Stereoselection in the Prins-Pinacol Synthesis of 2,2-Disubstituted 4-Acyltetrahydrofurans. Enantioselective Synthesis of (–)-Citreoviral

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Supporting Information

I. Preparation of (–)-Citreoviral.

(2*S*,3*R*)- and (2*S*,3*S*)-5-(Dimethylphenylsilyl)-3,4-dimethyl-(*E*)-pent-4-ene-2,3-diol (18). Following a general procedure,[1] freshly activated zinc[2] (5.2 g, 80 mmol) was added to a stirring suspension of $TaCl_5$ (18.7 g, 52 mmol) and dry DME–benzene (1:1, 200 mL). The resulting dark green-black solution was stirred vigorously for 40 min, before adding a solution of 1-(dimethylphenylsilyl)propyne[3] (4.52 g, 260 mmol) and dry DME–benzene (1:1, 10 mL). After 3 h of vigorous stirring, THF (160 mL) was added and the solution was stirred for a further 40 min.[4] At this point, a solution of (*S*)-3-(*tert*-butyldiphenylsiloxy)-2-butanone (**16**)[5] (8.46 g, 260 mmol) and dry benzene (5 mL) was added over 5 min. The resulting mixture was stirred for 1 h before 15% aqueous NaOH (70 mL) was added. After 2 h of vigorous stirring, the heterogeneous mixture was passed through Celite with EtOAc (300 mL). The filtrate was dried (Na_2SO_4) and concentrated to yield **17** as a crude oil.

This oil was taken up in THF (50 mL) and TBAF (1.0 M in THF, 52 mL, 52 mmol) was added. The resulting solution was maintained at rt for 8 h before being added to a saturated aqueous solution of NH_4Cl (100 mL). The organic layer was separated, the aqueous layer was

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[1] Kataoka, Y. Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57,* 1973–1981.
[2] Shriner, R. L.; Neumann, F. W. *Org. Synth., Coll. Vol. 3* **1955**, 73–75.
[3] Meinke, P. T.; Krafft, G. A.; Guram, A. *J. Org. Chem.* **1988**, *53*, 3632–3634.
[4] Introduction of THF at this point was essential to supress diene formation.
[5] Overman, L. E.; Rishton, G. M. *Org. Synth., Coll. Vol. 9* **1998**, 139–142.

extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1:9 → 3:7 EtOAc–hexanes) to afford 5.60 g (82%) of diols **18** as a 6:1 mixture of diastereomers (^{1}H NMR analysis). Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$, C–H signals only) δ 7.53–7.51 (m, 2H), 7.35–7.34 (m, 3H), 5.79 (s, 1H), 3.85–3.75 (m, 1H), 1.39 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.38 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 139.5, 134.8, 133.6, 127.7, 119.6, 78.5, 71.4, 25.0, 18.9, 17.5, –1.1, –1.2; IR (film) 3419, 3067, 2978, 1611, 1371, 1112 cm^{-1}; MS (CI) *m/z* 247.1492 (MH–H_2O, 247.1518 calcd for $C_{15}H_{23}OSi$), 219, 171. Anal. Calcd for $C_{15}H_{24}O_2Si$: C, 68.13; H, 9.15. Found: C, 67.88; H, 9.09.

(2*S*,3*R*)- and (2*S*,3*S*)-{[2,3-Dimethyl-3,4-bis(trimethylsiloxy)-(*E*)-pent-1-enyl]-dimethylsilanyl}benzene (19). A solution of diol **18** (300 mg, 1.14 mmol), CH_2Cl_2 (8 mL) and imidazole (670 mg, 10.2 mmol) was cooled to 0 °C and chlorotrimethylsilane (1.1 mL, 8 mmol) was added. After 10 min, the solution was poured into H_2O (10 mL) and the organic layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated keeping the temperature below 20 °C. The resulting crude oil was purified by flash chromatography (1:19 EtOAc–hexanes) to afford 464 mg (99%) of bis(trimethylsilyl) ether **19** as a clear colorless oil that was homogeneous by TLC analysis: Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.35 (m, 3H), 5.71 (s, 1H,), 3.85–3.75 (m, 1H), 1.71 (s, 3H), 1.31 (s, 3H), 1.04 (d, *J* = 6.1 Hz, 3H), 0.37 (s, 3H), 0.36 (s, 3H), 0.11 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 140.1, 133.8, 128.6, 127.7, 120.3, 81.8, 73.4, 22.1, 19.3, 17.9, 2.4, 0.3, –0.9, –1.1; IR (film) 3050, 2956, 1367, 1114, 1072 cm^{-1}; MS (CI) *m/z* 409 (MH), 319. Anal. Calcd for $C_{21}H_{40}O_2Si$: C, 61.70; H, 9.86. Found: C, 61.94; H, 9.95.

***tert*-Butyl-(2,2-dimethoxypropoxy)diphenylsilane (20).** *p*-Toluenesulfonic acid (0.3 g, 1.6 mmol) was added to a stirred solution of 1-(*tert*-butyldiphenylsiloxy)acetone[5] (5.00 g, 17.6 mmol), trimethyl orthoformate (5.6 g, 53 mmol) and 50 mL of methanol. The solution was maintained at rt for 18 h and then added to a 1:3 mixture of $NaHCO_3$–EtOAc (400 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (3 × 200 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was pruified by flash chromatography (1:19 EtOAc–hexane) to afford 3.8 g (66%) of ketal **20** as a clear colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.60 (m, 4H), 7.40–7.36 (m, 6H), 3.57 (s, 2H), 3.17 (s, 6H), 1.39 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 133.4, 129.6, 127.6, 101.0, 64.7, 48.2, 26.8, 19.9, 19.3; IR (film) 3049.4,

1427.9, 1114.1, 1069.4 cm^{-1}; MS (LSIMS) *m/z* 381.1856 (M+Na, 381.1862 calcd for $C_{21}H_{30}O_3SiNa$), 357, 343, 327. Anal. Calcd for $C_{21}H_{30}O_3Si$: C, 70.35; H, 8.43. Found: C, 70.44; H, 8.41.

(2*S*,3*S*,4*S*,5*R*)-1-[5-((*tert*-butyldiphenylsiloxy)methyl)-4-(dimethylphenylsilyl)-2,3,5-trimethyltetrahydrofuran-3-yl]ethanone (22) and Acetals 21. Trimethylsilyl triflate (0.45 mL, 2.5 mmol) was added to a stirring solution of **19** (4.54 g, 11.0 mmol), dimethoxyketal **20** (3.94 g, 11.0 mmol) and 50 mL of CH_2Cl_2 at –30 °C. The reaction was maintained at this temperature for 15 min and then poured into a saturated aqueous solution of NH_4Cl (60 mL). The aqueous layer was extracted with additional CH_2Cl_2 (3 × 75 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash chromatography (1:49 → 1:19 EtOAc–hexanes) to afford 2.86 g (47%) of tetrahydrofuran **22**, a colorless foam, and two fractions, totaling 2.49 g (41%), of a mixture of stereoisomeric cyclic ketals **21** (pale yellow oils).

22: ^{1}H NMR (500 MHz, $CDCl_3$) $[\alpha]_D^{21}$ +20.6, $[\alpha]_{577}^{21}$ +21.4, $[\alpha]_{546}^{21}$ +25.1, $[\alpha]_{435}^{21}$ +52.5, $[\alpha]_{405}^{21}$ +72.2 (*c* 3.0, $CHCl_3$); δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.41–7.21 (m, 9H), 3.88 (q, *J* = 6.4 Hz, 1H), 3.35 (d, *J* = 10.8 Hz, 1H), 3.14 (d, *J* = 10.9 Hz, 1H), 2.74 (s, 1H), 2.08 (s, 3H), 1.42 (s, 3H), 1.28 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.03 (s, 9H), 0.43 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 138.0, 136.0, 135.6, 133.9, 129.4, 129.1, 127.9, 127.5, 127.4, 87.0, 82.0, 69.7, 62.0, 38.3, 28.6, 26.7, 25.4, 23.5, 22.5, 19.2, 16.4, –0.7, –0.9; MS (CI) *m/z* 559 (MH), 257, 153, 115. Anal. Calcd for $C_{34}H_{46}O_3Si_2$: C, 73.06; H, 8.29. Found: C, 72.93; H, 8.36.

Mixture of ketals **21**: IR (neat) 3069, 3048, 2956, 1607, 1371, 1188, 1112 cm^{-1}. Anal. Calcd for $C_{34}H_{46}O_3Si_2$: C, 73.06; H, 8.29. Found: C, 73.35; H, 8.33.

Rearrangement of 21 to 22 with $SnCl_4$. Stannic chloride (0.23 mL, 2.0 mmol) was added dropwise to a stirring solution of cyclic ketals **21** (900 mg, 1.6 mmol) and CH_2Cl_2 (52 mL) at –78 °C. The resulting solution was maintained at this temperature for 48 h and then extracted with CH_2Cl_2 (3 × 70 mL). The extracts were washed with saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1:19 EtOAc–hexanes) to afford 796 mg (89%) of tetrahydrofuran **22** as a colorless foam.

(2*S*,3*S*,4*S*,5*R*)-1-(4-Dimethylphenylsilyl-5-hydroxymethyl-2,3,5-trimethyltetrahydrofuran-3-yl)ethanone (23). Aqueous 48% HF (0.11 mL, 2.8 mmol) was added to a stirring solution of tetrahydrofuran **22** (227 mg, 0.41 mmol) and dry CH_3CN (3.7 mL). The resulting

solution was maintained at room temperature for 18 h, at which time $MgSO_4$ (300 mg) and $NaHCO_3$ (270 mg) were added. The resulting suspension was stirred vigorously for 10 min and then filtered through a fine fritted funnel. The filter cake was washed with EtOAc (3 × 10 mL) and the combined filtrates were concentrated. Purification of the residue by flash chromatography (2:1 hexanes–EtOAc) afforded 109 mg (84%) of alcohol **23** as a clear colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.50 (m, 2H), 7.37–7.34 (m, 3H), 3.84 (q, *J* = 6.5 Hz, 1H), 3.09 (ddd, *J* = 4.6, 8.2, 11.6 Hz, 2H), 2.72 (s, 1H), 2.11 (dd, *J* = 4.6, 8.2 Hz, 1H), 2.03 (s, 3H), 1.42 (s, 3H), 1.26 (s, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.46 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 137.8, 133.8, 129.3, 127.9, 86.6, 81.8, 68.6, 61.7, 39.3, 28.3, 23.3, 22.0, 15.8, –0.93, –1.04; IR (film) 3462, 3070, 2971, 1698, 1461, 1428, 1192, 1114 cm^{-1}; MS (LSIMS) *m/z* 321.1875 (MH, 321.1886 calcd for $C_{18}H_{29}O_3Si$), 303, 289, 259, 135, 125, 109. Anal. Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.19; H, 8.80.

(1*R*,2*R*,5*S*,7*S*,8*S*)-(2-Methoxy-1,2,5,7-tetramethyl-3,6-dioxabicyclo[3.2.1]oct-8-yl)-dimethylphenylsilane (24). A solution of alcohol **23** (706 mg, 2.20 mmol), *p*-toluenesulfonic acid (43 mg, 0.23 mmol), dry methanol (75 mL) and freshly distilled trimethyl orthoformate (5.3 mL, 48 mmol) was maintained at room temperature for 45 min and then poured into a saturated aqueous solution of $NaHCO_3$ (53 mL) and diluted with ethyl acetate (160 mL). The aqueous layer was clarified by adding H_2O (~10 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the filtrate was concentrated to afford 679 mg (92%) of crude bicyclic ketal **24**. This crude productwas carried on without purification.

A pure sample of **24** (73%) was obtained by flash chromatography (7:1 hexanes–EtOAc with 1% Et_3N) as a pale yellow oil: $[\alpha]_D^{24}$ –63.2, $[\alpha]_{577}^{24}$ –65.4, $[\alpha]_{546}^{24}$ –73.9, $[\alpha]_{435}^{24}$ –117, $[\alpha]_{405}^{24}$ –138 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.55 (m, 2H), 7.34–7.32 (m, 3H), 3.88 (q, *J* = 6.8 Hz, 1H), 3.44 (d, *J* = 10.3 Hz, 1H), 3.25 (s, 3H), 3.19 (d, *J* = 10.7 Hz, 1H), 2.83 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.29 (s, 3H), 1.05 (s, 3H), 0.85 (s, 3H), 0.45 (s, 3H), 0.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 133.4, 128.5, 127.8, 101.1, 82.5, 80.8, 75.3, 53.9, 46.9, 38.6, 22.0, 19.7, 18.8, 16.8, 0.39, 0.36; IR (film) 2965, 1458, 1379 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04. Found: C, 68.16; H, 9.07.

(1*R*,2*R*,5*S*,7*S*,8*S*)-2-Methoxy-1,2,5,7-tetramethyl-3,6-dioxabicyclo[3.2.1]octan-8-ol (25). Anhydrous NH_3 (140 mL) was condensed into a solution of crude ketal **24** (300 mg, 0.90

mmol) and 1:1 THF–absolute ethanol (90 mL) at –78 °C. Freshly cleaned pieces of Li wire (280 mg, 40 mmol) were added to generate a dark blue solution. The reaction was maintained at –78 °C for 10 min, the bath was removed and the ammonia was allowed to evaporate. Water (90 mL) was added and the aqueous phase was extracted with EtOAc (90 mL). The aqueous washings were extracted with additional EtOAc (3 × 80 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated to afford the crude cyclohexadienylsilane as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76–5.70 (m, 2H), 5.62–5.58 (m, 2H), 3.91 (q, *J* = 6.8 Hz, 1H), 3.44 (d, *J* = 10.3 Hz, 1H), 3.23 (s, 3H), 3.23 (d, *J* = 13.5 Hz, 1H), 2.73–2.67 (m, 2H), 2.56 (s, 1H), 2.54 (m, 1H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.33 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H).

This intemediate was dissolved in THF (9.20 mL) and a 1.0 M THF solution of TBAF (1.9 mL, 1.9 mmol) was added at rt. The resulting solution was maintained at rt for 1.2 h and dry methanol (5 mL), $KHCO_3$ (140 mg, 1.4 mmol) and 30% aqueous H_2O_2 (0.9 mL, 9 mmol) were then added. The resulting suspension was stirred vigorously for 11 h, H_2O (45 mL) was added and the resulting mixture was extracted with EtOAc (45 mL) and brine (15 mL). The aqueous washings were extracted with additional EtOAc (3 × 45 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (3:2 hexanes–EtOAc with 1% Et_3N) afforded 120 mg (62%) of **25** as colorless crystals: mp 95–98 °C; $[\alpha]_D^{24}$ –118, $[\alpha]_{577}^{24}$ –123, $[\alpha]_{546}^{24}$ –139, $[\alpha]_{435}^{24}$ –230, $[\alpha]_{405}^{24}$ –272 (*c* 3.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (d, *J* = 6.7 Hz, 1H), 3.98 (q, *J* = 6.8 Hz, 1H), 3.45 (d, *J* = 11.1 Hz, 1H), 3.40 (d, *J* = 11.1 Hz, 1H), 3.18 (s, 3H), 2.24 (br s, 1H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.36 (s, 3H), 1.18 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 103.8, 80.4, 80.1, 76.7, 70.9, 53.6, 46.6, 19.4, 16.1, 15.2, 11.6; IR (film) 3424, 1463, 1378, 1048 cm^{-1}; MS (LSIMS) *m*/*z* 215.1288 (M–H, 215.1283, calcd for $C_{11}H_{19}O_4$), 185, 141, 123, 111. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.80; H, 9.31.

Benzoic Acid (1*R*,2*R*,5*S*,7*S*,8*S*)-2-Methoxy-1,2,5,7-tetramethyl-3,6-dioxabicyclo-[3.2.1]oct-8-yl Ester (26). A solution of alcohol **25** (186 mg, 0.86 mmol), benzoic anhydride (1.2 g, 5.2 mmol), DMAP (26 mg, 0.22 mmol) and pyridine (0.4 mL, 5 mmol) was maintained at room temperature for 24 h, during which time a colorless precipitate formed. The reaction was diluted with CH_2Cl_2 (30 mL) and the resulting solution washed with a saturated aqueous $NaHCO_3$ (30 mL) and the aqueous extracts were washed with additional CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the resudue was purified

by flash chromatography (5:1 hexanes–EtOAc with 1% Et_3N) to afford 204 mg (74%) of **26** as a colorless crystalline solid: mp 86–88 °C; $[\alpha]_D^{24}$ –137, $[\alpha]_{577}^{24}$ –140, $[\alpha]_{546}^{24}$ –158, $[\alpha]_{435}^{24}$ –274, $[\alpha]_{405}^{24}$ –329 (*c* 1.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.00 (s, 1H), 4.23 (q, *J* = 6.8 Hz, 1H), 3.62 (d, *J* = 11.1 Hz, 1H), 3.46 (d, *J* = 11.1 Hz, 1H), 3.25 (s, 3H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.41 (s, 3H), 1.13 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 133.0, 129.6, 129.6, 128.3, 103.7, 80.8, 80.0, 79.7, 70.9, 53.5, 46.7, 19.3, 16.0, 15.7, 12.0; IR (film) 2971, 1723, 1451, 1274, 710 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.75; H, 7.55. Found: C, 67.49; H, 7.56.

Benzoic Acid (2*R*, 3*R*,4*R*,5*S*)-4-Hydroxy-2-hydroxymethyl-2,4,5-trimethyltetrahydrofuran-3-yl Ester (27) and Acetate Derivative 28. Trifluoroacetic anhydride (0.52 mL, 3.7 mmol) was added dropwise to a stirring suspension of H_2O_2–urea (1.4 g, 15 mmol) and CH_2Cl_2 (2 mL) at 0° C.[6] The resulting mixture was stirred vigorously for 30 min, a solution of **26** (93 mg, 0.29 mmol) and CH_2Cl_2 (1.2 mL) was added, and the reaction was allowed to warm to rt. After 12 h, the pH was brought to 8.5 by careful addition of a saturated aqueous $NaHCO_3$ (~3.0 mL). The mixture was stirred for an additional 5 min, diluted with CH_2Cl_2 (20 mL), and extracted with saturated aqueous $NaHCO_3$ (15 mL). The aqueous washings were extracted with additional CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash chromatography (2:1 hexanes–EtOAc) to afford 58.5 mg (72%) of diol **27** as a colorless oil (homogeneous by TLC analysis) and 18.9 mg (20%) of acetate **28** as a colorless oil.

27: $[\alpha]_D^{24}$ –76.7, $[\alpha]_{577}^{24}$ –80.3, $[\alpha]_{546}^{24}$ –91.2, $[\alpha]_{435}^{24}$ –158, $[\alpha]_{405}^{24}$ –191 (*c* 4.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06–8.04 (m, 2H), 7.63–7.59 (m, 1H), 7.50–7.46 (m, 2H), 5.34 (s, 1H), 3.95 (q, *J* = 6.2 Hz, 1H), 3.82 (d, *J* = 11.2 Hz, 1H), 3.71 (d, *J* = 11.2 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.23 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 133.5, 129.6, 129.4, 128.6, 83.3, 79.6, 79.5, 67.5, 17.6, 17.5, 11.9; IR (film) 3356, 2979, 1722, 1272, 1112, 712 cm^{-1}; MS (CI) *m/z* 281.1383 (MH, 281.1389 calcd for $C_{15}H_{21}O_5$), 263, 249, 231. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27 ; H, 7.19. Found: C, 64.29 ; H, 7.26.

28: ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–8.03 (m, 2H), 7.64–7.59 (m, 1H), 7.50–7.45 (m, 2H), 5.25 (s, 1H), 4.28 (d, *J* = 11.5 Hz, 1H), 4.18 (d, *J* = 11.5 Hz, 1H), 3.93 (q, *J* = 6.2 Hz, 1H), 2.15 (s, 3H), 1.25 (app d, *J* = 6.6 Hz, 3H), 1.24 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz,

[6] Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533–535.

$CDCl_3$) δ 170.2, 165.5, 133.6, 129.6, 129.2, 128.6, 82.8, 81.8, 80.0, 79.1, 68.9, 20.9, 17.8, 17.7, 11.9; IR (film) 3512, 2984, 1724, 1379, 1112, 713 cm^{-1}.

Benzoic Acid (1*S*,3*S*,4*R*,7*S*)-1,3,4-Trimethyl-6-oxo-2,5-dioxabicyclo[2.2.1]hept-7-yl Ester (29). Tetrapropylammonium perruthenate (TPAP, 2.1 mg, 0.006 mmol) was added to a CH_2Cl_2 (1 mL) suspension of diol **27** (12 mg, 0.043 mmol), powdered activated 4 Å molecular sieves (19 mg) and *N*-methylmorpholine-*N*-oxide (10 mg, 0.089 mmol) at 0 °C.[7] The resulting dark suspension was stirred at 0 °C for 10 min and then allowed to warm to rt over 50 min. The reaction mixture was diluted with CH_2Cl_2 (5 mL), filtered through a 0.5 inch plug of silica gel, and the pad of silica gel was washed with additional CH_2Cl_2 (5 × 5 mL) and EtOAc (2 × 5 mL). The combined filtrates were concentrated to afford 9.6 mg (81%) of lactone **29** as a colorless oil that was homogeneous by TLC analysis: $[\alpha]_D^{24}$ –32.5, $[\alpha]_{577}^{24}$ –34.2, $[\alpha]_{546}^{24}$ –39.4, $[\alpha]_{435}^{24}$ –72.2, $[\alpha]_{405}^{24}$ –90.2 (*c* 4.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08–8.05 (m, 2H), 7.66–7.63 (m, 1H), 7.52–7.48 (m, 2H), 5.12 (s, 1H), 4.44 (q, *J* = 6.5 Hz, 1H), 1.52 (s, 3H), 1.46 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 165.0, 134.1, 129.9, 128.7, 128.3, 88.4, 82.1, 79.5, 77.4, 12.3, 11.0; IR (film) 2986, 2937, 1805, 1733, 1601, 1452, 1389, 1322, 1265, 1178, 1114, 1086, 1011, 914, 849, 710 cm^{-1}; MS (LSIMS) *m/z* 277.1079 (MH, 277.1076 calcd for $C_{15}H_{17}O_5$), 232, 189. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.20; H, 5.84. Found: C, 65.31 H, 5.89.

Benzoic Acid (1*S*,4*S*,6*S*,7*S*)-3-Hydroxy-1,4,6-trimethyl-2,5-dioxabicyclo[2.2.1]hept-7-yl Ester (**30**). A 1.0 M solution of DIBALH in hexanes (27 μL, 0.027 mmol) was added over 20 min to a solution of lactone **29** (7.0 mg, 0.027 mmol) and CH_2Cl_2 (0.27 mL) at –78°C. After 1 h at –78°C, the reaction was quenched by adding methanolic 1 M HCl (1 mL) and allowed to warm to rt. After diluting with CH_2Cl_2 (15 mL), the solution was extracted with 10% aqueous HCl (15mL) and the aqueous washings were extracted with additional CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), dried (Na_2SO_4), concentrated. The residue was purified by flash chromatography (2:1 hexanes–EtOAc) to afford 4.8 mg (69%) of **30** as a colorless oil that was homogeneous by TLC analysis: ^1H NMR (400 MHz, $CDCl_3$, major isomer) δ 8.10–8.05 (m, 2H), 7.65–7.59 (m, 1H), 7.53–7.46 (m, 2H), 5.21 (s, 1H), 4.36 (q, *J* = 6.4 Hz, 1H), 3.93 (bs, 1H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 203.2, 165.5, 133.7, 133.54, 129.8, 129.7, 128.6, 128.5, 99.8, 99.3, 84.4, 84.0, 83.5, 80.8, 79.9, 79.3, 78.7, 78.5, 29.7, 18.5, 17.0,

[7] Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13–19.

13.2, 13.2, 13.0, 12.5, 12.2, 12.0, 10.9; IR (film) 3404, 2978, 1729, 1271, 1115, 712 cm^{-1}; MS (CI) *m/z* 279.1226 (MH, 279.1232 calcd for $C_{15}H_{19}O_5$), 261, 249. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.47; H, 6.64.

Benzoic Acid (2*R* , 3*S*,4*R*,5*S*)-2-(2*E*-Ethoxycarbonylpropenyl)-4-hydroxy-2,4,5-trimethyltetrahydrofuran-3-yl Ester (31). A solution of lactol **30** (5.1 mg, 0.018 mmol), (carboethoxyethylidene)triphenylphosphorane (17 mg, 0.041 mmol) and dry benzene (0.19 mL) was heated at reflux for 18 h. Following dilution with diethyl ether (10 mL), the reaction mixture was extracted with saturated aqueous $NaHCO_3$ (10 mL) and brine (5 mL). The combined aqueous extracts were washed with diethyl ether (3 × 15 mL), and the combined oganic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (2:1 hexanes–EtOAc) to provide 3.4 mg (51%) of the *E* isomer **31**, 0.6 mg (9%) of the corresponding *Z* isomer, and 0.5 mg (7.5%) of mixed fractions.

31: $[\alpha]_D^{24}$ +21.6, $[\alpha]_{577}^{24}$ +22.3, $[\alpha]_{546}^{24}$ +26.6, $[\alpha]_{435}^{24}$ +54.7, $[\alpha]_{405}^{24}$ +70.0 (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08–8.06 (m, 2H), 7.64–7.60 (m, 1H), 7.51–7.47 (m, 2H), 7.01–7.00 (m, 1H), 5.44 (s, 1H), 4.25–4.14 (m, 2H), 4.03 (q, *J* = 6.3 Hz, 1H), 2.03 (d, *J* = 1.4 Hz, 3H), 1.38 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 165.3, 145.1, 133.6, 129.7, 129.2, 128.7, 128.5, 85.6, 83.3, 80.1, 79.3, 76.7, 60.90, 29.7, 20.9, 18.2, 14.2, 13.4, 12.4; IR (film) 3486, 2917, 1723, 1714, 1267, 1107, 711 cm^{-1}; MS (CI) *m/z* 363.1816 (MH, 363.1807 calcd for $C_{20}H_{27}O_6$), 317, 274.

Z-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.05–8.03 (m, 2H), 7.62–7.58 (m, 1H), 7.49–7.45 (m, 2H), 5.63 (m, 1H), 5.23 (s, 1H), 4.28–4.16 (m, 2H), 3.95 (q, *J* = 6.4 Hz, 1H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.220 (d, *J* = 6.3 Hz, 3H), 1.218 (s, 3H), 1.20 (s, 3H); IR (film) 3432.4, 3063.1, 2981.0, 1721.9, 1372.7, 1243.9, 1110.3, 713.1 cm^{-1}; MS (CI) *m/z* 363.1810 (MH, 363.1807 calcd for $C_{20}H_{27}O_6$), 317, 275.

(2*R*,3*S*,4*R*,5*S*)-2-(3-Hydroxy-2-methyl-propenyl)-2,4,5-trimethyltetrahydrofuran-3,4-diol (32). A solution of DIBALH (1.0 M in hexane, 0.13 mL, 0.13 mmol) was added dropwise to a solution of **31** (9.2 mg, 0.025 mmol), toluene (0.25 mL) and THF (1 mL) at 0 °C. The resulting solution was maintained at 0 °C for 1 h and then allowed to warm to rt. After 1.5 h, a saturated aqueous solution of Rochelle's salt (4 mL) was added and the mixture was stirred vigorously for 1 h. The resulting solution was extracted with EtOAc (3 × 10 mL) and the combined extracts were washed with brine (4 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1:1 hexanes–EtOAc → EtOAc) to afford 5.1 mg

(93%) of triol **32** as a colorless oil that was homogenous by TLC analysis. This sample, $[\alpha]_D^{24}$ +11.9, $[\alpha]_{577}^{24}$ +15.2, $+[\alpha]_{546}^{24}$ +16.6, $[\alpha]_{435}^{24}$ +29.3, $[\alpha]_{405}^{24}$ +35.7 (*c* 0.55, $CHCl_3$) showed ^1H and ^{13}C NMR spectra indistinguishable from those of an authentic specimen.

(–)-Citreoviral (2). A mixture of **32** (13.3 mg, 0.0627 mmol), 90% $BaMnO_4$ and benzene (1 mL) was heated at reflux for 3h at which time **32** was not visible by TLC analysis. After cooling to rt, the reaction was filtered through Celite and the Celite plug was washed with EtOAc (3 × 3 mL) and CH_2Cl_2 (3 × 3 mL). Concentration and purification of the residue by flash chromatography (2:1 hexanes–EtOAc) gave 6.6 mg (50%) of (–)-citreoviral (**2**): $[\alpha]_D^{24}$ –21.0 (c 0.6, $CHCl_3$).

II. Stereoselection in Prins-Pinacol Reactions of Unsymmetrical Ketones.

Preparation of Allylic Acetals.

Ketals **12** were prepared from 3,4-dimethyl-4-penten-2,3-diol (a 7:1 mixture of *anti* and *syn* isomers)[8] using one of three procedures and were purified by chromatography on silica gel (hexane-EtOAc).

Method A: 3,4-Dimethyl-4-penten-2,3-diol (5.0 mmol), ketone (50 mmol), *p*-toluenesulfonic acid (0.5 mmol, 0.1 g), $MgSO_4$ (5 g) and CH_2Cl_2 (10 mL) were allowed to react at rt.

Method B:[9] To a solution of TMSOTf (0.4 mmol, 0.77 mL) and CH_2Cl_2 (2 mL) was added the bis(trimethylsilyl) ether of 3,4-dimethyl-4-penten-2,3-diol (4 mmol, prepared from the diol, TMSCl and imidazole in DMF) and the ketone (4 mmol) at –78°C. The reaction solution was allowed to slowly warm to rt where it was quenched with pyridine (0.4 mL).

Method C: Bromine (5.0 mmol, 0.26 mL) was added to a solution of 2-methoxypropene (5.0 mmol, 0.48 mL) and CH_2Cl_2 (5 mL) at –78 to –70 °C. After 10 min, a solution of 3,4-dimethyl-4-penten-2,3-diol (5 mmol, 0.65 g) and CH_2Cl_2 (1 mL) was added and the reaction was allowed to warm –50°C where it was quenched with saturated aqueous $NaHCO_3$ (5 mL).

2-Ethyl-2,4,5-trimethyl-4-(1-methylethenyl)-1,3-dioxolane (12a). Prepared by method A: a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.20-1.38 (m, 2H), 1.38 (s, 3H), 1.45 (s, 3H), 1.75 (s, 3H), 4.12 (q, *J* = 6.3 Hz, 1H), 4.93 (d, *J* = 1.2 Hz, 1H), 4.95 (s, 1H); IR (film) 2979, 2938, 2881, 1373, 1103 cm^{-1}; MS (CI) *m/z*

[8] Overman, L. E.; Rishton, G. M. *Org. Synth., Coll. Vol. 9* **1998**, 4–9.
[9] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.

155.1071 (155.1073 calcd for $C_9H_{15}O_2$, M–Et).

2-Bromomethyl-2,4,5-trimethyl-4-(1-methylethenyl)-1,3-dioxolane (12b). Prepared by method C: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.61 (s, 3H), 1.75 (s, 3H), 3.25-3.60 (m, 2H), 4.18 (q, *J* = 6.6 Hz, 1H), 4.94 (s, 1H), 5.05 (s, 1H); IR (film) 2982, 2939, 1377, 1144, 1099 cm^{-1}; MS (CI) *m/z* 249.0500 (249.0490 calcd for $C_{10}H_{17}O_2{}^{79}Br$, MH).

2-Cyclohexyl-2,4,5-trimethyl-4-(1-methylethenyl)-1,3-dioxolane (12c). Prepared by method A: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.38 (s, 3H), 1.75 (s, 3H), 0.90-2.0 (m, 11H), 4.10 (q, *J* = 6.3 Hz, 1H), 4.92 (s, 1H), 4.97 (s, 1H); IR (film) 2989, 2933, 2856, 1375, 1250, 1165, 1106, 954 cm^{-1}; MS (CI) *m/z* 239.2016 (239.2012 calcd for $C_{15}H_{26}O_2$, MH). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.31; H, 11.04.

2,4,5-Trimethyl-4-(1-methylethenyl)-2-phenyl-1,3-dioxolane (12d). Prepared by method B: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.6 Hz, 3H), 1.23 (s, 3H), 1.62 (s, 3H), 1.87 (s, 3H), 3.71 (q, *J* = 6.6 Hz, 1H), 4.97 (s, 1H), 5.01 (s, 1H), 7.25-7.38 (m, 3H), 7.50-7.57 (m, 2H); IR (film) 2990, 2937, 2877, 1372, 1242, 1172, 1099, 952, 703 cm^{-1}; MS (CI) *m/z* 217.1228 (217.1229 calcd for $C_{14}H_{17}O_2$, M–Me).

2-Ethyl-2-(methoxymethyl)-4,5-dimethyl-4-(1-methylethenyl)-1,3-dioxolane (12e) Prepared by method B: a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.6 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.26 (s, 3H), 1.77 (s, 3H), 1.92 (q, *J* = 7.6 Hz, 2H), 3.39 (s, 2H), 3.40 (s, 3H), 4.13 (q, *J* = 6.6 Hz, 1H), 4.94 (s, 1H), 4.98 (s, 1H); IR (film) 2980, 2937, 2883, 1457, 1158, 1118, 1101 cm^{-1}; MS (CI) *m/z* 199.1334 (199.1335 calcd for $C_{11}H_{19}O_3$, M–Me).

General Procedure for Rearrangement of Allylic Acetals 12 with $SnCl_4$.

Stannic chloride (1.0 mmol, 0.12 mL; freshly distilled before use) was added dropwise to a solution of acetal **12** (1.0 mmol) and CH_2Cl_2 (2 mL) at –78°C. The reaction solution was maintained at –78°C for 2 h and then allowed to warm to –20°C. After 3 h, the reaction was recooled to –78°C, quenched with Et_3N (1.2 mmol, 0.17 mL), diluted with saturated aqueous $NaHCO_3$ (2 mL) and warmed to rt over 30 min. The mixture was extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (hexane-EtOAc) to give tetrahydrofurans **13** and **14** as colorless oils. The stereomeric ratio was determined by 500 MHz ^{1}H NMR analysis of the crude reaction product. The configuration at C5 was determined by nOe studies.

(*rel*-2*S*,3*S*,5*S*)-1-(5-Ethyl-2,3,5-trimethyltetrahydrofuran-3-yl)ethanone (13a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H), 1.25 (s, 3H), 1.26 s, 3H), 1.53 (d, *J* = 13.2 Hz, 1H), 1.71 (dq, *J* = 3.3, 6.6 Hz, 2H), 2.18 (s, 3H), 2.37 (d, *J* = 13.5 Hz, 1H), 3.93 (q, *J* = 6.3 Hz, 1H), minor isomer (2*S*,3*S*,5*R*): δ 2.20 (s, 3H) 2.29 (d, *J* = 13.5 Hz, 1H) 3.83 (q, *J* = 6.3 Hz, 1H); IR (film) 2978, 2937, 2881, 1705, 1463, 1384, 1354, 1104, 947 cm^{-1}; MS (CI) *m*/*z* 185.1540 (185.1542 calcd for $C_{11}H_{20}O_2$, MH).

The stereochemistry of the major stereoisomer **13a** was established by chemical correlation with **13b**; reaction of **13b** with $LiMe_2Cu$ (–40 °C in Et_2O).

(*rel*-2*S*,3*S*,5*S*)-1-(5-bromomethyl-2,3,5-trimethyltetrahydrofuran-3-yl)ethanone (13b): a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.6 Hz, 3H), 1.33 (s, 3H), 1.44 (s, 3H), 1.58 (d, *J* = 13.6 Hz, 1H), 2.16 (s, 3H), 2.66 (d, *J* = 13.6 Hz, 1H), 3.51 (d, *J* = 10.2 Hz, 1H), 3.59 (d, *J* = 10.2 Hz, 1H), 3.97 (q, *J* = 6.6 Hz, 1H); IR (film) 2975, 2937, 1702, 1459, 1364, 1355 cm^{-1}; MS (CI) *m*/*z* 249.0486 (249.0490 calcd for $C_{10}H_{17}O_2{}^{79}Br$, MH). Anal. Calcd for $C_{10}H_{17}O_2Br$: C, 48.21; H, 6.88. Found: C, 48.33; H, 6.86.

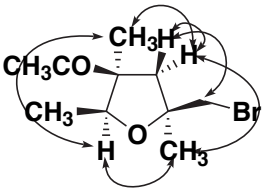
(*rel*-2*S*,3*S*,5*S*)-1-(5-Cyclohexyl-2,3,5-trimethyltetrahydrofuran-3-yl)ethanone (13c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95-1.95 (m, 11H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 3H), 1.25 (s, 3H), 1.54 (d, *J* = 13.5 Hz, 1H), 2.18 (s, 3H) 2.39 (d, *J* = 13.5 Hz, 1H), 3.93 (q, *J* = 6.6 Hz, 1H); IR (film) 2973, 2934, 2856, 1702, 1452, 1381, 1353, 1106, 950 cm^{-1}; MS (CI) *m*/*z* 239.2012 (239.2012 calcd for $C_{15}H_{26}O_2$, MH). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.45; H, 11.02.

(*rel*-2*S*,3*S*,5*S*)-1-(2,3,5-Trimethyl-5-phenyltetrahydrofuran-3-yl)ethanone (13d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.6 Hz, 3H), 1.31 (s, 3H), 1.58 (s, 3H), 1.93 (s, 3H), 2.13 (d, *J* = 13.5 Hz, 1H), 2.82 (d, *J* = 13.5 Hz, 1H), 4.12 (q, *J* = 6.6 Hz, 1H), 7.20-7.60 (m, 5H); IR (film) 2973, 2931, 288, 1704, 1446, 1104, 764, 703 cm^{-1}; MS (CI) *m*/*z* 217.1228 (217.1229 calcd for $C_{14}H_{17}O_2$, M–Me). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.61; H, 8.71.

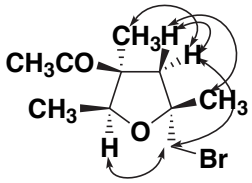
(*rel*-2*S*,3*S*,5*S*)-1-(2,3-Dimethyl-5-ethyl-5-methoxymethyltetrahydrofuran-3-yl)ethanone (13e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.5 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.25 (s, 3H), 1.60 (d, *J* = 13.7 Hz, 1H), 1.80-1.97 (m, 2H). 2.19 (s, 3H), 2.31 (d, *J* = 13.7 Hz, 1H), 3.38 (s, 3H), 3.37-3.47 (m, 2H), 3.98 (q, *J* = 6.6 Hz, 1H); IR (film) 2978, 2937, 2882, 1705, 1463, 1116 cm^{-1}; MS (CI) *m*/*z* 215.1648 (215.1648 calcd for $C_{12}H_{22}O_3$, MH). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.33; H, 10.33.

^{1}H nOe Data:

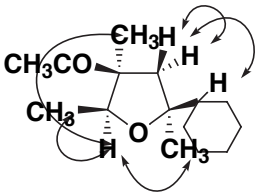
13b Major isomer



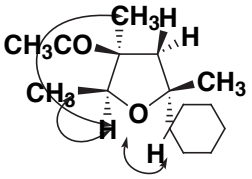
14b minor isomer



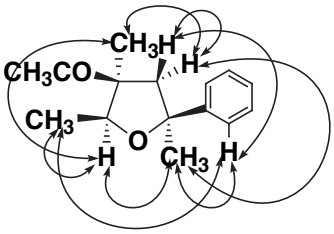
13c Major isomer



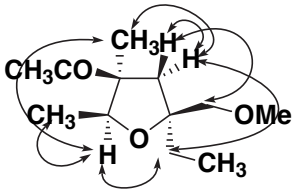
14c minor isomer



13d Major isomer



13e Major isomer



14e minor isomer