EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800338

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800338

Supported by ACES Asian Chemical Editorial Society

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First total synthesis of original chalcone-flavone dimers as cissampeloflavone analogues.

Marion Thévenin,[a] Sylviane Thoret,[a] and Joëlle Dubois*[a]

Abstract: Total synthesis of furoflavones closely related to natural product cissampeloflavone was explored according to different pathways. The involvement of a flavone as key intermediate proved to be the most efficient way to form the 7-phenyl-5*H*-furo[3,2-*g*]chromen-5-one scaffold and consisted in the first example of furoflavone formation. To go further on chalcone-flavone dimer synthesis two different strategies have been examined, either acylation at the very end of the synthesis or introduction of the 3-acyl group during furan ring formation. Ultimate acylation was hardly achievable with hindered benzoyl chlorides but a simpler 4-methoxybenzoyl group has been added on the furoflavone in modest yield. The alternative direct introduction of this acyl group during furan formation proved to be more efficient. Conjugate addition of an iodoflavone to an ynone followed by intramolecular Heck cyclization gave the best results affording the first synthetic chalcone-flavone dimer ever described.

Introduction

Flavonoids and their naturally occurring precursor chalconoids are polyphenolic compounds mainly extracted as secondary metabolites from plants and fungi. They often display biological activities because of their antioxidant properties. They have shown to be active as antimicrobial or anticancer agents. Complex molecules such as biflavonoids or chalcone-flavone dimers are also found in plants but less frequently. In the course of our search for new antiparasitic agents we were interested in original polyphenolic scaffolds. Cissampeloflavone **1** has naturally caught our attention because of its original chalcone-flavone dimer structure and of its activity on *Trypanosoma cruzi* (IC_{50} = 3.4 µM) and *T. brucei* (IC_{50} = 1 µM).[1] The 7-phenyl-5*H*-furo[3,2-*g*]chromen-5-one and more generally the chalcone-flavone dimer scaffold have seldom been observed in natural products. Besides cissampeloflavone **1** that was isolated from a Venezuelan plant (*Cissampelos pereira*), this motif has only been found in Ridiculuflavonylchalcone B isolated from the Brazilian plant *Aristolochia ridicula*. In those species, 6 other chalcone-flavone dimers have been isolated displaying the very similar 6-phenyl-8*H*-furo[2,3-*g*]chromen-8-one scaffold (Figure 1).[2] Among all these bi- and tetraflavonoids, antiparasitic activity was only evaluated for cissampeloflavone. Since the total synthesis of cissampeloflavone has never been carried out to date, we initiated a research program dedicated to the building of such 7-phenyl-5*H*-furo[3,2-*g*]chromen-5-one compounds. Many methodologies have been described to synthesize flavones. The most classical synthetic pathways involve either diaryl ß-diketones or chalcones as key intermediates, such as in Baker-Venkataraman and Claisen-Schmidt rearrangements, respectively.[3] However no synthetic methodology has been developed to access to chalcone-flavone dimer. Moreover no biosynthetic mechanism has really been proposed, only a possible oxidative coupling between 6-hydroxyflavone and chalcone derivatives that could further rearranged into benzofurane.[2a]

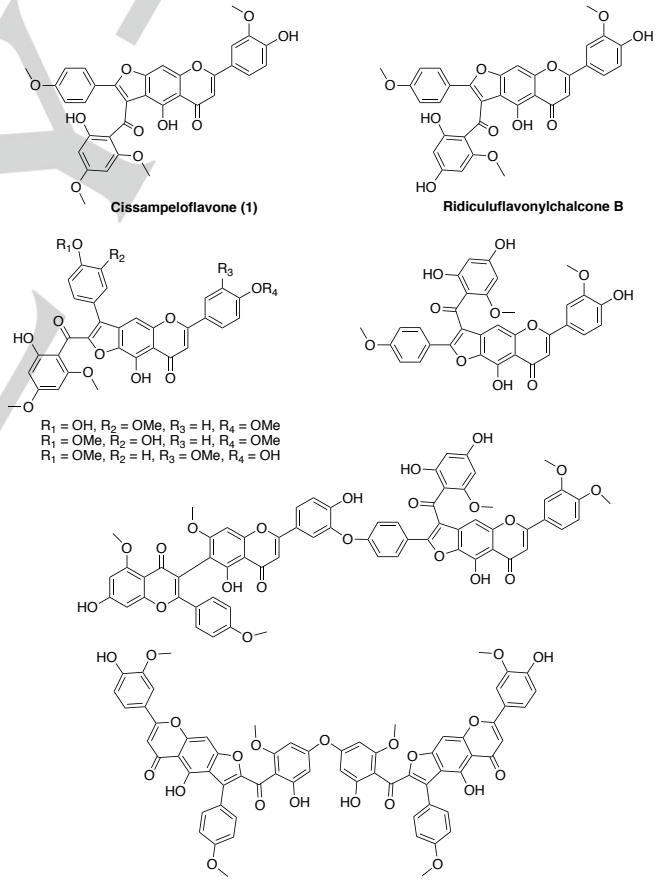

Figure 1. Natural bi- and tetraflavonoids

To achieve the total synthesis of cissampeloflavone **1** different synthetic pathways have been designed. The acylation of the C-3 position of the furan ring could be envisioned at the very end of the synthesis after construction of the 7-phenyl-5*H*-furo[3,2-

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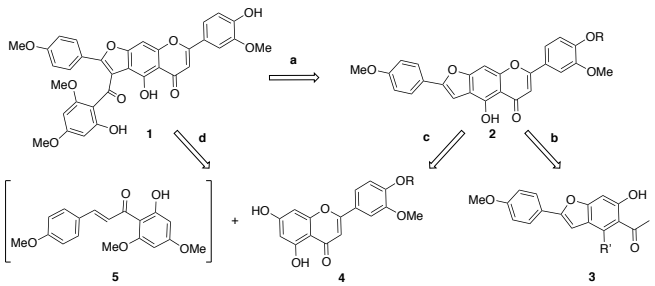
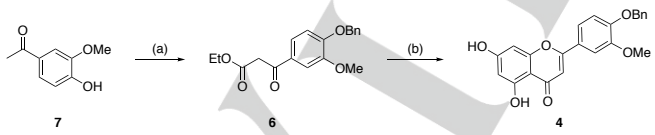
g]chromen-5-one **2** (path a) which can be obtained either from 5-acetylbenzofurane **3** (path b) or from the appropriate flavone **4** (path c). An alternative pathway (d) would consist in reacting the corresponding flavone with a chalcone analogue (Scheme 1).



Scheme 1. Retrosynthetic scheme for total synthesis of cissampeloflavone

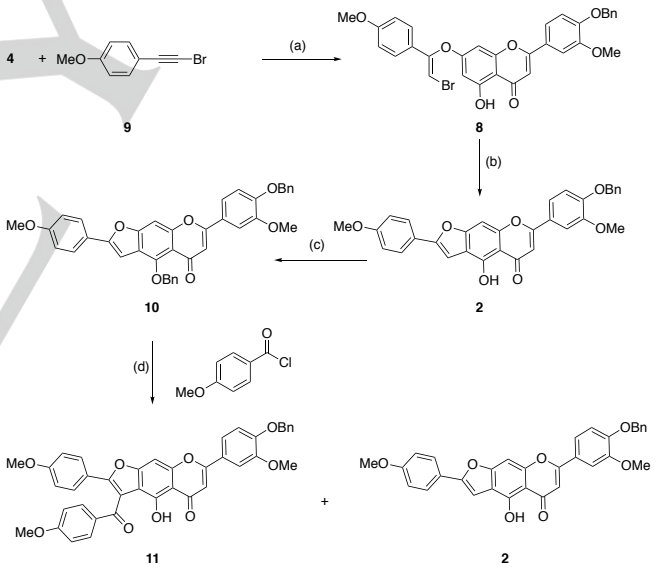
Results and Discussion

Widely used methods such as Claisen-Schmidt or Baker-Venkatamaran rearrangements were ineffective in the case of the furoflavone **2** synthesis from compound **3** when R = H (unpublished results).[4] Therefore we did not go further on path **b**. We thus focused on the synthesis of flavone **4**, the key intermediate in both **c** and **d** pathways. Many synthetic methodologies have been assayed. We observed that the flavone formation was greatly dependent on hydroxyl protecting groups in the privileged methods going through diaryl ß-diketone or chalcone. Finally, the shortest and most efficient way to get unprotected flavone **4** has been proved to be the direct condensation of phloroglucinol with β-ketoester **6** (Scheme 2). This method affording flavone **4** in excellent yield has been greatly and successfully improved when the reaction was carried out on 1 mmol scale. Ethyl benzoylacetate **6** was obtained from commercially available acetovanillone **7** by benzylation under phase transfer catalysis[5] followed by condensation with diethylcarbonate under basic conditions.[6] At last microwave irradiation of the neat mixture of phloroglucinol and compound **6** successfully afforded the desired flavone **4** in 85 % overall yield.[7]



Scheme 2. Reaction conditions: (a) *i* - BnCl, TBAI, K_2CO_3, DMF, rt, 30 h, quant.; *ii* - diethylcarbonate, NaH 60 %, toluene, reflux, 23 h, 95 %; (b) phloroglucinol, microwave 240 °C, 5 min, 89 %.

Among the available methods to form a furan ring from phenol, Wang procedure appeared to be the shortest way to synthesize furoflavone **2**.[8] Flavone **4** was turned into bromovinyl ether **8** by base-promoted addition of bromoethynyl anisol **9** easily obtained from 4-ethynyl anisol.[9] According to Wang *et al*. it was possible to close the furan ring without intermediate purification of the bromovinyl ether, but in our case isolation of bromovinyl derivative **8** prior to cyclization proved to be more efficient. Cyclization through a palladium-catalyzed intramolecular C-H functionalization afforded benzofuranone **2** in a reasonable yield. To avoid long reaction times at high temperature, we have carried out these reactions under microwave irradiation heating. The experiment duration was thus reduced from several hours to 10 min (Scheme 3). Based on our previous results [10], the free hydroxyl group of the furoflavone **2** had to be protected as a benzyl ether before Friedel-Crafts acylation. After benzylation using classical conditions, the Friedel-Crafts acylation of the furan ring was performed. Unfortunately, with the appropriate trisubstituted benzoyl chloride, it was impossible to get the desired product in detectable amounts possibly due to the steric hindrance coming from the phenyl substituents. Acylation with 4-methoxybenzoyl chloride was thus carried out on compound **10** leading to acylated derivative **11** in low yield that could not be further purified due to its low solubility. The main product of this acylation was furoflavone **2** resulting from the debenzylation of compound **10** in the presence of Lewis acid as previously observed.[10]



Scheme 3. Reaction conditions: (a) Cs_2CO_3, DMF, microwave, 110 °C, 10 min, 52 %; (b) $PdCl_2$, K_2CO_3, DMF, microwave, 130 °C, 10 min, 45 %; (c) BnCl, TBAI, K_2CO_3, DMF, rt, 2 days, 57 %; (d) $TiCl_4$, CH_2Cl_2, rt, 1 h, **11** 21 % and **2** 40 %.

In summary, **c** and **a** paths can afford the synthesis of chalcone-flavone dimer and compound **11** was the first chalcone-flavone derivative obtained by total synthesis in 2.2 % overall yield. The main problem is the final acylation step that could not be carried out with hindered benzoyl chlorides. Despite compound **2** has been obtained in only 5 steps in 20 % overall yield this synthetic scheme did not allow the synthesis of cissampeloflavone **1**.

Therefore we turned to the final retrosynthetic pathway **d** that avoided this final acylation step and that is formally the addition of a chalcone on a flavone, similar to the proposed biosynthetic pathway.

Recently the total syntheses of two natural products bearing 2-phenyl-3-benzoyl benzofuran moieties have been described. The synthesis of Daphnodorin B was realized by an intramolecular Heck reaction of a iodoaryl vinyl ether intermediate very similar to bromoaryl vinyl ether **8** that was formed by base promoted alkylation of a iodophenol with a diaryl ynone.[11] The crucial step of the synthesis of 2'''-Dehydroxycalodenin B was an iron-catalyzed oxidative cross coupling of phloroacetophenone and 1,3-bis(4-methoxyphenyl) propane 1,3-dione.[12] (Figure 2).

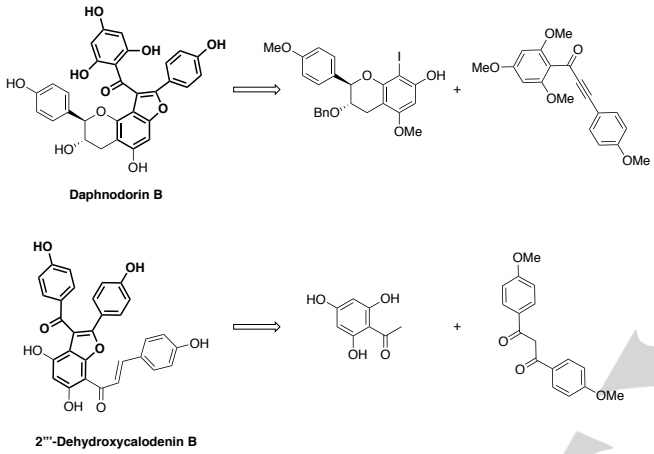
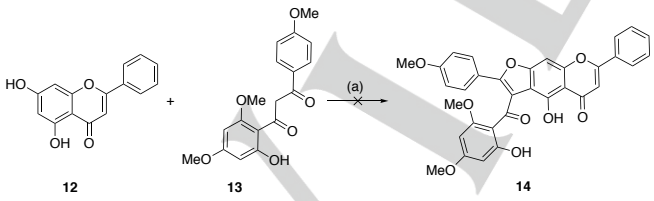


Figure 2. Natural products with 2-phenyl-3-benzoyl benzofuran structure

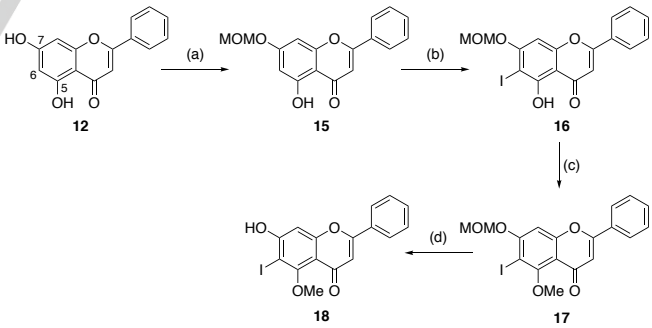
Though flavone **4** has been synthesized in good overall yield in only 3 steps, this method could not be scaled up to afford rapidly suitable amount, *i.e.* tens of grams, to perform methodological studies. Therefore, we decided to examine the feasibility of both syntheses on chrysin **12**, a flavone structurally close to flavone **4** and commercially available.



Scheme 4. *Reaction conditions*: (a) $Fe(ClO_4)_3$ hydrate or $FeCl_3$ hydrate, tBuOOtBu, TFE/HFIP (1:1) or TFE/DCE (1:1), rt or 45 °C overnight, 0 %.

The advantage of the iron-catalyzed oxidative cross coupling method is the use of unmodified chrysin and the easy synthesis of ß-diketone **13**, a formal analogue of chalcone **5**, by following an already reported procedure.[13] Though we were aware of the possibility to obtain regioisomers of **14** by this method we thought it would deserve some investigation. We tried the experimental methods described by Gaster *et al.* in different solvents (DCE, TFE, HFIP) with different iron salts ($Fe(ClO_4)_3$ or $FeCl_3$) at room temperature or with warm heating. None of these conditions were able to give even traces of chalcone-flavone dimer **14** or of any of its possible isomers (Scheme 4). Moreover, both starting materials were recovered unchanged except when the reaction mixture was warmed up to 45 °C. In that case we could isolate the fluorescent 4',5,7-trimethoxyflavone formed by dehydrative cyclization of ß-diketone **13**, in a very similar way as the iron-catalyzed formation of flavones from diaryl ß-diketones.[14]

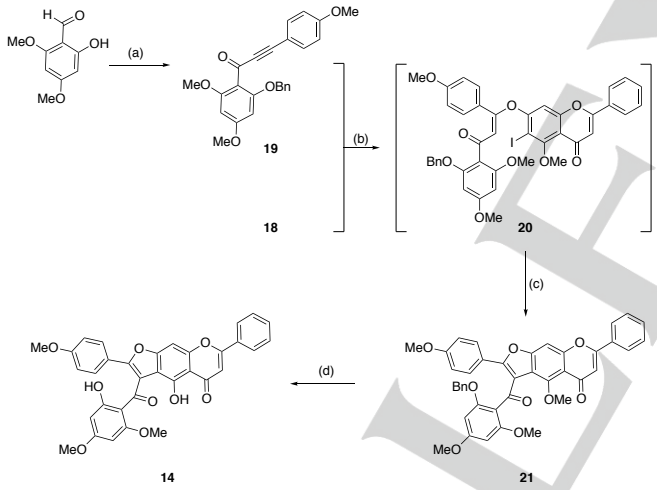
Therefore we tried the Zhang method used for the Daphnodorin B synthesis. Contrary to the previous method, modification of chrysin had to be modified to obtain the appropriate iodo derivative. Preliminary attempts on 6-iodochrysin proved to be unsuccessful. Therefore we decided to protect the 5-hydroxy group before cyclization. Though benzyl or tosyl group could easily be introduced on position 5, further synthetic steps were not conclusive. Suspecting these groups to hinder the cyclization reaction we decided to methylate the 5-hydroxy group leading to the choice of the 6-iodo-5-methoxy-chrysin **18** as the key intermediate. It was easily obtained in 4 steps from chrysin. The 7-hydroxyl group was protected as methoxymethyl ether before selective introduction of iodine in position 6 according to the Lewin's efficient method.[15] Methylation of 6-hydroxyl group by dimethyl sulfate followed by removal of the MOM protecting group afforded compound **18** in 68% overall yield (scheme 5). It is to note that this final step was tricky because of concomitant iodide removal when higher HCl concentrations were used, as experienced by Zhang's group during Daphnodorin A total synthesis.[16]



Scheme 5. *Reaction conditions*: (a) MOMCl, DIPEA, DMF, 0 °C to rt, 12 h, 91 %; (b) BTMA.ICl_2, $CaCO_3$, CH_2Cl_2/MeOH (1:1), rt, quant.; (c) Me_2SO_4, acetone, 60 °C, 83 %; (d) HCl 10 % in MeOH, 70 °C, 93 %.

The second reactant of the Daphnodorin-like synthesis was the diphenyl propynone **19**. It was obtained in 3 steps in 65 % overall yield from 4,6-dimethoxysalicyladehyde: after benzylation of the free hydroxyl group, the protected aldehyde was reacted with the 4-ethynylanisol carbanion followed by oxidation of the

alcohol without intermediate purification. Compound **19** purity appeared to be critical for the following steps leading us to rapidly use it after its formation. In Zhang's article, both *O*-alkylation and palladium-catalyzed cyclization have been carried out in acetonitrile. However, iodoflavone **18** was hardly soluble in this solvent and most of our assays performed in acetonitrile were unsuccessful. The reactants were much more soluble in DMF that was therefore chosen as solvent for both reactions. Another problem in this synthesis was the duration of conjugate addition since no reaction time data were given in the article.[11] Indeed the authors monitored the *O*-alkylation by TLC to carry out palladium-catalyzed following step only when the conjugate addition reached to completion. However in our case it proved difficult to follow the *O*-alkylation of iodoflavone **18** by TLC. Therefore we controlled the conversion of **18** to **20** by LC/MS. It appeared that we never reached completion, even after 48h heating at 75 °C. Nevertheless compound **20** was formed in about 50 % yield. When heating for 96 h, both compounds **18** and **20** were degraded. Contrary to what we observed for the formation of compounds **2** and **8** microwave heating has only led to degradation. Then different bases were tried for the conjugate addition and we found that *t*BuOK and K_3PO_4 gave the best results. To shorten reaction time we increased base amount to 5 equiv and compound **20** appeared to be formed in 48 % yield in 24 h when potassium phosphate was used as a base.



Scheme 6. *Reaction conditions*: (a) *i*) BnCl, K_2CO_3, acetone, rt, overnight, 83 %; *ii)* 4-ethynylanisol, *n*BuLi, THF, -78 °C, 2 h then 0 °C 30 min; *iii*) MnO_2, CH_2Cl_2, rt, 48h, 78 % for *ii* and *iii*; (b) K_3PO_4, DMF, 75 °C, 24 h; (c) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF, 115 °C, 15 h, 9 % for b and c ; (d) *i)* $MgBr_2.OEt_2$, CH_3CN, 80 °C, **14*i*** 61 %; *ii*) ammonium formate, Pd/C (10 %), EtOH, 40 °C, quant.

The palladium-catalyzed Heck reaction was also monitored by LC/MS. Some variations of the conditions described in reference 11 have been tried such as the palladium source ($Pd(OAc)_2$ and tetrakis triphenylphosphine palladium), the absence or the presence of silver carbonate, and the phosphine ligand (*o*-tolylphosphine, triphenylphosphine and polymer-bound triphenylphosphine). The best conditions for Heck-cyclization were palladium acetate with polymer-bound triphenylphosphine in the presence of silver carbonate that afforded compound **21** in 61% LC/MS-estimated yield. Therefore we applied our best conditions (5 equiv. K_3PO_4, 24 h at 75 °C then, without intermediate purification, $Pd(OAc)_2$, polymer-bound PPh_3, Ag_2CO_3, 115 °C, 15 h) to a larger amount of starting materials and compound **21** was obtained in 9 % isolated yield. The difference between LC/MS-estimated and isolated yields accounted for the difficulty to purify these derivatives because of their low solubility in many solvents. The subsequent steps were the selective deprotection of flavone methoxy group and debenzylation. Selective demethylation of **21** was performed with $MgBr_2.OEt_2$ according to the reported procedure[13] in 61% yield. This method was very efficient to selectively remove the methyl group *ortho* to the flavone carbonyl though we also observed partial *ortho* demethylation of the 2-(benzyloxy)-4,6-dimethoxybenzoyl group when the reaction was carried out for longer times. Final debenzylation was quantitatively carried out under classical conditions with ammonium formate and Pd/C affording the close analogue of cissampeloflavone **14**. In summary compound **14** was obtained in 7 steps from chrysin in 3.8 % overall yield.[17] Though overall yield was modest it was reasonable to attempt to synthesize cissampeloflavone by this method. The only modification to make in scheme 7 was related to the flavone precursor of cissampeloflavone, 3'-benzyloxy-4',5-dimethoxy-6-iodoflavone **22** that was easily synthesized from flavone **4** according to scheme 5 in 42 % overall yield. Then the optimized conditions were applied to this iodoflavone **22** and the reaction mixture was analyzed by LC/MS. Many products were formed in this reaction and compound **23** was detected but, as a minor product (5% determined from the UV profile of the reaction mixture). Its low formation yield discouraged us to attempt any purification.

Scheme 7. *Reaction conditions*: *i)* K_3PO_4, DMF, 75 °C, 24 h; *ii)* $Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF, 115 °C, 15 h, traces.

Chrysin derivative **18** and flavone **22** were very similar compounds bearing only a different substitution pattern of the phenyl ring. Contrary to what we expected this slight modification, far away from the reactive centers implied in the conjugate addition and intramolecular Heck cyclization, was significant for their reactivity. Therefore to achieve the total synthesis of cissampeloflavone both attempted methods using chrysin should be reexamined starting from flavone **4**.

Compounds **4, 21**, and **14** were evaluated for their inhibitory activity against parasitic growth. They were assayed on the bloodstream form of *Trypanosoma brucei* and on the intraerythrocytic stages of *Plasmodium falciparum*. Compounds **4**, **21** and **14** exhibited micromolar inhibitory activities against *T. brucei* (IC_{50} = 28 ± 6.9 µM, 3.8 ± 0.5 µM and 1.6 ± 0.1 µM

respectively). It is to note that trypanocidal activities are very similar if we compare flavone **4** with chrysin (IC_{50} = 14.4 ± 2.0 μM)[18] and compound **14** with cissampeloflavone (IC_{50} = 1 μM).[1] Both flavones (**4** and chrysin) were found to be inactive against *P. falciparum* (IC_{50} >50 μM) whereas compounds **21** and **14** displayed moderate anti-*plasmodium* activity (IC_{50} = 3.1 ± 0.1 μM and 24.9 ± 1.9 μM, respectively). When comparing the inhibitory activities of chrysin with flavone **4** and of compound **14** with cissampeloflavone (IC_{50} >50 μM)[1] the same order of potency also prevails against *P. falciparum*.

Conclusions

The first synthesis of chalcone-flavone dimer has been designed according to two different pathways. Our original pathways went through the building of the furoflavone scaffold from flavone. We have met many difficulties to synthesize flavone-chalcone dimers since there was no method to form these dimers and we have had to adapt those described with simple phenolic compounds to flavone as starting material. The successful synthesis of furoflavone **2** was easily achieved in only 5 steps and 20 % overall yield. It should be noted that this is the first synthesis of such a furoflavone derivative and more generally of this scaffold, since, to the best of our knowledge, no similar compound has been described so far. To go to chalcone-flavone dimer the last acylation step has proved to be difficult and only a simple benzoyl group has been introduced. The second pathway was more promising with direct formation of the dimer between an iodochalcone and an ynone. Considering the ynone as a chalcone analogue, this synthetic scheme appeared to be the most closely related to the hypothesized biosynthesis. We successfully synthesized the first chalcone-flavone dimer by this method, thus proving that the total synthesis of chalcone-flavone dimer was actually possible from commercially available chemicals in few steps. However the low solubility of flavonoids was detrimental to efficient synthesis that has nevertheless been overcome by carrying out reactions without solvent or in DMF, when possible. It should also be mentioned that the crucial formation of the benzoyl benzofurane described by Zhang's group in Daphnodorin A and B syntheses occurred in only 44 to 55 % optimized yield.

It is to note that the absence of substituents on the phenyl group of 7-phenyl-5*H*-furo[3,2-*g*]chromen-5-one has little influence on biological activity, especially against *Trypanosoma brucei* where both cissampeloflavone and its analogue **14** exhibited the same inhibitory potency.

Therefore the synthesis of new analogues could be envisioned through this scheme though many improvements remain to be done in this synthesis like using uncommon and innovative solvents. Indeed, this first synthesis of a complex furoflavone scaffold opens the way to the design and synthesis of more original structures.

Experimental Section

General: All commercial reagents were used without any further purification. Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under argon. All reactions were conducted in oven-dried glassware under an argon atmosphere, unless stated otherwise. Microwave heatings were performed with Anton Paar Microwave 300 or CEM Discover. Analytical thin-layer chromatography was carried out on precoated silica gel aluminium plates (SDS TLC plates, silica gel $60F_{254}$). Column chromatography was performed on prepacked Redisep columns. Preparative TLC (PLC) was performed on Merck TLC with silica gel $60F_{254}$. NMR spectra, including ^{1}H, ^{13}C (HMQC and HMBC) experiments, were recorded on a Brucker Avance 300 (300 MHz) and Avance 500 (500 MHz) spectrometers. Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm; 77.2 ppm) or DMSO- d_6 (2.50 ppm; 39.5 ppm). Splitting patterns are designed as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and combinations thereof. Coupling constants *J* are reported in hertz (Hz). IR spectra were recorded on a Perkin-Elmer Spectrum BX. Mass spectra were recorded on Thermoquest AQA Navigator with a TOF detection (ESI-HRMS) or on Waters LCT premier XE using electrospray ionization with a TOF detection (ESI-HRMS) coupled with Waters Acquity UPLC. Melting points were measured on Büchi b-450.

Ethyl 3-(4-(benzyloxy)-3-methoxyphenyl)-3-oxopropanoate (6): *(i) 4-benzyloxy-3-methoxy-acetophenone:* K_3PO_4 (6.25 g, 45.1 mmol, 1.5 equiv.) and tetra-*n*butylammonium iodide (1.11 g, 3.01 mmol, 0.1 equiv.) were added to a solution of acetovanillone (5 g, 30.1 mmol, 1equiv.) in dry DMF (45 mL). Benzyl chloride (4.22 mL, 36.1 mmol, 1.2 equiv.) was added dropwise and the reaction mixture was stirred for 30 h at room temperature. Ethyl acetate was added to the reaction mixture and the organic layer was washed twice with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was recrystallized in ethanol/heptane 1:4 (v/v) to afford 4-benzyloxy-3-methoxy acetophenone (7.71 g, quant.) as white needles. The ^{1}H and ^{13}C NMR chemical shifts of the product are in accordance with literature.[19] MS (ESI^+, MeOH + CH_2Cl_2): m/z 257.1 $[M+H]^+$; HRMS calcd for $C_{16}H_{17}O_3^+$ $[M+H]^+$ 257.1177, found 257.1176 *(ii) ethyl 3-(4-(benzyloxy)-3-methoxyphenyl)-3-oxopropanoate (**6**):* Diethyl carbonate (11.9 mL, 98.4 mmol, 2 equiv.) was added to NaH (60 % in oil) (5.93 g) in anhydrous toluene (63 mL) then a solution of 4-benzyloxy-3-methoxy-acetophenone in anhydrous toluene (63 mL) was added dropwise while refluxing. The solution was kept under reflux for 23 h. After cooling, acetic acid was added carefully until neutral pH was reached. A saturated solution of ammonium chloride was added and the solution was extracted 3 times by ethyl acetate. The combined organic layers were washed twice with saturated NH_4Cl, once with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was then purified by flash chromatography on silica gel (gradient toluene to toluene/EtOAc 95:5 (v/v) in 40 min) to afford compound **6** (15.3 g, 95%) as yellow oil. The ^{1}H and ^{13}C NMR chemical shifts of the product are in accordance with literature.[20] MS (ESI^+, MeCN + CH_2Cl_2): m/z 329.1 $[M+H]^+$; HRMS calcd for $C_{19}H_{21}O_5^+$ $[M+H]^+$ 329.1389, found 329.1393.

2-(4-(Benzyloxy)-3-methoxyphenyl)-5,7-dihydroxy-4*H*-chromen-4-one (4): Phloroglucinol (126 mg, 1 mmol) and compound **6** (1 g, 3 mmol, 3 equiv) were introduced in a pressure tube and heated at 240 °C for 5 min by microwave irradiation (Anton Paar, P = 900 W). After cooling, MTBE and aqueous 10% NaOH were added to the reaction mixture. The aqueous layer was extracted 6-times with MTBE to remove remaining compound **6** and acidified with concentrated HCl until a precipitate was formed. The solid was filtered, washed twice with water and dried to afford flavone **4** (347 mg, 89 %) as a brown amorphous solid. Mp: 265 °C; ^{1}H NMR (DMSO-d_6) δ 12.2 (s, 1H), 10.8 (s, 1H), 7.65 (d, 1H, *J* = 8.0 Hz), 7.59 (s, 1H), 7.47-7.35 (m, 5H), 7.21 (d, 1H, *J* = 8.0 Hz), 6.97 (s,

1H), 6.53 (s, 1H), 6.20 (s, 1H), 5.20 (s, 2H), 3.89 (s, 3H).; ^{13}C NMR (DMSO-d_6) δ 181.8, 164.2, 163.2, 161.4, 157.3, 151.1, 149.3, 136.5, 128.5 (2C), 128.0, 127.9 (2C), 123.2, 119.9, 113.2, 109.7, 103.9, 103.7, 98.9, 94.1, 69.9, 55.9; MS (ESI$^+$, MeCN + CH_2Cl_2): m/z 391.1 $[M+H]^+$; HRMS calcd for $C_{23}H_{19}O_6^+$ $[M+H]^+$ 391.1181, found 391.1227; IR (neat, cm^{-1}) 1737, 1637, 1582, 1503, 1456, 1423, 1333, 1254, 1210, 1165, 1143, 1026.

(*Z*)-2-(4-(benzyloxy)-3-methoxyphenyl)-7-((2-bromo-1-(4-methoxyphenyl)vinyl)oxy)-5-hydroxy-4*H*-chromen-4-one (8): A solution of flavone **4** (77 mg, 0.2 mmol), bromoethynyl-4-anisol **9** (125 mg, 0.59 mmol, 3 equiv) and Cs_2CO_3 (77 mg, 0.24 mmol, 1.2 equiv) in DMF (1 mL) were heated at 110 °C for 10 min by microwave irradiation (Discover CEM). The cooled reaction mixture was filtered over a Celite® pad that was washed with ethyl acetate. After concentration of the organic filtrate, the crude product was purified by flash chromatography on silica gel (gradient heptane to heptane/EtOAc 7:3 (v/v) in 25 min) to afford compound **8** (61.7 mg, 52%) as a yellow amorphous solid. Mp: 124 °C; ^{1}H NMR ($CDCl_3$) δ 12.8 (s, 1H), 7.46-7.32 (m, 9H), 6.96 (d, 1H, *J* = 8.4 Hz), 6.85 (d, 2H, *J* = 9.0 Hz), 6.56 (m, 2H), 6.49 (s, 1H), 6.46 (d, 1H, *J* = 2.1 Hz), 5.22 (s, 2H), 3.96 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 182.5, 164.3, 162.5, 161.8, 160.8, 157.7, 152.2, 151.6, 149.9, 136.3, 128.8 (2C), 128.3, 127.3 (2C), 127.0 (2C), 125.3, 124.0, 120.2, 114.5 (2C), 114.0, 109.5, 106.7, 104.9, 100.0, 94.6, 94.4, 71.0, 56.4, 55.4; MS (ESI$^+$, MeCN + CH_2Cl_2): m/z 601.1 $[M+H]^+$; HRMS calcd for $C_{32}H_{26}BrO_7^+$ $[M+H]^+$ 601.0862, found 601.0861; IR (neat, cm^{-1}) 1737, 1656, 1596, 1511, 1492, 1350, 1276, 1254, 1146, 1026.

7-(4-(benzyloxy)-3-methoxyphenyl)-4-hydroxy-2-(4-methoxyphenyl)-5*H*-furo[3,2-*g*]chromen-5-one (2): A solution of compound **8** (142 mg, 0.24 mmol), $PdCl_2$ (8 mg, 0.012 mmol, 0.05 equiv) and K_2CO_3 (65 mg, 0.47 mmol, 2 equiv) in DMF (0.4 mL) was heated at 130°C for 10 min by microwave irradiation (Discover CEM). Ethyl acetate and aqueous 1N HCl were added to the cooled reaction mixture and the aqueous layer was extracted 3 times with ethyl acetate. The combined organic layers were washed twice with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (gradient heptane to heptane/EtOAc 7:3 (v/v) in 25 min) to afford compound **2** (67.0 mg, 45%) as a yellow amorphous solid. Mp: 206 °C; ^{1}H NMR ($CDCl_3$) δ 12.8 (s, 1H), 7.75 (d, 2H, *J* = 8.7 Hz), 7.52 (dd, 1H, *J* = 8.4 Hz, *J'* = 2.1 Hz), 7.48-7.34 (m, 6H), 7.01 (d, 1H, *J* = 8.4 Hz), 7.01 (s, 1H), 6.97 (d, 2H, *J* = 8.7 Hz), 6.92 (s, 1H), 6.66 (s, 1H), 5.26 (s, 2H), 4.01 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.2, 163.7, 160.3, 159.1, 158.4, 155.9, 151.8, 150.1, 149.4, 136.4, 128.9 (2C), 128.3, 127.4 (2C), 126.3 (2C), 124.0, 122.6, 120.2, 114.5 (2C), 113.6, 110.7, 109.6, 107.6, 105.5, 96.1, 95.4, 71.1, 56.4, 55.5; MS (ESI$^+$, MeCN + CH_2Cl_2): m/z 521.2 $[M+H]^+$; HRMS calcd for $C_{32}H_{25}O_7^+$ $[M+H]^+$ 521.1600, found 521.1610; IR (neat, cm^{-1}) 1738, 1660, 1593, 1505, 1251, 1234, 1142, 1022.

4-benzyloxy-7-(4-(benzyloxy)-3-methoxyphenyl)-2-(4-methoxyphenyl)-5*H*-furo[3,2-*g*]chromen-5-one (10): K_2CO_3 (59 mg, 0.43 mmol, 2 equiv) and tetrabutylammonium iodide (8 mg, 0.022 mmol, 0.1 equiv) were added to a solution of compound **2** (112 mg, 0.22 mmol, 1equiv) in dry DMF (0.75 mL). Benzyl chloride (0.05 mL, 0.43 mmol, 2 equiv) was added and the reaction mixture was stirred for 48 h. Water was added to the reaction mixture and neutralized with aqueous 1N HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed 4 times with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (gradient toluene to toluene/EtOAc 8:2 (v/v) in 25 min) to afford compound **10** (75.0 mg, 57 %) as a yellow amorphous solid. Mp: 185 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, *J* = 8.4 Hz), 7.66 (d, 1H, *J* = 7.5 Hz), 7.48-7.30 (m, 10H), 7.02 (s, 1H), 6.99-6.94 (m, 4H), 6.65 (s, 1H), 5.27 (s, 2H), 5.24 (s, 2H), 3.99 (s, 3H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.9, 160.3, 160.2, 157.3, 156.4, 156.0, 151.4, 151.1, 149.8, 136.7, 136.5, 128.8 (2C), 128.7 (2C), 128.2, 127.7, 127.3 (2C), 126.8 (2C), 126.2 (2C), 124.3, 122.6, 119.5, 114.4 (2C), 113.4, 112.7, 111.7, 109.1, 108.5, 96.6, 94.0, 71.4, 71.0, 56.3, 55.5; MS (ESI$^+$, MeCN + CH_2Cl_2): m/z 611.2 $[M+H]^+$; HRMS calcd for $C_{39}H_{31}O_7^+$ $[M+H]^+$ 611.2070, found 611.2047; IR (neat, cm^{-1}) 1737, 1642, 1603, 1249, 1175, 1141, 1021.

7-(4-(benzyloxy)-3-methoxyphenyl)-4-hydroxy-3-(4-methoxybenzoyl)-2-(4-methoxyphenyl)-5*H*-furo[3,2-*g*]chromen-5-one (11): *p*-Anisoyl chloride (13,2 mg, 0.077 mmol, 1.2 equiv) and $TiCl_4$ (0.077 mL, 0.077 mmol, 1.2 equiv) were added to a solution of compound **10** (39 mg, 0.064 mmol) in dichloromethane (1.5 mL) cooled at 0°C. The reaction mixture was stirred for 1 h at room temperature and ice was added to stop the reaction. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were washed twice with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by TLC (dichloromethane/ MeOH 9:1 (v/v)) to afford compound **11** (8.9 mg, 21 %) and compound **2** (13.2 mg, 40 %) as yellow amorphous solids. Compound **11**: ^{1}H NMR ($CDCl_3$) δ 12.8 (s, 1H), 8.04 (d, 2H, *J* = 8.7 Hz), 7.76 (d, 2H, *J* = 8.8 Hz), 7.60-7.27 (m, 10H), 7.09-6.88 (m, 7H), 6.69 (s, 1H), 5.25 (s, 2H), 4.01 (s, 3H), 3.86 (s, 6H); MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 655.2 $[M+H]^+$;

5-Hydroxy-7-(methoxymethoxy)-2-phenyl-4*H*-chromen-4-one (15): A solution of chrysin (2.0 g, 7.8 mmol) and *N,N*-diisopropylethylamine (3.14 mL, 9.4 mmol, 1.1 equiv) in dry DMF (46 mL) was cooled to 0°C before dropwise addition of methoxymethyl chloride (0.72 mL, 9.4 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 6 h before adding water and saturated aqueous NH_4Cl. The aqueous layer was extracted 6 times with ethyl acetate, the combined organic layers were washed 3 times with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (Heptane/EtOAc 7:3, (v/v)) to afford compound **15** (2.13 g, 91%) as a yellow amorphous solid. ^{1}H NMR ($CDCl_3$) δ 12.6 (s, 1H), 7.81 (m, 2H), 7.45 (m, 3H), 6.60 (d, 1H, *J* = 2.2 Hz), 6,59 (s, 1H), 6.41 (d, 1H, *J* = 2.2 Hz), 5.17 (s, 2H), 3.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 182.6, 164.1, 163.1, 162.1, 157.7, 131.9, 131.3, 129.1, 126.3, 106.4, 105.9, 100.2, 94.4, 94.3, 56.4; MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 299.1 $[M+H]^+$; HRMS calcd for $C_{17}H_{15}O_5^+$ $[M+H]^+$ 299.0919, found 299.0925.

6-Iodo-5-hydroxy-7-(methoxymethoxy)-2-phenyl-4*H*-chromen-4-one (16): $CaCO_3$ (7 g, 70 mmol, 10 equiv) and benzyltrimethylammonium dichloroiodide (3.3 g, 7 mmol, 1 equiv) were added to a solution of compound **15** (2.1 g, 7.0 mmol) in CH_2Cl_2/MeOH (1:1 (v/v), 120 mL). The reaction mixture was stirred at room temperature for 15 h before adding water and aqueous 1 N HCl. The aqueous layer was extracted 3 times with CH_2Cl_2/MeOH (5:2 (v/v), the combined organic layers were washed twice with water, dried over $MgSO_4$ and concentrated under vacuum to afford compound **16** (3 g, quant) as a beige amorphous solid. ^{1}H NMR (DMSO- d_6) δ 13.8 (s, 1H), 8.11 (m, 2H), 7.59 (m, 3H), 7.14 (s, 1H), 7.06 (s, 1H), 5.42 (s, 2H), 3.45 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 181.5, 163.8, 160.7; 160.5, 157.2, 132.3, 130.3, 129.1, 126.5, 105.4, 105.2, 94.8, 93.8, 71.6, 56.3; MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 425.0 $[M+H]^+$; HRMS calcd for $C_{17}H_{14}IO_5^+$ $[M+H]^+$ 424.9886, found 424.9901.

5-Methoxy-6-iodo-7-(methoxymethoxy)-2-phenyl-4*H*-chromen-4-one (17): K_2CO_3 (1.94 g, 14.1 mmol, 6 equiv) was added to a solution of compound **16** (1g, 2.35 mmol) in acetone (42 mL). Dimethyl sulfate (1.32 mL, 14.1 mmol, 6 equiv) was added dropwise to the reaction mixture that was stirred at 60 °C for 6 h. After cooling, the reaction mixture was filtered and the precipitate was washed with water and dried to afford compound **17** (0.85 g, 83 %) as pale yellow needles. ^{1}H NMR ($CDCl_3$) δ

8.06 (m, 2H), 7.56 (m, 3H), 7.31 (s, 1H), 6.90 (s, 1H), 5.45 (s, 2H), 3.78 (s, 3H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.7, 160.4, 159.4, 159.2, 158.8, 131.6, 130.6, 129.0, 126.1, 113.0, 107.9, 99.4, 94.8, 84.5, 61.2, 56.4; MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 439.0 $[M+H]^+$; HRMS calcd for $C_{18}H_{16}IO_5^+$ $[M+H]^+$ 439.0043, found 439.0065.

7-Hydroxy-6-iodo-5-methoxy-2-phenyl-4*H*-chromen-4-one (18): Compound **17** (0.85 g, 1.94 mmol) was solubilized in a solution of HCl 10% in MeOH (52 mL). The reaction mixture was stirred under reflux for 5h. After addition of water to the cooled reaction mixture, precipitates were formed and filtered, washed with water and dried to afford compound **18** (0.711 g, 93 %) as a brown amorphous solid. ^{1}H NMR (DMSO- d_6) δ 11.78 (s, 1H), 8.04 (m, 2H), 7.58 (m, 3H), 6.97 (s, 1H), 6.84 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 174.7, 161.4, 160.2, 159.8, 158.7, 131.5, 130.8, 129.1, 126.1, 111.4, 107.8, 98.2, 83.2, 61.1; MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 395.0 $[M+H]^+$; HRMS calcd for $C_{16}H_{12}IO_4^+$ $[M+H]^+$ 394.9798, found 394.9780.

1-(2-(Benzyloxy)-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one (19): *(i) 2-(benzyloxy)-4,6-dimethoxybenzaldehyde.* K_2CO_3 (3.1 g, 22.4 mmol, 2 equiv) and benzyl chloride (2.7 mL, 22.4 mmol, 2 equiv) were successively added to a solution of 4,6-dimethoxybenzaldehyde (2 g, 11.3 mmol) in acetone (79 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated and diluted with dichloromethane. The organic layer was washed twice with water, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (Heptane/EtOAc 7:3, (v/v)) to afford 2-benzyloxy-4,6-dimethoxybenzaldehyde (2.6 g, 83 %) as a white amorphous solid. The ^{1}H and ^{13}C NMR chemical shifts of the product are in accordance with literature.[19] MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 273.1 $[M+H]^+$; *(ii) 1-(2-(benzyloxy)-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one.* A solution of 4-ethynylanisol (0.39 mL, 3.2 mmol, 2 equiv) in dry THF (3.2 mL) was cooled to -78 °C before dropwise addition of *n*BuLi (1.6 M in hexanes, 2.2 mL, 3.52 mmol, 2.2 equiv). The solution was stirred at -78 °C for 1 h, then 2-benzyloxy-4,6-dimethoxybenzaldehyde (0.43 g, 1.6 mmol) in dry THF (2.65 mL) was added dropwise. After stirring for 1 h at -78 °C then 30 min at 0 °C, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The solution was extracted with EtOAc, the combined organic layers were washed twice with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was diluted with dichloromethane (1.6 mL) and after addition of activated MnO_2 (0.695 g, 8.0 mmol, 5 equiv) the reaction mixture was stirred at room temperature for 48 h. The solution was filtered over a Celite® pad and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (Heptane/EtOAc 8:2, (v/v)) to afford compound **19** (0.5 g, 78 %) as a white amorphous solid. ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 4H), 7.26 (m, 3H), 6.84 (d, 2H, *J* = 8 Hz), 6.17 (dd, 2H, *J* = 10.3 Hz, *J'* = 2.2 Hz), 5.15 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.0, 163.3, 161.2, 159.9, 159.1, 136.5, 134.8, 128.5, 127.7, 127.0, 114.1, 113.1, 112.8, 92.2, 91.2, 90.7, 70.7, 56.1, 55.5, 55.4; MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 403.15 $[M+H]^+$; HRMS calcd for $C_{25}H_{23}O_5^+$ $[M+H]^+$ 403.1545, found 403.1531.

3-(2-(Benzyloxy)-4,6-dimethoxybenzoyl)-4-methoxy-2-(4-methoxyphenyl)-7-phenyl-5*H*-furo[3,2-*g*]chromen-5-one (21) : To a solution of iodoflavone **18** (98.7 mg, 0.25 mmol) and ynone **19** (100 mg, 0.25 mmol, 1 equiv) in dry DMF (2.0 mL) was added K_3PO_4 (266 mg, 1.25 mmol, 5 equiv), and then the reaction mixture was stirred at 75 °C for 24 h. After cooling, the reaction mixture was concentrated under vacuum and immediately diluted with dry DMF (2.5 mL). $Pd(OAc)_2$ (3.0 mg, 0.025 mmol, 0.05 equiv), polymer-bound triphenylphosphine (83 mg, 3 mmol/g, 1 equiv) and Ag_2CO_3 (69 mg, 0.25 mmol) were added to this solution and the reaction mixture was stirred in a pressure tube at 115 °C for 15 h. The solution was cooled to room temperature, filtered over a Celite® pad and concentrated under vacuum. The crude product was purified by preparative TLC (heptane/EtOAc 3:7 (v/v)) to afford compound **21** (15 mg, 9 %) as a light brown amorphous solid. ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.64 (d, 2H, *J* = 8.5 Hz), 7.56 (m, 3H), 7.28 (s, 1H), 7.12 (m, 3H), 6.96 (m, 2H), 6.81 (d, 2H, *J* = 8.5 Hz), 6.70 (s, 1H), 6.06 (dd, 2H, *J* = 15 Hz, *J'* = 2Hz), 4.75 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 188.5, 178.0, 163.6, 161.2, 160.5, 160.5, 156.2, 155.7, 154.9, 153.7, 135.6, 131.7, 131.3, 129.3, 129.0, 128.2, 127.6, 127.4, 126.1, 122.0, 121.0, 119.6, 114.5, 113.6, 113.1, 107.9, 96.0, 91.5, 91.2, 70.6, 62.9, 56.1, 55.3, 55.3; MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 669.2 $[M+H]^+$; HRMS calcd for $C_{41}H_{32}O_9Na^+$ $[M+Na]^+$ 691.1944, found 691.1940.

4-Hydroxy-3-(2-hydroxy-4,6-dimethoxybenzoyl)-2-(4-methoxyphenyl)-7-phenyl-5*H*-furo[3,2-*g*]chromen-5-one (14) : *(i) 4-Hydroxy-3-(2-(benzyloxy)-4,6-dimethoxybenzoyl)-2-(4-methoxyphenyl)-7-phenyl-5H-furo[3,2-g]chromen-5-one **14i**.* A solution of compound **21** (25 mg, 0.037 mmol) and $MgBr_2.OEt_2$ (24 mg, 0.093 mmol, 2.5 equiv) in acetonitrile (0.78 mL) was stirred in a pressure tube at 80 °C for 2 h. After concentration under vacuum, the crude product was purified by preparative TLC (heptane/EtOAc 3:7 (v/v)) to afford **14*i*** (14.7 mg, 61%) as a light orange amorphous solid. ^{1}H NMR ($CDCl_3$) δ 13.2 (s, 1H), 7.87 (m, 2H), 7.59 (m, 2H), 7.50 (m, 3H), 7.06 (m, 3H), 6.94 (m, 3H), 6.73 (d, 2H, *J* = 2.3 Hz), 6.62 (s, 1H), 5.98 (d, 2H, *J* = 2.3 Hz), 4.70 (s, 2H), 3.71 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.8, 163.4, 161.2, 160.5, 156.0, 155.4, 155.7, 135.9, 131.9, 131.4, 129.6, 129.1, 128.2, 127.6, 127.3, 126.4, 122.0, 113.9, 113.5, 113.3, 105.1, 91.6, 91.3, 90.0, 70.7, 56.3, 55.3; MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 655.2 $[M+H]^+$; HRMS calcd for $C_{40}H_{31}O_9^+$ $[M+H]^+$ 655.1968, found 655.1964. *(ii) 4-Hydroxy-3-(2-hydroxy-4,6-dimethoxybenzoyl)-2-(4-methoxyphenyl)-7-phenyl-5H-furo[3,2-g]chromen-5-one **14**.* A solution of **14*i*** (20 mg, 0.031 mmol), ammonium formate (17.4 mg, 0.27 mmol, 9 equiv) and Pd/C 10 % (5.6 mg) in ethanol (0.5 mL) was stirred at 40 °C for 2 h. The reaction mixture was filtered over a Celite® pad and concentrated under vacuum. The crude product was purified by preparative TLC (heptane/EtOAc 3:6 (v/v)) to afford final compound **14** (17 mg, quant) as a brown amorphous solid. NMR ($CDCl_3$) δ 13.7 (s, 1H), 13.3 (s, 1H), 7.95 (m, 2H), 7.67 (m, 2H), 7.57 (m, 3H), 7.18 (s, 1H), 6.92 (m, 2H), 6.62 (bs, 1H), 6.19 (d, 1H, *J* = 2.2 Hz), 5.82 (d, 1H, *J* = 2.2 Hz), 3.87 (s, 3H), 3.84 (s, 3H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.3, 184.0, 168.0, 167.5, 164.4, 163.3, 160.5, 157.2, 154.1, 152.2, 132.0, 131.4, 129.1, 128.2, 126.4, 121.9, 117.7, 114.3, 113.98, 107.7, 106.2, 105.2, 93.6, 91.2, 90.4, 55.7, 55.5, 55.4; MS (ESI$^+$, MeOH + CH_2Cl_2): m/z 564.15 $[M+H]^+$; HRMS calcd for $C_{33}H_{25}O_9^+$ $[M+H]^+$ 565.1499, found 565.1513.

Acknowledgements

This work was supported by ICSN and Centre National de la Recherche Scientifique (CNRS). The authors thank Pr G. Lewin, Drs Y.S. Wang and B. Darses for helpful discussions and O. Thoison and her co-workers for LC/MS analyses. They gratefully acknowledge Pr P. Grellier and E. Mouray for biological evaluations on *P. falciparum* and *T. brucei*.

Keywords: Natural products • total synthesis • oxygen heterocycles • flavonoids • 7-phenyl-5*H*-furo[3,2-*g*]chromen-5-ones

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10.1002/ejoc.201800338

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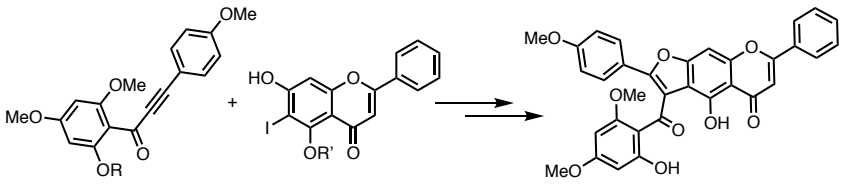

Total synthesis of furoflavones closely related to natural product cissampeloflavone was achieved according to different pathways. Conjugate addition of an iodoflavone to an ynone followed by intramolecular Heck cyclization gave the best results affording the first synthetic chalcone-flavone dimer ever described.

Natural product synthesis*

*Marion Thévenin, Sylviane Thoret and Joëlle Dubois**

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First total synthesis of original chalcone-flavone dimers as cissampeloflavone analogues