

## Reaction of *o*-(oxiranylmethyl)benzotriles with sodium borohydride or Grignard reagent/CuI: a new synthesis of substituted 3-alkyl-3,4-dihydroisocoumarins

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**Abstract.** A new method for the synthesis of substituted 3-alkyl-3,4-dihydroisocoumarins is described. *o*-(Oxiranylmethyl)benzotriles, prepared from isovanillin in five steps, when reacted with nucleophiles such as sodium borohydride or phenylmagnesium chloride/CuI, undergo an intramolecular cyclization to yield the target compounds in good yields, in one pot.

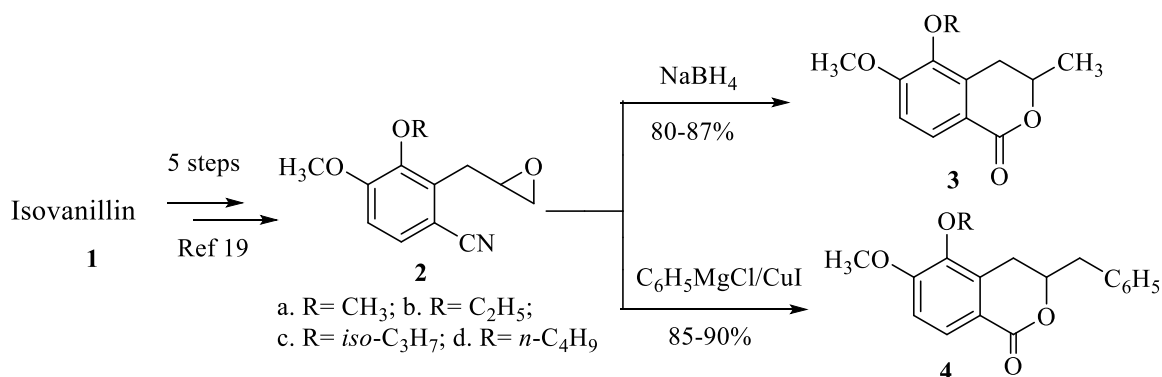
**Keywords:** Isovanillin, oxiranes, benzotriles, intramolecular cyclization, 3,4-dihydroisocoumarins

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### Introduction

3,4-Dihydroisocoumarins (DHIC), otherwise named 3,4-dihydroisochromen-1-ones, are abundantly distributed in a wide range of natural sources. For examples, DHIC isolated from *Kigelia pinnata*,<sup>1</sup> *Hydrangea macrophylla*,<sup>2</sup> Cape aloe,<sup>3</sup> *Montrouziera sphaeroidea*,<sup>4</sup> *Aloe hildebrandtii*,<sup>5</sup> *Cassia siamea*,<sup>6</sup> *Caryocar glabrum*,<sup>7</sup> as well as others have been reported. Furthermore, certain DHIC from natural sources have broadly biological activities. DHIC such as isolated from *Xyris pterygoblephara* exhibiting antifungi activity,<sup>8</sup> from *Aloe vera* exhibiting binding activity with human serum albumin,<sup>9</sup> from *Fusarium verticillioides* exhibiting antimalarial, antitubercular and antifungal activities,<sup>10</sup> as well as others. On the other hand, DHIC also play an important core structure for many biologically active compounds. For instance, AI-77-B, a naturally-occurring DHIC which chemically belongs to the amicoumacin family, was isolated from different *Bacillus* genera exhibiting an antiulcerogenic activity without common side effects.<sup>11</sup> Because of diverse biological activities, a number of synthetic strategies for DHIC have been developed. The major methods reported include the use of the Heck-

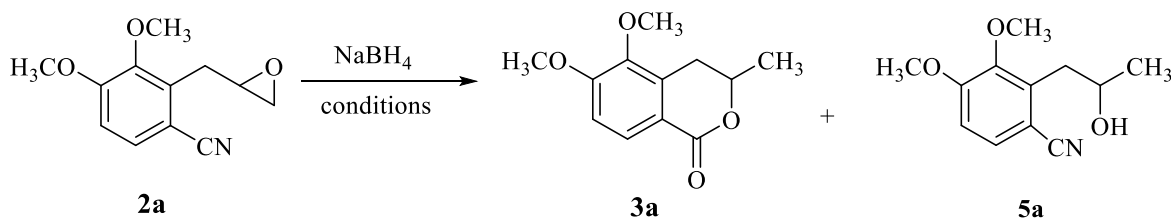
Matsuda reaction,<sup>12</sup> radical cyclization mediated by titanocene(III) chloride,<sup>13</sup> cyclization of  $\alpha$ -lithiated 2-toluenecarboxylates,<sup>14</sup> coupling of vinylic halides or triflates with *o*-(1-alkenyl)-benzoic acids,<sup>15</sup> the successive lateral and *ortho*-lithiations of 4,4-dimethyl-2-(*o*-toyl)oxazoline,<sup>16</sup> as well as others. However, those reported methods have some disadvantages including tedious reaction conditions, inaccessible starting materials or reagents, and low yields. Therefore, the development of a mild and efficient method for DHIC is requisite and of interest. On the other hand, the ring-opening of epoxides by various nucleophiles to yield diverse organic compounds has been well documented in organic synthesis.<sup>17</sup> The addition of various nucleophiles to cyano groups has also been well described.<sup>18</sup> However, studies on the addition of various nucleophiles to aryl compounds with an adjacent epoxy and cyano substituents has seldom been examined. In our previous study, we reported the reaction of *o*-(oxiranylmethyl)benzonitrile intermediates with TBAB/NaCN to yield various substituted 3,4-dihydroisoquinolin-1-ones.<sup>19</sup> Continuing our work on benzoheterocycles,<sup>20</sup> we herein report the synthesis of substituted 3-alkyl-3,4-dihydroisocoumarins from the reaction of *o*-(oxiranylmethyl)benzonitriles with nucleophiles such as sodium borohydride and Grignard reagent in the presence of copper iodide (Scheme 1).



**Scheme 1.** Synthesis of 3-alkyl-3,4-dihydroisocoumarins from *o*-(oxiranylmethyl)benzonitriles with NaBH<sub>4</sub> and C<sub>6</sub>H<sub>5</sub>MgCl/CuI nucleophiles.

## Results and Discussion

In order to optimize the reaction conditions, compound **2a** used as a model reaction was allowed to react with NaBH<sub>4</sub> under various conditions. The given results showed that 5,6-dimethoxy-3-methyl-dihydroisochroman (**3a**) together with 1-(2,3-dimethoxy-6-cyanophenyl)-2-propanol (**5a**) were formed in varying ratios. Compound **3a** was produced through a domino sequence, involving ring-opening of the epoxide, followed by the intramolecular cyclization of the forming alkoxide anion with the cyano functional group, and then hydrolysis. Compound **5a** was formed by simple ring opening of the epoxide by NaBH<sub>4</sub>. The results of this model reaction are compiled in Table 1.

**Table 1.** The reaction of compound **2a** with NaBH<sub>4</sub> under various conditions to yield **3a** and **5a**

Entry	Equiv. NaBH <sub>4</sub>	Solvent	Temp	Time (hr)	<b>3a</b> (%) <sup>a</sup>	<b>5a</b> (%) <sup>a</sup>
1	1	EtOH	rt	24	53	45
2	1	EtOH	reflux	1	59	33 <sup>20a</sup>
3	1.5	EtOH	reflux	1	62	38
4 <sup>b</sup>	1.5	EtOH	reflux	1	67	33
5	1.5	MeOH	reflux	1	11	40
6 <sup>b</sup>	1.5	MeOH	reflux	1	18	42
7 <sup>b</sup>	3.0	EtOH	reflux	1	80	-

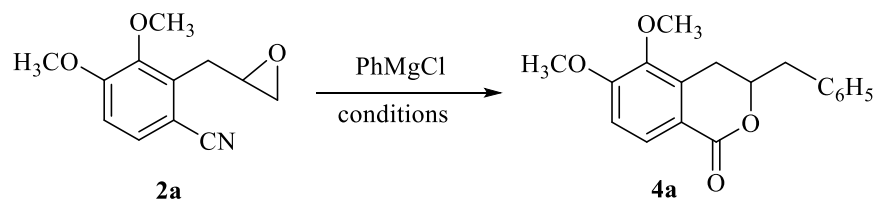
<sup>a</sup> Determined by isolated yields; <sup>b</sup> Anhydrous solvent was used.

Based on the results reported in Table 1, we concluded that ethanol (entries 1-4) is a better solvent than methanol (entries 5-6) and anhydrous ethanol (entries 4, 7) is the best solvent for the reaction. Three equivalents of NaBH<sub>4</sub> (entry 7) is better than 1 or 1.5 equivalents of NaBH<sub>4</sub> (entries 1-6), and heating under reflux is better than reaction at room temperature for the production of **3**. Thus, the use of excess NaBH<sub>4</sub> (3.0 equiv.) in refluxing ethanol (entry 7) gives a high yield (80%) of **3a** from **2a**. Based on these conditions, *o*-(oxiranylmethyl)benzonitriles **2a-d** gave the target compounds **3a-d** in high yields (80-87%), in the one pot procedure.

All spectral data, such as IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, EI-MS, and HRMS or EA, are consistent with the 3-methyl-3,4-dihydroisocoumarin structures (**3a-d**). The IR spectrum of compound **3a**, for example, showed absorption at 1707 cm<sup>-1</sup> (C=O) and the <sup>1</sup>H-NMR spectrum exhibited a doublet signal of methyl group bonded to C-3 (*J* 6.2 Hz at  $\delta$  1.46); two double doublet signals at  $\delta$  2.66 and 3.13 which respectively have coupling constants *J* 16.8, 11.4 and 16.8, 3.2 Hz assigned to H-4a and H-4b; two singlet methoxy signals at  $\delta$  3.78 and 3.89; a one proton signal at  $\delta$  4.59 coupled to neighboring protons assigned as H-3; and two aromatic protons at  $\delta$  6.88, and 7.82 with the same coupling constant *J* 8.4 Hz indicating their *ortho* relationship. In the <sup>13</sup>C-NMR twelve lines are observed consistent with that required for the structure. The HRMS (*m/z* 222.0887) and EA (C, 65.01; H, 6.41) are consistent with the structure. To increase the diversity, *o*-(oxiranylmethyl)benzonitriles (**2a-d**) were allowed to react with Grignard reagent

phenylmagnesium chloride/CuI. At the start of this study, **2a** was reacted with phenylmagnesium chloride under various conditions to yield the desired 3-benzyl-5,6-dimethoxydihydroisochroman **4a** and the results are shown in Table 2.

**Table 2.** The reaction of compound **2a** with C<sub>6</sub>H<sub>5</sub>MgBr under various conditions to yield **4a**



Entry	Nu <sup>-</sup>	Additive	Temp	Time (hr)	<b>4a</b> (%)
1	C <sub>6</sub> H <sub>5</sub> MgCl (1.2 equiv)	-	0°- r.t.	24	16
2	C <sub>6</sub> H <sub>5</sub> MgCl (1.2 equiv)	CuI (0.25 equiv)	0°-r.t.	24	47
3	C <sub>6</sub> H <sub>5</sub> MgCl (1.2 equiv)	CuI (0.50 equiv)	0°- r.t.	24	64
4	C <sub>6</sub> H <sub>5</sub> MgCl (1.2 equiv)	CuI (1.0 equiv)	0°- r.t.	24	66
5	C <sub>6</sub> H <sub>5</sub> MgCl (1.2 equiv)	CuI (1.0 equiv)	reflux	16	11
6	C <sub>6</sub> H <sub>5</sub> MgCl (2.4 equiv)	CuI (0.5 equiv)	reflux	24	86

<sup>a</sup>Isolated yield from column chromatography, other by products being neglected.

As shown in Table 2, in the absence of CuI, **4a** was formed in the low yield (16%) (entry 1) with the exception of entry 5 (11%) which was carried out for a shorter reaction time. This suggests the importance of CuI. A lower amount of Grignard reagent C<sub>6</sub>H<sub>5</sub>MgCl (entries 1-5) gave **4a** in low to modest yields (11-66%). On the other hand the reaction of **2a** with excess C<sub>6</sub>H<sub>5</sub>MgCl (2.4 equiv)/CuI (0.5 equiv) in refluxing THF (entry 6) for 24 hr provided the highest yield for **4a** (86%). These conditions were employed for the synthesis of 3-benzyl-3,4-dihydroisocoumarins **4a-d** from *o*-(oxiranylmethyl)benzonitriles **2a-d**, in yields of 85-90%.

The spectral data including IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, EI-MS, and HRMS or EA are all consistent with those required for the proposed 5-alkoxy-3-benzyl-6-methoxy-3,4-dihydroisocoumarin structures **4a-d**. The IR spectrum of compound **4a**, for example, shows absorption at 1717 cm<sup>-1</sup> (C=O) indicating the presence of carbonyl group. The <sup>1</sup>H-NMR spectrum exhibits two double doublet signals at δ 2.75 (dd, *J* 16.4, 11.2 Hz, 1H) and δ 3.11 (dd, *J* 16.4, 3.2 Hz, 1H) indicating the presence of H4-a and H4-b; other two double doublet signals at δ 3.04 (dd, *J* 14.0, 6.8 Hz, 1H, Ha-9) and δ 3.21 (dd, *J* 14.0, 6.0 Hz, 1H, Hb-9) indicating the presence of H-9a and H-9b (two benzylic protons), two three-protons singlet signals, each at δ 3.77, 3.93 indicating two OCH<sub>3</sub> groups, and one proton multiplet at δ 4.69 indicating H-3; two one-proton doublet aromatic protons at δ 6.91 and 7.88 with *ortho*-coupling constant *J* 8.4 Hz indicating the presence of H-7 and H-8 and one multiple signals of five protons at δ 7.30

indicating the presence of aromatic protons of benzyl group. In the  $^{13}\text{C}$ -NMR spectrum of compound **4a** shows sixteen lines which is consistent with carbon numbers required for the structure **4a**. Besides, the data of HRMS ( $m/z$  298.1204) and elemental analysis (C, 72.19; H, 6.03), all data are correct and consistent with the data required for compound **4a**.

## Conclusions

We have successfully prepared diverse 3-substituted 3,4-dihydroisocoumarins from the reaction of *o*-(oxiranylmethyl)benzonnitriles with nucleophiles ( $\text{NaBH}_4$  or Grignard reagent/ $\text{CuI}$ ). This reaction demonstrates that epoxide ring of *o*-(oxiranylmethyl)benzonnitrile opened by nucleophile to give alkoxide anion which attacks the neighboring nitrile to effect the intramolecular cyclization, and this is followed by hydrolysis to yield a series of substituted 3-alkyl-3,4-dihydroisocoumarins.

## Experimental Section

**General.** Melting points were measured with Yanaco micro melting-point apparatus.  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra were obtained on a Varian Unity plus 400 Spectrometer. Chemical shifts were measured in parts per million with respect to TMS. IR spectra were run on a Perkin-Elmer spectrometer (System 2000 FT-IR, series No. 35575). Elemental analyses were recorded on a Heraeus CHN-O Rapid analyzer. Mass spectra were recorded on a Chem/HP/middle spectrometer connected to a Hewlett Packard series II model gas-liquid chromatography. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Silica gel (230-400 mesh) for column chromatography and the pre-coated silica gel plates (60 F-254) for TLC were purchased from E. Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.

### General preparation of 5-alkoxy-6-methoxy-3-methyl-3,4-dihydroisocoumarins (**3a-d**).

3-Alkoxy-4-methoxy-2-(oxiranylmethyl)benzonnitriles (**2a-d**) (2.0 mmol) dissolved in EtOH (50 mL) was stirred and added  $\text{NaBH}_4$  (0.23 g, 6.0 mmol) in portions. Then, the reaction mixture was heated to the reflux for 1 hr (monitoring by TLC). The given mixture was quenched with  $\text{H}_2\text{O}$  (50 mL), and concentrated *in vacuo* to remove EtOH. The obtained residue was poured into separating funnel and extracted with  $\text{CH}_2\text{Cl}_2$  (50 mL  $\times$  3). The extracted solution was combined and washed with brine (30 mL  $\times$  2), dried with  $\text{MgSO}_4$ , and filtered in sequence. The resulting residue was purified from silica gel column chromatography (ethyl acetate: *n*-hexane = 1: 5) to give pure **3a-d**. Under the same reaction condition but with insufficient amount of  $\text{NaBH}_4$  (1 mmol), for example, **5a** was obtained.

**5,6-Dimethoxy-3-methyl-3,4-dihydroisocoumarin (3a).** Compound **3a** (0.35 g, 80%) was obtained as colorless crystals, mp 110-111  $^\circ\text{C}$  (EtOAc + *n*-hexane) (lit.<sup>9</sup> mp 127-128  $^\circ\text{C}$ ),  $R_f =$

0.31 (ethyl acetate: *n*-hexane = 1: 5); IR (neat)  $\nu_{\max}$ : 1707  $\text{cm}^{-1}$  (C=O);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  1.46 (d,  $J$  6.2 Hz, 3H, H-9), 2.66 (dd,  $J$  16.8, 11.4 Hz, 1H, Hb-4), 3.13 (dd,  $J$  16.8, 3.2 Hz, 1H, Ha-4), 3.78, 3.89 (each s,  $2 \times 3\text{H}$ ,  $2 \times \text{OCH}_3$ ), 4.59 (m, 1H, H-3), 6.88 (d,  $J$  8.4 Hz, 1H, ArH), 7.82 (d,  $J$  8.4 Hz, 1H, ArH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  20.9, 29.0, 55.8, 60.5, 74.6, 110.7, 117.8, 127.2, 133.0, 144.5, 156.7, 165.3; EIMS (70eV)  $m/z$  (rel. intensity, %) 222 ( $\text{M}^+$ , 72), 179 (16), 178 (38), 163 (18), 151 (10), 150 (100), 135 (17), 91 (13), 79 (9); HRMS Calcd for  $\text{C}_{12}\text{H}_{14}\text{O}_4$ : 222.0892. Found: 222.0887; Anal. Calcd for  $\text{C}_{12}\text{H}_{14}\text{O}_4$ : C, 64.85; H, 6.35. Found: C, 65.01; H, 6.41.

Under the same reaction condition but with insufficient amount of  $\text{NaBH}_4$  (1 mmol), for example, **3a** was obtained in 59% yield as well as by-product **5a** was obtained in 33% yield.

**2-(2-Hydroxypropyl)-3,4-dimethoxybenzotrile (5a)** (0.15 g, 33%) was obtained as a colorless liquid,  $R_f = 0.28$  (ethyl acetate: *n*-hexane = 1: 1);  $\text{IR}_{\max}$  (neat)  $\text{cm}^{-1}$ : 2217 (CN), 3407 (OH);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.30 (d,  $J$  6.4 Hz, 3H, H-3'), 2.00 (d,  $J$  5.2 Hz, 1H, OH), 3.02 (d,  $J$  6.8 Hz, 2H, H-1'), 3.87, 3.93 (each s,  $2 \times 3\text{H}$ ,  $2 \times \text{OCH}_3$ ), 4.12 (m, 1H, H-2'), 6.86, 7.41 (each d,  $J$  8.4 Hz, 1H, H-5 and H-6);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  23.56, 38.50, 55.92, 60.75, 68.49, 105.8, 110.9, 129.7, 131.5, 136.5, 150.8, 156.4; EI-MS (70eV)  $m/z$  (rel. intensity, %) 221 ( $\text{M}^+$ , 6), 178 (10), 177 (62), 163 (12), 162 (100), 134 (14), 131 (15), 106 (10); HRMS (EI,  $m/z$ ) Calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$ : 221.1052. Found: 221.1053.

**5-Ethoxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin (3b)**. Compound **3b** (0.40 g, 87%) was obtained as colorless liquid,  $R_f = 0.39$  (ethyl acetate: *n*-hexane = 1: 5); IR (neat)  $\nu_{\max}$ : 1713  $\text{cm}^{-1}$  (C=O);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  1.33 (t,  $J$  7.0 Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.48 (d,  $J$  6.2 Hz, 3H, H-9), 2.68 (dd,  $J$  16.8, 11.4 Hz, 1H, Hb-4), 3.16 (dd,  $J$  16.8, 3.2 Hz, 1H, Ha-4), 3.89 (s, 3H,  $\text{OCH}_3$ ), 4.01 (q,  $J$  7.0 Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.56 (m, 1H, H-3), 6.88 (d,  $J$  8.8 Hz, 1H, ArH), 7.84 (d,  $J$  8.8 Hz, 1H, ArH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  15.6, 21.0, 29.4, 55.8, 68.8, 74.7, 110.7, 117.9, 127.1, 133.4, 143.6, 156.9, 165.4; EIMS (70eV)  $m/z$  (rel. intensity, %) 236 ( $\text{M}^+$ , 58), 208 (27), 165 (17), 164 (100), 163 (18), 136(32), 135(28); HRMS Calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_4$ : 236.1049. Found: 236.1043.

**5-Isopropoxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin (3c)**. Compound **3c** (0.41 g, 83%) was obtained as colorless crystals, mp 83-84  $^\circ\text{C}$ ,  $R_f = 0.45$  (ethyl acetate: *n*-hexane = 1: 5); IR (neat)  $\nu_{\max}$ : 1718  $\text{cm}^{-1}$  (C=O);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  1.21 (d,  $J$  6.2 Hz, 6H,  $\text{OCH}(\text{CH}_3)_2$ ), 1.44 (d,  $J$  6.2 Hz, 3H, H-9), 2.61 (dd,  $J$  16.8, 11.4 Hz, 1H, Hb-4), 3.14 (dd,  $J$  16.8, 3.2 Hz, 1H, Ha-4), 3.85 (s, 3H,  $\text{OCH}_3$ ), 4.40 (hept,  $J$  6.2 Hz, 1H,  $\text{OCH}(\text{CH}_3)_2$ ), 4.51 (m, 1H, H-3), 6.85 (d,  $J$  8.8 Hz, 1H, ArH), 7.78 (d,  $J$  8.8 Hz, 1H, ArH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 50 MHz)  $\delta$  20.9, 22.4, 29.8, 55.7, 74.6, 74.8, 110.5, 117.8, 126.7, 133.7, 142.4, 156.9, 165.4; EIMS (70eV)  $m/z$  (rel. intensity, %) 250 ( $\text{M}^+$ , 7), 208 (50), 165 (17), 164 (100), 137 (9), 136 (33), 135 (17), 93 (5); HRMS Calcd for  $\text{C}_{14}\text{H}_{18}\text{O}_4$ : 250.1205. Found: 250.1200; Anal. Calcd for  $\text{C}_{14}\text{H}_{18}\text{O}_4$ : C, 67.18; H, 7.25. Found: C, 67.19; H, 7.25.

**5-Butoxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin (3d)**. Compound **3d** (0.42 g, 81% ) was obtained as colorless liquid,  $R_f = 0.46$  (ethyl acetate: *n*-hexane = 1: 5); IR (neat)  $\nu_{\max}$ : 1715  $\text{cm}^{-1}$  (C=O);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  0.95 (t,  $J$  7.4 Hz, 3H,  $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.47 (sixt,

$J$  7.4 Hz, 2H, OCH<sub>2</sub>-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.48 (d,  $J$  6.2 Hz, 3H, H-9), 1.71 (quint,  $J$  7.4 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.66 (dd,  $J$  16.8, 11.4 Hz, 1H, Hb-4), 3.15 (dd,  $J$  16.8, 3.2 Hz, 1H, Ha-4), 3.88 (s, 3H, OCH<sub>3</sub>), 3.91 (t,  $J$  7.4 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 4.55 (m, 1H, H-3), 6.87 (d,  $J$  8.4 Hz, 1H, ArH), 7.83 (d,  $J$  8.4 Hz, 1H, ArH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 50 MHz)  $\delta$  13.8, 19.1, 20.9, 29.2, 32.2, 55.7, 72.9, 74.7, 110.6, 117.7, 127.1, 133.2, 143.7, 156.9, 165.5; EIMS (70eV)  $m/z$  (rel. intensity, %) 264 (M<sup>+</sup>, 20), 208 (39), 165 (22), 164 (100), 136 (29), 135 (14), 93(5); HRMS Calcd for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>: 264.1362. Found: 264.1356.

### General preparation of 3-benzyl-5-alkoxy-6-methoxy-3,4-dihydroisocoumarins (4a-d).

3-Alkoxy-4-methoxy-2-(oxiranylmethyl)benzotrioles (**2a-d**) (2.0 mmol) dissolved in THF (20 mL) was stirred and added copper (I) iodide (0.22 g, 1.17 mmol) and then added phenylmagnesium chloride (2.0 M in THF) (5.6 mmol) dropwise at room temperature. The reaction mixture was continually stirred and heated to the reflux for 1 day (monitoring by TLC). Then, the reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution (30 mL), and concentrated *in vacuo* to remove THF. The residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL  $\times$  3). The extracted solution was combined and washed with brine (30 mL  $\times$  2), dried with MgSO<sub>4</sub>, and filtered. The filtrate was concentrated *in vacuo*. The resulting residue was purified from silica gel column chromatography (ethyl acetate: *n*-hexane = 1: 8) to give pure **4a-d**.

**3-Benzyl-5,6-dimethoxy-3,4-dihydroisocoumarin (4a)**. Compound **4a** (0.50 g, 86%) was obtained as colorless crystals, mp 141-142 °C,  $R_f$  = 0.31 (ethyl acetate: *n*-hexane = 1: 5); IR (neat)  $\nu_{\max}$  cm<sup>-1</sup>: 1717 cm<sup>-1</sup> (C=O); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  2.75 (dd,  $J$  16.4, 11.2 Hz, 1H, Ha-4), 3.04 (dd,  $J$  14.0, 6.8 Hz, 1H, Ha-9), 3.11 (dd,  $J$  16.4, 3.2 Hz, 1H, Hb-4), 3.21 (dd,  $J$  14.0, 6.0 Hz, 1H, Hb-9), 3.77, 3.93 (each s, 2  $\times$  3H, 2  $\times$  OCH<sub>3</sub>), 4.69 (m, 1H, H-3), 6.91 (d,  $J$  8.4 Hz, 1H, ArH), 7.30 (m, 5H, ArH), 7.88 (d,  $J$  8.4 Hz, 1H, ArH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  26.5, 41.2, 55.9, 60.6, 78.8, 110.8, 118.0, 126.9, 127.5, 128.6, 129.6, 132.9, 136.2, 144.7, 156.9, 165.3; EIMS (70eV)  $m/z$  (rel. intensity, %) 298 (M<sup>+</sup>, 19), 208 (9), 207 (73), 180 (11), 179 (100), 136 (7), 91 (11); HRMS Calcd for C<sub>18</sub>H<sub>18</sub>O<sub>4</sub>: 298.1205. Found: 298.1204; Anal. Calcd for C<sub>18</sub>H<sub>18</sub>O<sub>4</sub>: C, 72.47; H, 6.08. Found: C, 72.19; H, 6.03.

**3-Benzyl-5-ethoxy-6-methoxy-3,4-dihydroisocoumarin (4b)** Compound **4b** (0.55 g, 90%) was obtained as colorless liquid,  $R_f$  = 0.31 (ethyl acetate: *n*-hexane = 1: 5); IR (neat)  $\nu_{\max}$ : 1716 cm<sup>-1</sup> (C=O); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.28 (t,  $J$  7.2 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 2.73 (dd,  $J$  16.8, 10.8 Hz, 1H, Ha-4), 3.03 (dd,  $J$  14.0, 6.8 Hz, 1H, Ha-9), 3.13 (dd,  $J$  16.4, 3.2 Hz, 1H, Hb-4), 3.21 (dd,  $J$  14.0, 6.0 Hz, 1H, Hb-9), 3.91 (s, 3H, OCH<sub>3</sub>), 3.98 (q,  $J$  7.2 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.65 (m, 1H, H-3), 6.90 (d,  $J$  8.4 Hz, 1H, ArH), 7.30 (m, 5H, ArH), 7.86 (d,  $J$  8.4 Hz, 1H, ArH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  15.5, 26.9, 41.2, 55.8, 68.8, 78.8, 110.7, 118.0, 126.8, 127.3, 128.5, 129.6, 133.2, 136.3, 143.7, 157.0, 165.3; EIMS (70eV)  $m/z$  (rel. intensity, %) 312 (M<sup>+</sup>, 29), 222 (13), 221(97), 194 (22), 193(100), 165(21), 107(12), 91(8); HRMS Calcd for C<sub>19</sub>H<sub>20</sub>O<sub>4</sub>: 312.1362. Found: 312.1360.

**3-Benzyl-5-isopropoxy-6-methoxy-3,4-dihydroisocoumarin (4c)**. Compound **4c** (0.55 g, 85%) was obtained as colorless crystals, mp 77-78 °C,  $R_f$  = 0.32 (ethyl acetate: *n*-hexane = 1: 5); IR (neat)  $\nu_{\max}$ : 1718 cm<sup>-1</sup> (C=O); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.20 (d,  $J$  6.4 Hz, 3H, OCH(CH<sub>3</sub>)<sub>2</sub>),

2.69 (dd,  $J$  16.8, 11.2 Hz, 1H, Ha-4), 3.02 (dd,  $J$  14.0, 6.8 Hz, 1H, Ha-9), 3.15 (dd,  $J$  16.8, 3.2 Hz, 1H, Hb-4), 3.21 (dd,  $J$  13.6, 6.0 Hz, 1H, Hb-9), 3.90 (s, 3H, OCH<sub>3</sub>), 4.37 (hept,  $J$  6.4 Hz, 1H, OCH(CH<sub>3</sub>)<sub>2</sub>), 4.66 (m, 1H, H-3), 6.89 (d,  $J$  8.8 Hz, 1H, ArH), 7.31 (m, 5H, ArH), 7.85 (d,  $J$  8.4 Hz, 1H, ArH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  22.3, 22.5, 27.5, 41.2, 55.8, 75.2, 78.9, 110.6, 118.0, 126.8, 127.0, 128.5, 129.5, 133.7, 136.3, 142.5, 157.1, 165.5; EIMS (70eV)  $m/z$  (rel. intensity, %) 326 (M<sup>+</sup>, 5), 250 (7), 208 (99), 193 (37), 165 (70), 164 (100), 136 (37), 135 (21); HRMS Calcd for C<sub>20</sub>H<sub>22</sub>O<sub>4</sub>: 326.1518. Found: 326.1520. Anal. Calcd for C<sub>20</sub>H<sub>22</sub>O<sub>4</sub>: C, 73.60; H, 6.79. Found: C, 73.28; H, 6.78.

**3-Benzyl-5-butoxy-6-methoxy-3,4-dihydroisocoumarin (4d).** Compound **4d** (0.60 g, 89%) was obtained as colorless crystals, mp 115-116 °C,  $R_f$  = 0.31 (ethyl acetate: *n*-hexane = 1: 5); IR (neat)  $\nu_{\max}$ : 1719 cm<sup>-1</sup> (C=O); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  0.93 (t,  $J$  7.2 Hz, 3H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.40 (sextet,  $J$  7.2 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.63 (quint,  $J$  7.2 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.71 (dd,  $J$  16.8, 11.2 Hz, 1H, Ha-4), 3.02 (dd,  $J$  13.6, 7.2 Hz, 1H, Ha-9), 3.11 (dd,  $J$  16.8, 3.2 Hz, 1H, Hb-4), 3.23 (dd,  $J$  13.6, 6.0 Hz, 1H, Hb-9), 3.88 (t,  $J$  7.2 Hz, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 4.66 (m, 1H, H-3), 6.89 (d,  $J$  8.4 Hz, 1H, ArH), 7.29 (m, 5H, ArH), 7.86 (d,  $J$  8.4 Hz, 1H, ArH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  13.8, 19.1, 26.8, 32.2, 41.3, 55.8, 73.0, 78.8, 110.7, 118.0, 126.8, 127.2, 128.6, 129.6, 133.1, 136.2, 143.9, 157.0, 165.4; EIMS (70eV)  $m/z$  (rel. intensity, %) 340 (M<sup>+</sup>, 22), 250 (8), 249 (52), 194 (11), 193 (100), 166 (9), 165 (34), 91 (6); HRMS Calcd for C<sub>19</sub>H<sub>20</sub>O<sub>4</sub>: 340.1675. Found: 340.1677; Anal. Calcd for C<sub>21</sub>H<sub>24</sub>O<sub>4</sub>: C, 74.09; H, 7.11. Found: C, 73.88; H, 7.11.

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