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Preparation of Shortened Norbelladine Analogs

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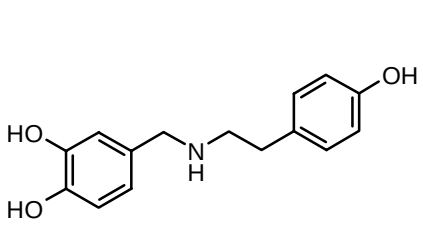
Abstract: The preparation of N-[(2-bromo-5-hydroxy-4-methoxyphenyl)methyl]-N-[(4-hydroxyphenyl)methyl]formamide (**5**) and 2-bromo-5-hydroxy-α-[(4-hydroxyphenyl)-methyl]-4-methoxypropaneamide (**10**) is reported.

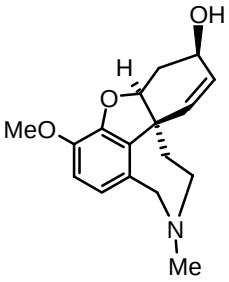
Keywords: O-dealkylation, norbelladine analogs.

Introduction

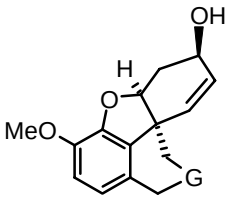
One of the key steps of the industrial synthesis [1] of the anti-Alzheimer drug galanthamine (Reminyl®, Nivalin®) [2] comprises a $K_3[Fe(CN)_6]$ induced phenol oxidation tandem cyclization [3]. In this reaction the 5-6-6-7 ring system is formed in one step starting from a suitable norbelladine derivative. We tried to extend this cyclization reaction towards the construction of 5-6-6-6 ring systems and prepared both N-[(2-bromo-5-hydroxy-4-methoxyphenyl)methyl]-N-[(4-hydroxyphenyl)methyl]-formamide (**5**) and 2-bromo-5-hydroxy-α-[(4-hydroxyphenyl)methyl]-4-methoxypropaneamide (**10**) as necessary intermediates. These intermediates were subjected to the conditions of the tandem cyclization [1], however the desired ring contracted galanthamine analog could not be obtained.



norbelladine



(-)-galanthamine



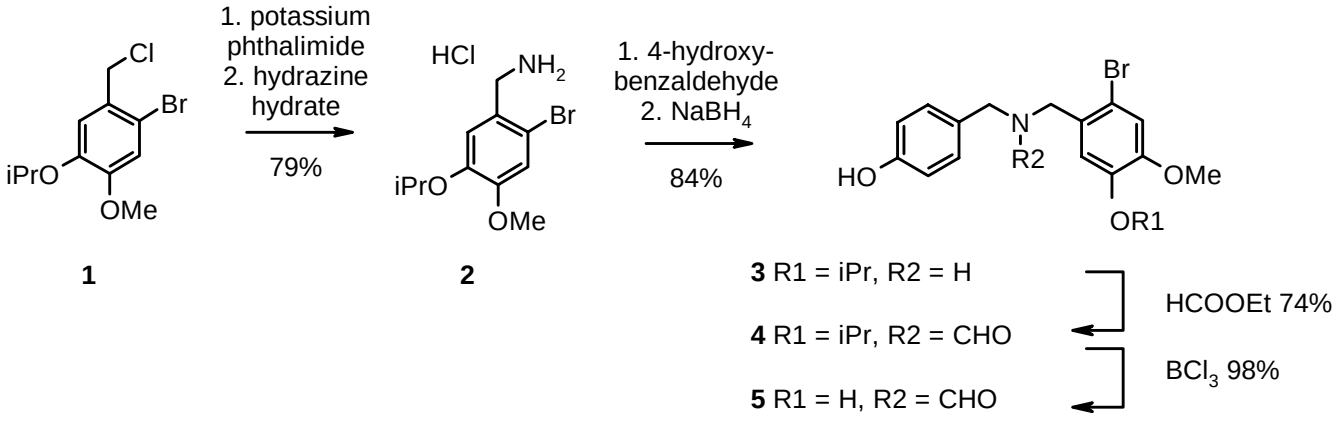
desired galanthamine analogs
G = NMe, $CHCONH_2$

The synthesized open chained norbelladine analogs **3** – **5**, which retain the partial structure of substituted benzylamines and thus are of potential pharmaceutical interest prompted this publication.

Results and Discussion

For the synthesis of diphenol compound (**5**) 1-bromo-2-(chloromethyl)-5-methoxy-4-(1-methylethoxy)benzene (**1**) [4] was converted into an amine by reaction with potassium phthalimide with subsequent hydrazinolysis and isolated as hydrochloride salt (**2**) with 79% yield. Reductive amination of 4-hydroxybenzaldehyde with the free base of **2** using sodium borohydride gave rise to the secondary amine (**3**) with 84% yield, which was reacted with ethyl formate in presence of catalytic amount of 4-(N,N-dimethylamino)pyridine to give the amide (**4**) with 74% yield. Isopropyl ether cleavage was performed under mild conditions in presence of the aryl-methy-ether substructure using boron trichloride with 98% yield (see Scheme 1) to give diphenol **5** as colorless crystals.

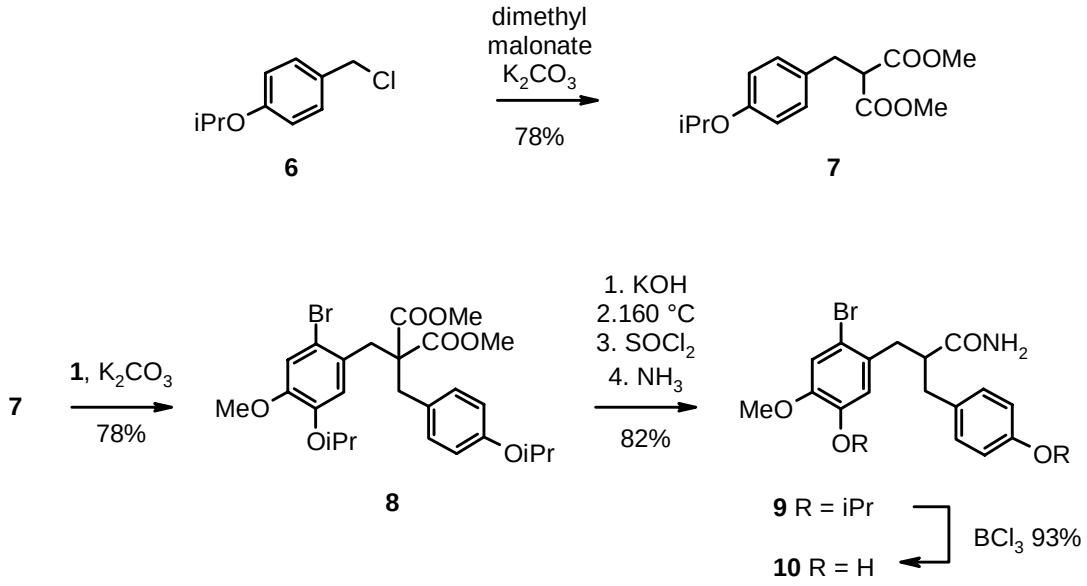
Scheme 1



10 was prepared starting from 1-(chloromethyl)-4-(1-methylethoxy)benzene (**6**) [5]. Reaction with dimethyl malonate and potassium carbonate gave **7** with a yield of 78%. The second alkylation step using 1-bromo-2-(chloromethyl)-5-methoxy-4-(1-methylethoxy)benzene (**1**) gave the ester (**8**) which was saponified and decarboxylated using a Kugelrohr apparatus. The obtained acid was converted into

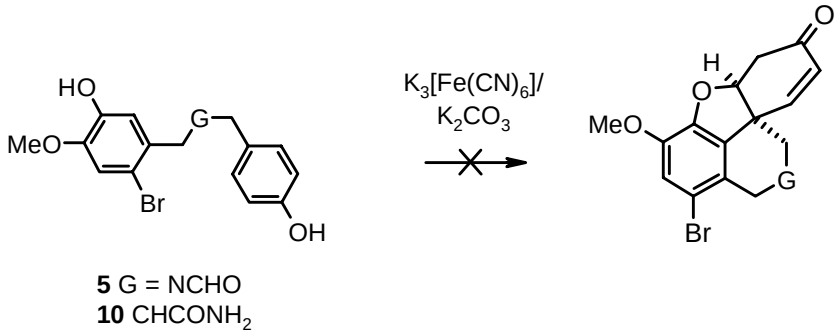
the amide (**9**) by subsequent treatment with thionyl chloride and a saturated solution of ammonia in dry formamide. Deprotection of **9**, isolated as colorless crystals with 76% yield, using boron trichloride for a selective isopropyl-aryl-ether cleavage gave rise to the norbelladine analog (**10)** with 93% yield (see Scheme 2).

Scheme 2



Tandem cyclization of **5** and **10** employing the conditions found to be optimal in the galanthamine synthesis [1] failed (see Scheme 3).

Scheme 3



Conclusions

In summary, we have developed efficient and high yielding routes towards the preparation of N-[(2-bromo-5-hydroxy-4-methoxyphenyl)methyl]-N-[(4-hydroxyphenyl)methyl]formamide (**5**) and 2-bromo-5-hydroxy-α-[(4-hydroxyphenyl)methyl]-4-methoxypropaneamide (**10**). Attempts to convert

both **5** and **10** into their corresponding bromoformylnarwedine analogs failed. Scope and limitations of this tandem cyclization were summarized elsewhere [6].

Experimental

General

Melting points were determined on a Kofler melting point apparatus. ^{1}H- and ^{13}C-NMR-spectra were recorded on a Bruker AC-200 (200 MHz) pulse Fourier-transform NMR spectrometer in $CDCl_3$ or DMSO-d_6 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-Bromo-4-methoxy-5-(1-methylethoxy)benzenemethanamine hydrochloride (**2**). 1-Bromo-2-(chloromethyl)-5-methoxy-4-(1-methylethoxy)benzene (**1**) (5.00 g, 17.0 mmol) and potassium phthalimide (3.47 g, 18.7 mmol) were stirred in dry DMF (60 mL) for 12 h at 60 °C. The suspension was filtered and concentrated *in vacuo*, and the residue was partitioned between water (150 mL) and Et_2O (150 mL). The aqueous layer was extracted with Et_2O (2 x 100 mL), the combined organic layer was washed with water (3 x 200 mL) and brine (1 x 200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was refluxed with hydrazine hydrate (1.28 g, 25.5 mmol) in dry EtOH (100 mL) for 24 h, cooled to ambient temperature and filtered. The residue was extracted with boiling EtOH (2 x 25 mL), the combined extracts were added to the filtrate and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), cooled to 0 °C and treated with HCl/Et_2O (satd. at 0 °C). The precipitated hydrochloride salt was collected by filtration and triturated with dry Et_2O (3 x 50 mL). Yield: colorless needles (4.15 g, 79%), mp. 235-237 °C. TLC: R_f = 0.7 ($CHCl_3$ - MeOH - conc. NH_3 = 89:10:1); Anal. Calcd for $C_{11}H_{16}BrNO_2$*HCl: C, 42.54; H, 5.52; N, 4.51. Found: C, 42.24; H, 5.40; N, 4.36. ^{1}H-NMR (DMSO-d_6): δ 8.73 (b, 3H), 7.41 (s, 1H), 7.18 (s, 1H), 4.61 (septet, *J* = 6.3 Hz, 1H), 4.03 (s, 2H), 3.86(s, 3H), 3.47(s, 2H), 1.22 (d, *J* = 6.3 Hz, 6H); ^{13}C-NMR (DMSO-d_6): δ 150.5 (s), 146.4 (s), 124.95 (s), 117.05 (s), 115.85 (d), 113.55 (d), 70.8 (d), 56.1 (q), 41.7 (t), 21.9 (2 q).

4-[[[2-Bromo-4-methoxy-5-(1-methylethoxy)phenylmethyl]amino]methyl]phenol (**3**). 2-Bromo-4-methoxy-5-(1-methylethoxy)benzenemethanamine (2.28 g. 7.30 mmol, extracted from **2** by partitioning the salt between $CHCl_3$ and conc. NH_3) and 4-hydroxybenzaldehyde (0.89 g, 7.30 mmol) in dry EtOH (60 mL) were stirred under reflux for 6 h. The mixture was cooled to 0 °C, then sodium borohydride (1.36 g, 36.5 mmol) was added and stirred for 30 min at this temperature and 1 h under reflux. 2 N HCl (10 mL) was added, the mixture was concentrated to a volume of 5 mL, neutralized with satd. $NaHCO_3$

and extracted with $CHCl_3$ (4 x 50 mL). The combined organic layer was washed with satd. $NaHCO_3$ (2 x 100 mL), water (1 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by MPLC (100 g SiO_2, $CHCl_3$: MeOH : conc. NH_3 = 89 : 10 : 1). Yield: colorless crystals (2.34 g, 84%). An analytical sample was converted into the hydrochloride salt by treatment with HCl/Et_2O to give colorless crystals (mp. 211 - 215 °C). TLC: R_f = 0.55 ($CHCl_3$ - MeOH - conc. NH_3 = 89:10:1); Anal. Calcd for $C_{18}H_{22}BrNO_3$*HCl: C, 51.88; H, 5.56; N, 3.36. Found: C, 51.93; H, 5.56; N, 3.31. ^{1}H-NMR (DMSO-d_6): δ 9.82 (b, 3H), 7.54 (s, 1H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.17 (s, 1H), 6.82 (d, *J* = 8.9 Hz, 2H), 4.61 (septet, *J* = 6,7 Hz, 1H), 4.10 (s, 2H), 4.06 (s, 2H), 3.80 (s, 3H), 1.26 (d, *J* = 6,7 Hz, 6H); ^{13}C-NMR (DMSO-d_6): δ 158.1 (s), 150.8 (s), 146.3 (s), 131.8 (d), 123.1 (s), 121.5 (s), 117.7 (s), 115.8 (d), 115.4 (d), 114.4 (d), 70.8 (d), 56.0 (q), 49.4 (t), 48.3 (t), 21.9 (q).

N-[[2-Bromo-4-methoxy-5-(1-methylethoxy)phenyl]methyl]-N-[(4-hydroxyphenyl)-methyl]formamide (**4**)**.** Compound **3** (1.50 g, 3.94 mmol), 4-(dimethylamino)pyridine (50 mg), ethyl formate (1.4 mL), formic acid (0.4 mL) and DMF (1.5 mL) were refluxed in dry dioxane for 6 h. The mixture was concentrated *in vacuo*, and the residue was partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), the combined organic layer was washed with 2 N HCl (3 x 50 mL), water (1 x 50 mL), satd. $NaHCO_3$ (2 x 50 mL) and brine (1 x 100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was triturated with *tert.*-butylmethylether (5 mL). Yield: colorless crystals (1.19 g, 74%), mp. 125 - 128 °C. TLC: R_f = 0.5 ($CHCl_3$ - MeOH - conc. NH_3 = 89:10:1); Anal. Calcd for $C_{19}H_{22}BrNO_4$: C, 55.89; H, 5.43; N, 3.43. Found: C, 55.91; H, 5.43; N, 3.44. ^{1}H-NMR (DMSO-d_6): δ 9.46 and 9.38 (s, 1H), 8.46 and 8.40 (s, 1H), 7.12 and 7.10 (s, 1H), 7.03 and 6.99 (d, *J* = 13.3 Hz, 2H), 6.78 (s, 1H), 6.73 and 6.99 (d, *J* = 13.3 Hz, 2H), 4.55 - 4.12 (m, 5H), 3.76 (s, 3H), 1.32 - 1.12 (m, 6H); ^{13}C-NMR (DMSO-d_6): δ 163.5 and 163.3 (d), 157.0 and 156.6 (s), 150.4 and 150.0 (s), 146.3 (s), 129.1 (s), 127.0 and 126.7 (d), 126.9 and 126.6 (s), 117.2 and 116.4 (s), 116.2 and 116.1 (d), 115.4 and 115.2 (d), 113.7 and 113 (d), 70.9 (d), 55.9 (q), 49.7 (t), 44.4 and 43.9 (t), 21.8 and 21.7 (q).

N-[(2-Bromo-5-hydroxy-4-methoxyphenyl)methyl]-N-[(4-hydroxyphenyl)methyl]formamide **(5**). To **4** (1.0 g, 2.45 mmol) in dry CH_2Cl_2 (5 mL) BCl_3 (10 mL, 10 mmol, 1 M in CH_2Cl_2) was added at -78 °C and stirred for 4 h at ambient temperature. Water (20 mL) was added dropwise, and the mixture was concentrated *in vacuo* to a volume of 15 mL. The precipitate was collected by filtration and triturated with water (6 x 20 mL) and iPr_2O (2 x 10 mL). Yield: colorless crystals (879 mg, 98%), mp. 94 - 96 °C. TLC: R_f = 0.2 ($CHCl_3$ - MeOH - conc. NH_3 = 89:10:1); Anal. Calcd for $C_{16}H_{16}BrNO_4$: C, 52.84; H, 4.40; N, 3.82. Found: C, 52.65; H, 4.61; N, 3.67. ^{1}H-NMR (DMSO-d_6): δ 9.50 (b, 1H), 9.40 (b, 1H), 8.50 and 8.40 (s, 1H), 7.31 - 6.81 (m, 3H), 6.81 - 6.55 (m, 3H), 4.51 - 4.11 (m, 4H), 3.79 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 163.5 and 163.3 (d), 157.1 and 156.7 (s), 148.3 and 147.9 (s), 146.5 (s)129.3 and 129.2 (s), 127.2 and 127.1(d), 126.6 and 126.5 (s), 116.7 and 116.3 (s), 116.0 and 115.8 (d), 115.5 and 115.4 (d), 111.1 and 110.6 (d), 56.1 (q), 49.5 and 49.2 (t), 43.7 and 43.6 (t).

2-[4-(1-Methylethoxy)phenylmethyl]propandioic acid dimethylester (**7**). 1-(Chloromethyl)-4-(1-methylethoxy)benzene (**6**) (20.5 g, 111 mmol), dimethyl malonate (102.5 g, 776 mmol) and potassium carbonate (46.5 g, 332 mmol, anhydrous, freshly ground) in dry DMF (250mL) were stirred for 24 h at 70 °C. The suspension was filtered and concentrated, and the residue was partitioned between water (250 mL) and Et_2O (250 mL). The aqueous layer was extracted with Et_2O (2 x 50 mL), the combined organic layer was washed with water (3 x 200 mL) and brine (1 x 150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The excess of dimethylmalonate was removed by distillation (160 °C/15 mbar), and the crude product was purified by kugelrohr distillation (130 °C/0.001 mbar). Yield: colorless oil (23.6 g, 78%). TLC: R_f = 0.8 (petroleum ether - EtOAc = 9:1); Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.28; H, 7.07. ^{1}H-NMR ($CDCl_3$): δ 7.07 (d, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 7.6 Hz, 2H), 4.48 (septet, *J* = 6.0 Hz, 1H), 3.67 (s, 6H), 3.61 (t, *J* = 8.0 Hz, 1H), 3.12 (d, *J* = 8.0 Hz, 2H), 1.29 (d, *J* = 6.0 Hz, 6H); ^{13}C-NMR ($CDCl_3$): δ 169.1 (s), 156.6 (s), 129.6 (d), 129.4 (s), 115.8 (d), 69.6 (d), 53.7 (d), 52.3 (q), 33.8 (t), 21.9 (q).

2-[[2-Bromo-4-methoxy-5-(1-methylethoxy)phenyl]methyl]-2-[[4-(1-methylethoxy)phenyl]methyl]-propanedioic acid dimethylester (**8**). Compound **7** (2.50 g, 8.92 mmol), 1-bromo-2-chloromethyl-5-methoxy-4-(1-methylethoxy)benzene (**1**) (2.62 g, 8.92 mmol) and potassium carbonate (3.71 g, 26.8 mmol, anhydrous, freshly ground) in dry acetonitrile (100 mL) were stirred for 24 h at 60 °C. The suspension was filtered and concentrated, and the residue was partitioned between water (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (1 x 50 mL), the combined organic layer was washed with water (3 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacu*o. The crude product was purified by kugelrohr distillation (180 °C/0.01 mbar). Yield: colorless oil (3.93 g, 82%). TLC: R_f = 0.5 (petroleum ether - EtOAc = 9:1); ^{1}H-NMR ($CDCl_3$): δ 7.02 (d, *J* = 8.1 Hz, 2H), 7.00 (s, 1H), 6.89 (s, 1H), 6.78 (d, *J* = 8.1 Hz, 2H), 4.58 - 4.31 (m, 2H), 3.78 (s, 3H), 3.59 (s, 6H), 3.37 (s, 2H), 3.26 (s, 2H), 1.37 - 1.26 (m, 12H); ^{13}C-NMR ($CDCl_3$): δ 171.2 (s), 156.8 (s), 149.5 (s), 146.1 (s), 130.9 (d), 128.1 (s), 127.8 (s), 118.0 (s), 116.1 (s), 115.8 (d), 115.5 (d), 71.3 (d), 69.7 (d), 60.2 (s), 56.0 (q), 52.2 (q), 39.9 (t), 38.6 (t), 22.0 (q), 21.9 (q).

2-Bromo-4-methoxy-5-(1-methylethoxy)-α-[[4-(1-methylethoxy)phenyl]methyl]-benzenepropanamide (**9**). Compound **8** (3.93 g, 7.31 mmol) and KOH (1.50 g, 26.8 mmol) were stirred in EtOH (50 mL)/water (5 mL) under reflux for 12 h. The solution was concentrated to 5 mL *in vacuo*, a pH < 1 was adjusted by dropwise addition conc. HCl, and the mixture was partitioned between water (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2 x 50 mL), the combined organic layer was washed with water (3 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was decarboxylated using a kugelrohr apparatus (160 °C, 30 min), and the formed carboxylic acid was purified by subsequent distillation (165 °C/0.01 mbar). The distillate was dissolved in thionyl chloride (10 mL), then DMF (100 µL) was added and stirred for 6 h

at ambient temperature. The mixture was concentrated *in vacuo*, dissolved in dry formamide, cooled to 0 °C and treated with a solution of NH_3 in formamide (20 mL, saturated at 0 °C). The mixture was stirred for 1 h and poured into water (500 mL). The precipitate was collected by filtration and triturated with water (5 x 100 mL). Yield: colorless crystals (2.58 g, 76%), mp. 129 - 131 °C. TLC: R_f = 0.7 (CH_2Cl_2 - MeOH = 9:1); Anal. Calcd for $C_{23}H_{30}BrNO_4$: C, 59.49; H, 6.51; N, 3.02. Found: C, 59.22; H, 6.24; N, 2.90. ^{1}H-NMR (DMSO-d_6): δ 7.22 (b, 1H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.07 (s, 1H), 6.88 (s, 1H), 6.80 (d, *J* = 8.1 Hz, 2H), 6.71 (b, 1H), 4.76 - 4.46 (m, 2H), 3.39 (s, 3H), 2.98 - 2.34 (m, 5H), 1.38 - 1.07 (m, 12H); ^{13}C-NMR (DMSO-d_6): δ 175.5 (s), 155.8 (s), 149.1 (s), 145.8 (s), 131.4 (s), 131.0 (s), 129.9 (d), 118.1 (s), 115.9 (d), 115.4 d), 114.1 (d), 70.7 (d), 69.0 (d), 55.8 (q), 48.0 (d), 37.6 (t), 37.0 (t), 22.0 (q), 21.9 (q), 21.8 (q).

2-Bromo-5-hydroxy-α-[(4-hydroxyphenyl)methyl]-4-methoxypropanamide (**10**). To **9** 2.00 g, 4.31 mmol) in dry CH_2Cl_2 (30 mL) BCl_3 (10 mL, 16 mmol, 1.6 M in CH_2Cl_2) was added at -78 °C and stirred for 1 h at this temperature and for additional 2 h at ambient temperature. Water (100 mL) was added dropwise, and the mixture was concentrated *in vacuo* to a volume of 80 mL. The precipitate was collected by filtration and triturated with water (6 x 50 mL) and iPr_2O (2 x 10 mL). Yield: colorless crystals (1.52 g, 93%), mp. 174 - 176 °C. TLC: R_f = 0.4 (CH_2Cl_2 - MeOH = 9:1); Anal. Calcd for $C_{17}H_{18}BrNO_4$: C, 53.70; H, 4.77; N, 3.68. Found: C, 53.48; H, 4.66; N, 3.50. ^{1}H-NMR (DMSO-d_6): δ 9.21 (b, 2H), 7.21 (b, 1H), 7.13 - 6.89 (m, 3H), 6.87 - 6.51 (m, 4H), 3.72 (s, 3H), 2.93 - 2.30 (m, 5H); ^{13}C-NMR (DMSO-d_6): δ 175.9 (s), 155.6 (s), 147.1 (s), 145.8 (s), 131.4 (s), 130.0 (d), 129.9 (s), 118.0 (s), 115.9 (d), 115.1 (d), 112.0 (d), 56.0 (q), 48.2 (d), 37.7 (t), 37.1 (t).

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Samples Availability: Available from the authors.