Stereoselection in the Prins-Pinacol Synthesis of Acyltetrahydrofurans

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Supporting Information

A. Representative Experimental Procedures[1]

Preparation of *rel*-(2*S*,4*R*,5*S*)-4-Ethenyl-4,5-dimethyl-2-isopropyl-1,3-dioxolane (6a). A solution of a 6:1 mixture of *anti*- and *syn*-3-methyl-4-penten-2,3-diols[2] (820 mg, 7.10 mmol), isobutyraldehyde (2.5 g, 35 mmol), $MgSO_4$ (15 g), CH_2Cl_2 (140 mL), and *p*-TSOH (130 mg, 0.68 mmol) was stirred at rt for 4 h before being poured into saturated aqueous NH_4Cl (50 mL). The resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography (20:1 hexanes-EtOAc) to give a 6:1 mixture of acetals **6a** and **6s** (900 mg, 74%) as a colorless oil. The major stereoisomer **6a** was separated by preparative MPLC (silica gel, 100:1 hexanes-EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dd, *J* = 10.7, 11.1 Hz, 1H), 5.23 (dd, *J* = 15.9, 1.6 Hz, 1H), 5.13 (dd, *J* = 9.1, 1.6 Hz, 1H), 4.70 (d, *J* = 5.2 Hz, 1H), 3.77 (q, *J* = 6.4 Hz, 1H), 1.86–1.67 (m, 1H), 1.32 (s, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 114.2, 106.3, 81.5, 81.3, 32.1, 22.5, 17.2, 17.1, 15.4; IR (film) 3015, 2977, 2933, 2874, 1473, 1412, 1384, 1108, 1006, 925 cm^{-1}; HRMS (EI) *m/z* 169.1229 (M–H, 169.1229 calcd for $C_{10}H_{17}O_2$). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.70; H, 10.67.

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[1] General experimental details have been described: Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210–9216.

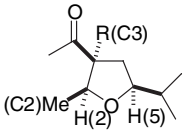
[2] Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354–65.

Rearrangement of Acetals with $SnCl_4$. Preparation of *rel*-(2*S*,3*S*,5*R*)-1-(2,3-Dimethyl-5-isopropyl-3-tetrahydrofuranyl)ethanone (13b) from Anti Acetal 7a. A CH_2Cl_2 solution of $SnCl_4$ (0.16 mL, 1.0 M) was added to a solution of *anti* acetal **7a** (27 mg, 0.15 mmol, 97% purity[3]) and CH_2Cl_2 (15 mL) at –78 °C. After 17 h, the solution was poured into saturated aqueous NH_4Cl (10 mL) and the resulting layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by silica gel chromatography (20:1 hexanes–EtOAc) to afford tetrahydrofurans **13b** and **12b** (26 mg, 96%) as a 92:8 mixture[3]. The major stereoisomer **13b** was separated by preparative MPLC (silica gel, 20:1 hexanes–EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (q, *J* = 6.2 Hz, 1H), 3.78 (app ABq, *J* = 8.1, 7.3 Hz, 1H), 2.19 (s, 3H), 2.04 (m, 1H), 1.87 (dd, *J* = 6.5, 6.5 Hz, 1H), 1.74–1.67 (m, 1H), 1.20 (s, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 82.0, 77.6, 57.9, 41.4, 33.7, 26.5, 19.2, 17.9, 16.7, 15.4; IR (film) 2961, 2874, 1704, 1469, 1384, 1358, 1237, 1085, 1023, 902, 869, 601 cm^{-1}; HRMS (EI) *m/z* 184.1463 (M, 184.1463 calcd for $C_{11}H_{20}O_2$). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.61; H, 10.89.

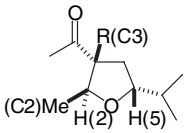
Rearrangement of Acetals with Trifluoromethanesulfonic Acid. Preparation of *rel*-(2*S*,3*R*,5*S*)-1-(2-Methyl-5-isopropyl-3-tetrahydrofuranyl)ethanone (12a) from Syn Acetal 6s. A CH_2Cl_2 solution of TfOH (0.60 mL, 0.5 M, 0.30 mmol) was added to a solution of *syn* acetal **6s** (17 mg, 0.10 mmol, >99% purity by capillary GLC analysis)[3] and CH_2Cl_2 (12 mL) at –78 °C and the reaction was maintained at this temperature for 14 h before being poured into saturated aqueous $NaHCO_3$ (5 mL). The resulting layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by silica gel chromatography (20:1 hexanes–EtOAc) to give **12a** (15 mg, 90%) as a single diastereomer[3]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (dq, *J* = 6.5, 1.6 Hz, 1H), 3.50 (app ABq, *J* = 7.4, 7.5 Hz, 1H), 3.26 (app ABq, *J* = 8.3, 8.4 Hz, 1H), 2.15 (s, 3H), 1.95–1.91 (m, 2H), 1.78–1.71 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 84.9, 75.1, 55.8, 33.3, 31.1, 30.8, 19.6, 18.5, 17.9; IR (film) 2960, 2873, 1714, 1469, 1382, 1385, 1244, 1168, 1096, 1042, 908 cm^{-1}; HRMS (EI) *m/z* 170.1303 (M, 170.1306 calcd for $C_{10}H_{18}O_2$). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.67; H, 10.61.

[3] GLC analyses were conducted with a Hewlett-Packard 5890 series II gas chromatograph equipped with a 30 m x 0.32 mm J&W DB-5 column and a flame ionization detector.

B. ^{1}H NOE Data for Tetrahydrofuran Stereoisomers 12 and 13.



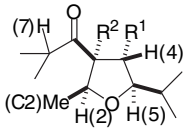
12a: R = H
12b: R = Me



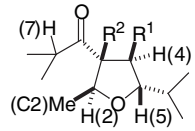
13a: R = H
13b: R = Me

R	compd	^{1}H DNOE enhancements[a]	
H	**12a**	H(2)/H(3),(5)	Me(C2)/$CHMe_2$[b]
Me	**12b**	Me(C3)/H(2),(5)	H(2)/H(5)
H	**13a**	Me(C2)/H(3),(5)	H(3)/H(5)
Me	**13b**	Me(C2)/Me(C3)	H(5)/Me(C3)

[a]For each entry, each hydrogen signal was separately irradiated to give the corresponding enhancements. [b]With methine hydrogen of the *i*-sopropyl group.



12d: $R^1 = R^2 = H$
12e: R^1–$R_2 = (CH_2)_3$



13d: $R^1 = R^2 = H$
13e: R^1–$R_2 = (CH_2)_3$

R^1	R^2	compd	^{1}H DNOE enhancements[a]	
H	H	**12d**	H(2)/H(3),(5)	H(5)/H(3)
$(CH_2)_3$		**12e**	H(7)/H(4),Me(C2)	H(2)/H(5)
H	H	**13d**	Me(C2)/H(3),(5)	
$(CH_2)_3$		**13e**	H(7)/H(2),(4)	Me(C2)/H(5)

[a]For each entry, each hydrogen signal was separately irradiated to give the corresponding enhancements.