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An Unusual Stereoselectivity in the Anomeric Substitution with Carbamates Promoted by HNTf₂.

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 \( H_2O \) (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 \( Na_2SO_4 \), 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 \( CH_2Cl_2 \) (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 \( H_2O \) (10 mL) at 0 °C and then warm to rt before extraction with \( CH_2Cl_2 \) (3 x 50 mL). The combined organic layers were washed with sat aq NaCl (50 mL), dried over \( Na_2SO_4 \), 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.

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\begin{align*}
\text{O} & \quad \text{OTBS} \\
\text{7} & \\
R_f = 0.60 \ [10\% \ EtOAc \ in \ hexane]; \ 1\text{H-NMR} \ (300\text{MHz, CDCl}_3) \delta \ 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); \ 13\text{C-NMR} \ (75 \text{MHz, CDCl}_3) \delta \ -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^{-1} \ 3080m, 3019m, 2955s, 2937s, 2859s, 1679s, 1548s; \ mass \ spectrum \ (GC-MS) \ for \ C_{14}H_{26}O_2Si: \ m/e \ (relative \ intensity) \ 253 \ (M+H)^+, 197 \ (43), 169 \ (100). 
\end{align*}
\]
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 CH₂Cl₂ (5 mL) were added pyridinium p-toluenesulfonate [PPTS] (27.6 mg, 0.11 mmol). 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.

IR (thin film) cm⁻¹ 2932s, 2857s, 1252m, 1060s, 837s; mass spectrum (ESI-MS) for C₁₅H₃₀O₃Si: m/e (relative intensity) 309.2 (M+Na)+ (40), 255.1 (100), 123.1 (35).

General Procedure for Anomeric Substitution Using Carbamate.

To a flame dried 5-mL RB-Flask blanked with N₂ were added TBS protected dihydropyran derivative 7 (30.0 mg, 0.118 mmol) and methyl carbamate (9.0 mg, 0.118 mmol). After which, CH₂Cl₂ (2 mL) was added via syringe. When all the solids dissolved, the resulting solution was cooled to –78 °C and the acid Tf₂NH (0.1 M in CH₂Cl₂, 1.18 mL, 0.118 mmol) was added via syringe. The reaction was stirred at –78 °C for 30 min before quenching with Et₃N (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 or 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.
**Cyclic Aminal 8a:** \( R_f = 0.30 \) [15% EtOAc in hexane]; \( mp = 115-117^\circ C \); \(^1\)H-NMR (300 MHz, 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); \(^{13}\)C-NMR (75 MHz, 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) cm\(^{-1}\) 3458brs, 2938s, 2859m, 1698m, 1632s, 1245m, 1092s, 838.7s; mass spectrum (ESI-LRMS) for C\(_{16}\)H\(_{31}\)NO\(_3\)Si: m/e (relative intensity) 368.2 (M+K\(^+\)) (10), 352.3 (M+Na\(^+\)) (100), 255.2 (8).

**Cyclic Aminal 8s:** \( R_f = 0.33 \) [15% EtOAc in hexane]; \(^1\)H-NMR (300 MHz, 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); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta \): -4.6, -4.4, 18.4, 25.2, 26.0, 27.2, 61.9, 75.6, 86.9, 113.3, 117.2, 136.9, 156.2; IR (thin film) cm\(^{-1}\) 3458brs, 2938s, 2859m, 1698m, 1632s, 1245m, 1092s, 838.7s; mass spectrum (ESI-LRMS) for C\(_{16}\)H\(_{31}\)NO\(_3\)Si: m/e (relative intensity) 368.2 (M+K\(^+\)) (10), 352.3 (M+Na\(^+\)) (100), 255.2 (8).

**Cyclic Aminal 9a:** \( R_f = 0.34 \) [15% EtOAc in hexane]; \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \( \delta = 0.01 \) (s, 3H), 0.02 (s, 3H), 0.09 (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); \(^{13}\)C-NMR (75 MHz, 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
Cyclic Aminal 9s: R_f = 0.37 [15% EtOAc in hexane]; ¹H-NMR (500 MHz, CDCl₃) δ 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); ¹³C-NMR (75 MHz, CDCl₃) δ - 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) cm⁻¹ 3441brm, 3055m, 2954s, 2858s, 1734s, 1503s, 1264s, 1099s, 739s; mass spectrum (ESI-LRMS) for C₂₂H₃₅NO₄Si: m/e (relative intensity) 444.2 (M+K)⁺ (45), 428.3 (M+Na)⁺ (100), 255.2 (13); m/e calcd for C₂₂H₃₅NNaO₄Si⁺ [M+Na]⁺ 428.2233, found 428.2240.

9s