Synthesis of Psoralen Analogues Based on Dibenzofuran

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The syntheses of four novel psoralen derivatives, **6a**–**d**, of the benzofurocoumarin (= benzofuro[1]benzopyranone) type containing an ester group are described. These compounds might be of interest in PUVA (psoralen long-wave ultraviolet radiation) therapy. The overall efficiency of the synthetic procedure is greatly limited by the low yields for the penultimate step, *i.e.*, formylation of the dibenzofuranols **3a**,**c** or protected dibenzofuranol **4d** to the carboxaldehydes **5** (*Scheme 4*). However, the final stage to form the pyranone ring from **5a**–**d** proceeds smoothly (*Scheme 5*).

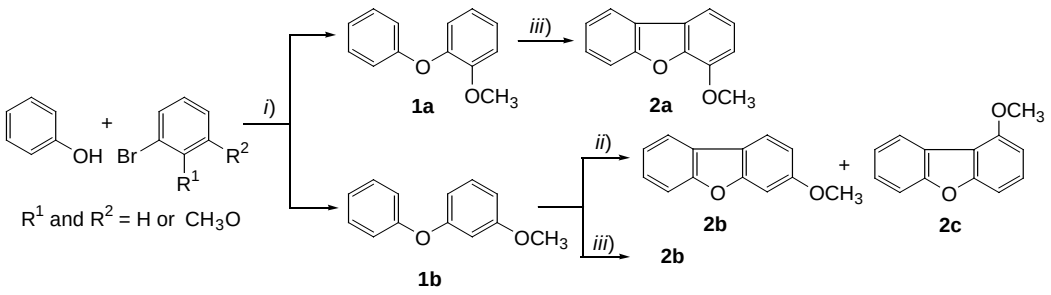
1. Introduction. – Benzopsoralens, which may be considered as benzofuro-fused coumarin systems (= benzofuro[1]benzopyranones), have previously been synthesized and their biological properties have been studied [1][2]. Introduction of a benzene ring fused to the furan moiety, or bulky or electron-withdrawing substituents at the pyranone ring have been proposed as potential ways to inhibit adduct formation with DNA [3]. In addition, *Gia et al.* [2] have shown that the introduction of an ester group into a benzopsoralen can provide derivatives that are efficient photosensitizers of singlet oxygen. Recently, the photophysical properties of three such compounds have been investigated, and it was shown that two of them could photochemically sensitize singlet-oxygen generation, with a quantum efficiency near unity. This efficiency is unusual for psoralens but is in accord with their measured long triplet lifetimes, and with their proposed state diagrams [4].

The purpose of this study was to synthesize new derivatives of this general type that have different fusion sites between the benzofuro and benzopyranone moieties, as a prelude to the study of their potential usefulness as photosensitizers in PUVA (= psoralen long-wave ultraviolet radiation) therapy. In the present work, we describe the preparation and characterization of four new psoralen analogues that are, potentially, strongly protected against DNA-adduct formation and in which both the furan ring is benzo-fused and the pyran ring is substituted with an electron withdrawing group.

2. Results and Discussion. – The synthesis of the dibenzofuran moiety of the benzopsoralens may be achieved by several methods. One approach involves *Goldberg*-type coupling [5] between phenol and bromoanisoles to give biphenyl ethers, which can then be cyclized. Thus, we obtained the diphenyl ethers **1a**,**b** in 78 and 93% yield, respectively (*Scheme 1*). Cyclization of compounds of type **1** to the dibenzofuran

system has been achieved either by oxidative coupling with palladium acetate [6] or by photolysis [7]. We found that cyclization with palladium acetate gave slightly better yields in AcOH than in CF_3COOH. For example, cyclization of **1a** with palladium acetate in AcOH gave **2a** in 15% yield, compared to 12% yield in CF_3COOH. Cyclization of **1b** with palladium acetate in AcOH gave only **2b** in 22% yield. On the other hand, photochemical cyclization of **1b** produced both MeO-substituted dibenzofurans **2b** and **2c**, in 9 and 30% yield, respectively (*Scheme 1*). Irradiation of **1a** under the same conditions gave only a complex mixture of unidentified products.

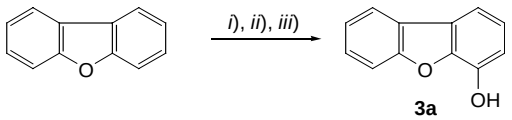
Scheme 1



i) K_2CO_3, Cu_2O, reflux. *ii*) C_6H_{12}, hν (150 W), I_2. *iii*) $Pd(OAc)_2$, AcOH or CF_3CO_2H (**1a**), Δ.

Demethylation of derivatives **2** with BBr_3 in CH_2Cl_2 [8] gave the corresponding dibenzofuranols **3a**–**c** in high yields (94–100%). Another satisfactory route to dibenzofuranol **3a** was the hydroxylation of commercial dibenzofuran by lithiation (*N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine ((TMEDA), BuLi) followed by treatment with tributylborate and hydrogen peroxide [9] (*Scheme 2*).

Scheme 2

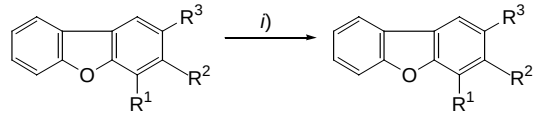


i) BuLi, TMEDA (= *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine), dry Et_2O, reflux. *ii*) $(BuO)_3B$, 0°. *iii*) H_2O_2, 0°, reflux.

To synthesize the coumarin part of the psoralen, several methods of formylation of dibenzofuranols **3a**–**c** and of the commercially available dibenzofuran-2-ol (**3d**) were attempted. The first approach involved protection of the OH function at C(2), C(3), or C(4) of the dibenzofuranols **3a**,**b**,**d** by conversion to the corresponding carbamates **4a**,**b**,**d**, which were obtained in good yields by reacting the benzopyranols **3** with $ClCONEt_2$ in pyridine [10] (*Scheme 3*) [11]. Subsequent formylation of **4d** by the method of *Snieckus* (*sec*-BuLi and TMEDA/THF at −78°, DMF treatment, and hydrolysis) giving the two aldehydes **5a** and **5b** (*Scheme 4*) in equal amounts (12% each). However, when the same procedure was applied to dibenzofuran-3-yl and dibenzofuran-4-yl carbamates **4b** and **4a**, respectively, only starting material was recovered. Similarly, attempted *Vilsmeier* formylation [12] of compounds **3a** and **3b** and

Duff formylation [13] of **3c** were unsuccessful, and none of the expected aldehydes could be detected. Finally, formylation of the dibenzofuranols **3a** and **3c** was attempted by the *Reimer-Tiemann* method [14][15] (*Scheme 4*), and, although the aldehydes **5c** and **5d** were obtained, the yields were low (13 and 17%, resp.).

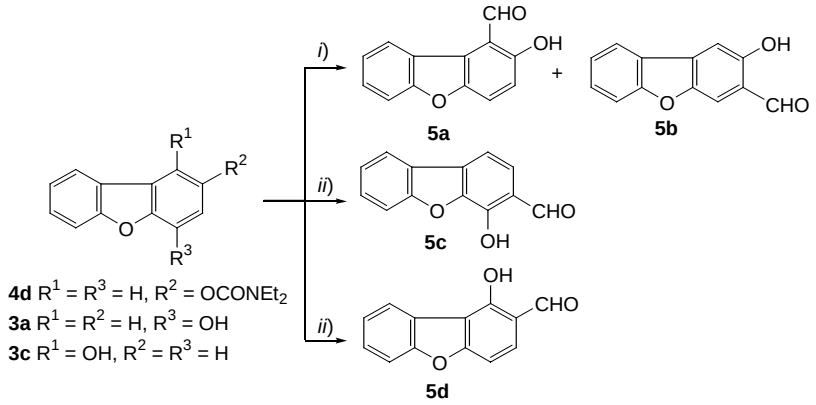
Scheme 3



3a R^1 = OH, R^2 = R^3 = H **4a** R^1 = $OCONEt_2$, R^2 = R^3 = H
b R^1 = R^3 = H, R^2 = OH **b** R^1 = R^3 = H, R^2 = $OCONEt_2$
d R^1 = R^2 = H, R^3 = OH **d** R^1 = R^2 = H, R^3 = $OCONEt_2$

i) $ClCONEt_2$, dry pyridine, 85°.

Scheme 4



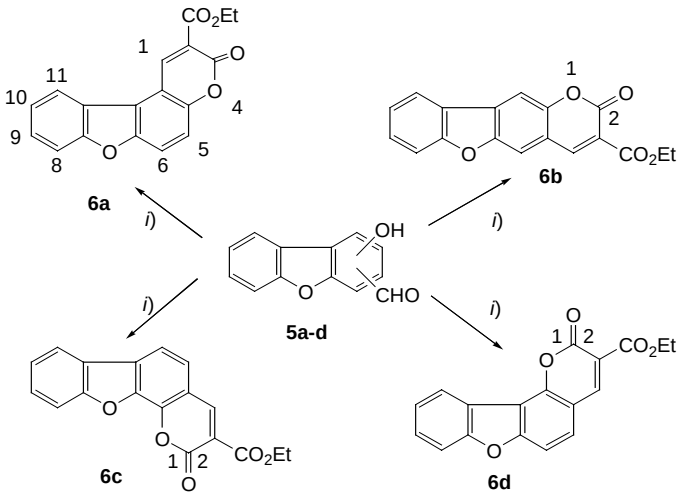
4d R^1 = R^3 = H, R^2 = $OCONEt_2$
3a R^1 = R^2 = H, R^3 = OH
3c R^1 = OH, R^2 = R^3 = H

i) 1. *sec*-BuLi, TMEDA, THF, –78°; 2. DMF. *ii*) 1. $CHCl_3$, NaOH, H_2O, Δ; 2. HCl.

Knoevenagel condensation [16] of *ortho*-hydroxyaldehydes **5a**–**d** with diethyl malonate in the presence of piperidine and AcOH (*Scheme 5*) afforded the corresponding final products **6a**–**d** in moderate to good yields. The structures of the products were confirmed by elemental analysis, mass spectrometry, IR spectroscopy, and also ^{1}H- and ^{13}C-NMR spectroscopy.

3. Conclusions. – The synthesis of the benzopsoralens **6a**–**d** requires the formylation of relevant intermediate dibenzofuranols **3**. Dibenzofuran-2-ol (**3d**) is commercially available, and **3a**–**c** can be obtained in a three-step synthesis involving sequential condensation of phenol with the appropriate bromoanisole, cyclization of the biphenyl ether, and demethylation of the resultant methoxydibenzofuran. Formylation proved difficult, and, when reactions were successful, yields were low. However, cyclization of the *o*-hydroxyaldehydes **5a**–**d** with diethyl malonate proceeded smoothly, readily giving the benzopsoralens **6a**–**d** in yields ranging from

Scheme 5



i) Diethyl malonate, piperidine, AcOH/EtOH, reflux.

20 to 87%. Studies on the therapeutic and/or toxic properties of the four novel compounds **6a**–**d** described in this paper are under way.

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Experimental Part

1. *General*. Light petroleum ether refers to solvent boiling in the range 40–60°. The photochemical experiments were conducted in a *Heraeus* UV-reactor system with a medium-pressure Hg-vapor immersion lamp (150 W). Column chromatography (CC): *Merck* silica gel *60* (70–230 mesh or 230–400 mesh). M.p.: *Gallenkamp* apparatus; uncorrected; for some compounds, no solvent of crystallization is indicated since the m.p. was determined for the compound obtained from CC. UV Spectra: *Hitachi 2000*; EtOH solns., λ_{max} (log ε [mol^{-1} dm^3 cm^{-1}]). IR Spectra: *Diffus IR-Bomem-MB* FT-IR spectrometer; in cm^{-1}. ^{1}H-NMR Spectra: *Varian Unity Plus* at 300 MHz (^{1}H) and 75.4 Hz (^{13}C); ^{1}H and ^{13}C assignments are based on irradiation and DEPT-45 experiments, resp.; $CDCl_3$ solns. (if not stated otherwise), δ in ppm rel. to internal $SiMe_4$ or solvent, resp., *J* in Hz. EI-MS and HR-MS: *AutoSpecE* spectrometer; in *m/z* (rel. %). Elemental analyses: *Leco CHNS-932*.

2. *Diphenyl Ethers: General Method*. A mixture of bromoanisole (=bromo(methoxy)benzene; 5.62 g, 30 mmol), phenol (3.5 g, 37 mmol), K_2CO_3 (2.1 g, 15 mmol), and Cu_2O (6.6 g, 46 mmol) was heated under reflux for 1 h. Another portion of phenol (0.5 g, 5 mmol) was added, and reflux was continued for another 1.5 h. After cooling, $CHCl_3$ (100 ml) was added, and the solids were separated by filtration. The org. soln. was washed with 1M NaOH (5 × 25 ml), dried ($MgSO_4$), and evaporated. The product was used without further purification.

2-Methoxyphenyl Phenyl Ether (=*1-Methoxy-2-phenoxybenzene*; **1a**): Yield 78%. Colorless crystals. M.p. 75.5–77.0° ([17]: 76°). IR (nujol): 1597, 1581, 1491, 1299, 1261, 1222, 1175, 1151, 1110, 1021, 871, 748, 688. ^{1}H-NMR: 7.31 (*dt*, *J* = 7.2, 2.0, H–C(3′) and H–C(5′)); 7.18–7.11 (*m*, H–C(4)); 7.06 (*tt*, *J* = 7.5, 1.0, H–C(4′)); 7.04–6.90 (*m*, 5 H); 3.85 (*s*, MeO).

3-Methoxyphenyl Phenyl Ether (=*1-Methoxy-3-phenoxybenzene*; **1b**): Yield 93%. Colorless oil [18]. IR (neat): 3066, 3039, 3004, 2958, 2940, 2835, 1586, 1486, 1450, 1263, 1217, 1139, 1042, 952, 759, 689. ^{1}H-NMR: 7.36

(*dt*, *J* = 7.2, 1.9, H–C(3′), H–C(5′)); 7.24 (*t*, *J* = 8.0, H–C(5)); 7.13 (*tt*, *J* = 7.5, 1.2, H–C(4′)); 7.05 (*dd*, *J* = 8.7, 1.2, H–C(2′), H–C(6′)); 6.70–6.65 (*m*, H–C(6)); 6.63–6.59 (*m*, H–C(4)); 6.60 (*t*, *J* = 2.1, H–C(2)); 3.80 (*s*, MeO).

3. *Cyclization of Diphenyl Ethers with Palladium Acetate: General Method*. 3.1. *In AcOH:* A mixture of **1a** or **1b** (0.7 g, 3.5 mmol), $Pd(OAc)_2$, (0.7 g, 3.1 mmol), and 99.4% AcOH (8 ml) was refluxed for 7 h. After cooling, $CHCl_3$ (50 ml) was added, the mixture filtered, and the solvent evaporated. The residual AcOH was removed by repeated codistillation with hexane. The dark brown oily residue was purified by CC (silica gel, $CHCl_3$/light petroleum ether 8:92): **2a** (15%) or **2b** (22%), resp.

4-Methoxydibenzofuran (**2a**): Colorless crystals. M.p. 49.0–50.5° ([19]: 52° (petroleum ether)). IR (KBr): 1636, 1601, 1583, 1502, 1451, 1428, 1334, 1312, 1272, 1196, 1180, 1152, 1131, 1095, 1023, 1008, 933, 844, 825, 783. ^{1}H-NMR: 7.95 (br. *d*, *J* = 7.5, H–C(9)); 7.64 (br. *d*, *J* = 8.4, H–C(6)); 7.57 (br. *d*, *J* = 7.8, H–C(3) or H–C(1)); 7.48 (*dt*, *J* = 7.2, 1.2, H–C(7)); 7.36 (*dt*, *J* = 7.2, 0.9, H–C(8)); 7.29 (*t*, *J* = 7.8, H–C(2)); 7.01 (*dd*, *J* = 8.1, 0.9, H–C(1) or H–C(3)); 4.08 (*s*, MeO).

3-Methoxydibenzofuran (**2b**): Colorless crystals. M.p. 81.0–83.0° ([20]: 95.0–95.5°). IR (KBr): 1635, 1604, 1501, 1457, 1440, 1302, 1278, 1195, 1188, 1150, 1115, 1100, 1033, 938, 847, 830, 817, 761, 750, 720. ^{1}H-NMR: 7.87 (br. *d*, *J* = 7.7, H–C(9)); 7.82 (*d*, *J* = 8.5, H–C(1)); 7.54 (br. *d*, *J* = 7.7, H–C(6)); 7.38 (*dt*, *J* = 7.7, 1.5, H–C(7)); 7.32 (*dt*, *J* = 7.7, 1.5, H–C(8)); 7.11 (*d*, *J* = 2.3, H–C(4)); 6.96 (*dd*, *J* = 8.5, 2.3, H–C(2)); 3.92 (*s*, MeO).

3.2. *In CF_3CO_2H*. A mixture of **1a** (1.0 g, 5.0 mmol), palladium acetate (1.3 g, 5.8 mmol), and 99% CF_3COOH (12 ml) was refluxed for 1 h. After cooling, Et_2O (50 ml) was added, the mixture filtered, and the solvent evaporated. The residual acid was removed by repeated codistillation with hexane. The dark brown oily residue was purified by CC (silica gel, $CHCl_3$/light petroleum ether 8:92): **2a** (12%). M.p. and spectroscopic data: identical to those reported above for **2a**.

4. *Dibenzofurans by Photochemical Cyclization: General Method.* A soln. of **1b** (0.6 g, 3.0 mmol) and I_2 (0.6 g) in cyclohexane (700 ml) was irradiated for 17 h. The solvent was evaporated and collected for reuse in further experiments. The remaining dark brown solids from several experiments were combined and then purified by CC (silica gel, light petroleum ether/$CHCl_3$ of increasing polarity): **2c** (30%) and then **2b** (9%).

1-Methoxydibenzofuran (**2c**). Colorless crystals. M.p. 53.5–55.0° ([21]: 56.0–57.5°). IR (nujol): 1597, 1504, 1276, 1236, 1196, 1090, 847, 784, 751, 717. ^{1}H-NMR: 8.15 (br. *d*, *J* = 7.5, H–C(9)); 7.56 (br. *d*, *J* = 7.8, H–C(6)); 7.43 (*dt*, *J* = 7.2, 1.2, H–C(7)); 7.40 (*t*, *J* = 8.1, H–C(3)); 7.35 (*dt*, *J* = 7.2, 1.0, H–C(8)); 7.21 (*d*, *J* = 8.1, H–C(4)); 6.81 (*d*, *J* = 8.1, H–C(2)); 4.07 (*s*, MeO).

3-Methoxydibenzofuran (**2b**): Colorless crystals. For data, see above.

5. *Demethylation with BBr_3: General Method*. To a soln. of methoxydibenzofuran **2a**–**c** (0.33 g, 1.66 mmol) in dry CH_2Cl_2 at −78°, 1M BBr_3 in CH_2Cl_2 (3.32 ml, 3.32 mmol) was added under N_2. The mixture was stirred overnight at r.t., crushed ice (100 g) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined org. layers were extracted with 1M NaOH (3 × 20 ml) and then acidified with 5M HCl. The aq. layer was extracted with Et_2O (3 × 30 ml) and the combined org. extract dried ($MgSO_4$) and evaporated: **3a** (100%), **3b** (97%), or **3c** (94%), resp., which were used without further purification.

Dibenzofuran-4-ol (**3a**): Off-white solid. M.p. 99–101° ([19]: 102° (petroleum ether or H_2O)). IR (nujol): 3192 (OH), 1639, 1604, 1311, 1249, 1192, 1080, 1050, 926, 844, 745. ^{1}H-NMR: 7.95 (br. *d*, *J* = 7.5, H–C(9)); 7.60 (br. *d*, *J* = 8.4, H–C(6)); 7.53 (*dd*, *J* = 7.8, 1.0, H–C(1) or H–C(3)); 7.48 (*dt*, *J* = 8.4, 1.2, H–C(7)); 7.36 (*dt*, *J* = 7.5, 1.2, H–C(8)); 7.23 (*t*, *J* = 7.8, H–C(2)); 7.03 (*dd*, *J* = 8.1, 1.0, H–C(3) or H–C(1)); 5.50 (br. *s*, OH).

Dibenzofuran-3-ol (**3b**): Off-white solid. M.p. 137.0–138.5° ([20]: 141.0–141.5° (H_2O)). IR (nujol): 3421 (OH), 1638, 1600, 1499, 1276, 1142, 1123, 950, 848, 741, 721. ^{1}H-NMR: 7.86 (br. *d*, *J* = 7.5, H–C(9)); 7.79 (*d*, *J* = 8.4, H–C(1)); 7.53 (br. *d*, *J* = 7.8, H–C(6)); 7.39 (*dt*, *J* = 7.5, 1.5, H–C(7)); 7.32 (*dt*, *J* = 7.2, 0.9, H–C(8)); 7.06 (*d*, *J* = 2.4, H–C(4)); 6.87 (*dd*, *J* = 8.1, 2.1, H–C(2)); 5.21 (*s*, OH).

Dibenzofuran-1-ol (**3c**): Off-white solid. M.p. 136–138° ([22]: 140.0–140.5° (H_2O)). IR (nujol): 3271 (OH), 1640, 1598, 1503, 1271, 1234, 1196, 1030, 1106, 775, 738, 709. ^{1}H-NMR: 8.12 (br. *d*, *J* = 7.5, H–C(9)); 7.56 (br. *d*, *J* = 7.8, H–C(6)); 7.45 (*dt*, *J* = 8.1, 1.5, H–C(7)); 7.36 (*dt*, *J* = 7.2, 1.2, H–C(8)); 7.30 (*t*, *J* = 8.4, H–C(3)); 7.18 (*dd*, *J* = 8.4, 0.6, H–C(2) or H–C(4)); 6.72 (*dd*, *J* = 8.1, 0.6, H–C(4) or H–C(2)); 5.55 (br. *s*, OH).

6. *Hydroxylation of Dibenzofuran: Dibenzofuran-4-ol* (**3a**). To a soln. of commercial dibenzofuran (2.0 g, 11.9 mmol) in dry Et_2O (50 ml) and *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA; 2.3 g, 14.2 mmol), 2.5M BuLi in hexanes (5.0 ml, 12.5 mmol) was added with stirring under N_2. The mixture was refluxed for 1 h (→ yellow precipitate) and then cooled to 0°. Tributyl borate (3.9 ml, 14.2 mmol) was added until the precipitate disappeared. After 45 min, the mixture was left for 1 h while it reached r.t. After cooling again to 0°, 30% H_2O_2 soln. (5 ml) was added dropwise with vigorous stirring (→ light yellow precipitate). This mixture was refluxed for 1.5 h, then cooled to 0° and acidified with 5M HCl (10 ml). The org. phase was washed with cold 10%

ammonium iron(II) sulfate ($(NH_4)_2Fe(SO_4)_2 \cdot H_2O$) soln. (2 × 50 ml) and extracted with 2M NaOH (3 × 50 ml). The combined aq. extract was acidified, extracted with Et_2O (3 × 100 ml), and dried ($MgSO_4$). Evaporation gave an orange oil (2.15 g) which was filtered through silica gel with 15% Et_2O/light petroleum ether: **3a** (1.56 g, 71%). Off-white solid. M.p. and spectroscopic data: identical with those reported above for **3a**.

7. *Carbamates: General Method:* A soln. of dibenzofuranol **3a**,**b**,**d** (0.6 g, 3.26 mmol) in dry pyridine (3 ml) and diethylcarbamic chloride (0.48 ml, 3.76 mmol) was heated for 15 h at 85°. The mixture was poured onto crushed ice (75 mg) and extracted with Et_2O (3 × 25 ml), and the org. extract was washed with 2M NaOH (3 × 25 ml) and H_2O (3 × 25 ml), dried ($MgSO_4$), and evaporated: **4a** (98%), **4b** (85%), or **4d** (69%), resp., brown oils, which were used without further purification.

Dibenzofuran-4-yl Diethylcarbamate (**4a**): Light brown oil. IR (neat): 3390, 3062, 2975, 2934, 1727 (C=O), 1588, 1473, 1452, 1421, 1309, 1274, 1253, 1212, 1153, 1084, 963, 847, 750. ^{1}H-NMR: 7.95 (br. *d*, *J* = 8.1, H–C(9)); 7.79 (*dd*, *J* = 7.2, 2.1, H–C(3) or H–C(1)); 7.59 (br. *d*, *J* = 7.8, H–C(6)); 7.46 (*dt*, *J* = 8.4, 1.2, H–C(7)); 7.35 (*dt*, *J* = 7.5, 1.2, H–C(8)); 7.35–7.26 (*m*, 3 H); 3.55 (*m*, 2 MeCH_2); 1.35 (*m*, 2 *Me*CH_2).

Dibenzofuran-3-yl Diethylcarbamate (**4b**): Light brown oil. IR (neat): 3348, 3071, 2975, 2934, 1723 (C=O), 1602, 1589, 1455, 1416, 1381, 1253, 1158, 1115, 968, 751, 722. ^{1}H-NMR: 7.93 (br. *d*, *J* = 7.5, H–C(9)); 7.90 (*d*, *J* = 8.3, H–C(1)); 7.56 (br. *d*, *J* = 7.5, H–C(6)); 7.44 (*dt*, *J* = 7.5, 1.3, H–C(7)); 7.39 (*d*, *J* = 2.0, H–C(4)); 7.34 (*dt*, *J* = 7.5, 1.3, H–C(8)); 7.14 (*dd*, *J* = 8.3, 1.8, H–C(2)); 3.45 (*m*, 2 MeCH_2); 1.25 (*m*, 2 *Me*CH_2).

Dibenzofuran-2-yl Diethylcarbamate (**4d**): Light brown oil. IR (neat): 3411, 3064, 2975, 2934, 1720 (C=O), 1590, 1470, 1448, 1418, 1262, 1210, 1166, 962, 843, 750. ^{1}H-NMR: 7.91 (br. *d*, *J* = 7.5, H–C(9)); 7.73 (*d*, *J* = 2.4, H–C(1)); 7.57 (br. *d*, *J* = 7.5, H–C(6)); 7.54 (*d*, *J* = 9.0, H–C(4)); 7.47 (*dt*, *J* = 7.5, 1.0, H–C(7)); 7.34 (*dt*, *J* = 7.2, 1.0, H–C(8)); 7.21 (*dd*, *J* = 9.0, 2.1, H–C(3)); 3.50 (*m*, 2 MeCH_2); 1.30 (*m*, 2 *Me*CH_2).

8. *Formylation of Carbamate* **4d**. A soln. of 0.13M *sec*-BuLi in cyclohexane (1.5 ml, 1.95 mmol) was added under N_2 to a stirred mixture of TMEDA (0.314 g, 1.95 mmol) in dry THF at −78°. After 5 min, a soln. of **4d** (0.500 g, 1.77 mmol) in dry THF (6 ml) was added. After 90 min, DMF (0.285 g, 3.9 mmol) was added, and the mixture was left for 1.5 h while it reached r.t. and then stirred for 48 h (yellow → brown). Sat. NH_4Cl soln. (75 ml) was added, and the mixture was extracted with $CHCl_3$ (3 × 20 ml). The combined org. extract was dried ($MgSO_4$) and evaporated and the brown oil submitted to CC (silica gel, 5% $CHCl_3$/light petroleum): **5a** (12%) and then **5b** (12%).

2-Hydroxydibenzofuran-1-carboxaldehyde (**5a**): Yellow solid. M.p. 135–138° ([15]: 118–121°). IR (KBr): 3442, 3068, 2925, 2882, 1648 (C=O), 1621, 1577, 1502, 1456, 1436, 1387, 1359, 1297, 1255, 1176, 1022, 992, 914, 840, 799, 747. ^{1}H-NMR: 11.68 (*s*, OH); 10.94 (*s*, CHO); 8.04 (br. *d*, *J* = 7.8, H–C(9)); 7.76 (*d*, *J* = 9.0, H–C(4)); 7.64 (br. *d*, *J* = 8.1, H–C(6)); 7.56 (*dt*, *J* = 7.5, 1.2, H–C(7)); 7.41 (*dt*, *J* = 7.5, 1.2, H–C(8)); 7.09 (*d*, *J* = 9.0, H–C(3)). ^{13}C-NMR: 192.59 (*s*, CHO); 159.57 (*s*); 157.11 (*s*); 149.34 (*s*); 128.21 (*d*); 123.92 (*s*); 123.34 (*d*, 2 × CH); 122.47 (*s*); 121.00 (*d*); 116.94 (*d*); 114.49 (*s*); 112.42 (*d*). Anal. calc. for $C_{13}H_8O_3$: C 73.58, H 3.80; found: C 73.38, H 4.02.

2-Hydroxydibenzofuran-3-carboxaldehyde (**5b**): Yellow solid (12%). M.p. 214–216°. IR (KBr): 3432, 3070, 2926, 2872, 1659 (C=O), 1581, 1438, 1383, 1341, 1298, 1196, 863, 818, 784, 749. ^{1}H-NMR: 11.04 (*s*, OH); 10.00 (*s*, CHO); 7.99 (br. *d*, *J* = 7.8, H–C(9)); 7.72 (*s*, H–C(4)); 7.59–7.57 (*m*, H–C(7)); 7.51 (*s*, H–C(1)); 7.41–7.36 (*m*, H–C(6) and H–C(8)). ^{13}C-NMR: 195.71 (*s*, CHO); 158.74 (*s*); 157.72 (*s*); 149.29 (*s*); 132.52 (*s*); 129.86 (*d*); 123.13 (*d*); 122.17 (*d*); 119.02 (*s*); 115.25 (*d*); 112.08 (*d*); 107.94 (*d*); one signal is missing, possibly hidden under δ 157.72 or 119.02. Anal. calc. for $C_{13}H_8O_3$: C 73.58, H 3.80; found: C 73.28, H 3.96.

9. Reimer-Tiemann *Formylation*. Dibenzofuranol **3a** or **3c** (0.480 g, 2.6 mmol) was dissolved in H_2O (50 ml) containing NaOH (1.04 g, 26 mmol), and the soln. was heated to 60–65°, with stirring. $CHCl_3$ (0.930 g, 7.8 mmol) was added over 30 min. Then the mixture was heated to 90° and maintained at this temp. for 15 min. After cooling, the mixture was acidified with 2M HCl and extracted with Et_2O (3 × 25 ml). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated giving a brown solid that was impure (TLC). Purification by CC (silica gel, Et_2O/light petroleum ether 5:95) gave **5c** (13%) or **5d** (17%), resp.

4-Hydroxydibenzofuran-3-carboxaldehyde (**5c**): Light yellow solid. M.p. 165–167°. IR (KBr): 3200, 3058, 2923, 2848, 1664 (C=O), 1571, 1494, 1471, 1455, 1430, 1394, 1336, 1278, 1216, 1091, 966, 930, 861, 806, 792, 767, 726. ^{1}H-NMR: 11.61 (*s*, OH); 10.04 (*s*, CHO); 8.01 (br. *d*, *J* = 8.4, H–C(9)); 7.70 (br. *d*, *J* = 8.4, H–C(6)); 7.61 (*d*, *J* = 8.4, H–C(2)); 7.59 (*dt*, *J* = 7.0, 1.2, H–C(7)); 7.54 (*d*, *J* = 8.1, H–C(1)); 7.42 (*dt*, *J* = 7.8, 1.2, H–C(8)). ^{13}C-NMR: 196.38 (*s*, CHO); 157.68 (*s*); 148.11 (*s*); 143.11 (*s*); 131.99 (*s*); 129.32 (*d*); 127.61 (*d*); 123.41 (*d*); 123.20 (*s*); 121.63 (*d*); 118.93 (*s*); 112.43 (*d*); 111.64 (*d*). EI-MS: 213 (17, $[M+1]^+$), 212 (100, M^+), 211 (100), 166 (10), 127 (12), 92 (8), 77 (6), 75 (6), 63 (6). HR-MS: 212.0482 (M^+, $C_{13}H_8O_3^+$; calc. 212.0473).

1-Hydroxydibenzofuran-2-carboxaldehyde (**5d**): Yellow solid. M.p. 111–113° ([23]: m.p. not quoted). IR (KBr): 3429, 3128, 2924, 2853, 2831, 1659 (C=O), 1584, 1146, 1427, 1368, 1291, 1280, 1247, 1210, 1192, 1088, 1032,

841, 755, 658. ^{1}H-NMR: 12.09 (*s*, OH); 9.96 (*s*, CHO); 8.21 (br. *d*, *J* = 7.2, H–C(9)); 7.63 (*d*, *J* = 8.4, H–C(3)); 7.60 (br. *d*, *J* = 7.2, H–C(6)); 7.50 (*dt*, *J* = 8.1, 1.5, H–C(7)); 7.43 (*dt*, *J* = 7.5, 1.2, H–C(8)); 7.23 (*d*, *J* = 8.4, H–C(4)). ^{13}C-NMR: 195.75 (*s*, CHO); 161.66 (*s*); 159.10 (*s*); 155.82 (*s*); 132.84 (*d*); 127.07 (*d*); 123.81 (*d*); 123.09 (*d*); 122.56 (*s*); 116.08 (*s*); 113.16 (*s*); 111.32 (*d*); 104.59 (*d*). EI-MS: 213 (14, $[M+1]^+$), 212 (100, M^+), 211 (76), 183 (10), 155 (13), 149 (11), 127 (9), 97 (8), 83 (8), 71 (9), 69 (10). HR-MS: 212.0467 (M^+, $C_{13}H_8O_3^+$; calc. 212.0473).

10. *Coumarins* **6** *by* Knoevenagel *Condensation of the* ortho-*Hydroxyaldehydes* **5**: *General Method*. To a soln. of *ortho*-hydroxyaldehyde **5** (0.0375 g, 0.177 mmol) in hot EtOH (10 ml) was added a soln. of diethyl malonate (0.032 g, 0.20 mmol) in EtOH (1 ml), piperidine (1 drop), and AcOH (1 drop). The mixture was refluxed for 5 h and then left at 0° overnight. The precipitate obtained was filtered and recrystallized from EtOH.

*Ethyl 3-Oxo-3*H-*benzofuro[3,2-*f*]-1-benzopyran-2-carboxylate* (**6a**): From **5a**. Yield 68%. Yellow crystals. M.p. 167–169° (EtOH). UV: 349 (4.25). IR (KBr): 3088, 2997, 2941, 1771*s* (br., C=O), 1615, 1567, 1478, 1448, 1432, 1372, 1280, 1236, 1126, 1096, 1034, 979, 950, 818, 794, 750. ^{1}H-NMR: 9.30 (*s*, H–C(1)); 8.22 (br. *d*, *J* = 8.4, H–C(11)); 7.86 (*d*, *J* = 9.0, H–C(5) or H–C(6)); 7.70 (br. *d*, *J* = 8.4, H–C(8)); 7.61 (*dt*, *J* = 7.5, 1.5, H–C(9)); 7.50 (*dt*, *J* = 7.5, 1.5, H–C(10)); 7.47 (*d*, *J* = 9.0, H–C(6) or H–C(5)); 4.50 (*q*, *J* = 7.2, MeC*H*$_2$); 1.50 (*t*, *J* = 7.2, *Me*CH$_2$). EI-MS: 309 (20, $[M+1]^+$), 308 (100, M^+), 263 (52), 236 (61), 208 (29), 179 (30), 150 (12). Anal. calc. for $C_{18}H_{12}O_5$: C 70.13, H 3.92; found: C 69.86, H 4.05.

*Ethyl 2-Oxo-2*H-*benzofuro[2,3-*g*]-1-benzopyran-3-carboxylate* (**6b**): From **5b**. Yield 87%. Yellow crystals. M.p. 186–187°(EtOH). UV: 348 (4.47). IR (KBr): 3063, 2983, 2905, 1760*s* (br., C=O), 1638, 1613, 1568, 1455, 1433, 1396, 1366, 1257, 1206, 1040, 859, 798, 749. ^{1}H-NMR ((D$_6$)acetone): 8.85 (*s*, H–C(4)); 8.30 (br. *d*, *J* = 7.5, H–C(10)); 8.17 (*s*, H–C(11) or H–C(5)); 8.16 (*s*, H–C(5) or H–C(11)); 7.74 (br. *d*, *J* = 8.9, H–C(7)); 7.70 (*dt*, *J* = 7.8, 1.2, H–C(8)); 7.51 (*dt*, *J* = 7.2, 1.5, H–C(9)); 4.37 (*q*, *J* = 7.2, MeC*H*$_2$); 1.38 (*t*, *J* = 7.2, *Me*CH$_2$). EI-MS: 309 (20, $[M+1]^+$), 308 (100, M^+), 263 (68), 236 (65), 208 (30), 179 (34), 150 (11). Anal. calc. for $C_{18}H_{12}O_5$: C 70.13, H 3.92; found: C 70.28, H 4.10.

*Ethyl 2-Oxo-2*H-*benzofuro[3,2-*h*]-1-benzopyran-3-carboxylate* (**6c**): From **5c**. Yield 44%. Light yellow crystals. M.p. 215–217° (EtOH) UV: 341 (4.27). IR (KBr): 3057, 2967, 1755 (C=O), 1693 (C=O), 1638, 1609, 1552, 1474, 1432, 1364, 1312, 1259, 1215, 1026, 976. ^{1}H-NMR: 8.70 (*s*, H–C(4)); 8.03 (br. *d*, *J* = 7.5, H–C(7)); 7.89 (*d*, *J* = 8.4, H–C(5)); 7.73 (br. *d*, *J* = 8.1, H–C(10)); 7.62 (*dt*, *J* = 7.2, 1.5, H–C(9)); 7.56 (*d*, *J* = 8.1, H–C(6)); 7.46 (*dt*, *J* = 7.5, 0.9, H–C(8)); 4.45 (*q*, *J* = 7.2, MeC*H*$_2$); 1.45 (*t*, *J* = 7.2, *Me*CH$_2$). MS: 309 (20, $[M+1]^+$), 308 (100, M^+), 263 (80), 236 (60), 208 (40), 179 (47), 150 (18). HR-MS: 308.0690 (M^+, $C_{18}H_{12}O_5^+$; calc. 308.0685).

*Ethyl 2-Oxo-2*H-*benzofuro[2,3-*h*]-1-benzopyran-3-carboxylate* (**6d**): From **5d**. Yield 20%. Light yellow crystals. M.p. 172–175° (EtOH). UV: 333 (4.22). IR (KBr): 3053, 2985, 2923, 1742 (C=O), 1700 (C=O), 1611, 1567, 1436, 1287, 1245, 1209, 1059, 812, 753. ^{1}H-NMR: 8.72 (*s*, H–C(4)); 8.45 (br. *d*, *J* = 8.7, H–C(11)); 7.69 (*d*, *J* = 8.4, H–C(5)); 7.66 (br. *d*, *J* = 8.4, H–C(8)); 7.58 (*dt*, *J* = 7.5, 1.5, H–C(9)); 7.56 (*d*, *J* = 8.4, H–C(6)); 7.50 (*dt*, *J* = 7.2, 1.2, H–C(10)); 4.45 (*q*, *J* = 7.2, MeC*H*$_2$); 1.45 (*t*, *J* = 7.2, *Me*CH$_2$). EI-MS: 309 (20, $[M+1]^+$), 308 (100, M^+), 263 (69), 236 (48), 208 (29), 179 (32). HR-MS: 308.0689 (M^+, $C_{18}H_{12}O_5^+$; calc. 308.0685).

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