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

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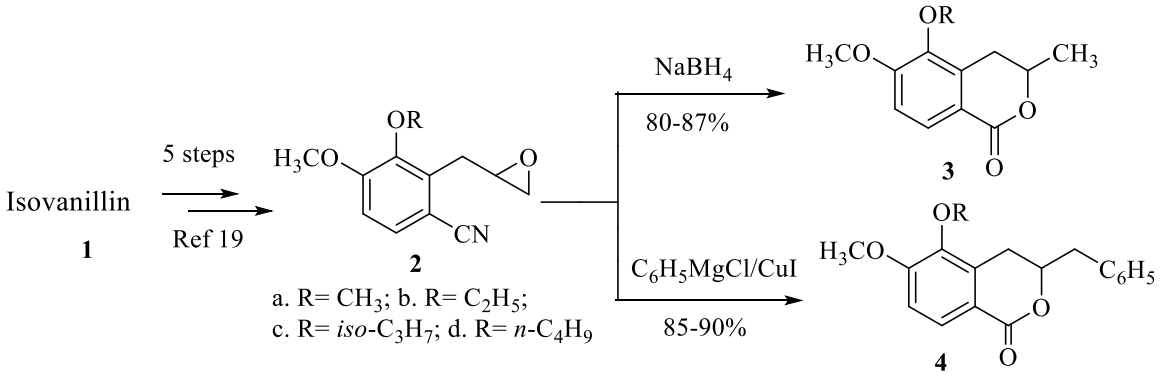
Abstract. A new method for the synthesis of substituted 3-alkyl-3,4-dihydroisocoumarins is described. *o*-(Oxiranylmethyl)benzonitriles, prepared from isovanillin in five steps, when reacted with nucleophiles such as sodium borohydride or phenylmagnesium chloride/CuI, undergo an intramolecular cyclization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

Keywords: Isovanillin, oxiranes, benzonitriles, intramolecular cyclization, 3,4-dihydroisocoumarins

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*,[1] *Hydrangea macrophylla*,[2] Cape aloe,[3] *Montrouziera sphaeroidea*,[4] *Aloe hildebrandtii*,[5] *Cassia siamea*,[6] *Caryocar glabrum*,[7] 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,[8] from *Aloe vera* exhibiting binding activity with human serum albumin,[9] from *Fusarium verticillioides* exhibiting antimalarial, antitubercular and antifungal activities,[10] 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.[11] 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,[12] radical cyclization mediated by titanocene(III) chloride,[13] cyclization of α-lithiated 2-toluenecarboxylates,[14] coupling of vinylic halides or triflates with *o*-(1-alkenyl)-benzoic acids,[15] the successive lateral and *ortho*-lithiations of 4,4-dimethyl-2-(*o*-toyl)oxazoline,[16] 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.[17] The addition of various nucleophiles to cyano groups has also been well described.[18] 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.[19] Continuing our work on benzoheterocycles,[20] 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).

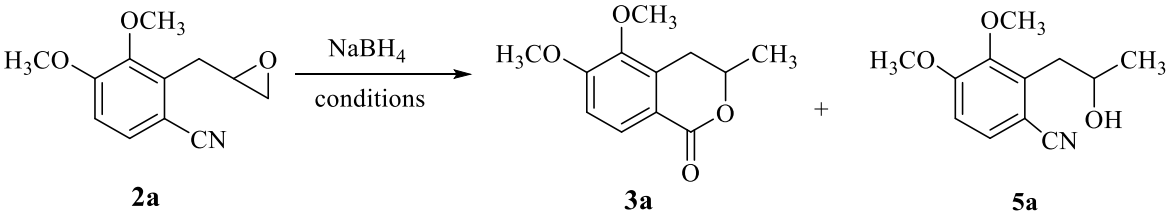


Scheme 1. Synthesis of 3-alkyl-3,4-dihydroisocoumarins from *o*-(oxiranylmethyl)benzonitriles with $NaBH_4$ and C_6H_5MgCl/CuI nucleophiles.

Results and Discussion

In order to optimize the reaction conditions, compound **2a** used as a model reaction was allowed to react with $NaBH_4$ under various conditions. The given results showed that 5,6-dimethoxy-3-methyldihydroisochroman (**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 $NaBH_4$. The results of this model reaction are compiled in Table 1.

Table 1. The reaction of compound **2a** with $NaBH_4$ under various conditions to yield **3a** and **5a**



2a **3a** **5a**

Entry	Equiv. $NaBH_4$	Solvent	Temp	Time (hr)	**3a** (%)[a]	**5a** (%)[a]
1	1	EtOH	rt	24	53	45
2	1	EtOH	reflux	1	59	33[20a]
3	1.5	EtOH	reflux	1	62	38
4[b]	1.5	EtOH	reflux	1	67	33
5	1.5	MeOH	reflux	1	11	40
6[b]	1.5	MeOH	reflux	1	18	42
7[b]	3.0	EtOH	reflux	1	80	-

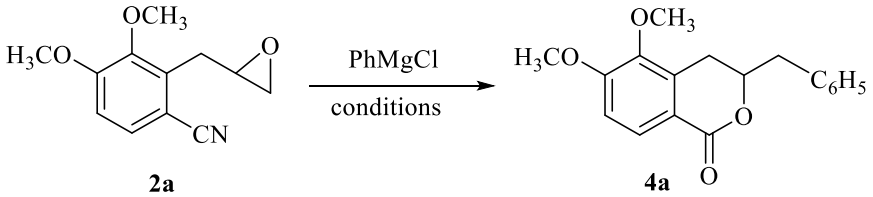
[a] Determined by isolated yields; [b]Anhydrous solvent was used.

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 quivalents of $NaBH_4$ (entry 7) is better than 1 or 1.5 equivalents of $NaBH_4$ (entries 1-6), and heating under reflux is better than reaction at room temperature for the production of **3**. Thus, the use of excess $NaBH_4$ (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, ^{1}H-NMR, ^{13}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^{-1} (C=O) and the ^{1}H-NMR spectrum exhibited a doublet signal of methyl group bonded to C-3 (*J* 6.2 Hz at δ 1.46); two double doublet signals at δ 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 δ 3.78 and 3.89; a one proton signal at δ 4.59 coupled to neighboring protons assigned as H-3; and two aromatic protons at δ 6.88, and 7.82 with the same coupling constant *J* 8.4 Hz indicating their *ortho* relationship. In the ^{13}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_6H_5MgBr under various conditions to yield **4a**



2a **4a**

Entry	Nu^-	Additive	Temp	Time (hr)	**4a** (%)
1	C_6H_5MgCl (1.2 equiv)	-	0°- r.t.	24	16
2	C_6H_5MgCl (1.2 equiv)	CuI (0.25 equiv)	0°-r.t.	24	47
3	C_6H_5MgCl (1.2 equiv)	CuI (0.50 equiv)	0°- r.t.	24	64
4	C_6H_5MgCl (1.2 equiv)	CuI (1.0 equiv)	0°- r.t.	24	66
5	C_6H_5MgCl (1.2 equiv)	CuI (1.0 equiv)	reflux	16	11
6	C_6H_5MgCl (2.4 equiv)	CuI (0.5 equiv)	reflux	24	86

[a]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_6H_5MgCl (entries 1-5) gave **4a** in low to modest yields (11-66%). On the other hand the reaction of **2a** with excess C_6H_5MgCl (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, ^{1}H-NMR, ^{13}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^{-1} (C=O) indicating the presence of carbonyl group. The ^{1}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_3 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}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)benzonitriles with nucleophiles ($NaBH_4$ or Grignard reagent/CuI). This reaction demonstrates that epoxide ring of *o*-(oxiranylmethyl)benzonitrile 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}H-NMR and ^{13}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)benzonitriles (**2a-d**) (2.0 mmol) dissolved in EtOH (50 mL) was stirred and added $NaBH_4$ (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 H_2O (50 mL), and concentrated *in vacuo* to remove EtOH. The obtained residue was poured into separating funnel and extracted with CH_2Cl_2 (50 mL × 3). The extracted solution was combined and washed with brine (30 mL × 2), dried with $MgSO_4$, 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 $NaBH_4$ (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 ºC (EtOAc + *n*-hexane) (lit.[9] mp 127-128 ºC), R_f =

0.31 (ethyl acetate: *n*-hexane = 1: 5); IR (neat) ν_{max}: 1707 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 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 × 3H, 2 × 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}C-NMR ($CDCl_3$, 50 MHz) δ 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 (M^+, 72), 179 (16), 178 (38), 163 (18), 151 (10), 150 (100), 135 (17), 91 (13), 79 (9); HRMS Calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 222.0887; Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.01; H, 6.41.

Under the same reaction condition but with insufficient amount of $NaBH_4$ (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-dimethoxybenzonitrile (**5a**) (0.15 g, 33%) was obtained as a colorless liquid, R_f = 0.28 (ethyl acetate: *n*-hexane = 1: 1); IR_{max} (neat) cm^{-1}: 2217 (CN), 3407 (OH); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 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 × 3H, 2 × 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}C-NMR ($CDCl_3$,100 MHz) δ 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 (M^+, 6), 178 (10), 177 (62), 163 (12), 162 (100), 134 (14), 131 (15), 106 (10); HRMS (EI, *m/z*) Calcd for $C_{13}H_{14}N_2O_3$: 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) ν_{max}: 1713 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.33 (t, *J* 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 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, OCH_3), 4.01 (q, *J* 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 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}C-NMR ($CDCl_3$, 50 MHz) δ 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 (M^+, 58), 208 (27), 165 (17), 164 (100), 163 (18), 136(32), 135(28); HRMS Calcd for $C_{13}H_{16}O_4$: 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 ºC, R_f = 0.45 (ethyl acetate: *n*-hexane = 1: 5); IR (neat)ν_{max}: 1718 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.21 (d, *J* 6.2 Hz, 6H, $OCH(C\underline{H}_3)_2$), 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, OCH_3), 4.40 (hept, *J* 6.2 Hz, 1H, $OC\underline{H}(CH_3)_2$), 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}C-NMR ($CDCl_3$, 50 MHz) δ 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 (M^+, 7), 208 (50), 165 (17), 164 (100), 137 (9), 136 (33), 135 (17), 93 (5); HRMS Calcd for $C_{14}H_{18}O_4$: 250.1205. Found: 250.1200; Anal. Calcd for $C_{14}H_{18}O_4$: 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)ν_{max}: 1715 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, *J* 7.4 Hz, 3H, $OCH_2CH_2CH_2C\underline{H}_3$), 1.47 (sixt,

J 7.4 Hz, 2H, OCH_2- $CH_2C\underline{H}_2CH_3$), 1.48 (d, *J* 6.2 Hz, 3H, H-9), 1.71 (quint, *J* 7.4 Hz, 2H, $OCH_2C\underline{H}_2CH_2\,CH_3$), 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_3), 3.91 (t, *J* 7.4 Hz, 2H, $OC\underline{H}_2CH_2CH_2CH_3$), 4.55 (m, 1H, H-3), 6.87 (d, *J* 8.4 Hz, 1H, ArH), 7.83 (d, *J* 8.4 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 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^+, 20), 208 (39), 165 (22), 164 (100), 136 (29), 135 (14), 93(5); HRMS Calcd for $C_{15}H_{20}O_4$: 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)benzonitriles (**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_4Cl solution (30 mL), and concentrated *in vacuo* to remove THF. The residue was extracted with CH_2Cl_2 (50 mL × 3). The extracted solution was combined and washed with brine (30 mL × 2), dried with $MgSO_4$, 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) ν_{max} cm^{-1}: 1717 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 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 × 3H, 2 × OCH_3), 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); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 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^+, 19), 208 (9), 207 (73), 180 (11), 179 (100), 136 (7), 91 (11); HRMS Calcd for $C_{18}H_{18}O_4$: 298.1205. Found: 298.1204; Anal. Calcd for $C_{18}H_{18}O_4$: 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)ν_{max}: 1716 cm^{-1} (C=O); ^{1} H-NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 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_3), 3.98 (q, *J* 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 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); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 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^+, 29), 222 (13), 221(97), 194 (22), 193(100), 165(21), 107(12), 91(8); HRMS Calcd for $C_{19}H_{20}O_4$: 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)ν_{max}: 1718 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, *J* 6.4 Hz, 3H, $OCH(C\underline{H}_3)_2$),

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_3), 4.37 (hept, *J* 6.4 Hz, 1H, $OC\underline{H}(CH_3)_2$), 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); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 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^+, 5), 250 (7), 208 (99), 193 (37), 165 (70), 164 (100), 136 (37), 135 (21); HRMS Calcd for $C_{20}H_{22}O_4$: 326.1518. Found: 326.1520. Anal. Calcd for $C_{20}H_{22}O_4$: 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) ν_{max}: 1719 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, *J* 7.2 Hz, 3H, $OCH_2CH_2CH_2C\underline{H}_3$), 1.40 (sextet, *J* 7.2 Hz, 2H, $OCH_2CH_2C\underline{H}_2CH_3$), 1.63 (quint, *J* 7.2Hz, 2H, $OCH_2C\underline{H}_2CH_2CH_3$), 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* 7.2Hz, 2H, $OC\underline{H}_2CH_2CH_2CH_3$), 3.90 (s, 3H, OCH_3), 4.66 (m, 1H, H-3), 6.89 (d, *J* 8.4 Hz, 1H, ArH), 7.29 (m, 5H, ArH), 7.86 (d, *J* 8.4Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 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^+, 22), 250 (8), 249 (52), 194 (11), 193 (100), 166 (9), 165 (34), 91 (6); HRMS Calcd for $C_{19}H_{20}O_4$: 340.1675. Found: 340.1677; Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.88; H, 7.11.

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