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USEFUL BUILDING BLOCKS FOR THE STEREOCONTROLLED ASSEMBLY OF 2,3,5-TRISUBSTITUTED PYRROLIDINES

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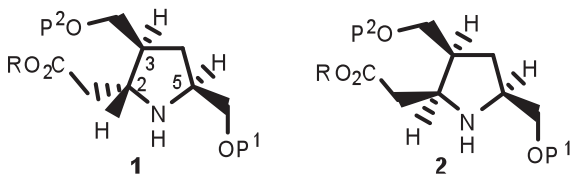
Abstract – A protected pyroglutamol derivative is converted into an *all-cis*, differentially protected 2,3,5-trisubstituted pyrrolidine, which is amenable to elaboration into more complex nitrogenous educts.

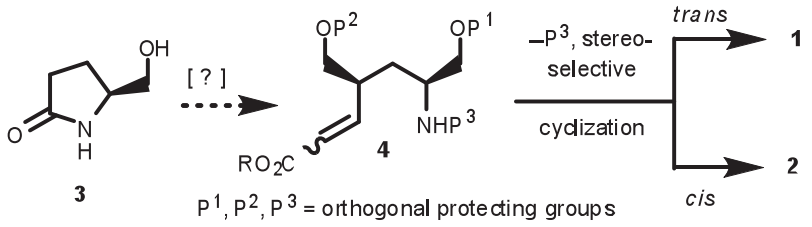
INTRODUCTION

An ongoing project revealed the desirability of accessing differentially protected 2,3,5-trisubstituted pyrrolidines of the type **1** and **2** in homochiral form (Scheme 1). Curiously, the CAS database (SciFinder) appears to record no examples of these substructures. Known avenues to structurally related compounds rely largely on 1,3-dipolar cycloaddition reactions of azomethine ylides,[1,2] a process that performs best when the pyrrolidine C-2 substituent is an aromatic ring, and that enables facile access to the *all-cis* stereochemical series; i.e., to products of the general type **2**, but not **1**. We thus set out to devise a synthesis of these materials. Our ideal route would deliver either **1** or **2** in a highly diastereoselective manner, and in an orthogonally blocked form, from a common precursor drawn from the chiral pool.

According to the hypothesis adumbrated in Scheme 2, the desired materials could ensue through a stereoselective cyclization of substrate **4**, which in turn appeared to be available by elaboration of readily available pyroglutamol, **3**. Herein, we detail how this surmise was translated into practice.



Scheme 1

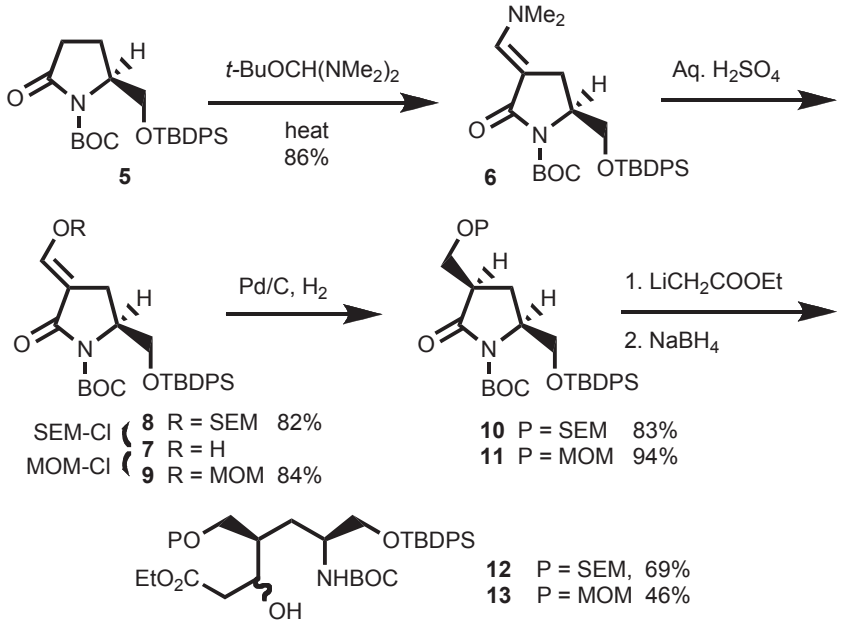


Scheme 2

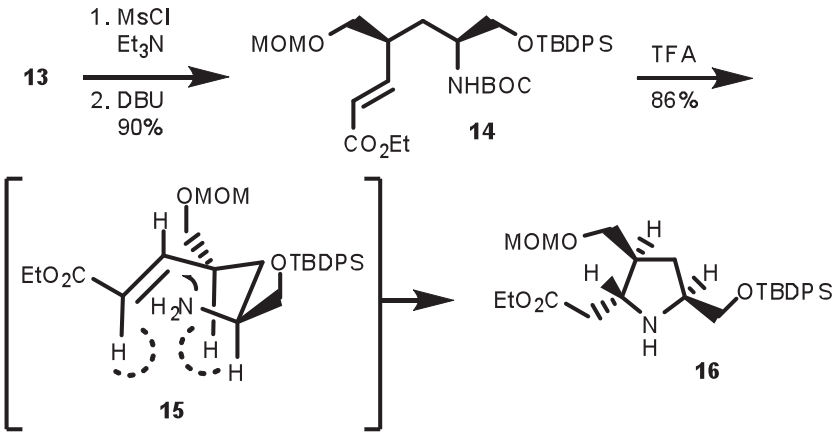
RESULTS AND DISCUSSION

Reaction of pyroglutamol derivative **5**[3] (Scheme 3) with the Bredereck reagent[4] furnished **6** in high yield.[5] In accord with Terashima,[6] the subsequent acidic hydrolysis of the vinylogous urea proceeded with no disturbance to the *N*-BOC group, and *O*-reprotection of the ensuing **7** (not thoroughly characterized) delivered **8** or **9**. Both of these compounds underwent stereoselective hydrogenation from the less encumbered α-face of the molecule to afford predominantly the 3,5-*cis*-products **10**–**11**.[7] It is worthy of note that the MOM derivative **11** afforded a higher level of diastereoselectivity in this step (dr = 14:1 vs. 10:1 for **10**). Pure *cis*-diastereomers were readily obtained in either case by column chromatography. Subsequent reaction with the enolate of EtOAc[8] afforded Claisen-type products that were not extensively characterized, but that were directly reduced ($NaBH_4$) to an essentially 1:1 mixture of diastereomers of alcohols **12** or **13**. These substances served as the precursors of the target pyrrolidines.

The 2,3-*trans* diastereomeric series was secured starting with mesylation of **13** and exposure of the resultant to the action of DBU, which occasioned β-elimination of methanesulfonic acid leading to *trans*-



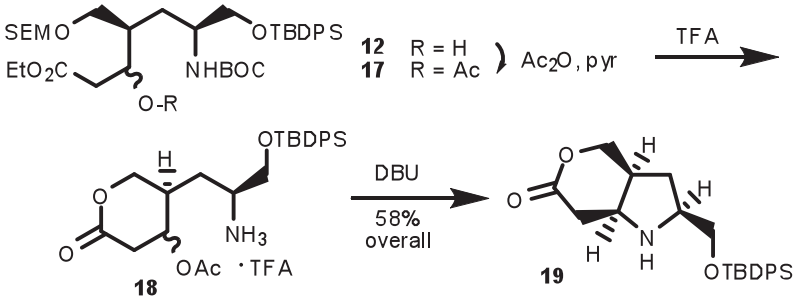
Scheme 3



Scheme 4

olefinic ester **14**. Subsequent treatment with TFA released the *N*-BOC group and triggered formation of 2,3-*trans* pyrrolidine **16** (single diastereomer by ^{1}H and ^{13}C NMR). Evidently, the transient free amine had undergone Michael cyclization from the *Si* face of the olefinic bond; probably from conformer **15**, wherein minimal $A^{1,3}$ interaction[9] subsists (Scheme 4; cf. the H-H interaction rendered by dashed semicircles). The stereochemical assignment of **16** finds additional support in the observation that release of the MOM group (4M HCl in dioxane, rt) produced a hydroxyester that failed to lactonize. Compound **16** is a congener of pyrrolidine **1** that satisfies the conditions established at the onset of this investigation, in that its oxygenated functionalities are orthogonally blocked.

Access to the *all cis* diastereomeric series necessitated an artifice that would override the conformational preferences of **14**/**15**, thereby permitting nucleophilic attack by the NH_2 group onto the *Re* face of the π bond. This was accomplished by inducing formation of lactone **18** prior to cyclization (Scheme 5). Exposure of the latter to the action of DBU promoted elimination of AcOH and conjugate addition of the amino group to the nascent α,β-unsaturated lactone, resulting in formation of stereochemically homogeneous **19**.[10] This material embodies a cyclic form of target compound **2**.



Scheme 5

In summary, compounds **12**-**13**, which are readily available from pyroglutamol, are useful building blocks for the stereodivergent assembly of 2,3,5-trisubstituted pyrrolidines **16** (2,3-*trans*; 3,5-*cis* series) and **19** (*all cis* series). While the present work was motivated by a problem encountered during research in natural product synthesis, the ubiquitous occurrence of pyrrolidines in biologically active molecules, natural[11] or otherwise,[12] should make the results described herein of interest to individuals involved in the creation of new bioactive scaffolds and to the medicinal chemistry community in general.

EXPERIMENTAL

Melting points were measured on a Mel-Temp apparatus and are uncorrected. Unless otherwise stated, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at room temperature on a Bruker Avance II 300 instrument. Chemical shifts are reported in parts per million (ppm) on the δ scale using the solvent residual peak as internal standard. High-resolution mass spectra (m/z) were obtained in the electrospray ionization (ESI) mode. Optical rotation was measured on a Jasco P-2000 polarimeter. IR spectroscopy was performed on a Perkin-Elmer Frontier instrument. THF was freshly distilled from Na/Ph_2CO under N_2, and CH_2Cl_2 was freshly distilled from CaH_2 under N_2. Flash chromatography was performed on 230–400 mesh silica gel. Analytical TLC was carried out on aluminum-backed Merck silica gel 60 plates with fluorescent indicator, with spots being visualized by alkaline aqueous $KMnO_4$. All reactions were performed under dry argon in oven–dried flasks equipped with Teflon™ stirbars. Flasks were fitted with rubber septa for the introduction of substrates, reagents and solvents via syringe.

***tert*-Butyl (3*E*,5*S*)-3-[(dimethylamino)methylene]-2-oxo-4-(*tert*-butyldiphenylsilyloxy)methyl-1-pyrrolidinecarboxylate (6)**. Neat *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent; 3.8 mL, 18.0 mmol) was added to a warm (50 °C) solution of **5** (5.5 g, 12.0 mmol) in 4 mL THF and the mixture was heated to 70 °C. Stirring at this temperature was continued overnight, during which time the solvent had partially evaporated and the reaction mixture had acquired a red color. The mixture was cooled, diluted with THF while still warm, and applied directly to a silica gel column. Flash chromatography (elution with a 30/70 to 60/40 EtOAc/hexanes gradient) gave **6** (5.3 g, 10.3 mmol, 86% yield) as a faintly yellow, viscous oil that solidified on long standing to form pale yellow crystals, mp 88–89 °C; $[\alpha]_D^{20}$ -19.2 (c 1.9, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.44 (s, 9H), 3.01 (s, 6H), 3.06-2.90 (m, 2H), 3.69 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.77 (dd, *J* = 9.8, 3.3 Hz, 1H), 4.13-4.19 (m, 1H), 7.11 (brs, 1H), 7.33-7.46 (m, 6H), 7.57-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 25.4, 26.8, 28.1, 41.9, 55.5, 64.8, 81.4, 93.8, 127.7, 127.7, 129.7, 133.3, 133.6, 135.5, 135.5, 145.9, 150.9, 170.6; IR (film, cm^{-1}): ν 1748, 1621; HRMS: calc. for $C_{29}H_{40}N_2O_4Na^{28}Si$ $[M + Na]^+$ 531.2655; found 531.2648.

***tert*-Butyl (3*E*,5*S*)-3-{[(2-trimethylsilylethoxy)methoxy]methylene}-2-oxo-4-(*tert*-butyldiphenylsilyloxy)methyl-1-pyrrolidinecarboxylate (8)**. A solution of **6** (3.0 g, 5.9 mmol) in THF (12 mL) was added to rapidly stirred aqueous H_2SO_4 (55 mL of 5% v/v solution) at rt and the resulting milky suspension was sonicated for 40 min. Solid $NaHCO_3$ was then added in portions (GAS EVOLUTION!) until gas evolution ceased. The residue was partitioned between H_2O and $CHCl_3$, and the organic extract was dried (Na_2SO_4), filtered, and concentrated under vacuum. The residual, crude **7**, yellow oil, was used without purification in the next reaction. To a CH_2Cl_2 (11 mL) solution of the residue and Hünig's base (2.1 mL, 12.0 mmol) at 0 °C was added SEMCl (1.6 mL, 9.0 mmol) over several minutes. The reaction was stirred until starting material had been consumed (TLC, about 30 min). Following dilution with CH_2Cl_2, the mixture was poured into a saturated aqueous solution of NH_4Cl, the layers were separated, and the aqueous layer was extracted with one additional portion of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. Silica gel chromatography of the residue (20/80 EtOAc/hexanes) gave **8** (3.0 g, 4.8 mmol), colorless oil, in 82% yield over two steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 9H), 0.95 (t, *J* = 8.3 Hz, 2H), 1.01 (s, 9H), 1.45 (s, 9H), 2,71 (ddd, *J* = 16.5, 8.9, 2.9 Hz, 1H), 2.82 (brd, *J* = 16.5 Hz, 1H), 3.65-3.71 (m, 3H), 3.83 (dd, *J* = 10.1, 4.6 Hz, 1H), 4.21-4.28 (m, 1H), 5.02-5.06 (m, 2H), 7.33-7.48 (m, 7H), 7.57-7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -1.4, 17.9, 19.2, 23.5, 26.7, 28.0, 56.1, 64.8, 66.9, 82.3, 96.5, 110.6, 127.7, 127.7, 129.7, 132.9, 133.3, 135.5, 150.3, 150.6, 168.5; HRMS: calc. for $C_{33}H_{49}NO_6Na^{28}Si_2$ $[M + Na]^+$ 634.2996; found 634.3007.

***tert*-Butyl (3*R*,5*S*)-3-{[(2-trimethylsilylethoxy)methoxy]methyl}-2-oxo-4-(*tert*-butyldiphenylsilyloxy)-methyl-1-pyrrolidinecarboxylate (10)**. A solution of **8** (3.0 g, 4.8 mmol) in EtOAc (60 mL) containing suspended 10% palladium on charcoal (1.3 g) was placed in a Parr reactor, which was pressurized to 1000 psi of H_2. After 24 h of rapid stirring at rt, the catalyst was removed by filtration over a pad of Celite. Evaporation of solvent under vacuum gave crude hydrogenated product as a 10:1 mixture of *cis* (**10**, major) and *trans* diastereomers. Pure **10** (2.5 g, 4.0 mmol, 83%), $[\alpha]_D^{20}$ -16.9 (c 1.1, EtOH), was readily isolated by flash chromatography (20/80 EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 9H), 0.92 (t, *J* = 8.3 Hz), 1.06 (s, 9H), 1.41 (s, 9H), 2.16-2.38 (m, 2H), 2.77-2.88 (m, 1H), 3.52-3.65 (m, 2H), 3.75-3.85 (m, 3H), 3.91 (dd, *J* = 9.9, 5.9 Hz, 1H), 4.10-4.18 (m, 1H), 4.60-4.65 (m, 2H), 7.34-7.46 (m, 6H), 7.61-7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -1.4, 18.0, 19.3, 23.6, 26.8, 27.9, 43.3, 56.9, 64.2, 65.1, 67.21, 82.8, 95.0, 127.7, 129.8, 133.1, 133.3, 135.5, 135.6, 150.0, 174.3; IR (film, cm^{-1}): ν 1785, 1713; HRMS: calc. for $C_{33}H_{51}NO_6Na^{28}Si_2$ $[M + Na]^+$ 636.5153; found 636.3143.

***tert*-Butyl (3*R*,5*S*)-3-[(methoxymethoxy)methyl]-2-oxo-4-(*tert*-butyldiphenylsilyloxy)methyl-1-pyrro-**

lidinecarboxylate (11) To a solution of crude **7** (8.4 mmol) in 20 mL CH_2Cl_2 at rt was added MOMCl (2.2 mL, 12.6 mmol) and diisopropylethylamine (1.0 mL, 12.6 mmol). The reaction was stirred for 1 h at rt before being diluted with CH_2Cl_2 and poured into saturated aqueous NH_4Cl. The organic layer was separated, dried (Na_2SO_4), and evaporated under vacuum. Flash chromatography (30/70 EtOAc/hexanes) gave **9** (3.7 g, 7.0 mmol, 84% yield) as a colorless oil. To a solution of this material (3.5 g, 6.7 mmol) in EtOAc (150 mL) was added Pd/C (2.0 g) and the reaction vessel was flushed with H_2. Stirring was continued overnight, when the mixture was filtered over Celite and evaporated to give **11** (3.32 g, 6.31 mmol, 94% yield) as a colorless oil, which was a ~14:1 mixture of diastereomers. $[\alpha]_D^{20}$ -18.1 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H); 1.41 (s, 9H); 2.17-2.40 (m, 2H); 2.77-2.89 (m, 1H); 3.32 (s, 3H); 3.72-3.95 (m, 4H); 4.10-4.21 (m, 1H); 4.54-4.59 (m, 2H); 7.34-7.48 (m, 6H); 7.60-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 23.5, 26.8, 27.9, 43.2, 55.3, 56.9, 64.2, 67.0, 82.9, 96.5, 127.7, 129.8, 133.13, 133.3, 135.5, 135.6, 149.9, 174.3; IR (film, cm^{-1}): ν 1784, 1715; HRMS: calc. for $C_{29}H_{41}NO_6{}^{28}Si$ [M + Na]+ 550.2601; found 550.2598.

Ethyl (4*S*,6*S*)-3-hydroxy-6-[[(1,1-dimethylethoxy)carbonyl]amino]-4-{[(2-trimethylsilylethoxy)-methoxy]methyl}-7-(*tert*-butyldiphenylsilyloxy)heptanoate (12). Commercial BuLi solution (1.6 M in hexanes, 13.4 mL, 21.4 mmol) was added to a solution of diisopropylamine (2.9 mL, 20.0 mmol) in THF (43 mL) at -78 °C, and the mixture was stirred for 15 min. Anhydrous EtOAc (2.0 mL, 20.4 mmol) was added (syringe), and stirring was continued for 1.5 h at the same temperature. A solution of **10** (6.1 g, 9.9 mmol) in THF (11 mL) was added (syringe) over several minutes, resulting in a lemon-yellow solution. The mixture was warmed to -25 °C and stirring was continued for 1.5 h, at which time TLC indicated that starting material had been consumed. The reaction was quenched with saturated aqueous NH_4Cl solution and stirring was continued as the mixture warmed to rt. The mixture was diluted with $CHCl_3$, washed with NH_4Cl, and the aqueous phase was extracted with additional $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent was removed under vacuum to give a clear oil that, being a mixture of isomers, was used in the next reaction without further purification. To a solution of the residue in EtOH (62 mL) at 0 °C was added $NaBH_4$ (430 mg, 11.4 mmol). The solution was stirred until TLC monitoring indicated convergence to a single spot, about 40 min. Aqueous NH_4Cl was then added (GAS EVOLUTION!) and stirring was continued for 15 min as the mixture was warmed to rt. The mixture was diluted with $CHCl_3$, and washed with additional NH_4Cl. The aqueous phase was extracted with more $CHCl_3$, and the combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed under vacuum. Silica gel chromatography using 20/80 to 25/75 EtOAc/hexanes gradient elution gave **12** (4.8 g, 6.8 mmol, 69% yield over two steps), colorless oil, as a 1:1 mixture of diastereomers. ^{1}H NMR

(300 MHz, $CDCl_3$): δ 0.08 (s, 9H), 0.93 (brt, 2H), 1.07 (s, 9H), 1.27 (brt, 3H), 1.43 (s, 9H), 1.55-1.71 (m, 2H), 1.71-1.84 (m, 1H), 2.43-2.59 (m, 2H), 3.54-3.82 (m, 8H), 4.17 (brq, 3H), 4.63 (m, 3H), 7.34-7.47 (m, 6H), 7.61-7.68 (m, 4H) ^{13}C NMR (75 MHz, $CDCl_3$): δ -1.4, 14.2, 18.0, 19.3, 26.9, 28.4, 28.6, 39.0, 39.5, 39.7, 49.9, 60.6, 65.4, 66.3, 66.6, 68.3, 70.2, 79.1, 95.1, 127.7, 129.8, 133.3, 135.6, 135.6, 155.7, 172.8 HRMS: calc. for $C_{37}H_{61}NO_8Na^{28}Si_2$ $[M + Na]^+$ 726.3833; found 768.3815.

Ethyl (4*S*,6*S*)-3-hydroxy-6-{[(1,1-dimethylethoxy)carbonyl]amino}-4-[(methoxymethoxy)methyl]-7-(*tert*-butyldiphenylsilyloxy)heptanoate (13). To a solution of diisopropylamine (82 μL, 0.58 mmol) in THF (3 mL) at –78 °C was added butyllithium (2.5 M in hexanes, 0.25 mL, 0.64 mmol), and the solution was stirred for 15 min. Anhydrous ethyl acetate (57 μL, 0.58 mmol) was then added, and stirring was continued at the same temperature for 1.5 h. Dropwise addition of a solution of **11** (252 mg, 0.48 mmol) in THF (1.5 mL) was performed before the reaction mixture was warmed to -15 °C. Stirring was continued at this temperature for 2 h, when TLC monitoring indicated consumption of starting material. The mixture was poured into saturated aqueous NH_4Cl prior to extraction with two portions of $CHCl_3$. The combined organic extracts were dried (Na_2SO_4), filtered, and stripped of volatiles under vacuum to give a colorless oil, which was carried on without purification. To the crude residue as an EtOH (1.5 mL) solution at rt was added $NaBH_4$ (22 mg, 0.58 mmol). The mixture was stirred at rt for 1 h, when TLC monitoring indicated convergence to a single spot. The mixture was quenched by careful addition of saturated aqueous NH_4Cl (GAS EVOLUTION!). The residue was extracted with CH_2Cl_2, and the organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography using 30/70 EtOAc/hexanes as eluent to give **13** (135 mg, 0.22 mmol, 46% over two steps), a 1:1 mixture of diastereomers, as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H); 1.24-1.33 (m, 3H); 1.43 (s, 9H); 1.55-1.70 (m, 1H); 1.73-1.85 (m, 1H); 2.44-2.62 (m, 2H); 3.24-3.43 (m, 4H); 3.54-3.88 (m, 5H); 4.08-4.27 (m, 3H); 4.55-4.74 (m, 3H); 7.33-7.49 (m, 6H); 7.58-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 19.3, 26.9, 28.4, 28.5, 30.2, 39.1, 39.5, 39.6, 49.9, 55.5, 60.7, 66.4, 66.6, 67.0, 68.1, 70.1, 79.2, 96.7, 127.7, 129.8, 133.2, 133.3, 135.6, 155.7, 172.8; HRMS: calc. for $C_{33}H_{52}NO_8{}^{28}Si$ $[M + H]^+$ 618.3462; found 618.3467.

Ethyl (2*E*,4*S*,6*S*)-6-{[(1,1-dimethylethoxy)carbonyl]amino}-4-[(methoxymethoxy)methyl]-7-(*tert*-butyldiphenylsilyloxy)hept-2-enoate (14). A CH_2Cl_2 (2 mL) solution of **13** (215 mg, 0.35 mmol), Et_3N (0.07 mL, 0.54 mmol), and MsCl (0.04 mL, 0.53 mmol) was stirred overnight at rt, then it was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and evaporated under vacuum to give a colorless oil, which was redissolved in CH_2Cl_2 (3 mL).

Addition of DBU (0.06 mL, 0.4 mmol) and stirring at rt for 2 h, caused complete conversion to **14** (TLC). The mixture was diluted with CH_2Cl_2 and poured into saturated aqueous NH_4Cl. The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated under vacuum. Flash chromatography (25/75 EtOAc/hexanes) gave **14** (192 mg, 0.32 mmol, 90% over two steps) as a colorless oil. $[\alpha]_D^{20}$ +5.8 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 9H); 1.29 (t, *J* = 7.1 Hz, 3H); 1.44 (s, 9H); 1.52-1.67 (m, 2H); 1.76-1.93 (m, 1H); 2.40-2.60 (m, 1H); 3.33 (s, 3H); 3.49-3.63 (m, 3H); 3.63-3.81 (m, 2H); 4.18 (q, *J* = 7.1 Hz, 2H); 4.59 (s, 2H); 4.67 (brd, *J* = 9.0 Hz, 1H); 5.81 (d, *J* = 15.8 Hz, 1H); 6.88 (dd, *J* = 15.8, 8.5 Hz, 1H); 7.34-7.50 (m, 6H); 7.59-7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 19.3, 26.9, 28.4, 32.9, 39.6, 50.0, 55.3, 60.2, 65.6, 69.6, 79.2, 96.5, 122.2, 127.8, 129.9, 133.1, 135.6, 149.7, 155.3, 166.3; IR (film, cm^{-1}): ν 1713; HRMS: calc. for $C_{33}H_{50}NO_7{}^{28}Si$ $[M + H]^+$ 600.3357; found 600.3365.

***tert*-Butyl (2*S*,3*S*,5*R*)-2-(ethyl-2-[carboxyethyl])-3-methoxymethyl-4-(*tert*-butyldiphenylsilyloxy)-methyl-1-pyrrolidinecarboxylate (16)**. A CH_2Cl_2 (3 mL) solution of **14** (112 mg, 0.19 mmol) and TFA (0.15 mL) was stirred at rt for 6 h, when TLC indicated consumption of starting material. The mixture was neutralized by careful addition of saturated $NaHCO_3$(aq) (GAS EVOLUTION!) and dilution with CH_2Cl_2 and the organic layer was separated, dried (Na_2SO_4), filtered, and evaporated under vacuum. The residue was dissolved in Et_2O, treated with activated charcoal (Norit®), and filtered through Celite, giving **14** (80 mg, 0.16 mmol, 86% yield) as a faintly yellow oil. $[\alpha]_D^{20}$ +15.5 (c 0.5, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H); 1.27 (m, 5H); 1.98-2.16 (m, 2H); 2.46 (dd, *J* = 15.9, 9.4 Hz, 1H); 2.69 (dd, *J* = 15.9, 3.7 Hz, 1H); 3.33 (s, 3H); 3.37-3.46 (m, 2H); 3.48 (d, *J* = 5.7 Hz, 1H); 3.56-3.61 (m, 2H); 4.16 (q, *J* = 7.1 Hz, 2H); 4.58 (s, 2H); 7.33-7.49 (m, 6H); 7.63-7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 19.2, 26.8, 31.2, 40.4, 44.5, 55.2, 57.1, 58.1, 60.4, 66.1, 69.7, 96.5, 127.7, 129.7, 133.4, 135.6, 172.4; IR (film, cm^{-1}): ν 1729; HRMS: calc. for $C_{28}H_{42}NO_5{}^{28}Si$ $[M + H]^+$ 500.2832; found 500.2838.

Ethyl (4*S*,6*S*)-6-[[(1,1-dimethylethoxy)carbonyl]amino]-3-acetoxy-4-{[(2-trimethylsilylethoxy)-meth- oxy]methyl}-7-(*tert*-butyldiphenylsilyloxy)heptanoate (17). A CH_2Cl_2 (26 mL) solution of **12** (2.5 g, 3.6 mmol), pyridine (3.3 mL, 42.1 mmol), Ac_2O (3.9 mL, 44.0 mmol), and DMAP (53 mg, 0.4 mmol), was stirred overnight at rt, then it was evaporated under vacuum. The residue was taken up in CH_2Cl_2, washed with 0.1 M HCl, dried (Na_2SO_4), filtered, and evaporated under vacuum. Flash chromatography (20/80 EtOAc/hexanes) of the residue gave **17** as a colorless oil (2.60 g, 3.48 mmol, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 9H), 0.92 (brt, 2H), 1.07 (s, 9H), 1.24 (brt, 3H), 1.43 (s, 9H), 1.51-1.66 (m, 3H), 2.03 (brs, 3H), 1.93-2.12 (m, 1H), 2.53-2.74 (m, 2H), 3.49-3.84 (m, 7H), 4.13 (brq, 2H), 4.61 (m, 2H), 5.34-5.44 (m, 1H), 7.35-7.47 (m, 6H), 7.60-7.68 (m, 4H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ -1.4, 14.2, 18.0, 19.3, 21.0, 26.9, 28.4, 29.2, 36.6, 37.1, 38.2, 38.3, 49.6, 49.8, 60.6, 65.3, 66.2, 66.3, 66.5, 66.6, 71.3, 71.7, 79.2, 95.0, 95.1, 127.7, 129.8, 129.8, 133.2, 133.30, 135.56, 135.6, 155.5, 155.6, 169.9, 170.1, 170.6, 170.7; HRMS: calc. for $C_{39}H_{63}NO_9Na^{28}Si_2$ $[M + Na]^+$ 768.3939; found 768.3938.

(2*S*,3a*S*,7a*S*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]hexahydropyrano[4,3-*b*]pyrrol-6(1*H*)-one (19)

To rapidly stirred TFA (50 mL) at rt was added a solution of **17** (2.57 g, 3.44 mmol) in CH_2Cl_2 (5.0 mL). The mixture was stirred at rt for 45 min, then it was diluted with CH_2Cl_2 and evaporated at ambient temperature. Periodic addition of CH_2Cl_2 during evaporation ensured removal of most of the TFA. The residue was taken up in more CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and stripped of volatiles under vacuum to leave a yellow-brown oil. The residue was dissolved in CH_2Cl_2 (70 mL) at rt with stirring and DBU (0.6 mL, 4.1 mmol) was added. The solution was stirred for 30 min before being evaporated under reduced pressure. The residue was loaded on reverse phase (C18) silica gel, washed with water, and eluted with EtOH to give **19** (831 mg, 2.03 mmol, 58% yield over two steps), colorless oil. $[\alpha]_D^{20}$ -30.1 (c 1.1, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.25-1.38 (m, 1H), 1.90-1.99 (m, 1H), 2.51-2.60 (m, 2H), 2.68 (dd, *J* = 15.3, 5.4 Hz, 1H), 3.19-3.28 (m, 1H), 3.61 (dd, *J* = 10.1, 6.5 Hz, 1H), 3.69-3.77 (m, 2H), 4.08 (dd, *J* = 11.7, 5.2 Hz, 1H), 4.22 (dd, *J* = 11.6, 4.4, 1H), 7.35-7.47 (m, 6H), 7.61-7.70 (m, 4H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.8, 30.8, 36.4, 36.5, 53.3, 59.9, 67.0, 69.2, 127.7, 129.7, 133.4, 133.5, 135.5, 135.6, 172.2; IR (film, cm^{-1}): ν 1747; HRMS: calc. for $C_{24}H_{32}NO_3{}^{28}Si$ $[M + H]^+$ 410.2151; found 410.2148.

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