

Synthesis of Precursors for the Oxidative Tandem Cyclization of Diphenols to Galanthamine Analogs

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Abstract: Methods for the preparation of 4-bromo-5-[2-(4-hydroxybenzyl)benzyl]-2-methoxyphenol and 4-bromo-5-[4-(4-hydroxyphenyl)butyl]-2-methoxyphenol are described.

Keywords: Tandem cyclization, isopropyl-ether protecting group, O-dealkylation, deoxygenation of benzyl alcohols.

Introduction

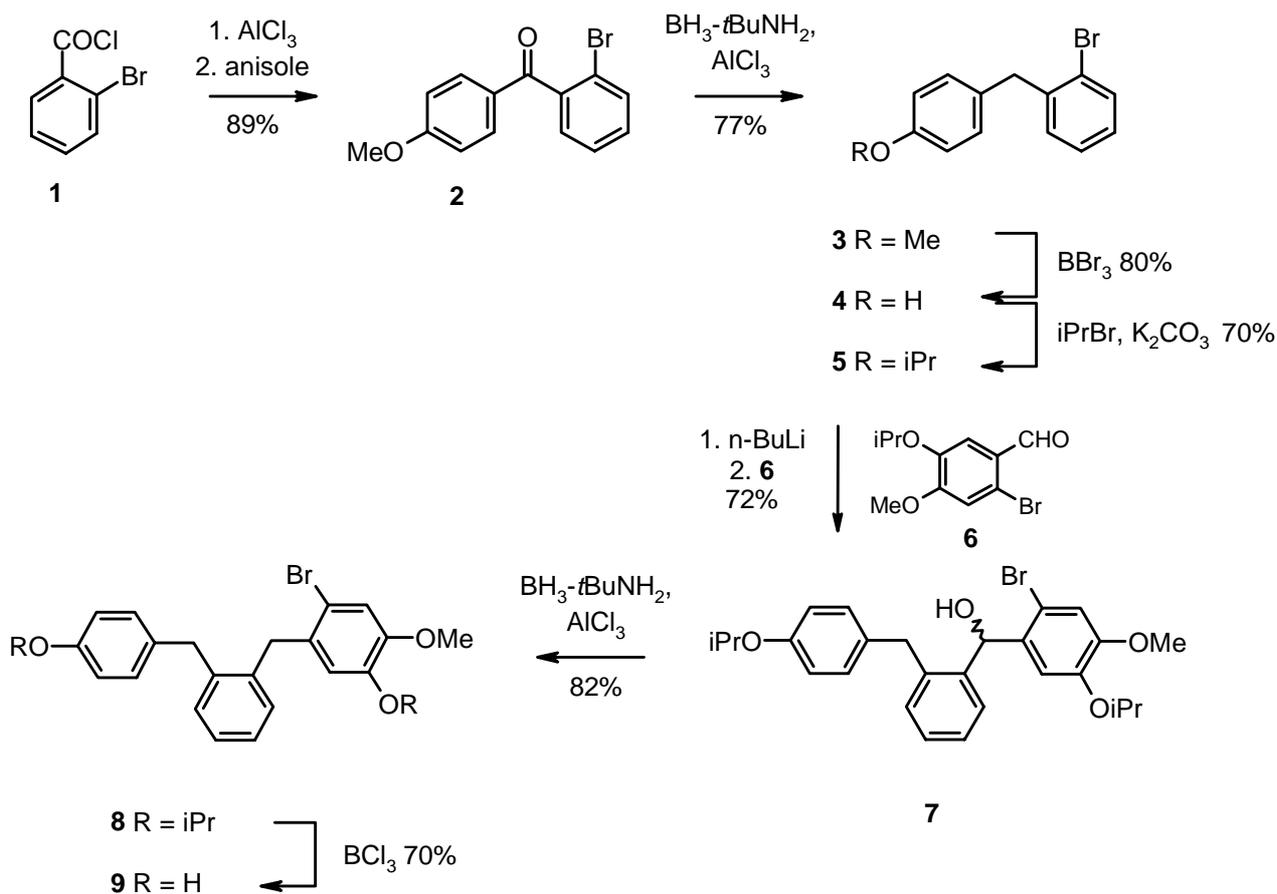
Galanthamine is an alkaloidal acetylcholinesterase inhibitor (AChEI) which has been approved in several countries for treating symptoms of Alzheimer's type senile dementia [1, 2]. In the course of our investigations into the oxidative tandem cyclization protocol [3, 4, 5, 6, 7, 8] we sought to extend this reaction type to the preparation of carbocyclic galanthamine analogs. To study this approach, we needed 4-bromo-5-[2-(4-hydroxybenzyl)benzyl]-2-methoxyphenol (**9**) and 4-bromo-5-[4-(4-hydroxyphenyl)butyl]-2-methoxyphenol (**13**) as substrates for such oxidative tandem cyclizations.

Results and Discussion

The ketone **2** [9] was prepared in a Friedel-Crafts type reaction starting from anisole and 2-bromobenzoyl chloride (**1**) [10] in 89% yield. For the reduction of the carbonyl functionality of **2**, borane-*tert.*-butylamine complex/aluminum chloride was employed, yielding the diphenylmethane derivative **3**

as a colorless oil in 77% yield. This reduction had previously been performed using $\text{HSiEt}_3/\text{TFA}$ [11]. O-demethylation using boron tribromide afforded the phenol **4** [12] in 80% yield as colorless crystals. To summarize, we have found a short and convenient synthetic pathway for the preparation of **4** in an overall yield of 55% using readily available starting materials.

Scheme 1.

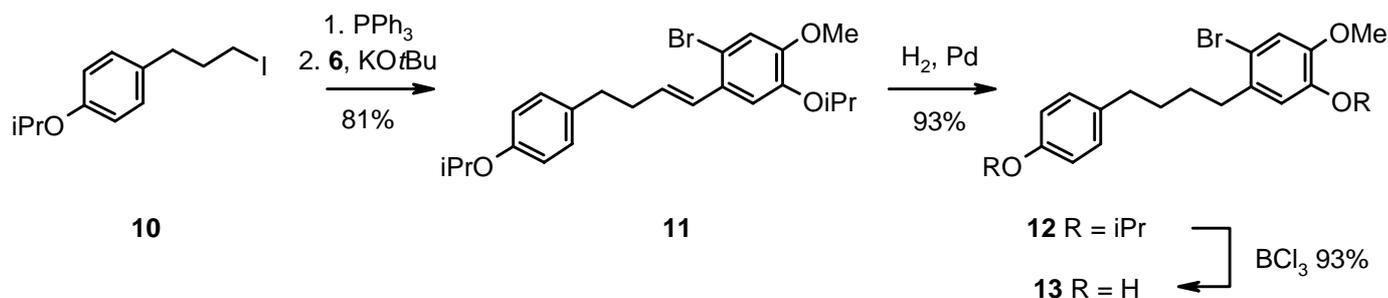


The conversion of compound **4** into the corresponding isopropyl ether **5** (isopropyl bromide, potassium carbonate) was achieved with a yield of 70%. Compound **5** was then metallated using *n*-butyl lithium and afterwards quenched with 2-bromo-5-isopropoxy-4-methoxybenzaldehyde (**6**) [13] to give the alcohol **7** in 72% yield. The use of the borane-*tert*-butylamine complex/aluminum chloride reduction system for the deoxygenation of aryl ketones has been described [14]. We have now extended this method to the reduction of benzyl alcohols and thus obtained the dibenzyl substituted benzene derivative **8** in 82% yield. The cleavage of the isopropyl ethers was accomplished using boron trichloride and gave rise to the desired diphenol compound **9** in a yield of 70% (see Scheme 1).

4-Bromo-5-[4-(4-hydroxyphenyl)butyl]-2-methoxyphenol (**13**) was prepared from 1-(3-iodopropyl)-4-isopropoxybenzene (**10**) [15], via the corresponding triphenylphosphonium salt and 2-bromo-

4-methoxy-5-isopropoxybenzaldehyde (**6**) in the presence of KO t Bu. The alkene **11**, isolated in 81% yield after purification by column chromatography, was hydrogenated over palladium on carbon to give the saturated compound **12**. Deprotection of the phenolic hydroxy groups using boron trichloride gave the target compound **13** in 93% yield (see Scheme 2).

Scheme 2.



Conclusions

We have presented facile and straightforward routes for the preparation of 4-bromo-5-[2-(4-hydroxybenzyl)benzyl]-2-methoxyphenol (**9**) and 4-bromo-5-[4-(4-hydroxyphenyl)butyl]-2-methoxyphenol (**13**) employing isopropyl ethers as phenol protecting groups.

Experimental

General

Melting points were determined on a Kofler melting point apparatus. ^1H - and ^{13}C -NMR spectra were recorded on a Bruker AC-200 (200 MHz) pulse Fourier-transform NMR spectrometer in CDCl_3 using tetramethylsilane as an internal standard. Thin layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets silica 60 F $_{254}$) with detection by UV light or with phosphomolybdic acid in aqueous EtOH by heating. All reactions were magnetically stirred under an argon atmosphere. MPLC (medium pressure liquid chromatography) was performed using SiO_2 (Baker), a LC-8A pump (Shimadzu), a SPD-6AV UV-detector (Shimadzu) and Büchi glass columns.

(2-Bromophenyl)-(4-methoxyphenyl)methanone (**2**). 2-Bromobenzoyl chloride (**1**) (213.0 g, 970 mmol) in dry CHCl_3 (250 mL) was added at 15 °C to anhydrous aluminum chloride (138.67 g, 1.04 mol) in dry CHCl_3 (350 mL) and the resulting mixture stirred for 15 min at ambient temperature. Anisole (125.80 g, 1.16 mol) in dry CHCl_3 (100 mL) was then added dropwise, and the mixture was stirred for 12 h at ambient temperature. 2 N HCl (250 mL) was added, the layers were separated, and the aqueous layer was extracted with CHCl_3 (3 x 200 mL). The combined organic layer was washed with 2 N HCl (3 x

300 mL), satd. NaHCO₃ (2 x 300 mL) and brine (2 x 300 mL), dried over Na₂SO₄/charcoal, filtered and concentrated *in vacuo*. The residue was recrystallized from MeOH (500 mL) to afford the title compound as colorless crystals (256.3 g, 89%), mp. 94-96 °C (lit. [9] 95-95.5 °C). TLC: R_f = 0.6 (9:1 petroleum ether-EtOAc). ¹H-NMR (CDCl₃): δ 7.80 (dd, *J* = 12.7 Hz, *J* = 3.2 Hz, 2H), 7.60 (d, *J* = 6.4 Hz, 1H), 7.25 - 7.45 (m, 3H), 6.90 (dd, *J* = 3.2 Hz, *J* = 12.7 Hz, 2H), 3.80 (s, 3H); ¹³C-NMR (CDCl₃): δ 194.3 (s), 164.0 (s), 140.9 (s), 132.9 (d), 132.5 (d), 130.7 (d), 128.9 (s), 128.6 (d), 127.1 (d), 119.3 (s), 113.8 (d), 55.4 (q).

1-Bromo-2-(4-methoxybenzyl)benzene (**3**). To anhydrous aluminum chloride (71.94 g, 541 mmol) in dry CH₂Cl₂ (1200 mL), borane-*tert.*-butylamine complex (92 g, 1.06 mmol) was added at 0 °C and the mixture stirred for 1 h at this temperature. Compound **2** (102 g, 350 mmol) in dry CH₂Cl₂ (600 mL) was then added within 1 h and the resulting mixture was stirred for 1 h at 0 °C. 0.1 N HCl (1000 mL) was added dropwise, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 200 mL). The combined organic layer was washed with 2 N HCl (3 x 300 mL), satd. NaHCO₃ (2 x 300 mL) and brine (2 x 300 mL), dried over Na₂SO₄/charcoal, filtered and concentrated *in vacuo* to give **3** as a colorless oil. Yield: 75 g (77%). TLC: R_f = 0.8 (9:1 petroleum ether-EtOAc). ¹H-NMR (CDCl₃): δ 7.60 (d, *J* = 9.5 Hz, 1H), 7.05 - 7.30 (m, 5H), 6.85 (d, *J* = 9.5 Hz, 2H), 4.05 (s, 2H), 3.85 (s, 3H); ¹³C-NMR (CDCl₃): δ 158.0 (s), 140.7 (d), 132.8 (d), 131.5 (s), 130.9 (s), 129.9 (d), 127.7 (d), 127.4 (s), 124.8 (d), 113.9 (d), 55.2 (q), 40.8 (t).

4-(2-Bromobenzyl)phenol (**4**). To **3** (75 g, 271 mmol) in dry CH₂Cl₂ (600 mL), BBr₃ (48.5 g, 194 mmol) was added at -80 °C. The mixture was warmed up to ambient temperature and stirred for 12 h. 2 N HCl (200 mL) was added, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 200 mL). The combined organic layer was washed successively with 2 N HCl (4 x 150 mL), satd. NaHCO₃ (2 x 200 mL) and brine (2 x 200 mL), dried over Na₂SO₄/charcoal, filtered and concentrated *in vacuo*. The crude product was recrystallized from n-heptane (200 mL) to give colorless crystals of compound **4** (56.8 g, 80%), mp. 83 - 85 °C (Lit.: 85 - 85.5 °C). TLC: R_f = 0.4 (9:1 petroleum ether-EtOAc). ¹H-NMR (CDCl₃): δ 7.61 (dd, *J* = 7.0 Hz, *J* = 1.5 Hz, 1H), 7.36 - 7.04 (m, 5H), 6.82 (d, *J* = 8.3 Hz, 2H), 6.67 (b, 1H), 4.10 (s, 2H); ¹³C-NMR (CDCl₃): δ 153.6 (s), 140.6 (s), 132.7 (d), 131.8 (s), 130.9 (d), 130.1 (d), 127.7 (d), 127.4 (d), 124.7 (s), 115.3 (d), 40.8 (t).

1-Bromo-2-(4-isopropoxybenzyl)benzene (**5**). Compound **4** (56.8 g, 216 mmol), 2-bromopropane (79.75 g, 648 mmol), and freshly ground anhydrous K₂CO₃ (89.6 g, 648 mmol) were stirred in dry acetonitrile (400 mL) at 60 °C for 96 h. The mixture was filtered and evaporated *in vacuo*. The residue was dissolved in Et₂O (250 mL) and washed with water (250 mL). The aqueous layer was extracted with Et₂O (4 x 50 mL), the combined organic layer was washed with water (4 x 100 mL) and brine (1 x 300 mL), dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by Kugelrohr distillation (115-125 °C/0.01 mbar) to afford **5** as a colorless oil (45.7 g, 70%). TLC: R_f = 0.8 (9:1 petroleum ether-EtOAc). Anal. Calcd for C₁₆H₁₇BrO: C, 62.96; H, 5.61. Found: C, 62.74; H,

5.49. $^1\text{H-NMR}$ (CDCl_3): δ 7.60 (d, $J = 6.4$ Hz, 1H), 7.05 - 7.30 (m, 5H), 6.85 (d, $J = 6.4$ Hz, 2H), 4.55 (septet, $J = 6.4$ Hz, 1H), 4.05 (s, 2H), 1.30 (d, $J = 6.4$ Hz, 6H); $^{13}\text{C-NMR}$ (CDCl_3): δ 156.3 (s), 140.8 (d), 132.8 (s), 131.3 (s), 130.9 (d), 129.9 (d), 127.7 (s), 127.4 (d), 124.7 (d), 115.8 (d), 69.8 (d), 40.8 (t), 22.1 (q).

2-Bromo-5-isopropoxy-4-methoxyphenyl-[2-(4-isopropoxybenzyl)]-phenylmethanol (7). To **5** (10.0 g, 32.76 mmol) in dry THF (100 mL) *n*-BuLi (21.09 mL, 33.74 mmol, 1.6 M in hexane) was added under argon at -80 °C and the resulting mixture was stirred for 1 h at this temperature. 2-bromo-4-methoxy-5-isopropoxy-benzaldehyde (**6**) (9.04 g, 33.09 mmol) in dry THF (25 mL) was then added as fast as possible at -90 °C and stirred for 2 h at ambient temperature. Satd. NH_4Cl (150 mL) was added, the mixture was concentrated to a volume of 150 mL under reduced pressure and extracted with Et_2O (5 x 50 mL). The combined organic layer was washed with satd. NH_4Cl (3 x 80 mL), water (2 x 80 mL) and brine (1 x 80 mL), dried over Na_2SO_4 , and evaporated under reduced pressure. The residue was purified by MPLC (500 g SiO_2 , 4:1 petroleum ether- Et_2O) to afford the title compound as a slightly yellow oil. Yield: 11.73 g (72%). TLC: $R_f = 0.4$ (4:1 petroleum ether- EtOAc). Anal. Calcd for $\text{C}_{27}\text{H}_{31}\text{BrO}_4$: C, 64.93; H, 6.26. Found: C, 64.63; H, 6.18. $^1\text{H-NMR}$ (CDCl_3): δ 7.10 - 7.35 (m, 3H), 7.05 (d, $J = 6.4$ Hz, 4H), 6.90 (s, 1H), 6.80 (d, $J = 6.4$ Hz, 2H), 6.25 (s, 1H), 4.25 - 4.60 (m, 2H), 4.05 (s, 1H), 4.00 (s, 1H), 3.90 (s, 3H), 1.95 (s, 1H), 1.15 - 1.40 (m, 12H); $^{13}\text{C-NMR}$ (CDCl_3): δ 156.2 (s), 150.2 (s), 146.6 (s), 140.2 (s), 138.9 (s), 133.9 (s), 132.3 (s), 130.6 (d), 129.7 (d), 127.8 (d), 126.9 (d), 126.6 (d), 116.0 (d), 115.9 (s), 115.8 (d), 113.6 (d), 71.5 (d), 71.3 (d), 69.8 (d), 56.1 (q), 37.9 (t), 21.9 (q).

1-Bromo-4-isopropoxy-2-[2-(4-isopropoxybenzyl)-benzyl]-5-methoxybenzene (8). Borane-*tert*.-butylamine complex (11.80 g, 135.5 mmol) was added at 0 °C to anhydrous aluminum chloride (6.49 g, 48.80 mmol) in dry CH_2Cl_2 (160 mL) and the mixture stirred for 1 h at this temperature. Compound **7** (22.55 g, 45.15 mmol) in dry CH_2Cl_2 (100 mL) was then added within 1 h and stirred for 20 min at ambient temperature. 2 N HCl (150 mL) was added dropwise, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was washed with 2 N HCl (3 x 150 mL), satd. NaHCO_3 (2 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4 /charcoal, filtered and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation (170 - 180 °C/ 0.005 mbar) to give **8** as a colorless oil. Yield: 16.95 g (82%). TLC: $R_f = 0.5$ (4:1 petroleum ether- EtOAc). $^1\text{H-NMR}$ (CDCl_3): δ 7.10 - 7.25 (m, 3H), 7.05 (d, $J = 6.4$ Hz, 2H), 6.98 (s, 2H), 6.80 (s, 1H), 6.78 (d, $J = 12.7$ Hz, 1H), 6.40 (s, 1H), 4.5 (septet, $J = 12.7$ Hz, 1H), 4.25 (septet, $J = 12.7$ Hz, 1H), 3.95 (s, 2H), 3.90 (s, 2H), 3.85 (s, 3H), 1.35 (d, $J = 6.4$ Hz, 6H), 1.25 (d, $J = 6.4$ Hz, 6H); $^{13}\text{C-NMR}$ (CDCl_3): δ 156.1 (s), 149.4 (s), 146.5 (s), 139.4 (s), 137.9 (s), 132.1 (s), 131.7 (s), 130.3 (d), 129.7 (d), 126.5 (d), 117.9 (s), 116.0 (d), 115.1 (d), 71.5 (d), 69.8 (d), 56.2 (q), 38.3 (t), 21.9 (q).

4-bromo-5-[2-(4-hydroxybenzyl)benzyl]-2-methoxyphenol (9). To **8** (14.11 g, 29.2 mmol) in dry CH_2Cl_2 (50 mL), BCl_3 (150 mL, 150 mmol, 1 M in CH_2Cl_2) was added at -78 °C and stirred for 1 h at ambient temperature. 2 N HCl (150 mL) was added dropwise, the layers were separated, and the aqueous layer

was extracted with CH₂Cl₂ (5 x 50 mL). The combined organic layer was washed with 2 N HCl (2 x 100 mL), water (2 x 100 mL) and brine (1 x 100 mL), dried over Na₂SO₄/charcoal, filtered and concentrated *in vacuo*. The residue was recrystallized from iPr₂O (50 mL) to give colorless crystals of **9** (7.81 g, 70%), mp. 119 - 123 °C. TLC: R_f = 0.4 (4:1 petroleum –EtOAc). Anal. Calcd for C₂₁H₁₉BrO₃: C, 63.17; H, 4.80. Found: C, 62.89; H, 4.79. ¹H-NMR (CDCl₃): δ 8.45 (s, 1H), 7.95 (s, 1H), 6.90 (d, *J* = 6.4 Hz, 3H), 6.60 - 6.80 (m, 4H), 6.50 (d, *J* = 6.4 Hz, 2H), 6.20 (s, 1H), 3.65 (s, 3H), 3.60 (s, 4H), 2.75 (s, 1H); ¹³C-NMR (CDCl₃): δ 154.9 (s), 146.0 (s), 145.2 (s), 139.5 (s), 137.7 (s), 132.0 (s), 130.8 (s), 130.8 (d), 129.6 (d), 129.5 (d), 126.3 (d), 126.2 (d), 116.7 (d), 115.2 (d), 115.1 (d), 112.9 (s), 56.0 (q), 38.1 (t), 37.9 (t).

1-Bromo-4-isopropoxy-2-[4-(4-isopropoxyphenyl)-but-1-enyl]-5-methoxybenzene (11). PPh₃ (7.13 g, 27.2 mmol) and 1-(3-iodopropyl)-4-isopropoxybenzene (**10**) (7.52 g, 24.7 mmol) in dry acetonitrile were stirred under reflux for 30 h. The mixture was concentrated *in vacuo*, the residue was crystallized from iPr₂O and triturated with Et₂O (3 x 50 mL) to yield the triphenylphosphonium salt as a colorless solid (13.8 g, 98.5%), mp. 159-161°C. This salt was suspended in dry THF (100 mL), treated with KO^tBu (3.30 g, 29.4 mmol) at 5°C within 15 min and stirred for additional 15 min. 2-Bromo-5-isopropoxy-4-methoxybenzaldehyde (**6**) (6.32 g, 23.1 mmol) was added within 15 min and stirred for 30 min at ambient temperature. The mixture was concentrated *in vacuo*, dissolved in iPr₂O (50 mL) and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by MPLC (200 g SiO₂, 95:5 petroleum ether-Et₂O) to afford compound **11** as a colorless oil (8.25 g, 82%). TLC: R_f = 0.8 (4:1 petroleum ether-EtOAc). ¹H-NMR (CDCl₃): δ 7.21 - 7.01 (m, 3H), 6.89 - 6.73 (m, 3H), 6.65 and 6.41 (d, *J* = 15.9 Hz and *J* = 11.4 Hz, 1H), 6.14 - 5.98 and 5.82 - 5.62 (m, 1H), 4.62 - 4.28 (m, 2H), 3.82 (s, 3H), 2.86 - 2.62 (m, 2H), 2.51 (quintet, *J* = 6.0 Hz, 2H), 1.48 - 1.27 (m, 12H); ¹³C-NMR (CDCl₃): δ 156.0 (s), 150.3 and 150.0 (s), 146.6 and 145.8 (s), 133.5 and 133.4 (s), 132.1 (s), 131.1 (d), 129.7 and 129.5 (d), 129.3 and 129.2 (d), 128.7 and 128.6 (s), 117.9 and 115.9 (d), 115.8 and 115.7 (d), 114.7 and 114.1 (d), 71.8 and 71.7 (d), 69.8 (d), 56.1 (q), 34.9 (t), 34.8 (t), 34.7 (t), 30.2 (t), 22.0 (q), 21.9 (q).

1-Bromo-4-isopropoxy-2-[4-(4-isopropoxyphenyl)butyl]-5-methoxybenzene (12). Pd (2.5 g, 10% on carbon) in MeOH (25 mL) was prehydrogenated (15 min, rt, 70 psi) using a Parr apparatus. Compound **11** (5.0 g, 11.5 mmol) in MeOH (20 mL) was added and the mixture was hydrogenated at 75 psi and rt for 48 h. The mixture was filtered, the filtrate was concentrated *in vacuo*, and the residue was purified by MPLC (100 g SiO₂, 95:5 petroleum ether-Et₂O) to give **12** as a colorless oil (4.63 g, 93%). TLC: R_f = 0.3 (2:1 petroleum ether-Et₂O). ¹H-NMR (CDCl₃): δ 7.12 (d, *J* = 7.9 Hz, 2H), 6.99 - 6.71 (m, 4H), 4.68 - 4.42 (m, 2H), 3.87 (s, 3H), 2.80 - 2.50 (m, 4H), 2.86 - 2.57 (m, 4H), 1.55 - 1.29 (m, 12H), ¹³C-NMR (CDCl₃): δ 155.8 (s), 148.5 (s), 146.9 (s), 135.1 (s), 134.4 (s), 129.1 (d), 120.7 (s), 116.6 (d), 115.7 (d), 112.0 (d), 71.3 (d), 69.7 (d), 55.9 (q), 35.1 (t), 34.7 (t), 22.0 (q), 22.0 (q).

4-Bromo-5-[4-(4-hydroxyphenyl)butyl]-2-methoxyphenol (13). BCl₃ (15 mL, 1.6 M in CH₂Cl₂) was added at -78°C to **12** (4.0 g, 11.4 mmol) in dry CH₂Cl₂ (50 mL) and the resulting mixture was stirred

for 1 h at this temperature and then for an additional 2 h at ambient temperature. Water (100 mL) was added dropwise, and the mixture was concentrated to ca. 80 mL *in vacuo*. The precipitate formed was collected by filtration and triturated with water (6 x 100 mL) and *i*Pr₂O (2 x 10 mL) to give colorless crystals of compound **13** (3.71 g, 93%), mp. 98 - 101 °C. TLC: R_f = 0.8 (2:1 petroleum ether-Et₂O). ¹H-NMR (CDCl₃): δ 8.22 (b, 1H), 7.08 - 6.81 (m, 2H), 6.80 - 6.60 (m, 4H), 6.59 - 6.44 (m, 1H), 3.76 (s, 3H), 2.48 (s, 4H), 1.57 (s, 4H); ¹³C-NMR (CDCl₃): δ 154.4 (s), 145.3 (s), 144.7 (s), 135.4 (s), 133.1 (s), 128.8 (d), 119.1 (s), 114.9 (d), 114.8 (d), 110.7 (d), 55.6 (q), 34.7 (t), 34.4 (t), 30.9 (t), 30.7 (t).

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 15. Unpublished results

Sample Availability: Samples of compounds **2**, **4**, **5**, **9** and **13** are available from MDPI.

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