**A domino transformation of D-glucal to
 α -substituted α -hydroxymethyl furfuryl derivatives**

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Section A: General Information

^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 200 and 500 MHz spectrometers with TMS as the internal standard. Chemical shifts were expressed in parts per million (δ ppm). MS were recorded on JEOL MSD-300 and Bruker Esquire 3000 LC-Mass spectrometer. Silica gel coated aluminium plates were used for TLC. Elemental analyses were performed on Elementar Vario EL-III. Optical rotations were measured on Perkin-Elmer 241 polarimeter at 25 °C using sodium D light. Reagents and solvents used were mostly of LR grade.

Section B: Experimental procedure

(1) General procedure for $\text{In}(\text{OTf})_3$ catalysed synthesis of α -substituted α -hydroxy methyl furfuryl derivatives

The nucleophile (1.5 equiv.) and $\text{In}(\text{OTf})_3$ (1 mol %) were successively added to a solution of glugal (1eqv.) in acetonitrile (3 mL/mmol substrate) and stirred for the specified time (Table 1). The reaction mixture was concentrated, diluted with ethyl acetate and washed with saturated sodium bicarbonate solution (10 mL). The organic layer was separated, evaporated and the crude mixture was subjected to flash chromatography over silica gel (100-200 mesh) to afford corresponding pure product. The following nucleophiles were used for the transformations.

Figure 1. Nucleophiles **a-w** employed in the reaction with glugal

On a larger scale (~20 mol of the substrate), the reaction proceeded in a similar manner even with a lower catalyst loading (0.5 mol %) thus making this process amenable for easy scale up.

(2) Optimization of the protocol

(a) Comparison of catalytic efficacy of different Lewis acids

Table 1: Reaction of D-glucal (1 eqv.) with MeOH (1.5 eqv.) in the presence of different Lewis acids:

Entry	Acid catalyst ^a	Time(h)	Yield ^b (2 : 3 : 4)%
1	InCl ₃	1.2	40 (3:6:1)
2	InBr ₃	.5	65 (2:7:1)
3	Sc(OTf) ₃	.5	60 (1:5.5:2)
4	In(OTf) ₃	.2	76 (1.1:9:1)
5	HClO ₄ .silica	1.5	35 (2:1.5:1)
6	InCl ₃ .H ₂ O	1.2	30 (4:3:1)
7	HgSO ₄	1.8	20 (3:1.5:1)

a. Catalyst loading 1 mol %

b. Isolated yield of compound **3a** after column chromatography.

c. Rotation value of compound **2** is +34 (c 1.3, CHCl₃)

(b) Solvent effect on domino reaction

Table 2: Solvent effect on reaction of D-glucal (1eqv.) with MeOH (1.5eqv.) in presence of 1mol% In(OTf)₃

Entry	Solvent ^a	Time (h)	Yield ^b %
1	DMF	1.2	52
2	THF	1.8	45
3	Acetone	2.3	60
5	Acetonitrile	0.2	76
6	Ionic liquid	1	55

a. In every case 3 ml/mmol of solvent was used .

b. Isolated yield after column chromatography.

(3) Experimental procedure for the reaction of D-glucal with TMSN₃ using water as a solvent: TMSN₃ (1.5eqv.), In(OTf)₃ (1mol %) were successively added to a solution of glucal (1eqv.) in water (3 mL/mmol) and stirred for 2 h. The reaction mixture was extracted with ethyl acetate, washed with saturated sodium bicarbonate solution (10 mL). The organic layer was separated, evaporated and the crude mixture was subjected to flash chromatography over silica gel (60-120 mesh) to afford the pure product. (Caution: Care should be taken while using TMSN₃ in water due to the formation of hydrazoic acid.)

(4) Spectral analysis:

2-(Furan-2-yl)-2-methoxy-ethanol (3a).^{3f} Prepared by the general procedure **1** and purified on silica gel (EtOAc/PE: 8/92) to obtain the product (76%) as oily liquid; ¹H NMR (200 MHz, CDCl₃): δ 7.34 (bs, 1H), 6.29 (bs, 2H), 4.27 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.83 (dd, *J* = 11.6, 8.1 Hz, 1H), 3.67 (dd, *J* = 11.6, 3.9 Hz, 1H), 3.26 (s, 3H); ¹³C NMR (50 MHz, CDCl₃): δ 150.0, 141.0, 109.0, 107.0, 77.0, 63.0, 55.0; ESI-MS (*M*⁺+Na) = 165; Anal. Calc for C₇H₁₀O₃: C, 59.14; H, 7.09; Found; C, 59.10; H, 7.19.

2-(1, 2-Dimethoxy-ethyl)-furan (4). Prepared by the general procedure **1** and purified on silica gel (EtOAc/PE: 3/97) to obtain (7%) as oily liquid; ¹H NMR (200 MHz, CDCl₃): δ 7.41-7.43 (m, 1H), 6.38 (d, *J* = 1.6 Hz, 1H), 6.35 (d, *J* = 1.6 Hz, 1H), 4.43 (dd, *J* = 7.8, 4.4 Hz, 1H), 3.76 (dd, *J* = 10.2, 7.6 Hz, 1H), 3.60 (dd, 10.2, 4.3Hz, 1H), 3.40 (s, 3H), 3.20 (s, 3H); ¹³C NMR (50 MHz, CDCl₃): δ 150.9, 141.6, 109.1, 107.6, 74.7, 73.0, 58.3, 55.8; ESI-MS (*M*⁺+Na) = 179; Anal. Calc for C₈H₁₂O₃: C, 61.52; H, 7.74; Found; C, 61.58.10; H, 7.79.

2-Ethoxy-2-(furan-2-yl)-ethanol (3b).^{3f} Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 5/95) to obtain the product (79%) as oily liquid; ¹H NMR (200 MHz, CDCl₃): δ 7.4 (s, 1H), 6.31-6.36 (m, 2H), 4.41-4.47 (m, 1H), 3.71-3.88 (m, 1H), 3.42-3.55 (m, 1H), 2.1 (bs, 1H), 1.20 (t, *J* = 7, 14 Hz, 3H). ¹³C NMR (50 MHz, CDCl₃): δ 152.6, 142.9, 110.5, 108.7, 75.9, 70.2, 68.2, 15.5; ESI-MS (*M*⁺+Na) = 179; Anal. Calc for C₈H₁₂O₃; C, 61.52; H, 7.74; Found; C, 61.47; H, 7.79.

2-Furan-2-yl-2-isopropoxy-ethanol (3c). Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 4/96) to obtain the product (78%) as oily liquid;. ¹H NMR (200 MHz, CDCl₃): δ 7.39-7.40 (m, 1H), 6.30-6.36 (m, 2H), 4.36 (dd, *J* = 7.96, 4.46 Hz, 1H), 3.65- 3.88 (m, 3H), 1.23 (d, 1H, *J* = 9.50 Hz, 1H), 1.10 (d, 1H, *J* = 6.19 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 153.0, 142.5, 110.2, 108.0, 73.3, 70.2, 64.6, 23.0, 22.0; ESI-MS (*M*⁺+Na) = 193; Anal. Calc for C₉H₁₄O₃; C, 63.51; H, 8.29; Found; 63.48; H, 8.32.

2-Allyloxy-2-furan-2-yl-ethanol (3d).^{3f} Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 4/96) to obtain the product (80%) as oily liquid;. ¹H NMR (200 MHz, CDCl₃): δ 7.39-7.40 (m, 1H), 6.34-6.35 (m, 2H), 5.79-5.95 (m, 1H), 5.15-5.30 (m, 2H), 4.51 (dd, *J* = 7.9, 4.2 Hz, 1H), 3.71- 4.07 (m, 4H), 2.72 (bs, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 151.9, 142.7, 134.4, 117.3, 110.2, 107.6, 75.0, 69.9, 64.2; ESI-MS (*M*⁺+Na) = 191; Anal. Calc for C₉H₁₂O₃; C, 64.27; H, 7.19; Found; C, 64.21; H, 7.24.

2-Furan-2-yl-2-(2-trimethylsilanyloxy)-ethanol (3e). Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 3/97) to obtain the product (75%) as oily liquid; ^1H NMR (200 MHz, CDCl_3): δ 7.39 (bs, 1H), 6.34-6.30 (m, 2H), 4.42 (dd, J = 8.0, 4.3 Hz, 1H), 3.6-3.7 (m, 4H), 0.96 (t, J = 6.6 Hz, 2H), -5.0 (s, 9H); ^{13}C NMR (50 MHz, CDCl_3): δ 151.7, 143.9, 111.5, 109.7, 76.7, 68.0, 65.7, 19.6, 0.01; ESI-MS ($\text{M}^+ + \text{Na}$) = 251; Anal. Calc for $\text{C}_{11}\text{H}_{20}\text{O}_3\text{Si}$; C, 57.85; H, 8.83; Found; C, 57.80; H, 8.88.

2-Ethylsulfanyl-2-furan-2-yl-ethanol (3i). Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 6/94) to obtain the product (79%) as oily liquid; ^1H NMR (200 MHz, CDCl_3): δ 7.39 (t, J = 0.8 Hz, 1H), 6.36 (t, J = 3 Hz, 1H), 6.26 (d, J = 3 Hz, 1H), 3.81-4.11 (m, 3H), 2.47-2.59 (m, 2H), 2.25 (bs, 1H), 1.26 (t, J = 7.4 Hz, 3H). ^{13}C NMR (50 MHz, CDCl_3): δ 152.5, 142.2, 110.4, 107.4, 63.0, 45.6, 24.7, 14.8; ESI-MS ($\text{M}^+ + \text{Na}$) = 195; Anal. Calc $\text{C}_8\text{H}_{12}\text{O}_2\text{S}$; C, 55.78; H, 7.02; S, 18.40; Found; C, 55.72; H, 7.07; S, 18.40.

2-Furan-2-yl-2-phenylsulfanyl-ethanol (3j). Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 4/96) to obtain the product (75%) as oily liquid; ^1H NMR (200 MHz, CDCl_3): δ 7.30-7.50 (m, 6H), 6.30-6.33 (m, 1H), 6.13 (d, J = 2.09, 1H), 4.39 (t, J = 6.6 Hz, 1H), 3.82-4.03 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ 151.7, 142.3, 133.6, 133.1, 132.6, 129.2, 129.0, 128.1, 110.5, 108.1, 62.9, 49.5; ESI-MS ($\text{M}^+ + \text{Na}$)

=243; Anal. Calc for $C_{12}H_{12}O_2S$. C, 63.74; H, 5.35; S, 14.56; Found; C, 63.70; H, 5.31; S, 14.62.

2-(2-Bromo-phenylsulphanyl)-2-furan-2-yl-ethanol (3k). Prepared by the general procedure and purified on silica gel (EtOAc /PE: 4/96) to obtain the product (83%) as oily liquid;. 1H NMR (200 MHz, $CDCl_3$): δ 7.60 (dd, $J = 7.74, 1.55$ Hz, 1H), 7.4 (dd, $J = 3.3, 1.7$ Hz, 1H), 7.13-7.35 (m, 3H), 6.33 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.23 (d, $J = 3.2$ Hz, 1H), 4.54 (t, $J = 6.4$ Hz, 1H), 3.89-4.06 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.2, 142.5, 134.4, 134.1, 133.3, 129.1, 127.9, 127.9, 110.6, 108.5, 63.1, 48.9; ESI-MS ($M^+ + Na$) = 323: 321(1:1); Anal.Calc for $C_{12}H_{11}BrO_2S$.; C, 48.17; H, 3.71; S, 10.72; Found; C, 48.12; H, 3.77; S, 10.80.

2-(2-Chloro-phenylsulphanyl)-2-furan-2-yl-ethanol (3l). Prepared by the general procedure and purified on silica gel (EtOAc /PE: 4/96) to get the product (80%) as oily liquid;. 1H NMR (200 MHz, $CDCl_3$): δ 7.15 -7.33 (m, 5H), 6.21-6.24 (m, 1H), 6.01 (d, $J = 3.2$ Hz, 1H), 4.25 (t, $J = 6.2$ Hz, 1H), 3.81-3.87 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.7, 141.3, 133.9, 133.4, 128.3, 130.1, 128.0, 109.5, 107.2, 61.8, 48.4; ESI-MS ($M^+ + Na$) = 277; Anal. Calc for $C_{12}H_{11}ClO_2S$.; C, 56.58; H, 4.35; S, 12.59 Found; C, 56.50; H, 4.31; S, 12.50.

2-Furan-2-yl-2-(4-methoxy-phenylsulfanyl)-ethanol. (3m). Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 4/96) to get the product (85%) as oily liquid; ^1H NMR (200 MHz, CDCl_3): δ 7.48-7.25 (m, 3H), 6.83 (dd, J = 11.7, 8.7 Hz, 2H), 6.29 (dd, J = 3.1, 1.9 Hz, 1H), 6.05 (d, J = 3.2, 1H), 4.19 (m, 1H), 3.82 (s, 3H); ^{13}C NMR (50 MHz, CDCl_3): δ 160.2, 151.7, 142.2, 136.8, 136.2, 122.1, 114.7, 114.5, 110.4, 107.9, 62.6, 55.4, 50.2; ESI-MS ($\text{M}^+ + \text{Na}$) = 273; Anal.Calc $\text{C}_{13}\text{H}_{14}\text{O}_3\text{S}$.; C, 62.38; H, 5.64; S, 12.81; Found; C, 62.30; H, 5.56; S, 12.89.

2-(1,2-Bis(4-methoxyphenylthio)ethyl)furan: Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 2/98) to get the product (85%) as oily liquid; ^1H NMR (200 MHz, CDCl_3): δ 7.3 (s, 1H), 7.1- 7.2 (m, 4H), 6.7-6.8 (m, 4H), 6.2-6.3 (m, 1H), 5.9 (d, J = 3.16 Hz, 1H), 4.13 (t, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.27 (d, J = 7.4 Hz, 2H). ESI-MS ($\text{M}^+ + \text{Na}$) = 372; Anal.Calc $\text{C}_{20}\text{H}_{20}\text{O}_3\text{S}_2$.; C, 64.49; H, 5.41; S, 17.22; Found; C, 64.41; H, 5.49; S, 17.30.

2-Hydroxy-1-(2-furyl) ethyl azide (3o).^{2a} Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 8/92) to obtain the product (80%) as oily liquid; ¹H NMR (200 MHz, CDCl₃): δ 7.38-7.43 (m, 1H), 6.39 (s, 2H), 4.63 (t, *J* = 6.20 Hz, 1H), 3.89 (d, *J* = 6.20 Hz, 1H), 2.47 (bs, -OH); ¹³C NMR (50 MHz, CDCl₃): δ 149.8, 143.0, 110.4, 108.6, 63.1, 60.6; ESI-MS (*M*⁺+Na) = 176; Anal. Calc for C₆H₇N₃O₂; C, 47.06; H, 4.61; N, 27.44; Found; 47.0; H, 4.67; N, 27.47.

2-Furan-2-yl-2-(2-hydroxynaphthyl)-ethanol (3r). Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 10/90) to obtain the product (80%) as oily liquid; ¹H NMR (500 MHz, CDCl₃): δ 7.75 (d, *J* = 8.14 Hz, 1H), 7.69 (d, *J* = 8.79, 1H), 7.51 (d, *J* = 8.38, 1H), 7.23-7.33 (m, 2H), 7.13 (d, *J* = 7.75, 1H), 6.21 (dd, *J* = 1.7, 3.1, 1H), 5.94 (d, *J* = 3.1 Hz), 4.99-5.01 (m, 1H), 4.82-4.86 (m, 1H), 4.69-4.72 (m, 1H). ¹³C NMR (50 MHz, CDCl₃): δ 158.2, 155.3, 142.1, 130.9, 130.5, 129.4, 129.0, 127.1, 123.1, 122.7, 118.6, 112.5, 110.6, 106.6, 77.0, 41.5, ESI-MS (*M*⁺+Na) = 277; Anal. Calc for C₁₆H₁₄O₃; C, 75.57; H, 5.55; Found; C, 75.51; H, 5.59.

Diacetylated derivative of (3r). Obtained after acetylation of **3r** with acetic anhydride and pyridine in quantitative yield. ¹H NMR (500 MHz, CDCl₃): δ 7.85 – 7.87 (m, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.46-7.48 (m, 2H), 7.26-7.31 (m, 2H), 7.22 (d, *J* = 8.9 Hz, 1H), 6.33-6.35 (m, 1H), 6.18 (d, *J* = 3.3 Hz, 1H), 5.34 (t, *J* = 7.3, 1H), 5.04 (dd, *J* = 10.9, 7.5 Hz, 1H), 4.68 (dd, *J* = 10.9, 3.8 Hz, 1H), 2.23 (s, 3H), 1.97 (s, 3H); ESI-MS (*M*⁺+Na) = 361; ¹³C NMR (50 MHz, CDCl₃): δ 171.5, 169.7, 154.1, 147.8, 141.9, 133.0, 132.7, 129.8,

129.4, 126.8, 125.8, 124.8, 124.2, 122.6, 110.7, 106.3, 64.9, 37.1, 21.4, 21.3. Anal. Calc for $C_{20}H_{18}O_5$; C, 70.99; H, 5.36; Found; C, 70.91; H, 5.28.

4-(1-Furan-2-yl-2-hydroxy-ethyl)-2-isopropyl-5-methyl-phenol (3s). Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 8/92) to obtain the product (83%) as oily liquid; 1H NMR (500 MHz, $CDCl_3$): δ 7.36 (m, 1H), 7.01 (s, 1H), 6.57 (s, 1H), 6.32 (dd, $J = 3.1, 1.9$ Hz, 1H), 6.07 (d, $J = 1$ Hz, 1H), 5.58 (bs, 1H), 4.42 (t, $J = 7.1$ Hz, 1H), 4.16 (dd, $J = 10.9, 7.6$ Hz, 1H), 3.99 (dd, $J = 10.9, 6.7$ Hz, 1H), 3.13-3.18 (m, 1H), 2.27 (d, $J = 6.90$ Hz, 3H), 1.21 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.6, 151.9, 141.7, 135.0, 132.4, 128.8, 125.4, 117.5, 110.2, 106.6, 65.1, 43.3, 27.0, 22.7, 22.6; ESI-MS ($M^+ + Na$) = 283; Anal. Calc for $C_{16}H_{20}O_3$; C, 73.82; H, 7.74; Found; C, 73.76; H, 7.79.

4-(1-Furan-2-yl-2-hydroxy-ethyl)-5-isopropyl-2-methyl-phenol (3t). Prepared by the general procedure and purified on silica gel (EtOAc /PE: 8/92) to obtain the product (79%) as oily liquid; 1H NMR (500 MHz, $CDCl_3$): δ 7.36 (m, 1H), 6.93 (s, 1H), 6.73 (s, 1H), 6.31 (dd, $J = 3.1, 1.9$ Hz, 1H), 4.52 (t, $J = 7.14$, 1H), 4.10-4.19 (m, 1H), 3.92-3.97 (m, 1H), 3.21-3.26 (m, 1H), 2.17 (s, 3H), 1.24 (d, $J = 6.8$, 3H), 1.19 (d, $J = 6.8$, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.9, 153.1, 146.5, 141.7, 130.1, 127.7, 121.3, 112.2, 110.2, 106.4,

65.6, 42.1, 28.4, 24.3, 15.5; ESI-MS ($M^+ + Na$) = 283; Anal. Calc for $C_{16}H_{20}O_3$; C, 73.82; H, 7.74; Found; C, 73.76; H, 7.78.

4-(1-Furan-2-yl-2-hydroxy-ethyl)-2-methyl-phenol (3u). Prepared by the general procedure and purified on silica gel (EtOAc /PE: 10/90) to obtain the product (82%) as oily liquid; 1H NMR (500 MHz, $CDCl_3$): δ 7.35 (m, 1H), 7.0 (s, 1H), 6.95 (dd, J = 1.8, 8.1 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.11 (dd, J = 2.1, 2.6 Hz, 1H), 4.09-4.13 (m, 1H), 3.94-3.98 (m, 1H), 2.20 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.3, 153.3, 141.8, 130.9, 130.9, 126.8, 124.4, 115.2, 110.3, 106.5, 65.6, 47.4, 15.9; ESI-MS ($M^+ + Na$) = 241; Anal. Calc for $C_{13}H_{14}O_3$; C, 71.54; H, 6.47; Found; C, 71.47; H, 6.54.

4-(1-Furan-2-yl-2-hydroxy-ethyl)-3-methyl-phenol (3v). Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 10/90) to obtain the product (78%) as oily liquid; 1H NMR (500 MHz, $CDCl_3$): δ 7.34 (s, 1H), 7.25 (d, J = 1.36 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 6.30 (t, J = 1.5 Hz, 1H), 6.06 (d, J = 2.4 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.4, 154.5, 141.8, 137.0, 129.4, 128.6, 117.6, 113.2, 110.3, 106.6, 65.0, 43.1, 14.2; ESI-MS ($M^+ + Na$) = 241; Anal. Calc for $C_{13}H_{14}O_3$; C, 71.54; H, 6.47; Found; C, 71.46; H, 6.53.

4-(1-Furan-2-yl-2-hydroxy-ethyl)-benzene-1,3-diol (3x). Prepared by the general procedure **1** and purified on silica gel (EtOAc /PE: 16/84) to obtain the product (81%) as oily liquid; ^1H NMR (500 MHz, CDCl_3): δ 7.30 (m, 1H), 6.81 (d, $J = 8.33$ Hz, 1H), 6.28 (m, 1H), 6.29 (dd, $J = 8.3, 2.3$ Hz, 1H), 6.33 (d, $J = 2.3$, 1H), 6.11 (d, $J = 3$ Hz, 1H), 4.47 (t, $J = 6.2$ Hz, 1H), 4.03 (d, $J = 6.2$, 2H), 2.1 (bs, 1H). ^{13}C NMR (50 MHz, CDCl_3): δ 160.6, 159.6, 159.3, 145.7, 134.3, 122.2, 114.5, 111.6, 110.9, 107.6, 68.9, 45.7; ESI-MS ($\text{M}^+ + \text{Na}$) = 243; Anal. Calc for $\text{C}_{12}\text{H}_{12}\text{O}_4$.; C, 65.45; H, 5.49; Found; C, 65.51; H, 5.53.