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Three-step synthesis of substituted isochromenes

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ABSTRACT

A synthetic route toward isochromenes **6**, starting with aldehydes **3**, in good to excellent yield is described herein. This novel approach was carried out by the Henry reaction of **3** with NH_4OAc and nitroalkanes ($MeNO_2$ or $EtNO_2$), aerobic Wacker-type oxidation of the resulting nitroalkenes **4**, followed by K_2CO_3-promoted intramolecular Michael cyclization in modest to good yields.

1. Introduction

Isochromenes are significant classes of heterocyclic compounds, owing to some natural products and bioactive compound structures containing meaningful moiety.[1] For example, pyranonapthoquinone exhibits pharmaceutical activity: the carboxamides analog, BCH-2051 (**1**), acts an anticancer agent in its ability to fight cancer cell line SKOV3 and methyl 1,5,8-trimethoxy-1*H*-isochromene-3-carboxylate (**2**) displays a moderate antitumor function.[2] It is noteworthy that, the ubiquitous core skeleton, oxygen-/nitrogen-containing hetero-cycles, has appeared in pharmaceutically important compounds and has also drawn a lot of attention (see Fig. 1).[3]

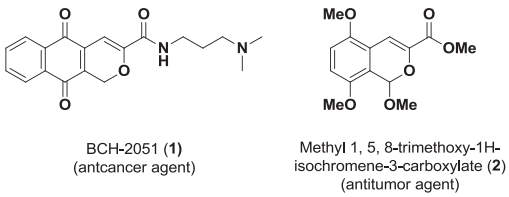

Fig. 1. Bioactive isochromene derivatives.

Many excellent organic chemists are committed to the development of efficient and facile ways to synthesize isochromene and its derivatives.[4] For example, many procedures for the synthetic isochromene, cyclization reaction have been applied using the metal-catalyzed method.[4a–d] Transition metal-catalyzed cyclization has also been a ubiquitous method, such as the representative Pd(II) Heck reaction,[5] cycloisomerization of Au(I)[3b,4e,4k] or Pd(II)[4f] catalyzed, Os-catalyzed,[6] Ru(II)-catalyzed,[7] complex with a tetradentate N–P mixed ligand,[8] Ir pincer complexes-catalyzed,[9] or Rh(III)-catalyzed oxidative coupling.[10]

Nitromethyl isochromenes have also drawn attention recently. In 2011, copper(II)-catalyzed Henry reaction and gold(I)-mediated cycloisomerization were utilized by Gong's group to produce nitromethyl isochromenes.[4e] Kundu and co-workers developed a domino reaction to obtain the desired isochromenes.[4i]

2. Results and discussions

Recently, we have become interested in the development of new synthetic routes for the construction of a benzofused bicyclic system derived from the versatile 2-allylbenzaldehyde **3** including benzazepines and 2-naphthols, as shown in Scheme 1.[11] The starting skeleton **3** was easily provided by commercially available isovanillin in moderate overall three-step yields with a reaction sequence of O-allylation and a Claisen rearrangement followed by O-alkylation. In 2012, we studied the treatment of **3** via Henry reaction, reduction and oxidative cleavage annulation providing tetrahydro-3-benzazepine analogs.[12a] Furthermore, we examined the treatment of **3** by Wacker-type oxidation and intramolecular aldol cyclization which afforded 2-naphthols derivatives in 2013.[12b]

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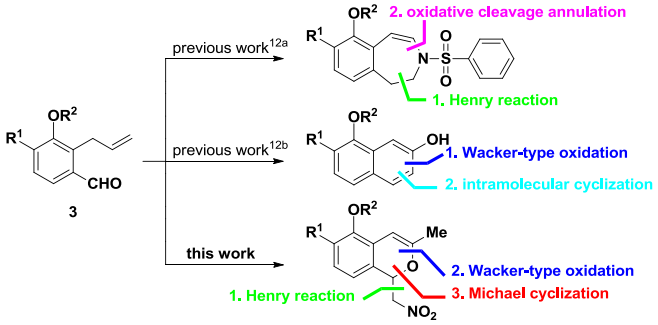
0040-4020/

Following the experience of our previous work,[12] we aim to develop a facile synthetic route for isochromene based on skeleton **3** by the above synthetic routes (Henry reaction, Wacker-type oxidation and Michael cyclization).



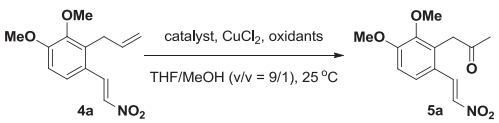
Scheme 1. Synthetic applications of **3**.

Initially, **3a** (R^1=OMe, R^2=Me) was selected as the model substrate to conduct the Henry reaction to afford **4a** and then, to explore the oxidation conditions. Wacker-type oxidation was also employed to promote the allyl group into methylketone **5a**. In this case, there may be a nitrovinyl group besides the allyl group that enhances the difficulty of the oxidation on the allyl group. Hence, we wanted to examine the catalytic oxidation condition. Some Pd(II) catalysts were tried, such as, $PdCl_2$, $Pd(OAc)_2$, $PdBr_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$, as shown in Table 1. As a result, Wacker-type oxidation in this case was not easy under our previous conditions.[12b] So, **4a** was chosen as the model substrate to try other conditions, such as catalysts, equivalents of $CuCl_2$ and oxidants. When the catalyst ($PdCl_2$) and some oxidants (DDQ or CAN) were selected, only 20% and 18% (entries 1–2) and some unknown products were obtained. When the reaction was conducted under air or O_2, the desired **5a** was isolated in 62–87%, and trace amounts of unknown products were isolated under different equivalents of $PdCl_2$ and $CuCl_2$ (entries 3–6). When the equivalents of $CuCl_2$ and $PdCl_2$ were reduced, **5a** was isolated in 72% and **4a** was also recovered in 5% (entry 7). Besides $PdCl_2$ being tested, some other Pd(II) catalysts, including $Pd(OAc)_2$, $PdBr_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$ were tested under an O_2 environment, and the yields were between 70 and 84% (entries 8–12). We have learned that this oxidation step, $PdCl_2$ (6.5%), $CuCl_2$ (1.5 equiv) in an oxygen environment is the best condition for this process.

As far as we know, the Michael addition displayed a very common reaction for cyclization.[13] Considering the characteristics of skeleton **5**, a cyclization reaction may be the required task. Furthermore, cyclization of **5** was our goal. In 2012, Fu and co-workers published a report on K_2CO_3-catalyzed cyclization to synthesize chromones and 4-quinolones.[14] Moreover, the base-promoted Michael cyclization was adopted first in this step. **5a** was employed as the model substrate to test the conditions with different bases such as K_2CO_3, Cs_2CO_3, Na_2CO_3, $NaHCO_3$ and Et_3N, following this protocol. K_2CO_3 was first tested with the equivalent of 3.5 in acetone at room temperature, showing only a 65% isolated yield and 15% of the starting material was recovered (entry 1). Increasing the reaction temperature to 56 °C, the yield of product **6a** was upgraded to 68% (entry 2). In entry 3, the solvent was changed to THF and the yield reached 72% at room temperature. This phenomenon can be attributed to the fact that solvent was an important factor, therefore, THF was more suitable than acetone. When the equivalent of K_2CO_3 was increased to 4.7, the yield was better than 6.2 in 66 °C reaching 87% (entries 4 and 5). On the basis of these conditions, M_2CO_3 (M=Cs, Na) was examined, perhaps the metal radius of Cs was greater than K, causing the yields of the desired product was not excellent and an unknown product was isolated (entries 6 and 7). Intriguingly, changing the smaller radius of metal like Na_2CO_3, the reaction took a longer time with no good yields (entry 8). $NaHCO_3$ and Et_3N were also not suitable for this strategy, they not only required a long time but also unknown products appeared (entries 9 and 10). Overviewing the scope of the various bases in THF by different equivalents, we learned that the K_2CO_3 was the best one in this base-mediated strategy (see Table 2).

We next explored the scope and generality of the Henry reaction, Wacker-type oxidation and K_2CO_3-mediated cyclization with the optimized reaction conditions in hand. As shown in Table 3, various substituents (methyl, butyl, cyclopentyl, benzyl or isopropyl) on the R^1 position of **4a**–**j** were obtained in moderate yields (78–85%) via the Henry reaction. The R^1 position of **5a**–**e** was a methoxy group, **5f**–**j** was a hydrogen atom, and all of their isolated yields were between 79 and 87%. Base-mediated cyclization was conducted smoothly, and the desired products were all in good to excellent performance. Entries 1–5, R^1 was an OMe group, R^2 bearing methyl, butyl, cyclopentyl, benzyl and isopropyl groups,

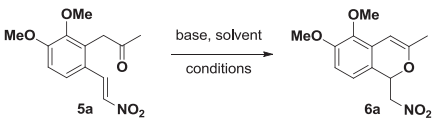
Table 1
Reaction conditions of **4a**[a]



Entry	catalyst (mol %), $CuCl_2$ (equiv), oxidants (equiv)	Yield (%)[b]
1	$PdCl_2$ (5.1), $CuCl_2$ (1.5), DDQ (1.0)	20[c]
2	$PdCl_2$ (5.1), $CuCl_2$ (1.5), CAN (1.0)	18[c]
3	$PdCl_2$ (5.1), $CuCl_2$ (1.5), air	62[d]
4	$PdCl_2$ (5.1), $CuCl_2$ (1.5), O_2	78[d]
5	$PdCl_2$ (6.5), $CuCl_2$ (1.5), O_2	87[d]
6	$PdCl_2$ (8.2), $CuCl_2$ (1.5), O_2	80[d]
7	$PdCl_2$ (4.3), $CuCl_2$ (1.5), O_2	72[e]
8	$Pd(OAc)_2$ (6.5), $CuCl_2$ (1.5), O_2	76[d]
9	$PdBr_2$ (6.5), $CuCl_2$ (1.5), O_2	70[d]
10	$PdCl_2(MeCN)_2$ (6.5), $CuCl_2$ (1.5), O_2	71[d]
11	$PdCl_2(PPh_3)_2$ (6.5), $CuCl_2$ (1.5), O_2	83[d]
12	$Pd_2(dba)_3$ (6.5), $CuCl_2$ (1.5), O_2	84[d]

[a] The reactions were conducted on a 1.0 mmol scale with **4a**.
[b] **5a** was >95% pure as determined by ^1H NMR analysis.
[c] Unknown products were obtained (entry1, 5%, entry 2, 6%).
[d] Trace amounts (<5%) of unknown products were obtained.
[e] **4a** was recovered by 15%.

Table 2
Base-mediated cyclization of **5a**[a]



Entry	Base (equiv), solvents, time (h), temp (°C)	Yield (%)[b]
1	K_2CO_3 (3.5), acetone, 2, 25	65[c,d]
2	K_2CO_3 (3.5), acetone, 2, 56	68[c]
3	K_2CO_3 (3.5), THF, 2, 25	72[c,d]
4	K_2CO_3 (4.7), THF, 2, 66	87[c]
5	K_2CO_3 (6.2), THF, 2, 66	80[c]
6	Cs_2CO_3 (3.5), THF, 3, 66	25[e]
7	Cs_2CO_3 (4.7), THF, 2, 66	20[e]
8	Na_2CO_3 (4.7), THF, 30, 66	53[d]
9	$NaHCO_3$ (4.7), THF, 70, 66	25
10	Et_3N (4.7), THF, 4, 66	25

[a] The reactions were conducted on a 1.0 mmol scale with **5a**.
[b] **6a** was >95% pure as determined by ^1H NMR analysis.
[c] Trace amounts (<5%) of unknown products were obtained.
[d] **5a** was recovered (entry 1, 15%; entry 3, 10%).
[e] Unknown products were obtained (entry 6, 5%; entry 7, 4%).

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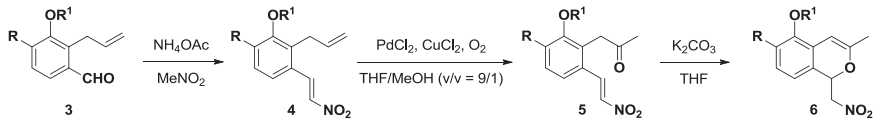
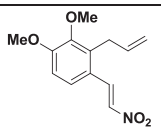
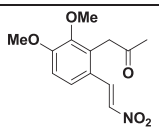
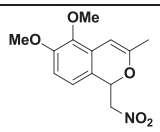
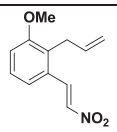
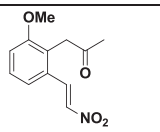
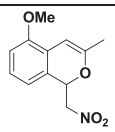
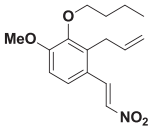
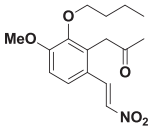
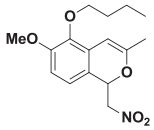
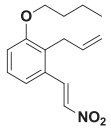
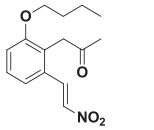
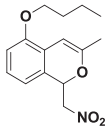
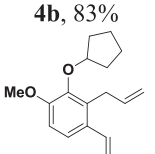
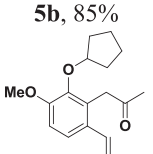
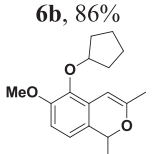
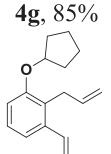
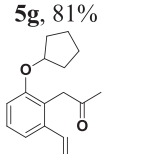
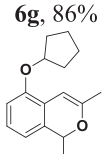
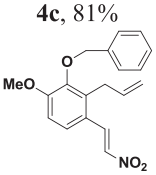
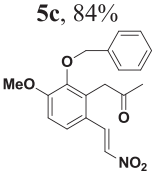
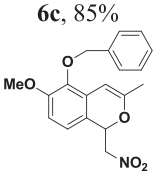
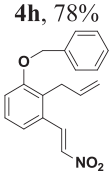
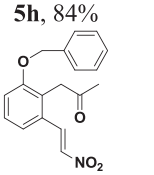
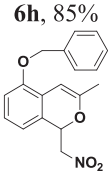
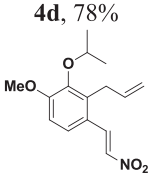
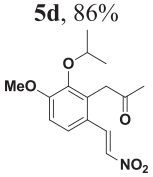
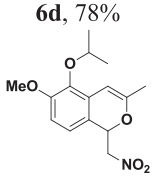
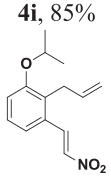
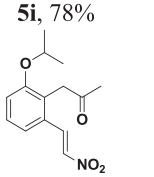
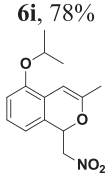
Table 3
Three-step synthesis of substituted isochromenes **6**[a,b]



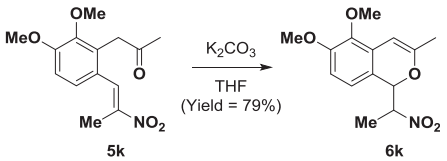
entry	compound **4**	compound **5**	compound **6**	entry	compound **4**	compound **5**	compound **6**
1	 **4a**, 85%	 **5a**, 87%	 **6a**, 88%	6	 **4f**, 84%	 **5f**, 82%	 **6f**, 88%
2	 **4b**, 83%	 **5b**, 85%	 **6b**, 86%	7	 **4g**, 85%	 **5g**, 81%	 **6g**, 86%
3	 **4c**, 81%	 **5c**, 84%	 **6c**, 85%	8	 **4h**, 78%	 **5h**, 84%	 **6h**, 85%
4	 **4d**, 78%	 **5d**, 86%	 **6d**, 78%	9	 **4i**, 85%	 **5i**, 78%	 **6i**, 78%
5	 **4e**, 82%	 **5e**, 82%	 **6e**, 81%	10	 **4j**, 83%	 **5j**, 83%	 **6j**, 81%

[a] The optimal reaction conditions: (i) Henry reaction: **3a-j** (3.0 mmol), NH_4OAc (234 mg, 3.0 mmol), $MeNO_2$ (10 mL), 100 °C, 6h. (ii) Wacker-type oxidation: **4a-j** (1.0 mmol), $PdCl_2$ (12 mg, 6.5 mol %), $CuCl_2$ (200 mg, 1.5 mmol), O_2 (bubbled), THF/MeOH (v/v = 9:1, 20 mL), 25 °C, 12 h. (iii) Michael cyclization: **5a-j** (1.0 mmol), K_2CO_3 (650 mg, 4.7 mmol), THF (15 mL), 66 °C, 3 h.

[b] **4a-j**, **5a-j** and **6a-j** were >95% pure as determined by ^1H NMR analysis.

and 82–87% of **6a**–**e** was isolated. As far as we know, the methoxy group was an electron-donating group, the electron effect brought about the cyclization conformation. Fortunately, changing the group of R_1 from OMe to H, allowed the cyclization to be conducted smoothly and the isolated yields of **6f**–**j** ranged from 75 to 79%. For the formation of **6a**, we believed that a possible pathway could be K_2CO_3-mediated abstraction of benzylic proton of **5a** to form a more conjugated enolate intermediate followed by intramolecular Michael-type cyclization of the resulting stable enolate that protonation afforded **6a** smoothly.

As expected, altering the solvent of the Henry reaction from nitromethane to nitroethane, followed by Wacker oxidation resulted in the desired product **5k** being isolated in an excellent yield (88%) and the single-crystal X-ray structure was shown in (Fig. 2).[15] The K_2CO_3-promoted step was also applied to this configuration forming isochromene derivative **6k** (Scheme 2).



Scheme 2. Synthesis of **6k**.

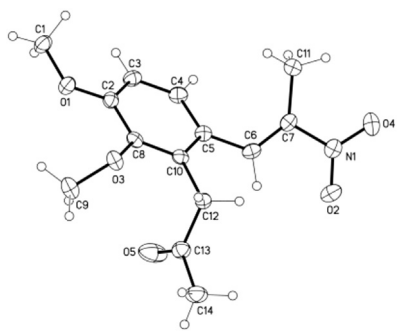
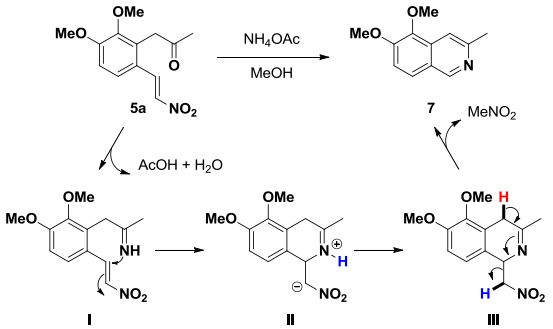


Fig. 2. X-ray structure of **5k**.

The isoquinoline nucleus is an important skeleton because many natural products contain the scaffold exhibiting many biological activities.[16] Therefore, many efficient synthetic ways for substituted isoquinolines were developed.[17] Intriguingly, when NH_4OAc was the additive as a base conducted with **5a** in methanol, the isoquinoline derivative was obtained in good isolated yield (86%). We guessed that the mechanism of isoquinoline **7** was that amine condensed with ketone first to get **I**. In the basic condition, amine attacked the double bond to form **II**. Through the electron exchange, **III** was formed producing compound **7** in a 78% yield (Scheme 3).



Scheme 3. The possible mechanism.

3. Conclusion

In summary, a facile and efficient way to synthesize isochromene derivatives was found. Through the Wacker-type oxidation reaction, we obtained ketones **5a**–**j**. K_2CO_3 promoted the cyclization of ketones **5a**–**j** to obtain compound **6a**–**j** smoothly. Interesting, when the base was changed to NH_4OAc, the desired product was not increased; however we acquired the isoquinoline analogs. The characteristic of the framework of **5** include the ability to produce substituted isochromenes or isoquinolines with a change of bases.

4. Experimental section

4.1. General

All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. Melting points were determined with a SMP3 melting apparatus. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 and at 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Buker microTOF-Q. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

4.2. A representative synthetic procedure of skeleton 4 is as follows

Ammonium acetate (NH_4OAc, 234 mg, 3.0 mmol) was added to a solution of skeleton **3** (3.0 mmol) in nitromethane (for **4a**–**j**, $MeNO_2$, 10 mL) or nitroethane (for **4k**, $EtNO_2$, 10 mL) at 25 °C. The reaction mixture was stirred at reflux for 6 h. The reaction mixture was cooled to 25 °C. Saturated $NaHCO_3$ (5 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc=10/1–6/1) afforded skeleton **4**.

*4.2.1. (E)-2-Allyl-3,4-dimethoxy-1-(2-nitrovinyl)benzene (**4a**).*[11] Yield=85% (635 mg); Yellowish oil; HRMS (ESI, M^++H) calcd for $C_{13}H_{16}NO_4$ 250.1079, found 250.1080; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J=13.2 Hz, 1H), 7.45 (d, J=13.2 Hz, 1H), 7.35 (d, J=8.8 Hz, 1H), 6.86 (d, J=8.8 Hz, 1H), 6.01–5.91 (m, 1H), 5.07 (dq, J=1.6, 10.4 Hz, 1H), 4.90 (dq, J=1.6, 17.2 Hz, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.61 (dt, J=1.6, 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.75, 147.68, 136.92, 136.16 (2×), 135.09, 123.97, 122.34, 116.27, 110.76, 60.99, 55.79, 30.12.

*4.2.2. (E)-2-Allyl-3-butoxy-4-methoxy-1-(2-nitrovinyl)benzene (**4b**).* Yield=83% (725 mg); Colorless solid; mp=51–52 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{16}H_{21}NO_4Na$ 314.1368, found 314.1363; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J=13.2 Hz, 1H), 7.44 (d, J=13.6 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H), 6.84 (d, J=8.8 Hz, 1H), 5.99–5.89 (m, 1H), 5.05 (dq, J=1.6, 10.0 Hz, 1H), 4.90 (dq, J=1.6, 17.2 Hz, 1H), 3.91 (t, J=6.4 Hz, 2H), 3.89 (s, 3H), 3.60 (dt, J=1.6, 5.6 Hz, 2H), 1.78–1.71 (m, 2H), 1.52–1.47 (m, 2H), 0.97 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.84, 146.91, 137.02, 136.22, 135.96, 135.07, 123.71, 122.24, 116.11, 110.64, 73.19, 55.68, 32.22, 30.14, 19.06, 13.79.

*4.2.3. (E)-2-Allyl-3-(cyclopentyloxy)-4-methoxy-1-(2-nitrovinyl) benzene (**4c**).* Yield=81% (737 mg); Colorless gum; HRMS (ESI, M^++Na) calcd for $C_{17}H_{21}NO_4Na$ 326.1368, found 326.1364; ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J=13.6 Hz, 1H), 7.45 (d, J=13.2 Hz, 1H), 7.31 (d, J=8.8 Hz, 1H), 6.84 (d, J=8.8 Hz, 1H), 5.97–5.87 (m, 1H), 5.07 (dq, J=2.0, 10.4 Hz, 1H), 4.91 (dq, J=2.0, 17.2 Hz, 1H), 4.85–4.82 (m, 1H), 3.90 (s, 3H), 3.61 (dt, J=2.0, 5.6 Hz, 2H), 1.89–1.77 (m, 4H), 1.76–1.67 (m, 2H), 1.64–1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.71, 145.81, 137.45, 136.13, 135.98, 135.32, 123.26, 122.51, 116.30, 110.69, 84.90, 55.74, 32.81 (2×), 30.45, 23.62 (2×).

*4.2.4. (E)-2-Allyl-3-(benzyloxy)-4-methoxy-1-(2-nitrovinyl)benzene (**4d**).* Yield=78% (814 mg); Colorless solid; mp=73–74 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{19}H_{19}NO_4Na$ 348.1212, found 348.1209; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J=13.2 Hz, 1H), 7.47 (d, J=13.2 Hz, 2H), 7.48–7.40 (m, 5H), 6.91 (d, J=8.8 Hz, 1H), 5.96–5.86 (m, 1H), 5.08 (dq, J=2.0, 10.4 Hz, 1H), 5.00 (s, 2H), 4.90 (dq, J=2.0, 17.2 Hz, 1H), 3.95 (s, 3H), 3.60 (dt, J=1.6, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.78, 146.38, 137.23, 136.92, 136.10, 136.08, 135.29, 128.36 (2×), 128.04 (2×), 128.02, 124.07, 122.33, 116.23, 110.75, 74.93, 55.77, 30.26.

*4.2.5. (E)-2-Allyl-3-isopropoxy-4-methoxy-1-(2-nitrovinyl)benzene (**4e**).* Yield=82% (738 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{15}H_{19}NO_4Na$ 300.1212, found 300.1207; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J=13.6 Hz, 1H), 7.44 (d, J=13.6 Hz, 1H), 7.31 (d, J=8.4 Hz, 1H), 6.60 (d, J=8.8 Hz, 1H), 5.95–5.85 (m, 1H), 5.05 (dq, J=2.0, 10.0 Hz, 1H), 4.90 (dq, J=2.0, 17.2 Hz, 1H), 4.54–4.48 (m, 1H), 3.88 (s, 3H), 3.63 (dt, J=2.0, 5.6 Hz, 2H), 1.26 (d, J=6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.81, 145.32, 137.35, 136.10, 135.79, 135.31, 123.30, 122.32, 116.18, 110.47, 74.89, 55.61, 30.43, 22.44 (2×).

*4.2.6. (E)-2-Allyl-1-methoxy-3-(2-nitrovinyl)benzene (**4f**).*[11] Yield=84% (552 mg); colorless solid; mp=55–70 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++H) calcd for $C_{12}H_{14}NO_3$ 220.0974, found 220.0977; ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J=13.6 Hz, 1H), 7.48 (d, J=13.6 Hz, 1H), 7.26 (t, J=7.6 Hz, 1H), 7.13 (d, J=7.6 Hz, 1H), 7.00 (d, J=7.6 Hz, 1H), 5.98–5.88

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(m, 1H), 5.03 (dq, *J*=1.6, 10.0 Hz, 1H), 4.91 (dq, *J*=1.6, 16.8 Hz, 1H), 3.85 (s, 3H), 3.58 (dt, *J*=1.6, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.91, 138.26, 136.95, 135.75, 130.33, 129.41, 127.80, 119.27, 115.66, 113.47, 55.84, 29.83.

*4.2.7. (E)-2-Allyl-1-butoxy-3-(2-nitrovinyl)benzene (**4g**).* Yield=85% (666 mg); Colorless solid; mp=40–41 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{15}H_{19}NO_3Na$ 284.1263, found 284.1259; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J*=13.6 Hz, 1H), 7.48 (d, *J*=13.6 Hz, 1H), 7.23 (t, *J*=8.4 Hz, 1H), 7.11 (d, *J*=8.4 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 5.96–5.87 (m, 1H), 5.03 (dq, *J*=1.6, 10.0 Hz, 1H), 4.94 (dq, *J*=1.6, 16.8 Hz, 1H), 3.99 (t, *J*=6.4 Hz, 2H), 3.59 (dt, *J*=1.6, 6.0 Hz, 2H), 1.83–1.76 (m, 2H), 1.56–1.48 (m, 2H), 0.98 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.39, 138.17, 137.08, 135.83, 130.23, 129.62, 127.72, 119.03, 115.64, 114.30, 68.19, 31.28, 30.03, 19.30, 13.79.

*4.2.8. (E)-2-Allyl-1-(cyclopentyloxy)-3-(2-nitrovinyl)benzene (**4h**).* Yield=78% (639 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{16}H_{19}NO_3Na$ 296.1263, found 296.1260; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J*=13.6 Hz, 1H), 7.47 (d, *J*=13.6 Hz, 1H), 7.21 (t, *J*=8.4 Hz, 1H), 7.08 (d, *J*=8.4 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 5.94–5.84 (m, 1H), 5.01 (dq, *J*=1.6, 10.0 Hz, 1H), 4.93 (dq, *J*=1.6, 17.2 Hz, 1H), 4.82–4.78 (m, 1H), 3.54 (dt, *J*=1.6, 5.6 Hz, 2H), 1.82–1.74 (m, 4H), 1.69–1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.25, 138.10, 137.19, 135.86, 130.31, 130.15, 127.53, 118.74, 115.55, 115.49, 79.61, 32.78 (2×), 30.19, 23.94 (2×).

*4.2.9. (E)-2-Allyl-1-(benzyloxy)-3-(2-nitrovinyl)benzene (**4i**).* Yield=85% (636 mg); Colorless solid; mp=84–85 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{18}H_{17}NO_3Na$ 318.1106, found 318.1103; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J*=13.6 Hz, 1H), 7.49 (d, *J*=13.2 Hz, 1H), 7.45–7.32 (m, 5H), 7.24 (t, *J*=8.0 Hz, 1H), 7.15 (d, *J*=8.0 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 6.01–5.91 (m, 1H), 5.12 (s, 2H), 5.06 (dq, *J*=1.6, 10.0 Hz, 1H), 4.94 (dq, *J*=1.6, 17.2 Hz, 1H), 3.65 (dt, *J*=1.6, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.95, 138.30, 136.92, 136.64, 135.70, 130.48, 129.81, 128.60 (2×), 128.01, 127.77, 127.09 (2×), 119.59, 115.84, 114.90, 70.41, 30.09.

*4.2.10. (E)-2-Allyl-1-isopropoxy-3-(2-nitrovinyl)benzene (**4j**).* Yield=83% (540 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{14}H_{17}NO_3Na$ 270.1106, found 270.1102; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J*=13.6 Hz, 1H), 7.47 (d, *J*=13.2 Hz, 1H), 7.22 (t, *J*=8.0 Hz, 1H), 7.09 (d, *J*=8.0 Hz, 1H), 6.99 (d, *J*=8.0 Hz, 1H), 5.95–5.85 (m, 1H), 5.02 (dq, *J*=1.6, 10.4 Hz, 1H), 4.94 (dq, *J*=2.0, 17.6 Hz, 1H), 4.60–4.54 (m, 1H), 3.57 (dt, *J*=1.6, 6.0 Hz, 2H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.22, 138.09, 137.21 (2×), 135.89, 130.49, 127.60, 119.04, 115.99, 115.64, 70.56, 30.15, 22.03 (2×).

*4.2.11. (E)-2-Allyl-3,4-dimethoxy-1-(2-nitroprop-1-en-1-yl)benzene (**4k**).*[11] Yield=86% (226 mg); Yellowish oil; HRMS (ESI, M^++H) calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1238; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.02 (d, *J*=8.4 Hz, 1H), 6.86 (d, *J*=8.8 Hz, 1H), 5.93–5.84 (m, 1H), 5.02 (dq, *J*=1.6, 10.0 Hz, 1H), 4.90 (dq, *J*=1.6, 17.2 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.47 (dt, *J*=1.6, 6.0 Hz, 2H), 2.32 (d, *J*=0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.86, 147.47, 135.77 (2×), 133.88, 132.48, 125.29, 125.01, 115.76, 110.13, 60.95, 55.71, 31.09, 13.91.

4.3. A representative synthetic procedure of skeleton 5 is as follows

$PdCl_2$ (13 mg, 6.5 mol %) and $CuCl_2$ (200 mg, 1.5 mmol) were added to a solution of skeleton **4** (1.0 mmol) in co-solvent of THF and methanol (20 mL, *v*/*v*=9:1) at 25 °C. Then oxygen was bubbled into the mixture for 3 h, and stirred at 25 °C for 10 h. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc=10/1–6/1) afforded skeleton **5**.

*4.3.1. (E)-1-(2,3-Dimethoxy-6-(2-nitrovinyl)phenyl)propan-2-one (**5a**).* Yield=87% (231 mg); Colorless solid; mp=103–104 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++H) calcd for $C_{13}H_{15}NO_5Na$ 288.0848, found 288.0840; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J*=13.6 Hz, 1H), 7.43 (d, *J*=13.6 Hz, 1H), 7.35 (d, *J*=8.4 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 3.96 (s, 2H), 3.91 (s, 3H), 3.78 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.97, 155.40, 147.63, 136.58, 136.21, 130.43, 123.86, 122.47, 111.58, 60.59, 55.78, 41.17, 29.84.

*4.3.2. (E)-1-(2-Butoxy-3-methoxy-6-(2-nitrovinyl)phenyl)propan-2-one (**5b**).* Yield=85% (261 mg); Colorless solid; mp=87–88 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{16}H_{21}NO_5Na$ 330.1317, found 330.1313; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J*=13.2 Hz, 1H), 7.43 (d, *J*=13.2 Hz, 1H), 7.34 (d, *J*=8.8 Hz, 1H), 6.89 (d, *J*=8.8 Hz, 1H), 3.98 (s, 2H), 3.92 (t, *J*=6.8 Hz, 2H), 3.90 (s, 3H), 2.27 (s, 3H), 1.75–1.68 (m, 2H), 1.50–1.44 (m, 2H), 0.97 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.90, 155.52, 147.05, 136.56, 136.38, 130.43, 123.67, 122.57, 111.54, 73.01, 55.78, 41.40, 32.28, 29.79, 19.12, 13.82.

*4.3.3. (E)-1-(2-(Cyclopentyloxy)-3-methoxy-6-(2-nitrovinyl)phenyl) propan-2-one (**5c**).* Yield=84% (268 mg); Colorless solid; mp=100–101 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{17}H_{21}NO_5Na$ 342.1317, found 342.1314; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J*=13.2 Hz, 1H), 7.44 (d, *J*=13.2 Hz, 1H), 7.33 (d, *J*=8.8 Hz, 1H), 6.89 (d, *J*=8.8 Hz, 1H), 4.90–4.88 (m, 1H), 3.98 (s, 2H), 3.90 (s, 3H), 2.24 (s, 3H), 1.80–1.74 (m, 4H), 1.73–1.71 (m, 2H), 1.70–1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.89, 155.30, 145.84, 136.64, 136.51, 130.58, 123.21, 122.76, 111.53, 84.85, 55.78, 41.74, 32.82 (2×), 29.71, 23.63 (2×).

*4.3.4. (E)-1-(2-(Benzyloxy)-3-methoxy-6-(2-nitrovinyl)phenyl) propan-2-one (**5d**).* Yield=86% (293 mg); Colorless solid; mp=118–119 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{19}H_{19}NO_5Na$ 364.1161, found 364.1157; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J*=13.2 Hz, 1H), 7.44 (d, *J*=13.2 Hz, 1H), 7.40–7.33 (m, 6H), 6.95 (d, *J*=8.8 Hz, 1H), 4.98 (s, 2H), 3.96 (s, 3H), 3.87 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.86, 155.42, 146.71, 137.14, 136.66, 136.34, 130.75, 128.55 (2×), 128.24, 128.19 (2×), 123.97, 122.66, 111.60, 75.04, 55.89, 41.46, 29.79.

*4.3.5. (E)-1-(2-Isopropoxy-3-methoxy-6-(2-nitrovinyl)phenyl) propan-2-one (**5e**).* Yield=82% (240 mg); Colorless solid; mp=69–70 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{15}H_{19}NO_5Na$ 316.1161, found 316.1158; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J*=13.6 Hz, 1H), 7.44 (d, *J*=13.6 Hz, 1H), 7.33 (d, *J*=8.8 Hz, 1H), 6.88 (d, *J*=8.8 Hz, 1H), 4.58–4.52 (m, 1H), 4.00 (s, 2H), 3.89 (s, 3H), 2.24 (s, 3H), 1.23 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.93, 155.46, 145.47, 136.68, 136.43, 130.77, 123.30, 122.72, 111.34, 74.98, 55.72, 41.75, 29.77, 22.47 (2×).

*4.3.6. (E)-1-(2-Methoxy-6-(2-nitrovinyl)phenyl)propan-2-one (**5f**).* Yield=82% (193 mg); Colorless solid; mp=95–96 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{12}H_{13}NO_4Na$ 258.0742, found 258.0736; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J*=13.6 Hz, 1H), 7.46 (d, 13.6 Hz, 1H), 7.30 (t, *J*=8.0 Hz, 1H), 7.14 (d, *J*=8.0 Hz, 1H), 7.00 (d, *J*=8.0 Hz, 1H), 3.92 (s, 2H), 3.83 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.12,

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157.79, 138.72, 136.36, 130.78, 128.62, 124.87, 119.40, 113.20, 55.77, 40.80, 29.80.

*4.3.7. (E)-1-(2-Butoxy-6-(2-nitrovinyl)phenyl)propan-2-one (**5g**).* Yield=81% (224 mg); Colorless solid; mp=81–82 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{15}H_{19}NO_4Na$ 300.1212, found 300.1208; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J*=13.6 Hz, 1H), 7.49 (d, *J*=13.6 Hz, 1H), 7.27 (t, *J*=8.0 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 6.97 (d, *J*=8.0 Hz, 1H), 3.97 (t, *J*=6.4 Hz, 2H), 3.91 (s, 2H), 2.23 (s, 3H), 1.80–1.73 (m, 2H), 1.52–1.43 (m, 2H), 0.97 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.15, 157.20, 138.59, 136.43, 130.69, 128.51, 124.94, 119.08, 113.89, 68.10, 40.83, 31.09, 29.74, 19.16, 13.68.

*4.3.8. (E)-1-(2-(Cyclopentyloxy)-6-(2-nitrovinyl)phenyl)propan-2-one (**5h**).* Yield=84% (243 mg); Colorless solid; mp=91–92 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{16}H_{19}NO_4Na$ 312.1212, found 312.1209; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J*=13.6 Hz, 1H), 7.45 (d, *J*=13.6 Hz, 1H), 7.25 (t, *J*=8.0 Hz, 1H), 7.10 (d, *J*=8.0 Hz, 1H), 6.97 (d, *J*=8.0 Hz, 1H), 4.81–4.77 (m, 1H), 3.86 (s, 2H), 2.22 (s, 3H), 1.95–1.80 (m, 4H), 1.79–1.70 (m, 2H), 1.69–1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.21, 156.14, 138.55, 136.55, 130.81, 128.35, 125.45, 118.81, 115.01, 79.74, 41.02, 32.70 (2×), 29.73, 23.90 (2×).

*4.3.9. (E)-1-(2-(Benzyloxy)-6-(2-nitrovinyl)phenyl)propan-2-one (**5i**).* Yield=78% (243 mg); Colorless solid; mp=86–87 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{18}H_{17}NO_4Na$ 334.1055, found 334.1051; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J*=13.2 Hz, 1H), 7.46 (d, *J*=13.2 Hz, 1H), 7.43–7.34 (m, 5H), 7.29 (t, *J*=8.0 Hz, 1H), 7.16 (d, *J*=8.0 Hz, 1H), 7.06 (d, *J*=8.0 Hz, 1H), 5.07 (s, 2H), 3.96 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.09, 156.89, 138.71, 136.29, 136.14, 130.87, 128.59 (2×), 128.54, 128.15, 127.35 (2×), 125.26, 119.59, 114.44, 70.53, 40.89, 29.93.

*4.3.10. (E)-1-(2-Isopropoxy-6-(2-nitrovinyl)phenyl)propan-2-one (**5j**).* Yield=83% (218 mg); Colorless solid; mp=67–68 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{14}H_{17}NO_4Na$ 286.1055, found 286.1051; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J*=13.2 Hz, 1H), 7.47 (d, *J*=13.2 Hz, 1H), 7.28 (t, *J*=8.4 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 1H), 4.62–4.56 (m, 1H), 3.89 (s, 2H), 2.25 (s, 3H), 1.33 (d, *J*=6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.31, 156.12, 138.69, 136.65, 131.08, 128.49, 125.81, 119.07, 115.16, 70.54, 41.12, 29.93, 22.01, 21.94.

*4.3.11. (E)-1-(2,3-Dimethoxy-6-(2-nitroprop-1-en-1-yl)phenyl) propan-2-one (**5k**).* Yield=88% (246 mg); Colorless solid; mp=67–68 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++Na) calcd for $C_{14}H_{17}NO_5Na$ 302.1004, found 302.1000; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 6.99 (d, *J*=8.4 Hz, 1H), 6.89 (d, *J*=8.4 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 2H), 3.77 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.02, 153.43, 148.23, 147.48, 131.67 (2×), 129.22, 125.01 (2×), 60.48, 55.63, 41.92, 29.78, 13.72. Single-crystal X-ray diagram: crystal of **5k** was grown by slow diffusion of EtOAc into a solution of **5k** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/c, *a*=12.9058(14) Å, *b*=13.0754(14) Å, *c*=8.2832(9) Å, *V*=1379.5(3) Å^3, *Z*=4, d_{calcd}=1.345 g/cm^3, *F*(000)=592, 2θ range 1.60–26.40°, *R* indices (all data) *R*1=0.0653, w*R*2=0.1116.

4.4. A representative synthetic procedure of skeleton 6 is as follows

Potassium carbonate (K_2CO_3, 276 mg, 2.0 mmol) was added to a solution of skeleton **5** (1.0 mmol) in THF (10 mL) at 25 °C. The reaction mixture was stirred at reflux for 3 h. The reaction mixture was cooled to 25 °C. Water (5 mL) was added to the reaction mixture and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc=10/1–6/1) afforded skeleton **6**.

*4.4.1. 5,6-Dimethoxy-3-methyl-1-(nitromethyl)-1H-isochromene (**6a**).* Yield=88% (253 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{13}H_{15}NO_5Na$ 288.0848, found 288.0845; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, *J*=8.4 Hz, 1H), 6.71 (d, *J*=8.4 Hz, 1H), 6.00 (s, 1H), 5.84 (dd, *J*=3.6, 10.4 Hz, 1H), 4.84 (dd, *J*=10.4, 12.0 Hz, 1H), 4.24 (dd, *J*=3.6, 12.0 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.27, 151.82, 142.35, 124.76, 120.16, 109.85, 95.56, 76.74, 74.17, 62.16, 60.91, 55.78, 19.91.

*4.4.2. 5-Butoxy-6-methoxy-3-methyl-1-(nitromethyl)-1H-isochromene (**6b**).* Yield=86% (264 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{16}H_{21}NO_5Na$ 330.1317, found 330.1314; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (d, *J*=8.0 Hz, 1H), 6.70 (d, *J*=8.0 Hz, 1H), 5.99 (s, 1H), 5.84 (dd, *J*=3.2, 10.4 Hz, 1H), 4.84 (dd, *J*=10.4, 11.6 Hz, 1H), 4.24 (dd, *J*=3.6, 11.6 Hz, 1H), 3.96–3.88 (m, 2H), 3.83 (s, 3H), 1.95 (s, 3H), 1.79–1.72 (m, 2H), 1.56–1.46 (m, 2H), 0.98 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.39, 151.58, 141.71, 124.95, 119.90, 117.71, 109.92, 95.86, 76.78, 74.23, 73.29, 55.83, 32.28, 19.97, 19.17, 13.88.

*4.4.3. 5-(Cyclopentyloxy)-6-methoxy-3-methyl-1-(nitromethyl)-1H-isochromene (**6c**).* Yield=85% (271 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{17}H_{21}NO_5Na$ 342.1317, found 342.1313; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, *J*=8.0 Hz, 1H), 6.70 (d, *J*=8.0 Hz, 1H), 5.96 (s, 1H), 5.84 (dd, *J*=3.6, 10.4 Hz, 1H), 4.83 (dd, *J*=10.4, 11.6 Hz, 1H), 4.83–4.81 (m, 1H), 4.24 (dd, *J*=3.6, 11.6 Hz, 1H), 3.83 (s, 3H), 1.95 (s, 3H), 1.88–1.81 (m, 4H), 1.74–1.68 (m, 2H), 1.66–1.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.40, 151.27, 140.54, 125.57, 119.60, 117.74, 109.99, 96.29, 84.72, 76.77, 74.29, 55.81, 32.83, 32.68, 23.67, 23.63, 20.00.

*4.4.4. 5-(Benzyloxy)-6-methoxy-3-methyl-1-(nitromethyl)-1H-isochromene (**6d**).* Yield=78% (266 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{19}H_{19}NO_5Na$ 364.1161, found 364.1157; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.45 (m, 2H), 7.40–7.33 (m, 3H), 6.79 (d, *J*=8.4 Hz, 1H), 6.73 (d, *J*=8.4 Hz, 1H), 5.90 (s, 1H), 5.83 (dd, *J*=3.2, 10.4 Hz, 1H), 5.01 (d, *J*=11.2, 1H), 4.95 (d, *J*=11.2 Hz, 1H), 4.80 (dd, *J*=10.4, 12.0 Hz, 1H), 4.22 (dd, *J*=3.2, 12.0 Hz, 1H), 3.86 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.39, 151.67, 141.12, 137.43, 128.36, 128.30 (2×), 128.07, 125.23, 120.28, 117.68, 109.86, 95.89, 76.67 (2×), 75.08, 74.18, 55.86, 19.88.

*4.4.5. 5-Isopropoxy-6-methoxy-3-methyl-1-(nitromethyl)-1H-isochromene (**6e**).* Yield=81% (237 mg); Colorless gum; HRMS (ESI, M^++Na) calcd for $C_{15}H_{19}NO_5Na$ 316.1161, found 316.1157; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (d, *J*=8.4 Hz, 1H), 6.70 (d, *J*=8.4 Hz, 1H), 6.00 (br s, 1H), 5.83 (dd, *J*=3.6, 10.4 Hz, 1H), 4.83 (dd, *J*=10.4, 12.0 Hz, 1H), 4.41 (m, 1H), 4.24 (dd, *J*=3.6, 12.0 Hz, 1H), 3.82 (s, 3H), 1.95 (s, 3H), 1.29 (d, *J*=6.4 Hz, 3H), 1.27 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.54, 151.27, 140.39, 125.65, 119.69, 117.71, 109.81, 96.47, 76.77, 75.26, 74.26, 55.77, 22.56, 22.50, 19.96.

*4.4.6. 5-Methoxy-3-methyl-1-(nitromethyl)-1H-isochromene (**6f**).* Yield=78% (201 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{12}H_{13}NO_4Na$ 258.0742, found 258.0734; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (dd, *J*=7.6, 8.0 Hz, 1H), 6.81 (d, *J*=8.0 Hz, 1H), 6.68 (d, *J*=7.6 Hz, 1H), 6.03–6.02 (m, 1H), 5.89 (dd, *J*=3.2, 10.4 Hz, 1H), 4.89 (dd, *J*=10.4, 11.6 Hz, 1H), 4.27 (dd, *J*=3.2, 11.6 Hz, 1H), 3.84 (s, 3H),

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1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.87, 150.83, 127.15, 125.26, 119.94, 116.67, 110.96, 95.42, 76.33, 74.42, 55.53, 19.83.

*4.4.7. 5-Butoxy-3-methyl-1-(nitromethyl)-1H-isochromene (**6g**).* Yield=76% (228 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{15}H_{19}NO_4Na$ 300.1212, found 300.1204; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (dd, *J*=7.6, 8.4 Hz, 1H), 6.79 (d, *J*=8.4 Hz, 1H), 6.66 (d, *J*=7.6 Hz, 1H), 6.04 (s, 1H), 5.88 (dd, *J*=3.6, 10.4 Hz, 1H), 4.89 (dd, *J*=10.4, 12.0 Hz, 1H), 4.26 (dd, *J*=3.6, 12.0 Hz, 1H), 3.97 (t, *J*=6.4 Hz, 2H), 1.95 (s, 3H), 1.84–1.77 (m, 2H), 1.57–1.47 (m, 2H), 1.00 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.41, 150.64, 127.10, 125.27, 120.04, 116.44, 111.88, 95.55, 76.39, 74.45, 68.00, 31.30, 19.84, 19.30, 13.85.

*4.4.8. 5-(Cyclopentyloxy)-3-methyl-1-(nitromethyl)-1H-isochromene (**6h**).* Yield=75% (234 mg); Colorless gum; HRMS (ESI, M^++Na) calcd for $C_{16}H_{19}NO_4Na$ 312.1212, found 312.1207; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (t, *J*=8.0 Hz, 1H), 6.80 (d, *J*=8.0 Hz, 1H), 6.64 (d, *J*=8.0 Hz, 1H), 5.99 (s, 1H), 5.87 (dd, *J*=3.2, 10.4 Hz, 1H), 4.88 (dd, *J*=10.4, 12.0 Hz, 1H), 4.78–4.74 (m, 1H), 4.26 (dd, *J*=3.2, 12.0 Hz, 1H), 1.95 (s, 3H), 1.90–1.74 (m, 4H), 1.69–1.59 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.38, 150.48, 126.95, 120.53, 116.19, 113.26, 112.71, 95.73, 79.65, 76.93, 74.47, 32.88, 32.86, 24.06, 24.04, 19.85.

*4.4.9. 5-(Benzyloxy)-3-methyl-1-(nitromethyl)-1H-isochromene (**6i**).* Yield=75% (251 mg); Colorless gum; HRMS (ESI, M^++Na) calcd for $C_{18}H_{17}NO_4Na$ 334.1055, found 334.1052; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.35 (m, 5H), 7.11 (t, *J*=8.0 Hz, 1H), 6.87 (d, *J*=8.0 Hz, 1H), 6.69 (d, *J*=8.0 Hz, 1H), 6.09 (s, 1H), 5.90 (dd, *J*=3.6, 10.4 Hz, 1H), 5.08 (s, 2H), 4.90 (dd, *J*=10.4, 12.0 Hz, 1H), 4.27 (dd, *J*=3.6, 12.0 Hz, 1H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.05, 150.91, 136.77, 128.62 (2×), 128.04, 127.34 (2×), 127.10, 125.42, 120.37, 116.98, 112.44, 95.58, 74.43, 70.28, 29.69, 19.85.

*4.4.10. 5-Isopropoxy-3-methyl-1-(nitromethyl)-1H-isochromene (**6j**).* Yield=79% (226 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{14}H_{17}NO_4Na$ 286.1055, found 286.1049; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (dd, *J*=7.6, 8.4 Hz, 1H), 6.81 (d, *J*=8.4 Hz, 1H), 6.65 (d, *J*=7.6 Hz, 1H), 6.03 (br s, 1H), 5.87 (dd, *J*=3.6, 10.4 Hz, 1H), 4.88 (dd, *J*=10.4, 12.0 Hz, 1H), 4.56–4.50 (m, 1H), 4.26 (dd, *J*=3.6, 12.0 Hz, 1H), 1.95 (s, 3H), 1.36 (d, *J*=6.0 Hz, 3H), 1.34 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.26, 150.28, 126.99, 125.26, 121.03, 116.49, 113.77, 95.81, 76.42, 74.47, 70.60, 22.12, 22.06, 19.85.

*4.4.11. 5,6-Dimethoxy-3-methyl-1-(1-nitroethyl)-1H-isochromene (**6k**).* Four isomers; Yield=79% (221 mg); Colorless oil; HRMS (ESI, M^++Na) calcd for $C_{14}H_{17}NO_5Na$ 302.1004, found 302.0997; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, *J*=8.4 Hz, 1H), 6.71 (d, *J*=8.4 Hz, 1H), 5.99 (s, 1H), 5.32 (d, *J*=9.6 Hz, 1H), 4.92–4.94 (m, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 1.92 (s, 3H), 1.33 (d, *J*=6.8 Hz, 3H).

4.5. 5,6-Dimethoxy-3-methylisoquinoline (7)

Ammonium acetate (NH_4OAc, 115 mg, 1.5 mmol) was added to a solution of skeleton **5** (1.0 mmol) in MeOH (10 mL) at 25 °C. The reaction mixture was stirred at reflux for 4 h. The reaction mixture was cooled to 25 °C. The reaction mixture was concentrated, diluted with water (10 mL), and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc=10/1–6/1) afforded compound **7**. Yield=78% (158 mg); Colorless solid; mp=83–84 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++H) calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1017; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H), 7.67 (d, *J*=9.2 Hz, 1H), 7.66 (s, 1H), 7.27 (d, *J*=9.2 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.51, 151.45, 151.43, 140.88, 132.35, 124.36, 123.01, 114.64, 111.95, 61.03, 56.44, 24.31.

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Supplementary data

Supplementary data related to this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.12.021.

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