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Total Synthesis of Both Enantiomers of *trans*-2,3-*cis*-3,4-Dihydroxyproline

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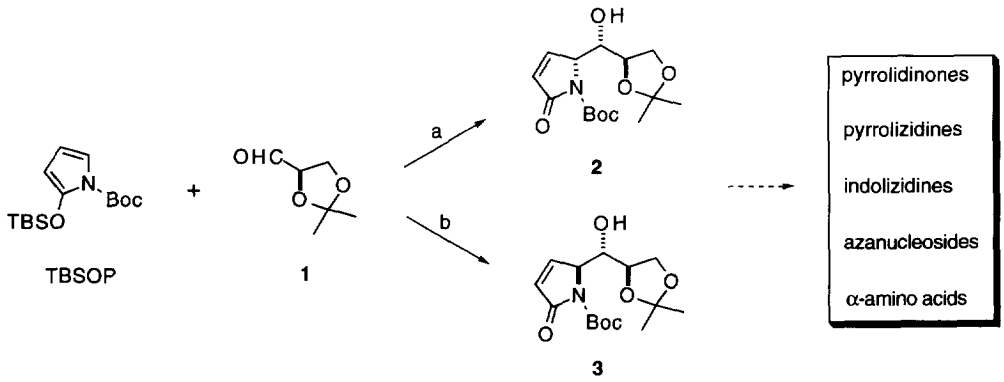
Abstract: Both enantiomers of *trans*-2,3-*cis*-3,4-dihydroxyproline, **4** and **5**, have been stereoselectively synthesized from 2,3-*O*-isopropylidene-D-glyceraldehyde **1**, by taking advantage of a divergent and parallel synthetic strategy, utilizing *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP) as the common four-carbon synthon.

Recently, we have been engaged in developing new strategies towards the synthesis of biologically significant molecules exploiting the potential of the pyrrole-based siloxydiene *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (hereafter TBSOP) as the key nucleophilic synthon.[1]

Scheme 1[a]



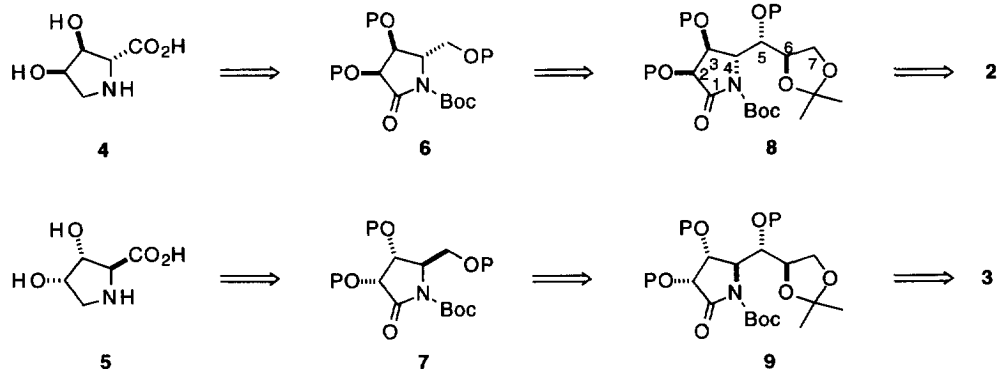
[a] Reagents: (a) $SnCl_4$ (1.5 equiv), Et_2O, -85°C; (b) BF_3 etherate (1.0 equiv), Et_2O, -85°C.

In particular, the Lewis acid-catalyzed condensation of TBSOP with protected D-glyceraldehyde **1** (Scheme 1) allowed the diastereoselective formation of either seven-carbon lactam **2** ($SnCl_4$ as a catalyst), or **3** (BF_3 etherate as a catalyst),[2] which were easily transformed, according to uniformed synthetic protocols, into a variety of structurally and stereochemically diverse targets, comprising pyrrolidinones,[2a] pyrrolizidines,[3] indolizidines,[4] azanucleosides,[5] and α-amino acids.[6] As a further exploitation of our synthetic plan, we now

wish to describe the total synthesis of enantiomeric *trans*-2,3-*cis*-3,4-dihydroxyprolines **4** and **5** by employing lactams **2** and **3**, respectively. Enantiospecific syntheses of **4** and **5** have already been reported[7] and, in addition, L-dihydroxyproline **5** is a naturally occurring α-amino acid, recently isolated from an unusual animal adhesive protein (Mefp1) found in the mussel *Mytilus Edulis*.[8]

Planning. The target dihydroxylated prolines **4** and **5** could be planned according to the retrosynthetic paths outlined in Scheme 2. α-Amino acids **4** and **5**, in fact, can be envisioned as being derived from the respective lactam precursors **6** and **7** by reduction of the carbonyl function at C(1), followed by hydroxymethyl- to- carboxyl oxidation at the C(5) position. Enantiomeric pyrrolidinones **6** and **7** can be, in turn, generated from diastereomeric lactams **8** and **9** by oxidative fission of the C(5)-C(6) carbon-carbon bond and subsequent reduction. Functionalized lactams **8** and **9** may easily derive from the respective precursors **2** and **3** by dihydroxylation of the C(2)-C(3) double bond and subsequent protection. Thus, while the nitrogen and the four carbons of the proline cores of the target amino acids are both furnished by TBSOP, the carboxylic function within **4** and **5** is guaranteed by manipulation of the starting glyceraldehyde portion.

Scheme 2



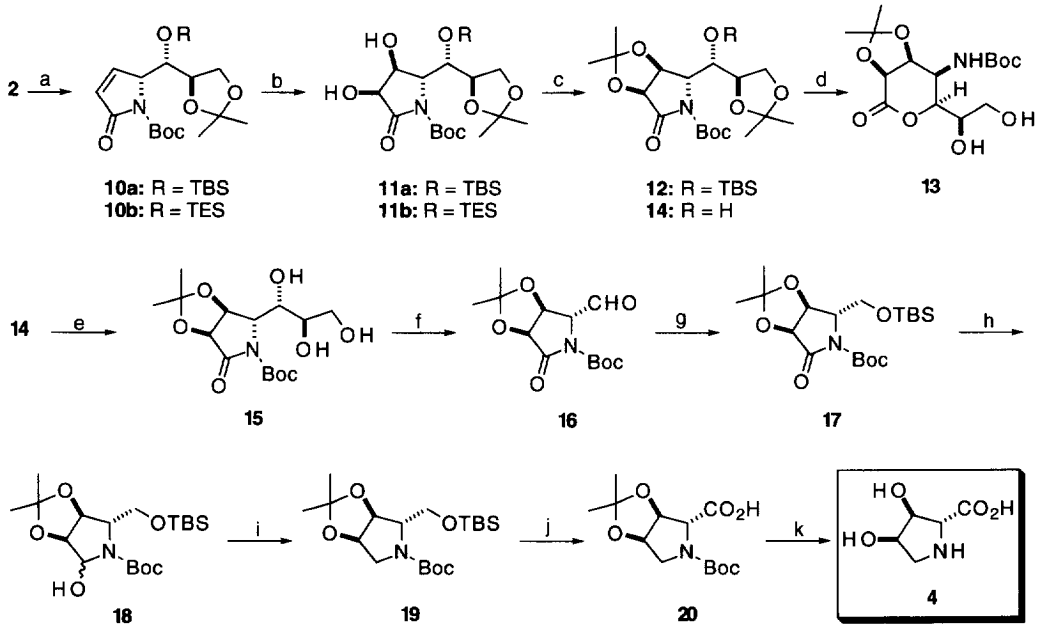
P = suitable protecting groups

Synthesis of *trans*-2,3-*cis*-3,4-Dihydroxy-D-proline 4. The multistep stereoselective synthesis of proline **4** started with the condensation of TBSOP with 2,3-*O*-isopropylidene-D-glyceraldehyde **1**. Thus, as depicted in Scheme 1, treatment of **1** with TBSOP at -85°C in the presence of 1.5 equivalents of $SnCl_4$ gave the crystalline D-*arabino*-configured lactam **2** as the major diastereoisomer in 80% yield, accompanied by minor amounts of its D-*ribo*-configured counterpart **3**. After protection of the free hydroxyl group within **2** as *tert*-butyldimethylsilyl ether (TBSCl, imidazole) (Scheme 3), there was obtained α,β-unsaturated lactam **10a** in 94% yield. Diastereoselective $KMnO_4$-promoted dihydroxylation of lactam **10a** gave pyrrolidinone **11a**, which was directly transformed into protected derivative **12** by treatment with 2,2-dimethoxypropane (DMP) and catalytic *p*-toluensulfonic acid (57% yield from **10a**). The subsequent stages of the synthesis should have involved the selective deprotection of the terminal acetonide group within **12**, followed by removal of the TBS protection to access **15**. While the former operation was successfully effected by acidic treatment (70% aq AcOH, 40°C), to give a partially deprotected intermediate, the subsequent removal of the 5-*O*-TBS group under

rather forcing conditions (excess TBAF at 0°C) disappointingly produced the undesired expanded pyranose derivative **13**, unsuitable for our purpose.[9]

Facing this problem, we next turned to lactam **2** and decided to replace the resistant TBS with the more easily removable TES group. Thus, treatment of lactam **2** with TESOTf and 2,6-lutidine almost quantitatively afforded protected lactam **10b**, which was subjected to the same dihydroxylation-protection route previously used to transform **10a** into **12**. Oxidation of compound **10b** with $KMnO_4$ produced diol **11b**, which was used as such in the next protection reaction (DMP, *p*-TsOH) furnishing pyrrolidinone **14** in 60% yield. Fortunately, the presence of catalytic *p*-TsOH allowed simultaneous acetonide protection of the *cis*-disposed hydroxyl functions, along with clean deprotection of the OH group at C(5).

Scheme 3[a]



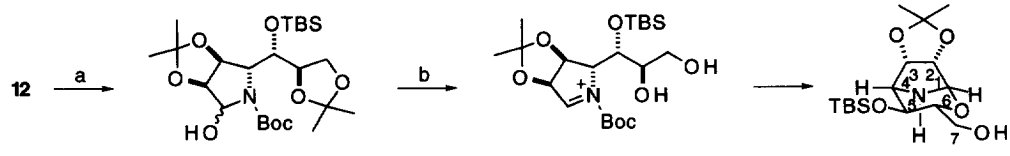
[a] Reagents: (a) for **10a**: TBSCl, imidazole, DMF, rt; for **10b**: TESOTf, 2,6-lutidine, CH_2Cl_2, rt; (b) $KMnO_4$, DCH-18-crown-6 ether, CH_2Cl_2, rt; (c) DMP, *p*-TsOH, rt; (d) **12** to **13**: 70% aq AcOH, 40°C; then TBAF, THF, 0°C; (e) citric acid, MeOH, 40 to 65°C; (f) 0.65M aq $NaIO_4$, SiO_2, CH_2Cl_2, rt; (g) $NaBH_4$, THF/H_2O (3:1), -30°C; then TBSCl, imidazole, CH_2Cl_2, rt; (h) $LiEt_3BH$, THF, -80°C; (i) Et_3SiH, BF_3 etherate, CH_2Cl_2, -80°C; (j) TBAF, THF, rt; then $NaIO_4$, hydrated RuO_2, MeCN/CCl_4/H_2O/acetone (1:1:1.4:0.3); (k) 3N aq HCl, THF, rt; then DOWEX (OH^- form).

The key intermediate **17** was then synthesized employing a well established set of four reactions, namely, selective deprotection of the terminal acetonide within **14** (citric acid, 40-65°C) to furnish **15**, oxidative breakdown of the C(5)-C(6) carbon-carbon bond with aq $NaIO_4$ to give aldehyde **16**, subsequent $NaBH_4$-promoted reduction (-30°C) of the formyl moiety within **16** to CH_2OH, and final protection of the primary carbinol (TBSCl, imidazole) to produce **17**. The entire four-step sequence furnished pyrrolidinone **17** in 35% yield from **14**.

Having installation of both the C(5)-appendage and the entire chirality secured, we next turned to the left side of the molecule, in order for the pyrrolidinone ring to be transformed into a pyrrolidine. This was accomplished by a two-step reaction involving preliminary lactam-to-lactol reduction ($LiEt_3BH$ at -80°C), to give the α,β-anomeric mixture **18** (98%) followed by lactol reduction employing BF_3 etherate as a catalyst and triethylsilane as a hydride source. There was obtained pyrrolidine **19** in 65% yield, which was finally converted into amino acid **4** by conventional chemistry. Thus, **19** was transformed to **20** by removal of the 5-*O*-TBS group (TBAF, THF), followed by quantitative oxidation of the free hydroxymethyl group to CO_2H ($NaIO_4$, RuO_2); and, finally, proline **4** was easily liberated from **20** by 3N aq HCl and proper ion exchange (OH^- form) chromatographic purification. Overall, *trans*-2,3-*cis*-3,4-dihydroxy-D-proline **4** was obtained in 11 steps with a 10% yield from **1**. The ^1H and ^{13}C spectroscopic data of our specimen, as well as its specific rotation [$[\alpha]^{20}_D$ -7.4 (*c* 0.5, H_2O)] confidentially matched the reported values for authentic 2*R*,3*S*,4*R*-dihydroxyproline **4** [lit.[7a-b] $[\alpha]^{20}_D$ -6.8 (*c* 0.43, water)].

An Abortive Attempt to Proline 4. To access amino acid **4**, an alternative procedure was also attempted involving the preparation of the pyrrolidine ring prior to C(5)-C(6) bond cleavage (Scheme 4). Thus, following the two-step reductive protocol as that previously utilized to convert **17** into **19**, protected intermediate **12** was first successfully subjected to partial reduction to give aminol **21**, which was then treated with triethylsilane and BF_3 etherate. Surprisingly enough, none of the expected pyrrolidine derivatives were obtained, being the major product of the reaction identified as the tricyclic compound **23** (50% yield from **12**), probably arising from iminium intermediate **22** via stereoselective ring closure involving the free C(6)-hydroxyl function.[10]

Scheme 4[a]

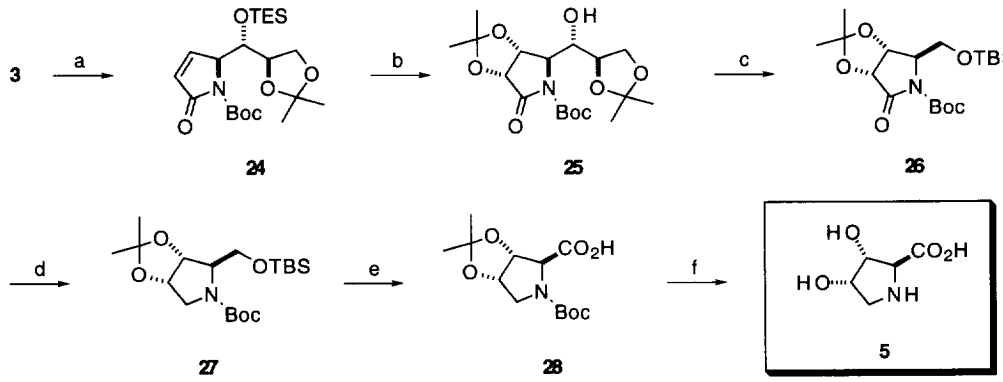


[a] Reagents: (a) $LiEt_3BH$, THF, -80°C; (b) Et_3SiH, BF_3 etherate, CH_2Cl_2, -80 to -30°C.

Detailed ^1H NMR experiments strongly supported the structure and the stereochemistry of **23**, an unprecedented nitrogen heterocycle reminiscent of the key bicyclic core of the naturally occurring zaragozic acid-squalestatin complex.[11] In particular, the *R*-configuration assigned to the newly formed stereocenter at C(1) was secured by the absence of any coupling constant between equatorial H(1) and the vicinal proton H(2) ($J_{1,2}$ = 0.0 Hz, $\phi_{1,2}$ = 90°), while the *R*-configuration of C(4) was evident from the observed coupling constants between equatorial H(4) and the vicinal protons H(3) and H(5), with $J_{3,4}$ = 0.0 Hz and $J_{4,5}$ = 4.0 Hz. In addition, the large coupling constants observed between H(5) and H(6) in the *pseudo*-pyranose ring ($J_{5,6}$ = 9.1 Hz) strongly corroborated the anti-diaxial location of these protons.

Synthesis of *trans*-2,3-*cis*-3,4-Dihydroxy-L-proline 5. Naturally occurring L-dihroxyproline **5** was synthesized from **3**, which, in turn, derived from the BF_3 etherate-catalyzed condensation (Et_2O, -85°C) of TBSOP with D-glyceraldehyde **1** (see Scheme 1), following the same set of reactions previously described for the D-enantiomeric counterpart **4**. Thus, as depicted in Scheme 5, treatment of the D-*ribo*-configured lactam **3** with TESOTf and 2,6-lutidine afforded protected lactam **24** (97% yield), whose carbon-carbon double bond was then stereoselectively dihydroxylated by the $KMnO_4$/dicyclohexano-18-crown-6 ether system to furnish, after acetonide protection (DMP, *p*-TsOH), intermediate lactam **25** (63%). The transformation of **25** into the five-carbon pyrrolidinone **26** was effected in 35% overall yield through a four-step sequence involving highly regioselective deprotection of the terminal acetonide group, oxidative fission of the C(5)-C(6) linkage to give an aldehyde intermediate, and subsequent $NaBH_4$ reduction of the formyl moiety to hydroxymethyl function followed by OH protection as TBS ether.

Scheme 5[a]



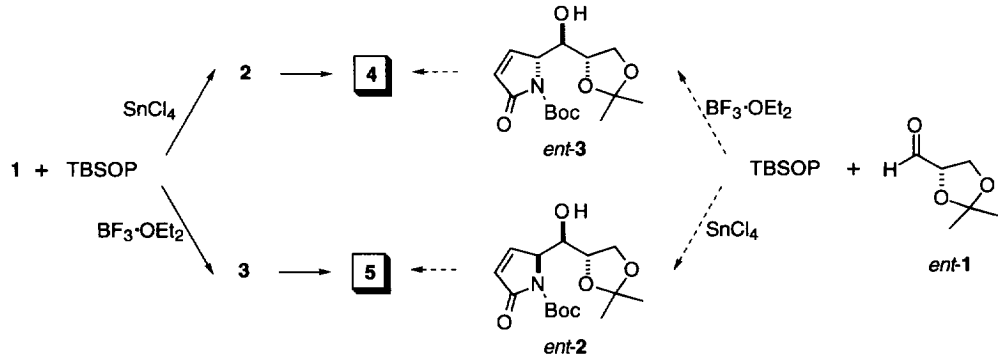
[a] Reagents: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, rt; (b) $KMnO_4$, DCH-18-crown-6 ether, CH_2Cl_2, rt; then DMP, *p*-TsOH, rt; (c) citric acid, MeOH, 40 to 65°C; then 0.65M aq $NaIO_4$, SiO_2, CH_2Cl_2, rt; then $NaBH_4$, THF/H_2O (3:1), -30°C; then TBSCl, imidazole, CH_2Cl_2, rt; (d) $LiEt_3BH$, THF, -80°C; then Et_3SiH, BF_3 etherate, CH_2Cl_2, -80°C; (e) TBAF, THF, rt; then $NaIO_4$, hydrated RuO_2, MeCN/CCl_4/H_2O/acetone (1:1:1.4:0.3); (f) 3N aq HCl, THF, rt; then DOWEX, (OH^- form).

Again, the remaining steps of the synthesis, *i.e.* transformation of **26** into **5**, took advantage of the previously experienced protocol (see also Scheme 3), which involved reduction of the carbonyl function within **26** to give pyrrolidine **27**, deprotection of the primary OH, and oxidation of the primary carbinol function to carboxylic acid affording protected proline **28** in 56% yield from **26**. As usual, exposure of **28** to 3N aq HCl in THF at room temperature ensured complete removal of all the protective groups within **28**, furnishing, after OH^- ion exchange chromatography, *trans*-2,3-*cis*-3,4-dihydroxy-L-proline **5** (quantitative), whose ^1H and ^{13}C NMR spectra were superimposable to those of its enantiomer **4**. The identity of this material was also proved by specific rotation determinations [$[\alpha]^{20}_D$ +7.5 (*c* 0.5, H_2O), lit.[7c] $[\alpha]^{20}_D$ +7.5 (*c* 0.16, H_2O); lit.[7d] $[\alpha]^{20}_D$ +7.2 (*c* 0.5, H_2O)] and by comparison of the reported proton NMR data[7c-d,8] with our own values. Overall, the entire sequence comprises 11 steps, furnishing α-amino acid **5** in ~9% yield from glyceraldehyde **1**.

Conclusion. What we have presented is a clean, diastereoselective synthesis of naturally occurring L-dihydroxyproline **5** and its D-enantiomer **4** employing easily available D-glyceraldehyde acetonide **1** as the sole source of chirality. The outlined synthetic plan was based on a divergence logic, springing both enantiomers **4** and **5** from the same reactants, TBSOP and **1**, simply by the intervention of different catalytic systems, $SnCl_4$ or BF_3 etherate, during the initial homologative step.

In principle, the adopted plan could be also envisaged as a convergent procedure, if one considers that the same results would have been reached by employing the enantiomeric L-glyceraldehyde counterpart *ent*-**1** in lieu of **1** (Scheme 6). In the event, *ent*-**2** (from TBSOP and *ent*-**1**, $SnCl_4$ as a catalyst) would have been the requisite precursor of **5**, while *ent*-**3** (from TBSOP and *ent*-**1**, BF_3 etherate as a catalyst) would have furnished amino acid **4**. As a consequence, each proline derivative, **4** and **5**, may derive from either enantiomer of glyceraldehyde, **1** or *ent*-**1**, by adopting the same set of chemical transformations.

Scheme 6



EXPERIMENTAL

General. Melting points were determined on an Electrothermal apparatus and are recorded uncorrected. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. ^1H (300.0 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded using a Bruker AC-300 spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.0 ppm), and coupling constants (*J*) are measured in Hertz. TLC was carried out on Merck Kieselgel 60 F_{254} glass-backed plates. Silica gel (particle size 70-230 mesh), supplied from Merck, was employed for flash chromatography. All the solvents were distilled before use: THF over Na/benzophenone, Et_2O over $LiAlH_4$, CH_2Cl_2 over CaH_2. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari.

Materials. *N*-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP) was prepared from pyrrole (Aldrich) according to a described protocol.[2a] 2,3-*O*-Isopropylidene-D-glyceraldehyde **1** was prepared from D-mannitol (Aldrich) following a convenient described procedure.[12]

(4*R*,5*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-6,7-*O*-isopropylidene-2,3-dideoxy-hept-2-enono-1,4-lactam 2. The title compound was obtained in 80% yield (2.9 g) from D-glyceraldehyde **1** (1.5 g, 11.5 mmol), TBSOP (3.4 g, 11.5 mmol), and $SnCl_4$ (1.94 mL, 17.0 mmol), employing a described protocol.[2] Salient data for **2**: white solid; mp 138-140°C; $[\alpha]^{20}_D$ +197.6 (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, 1H, *J* = 6.3, 2.1 Hz), 6.13 (dd, 1H, *J* = 6.3, 1.5 Hz), 4.81 (dt, 1H, *J* = 5.7, 2.4 Hz), 4.09 (ddd, 1H, *J* = 6.0, 5.7, 3.9 Hz), 4.01 (q, 1H, *J* = 6.0 Hz), 3.94 (dd, 1H, *J* = 8.1, 6.0 Hz), 3.86 (dd, 1H, *J* = 8.1, 6.0 Hz), 3.63 (d, 1H, *J* = 3.9 Hz), 1.57 (s, 9H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.9, 150.9, 148.2, 126.9, 109.2, 83.8, 75.6, 72.6, 66.4, 65.6, 28.0 (3C), 26.4, 25.1.

(4*S*,5*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-6,7-*O*-isopropylidene-2,3-dideoxy-hept-2-enono-1,4-lactam 3. The title compound was recovered in 70% yield (2.5 g) from D-glyceraldehyde **1** (1.5 g, 11.5 mmol), TBSOP (3.4 g, 11.5 mmol), and BF_3 etherate (1.4 mL, 11.5 mmol), following a described procedure.[2] Salient data for **3**: colourless needles; mp 118-120°C; $[\alpha]_D$ -120.0 (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, 1H, *J* = 6.3, 2.1 Hz), 6.16 (dd, 1H, *J* = 6.3, 2.0 Hz), 4.97 (q, 1H, *J* = 2.1 Hz), 4.20 (m, 1H), 4.15 (td, 1H, *J* = 6.6, 2.2 Hz), 4.03 (m, 2H), 3.49 (d, 1H, *J* = 6.6 Hz), 1.56 (s, 9H), 1.46 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.0, 149.7, 147.2, 128.0, 109.9, 83.5, 76.3, 71.4, 67.9, 65.1, 28.1 (3C), 26.7, 24.5.

(4*R*,5*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-5-*O*-(*tert*-butyldimethylsilyl)-6,7-*O*-isopropylidene-2,3-dideoxy-hept-2-enono-1,4-lactam 10a. To a solution of lactam **2** (2.7 g, 8.6 mmol) in dry dimethylformamide (40 mL) under nitrogen atmosphere were added TBSCl (12.96 g, 86 mmol) and imidazole (5.85 g, 86 mmol), and the mixture was stirred at room temperature for 5 h. Two further additions of TBSCl (2x3.2 g, 2x21.5 mmol) and imidazole (2x1.46 g, 2x21.5 mmol) were effected at regular intervals and, after 20 h, the mixture was quenched with 5% aq citric acid (80 mL). The resulting slurry was extracted with Et_2O (3x50 mL) and the extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give crude product **10a** which was flash chromatographed on silica gel eluting with 7:3 hexanes/ethyl acetate, to afford 3.45 g (94%) of pure protected lactam **10a** as a white solid: mp 140-142°C; $[\alpha]^{20}_D$ +180.4 (*c* 0.92, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, 1H, *J* = 6.0, 2.1 Hz), 6.20 (dd, 1H, *J* = 6.0, 1.5 Hz), 4.65 (m, 1H), 4.60 (bt, 1H, *J* = 4.5 Hz), 3.6-3.8 (m, 3H), 1.58 (s, 9H), 1.35 (s, 3H), 1.24 (s, 3H), 0.93 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.0, 149.3, 147.4, 128.4, 109.0, 83.2, 74.7, 71.2, 66.1, 65.2, 28.2 (3C), 26.3, 25.7 (3C), 25.0, 17.9, -4.1, -5.2. Anal. Calcd for $C_{21}H_{37}NO_6Si$: C, 58.99; H, 8.72; N, 3.28. Found: C, 58.80; H, 8.70; N, 3.20.

(2*S*,3*S*,4*S*,5*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-2,3:6,7-di-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-heptono-1,4-lactam 12. To a stirring solution of unsaturated lactam **10a** (3.1 g, 7.26 mmol) in dry CH_2Cl_2 (75 mL) were added dicyclohexano-18-crown-6 ether (338 mg, 0.9 mmol) and powdered $KMnO_4$ (450 mg, 2.85 mmol) under nitrogen at room temperature. After being stirred for 5 h, the reaction mixture was quenched with saturated aq Na_2SO_3 (40 mL) and with saturated aq citric acid until the brown colour of the solution completely disappeared. The solution was then thoroughly extracted with ethyl acetate (5x50 mL) and the extracts were dried ($MgSO_4$) and evaporated under vacuum, to furnish crude lactam **11a** as an oily residue (2.18 g, 65%) which was used as such in the next reaction. Thus, the entire material **11a**

was dissolved in 2,2-dimethoxypropane (23 mL, 189 mmol) under nitrogen and the resulting solution was treated with a catalytic amount of *p*-toluensulfonic acid (100 mg) under stirring at room temperature. After 2 h, the solution was quenched by the addition of 20 mL of a saturated aqueous $NaHCO_3$ solution and then extracted with CH_2Cl_2 (3x15 mL). After being dried ($MgSO_4$), the organic layer was filtered and concentrated under vacuum to give an oily residue which was purified by flash chromatography (8:2 hexanes/ethyl acetate) affording 2.07 g (88%) (54% yield from **10a**) of pure compound **12** as a white crystalline solid: mp 94-96°C; $[\alpha]^{20}_D$ +32.34 (*c* 4.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.75 (d, 1H, J = 5.5 Hz), 4.66 (d, 1H, J = 5.5 Hz), 4.21 (d, 1H, J = 3.5 Hz), 4.10 (m, 2H), 3.83 (m, 1H), 3.72 (dd, 1H, J = 8.1, 5.7 Hz), 1.54 (s, 9H), 1.45 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H), 0.91 (s, 9H), 0.23 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.6, 150.0, 111.7, 110.2, 83.0, 77.6, 76.0, 71.8, 69.8, 68.9, 63.2, 28.0 (3C), 26.9, 26.1, 25.4 (3C), 24.9 (2C), 17.6, -4.2, -5.1. Anal. Calcd for $C_{24}H_{43}NO_8Si$: C, 57.46; H, 8.64; N, 2.79. Found: C, 57.41; H, 8.59; N, 2.85.

(2*S*,3*S*,4*S*,5*S*,6*R*)-2,3-*O*-Isopropylidene-4-[*N*-(*tert*-butoxycarbonylamino)]-4-deoxy-heptono-1,5-lactone 13. Crystalline lactam **12** (1.5 g, 3.0 mmol) was treated with 70% aq acetic acid and, after being stirred at 40°C for 22 h, the resulting solution was concentrated under reduced pressure. The crude residue was then purified by flash chromatography on silica gel (7:3 ethyl acetate/hexanes) to give 0.94 g (68%) of a mono-acetonide intermediate (not shown), whose salient data are as follows: colourless oil; $[\alpha]^{20}_D$ +61.15 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (m, 2H), 4.25 (d, 1H, J = 4.1 Hz), 4.15 (dd, 1H, J = 7.5, 4.1 Hz), 3.74 (m, 1H), 3.51 (m, 2H), 2.83 (bs, 1H), 2.82 (bs, 1H), 1.53 (s, 9H), 1.43 (s, 3H), 1.36 (s, 3H), 0.92 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.8, 150.3, 111.7, 83.9, 77.7, 73.3, 72.8, 68.2, 63.8, 63.7, 28.0 (3C), 26.8, 25.6 (3C), 25.2, 17.8, -4.2, -5.0. Anal. Calcd for $C_{21}H_{39}NO_8Si$: C, 54.64; H, 8.52; N, 3.03. Found: C, 54.49; H, 8.68; N, 2.91.

This intermediate (0.7 g, 1.5 mmol) was dissolved in dry THF under nitrogen and the solution was cooled under stirring at 0°C. Then, small portions of tetrabutylammonium fluoride (in total: 300 mg) were added at the same temperature over the period of 3 h, after which time the reaction mixture was concentrated under vacuum, to leave an oily residue which was purified by flash chromatography on silica gel (99:1 ethyl acetate/methanol as an eluant). There were obtained 274 mg (52%) of 2-pyranone **13**, along with only minor amounts of deprotected five-member ring lactam **15**. Compound **13**: colourless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 4.80 (d, 1H, J = 7.2 Hz), 4.49 (d, 1H, J = 5.4 Hz), 4.44 (d, 1H, J = 5.4 Hz), 4.16 (bs, 1H), 4.04 (m, 2H), 3.70 (m, 1H), 3.63 (dd, 1H, J = 11.9, 2.5 Hz), 3.48 (dd, 1H, J = 11.9, 5.2 Hz), 1.40 (s, 9H), 1.37 (s, 3H), 1.28 (s, 3H). Anal. Calcd for $C_{15}H_{25}NO_8$: 51.87; H, 7.25; N, 4.03. Found: C, 52.05; H, 7.39; N, 3.90.

(4*R*,5*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-5-*O*-(triethylsilyl)-6,7-*O*-isopropylidene-2,3-di-deoxy-hept-2-enono-1,4-lactam 10b. To a stirring solution of unsaturated lactam **2** (2.2 g, 7.0 mmol) in dry CH_2Cl_2 (90 mL) under nitrogen atmosphere at room temperature were sequentially added 2,6-lutidine (0.82 mL, 7.0 mmol) and triethylsilyltriflate (1.58 mL, 7.0 mmol). After being stirred at room temperature for 3 h, a further addition of 2,6-lutidine (0.82 mL, 7.0 mmol) and TESOTf (1.58 mL, 7.0 mmol) was effected and the mixture was allowed to stir for 1 h. The solvent was removed under reduced pressure, leaving a yellow residue which was purified by flash chromatography eluting with a 7:3 hexanes/ethyl acetate mixture. There were obtained 2.93 g (98%) of pure protected lactam **10b** as a colourless oil: $[\alpha]^{20}_D$ +147.95 (*c* 3.0, $CHCl_3$); ^1H

NMR (300 MHz, $CDCl_3$) δ 7.12 (dd, 1H, J = 6.1, 1.9 Hz), 5.99 (dd, 1H, J = 6.1, 1.2 Hz), 4.48 (m, 1H), 4.42 (m, 1H), 3.56 (m, 3H), 1.39 (s, 9H), 1.15 (s, 3H), 1.04 (s, 3H), 0.83 (t, 9H, J = 7.9 Hz), 0.53 (q, 6H, J = 7.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.4, 149.1, 147.1, 128.0, 108.7, 82.5, 74.7, 71.0, 65.9, 65.0, 27.8 (3C), 26.0, 24.7, 6.4 (3C), 4.6 (3C). Anal. Calcd for $C_{21}H_{37}NO_6Si$: C, 58.99; H, 8.72; N, 3.28. Found: C, 58.86; H, 8.63; N, 3.25.

(2*S*,3*S*,4*S*,5*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-2,3:6,7-di-*O*-isopropylidene-heptono-1,4-lactam 14. The title compound **14** was prepared from protected lactam **10b** (2.9 g, 6.8 mmol) through hydroxylated intermediate **11b**, following the same procedure described to transform **10a** into **12**. After flash chromatographic purification of the crude residue on silica gel (6:4 ethyl acetate/hexanes as an eluant), pure compound **14** (1.58 g, 60%) was obtained as white crystals: mp 142-144°C; $[\alpha]^{20}_D$ +82.8 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, 1H, J = 5.2 Hz), 4.60 (d, 1H, J = 5.2 Hz), 4.47 (d, 1H, J = 3.0 Hz), 4.03 (m, 3H), 3.88 (d, 1H, J = 7.3 Hz), 3.72 (m, 1H), 1.47 (s, 9H), 1.37 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.8, 150.4, 111.7, 109.4, 83.8, 77.8, 76.2, 75.8, 72.5, 66.9, 62.4, 27.7 (3C), 27.0, 26.6, 25.6, 25.0. Anal. Calcd for $C_{18}H_{29}NO_8$: C, 55.80; H, 7.54; N, 3.62. Found: C, 55.92; H, 7.47; N, 3.50.

(2*S*,3*S*,4*S*,5*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-2,3-*O*-isopropylidene-heptono-1,4-lactam 15. To a stirring solution of 1.5 g (3.9 mmol) of compound **14** in methanol (70 mL) was added a catalytic amount of solid citric acid under nitrogen at 40°C. After 3 h, the temperature was allowed to rise to 65°C and the reaction mixture stirred for further 2 h. The solvent was then removed under vacuum and the oily residue was passed through a short chromatographic column on silica gel and very rapidly purified to furnish heptonolactam **15** (0.89 g, 66%) as a pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, 1H, J = 5.1 Hz), 4.59 (d, 1H, J = 5.1 Hz), 4.58 (bs, 1H), 3.82 (m, 6H), 3.35 (dt, 1H, J = 9.4, 4.4 Hz), 1.54 (s, 9H), 1.40 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.9, 153.0, 111.7, 85.0, 78.2, 77.1, 72.7, 69.9, 63.9, 60.7, 27.8 (3C), 27.0, 25.6. Anal. Calcd for $C_{15}H_{25}NO_8$: C, 51.87; H, 7.25; N, 4.03. Found: C, 51.91; H, 7.18; N, 3.94.

(3*S*,4*S*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-3,4-*O*-isopropylidene-5-(*tert*-butyldimethylsiloxymethyl)-2-pyrrolidinone 17. To a solution of lactam **15** (0.89 g, 2.6 mmol) in CH_2Cl_2 (75 mL) was added SiO_2 (230-400 mesh, 3.0 g) and the resulting slurry was treated under vigorous stirring with 0.65M aq $NaIO_4$ (25 mL) at room temperature. After 20 min, the slurry was filtered under suction and the silica was thoroughly washed with ethyl acetate and some drops of methanol. The filtrates were evaporated under vacuum to leave crude aldehyde **16** which was purified by flash chromatography on silica gel and eluted with 8:2 ethyl acetate/hexanes to furnish a colourless oil (0.5 g, 68%); ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.84 (s, 1H), 4.64 (d, 1H, J = 1.6 Hz), 4.62 (d, 1H, J = 1.6 Hz), 1.53 (s, 3H), 1.52 (s, 9H), 1.48 (s, 3H).

The aldehyde **16** (0.5 g, 1.75 mmol) was dissolved in a 3:1 THF/H_2O mixture (30 mL) and the resulting solution was cooled at -30°C. $NaBH_4$ (40 mg, 1.0 mmol) was then added portionwise at this temperature under stirring and the reaction was carefully followed by TLC till complete disappearance of the starting aldehyde (2 h). After quenching with a saturated aq NH_4Cl solution, the mixture was extracted with ethyl acetate (4x15 mL)

and the extracts, once dried ($MgSO_4$), were filtered and evaporated under vacuum. The crude residue so obtained was dissolved in dry CH_2Cl_2 (10 mL) and the resulting solution was treated with 0.25 g (1.68 mmol) of TBSCl and 114 mg (1.68 mmol) of imidazole at room temperature under stirring. After 20 h, the mixture was quenched with a 5% aq citric acid solution and extracted with ethyl acetate (3x5 mL).After drying ($MgSO_4$) the extracts were filtered and concentrated to afford crude pyrrolidinone **17**, which was flash chromatographed on silica gel (7:3 hexanes/ethyl acetate) to furnish 0.55 g (78% from aldehyde **16**) of pure **17** as white crystals: mp 54-55°C; $[\alpha]^{20}_D$ +81.02 (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (d, 1H, J = 5.5 Hz), 4.42 (d, 1H, J = 5.5 Hz), 4.12 (dd, 1H, J = 2.2, 1.4 Hz), 3.90 (dd, 1H, J = 10.6, 2.2 Hz), 3.68 (dd, 1H, J = 10.6, 1.4 Hz), 1.43 (s, 9H), 1.34 (s, 3H), 1.26 (s, 3H), 0.76 (s, 9H), -0.07 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.6, 149.7, 111.5, 83.2, 78.0, 75.5, 61.8, 61.6, 27.8 (3C), 26.9, 25.6 (3C), 25.4, 17.9, -5.9, -6.0. Anal. Calcd for $C_{19}H_{35}NO_6Si$: C, 56.83; H, 8.79; N, 3.49. Found: C, 56.71; H, 8.88; N, 3.53.

(2*RS*,3*S*,4*S*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-2,3,4-trihydroxy-3,4-*O*-isopropylidene-5-(*tert*-butyldimethylsiloxymethyl)pyrrolidine 18. A stirring solution of pyrrolidinone **17** (0.55 g, 1.25 mmol) in dry THF (10 mL) cooled at -80°C under nitrogen atmosphere was treated with $LiEt_3BH$ (3.1 mL of a 1M THF solution, 3.1 mmol). After being stirred at -80°C for 20 min, the solution was quenched at this temperature with methanol (~4 mL) and subsequently with 6 mL of a saturated aq $NaHCO_3$ solution. The resulting foamy slurry was allowed to rise to room temperature under stirring (1 h) and then it was vigorously extracted with ethyl acetate (4x10 mL). The extracts were dried and filtered, and the solvent was removed under vacuum, leaving pyrrolidine **18** (0.49 g, 98%) as a colourless oil, which didn't require any further purification: $[\alpha]^{20}_D$ -74.01 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 3:7 α/β mixture) δ 5.43 (d, 0.3H, J = 9.2 Hz), 5.28 (d, 0.7H, J = 11.3 Hz), 4.63 (m, 1H), 4.48 (m, 1H), 4.20 (bs, 0.7H), 4.16 (bs, 0.3H), 3.92 (d, 0.7H, J = 11.3 Hz), 3.84 (d, 0.3H, J = 9.2 Hz), 3.72 (m, 2H), 1.48 (bs, 9H), 1.42 (s, 3H), 1.30 (s, 3H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$, major isomer) δ 154.0, 111.8, 85.7, 81.0, 80.5, 77.5, 62.7, 61.8, 28.3 (3C), 26.6, 25.7 (3C), 25.0, 17.9, -5.7, -5.8. Anal. Calcd for $C_{19}H_{37}NO_6Si$: C, 56.54; H, 9.24; N, 3.47. Found: C, 56.42; H, 9.37; N, 3.29.

(3*R*,4*S*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-3,4-*O*-isopropylidene-5-(*tert*-butyldimethylsiloxymethyl)pyrrolidine 19. A solution of the anomeric mixture **18** (0.5 g, 1.24 mmol) and triethylsilane (0.2 mL, 1.24 mmol) in dry CH_2Cl_2 (18 mL) under nitrogen atmosphere was cooled at -80°C, and BF_3 etherate (166 µL, 1.35 mmol) was then added dropwise under stirring. After 30 min, were added further 0.2 mL (1.24 mmol) of triethylsilane and 166 µL (1.35 mmol) of BF_3 etherate and the temperature was allowed to rise to -60°C. After 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (9 mL), extracted with ethyl acetate (3x10 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under vacuum and the crude residue was purified by flash chromatography on silica gel (8:2 hexanes/ethyl acetate) to give pure pyrrolidine **19** (312 mg, 65%) as a colourless oil: $[\alpha]^{20}_D$ +60.2 (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, CD_2Cl_4, 70°C) δ 4.64 (d, 1H, J = 6.1 Hz), 4.60 (d, 1H, J = 6.1 Hz), 3.95 (m, 1H), 3.61 (ABq, 2H, J = 9.9 Hz, $\Delta\nu$ = 2.0 Hz), 3.42 (ABq, 2H, J = 12.3 Hz, $\Delta\nu$ = 5.0 Hz), 1.40 (s, 9H), 1.39 (s, 3H), 1.27 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75.4 MHz, CD_2Cl_4, 70°C) δ 154.6, 111.8, 83.3, 81.4, 79.9, 65.4, 63.9, 54.2, 29.0 (3C), 27.7, 26.3 (3C), 25.8, 18.5, -5.0, -5.1. Anal. Calcd for $C_{19}H_{37}NO_5Si$: C, 58.88; H, 9.62; N, 3.61. Found: C, 59.02; H, 9.70; N, 3.50.

(2*R*,3*S*,4*R*)-*N*-(*tert*-Butoxycarbonyl)-3,4-*O*-isopropylidene-3,4-dihydroxyproline 20. To a stirring solution of protected pyrrolidine **19** (230 mg, 0.59 mmol) in dry THF (15 mL) was added tetrabutylammonium fluoride (50 mg) at room temperature, under nitrogen atmosphere. After being stirred for 4 h, the reaction mixture was concentrated under vacuum. The obtained residue was dissolved in 10 mL of a 1:1 hexanes/ethyl acetate mixture and treated with 1.0 g of SiO_2 (230-400 mesh) under stirring; the resulting slurry was then filtered under suction affording, after removal of the solvents, a partially protected prolinol intermediate (161 mg, quantitative) whose salient data are the following: colourless powder; $[\alpha]^{20}_D$ +55.9 (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (m, 2H), 4.11 (bs, 1H), 3.75 (m, 2H), 3.64 (dd, 1H, J = 10.9, 5.1 Hz), 3.48 (dd, 1H, J = 12.6, 5.2 Hz), 3.05 (bs, 1H), 1.45 (s, 9H), 1.44 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 150.7, 111.0, 82.8, 81.9, 78.9, 65.0, 63.2, 52.6, 28.3 (3C), 26.9, 24.9.

The prolinol intermediate (whole amount) was dissolved in 7 mL of a 1:1:1.4:0.3 $MeCN/CCl_4/H_2O$/acetone mixture and the resulting solution was treated with solid $NaIO_4$ (250 mg, 1.1 mmol) and a catalytic amount of hydrated RuO_2 (~30 mg). After the reaction mixture had been stirred for 30 min at room temperature, it was quenched with propan-2-ol (3 mL) and filtered on a Celite pad. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel eluting with a 75:25 ethyl acetate/methanol mixture to furnish 168 mg (quantitative) of protected proline **20** as a colourless oil: $[\alpha]^{20}_D$ +43.7 (*c* 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (bs, 1H), 4.75 (m, 2H), 4.41 (m, 1H), 3.70 (ABq, 2H, J = 12.0 Hz, $\Delta\nu$ = 22.0 Hz), 1.45 (s, 9H), 1.40 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.0, 153.6, 111.6, 82.0, 81.1, 80.0, 66.6, 51.8, 28.3 (3C), 26.6, 25.0. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.30; H, 7.49; N, 4.78.

(2*R*,3*S*,4*R*)-3,4-Dihydroxyproline 4. To a solution of 100 mg (0.35 mmol) of protected proline **20** in 5 mL of THF was added a solution of 3N HCl in THF (1:1 v/v, 10 mL) dropwise at room temperature. After being stirred for 15 min, the solution was evaporated to dryness under high vacuum to leave a glassy residue which was subjected to ion exchange chromatographic purification (DOWEX, OH^- form). There was obtained pure proline **4** (48 mg, 95%) as a white powder: mp 250°C; $[\alpha]^{20}_D$ -7.4 (*c* 0.5, H_2O) [lit.[7a-b] $[\alpha]^{20}_D$ -6.8 (*c* 0.43, H_2O)]; ^1H NMR (300 MHz, D_2O) δ 4.33 (m, 2H), 3.86 (d, 1H, J = 4.1 Hz), 3.53 (dd, 1H, J = 12.0, 4.4 Hz), 3.19 (dd, 1H, J = 12.0, 3.6 Hz); ^{13}C NMR (75.4 MHz, D_2O) δ 172.0, 74.1, 69.9, 64.2, 48.5. Anal. Calcd for $C_5H_9NO_4$: C, 40.82; H, 6.17; N, 9.52. Found: C, 40.69; H, 6.37; N, 9.40.

Tricyclic compound 23. A stirring solution of lactam **12** (0.2 g, 0.4 mmol) in dry THF (5 mL) cooled at -80°C under nitrogen atmosphere was treated with $LiEt_3BH$ (1.0 mL of a 1M THF solution, 1.0 mmol). After being stirred at -80°C for 1 h, the solution was quenched at this temperature with methanol (~3 mL) and subsequently with 5 mL of a saturated aq $NaHCO_3$ solution. The resulting mixture was allowed to rise to room temperature under stirring and then was extracted with CH_2Cl_2 (3x5 mL) and ethyl acetate (2x5 mL). The extracts were dried and filtered, and the solvents were removed under vacuum, leaving compound **21** (0.2 g) as a colourless oil, which didn't require any further purification. A solution of the anomeric mixture **21** (0.2 g, 0.4 mmol) and triethylsilane (64 µL, 0.4 mmol) in dry CH_2Cl_2 (6 mL) under nitrogen atmosphere was cooled at -80°C, and BF_3 etherate (49 µL, 0.4 mmol) was then added dropwise under stirring. After 30 min, were added further 64 µL (0.4 mmol) of triethylsilane and 49 µL (0.4 mmol) of BF_3 etherate and the temperature was allowed to raise to -30°C. After 3 h, the reaction mixture was quenched with aq $NaHCO_3$ (4 mL), extracted with CH_2Cl_2 (3x5 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under

vacuum and the crude residue was flash chromatographed on silica gel (ethyl acetate as an eluant) to give 70 mg (50% yield from **12**) of tricyclic compound **23** as an oil; $[\alpha]^{20}_D$ +17.5 (*c* 0.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (d, 1H, *J* = 5.4 Hz, H-2), 4.78 (s, 1H, H-1), 4.63 (d, 1H, *J* = 5.4 Hz, H-3), 3.72 (dd, 1H, *J* = 9.1, 4.2 Hz, H-5), 3.69 (dd, 1H, *J* = 11.8, 2.6 Hz, H-7a), 3.56 (dd, 1H, *J* = 11.8, 4.1 Hz, H-7b), 3.41 (d, 1H, *J* = 4.2 Hz, H-4), 3.19 (ddd, 1H, *J* = 9.1, 4.1, 2.6 Hz, H-6), 1.80 (bs, 2H, OH and NH), 1.48 (s, 3H, Me), 1.36 (s, 3H, Me), 0.90 (s, 9H, Bu^t), 0.12 (s, 3H, Me), 0.09 (s, 3H, Me). Anal. Calcd for $C_{16}H_{31}NO_5Si$: C, 55.62; H, 9.04; N, 4.05. Found: C, 55.50; H, 9.23; N, 3.96.

(4*S*,5*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-5-*O*-(triethylsilyl)-6,7-*O*-isopropylidene-2,3-dideoxy-hept-2-enono-1,4-lactam 24. The title compound was prepared by starting with lactam **3** (2.0 g, 6.4 mmol) by following the above procedure described for **10b**. There were obtained 2.65 g (97%) of protected lactam **24** as a colourless oil: $[\alpha]^{20}_D$ -80.0 (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, 1H, *J* = 6.3, 2.1 Hz), 6.11 (dd, 1H, *J* = 6.3, 1.8 Hz), 4.96 (m, 1H), 4.37 (dd, 1H, *J* = 7.5, 1.5 Hz), 4.13 (dd, 1H, *J* = 8.1, 6.3 Hz), 4.05 (ddd, 1H, *J* = 7.5, 6.3, 5.4 Hz), 3.85 (dd, 1H, *J* = 8.1, 5.4 Hz), 1.57 (s, 9H), 1.47 and 1.38 (2s, each 3H), 0.86 (t, 9H, *J* = 7.9 Hz), 0.56 (q, 6H, *J* = 7.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.5, 149.6, 147.5, 127.8, 109.8, 82.8, 77.4, 72.2, 68.0, 64.8, 28.1 (3C), 26.5, 25.1, 6.4 (3C), 4.6 (3C). Anal. Calcd for $C_{21}H_{37}NO_6Si$: C, 58.99; H, 8.72; N, 3.28. Found: 59.10; H, 8.81; N, 3.35.

(2*R*,3*R*,4*R*,5*S*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-2,3:6,7-di-*O*-isopropylidene-heptono-1,4-lactam 25. The title compound was prepared by starting with 2.65 g (6.2 mmol) of unsaturated lactam **24** by paralleling the procedure described to transform **10b** into **14**. After flash chromatography purification on silica gel (6:4 ethyl acetate/hexanes as an eluant), there was obtained pyrrolidinone **25** (1.5 g, 63%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.76 (d, 1H, *J* = 5.4 Hz), 4.71 (d, 1H, *J* = 5.4 Hz), 4.52 (bs, 1H), 4.15 (m, 3H), 3.97 (m, 1H), 2.52 (m, 1H), 1.52 (s, 9H), 1.45 and 1.43 (2s, each 3H), 1.37 and 1.35 (2s, each 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.2, 149.7, 112.1, 110.2, 83.4, 76.3, 75.1, 73.2, 71.6, 66.6, 58.9, 27.4 (3C), 26.7, 26.2, 25.4, 24.8. Anal. Calcd for $C_{18}H_{29}NO_8$: C, 55.80; H, 7.54; N, 3.62. Found: 55.71; H, 7.39; N, 3.57.

(3*R*,4*R*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-3,4-*O*-isopropylidene-5-(*tert*-butyldimethylsiloxymethyl)-2-pyrrolidinone 26. The title compound was prepared from lactam **25** (1.5 g, 3.9 mmol) by following the above procedure used to convert **14** into **17**; pyrrolidinone **26** was obtained as a white solid (0.55 g, 35%): mp 55-56°C; $[\alpha]^{20}_D$ -80.34 (*c* 2.0, $CHCl_3$). The ^1H and ^{13}C NMR spectral data are identical to those reported for its enantiomer **17**. Anal. Calcd for $C_{19}H_{35}NO_6Si$: C, 56.83; H, 8.79; N, 3.49. Found: C, 56.69; H, 8.70; N, 3.60.

(3*S*,4*R*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-3,4-*O*-isopropylidene-5-(*tert*-butyldimethylsiloxymethyl)pyrrolidine 27. The title compound was prepared from pyrrolidinone **26** (0.55 g, 1.37 mmol) by following the above procedure described to transform **17** into **19**; pyrrolidine **27** was obtained as a colourless oil (318 mg, 60%): $[\alpha]^{20}_D$ -60.6 (*c* 0.3, $CHCl_3$). The ^1H and ^{13}C NMR spectral data are identical to those reported for its enantiomer **19**. Anal. Calcd for $C_{19}H_{37}NO_5Si$: C, 58.88; H, 9.62; N, 3.61. Found: C, 59.07; H, 9.75; N, 3.69.

(2*S*,3*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-3,4-*O*-isopropylidene-3,4-dihydroxyproline 28. The title compound was prepared from pyrrolidine **27** (300 mg, 1.1 mmol) by following the above procedure for its enantiomer **20**; protected proline **28** (297 mg, 94%) was obtained as an oil: $[\alpha]^{20}_D$ -44.0 (*c* 0.05, $CHCl_3$). The ^1H and ^{13}C NMR spectral data are identical to those reported for its enantiomer **20**. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.40; H, 7.51; N, 4.80.

(2*S*,3*R*,4*S*)-3,4-Dihydroxyproline 5. The title compound was prepared from protected proline **28** (250 mg, 0.87 mmol) by following the above procedure for its enantiomer **4**; proline **5** (128 mg, quantitative) was obtained as a white powder: mp 250°C; $[\alpha]^{20}_D$ +7.5 (*c* 0.5, H_2O) [lit.[7c] $[\alpha]^{20}_D$ +7.5 (*c* 0.16, H_2O); lit.[7d] $[\alpha]^{20}_D$ +7.2 (*c* 0.5, H_2O)]. The ^1H and ^{13}C NMR spectral data are identical to those reported for its enantiomer **4**. Anal. Calcd for $C_5H_9NO_4$: C, 40.82; H, 6.17; N, 9.52. Found: C, 40.71; H, 6.28; N, 9.64.

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9. Quite unexpectedly, treatment of compound **12** with 40% aq HF led to complete deacetonidation of the molecule, leaving the TBS group unaltered.
10. Likely, the labile terminal acetonide protection and the *N*-Boc fragment within **21** did not survive the "acidic" BF_3 etherate treatment and the subsequent work-up manipulations. For a similar annulation

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