Directed *Ortho*-Metalation of Unprotected Benzoic Acids. Methodology and Regioselective Synthesis of Useful Contiguously 3- and 6-Substituted 2-Methoxybenzoic acid Building Blocks

SUPPORTING INFORMATION

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A. General

For standard working practice, see refs^(1,2). Reactions were carried out under argon in oven-dried glassware. Tetrahydrofuran was dried from sodium benzophenone. Iodomethane, *N,N*-dimethylformamide and benzaldehyde were dried with CaH₂ and distilled prior to use. NMR spectra were recorded on a 200- or 400-MHz spectrometer. ¹³C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in CDCl₃, chemical shifts were recorded relative to the internal TMS (tetramethylsilane) reference signal. For acetone-*d*₆, chemical shifts are given relative to the solvent signals. All melting points are uncorrected.

n-BuLi (1.6 M in hexanes) and *s*-BuLi (1.3 M in cyclohexane-hexanes) were titrated periodically against 2,5-dimethoxybenzyl alcohol. *N,N,N',N'*-Tetramethyl-1,2-ethylenediamine (TMEDA) was distilled from CaH₂. Potassium *tert*-butylate (*t*-BuOK) was sublimated.

B. General procedure for the preparation of 6-substituted 2-methoxybenzoic acids (9a-f,i,j). Preparation of 3-hydroxy-7-methoxyisobenzofuran-1(3*H*)-one (16) and 7-methoxy-3-phenylisobenzofuran-1(3*H*)-one (17)

To a stirred solution of a 1:1 *s*-BuLi/TMEDA complex (11 mmol) in anhydrous THF at –78 °C was added dropwise under argon the recrystallized 2-methoxybenzoic acid (**11**) (0.76 g, 5 mmol) dissolved in dry THF (5 mL). After 2 h at this temperature, the mixture was treated with an excess of the appropriate electrophile (20 mmol) dissolved in THF. The resulting solution was then slowly allowed to warm to ambient temperature, and water was added. The aqueous layer was washed with diethyl ether (2 × 30 mL), and shaken, and acidified with 2M HCl. The mixture was then diluted with diethyl ether and the organic layer was separated and dried with MgSO₄.

¹ Schlosser, M. *Organometallics in Synthesis. A Manual*; Wiley: Chichester, 2nd Edition, 2002.

² (a) Cantegril, R.; Mortier, J.; Croisat, D.; Peignier, R. Wo. Pat. 9602138, 1996. (b) Cantegril, R.; Croisat, D.; Desbordes, P.; Guigues, F.; Mortier, J.; Peignier, R.; Vors, J.-P. U. S. Pat. 5945382, 1999.

Filtration and concentration *in vacuo* gave the crude benzoic acids, which were purified by recrystallization or chromatography for characterisation in each case.

2-Methoxy-6-methylbenzoic acid (**9a**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by MeI (2.84 g, 20 mmol). Workup in the usual manner followed by recrystallization (heptane/ethylacetate) afforded **9a** (0.51 g, 61%) as a white solid: mp 138.5-139.0 °C (lit.⁽³⁾ 137-138°C). ¹H NMR (200 MHz, CDCl₃) δ ppm: 2.45 (s, 3H), 3.88 (s, 3H), 6.82 (d, 1H, *J* = 8.0 Hz), 6.83 (d, 1H, *J* = 8.0 Hz), 7.29 (t, 1H, *J* = *J* = 8.0Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 20.6, 56.6, 109.2, 122.1, 123.6, 131.6, 138.7, 157.4, 173.1. IR (neat): 2995, 1692, 1585, 1471, 1267, 1087, 915 cm⁻¹. Anal. Calcd for C₉H₁₀O₃: C, 65.05; H, 6.07. Found: C, 65.03; H, 6.05.

2-Methoxy-6-(trimethylsilyl)benzoic acid (**9b**) (*in situ* quench technique)

To a solution of LTMP (9 mmol) in THF (20 mL) at -78 °C were added successively chlorotrimethylsilane (1.38 mL, 10.5 mmol) in THF (5 mL) and 2-methoxybenzoic acid (**6**) (0.46 g, 3 mmol) in THF (3 mL). After being warmed gradually to rt for 4 h, the solution was allowed to warm to rt. Aqueous 2M NaOH was added until the pH reached 10. The aqueous layer was washed with diethyl ether, acidified with aqueous 4M HCl, and extracted with diethyl ether. The organic layer was dried over MgSO₄, filtrated, and concentrated in *vacuo*. The residue was purified by colum chromatography on silicagel (cyclohexane/diethyl ether 90:10) to give **9b** (0.60 g, 89%) as a white solid (mp 85.5-87.0 °C). ¹H NMR (200 MHz, CDCl₃) δ ppm: 0.33 (s, 9H), 3.98 (s, 3H), 7.05 (d, 1H, *J* = 8.4 Hz), 7.37 (d, 1H, *J* = 7.8 Hz), 7.51 (dd, 1H, *J* = 8.4 Hz, *J* = 7.8 Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 0.6 (3C), 56.0, 112.1, 124.2, 127.9, 131.8, 144.4, 157.2, 170.3. IR (neat): 2840, 1681, 1571, 1445, 1243,

³ Reitz, D. B.; Massey, S. M. *J. Org. Chem.* **1990**, *55*, 1375.

1126, 950 cm^{-1} . Anal. calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_3\text{Si}$: C, 58.89; H, 7.19. Found: C, 58.94; H, 7.12.

2-Chloro-6-methoxybenzoic acid (**9c**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by hexachloroethane (4.73 g, 20 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 80:20) afforded **9c** (0.54 g, 58%) as a white solid: mp 142.5-144 °C (Lit.⁽⁴⁾ 140-141 °C). ^1H NMR (200 MHz, CDCl_3) δ ppm: 3.88 (s, 3H), 6.88 (dd, 1H, $J = 8.4$ Hz, $J = 0.8$ Hz), 7.03 (dd, 1H, $J = 8.2$ Hz, $J = 0.8$ Hz), 7.29 (dd, 1H, $J = 8.4$ Hz, $J = 8.2$ Hz). ^{13}C NMR (200 MHz, CDCl_3) δ ppm: 56.1, 110.4, 120.9, 124.9, 129.2, 130.9, 156.3, 165.9. IR (neat): 2839, 2531, 1713, 1589, 1467, 1262, 1029, 924 cm^{-1} . Anal. Calcd for $\text{C}_8\text{H}_7\text{ClO}_3$: C, 51.50; H, 3.78. Found: C, 51.81; H, 3.71.

2-Bromo-6-methoxybenzoic acid (**9d**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by dibromotetrachloroethane (6.51 g, 20 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 80:20) afforded **9d** (0.68 g, 59%) as a white solid: mp 127-129 °C (Lit.⁽⁵⁾ 124-127 °C). ^1H NMR (200 MHz, CDCl_3) δ ppm: 3.89 (s, 3H), 6.87 (dd, 1H, $J = 8.4$ Hz, $J = 0.8$ Hz), 7.02 (dd, 1H, $J = 8.1$ Hz, $J = 0.8$ Hz), 7.32 (dd, 1H, $J = 8.4$ Hz, $J = 8.1$ Hz). ^{13}C NMR (50 MHz, CDCl_3) δ ppm: 56.3, 109.6, 121.7, 122.7, 131.5, 131.6, 157.3, 171.3. IR (neat): 2841, 1719, 1589, 1469, 1262 cm^{-1} .

⁴ Postmus, C. Jr.; Kaye, I. A.; Craig, C. A.; Matthews, R. S. *J. Org. Chem.* **1964**, *29*, 2693.

⁵ Sugaya, T.; Mimura, Y.; Kato, N.; Ikuta, M.; Mimura, T.; Kasai, M.; Tomioka, S. *Synthesis* **1994**, 73.

2-Iodo-6-methoxybenzoic acid (**9e**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by iodine (5.07 g, 20 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 80:20) afforded **9e** (0.64 g, 46%) as a brown solid: mp 129-131 (Lit.⁽⁶⁾ 128-130 °C). ¹H NMR (200 MHz, CDCl₃) 3.84 (s, 3H), 6.92 (dd, 1H, *J* = 8.4 Hz, *J* = 0.9 Hz), 7.10 (dd, 1H, *J* = 8.4 Hz, *J* = 8.1 Hz), 7.44 (dd, 1H, *J* = 8.1 Hz, *J* = 0.9 Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 56.6, 92.2, 110.9, 129.2, 131.2, 131.9, 156.7, 172.6. IR (neat): 2841, 1719, 1589, 1469, 1262 cm⁻¹.

2-Methoxy-6-(methylthio)benzoic acid (**9f**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by dimethyl disulfide (1.88 g, 20 mmol). Workup in the usual manner followed by recrystallization (cyclohexane/ethylacetate) afforded **9f** (0.47 g, 47%) as a white solid: mp 182-184 °C (Lit.⁽⁷⁾ 184-185 °C). ¹H NMR (200 MHz, CDCl₃) δ ppm: 2.45 (s, 3H), 3.98 (s, 3H), 6.80 (d, 1H, *J* = 8.2 Hz), 6.98 (d, 1H, *J* = 8.2 Hz), 7.40 (t, 1H, *J* = 8.2 Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 17.0, 56.6, 107.6, 107.9, 119.4, 131.9, 142.6, 157.9, 169.1. IR (neat): 2941, 1688, 1578, 1461, 1261, 1040, 927 cm⁻¹. Anal. Calcd for C₉H₁₀O₃S: C, 54.53; H, 5.08. Found: C, 54.41; H, 5.01.

3-Hydroxy-7-methoxyisobenzofuran-1(3*H*)-one (**16**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by DMF (1.46 g, 20 mmol)

⁶ Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104.

⁷ Cabiddu, S.; Melis, S.; Piras, P. P.; Secci, M. *J. Organometallic Chem.* **1977**, 132 (3), 321-326.

(reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 70:30) afforded **16** (0.39 g, 43%) as a white solid: mp 155-157 °C (Lit.⁽⁸⁾ 155-156 °C). ¹H NMR (200 MHz, CDCl₃) δ ppm: 3.99 (s, 3H), 6.53 (s, 1H), 7.01 (d, 1H, *J* = 8.4 Hz), 7.18 (d, 1H *J* = 7.4 Hz), 7.53 (dd, 1H, *J* = 8.4 Hz, *J* = 7.4 Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 55.6, 96.5, 112.3, 115.1, 121.2, 130.6, 133.0, 158.0, 167.3. IR (neat): 2987, 1754, 1601, 1486, 1296, 1197, 1027 cm⁻¹.

7-Methoxy-3-phenylisobenzofuran-1(3*H*)-one (**17**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by benzaldehyde (2.12 g, 20 mmol) (reverse addition). Workup in the usual manner followed by recrystallization (cyclohexane/ethylacetate 70:30) afforded **17** (0.624 g, 52%) as a white solid: mp 136-138 °C (Lit.⁽⁹⁾ 139-141.5 °C). ¹H NMR (200 MHz, CDCl₃) δ ppm: 4.02 (s, 3H), 6.31 (s, 1H), 6.84 (d, 1H, *J* = 7.6 Hz), 6.94 (d, 1H, *J* = 8.4 Hz), 7.25-7.39 (m, 5H), 7.53 (dd, 1H, *J* = 7.6 Hz, *J* = 8.4 Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 56.1, 81.6, 110.9, 112.9, 114.5, 126.9, 128.9 (2C), 129.1 (2C), 136.6, 136.7, 152.5, 158.5, 168.6. IR (neat): 2985, 1754, 1600, 1486, 1296, 1196, 1027 cm⁻¹. Anal. Calcd for C₁₅H₁₂O₃: C, 74.99; H, 5.03. Found: C, 74.56; H, 5.03.

2-Allyl-6-methoxybenzoic acid (**9i**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by allyl bromide (2.42 g, 20 mmol) (reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 85:15) afforded **9i** (0.43 g, 45%) as a

⁸ Freskos, J. N.; Morrow, G. W. Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805-810.

⁹ Harland, P.; Hodge, P. *Synthesis* **1983**, 419.

white solid: mp 89-91 °C (Lit.⁽¹⁰⁾ 91 °C). ¹H NMR (200 MHz, CDCl₃) δ ppm: 3.54 (d, 2H, *J* = 6.7 Hz), 3.89 (s, 3H), 5.04-5.15 (m, 2H), 5.87-6.07 (m, 1H), 6.85 (d, 1H, *J* = 8.2 Hz), 6.91 (d, 1H, *J* = 7.8 Hz), 7.34 (dd, 1H, *J* = 8.2 Hz, *J* = 7.8 Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 37.9, 56.1, 109.3, 116.4, 122.1, 122.3, 131.2, 136.4, 139.6, 156.8, 172.9. IR (neat): 2951, 1685, 1581, 1471, 1289, 1061, 918 cm⁻¹.

2-Benzyl-6-methoxybenzoic acid (9j)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.76 g, 5 mmol) in THF was added dropwise to a stirred solution of *s*-BuLi/TMEDA (11 mmol). The solution was quenched by benzyl bromide (3.40 g, 20 mmol) (reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 80:20) afforded **9j** (0.57 g, 47%) as a white solid: mp 148 -149.5 °C. ¹H NMR (200 MHz, CDCl₃) δ ppm: 3.90 (s, 3H), 4.14 (s, 2H), 6.82 (dd, 2H, *J* = 7.9 Hz, *J* = 9.9 Hz), 7.16-7.34 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 39.2, 56.1, 108.9, 109.2, 122.8, 126.3, 128.4 (2C), 129.2 (2C), 131.2, 140.0, 140.8, 156.8, 172.6. IR (neat): 2941, 1690, 1597, 1469, 1293, 1080, 932 cm⁻¹.

C. General procedure for the preparation of 3-substituted 2-methoxybenzoic acids (10a-f,h)

2-Methoxybenzoic acid (0.46 g, 3 mmol) in THF (5 mL) was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1 ratio, 12 mmol) in THF (30 mL) at -78 °C. After being stirred -78 °C for 2 h, the reaction mixture was quenched with the electrophile (18 mmol) in THF (5 mL). Stirring was maintained for 1 h and the resulting mixture was allowed to warm to rt and hydrolyzed with water (30 mL). The aqueous layer was washed with diethyl ether (2 × 30 mL), acidified with aqueous (2M) HCl until pH reached 1, and extracted with diethyl ether (3 × 30 mL). The organic layer was dried over MgSO₄, filtrated and concentrated *in vacuo* to give the

¹⁰ Yang, K. L.; Balckman, B.; Diedrich, W.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Ahn, Y. M.; Georg, G. I. *J. Org. Chem.* **2003**, *68*, 10030.

crude benzoic acids (**10a-f,h**) which were purified by chromatography or fractional crystallization.

2-Methoxy-3-methylbenzoic acid (**10a**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1 ratio, 12 mmol). The solution was quenched by MeI (2.55 g, 18 mmol). Workup in the usual manner followed by recrystallization (cyclohexane/ethylacetate) afforded **10a** (0.199 g, 40%) as a white solid: mp 81-83 °C. ¹H NMR (200 MHz, CDCl₃) δ ppm: 2.37 (s, 3H), 3.93 (s, 3H), 7.17 (dd, 1H *J* = 7.8 Hz, *J* = 7.4 Hz), 7.43 (d, 1H, *J* = 7.4 Hz), 7.91 (d, 1H, *J* = 7.8 Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 16.0, 62.1, 122.2, 124.8, 130.6, 131.9, 136.9, 158.1, 167.6. IR (neat): 2833, 2575, 1667, 1589, 1468, 1307, 1089, 949 cm⁻¹. HRMS (EI) *m/z* calcd. for C₉H₁₀O₃ (M⁺): 166.0629. Found: 166.0628.

2-Methoxy-3-(trimethylsilyl)benzoic acid (**10b**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1 ratio, 12 mmol). The solution was quenched by chlorotrimethylsilane (1.96 g, 18 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 90:10) afforded **10b** (0.269 g, 40%) as a white solid: mp 96-98 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 0.34 (s, 9H), 3.89 (s, 3H), 7.21 (t, 1H, *J* = 7.3 Hz), 7.64 (dd, 1H, *J* = 7.3 Hz, *J* = 1.8 Hz), 8.04 (dd, *J* = 7.6 Hz, *J* = 1.8 Hz). ¹³C NMR (50 MHz, CDCl₃) δ ppm: 0.6 (3C), 63.7, 121.6, 124.2, 134.5, 135.0, 141.2, 166.1, 170.6. IR (neat): 2947, 2651, 1677, 1579, 1452, 1298, 1127, 920 cm⁻¹. HRMS (EI) *m/z* calcd. for C₁₀H₁₃O₃Si (M⁺): 224.0868. Found: 224.0860.

3-Chloro-2-methoxybenzoic acid (**10c**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1 ratio, 12 mmol). The solution was quenched by hexachloroethane (4.26 g, 18 mmol). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 80:20) afforded **10c** (0.218 g, 39%) as a yellow solid: mp 114-116 °C. ¹H NMR (200 MHz, CDCl₃) δ ppm: 4.06 (s, 3H), 7.21 (t, 1H, *J* = 8.0 Hz), 7.62 (dd, 1H, *J* = 8.0 Hz, *J* = 1.6 Hz), 7.99 (dd, 1H, *J* = 8.0 Hz, *J* = 1.6 Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 62.5, 124.6, 125.3, 129.0, 131.2, 135.7, 155.9, 167.6. IR (neat): 2826, 2558, 1667, 1586, 1463, 1234, 1076, 917 cm⁻¹. HRMS (EI) *m/z* calcd. for C₈H₇O₃Cl (M⁺): 186.0083. Found: 186.0079.

3-Bromo-2-methoxybenzoic acid (**10d**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1 ratio, 12 mmol). The solution was quenched by dibromotetrachloroethane (5.86 g, 18 mmol) (reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 80:20) afforded **10d** (0.235 g, 34%) as a white solid: mp 119-121 °C (Lit.⁽¹¹⁾ 121 °C). ¹H NMR (200 MHz, CDCl₃) δ ppm: 4.07 (s, 3H), 7.22 (t, 1H, *J* = 8.0 Hz), 7.63 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz), 8.01 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 61.6, 124.9, 125.1, 128.2, 129.5, 133.4, 154.5, 166.4. IR (neat): 2952, 1669, 1588, 1465, 1222, 1077, 992 cm⁻¹.

3-Iodo-2-methoxybenzoic acid (**10e**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1 ratio, 12 mmol). The solution was quenched by iodine (4.57 g, 18 mmol) (reverse addition). Workup in the usual manner followed by chromatography

¹¹ Pudleiner, H.; Laatsch, H. *Synthesis* **1989**, 4, 286.

(cyclohexane/ethylacetate 80:20) afforded **10e** (0.225 g, 27%) as a white solid: mp 122-124 °C. ^1H NMR (200 MHz, CDCl_3) δ ppm: 3.99 (s, 3H), 7.01 (t, 1H, $J = 7.8$ Hz), 8.00-8.07 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 62.8, 93.1, 123.9, 126.4, 132.3, 144.9, 159.6, 168.1. IR (neat): 2924, 1673, 1581, 1456, 1402, 1296, 1074, 992 cm^{-1} .

2-Methoxy-3-(methylthio)benzoic acid (**10f**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1 ratio, 12 mmol). The solution was quenched by dimethyl disulfide (1.69 g, 18 mmol). Workup in the usual manner followed by recrystallization (cyclohexane/ethylacetate) afforded **10f** (0.27 g, 45%) as a white solid: mp 77-79 °C. ^1H NMR (200 MHz, CDCl_3) δ ppm: 2.49 (s, 3H), 4.03 (s, 3H), 7.25 (t, 1H, $J = 7.8$ Hz), 7.42 (dd, 1H, $J = 7.8$ Hz, $J = 1.6$ Hz), 7.89 (dd, $J = 7.8$ Hz, $J = 1.6$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 14.8, 61.7, 124.5, 124.9, 128.3, 130.1, 134.2, 156.1, 168.5. HRMS (EI) m/z calcd. for $\text{C}_9\text{H}_{10}\text{O}_3\text{S}$ (M^+): 198.0350. Found: 198.0339.

3-(Hydroxy(phenyl)methyl)-2-methoxybenzoic acid (**10h**)

According to the general procedure, the recrystallized 2-methoxybenzoic acid (**11**, 0.46 g, 3 mmol) in THF was added dropwise to a stirred solution of *n*-BuLi/*t*-BuOK (1:1 ratio, 12 mmol). The solution was quenched by benzaldehyde (1.91 g, 18 mmol) (reverse addition). Workup in the usual manner followed by chromatography (cyclohexane/ethylacetate 70:30) afforded **10h** (0.318 g, 41%) as a white solid: mp 124-126 °C. ^1H NMR (200 MHz, CDCl_3) δ ppm: 3.72 (s, 3H), 6.16 (s, 1H), 7.23-7.30 (m, 3H), 7.31-7.38 (m, 3H), 7.69 (dd, 1H, $J = 7.6$ Hz, $J = 1.5$ Hz), 7.98 (dd, 1H, $J = 7.8$ Hz, $J = 1.5$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 63.1, 71.0, 124.4, 126.6, 127.7, 128.5, 132.2, 133.4, 138.3, 143.1, 158.0, 171.5. IR (neat): 3427, 2939, 1708, 1590, 1429, 1210, 992, 752 cm^{-1} .

C- Synthesis of lunularic acid (**18**)

2-Methoxy-6-(4-methoxyphenethyl)benzoic acid

To a solution of LDA (6 mmol) in dry THF (10 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise 2-methoxy-6-methylbenzoic acid (**9a**) (0.25 g, 1.5 mmol) in THF (4 mL). After 2 h at this temperature, the mixture was quenched by 1-(chloromethyl)-4-methoxybenzene (1.22 mL, 9 mmol). The resulting solution was stirred for 2 additional hours, and was then slowly allowed to warm to ambient temperature, after which water (30 mL) was added. The aqueous layer was washed with diethyl ether ($2 \times 30\text{ mL}$), and shaken, and then acidified with 2M HCl. The mixture was diluted with diethyl ether and the organic layer was separated and dried with MgSO_4 . Filtration and concentration in vacuo gave crude 2-methoxy-6-(4-methoxyphenethyl)benzoic acid as a viscous oil which was used as such for the next step. The yield was estimated to be $> 99\%$ by ^1H NMR. ^1H NMR (200 MHz, CDCl_3) δ ppm: 2.78-2.91 (m, 2H), 2.97-3.06 (m, 2H), 3.76 (s, 3H), 3.89 (s, 3H), 6.77-6.85 (m, 4H), 7.09-7.10 (m, 2H), 7.22 (m, 1H). ^{13}C NMR (50 MHz, CDCl_3) δ ppm: 36.5, 36.9, 55.3, 56.1, 109.1, 113.9 (2C), 122.3, 129.5 (2C), 131.1, 133.8, 141.2, 156.7, 157.9, 173.4. IR (neat): 3004, 2932, 1714, 1662, 1584, 1512, 1469, 1232, 1075, 795 cm^{-1} .

2-Hydroxy-6-(4-hydroxyphenethyl)benzoic acid (lunularic acid (**18**))

Boron tribromide (13.5 mL, 13.5 mmol, 1 M in dichloromethane) was added dropwise to a stirred solution of crude 2-methoxy-6-(4-methoxyphenethyl)benzoic acid (0.43 g, 1.5 mmol) in dichloromethane (15 mL) under argon at $-78\text{ }^{\circ}\text{C}$. After being stirred for 1 h at this temperature, the solution was allowed to warm up to rt overnight. Water (10 mL) was added and the aqueous layer was extracted with dichloromethane ($2 \times 10\text{ mL}$). The solvent was removed *in vacuo* and the residue was chromatographed (ethyl acetate/cyclohexane/acetic acid 30:65:5) to afford 2-hydroxy-6-(4-hydroxyphenethyl)benzoic acid (lunularic acid (**18**)) as a white solid

(0.34 g, 87%): mp 195-197 °C (Lit.⁽¹²⁾ 199-200 °C). ¹H NMR (200 MHz, CDCl₃) δ ppm: 2.79-3.00 (m, 2H), 3.21-3.37 (m, 2H), 6.62-6.77 (m, 4H), 6.98 (t, 2H, *J* = 8 Hz), 7.16 (t, 1H, *J* = 8.0 Hz). ¹³C NMR (100 MHz, acetone-*d*₆) δ ppm: 37.9, 39.2, 112.6, 115.4 (2C), 115.8, 122.8, 129.7 (2C), 133.3, 134.4, 145.9, 155.8, 163.2, 173.2. IR (neat): 2350-3360, 1685, 1581, 1471, 1266, 1061, 918, 745 cm⁻¹.

¹² Yoshikawa, H.; Ichiki, Y.; Sakakibara, K. (D.); Tamura, H.; Suiko, M. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 840.