γ -Hydroxynitrile Alkylations: Electrophile-Dependent Selectivity

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Stereochemical Determinations

Chemical correlations:

NOESY and NOE

Crystallography

By Analogy to 2c

General Experimental Procedures: All reactions were carried out with magnetic stirring in flame-dried, round-bottom flasks under argon. Plastic syringes were purged with argon prior to use. Benzaldehyde, allyl bromide, ethyl trimethylacetate and diethyl carbonate were freshly distilled. Propyl iodide and propargyl bromide were successively passed through basic alumina and silica prior to use. *i*-PrMgCl and methyl cyanoformate were used as received. THF was distilled over sodium-benzophenone ketyl. The hydroxynitriles were synthesized by a known procedure.¹

TLC was performed with glass-backed silica gel plates and visualized either by UV detection or Ceric Ammonium Molybdate (CAM) stain. IR Spectra were recorded on a Nicolet 380 FT-IR neat. NMR spectra were recorded on Bruker Avance^{II} 500 or 400 MHz NMR instruments in CDCl₃ using TMS as an internal standard. High resolution mass spectra (HRMS) were recorded using electrospray ionization on an Agilent LC/MSD 1200 Series Nanoflow Time of Flight (TOF) mass spectrometer. Crystallographic analyses were performed on a Bruker Smart Apex II CCD Diffractometer.

General procedure: A THF solution of *i*-PrMgCl (5.0 equiv., 2.0M solution) was added to a -78 °C, THF solution of the hydroxynitrile (1 equiv). After 5 min, the cold bath was removed and the reaction was allowed to warm up to room temperature. After 30 min the reaction was cooled to -78 °C, the electrophile (5-10 equiv) was added neat, and then the cooling bath was removed. After 16 h a saturated, aqueous solution of NH₄Cl was added, the phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried over Na₂SO₄, concentrated, and purified by either silica gel (230-400 mesh) or radial chromatography to afford analytically pure material.

(2*R, 4*S**)-4-Hydroxy-2-methyl-2-propyl-pentanenitrile (2a)**

The reaction was carried out according to the general procedure using nitrile **1a** (107.8 mg, 0.95 mmol), *i*-PrMgCl (2.02 mL, 4.04 mmol), and PrI (1.00 mL, 10.28 mmol) to give a crude product that was purified by radial chromatography employing 90:10 (hexanes:EtOAc) to afford a 3.6:1 ratio of diastereomers (140.4 mg, 95% yield) as a colorless oil.

Major Isomer:

¹H NMR (500 MHz, CDCl₃): δ 4.15 – 4.05 (m, 1H), 2.18 (br s, 1H), 1.69 – 1.59 (m, 2H), 1.53-1.42 (m, 2H), 1.39 (s, 3H), 1.25 (d, *J* = 6.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 124.67, 65.20, 47.47, 42.24, 35.41, 25.03, 24.60, 17.93, 13.97.

Minor Isomer:

¹H NMR (500 MHz, CDCl₃): δ 1.82 (dd, *J* = 5.5, 9.5 Hz, 1H), 1.35 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 64.72, 47.60, 42.19, 34.80, 24.57, 24.10.

Mixture:

IR (neat): 3443 (OH), 2234 (CN)

HRMS *m/z* calcd. for C₉H₁₇NONa (M + Na): 178.1208; expt. 178.1230.

(2*R, 4*S**)-4-Hydroxy-2,5-dimethyl-2-propyl-hexanenitrile (2b)**

The reaction was performed according to the general procedure using nitrile **1b** (75.2 mg, 0.533 mmol), *i*-PrMgCl (1.33 mL, 2.66 mmol), and PrI (1.00 mL, 10.28 mmol) to give a crude product that was purified by radial chromatography employing 90:10 (hexanes:EtOAc) to afford 92.5 mg (95% yield) of **2b** in a 5.8:1 ratio of diastereomers as a colorless oil.

Major Isomer:

¹H NMR (500 MHz, CDCl₃): δ 3.72 (ddd, *J* = 1.5, 4.5, 9.5 Hz, 1H), 1.79 (very br s, 1H), 1.74-1.63 (m, 2H), 1.59-1.45 (m, 4H), 1.42 (s, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 124.82, 73.66, 43.17, 42.28, 35.90, 35.20, 24.79, 18.33, 18.09, 16.77, 14.07.

Minor Isomer:

¹H NMR (500 MHz, CDCl₃): δ 3.68 (ddd, *J* = 1.5, 4.5, 9.5 Hz, 1H), 1.36 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 124.82, 73.21, 43.38, 42.26, 34.70, 24.25, 17.00.

Mixture:

IR (neat): 3456 (OH), 2234 (CN)

HRMS *m/z* calcd. for C₁₁H₂₁NONa (M + Na): 206.1521; expt. 206.1526.

(2*R,4*S**)-4-hydroxy-2,5,5-trimethyl-2-propylhexanenitrile (2c)**

The reaction was performed according to the general procedure using nitrile **1c** (57.1 mg, 0.368 mmol), *i*-PrMgCl (0.92 mL, 1.84 mmol), and PrI (0.36 mL, 3.70 mmol) to give a

product residue that was purified by radial chromatography employing 90:10 (hexanes:EtOAc) to afford 66.1 mg (91% yield) of **2c** and **2d** (16.2:1 ratio) as a colorless oil.

Using MeMgCl as the base: The reaction was performed according to the general procedure using nitrile **1c** (65.1 mg, 0.419 mmol), MeMgCl (0.70 mL, 2.10 mmol), and PrI (0.50 mL, 5.14 mmol) to give a crude product that was purified by radial chromatography employing 98:2 (hexanes:EtOAc) to afford 46.1 mg (56% yield) of **2c** as an oily mixture of diastereomers (2.5:1 ratio).

By hydrogenation of 2e: A MeOH solution (15 mL) of hydroxynitrile **2e** (75.4 mg, 0.386 mmol) was hydrogenated for 4 h in a Parr shaker at 50 psi using 5% Pd/C (5.1 mg, 0.048 mmol). The methanol was then evaporated, the residue redissolved in EtOAc, and then passed through a short pad of silica gel to afford 67.1 mg (88%) of **2c**.

By hydrogenation of 2f: A methanolic solution (15 mL) of hydroxynitrile **2f** (44.2 mg, 0.229 mmol) was hydrogenated for 4 h in a Parr shaker at 50 psi using 5% Pd/C (6.3 mg, 0.059 mmol). The methanol was then evaporated, the crude product was redissolved in EtOAc, and then passed through a short pad of silica gel to afford 42.5 mg (94%) of **2c** as a colorless oil.

¹H NMR (500 MHz, CDCl₃): δ 3.54 (d, *J* = 9.3 Hz, 1H), 1.81 (overlapping br s, 1H and d, *J* = 4.9 Hz), 1.69 - 1.61 (m, 1H), 1.57 – 1.43 (m, 4H), 1.42 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.92 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 124.88, 76.98, 42.29, 41.12, 36.15, 35.29, 25.35, 24.89, 18.17, 14.13.

IR (neat): 3498 (OH), 2234 (CN).

HRMS *m/z* calcd. for C₁₂H₂₃NONa (M + Na): 220.1677; expt. 220.1700.

(2*S,4*S**)-4-hydroxy-2,5,5-trimethyl-2-propylhexanenitrile (2d)**

The reaction was performed according to the general procedure using nitrile **1d** (101.5 mg, 0.554 mmol), *i*-PrMgCl (1.39 mL, 2.78 mmol), and methyl iodide (0.35 mL, 5.62 mmol) to give a crude product that was purified by radial chromatography employing 80:20 (hexanes:EtOAc) to afford 103.9 mg (95%) of **2d** and **2c** as an oily mixture of diastereomers (9.4:1 ratio).

¹H NMR (500 MHz, CDCl₃): δ 3.53-3.48 (d, *J* = 9.3 Hz, 1H), 1.81 (overlapping br s, 1H and d, *J* = 4.9 Hz), 1.74 - 1.70 (m, 1H), 1.57 – 1.43 (m, 4H), 1.36 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.92 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 124.88, 76.46, 42.35, 41.11, 35.31, 29.69, 25.35, 24.89, 24.14, 18.15.

(2*R,4*S**)-2-allyl-4-hydroxy-2,5,5-trimethylhexanenitrile (2e)**

Performing the general procedure with nitrile **1c** (72.8 mg, 0.469 mmol), *i*-PrMgCl (1.25 mL, 2.50 mmol), and allyl bromide (0.41 mL, 4.74 mmol) gave a crude product that was purified

by radial chromatography employing 98:2 (hexanes:EtOAc) to afford 85.2 mg (93%) of **2e** as an oily mixture of diastereomers (4.7:1 ratio).

Major Isomer:

¹H NMR (500 MHz, CDCl₃): δ 5.95 – 5.82 (m, 1H), 5.25 – 5.17 (m, 2H), 3.55 (m, 1H), 2.43 (dd, *J* = 14.6, 7.4 Hz, 1H), 2.29 (dd, *J* = 14.6, 7.4 Hz, 1H), 1.92 (br s, 1H), 1.83 (d, *J* = 14.6 Hz, 1H), 1.46 (m, 1H), 1.43 (s, 3H), 0.91 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 132.05, 124.33, 120.01, 76.79, 44.16, 40.36, 35.84, 35.22, 25.31, 24.73.

Minor Isomer:

¹H NMR (500 MHz, CDCl₃): δ 5.95 – 5.82 (m, 1H), 5.25 – 5.17 (m, 2H), 3.52 (d, *J* = 5.9 Hz, 1H), 2.53 (dd, *J* = 14.6, 7.4 Hz, 1H), 2.32 (dd, *J* = 14.6, 7.4 Hz, 1H), 1.92 (br s, 1H), 1.65 (d, *J* = 5.9 Hz, 1H), 1.35 (s, 3H), 0.91 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 132.20, 124.53, 119.99, 76.43, 44.07, 40.68, 35.27, 35.17, 25.34, 24.17.

Mixture:

IR (neat): 3508 (OH), 1643 (C=C).

HRMS *m/z* calcd. for formula: C₁₂H₂₁NONa (M + Na); 218.1521; expt. 218.1570.

(2*R,4*S**)-4-hydroxy-2,5,5-trimethyl-2-(prop-2-ynyl)hexanenitrile (2f)**

Performing the general procedure with nitrile **1c** (108.1 mg, 0.696 mmol), *i*-PrMgCl (2.09 mL, 4.18 mmol), and propargyl bromide (1.00 mL, 13.28 mmol) gave a crude product that was purified by radial chromatography employing a gradient solvent system starting with pure

hexanes to 90:10 (hexanes:EtOAc) to afford 101.0 mg (75%) of **2f** as an oily mixture of diastereomers (5.0:1 ratio).

Major Isomer:

¹H NMR (500 MHz, CDCl₃): δ 3.52-3.57 (m, 1H), 2.65-2.55 (m, 2H), 2.19-2.16 (m, 1H), 1.95 (d, *J* = 14.6 Hz, 1H), 1.74 (d, *J* = 4.3 Hz, 1H), 1.61 (dd, *J* = 9.8, 14.6 Hz, 1H), 1.54 (s, 3H), 0.93 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 123.83, 76.74, 72.58, 39.43, 35.28 29.65, 25.33, 24.89.

IR (neat): 3494 (OH), 3314 (alkyne), 2239 (CN), 2123 (alkyne).

HRMS *m/z* calcd. for formula: C₁₂H₁₉NONa (M + Na); 216.1364; expt. 216.1335.

(2*R,4*S**)-4-hydroxy-2,5,5-trimethyl-2-(phenylthio)hexanenitrile (2g)**

Using PhSSPh as the electrophile: Performing the general procedure with nitrile **1c** (82.2 mg, 0.530 mmol), *i*-PrMgCl (1.32 mL, 2.64 mmol), and diphenyl disulfide (0.69 g, 2.65 mmol) gave a crude product that was purified by radial chromatography employing 90:10 (hexanes:EtOAc) to afford 133.9 mg (96%) of **2g** as an oily mixture of diastereomers (12.7:1 ratio).

Using PhSO₂SPh as the electrophile: Performing the general procedure with nitrile **1c** (70.1 mg, 0.452 mmol), *i*-PrMgCl (1.13 mL, 2.26 mmol), and *S*-phenyl benzenethiosulfonate (0.5674g, 2.27 mmol) gave a crude product that was purified by column chromatography employing 95:5 (hexanes:EtOAc) to afford 113.1 mg (95%) of **2g** and **2g'** as an oily mixture of diastereomers (1.3:1 ratio).

¹H NMR (500 MHz, CDCl₃): δ 7.70 (br d, *J* = 7.0 Hz, 2H), 7.49 – 7.40 (m, 3H), 3.66 (d, *J* = 9.5 Hz, 1H), 2.02 (d, *J* = 14.5 Hz, 1H), 1.96 (very br s, 1H), 1.81 (dd, *J* = 9.5, 14.5 Hz, 1H), 1.66 (s, 3H), 0.89 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 137.07, 130.34, 129.38, 129.24, 121.88, 77.06, 43.91, 41.41, 35.32, 26.73, 25.31.

IR (neat): 3503 (OH), 2231 (CN).

HRMS *m/z* calcd. for formula: C₁₅H₂₁NOSNa (M + Na); 286.1242; expt. 286.1209.

(2*S,4*S**)-4-hydroxy-2,5,5-trimethyl-2-(phenylthio)hexanenitrile (2g')**

¹H NMR (500 MHz, CDCl₃): δ 7.70 (br d, *J* = 7.0 Hz, 2H), 7.49 – 7.40 (m, 3H), 3.66 (d, *J* = 9.4 Hz, 1H), 2.01 (d, *J* = 14.5 Hz, 1H), 1.92 (dd, *J* = 9.4, 14.5 Hz, 1H), 1.59 (s, 3H), 0.93 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 137.02, 130.32, 129.41, 129.24, 122.19, 76.20, 43.38, 41.90, 35.26, 25.88, 25.45.

(2*S,4*S**)-4-hydroxy-2-((*S**)-hydroxy(phenyl)methyl)-2,5,5-trimethylhexanenitrile (2h)**

Performing the general procedure with nitrile **1c** (76.1 mg, 0.490 mmol), *i*-PrMgCl (1.23 mL, 2.46 mmol), and benzaldehyde (0.25 mL, 2.45 mmol) with the exception of maintaining the reaction at -78 °C before addition of saturated, aqueous NH₄Cl, afforded a crude product that was purified by radial chromatography to afford 117.8 mg (92%) of **2h** as an oily mixture of three diastereomers (**2h** : **2h'** : **2h''**, 1.0:1.0:2.0 ratio). The diastereomers were separated by preparative HPLC.

¹H NMR (500 MHz, CDCl₃): δ 7.48 (br d, *J* = 7.8 Hz, 2H), 7.40 – 7.29 (m, 3H), 5.12 (s, 1H), 4.20 (s, 1H), 3.83 (d, *J* = 8.3 Hz, 1H), 2.34 (s, 1H), 1.89 (d, *J* = 15.2 Hz, 1H), 1.83 (dd, *J* = 8.3, 15.2 Hz, 1H), 1.12 (s, 3H), 0.98 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 138.38, 128.00, 127.97, 127.26, 127.00, 77.44, 73.83, 42.31, 38.72, 35.18, 25.15, 20.11.

IR (neat): 3397 (OH), 2238 (CN).

HRMS *m/z* calcd. for formula: C₁₆H₂₃NO₂Na (M + Na); 284.1626; expt. 284.1664.

(2*S,4*S**)-4-hydroxy-2-((*R**)-hydroxy(phenyl)methyl)-2,5,5-trimethylhexanenitrile (2h')**

¹H NMR (500 MHz, CDCl₃): δ 7.52 – 7.48 (m, 2H), 7.39 – 7.34 (m, 3H), 4.66 (d, *J* = 2.4 Hz, 1H), 4.59 (d, *J* = 1.9 Hz, 1H), 3.80-3.83 (m, 1H), 2.66 (d, *J* = 2.8 Hz, 1H), 1.95 (d, *J* = 14.6 Hz, 1H), 1.81 (dd, *J* = 9.4, 14.6 Hz, 1H), 1.12 (s, 3H), 0.97 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 139.38, 128.67, 128.34, 127.57, 122.09, 79.30, 77.09, 43.40, 42.02, 35.15, 25.45, 24.53.

IR (neat): 3311 (OH), 3111 (OH), 2237 (CN).

HRMS m/z calcd. for formula: $C_{16}H_{23}NO_2Na$ ($M + Na$); 284.1626; expt. 284.1625.

(2*R,4*S**)-4-hydroxy-2-((*S**)-hydroxy(phenyl)methyl)-2,5,5-trimethylhexanenitrile (2h'')**

1H NMR (500 MHz, $CDCl_3$): δ 7.51 – 7.47 (m, 2H), 7.40 – 7.34 (m, 3H), 4.66 (d, J = 3.3 Hz, 1H), 3.60 (m, 1H), 3.47 (d, J = 4 Hz, 1H), 2.11 (overlapping s, 1H and d, J = 14.9 Hz, 1H), 1.99 (dd, J = 9.5, 14.9 Hz, 1H), 1.25 (s, 3H), 0.95 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.70, 128.71, 128.30, 127.60, 122.98, 77.20, 76.03, 43.15, 38.41, 35.35, 25.24, 21.48.

IR (neat): 3421 (OH), 3376 (OH), 3239 (CN).

HRMS m/z calcd. for formula: $C_{16}H_{23}NO_2Na$ ($M + Na$); 284.1626; expt. 284.1648.

(3*S*,5*S*)-5-(tert-Butyl)-3-methyl-2-oxotetrahydrofuran-3-carbonitrile

Using MeOCO(CN) as the electrophile: Performing the general procedure with nitrile **1c** (52.1 mg, 0.336 mmol), *i*-PrMgCl (0.84 mL, 1.68 mmol), and methyl cyanoformate (0.16 mL, 2.01 mmol) gave a crude product that was purified by column chromatography employing

98:2 (hexanes:EtOAc) to afford 54.8 mg (90%) of **2i** and **2i'** as an oily mixture of diastereomers (1:1 ratio).

Using (EtO)₂CO as the electrophile: Performing the general procedure with nitrile **1c** (84.0 mg, 0.541 mmol), *i*-PrMgCl (1.35 mL, 2.70 mmol), and diethyl carbonate (0.33 mL, 2.72 mmol) to gave a crude product that was purified by radial chromatography employing 98:2 (hexanes:EtOAc) to afford 88.3 mg (90%) of **2i** and **2i'** in a 50.0:1 ratio (determined by GCMS) as a colorless oil.

From the intramolecular cyclization of 3c: *i*-PrMgCl (0.16 mL, 0.32 mmol) was added to a -78 °C, THF solution (5mL) of nitrile **1c** (49.2 mg, 0.317 mmol). After 5 min neat methyl cyanoformate (0.03 mL, 0.378 mmol) was added and the cooling bath was then removed. After 5 min, saturated, aqueous NH₄Cl was added, the phases separated, and the aqueous phase was then extracted with EtOAc. The combined organic phase was dried (Na₂SO₄), filtered through a short pad of silica gel, and concentrated to afford crude **3c** that was used without further purification. A THF solution (2 mL) of **3c** was added to a -42 °C, THF solution of LiNEt₂. After 45 min, saturated, aqueous NH₄Cl was added, the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phase was dried over sodium sulfate, and concentrated to afford a crude product that was purified by column chromatography to afford 36.2 mg (64%) of **2i** and **2i'** as an oily mixture of diastereomers (1:1 ratio).

¹H NMR (500 MHz, CDCl₃): δ 4.39 (dd, *J* = 5.2, 11.2 Hz, 1H), 2.66 (dd, *J* = 5.2, 13.2 Hz, 1H), 1.97 (dd, *J* = 11.2, 13.2 Hz, 1H), 1.68 (s, 3H), 0.98 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 170.49, 118.07, 85.51, 39.77, 37.46, 33.10, 24.84, 21.48.

IR (neat): 2240 (CN), 1783 (lactone).

HRMS m/z calcd. for formula: $C_{10}H_{15}NO_2Na$ ($M + Na$); 204.1000; expt. 204.1012.

(3*R,5*S**)-5-tert-butyl-3-methyl-2-oxotetrahydrofuran-3-carbonitrile (2i')**

1H NMR (500 MHz, $CDCl_3$): δ 4.24 (dd, $J = 6.2, 10.4$ Hz, 1H), 2.52 (dd, $J = 10.4, 13.3$ Hz, 1H), 2.27 (dd, $J = 6.2, 13.3$ Hz, 1H), 1.72 (s, 3H), 0.99 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.41, 118.68, 85.41, 39.90, 36.01, 33.52, 24.74, 22.09.

IR (neat): 2248 (CN), 1774 (lactone).

HRMS m/z calcd. for formula: $C_{10}H_{15}NO_2Na$ ($M + Na$); 204.1000; expt. 204.1020.

(2*R,3*S**,5*S**)-2,5-di-tert-butyl-2-hydroxy-3-methyltetrahydrofuran-3-carbonitrile (2j)**

Performing the general procedure with nitrile **1c** (62.1 mg, 0.400 mmol), *i*-PrMgCl (1.00 mL, 2.00 mmol), and ethyl trimethylacetate (0.31 mL, 2.03 mmol) gave a crude product that was purified by column chromatography employing 95:5 (hexanes:EtOAc) to afford 59.2 mg (62%) of **2j** and **2j'** as a mixture of diastereomers (5.9:1 ratio).

¹H NMR (500 MHz, CDCl₃): δ 3.80 (dd, *J* = 6.6, 8.2 Hz, 1H), 2.32 (dd, *J* = 5.6, 6.6 Hz, 1H), 2.09 (dd, *J* = 5.6, 8.2 Hz, 1H), 2.00 (s, 1H), 1.61 (s, 3H), 1.23 (s, 9H), 0.93 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 125.24, 107.77, 82.37, 43.34, 42.09, 39.60, 33.22, 25.86, 25.65, 23.82.

IR (neat): 3443 (OH), 2254 (CN).

HRMS *m/z* calcd. for formula: C₁₄H₂₅NO₂Na (M + Na); 262.1783; expt. 262.1788.

(2R*,3R*,5S*)-2,5-di-tert-butyl-2-hydroxy-3-methyltetrahydrofuran-3-carbonitrile (2j')

¹H NMR (500 MHz, CDCl₃): δ 3.87 (dd, *J* = 5.6, 6 Hz, 1H), 2.66-2.71 (m, 1H), 1.81 (dd, *J* = 5.6, 6.3 Hz, 1H), 1.56 (s, 3H), 1.16 (s, 9H), 0.89 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 122.78, 108.28, 86.02, 46.19, 40.17, 39.75, 33.26, 26.13, 25.73, 22.34.

(2S*,4S*)-4-hydroxy-2-((R)*-1-hydroxy-2-methylpropyl)-2,5,5-trimethylhexanenitrile (10c)

Performing the general procedure with nitrile **1c** (112.1 mg, 0.722 mmol), *i*-PrMgCl (1.80 mL, 3.60 mmol), and ethyl isobutyrate (0.49 mL, 3.66 mmol) gave a crude product that was purified by column chromatography employing 90:10 (hexanes:EtOAc) to afford 54.8 mg (90%) of **10c** as white crystals.

MPt. 65-67°C.

¹H NMR (500 MHz, CDCl₃): δ 4.12 (br s, 1H), 3.72 (d, *J* = 8.5 Hz, 1H), 3.36 (d, *J* = 2.2 Hz, 1H), 2.53 (br s, 1H), 1.97-2.06 (m, 1H), 1.88 (dd, *J* = 1.3, 13.5 Hz, 1H), 1.69 (dd, *J* = 13.5, 8.5 Hz, 1H), 1.35 (s, 3H), 1.10 (d, *J* = 6.9 Hz), 1.06 (d, *J* = 6.9 Hz, 1H), 0.94 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 123.01, 79.73, 76.97, 43.76, 41.33, 35.11, 30.01, 25.46, 23.74, 21.75, 14.62.

IR (neat): 3385 (OH), 3294 (OH), 2245 (CN).

HRMS *m/z* calcd. for formula: C₁₃H₂₅NO₂Na (M + Na); 250.1783; expt. 250.1790.

(3*S,5*S**)-5-tert-butyl-3-methyl-3-propyldihydrofuran-2(3*H*)-one (i)**

A THF solution of NaHMDS (0.55 mL, 0.55 mmol) was added to a 0° C, THF solution (5 mL) of **2d** (54.3 mg, 0.275 mmol). After 30 min, 200 Proof EtOH (3 mL) was added and then the crude reaction mixture was concentrated to afford the crude product. Column chromatography afforded the lactone **i** and the imino lactone resulting from incomplete hydrolysis.

¹H NMR (500 MHz, CDCl₃): δ 4.13 (dd, *J* = 4.7, 11.0 Hz, 1H), 1.95 (dd, *J* = 6.6, 11.0 Hz, 1H), 1.76 (dd, *J* = 4.7, 6.6 Hz, 1H), 1.59 – 1.53 (m, 2H), 1.49 – 1.46 (m, 1H), 1.25 (s, 3H), 0.94 (overlapping singlet, 9H and triplet 3H).

¹³C NMR (100 MHz, CDCl₃): δ 181.79, 84.23, 44.39, 39.76, 35.00, 33.37, 24.97, 23.06, 17.74, 14.42.

IR (neat): 1761 (lactone).

HRMS *m/z* calcd. for formula: C₁₂H₂₂O₂Na (M + Na); 221.1517; expt. 221.1520.

(3*R,5*S**)-5-tert-butyl-3-methyl-3-(phenylthio)dihydrofuran-2(3*H*)-one**

A THF solution of NaHMDS (0.54 mL, 0.54 mmol) was added to a 0° C, THF solution (5 mL) of **2g** (70.7 mg, 0.268 mmol). After 30 min, 200 proof EtOH (3 mL) was added and then the mixture was concentrated to afford the crude lactone. Column chromatography afforded a mixture of the lactone **ii** and an unstable imino lactone.

¹H NMR (500 MHz, CDCl₃): δ 7.58 – 7.54 (m, 2H), 7.46 – 7.41 (m, 2H), 7.38 – 7.34 (m, 2H), 4.21 (dd, *J* = 5.0, 10.7 Hz, 1H), 2.24 (dd, *J* = 3.1, 5.0 Hz, 1H), 2.09 (dd, *J* = 3.1, 10.7 Hz, 1H), 1.48 (s, 3H), 0.93 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 176.09, 137.18, 130.02, 129.61, 128.91, 84.04, 51.52, 38.62, 33.05, 24.91, 23.46.

IR (neat): 1761 (lactone).

HRMS *m/z* calcd. for formula: C₁₅H₂₀SO₂Na (M + Na); 287.1082; expt. 287.1102.

2g

firstPhCH Ocarbon

firstPhCH Ocarbon

138.38
128.00
127.26
123.56

77.44
77.25
77.00
76.74
73.83

42.31
38.72
35.18
26.15
20.11

"NOESY of LACTONE" 1 1 C:\Bruker\TOPSPIN\flaming rj

References

¹ Taylor, S. K.; De Young, D.; Simons, L. J.; Vyvyan, J. R.; Wemple, M. A.; Wood, N. K. *Synth. Commun.* **1998**, 28, 1691.