Application of Carbohydrates with Methylene and Vinyl groups in Heck-Mizoroki Cross-coupling Reactions with *O*-heterocycles

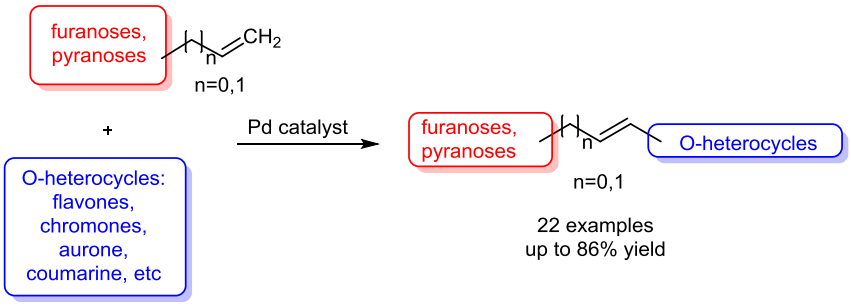
Zoltán Kondor,[a]
Mihály Herczeg,[b]
Anikó Borbás,[b]
Tamás Patonay,[a]
Krisztina Kónya[a,*]

[a] Department of Organic Chemistry, University of Debrecen, 4032 Debrecen, Egyetem tér 1., Hungary,Telephone: +36-52-512-900 ext. 22465 Fax: +36-52-512-766

[b] Department of Pharmaceutical Chemistry, University of Debrecen, 4032 Debrecen, Egyetem tér 1., Hungary .

konya.krisztina@science.unideb.hu.

Dedicated to the memory of Prof. Tamás Patonay.



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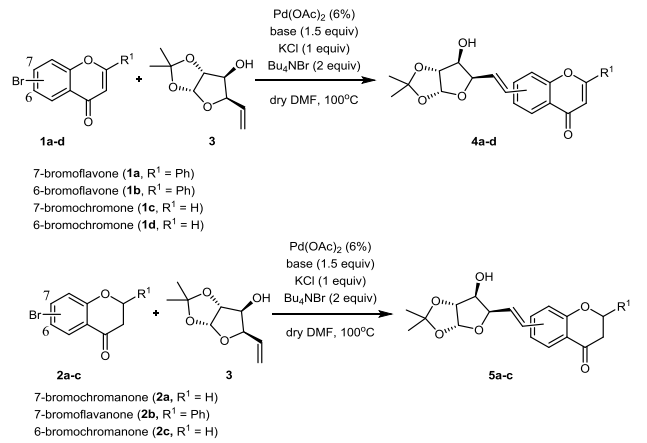
Abstract The synthesis of structurally new carbohydrate-*O*-heterocycles molecules with various unsaturated carbon bridge has been accomplished by palladium catalyzed cross-coupling reaction.

Key words *O*-heterocycles, Heck-Mizoroki reaction, methylene, vinyl, carbohydrate

Flavonoids represent a notable group of phenolic plant components. Usually, these flavonoids are bioactive compounds and their beneficent properties have been observed for a long while. Nowadays, their bioavailability, metabolic ability, and detailed health effects have been studying in numerous medical researches.[1a] Since flavonoids are potent antioxidants in vitro, these compounds are in the main interests of the investigation of e. g. protection against cardiovascular disease. Further, these natural compounds often contain a carbohydrate moiety in different position on the skeleton. Especially, *C*-glycosyl flavonoids show wide and interesting biological activities such as antiviral,[1b] cytotoxic,[2] anti-inflammatory[3] and DNA binding activities.[4] Therefore, our research is focused on the synthesis of new compounds of flavones/chromone (**1**) and flavanones/chromanones (**2**) by Heck-Mizoroki reactions, applying carbohydrates with a vinyl or a methylene group at different position at a furanose or a pyranose ring.

First, the synthesis of 5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hex-5-enofuranose (**3**) was performed and then the substrates scope was surveyed. Furanose **3** was formed in 49% yield using a literature procedure[5] (I_2/TTP/imidazole/dry CH_2Cl_2/ 0°C to rt/ 2h) to afford terminal alkene **3**.

The reactions of vinyl furanose **3** and bromo derivatives **1a,b,** under a phosphine free Jeffery's condition,[6a] provided the corresponding compounds **4a,b** in 79% and 70% yield as *trans* isomers, respectively (Scheme 1, Table 1). However, if the amount of the Bu_4NBr was halved or 2 equiv Bu_4NCl was applied instead of 2 equiv Bu_4NBr; only dehalogenation was observed and flavone was isolated in ~30-40% yields.



Scheme 1

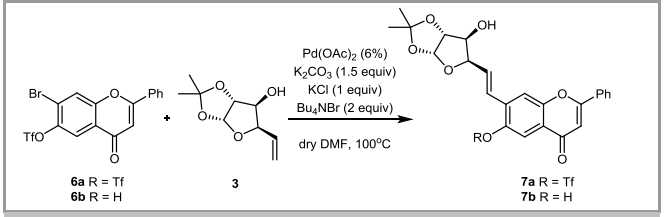
Table 1 Yields of reaction compound **3** under Jeffery condition

Reactant	Condition	Time	Product	Yield
7-bromoflavone	Jeffery	3h	**4a**	79%[a]
6-bromoflavone	Jeffery	4h	**4b**	70%
7-bromochromone	Jeffery	3h	**4c**	71%
6-bromochromone	Jeffery	4h	**4d**	72%
7-bromochromanone	Jeffery*	1h	**5a**	10%[b]
7-bromoflavanone	Jeffery*	1h	**5b**	33%[c]
6-bromochromanone	Jeffery*	1h	**5c**	20%

Jeffery: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1 equiv KCl, 2 equiv Bu_4NBr, 1.5 equiv K_2CO_3, dry DMF, 100°C, N_2 atmosphere. *Jeffery**: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 2 equiv Bu_4NBr, 1.5 equiv HCOONa, solvent, 100°C, N_2 atmosphere; [a] using 1 equiv Bu_4NBr or 2 equiv Bu_4NCl yield is 0%, only dehalogenation occurred in 30-40% yield; [b]: conversion 19%, [c]: flavone and chalcone mixture

The bromochromones **1c,d** showed identical stereoselectivity and the yields (**4c**: 71%, **4d**: 72%) were comparable with the reactions of bromoflavones. However, the chromanone derivatives decomposed under these conditions. Since these *O*-heterocycles are base sensitive compounds, the application of HCOONa[6b] proved to be a key to solve this problem. Hence, the syntheses of chromanone derivatives **2a,c** and flavanone **2b** were managed to attain in low yields (10-33%). The reaction of vinyl furanose **3** with different oxygen containing heterocycles showed only *trans* stereoselectivity.

In order to prepare a disubstituted compound, 7-bromo-6-triflyloxyflavone (**6a**) was involved in the study, since this compound has two substituents which can take part in the cross-coupling reaction (Scheme 2, Table 2).



Scheme 2

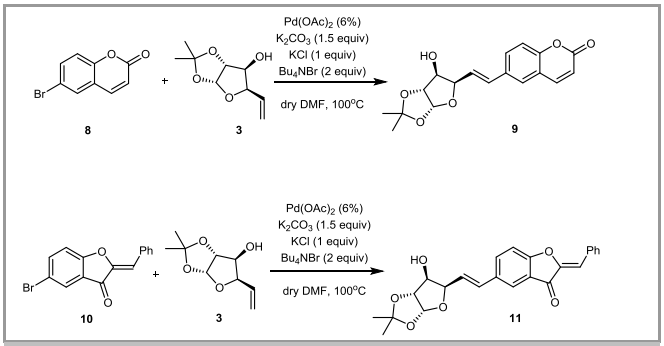
Table 2 Results of reactions of triflates derivative **6a** and compound **6b**

Reactant	Condition	Time	Product	Yield
7-bromo-6-triflyloxyflavone	Jeffery	1h	7b	44%
7-bromo-6-hydroxyflavone	Jeffery	3h	7b	no reaction

Jeffery: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1 equiv KCl, 2 equiv Bu_4NBr, 1.5 equiv K_2CO_3, DMF, 100°C, N_2 atmosphere.

In different palladium catalyzed reactions, the application of a pseudo halide (OTf) is well known in the literature. Thus, we envisioned that these transformations could be selectively controlled at various stages to afford the desired products by tuning the reaction parameters. The reaction proceeded smoothly but compound **7a** was not detected in the reaction mixture only the hydrolyzed derivative **7b** was isolated in 44% yield. In order to investigate whether the hydrolysis or the cross-coupling reaction occurred first, the reaction of 7-bromo-6-hydroxyflavone (**6b**) was carried out, but no transformation was occurred (Scheme 2). It means, the cross-coupling reaction was successful, and then the formed product **7a** was hydrolyzed to **7b**.

In order to further broaden the scope of this reaction with respect to the *O*-heterocycle components, we employed a bromocoumarin **8** as well as -aurone **10** in this process, and each of the desired compounds were formed in moderate to good yields (**9**: 86%, **11**: 47%) (Scheme 3).

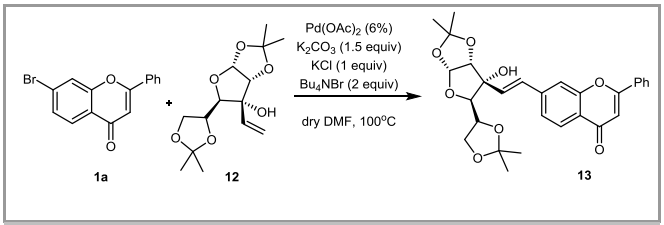


Scheme 3

Table 3 Yields of coumarine **8** and aurone **10** derivatives

Reactant	Condition	Time	Product	Yield
6-bromocoumarine	Jeffery	4h	**9**	86%
5-bromoaurone	Jeffery	3h	**11**	47%

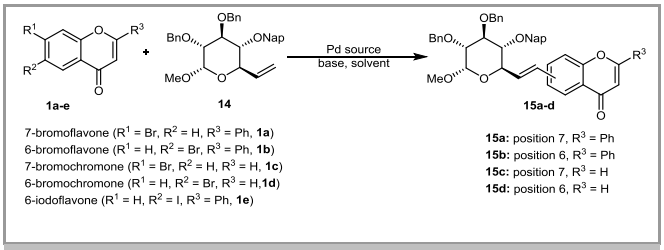
Jeffery: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1 equiv KCl, 2 equiv Bu_4NBr, 1.5 equiv K_2CO_3, DMF, 100°C,N_2 atmosphere



Scheme 4

The synthesis of another 'vinyl-sugar' **12** was achieved[12] from 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexulofuranos-3-ulose with vinylmagnesium bromide *via* Grignard reaction, however this reaction afforded the product **12** in low yield. Therefore, only one cross-coupling reaction was performed with flavone **1a** and 3-*C*-ethenyl-1,2:5,6-bis-O-(1-methylethylidene)-α-D-allofuranose (**12**), giving the desired product **13** in good yield (56%) (Scheme 4). The applied conditions did not cause the cleavage of the acetal protecting groups.

After these promising results regarding to the furanose compounds, we began the investigation of the 'vinyl-pyranose' derivatives **14,**[7] **16**[8] in palladium catalyzed reactions. Palladium-catalyzed Heck reaction[6c] of **1a** and methyl 6,7-dideoxy-4-*O*-(2-naphthalenylmethyl)-2,3-bis-*O*-(phenylmethyl)-α-D-*gluco*-hept-6-enopyranoside (**14**) using $Pd(OAc)_2/Ph_3P$ as catalyst-ligand pair was used to afford the desired **15a** in 49% yield under these classical Heck condition.



Scheme 5

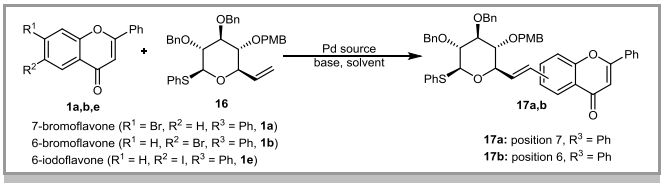
Table 4 Yields of reactions of haloflavones/chromones **1**

Reactant	Condition	Product	Yield
7-bromoflavone	Heck	**15a**	49%
7-bromoflavone	B	**15a**	30%
7-bromoflavone	A	**15a**	59%
7-bromoflavone	A*	**15a**	84%
6-bromoflavone	A*	**15b**	86%
6-iodoflavone	B*	**15b**	74%
7-bromochromone	A*	**15c**	50%
6-bromochromone	A*	**15d**	49%

Heck conditions: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1.1 equiv triethylamine (TEA), 10% triphenylphosphine (TPP), NMP, 100-110 °C/N_2 atm, 3h
A conditions: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1 equiv KCl, 2 equiv Bu_4NBr, 1.5 equiv K_2CO_3, DMF, 100°C, 3 h, N_2 atmosphere.
B conditions: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1 equiv KCl, 2 equiv Bu_4NBr, 1.5 equiv HCOONa, DMF, 100°C, 3 h, N_2 atmosphere, 3h
A conditions*: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1 equiv KCl, 2 equiv Bu_4NBr, 1.5 equiv K_2CO_3, 10% $AgNO_3$, DMF, 100°C, 3 h, N_2 atmosphere
B conditions*: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1 equiv KCl, 2 equiv Bu_4NBr, 1.5 equiv HCOONa, 10% $AgNO_3$, DMF, 100°C, 3 h, N_2 atmosphere

While the previously successfully used phosphine free Jeffery's condition ($Pd(OAc)_2$, HCOONa, TBAB, KCl) resulted the same product in 30% yield. It is known from the literature, the application of silver(I) salts can increase the efficiency of the cross-coupling reactions.[13] Therefore, 10% $AgNO_3$ was applied as an additive in the reaction and the yield was doubled (59%). If we used K_2CO_3 as base the yield was increased up to 84%. In case of **1b** the coupled derivative **15b** was isolated in 86% yield. It is well known iodo compounds can react more readily than bromo one. Whereas, we carried out the cross coupling reaction of 6-iodoflavone (**1e**) and **14** and even using a weaker base (HCOONa) the product was isolated in good yield (74%) due to the increased reactivity of *O*-heterocyclic compound. The phosphine free condition with K_2CO_3 worked well in case of bromochromones **1c**,**d** and the transformation successfully afforded the chromone-glucopyranoside derivatives **15c**,**d** (50%; 49% respectively). The applied conditions were suitable to keep the ether type protecting groups (Scheme 5).

In the survey another pyranoside type compound was tested, namely the 6,7-dideoxy-4-*O*-[(4-methoxyphenyl)methyl]-2,3-bis-*O*-(phenylmethyl)-1-phenylthio-β-D-gluco-hept-6-enopyranoside (**16**).



Scheme 6

Table 5 Cross-coupling reactions of pyranose **16**

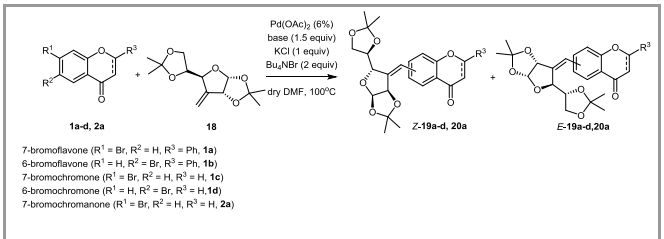
Reactant	Conditions	Product	Yield
7-bromoflavone	A*	**17a**	70%
6-bromoflavone	A*	**17b**	68%
6-iodoflavone	A*	**17b**	88%

A conditions*: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1 equiv KCl, 2 equiv Bu_4NBr, 1.5 equiv K_2CO_3, 10% $AgNO_3$, DMF, 100°C, 3 h, N_2 atmosphere

This compound was available in limited amount, because of this reason it was reacted only with haloflavones. 7- and 6-bromoflavone (**1a,b**) and 6-iodoflavone (**1e**) were used; under the phosphine free Jeffery condition ($AgNO_3$, K_2CO_3) the products **17a-e** were obtained in good yields (70-88%) (Scheme 6).

To increase the variety of the carbohydrate compounds; 1,2:5,6-di-*O*-isopropylidene-3-methylene-α-D-allofuranose (**18**) was synthetized,[8-11] and then used in further reactions. The preparation of compound **18** started from the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, which compound was oxidized by Swern oxidation to afford the 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexulofuranos-3-ulose. The isolated product was converted into 1,2:5,6-di-*O*-isopropylidene-3-methylene-α-D-allofuranose (**18**) by the treatment of methyltriphenylphosphonium bromide.

First, the Jeffery's conditions were tested with 7-bromo-, 6-bromoflavones (**1a,b**) as substrates.



Scheme 7

Table 6 Cross-coupling reactions of pyranose **18**

Reactant	Condition	Time	Product	Yield (*Z*)	Yield (*E*)
7-bromoflavone	Jeffery	3h	**19a**	33%	30%
6-bromoflavone	Jeffery	4h	**19b**	37%	37%
7-bromochromone	Jeffery	3h	**19c**	14%	15%
6-bromochromone	Jeffery	3h	**19d**	28%	27%
7-bromochromanone	Jeffery*	1h	**20a**	14%	-

Jeffery: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 1 equiv KCl, 2 equiv Bu_4NBr, 1.5 equiv K_2CO_3, DMF, 100°C, N_2 atmosphere. *Jeffery**: 1 equiv substrate, 1 equiv ArBr, 6% $Pd(OAc)_2$, 2 equiv Bu_4NBr, 1.5 equiv HCOONa, solvent, 100°C, N_2 atmosphere

The 2D NMR measurements of the separated compounds revealed that during the reaction *Z* and *E* isomers were formed approximately in 1:1 ratio (*Z*-**19a** = 33%, *E*-**19a** =30%) (Scheme 15). Similar observation was found in case of 6-bromoflavone (*Z*-**19b**= 37%, *E*-**19b** =37%).

Then, the cross coupling reaction of bromochromones **1c,d** and **18** was performed using the Jeffery's methods. The chromone derivatives also provided the *cis* and *trans* isomers in moderate yields (*Z*-**19c**= 14%, *E*-**19c**=15%; 6-bromochromone: *Z*-**19c**= 27%, *E*-**19c**=28%) in the same ratio as in the case of flavones.

The reaction of 7-bromochromanone (**2a**) with the same carbohydrate derivative under modified Jeffery's conditions resulted in the desired coupled product **20a**, although the yield was low (14%) and only the *trans* isomer was formed (Scheme 7).

As a summary, in order to create unique compounds, which are new analogs of the naturally-occurring *C*-glycosyl flavonoids in good yields, we successfully performed the palladium catalyzed cross-coupling reactions of carbohydrates with vinyl and methylene group and different oxygen-heterocycles. In the frame of this project the Heck reaction of chromanones and flavanones were also investigated. We have found effective reaction conditions to transform these base sensitive compounds *via* Heck-Mizoroki reactions. In the case of isolated derivatives with vinyl linkers, we found high *trans* stereoselectivity. The reactions with methylidene group showed the formation of both isomers usually in 1:1 ratio. The biological assays already have been started with some selected derivatives. These structurally novel derivatives with various alkenyl spacers are interesting for biological tests and may provide new hits for pharmaceutical R&D by improving metabolism and adsorption properties compare to natural *C*-glysosyl flavonoids. By this modern cross-coupling reaction, we managed to prepare such derivatives which synthesis is currently not solved on other pathways.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References and Notes

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(6) **a) General procedures for coupled products 4a–d, 7b, 9, 11, 13, 15a–d, 17a,b, and 19a–d; a Typical Jeffery Procedure;** A mixture of compound **1a** (150 mg, 0.5 mmol), **3** (93 mg, 0.5 mmol), TBAB (322 mg, 1 mmol), K_2CO_3 (104 mg, 0.75 mmol), and $Pd(OAc)_2$ (7 mg, 6 mol%) was stirred in anhydrous DMF (10 mL) at 100 °C for 3 h. Then the solvent was removed under reduced pressure and the crude product was purified by silica gel (60–120 mesh) column chromatography using hexane–EtOAc (1:2) as an eluent to give the solid compound **4a**; yield: 160 mg (79%); white solid; mp 198–200 °C.

7-((E)-2-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)vinyl)-2-phenyl-4H-chromen-4-one (4a). Yield: 160 mg (79%); white solid; mp 198–200 °C; eluent: hexane–EtOAc (1:2). IR (KBr): 1013, 1076, 1164, 1375, 1431, 1451, 1627, 2933, 2987, 3423 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 7.81 – 7.73 (m, 3H), 7.54 – 7.39 (m, 3H), 7.22 (s, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.74 (d, *J* = 16.1 Hz, 1H), 6.68 (s, 1H), 6.43 (dd, *J* = 16.0, 5.7 Hz, 1H), 6.10 (d, *J* = 3.6 Hz, 1H), 4.89 (d, *J* = 5.2 Hz, 1H), 4.71 (d, *J* = 3.6 Hz, 1H), 4.38 (s, 1H), 1.57 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.3, 163.6, 156.1, 142.5, 131.9, 131.4, 131.2, 129.1, 128.2, 126.3, 125.5, 123.5, 122.4, 115.3, 111.8, 107.2, 105.0, 85.4, 81.3, 76.7, 27.0, 26.3. Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.93; H, 5.46. Found: C, 70.97; H, 5.48.

6-((E)-2-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)vinyl)-2H-chromen-2-one (9). Yield: 143 mg (86%); white; mp 143–144 °C; eluent: hexane–EtOAc (1:1). IR (KBr): 821, 1004, 1075, 1100, 1164, 1215, 1719, 2935, 2985, 3438 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 7.62 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 16.1 Hz, 1H), 6.37 (d, *J* = 9.5 Hz, 1H), 6.29 (dd, *J* = 16.0, 5.6 Hz, 1H), 6.09 – 5.97 (m, 1H), 4.88 (s, 1H), 4.70 – 4.56 (m, 1H), 4.24 (s, 1H), 1.55 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.9, 153.4, 143.5, 133.2, 132.0, 129.9, 125.8, 123.9, 118.9, 117.2, 116.9, 111.9, 104.7, 85.2, 81.0, 76.4, 26.9, 26.3. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.48; H, 5.54.

2-((Z)-benzylidene)-5-((E)-2-((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)vinyl)benzofuran-3(2H)-one (11). Yield: 96 mg (47%); yellow solid; mp 206–208 °C; eluent: hexane–EtOAc (3:2). IR (KBr): 1016, 1074, 1163, 1485, 1613, 1649, 1707, 2932, 2988, 3403 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 2H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.61 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.48 – 7.37 (m, 3H), 7.20 (d, *J* = 8.5 Hz, 1H), 6.87 – 6.76 (m, 2H), 6.25 (dd, *J* = 16.0, 5.7 Hz, 1H), 6.04 (d, *J* = 3.9 Hz, 1H), 4.91 – 4.86 (m, 1H), 4.64 (d, *J* = 3.7 Hz, 1H), 4.23 (d, *J* = 2.9 Hz, 1H), 1.55 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 184.6, 165.7, 147.3, 135.4, 132.5, 132.3, 131.7, 130.2, 129.0, 123.3, 122.2, 121.9, 113.7, 113.1, 112.0,

104.8, 85.3, 81.0, 76.5, 26.9, 26.3. Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.93; H, 5.46. Found: C, 70.98; H, 5.49.

b) Coupled Products 5a–c, and 20a; Compound 5a; a Typical Jeffery* Procedure

A mixture of compound **2a** (150 mg, 0.5 mmol), **3** (93 mg, 0.5 mmol), TBAB (322 mg, 1 mmol), HCOONa (51 mg, 0.75 mmol), and $Pd(OAc)_2$ (7 mg, 6 mol%) was stirred in THF (10 mL) at 100 °C for 1 h. Then the solvent was removed under reduced pressure and the crude product was purified by silica gel (60–120 mesh) column chromatography using hexane–EtOAc (3:1) as an eluent to give the solid compound **4a**; yield: 15 mg (79%); pale yellow solid; mp 145–150°C.

7-((E)-2-((3aR,5R,6*S*,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)vinyl)chroman-4-one (5a)

Yield: 15 mg (10%); pale yellow solid; mp 145–150 °C; eluent: hexane–EtOAc (3:1). IR (KBr): 1018, 1076, 1163, 1215, 1256, 1434, 1612, 1684, 2926, 3399 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 1H), 7.07 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.96 (s, 1H), 6.80 (d, *J* = 16.0 Hz, 1H), 6.37 (dd, *J* = 16.1, 5.4 Hz, 1H), 6.01 (d, *J* = 3.7 Hz, 1H), 4.92 – 4.87 (m, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 4.53 (t, *J* = 6.4 Hz, 2H), 4.21 (d, *J* = 2.6 Hz, 1H), 2.80 (d, *J* = 6.4 Hz, 2H), 1.54 (s, 3H), 1.35 (*s*, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 191.5, 162.2, 144.0, 133.0, 127.7, 126.3, 120.8, 119.7, 115.9, 112.1, 104.8, 85.2, 80.7, 76.4, 67.2, 37.8, 26.9, 26.3. Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.08; H, 6.10.

7-((E)-2-((3aR,5R,6R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)vinyl)-2-phenyl-4H-chromen-4-one (13)

Yield: 141 mg (56%); white solid; mp 177–178 °C eluent: hexane–EtOAc (1:1). IR (KBr): 1069, 1164, 1216, 1373, 1431, 1608, 1623, 1640, 2986, 3451 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.96 – 7.88 (m, 2H), 7.60 – 7.50 (m, 3H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 16.0 Hz, 1H), 6.81 (s, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 5.93 (d, *J* = 3.7 Hz, 1H), 4.40 (d, *J* = 3.6 Hz, 1H), 4.25 – 4.15 (m, 1H), 4.06 – 3.97 (m, 3H), 3.15 (s, 1H), 1.66 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 163.5, 156.7, 142.1, 131.8, 131.7, 130.1, 129.9, 129.1, 126.3, 126.1, 123.4, 123.3, 115.9, 113.4, 109.7, 107.8, 103.8, 83.8, 81.6, 80.7, 73.9, 26.8, 26.7, 26.6, 25.4. Anal. Calcd for $C_{29}H_{30}O_8$: C, 68.76; H, 5.97. Found: C, 68.80; H, 6.01.

6-((E)-2-((2R,3R,4S,5R,6*S*)-4,5-bis(benzyloxy)-6-methoxy-3-(naphthalen-2-ylmethoxy)tetrahydro-2H-pyran-2-yl)vinyl)-2-phenyl-4H-chromen-4-one (15b). Yield: 245 mg (86%); white solid; mp 159–163 °C; eluent: hexane–EtOAc (3:1). IR (KBr): 696, 736, 1042, 1077, 1357, 1451, 1616, 1648, 2908, 3030 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.30 (m, 23H), 6.84 (s, 1H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.15 (dd, *J* = 15.9, 6.8 Hz, 1H), 4.64 (m, 7H), 4.25 (t, *J* = 8.2 Hz, 1H), 4.06 (t, *J* = 9.3 Hz, 1H), 3.58 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.38 (m, 4H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 178.2, 163.3, 155.6, 138.7, 138.1, 133.8, 133.4, 133.1, 132.9, 131.7, 131.6, 131.4, 131.3, 129.0, 128.4, 128.0, 127.8, 127.6, 127.0, 126.3, 125.9, 125.8, 123.8, 123.3, 118.3, 107.5, 98.2, 82.0, 79.9, 75.9, 75.3, 73.4, 71.1, 55.3.Anal. Calcd for $C_{48}H_{42}O_7$: C, 78.88; H, 5.79. Found: C, 78.93; H, 5.81.

7-((E)-2-((2R,3R,4S,5R)-4,5-bis(benzyloxy)-3-((4-methoxybenzyl)oxy)-6-(phenylthio)tetrahydro-2H-pyran-2-yl)vinyl)-2-phenyl-4H-chromen-4-one (17a). Yield: 136 mg (70%); white solid; mp 139–140 °C; eluent: hexane–EtOAc (2:1).IR (KBr): 1028, 1067, 1251, 1369, 1430, 1450, 1608, 1649, 2901, 3005 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ: 8.17 (s, 1H), 7.93 (m, 2H), 7.24 (m, 20H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.74 (m, 4H), 6.31 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.74 (m, 6H), 4.53 (d, *J* = 10.9 Hz, 1H), 3.96 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.72 (t, *J* = 8.9 Hz, 1H), 3.68 (s, 3H), 3.52 (t, *J* = 9.3 Hz, 1H), 3.40 (t, *J* = 9.3, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 178.0, 163.4, 159.4, 156.5, 142.3, 138.2, 137.9, 133.5, 132.1, 131.7, 131.6, 130.9, 129.9-127.7, 126.2, 125.9, 123.4, 123.1, 115.7, 113.8, 107.7, 87.7, 86.5, 81.1, 80.9, 79.21, 76.0, 75.5, 74.9, 55.1. Anal. Calcd for $C_{50}H_{44}O_7S$: C, 76.12; H, 5.62. Found: C, 76.16; H, 5.66.

6-((Z)-((3aR,5*S*,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydrofuro[2,3-d][1,3]dioxol-6(5H)-ylidene)methyl)-2-phenyl-4H-chromen-4-one (*Z*-19b). Yield: 88 mg (37%); white solid; mp 114-116 °C; eluent: hexane–EtOAc (3:1). IR (KBr): 1019, 1068, 1354, 1371, 1381, 1453, 1613, 1646, 2933, 2987 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.95 – 7.88 (m), 7.60 (d, *J* = 8.7 Hz, 1H), 7.53 (m, 3H), 7.12 (s, 1H), 6.82 (s, 1H), 5.87 (d, *J* = 3.7 Hz, 1H), 5.13 (d, *J* = 2.7 Hz, 1H), 4.80 (d, *J* = 6.1 Hz, 1H), 4.18 – 4.01 (m, 3H), 1.60 (s, 3H), 1.49 (s, 3H), 1.47 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 163.5, 155.7, 140.3, 134.1, 133.4, 131.8, 131.7, 129.1, 126.7, 126.4, 125.9, 123.9, 118.5, 112.7, 110.1, 107.6, 105.2, 80.8, 79.1, 77.5, 67.4, 27.5, 27.3, 26.9, 25.7. Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.58; H, 5.92. Found: C, 70.60; H, 5.94.

6-((E)-((3aR,5*S*,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydrofuro[2,3-d][1,3]dioxol-6(5H)-ylidene)methyl)-2-phenyl-4H-chromen-4-one (*E*-19b). Yield: 88 mg (37%); white solid; mp 200-206 °C; eluent: hexane–EtOAc (3:1). IR (KBr): 1042, 1207, 1355, 1370, 1381, 1454, 1609, 1646, 2932, 2987 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.55 (m, 4H), 6.94 (s, 1H), 6.84 (s, 1H), 5.93 (d, *J* = 4.4 Hz, 1H) 5.52 (s, 1H), 5.25 – 5.16 (m, 1H), 4.11 (dd, *J* = 11.7, 6.1 Hz, 1H), 3.88 (t, *J* = 7.5 Hz, 1H), 3.59 (t, *J* = 7.7 Hz, 1H), 1.52 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 163.6, 155.6, 140.8, 133.8, 133.5, 131.8, 131.6, 129.1, 127.4, 126.4, 125.6, 124.0, 118.6, 113.2, 109.9, 107.7, 103.9, 83.0, 79.7, 77.2, 65.9, 28.0, 27.9, 26.1, 25.5. Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.58; H, 5.92. Found: C, 70.61; H, 5.94.

c) Heck Condition: A stirred mixture of bromoflavone **1a** (75 mg, 0.249 mmol), **14** (0.249 mmol, 1.0 equiv), Et_3N (39 µl, 0.274 mmol, 1.1 equiv), Ph_3P (7 mg, 0.025 mmol, 10 mol%), and $Pd(OAc)_2$ (4mg, 0.015 mmol, 6 mol%) in anhyd DMF (5 mL) was heated at 110°C for 2 h under N_2. The mixture was cooled, silica gel was added, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography.

7-((E)-2-((2R,3R,4S,5R,6*S*)-4,5-bis(benzyloxy)-6-methoxy-3-(naphthalen-2-ylmethoxy)tetrahydro-2H-pyran-2-yl)vinyl)-2-phenyl-4H-chromen-4-one (15a). Yield: 100 mg (70%); white solid; mp 151–153 °C; eluent: hexane–EtOAc (3:1). IR (KBr): 734, 1050, 1068, 1367, 1430, 1622, 1646, 2925, 3030, 3060 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 8.2 Hz, 1H), 7.90 (m, 2H), 7.54 (m, 7H), 7.22 (m, 15H), 6.85 (s, 1H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.20 (dd, *J* = 16.0, 6.5 Hz, 1H), 4.64 (m, 7H), 4.26 (t, *J* = 8.0 Hz, 1H), 4.07 (t, *J* = 9.2 Hz, 1H), 3.58 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.38 (m, 4H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 178.1, 163.4, 156.4, 142.4, 138.6, 138.1, 135.3, 133.1, 132.9, 131.7, 131.6, 130.9, 130.6, 129.0, 128.5, 128.1, 128.0, 127.7, 127.5, 127.1, 126.3, 126.0, 125.9, 125.8, 123.3, 123.0, 115.4, 107.6, 98.2, 81.9, 81.8, 79.9, 76.0, 75.4, 73.5, 70.8. Anal. Calcd for $C_{48}H_{42}O_7$: C, 78.88; H, 5.79. Found: C, 78.90; H, 5.80.

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