Practical Synthesis of the C-1027 Aminosugar Moiety

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General methods. Otherwise indicated, all reactions were carried out in flame-dried round-bottom flasks under a positive pressure of argon or nitrogen. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm E. Merck silica gel (60F-254) plates. Kanto Chemical Co., Inc. Silica Gel 60N (particle size 0.10-0.21 mm) was used for column chromatography, and Kanto Chemical Co., Inc. Silica Gel 60N (particle size 0.040-0.050 mm) was used for flash column chromatography. All compounds given below bear the same formula numbers as used in the main text.

NMR spectra were recorded on Varian-400 (400MHz), instruments. FT-IR spectra were recorded on a Perkin Elmer spectrum BX FT-IP spectrometer. Optical rotations were determined by using a JASCO DIP-370 polarimeter. High resolution ESI-FT mass spectra were measured on a Thermo Fisher Scientific LTQ-Orbitrap Discovery. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus.

Lactam 4. According to the literature,1 L-glutamic acid (25.0g, 170 mmol) was converted to L-pyroglutamic acid ethyl ester as a crude brown oil. To a solution of L-pyroglutamic acid ethyl ester in THF (795 ml) was added MeLi in Et2O (1.60 M, 248 ml, 397 mmol) at -78 °C over 30 min. The mixture was gradually warmed. After 30 min, Et3N (134 ml) and TMSCl (121 ml) were added to the solution. After stirring for 4 h, the reaction was quenched by adding saturated aqueous NH4Cl at 0 °C. The mixture was diluted and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was purified by flash column chromatography (Hexane / EtOAc = 1 / 1) to afford (S)-5-(2-(trimethylsilyloxy)propan-2-yl)pyrrolidin-2-one as a colorless oil (23.3 g, 108 mmol, 68%).

To a solution of (S)-5-(2-(trimethylsilyloxy)propan-2-yl)pyrrolidin-2-one (23.3 g, 108 mmol) in CH3CN (515 ml) were added Et3N (30.1 ml, 216 mmol), DMAP (2.64 g, 21.6 mmol), and (Boc)2O (47.3 ml, 206 mmol). After stirring for 8 h, the reaction was quenched with saturated aqueous NH4Cl at 0 °C. The mixture was diluted and then extracted with EtOAc. The combined
organic extracts were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane/EtOAc = 4/1) to give 4 as a colorless oil (31.8 g, 101 mmol, 54%). 4: Colorless oil; [α]D²⁹ -66.7 (c 1.00, CH₂Cl₂); FT-IR (film) ν 2979, 1785, 1716, 1366, 1037, 842 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.09 (9H, s, Si-(CH₃)₃), 1.22 (3H, s, H6), 1.26 (3H, s, H6), 1.87 (1H, ddd, J = 12.8, 8.8, 1.2 Hz, H3), 2.00 (1H, dd, 12.8, 9.2 Hz, H3), 2.29 (1H, ddd, J = 17.6, 11.6, 1.2 Hz, H2), 2.67 (1H, ddd, J = 17.6, 11.6, 9.2 Hz, H2), 4.05 (1H, d, J = 8.8 Hz, H4); ¹³C NMR (100 MHz, CDCl₃) ppm 2.37 (Si-(CH₃)₃), 20.6 (C2), 27.2 (C6), 27.9 (C6), 27.9 (tBu), 32.9 (C3), 64.1 (C4), 75.4 (C5), 82.6 (tBuO), 150.8 (-OCO-N), 175.7 (C1); HRMS (ESI-FT), calcd for C₁₅H₂₉NNaO₄Si⁺ [M+Na⁺] 338.1758, found 338.1758

α,β-Unsaturated lactam 5. To a solution of 1,1,1,3,3,3-Hexamethyldisilazane (31.9 ml, 151 mmol) in THF (202 ml) was added n-BuLi (1.57 M solution in hexane, 96.5 ml, 151 mmol) dropwise at 0 °C over 5 min. After the resulting solution of LiN(TMS)₂ was stirred for 0.5 h at 0 °C, a solution of 4 (31.8 g, 101 mmol) in THF (202 ml) was added via cannula over a period of 10 min at −78 °C. After stirring for 0.5 h, the solution of PhSeCl (21.1 g, 111 mmol) in THF (101 ml) was added dropwise to the mixture. After stirring at -78 °C for 1.5 h, the reaction mixture was quenched by adding saturated aqueous NH₄Cl. The mixture was diluted and then extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄. After the solvent was removed under reduced pressure, a remaining red oil was dissolved in CH₂Cl₂ (505 ml). The solution was cooled to 0 °C and pyridine (24.5 ml) was added. 30% H₂O₂ (35.0 ml) was added slowly and the mixture was stirred for 1 h. The mixture was washed subsequently with H₂O (250 ml), saturated aqueous Na₂S₂O₃ and brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane / EtOAc = 5 / 1) to give α,β-unsaturated lactam 5 as a pale yellow oil (25.0 g, 79.8 mmol, 79%). 5: Pale yellow oil; [α]D²⁹ -109.6 (c 1.00, CH₂Cl₂); FT-IR (film) ν 2980, 1781, 1782, 1745, 1303, 1251, 1159, 1043, 843 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.12 (9H, s, Si-(CH₃)₃), 1.08 (3H, s, H6), 1.36 (3H, s, H6), 1.54 (9H, s, Boc), 4.71 (1H, dd, J = 1.6, 1.6 Hz, H4), 6.08 (1H, dd, J = 6.0, 1.6 Hz, H2), 7.24 (1H, dd, J = 6.0, 1.6 Hz, H3); ¹³C NMR (100 MHz, CDCl₃) ppm 0.00 (Si-(CH₃)₃), 23.1 (C6), 25.6 (tBu), 27.3 (C6), 67.6 (C4), 73.9 (C5), 80.6 (tBuO), 124.1 (C2), 147.9 (-OCO-N), 148.8 (C3), 168.1 (C1); HRMS (ESI-FT), calcd for C₁₅H₂₇NNaO₄Si⁺ [M+Na⁺] 336.1602, found 336.1602.

Diol 6. To a stirred solution of the α,β-unsaturated lactam 5 (25.0 g, 79.8 mmol) in water and acetone (H₂O:acetone=1:9, 26.6 ml) were added N-methylmorpholine N-oxide (4.8 M sol. in H₂O, 33.3 ml, 160 mmol) and then 0.1 M t-BuOH solution of OsO₄ (79.8 ml, 7.98 mmol). After stirring for 10 h at rt, the mixture was poured into saturated aqueous Na₂S₂O₃ (26.6 ml) at 0 °C. After the mixture was vigorously stirred for 30 min, the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous Na₂S₂O₃ and brine. The organic layer was dried over
Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Hexane / EtOAc = 2 / 1) to give diol 6 as a pale yellow oil (25.2 g, 72.6 mmol, 91%). 6: Pale yellow oil; [α]$_D^{29}$ -75.8 (c 1.00, CH$_2$Cl$_2$); FT-IR (film) ν 3441, 2980, 1781, 1727, 1369, 1296, 1253, 1161, 1032, 897, 842 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.11 (9H, s, Si-(CH$_3$)$_3$), 1.25 (3H, s, H6), 1.44 (3H, s, H6), 1.54 (9H, s, Boc), 2.83 (1H, br d, J = 2.0 Hz, C2-OH), 4.02 (1H, s, H4), 4.47 (1H, d, J = 5.2 Hz, H3), 4.60 (1H, dd, J = 5.2, 2.0 Hz, H2); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 2.3 (Si-(CH$_3$)$_3$), 27.7 (C6), 27.8 (tBu), 28.1 (C6), 68.7 (C2), 71.7 (C3), 71.8 (C4), 75.3 (C5), 83.3 (tBuO-), 150.8 (OCO-N), 175.1 (C1); HRMS (ESI-FT), calcd for C$_{15}$H$_{29}$NNaO$_6$Si$^+$ [M+Na$^+$] 370.1656, found 370.1656.

δ-Lactone 7: To a stirred solution of the diol 6 (25.2 g, 72.6 mmol) in THF (242 ml) was added a solution of LiOH·H$_2$O (9.14 g, 2.18 mmol) in water (200 ml) at 0 °C. After 2 h, the reaction mixture was diluted with water (121 ml) and acidified with 15% KHSO$_4$. NaCl was added to the solution until the undissolved NaCl was precipitated. The solution was extracted with EtOAc and concentrated *in vacuo*. Resulted yellow oil was dissolved in CH$_2$Cl$_2$ (242 ml). p-Toluenesulfonic acid (690 mg, 3.63 mmol) was added to the solution. After stirring for 6 h, the mixture was filtered and the filtrate was poured into saturated aqueous NaHCO$_3$ at 0 °C. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Hexane / EtOAc = 1 / 1) to give δ-lactone 7 as a colorless oil (16.4 g, 59.5 mmol, 82%). 7: colorless oil; [α]$_D^{24}$ +16.7 (c 1.00, CH$_2$Cl$_2$); FT-IR (film) ν 3441, 2980, 2935, 1718, 1501, 1367, 1251, 1166, 1119 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.46 (9H, s, Boc), 1.48 (3H, s, C6), 1.49 (3H, s, H6), 3.48 (1H, br s, OH), 3.98 (1H, br s, OH), 4.10 (1H, dd, J = 9.6, 2.0 Hz, H4), 4.25 (1H, s, H3), 4.26 (1H, s, H2), 5.43 (1H, d, J = 9.6 Hz, NH); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 25.5 (C6), 28.3 (tBu), 30.1 (C6), 53.6 (C4), 69.7 (C3), 70.7 (C2), 80.5 (tBuO), 87.7 (C5), 155.4 (OCO-N), 172.5 (C1); HRMS (ESI-FT), calcd for C$_{12}$H$_{21}$NNaO$_6$N+$^+$, [M+Na$^+$] 298.1261, found 298.1273.

N,N-Dimethylamine 8. To a solution of δ-lactone 7 (16.4 g, 59.5 mmol) in CH$_2$Cl$_2$ (476 ml) was added TFA (119 ml) dropwise at 0 °C. After stirring for 1.5 h at rt, toluene was added to the mixture and the volatile were azeotropically removed. The residue was dissolved in CH$_3$CN (288 ml) at 0 °C and 30% aq. formaldehyde solution (198 ml, 595 mmol), formic acid (4.49 ml, 119 mmol) and NaBH$_3$CN (7.48 g, 119 mmol) were added to the solution. The mixture was allowed to warm and stirred for 3 h at rt. The reaction was quenched with saturated aqueous NaHCO$_3$ at 0 °C. After the mixture was saturated by adding NaCl, the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Hexane / EtOAc = 2 / 1 then Hexane / EtOAc = 1 / 1 with 3% Et$_3$N) to give 8 as a colorless amorphous solid (9.55 g, 47.0 mmol, 79%). 8: colorless amorphous solid; [α]$_D^{29}$ +37.0 (c 1.00, CH$_2$Cl$_2$); FT-IR (film) ν 3410,
2939, 1713, 1277, 1113, 747 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.49 (3H, s, C6), 1.63 (3H, s, H6), 2.52 (6H, s, NMe\textsubscript{2}), 2.63 (1H, d, \(J = 2.0\) Hz, H4), 2.86 (1H, br s, OH), 3.70 (1H, br s, OH), 4.06 (1H, d, \(J = 2.8\) Hz, H2), 4.50 (1H, dd, \(J = 2.8, 2.0\) Hz, H3); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) ppm 25.3 (C6), 30.5 (C6), 45.2 (NMe\textsubscript{2}), 65.7 (C3), 67.4 (C4), 71.4 (C2), 90.4 (C5), 178.6 (C1); HRMS (ESI-FT), calcd for C\textsubscript{9}H\textsubscript{17}NNaO\textsubscript{4}\textsuperscript{+} [M+Na\textsuperscript{+}] 226.1050, found 226.1053.

Disiloxane 9. To a solution of 8 (9.55 g, 47.0 mmol) in DMF (235 ml) was added imidazole (12.8 g, 188 mmol). 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (30.1 ml, 94.0 mmol) was added to the solution. After stirring for 8 h, the reaction mixture was poured into saturated aqueous NaHCO\textsubscript{3} at 0 °C. The mixture was extracted with Et\textsubscript{2}O. The combined organic extracts were washed with H\textsubscript{2}O, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane / EtOAc = 2 / 1 to 5 / 1 with 3% Et\textsubscript{3}N) to give 9 as a colorless solid (11.7 g, 26.3 mmol, 56%). 9: Colorless needles; mp 162-164 °C (EtOAc/ hexane); [\(\alpha\)]\textsubscript{D}\textsuperscript{29} +8.6 (c 1.00, CHCl\textsubscript{3}); FT-IR (film): \(\nu\) 2944, 1742, 1458, 1275, 1179, 1114, 1041, 1014, 884, 801, 695 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 0.94-1.15 (28H, m, TIDPS), 1.45 (3H, s, H6), 1.61 (3H, s, H6), 2.53 (6H, s, NMe\textsubscript{2}), 2.71 (1H, d, \(J = 1.6\) Hz, H4), 4.43 (1H, d, \(J = 2.4\) Hz, H2), 4.82 (1H, dd, \(J = 2.4, 1.6\) Hz, H3); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) ppm 12.8, 13.3, 14.0, 14.3, 16.8, 16.9, 17.2, 17.2, 17.3, 17.6, 17.6, 17.9, 25.7, 24.6 (C6), 31.4 (C6), 45.0 (NMe\textsubscript{2}), 68.7 (C4), 71.8 (C3), 76.7 (C2), 87.4 (C5), 169.3 (C1); HRMS (ESI): calcd for C\textsubscript{21}H\textsubscript{43}NNaOSi\textsubscript{2}\textsuperscript{+} [M+Na\textsuperscript{+}] 468.2572, found 468.2575.

Aminosugar moiety 2. To a solution of 9 (11.7 g, 26.3 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (263 ml) was added DIBAL 1.0 M sol. in Hexane at -78 °C. After stirring for 1 h at -78 °C, the reaction mixture was poured into saturated aqueous Rochelle salt and the mixture was vigorously stirred for 2 h at rt. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane / EtOAc = 3 / 1 with 3% Et\textsubscript{3}N) to give 2 as a colorless oil (10.6 g, 2.37 mmol, 90%). 2: Colorless oil; [\(\alpha\)]\textsubscript{D}\textsuperscript{27} -19.0 (c 1.00, CHCl\textsubscript{3}); FT-IR (film): \(\nu\) 3386, 2867, 1465, 1386, 1364, 1248, 1137 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.03-1.13 (28H, m, TIPDS), 1.30 (3H, s, H6), 1.60 (3H, s, H6), 2.46 (1H, d, \(J = 2.4\) Hz, H4), 2.55 (6H, s, NMe\textsubscript{2}), 2.76 (1H, br s, OH), 3.49 (1H, dd, \(J = 8.0, 3.2\) Hz, H2), 4.73 (1H, dd, \(J = 3.2, 2.4\) Hz, H3), 5.01 (1H, br d, \(J = 8.0\) Hz, H1); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) ppm 13.0, 13.1, 13.3, 13.6, 14.4, 17.1, 17.1, 17.4, 17.4, 17.5, 17.5, 17.6, 23.7 (C6), 30.8 (C6), 44.5 (NMe\textsubscript{2}), 69.4 (C4), 74.8 (C3), 78.1 (C2), 78.4 (C5), 90.5 (C1); HRMS (ESI): calcd for C\textsubscript{21}H\textsubscript{46}NO\textsubscript{5}Si\textsubscript{2}\textsuperscript{+} [M+H\textsuperscript{+}] 448.2909, found 448.2910.

References
File: emp
Pulse Sequence: s2pul
Solvent: ddmso
Addition temperature: 25.0
Operator: welting
Venus-400 "CHIRAL"

Relax. delay 1.500 sec
Pulse 44.0 degrees
Acq. Time 2.500 sec
Width 6410.3 Hz
10 replications
ORDER: H1, 205.675675 MHz
DATA PROCESSING
Line broadening: 0.2 Hz
FT size 4096
Total time 1 min, 39 sec
Pulse sequence: 3Jpp1
Solvent: ddCl3
Ambient temperature: 298 K
Operator: ms16
Wavemeter: UVG-900 "400 MHz"

Relax. delay 0.700 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 3450.8 Hz
256 repetitions
COVARES 1H: 100.499979 MHz
DECOUPL 1H, 399.870704 MHz
Power 41 dB
continuously on
NAVS-14 modulated
DATA PROCESSING
List broadcasting 1.0 Hz
FT size 65536
Total time 8 min, 34 sec
ONO

\((i-Pr)_2Si-O-Si(i-Pr)_2\)

9

\[\text{ppm}\]
\[
\text{ON OH Si}(i-\text{Pr})_2(i-\text{Pr})_2\text{Si O}
\]