

Supporting Information for  
Synthesis of a Tripeptide Derivative Containing the Gln-Arg Hydroxyethylene  
Dipeptide Isostere

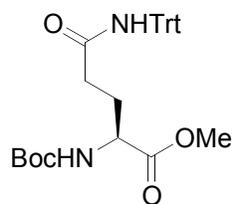
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**General:**

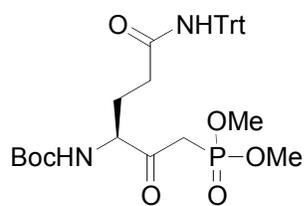
All reactions were carried out under an atmosphere of argon using flame-dried glassware. Tetrahydrofuran (THF) was distilled from sodium metal-benzophenone ketyl. Dichloromethane ( $\text{CH}_2\text{Cl}_2$ ), DMPU, diisopropylamine, and toluene were distilled from calcium hydride. All other solvents and reagents were used without further purification. N,N'-bis-Boc-1-guanylpiperazine was purchased from Advanced ChemTech. N-(9-Fluorenylmethoxycarbonyloxy)succinimide was purchased from Chem-Impex. All other reagents were purchased from Aldrich.

Flash column chromatography was performed using Merck grade 60 silica gel (230-400 mesh).  $^1\text{H}$  NMR spectra were taken on a Bruker AC 300 or a Bruker AC 250 spectrometer in  $\text{CDCl}_3$  at ambient temperature unless otherwise noted. Chemical shifts were reported in ppm ( $\delta$  units) downfield from tetramethylsilane. Mass spectra were taken on a Micromass AutoSpec magnetic sector mass spectrometer using 3-nitrobenzyl alcohol as the matrix.

**2-tert-Butoxycarbonylamino-4-(trityl-carbamoyl)-butyric acid methyl ester (7).**

To a solution of BocGln(Trt)-OH (10.13g, 20.76 mmol) in toluene:methanol (7:1, 300 mL) was added a solution of TMSCHN<sub>2</sub> (12.5 mL, 2.0 mol/L). The mixture was allowed to stir at rt until the evolution of N<sub>2</sub> ceased (ca. 6 h).

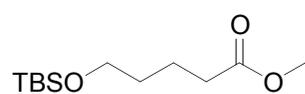
The solvents were removed *in vacuo* to provide BocGln(Trt)-Ome (**7**) in quantitative yield. m.p. 153-154°C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ : 7.12 - 7.40 (m, 16 H), 5.28 (d, J = 7.7, 1 H), 4.29 (td, J = 8.1, 3.3, 1 H), 3.70 (s, 3 H), 2.27 - 2.46 (m, 2H), 2.07 - 2.22 (m, 1 H), 1.77 - 1.95 (m, 1 H), 1.43 (s, 9 H); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ : 172.74, 170.88, 155.84, 144.60, 128.67, 127.83, 126.88, 80.06, 70.54, 52.97, 52.35, 33.55, 29.02, 28.22; EI calculated for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>: 502.2468. Found 502.2468.

**[3-tert-Butoxycarbonylamino-2-oxo-5-(trityl-carbamoyl)-pentyl]-phosphonic acid dimethyl ester (4).**

To a solution of dimethylmethylphosphonate (12.94 ml, 119.4 mmol) in THF (120 mL) at -78°C was added nBuLi in hexane (49.34 mL, 119.4 mmol, 2.42 mol/L) in a dropwise manner. The solution was allowed to stir at this temperature for 45 min at which point a solution of ester **7** (2.481 g, 4.973 mmol) in THF (100 mL) was added. The reaction was allowed to stir at -78°C for 1 h, the cooling bath was warmed to -30 °C, the mixture stirred for an additional hour and then quenched by dropwise addition of glacial acetic acid (0.56 ml). The mixture was partitioned between ethyl acetate and saturated aqueous NH<sub>4</sub>Cl, the layers were separated and the aqueous was extracted twice more with ethyl acetate. The organics were combined, washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub>,

and concentrated to ca. 5% volume. Petroleum ether was added in a smooth stream with efficient stirring to provide a white solid which was stirred overnight at room temperature and then isolated by filtration to provide 10.26 g (87%) of phosphonate **4**. m.p. 183-184 °C;  $[\alpha_D]$   $-21.89$  (c 1.0, MeOH); TLC  $R_f = 0.22$  (EtOAc);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  : 7.18 - 7.32 (m, 16 H), 5.56 (d,  $J = 7.3$  Hz, 1 H), 4.31 (m, 1 H), 3.74 (d,  $J = 11.4$ , 3 H), 3.72 (d,  $J = 11.4$ , 3 H), 3.24 (dd,  $J = 22.3, 14.5$ , 1 H), 3.05 (dd,  $J = 21.9, 14.4$ , 1 H), 2.28 - 2.46 (m, 2 H), 2.16-2.26 (m, 1 H), 1.76 - 1.86 (m, 1 H), 1.43 (s, 9 H);  $^{13}\text{C NMR}$  (75.4 MHz)  $\delta$  : 201.13, 171.24, 155.96, 144.84, 128.89, 128.04, 127.09, 80.36, 70.72, 60.10, 53.26, 37.86 (d,  $J = 128$  Hz), 33.24, 28.47, 27.16; ESI calculated for  $[\text{C}_{32}\text{H}_{39}\text{N}_2\text{O}_7\text{PNa}]^+$ : 617.2393. Found 617.2386.

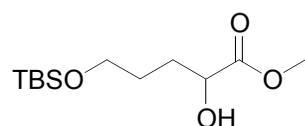
**5-(tert-Butyl-dimethyl-silanyloxy)-pentanoic acid methyl ester (9).**



A solution of  $\delta$ -valerolactone (16.19 g, 161.7 mmol) containing concentrated  $\text{H}_2\text{SO}_4$  (11 drops) was heated at reflux in anhydrous MeOH (350 mL) for 5 h. {Huckstep, 1982 #257} The mixture cooled to rt and then in an ice-salt bath,  $\text{NaHCO}_3$  (1.85 g) was added, the mixture was allowed to stir for 10 min and was then placed in the freezer for 2 h. The cold mixture was filtered and the solvent was removed *in vacuo*, without heating, and then under high vacuum. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (250 mL), cooled to 0 °C, and TBSCl (28.5 g, 189 mmol) and imidazole (29 g, 426 mmol) were added. The reaction mixture was allowed to stir while warming to rt over 14 h. The mixture was diluted with  $\text{H}_2\text{O}$  and the layers were separated. The organic layer was washed with water, twice with saturated aqueous  $\text{CuSO}_4$ , brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was purified by flash column chromatography (10:1 petroleum ether : diethyl ether) to yield 30.41 g (76%) of title compound **9**. b.p. 87 – 90 °C @ 1.0 mmHg.  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  : 3.67

(s, 3 H), 3.62 (t, J = 6.2, 2 H), 2.34 (t, J = 7.4 Hz, 2H), 1.63 – 1.72 (m, 2 H), 1.51 – 1.57 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 6 H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 174.07, 62.61, 51.38, 33.77, 32.13, 25.90, 21.42, 18.28, -5.38; ESI calculated for  $[\text{C}_{12}\text{H}_{26}\text{O}_3\text{SiNa}]^+$ : 269.1549. Found 269.1556.

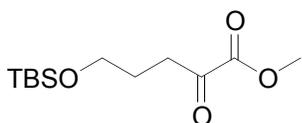
**5-(tert-Butyl-dimethyl-silanyloxy)-2-hydroxy-pentanoic acid methyl ester (10).**



To a solution of KHMDS (6.39 g, 20.3 mmol) in THF (250 mL) at  $-78^\circ\text{C}$  was added a solution of ester **9** (5.00 g, 20.3 mmol) in THF (50 mL) in a dropwise manner via cannula. The solution was stirred for 20 min at this temperature and Davis oxaziridine (6.45 g, 24.7 mmol) in THF (50 ml) was added in a dropwise manner *via* cannula. After 20 min the reaction was quenched with sat  $\text{NH}_4\text{Cl}$  (50 mL), the cooling bath was removed, and the mixture was allowed warm to room temperature. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate, washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was suspended in chloroform (100 ml) and a white precipitate was removed by filtration and discarded. To the mother liquor was added  $\text{tBuNH}_2$  (3 ml) and the mixture was allowed to stand 5 min. The solvent was removed *in vacuo*, the residue was suspended in a 5 to 1 mixture of hexanes and ethyl acetate (30 ml), and the solution was refrigerated overnight. The resulting precipitate was removed by filtration and discarded, the mother liquor was concentrated, and the residue purified by flash column chromatography (80:20 hexane : ethyl acetate) to afford 3.79 g (71%) of the title compound as a light yellow liquid. TLC  $R_f$  = 0.43 (80:20 Hexane:EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.24 (dt, J = 6.3, 5.2, 1 H), 3.78 (s, 3 H), 3.66 (t, J = 5.7, 2 H), 3.30 (d, J = 5.4 Hz, 1H), 1.91 (dddd, J = 14.0, 9.1, 6.6, 4.3, 1

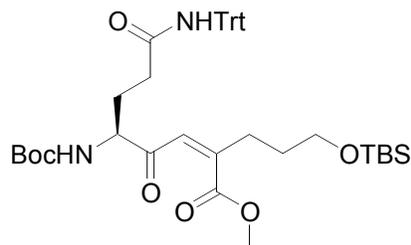
H), 1.56 – 1.82 (m, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H);  $^{13}\text{C}$  NMR (62.9 MHz)  $\delta$  : 175.36, 70.34, 62.73, 52.22, 31.30, 28.12, 25.78, 18.19, -5.49.

**5-(tert-Butyl-dimethyl-silyloxy)-2-oxo-pentanoic acid methyl ester (11).**



To a solution of Dess-Martin periodinane (8.67 g, 20.44 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at rt was added tBuOH (1.54 g, 20.8 mmol) and the solution was stirred for 20 min. A solution of alcohol **10** (4.123 g, 15.71 mmol) in  $\text{CH}_2\text{Cl}_2$  (17 mL) was added dropwise via cannula. The reaction mixture was allowed to stir for 15 min and was then poured into an efficiently stirring aqueous solution of  $\text{NaHCO}_3$  (200 mL, 1 mol/L) containing  $\text{Na}_2\text{S}_2\text{O}_3$  (36.3 g, 146.3 mmol). After stirring for 30 min the layers were separated and the aqueous phase was extracted twice more with dichloromethane. The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$ , water, brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by flash column chromatography (8:1 hexane : diethyl ether) to afford 2.65 g (65%) of title compound **11** as a liquid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  : 3.87 (s, 3 H), 3.65 (t,  $J = 6.0$  Hz, 2 H), 2.92 (t,  $J = 7.0$  Hz, 2 H), 1.88 (tt,  $J = 7.0, 6.0$ , 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.4 MHz)  $\delta$  : 194.01, 161.40, 61.76, 52.76, 36.01, 26.50, 25.87, 18.26, -5.41.

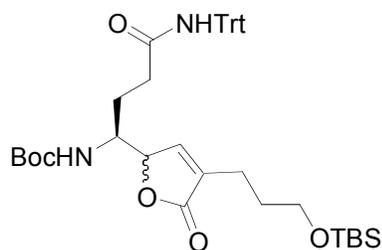
**5-tert-Butoxycarbonylamino-2-[3-(tert-butyl-dimethyl-silyloxy)-propyl]-4-oxo-7-(trityl-carbamoyl)-hept-2-enoic acid methyl ester (12).**



To a suspension of NaH (1.65 g, 41.2 mmol, 65% emulsion) in THF (96 ml) at 0 °C was added a 0 °C solution of ketophosphonate **4** (7.91 g, 13.3 mmol) in THF (260 mL). The

mixture was stirred at 0 °C for 1 h, cooled to -78 °C, and a solution of ketoester **11** (4.50 g, 17.3 mmol) in THF (26 mL) was added. Stirring was continued at -78 °C for 0.5 h at which point the reaction was transferred to a -30 °C bath and kept at this temperature for 14 h. The reaction was quenched over an hour-long period by the slow addition of a solution of glacial acetic acid (12.53 ml) in THF (25 ml), and then warmed to room temperature and concentrated. The residue was partitioned between ethyl acetate and water and the layers were separated. The aqueous phase was extracted twice more with ethyl acetate and the organics were combined, washed with water, saturated aqueous NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to an oil that solidified upon standing. Purification by column chromatography (3:1 hexane : ethyl acetate) afforded title compound **12** as a colorless foam (7.79 g, 80%). TLC R<sub>f</sub> = 0.25 (3:1 Hexane:EtOAc); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ : 7.63 (s, 1 H), 7.19 – 7.32 (m, 15 H), 6.03 (s, 1 H), 5.46 (d, J = 7.3, 1 H), 4.29 (t, J = 7.6, 1 H), 3.77 (s, 3 H), 3.62 (t, J = 6.1, 2 H), 2.36 – 2.52 (m, 3 H), 2.31 (dt, J = 14.2, 5.4, 1 H), 2.14-2.23 (m, 1 H), 1.67 (pent, J = 6.4, 2 H), 1.52 – 1.60 (m, 1 H), 1.41 (s, 9 H), 0.90 (s, 9 H), 0.05 (s, 6 H); <sup>13</sup>C NMR (75.4 MHz) δ : 196.6, 171.2, 169.2, 156.0, 149.6, 144.7, 128.6, 127.6, 126.6, 124.5, 79.7, 70.3, 61.8, 58.3, 52.0, 33.2, 30.9, 30.2, 28.5, 28.1, 25.8, 18.1, -5.5; ESI calculated for [C<sub>42</sub>H<sub>56</sub>N<sub>2</sub>O<sub>7</sub>SiNa]<sup>+</sup>: 751.3755. Found 751.3779.

**[1-{4-[3-(tert-Butyl-dimethyl-silyloxy)-propyl]-5-oxo-2,5-dihydro-furan-2-yl}-3-(trityl-carbamoyl)-propyl]-carbamic acid tert-butyl ester (13a, 13b).**

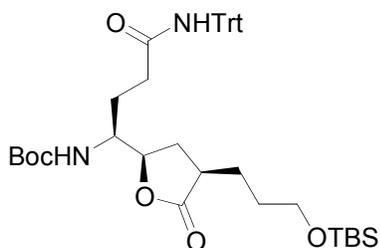


**Procedure 1.** To a solution of  $\alpha,\beta$ -unsaturated ester **12** (1.051 g, 1.415 mmol) in MeOH (50 mL) which was cooled to -30°C by

means of a dry ice acetone bath, was added NaBH<sub>4</sub> (54.3 mg, 1.453 mmol). The solution was allowed to stir for 30 min during which time the temperature rose to -20°C. The solvent was removed on the rotary evaporator and the residue was purified by column chromatography (1% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give the title compounds as a colorless foam (730.5 mg, 74%), as an inseparable mixture of diastereomers in a 2:3 ratio (by <sup>1</sup>H NMR) favoring the 4S isomer **13b**. The mixture of diastereomers was carried on without further purification. TLC R<sub>f</sub> = 0.19 (7:3 Hexane:EtOAc); EI calculated for [C<sub>41</sub>H<sub>54</sub>N<sub>2</sub>O<sub>6</sub>Si]<sup>+</sup> 698.3751. Found 698.3732.

**Procedure 2.** To a -30°C solution of α,β-unsaturated ester **12** (5.33 g, 7.32 mmol) in MeOH (275 mL) was added NaBH<sub>4</sub> (285 mg, 7.54 mmol). After 30 min at this temperature the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl, and the solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate and water, the layers were separated and the aqueous was extracted twice more with ethyl acetate. The combined organics were washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the title compound as an inseparable mixture of diastereomers (5.16 g, 100%), in a 2:1 ratio (by <sup>1</sup>H NMR) favoring the 4R isomer **13a**. The colorless foam was carried on without further purification.

**[1-{4-[3-(tert-Butyl-dimethyl-silyloxy)-propyl]-5-oxo-tetrahydro-furan-2-yl}-3-(trityl-carbamoyl)-propyl]-carbamic acid tert-butyl ester (**15a**, **15b**).**



To a stirred solution of the diastereomeric mixture of olefins **13a** and **13b** (5.032 g, 7.20 mmol) formed by reduction procedure 2, in ethanol (250 ml) under a nitrogen atmosphere was added Pt(IV) oxide (0.20 g). The reaction vessel was evacuated and purged with nitrogen three times, and then

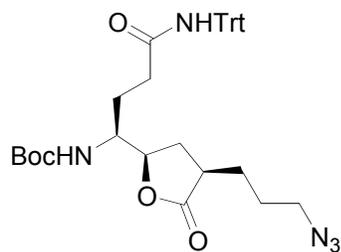
placed under an atmosphere of hydrogen using a balloon until TLC showed complete consumption of starting material (ca. 3 h). At this time the hydrogen gas was evacuated, the catalyst was removed by filtration, and the solvent was removed *in vacuo*. Separation of the resulting diastereomers proved difficult but was achieved by several rounds of careful flash column chromatography (1:1:0.5 petroleum ether : diethyl ether : dichloromethane) to provide 3.14 g (62%) of [(1S)-1-{(4R)-4-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-5-oxo-tetrahydrofuran-(2R)-2-yl}-3-(trityl-carbamoyl)-propyl]-carbamic acid tert-butyl ester **15a** along with 1.52 g (30%) of [(1S)-1-{(4S)-4-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-5-oxo-tetrahydrofuran-(2S)-2-yl}-3-(trityl-carbamoyl)-propyl]-carbamic acid tert-butyl ester **15b**.

**2R-lactone 15a:** TLC  $R_f = 0.20$  (1:1:0.5 Petroleum Ether:Et<sub>2</sub>O:CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  : 7.18 – 7.30 (m, 15 H), 7.07 (s, 1 H), 4.99 (d, J = 9.2, 1 H), 4.18 - 4.25 (m, 1 H), 3.69 – 3.59 (m, 1 H), 3.62 (t, J = 6.2, 2 H), 2.49 – 2.60 (m, 1 H), 2.25 (t, J = 7.0, 2 H) 2.25 – 2.38 (m, 1 H), 1.85 – 2.02 (m, 2 H), 1.52 – 1.69 (m, 4 H), 1.41 – 1.51 (m, 1 H), 1.43 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  : 178.35, 171.64, 156.20, 144.78, 128.82, 128.00, 127.07 80.24, 79.91, 70.67, 62.83, 53.04, 40.49, 33.70, 31.86, 30.52, 28.47, 26.96, 26.36, 26.09, 18.43, -5.19; ESI calculated for [C<sub>41</sub>H<sub>56</sub>N<sub>2</sub>O<sub>6</sub>SiNa]<sup>+</sup>: 723.3805. Found 723.3818.

**2S-lactone 15b:** TLC  $R_f = 0.26$  (1:1:0.5 Petroleum Ether:Et<sub>2</sub>O:CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR for the S isomer (500 MHz, CDCl<sub>3</sub>)  $\delta$  : 7.16 – 7.29 (m, 16 H), 4.79 (d, J = 9.8, 1 H), 4.25 (br t, J = 6.6, 1 H), 3.68 (t, J = 10.1, 1 H), 3.62 (t, J = 6.2 Hz, 2H), 2.48-2.62 (m, 1 H), 2.30 (t, J = 6.5 Hz, 2 H), 2.19 – 2.34 (m, 1 H), 1.80 – 1.96 (m, 2 H), 1.66 – 1.79 (m, 1 H), 1.52-1.65 (m, 3 H), 1.42 (s, 10 H), 0.89 (s, 9 H), 0.05 (s, 6 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) $\delta$  : 178.46, 171.26, 156.48, 144.75, 128.74, 127.83, 126.87, 79.91, 79.82, 70.48, 62.74, 53

.53, 51.79, 40.25, 33.65, 31.29, 30.25, 29.26, 28.35, 26.87, 25.98, 18.31, -5.30; ESI calculated for  $[C_{41}H_{56}N_2O_6SiNa]^+$ : 723.3805. Found 723.3826.

**[(1S)-1-[(4R)-4-(3-Azido-propyl)-5-oxo-tetrahydro-furan-(2R)-2-yl]-3-(trityl-carbamoyl)-propyl]-carbamic acid tert-butyl ester (17).**

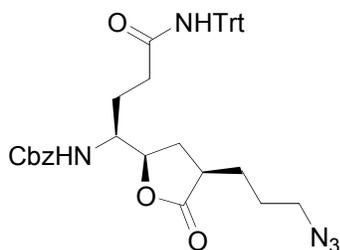


Step 1: To a solution of 2R-lactone **15a** (3.21 g, 4.57 mmol) in methanol (25 ml) was added 25 ml of a mixture composed of acetonitrile (70%), water (30%) and TFA (0.1%). The reaction was stirred at room temperature for 1 h and concentrated to remove most of the organics. The remainder was partitioned between ethyl acetate and saturated aqueous  $NaHCO_3$ , the layers were separated and the aqueous was extracted again with ethyl acetate. The organics were combined, washed with water and brine, dried over  $Na_2SO_4$  and concentrated to provide a foam.

Step 2: The foam from step 1 was dissolved in anhydrous toluene (30 ml) and cooled to 0 °C. Diisopropyl ethylamine (1.04 ml, 5.95 mmol) was added and a waxy solid formed. Methane sulfonyl chloride (0.459 ml, 5.95 mmol) was added and the hazy solution was warmed to room temperature. After a period of 0.5 h an additional 0.5 ml of methane sulfonyl chloride and 0.4 ml of diisopropyl ethylamine were added and the reaction was stirred for 10 min more. To this mixture was added an aqueous mixture (15 ml) of sodium azide (2.38 g, 36.6 mmol) and tetrabutylammonium bromide (0.147 g, 0.458 mmol) and the reaction was warmed to reflux for 3 h and then cooled to room temperature. The mixture was diluted with diethyl ether and the layers were separated. The aqueous was extracted twice more with diethyl ether and the organics were combined and washed with water, brine, dried over  $MgSO_4$ , and concentrated. The residue was

purified by flash column chromatography (85:15, CH<sub>2</sub>Cl<sub>2</sub>:Et<sub>2</sub>O) to provide 2.61 g (93% over 2 steps) of azide **17** as a colorless foam. TLC R<sub>f</sub> = 0.20 (85:15 CH<sub>2</sub>Cl<sub>2</sub>:Et<sub>2</sub>O); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ : 7.19 – 7.32 (m, 15 H), 6.99 (s, 1 H), 4.91 (d, J = 8.8, 1 H), 4.24 – 4.30 (m, 1 H), 3.64 – 3.72 (m, 1 H), 3.32 (t, J = 6.8, 2 H), 2.52 – 2.61 (m, 1 H), 2.39 (t, J = 6.8, 2 H), 2.30 – 2.41 (m, 1 H), 1.98 – 2.05 (m, 1 H), 1.88 – 1.96 (m, 1 H), 1.56 – 1.76 (m, 4 H), 1.45 – 1.55 (m, 1 H), 1.44 (s, 9 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ : 177.84, 171.74, 156.04, 144.45, 128.48, 127.52, 126.58, 79.67, 79.19, 70.14, 52.84, 50.75, 39.69, 33.18, 31.22, 28.12, 27.10, 26.76, 26.27, 25.53; ESI calculated for [C<sub>35</sub>H<sub>41</sub>N<sub>5</sub>O<sub>5</sub>Na]<sup>+</sup>: 634.3005. Found 634.3002.

**[1-[4-(3-Azido-propyl)-5-oxo-tetrahydro-furan-2-yl]-3-(trityl-carbamoyl)-propyl]-carbamic acid benzyl ester (18).**



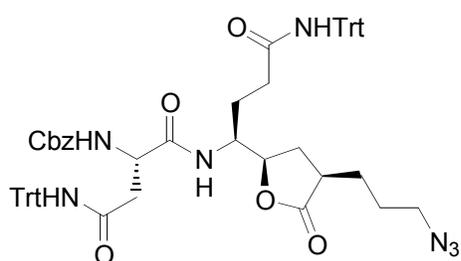
Step 1: To a rt solution of lactone **17** (0.50 g, 0.817 mmol) in anhydrous dichloromethane (10 mL) containing 2,6-lutidine (0.190 mL, 1.63 mmol) was added TBSOTf (0.282 mL, 1.23 mmol). After 1 h the reaction mixture was quenched with saturated aqueous

NH<sub>4</sub>Cl and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated.

Step 2: The residue from Step 1 was dissolved in THF (25 ml), benzyl bromide (0.292 ml, 2.45 mmol) was added and the mixture cooled to 0 °C. To this was added a 1 M solution of tetrabutyl ammonium fluoride in THF (0.98 ml, 0.98 mmol) and after 2 h the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted three times with diethyl ether. The organics were combined and washed with saturated aqueous CuSO<sub>4</sub>, twice with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub>

and concentrated. The residue was purified by column chromatography (60:40 hexane : ethyl acetate) to afford 0.379 g (72%) of the title compound **18** as a colorless foam.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  : 7.12 – 7.33 (m, 20H), 6.79 (s, 1H), 5.28 (d,  $J = 9.0$  Hz, 1H), 5.12 (d,  $J = 12.5$  Hz, 1H), 5.04 (d,  $J = 12.5$  Hz, 1H), 4.21 (m, 1H), 3.70 (m, 1H), 3.29 (t,  $J = 6.5$  Hz, 2H), 2.45 – 2.55 (m, 1H), 2.38 (t,  $J = 6.5$  Hz, 2H), 2.23 – 2.31 (m, 1H), 1.73 – 2.03 (m, 2H), 1.44 – 1.69 (m, 5H);  $^{13}\text{C}$  NMR (62.9 MHz)  $\delta$  : 177.5, 171.5, 156.5, 144.37, 136.2, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 126.9, 79.76, 70.43, 66.78, 53.62, 50.94, 39.92, 33.20, 31.41, 27.23, 26.47, 25.86.

**[1-[1-[4-(3-Azido-propyl)-5-oxo-tetrahydro-furan-2-yl]-3-(trityl-carbamoyl)-propylcarbamoyl]-2-(trityl-carbamoyl)-ethyl]-carbamic acid benzyl ester (20).**



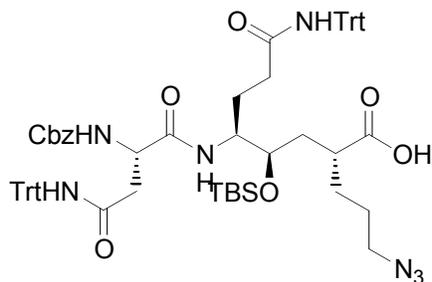
Step 1: To a rt solution of Boc-lactone **17** (1.33 g, 2.24 mmol) in anhydrous dichloromethane (30 mL) containing 2,6-lutidine (0.522 mL, 4.48 mmol) was added TBSOTf (0.772 mL, 3.36 mmol). After 1 h the reaction mixture was

cooled to 0 °C and a 1 M solution of tetrabutyl ammonium fluoride in THF (4.7 ml, 4.7 mmol) was carefully added. The reaction was warmed to room temperature, and after 1 h quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated to an oil.

Step 2: The residue from Step 1 was dissolved in DMF (25 ml) and added to a 0 °C mixture of Cbz-Asn(Trt)-OH (1.37 g, 2.69 mmol), HOBt (0.535 g, 3.96 mmol), and EDCI (0.566 g, 2.96 mmol) in DMF (25 ml). The reaction was allowed to warm to room temperature over 14 h, at which point the solvents were removed *in vacuo*. The residue was partitioned between ethyl acetate and aqueous 10% citric acid, the layers were separated and the aqueous extracted twice

more with ethyl acetate. The organics were combined and washed with water, saturated aqueous NaHCO<sub>3</sub>, and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by flash column chromatography (80:18:2 dichloromethane: diethyl ether: methanol) to provide 2.11 g (94%) of title compound **20**. TLC R<sub>f</sub> = 0.34 (80:18:2 CH<sub>2</sub>Cl<sub>2</sub>:Et<sub>2</sub>O:MeOH); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ : 7.10-7.32 (m, 35 H), 7.00 (br s, 1 H), 6.95 (d, J = 8.3, 1 H), 6.76 (s, 1 H), 6.13 (s, 1 H), 5.04 (d, J = 12.6, 1 H), 4.96 (d, J = 12.3, 1 H), 4.38-4.44 (br m, 1 H), 3.98-4.06 (br m, 1 H), 3.86-3.94 (br m, 1 H), 3.213 (t, J = 6.8, 2 H), 2.97 (d, J = 13.7, 1 H), 2.59 (dd, J = 15.6, 4.87, 1 H), 2.35-2.44 (br m, 1 H), 1.99-2.20 (m, 3 H), 1.75-1.96 (m, 3 H), 1.35-1.66 (m, 4 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ : 178.03, 171.88, 171.55, 170.12, 156.42, 144.74, 144.45, 136.19, 128.84, 128.83, 128.66, 128.34, 128.18, 128.08, 127.97, 127.21, 127.02, 79.87, 70.90, 70.58, 67.28, 52.07, 51.95, 51.21, 40.14, 38.64, 32.96, 31.62, 27.42, 26.71, 25.89; ESI calculated for [C<sub>61</sub>H<sub>59</sub>N<sub>7</sub>O<sub>7</sub>Na]<sup>+</sup>: 1024.4374. Found 1024.4370.

**(2R)-2-(3-Azido-propyl)-(5S)-5-[(2S)-2-benzyloxycarbonylamino-3-(trityl-carbamoyl)-propionylamino]-(4R)-4-(tert-butyl-dimethyl-silyloxy)-7-(trityl-carbamoyl)-heptanoic acid (21).**

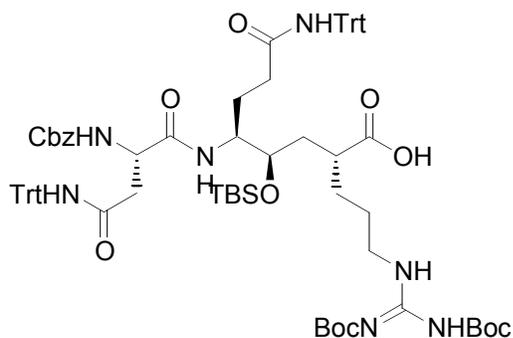


Step 1: To a rt solution of lactone **20** (2.06 g, 2.05 mmol) in dioxane (60 ml) was added a 1 M aqueous solution of LiOH (12.31 ml, 12.3 mmol). After 20 min the reaction was partitioned between a 0 °C mixture of ethyl acetate and ethanol (8:2) and saturated aqueous NaHCO<sub>3</sub> and brine (1:1). The layers were separated and the aqueous was extracted twice more with fresh 0 °C organic. The organic layers were combined,

washed with 0 °C brine, dried over a 1:1 mixture of MgSO<sub>4</sub> and K<sub>2</sub>CO<sub>3</sub>, and concentrated *in vacuo* without heating, and then thoroughly dried under high vacuum.

Step 2: To a 0 °C mixture of the residue from Step 1 and 2,6-lutidine (1.91 ml, 16.4 mmol) in anhydrous dichloromethane (50 ml) was added TBSOTf (1.88 ml, 8.2 mmol). After 1 h methanol (20 ml) was added, the reaction was warmed to room temperature and the solvents were removed *in vacuo*. The residue was dissolved in methanol (50 ml), K<sub>2</sub>CO<sub>3</sub> (0.34 g) was added and the mixture was stirred overnight. The reaction was concentrated, the residue partitioned between ethyl acetate and aqueous 10% citric acid, the layers separated, and the aqueous extracted twice more with ethyl acetate. The organics were combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by flash column chromatography (dichloromethane followed by 88 : 18 : 2 : 0.1 dichloromethane : diethyl ether : methanol : acetic acid) to provide 1.85 g (80 % over two steps) of the title compound **21** as a foam. TLC R<sub>f</sub> = 0.22 (95:5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ : 7.09-7.36 (m, 36 H), 6.74 (d, J = 10.2, 1 H), 6.71 (s, 1 H), 6.17 (d, J = 9.0, 1 H), 5.06 (d, J = 12.2, 1 H), 4.98 (d, J = 12.2, 1 H), 4.57 (dt, 9.0, 4.4, 1 H), 4.09 (br t, J = 10.5, 1 H), 3.64-3.75 (br s, 1 H), 3.35 (dd, J = 16.1, 4.4, 1 H), 2.95-3.06 (m, 2 H), 2.64 (dd, J = 16.1, 4.2, 1 H), 2.31-2.39 (br m, 1 H), 2.01-2.14 (m, 2 H), 1.84-1.94 (m, 1 H), 1.70-1.78 (m, 1 H), 1.25-1.63 (m, 6 H), 0.82 (s, 9 H), 0.02 (s, 3 H), -0.04 (s, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ : 178.16, 172.10, 171.38, 170.57, 156.33, 144.72, 144.30, 135.82, 128.70, 128.63, 128.45, 128.18, 128.09, 127.81, 127.70, 126.92, 126.62, 72.21, 70.65, 70.22, 67.13, 52.14, 51.77, 50.94, 49.94, 40.50, 37.87, 36.84, 33.06, 30.02, 26.26, 25.73, 23.67, 17.80, -4.34, -4.88; ESI calculated for [C<sub>67</sub>H<sub>74</sub>N<sub>7</sub>O<sub>8</sub>Si]<sup>+</sup>: 1132.5368. Found 1132.5374.

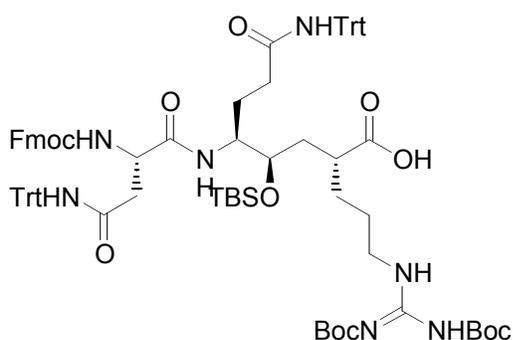
**(5S)-5-[(2S)-2-benzyloxycarbonylamino-3-(trityl-carbamoyl)-propionylamino]-(4R)-4-(tert-butyl-dimethyl-silanyloxy)-(2R)-2-(3-N,N'-bis-*t*-Boc-guanidino-propyl)-7-(tritylcarbamoyl)-heptanoic acid (**22**).**



To a solution of azide **21** (0.826 g, 0.728 mmol), N,N'-bis-Boc-1-guanylpyrazole (0.452 g, 1.68 mmol), and aqueous 1M LiOH (1.46 ml) in a mixture of THF (16.5 ml) and water (1.5 ml) was added triphenylphosphine (0.573 g, 2.18 mmol). Gas evolution commenced, and the reaction was allowed to stir at room temperature for 48 h. The THF was removed *in vacuo*, the residue was partitioned between aqueous 10% citric acid and ethyl acetate, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate, the organics were combined, washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. In order to separate the triphenylphosphine oxide, the residue was dissolved in 20 ml of 9:1 mixture of diethyl ether and dichloromethane and filtered through alumina (35 g) in a sintered glass funnel. The flask was rinsed twice with 10 ml portions of the organic and these were also passed through the alumina. The alumina was rinsed with 300 ml of a 93 : 7 mixture of diethyl ether and methanol. The mother liquor was discarded and the desired product was flushed from the alumina with methanol (ca. 600 ml). The methanol was removed *in vacuo* and the residue was purified by flash column chromatography (95 : 5 dichloromethane : methanol) to provide 0.548 g (56%) of the title compound **22** as a foam. TLC R<sub>f</sub> = 0.20 (95:5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ : 11.49 (s, 1 H), 8.20 (t, J = 6.5, 1 H), 7.10-7.35 (m, 36 H), 6.84 (br s, 1 H), 6.77 (s, 1 H), 6.25 (s, 1 H), 5.04 (d, J = 15.0, 1 H), 4.97 (d, J = 15.0, 1 H), 4.54 (dt, J = 11.0, 6.0, 1 H), 4.06 (br t, J = 11.5, 1 H), 3.62-3.75 (br s, 1 H), 3.12 – 3.38 (m, 3 H), 2.63 (d, J = 18.0, 1 H), 2.34

(br s, 1 H), 1.99-2.16 (m, 2 H), 1.81-1.94 (m, 1 H), 1.68-1.79 (m, 1 H), 1.30-1.60 (m, 24 H), 0.82 (s, 9 H), 0.02 (s, 3 H), -0.05 (s, 3 H);  $^{13}\text{C}$  NMR (100 MHz)  $\delta$  : 178.84, 172.29, 171.50, 170.79, 163.67, 156.48, 156.13, 153.22, 144.90, 144.54, 136.02, 128.87, 128.62, 128.29, 128.00, 127.86, 127.09, 126.80, 83.01, 79.19, 72.40, 70.82, 70.38, 67.31, 52.28, 52.00, 41.40, 40.77, 38.00, 37.04, 33.33, 30.62, 28.44, 28.21, 26.80, 25.90, 23.81, 17.96, -4.12, -4.77; ESI calculated for  $[\text{C}_{78}\text{H}_{94}\text{N}_7\text{O}_{12}\text{Si}]$ : 1348.6730. Found 1348.6714.

**(4R)-4-(tert-butyl-dimethyl-silyloxy)-(5S)-5-[(2S)-2-(9,9a-dihydro-4aH-flouren-9-ylmethoxycarbonylamino)-3-(trityl-carbamoyl)-propionylamino]-(2R)-2-(3-N,N'-bis-t-Boc-guanidino-propyl)-7-(tritylcarbamoyl)-heptanoic acid (1).**



Step 1: To a stirred solution of guanidine **22** (0.548 g, 0.405 mmol) in MeOH (20 ml) under a nitrogen atmosphere was added 20% Pd(OH)<sub>2</sub> on carbon (0.06 g). The reaction vessel was evacuated and purged with nitrogen three times, and then placed under an atmosphere of hydrogen using a balloon until TLC showed complete consumption of starting material (ca. 24 h). At this time the hydrogen gas was evacuated, the catalyst was removed by filtration, and the solvent was removed in vacuo.

Step 2: The residue from Step 1 was dissolved in dioxane (5 ml), aqueous 10% sodium carbonate (3.2 ml) was added, and the mixture was cooled to 0 °C. To this was added N-(9-Fluorenylmethoxycarbonyloxy)succinimide (0.21 g, 0.061 mmol) and the reaction was allowed to warm to room temperature overnight. The reaction mixture was partitioned between aqueous 10% citric acid and ethyl acetate and the layers were separated. The aqueous layer was extracted

twice with ethyl acetate, the organics were combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The product was purified by flash column chromatography (98 / 2 dichloromethane / methanol) to yield 0.181 g (31% over two steps) of title compound **1** as a foam: TLC R<sub>f</sub> = 0.18 (95:5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ : 11.48 (s, 1 H), 8.18 (br t, J = 6.5, 1 H), 7.74 (d, J = 7.3, 1 H), 7.70 (d, J = 7.3, 1 H), 7.53 (d, J = 7.3, 1 H), 7.48 (d, J = 7.3, 1 H), 7.35-7.42 (m, J = 2 H), 7.23-7.29 (m, 2 H), 7.11-7.22 (m, 31 H), 6.80 (br s, 2 H), 6.22 (br s, 1 H), 4.56 (br s, 1 H), 4.40 (br s, 1 H), 4.04-4.22 (br m, 3 H), 3.70 (br s, 1 H), 3.33 (d, J = 11.2, 1 H), 3.23 (br d, J = 4.9, 2 H), 5.21 (br d, J = 14.2, 1 H), 2.12 (br s, 2 H), 1.90 (dt, J = 12.7, 7.8, 1 H), 1.76 (td, J = 10.2, 3.9, 1 H), 1.20-1.63 (m, 24 H), 0.80 (s, 9 H), 0.02 (s, 3 H), -0.05 (s, 3 H); <sup>13</sup>C NMR (62.9 MHz) δ : 178.24, 172.14, 171.32, 170.89, 163.69, 156.55, 156.12, 153.21, 144.93, 144.52, 143.89, 143.68, 141.38, 141.32, 128.89, 128.81, 128.04, 127.87, 127.29, 127.22, 127.16, 126.78, 125.41, 125.22, 120.12, 120.02, 82.99, 79.18, 72.48, 70.88, 70.40, 67.58, 52.34, 51.87, 47.11, 41.01, 40.72, 38.10, 37.10, 33.41, 30.57, 29.80, 28.45, 28.21, 26.74, 25.91, 23.88, 17.96, -4.12, -4.70; ESI calculated for [C<sub>85</sub>H<sub>98</sub>N<sub>7</sub>O<sub>12</sub>Si]<sup>+</sup>: 1436.7043. Found 1436.7062.

### Crystallographic Experimental Section for *ent*-15a.

#### Data Collection

A colorless crystal with approximate dimensions 0.5 x 0.4 x 0.4 mm<sup>3</sup> was selected under oil under ambient conditions and attached to the tip of a glass capillary. The crystal was mounted in a stream of cold nitrogen at 100(2) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer with Mo K<sub>α</sub> (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.9 cm.

The initial cell constants were obtained from three series of  $\omega$  scans at different starting angles. Each series consisted of 20 frames collected at intervals of  $0.3^\circ$  in a  $6^\circ$  range about  $\omega$  with the exposure time of 10 seconds per frame. A total of 184 reflections was obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of 16953 strong reflections from the actual data collection.

The data were collected by using the hemisphere data collection routine. The reciprocal space was surveyed to the extent of a full sphere to a resolution of  $0.80 \text{ \AA}$ . A total of 30516 data were harvested by collecting three sets of frames with  $0.3^\circ$  scans in  $\omega$  with an exposure time 30 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1]

### Structure Solution and Refinement

The systematic absences in the diffraction data were consistent for the space groups  $Pna2_1$  and  $Pnma$ . The  $E$ -statistics strongly suggested the non-centrosymmetric space group  $Pna2_1$  that yielded chemically reasonable and computationally stable results of refinement [2]. A successful solution by the direct methods provided most non-hydrogen atoms from the  $E$ -map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

The final least-squares refinement of 572 parameters against 7950 data resulted in residuals  $R$  (based on  $F^2$  for  $I \geq 2\sigma$ ) and  $wR$  (based on  $F^2$  for all data) of 0.0412 and 0.1083, respectively. The final difference Fourier map was featureless.

The ORTEP diagram is drawn with 30% probability ellipsoids.

### References

- [1] Blessing, R.H. *Acta Cryst.* **1995**, *A51*, 33-38.

[2] All software and sources of the scattering factors are contained in the SHELXTL (version 5.1) program library (G. Sheldrick, Bruker Analytical X-Ray Systems, Madison, WI).

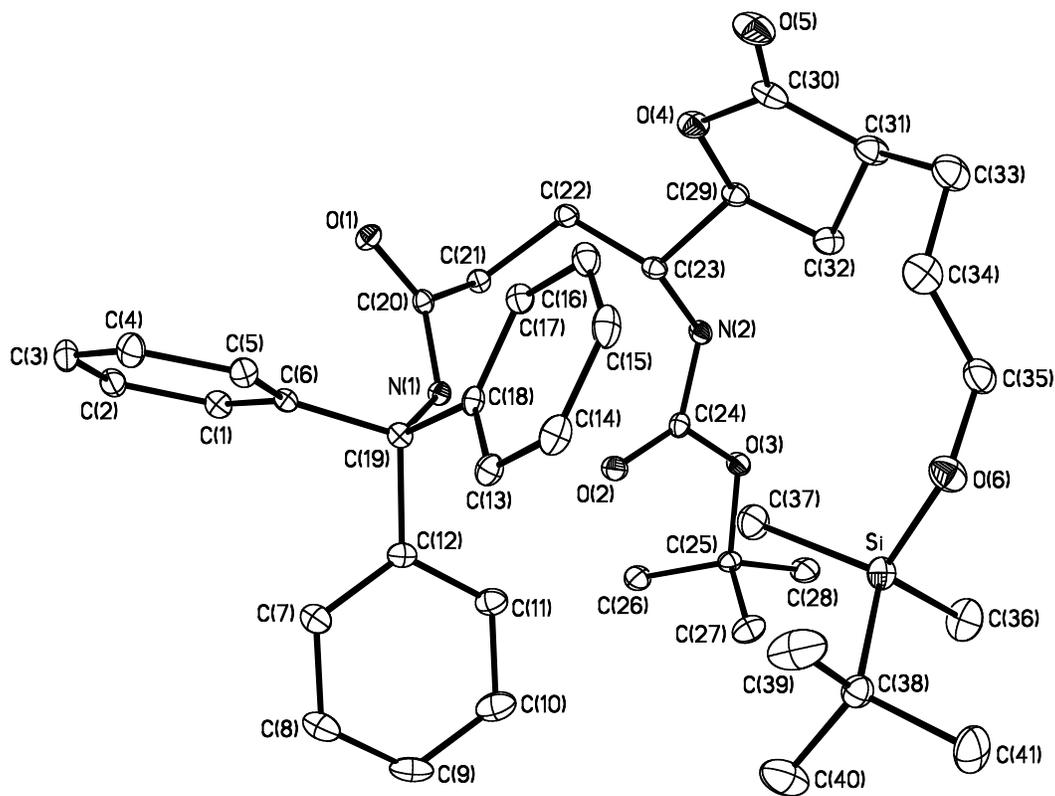


Table 1. Crystal data and structure refinement for rich08.

Identification code	rich08	
Empirical formula	C <sub>41</sub> H <sub>56</sub> N <sub>2</sub> O <sub>6</sub> Si	
Formula weight	700.97	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2 <sub>1</sub>	
Unit cell dimensions	a = 14.3530(13) Å	α = 90°.
	b = 15.3106(13) Å	β = 90°.
	c = 17.6827(15) Å	γ = 90°.
Volume	3885.8(6) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.198 Mg/m <sup>3</sup>	
Absorption coefficient	0.108 mm <sup>-1</sup>	
F(000)	1512	
Crystal size	0.50 x 0.40 x 0.40 mm <sup>3</sup>	
Theta range for data collection	1.76 to 26.40°.	
Index ranges	-17<=h<=17, -19<=k<=19, -22<=l<=22	
Reflections collected	30516	
Independent reflections	7950 [R(int) = 0.0441]	
Completeness to theta = 26.40°	99.9 %	
Absorption correction	Empirical with SADABS	
Max. and min. transmission	0.9580 and 0.9479	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	7950 / 1 / 459	
Goodness-of-fit on F <sup>2</sup>	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0412, wR2 = 0.1071	
R indices (all data)	R1 = 0.0428, wR2 = 0.1083	
Absolute structure parameter	0.05(10)	
Largest diff. peak and hole	0.428 and -0.217 e.Å <sup>-3</sup>	

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for rich08.  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U^{ij}$  tensor.

	x	y	z	$U(\text{eq})$
Si	1885(1)	10648(1)	4915(1)	23(1)
N(1)	5370(1)	9332(1)	2854(1)	16(1)
N(2)	2880(1)	7990(1)	2752(1)	19(1)
O(1)	6383(1)	8207(1)	3030(1)	20(1)
O(2)	3368(1)	9352(1)	2413(1)	22(1)
O(3)	1946(1)	8816(1)	2079(1)	20(1)
O(4)	4032(1)	7013(1)	4407(1)	25(1)
O(5)	4176(1)	6785(1)	5647(1)	36(1)
O(6)	1843(1)	10013(1)	5669(1)	32(1)
C(1)	7299(1)	9878(1)	2575(1)	20(1)
C(2)	8264(1)	9923(1)	2502(1)	23(1)
C(3)	8816(1)	10065(1)	3136(1)	24(1)
C(4)	8403(1)	10156(1)	3839(1)	24(1)
C(5)	7437(1)	10102(1)	3911(1)	20(1)
C(6)	6875(1)	9966(1)	3281(1)	17(1)
C(7)	6089(2)	11585(1)	2894(1)	31(1)
C(8)	5761(2)	12385(2)	2631(2)	44(1)
C(9)	4826(2)	12515(1)	2504(2)	41(1)
C(10)	4204(2)	11842(1)	2648(1)	35(1)
C(11)	4527(1)	11046(1)	2912(1)	25(1)
C(12)	5475(1)	10901(1)	3031(1)	19(1)
C(13)	5403(1)	10618(1)	4645(1)	21(1)
C(14)	5187(1)	10516(1)	5408(1)	26(1)
C(15)	5044(1)	9690(2)	5710(1)	28(1)
C(16)	5132(1)	8962(1)	5244(1)	25(1)
C(17)	5360(1)	9065(1)	4481(1)	21(1)
C(18)	5491(1)	9894(1)	4174(1)	17(1)
C(19)	5810(1)	10008(1)	3343(1)	16(1)
C(20)	5665(1)	8503(1)	2757(1)	16(1)
C(21)	5018(1)	7921(1)	2291(1)	17(1)
C(22)	4460(1)	7315(1)	2816(1)	19(1)
C(23)	3670(1)	7779(1)	3247(1)	17(1)
C(24)	2784(1)	8768(1)	2415(1)	17(1)
C(25)	1668(1)	9601(1)	1656(1)	18(1)
C(26)	2314(2)	9755(1)	988(1)	28(1)
C(27)	1619(2)	10390(1)	2175(1)	30(1)
C(28)	693(1)	9364(1)	1380(1)	30(1)
C(29)	3277(1)	7208(1)	3878(1)	19(1)
C(30)	3688(2)	6969(1)	5124(1)	27(1)
C(31)	2647(2)	7155(1)	5121(1)	29(1)
C(32)	2533(1)	7640(1)	4365(1)	23(1)
C(33)	2279(2)	7579(2)	5842(1)	36(1)
C(34)	2458(2)	8562(2)	5915(1)	36(1)
C(35)	1635(2)	9102(1)	5625(1)	32(1)
C(36)	738(2)	10634(2)	4423(1)	37(1)
C(37)	2785(2)	10248(2)	4239(1)	32(1)
C(38)	2164(1)	11781(1)	5265(1)	25(1)
C(39)	3023(2)	11773(2)	5772(2)	53(1)
C(40)	2332(2)	12386(2)	4582(2)	47(1)
C(41)	1358(2)	12146(2)	5726(2)	45(1)

Table 3. Bond lengths [Å] and angles [°] for rich08.

Si-O(6)	1.6518(16)	C(10)-C(11)	1.384(3)
Si-C(36)	1.861(2)	C(11)-C(12)	1.394(3)
Si-C(37)	1.863(2)	C(12)-C(19)	1.551(2)
Si-C(38)	1.886(2)	C(13)-C(18)	1.393(3)
N(1)-C(20)	1.349(2)	C(13)-C(14)	1.393(3)
N(1)-C(19)	1.489(2)	C(14)-C(15)	1.388(3)
N(2)-C(24)	1.339(2)	C(15)-C(16)	1.392(3)
N(2)-C(23)	1.468(2)	C(16)-C(17)	1.398(3)
O(1)-C(20)	1.225(2)	C(17)-C(18)	1.392(3)
O(2)-C(24)	1.227(2)	C(18)-C(19)	1.549(2)
O(3)-C(24)	1.344(2)	C(20)-C(21)	1.528(2)
O(3)-C(25)	1.471(2)	C(21)-C(22)	1.538(2)
O(4)-C(30)	1.362(2)	C(22)-C(23)	1.539(3)
O(4)-C(29)	1.462(2)	C(23)-C(29)	1.526(2)
O(5)-C(30)	1.194(2)	C(25)-C(27)	1.518(3)
O(6)-C(35)	1.428(3)	C(25)-C(26)	1.520(3)
C(1)-C(2)	1.393(3)	C(25)-C(28)	1.526(3)
C(1)-C(6)	1.397(3)	C(29)-C(32)	1.523(3)
C(2)-C(3)	1.390(3)	C(30)-C(31)	1.521(3)
C(3)-C(4)	1.385(3)	C(31)-C(33)	1.526(3)
C(4)-C(5)	1.394(3)	C(31)-C(32)	1.537(3)
C(5)-C(6)	1.390(3)	C(33)-C(34)	1.532(3)
C(6)-C(19)	1.533(2)	C(34)-C(35)	1.530(3)
C(7)-C(12)	1.390(3)	C(38)-C(41)	1.521(3)
C(7)-C(8)	1.391(3)	C(38)-C(39)	1.524(3)
C(8)-C(9)	1.375(4)	C(38)-C(40)	1.540(3)
C(9)-C(10)	1.387(4)		
O(6)-Si-C(36)	109.77(10)	C(15)-C(14)-C(13)	120.41(18)
O(6)-Si-C(37)	110.47(10)	C(14)-C(15)-C(16)	119.27(18)
C(36)-Si-C(37)	108.10(11)	C(15)-C(16)-C(17)	120.16(19)
O(6)-Si-C(38)	106.49(9)	C(18)-C(17)-C(16)	120.73(18)
C(36)-Si-C(38)	110.56(10)	C(17)-C(18)-C(13)	118.64(17)
C(37)-Si-C(38)	111.46(10)	C(17)-C(18)-C(19)	120.84(15)
C(20)-N(1)-C(19)	126.49(14)	C(13)-C(18)-C(19)	120.33(16)
C(24)-N(2)-C(23)	122.72(14)	N(1)-C(19)-C(6)	110.68(14)
C(24)-O(3)-C(25)	120.87(13)	N(1)-C(19)-C(18)	110.25(14)
C(30)-O(4)-C(29)	109.69(15)	C(6)-C(19)-C(18)	110.92(14)
C(35)-O(6)-Si	122.52(14)	N(1)-C(19)-C(12)	105.96(13)
C(2)-C(1)-C(6)	120.75(17)	C(6)-C(19)-C(12)	108.72(14)
C(3)-C(2)-C(1)	120.08(18)	C(18)-C(19)-C(12)	110.19(14)
C(4)-C(3)-C(2)	119.66(18)	O(1)-C(20)-N(1)	124.22(16)
C(3)-C(4)-C(5)	120.10(18)	O(1)-C(20)-C(21)	120.54(15)
C(6)-C(5)-C(4)	120.90(17)	N(1)-C(20)-C(21)	115.22(15)
C(5)-C(6)-C(1)	118.50(16)	C(20)-C(21)-C(22)	110.01(14)
C(5)-C(6)-C(19)	121.06(16)	C(21)-C(22)-C(23)	113.76(14)
C(1)-C(6)-C(19)	120.12(16)	N(2)-C(23)-C(29)	106.02(14)
C(12)-C(7)-C(8)	120.5(2)	N(2)-C(23)-C(22)	112.06(14)
C(9)-C(8)-C(7)	120.8(2)	C(29)-C(23)-C(22)	111.70(14)
C(8)-C(9)-C(10)	119.4(2)	O(2)-C(24)-N(2)	125.39(16)
C(11)-C(10)-C(9)	120.0(2)	O(2)-C(24)-O(3)	124.79(16)
C(10)-C(11)-C(12)	121.17(19)	N(2)-C(24)-O(3)	109.83(14)
C(7)-C(12)-C(11)	118.18(17)	O(3)-C(25)-C(27)	110.82(15)
C(7)-C(12)-C(19)	121.96(17)	O(3)-C(25)-C(26)	110.86(14)
C(11)-C(12)-C(19)	119.80(16)	C(27)-C(25)-C(26)	112.05(16)
C(18)-C(13)-C(14)	120.78(18)	O(3)-C(25)-C(28)	102.51(14)

C(27)-C(25)-C(28)	109.87(16)	C(29)-C(32)-C(31)	101.95(15)
C(26)-C(25)-C(28)	110.34(16)	C(31)-C(33)-C(34)	115.50(19)
O(4)-C(29)-C(32)	104.29(14)	C(35)-C(34)-C(33)	111.9(2)
O(4)-C(29)-C(23)	108.11(14)	O(6)-C(35)-C(34)	110.34(18)
C(32)-C(29)-C(23)	115.11(15)	C(41)-C(38)-C(39)	107.6(2)
O(5)-C(30)-O(4)	121.3(2)	C(41)-C(38)-C(40)	108.6(2)
O(5)-C(30)-C(31)	128.61(19)	C(39)-C(38)-C(40)	109.8(2)
O(4)-C(30)-C(31)	110.06(16)	C(41)-C(38)-Si	110.69(15)
C(30)-C(31)-C(33)	114.60(18)	C(39)-C(38)-Si	110.90(15)
C(30)-C(31)-C(32)	101.43(16)	C(40)-C(38)-Si	109.20(15)
C(33)-C(31)-C(32)	118.97(17)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for rich08. The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{23}$	$U^{13}$	$U^{12}$
Si	22(1)	27(1)	19(1)	-2(1)	0(1)	-1(1)
N(1)	14(1)	17(1)	16(1)	0(1)	-3(1)	-1(1)
N(2)	15(1)	20(1)	21(1)	4(1)	-4(1)	-4(1)
O(1)	16(1)	20(1)	23(1)	-3(1)	-3(1)	3(1)
O(2)	19(1)	19(1)	28(1)	2(1)	-5(1)	-2(1)
O(3)	18(1)	20(1)	22(1)	5(1)	-4(1)	-2(1)
O(4)	26(1)	27(1)	22(1)	6(1)	-7(1)	-1(1)
O(5)	43(1)	39(1)	27(1)	13(1)	-13(1)	-5(1)
O(6)	42(1)	31(1)	24(1)	1(1)	1(1)	-4(1)
C(1)	22(1)	20(1)	17(1)	-1(1)	-2(1)	-2(1)
C(2)	22(1)	21(1)	26(1)	-1(1)	4(1)	-2(1)
C(3)	17(1)	26(1)	31(1)	0(1)	3(1)	-3(1)
C(4)	20(1)	26(1)	26(1)	-5(1)	-4(1)	-5(1)
C(5)	21(1)	20(1)	19(1)	-3(1)	2(1)	-1(1)
C(6)	17(1)	13(1)	22(1)	0(1)	0(1)	-2(1)
C(7)	31(1)	23(1)	40(1)	4(1)	7(1)	-1(1)
C(8)	48(1)	24(1)	60(2)	13(1)	10(1)	-2(1)
C(9)	54(2)	22(1)	46(1)	13(1)	-4(1)	8(1)
C(10)	37(1)	30(1)	37(1)	-1(1)	-11(1)	9(1)
C(11)	26(1)	20(1)	28(1)	-3(1)	-6(1)	1(1)
C(12)	25(1)	17(1)	15(1)	-1(1)	0(1)	2(1)
C(13)	18(1)	25(1)	22(1)	-3(1)	-2(1)	0(1)
C(14)	23(1)	36(1)	19(1)	-10(1)	0(1)	2(1)
C(15)	20(1)	48(1)	15(1)	1(1)	1(1)	-2(1)
C(16)	21(1)	34(1)	21(1)	6(1)	0(1)	-3(1)
C(17)	20(1)	24(1)	19(1)	0(1)	-1(1)	-1(1)
C(18)	12(1)	23(1)	14(1)	-2(1)	-1(1)	0(1)
C(19)	18(1)	16(1)	14(1)	-2(1)	-1(1)	-2(1)
C(20)	16(1)	17(1)	14(1)	-1(1)	3(1)	-1(1)
C(21)	19(1)	17(1)	17(1)	-2(1)	1(1)	-1(1)
C(22)	18(1)	16(1)	23(1)	1(1)	-3(1)	-2(1)
C(23)	19(1)	15(1)	18(1)	1(1)	-3(1)	-2(1)
C(24)	15(1)	22(1)	15(1)	0(1)	2(1)	1(1)
C(25)	19(1)	17(1)	18(1)	2(1)	-2(1)	2(1)
C(26)	31(1)	28(1)	23(1)	8(1)	5(1)	6(1)
C(27)	33(1)	28(1)	27(1)	-5(1)	-3(1)	8(1)
C(28)	25(1)	29(1)	36(1)	8(1)	-9(1)	2(1)
C(29)	22(1)	19(1)	18(1)	3(1)	-4(1)	-1(1)

C(30)	38(1)	21(1)	23(1)	6(1)	-5(1)	-6(1)
C(31)	39(1)	27(1)	21(1)	5(1)	1(1)	1(1)
C(32)	31(1)	24(1)	16(1)	0(1)	0(1)	3(1)
C(33)	47(1)	33(1)	26(1)	2(1)	5(1)	-2(1)
C(34)	43(1)	39(1)	24(1)	-5(1)	-2(1)	-2(1)
C(35)	39(1)	30(1)	28(1)	2(1)	9(1)	-2(1)
C(36)	28(1)	50(1)	35(1)	-8(1)	-10(1)	-3(1)
C(37)	35(1)	32(1)	29(1)	-3(1)	8(1)	1(1)
C(38)	25(1)	25(1)	25(1)	-2(1)	1(1)	1(1)
C(39)	49(2)	35(1)	76(2)	-11(1)	-32(1)	4(1)
C(40)	76(2)	29(1)	36(1)	-1(1)	7(1)	-5(1)
C(41)	44(1)	43(1)	47(1)	-21(1)	18(1)	-6(1)

Table 5. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^{-3}$ ) for rich08.

	x	y	z	U(eq)
H(1)	4866	9488	2604	19
H(2)	2452	7588	2674	22
H(1A)	6925	9787	2139	24
H(2A)	8545	9857	2019	27
H(3)	9474	10100	3087	29
H(4)	8778	10255	4273	29
H(5)	7159	10159	4396	24
H(7)	6736	11506	2980	38
H(8)	6189	12846	2539	53
H(9)	4609	13061	2320	49
H(10)	3556	11927	2566	42
H(11)	4095	10591	3014	30
H(13)	5491	11187	4444	26
H(14)	5137	11016	5724	31
H(15)	4888	9622	6229	33
H(16)	5038	8394	5445	30
H(17)	5425	8565	4168	25
H(21A)	5390	7567	1933	21
H(21B)	4584	8289	1994	21
H(22A)	4892	7049	3188	23
H(22B)	4189	6836	2511	23
H(23)	3918	8332	3471	21
H(26A)	2928	9935	1172	41
H(26B)	2055	10214	664	41
H(26C)	2374	9214	696	41
H(27A)	1250	10244	2624	44
H(27B)	1326	10878	1907	44
H(27C)	2250	10556	2330	44
H(28A)	728	8850	1052	44
H(28B)	431	9856	1096	44
H(28C)	294	9235	1816	44
H(29)	3029	6652	3660	23
H(31)	2323	6580	5067	35
H(32A)	1903	7552	4150	28
H(32B)	2651	8273	4423	28
H(33A)	2566	7282	6281	43
H(33B)	1598	7477	5870	43

H(34A)	2572	8707	6453	43
H(34B)	3024	8717	5625	43
H(35A)	1501	8941	5093	39
H(35B)	1075	8972	5931	39
H(36A)	590	10035	4268	56
H(36B)	767	11011	3976	56
H(36C)	254	10848	4767	56
H(37A)	3375	10159	4508	48
H(37B)	2874	10681	3837	48
H(37C)	2581	9694	4017	48
H(39A)	3124	12358	5980	80
H(39B)	3568	11597	5475	80
H(39C)	2928	11357	6186	80
H(40A)	1783	12378	4252	70
H(40B)	2877	12181	4299	70
H(40C)	2442	12983	4761	70
H(41A)	1225	11754	6150	67
H(41B)	805	12195	5404	67
H(41C)	1526	12725	5920	67

Table 6. Torsion angles [°] for rich08.

C(36)-Si-O(6)-C(35)	59.45(19)	C(5)-C(6)-C(19)-C(12)	101.89(18)
C(37)-Si-O(6)-C(35)	-59.66(18)	C(1)-C(6)-C(19)-C(12)	-71.58(19)
C(38)-Si-O(6)-C(35)	179.16(15)	C(17)-C(18)-C(19)-N(1)	37.1(2)
C(6)-C(1)-C(2)-C(3)	-0.6(3)	C(13)-C(18)-C(19)-N(1)	-148.07(15)
C(1)-C(2)-C(3)-C(4)	0.4(3)	C(17)-C(18)-C(19)-C(6)	-85.81(19)
C(2)-C(3)-C(4)-C(5)	0.2(3)	C(13)-C(18)-C(19)-C(6)	88.98(19)
C(3)-C(4)-C(5)-C(6)	-0.7(3)	C(17)-C(18)-C(19)-C(12)	153.75(16)
C(4)-C(5)-C(6)-C(1)	0.4(3)	C(13)-C(18)-C(19)-C(12)	-31.5(2)
C(4)-C(5)-C(6)-C(19)	-173.13(17)	C(7)-C(12)-C(19)-N(1)	-132.07(18)
C(2)-C(1)-C(6)-C(5)	0.2(3)	C(11)-C(12)-C(19)-N(1)	50.8(2)
C(2)-C(1)-C(6)-C(19)	173.82(16)	C(7)-C(12)-C(19)-C(6)	-13.1(2)
C(12)-C(7)-C(8)-C(9)	0.2(4)	C(11)-C(12)-C(19)-C(6)	169.81(16)
C(7)-C(8)-C(9)-C(10)	0.7(4)	C(7)-C(12)-C(19)-C(18)	108.7(2)
C(8)-C(9)-C(10)-C(11)	-0.5(4)	C(11)-C(12)-C(19)-C(18)	-68.4(2)
C(9)-C(10)-C(11)-C(12)	-0.7(3)	C(19)-N(1)-C(20)-O(1)	-4.6(3)
C(8)-C(7)-C(12)-C(11)	-1.3(3)	C(19)-N(1)-C(20)-C(21)	173.52(15)
C(8)-C(7)-C(12)-C(19)	-178.4(2)	O(1)-C(20)-C(21)-C(22)	75.8(2)
C(10)-C(11)-C(12)-C(7)	1.5(3)	N(1)-C(20)-C(21)-C(22)	-102.36(17)
C(10)-C(11)-C(12)-C(19)	178.74(18)	C(20)-C(21)-C(22)-C(23)	74.73(18)
C(18)-C(13)-C(14)-C(15)	-0.8(3)	C(24)-N(2)-C(23)-C(29)	143.20(16)
C(13)-C(14)-C(15)-C(16)	0.9(3)	C(24)-N(2)-C(23)-C(22)	-94.69(19)
C(14)-C(15)-C(16)-C(17)	-0.2(3)	C(21)-C(22)-C(23)-N(2)	73.44(18)
C(15)-C(16)-C(17)-C(18)	-0.7(3)	C(21)-C(22)-C(23)-C(29)	-167.76(14)
C(16)-C(17)-C(18)-C(13)	0.8(3)	C(23)-N(2)-C(24)-O(2)	7.7(3)
C(16)-C(17)-C(18)-C(19)	175.68(16)	C(23)-N(2)-C(24)-O(3)	-172.17(15)
C(14)-C(13)-C(18)-C(17)	-0.1(3)	C(25)-O(3)-C(24)-O(2)	1.1(3)
C(14)-C(13)-C(18)-C(19)	-174.98(16)	C(25)-O(3)-C(24)-N(2)	-179.07(14)
C(20)-N(1)-C(19)-C(6)	40.6(2)	C(24)-O(3)-C(25)-C(27)	-62.9(2)
C(20)-N(1)-C(19)-C(18)	-82.5(2)	C(24)-O(3)-C(25)-C(26)	62.1(2)
C(20)-N(1)-C(19)-C(12)	158.28(16)	C(24)-O(3)-C(25)-C(28)	179.88(16)
C(5)-C(6)-C(19)-N(1)	-142.12(16)	C(30)-O(4)-C(29)-C(32)	22.69(18)
C(1)-C(6)-C(19)-N(1)	44.4(2)	C(30)-O(4)-C(29)-C(23)	145.65(15)
C(5)-C(6)-C(19)-C(18)	-19.4(2)	N(2)-C(23)-C(29)-O(4)	-177.42(13)
C(1)-C(6)-C(19)-C(18)	167.12(15)	C(22)-C(23)-C(29)-O(4)	60.24(18)

N(2)-C(23)-C(29)-C(32)	-61.32(19)	C(31)-C(33)-C(34)-C(35)	93.8(2)
C(22)-C(23)-C(29)-C(32)	176.35(15)	Si-O(6)-C(35)-C(34)	118.25(17)
C(29)-O(4)-C(30)-O(5)	177.23(18)	C(33)-C(34)-C(35)-O(6)	-177.34(17)
C(29)-O(4)-C(30)-C(31)	-1.1(2)	O(6)-Si-C(38)-C(41)	-67.41(18)
O(5)-C(30)-C(31)-C(33)	31.8(3)	C(36)-Si-C(38)-C(41)	51.78(19)
O(4)-C(30)-C(31)-C(33)	-150.00(17)	C(37)-Si-C(38)-C(41)	172.04(17)
O(5)-C(30)-C(31)-C(32)	161.3(2)	O(6)-Si-C(38)-C(39)	52.0(2)
O(4)-C(30)-C(31)-C(32)	-20.5(2)	C(36)-Si-C(38)-C(39)	171.17(19)
O(4)-C(29)-C(32)-C(31)	-34.18(18)	C(37)-Si-C(38)-C(39)	-68.6(2)
C(23)-C(29)-C(32)-C(31)	-152.45(16)	O(6)-Si-C(38)-C(40)	173.14(16)
C(30)-C(31)-C(32)-C(29)	32.47(19)	C(36)-Si-C(38)-C(40)	-67.67(19)
C(33)-C(31)-C(32)-C(29)	159.16(19)	C(37)-Si-C(38)-C(40)	52.59(19)
C(30)-C(31)-C(33)-C(34)	78.7(2)		
C(32)-C(31)-C(33)-C(34)	-41.5(3)		

Table 7. Hydrogen bonds for rich08 [ $\text{\AA}$  and  $^\circ$ ].

D-H...A	d(D-H)	d(H...A)	d(D...A)	$\angle$ (DHA)
N(1)-H(1)...O(2)	0.88	2.19	2.9767(19)	149(1)
N(2)-H(2)...O(1)#1	0.88	2.06	2.8665(19)	152(1)

Symmetry transformations used to generate equivalent atoms:

#1  $x-1/2, -y+3/2, z$

## Brewer/James/Rich Supporting Information