# Synthesis of Isoflavonoids from African Medicinal Plants with Activity against Tropical Infectious Diseases

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“The greatest glory in living lies not in never falling, but in rising every time we fall.”

… Nelson Mandela

# Declaration

I declare that I have completed this thesis independently, using only the specified resources. Where other people's work has been used, this has been well acknowledged and referenced. I confirm that this work has not been published or submitted to any other institution of higher learning for examination or award of a degree.

Potsdam, Date …26.07.2022…….

……...

George Kwesiga

# Dedication

This thesis is dedicated to my wife; Julian and my daughters; Jemimah, Josephine and Joseline.

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# Publications related to this work

## Journal Articles

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2. Kwesiga, G.; Sperlich, E.; Schmidt, B. Scope and Applications of 2,3-Oxidative Aryl Rearrangements for the Synthesis of Isoflavone Natural Products. *J. Org. Chem.* **2021**, *86*, 10699-10712. DOI: 10.1021/acs.joc.1c01375
3. Kwesiga, G.; Kelling, A.; Kersting, S.; Sperlich, E.; von Nickisch-Rosenegk, M.; Schmidt, B. Total Syntheses of Prenylated Isoflavones from *Erythrina sacleuxii* and Their Antibacterial Activity: 5-Deoxy-3′-prenylbiochanin A and Erysubin F. *J. Nat. Prod.* **2020**, *83*, 3445-3453. DOI: 10.1021/acs.jnatprod.0c00932

## Poster Presentations

1. "Application of Suzuki-Miyaura Coupling/ Cross Metathesis Reactions for the Synthesis of Prenylated Isoflavone Natural Products" George Kwesiga and Bernd Schmidt, Frühjahrssymposium 2022; 23$^{rd}$ – 26$^{th}$ March 2022, Hannover, Germany.
2. "Application of 2,3-Oxidative Aryl Rearrangements for the Synthesis of Isoflavone Natural Products" George Kwesiga, and Bernd Schmidt, GDCh – Science Forum Chemistry 2021; 29$^{th}$ August – 1$^{st}$ September 2021, virtual.
3. "Application of 2,3-Oxidative Aryl Rearrangements for the Synthesis of Isoflavone Natural Products" George Kwesiga, and Bernd Schmidt, 32$^{nd}$ Chemistry Day (32. Tag der Chemie); 6$^{th}$ July 2021, virtual.
4. Isolation, Modification and Total Synthesis of Bioactive Isoflavonoids from *Erythrina sacleuxii*" George Kwesiga, Abiy Yenesew, Albert Ndakala, Matthias Heydenreich and Bernd Schmidt, Leibniz Symposium 2020; 14$^{th}$ February 2020, Hannover, Germany.

## Oral Presentations

1. "Studies on the Synthesis of Isoflavonoids Isolated from Indigenous East African *Erythrina* species with Activity against Tropical Infectious Diseases" George Kwesiga, Potsdamer JCF - Symposium 2019; 23$^{rd}$ October 2019, Potsdam, Germany.

# Zusammenfassung

Ziel dieser Studie war es, aus afrikanischen Heilpflanzen isolierte Naturstoffe künstlich herzustellen, die zur Behandlung tropischer Infektionskrankheiten wie Malaria und bakterieller Infektionen eingesetzt werden, um Schlüsselsubstanzen für die Entwicklung neuer Medikamente zu identifizieren. Sechs Naturstoffe aus afrikanischen Heilpflanzen wie dem Korallenbaum (*Erythrina*-species) wurden erstmals künstlich hergestellt. Bei der Herstellung dieser Naturstoffe wurden auch sechs weitere verwandte nicht-natürliche Analoga hergestellt.

Zwei Naturstoffe (5-Deoxy-3′-prenylbiochanin A und Erysubin F) aus dem Korallenbaum (*Erythrina sacleuxii*) und eine verwandte nicht-natürliche Substanz wurden auf ihre antimikrobielle Aktivität gegen drei Bakterienstämme und einen Pilzstamm getestet. Alle drei Substanzen waren nicht wirksam gegen *Escherichia coli*, ein Bakterium, das Harnwegsinfektionen und Durchfall verursacht; *Salmonella entrica*, das Typhus verursacht, und *Candida albicans*, das Candidiasis verursacht. Erysubin F und sein nicht-natürliches Analogon waren sehr aktiv gegen Methicillin-resistente *Staphylococcus aureus* (MRSA), ein Bakterium, das hauptsächlich in sehr geringen Konzentrationen Hautinfektionen verursacht. 5-Deoxy-3'-prenylbiochanin A war gegen diesen MRSA-Stamm nicht aktiv. Erysubin F und sein nicht-natürliches Analogon könnten als Schlüsselsubstanzen für die Entwicklung eines neuen Medikaments gegen Infektionen durch MRSA dienen.

# Abstract

Two approaches for the synthesis of prenylated isoflavones were explored: the 2,3-oxidative rearrangement/cross metathesis approach, using hypervalent iodine reagents as oxidants and the Suzuki-Miyaura cross-coupling/cross metathesis approach. Three natural prenylated isoflavones: 5-deoxy-3′-prenylbiochanin A (**59**), erysubin F (**61**) and 7-methoxyebenosin (**64**), and non-natural analogues: 7,4′-dimethoxy-8,3′-diprenylisoflavone (**126j**) and 4′-hydroxy-7-methoxy-8,3′-diprenylisoflavone (**128**) were synthesized for the first time via the 2,3-oxidative rearrangement/cross metathesis approach, using mono- or diallylated flavanones as key intermediates. The reaction of flavanones with hypervalent iodine reagents afforded isoflavones via a 2,3-oxidative rearrangement and the corresponding flavone isomers via a 2,3-dehydrogenation. This afforded the synthesis of 7,4′-dimethoxy-8-prenylflavone (**127g**), 7,4′-dimethoxy-8,3′-diprenylflavone (**127j**), 7,4′-dihydroxy-8,3′-diprenylflavone (**129**) and 4′-hydroxy-7-methoxy-8,3′-diprenylflavone (**130**), the non-natural regioisomers of 7-methoxyebenosin, **126j**, erysubin F and **128** respectively. Three natural prenylated isoflavones: 3′-prenylbiochanin A (**58**), neobavaisoflavone (**66**) and 7-methoxyneobavaisoflavone (**137**) were synthesized for the first time using the Suzuki-Miyaura cross-coupling/cross metathesis approach. The structures of 3′-prenylbiochanin A (**58**) and 5-deoxy-3′-prenylbiochanin A (**59**) were confirmed by single crystal X-ray diffraction analysis. The 2,3-oxidative rearrangement approach appears to be limited to the substitution pattern on both rings A and B of the flavanone while the Suzuki-Miyaura cross-coupling approach appears to be the most suitable for the synthesis of simple isoflavones or prenylated isoflavones whose prenyl substituents or allyl groups, the substituents that are essential precursors for the prenyl side chains, can be regioselectively introduced after the construction of the isoflavone core.

The chalcone-flavanone hybrids **146**, **147** and **148**, hybrids of the naturally occurring bioactive flavanones liquiritigenin-7-methyl ether, liquiritigenin and liquiritigenin-4′-methyl ether respectively were also synthesized for the first time, using Matsuda-Heck arylation and allylic/benzylic oxidation as key steps.

The intermolecular interactions of 5-deoxy-3′-prenylbiochanin A (**59**) and its two closely related precursors **106a** and **106b** was investigated by single crystal and Hirshfeld surface analyses to comprehend their different physicochemical properties. The results indicate that the presence of strong intermolecular O-H···O hydrogen bonds and an increase in the number of π-stacking interactions increases the melting point and lowers the solubility of isoflavone derivatives. However, the strong intermolecular O-H···O hydrogen bonds have a greater effect than the π-stacking interactions.

5-Deoxy-3′-prenylbiochanin A (**59**), erysubin F (**61**) and 7,4′-dihydroxy-8,3′-diprenylflavone (**129**), were tested against three bacterial strains and one fungal pathogen. All the three compounds were inactive against *Salmonella enterica* subsp. *enterica* (NCTC 13349), *Escherichia coli* (ATCC 25922), and *Candida albicans* (ATCC 90028), with MIC values greater than 80.0 μM. The diprenylated isoflavone erysubin F (**61**) and its flavone isomer **129** showed *in vitro* activity against methicillin-resistant *Staphylococcus aureus* (MRSA, ATCC 43300) at MIC values of 15.4 and 20.5 μM, respectively. 5-Deoxy-3′-prenylbiochanin A (**59**) was inactive against this MRSA strain. Erysubin F (**61**) and its flavone isomer **129** could serve as lead compounds for the development of new alternative drugs for the treatment of MRSA infections.

# Table of Contents


1 Introduction ..... 1

2 Objectives ..... 5

3 Theoretical Background ..... 6

3.1 Tropical Infectious Diseases ..... 6

3.1.1 Transmission of Tropical Infectious Diseases ..... 6

3.1.2 Treatment of Tropical Infectious Diseases ..... 7

3.1.2.1 Antibacterial Drugs (Antibiotics) ..... 7

3.1.2.2 Antifungal Drugs ..... 8

3.1.2.3 Antiviral Drugs ..... 9

3.1.2.4 Antiparasitic Drugs ..... 10

3.2 African Medicinal Plants ..... 12

3.3 Isoflavonoids ..... 21

3.3.1 Biosynthesis of Isoflavonoids ..... 22

3.3.2 Isoflavones ..... 23

3.3.2.1 Synthesis of Isoflavones ..... 27

3.3.2.1.1 Deoxybenzoin Route ..... 27

3.3.2.1.2 Chalcone Route ..... 28

3.3.2.1.3 Oxidative Rearrangement of Flavanones ..... 31

3.3.2.1.4 Suzuki-Miyaura Cross-Coupling Reactions ..... 37

3.3.2.1.5 Synthesis of prenylated Isoflavones ..... 40

4 Results and Discussion ..... 42

4.1 Synthesis of Isoflavones via 2,3-Oxidative Aryl Rearrangement of Flavanones ..... 42

4.1.1 Synthesis of 5-Deoxy-3′-prenylbiochanin A (**59**) ..... 42

4.1.2 Optimization of the 2,3-Oxidative Aryl Rearrangement Reaction ..... 46

4.1.3 Synthesis of Other Isoflavones ..... 48

4.1.3.1 Synthesis of Flavanones as Substrates for 2,3-Oxidative Rearrangement Reactions ..... 48

4.1.3.2 Scope of the Oxidative Rearrangement Reactions of Flavanones **107** and **121** under Optimized Conditions ..... 51

4.1.3.3 Synthesis of Prenylated Isoflavones and Flavones via Olefin Cross Metathesis 56

4.2 Synthesis of Isoflavones via Suzuki-Miyaura Cross-Coupling Reactions ..... 58

4.2.1 Retrosynthesis of 3′-Prenylisoflavones via Suzuki-Miyaura Cross-Coupling Reactions ..... 58
4.2.2 Synthesis of 3-Iodochromones **104** as Substrates for Suzuki-Miyaura Cross-Coupling Reactions ..... 59
4.2.3 Optimization of the Suzuki – Miyaura Cross-Coupling Reaction ..... 59
4.2.4 Synthesis of Isoflavones **133** ..... 60
4.2.5 Synthesis of 3′-Allylisoflavones **132** ..... 62
4.2.6 Synthesis of Prenylated Isoflavones **131** via Olefin Cross Metathesis ..... 63
4.3 Synthesis of Chalcone-Flavanone Hybrids ..... 66
4.3.1 Matsuda-Heck Arylation of 8-Allyl Flavanones **141** ..... 67
4.3.2 Allylic/Benzylic Oxidation of **143** ..... 69
4.4 Intermolecular Interactions in the Solid-State Structures of 5-Deoxy-3′-prenylbiochanin A (**59**) and its Precursors, **106a** and **106b** ..... 71
4.5 *In Vitro* Antimicrobial Activities of Some Synthesized Compounds ..... 78
5 Conclusions and Outlook ..... 83
6 Experimental Section ..... 87
6.1 General methods ..... 87
6.2 Synthesis of Isoflavones via 2,3-Oxidative Aryl Rearrangement of Flavanones ..... 88
6.2.1 Preparation of Acetophenone and Benzaldehyde Precursors ..... 88
6.2.2 General Procedure 1 for the Synthesis of Chalcones **108** and **119** ..... 93
6.2.3 General Procedure 2 for the Synthesis of Flavanones **107** ..... 99
6.2.4 Attempted Microwave Promoted Domino Claisen Rearrangement/ Oxa-Michael Addition Reaction of Chalcone **119ce** ..... 102
6.2.5 Two Step Synthesis of **121ce** ..... 103
6.2.6 General Procedure 3 for the Synthesis of 8-Allyl Flavanones **121** ..... 103
6.2.7 2,3-Oxidative Rearrangement of Flavanone **107aa** ..... 105
6.2.7.1 One-Pot 2,3–Oxidative Rearrangement/MOM- Deprotection of Flavanone **107aa** ..... 105
6.2.7.2 2,3-Oxidative Rearrangement of Flavanone **107aa** without MOM-Deprotection ..... 107
6.2.8 Olefin Cross Metathesis of **106a** and **106b** ..... 108
6.2.9 Synthesis of 5-Deoxy-3'-prenylbiochanin A (**59**) from **114** ..... 109
6.2.10 Optimization of Reaction Conditions for the 2,3-Oxidative Rearrangement of Flavanone **107aa** ..... 110

6.2.10.1 General Procedure 4 for the Reaction with HTIB, PIDA or PIFA in Methanol or Acetonitrile ..... 110
6.2.10.2 General Procedure 5 for the Reaction with PIDA or PIFA in TMOF in the Presence of Sulfuric Acid or Trifluoroacetic Acid ..... 111
6.2.10.3 Oxidative Rearrangement of Flavanones **107** and **121** ..... 112
6.2.11 General Procedure 6 for the Cross Metathesis of Allyl Isoflavones and Allyl Flavones with 2-Methyl-2-butene. ..... 119
6.2.12 General Procedure 7 for MOM-Ether Cleavage ..... 123
6.2.13 Attempted Synthesis of an Enol Silyl Ether ..... 126
6.3 Synthesis of Isoflavones via Suzuki-Miyaura Cross-Coupling Reactions ..... 126
6.3.1 General Procedure 8 for the Synthesis of Enamino ketones **103** ..... 126
6.3.2 General Procedure 9 for the Synthesis of 3-Iodochromones **104** ..... 128
6.3.3 Optimization of Suzuki-Miyaura Cross-Coupling Reaction ..... 129
6.3.4 General Procedure 10 for the Suzuki-Miyaura Cross-Coupling Reacctions under Optimized Conditions ..... 132
6.3.5 General Procedure 11 for the Synthesis of 4′-Allyloxyisoflavones **135** ..... 133
6.3.6 Claisen Rearrangement of 4′-Allyloxyisoflavones **135** ..... 135
6.3.6.1 Attempted Claisen Rearrangement of **135b** Using DMF as a Solvent ..... 135
6.3.6.2 General Procedure 12 for the Synthesis of 3′-Allylisoflavones **136** ..... 135
6.3.7 MOM-Protection and Methylation of Isoflavones **136** ..... 137
6.3.8 Synthesis of Prenylated Isoflavones **58**, **66**, **131d** and **137** via Olefin Cross Metathesis ..... 139
6.4 Synthesis of Chalcone-Flavanone Hybrids ..... 142
6.4.1 Synthesis of 8-Allyl Flavanones **141** ..... 142
6.4.2 General Procedure 13 for Matsuda-Heck Arylation of 8-Allyl Flavanones **141** ..... 145
6.4.3 General Procedure 14 for the Allylic/Benzylic Oxidation of **143** ..... 147
6.5 X-ray Crystal Structure Analysis ..... 151
6.6 Antimicrobial Assay Testing ..... 151
7 References ..... 153

# List of Figures

**Figure 1:** Examples of early standardized natural, semi-synthetic and fully synthetic drugs ..... 2
**Figure 2**: Examples of previously synthesized natural prenylated isoflavonoids ..... 4
**Figure 3:** Structures of penicillins and chlortetracycline ..... 8
**Figure 4:** Examples of the recently approved antibiotics ..... 8
**Figure 5:** Some commercially available antifungal drugs ..... 9
**Figure 6:** Some commercially available antiviral drugs ..... 10
**Figure 7:** Examples of drugs used for the treatment of NTDs ..... 11
**Figure 8:** Examples of antimalarial drugs ..... 12
**Figure 9:** Map showing the climatic zones of Africa ..... 13
**Figure 10:** Native geographical distribution of *E. abyssinica* ..... 14
**Figure 11:** Different subclasses of isoflavonoids and their numbering systems ..... 21
**Figure 12:** Different groups of isoflavones ..... 24
**Figure 13:** Examples of bioactive natural prenylated isoflavones ..... 26
**Figure 14:** Catalytic cycle of the Suzuki-Miyaura cross-coupling reaction ..... 38
**Figure 15:** Single -crystal X-ray structure analysis of 5-deoxy-3′-prenylbiochanin A (**59**) ..... 45
**Figure 16:** Arrangement of the molecules of 5-deoxy-3′-prenylbiochanin A (**59**) formed by intermolecular interactions leading to chains along the b axis ..... 46
**Figure 17:** HMBC correlations of C5-OH and H-6 in compound **124** ..... 53
**Figure 18:** Single crystal X-ray structure analysis of compound **123j** ..... 56
**Figure 19:** Single-crystal X-ray structure analysis of 3′-prenylbiochanin A (**58**) ..... 64
**Figure 20:** Arrangement of the molecules of 3′-prenylbiochanin A (**58**) formed by intermolecular interactions leading to chains along a axis ..... 65
**Figure 21:** Examples of naturally occurring bioactive flavanones ..... 66
**Figure 22:** HMBC correlations of allylic protons in compounds **143** ..... 68
**Figure 23:** Single-crystal X-ray structure analysis of **143cc** ..... 68
**Figure 24:** HMBC correlations of H-1″ and H-2‴/H-6‴ in compounds **145** ..... 70
**Figure 25:** Molecular structures of compounds **59**, **106a** and **106b** ..... 72
**Figure 26:** Representation of the composition (%) of the Hirshfeld surface from different intermolecular contacts in compounds **59**, **106a** and **106b** ..... 74
**Figure 27:** Illustration of the Hirshfeld surface of the O···H/H···O contacts and the molecular view with atom labels of compounds **59**, **106a** and **106b** ..... 75
**Figure 28:** Representation of the Hirshfeld surface of the C···C contacts and molecular view with labels of compounds **59**, **106a** and **106b** ..... 77
**Figure 29:** Pictorial representation of the antibacterial activities of 5-deoxy-3′-prenylbiochanin A (**59**), erysubin F (**61**) and 7,4′-dihydroxy-8,3′-diprenylflavone (**129**) against MRSA (ATCC43300) ..... 80
**Figure 30:** Structures of some antibacterial isoflavones and their bioactivities ..... 81
**Figure 31:** An overview of successfully synthesized compounds via the 2,3-oxidative rearrangement of flavanones ..... 83
**Figure 32:** An overview of the successfully synthesized isoflavones via the Suzuki-Miyaura cross-coupling reactions ..... 84

**Figure 33:** An overview of successfully synthesized chalcone-flavanone hybrids ..... 85

# List of Tables

**Table 1:** Common medicinal plants used in African traditional medicine ..... 15
**Table 2:** Synthesis of isoflavones via a 2,3-oxidative aryl rearrangement of flavanones..... 33
**Table 3:** Optimization of 2,3-oxidative aryl rearrangement reaction..... 47
**Table 4:** Synthesis of flavanones **107** without 8-allyl substituent ..... 49
**Table 5:** Synthesis of 8-allylflavanones **121** ..... 51
**Table 6:** Scope of the oxidative rearrangement reaction of flavanones **107** and **121** under optimized conditions ..... 55
**Table 7:** Optimization of the Suzuki-Miyaura cross-coupling reaction..... 60
**Table 8:** Synthesis of isoflavones **77a**, **101** and **133**..... 61
**Table 9:** Synthesis of 3′-allylisoflavones **132** ..... 63
**Table 10:** Synthesis of 8-allyl flavanones **141** ..... 67
**Table 11:** Crystallographic data and refinement data for compounds **59**, **106a** and **106b** ..... 72
**Table 12:** Molar mass, melting points and solubility behavior of compounds **59**, **106a** and **106b** ..... 73
**Table 13:** Bonding distances and angles of hydrogen bonds with O-acceptors in compounds **59**, **106a** and **106b** ..... 75
**Table 14:** Distances and angles of parallel-shifted stacking interactions in compounds **59**, **106a** and **106b** with X as the center and p as the plane of the aromatic ring..... 77
**Table 15:** Antimicrobial activities of compounds **59**, **61** and **129** ..... 79

# List of Schemes

**Scheme 1:** Biosynthesis of isoflavonoids ..... 23
**Scheme 2:** General synthesis of isoflavones via the deoxybenzoin route ..... 27
**Scheme 3:** General synthesis of isoflavones via the chalcone route ..... 28
**Scheme 4:** Synthesis of dimethyldaidzein (**77a**) ..... 28
**Scheme 5:** Proposed mechanism for the transformation of chalcones to aurones ..... 29
**Scheme 6:** Synthesis of parvisoflavones A (**81**) and B (**82**) ..... 30
**Scheme 7:** Synthesis of barbigerone (**92a**) and related isoflavones ..... 31
**Scheme 8:** General synthesis of isoflavones via the 2,3-oxidative aryl rearrangement of flavanones ..... 32
**Scheme 9:** Proposed mechanism for the transformation of flavanones to isoflavones and flavones ..... 33
**Scheme 10:** Plausible mechanism of ring contraction to form benzofurans **98** ..... 34
**Scheme 11:** Synthesis of isoflavones via 2,3-oxidative rearrangement of flavanones by Prakash *et al.* ..... 34
**Scheme 12:** Oxidative rearrangement of flavanone **93c** using thallium(III) acetate, thallium(III) *p*-tosylate and thallium(III) nitrate ..... 35
**Scheme 13:** Effect of substitution pattern on the oxidative rearrangement of flavanones ..... 36
**Scheme 14:** Synthesis of isoflavones via 2,3-oxidative rearrangement of flavanones by Singh and Muthukrishman ..... 36
**Scheme 15:** General representation of a Suzuki-Miyaura cross-coupling reaction ..... 37
**Scheme 16:** Synthesis of isoflavones by Suzuki-Miyaura cross-coupling reaction ..... 39
**Scheme 17:** Gammill's protocol for the synthesis of 3-halochromones ..... 39
**Scheme 18:** Preparation of MOM-protected arylboronic acid from aryl iodide ..... 40
**Scheme 19:** Preparation of 2,4-di-MOM-protected arylboronic acid from resorcinol ..... 40
**Scheme 20:** *O*-Prenylation and *C*-prenylation via *O*-propargylation of isoflavones ..... 41
**Scheme 21:** *C*-Prenylation of isoflavones by allylation/cross metathesis protocol. ..... 41
**Scheme 22:** *C*-Prenylation of isoflavones via palladium catalyzed coupling ..... 41
**Scheme 23:** Retrosynthesis of 5-deoxy-3′-prenylbiochanin A (**59**) ..... 42
**Scheme 24:** Synthesis of 5-deoxy-3′-prenylbiochanin A (**59**) ..... 44
**Scheme 25:** Attempted microwave promoted domino Claisen rearrangement/ oxa-Michael addition reaction of chalcone **119ce** ..... 50
**Scheme 26:** Synthesis of 8-allylflavanone **121ce** via one-pot two reactions sequence and two-pots two reactions sequence ..... 50
**Scheme 27:** Plausible mechanism for the oxidation of **107ca** to **124** ..... 53
**Scheme 28:** Attempted reaction for the formation of an enol silyl ether of **107ba** ..... 54
**Scheme 29:** Synthesis of prenylisoflavones and prenylflavones via olefin cross metathesis ..... 57
**Scheme 30:** Retrosynthesis of 3′-prenylisoflavones via Suzuki-Miyaura cross-coupling reaction ..... 59
**Scheme 31:** Synthesis of 3-iodochromones **104** ..... 59
**Scheme 32:** Synthesis of 3′-prenylisoflavones via olefin cross metathesis ..... 64
**Scheme 33:** Matsuda-Heck arylation of 8-allyl flavanones **141** ..... 67

**Scheme 34:** Matsuda-Heck arylation of 8,3′-diallyl-7,4′-dimethoxyflavanone (**121ba**) ..... 69
**Scheme 35:** Allylic/benzylic oxidation of **143** and MOM-ether cleavage..... 70

# List of Abbreviations and Acronyms

| | |
|---|---|
| 2-HID | 2-Hydroxyisoflavanone dehydratase |
| 2-HIS | 2-Hydroxyisoflavanone synthase |
| AcCl | Acyl chloride |
| AIDS | Acquired immunodeficiency syndrome |
| Ar | Aryl |
| ATR-FTIR | Attenuated total reflectance- Fourier transform infrared spectroscopy |
| $B(^{i}PrO)_3$ | Triisopropyl borate |
| Bn | Benzyl |
| Bz | Benzoyl |
| CA | Central Africa |
| CFU | Colony forming unit |
| CHI | Chalcone isomerase |
| CHR | Chalcone reductase |
| CHS | Chalcone synthase |
| CIF | Crystallographic Information File |
| CM | Cross metathesis |
| CoA | Coenzyme A |
| COSY | Homonuclear Correlation Spectroscopy |
| COVID-19 | Coronavirus disease of 2019 |
| dba | Dibenzylideneacetone |
| DBU | Diazabicycloundecene |
| DDQ | 2,3-Dichloro-5,6-dicynobenzoquinone |
| DEAD | Diethyl azodicarboxylate |
| DIPA | Diisopropylamine |
| DIPEA | Diisopropylethylamine |
| DMA | *N*,*N*-Dimethylaniline |
| DMAP | 4-Dimethylaminopyridine |
| DMAPP | Dimethylallyl diphosphate |
| DMF | *N*,*N*-Dimethylformamide |
| DMF-DMA | *N*,*N*-Dimethylformamide dimethyl acetal |
| DMSO | Dimethylsulfoxide |
| DRC | Democratic Republic of Congo |
| e.g., | For example, |
| EA | Eastern Africa |
| $ED_{50}$ | Median effective dose |
| EI-TOF | Electron ionization time of flight |
| ERs | Estrogen receptors |
| ESI-TOF | Electrospray ionization time of flight |
| $Et_2O$ | Diethyl ether |
| EtOAc | Ethyl acetate |
| EtOH | Ethanol |
| $Eu(fod)_3$ | Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III) |

| | |
|---|---|
| FDA | Food and Drug Administration |
| GC-MS | Gas chromatography–mass spectrometry |
| $HC(OEt)_3$ | Triethyl orthoformate |
| $HCO_2Et$ | Ethyl formate |
| HIV | Human immunodeficiency virus |
| HMBC | Heteronuclear Multiple Bond Connectivity |
| HRMS | High resolution mass spectrometry |
| HS | Hirshfeld surfaces |
| HSQC | Heteronuclear Single Quantum Coherence |
| HTIB | [Hydroxy(tosyloxy)iodo]benzene |
| i.e., | That is, |
| I2′H | Isoflavone-2′-hydroxylase |
| $IC_{50}$ | 50% Inhibitory concentration |
| IFD | Isoflavanol dehydrotase |
| IFR | Isoflavone reductase |
| IFS | Isoflavone synthase |
| IR | Infrared |
| LRMS | Low resolution mass spectrometry |
| MeCN | Acetonitrile |
| MeOH | Methanol |
| MHz | Megahertz |
| MIC | Minimum inhibitory concentration |
| MOMBr | Bromomethyl methyl ether |
| MOMCl | Chloromethyl methyl ether |
| MRSA | Methicillin resistant *Staphylococcus aureus* |
| MTBE | Methyl *tert*-butyl ether |
| MW | Microwave |
| NaOAc | Sodium acetate |
| *n*-BuLi | *n*-Butyllithium |
| NCDs | Non-communicable diseases |
| NMR | Nuclear magnetic resonance |
| NOESY | Nuclear Overhauser Effect Spectroscopy |
| NTDs | Neglected tropical diseases |
| OTf | Trifluoromethane sulfonate |
| $PCy_3$ | Tricyclohexylphosphine |
| $Pd(OAc)_2$ | Palladium acetate |
| $PhNEt_2$ | *N*,*N*-Diethylaniline |
| PIDA | Phenyliodonium diacetate |
| PIFA | Phenyliodonium bis(trifluoroacetate) |
| PMA | Phorbol-12-myristate-13-acetate |
| $PPh_3$ | Triphenylphosphine |
| PTP1B | Protein tyrosine phosphatase 1B |
| SA | Southern Africa |
| SAMT | *S*-Adenosyl methionine-dependent methyltransferase |
| SAR | Structure-activity relationships |

| | |
|---|---|
| TB | Tuberculosis |
| TBSCl | *tert*-Butyldimethylsilyl chloride |
| TEA | Triethylamine |
| THF | Tetrahydrofuran |
| TIDs | Tropical infectious diseases |
| TLC | Thin layer chromatography |
| TMOF | Trimethyl orthoformate |
| TsCl | Toluene sulfonyl chloride |
| TTA | Thallium(III) acetate |
| TTN | Thallium(III) nitrate trihydrate |
| TTS | Thallium(III) *p*-tosylate |
| U.S.A | United States of America |
| UTIs | Urinary tract infections |
| UV | Ultraviolet |
| VR | Vestitone reductase |
| WA | Western Africa |
| WHO | World Health Organization |

# 1 Introduction

Tropical infectious diseases (TIDs) are diseases caused by pathogenic microorganisms such as bacteria, fungi, viruses, or parasites and occur predominantly in the tropical region of the world.[1] They are classified according to their causal pathogens, that is, bacterial (e.g., tuberculosis (TB), diarrhea, cholera, gonorrhea, syphilis, pneumonia, urinary tract infections (UTIs), skin and soft tissue infections), fungal (e.g., candidiasis), viral (e.g., HIV/AIDS, Ebola, Marburg), and parasitic (e.g., malaria, trypanosomiasis).[1–8] Infectious diseases pose a severe threat to the global public health, accounting for more than 25% of all the illness around the world[9] with an estimated 1 billion people affected by at least one tropical infectious disease globally.[2] TIDs were the major cause of deaths, accounting for approximately 15 million deaths each year globally, of which TB, HIV/AIDS and malaria alone accounted for 40%[1] until the current corona virus (COVID-19) pandemic.[10] Worse still, they are more prevalent in developing countries with poor health systems.[11]

Although several drugs for the treatment of various infectious diseases are commercially available, they suffer from a variety of shortcomings such as high toxicity, adverse side effects and lack of availability to most poor communities.[2,12] In addition to the aforementioned shortcomings, the development of resistant pathogens to the currently used drugs has continued,[13–16] and there is a limited range of alternative drug classes to meet this challenge. It is therefore necessary to develop alternative drugs possibly with different mechanisms of action against these pathogens.

Plant based products have historically been the first remedies against various diseases, including TIDs in all cultures and regions all over the world.[17] The development of chemistry as a science and particularly organic chemistry resulted in the replacement of plants and crude plant extracts with isolated secondary metabolites as standardized drugs (e.g., quinine (**1**)) in the early 19$^{th}$ century. Since then, increased knowledge on chemical reactions and reactivities led to the development of semi-synthetic drugs (e.g., synthetically modified natural products such as heroin (**2**) and aspirin (**3**)) and eventually to fully synthetic drugs, with the anti-inflammatory agent phenacetin (**4**) and the anti-syphilis drug salvarsan (**5**) (Figure 1) being early examples. Over the recent decades, natural products guided drug development has been impressive because natural products are recognized as biologically validated lead structures for the design of chemical libraries.[18,19] The recognition, together with the possibility to study the interactions of small

molecules with protein domains using nuclear magnetic resonance (NMR) and other spectroscopic techniques has been the starting point of the new era of natural products drug design and development.

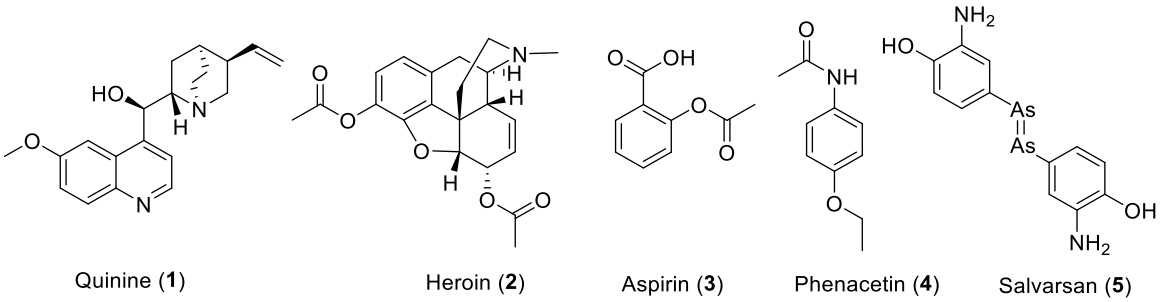


**Figure 1:** Examples of early standardized natural, semi-synthetic and fully synthetic drugs

To date, more than 75% of the world's population, most of whom live in developing countries including tropical Africa still use plants for their primary health care.[17,20] More than 53000 plant species are currently reported to be used in herbal medicine worldwide, of which more than 10% are indigenous to Africa.[21] The African medicinal plants, most of which belong to the Leguminosae and Asteraceae families are used traditionally for the treatment of infectious diseases[22–32] and other non-communicable diseases (NCDs) such as cancer and diabetes.[21,23,27,33,34] Some of these plants have been reported to elaborate anti-infective secondary metabolites including alkaloids, flavonoids, isoflavonoids and anthraquinones,[30,35–40] justifying their use in traditional medicine. Within the Leguminosae family, *Erythrina* and *Millettia* genera comprise the highest number of species used, of which *E. abyssinica* is the most widely distributed and used species in Africa for the treatment of a variety of ailments.[41]

Isoflavonoids are secondary plant metabolites mainly restricted to the subfamily Papilionoideae of the Leguminosae.[42–46] Their structures are characterized by a 3-phenylchroman skeleton[45] which results biosynthetically from an oxidative migration of the aryl substituent of flavanones from C-2 to C-3 catalyzed by isoflavone synthase (IFS).[47–50] Isoflavonoids can be further subdivided into structurally different subclasses including isoflavones and pterocarpans among others,[43–46] of which isoflavones constitute the largest subclass of natural isoflavonoids. Isoflavonoids have been reported to exhibit a wide range of fascinating bioactivities including antioxidant,[51–53] antibacterial,[54–56] antifungal,[57,58] anti-plasmodial,[37,59] anti-inflammatory[60] and antiproliferative[61–

[63] activities while some isoflavonoids act as phytoestrogens.[53,64,65] Among the isoflavonoids, prenylated derivatives are reported to be more bioactive[66,67] due to their increased lipophilicity that enables them to permeate more rapidly through cell membranes and bind more efficiently to target proteins.[68]

The value of natural products for the treatment of infectious diseases has recently been impressively recognized by awarding the 2015 Nobel Prize for medicine to Tu for the discovery of artemisinin for the treatment of malaria.[69] Over the past years, ethnobotany has been recognized as a powerful guiding principle for the discovery of secondary plant metabolites including isoflavonoids with activity against infectious diseases. These natural products may in turn serve as lead structures for the development of new drugs.[12,20,70] However, these natural products are isolated in very minute quantities and their plant sources are faced with the threat of extinction due to overexploitation,[17] hence the need to synthesize them.

The fascinating estrogenic and other bioactivities of isoflavone natural products, and the threat of extinction of their natural plant sources has increased researchers' interest in developing methodologies for their synthesis. Most of these syntheses start from deoxybenzoins,[71] with only a few using the more conveniently accessible chalcones as precursors.[72] The conversion of chalcones into isoflavones involves an oxidative aryl migration step after the cyclization. While this step is biosynthetically accomplished by IFS enzymes, it is reported to be accomplished by thallium(III) salts in chemical syntheses.[73–75] The chalcone route has been improved upon over the years,[76–81] but it still faces setbacks of the toxicity of Tl(III) salts which must be used in excess. Although hypervalent iodine compounds have emerged as less hazardous substitutes to Tl(III) salts,[82] the oxidative rearrangement method has not been widely utilized in the synthesis of natural isoflavones and its scope has not been well explored. Since the late 1980s Suzuki-Miyaura cross-coupling reactions of 3-halochromones and arylboronic acids has emerged as a useful method for the synthesis of isoflavones,[83] and it has been applied in the synthesis of some natural isoflavones over the years.[84–88] All three methods mentioned above have not been widely applied in the synthesis of *C*-prenylated natural isoflavones. For instance, only one example where each of the methods, that is, cyclization of deoxybenzoin, oxidative aryl rearrangement and Suzuki-Miyaura cross-coupling reactions has been used as a key step for the total synthesis of prenylated isoflavones derrubone (**6**),[89] wighteone (**7**)[90] and kwakhurin (**8**),[88] respectively (Figure 2) has been

described. In each case the prenyl substituent was introduced after the construction of the isoflavone core. For the synthesis of derrubone, regioselective olefin cross metathesis was used as a key step for the introduction of the prenyl substituent. The synthesis of some natural prenylated pterocarpans has also been reported. For example, the synthesis of (±)-sophorapterocarpan A (**9**) (Figure 2) using a 1,3-Michael–Claisen condensation of γ-butyrolactone with a substituted ketone as a key step has been reported.[91]

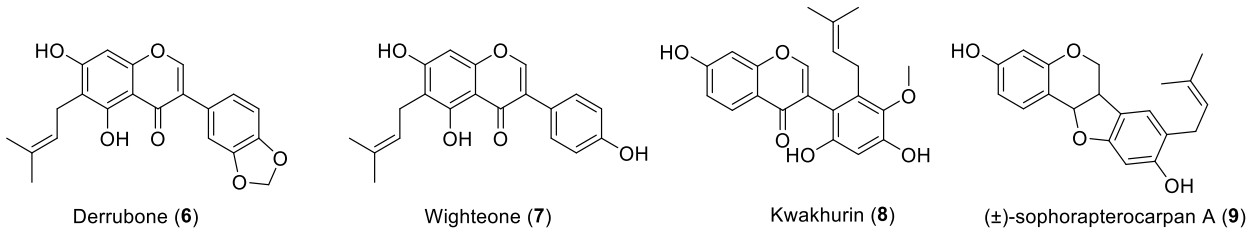


**Figure 2**: Examples of previously synthesized natural prenylated isoflavonoids

Although a combination of any of the methods mentioned above for the construction of an isoflavone core and olefin cross metathesis could accomplish the synthesis of prenylated isoflavones, the synthesis of prenylated isoflavone natural products is still scanty. Thus, to address this deficiency in the current study, some prenylated natural isoflavones isolated from African medicinal plants with activity against TIDs and other related non-natural analogues have been synthesized using either 2,3-oxidative aryl rearrangement of flavanones mediated by hypervalent iodine reagents or Suzuki-Miyaura cross-coupling of 3-iodochromones and arylboronic acids, and regioselective olefin cross metathesis as key steps. In the process, the scope of the 2,3-oxidative rearrangement of flavanones using hypervalent iodine reagents has been investigated. Chalcone-flavanone hybrids of some bioactive natural flavanones have also been synthesized using Matsuda-Heck arylation and benzylic/allylic oxidation as the key steps. The intermolecular interactions of 5-deoxy-3′-prenylbiochanin A, one of the natural products synthesized in the study and its two closely related precursors has also been investigated by single crystal and Hirshfeld surface analyses to comprehend their different physicochemical properties despite their closely related molecular structures. Some of the synthesized compounds were tested for antimicrobial activity against Gram-positive and Gram-negative bacterial and fungal strains.

# 2 Objectives

The main objective of the current study was to synthesize novel isoflavones isolated from African medicinal plants and evaluate them for activity against tropical infectious diseases.

The specific objectives of the study were to:

i. Synthesize sufficient quantities of prenylated isoflavones reported from African medicinal plants via the 2,3-oxidative aryl rearrangement of flavanones and Suzuki-Miyaura cross-coupling reactions.
ii. Explore the scope of the 2,3-oxidative rearrangement of flavanones using hypervalent iodine reagents in the synthesis of natural isoflavones.
iii. Evaluate the antimicrobial activities of the synthesized compounds against pathogens causing tropical infectious diseases.
iv. Synthesize non-natural analogues, with a view to elucidating structure-activity relationships (SAR) and possibly identifying simplified truncated compounds with comparable bioactivity.
v. Investigate how the intermolecular interactions of isoflavones affect their physicochemical properties.

# 3 Theoretical Background

## 3.1 Tropical Infectious Diseases

Tropical infectious diseases (TIDs) are diseases caused by microbes such as bacteria, fungi, viruses, or parasites and occur predominantly in the tropical region of the world.[1] Such diseases can spread directly or indirectly among individuals. They are classified according to their causal pathogens, that is, bacterial (e.g., tuberculosis (TB), diarrhea, cholera, gonorrhea, syphilis, pneumonia, urinary tract infections (UTIs), skin and soft tissue infections), fungal (e.g., candidiasis), viral (e.g., HIV/AIDS, Ebola, Marburg), and parasitic (e.g., malaria, trypanosomiasis, leishmaniasis).[1–8] In their recent review, Adegboye *et al*. listed 41 TIDs as defined by the World Health Organization (WHO), out of which 21 were classified as neglected tropical diseases (NTDs).[2,11] NTDs are a group of infectious diseases which are prevalent in many tropical and subtropical developing countries, but receive less attention from the scientific community and stakeholders than other tropical diseases,[2,11,12] probably due to their non-profitability to the pharmaceutical industry.[69] Examples of NTDs include African trypanosomiasis, Chagas disease, leishmaniasis, dengue fever, chikungunya and Buruli ulcer among others.

The most recent outbreaks of TIDs have been reported in Sub-Saharan Africa and some parts of South America.[2,4,6,92] However, increased migration, international travels, climate change and global warming have led and increased the spread of TIDs to other parts of the world including the United States of America (U.S.A) and Europe.[93] For example, the outbreak of chikungunya was reported in France and Italy in 2017,[92,94,95] and in 2019 the first locally acquired case of Zika virus in Europe was reported in France.[96] These outbreaks indicate the potential of TIDs to spread across the world and thus necessitates urgent intervention.

### 3.1.1 Transmission of Tropical Infectious Diseases

The various modes of transmission of TIDs have been reviewed by Adegboye *et al*.[2] Some TIDs such as Ebola and scabies can be transmitted via direct body contact with infected persons or indirectly though body fluids or contact with contaminated surfaces. Some diseases (e.g., TB) can be transmitted by inhalation of contaminated aerosol droplets while some (e.g., cholera) can be transmitted via ingestion of contaminated food or/and water. Most parasitic and viral diseases are

transmitted through the bite of infected vectors. For example, malaria, yellow fever, and dengue fever are transmitted by mosquitoes. The transmission of TIDs could therefore be prevented by high level standards of hygiene and sanitation, but this is hindered by poverty in the tropical and sub-tropical developing countries where the diseases are prevalent.[8]

### 3.1.2 Treatment of Tropical Infectious Diseases

TIDs are treated according to their classifications. Bacterial, fungal, viral, and parasitic diseases are treated using antibacterial (antibiotics), antifungal, antiviral and antiparasitic drugs, respectively. In addition to the commercially available drugs, TIDs are also treated traditionally using herbal remedies from natural sources (mainly plants).[22–26,30,35,41,97,98] In most poor communities such as Sub-Saharan Africa, traditional medicine is the only source of primary health care compared to western medicine which is not affordable for the vulnerable poor patients.

#### 3.1.2.1 Antibacterial Drugs (Antibiotics)

For close to a century, various antibiotics have been discovered, developed, and used for treating various bacterial infections.[2,99–102] The birth of the antibiotic era started with the discovery of penicillin F (**10**), a natural product from *Penicillium notatum* by Dr. Alexander Fleming in 1928.[99] Other penicillins were later discovered and became the first non-toxic effective antibiotics against infections caused by *Staphylococci* and *Streptococci*. This marked the beginning of the widespread clinical use of antibiotics which greatly improved public health and reduced death and disability from bacterial infections.[99] Some penicillins such as penicillins G (**11**), and V (**12**), amoxicillin (**13**) and ampicillin (**14**) (Figure 3) are still widely used today for treating various bacterial infections such as pneumonia, syphilis, urinary tract infections, otitis, meningitis, and skin and soft tissue infections among others.[101] However, due to extensive use, some bacteria have developed resistance to penicillin. This has led to continuous research aimed at discovering and developing new antibiotics.[103] Consequently, various antibiotics have been developed and approved for clinical use over the past decades.[100,102,104] For example, tetracyclines such as chlortetracycline (**15**) (Figure 3), natural products isolated from *Streptomyces* species were discovered in the late 1940s.[100] Tetracyclines are broad-spectrum antibiotics mainly used for treating chlamydia and mycoplasma infections.[100] Most of the currently used antibiotics, the respective infections they treat, and their mode of administration have been summarized by the WHO in their 22$^{nd}$ model list

of essential medicines[101] while others have been recently reviewed by Adegboye *et al*.[2] Owing to the persistent antimicrobial resistance of bacteria to the available antibiotics, the search and development of new antibiotics has continued. For example, lefamulin (**16**) and cefiderocol (**17**) (Figure 4) are the recent antibiotics that were approved in 2019 by the Food and Drug Administration (FDA) for the treatment of community-acquired bacterial pneumonia and complicated UTIs respectively.[102]

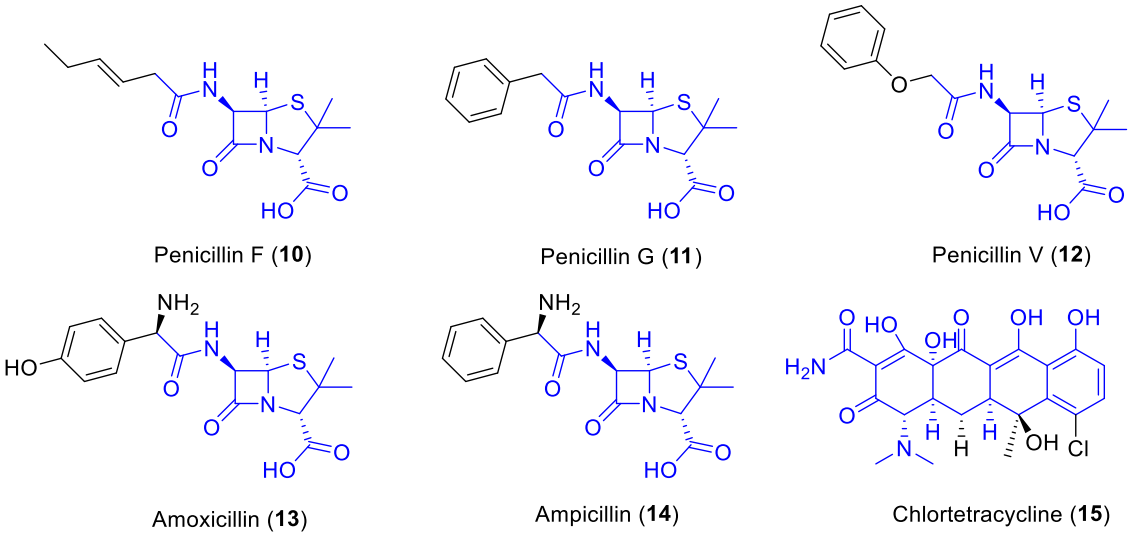


**Figure 3:** Structures of penicillins and chlortetracycline

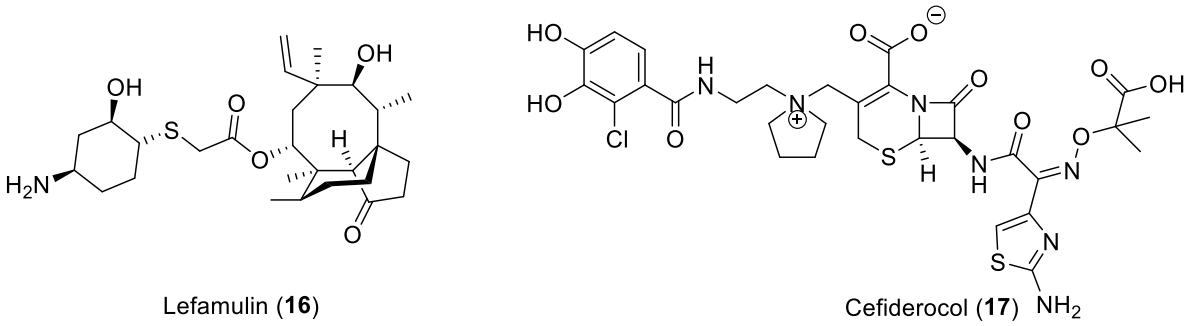


**Figure 4:** Examples of the recently approved antibiotics

### 3.1.2.2 Antifungal Drugs

Some of the commercially available antifungal drugs include amphotericin B (**18**), clotrimazole (**19**), fluconazole (**20**), flucytosine (**21**), griseofulvin (**22**), itraconazole (**23**), ketoconazole (**24**),

nystatin (**25**) (Figure 5) and potassium iodide.[2,101,103] They are used to treat a range of fungal infections such as candidiasis, chromoblastomycosis, lobomycosis and mycetoma among others. Most antifungal drugs are associated with high toxicity and adverse side effects such as headache, diarrhea, rash, nausea, and muscle or joint pains.

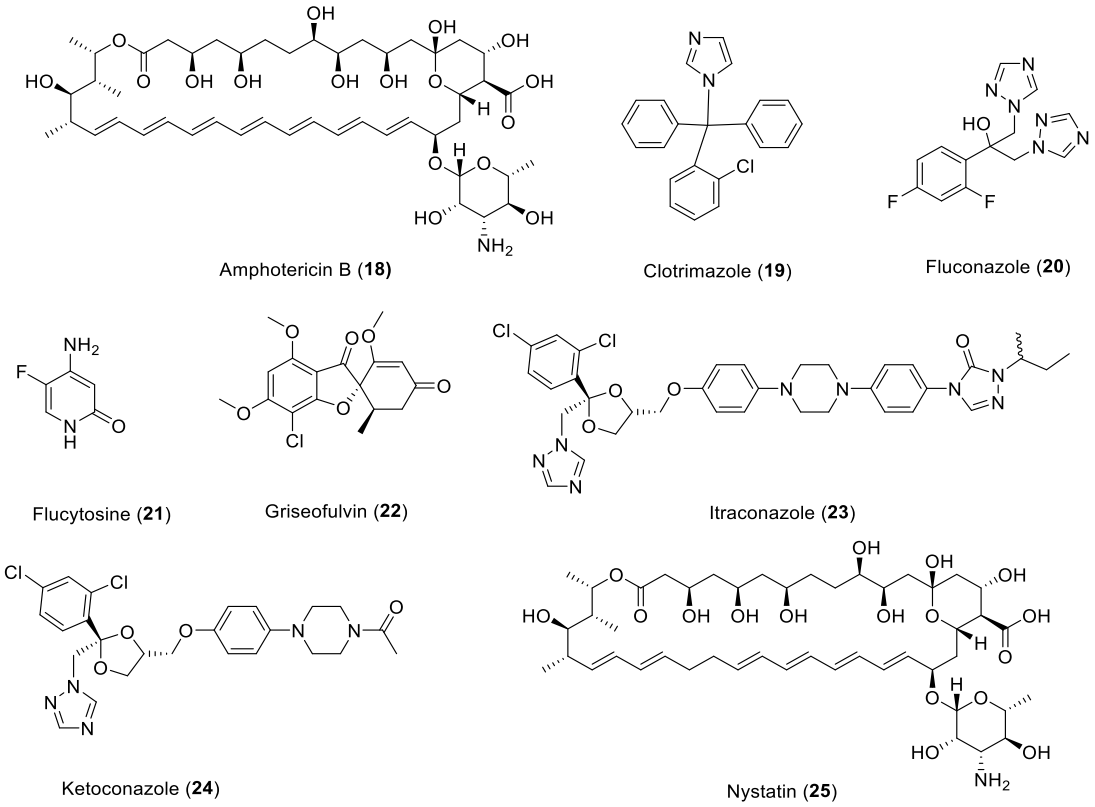


**Figure 5:** Some commercially available antifungal drugs

### 3.1.2.3 Antiviral Drugs

Whereas there are more available antibacterial, antifungal and antiparasitic drugs, there is a limited number of commercially available antiviral drugs.[2,101] Symptomatic treatment is a common practice for most viral infections.[2,11] Some of the marketed antiviral drugs include antihepatitic drugs such as ribavirin (**26**), entecavir (**27**), sofosbuvir (**28**) and dasabuvir (**29**), and antiretrovirals such as abacavir(**30**), lamivudine (**31**) and zidovudine (**32**) used for the treatment and prevention of HIV (Figure 6).[101] As research in the discovery and development of new antiviral drugs continues, the FDA's Center for Drug Evaluation and Research recently approved Ansuvimab-zykl, a human monoclonal antibody under the trade name Ebanga for the treatment of Zaire Ebola

virus infections.[105] In the absence of antiviral drugs for most viral diseases, the WHO recommends boosting the humans' immunity against such diseases through vaccination. Consequently, vaccines against some viral diseases such as yellow fever, dengue fever, Ebola, Japanese encephalitis, rabies, and tick-bone encephalitis have been developed and are currently in use. More vaccine candidates including for other viral diseases such as chikungunya, Crimean-Congo hemorrhagic fever, Lassa fever, Marburg, rift valley fever, West Nile fever and zika are still under investigation.[2]

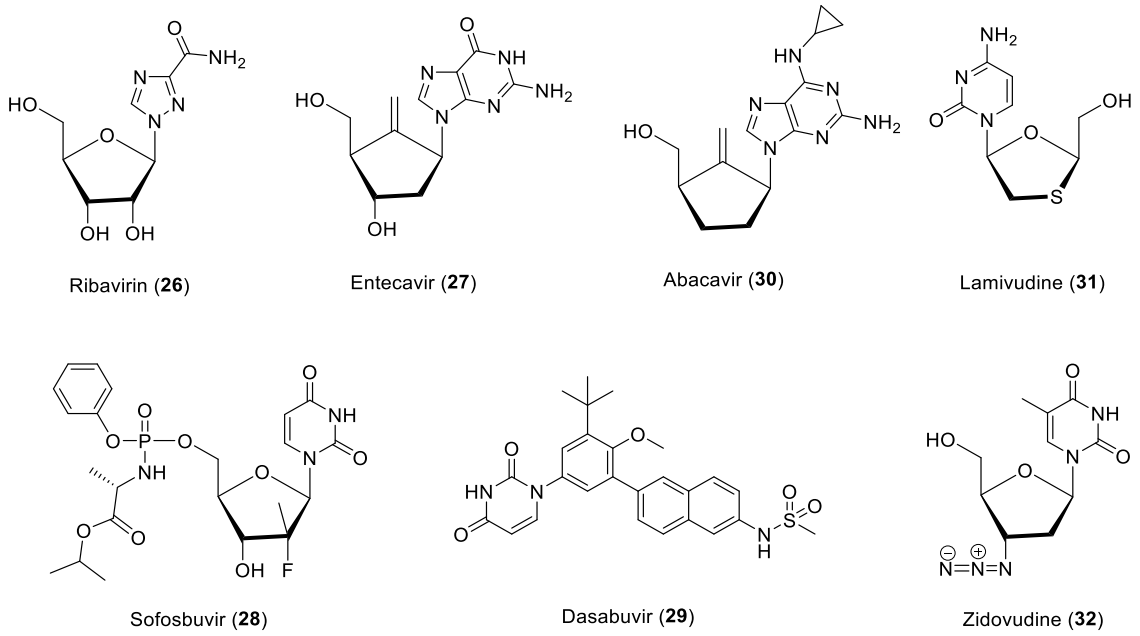


**Figure 6:** Some commercially available antiviral drugs

### 3.1.2.4 Antiparasitic Drugs

With exception of malaria, most parasitic diseases are NTDs[2,11,101] and therefore they attract less attention from the scientific community and the pharmaceutical industry. As a result, only a few drugs are available for the treatment of these diseases. Examples of these drugs (Figure 7) include ivermectin (**33**) used for the treatment of river blindness, scabies and strongyloidiasis (round worm); mebendazole (**34**) and benznidazole (**35**) for the treatment of intestinal worms and American trypanosomiasis, respectively; and pentamidine (**36**), melarsoprol (**37**) and eflornithine (**38**) for the treatment of African trypanosomiasis.[2,11,101] Although some vaccine candidates for these NTDs are under investigation no vaccine has yet been approved.

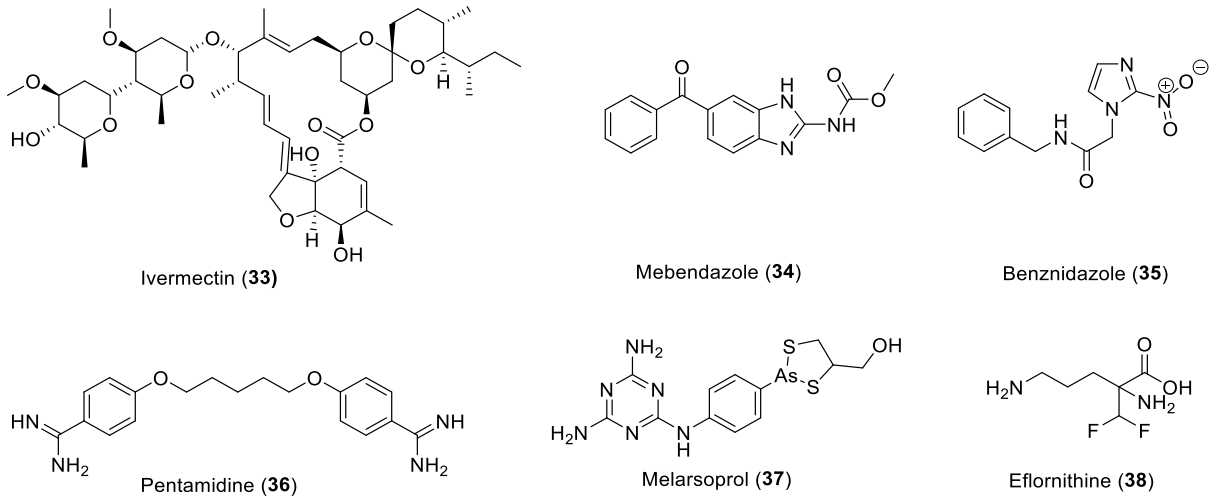


**Figure 7:** Examples of drugs used for the treatment of NTDs

There are more commercially available antimalarial drugs than against other parasitic diseases. This could be attributed to the fact that malaria is the most prevalent infectious disease across the world.[35,106,107] The first and only antimalarial drug used until the 1930s was quinine (**1**), a natural alkaloid isolated from a *Cinchona* species which has been used for centuries in traditional medicine for treating malaria.[8] In the 1930s, it was replaced by other synthetic drugs such as primaquine (**39**), chloroquine (**40**) and amodiaquine (**41**) (Figure 8). Later the malaria parasite (*Plasmodium falciparum*) became resistant to chloroquine. This led to the continuous search and development of alternative antimalarial drugs including artemisinin (**42**).[8,69] Artemisinin is a natural product isolated from *Artemisia annua*, a plant which is still used in the Chinese traditional medicine for the treatment of malaria.[8] Today artemisinin derivatives, artemether (**43**) and artesunate (**44**) are the most used antimalarial drugs.[2,101] However, due to the development of multi-drug resistant strains of *P. falciparum*, WHO recommends the use of these antimalarials in combination therapies.[101,106] These artemisinin-based combination therapies have reduced the global malaria burden by more than 50%.[5]

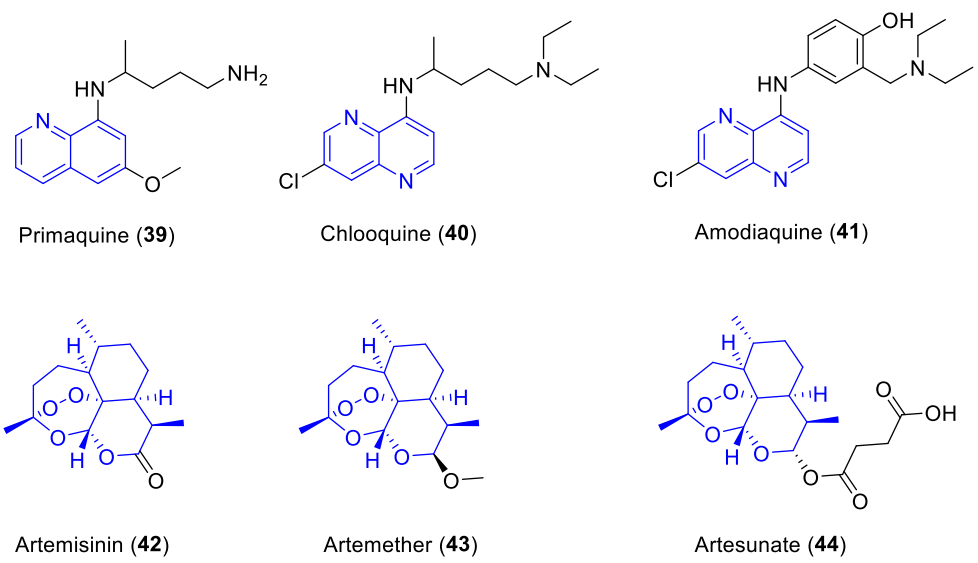


**Figure 8:** Examples of antimalarial drugs

## 3.2 African Medicinal Plants

The African continent has more than 50000 plant species classified into 274 families and 3802 genera,[108] of which approximately 35000 are indigenous.[109] These plants mainly grow in the Sub-Saharan Africa[108] within the tropical rain forest, humid and dry savannah climatic zones (Figure 9). The five largest plant families inhabiting the Sub-Saharan Africa are Leguminosae, Asteraceae, Rubiaceae, Poaceae and Euphorbiaceae, respectively.[108] The largest five genera are *Erica* (Ericaceae), *Euphorbia* (Euphorbiaceae), *Crotalaria* (Leguminosae), *Indigofera* (Leguminosae) and *Senecio* (Asteraceae).[108] Out of these species, more than 5400 are used in African traditional medicine[21] for the treatment of infectious diseases[22–25,28–32] and other noncommunicable diseases.[21,23,33,34] such as diabetes and cancer. With malaria being the most prevalent infectious disease in Africa,[35,106] more than 1000 plant species have been reported to be used across Africa for its prevention and/or treatment.[30] Some of them have been reported to elaborate uniquely effective antimalarial and /or antimicrobial compounds including alkaloids, flavonoids, isoflavonoids and anthraquinones.[30,35–37,110] More than 230 species have also been reported to be used in African traditional medicine for the treatment of TB.[22] The plant species commonly used in African traditional medicine are presented in Table 1. The Leguminosae and Asteraceae families comprise the highest number of species commonly used in African traditional medicine (Table 1). Within the Leguminosae family, *Erythrina* and *Millettia* genera comprise the highest number of

species used, of which *E. abyssinica* is the most widely distributed (Figure 10) and used species in Africa for the treatment of a variety of ailments.[41]

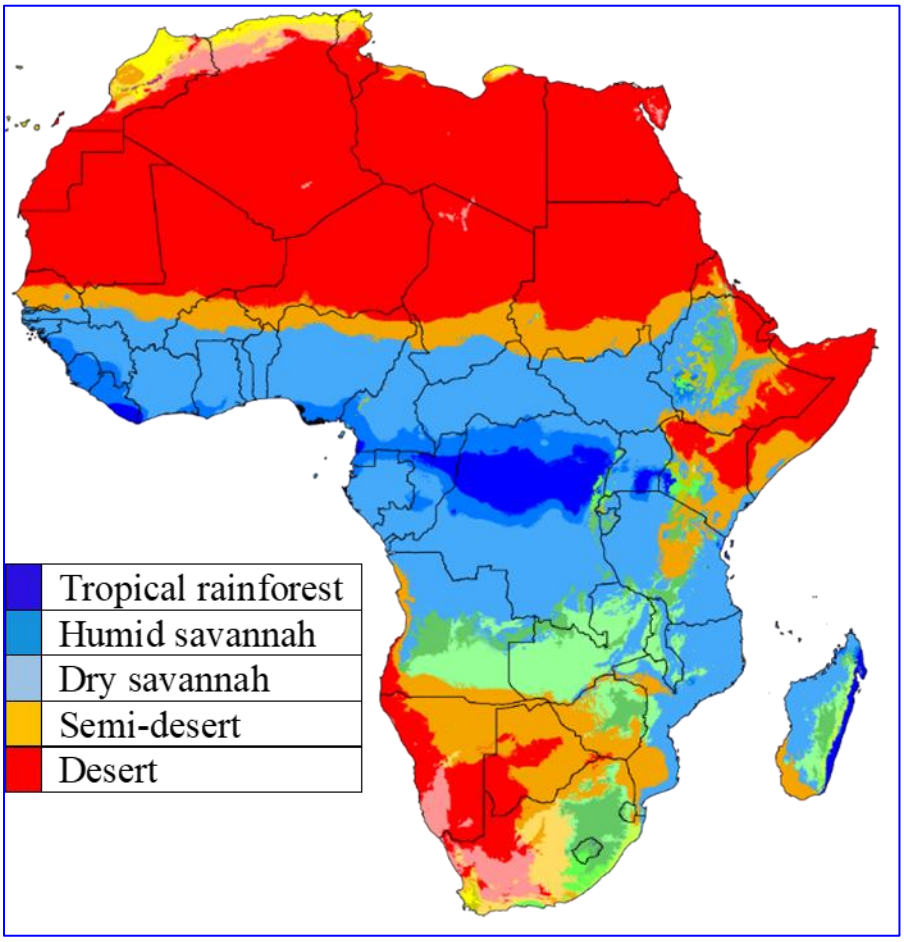


**Figure 9:** Köppen-Geiger climate classification map for Africa. (Adapted from https://commons.wikimedia.org/wiki/File:Koppen-Geiger_Map_Africa_present.svg

Beck, H.E., Zimmermann, N. E., McVicar, T. R., Vergopolan, N., Berg, A., & Wood, E. F.

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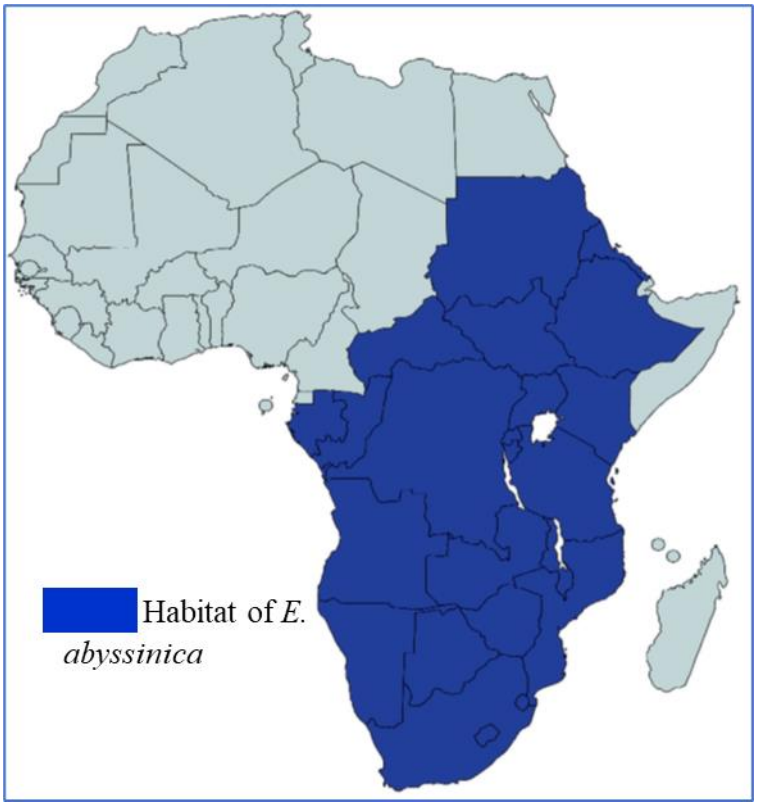


**Figure 10:** Native geographical distribution of *E. abyssinica*[41]

(Adapted from: Obakiro, S. B.; Kiprop, A.; Kigondu, E.; K'Owino, I.; Odero, M. P.; Manyim, S.; Omara, T.; Namukobe, J.; Owor, R. O.; Gavamukulya, Y.; Bunalema, L. Traditional Medicinal Uses, Phytochemistry, Bioactivities, and Toxicities of *Erythrina abyssinica* Lam. ex DC. (Fabaceae): A Systematic Review. *Evid. Based Complementary Altern. Med.* **2021**, 5513484. Available at https://www.hindawi.com/journals/ecam/2021/5513484/

**Table 1:** Common medicinal plants used in African traditional medicine

| Genus (Family) | Species | Geographical distribution (region/country) | Plant part(s) used | Usage and disease(s) treated |
|---|---|---|---|---|
| *Abrus* (Leguminosae) | *A. precatorius* L.[21] | Madagascar | Leaves, seeds | Asthma, bronchitis, cough, stomach cramps, wounds, physical and sexual asthenia. |
| *Acacia* (Leguminosae) | *A. hockii* De Wild.[23,98] | EA | Stem, flowers, fruits | Anemia, TB, and colic pain in babies. |
| | *A. karroo* Hayne[21,111] | EA, SA | Roots, stem bark | Diarrhea, TB |
| | *A. Senegal* L.[21] | EA, WA | Roots, stem bark | Wound healing; emollient |
| *Acanthus* (Acanthaceae) | *A. pubescens* (T. Thoma.)[23,27] | EA | Leaves | Liver and spleen ailments; Aphrodisiac. |
| *Ageratum* (Asteraceae) | *A. conyzoides* L.[21,23,25] | CA, EA, WA | Leaves, roots | Diarrhea and wounds; remedy for cough, ulcers fibroids and pregnancy disorders. |
| *Albizia* (Leguminosae) | *A. anthelmintica*[27] | EA | Leaves, bark, roots | Malaria, gonorrhea; anthelmintic and sexual stimulant for women. |
| | *A. coriaria* Oliv.[27,97] | Uganda | Bark, roots | Cough, TB, menorrhagia, pneumonia, anthrax, anemia, kidney, and heart ailments. |
| | *A. gummifera*[27] | EA | Bark, roots, pods | Malaria, stomachache, and skin diseases. |
| | *A. zygia*[27] | EA | Bark | Malaria |
| *Alchornea* (Euphorbiaceae) | *A. cordifolia* (Schum & Thonn)[23] | Uganda | Twigs | Pre-hepatic jaundice, fever, and pregnancy related illness. |
| *Alepidea* (Apiaceae) | *A. amatymbica*[21] | EA, SA | Rhizomes, roots | Respiratory ailments, colds, and influenza. |
| *Aloe* (Asphodelaceae) | *A. ferox* Mill.[112] | Kenya, South Africa | Leaves | Sexually transmitted infections, skin infections and internal parasites. |
| | *A. maculata*<br>*A. globuligemma*<br>*A. zebrina*<br>*A. hereroensis*<br>*A. litoralis*<br>*A. humillis* | SA | Leaves | Sexually transmitted infections and internal parasites. |
| | *A. marlothii*<br>*A. tenuior*<br>*A. variegata* | | | Ailments of the digestive system |
| | *A. greatheadii*<br>*A. esculenta* | | | Injuries |
| | *A. arborescens* Mill.<br>*A. cooperi*<br>*A. ecklonis* | | | Pregnancy, labor, and postnatal care |
| | *A. vera* | Whole Africa | Leaves | Diversity of ailments |

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|---|---|---|---|---|
| | *A. volkensii* Engl.[23] | Uganda | Leaves | Fever |
| *Antidesma* (Asphodelaceae) | *A.madagascariense* Lam.[21] | Madagascar | Leaves, bark | Dysentery, fever, and diabetes. |
| *Artemisia* (Asteraceae) | *A. afra* Jacq. Ex. Willd.[21] | EA, SA | Areal parts | Digestive and respiratory ailments. |
| *Aspalanthus* (Leguminosae) | *A. linearis* (Burn.f.) R.[21] | South Africa | Leaves | Malaria. |
| *Aspilia* (Asteraceae) | *A. Africana* (Pers.) C.D. Adams[23] | Uganda | Stem | Intestinal worms. |
| *Bersama* (Melianthaceae) | *B. abyssinica*[21] | EA, SA, WA | Leaves, roots, bark | Dysentery and parasitic worms. |
| *Bidens* (Asteraceae) | *B. pilosa* L.[25] | EA | Leaves | Anemia, wounds, and HIV/AIDS; aids conception. |
| *Boerhavia* (Asteraceae) | *B. diffusa* L.[25] | Tanzania | Areal parts | Peptic ulcers. |
| *Boophone* (Amaryllidaceae) | *B. disticha* (L.f.) Herb.[21] | SA | Bulb | Analgesic and wound healing. |
| *Bowiea* (Hyacinthaceae) | *B. volubilis* Harv. Ex Hook.f.[21] | SA | Bulb | Headache, constipation, oedema, and cystitis. |
| *Brucea* (Simaroubaceae) | *B. antidysenterica* J.F.Mill.[21] | EA | Leaves, roots | Diarrhea, digestive ailments, skin infections and leprosy. |
| *Calotropis* (Apocynaceae) | *C. procera* (Aiton) W.T. Aiton[21] | EA, WA | Leaves, roots | Diarrhea, dysentery, and dyspepsia. |
| *Capparis* (Capparaceae) | *C. tomentosa* Lam.[25] | Tanzania | Roots | Chest pains, loss of speech and skin infections. |
| *Carissa* (Apocynaceae) | *C. edulis* (Forssk.) Vahl.[21] | Whole Africa | Leaves, roots, bark | Various ailments. |
| | *C. spinarum* L. Mantas[25] | Tanzania | Roots | Hernia and backache; aphrodisiac. |
| *Catharanthus* (Apocynaceae) | *C. roseus* (L.) G.Don[21] | EA | Areal parts | Cancer. |
| *Cinchona* (Rubiaceae) | *C. ledgeriana* (How.)[21] | Madagascar, SA | Bark | Malaria. |
| *Cissampelos*[21] (Menispermaceae) | C. *pareira L* *C.mucronata* A.Rich. | Whole Africa | Areal parts | Syphilis and other ailments. |
| *Citrus* (Rutaceae) | *C. limon* L.[23] | EA | Fruit | Malaria. |
| *Clerodendrum* (Verbenaceae) | *C. myricoide* Bak[25] | Tanzania | Roots, stem bark | Malaria, febrile convulsions and abdominal colics. |
| *Combretum* (Combretaceae) | *C. collinum* Frensen[25] | Tanzania | Roots | Diarrhea and dysentery. |
| *Craterispermu*m (Rubiaceae) | *C. schweinfirthii* Hiern.[25] | Tanzania | Leaves, stem bark | Yellow fever. |
| *Cryptolepis* (Apocynaceae) | *C. sanguinolenta* (Lindl.)[21,113,114] | EA, WA | Roots | Malaria, TB |
| *Dalbergia* (Leguminosae) | *D. nitidula* Bak.[25] | Tanzania | Leave | Malaria |
| *Danias* (Rubiaceae) | *D. fragrans* C.F.Gaertn.[21] | Madagascar | Roots, bark | Skin infections; pain relief. |

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| *Deamodium* (Leguminosae) | *D. salicifolium* Poir. DC.[25] | EA | Leave, roots | Aphrodisiac. |
| *Dichrocephala* (Asteraceae) | *D. integrifolia* L.f.) Kuntze | Tanzania | Leaves | Mouth ulcers and eye infections. |
| *Dicliptera* (Acanthaceae) | *D. laxata* C. B. Cl.[23] | Uganda | Leaves | Poison antidote. |
| *Draceana* (Agavaceae) | *D. steudneri* Engl. | EA | Leave | Hernia, splenomegaly, asthma, chest problems and fibroids. |
| *Drosera* (Droseraceae) | *D. madagascariensis* DC[21] | Madagascar | Whole plant | Respiratory ailments. |
| *Echinops* (Asteraceae) | *E. kebericho* Mesfin[21] | EA | Roots | Diarrhea, stomachache, fever, and typhus. |
| *Entanda* (Leguminosae) | *E. abyssinica* Steud ex A. Rich.[23,97] | EA | Leaves, bark | Malaria, cough, syphilis, backache, TB, skin rashes in babies and pregnancy related illness. |
| *Elaeodendron* (Celastraceae) | *E. buchananii* Loes.[25] | Tanzania | Roots | A strong aphrodisiac. |
| *Eriosema* (Leguminosae) | *E. psoraliodes* G.Don. Lam.[25] | Tanzania | Leaves, roots | Malaria; aphrodisiac. |
| | *E. stanerianum* Hauman[23] | Uganda | Leaves | Malaria. |
| *Erythrina* (Leguminosae) | *E. abyssinica*[23,41,97,115,116] | EA | Leaves, flowers, roots, and stem bark | Malaria, TB, syphilis, gonorrhea, trachoma, hepatitis, anthrax, leprosy, dysentery, abdominal pains, elephantiasis, and snakebites. |
| | *E. caffra* Thunb[117] | South Africa | Leaves, roots, stem bark | Tuberculosis, sores, wounds, respiratory infections, abscesses, arthritis, toothache, earache, and sprains. |
| | *E. indica*[38] | Cameroon | Not specified | Trachoma, elephantiasis, and microbial infections. |
| | *E. letissima*[118] | SA | Roots, stem | Wounds. |
| | *E. livingstoniana*[119] | Zimbabwe, Mozambique | Not specified | Wounds |
| | *E. lysistemon*[120,121] | Tanzania, South Africa | Leaves, roots, stem bark | Wounds, abscesses, arthritis, and earache |
| | *E. sacleuxii*[26,122] | Kenya, Tanzania | Leaves, root bark | Malaria and microbial infections. |
| | *E. schliebenii*[123] | Tanzania | Not specified | Stomachache and diarrhea; prevention of jaundice of newborn babies; abortive agent. |
| | *E. senegalensis*[124] | WA | Leaves, flowers, roots, stem bark | Malaria, amenorrhea, inflammation, jaundice, pneumonia, wounds, diarrhea, and snakebites. |
| | *E. sigmoidea*[109] | CA | Not specified | Arthritis, rheumatism, pulmonary and stomach problems, infectious and kidney disease; antidote for venomous stings and bites. |
| *Flueggea* (Euphorbaiaceae) | *F. virosa* (Willd.) Voidt[23,25] | EA | Leaves | Gonorrhea, skin infections and pregnancy related illness. |

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| *Hallea* (Rubiaceae) | *H. rubrostipulata* (K. Schum.) J-F. Leroy[23] | Uganda | Roots, bark | Malaria, diabetes, pre-hepatic jaundice, backache, salpingitis and pregnancy related illness. |
| *Hoslundia* (Labiatae) | *H. opposite* Vahl.[23] | Uganda | Stem | Stomachache. |
| *Hygrophylla* (Acanthaceae) | *H. auriculata* (Schum). Hein[25] | Tanzania | Areal parts | Malaria and gonorrhea; increases immunity. |
| *Indigofera* (Leguminosae) | *I. arrecta* A. Rich.[23] | Uganda | Stem | Dislocated bones. |
| | *I. congesta* Welw. ex Bak.f.[23] | Uganda | Stem | Malaria and fever. |
| *Kigelia* (Bignoniaceae) | *K. africana* (Lam) Benth[23,25] | EA | Leaves, stem bark, pod | Hypertension and hemorrhoids; hematinic |
| *Lantana* (Verbenaceae) | *L. camara* L.[25] | EA | Leaves, roots | Gonorrhea, syphilis, swollen legs, cough and to dilate vagina during labor. |
| *Mangifera* (Anacardiaceae) | *M. indica* L.[23,97] | Tropical Africa | Leaves | Cough, TB |
| *Margaritaria* (Euphorbiaceae) | *M. discoidea* (Baill)[29] | CA, WA | Leaves | Malaria, fever, HIV, diabetes, boils, and wounds. |
| *Maytenus* (Celastraceae) | *M. senegalensis* Exel Lam.[25] | CA, EA, WA | Roots, stem bark | Burning sensation of the feet, joint pains, skin rashes and weeping rashes. |
| *Melanthera* (Asteraceae) | *M. scandens* Schumac & Thonn[25] | Tanzania | Leaves | Ulcers, wounds and diabetes. |
| *Microglossa* (Asteraceae) | *M. pyrifolia* Lam[25] | Tanzania | Leaves | Cough, colds and flu. |
| *Millettia* (Leguminosae) | *M. aboensis* (Hook.f.) Baker[125] | WA | Leaves, roots, twigs | Respiratory difficulties, constipation, jaundice, hernias, colds, and headaches. |
| | *M. angustidentata* De Wild[125] | DRC, Tanzania | Leaves | Blennorrhea |
| | *M. aromatica* Dunn[125] | Angola | Trunk | Headaches |
| | *M. barteri* (Benth.) Dunn[126] | CA | Stem, root bark, twigs | Headaches, eye diseases, fever, cardiac pain, vaginal disorders, pulmonary pains, bronchitis, cough, dysmenorrhea, and toothache; fish poison |
| | *M. bicolor* Dunn[125] | Congo | Leave, roots | Otitis, toothache, vaginal diseases, heart aches and fever |
| | *M. congolensis* De Wild[125] | Congo, DRC | Leaves, roots, seeds | Otitis, toothache, vaginal diseases, viral diseases, heart aches and fever |
| | *M. conraui* Harms[125,127] | Cameroon, Nigeria | Stem bark | Infertility, amenorrhea, menopausal disorders, and internal parasites and colic in children; insecticide, pesticide. |
| | *M. drastica* Baker[125,128] | CA | Whole plant | Infertility, diabetes, intestinal, headache and sinusitis. |

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| | *M. duchesnei* De Wild[129] | Cameroon | Twig | Fish poison, insecticide |
| | *M. dura* Dunn[130] | EA | Stem bark | Diarrhea, hernia, wounds, and menstrual irregularities; insecticidal, pesticidal and larvicidal |
| | *M. eetveldeana* (Micheli) Hauman[125,128] | Congo, DRC | Leaves, roots, stem bark | Stiff neck, epilepsy, feverish aches, and general tiredness. |
| | *M. elongatistyla* Gillet[125] | Tanzania | Roots | Schistosomiasis and malaria |
| | *M. elskensii* De wild[125] | DRC | Leaves, pods | Remedy for lumbar pains, bronchitis and intestinal parasitosis |
| | *M. ferruginea* (Hochst) Baker[131] | Ethiopia | Seeds | Fish poison |
| | *M. griffoniana*[132–134] | CA, WA | Roots and stem bark | Boils, insect bites, inflammation, amenorrhea, sterility, and menopausal syndromes |
| | *M. impressa* Harms[125] | Tanzania | Stem bark | Schistosomiasis |
| | *M. lasiantha* Dunn[125] | Kenya | Roots | Aphrodisiac |
| | *M. laurentii* De Wild[34,125] | CA, EA | Roots, stem bark | Hernia, convulsive cough, asthma, female sterility; remedy for feverish aches, sickle cells, epilepsy, and leprosy. |
| | *M. oblata*[132] | Kenya, Tanzania | Stem bark, leaves | Stomachache; remedy for cough, swollen body, and bladder problems. |
| | *M. pallens* Stapf[125] | WA | Stem bark | Remedy for cough. |
| | *M. perville ana* Viguier[125] | Madagascar | Root bark | Fish poison, insecticide and antimalarial |
| | *M. punguensis* Gillet[125] | Kenya | Roots | Umbilical hernia |
| | *M. rhodantha* Baillon[125] | WA | Roots, stem bark | Remedy for stomachaches and cough. |
| | *M. sanagana* Harms[125] | CA, WA | Leaves, roots, stem bark | Hernia, hypertension, otitis, dysmenorrhea, stomachache and intestinal parasitosis; fish poison. |
| | *M. stenopetala* Hauman[128] | DRC | Stem bark | Fish poison. |
| | *M. stuhlmannii* Taub[125] | South Africa | Bark | Stomachache. |
| | *M. usaramensis*[26] | Kenya | Roots | Antidote against snake bite |
| | *M. versicolor* Baker[135] | Congo | Stem bark, leaves | Intestinal parasitosis, feverish aches, kidney pains, cough, female infertility, syphilis, and helminthiasis. |
| *Pappea* (Sapindaceae) | *P. capensis* Echl. Zeyh.[25] | Tanzania | Leaves | Backache |
| *Parinari* (Chrysobalanaceae) | *C. curetellifolia* Plauch Benth.[25] | Tanzania | Root bark | Cancers, fungal infections, athlete foot rot, burning sensation of the feet, joint pains, skin rashes and weeping rashes. |
| *Pseudarthria* (Leguminosae) | *P. confertflora* (A. Rich) Bak[23] | Uganda | Leaves, roots | Pre-hepatic jaundice and colic pain in babies. |
| | *P. hookeri* Wight & Arn[23] | Uganda | Leaves | Sore eyes |

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| *Psidium* (Myrtaceae) | *P. guajava* L.[23] | Uganda | Leaves, bark | Cough. |
| *Psorespermum* (Guttiferae) | *P. febrifugum* Spach.[23] | Uganda | Leaves, bark | Syphilis, pre-hepatic jaundice, fever, and skin rashes in children; induces labor. |
| *Rhus* (Anacardiaceae) | *R. natalensis* DC.[23,25] | EA | Leaves | Chicken pox and syphilis. |
| | *R. vulgaris* Meikle.[23] | Uganda | Leaves | Stomachache. |
| *Rubia* (Rubiaceae) | *R. cordifolia* L.[25] | Tanzania | Areal parts | Warts; reduces excessive menstrual bleeding. |
| *Sapium* (Euphorbiaceae) | *S. ellipticum* Pax.[23] | Uganda | Leaves, bark | Retained placenta, syphilis, and pre-hepatic jaundice. |
| *Senna* (Caesalpiniaceae) | *S. alata* L.[25] | Tanzania | Leaves, roots | Malaria and dysentery. |
| *Tragia* (Euphorbiaceae) | *T. furialis* Boj.[25] | Tanzania | Roots | Hernia and backache; aphrodisiac. |
| *Trema* (Ulmaceae) | *T. orientalis* L.[25] | Tanzania | Leaves, roots | Yellow fever; hematinic. |
| *Vernonia* (Asteraceae) | *V. adoensis*[136,137] | Kenya | Leaves, roots | Fever, upper respiratory infections, TB, and gonorrhea. |
| | *V. amygladina* Del.[23,25] | EA | Leaves, roots | Malaria, fever, febrile convulsions, and mastitis in cows. |
| | *V. lasiopus* O. Hoffin[23] | EA | Leaves | Febrile convulsion. |
| | *V. stenocephala* Oliv.[23] | EA | Leaves | Pre-hepatic jaundice. |
| *Warburgia* (Canellaceae) | *W. ugandesis* Sprague[23,97] | EA | Bark | Malaria, TB |
| *Zanthoxylum* (Rutaceae) | *Z. chalybeum* Engl.[23,97] | EA | Roots | Malaria, TB, backache. |
| | *Z. leprieurii* Guill and Perr.[138] | Uganda | Stem bark | Tuberculosis and cough related infections. |

## 3.3 Isoflavonoids

Isoflavonoids are secondary plant metabolites mainly restricted to the subfamily Papilionoideae of the Leguminosae,[42–46] the largest and third largest family of flowering plants in Africa[108] and the world,[43] respectively. Their structures are characterized by a 3-phenylchroman skeleton[45] which results biosynthetically from an oxidative migration of the aryl substituent of flavanones from C-2 to C-3 catalyzed by isoflavone synthase (IFS).[47–50] Isoflavonoids can be further subdivided into structurally different subclasses including isoflavones, isoflavanones, pterocarpans, rotenoids, isoflavans, isoflavanols and isoflav-3-enes (Figure 11) among others.[43–46] Isoflavones constitute the largest subclass of natural isoflavonoids followed by pterocarpans, isoflavanones, rotenoids and isoflavans respectively. To date more than 2500 natural isoflavonoids are known,[43–46,139–141] of which 391 were isolated in the period 2012 to 2017.[46] Although isoflavonoids are mainly restricted to the Leguminosae family, a few isoflavonoids have been reported in 31 non-leguminous families.[141] Isoflavonoids have been reported to exhibit a wide range of bioactivities including antioxidant,[51–53] antibacterial,[54–56] antifungal,[57,58] anti-plasmodial,[37,59] anti-inflammatory[60] and antiproliferative[61–63] activities. Some isoflavonoids act as phytoestrogens.[53,64,65] In addition to the fascinating bioactivities, isoflavonoids also play several important roles in plants such as modulating symbiotic interactions with microbes in the rhizosphere,[142] protecting plants against oxidative and other environmental stressors[143,144] and acting as antimicrobial phytoalexins.[143,144]

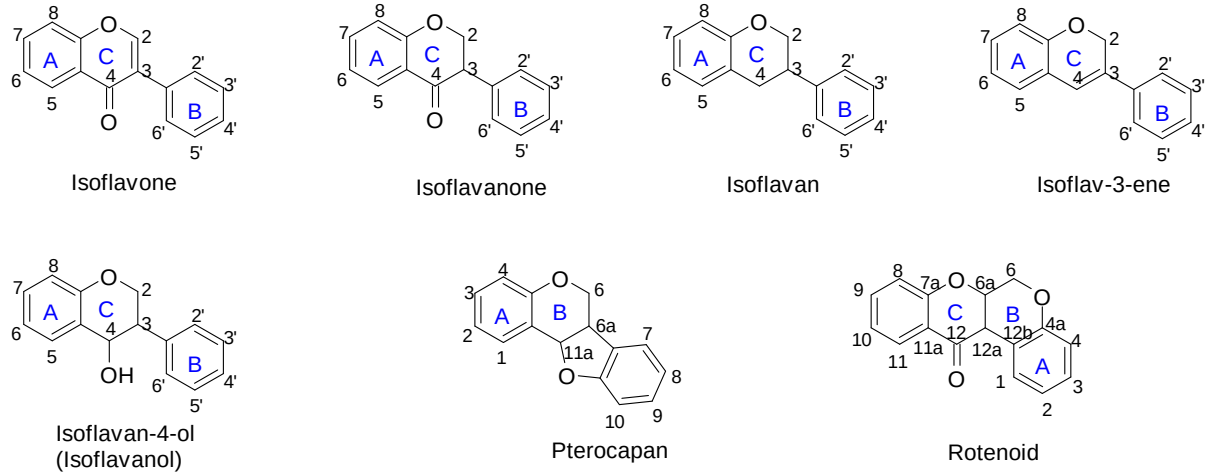
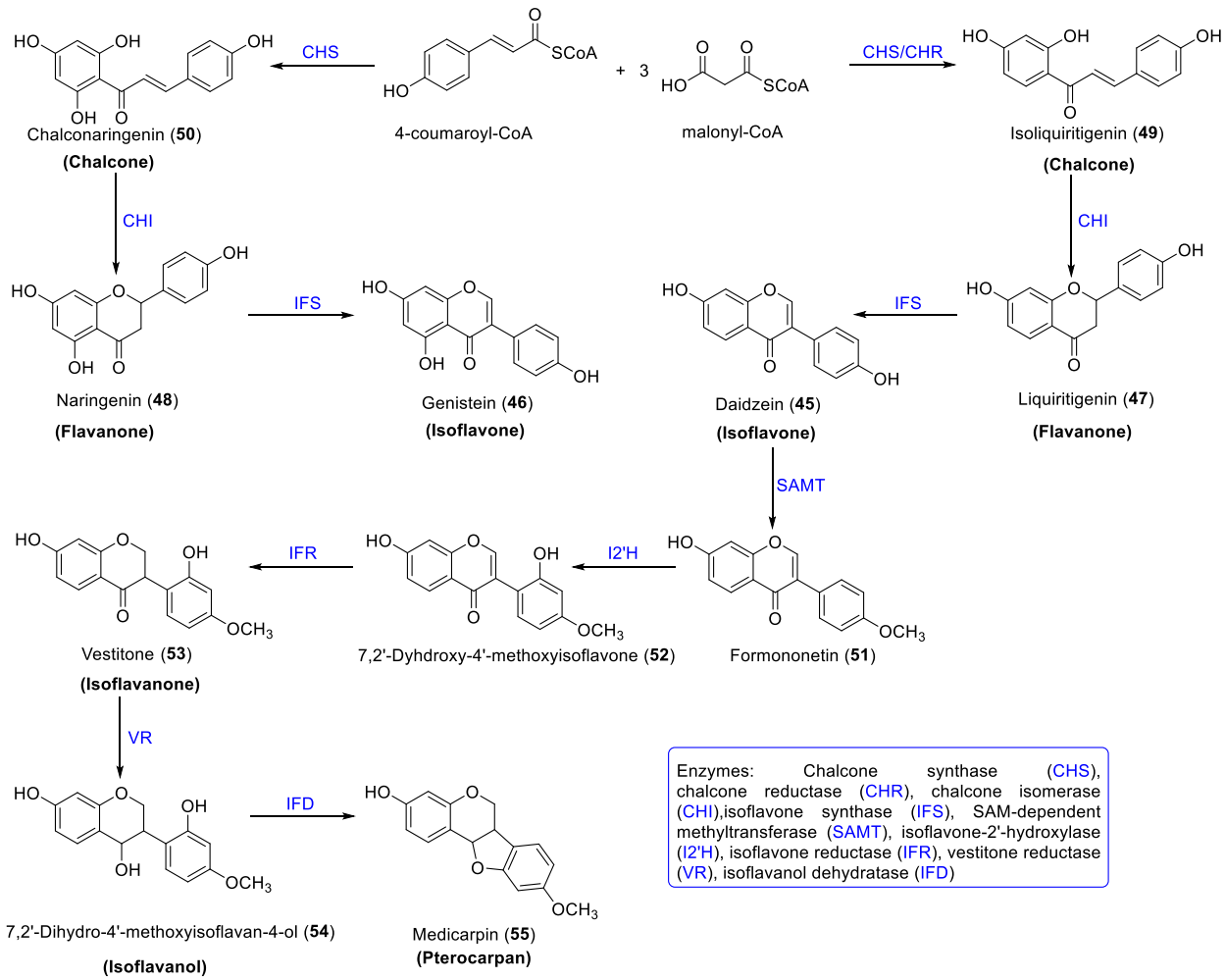



**Figure 11:** Different subclasses of isoflavonoids and their numbering systems

### 3.3.1 Biosynthesis of Isoflavonoids

The biosynthesis of isoflavonoids stems from an oxidative migration of the aryl substituent of flavanones from C-2 to C-3 catalyzed by isoflavone synthase (IFS) to produce isoflavones[47–50] as the primary isoflavonoids. IFS is a combination of two enzymes; 2-hydroxyisoflavanone synthase (2-HIS) which is a cytochrome P450 hydroxylase that catalyzes a migration of the aryl substituent and a hydroxylation at C-2 to give a 2-hydroxyisoflavanone and 2-hydroxyisoflavanone dehydratase (2-HID) which catalyzes the dehydration of the 2-hydroxyisoflavanone.[44,49] Biosynthetically, the primary isoflavones produced are daidzein (**45**) or genistein (**46**) resulting from the transformation of the flavanones liquiritigenin (**47**) or naringenin (**48**), respectively. The flavanones are biosynthesized from chalcones, which are formed via the phenylpropanoid pathway from 4-coumaroyl-CoA and three units of malonyl-CoA in the presence of chalcone synthase (CHS) and chalcone reductase (CHR). Chalcone isomerase (CHI) then induces a 6-endo-trig cyclization to flavanones, which are the central branching point in the biosynthesis of various flavonoids (Scheme 1).[44,47–50]

The primary isoflavones daidzein (**45**) and genistein (**46**) then undergo further modifications including hydroxylation catalyzed by hydroxylases, *O*- or *C*-methylation catalyzed by *S*-adenosyl methionine (SAM)-dependent methyltransferases and *O*- or *C*-prenylation by transfer of prenyl groups from dimethylallyl diphosphate (DMAPP) catalyzed by prenyl transferases to give a diversity of isoflavones.[43,50,145] Further modification of isoflavones also produce the various subclasses of isoflavonoids (Scheme 1).[43,50]




**Scheme 1:** Biosynthesis of isoflavonoids

### 3.3.2 Isoflavones

Isoflavones constitute the largest group of natural isoflavonoids[45] with the highest number of all the isoflavonoids reported in several reviews for every reporting period.[43–46,139–141] To date more than 840 isoflavones are known[43–46,139–141] representing approximately 34% of all the known isoflavonoids. They are characterized by a 3-phenylchromone skeleton.[50] Based on their biosynthesis, most isoflavones are oxygenated at positions 7 and 4′ although other substitution patterns do exist. The most common oxygenation patterns in their descending order are 5,7,4′ > 5,7,2′,4′ > 5,7,3′,4′ > 5,7,2′,4′,5′ > 7,4′ > 5,7,3′,4′,5′ > 7,2′,4′.[46] Isoflavones are classified into three main groups based on their substitution patterns. These groups include simple isoflavones (e.g., biochanin A (**56**)), characterized by simple substitution patterns (i.e., hydroxy, methoxy,

methylenedioxy and acetyl), isoflavone glycosides (e.g., genistin (**57**)) and prenylated isoflavones (e.g., 3′-prenylbiochanin A (**58**)) (Figure 12).

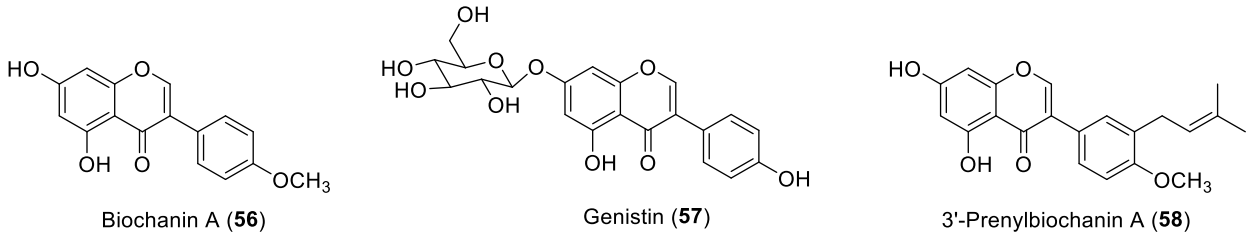



**Figure 12:** Different groups of isoflavones

Isoflavones are referred to as phytoestrogens due to their structural similarity to 17β-estradiol and ability to bind to mammalian estrogen receptors (ERs).[64] They are therefore capable of exerting receptor-mediated estrogenic, anti-estrogenic and non-genomic effects in various tissues.[146] Some epidemiologic studies have suggested dietary isoflavones, daidzein (**45**), genistein (**46**), formononetin (**51**) and biochanin A (**56**) to have beneficial effects on human health including reduction in cardiovascular diseases, increased memory, improved bone health, treatment of menopausal symptoms and chemoprevention of hormone-dependent cancers such as breast and prostate cancers.[146–148] In addition, isoflavones have been reported to exhibit a wide range of biological activities including antimicrobial,[54,56,58,123,149] anti-plasmodial,[37,150] antioxidant,[151] cytotoxic[38,123,152] and anti-inflammatory[151,153] activities.

Prenylated derivatives are reported to be more bioactive[66,67] due to their increased lipophilicity that enables them to permeate more rapidly through cell membranes and bind more efficiently to target proteins.[68] For instance, the prenylated isoflavones, 3′-prenylbiochanin A (**58**), 5-deoxy-3′-prenylbiochanin A (**59**), corylin (**60**), erysubin F (**61**), 5′-prenylprantensein (**62**) and 2,3-dehyrokievitone (**63**) (Figure 13), all isolated from *Erythrina sacleuxii* showed potential anti-plasmodial activity against chloroquine sensitive and resistant strains of *P. falciparum* at micromolar concentration.[37] Erysubin F (**61**) also showed antimycobacterial activity against *Mycobacterium tuberculosis* (MIC = 32.0 µM),[149] growth inhibition against methicillin resistant *Staphylococcus aureus* (MRSA)[56] and inhibition to protein tyrosine phosphatase 1B (PTP1B), a potential drug target in the therapy of ovarian and breast cancers.[66] 3′-Prenylbiochanin A (**58**) also showed antimycobacterial activity,[123] cytotoxicity against human breast cancer cell line MDA-MB-231[123] as well as inhibition to PTP1B.[154] 7-Methoxyebenosin (**64**) and griffonianone E (**65**),

isolated from *Millettia griffoniana* exhibited moderate trypanocidal and antiplasmodial activities.[134] Neobavaisoflavone (**66**), isolated from *Psoralea corylifolia*,[155] and *E. sigmoidea*,[54,58] showed significant antibacterial activity *in vitro* against *S. aureus*,[54] and moderate antifungal activity against *Aspergillus fumigatus* and *Cryptococcus neoformans*.[58] The same compound also showed significant inhibition of platelet aggregation induced by arachidonic acid (AA) and platelet activating factor (PAF)[153] as well as inhibition of reactive oxygen species (ROS), reactive nitrogen species (RNS) and cytokines: IL-1β, IL-6, IL-12p40, IL-12p70, TNF-α in LPS+IFN-γ- or PMA-stimulated RAW364.7 macrophages.[151] 8-Prenyldaidzein (**67**), isolated from *E. fusca* exhibited significant anti-plasmodial activity against the multi-drug resistant (K1) strain of *P. falciparum* ($IC_{50}$ = 12.1 μM).[150] Other prenylated isoflavones, isolated from *E. indica* including alpinumisoflavone (**68**), erysenegalensein E (**69**), 8-prenylerythrinin C (**70**) and wighteone (**7**) showed cytotoxic activity against KB cancer cell line with effective dose ($ED_{50}$) values at micromolar concentrations.[38] Wighteone also exhibited significant antibacterial activity against *Listeria monocytogenes* at micromolar concentration.[156] Among the 120 isoflavonoids investigated in a computational molecular docking study to the Dengue virus protase DENV NS2B-NS3, a potential drug target,[157] three prenylated isoflavones, **59**, **62** and glycyrrhisoflavone (**71**) gave calculated docking energies in the range of those of the known inhibitor M9P. Isowighteone (**72**) which was first isolated from *Cajanus cajan*[158] showed moderate antibacterial activity (MIC = 59.1 μM ) against both *L. monocytogenes* and *Escherichia coli*.[156] The 5,7,4′-trihydroxy-8,3′-diprenylisoflavone, isolupalbigenin (**73**), which was first isolated from *Lupinus luteus*,[159] and later from *E. poeppigiana*[160] has so far been reported to exhibit the highest antibacterial activity (MIC ranging from 3.8 to 7.7 μM) against MRSA among the isoflavones.[160]

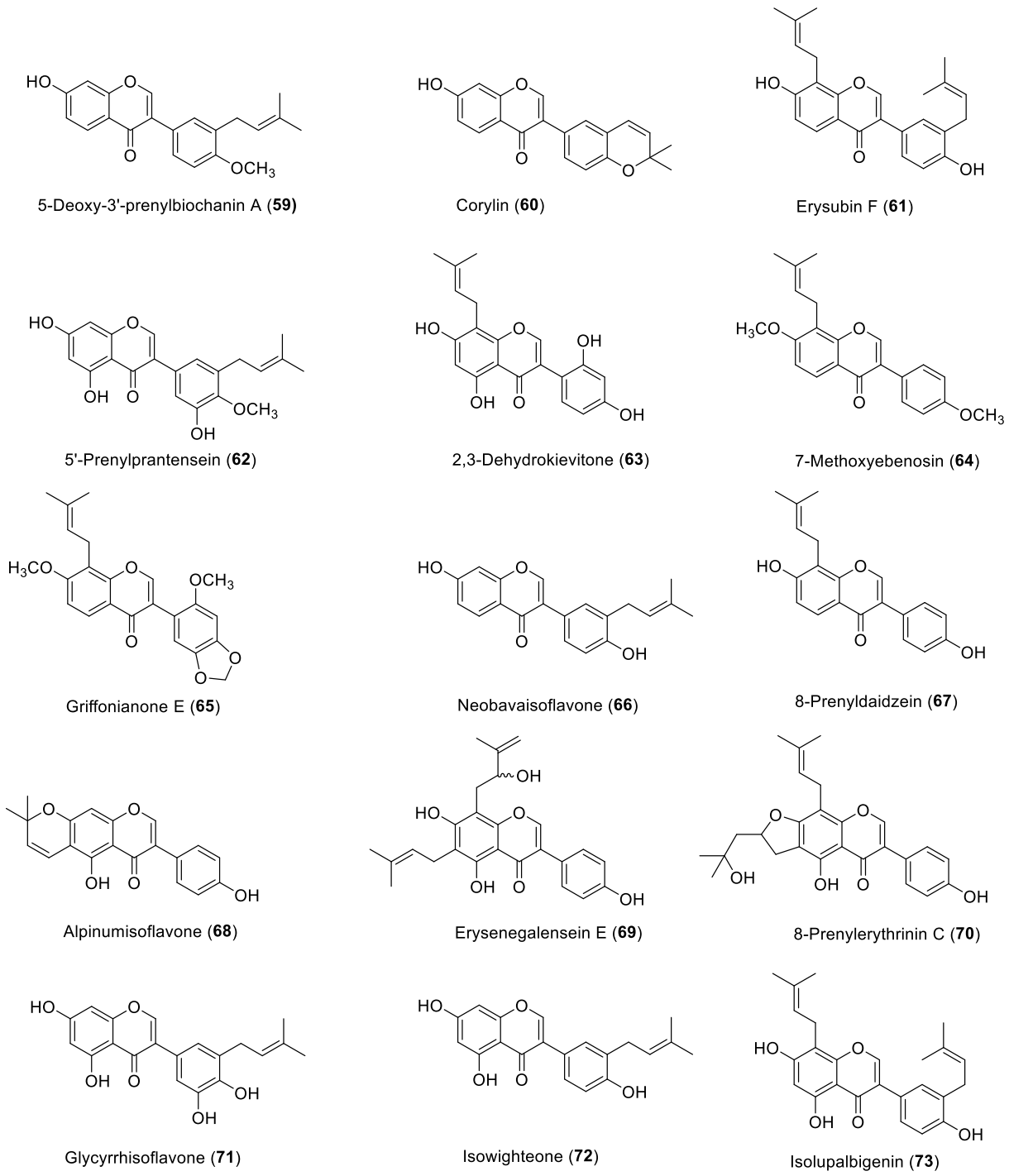


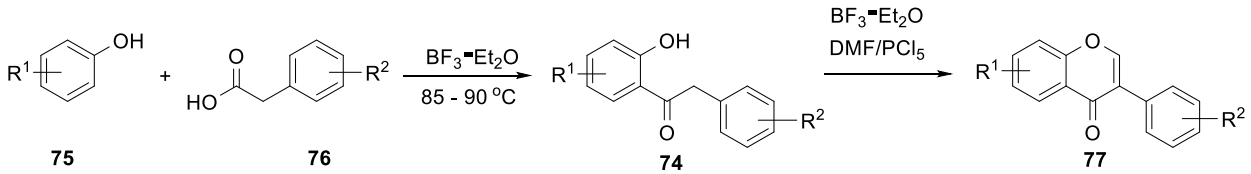

**Figure 13:** Examples of bioactive natural prenylated isoflavones

### 3.3.2.1 Synthesis of Isoflavones

There are four well established procedures which have for long been applied in the synthesis of isoflavones, i.e., the deoxybenzoin route,[89,161–165] the chalcone route,[75,76,166] oxidative rearrangement of flavanones[78,80,81,167–169] and Suzuki-Miyaura cross-coupling reactions of 3-halochromones with arylboronic acids.[83,84,86,88] All these methods have been utilized in the synthesis of some natural isoflavones. However, some methods have a limited scope and may not be applied to the synthesis of polyhydroxylated isoflavones and isoflavones bearing other naturally occurring substitution patterns such as prenyl groups.[85] Other methods such as rearrangement of chalcone epoxides[85] and intramolecular ketene cycloaddition followed by decarboxylation[170] have also been described, although they have not been frequently utilized.

#### *3.3.2.1.1 Deoxybenzoin Route*

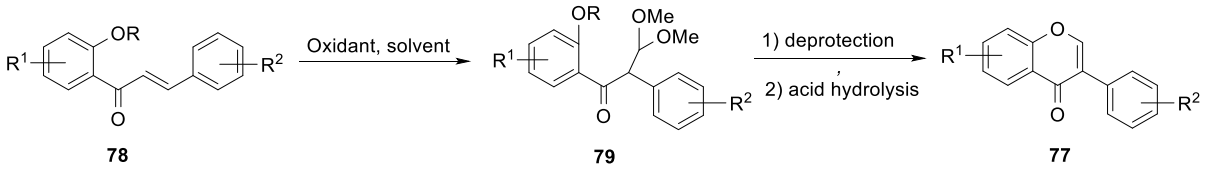
The deoxybenzoin route is the oldest known method for the synthesis of isoflavones. It was first described by Baker and Robinson in 1925.[171] The key step in the deoxybenzoin route is cyclization of the deoxybenzoin **74**, which is preceded by addition of one carbon unit required for the C-ring formation.[163] The deoxybenzoins **74** are prepared by regioselestive acylation of appropriately substituted phenols **75** with aryl acetyl chlorides or aryl acetic acids **76**.[164,165] Formylation of the deoxybenzoins introduces the additional carbon atom and cyclization of the resultant intermediate furnishes the isoflavones **77**. Formylation and cyclization of the deoxybenzoin can be achieved in a one pot single step reaction by reacting it with one of the following combinations of reagents: $BF_3$•$Et_2O$/DMF/$CH_3SO_2Cl$,[172] $BF_3$•$Et_2O$/DMF/$PCl_5$,[164] $HCO_2Et$/Na,[163] $HC(OEt)_3$/DMAP[163] or DMF-DMA/$C_6H_6$[162,165] (Scheme 2). The deoxybenzoin route has an advantage of possibility of being used for substrates with free phenolic hydroxyl groups. However, the acylation and some of the formylation/cyclization processes involved suffer shortcomings of low yields, harsh reaction conditions, lengthy reaction times and the use of toxic reagents.[163,165]



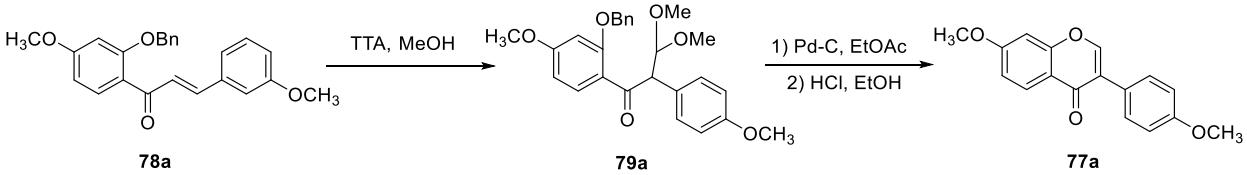

**Scheme 2:** General synthesis of isoflavones via the deoxybenzoin route

### *3.3.2.1.2 Chalcone Route*

The chalcone route involves an oxidative 1,2-aryl migration of a 2′-*O*-protected chalcone **78** to give 1,2-diaryl-3,3-dimethoxypropan-1-one derivatives **79**. The consecutive deprotection and acid hydrolysis of the acetal **79** affords the target isoflavone **77**.[74,75] (Scheme 3). This method was first described by Ollis and coworkers in 1968.[75] In their work, 2′-benzyloxy-4,4′-methoxychalcone (**78a**) was oxidized with thallium acetate in methanol to give the acetal **79a**. The consecutive palladium catalyzed hydrogenolysis and acid hydrolysis of **79a** afforded dimethyldaidzein (**77a**) (Scheme 4).

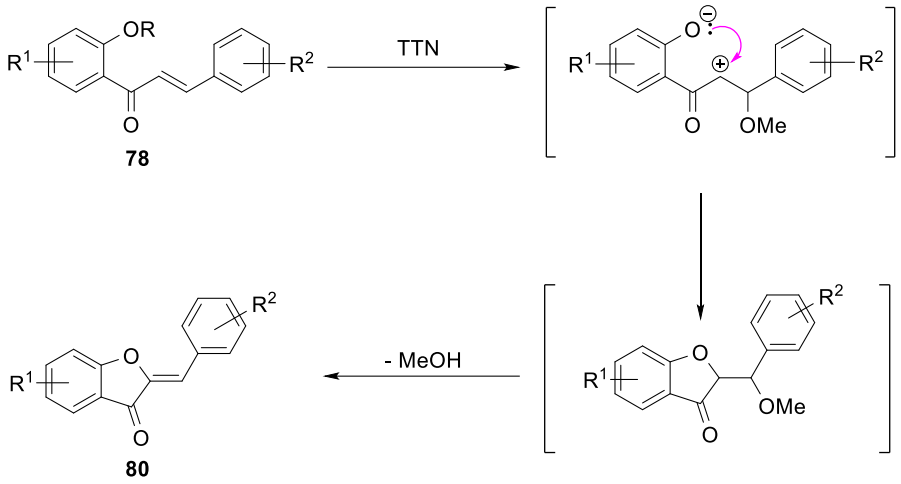



**Scheme 3:** General synthesis of isoflavones via the chalcone route



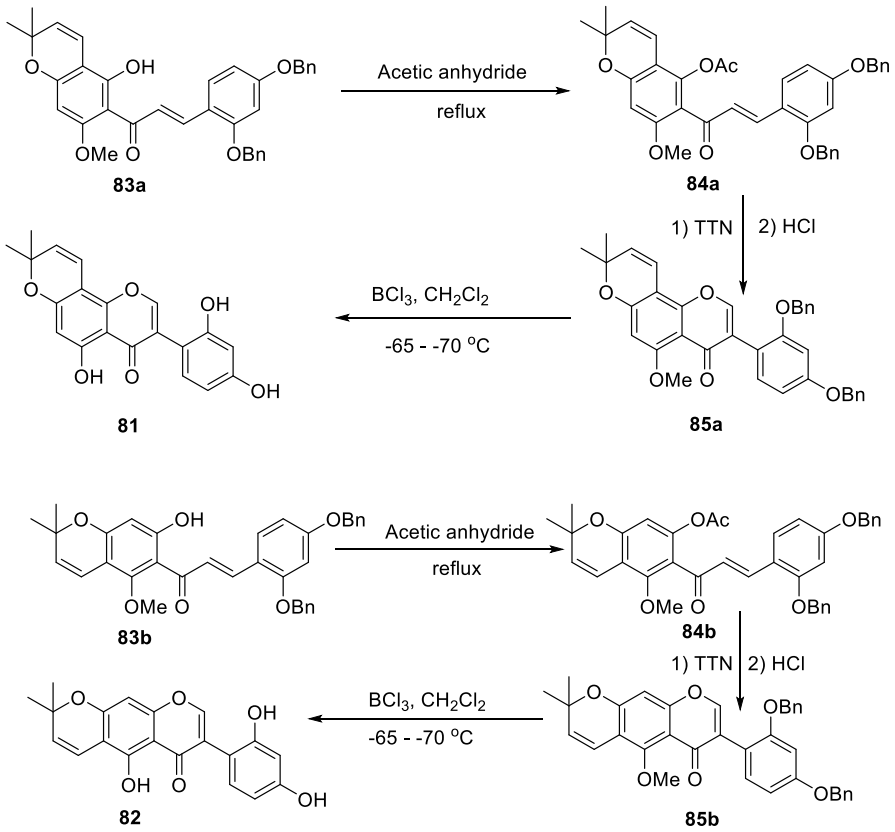

**Scheme 4:** Synthesis of dimethyldaidzein (**77a**) by Ollis *et al*.[75]

The chalcone route has an advantage of the easily available or accessible starting 2′-hydroxychalcones over the deoxybenzoin route. However, the oxidative rearrangement of 2′-hydroxychalcones using thallium nitrate has sometimes been reported to produce aurones **80** as side products or the sole isolable product.[171] A mechanism for this transformation has also been proposed (Scheme 5).



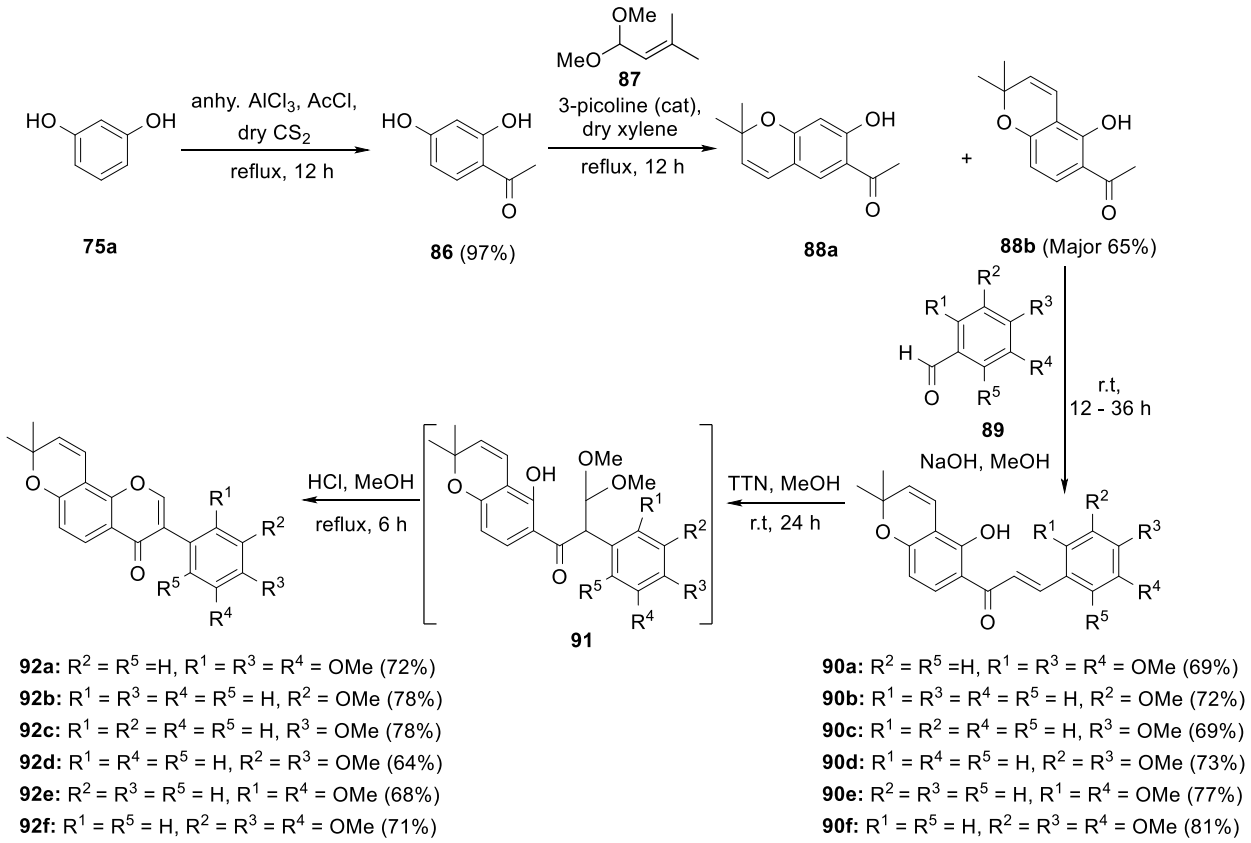

**Scheme 5:** Proposed mechanism for the transformation of chalcones to aurones[171]

The chalcone route was later utilized by Tsukayama *et al*. for the synthesis of parvisoflavones A (**81**) and B (**82**).[76] In their procedure, the pre-synthesized angular and linear pyranochalcones **83a** and **83b** were acetylated to give **84a** and **84b**, respectively. The consecutive oxidative rearrangement of **84a** and **84b** with thallium (III) nitrate trihydrate (TTN) and cyclization of the resultant compounds with dilute HCl under reflux furnished the corresponding pyranoisoflavones **85a** and **85b**. Simultaneous debenzylation and demethylation of **85a** and **85b** using a solution of boron trichloride in dichloromethane afforded the target isoflavones parvisoflavones A (**81**) and B (**82**), respectively (Scheme 6).




**Scheme 6:** Synthesis of parvisoflavones A (**81**) and B (**82**) by Tsukayama *et al.*[76]

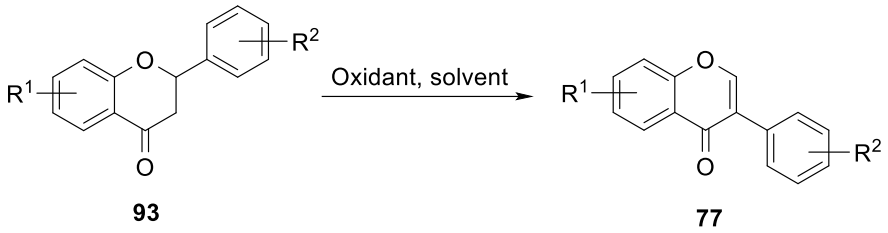
In 2014, Wei and coworkers also utilized the chalcone route to synthesize a series of natural and non-natural isoflavones[166] (Scheme 7). Their synthesis started with the Friedel Crafts acylation of resorcinol (**75a**) to give 2′,4′-dihydroxyacetophenone (**86**). Compound **86** was then refluxed with 1,1-dimethoxy-3-methylbut-2-ene (**87**) in the presence of catalytic picoline in dry xylene to afford **88a** and **88b**. Condensation of **88b** with various arylaldehydes **89** gave the corresponding chalcones **90**. Oxidative rearrangement of the chalcones **90** using TTN in methanol afforded the corresponding acetals **91**, which on cyclization with dilute HCl in methanol furnished the target isoflavones **92**. The isoflavones included barbigerone (**92a**), calopogoniumisoflavone A (**92c**), 3′4′-dimethoxy-5″,6″-dimethylpyranoisoflavone (**92d**), and non-natural analogues **92b**, **92e** and **92f**. Their protocol demonstrated the possibility of the oxidative rearrangement of unprotected 2′-hydroxychalcones.




**Scheme 7:** Synthesis of barbigerone (**92a**) and related isoflavones by Wei *et al.*[166]

### *3.3.2.1.3 Oxidative Rearrangement of Flavanones*

The conversion of flavanones into isoflavones was first reported in the early 1960s.[173] It involves an oxidative aryl migration from C-2 to C-3 of a flavanone **93** (Scheme 8).[80,81,167,169] The reagents which have been used for this oxidative rearrangement include thallium(III) salts[78,80,81,169] such as thallium(III) nitrate, thallium(III) acetate, thallium(III) *p*-tosylate, and hypervalent iodine reagents[167,168] such as phenyliodonium diacetate, (PIDA), phenyliodonium bis(trifluoroacetate) (PIFA) and [hydroxy(tosyloxy)iodo]benzene (HTIB). Hypervalent iodine reagents have an advantage of being environmentally friendly over the toxic thallium(III) salts.[174,175] The reaction mimics the in vivo rearrangement of flavanone precursors in the biosynthesis of isoflavones (Scheme 1).

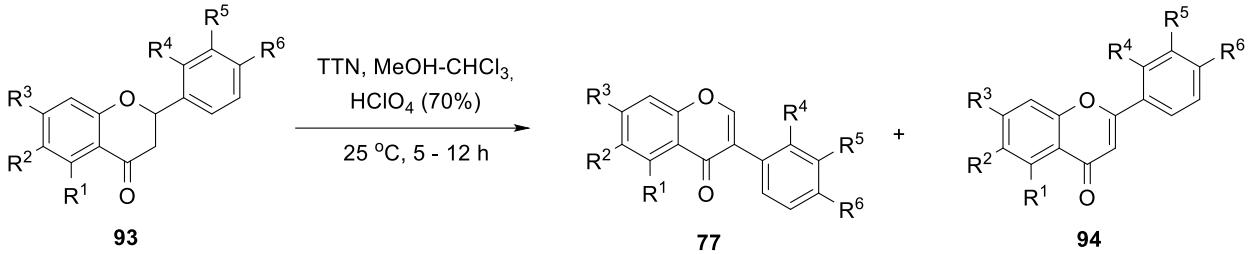



**93** **77**

**Scheme 8:** General synthesis of isoflavones via the 2,3-oxidative aryl rearrangement of flavanones

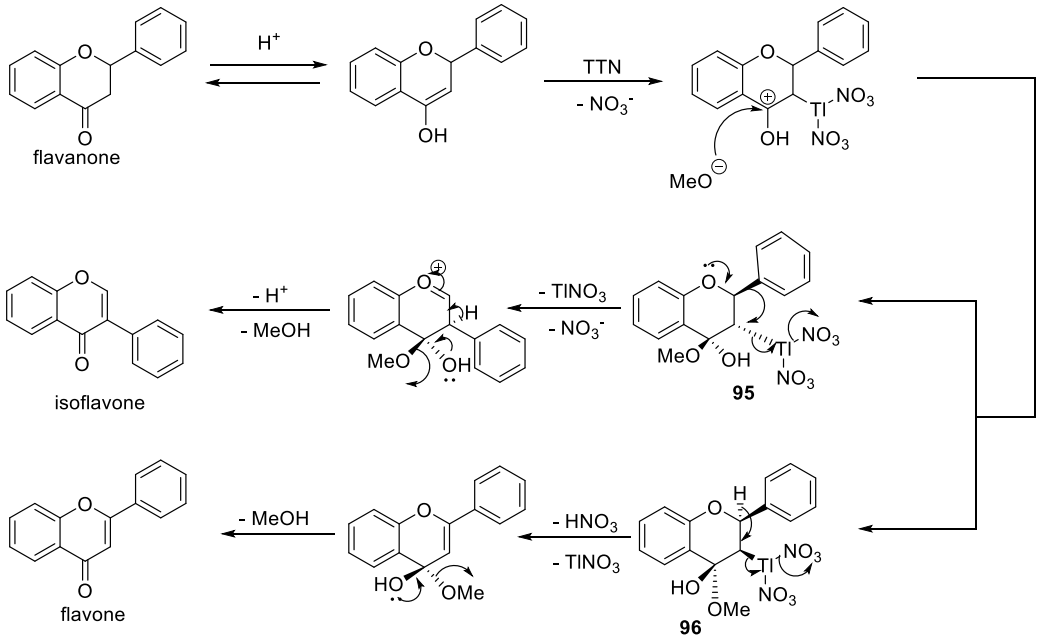
Kinoshita and coworkers utilized this method in 1990 to synthesize isoflavones with varying substitution patterns on both rings A and B.[169] They prepared flavanones with various substitution patterns by the acid catalyzed cyclization of the corresponding chalcones in 60 - 80% yield. The flavanones were converted into isoflavones by reacting them with TTN in methanol-$CHCl_3$ mixture containing 70% perchloric acid (Table 2). In their experiments, the corresponding flavones were also produced as side products. Kinoshita *et al*. also proposed a mechanism of the 2,3-oxidative aryl rearrangement of flavanones (Scheme 9). The initial step is the acid catalyzed enolization of the flavanone followed by alkoxythalliation to give two unstable thalliated intermediates **95** and **96**. The *anti*-intermediate **95** is predominant and its dethalliation proceeds via migration of the aryl group followed by elimination of methanol and a proton resulting in the formation of the corresponding isoflavone. The minor *syn*-intermediate **96** only undergoes dethalliation accompanied by elimination of a proton and methanol to afford the corresponding flavone. A similar mechanism is plausible when using hypervalent iodine reagents as oxidants.[176] When trimethyl orthoformate is used as solvent in the presence of an acid catalyst, with PIDA as an oxidant, the *anti*-intermediate **95** can also undergo a ring contraction by 1,2 migration of the A-ring aryl moiety to give the intermediate carbenium ion **97**. Abstraction of a proton from the carbenium ion **97** affords benzofurans **98** as the major product[176] (Scheme 10).

**Table 2:** Synthesis of isoflavones via a 2,3-oxidative aryl rearrangement of flavanones by Kinoshita *et al*.

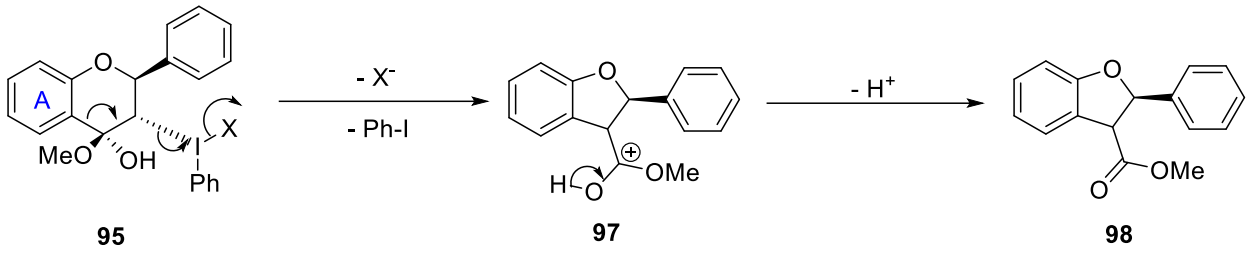



**93** **77** **94**

| entry | **93** | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | **77** | yield (%) | **94** | yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **93a** | H | H | OMe | H | H | OMe | **77a** | 28 | **94a** | 6 |
| 2 | **93b** | H | H | H | H | H | Me | **77b** | 63 | **94b** | 15 |
| 3 | **93c** | H | H | H | H | H | OMe | **77c** | 59 | **94c** | 10 |
| 4 | **93d** | H | H | H | H | H | F | **77d** | 75 | **94d** | 9 |
| 5 | **93e** | H | H | H | H | H | Cl | **77e** | 65 | **94e** | 7 |
| 6 | **93f** | H | H | H | H | H | Br | **77f** | 73 | **94f** | 8 |
| 7 | **93g** | H | H | H | H | H | H | **77g** | 65 | **94g** | 13 |
| 8 | **93h** | H | H | OMe | H | H | H | **77h** | 48 | **94h** | 10 |
| 9 | **93i** | H | H | OMe | H | H | F | **77i** | 57 | **94i** | 14 |
| 10 | **93j** | OMe | H | OMe | H | H | OMe | **77j** | 28 | **94j** | 6 |
| 11 | **93k** | H | H | OBz | H | H | OMe | **77k** | 29 | **94k** | 7 |
| 12 | **93l** | H | OMe | OMe | H | OMe | OMe | **77l** | 25 | **94l** | 6 |

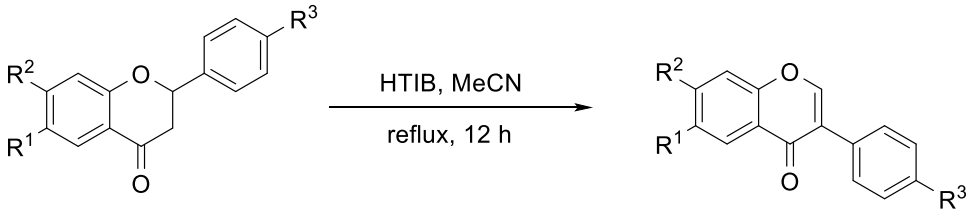



**Scheme 9:** Proposed mechanism for the transformation of flavanones to isoflavones and flavones[169]




**Scheme 10:** Plausible mechanism of ring contraction to form benzofurans **98**

In the same year, 1990, Prakash *et al*. accomplished a similar oxidative rearrangement of flavanones using the hypervalent iodine reagent, HTIB as an oxidant in acetonitrile.[167] They produced isoflavones including dimethyldaidzein (**77a**) in yields of 72-80%. They did not report the isolation of any flavone as a side product (Scheme 11).

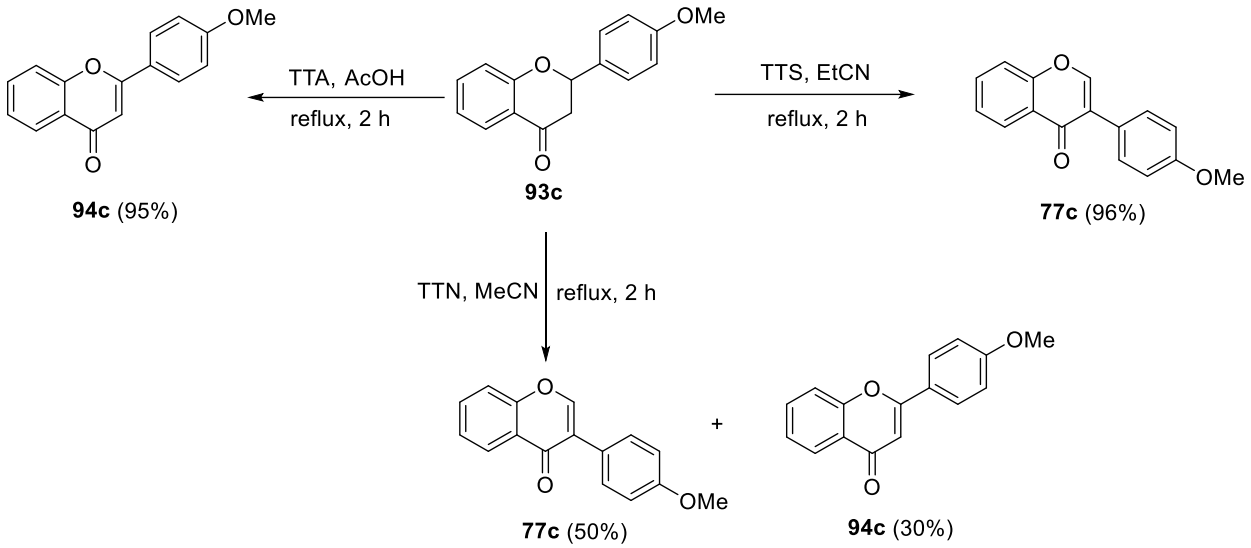



**77a:** $R^1$ = H, $R^2$ = $R^3$ = OMe (74%)
**77c:** $R^1$ = $R^2$ = H, $R^3$ = OMe (76%)
**77g:** $R^1$ = $R^2$ = $R^3$ = H (75%)
**77m:** $R^1$ = Cl, $R^2$ = H, $R^3$ = OMe (80%)
**77n:** $R^1$ = Cl, $R^2$ = H, $R^3$ = Me (78%)
**77o:** $R^1$ = Me $R^2$ = H, $R^3$ = Cl (75%)
**77p:** $R^1$ = Cl, $R^2$ = $R^3$ = H (72%)

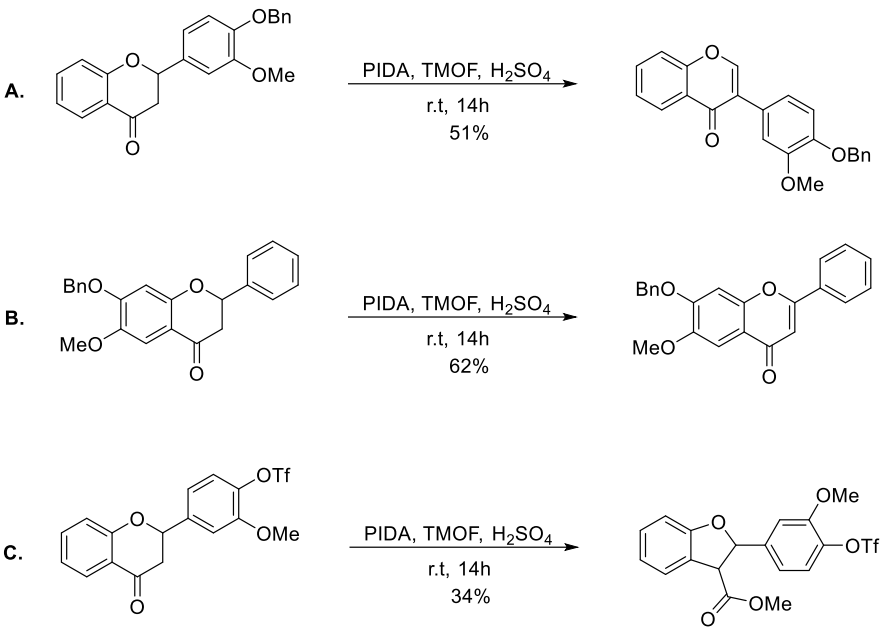
**Scheme 11:** Synthesis of isoflavones via 2,3-oxidative rearrangement of flavanones by Prakash *et al*.[167]

On further investigation on the scope of the oxidative rearrangement of flavanones, Khanna *et al*. indicated that when using thallium(III) salts as oxidants, the product is dependent on the thallium (III) salt and the solvent used.[81] The reaction of a flavanone with thallium(III) acetate (TTA) in acetic acid or acetonitrile affords a flavone as the sole product while its reaction with thallium(III) *p*-tosylate (TTS) or TTN in propionitrile or acetonitrile, respectively affords isoflavones in high yields. For instance, the reaction of 4′-methoxyflavanone (**93c**) with TTA in acetic acid afforded

4′-methoxyflavone (**94c**) as the sole product in 95% yield. When the same flavanone was reacted with TTN in acetonitrile, it afforded a mixture of 4′-methoxyisoflavone (**77c**) and the flavone **94c** in the ratio of ca. 5:3 while its reaction with TTS in propionitrile afforded the isoflavone **77c** as the sole product in 96% yield (Scheme 12). Bhatti and coworkers also indicated that the oxidative rearrangement of flavanones is dependent on the substitution pattern on both aromatic rings of the flavanone.[168] In their investigation, they noted that an electron donating group at C-4′ of the B-ring is essential for the oxidative 2,3-aryl migration of a flavanone using PIDA as an oxidant (Scheme 13 A.) while unsubstituted ring B and more substitution on ring A favors dehydrogenation to afford a flavone (Scheme 13B.). Oxidative rearrangement of a flavanone with a triflate substituent at the C-4′of the B-ring afforded a 2,3-dihydrobenzofuran (Scheme 13C.).

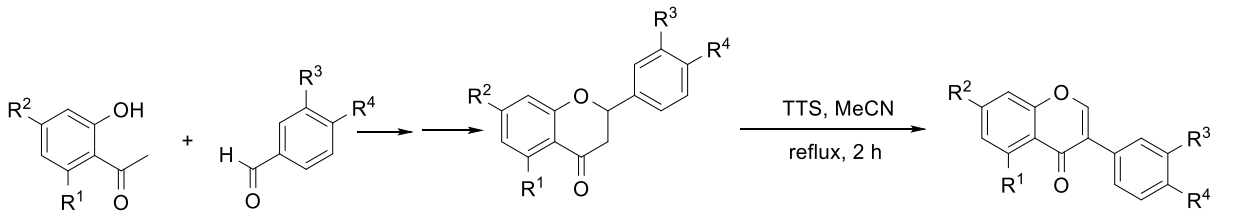



**Scheme 12:** Oxidative rearrangement of flavanone **93c** using thallium(III) acetate, thallium(III) *p*-tosylate and thallium(III) nitrate by Khanna et al.[81]




**Scheme 13:** Effect of substitution pattern on the oxidative rearrangement of flavanones

In 2005, Singh and Muthukrishman synthesized a number of naturally occurring isoflavones in high yields via the 2,3-oxidative rearrangement of the respective flavanones using TTS.[78] The flavanones were produced by the base catalyzed cyclization of the respective chalcones which were synthesized by the condensation of the corresponding acetophenones and benzaldehydes (Scheme 14).

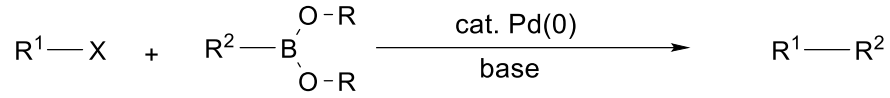



**77a:** $R^1 = R^3 = H$, $R^2 = R^4 = OMe$ (90%)
**77q:** $R^1 = H$, $R^2 = R^3 = R^4 = OMe$ (86%)
**77r:** $R^1 = R^2 = R^4 = OMe$, $R^3 = H$ (85%)
**77s:** $R^1 = R^2 = OMe$, $R^3$, $R^4$ = $-OCH_2O-$ (82%)

**Scheme 14:** Synthesis of isoflavones via 2,3-oxidative rearrangement of flavanones by Singh and Muthukrishman[78]

#### *3.3.2.1.4 Suzuki-Miyaura Cross-Coupling Reactions*

The Suzuki-Miyaura cross-coupling reaction was developed by Suzuki, Miyaura and Yamada, and it was first published in 1979.[177] It is a reaction of an alkenyl, alkynyl or aryl halide with an alkenyl or aryl borane to give the coupled product using a palladium catalyst and a base (Scheme 15). A wide range of palladium(0) catalysts or precursors such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, Pd/C or $Pd(OAc)_2$ and $Pd_2(dba)_3$ plus phosphine ligands such as $PPh_3$ or $PCy_3$ can be used for this reaction,[83–86,178–182] of which $Pd(PPh_3)_4$ is the most commonly used.




**Scheme 15:** General representation of a Suzuki-Miyaura cross-coupling reaction

The catalytic cycle involves three main steps, i.e., oxidative addition, transmetalation and reductive elimination (Figure 14).[183] It begins with the oxidative addition of the alkenyl, alkynyl or aryl halide to the Pd(0) to form a Pd(II) complex. A molecule of the hydroxide base then substitutes the halide on the palladium(II) complex. This is followed by transmetalation, where the alkenyl or aryl group of the borane, after being activated by the base substitutes the hydroxide anion on the palladium(II) complex. Reductive elimination then gives the final coupled product, regenerating the palladium(0) catalyst, and the catalytic cycle continues. The oxidative addition is the rate determining step and the relative reactivity of the organohalides increases in the order Cl << Br < OTf < I.[183]

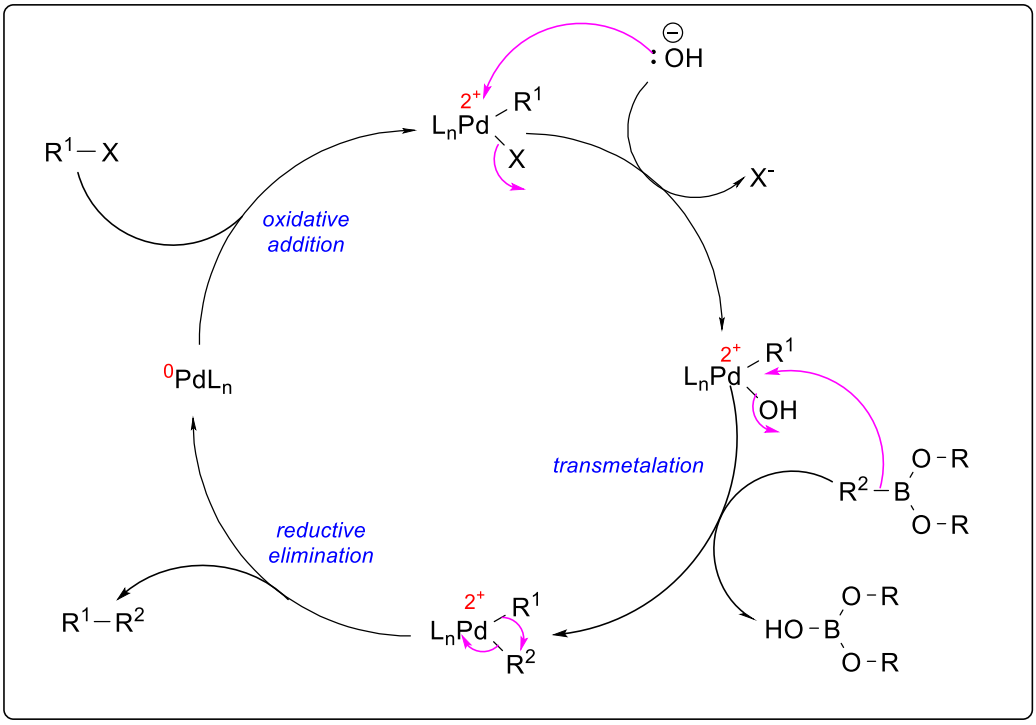
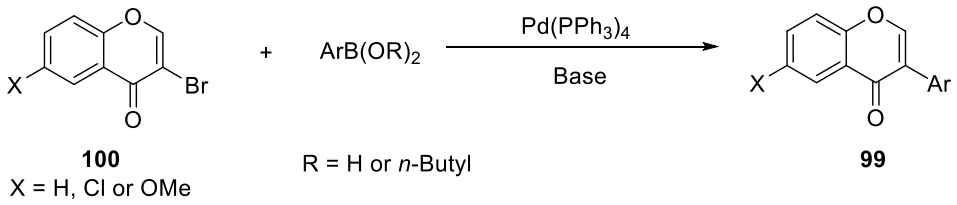


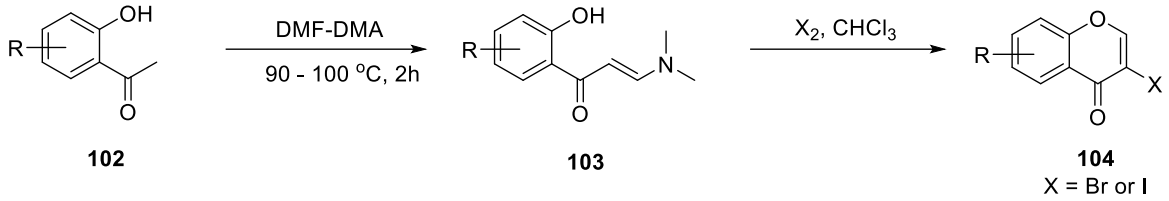

**Figure 14:** Catalytic cycle of the Suzuki-Miyaura cross-coupling reaction

Since the Suzuki-Miyaura cross-coupling reaction is used for the creation of C-C bonds between alkenyl and/or aryl carbon atoms, it can be applied to the flavonoid synthesis to construct chalcone, flavone and isoflavone cores. Its application to the synthesis of isoflavones was first demonstrated by Suzuki and coworkers in 1988 when they synthesized isoflavones **99** by the cross-coupling reaction of 3-bromochromones **100** and arylboronic acids/esters using $Pd(PPh_3)_4$ catalyst (Scheme 16).[83] Since then, the Suzuki-Miyaura cross-coupling reaction of 3-halochromones and arylboronic acids has been widely applied in the synthesis of isoflavones[84–88] including natural isoflavones such as genistein (**46**), daidzein (**45**) and its methylated derivatives, isoformononetin (**101**) and dimethyldaidzein (**77a**). The application of Suzuki-Miyaura cross-coupling reaction to the synthesis of isoflavones and other flavonoids has been reviewed by Selepe and Heerden.[85]



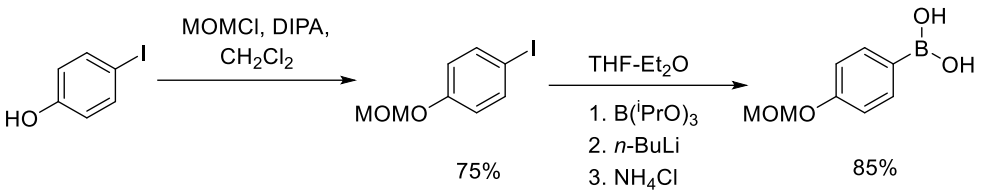

**Scheme 16:** Synthesis of isoflavones by Suzuki-Miyaura cross-coupling reaction[83]

A convenient method for the preparation of the 3-halochromone precursors for isoflavone synthesis was developed by Gammill in 1979.[184] It involves the condensation of the appropriately substituted 2′-hydroxyacetophenones **102** with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) to form enamino ketones **103**. The enamino ketones undergo halogen-mediated ring closure to afford the corresponding 3-halochromones **104** (Scheme 17). Most 3-halochromone precursors for isoflavone synthesis have been prepared by this protocol.[84,86–88]

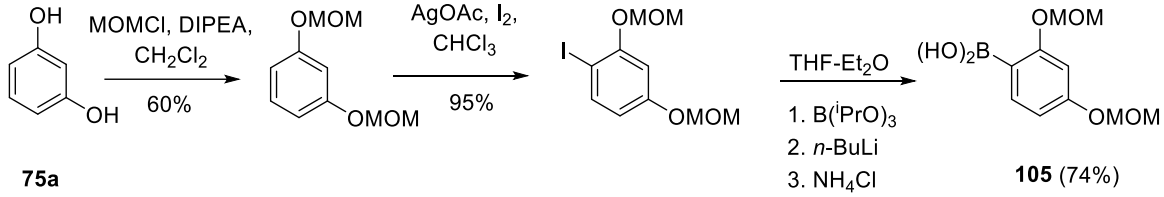



**Scheme 17:** Gammill's protocol for the synthesis of 3-halochromones[184]

In 2010, Selepe and coworkers also reported a protocol for the preparation of arylboronic acids from aryl iodides (Scheme 18).[86] It involves a lithium – iodine exchange with *n*-BuLi, followed by treatment of the phenyl lithium with triisopropyl borate and hydrolysis of the resulting boronated ester. This protocol can be applied to the synthesis of arylboronic acids which are either not readily available or expensive. For instance, Selepe *et al*. applied this protocol to prepare arylboronic acid **105** starting from the readily available resorcinol (**75a**) (Scheme 19).[185] Boronic acid **105** is a suitable precursor for the synthesis of 2′,4′-dihydroxylated natural isoflavones.



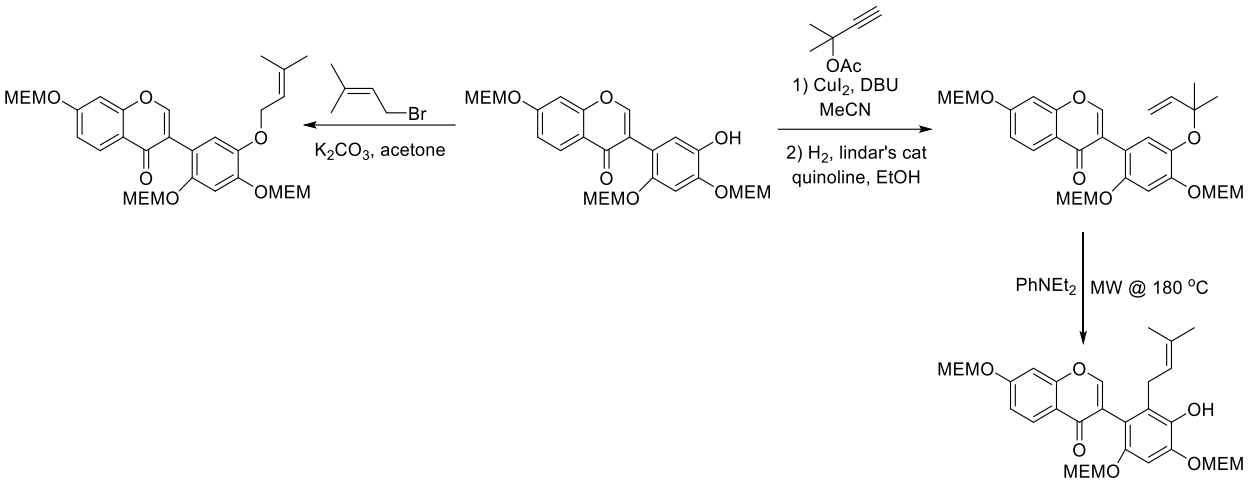

**Scheme 18:** Preparation of *MOM*-protected arylboronic acid from aryl iodide[86]



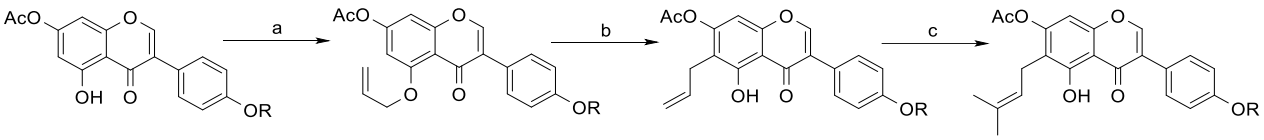

**Scheme 19:** Preparation of 2,4-di-*MOM*-protected arylboronic acid from resorcinol[185]

### *3.3.2.1.5 Synthesis of prenylated Isoflavones*

*C*- or *O*-Prenylated isoflavones are produced by *C*- or *O*-prenylation, respectively. Whereas *O*-prenylation can easily be achieved in a single step $S_N2$ reaction of prenyl bromide with a phenolic OH- group of the isoflavone[88,166,186] (Scheme 20), *C*- prenylation is more challenging. For most reported syntheses of *C*-prenylated isoflavones, the prenyl group was introduced after the construction of the isoflavone core via *O*-allylation followed by Claisen rearrangement and olefin cross metathesis[89,187] (Scheme 21) or *O*-propargylation followed by reduction of the propargyl group and Claisen rearrangement of the resultant 1,1- dimethylallyl ether[88] (Scheme 20). *C*-prenylation of isoflavones has also been achieved via a palladium catalyzed coupling of 3-methyl-3-buten-2-ol with an appropriate iodoisoflavone followed by hydrogenation and then dehydration of the resulting saturated side chain alcohol[90] (Scheme 22).

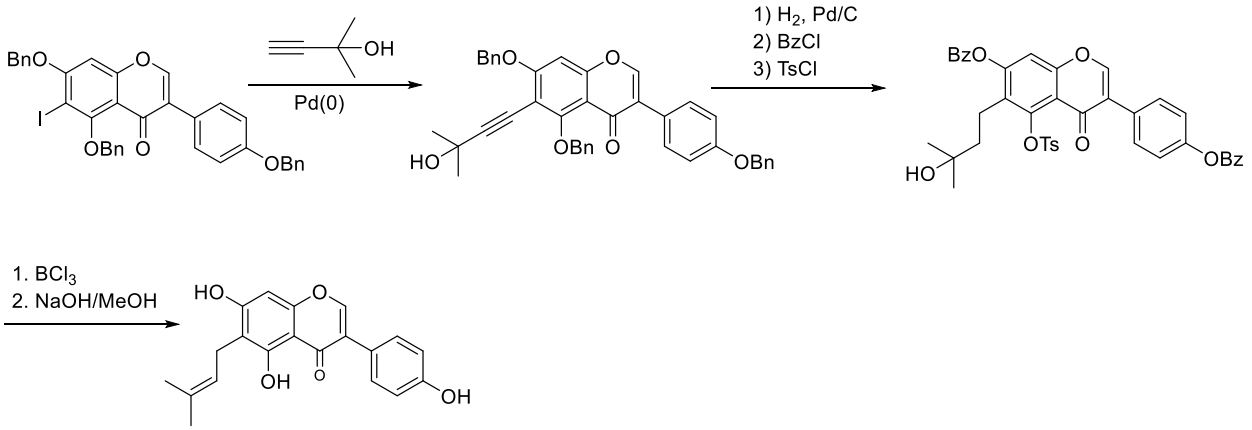



**Scheme 20:** *O*-Prenylation and *C*-prenylation via *O*-propargylation of isoflavones




*Reagents and conditions:* a) allyl alcohol, $PPh_3$, DEAD, THF, 0 ºC - r.t; b) 10 mol% $Eu(fod)_3$, $CHCl_3$, 85 ºC; c) 2-methyl-2-butene, benzene, Grubbs II cat., r. t.

**Scheme 21:** *C*-Prenylation of isoflavones by allylation/cross metathesis protocol.




**Scheme 22:** *C*-Prenylation of isoflavones via palladium catalyzed coupling

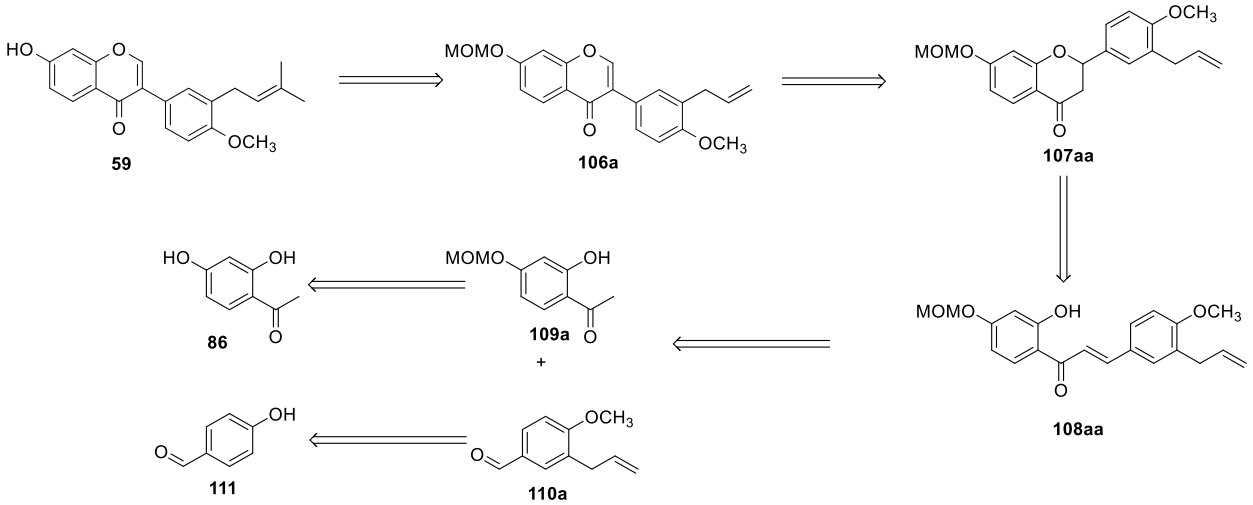
# 4 Results and Discussion

## 4.1 Synthesis of Isoflavones via 2,3-Oxidative Aryl Rearrangement of Flavanones

The objective was to synthesize naturally occurring *C*-prenylated isoflavones and related analogues via 2,3-oxidative aryl rearrangement of the respective flavanones using hypervalent iodine reagents, and to investigate the scope of the method.

### 4.1.1 Synthesis of 5-Deoxy-3′-prenylbiochanin A (59)

The synthesis of 5-deoxy-3′-prenylbiochanin A (**59**) was used as a model synthesis and for the optimization of reaction conditions for the synthesis of other related prenylated isoflavones. Its retrosynthesis is outlined in Scheme 23. Compound **59** was envisaged from olefin cross metathesis (CM) and MOM- deprotection of **106a**. **106a** could be obtained by the 2,3-oxidative aryl rearrangement of flavanone **107aa**, which could arise from the base catalyzed cyclization of chalcone **108aa**. Chalcone **108aa** could be afforded by the Claisen-Schmidt condensation of acetophenone **109a** and benzaldehyde **110a**, which could be prepared from the commercially available 2′,4′-dihydroxyacetophenone (**86**) and 4-hydoxybenzaldehyde (**111**), respectively.



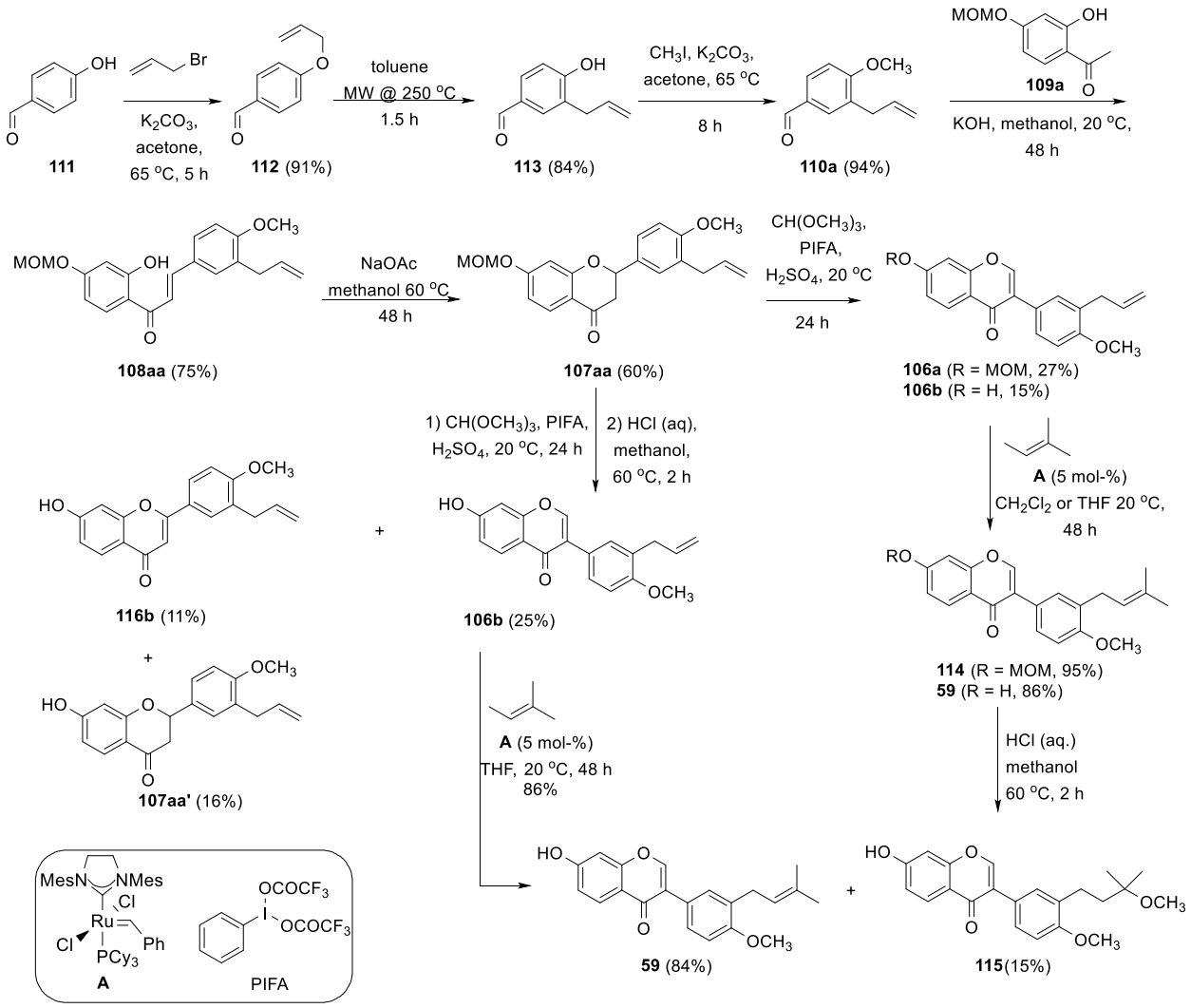

**Scheme 23:** Retrosynthesis of 5-deoxy-3′-prenylbiochanin A (**59**)

The 3′-allyl-4′-methoxyflavanone **107aa** was conceived as a key intermediate for the synthesis of **59** and it was therefore synthesized starting from 2′,4′-dihydroxyacetophenone (**86**) and 4-hydroxybenzaldehyde (**111**) (Scheme 24). Compound **111** was oxy-allylated to afford the allyl ether **112**. Claisen rearrangement of **112** under microwave irradiation at 250 ºC furnished **113**. Microwave irradiation was preferred for this transformation to the previously reported conventional heating protocol[188] due to its relatively shorter reaction time. Methylation of **113** and Claisen-Schmidt condensation[189] of the resulting benzaldehyde **110a** with acetophenone **109a**, which was prepared by MOM-etherification of 2′,4′-dihydroxyacetophenone (**86**)[190] afforded chalcone **108aa**. The base catalyzed cyclization of **108aa** furnished the flavanone **107aa**.

Flavanone **107aa** was then used for optimization of the 2,3-oxidative rearrangement reaction (Table 3). In the optimization study, the 2,3-oxidative rearrangement of **107aa** using PIFA in trimethyl orthoformate (TMOF) in the presence of catalytic sulfuric acid gave the highest yield of isoflavones **106** (i.e., **106a**, 27% and **106b**, 15%). The two isoflavones **106a** and **106b** and the unreacted substrate **107aa** were separated by column chromatography on silica gel.

The prenyl group was introduced by an olefin cross metathesis reaction[191] of **106** with 2-methyl-2-butene, a previously reported valuable and convenient cross metathesis partner for the regioselective construction of prenyl substituents.[89,187,190,192] The MOM-protected 3′-allylisoflavone **106a** was converted to 3′-prenylisoflavone **114** in the presence of 5 mol % of second-generation Grubbs' catalyst (**A**)[193] in dichloromethane in excellent yield and selectivity. There was no self CM products or CM products with a crotyl substituent observed, which was previously reported by Sytniczuk and coworkers in a catalyst screening for the olefin cross metathesis of methyl oleate with 2-methyl-2-butene.[194] The second generation Grubbs' catalyst was selected as the catalyst of choice because Sytniczuk *et al*. had reported the less active first generation catalysts to favor self-metathesis dimerization of the CM partner.[194] The MOM-deprotection of **114** by refluxing it with aqueous HCl (4M) in methanol furnished the target 5-deoxy-3′-prenylbiochanin A (**59**) in 84% yield and the methyl ether **115** in 15% yield resulting from concomitant acid catalyzed addition of methanol to the prenyl substituent. Olefin cross metathesis of the MOM-deprotected 3′-allylisoflavone **106b** in THF as a solvent was also successful and it furnished the target 5-deoxy-3′-prenylbiochanin A (**59**) in 86% yield. THF was used as a solvent because **106b** was sparingly soluble in dichloromethane, the most conveniently

used solvent for cross metathesis reactions.[89,190–192,195] Although sometimes coordinating groups in the substrate, including phenolic OH groups can lead to catalyst inhibition through coordination to the metathesis catalyst,[190,196] it was not expected in this case because the phenolic OH group is not in proximity with the allyl substituent.




**Scheme 24:** Synthesis of 5-deoxy-3′-prenylbiochanin A (**59**)

With the successful olefin cross metathesis of **106b**, it was then opted that the oxidative rearrangement and the MOM-ether cleavage be done in a one pot two step reactions, followed by olefin cross metathesis of the resulting 3′-allylisoflavone **106b** to furnish the target 5-deoxy-3′-prenylbiochanin A (**59**). This would eliminate the formation of the undesired side product **115** in the MOM-ether cleavage step of the already prenylated isoflavone **114**. Thus, the MOM-protected

flavanone **107aa** was converted into the deprotected 3′-allyisoflavone **106b** (25%) in a one-pot sequence of oxidative rearrangement using PIFA in (TMOF) in the presence of catalytic $H_2SO_4$ and acid-mediated cleavage of the MOM-ether group. A small quantity of the flavone regioisomer **116b** (11%), resulting from the competing oxidation without a collateral 2,3-aryl rearrangement and the MOM-deprotected flavanone **107aa′** (16%) were also isolated. Compounds **106b**, **107aa′** and **116b** were separated by column chromatography on silica gel. Olefin cross metathesis of **106b** with 2-metyl-2-butene furnished 5-deoxy-3′-prenylbiochanin A (**59**) in 86% yield.[197]

The structure of compound **59** was explicitly confirmed by single crystal X-ray diffraction analysis (Figure 15) in addition to the comparison of its spectral data with those reported for the natural product.[39] In the solid state, noncovalent intermolecular interactions (hydrogen bonds between O-1-H and O-3, and π-stacking interactions between both rings of the chromone moieties) lead to the formation of molecule chains along the b axis (Figure 16).

5-Deoxy-3′-prenylbiochanin A (**59**) is a natural product that was isolated from *Erythrina sacleuxii*,[37,39] a medicinal tree growing exclusively in Kenya and Tanzania.[26] The plant is traditionally used for the treatment of malaria and microbial infections.[26] To date, 5-deoxy-3′-prenylbiochanin A (**59**) has not been reported from any other plant. The compound has been only tested for antiplasmodial activity, in which it showed activity against *P. falciparum* at a micromolar concentration.[37] The total synthesis of 5-deoxy-3′-prenylbiochanin A (**59**) has not been reported previously, but it was partially synthesized by the hydrolysis of its naturally occurring glycoside.[198]

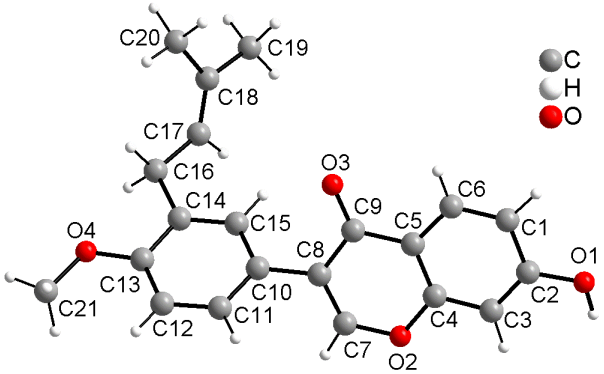



**Figure 15:** Single -crystal X-ray structure analysis of 5-deoxy-3′-prenylbiochanin A (**59**)

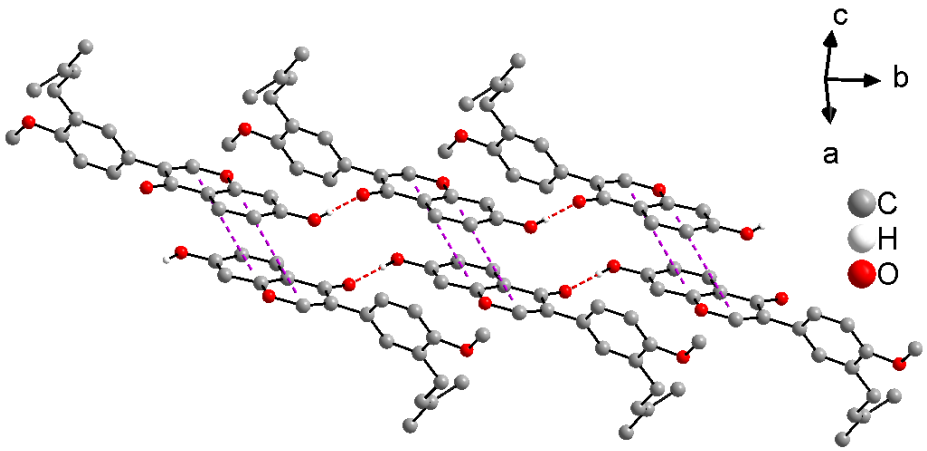


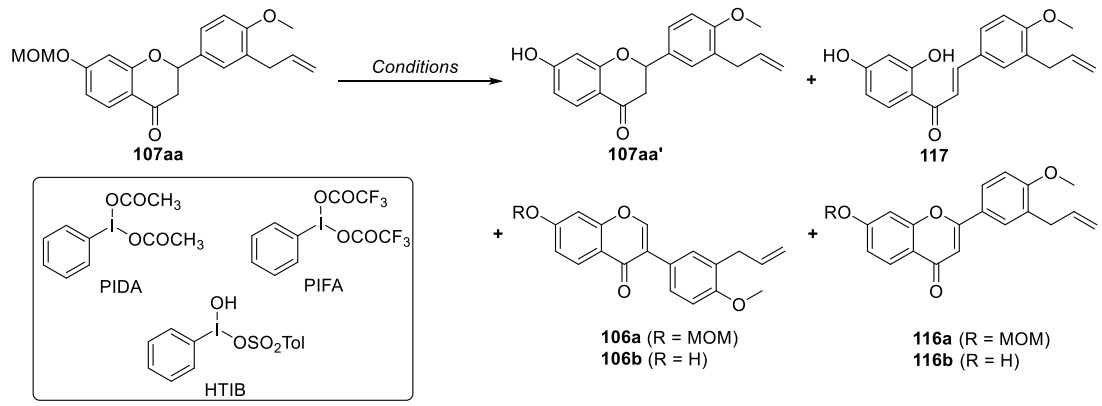

**Figure 16:** Arrangement of the molecules of 5-deoxy-3′-prenylbiochanin A (**59**) formed by intermolecular interactions leading to chains along the b axis (non-acidic hydrogens were omitted)

### 4.1.2 Optimization of the 2,3-Oxidative Aryl Rearrangement Reaction

The optimization study was carried out by screening various hypervalent iodine reagents with the MOM-protected flavanone **107aa** under various reaction conditions (Table 3).[199] [Hydroxy(tosyloxy)iodo]benzene (HTIB) was first tested as an oxidant because it was previously reported to selectively promote the 2,3-oxidative aryl rearrangement of flavanones to isoflavones in acetonitrile.[167] When HTIB was used in acetonitrile at 20 ºC, only MOM-deprotection was observed and the 7-hydroxyflavanone **107aa′** was isolated in 46% yield (entry 1). Replacing acetonitrile by methanol as a solvent also gave **107aa′** as the major product in addition to minor quantities of the MOM-deprotected chalcone **117** and the desired MOM-deprotected isoflavone **106b** (entry 2). When HTIB was used in excess, the amount of the desired product increased, but the deprotected flavanone **107aa′** and chalcone **117** were still isolated in significant amounts. (entry 3). Heating the reaction mixture to 60 ºC did not significantly accelerate the desired oxidative rearrangement reaction but caused competing oxidation without 2,3-aryl migration to afford a small quantity of the deprotected flavone regioisomer **116b** in addition to the isoflavone **106b** and chalcone **117** (entry 4). When HTIB was replaced by phenyliodonium diacetate (PIDA) in acetonitrile or methanol, no reaction was detected and the unreacted substrate **107aa** was recovered in each case (entries 5 and 6). The same result was observed with PIFA in acetonitrile (entry 7), but in methanol, a small quantity of MOM-protected flavone **116a** was isolated as the

sole product along with the unreacted substrate **107aa** (entry 8). An attempt to catalyze the reaction in acetonitrile by adding catalytic amount of *p*-toluene sulfonic acid failed and led to recovery of the substrate **107aa** (entry 9).

**Table 3:** Optimization of 2,3-oxidative aryl rearrangement reaction




| entry | oxidant (equiv.) | solvent | additive (equiv.) | Temp (° C) | **107aa′** (%) | **117** (%) | **106a** (%) | **106b** (%) | **116a** (%) | **116b** (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HTIB (1.0) | $CH_3CN$ | -- | 20 | 46 | n. d. | n. d. | n. d. | n. d. | n. d. |
| 2 | HTIB (1.0) | $CH_3OH$ | -- | 20 | 39 | 10 | n. d. | 15 | n. d. | n. d. |
| 3 | HTIB (1.5) | $CH_3OH$ | -- | 20 | 25 | 6 | n. d. | 28 | n. d. | n. d. |
| 4 | HTIB (1.5) | $CH_3OH$ | -- | 60 | 26 | 18 | n. d. | 25 | n. d. | 9 |
| 5 | PIDA (1.0) | $CH_3CN$ | -- | 20 | no conversion | | | | | |
| 6 | PIDA (1.0) | $CH_3OH$ | -- | 20 | no conversion | | | | | |
| 7 | PIFA (1.0) | $CH_3CN$ | -- | 20 | no conversion | | | | | |
| 8 | PIFA (1.0) | $CH_3OH$ | -- | 20 | n. d. | n. d. | n. d. | n. d. | 16 | n. d. |
| 9 | PIDA (1.0) | $CH_3CN$ | *p*-TSA (0.4) | 20 | no conversion | | | | | |
| 10 | PIDA (1.5) | $CH(OMe)_3$ | $H_2SO_4$ (0.4) | 20 | n. d. | n. d. | 20 | n. d. | 16 | n. d. |
| 11 | PIFA (1.5) | $CH(OMe)_3$ | $H_2SO_4$ (0.4) | 20 | n. d. | n. d. | 27 | 15 | n. d. | n. d. |
| 12 | PIDA (1.5) | $CH(OMe)_3$ | $CF_3CO_2H$ (0.4) | 20 | no conversion | | | | | |

[a]n.d: not detected

The attention was then shifted to the use of conditions involving the use of TMOF as a solvent in the presence of an acid catalyst despite this procedure being previously reported to preferentially induce a ring contraction to afford benzofurans.[77,176,200] Motivated by a more recent publication which indicated that the selectivity of the reaction under these conditions was dependent on the substitution on both aryl rings of the flavanone,[168] these conditions were applied to the flavanone

**107aa**. When these conditions were applied to the flavanone **107aa** using PIDA as an oxidant, only the MOM-protected isoflavone **106a** and its flavone regioisomer **116a** were isolated in comparable yields (entry 10). Replacing PIDA by PIFA improved the selectivity towards the oxidative 2,3-aryl migration pathway and a mixture of MOM-protected isoflavone **106a** and deprotected isoflavone **106b** was obtained in an overall yield of 42% (entry 11). An attempt to suppress the cleavage of the MOM- group by using a slightly weaker acid failed and led to the recovery of the substrate **107aa** (entry 12). It was therefore noted that the reaction conditions expected to favor the selective synthesis of isoflavones turned out to be unsuitable for the substrate **107aa** while those that presumably yield the undesired ring contraction product selectively afforded isoflavones in acceptable yield and selectivity (entry 11). Therefore, the substitution pattern on the substrate **107aa** does not favor the ring contraction pathway.

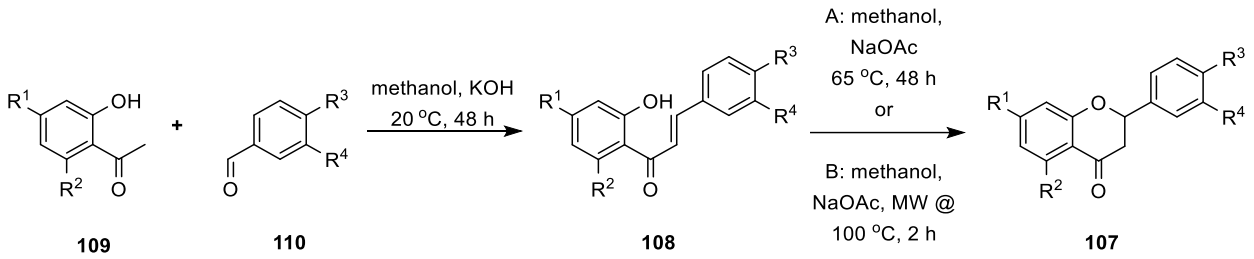
### 4.1.3 Synthesis of Other Isoflavones

For the synthesis of all the isoflavones, the 2,3-oxidative aryl rearrangement of the respective flavanones **107** or **121** was a key step. Thus, the respective flavanones, the key substrates for this transformation were synthesized first starting from the corresponding acetophenones **109** or **118** and benzaldehydes **110**. For the prenylated isoflavones, the appropriate allyl flavanones were used as substrates for the 2,3-oxidative aryl rearrangement reaction. Olefin cross metathesis of the resulting allyl isoflavones followed by MOM-ether cleavage where necessary furnished the target isoflavones.

#### 4.1.3.1 Synthesis of Flavanones as Substrates for 2,3-Oxidative Rearrangement Reactions

To explore the scope of the 2,3-oxidative rearrangement reaction and its application to the synthesis of isoflavones, more flavanones were synthesized. Three flavanones bearing the same 3′-allyl-4′-methoxyphenyl substituent as compound **107aa** and two flavanones without a 3′-allyl substituent were synthesized first. The synthesis started from the corresponding acetophenones **109** and benzaldehydes **110** that were either commercially available or prepared following literature procedure. Claisen-Schmidt condensation of **109** and **110** afforded chalcones **108**, which underwent oxa-Michael addition to furnish the desired flavanones **107** in methanol in the presence of NaOAc as a base, either under conventional heating conditions or, in a notably shorter reaction time, by microwave irradiation (Table 4).

**Table 4:** Synthesis of flavanones **107** without 8-allyl substituent



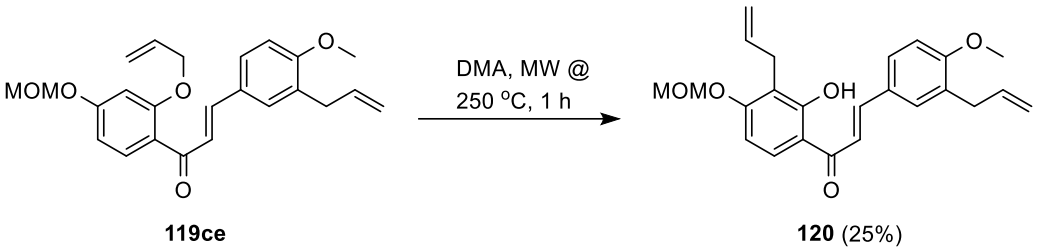

**109** **110** **108** **107**

| entry | **109**[a] | $R^1$ | $R^2$ | **110**[a] | $R^3$ | $R^4$ | **108** | yield (%) | **107** | yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **109b**[b] | H | H | **110a**[a] | $OCH_3$ | $CH_2CH{=}CH_2$ | **108ba** | 88 | **107ba** | 50[c] |
| 2 | **109c**[a] | OMOM | OMOM | **110a**[a] | $OCH_3$ | $CH_2CH{=}CH_2$ | **108ca** | 93 | **107ca** | 51[c] |
| 3 | **109d**[a] | $OCH_3$ | $OCH_3$ | **110a**[a] | $OCH_3$ | $CH_2CH{=}CH_2$ | **108da** | 80 | **107da** | 50[c] |
| 4 | **109e**[a] | $OCH_3$ | H | **110b**[a] | OMOM | H | **108eb** | 70 | **107eb** | 54[d] |
| 5 | **109a**[a] | OMOM | H | **110c**[b] | $OCH_3$ | H | **108ac** | 68 | **107ac** | 56[d] |

[a]Synthesis described in the experimental section. [b]Commercially available. [c]Conditions A. [d]Conditions B.

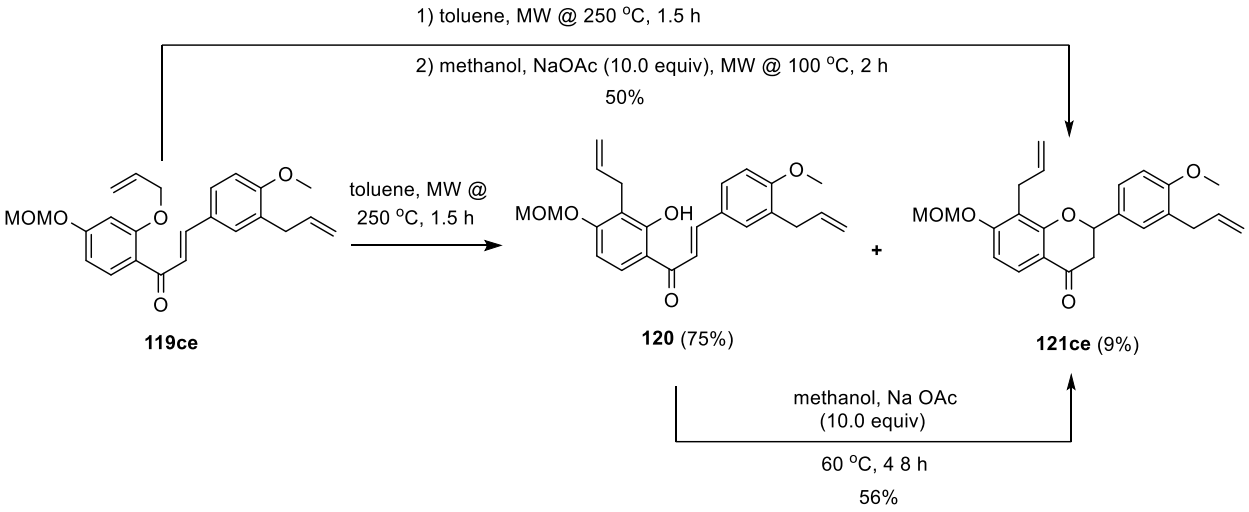
The synthesis of 8-allyl flavanones **121**, was first conceived to be accomplished via a microwave promoted domino Claisen rearrangement/ oxa-Michael addition of the respective 2′-allyloxychalcones. The 2′-allyloxy acetophenones **118b** and **118c** were prepared by the *O*-allylation of the previously synthesized acetophenones **109e** and **109a** respectively following literature procedure[188,190] in good to excellent yields. Benzaldehyde **110e** was prepared by the MOM protection of **113**. Claisen-Schmidt condensation of the 2′-allyloxy acetophenones **118** with benzaldehydes **110** afforded chalcones **119**. A domino Claisen rearrangement/ oxa-Michael addition of the chalcone **119ce** was attempted, but it was not successful. When the 2′-allyloxychalcone **119ce** was heated in *N*,*N*-dimethylaniline (DMA) at 250 °C under microwave irradiation,[201] the diallyl chalcone **120** (Scheme 25) was the only product isolated in 25% yield. This protocol was then discarded, and it was opted to perform this transformation in a sequence of two reactions. Firstly, chalcone **119ce** was heated in toluene at 250 °C under microwave irradiation for 1.5 h to induce a Claisen rearrangement that installs the 8-allyl substituent. Purification of the crude reaction mixture afforded chalcone **120** and the 8-allyflavanone **121ce** in 75% and 9% yield respectively. Refluxing chalcone **120** in methanol for 48 h in the presence of NaOAc as a base induced oxa-Michael addition and furnished flavanone **121ce** in 56% yield (Scheme 26). Secondly, chalcone **119ce** was heated in toluene at 250 °C under microwave irradiation for 1.5 h. After changing the solvent to methanol and addition of NaOAc as a base the crude reaction mixture was heated at 100 °C under microwave irradiation. This furnished the 8-allyl flavanone **121ce** in 50% yield (Scheme 26; Table 5, entry 5). The latter procedure gave the flavanone **121ce** in a yield

comparable to the overall yield of the two steps in the former procedure in a relatively shorter time and with reduced workload. Therefore, the latter sequence was preferred and applied for the synthesis of the other 8-allylflavanones **121** (Table 5). This sequence was previously developed in our group and used for the synthesis of the 8-allylflavanone **121ad**.[202]




**119ce** **120** (25%)

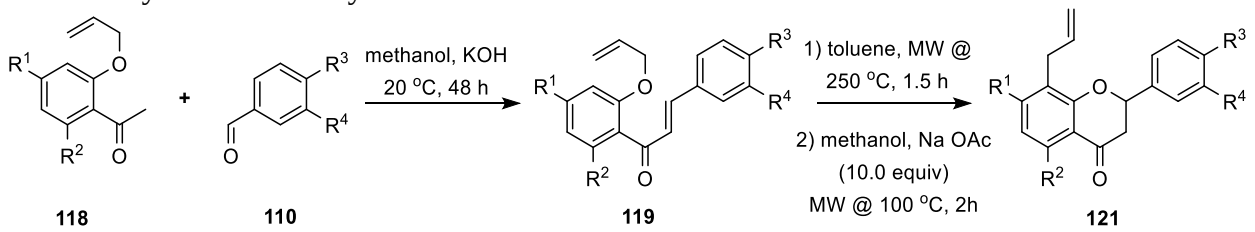
**Scheme 25:** Attempted microwave promoted domino Claisen rearrangement/ oxa-Michael addition reaction of chalcone **119ce**




**119ce** **120** (75%) **121ce** (9%)

**Scheme 26:** Synthesis of 8-allylflavanone **121ce** via one-pot two reactions sequence and two-pots two reactions sequence

**Table 5:** Synthesis of 8-allylflavanones **121**




118 110 119 121

| entry | **118**[a] | $R^1$ | $R^2$ | **110**[a] | $R^3$ | $R^4$ | **119**[a] | yield (%) | **121**[a] | yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **118a**[202] | H | H | **110d**[c] | H | H | **119ad** | --[202] | **121ad** | --[202] |
| 2 | **118b**[b] | $OCH_3$ | H | **110c**[c] | $OCH_3$ | H | **119bc** | 60 | **121bc** | 47 |
| 3 | **118b**[b] | $OCH_3$ | H | **110e**[b] | OMOM | $CH_2CH=CH_2$ | **119be** | 65 | **121be** | 45 |
| 4 | **118b**[b] | $OCH_3$ | H | **110a**[b] | $OCH_3$ | $CH_2CH=CH_2$ | **119ba** | 81 | **121ba** | 45 |
| 5 | **118c**[b] | OMOM | H | **110e**[b] | OMOM | $CH_2CH=CH_2$ | **119ce** | 74 | **121ce** | 50 |

[a]References describing synthesis and analytical data. [b]Synthesis described in experimental section. [c]Commercially available

### 4.1.3.2 Scope of the Oxidative Rearrangement Reactions of Flavanones 107 and 121 under Optimized Conditions

The two most successful oxidative rearrangement conditions from table 3, the reaction with HTIB in methanol at 60 °C and the reaction with PIFA in TMOF in the presence of $H_2SO_4$ at ambient temperature were mostly applied for the oxidative rearrangement of flavanones **107** and **121**. Although the reaction with PIDA in TMOF in the presence of $H_2SO_4$, was less successful in the optimization study, it was also applied to some other substrates (Table 6).[199] The results can be summarised as follows:

a. Allyl groups, substituents that are essential precursors for prenyl side chains along the synthetic route in question, were well tolerated under all conditions. No product arising from either allylic oxidation, oxidation of the C-C-double bond, or acid-catalysed isomerization was observed.
b. The isoflavone **122c** (entry 5), could be isolated as a single reaction product for only one example. In all other cases the flavone regioisomer **123** was formed as a side product, sometimes together with either unreacted or deprotected starting material. Interestingly, benzofuran derivatives of the general formula **98** (scheme10), were not detected in all cases. Considering several literature reports claiming this mode of rearrangement to be the major pathway in the reaction of flavanones with hypervalent iodine compounds the complete absence of ring contraction products in this study is quite surprising. Presumably

oxygenation on the aryl rings of the flavanone disfavours ring contraction pathway as it has been mostly reported in flavanones with deoxygenated aryl rings[77,176,200] or electron withdrawing groups on the B-ring.[168]

c. Unprotected OH-groups appear to hinder the reaction greatly. With flavanone **107aa′**, possessing a free OH- group at C7, the yield of isoflavone **106b** was less than 10% (entry 15), compared to 28% starting from the MOM-protected analogue (Table 3, entry 3). Regardless of the reaction conditions, MOM-ethers underwent cleavage to a considerable extent, which resulted in a lower yield, whereas methyl ethers are well tolerated. For instance, the dimethyl ether **121ba** (entry 14) reacts to **122j** and **123j** in a combined yield of 83% and a 3:1 ratio of isomers, whereas **121be** with a MOM-ether at C4′-position reacts to isoflavone **122i** and flavone **123i** in a 1:1 ratio and a combined yield of approximately 40% (entry 13). A complete MOM-ether cleavage was observed with HTIB (entries 7 and 8). Thus, this condition was unsuitable for the synthesis of isoflavones in which the MOM protection was still required in the proceeding reaction steps. However, it was the most convenient for isoflavones which did not require a MOM protection any further because the oxidative rearrangement and MOM-ether cleavage could be accomplished in a single reaction step. For example, formononetin (**51**) and isoformononetin (**101**), and their respective flavone isomers pratol (**123d**) and isopratol (**123e**) were obtained in this single step.

d. An electron donating substituent is required at the migrating aryl group. With an unsubstituted phenyl ring no rearrangement product **122** was observed, as was shown for **121ad** (entry 9) which reacted to flavone **123f** in only 12% yield.

e. On the other hand, alkoxy or hydroxy groups at C5 apparently seem to disfavour the oxidative rearrangement reaction. Isoflavone **122c** (entry 5) was isolated in only 32% yield, compared to 65% for **122a** (entry 3) and 61% for **122j** (entry 14) without a C5-methoxy group. With the analogous bis-MOM-ether **107ca** (entry 4) a complex mixture of products was obtained. No signals were observed in the NMR-spectra pointing at the formation of isoflavone **122b** or flavone **123b**. Instead, an 8-oxygenated and C5-OH deprotected flavanone **124** was isolated as the only identifiable product in 8% yield. The structural assignment was based on HMBC correlations between C5(OH) (δ 11.63 (s, 1H)) and C6 (δ 96.5), and H-6 (δ 6.28 (s, 1H)) and C8 (δ 128.9) (Figure 17), which appears as a

quaternary carbon in the HSQC spectrum. The high-resolution mass spectrum agrees with the molecular formula $C_{21}H_{22}O_7$ and thus confirms the presence of an additional OH-group.

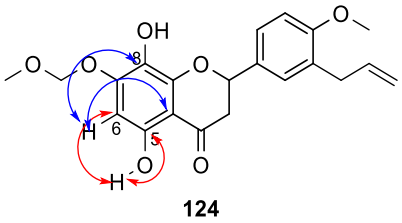
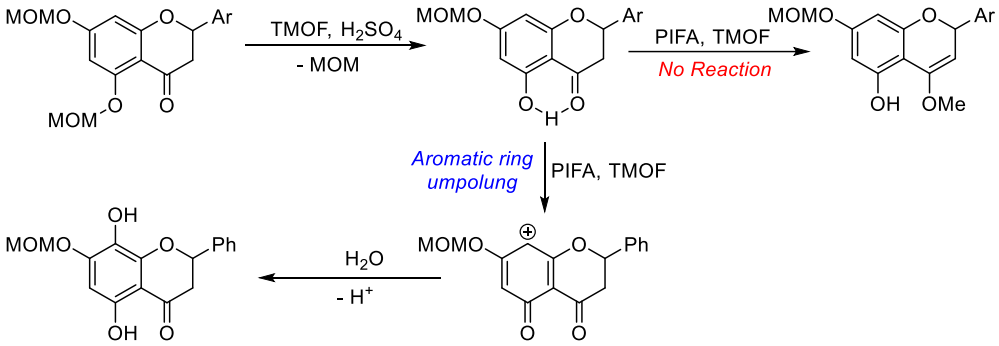



**Figure 17:** HMBC correlations of C5-OH and H-6 in compound **124**

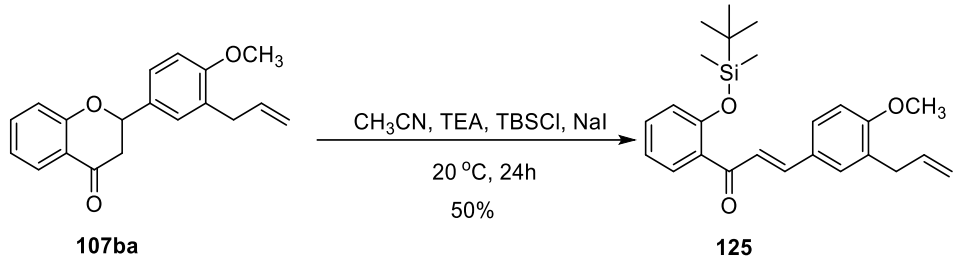
The failure of the bis-MOM-ether **107ca** to undergo oxidative rearrangement could be presumably due to the instability of the C5-MOM ether group under the acidic reaction conditions. It was therefore cleaved to C5-OH, which then underwent intramolecular hydrogen bonding with the C4 carbonyl group. Owing to the plausible mechanism for the oxidative rearrangement reaction (Scheme 9), the hydrogen bonded carbonyl group of **107ca** could not form an enol and thus the oxidative rearrangement could not proceed. It instead underwent an aromatic ring umpolung[203] followed by a nucleophilic attack in the aqueous workup (Scheme 27).




**Scheme 27:** Plausible mechanism for the oxidation of **107ca** to **124**

An alternative protocol for the oxidative rearrangement of **107ca** to the isoflavone **122b** was sought because **122b** was envisaged as a key intermediate for the synthesis of 3′-prenylbiochanin A (**58**), one of the targeted prenylated isoflavones in the study. To avoid the acidic reaction conditions, it was opted to do the oxidative rearrangement via the formation of an enol silyl ether. Unfortunately, an attempt to produce an enol silyl ether of **107ba** (as a test substrate) following

literature procedure[204] failed. Under the basic reaction condition, ring C of the flavanone opened to give a chalcone and the reaction instead yielded the silyl ether **125** in 50% yield (Scheme 28). It was evident that the enol formation could only be activated by protonation of the carbonyl oxygen. This protocol was also discarded and an alternative route for the synthesis of 3′-prenylbiochanin A (**58**) had to be sought.

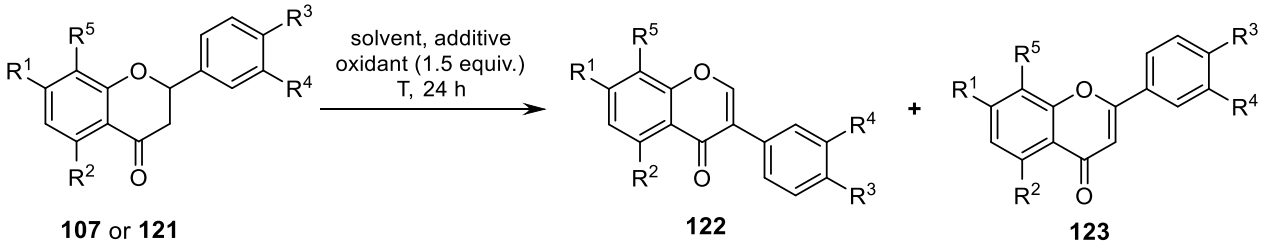



**107ba** **125**

TEA - triethylamine; TBSCl -*tert*-butyldimethylsilyl chloride

**Scheme 28:** Attempted reaction for the formation of an enol silyl ether of **107ba**

**Table 6:** Scope of the oxidative rearrangement reaction of flavanones **107** and **121** under optimized conditions




| entry | **107**/ **121** | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | solvent-additive | oxidant | T (°C) | **122** | yield (%) | **123** | yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **107ba** | H | H | $OCH_3$ | $CH_2CH{=}CH_2$ | H | $CH(OCH_3)_3$, $H_2SO_4$ | PIDA[a] | 20 | **122a** | 15 | **123a** | -- |
| 2 | **107ba** | H | H | $OCH_3$ | $CH_2CH{=}CH_2$ | H | $CH(OCH_3)_3$, $H_2SO_4$ | PIDA | 20 | **122a** | 47 | **123a** | 20 |
| 3 | **107ba** | H | H | $OCH_3$ | $CH_2CH{=}CH_2$ | H | $CH(OCH_3)_3$, $H_2SO_4$ | PIFA | 20 | **122a** | 65 | **123a** | -- |
| 4 | **107ca** | OMOM | OMOM | $OCH_3$ | $CH_2CH{=}CH_2$ | H | $CH(OCH_3)_3$, $H_2SO_4$ | PIFA | 20 | **122b** | --[b] | **123b** | --[b] |
| 5 | **107da** | $OCH_3$ | $OCH_3$ | $OCH_3$ | $CH_2CH{=}CH_2$ | H | $CH(OCH_3)_3$, $H_2SO_4$ | PIFA | 20 | **122c** | 32 | **123c** | -- |
| 6 | **107ac** | OMOM | H | $OCH_3$ | H | H | $CH(OCH_3)_3$, $H_2SO_4$ | PIFA | 20 | **51** | 19[c] | **123d** | 19[c] |
| 7 | **107ac** | OMOM | H | $OCH_3$ | H | H | $CH_3OH$ | HTIB | 60 | **51** | 42[c] | **123d** | 9[c] |
| 8 | **107eb** | $OCH_3$ | H | OMOM | H | H | $CH_3OH$ | HTIB | 60 | **101** | 26[d] | **123e** | 8[d] |
| 9 | **121ad** | H | H | H | H | $CH_2CH{=}CH_2$ | $CH(OCH_3)_3$, $H_2SO_4$ | PIDA | 20 | **122f** | -- | **123f** | 12 |
| 10 | **121bc** | $OCH_3$ | H | $OCH_3$ | H | $CH_2CH{=}CH_2$ | $CH(OCH_3)_3$, $H_2SO_4$ | PIFA | 20 | **122g** | 22 | **123g** | 50 |
| 11 | **121bc** | $OCH_3$ | H | $OCH_3$ | H | $CH_2CH{=}CH_2$ | $CH_3OH$ | HTIB | 60 | **122g** | 52 | **123g** | 20 |
| 12 | **121ce** | OMOM | H | OMOM | $CH_2CH{=}CH_2$ | $CH_2CH{=}CH_2$ | $CH(OCH_3)_3$, $H_2SO_4$ | PIFA | 20 | **122h** | 20 | **123h** | 18 |
| 13 | **121be** | $OCH_3$ | H | OMOM | $CH_2CH{=}CH_2$ | $CH_2CH{=}CH_2$ | $CH(OCH_3)_3$, $H_2SO_4$ | PIFA | 20 | **122i** | 20 | **123i** | 17 |
| 14 | **121ba** | $OCH_3$ | H | $OCH_3$ | $CH_2CH{=}CH_2$ | $CH_2CH{=}CH_2$ | $CH_3OH$ | HTIB | 60 | **122j** | 61 | **123j** | 22 |
| 15 | **107aa′** | OH | H | $OCH_3$ | $CH_2CH{=}CH_2$ | H | $CH_3OH$ | HTIB | 60 | **106b** | 6 | **116b** | -- |

[a]1.0 equiv. [b]Complex mixture of products; partial oxidation at C8; compound **124** isolated in 8% yield as sole identifiable product. [c]Cleavage of MOM-ether under reaction conditions; $R^1$ = OH. [d]Cleavage of MOM-ether under reaction conditions; $R^3$ = OH.

The isoflavones **51** (formononetin) and **101** (isoformononetin) and their flavone regioisomers **123d** (pratol) and **123e** (isopratol) are naturally occurring secondary plant metabolites. Formononetin (**51**) is a common phytoestrogen found in many edible plants.[205] Isoformononetin (**101**) has been isolated from various plants including soybeans.[206] Both formononetin and isoformononetin were previously synthesized via base catalysed condensation of deoxybenzoins,[162,164] oxidative rearrangement of chalcones[207] and methylation of daidzein.[208,209] Isoformononetin has also been previously synthesized via a Suzuki-Miyaura cross-coupling reaction[87] and it exhibited moderate antiestrogenic activity.[209] Pratol (**123d**) was isolated from the flowers of *Trifolium pratense*[210] and the seeds of *Caragana microphylla* Lam. together with its isoflavone isomer formononetin (**51**) [211] among other plants. Pratol (**123d**) has been previously synthesized via Co-catalysed dehydrogenation of a flavanone precursor.[212] Isopratol (**123e**) was isolated from the roots of the shrub *Gynerium sagittatum*, an anti-inflammatory remedy used in Mexico and South America,[213] and previously synthesized through cyclocondensation of 1,3-diketones.[214]

For the case of 8,3′-diallyl-7,4′-dimethoxyflavone (**123j**), crystals suitable for single crystal X-ray analysis were obtained and its structure was explicitly determined (Figure 18).

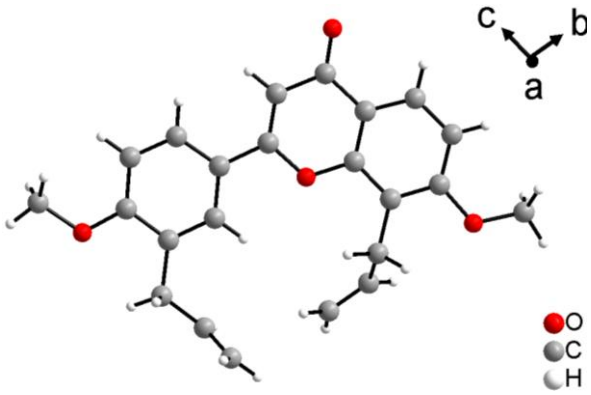
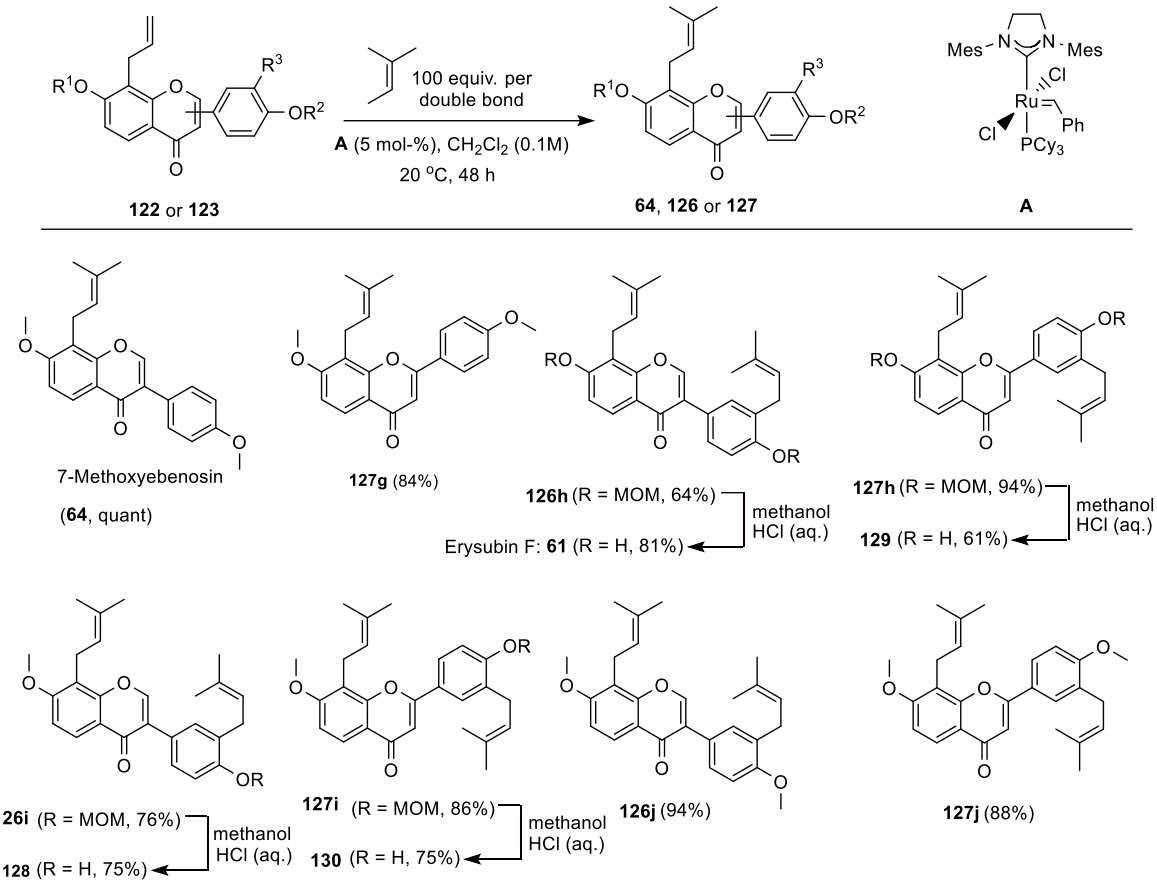



**Figure 18:** Single crystal X-ray structure analysis of compound **123j**

#### 4.1.3.3 Synthesis of Prenylated Isoflavones and Flavones via Olefin Cross Metathesis

The cross metathesis reactions of allyl isoflavones **122g-j** and their flavone regioisomers **123g-j** with 2-methyl-2-butene in the presence of 5 mol-% second generation Grubbs catalyst **A**[193] at ambient temperature furnished the respective prenyl isoflavones **64**, **126h-j** and prenylflavones **127g-j** in good to excellent yields and selectivity (Scheme 29). Just like in the cross metathesis of

the 3′-allylisoflavones **106a**,**b**, reported above in the synthesis of 5-deoxy-3′-prenylbiochanin A (**59**), in no case were the self CM products or CM products with a crotyl substituent observed. The MOM-ether protecting groups on the isoflavones **126h**,**i**, and flavones **127h**,**i** could be cleaved in methanol in the presence of aqueous HCl without concomitant acid catalysed addition of methanol to the prenyl substituent (Scheme 29).




**Scheme 29:** Synthesis of prenylisoflavones and prenylflavones via olefin cross metathesis

Isoflavone **61** is erysubin F, a natural product that was first isolated from the roots of *Erythrina suberosa* var. *glabrescences*, a useful medicinal plant used in India and Pakistan for the treatment of various ailments.[215] The same compound was later isolated from *Erythrina variegata*,[56] *E. poeppigiana*,[216] *E. sacleuxii*,[37] *E. subumbrans*,[217] *E. addisoniae*[66] and *E. brucei*.[218] As already mentioned in the theoretical background, erysubin F (**61**) showed antiplasmodial activity against *P. falciparum*,[37,149] antibacterial activity against *M. tuberculosis*,[149] and MRSA and inhibition to protein tyrosine phosphatase 1B (PTP1B)[66] at micromolar concentrations. Erysubin F (**61**) has not

been synthesized previously, and in the current study its synthesis is being reported for the first time.

Isoflavone **64** is 7-methoxyebenosin, a natural product that was first isolated from the seeds of *Millettia griffoniana*, an indigenous tree in Western Africa.[134] 7-Methoxyebenosin (**64**) was later isolated from *M. pulchra*[219] and *Sophora tonkinensis*.[220] As already mentioned in the theoretical background, 7-methoxyebenosin (**64**) exhibited moderate antiplasmodial and trypanocidal activities at a micromolar concentration.[134] The compound also inhibited nitric oxide production at a micromolar concentration.[220] To date, no chemical synthesis of 7-methoxyebenosin (**64**) has been reported, and in the current study, it is being reported for the first time.

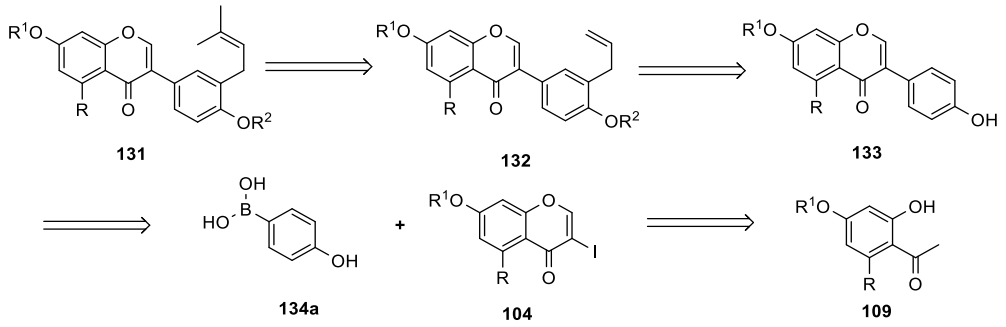
Isoflavones **126j** and **128**, whose synthesis is being reported for the first time in this study, are non-natural di- and monomethyl ether analogues of erysubin F (**61**). Flavones **127g**, **127j**, **129** and **130** are the flavone regioisomers of 7-methoxyebenosin (**64**), **126j**, erysubin F (**61**) and **128** respectively. The flavones **127g**, **127j**, **129** and **130** are all non-natural compounds and they have not been synthesized previously.

## 4.2 Synthesis of Isoflavones via Suzuki-Miyaura Cross-Coupling Reactions

The objective was to synthesize naturally occurring 3′-prenylisofavones and related analogues via Suzuki-Miyaura cross-coupling reactions of 3-iodochromones and phenylboronic acids, and regioselective olefin cross metathesis.

### 4.2.1 Retrosynthesis of 3′-Prenylisoflavones via Suzuki-Miyaura Cross-Coupling Reactions

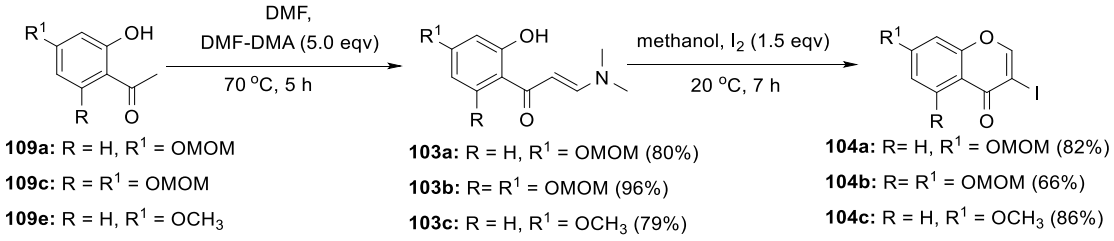
The retrosynthesis of 3′-prenylisoflvones via the Suzuki-Miyaura cross-coupling reaction is outlined in scheme 30. The 3′-prenylisoflavones **131** could be obtained by the olefin cross metathesis of the 3′-allylisoflavones **132**. The 3′-allylisoflavones **132** could be produced via 4′-oxy-allylation of **133** followed by Claisen rearrangement and appropriate etherification of the resulting 3′-allyl-4′-hydroxyisoflavones. The isoflavone core **133** could be constructed by the Suzuki-Miyaura cross-coupling reaction of 3-iodochromones **104** and 4-hydroxyphenylboronic acid (**134a**). The 3-iodochromones **104** could be synthesized from the corresponding acetophenones **109**.




**Scheme 30:** Retrosynthesis of 3′-prenylisoflavones via Suzuki-Miyaura cross-coupling reaction

### 4.2.2 Synthesis of 3-Iodochromones 104 as Substrates for Suzuki-Miyaura Cross-Coupling Reactions

The 3-iodochromones **104** were synthesized from the corresponding acetophenones **109** using Gammill's protocol.[184] Condensation of acetophenones **109a**,**c**,**e** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in DMF as a solvent afforded enamino-ketones **103a-c** in good to excellent yields (Scheme 31). Tandem iodination and cyclization of **103a-c** by their reaction with iodine in methanol at 20 °C[84] furnished the 3-iodochromones **104a-c** in moderate to good yields (Scheme 31).



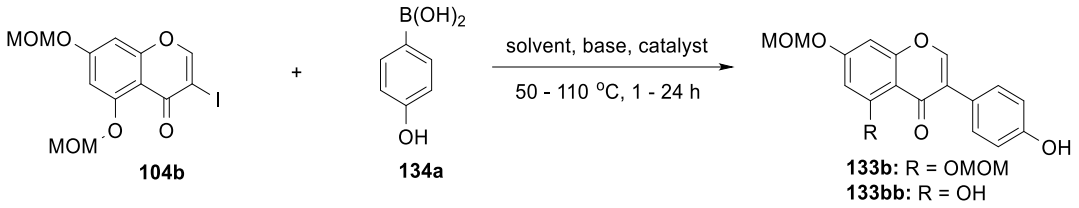

**Scheme 31:** Synthesis of 3-iodochromones **104**

### 4.2.3 Optimization of the Suzuki – Miyaura Cross-Coupling Reaction

The Suzuki – Miyaura cross-coupling reaction was optimized by reacting 3-iodochromone **104b** with 4-hydroxyphenylboronic acid (**134a**) under various conditions of solvent, base, catalyst, temperature and reaction time.[84,178–180] The results are summarized in Table 7. The optimal conditions were stirring the mixture of **104b** and **134a** (2.0 equiv.) in the presence of $K_2CO_3$ (3.0

equiv.) as a base, a mixture of tricyclohexylphosphine [$PCy_3$] (8 mol-%) and bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$] (4 mol-%) to generate $Pd(PCy_3)_4$ catalyst in situ in 1,4-dioxane-water (7:3) mixture as a solvent at 50 ºC for 1 hour[178] (Table 7, entry 7). The relatively cheaper precatalyst [$Pd(dba)_2$] gave a slightly higher yield than tris(dibezylideneacetone)dipalladium(0) previously used by Ciesielski and Metz[178] at the same loading level.

**Table 7:** Optimization of the Suzuki-Miyaura cross-coupling reaction



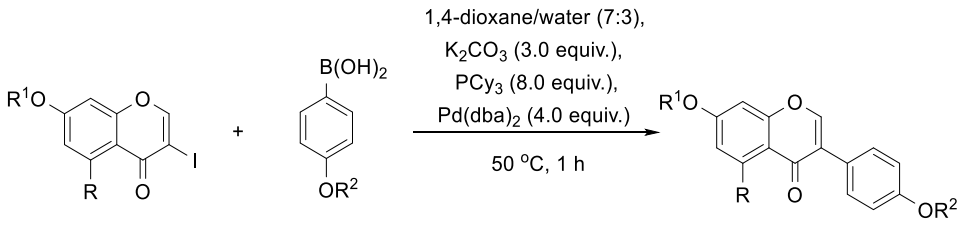

| entry | equiv. of 134a | solvent | catalyst (mol%) | base (equiv.)/ additive | temp (ºC) | time (h) | yield (%)[a] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 133b | 133bb |
| 1 | 2.8 | methanol | $Pd(OAc)_2$ (3.0) | $Na_2CO_3$ (2.5) PEG10000 | 50 | 3 | inseparable mixture | |
| 2 | 1.3 | ethanol/ water (1:1) | 10% Pd/C (2.0) | $K_2CO_3$ (4.0) | 80 | 3 | 31 | 10 |
| 3 | 1.3 | ethanol/ water (1:1) | 10% Pd/C (2.0) | $K_2CO_3$ (4.0) | 80 | 5 | 21 | 30 |
| 4 | 1.3 | ethanol/ water (1:1) | 10% Pd/C (2.0) | KF (3.0) | 80 | 3 | 12 | 22 |
| 5 | 1.4 | 1,4-dioxane | 10% Pd/C (2.0) | $K_2CO_3$ (4.0) | 110 | 24 | 54 | --- |
| 6 | 2.0 | 1,4-dioxane | $Pd(PPh_3)_4$ (5.0) | $K_2CO_3$ (4.0) | 110 | 24 | 68 | --- |
| 7 | 2.0 | 1,4-dioxane /water (7:3) | $PCy_3$ (8.0), $Pd(dba)_2$ (4.0) | $K_2CO_3$ (3.0) | 50 | 1 | 91 | --- |

[a]Isolated yield

### 4.2.4 Synthesis of Isoflavones 133

Isoflavones **133** were synthesized in good to excellent yields by the Suzuki-Miyaura cross-coupling reactions of the corresponding 3-iodochromones **104** and phenylboronic acids **134** under optimized conditions (Table 8). A lower yield was noted for the isoflavone **77a** (entry 4) than that of **101** (entry 3), from the same 3-iodochromone precursor **104c**. This is probably due to the reduced reactivity of the 4-methoxyphenylboronic acid (**134b**), resulting from the slightly lower nucleophilicity of its 4-methoxyphenyl ring as compared to that of the 4-hydroxyphenyl ring of the boronic acid **134a**.

**Table 8:** Synthesis of isoflavones **77a**, **101** and **133**




| entry | **104** | R | $R^1$ | **134** | $R^2$ | **133** | yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | **104a** | H | MOM | **134a** | H | **133a** | 96 |
| 2 | **104b** | OMOM | MOM | **134a** | H | **133b** | 91 |
| 3 | **104c** | H | $CH_3$ | **134a** | H | **101** | 88 |
| 4 | **104c** | H | $CH_3$ | **134b** | $CH_3$ | **77a** | 70 |

[a]Isolated yield

The isoflavones **77a** (dimethyldaidzein) and **101** (isoformononetin) are naturally occurring secondary plant metabolites. Dimethyldaidzein (**77a**) was first isolated from *Dalbergia violaceae*[221] and later from *Amorpha fruticosa*,[222] *Albizia lebbeck*[57] and *Ateleia herbert-smithii*.[223] Isoformononetin (**101**) has been isolated from different plants including soybeans.[206] Both dimethyldaidzein (**77a**) and isoformononetin (**101**) were previously synthesized via base catalyzed condensation of deoxybenzoin,[162–164] oxidative rearrangement of chalcones[75,207] and methylation of daidzein.[208,209] Dimethyldaidzein (**77a**) was also earlier synthesized via a 2,3-oxidative aryl rearrangement of a flavanone.[78,167] Isoformononetin (**101**) has also been synthesized via 2,3-oxidative aryl rearrangement of a flavanone in the current study.[199] Although both dimethyldaidzein (**77a**) and isoformononetin (**101**) have been previously synthesized via Suzuki-Miyaura cross-coupling reaction using polyethylene glycol (PG10000) as the ligand for the palladium catalyst,[87] it was opted to apply the optimized conditions in the current study for their syntheses as the polyethylene glycol ligand did not yield desirable results in the optimization study. The Suzuki-Miyaura cross-coupling reaction route afforded isoformononetin (**101**) in a better yield of 60% over three steps than the 2,3-oxidative aryl rearrangement route which afforded isoformononetin (**101**) in 10% yield over three steps, starting from the same acetophenone precursor **109e**.

Dimethyldaidzein (**77a**) showed moderate *in vitro* antifungal activity against some plant pathogenic fungi of the *Alternaria* and *Curvularia* genera.[57] Isoformononetin (**101**) exhibited

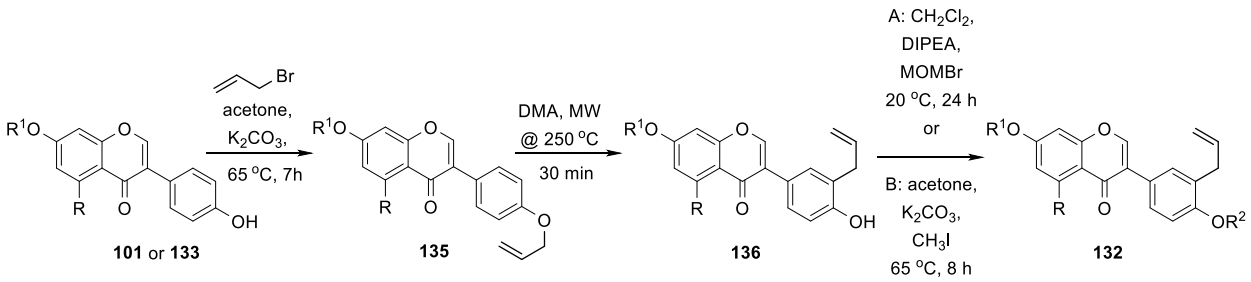
moderate antiestrogenic activity by reducing the estrogen stimulated MCF-7 cell tumorigenesis.[209] Both dimethyldaidzein (**77a**) and isoformononetin (**101**) retarded lipid oxidation in liposomal membranes by radical scavenging or/and changing the membrane fluidity.[208]

### 4.2.5 Synthesis of 3′-Allylisoflavones 132

The synthesis of 3′-allylisoflavones **132** was accomplished via oxy-allylation of the 4′-hydroxyisoflavones **101** or **133**, followed by Claisen rearrangement and methylation or MOM-ether protection of the resulting 3′-allyl-4′-hydroxyisoflavones **136**. The oxy-allylation of the isoflavones **101** or **133** afforded the 4′-allyloxyisoflavones **135** in excellent to quantitative yields (Table 9). The first attempt to induce a Claisen rearrangement of **135b** by microwave irradiation of its solution in toluene at 250 ºC, a condition previously applied to induce Claisen rearrangements of allyloxy chalcones and simple allyloxy aryl systems[197,199,202] failed due to poor absorbance of microwave radiations by the solution. This poor absorbance could be due to the low loss tangent (0.040) of toluene as a microwave solvent.[224] *N*,*N*-Dimethylformamide (DMF) was then selected as an alternative solvent for the Claisen rearrangement reaction under microwave irradiation owing to its medium loss tangent (0.161).[224] Surprisingly, when DMF was used as the solvent, the reaction was still not successful. It gave a mixture of inseparable products including an insignificant amount 3′-allyl-5,7,4′-trihydroxyisoflavone as detected by $^{1}H$ and $^{13}C\{^{1}H\}$ NMR spectroscopy, and GC-MS analysis. This could not enable selective methylation of the 4′-OH group; hence the synthesis could not proceed.

It was then opted to optimize the Claisen rearrangement reaction with a related 5-deoxyisoflavone substrate **135a**. Microwave irradiation of a solution of **135a** in *N*,*N*-dimethylaniline (DMA)[190,201] at 250 ºC for 30 minutes induced the Claisen rearrangement to afforded **136a** in 67% yield. DMA was therefore identified as a suitable solvent for this reaction. Thus, microwave irradiation of the solutions of 4′-allyloxy isoflavones **135** in DMA at 250 ºC for 30 minutes induced the Claisen rearrangement to afford the 3′-ally-4′-hydroxyisoflavones **136** in good yields (Table 9). Methylation or MOM-ether protection of the isoflavones **136** afforded the corresponding 3′-allylisoflavones **132** in moderate to excellent yields (Table 9).

**Table 9:** Synthesis of 3′-allylisoflavones **132**




| entry | **101**/ **133** | R | $R^1$ | **135** | yield (%)[a] | **136** | yield (%)[a] | **132** | $R^2$ | yield (%)[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **133a** | H | MOM | **135a** | 90 | **136a** | 67 | **132a** | MOM | 58[c] |
| 2 | **133b** | OMOM | MOM | **135b** | quant. | **136b** | 67[b] | **132b** | $CH_3$ | 72[d] |
| 3 | **101** | H | $CH_3$ | **135c** | quant. | **136c** | 66 | **132c** | MOM | 60[c] |
| 4 | **101** | H | $CH_3$ | **135c** | quant. | **136c** | 66 | **132d** | $CH_3$ | 94[d] |

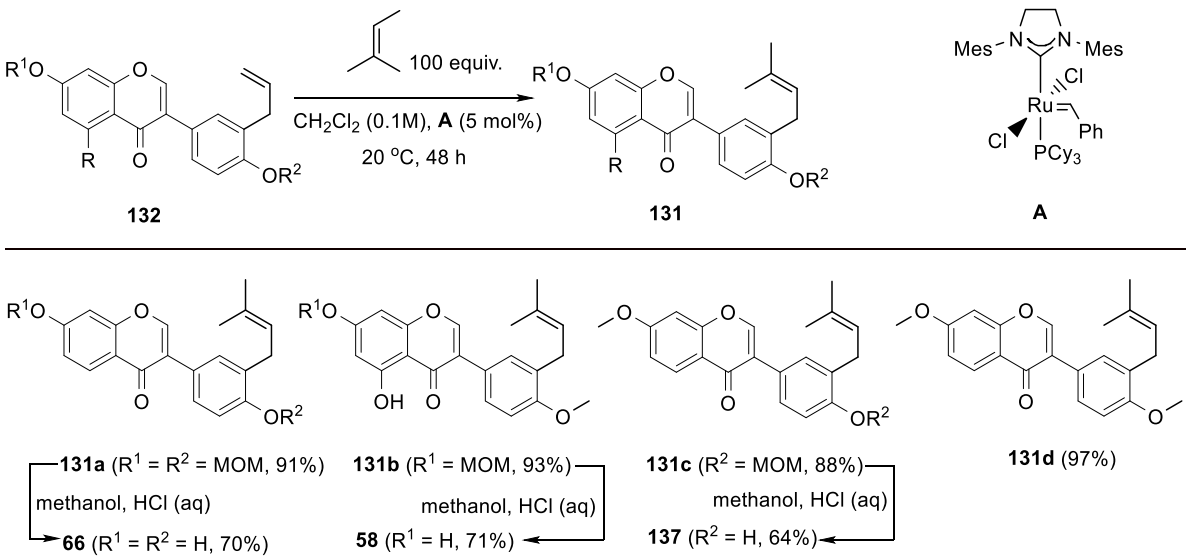
[a]Isolated yield. [b]Cleavage of MOM-ether under reaction conditions, R = OH. [c]Conditions A. [d]Conditions B.

### 4.2.6 Synthesis of Prenylated Isoflavones 131 via Olefin Cross Metathesis

The olefin cross metathesis reactions of 3′allylisoflavones **132** with 2-methyl-2-butene in the presence of 5 mol-% second generation Grubbs' catalyst **A**[193] at ambient temperature furnished the respective 3′-prenylisoflavones **131** in good to excellent yields and selectivity (Scheme 32). The MOM-ethers protecting groups on the isoflavones **131a-c** could be deprotected in methanol in the presence of aqueous HCl (4.0 M) without concomitant acid catalysed addition of methanol to the prenyl substituent (Scheme 32).

Isoflavone **58** is 3′-prenylbiochanin A, a natural product that was first isolated from the stem bark of *Erythrina sacleuxii*,[37,39] an indigenous medicinal tree growing exclusively in Kenya and Tanzania.[26] The same compound was later isolated from the stem bark of *Brosimum utile*[225] in Venezuela, the stem bark of *Ficus nymphaefolia*,[226] in France, the whole plant of *Ficus tikoua*[154] and the twigs of *Ficus hispida*[227] in China, and *E. schliebenii*[123] in Tanzania. The structure of compound **58** could be unambiguously determined by single crystal X-ray diffraction analysis (Figure 19) in addition to the comparison of its spectral data with those reported for the natural product.[39] In the solid state, intermolecular hydrogen bonding interactions between O-4-H and O-2 lead to the formation of molecule chains along the a axis (Figure 20).

3′-Prenylbiochanin A (**58**) has not been previously synthesized. The compound showed moderate *in vitro* antiplasmodial activity against the chloroquine sensitive (D6) and chloroquine resistant (W2) strains of *P. falciparum*,[37] antimycobacterial activity,[123] cytotoxicity against human breast cancer cell line MDA-MB-231[123] as well as inhibition to protein tyrosine phosphatase 1B (PTP1B).[154]




**Scheme 32:** Synthesis of 3′-prenylisoflavones via olefin cross metathesis

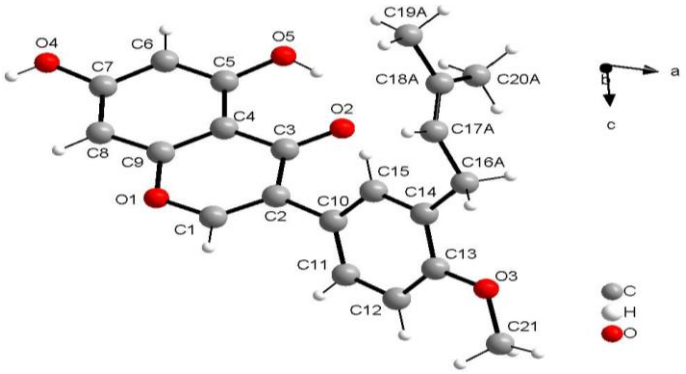


**Figure 19:** Single-crystal X-ray structure analysis of 3′-prenylbiochanin A (**58**)

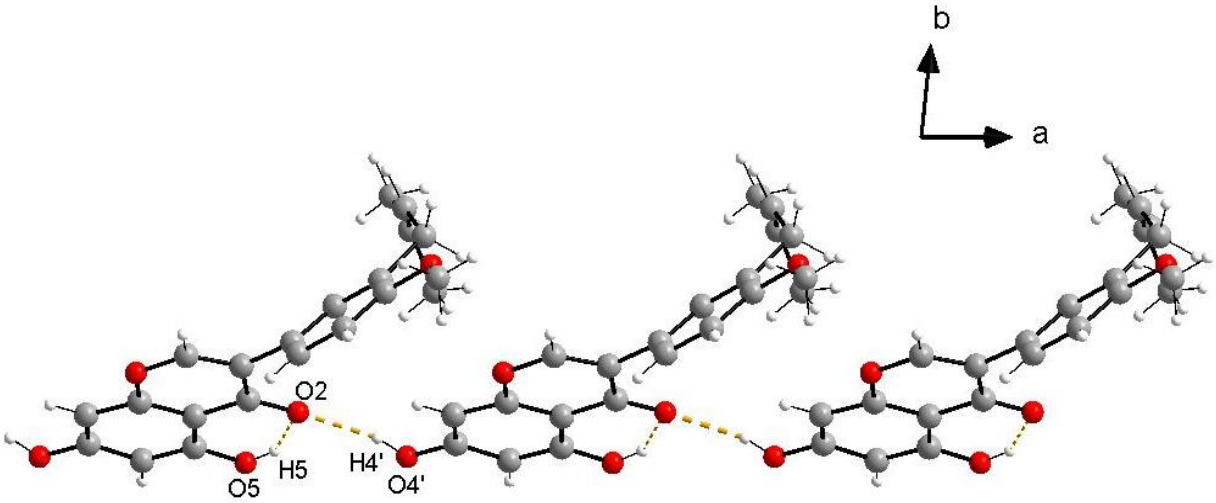



**Figure 20:** Arrangement of the molecules of 3′-prenylbiochanin A (**58**) formed by intermolecular interactions leading to chains along a axis

Isoflavone **66** is neobavaisoflavone, a natural product which was first isolated from the seeds of *Psoralea corylifolia*,[155] a plant used in traditional Chinese medicine.[228] The same compound was later isolated from *E. sigmoidea*,[54,58] an indigenous plant in Cameron. Neobavaisoflavone (**66**) has not been synthesized previously. The structure of compound **66** was confirmed by comparison of its $^{1}H$ and $^{13}C\{^{1}H\}$ NMR spectral data with those reported for the natural product.[52] The compound exhibited significant antibacterial activity *in vitro* against *S. aureus*,[54] and moderate antifungal activity against *Aspergillus fumigatus* and *Cryptococcus neoformans*.[58] The compound also showed significant inhibition of platelet aggregation induced by arachidonic acid (AA) and platelet activating factor (PAF)[153] as well as inhibition of reactive oxygen species (ROS), reactive nitrogen species (RNS) and cytokines: IL-1β, IL-6, IL-12p40, IL-12p70, TNF-α in LPS+IFN-γ- or PMA-stimulated RAW364.7 macrophages.[151]

Isoflavone **137** is 7-methoxyneobavaisoflavone, a natural product which was isolated from the seeds of *Psoralea corylifolia*[229] and it has not been reported from any other plant. 7-Methoxyneobavaisoflavone (**137**) has also not been previously synthesized. The structure of 7-methoxyneobavaisoflavone (**137**) was determined previously only by high resolution mass spectrometry (HRMS), UV and IR spectroscopy.[229] In the current study, the $^{1}H$ and $^{13}C\{^{1}H\}$ NMR

spectral data of compound **137** is being reported for the first time. To date, there is no report on the biological activity of 7-methoxyneobavaisoflavone (**137**), probably due to its scarcity.

Isoflavone **131d** is a non-natural dimethyl ether analogue of neobavaisoflavone (**66**). Compound **131d** was previously synthesized by methylation of neobavaisoflavone (**66**).[54]

## 4.3 Synthesis of Chalcone-Flavanone Hybrids

The objective was to establish a suitable method for the synthesis of chalcone-flavanone hybrids of naturally occurring bioactive flavanones such as liquiritigenin (**47**), liquiritigenin-7-methyl ether (**138**) and liquiritigenin-4′-methyl ether (**139**)[230–233] (Figure 21) because chalcone hybrids are reported to exhibit a wide range of bioactivities such as neuronal differentiation activity,[234] cytotoxicity, and inhibition of monoamine oxidases and butyrylcholinesterase.[235] The method established in the study could be then applied in the synthesis of chalcone-isoflavone hybrids of naturally occurring bioactive isoflavones. The bioactivities and mechanisms of action of these hybrids of natural product scaffolds could then be tested and compared with those of the simple isoflavones or/and chalcones. Flavanones were preferred in the current study because they could be more easily accessed than the isoflavones.

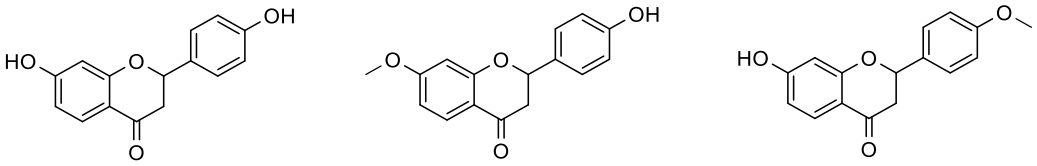
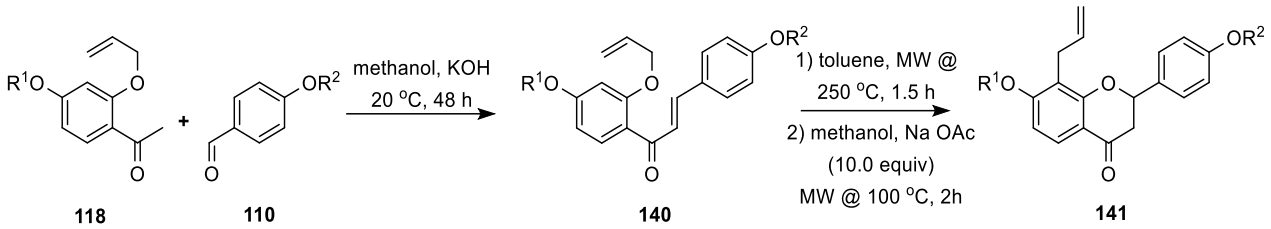



**Figure 21:** Examples of naturally occurring bioactive flavanones

Allyl flavanones were envisaged as key precursors for the synthesis of chalcone-flavanone hybrids. Thus, 8-allyl flavanones **141** were prepared using the previously applied protocol in this study for the synthesis of 8-allyl flavanones **121** (Table 5). Claisen-Schmidt condensation of acetophenones **118** and benzaldehydes **110** afforded chalcones **140** in moderate yields. Microwave irradiation of a solution of the chalcones **140** in toluene at 250 ºC for 1.5 h to induce Claisen rearrangement followed by further microwave irradiation of the resultant crude reaction mixture in methanol in the presence of NaOAc as a base at 100 ºC for 2 h induced oxa-Michael addition to furnish the 8-allyl flavanones **141** (Table 10).

**Table 10:** Synthesis of 8-allyl flavanones **141**

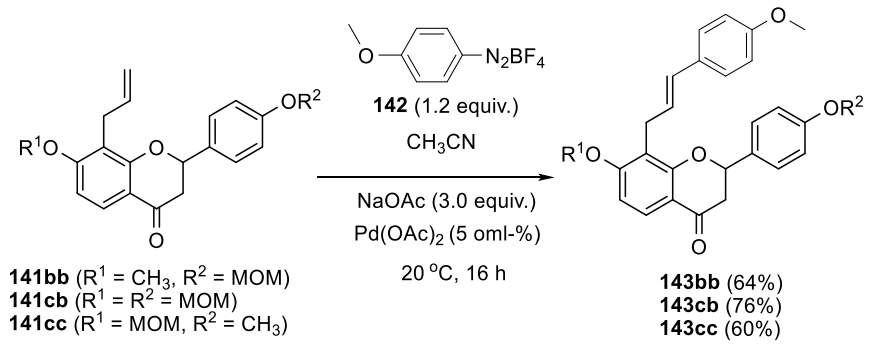



| entry | **118** | $R^1$ | **110** | $R^2$ | **140** | yield (%)[a] | **141** | yield (%)[a] |
|---|---|---|---|---|---|---|---|---|
| 3 | **118b** | $CH_3$ | **110b** | MOM | **140bb** | 65 | **141bb** | 45 |
| 4 | **118c** | MOM | **110b** | MOM | **140cb** | 60 | **141cb** | 45 |
| 5 | **118c** | MOM | **110c** | $CH_3$ | **140cc** | 62 | **141cc** | 46 |

[a]Isolated yield

### 4.3.1 Matsuda-Heck Arylation of 8-Allyl Flavanones 141

Matsuda-Heck arylation of 8-allyl flavanones **141** with 4-methoxybenzenediazonium tetrafluoroborate (**142**) in acetonitrile as solvent in the presence of $Pd(OAc)_2$ (5 mol-%) as a catalyst and NaOAc (3.0 equiv.) as a base at ambient temperature, a reaction condition previously optimized in our group[236] afforded **143** in moderate to good yields (Scheme 33). The arene diazonium salt **142** was synthesized according to literature procedure.[237] The structures of **143** were determined by 1D and 2D NMR spectroscopy. The assignment of the position of the C-C double bond was based on the HMBC correlations of the allylic protons, H-1″ with the oxygenated carbons C7 and C8a (Figure 22).




**Scheme 33:** Matsuda-Heck arylation of 8-allyl flavanones **141**

Recrystallization of **143cc** from methanol afforded crystals suitable for single crystal X-ray diffraction analysis. Thus, the structure of **143cc** could be unambiguously confirmed by single

crystal X-ray diffraction analysis (Figure 23), in which the C-C double bond position agreed with that determined from the HMBC correlations. Although a C-C double bond shift has been reported in the Matsuda-Heck arylation of glycal,[236] it was not observed in this case with the allyl substrates.

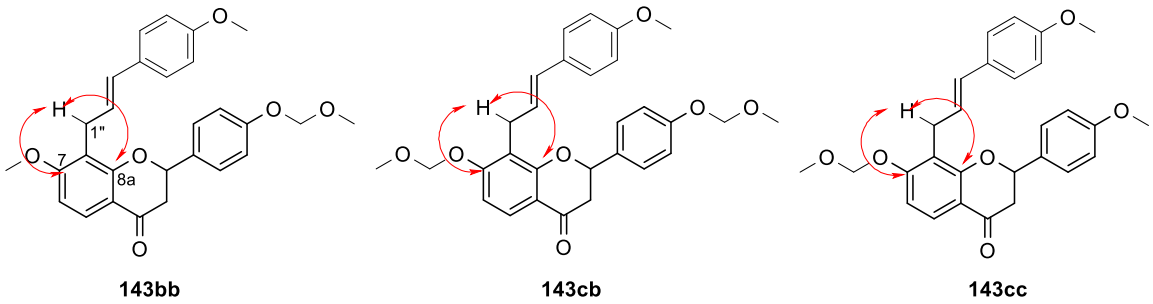



**Figure 22:** HMBC correlations of allylic protons in compounds **143**

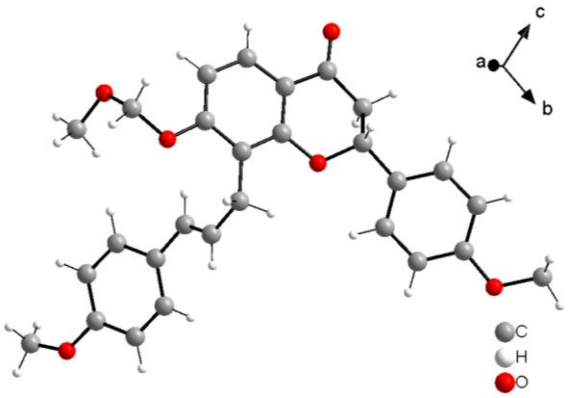
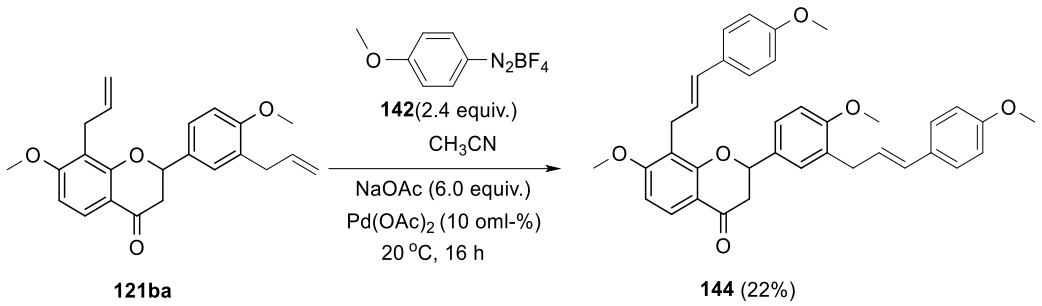



**Figure 23:** Single-crystal X-ray structure analysis of **143cc**

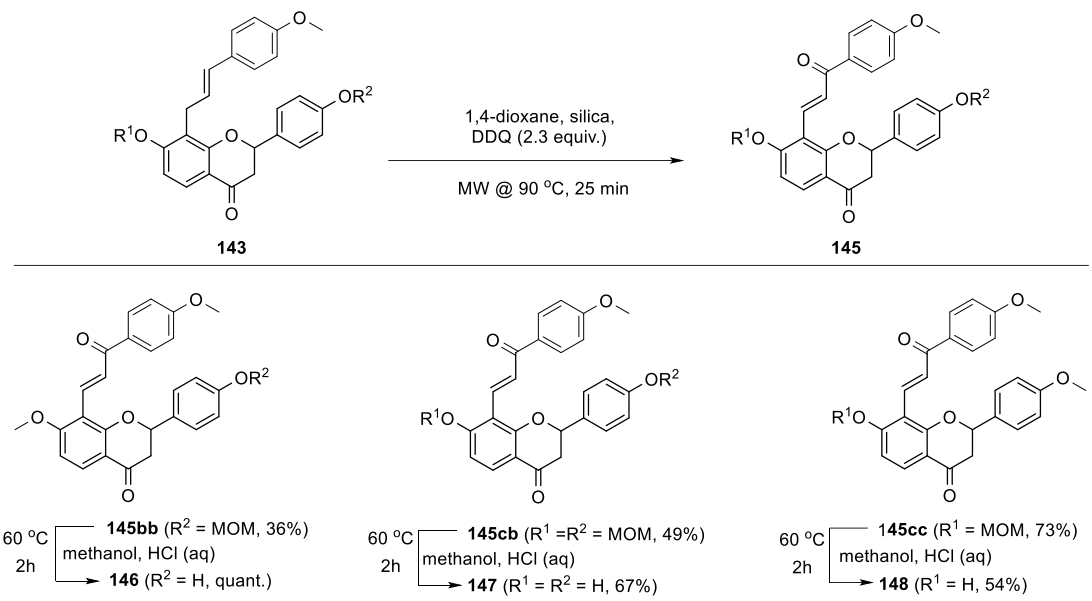
Matsuda-Heck arylation of 8,3′-diallyl-7,4′-dimethoxyflavanone (**121ba**) under similar conditions afforded the expected diarylated product **144** in 22% yield alongside a mixture of two mono-arylated isomers which could not be separated (Scheme 34). Compound **144** could be separated from the mixture by column chromatography on silica. The two mono-arylated isomers are most likely the isomer arylated at the 8-allyl substituent and the isomer arylated at the 3′-allyl substituent. The possibility of two isomers arylated at the same allyl substituent with alternating C-C double bond is ruled out as this was not observed with the arylation of **141bb** bearing a similar 7-methoxy substituent neighboring the 8-allyl substituent which undergoes the arylation.




**Scheme 34:** Matsuda-Heck arylation of 8,3′-diallyl-7,4′-dimethoxyflavanone (**121ba**)

### 4.3.2 Allylic/Benzylic Oxidation of 143

The allylic/benzylic oxidation of **143** using 2,3-dichloro-5,6-dicynobenzoquinone (DDQ) as an oxidant in 1,4-dioxane in the presence of silica under microwave irradiation at 90 ºC[238] afforded the chalcone-flavanone hybrids **145** in yields ranging from 36% to 73% (Scheme 35). The structures of **145** were determined by 1D and 2D NMR spectroscopy. In each case a C-C double bond shift was observed in the product. The position of the C-C double bond and the carbonyl group at C3″ was confirmed from HMBC correlations. For example, for the compound **145bb**, the vinylic proton H-1″ (δ 8.16 (d, *J* = 15.9 Hz, 1H)) correlated with the carbonyl carbon, C3″ (δ 189.4), and the oxygenated carbons C7 (δ 165.0) and C8a (δ 162.3) while the aromatic protons H-2‴/H-6‴ (7.76 (d, *J* = 8.8 Hz, 2H)) correlated with C3″ (δ 189.4) and C4‴ (δ 163.3) (Figure 24).




**Scheme 35:** Allylic/benzylic oxidation of **143** and MOM-ether cleavage

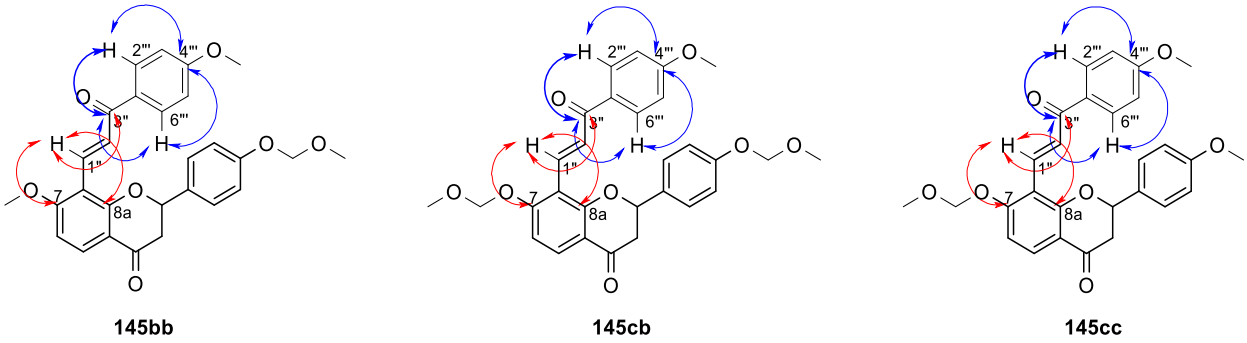



**Figure 24:** HMBC correlations of H-1″ and H-2‴/H-6‴ in compounds **145**

MOM-ether cleavage of **145** by refluxing their solutions in methanol with aqueous HCl at 60 ºC for 2h furnished the respective target chalcone-flavanone hybrids. Compounds **146**, **147** and **148** are hybrids of liquiritigenin-7-methyl ether (**138**), liquiritigenin (**47**) and liquiritigenin-4′-methyl ether (**139**) respectively, natural products which have inter alia been isolated from *Bauhinia manca*, a plant traditionally used in Costa Rica as an antidiabetic agent.[231] Compounds **138** and **139** have also been isolated from *Terminalia fagifolia*[232] and **138** was tested for cytotoxicity against $Hep_2$ and $H_{292}$ cell lines. Liquiritigenin (**47**) is a strong and selective phytoestrogen,[230] and it also exhibits significant anti-inflammatory activity.[233] Owing to the bioactivities of these natural

flavanones, chalcones[239,240] and chalcone hybrids,[234,235] the chalcone-flavanone hybrids synthesized in this study could be used to investigate the synergistic or antagonistic effects of flavanones and chalcones on their bioactivities. Previous studies on the bioactivities and mechanisms of action of stilbene-chalcone and stilbene-flavanone hybrids[241] indicate that the hybrids mimic either one of the simple scaffolds or both simple scaffolds. If the hybrids mimic both simple scaffolds, this might produce a synergistic effect, which might in turn enhance the bioactivity. The method used in the current study for the synthesis of chalcone-flavanone hybrids could also be applied in the synthesis of chalcone-isoflavone hybrids.

## 4.4 Intermolecular Interactions in the Solid-State Structures of 5-Deoxy-3′-prenylbiochanin A (59) and its Precursors, 106a and 106b

The isoflavones 5-deoxy-3′-prenylbiochanin A (**59**) and its precursors, **106a** and **106b** are closely related, but differ only with respect to the substituent at the C7 and C3′ positions. Their molecular structures were determined by single crystal X-ray diffraction. The single crystal X-ray diffraction was performed by Dr. Eric Sperlich, who provided all data and figures.

The molecular structures of the three compounds are shown in Figure 25 with atomic numbering.[242] The carbon atoms at the C7 and C3′ positions are labelled C2 and C14 respectively on the molecular structures (Figure 25). Compounds **59** and **106b** are substituted at C2 by a hydroxyl group while compound **106a** is substituted by a methoxymethoxy group at this position (Figure 25). Compound **59** has a prenyl substituent at C14, while **106a** and **106b** possess an allyl substituent at this position. The observed differences in the melting point and in the solubility behavior of the three compounds can be attributed to these varying substituents. Despite the major similarities of the molecular structures of **59**, **106a** and **106b**, there are large differences in the crystal structure due to the different arrangement of the molecules in the solid state. Thus, the three compounds even crystallize in different crystal systems. The crystallographic data and the refinement data of the three compounds are listed in Table 11.[242]

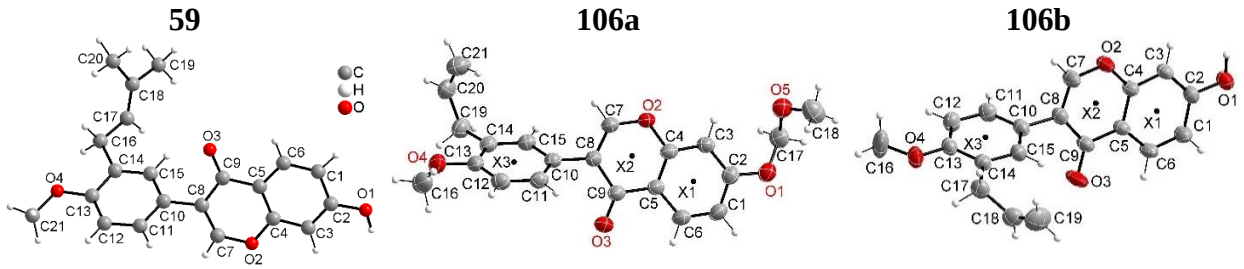



**Figure 25:** Molecular structures of compounds **59**, **106a** and **106b**

**Table 11:** Crystallographic data and refinement data for compounds **59**, **106a** and **106b**

| **Compound** | **59** | **106a** | **106b** |
|---|---|---|---|
| Empirical formula | $C_{21}H_{20}O_4$ | $C_{21}H_{20}O_5$ | $C_{19}H_{16}O_4$ |
| $M$ [g mol$^{-1}$] | 336.37 | 352.37 | 308.32 |
| $T$ [K] | 288 | 210 | 210 |
| λ [Å] | 0.71073 (Mo $K\alpha$) | 0.71073 (Mo $K\alpha$) | 0.71073 (Mo $K\alpha$) |
| Crystal system | monoclinic | orthorhombic | triclinic |
| Space group | $P2_1/n$ | $P$ n a $2_1$ | $P$ -1 |
| **Unit cell dimensions** | | | |
| $a$ [Å] | 14.8274(4) | 17.9139(2) | 8.0184(16) |
| $b$ [Å] | 8.16970(10) | 14.6001(4) | 8.4831(17) |
| $c$ [Å] | 15.5656(4) | 6.6911(7) | 11.867(2) |
| $\alpha$ [°] | 90 | 90 | 104.02(3) |
| $\beta$ [°] | 114.139(2) | 90 | 94.03(3) |
| $\gamma$ [°] | 90 | 90 | 101.24(3) |
| $V$ [Å$^3$] | 1720.67(7) | 1750.02(19) | 762.2(3) |
| $Z$ | 4 | 4 | 2 |
| $\rho_{calc}$ [g cm$^{-3}$] | 1.298 | 1.337 | 1.343 |
| $\mu$ [mm$^{-1}$] | 0.089 | 0.095 | 0.094 |
| $F$(000) | 712 | 744 | 324 |
| Crystal description | colorless, plate | colorless, long prism | colorless, long prism |
| Crystal size [mm$^3$] | 1.00 x 0.60 x 0.20 | 0.85 x 0.21 x 0.10 | 0.75 x 0.28 x 0.13 |
| $\theta_{min}$ / $\theta_{max}$ [°] | 1.43 - 29.7 | 3.013 – 33.142 | 2.692 – 30.504 |
| Index ranges | -19 ≤ h ≤ 19 | -27 ≤ $h$ ≤ 27 | -11 ≤ $h$ ≤ 11 |
| | -10 ≤ k ≤ 10 | -22 ≤ $k$ ≤ 22 | -12 ≤ $k$ ≤ 12 |
| | -20 ≤ l ≤ 20 | -10 ≤ $l$ ≤ 10 | -16 ≤ $l$ ≤ 15 |
| Reflection collected | 22586 | 58225 | 21354 |
| Independent reflection | 3955 | 6617 | 4636 |
| $R_{int}$ | 0.028 | 0.0504 | 0.0336 |
| Reflections I>2$\sigma$(I) | 3600 | 5353 | 3467 |
| Parameter | 307 | 237 | 212 |
| $R_1/wR_2$ [I>2$\sigma$(I)] | 0.040/0.112 | 0.0427/0.1062 | 0.0465/0.1318 |
| $R_1/wR_2$ [all data] | 0.043/0.117 | 0.0584/0.1137 | 0.0638/0.1419 |
| min./max. $\Delta\rho$ [10$^{-6}$ e pm$^{-3}$] | -0.17/0.20 | -0.141/0.334 | -0.245/0.344 |
| GooF | 1.040 | 1.039 | 1.079 |
| CCDC | 2013149 | 2121813 | 2121812 |

Compound **59** crystallizes in the monoclinic space group $P2_1/n$ with four formula units per unit cell (Z), compound **106a** in the orthorhombic space group $Pna2_1$ with Z = 4, and compound **106b** in the triclinic space group $P\bar{1}$ with $Z = 2$. Despite the molecular similarity of compounds **59**, **106a** and **106b**, they have different arrangement of molecules in the solid state. Consequently, their melting points and solubilities show significant differences (Table 12).[242] For instance, compound **106a** has the highest molar mass (352.37 g/mol) but the lowest melting point at 104 °C and is soluble in most common organic solvents tested. Compound **106b** has the lowest molar mass (308.32 g/mol) but the highest melting point at 207 °C and is the least soluble in the solvents tested. Compound **59** has a molar mass of 336.37 g/mol, a melting point at 198 °C and its solubility lies between that of compounds **106a** and **106b**.

**Table 12:** Molar mass, melting points and solubility behavior of compounds **59**, **106a** and **106b**

| **Compound** | **Molecular weight** | **Melting point** | **Solvent** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | hexane | $CH_2Cl_2$ | $CHCl_3$ | acetone | MeCN | EtOH | MeOH | DMSO | $H_2O$ |
| **59** | 336.37 | 198 °C | | | | | | | | | |
| **106a** | 352.37 | 104 °C | | | | | | | | | |
| **106b** | 308.32 | 207 °C | | | | | | | | | |
| | Completely soluble at room temperature | | | | | | | | | | |
| | Slightly soluble at room temperature, but completely soluble on warming | | | | | | | | | | |
| | Insoluble at room temperature and on warming | | | | | | | | | | |

To determine the influence of the different solid-state structures on the macroscopic properties, the intermolecular non-covalent interactions in compounds **59**, **106a** and **106b** were investigated by performing Hirshfeld surface analysis on the molecular structures of the three compounds, from which information on the short intermolecular contacts in the solid-state structure was obtained. The Hirshfeld surface analysis was performed by Dr. Eric Sperlish, who provided all data and figures.

The Hirshfeld surface analysis can be used to determine the contribution of various intermolecular contacts to the total surface area of a molecule. Thus, for the molecules of the compounds **59**, **106a** and **106b**, particularly short contacts of the form H···H, C···H/H···C, O···H/H···O, C···O/O···C, C···C and O···O are found with decreasing frequency (Figure 26).

The contacts which lead to the intermolecular attractions would be considered to predict the trend of melting points and solubilities of the three compounds. The hydrogen bonds with O acceptors (O···H/H···O) contacts are the most relevant, followed by π-stacking interactions with the C···C

contacts. When comparing the percentage of O···H/H···O surface contacts in the three compounds, these occur most frequently in **106a** followed by **106b** and lastly **59** with 21.7%, 20.0%, and 17.9% respectively (Figure 26). In contrast to previous investigations,[243] the melting points of compounds **59**, **106a** and **106b** seems not to directly depend on the percentage of O···H/H···O surface contacts. This is probably due to the difference in the bond length and strength of these contacts.

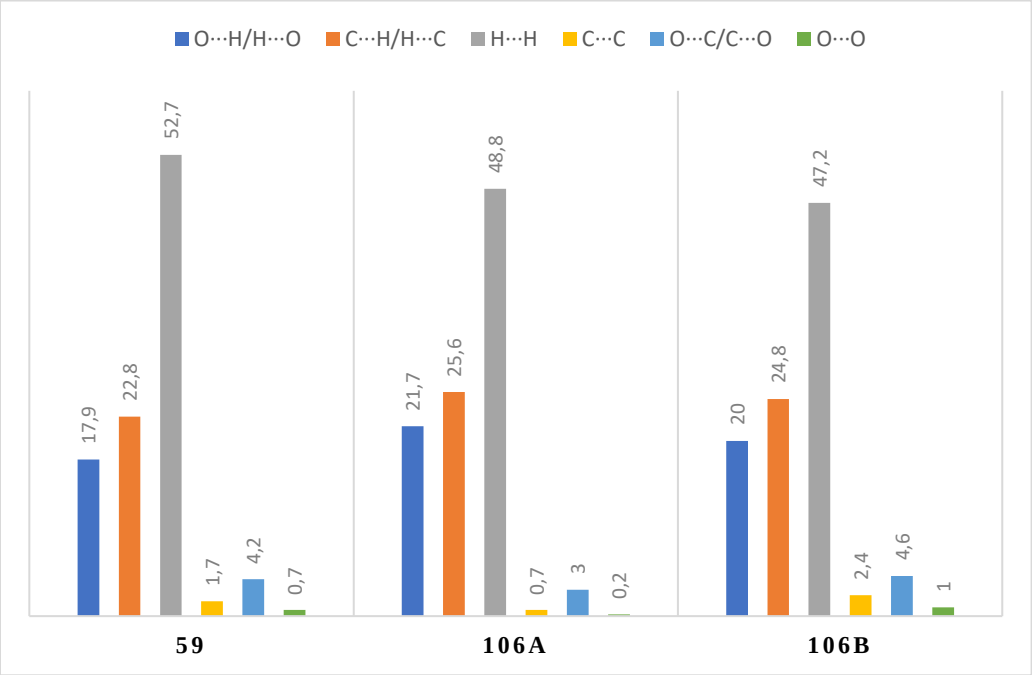



**Figure 26:** Representation of the composition (%) of the Hirshfeld surface from different intermolecular contacts in compounds **59**, **106a** and **106b**

To analyze the strength of the O···H/H···O contacts, the strongest hydrogen bonds with O-acceptor for the three compounds are shown in Figure 27.[242] The Hirshfeld surface of the O···H/H···O contacts (top) and the molecular view with atom labels (bottom) are shown. The red regions on the Hirshfeld surface indicate short contact distance (stronger bonds) while the blue regions indicate relatively longer contact distance (relatively weak bonds). The bond distances and angles of all hydrogen bonds with O-acceptor of the three compounds **59**, **106a** and **104b** are shown in Table 13.[242]

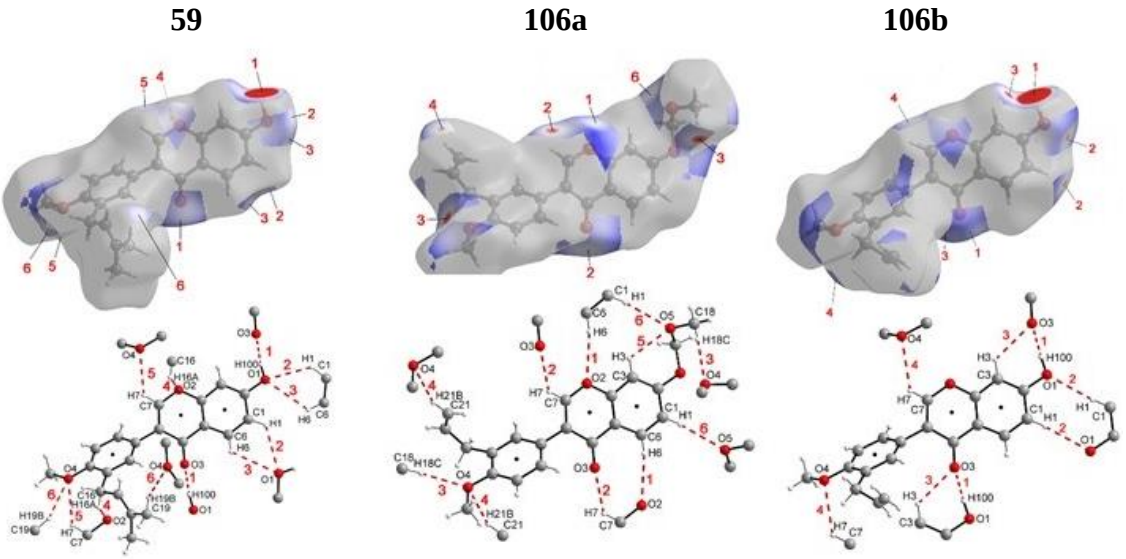



**Figure 27:** Illustration of the Hirshfeld surface of the O···H/H···O contacts (top) and the molecular view with atom labels (bottom) of compounds **59**, **106a** and **106b**

**Table 13:** Bonding distances and angles of hydrogen bonds with O-acceptors in compounds **59**, **106a** and **106b**

| **Compound 59** | **D-H [Å]** | **H···A [Å]** | **D···A [Å]** | **Σ (D-H + H···A) [Å]** | **D-H···A [°]** |
|---|---|---|---|---|---|
| 1 (O1-H100···O3) | 0.89 | 1.77 | 2.66 | 2.66 | 170.5 |
| 2 (C1-H1···O1) | 1.01 | 2.75 | 3.41 | 3.76 | 123.1 |
| 3 (C6-H6···O1) | 0.96 | 2.88 | 3.48 | 3.84 | 121.7 |
| 4 (C16-H16A···O2) | 0.99 | 2.63 | 3.37 | 3.62 | 132.0 |
| 5 (C7-H7···O4) | 0.97 | 2.73 | 3.39 | 3.70 | 125.8 |
| 6 (C19-H19···O4) | 1.00 | 2.78 | 3.69 | 3.78 | 150.6 |
| **Compound 106a** | | | | | |
| 1 (C6-H6···O2) | 0.94 | 2.72 | 3.59 | 3.66 | 154.2 |
| 2 (C7-H7···O3) | 0.94 | 2.56 | 3.25 | 3.50 | 130.6 |
| 3 (C18-H18C···O4) | 0.97 | 2.54 | 3.50 | 3.51 | 174.6 |
| 4 (C21-H21B···O4) | 0.94 | 2.67 | 3.51 | 3.61 | 148.7 |
| 5 (C3-H3···O5) | 0.94 | 2.46 | 3.00 | 3.40 | 116.8 |
| 6 (C1-H1···O5) | 0.94 | 2.75 | 3.67 | 3.69 | 167.1 |
| **Compound 106b** | | | | | |
| 1 (O1-H100···O3) | 0.94 | 1.74 | 2.67 | 2.68 | 174.5 |
| 2 (C1-H1···O1) | 0.94 | 2.66 | 3.55 | 3.60 | 157.9 |
| 3 (C3-H3···O3) | 0.94 | 2.57 | 3.23 | 3.51 | 128.2 |
| 4 (C7-H7···O4) | 0.94 | 2.77 | 3.40 | 3.71 | 125.4 |

In compound **106a**, eleven hydrogen bonds with O-acceptor result for each molecule, and these are six symmetry-independent hydrogen bonds. For each molecule, the hydrogen bonds **1**, **2**, **3**, **4**

and **6** are present twice since the molecule acts once as a proton donor and the second time as a proton acceptor. Only the intramolecular hydrogen bond **5** is present once. It is evident from Figure 27 and Table 13 that all the contacts shown for compound **106a** are relatively weak C-H···O hydrogen bonds. This accounts for its lowest melting point and the best solubility of all the three compounds.

In compound **59**, each molecule forms a total of twelve hydrogen bonds, six symmetry-independent bonds **1**, **2**, **3, 4, 5** and **6**, in which each molecule is involved both as a proton donor and as a proton acceptor. When looking at the Hirshfeld surface of compound **59** in Figure 27, it is evident that hydrogen bond **1** has a particularly large red area on the surface. In contrast to the other hydrogen bonds, this is an O-H···O hydrogen bond with a particularly high bond strength. It is formed between the hydroxyl group with O1 and the O3 of the keto group. All other contacts shown for this compound in Figure 27 are C-H···O hydrogen bonds. Also, in compound **106b**, very strong O-H···O hydrogen bonds **1** and a total of three other symmetry-independent C-H···O hydrogen bonds **2**, **3** and **4** are present, resulting in a total of eight O-acceptor hydrogen bonds for each molecule.

The two very strong O-H···O hydrogen bonds **1** present in each of the compounds **59** and **106b** account for their significantly higher melting points. The fact that compound **59** has a lower melting point than compound **106b** despite having a higher molar mass, cannot be concluded from the O-H···O hydrogen bond strength. This is because the O-H···O hydrogen bonds **1**, seem to be approximately equally strong for both compounds **59** and **106b** (Table 13). Thus, there should be other intermolecular attractions influencing the melting points of these compounds.

In addition to hydrogen bonds, attractive interactions between the aromatic rings of the molecules also occurs in compounds **59**, **106a** and **106b**. These π-stacking interactions can be analyzed by imaging the C···C contacts on the Hirshfeld surface. These Hirshfeld surfaces and the representation of the molecular structures are shown in Figure 28 (top and bottom respectively).[242] The distances of the aromatic-aromatic separations (X···X) and the angles between the interacting aromatics are summarized in Table 14.[242]

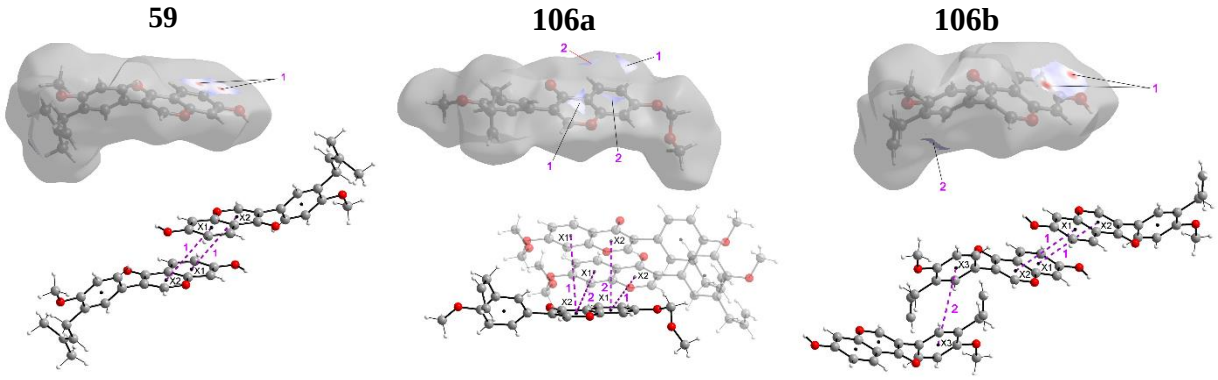



**Figure 28:** Representation of the Hirshfeld surface of the C···C contacts (top) and molecular view with labels of compounds **59**, **106a** and **106b**

**Table 14:** Distances and angles of parallel-shifted stacking interactions in compounds **59**, **106a** and **106b** with X as the center and p as the plane of the aromatic ring

| **Compound 59** | **d(X···X) [Å]** | **<(pp) [°]** |
|---|---|---|
| 1 (X1···X2) (two times) | 4.17 | 0 |
| **Compound 106a** | **d(X···X) [Å]** | **<(pp) [°]** |
| 1 (X1···X2) (two times) | 4.25 | 20.9 |
| 2 (X2···X1) (two times) | 5.40 | 20.9 |
| **Compound 106b** | **d(X···X) [Å]** | **<(pp) [°]** |
| 1 (X1···X2) (two times) | 4.21 | 0 |
| 2 (X3···X3) | 4.66 | 0 |

The molecules of compound **106a** form stacking interactions with two neighboring molecules in the solid state (Figure 28, middle). For each neighboring molecule, there are two different aromatic-aromatic distances (X1···X2) with 4.25 Å (**1**) and 5.40 Å (**2**). Although these distances are in the range expected for classical stacking interactions,[244] it is evident from the low coloration of the Hirshfeld surface, as well as from the arrangement of the molecules that the interaction energy between the molecules is not very large. The aromatic rings are not parallel to each other, instead they are arranged at an angle of 20.9° to each other. This also results in the lower value of the C···C surface contacts of compound **106a** with 0.7 %. This further accounts for the lower melting point and the better solubility of compound **106a**. The molecules of compounds **59** and **106b** interact with only one neighboring molecule via the aromatics with the centers X1 and X2, resulting in aromatic-aromatic distances **1** of 4.17 Å for **59** and 4.21 Å for **106b**. Here, the

interacting aromatics are parallel to each other, and the short distance and good overlap can be clearly seen in the red regions on the Hirshfeld surface (Figure 28, top left, and top right).

The reason for the higher melting point and lower solubility of **106b** compared to **59** is probably also due to stacking interactions since it could not be concluded from the O-H···O hydrogen bond strength. This is because the molecules in **106b** interact with another molecule via the aromatic rings with X3, resulting in an aromatic-aromatic distance **2** of 4.66 Å (Figure 28). In addition, the molecules are parallel to each other. These stacking interactions cannot be formed in the structure of compound **59** because the steric hindrance due to the prenyl substituents at C14 prevents the molecules from approaching each other.

## 4.5 *In Vitro* Antimicrobial Activities of Some Synthesized Compounds

To assess the antimicrobial activities of the prenylated isoflavones 5-deoxy-3′-prenylbiochanin A (**59**) and erysubin F (**61**), their minimum inhibitory concentration (MIC) values against methicillin resistant *Staphylococcus aureus* (MRSA) (ATCC 43300), *Salmonella enterica* subsp. *enterica* (NCTC 13349), *Escherichia coli* (ATCC 25922) and *Candida albicans* (ATCC 90028) were determined. To investigate the structure-activity relationship, the antimicrobial activity of 7,4′-dihydroxy-8,3′-diprenylflavone (**129**), a non-natural flavone isomer of erysubin F, obtained during the synthesis of erysubin F was also tested. This experiment was intended to investigate if and how a switch from an isoflavone to a flavone structure would affect the bioactivity when all other structural features are retained. The antibiotics vancomycin and ampicillin were used as a positive control for MRSA, and *S. enterica* and *E. Coli*, respectively while amphotericin B was used as a positive control for antifungal assay against *C. albicans*. DMSO was used as a negative control. The antimicrobial testing was performed in the Fraunhofer Institute IZI-BB by Dr. M. v. Nickisch-Rosenegk and Dr. S. Kersting, who provided the raw data (in µg/mL) and photos. The results from the antimicrobial assays are summarized in Table 15.[197]

All prenylated flavonoids investigated in the current study were inactive against the Gram-negative bacteria *S. enterica* subsp. *enterica* and *E. coli* and against the fungal pathogen *C. albicans*. 5-Deoxy-3′-prenylbiochanin A (**59**) was also inactive against the Gram-positive MRSA, but interestingly both erysubin F (**61**) and its non-natural flavone isomer **129** showed comparable activities against this MRSA strain, with MIC values of 15.4 and 20.5 µM, respectively (Table 15;

Figure 29). These results suggest that the isoflavone structure with the sterically less hindered electrophilic C2-position is apparently less decisive for antibiotic activity than the increased lipophilicity caused by the presence of two prenyl groups.

**Table 15:** Antimicrobial activities of compounds **59**, **61** and **129**

| compound | MIC (μM) | | | |
|---|---|---|---|---|
| | MRSA (ATCC 43300) | *S. enterica* subsp. *enterica* (NCTC 13349) | *E. coli* (ATCC 25922) | *C. albicans* (ATCC 90028) |
| **59** | > 154.6 | > 190.3 | > 95.1 | > 95.1 |
| **61** | 15.4 | > 82.0 | > 82.0 | > 82.0 |
| **129** | 20.5 | > 82.0 | > 82.0 | > 82.0 |
| vancomycin | 0.5 | -- | -- | -- |
| ampicillin | -- | 11.4 | 11.4 | -- |
| amphotericin B | -- | -- | -- | 0.5 |
| DMSO | not active | not active | not active | not active |

To some extent the observations in this study agree with previously published results, but there are also some remarkable disparities. It was shown that the antibacterial activity of various natural flavanones and flavones strongly depends on a well-balanced lipophilicity, and that Gram-positive bacteria are susceptible to a wider range of lipophilicity than Gram-negative ones.[245] This might explain why the Gram-negative bacteria investigated in this study are not affected by any of the compounds tested. It might also explain why the presumably less lipophilic 5-deoxy-3′-prenylbiochanin A (**59**) is much less active against MRSA than erysubin F (**61**) and its flavone isomer **129**. Another important factor is the position of prenylation: when 30 prenylated (iso)flavonoids were tested against the Gram-positive bacterium *Listeria monocytogenes*, significant differences were observed between C6-, C8- and C3′-prenylated isoflavones. The C8-prenylated isoflavone lupiwighteone (**149**) was inactive (MIC > 147.8 μM) whereas the C6-prenylated isomer wighteone (**7**) showed high activity (MIC = 29.6 μM) and the C3′-prenylated isomer isowighteone (**72**) was moderately active (MIC = 59.1 μM) (Figure 29).[156] A similar effect of the prenylation pattern on antibacterial activity was observed with *S. aureus* and MRSA.[246] The low activity of 5-deoxy-3′-prenylbiochanin A (**59**), with no prenyl substituent at C6 or C8, is in agreement with these literature reports. The very high activity of erysubin F (**61**), however, is somewhat surprising because a C8-prenyl group would normally be considered to decrease the bioactivity. The C6-prenylated isomer of erysubin F is unknown and therefore no data is available for comparison.

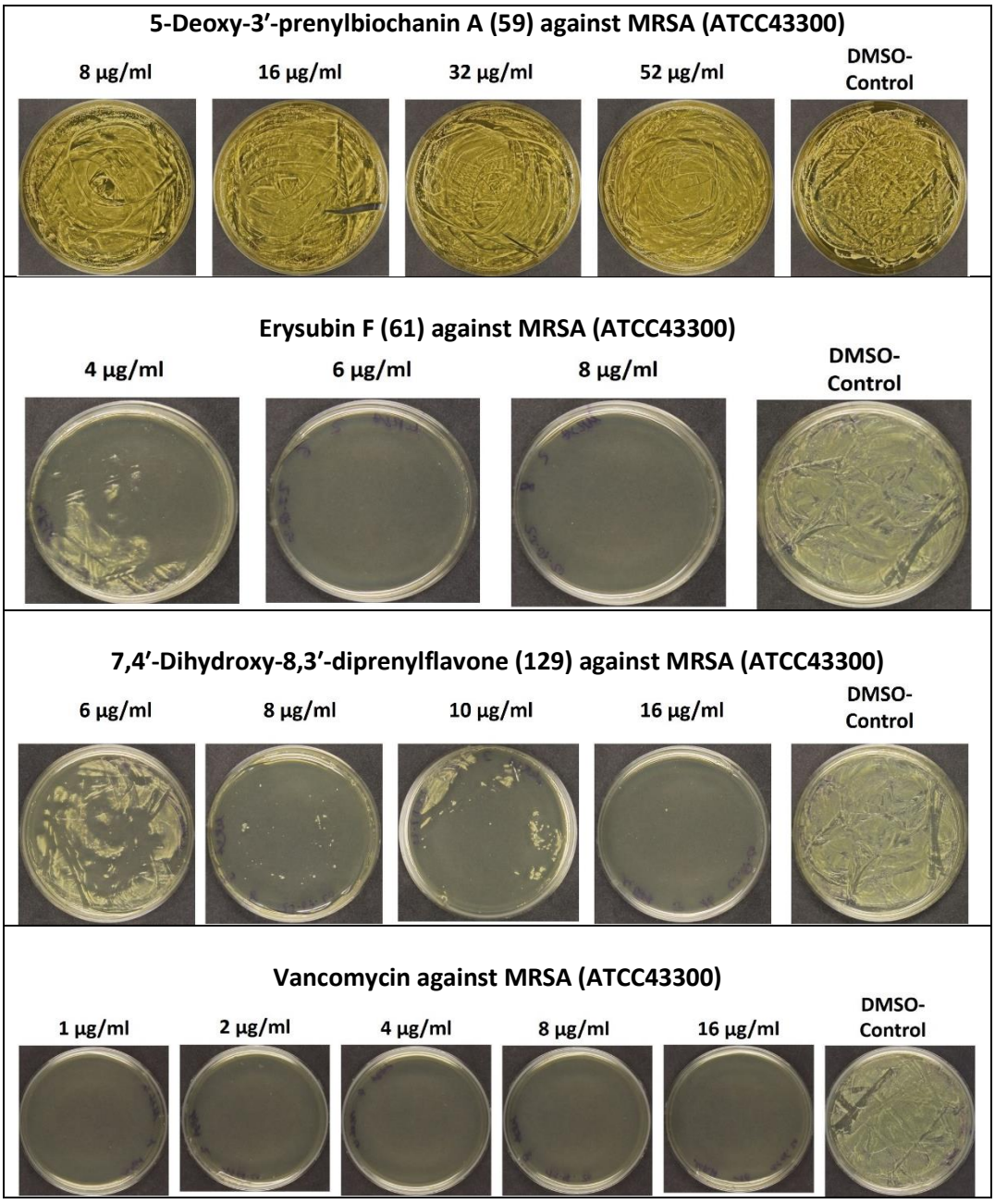



**Figure 29:** Pictorial representation of the antibacterial activities of 5-deoxy-3′-prenylbiochanin A (**59**), erysubin F (**61**) and 7,4′-dihydroxy-8,3′-diprenylflavone (**129**) against MRSA (ATCC43300) (Photos kindly provided by Dr. S. Kersting (Fraunhofer Institute IZI-BB))

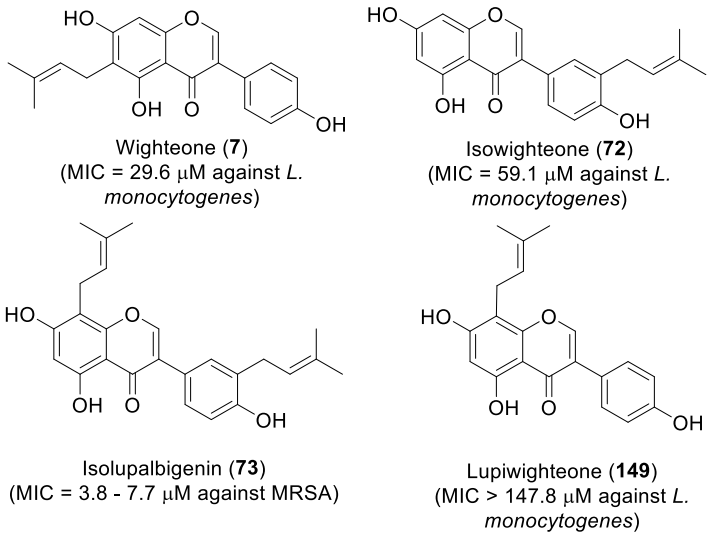



**Figure 30:** Structures of some antibacterial isoflavones and their bioactivities[156,160]

The remarkable discrepancy between the results of the current study and previously published results concerns the MIC value of erysubin F (**61**). Tanaka *et al*. reported an MIC value of 256.1 μM against MRSA for erysubin F (**61**) that was isolated from the roots of *Erythrina variegata*.[56] The MIC value determined in the current study (MIC = 15.4 μM) for synthetic erysubin F (**61**) is reproducibly between one and two orders of magnitude lower (Table 15). The possibility that the high antibacterial activity is an artifact caused by impurities from the chemical synthesis is ruled out because essentially the same synthetic methods and reagents were also used for 5-deoxy-3′-prenylbiochanin A (**59**), which is inactive against MRSA. In a later study Sato *et al*. screened six isoflavones for their antibacterial activity against MRSA and found isolupalbigenin (**73**) (Figure 30) to be the most active compound, with MIC values between 3.8 and 7.7 μM.[160] As isolupalbigenin (**73**) is the C5-hydroxylated analogue of erysubin F (**61**), it was reasoned that a phenolic hydroxy group at the C5 position of the A-ring is an "essential requirement for anti-MRSA activity in isoflavones".[160] The MIC values of the isoflavone erysubin F (**61**) (MIC = 15.4 μM) and its non-natural flavone isomer **129** (MIC = 20.5 μM) differ only slightly. Although several reports on the relationship of antibacterial activity and molecular structure of flavonoids and isoflavonoids exist,[156,247] to date, there is no report on the relationship of the antibacterial activity of flavone and isoflavone constitutional isomers with otherwise identical substitution patterns under comparable conditions. Several modes of actions have been discussed for

antibacterial plant (iso)flavonoids,[248] including interference with bacterial topoisomerase. This mechanism has been particularly emphasized for isoflavones, which structurally resemble the clinically used 4-quinolone topoisomerase inhibitors.[246] The results of the current study point towards a mode of action that does not necessarily rely on an isoflavone skeleton because the isoflavone and flavone isomers show comparable antibacterial activities, but a detailed mechanistic investigation is required before any conclusions can be drawn.

# 5 Conclusions and Outlook

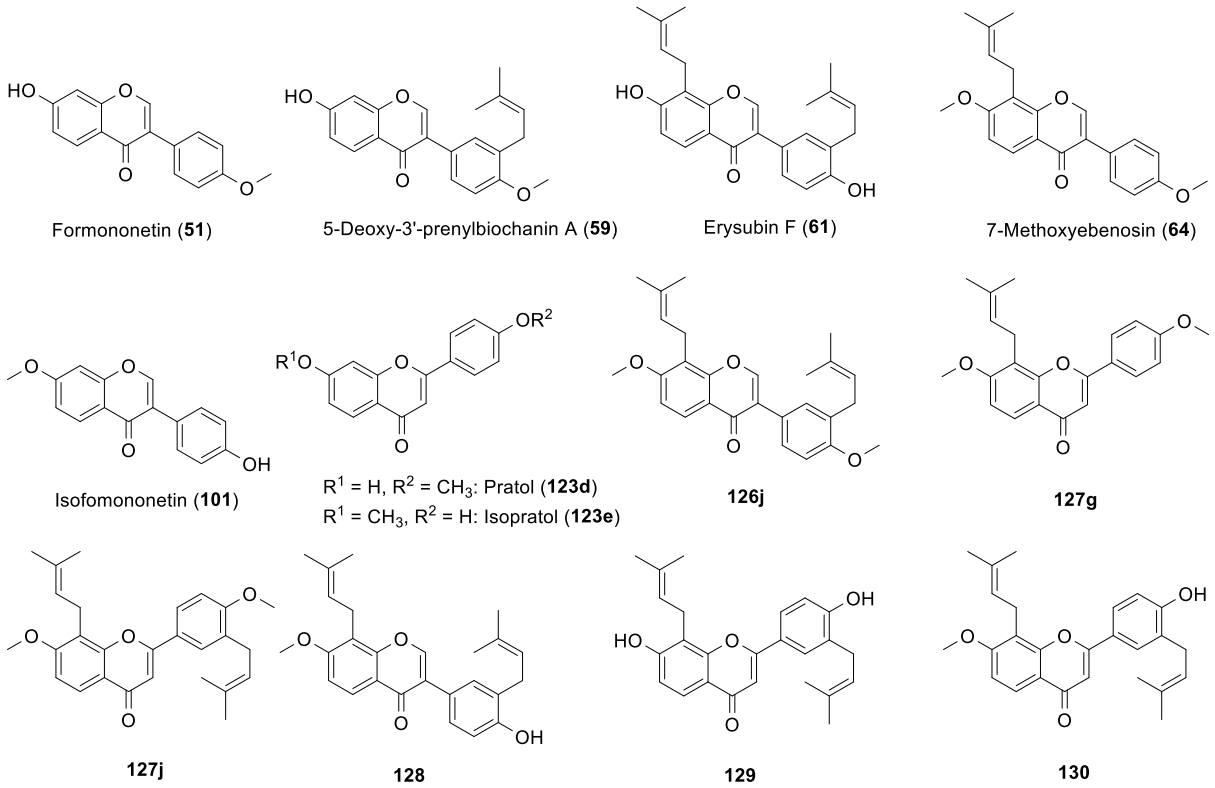



**Figure 31:** An overview of successfully synthesized compounds via the 2,3-oxidative rearrangement of flavanones

The first syntheses of the naturally occurring prenylated isoflavones 5-deoxy-3′-prenylbiochanin A (**59**), erysubin F (**61**) and 7-methoxyebenosin (**64**), and the hitherto unknown isoflavones 7,4′-dimethoxy-8,3′-diprenylisoflavone (**126j**) and 4′-hydroxy-7-methoxy-8,3′-diprenylisoflavone (**128**), the respective di- and monomethyl ether analogues of erysubin F (**61**) (Figure 31), using a 2,3-oxidative rearrangement of flavanones and a regioselective olefin cross metathesis as key steps are reported. During these syntheses, the scope of the 2,3-oxidative rearrangement of flavanones using hypervalent iodine compounds as oxidants has been explored. In contrast to earlier literature reports, products resulting from a ring contraction pathway were not detected for the examples tested in the current study. In almost all cases, the desired isoflavones were obtained together with their flavone isomers. Thus, the naturally occurring flavones pratol (**123d**), isopratol (**123e**) and the previously unknown flavones 7,4′-dimethoxy-8-prenylflavone (**127g**), 7,4′-dimethoxy-8,3′-

diprenylflavone (**127j**), 7,4′-dihydroxy-8,3′-diprenylflavone (**129**) and 4′-hydroxy-7-methoxy-8,3′-diprenylflavone (**130**) (Figure 31) were obtained. The flavones result from an oxidation of the flavanone without collateral migration of the 2-aryl substituent. The allyl substituent at either the A-ring or B-ring of the flavanone is well tolerated while the hydroxyl group at the C5 position of the flavanone favours an oxidation of the arene. This is a limitation of the method in addition to the incompatibility of unprotected phenols and the low tolerance to acid-sensitive protecting groups. Despite the limited substrate scope and the failure to completely resolve the selectivity issue arising from the competing formation of flavones, the 2,3-oxidative rearrangement/cross metathesis is synthetically useful for some substitution patterns relevant for prenylated polyphenol natural products.

The first syntheses of the naturally occurring prenylated isoflavones 3′-prenylbiochanin A (**58**), neobavaisoflavone (**66**) and 7-methoxyneobavaisoflavone (**137**) (Figure 32), using a Suzuki-Miyaura cross-coupling of 3-iodochromones and phenylboronic acids and a regioselective olefin cross metathesis as key steps are also reported. The results indicate that Suzuki-Miyaura cross-coupling reaction is a better method than the 2,3-oxidative rearrangement of flavanones for the synthesis of simple isoflavones or prenylated isoflavones whose prenyl substituents or allyl groups, the substituents that are essential precursors for the prenyl side chains, can be regioselectively introduced after the construction of the isoflavone core. However, the possibility of preparing allylated or prenylated 3-iodochromones or/and allylated or prenylated phenylboronic acids, hence the Suzuki-Miyaura cross-coupling of the allylated or prenylated substrates needs to be investigated.

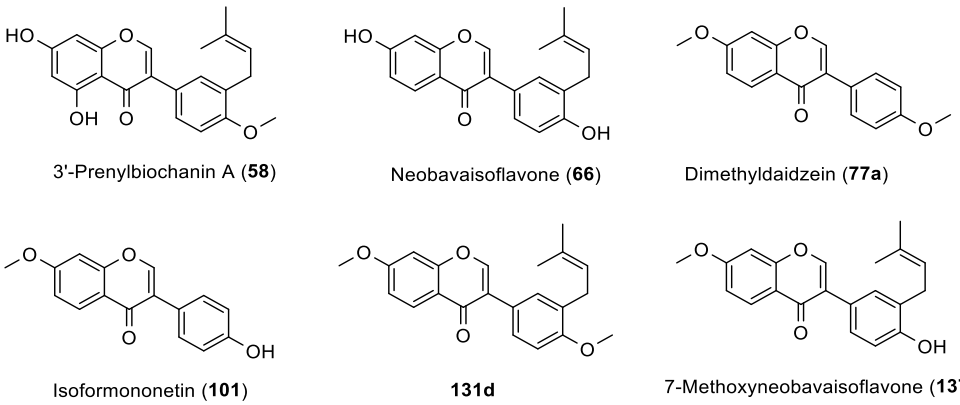



**Figure 32:** An overview of the successfully synthesized isoflavones via the Suzuki-Miyaura cross-coupling reactions

The first syntheses of the chalcone-flavanone hybrids **146**, **147** and **148** (Figure 33), the hybrids of the naturally occurring bioactive flavanones liquiritigenin-7-methyl ether (**138**), liquiritigenin (**47**) and liquiritigenin-4′-methyl ether (**139**), respectively using Matsuda-Heck arylation and allylic/benzylic oxidation as key steps is also reported.

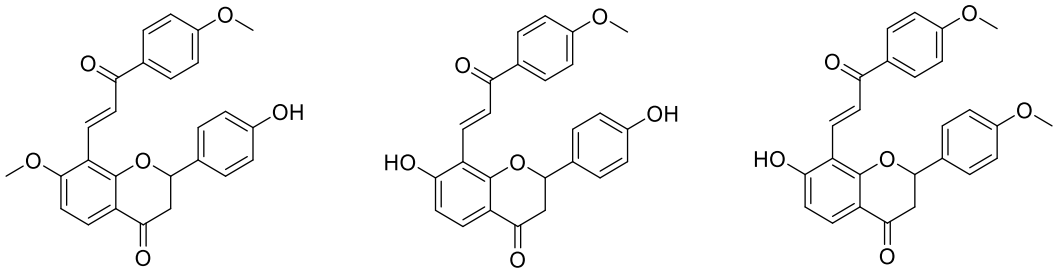



**Figure 33:** An overview of successfully synthesized chalcone-flavanone hybrids

The intermolecular interactions of 5-deoxy-3′-prenylbiochanin A (**59**) and its closely related precursors **106a** and **106b** has been investigated by single crystal and Hirshfeld surface analyses to comprehend their different physicochemical properties despite their closely related molecular structures. The relatively low melting point of **106a** despite its highest molar mass and good solubility in organic solvents can be attributed to the absence of strong intermolecular O-H···O hydrogen bonds. The significantly higher melting points and the lower solubility, especially in nonpolar organic solvents of 5-deoxy-3′-prenylbiochanin A (**59**) and **106b** can be attributed to the OH group at the C7-position of the isoflavones and the formation of strong intermolecular O-H···O hydrogen bonds. The higher melting point of compound **106b** than that of **59** despite its lower molar mass can be attributed to the additional strong parallel-shifted π-stacking interaction between the 3-phenyl rings of compound **106b**, which is not possible in compound **59** because of the bulky prenyl substituents at the C3′-position of the isoflavone, which prevent a close arrangement of the aromatics in the solid state. The different solubility behavior of **106b** and **59** can also be attributed to the stacking interaction since the lattice energy in **106b** is slightly higher than in **59** due to the additional π-stacking interaction. Overall, it can be concluded that the solubility of isoflavone derivatives is particularly good in the absence of acidic protons, avoiding strong hydrogen bonds, and by substituting bulky ligands that make it difficult to form strong stacking interactions.

The natural products 5-deoxy-3′-prenylbiochanin A (**59**) and erysubin F (**61**), and its flavone regioisomer (**129**) were tested for antimicrobial activity. While all compounds tested were inactive against *Salmonella enterica* subsp. *enterica* (NCTC 13349), *Escherichia coli* (ATCC 25922) and *Candida albicans* (ATCC 90028), both erysubin F (**61**) and its flavone regioisomer **129** were highly active against methicillin resistant *Staphylococcus aureus* (ATCC 43300) with MIC values of 15.4 and 20.5 μM, respectively. The results of the antibacterial activities in the current study agree to some extent with the previous reports, but with some notable discrepancies. In the current study, a comparison between the antibacterial activities of isoflavone and flavone constitutional isomers with identical substitution pattern under similar conditions is reported for the first time. The results of the current study point towards erysubin F having a mode of action that does not necessarily rely on an isoflavone skeleton because its antibacterial activity was comparable to that of its flavone isomer, but a detailed mechanistic investigation is required before any conclusions can be drawn. Alternatively, the antibacterial activities of other isoflavone and flavone constitutional isomers with identical substitution patterns should be tested to compare the results. The C6-prenylated and C5-hydroxylated isomers of erysubin F should also be synthesized and their antibacterial activities compared with that of erysubin F to ascertain literature reports that an OH group and a prenyl group at C5 and C6 positions respectively enhances the antibacterial activity of isoflavones.

# 6 Experimental Section

## 6.1 General methods

All experiments involving substances which are sensitive to air or moisture were conducted in dry reaction vessels under an atmosphere of dry nitrogen. All commercially available chemicals were purchased from chemical suppliers (Sigma Aldrich, Merck, ABCR, Alfa Aesar and Across Organics) and were used without further purification unless otherwise stated. Solvents were purified by standard procedures. Unless otherwise mentioned, reaction mixtures were heated with silicon oil baths. Microwave reactions were carried out in an Anton-Paar-monowave 300 or Anton-Paar-monowave 400 reactor (monowave, maximum power 850 W, temperature control by IR-sensor, vial volumes 4, 10, or 20 mL). Purification by column chromatography was carried out on Merck silica gel 60 (particle size 60-200 µm). TLC was performed on Merck silica gel 60 $F_{254}$ precoated aluminium sheets and spots were viewed under UV light ($\lambda$ = 254 or 365 nm) or detected by an aqueous alkaline solution of $KMnO_4$.

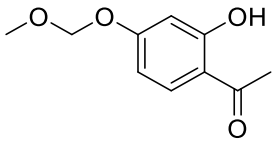
NMR spectra were recorded variously on Bruker Avance-300, Bruker NEO-400 and Bruker Avance-500 instruments operating at 300, 400, or 500 MHz, respectively (for $^1$H NMR spectroscopy) using $CDCl_3$ with C*H*$Cl_3$ ($\delta$ = 7.26 ppm) as an internal standard. Coupling constants are given in Hertz (Hz) and multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). $^{13}C\{^1H\}$ NMR spectra were recorded at 75, 100, or 125 MHz in $CDCl_3$ with $CDCl_3$ ($\delta$ = 77.1 ppm) as an internal standard. Whenever the solubility of the sample was insufficient in $CDCl_3$, it was replaced by either acetone-$d_6$ (acetone-$d_5$ as internal standard for $^1$H NMR spectroscopy, $\delta$ = 2.05 ppm, acetone-$d_6$ as internal standard for $^{13}C\{^1H\}$ NMR spectroscopy, $\delta$ = 29.9 ppm) or DMSO-$d_6$ (DMSO-$d_5$ as internal standard for $^1$H NMR spectroscopy, $\delta$ = 2.50 ppm, DMSO-$d_6$ as internal standard for $^{13}C\{^1H\}$ NMR spectroscopy, $\delta$ = 39.5 ppm). In all cases where signal assignments are given for $^1$H and $^{13}C\{^1H\}$ NMR data, these are based on 2D-NMR spectra such as $^1H$–$^1H$–COSY, HSQC, HMBC, and NOESY. IR spectra were recorded as ATR-FTIR spectra using a PerkinElmer UART TWO FT-IR-spectrometer. Wavenumbers ($\tilde{\nu}$) are given in $cm^{-1}$. The peak intensities are defined as strong (s), medium (m) or weak (w). Low- and high-resolution mass spectra were obtained by EI-TOF (70 eV) or ESI-TOF using Waters Micro-mass

(Manchester, UK.) spectrometers. Melting points were measured using a SMP-10 instrument from Bibby Scientific (Stuart).

## 6.2 Synthesis of Isoflavones via 2,3-Oxidative Aryl Rearrangement of Flavanones

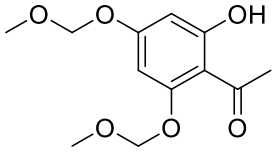
### 6.2.1 Preparation of Acetophenone and Benzaldehyde Precursors

**1-(2-Hydroxy-4-(methoxymethoxy)phenyl)ethan-1-one (109a)[190]**



To a solution of 2′,4′-dihydroxyacetophenone (3.05 g, 20 mmol) in dry $CH_2Cl_2$ (100 mL) cooled to 0 ºC was added *N*,*N*-diisopropylethylamine (DIPEA) (5.22 mL, 30 mmol) dropwise. The mixture was stirred at 0 ºC for 20 minutes. Bromomethyl methyl ether (MOMBr) (2.26 mL, 25 mmol) was then slowly added to the mixture under nitrogen atmosphere and the mixture was further stirred at 0 ºC for 20 minutes. The mixture was then allowed to warm to ambient temperature and it was stirred at ambient temperature for 16 h. After completion of the reaction, a saturated aqueous solution of $NH_4Cl$ (20 mL) and EtOAc (20 mL) were added to the mixture. The organic layer was separated off, and the aqueous solution was extracted with EtOAc (2 x 30 mL). The combined organic phase was dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (4:1 (v/v)) as eluent to afford **109a** (3.67 g, 18.72 mmol, 94%): colorless crystals, m.p 36 – 37 ºC; $^1$H NMR (300 MHz, $CDCl_3$) δ 12.59 (s, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 6.52 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.18 (s, 2H), 3.45 (s, 3H), 2.54 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 202.8, 164.9, 163.7, 132.5, 114.8, 108.2, 103.8, 94.1, 56.4, 26.3; IR (ATR) $\tilde{\nu}$ 2926 (w), 2837 (w), 1612 (s), 1568 (m), 1360 (s), 1244 (s), 1156 (s); HRMS (EI) calcd for $C_{10}H_{12}O_4$ [$M^+$] 196.0736, found 196.0738.

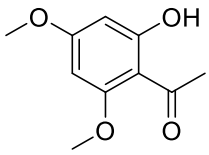
**1-(2-Hydroxy-4,6-bis(methoxymethoxy)phenyl)ethan-1-one (109c)**



To a suspension of 2′,4′,6′-trihydroxyacetophenone (1.68 g, 10 mmol) in dry $CH_2Cl_2$ (100 mL) at 0 ºC was added DIPEA (5.22 mL, 30 mmol) dropwise and the mixture was stirred at 0 ºC for 20 minutes. MOMBr (2.26 mL, 25 mmol) was then slowly added to the mixture under nitrogen atmosphere. The mixture was

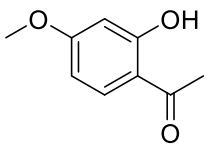
stirred at 0 ºC for 20 minutes and then allowed to warm to room temperature. It was then stirred at room temperature for 16 h. After completion of the reaction, a saturated aqueous solution of $NH_4Cl$ (10 mL) and water (50 mL) were added to the mixture. The organic layer was separated off and the aqueous solution was extracted with EtOAc (2 x 30 mL). The combined organic phase was dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (4:1 (v/v)) as eluent to afford **109c** (1.42 g, 6.0 mmol, 60%): colorless crystals, m.p 48 – 49 ºC; $^1$H NMR (300 MHz, $CDCl_3$) δ 13.70 (s, 1H), 6.24 (d, *J* = 2.4 Hz, 1H), 6.22 (d, *J* = 2.4 Hz, 1H), 5.23 (s, 2H), 5.15 (s, 2H), 3.50 (s, 3H), 3.45 (s, 3H), 2.63 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 203.3, 166.9, 163.5, 160.5, 107.0, 97.2, 94.6, 94.1(2C), 56.8, 56.5, 33.1; IR (ATR) $\tilde{\nu}$ 2963 (w), 1615 (s), 1591 (s), 1361 (m), 1267 (m), 1147 (s); HRMS (EI) calcd for $C_{12}H_{16}O_6$ [$M^+$] 256.0947, found 256.0949.

**1-(2-Hydroxy-4,6-dimethoxyphenyl)ethan-1-one (109d)[249]**




To a refluxing mixture of 2′,4′,6′-trihydroxyacetophenone (1.68 g, 10 mmol) and $K_2CO_3$ (2.0 g, 14 mmol) in acetone (50 mL) was added $(CH_3)_2SO_4$ (1.6 mL, 16.6 mmol) in 3 portions (3 x 533µL each) at intervals of 2h. The mixture was all together refluxed for 6h at 65 ºC. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (3:1 (v/v)) as eluent to afford **109d** (1.79 g, 9.1 mmol, 91%): colorless solid, m.p 79 – 80 ºC; $^1$H NMR (300 MHz, $CDCl_3$) δ 14.02 (s, 1H), 6.05 (d, *J* = 2.5 Hz, 2H), 5.91 (d, *J* = 2.5 Hz, 2H), 3.54 (s, 3H), 3.81 (s, 3H), 2.60 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 203.3, 167.7, 166.2, 163.0, 106.1, 93.6, 90.8, 55.7 (2C), 33.0; IR (ATR) $\tilde{\nu}$ 3006 (w), 2915 (s), 1730 (m), 1622 (w), 1586 (s), 1424 (m), 1273 (s), 1157 (s); HRMS (ESI) calcd for $C_{10}H_{13}O_4$ [M+H]$^+$ 197.0814, found 197.0809.

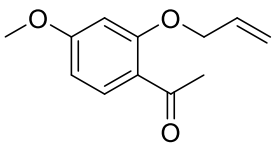
**1-(2-Hydroxy-4-methoxyphenyl)ethan-1-one (109e)**




To a refluxing mixture of 2′,4′-dihydroxyacetophenone (6.08 g, 40 mmol) and $K_2CO_3$ (4.44 g, 32.0 mmol) in acetone (200 mL) was added $(CH_3)_2SO_4$ (3.3 mL, 33.4 mmol) in 3 portions (3 x 1.1 mL each) at intervals of 2h. The mixture was all together refluxed for 6h at 65 ºC. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column

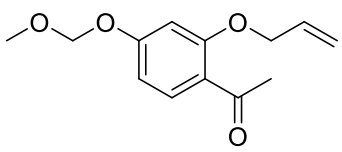
chromatography on silica using hexane – MTBE mixture (3:1) to afford **109e** (5.84 g, 35.2 mmol, 88%): colorless crystals, m.p 51 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 12.74 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 6.43 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 3.83 (s, 3H), 2.55 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 202.7, 166.2, 165.4, 132.4, 114.0, 107.8, 101.0, 55.7, 26.3; IR (ATR) $\tilde{\nu}$ 2974 (w), 1598 (s), 1366 (s), 1249 (s); HRMS (ESI) calcd for $C_{19}H_{11}O_3$ $[M+H]^+$ 167.0708, found 167.0775.

**1-(2-(Allyloxy)-4-methoxyphenyl)ethan-1-one (118b)[188,202]**



To a solution of **109e** (6.64g, 40.0 mmol) in acetone (200 mL) was added $K_2CO_3$ (11.04 g, 80.0 mmol) and the mixture warmed to 65 ºC. The mixture was stirred at 65 ºC for 15 minutes and then a solution of allyl bromide (5.3 mL, 60.0 mmol) in acetone (10 mL) was added dropwise. The mixture was refluxed at 65 ºC for 24 h. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica using hexane – MTBE mixture (4:1) to afford **118b** (5.36 g, 26.0 mmol, 65%): colorless crystals, m.p 40 – 41 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 6.08 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 1H), 5.44 (dm, *J* = 17.3 Hz, 1H), 5.32 (dm, *J* = 10.5 Hz, 1H), 4.62 (dt, *J* = 5.3, 1.5 Hz, 2H), 3.84 (s, 3H), 2.60 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 197.9, 164.5, 160.2, 132.8, 132.7, 121.6, 118.5, 106.5, 99.5, 69.6, 55.7, 32.2; IR (ATR) $\tilde{\nu}$ 2929 (w), 1646 (s), 1596 (s), 1249 (s), 1009 (m); HRMS (ESI) calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.1021, found 207.1021.

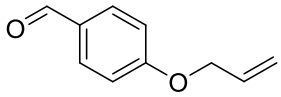
**1-(2-(Allyloxy)-4-(methoxymethoxy)phenyl)ethan-1-one (118c)**



To a solution of **109a** (6.195g, 31.5 mmol) in acetone (150 mL) was added $K_2CO_3$ (8.7g, 63 mmol) and the mixture heated to 65 ºC. The mixture was stirred at 65 ºC for 15 minutes and then a solution of allyl bromide (4.2 mL, 48 mmol) in acetone (10 mL) was added dropwise. The mixture was refluxed at 65 ºC for 24 h. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (5:1 (v/v)) as eluent to afford **118c** (7.13 g, 30.2 mmol, 96%): colorless oil; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.7 Hz, 1H), 6.65 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.59 (d, *J* = 2.3 Hz, 1H), 6.07 (ddt, *J* = 17.3, 10.5, 5.4 Hz, 1H), 5.43 (dm,

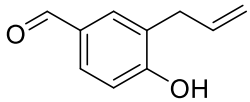
*J* = 17.3 Hz, 1H), 5.32 (dm, *J* = 10.5 Hz, 1H), 5.19 (s, 2H), 4.61 (dt, *J* = 5.4, 1.5 Hz, 2H), 3.47 (s, 3H), 2.59 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 198.0, 162.1, 160.0, 132.6, 132.5, 122.3, 118.5, 108.0, 101.0, 94.3, 69.6, 56.4, 32.1; IR (ATR) $\tilde{\nu}$ 2929 (w), 1663 (s), 1597 (s), 1421 (m), 1251 (s), 1152 (s); HRMS (EI) calcd for $C_{13}H_{16}O_4$ [$M^+$] 236.1049, found 236.1059.

**4-Allyloxybenzaldehyde (112)[188]**



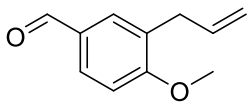
To a solution of 4-hydroxybenzaldehyde (**111**) (24.4 g, 200 mmol) in acetone (200 mL) was added $K_2CO_3$ (82.8 g, 600 mmol) and the mixture was stirred at 20 ºC for 15 minutes. A solution of allyl bromide (30.3 mL, 346 mmol) in acetone (60 mL) was then added to the reaction mixture dropwise and the mixture was further stirred at 20 ºC for 30 minutes. The reaction mixture was then heated to reflux at 65 ºC for 7 h. After the reaction, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (5:1 (v/v)) as eluent to afford **112** (29.5 g, 182 mmol, 91%): yellow oil; $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.80 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.02 (ddt, *J* = 17.4, 10.5, 5.4 Hz, 1H), 5.40 (dm, *J* = 17.4 Hz, 1H), 5.30 (dm, *J* = 10.5 Hz, 1H), 4.59 (d, *J* = 5.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 190.7, 163.7, 132.4, 132.0 (2C), 130.1, 118.4, 115.1 (2C), 69.0; IR (ATR) $\tilde{\nu}$ 2839 (w), 1687 (s), 1596 (s), 1507 (m), 1250 (s), 1158 (s); HRMS (EI) calcd for $C_{10}H_{10}O_2$ [$M^+$] 162.0681, found 162.0686.

**3-Allyl-4-hydroxybenzaldehyde (113)[202]**



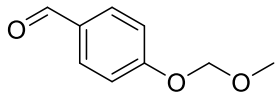
A solution of **112** (3.00 g, 18.5 mmol) in toluene (18 mL) was placed in a vessel suited for microwave irradiation and the vial was sealed. The solution was then irradiated in a microwave reactor at 250 ºC for 1.5 h. The solution was transferred into a flask, the solvent evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (5:1) as eluent to afford **113** (2.52 g, 15.6 mmol, 84%): colorless crystals, m.p 68 – 70 ºC; $_{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.83 (s, 1H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.69 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.86 (s, 1H), 6.02 (ddt, *J* = 17.4, 10.5, 6.3 Hz, 1H), 5.19 (dm, *J* = 17.4 Hz, 1H), 5.15 (dm, *J* = 10.5 Hz, 1H), 3.47 (d, *J* = 6.3 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 191.8, 160.5, 135.5, 132.7, 131.0, 129.9, 126.9, 117.3, 116.3, 34.6: IR (ATR) $\tilde{\nu}$ 3142 (s), 1654 (s), 1582 (s), 1437 (m), 1279 (s), 1089 (m); HRMS (EI) calcd for $C_{10}H_{10}O_2$ [$M^+$] 162.0681, found 162.0679.

**3-Allyl-4-methoxybenzaldehyde (110a)[188]**



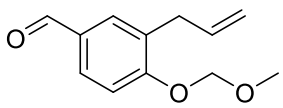
To a solution of compound **113** (3.24 g, 20.0 mmol) in acetone (50 mL) was added $K_2CO_3$ (8.40 g, 60.0 mmol) and the mixture was stirred at 20 ºC for 15 minutes. To the mixture was then added dropwise a solution of iodomethane (5.68 g, 40.0 mmol) in acetone (10 mL) and the reaction mixture was stirred at 20 ºC for 10 minutes. It was then heated to reflux at 65 ºC for 8 h. The mixture was cooled to room temperature and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (10:1) to afford **110a** (3.33 g, 18.8 mmol, 94%): yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.85 (s, 1H), 7.73 (dd, $J$ = 8.4, 2.1 Hz, 1H), 7.68 (d, $J$ = 2.1 Hz, 1H), 6.95 (d, $J$ = 8.4 Hz, 1H), 5.97 (ddt, $J$ = 17.4, 10.5, 6.6 Hz, 1H), 5.08 (dm, $J$ = 17.4 Hz, 1H), 5.05 (dm, $J$ = 10.5 Hz, 1H), 3.90 (s, 3H), 3.40 (d, $J$ = 6.6 Hz, 2H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 191.1, 162.5, 135.9, 131.0, 130.9, 129.8, 129.8, 116.4, 110.2, 55.8, 34.1; IR (ATR) $\tilde{\nu}$ 2909 (w), 1683 (s), 1597 (s), 1497 (m), 1252 (s), 1120 (m); HRMS (EI) calcd for $C_{11}H_{12}O_2$ [$M^+$] 176.0832, found 176.0830.

**4-(Methoxymethoxy)benzaldehyde (110b)**



To a solution of 4-hydroxybenzaldehyde (**111**) (4.88 g, 40.0 mmol) in dry $CH_2Cl_2$ (200 mL) cooled to 0 ºC was added dropwise DIPEA (10.44 mL, 60.0 mmol) and the mixture was stirred at 0 ºC for 20 minutes. To the mixture was then slowly added MOMBr (4.58 mL, 50.0 mmol) under nitrogen atmosphere. The mixture was further stirred at 0 ºC for 20 minutes. After 20 minutes the reaction mixture was allowed to warm to ambient temperature. The mixture was stirred at ambient temperature for 16 h. After completion of the reaction, a saturated aqueous solution of $NH_4Cl$ (40 mL) and water (200 mL) were added to the mixture. The organic phase was separated off and the aqueous solution was extracted with EtOAc (2 x 100 mL). The combined organic phase was dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – MTBE mixture (5:1) as eluent to afford **110b** (5.38 g, 32.4 mmol, 81%); colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.86 (s, 1H), 7.80 (d, $J$ = 8.7 Hz, 2H), 7.11 (d, $J$ = 8.7 Hz, 2H), 5.22 (s, 2H), 3.46 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 190.9, 162.3, 131.9 (2C), 130.8, 116.3 (2C), 94.1, 56.4; IR (ATR) $\tilde{\nu}$ 2953 (w), 2828 (w), 1612 (m), 1510 (s), 1234 (s), 1152 (s); HRMS (EI) calcd for $C_9H_{10}O_3$ [$M^+$] 166.0623, found 166.0624.

**3-Allyl-4-(methoxymethoxy)benzaldehyde (110e)**

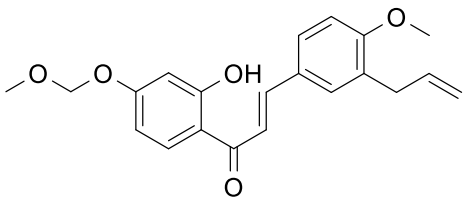


To a solution of **113** (7.45 g, 46.0 mmol) in dry $CH_2Cl_2$ (200 mL) at 0 ºC was added DIPEA (10.2 mL, 60.0 mmol) dropwise and the mixture was stirred at 0 ºC for 20 minutes. MOMBr (4.60 mL, 50.0 mmol) was slowly added to the mixture under nitrogen atmosphere. The mixture was further stirred at 0 ºC for 20 minutes and then allowed to warm to ambient temperature. It then was stirred at ambient temperature for 16 h. After completion of the reaction, a saturated aqueous solution of $NH_4Cl$ (40 mL) and water (200 mL) were added to the mixture. The organic phase was separated off and the aqueous solution was extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (9 : 1) as eluent to afford **110e** (7.68 g, 37.7 mmol, 82%): colourless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.86 (s, 1H), 7.70 (dd, $J$ = 9.0, 2.1 Hz, 1H), 7.69 (d, $J$ = 2.1 Hz, 1H), 7.17 (d, $J$ = 9.0 Hz, 1H), 5.97 (ddt, $J$ = 17.7, 9.4, 6.6 Hz,1H), 5.27 (s, 2H), 5.06 (dm, $J$ = 17.7, Hz, 1H), 5.05 (dm, $J$ = 9.4 Hz, 1H), 3.47 (s, 3H), 3.43 (d, $J$ = 6.6 Hz, 2H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 191.2, 160.0, 135.9, 131.3, 130.6, 130.6, 130.1, 116.4, 113.4, 94.1, 56.4, 34.3; IR (ATR) $\tilde{\nu}$ 2908 (w), 1687 (s), 1598 (s), 1493 (m), 1242 (s), 1076 (s); HRMS (EI) calcd for $C_{12}H_{14}O_3$ [$M^+$] 206.0943, found 206.0941.

## 6.2.2 General Procedure 1 for the Synthesis of Chalcones 108 and 119.[189]

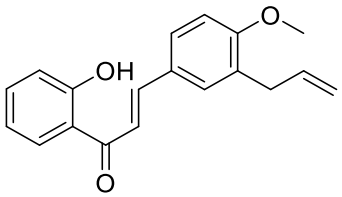
A solution of KOH in methanol (60 wt %, 20 mL) was added dropwise to a well stirred solution of the appropriate acetophenone **109** or **118** (5.0 mmol) and benzaldehyde **110** (5.0 mmol) in methanol (10 mL) at 20 ºC. The reaction mixture was stirred at 20 ºC for 48 h. It was then poured into ice cold water (50 mL) and neutralized with aqueous HCl (4 M). The aqueous solution was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica using hexane − EtOAc mixture (5:1 (v/v)) as eluent to afford the respective chalcone **108** or **119**.

**(E)-3-(3-Allyl-4-methoxyphenyl)-1-(2-hydroxy-4-(methoxymethoxy)phenyl)prop-2-en-1-one (108aa)**



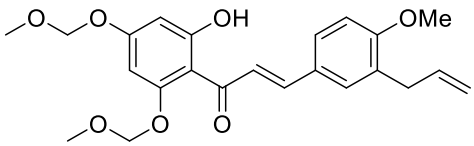
Following the general procedure 1, compounds **109a** (980 mg, 5.0 mmol) and **110a** (880 mg, 5.0 mmol) were reacted to **108aa** (1.33 g, 3.75 mmol, 75%); purification by column chromatography (hexane − EtOAc mixtures of increasing polarity, 9:1 to 4:1 (v/v)): yellow, amorphous solid, m.p 74 – 76 ºC; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 13.41 (s, 1H), 7.86 (d, *J* = 15.5 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.50 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.44 (d, *J* = 15.5 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 6.59 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.01 (ddt, *J* = 17.6, 10.9, 6.6 Hz, 1H), 5.22 (s, 2H), 5.10 (dm, *J* = 17.6 Hz, 1H), 5.09 (dm, *J* = 10.9 Hz, 1H), 3.88 (s, 3H), 3.49 (s, 3H), 3.41 (d, *J* = 6.6 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) $\delta$ 192.2, 166.3, 163.6, 159.8, 144.9, 136.4, 131.4, 129.9, 129.6, 129.3, 127.4, 117.7, 116.1, 115.2, 110.7, 108.2, 104.1, 94.2, 56.5, 55.7, 34.3; IR (ATR) $\tilde{\nu}$ 3076 (w), 2904 (w), 1630 (s), 1562 (s), 1496 (m), 1205 (m), 1126 (m); HRMS (EI) calcd for $C_{21}H_{22}O_5$ [$M^+$] 354.1467, found 354.1453.

**(E)-3-(3-Allyl-4-methoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (108ba)**



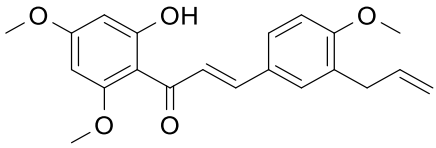
Following the general procedure 1, 2′-hydroxyacetophenone (**109b**) (680 mg, 5.0 mmol) and **110a** (880 mg, 5.0 mmol) were reacted to **108ba** (1.30 g, 4.42 mmol, 88%); purification by column chromatography (hexane − EtOAc mixture, 5:1 (v/v)): yellow crystalline solid, m.p 94 – 95 ºC; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 12.98 (s, 1H), 7.94 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.89 (d, *J* = 15.3 Hz, 1H), 7.53 (d, *J* = 15.3 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.49 (d, *J* = 1.7 Hz, 1H), 7.47 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.02 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.94 (ddd, *J* = 8.4, 8,0, 1.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.02 (ddt, *J* = 17.5, 9.6, 6.6 Hz, 1H), 5.11 (dm, *J* = 17.5 Hz, 1H), 5.06 (dm, *J* = 9.5 Hz, 1H), 3.87 (*s*, 3H), 3.42 (d, *J* = 6.6 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 193.8, 163.7, 160.0, 145.8, 136.3, 136.2, 130.0, 129.7, 129.6, 129.5, 127.2, 120.3, 118.9, 118.7, 117.5, 116.2, 110.7, 55.7, 34.3; IR (ATR) $\tilde{\nu}$ 3070 (w), 2918 (w), 1633(s), 1550 (m), 1445 (s), 1256 (m), 1118 (m); HRMS (EI) calcd for $C_{19}H_{18}O_3$ [$M^+$] 294.1256, found 294.1246.

**(E)-3-(3-Allyl-4-methoxyphenyl)-1-(2-hydroxy-4,6-bis(methoxymethoxy)phenyl)prop-2-en-1-one (108ca)**



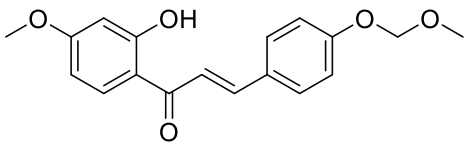
Following the general procedure 1, compounds **109c** (1.28 g, 5.0 mmol) and **110a** (880 mg, 5.0 mmol) were reacted to **108ca** (1.93 g, 4.65 mmol, 93%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): yellow solid, m.p 96 – 97 ºC; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 13.95 (s, 1H), 7.84 (d, *J* = 15.5 Hz, 1H), 7.77 (d, *J* = 15.5 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.44 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.00 (ddt, *J* = 17.5, 9.7, 6.7 Hz, 1H), 5.28 (s, 2H), 5.19 (s, 2H), 5.09 (dm, *J* = 17.5 Hz, 1H), 5.08 (dm, *J* = 9.7 Hz, 1H), 3.88 (s, 3H), 3.54 (s, 3H), 3.48 (s, 3H), 3.40 (d, *J* = 6.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 193.0, 167.4, 163.4, 159.9, 159.4, 143.1, 136.5, 129.4, 129.4, 129.0, 128.0, 125.0, 116.1, 110.6, 107.7, 97.6, 95.3, 94.8, 94.2, 57.0, 56.6, 55.7, 34.2; IR (ATR) $\tilde{\nu}$ 2910 (w), 2830 (w), 1617 (s), 1579 (m), 1419 (m), 1206 (m), 1148 (s); HRMS (EI) calcd for $C_{23}H_{26}O_7$ [$M^+$] 414.1679, found 414.1672.

**(E)-3-(3-Allyl-4-methoxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (108da)**



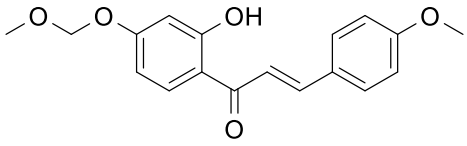
Following the general procedure 1, compounds **109d** (980 mg, 5.0 mmol) and **110a** (880 mg, 5.0 mmol) were reacted to **108da** (1.42 g, 4.0 mmol, 80%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): %): yellow crystalline solid, m.p 145 – 146 ºC; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 14.45 (s, 1H), 7.82 (d, *J* = 15.5 Hz, 1H), 7.75 (d, *J* = 15.5 Hz, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.45 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.10 (d, *J* = 2.5 Hz, 1H), 6.02 (ddt, *J* = 17.3, 10.7, 6.6 Hz, 1H), 5.95 (d, *J* = 2.5 Hz, 1H), 5.11 (dm, *J* = 17.3 Hz, 1H), 5.09 (dm, *J* = 10.7 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.40 (d, *J* = 6.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 192.7, 168.5, 166.1, 162.6, 159.3, 142.8, 136.5, 129.7, 129.3, 128.7, 128.1, 125.1, 116.1, 110.5, 106.5, 93.9, 91.3, 55.9, 55.7, 55.7, 34.1; IR (ATR) $\tilde{\nu}$ 2919 (w), 2844 (w), 1620 (s), 1552 (s), 1442 (m), 1205 (s), 1111 (m); HRMS (EI) calcd for $C_{21}H_{22}O_5$ [$M^+$] 354.1467, found 354.1465.

**(E)-1-(2-Hydroxy-4-methoxyphenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (108eb)**



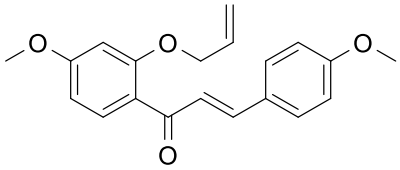
Following the general procedure 1, compounds **109e** (2.06 g, 10.0 mmol) and **110b** (1.68 g, 10.0 mmol) were reacted to **108eb** (2.20 g, 7.0 mmol, 70%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): %): yellow solid, m.p 74 – 75 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 13.52 (s, 1H), 7.86 (d, *J* = 15.4 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 15.4 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.48 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.47 (d, *J* = 2.5 Hz, 1H), 5.22 (s, 2H), 3.86 (s, 3H), 3.49 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 192.0, 166.8, 166.2, 159.5, 144.2, 131.3, 130.4 (2C), 128.7, 118.5, 116.7 (2C), 114.3, 107.8, 101.2, 94.3, 56.3, 55.7; IR (ATR) $\tilde{\nu}$ 2899 (w), 1602 (s), 1507 (s), 1150 (s), 1076 (m); HRMS (EI) calcd for $C_{18}H_{18}O_5$ [$M^+$] 314.1154, found 314.1151.

**(E)-1-(2-Hydroxy-4-(methoxymethoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (108ac)**



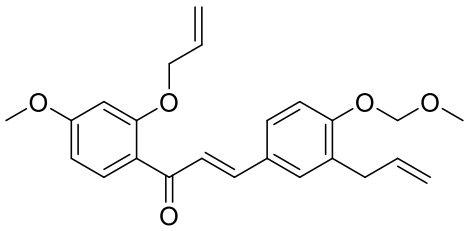
Following the general procedure 1, compounds **109a** (1.96 g, 10.0 mmol) and **110c** (1.37 g, 10.0 mmol) were reacted to **108ac** (2.14 g, 6.8 mmol, 68%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): %): yellow solid, m.p 80 – 81 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 13.39 (s, 1H), 7.86 (d, *J* = 15.4 Hz, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 15.4 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 2.6 Hz, 1H), 6.58 (dd, *J* = 9.0, 2.6 Hz, 1H), 5.22 (s, 2H), 3.86 (s, 3H), 3.49 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 192.2, 166.3, 163.6, 162.0, 144.6, 131.3, 130.5 (2C), 127.6, 117.9, 115.1, 114.6 (2C), 108.2, 104.1, 94.1, 56.5, 55.6; IR (ATR) $\tilde{\nu}$ 2831 (w), 1626 (m), 1564 (s), 1279 (s), 1159 (s); HRMS (ESI) calcd for $C_{18}H_{19}O_5$ [M+H]$^+$ 315.1232, found 315.1236.

**(E)-1-(2-(Allyloxy)-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (119bc)**



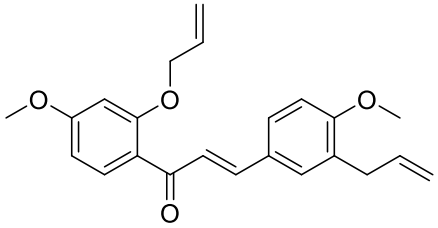
Following the general procedure 1, compounds **118b** (2.06 g, 10.0 mmol) and **110c** (1.37 g, 10.0 mmol) were reacted to **119bc** (1.94 g, 6.0 mmol. 60%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): %): pale yellow solid, m.p 84 – 85 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 15.7 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 15.7 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.56 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.05 (ddt, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.45 (dm, *J* = 17.3 Hz, 1H), 5.27 (dm, *J* = 10.5 Hz, 1H), 4.61 (dt, *J* = 5.2, 1.7 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 190.5, 164.0, 161.3, 159.3, 141.8, 133.0, 132.6, 130.0, 128.3, 125.3, 122.9, 118.0, 114.4, 105.7, 99.9, 69.5, 55.6, 55.5; IR (ATR) $\tilde{\nu}$ 2841 (w), 1644 (m), 1597 (s), 1509 (m), 1247 (s), 1170 (s); HRMS (ESI) calcd for $C_{20}H_{21}O_4$ $[M+H]^+$ 325.1440, found 325.1434.

**(E)-3-(3-Allyl-4-(methoxymethoxy)phenyl)-1-(2-(allyloxy)-4-methoxyphenyl)prop-2-en-1-one (119be)**



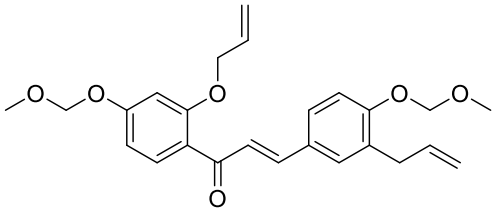
Following the general procedure 1, compounds **118b** (2.06 g, 10.0 mmol) and **110e** (2.06 g, 10.0 mmol) were reacted to **119be** (2.56 g, 6.5 mmol, 65%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): pale yellow crystals, m.p 27 – 28 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 15.8 Hz, 1H), 7.50 (d, *J* = 15.8 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.40 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.57 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 6.11 – 5.94 (m, 2H), 5.46 (dm, *J* = 17.3 Hz, 1H), 5.26 (dm, *J* = 10.5 Hz, 1H), 5.23 (s, 2H), 5.08 (dm, *J* = 16.2 Hz, 1H), 5.07 (dm, *J* = 11.1 Hz, 1H), 4.61 (dt, *J* = 5.2, 1.7 Hz, 2H), 3.85 (s, 3H), 3.48 (s, 3H), 3.41 (d, *J* = 6.5 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 190.5, 164.0, 159.4, 156.6, 141.9, 136.5, 133.0, 132.6, 130.0, 129.7, 129.1, 128.4, 125.6, 122.8, 118.1, 116.0, 113.9, 105.7, 99.8, 94.2, 69.5, 56.3, 55.6, 34.4; IR (ATR) $\tilde{\nu}$ 2935 (w), 2825 (w), 1595 (s), 1493 (m), 1242 (s), 1119 (m); HRMS (EI) calcd for $C_{24}H_{26}O_5$ $[M^+]$ 394.1780, found 394.1783.

**(E)-3-(3-Allyl-4-methoxyphenyl)-1-(2-(allyloxy)-4-methoxyphenyl)prop-2-en-1-one (119ba)**



Following the general procedure 1, compounds **118b** (2.06 g, 10.0 mmol) and **110a** (1.76 g, 10.0mmol) were reacted to **119ba** (2.95 g, 8.1 mmol, 81%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): pale yellow solid, m.p 106 – 107 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 15.6 Hz, 1H), 7.49 (d, *J* = 15.6 Hz, 1H), 7.44 – 7.41 (m, 2H), 6.85 (d, *J* = 8.9 Hz, 1H), 6.57 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 6.12 – 5.94 (m, 2H), 5.46 (dm, *J* = 17.3 Hz, 1H), 5.27 (dm, *J* = 10.6 Hz, 1H), 5.07 (dm, *J* = 16.9 Hz, 1H), 5.06 (dm, *J* = 11.8 Hz, 1H), 4.61 (dt, *J* = 5.1, 1.7 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.38 (d, *J* = 6.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 190.6, 164.0, 159.3, 159.1, 142.2, 136.5, 133.0, 132.6, 129.5, 129.2, 128.9, 128.0, 125.1, 122.9, 118.1, 115.9, 110.5, 105.6, 99.9, 69.5, 55.6, 55.6, 34.3; IR (ATR) $\tilde{\nu}$ 2840 (w), 1642 (m), 1598 (s), 1250 (s), 1202 (m); HRMS (EI) calcd for $C_{23}H_{24}O_4$ [$M^+$] 364.1675, found 364.1677.

**(E)-3-(3-Allyl-4-(methoxymethoxy)phenyl)-1-(2-(allyloxy)-4-(methoxymethoxy)phenyl)prop-2-en-1-one (119ce)**



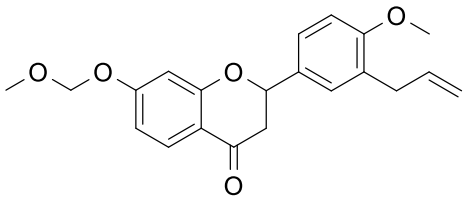
Following the general procedure 1, compounds **118c** (1.18 g, 5.0 mmol) and **110e** (1.03 g, 5.0 mmol) were reacted to **119ce** (1.57 g, 3.7 mmol, 74%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): yellow oil; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 15.8 Hz, 1H), 7.47 (d, *J* = 15.8 Hz, 1H), 7.42 (s, 1H), 7.39 (d, *J* = 2.3 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 6.12 – 5.92 (m, 2H), 5.45 (dm, *J* = 17.3 Hz, 1H), 5.28 (dm, *J* = 10.5 Hz, 1H), 5.23 (s, 2H), 5.22 (s, 2H), 5.08 (dm, *J* = 17.5 Hz, 1H), 5.07 (dm, *J* = 10.2 Hz, 1H), 4.62 (dt, *J* = 5.2, 1.6 Hz, 2H), 3.49 (s, 3H), 3.48 (s, 3H), 3.41 (d, *J* = 6.5 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 190.8, 161.6, 159.2, 156.7, 142.1, 136.5, 132.7, 132.6, 130.0, 129.7, 129.1, 128.4, 125.5, 123.7, 118.2, 116.0, 113.9, 108.3, 101.3, 94.4, 94.3, 69.6, 56.4, 56.3, 34.5; IR (ATR) $\tilde{\nu}$ 3167 (w), 2915 (w), 1601 (s), 1581 (s), 1415 (m), 1226 (m), 1145 (s); HRMS (EI) calcd for $C_{25}H_{28}O_6$ [$M^+$] 424.1886, found 424.1874.

### 6.2.3 General Procedure 2 for the Synthesis of Flavanones 107

Method A (conventional heating):[189] To a solution of the appropriate chalcone **108** (2.0 mmol) in methanol (20 mL) was added NaOAc (1.640 g, 20.0 mmol) and the mixture was heated to reflux at 60 ºC for 48 h. It was then cooled to ambient temperature and the solvent was evaporated under reduced pressure. Water (50 mL) was added to the residue and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane − EtOAc mixture (5:1 (v/v)) as eluent to afford the respective flavanone **107**.

Method B (microwave heating):[202] A solution of the appropriate chalcone **108** (2.0 mmol) in methanol (20 mL) was placed in a vessel suited for microwave irradiation. NaOAc (1.680 g, 20.0 mmol) was added, the vessel was sealed, and irradiated in a microwave reactor at 100 ºC for 2 h. The mixture was transferred into a flask and the solvent was evaporated. The residue was mixed with water (50 mL) and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica using hexane − EtOAc mixture (5:1 (v/v)) as eluent to afford the respective flavanone **107**.

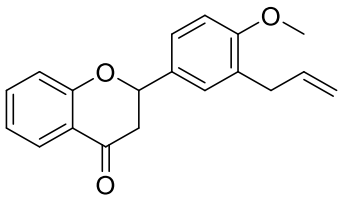
**2-(3-Allyl-4-methoxyphenyl)-7-(methoxymethoxy)chroman-4-one (107aa)**



Following the general procedure 2, method A, compound **108aa** (710 mg, 2.0 mmol) was converted to **107aa** (426 mg, 1.20 mmol, 60%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): pale yellow solid, m.p 80 – 81 ºC; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J$ = 8.5 Hz, 1H), 7.31 (dd, $J$ = 8.4, 2.4 Hz, 1H), 7.26 (d, $J$ = 2.4 Hz, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 6.71 (dd, $J$ = 8.5, 2.4 Hz, 1H), 6.68 (d, $J$ = 2.4 Hz, 1H), 6.00 (ddt, $J$ = 16.8, 10.5, 6.9 Hz, 1H), 5.40 (dd, $J$ = 13.5, 3.0 Hz, 1H), 5.21 (s, 2H), 5.09 (dm, $J$ = 16.8 Hz, 1H), 5.07 (dm, $J$ = 10.5 Hz, 1H), 3.86 (s, 3H), 3.48 (s, 3H), 3.42 (d, $J$ = 6.9 Hz, 2H), 3.07 (dd, $J$ = 16.9, 13.5 Hz, 1H), 2.80 (dd, $J$ = 16.9, 3.0 Hz, 1H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl3) $\delta$ 191.2, 163.7, 163.5, 157.8, 136.6, 130.7, 129.3, 128.9, 128.1, 125.6, 116.0, 115.8, 111.2, 110.5, 103.7, 94.2, 80.0, 56.5, 55.7, 44.3, 34.4; IR (ATR) $\tilde{\nu}$ 2930 (w),

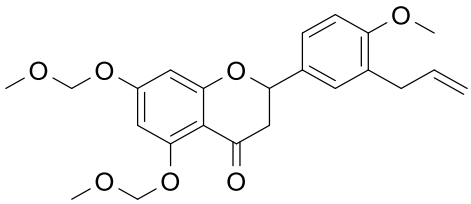
1671 (m), 1607(s), 1574 (m), 1246 (s), 1153 (s); HRMS (EI) calcd for $C_{21}H_{22}O_5$ [$M^+$] 354.1467, found 354.1455.

**2-(3-Allyl-4-methoxyphenyl)chroman-4-one (107ba)**



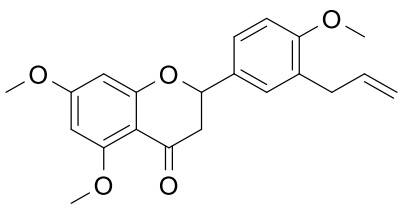
Following the general procedure 2, method A, compound **108ba** (590 mg, 2.0 mmol) was converted to **107ba** (295 mg, 1.0 mmol, 50%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): pale yellow solid, m.p 64 – 65 ºC; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.92(dd, *J* = 8.1, 1.8 Hz, 1H), 7.49 (td, *J* = 7.2, 1.8 Hz, 1H), 7.31 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 1H), 7.07 – 7.02 (m, 2H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.99 (ddt, *J* = 16.8, 10.5, 6.7 Hz, 1H), 5.40 (dd, *J* = 13.5, 3.0 Hz, 1H), 5.08 (dm, *J* = 16.8 Hz, 1H), 5.06 (dm, *J* = 10.5 Hz, 1H), 3.85 (s, 3H), 3.41 (d, *J* = 6.7 Hz, 2H), 3.11 (dd, *J* = 17.1, 13.5 Hz, 1H), 2.84 (dd, *J* = 17.1, 3.0 Hz, 1H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 192.5, 161.8 157.8, 136.6, 136.3, 130.6, 129.3, 128.1, 127.2, 125.6, 121.6, 121.1, 118.3, 116.0, 110.5, 79.7, 55.7, 44.6, 34.4; IR (ATR) $\tilde{\nu}$ 2920 (w), 1690 (s), 1606 (m), 1462 (s), 1254 (s), 1153 (m); HRMS (EI) calcd for $C_{19}H_{18}O_3$ [$M^+$] 294.1256, found 294.1248.

**2-(3-Allyl-4-methoxyphenyl)-5,7-bis(methoxymethoxy)chroman-4-one (107ca)**



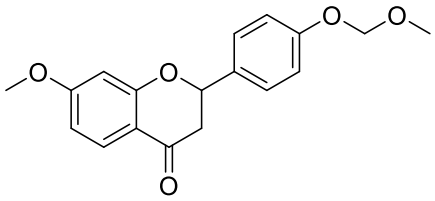
Following the general procedure 2, method A, compound **108ca** (830 mg, 2.0 mmol) was converted to **107ca** (424 mg, 1.02 mmol, 51%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): yellow solid, m.p 84 – 85 ºC; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 2.3 Hz, 1H), 6.38 (d, *J* = 2.3 Hz, 1H), 5.99 (ddt, *J* = 16.8, 10.5, 6.7 Hz, 1H), 5.33 (dd, *J* = 13.4, 2.8 Hz, 1H), 5.27 (s, 2H), 5.16 (s, 2H), 5.07 (dm, *J* = 16.8 Hz, 1H), 5.06 (dm, *J* = 10.5 Hz, 1H), 3.84 (s, 3H), 3.53 (s, 3H), 3.47 (s, 3H), 3.40 (d, *J* = 6.7 Hz, 2H), 3.04 (dd, *J* = 16.5, 13.4 Hz, 1H), 2.74 (dd, *J* = 16.5, 2.8 Hz, 1H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 189.6, 164.8, 163.3, 159.7, 157.7, 136.6, 130.6, 129.2, 128.1, 125.5, 115.9, 110.5, 107.5, 98.2, 97.6, 95.2, 94.2, 79.2, 56.7, 56.6, 55.7, 45.8, 34.4; IR (ATR) $\tilde{\nu}$ 2908 (w), 2838 (w), 1670 (m), 1606 (s), 1571 (m), 1251 (s), 1143 (s); HRMS (EI) calcd for $C_{23}H_{26}O_7$ [$M^+$] 414.1679, found 414.1676.

**2-(3-Allyl-4-methoxyphenyl)-5,7-dimethoxychroman-4-one (107da)**



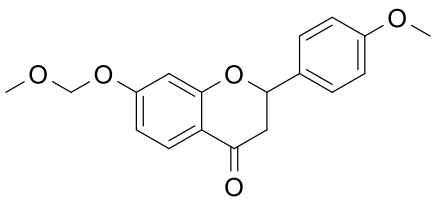
Following the general procedure 2, method A, compound **108da** (710 mg, 2.0 mmol) was converted to **107da** (355 mg, 1.0 mmol, 50%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): pale yellow solid, m.p 135 – 136 ºC; $^{1}$H NMR (300 MHz, acetone-$d_6$) δ 7.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.17 (d, *J* = 2.4 Hz, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 6.00 (ddt, *J* = 16.9, 10.3, 6.7 Hz, 1H), 5.39 (dd, *J* = 12.9, 3.0 Hz, 1H), 5.06 (dm, *J* = 16.9 Hz, 1H), 5.00 (dm, *J* = 10.3 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.39 (d, *J* = 6.7 Hz, 2H), 2.98 (dd, *J* = 16.4, 12.9 Hz, 1H), 2.59 (dd, *J* = 16.4, 3.0 Hz, 1H); $^{13}$C{$^{1}$H} NMR (75 MHz, acetone-$d_6$) δ 187.2, 165.7, 164.9, 162.3, 157.5, 136.8, 131.3, 128.5, 128.0, 125.8, 114.9, 110.4, 105.8, 93.5, 92.7, 78.9, 55.3, 55.1, 55.0, 45.4, 34.1; IR (ATR) $\tilde{\nu}$ 2907 (w), 2838 (w), 1667 (s), 1612 (s), 1455 (m), 1257 (s), 1113 (s); HRMS (EI) calcd for $C_{21}H_{22}O_5$ [$M^+$] 354.1467, found 354.1469.

**7-Methoxy-2-(4-(methoxymethoxy)phenyl)chroman-4-one (107eb)**



Following the general procedure 2, method B, compound **108eb** (630 mg, 2.0 mmol) was converted to **107eb** (340 mg, 1.08 mmol, 54%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): yellow solid, m.p 106 – 107 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.61 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.48 (d, *J* = 2.5 Hz, 1H), 5.42 (dd, *J* = 13.3, 3.0 Hz, 1H), 5.20 (s, 2H), 3.83 (s, 3H), 3.48 (s, 3H), 3.04 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.80 (dd, *J* = 16.9, 3.0 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 190.9, 166.3, 163.7, 157.7, 132.2, 128.9, 127.8 (2C), 116.6 (2C), 114.9, 110.3, 101.0, 94.5, 19.8, 56.2, 55.8, 44.3; IR (ATR) $\tilde{\nu}$ 2950 (w), 1671 (s), 1613 (s), 1593 (s), 1511 (m), 1235 (m), 1150 (s); HRMS (EI) calcd for $C_{18}H_{18}O_5$ [$M^+$] 314.1154, found 314.1150.

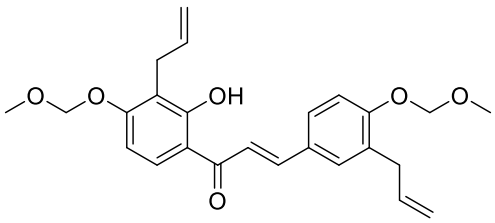
**7-(Methoxymethoxy)-2-(4-methoxyphenyl)chroman-4-one (107ac)**



Following the general procedure 2, method B, compound **108ac** (630 mg, 2.0 mmol) was converted to **107ac** (352 mg, 1.12 mmol, 56%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): pale yellow solid, m.p 72 – 73 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.70 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 5.41 (dd, *J* = 13.3, 2.9 Hz, 1H), 5.19 (s, 2H), 3.83 (s, 3H), 3.47 (s, 3H), 3.05 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.80 (dd, *J* = 16.9, 2.9 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 191.1, 163.7, 163.5, 160.1, 130.9, 128.9, 127.8 (2C), 115.7, 114.3 (2C), 112.2, 103.7, 94.2, 79.8, 56.5, 55.5, 44.3; IR (ATR) $\tilde{\nu}$ 2904 (w), 1675 (m), 1603 (s), 1512 (m), 1243 (s), 1149 (s); HRMS (ESI) calcd for $C_{18}H_{19}O_5$ $[M+H]^+$ 315.1232, found 315.1237.

## 6.2.4 Attempted Microwave Promoted Domino Claisen Rearrangement/ Oxa-Michael Addition Reaction of Chalcone 119ce

A solution of **119ce** (200 mg, 0.47 mmol) in *N*,*N*-dimethylaniline (DMA) (4 mL) was placed in a vessel suited for microwave irradiation. The vessel was sealed and irradiated in a microwave reactor at 250 ºC for 1 h. After the reaction, the solution transferred into a flask, diluted with EtOAc (50 mL) and washed with aqueous HCl (1M, 3 x 10 mL). It was then dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixtures of increasing polarity (9:1 – 5:1, (v/v)) to afford **120** (50 mg, 0.12 mmol, 25%).

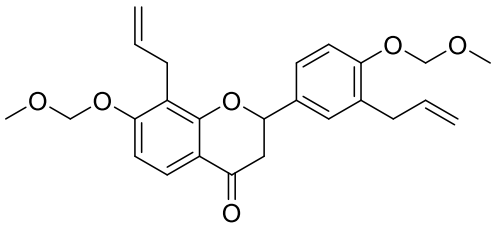


*(E)-1-(3-Allyl-2-hydroxy-4-(methoxymethoxy)phenyl)-3-(3-allyl-4-(methoxymethoxy)-phenyl)-prop-2-en-1-one* ***(120)***: yellow oil; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 13.54 (s, 1H), 7.84 (d, *J* = 15.5 Hz, 1H), 7.80 (d, *J* = 9.3 Hz, 1H), 7.50 – 7.45 (m, 3H), 7.11 (d, *J* = 9.1 Hz, 1H), 6.70 (d, *J* = 9.1 Hz, 1H), 6.08 - 5.93 (m, 2H), 5.28 (s, 2H), 5.25 (s, 2H), 5.10 (dm, *J* = 17.2 Hz, 2H), 5.03 – 4.96 (m, 2H), 3.49 (s, 3H), 3.48 (s, 3H), 3.44 (d, *J* = 6.7 Hz, 4H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 192.6, 163.5, 160.9, 157.2, 144.6, 136.4, 136.0, 130.4, 130.0, 129.3, 128.7, 128.5, 118.5, 116.7,

116.1, 115.2, 114.7, 114.1, 104.9, 94.3, 94.0, 56.4, 56.3, 34.5, 27.0; IR (ATR) $\tilde{\nu}$ 3176 (w), 2902 (w), 1611 (s), 1493 (s), 1239 (s), 1148 (s); HRMS (EI) calcd for $C_{25}H_{28}O_6$ [$M^+$] 424.1886, found 424.1871.

### 6.2.5 Two Step Synthesis of 121ce

*(E)-1-(3-Allyl-2-hydroxy-4-(methoxymethoxy)phenyl)-3-(3-allyl-4-(methoxymethoxy)-phenyl)-prop-2-en-1-one (**120**)*: A solution of **119ce** (1,27 g, 3.0 mmol) in toluene (20 mL) was placed in a vessel suited for microwave irradiation. The vessel was sealed, and irradiated in a microwave reactor at 250 ºC for 1.5 h. After the reaction, the solution was transferred into a flask and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica, using hexane – EtOAc mixture (5:1 (v/v)) to afford **120** (955 mg, 2.25 mmol, 75%) and **121ce** (115 mg, 0.27 mmol, 9%).



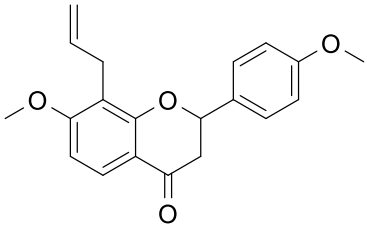
*4-(Methoxymethoxy)phenyl)-7-(methoxymethoxy)-chroman-4-one (**121ce**)*: Following the general procedure 2, method A, compound **120** (850 mg, 2.00 mmol) was converted to **121ce** (475 mg, 1.12 mmol, 56%); purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)): yellow solid, m.p 63 – 64 ºC; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.82 (d, $J$ = 8.9 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.12 (d, $J$ = 9.1 Hz, 1H), 6.82 (d, $J$ = 8.9 Hz, 1H), 6.07 – 5.86 (m, 2H), 5.39 (dd, $J$ = 12.8, 3.3 Hz, 1H), 5.26 (s, 2H), 5.23 (s, 2H), 5.09 (dm, $J$ = 17.0 Hz, 1H), 5.08 (dm, $J$ = 10.4 Hz, 1H), 5.02 (dm, $J$ = 17.0 Hz, 1H), 4.96 (dm, $J$ = 10.1 Hz, 1H), 3.49 (s, 3H), 3.47 (s, 3H), 3.46 – 3.40 (m, 4H), 2.99 (dd, $J$ = 16.9, 12.8 Hz, 1H), 2.84 (dd, $J$ = 16.9, 3.3 Hz, 1H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) $\delta$ 191.7, 161.0, 160.7, 155.1, 136.6, 136.0, 132.5, 129.7, 127.9, 126.6, 125.1, 117.0, 116.0, 116.0, 115.0, 114.0, 107.8, 94.5, 94.1, 79.3, 56.5, 56.2, 44.4, 34.5, 27.5; IR (ATR) $\tilde{\nu}$ 2946 (w), 2827 (w), 1688 (s), 1595 (s), 1257 (m), 1036 (s); HRMS (EI) calcd for $C_{25}H_{28}O_6$ [$M^+$] 424.1886, found 424.1875.

### 6.2.6 General Procedure 3 for the Synthesis of 8-Allyl Flavanones 121

A solution of the respective *O*-allyloxy chalcone **119** (2.0 mmol) in toluene (10 mL) was placed in a vessel suited for microwave irradiation. The vessel was sealed and irradiated in a microwave reactor at 250 ºC for 1.5 h. The solvent was evaporated, and the residue was redissolved in

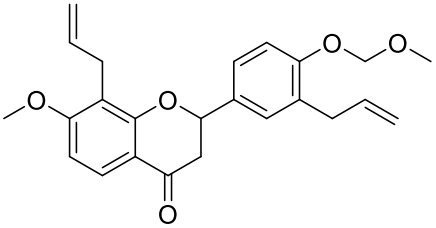
methanol (20 mL) in a vessel suited for microwave irradiation. NaOAc (1.68 g, 20.00 mmol) was added to the solution, the vessel was sealed again, and the mixture was further irradiated in a microwave reactor at 100 ºC for 2 h. The solvent was then evaporated, and water (50 mL) was added to the residue. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexanes − MTBE mixture (4:1 (v/v)) to afford the respective 8-allyl flavanone **121**.

**8-Allyl-7-methoxy-2-(4-methoxyphenyl)chroman-4-one (121bc)**



Following the general procedure 3, compound **119bc** (650 mg, 2.0 mmol) was converted to **121bc** (305 mg, 0.94 mmol, 47%); purification by column chromatography (hexane – MTBE mixture 4:1 (v/v)): pale yellow solid, m.p 109 – 110 ºC; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 1H), 5.91 (ddt, *J* = 17.0, 10.2, 6.4 Hz, 1H), 5.41 (dd, *J* = 12.8, 3.0 Hz, 1H), 4.98 (dm, *J* = 17.0 Hz, 1H), 4.95 (dm, *J* = 10.2 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.41 (d, *J* = 6.4 Hz, 2H), 3.00 (dd, *J* = 17.0, 12.8 Hz, 1H), 2.85 (dd, *J* = 17.0, 3.0 Hz, 1H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 191.8, 163.5, 160.5, 159.8, 136.0, 131.5, 127.5 (2C), 126.9, 116.1, 115.5, 114.8, 114.2 (2C), 105.0, 79.2, 56.1, 55.5, 44.4, 27.3; IR (ATR) $\tilde{\nu}$ 2970 (w), 1666 (s), 1600 (s), 1255 (s), 1120 (s); HRMS (ESI) calcd for $C_{20}H_{21}O_4$ $[M+H]^+$ 325.1440, found 325.1432.

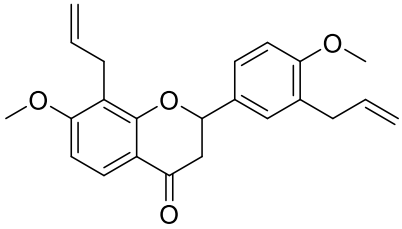
**8-Allyl-2-(3-allyl-4-(methoxymethoxy)phenyl)-7-methoxychroman-4-one (121be)**



Following the general procedure 3, compound **119be** (790 mg, 2.0 mmol) was converted to **121be** (355 mg, 0.90 mmol, 45%); purification by column chromatography (hexane – MTBE mixture 4:1 (v/v)): yellow solid, m.p 74 – 75 ºC; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.12 (d, *J* = 9.0 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 6.05 - 5.86 (m, 2H), 5.39 (dd, *J* = 12.8, 2.9 Hz, 1H), 5.23 (s, 2H), 5.09 (dm, *J* = 17.3 Hz, 1H), 5.07 (dm, *J* = 11.2 Hz, 1H), 5.00 (dm, *J* = 17.0 Hz, 1H), 4.96 (dm, *J* = 10.0 Hz, 1H), 3.89 (s, 3H), 3.49 (s, 3H), 3.44 (d, *J* = 6.7 Hz, 2H), 3.41 (d, *J* = 6.2 Hz, 2H), 2.99 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.84 (dd, *J* = 16.8, 2.9 Hz, 1H); $^{13}$C{$^1$H}

NMR (100 MHz, $CDCl_3$) δ 191.7, 163.4, 160.5, 155.0, 136.6, 136.0, 132.5, 129.7, 126.8, 125.1, 116.1, 116.0, 115.4, 114.9, 114.0, 105.0, 94.5, 79.2, 56.2, 56.1, 44.5, 34.5, 27.3; IR (ATR) $\tilde{\nu}$ 3075 (w), 2901 (w), 1664 (m), 1602 (s), 1341 (m), 1274 (m), 1068 (s); HRMS (EI) calcd for $C_{24}H_{26}O_5$ [$M^+$] 394.1780, found 394.1779.

**8-Allyl-2-(3-allyl-4-methoxyphenyl)-7-methoxychroman-4-one (121ba)**



Following the general procedure 3, compound **119ba** (730 mg, 2.0 mmol) was converted to **121ba** (330 mg, 0.90 mmol, 45%); purification by column chromatography (hexane – MTBE mixture 4:1 (v/v)): yellow solid, m.p 76 – 77 ºC; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.30 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 6.05 - 5.86 (m, 2H), 5.39 (dd, *J* = 12.9, 3.0 Hz, 1H), 5.09 (dm, *J* = 17.1 Hz, 1H), 5.07 (dm, *J* = 10.0 Hz, 1H), 5.00 (dm, *J* = 17.1 Hz, 1H), 4.95 (dm, *J* = 10.0 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.41 (d, *J* = 6.2 Hz, 4H), 3.00 (dd, *J* = 16.8, 12.9 Hz, 1H), 2.84 (dd, *J* = 16.8, 3.0 Hz, 1H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 191.8, 163.4, 160.5, 157.4, 136.6, 136.1, 131.3, 129.1, 127.8, 126.8, 125.1, 116.1, 116.0, 115.5, 114.9, 110.4, 105.0, 79.3, 56.1, 55.6, 44.4, 34.3, 27.3; IR (ATR) $\tilde{\nu}$ 3077 (w), 2838 (w), 1667 (s), 1593 (s), 1503 (m), 1264 (s), 1115 (s); HRMS (EI) calcd for $C_{23}H_{24}O_4$ [$M^+$] 364.1675, found 364.1685.

**8-Allyl-2-(3-allyl-4-(methoxymethoxy)phenyl)-7-(methoxymethoxy)-chroman-4-one (121ce)**

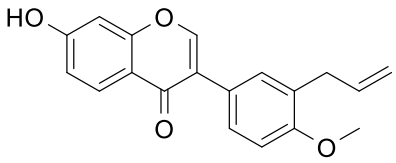
Following the general procedure 3, compound **119ce** (850 mg, 2.0 mmol) was converted to **121ce** (420 mg, 1.00 mmol, 50%) and **120** (225 mg, 0.53 mmol, 27%); separation and purification by column chromatography (hexane – EtOAc mixture 5:1 (v/v)).

## 6.2.7 2,3-Oxidative Rearrangement of Flavanone 107aa

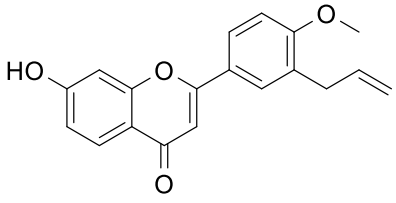
### 6.2.7.1 One-Pot 2,3–Oxidative Rearrangement/MOM Deprotection of Flavanone 107aa

To a solution of **107aa** (710 mg, 2.00 mmol) in trimethyl orthoformate (TMOF) (20 mL) was added conc. $H_2SO_4$ (40 μL, 0.75 mmol) and the mixture was stirred at 20 ºC for 5 minutes. To the mixture was added dropwise a solution of PIFA (1.290 g, 3.00 mmol) in TMOF (5 mL). The mixture was stirred at 20 ºC for 24 hours. The solvent was evaporated, and water (40 mL) was

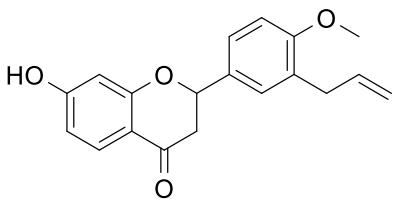
added to the residue. The mixture was further stirred at 20 ºC for 2 hours. The mixture was then extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried with $MgSO_4$ and filtered. The solvent was evaporated, and the residue redissolved in MeOH (40 mL). Aqueous HCl (6 M, 1 mL, 6.0 mmol) was added and the mixture was heated to reflux at 60 ºC for 2 hours. The solvent was evaporated, and water (50 mL) was added to the residue. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried with $MgSO_4$ and filtered. The solvent was evaporated, and the residue was purified by column chromatography on silica using hexane – EtOAc mixtures of increasing polarity (3:1 to 2:3 (v/v)) as eluent to afford the isoflavone **106b** (155 mg, 0.50 mmol, 25%), flavone **116b** (65 mg, 0.21 mmol, 11%) and the MOM deprotected flavanone **107aa′** (100 mg, 0.32 mmol, 16%).



*Analytical data for 3-(3-allyl-4-methoxyphenyl)-7-hydroxy-4H-chromen-4-one (**106b**)*: colourless crystals, m.p 206 – 207 ºC; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.78 (s, 1H), 8.30 (s, 1H), 7.96 (d, $J$ = 8.8 Hz, 1H), 7.40 (dd, $J$ = 8.5, 2.2 Hz, 1H), 7.33 (d, $J$ = 2.2 Hz, 1H), 7.01 (d, $J$ = 8.5 Hz, 1H), 6.94 (dd, $J$ = 8.8, 2.1 Hz, 1H), 6.86 (d, $J$ = 2.1 Hz, 1H), 5.96 (ddt, $J$ = 17.0, 10.2, 6.6 Hz, 1H), 5.05 (dm, $J$ = 17.0 Hz, 1H), 5.01 (dm, $J$ = 10.2 Hz, 1H), 3.81 (s, 3H), 3.34 (d, $J$ = 6.6 Hz, 2H); $^{13}$C{$^1$H} NMR (75 MHz, DMSO-$d_6$) $\delta$ 174.6, 162.5, 157.4, 156.6, 153.1, 136.7, 130.1, 128.0, 127.3, 127.3, 124.0, 123.3, 116.6, 115.7, 115.1, 110.4, 102.1, 55.5, 33.8; IR (ATR) $\tilde{\nu}$ 3205 (m), 1625 (s), 1567 (s), 1497 (m), 1237 (s), 1029 (m); HRMS (ESI) calcd for $C_{19}H_{17}O_4$ $[M+H]^+$ 309.1127, found 309.1123.



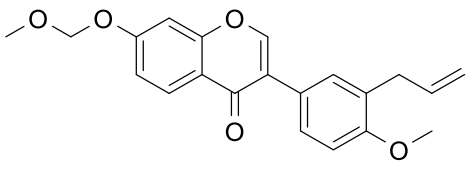
*Analytical data for 2-(3-allyl-4-methoxyphenyl)-7-hydroxy-4H-chromen-4-one (**116b**)*: colourless crystals, m.p 204 – 205 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.91 (dd, $J$ = 8.7, 2.5 Hz, 1H), 7.86 (d, $J$ = 8.7 Hz, 1H),7.79 (d, $J$ = 2.5 Hz, 1H), 7.11 (d, $J$ = 8.7 Hz, 1H), 6.97 (d, $J$ = 2.3 Hz, 1H), 6.91 (dd, $J$ = 8.7, 2.3 Hz, 1H), 6.74 (s, 1H), 5.99 (ddt, $J$ = 17.0, 10.2, 6.6 Hz, 1H), 5.06 (dm, $J$ = 17.0 Hz, 1H), 5.05 (dm, $J$ = 10.2 Hz, 1H), 3.86 (s, 3H), 3.38 (d, $J$ = 6.6 Hz, 2H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) $\delta$ 176.4, 162.7, 162.2, 159.7, 157.5, 136.4, 128.6, 127.5, 126.5, 126.3, 123.2, 116.2, 116.0, 114.9, 111.2, 105.1, 102.6, 55.8, 33.8; IR (ATR) $\tilde{\nu}$ 2843 (w), 2599 (w), 1603 (m), 1548 (m), 1521 (s), 1255 (s), 1243 (m); HRMS (ESI) calcd for $C_{19}H_{17}O_4$ $[M+H]^+$ 309.1127, found 309.1113.



*Analytical data for 2-(3-allyl-4-methoxyphenyl)-7-hydroxychroman-4-one (**107aa'**)*: pale yellow solid, m.p 152 – 153 ºC; $^{1}$H NMR (400 MHz, acetone-$d_6$) $\delta$ 9.39 (s, 1H), 7.74 (d, $J$ = 8.7 Hz, 1H), 7.39 (dd, $J$ = 8.4, 2.4 Hz, 1H), 7.34 (d, $J$ = 2.4 Hz, 1H), 7.00 (d, $J$ = 8.4 Hz, 1H), 6.58 (dd, $J$ = 8.7, 2.3 Hz, 1H), 6.43 (d, $J$ = 2.3 Hz, 1H), 6.00 (ddt, $J$ = 17.0, 10.0, 6.7 Hz, 1H), 5.46 (dd, $J$ = 13.0, 2.9 Hz, 1H), 5.06 (dm, $J$ = 17.0 Hz, 1H), 5.00 (dm, $J$ = 10.0 Hz, 1H), 3.86 (s, 3H), 3.39 (dm, $J$ = 6.6 Hz, 2H), 3.05 (dd, $J$ = 16.8, 13.0 Hz, 1H), 2.68 (dd, $J$ = 16.8, 2.9 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, acetone-$d_6$) $\delta$ 190.5, 165.2, 164.5, 158.3, 137.7, 132.2, 129.5, 129.4, 129.0, 126.7, 115.8, 115.2, 111.2, 111.2, 103.7, 80.5, 55.9, 44.7, 35.0; IR (ATR) $\tilde{\nu}$ 2936 (w), 1647 (w), 1566 (s), 1499 (m), 1234 (s), 1116 (m); HRMS (EI) calcd for $C_{19}H_{18}O_4$ [$M^+$] 310.1205, found 310.1211.

### 6.2.7.2 2,3-Oxidative Rearrangement of Flavanone 107aa without MOM-Deprotection

To a solution of flavanone **107aa** (710 mg, 2.00 mmol) in TMOF (40 mL) was added conc $H_2SO_4$ (40 µL, 0.75 mmol) and the mixture was stirred at 20 ºC for 5 minutes, followed by dropwise addition of a solution of PIFA (1.290 g, 3.00 mmol) in TMOF (8 mL) at 20 ºC. The mixture was stirred at 20 ºC for 24 h. The solvent was evaporated, and water (60 mL) was added to the resulting residue. The mixture was further stirred at 20 ºC for 2 h. It was then extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with a saturated. aqueous solution of $NaHCO_3$ dried with $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica using hexane – EtOAc mixtures of increasing polarity (9:1 to 1:1 (v/v)) as eluent to afford the MOM-protected isoflavone **106a** (190 mg, 0.54 mmol, 27%) and the deprotected isoflavone **106b** (93 mg, 0.30 mmol, 15%). To obtain crystals suitable for single crystal X-ray analysis, compounds **106a** and **106b** (90 mg) were separately dissolved in methanol (2.0 mL) and the solutions were kept at 20 °C for 24 h in open vessels. Crystals in form of needles were isolated by decanting the supernatant solutions. The crystals were dried in air at 20 °C.

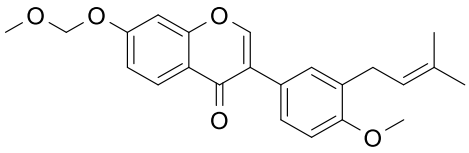


*Analytical data for 3-(3-Allyl-4-methoxyphenyl)-7-(methoxymethoxy)-4H-chromen-4-one (**106a**)*: colourless crystals, m.p 104 – 105 ºC; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.22 (d, $J$ = 8.5 Hz, 1H), 7.92 (s, 1H), 7.42 (dd, $J$ = 8.5, 2.3

Hz, 1H), 7.33 (d, *J* = 2.3 Hz, 1H), 7.09 – 7.05 (m, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.02 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.27 (s, 2H), 5.08 (dm, *J* = 16.9 Hz, 1H), 5.05 (dm, *J* = 10.2 Hz, 1H), 3.86 (s, 3H), 3.51 (s, 3H), 3.42 (d, *J* = 6.7 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl^{3}$) $\delta$ 176.0, 161.5, 157.8, 157.5, 152.3, 136.9, 130.5, 128.8, 128.2, 127.9, 125.1, 124.1, 119.3, 115.7, 115.5, 110.5, 103.2, 94.5, 56.5, 55.7, 34.4; IR (ATR) $\tilde{\nu}$ 2928 (w), 1621 (s), 1501 (m), 1445 (s), 1250 (s), 1149 (m); HRMS (EI) calcd for $C_{21}H_{20}O_5$ [$M^+$] 352.1311, found 352.1301.

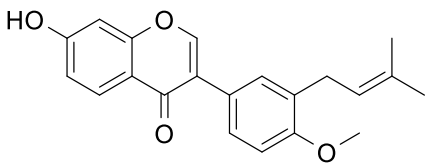
### 6.2.8 Olefin Cross Metathesis of 106a and 106b

**3-[4-Methoxy-3-(3-methylbut-2-en-1-yl)phenyl]-7-(methoxymethoxy)-4*H*-chromen-4-one (114)**.



To a solution of **106a** (140 mg, 0.40 mmol) in dry and degassed $CH_2Cl_2$ (5 mL) at 20 ºC was added 2-methyl-2-butene (4.0 mL, 37.7 mmol) and second-generation Grubbs catalyst **A** (17.0 mg, 5 mol-%). The reaction mixture was stirred at 20 ºC under dry nitrogen atmosphere for 48 h. After completion of the reaction, the volatiles were evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (7:3 (v/v)) to afford **114** (145 mg, 0.38 mmol, 95%): colourless solid, m.p 83 – 84 ºC; $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.22 (d, *J* = 9.4 Hz, 1H), 7.91 (s, 1H), 7.40 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.08 - 7.06 (m, 2H), 6.90 (d, *J* = 8.5 Hz, 1H), 5.33 (tm, *J* = 7.4 Hz, 1H), 5.27 (s, 2H), 3.86 (s, 3H), 3.51 (s, 3H), 3.36 (d, *J* = 7.4 Hz, 2H), 1.73 (s, 3H), 1.72 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 176.1, 161.5, 157.8, 157.5, 152.3, 132.6, 130.3, 130.1, 128.0, 127.8, 125.3, 124.0, 122.5, 119.4, 115.5, 110.4, 103.2, 94.5, 56.5, 55.6, 28.7, 25.9, 17.9; IR (ATR) $\tilde{\nu}$ 2905 (w), 1625 (s), 1501 (w), 1442 (s), 1253 (s), 1156 (s); HRMS (EI) calcd for $C_{23}H_{24}O_5$ [$M^+$] 380.1624, found 380.1623.

**5-Deoxy-3'-prenylbiochanin A (59)**

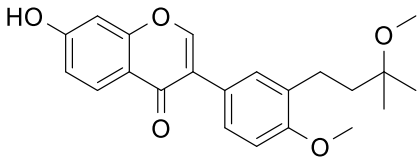


Following the procedure given above for the synthesis of **114** (but replacing the solvent $CH_2Cl_2$ by THF), compound **106b** (38 mg, 0.12 mmol) was converted to 5-deoxy-3′-prenylbiochanin A (**59**) (35 mg, 0.10 mmol, 86%): colourless crystals, m.p 197 – 199 ºC; $^{1}H$ NMR (500 MHz, acetone-

$d_6$) $\delta$ 8.13 (s, 1H), 8.06 (d, $J$ = 8.7 Hz, 1H), 7.42 (dd, $J$ = 8.4, 2.3 Hz, 1H), 7.39 (d, $J$ = 2.3 Hz, 1H), 6.99 (dd, $J$ = 8.7, 2.3 Hz, 1H), 6.98 (d, $J$ = 8.4 Hz, 1H), 6.89 (d, $J$ = 2.3 Hz, 1H), 5.32 (tm, $J$ = 7.3 Hz, 1H), 3.87 (s, 3H), 3.33 (d, $J$ = 7.3 Hz, 2H), 1.72 (s, 3H), 1.70 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, acetone-$d_6$) $\delta$ 175.7, 163.3, 158.8, 158.1, 153.3, 132.5, 130.9, 130.3, 128.6, 128.5, 125.4, 125.3, 123.6, 118.6, 115.7, 111.0, 103.2, 55.8, 29.3, 25.9, 17.8; IR (ATR) $\tilde{\nu}$ 3219 (m), 2633 (w), 1622 (s), 1582 (m), 1493 (m), 1233 (s), 1125 (m); HRMS (EI) calcd for $C_{21}H_{20}O_4$ [$M^+$] 336.1362, found 336.1368. Analytical data match those previously reported for the natural product.[39]

### 6.2.9 Synthesis of 5-Deoxy-3'-prenylbiochanin A (59) from 114

To a solution of **114** (115 mg, 0.30 mmol) in MeOH (10 mL) was added aqueous HCl (4 M, 225 µL, 0.90 mmol) and the mixture was heated to reflux for 2 h at 60 ºC. The mixture was then cooled to room temperature and quenched with water (30 mL). It was then extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixtures of increasing polarity (7:3 to 1:1 (v/v)) as eluent to afford **59** (85 mg, 0.25 mmol, 84%) and **115** (16 mg, 0.05 mmol, 15%). To obtain crystals suitable for single crystal X-ray analysis, compound **59** (85 mg) was dissolved in methanol (2.0 mL) and the solution was kept at 20 °C for 24 h in an open vessel. Crystals in form of needles were isolated by decanting the supernatant solution. The crystals were dried in air at 20 °C.

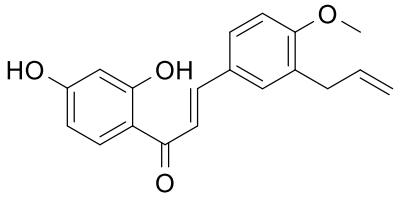



*Analytical data for 7-hydroxy-3-(4-methoxy-3-(3-methoxy-3-methylbutyl)phenyl)-4H-chromen-4-one (**115**)*: colourless solid, m.p 187 – 188 ºC; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.07 (brs, 1H), 8.11 (d, $J$ = 8.9 Hz, 1H), 7.89 (s, 1H), 7.33 (dd, $J$ = 8.3, 2.3 Hz, 1H), 7.30 (d, $J$ = 2.3 Hz, 1H), 6.92 (dd, $J$ = 8.9, 2.3 Hz, 1H), 6.87 (d, $J$ = 8.3 Hz, 1H), 6.83 (d, $J$ = 2.3 Hz, 1H), 3.82 (s, 3H), 3.25 (s, 3H), 2.68 - 2.62 (m, 2H), 1.78 - 1.73 (m, 2H),1.23 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) $\delta$ 177.0, 162.5, 158.3, 157.7, 152.8, 131.4, 130.6, 127.9, 127.9, 125.0, 123.9, 117.6, 115.7, 110.4, 102.9, 75.4, 55.5, 49.2, 39.4, 25.3, 25.1; IR (ATR) $\tilde{\nu}$ 3125 (w), 2919 (m), 1615 (m), 1500 (m), 1451 (s), 1270 (s), 1192 (m); HRMS (EI) calcd for $C_{22}H_{24}O_5$ [$M^+$] 368.1624, found 368.1631.

### 6.2.10 Optimization of Reaction Conditions for the 2,3-Oxidative Rearrangement of Flavanone 107aa

#### 6.2.10.1 General Procedure 4 for the Reaction with HTIB, PIDA or PIFA in Methanol or Acetonitrile

To a solution of **107aa** (355 mg, 1.00 mmol) in the solvent indicated in Table 3 or Table 6 (acetonitrile or methanol, 10 mL) was added dropwise a solution of HTIB (395 mg, 1.00 mmol or 590 mg, 1.5 mmol), PIDA (322 mg, 1.00 mmol) or PIFA (430 mg, 1.00 mmol) in the same solvent (2 mL). The mixture was stirred at 20 °C or at 60 °C (as indicated in Table 3 or Table 6) for 24 h. The solvent was evaporated, water (20 mL) was added, and the mixture was further stirred at 20 ºC for 2 h. The mixture was then extracted with EtOAc (3 x 15 mL). The organic extracts were dried with anhydrous MgSO4, filtered, and the solvent evaporated under reduced pressure. The products were separated by column chromatography on silica using a hexane − EtOAc mixture (4:1 (v/v)) as eluent. In a typical experiment (Table 3, entry 9: solvent acetonitrile; oxidant PIDA) *p*-toluene sulfonic acid (69 mg, 0.4 mmol) was added to the solution prior to the addition of the oxidant, but no reaction was detected and the substrate **107aa** was recovered. In a typical experiment (Table 3, entry 2: solvent methanol; oxidant HTIB) the deprotected flavanone **107aa′** (121 mg, 0.39 mmol, 39%), the deprotected chalcone **117** (31 mg, 0.10 mmol, 10%), and the deprotected isoflavone **106b** (47 mg, 0.15 mmol, 15%) were obtained.

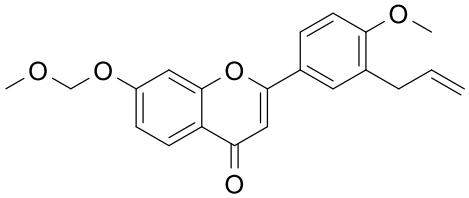



*Analytical data for (E)-3-(3-allyl-4-methoxyphenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one (**117**)*: yellow solid, mp 163 − 164 ºC; $^{1}$HNMR(400 MHz, acetone-$d_6$) δ 13.62 (s, 1H), 9.47 (s, 1H), 8.08 (d, *J* = 8.9 Hz, 1H), 7.84 (d, *J* = 15.4 Hz, 1H), 7.78 (d, *J* = 15.4 Hz, 1H), 7.69 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 1H), 6.47 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.01 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.07 (dm, *J* = 17.0 Hz, 1H), 5.02 (dm, *J* = 10.2 Hz, 1H), 3.90 (s, 3H), 3.39 (d, *J* = 6.6 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, acetone-$d_6$) δ 192.8, 167.6, 165.6, 160.6, 145.1, 137.5, 133.3, 130.9, 130.3, 130.0, 128.3, 118.8, 115.9, 114.5, 111.7, 108.7, 103.8, 56.0, 34.9; IR (ATR) $\tilde{\nu}$ 3283 (w), 1628 (m), 1557 (m), 1494 (s), 1259 (m), 1193 (s); HRMS (EI) calcd for $C_{19}H_{18}O_4$ [$M^+$] 310.1205, found 310.1200.

### 6.2.10.2 General Procedure 5 for the Reaction with PIDA or PIFA in TMOF in the Presence of Sulfuric Acid or Trifluoroacetic Acid

To a solution of **107aa** (710 mg, 2.00 mmol) in TMOF (20 mL) was added conc. $H_2SO_4$ (40 µL, 0.75 mmol) and the solution was stirred for 5 min at 20°C. A solution of PIDA (966 mg, 3.00 mmol) or PIFA (1.290 g, 3.00 mmol) in TMOF (5 mL) was added dropwise and the mixture was stirred at 20 ºC for 24 h. The solvent was evaporated, water (40 mL) was added, and the mixture was further stirred at 20 °C for 2 h. The mixture was then extracted with EtOAc (3 x 30 mL). The organic extracts were dried with anhydrous $MgSO_4$, filtered, and the solvent evaporated. The products were separated by column chromatography on silica using hexane − EtOAc mixtures of increasing polarity (5:1 to 3:1 (v/v)) as eluent. In a typical experiment (Table 3, entry 12; oxidant PIDA), $H_2SO_4$ was replaced by trifluoroacetic acid, but no reaction was detected and the substrate **107aa** was recovered. In a typical experiment (Table 3, entry 10: oxidant PIDA) MOM-protected isoflavone **106a** (141 mg, 0.40 mmol, 20%) and MOM-protected flavone **116a** (113 mg, 0.32 mmol, 16%) were obtained. With PIFA as oxidant (Table 3, entry 11) MOM-protected isoflavone **106a** (190 mg, 0.54 mmol, 27%) and deprotected isoflavone **106b** (91 mg, 0.30 mmol, 15%) were isolated.

*Analytical data for 2-(3-allyl-4- methoxyphenyl)-7-(methoxymethoxy)-4H-chromen-4-one (**116a**)*:

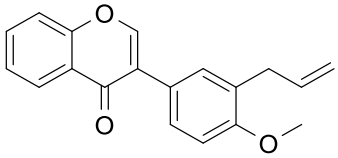


colourless solid, mp 150 – 151 °C; $^1$H NMR (400 MHz, acetone-$d_6$) δ 8.00 (d, $J$ = 8.8 Hz, 1H), 7.90 (dd, $J$ = 8.7, 2.4 Hz, 1H), 7.82 (d, $J$ = 2.4 Hz, 1H), 7.25 (d, $J$ = 2.4 Hz, 1H), 7.11 (d, $J$ = 8.7 Hz, 1H), 7.08 (dd, $J$ = 8.8, 2.4 Hz, 1H), 6.65 (s, 1H), 6.04 (ddt, $J$ = 17.0, 10.2, 6.7 Hz, 1H), 5.37 (s, 2H), 5.10 (dm, $J$ = 17.0 Hz, 1H), 5.04 (dm, $J$ = 10.2 Hz, 1H), 3.92 (s, 3H), 3.50 (s, 3H), 3.44 (d, $J$ = 6.7 Hz, 2H); $^{13}$C{$^1$H} NMR (100 MHz, acetone-$d_6$) δ 177.1, 163.8, 162.4, 161.0, 158.3, 137.3, 130.1, 128.4, 127.3, 127.0, 124.6, 119.3, 116.1, 115.9, 111.6, 106.3, 104.1, 95.2, 56.5, 56.1, 34.9; IR (ATR) $\tilde{\nu}$ 2924 (w), 1622 (s), 1599 (m), 1445 (s), 1251 (s), 1149 (s); HRMS (ESI) calcd for $C_{21}H_{21}O_5$ $[M+H]^+$ 353.1389, found 353.1379.

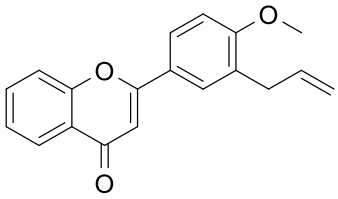
### 6.2.10.3 Oxidative Rearrangement of Flavanones 107 and 121

**3-(3-Allyl-4-methoxyphenyl)-4*H*-chromen-4-one (122a) and 2-(3-allyl-4-methoxyphenyl)-4*H*-chromen-4-one (123a)**

Following the general procedure 5 using PIDA as an oxidant, compound **107ba** (295 mg, 1.00 mmol) was converted to **122a** (138 mg, 0.47 mmol, 47%) and **123a** (58 mg, 0.20 mmol, 20%). Following the general procedure 5 using PIFA as an oxidant, **107ba** (295 mg, 1.00 mmol) was converted selectively to **122a** (190 mg, 0.65 mmol, 65%); separation and purification by column chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)).

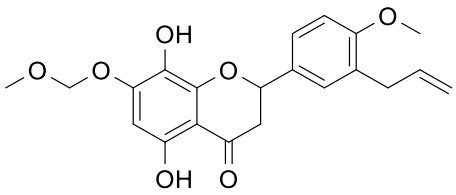


*Analytical data for **122a***: colourless solid, mp 98 – 100 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.99 (s, 1H), 7.67 (td, *J* = 7.8, 1.8 Hz, 1H), 7.49 − 7.39 (m, 3H), 7.35 (d, *J* = 2.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.02 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.09 (dm, *J* = 17.0 Hz, 1H), 5.05 (dm, *J* = 10.3 Hz, 1H), 3.87 (s, 3H), 3.43 (d, *J* = 6.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 176.6, 157.5, 156.3,152.6, 136.9, 133.6, 130.5, 128.9, 128.2, 126.5, 125.3,125.2, 124.7, 124.0, 118.1, 115.8,110.5, 55.7, 34.4; IR (ATR) $\tilde{\nu}$ 3072 (w), 2913 (w), 1715 (m), 1632 (m), 1607 (s), 1461 (s), 1247 (s), 762 (s); HRMS (EI) calcd for $C_{19}H_{16}O_3$ [$M^+$] 292.1099, found 292.1090.



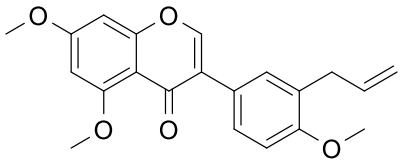
*Analytical data for **123a***: pale yellow solid, mp 146 – 147 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.81 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.67 (td, *J* = 7.1, 1.8 Hz, 1H), 7.56 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.40 (td, *J* = 7.1, 1.2 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 6.80 (s, 1H), 6.00 (ddt, *J* = 17.6, 11.1, 6.7 Hz, 1H), 5.11 (dm, *J* = 17.6 Hz, 1H), 5.10 (dm, *J* = 11.1 Hz, 1H), 3.91 (s, 3H), 3.44 (d, *J* = 6.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 178.5, 164.1, 160.4, 156,3, 136.1, 133.7, 129.7, 128.0, 126.4, 125.8, 125.2, 123.9, 123.8, 118.1, 116.4, 110.6, 106.2, 55.8, 34.3; IR (ATR) $\tilde{\nu}$ 2915 (s), 2849 (m), 1729 (m), 1636 (m), 1602 (s), 1374 (s), 1248 (s); HRMS (EI) calcd for $C_{19}H_{16}O_3$ [$M^+$] 292.1099, found 292.1092.

**Attempted Oxidative Rearrangement of 107ca: 2-(3-Allyl-4-methoxyphenyl)-5,8-dihydroxy-7-(methoxymethoxy)chroman-4-one (124)**



Following the general procedure 5, using PIFA as an oxidant, compound **107ca** (415 mg, 1.00 mmol) was converted to a complex mixture of products from which only compound **124** (30 mg, 0.08 mmol, 8%) could be isolated and characterized; separation and purification by chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)): yellow solid, m.p 129 – 130 °C; $^{1}$H NMR (500 MHz, acetone-$d_6$) δ 11.63 (s, 1H), 7.41 (dd, *J* = 8.4, 2.3 Hz,1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.28 (s, 1H), 6.00 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.48 (dd, *J* = 12.6, 3.0 Hz, 1H), 5.29 (s, 2H), 5.07 (dm, *J* = 17.0 Hz, 1H), 5.00 (dm, *J* = 10.2 Hz, 1H), 3.87 (s, 3H), 3.46 (s, 3H), 3.39 (d, *J* = 6.7 Hz, 2H), 3.21(dd, *J* = 17.0, 12.6 Hz, 1H), 2.78 (dd, *J* = 17.0, 3.0 Hz, 1H); $^{13}$C{$^{1}$H} NMR (125 MHz, acetone-$d_6$) δ 198.1, 158.5, 156.8, 154.7, 149.4, 137.7, 131.8, 129.4, 129.2, 128.9, 127.1, 115.9, 111.3, 104.3, 96.5, 95.6, 80.3, 56.7, 56.0, 44.1, 35.1; IR (ATR) $\tilde{\nu}$ 3287 (w), 2834 (w), 1645 (m), 1620 (s), 1496 (s), 1224 (s), 1049 (s); HRMS (EI) calcd for $C_{21}H_{22}O_7$ [$M^+$] 386.1360, found 386.1354.

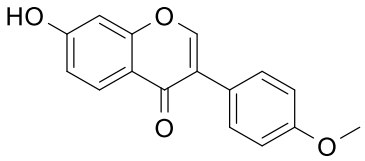
**3-(3-Allyl-4-methoxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (122c)**



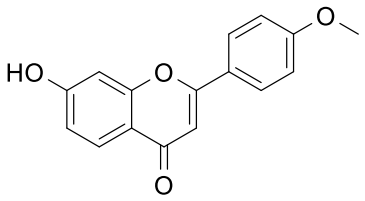
Following the general procedure 5, using PIFA as an oxidant, compound **107da** (355 mg, 1.00 mmol) was converted to **122c** (112 mg, 0.32 mmol, 32%); purification by chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)): colourless solid, m.p 128 − 129 °C; $^{1}$H NMR (300 MHz, acetone-$d_6$) δ 7.94 (s, 1H), 7.37 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.00 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.07 (dm, *J* = 17.0 Hz, 1H), 4.99 (dm, *J* = 10.1 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.38 (d, *J* = 6.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, acetone-$d_6$) δ 174.7, 164.9, 162.5, 160.7, 158.0, 151.2, 138.1, 131.6, 129.2, `28.7, 126.6, 125.8, 115.7, 111.0, 110.7, 96.9, 93.6, 56.6, 56.4, 55.9, 35.1; IR (ATR) $\tilde{\nu}$ 2968 (w), 1650 (s), 1607 (s), 1452 (m), 1243 (s), 1213 (s); HRMS (EI) calcd for $C_{21}H_{20}O_5$ [$M^+$] 352.1311, found 352.1306.

**Formononetin (51) and Pratol (123d)**

Following the general procedure 4, using HTIB as an oxidant compound **107ac** (315 mg, 1.00 mmol) was converted to formononetin (**51**) (113 mg, 0.42 mmol, 42%) and pratol (**123d**) (25 mg, 0.09 mmol, 9%). Following the general procedure 5, using PIFA as an oxidant **107ac** (315 mg, 1.00 mmol) was converted to **51** (51 mg, 0.19 mmol, 19%) and **123d** (51 mg, 0.19 mmol, 19%); separation and purification by column chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)).



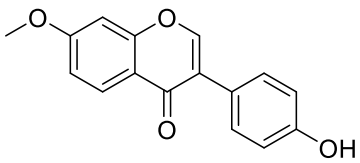
*Analytical data for formononetin (**51**)*: pale yellow solid, m.p 256 – 257 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.84 (s, 1H), 8.33 (s, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.94 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 3.78 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, DMSO-$d_6$) δ 174.7, 162.6, 159.0, 157.5, 153.2, 130.2 (2C), 127.5, 124.3, 123.2, 116.7, 115.3, 113.7 (2C), 102.2, 55.2; IR (ATR) $\tilde{\nu}$ 3077 (w), 1594 (m), 1512 (s), 1451 (s), 1245 (s), 1178 (s); HRMS (ESI) calcd for $C_{16}H_{13}O_4$ $[M+H]^+$ 269.0814, found 269.0814. Analytical data match those previously reported in the literature.[250]



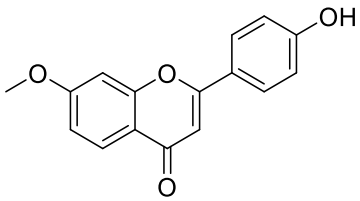
*Analytical data for pratol (**123d**)*: pale yellow solid, m.p 262 – 263 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.00 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.91 (dd *J* = 8.6, 2.2 Hz, 1H), 6.78 (s, 1H), 3.84 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, DMSO-$d_6$) δ 176.4, 162.7, 162.1, 162.0, 157.5, 128.1 (2C), 126.6, 123.5, 116.1, 115.0, 114.6 (2C), 105.2, 102.6, 55.6; IR (ATR) $\tilde{\nu}$ 3500 (w), 2842 (w), 1609 (m), 1509(s), 1386 (m), 1264 (s), 1175 (s); HRMS (ESI) calcd for $C_{16}H_{13}O_4$ $[M+H]^+$ 269.0814, found 269.0797. Analytical data match that previously reported in the literature.[251]

**Isoformononetin (101) Isopratol (123e)**

Following the general procedure 4, using HTIB as an oxidant, compound **107eb** (315 mg, 1.00 mmol) was converted to isoformononetin (**101**) (70 mg, 0.26 mmol, 26%) and isopratol (**123e**) (20 mg, 0.08 mmol, 8%); separation and purification by column chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)).

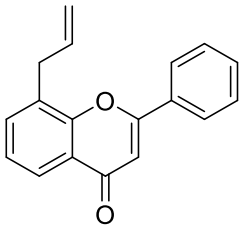


*Analytical data forisoformononetin (**101**)*: pale yellow solid, m.p 225 − 226 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 9.55 (s, 1H), 8.35 (s, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.89 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, DMSO-$d_6$) δ 174.7, 163.7, 157.4, 157.3, 153.1, 130.1 (2C), 126.9, 123.7, 122.4, 117.6, 115.0 (2C), 114.7, 100.5, 56.1; IR (ATR) $\tilde{\nu}$ 3167 (w), 1620 (s), 1582 (m), 1438 (s), 1252 (s); HRMS (ESI) calcd for $C_{16}H_{13}O_4$ $[M+H]^+$ 269.0814, found 269.0806. Analytical data match those previously reported in the literature.[87]



*Analytical data for isopratol (**123e**)*: pale yellow solid, m.p 265 − 266 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 10.28 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.03 (dd *J* = 8.8, 2.4 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.76 (s, 1H), 3.90 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, DMSO-$d_6$) δ 176.3, 163.7, 162.7, 160.8, 157.4, 128.2 (2C), 126.1, 121.7, 117.1, 115.9 (2C), 114.4, 104.6, 100.9, 56.0; IR (ATR) $\tilde{\nu}$ 3025 (w), 1623 (m), 1573 (s), 1440 (s), 1224 (m), 1165 (s); HRMS (ESI) calcd for $C_{16}H_{13}O_4$ $[M+H]^+$ 269.0814, found 269.0804. Analytical data match those previously reported in the literature.[251]

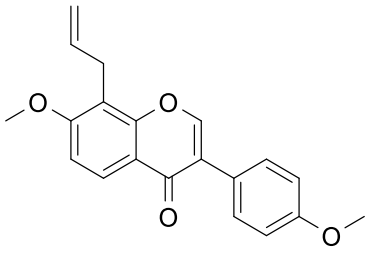
**Attempted Oxidative Rearrangement of 121ad: 8-Allyl-2-phenyl-4*H*-chromen-4-one (123f)**



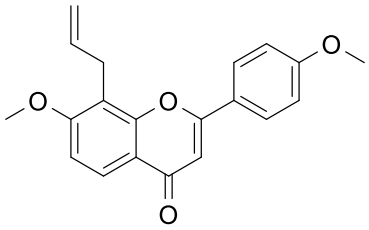
Following the general procedure 5, using PIDA as an oxidant, compound **121ad** (265 mg, 1.00 mmol) was converted to **123f** (32 mg, 0.12 mmol, 12%) and unreacted starting material was recovered; separation and purification by column chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)): colorless solid, m.p 134 – 135 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.94 – 7.91 (m, 2H), 7.57 – 7.51 (m, 4H), 7.36 (t, *J* = 7.7 Hz, 1H), 6.84 (s, 1H), 6.08 (ddt, *J* = 17.6, 9.6, 6.6 Hz, 1H), 5.17 (dm, *J* = 17.6 Hz, 1H), 5.16 (dm, *J* = 9.6 Hz, 1H), 3.77 (d, *J* = 6.6 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 178.9, 163.2, 154.4, 135.4, 134.2, 132.2, 131.7, 129.7, 129.3 (2C), 126.4(2C), 125.1, 124.2, 124.1, 117.1, 107.6, 34.1; IR (ATR) $\tilde{\nu}$ 3061 (w), 2922 (w), 1632 (s), 1482 (m), 1378 (s), 1212 (w), 1139 (w); HRMS (EI) calcd for $C_{18}H_{14}O_2$ $[M^+]$ 262.0994, found 262.0983.

**8-Allyl-7-methoxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one (122g) and 8-allyl-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (123g)**

Following the general procedure 4, using HTIB as an oxidant compound **121bc** (325 mg, 1.00 mmol) was converted to **122g** (168 mg, 0.52 mmol, 52%) and **123g** (65 mg, 0.20 mmol, 20%). Following the general procedure 5, using PIFA as an oxidant **121bc** (315 mg, 1.00 mmol) was converted to **122g** (71 mg, 0.22 mmol, 22%) and **123g** (161 mg, 0.50 mmol, 50%); separation and purification by column chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)).



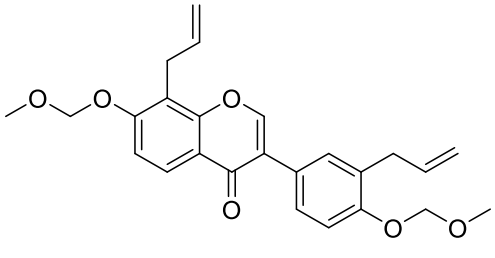
*Analytical data for **122g***: pale yellow solid, m.p 97 − 98 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 1H), 7.97 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 5.97 (ddt, *J* = 16.9, 10.2, 6.2 Hz, 1H), 5.03 (dm, *J* = 16.9 Hz, 1H), 5.01 (dm, *J* = 10.2 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.62 (d, *J* = 6.2 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.5, 161.2, 159.6, 155.3, 152.5, 135.3, 130.2 (2C), 125.9, 124.5, 124.3, 118.7, 115.8, 115.3, 114.1 (2C), 109.1, 56.3, 55.4, 27.1; IR (ATR) $\tilde{\nu}$ 2840 (w), 1636 (m), 1607 (s), 1513 (m), 1268 (s), 1251 (s); HRMS (EI) calcd for $C_{20}H_{18}O_4$ [$M^+$] 322.1205, found 322.1194.



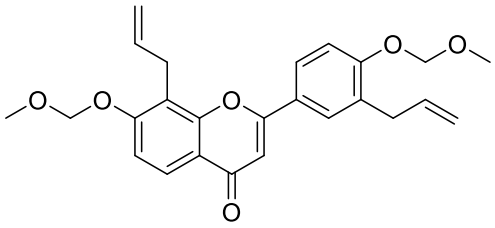
*Analytical data for **123g***: colorless solid, m.p 154 – 155 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.76 (s, 1H), 6.02 (ddt, *J* = 16.8, 10.2, 6.1 Hz, 1H), 5.06 (dm, *J* = 16.8 Hz, 1H), 5.02 (dm, *J* = 10.2 Hz, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.71 (d, *J* = 6.1 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 178.4, 163.6, 162.5, 161.4, 155.2, 135.3, 128.1 (2C), 125.1, 124.4, 117.7, 116.0, 115.5, 114.6 (2C), 109.1, 105.3, 56.3, 55.6, 27.5; IR (ATR) $\tilde{\nu}$ 2843 (w), 1635 (s), 1595 (s), 1375 (m), 1249 (m), 1186 (s); HRMS (EI) calcd for $C_{20}H_{18}O_4$ [$M^+$] 322.1205, found 322.1201.

**8-Allyl-3-[3-allyl-4-(methoxymethoxy)phenyl]-7-(methoxymethoxy)-4*H*-chromen-4-one (122h) and 8-allyl-2-[3-allyl-4-(methoxymethoxy)phenyl]-7-(methoxymethoxy)-4*H*-chromen-4-one (123h)**.

Following the general procedure 5, using PIFA as an oxidant, compound **121ce** (424 mg, 1.00 mmol) was converted to **122h** (85 mg, 0.20 mmol, 20%) and **123h** (75 mg, 0.18 mmol, 18%); separation and purification by column chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)).



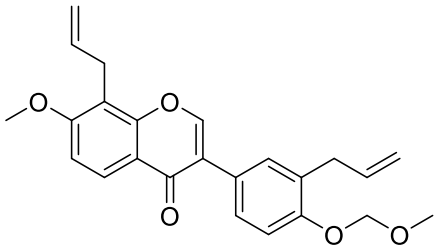
*Analytical data for **122h***: yellow oil; $^{1}$H NMR (300 MHz, acetone-$d_6$) $\delta$ 8.26 (s, 1H), 8.07 (d, $J$ = 9.0 Hz, 1H), 7.46 (d, $J$ = 2.3 Hz, 1H), 7.44 (dd, $J$ = 8.9, 2.3 Hz, 1H), 7.29 (d, $J$ = 8.9 Hz, 1H), 7.13 (d, $J$ = 9.0 Hz, 1H), 6.10 – 5.94 (m, 2H), 5.39 (s, 2H), 5.27 (s, 2H), 5.15 – 5.05 (m, 2H), 5.04 – 4.97 (m, 2H), 3.65 (d, $J$ = 6.2 Hz, 2H), 3.48 (s, 3H), 3.46 (s, 3H), 3.43 (d, $J$ = 6.5 Hz, 2H); $^{13}$C{$^{1}$H} NMR (75 MHz, acetone-$d_6$) $\delta$ 176.1, 159.7, 156.1, 155.7, 154.0, 138.0, 136.3, 131.6, 129.8, 129.0, 126.6, 126.0, 124.8, 120.1, 117.6, 115.9, 115.8, 114.7, 113.0, 95.4, 95.2, 56.7, 56.3, 35.3, 27.9; IR (ATR) $\tilde{\nu}$ 3076 (w), 2906 (w), 1639(s), 1498 (m), 1432 (s), 1252 (s), 1150 (m); HRMS (EI) calcd for $C_{25}H_{26}O_6$ [$M^+$] 422.1729, found 422.1717.



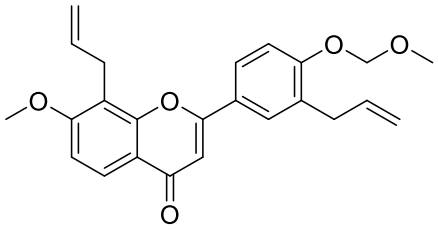
*Analytical data for **123h***: colorless solid, m.p 129 – 130 °C; $^{1}$H NMR (300 MHz, acetone-$d_6$) $\delta$ 7.96 (d, $J$ = 8.9 Hz, 1H), 7.90 (dd, $J$ = 8.9, 2.3 Hz, 1H), 7.89 (d, $J$ = 2.3 Hz, 1H), 7.27 (d, $J$ = 8.9 Hz, 1H), 7.27 (d, $J$ = 8.9 Hz, 1H), 6.67 (s, 1H), 6.14 – 6.01 (m, 2H), 5.40 (s, 2H), 5.35 (s, 2H), 5.19 – 5.00 (m, 4H), 3.77 (d, $J$ = 6.3 Hz, 2H), 3.50 (d, $J$ = 6.6 Hz, 2H), 3.49 (s, 3H), 3.48 (s, 3H); $^{13}$C{$^{1}$H} NMR (75 MHz, acetone-$d_6$) $\delta$ 177.5, 163.5, 159.7, 158.4, 155.9, 137.3, 136.5, 130.8, 128.7, 126.7, 125.9, 125.1, 119.1, 117.7, 116.4, 115.7, 114.9, 112.7, 106.2, 95.3, 95.0, 56.6, 56.4, 35.0, 28.2; IR (ATR) $\tilde{\nu}$ 2957 (w), 1635 (s), 1601 (s), 1499 (m), 1248 (s), 1024 (s); HRMS (EI) calcd for $C_{25}H_{26}O_6$ [$M^+$] 422.1729, found 422.1720.

**8-Allyl-3-(3-allyl-4-(methoxymethoxy)phenyl)-7-methoxy-4*H*-chromen-4-one (122i) and 8-allyl-2-(3-allyl-4-(methoxymethoxy)phenyl)-7-methoxy-4*H*-chromen-4-one (123i)**

Following the general procedure 5, using PIFA as an oxidant, compound **121be** (395 mg, 1.00 mmol) was converted to **122i** (80 mg, 0.20 mmol, 20%) and **123i** (67 mg, 0.17 mmol, 17%); separation and purification by column chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)).



*Analytical data for **122i***: yellow oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.9 Hz, 1H), 7.97 (s, 1H), 7.38 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 6.07 – 5.92 (m, 2H), 5.23 (s, 2H), 5.11 – 4.99 (m, 4H), 3.96 (s, 3H), 3.62 (d, *J* = 6.1 Hz, 2H), 3.49 (s, 3H), 3.45 (d, *J* = 6.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.5, 161.2, 155.3, 155.0, 152.6, 136.9, 135.3, 130.8, 129.4, 128.1, 125.9, 125.5, 124.4, 118.7, 115.8, 115.8, 115.3, 114.0, 109.1, 94.4, 56.3, 56.2, 34.6, 27.1; IR (ATR) $\tilde{\nu}$ 3076 (w), 2944 (w), 1638 (m), 1599 (s), 1430 (m), 1265 (s), 1067 (s); HRMS (EI) calcd for $C_{24}H_{24}O_5$ [$M^+$] 392.1624, found 392.1621.

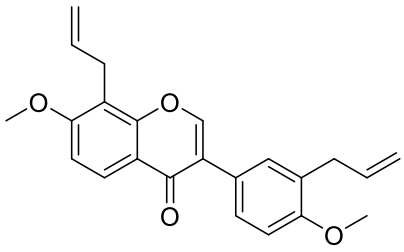


*Analytical data for **123i***: colorless solid, m.p 143 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.0 Hz, 1H), 7.75 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 6.75 (s, 1H), 6.06 – 5.96 (m, 2H), 5.28 (s, 2H), 5.15 – 5.01 (m, 4H), 3.96 (s, 3H), 3.71 (d, *J* = 6.1 Hz, 2H), 3.49 (s, 3H), 3.47 (d, *J* = 6.8 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 178.5, 163.6, 161.4, 157.7, 155.2, 136.0, 135.4, 130.1, 128.1, 126.0, 125.3, 125.1, 117.8, 116.6, 116.0, 115.5, 114.0, 109.0, 105.6, 94.2, 56.4, 56.3, 34.4, 27.5; IR (ATR) $\tilde{\nu}$ 2963 (w), 1632 (s), 1594 (s), 1380 (s), 1247 (s), 1081 (m); HRMS (EI) calcd for $C_{24}H_{24}O_5$ [$M^+$] 392.1624, found 392.1626.

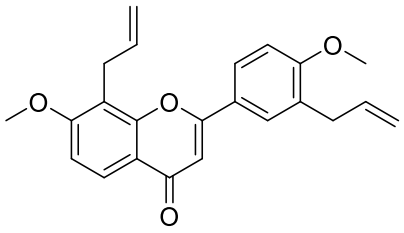
**8-Allyl-3-(3-allyl-4-methoxyphenyl)-7-methoxy-4*H*-chromen-4-one (122j) and 8-allyl-2-(3-allyl-4-methoxyphenyl)-7-methoxy-4*H*-chromen-4-one (123j)**

Following the general procedure 4, using HTIB as an oxidant compound **121ba** (365 mg, 1.00 mmol) was converted to **122j** (222 mg, 0.61 mmol, 61%) and **123j** (80 mg, 0.22 mmol, 22%);

separation and purification by column chromatography (hexane − EtOAc mixtures of increasing polarity, 5:1 to 3:1 (v/v)). To obtain crystals suitable for single crystal X-ray analysis, compound **123j** (80 mg) was dissolved in methanol (2.0 mL) and the solution was kept at 20 °C for 24 h in an open vessel. Crystals in form of needles were isolated by decanting the supernatant solution. The crystals were dried in air at 20 °C.



*Analytical data for **122j***: pale yellow solid, m.p 106 − 107 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.9 Hz, 1H), 7.89 (s, 1H), 7.44 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.40 (d, *J* = 2.3 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.03 – 5.94 (m, 2H), 5.11 – 4.99 (m, 4H), 3.96 (s, 3H), 3.86 (s, 3H), 3.62 (d, *J* = 6.1 Hz, 2H), 3.43 (d, *J* = 6.6 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.6, 161.1, 157.4, 155.3, 152.5, 136.9, 135.4, 130.5, 128.8, 128.2, 125.9, 124.4, 124.2, 118.7, 115.8, 115.7, 115.3, 110.5, 109.1, 56.3, 55.6, 34.4, 27.1; IR (ATR) $\tilde{\nu}$ 3072 (w), 2901 (w), 1648 (s), 1500 (m), 1426 (m), 1235 (s), 1059 (m); HRMS (EI) calcd for $C_{23}H_{22}O_4$ [$M^+$] 362.1518, found 362.1526.



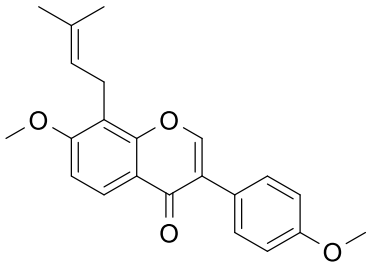
*Analytical data for **123j***: colorless crystals, m.p 160 − 161 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.8 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.75 (s, 1H), 6.06 – 5.95 (m, 2H), 5.15 – 5.00 (m, 4H), 3.96 (s, 3H), 3.90 (s, 3H), 3.71 (d, *J* = 6.2 Hz, 2H), 3.43 (d, *J* = 6.8 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 178.4, 163.8, 161.4, 160.2, 155.2, 136.0, 135.4, 129.7, 127.8, 126.1, 125.1, 124.1, 117.7, 116.6, 116.0, 115.5, 110.6, 109.0, 105.3, 56.3, 55.8, 34.1, 27.5; IR (ATR) $\tilde{\nu}$ 3072 (w), 2841 (w), 1594 (s), 1431 (m), 1378 (m), 1257 (s); HRMS (EI) calcd for $C_{23}H_{22}O_4$ [$M^+$] 362.1518, found 362.1514.

### 6.2.11 General Procedure 6 for the Cross Metathesis of Allyl Isoflavones and Allyl Flavones with 2-Methyl-2-butene

To a solution of the cross-metathesis precursor **122** or **123** (0.50 mmol) in dry and degassed $CH_2Cl_2$ (5 mL) were added 2-methyl-2-butene (5.27 mL (50 mmol, 100 equiv.) per allyl group) and Grubbs second generation catalyst **A** (21 mg, 5 mol %) at 20 °C. The solution was stirred at 20 °C for 48 h, all volatiles were evaporated, and the residue was purified by column chromatography on silica

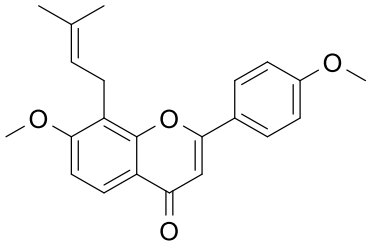
using hexane − EtOAc mixture (3:1 (v/v)), to furnish the respective prenyl isoflavone **64**, **126** or prenyl flavone **127**.

**7-Methoxyebenosin (64)**



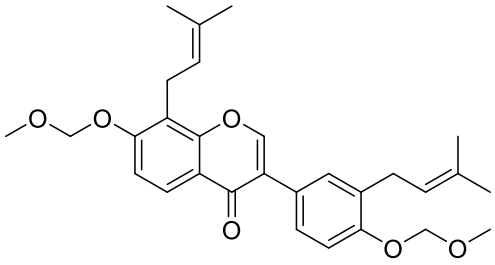
Following the general procedure 6, compound **122g** (210 mg, 0.65 mmol) was converted to 7-methoxyebenosin (**64**) (226 mg, 0.65 mmol, quant.); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): yellow oil; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.9 Hz, 1H), 7.98 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 5.21 (tm, *J* = 7.2 Hz, 1H), 3.96 (s, 3H), 3.84 (s, 3H), 3.56 (d, *J* = 7.2 Hz, 2H), 1.82 (s, 3H), 1.69 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.6, 161.0, 159.6, 155.2, 152.5, 132.6, 130.2 (2C), 125.4, 124.6, 124.2, 121.5, 118.7, 117.7, 114.1 (2C), 109.1, 56.3, 55.5, 25.9, 22.2, 18.0; IR (ATR) $\tilde{\nu}$ 2912 (w), 2838 (w), 1640 (m), 1511 (s), 1428 (m), 1265 (s), 1176 (s); HRMS (EI) calcd for $C_{22}H_{22}O_4$ [$M^+$] 350.1518, found 350.1532. Analytical data match those previously reported for the natural product.[134]

**7,4′-Dimethoxy-8-prenylflavone (127g)**



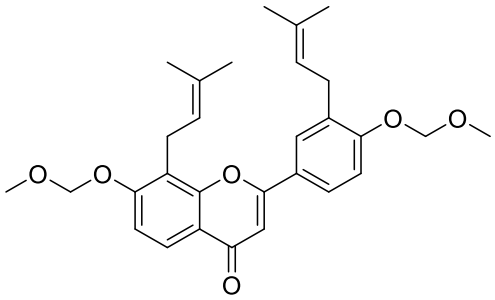
Following the general procedure 6, compound **123g** (55 mg, 0.17 mmol) was converted to **127g** (50 mg, 0.14 mmol, 84%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): colorless solid, m.p 162 – 163 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.9 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 1H), 6.72 (s, 1H), 5.25 (tm, *J* = 7.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.66 (d, *J* = 7.0 Hz, 2H), 1.83 (s, 3H), 1.69 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 178.5, 163.4, 162.4, 161.2, 155.2, 132.6, 128.1 (2C), 124.6, 124.6, 121.8, 121.8, 117.9, 114.6 (2C), 109.0, 105.5, 56.3, 55.6, 25.9, 22.6, 18.1; IR (ATR) $\tilde{\nu}$ 2847 (w), 1636 (s), 1595 (s), 1383 (s), 1262 (s), 1089 (s); HRMS (EI) calcd for $C_{22}H_{22}O_4$ [$M^+$] 350.1518, found 350.1515.

**7-(Methoxymethoxy)-3-[4-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl]-8-(3-methylbut-2-en-1-yl)-4*H*-chromen-4-one (126h)**



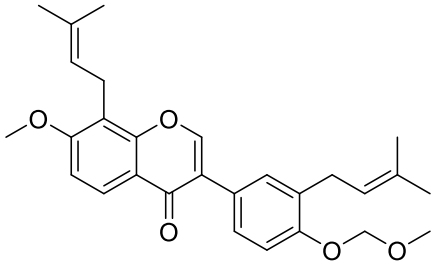
Following the general procedure 6, compound **122h** (300 mg, 0.70 mmol) was converted to **126h** (215 mg, 0.45 mmol, 64%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): yellow oil; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.14 (d, $J$ = 9.0 Hz, 1H), 7.98 (s, 1H), 7.36 (dd, $J$ = 8.9, 2.3 Hz, 1H), 7.35 (d, $J$ = 2.3 Hz, 1H), 7.19 (d, $J$ = 8.9 Hz, 1H), 7.12 (d, $J$ = 9.0 Hz, 1H), 5.33 (tm, $J$ = 7.2 Hz, 1H), 5.32 (s, 2H), 5.24 (s, 2H), 5.23 (tm, $J$ = 7.2 Hz, 1H), 3.59 (d, $J$ = 7.2 Hz, 2H), 3.50 (s, 3H), 3.49 (s, 3H), 3.39 (d, $J$ = 7.2 Hz, 2H), 1.84 (s, 3H), 1.73 (s, 3H), 1.73 (s, 3H), 1.69 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) $\delta$ 176.5, 158.6, 155.3, 155.0, 152.5, 132.6, 132.5, 131.0, 130.4, 127.8, 125.4, 125.2, 124.6, 122.7, 121.5, 119.5, 118.7, 113.9, 112.1, 94.5, 94.4, 56.4, 56.1, 29.0, 25.9, 25.9, 22.4, 18.0, 18.0; IR (ATR) $\tilde{\nu}$ 2962 (w), 2911 (w), 1643 (s), 1599 (m), 1431 (s), 1252(s), 1149 (s); HRMS (EI) calcd for $C_{29}H_{34}O_6$ [$M^+$] 478.2355, found 478.2339.

**7-(Methoxymethoxy)-2-[4-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl]-8-(3-methylbut-2-en-1-yl)-4*H*-chromen-4-one (127h)**



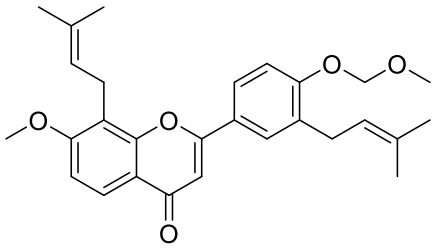
Following the general procedure 6, compound **123h** (140 mg, 0.33 mmol) was converted to **127h** (148 mg, 0.31 mmol, 94%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): colourless solid, m.p 81 – 82 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.04 (d, $J$ = 9.0 Hz, 1H), 7.74 (dd, $J$ = 9.0, 2.4 Hz, 1H), 7.73 (d, $J$ = 2.4 Hz, 1H), 7.20 – 7.13 (m, 2H), 6.69 (s, 1H), 5.35 - 5.28 (m, 2H), 5.31 (s, 2H), 5.28 (s, 2H), 3.68 (d, $J$ = 7.2 Hz, 2H), 3.50 (s, 3H), 3.50 (s, 3H), 3.40 (d, $J$ = 7.2 Hz, 2H), 1.84 (s, 3H), 1.76 (s, 3H), 1.73 (s, 3H), 1.68 (s, 3H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) $\delta$ 178.5, 163.4, 158.8, 157.7, 155.2, 133.8, 132.5, 131.6, 127.6, 125.5, 125.3, 124.4, 121.7, 121.6, 118.8, 118.8, 113.8, 111.9, 105.9, 94.5, 94.2, 56.4, 56.3, 28.7, 25.9, 25.9, 22.8, 18.1, 17.9; IR (ATR) $\tilde{\nu}$ 2912 (w), 1645 (s), 1597 (m), 1377 (s), 1256 (s), 1069 (s); HRMS (EI) calcd for $C_{29}H_{34}O_6$ [$M^+$] 478.2355, found 478.2343.

**7-Methoxy-3-(4-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)-8-(3-methylbut-2-en-1-yl)-4*H*-chromen-4-one (126i)**



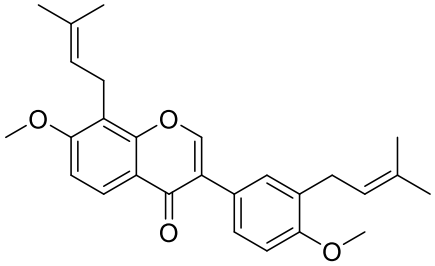
Following the general procedure 6, compound **122i** (150 mg, 0.38 mmol) was converted to **126i** (130 mg, 0.29 mmol, 76%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): yellow oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.9 Hz, 1H), 7.97 (s, 1H), 7.36 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 5.33 (tm, *J* = 7.3 Hz, 1H), 5.24 (s, 2H), 5.21 (tm, *J* = 7.1 Hz, 1H), 3.96 (s, 1H), 3.56 (d, *J* = 7.1 Hz, 2H), 3.49 (s, 1H), 3.39 (d, *J* = 7.3 Hz, 2H), 1.82 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.6, 161.0, 155.2, 155.0, 152.6, 132.6, 132.5, 131.0, 130.4, 127.8, 125.5, 125.4, 122.7, 121.5, 118.8, 117.7, 113.9, 109.1, 94.4, 56.2, 56.1, 29.0, 25.9, 25.9, 22.2, 18.0 (2C); IR (ATR) $\tilde{\nu}$ 2963 (w), 2911 (w), 1642 (s), 1598 (m), 1429 (s), 1265 (s), 1068 (s); HRMS (EI) calcd for $C_{28}H_{32}O_5$ [$M^+$] 448.2250, found 448.2249.

**7-Methoxy-2-(4-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)-8-(3-methylbut-2-en-1-yl)-4*H*-chromen-4-one (127i)**



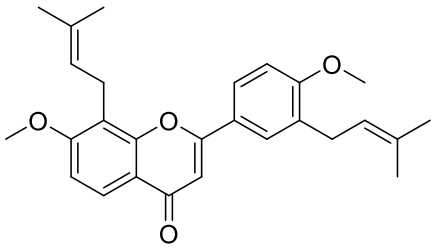
Following the general procedure 6, compound **123i** (205 mg, 0.52 mmol) was converted to **127i** (201 mg, 0.45 mmol, 86%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): colorless solid, m.p 91 − 92 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.74 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 9.0 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.70 (s, 1H), 5.33 (tm, *J* = 7.3 Hz, 1H), 5.29 (s, 2H), 5.27 (tm, *J* = 7.0 Hz, 1H), 3.96 (s, 3H), 3.66 (d, *J* = 7.0 Hz, 2H), 3.502 (s, 3H), 3.40 (d, *J* = 7.3 Hz, 2H), 1.82 (s, 3H), 1.77 (s, 3H), 1.74 (s, 3H), 1.68 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 178.7, 163.5, 161.2, 157.7, 155.1, 133.7, 132.6, 131.6, 127.7, 125.6, 125.4, 124.6, 121.7, 121.6, 118.0, 117.9, 113.8, 108.9, 105.7, 94.2, 56.3, 56.2, 28.7, 25.9 (2C), 22.5, 18.1, 17.9; IR (ATR) $\tilde{\nu}$ 2911 (w), 1636 (s), 1599 (m), 1376 (m), 1240 (m), 1072 (s); HRMS (EI) calcd for $C_{28}H_{32}O_5$ [$M^+$] 448.2250, found 448.2242.

**7,4′-Dimethoxy-8,3′-diprenylisoflavone (126j)**



Following the general procedure 6, compound **122j** (260 mg, 0.72 mmol) was converted to **126j** (286 mg, 0.68 mmol, 94%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): yellow solid, m.p 50 − 51 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.9 Hz, 1H), 7.97 (s, 1H), 7.41 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.34 (tm, *J* = 7.3 Hz, 1H), 5.22 (tm, *J* = 7.2 Hz, 1H), 3.96 (s, 1H), 3.86 (s, 1H), 3.56 (d, *J* = 7.2 Hz, 2H), 3.36 (d, *J* = 7.3 Hz, 2H), 1.83 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.70 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.7, 160.9, 157.4, 155.2, 152.5, 132.6, 132.6, 130.3, 130.1, 127.9, 125.4, 124.6, 124.2, 122.6, 121.6, 118.8, 117.7, 110.4, 109.1, 56.2, 55.6, 18.7, 16.0, 25.9, 22.2, 18.0, 18.0; IR (ATR) $\tilde{\nu}$ 2964 (w), 2911 (w), 1640 (s), 1500 (m), 1484 (s), 1264 (s), 1070 (s); HRMS (EI) calcd for $C_{27}H_{30}O_4$ [$M^+$] 418.2144, found 418.2137.

**7,4′-Dimethoxy-8,3′-diprenylflavone (127j)**



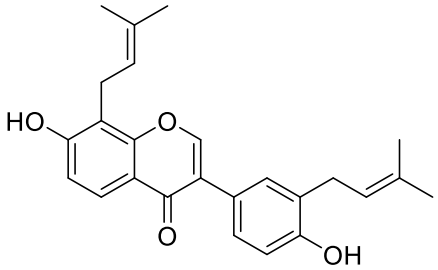
Following the general procedure 6, compound **123j** (95 mg, 0.26 mmol) was converted to **127j** (98 mg, 0.23 mmol, 88%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): colorless solid, m.p 144 − 145 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.9 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.4 Hz, 1H),7.72 (d, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 1H), 6.70 (s, 1H), 5.32 (tm, *J* = 7.4 Hz, 1H), 5.28 (tm, *J* = 7.1 Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.66 (d, *J* = 7.1 Hz, 2H), 3.38 (d, *J* = 7.4 Hz, 2H), 1.83 (s, 3H), 1.77 (s, 3H), 1.72 (s, 3H), 1.68 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 178.7, 163.7, 161.1, 160.2, 155.1, 133.9, 132.6, 131.0, 127.4, 125.7, 124.6, 121.8, 121.5, 118.0, 117.9, 110.4, 108.9, 105.5, 56.2, 55.7, 28.4, 25.9 (2C), 22.6, 18.1, 17.9; IR (ATR) $\tilde{\nu}$ 2963 (w), 2912 (w), 1642 (m), 1595 (s), 1375 (s), 1253 (s); HRMS (EI) calcd for $C_{27}H_{30}O_4$ [$M^+$] 418.2144, found 418.2143.

## 6.2.12 General Procedure 7 for MOM-Ether Cleavage

To a solution of the corresponding substrate **126** or **127** in methanol (10 mL) was added aqueous HCl (4 M, 3.0 equiv. per MOM-group) and the mixture was heated to reflux at 60 ºC for 2 h. The

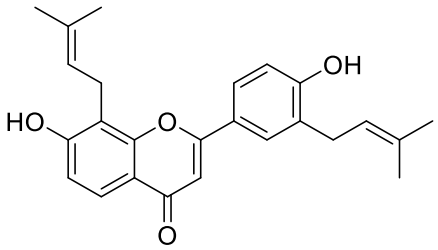
mixture was then cooled to ambient temperature, diluted with water (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane − EtOAc mixture (3:1 (v/v)) as eluent.

**Erysubin F (61)**




Following the general procedure 7, compound **126h** (180 mg, 0.38 mmol) was converted to erysubin F (**61**) (120 mg, 0.31 mmol, 81%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): yellow solid, m.p 162 – 163 ºC; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 9.47 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 7.93 (d, $J$ = 8.7 Hz, 1H), 7.38 (d, $J$ = 2.3 Hz, 1H), 7.30 (dd, $J$ = 8.4, 2.3 Hz, 1H), 7.03 (d, $J$ = 8.7 Hz, 1H), 6.88 (d, $J$ = 8.4 Hz, 1H), 5.38 (tm, $J$ = 7.4 Hz, 1H), 5.29 (tm, $J$ = 7.2 Hz, 1H), 3.57 (d, $J$ = 7.2 Hz, 1H), 3.36 (d, $J$ = 7.4 Hz, 2H), 1.83 (s, 3H), 1.73 (s, 3H), 1.70 (s, 3H), 1.66 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, acetone-$d_6$) $\delta$ 176.3, 160.1, 156.6, 155.7, 153.3, 132.5, 132.3, 131.2, 128.5, 128.5, 125.3, 125.0, 124.6, 123.8, 122.5, 118.8, 116.3, 115.5, 114.8, 29.2, 25.9, 25.9, 22.6, 18.0, 17.9; IR (ATR) $\tilde{\nu}$ 3245 (w), 2912 (w), 1616 (m), 1587 (m), 1430 (s), 1271 (s), 1159 (m); HRMS (EI) calcd for $C_{25}H_{26}O_4$ [$M^+$] 390.1831, found 390.1821. Analytical data match those previously reported for the natural product.[215]

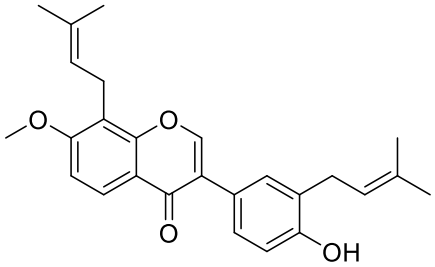
**7,4′-Dihydroxy-8,3′-diprenylflavone (129)**




Following the general procedure 7, compound **127h** (134 mg, 0.28 mmol) was converted to **129** (67 mg, 0.17 mmol, 61%); purification by column chromatography (hexane − EtOAc mixture 1:1 (v/v)): yellow solid, m.p 216 – 218 ºC; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 9.64 (s, 1H), 9.23 (s, 1H), 7.85 (d, $J$ = 8.7 Hz, 1H), 7.84 (d, $J$ = 2.3 Hz, 1H), 7.76 (dd, $J$ = 8.4, 2.3 Hz, 1H), 7.04 (d, $J$ = 8.4 Hz, 1H), 7.04 (d, $J$ = 8.7 Hz, 1H), 6.63 (s, 1H), 5.44 – 5.36 (m, 2H), 3.70 (d, $J$ = 7.2 Hz, 2H), 3.42 (d, $J$ = 7.2 Hz, 2H), 1.84 (s, 3H), 1.75 (s, 3H), 1.75 (s, 3H), 1.66 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, acetone-$d_6$) $\delta$ 178.1, 164.2, 160.4, 159.2, 156.5, 133.5, 132.6, 129.8, 128.6, 126.4, 124.6, 124.1, 122.9, 122.9, 118.0, 116.7, 116.3, 114.7, 106.2, 29.0, 25.9, 25.9, 23.0, 18.2, 17.9; IR (ATR) $\tilde{\nu}$ 3125

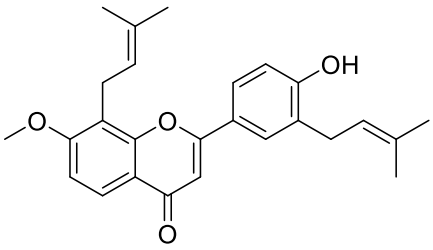
(w), 2912 (w), 1621 (m), 1561 (m), 1382 (s), 1255 (s); HRMS (EI) calcd for $C_{25}H_{26}O_4$ [$M^+$] 390.1831, found 390.1827.

**4′-Hydroxy-7-methoxy-8,3′-diprenylisoflavone (128)**



Following the general procedure 7, compound **126i** (105 mg, 0.23 mmol) was converted to **128** (70 mg, 0.17 mmol, 75%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): yellow solid, m.p 104 – 105 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.9 Hz, 1H), 7.97 (s, 1H), 7.27 (d, *J* = 2.3 Hz, 1H), 7.23 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.18 (s, 1H), 5.35 (tm, *J* = 7.2 Hz, 1H), 5.21 (tm, *J* = 7.1 Hz, 1H), 3.96 (s, 1H), 3.56 (d, *J* = 7.1 Hz, 2H), 3.37 (d, *J* = 7.2 Hz, 2H), 1.82 (s, 3H), 1.76 (s, 6H), 1.69 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 177.0, 161.1, 155.3, 154.7, 152.7, 134.3, 132.6, 130.6, 128.2, 127.5, 125.4, 124.7, 124.0, 122.2, 121.5, 118.7, 117.7, 116.0, 109.2, 56.3, 29.7, 25.9, 25.9, 22.2, 18.0, 18.0; IR (ATR) $\tilde{\nu}$ 3264 (w), 2913 (w), 1619 (s), 1591 (m), 1428 (s), 1266 (s), 1070 (m); HRMS (EI) calcd for $C_{26}H_{28}O_4$ [$M^+$] 404.1988, found 404.1983.

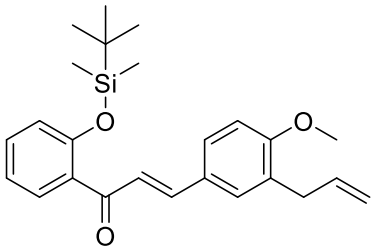
**4′-Hydroxy-7-methoxy-8,3′-diprenylflavone (130)**



Following the general procedure 7, compound **127j** (150 mg, 0.33 mmol) was converted to **130** (100 mg, 0.25 mmol, 75%); purification by column chromatography (hexane − EtOAc mixture 1:1 (v/v)): colorless solid, m.p, 189 − 190 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.29 (s, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 2.5 Hz, 1H),7.72 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.70 (s, 1H), 5.30 (t, *J* = 7.6 Hz, 1H), 5.20 (t, *J* = 7.2 Hz, 1H), 3.91 (s, 1H), 3.55 (d, *J* = 7.2 Hz, 2H), 3.27 (d, *J* = 7.6 Hz, 2H), 1.74 (s, 3H), 1.69 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) δ 176.8, 162.9, 160.6, 158.6, 154.1, 132.3, 131.9, 128.4, 127.4, 125.7, 123.9, 122.1, 121.9, 121.5, 117.3, 117.0, 115.4, 109.4, 104.1, 56.4, 28.0, 25.5, 25.5, 22.0, 17.8, 17.6; IR (ATR) $\tilde{\nu}$ 3191 (w), 2912 (w), 1625 (m), 1597 (s), 1383 (s), 1267 (s), 1092 (s); HRMS (ESI) calcd for $C_{26}H_{29}O_4$ [M+H]$^+$ 405.2066, found 405.2076.

### 6.2.13 Attempted Synthesis of an Enol Silyl Ether

**(E)-3-(3-Allyl-4-methoxyphenyl)-1-(2-((tert-butyldimethylsilyl)oxy)phenyl)prop-2-en-1-one (125)**



To a solution of **107ba** (150 mg, 0.5 mmol) in $CH_3CN$ (5 mL) was added triethylamine (TEA) (300 µL, 2.2 mmol) under nitrogen atmosphere and the mixture stirred at 20 °C for 5 minutes. To the mixture was then added tert-butyldimethylsilyl chloride (TBSCl) (165 mg, 1.1 mmol) and NaI (165 mg, 1.1 mmol) and the mixture was stirred at 20 °C for 24 h. The reaction was quenched with aqueous $NaHCO_3$ (15 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The organic extract was dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane − EtOAc mixture (3:1 (v/v)) as eluent to afford **125** (100 mg, 0.25 mmol, 50%): yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.57(d, *J* = 16.0 Hz, 1H), 7.51 (d, *J* = 15.3 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.34 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.20 (d, *J* = 16.0 Hz, 1H), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H), 6.90 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 5.98 (*m*, 1H), 5.11 (d, *J* = 1.5 Hz, 1H), 5.06 (dd, *J* = 3.3, 1.2 Hz, 1H), 3.87 (*s*, 3H), 3.40 (d, *J* = 6.9 Hz, 2H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 194.0, 159.4, 143.6, 136.4, 132.8, 132.2, 130.3, 129.7, 129.3, 127.5, 124.9, 121.6, 120.5, 116.1, 110.5, 55.6, 34.2, 25.8 (3C), 18.3, -4.1; IR (ATR) $\tilde{\nu}$ 2954 (w), 2929 (w), 1658 (w), 1596 (s), 1250 (w), 1023 (m); LRMS (EI) gave $C_{25}H_{32}O_3Si$ $[M\text{-}C(CH_3)_3]^+$, 351.

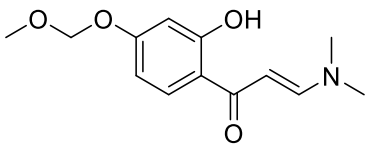
## 6.3 Synthesis of Isoflavones via Suzuki-Miyaura Cross-Coupling Reactions

### 6.3.1 General Procedure 8 for the Synthesis of Enamino ketones 103[84,184]

To a solution of the appropriate acetophenone **109** (10.0 or 20 mmol) in dry *N*,*N*-dimethylformamide (DMF) (100 or 200 mL) heated to 70 °C was added *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) (5.0 equiv.) dropwise and the mixture was stirred at 70 °C for 5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to ambient temperature and water (300 mL) was added. The solution was extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with water, dried with

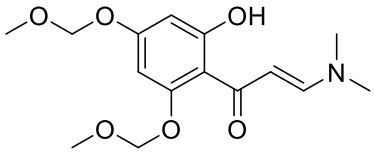
anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixtures of varying polarity (3:1 to 3:2 (v/v)) as eluent to afford the respective enamino ketone **103**.

**(E)-3-(Dimethylamino)-1-(2-hydroxy-4-(methoxymethoxy)phenyl)prop-2-en-1-one (103a)**



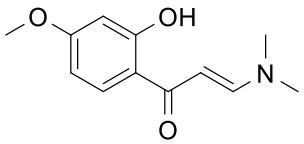
Following the general procedure 8, compound **109a** (3.95 g, 20.0 mmol) was converted to **103a** (4.02 g, 16.0 mmol, 80%); purification by column chromatography (hexane – EtOAc mixture 3:1 (v/v)): yellow crystals, m.p 89 – 90 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 14.33 (s, 1H), 7.81 (d, *J* = 12.1 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.46 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.65 (d, *J* = 12.1 Hz, 1H), 5.16 (s, 2H), 3.45 (s, 3H), 3.14 (s, 3H), 2.92 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 190.7, 165.2, 161.8, 154.7, 129.8, 115.0, 107.1, 104.1, 94.1, 89.9, 56.3, 45.4, 37.4; IR (ATR) $\tilde{\nu}$ 2907 (w), 1618 (s), 1581 (m), 1487 (s), 1139 (m); HRMS (EI) calcd for $C_{13}H_{17}NO_4$ [$M^+$] 251.1158, found 251.1150.

**(E)-3-(Dimethylamino)-1-(2-hydroxy-4,6-bis(methoxymethoxy)phenyl)prop-2-en-1-one (103b)**



Following the general procedure 8, compound **109c** (2.57 g, 10.0 mmol) was converted to **103b** (2.98 g, 9.58 mmol, 96%): purification by column chromatography (hexane – EtOAc mixture 3:2 (v/v)): yellow crystals, m.p 98 – 99 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 15.08 (s, 1H), 7.91 (d, *J* = 12.3 Hz, 1H), 6.28 (d, *J* = 12.3 Hz, 1H) 6.26 (d, *J* = 2.3 Hz, 1H), 6.16 (d, *J* = 2.3 Hz, 1H), 5.20 (s, 2H), 5.14 (s, 2H), 3.51 (s, 3H), 3.45 (s, 3H), 3.14 (s, 3H), 2.91 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 190.1, 167.0, 161.4, 159.0, 154.6, 107.1, 98.0, 97.0, 95.3, 94.6, 94.1, 56.8, 56.4; IR (ATR) $\tilde{\nu}$ 3163 (w), 2911 (w), 1582 (s), 1533 (s), 1353 (s), 1227 (s), 1145 (s); HRMS (EI) calcd for $C_{15}H_{21}NO_6$ [$M^+$] 311.1369, found 311.1357.

**(E)-3-(Dimethylamino)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one (103c)**

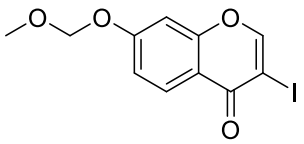


Following the general procedure 8, compound **109e** (3.32 g, 20.0 mmol) was converted to **103c** (3.51 g, 15.8 mmol, 79%); purification by column chromatography (hexane – EtOAc mixture 3:1 (v/v)): yellow crystals, m.p 142 – 143 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 14.47 (s, 1H), 7.82 (d, *J* = 12.1 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 6.40 (d, *J* = 2.6 Hz, 1H), 6.37 (dd, *J* = 8.8, 2.6 Hz, 1H), 5.66 (d, *J* = 12.1 Hz, 1H), 3.80 (s, 3H), 3.15 (s, 3H), 2.94 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 190.7, 165.7, 164.5, 154.1, 129.8, 114.0, 106.5, 101.2, 89.9, 55.5, 45.4, 37.5; IR (ATR) $\tilde{\nu}$ 2925 (w), 1580 (m), 1538 (m), 1441 (m), 1271 (s); HRMS (ESI) calcd for $C_{12}H_{16}NO_3$ $[M+H]^+$ 222.1130, found 222.1131.

## 6.3.2 General Procedure 9 for the Synthesis of 3-Iodochromones 104[84,184]

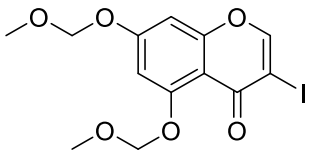
To a solution of the appropriate enamino ketone **103** (5.0 mmol) in MeOH (100 mL) was added solid iodine (1.91 g, 7.5 mmol) and the mixture was stirred at 20 °C for 7 h. After completion of the reaction, a saturated aqueous solution of $Na_2S_2O_3$ was added to the mixture until the mixture was clear. The mixture was then concentrated under reduced pressure and water (100 ml) was added. The mixture was extracted with $CH_2Cl_2$ (3 x 60 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (7:3 (v/v)) as eluent to afford the corresponding 3-iodochromone **104**.

**3-Iodo-7-(methoxymethoxy)-4*H*-chromen-4-one (104a)**



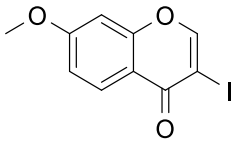
Following the general procedure 9, compound **103a** (1.26 g, 5.0 mmol) was converted to **104a** (1.36 g, 4.1 mmol, 82%); purification by column chromatography (hexane – EtOAc mixture 7:3 (v/v)): colorless crystals, m.p 110 – 111 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.08 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.05 (d, *J* = 2.5 Hz, 1H), 5.26 (s, 2H), 3.49 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 172.8, 161.9, 157.8, 157.5, 128.2, 116.5, 116.3, 103.1, 94.5, 87.1, 56.6; IR (ATR) $\tilde{\nu}$ 3062 (w), 2879 (w), 1622 (s), 1439 (m), 1144 (s), 1058 (m); HRMS (ESI) calcd for $C_{11}H_{10}O_4I$ $[M+H]^+$ 332.9624, found 332.9641.

**3-Iodo-5,7-bis(methoxymethoxy)-4*H*-chromen-4-one (104b)**



Following the general procedure 9, compound **103b** (1.56 g, 5.0 mmol) was converted to **104b** (1.29 g, 3.3 mmol, 66%); purification by column chromatography (hexane – EtOAc mixture 7:3 (v/v)): colorless crystals, m.p 139 – 140 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 6.74 (d, *J* = 2.3 Hz, 1H), 6.71 (d, *J* = 2.3 Hz, 1H), 5.29 (s, 2H), 5.22 (s, 2H), 3.53 (s, 3H), 3.48 (s, 3H); $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 171.3, 161.7, 159.3, 158.3, 155.8, 108.9, 102.2, 96.9, 95.6, 94.5, 89.5, 56.8, 56.7; IR (ATR) $\tilde{\nu}$ 3058 (w), 2903 (w), 1620 (s), 1434 (m), 1274 (s), 1138 (s); HRMS (ESI) calcd for $C_{13}H_{13}O_6NaI$ $[M+Na]^+$ 414.9655, found 414.9646.

**3-Iodo-7-methoxy-4*H*-chromen-4-one (104c)**



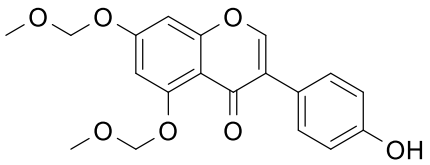
Following the general procedure 9, compound **103c** (1.11 g, 5.0 mmol) was converted to **104c** (1.30 g, 4.3 mmol, 86%); purification by column chromatography (hexane – EtOAc mixture 3:1 (v/v)): colorless crystals, m.p 163 – 164 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 6.98 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 3.90 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 172.7, 164.4, 158.1, 157.3, 128.2, 115.8, 115.4, 100.2, 87.3, 56.0; IR (ATR) $\tilde{\nu}$ 3063 (w), 2963 (w), 1608 (m), 1430 (m), 1258 (s), 1015 (s); HRMS (ESI) calcd for $C_{10}H_8O_3I$ $[M+H]^+$ 302.9518, found 302.9507.

### 6.3.3 Optimization of Suzuki-Miyaura Cross-Coupling Reaction

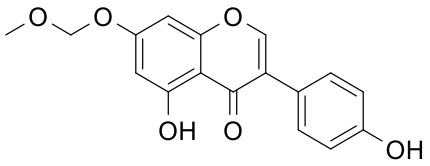
**Procedure A:**[84] Polyethylene glycol (PEG10000) (2.8 g) ground to a fine consistence and $Pd(OAc)_2$ (4 mg, 0.015 mmol, 5 mol-%) were added to a stirred mixture of $Na_2CO_3$ (80 mg, 0.75 mmol) and methanol (5 mL). The mixture was warmed to 50 ºC. When the mixture had turned black, **104b** (120 mg, 0.3 mmol) and 4-hydroxyphenylboronic acid (**134a**) (125 mg, 0.9 mmol) were added and the mixture was stirred at 50 ºC for 3 h. After the reaction, the mixture was cooled to ambient temperature and diethyl ether (10 mL) was added. The mixture was filtered, and the residue was washed with diethyl ether (3 x 10 mL). The combined organic extract was concentrated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (3:1 (v/v)) as eluent to afford **133bb** in an inseparable mixture (detected

by $^{1}H$ and $^{13}C\{^{1}H\}$ NMR spectroscopy). **Procedure B:**[180] To a suspension of **104b** (395 mg, 1.0 mmol), **134a** (186 mg, 1.35 mmol) and $K_2CO_3$ (545 mg, 4.0 mmol) in ethanol – water mixture (1:1 (v/v)) (10 mL) was added 10% Pd/C (20 mg, 2 mol-%). The mixture was heated to 80 ºC and it was stirred at 80 ºC for 3 h. The mixture was then cooled to ambient temperature and quenched with aqueous HCl (1M, 3.0 mL). The mixture was extracted with MTBE (3 x 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixtures of increasing polarity (3:2 to 1:1 (v/v)) as eluent to afford **133b** (110 mg, 0.31 mmol, 31%) and **133bb** (32 mg, 0.10 mmol, 10%). This procedure was repeated, increasing the reaction time to 5 h. This afforded **133b** (75 mg, 0.21 mmol, 21%) and **133bb** (95 mg, 0.30 mmol, 30%). The reaction was repeated following the same procedure but replacing $K_2CO_3$ by KF (3.0 equiv.) as base. The reaction was run for 3 h and it afforded **133b** (43 mg, 0.12 mmol, 12%) and **133bb** (70 mg, 0,22 mmol, 22%). **Procedure C:**[179,180] To a solution of **104b** (196 mg, 0.50 mmol) in 1,4-dioxane (5 mL) was added $K_2CO_3$ (280 mg, 2.00 mmol), **134a** (93 mg, 0.68 mmol) and 10% Pd/C (10 mg, 2 mol-%). The mixture was heated to reflux at 110 ºC for 24 h. The mixture was then cooled to ambient temperature and filtered. The solvent was evaporated, and water (20 mL) was added to the residue. The mixture was neutralized with aqueous HCl (1M, 2 mL) and then extracted with MTBE (3 x 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixtures of increasing polarity (3:2 to 1:1 (v/v)) as eluent to afford **133b** (95 mg, 0.27 mmol, 54%). **Procedure D:**[179] To a solution of **104b** (196 mg, 0.50 mmol) in dry 1,4-dioxane (5 mL) was added $K_2CO_3$ (280 mg, 2.00 mmol) and **134a** (138 mg, 1.00 mmol). The mixture was stirred at ambient temperature under nitrogen atmosphere for 20 minutes. $Pd(PPh_3)_4$ (29 mg, 5 mol-%) was added to the mixture and the mixture was heated to reflux at 110 ºC for 24 h. The mixture was then cooled to ambient temperature and filtered. The solvent was evaporated, and water (20 mL) was added to the residue. The mixture was neutralized with aqueous HCl (1M, 2 mL) and then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixtures of increasing polarity (3:2 to 1:1 (v/v)) as eluent to afford **133b** (121 mg, 0.34 mmol, 68%). **Procedure E:**[178] To a solution of

**104b** (395 mg, 1.0 mmol) in 1,4-dioxane (7 mL) was added water (3 mL), $K_2CO_3$ (420 mg, 3.0 mmol) and **134a** (280 mg, 2.00 mmol). The mixture was stirred at ambient temperature under nitrogen atmosphere for 10 minutes. To the mixture was then successively added tricyclohexylphosphine [$PCy_3$] (23 mg, 8 mol-%) and bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$] (23 mg, 4 mol-%) and the mixture was warmed to 50 ºC. The mixture was stirred at 50 ºC for 1 h. The mixture was then cooled to ambient temperature and a saturated aqueous solution of $NH_4Cl$ (10 mL) was added. The mixture was filtered. The residue was dissolved in EtOAc (40 mL), partitioned with water (50 mL) and the organic phase was separated off. The combined aqueous phase was extracted with EtOAc (40 mL). The combine organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (1:1 (v/v)) as eluent to afford **133b** (324 mg, 0.91 mmol, 91%).



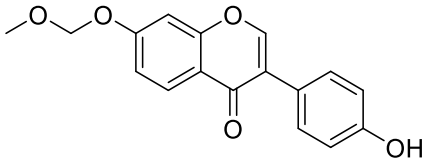
*Analytical data for 3-(4-hydroxyphenyl)-5,7-bis(methoxymethoxy)-4H-chromen-4-one (**133b**)*: colorless solid, m.p 157 – 159 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.52 (s, 1H), 8.16 (s, 1H), 7.32 (d, $J$ = 8.6 Hz, 2H), 6.80 (d, $J$ = 2.4 Hz, 1H), 6.79 (d, $J$ = 8.6 Hz, 2H), 6.68 (d, $J$ = 2.4 Hz, 1H), 5.31 (s, 2H), 5.26 (s, 2H), 3.43 (s, 3H), 3.41 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) δ 173.9, 160.5, 158,7, 157.9, 157.2, 151.0, 130.3, (2C), 124.9, 122.5, 114.9, (2C), 110.4, 101.4, 96.7, 95.2, 94.1, 56.2, 56.1; IR (ATR) $\tilde{\nu}$ 3277 (w), 1637 (m), 1607 (s), 1137 (s), 1037 (s); HRMS (EI) calcd for $C_{19}H_{18}O_7$ [$M^+$] 358.1053, found 358.1049.



*Analytical data for 5-hydroxy-3-(4-hydroxyphenyl)-7-(methoxymethoxy)-4H-chromen-4-one (**133bb**)*: colorless solid, m.p 224 – 226 ºC; $^1$H NMR (300 MHz, acetone-$d_6$) δ 12.98 (s, 1H), 8.22 (s, 1H), 7.46 (d, $J$ = 8.6 Hz, 2H), 6.91 (d, $J$ = 8.6 Hz, 2H), 6.62 (d, $J$ = 2.4 Hz, 1H), 6.44 (d, $J$ = 2.4 Hz, 1H), 5.32 (s, 2H), 3.48 (s, 3H); $^{13}$C{$^1$H} NMR (75 MHz, acetone-$d_6$) δ 181.9, 164.1, 163.5, 163.2, 158.5, 154.7, 131.2, 128.2, 122.9, 116.4, 116.0, 100.3, 95.1, 95.0, 56.6; IR (ATR) $\tilde{\nu}$ 3326 (m), 1652 (m), 1613 (s), 1513 (s), 1470 (s), 1210 (s), 1144 (s); HRMS (EI) calcd for $C_{17}H_{14}O_6$ [$M^+$] 314.0790, found 314.0791.

### 6.3.4 General Procedure 10 for the Suzuki-Miyaura Cross-Coupling Reacctions under Optimized Conditions

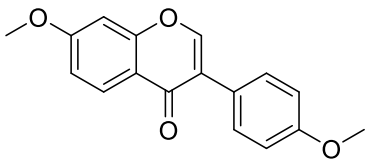
To a solution of the appropriate 3-iodochromone **104** (1.0 mmol) in 1,4-dioxane – water mixture (7:3 (v/v)) (10 mL) was added $K_2CO_3$ (420 mg, 3.0 mmol) and the appropriate phenylboronic acid **134** (2.0 mmol). The mixture was purged with nitrogen for 10 minutes. To the mixture was then successively added $PCy_3$ (23 mg, 8 mol-%) and $Pd(dba)_2$ (23 mg, 4 mol-%). The mixture was warmed to 50 ºC and then stirred at 50 ºC for 1 h. The mixture was then cooled to ambient temperature. A saturated aqueous solution of $NH_4Cl$ (10 mL) was added to the mixture and the mixture was filtered. The residue was dissolved in EtOAc (30 mL), and the solution was partitioned with water (50 mL). The organic phase was separated off and the combined aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (3:2 (v/v)) as eluent to afford the corresponding isflavone **77a**, **101** or **133**.




**3-(4-Hydroxyphenyl)-7-(methoxymethoxy)-4*H*-chromen-4-one (133a)**

Following the general procedure 10, compounds **104a** (335 mg, 1.0 mmol) and **134a** (280 mg, 2.0 mmol) were reacted to **133a** (287 mg, 0.96 mmol, 96%); purification by column chromatography (hexane – EtOAc mixture 3:2 (v/v)): colorless solid, m.p 165 – 167 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.59 (s, 1H), 8.24 (s, 1H), 8.04 (d, $J$ = 8.8 Hz, 1H), 7.39 (d, $J$ = 8.7 Hz, 2H), 7.18 (d, $J$ = 2.3 Hz, 1H), 7.13 (dd, $J$ = 8.8, 2.3 Hz, 1H), 6.81 (d, $J$ = 8.7 Hz, 2H), 5.34 (s, 2H), 3.41 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$) δ 174.9, 161.0, 157.3, 157.1, 153.3, 130.2 (2C), 127.2, 123.8, 122.4, 118.4, 115.5, 115.1 (2C), 103.1, 94.1, 56.1; IR (ATR) $\tilde{\nu}$ 3276 (m), 2919 (w), 1637 (s), 1607 (s), 1253 (m), 1138 (s), 1037 (s); HRMS (ESI) calcd for $C_{17}H_{15}O_5$ $[M+H]^+$ 299.0919, found 299.0933.

**Dimethyldaidzein (77a)**



Following the general procedure 10, compounds **104c** (305 mg, 1.0 mmol) and **134b** (305 mg, 2.0 mmol) were reacted to dimthyldaidzein (**77a**) (198 mg, 0.7 mmol, 70%); purification by column chromatography (hexane – EtOAc mixture 3:2 (v/v)): colorless solid, mp 155 – 156 °C; $^{1}$H NMR (400MHz, DMSO-$d_6$) δ 8.41 (s, 1H), 8.03 (d, $J$ = 8.9 Hz, 1H), 7.52 (d, $J$ = 8.7 Hz, 2H), 7.15 (d, $J$ = 2.4 Hz, 1H), 7.08 (dd, $J$ = 8.9, 2.4 Hz, 1H), 6.99 (d, $J$ = 8.7 Hz, 2H), 3.90 (s, 3H), 3.79 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, DMSO-$d_6$) δ 174.7, 163.7, 159.0, 157.5, 153.5, 130.1 (2C), 127.0, 124.1, 123.4, 117.6, 114.8, 113.6 (2C), 100.6, 56.1, 55.2; IR (ATR) $\tilde{\nu}$ 2957 (w), 1621 (s), 1592 (m), 1436 (m), 1247 (s); HRMS (ESI) calcd for $C_{17}H_{15}O_4$ $[M+H]^+$ 283.0970, found 283.0963. Analytical data match those previously reported for the natural product.[223]

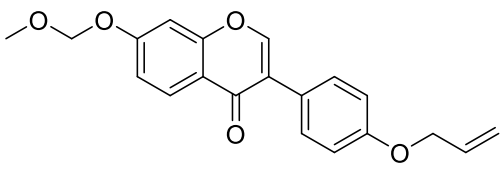
**Isoformononetin (101)**

Following the general procedure 10, compounds **104c** (305 mg, 1.0 mmol) and **134a** (280 mg, 2.0 mmol) were reacted to isoformononetin (**101**) (236 mg, 0.88 mmol, 88%); purification by column chromatography (hexane – EtOAc mixture 3:2 (v/v)).

### 6.3.5 General Procedure 11 for the Synthesis of 4′-Allyloxyisoflavones 135

To a solution of the appropriate isoflavone **101** or **133** (2.0 mmol) in acetone (20 mL) was added $K_2CO_3$ (552 mg, 4.0 mmol) and the mixture was heated to 65 °C. To the mixture was then added allyl bromide (0.25 mL, 3.0 mmol) and the mixture was refluxed at 65 °C for 7 h. The mixture was then cooled to ambient temperature and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (2:1 (v/v)) as eluent to afford the respective 4′-allyloxyisoflavone **135**.

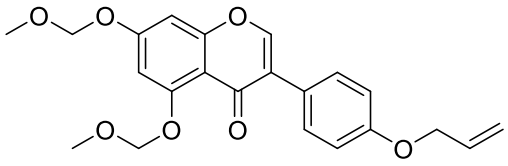
**3-(4-(Allyloxy)phenyl)-7-(methoxymethoxy)-4*H*-chromen-4-one (135a)**



Following the general procedure 11, compound **133a** (600 mg, 2.0 mmol) was converted to **135a** (617 mg, 1.83 mmol, 92%); purification by column chromatography (hexane − EtOAc mixture 2:1 (v/v)):

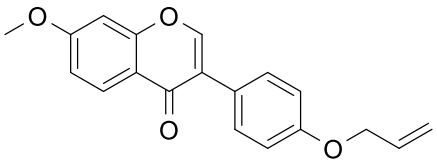
colorless solid, m.p 107 − 108 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.4 Hz, 1H), 7.92 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.09-7.06 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.07 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.43 (dm, *J* = 17.2 Hz, 1H), 5.30 (dm, *J* = 10.5 Hz, 1H), 5.27 (s, 2H), 4.57 (dt, *J* = 5.3, 1.6 Hz, 2H), 3.51 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.0, 161.5, 158.7, 157.7, 152.4, 133.3, 130.2 (2C), 127.9, 124.9, 124.5, 119.3, 117.8, 115.6, 114.9 (2C), 103.2, 94.5, 69.0, 56.5; IR (ATR) $\tilde{\nu}$ 2907 (w), 1623 (s), 1509 (m), 1443 (m), 1229 (m), 1151 (m); HRMS (EI) calcd for $C_{20}H_{18}O_5$ [$M^+$] 338.1154, found 338.1167.

**3-(4-(Allyloxy)phenyl)-5,7-bis(methoxymethoxy)-4*H*-chromen-4-one (135b)**



Following the general procedure 11, compound **133b** (720 mg, 2.0 mmol) was converted to **135b** (792 mg, 2.0 mmol, quant.); purification by column chromatography (hexane − EtOAc mixture 2:1 (v/v)): colorless solid, m.p 96 − 97 °C; $^{1}$H NMR (400 MHz, acetone-$d_6$) δ 8.03 (s, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.72 (d, *J* = 2.3 Hz, 1H), 6.09 (ddt, *J* = 17.3, 10.6, 5.3 Hz, 1H), 5.43 (dm, *J* = 17.3 Hz, 1H), 5.32 (s, 2H), 5.27 (s, 2H), 5.26 (dm, *J* = 10.6 Hz, 1H), 4.61 (dt, *J* = 5.3, 1.6 Hz, 2H), 3.51 (s, 3H), 3.48 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, acetone-$d_6$) δ 174.7, 162.0, 160.1, 159.5, 159.3, 151.6, 134.7, 131.2 (2C), 126,2, 125.8, 117.4, 115.1 (2C), 112.1, 103.0, 97.8, 96.6, 95.2, 69.3, 56.7, 56.6; IR (ATR) $\tilde{\nu}$ 2912 (w), 1651 (s), 1607 (s), 1510 (m), 1282 (m), 1220 (s); HRMS (EI) calcd for $C_{22}H_{22}O_7$ [$M^+$] 398.1366, found 398.1350.

**3-(4-(Allyloxy)phenyl)-7-methoxy-4*H*-chromen-4-one (133c)**



Following the general procedure 11, isoformononetin (**101**) (536 mg, 2.0 mmol) was converted to **135c** (615 mg, 2.0 mmol, quant.); purification by column chromatography (hexane − EtOAc mixture 2:1 (v/v)): colorless solid, m.p, 140 – 141 °C; $^{1}$H NMR (400 MHz, acetone-$d_6$) δ 8.21 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.05 (dd, *J* = 8.7, 2.5Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.09 (ddt, *J* = 17.3, 10.6, 5.2 Hz, 1H), 5.43 (dm, *J* = 17.3 Hz, 1H), 5.26 (dm, *J* = 10.6 Hz, 1H), 4.61 (d, *J* = 5.2 Hz, 2H), 3.96 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, acetone-$d_6$) δ 175.6, 165.0, 159.4, 158.8, 153.6, 134.7, 131.0 (2C), 128.1, 125.6, 125.1, 119.1, 117.4, 115.4, 115.2 (2C), 101.1, 69.3, 56.4; IR (ATR) $\tilde{\nu}$ 2912 (w), 1622

(s), 1510 (m), 1441 (m), 1260 (m), 1106 (m); HRMS (EI) calcd for $C_{19}H_{16}O_4$ [$M^+$] 308.1049, found 308.1061.

## 6.3.6 Claisen Rearrangement of 4′-Allyloxyisoflavones 135

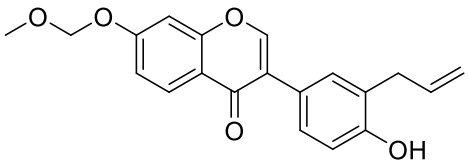
### 6.3.6.1 Attempted Claisen Rearrangement of 135b Using DMF as a Solvent

A solution of **135b** (400 mg, 1.0 mmol) in dry DMF (10 mL) was placed in a vessel suited for microwave irradiation. The vessel was sealed and irradiated in a microwave reactor at 250°C for 30 minutes. After the reaction, the reaction mixture was transferred into a flask, water (50 mL) was added, and the solution was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using with hexane − EtOAc mixtures of increasing polarity (5:1 to 3:1 (v/v)) to afford a mixture of substances which could not be further separated.

### 6.3.6.2 General Procedure 12 for the Synthesis of 3′-Allylisoflavones 136

A solution of **135** (1.0 mmol) in *N*,*N*-dimethylaniline (DMA) (10 mL) was placed in a vessel suited for microwave irradiation. The vessel was sealed and irradiated in a microwave reactor at 250 °C for 30 minutes. After the reaction, the solution was transferred into a flask and diluted with EtOAc (120 mL). The solution was then washed with aqueous HCl (1M, 3 x 40 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica using hexane − EtOAc mixture (3:1 (v/v)) as eluent to afford the respective 3′-allylisoflavone **136**.

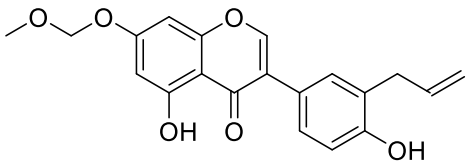
**3-(3-Allyl-4-hydroxyphenyl)-7-(methoxymethoxy)-4*H*-chromen-4-one (136a)**




Following the general procedure 12, compound **135a** (340 mg, 1.0 mmol) was converted to **136a** (227 mg, 0.67 mmol, 67%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): colorless solid, m.p 173 – 174 °C; $^1$H NMR (400 MHz, acetone-$d_6$) δ 8.41 (s, 1H), 8.18 (s, 1H), 8.12 (d, *J* = 9.6 Hz, 1H), 7.38 (d, *J* = 2.3 Hz, 1H), 7,33 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.13 (d, *J* = 2.3 Hz, 1H), 7.12 (dd, *J* = 9.6, 2.3 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.05 (ddt, *J* = 17.1, 10.1, 6.6 Hz, 1H), 5.37 (s, 2H), 5.10 (dm, *J* = 17.1 Hz, 1H), 5.00 (dm, *J* = 10.1 Hz,

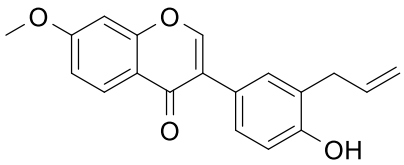
1H), 3.49 (s, 3H), 3.42 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-$d_6$) δ 175.7, 162.3, 158.4, 155.7, 153.5, 138.0, 131.5, 128.9, 128.2, 127.1, 125.5, 124.4, 119.9, 116.2, 115.6, 115.6, 103.9, 95.2, 56.5, 35.0; IR (ATR) $\tilde{\nu}$ 3312 (m), 2892 (w), 1595 (s), 1439 (m), 1251 (s), 1155 (m), 1071 (m); HRMS (EI) calcd for $C_{20}H_{18}O_5$ [$M^+$] 338.1154, found 338.1157.

**3-(3-Allyl-4-hydroxyphenyl)-5-hydroxy-7-(methoxymethoxy)-4*H*-chromen-4-one (136b)**



Following the general procedure 12, compound **135b** (400 mg, 1.0 mmol) was converted to **136b** (238 mg, 0.67 mmol, 67%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): colorless solid, m.p 167 – 168 °C; $^{1}H$ NMR (400 MHz, acetone-$d_6$) δ 12.99 (s, 1H), 8.48 (s, 1H), 8.20 (s, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7,32 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 2.2 Hz, 1H), 6.43 (d, *J* = 2.2 Hz, 1H), 6.04 (ddt, *J* = 17.0, 10.1, 6.6 Hz, 1H), 5.32 (s, 2H), 5.10 (dm, *J* = 17.0 Hz, 1H), 5.01 (dm, *J* = 10.1 Hz, 1H), 3.48 (s, 3H), 3.42 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-$d_6$) δ 181.9, 164.1, 163.5, 158.7, 156.0, 154.7, 137.9,131.6, 129.0, 127.3, 124.4, 123.1, 115.7, 115.6, 107.3, 100.3, 95.1, 94.9, 56.6, 34.9; IR (ATR) $\tilde{\nu}$ 3377 (s), 2909 (w), 1645 (s), 1569 (m), 1250 (m), 1139 (s); HRMS (EI) calcd for $C_{20}H_{18}O_6$ [$M^+$] 354.1103, found 354.1115.

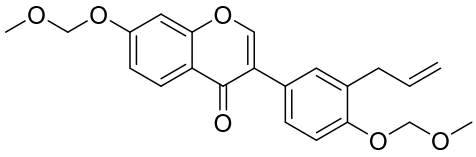
**3-(3-Allyl-4-hydroxyphenyl)-7-methoxy-4*H*-chromen-4-one (136c)**



Following the general procedure 12, compound **135c** (310 mg, 1.0 mmol) was converted to **136c** (203 mg, 0.66 mmol, 66%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): colorless solid, m.p 200 − 201 °C; $^{1}H$ NMR (400 MHz, DMSO-$d_6$) δ 9.55 (s, 1H), 8.32 (s, 1H), 8.01 (d, *J* = 8.9 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 7,24 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 5.97 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.06 (dm, *J* = 17.0 Hz, 1H), 5.01 (dm, *J* = 10.2 Hz, 1H), 3.89 (s, 3H), 3.32 (d, *J* = 6.7 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-$d_6$) δ 174.8, 163.7, 157.5, 154.9, 153.1, 137.0, 130.0, 127.8, 127.0, 125.8, 123.9, 122.5, 117.7, 115.5, 114.8, 114.7, 100.5, 56.1, 33.9; IR (ATR) $\tilde{\nu}$ 3278 (m), 1624 (s), 1439 (m), 1262 (s); HRMS (EI) calcd for $C_{19}H_{16}O_4$ [$M^+$] 308.1049, found 308.1056.

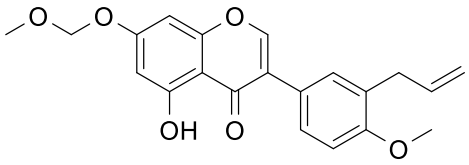
### 6.3.7 MOM-Protection and Methylation of Isoflavones 136

**3-(3-Allyl-4-(methoxymethoxy)phenyl)-7-(methoxymethoxy)-4*H*-chromen-4-one (132a)**



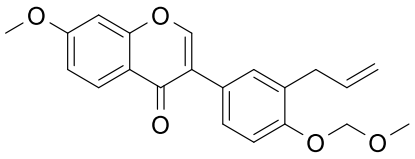
Following the procedure given above for the synthesis of **110e**, compound **136a** (340 mg, 1.0 mmol) was converted to **132a** (222 mg, 0.58 mmol, 58%); purification by column chromatography (hexane − EtOAc mixture 4:1 (v/v)): colorless solid, m.p 89 – 91 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.4 Hz, 1H), 7.92 (s, 1H), 7,37 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.13 (d, *J* = 9.1 Hz, 1H), 7.09-7.06 (m, 2H), 6.02 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.27 (s, 2H), 5.23 (s, 2H), 5.09 (dm, *J* = 17.0 Hz, 1H), 5.05 (dm, *J* = 10.2 Hz, 1H), 3.51 (s, 3H), 3.48 (s, 3H), 3.45 (d, *J* = 6.6 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.0, 161.5, 157.7, 155.0, 152.4, 136.9, 130.8, 129.4, 128.1, 127.9, 125.3, 125.0, 119.3, 115.8, 115.5, 114.0, 103.2, 94.5, 94.4, 56.5, 56.2, 34.6; IR (ATR) $\tilde{\nu}$ 3074 (w), 2927 (w), 1623 (s), 1599 (m), 1441 (m), 1250 (s); HRMS (EI) calcd for $C_{22}H_{22}O_6$ [$M^+$] 382.1416, found 382.1407.

**3-(3-Allyl-4-methoxyphenyl)-5-hydroxy-7-(methoxymethoxy)-4*H*-chromen-4-one (132b)**



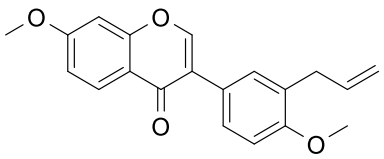
Following the procedure given above for the synthesis of **110a**, compound **136b** (355 mg, 1.0 mmol) was converted to **132b** (265 mg, 0.72 mmol, 72%); purification by column chromatography (hexane − EtOAc mixture 4:1 (v/v)): yellow paste; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 12.84 (s, 1H), 7.86 (s, 1H), 7,39 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.27 (d, *J* = 2.3 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.49 (d, *J* = 2.3 Hz, 1H), 6.01 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.23 (s, 2H), 5. 09 (dm, *J* = 17.0 Hz, 1H), 5.05 (dm, *J* = 10.2 Hz, 1H), 3.86 (s, 3H), 3.50 (s, 3H), 3.43 (d, *J* = 6.6 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 181.1, 163.1, 162.7, 157.9, 157.7, 152.9, 136.8, 130.4, 129.1, 128.2, 124.0, 122.8, 115.8, 110.5, 107.0, 100.1, 98.3, 94.4, 56.6, 55.7, 34.4; IR (ATR) $\tilde{\nu}$ 2906 (w), 1651 (s), 1503 (s), 1439 (m), 1248 (s), 1136 (s); HRMS (EI) calcd for $C_{21}H_{20}O_6$ [$M^+$] 368.1260, found 368.1251.

**3-(3-Allyl-4-(methoxymethoxy)phenyl)-7-methoxy-4*H*-chromen-4-one (132c)**



Following the procedure given above for the synthesis of **110e**, compound **136c** (310 mg, 1.0 mmol) was converted to **132c** (212 mg, 0.60 mmol, 60%); purification by column chromatography (hexane − EtOAc mixture 4:1 (v/v)): colorless solid, m.p 115 − 116 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.9 Hz, 1H), 7.91 (s, 1H), 7.37 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.36 (d, *J* = 2.6 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 1H), 6.98 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.02 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.23 (s, 2H), 5.09 (dm, *J* = 16.9 Hz, 1H), 5.05 (dm, *J* = 10.1 Hz, 1H), 3.91 (s, 3H), 3.49 (s, 3H), 3.45 (d, *J* = 6.6 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 175.9, 164.1, 158.1, 155.0, 152.3, 136.9, 130.8, 129.4, 128.1, 127.9, 125.4, 125.1, 118.6, 115.8, 114.6, 114.0, 100.2, 94.4, 56.2, 55.9, 34.6; IR (ATR) $\tilde{\nu}$ 3075 (w), 2930 (w), 1631 (s), 1599 (m), 1441 (m), 1262 (s); HRMS (EI) calcd for $C_{21}H_{20}O_5$ [$M^+$] 352.1311, found 352.1319.

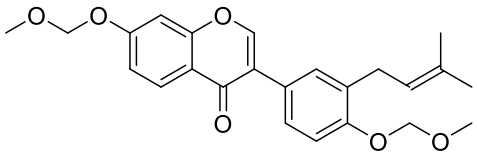
**3-(3-Allyl-4-methoxyphenyl)-7-methoxy-4*H*-chromen-4-one (132d)**



Following the procedure given above for the synthesis of **110a**, compound **136c** (310 mg, 1.0 mmol) was converted to **132d** (302 mg, 0.94 mmol, 94%); purification by column chromatography (hexane − EtOAc mixture 4:1 (v/v)): colorless solid, m.p 157 – 158 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.0 Hz, 1H), 7.90 (s, 1H), 7.42 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.33 (d, *J* = 2.3 Hz, 1H), 6.98 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.02 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.08 (dm, *J* = 17.0 Hz, 1H), 5.05 (dm, *J* = 10.2 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.42 (d, *J* = 6.6 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.0, 164.0, 158.0, 157.4, 152.2, 136.9, 130.5, 128.8, 128.2, 127.9, 125.1, 124.1, 118.6, 115.7, 114.6, 110.5, 100.2, 55.9, 55.6, 34.4; IR (ATR) $\tilde{\nu}$ 2999 (w), 2834 (w), 1630 (s), 1440 (m), 1247 (s); HRMS (EI) calcd for $C_{20}H_{18}O_4$ [$M^+$] 322.1205, found 322.1210.

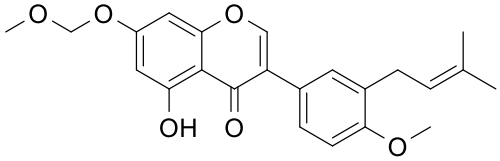
### 6.3.8 Synthesis of Prenylated Isoflavones 58, 66, 131d and 137 via Olefin Cross Metathesis

**7-(Methoxymethoxy)-3-(4-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)-4*H*-chromen-4-one (131a)**



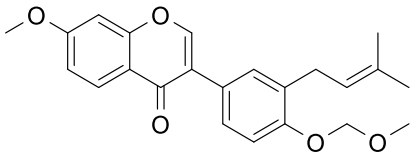
Following the general procedure 6, compound **132a** (192 mg, 0.50 mmol) was converted to **131a** (187 mg, 0.456 mmol, 91%); purification by column chromatography (hexane − EtOAc mixture 4:1 (v/v)): colorless solid, m.p 59 − 60 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.4 Hz, 1H), 7.91 (s, 1H), 7,34 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 9.2 Hz, 1H), 7.09-7.06 (m, 2H), 5.33 (tm, *J* = 7.3 Hz, 1H), 5.27 (s, 2H), 5.23 (s, 2H), 3.51 (s, 3H), 3.49 (s, 3H), 3.38 (d, *J* = 7.3 Hz, 2H), 1.73 (s, 3H), 1.72 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.0, 161.5, 157.8, 155.0, 152.4, 132.5, 131.0, 130.4, 128.0, 127.8, 125.2, 125.2, 122.6, 119.4, 115.5, 113.9, 103.2, 94.5, 94.4, 56.5, 56.1, 29.0, 25.9, 18.0; IR (ATR) $\tilde{\nu}$ 2919 (w), 1641 (s), 1599 (s), 1377 (s), 1256 (m), 1069 (s); HRMS (EI) calcd for $C_{24}H_{26}O_6$ [$M^+$] 410.1729, found 410.1743.

**5-Hydroxy-3-(4-methoxy-3-(3-methylbut-2-en-1-yl)phenyl)-7-(methoxymethoxy)-4*H*-chromen-4-one (131b)**



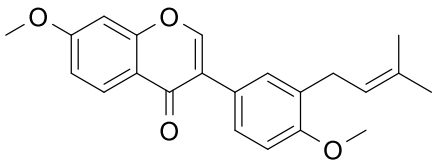
Following the general procedure 6, compound **132b** (185 mg, 0.50 mmol) was converted to **131b** (184 mg, 0.465 mmol, 93%); purification by column chromatography (hexane − EtOAc mixture 4:1 (v/v)): yellow paste; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 12.86 (s, 1H), 7.86 (s, 1H), 7.36 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.24 (d, *J* = 2.3 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.49 (d, *J* = 2.3 Hz, 1H), 5.32 (tm, *J* = 7.2 Hz, 1H), 5.23 (s, 2H), 3.86 (s, 3H), 3.50 (s, 3H), 3.35 (d, *J* = 7.2 Hz, 2H), 1.74 (s, 3H), 1.72 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 181.2, 163.1, 162.8, 157.9, 157.7, 152.9, 132.9, 130.6, 130.0, 127.8, 124.1, 122.7, 122.3, 110.4, 107.1, 100.1, 94.4 (2C), 56.6, 55.6, 28.6, 26.0, 17.9; IR (ATR) $\tilde{\nu}$ 2911 (w), 1711 (w), 1651 (s), 1500 (s), 1440 (m), 1254 (s), 1139 (s); HRMS (EI) calcd for $C_{23}H_{24}O_6$ [$M^+$] 396.1573, found 396.1579.

**7-Methoxy-3-(4-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)-4*H*-chromen-4-one (131c)**



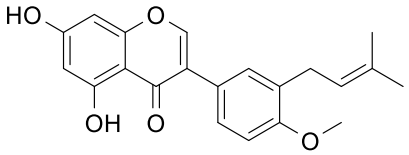
Following the general procedure 6, compound **132c** (176 mg, 0.50 mmol) was converted to **131c** (167 mg, 0.44 mmol, 88%); purification by column chromatography (hexane − EtOAc mixture 4:1 (v/v)): colorless oil; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.9 Hz, 1H), 7.90 (s, 1H), 7.34 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.33 (d, *J* = 2.3 Hz, 1H), 7.11 (d, *J* = 9.2 Hz, 1H), 6.98 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.84 (d, *J* = 2.5 Hz, 1H), 5.33 (tm, *J* = 7.3 Hz, 1H), 5.23 (s, 2H), 3.91 (s, 3H), 3.49 (s, 3H), 3.38 (d, *J* = 7.3 Hz, 2H), 1.73 (s, 3H), 1.72 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.0, 164.1, 158.1, 155.0, 152.3, 132.5, 131.0, 130.4, 127.9, 127.8, 125.3, 125.2, 122.6, 118.6, 114.6, 113.9, 100.2, 94.4, 56.1, 55.9, 29.0, 25.9, 18.0; IR (ATR) $\tilde{\nu}$ 2924 (w), 1628 (s), 1499 (m), 1440 (s), 1256 (s); HRMS (EI) calcd for $C_{23}H_{24}O_5$ [$M^+$] 380.1624, found 380.1614.

**7,4′-Dimethoxy-3′-prenylisoflavone (131d)**



Following the general procedure 6, compound **132d** (162 mg, 0.50 mmol) was converted to **131d** (170 mg, 0.486 mmol, 97%); purification by column chromatography (hexane − EtOAc mixture 4:1 (v/v)): colorless solid, m.p 85 − 86 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.9 Hz, 1H), 7.90 (s, 1H), 7.40 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 6.98 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 5.33 (tm, *J* = 7.3 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.36 (d, *J* = 7.3 Hz, 2H), 1.73 (s, 3H), 1.72 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 176.0, 164.0, 158.1, 157.5, 152.2, 132.6, 130.3, 130.1, 127.9, 127.8, 125.3, 124.0, 122.5, 118.6, 114.5, 110.4, 100.2, 55.9, 55.6, 28.7, 25.9, 17.9; IR (ATR) $\tilde{\nu}$ 2916 (w), 1627 (s), 1502 (m), 1439 (s), 1259 (s); HRMS (EI) calcd for $C_{22}H_{22}O_4$ [$M^+$] 350.1518, found 350.1506.

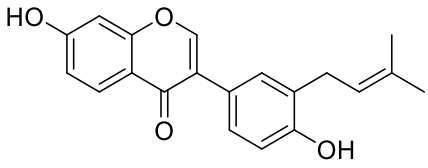
**3′-Prenylbiochanin A (58)**



Following the general procedure 7, compound **131b** (158 mg, 0.40 mmol) was converted to 3′-prenylbiochanin A (**58**) (100 mg, 0.285 mmol, 71%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)). To obtain crystals suitable for single crystal X-ray analysis,

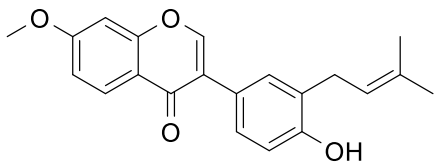
compound **58** (100 mg) was dissolved in methanol (2.0 mL) and the solution was kept at 20 °C for 24 h in an open vessel. Cubic crystals were isolated by decanting the supernatant solution. The crystals were dried in air at 20 °C: colorless crystals, mp 195 °C; $^{1}$H NMR (400 MHz, acetone-$d_6$) δ 13.03 (s, 1H), 8.13 (s, 1H), 7.40 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.28 (d, *J* = 2.2 Hz, 1H), 5.31 (tm, *J* = 7.3 Hz, 1H), 3.87 (s, 3H), 3.33 (d, *J* = 7.3 Hz, 2H), 1.72 (s, 3H), 1.70 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, acetone-$d_6$) δ 181.5, 165.0, 163.6, 159.0, 158.3, 154.4, 132.6, 130.9, 130.4, 128.7, 124.1, 124.0, 123.5, 111.0, 106.1, 99.7, 94.5, 55.8, 29.3, 25.9, 17.8; IR (ATR) υ 3401 (m), 2910 (w), 1646 (m), 1574 (s), 1496 (m), 1238 (s), 1144 (s); HRMS (EI) calcd for $C_{21}H_{20}O_5$ [$M^+$] 352.1311, found 352.1304. Analytical data match those previously reported for the natural product.[39]

**Neobavaisoflavone (66)**




Following the general procedure 7, compound **131a** (170 mg, 0.40 mmol) was converted to neobavaisoflavone (**66**) (90 mg, 0.28 mmol, 70%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): colorless solid, m.p 190 − 191 °C; $^{1}$H NMR (400 MHz, acetone-$d_6$) δ 9.60 (s, 1H), 8.35 (s, 1H), 8.10 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.28 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.99 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.89 (d, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.38 (tm, *J* = 7.3 Hz, 1H), 3.36 (d, *J* = 7.3 Hz, 2H), 1.73 (s, 3H), 1.70 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, acetone-$d_6$) δ 175.8, 163.1, 158.8, 155.7, 153.2, 132.3, 131.2, 131.2, 128.5, 128.5, 125.5, 124.5, 123.8, 118.6, 115.6, 115.5, 103.2, 29.2, 25.9, 17.9; IR (ATR) $\tilde{\nu}$ 3445 (m), 3102 (m), 1620 (s), 1571 (s), 1376 (m), 1243 (s), 1096 (m); HRMS (EI) calcd for $C_{20}H_{18}O_4$ [$M^+$] 322.1205, found 322.1209. Analytical data match those reported for the natural product.[52]

**7-Methoxyneobavaisoflavone (137)**



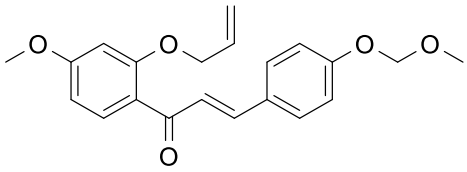

Following the general procedure 7, compound **131c** (80 mg, 0.21 mmol) was converted to7-methoxyneobavaisoflavone (**137**) (45 mg, 0.13 mmol, 64%); purification by column chromatography (hexane − EtOAc mixture 3:1 (v/v)): colorless solid, m.p 150 – 151 °C; $^{1}$H NMR (400 MHz, acetone-$d_6$) δ 8.14 (s, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.28 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.04 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.3 Hz,

1H), 5.38 (tm, *J* = 7.4 Hz, 1H), 3.95 (s, 3H), 3.36 (d, *J* = 7.4 Hz, 2H), 1.73 (s, 3H), 1.70 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-$d_6$) δ 175.8, 165.0, 158.8, 155.7, 153.3, 132.3, 131.2, 128.4, 128.1, 125.6, 124.3, 123.8, 119.2, 115.4, 115.3, 101.2, 101.0, 36.4, 29.2, 25.9, 17.9; IR (ATR) $\tilde{\nu}$ 3223 (w), 2923 (w), 1620 (s), 1438 (s), 1263 (s); HRMS (EI) calcd for $C_{21}H_{20}O_4$ [$M^+$] 336.1362, found 336.1139. Analytical data match those previously reported for the natural product.[229]

## 6.4 Synthesis of Chalcone-Flavanone Hybrids

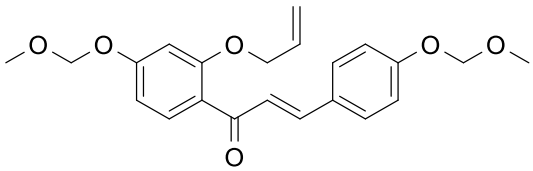
### 6.4.1 Synthesis of 8-Allyl Flavanones 141

**(E)-1-(2-(Allyloxy)-4-methoxyphenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (140bb)**



Following the general procedure 1, compounds **118b** (2.06 g, 10.0 mmol) and **110b** (1.66 g, 10.0 mmol) were reacted to **140bb** (2.30 g, 6.49 mmol, 65%); purification by column chromatography (hexane – MTBE mixture 5:1 (v/v)): pale yellow solid, m.p 81 – 83 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 15.7 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 15.7 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.57 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 6.06 (ddt, *J* = 17.2, 10.6, 5.1 Hz, 1H), 5.45 (dm, *J* = 17.2 Hz, 1H), 5.28 (dm, *J* = 10.6 Hz, 1H), 5.21 (s, 2H), 4.62 (dt, *J* = 5.1, 1.6 Hz, 2H), 3.86 (s, 3H), 3.49 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 190.7, 164.1, 159.4, 158.9, 141.7, 133.1, 132.6, 130.0 (2C), 129.4, 125.7, 122.8, 118.1, 116.5 (C), 105.7, 99.9, 94.4, 69.5, 56.3, 55.7; IR (ATR) $\tilde{\nu}$ 2903 (w), 1649 (m), 1584 (s), 1244 (m), 1149 (s); HRMS (EI) calcd for $C_{21}H_{22}O_5$ [$M^+$] 354.1467, found 354.1472.

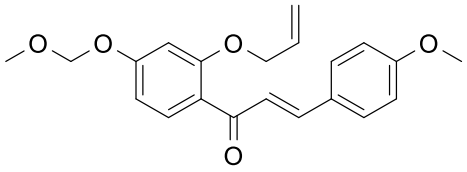
**(E)-1-(2-(Allyloxy)-4-(methoxymethoxy)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (140cb)**



Following the general procedure 1, compounds**118c** (2.36 g, 10.0 mmol) and **110b** (1.66 g, 10.0 mmol) were reacted to **140cb** (2.31 g, 6.01 mmol, 60%); purification by column chromatography (hexane – MTBE mixture 5:1 (v/v)): pale yellow solid, m.p 28 – 30 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.73

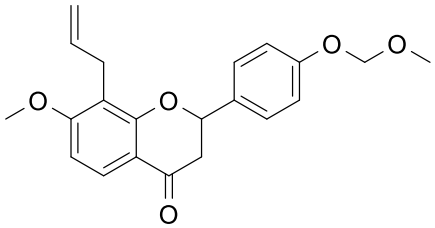
(d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 15.7 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 15.7 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.71 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 6.05 (ddt, *J* = 17.3, 10.6, 5.1 Hz, 1H), 5.45 (dm, *J* = 17.3 Hz, 1H), 5.28 (dm, *J* = 10.6 Hz, 1H), 5.22 (s, 2H), 5.21 (s, 2H), 4.62 (dt, *J* = 5.1, 1.6 Hz, 2H), 3.49 (s, 3H), 3.49 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 190.9, 161.7, 159.3, 159.0, 141.9, 132.8, 132.6, 130.1 (2C), 129.3, 125.7, 123.7, 118.2, 116.6 (2C), 108.4, 101.4, 94.4, 94.4, 69.6, 56.4, 56.3; IR (ATR) $\tilde{\nu}$ 3005 (w), 2907 (w), 1647(m), 1597 (s), 1254 (m), 1151 (s); HRMS (EI) calcd for $C_{22}H_{24}O_6$ [$M^+$] 384.1173, found 384.1562.

**(E)-1-(2-(Allyloxy)-4-(methoxymethoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one 140cc)**



Following the general procedure 1, compounds **118c** (2.36 g, 10.0 mmol) and **110c** (1.36 g, 10.0 mmol) were reacted to **140cc** (2.20 g, 6.21 mmol, 62%); purification by column chromatography (hexane – MTBE mixture 5:1 (v/v)): pale yellow solid, m.p 88 – 89 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 15.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 15.8 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.71 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 6.05 (ddt, *J* = 17.2, 10.7, 5.0 Hz, 1H), 5.45 (dm, *J* = 17.2 Hz, 1H), 5.27 (dm, *J* = 10.7 Hz, 1H), 5.21 (s, 2H), 4.62 (dt, *J* = 5.0, 1.6 Hz, 2H), 3.84 (s, 3H), 3.49 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 190.8, 161.6, 161.4, 159.2, 142.0, 132.7, 132.6, 130.1 (2C), 128.3, 125.2, 123.8, 118.1, 114.4 (2C), 108.3, 101.4, 94.4, 69.5, 56.4, 55.5; IR (ATR) $\tilde{\nu}$ 2928 (w), 2835 (w), 1648(m), 1599 (s), 1247 (s), 1158 (s); HRMS (EI) calcd for $C_{22}H_{24}O_6$ [$M^+$] 354.1467, found 354.1478.

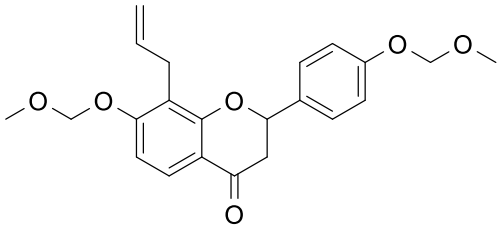
**8-Allyl-7-methoxy-2-(4-(methoxymethoxy)phenyl)chroman-4-one (141bb)**



Following the general procedure 3, compound **140bb** (710 mg, 2.0 mmol) was converted to **141bb** (320 mg, 0.90 mmol, 45%); purification by column chromatography (hexane – MTBE mixture 4:1 (v/v)): pale yellow solid, m.p 87 – 89 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 1H), 5.91 (ddt, *J* = 17.1, 10.0, 6.3 Hz, 1H), 5.39 (dd, *J* = 12.8, 3.0 Hz, 1H), 5.18 (s, 2H), 4.98 (dm, *J* = 17.1 Hz, 1H), 4.94 (dm, *J* = 10.0 Hz, 1H), 3.87 (s, 3H), 3.47 (s, 3H), 3.41 (d, *J* = 6.3, Hz, 2H), 2.97 (dd, *J* = 16.8, 12.8 Hz,

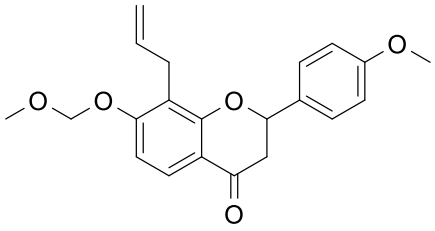
1H), 2.82 (dd, *J* = 16.8, 3.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.5, 163.3, 160.3, 157.3, 135.8, 132.6, 127.3 (2C), 126.7, 116.3 (2C), 115.9, 115.3, 114.7, 104.9, 94.3, 79.0, 56.0, 55.9, 44.2, 27.1; IR (ATR) $\tilde{\nu}$ 2901 (w), 2884 (w), 1667 (s), 1601 (s), 1234 (m), 1022 (s); HRMS (EI) calcd for $C_{21}H_{22}O_5$ [$M^+$] 354.1467, found 354.1481.

**8-Allyl-7-(methoxymethoxy)-2-(4-(methoxymethoxy)phenyl)chroman-4-one (141cb)**



Following the general procedure 3, compound **140cb** (770 mg, 2.0 mmol) was converted to **141cb** (346 mg, 0.90 mmol, 45%); purification by column chromatography (hexane – MTBE mixture 4:1 (v/v)): pale yellow solid, m.p 63 – 65 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 1H), 5.92 (ddt, *J* = 17.1, 10.1, 6.3 Hz, 1H), 5.41 (dd, *J* = 12.9, 3.1 Hz, 1H), 5.26 (s, 2H), 5.20 (s, 2H), 5.00 (dm, *J* = 17.1 Hz, 1H), 4.96 (dm, *J* = 10.1 Hz, 1H), 3.50 (s, 3H), 3.47 (s, 3H), 3.44 (dd, *J* = 6.3, 1.5 Hz, 2H), 3.00 (dd, *J* = 16.8, 12.9 Hz, 1H), 2.85 (dd, *J* = 16.8, 3.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.6, 161.0, 160.6, 157.5, 136.0, 132.7, 127.5 (2C), 126.6, 117.0, 116.5 (2C), 116.0, 115.0, 107.9, 94.5, 94.1, 79.3, 56.5, 56.2, 44.4, 27.5; IR (ATR) $\tilde{\nu}$ 2902 (w), 2828 (w), 1687 (m), 1592 (s), 1238 (m), 1152 (s); HRMS (EI) calcd for $C_{22}H_{24}O_6$ [$M^+$] 384.1573, found 344.1578.

**8-Allyl-7-(methoxymethoxy)-2-(4-methoxyphenyl)chroman-4-one (141cc)**



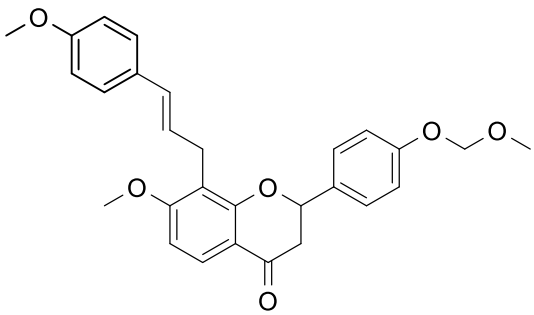
Following the general procedure 3, compound **140cc** (710 mg, 2.0 mmol) was converted to **141cc** (326 mg, 0.92 mmol, 46%); purification by column chromatography (hexane – MTBE mixture 4:1 (v/v)): pale yellow solid, m.p 94 – 95 °C; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 1H), 5.92 (ddt, *J* = 17.1, 10.1, 6.3 Hz, 1H), 5.41 (dd, *J* = 12.8, 3.1 Hz, 1H), 5.26 (s, 2H), 4.99 (dm, *J* = 17.1 Hz, 1H), 4.96 (dm, *J* = 10.1 Hz, 1H), 3.84 (s, 3H), 3.47 (s, 3H), 3.44 (d, *J* = 6.3 Hz, 2H), 3.01 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.85 (dd, *J* = 16.8, 3.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.7, 161.0, 160.7, 159.9, 136.0, 131.4, 127.5 (2C), 126.6, 117.0, 116.0, 114.9, 114.2 (2C), 107.9, 94.2, 79.3, 56.5,

55.5, 44.4, 27.5; IR (ATR) $\tilde{\nu}$ 2901 (w), 1667 (s), 1601 (s), 1234 (m), 1022 (s); HRMS (EI) calcd for $C_{21}H_{22}O_5$ [$M^+$] 354.1467, found 354.1468.

### 6.4.2 General Procedure 13 for Matsuda-Heck Arylation of 8-Allyl Flavanones 141[236]

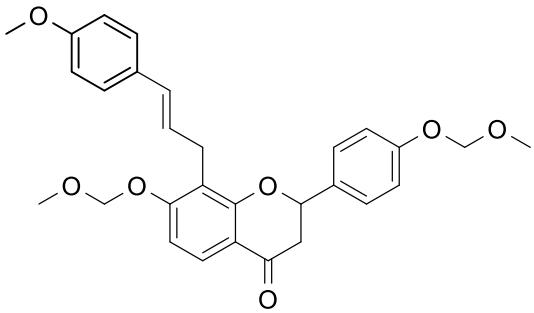
A solution of the diazonium salt **142** (270 mg, 1.2 mmol) in $CH_3CN$ (10 mL) was purged with dry nitrogen. To the solution was then added $Pd(OAc)_2$ (11.2 mg, 5 mol-%) and NaOAc (252 mg, 3.0 mmol), and the mixture was stirred at 20 °C for 10 minutes. To the mixture was then added a solution of the flavanone **141** (1.0 mmol) in $CH_3CN$ (4 mL) and the mixture was stirred at 20 °C for 16 h. After the reaction, the solvent was evaporated under reduced pressure, EtOAc (20 mL) was added to the residue and the solution filtered off. The solution was washed with water (2 x 30 mL), dried with anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane – EtOAc mixture (4:1 (v/v)) as eluent to afford the chalcone-flavanone hybrid **143**.

**(E)-7-Methoxy-2-(4-(methoxymethoxy)phenyl)-8-(3-(4-methoxyphenyl)allyl)chroman-4-one (143bb)**



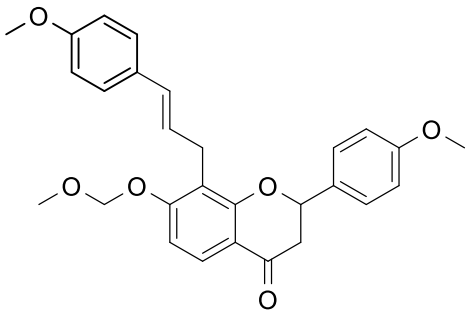
Following the general procedure 13, compounds **141bb** (355 mg, 1.0 mmol) and **142** (270 mg, 1.2 mmol) were reacted to **143bb** (295 mg, 0.64 mmol, 64%); purification by column chromatography (hexane – EtOAc mixture 4:1 (v/v)): yellow paste; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 6.12 (dt, *J* = 15.9, 6.7 Hz, 1H), 5.43 (dd, *J* = 12.8, 3.1 Hz, 1H), 5.20 (s, 2H), 3.92 (s, 3H), 3.79 (s, 3H), 3.52 (ddd, *J* = 6.7, 3.7, 1.5 Hz, 2H), 3.50 (s, 3H), 3.01 (dd, *J* = 16.9, 12.8 Hz, 1H), 2.84 (dd, *J* = 16.9, 3.1 Hz, 1H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 191.6, 163.4, 160.5, 158.8, 157.4, 132.7, 130.7, 129.9, 127.6 (2C), 127.2 (2C), 126.8, 125.6, 116.5 (2C), 116.4, 115.5, 114.0 (2C), 105.0, 94.5, 79.2, 56.2, 56.1, 55.4, 44.3, 26.5; IR (ATR) $\tilde{\nu}$ 2902 (w), 2837 (w), 1681 (s), 1595 (s), 1510 (s), 1243 (s), 1108 (s); HRMS (EI) calcd for $C_{28}H_{28}O_6$ [$M^+$] 460.1886, found 460.1870.

**(E)-7-(Methoxymethoxy)-2-(4-(methoxymethoxy)phenyl)-8-(3-(4-methoxyphenyl)allyl) chroman-4-one (143cb)**



Following the general procedure 13, compounds **141cb** (390 mg, 1.0 mmol) and **142** (270 mg, 1.2 mmol) were reacted to **143cb** (372 mg, 0.76 mmol, 76%); purification by column chromatography (hexane – EtOAc mixture 4:1 (v/v)): yellow solid, m.p 105 – 107 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.9 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.13 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.44 (dd, *J* = 12.8, 3.0 Hz, 1H), 5.29 (s, 2H), 5.21 (s, 2H), 3.79 (s, 3H), 3.56 (ddd, *J* = 6.7, 3.2, 1.5 Hz, 2H), 3.50 (s, 3H), 3.48 (s, 3H), 3.02 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.85 (dd, *J* = 16.8, 3.0 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 191.6, 161.0, 160.7, 158.8, 157.5, 132.6, 130.7, 129.9, 127.6 (2C), 127.2 (2C), 126.6, 125.5, 117.2, 116.5 (2C), 116.0, 114.0 (2C), 107.9, 94.5, 94.2, 79.3, 56.5, 56.2, 55.4, 44.3, 26.7; IR (ATR) $\tilde{\nu}$ 2886 (w), 1689 (s), 1595 (m), 1510 (s), 1244 (s), 1150 (s); HRMS (EI) calcd for $C_{29}H_{30}O_7$ [$M^+$] 490.1992, found 490.1984.

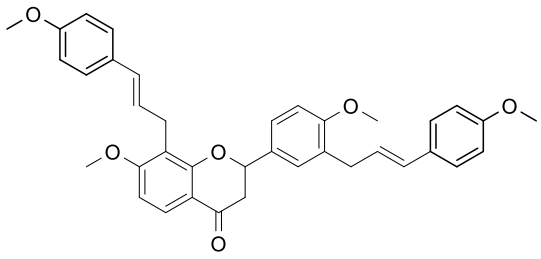
**(E)-7-(Methoxymethoxy)-2-(4-methoxyphenyl)-8-(3-(4-methoxyphenyl)allyl)chroman-4-one (143cc)**



Following the general procedure 13, compounds **141cc** (355 mg, 1.0 mmol) and **142** (270 mg, 1.2 mmol) were reacted to **143cc** (275 mg, 0.60 mmol, 60%); purification by column chromatography (hexane – EtOAc mixture 4:1 (v/v)): yellow solid, m.p 101 – 102 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.9 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.33 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.44 (dd, *J* = 12.7, 3.1 Hz, 1H), 5.28 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.56 (dq, *J* = 6.7, 1.3 Hz, 2H), 3.47 (s, 3H), 3.03 (dd, *J* = 16.9, 12.7 Hz, 1H), 2.86 (dd, *J* = 16.9, 3.1 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 191.7, 161.0, 160.7, 159.9, 158.8, 131.4, 130.7, 129.9, 127.7 (2C), 127.2 (2C), 126.6, 125.5, 117.2, 116.0, 114.2 (2C), 114.0 (2C), 107.8, 94.2, 79.3, 56.5, 55.5, 55.4, 44.2, 26.7; IR (ATR) $\tilde{\nu}$ 2892 (w), 1688

(m), 1588 (s), 1510 (s), 1250 (s), 1032 (s); HRMS (EI) calcd for $C_{28}H_{28}O_6$ [$M^+$] 460.1886, found 460.1893.

**7-Methoxy-2-(4-methoxy-3-((E)-3-(4-methoxyphenyl)allyl)phenyl)-8-((E)-3-(4-methoxyphenyl)allyl)chroman-4-one (144)**

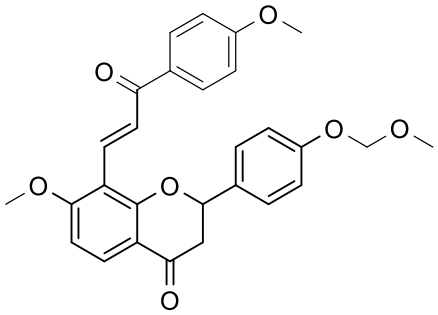


Following the general procedure 13, and doubling the quantity of $Pd(OAc)_2$ and NaOAc, compounds **121ba** (365 mg, 1.0 mmol) and **142** (533 mg, 2.4 mmol) were reacted to **144** (125 mg, 0.22 mmol, 22%); purification by column chromatography (hexane – EtOAc mixture 4:1 (v/v)): pale yellow solid, m.p 127 – 129 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.9 Hz, 1H), 7.32 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 8.9 Hz, 1H), 6.37 (d, *J* = 15.7 Hz, 1H), 6.32 (d, *J* = 15.7 Hz, 1H), 6.22 (dt, *J* = 15.7, 6.7 Hz, 1H), 6.12 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.41 (dd, *J* = 12.7, 3.0 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.52 (d, *J* = 6.7, Hz, 4H), 3.03 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.85 (dd, *J* = 16.8, 3.0 Hz, 1H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 191.8, 163.4, 160.6, 158.9, 158.8, 157.5, 131.3, 130.8, 130.6, 130.5, 129.7, 129.4, 128.0, 127.3 (2C), 127.2 (2C), 126.8, 126.3, 125.7, 125.3, 116.4, 115.5, 114.0 (2C), 113.9 (2C), 110.5, 105.0, 79.3, 56.1, 55.7, 55.4 (2C), 44.3, 33.6, 26.5; IR (ATR) $\tilde{\nu}$ 2880 (w), 1683 (m), 1591 (s), 1509 (s), 1245 (s), 1109 (s); HRMS (EI) calcd for $C_{37}H_{36}O_6$ [$M^+$] 576.2512, found 576.2521.

### 6.4.3 General Procedure 14 for the Allylic/Benzylic Oxidation of 143[238]

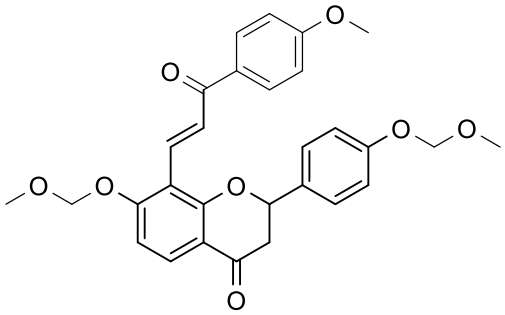
To a well stirred mixture of **143** (0.30 – 0.50 mmol), 1,4-dioxane (3.0 – 6.0 mL) and silica gel (100 – 200 mg) in a vessel suited for microwave irradiation was added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (2.3 equiv.) and the vessel was sealed. The mixture was heated at 90 °C under microwave irradiation for 25 minutes. The reaction mixture was then transferred into a flask, diluted with EtOAc (40 mL) and filtered. The filtrate was washed with water (3 x 100 mL), dried with anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using hexane – EtOAc mixture (3:2 (v/v)) as eluent to afford **145**.

**(E)-7-Methoxy-2-(4-(methoxymethoxy)phenyl)-8-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)chroman-4-one (145bb)**



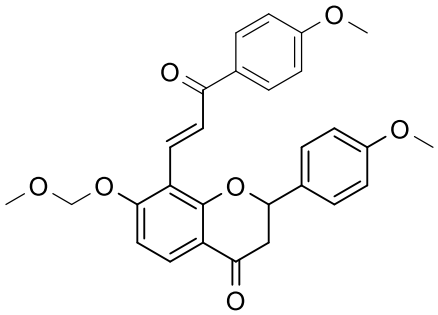
Following the general procedure 14, compound **143bb** (230 mg, 0.50 mmol) was converted to **145bb** (85 mg, 0.18 mmol, 36%); purification by column chromatography (hexane – EtOAc mixture 3:2 (v/v)): yellow solid, m.p 198 – 199 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 15.9 Hz, 1H), 8.02 (d, *J* = 15.9 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 1H), 5.52 (dd, *J* = 13.5, 2.8 Hz, 1H), 5.24 (s, 2H), 3.98 (s, 3H), 3.85 (s, 3H), 3.52 (s, 3H), 3.15 (dd, *J* = 16.9, 13.5 Hz, 1H), 2.88 (dd, *J* = 16.9, 2.8 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 190.9, 189.4, 165.0, 163.3, 162.3, 157.9, 133.0, 131.9, 131.5, 130.9 (2C), 130.3, 128.1 (2C), 125.6, 116.7 (2C), 115.4, 113.7 (2C), 112.7, 105.1, 94.5, 80.3, 56.4, 56.3, 55.5, 43.8; IR (ATR) $\tilde{\nu}$ 2936 (w), 2837 (w), 1675 (m), 1601 (s), 1580 (s), 1230 (s), 1081 (s); HRMS (EI) calcd for $C_{28}H_{26}O_7$ [$M^+$] 374.1673, found 374.1676.

**(E)-7-(Methoxymethoxy)-2-(4-(methoxymethoxy)phenyl)-8-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)chroman-4-one (145cb)**



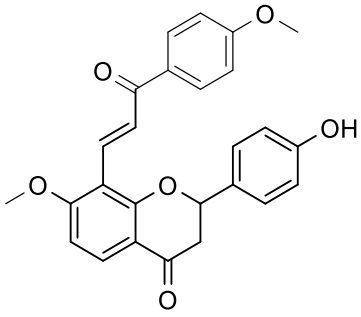
Following the general procedure 14, compound **143cb** (240 mg, 0.49 mmol) was converted to **145cb** (120 mg, 0.24 mmol, 49%); purification by column chromatography (hexane – EtOAc mixture 3:2 (v/v)): yellow solid, m.p 143 – 144 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 16.0 Hz, 1H), 8.06 (d, *J* = 16.0 Hz, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.53 (dd, *J* = 13.6, 2.8 Hz, 1H), 5.35 (s, 2H), 5.24 (s, 2H), 3.86 (s, 3H), 3.52 (s, 6H), 3.16 (dd, *J* = 16.8, 13.6 Hz, 1H), 2.89 (dd, *J* = 16.8, 2.8 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 190.8, 189.3, 163.4, 162.7, 158.0, 133.0, 131.8, 131.4, 130.9 (2C), 130.1, 128.2 (2C), 125.8, 116.8 (2C), 116.0, 113.8 (2C), 113.5, 108.2, 94.7, 94.5, 80.4, 56.9, 56.3, 55.5, 43.8; IR (ATR) $\tilde{\nu}$ 2839 (w), 1673 (m), 1658 (m), 1578 (s), 1256 (m), 1026 (s); HRMS (EI) calcd for $C_{29}H_{28}O_8$ [$M^+$] 504.1784, found 504.1782.

**(E)-7-(Methoxymethoxy)-2-(4-methoxyphenyl)-8-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)chroman-4-one (145cc)**



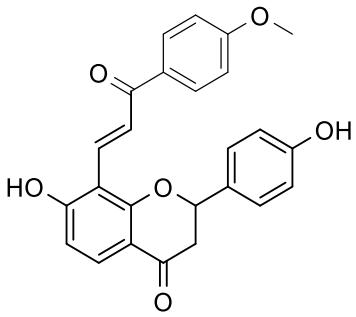
Following the general procedure 14, compound **143cc** (137 mg, 0.30 mmol) was converted to **145cc** (104 mg, 0.22 mmol, 73%); purification by column chromatography (hexane – EtOAc mixture 3:2 (v/v)): yellow solid, m.p 188 – 189 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 16.0 Hz, 1H), 8.04 (d, *J* = 16.0 Hz, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.52 (dd, *J* = 13.7, 2.7 Hz, 1H), 5.35 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.52 (s, 3H), 3.19 (dd, *J* = 16.9, 13.7 Hz, 1H), 2.89 (dd, *J* = 16.9, 2.7 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ 190.9, 189.3, 163.3, 162.7, 162.4, 160.3, 132.9, 131.5, 130.9 (2C), 130.6, 130.1, 128.4 (2C), 125.8, 116.0, 114.5 (2C), 113.7 (2C), 113.5, 108.2, 94.7, 80.5, 56.9, 55.5, 55.5, 43.6; IR (ATR) $\tilde{\nu}$ 2839 (w), 1673 (m), 1654 (m), 1578 (s), 1255 (m), 1026 (s); HRMS (EI) calcd for $C_{28}H_{26}O_7$ [$M^+$] 374.1679, found 374.1692.

**(E)-2-(4-Hydroxyphenyl)-7-methoxy-8-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)chroman-4-one (146)**



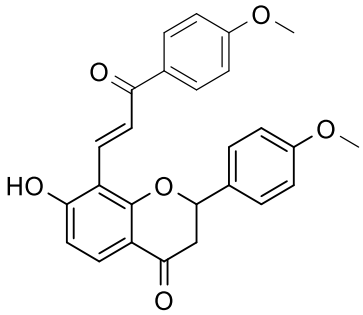
Following the general procedure 7, compound **145bb** (40 mg, 0.08 mmol) was converted to **146** (34 mg, 0.08 mmol, quant.); purification by column chromatography (hexane – EtOAc mixture 1:1 (v/v)): yellow solid, m.p 214 – 215 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 9.82 (s, 1H), 7.98 (d, *J* = 16.0 Hz, 1H), 7.92 (d, *J* = 16.0 Hz, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 4H), 6.89 (d, *J* = 8.9 Hz, 1H), 5.62 (dd, *J* = 13.8, 2.7 Hz, 1H), 3.98 (s, 3H), 3.84 (s, 3H), 3.37 (dd, *J* = 16.7, 13.8 Hz, 1H), 2.74 (dd, *J* = 16.7, 2.7 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, DMSO-$d_6$) δ 190.7, 187.6, 164.2, 163.0, 161.9, 158.2, 132.3, 130.6, 130.3 (2C), 130.1, 128.9 (2C), 128.8, 124.4, 115.5 (2C), 115.0, 113.9 (2C), 111.2, 105.4, 80.1, 56.8, 55.5, 42.3; IR (ATR) $\tilde{\nu}$ 3279 (w), 2832 (w), 1681 (m), 1588 (s), 1230 (s), 1162 (s); HRMS (ESI) calcd for $C_{26}H_{23}O_6$ [M+H]$^+$ 431.1495, found 431.1475.

**(E)-7-Hydroxy-2-(4-hydroxyphenyl)-8-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)chroman-4-one (147)**



Following the general procedure 7, compound **145cb** (75 mg, 0.15 mmol) was converted to **147** (40 mg, 0.10 mmol, 67%); purification by column chromatography (hexane – EtOAc mixture 1:1 (v/v)): yellow solid, m.p, 170 – 171 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 11.52 (s,1H), 9.79 (s, 1H), 8.01 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 15.9 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 1H), 5.63 (dd, *J* = 13.8, 2.6 Hz, 1H), 3.85 (s, 3H), 3.35 (dd, *J* = 16.8, 13.8 Hz, 1H), 2.71 (dd, *J* = 16.8, 2.6 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, DMSO-$d_6$) δ 190.3, 187.7, 164.2, 163.0, 162.8, 158.1, 133.1, 130.7, 130.2 (2C), 129.7, 128.9, 128.9 (2C), 123.5, 115.4 (2C), 113.9 (2C), 113.7, 109.9, 109.9, 79.9, 55.5, 42.2; IR (ATR) $\tilde{\nu}$ 3270 (w), 2972 (w), 1657 (m), 1601 (s), 1576 (s), 1233 (s), 1165 (s); HRMS (ESI) calcd for $C_{25}H_{21}O_6$ $[M+H]^+$ 417.1338, found 417.1348.

**(E)-7-Hydroxy-2-(4-methoxyphenyl)-8-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)chroman-4-one (148)**



Following the general procedure 7, compound **145cc** (70 mg, 0.15 mmol) was converted to **148** (35 mg, 0.08 mmol, 54%); purification by column chromatography (hexane – EtOAc mixture 1:1 (v/v)): yellow solid, m.p, 186 – 187 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.98 (s, 2H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 1H), 5.67 (dd, *J* = 13.6, 2.8 Hz, 1H), 3.83 (s, 6H), 3.32 (dd, *J* = 16.8, 13.6 Hz, 1H), 2.72 (dd, *J* = 16.8, 2.8 Hz, 1H); $^{13}$C{$^{1}$H} NMR (100 MHz, DMSO-$d_6$) δ 190.3, 187.9, 164.3, 163.0, 162.7, 159.8, 133.2, 130.8, 130.8, 130.3 (2C), 129.7, 128.2 (2C), 123.6, 114.2 (2C), 113.9 (2C), 113.7, 110.1, 110.0, 79.8, 55.5, 55.4, 42.2; IR (ATR) $\tilde{\nu}$ 3120 (w), 2931 (w), 1687 (m), 1594 (s), 1437 (s), 1254 (s), 1160 (s); HRMS (ESI) calcd for $C_{26}H_{23}O_6$ $[M+H]^+$ 431.1495, found 431.1500.

## 6.5 X-ray Crystal Structure Analysis

The crystal structures of the compounds, 3′-prenylbiochanin A (**58**), 5-deoxy-3′-prenylbiochanin A (**59**), **106a**, **106b**, **122j** and **143cc** were determined by single crystal X-ray structure analysis. Crystals suitable for single crystal X-ray analysis were obtained by recrystallizing of each of the compounds **58**, **59**, **106a**, **106b**, **122j** and **143cc** from methanol. Suitable single crystals were selected using an optical microscope and were separated with oil. X-ray crystal structure analysis was performed on a Stadivari diffractometer (Stoe) with Mo-$K\alpha$ radiation ($\lambda$ = 0.71073 Å). The data were corrected using the program X-Area[252] and the structure was solved by direct methods and refined against $F^2$ on all data by full-matrix least-squares using the SHELX suite of programs.[253,254] The crystal structure was visualized with Diamond.[255] The data (**58**: CCDC 2156924; **59**: CCDC 2013149; **106a**: CCDC 2121813; **106b**: CCDC 2121812; **122j**: CCDC 2083190; **143cc**: CCDC 2156920) can be obtained free of charge from The Cambridge Crystallographic Data Centre, http://www.ccdc.cam.ac.uk.

The molecular Hirshfeld Surfaces (HS) of 5-deoxy-3′prenylbiochanin A (**59**), **106a** and **106b** were obtained using the CIF of **59**, **106a** and **106b**, respectively as input file in the program Crystal Explorer 17.[256] The HS was calculated using a high surface resolution, with the $d_{norm}$ surfaces mapped over the color scale range of -0.1 (red) to 1.4 Å (blue). The red spots on the Hirshfeld surface indicate the closest interactions between the atoms of neighboring molecules.

## 6.6 Antimicrobial Assay Testing

The minimum inhibitory concentration (MIC) of 5-deoxy-3′-prenylbiochanin A (**59**), erysubin F (**61**), and 7,4′-dihydroxy -8,3′-diprenylflavone (**129**) were determined using a standardized agar dilution method.[257] Three bacterial strains and one pathogenic yeast strain were utilized in these experiments: methicillin-resistant *Staphylococcus aureus* (ATCC 43300), *Salmonella enterica* subsp. *enterica* (NCTC 13349), *Escherichia coli* (ATCC 25922), and *Candida albicans* (ATCC 90028). Each test compound was dissolved in DMSO, and serial dilutions in the solvent were prepared. These dilutions were added to Mueller Hinton agar medium or, for *C. albicans*, to yeast extract peptone dextrose (YPD) (1% v/v) to give the final test concentration. The antibiotics vancomycin (*S. aureus*) and ampicillin (*S. enterica* and *E. coli*) and the antimycotic amphotericin B (*C. albicans*) were used as positive controls and to verify that MIC values of each individual

strain agreed with known MIC ranges. Agar plates containing only DMSO (1% v/v) were used as negative controls. Inocula of all test organisms were prepared using overnight cultures, photometrically adjusted to approximate 108 CFU/mL for bacteria and 107 CFU/mL for *C. albicans*. Agar plates were incubated aerobically at 37 °C for 18 h with the three bacterial strains and 30 °C for 48 h with *C. albicans*. The MIC values were defined as the lowest concentrations of compound that prevented visible growth of the microorganism after incubation.

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