SYNTHESIS OF BIOLOGICALLY RELEVANT BIFLAVANOIDS - A REVIEW

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Abstract

Recent investigations show that naturally occurring biflavanoids possess antiinflammatory, anti-cancer, anti-viral, anti-microbial, vasorelaxant, and anti-clotting activities. These activities have been discovered from the small number of biflavanoid structures that have been investigated, although the natural biflavanoid library is likely to be large. Structurally, biflavanoids are polyphenolic molecules comprised of two identical or non-identical flavanoid units conjoined in a symmetrical or unsymmetrical manner through an alkyl or an alkoxy-based linker of varying length. These possibilities introduce significant structural variation in biflavanoids, which is further amplified by the positions of functional groups – hydroxy, methoxy, keto or double bond – and chiral centers on the flavanoid scaffold. In combination, the class of biflavanoids represents a library of structurally diverse molecules, which remains to be fully exploited. Since the time of their discovery, several chemical approaches utilizing coupling and rearrangement strategies have been developed to synthesize biflavanoids. This review compiles these synthetic approaches into nine different methods including Ullmann coupling of halogenated flavones, biphenyl-based construction of biflavanoids, metal-catalyzed crosscoupling of flavones, Wessely-Moser rearrangements, oxidative coupling of flavones, Ullmann condensation with nucleophiles, nucleophilic substitutions for alkoxy biflavanoids, and dehydrogenation-based or hydrogenation-based synthesis. Newer, more robust synthetic approaches are necessary to realize the full potential of the structurally diverse class of biflavanoids.

I. Introduction

Biflavanoids, the small polyphenolic molecules more commonly referred to as biflavonoids, are gaining increasing recognition as modulators of physiological and pathological responses. Biflavanoids occur in many fruits, vegetables and plants. Since the time Furukawa extracted leaves of maidenhair tree, Ginko biloba L, to obtain a yellow pigment, which later proved to be a biflavonoid (I-4', I-7-dimethoxy, II-4', I-5, II-5, II-7-tetrahydroxy [I-3', II-8] biflavone) and given the name ginkgetin (Fig. 1) [1], the number of biflavanoids isolated and characterized from nature keeps growing [2-15]. Biflavanoids have been found to possess interesting biological activities including anti-inflammatory [16-31], anti-cancer [32-36], antiviral [37-40], anti-microbial [41-47], vasorelaxant [48,49], anti-clotting [50] and others [51-54]. Another property with potential applicability is the anti-oxidant property of biflavanoids, although their potency appears to be lower than that of mono-flavanoids despite of the presence of nearly double the number of phenolic -OH groups [55]. Finally, biflavanoids may inhibit metabolic enzymes. At least one biflavanoid, amentoflavone, has been found to inhibit a human cytochrome P450 enzyme with nanomolar potency suggesting that the determinants of pharmaceutical activity may also impede their usage [56].

Of the large number of biflavanoids that are suggested to exist in nature, only a couple of dozen natural biflavanoids have been explored for biological activity studies. The most studied biflavanoids include ginkgetin, isoginkgetin, amentoflavone, morelloflavone, robustaflavone, hinokiflavone, and ochnaflavone (Fig. 1). Each of these biflavanoids is based on an essentially identical 5,7,4'-trihydroxy flavanoid parent structure, except for the difference in the nature and position of the inter-flavanoid linkage. The resulting range of biological activities in this group

of biflavanoids is fairly similar with potencies, e.g., anti-cancer [32-36], anti-viral [37-40], and anti-microbial [41-47], in the low to mid micromolar range.

[Figure 1]

The anti-inflammatory activity of biflavanoids has been studied in sufficient detail at a molecular level. Amentoflavone, ginkgetin, ochnaflavone, and morelloflavone have been shown to inhibit phospholipase A2 and cyclooxygenase-2 resulting in decreased biosynthesis of prostaglandins, the key mediators of inflammation [7,16,18,19,27,29,31]. In addition, the biflavanoids also suppress activation of nuclear factor– κ B to down regulate the synthesis of inducible nitric oxide synthase [14,20,21,23]. Thus, biflavanoids are likely to be effective anti-inflammatory agents in a number of disorders, including cancer.

Structurally, biflavanoids are polyphenolic molecules comprised of two identical or nonidentical flavanoid units conjoined in a symmetrical or unsymmetrical manner through an alkyl or an alkoxy-based linker of varying length (Fig. 2). The variations possible in the parent flavanoid units coupled with the large number of permutations possible in the position and nature of the inter-flavanoid linkage introduce significant structural diversity in biflavanoids. This diversity is further amplified by variably positioned functional groups, e.g., hydroxy, methoxy, keto or double bond, and chiral centers on the flavanoid scaffold. In combination, the class of biflavanoids represents a library of some 20,000 diverse molecules, each of which is capable of multiple hydrogen-bonding and hydrophobic interactions. Not all of these have been found to exist in nature as yet. However, in an age that values structural diversity, the theoretical library of biflavanoids spans a wide range of configurational and conformational space suggesting that possibilities of interesting biological activity are strong. Despite the large number of structural opportunities embedded in biflavanoids, only two reviews have appeared on this interesting class of natural products. The first, by Geiger and Quinn, was published in 1975, and then expanded later in 1982. The review focused on naturally occurring biflavanoids, with little emphasize on their synthesis [57]. Later, Locksley reviewed biflavanoids with a particular emphasis on their analytical aspects [58]. It is expected that the availability of greater number of biflavanoids, synthetic or natural, will greatly improve the range and potency of biological activity.

Several synthetic approaches utilizing coupling and rearrangement strategies have been used to synthesize biflavanoids. This review compiles these reactions into nine different methods: a) Ullmann coupling of halogenated flavones; b) construction of biflavanoids via biphenyls; c) metal catalyzed cross coupling of flavones; d) Wessely-Moser rearrangements; e) phenol oxidative coupling of flavones; f) Ullmann condensation of flavone salts and halogenated flavones; g) nucleophilic substitutions; h) dehydrogenation of biflavanones into biflavones; and i) hydrogenation of biflavones into biflavanones. Although the authors have tried to be as comprehensive as possible, some loss is inevitable.

II. Nomenclature of Biflavanoids

The rapid growth in literature on biflavanoids led to various systems of naming these compounds. To rationalize and standardize the nomenclature, Locksley proposed some general rules [58]. He advocated that the generic name 'biflavanoid' be used in place of 'biflavonyl' and others to describe the family. In this nomenclature, the term 'biflav*an*oid' has been adopted in preference to 'biflav*on*oid', as it more accurately reflects the saturated system as being the parent system. The ending 'oid' may then be modified to cover specific types of homogeneous

5

flavanoid dimers, such as biflavanone, biflavone, biflavan, and others, while for mixed systems, the description 'flavanone-flavone' should be used. This system generally follows the IUPAC recommendations. Locksley also standardized the nomenclature of the rings and the positions on rings. Each monomer unit is assigned a Roman numeral I and higher in a sequential manner. The inter-monomer linkage is identified using a Roman numeral, which corresponds to the flavanoid unit, and an Arabic numeral, which corresponds to the position of the linkage. The two numerals, for both the flavanoid monomers constituting the dimer are coupled with a hyphen and enclosed within square brackets. This represents the inter-monomer linkage. The numbering of substituent groups on the monomeric units follows the IUPAC system for flavones, in which the three rings are referred to A, B, and C (Fig. 2).

[Figure 2]

Some examples will clarify the use of Locksley's system. Biflavonoid **16b** (Table 5),[#] also called hexamethylmorelloflavone, would be named as I-3', II-3', I-5, II-5, I-7, II-7hexamethoxyflavanone [I-3, II-8] flavone under the Locksley rule, while amentoflavone **70** would be named I-4', II-4', I-5, II-5, I-7, II-7-hexahydroxy [I-3', II-8] biflavone. Hinokiflavone **18a** (Table 6), whose flavone units are linked through an oxygen atom, would be named II-4', I-5, II-5, II-5, I-7, II-7, II-7-pentahydroxy [I-4'-O-II-6] biflavone, while the biflavonyl-oxyalkane **29a** (Fig. 3, Table 7) would be named I-3, II-3, I-7, II-7-tetrahydroxy [I-8-OCH₂O-II-8] biflavone.

[Figure 3]

IUPAC has also devised its own system of nomenclature for biflavanoids. For example, hexamethylmorelloflavone **16b** would be called 5,7,5',7'-tetramethoxy-2,2'-bis-(4-methoxy-phenyl)-2,3-dihydro-[3,8']bichromenyl-4,4'-dione in the IUPAC nomenclature, while

[#] Note: To ease cataloging and retrieval, biflavanoids have been numbered in sequence according to their entry in Tables, rather than in text. Tables 1 to 9 have been arranged in the approximate order of complexity of the biflavanoid structure.

amentoflavone **70** would be named 8-[5-(5,7-dihydroxy-4-oxo-4H-chromen-2-yl)-2-hydroxyphenyl]-5,7-dihydroxy-2-(4-hydroxy-phenyl)-chromen-4-one. Likewise, hinokiflavone **18a** would be named 6-[4-(5,7-Dihydroxy-4-oxo-4H-chromen-2-yl)-phenoxy]-5,7-dihydroxy-2-(4-hydroxyphenyl)-chromen-4-one. The fundamental difference between the Locksley system and the IUPAC system is the reference skeleton. Whereas the IUPAC system considers the majority of biflavanoids as derivatives of the chromene structure, the Locksley system uses the flavanoid structure. Thus, for oxyalkane-linked biflavanoids, e.g., **29a** (Fig. 3), the IUPAC system has to change its reference skeleton and this introduces considerable complexity in nomenclature. It is important to mention that very few scientists utilize either of the systems, primarily because common names, e.g., amentoflavone, cupressuflavone, and agathisflavone, are easier. These names, however, are limited because they contain no structural descriptors. The Locksley system is intuitive, logical and structure-explicit, and hence is adopted here.

III. Methods for Biflavanoid Synthesis

A. Ullmann Coupling of Halogenated Flavones

Ullmann coupling, named after Fritz Ullmann, is a reaction of aryl halide mediated by elemental copper. A typical example of Ullmann reaction is the coupling of *O*-chloronitrobenzene with copper bronze alloy to yield 2,2'-dinitrobiphenyl (**Scheme 1A**). The Ullmann reaction has been classified into two major categories; the 'classic' coupling reaction of aryl halides to give symmetrical biaryls (**Scheme 1A & B**) and the 'modified' reaction involving copper-catalyzed coupling of aryl halide and a nucleophile, e.g., a phenoxide or an amine (**Scheme 1C**). The modified Ullmann reaction is covered in *Method F* (below).

[Scheme 1]

The classical Ullmann reaction has received the most attention in the synthesis of biflavonoids. However, a major drawback of the reaction is the requirement of temperatures in the region 260-300 ^oC, which results considerable resinification and poor yields. Nakazawa et al. investigated the effect of various solvents on the coupling of monoflavones and determined that DMF and DMSO worked best giving yields of approximately 30% [59].

The Ullmann reaction has been used to synthesize symmetrical biflavones with [I-3, II-3], [I-5, II-5], [I-6, II-6], [I-7, II-7], [I-8, II-8], [I-3', II-3'], and [I-4', II-4'] linkages [60-73]. Interestingly, cupressuflavone hexamethyl ether **6f** a symmetrical biflavanoid (Table 1), was prepared in 33% yield [58,74] two years before the isolation of the parent biflavanoid, cupressuflavone **6j** by Seshadri from *Rhus succedanea* [75]. The Ullmann synthesis of cupressuflavone **6j** (Table 1) has been recently revisited by Zhang et al. to improve its yields [70] (**Scheme 2**).

[Scheme 2]

Symmetrical biflavanoids with linkages other than 3, 5, 6, 7, 8, 3', and 4' have not been synthesized because it is difficult to introduce halogens on these carbons. Typically, the bromoand iodo- flavones have been found to yield biflavones under the Ullmann conditions. The chloroflavones are unreactive because of the higher electronegativity of the chlorine substituent, which makes the formation of C-Cu-Cl bond more difficult. Although the coupling of iodoflavones is expected to be higher yielding than that of the bromoflavones, this is not observed because of a slightly higher level of reductive dehalogenation.

The Ullmann reaction was also studied for synthesis of the unsymmetrical biflavone ginkgetin **7c**. Condensation of the two iodinated flavones using activated copper powder in DMF unexpectedly resulted in only the symmetrical I-8, II-8-coupled product. However, omission of the

8

solvent completely changed the course of the reaction and the I-3', II-8 coupled ginkgetin **7c** was obtained in 21% overall yield [59] (**Scheme 3**). Hexamethyl and tetramethyl ethers, **7d** and **7o** (Table 2), respectively, of amentoflavone, which have the I-3', II-8 linkage, were the first unsymmetrical biflavones synthesized by Nakazawa et al. using the Ullmann reaction [59,76]. Following this initial success, a number of unsymmetrical biflavanoids were synthesized [76,77]. However, the overall yields remain low because of the competing symmetrical coupling as well as due to resinification that accompanies the high temperature conditions.

[Scheme 3]

B. Synthesis of Biflavones via Biphenyls

Mathai et al. first introduced this approach of utilizing a biphenyl skeleton to the synthesis of biflavones [60, 61]. 4,4'-Dimethoxy-3,3'-diformylbiphenyl **34** was condensed with 2hydroxyacetophenone **35** in the presence of ethanolic potassium hydroxide to give the bichalconyl derivative **36**, which on refluxing with selenium dioxide in amyl alcohol gave the symmetrical 3',3'-biflavonyl derivative **9f** (Table 1) [60] (**Scheme 4**). Several scientists have followed the Mathai approach to synthesize a number of biflavanoids including **9h** (Table 1), with variety of modification, requiring less reaction time, higher yields, and easier separations [63,73,78-83].

[Scheme 4]

The biphenyl precursor is a key intermediate in this synthetic approach and is often the most difficult step. For example, the synthesis of 3,3'-diacetyl-2,2',4,4',6,6'-hexamethoxybiphenyl **38** using Ullmann coupling of yielded the biphenyl in only 3% yield (**Scheme 5**). Alternatively, 2,2',4,4',6,6'-hexamethoxybiphenyl **40** was prepared in 60% yield through Ullmann coupling of 2,4,6-trimethoxy-iodobenzene **39**. Friedel-Craft acylation of **40** gave the required biphenyl **38** in

good overall yields. Using this key intermediate, racemic **6f** (Table 1) was successfully synthesized [62,63].

[Scheme 5]

Enantioselective synthesis of biflavanoids **6f** and **6j** has also been reported [84]. The chirality of biflavones is due to the atropisomerism of the biflavone moiety. As shown in Scheme 6, chiral tetra-ether 45 was first prepared through sequential introduction of 2-iodo-3,5-dimethoxyphenol moieties on the erythrytyl skeleton 41. In this process, the second Mitsunobu reaction (conversion of 44 to 45) is low yielding because of steric hindrance. Also it is interesting to note that simultaneous introduction of two molecules of 2-iodo-3,5-dimethoxyphenol on 41 failed miserably. Treatment of 45 with n-BuLi followed by the addition of CuCN-TMEDA led to the in situ formation of a higher order cyanocuprate intermediate, which gave 46 upon exposure to dry oxygen at -78 °C in 75% yield. This process induces chirality in biphenyl 46, which is converted to biphenol 50 in four steps (Scheme 6). The diastereomeric excess of 50 was found to be 81% by an examination of ¹H-NMR spectra of the corresponding (S)-Mosher's ester **51**. Diacetate **52**, synthesized from 50, underwent a TiCl₄-promoted Friedel-Crafts rearrangement to afford 53 in 94% yield. Following Aldol reaction with *p*-anisaldehyde, bichalcone 54 was obtained in 80% yield, which was cyclized to biflavanoid **6f** using I₂-DMSO in 60% yield. Selective demethylation of **6f** with BCl₃ in CH₂Cl₂ at 0 ^oC gave (+)-**6j** in 84% yield. The absolute configuration of the synthetic (+)-6j [$[\alpha]^{22}_{d}$ +76.6 (EtOH)] was found to be 'R' [84].

[Scheme 6]

Similar approach has been used to synthesize biflavonoids **3f** and **13a** (Tables 1 and 3) in four steps from benzyl 4-iodo-3,5-dimethoxyphenylether **55** (**Scheme 7**). Aryl iodide **55** was subjected to the Ullmann coupling to give 4,4'-dibenzyloxy-2,2',6,6'-tetramethoxybiphenyl **56**,

which on Hoesch reaction yielded 4,4'dihydroxy-3,3'-diacetyl-2,2',6,6'-tetramethoxybiphenyl **57**. Aldol condensation with *p*-anisaldehyde, followed by oxidative cyclization with selenium dioxide gave I-6, II-6-biapigenin **3f**. In contrast, bichalcone **58** in refluxing alcoholic phosphoric acid for three weeks gave 6,6''-binarigenin hexamethylether **13a** [78,81].

[Scheme 7]

[I-3, II-3]-Biflavones **1b** and **1c** (Table 1) have also been synthesized using the biphenyl precursor approach. Friedel-Crafts acylation of **59** with succinyl chloride gave butane-1,4-dione **60** in 65% yield, which on selective demethylation with boron trichloride gave **61** in 98% yield. Esterification of **61** with either benzoyl or anisoyl chloride afforded ester **62a** and **62b**, respectively, which on Baker-Venkataraman rearrangement gave phenols **63a** (90% yield) and **63b** (89% yield), respectively. Acid-catalyzed ring closure of the phenols yielded [I-3,II-3]-biflavones **1b** and **1c** in yields of 95% and 88%, respectively [85] (**Scheme 8**). This appears to be the best yielding synthesis of biflavones and open up a novel route to the synthesis of sterically hindered [I-3, II-3]-linked biflavanoids.

[Scheme 8]

Only one biflavonoid containing an oxymethylene linker has been synthesized using the biphenyl precursor approach, although it is expected to work with many similar systems. Quinacetophenone **64** was methylenated with methylene iodide in the presence of potassium carbonate to obtain **65**, which was condensed with benzoic anhydride to yield [I-6,II-6]-biflavonyloxymethane **27a** (Table 7) in good yields [86] (**Scheme 9**).

[Scheme 9]

[I-4',II-4']-Linked biflavonylethers **20d** and **17a** (Table 6) have also been synthesized by building upon the biphenyl structure. Biphenylether **66** was esterified with 2'-hydroxy-4'6'-

dimethoxyacetophenone to obtain **67**, which on heating at 120 ^oC under basic conditions for 10 minutes rearranged to **68**. Cyclization of **68** under strongly acidic conditions gave **17a**. An identical procedure was followed for synthesizing **20d** [87] (**Scheme 10**).

[Scheme 10]

C. Metal-Catalyzed Cross-Coupling of Flavones

Although several metal-catalyzed cross-coupling reactions are being used to form carboncarbon bonds, the synthesis of biflavanoids has primarily involved Stille coupling and Suzuki coupling only, both of which utilize the exquisite ability of palladium to cross-couple aryl groups. Stille, the father of coupling reactions with organostannanes, synthesized symmetrical [I-7,II-7]biflavone **5b** (Table 1) by cross-coupling of flavone triflate **72** with 0.5 equivalents of distannane [88] (**Scheme 11**). Flavone triflates have been found to cross-couple with a variety of organostannanes under neutral conditions in the presence of lithium chloride and a Pd(0) catalyst. The technique tolerates various functional groups including alcohol, ester, nitro, acetal, ketone, and aldehyde. The concentration of hexamethylditin determines whether an aryltrimethylstannane or a symmetrical biaryl is formed. Stille et al. standardized all palladium-catalyzed cross-coupling reactions with organostannanes into two methods involving the use of Pd(PPh₃)₄ or PdCl₂(PPh₃)₂ in either dioxane or DMF, respectively [88].

[Scheme 11]

Suzuki coupling, which utilizes arylboronic acids, has also been used to synthesize biflavanoids **7e-j** [89] (**Scheme 12**). Two approaches have been devised to synthesize biflavones. In the first approach, flavoneboronic acids were synthesized, followed by their catalytic coupling with appropriate iodoflavones. Thus, 8-flavoneboronic acids **76** and **77** were prepared by lithiation of iodoflavones **73** and **74** at -78 ^oC followed by reaction with trimethylborate. Partial solubility of

iodoflavone **75** at -78 ^oC limits successful lithiation. Another problem with this approach is the catalytic coupling of boronic acids **76** and **77** with 3'-iodoflavones **78** and **79** in which competitive protodeboronation of the boronic acid moiety occurs resulting in lower yields. However, the yield of the coupled products, biflavones **7e** – **7j** (Table 2) could be improved to nearly 90% through use of excess boronic acid derivatives [89] (**Scheme 12**).

[Scheme 12]

Alternatively, instead of direct coupling of the two flavone rings, the second flavone ring could be built after the Suzuki coupling of a phenyl boronic acid, as exemplified in the synthesis of **7d** (Table 2) (**Scheme 13**) [87]. Thus, boronic acid **80** was coupled with iodoflavone **78**, followed by Lewis-acid catalyzed acylation of **81** with *p*-methoxy cinnamic acid. In the course of acylation, regioselective demethylation of the diorthosubstituted methoxy group occurred to give chalcone **82**, from which the second flavone ring of [I-3',II-8] biflavone **7d** was built through a standard oxidative cyclization reaction [89] (**Scheme 13**).

[Scheme 13]

The Suzuki coupling was also exploited to synthesize **8a** from iodoflavone **88** boronate ester **93** [74,90] (**Scheme 14**). In this convergent process, **88** and **93** were synthesized independently in five and three steps, respectively, by employing traditional reactions. An interesting aspect of these reactions was the chemoselective 4'-*O* and 7-*O*-gem-difluoromethylenation of **85** to give **86** using HCF₂Cl under basic conditions, which did not difluoroalkylate the strongly hydrogen bonded 5-OH group. Regioselective iodination, followed by methylation of **86** gave **88** in good yields. A nearly identical set of reactions, i.e., acylation, aldol condensation, iodination, and methylation, lead to the synthesis of **93** in good yields. The final tetrakistriphenylphosphine-catalyzed cross-

coupling of **88** and **93** under standard Suzuki conditions gave the unsymmetrical [I-3', II-6] biflavone **8a** in 33% yield.

[Scheme 14]

The synthesis of robustaflavone **8b** (Table 2) was attempted by both Stille and Suzuki couplings [90]. Apigenin 7,4'-dimethyl ether **95** was regioselectively iodinated using thallium-assisted iodination. This appears to be the only method for the preparation of 6-iodoapigenin derivatives and is likely to be the most only efficient method for the synthesis of 6-halogenated flavones. The other coupling partner necessary for Stille and Suzuki couplings, i.e., **99** and **100**, respectively, was prepared from 3'-iodoapigenin trimethyl ether **98**. Whereas the 3'-stannane **100** repeatedly failed to couple with **97** under several different Stille conditions, Suzuki coupling between boronate **99** and iodide **97** worked successfully to give robustaflavone hexamethyl ether **8b** in reasonably good yields [90] (**Scheme 15**).

[Scheme 15]

The exact reasons why Stille coupling failed, where Suzuki coupling succeeded are not clear. Transmetalation from tin to palladium is the rate-limiting step in Stille couplings. Because the iodide **97** is particularly reactive toward oxidative addition, which is made more feasible by the presence of two electron-donating methoxy groups, reduction of the aryl iodide occurs much faster than transmetallation. In contrast, transmetalation from boron to palladium in Suzuki coupling is rapid and oxidative addition, and is generally the rate limiting step [90].

D. Wessely-Moser Rearrangements

The Wessely-Moser rearrangement occurs frequently in monoflavanoids and is characterized by the reorganization of 5,7,8-subsituents to a 5,6,7-substitution pattern under acidic conditions (**Scheme 16**). In this process, the heterocyclic ring of the monoflavanoid undergoes acid-catalyzed ring opening, followed by recyclization with either of the two *ortho*–OH groups to give an equilibrium mixture of the two substitution patterns.

[Scheme 16]

Nakazawa showed that hydroiodic acid in acetic anhydride can convert the C4'-O-C8 isomer of hinokiflavone pentamethyl ether into the natural C4'-O-C6 hinokiflavone *via* the Wessely-Moser rearrangement [91]. Later, Seshadri and co-workers, who had previously reported an incorrect linkage of the natural product, hinokiflavone, established that the same rearrangement had occurred during the course of their Ullmann reaction [92]. Likewise, Pelter et al. treated (+)cupressuflavone hexamethyl ether **6f** with hydroiodic acid at 130-140 ^OC for 8 hours followed by per-methylation to give a mixture of (\pm)-agithisflavone hexamethyl ether **4a** (Table 2) and (\pm)cupressuflavone hexamethyl ether **6f** in a ratio of 3:2 (w/w) [93] (**Scheme 17**). This equilibrium conversion represented the first preparation of a member of the agathisflavone family. Benzeneinduced ¹H NMR solvent shifts were used to verify the linkage positions in agathisflavone and cupressuflavone [69,93].

[Scheme 17]

E. Phenol Oxidative Coupling of Flavones

In view of the success achieved in synthesizing natural products by oxidative coupling of phenolic monomers using one-electron oxidizing agents, flavanoid chemists have also attempted to synthesize biflavanoids using a similar strategy. Further, oxidative coupling of monoflavanoids provides a unique route because it is likely to follow the natural biosynthetic process. Also, this approach can work on an unprotected polyphenol skeleton, unlike several other synthetic approaches that require the use of protection-deprotection strategies.

15

Apigenin **101** was subjected to oxidative coupling using alkaline potassium ferricyanide to produce two biflavanoids, **3I** and **1b** (Table 1 and 2), with [I-3',II-3] and [I-3, II-3] linkages [94] (**Scheme 18**). The investigators suggested that these inter-flavone linkages arise due to coupling of two radicals. Though these inter-flavone linkages have not been encountered in nature thus far, it is likely that they will be found. Coupling of mesomeric radicals does not explain the formation of the natural biflavones that possess inter-flavone linkages at C-6 and C-8 positions of the A ring. Electron spin resonance studies show that delocalization of an unpaired electron at the C-4' –OH group in apigenin **101** occurs only in the B and C ring [94]. Thus, the radical generated on C-4' –OH group of apigenin **101** through oxidative coupling can delocalize to C-3', C-1', or C-3 positions. This delocalized radical then attacks the electron rich C-6 and C-8 positions of ring A resulting in the electrophilic substitution, rather than electron pairing.

[Scheme 18]

Other investigators have suggested that radical generation on the A ring of apigenin is possible when the C-4' and C-7 hydroxyls are protected with methyl groups. A plausible proof of this hypothesis is the oxidative dimerization of apigenin-4',7-dimethyl ether **102** with ferric chloride in boiling dioxane that gives a [I-6,II-6]-coupled biflavone **3k** (Table 1) in 6% yield [58] (**Scheme 19**). Like flavones, oxidative dimerization of flavanones has been found to produce biflavanones [95,96].

[Scheme 19]

Electrochemical reduction of flavone **103** using a H-type cell and glass-filter diaphragm equipped with a series of electrodes and supporting electrolytes, including sulfuric acid or *p*-toluenesulfonic acid, yielded two dimers, racemic and meso forms of 2,2'-biflavanone **11a** (Table 3), and a reduced monomer, flavanone **104** [97] (**Scheme 20**). Yields in the electrochemical

reduction were largely affected by the nature of electrodes and the supporting electrolytes, as well as the reaction temperatures. Electrolytic coupling of α , β -unsaturated carbonyl compounds have two primary modes of dimerization that include coupling at the β -carbon or at the α -carbon. Often β , β -coupling is major reaction outcome. Interestingly, although flavone **103** has a phenyl substituent at the 2-position, coupling at the β -position was still the major mode. The proposed mechanism of the electrochemical reduction of flavone **103** is as shown in **Scheme 21**.

[Scheme 20]

Protonation of flavone **103** followed by electrochemical reduction is likely to give a 2flavonyl radical **107**. This radical is proposed to react with monomer **103** to give a radical intermediate, which is further electrochemically reduced to give 2,2-linked biflavanone **11a** (Table 3). The coupling between **107** and **103** could either be symmetrical or unsymmetrical resulting in either racemic or meso products. Alternatively, radical **107** may undergo protonation and one electron reduction to give the reduced mono flavonoid **104**, which is a byproduct of the reaction (**Scheme 21**) [97].

In a manner similar to electrochemical reduction, photolysis of flavone **103** using 254 nm or 306 nm UV light in the presence of an electron donating amine, e.g., Et₃N, in acetonitrile readily produces racemic and meso [I-2,II-2]-biflavanone **11a** and reduced flavanone **104** (**Scheme 20**). The yield of **11a** is dependent on the molar ratio of substrate to amine, the type of amine and solvent, and the irradiation source [98] (**Scheme 20**).

The proposed mechanism of this photolysis is also depicted in **Scheme 21**, as it is similar to that of electrochemical reduction. Photolysis of flavone **103** with electron donor triethylamine undergoes a dominant pathway of single electron transfer (SET) to produce an exciplex **105** or contact ion radical pair **106**, followed by the proton transfer to yield a contact ion radical in a cage.

17

This radical has a structure similar to that of **107**, except for its location in a cage with an associated amine. After escaping out of the cage, radical **107** follows a process described above in case of electrochemical reduction to yield racemic or meso **11a**. The photolytic process also affords reduced byproduct flavanone **104** through enol **112** (**Scheme 21**) [98].

[Scheme 21]

F. Ullmann Condensation with Flavone Salts

This is a modified Ullmann reaction which involves the copper-catalyzed coupling of a halogenated flavone with a nucleophilic flavone salt, thereby providing a hetero-atom-linked biflavanoid in a single step. The reactivity of the halogen atom for Ullmann condensation could be enhanced by introducing an electron withdrawing nitro group *ortho* to the halogen. Thus, flavones **151** and **152** were successfully coupled under the modified Ullmann conditions in 85% yield using DMSO as the high boiling solvent. Reductive elimination of the nitro group produced the C4'-O-C8-linked biflavanoid **19a** (Table 6) [91] (**Scheme 22**). Likewise, the synthesis of the isomeric C4'-O-C6-linked biflavanoid, hinkoflavone pentamethyl ether **18b** (Table 6), was also accomplished using this methodology from the flavones **151** and **153** (**Scheme 23**). The synthesis of **18b** and **19a** provided the conclusive proof that hinokiflavone has C4'-O-C6 linkage, rather than the C4'-O-C8 linkage [91]. The resolution of poor reactivity of halo-flavones in Ullmann condensation using the nitro group strategy paved the way for the synthesis of several other biflavanoids, e.g., **20a** – **20c** (Table 6) [99,100].

[Scheme 22]

[Scheme 23]

Nakazawa and co-workers have further shown that Wessely-Moser rearrangement (Method D) could convert the C4'–O–C8-linked **19a** to a C4'–O–C6-linked **18a** [91]. These findings were

confirmed by Seshadri and coworkers [77]. They studied the possible rearrangement of C4[°]–O–C8-linked biflavonyl ether under several conditions including heating with activated copper bronze in the presence and absence of a base. In each case, the flavone underwent demethylation, except in the presence of a base where it underwent the Wessely-Moser rearrangement [92].

G. Nucleophilic Substitution

Methylenation of a phenolic group is a common natural process, often encountered in lignan, alkaloid, and flavanoid biosynthesis. Mono-methylenation is straightforward when only two symmetrical –OH groups are to be alkylated, however, when the scaffold contains several hydroxyl groups, numerous competing reactions make the reaction challenging [101]. Nucleophilic substitution reactions have been most commonly used to produce dialkyl-linked biflavones and biflavanones. The procedure involves refluxing monohydroxyflavones in acetone solution with alkyl di-iodide or di-bromide in the presence of potassium carbonate to produce biflavonyloxyalkanes. This method has produced symmetrical biflavonyloxymethanes 21e, 21j, 21k, 21l, 21m, 21n, 21o, 21p, 21q, 27a, 28a, 28b, 29a, 30a and 31a (Table 7) [50,51,101-103] and the symmetrical biflavanyloxymethanes 32a and 32b (Table 9) [103]. Thus, the flavanoid skeletons have been linked at 3, 6, 7, 8, 2' and 4' positions. An illustrative example of these reactions is the synthesis of biisoflavone 156 (Table 7) as shown in Scheme 24. Finally, despite its simplicity, attempts to isolate [I-5-OCH₂O-II-5]-biflavonyloxymethanes from techochrysin, apigenin dimethyl ether, and galangin dimethyl ether were unsuccessful due to extensive resinification [101].

An interesting nucleophilic substitution reaction was utilized by Seshadri et al. to synthesize biflavonylmethane **159** (**Scheme 25**). Reaction of resacetophenone **157** with methylene iodide

19

under alkaline conditions gave the *C*-methylenated product **158**, which could be elaborated into biflavanoid **159** [101].

[Scheme 24]

[Scheme 25]

In contrast to the symmetrical molecules discussed above, unsymmetrical dialkoxybiflavanoids are more challenging, although unsymmetrical biflavonyloxymethanes **22a**, **22b**, **23a**, **23b**, **23c**, **23d**, **23e**, **24a**, **24b**, **25a**, **25b**, and **27a** (Table 8 and 9) [102,104,105] have been synthesized starting from two different hydroxyflavones. In nearly all cases, a mixture of three compounds, two symmetrical products and one unsymmetrical product, was observed. However, when 7-methoxyflavanol was used, only two compounds were obtained, of which the unsymmetrical biflavonyloxymethane **22a** was the major product. Interestingly, the symmetrical [I-3,II-3]-biflavonyloxymethane was not formed. Competition at the initial nucleophilic displacement stage, where the phenoxide ion reacts with methylene iodide to yield the intermediate iodomethyl derivative, governs the rate of the reaction. The predominance of the phenoxide ion, and its iodomethyl derivative, is based on the acidity of the hydroxyl groups [105].

Higher-ordered alkoxybiflavanoids **21i** and **21f** – **21h** (Table 7) were synthesized by heating the appropriate flavanol with 1,4-dibromobutane or 1,2-dibromoethane in the presence of anhydrous potassium carbonate until the solution gave a negative ferric chloride test. These biflavonyloxyalkanes were recrystallized in 20-30% yield [106]. An alternative method involving a phase transfer catalyst, tetrabutylammonium iodide, has been used in the synthesis of biflavonyloxyalkanes **21a** – **21d** (Table 7) from appropriate 1,n-dibromoalkanes. Instead of long reaction times in the previous case, the synthesis here was complete in one hour. The use of tetrabutylammonium iodide is a new introduction to this nucleophilic substitution, which appears to solubilize K_2CO_3 in acetone, thereby speeding up the reaction and giving higher yields (45-60%) [107]. **27a** (Table 7) is the only biflavonyloxymethane that has been synthesized both by this method and Method B.

H. Dehydrogenation of Biflavanones into Biflavones

Dehydrogenation of the saturated biflavanoid ring system to the α , β -unsaturated system is an attractive way to generate analogs for structure-activity studies and has also been used to characterize natural biflavanoids. Most work on the conversion of biflavanone to biflavone has been conducted on [I-3,II-3]-dimers. Dehydrogenation is typically achieved with either Fenton's reagent, alkaline potassium ferricyanide, SeO₂, or NBS.

The oxidation of 4-oximinoflavan **160** with SeO₂ in aqueous dioxane gave flavane **165**, which on oxidative dimerization resulted in the formation of the [I-3,II-3] biflavone **12a**. Dehydrogenation with NBS gave biflavone **1a** [95] (**Scheme 26**). Likewise, flavanone hydrazones have also been oxidized with SeO₂ in aqueous dioxane to produce flavones, which on oxidative coupling and dehydrogenation using NBS generate [I-3,II-3] biflavones **1a**, **1f**, **1g** and **1h** [96] (**Scheme 26**). NBS is the favored reagent for dehydrogenation of **14a** and **14b** (Table 4) to synthesize **4a** and **4c**, respectively [78]. It has also been used to synthesize **6j** [108]. Alternatively, dehydrogenation of semicarpetin and galluflavanone was achieved with iodine and potassium acetate in acetic acid under reflux to generate **7d** [109], and **7k** and **7l** [110] (**Scheme 27**).

[Scheme 26]

[Scheme 27]

I. Hydrogenation of Biflavone into Biflavanone

The reverse of dehydrogenation, i.e., hydrogenation, is also a useful strategy for rapid generation of analogs. However, in contrast to dehydrogenation, hydrogenation can be controlled

to generate mono-hydrogenated and di-hydrogenated biflavanoids, thereby affording greater structural diversity. When catalytic hydrogenation of biflavone **1e** was performed at 80 ^oC in glacial acetic acid for 4 h, mono-hydrogenated **15a** was obtained almost exclusively, while prolonging the reaction time to 12 h generated both **15a** and **12k** (**Scheme 28**). Unfortunately, the overall yield in this process is not very attractive (~37% yield). As would be expected, it was possible to get **12k** from **15a** by extended hydrogenation [111]. The reason hydrogenation of **1e** is difficult is because double bond is fully substituted. Li et al. experimented with several hydrogenating conditions including Pd/C-EtOH, Pd/C-EtOAc, PtO₂-EtOH, PtO₂-EtOAc, Raney-Ni, TiCl₃ and Pd/C-NH₄-COOH-MeOH, but none of the conditions gave high yields [111].

[Scheme 28]

III. Conclusions

The discovery of several biological activities associated with natural biflavanoids has greatly increased the need for rapid synthesis of these structures. Since the time of their discovery, a number of synthetic approaches have been devised, although a majority of the reported strategies focus on preparing a select group of biflavanoid structures. Thus, symmetrical biflavanoids are made through Ullmann coupling, while their unsymmetrical counterparts are synthesized using Stille or Suzuki coupling. Likewise, the synthesis of diether-linked or alkyl-linked biflavanoids appears to utilize nucleophilic substitution approach, while electrochemical or photochemical approaches have been devised to prepare the sterically hindered [I-2,II-2]-linked structures. A significant concern with these approaches is the yield of synthesis. Further, a robust approach that rapidly generates a large number of biflavanoids for structure-activity studies is highly desirable. Yet, the current approaches have yielded a large number of structurally diverse biflavanoids.

Further improvement in the synthetic strategies is expected to result in the discovery of more potent biflavanoids.

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Table 1. Carbon-Carbon Linked Symmetrical Biflavones

	R _{I/II-3}	R _{I/II-5}	R _{I/II-6}	R _{I/II-7}	R _{I/II-8}	R _{I/II-2} ,	R _{I/II-3'}	R _{I/II-4} ,	R _{I/II-5} ,	R _{I/II-6} ,	Method	Reference
[I-3, II	-3] –Linke	ed										
1a	[-]*	Н	Η	Η	Н	Н	Н	Н	Н	Н	A,E,H	[64,95,96,112]
1b	[-]*	OMe	Н	OMe	Н	Н	Н	OMe	Н	Н	E,B	[85,93]
1c	[-]*	OMe	Н	OMe	Н	Н	Н	Η	Н	Н	В	[85,111]
1d	[-]*	OH	Н	OMe	Н	Н	Н	Н	Н	Н	В	[111]
1e	[-]*	OMe/OH	Н	OMe	Н	Н	Н	Η	Н	Н	В	[111]
1f	[-]*	Н	Н	Η	Н	Н	Н	OMe	Н	Н	E,H	[96]
1g	[-]*	Н	Me	Η	Н	Н	Н	Н	Н	Н	E,H	[96]
1h	[-]*	Н	Me	Η	Н	Н	Н	OMe	Н	Н	E,H	[96]
[I-5, II-5] –Linked												
2a	Н	[-]*	OMe	Н	Н	Н	Н	Η	Н	Н	А	[65]
[I-6, II-6] –Linked												
3a	Н	Н	[-]*	Η	Н	Н	Н	Н	Н	Н	A,B	[60,64,112]
3 b	Н	Н	[-]*	OMe	Н	Н	Н	Η	Н	Н	A,B	[65,66,113]
3c	COPh	Н	[-]*	OMe	Н	Н	Н	Н	Н	Н	А	[66]
3d	COPh	Н	[-]*	Η	Н	Н	Н	Н	Н	Н	A,B	[60]
3e	Н	Н	[-]*	OMe	Н	Н	Н	OMe	Н	Н	A,B	[65,80]
3f	Н	OMe	[-]*	OMe	Н	Н	Н	OMe	Н	Н	В	[45,81,114]
3g	Н	Н	[-]*	Н	Н	Н	Н	OMe	Н	Н	А	[112]
3h	Н	OMe	[-]*	OMe	Н	Н	Н	Н	Н	Н	В	[66]
3i	Н	OH	[-]*	OMe	Н	Н	Н	Н	Н	Н	В	[66]
3ј	Н	Ots	[-]*	OMe	Н	Н	Н	Η	Н	Н	В	[66]
3k	Н	OH	[-]*	OH	Н	Н	Н	OH	Н	Н	С	[58]
[I-7, II	-7] –Linke	ed										
5a	Н	Н	Н	[-]*	Н	Н	Н	Η	Н	Н	А	[64,112]
5b	Н	OH	Η	[-]*	Н	Н	Н	Н	Н	Н	С	[88]
5c	Н	Н	Н	[-]*	Н	Н	Н	OMe	Н	Н	А	[64,112]
[I-8, II	-8] –Linke	ed										
6a	Н	H/OMe	Н	OMe	[-]*	Н	Н	Н	Н	Н	В	[115]
6b	Н	Н	Н	OMe	[-]*	Н	Н	OMe	Н	Н	A,B	[67,80]

6c	Н	Н	Н	Н	[-]*	Н	Н	OH	Н	Н	А	[67]
6d	Н	Н	Н	OMe	[-]*	Н	Н	Н	Н	Н	А	[66,67]
6e	Н	Н	Н	OH	[-]*	Н	Н	Н	Н	Н	А	[67]
6f	Н	OMe	Н	OMe	[-]*	Н	Η	OMe	Н	Н	A,B,D	[63,68-72,75,80,82-84,116]
6g	Н	OH	Н	OMe	[-]*	Н	Η	OMe	Н	Н	A,B	[63,70,72,82-83]
6h	Н	Н	Н	Н	[-]*	Н	Н	Н	Н	Н	А	[64,112]
6i	OBz	Н	Н	OMe	[-]*	Н	Η	Н	Н	Н	А	[66]
6j	Н	OH	Н	OH	[-]*	Н	Н	OH	Η	Н	A,H	[72,75,108]
6k	OH	OMe	Н	OMe	[-]*	Н	Н	OMe	Н	Н	В	[117]
61	OAc	OMe	Н	OMe	[-]*	Н	Н	OMe	Н	Н	В	[117]
6m	Н	OMe	Н	OMe	[-]*	Н	Η	Н	Η	Н	A,B,D	[62,71-73,93]
6n	Н	OH	Н	OMe	[-]*	Н	Н	OH	Η	Н	А	[72]
60	Н	OH/OMe	Н	OMe	[-]*	Н	Η	OH	Н	Н	А	[72]
6р	OMe	OMe	Н	OMe	[-]*	Н	Η	OMe	Н	Н	А	[118]
6q	OH	ОН	Н	OH	[-]*	Н	Η	OH	Н	Н	А	[118]
6r	Н	OH	Н	OMe	[-]*	Н	Н	Н	Н	Н	А	[62]
6 s	Н	Oac	Н	OMe	[-]*	Н	Н	Н	Н	Н	А	[62]
[I-3', II-3'] –Linked												
9a	Н	Н	Н	OMe	Η	Н	[-]*	Н	Н	OMe	В	[61]
9b	Н	Н	Н	OMe	Н	Н	[-]*	OMe	Н	Н	В	[61]
9c	Н	Н	Н	Н	Н	OMe	[-]*	OMe	Н	Н	В	[61]
9d	Н	Н	Н	Н	Н	Н	[-]*	OMe	Н	OMe	В	[61]
9e	Н	Н	Н	Н	Н	Н	[-]*	Н	Н	Н	А	[64,112]
9f	Н	Н	Н	Н	Н	Н	[-]*	Н	Н	OMe	A,B	[60]
9g	Н	Н	Н	Н	Н	Н	[-]*	OMe	Н	Н	A,B	[60]
9h	Н	Н	H	OMe	H	H/OMe	[-]*	OMe	Н	OMe/H	В	[79]
9i	Н	OMe	Н	OMe	Н	Н	[-]*	OMe	OMe	Н	A	[118]
<u> </u>	H	OH	Н	OH	Н	Н	[-]*	OH	OH	Н	А	[118]
[1-4', 1	I-4'] –Lin	ked		**				5.3.4	**			564.4403
10a	Н	Н	H	H	H	Н	H	[-]*	Н	Н	A	[64,112]
10b	OH	H	H	H	H	OMe	H	[-]* □ יי	OMe	H	E	[119]
10C	UAC	H	H	H	H	OMe	H	[-]* □	OMe	H	E D	[119]
10d	Н	H	H	H	H	OMe	H	[-]* □ יי	OMe	H	В	[/9]
10e	Н	Н	Н	OMe	Н	OMe	Н	[-]*	OMe	Н	В	[79]

Table 2. Carbon-Carbon Linked Unsymmetrical Biflavones

	R _{I-3}	R _{I-5}	R _{I-6}	R _{I-7}	R _{I-3'}	R _{I-4'}	R _{I-5'}	R _{II-5}	R _{II-6}	R _{II-7}	R _{II-8}	R _{II-3'}	R _{II-4} ,	R _{II-5'}	Method	References
[I-3, II	[-3'] –Lii	nked														
31	[-]*	OMe	Н	OMe	Η	OMe	Н	OMe	Н	OMe	Η	[-]*	OMe	Н	Е	[94]
[I-6, II	[-8] –Lin	ked														
4a	Н	OMe	[-]*	OMe	Η	OMe	Н	OMe	Н	OMe	[-]*	Η	OMe	Н	B,D,H	[69,78,92,116]
4b	Н	Н	[-]*	OMe	Н	OMe	Н	Н	Η	OMe	[-]*	Η	OMe	Н	В	[80]
4 c	Н	OH	[-]*	OH	Η	OH	Н	OH	Н	OH	[-]*	Η	OH	Н	B,H	[78]
[I-3', I	I-8] –Lii	nked														
7a	Н	OBn	Н	OMe	[-]*	OMe	Н	OBn	Н	OBn	[-]*	Н	OBn	Н	А	[59,120]
7b	Н	OBn	Н	OMe	[-]*	OMe	Н	OBn	Η	OBn	[-]*	Η	OBn	Н	А	[59,120]
7c	Н	OH	Н	OMe	[-]*	OMe	Н	OH	Η	OH	[-]*	Η	OH	Н	А	[59,120]
7d	Н	OMe	Н	OMe	[-]*	OMe	Н	OMe	Н	OMe	[-]*	Η	OMe	Н	A,B,C,H	[76,89,109,121,122]
7e	Н	OMe	Н	OMe	[-]*	OiPr	Н	OiPr	Η	OiPr	[-]*	Η	OiPr	Н	С	[89]
7f	Н	OH	Н	OMe	[-]*	OH	Н	OH	Н	OH	[-]*	Η	OH	Н	С	[89]
7g	Н	OMe	Н	OMe	[-]*	OMe	Н	OiPr	Н	OiPr	[-]*	Η	OiPr	Н	С	[89]
7h	Н	OH	Н	OMe	[-]*	OMe	Н	OH	Н	OH	[-]*	Η	OH	Н	С	[89]
7i	Н	OMe	Н	OMe	[-]*	OMe	Н	OiPr	Η	OiPr	[-]*	Η	OMe	Н	С	[89]
7j	Н	OH	Н	OMe	[-]*	OMe	Н	OH	Н	OH	[-]*	Η	OMe	Н	С	[89]
7k	Н	Н	Н	OH	[-]*	OH	OH	Н	Н	OH	[-]*	OH	OH	OH	Н	[110]
71	Н	Н	Н	OMe	[-]*	OMe	OMe	Н	Н	Н	[-]*	OMe	OMe	OMe	Н	[110]
7m	Н	Η	Н	OMe	[-]*	OMe	Н	Н	Н	OH	[-]*	OMe	OMe	Н	Н	[123]
7n	Н	Н	Н	OMe	[-]*	OMe	Н	Н	Н	OMe	[-]*	OMe	OMe	Н	Н	[123]
7o	Н	OH	Н	OMe	[-]*	OMe	Н	OH	Н	Н	[-]*	Η	OMe	Н	А	[76]
7p	Н	OMe	Н	OMe	[-]*	OMe	Н	OMe	Н	OMe	[-]*	OMe	OMe	Н	А	[118]
[I-3', I	I-6] –Li	nked														
8a	Н	Н	Н	OMe	[-]*	OMe	Н	OMe	[-]*	OCF ₂ H	Η	Н	OCF ₂ H	Н	С	[74]
8b	Н	OH	Н	OH	[-]*	OH	Н	OH	[-]*	OH	Η	Η	OH	Н	С	[90]
8c	Н	OMe	Н	OMe	[-]*	OMe	Н	OMe	[-]*	OMe	Η	Η	OMe	Н	В	[122]

Table 3. Carbon-Carbon Linked Symmetrical Biflavanones

	R _{I/II-2}	R _{I/II-3}	R _{I/II-5}	R _{I/II-6}	R _{I/II-7}	R _{I/II-3} ,	R _{I/II-4} ,	Methods	Reference
[I-2, II-2] -	-Linked								
11a	[-]*	Н	Н	Н	Н	Н	Н	Е	[97,98,124-126]
11b	[-]*	Н	Н	Me	Н	Н	Н	E	[124]
[I-3, II-3] -	-Linked								
12a	Н	[-]*	Н	Н	Н	Н	Н	C,E	[95,96,127,128]
12b	Н	[-]*	Н	Н	Н	Η	OMe	C,E	[96,127,128]
12c	Н	[-]*	Н	Me	Н	Η	Н	E	[96,127]
12d	Н	[-]*	Н	Me	Н	Η	OMe	E	[96,127]
12e	Н	[-]*	Н	Η	Н	OMe	OMe	E	[127]
12f	Н	[-]*	Н	Me	Н	OMe	OMe	E	[127]
12g	Н	[-]*	Н	Н	OMe	Н	OMe	С	[128]
12h	Н	[-]*	OMe	Н	OMe	Н	OMe	С	[128]
12i	Н	[-]*	OH	Н	OMe	Н	OMe	С	[128]
12j	Н	[-]*	OH	Н	OH	Н	OH	С	[128]
12k	Н	[-]*	OMe	Н	OMe	Н	Н	Ι	[111]
[I-6, II-6] -	-Linked								
13a	Н	Н	OMe	[-]*	OMe	Н	OMe	В	[45,81]
13b	Н	OH	OMe	[-]*	OMe	Н	OMe	В	[114]

Table 4. Carbon-Carbon Linked Unsymmetrical Biflavanones

	R _{I-5}	R _{I-6}	R _{I-7}	R _{I-4} ,	R _{II-5}	R _{II-7}	R _{II-8}	R _{II-4} ,	Methods	References
[I-6, II-8]	-Linked									
14a	OH	[-]*	OH	OH	OH	OH	[-]*	OH	В	[78]
14b	OMe	[-]*	OMe	OMe	OMe	OMe	[-]*	OMe	В	[78]
Table 5. Carbon-Carbon Linked Flavanone-Flavone Dimers

	R _{I-3}	R _{I-5}	R _{I-7}	R _{I-4'}	R _{II-3}	R _{II-5}	R _{II-7}	R _{II-8}	R _{II-4} ,	Methods	References
[I-3, II-3]] –Linked										
15a	[-]*	OMe	OMe	Н	[-]*	OMe	OMe	Н	Н	Ι	[111]
[I-3, II-8]] –Linked										
16a	[-]*	Н	Н	OMe	Н	OMe	OMe	[-]*	OMe	Ι	[129]
16b	[-]*	OMe	OMe	OMe	Н	OMe	OMe	[-]*	OMe	В	[130]

*indicates site of linkage

Table 6. Monoether Linked Symmetrical and Unsymmetrical Biflavones

	R _{I-5}	R _{I-7}	R _{I-3'}	R _{I-4'}	R _{II-5}	R _{II-6}	R _{II-7}	R _{II-8}	R _{II-4} ,	Methods	Reference
[I-3'-O	-II-4'] –L	linked									
17a	OMe	OMe	[- O -]*	OMe	OMe	Н	OMe	Н	[-0-]*	В	[87]
[I-4'-O	-II-6] –Li	inked									
18a	OH	OH	Н	[-0-]*	OH	[-0-]*	OH	Н	OH	F	[91,92]
18b	OMe	OMe	Н	[-O-]*	OMe	[-O-]*	OMe	Н	OMe	F	[91,92]
18c	OMe	OMe	NO_2	[-O-]*	OMe	[-O-]*	OMe	Н	OMe	F	[91]
18d	OMe	OMe	NH_2	[-0-]*	OMe	[-0-]*	OMe	Н	OMe	F	[91]
18e	OMe	OMe	NHCOCH ₃	[-0-]*	OMe	[-0-]*	OMe	Н	OMe	F	[91]
18f	OH	OMe	Н	[-0-]*	OH	[-0-]*	OMe	Н	OMe	F	[91]
18g	OAc	OMe	Н	[-0-]*	OAc	[-0-]*	OMe	Н	OMe	F	[91]
18h	OAc	OAc	Н	[-0-]*	OAc	[-0-]*	OAc	Н	OAc	F	[91]
[I-4'-O	-II-8] –Li	inked									
19a	OMe	OMe	Н	[-0-]*	OMe	Н	OMe	[-0-]*	OMe	F	[68,77,91]
19b	OH	OH	Н	[-O-]*	OH	Н	OH	[-O-]*	OH	F	[77,91]
19c	OMe	OMe	NO_2	[-0-]*	OMe	Н	OMe	[-O-]*	OMe	F	[91]
19d	OMe	OMe	NH_2	[-O-]*	OMe	Н	OMe	[-O-]*	OMe	F	[91]
19e	OMe	OMe	NHCOCH ₃	[-0-]*	OMe	Н	OMe	[-O-]*	OMe	F	[91]
19f	OH	OMe	Н	[-0-]*	OH	Н	OMe	[-O-]*	OMe	F	[91]
19g	OAc	OMe	Н	[-0-]*	OAc	Н	OMe	[-O-]*	OMe	F	[91]
[I-4'-O	-II-4'] –L	linked									
20a	Н	Н	NO ₂	[-0-]*	Н	Н	Н	Н	[-0-]*	F	[99,100]
20b	Н	Н	NH_2	[-O-]*	Η	Н	Н	Н	[- O -]*	F	[99,100]
20c	Н	Н	Н	[-O-]*	Н	Н	Н	Н	[- O-]*	F	[99,100]
20d	OMe	OMe	OMe	[-O-]*	OMe	Н	OMe	Н	[-O-]*	В	[87]

*indicates site of linkage

Table 7. Diether-Linked Symmetrical Biflavones

	R _{I/II-3}	R _{I/II-6}	R _{I/II-7}	R _{I/II-8}	R _{I/II-2} ,	R _{I/II-3'}	R _{I/II-4} ,	Ν	Methods	Reference
[I-3-O (CH ₂) _n	0-II-3] –L	inked								
21a	[-n-]*	Cl	Η	Η	Н	Η	Н	2	G	[107]
21b	[-n-]*	Cl	Η	Η	Н	Η	Н	3	G	[107]
21c	[-n-]*	Cl	Η	Н	Н	Η	Н	4	G	[107]
21d	[-n-]*	Cl	Н	Н	Н	Н	Н	5	G	[107]
21e	[-n-]*	Н	Н	Н	Н	Η	OMe	1	G	[131]
21f	[-n-]*	Н	Н	Н	Н	Η	OMe	4	G	[106]
21g	[-n-]*	Me	Н	Н	Н	Н	Н	4	G	[106]
21h	[-n-]*	Me	Н	Н	Н	Η	OMe	4	G	[106]
21i	[-n-]*	Me	Н	Н	Н	Н	OMe	2	G	[106]
21j	[-n-]*	Н	OMe	Н	Н	Н	Н	1	G	[103]
21k	[-n-]*	Н	Н	Н	Н	Н	OMe	1	G	[103]
211	[-n-]*	Н	Н	Н	Н	Н	Н	1	G	[132]
21m	[-n-]*	Н	Н	Н	Н	Н	OMe	1	G	[132]
21n	[-n-]*	OMe	Н	Н	Н	Н	Н	1	G	[132]
210	[-n-]*	Me	Н	Н	Н	Н	OMe	1	G	[132]
21p	[-n-]*	Н	Н	Н	Н	OMe	OMe	1	G	[132]
21 q	[-n-]*	Me	Н	Н	Н	OMe	OMe	1	G	[132]
[I-6-O(CH ₂) _n	0-II-6] –L	inked								
27a	Н	[-n-]*	Н	Н	Н	Н	Н	1	G,J	[86,102]
[I-7-O(CH ₂) _n	0-II-7] –L	inked								
28a	Н	Н	[-n-]*	Н	Н	Н	Н	1	G	[101]
28b	OMe	Н	[-n-]*	Н	Н	Η	Н	1	G	[101]
[I-8-O(CH ₂) _n	0-II-8] –L	inked								
29a	OMe	Н	OMe	[-n-]*	Н	Н	Н	1	G	[102]
[I-2'-O(CH ₂)]		Linked								
30a	Η	Η	Η	Н	[-n-]*	Η	Н	1	G	[102]
[I-4'-O(CH ₂)]	n O-II-4'] –	Linked								
31 a	Н	Н	Н	Н	Н	Н	[-n-]*	1	G	[102]

*indicates site of linkage

Table 8. Diether Linked Unsymmetrical Biflavones

	R _{I-3}	R _{I-6}	R _{I-7}	R _{I-4'}	R _{II-6}	R _{II-7}	R _{II-8}	R _{II-2} ,	R _{II-4} ,	n	Methods	Reference
[I-3-O(CH ₂) _n O-II-3	3] –Link	ed									
22a	[-n-]*	Н	OMe	Н	[-n-]*	Η	Η	Н	Н	1	G	[105]
22b	[-n-]*	Н	Н	OMe	[-n-]*	Η	Н	Н	Н	1	G	[105]
[I-3-O(CH ₂) _n O-II-7	7] –Link	ed									
23a	[-n-]*	Н	Н	Н	Н	[-n-]*	Η	Н	Н	1	G	[104]
23b	[-n-]*	Н	Н	OMe	Н	[-n-]*	Н	Н	Н	1	G	[104,105]
23c	[-n-]*	Me	Н	Н	Н	[-n-]*	Н	Н	Н	1	G	[104]
23d	[-n-]*	Me	Н	OMe	Н	[-n-]*	Н	Н	Н	1	G	[104]
23e	[-n-]*	Н	OMe	Н	Н	[-n-]*	Н	Н	Н	1	G	[105]
[I-3-O(CH ₂) _n O-II-8	8] –Link	ed									
24a	[-n-]*	Н	OMe	Н	Н	Н	[-n-]*	Н	Н	1	G	[105]
24b	[-n-]*	Н	Н	OMe	Н	Η	[-n-]*	Н	Н	1	G	[105]
[I-3-O(CH ₂) _n O-II-2	2'] –Linl	ked									
25a	[-n-]*	Н	OMe	Н	Н	Н	Н	[-n-]*	Н	1	G	[105]
25b	[-n-]*	Η	Н	OMe	Н	Η	Н	[-n-]*	Н	1	G	[105]
[I-3-O(CH ₂) _n O-II-4	4'] –Linl	ked									
26a	[-n-]*	Н	OMe	Н	Н	Η	Н	Н	[-n-]*	1	G	[105]
26b	[-n-]*	Η	Н	OMe	Н	Η	Н	Н	[-n-]*	1	G	[105]

*indicates site of linkage

Table 9. Diether-Linked Symmetrical Biflavanones

	R _{I-7}	R _{I-4'}	R _{II-7}	R _{II-4} ,	n	Methods	Reference
[I-7-O(CH	2)n O-II-7] –Li	nked					
32a	[-n-]*	Н	[-n-]*	Н	1	G	[101]
33 a	[-n-]*	OH	[-n-]*	OH	1	G	[101]

*indicates site of linkage

Figure Legends

- **Figure 1. Structure of biologically important biflavanoids.** These biflavanoids, isolated from nature, have been the earliest molecules studied for biological activity. See text for details.
- Figure 2. Basic scaffold of flavanoids and biflavanoids. The bicyclic ring system is identified as rings A and B, while the unicyclic ring names as ring C. The two monomeric units in biflavanoids are identified using Roman numerals I and II. The numbering of positions in each case begins with the ring containing the oxygen atom. Note positions 9 and 10 refer to carbons at the fusion point.
- Figure 3. Structure of biflavanoid 29a.







Scheme Legends

- Scheme 1. Classical and modified Ullmann coupling.
- **Scheme 2.** Synthesis of cupressubiflavone hexamethylether and cupressubiflavone from iodo derivative of apigenin using Ullmann reaction. i) Cu/DMF, reflux; ii) AlCl₃.
- Scheme 3. Synthesis of ginkgetin using Ullmann coupling. i) Cu, neat, reflux; ii) 10% H_3PO_4 , acetic acid, 110 ^{O}C .
- Scheme 4. Synthesis of biflavonoid 9f.
- Scheme 5. Synthesis of biphenyls, the precursors of biflavanoids.
- Scheme 6. Synthesis of biflavonoid 6f and 6j. i) TBDSCl, imidazole, DMF; ii) 2-Iodo-3,5-dimethyloxyphenol, DEAD, n-Bu₃P: iii) n-BuNF; iv) 2-Iodo-3,5-dimethyloxyphenol, DEAD, n-Bu₃P; v) n-BuLi, CuCN-TMEDA (1:3), dry O₂; vi) 10% Pd/C, H₂; vii) NaI, acetone; ix) activated Zn-powder, EtOH; x) (S)-α-methoxy-α-trifluoromethyl)-phenylacetyl chloride, 4-DMAP, Et₃N; xi) TiCl₄, benzene; xii) *p*-anisaldehyde, KOH, cat. TEBACl, EtOH-H₂O (3:2); xiii) I₂, DMSO; xiv) BCl₃, CH₂Cl₂.
- Scheme 7. Synthesis of biflavonoid 3f and 13a. i) Ullmann coupling; ii) Hoesh reaction (MeCN, ZnCl₂), HCl; iii) *p*-Anisaldehyde, base; iv) SeO₂, dioxane. v) H₃PO₄.
- Scheme 8. Synthesis of biflavonoid 1b and 1c. i) succinyl chloride (Friedel-Crafts reaction);
 ii) BBr₃; iii) Benzoyl chloride and anisoyl chloride, Py.; iv) Baker-Venkatraman rearrangement; v) acetic acid, H₂SO₄.
- Scheme 9. Synthesis of biflavonoid 27a.
- Scheme 10. Synthesis of biflavonoids 17a and 20d. i) SO₂Cl₂, 2'-hydroxy-4,6dimethoxyacetophenone; ii) Py., KOH, heat; iii) acetic acid, H₂SO₄.

- Scheme 11. Synthesis of biflavanoid 5b.
- Scheme 12. Synthesis of biflavonoids 7d and 7f-j. i) BuLi, B(OCH₃); ii) K₂CO₃, Pd(TPP)₄;
 iii) BCl₃/CH₂Cl₂.
- Scheme 13. Synthesis of biflavonoid 7d. i) K₂CO₃, Pd(TPP)₄; ii) *p*-CH₃O-C₆H₄-CH=CH-COOH, BF₃-Et₂O; iii) I₂, DMSO, H₂SO₄.
- Scheme 14. Synthesis of biflavonoid 8a. i-a) ClCH₂CN/ZnCl₂/HCl, i-b) H₂O; ii-a) phydroxybenzaldehyde, NaOH; iib) HCl; iii) HCF₂Cl/NaOH; iv) AgOAc/I₂; v) MeI/K₂CO₃; vi-b) ClCH₂CN/ZnCl₂/HCl; vi-b) H₂O; vii) 3-iodo-4methoxybenzaldehyde, NaOH; viii) MeI/K₂CO₃; ix) bis(pinacolato)diboran, PdCl₂(dppf), MeI/K₂CO₃; x) Pd(PPh₃)₄.
- Scheme 15. Synthesis of biflavonoid 8b. i) BBr₃; ii) TlOAc, I₂; iii) Me₂SO₄; iv) bis(pinacolato)diboran, PdCl₂, K₂CO₃; v) (SnMe₃)₂, Pd(PPh₃)₄; vi) Pd(PPh₃)₄, DMF/H₂O, NaOH.
- Scheme 16. Wessely-Moser rearrangement.
- Scheme 17. Synthesis of biflavonoid 4a. i) HI, (MeCO)₂O, heat.
- Scheme 18. Synthesis of biflavonoid **3l** and **1b**. i) Alkaline K₃Fe(CN)₆, (CH₃)₂SO₄.
- **Scheme 19.** Synthesis of biflavonoid **3k**. i) FeCl₃ in boiling dioxane.
- Scheme 20. Synthesis of biflavonoid 11a. i) Electrochemical reduction using MeOH/H₂SO₄;
 ii) Photolysis (300 nm), Et₃N, MeCN.
- **Scheme 21.** Mechanism of biflavanoid formation through electrochemical reduction and coupling or photolysis in the presence of amines.
- Scheme 22. Synthesis of 19a. i) Ullmann conditions; ii) H₃PO₄; iii) HI-Ac₂O.
- **Scheme 23.** Synthesis of **18a**. i) Ullmann conditions; ii) H₃PO₄; iii) HI-Ac₂O.

- Scheme 24. Synthesis of biisoflavone 156. i) CH₂I₂, K₂CO₃.
- Scheme 25. Synthesis of biflavonylmethane 159. i) CH₂I₂, NaOEt; ii) PhCl, K₂CO₃, then H₂SO₄, AcOH.
- Scheme 26. Synthesis of I-3, II-3 biflavanones and biflavones. i) SeO₂, Aq. dioxane; ii) SeO₂ in dioxane, reflux; iii) NBS.
- Scheme 27. Dehydrogenation of biflavanones. I) I₂, AcOK, AcOH.
- Scheme 28. Synthesis of biflavanoids 12k and 15a. i) Pd/C, H₂, AcOH, 4h; ii) Pd/C, H₂, AcOH, 12h.









Scheme 4







Scheme 6



Scheme 7



Scheme 8





Scheme 10









Scheme 14



Scheme 15







Scheme 18







Scheme 21








Scheme 25



- **162** $R_1 = H$, $R_2 = OMe$, $R_3 = NH_2$ **167** $R_1 = Me$, $R_2 = H$ **163** $R_1 = Me$, $R_2 = H$, $R_3 = NH_2$ **168** R_1 = Me, R_2 = OMe **164** $R_1 = Me$, $R_2 = OMe$, $R_3 = NH_2$
- **12b** R₁ = H, R₂ = OMe **12c** R₁ = Me, R₂ = H **12d** $R_1 = Me, R_2 = OMe$

1f $R_1 = H, R_2 = OMe$ **1g** $R_1 = Me, R_2 = H$ **1h** R_1 = Me, R_2 = OMe



