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Enantioselective synthesis of 4-hydroxy-D-pyroglutamic acid derivatives by an asymmetric 1,3-dipolar cycloaddition

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Abstract—The 1,3-dipolar cycloaddition of a chiral nitrone derived from glyoxylic acid and protected D-ribosyl hydroxylamine with the acrylamide of Oppolzer's sultam provides a perfectly stereoselective approach to protected (2*R*,4*R*)-4-hydroxy-D-pyroglutamic acid.

1. Introduction

Pyroglutamic acids (the cyclic forms of the glutamic acids) **1** and their derivatives have a wide range of synthetic applications.[1] Protected derivatives of **1** (Fig. 1) have been used for the asymmetric synthesis of a number of natural and pharmacologically interesting products.[2] However, in spite of this synthetic activity with compounds **1**, 4-hydroxy pyroglutamic acids **2** have not received attention until recently.[3] Compounds **2**, formally derived from the natural L-series, and their enantiomers *ent*-**2**, in their protected forms, are useful synthons since they are highly functionalized pyrrolidines.[4] In addition, compounds **2** are an entry to 4-substituted glutamic acids of biological importance.[5]

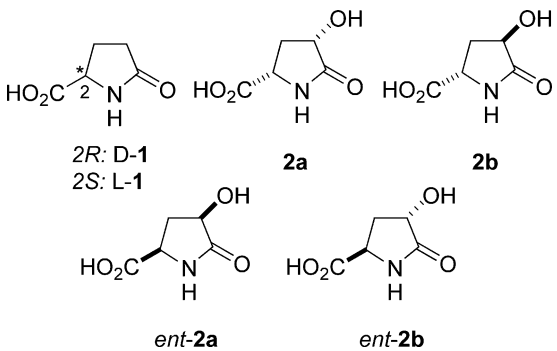

Figure 1. Pyroglutamic acids and their 4-hydroxy derivatives.

Preparation of compound **2a** in homochiral form can be accomplished by oxidation of the enolate derived from protected L-pyroglutamic acid.[6] Very recently, a multigram scale preparation has been reported for both **2a** and its *trans* isomer **2b**, starting from *trans*-4-hydroxy-L-proline.[7] These syntheses, however, only allow preparation of L-isomers due to the availability of L-amino acid starting materials in both cases.[8] One of our laboratories has reported an approach to *ent*-**2a** based on nitrone chemistry.[9] The approach used the furan ring as a surrogate of the carboxylic function; so subsequent ruthenium-mediated oxidation was needed to deliver the desired pyroglutamates.[10]

2. Results and discussion

Herein, we describe the use of a chiral glyoxylic acid derived nitrone, in which the carboxyl group is already present, as a suitable material for a straightforward approach to 4-hydroxy-D-pyroglutamic acid derivatives.[11] This method obviates the need for metal-assisted oxidations.

Nitrone **3** was easily prepared in situ as previously described by one of us[12] and made to react with methyl acrylate **4a** in a sealed tube for 18 h. After evaporation and purification, two adducts **5a** and **6a**, in a 2:1 ratio, and 80% chemical yield were obtained and separated

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(see Section 4). When the reaction was carried out with the Oppolzer's sultam derived acrylamide **4b**,[13] the **5b**:**6b** ratio increased to 20:1 (Scheme 1).

The diastereomeric ratios of the products were determined by HPLC and NMR spectroscopy on crude mixtures. In both cases a preference for *trans* adducts was observed. The regiochemistry of the adducts was readily deduced from ^{1}H NMR data. In each case, there was one proton signal at 4.55–5.11 ppm which corresponded to the H_5 proton; the alternative regioisomers are not reported to show a resonance at this chemical value. The relative stereochemistry of compounds **5** and **6** were determined by extensive NOEDS experiments (Fig. 2).

Thus, for *trans* adduct **5a**, irradiation of H_{4a} (2.47 δ) gave rise to a NOE effect for the geminal proton H_{4b} (2.81 δ; 28%) and for H_3 (4.16 δ; 10%), while irradiation of H_{4b} gave rise to a positive NOE effect for H_{4a} (25%) and H_5 protons (4.55 δ; 13%): these data unambiguously indicate a *syn* relationship between H_{4a} and H_3 and between H_{4b} and H_5 protons, respectively. Conversely, in the *cis* adduct **6a** irradiation of H_{4a} (2.70 δ) produced a positive NOE effect for the geminal proton H_{4b} (2.87 δ; 33%), for H_3 (4.19 δ; 9%) and H_5 (4.77 δ; 12%); moreover, the irradiation of H_5 gave rise to a positive enhancement for H_{4a} (7%) and H_3 (0.5%), so indicating a *cis* topological arrangement between H_5, H_{4a} and H_3 protons.

For *trans* adduct **5b** irradiation of H_5 (5.11 δ) gave rise to a positive enhancement of H_{4b} (2.82 δ; 5%), while irradiation of H_3 (4.28 δ) produced a positive NOE for H_{4a} (2.87 δ; 6%). Instead, for *cis* compound **6b** the irradiation of H_5 (4.74 δ) gave rise to a NOE effect for H_{4a} (2.45 δ; 5%) and for H_3 (3.95 δ; 1%), thus indicating a *cis* relationship between these protons.

The predominant *Re*-face attack at the nitrone carbon was confirmed by chemical correlation as discussed below.

The observed stereochemical results are in good agreement with the precedents existing for cycloaddition reactions of nitrones bearing an electron-withdrawing group at the nitrone carbon atom, which exist as mixtures of *E* and *Z* isomers.[12]

As shown in Fig. 3, the *trans* adducts **5** could be formed by *exo* attack on the (*E*)-nitrone, or by *endo* attack on the (*Z*)-nitrone. Similarly, the minor *cis* adducts **6** could be formed by *endo* attack on the (*E*)-nitrone or by *exo* attack on the (*Z*)-nitrone. The nitrone cycloadditions with monosubstituted electron-poor dipolarophiles (such as methyl acrylate **4a** and acrylamide **4b**), capable of secondary orbital interactions,[14] proceed through *endo* transition states.[15] According to this rule, one might expect the preferred path to involve *endo* attack on the (*Z*)-nitrone, and not *exo* attack on the (*E*)-nitrone. Previous results with configurationally stable (*Z*)-nitrones[9,16] showed that changing from methyl acrylate **4a** to acrylamide **4b** afforded greater amounts of *trans*-isomers, thus supporting the hypothesis that bulky groups at the carbonyl moiety of the dipolarophile favour *endo* attack of (*Z*)-nitrones. Admittedly, this interpretation is speculative and the possibility of *E*-*exo* attack should not be discarded.[17]

The preferential diastereofacial *Re* selectivity (induced by the sugar moiety) observed in the cycloaddition with methyl acrylate **4** is in agreement with previously reported data.[12,18,19] In the reaction of **3** with **4b**, the

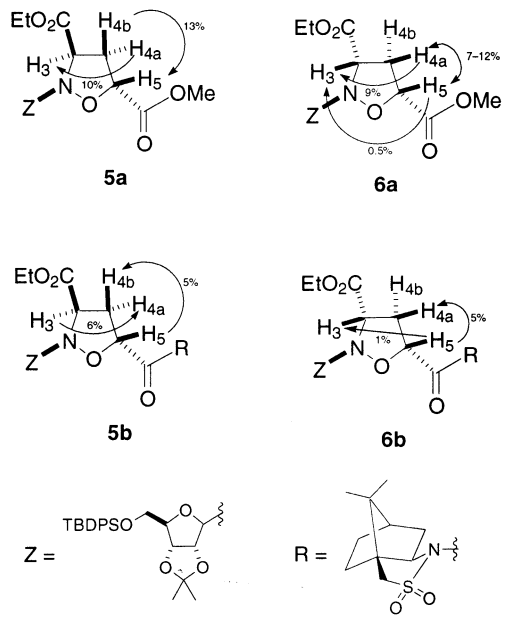
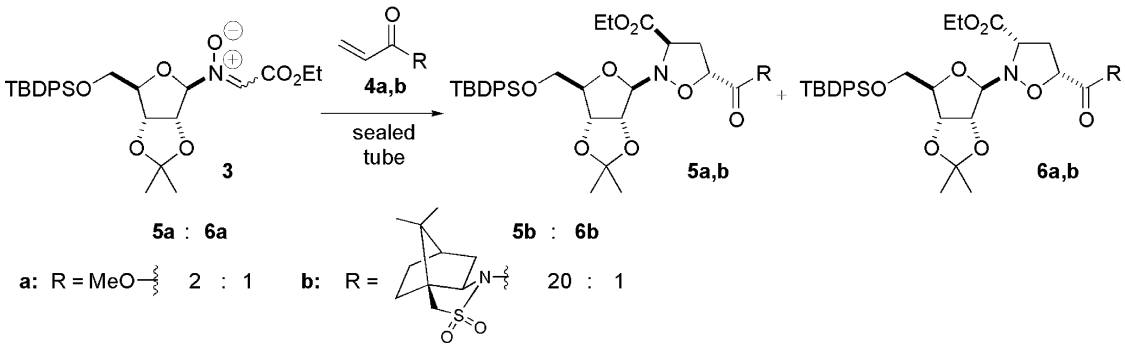


Figure 2. Selected NOEs observed for compounds **5** and **6**.



Scheme 1.

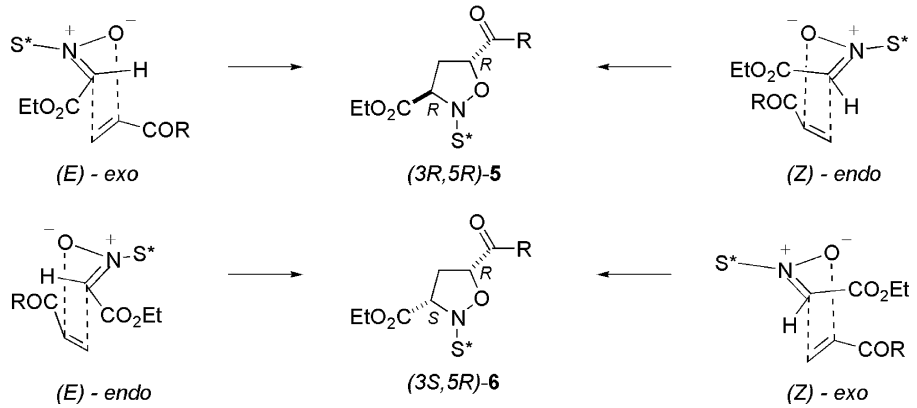
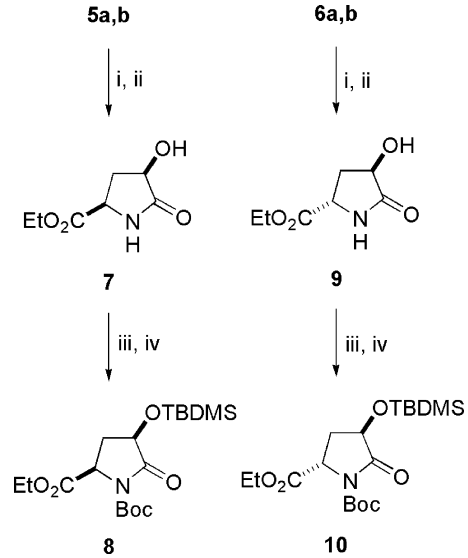


Figure 3. The four possible attacks to (*E*)- and (*Z*)-**3**. S* = 1-deoxy-5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-*O*-isopropylidene-D-ribo-1,4-pentofuranose-1-yl; R = OMe; Oppolzer's sultam.

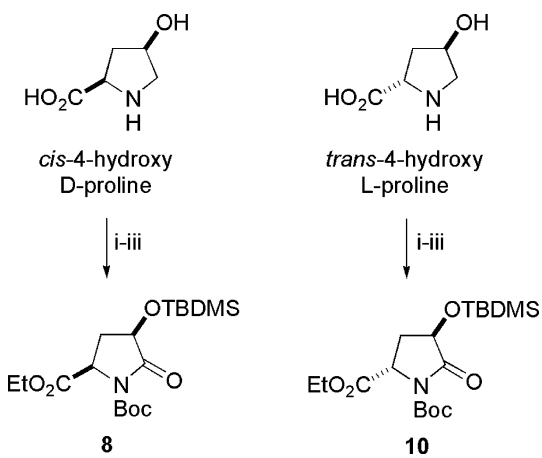
sultam moiety favors *Re* face attack of the alkene, and the ribosyl group again has a tendency for *Re* face attack of the nitrone. As shown in Fig. 3, the formation of (3*R*,5*R*)-**5** as the predominant adduct comes from a *Re–Re* attack either by an *E-exo* or a *Z-endo* attack.

Compounds **5** and **6** were converted to the target 4-hydroxy-D-pyroglutamic acid derivatives in a one-flask procedure consisting of four sequential steps (Scheme 2). Elimination of the sugar moiety by acidic hydrolysis and subsequent *N–O* cleavage by hydrogenolysis gave unprotected ethyl 4-hydroxy-D-pyroglutamates **7** and **9**. We did not observe, in any case, competitive formation of the corresponding lactone by intramolecular cyclization with the hydroxyl group at C(4). In this respect, the formation of lactams versus lactones is clearly favoured, as has been described elsewhere.[10] In situ protection of these compounds with *tert*-butyldimethylsilyl (TBDMS) and *tert*-butoxycarbonyl (Boc) groups afforded the protected compounds **8** and **10**. In the case of compounds **5b** and **6b** it was possible to recover the Oppolzer's sultam in near to 60% yield.



Scheme 2. (i) HCl, EtOH, rt, 6 h; (ii) $Pd(OH)_2/C$, MeOH, H_2, 2000 psi, rt, 48 h; (iii) TBDMSCl, imidazol, DMF, 70°C, 3 h; (iv) Boc_2O, DMAP, Et_3N, CH_2Cl_2, rt, overnight.

Confirmation of the absolute stereochemistry came from an alternative synthesis. Starting from *cis*-4-hydroxy-D-proline[8] and following the recently reported procedure for *trans*-4-hydroxy-L-proline,[7] compound **8** was prepared (Scheme 3). The physical and spectroscopic properties of the obtained compound were identical to those obtained from the cycloadducts **5a** and **5b**. Similarly, starting from *trans*-4-hydroxy-L-proline, compound **10** was synthesized. The physical and spectroscopic properties of this compound were identical to those obtained from the cycloadducts **6a** and **6b**. Thus, the absolute configuration of **8** and **10** could be unambiguously assigned.



Scheme 3. (i) 1. EtOH, HCl, reflux, 2. $(Boc)_2O$, Et_3N, CH_2Cl_2; (ii) TBDMSCl, imidazole, DMF; (iii) RuO_2(cat), $NaIO_4$, $EtOAc/H_2O$.

3. Conclusions

In summary, we have developed a five-step asymmetric synthesis of protected 4-hydroxy-D-pyroglutamic acid **8** using D-ribose and Oppolzer's sultam as highly efficient chiral auxiliaries. In fact, this approach has led to the

preparation of the target compound (protected (2*S*,4*R*)-4-hydroxypyroglutamic acid) in a more efficient way (d.r. = 20:1) than that reported previously (d.r. = 6:1).[9] The synthesis avoids low temperature reactions, oxidations and difficult purifications, thus making it amenable for large-scale preparations. Further studies related to the utility of the product **8** as a chiral building block will be reported in due course.

4. Experimental

The reaction flasks and other glass equipment were heated in an oven at 130°C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots was detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic fosfomolibdic acid and iodine. Preparative column chromatography was performed on columns of silica gel (60–240 mesh) and with solvents that were distilled prior to use. Preparative centrifugally accelerated radial thin-layer chromatography (PCAR-TLC) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA); the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34, 644–6) and the eluting solvents were delivered by the pump at a flow rate of 0.5–1.5 mL min^{-1}. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity or on a Bruker 300 instrument in $CDCl_3$ at 55°C. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ ($\delta = 7.26$) in $CDCl_3$. Optical rotations were taken at 25°C on a Perkin–Elmer 241 polarimeter. Elemental analysis were performed on a Perkin Elmer 240B microanalyzer. Methyl acrylate **3a** was purchased (Aldrich) and distilled prior to use. Nitrone **3**[12] and acrylamide **4b**[20] were prepared according the reported procedures.

4.1. Cycloaddition of nitrone 3 with dipolarophiles 4a and 4b

A solution of 5-(*tert*-butyldiphenylsilyl)-1-deoxy-1-hydroxyamino-2,3-*O*-isopropylidene-D-ribo-1,4-pentofuranose (5 mmol), dipolarophile (15 mmol and 6 mmol of **4a** and **4b**, respectively) and ethyl glyoxylate (150 mmol, 50% solution in toluene) was heated at 75°C, in a sealed tube (18 h and 40 h for **4a** and **4b**, respectively). The reaction mixture was evaporated and the residue was purified by column flash chromatography (cyclohexane/ethyl acetate, 4:1), and then by HPLC (*n*-hexane/2-propanol, 97:3). Preparative HPLC was performed with a microsorb silica DYNAMAX-100 Å (21×250 mm) column, with a Varian Pro Star instrument.

4.1.1. (3*R*,5*R*)-5-Acetyl-2-[5-(*tert*-butyldiphenylsilyl)-1-deoxy-2,3-*O*-isopropylidene-D-ribo-1,4-pentofuranose-1-yl]-isoxazolidine-3-carboxylic acid ethyl ester 5a. **5a** (1.582 g, 53%); HPLC: t_R 11.2 min; sticky oil; $[\alpha]_D^{25} = -12$ (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, 3H, $J = 7.1$ Hz), 0.98 (s, 9H), 1.27 (s, 3H), 1.42 (s, 3H), 2.47 (dt, 1H, $J = 8.1$, 12.9 Hz), 2.81 (ddd, 1H, $J = 1.8$, 8.8, 12.9 Hz), 3.63 (dd, 1H, $J = 5.3$, 10.6 Hz), 3.68 (s, 3H), 3.74 (dd, 1H, $J = 8.6$, 10.6 Hz), 3.78 (dd, 1H, $J = 7.1$, 10.8 Hz), 3.91 (dd, 1H, $J = 7.1$, 10.8 Hz), 4.15 (ddd, 1H, $J = 1.7$, 5.3, 8.6 Hz), 4.16 (dd, 1H, $J = 1.8$, 8.1 Hz), 4.55 (dd, 1H, $J = 8.1$, 8.8 Hz), 4.57 (d, 1H, $J = 1.3$ Hz), 4.68 (dd, 1H, $J = 1.7$, 6.3 Hz), 4.83 (dd, 1H, $J = 1.3$, 6.3 Hz), 7.28–7.60 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 19.2, 25.0, 26.7, 26.8, 34.2, 52.5, 61.4, 62.4, 64.1, 77.6, 82.1, 84.1, 87.5, 98.4, 112.4, 127.7, 127.7, 129.7, 129.7, 133.3, 133.4, 135.5, 135.5, 170.4, 172.1. Anal. calcd for $C_{32}H_{43}NO_8Si$: C, 64.30; H, 7.25; N, 2.34. Found: C, 64.56; H, 7.01; N, 2.40%.

4.1.2. (3*S*,5*R*)-5-Acetyl-2-[5-(*tert*-butyldiphenylsilyl)-1-deoxy-2,3-*O*-isopropylidene-D-ribo-1,4-pentofuranose-1-yl]-isoxazolidine-3-carboxylic acid ethyl ester 6a. **6a** (0.807 g, 27%); HPLC: t_R 10.8 min; sticky oil; $[\alpha]_D^{25} = +45$ (*c* 0.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.02 (t, 3H, $J = 7.1$ Hz), 1.05 (s, 9H), 1.33 (s, 3H), 1.50 (s, 3H), 2.70 (ddd, 1H, $J = 8.6$, 10.1, 13.2 Hz), 2.87 (ddd, 1H, $J = 2.1$, 4.4, 13.2 Hz), 3.72 (dd, 1H, $J = 5.4$, 10.9 Hz), 3.74 (s, 3H), 3.84 (dd, 1H, $J = 8.1$, 10.9 Hz), 3.89 (dd, 1H, $J = 7.1$, 10.6 Hz), 3.98 (dd, 1H, $J = 7.1$, 10.6 Hz), 4.19 (dd, 1H, $J = 2.1$, 8.6 Hz), 4.24 (ddd, 1H, $J = 1.6$, 5.4, 8.1 Hz), 4.48 (d, 1H, $J = 1.4$ Hz), 4.76 (dd, 1H, $J = 1.6$, 6.2 Hz), 4.77 (dd, 1H, $J = 4.4$, 10.1 Hz), 4.90 (dd, 1H, $J = 1.4$, 6.2 Hz), 7.36–7.66 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 19.2, 24.9, 26.6, 26.8, 34.0, 52.5, 61.2, 61.4, 63.9, 76.5, 81.9, 83.87, 87.3, 98.4, 112.7, 127.8, 127.8, 129.8, 129.8, 133.2, 133.3, 135.5, 135.5, 170.4, 170.5. Anal. calcd for $C_{32}H_{43}NO_8Si$: C, 64.30; H, 7.25; N, 2.34. Found: C, 64.12; H, 7.11; N, 2.56%.

4.1.3. (3*R*,5*R*)-2-[5-(*tert*-Butyldiphenylsilyl)-1-deoxy-2,3-*O*-isopropylidene-D-ribo-1,4-pentofuranose-1-yl]-5-[(1*S*,5*R*,7*R*)-10,10-dimethyl-3,3-dioxo-3λ⁶-thia-4-aza-tricyclo[5.2.1.0^{1,5}]decane-4-carbonyl]-isoxazolidine-3-carboxylic acid ethyl ester 5b. **5b** (2.272 g, 57%); HPLC: t_R 8.6 min; white solid; mp = 55–56°C; $[\alpha]_D^{25} = -62$ (*c* 1.31, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, 3H, $J = 7.3$ Hz), 0.97 (s, 3H), 1.04 (s, 9H), 1.19 (s, 3H), 1.29 (s, 3H), 1.30–1.41 (m, 2H), 1.46 (s, 3H), 1.82–1.95 (m, 3H), 2.03 (dd, 1H, $J = 7.7$, 13.9 Hz), 2.29 (ddd, 1H, $J = 4.7$, 7.3, 13.9 Hz), 2.82 (ddd, 1H, $J = 1.8$, 8.4, 13.1 Hz), 2.87 (dt, 1H, $J = 7.7$, 13.1 Hz), 3.43 (d, 1H, $J = 13.9$ Hz), 3.52 (d, 1H, $J = 13.9$ Hz), 3.69 (dd, 1H, $J = 5.1$, 10.6 Hz), 3.80 (dd, 1H, $J = 8.8$, 10.6 Hz), 3.81 (dq, 1H, $J = 7.3$, 10.6 Hz), 3.91 (dd, 1H, $J = 4.7$, 7.7 Hz), 3.96 (dq, 1H, $J = 7.3$, 10.6 Hz), 4.24 (ddd, 1H, $J = 1.1$, 5.1, 8.8 Hz), 4.28 (dd, 1H, $J = 1.8$, 7.7 Hz), 4.64 (s, 1H), 4.75 (dd, 1H, $J = 1.1$, 6.2 Hz), 4.86 (d, 1H, $J = 6.2$ Hz), 5.11 (dd, 1H, $J = 7.7$, 8.4 Hz), 7.35–7.66 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 19.1, 19.9, 20.9, 25.1, 26.4, 26.6, 26.7, 32.0, 32.9, 37.8, 44.7, 47.7, 48.7, 53.0, 61.2, 63.3, 64.0, 65.5, 78.0, 82.6, 83.9, 87.7, 97.8, 112.1, 127.6, 127.7, 129.6, 129.7, 133.4, 133.4, 135.4, 135.5, 169.7, 170.3. Anal. calcd for $C_{41}H_{56}N_2O_{10}SSi$: C, 61.78; H, 7.08; N, 3.51. Found: C, 61.93; H, 6.89; N, 3.62%.

4.1.4. (3*S*,5*R*)-2-[5-(*tert*-Butyldiphenylsilyl)-1-deoxy-2,3-*O*-isopropylidene-D-ribo-1,4-pentofuranose-1-yl]-5-[(1*S*,5*R*,7*R*)-10,10-dimethyl-3,3-dioxo-3λ⁶-thia-4-azatricyclo[5.2.1.0^{1,5}]decane-4-carbonyl]-isoxazolidine-3-carboxylic acid ethyl ester 6b. **6b** (0.120 g, 3%); HPLC: t_R 7.2 min; sticky oil; $[\alpha]_D^{25}=-51$ (*c* 0.34, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (s, 3H), 1.07 (s, 9H), 1.18 (s, 3H), 1.26 (t, 3H, $J=7.2$ Hz), 1.29 (s, 3H), 1.32–1.39 (m, 2H), 1.51 (s, 3H), 1.84–1.96 (m, 2H), 2.00 (dd, 1H, $J=7.7$, 13.8 Hz), 2.03–2.11 (m, 2H), 2.45 (ddd, 1H, $J=8.6$, 9.5, 12.6 Hz), 2.99 (ddd, 1H, $J=4.0$, 6.4, 12.6 Hz), 3.38 (d, 1H, $J=13.5$ Hz), 3.47 (d, 1H, $J=13.5$ Hz), 3.78 (dd, 1H, $J=7.2$, 10.6 Hz), 3.83 (dd, 1H, $J=5.7$, 10.6 Hz), 3.89 (dd, 1H, $J=4.8$, 7.7 Hz), 3.95 (dd, 1H, $J=6.4$, 9.5 Hz), 4.18 (q, 2H, $J=7.2$ Hz), 4.19 (ddd, 1H, $J=4.0$, 5.7, 7.2 Hz), 4.54 (dd, 1H, $J=4.0$, 6.1 Hz), 4.74 (dd, 1H, $J=4.0$, 8.6 Hz), 4.91 (dd, 1H, $J=1.4$, 6.1 Hz), 5.06 (d, 1H, $J=1.4$ Hz), 7.37–7.70 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 19.3, 19.9, 21.2, 25.3, 26.3, 26.8, 27.2, 33.2, 34.7, 38.3, 45.0, 47.7, 48.6, 53.2, 60.4, 61.3, 64.9, 65.9, 76.0, 81.2, 83.5, 87.4, 96.9, 112.6, 127.6, 127.6, 127.7, 127.7, 129.5, 129.6, 133.7, 133.7, 135.5, 135.5, 135.6, 135.7, 169.5, 169.7. Anal. calcd for $C_{41}H_{56}N_2O_{10}SSi$: C, 61.78; H, 7.08; N, 3.51. Found: C, 61.84; H, 6.92; N, 3.40%.

4.2. Reduction of compounds 5 and 6

4.2.1. 1-*tert*-Butyl 2-ethyl (2*R*,4*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-5-oxo-pyrrolidine-1,2-dicarboxylate 8. A solution of **5a** (0.57 g, 0.93 mmol) in ethanol (7 mL) was treated with concentrated HCl (1.2 mL) at ambient temperature and the resulting solution is stirred until no starting material remained (hexane/EtOAc, 4:1, $R_f=0.32$) (ca. 6 h). The reaction mixture was poured into a saturated aqueous solution of sodium carbonate (35 mL) and extracted with EtOAc (4×25 mL). The organic layers were combined, dried over magnesium sulfate and evaporated on a rotary evaporator to give a residue which was taken up in ethanol (20 mL), treated with Pearlman's catalyst, $Pd(OH)_2$–C (60 mg) and stirred under hydrogen at ambient temperature and 2000 psi. After 48 h, the reaction mixture was filtered through Celite, which was washed with ethanol, and the filtrate was evaporated under reduced pressure to give crude **7**. The formation of **7** was confirmed by TLC (hexane/EtOAc, 1:1, $R_f=0.12$ or EtOAc/MeOH, 5:1, $R_f=0.62$).

Crude **7** was dissolved in DMF (9 mL) and treated with imidazole (0.378 g) and TBDMSCl (0.452 g, 3 mmol). The resulting solution was stirred at 70°C until no starting material was observed by TLC (ca. 3 h). Methanol (3 mL) and water (30 mL) were added and the resulting mixture was extracted with EtOAc (3×25 mL). The organic layers were combined, dried (magnesium sulfate) and evaporated under reduced pressure to give crude **4**, which was dissolved in CH_2Cl_2 (15 mL) and treated with Boc_2O (0.41 g, 1.86 mmol), Et_3N (0.15 mL, 1 mmol) and DMAP (0.122 g, 1 mmol). The reaction mixture was stirred at ambient temperature overnight, at which time 1N $KHSO_4$ (15 mL) was added. The organic layer was separated, washed with water (1×15 mL) and brine (1×15 mL), dried over magnesium sulfate and evaporated to give crude **8**, which is purified by radial chromatography (hexane/EtOAc, 9:1, $R_f=0.27$) to afford pure **8** as an oil (0.187 g, 52%). $[\alpha]_D^{25}=+44$ (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.11 (s, 3H), 0.15 (s, 3H), 0.88 (s, 9H), 1.23 (t, 3H, $J=7.3$ Hz), 1.49 (s, 9H), 1.95 (dt, 1H, $J=6.8$, 13.1 Hz), 2.54 (dt, 1H, $J=7.8$, 13.1 Hz), 4.18 (dq, 1H, $J=7.3$, 10.7 Hz), 4.22 (dq, 1H, $J=7.3$, 10.7 Hz), 4.26 (dd, 1H, $J=6.8$, 7.8 Hz), 4.41 (dd, 1H, $J=6.8$, 7.8 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −5.4, −4.6, 14.0, 18.9, 25.6, 27.9, 32.1, 55.7, 61.6, 70.5, 83.7, 149.8, 170.4, 171.4. Anal calcd for $C_{18}H_{33}NO_6Si$ C, 55.79; H, 8.58; N, 3.61. Found: C, 55.93; H, 8.32; N, 3.97%.

The same procedure was applied to **5b** (0.42 g, 0.53 mmol) and pure **8** (0.115 g, 56%) was obtained. The physical and spectroscopic properties were identical to those obtained for the compound prepared from **5a**.

4.2.2. 1-*tert*-Butyl 2-ethyl (2*S*,4*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-5-oxo-pyrrolidine-1,2-dicarboxylate 10. The same procedure described above for the conversion of **5a** to **8** was applied to **6a** (0.130 g, 0.21 mmol). After radial chromatography (hexane/EtOAc, 9:1, $R_f=0.21$) of the crude product, pure **10** (0.044 g, 54%) was obtained as an oil. $[\alpha]_D^{25}=+39$ (*c* 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 3H), 0.13 (s, 3H), 0.85 (s, 9H), 1.25 (t, 3H, $J=7.2$ Hz), 1.45 (s, 9H), 2.16 (dt, 1H, $J=9.8$, 13.2 Hz), 2.30 (ddd, 1H, $J=1.5$, 8.3, 13.2 Hz), 4.29 (q, 2H, $J=7.2$ Hz), 4.38 (dd, 1H, $J=8.3$, 10.0 Hz), 4.51 (dd, 1H, $J=1.5$, 9.6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −5.3, −4.5, 14.1, 18.2, 25.6, 27.9, 32.2, 55.1, 61.7, 69.7, 83.7, 149.5, 171.2, 172.0. Anal. calcd for $C_{18}H_{33}NO_6Si$: C, 55.79; H, 8.58; N, 3.61. Found: C, 55.62; H, 8.67; N, 3.72%.

The same procedure was applied to **6b** (0.21 g, 0.26 mmol) and pure **10** (0.115 g, 59%) was obtained. The physical and spectroscopic properties were identical to those obtained for the compound prepared from **6a**.

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