Brønsted Acid-Catalyzed Allylboration:
Short and Stereodivergent Synthesis of All Four Eupomatilone Diastereomers with Crystallographic Assignments

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1. General information

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Tetrahydrofuran was distilled over sodium-benzophenone ketyl. Toluene, CH$_2$Cl$_2$ and HMPA were distilled over CaH$_2$ before use. NH$_4$Cl$_{(aq)}$ and NaHCO$_3$(aq) refer to saturated aqueous solutions. All liquid aldehydes were purified by Kugelrohr distillation prior to use. Methyllithium was titrated according to the Gilman double titration method. Iodomethaneboronate, chloromethaneboronate, and 2-bromo-3,4,5-trimethoxybenzaldehyde were prepared according to literature procedures. TfOH was stored in a closed pear-shaped flask under Ar and placed in a jar filled with anhydrous calcium sulfate (Drierite®) which was then stored at 0 °C. All other chemicals were used as received from commercial sources. Thin layer chromatography (TLC) was performed on Silica Gel 60 F$_{254}$ plates and were visualized with UV light and aqueous KMnO$_4$ solution. NMR spectra were recorded on 300, 400 or 500 MHz instruments. The residual solvent protons (H) or the solvent carbons (C) were used as internal standards. H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, integration, coupling constant). The following abbreviations are used in reporting NMR data: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dq, doublet of quartets; dt, doublet of triplets; qt, quartet of triplets; m, multiplet. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using electron impact (EI) or electrospray (ES) ionization techniques. Elemental analyses were performed by the University of Alberta Micro-Analytical Lab. Infrared spectra and X-ray diffraction data were collected by the University of Alberta Spectral Services and X-Ray Crystallography Laboratory, respectively.
2. Preparation of 4,4-dimethyl-3-methylene-5-phenyl-dihydro-furan-2-one (3) under the optimal conditions

A solution of allylboronate 2 (R = (-)-menthol, 71.1 mg, 0.188 mmol) and benzaldehyde (38 µL, 0.37 mmol) in toluene (0.2 mL) was treated with TfOH (1.7 µL, 0.019 mmol) and stirred at 0 °C under Ar atmosphere for 16 h. The mixture was then diluted with NH₄Cl(aq)/NH₄OH (9:1 v/v, 3 mL) and extracted with Et₂O (3 × 3 mL). The combined extracts were washed with brine (2 × 3 mL), dried with anhydrous Na₂SO₄ and concentrated. Flash chromatography (15 % Et₂O/hexane) gave the lactone product 3 (38 mg, 0.19 mmol, 99 %). This material possessed identical spectroscopic characteristics to those reported in the literature.⁴

3. Preparation of methyl (2E)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-but-2-enoate (E-4)

A slurry of recrystallized CuBr·SMₑ₂ (833 mg, 4.05 mmol) in anhydrous THF (11 mL) at 0 °C under Ar atmosphere was treated with MeLi (1.60 M in Et₂O, 5.1 mL, 8.1 mmol) using an air-tight syringe. An orange precipitate was formed initially then disappeared as the addition proceeded. The resulting clear colourless solution was stirred at 0 °C for an additional 10 min and then cooled to -78 °C in an acetone/CO₂ bath. A -78 °C solution of methyl propiolate (0.36 mL, 4.0 mmol) in THF (1 mL) was added via cannulation with THF rinse (3 × 1 mL). The resulting light brown mixture was stirred at -78 °C for 1 h and then injected with a -78 °C solution of freshly distilled iodomethaneboronate² (2.99 g, 11.2 mmol) in THF (2 mL) via cannulation with THF rinse (3 × 1 mL). HMPA (6.35 mL, 36.4 mmol) was quickly added. Stirring continued at -78 °C for another 10 min. The mixture was then brought to 0 °C, stirred for 1 h and...
finally brought to rt, stirred for 1 h. The milky slurry was quenched with NH₄Cl (aq) (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (4 × 20 mL). The combined organic layers were washed with water (6 × 20 mL) and brine (1 × 20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. Flash chromatography (25 % Et₂O/ hexane) gave the product as a yellowish liquid (740 mg, 3.12 mmol, 77 %). This material possessed identical spectroscopic characteristics to those reported in the literature.⁴

4. Preparation of allylboration adducts 7 and 13

rac-(4R*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-4-methyl-3-methylene-dihydrofuran-2-one (7)

A slurry of allylboronate E-4 (323 mg, 1.34 mmol) and 2-bromo-3,4,5-trimethoxybenzaldehyde 6³ (740 mg, 2.69 mmol) in toluene (1.34 mL) at 0 °C was treated with TfOH (24 µL, 0.27 mmol) and stirred at 0 °C under Ar atmosphere for 16 h. The mixture was then diluted with NH₄Cl (aq)/NH₄OH (9:1 v/v, 20 mL) and extracted with Et₂O (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL), dried with anhydrous Na₂SO₄ and concentrated. Flash chromatography (25 % EtOAc/hexane) gave the lactone product 7 (272 mg, 0.762 mmol, 57 %).

¹H NMR (500 MHz, CDCl₃): δ 6.63 (s, 1H), 6.32 (d, 1H, J = 2.7 Hz), 5.62 (d, 1H, J = 2.4 Hz), 5.44 (d, 1H, J = 5.3 Hz), 3.91 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 2.98 (m, 1H), 1.46 (d, 3H, J = 7.0); ¹³C NMR (100 MHz, CDCl₃): δ 170.2, 153.3, 151.0, 143.1, 139.8, 134.0, 129.0, 122.1, 108.2, 105.4, 83.9, 61.0, 56.2, 43.5, 18.6; IR (CH₂Cl₂ cast film, cm⁻¹): 2969, 2938, 1769, 1485, 1396, 1325, 1248, 1107, 1000; HRMS (EI, m/z) Calcd for C₁₅H₁₇BrO₅: 358.02390. Found: 358.02432.
rac-(4S*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-4-methyl-3-methylene-dihydrofuran-2-one (13)

A slurry of allylboronate E-4 (358 mg, 1.49 mmol) and 2-bromo-3,4,5-trimethoxybenzaldehyde 6 (410 mg, 1.49 mmol) in toluene (1.5 mL) was heated at 110 °C under Ar atmosphere for 48 h. A spatula tip of pTSA•H2O was then added and the mixture was stirred for 3 h at rt. The reaction was quenched with NaHCO₃(aq) (20 mL) and extracted with Et₂O (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried with anhydrous Na₂SO₄ and concentrated. Flash chromatography (35 % EtOAc/hexane) gave the lactone product 13 (394 mg, 1.10 mmol, 74 %).

¹H NMR (300 MHz, CDCl₃): δ 6.69 (s, 1H), 6.32 (d, 1H, J = 2.3 Hz), 5.82 (dd, 1H, J = 0.6, 7.3 Hz), 5.66 (d, 1H, J = 2.0 Hz), 3.89 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.68 (m, 1H), 0.78 (d, 3H, J = 7.3); ¹³C NMR (100 MHz, CDCl₃): δ 169.8, 152.9, 150.6, 142.6, 140.3, 131.2, 122.7, 107.3, 105.8, 80.7, 60.9, 56.1, 37.1, 16.6; IR (CH₂Cl₂ cast film, cm⁻¹): 2971, 2938, 1772, 1484, 1397, 1324, 1244, 1108, 1004; HRMS (EI, m/z) Calcd for C₁₅H₁₇⁷⁹BrO₅: 356.02594. Found: 356.02523. Calcd for C₁₅H₁₇⁸₁BrO₅: 358.0290. Found: 358.02347.

5. Preparation of hydrogenated products 8, 10 and 14

rac-(3S*, 4S*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyl-dihydrofuran-2-one (8)
A solution of lactone 7 (78 mg, 0.22 mmol) in EtOH (2.4 mL) was hydrogenated at 1 atm with 10 % Pd/C (7 mg) for 6 h. The mixture was then filtered through Celite® 545 with EtOH rinse followed by solvent removal to give hydrogenated product 8 as the major diastereomer (6:1 dr). Flash chromatography (35 % EtOAc/hexane) separated the diastereomers and yielded the pure 8 (49 mg, 0.14 mmol, 64 %). Single crystals suitable for X-ray diffraction were obtained by dissolving 8 in hot pentane followed by storing the resulting solution at 0 °C in a closed vial.

\[ ^1H \text{NMR (300 MHz, CDCl}_3\text{): } \delta 6.70 (s, 1H), 5.44 (d, 1H, } J = 9.5 \text{ Hz), 3.91 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 2.40 (dq, 1H, } J = 11.5, 7.0 \text{ Hz), 2.01 (m, 1H), 1.31 (d, 3H, } J = 7.0 \text{ Hz), 1.23 (d, 3H, } J = 6.6 \text{ Hz);}\]

\[ ^{13}C \text{ NMR (125 MHz, CDCl}_3\text{): } \delta 178.4, 153.3, 150.6, 143.4, 132.5, 109.6, 106.1, 83.9, 61.0, 60.9, 56.2, 48.6, 43.3, 14.9, 12.9; IR (CH}_2\text{Cl}_2 \text{ cast film, cm}^{-1}): 2968, 2937, 1776, 1486, 1397, 1333, 1241, 1169, 1107, 1002; HRMS (EI, m/z) Calcd for C\textsubscript{15}H\textsubscript{19}BrO\textsubscript{5}: 358.04160. Found: 358.04184. Calcd for C\textsubscript{15}H\textsubscript{19}BrO\textsubscript{5}: 360.03955. Found: 360.03992; Anal. Calcd for C\textsubscript{15}H\textsubscript{19}BrO\textsubscript{5}: C, 50.16; H, 5.33. Found: C, 50.17; H, 5.35. X-ray crystallographic data can be found in the on-line CIF files.
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.63 (s, 1H), 5.34 (d, 1H, $J = 2.5$ Hz), 3.91 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 2.74 (app quintet, 1H, $J = 7.2$ Hz), 1.19 (d, 3H, $J = 7.3$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 179.7, 153.1, 151.2, 142.7, 133.8, 107.4, 104.7, 84.2, 61.0, 56.2, 41.1, 36.3, 14.2, 9.5; IR (CH$_2$Cl$_2$ cast film, cm$^{-1}$): 2973, 2939, 1779, 1483, 1396, 1330, 1240, 1168, 1110, 1000; HRMS (EI, m/z) Calcd for C$_{15}$H$_{19}$BrO$_5$: 358.04160. Found: 358.04156. Calcd for C$_{15}$H$_{19}$81BrO$_5$: 360.03955. Found: 360.04031; Anal. Calcd for C$_{15}$H$_{19}$BrO$_5$: C, 50.16; H, 5.33. Found: C, 49.91; H, 5.32. X-ray crystallographic data can be found in the on-line CIF files.

rac-(3S*, 4R*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyl-dihydrofuran-2-one (14)

A solution of lactone 13 (55 mg, 0.16 mmol) in toluene (8 mL) was treated with Wilkinson’s catalyst (36 mg, 0.039 mmol) and hydrogenated at 1 atm for 6 h. Solvent removal followed by flash chromatography (35 % EtOAc/hexane) gave the hydrogenated product 14 as the only diastereomer observed (44 mg, 0.13 mmol, 79 %). Single crystals suitable for X-ray diffraction were obtained by dissolving 14 in hot pentane followed by storing the resulting solution at 0 °C in a closed vial.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.81 (s, 1H), 5.63 (dd, 1H, $J = 0.6, 5.0$ Hz), 3.90 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.21 (m, 1H), 3.03 (app quintet, 1H, $J = 7.2$ Hz), 1.22 (d, 3H, $J = 7.2$ Hz), 0.52 (d, 3H, $J = 7.3$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 178.5, 153.0, 150.8, 142.5, 131.1, 106.6, 106.3, 81.9, 61.1, 61.0, 56.3, 40.5, 37.3, 10.0, 9.7; IR (CH$_2$Cl$_2$ cast film, cm$^{-1}$): 2974, 2939, 1780, 1484, 1396, 1338, 1242, 1170, 1108, 997; HRMS (EI, m/z) Calcd for C$_{15}$H$_{19}$79BrO$_5$: 358.04160. Found: 358.04174. Calcd for C$_{15}$H$_{19}$81BrO$_5$: 360.03955. Found: 360.03961; Anal. Calcd for C$_{15}$H$_{19}$BrO$_5$: C, 50.16; H, 5.33. Found: C, 49.63; H, 5.33. X-ray crystallographic data can be found in the on-line CIF files.
6. Preparation of Suzuki-coupling\textsuperscript{5} products \textit{3,4-epi-1}, \textit{4-epi-1} and \textit{3-epi-1}

\textbf{3,4-epi-1}

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An oven-dried resealable Schlenk tube containing a magnetic stir bar was charged with arylbromide \textit{8} (90 mg, 0.25 mmol), boronic acid \textit{9} (62 mg, 0.38 mmol), K\textsubscript{3}PO\textsubscript{4} (106 mg, 0.5 mmol), Pd(OAc)\textsubscript{2} (0.6 mg, 0.0025 mmol) and SPhos ligand (2.3 mg, 0.005 mmol). Capped with a rubber septum, the Schlenk tube was evacuated and backfilled with Ar (this sequence was repeated four times). Toluene (0.5 mL) was then added and the resulting mixture was degassed. Backfilled with Ar, the Schlenk tube was quickly sealed with a Teflon\textsuperscript{\textregistered} screwcap. The mixture was heated at 110 °C with vigorous stirring for 12 h. Cooled to rt, the mixture was diluted with Et\textsubscript{2}O followed by filtration through a thin pad of silica gel with Et\textsubscript{2}O rinse. Solvent evaporation followed by flash chromatography (40 \% EtOAc/hexane) gave \textit{3,4-epi-1} as the only diastereomer observed (96 mg, 0.24 mmol, 98 \%). Single crystals suitable for X-ray diffraction were obtained by dissolving \textit{3,4-epi-1} in hot Et\textsubscript{2}O followed by storing the resulting solution at rt in a bigger, screwcapped vial containing hexane.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}, two atropisomers): \textit{\delta} 6.85 (s, 1H), 6.84 (s, 1H), 6.72 (d, 1H, \textit{J} = 1.6 Hz), 6.71-6.68 (m, 4H), 6.64 (dd, 1H, \textit{J} = 1.7, 7.9 Hz), 6.00 (m, 2H), 5.99 (m, 2H), 4.80 (d, 1H, \textit{J} = 9.8 Hz), 4.78 (d, 1H, \textit{J} = 9.8 Hz), 3.90 (s, 6H), 3.89 (s, 6H), 3.62 (s, 3H), 3.61 (s, 3H), 2.14 (m, 2H), 2.03 (m, 2H), 1.23 (d, 6H, \textit{J} = 6.9 Hz), 0.87 (d, 3H, \textit{J} = 6.4 Hz), 0.86 (d, 3H, \textit{J} = 6.4 Hz); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \textit{\delta} 178.5, 178.4, 153.2, 151.2, 151.1, 147.4, 147.3, 146.8, 142.5, 130.7, 130.6, 129.8, 128.9, 128.8, 124.2, 123.3, 111.3, 110.5, 108.0, 107.8, 105.2, 105.1, 101.1, 101.0, 82.6, 82.5, 61.0, 60.9, 60.7, 56.1, 47.4, 43.2, 14.2, 12.8; IR (CH\textsubscript{2}Cl\textsubscript{2}, cast film, cm\textsuperscript{-1}): 2966, 2935, 1774, 1484, 1459, 1324, 1238, 1039, 982; HRMS (EI, m/z) Calcd for C\textsubscript{22}H\textsubscript{24}O\textsubscript{7}: 400.15219. Found: 400.15220. X-ray crystallographic data can be found in the on-line CIF files. The compound crystallized into a single atropisomer.
An oven-dried resealable Schlenk tube containing a magnetic stir bar was charged with arylbromide 10 (90 mg, 0.25 mmol), boronic acid 9 (62 mg, 0.38 mmol), K$_3$PO$_4$ (106 mg, 0.5 mmol), Pd(OAc)$_2$ (0.6 mg, 0.0025 mmol) and SPhos ligand (2.3 mg, 0.005 mmol). Capped with a rubber septum, the Schlenk tube was evacuated and backfilled with Ar (this sequence was repeated four times). Toluene (0.5 mL) was then added and the resulting mixture was degassed. Backfilled with Ar, the Schlenk tube was quickly sealed with a Teflon® screwcap. The mixture was heated at 110 °C with vigorous stirring for 12 h. Cooled to rt, the mixture was diluted with Et$_2$O followed by filtration through a thin pad of silica gel with Et$_2$O rinse. Solvent evaporation followed by flash chromatography (40 % EtOAc/hexane) gave 4-epi-1 along with ca. 10 % of 3,4-epi-1 (88 mg, 0.22 mmol, 88 % total yield). The major diastereomer 4-epi-1 possessed identical spectroscopic characteristics to those reported in the literature. Single crystals suitable for X-ray diffraction were obtained by dissolving 4-epi-1 in hot Et$_2$O followed by storing the resulting solution at rt in a bigger, screwcapped vial containing hexane.

$^1$H NMR (500 MHz, CDCl$_3$, two atropisomers): δ 6.90 (s, 1H), 6.88 (s, 1H), 6.75-6.61 (m, 6H), 6.02 (m, 4H), 5.11 (d, 1H, J = 4.5 Hz), 5.01 (d, 1H, J = 4.5 Hz), 3.90 (s, 6H), 3.88 (s, 6H), 3.65 (s, 3H), 3.64 (s, 3H), 2.75 (m, 2H), 2.39 (m, 2H), 1.08 (d, 3H, J = 7.3 Hz), 1.07 (d, 3H, J = 7.3 Hz), 0.69 (d, 3H, J = 7.1 Hz), 0.66 (d, 3H, J = 7.1 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 179.9, 153.1, 153.0, 151.8, 151.7, 147.7, 146.9, 146.8, 142.0, 132.8, 129.0, 128.9, 124.1, 122.9, 111.2, 110.1, 108.4, 108.2, 103.6, 101.2, 101.1, 82.8, 61.1, 61.0, 60.8, 56.2, 41.6, 41.5, 37.1, 13.3, 9.8. X-ray crystallographic data can be found in the on-line CIF files. The compound crystallized into a single atropisomer.
An oven-dried resealable Schlenk tube containing a magnetic stir bar was charged with arylbromide 14 (92 mg, 0.26 mmol), boronic acid 9 (63 mg, 0.38 mmol), K₃PO₄ (108 mg, 0.51 mmol), Pd(OAc)₂ (2.8 mg, 0.012 mmol) and SPhos ligand (12 mg, 0.026 mmol). Capped with a rubber septum, the Schlenk tube was evacuated and backfilled with Ar (this sequence was repeated four times). Toluene (0.5 mL) was then added and the resulting mixture was degassed. Backfilled with Ar, the Schlenk tube was quickly sealed with a Teflon® screwcap. The mixture was heated at 110 °C with vigorous stirring for 12 h. Cooled to rt, the mixture was diluted with Et₂O followed by filtration through a thin pad of silica gel with Et₂O rinse. Solvent evaporation followed by flash chromatography (35 % EtOAc/hexane) gave 3-epi-1 along with ca. 17 % of 1 (100 mg, 0.25 mmol, 96 % total yield). The major diastereomer 3-epi-1 possessed identical spectroscopic characteristics to those reported in the literature.⁷

¹H NMR (300 MHz, CDCl₃, two atropisomers): δ 6.88 (s, 1H), 6.86 (s, 1H), 6.84 (s, 1H), 6.82 (s, 1H), 6.73 (d, 1H, J = 1.6 Hz), 6.70 (dd, 1H, J = 1.6, 7.8 Hz), 6.62 (d, 1H, J = 1.6 Hz), 6.58 (dd, 1H, J = 1.7, 7.9 Hz), 6.04 (m, 2H), 6.02 (m, 2H), 5.41 (d, 1H, J = 4.9 Hz), 5.32 (d, 1H, J = 4.9 Hz), 3.91 (s, 12H), 3.66 (s, 3H), 3.65 (s, 3H), 2.75 (m, 2H), 2.20 (m, 2H), 1.12 (d, 6H, J = 7.2 Hz), 0.56 (app triplet, 6H, J = 7.2 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 178.6, 152.7, 151.4, 147.6, 147.5, 146.9, 146.8, 141.4, 130.1, 129.1, 129.0, 126.3, 126.2, 123.4, 122.2, 110.5, 109.5, 108.3, 108.1, 104.8, 104.7, 101.1, 80.4, 80.3, 61.1, 61.0, 60.7, 56.1, 40.6, 38.7, 38.5, 9.8, 9.7, 9.6.
7. DBU-promoted epimerization\textsuperscript{8} of 3-\textit{epi}-1 to eupomatilone-6 (1)

In a resealable Schlenk tube, a small mixture which contained mainly 3-\textit{epi}-1 in 1:1 toluene/MeOH (2 mL) was treated with DBU (~ 1.5 equiv.). The Schlenk tube was sealed with a Teflon\textsuperscript{®} screwcap and the mixture was heated at 80 °C with vigorous stirring for 2 days. The now almost 1:1 (based on \textsuperscript{1}H NMR) mixture of 3-\textit{epi}-1 and eupomatilone-6 (1) was submitted to preparative TLC (20 % EtOAc/hexane with multiple developments)\textsuperscript{7} and an analytically pure sample of 1 was obtained by de-absorption with CH\textsubscript{2}Cl\textsubscript{2}, filtration and concentration. This material possessed identical spectroscopic characteristics to those reported in the literature.\textsuperscript{7}

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}, two atropisomers): \(\delta\) 6.88 (d, 1H, \(J = 8.1\) Hz), 6.87 (d, 1H, \(J = 8.1\) Hz), 6.73 (d, 1H, \(J = 1.4\) Hz), 6.70 (dd, 1H, \(J = 1.6, 7.8\) Hz), 6.67 (s, 1H), 6.66 (s, 1H), 6.65 (d, 1H, \(J = 1.4\) Hz), 6.59 (dd, 1H, \(J = 1.6, 8.1\) Hz), 6.03 (m, 2H), 6.02 (m, 2H), 5.65 (d, 1H, \(J = 7.0\) Hz), 5.53 (d, 1H, \(J = 7.0\) Hz), 3.91 (s, 6H), 3.89 (s, 6H), 3.65 (s, 3H), 3.64 (s, 3H), 2.36 (m, 2H), 2.05-1.96 (m, 2H), 1.20 (d, 3H, \(J = 7.6\) Hz), 1.19 (d, 3H, \(J = 7.6\) Hz), 0.73 (d, 3H, \(J = 7.2\) Hz), 0.70 (d, 3H, \(J = 7.2\) Hz).

8. Preliminary mechanistic investigations

Treatment of allylboronate \textit{E}-4 with TfOH

Isomerically pure allylboronate \textit{E}-4 (23 mg, 0.096 mmol) was dissolved in toluene (0.1 mL), cooled to 0 °C, treated with TfOH (1.7 \(\mu\)L, 0.019 mmol) and stirred at 0 °C under Ar atmosphere for 16 h. The mixture was then diluted with NH\textsubscript{4}Cl\textsubscript{(aq)}/NH\textsubscript{4}OH (9:1 v/v, 2 mL) and extracted with Et\textsubscript{2}O (3 \(\times\) 2 mL). The combined extracts were washed with brine (1 \(\times\) 2 mL), dried with anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated. \textsuperscript{1}H NMR analysis of the crude reaction mixture showed mainly starting allylboronate \textit{E}-4 (ca. 66 %) along with other unidentified side products. No \textit{Z}-4 isomer was observed.
Treatment of lactone 13 with TfOH

Diastereomerically pure lactone 13 (34 mg, 0.095 mmol) was dissolved in toluene (0.1 mL), cooled to 0 °C, treated with TfOH (1.7 µL, 0.019 mmol) and stirred at 0 °C under Ar atmosphere for 16 h. The mixture was then diluted with NH₄Cl(aq)/NH₄OH (9:1 v/v, 2 mL) and extracted with Et₂O (3 × 2 mL). The combined extracts were washed with brine (1 × 2 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. ¹H NMR analysis of the crude reaction mixture showed mainly starting lactone 13 (ca. 80 %) along with ca. 20 % of lactone 7.

Preparation of ethyl (2Z)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]but-2-enoate (Z-4)⁹

To a stirring solution of HMPA (1.56 mL, 8.97 mmol) in toluene (9 mL) under Ar atmosphere at 0 °C, DIBALH (1.0 M in toluene, 4.48 mL, 4.48 mmol) was added dropwise. After stirring at 0 °C for 1 h, freshly distilled ethyl 2-butynoate (0.35 mL, 3.0 mmol) was added and stirring continued at 0 °C for another 5 h. Freshly distilled chloromethaneboronate¹⁰ (632 mg, 3.58 mmol) in toluene (2 mL) was added via cannulation with toluene rinse (3 × 1 mL) and the resulting mixture was allowed to warm up to rt and stirred under Ar atmosphere for 16 h. The reaction was then quenched with 1 M HCl (16 mL) and extracted with Et₂O (4 × 20 mL). The combined organic phase was washed with 1 M HCl (3 × 16 mL), NaHCO₃(aq) (1 × 16 mL), water (1 × 16 mL), brine (1 × 16 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. Flash chromatography (25 % Et₂O/hexane) gave the product Z-4 along with ca. 20 % of the E-isomer (224 mg, 0.882 mmol, 30 % combined yield).

¹H NMR (300 MHz, CDCl₃): δ 6.04 (qt, 1H, J = 7.2, 1.3 Hz), 4.20 (q, 2H, J = 7.1 Hz), 2.00 (dt, 3H, J = 7.2, 1.3 Hz), 1.84 (s, 2H), 1.30 (t, 3H, J = 7.1 Hz), 1.24 (s, 12H); ¹³C NMR (125 MHz, CDCl₃): δ 168.0, 136.8, 129.1, 83.2, 60.0, 24.7, 15.8, 14.2; IR (microscope, cm⁻¹): 2980, 1717, 1353, 1323, 1146, 968, 847; HRMS (EI, m/z) Calcd for C₁₃H₂₃¹¹BO₄: 254.16985. Found: 254.16918.
Preparation of rac-(4R*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-4-methyl-3-methylene-dihydro-furan-2-one (7) by TfOH-catalyzed allylboration with Z-4

A slurry of Z-4 (Z/E = 80:20, 60.4 mg, 0.238 mmol) and 2-bromo-3,4,5-trimethoxybenzaldehyde 63 (131 mg, 0.476 mmol) in toluene (0.24 mL) at 0 °C was treated with TfOH (4.2 µL, 0.048 mmol) and stirred at 0 °C under Ar atmosphere for 16 h. The mixture was then diluted with NH₄Cl(aq)/NH₄OH (9:1 v/v, 4 mL) and extracted with Et₂O (3 × 4 mL). The combined extracts were washed with brine (2 × 2 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. Flash chromatography (25 % EtOAc/hexane) gave the diastereomerically pure lactone product 7 (85 mg, 0.238 mmol, 100 %). This material possessed identical spectroscopic characteristics to those reported above for 7.
9. Copies of $^1$H and $^{13}$C NMR spectra

(4R*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-4-methyl-3-methylene-dihydro-furan-2-one (7)

$^1$H (500 MHz) and $^{13}$C (100 MHz) NMR in CDCl$_3$
(4S*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-4-methyl-3-methylene-dihydro-furan-2-one (13)

$^1$H (300 MHz) and $^{13}$C (100 MHz) NMR in CDCl$_3$
(3S*, 4S*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyl-dihydro-furan-2-one (8)

$^1$H (300 MHz) and $^{13}$C (125 MHz) NMR in CDCl$_3$
(3R*, 4S*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyl-dihydro-furan-2-one (10)

$^1$H (300 MHz) and $^{13}$C (125 MHz) NMR in CDCl$_3$
(3S*, 4R*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyl-dihydro-furan-2-one (I4) 

$^1$H (300 MHz) and $^{13}$C (125 MHz) NMR in CDCl$_3$
3,4-epi-1
\(^1\)H (500 MHz) and \(^{13}\)C (125 MHz) NMR in CDCl\(_3\)

![NMR Spectra](image-url)
4-epi-1
^1H (400 MHz) and ^13C (125 MHz) NMR in CDCl₃
3-epi-1
$^1$H (300 MHz) and $^{13}$C (125 MHz) NMR in CDCl$_3$. 
Eupomatilone-6 (1)
$^1$H (500 MHz) NMR in CDCl$_3$
Ethyl (2Z)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl] but-2-enoate (Z-4)

$^1$H (300 MHz) and $^{13}$C (125 MHz) NMR in CDCl$_3$
10. Summary table of $^1$H NMR correspondences for the lactone moiety$^{6,7,11,12}$

<table>
<thead>
<tr>
<th></th>
<th>Original 1 (Taylor$^1$)</th>
<th>4-epi-1 (McIntosh$^1$)</th>
<th>3-epi-1 (Gurjar$^{12}$)</th>
<th>3-epi-1 (Coleman$^1$)</th>
<th>Revised 1 (Coleman$^1$)</th>
<th>3,4-epi-1 (this work)</th>
<th>4-epi-1 (this work)</th>
<th>3-epi-1 (this work)</th>
<th>I (this work)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-3</td>
<td>δ 2.36, 2.37, m, $J = 7.0, 5.2$</td>
<td>δ 2.75, m</td>
<td>δ 2.74, m</td>
<td>δ 2.74, app sextet, $J = 7.0$</td>
<td>δ 2.37, sextet, $J = 7.2$</td>
<td>δ 2.14, m</td>
<td>δ 2.75, m</td>
<td>δ 2.75, m</td>
<td>δ 2.36, m</td>
</tr>
<tr>
<td>H-4</td>
<td>δ 2.02, 1.97, m, $J = 7.0, 7.0, 5.2$</td>
<td>δ 2.36, m</td>
<td>δ 2.20, m</td>
<td>δ 2.20-2.10, m</td>
<td>δ 2.05-1.96, m</td>
<td>δ 2.03, m</td>
<td>δ 2.39, m</td>
<td>δ 2.20, m</td>
<td>δ 2.05-1.96, m</td>
</tr>
<tr>
<td>H-5</td>
<td>δ 5.54, 5.65, d, $J = 7.0$</td>
<td>δ 5.60, d, $J = 4.35$</td>
<td>δ 5.32, 5.41, d, $J = 5.0$</td>
<td>δ 5.32, 5.40, d, $J = 4.9$</td>
<td>δ 5.54, 5.65, d, $J = 6.9$</td>
<td>δ 4.78, 4.80, d, $J = 9.8$</td>
<td>δ 5.01, d, $J = 4.5$</td>
<td>δ 5.11, d, $J = 4.5$</td>
<td>δ 5.32, 5.41, d, $J = 4.9$</td>
</tr>
<tr>
<td>3-Me</td>
<td>δ 1.20, 1.19, d, $J = 7.0$</td>
<td>δ 1.06, d, $J = 7.51$</td>
<td>δ 1.13, d, $J = 7.2$</td>
<td>δ 1.12, d, $J = 7.3$</td>
<td>δ 1.19, 1.20, d, $J = 7.4$</td>
<td>δ 1.23, d, $J = 6.9$</td>
<td>δ 1.07, d, $J = 7.3$</td>
<td>δ 1.08, d, $J = 7.3$</td>
<td>δ 1.12, d, $J = 7.2$</td>
</tr>
<tr>
<td>4-Me</td>
<td>δ 0.70, 0.73, d, $J = 7.0$</td>
<td>δ 0.65, d, $J = 6.92$</td>
<td>δ 0.54, 0.56, d, $J = 7.2$</td>
<td>δ 0.54, 0.56, d, $J = 7.3$</td>
<td>δ 0.70, 0.72, d, $J = 7.1$</td>
<td>δ 0.86, 0.87, d, $J = 6.4$</td>
<td>δ 0.66, d, $J = 7.1$</td>
<td>δ 0.69, d, $J = 7.1$</td>
<td>δ 0.56, app triplet, $J = 7.2$</td>
</tr>
</tbody>
</table>
11. ORTEP reproductions for 8, 10, 14, 3,4-epi-1, 4-epi-1

rac-(3S*, 4S*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyl-dihydrofuran-2-one (8)
rac-(3R*, 4S*, 5S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyl-dihydrofuran-2-one (10)
rac-(3*S*, 4*R*, 5*S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyl-dihydrofuran-2-one (14)
3,4-epi-1
4-epi-1
12. References