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Synthesis of Furo[3,2-*c*]benzopyrans via an Intramolecular [4 + 2] Cycloaddition Reaction of *o*-Quinonemethides

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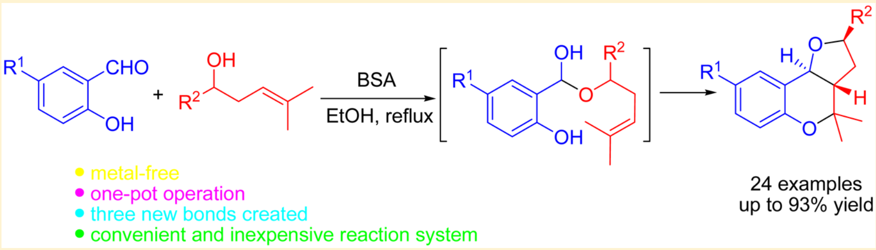
Supporting Information



ABSTRACT: An intramolecular [4 + 2] cycloaddition reaction of *o*-quinonemethides generated from salicylaldehydes and α-prenylated alcohols is described. In the presence of a catalytic amount of benzenesulfonic acid (BSA), the reaction proceeded smoothly in EtOH to afford furo[3,2-*c*]benzopyrans through a three-bond forming process in moderate to excellent yields with high diastereoselectivity. This reaction provides a simple and straightforward protocol to efficiently construct furo[3,2-*c*]benzopyran skeletons. A possible mechanism involving hemiacetal formation/hetero-Diels–Alder reaction is proposed to rationalize the observed results.

Polycyclic oxygen heterocycles are an important class of fused heterocycles found in numerous natural products and are reported to possess interesting biological activity.[1] In particular, the furan-fused heterocycle furo[3,2-*c*]benzopyran is the key structural motif of many natural products and biologically active molecules.[2] For example, pterocarpans and cordigol have this central motif of furo[3,2-*c*]benzopyran (Figure 1). The furo[3,2-*c*]benzopyran derivatives are also known for their wide range of biological activities, such as antifungal,[3] antibacterial,[3] antisnake venom,[4] anti-HIV,[5] anti-inflammatory,[6] antiosteoporotic,[7] ER antagonistic or agonistic,[8] and so forth.

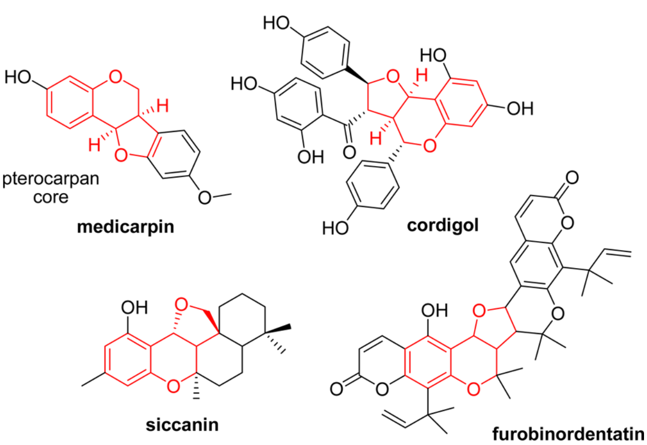


Figure 1. Representative molecules containing furo[3,2-*c*]benzopyran motifs.

The hetero-Diels–Alder (HDA) reaction is an efficient and powerful method for the construction of polycyclic oxygen heterocycles.[9] *o*-Quinonemethides as important intermediates have a special position in the synthesis of polycyclic ring systems by means of an HDA reaction. They can act as heterodiene cycloaddition partners in inter- and intramolecular Diels–Alder [4 + 2] cylcoadditions with alkenes to afford various oxygenated heterocycles.[10] However, the synthesis of fused polycyclic oxygen heterocycles utilizing [4 + 2] cycloaddition reactions of *o*-quinonemethides is mostly limited to the synthesis of pyranobenzopyrans,[11] and there are only limited cases with limited examples (that hinders diversification) reporting the synthesis of furo[3,2-*c*]benzopyrans in this manner.[11b,d] Furthermore, the reported reactions require the use of stoichiometric quantities of combined reagents (e.g., $CH(OMe)_3$/*p*-TsOH[11b] or $CH(OMe)_3/I_2$[11d]) and toxic solvents (e.g., benzene[11b]), thus increasing the cost and limiting their applications. Recently, Spivey et al. reported the synthesis of the core 2,3-*cis*-THF ring system of cordigol via oxonium-Prins cyclization.[12] However, despite its elegance, low temperature (−78 °C) and stoichiometric $SnCl_4$ (1.1 equiv) were required. In a chemical reaction, the reagent and the solvent are the major source of waste, and therefore, minimizing the use of chemical reagents and substituting a toxic solvent with a less

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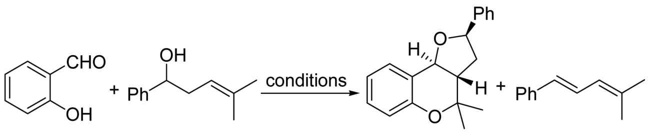
Table 1. Optimization of the Reaction Conditions[a]



entry	acid (mol %)	solvent	temp	t (h)	3a (%)[b]	dr[c]	4a (%)[b]	recovery of 1a (%)[b]	recovery of 2a (%)[b]
1	$SnCl_4$ (100)	CH_2Cl_2	r.t.	0.5	0		45	80	0
2	$In(OTf)_3$ (100)	CH_2Cl_2	r.t.	6	0		34	90	0
3	*p*-TsOH (30)	benzene	r.t.	4	30	92:8	21	30	8
4	*p*-TsOH (30)	CH_2Cl_2	reflux	4	60	ND[d]	12	10	0
5	*p*-TsOH (30)	MeOH	reflux	5	42	ND	0	21	0
6	*p*-TsOH (30)	EtOH	reflux	5	73	91:9	0	12	0
7	$C_6H_5SO_3H$ (30)	EtOH	reflux	5	87	90:10	0	trace	0
8	CF_3SO_3H (30)	EtOH	reflux	8	50	95:5	0	30	23
9	CH_3SO_3H (30)	EtOH	reflux	24	0		0	57	60
10	H_2SO_4 (10)	EtOH	reflux	24	0		36	84	0
11	CH_3COOH (100)	EtOH	reflux	24	0		0	100	100
12	$C_6H_5SO_3H$ (15)	EtOH	reflux	5	48	ND	0	37	25
13	$C_6H_5SO_3H$ (50)	EtOH	reflux	5	90	88:12	0	trace	0

[a]Reactions were carried out with **1a** (0.5 mmol), **2a** (0.5 mmol), and acid in solvent (5 mL). [b]Isolated yield. [c]The diastereomeric ratio (dr) was determined by ^{1}H NMR. [d]Not determined.

toxic solvent are the crucial points in designing environmentally improved methods toward functionalized heterocycles. Therefore, it remains a challenging, but very attractive, task to find more economical and practical methods with a broader substrate scope for the preparation of furo[3,2-*c*]benzopyran derivatives from inexpensive and simple reagents and conditions. Moreover, the development of methodology that uses simple reagents and conditions that lead to convenient procedures and better yields is highly desirable.

In the continuation of our interest on homoallylic compounds[13] and oxygen heterocycles,[14] we report herein a novel method for the synthesis of angularly fused furo[3,2-*c*]benzopyrans through an HDA reaction of salicylaldehydes with *α*-prenylated alcohols. The present method features a broad substrate scope on furo[3,2-*c*]benzopyrans synthesis, ease of manipulation, high degree of synthetic flexibility, and eliminates the requirement of complex and stoichiometric reagents as well as toxic solvents.

Optimization of the reaction conditions was performed with salicylaldehyde **1a** and 4-methyl-1-phenylpent-3-en-1-ol **2a** as model substrates, and the results are presented in Table 1. Spivey and co-workers previously reported similar cyclization using salicylaldehyde as the aldehyde component and (*E*)-4-phenylbut-3-en-1-ol as the homoallylic alcohol component in the presence of stoichiometric $SnCl_4$ in CH_2Cl_2 at −78 °C.[12] Analogous to this procedure, we initially employed equimolar amounts of **1a** and **2a** and 100 mol % of $SnCl_4$ as a catalyst in CH_2Cl_2. To avoid using harsh reaction conditions, we performed the reaction at room temperature. Disappointingly, the reaction at room temperature led to the recovery of the starting precursor salicylaldehyde **1a** and significant amounts of eliminated byproduct **4a** (Table 1, entry 1). When indium triflate, a new type of Lewis acid that differs from typical Lewis acids, such as $AlCl_3$ and $SnCl_4$, was used, a similar result was observed (entry 2). These observations suggest that the Lewis acids might not be ideal catalysts for this reaction. Thus, we attempted the reaction in the presence of Brønsted acids instead of Lewis acids. The reaction was first studied with a catalytic amount of Brønsted acid *p*-toluene sulfonic acid (*p*-TsOH) in benzene at room temperature. To our delight, our attempts to catalyze the cyclization using 30 mol % *p*-TsOH between **1a** and **2a** in the absence of any additive resulted in the desired **3a** in 30% yield, albeit with the dehydration byproduct **4a** (entry 3). It is noteworthy that trimethyl orthoformate (TMOF) was found to be vital to this kind of cycloaddition reaction when using acid or iodine as the catalyst.[11b,d,15] However, our experiment in the absence of TMOF afforded the cyclized product, suggesting that TMOF is not an essential requirement for the desired transformation. Subsequently, screening with different solvents (CH_2Cl_2, MeOH, and EtOH) using 30 mol % catalyst loading led to further improvement in the yield (entries 4−6). Ethanol was the most efficient among the tested solvents (entry 6). From the viewpoint of green chemistry, this is of relevance because ethanol is a safe and cheap solvent, whereas the majority of the solvents are organic chemicals with hazardous, toxic, and costly properties. In a quest to improve the conversion of **1a**, other Brønsted acids, such as $C_6H_5SO_3H$ (BSA), CH_3SO_3H, CF_3SO_3H, H_2SO_4, and CH_3COOH, were used in lieu of *p*-TsOH (entries 7−11). Gratifyingly, the reaction was found to not only lead to the complete conversion of starting precursor **1a** but also successfully avoided the formation of dehydration byproduct **4a** and gave **3a** in an improved yield of 87% with slightly lower diastereoselectivity when the acid *p*-TsOH was replaced by BSA (entry 7). Other acids, such as CF_3SO_3H, CH_3SO_3H, H_2SO_4, and CH_3COOH, all gave disappointing results. For example, the use of CF_3SO_3H as the catalyst led to a significant decrease in efficiency of the catalytic system with even the reaction time prolonged to 8 h (entry 8). Moreover, no desired product **3a** was observed when the reaction was conducted in the presence of CH_3SO_3H, H_2SO_4, and CH_3COOH (entries 9−11, respectively). Finally, the amount of BSA was examined, and the results showed that the reaction efficiency was obviously lower with decreased catalyst loading (entry 12). The use of higher catalyst loading did not result in significant improvement in the yield or diastereoselectivity of the reaction (entry 13). Therefore, the optimized conditions for

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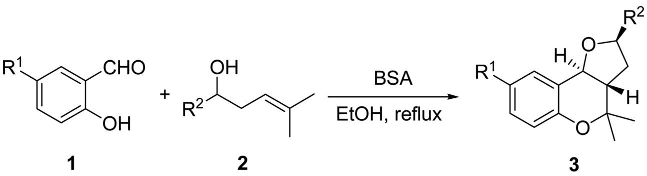
this cycloaddition reaction are as follows: 30 mol % of BSA as the acid and EtOH as the solvent at reflux.

With the optimized reaction conditions in hand, the substrate scope with respect to various kinds of substituted salicylaldehydes **1** and α-prenylated alcohols **2** was examined, and the results are summarized in Table 2. The influence of the substituents at the α-prenylated alcohol moiety was first investigated by submitting salicylaldehyde **1a** with various α-prenylated alcohols **2**. In this event, the reaction could proceed well using diverse α-prenylated alcohols **2b**–**h** with an electron-withdrawing group (F, Cl, or Br) or an electron-donating group (Me or MeO) on the phenyl ring to give the corresponding products **3b**–**h** in moderate to good yields (entries 1–7). Generally, the phenyl ring with electron-withdrawing substituents were relatively more reactive than those with electron-donating ones and thus gave relatively higher yields (entries 1–4). Lower yields are observed for substrates bearing electron-donating substituents on the phenyl ring, as observed for the reactions of **2f**–**h** (entries 5–7, respectively). Subsequently, the influence of the substituent at the salicylaldehyde on the cycloaddition reaction was also examined. Both electron-rich and -deficient salicylaldehyde participated in the reaction efficiently. For example, salicylaldehydes bearing an electron-withdrawing bromo group at the 5-position (**1b**) could react well with various α-prenylated alcohols to afford cyclized products **3i**–**q** in moderate to good yields (entries 8–16). Similarly, examples of the electron-withdrawing chloro group at the 5-position (**1c**) of salicylaldehyde led to good yields for **3r** (81%) and **3s** (76%) (entries 17 and 18, respectively). Particularly noteworthy was that 5-nitro salicylaldehyde **1d** reacted well with α-prenylated alcohols **2a** and **2f** to deliver products **3t** and **3u** in 93 and 70% yields (entries 19 and 20, respectively). This is particularly important because many reactions are incompatible with nitro substituents due to their strong electron-withdrawing characteristics. Gratifyingly, the substituent on the salicylaldehyde is not limited to electron-withdrawing substituents. The salicylaldehyde substrate bearing an electron-donating methyl group substituted at the 5-position (**1e**) proceeded smoothly to afford corresponding products **3v**–**x** in synthetically useful yields (51–67%). These outcomes from the successful formation of products **3i**–**x** thus emphasized the usefulness of this catalytic method for the synthesis of furo[3,2-*c*]benzopyran scaffold, which could easily lead to analogues of biologically active pterocarpans. Moreover, the halogen groups in the product offer useful handles for further functionalization. Besides the wide substrate scope, another impressive feature of the current reaction is its high diastereoselectivity. For instance, in most cases, salicylaldehydes **1** and α-prenylated alcohols **2** gave furo[3,2-*c*]benzopyran derivatives **3** as single diastereomers (entries 2, 4, 5, 7, 9, 11, 12, 14, 16, 17, and 19–23). In the case of **1a** and **2b** (entry 1), **1a** and **2d** (entry 3), **1a** and **2g** (entry 6), **1b** and **2a** (entry 8), **1b** and **2c** (entry 10), **1b** and **2j** (entry 13), **1b** and **2f** (entry 15), and **1c** and **2j** (entry 18), the reaction yielded mixtures of diastereomers **3b**, **3d**, **3g**, **3i**, **3k**, **3n**, **3p**, and **3s** with a ratio ranging from 78:22 to 94:6, respectively. All the products were identified through their NMR and HRMS. The structure of **3g** was further confirmed by X-ray crystallography (CCDC ref. No. 1426296; see the Supporting Information).

On the basis of these results and previous reports,[11b,16] a plausible explanation of the reaction mechanism is depicted in Scheme 1. First, hemiacetal **I** is formed in situ from aldehyde **1** and α-prenylated **2** after activation with BSA. Subsequent elimination of H_2O from **I** would generate *o*-quinonemethide **II**. Then, an intramolecular HDA reaction occurs via transition state A (TS-A) with the simultaneous formation of the C–C and C–O bonds or in a stepwise manner to provide *trans*-fused **3**. The excellent diaseteroselectivity of this reaction to yield *trans*-fused **3** can be explained on the basis of the transition state proposed in Scheme 1. Because of the nonbonded interaction between the hydrogen at 6-position of the phenyl ring and an axial hydrogen of the homoallylic moiety, cycloaddition via TS-B appears to be disfavored. Conversely, such steric interaction is absent in TS-A, and thus, it seems to be more stable than TS-B. Consequently, *trans*-**3** is predominantly formed.

In conclusion, the use of salicylaldehydes in [4 + 2] cycloaddition with α-prenylated alcohols affords rapid access to furo[3,2-*c*]benzopyrans in good yields with high diastereoselectivity. The reaction sequence involved an acetal reaction under catalytic Brønsted acid conditions followed by intramolecular Diels–Alder cyclization to create three new bonds in one process. Inexpensive BSA could be used as the catalyst, and EtOH was the best solvent. The catalytic method uses readily available substrates, avoids the use of combined reagents, toxic solvents, and drastic reaction conditions, and a variety of synthetically useful yet sensitive functional groups are well-tolerated under the reaction conditions used. Thus, this novel

Table 2. Substrate Scope[a]



entry	1	R^1	2	R^2	3	yield (%)[b]	*trans*:*cis*[c]
1	**1a**	H	**2b**	3-FC_6H_4	**3b**	89	94:6
2	**1a**	H	**2c**	4-FC_6H_4	**3c**	83	>99:1
3	**1a**	H	**2d**	4-BrC_6H_4	**3d**	79	94:6
4	**1a**	H	**2e**	2,6-$Cl_2C_6H_3$	**3e**	80	>99:1
5	**1a**	H	**2f**	2-MeC_6H_4	**3f**	73	>99:1
6	**1a**	H	**2g**	4-MeC_6H_4	**3g**	52	82:18
7	**1a**	H	**2h**	3-$MeOC_6H_4$	**3h**	44	>99:1
8	**1b**	5-Br	**2a**	Ph	**3i**	64	92:8
9	**1b**	5-Br	**2b**	3-FC_6H_4	**3j**	72	>99:1
10	**1b**	5-Br	**2c**	4-FC_6H_4	**3k**	85	78:22
11	**1b**	5-Br	**2i**	4-ClC_6H_4	**3l**	65	>99:1
12	**1b**	5-Br	**2d**	4-BrC_6H_4	**3m**	74	>99:1
13	**1b**	5-Br	**2j**	3,4-$Cl_2C_6H_3$	**3n**	68	87:13
14	**1b**	5-Br	**2e**	2,6-$Cl_2C_6H_3$	**3o**	76	>99:1
15	**1b**	5-Br	**2f**	2-MeC_6H_4	**3p**	63	90:10
16	**1b**	5-Br	**2g**	4-MeC_6H_4	**3q**	57	>99:1
17	**1c**	5-Cl	**2k**	2-BrC_6H_4	**3r**	81	>99:1
18	**1c**	5-Cl	**2j**	3,4-$Cl_2C_6H_3$	**3s**	76	85:15
19	**1d**	5-NO_2	**2a**	Ph	**3t**	93	>99:1
20	**1d**	5-NO_2	**2f**	2-MeC_6H_4	**3u**	70	>99:1
21	**1e**	5-Me	**2a**	Ph	**3v**	67	>99:1
22	**1e**	5-Me	**2d**	4-BrC_6H_4	**3w**	66	>99:1
23	**1e**	5-Me	**2l**	3-MeC_6H_4	**3x**	51	>99:1

[a]Reactions were carried out at the 0.5 mmol scale and catalyzed by 30 mol % BSA in EtOH (5 mL) at reflux for 5 h. [b]Isolated yield. [c]The ratio was determined by ^1H NMR.

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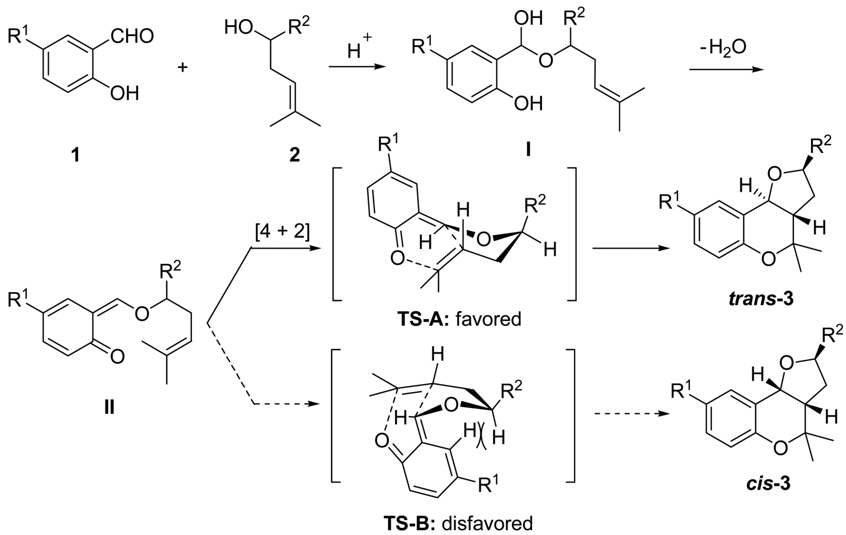
Scheme 1. Proposed Reaction Mechanism



BSA-catalyzed reaction offers good economic and environmental benefits and can be an alternative protocol for the synthesis of valuable furo[3,2-*c*]benzopyrans.

■ EXPERIMENTAL SECTION

General Methods. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz in $CDCl_3$ with chemical shift (δ) given in ppm relative to TMS as the internal standard. Multiplicities were indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), and so forth; coupling constants (J) were given in Hertz (Hz). High resolution mass spectra (HRMS) were recorded using atmospheric pressure chemical ionization (APCI) and time-of-flight (TOF) mass analysis. α-Prenylated alcohols **2** were prepared according to the procedure described previously by our group.[13a]

*General Procedure for the Synthesis of Furo[3,2-c]benzopyran **3** from Salicylaldehydes **1** and α-Prenylated Alcohols **2**.* To a round-bottom flask (25 mL) were added salicylaldehydes (0.5 mmol) and α-prenylated alcohols (0.5 mmol) in EtOH (5.0 mL), and then, benzenesulfonic acid (30 mol %) was added. The mixture was heated to reflux for 5 h. After being cooled to room temperature, the solvent was evaporated in vacuum, water was added, and it was then extracted with ethyl acetate (3 × 5.0 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 40:1) to afford corresponding product **3**.

*2-Phenyl-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]-chromene (**3a**).* White solid (122 mg, 87% yield); mp 83–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 7.6 Hz, 1H), 7.36–7.28 (m, 4H), 7.28–7.16 (m, 2H), 6.93 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 5.43 (dd, J = 9.4, 2.7 Hz, 1H), 4.69 (d, J = 11.1 Hz, 1H), 2.37–2.29 (m, 1H), 2.23–2.15 (m, 1H), 1.99–1.93 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 143.9, 128.7, 128.5, 127.4, 125.9, 124.9, 124.6, 119.9, 116.6, 81.5, 79.7, 75.7, 49.5, 36.0, 29.8, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{21}O_2$ [M + H]$^+$, 281.1542; found, 281.1545.

*2-(3-Fluorophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo-[3,2-c]chromene (**3b**).* Yellow oil (133 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 7.5 Hz, 1H), 7.29–7.25 (m, 1H), 7.22–7.17 (m, 1H), 7.07 (dd, J = 14.9, 9.8 Hz, 2H), 6.96–6.90 (m, 2H), 6.89–6.81 (m, 1H), 5.41 (dd, J = 9.5, 2.5 Hz, 1H), 4.69 (d, J = 11.2 Hz, 1H), 2.39–2.29 (m, 1H), 2.18–2.10 (m, 1H), 1.98–1.92 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 (J = 244.3 Hz), 153.1, 146.6, 130.0 (J = 8.2 Hz), 128.8, 124.8, 124.3, 121.3, 119.9, 116.6, 114.2 (J = 21.1 Hz), 112.8 (J = 22.0 Hz), 80.8, 79.6, 75.8, 49.4, 36.0, 29.7, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{20}FO_2$ [M + H]$^+$, 299.1447; found, 299.1468.

*2-(4-Fluorophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo-[3,2-c]chromene (**3c**).* White solid (124 mg, 83% yield); mp 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 3.5 Hz, 1H), 7.33–7.22 (m, 4H), 7.02 (t, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 1H), 5.39 (dd, J = 9.4, 2.7 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 2.37–2.25 (m, 1H), 2.15–2.08 (m, 1H), 1.96–1.90 (m, 1H), 1.41 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (J = 243.8 Hz), 152.2, 139.3, 131.7, 127.6 (J = 44.0 Hz), 127.5, 126.3, 118.5, 115.4 (J = 21.4 Hz), 112.1, 81.0, 80.2, 75.2, 49.43, 35.9, 29.6, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{20}FO_2$ [M + H]$^+$, 299.1447; found, 299.1464.

*2-(4-Bromophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo-[3,2-c]chromene (**3d**).* White solid (141 mg, 79% yield); mp 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.39 (m, 3H), 7.23–7.16 (m, 3H), 6.93 (t, J = 7.0 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 5.37 (dd, J = 9.5, 2.6 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 2.38–2.27 (m, 1H), 2.18–2.08 (m, 1H), 1.94–1.87 (m, 1H), 1.41 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 142.9, 131.6, 128.8, 127.6, 124.8, 124.4, 121.2, 119.9, 116.6, 80.8, 79.6, 75.8, 49.4, 36.0, 29.7, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{20}BrO_2$ [M + H]$^+$, 359.0647; found, 359.0673.

*2-(2,6-Dichlorophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3e**).* Yellow oil (139 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 3.8 Hz, 2H), 7.17 (t, J = 8.0 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 5.95 (dd, J = 9.8, 5.9 Hz, 1H), 4.58 (d, J = 11.5 Hz, 1H), 2.74–2.65 (m, 1H), 2.23–2.14 (m, 2H), 1.47 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 135.6, 134.7, 131.6, 129.7, 129.6, 127.4, 126.1, 118.4, 112.0, 80.7, 78.2, 75.7, 50.7, 31.8, 29.8, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{19}Cl_2O_2$ [M + H]$^+$, 349.0762; found, 349.0733.

*2-o-Tolyl-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]-chromene (**3f**).* White solid (107 mg, 73% yield); mp 145–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 7.5 Hz, 1H), 7.19 (t, J = 7.3 Hz, 2H), 7.06–6.97 (m, 4H), 6.79 (d, J = 8.2 Hz, 1H), 5.28 (dd, J = 10.5, 5.7 Hz, 1H), 5.18 (d, J = 7.9 Hz, 1H), 2.74–2.67 (m, 1H), 2.50–2.43 (m, 1H), 2.29 (s, 3H), 1.69 (q, J = 10.8 Hz, 1H), 1.37 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 140.7, 134.1, 130.3, 130.0, 129.1, 127.0, 126.4, 125.4, 123.0, 121.1, 117.4, 78.9, 75.9, 73.6, 47.7, 35.3, 26.8, 26.0, 19.4. HRMS (APCI): m/z calcd for $C_{20}H_{23}O_2$ [M + H]$^+$, 295.1698; found, 295.1684.

*2-p-Tolyl-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]-chromene (**3g**).* White solid (76 mg, 52% yield); mp 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 6.7 Hz, 3H), 7.12 (d, J = 8.0 Hz, 2H), 6.92 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 5.39 (dd, J = 9.3, 2.7 Hz, 1H), 4.67 (d, J = 11.0 Hz, 1H), 2.37–2.27 (m, 4H), 2.23–2.15 (m, 1H), 1.97–1.92 (m, 1H), 1.41 (s,

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3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 140.9, 137.1, 129.4, 129.2, 128.7, 125.9, 125.6, 124.9, 124.7, 119.8, 116.5, 81.5, 79.7, 75.6, 49.6, 36.0, 29.8, 22.0, 21.2. HRMS (APCI): m/z calcd for $C_{20}H_{23}O_2$ [M + H]$^+$, 295.1698; found, 295.1668.

*2-(3-Methoxyphenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3h**).* Yellow oil (68 mg, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 7.5 Hz, 1H), 7.23−7.17 (m, 2H), 6.94−6.89 (m, 3H), 6.86−6.84 (m, 1H), 6.79−6.77 (m, 1H), 5.40 (dd, J = 9.4, 2.6 Hz, 1H), 4.69 (d, J = 11.1 Hz, 1H), 3.77 (s, 3H), 2.37−2.28 (m, 1H), 2.21−2.13 (m, 1H), 1.99−1.94 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 153.1, 145.6, 129.6, 128.7, 124.9, 124.6, 119.9, 118.2, 116.5, 112.5, 111.7, 81.4, 79.7, 75.7, 55.3, 49.5, 36.0, 29.8, 22.0. HRMS (APCI): m/z calcd for $C_{20}H_{23}O_3$ [M + H]$^+$, 311.1647; found, 311.1673.

*8-Bromo-2-phenyl-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo-[3,2-c]chromene (**3i**).* Yellow oil (115 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, J = 2.5, 1.1 Hz, 1H), 7.35−7.30 (m, 4H), 7.29−7.24 (m, 2H), 6.73 (d, J = 8.7 Hz, 1H), 5.42 (dd, J = 9.5, 2.8 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 2.37−2.27 (m, 1H), 2.19−2.10 (m, 1H), 1.97 (m, 1H), 1.41 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 143.5, 131.6, 128.6, 127.6, 127.6, 126.5, 125.8, 118.4, 112.0, 81.6, 80.2, 75.2, 49.4, 35.8, 29.6, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{20}BrO_2$ [M + H]$^+$, 359.0647; found, 359.0667.

*8-Bromo-2-(3-fluorophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3j**).* Yellow oil (135 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, J = 2.5, 1.1 Hz, 1H), 7.32−7.27 (m, 2H), 7.09 (d, J = 7.7 Hz, 1H), 7.05−7.02 (m, 1H), 6.97−6.92 (m, 1H), 6.73 (d, J = 8.7 Hz, 1H), 5.40 (dd, J = 9.5, 2.6 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 2.42−2.26 (m, 1H), 2.14−2.06 (m, 1H), 1.98−1.93 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (J = 244.0 Hz), 152.2, 139.3, 131.7, 127.6, 127.5, 127.5, 126.3, 118.5, 115.5, 115.3, 112.1, 81.0, 80.2, 75.2, 49.4, 35.9, 29.6, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{19}BrFO_2$ [M + H]$^+$, 377.0552; found, 377.0536.

*8-Bromo-2-(4-fluorophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3k**).* Yellow oil (160 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 2.4 Hz, 1H), 7.31−7.26 (m, 3H), 7.02 (t, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 1H), 5.39 (dd, J = 9.4, 2.6 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 2.36−2.27 (m, 1H), 2.16−2.07 (m, 1H), 1.96−1.90 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (J = 243.9 Hz), 152.2, 139.2 (J = 31.0 Hz), 131.6, 127.6 (J = 45.0 Hz), 127.5, 126.3, 118.5, 115.4 (J = 21.3 Hz), 112.1, 81.0, 80.2, 75.2, 49.4, 35.9, 29.6, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{19}BrFO_2$ [M + H]$^+$, 377.0552; found, 377.0526.

*8-Bromo-2-(4-chlorophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3l**).* Yellow oil (127 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 2.4 Hz, 1H), 7.31−7.24 (m, 5H), 6.73 (d, J = 8.7 Hz, 1H), 5.39 (dd, J = 9.5, 2.5 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 2.36−2.28 (m, 1H), 2.13−2.04 (m, 1H), 1.97−1.88 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 142.0, 133.3, 131.7, 128.7, 127.6, 127.2, 126.3, 118.5, 112.1, 80.9, 80.1, 75.3, 49.3, 35.9, 29.6, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{19}BrClO_2$ [M + H]$^+$, 393.0257; found, 393.0275.

*8-Bromo-2-(4-bromophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3m**).* Yellow oil (161 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 1.0 Hz, 1H), 7.46−7.42 (m, 2H), 7.30−7.27 (m, 1H), 7.20−7.18 (m, 2H), 6.73 (d, J = 8.7 Hz, 1H), 5.37 (dd, J = 9.5, 2.6 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 2.37−2.27 (m, 1H), 2.13−2.02 (m, 1H), 1.96−1.87 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 142.6, 131.7, 131.6, 127.5, 127.5, 126.3, 121.4, 118.5, 112.1, 80.9, 80.1, 75.3, 49.3, 35.8, 29.6, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{19}Br_2O_2$ [M + H]$^+$, 436.9752; found, 436.9778.

*8-Bromo-2-(3,4-dichlorophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3n**).* Yellow oil (145 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, J = 2.5, 0.9 Hz, 1H), 7.42−7.37 (m, 2H), 7.29 (dd, J = 9.0, 2.8 Hz, 1H), 7.16 (dd, J = 8.2, 1.8 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 5.35 (dd, J = 9.5, 2.6 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 2.38−2.28 (m, 1H), 2.11−2.02 (m, 1H), 1.95−1.90 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 143.8, 132.7, 131.8, 131.4, 130.5, 127.8, 127.6, 125.9, 125.2, 118.6, 112.1, 80.2, 80.0, 75.4, 49.2, 35.8, 29.6, 21.9. HRMS (APCI): m/z calcd for $C_{19}H_{18}BrCl_2O_2$ [M + H]$^+$, 426.9867; found, 426.9850.

*8-Bromo-2-(2,6-dichlorophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3o**).* Yellow oil (162 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.30 (m, 2H), 7.21−7.12 (m, 2H), 6.90−6.85 (m, 2H), 5.96 (dd, J = 9.7, 6.0 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 2.78−2.70 (m, 1H), 2.31−2.13 (m, 2H), 1.49 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 135.6, 135.1, 129.6, 129.6, 128.7, 124.7, 124.3, 119.8, 116.5, 80.1, 78.2, 76.2, 51.0, 32.0, 29.9, 22.0. HRMS (APCI): m/z calcd for $C_{19}H_{18}BrCl_2O_2$ [M + H]$^+$, 426.9867; found, 426.9849.

*8-Bromo-2-o-tolyl-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo-[3,2-c]chromene (**3p**).* Yellow oil (117 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.45−7.43 (m, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.16 (s, 3H), 6.74 (d, J = 7.5 Hz, 1H), 5.58 (d, J = 9.3 Hz, 1H), 4.66 (d, J = 11.3 Hz, 1H), 2.38−2.29 (m, 4H), 2.14−2.07 (m, 1H), 1.88−1.83 (m, 1H), 1.39 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 141.7, 133.6, 131.6, 130.2, 127.7, 127.2, 126.5, 126.2, 125.2, 118.5, 112.1, 80.2, 78.8, 74.9, 49.1, 34.7, 29.6, 22.1, 19.4. HRMS (APCI): m/z calcd for $C_{20}H_{22}BrO_2$ [M + H]$^+$, 373.0803; found, 373.0775.

*8-Bromo-2-p-tolyl-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo-[3,2-c]chromene (**3q**).* Yellow oil (106 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 2.5 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 7.22−7.20 (m, 2H), 7.15−7.13 (m, 2H), 6.72 (d, J = 8.7 Hz, 1H), 5.38 (dd, J = 9.4, 2.7 Hz, 1H), 4.62 (d, J = 11.1 Hz, 1H), 2.34−2.25 (m, 4H), 2.18−2.10 (m, 1H), 1.99−1.92 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 140.6, 137.3, 131.5, 129.6, 129.3, 127.7, 126.6, 125.8, 119.5, 118.4, 112.0, 81.6, 80.2, 75.11, 49.53, 35.9, 29.7, 22.0, 21.3. HRMS (APCI): m/z calcd for $C_{20}H_{22}BrO_2$ [M + H]$^+$, 373.0803; found, 373.0778.

*8-Chloro-2-(2-bromophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3r**).* Yellow oil (158 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55−7.43 (m, 3H), 7.29 (d, J = 7.5 Hz, 1H), 7.17−7.10 (m, 2H), 6.78 (d, J = 8.7 Hz, 1H), 5.63 (dd, J = 9.5, 2.2 Hz, 1H), 4.68 (d, J = 11.0 Hz, 1H), 2.48−2.39 (m, 1H), 2.04−1.92 (m, 2H), 1.39 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 142.7, 132.6, 128.8, 128.7, 127.6, 127.6, 125.9, 124.8, 124.6, 121.1, 118.0, 80.7, 80.2, 75.3, 48.8, 35.0, 29.6, 22.1. HRMS (APCI): m/z calcd for $C_{19}H_{19}BrClO_2$ [M + H]$^+$, 393.0257; found, 393.0277.

*8-Chloro-2-(3,4-dichlorophenyl)-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3s**).* Yellow oil (145 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 3H), 7.17−7.14 (m, 2H), 6.78 (d, J = 8.7 Hz, 1H), 5.36 (dd, J = 9.5, 2.5 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 2.38−2.29 (m, 1H), 2.11−2.02 (m, 1H), 1.96−1.90 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 143.8, 132.7, 131.4, 130.5, 128.9, 127.8, 125.4, 125.2, 124.9, 124.7, 118.1, 80.2, 80.0, 75.5, 49.2, 35.8, 29.6, 21.9. HRMS (APCI): m/z calcd for $C_{19}H_{18}Cl_3O_2$ [M + H]$^+$, 383.0372; found, 383.0362.

*8-Nitro-2-phenyl-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3t**).* Yellow solid (151 mg, 93% yield); mp 82−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, J = 2.5 Hz, 1H), 8.09 (dd, J = 9.1, 2.8 Hz, 1H), 7.24−7.16 (m, 3H), 7.02−7.01 (m, 2H), 6.87 (d, J = 9.1 Hz, 1H), 5.23 (d, J = 8.0 Hz, 1H), 5.12 (dd, J = 10.7, 5.7 Hz, 1H), 2.82−2.75 (m, 1H), 2.49−2.42 (m, 1H), 1.80 (q, J = 12.0 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 141.9, 141.8, 128.5, 127.7, 126.9, 125.8, 125.0, 123.8, 118.2, 82.4, 77.9, 72.8, 47.1, 36.4, 27.0, 26.0. HRMS (APCI): m/z calcd for $C_{19}H_{20}NO_4$ [M + H]$^+$, 326.1392; found, 326.1418.

*8-Nitro-2-o-tolyl-4,4-dimethyl-**3**,**3a**,4,**9b**-tetrahydro-2H-furo[3,2-c]chromene (**3u**).* Yellow solid (118 mg, 70% yield); mp 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 2.7 Hz, 1H), 8.09 (dd, J = 9.1, 2.8 Hz, 1H), 7.11−6.97 (m, 4H), 6.87 (d, J = 9.1 Hz, 1H), 5.31 (dd, J = 10.6, 5.6 Hz, 1H), 5.21 (d, J = 8.0 Hz, 1H), 2.82−2.76 (m, 1H), 2.54−2.46 (m, 1H), 2.29 (s, 3H), 1.64 (q, J = 11.1 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 141.9, 139.8, 134.2, 130.2, 127.3, 126.9, 126.5, 125.1, 124.9, 123.7, 118.2, 79.3, 77.9, 72.5, 47.2, 34.8, 26.7, 26.1, 19.4. HRMS (APCI): m/z calcd for $C_{20}H_{22}NO_4$ [M + H]$^+$, 340.1549; found, 340.1577.

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*2-Phenyl-4,4,8-trimethyl-**3,3a,4,9b**-tetrahydro-2H-furo[3,2-c]chromene (**3v**).* Yellow oil (98 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.34 (m, 3H), 7.31−7.26 (m, 1H), 6.86 (dd, J = 8.1, 1.9 Hz, 1H), 6.74 (s, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.13 (s, 1H), 4.47 (dd, J = 8.3, 4.7 Hz, 1H), 3.45−3.28 (m, 2H), 2.64−2.58 (m, 1H), 2.37−2.32 (m, 1H), 2.24 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9, 142.7, 138.3, 130.0, 128.8, 128.6, 127.8, 126.7, 126.3, 122.7, 120.4, 115.8, 81.0, 78.8, 64.4, 40.5, 26.0, 25.9, 20.7, 15.45. HRMS (APCI): m/z calcd for $C_{20}H_{23}O_2$ $[M + H]^+$, 295.1698; found, 295.1681.

*2-(4-Bromophenyl)-4,4,8-trimethyl-**3,3a,4,9b**-tetrahydro-2H-furo[3,2-c]chromene (**3w**).* Yellow solid (123 mg, 66% yield); mp 58−60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.4 Hz, 3H), 7.00 (dd, J = 8.3, 2.2 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 5.36 (dd, J = 9.5, 2.7 Hz, 1H), 4.65 (d, J = 11.1 Hz, 1H), 2.33−2.27 (m, 4H), 2.17−2.09 (m, 1H), 1.92−1.87 (m, 1H), 1.39 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 142.9, 131.6, 129.4, 129.2, 127.7, 125.2, 123.9, 121.3, 116.4, 80.9, 79.3, 75.9, 49.6, 36.0, 29.7, 21.8, 20.7. HRMS (APCI): m/z calcd for $C_{20}H_{22}BrO_2$ $[M + H]^+$, 373.0803; found, 373.0776.

*2-m-Tolyl-4,4,8-trimethyl-**3,3a,4,9b**-tetrahydro-2H-furo[3,2-c]chromene (**3x**).* Yellow oil (79 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 1.8 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.02−6.97 (m, 2H), 6.86 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 6.70 (d, J = 8.3 Hz, 1H), 5.14 (d, J = 7.9 Hz, 1H), 5.02 (dd, J = 10.5, 5.9 Hz, 1H), 2.71−2.60 (m, 1H), 2.43−2.35 (m, 1H), 2.30 (s, 3H), 2.20 (s, 3H), 1.83 (q, J = 11.1 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 142.6, 137.9, 130.5, 130.2, 129.8, 128.2, 128.2, 127.1, 123.3, 122.7, 117.0, 82.3, 75.6, 74.0, 47.8, 36.9, 27.0, 25.8, 21.5, 20.7. HRMS (APCI): m/z calcd for $C_{21}H_{25}O_2$ $[M + H]^+$, 309.1855; found, 309.1885.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01641.

Copies of ^{1}H and ^{13}C NMR spectra for all prepared products and X-ray crystal structure of **3g** (PDF)
Crystal data of **3g** in CIF format(CIF)

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Notes

The authors declare no competing financial interest.

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