Synthesis of Two Natural Furan-Cyclized Diarylheptanoids *via* 2-Furaldehyde

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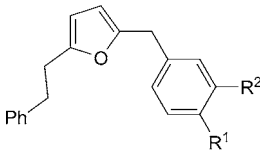
Two natural diarylheptanoids, 2-benzyl-5-(2-phenylethyl)furan (**1**) and 2-methoxy-4-{[5-(2-phenylethyl)furan-2-yl]methyl}phenol (**2**), were synthesized starting from 2-furaldehyde. A *Wittig* reaction of 2-furaldehyde with benzyltriphenylphosphonium bromide followed by reduction of the alkene C=C bond with Mg gave 2-(2-phenylethyl)furan (**5**). Lithiation of **5** with BuLi at $-78°$ followed by alkylation with benzyl bromide gave natural product **1**. In another approach, *Friedel–Crafts* acylation of compound **5** with benzoyl chloride followed by deoxygenation of the C=O group afforded **1**. The natural product **2** was also synthesized by acylation of **5** with 4-acetoxy-3-methoxybenzoyl chloride (**16**) followed by deoxygenation and deacetylation.

Introduction. – Diarylheptanoids, bearing two aryl groups at C(1) and C(7) of a C_7-chain, are a special class of natural products. So far, over 400 naturally occurring diarylheptanoids have been isolated from nature and reviewed in different articles [1–6]. In general, diarylheptanoids are classified into three categories: *i*) linear diarylheptanoids, *ii*) macrocyclic biarylheptanoids, and *iii*) macrocyclic diaryl ether heptanoids. Besides these three classes, there are also few C_7 chain-cyclized diarylheptanoids. In particular, 'pyran-cyclized' natural diarylheptanoids with the structure of 2-arylethyl-6-aryl-tetrahydro-2*H*-pyran have been long known. However, 'furan-cyclized' natural diarylheptanoids were only recently discovered, and there are only two examples of them in the literature (*Fig.*). *Sun et al.* [7] isolated two furan-cyclized diarylheptanoids **1** and **2** from rhizomes of *Alpinia officinarum* HANCE (Zingiberaceae) as minor components in milligram quantities and reported compound **2** as having moderate cytotoxic activity against the IMR-32 human neuroblastoma cell line. In a different study, *An et al.* [8] also isolated compound **2** from rhizomes of *Alpinia officinarum*. To the best of our knowledge, there is no described synthetic method for the preparation of compounds **1**[1]) and **2**. We assume that a synthetic methodology for the preparation of compounds **1** and **2** would facilitate further chemical and biological studies on these compounds. Therefore, we herein present a synthetic methodology for preparation of compounds **1** and **2**.

Results and Discussion. – We used 2-furaldehyde as the starting compound to synthesize natural product **1**. First benzyl bromide **3** was reacted with PPh_3 to give benzylphosphonium bromide, which was then condensed with 2-furaldehyde by *Wittig*

[1]) In spite of the use of compound **1** in the synthesis of some naphthofuran derivatives, no descriptions for its preparation are given. See [9].



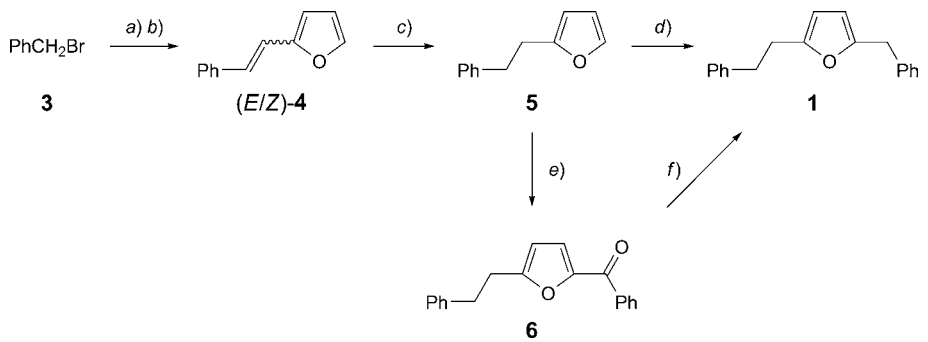
	R^1	R^2
1	H	H
2	OH	MeO

Figure. *'Furan-cyclized' natural diarylheptanoids*

reaction to give (*E*/*Z*)-2-styrylfuran (**4**) in a yield of 87%. *Cabares* and *Mavoungou-Gomes* [10] selectively reduced **4** with Mg to afford 2-(2-phenylethyl)furan (**5**). Following this procedure, we reduced **4** to give **5** in a good yield (82%). Lithiation of **5** by treatment with BuLi followed by addition of benzyl bromide (**3**) gave natural product **1** (78%). In a second synthetic method, we reacted 2-(2-phenylethyl)furan with benzoyl chloride in the presence of $AlCl_3$ to give ketone **6** (73%). *Box* and *Meleties* [11] developed a method for deoxygenation of aromatic aldehydes and ketones by reduction with $NaBH_3CN$/TMSCl. We applied this methodology for the reduction of **6** to give **1** (81%; *Scheme 1*).

We assumed that the synthesis of natural product **2** could be performed by incorporating a 4-hydroxy-3 methoxy-benzyl(benzoyl) moiety to 2-(2-phenylethyl)furan (**5**) as in the synthesis of **1**. In this context, we thought that the most suitable starting material was vanillin (**7**) for the preparation of the 4-hydroxy-3-methoxy-benzyl(benzoyl) residue. For this purpose, starting with **7**, we prepared two *O*-MOM and *O*-TBDPS protected vanillin compounds **8** and **9** (*Scheme 2*) and submitted them to a reaction with lithiated **5**. Although a reaction occurred, the product decomposed within a short time. Secondly, we prepared the *O*-TBDPS protected benzyl iodide **11** as an alkylating reagent and submitted it to the reaction with lithiated **5**. In this reaction, an alkylation product was not observed. Thirdly, benzoyl chloride **13** was prepared as an

Scheme 1

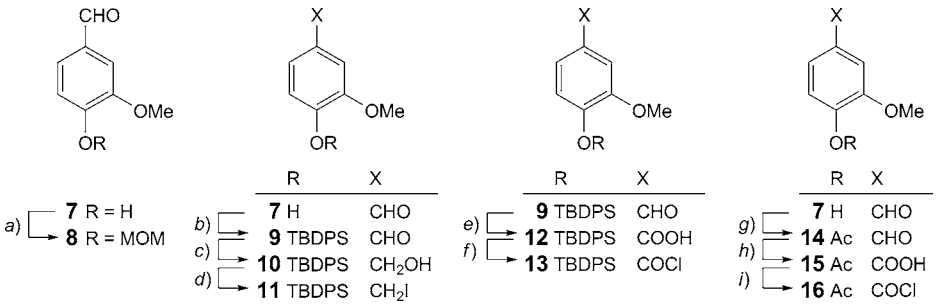


a) PPh_3, MeCN, N_2 atm, reflux, 24 h, quant. *b*) NaH, CH_2Cl_2, N_2 atm, 0°, then 2-furaldehyde, 48 h, 87%. *c*) Mg, MeOH, reflux, 6 h, 82%. *d*) BuLi, THF, N_2 atm, $-78° \rightarrow -5°$, then $PhCH_2Br$, r.t., 12 h, 78%. *e*) PhCOCl, $AlCl_3$, CH_2Cl_2, N_2 atm, 0°, 30 min, 73%. *f*) $NaBH_3CN$/TMSCl, MeCN, N_2 atm, $0° \rightarrow 25°$, 12 h, 81%.

acylating reagent and submitted to the reaction with **5** in the presence of $AlCl_3$. Unfortunately, no acylation occurred. We supposed that the bad reactivity of compounds **11** and **13** was due to the protecting groups. Therefore, we decided to change the protecting group, and we prepared 4-(acetyloxy)-3-methoxybenzoyl chloride (**16**) as outlined in *Scheme 2*.

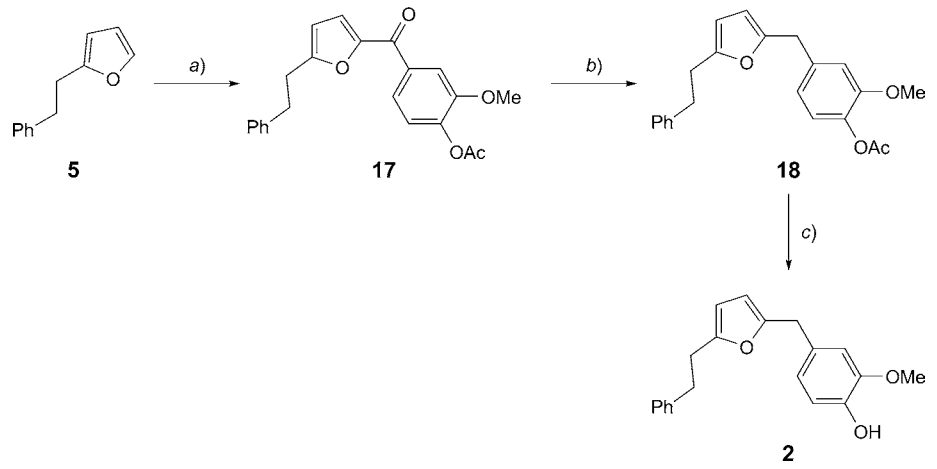
After the preparation of benzoyl chloride **16**, it was condensed with 2-(2-phenylethyl)furan (**5**) by *Friedel–Crafts* reaction to give ketone **17** in a moderate yield (59%). Deoxygenation of ketone by reduction with $NaBH_3CN$/TMSCl afforded **18** (80%), from which the natural product **2** was obtained by deacetylation with aqueous $NaHCO_3$ solution (83%; *Scheme 3*).

Scheme 2



a) MOMCl, NaH, DMF, N_2 atm, 0° → 25°, 5 h, 86%. *b*) TBDPSCl, imidazole, CH_2Cl_2, 25°, 12 h, 91%. *c*) $NaBH_4$, EtOH, 0° → 25°, 4 h, 86%. *d*) PPh_3, imidazole, I_2, CH_2Cl_2, 0° → 25°, 36 h, 64%. *e*) *Jones* reagent, acetone, 0° → 25°, 12 h, 73%. *f*) $SOCl_2$, reflux, 12 h, quant. *g*) Ac_2O, pyridine, 0° → 25°, 24 h, 90%. *h*) *Jones* reagent, acetone, 0° → 25°, 12 h, 76%. *i*) $SOCl_2$, reflux, 12 h, quant.

Scheme 3



a) 4-(Acetyloxy)-3-methoxybenzoyl chloride (**16**), $AlCl_3$, CH_2Cl_2, N_2 atm, 0°, 30 min, 59%. *b*) $NaBH_3CN$/TMSCl, MeCN, N_2 atm, 0° → 25°, 12 h, 80%. *c*) $NaHCO_3$, MeOH/H_2O 4 : 1, 25°, 4 h, 83%.

In conclusion, starting from 2-furaldehyde, we developed two alternative strategies for the synthesis of natural product **1** in three or four steps. We also synthesized the natural product **2** for the first time by a convergent method in eight steps. We think that our synthetic methods will be valuable for the preparation of various 2,5-dialkylated furan derivatives.

The authors thank the *Scientific and Technological Research Council of Turkey* for support (TÜBİTAK, 113Z197). They are also thankful to Prof. Dr. *Simeon Arseniyadis* for providing some literature, and Prof. Dr. *Ramazan Altundaş* and Dr. *Ahmet C. Gören* for helpful discussions.

Experimental Part

General. Anh. THF was distilled over Na in the presence of benzophenone. CH_2Cl_2 and MeCN were obtained by distillation from molecular sieve (4 Å). All other solvents and reagents were used as received. Reactions were monitored by thin-layer chromatography (TLC) with TLC *Merck* silica gel *60* F_{254}. Column chromatography (CC): *Fluka* silica gel *60* (SiO_2; 0.063 – 0.2 mm). Column eluents were visualized using UV light (254 nm) and a soln. of phosphomolybdic acid in EtOH (5 wt.-%). M.p.: *Büchi 539* capillary melting apparatus; uncorrected. ^{1}H- and ^{13}C-NMR spectra: *Varian* 400 MHz instrument (^{1}H-NMR at 400 MHz and ^{13}C-NMR at 100 MHz).

*(*E/Z*)-2-Styrylfuran* (=*2-[(*E/Z*)-2-Phenylethenyl]furan*; **4**) [12]. To a soln. of benzyl bromide (=(bromomethyl)benzene, **3**; 5.00 g, 29.2 mmol) in MeCN (150 ml), PPh_3 (8.43 g, 32.2 mmol) was added, and the mixture was heated at reflux for 24 h. Evaporation of the solvent afforded benzyltriphenylphosphonium bromide as a colorless solid, which was used for further reaction without purification (13.43 g, quant.). To a slurry of NaH (540 mg, 22.5 mmol) in CH_2Cl_2 (25 ml) was added a soln. of benzyltriphenylphosphonium bromide (4.00 g, 10.5 mmol) in CH_2Cl_2 (60 ml) under N_2 atm at 0°; the mixture was stirred for 1 h. 2-Furaldehyde (720 mg, 7.5 mmol) was added to the mixture and it was stirred for 48 h at r.t. A sat. aq. NH_4Cl soln. (20 ml) was added to the mixture. The org. phase was separated and dried (Na_2SO_4), and the solvent was evaporated. CC of the residue with AcOEt/hexane 1:4 gave **4** as a yellow oil (1.09 g, 87%). The (*E*/*Z*) mixture was used in the next step without purification.

2-(2-Phenylethyl)furan (**5**) [10]. Compound **5** was synthesized from **4** according to the procedure described in [10] (colorless oil, 82%). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.18 (*m*, 5 arom. H, H–C(5)); 6.28 (br. *t*, *J* = 2.9, H–C(4)); 5.98 (br. *d*, *J* = 3.2, H–C(3)); 3.00 – 2.92 (*m*, CH_2CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 155.6 (C(2)); 141.4 (C(1″)); 141.1 (C(5)); 128.6 (C(2″/6″)); 128.5 (C(3″/5″)); 126.2 (C(4″)); 110.4 (C(4)); 105.4 (C(3)); 34.6 (Ph*C*H_2); 30.1 (furyl–*C*H_2).

2-Benzyl-5-(2-phenylethyl)furan (**1**) [7][9]. A soln. of **5** (1.00 g, 5.81 mmol) in THF (20 ml) was cooled to −78° and BuLi (1.6M, 4.35 ml, 6.97 mmol) was added dropwise. The mixture was warmed to −5° and then recooled to −78°. At this temp., benzyl bromide (**3**; 1.09 g, 6.39 mmol) was added. The mixture was allowed to warm to r.t. and stirred for 12 h. An aq. sat. NH_4Cl soln. (10 ml) was added to the mixture at 0°. THF was evaporated, and the org. phase was extracted with AcOEt (3 × 50 ml) and dried (Na_2SO_4). CC of the crude product with hexane/AcOEt (98:2) gave **1** as a yellow oil (1.19 g, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.15 (*m*, 10 arom. H); 5.87 (br. *s*, H–C(3), H–C(4)); 3.95 (br. *s*, Ph*C*H_2–furyl)); 2.94 – 2.90 (*m*, CH_2CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 154.5, 153.0 (C(5), C(2)); 141.5, 138.7 (C(1′), (C(1″)); 128.9, 128.67 (C(2′/6′), C(2″/6″)); 128.62, 128.56 (C(3′/5′), C(3″/5″)); 126.6, 126.2 (C(4′), C(4″)); 107.0 (C(4)); 106.0 (C(3)); 34.8 (Ph*C*H_2); 34.6 (Ph*C*H_2); 30.2 (furyl–*C*H_2). The ^{1}H- and ^{13}C-NMR data are in agreement with the data given for isolated **1** in [7].

Phenyl[5-(2-phenylethyl)furan-2-yl]methanone (**6**) [13]. Under N_2 atmosphere, a soln. of benzoyl chloride (1.50 g, 10.7 mmol) in CH_2Cl_2 (30 ml) was cooled to 0° and $AlCl_3$ (2.85 g, 21.3 mmol) was added to the soln. At the same temp., a soln. of 2-(2-phenylethyl)furan (**5**; 1.83 g, 10.7 mmol) in CH_2Cl_2 (10 ml) was added. The mixture was stirred for 30 min, and then, ice (50 g) was added to quench the reaction. The org. phase was extracted with CH_2Cl_2 (3 × 70 ml), washed (5% aq. $NaHCO_3$), and dried (Na_2SO_4). Evaporation of the solvent and CC of the residue with hexane/AcOEt 95:5 gave **6** as a yellow oil (2.15 g, 73%). R_f (AcOEt/hexanes 7:3) 0.55. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.90 (*dd*, *J* = 7.3, 1.1, H–C(2′/6′)); 7.57

(*quasi-t*, $J = 7.9$, H–C(4′)); 7.30 (*quasi-t*, $J = 7.6$, H–C(3‴/5‴)); 7.26–7.19 (*m*, H–C(4‴), H–C(2‴), H–C(6‴)); 7.12 (*d*, $J = 3.1$, H–C(3″)); 6.18 (*d*, $J = 3.1$, H–C(4″)); 3.11–3.04 (*m*, CH_2CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 182.5 (C=O); 161.6 (C(5″)); 151.2 (C(2″)); 140.6 (C(1‴)); 137.9 (C(1′)); 132.5 (C(4′)); 129.3 (C(2′/6′)); 128.8 (C(2‴/6‴)); 128.60 (C(3′/5′)); 128.57 (C(3‴/5‴)); 126.6 (C(4‴)); 122.8 (C(3″)); 109.0 (C(4″)); 34.1 ($PhCH_2$); 30.5 (furyl–CH_2). HR-ESI-MS: 277.1231 ($[M+H]^+$, $C_{19}H_{17}O_2^+$; calc. 277.1223).

Preparation of Compound **1** *from Ketone* **6**. Under N_2 atmosphere, a soln. of ketone **6** (0.80 g, 2.9 mmol) in MeCN (50 ml) was cooled to 0° and $NaBH_3CN$ (1.09 g, 17.4 mmol) was added in portions over the course of 30 min. At the same temp., TMSCl (2.39 g, 2.79 ml; 22.0 mmol) was added dropwise. The mixture was stirred at r.t. for 12 h. To the mixture was added 5% $NaHCO_3$ soln. (10 ml), and the mixture was stirred for 5 min. The org. phase was extracted with CH_2Cl_2 (3×60 ml) and dried (Na_2SO_4). Removal of the solvent under reduced pressure and CC of the residue with hexane/AcOEt 95 :5 gave **1** as a yellow oil (0.61 g, 81%).

3-Methoxy-4-(methoxymethoxy)benzaldehyde (**8**). Compound **8** was synthesized from vanillin (**7**) according to [14]. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.85 (*s*, CHO); 7.42 (*s*, H–C(2)); 7.41 (*dd*, $J = 8.4, 1.8$, H–C(6)); 7.25 (*d*, $J = 8.4$, H–C(5)); 5.31 (*s*, OCH_2O); 3.93 (*s*, MeO); 3.50 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 191.2 (CHO); 152.2 (C(4)); 150.3 (C(3)); 131.3 (C(1)); 126.6 (C(6)); 114.9 (C(5)); 109.7 (C(2)); 95.2 (OCH_2O); 56.7 (MeO); 56.3 (MeO). ^{1}H- and ^{13}C-NMR data are in agreement with the data given in [15].

*4-{[*tert-*Butyl(diphenyl)silyl]oxy}-3-methoxybenzaldehyde* (**9**) [16]. To a soln. of **7** (2.50 g, 16.4 mmol) in CH_2Cl_2 (60 ml) was added imidazole (2.23 g, 32.9 mmol). After the mixture was stirred for 15 min, *tert*-butyl(diphenyl)silyl chloride (= *tert*-butyl(chloro)diphenylsilane; 4.29 g, 4.05 ml, 15.6 mmol) was added dropwise. The mixture was stirred at r.t. for 12 h, then H_2O (20 ml) was added, and the org. phase was extracted with CH_2Cl_2 (3×60 ml) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was subjected to CC with hexane/AcOEt 95 :5 to give **9** as a yellow oil (5.84 g, 91%). R_f (AcOEt/hexanes 1 :4) 0.80. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.77 (CHO); 7.72–7.69 (*m*, $2 \times$ H–C(1′), $2 \times$ H–C(2′)); 7.42–7.34 (*m*, $2 \times$ H–C(3′), $2 \times$ H–C(4′), $2 \times$ H–C(5′)); 7.31 (*d*, $J(2,6) = 2.0$, H–C(2)); 7.17 (*dd*, $J(5,6) = 8.0$, $J(2,6) = 2.0$, H–C(6)); 6.79 (*d*, $J(5,6) = 8.0$, H–C(5)); 3.64 (*s*, MeO); 1.13 (*s*, Me_3C). ^{13}C-NMR (100 MHz, $CDCl_3$): 191.1 (CHO); 151.3 (C(4)); 151.1 (C(3)); 135.2 (C(2′/6′)); 132.7 (C(1′)); 130.7 (C(1)); 129.9 (C(4′)); 127.7 (C(3′/5′)); 126.0 (C(6)); 120.0 (C(5)); 110.1 (C(2)); 55.3 (MeO); 26.5 (Me_3C); 19.8 (Me_3C). ^{1}H- and ^{13}C-NMR data are in agreement with the data given in [17].

*(4-{[*tert-*Butyl(diphenyl)silyl]oxy}-3-methoxyphenyl)methanol* (**10**) [17]. To a soln. of benzaldehyde **9** (5.20 g, 13.3 mmol) in EtOH (80 ml) was added $NaBH_4$ (0.60 g, 16.0 mmol), and the mixture was stirred for 4 h. The solvent was removed under reduced pressure. AcOEt (10 ml) and aq. sat. NH_4Cl (20 ml) were added to the residue at 0°. The org. phase was extracted with AcOEt (3×80 ml) and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave **10** as a colorless oil (4.50 g, 86%). R_f (AcOEt/hexane 3 :7) 0.44. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.70 (*d*, $J = 7.3$, $2 \times$ H–C(2″), $2 \times$ H–C(6″)); 7.42–7.25 (*m*, $2 \times$ H–C(3″), $2 \times$ H–C(4″), $2 \times$ H–C(5″)); 6.81 (*d*, $J(2',6') = 1.8$, H–C(2′)); 6.66 (*d*, $J(5',6') = 8.1$, H–C(5′)); 6.61 (*dd*, $J(5',6') = 8.1$, $J(2',6') = 1.8$, H–C(6′)); 4.54 (*s*, CH_2OH), 3.59 (*s*, MeO); 1.10 (*s*, Me_3C). ^{13}C-NMR (100 MHz, $CDCl_3$): 150.8 (C(4′)); 144.8 (C(3′)); 135.5 ($2 \times$ C(2″/6″)); 134.3 (C(1′)); 133.7 ($2 \times$ C(1″)); 129.8 ($2 \times$ C(4″)); 127.7 ($2 \times$ C(3″/5″)); 120.2 (C(6′)); 119.5 (C(5′)); 111.6 (C(2′)); 65.6 (CH_2OH); 55.6 (MeO); 26.9 (Me_3C); 20.0 (Me_3C). ^{1}H- and ^{13}C-NMR data are in agreement with the data given in [17].

tert-*Butyl[4-(iodomethyl)-2-methoxyphenoxy]diphenylsilane* (**11**). Compound **11** was synthesized following the procedure described for the iodination of benzyl alcohols in [18] as a yellow oil (64%). Compound **11** decomposes when stored, even in refrigerator. Therefore, it was used immediately after synthesis. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.70–7.67 (*m*, $2 \times$ H–C(2′), $2 \times$ H–C(6′)); 7.41–7.32 (*m*, $2 \times$ H–C(3′), $2 \times$ H–C(4′), $2 \times$ H–C(5′)); 6.77 (*d*, $J(3,5) = 2.2$, H–C(3)); 6.67 (*dd*, $J(5,6) = 8.2$, $J(3,5) = 2.2$, H–C(5)); 6.58 (*d*, $J(5,6) = 8.2$, H–C(6)); 4.39 (*s*, CH_2I), 3.56 (*s*, MeO); 1.10 (*s*, Me_3C). ^{13}C-NMR (100 MHz, $CDCl_3$): 150.7 (C(1)); 145.1 (C(2)); 135.6 ($2 \times$ C(2′/6′)); 133.6 ($2 \times$ C(1′)); 132.4 (C(4)); 129.9 ($2 \times$ C(4′)); 127.7 ($2 \times$ C(3′/5′)); 121.2 (C(5)); 120.3 (C(6)); 113.0 (C(3)); 55.6 (MeO); 26.8 (Me_3C); 20.0 (Me_3C); 7.5 (CH_2I).

*4-{[*tert-*Butyl(diphenyl)silyl]oxy}-3-methoxybenzoic Acid* (**12**). A soln. of benzaldehyde **9** (2.50 g, 6.40 mmol) in acetone (40 ml) was cooled to 0° and *Jones* reagent (2.67M, 12 ml, 32.0 mmol) was added. The mixture was allowed to warm to r.t. and was stirred for 12 h. 2-Propanol (60 ml) was added, and the mixture was stirred for 20 min, and then filtered, and the solid parts were separated. The solvent of the filtrate was removed under reduced pressure, and the residue was filtered over a short SiO_2 column eluting with AcOEt to give colorless **12** (1.90 g, 73%). M.p. 123–124°. R_f (AcOEt/hexane 1:1) 0.65. ^{1}H-NMR (400 MHz, $CDCl_3$): 12.70–11.30 (br. *s*, OH); 7.74 (*d*, *J* = 7.7, 2 × H–C(2′), 2 × H–6′)); 7.54 (*d*, *J*(2,6) = 1.5, H–C(2)); 7.53 (*dd*, *J*(5,6) = 8.8, *J*(2,6) = 1.5, H–C(6)); 7.44–7.37 (*m*, 2 × H–C(3′), 2 × H–C(4′), 2 × H–C(5′)); 6.79 (*d*, *J*(5,6) = 8.8, H–C(5)); 3.64 (*s*, MeO); 1.17 (*s*, Me_3C). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.5 (COOH); 150.64 (C(4)); 150.60 (C(3)); 135.5 (2 × C(2′/6′)); 133.2 (2 × C(1′)); 130.1 (2 × C(4′)); 127.9 (2 × C(3′/5′)); 124.3 (C(6)); 122.7 (C(1)); 120.1 (C(5)); 113.7 (C(2)); 55.5 (MeO); 26.8 (*Me*$_3$C); 20.0 (Me$_3$*C*). HR-ESI-MS: 407.1677 ($[M+H]^+$, $C_{24}H_{27}O_4Si^+$; calc. 407.1673).

*4-{[*tert-*Butyl(diphenyl)silyl]oxy}-3-methoxybenzoyl Chloride* (**13**). Benzoic acid **12** (0.82 g, 2.01 mmol) was dissolved in $SOCl_2$ (2 ml) and the mixture was heated at reflux for 12 h. The unreacted $SOCl_2$ was removed under reduced pressure to give **13** as a yellow oil (0.86 g, quant.), which was used for further reaction without purification. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.71 (*dd*, *J* = 8.1, 1.5, 2 × H–C(2′), 2 × H–C(6′)); 7.50–7.48 (*m*, H–C(2), H–C(6)); 7.42–7.34 (*m*, 2 × H–C(3′), 2 × H–C(4′), 2 × H–C(5′)); 6.75 (*d*, *J*(5,6) = 8.8, H–C(5)); 3.62 (*s*, MeO); 1.14 (*s*, Me_3C). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.3 (COCl); 150.6 (C(4)); 150.5 (C(3)); 135.5 (2 × C(2′/6′)); 133.1 (2 × C(1′)); 130.1 (2 × C(4′)); 127.9 (2 × C(3′/5′)); 124.2 (C(6)); 122.6 (C(1)); 120.0 (C(5)); 113.6 (C(2)); 55.6 (MeO); 26.8 (*Me*$_3$C); 20.0 (Me$_3$*C*).

4-(Acetyloxy)-3-methoxybenzaldehyde (= *4-Formyl-2-methoxyphenyl Acetate*; **14**) [19]. Vanillin (**7**) was acetylated with Ac_2O/pyridine as described in [19] to give yellow solid **14** (90%). M.p. 76–77° ([20]: 76–77°). ^{1}H-NMR (400 MHz, $CDCl_3$): 9.93 (*s*, 1 H, CHO); 7.48 (*d*, *J*(2,6) = 1.7, H–C(2)); 7.46 (*dd*, *J*(5,6) = 7.7, *J*(2,6) = 1.7, H–C(6)); 7.20 (*d*, *J*(5,6) = 7.7, H–C(5)); 3.89 (*s*, MeO); 2.33 (*s*, C(O)Me). ^{13}C-NMR (100 MHz, $CDCl_3$): 191.2 (CHO); 168.5 (CO of Ac); 152.2 (C(4)); 145.1 (C(3)); 135.5 (C(1)); 124.9, 123.6 (C(6), C(5)); 111.0 (C(2)); 56.3 (MeO); 20.8 (C(O)*Me*). ^{1}H-NMR data are in agreement with the data given in [19].

4-(Acetyloxy)-3-methoxybenzoic Acid (**15**) [21]. The procedure described above for the synthesis of benzoic acid **12** was applied to benzaldehyde **14** to give **15** (76%). M.p. 141–142° ([20]: 141–142°). R_f (AcOEt/hexane 4:1) 0.46. ^{1}H-NMR (400 MHz, $CDCl_3$): 12.23 (br. *s*, COOH), 7.76 (*dd*, *J*(5,6) = 8.0, *J*(2,6) = 1.8, H–C(6)); 7.71 (*d*, *J*(2,6) = 1.8, H–C(2)); 7.14 (*d*, *J*(5,6) = 8.0, H–C(5)); 3.90 (*s*, MeO); 2.34 (*s*, C(O)Me). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.6 (COOH); 168.7 (CO of ester); 151.4 (C(4)); 144.6 (C(3)); 128.1 (C(1)); 123.6, 123.2 (C(6), C(5)); 114.0 (C(2)); 56.3 (MeO); 20.9 (C(O)*Me*). ^{1}H- and ^{13}C-NMR data are in agreement with the data given in [21].

4-(Acetyloxy)-3-methoxybenzoyl Chloride (= *4-(Chlorocarbonyl)-2-methoxyphenyl Acetate*; **16**). 4-(Acetyloxy)-3-methoxybenzoic acid (**15**) was reacted with $SOCl_2$ as described in [22] to give **16** as a colorless oil. Yield: quantitative. Benzoyl chloride **16** was used for further reaction without purification. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.80 (*dd*, *J*(5,6) = 8.4, *J*(2,6) = 2.0, H–C(6)); 7.65 (*d*, *J*(2,6) = 2.0, H–C(2)); 7.18 (*d*, *J*(5,6) = 8.4, H–C(5)); 3.90 (*s*, MeO); 2.34 (*s*, C(O)Me). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.3 (CO); 167.8 (CO); 151.6 (C(4)); 145.9 (C(3)); 131.9 (C(1)); 125.5, 123.5 (C(6), C(5)); 114.5 (C(2)); 56.4 (MeO); 20.8 (C(O)*Me*).

2-Methoxy-4-{[5-(2-phenylethyl)furan-2-yl]carbonyl}phenyl Acetate (**17**). The *Friedel–Crafts* reaction described above for the synthesis of compound **6** was applied to **12** to give ketone **17** as a yellow oil (59%). R_f (AcOEt/hexane 7:3) 0.33. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.54 (br. *s*, H–C(3), overlapped with H–C(5)); 7.53 (*dd*, *J*(5,6) = 8.0, *J*(3,5) = 1.8, H–C(5)); 7.32–7.19 (*m*, 5 arom. H); 7.16 (*d*, *J*(3′,4′) = 3.5, H–C(3′)); 6.20 (*d*, *J*(3′,4′) = 3.5, H–C(4′)); 3.90 (*s*, MeO); 3.10–3.03 (*m*, CH_2CH_2); 2.35 (*s*, C(O)*Me*). ^{13}C-NMR (100 MHz, $CDCl_3$): 180.9 (CO of ketone); 168.6 (CO of ester); 161.7 (C(5′)); 151.3 (C(2′)); 150.8 (C(1)); 143.2 (C(2)); 140.3 (C(1″)); 136.2 (C(4)); 128.6 (C(2″/6″)); 128.3 (C(3″/5″)); 126.4 (C(4″)); 122.6, 122.5, 122.3 (C(6), C(5), C(3′)); 113.0 (C(3)); 108.9 (C(4′)); 56.1 (MeO); 34.0 (Ph*C*H$_2$); 30.2 (furyl *C*H$_2$); 20.6 (C(O)*Me*). HR-ESI-MS: 365.1384 ($[M+H]^+$, $C_{22}H_{20}O_5^+$; calc. 365.1384).

2-Methoxy-4-{[5-(2-phenylethyl)furan-2-yl]methyl}phenyl Acetate (**18**). The reduction method described above for **6** was applied to ketone **17** to give **18** as a yellow oil (80%). R_f (AcOEt/hexane 7:3) 0.50. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.27 (*quasi-t*, *J* = 7.1, H–C(2″), H–C(6″)); 7.21–7.15 (*m*, H–C(3″/

4″/5″)); 6.96 (*d*, *J*(5,6) = 8.0, H–C(6)); 6.85 (*d*, *J*(3,5) = 2.0, H–C(3)); 6.80 (*dd*, *J*(5,6) = 8.0, *J*(3,5) = 2.0, H–C(5)); 5.91, 5.88 (2*d*, *J*(3′,4′) = 2.9, H–C(3′), H–C(4′)); 3.91 (*s*, ArC*H*$_2$–furyl); 3.80 (*s*, MeO); 2.95 – 2.87 (*m*, CH_2CH_2); 2.31 (*s*, C(O)Me). ^{13}C-NMR (100 MHz, $CDCl_3$): 169.5 (CO); 154.7, 152.5 (C(5′), C(2′)); 151.1 (C(1)); 141.5 (C(2)); 138.4 (C(1″)); 137.7 (C(4)); 128.60 (C(2″/6″)); 128.57 (C(3″/5″)); 126.2 (C(4″)); 122.8 (C(5)); 121.0 (C(6)); 113.0 (C(3)); 107.2 (C(4′)); 106.0 (C(3′)); 56.0 (MeO); 34.6 (2 × Ph*C*H$_2$); 30.2 (furyl–*C*H$_2$); 20.9 (C(O)*Me*). HR-ESI-MS: 373.1410 ([*M* + Na]$^+$, $C_{22}H_{22}NaO_4^+$; calc. 373.1410).

2-Methoxy-4-{[5-(2-phenylethyl)furan-2-yl]methyl}phenol (**2**) [7]. To a soln. of acetate **18** (0.20 g, 0.57 mmol) in MeOH (8 ml) was added a sat. $NaHCO_3$ soln. (2 ml). The mixture was stirred at r.t. for 4 h. MeOH was evaporated, and org. phases were extracted with AcOEt (3 × 50 ml) and dried (Na_2SO_4). The solvent was removed and the residue was purified by CC with AcOEt/hexane (15 : 85) to give **2** as a yellow oil (149 mg, 83%). R_f (AcOEt/hexane 2 : 3) 0.60. ^{1}H-NMR (400 MHz, $CDCl_3$):7.27 (*quasi-t*, *J* = 7.4, H–C(3″/5″)); 7.21 – 7.15 (*m*, H–C(2″/4″/6″)); 6.86 (*d*, *J*(5,6) = 8.0, H–C(6)); 6.75 (br. *s*, H–C(3)); 6.74 (*d*, *J*(5,6) = 8.0, H–C(5)); 5.87 (br. *s*, H–C(3′), H–C(4′)); 5.50 (*s*, OH); 3.86 (*s*, MeO, ArC*H*$_2$–furyl); 2.95 – 2.87 (*m*, CH_2CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 154.3, 153.2 (C(5′), C(2′)); 146.4 (C(1)); 144.2 (C(2)); 141.3 (C(1″)); 130.3 (C(4)); 128.35 (C(2″/6″)); 128.31 (C(3″/5″)); 126.0 (C(4″)); 121.4 (C(5)); 114.2 (C(6)); 111.2 (C(3)); 106.5 (C(4′)); 105.7 (C(3′)); 55.8 (MeO); 34.4 (Ph*C*H$_2$); 34.2 (Ph*C*H$_2$); 30.0 (furyl *C*H$_2$). ^{1}H- and ^{13}C-NMR data are in agreement with the data given in [7]. HR-ESI-MS: 309.1480 ([*M* + H]$^+$, $C_{20}H_{21}O_3^+$; calc. 309.1485).

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Received August 23, 2014