Heteroatomic Effects on the Reducibility of C-2 Carbinol Centers in 6-Ethoxy-3,6-dihydropyrans and -thiopyrans

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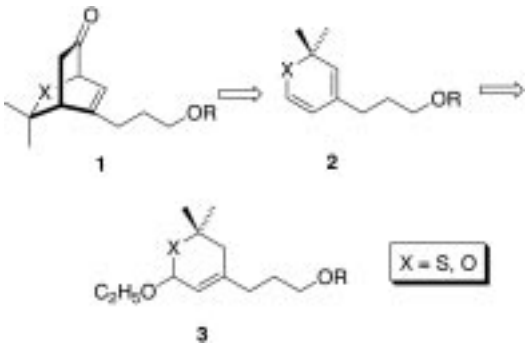
Ketones of type **1**, which we considered to be accessible by Diels−Alder cycloaddition of a chiral α-acyloxy acrylonitrile[1] to the appropriate 2*H*-pyran or thiopyran (**2**),[2−5] were desired in conjunction with a current synthetic undertaking (Scheme 1). The feasibility of advancing to **2** from alkoxy precursors[6] exemplified by **3** led to the search for a mild and generally useful method for their preparation. This paper records a practical route to the sulfur analogue and demonstrates an unanticipated reactivity difference that disallows comparable access in the oxygen series.

Carboxylic acid **4** was prepared by heating γ-butyrolactone with *p*-methoxyphenol and potassium hydroxide pellets at 190 °C according to a modification of literature methods.[7,8] Ensuing conversion[9] to the Weinreb amide **5** proceeded in 70% yield and set the stage for the nucleophilic addition of an equivalent of (*Z*)-2-ethoxy-1-ethenyllithium[10] to provide the α,β-unsaturated ketone **6** (65%, Scheme 2). To secure arrival at the labile diene **7** in an acceptable yield, it was imperative that olefination be performed under neutral conditions. It was soon discovered that dimethyltitanocene in THF at 55 °C[11] was well-suited to this task.

Scheme 1



A (4 + 2)π intermolecular cycloaddition involving **7** and thiodiethylpyrocarboxylate (generated in situ), which would result in assembly of the sulfur-containing six-membered ring, was considered probable if **7** possessed intrinsic reactivity approaching that exhibited by the Danishefsky diene.[12] Indeed, slow addition of diethyl bromomalonate to an acetonitrile solution containing sulfur, triethylamine, and **7** at room temperature gave rise to the desired adduct **8** in virtually quantitative yield.

Reduction of the geminal diester groups within **8** with DIBAL-H furnished the diol, whose unpurified dimesylate derivative underwent 2-fold hydride displacement in the presence of lithium triethylborohydride to generate the desired **10** without event.

In the hope that **14** could be generated in a comparable manner, **7** was subjected to hetero Diels−Alder reaction[13−15] with ethyl glyoxylate in toluene at room temperature. This simple protocol produced **11** as a diastereomeric mixture in 98% yield (Scheme 3). Interestingly, doubly activated dienophiles such as diethyl pyrocarbonate did not cycloadd to **7**, presumably for steric reasons. Recourse to high-pressure conditions was to no avail. This problem was solved by virtue of the ease with which the enolate anion of **11** could be generated. Exposure of this reactive intermediate to methyl cyanoformate and to methyl iodide produced **12** and **15**, respectively. The carboalkoxy substituents projecting from the C2 position of these esters proved amenable to hydride reduction. Unfortunately, all efforts to realize the further reduction of **13** and **16** to **14** were unsuccessful. Quite unlike the dimesylate of **9** which was transformed cleanly into **10**, the sulfonate esters derived from diol **13** and alcohol **16** afforded very complex product mixtures. Direct reduction with lithium triethylborohydride and the other hydridic reagents with a view to minimizing degradation gave no sign of the desired *gem*-dimethyl product.

A possible explanation for this dichotomy in chemical behavior is the availability of an activation process in the sulfur series not shared comparably by the oxa

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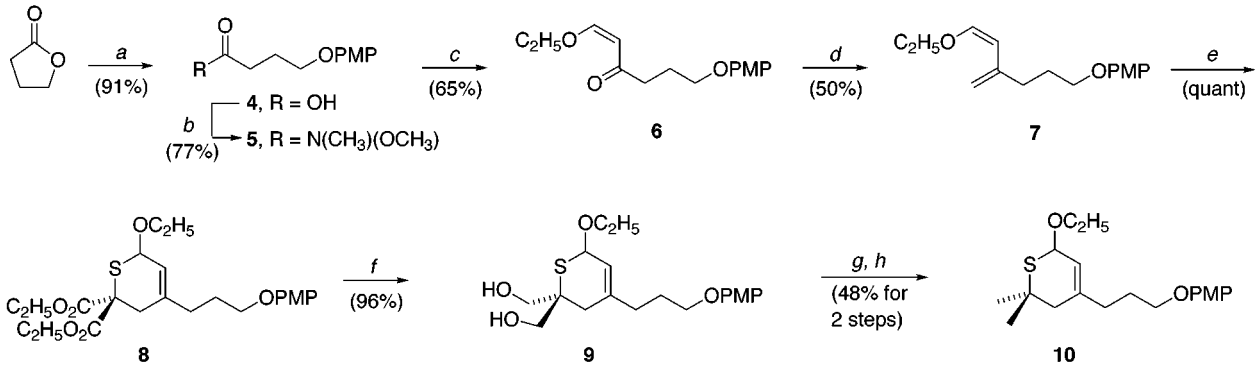
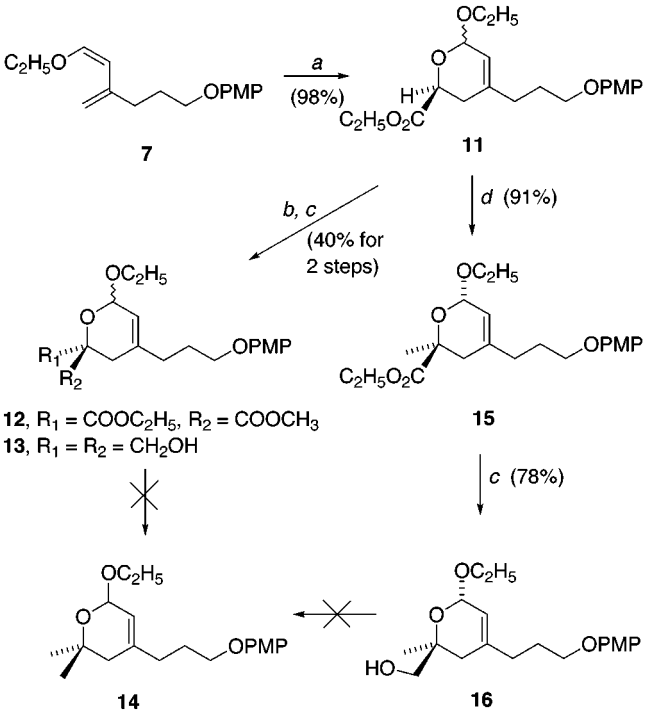
Scheme 2



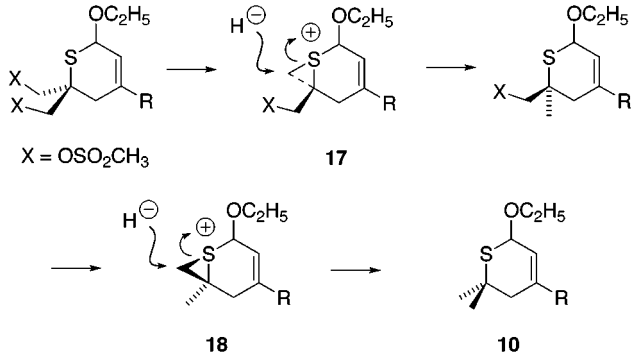
[a] *p*-Methoxyphenol, KOH, 190 °C, 5 h. [b] $HN(OCH_3)(CH_3)$, PPh_3, CBr_4, py, CH_2Cl_2, rt, 2 h. [c] (*Z*)-2-ethoxy-1-butenyllithium, THF, -78 °C, 1 h; 5% HCl, -78 → 0 °C. [d] $Cp_2(CH_3)_2$, THF, 55 °C, 20 h. [e] Diethyl bromomalonate, S_8, Et_3N, CH_3CN, rt, 27 h. [f] $(i\text{-Bu})_2AlH$, CH_2Cl_2, -15 °C → rt, 30 min. [g] CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C → rt. [h] $LiEt_3BH$, THF, 0 °C → rt.

Scheme 3



[a] Ethyl glyoxylate, toluene, rt, 1 h. [b] $NaN(SiMe_3)_2$, THF, -78 °C, 2 h; $NCCOOCH_3$, 1 h. [c] $LiAlH_4$, THF, 0 °C, 2 h, 1 h. [d] $KN(SiMe_3)_2$, THF, -78 → 0 °C; CH_3I, THF, -78 °C → rt;1 h.

Scheme 4



analogues. Thus, the substantial nucleophilicity of divalent sulfur could prove conducive to transient sulfonium ion formation as in **17** and **18**,[16] thereby providing for an enhanced rate of hydride attack at the neopentyl centers (Scheme 4). In the absence of this neighboring group participation, ill-defined reaction pathways less affected by steric retardation appear to gain a kinetic advantage.

Experimental Section

General Methods. Yields were calculated for material judged to be homogeneous by TLC and NMR. Magnetic stirring was used for all reactions. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} aluminum-backed plates. Flash column chromatography was accomplished in glass columns with Woelm silica gel (230−400 mesh). NMR spectra were acquired at 300 MHz for ^1H and 75 MHz for ^{13}C. Melting points are uncorrected. Solvents were reagent grade and in most cases dried prior to use. The high-resolution mass spectra were obtained at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

4-(*p*-Methoxyphenoxy)butyric Acid (4).[5] To a mechanically stirred suspension of 4-methoxyphenol (62.1 g, 0.50 mol) in water (20 mL) was added KOH pellets (34.6 g, 0.52 mol) followed by careful addition of butyrolactone (77 mL, 1 mol). The flask was equipped with a Dean−Stark trap and thermometer, and the mixture was heated at 150 °C under N_2 for 3 h and at 195 °C until no more water was removed (ca. 5 h overall). After cooling to room temperature, 150 mL of water was introduced, and the mixture was heated to 60 °C until all of the solid had dissolved. The resulting hot brown solution was poured into 5% HCl, and the heterogeneous mixture was cooled at 0 °C for 3 h. The crystals were collected by filtration and rinsed with cold water until colorless. The crude product was dried under vacuum to afford acid **4** (132.43 g, 93%) as a white crystalline solid; IR (film, cm^{-1}) 3387, 1704; ^1H NMR (300 MHz, $CDCl_3$) δ 10.30 (br s, 1 H), 6.83 (s, 4 H), 3.97 (t, J = 6.1 Hz, 2 H), 3.77 (s, 3 H), 2.58 (t, J = 7.2 Hz, 2 H), 2.09 (tt, J = 7.2, 6.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 153.9, 152.9, 115.5, 114.7, 67.2, 55.7, 30.6, 24.5; MS *m*/*z* (M^+) calcd 210.0892, obsd 210.0893.

***N*-Methoxy-4-(*p*-methoxyphenoxy)-*N*-methylbutyramide (5).** To a mixture of **4** (2.10 g, 10.0 mmol), *N*-methoxy-*N*-methylamine hydrochloride (1.075 g, 11.0 mmol), pyridine (0.9 mL, 11.0 mmol), and carbon tetrabromide (3.65 g, 11.0 mmol) in CH_2Cl_2 (25 mL) was added triphenylphosphine (2.88 g, 11.0 mmol) in portions during 5 min at room temperature. After 2 h of stirring, the solvent was evaporated, 20 mL of 1:1 hexanes−ethyl acetate was poured onto the residue, the solid waste was filtered off, and the solution was concentrated to furnish a residue that was purified by flash chromatography on silica gel

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(elution with ethyl acetate/hexanes 1:1) to yield **5** as a colorless oil (1.83 g, 77%); IR (film, cm^{-1}) 1661; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 4 H), 3.98 (t, J = 6.1 Hz, 2 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.18 (s, 3 H), 2.63 (t, J = 7.2 Hz, 2 H), 2.10 (tt, J = 7.2, 6.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 153.6, 152.9, 115.3, 114.5, 67.5, 61.0, 55.5, 32.1, 28.1, 24.2; MS m/z (M^+) calcd 253.1314, obsd 253.1321. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.63; H, 7.57. Found: C, 61.79; H, 7.64.

(*Z*)-1-Ethoxy-6-(*p*-methoxyphenoxy)-1-hexen-3-one (6). A flame-dried, two-necked, round-bottomed flask was charged with (2(*Z*)-ethoxyethenyl)-1-tributylstannane (0.248 g, 0.688 mmol) and THF (2.5 mL) into which *n*-butyllithium (1.3 M in hexanes, 0.58 mL) was dropped at −78 °C, and the solution was stirred at this temperature for 1 h. A solution of **5** (0.158 g, 0.625 mmol) in THF (2.5 mL) was added during 2 min at the same temperature. The resulting mixture was stirred for another 1 h, allowed to warm to room temperature during 0.5 h, poured into ice-cooled 5% HCl, and diluted with ether and brine. The separated aqueous phase was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine and then dried. Filtration and concentration in vacuo provided a pale yellow product which was purified by flash chromatography on silica gel (elution with ethyl acetate/hexanes 1:1) to yield pure **6** as a colorless oil (0.133 g, 76%). IR (neat, cm^{-1}) 1683, 1637, 1617; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 12.7 Hz, 1 H), 6.82 (s, 4 H), 5.62 (d, J = 12.7 Hz, 1 H), 3.94 (m, 4 H), 3.76 (s, 3 H), 2.65 (t, J = 7.2 Hz, 2 H), 2.06 (tt, J = 7.2, 6.1 Hz, 2 H), 1.34 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 161.9, 153.8, 153.3, 115.4, 114.7, 106.1, 67.6, 67.0, 55.7, 37.3, 24.1, 14.3; MS m/z (M^+) calcd 264.1361, obsd 264.1362. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.14; H, 7.63. Found: C, 67.74; H, 7.68.

1-[[(*Z*)-6-Ethoxy-4-methylene-5-hexenyl]oxy]-4-methoxybenzene (7). A base-washed, round-bottomed flask was charged with **6** (0.486 g, 1.84 mmol) and anhydrous THF (2 mL) to which a solution of dimethyltitanocene (12.4 mL of 0.3 M in THF, 3.69 mmol) was added. The mixture was heated at 55 °C under N_2 for 20 h. The resulting dark-red solution was diluted with hexanes (100 mL containing 1% of triethylamine), and the precipitate was removed by filtration. Concentration followed by flash chromatography on silica gel (elution with ethyl acetate/hexanes 1:30 containing 1% triethylamine) afforded **7** (0.24 g, 50%) as an unstable yellowish oil; IR (film, cm^{-1}) 1509, 1232, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 6.88−6.80 (m, 4 H), 6.67 (d, J = 13.0 Hz, 1 H), 5.73 (d, J = 13.0 Hz, 1 H), 4.95 (s, 1 H), 4.83 (s, 1 H), 3.73 (t, J = 6.2 Hz, 2 H), 3.44 (q, J = 4.7 Hz, 2 H), 3.39 (s, 3 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.93 (tt, J = 7.4, 4.7 Hz, 2 H), 1.05 (t, J = 4.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 153.8, 148.1, 143.8, 115.7, 115.0, 110.6, 108.4, 67.8, 65.1, 55.2, 29.6, 28.5, 14.8; MS m/z (M^+) calcd 262.1569, obsd 262.1565.

Diethyl 6-Ethoxy-3,6-dihydro-4-[3-(*p*-methoxyphenoxy)propyl]-2*H*-thiopyran-2,2-dicarboxylate (8). To a stirred solution of **7** (52 mg, 0.20 mmol), triethylamine (66 mg, 0.5 mmol), and sulfur (23 mg, 0.72 mmol) in acetonitrile (1 mL) was added dropwise via syringe pump a solution of diethyl bromomalonate (96 mg, 0.40 mmol) in acetonitrile (1 mL) at room temperature during 3 h. The resulting suspension was stirred for 24 h, filtered through a small pad of Celite, and concentrated. Chromatography of the residue on silica gel (elution with ethyl acetate/hexanes 1:5) afforded 95 mg (100%) of **8** as a yellowish oil; IR (film, cm^{-1}) 1732, 1505; ^1H NMR (300 MHz, C_6D_6) δ 6.89−6.74 (m, 4 H), 5.78 (dt, J = 2.4, 0.6 Hz, 1 H), 4.59 (d, J = 4.5 Hz, 1 H), 4.14−3.87 (series of m, 4 H), 3.67 (t, J = 2.7 Hz, 2 H), 3.64−3.36 (m, 2 H), 3.35 (s, 3 H), 3.09 (d, J = 17.3 Hz, 1 H), 2.92 (d, J = 17.3 Hz, 1 H), 2.00 (t, J = 7.3 Hz, 2 H), 1.63 (quintet, J = 6.8 Hz, 2 H), 1.02 (t, J = 7.0 Hz, 3 H), 0.98 (t, J = 7.1 Hz, 3 H), 0.91 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 167.8, 166.9, 154.4, 153.8, 137.4, 122.5, 115.6, 115.0, 72.2, 67.2, 64.8, 61.9, 61.7, 61.3, 55.2, 34.4, 27.8, 27.3, 15.8, 14.0, 13.9; MS m/z (M^+) calcd 452.1868, obsd 452.1881. Anal. Calcd for $C_{23}H_{32}O_7S$: C, 61.04; H, 7.13. Found: C, 60.90; H, 7.16.

6-Ethoxy-3,6-dihydro-4-[3-(*p*-methoxyphenoxy)propyl]-2*H*-thiopyran-2,2-dimethanol (9). A cold (−15 °C), magnetically stirred solution of **8** (110 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was slowly treated with DIBAL-H (1.45 mL of 1.0 M in hexanes), allowed to warm to room temperature during 15 min, and quenched with saturated sodium potassium tartrate solution at −15 °C. The separated aqueous layer was extracted with CH_2Cl_2 and ethyl acetate, the combined organic layers were dried and evaporated, and the resulting diol (85 mg, 96%) was used directly; IR (film, cm^{-1}) 3418, 1504; ^1H NMR (300 MHz, C_6D_6) δ 6.80 (m, 4 H), 5.42 (d, J = 1.1 Hz, 1 H), 4.15 (m, 1 H), 4.16−3.78 (series of m, 4 H), 3.57 (t, J = 6.1 Hz, 2 H), 3.34 (s, 3 H), 3.36−3.27 (m, 1 H), 3.14−3.04 (m, 1 H), 2.72 (d, J = 17.0 Hz, 1 H), 2.53 (d, J = 17.0 Hz, 1 H), 1.89 (t, J = 7.5 Hz, 2 H), 1.54 (m, 2 H), 0.88 (t, J = 7.0 Hz, 3 H), 0.48 (br s, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 153.5, 152.7, 135.6, 122.8, 114.7, 114.0, 76.4, 66.5, 64.6, 64.2, 63.1, 54.2, 51.0, 32.8, 26.6, 24.8, 14.4; MS m/z (M^+) calcd 368.1657, obsd 368.1663.

6-Ethoxy-3,6-dihydro-4-[3-(*p*-methoxyphenoxy)propyl]-2*H*-dimethyl-2*H*-thiopyran (10). A solution of **9** (90 mg, 0.20 mmol) and triethylamine (0.11 mL, 0.80 mmol) in CH_2Cl_2 (3 mL) was treated dropwise at 0 °C with methanesulfonyl chloride (80 mg, 0.70 mmol). The reaction mixture was stirred at room temperature for 2.5 h prior to dilution with CH_2Cl_2, and the combined organic phases were dried and concentrated to give the dimesylate. The yellow oil was dissolved in dry THF (1 mL) and treated dropwise with lithium triethylborohydride (0.6 mL of 1.0 M in THF) at 0 °C. After 5 min, the reaction mixture was allowed to warm to room temperature for 1 h, quenched with ether and water, and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated to leave a residue that was purified by chromatography on silica gel. Elution with hexanes/ethyl acetate (1:10) gave **10** (39 mg, 48% overall) as a colorless syrup; IR (film, cm^{-1}) 1509, 1232; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 4 H), 5.48 (br s, 1 H), 3.91 (t, J = 6.3 Hz, 2 H), 3.78 (br s, 1 H), 3.77 (s, 3 H), 3.76−3.65 (m, 1 H), 3.53−3.47 (m, 1 H), 3.25 (m, 1 H), 2.84 (m, 1 H), 2.19 (m, 2 H), 1.91 (m, 2 H), 1.29 (s, 3 H), 1.26 (s, 3 H), 1.20 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 152.4, 138.3, 122.0, 115.4, 114.6, 73.0, 67.5, 65.4, 55.7, 51.7, 46.3, 33.9, 27.3, 26.8, 15.5 (1 C overlapping); MS m/z (M^+) calcd 336.1754, obsd 336.1761.

Ethyl 6-Ethoxy-3,6-dihydro-4-[3-(*p*-methoxyphenoxy)propyl]-2*H*-pyran-2-carboxylate (11). A solution of **7** (0.240 g, 0.92 mmol) in toluene (10 mL) was suspended with sodium bicarbonate (200 mg) for couple of minutes, filtered, and concentrated. Ethyl glyoxylate (0.467 g, 4.6 mmol) dissolved in dry toluene (1 mL) was introduced, and the reaction mixture was stirred at room temperature for 1 h under N_2. The volatile material was removed to leave a pale yellow viscous residue, which was purified by flash chromatography (silica gel elution with ethyl acetate/hexanes 1:5) to afford **11** as a colorless oily 2:1 mixture of cis and trans isomers (0.314 g, 99%); IR (film, cm^{-1}) 2936, 1736, 1508, 1231; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 4 H), 5.53 (d, J = 0.7 Hz, 1 H, minor isomer), 5.46 (d, J = 1.5 Hz, 1 H, major isomer), 5.12 (d, J = 1.7 Hz, 1 H), 4.54 (dd, J = 10.0, 2.3 Hz, 1 H, minor isomer), 4.35 (dd, J = 7.0, 5.0 Hz, 1 H, major isomer), 4.30−4.14 (series of m, 2 H), 3.99−3.78 (series of m, 3 H), 3.76 (s, 3 H), 3.57 (m, 1 H), 2.42−2.22 (series of m, 4 H), 1.97−1.90 (m, 2 H), 1.34−1.22 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 171.2, 153.8, 153.1, 139.1, 120.5, 119.7, 115.5, 114.7, 96.7, 95.1, 69.9, 67.9, 67.8, 66.2, 63.7, 63.6, 61.1, 61.0, 55.7, 33.0, 32.9, 31.0, 29.5, 27.0, 26.7, 15.3, 15.1, 14.2, 14.1; MS m/z (M^+) calcd 364.1886, obsd 364.1880. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.90; H, 7.75. Found: C, 65.82; H, 7.74.

Ethyl Methyl 6-Ethoxy-3,6-dihydro-4-[3-(*p*-methoxyphenoxy)propyl]-2*H*-pyran-2,2-dicarboxylate (12). To a solution of **11** (2.0 g, 5.49 mmoL) in anhydrous THF (50 mL) was added slowly a solution of sodium hexamethyldisilazide in THF (16.5 mL, 1.0 M in THF) at −78 °C under N_2 during 5 min, and the pale yellow solution was stirred at the same temperature for 2 h prior to the slow introduction of neat methyl cyanoformate (1.44 mL, 18.1 mmol). After being stirred at the same temperature for further hour, the reaction mixture was quenched with an excess of water at −78 °C, allowed to warm to room temperature, and diluted with ether. The separated aqueous layer was extracted with ether, and the combined organic phases were washed with brine, dried, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with ethyl acetate/hexanes 1:5 containing 2% triethylamine) to provide **12** as a colorless oil (1.22 g, 53%); IR (film, cm^{-1}) 1770, 1748; ^1H NMR (300 MHz, C_6D_6) δ 6.82−6.74 (m, 4 H), 5.38 (m, 1 H), 5.16 (d, J = 1.2 Hz, 1 H), 4.19−3.82 (series of m, 3 H), 3.64 (t, J = 5.4 Hz, 2 H), 3.40−3.29 (m, 1 H), 3.35 (s, 3 H), 3.34

(s, 3 H), 2.89 (dd, J = 16.9, 9.2 Hz, 1 H), 2.26 (ddd, J = 16.7, 12.7, 1.8 Hz, 1 H), 2.08 (m, 2 H), 1.73 (m, 2 H), 1.02 (q, J = 7.0 Hz, 3 H), 0.91 (q, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 169.5, 169.3, 168.8, 168.7, 154.4, 153.7, 137.4, 119.6, 119.5, 115.7, 114.9, 99.9, 95.7, 95.6, 77.8, 77.6, 67.5, 63.9, 61.7, 61.6, 33.1, 33.0, 32.1, 32.0, 26.8, 15.1, 14.0, 13.7; MS m/z (M^+) calcd 422.1940, obsd 422.1952.

6-Ethoxy-3,6-dihydro-4-[3-*p*-methoxyphenoxy)propyl]-2*H*-pyran-2,2-dimethanol (13). To a solution of **12** (0.721 g, 1.72 mmoL) in anhydrous THF (25 mL) was added lithium aluminum hydride (1.0 M in THF, 17.2 mL) dropwise at 0 °C. After completion of the addition, the cooling bath was removed, and warming to room temperature occurred over 3 h with continued stirring until no gas was evolved. The reaction mixture was carefully quenched by the slow addition of saturated Na_2SO_4 solution followed by solid Na_2SO_4. The white precipitate was separated by filtration and washed with CH_2Cl_2. The white filter cake was ground into a fine powder and extracted with ethyl acetate overnight. The combined organic layers were concentrated under reduced pressure to give **13** as a viscous colorless syrup (0.418 g, 76%); IR (film, cm^{-1}) 3464, 1508, 1231; ^{1}H NMR (300 MHz, C_6D_6) δ 6.78 (m, 4 H), 5.34 (br s, 1 H), 4.86 (br s, 1 H), 3.74−3.15 (series of m, 11 H), 2.86 (br s, 1 H), 2.38−1.84 (m, 4 H), 1.68 (q, J = 6.0 Hz, 2 H), 1.32 (br s, 1 H), 1.01 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 154.5, 153.8, 138.8, 118.7, 115.8, 115.0, 95.2, 75.9, 67.7, 67.3, 66.0, 64.0, 55.2, 33.4, 30.0, 27.1, 15.3; MS m/z (M^+) calcd 352.1886, obsd 352.1885.

Ethyl (2*R,6*R**)-6-Ethoxy-3,6-dihydro-4-(3-(*p*-methoxyphenoxy)propyl]-2-methyl-2*H*-pyran-2-carboxylate (15).** A stirred solution of **11** (0.299 g, 0.821 mmol) in anhydrous THF (5 mL) was treated with a solution of potassium hexamethyldisilazide (0.5 M in toluene, 2.5 mL) at −78 °C and stirred at this temperature for 1 h. The resulting yellow solution was treated with an excess of methyl iodide (0.5 mL), stirred at −78 °C for 2 h, allowed to warm to room temperature during 1 h, and quenched with saturated NH_4Cl solution (0 °C) followed by ether. The aqueous phase was extracted with ether, and the combined organic layers were washed with brine, dried, and evaporated under reduced pressure. The crude material was purified by flash chromatography (silica gel, elution with ethyl acetate/hexanes 1:6) to give the two separable methylated esters **15** and its epimer (0.28 g, 91%), both as colorless oils. Diastereomer **15** predominated by a factor in excess of 10:1.

For **15**: IR (neat, cm^{-1}) 2962, 1738, 1510, 1047; ^{1}H NMR (300 MHz, C_6D_6) δ 6.65 (m, 4 H), 5.57 (d, J = 1.0 Hz, 1 H), 5.46 (d, J = 1.0 Hz, 1 H), 3.94 (m, 3 H), 3.60 (t, J = 6.3 Hz, 2 H), 3.55 (m, 1 H), 3.35 (s, 3 H), 2.50 (d, J = 16.7 Hz, 1 H), 2.02−1.96 (series of m, 3 H), 1.72−1.63 (m, 2 H), 1.54 (s, 3 H), 1.16 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 173.8, 154.5, 153.8, 138.2, 121.0, 115.8, 115.0, 96.0, 76.7, 67.7, 63.0, 60.8, 55.2, 36.4, 33.3, 26.9,,25.8, 15.6, 14.1; MS m/z (M^+) calcd 378.2042, obsd 378.2049.

For *epi*-**15**: ^{1}H NMR (300 MHz, C_6D_6) δ 6.85−6.74 (m, 4 H), 5.42 (d, J = 0.4 Hz, 1 H), 5.05 (t, J = 1.2 Hz, 1 H), 4.10 (m, 2 H), 3.89 (m, 1 H), 3.69 (t, J = 6.2 Hz, 2 H), 3.35 (s, 3 H), 3.34 (m, 1 H), 2.54 (d, J = 16.9 Hz, 1 H), 2.19−2.01 (series of m, 2 H), 1.86−1.77 (series of m, 3 H), 1.45 (s, 3 H), 1.12 (t, J = 7.0 Hz, 3 H), 1.00 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 173.9, 154.4, 153.8, 138.5, 119.4, 115.8, 115.0, 95.9, 72.9, 67.8, 63.5, 60.7, 55.2, 35.5, 33.2, 27.0, 26.7, 15.2, 13.9.

(2*R,6*R**)-6-Ethoxy-3,6-dihydro-4-[3-(*p*-methoxyphenoxy)propyl]-2-methyl-2*H*-pyran-2-methanol (16).** A stirred THF solution of **15** (57.6 mg, 0.1523 mmol) in THF (1 mL) was treated with a solution of lithium aluminum hydride (1.0 M in THF, 0.31 mL) at −5 to 0 °C dropwise by syringe during 1 min, and the resulting mixture was stirred at this temperature for 2 h, allowed to warm to room temperature during 4 h, and carefully quenched with saturated Na_2SO_4 solution until a white precipitate formed. After filtration, the filtrate was concentrated under reduced pressure to yield a colorless residue which was subjected to flash chromatographic purification to provide **16** (40 mg, 78%) as a colorless oil; IR (film, cm^{-1}) 3475, 1510, 1232; ^{1}H NMR (300 MHz, C_6D_6) δ 6.84 (m, 4 H), 5.54 (s, 1 H), 5.05 (s, 1 H), 3.85 (m, 1 H), 3.68 (t, J = 6.3 Hz, 2 H), 3.54 (d, J = 11.0 Hz, 1 H), 3.40 (s, 3 H), 3.39−3.32 (m, 1 H), 2.41 (d, J = 17.9 Hz, 1 H), 2.05 (d, J = 7.6 Hz, 2 H), 1.89 (m, 1 H), 1.73 (m, 2 H), 1.39 (d, J = 17.9 Hz, 2 H), 1.29 (s, 3 H), 1.18 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 154.2, 153.5, 137.4, 119.3, 115.5, 114.8, 95.2, 72.3, 70.2, 67.5, 62.8, 55.0, 33.5, 33.4, 26.9, 22.3, 15.3; MS m/z (M^+) calcd 336.1937, obsd 336.1940.

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Supporting Information Available: High-field ^{1}H NMR spectra of those compounds lacking combustion analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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