Synthesis of Acyclic Precursors to (3*S*,4*S*)-4-Hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic Acid and Incorporation into a Luzopeptin/Quinoxapeptin Dipeptide

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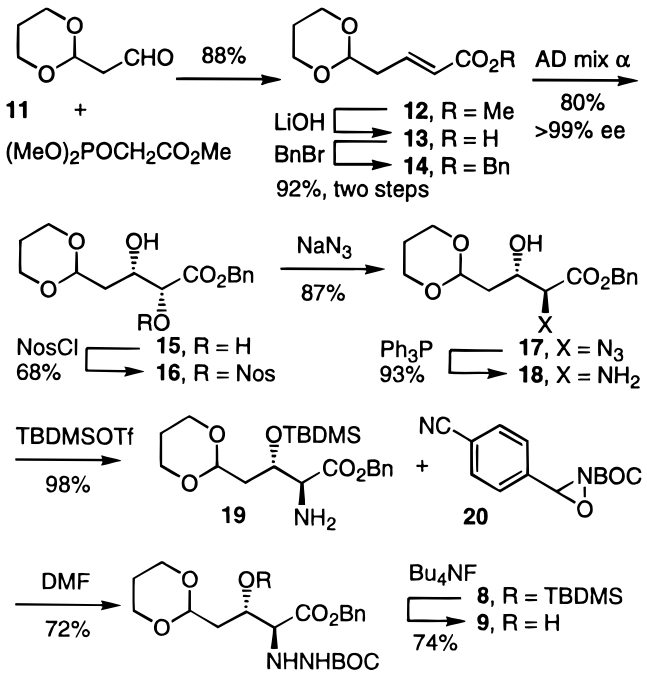
The luzopeptins (**1**−**3**, Figure 1) are potent antitumor antibiotics that were isolated from *Actinomadura luzonensis*[1] and identified in a single-crystal X-ray structure determination of **1**.[2] They constitute the initial members of a growing class of C2 symmetric cyclic decadepsipeptides bearing two pendant chromophores which now include the quinoxapeptins (**4**−**5**),[3] quinaldopeptin,[4] and sandramycin (**6**)[5−8] that bind to DNA with bisintercalation.[6−12] In addition to their potent cytotoxic and antitumor activity,[1,13] which includes members exhibiting 1−100 pM IC_{50}'s,[8,14] they are potent inhibitors of HIV reverse transcriptase (RT)[8,15] including single and double mutants[3] responsible for the emerging clinical resistance to recently introduced RT inhibitors. Moreover, the cytotoxic potency of the luzopeptins (A > B ≫ C) and their antiviral potency/HIV RT inhibition (C > B > A) are reversed, with luzopeptin C exhibiting suppression of HIV replication in infected MT-4 cells at noncytotoxic concentrations,[15] and similar, albeit structurally distinct, divergent cytotoxic/HIV RT structure−activity relationships have been described in a more recent series of sandramycin analogues.[8] In an extension of our efforts which have resulted in the only total synthesis to date of a member of this class of antitumor antibiotics, sandramycin (**6**),[6,7] herein we detail the preparation of the acyclic precursors **8** and **9** to (3*S*,4*S*)-4-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (**7**, Htp) and their incorporation into a luzopeptin/quinoxapeptin dipeptide **10** which complements the studies disclosed to date.[16−18]

Scheme 1



Condensation of 2-(1,3-dioxan-2-yl)acetaldehyde (**11**)[19] with trimethyl phosphonoacetate (88%) followed by conversion of **12** to the corresponding benzyl ester **14** (92%, two steps) provided our starting material (Scheme 1). Sharpless asymmetric dihydroxylation[20] of **14** conducted with AD mix α (*t*-BuOH/H_2O, 80%) provided the (2*R*,3*S*)-diol **15** in superb enantiomeric excess (>99% ee).[21]

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(21) The ee was established by HPLC on a ChiraCel OD column (0.46 × 25 cm, 25% *i*-PrOH/hexane, flow rate = 1 mL/min) enlisting racemic **15** as a standard: t_R((2*R*,3*S*)-**15**) = 8.99 min, t_R((2*S*,3*R*)-**15**) = 7.83 min; α = 1.15.

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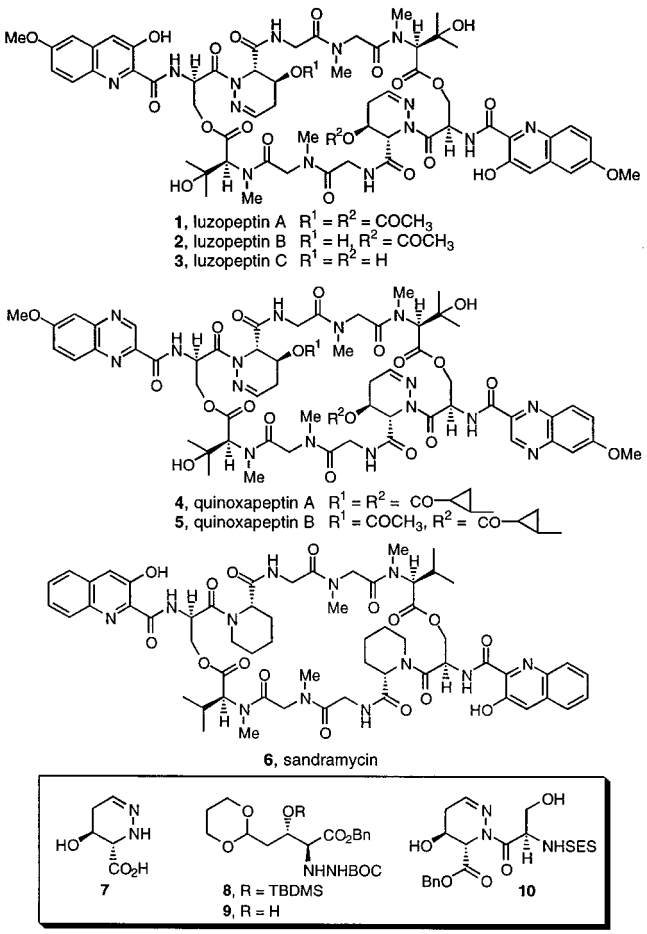
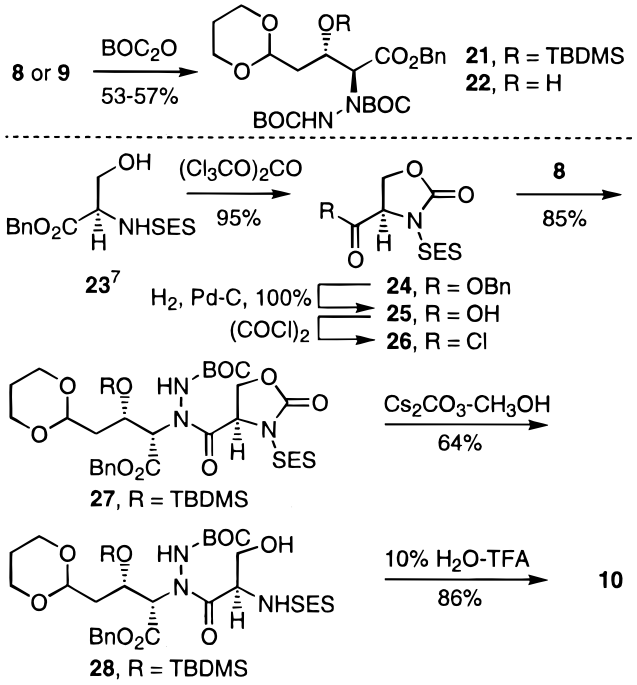


Figure 1.

Selective sulfonation of the C2 hydroxy group upon reaction with 4-nitrobenzenesulfonyl chloride as described by Fleming and Sharpless[22] cleanly provided **16** (68%). Subsequent NaN_3 displacement of the nosylate[22] provided the azide **17** (87%) with clean inversion of the C2 stereochemistry and without detection of a second, minor diastereomer derived from racemization. Staudinger reduction afforded the amine **18** (93%), and TBDMSOTf protection of the alcohol provided **19** (98%), a suitably protected substrate for oxaziridine N-amination. Treatment of **19** with oxaziridine **20**[23] (1 equiv, DMF, 23 °C, 24 h) served to transfer the NHBOC and provided the selectively protected acyclic α-hydrazino carboxylic acid **8** (72%) along with a small amount of reisolated **19** (15%). Initial efforts enlisting the conditions disclosed by Collet[23] (Et_2O or $CHCl_3$) provided only low yields of N-amination and predominantly recovered starting material (40−60%) which was substantially improved in switching to DMF as solvent.[24] Treatment of **8** with Bu_4NF (THF, 30 min, 74%) provided the free alcohol **9**.

Preliminary studies conducted with both **8** and **9** indicated that although both may couple with activated

Scheme 2



acylating agents including $(BOC)_2O$ in the presence of DMAP (2 equiv, CH_2Cl_2, 0 °C, 4 h, 53−57%, Scheme 2), both did not couple with SESNH-Ser-CO_2H, SESNH-Ser(OTBDMS)-CO_2H (SES = 2-trimethylsilylethanesulfonyl) or **25** under a wide variety of conventional coupling procedures.[25] Adopting a protocol introduced by Ciufolini enlisting an acid chloride,[17] the acid **25** prepared from D-Ser was converted to the corresponding acid chloride **26** ($(COCl)_2$, cat. DMF, CH_2Cl_2, 25 °C) and in situ coupled with **8** utilizing K_2CO_3 as a base[26] to provide **27** (85%) during which little racemization was observed (ca. ≥ 11:1), Scheme 2. Selective methanolysis (0.3 equiv of Cs_2CO_3, CH_3OH, 25 °C, 35 min) of the SES-activated cyclic carbamate released the dipeptide **28** (64%) suitably protected for direct incorporation into the synthesis of **1**−**5**. In this regard, the N-sulfonyl versus N-acyl protection of the D-Ser amine disclosed by Ciufolini[17] serves to activate and direct hydrolysis to the cyclic carbamate and provides intermediates bearing protecting groups analogous to those enlisted in our synthesis of sandramycin ensuring their smooth incorporation into ongoing efforts on **1**−**5**. In efforts which established for us the chemical behavior of N-acylated Htp derivatives, treatment of **28** with 10% H_2O−TFA (25 °C, 2 h) provided **10** (86%) which proved stable to conventional isolation, purification (SiO_2), and characterization techniques.[27] In contrast, analogous attempts to cyclize **28** with 3 N HCl−EtOAc provided **10** (20%) in much lower conversions.

Efforts on the incorporation of **28** into the total synthesis of **1**−**5** are in progress and will be disclosed in due course.

Experimental Section

Methyl 4-(1,3-Dioxan-2-yl)-(*E*)-2-butenoate (12). 2-(1,3-Dioxan-2-yl)acetaldehyde **11**[19] (4.26 g, 32.6 mmol) in CH_3OH (20 mL) was added at 0 °C to a stirred solution of trimethyl

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(24) The corresponding dimethyl acetal was also examined and did provide the analogous intermediates **11**−**19** but underwent subsequent acetal cleavage and condensation reactions under the N-amination reaction conditions.

(25) This included BOP-Cl/Et_3N, EDCI or DCC/HOBt or HOAt, PyBOP, PyBrOP/i-Pr_2NEt, PyBrOP−DMAP, DCC−DMAP, HBTU/HOBt, and DPPA.
(26) No reaction was observed enlisting collidine[17] as the base.
(27) Similar efforts to close **8** or **9** upon treatment with 10% H_2O−TFA failed to provide the benzyl ester of **7**.

phosphonoacetate (6.88 g, 37.8 mmol) and *t*-BuOK (4.4 g, 19.6 mmol) in CH_3OH (140 mL), allowed to warm to 23 °C, and stirred for 1 h. The mixture was concentrated and partitioned between Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The Et_2O layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. Chromatography (SiO_2, 10 × 20 cm, 20% EtOAc−hexane) afforded **12** as a clear oil (5.12 g, 88%): IR (neat) ν_{max} 2954, 2852, 1725, 1660, 1331, 1176, 1027 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.93 (dt, 1H, J = 7.2, 15.8 Hz), 5.89 (dt, 1H, J = 1.4, 15.8 Hz), 4.62 (t, 1H, J = 5.0 Hz), 4.12−4.05 (m, 2H), 3.80−3.68 (m, 2H), 3.70 (s, 3H), 2.52−2.14 (m, 2H), 2.16−1.97 (m, 1H), 1.36−1.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 143.0, 123.3, 100.1, 66.7, 51.2, 37.8, 25.4; FABHRMS (NBA-NaI) *m*/*z* 209.0783 (M + Na^+, $C_9H_{14}O_4$ requires 209.0790)

Benzyl 4-(1,3-Dioxan-2-yl)-(*E*)-2-butenoate (14). Lithium hydroxide monohydrate (942 mg, 22.4 mmol) was added at 4 °C to a solution of **12** (3.8 g, 20.4 mmol) in THF−H_2O (1:1, 100 mL), and the resulting mixture was stirred for 18 h at 23 °C. The solvents were removed in vacuo, the residue containing **13** was dissolved in DMF (40 mL), and benzyl bromide (3.6 mL, 30.2 mmol) was added. The mixture was stirred at 23 °C before ice water was added, and the product was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phases were washed with 1 N aqueous HCl and H_2O, dried ($MgSO_4$), and concentrated. Chromatography (SiO_2, 10 × 20 cm, 20% EtOAc−hexane) afforded **14** (4.9 g, 92%) as a pale yellow oil: IR (neat) ν_{max} 1720, 1713, 1660, 1374, 1170, 1129, 1027 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H), 6.97 (dt, 1H, J = 15.7, 7.2 Hz), 5.93 (dt, 1H, J = 1.3, 15.7 Hz), 5.15 (s, 2H), 4.62 (t, 1H, J = 5.0 Hz), 4.12−4.04 (m, 2H), 3.79−3.68 (m, 2H), 2.51−2.46 (m, 2H), 2.14−1.98 (m, 1H), 1.35−1.27 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.0, 143.5, 136.0, 128.5, 128.2, 128.1, 123.5, 100.2, 66.9, 66.1, 38.1, 25.5; FABHRMS (NBA-NaI) *m*/*z* 263.1291 (M + H^+, $C_{15}H_{18}O_4$ requires 263.1283).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.50; H, 6.71.

Benzyl (2*R*,3*S*)-4-(1,3-Dioxan-2-yl)-2,3-dihydroxybutanoate (15). A cooled mixture of AD mix α (21.4 g), methane sulfonamide (1.43 g), *t*-BuOH (90 mL) and H_2O (90 mL), was treated with **14** (4.0 g, 15.2 mmol), and the resulting suspension was stirred for 24 h at 4 °C. Sodium sulfite (23.0 g) was added, and the mixture was allowed to warm to 23 °C. The product was extracted with EtOAc (5 × 50 mL), and the combined organic phases were washed with 2 N aqueous KOH and H_2O, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 6 × 20 cm, 50% EtOAc−hexane) afforded **15** (3.6 g, 80%, >99% ee)[21] as a colorless oil: $[\alpha]^{23}_D$ −1.1 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3436, 2964, 1743, 1210, 1143, 1117, 1066 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37−7.31 (m, 5H), 5.29 (d, 1H, J = 12.3 Hz), 5.17 (d, 1H, J = 12.3 Hz), 4.81 (t, 1H, J = 4.6 Hz), 4.30 (br dt, 1H, J = 9.3, 2.2 Hz), 4.13−4.06 (m, 3H), 3.82−3.70 (m, 2H), 3.09 (br s), 2.10−1.98 (m, 2H), 1.87−1.77 (m, 1H), 1.37−1.31 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.8, 128.6, 128.4, 128.3, 100.7, 73.9, 68.9, 67.4, 66.9, 66.8, 38.1, 25.6; FABHRMS (NBA-NaI) *m*/*z* 319.1151 (M + Na^+, $C_{15}H_{20}O_6$ requires 319.1158).

Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 61.02; H, 7.29.

Benzyl (2*R*,3*S*)-4-(1,3-Dioxan-2-yl)-3-hydroxy-2-((4-nitrobenzenesulfonyl)oxy)butanoate (16). A solution of **15** (3.05 g, 10.3 mmol), 4-nitrobenzenesulfonyl chloride (2.28 g, 10.3 mmol), and Et_3N (2.08 g, 20.5 mmol) in CH_2Cl_2 (90 mL) was stirred for 12 h at 4 °C. The mixture was concentrated, and the residue was dissolved in Et_2O, washed twice with ice-cold 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried ($MgSO_4$). Chromatography (SiO_2, 6 × 20 cm, 40% EtOAc−hexane) afforded the unstable **16** (3.36 g, 68%) which was used without further characterization in the next step.

Benzyl (2*S*,3*S*)-4-(1,3-Dioxan-2-yl)-2-azido-3-hydroxybutanoate (17). A mixture of **16** (3.36 g, 7.0 mmol) and NaN_3 (2.73 g, 42 mmol) in DMF (80 mL) was stirred for 14 h at 50 °C. Water was added, and the water phase was extracted with Et_2O (5 × 25 mL). The combined organic phases were washed with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). Chromatography (SiO_2, 6 × 20 cm, 20% EtOAc−hexane) afforded **17** (1.96 g, 87%) as a yellow oil: $[\alpha]^{23}_D$ −8.3 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3487, 2861, 2102, 1738, 1174, 1138, 733, 692 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 5.22 (s, 2H), 4.78 (t, 1H, J = 4.4 Hz), 4.35 (ddd, 1H, J = 3.0, 5.5, 8.6 Hz), 4.13−4.05 (m, 2H), 4.00 (d, 1H, J = 5.5 Hz), 3.81−3.69 (m, 2H), 2.15−1.80 (m, 3H), 1.37−1.30 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.5, 128.6, 128.3, 100.6, 68.9, 67.5, 66.9, 66.8, 65.9, 37.1, 25.5; FABHRMS (NBA-NaI) *m*/*z* 344.1228 (M + Na^+, $C_{15}H_{19}N_3O_5$ requires 344.1222).

Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 56.20; H, 6.13; N, 13.27.

Benzyl (2*S*,3*S*)-4-(1,3-Dioxan-2-yl)-2-amino-3-hydroxybutanoate (18). A mixture of **17** (1.84 g, 5.7 mmol), Ph_3P (3.0 g, 11.4 mmol), THF (20 mL), and H_2O (1.03 mL) was stirred overnight at 50 °C. The solvent was removed *in vacuo*, and chromatography (SiO_2, 5 × 15 cm, 5% CH_3OH−CH_2Cl_2) afforded **18** (1.56 g, 93%) as a white solid: $[\alpha]^{23}_D$ +6.0 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 3374, 3292, 2964, 2861, 1733, 1456, 1195, 1143, 753, 697 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35−7.32 (m, 5H), 5.17 (s, 2H), 4.75 (t, 1H, J = 4.7 Hz), 4.16 (ddd, 1H, J = 3.5, 4.7, 8.3 Hz), 4.09−4.04 (m, 2H), 3.80−3.67 (m, 2H), 3.64 (d, 1H, J = 4.7 Hz), 2.63 (br s, 3H), 2.13−1.98 (m, 1H), 1.88−1.70 (m, 2H), 1.30−1.29 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.5, 128.6, 128.3, 100.8, 69.2, 66.9, 58.8, 37.4, 25.6; FABHRMS (NBA-NaI) *m*/*z* 296.1489 (M + H^+, $C_{15}H_{21}NO_5$ requires 296.1498).

Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.82; H, 6.95; N, 4.57.

Benzyl (2*S*,3*S*)-4-(1,3-Dioxan-2-yl)-2-amino-3-((*tert*-butyldimethylsilyl)oxy)butanoate (19). A solution of **18** (1.56 g, 5.3 mmol) in CH_2Cl_2 (100 mL) was treated with 2,6-lutidine (2.77 mL, 23.8 mmol) and *tert*-butyldimethylsilyltriflate (4.87 mL, 21.2 mmol) at 0 °C, and the resulting mixture was stirred for 3.5 h. The mixture was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried ($MgSO_4$). The solution was concentrated, and chromatography (SiO_2, 5 × 15 cm, 5% CH_3OH−CH_2Cl_2) afforded **19** (2.13 g, 98%) as a colorless oil: $[\alpha]^{23}_D$ +6.0 (*c* 1, $CHCl_3$); IR (neat) ν_{max} 2951, 2859, 1737, 1460, 1245, 1137, 1096, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.15 (s, 2H), 4.62 (dd, 1H, J = 4.4, 6.4 Hz), 4.18 (td, 1H, J = 4.4, 8.5 Hz), 4.08−4.01 (m, 2H), 3.75−3.63 (m, 2H), 3.70 (d, 1H, J = 4.0 Hz), 2.11−1.81 (m, 4H), 1.73−1.62 (m, 1H), 1.32−1.26 (m, 1H), 0.86 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.2, 128.5, 128.2, 99.5, 70.4, 66.9, 66.7, 66.6, 59.5, 38.0, 25.7; FABHRMS (NBA-NaI) *m*/*z* 410.2374 (M + H^+, $C_{21}H_{35}NO_5Si$ requires 410.2363).

Anal. Calcd for $C_{21}H_{35}NO_5Si$: C, 61.58; H, 8.61; N, 3.42. Found: C, 61.36; H, 8.71; N, 3.15.

Benzyl (2*S*,3*S*)-4-(1,3-Dioxan-2-yl)-2-(*N*′-*tert*-butyloxycarbonylhydrazino)-3-((*tert*-butyldimethylsilyl)oxy)butanoate (8). A solution of **19** (922 mg, 2.25 mmol) and **20**[23] (556 mg, 2.25 mmol) in DMF (15 mL) was stirred for 24 h at 23 °C. The mixture was concentrated, and chromatography (SiO_2, 5 × 15 cm, 75% EtOAc−hexane gradient) afforded **8** (852 mg, 72%) and recovered **19** (138 mg, 15%). For **8**: $[\alpha]^{23}_D$ −3 (*c* 1.55, $CHCl_3$); IR (neat) ν_{max} 2926, 2855, 1718, 1457, 1253, 1131, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.28 (m, 5H), 6.16 (br m, 1H), 5.19 (d, 1H, J = 12.5 Hz), 5.13 (d, 1H, J = 12.5 Hz), 4.59 (dd, 1H, J = 6.5, 4.0 Hz), 4.25 (dt, 1H, J = 4.5, 6.5 Hz), 4.03 (dd, 2H, J = 4.0, 11.5 Hz), 3.77 (br s, 1H), 3.72−3.64 (m, 2H), 2.04−1.95 (m, 2H), 1.78−1.76 (m, 1H), 1.41 (s, 9H), 1.29 (br d, 1H), 0.85 (s, 9H), 0.077 (s, 3H), 0.049 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 155.9, 135.5, 128.5, 128.4, 128.1, 128.0, 99.5, 69.2, 66.8, 66.6, 66.5, 39.2, 28.3, 25.8, −4.5, −5.0; FABHRMS (NBA-CsI) *m*/*z* 657.1985 (M + Cs^+, $C_{26}H_{44}N_2O_7Si$ requires 657.1972).

Benzyl (2*S*,3*S*)-4-(1,3-Dioxan-2-yl)-2-(*N*′-*tert*-butyloxycarbonylhydrazino)-3-hydroxybutanoate (9). A sample of **8** (78.6 mg, 0.16 mmol) was treated with 1 N Bu_4NF in THF (0.5 mL) at 0 °C for 30 min. EtOAc was added, and the mixture was washed with H_2O and saturated aqueous NaCl. The organic phase was dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, 1 × 10 cm, 40% CH_3OH−CH_2Cl_2) afforded **9** as a white solid (45.6 mg, 74%): mp 98 °C (EtOAc−hexane); $[\alpha]^{23}_D$ −16 (*c* 1.1, $CHCl_3$); IR (neat) ν_{max} 2964, 2861, 1723, 1246, 1159, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 6.28 (s, 1H), 5.19 (d, 1H, J = 12.5 Hz), 5.16 (d, 1H, J = 12.5 Hz), 4.72 (t, 1H, J = 4.8 Hz), 4.25−4.20 (m, 1H), 4.07−4.03 (m, 2H), 3.77−3.65 (m, 2H), 3.61 (d, 1H, J = 3.9 Hz), 2.10−1.97 (m, 1H), 1.93−

1.85 (m, 1H), 1.77−1.71 (m, 1H), 1.40 (s, 9H), 1.33−1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 156.6, 135.4, 128.7, 128.5, 100.7, 80.8, 68.0, 67.2, 66.8, 38.0, 28.2, 25.7; FABHRMS (NBA-CsI) *m/z* 543.1088 (M + Cs^+, $C_{20}H_{30}N_2O_7$ requires 543.1107).

Benzyl (2*S*,3*S*)-4-(1,3-Dioxan-2-yl)-2-(*N*,*N*′-di(*tert*-butyloxycarbonyl)hydrazino)-3-((*tert*-butyldimethylsilyl)oxy)-butanoate (21). A solution of **8** (7 mg, 0.013 mmol) and Et_3N (2.7 mg, 0.027 mmol) in CH_2Cl_2 (50 μL) was treated for 12 h at 0 °C with $(BOC)_2O$ (5.8 mg, 0.027 mmol) and DMAP (0.3 mg). Water was added, and the mixture was washed with dilute aqueous HCl and saturated aqueous NaCl and dried ($MgSO_4$). Chromatography (PTLC, 25% EtOAc−hexane) afforded **21** (4.4 mg, 53%) as a colorless oil: $[\alpha]^{23}_D$ +26 (*c* 0.21, $CHCl_3$); IR (neat) ν_{max} 2943, 1739, 1369, 1241, 1148 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 5.28 (s, 1H), 5.13 (s, 2H), 4.61 (dd, 1H, *J* = 6.1, 4.6 Hz), 4.33−4.28 (m, 1H), 4.02 (br dd, 2H, *J* = 11.9, 4.6 Hz), 3.68 (dt, 2H, *J* = 9.6, 3.4 Hz), 2.10−1.88 (m, 2H), 1.46 (s, 18H), 1.29−1.23 (m, 1H), 0.83 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.3, 135.6, 128.4, 128.1, 128.0, 99.7, 88.3, 83.0, 70.2, 68.5, 66.8, 66.7, 66.6, 39.9, 28.0, 25.8, 17.9, −4.5, −4.9; FABHRMS (NBA-CsI) *m/z* 757.2520 (M + Cs^+, $C_{31}H_{52}N_2O_9Si$ requires 757.2496).

Benzyl (2*S*,3*S*)-4-(1,3-Dioxan-2-yl)-2-(*N*,*N*′-di(*tert*-butyloxycarbonyl)hydrazino)-3-hydroxybutanoate (22). A solution of **9** (4 mg, 0.0098 mmol) and Et_3N (1.97 mg, 0.0195 mmol) in CH_2Cl_2 (50 μL) was treated for 12 h at 0 °C with $(BOC)_2O$ (4.25 mg, 0.0195 mmol) and DMAP (0.3 mg). Water was added, and the mixture was washed with dilute aqueous HCl and saturated aqueous NaCl and dried ($MgSO_4$). Chromatography (PTLC, 40% EtOAc−hexane) afforded **22** (2.8 mg, 57%) as a colorless oil: $[\alpha]^{23}_D$ −24 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 2978, 1738, 1369, 1242, 1147 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 5.20 (d, 1H, *J* = 12.4 Hz), 5.15 (d, 1H, *J* = 12.4 Hz), 4.77 (dd, 1H, *J* = 7.2, 3.2 Hz), 4.09−4.03 (m, 3H), 3.75 (br t, 1H, *J* = 12.1 Hz), 3.53 (d, 1H, *J* = 3.5 Hz), 2.10−1.91 (m, 2H), 1.72−1.61 (m, 2H), 1.46 (s, 18H), 1.35−1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 152.7, 135.2, 128.5, 128.3, 128.2, 100.2, 84.1, 68.1, 67.2, 67.0, 66.9, 66.7, 37.8, 27.9, 25.8; FABHRMS (NBA-CsI) *m/z* 643.1609 (M + Cs^+, $C_{25}H_{38}N_2O_9$ requires 643.1632).

Benzyl (4*R*)-2-Oxo-3-(2-trimethylsilylethanesulfonyl)-1,3-oxazolidine-4-carboxylate (24). A solution of **23**[7] (690 mg, 1.92 mmol) in CH_2Cl_2 (8 mL) was treated for 1 h with Et_3N (1.34 g, 13.2 mmol) and triphosgene (684 mg, 2.3 mmol) at 0 °C. The mixture was concentrated, and chromatography (SiO_2, 2.5 × 15 cm, 20% EtOAc−hexane) afforded **24** (706 mg, 95%) as a colorless oil: $[\alpha]^{23}_D$ +85 (*c* 0.75, $CHCl_3$); IR (neat) ν_{max} 2956, 1788, 1748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.31 (m, 5H), 5.28 (m, 2H), 5.20 (d, 1H, *J* = 12.0 Hz), 5.98 (dd, 1H, *J* = 3.5, 9.4 Hz), 4.60 (t, 1H, *J* = 9.3 Hz), 4.34 (dd, 1H, *J* = 3.5, 9.2 Hz), 3.67 (dt, 1H, *J* = 4.7, 13.6 Hz), 3.51 (dt, 1H, *J* = 4.7, 13.6 Hz), 1.15−1.07 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 152.0, 134.1, 128.9, 128.5, 68.4, 65.6, 56.7, 50.6, 8.5, −2.1; FABHRMS (NBA-NaI) *m/z* 408.0913 (M + Na^+, $C_{16}H_{23}NO_6SSi$ requires 408.0913).

(4*R*)-2-Oxo-3-(2-trimethylsilylethanesulfonyl)-1,3-oxazolidine-4-carboxylic Acid (25). A mixture of **24** (133 mg, 0.34 mmol), catalytic 10% Pd−C, and CH_3OH (2.5 mL) was stirred under H_2 for 2 h at 23 °C. The mixture was concentrated and filtered through a short column of SiO_2 (5% CH_3OH−CH_2Cl_2) to afford **25** (100 mg, 100%) as a white foam: $[\alpha]^{23}_D$ +98 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3560, 2943, 1394, 1359, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 5.00 (dd, 1H, *J* = 9.6, 3.5 Hz), 4.69 (t, 1H, *J* = 9.4 Hz), 4.48 (dd, 1H, *J* = 9.3, 3.5 Hz), 3.64 (dt, 1H, *J* = 13.8, 4.5 Hz), 3.48 (dt, 1H, *J* = 13.8, 4.5 Hz), 1.15−1.05 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 152.3, 65.7, 56.6, 50.8, 8.7, −2.1; FABHRMS (NBA-NaI) *m/z* 318.0456 (M + Na^+, $C_9H_{17}NO_6SSi$ requires 318.0444).

Benzyl (2*S*,3*S*)-4-(1,3-Dioxan-2-yl)-2-(*N*-((4*R*)-2-oxo-3-(2-trimethylsilylethanesulfonyl)-1,3-oxazolidine-4-carbonyl)-*N*′-(*tert*-butyloxycarbonyl)hydrazino)-3-((*tert*-butyldimethylsilyl)oxy)butanoate (27). A solution of **25** (592 mg, 2.01 mmol) in CH_2Cl_2 (20 mL) was stirred for 2 h at 23 °C with 1 drop of DMF and oxalyl chloride (2.00 mL, 2 N solution in CH_2Cl_2). The mixture was concentrated, and crude **26** was used directly in the next step. A solution of **26** (2.01 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C to a mixture of **8** (526 mg, 1.00 mmol), K_2CO_3 (552 mg, 4.0 mmol), and CH_2Cl_2 (15 mL). After complete addition a further amount of K_2CO_3 (440 mg) was added. The mixture was stirred for 2 h at 0 °C, washed with dilute aqueous HCl and H_2O, and dried ($MgSO_4$). Evaporation of the solvent and chromatography (SiO_2, 2.5 × 15 cm, 25% EtOAc−hexane) afforded **27** (680 mg, 85%): $[\alpha]^{23}_D$ +5.3 (*c* 0.75, $CHCl_3$); IR (neat) ν_{max} 2958, 1792, 1736, 1251, 1153, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 7.36−7.29 (m, 5H), 5.38 (br t, 1H, *J* = 8.0 Hz), 5.17 (d, 1H, *J* = 12.5 Hz), 5.10 (d, 1H, *J* = 12.5 Hz), 4.65 (t, 1H, *J* = 5.0 Hz), 4.57 (br, 1H), 4.52 (dd, 1H, *J* = 5.5, 10.5 Hz), 4.34−4.32 (m, 2H), 4.11−4.00 (m, 2H), 3.73−3.65 (m, 2H), 3.58 (dt, 1H, *J* = 4.5, 14 Hz), 3.39 (dt, 1H, *J* = 4.5, 14 Hz), 2.08−1.99 (m, 2H), 1.87−1.81 (m, 1H), 1.43 (s, 9H), 1.29 (br d, 1H, *J* = 13 Hz), 1.15−1.01 (m, 2H), 0.84 (s, 9H), 0.06 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 167.2, 154.5, 152.6, 135.0, 128.5, 128.3, 100.3, 99.0, 83.0, 68.1, 67.3, 66.8, 66.7, 66.4, 65.9, 57.4, 54.1, 51.0, 50.6, 39.0, 28.0, 25.8, 25.6, 17.9, 8.4, −2.1, −4.7; FABHRMS (NBA-CsI) *m/z* 934.2447 (M + Cs^+, $C_{35}H_{59}N_3O_{12}SSi_2$ requires 934.2412).

Anal. Calcd for $C_{35}H_{59}N_3O_{12}SSi_2$: C, 52.41; H, 7.41; N, 5.24; S, 4.00. Found: C, 52.03; H, 7.89; N, 5.11; S, 3.91.

Benzyl (2*S*,3*S*)-4-(1,3-Dioxan-2-yl)-2-(*N*-(*N*-(2-trimethylsilylethanesulfonyl)-D-serinyl)-*N*′-(*tert*-butyloxycarbonyl)-hydrazino)-3-((*tert*-butyldimethylsilyl)oxy)butanoate (28). A solution of **27** (35 mg, 0.044 mmol) in CH_3OH (0.5 mL) was treated for 35 min with Cs_2CO_3 (4.2 mg, 0.013 mmol). The mixture was concentrated, and chromatography (PTLC, 50% EtOAc−hexane) afforded **28** (21.7 mg, 64%) as a colorless oil: $[\alpha]^{23}_D$ −4.4 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 2954, 1736, 1251, 1155, 1104, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.36−7.27 (m, 5H), 5.44 (d, 1H, *J* = 8.8 Hz), 5.20−5.08 (m, 2H), 4.89 (d, 1H, *J* = 12.7 Hz), 4.72 (t, 1H, *J* = 4.6 Hz), 4.41−4.30 (m, 2H), 4.14−4.04 (m, 2H), 3.84−3.70 (m, 5H), 3.05−2.84 (m, 2H), 2.10−2.01 (m, 2H), 1.92−1.72 (m, 1H), 1.45 (s, 9H), 1.39 (br d, 1H, *J* = 14 Hz), 0.74 (s, 9H), 0.04 (s, 3H), −0.04 (s, 9H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.7, 154.4, 135.3, 128.4, 128.0, 127.8, 99.9, 82.9, 67.1, 67.0, 66.2, 64.9, 60.6, 55.5, 48.4, 39.6, 29.7, 28.0, 25.6, 25.5, 17.9, 10.0, −2.0, −4.4, −5.3; FABHRMS (NBA-CsI) *m/z* 908.2603 (M + Cs^+, $C_{34}H_{61}N_3O_{11}SSi_2$ requires 908.2620).

Anal. Calcd for $C_{34}H_{61}N_3O_{11}SSi_2$: C, 52.62; H, 7.92; N, 5.41; S, 4.13. Found: C, 52.52; H, 7.81; N, 5.24; S, 4.35.

Benzyl (3*S*,4*S*)-4-Hydroxy-2-(*N*-(2-trimethylsilylethanesulfonyl)-D-serinyl)-2,3,4,5-tetrahydropyridazine-3-carboxylate (10). A solution of **28** (15 mg, 0.019 mmol) in 10% H_2O−TFA (0.4 mL) was stirred for 2 h at 23 °C. The mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqeous $NaHCO_3$, and dried ($MgSO_4$). Chromatography (PTLC, 100% EtOAc) afforded **10** (7.9 mg, 86%) as a colorless oil: $[\alpha]^{23}_D$ −26 (*c* 0.35, $CHCl_3$); IR (neat) ν_{max} 2954, 1746, 1678, 1633, 1454, 1403, 1325, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 6.86 (br m, 1H), 6.00 (d, 1H, *J* = 9.5 Hz), 5.23 (t, 1H, *J* = 2.7 Hz), 5.19 (d, 1H, *J* = 12.1 Hz), 5.11 (dt, 1H, *J* = 9.5, 3.4 Hz), 5.06 (d, 1H, *J* = 12.1 Hz), 4.53 (br m, 1H), 3.98 (dd, 1H, *J* = 11.6, 3.5 Hz), 3.86 (dd, 1H, *J* = 11.6, 3.5 Hz), 2.96−2.83 (m, 2H), 2.28−2.21 (m, 1H), 1.91 (br dd, 1H, *J* = 18.4, 4.0 Hz), 1.11−0.99 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 166.6, 141.9, 134.8, 128.7, 128.3, 67.7, 64.9, 59.7, 57.6, 56.5, 49.4, 28.5, 16.1, 10.0, −2.0; FABHRMS (NBA-CsI) *m/z* 508.1532 (M + Cs^+, $C_{20}H_{31}N_3O_7SSi$ requires 508.1550).

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Supporting Information Available: ^{1}H NMR spectra of **8**−**10**, **12**, **15**, **21**, **22**, **24**, and **25** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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