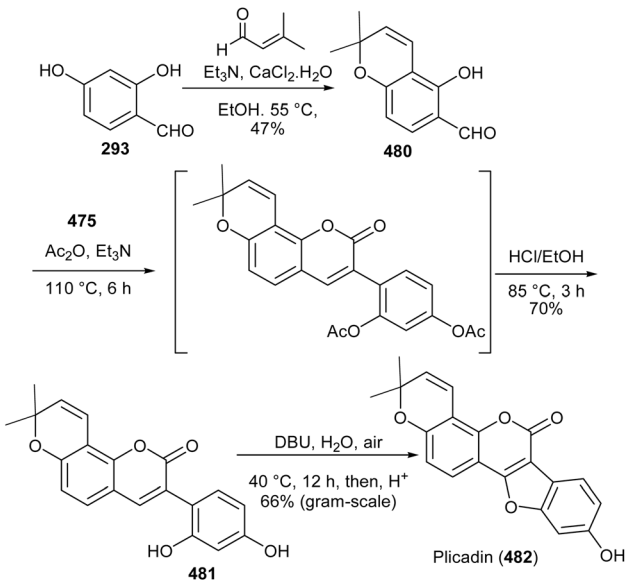
Scheme 65 Synthesis of intermediate isoflavylium **463**, anhydrobase **464**, and santalin AC (**453**).



Scheme 66 Biomimetic synthesis of santalin Y (**454**).

The sequential monoallylation of resorcinol (**220**), protection of the hydroxy group by the silyl group, Lewis acid-catalysed Claisen rearrangement of **465**, mild methylation with MeO_3BF_4, and subsequent desilylation afforded the allylresorcinol **466** in a 73% overall yield from four synthesis steps. The styrene **468** which is a coupling partner of allylresorcinol

466 was synthesised in two steps from 3,4-dihydroxybenzaldehyde (**467**) by silyl protection of the hydroxy groups and subsequent Wittig olefination.[227,228] Therefore, with the successful synthesis of allylresorcinol **466** and styrene **468**, the intermediate benzylstyrene **469** was synthesised employing olefin cross metathesis (Scheme 66). Thus, the union of anhydrobase **464** with benzylstyrene **469** while utilising Et_3N as a base in trifluoroethanol led to the formation of santalin Y (**454**) in 67% isolatable yields. This reaction proceeds through the concerted oxidopyrylium [2 + 3]-cycloaddition reaction and subsequent *in situ* Friedel–Crafts alkylation facilitated by the keto–enol tautomerisation and activation of the carbonyl functionality by the Brønsted base. It is important to mention that these reactions were happening asynchronously as confirmed by the computations done to model the reaction sequence. The use of bifunctional organocatalysts **470** (Takemoto catalyst) and **471** (Shreiner's catalyst) provided moderate to no formation of santalin Y (**454**). Interestingly, when Takemoto's catalyst **470** was used in conjunction with Et_3N santalin Y(**454**) was obtained in 45% yield and Shreiner's catalyst did not work at all.[228]



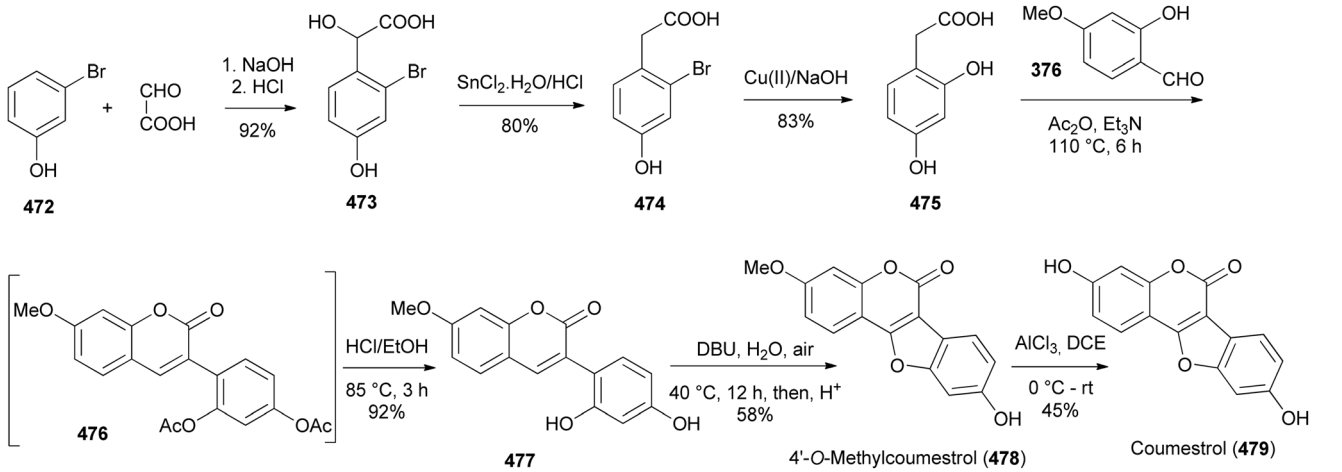
Scheme 68 Synthesis of plicadin (**482**).

8. Synthesis of coumestans

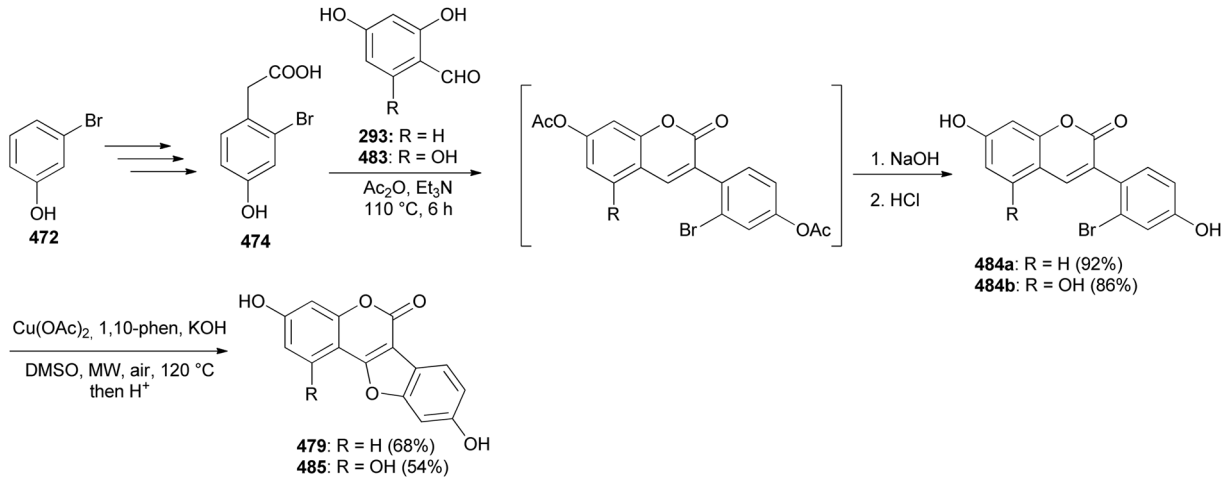
Coumestans are tetracyclic isoflavonoids characterised by fused coumarin and benzofuran ring systems. They have mainly been isolated from the Leguminosae and Asteraceae families,[21,236,237] and have been reported to exhibit anticancer,[238,239] antiarthritic,[28] immunosuppressive,[240] anti-inflammatory,[241] anti-snake-venom,[242] antiosteoporsis,[42] estrogenic,[243] and other activities.[21] Several synthetic strategies have been developed for the coumestan scaffold and their applications have been demonstrated on the synthesis natural coumestans that include coumestrol,[236,237,244] 4′-*O*-methylcoumestrol,[237,244,245] flemichapparin C,[245,246] medicagol,[245] aureol,[236] wedelolactone,[247] plicadin,[237,248] hirtellanine B[54] and lespeflorin I_1.[249] The coumestans have mainly been constructed from 3-arylcoumarin,[236,237,244,245,250] 4-phenoxycoumarin,[63,64] 4-hydroxycoumarin[54,246,251,252] and benzofuran precursors.[247,248,253,254] Other strategies involved oxidative rearrangement of chalcones and intramolecular cyclisation of oxodiphenylpropanoate.[43,249]

8.1. Synthesis from 3-arylcoumarin precursors

Coumestans have been synthesised by oxidative coupling of 2′-hydroxy-3-arylcoumarins using reagents that include $Pb(OAc)_4$,[255] DDQ,[256] $PdCl_2$,[257] I_2 (ref. 258) and $Cu(OAc)_2$.[244,245] Recently, Yan and colleagues developed a method for the synthesis of coumestans using DBU as a catalyst and applied it to the synthesis of 4′-*O*-methylcoumestrol (**478**), coumestrol (**479**), and plicadin (**482**).[237] The reaction is postulated to proceed *via* dehydrogenation and oxa-Michael addition. The syntheses of the compounds are shown in Schemes 67 and 68. The reaction of 3-bromophenol **472** with oxoacetic acid gave 4-hydroxyphenylglycolic acid **473**, which was reduced and hydroxylated to give phenylacetic acids **474** and **475**,



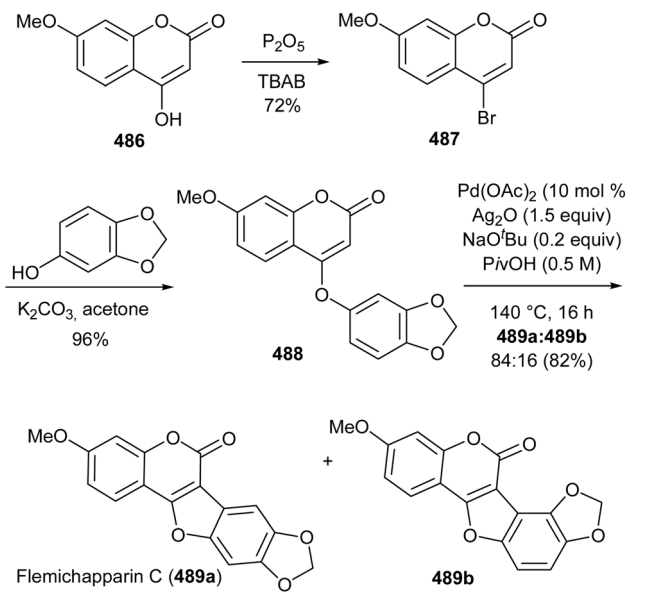
Scheme 67 Synthesis of 4′-*O*-methylcoumestrol (**478**) and coumestrol (**479**).



Scheme 69 Synthesis of coumestrol (**479**) and aureol (**485**).

respectively. Perkin condensation of **475** with 2-hydroxy-4-methoxybenzaldehyde (**376**), followed by deacetylation gave 3-phenylcoumarin **477**. Treatment of **477** with DBU rendered 4′-*O*-methylcoumestrol (**478**), which upon demethylation afforded coumestrol (**479**), Scheme 67. Similarly, plicadin (**482**) was synthesised by BDU-catalysed cyclisation of 2′,4′-dihydroxy-3-phenylcoumarin **481**, which was in turn prepared by Perkin condensation of pyranobenzaldehyde **480** with phenylacetic acid **475**. Compound **480** was synthesised by condensation of benzaldehyde **293** with prenal, Scheme 68.[237]

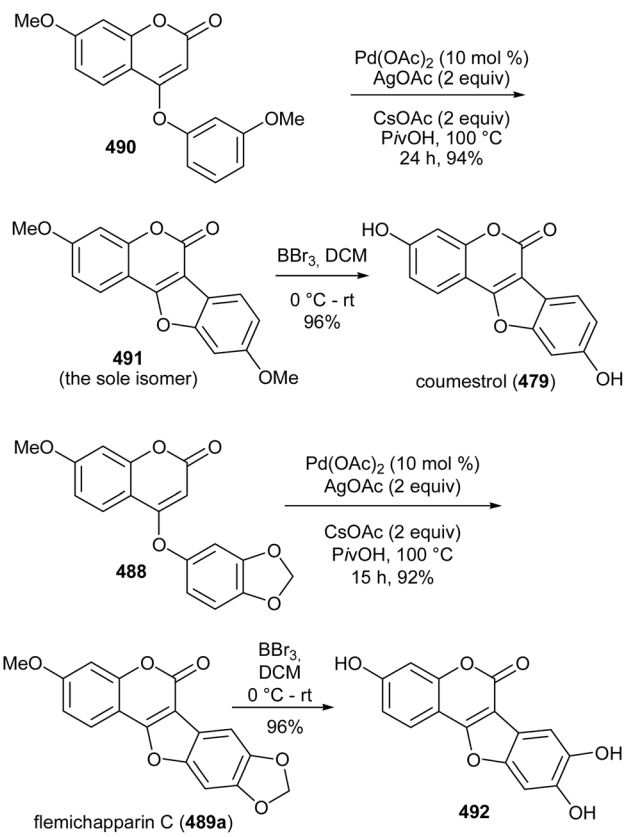
Alternative to 2′-hydroxy-3-arylcoumarin precursors, Sheng and co-workers synthesised coumestrol (**479**) and aureol (**485**) by a one-pot Cu(II)-catalysed hydroxylation and oxidative coupling of 2′-bromo-3-arylcoumarins **484a** and **484b**, which were obtained by Perkin condensation of benzaldehydes **293** and **483** with bromophenylacetic acid **474**. Bromophenylacetic acid **474** was derived from 3-bromophenol (**472**), Scheme 69.[236]



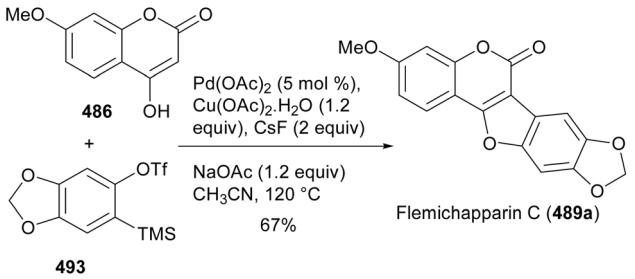
Scheme 70 Synthesis of flemichapparin C (**489a**).

8.2. Synthesis from 4-hydroxy- and 4-phenoxycoumarins precursors

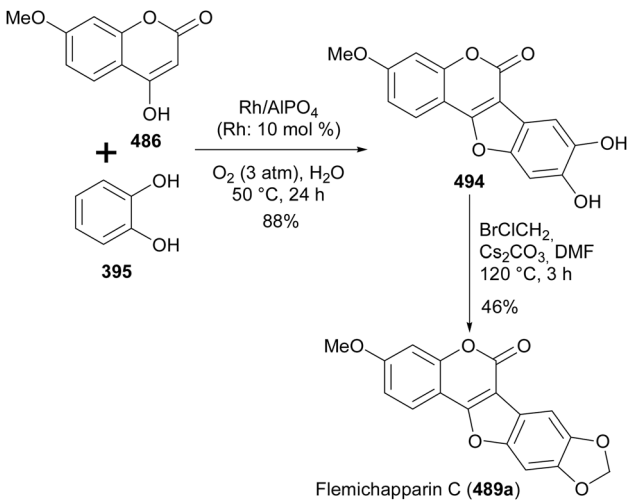
Examples of methods used for the synthesis of coumestans that proceed through the 4-hydroxy- and 4-phenoxycoumarin precursors include: Pd-catalysed cascade reaction of 4-hydroxycoumarins with *in situ* generated arynes,[246] coupling of 4-hydroxycoumarins with catechols using $Rh/AlPO_4$ nanoparticle



Scheme 71 Synthesis of coumestrol (**479**) and flemichapparin C (**489a**).



Scheme 72 Synthesis of flemichapparin C (489a).



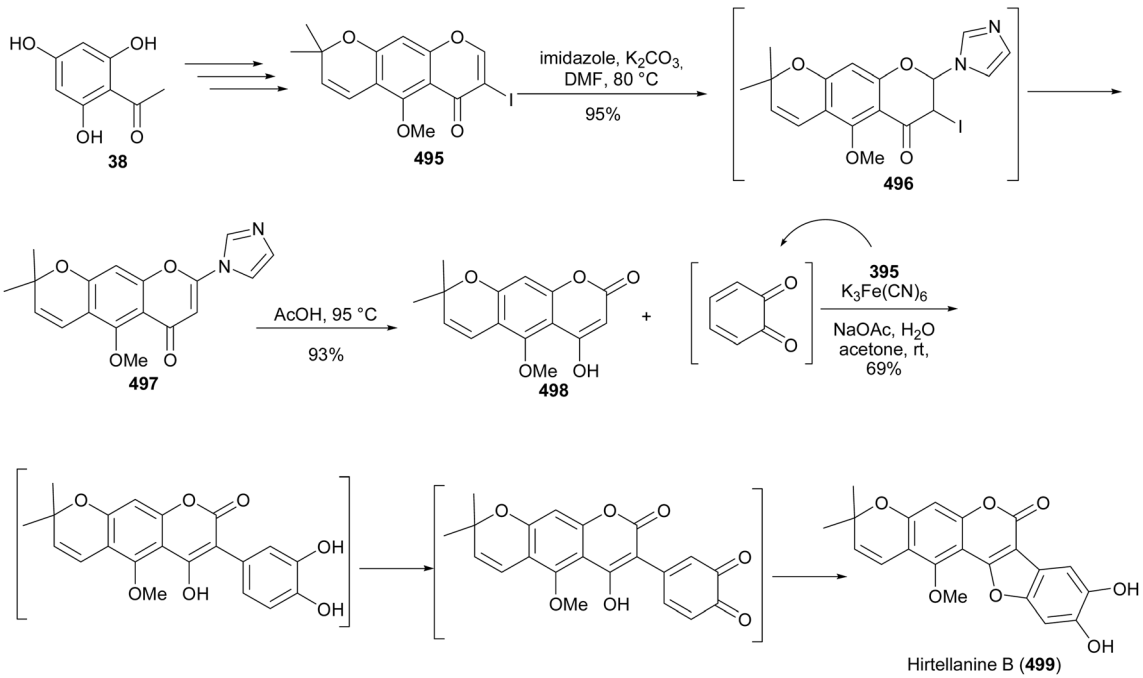
Scheme 73 Synthesis of flemichapparin C (489a).

catalyst[252] or $K_3Fe(CN)_6$ (ref. 54) and Pd-catalysed double C–H activation of phenoxycoumarins.[63,64]

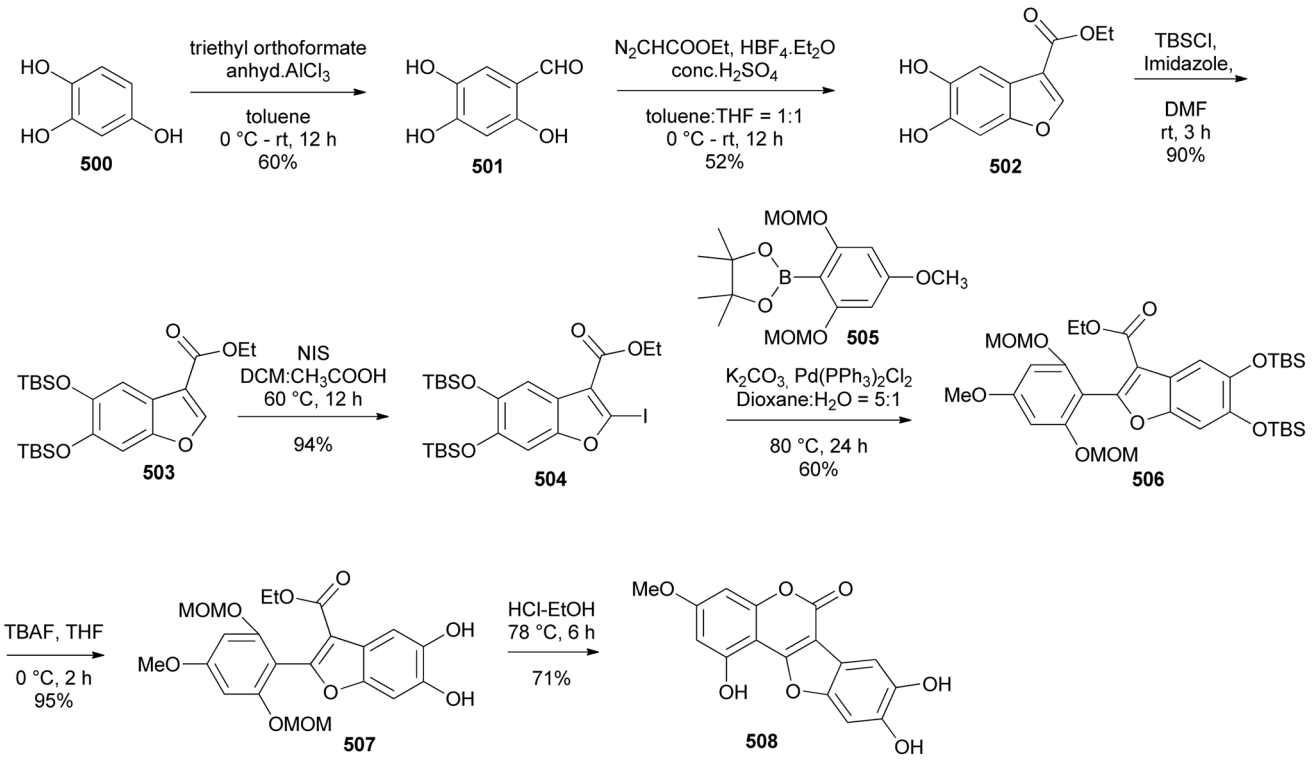
The synthesis of coumestans has also been attained from 4-phenoxycoumarin or 4-hydroxycoumarin precursors.[54,63,64,246,252,259] From 4-phenoxycoumarins, the coumestans were synthesised by direct arylation involving double C–H activation using palladium catalysts and silver salts as oxidants, thereby avoiding the utilisation of pre-derivatised building blocks.[63,64] The natural coumestan, flemichapparin C (**489a**) was synthesised by this protocol by McGlacken's group in 2016.[63] As shown in Scheme 70, the synthesis commenced with the preparation of the 4-phenoxychromone **488** by bromination of 4-hydroxycoumarin **486** and coupling of 4-bromocoumarin **487** with sesamol. The intramolecular double dehydrogenative cyclisation of the phenoxycoumarin **488** using $Pd(OAc)_2$, AgO, and NaO-*t*-Bu gave the targeted flemichapparin C (**489a**) and its isomer **489b** in ratio of 84 : 16 and 82% yield, Scheme 70.[63]

Xu's group concurrently reported a similar protocol and demonstrated its application in the synthesis of coumestrol (**479**) and flemichapparin C (**489a**). Intramolecular cross dehydrogenative coupling of phenoxycoumarins **490** and **488** using $Pd(OAc)_2$ catalyst, AgOAc as oxidant and CsOAc as a base exclusively rendered coumestan **491** and flemichapparin C (**489a**), respectively (Scheme 71). The compounds were obtained in high yields and good regioselectivity. Demethylation of **491** and flemichapparin C (**489a**) gave coumestrol (**479**) and demethylflemichapparin C (**492**), respectively.[64]

4-Hydroxycoumarins have been successfully employed for the synthesis of coumestans.[54,246,252] Neog and colleagues synthesised coumestans including flemichapparin C (**489a**) by palladium-catalysed coupling of 4-hydroxycoumarins with arynes generated *in situ* from *o*-trimethylsilylphenyl



Scheme 74 The synthesis of hirtellanine B (499).



Scheme 75 Total synthesis of wedelolactone (**508**).

triflates.[246,260] The reaction proceeded *via* tandem C–H activation followed by C–O and C–C bond formations.[246] As shown in Scheme 72, the reaction of 4-hydroxycoumarin **486** with *o*-trimethylsilylphenyl triflate **493** under optimised conditions gave flemichapparin C (**489a**).

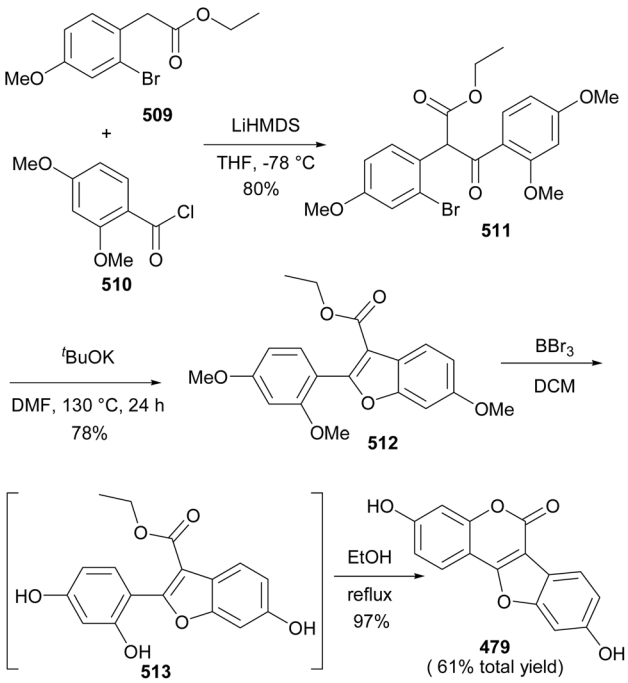
Maeno and co-workers synthesised flemichapparin C (**489a**) by oxidative annulation of 4-hydroxycoumarin **486** and *o*-quinones generated from catechol (**395**) using $AlPO_4$-supported Rh nanoparticle and O_2 as oxidant, and subsequent reaction of the resulting coumestan **494** with bromochloromethane, Scheme 73.[252]

Hirtellanine B (**499**) was synthesised by oxidative coupling of catechol with 4-hydroxypyranocoumarin **498** using K_3FeCN as oxidant.[54] The 4-hydroxypyranocoumarin **498** was prepared in a sequence of steps that involved the synthesis of 3-iodochromone **495** from phloroacetophenone (**38**)[32] and the conversion of **495** into 2-imidazolylchromone **497** (Scheme 74).[261,262]

8.3. Synthesis from benzofuran precursors

2-Phenylbenzofurans have proven to be important building blocks for the synthesis of coumestans. Syntheses of the 2-phenylbenzofuran derivatives have been attained by methods that include palladium-catalysed carbonylative cyclisation of diaryl alkynes,[263] the Suzuki–Miyaura coupling of 2-halobenzofurans with boronate esters,[247] and newly developed methods that include base-catalysed cyclisation of 2-bromobenzylketones[253] and indium-catalysed restructuring of phenylethynyl pyrones.[254]

Wedelolactone (**508**) is an important coumestan, which has been synthesised by several research groups.[250,258,263] Recently, Gou and colleagues synthesised wedelolactone (**508**) by lactonisation of ethyl 2-phenylbenzofuran-3-carboxylate **507**.[247] The 2-phenylbenzofuran-3-carboxylate **507** was synthesised by TBS deprotection of the benzofuran **506,** which was in turn assembled by the Suzuki–Miyaura coupling of two key precursors: the 2-



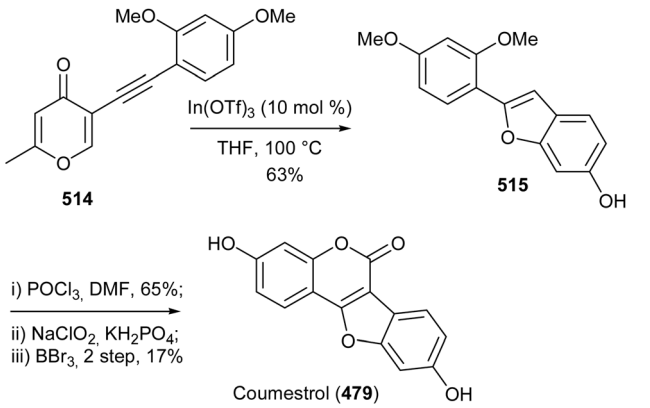
Scheme 76 Total synthesis of coumestrol (**479**).

iodobenzofuran-3-carboxylate **504** and the boronate ester **505** (Scheme 75). The boronate ester was synthesised in a sequence of steps from phloroglucinol, while the 2-iodobenzofuran-3-carboxylate **504** was prepared by formylation of trihydroxybenzene **500** to give benzaldehyde **501**. The reaction of benzaldehyde **501** with ethyl diazoacetate in the presence of boron tetrafluoride/ether and subsequent treatment with sulphuric acid rendered 3-ethoxycarbonylbenzofuran **502**.[264] TBS protection and iodination of the benzofuran **503** gave **504** (Scheme 75).[247]

Zhang and co-workers developed a method for the synthesis of 2-arylbenzofurans that involved *t*-BuOK-catalysed cyclisation of 2-bromobenzylketones.[253] The utility of the method was demonstrated in the synthesis of coumestrol (**479**). The synthesis proceeded *via* condensation of the 2-bromophenylacetate **509** with dimethoxybenzoyl chloride **510** to give 2-bromobenzylketone **511**. Treatment of **511** with *t*-BuOK gave 2-arylbenzofuran-3-carboxylate **512**. Demethylation of **512** with BBr_3 followed by intramolecular esterification of the resulting intermediate **513** afforded coumestrol (**479**), Scheme 76.[253]

Zhu's group developed a method that transformed kojic acid-derived alkynes into 2-phenylbenzofurans using indium triflate as a catalyst.[254] The 2-phenylbenzofurans were further elaborated to afford several benzofuran-containing natural compounds, including coumestrol (**479**). As shown in Scheme 77, coumestrol (**479**) was synthesised by a sequence of steps that involved C-3 formylation of **515**, followed by conversion of the formyl group into hydroxycarbonyl group by Pinnick oxidation, demethylation, and spontaneous lactonisation. The benzofuran **515** resulted from indium triflate-catalysed reassembly of phenylethynyl pyrone **514**.[254]

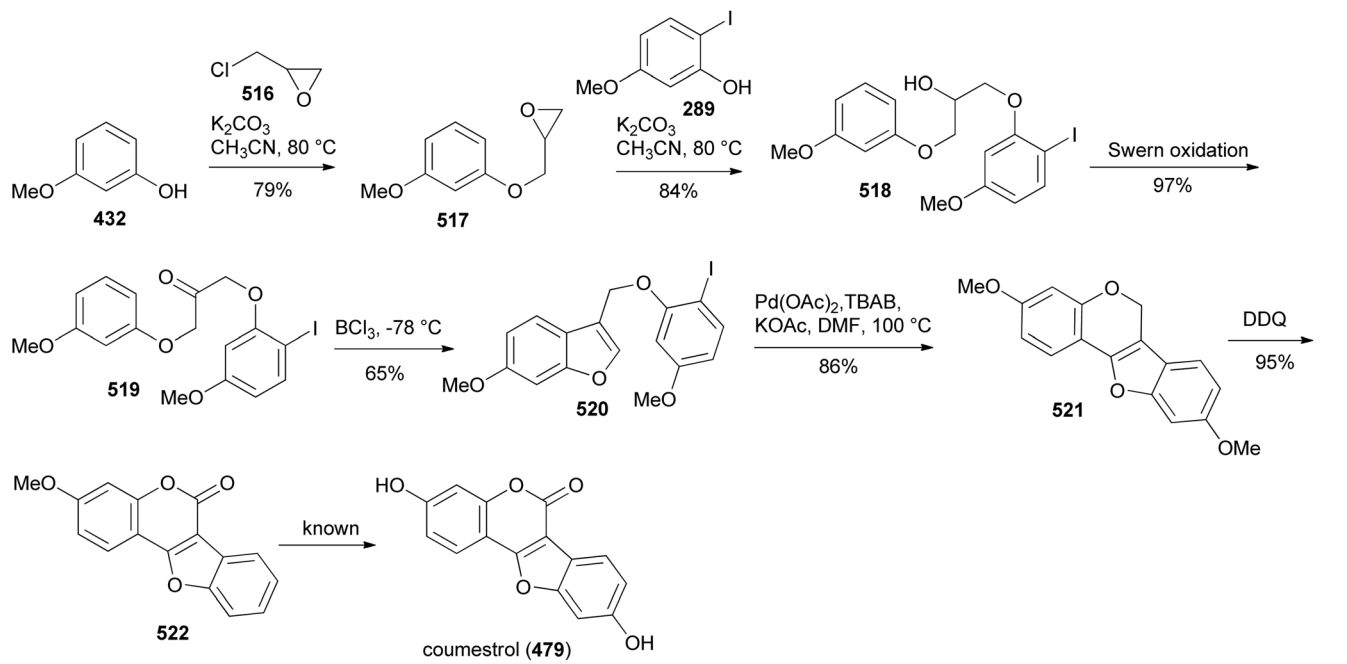
Alternative to 2-phenylbenzofurans, Nayak and colleagues synthesised pterocarpens and coumestans from 3-phenoxymethylbenzofurans constructed by BCl_3-mediated cyclisation of 1,3-diphenoxypropanones.[248,265] As shown in Scheme 78, the diaryloxyacetone **519** was synthesised by consecutive *O*-alkylation of phenols **432** and **289** with epichlorohydrin **516** and subsequent oxidation of the resulting alcohol **518**. Treatment of **519** with BCl_3 gave the 3-phenoxymethylbenzofuran **520** in 65% yield.[265] Intramolecular Heck coupling of **520** gave pterocarpene **521** in 86% yield, which was oxidised into coumestan **522**.[248] Compound **522** could be demethylated to render coumestrol (**479**). Other coumestans that include flemichapparin C (**489a**) and proposed plicadin (**482**) were also synthesised from appropriately substituted 1,3-diaryloxyketones following the same sequence.[248]



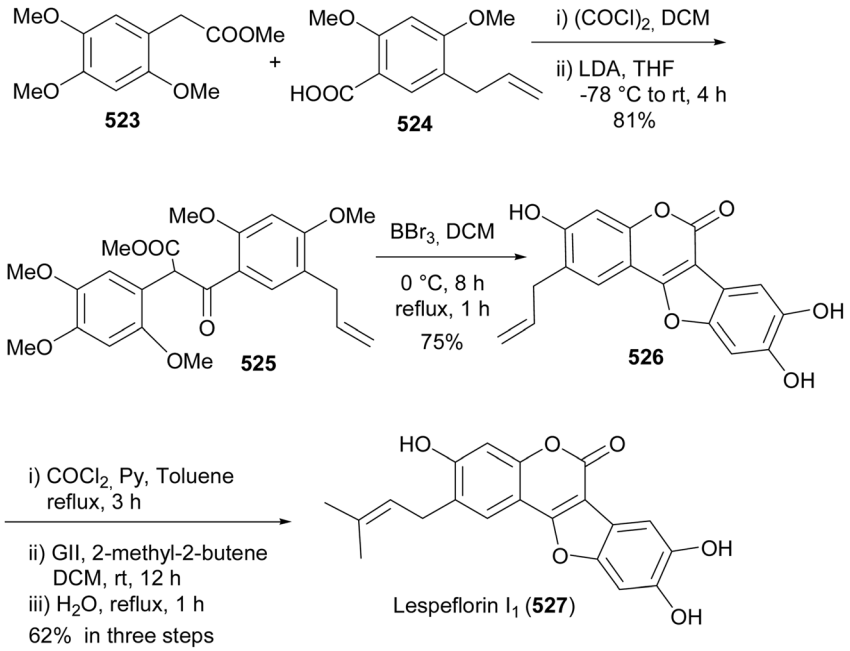
Scheme 77 Synthesis of coumestrol (**479**).

8.4. Other

Pahari and colleagues synthesised prenylated coumestans that include psoralidin (**6**), lespeflorin I_1 (**527**) and their derivatives



Scheme 78 Synthesis of coumestrol (**479**).



Scheme 79 Synthesis of lespeflorin I_1 (**527**).

from oxodiphenylpropanoate precursors.[43,249] As illustrated for the synthesis of lespeflorin I_1 (**527**), LDA-mediated coupling of phenyl acetate **523** with benzoyl chloride generated from benzoic acid **524** gave oxodiphenylpropanoate **525**, which upon treatment with BBr_3 underwent demethylation and spontaneous intramolecular cyclisation to give the coumestan **526**. Protection of the adjacent hydroxy groups with phosgene followed by metathesis protocol (catalysed by second generation Grubb's catalyst) and hydrolysis of the cyclic carbonate group gave lespeflorin I_1 (**527**), Scheme 79.[249]

9. Conclusions

Isoflavonoids are phenolic natural compounds with diverse structural variation and important biological activities. Owing to their interesting structures and potential benefits for human health, isoflavonoids have been synthesised by several research groups. Conventional methods that include oxidative rearrangements, classical condensations (Perkin reaction, Claisen condensation, aldol condensation *etc.*) and sigmatropic rearrangements are still widely employed for the construction of isoflavonoid core structures and the incorporation of substituents found in natural isoflavonoids. Alternative to the classical methodologies, isoflavonoids have been conveniently accessed by transition metal-catalysed reactions of pre-functionalised building blocks that include the Suzuki–Miyaura, the Negishi, the Stille, and the Heck cross-coupling reactions, as well as cross-coupling metathesis reactions. Of these methods, the Suzuki–Miyaura reaction has been widely applied to the synthesis of different classes of isoflavonoid compounds such as isoflavones, coumarins, and isoflavenes, which also serve as precursors for other elaborate isoflavonoid compounds. Although additional steps are required for the preparation of non-commercial boronic acids/esters and their coupling partners, the Suzuki reaction continues to be the most preferred method, due to the benign conditions that enable introduction of sensitive substituents in the early and late stages of the synthesis, thereby facilitating regiocontrol. The cross-coupling metathesis using Grubs II catalyst has been employed for the synthesis of isoflavenes, and several research groups have used the reaction for the assembly of the prenyl substituents in the late stages of the synthesis. This has been particularly useful when highly acidic or oxidative conditions were employed for the synthesis of isoflavonoid scaffolds.

Advancements in the syntheses of isoflavonoids using metal catalysts have been realised through C–H activation protocols that utilise single pre-derivatised precursors. The applications of these have been demonstrated in the synthesis of isoflavones through direct arylation of 2-hydroxyenaminoketones[90] and the synthesis of coumestans by tandem arylation and oxycyclisation of 4-hydroxycoumarins with arynes generated *in situ* from *O*-trimethylsilylphenyl triflates.[246,260] Isoflavonoids have also been synthesised by double C–H activation involving C–C bond formation from unfunctionalised carbon atoms. Examples include the syntheses of coumaronochromones and coumestans by double dehydrogenative C–C coupling of 2-phenoxychromones and 4-phenoxycoumarins, respectively.[62–64] The development of a new synthetic strategy for coumaronochromones is commendable, considering that coumaronochromones have mainly been synthesised by oxidative coupling of 2′-hydroxyisoflavones. Other methods that do not utilise pre-functionalised precursors include oxidative annulation of 4-hydroxycoumarins or chromenes with quinones to afford coumestans or pterocarpans, respectively.[54,157,252]

Lewis acids and superacids such as BBr_3, BCl_3 and $In(OTf)_3$ have also facilitated transformations leading to the formation

of different classes of isoflavonoids, particularly coumestans and isoflavones. BCl_3 and BBr_3 have mainly been used for tandem demethylation and intramolecular *O*-cyclisation in the synthesis of coumestans that include coumestrol and lespeflorin I_1.[248,249,253] While tandem processes involving deprotection of the methyl ether and spontaneous oxycyclisation are widely reported in the synthesis of natural compounds, a rather unexpected transformation that involved the conversion of methoxybenzoylbenzofurans into isoflavones was reported by Kunyane and colleagues.[87] It proceeded through a cascade of processes that involved demethylation and intramolecular *O*-cyclisation, resulting in furan ring-opening and the formation of a new chromone ring of isoflavones.[87] Another interesting novel method was developed by Zhu's group that transformed kojic acid-derived alkynes (with pyrone moiety) into 2-phenylbenzofurans using $In(OTf)_3$ as a catalyst.[254] The 2-phenylbenzofurans were further elaborated to afford several benzofuran-containing natural compounds, including coumestrol.[254]

Although several new methods have been developed for the synthesis of isoflavonoid compounds, the application of most of them has mainly been demonstrated in the synthesis of simple natural isoflavonoids. An exceptional example is the zinc-mediated Negishi coupling reaction, which facilitated the synthesis of complex isoflavene-derived santarubins and santalins.[57,227,228] Conventional methods are still utilised frequently for the synthesis of isoflavonoids with intricate structures. Therefore, future studies could take advantage of the newly developed methods for the syntheses of more complex natural isoflavonoids, especially the atom-economic strategies based on C–H activation and direct annulation of non-functionalised precursors.

The syntheses of chiral isoflavonoids that include isoflavanones, isoflavans, pterocarpans, and rotenoids have been accomplished in racemic form and stereoselectively. The syntheses of racemates were accompanied by resolution using chiral-phase chromatography in several instances. The stereoselective syntheses employed chiral pool building blocks,[65–67] chiral ligands,[68,69] chiral organocatalysts,[70–72] and chiral transition metal catalysts that facilitated stereoselective hydrogenation and hydrogen transfer.[76–78] Although natural isoflavonoids could be obtained in good ee in the reported stereoselective syntheses, most of them proceeded *via* dynamic kinetic resolution of racemic isoflavonoids and intermediates. The exceptions were the solvent-free benzoin reaction that gave optically active 3-hydroxyisoflavanone upon intramolecular cyclisation in the presence of the chiral NHC catalyst,[70,73] as well as the organo-catalysed stereoselective arylation for the synthesis of *S*-equol.[75] The chiral pool strategy in conjunction with stereocontrolled epoxidation or Sharpless asymmetric dihydroxylation also furnished the requisite stereogenicity from the onset of the syntheses and were successfully employed in the stereoselective synthesis of complex isoflavonoids that included stachyodin A,[67] a pterocarpan with a rare spirotetrahydrofuran ring and the rotenoids, (−)-rotenone and (−)-dalpanol.[66]

10. Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

11. Author contributions

All the authors wrote, reviewed and edited the manuscript.

12. Conflicts of interest

There are no conflicts to declare.

13. Acknowledgements

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