Total Synthesis of (+)-Virgatusin via AlCl$_3$–Catalyzed [3 + 2] Cycloaddition

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Supporting Information

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Experimental Section

Materials and Methods: General Information. Infrared (IR) spectra were obtained using a JACSO FT/IR 460-plus infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (\(^1\)H and \(^{13}\)C NMR) were recorded on the following instruments: Bruker model Avance 400 (\(^1\)H NMR at 400 MHz and \(^{13}\)C NMR at 100 MHz) and Varian Gemini 300 (\(^1\)H NMR at 300 MHz and \(^{13}\)C at 75 MHz) spectrometers with solvent resonance as the internal standard (\(^1\)H NMR: CDCl$_3$ at 7.27 ppm or TMS at 0.00 ppm and \(^{13}\)C NMR: CDCl$_3$ at 77.0 ppm). \(^1\)H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, q = quartet, quint = quintuplet, sep = septet, m = multiplet), coupling constants (Hz), and integration. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Mass spectra were obtained on a Micromass Quattro II Triple Quadrupole Spectrometer using ESI ionization. Structural assignments were made using NOESY experiments. Enantiomeric ratios were obtained using a Berger Supercritical fluid Chromatograph mode FCM 1100/1200 equipped with an Agilent 1100 series UV-Vis detector using one of the following chiral HPLC columns: Chiralcel Chiralpak AD, WO, or OD column. Samples were eluted with SFC grade CO$_2$ and the indicated percentage of MeOH. Visualization was accomplished with UV light and aqueous ceric ammonium nitrate molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Sorbent Technologies silica gel 60 (32-63 \(\mu\)m). Yield refers to isolated yield of analytically pure material. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables and equations, which are averages of at least two experiments. Methylene chloride, THF, and toluene were dried by passage through a
column of neutral alumina under nitrogen prior to use. Unless otherwise noted, reagents were obtained from commercial sources and used without further purification.

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\text{Benzylbromoacetate (30.00 g, 131 mmol) was stirred with dimethyl sulfide (9.76 g, 157.2 mmol) in 10 mL of acetone. The reaction was allowed to stir overnight. During the course of the reaction small portions of acetone were added to aid in stirring the white precipitate that is formed. An ice bath can be used if the product does not fully precipitate. The mixture was filtered and the white solid was washed with cold hexanes to obtain 29.7 g (78%) of the dimethylsulfonium bromide. The filtrate can be concentrated to obtain more material if desired.}
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Analytical data: mp 94-95 °C; IR (thin film, cm\(^{-1}\)) 2970, 2723, 1719, 1459, 1377, 1156; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.34 (s, 5H), 5.26 (s, 2H), 5.19 (s, 2H), 3.37 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 164.4, 134.0, 129.0, 128.8, 128.7, 128.6, 68.9, 44.3, 25.3; Anal. Calcd. for C\(_{11}\)H\(_{15}\)BrO\(_2\)S: C, 45.37; H, 5.19. Found: C, 45.23; H, 5.13; HRMS (ESI) calcd. for C\(_{11}\)H\(_{15}\)O\(_2\)S \([\text{M}]^+\) : 211.0787. Found \([\text{M}]^+\) = 211.0777.

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\text{Dibenzyl 2-(3,4-dimethoxybenzylidene)malonate: A 250 mL round-bottomed flask equipped with a Dean-stark trap, condenser, and stirbar was charged with benzene (45 mL), dibenzyl malonate (14 g, 49.2 mmol), 3,4-dimethoxybenzaldehyde (9.82 g, 59.1 mmol), and 5 mol % piperidinium acetate. The mixture was brought to reflux and allowed to stir for 16 hours upon which TLC analysis showed disappearance of starting material. The reaction was allowed to cool to room temperature. The clear orange liquid was diluted with 20 mL of C\(_6\)H\(_6\) and washed twice with 1 M HCl (25mL). The organic layer was washed once with saturated NaHCO\(_3\) (20 mL) and once with brine (30 mL). The organic portion was dried over Na\(_2\)SO\(_4\), filtered, and concentrated to an orange oil. The material formed a solid upon standing and was recrystallized with EtOAc/hexanes to yield 16.6 g (78%) of the benzylidene malonate.}
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Analytical data: mp 74-75 °C; IR (thin film, cm\(^{-1}\)) 2957, 2838, 1729, 1517, 1255, 1226, 1191, 1144; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.73 (s, 1H), 7.36-7.27 (m, 10H), 7.02-6.99 (m, 2H), 6.75 (d, \(J = 8.4\) Hz, 1H), 5.29 (d, \(J = 10.8\) Hz), 3.90 (s, 3H), 3.75 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 166.9, 164.2, 151.5, 149.0, 143.1, 135.7, 135.1, 128.6, 128.5, 128.4, 128.2, 128.0, 125.5, 124.3, 123.3, 112.0, 111.1, 67.4, 55.9, 55.8; TLC (30% EtOAc/hexanes) \(R_f\) 0.31; Anal. Calcd. for C\(_{26}\)H\(_{24}\)O\(_6\); C, 72.21; H, 5.59. Found: C, 71.97; H, 5.61; HRMS (ESI) calculated for C\(_{26}\)H\(_{24}\)O\(_6\)Cs \([\text{M+Cs}]^+\) : 565.0627. Found: \([\text{M+Cs}]^+\) = 565.0651.
**Dimethyl 2-(3,4-dimethoxybenzylidene)malonate:** A 250 mL round bottomed flask equipped with a Dean-stark trap, condenser, and stirbar was charged with benzene (45 mL), dimethyl malonate (10 g, 75.7 mmol), 3,4-dimethoxybenzaldehyde (15.1 g, 90.8 mmol), and 10 mol % piperidinium acetate. The mixture was brought to reflux and allowed to stir for 24 hours upon which TLC analysis showed disappearance of starting material. The reaction was allowed to cool to room temperature. The clear orange liquid was diluted with C₆H₆ (20 mL) and washed with 1M HCl (25 mL). The organics were then washed once with saturated NaHCO₃ (20 mL) and once with brine (30 mL). The organic portion was dried over Na₂SO₄, filtered, and concentrated to an orange oil. The material formed a solid upon standing and was recrystallized with EtOAc/hexanes to yield 17.6 g (83%) of the benzylidene malonate.

**Analytical Data:**

**1H NMR** (400 MHz, CDCl₃) δ 7.71 (s, 1H), 7.09-7.07 (m, 1H), 7.00-6.99 (m, 1H), 6.87 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 6H), 3.85 (s, 3H). Complete analytical data for this compound has been published previously.¹

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The sulfonium salt (8.3 g, 28.4 mmol) was placed in a round-bottomed flask under N₂ and partially dissolved in 20 mL of CH₂Cl₂ at 0 °C. DBU (4.2 mL, 28.4 mmol) was added and the mixture was allowed to stir for 30 minutes, at which time all solids had gone into solution. The benzylidene malonate (5.3 g, 18.9 mmol) was added and the reaction was allowed to stir at 0 °C for 12 hours. The reaction was then washed with 1 M HCl (20 mL) and brine (20 mL). The organic layer was dried with Na₂SO₄ and concentrated. The material was subjected to flash chromatography with 30% EtOAc/hexanes to give 6.6 g (82%) of the product as a viscous liquid. Upon standing, this material formed a white solid. This material can also be purified by adding MeOH to precipitate the solid and recrystallizing with EtOAc/hexanes.

**Analytical data:**

mp 70-72 °C; IR (thin film, cm⁻¹) 2954, 2838, 1739, 1590, 1520, 1252, 1162, 1027; **1H NMR** (400 MHz, CDCl₃) δ 7.39-7.36 (m, 5H), 6.78-6.76 (m, 3H), 5.21 (d, J = 12 Hz, 1H), 5.15 (d, J = 12 Hz, 1H), 3.86 (s, 3H) 3.85 (s, 3H), 3.68 (s, 3H), 3.62 (d, J = 7.6 Hz, 1H), 3.51 (s, 3H), 3.26 (d, J = 7.6 Hz, 1H). **13C NMR** δ 168.9, 166.4, 165.6, 148.7, 148.6, 135.2, 128.6, 128.6, 128.5, 125.1, 120.8, 111.6, 110.8, 67.4, 55.9, 55.8, 53.0, 53.0, 44.3, 35.8, 31.3; TLC (30% EtOAc/hexanes) Rf 0.18; **Anal.** Calcd. for
C$_{23}$H$_{24}$O$_8$: C, 64.48; H, 5.65. Found: C, 64.59; H, 5.61; **HRMS (ESI)** calculated for C$_{23}$H$_{24}$O$_8$Cs [M+Cs]$^+$ : 565.0525. Found: [M+Cs]$^+$ = 565.0651.

(2R,3S)-1,1-dibenzyl 2-ethyl 3-(3,4-dimethoxyphenyl)cyclopropane-1,1,2-tricarboxylate: The sulfonium salt (6 g, 13.9 mmol) was placed in a round-bottomed flask under N$_2$ and partially dissolved in 20 mL of toluene/CH$_2$Cl$_2$ (3:2) at 0 °C. DBU (3.1 mL, 20.8 mmol) was added and the mixture was allowed to stir for 30 minutes. At this time, all solids had gone into solution. The benzylidene malonate (4.8 g, 20.8 mmol) was added and the reaction was allowed to stir at 45 °C for 6 hours. The reaction was then washed with 1 M HCl (20 mL) and brine (20 mL). The organic layer was dried with Na$_2$SO$_4$ and concentrated. Upon standing, a solid was formed which was recrystallized with EtOH to give 6.7 g (80%) of the product as a white solid.

Analytical data: **mp** 98-100 °C; **IR** (thin film, cm$^{-1}$) 2959, 2837, 1734, 1520, 1456, 1252, 1028; $^1$H **NMR** (400MHz, CDCl$_3$) δ 7.35-7.22 (m, 7H), 6.99 (d, $J$ = 6.8 Hz, 1H), 6.79-6.71 (m, 3H), 5.25 (d, $J$ = 12.4 Hz, 1H) 5.21 (d, $J$ = 12.4 Hz, 1H), 4.96 (d, $J$ = 12 Hz, 1H), 4.87 (d, $J$ = 12 Hz, 1H) 4.17-4.11 (m, 2H), 4.07 (d, $J$ = 12 Hz, 1H) 4.06 (d, $J$ = 12 Hz, 1H) 3.87 (s, 3H), 3.75 (s, 3H), 3.67 (d, $J$ = 7.6 Hz, 1H), 3.26 (d, $J$ = 7.6 Hz, 1H) 1.26 (t, $J$ = 7.2 Hz, 3H); $^{13}$C **NMR** δ 168.8, 165.8, 165.1, 148.8, 148.6, 135.4, 134.9, 128.5, 128.4, 128.3, 128.2, 128.1, 125.1, 121.1, 111.9, 110.8, 67.8, 67.5, 61.6, 55.8, 44.3, 35.8, 31.5, 14.1; **TLC** (30% EtOAc/hexane) $R_f$ 0.32;

**Anal.** Calcd. for C$_{30}$H$_{30}$O$_8$: C, 69.49; H, 5.83. Found: C, 69.30; H, 5.81; **HRMS (ESI)** calculated for C$_{30}$H$_{30}$O$_8$Cs [M+Cs]$^+$ : 651.0995. Found: [M+Cs]$^+$ = 651.1064.

(2S,4S,5S)-4-benzyl 3,3-dimethyl 2-(benzo[d][1,3]dioxol-5-yl)-5-(3,4-dimethoxyphenyl)dihydrofuran-3,3,4(2H)-tricarboxylate (3): A 125 mL round bottom flask with a stirbar was charged with 9.8 g of the cyclopropane (23 mmol), aldehyde (6.9 g, 46 mmol), and AlCl$_3$ (0.46 g, 3.5 mmol). Outside the glove box, CH$_2$Cl$_2$ was added under N$_2$ and the reaction was allowed to stir at room temperature. The reaction was allowed to become homogenous and then diluted with diethyl ether after 5 minutes. The solution was run through a silica plug with CH$_2$Cl$_2$ and concentrated. The reaction was allowed to become homogenous and then diluted with diethyl ether after 5 minutes. The solution was run through a silica plug with CH$_2$Cl$_2$ and concentrated. The reaction was allowed to become homogenous and then diluted with diethyl ether after 5 minutes. The solution was run through a silica plug with CH$_2$Cl$_2$ and concentrated. 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recrystallization the er was 99:1 (Chiralpak AD, 6.0% MeOH, 2.0 mL/min, 200 psi, 27 °C, 220 nm, tₘ-major, 18.5 min, tₘ-minor 16.3 min).

Analytical data: [α]ᴰ²⁴.⁷ -15.5 (c = 0.40, CH₂Cl₂) at 80 % ee; [α]ᴰ²⁴.⁵ -20.32 (c = 0.50, CH₂Cl₂) at 98 % ee; mp 117-118; IR (thin film, cm⁻¹) 2953, 1735, 1519, 1446, 1265, 1165, 1036; ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.025 (m, 8H), 6.99 (d, J = 8 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 5.94 (s, 2H), 5.75 (s, 1H), 5.11 (m, 2H), 5.02 (d, J = 8.8 Hz, 1H), 4.13, (d, J = 8.8 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.51 (s, 3H), 3.26 (s, 3H); ¹³C NMR δ 171.1, 168.5, 168.5, 149.4, 149.2, 147.6, 147.3, 135.4, 130.7, 130.3, 128.5, 128.3, 120.8, 119.4, 111.4, 110.1, 107.8, 107.8, 101.0, 84.85, 83.8, 69.1, 67.0, 58.9, 55.9, 52.7, 52.5; Anal. Calcd. for C₃₁H₃₀O₁₁: C, 64.35; H, 5.23. Found: C, 64.33; H, 5.12; HRMS (ESI) calculated for C₃₁H₃₀O₁₁Cs [M+Cs]⁺ : 711.0842. Found: [M+Cs]⁺ = 711.0831.

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\text{(2S,4S,5S)-3,3-dibenzyl 4-ethyl 2-(benzo[\text{d}][1,3]dioxol-5-yl)-5-(3,4-dimethoxyphenyl)dihydrofuran-3,3,4(2H)-tricarboxylate: A 125 mL round bottom flask with a stirbar was charged with 1.29 g of the cyclopropane (2.5 mmol), piperonal (0.75 g, 5 mmol), and AlCl₃ (0.07 g, 0.5 mmol). Outside the glove box, CH₂Cl₂ was added under N₂ and the reaction was allowed to stir. The reaction was allowed to become homogenous and then diluted with diethyl ether after 5 minutes. The solution was run through a silica plug and}
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concentrated. The reaction was flashed with 60% ether/petroleum ether to give the product in 81 % yield (1.35 g). Upon concentration the cycloadduct was obtained as an oil; MeOH can be used to precipitate the product as a white solid, which can be recrystallized with EtOAc/hexanes.

Analytical data: mp 129-130 °C; IR (thin film, cm⁻¹) 2937, 2834, 1733, 1519, 1447, 1264, 1037; ¹H NMR (400 MHz, CDCl₃) δ 7.23-7.04 (m, 12 H), 6.92 (s, 1H), 6.90 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 5.88 (d, J = 13.6 Hz, 2H), 5.80 (s, 1H), 5.14 (d, J = 12 Hz, 1H), 5.06 (d, J = 8.8 Hz, 1H), 5.00 (d, J = 12, 1H), 4.84 (d, J = 12.4 Hz, 1H), 4.41 (d, J = 12.4 Hz, 1H), 4.11 (d, J = 8.8 Hz, 1H), 3.97-3.95 (m, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.85-3.83 (m, 1H), 1.07 (t, J = 6.8 Hz, 3H); ¹³C NMR δ 149.3, 149.1, 147.6, 147.3, 134.6, 134.5, 130.8, 130.1, 128.5, 128.4, 128.3, 128.2, 127.9, 120.8, 119.4, 110.9, 109.9, 107.9, 101.0, 84.9, 83.9, 69.2, 67.8, 61.3, 59.0, 55.9, 14.0; TLC (30% EtOAc/hexane) R_f 0.21; Anal. Calcd. for C₃₈H₃₆O₁₁: C, 68.25; H, 5.43. Found: C, 68.03; H, 5.53; HRMS (ESI) calculated for C₃₈H₃₆O₁₁Cs [M+Cs]+ : 801.1312. Found: [M+Cs]+ = 801.1338. The relative stereochemistry was confirmed via an X-ray diffraction study. CCDC 734858 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(2S,3S,5S)-5-(benzo[d][1,4]dioxol-5-yl)-2-(3,4-dimethoxyphenyl)-4,4-bis(methoxycarbonyl)tetrahydrofuran-3-carboxylic acid: 10 % Pd/C (975 mg, 0.92 mmol) was added to a round bottom flask. The benzyl ester cycloadduct (5.3 g, 9.2 mmol) was then added in a 9:1 CH₂Cl₂/EtOAc mixture. A hydrogen ballon was added and the reaction was allowed to stir for 18 hours. After removal of the hydrogen balloon, the reaction contents were run through a celite plug and washed with EtOAc and CH₂Cl₂. To ensure product removal from the celite, a final wash was done with 5% MeOH/CH₂Cl₂. This material was also synthesized asymmetrically on a 0.4 mmol (0.22 g) scale.

Analytical data: [α]D²⁴.⁵ -24.1 (c = 1.00, CH₂Cl₂); mp 129 °C; IR (thin film, cm⁻¹) 2954, 2841, 1734, 1610, 1519, 1446, 1265, 1037; ¹H NMR (400MHz, CDCl₃) δ 7.26-6.99 (m, 4H), 6.86 (d, J = 8 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.94 (s, 2H), 5.72 (s, 1H), 5.04 (d, J = 8.8 Hz, 1H), 4.12 (d, J = 9.2 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.67 (s, 3H), 3.28 (s,
(2S,3S,4S,5R)-5-(benzo[d][1,3]dioxol-5-yl)-2-(3,4-dimethoxyphenyl)-4-(methoxycarbonyl)tetrahydrofuran-3-carboxylic acid (4): The tetrahydrofuran acid (3.0 g, 6.1 mmol) was added to a reaction tube with KOAc (1.2 g, 12.3 mmol). DMSO (10 mL) was added to dissolve the reagents followed by 0.5 mL of H2O. The reaction tube was heated to 100 °C with stirring. After 16 hours the reaction was allowed to cool to room temperature and partitioned between Et2O (20 mL) and H2O (20 mL). After separation, the aqueous layer was extracted with three portions of Et2O (20 mL). The combined organic extracts were washed with three portions of H2O (20 mL), brine (20 mL), dried over MgSO4, filtered and concentrated under rotary evaporation. This material was also synthesized asymmetrically on a 0.3 mmol (0.16 g) scale.

Analytical data: [α]D24.9 33.3 (c = 1.00, CH2Cl2); IR (thin film, cm⁻¹) 2951, 2834, 1735, 1519, 1445, 1242, 1035; 1H NMR (400 MHz, CDCl3) δ 7.24 (s, 1H), 7.16-7.13 (m, 1H), 6.91-6.78 (m, 4H), 5.97 (s, 2H), 5.26 (d, J = 7.6 Hz, 1H), 5.02 (d, J = 6.8 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.80-3.77 (m, 2H), 3.33 (s, 3H); 13C NMR δ 177.3, 171.5, 149.3, 149.2, 147.4, 147.4, 131.1, 130.8, 120.1, 119.7, 110.9, 110.2, 108.1, 107.1, 101.1, 83.3, 82.4, 56.0, 55.9, 54.4, 54.3, 52.0; TLC (5% MeOH/CH2Cl2) Rf 0.34; Anal. Calcd. for C22H22O9: C, 61.39; H, 5.15. Found: C, 61.10; H, 5.26; HRMS (ESI) calculated for C22H22O9Cs [M+Cs]+ : 563.0318. Found: [M+Cs]+ = 563.0321.

((2R,3R,4R,5S)-2-(benzo[d][1,3]dioxol-5-y1)-5-(3,4-dimethoxyphenyl)tetrahydrofuran-3,4-diyl)dimethanol: A solution of 1 M LiAlH4 (7.5 mL) in THF (10 mL) at 0 °C was treated with a solution of the cycloadduct (1.15 g, 2.5 mmol) in THF (5 mL) via syringe. After the addition the reaction was allowed to warm to room temperature with stirring. After two hours the reaction was quenched with 0.5 mL H2O, 0.5 mL of a 15% NaOH solution, and 1.5 mL of H2O. The solution was filtered through a Buchner funnel and the filter cake was washed with several portions of Et2O (5 mL). The filtrate was dried over MgSO4, filtered, and concentrated by rotary evaporation affording a white solid in 99% yield (0.97 g). This material was also synthesized asymmetrically on a 0.3 mmol (0.15 g) scale.
Analytical data: \([\alpha]_D^{27.5}\) 19.9 (c = 1.5, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) 3365, 2931, 2904, 1608, 1594, 1518, 1490, 1444, 1261, 1035; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.01-6.76 (m, 6H), 5.95 (s, 2H), 5.08 (d, \(J = 8.8\) Hz, 1H), 4.46 (d, \(J = 9.2\) Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.73-3.70 (m, 1H), 3.58-3.53 (m, 1H), 3.33-3.30 (m, 1H), 3.14-3.09 (m, 1H), 2.59-2.57 (m, 1H), 2.27-2.24 (m, 1H); \(^{13}\)C NMR \(\delta\) 149.2, 149.1, 147.7, 147.1, 132.9, 132.5, 119.8, 119.2, 111.3, 110.2, 108.1, 107.0, 101.1, 82.6, 81.3, 63.7, 63.0, 56.0, 55.1, 50.9; TLC (5% MeOH/CH\(_2\)Cl\(_2\)) \(R_f\) 0.28; HRMS (ESI) calculated for C\(_{21}\)H\(_{24}\)O\(_7\)Cs [M+Cs\(^+\)]: 521.0576. Found: [M+Cs\(^+\)] = 521.0616.

5-((2R,3R,4R,5S)-5-(3,4-dimethoxyphenyl)-3,4-bis(methoxymethyl)tetrahydrofuran-2-yl)benzo[d][1,1]dioxole: To a suspension of NaH (0.12 g, 3.1 mmol) in THF (4 mL) at room temperature was added a solution of the diol (0.50 g, 1.3 mmol) in THF (3 mL) followed by 18-crown-6 (0.02 g, 0.06 mmol), in a flame dried round bottom flask. This mixture was allowed to stir at room temperature for one hour. The mixture was then heated to 35 °C followed by addition of CH\(_3\)I (2.75 g, 19.4 mmol). This mixture was allowed to stir under N\(_2\) for 16 hours. After cooling, the reaction was diluted with Et\(_2\)O, dried with MgSO\(_4\), filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography using 30% EtOAc/hexanes to obtain 405 mg of the product (75%). This material was also synthesized asymmetrically on a 0.15 mmol (0.06 g) scale.

Analytical data: \([\alpha]_D^{28.7}\) 9.5 (c = 1.1, CH\(_2\)Cl\(_2\)); IR (thin film, cm\(^{-1}\)) 2927, 2830, 1593, 1516, 1444, 1238, 1033; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.04 (d, \(J = 1.2\) Hz, 1H), 7.00 (d, \(J = 8\) Hz, 1H), 6.90 (s, 1H), 6.85-6.82 (m, 2 H), 6.75 (d, \(J = 8\) Hz, 1H), 5.93 (s, 2H), 5.04 (d, \(J = 7.2\) Hz, 1H), 4.69 (d, \(J = 3\) Hz, 3H), 3.86 (s, 3H), 3.53-3.45 (m, 2H), 3.33 (s, 3H), 3.06 (s, 3H), 3.04-3.02 (m, 1H), 2.97-2.94 (m, 1H), 2.61-2.54 (m, 1H), 2.35-2.29 (s, 1H); \(^{13}\)C NMR \(\delta\) 148.9, 148.5, 147.4, 147.6, 146.6, 134.1, 132.8, 119.6, 118.8, 111.0, 109.9, 107.8, 107.0, 100.9, 82.6, 81.4, 73.1, 73.0, 59.0, 58.6, 55.9, 55.8, 50.9, 46.5; Anal. Calcd. for C\(_{23}\)H\(_{28}\)O\(_7\): C, 66.33; H, 6.78. Found: C, 66.28; H, 6.76; HRMS (ESI) calculated for C\(_{23}\)H\(_{28}\)O\(_7\)Cs [M+Cs\(^+\)]: 549.0889. Found: [M+Cs\(^+\)] = 549.0935.

(E)-3-(3,4-dimethoxyphenyl)acrylonitrile: The phosphonate (4.9 g, 27.4 mmol) was deprotonated in 40 mL of dry THF with \(^{t}\)BuLi (25.5 mmol) at 0 °C for 45 minutes. 4.9 g
of the aldehyde (18.3 mmol) was dissolved in 15 mL of dry THF. The Wittig solution was added to the aldehyde dropwise via cannula transfer. After the addition was complete the reaction was allowed to stir for 20 more minutes. The reaction was then concentrated and purified by column chromatography with 30% EtOAc/hexanes to give 2.9 g (83%) of the nitrile in a 7:1 ratio for the desired isomer. $^1$H-NMR data is consistent with that reported previously.\(^2\)

\[ \text{(E)-3-(3,4-dimethoxyphenyl)acrylaldehyde (8):} \]

0.70 g of the nitrile was cooled in 25 mL of toluene to -78 °C with stirring. A 0.562 M solution of DIBALH in toluene (10.7 mL) was added dropwise to the nitrile via cannula transfer. The solution was allowed to stir for 2 hours. At -78 °C MeOH (2 mL) was added to quench the reaction. The reaction flask was allowed to warm to room temperature then stirred with 1M HCl (4 mL) for two minutes. The reaction was diluted with 20 mL of EtOAc and extracted. The aqueous layer was extracted twice with 10 mL of EtOAc. The combined organics were washed with brine and dried over Na$_2$SO$_4$. After concentration the material was purified by column chromatography to give the desired isomer in a 76% yield (0.55 g). $^1$H NMR data is consistent with that reported previously.\(^2\)

\[ \text{(2S,3R)-dimethyl 2-(3,4-dimethoxyphenyl)-3-formylcyclopropane-1,1-dicarboxylate (10): } \]

To a mixture of bromomalonate ester (1.66 g, 7.9 mmol), 2,6-lutidine (1 mL, 8.6 mmol), and the proline catalyst\(^3\) (0.77 g, 2.4 mmol) was added the aldehyde (1.66 g, 8.6 mmol) at room temperature. The reaction was allowed to stir in a sealed scintillation vial for three days. At this time the reaction contents were washed with 1M HCl. The organic portion was dried and concentrated. This material was analyzed by $^1$H NMR to confirm formation of the product. The crude material was taken on to the oxidation. Column chromatography resulted in complete racemization of the aldehyde by SFC analysis.
(1R,3S)-3-(3,4-dimethoxyphenyl)-2,2-bis(methoxycarbonyl)cyclopropanecarboxylic acid: A solution of the aldehyde (0.63 g, 2.0 mmol) in acetonitrile (6 mL) was cooled to 0 °C and a solution of KH$_2$PO$_4$ (0.53 g, 3.9 mmol) and H$_2$O$_2$ in H$_2$O (8 mL) was added under rigorous stirring. After addition of a solution of NaClO$_2$ (0.71 g, 7.8 mmol) H$_2$O (8 ml), the mixture was stirred at 0 °C. After 3 hours, Na$_2$SO$_3$ was added to destroy excess NaClO$_2$. The solution was made basic with 6M NaOH and extracted with EtOAc. The aqueous solution was acidified with 6M HCl (pH 3). It was extracted with EtOAc twice, once with brine, and dried with magnesium sulfate. This material was taken on to the benzylation without further purification.

(2R,3S)-2-benzyl 1,1-dimethyl 3-(3,4-dimethoxyphenyl)cyclopropane-1,1,2-tricarboxylate (2R,3S)-1: The cyclopropane acid (1.1 g, 3.2 mmol), triethylamine (2.2 mL, 16 mmol), and benzyl bromide (1.88 mL, 16 mmol) were dissolved in 25 mL THF and allowed to stir at reflux overnight. TLC analysis indicated the disappearance of starting material. The reaction was cooled to room temperature and diluted with 15 mL of H$_2$O. The solution was extracted three times with Et$_2$O (15 mL) and the combined organics were washed with H$_2$O and brine, dried over MgSO$_4$, and concentrated to give (2R,3S)-1 in 43% over three steps. $[\alpha]_D^{25.7} -9.2$ (c = 0.42, CH$_2$Cl$_2$).

(2R,4S,5R)-4-benzyl 3,3-dimethyl 2-(benzo[d][1,3]dioxol-5-yl)-5-(3,4-dimethoxyphenyl)dihydrofuran-3,3,4(2H)-tricarboxylate and (2S,4S,5S)-4-benzyl 3,3-dimethyl 2-(benzo[d][1,3]dioxol-5-yl)-5-(3,4-dimethoxyphenyl)dihydrofuran-3,3,4(2H)-tricarboxylate: A flame dried shell vial with a stirbar was charged with 0.15 g of the cyclopropane (0.35 mmol) and piperonal (0.11g, 0.7 mmol). Outside the glove box, a solution of SnCl$_4$ (0.07 g, 0.3 mmol) in CH$_2$Cl$_2$ was added under N$_2$ and the reaction
was allowed to stir for 16 hours. The reaction was then diluted with diethyl ether and the solution was run through a silica plug and concentrated. The reaction was flashed with 60% ether/petroleum ether to isolate 5.

Analytical data: IR (thin film, cm$^{-1}$) 2940, 2845, 1730, 1530, 1430, 1227; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36-7.12 (m, 2H), 7.05 (d, $J = 4$ Hz, 1H), 7.02-6.99 (m, 4H), 6.80-6.77 (m, 2H), 5.98 (s, 2H), 5.47 (s, 1H), 5.19 (d, $J = 6.8$ Hz, 1H), 4.83 (d, $J = 12$ Hz, 1H), 4.67 (d, $J = 12$ Hz, 1H), 4.04 (d, $J = 6.8$ Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.33 (s, 3H); $^{13}$C NMR $\delta$ 170.5, 168.7, 166.5, 148.8, 148.8, 147.5, 147.2, 135.2, 130.6, 128.9, 128.5, 128.3, 128.1, 122.1, 119.2, 110.8, 110.2, 109.1, 107.5, 100.9, 84.7, 80.5, 68.0, 66.8, 57.5, 55.9, 55.9, 53.6, 52.1; HRMS (ESI) calculated for C$_{31}$H$_{30}$O$_{11}$Cs [M+Cs]$^+$ : 711.0843. Found: [M+Cs]$^+$ = 711.0842.

$\text{(2S,4S,5S)-4-benzyl 3,3-dimethyl 2-(benzo[d][1,3]dioxol-5-yl)-5-(3,4-dimethoxyphenyl)dihydrofuran-3,3,4(2H)-tricarboxylate and piperonal:}$ A flame-dried shell vial with a stir bar was charged with 5 (45 mg, 0.12 mmol) and AlCl$_3$ (1.6 mg, 0.12 mmol) inside the glovebox. Outside the box CH$_2$Cl$_2$ was added to the vial under N$_2$. After the addition, the reaction was stirred for two minutes. It was then diluted with Et$_2$O and concentrated. $^1$H NMR analysis confirmed formation of 3 and 2 with loss of 5. Aldehyde 2 was obtained in 48% yield and cycloadduct 3 in 36% yield as determined using mesitylene as an internal standard.

References
