**Supporting Information**

# Optimization of (2,3-Dihydro-1-Benzofuran-3-yl)acetic Acids: Discovery of a Non-Free Fatty Acid-Like, Highly Bioavailable G Protein-Coupled Receptor 40/Free Fatty Acid Receptor 1 Agonist as a Glucose-Dependent Insulinotropic Agent

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Abbreviations of the solvents and reagents are used as follows: $CDCl_3$, deuterochloroform; DMSO-$d_6$, hexadeuterodimethyl sulfoxide; AcOEt, ethyl acetate; MeOH, methanol; EtOH, ethanol; IPA, 2-propanol; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; $Et_2O$, diethyl ether; DME, 1,2-dimethoxyethane; $CH_3CN$, acetonitrile; $CH_2Cl_2$, dichloromethane; $NaBH_4$, sodium borohydride; $LiAlH_4$, lithium aluminum hydride; $AlCl_3$, aluminum chloride; NaOH, sodium hydroxide; HCl, hydrochloric acid; $NH_4Cl$, ammonium chloride; $NaHCO_3$, sodium hydrogen carbonate; $MgSO_4$, magnesium sulfate; $Na_2SO_4$, sodium sulfate; $Na_2S_2O_3$, sodium thiosulfate; $K_2CO_3$, potassium carbonate; $Cs_2CO_3$, cesium carbonate; $K_3PO_4$, potassium phosphate; TBAF, tetrabutylammonium fluoride; KI, potassium iodine; *m*-CPBA, *m*-chloroperbenzoic acid; Pd/C, palladium on carbon; $Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium(0); *n*-BuLi, *n*-butyl lithium; B(*i*-PrO)$_3$, triisopropyl borate; ADDP, 1,1′-(azodicarbonyl)dipiperidine; P(*n*-Bu)$_3$, tributylphosphine; $PPh_3$, triphenylphosphine; DEAD, diethyl azodicarboxylate; *p*-TsCl, *p*-toluenesulfonyl chloride; $Et_3N$, triethylamine; TBSCl, *tert*-butyldimethylchlorosilane; *n*-$Bu_4NBr_3$, tetrabutylammonium tribromide; $TiCl_4$, titanium (IV) chloride; $Br_2$, bromine; AcOH, acetic acid; $PdCl_2(dppf)\cdot CH_2Cl_2$, [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane; NCS, *N*-chlorosuccinimide.

The following compounds **7**–**13** were also prepared from appropriate phenols **4a**–**c** and alcohols **5a**–**c** by a method similar to that described for **6**.

**[(3*R*)-6-{[4′-(2-Ethoxyethoxy)-2′,6′-dimethylbiphenyl-3-yl]methoxy}-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (7).**

Step 1: Methyl [(3*R*)-6-{[4′-(2-ethoxyethoxy)-2′,6′-dimethylbiphenyl-3-yl]methoxy}-2,3-dihydro-1-benzofuran-3-yl]acetate in 89% yield as a colorless oil. $^1$H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.98 (s, 6H), 2.50–2.61 (m, 1H), 2.69–2.79 (m, 1H), 3.62 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 3.74–3.85 (m, 3H), 4.11–4.16 (m, 2H), 4.26 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.05 (s, 2H), 6.44–6.51 (m, 2H), 6.68 (s, 2H), 7.01 (d, *J* = 8.1 Hz, 1H), 7.08 (dt, *J* = 7.2, 1.6 Hz, 1H), 7.16 (s, 1H), 7.34–7.45 (m, 2H). MS *m/z* 491 $(M + H)^+$. HPLC purity (220 nm) 100.0%.

Step 2: **7** in 80% yield as colorless crystals (hexane–AcOEt). mp 59–60 °C. $[\alpha]_D$ −7.5° (c 0.31, $CH_3CN$). 99.8% ee [column: CHIRALPAK AD, 4.6 mmID × 250 mmL; mobile phase: hexane/IPA/TFA (85/15/0.1) (v/v/v) by isocratic elution; flow rate: 0.5 mL/min; detection: UV 220 nm; temperature: room temperature]. $^1$H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.0 Hz, 3H), 1.98 (s, 6H), 2.55–2.67 (m, 1H), 2.76–2.85 (m, 1H), 3.62 (q, *J* = 7.0 Hz, 2H), 3.75–3.86 (m, 3H), 4.14 (t, *J* = 5.0 Hz, 2H), 4.28 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.05 (s, 2H), 6.44–6.52 (m, 2H), 6.68 (s, 2H), 7.02–7.11 (m, 2H), 7.16 (s, 1H), 7.34–7.45 (m, 2H). MS *m/z* 477 $(M + H)^+$. HPLC purity (220 nm) 100.0%. Anal. Calcd for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77. Found: C, 73.02; H, 6.77.

**[6-({2′,6′-Dimethyl-4′-[(3-methyloxetan-3-yl)methoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (8).**

Step 1: Methyl [6-({2′,6′-dimethyl-4′-[(3-methyloxetan-3-yl)methoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 89% yield as a yellow oil. $^1$H NMR ($CDCl_3$) δ 1.45 (s, 3H), 2.00 (s, 6H), 2.49–2.61 (m, 1H), 2.69–2.80 (m, 1H), 3.71 (s, 3H), 3.74–3.86 (m, 1H), 4.04 (s, 2H), 4.26 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.47 (d, *J* = 5.9 Hz, 2H), 4.64 (d, *J* = 5.9 Hz, 2H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.51 (m, 2H), 6.70 (s, 2H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.08 (dt, *J* = 7.1, 1.5 Hz, 1H), 7.17 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* 503 $(M + H)^+$.

Step 2: **8** in 65% yield as colorless crystals (hexane–AcOEt). mp 150–151 °C. $^1$H NMR ($CDCl_3$) δ 1.45 (s, 3H), 2.00 (s, 6H), 2.55–2.67 (m, 1H), 2.75–2.86 (m, 1H), 3.75–3.87 (m, 1H), 4.04 (s, 2H), 4.28 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.48 (d, *J* = 5.9 Hz, 2H), 4.65 (d, *J* = 5.9 Hz, 2H), 4.76 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.52 (m, 2H), 6.70 (s, 2H), 7.01–7.11 (m, 2H), 7.17 (s, 1H), 7.34–7.46 (m, 2H). MS *m/z* 489 $(M + H)^+$. HPLC purity (220 nm) 99.9%. Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.53; H, 6.61.

**[(3*S*)-6-({2′,6′-Dimethyl-4′-[(3-methyloxetan-3-yl)methoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (9).**

Step 1: Methyl [(3*S*)-6-({2′,6′-dimethyl-4′-[(3-methyloxetan-3-yl)methoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 95% yield as a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 1.45 (s, 3H), 2.00 (s, 6H), 2.50–2.60 (m, 1H), 2.70–2.79 (m, 1H), 3.72 (s, 3H), 3.74–3.86 (m, 1H), 4.04 (s, 2H), 4.26 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.47 (d, *J* = 5.8 Hz, 2H), 4.64 (d, *J* = 5.8 Hz, 2H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.51 (m, 2H), 6.70 (s, 2H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.05–7.11 (m, 1H), 7.17 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* not detected.

Step 2: **9** in 66% yield as colorless crystals (hexane–AcOEt). mp 140–142 °C. $[\alpha]_D$ +5.6° (c 0.30, $CH_3CN$). 99.8% ee [column: CHIRALPAK OD, 4.6 mmID × 250 mmL; mobile phase: hexane/IPA/TFA (80/20/0.1) (v/v/v) by isocratic elution; flow rate: 0.5 mL/min; detection: UV 220 nm; temperature: 30 °C]. $^1$H NMR ($CDCl_3$) δ 1.45 (s, 3H), 2.00 (s, 6H), 2.56–2.67 (m, 1H), 2.76–2.85 (m, 1H), 3.75–3.86 (m, 1H), 4.04 (s, 2H), 4.29 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.48 (d, *J* = 5.9 Hz, 2H), 4.65 (d, *J* = 5.9 Hz, 2H), 4.76 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.52 (m, 2H), 6.70 (s, 2H), 7.02–7.11 (m, 2H), 7.17 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* 489 $(M + H)^+$. HPLC purity (220 nm) 98.0%. Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.50; H, 6.73.

**[(3*R*)-6-({2′,6′-Dimethyl-4′-[(3-methyloxetan-3-yl)methoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (10).**

Step 1: Methyl [(3*R*)-6-({2′,6′-dimethyl-4′-[(3-methyloxetan-3-yl)methoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 90% yield as a colorless oil. $^1$H NMR ($CDCl_3$) δ 1.45 (s, 3H), 2.00 (s, 6H), 2.50–2.61 (m, 1H), 2.70–2.80 (m, 1H), 3.72 (s, 3H), 3.74–3.86 (m, 1H),

4.04 (s, 2H), 4.26 (dd, *J* = 9.0, 6.1 Hz, 1H), 4.47 (d, *J* = 5.8 Hz, 2H), 4.64 (d, *J* = 5.8 Hz, 2H), 4.75 (t, *J* = 9.0 Hz, 1H), 5.06 (s, 2H), 6.44–6.51 (m, 2H), 6.70 (s, 2H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.08 (dt, *J* = 7.1, 1.6 Hz, 1H), 7.17 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* not detected.

Step 2: **10** in 56% yield as colorless crystals (hexane–AcOEt). mp 136–138 °C. $[\alpha]_D$ −5.6° (c 0.31, $CH_3CN$). 99.4% ee [column: CHIRALPAK OD, 4.6 mmID × 250 mmL; mobile phase: hexane/IPA/TFA (80/20/0.1) (v/v/v) by isocratic elution; flow rate: 0.5 mL/min; detection: UV 220 nm; temperature: 30 °C]. $^1$H NMR ($CDCl_3$) δ 1.45 (s, 3H), 2.00 (s, 6H), 2.55–2.67 (m, 1H), 2.75–2.86 (m, 1H), 3.75–3.87 (m, 1H), 4.04 (s, 2H), 4.29 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.48 (d, *J* = 5.8 Hz, 2H), 4.65 (d, *J* = 6.0 Hz, 2H), 4.76 (t, *J* = 9.0 Hz, 1H), 5.06 (s, 2H), 6.44–6.52 (m, 2H), 6.71 (s, 2H), 7.02–7.11 (m, 2H), 7.17 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* 489 $(M + H)^+$. Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.58; H, 6.77.

**[6-({4′-[(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-2′,6′-dimethylbiphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (11).**

Step 1: Methyl [6-({4′-[(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-2′,6′-dimethylbiphenyl-3-yl}-methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 93% yield as a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 1.99 (s, 6H), 2.31–2.60 (m, 5H), 2.70–2.79 (m, 1H), 2.89–3.00 (m, 2H), 3.39–3.52 (m, 2H), 3.72 (s, 3H), 3.75–3.86 (m, 1H), 4.26 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.64–4.70 (m, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.50 (m, 2H), 6.67 (s, 2H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.07 (dt, *J* = 7.1, 1.5 Hz, 1H), 7.16 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* 551 $(M + H)^+$. HPLC purity (220 nm) 99.6%.

Step 2: **11** in 80% yield as colorless crystals (hexane–AcOEt). mp 159–161 °C. $^1$H NMR ($CDCl_3$) δ 1.99 (s, 6H), 2.31–2.56 (m, 4H), 2.56–2.67 (m, 1H), 2.76–2.85 (m, 1H), 2.90–3.00 (m, 2H), 3.39–3.52 (m, 2H), 3.75–3.87 (m, 1H), 4.29 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.64–4.70 (m, 1H), 4.76 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.52 (m, 2H), 6.67 (s, 2H), 7.03–7.10 (m, 2H), 7.16 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* 537 $(M + H)^+$. HPLC purity (220 nm) 100.0%. Anal. Calcd for $C_{30}H_{32}O_7S$: C, 67.14; H, 6.01. Found: C, 66.97; H, 6.12.

**[(3*S*)-6-({4′-[(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-2′,6′-dimethylbiphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (12).**

Step 1: Methyl [(3*S*)-6-({4′-[(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-2′,6′-dimethyl biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 79% yield as a colorless oil. $^1$H NMR ($CDCl_3$) δ 1.99 (s, 6H), 2.31–2.60 (m, 5H), 2.70–2.79 (m, 1H), 2.89–3.00 (m, 2H), 3.39–3.52 (m, 2H), 3.72 (s, 3H), 3.75–3.86 (m, 1H), 4.26 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.64–4.69 (m, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.50 (m, 2H), 6.67 (s, 2H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.04–7.09 (m, 1H), 7.16 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* 551 $(M + H)^+$.

Step 2: **12** in 85% yield as colorless crystals (heptane–AcOEt). mp 154–155 °C. $[\alpha]_D$ +6.1° (c 0.30, $CH_3CN$). $^1H$ NMR ($CDCl_3$) δ 1.99 (s, 6H), 2.30–2.44 (m, 2H), 2.45–2.56 (m, 2H), 2.56–2.67 (m, 1H), 2.75–2.86 (m, 1H), 2.89–3.00 (m, 2H), 3.38–3.52 (m, 2H), 3.75–3.87 (m, 1H), 4.29 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.63–4.70 (m, 1H), 4.76 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.52 (m, 2H), 6.67 (s, 2H), 7.02–7.10 (m, 2H), 7.16 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* 537 $(M + H)^+$. HPLC purity (220 nm) 99.8%. Anal. Calcd for $C_{30}H_{32}O_7S$: C, 67.14; H, 6.01. Found: C, 67.10; H, 6.06.

**[(3*R*)-6-({4′-[(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-2′,6′-dimethylbiphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (13).**

Step 1: Methyl [(3*R*)-6-({4′-[(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-2′,6′-dimethylbiphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 86% yield as a colorless foam. $^1H$ NMR ($CDCl_3$) δ 1.99 (s, 6H), 2.30–2.61 (m, 5H), 2.70–2.79 (m, 1H), 2.89–2.99 (m, 2H), 3.38–3.52 (m, 2H), 3.72 (s, 3H), 3.74–3.86 (m, 1H), 4.26 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.63–4.69 (m, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.42–6.50 (m, 2H), 6.67 (s, 2H), 6.99–7.10 (m, 2H), 7.16 (s, 1H), 7.35–7.46 (m, 2H).

Step 2: **13** in 92% yield as colorless crystals (heptane–AcOEt). mp 156–157 °C. $[\alpha]_D$ −4.4° (c 0.30, $CH_3CN$). $^1H$ NMR ($CDCl_3$) δ 1.99 (s, 6H), 2.30–2.44 (m, 2H), 2.45–2.67 (m, 3H), 2.74–2.86 (m, 1H), 2.89–3.00 (m, 2H), 3.38–3.52 (m, 2H), 3.75–3.87 (m, 1H), 4.29 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.63–4.69 (m, 1H), 4.76 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.52 (m, 2H), 6.67 (s, 2H), 7.02–7.10 (m, 2H), 7.16 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* 537 $(M + H)^+$. HPLC purity (220 nm) 99.8%. Anal. Calcd for $C_{30}H_{32}O_7S$: C, 67.14; H, 6.01. Found: C, 66.94; H, 6.02.

The following compound **17b** was prepared from **4b** and **5h** by a method similar to that described for **17a**.

**Methyl {(3*S*)-6-[(3′-Chloro-4′-hydroxy-2′,6′-dimethylbiphenyl-3-yl)methoxy]-2,3-dihydro-1-benzofuran-3-yl}acetate (17b).**

Step 1: Methyl {(3*S*)-6-[(4′-{[*tert*-butyl(dimethyl)silyl]oxy}-3′-chloro-2′,6′-dimethylbiphenyl-3-yl)methoxy]-2,3-dihydro-1-benzofuran-3-yl}acetate in 77% yield as colorless crystals. $^1H$ NMR ($CDCl_3$) δ 0.26 (s, 6H), 1.06 (s, 9H), 1.92 (s, 3H), 2.04 (s, 3H), 2.50–2.61 (m, 1H), 2.70–2.79 (m, 1H), 3.71 (s, 3H), 3.75–3.86 (m, 1H), 4.26 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.05 (s, 2H), 6.44–6.51 (m, 2H), 6.65 (s, 1H), 6.99–7.07 (m, 2H), 7.14 (s, 1H), 7.36–7.46 (m, 2H). MS *m/z* 567 $(M + H)^+$.

Step 2: **17b** in 88% yield as a colorless oil. $^1H$ NMR ($CDCl_3$) δ 1.94 (s, 3H), 2.04 (s, 3H), 2.49–2.61 (m, 1H), 2.69–2.80 (m, 1H), 3.71 (s, 3H), 3.74–3.86 (m, 1H), 4.26 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 5.55 (s, 1H), 6.43–6.51 (m, 2H), 6.81 (s, 1H), 6.99–7.07 (m, 2H), 7.13 (s, 1H), 7.36–7.47 (m, 2H). MS *m/z* 453 $(M + H)^+$.

The following compounds **20** and **21** were also prepared from **17a** and appropriate alcohols by a method similar to that described for **18**.

**[(3*S*)-6-({4′-[(2,4-Dimethyl-1,3-thiazol-5-yl)methoxy]-2′,6′-dimethylbiphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (20).**

Step 1: Methyl [(3*S*)-6-({4′-[(2,4-dimethyl-1,3-thiazol-5-yl)methoxy]-2′,6′-dimethylbiphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate as a crude product (a colorless oil). MS *m/z* 544 $(M + H)^+$.

Step 2: **20** in 24% yield (from **17a**) as colorless crystals (hexane–AcOEt). mp 158–159 °C. $^1$H NMR ($CDCl_3$) δ 1.91 (s, 6H), 2.34 (s, 3H), 2.59 (s, 3H), 2.61–2.80 (m, 2H), 3.56–3.74 (m, 1H), 4.18 (dd, *J* = 9.0, 6.8 Hz, 1H), 4.68 (t, *J* = 9.0 Hz, 1H), 5.09 (s, 2H), 5.20 (s, 2H), 6.42–6.56 (m, 2H), 6.77 (s, 2H), 7.02–7.16 (m, 3H), 7.35–7.49 (m, 2H). MS *m/z* 530 $(M + H)^+$. HPLC purity (220 nm) 99.1%.

**[(3*S*)-6-{[4′-(Imidazo[1,2-*a*]pyridin-5-ylmethoxy)-2′,6′-dimethylbiphenyl-3-yl]methoxy}-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (21).**

Step 1: Methyl [(3*S*)-6-{[4′-(imidazo[1,2-*a*]pyridin-5-ylmethoxy)-2′,6′-dimethylbiphenyl-3-yl]methoxy}-2,3-dihydro-1-benzofuran-3-yl]acetate as a crude product (a colorless oil). MS *m/z* 549 $(M + H)^+$.

Step 2: **21** in 16% yield (from **17a**) as colorless crystals (hexane–AcOEt). mp 204–205 °C. $^1$H NMR (DMSO-$d_6$) δ 1.93 (s, 6H), 2.38 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.62 (dd, *J* = 16.5, 5.5 Hz, 1H), 3.56–3.71 (m, 1H), 4.16 (dd, *J* = 9.0, 6.9 Hz, 1H), 4.66 (t, *J* = 9.0 Hz, 1H), 5.09 (s, 2H), 5.46 (s, 2H), 6.41–6.49 (m, 2H), 6.90 (s, 2H), 7.03–7.12 (m, 2H), 7.12–7.17 (m, 2H), 7.31 (dd, *J* = 9.0, 6.8 Hz, 1H), 7.35–7.48 (m, 2H), 7.60–7.71 (m, 2H), 7.93 (s, 1H). MS *m/z* 535 $(M + H)^+$. HPLC purity (220 nm) 99.3%.

The following compounds **22**–**26** were also prepared from **4b** and appropriate alcohols **5i**–**m** by a method similar to that described for **6**.

**[(3*S*)-6-({2′,6′-Diethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (22).**

Step 1: Methyl [(3*S*)-6-({2′,6′-diethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 93% yield as a yellow oil. $^1$H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.5 Hz, 6H), 2.22–2.43 (m, 6H), 2.49–2.60 (m, 1H), 2.70–2.78 (m, 1H), 2.97 (s, 3H), 3.25–3.33 (m, 2H), 3.71 (s, 3H), 3.74–3.85 (m, 1H), 4.12–4.18 (m, 2H), 4.25 (dd, *J* = 9.0, 6.1 Hz, 1H), 4.74 (t, *J* = 9.0 Hz, 1H), 5.06 (s, 2H), 6.43–6.49 (m, 2H), 6.66 (s, 2H), 7.00 (d, *J* = 8.1 Hz, 1H), 7.07–7.11 (m, 1H), 7.18 (s, 1H), 7.36–7.44 (m, 2H). MS *m/z* 567 $(M + H)^+$.

Step 2: **22** in 81% yield as colorless crystals (heptane–AcOEt). mp 87–89 °C. $[\alpha]_D$ +5.5° (c 0.30, $CH_3CN$). $^1H$ NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.5 Hz, 6H), 2.22–2.42 (m, 6H), 2.55–2.66 (m, 1H), 2.75–2.85 (m, 1H), 2.97 (s, 3H), 3.25–3.33 (m, 2H), 3.74–3.86 (m, 1H), 4.15 (t, *J* = 5.7 Hz, 2H), 4.28 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.07 (s, 2H), 6.43–6.51 (m, 2H), 6.66 (s, 2H), 7.04 (d, *J* = 8.3 Hz, 1H), 7.06–7.12 (m, 1H), 7.18 (s, 1H), 7.35–7.45 (m, 2H). MS *m/z* 553 $(M + H)^+$. HPLC purity (220 nm) 99.9%. Anal. Calcd for $C_{29}H_{32}O_8S \cdot 0.15$ heptane: C, 67.81; H, 6.82. Found: C, 67.88; H, 6.84.

**[(3*S*)-6-({4′-[(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-2′,3′,5′,6′-tetramethylbiphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (23).**

Step 1: Methyl [(3*S*)-6-({4′-[(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-2′,3′,5′,6′-tetramethyl biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 81% yield as a colorless amorphous powder. $^1H$ NMR ($CDCl_3$) δ 1.87 (s, 6H), 2.20 (s, 6H), 2.30–2.60 (m, 5H), 2.70–2.79 (m, 1H), 2.95–3.08 (m, 2H), 3.31–3.43 (m, 2H), 3.72 (s, 3H), 3.75–3.86 (m, 1H), 3.94–4.03 (m, 1H), 4.26 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.05 (s, 2H), 6.44–6.51 (m, 2H), 6.99–7.06 (m, 2H), 7.12 (s, 1H), 7.35–7.45 (m, 2H). MS *m/z* 579 $(M + H)^+$.

Step 2: **23** in 64% yield as colorless crystals (heptane–AcOEt). mp 143–145 °C. $[\alpha]_D$ +2.8° (c 0.30, $CHCl_3$). $^1H$ NMR ($CDCl_3$) δ 1.87 (s, 6H), 2.20 (s, 6H), 2.29–2.55 (m, 4H), 2.55–2.67 (m, 1H), 2.75–2.85 (m, 1H), 2.95–3.08 (m, 2H), 3.31–3.44 (m, 2H), 3.74–3.87 (m, 1H), 3.94–4.04 (m, 1H), 4.28 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.76 (t, *J* = 9.1 Hz, 1H), 5.05 (s, 2H), 7.00–7.08 (m, 2H), 7.12 (s, 1H), 7.35–7.46 (m, 2H). MS *m/z* 565 $(M + H)^+$. HPLC purity (220 nm) 99.6%. Anal. Calcd for $C_{32}H_{36}O_7S$: C, 68.06; H, 6.43. Found: C, 67.80; H, 6.40.

**[(3*S*)-6-({2′,3′,5′,6′-Tetramethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (24).**

Step 1: Methyl [(3*S*)-6-({2′,3′,5′,6′-tetramethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl} methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 82% yield as a colorless oil. $^1H$ NMR ($CDCl_3$) δ 1.87 (s, 6H), 2.19 (s, 6H), 2.32–2.43 (m, 2H), 2.50–2.61 (m, 1H), 2.70–2.79 (m, 1H), 3.00 (s, 3H), 3.35–3.43 (m, 2H), 3.71 (s, 3H), 3.74–3.90 (m, 3H), 4.26 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.05 (s, 2H), 6.43–6.51 (m, 2H), 6.99–7.07 (m, 2H), 7.13 (s, 1H), 7.35–7.45 (m, 2H). MS *m/z* 567 $(M + H)^+$.

Step 2: **24** in 94% yield as colorless crystals (heptane–AcOEt). mp 160–162 °C. $[\alpha]_D$ +6.3° (c 0.30, $CH_3CN$). $^1H$ NMR ($CDCl_3$) δ 1.87 (s, 6H), 2.19 (s, 6H), 2.32–2.43 (m, 2H), 2.56–2.66 (m, 1H), 2.75–2.85 (m, 1H), 3.00 (s, 3H), 3.35–3.43 (m, 2H), 3.75–3.89 (m, 3H), 4.28 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.76 (t, *J* = 9.1 Hz, 1H), 5.05 (s, 2H), 6.44–6.52 (m, 2H), 7.01–7.07 (m, 2H), 7.13 (s, 1H), 7.35–7.45 (m, 2H). MS *m/z* 553 $(M + H)^+$. HPLC purity (220 nm) 99.3%. Anal. Calcd for $C_{31}H_{36}O_7S$: C, 67.37; H, 6.57. Found: C, 67.39; H, 6.64.

**[(3*S*)-6-({4′-[(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-3′-fluoro-2′,6′-dimethylbiphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (25).**

Step 1: Methyl [(3*S*)-6-({4′-[(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-3′-fluoro-2′,6′-dimethylbiphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate as a crude product (a colorless oil). MS *m/z* 569 $(M + H)^+$.

Step 2: **25** in 15% yield (from **43c**) as colorless crystals (hexane–diisopropyl ether). mp 112–113 °C. $^1$H NMR ($CDCl_3$) δ 1.89–1.97 (m, 6H), 2.29–2.45 (m, 2H), 2.46–2.56 (m, 2H), 2.61 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.81 (dd, *J* = 16.8, 5.7 Hz, 1H), 2.90–3.01 (m, 2H), 3.46–3.59 (m, 2H), 3.75–3.86 (m, 1H), 4.29 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.56–4.64 (m, 1H), 4.76 (t, *J* = 9.2 Hz, 1H), 5.06 (s, 2H), 6.44–6.51 (m, 2H), 6.74 (d, *J* = 8.3 Hz, 1H), 7.02–7.08 (m, 2H), 7.14 (s, 1H), 7.37–7.48 (m, 2H). MS *m/z* 535 $(M + H)^+$. HPLC purity (220 nm) 99.4%.

**[6-({3′-Fluoro-2′,6′-dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (26).**

Step 1: Methyl [(3*S*)-6-({3′-fluoro-2′,6′-dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 77% yield as colorless crystals (heptane–AcOEt). mp 101–103 °C. $^1$H NMR ($CDCl_3$) δ 1.90–1.93 (m, 3H), 1.96 (s, 3H), 2.33–2.44 (m, 2H), 2.55 (dd, *J* = 16.5, 5.7 Hz, 1H), 2.75 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.98 (s, 3H), 3.28–3.35 (m, 2H), 3.72 (s, 3H), 3.74–3.86 (m, 1H), 4.17–4.29 (m, 3H), 4.75 (t, *J* = 9.0 Hz, 1H), 5.06 (s, 2H), 6.44–6.51 (m, 2H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.99–7.07 (m, 2H), 7.13 (s, 1H), 7.36–7.46 (m, 2H). MS *m/z* 557 $(M + H)^+$. Anal. Calcd for $C_{30}H_{33}FO_7S$: C, 64.73; H, 5.98. Found: C, 64.75; H, 5.90.

Step 2: **26** in 90% yield as colorless crystals (heptane–AcOEt). mp 115–117 °C. $[\alpha]_D$ +5.9° (c 0.30, $CH_3CN$). $^1$H NMR ($CDCl_3$) δ 1.89–1.98 (m, 6H), 2.32–2.44 (m, 2H), 2.60 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.80 (dd, *J* = 16.8, 5.4 Hz, 1H), 2.98 (s, 3H), 3.27–3.35 (m, 2H), 3.73–3.86 (m, 1H), 4.20 (t, *J* = 5.7 Hz, 2H), 4.28 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.75 (t, *J* = 9.2 Hz, 1H), 5.06 (s, 2H), 6.44–6.51 (m, 2H), 6.70 (d, *J* = 8.1 Hz, 1H), 7.02–7.08 (m, 2H), 7.13 (s, 1H), 7.37–7.46 (m, 2H). MS *m/z* 543 $(M + H)^+$. HPLC purity (220 nm) 99.9%. Anal. $C_{29}H_{31}FO_7S$: C, 64.19; H, 5.76. Found: C, 64.40; H, 5.92.

The following compound **28** was prepared from **4b** and **5n** by a similar to that described for **6**.

**[(3*S*)-6-({3′,5′-Dichloro-2′,6′-dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic Acid (28).**

Step 1: Methyl [(3*S*)-6-({3′,5′-dichloro-2′,6′-dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetate in 89% yield as a yellow oil. $^1$H NMR

($CDCl_3$) δ 2.02 (s, 6H), 2.35–2.47 (m, 2H), 2.50–2.61 (m, 1H), 2.70–2.79 (m, 1H), 3.00 (s, 3H), 3.43–3.52 (m, 2H), 3.72 (s, 3H), 3.75–3.86 (m, 1H), 4.16 (t, *J* = 5.7 Hz, 2H), 4.26 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.75 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.43–6.50 (m, 2H), 6.99–7.05 (m, 2H), 7.11 (s, 1H), 7.39–7.49 (m, 2H). MS *m/z* 607 $(M + H)^+$.

Step 2: **28** in 86% yield as colorless crystals (heptane–AcOEt). mp 115–116 °C. $[\alpha]_D$ +4.7° (c 0.30, $CH_3CN$). $^1H$ NMR ($CDCl_3$) δ 2.02 (s, 6H), 2.36–2.47 (m, 2H), 2.56–2.67 (m, 1H), 2.76–2.85 (m, 1H), 3.00 (s, 3H), 3.43–3.52 (m, 2H), 3.75–3.87 (m, 1H), 4.16 (t, *J* = 5.7 Hz, 2H), 4.29 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.76 (t, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 6.44–6.51 (m, 2H), 7.00–7.08 (m, 2H), 7.11 (s, 1H), 7.39–7.49 (m, 2H). MS *m/z* 593 $(M + H)^+$. HPLC purity (220 nm) 99.8%. Anal. Calcd for $C_{29}H_{30}Cl_2O_7S$: C, 58.69; H, 5.09. Found: C, 58.69; H, 4.99.

**{4′-[2-(Ethylthio)ethoxy]-2′,6′-dimethylbiphenyl-3-yl}methanol (5e).**

The title compound was prepared from **32** and 2-chloroethyl ethyl sulfide by a method similar to that described for **5a** in 47% yield as a colorless oil. $^1H$ NMR ($CDCl_3$) δ 1.31 (t, *J* = 7.3 Hz, 3H), 1.67 (t, *J* = 5.8 Hz, 1H), 2.00 (s, 6H), 2.67 (q, *J* = 7.3 Hz, 2H), 2.92 (t, *J* = 7.0 Hz, 2H), 4.16 (t, *J* = 7.0 Hz, 2H), 4.73 (d, *J* = 5.8 Hz, 2H), 6.66 (s, 2H), 7.06 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.12 (s, 1H), 7.30–7.36 (m, 1H), 7.41 (t, *J* = 7.3 Hz, 1H). MS *m/z* 299 $(M - 18 + H)^+$.

Compounds **33a–c** were prepared from **31** and appropriate alkylating agents (**30a**, 1-oxa-6-thiaspiro[2.5]octane, or **30b**) by a method similar to that described for **5a**.

**2′,6′-Dimethyl-4′-[(3-methyloxetan-3-yl)methoxy]biphenyl-3-carbaldehyde (33a).**

98% yield as a colorless oil. $^1H$ NMR ($CDCl_3$) δ 1.46 (s, 3H), 2.01 (s, 6H), 4.06 (s, 2H), 4.48 (d, *J* = 5.8 Hz, 2H), 4.65 (d, *J* = 5.8 Hz, 2H), 6.73 (s, 2H), 7.42 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 1.4 Hz, 1H), 7.87 (dt, *J* = 7.6, 1.4 Hz, 1H), 10.05 (s, 1H). MS *m/z* 333 $(M + Na)^+$.

**4′-[(4-Hydroxytetrahydro-2*H*-thiopyran-4-yl)methoxy]-2′,6′-dimethylbiphenyl-3-carbaldehyde (33b).**

89% yield as colorless crystals. $^1H$ NMR ($CDCl_3$) δ 1.70 (t, *J* = 5.8 Hz, 1H), 1.76–1.90 (m, 2H), 2.01 (s, 6H), 2.05–2.16 (m, 2H), 2.20 (s, 1H), 2.40–2.53 (m, 2H), 3.03–3.18 (m, 2H), 3.80 (s, 2H), 4.73 (d, *J* = 5.8 Hz, 2H), 6.67 (s, 2H), 7.02–7.09 (m, 1H), 7.12 (s, 1H), 7.31–7.37 (m, 1H), 7.41 (t, *J* = 7.4 Hz, 1H).

**2′,6′-Dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-carbaldehyde (33c).**

77% yield as colorless crystals. mp 91–94 °C. $^1H$ NMR ($CDCl_3$) δ 1.99 (s, 6H), 2.30–2.42 (m, 2H), 2.97 (s, 3H), 3.24–3.32 (m, 2H), 4.14 (t, *J* = 5.7 Hz, 2H), 6.67 (s, 2H), 7.41 (dt, *J* = 7.6, 1.5 Hz,

1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 1.5 Hz, 1H), 7.87 (dt, *J* = 7.6, 1.5 Hz, 1H), 10.05 (s, 1H). MS *m/z* 347 $(M + H)^+$. Anal. Calcd for $C_{19}H_{22}O_4S$: C, 65.87; H, 6.40. Found: C, 65.82; H, 6.47.

Compounds **5b**, **d**, **f**, and **g** were prepared from **33a**–**d** by a method similar to that described for **32**.

**{2′,6′-Dimethyl-4′-[(3-methyloxetan-3-yl)methoxy]biphenyl-3-yl}methanol (5b).**

92% yield as colorless crystals. mp 82 °C. $^1$H NMR ($CDCl_3$) δ 1.45 (s, 3H), 1.68 (t, *J* = 5.9 Hz, 1H), 2.01 (s, 6H), 4.05 (s, 2H), 4.47 (d, *J* = 5.9 Hz, 2H), 4.65 (d, *J* = 5.9 Hz, 2H), 4.74 (d, *J* = 5.9 Hz, 2H), 6.71 (s, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.13 (s, 1H), 7.32–7.37 (m, 1H), 7.41 (t, *J* = 7.5 Hz, 1H). MS *m/z* 313 $(M + H)^+$. HPLC purity (220 nm) 98.0%. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.71; H, 7.87.

**4-({[3′-(Hydroxymethyl)-2,6-dimethylbiphenyl-4-yl]oxy}methyl)tetrahydro-2*H*-thiopyran-4-ol (5d).**

94% yield as colorless crystals. $^1$H NMR ($CDCl_3$) δ 1.70 (t, *J* = 5.8 Hz, 1H), 1.76–1.90 (m, 2H), 2.01 (s, 6H), 2.05–2.16 (m, 2H), 2.20 (s, 1H), 2.40–2.53 (m, 2H), 3.03–3.18 (m, 2H), 3.80 (s, 2H), 4.73 (d, *J* = 5.8 Hz, 2H), 6.67 (s, 2H), 7.02–7.09 (m, 1H), 7.12 (s, 1H), 7.31–7.37 (m, 1H), 7.41 (t, *J* = 7.4 Hz, 1H).

**{2′,6′-Dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methanol (5f).**

97% yield as colorless crystals. mp 96–98 °C. $^1$H NMR ($CDCl_3$) δ 1.68 (t, *J* = 5.9 Hz, 1H), 2.00 (s, 6H), 2.30–2.40 (m, 2H), 2.97 (s, 3H), 3.24–3.31 (m, 2H), 4.13 (t, *J* = 5.7 Hz, 2H), 4.73 (d, *J* = 5.9 Hz, 2H), 6.64 (s, 2H), 7.03–7.08 (m, 1H), 7.12 (s, 1H), 7.31–7.37 (m, 1H), 7.41 (t, *J* = 7.5 Hz, 1H). MS *m/z* 331 $(M - 18 + H)^+$. Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.49; H, 6.94. Found: C, 65.25; H, 7.19.

**(4′-{*tert*-Butyl(dimethyl)silyl}oxy)-2′,6′-dimethylbiphenyl-3-yl)methnol (5g).**

94% yield as colorless crystals. $^1$H NMR ($CDCl_3$) δ 0.23 (s, 6H), 1.00 (s, 9H), 1.96 (s, 6H), 4.73 (s, 2H), 6.58 (s, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.13 (s, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H).

Compound **42a**–**c** was prepared from **38a**–**c** and 3-formylphenylboronic acid by a method similar to that described for **5b**-step 1.

**2′,6′-Diethyl-4′-hydroxybiphenyl-3-carbaldehyde (42a).**

68% yield as a yellow oil. $^1$H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 6H), 2.25 (q, *J* = 7.5 Hz, 4H), 4.92 (s, 1H), 6.65 (s, 2H), 7.44 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 1.5 Hz, 1H), 7.87 (dt, *J* = 7.6, 1.5 Hz, 1H), 10.05 (s, 1H). MS *m/z* 255 $(M + H)^+$.

**4′-Hydroxy-2′,3′,5′,6′-tetramethylbiphenyl-3-carbaldehyde (42b).**

79% yield as colorless crystals. mp 136–137 °C. $^1$H NMR ($CDCl_3$) δ 1.90 (s, 6H), 2.22 (s, 6H), 4.73 (s, 1H), 7.39 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 1.5 Hz, 1H), 7.86 (dt, *J* = 7.6, 1.5 Hz, 1H), 10.05 (s, 1H). MS *m/z* 255 $(M + H)^+$. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.36; H, 7.20.

**3′-Fluoro-4′-hydroxy-2′,6′-dimethylbiphenyl-3-carbaldehyde (42c).**

49% yield as colorless crystals (heptane–AcOEt). mp 116–117 °C. $^1$H NMR ($CDCl_3$) δ 1.91–1.97 (m, 6H), 5.10 (d, *J* = 4.7 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 1H), 7.40 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 1.5 Hz, 1H), 7.88 (dt, *J* = 7.6, 1.5 Hz, 1H), 10.06 (s, 1H). MS *m/z* 245 $(M + H)^+$. Anal. Calcd for $C_{15}H_{13}FO_2$: C, 73.76; H, 5.36. Found: C, 73.64; H, 5.29.

Compounds **43b**–**c** were prepared from **42b**–**c** by a method similar to that described for **32**.

**3′-(Hydroxymethyl)-2,3,5,6-tetramethylbiphenyl-4-ol (43b).**

93% yield as colorless crystals (heptane−AcOEt). mp 152–153 °C. $^1$H NMR ($CDCl_3$) δ 1.65 (t, *J* = 5.9 Hz, 1H), 1.91 (s, 6H), 2.21 (s, 6H), 4.68 (s, 1H), 4.73 (d, *J* = 5.9 Hz, 2H), 7.01–7.06 (m, 1H), 7.08–7.10 (m, 1H), 7.31–7.36 (m, 1H), 7.40 (t, *J* = 7.4 Hz, 1H). MS *m/z* 239 $(M - 18 + H)^+$. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.32; H, 7.97.

**3-Fluoro-3′-(hydroxymethyl)-2,6-dimethylbiphenyl-4-ol (43c).**

65% yield as colorless crystals. mp 123–124 °C. $^1$H NMR ($CDCl_3$) δ 1.68 (t, *J* = 6.0 Hz, 1H), 1.90–1.97 (m, 6H), 4.74 (d, *J* = 6.0 Hz, 2H), 5.04 (d, *J* = 4.7 Hz, 1H), 6.75 (d, *J* = 8.9 Hz, 1H), 7.00–7.07 (m, 1H), 7.11 (s, 1H), 7.32–7.46 (m, 2H). MS *m/z* 229 $(M - 18 + H)^+$.

Compounds **5j–l** were prepared from **43b–c** and appropriate tosylates (1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl 4-methylbenzenesulfonate or **30b**) by a method similar to that described for **5a**.

**{4′-[(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-2′,3′,5′,6′-tetramethylbiphenyl-3-yl}methanol (5j).**

88% yield as colorless crystals (heptane–AcOEt). mp 203–205 °C. $^1$H NMR ($CDCl_3$) δ 1.67 (t, *J* = 5.9 Hz, 1H), 1.88 (s, 6H), 2.21 (s, 6H), 2.29–2.55 (m, 4H), 2.96–3.08 (m, 2H), 3.31–3.44 (m,

2H), 3.95–4.04 (m, 1H), 4.74 (d, *J* = 5.9 Hz, 2H), 7.02 (d, *J* = 7.4 Hz, 1H), 7.08 (s, 1H), 7.32–7.37 (m, 1H), 7.41 (t, *J* = 7.4 Hz, 1H). MS *m/z* 371 $(M - 18 + H)^+$. Anal. Calcd for $C_{22}H_{28}O_4S$: C, 68.01; H, 7.26. Found: C, 67.93; H, 7.32.

**{2′,3′,5′,6′-Tetramethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methanol (5k).**

85% yield as colorless crystals (heptane–AcOEt). mp 132–134 °C. $^1$H NMR ($CDCl_3$) δ 1.66 (t, *J* = 5.9 Hz, 1H), 1.88 (s, 6H), 2.20 (s, 6H), 2.32–2.43 (m, 2H), 3.00 (s, 3H), 3.35–3.43 (m, 2H), 3.86 (t, *J* = 5.8 Hz, 2H), 4.73 (d, *J* = 5.9 Hz, 2H), 7.03 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.09 (s, 1H), 7.31–7.36 (m, 1H), 7.41 (t, *J* = 7.3 Hz, 1H). MS *m/z* 359 $(M - 18 + H)^+$. Anal. Calcd for $C_{21}H_{28}O_4S$: C, 66.99; H, 7.50. Found: C, 66.67; H, 7.32.

**{4′-[(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)oxy]-3′-fluoro-2′,6′-dimethylbiphenyl-3-yl}methanol (5l).**

A crude product (quantitative) as a colorless oil. MS *m/z* 361 $(M - 18 + H)^+$.

**4′-{[*tert*-Butyl(dimethyl)silyl]oxy}-3′-chloro-2′,6′-dimethylbiphenyl-3-carbaldehyde (44a).**

The title compound was prepared from **42d** by a method similar to that described for **31d** in 88% yield as a colorless oil. $^1$H NMR ($CDCl_3$) δ 0.27 (s, 6H), 1.06 (s, 9H), 1.92 (s, 3H), 2.04 (s, 3H), 6.68 (s, 1H), 7.37–7.42 (m, 1H), 7.56–7.66 (m, 2H), 7.85–7.90 (m, 1H), 10.05 (s, 1H). MS *m/z* 375 $(M + H)^+$.

Compounds **44b**–**d** were prepared from tosylate **30b** and phenols **42a**, **42c**, or **42e** by a method similar to that described for **5a**.

**2′,6′-Diethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-carbaldehyde (44b).**

80% yield as a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 6H), 2.27 (q, *J* = 7.5 Hz, 4H), 2.32–2.43 (m, 2H), 2.98 (s, 3H), 3.24–3.33 (m, 2H), 4.17 (t, *J* = 5.9 Hz, 2H), 6.69 (s, 2H), 7.40–7.46 (m, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.65–7.70 (m, 1H), 7.84–7.90 (m, 1H), 10.05 (s, 1H). MS *m/z* 375 $(M + H)^+$.

**3′-Fluoro-2′,6′-dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-carbaldehyde (44c).**

95% yield as colorless crystals (heptane–AcOEt). mp 117–118 °C. $^1$H NMR ($CDCl_3$) δ 1.93 (d, *J* = 2.8 Hz, 3H), 1.97 (s, 3H), 2.34–2.45 (m, 2H), 2.99 (s, 3H), 3.28–3.36 (m, 2H), 4.22 (t, *J* = 5.7 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 1H), 7.39 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.58–7.66 (m, 2H), 7.89 (dt, *J* = 7.6, 1.4 Hz, 1H), 10.06 (s, 1H). MS *m/z* 365 $(M + H)^+$. Anal. Calcd for $C_{19}H_{21}FO_4S$: C, 62.62; H, 5.81. Found: C, 62.66; H, 5.81.

**3′,5′-Dichloro-2′,6′-dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-carbaldehyde (44d).**

53% yield as colorless crystals (heptane–AcOEt). mp 135–136 °C. $^1$H NMR ($CDCl_3$) δ 2.03 (s, 6H), 2.37–2.48 (m, 2H), 3.00 (s, 3H), 3.44–3.51 (m, 2H), 4.18 (t, *J* = 5.7 Hz, 2H), 7.34–7.39 (m, 1H), 7.61–7.68 (m, 2H), 7.89–7.94 (m, 1H), 10.06 (s, 1H). MS *m/z* 415 $(M + H)^+$. Anal. Calcd for $C_{19}H_{20}Cl_2O_4S$: C, 54.94; H, 4.85. Found: C, 54.93; H, 4.89.

Compounds **5h**, **i**, **m**, and **n** were prepared from **44a**–**d** by a method similar to that described for **32**.

**(4′-{[*tert*-Butyl(dimethyl)silyl]oxy}-3′-chloro-2′,6′-dimethylbiphenyl-3-yl)methanol (5h).**

97% yield as a colorless oil. $^1$H NMR ($CDCl_3$) δ 0.26 (s, 6H), 1.06 (s, 9H), 1.69 (br s, 1H), 1.93 (s, 3H), 2.05 (s, 3H), 4.74 (s, 2H), 6.66 (s, 1H), 7.01–7.07 (m, 1H), 7.09–7.13 (m, 1H), 7.32–7.45 (m, 2H). MS *m/z* 377 $(M + H)^+$.

**{2′,6′-Diethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methanol (5i).**

84% yield as colorless crystals (heptane–AcOEt). mp 115–116 °C. $^1$H NMR ($CDCl_3$) δ 1.01 (t, *J* = 7.5 Hz, 6H), 1.66 (t, *J* = 5.9 Hz, 1H), 2.24–2.42 (m, 6H), 2.97 (s, 3H), 3.25–3.33 (m, 2H), 4.16 (t, *J* = 5.7 Hz, 2H), 4.73 (d, *J* = 5.9 Hz, 2H), 6.67 (s, 2H), 7.06–7.10 (m, 1H), 7.12–7.16 (m, 1H), 7.32–7.43 (m, 2H). MS *m/z* 359 $(M - 18 + H)^+$. Anal. Calcd for $C_{21}H_{28}O_4S$: C, 66.99; H, 7.50. Found: C, 66.92; H, 7.46.

**{3′-Fluoro-2′,6′-dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methanol (5m).**

94% yield as colorless crystals (heptane–AcOEt). mp 62–63 °C. $^1$H NMR ($CDCl_3$) δ 1.70 (t, *J* = 5.9 Hz, 1H), 1.93 (d, *J* = 3.0 Hz, 3H), 1.97 (s, 3H), 2.32–2.45 (m, 2H), 2.98 (s, 3H), 3.27–3.37 (m, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 4.74 (d, *J* = 5.9 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.99–7.08 (m, 1H), 7.10 (s, 1H), 7.32–7.47 (m, 2H). MS *m/z* 349 $(M - 18 + H)^+$. Anal. Calcd for $C_{19}H_{23}FO_4S$: C, 62.27; H, 6.33. Found: C, 62.63; H, 6.65.

**{3′,5′-Dichloro-2′,6′-dimethyl-4′-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methanol (5n).**

98% yield as a colorless oil. $^1$H NMR ($CDCl_3$) δ 1.76 (t, *J* = 5.7 Hz, 1H), 2.03 (s, 6H), 2.36–2.47 (m, 2H), 3.00 (s, 3H), 3.43–3.51 (m, 2H), 4.16 (t, *J* = 5.7 Hz, 2H), 4.75 (d, *J* = 5.7 Hz, 2H), 6.97–7.03 (m, 1H), 7.07–7.08 (m, 1H), 7.36–7.48 (m, 2H). MS *m/z* 417 $(M + H)^+$.

**X-Ray Crystallographic Data for Compound 16**

A. Crystal Data

| | |
|---|---|
| Empirical Formula | $C_{29}H_{32}O_7S \cdot 1/2H_2O$ |
| Formula Weight | 533.64 |
| Crystal Color, Habit | colorless, platelet |
| Crystal Dimensions | 0.30 x 0.20 x 0.05 mm |
| Crystal System | triclinic |
| Lattice Type | Primitive |
| No. of Reflections Used for Unit | |
| Cell Determination ($2\theta$ range) | 25654 (7.3–136.5°) |
| Indexing Images | 3 oscillations at 3.0 minutes |
| Camera Radius | 127.40 mm |
| Lattice Parameters | a = 7.912(2) *Å*<br>b = 9.698(3) *Å*<br>c = 36.602(9) *Å*<br>α = 91.59(2)°<br>β = 92.35(2)°<br>γ = 107.59(2)°<br>V = 2672(4) *Å*$^3$ |
| Space Group | P1(#1) |
| Z value | 4 |
| $D_{calc}$ | 1.326 g/cm$^3$ |
| $F_{000}$ | 1132.00 |
| μ(CuKα) | 14.80 cm$^{-1}$ |

B. Intensity Measurements

| | |
|---|---|
| Diffractometer | Rigaku RAXIS-RAPID Imaging Plate |
| Radiation | CuKα (λ = 1.54186 *Å*)<br>graphite monochromated |
| Temperature | −173.0 °C |
| Voltage, Current | 50 kV, 100 mA |
| Collimator Size | 0.5 mm |
| Detector Aperture | 460.0 mm x 256.0 mm |
| Data Images | 45 exposures at 1.5 minutes per degree |
| Oscillation Range ($\phi$ = 0.0°,$\chi$ = 50.0°) | ω50.0–230.0° with 20.0° step |

| | |
|---|---|
| Oscillation Range ($\phi$ = 90.0°,$\chi$ = 50.0°) | ω50.0–230.0° with 20.0° step |
| Oscillation Range ($\phi$ = 195.0°,$\chi$ = 50.0°) | ω50.0–230.0° with 20.0° step |
| Oscillation Range ($\phi$ = 270.0°,$\chi$ = 50.0°) | ω50.0–230.0° with 20.0° step |
| Oscillation Range ($\phi$ = 60.0°,$\chi$ = 10.0°) | ω50.0–230.0° with 20.0° step |
| Camera Radius | 127.40 mm |
| Pixel Size | 0.100 mm |
| $2\theta_{max}$ | 136.5° |
| No. of Reflections Measured | Total: 27623<br>Unique: 8873 ($R_{int}$ = 0.040) |
| Corrections | Lorentz-polarization<br>Absorption<br>(trans. factors: 0.6381–0.9287) |

C. Structure Solution and Refinement

| | |
|---|---|
| Structure Solution | Direct Methods (SIR92) |
| Refinement | Full-matrix least-squares (SHELXL-97) |
| Function Minimized | $\Sigma\omega(Fo^2 - Fc^2)^2$ |
| Least Squares Weights | $\omega = [\sigma^2(Fo^2)+(0.0587P)^2 + 0.0000P]^{-1}$<br>where $P=(Fo^2 + 2Fc^2)/3$ |
| No. of Reflections | 12146 |
| No. Variables | 1348 |
| Reflection/Parameter Ratio | 9.01 |
| Residuals: R; Rw | 0.063 ; 0.166 |
| Goodness of Fit Indicator | 1.01 |
| Max Shift/Error in Final Cycle | 0.00 |
| Maximum peak in Final Diff. Map | 0.70 $e^-/Å^3$ |
| Minimum peak in Final Diff. Map | -0.55 $e^-/Å^3$ |
| Flack Parameter | -0.05(2) |