Novel and Convenient Synthesis of Benzofurans from Dihydrocoumarins

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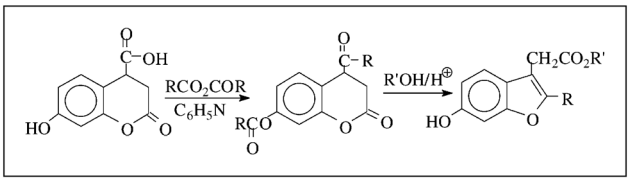

7-Hydroxy-3,4-dihydrocoumarin-4-carboxylic acid (**7**), conveniently prepared from *m*-resorcinol and maleic anhydride, was surprisingly transformed by acid anhydride and pyridine into the corresponding ketone, 4-alkanoyl analog **11**. The latter reacted in turn with acidic alcohol yielding benzofuran-3-yl-acetic ester **16.**

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INTRODUCTION

The benzofuran ring is a common moiety in many biologically active natural and therapeutic products [1] and represents a very important heterocyclic pharmacophore. As a result, benzofuran-containing entities constitute an important target for pharmaceutical research [2]. We describe our serendipitous discovery of a novel and convenient synthetic route to this moiety, beginning with the easily accessible 7-hydroxy-3,4-dihydrocoumarin system. The coumarin system itself exhibits useful and diverse biological activity [3], and finds application in pharmaceuticals, fragrances, agrochemicals, and insecticides [4]. Because of our studies on the superoxide mediate saponification of coumarins [Scheme 1; eq. (1)] [5] we were interested in exploring a similar reaction with 3,4-dihydro analogs **3** [eq. (2)].

RESULTS AND DISCUSSION

To this end, we began with the Gunnewegh synthesis of dihydrocoumarin **7** from resorcinol (**5**) and maleic anhydride (**6**), as shown in Scheme 2 [6]. The desired product is obtained in a 60% yield along with variable amounts (0–30%) of a side product, ketone **8**. The latter is formed in a subsequent Friedel–Crafts addition of the primary product **7** on the starting resorcinol **5**. The yield of this side product can be decreased dramatically by lowering the concentrations of the starting reagents (see the Experimental section).

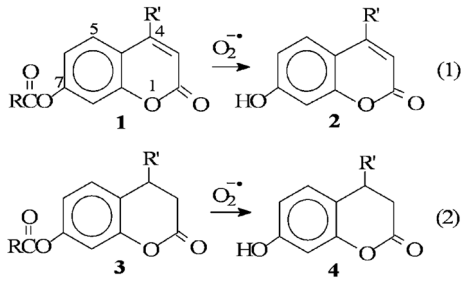
In the next step (Scheme 3), we attempted to acylate the phenolic group of coumarin **7** at C-7 with acetic anhydride **9a** in the presence of pyridine; the reaction was quenched with methanol to solvolyze all the remaining anhydrides. Much to our astonishment, the observed product was not dihydrocoumarin diester **10a—**with a ^{13}C-NMR carbonyl absorption at ca.172, but rather ketone **11a**—with a carbonyl resonance at 207 ppm. This reaction repeated itself as well with other anhydrides, **9b–e**, yielding ketones **11b–e** in similar yields of about 30% (Scheme 3).

In our search for precedents, we discovered that more than half-a-century ago, Lawson [4] described similar examples of decarboxylative acylation with anhydrides. A plausible mechanism for this transformation is outlined in Scheme 4 [8]. The initial step is the expected acylation of the hydroxyl groups of the C-7 phenol and the C-4 carboxylic acid, presumably yielding anhydride ester **12**. In the key step, facile deprotonation and subsequent acylation occurs at doubly activated C-4, which is both benzylic and α to the anhydride carbonyl. The resulting β-ketoanhydride **14** undergoes decarboxylation yielding the observed ketone **11**.

Another surprise awaited us when we attempted to solvolyze the C-7 esters **11a–f**. Instead of isolating dihydrocoumarins **15**, we obtained benzofuran-3-yl acetates **16a–f** in a 50% yield (Scheme 5) [7,9].

The proposed mechanism for this transformation appears in Scheme 6. Alcoholysis of both the ester linkage at C-7 and the lactone at C-2, generates *m*-cresol **17**. Cyclization of the generated phenol into the ketone carbonyl results in the formation of furanol **18**, which dehydrates in turn, generating benzofuran-3-yl-acetic esters **16**.

Scheme 1. Superoxide mediated saponification of coumarins **1** and dihydrocoumarins **3**.



CONCLUSIONS

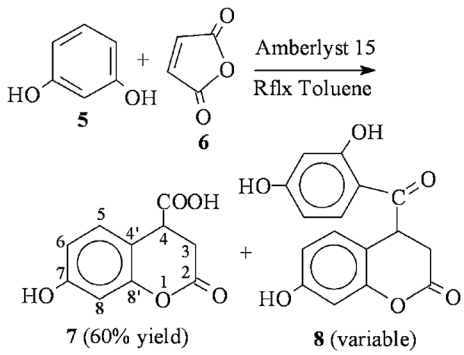
In conclusion, we have described a convenient synthesis of a broad family of 6-hydroxybenzofurans **16** beginning with 7-hydroxy-3.4-dihydrocoumarins **7** and proceeding *via* coumarins **11**. The double activation of C-4 in **11** and the 1,4-relationship of the two carbonyls in dihydrocoumarins **11** is at the core of the two surprising transformations observed.

EXPERIMENTAL

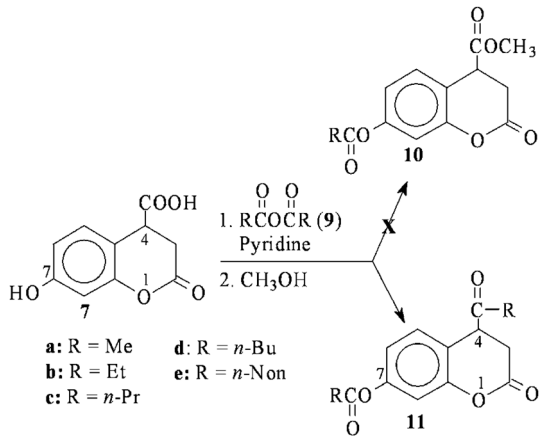
High-resolution mass spectra were run on a VG-Fison AutoSpecE high resolution spectrometer. The NMR spectra were recorded on a Bruker AM 300 or Bruker DMX 600 Fourier transform spectrometer. For 1D NMR spectra, we used a QNP probe. All 2D experiments (COSY, HMQC, HMBC, and NOSEY) were run using the programs from the Bruker software library. NMR spectra were generally taken at 25 ± 1°C and recorded while locked on the deuterium signals of the respective deuterated solvent. The numbering of the carbons and hydrogens in the NMR spectra of dihydrocoumarin **7**, ketones **11**, and benzofurans **16** are exemplified below in Scheme 7.

7-Hydroxy-3,4-dihydrocoumarin-4-carboxylic acid (7) [6]. A solution of resorcinol (**5**, 0.05 mol), maleic anhydride (**6**, 0.05 mol), and wet [10] amberlyst 15 ion exchange resin (5 g) in toluene (500 mL) were refluxed while stirring with a mechanical stirrer for 48 h. For isolation and purification of the compound, the resin catalysts were removed by warm filtration, followed by carefully and repeatedly washing the resin with acetone. The pure product was isolated by acetone evaporation as a red solid.

Scheme 2. Gunnewegh synthesis of dihydrocoumarin **7**.



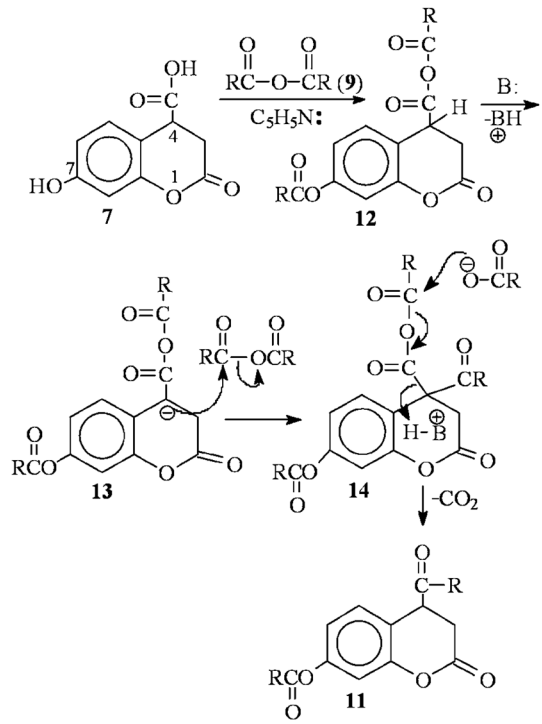
Scheme 3. Acylation of dihydrocoumarin-4-carboxylic acid **7** with anhydrides **9**.



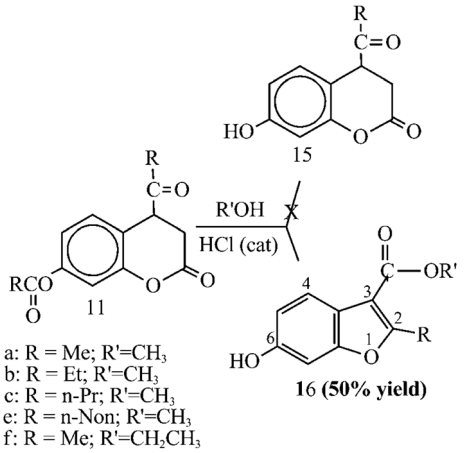
Yield: 5 g (60%); mp 153–155°C. IR (KBr pellet) 1761 (CO ester), 1695 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, CD_3COCD_3): δ 2.97 (1H, dd, J = 6.14 Hz and 17.7 Hz, $H_3\beta$), 3.1 (1H, dd, J = 4 Hz and 17.7 Hz, $H_3\alpha$), 3.9 (1H, m, H_4). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 35.06 (C-3), 40.05 (C-4), 99.11 (C-8), 111.36 (C-6), 118.57 (C-4′), 125.43 (C-5), 155.88 (C-8′), 159.04 (C-7), 171.82 (C-2), 177.54 (C-9). HRMS, *m/z* (CI, CH_4): Calcd for $C_{10}H_7O_5$ (M^+-H) 207.0293. Found 207.0289.

General procedure for the preparation of ketones 11a-e. To a solution containing 7-hydroxy-3,4-dihydrocoumarin-4-carboxylic acid (**7**; 0.009 mol), the desired anhydride **9** (acetic, propionic, butyric, valeric or capric; 2 equiv, 0.019 mol), and

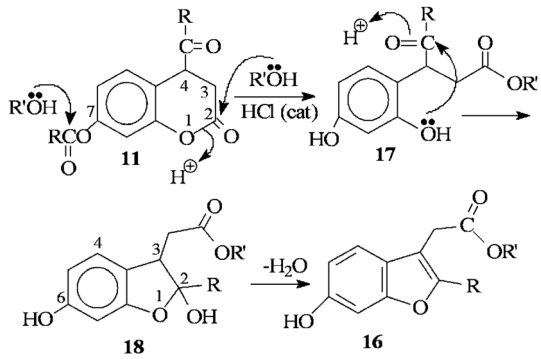
Scheme 4. Mechanism for the transformation of dihydrocoumarin **7** to ketones **11**.



Scheme 5. Acid alcoholysis of dihydrocoumarin **11**.



Scheme 6. Transformation of 4-acyldihydrocoumarin **11** to benzofuran **16**.



pyridine (4 equiv, 0.038 mol, 3 mol), a catalytic amount of 4-dimethylaminopyridine (56 mg) was added. The reaction mixture was stirred at r.t. for 12 h. The reaction was quenched with ice–cold methanol and evaporated. Water was then added to the brown-red solution, and the aqueous reaction mixture was extracted thrice with ethyl acetate. The combined ethyl acetate extracts were washed with aqueous sodium bicarbonate solution and evaporated, yielding crude **11**. The latter was recrystallized from a mixture of methanol and acetone to give a white solid. The yield was consistently around 30%.

Acetic acid 4-acetyl-3,4-dihydrocoumarin-7-yl ester (11a). Mp 136–138°C, R_f = 0.33 (30% ethyl acetate in hexane). IR 1769 (CO ester), 1698 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36 (1H, d, J = 8.4, H_5), 6.95 (1H, dd, J = 8.4 and 2.4 Hz, H_6), 6.85 (1H, d, J = 2.0 Hz, H_8), 3.90 (1H, dd, J = 6.5 and 2 Hz, H_4), 3.10 (1H, dd, J = 15.3 and 2 Hz, $H_3\alpha$), 2.69 (1H, dd, J = 15.3 and 6.5 Hz, $H_3\beta$), 2.31 (3H, s, $H_{10'}$), 2.26 (3H, s, H_{10}). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.21 (C-9′), 169.13 (C-9), 166.09 (C-2), 152.42 (C-8′), 151.45 (C-7), 129.22 (C-5), 118.31 (C-6), 117.22 (C-4′), 111.83 (C-8), 48.49 (C-4), 30.51 (C-10), 27.71 (C-10′), 21.24 (C-3). HRMS, *m/z* (CI, CH_4): Calcd for $C_{13}H_{13}O_5$ (MH^+) 249.0790. Found 249.0763.

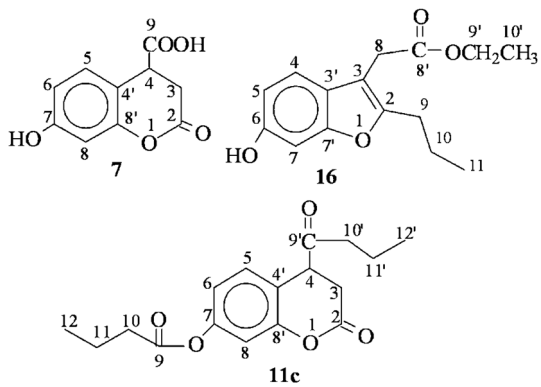
Propionic acid 4-propionyl-3,4-dihydrocoumarin-7-yl ester (11b). Mp 111–113°C. IR (KBr pellet): 1761 (CO ester), 1704 (CO) cm^{-1}. ^{1}H-NMR (300 MHz ,$CDCl_3$): δ 7.35 (1H, d, J = 8.4, H_5), 6.93 (1H, dd, J = 8.4 and 2.4 Hz, H_6), 6.84 (1H, d, J = 2.4 Hz, H_8), 4.00 (1H, dd, J = 5.7 and 2.1 Hz, H_4), 3.1 (1H, dd, J = 16.2 Hz and 2.4 Hz, $H_3\alpha$), 2.72 (1H, dd, J = 14 Hz and 5.9 Hz, $H_3\beta$), 2.63 (4H ,m, H_{10}, $H_{10'}$), 1.25 (3H, t, J = 7.5 Hz, $H_{11'}$), 1.02 (3H, t, J = 6.4 Hz, H_{11}). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 207.2 (C-9′), 172.68 (C-9), 166.24 (C-2), 152.41 (C-7), 151.5 (C-8′), 129.05 (C-5), 118.23 (C-6), 117.5 (C-4′), 111.76 (C-8), 47.6 (C-4), 33.67 (C-3), 30.72 (C-10), 27.78 (C-10′), 9.06 (C-11), 7.49 (C-11′). HRMS, *m/z* (CI, CH_4): Calcd for $C_{15}H_{16}O_5$ (M^+) 276.0998. Found 276.1015.

Butyric acid 4-butyryl-3,4-dihydrocoumarin-7-yl ester (11c). Mp 111–123°C. IR (KBr pellet):1765 (CO ester), 1706 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, acetone-d_6): δ 7.58 (1H, d, J = 8.4, H_5), 6.93 (1H, dd, J = 8.4 and 2.4 Hz, H_6), 6.80 (1H, dd, J = 2.4 Hz, H_8), 4.27(1H, dd, J = 5.1 and 2.7 Hz, H_4), 3.1 (1H, dd, J = 16.2 Hz and 2.4 Hz, $H_3\alpha$), 2.72 (1H, dd, J = 14 Hz and 5.9 Hz, $H_3\beta$), 2.64 (2H, t, $J_{10',11'}$ = 7.2, $H_{10'}$), 2.50 (2H, t, $J_{10,11}$ = 7.5, H_{10}), 1.69 (2H, sex, $J_{10,11}$ = $J_{11,12}$ = 7.5 Hz, H_{11}), 1.44 (2H, sex, $J_{10',11'}$ = $J_{11',12'}$ = 7.2 Hz, $H_{11'}$), 0.97 (3H, t, $J_{11',12'}$ = 7.2, $H_{12'}$), 0.75 (3H, t, $J_{11,12}$ = 7.5, H_{12}). ^{13}C-NMR (75 MHz, acetone-d_6) δ 208 (C-9′), 172.04 (C-9), 166.68 (C-2), 153.39 (C-8′), 152.27 (C-7), 130.45 (C-5), 118.92 (C-4′), 118.63 (C-6), 111.84 (C-8), 48.16 (C-4), 42.38 (C-10′), 36.31 (C-3), 18.87 (C-11), 17.37 (C-11′), 13.72 (C-12′), 13.72(C-12). HRMS, *m/z* (CI, CH_4): Calcd for $C_{17}H_{20}O_5$ (M^+) 304.1311. Found 304.1274.

Pentanoic acid 4-pentanoyl-3,4-dihydrocoumarin-7-yl ester (11d). Mp 111–114°C. IR (KBr pellet): 1765 (CO ester), 1695 (CO) cm^{-1}. ^{1}H-NMR (300 MHz ,$CDCl_3$): δ 7.33(1H, d ,J = 8.4, H_5), 6.93 (1H, dd, J = 8.4 and 2.4 Hz, H_6), 6.84 (1H, dd, J = 2.4 Hz, H_8), 4.00 (1H, dd J = 5.7 and 2.1 Hz, H_4), 3.10 (1H, dd, J = 16.2 Hz and 2.4 Hz, $H_3\alpha$), 2.71 (1H, dd, J = 16.2 Hz and 6.00 Hz, $H_3\beta$), 2.55 (4H, m, $H_{10,}$ $H_{10'}$), 1.77 (2H, quint, J = 7.2, H_{11}), 1.51 (4H, m, $H_{11'}$ and H_{12}), 1.25 (2H, sex, J = 7.4, $H_{12'}$), 0.995 (3H, t, $J_{12',13'}$ = 7.2 Hz, $H_{13'}$), 0.84 (3H, t, $J_{12,13}$ = 7.2 Hz, H_{13}). ^{13}C-NMR δ 206.48 (C-9′), 171.78 (C-9), 165.88 (C-2), 152.44 (C-7), 151.51 (C-8′), 128.87 (C-5), 118.06 (C-6), 117.32 (C-4′),111.68 (C-8) , 47.84 (C-4), 39.96 (C-3), 34.05 (C-10′), 30.67 (C-10), 26.91 (C-11), 25.47 (C-11′), 22.22 (C-12), 22.11 (C-12′), 13.67(C-13, C-13′). HRMS, *m/z* (CI, CH_4): Calcd for $C_{19}H_{25}O_5$ (MH^+) 333.1711. Found 333.1702.

Decanoic acid 4-decanoyl-3,4-dihydrocoumarin-7-yl ester (11e). IR (KBr pellet) 1765 (CO, ester), 1695 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35 (1H, d, J = 8.4, H_5), 6.92

Scheme 7. Numbering of the hydrogens and carbons in compounds **7**, **11**, and **16**.



(1H, dd, J = 8.4 and 2.4 Hz, H_6), 6.831 (1H, d, J = 2.4 Hz, H_8), 3.97 (1H, dd, J = 6 and 2.4 Hz, H_4), 3.0 (1H, dd, J = 16.2 Hz and 1.4 Hz, C-$H_3\alpha$), 2.70 (1H, dd, J = 15.6 Hz and 5.4 Hz, $H_3\beta$), 2.56 (4H, m, H_{10}, $H_{10'}$), 1.75 (2H, m, $H_{11'}$), 1.75 (2H, m ,H_{11}), 1.28 (12H, m, $H_{12'}$–$H_{17'}$), 1.20 (12H, m, H_{12}–H_{17}), 0.87 (6H, m, H_{18} and H_{18}'). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 206.75 (C-9′), 171.98 (C-9), 166.21 (C-2), 152.45 (C-7), 151.49 (C-8′), 129.04 (C-5), 118.19 (C-6), 117.39 (C-4′), 111.74 (C-8) , 47.86 (C-4), 40.30 (C-3), 34.40 (C-10′), 31.94 (C-16, C-16′), 30.69 (C-10), 29.40 (C-13-C-15, C-11′-C-15′) 24.93 (C-11), 23.45 (C-12), 22.76 (C-17, C-17′), 14.20 (C-18, C-18′). HRMS, *m/z* (CI, CH_4): Calcd ($C_{29}H_{45}O_5$, MH^+) 473.3267, obsd 473.3253

Preparation of hydroxybenzofurans 16a–c, e, and f. The acetoxydihydrocoumarins (**11a–c** and **e**, 60 mg) were dissolved in 5 mL of methanol (for **16a–c**, **e**) or ethanol (**16f**) containing five to eight drops of hydrochloric acid. The reaction mixture was stirred at r.t. for 12 h and quenched by the addition of aqueous sodium bicarbonate solution (10 mL). The reaction mixture was then extracted with chloroform, dried over anhydrous Na_2SO_4, and evaporated to dryness at reduced pressure to yield the desired product. These compounds are essentially unknown. The only related compounds we have been able to locate in the literature are ethyl 4,6-dimethoxy-2-methyl-3-benzofuranacetate and its 2,5-dimethyl analog [9].

Methyl (6-hydroxy-2-methylbenzofuran-3-yl)-acetate (16a). Yield: 58%; white oily solid; R_f = 0.41 (50% hexane in ethyl acetate). ^{1}H-NMR (300 MHz ,$CDCl_3$): δ 7.23 (1H, d, J = 8.41 Hz, H_4), 6.84 (1H, d, J = 2.1 Hz, H_7), 6.70 (1H, dd, J = 8.41 Hz and 2.1 Hz, H_5), 3.7 (3H, s, $H_{9'}$), 3.59 (2H, s, H_8), 2.38 (3H, s, H_9). ^{13}C-NMR (75 MHz, $CDCl_3$) δ170.72 (C-8′), 154.72 (C-6), 153.34 (C-7′), 151.53 (C-2), 122.5 (C-3′), 118.97 (C-4), 111.47 (C-5), 107.28 (C-3), 98.15 (C-7), 52.45 (C-9′), 29.78 (C-8), 13.92 (C-9). HRMS, *m/z* (CI, CH_4): Calcd for $C_{12}H_{12}O_4$, (M^+) 220.0746. Found 220.0746.

Methyl (6-hydroxy-2-ethylbenzofuran-3-yl)-acetate (16b). Yield: 47%; yellow oil; R_f = 0.47 (50% hexane in ethyl acetate). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.252 (1H, d, J = 8.1 Hz, H_4), 6.859 (1H, d, $J_{5,7}$ = 2.1 Hz, H_7), 6.7 (1H, dd, J = 8.41 Hz and 2.1 Hz, H_5), 3.68 (3H, s, $H_{9'}$), 3.58 (2H, s, H_8), 2.73 (2H, q, $J_{9,10}$ = 7.5 Hz, H_9), 1.28 (3H, q, $J_{9,10}$ = 7.5 Hz, H_{10}). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.8 (C-8′), 156.46 (C-6), 154.76 (C-7′), 153.3 (C-2), 122.70 (C-3′), 119.37(C-4), 111.37 (C-5), 106.47 (C-3), 99.20 (C-7), 52.18 (C-9′), 29.65 (C-8), 19.86 (C-9), 12.70 (C-10). HRMS, *m/z* (CI, CH_4): Calcd for $C_{13}H_{14}O_4$ (M^+) 234.0892. Found 234.0863.

Methyl (6-hydroxy-2-n-propylbenzofuran-3-yl)-acetate (16c). Yield: 47%; yellow oil; R_f = 0.51 (50% hexane in ethyl acetate). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.27 (1H, d, J = 8.4 Hz, H_4), 6.92 (1H, d, $J_{7,5}$ = 2.1 Hz, H_7), 6.7 (1H, dd, J = 8.1 Hz and 2.1 Hz, H_5), 3.69 (3H, s, $H_{9'}$), 3.58 (2H, s, H_8), 2.64 (2H, t, $J_{9,10}$ = 7.2 Hz, H_9), 1.70 (2H, sex, $J_{9,10}$ = $J_{10,11}$ = 7.2 Hz, H_{10}), 0.955 (3H, t, $J_{10,11}$ = 7.2 Hz, H_{11}). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.22 (C-8′), 155.25 (C-6), 154.75 (C-7′), 153.23 (C-2), 122.66 (C-3′), 119.15 (C-4), 111.30 (C-5), 107.28 (C-3), 98.12 (C-7), 52.09 (C-9′), 29.70 (C-8), 28.23 (C-9), 21.50 (C-10) ,13.65 (C-11). HRMS, *m/z* (CI, CH_4): Calcd for $C_{14}H_{16}O_4$ (M^+) 248.1049. Found 248.1068.

Methyl (6-hydroxy-2-nonylbenzofuran-3-yl)-acetate (16e). Yield: 50%; yellow oil; R_f = 0.59 (50% hexane in ethyl acetate). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.26 (1H, d, J = 8.4 Hz, H_4), 6.89 (1H, d, $J_{7,5}$ = 2.4 Hz, H_7), 6.74 (1H, dd, J = 8.4 Hz and 2.4 Hz, H_5), 3.70 (3H, s, $H_{9'}$), 3.59 (2H, s, H_8), 2.71 (2H, t, $J_{9,10}$ = 7.5 Hz, H_9), 1.70 (2H, sex, $J_{15,16}$ = $J_{16,17}$ = 7.5 Hz, H_{16}), 1.37–1.25 (12H, m, H_{10}-H_{15}), 0.955 (3H, t, $J_{16,17}$ = 7.5 Hz, H_{17}). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.82 (C-8′), 155.56 (C-6), 154.83 (C-7′), 153.41 (C-2), 122.70 (C-3′), 119.28 (C-4), 111.39 (C-5), 107.19 (C-3), 98.22 (C-7), 52.28 (C-9′), 34.30 (C-8) 31.83 (C-15), 29.43 (C-11, C-12, C-13), 28.36 (C-9), 26.51 (C-14), 25.51 (C-10), 22.80 (C-16), 14.24 (C-17). HRMS, *m/z* (CI, CH_4): Calcd for $C_{20}H_{28}O_4$ (M^+) 322.1988. Found 332.1981.

Ethyl (6-hydroxy-2-methylbenzofuran-3-yl)-acetate (16f). Yield: 47%; yellow oil; R_f = 0.47 (50% hexane in ethyl acetate). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.272 (1H, d, J = 8.41 Hz, H_4), 6.917 (1H, d, J = 2.4 Hz, H_7), 6.80 (1H, dd, J = 8.41 Hz and 2.1, H_5), 4.10 (2H, q, J = 7.2 Hz, $H_{9'}$), 3.59 (3H, s, H_9), 2.34 (2H, s, H_8), 1.19 (3H, t, J = 7.2 Hz, $H_{10'}$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.73 (C-8′), 155.17 (C-6), 155.4 (C-7′), 150.55 (C-2), 122 (C-3′), 119.34 (C-4), 111.54 (C-5), 108.2 (C-3), 97.6 (C-7), 60.61 (C-9′), 13.92 (C-10′), 11.29 (C-9).

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