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**An Unusual Stereoselectivity in the Anomeric Substitution with  
Carbamates Promoted by HNTf<sub>2</sub>.**

authored by

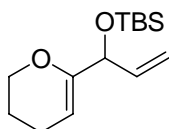
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### General Procedure for Metallation, Addition to Acrolein, and Protection of the Alcohol.

To a flame dried 25-mL RB-Flask were added 4,5-dihydropyran (5.0 mL, 52.5 mmol) and anhyd THF (5 mL). After which, *t*-BuLi (1.7 M in pentane, 30.6 mL, 52.3 mmol) was added dropwise at -78 °C, and the resulting bright yellow solution was allowed to warm to 0 °C slowly and stirred for an additional 1 h. The reaction mixture was cooled down to -78 °C before a solution of acrolein (3.24 mL, 43.5 mmol) was added via cannula. After 0.5 h, TLC analysis indicated the disappearance of starting material. The reaction was quenched with H<sub>2</sub>O (3 mL) dropwise at -78 °C, and was allowed to warm to rt before extraction with ether (3 x 30 mL). The combined organic layers were washed with sat aq NaCl (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude allylic alcohol (5.26 g, 37.5 mmol) was used for the next step without further purification.

To a 250-mL RB-Flask were added crude allylic alcohol (5.26 g, 37.5 mmol) and anhyd CH<sub>2</sub>Cl<sub>2</sub> (100 mL). After which, imidazole (5.62 g, 82.6 mmol) was added at 0 °C and the solution was stirred at 0 °C until all the solids were dissolved. To the reaction mixture was added TBSCl (6.78 g, 45.0 mmol) at 0 °C. The resulting reaction mixture was allowed to warm to rt and stirred for 3-4 h and monitored by TLC. On disappearance of the starting material, the reaction was quenched with H<sub>2</sub>O (10 mL) at 0 °C and then warm to rt before extraction with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined organic layers were washed with sat aq NaCl (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. Further purification was performed using silica gel flash column chromatography (gradient eluent: 40:1 to 10:1 hexane/EtOAc) to afford the pure TBS-protected dihydropyran derivative **7** (8.39 g, 79% over two steps) as colorless oil.

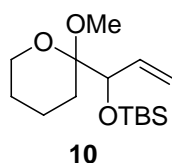


**7**

R<sub>f</sub> = 0.60 [10% EtOAc in hexane]; <sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>) δ 0.01 (s, 6H), 0.92 (s, 9H), 1.80 (tt, *J* = 5.4 and 6.3 Hz, 2H), 2.04 (dt, *J* = 3.9 and 5.7 Hz, 2H), 3.92-4.12(m, 2H), 4.43 (dd, *J* = 0.9 and 5.1 Hz, 2H), 4.82 (t, *J* = 3.9 Hz, 2H), 5.13 (ddd, = *J* = 1.5, 1.8 and 10.5 Hz, 1H), 5.32 (ddd, *J* = 1.5, 1.8 and 17.1 Hz, 1H), 5.92 (ddd, *J* = 5.1, 10.5 and 17.1 Hz, 1H); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ -4.8, -4.8, 18.5, 20.0, 22.5, 25.9, 66.4, 73.7, 96.0, 114.4, 138.9, 154.8; IR (thin film) cm<sup>-1</sup> 3080m, 3019m, 2955s, 2937s, 2859s, 1679s, 1255s, 1067s, 857s; mass spectrum (GC-MS) for C<sub>14</sub>H<sub>26</sub>O<sub>2</sub>Si: *m/e* (relative intensity) 253 (M+H)<sup>+</sup>, 197 (43), 169 (100).

### Procedure for Synthesis of Ketal Precursor **10**.

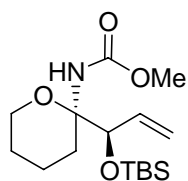
To a mixture of TBS-protected dihydropyran derivative **7** (280.0 mg, 1.1 mmol) and MeOH (0.13 mL, 3.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added pyridinium *p*-toluenesulfonate [PPTS] (27.6 mg, 0.11mmol). The reaction mixture was stirred at rt for 24 h. The solvent was removed *in vacuo* and the crude product was purified using silica gel flash column chromatography (gradient eluent: 20:1 to 10:1 hexanes/EtOAc) to afford cyclic ketal **10** (250.0 mg, 80%) with 1.6:1 diastereomeric ratio for *anti* : *syn*. The resulting diastereomeric mixtures were used for the anomeric substitution reaction.



$R_f = 0.58$  [15% EtOAc in hexane]; <sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) *anti* diastereomer:  $\delta$  0.06 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.33-1.60 (m, 4H), 1.63-1.81 (m, 2H), 3.28 (s, 3H), 3.54-3.69 (m, 2H), 4.23 (ddd,  $J = 1.6, 2.0$  and 4.4 Hz, 1H), 5.16 ddd,  $J = 1.6, 2.4$  and 10.8 Hz, 1H), 5.35 (ddd,  $J = 2.0, 2.4$  and 17.2 Hz, 1H), 5.90 (ddd,  $J = 4.4, 10.8$  and 17.2 Hz, 1H); *syn* diastereomer:  $\delta$  0.04 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.33-1.60 (m, 4H), 1.63-1.81 (m, 2H), 3.28 (s, 3H), 3.54-3.69 (m, 2H), 4.20 (ddd,  $J = 1.6, 2.0$  and 5.6 Hz, 1H), 5.17 (ddd,  $J = 1.6, 2.0$  and 10.4 Hz, 1H), 5.28 (ddd,  $J = 2.0, 2.4,$  and 17.2 Hz, 1H), 5.93 (ddd,  $J = 5.6, 10.4$  and 17.2 Hz, 1H); IR (thin film) cm<sup>-1</sup> 2932s, 2857s, 1252m, 1060s, 837s; mass spectrum (ESI-MS) for C<sub>15</sub>H<sub>30</sub>O<sub>3</sub>Si: m/e (relative intensity) 309.2 (M+Na)<sup>+</sup> (40), 255.1 (100), 123.1 (35).

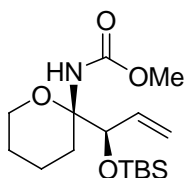
### General Procedure for Anomeric Substitution Using Carbamate.

To a flame dried 5-mL RB-Flask blanked with N<sub>2</sub> were added TBS protected dihydropyran derivative **7** (30.0 mg, 0.118 mmol) and methyl carbamate (9.0 mg, 0.118 mmol). After which, CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added via syringe. When all the solids dissolved, the resulting solution was cooled to -78 °C and the acid Tf<sub>2</sub>NH (0.1 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.18 mL, 0.118 mmol) was added via syringe. The reaction was stirred at -78 °C for 30 min before quenching with Et<sub>3</sub>N (0.1 mL) at the same temperature. The mixture was warmed to rt and filtered through Celite. After evaporation of the solvent under reduced pressure, the resulting crude residue was purified by silica gel flash column chromatography (gradient eluent: 6:1 to 2:1 hexanes/EtOAc) to afford cyclic aminals **8a** and **8s** with a diastereomeric ratio of 20 : 1 and a combined yield of 64% (25.0 mg). Isomers **8a** and **8s** can be cleanly separated via a second and more careful flash column chromatography. The pure *anti* isomer **8a** was found as a white solid and the pure *syn* isomer **8s** was a colorless liquid.



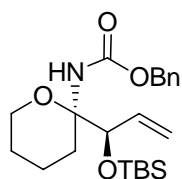
**8a**

**Cyclic Aminal 8a:**  $R_f = 0.30$  [15% EtOAc in hexane]; mp = 115-117 °C;  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.02 (s, 3H), 0.03 (s, 3H), 0.90 (s, 9H), 1.44-1.74 (m, 5H), 1.88-2.02 (m, 1H), 3.65 (s, 3H), 3.70 (ddd,  $J = 0.3, 4.2$  and  $7.8$  Hz, 2H), 4.56 (ddd,  $J = 1.2, 1.5$  and  $5.4$  Hz, 1H), 4.91 (s, 1H), 5.20 (ddd,  $J = 1.2, 2.1$  and  $10.5$  Hz, 1H), 5.30 (ddd,  $J = 1.5, 2.1$  and  $17.4$  Hz, 1H), 5.95 (ddd,  $J = 5.4, 10.5$  and  $17.4$  Hz, 1H);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  - 5.1, - 4.3, 18.4, 18.9, 25.2, 26.1, 27.4, 51.9, 61.6, 75.8, 86.9, 116.6, 137.3, 154.9; IR (thin film)  $\text{cm}^{-1}$  3458brs, 2938s, 2859m, 1698m, 1632s, 1245m, 1092s, 838.7s; mass spectrum (ESI-LRMS) for  $\text{C}_{16}\text{H}_{31}\text{NO}_4\text{Si}$ :  $m/e$  (relative intensity) 368.2 ( $\text{M}+\text{K}$ ) $^+$  (10), 352.3 ( $\text{M}+\text{Na}$ ) $^+$  (100), 255.2 (8).



**8s**

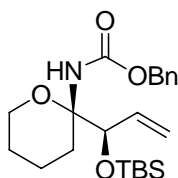
**Cyclic Aminal 8s:**  $R_f = 0.33$  [15% EtOAc in hexane];  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.04 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.50-1.89 (m, 5H), 2.00-2.10 (m, 1H), 3.65 (s, 3H), 3.73 (dq,  $J = 0.9$  and  $3.3$  Hz, 2H), 4.50 (ddd,  $J = 1.2, 1.5$  and  $6.3$  Hz, 1H), 4.85 (s, 1H), 5.20 (ddd,  $J = 1.2, 2.1$  and  $10.5$  Hz, 1H), 5.31 (ddd,  $J = 1.5, 2.1$  and  $17.4$  Hz, 1H), 5.89 (ddd,  $J = 6.3, 10.5$  and  $17.4$  Hz, 1H);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  - 4.6, - 4.4, 18.4, 25.2, 26.0, 27.2, 61.9, 76.5, 86.9, 113.3, 117.2, 136.9, 156.2; IR (thin film)  $\text{cm}^{-1}$  3458brs, 2938s, 2859m, 1698m, 1632s, 1245m, 1092s, 838.7s; mass spectrum (ESI-LRMS) for  $\text{C}_{16}\text{H}_{31}\text{NO}_4\text{Si}$ :  $m/e$  (relative intensity) 368.2 ( $\text{M}+\text{K}$ ) $^+$  (10), 352.3 ( $\text{M}+\text{Na}$ ) $^+$  (100), 255.2 (8).



**9a**

**Cyclic Aminal 9a:**  $R_f = 0.34$  [15% EtOAc in hexane]; mp = 58-60°C;  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.01 (s, 3H), 0.02 (s, 3H), 0.89 (s, 9H), 1.46-1.70 (m, 5H), 1.85-2.0 (m, 1H), 3.69 (ddd,  $J = 3.0, 12.0$  and  $19.5$  Hz, 1H), 3.69-3.74 (m, 1H), 4.61 (d,  $J = 5.0$  Hz, 2H), 5.04 (dd,  $J = 1.5$  and  $2.7$  Hz, 1H), 5.12 (d,  $J = 12$  Hz, 1H), 5.18 (ddd,  $J = 1.5, 2.0$  and  $11.0$  Hz, 1H), 5.29 (ddd,  $J = 1.5, 2.0$  and  $17.5$  Hz, 1H), 5.96 (ddd,  $J = 5.5, 11.0$  and  $17.5$  Hz, 1H), 7.28-7.40 (m, 5H);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  - 5.0, - 4.3, 18.3, 18.9, 25.2, 26.1, 27.4, 61.6, 66.5, 75.9, 87.0, 116.6, 128.3, 128.5, 128.7, 136.7, 137.3, 154.2; IR

(thin film)  $\text{cm}^{-1}$  3441brm, 3055m, 2954s, 2858s, 1734s, 1503s, 1264s, 1099s, 739s; mass spectrum (ESI-LRMS) for  $\text{C}_{22}\text{H}_{35}\text{NO}_4\text{Si}$ : m/e (relative intensity) 444.2 ( $\text{M}+\text{K}$ )<sup>+</sup> (45), 428.3 ( $\text{M}+\text{Na}$ )<sup>+</sup> (100), 255.2 (13); m/e calcd for  $\text{C}_{22}\text{H}_{35}\text{NNaO}_4\text{Si}^+$  [ $\text{M}+\text{Na}$ ]<sup>+</sup> 428.2233, found 428.2240.



**9s**

**Cyclic Aminal 9s:**  $R_f = 0.37$  [15% EtOAc in hexane];  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.03 (s, 3H), 0.08 (s, 3H), 0.94 (s, 9H), 1.38-1.86 (m, 5H), 1.80-2.10 (m, 1H), 3.69-3.74 (m, 2H), 4.51 (ddd,  $J = 1.5, 1.5$  and  $5.7$  Hz, 1H), 4.91 (s, 1H), 5.08 (s, 2H), 5.17 (ddd,  $J = 1.5, 1.8$  and  $11.0$  Hz, 1H), 5.29 (ddd,  $J = 1.5, 1.8$  and  $17.4$  Hz, 1H), 5.88 (ddd,  $J = 5.7, 11.0,$  and  $17.4$  Hz, 1H), 7.32-7.48 (m, 5H);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  - 4.5, - 4.4, 18.5, 19.0, 25.2, 26.1, 27.2, 61.9, 66.6, 77.1, 87.1, 117.3, 128.3, 128.7, 136.8, 136.9, 136.9, 154.2; IR (thin film)  $\text{cm}^{-1}$  3441brm, 3055m, 2954s, 2858s, 1734s, 1503s, 1264s, 1099s, 739s; mass spectrum (ESI-LRMS) for  $\text{C}_{22}\text{H}_{35}\text{NO}_4\text{Si}$ : m/e (relative intensity) 444.2 ( $\text{M}+\text{K}$ )<sup>+</sup> (43), 428.3 ( $\text{M}+\text{Na}$ )<sup>+</sup> (100), 255.2 (7); m/e calcd for  $\text{C}_{22}\text{H}_{35}\text{NNaO}_4\text{Si}^+$  [ $\text{M}+\text{Na}$ ]<sup>+</sup> 428.2233, found 428.2232.