Total Synthesis of 3′,3‴-Binaringenin and Related Biflavonoids

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Abstract: The synthesis of natural 3′,3‴-binaringenin and four related biflavonoids was performed in good overall yield (15–35%) starting from readily available phloroglucinol and 4-hydroxy- or 4-methoxybenzaldehyde. Preliminary results indicate that some of these compounds have an interesting activity against *S. aureus*.

Key words: binaringenin, biapigenin, protecting groups, antibacterial activity

The biflavonoids are dimers of flavonoids with a carbonyl group on C4 (i.e., chalcones, flavanones, flavones, flavanols, flavonols, aurones, and isoflavones) that vary with the oxygenation pattern of their monomers, oxidation level of the C3 moiety, and interflavonyl linkage.[1–4]

The substitution pattern more commonly encountered is hydroxylation on C5, C7, and C4′, so the most abundant monomers are apigenin (4′,5,7-trihydroxyflavone, **1**), naringenin (4′,5,7-trihydroxyflavanone, **2**), and aromadendrin (4′5,7-trihydroxyflavanol, **3**) (Figure 1). The interflavonyl linkage may involve the A ring (at positions 5, 6, 7, or 8), the B ring (at positions 2′, 3′, 4′, 5′, or 6′), or the C ring (at positions 2 or 3), through C–C or C–O–C bonds. In this way, biflavonoids can be classified indicating the rings involved in the interflavonyl linkage (AA, BB, AB, CC, etc.).

Most natural biflavonoids contain an interflavonyl linkage between the B ring of one and the A ring of the other flavonoid moiety (AB type) or between two A rings (AA type) and are widely distributed in *Gymnosperms.* This is the case for cupressuflavone ([I-8,II-8]-biapigenin, **4**) and robustaflavone ([I-6,II-3′]-biapigenin, **5**). The interflavonyl linkage between the two B rings (BB type) is less common. In vascular plants, biflavonoids of this type are very rare, being found in *Pseudotsuga menziesii*[5] and some ferns such as *Selaginella chrysocaulos*.[6] They are often found, however, in mosses. For example the dimers 3′,3‴-binaringenin (**6**), and 3′,3‴-naringeninapigenin (**8**) were isolated from *Homalothecium lutescens* (Figure 1).[7] Recently, Zhao and Jiang isolated 3′,3‴-binaringenin (**6**) and its 5-monomethyl ether, thuidinin (4′,4‴,5″,7,7″-pentahydroxy-5-methoxy-3′,3‴-biflavanone, **7**) from *Thuidium kanedae*.[8] 3′,3‴-Binaringenin was also isolated from some species of *Pilotrichella*.[9–11]

Biflavonoids of the 3,3″-CC type, such as chamaejasmine (**10**) are very rare.[12–14]

Biflavonoids display several types of biological activity, namely antifungal,[15–17] antiviral,[18–20] antibacterial,[21,22] antioxidant,[23,24] antitumor,[18,25–29] antiplasmodial,[30] antiallergenic, anti-inflammatory,[31,32] hepatoprotective,[33–35] vasodilating,[36,37] and hypotensive[19,38–41] activity, sometimes better than that of the corresponding monomers.[31,42]

It is widely accepted that natural biflavonoids can be produced in vivo by formation of free radicals of two molecules of flavonoid, followed by oxidative coupling and modification of the C3 moiety. Considering this way of formation of biflavonoids and the fact that 3′,3‴-binaringenin (**6**) and 3′,3‴-naringeninapigenin (**8**) are natural, it was suggested that 3′,3‴-biapigenin (**9**) might be also a naturally occurring substance.[7]

To our knowledge, the total synthesis of 3′,3‴-binaringenin and 3′,3‴-biapigenin has not been described in the literature. However, 3′,3‴-biapigenin was obtained semisynthetically by dehydrogenation of natural 3′,3‴-binaringenin with iodine[7] and its methylated precursor (hexamethylbiapigenin) was obtained by Nakazawa by Ullmann condensation of 3-iodo-4,4′,6′-trimethylapigenin in 0.6% yield.[43]

As part of an ongoing project on the synthesis and biological evaluation of phenolic compounds,[44–47] we became interested in the preparation of biflavonoids. In particular, we describe in this paper the synthesis of some 3′,3‴-linked biflavonoids, **6**, **9**, and **14–16** from readily available reagents [phloroglucinol (**11**) and 4-hydroxybenzaldehyde (**12**) or *p*-anisaldehyde (**13**)] (Scheme 1). Previously, we reported the synthesis of hexa-*O*-methylbinaringenin,[46] but attempts at deprotection with boron tribromide under different conditions resulted in decomposition.[48] Considering the high functionalization of the biflavonoids shown in Scheme 1 and the difficulties encountered in deprotection of hexamethylbinaringenin, we decided to test all reactions using the model compounds **21**, **23**, **25**, **27**, and **30**. After some experimentation, the best conditions we found to obtain the model compounds are those indicated in Scheme 2.

The starting 2′-hydroxy-4-methoxychalcone (**20**) was prepared by aldol condensation of 2′-hydroxyacetophenone (**17**) with *p*-anisaldehyde (**13**) using sodium hydride in tetrahydrofuran at room temperature.[49–51] Deprotection of **20** under several different conditions was unsuccessful. Thus, treatment with two equivalents of boron tribromide,

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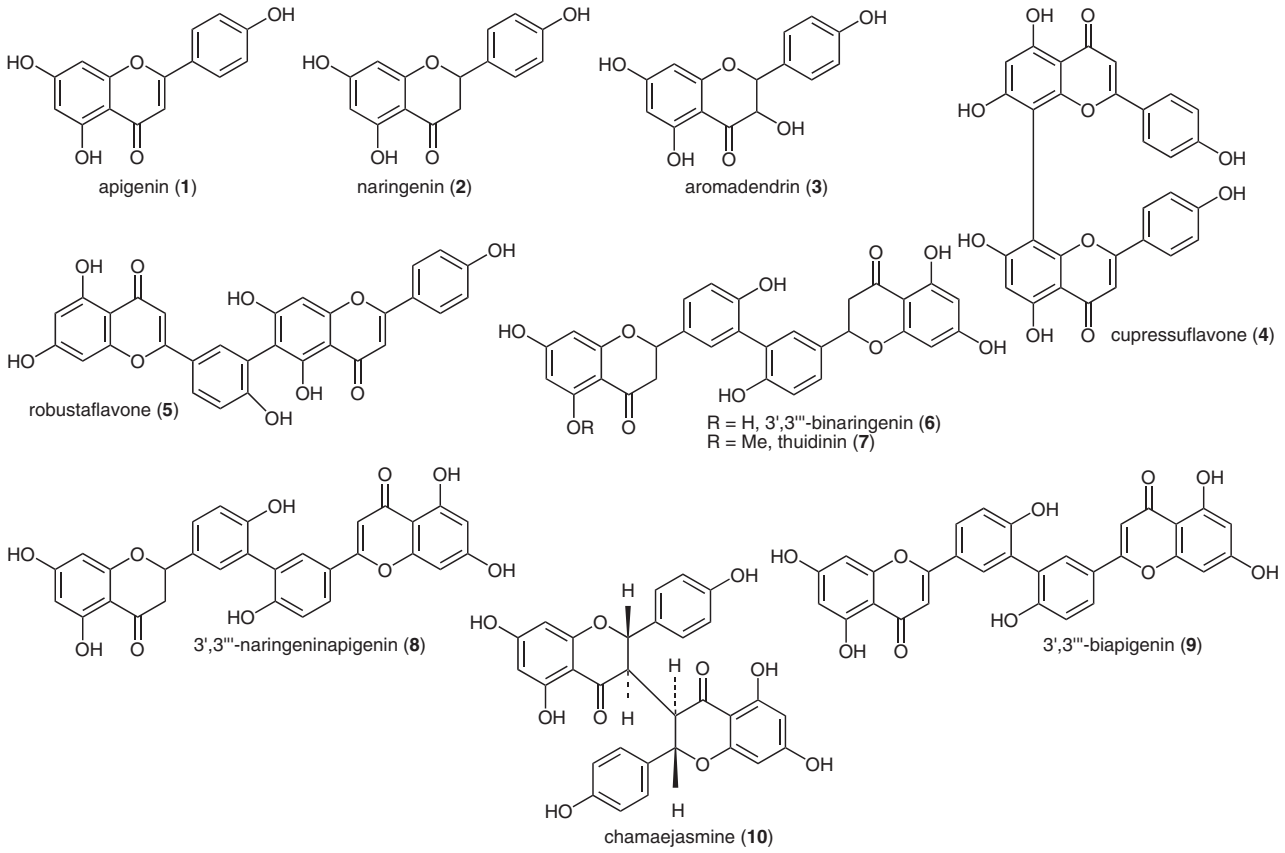
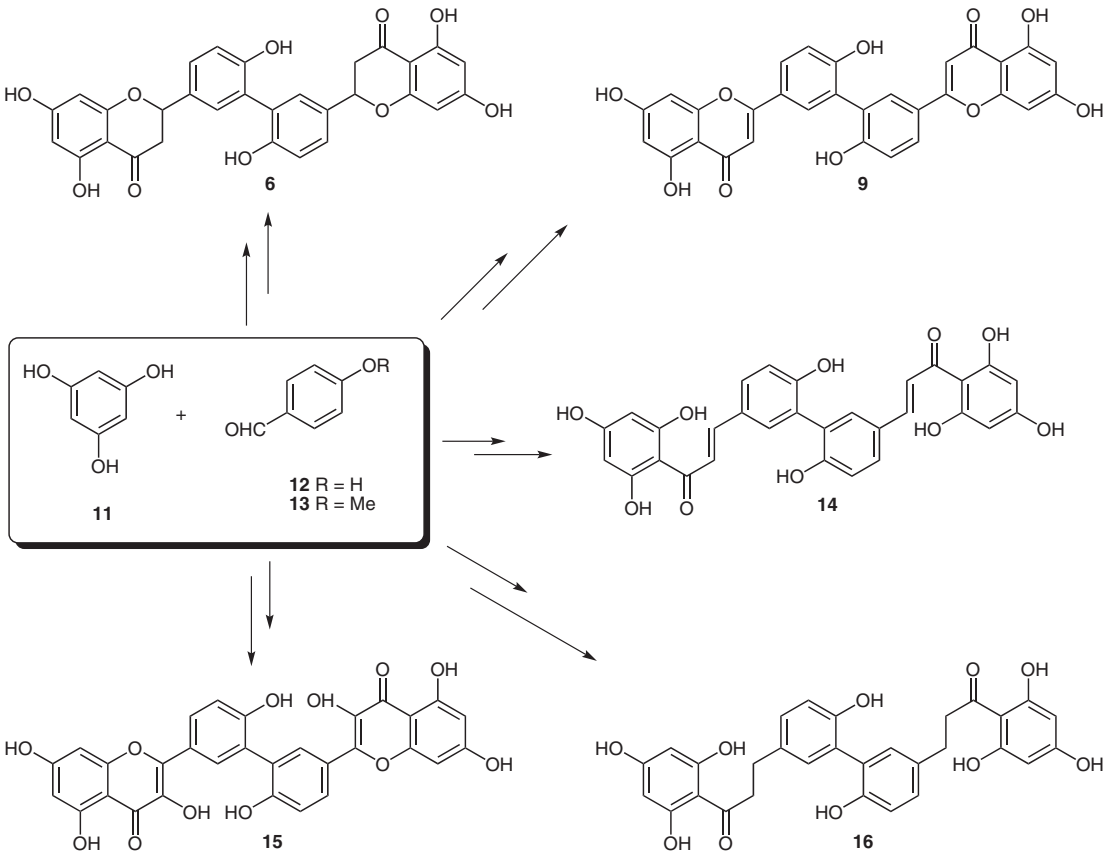


Figure 1 Flavonoid units commonly encountered in biflavonoids and some representative biflavonoids of the AA, AB, BB and CC types



Scheme 1 Biflavonoids synthesized in this work

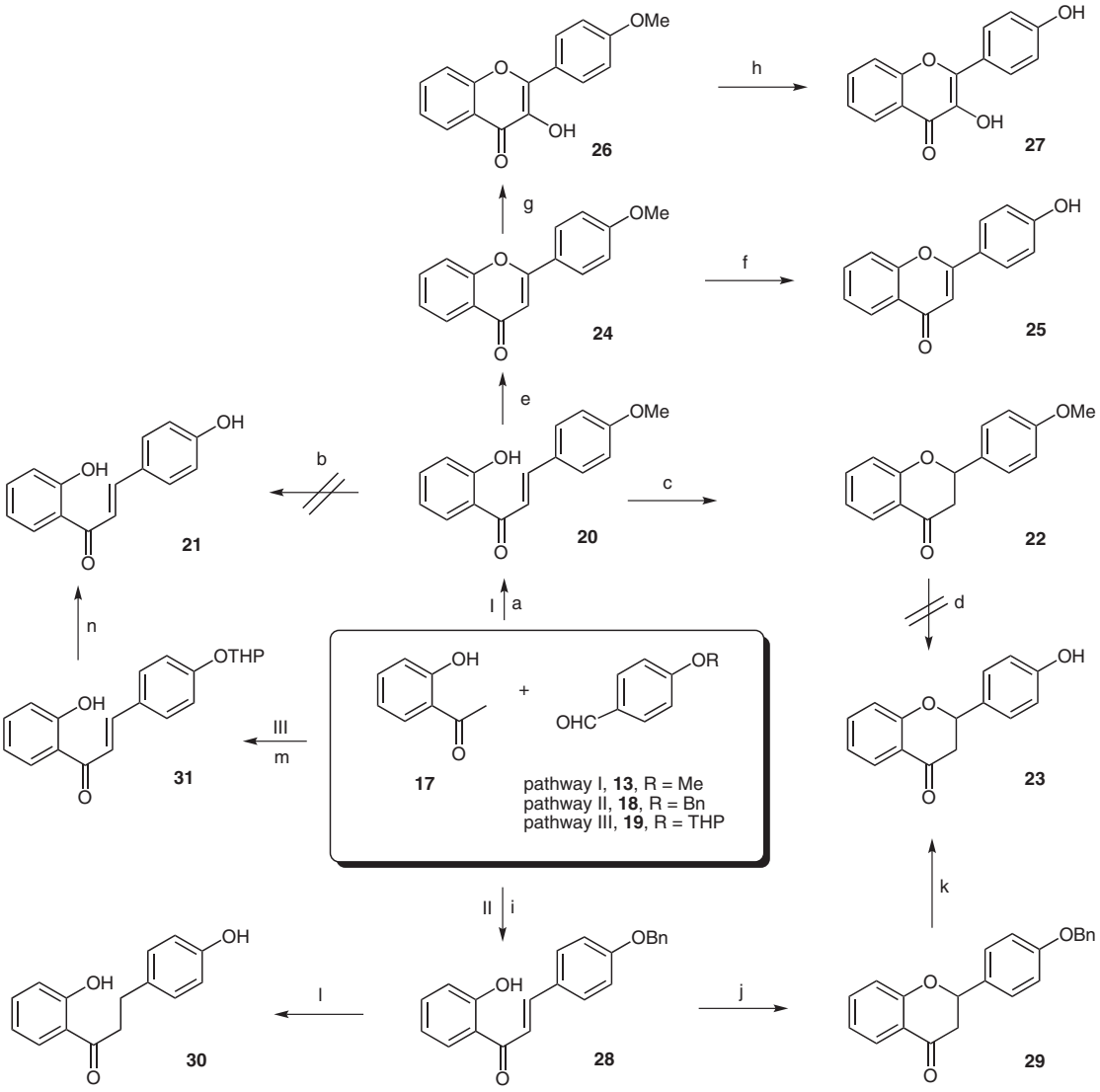
either in dichloromethane at room temperature or in toluene at reflux, gave no reaction,[52,53] whereas the treatment with aluminum(III) chloride (without solvent) at 100 °C resulted in decomposition. Modest yields of **21** (30%) were obtained by treatment of **20** with aluminum(III) chloride in dry benzene at reflux for six hours.[52,53]

Racemic 4′-methoxyflavanone (**22**) was obtained by microwave irradiation of **20** with 30% trifluoroacetic acid over silica gel, as reported by us previously.[47]

Also in this case, the deprotection of **22** under several conditions was unsuccessful.[54]

4′-Hydroxyflavone (**25**) was obtained in two steps by oxidative cyclization of **20** using a catalytic amount of iodine in dimethyl sulfoxide at reflux, to give 4′-methoxyflavone (**24**) followed by deprotection with boron tribromide. 4′-Hydroxyflavonol (**27**) was obtained from 4′-methoxyflavone, (**24**) by oxidative cyclization using iodobenzene diacetate (IBD), followed by deprotection with boron tribromide.

4′-Hydroxyflavanone (**23**) and 2′,4-dihydroxydihydrochalcone (**30**) were obtained from 4-(benzyloxy)-2′-hydroxychalcone (**28**) by acidic cyclization and debenzylation or hydrogenation, respectively. The synthesis of flavanone **23** directly from 4-(benzyloxy)-2′-hydroxychalcone (**28**) according to the procedure reported by Konieczny et al.[57,58] (treatment with trifluoroacetic acid in chloroform at reflux) was not applicable in this case due to benzyl migration, as we have previously reported.[59] 2′,4-Dihydroxydihydrochalcone (**30**) was obtained by hydrogenation of **28**. Finally, 2′,4-dihydroxychalcone (**21**) was obtained in high yield by protection of **12** as the tetrahydropyranyl ether **19**, followed by aldol condensation using barium hydroxide octahydrate in methanol , and final deprotection of chalcone **31** with 4-toluenesulfonic acid in methanol.[60]



Scheme 2 Synthesis of model compounds **21**, **23**, **25**, **27**, **30**. *Reagents and conditions:* (a) NaH, THF,[49,55] r.t., 16 h, 89%; (b) see text; (c) 30% TFA on silica gel, microwave, 9 min, 79%; (d) different conditions (ring opening or decomposition); (e) I_2 (cat.), DMSO, reflux, 1 h, 96%; (f) BBr_3, CH_2Cl_2, –60 °C to r.t., 24 h, 95%; (g) IBD, KOH, MeOH, r.t., 72 h, 93%; (h) BBr_3, CH_2Cl_2, –60 °C to r.t., 24 h, 90%; (i) NaH, THF, r.t., 16 h, 85%; (j) AcOH, reflux, 72 h, 64%; (k) H_2, 10% Pd/C, EtOAc, r.t., 1 h, 85%;[56] (l) H_2, 10% Pd/C, EtOAc, r.t., 1 h, 90%; (m) $Ba(OH)_2 \cdot 8H_2O$, MeOH, 60 °C, 12 h, 87%; (n) TsOH, MeOH, r.t., 2 h, 98%.

With a reliable set of conditions to perform the synthesis of model compounds, these methods were applied to the synthesis of biflavonoids **6**, **9**, and **14**–**16**.

For the synthesis of **9** and **15**, the key intermediate is the bichalcone **37**, which was obtained by aldol condensation of dialdehyde **36** and 2′-hydroxy-4′,6′-dimethoxyacetophenone (brevifolin, **34**) (Scheme 3). These compounds, in turn, were prepared in good yields by optimization of known sequences. Thus, dialdehyde **36** was obtained in 73% overall yield from *p*-anisaldehyde by iodination and further Ullmann condensation.[61–64] The iodination was performed using the system iodine–iodic acid, affording 3-iodo-*p*-anisaldehyde (**35**) in a clean reaction in 96% yield, which compares favorably with reported results using iodine monochloride.[64] Best results for the Ullmann condensation of **35** were obtained with activated copper, giving **36** in 76% yield.

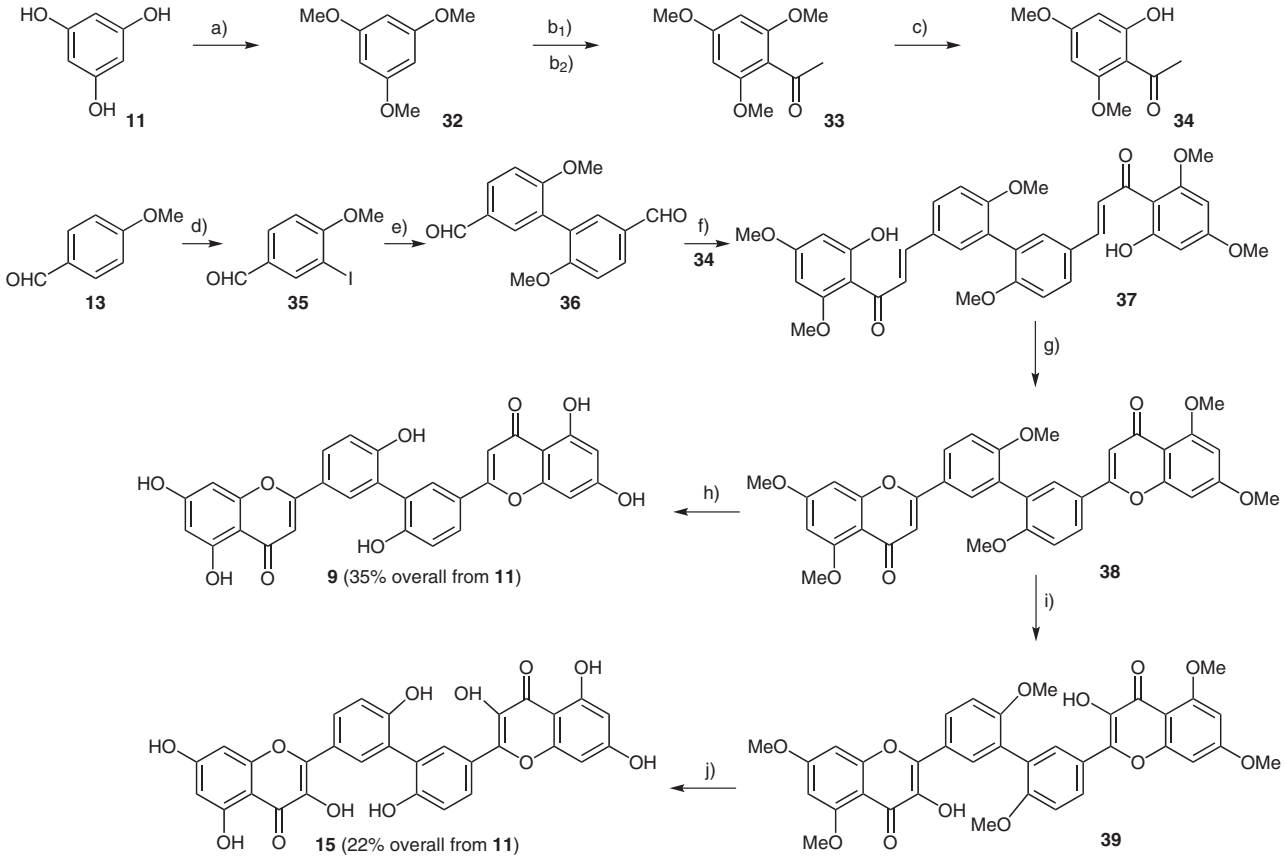
The acetophenone **34** was obtained in three steps and 60% overall yield from phloroglucinol (**11**) through *O*-selective permethylation,[65–68] ketimine formation,[70] hydrolysis, and selective *ortho*-demethylation.[52,53]

It is worth mentioning that the outcome of the hydrolysis of the intermediate ketimine salt is dependent on the temperature, due to competing deacylation. Thus, whereas at 60 °C the desired ketone **33** was obtained in 75% yield, at 100 °C, tri-*O*-methylphloroglucinol (**32**) was quantitatively obtained by deacylation.

The bichalcone **37** was then prepared by aldol condensation of **34** and **36**. The molecule has a center of symmetry (at the middle point of the C3′–C3‴ bond) and since the B rings possess *ortho*-monosubstitution with small groups with respect to C3, we assumed free rotation around this bond. In agreement with this, the ^{1}H NMR spectrum shows a single set of five spin systems and low temperature ^{1}H NMR experiments show no change among the spectra recorded at 30 °C, 0 °C, and –50 °C. Also, the ^{13}C NMR spectrum shows 18 signals, which is in accord with a symmetrical structure.

Treatment of bichalcone **37** with dimethyl sulfoxide/iodine produced a high-yielding cyclization to biflavone **38**, which was then demethylated to afford biflavone **9**. The ^{1}H NMR spectrum of **38**, compared to **37**, shows the disappearance of the signals corresponding to 2′-OH and $H_\alpha + H_\beta$ and the presence of the signal characteristic of H3 (singlet at $\delta = 6.67$).

Treatment of biflavone **38** with iodobenzene diacetate formed the hexa-*O*-methylbiflavonol **39**, which was deprotected with boron tribromide to give the biflavonol **15**. Compared to **38**, the ^{1}H NMR spectrum of **39** lacks the signal corresponding to H3. The solubility of the bifla-



Scheme 3 Synthesis of biflavonoids **9** and **15**. *Reagents and conditions:* (a) Me_2SO_4, K_2CO_3, acetone,[65–68] reflux, 48 h (92%); (b_1) MeCN, $ZnCl_2$, Et_2O saturated with HCl (g), 0–5 °C, 3 d, (b_2) H_2O (60 °C), 2 h, 75%; (c) $AlCl_3$, anhyd benzene, reflux, 8 h,[52,53] 86%; (d) I_2–HIO_3, AcOH–H_2O–EtOH, reflux, 3 h, 96%; (e) Cu (activated),[69] 205–220 °C, 30 min, 76%; (f) NaH, THF, r.t., 24 h, 85%; (g) DMSO, I_2 (ratio chalcone/I_2 100:2), reflux, 1 h, 87%; (h) BBr_3, CH_2Cl_2, –60 °C to r.t., 7 d, 79%; (i) IBD, KOH, MeOH, r.t., 48 h, 62%; (j) BBr_3, CH_2Cl_2, –60 °C to r.t., 72 h, 81%.

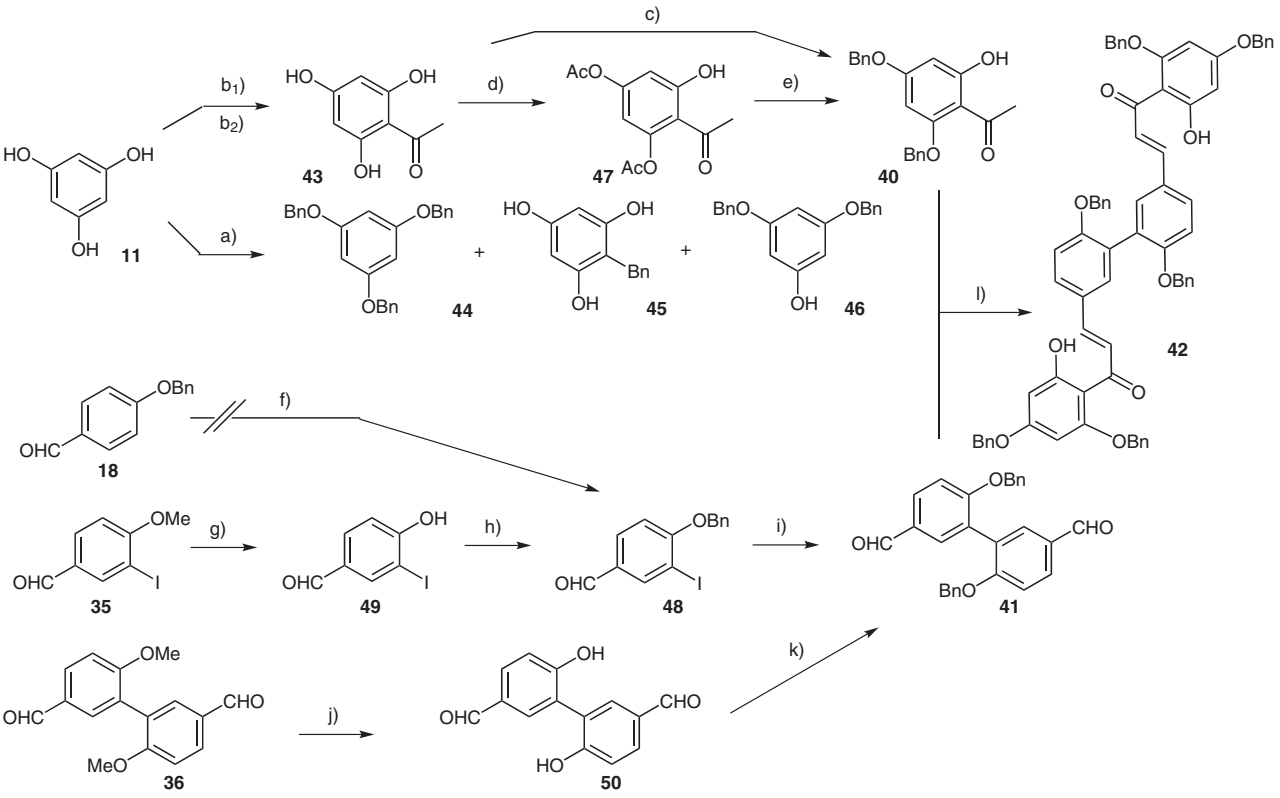
vonol **15** in acetone-d_6 at room temperature is sufficient to perform ^{1}H NMR experiments, but the hydroxy protons are rapidly exchanged giving very broad signals. The use of DMSO-d_6 (more viscous) allowed the observation of these protons as four singlets. Particularly noted are the signals corresponding to 5-OH (appearing at $\delta = 12.45$, by formation of an intramolecular hydrogen bond) and the 3-OH, which appears at $\delta = 8.27$.[71] For the synthesis of binaringenin **6** and the bidihydrochalcone **16**, the key intermediate is the bichalcone **42**, which was obtained by aldol condensation of 2′,4′-bis(benzyloxy)-6′-hydroxyacetophenone (**40**) and dialdehyde **41** (Scheme 4).

First, the synthesis of **40** was attempted via a sequence similar to the one used for brevifolin (preparation of tri-*O*-benzylphloroglucinol, acylation, and selective debenzylation, Scheme 4). However, the treatment of phloroglucinol (**11**) with benzyl chloride and potassium carbonate in a large volume of *N*,*N*-dimethylformamide at reflux resulted in a complex mixture of C- and O-benzylated products. The separation of this mixture was very difficult and only 10% of pure tri-*O*-benzylphloroglucinol (**44**) was isolated, together with minor quantities of *C*-benzylphloroglucinol **45** and di-*O*-benzylphloroglucinol (**46**). So we decided to run the benzylation on 2′,4′,6′-trihydroxyacetophenone (**43**) which was prepared by acylation of phloroglucinol (**11**) with acetonitrile in the presence of a Lewis acid ($ZnCl_2$). In this event, treatment of **43** with benzyl chloride and potassium carbonate in *N*,*N*-dimethylformamide at reflux formed a mixture from which **40** was isolated in 76% yield. Here again the separation was difficult due to the formation of O- and C-benzylated products. In order to avoid the formation of these secondary products we first prepared the diacetate **47**, which was then benzylated giving pure **40** in high yields (92% from **11**).

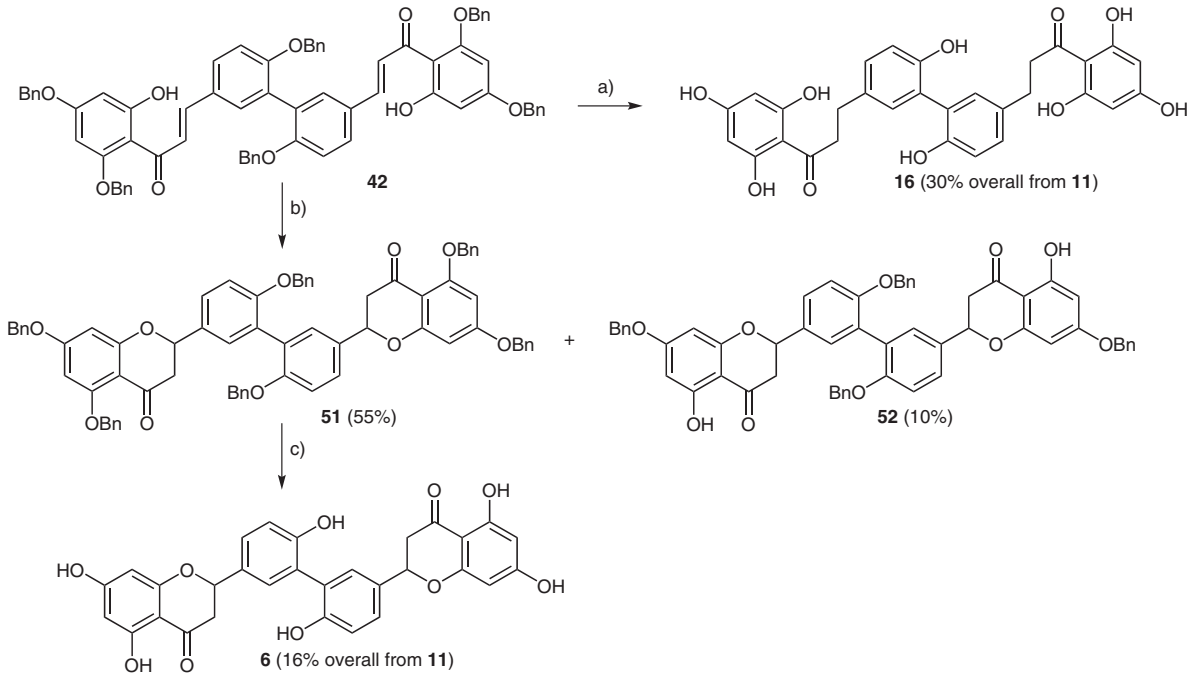
The synthesis of the benzylated dialdehyde **41** was attempted by Ullmann biaryl coupling reactions (Scheme 4).

The iodination of 4-(benzyloxy)benzaldehyde (**18**) produced only traces of 4-(benzyloxy)-3-iodobenzaldehyde (**48**) probably due to reaction with the benzyl group. Therefore, **48** was obtained from 3-iodoanisaldehyde (**35**) through standard demethylation (BBr_3, CH_2Cl_2, –70 °C to r.t., 89%) and benzylation in *N*,*N*-dimethylformamide. The Ullmann condensation of **48** using activated copper[69] formed a mixture of **41**/**48** in 0.35:1 ratio (as determined by ^{1}H NMR analysis) from which only 10% of **41** was isolated. In view of these poor results we decided to prepare the dialdehyde **41**, from dialdehyde **36**, via demethylation followed by benzylation. In this way, dimer **41** was obtained in 74% yield from **36**.

With **40** and **41** in hand, the benzylated bichalcone **42** was prepared in high yield by aldol condensation (Scheme 4). The ^{1}H and ^{13}C NMR spectra of **42** have similar character-



Scheme 4 Synthesis of bichalcone **42**. *Reagents and conditions:* (a) BnCl, K_2CO_3, DMF, reflux, 24 h, 10% (**44**); (b_1) MeCN, $ZnCl_2$, Et_2O saturated with HCl (g), 0–5 °C, 3 d, (b_2) H_2O (60 °C), 2 h, 50%; (c) BnCl, K_2CO_3, DMF, reflux, 6 h, 76%; (d) Ac_2O, DMAP, Py, 60 °C, 3 h, 95%; (e) BnCl, K_2CO_3, DMF, reflux, 6 h,[72–74] 97%; (f) I_2, HIO_3, AcOH–EtOH–H_2O, reflux, 3 h (traces); (g) BBr_3, CH_2Cl_2, –70 °C to r.t., 24 h, 89%; (h) BnCl, K_2CO_3, DMF, reflux, 6 h, 87%; (i) Cu (activated),[69] 200–210 °C, 60 min, 10%; (j) BBr_3, CH_2Cl_2, –70 °C to r.t., 24 h, 82%; (k) BnCl, K_2CO_3, DMF, reflux, 6 h, 90%; (l) NaH, THF, r.t., 24 h, 81%.

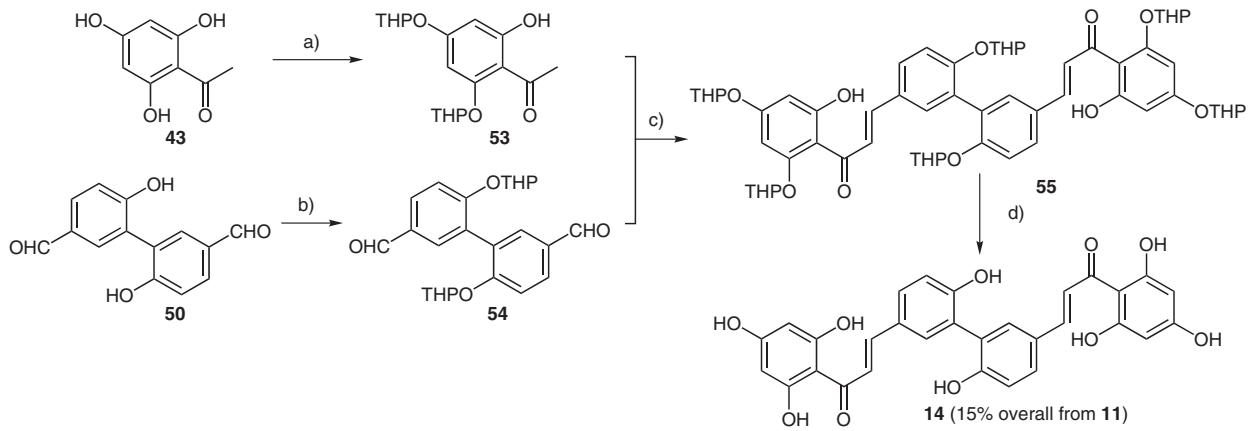


Scheme 5 Synthesis of compounds **6** and **16**. *Reagents and conditions:* (a) H_2, 10% Pd/C, EtOAc, 1 h, 81%; (b) AcOH, reflux, 96 h; (c) H_2, 10% Pd/C, EtOAc, r.t., 6 h, 79%.

istics to that of **37**. The bidihydrochalcone **16** was then obtained by catalytic hydrogenation of **42** in 30% overall yield from **11** (Scheme 5). Refluxing the chalcone **42** in acetic acid for 96 hours resulted in a mixture of cyclized products from which benzylated flavanone **51** was isolated in 55% yield together with the 5-debenzylated compound **52** in 10% yield. The formation of the latter compound by selective debenzylation is consistent with the presence of intramolecular hydrogen bonding between the 5-OH and the carbonyl group. The use of longer reaction times increased the amount of the 5-deprotected product, also noted for the cyclization of similar 2′,4′-bis(benzyloxy)-6′-hydroxychalcones.[59] Catalytic hydrogenation of **51** afforded racemic binaringenin **6** in high yield. The spectral data of **6** show good correlation with reported data.[8] The compound has the same substitution pattern as **37**, so it has free rotation around the C3′–C3‴ bond. The ^{1}H NMR spectra of **6** show a single set of signals at 30 °C and –50 °C.

For the synthesis of **14**, we first prepared 2′-hydroxy-4′,6′-bis(tetrahydropyran-2-yloxy)acetophenone (**53**) and of the corresponding dihydroxydialdehyde **54** (Scheme 6). The protection of 2′,4′,6′-trihydroxyacetophenone (**43**) was sluggish, giving **53** in only 44% yield due to the formation of other *C*- and *O*-tetrahydropyranyl compounds, in agreement with the report by Adams et al.[75] The presence of two stereogenic centers, given by the THP residues, causes the duplication of the signals in both ^{1}H NMR and ^{13}C NMR spectra of **53** and **54**.

The aldol condensation of the tetrahydropyranyl ethers **53** and **54** was done in the presence of barium hydroxide octahydrate and the protected bichalcone **55** was obtained in 79% yield as an oil. This compound was characterized



Scheme 6 Synthesis of bichalcone **14**. *Reagents and conditions:* (a) DHP, PPTS, CH_2Cl_2, r.t., 30 min, 44%; (b) DHP, PPTS, CH_2Cl_2, r.t., 30 min, 86%; (c) $Ba(OH)_2{\cdot}8H_2O$, MeOH, 60 °C, 24 h, 79%; (d) TsOH, MeOH, r.t., 12 h, 85%.

only by ^{1}H NMR and also showed duplication of signals. Finally, acidic deprotection of **55** formed bichalcone **14** in 85% yield. The overall yield of **14** from **43** was a modest 30% due to the low yield of formation of the ether **53**.

With five dimeric flavonoid in hand some biological tests were assayed since, as Kim et al. reported, not only naturally occurring biflavonoids, but also synthetic biflavonoids show antibacterial, antifungal, and antiviral activity.

Preliminary results show interesting antibacterial activity of these compounds, selective against *Staphylococcus aureus* for binaringenin **6** and the biflavonol **14**. The antibacterial and antifungal activities of this set of biflavonoids will be described in due course.

All reagents were purchased from commercial sources and used without purification, unless otherwise indicated. All solvents were dried and distilled prior to use. THF was dried by refluxing with benzophenone over Na wire until a blue color persisted and then distilled. CH_2Cl_2 was dried by refluxing over P_2O_5 for 3 h and then distilled. All reactions were monitored by TLC (Alugram Sil G/UV_{254} on polyester plates using different solvent systems). Column chromatography was carried out on silica gel (Merck, 60–230 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 30 °C on a Bruker DPX-400 spectrometer (400 MHz and 100 MHz, respectively). ^{1}H NMR were recorded using TMS as the internal reference. ^{13}C NMR were recorded using the residual solvent as the internal reference (the central peak of the $CDCl_3$ triplet was assigned to $\delta = 77.00$). Assignment of peaks was on the basis of 2D NMR (^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC) experiments. Mass spectra were recorded on a Shimadzu GC-MS QP 1100 EX spectrometer at 70 eV. HRMS were recorded on an AutoSpecQ spectrometer at 70 eV (EI, positive mode). Melting points were determined using a Gallenkamp capillary melting point apparatus and are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over P_2O_5 r.t./4–5.3 mbar, 24 h) and performed on a Fisons EA1108 CHNS-O analyzer.

Assignments of H and C are given according to the numbering scheme in Figures 2 and 3 (in flavanones, C=O is C4).

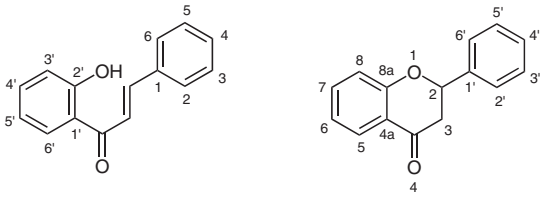


Figure 2 Numbering of flavones and flavanones

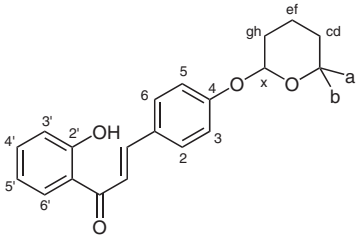


Figure 3 Numbering for structures **53**, **55**

2′-Hydroxy-4-methoxychalcones and 4-(Benzyloxy)-2′-hydroxychalcones (Pathways I and II, Scheme 2); General Procedure 1

This procedure is adapted from one reported by Stout).[49] To a soln of the corresponding 2′-hydroxyacetophenone (10 mmol) in anhyd THF (25 mL) was added in portions 50% NaH dispersion in mineral oil (1.2 g, 25 mmol), under N_2 and with vigorous stirring. When the evolution of H_2 ceased, a soln of the corresponding benzaldehyde (10 mmol) in anhyd THF (25 mL) was added dropwise over 15 min and the mixture was stirred at r.t. for the indicated time. The mixture was poured cautiously over ice water (50 mL) to destroy excess NaH and stirred until the evolution of H_2 ceased. The mixture was acidified with 25% HCl and extracted with EtOAc (3×50 mL). The combined organic layers were washed with H_2O (3×50 mL) and brine (50 mL) and dried (anhyd $MgSO_4$). The soln was concentrated under vacuum at 40 °C, until it reached one-third of its original volume. The soln was cooled to 0 °C for 12 h to give a crystalline product which was separated by filtration. The 2′-hydroxychalcones obtained in this way are sufficiently pure for most purposes. Analytical samples were obtained after purification by column chromatography (silica gel, hexanes then CH_2Cl_2–hexanes, EtOAc–hexanes, or EtOAc–CH_2Cl_2–hexanes).

(Benzyloxy)flavanones; General Procedure 2

A soln of the corresponding (benzyloxy)chalcone (1 mmol) in glacial AcOH (15 mL) was refluxed for the indicated time under N_2. Then, the soln was poured into cold H_2O (25 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were washed with H_2O (3×25 mL) and brine (25 mL) and dried (anhyd $MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes then CH_2Cl_2–hexanes, EtOAc–hexanes, or EtOAc–CH_2Cl_2–hexanes).

Hydrogenation of 4-(Benzyloxy)-2′-hydroxychalcones and (Benzyloxy)flavanones; General Procedure 3

To a soln of the corresponding (benzyloxy)chalcone or (benzyloxy)flavanone (0.5 mmol) in EtOAc (50 mL) was added 10% Pd/C (50 mg) and the mixture was stirred at r.t. under a H_2 atmosphere. After 1 h or the indicated time, the mixture was filtered and washed with EtOAc (3×50 mL). The solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexanes then CH_2Cl_2–hexanes, EtOAc–hexanes, or EtOAc–CH_2Cl_2–hexanes).

Synthesis of Flavones; General Procedure 4

To a soln of the corresponding 2′-hydroxychalcone (1 mmol) in DMSO (15 mL) was added I_2 (2.5 mg, 0.01 mmol) and the mixture was refluxed for 1 h. H_2O (50 mL) was then added and the mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with 5% $NaHSO_3$ soln (50 mL), H_2O (3×50 mL), and brine (50 mL) and dried (anhyd $MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes then CH_2Cl_2–hexanes, EtOAc–hexanes, or EtOAc–CH_2Cl_2–hexanes).

Deprotection of Methoxyflavones and Methoxyflavonols; General Procedure 5

The corresponding methoxyflavone or methoxyflavonol (1 mmol) was dissolved in anhyd CH_2Cl_2 (15 mL) under N_2. The soln was cooled to –70 °C and 1 M BBr_3 in CH_2Cl_2 (3 mL per mmol of OMe, 3 mmol/mmol OMe) was added dropwise from an equalizer funnel. The mixture was stirred at r.t. for the indicated time. The mixture was poured cautiously over ice water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with H_2O (3×50 mL) and brine (50 mL) and dried (anhyd $MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes then CH_2Cl_2–hexanes, EtOAc–hexanes, or EtOAc–CH_2Cl_2–hexanes).

Flavonols; General Procedure 6

To a soln of the corresponding flavone (1 mmol) in MeOH (15 mL) was added with stirring a soln of KOH (170 mg, 3 mmol) in MeOH (15 mL) at r.t. IBD (350 mg, 1.1 mmol) was then added in 4 portions. The mixture was stirred at r.t. for the indicated time. H_2O (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and brine (50 mL) and dried (anhyd $MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes then CH_2Cl_2–hexanes, EtOAc–hexanes, or EtOAc–CH_2Cl_2–hexanes).

Polyhydroxychalcones (Pathway III, Scheme 2); General Procedures 7

This procedure is adapted from one reported by Sogawa.[60]

Tetrahydropyranyl Ethers; General Procedure 7a

To a stirred suspension of the corresponding phenol (0.1 mol) in anhyd CH_2Cl_2 (100 mL) was added anhyd TsOH (0.85 g, 0.005 mol) and anhyd pyridine (freshly distilled from KOH) (0.40 mL, 0.39 g, 0.005 mol) under N_2. Then 3,4-dihydro-2*H*-pyran (10.5 g, 0.125 mol, 11.4 mL per OH group) was added dropwise. The mixture was stirred at r.t. for 1 h, and after this time, a clear soln was obtained. The solvent was removed under vacuum and the residue was dissolved in EtOAc (500 mL). The organic layer was extracted with 10% NaOH (3 × 100 mL) to remove the unreacted phenol. The organic layer was washed with H_2O (3 × 100 mL) and brine (100 mL) and dried (anhyd $MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes then CH_2Cl_2–hexanes, 1:9).

2′-Hydroxy-4-(tetrahydropyran-2-yloxy)chalcones; General Procedure 7b

To a soln of the corresponding 2′-hydroxyacetophenone (10 mmol) and benzaldehyde (10 mmol) in abs MeOH (25 mL) was added with vigorous stirring $Ba(OH)_2{\cdot}8H_2O$ (3.2 g, 0.01 mol) under N_2. The mixture was stirred at 60 °C for the indicated time and then it was neutralized with 10% HCl and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and brine (50 mL) and dried (anhyd $MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes then CH_2Cl_2–hexanes, EtOAc–hexanes, or EtOAc–CH_2Cl_2–hexanes).

Deprotection of 2′-Hydroxy-4-(tetrahydropyran-2-yloxy)chalcones; General Procedure 7c

To a soln of the corresponding 2′-hydroxy-4-(tetrahydropyran-2-yloxy)chalcone (1 mmol) in abs MeOH (20 mL) was added TsOH (10 mg, 0.05 mmol). The mixture was stirred at r.t. for the indicated time and then the solvent was removed under vacuum. H_2O (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and brine (50 mL) and dried (anhyd $MgSO_4$). The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes then CH_2Cl_2–hexanes, EtOAc–hexanes, or EtOAc–CH_2Cl_2–hexanes).

(±)-4′,4‴,5,5″,7,7″-Hexahydroxy-3′,3‴-biflavanone (3′,3‴-Binaringenin, 6)[8]

Following general procedure 3 from **51** (108 mg, 0.1 mmol) stirring at r.t. under H_2 for 6 h to give **6** as a white solid; yield: 43 mg (79%); mp 235– 238 °C dec (Lit.[8] 241–243 °C).

^{1}H NMR (400 MHz, acetone-d_6): δ = 12.16 (s, 1 H, 5-OH), 8.06 (s, 1 H, 7-OH or 4′-OH), 8.02 (s, 1 H, 7-OH or 4′-OH), 7.03 (s, 1 H, H2′), 6.87–6.85 (m, 2 H, H5′, H6′), 5.96 (d, J_{86} = 2.1 Hz, 1 H, H8), 5.94 (d, J_{68} = 2.1 Hz, 1 H, H6), 5.40 (dd, $J_{2,3ax}$ = 12.6 Hz, $J_{2,3eq}$ = 3.1 Hz, 1 H, H2), 3.13 (dd, $J_{3ax,3eq}$ = 17.1 Hz, $J_{3ax,2}$ = 12.6 Hz, 1 H, $H3_{ax}$), 2.73 (dd, $J_{3eq,3ax}$ = 17.1 Hz, $J_{3eq,2}$ = 3.1 Hz, 1 H, $H3_{eq}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7 (C=O), 166.9 (C7), 163.8 (C5), 162.8 (C8a), 155.4 (C4′), 130.1 (C2′), 129.5 (C1′), 127.1 (C6′), 126.0 (C3′), 115.2 (C5′), 102.1 (C4a), 96.3 (C6), 95.4 (C_8), 78.8 (C2), 42.4 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 544 (13.4) [M^+ + 2], 543 (23.8) [M^+ + 1], 542 (75.3) [M^+], 541 (54.0) [M^+ – 1], 524 (11.2) [$M^+ - H_2O$], 515 (26.6) [M^+ + H – CO], 391 (16.7), 390 (100.0), 377 (47.3), 364 (10.4), 179 (13.2), 153 (48.4), 125 (11.2) [$C_6H_3(OH)_2O^+$], 108 (8.4).

Anal. Calcd for $C_{30}H_{22}O_{10}$: C, 66.42; H, 4.09. Found: C, 66.74; H, 4.28.

4′,4‴,5,5″,7,7″-Hexahydroxy-3′,3‴-biflavone (3′,3‴-Biapigenin, 9)[7]

Following general procedure 5 using biflavone **38** (62 mg, 0.1 mmol) and 1 M BBr_3 in CH_2Cl_2 (1.8 mL, 1.8 mmol) stirring at r.t. for 7 d to give **9** as a white solid; yield: 43 mg (79%); mp 269–270 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.44 (s, 1 H, 5-OH), 8.75–7.90 (br s, 2 H, 7-OH, 4′-OH), 6.90–6.82 (m, 3 H, H2′, H5′, H6′), 5.95–5.93 (m, 2 H, H6, H8).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.0 (C=O), 163.7 (C7), 163.2 (C2), 161.8 (C5), 158.2 (C4′), 157.4 (C8a), 129.5 (C2′), 127.3 (C6′), 125.7 (C3′), 121.1 (C1′), 116.2 (C5′), 103.7 (C4a), 103.2 (C3), 98.1 (C6), 94.0 (C8).

MS (EI, 70 eV): *m*/*z* (%) = 540 (11.0) [M^+ + 2], 539 (33.2) [M^+ + 1], 538 (100.0) [M^+], 537 (24.8) [M^+ – 1], 520 (15.4) [$M^+ - H_2O$], 511 (38.6) [M^+ + 1 – CO], 497 (10.3) [$M^+ - C_2H_2O$], 493 (11.3) [M^+ + 1 – H_2O – CO], 389 (15.7), 387 (29.7), 269 (12.0) [M^+/2], 152 (54.2), 125 (12.0) [$C_6H_3(OH)_2O^+$].

Anal. Calcd for $C_{30}H_{18}O_{10}$: C, 66.92; H, 3.37. Found: C, 67.24; H, 3.20.

2′,2‴,4,4′,4″,4‴,6′,6‴-Octahydroxy-3,3″-bichalcone (14)

Following general procedure 7c using **55** (52 mg, 0.05 mmol) and TsOH (1.5 mg, 0.0075 mmol) with stirring at r.t. for 12 h to give **14** as a yellow solid; yield: 23 mg (85%); mp 133–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$–acetone-d_6): δ = 13.99 (s, 1 H, 2′-OH), 7.81 (d, $J_{\beta\alpha}$ = 15.3 Hz, 1 H, H_β), 7.70 (d, $J_{\alpha\beta}$ = 15.3 Hz, 1 H, H_α), 7.64 (dd, J_{65} = 8.6 Hz, J_{62} = 2.2 Hz, 1 H, H6), 7.52 (d, J_{26} = 2.2 Hz, 1 H, H2), 6.78 (d, J_{56} = 8.6 Hz, 1 H, H5), 5.95 (s, 2 H, H3′, H5′).

^{13}C NMR (100 MHz, $CDCl_3$–acetone-d_6): δ = 191.9 (C=O), 167.9, 164.5 (C2′, C4′, C6′), 159.3 (C4), 151.8 (C1), 143.0 (C_β), 131.6 (C2), 128.6, 127.9 (C3, C5), 127.2 (C6), 125.2 (C_α), 105.6 (C1′), 94.3 (C5′, C3′).

MS (EI, 70 eV): *m*/*z* (%) = 544 (10.6) [M^+ + 2], 543 (18.4) [M^+ + 1], 542 (78.0) [M^+], 541 (32.0) [M^+ – 1], 524 (15.3) [$M^+ - H_2O$], 515 (19.4) [M^+ + H – CO], 390 (100.0), 377 (39.4), 364 (9.8), 271 (10.5) [M^+/2], 179 (16.5), 153 (44.2), 125 (13.0) [$C_6H_3(OH)_2O^+$].

Anal. Calcd for $C_{30}H_{22}O_{10}$: C, 66.42; H, 4.09. Found : C, 66.21; H, 3.85.

3,3″,4′,4‴,5,5″,7,7″-Octahydroxy-3′,3‴-biflavone (15)

Following general procedure 5 using **39** (65 mg, 0.1 mmol), BBr_3 (0.3 mmol) with stirring at r.t. for 72 h gave **15** as a whitish solid; yield: 46 mg (81%); mp 234–236.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.45 (s, 1 H, 5-OH), 10.73 (s, 1 H, OH), 9.53 (s, 1 H, OH), 8.27 (s, 1 H, 3-OH), 7.67 (d, $J_{2'6'}$ = 2.2 Hz, 1 H, H2′), 7.53 (d, $J_{6'5'}$ = 8.5 Hz, $J_{6'2'}$ = 2.2 Hz, 1 H, H6′), 6.88 (d, $J_{5'6'}$ = 8.5 Hz, 1 H, H5′), 6.39 (d, J_{86} = 2.0 Hz, 1 H, H8), 6.17 (d, J_{68} = 2.0 Hz, 1 H, H6).

^{13}C NMR (100 MHz, acetone-d_6): δ = 176.6 (C=O), 165.0 (C8a), 162.4 (C4′, C7), 157.8 (C5), 148.4 (C_2), 145.8 (C1′), 136.8 (C3), 132.8 (C3′), 130.5 (C2′), 126.2, 125.8 (C5′, C6′), 104.2 (C4a), 99.2 (C6), 94.5 (C8).

MS (EI, 70 eV): *m/z* (%) = 572 (10.3) [M^+ + 2], 571 (28.6) [M^+ + 1], 570 (100.0) [M^+], 569 (33.4) [M^+ – 1], 553 (11.4) [M^+ + H – H_2O), 552 (14.8) [M^+ – H_2O], 543 (64.6) [M^+ + H – CO], 525 (19.5) [M^+ – 1 – H_2O – CO], 515 (34.1) [M^+ + H – 2 CO], 431 (12.4), 417 (19.0), 405 (17.6), 285 (15.6) [M^+/2], 165 (73.5), 153 (79.6), 152 (23.4), 137 (16.9), 127 (17.3).

Anal. Calcd for $C_{30}H_{18}O_{12}$: C, 63.16; H, 3.18. Found: C, 63.02; H, 3.27.

2′,2‴,4,4′,4″,4‴,6′,6‴-Octahydroxy-3,3″-bidihydrochalcone (16)

Following general procedure 3 using **42** (108 mg, 0.1 mmol) stirring at r.t. for 1 h gave **16** as a whitish solid; yield: 44 mg (81%); mp 155.5–158 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.95 (s, 1 H, 2′-OH), 6.75–6.71 (m, 2 H, H2, H6), 6.46–6.36 (m, 1 H, H5), 6.17 (d, $J_{5'3'}$ = 2.0 Hz, 1 H, H5′), 6.09 (d, $J_{3'5'}$ = 2.0 Hz, 1 H, H3′), 3.23 (t, $J_{\alpha\beta}$ = 7.8 Hz, 2 H, $CH_{2\alpha}$), 2.81 (t, $J_{\beta\alpha}$ = 7.7 Hz, 2 H, $CH_{2\beta}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.5 (C=O), 167.6 (C6′), 164.9 (C4′), 161.8 (C2′), 148.9 (C4), 135.4, 135.0 (C1′, C2′), 127.3 (C3, C6), 115.6 (C5), 106.1 (C1′), 94.9 (C5′), 92.4 (C3′), 45.9 ($CH_{2\alpha}$), 29.8 ($CH_{2\beta}$).

MS (EI, 70 eV): *m/z* (%) = 548 (3.2) [M^+ + 2], 547 (11.4) [M^+ + 1], 546 (22.0) [M^+], 545 (3.7) [M^+ – 1], 528 (18.3) [M^+ – H_2O], 527 (20.0) [M^+ – H_2O – H], 393 (76.4), 379 (43.8), 273 (8.2) [M^+/2], 210 (10.1), 153 (100.0) [$C_6H_2(OH)_3CO^+$], 152 (38.4) [$C_6H_2(OH)_3CO$ – 1]$^+$.

Anal. Calcd for $C_{30}H_{26}O_{10}$: C, 65.93; H, 4.79. Found: C, 66.25; H, 5.03.

2′,2‴-Dihydroxy-4,4′,4″,4‴,6′,6‴-hexamethoxy-3,3″-bichalcone (37)[46]

Following general procedure 1 using **34** (2 mmol), **36** (1 mmol), and NaH (5 mmol) stirring at r.t. for 24 h gave **37** as a yellow solid; yield: 532 mg (85%); mp 178.3–182.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.34 (s, 1 H, 2′-OH), 7.83 (d, $J_{\beta\alpha}$ = 15.4 Hz, 1 H, Hb), 7.79 (d, $J_{\alpha\beta}$ = 15.4 Hz, 1 H, Ha), 7.62 (dd, J_{65} = 8.6 Hz, J_{62} = 2.3 Hz, 1 H, H6), 7.53 (d, J_{26} = 2.2 Hz, 1 H, H2), 7.01 (d, J_{56} = 8.6 Hz, 1 H, H5), 6.10 (d, $J_{3'5'}$ = 2.4 Hz, 1 H, H3′), 5.94 (d, $J_{5'3'}$ = 2.4 Hz, 1 H, H5′), 3.87 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.82 (s, 3 H, OMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6 (C=O), 168.3, 166.1, 162.5 (C2′, C4′, C6′), 158.9 (C4), 152.0 (C1), 142.4 (C_β), 131.5 (C2), 129.9 (C6), 128.2, 127.7 (C5, C3), 125.5 (C_α), 106.5 (C1′), 93.9 (C5′), 91.3 (C3′), 55.92 (OMe), 55.88 (OMe), 55.6 (OMe).

MS (EI, 70 eV): *m/z* (%) = 627 (13.0) [M^+ + 1], 626 (34.9) [M^+], 625 (15.9) [M^+ – 1], 611 (25.0) [M^+ – CH_3], 446 (23.4), 445 (53.3), 433 (17.6), 266 (24.0) [M^+/2 –1 – H_2O – CO], 253 (42.7) [M^+/2 + 1 – H_2O – CO – CH_3], 207 (54.7), 182 (10.6), 181 (100.0), 180 (10.3), 166 (10.4), 152 (11.1), 137 (17.7).

HRMS (EI+, 70 eV): *m/z* [M]$^+$ calcd for $C_{36}H_{34}O_{10}$: 626.2152; found: 626.2130.

4′,4‴,5,5″,7,7″-Hexamethoxy-3′,3‴-biflavone (38)[43]

Following general procedure 4 using bichalcone **37** (313 mg, 0.5 mmol) and I_2 (2.5 mg, 0.01 mmol) gave **38** as a white solid; yield: 270 mg (87%); mp 348–349.6 °C (Lit.[43] 354 °C).

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.90 (dd, $J_{6'5'}$ = 8.7 Hz, $J_{6'2'}$ = 2.3 Hz, 1 H, H6′), 7.80 (d, $J_{2'6'}$ = 2.2 Hz, 1 H, H2′), 7.10 (d, $J_{5'6'}$ = 8.8 Hz, 1 H, H5′), 6.67 (s, 1 H, H3), 6.56 (d, J_{68} = 2.1 Hz, 1 H, H6), 6.37 (d, J_{86} = 2.1 Hz, 1 H, H8), 3.95 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.86 (s, 3 H, OMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5 (C=O), 164.0 (C2), 162.1 (C4′), 161.0 (C7, C8a), 157.9 (C5), 144.8 (C1′), 129.5 (C2′), 129.1 (C6′), 126.2 (C3′, C5′), 112.9 (C4a), 112.2 (C8), 104.0 (C3), 94.3 (C6), 56.0, 55.8, 55.7 (3 OMe).

MS (EI, 70 eV): *m/z* (%) = 623 (29.6) [M^+ + 1], 622 (59.9) [M^+], 621 (7.4) [M^+ – 1], 608 (29.6), 607 (100.0) [M^+ – CH_3], 310 (5.6, [M^+/2 – 1], 302 (16.7), 296 (23.5), 126 (8.0) [$C_6H_3(OH)_3^+$], 97 (7.4) [$C_6H_3(OH)_3$ – 1 – CO], 43 (8.0) [CH_3CO^+].

Anal. Calcd for $C_{36}H_{30}O_{10}$: C, 69.45; H, 4.86. Found: C, 69.68; H, 4.55.

3,3″-Dihydroxy-4′,4‴,5,5″,7,7″-hexamethoxy-3′,3‴-biflavone (39)

Following general procedure 6 using **38** (125 mg, 0.2 mmol), KOH (1 mmol), and IBD (0.44 mmol) with stirring at r.t. for 48 h to give **39**; yield: 81 mg (62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1 H, 3-OH), 7.69 (d, $J_{2'6'}$ = 2.2 Hz, 1 H, H2′), 7.51 (d, $J_{6'5'}$ = 8.4 Hz, $J_{6'2'}$ = 2.2 Hz, 1 H, H6′), 6.90 (d, $J_{5'6'}$ = 8.4 Hz, 1 H, H5′), 6.42 (d, J_{86} = 2.1 Hz, 1 H, H8), 6.19 (d, J_{68} = 2.1 Hz, 1 H, H6), 3.89 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.84 (s, 3 H, OMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (C=O), 165.3 (C8a), 162.8 (C4′, C7), 158.2 (C5), 148.2 (C2), 145.2 (C1′), 136.9 (C3), 132.9 (C3′), 130.7 (C2′), 126.7, 126.2 (C5′, C6′), 104.3 (C4a), 99.8 (C6), 95.1 (C8), 56.1, 55.9, 55.6 (3 OMe).

MS (EI, 70 eV): *m/z* (%) = 656 (9.2) [M^+ + 2], 655 (15.4) [M^+ + 1], 654 (100.0) [M^+], 570 (43.4).

Anal. Calcd for $C_{36}H_{30}O_{12}$: C, 66.05; H, 4.62. Found: C, 66.32; H, 4.80.

2′,2‴4,4′,4″,4‴-Hexakis(benzyloxy)-6′,6‴-dihydroxy-3,3″-bichalcone (42)

Following general procedure 1 using **40** (2 mmol), **41** (1 mmol), and NaH (5 mmol) stirring at r.t. for 24 h gave **42** as a yellow solid; yield: 875 mg (81%); mp 133.5–136.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.99 (s, 1 H, 2′-OH), 7.80 (d, $J_{\beta\alpha}$ = 15.6 Hz, 1 H, H_β), 7.75 (d, $J_{\alpha\beta}$ = 15.6 Hz, 1 H, H_α), 7.44–6.95 (m, 17 H, 15 H_{Ph}, H2, H6), 6.78 (d, J_{56} = 8.6 Hz, 1 H, H5), 6.23 (d, $J_{5'3'}$ = 2.3 Hz, 1 H, H5′), 6.15 (d, $J_{3'5'}$ = 2.3 Hz, 1 H, H3′), 5.10 (s, 2 H, CH_2), 5.01 (s, 2 H, CH_2), 5.00 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6 (C=O), 168.6 (C4′), 165.1 (C2′), 161.7 (C6′), 157.9 (C4), 149.8 (C1), 142.9 (C_β), 136.9, 135.9, 135.4 (3 $C1_{Ph}$), 132.0 (C2), 129.5, 128.71, 128.68, 128.4, 128.3, 128.14, 128.11, 128.0, 127.6, (3 $C2_{Ph}$–C6Ph, C3), 126.5, 125.4 (C5, C6, C_α), 106.6 (C1′), 95.1 (C5′), 92.6 (C3′), 71.3 (CH_2), 70.3 (CH_2), 70.2 (CH_2).

MS (EI, 70 eV): *m/z* (%) = 627 (7.8) [M^+ – 5 Bn], 537 (12.3) [M^+ + 1 – 6 Bn], 536 (2.8) M^+ – 6 Bn], 518 (5.0) [M^+ – 6 Bn – H_2O], 269 (5.1) [(M^+ – 6 Bn)/2 + 1], 152 (21.2), 125 (5.6 [$C_6H_3(OH)_2O^+$], 91 (100.0) [Bn^+].

Anal. Calcd for $C_{72}H_{58}O_{10}$: C, 79.85; H, 5.36. Found: C, 80.14; H, 5.15.

4′,4‴,5,5″,7,7″-Hexakis(benzyloxy)-3′,3‴-biflavanone (51) and 4′,4‴,7,7″-Tetrakis(benzyloxy)-5,5″-dihydroxy-3′,3‴-biflavanone (52)

Following general procedure 2 using bichalcone **42** (541 mg, 0.5 mmol) at reflux for 96 h gave **51** (297 mg, 55%) and **52** (55 mg, 10%).

4′,4‴,5,5″,7,7″-Hexakis(benzyloxy)-3′,3‴-biflavanone (51)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.30 (m, 15 H, 15 H_{Ph}), 7.07 (br s, 1 H, H5′), 6.96 (br s, 2 H, H2′, H6′), 6.23 (d, J_{68} = 2.0 Hz, 1 H, H6), 6.22 (d, J_{86} = 2.1 Hz, 1 H, H8), 5.31 (dd, $J_{2ax,3ax}$ = 13.2 Hz, $J_{2ax,3eq}$ = 2.7 Hz, 1 H, H2), 5.19 (s, 2 H, CH_2), 5.18 (s, 2 H, CH_2), 5.16 (s, 2 H, CH_2), 2.98 (dd, $J_{3ax,3eq}$ = 16.5 Hz, $J_{3ax,2ax}$ = 13.2 Hz, 1 H, $H3_{ax}$), 2.73 (dd, $J_{3eq,3ax}$ = 16.5 Hz, $J_{3eq,2ax}$ = 2.8 Hz, 1 H, $H3_{eq}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9 (C=O), 164.9 (C7), 161.1 (C5, C8a), 149.2 (C4′), 137.1, 136.4, 135.8, 131.9 (3 $C1_{Ph}$, C1′), 128.7, 128.56, 128.51, 128.3, 127.90, 127.85, 127.6, 127.5, 127.4, 127.3 (C2′, C3′, (2 $C2_{Ph}$–$C6_{Ph}$), 119.6 (C6′), 115.0 (C5′), 113.5 (C4a), 95.2 (C6), 94.8 (C8), 79.1 (C2), 71.6 (CH_2), 71.3 (CH_2), 70.5 (CH_2), 45.6 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 627 (9.4) [M^+ – 5 Bn], 536 (14.2) [M^+ – 6 Bn], 152 (26.2), 91 (100.0) [Bn^+].

Anal. Calcd for $C_{72}H_{58}O_{10}$: C, 79.83; H, 5.40. Found: C, 79.51; H, 5.63.

4′,4‴,7,7″-Tetrakis(benzyloxy)-5,5″-dihydroxy-3′,3‴-biflavanone (52)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.98 (s, 1 H, 5-OH), 7.45–7.29 (m, 10 H, 10 H_{Ph}), 7.04 (br s, 1 H, H5′), 6.97–6.93 (m, 2 H, H2′, H6′), 6.15 (d, J_{68} = 2.3 Hz, 1 H, H6), 6.10 (d, J_{86} = 2.3 Hz, 1 H, H8), 5.30 (dd, $J_{2,3ax}$ = 12.8 Hz, $J_{2,3eq}$ = 3.0 Hz, 1 H, H2), 5.18 (s, 2 H, CH_2), 5.08 (s, 2 H, CH_2), 3.01 (dd, $J_{3ax,3eq}$ = 17.2 Hz, $J_{3ax,2}$ = 12.9 Hz, 1 H, $H3_{ax}$), 2.74 (dd, $J_{3eq,3ax}$ = 17.2 Hz, $J_{3eq,2}$ = 3.1 Hz, 1 H, $H3_{eq}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.9 (C=O), 167.0 (C7), 164.1 (C8a), 162.8 (C5), 149.6 (C4′), 137.1, 137.0, 135.8 (2 $C1_{Ph}$, C1′), 131.5 (C2′, C3′), 128.7, 128.5, 128.3, 127.94, 127.88, 127.4, 127.2 ($C2_{Ph}$–$C6_{Ph}$, C6′), 113.5 (C5′), 103.3 (C4a), 96.0 (C8), 95.0 (C6′), 79.0 (C2), 71.6 (CH_2), 71.3 (CH_2), 43.2 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 627 (6.3) [M^+ – 3 Bn], 536 (11.1) [M^+ – 4 Bn], 91 (100.0) [Bn^+].

Anal. Calcd for $C_{58}H_{46}O_{10}$: C, 77.15; H, 5.13. Found: C, 77.43; H, 5.38.

2′-Hydroxy-4′,6′-bis(tetrahydropyran-2-yloxy)acetophenone (53)[75]

Following general procedure 7a using **43** (1.68 g, 0.01 mol) and DHP (2.1 g, 0.0250 mol) gave **53**; yield: 1.48 g (44%).

6,6′-Bis(tetrahydropyran-2-yloxy)biphenyl-3,3′-dicarbaldehyde (54)

Following general procedure 7a using dialdehyde **50** (242 mg, 1 mmol) and DHP (0.21 g, 2.5 mmol) gave **54** as a clear oil; yield: 352 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.93 (s, 1 H, CHO), 9.92 (s, 1 H, CHO), 7.922 (dd, J_{45} = 8.6 Hz, J_{42} = 2.2 Hz, 1 H, H4)[a], 7.920 (dd, $J_{4'5'}$ = 8.6 Hz, $J_{4'2'}$ = 2.2 Hz, 1 H, H4′)[a], 7.78 (d, J_{24} = 2.2 Hz, 1 H, H2)[b], 7.77 (d, $J_{2'4'}$ = 2.2 Hz, 1 H, H2′)[b], 7.09 (d, J_{54} = 8.6 Hz, 1 H, H5)[c], 7.08 (d, $J_{5'4'}$ = 8.6 Hz, 1 H, H5′)[c], 5.52–5.45 (m, 2 H, 2 H_x), 4.25–3.85 (m, 2 H, 2 H_a or H_b), 3.70–3.64 (m, 2 H, 2 H_a or H_b), 2.11–1.55 (m, 12 H, 2 H_c, 2 H_d, 2 H_e, 2 H_f, 2 H_g, 2 H_h). [a], [b], and [c] indicate interchangeable assignments.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8 (CHO), 161.8, 161.7 (C6, C6′), 133.32, 133.31 (C2, C2′), 131.88, 131.87 (C4, C4′), 129.6, 129.5 (C3, C3′), 126.8 126.7 (C1, C1′), 111.2, 111.1 (C5, C5′), 96.4 (C_x), 62.3 (C_{ab}), 30.0 (C_{gh}), 25.2 (C_{cd}), 18.4 (C_{ef}).

MS (EI, 70 eV): *m*/*z* (%) = 411 (11.3) [M^+ + 1], 410 (34.2) [M^+], 240 (55.3).

2′,2‴-Dihydroxy-4,4′,4″,4‴,6′,6‴-hexakis(tetrahydropyran-2-yloxy)-3,3″-bichalcone (55)

Following general procedure 7b using **53** (67 mg, 0.2 mmol) and **54** (41 mg, 0.1 mmol) at 60 °C for 24 h gave **55** as a yellow oil; yield: 82.6 mg (79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.90 (s, 1 H, 2′-OH or 2‴-OH), 12.89 (s, 1 H, 2′-OH or 2‴-OH), 7.82 (d, $J_{\beta\alpha}$ = 15.4 Hz, 2 H, 2 H_β), 7.73 (d, $J_{\alpha\beta}$ = 15.4 Hz, 2 H, 2 H_α), 7.64 (dd, J_{65} = 8.6 Hz, J_{62} = 2.2 Hz, 1 H, H6)[a], 7.63 (dd, $J_{6''5''}$ = 8.6 Hz, $J_{6''2''}$ = 2.2 Hz, 1 H, H6″)[a], 7.520 (d, J_{26} = 2.2 Hz, 1 H, H2)[b], 7.517 (d, $J_{2''6''}$ = 2.2 Hz, 1 H, H2″)[b], 6.78 (d, J_{56} = 8.6 Hz, 1 H, H5)[c], 6.77 (d, $J_{5''6''}$ = 8.6 Hz, 1 H, H5″)[c], 5.97–5.92 (m, 4 H, H3′, H5′, H3‴, H5‴), 5.58–5.45 (m, 6 H, 6 H_x), 4.22–3.85 (m, 6 H, 6 H_a or H_b), 3.75–3.50 (m, 6 H, 6 H_a or H_b), 2.60–1.40 (m, 36 H, 6 H_c, 6 H_d, 6 H_e, 6 H_f, 6 H_g, 6H_h). [a], [b], and [c] indicate interchangeable assignments.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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