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Conformational Analysis of δ-Lactams

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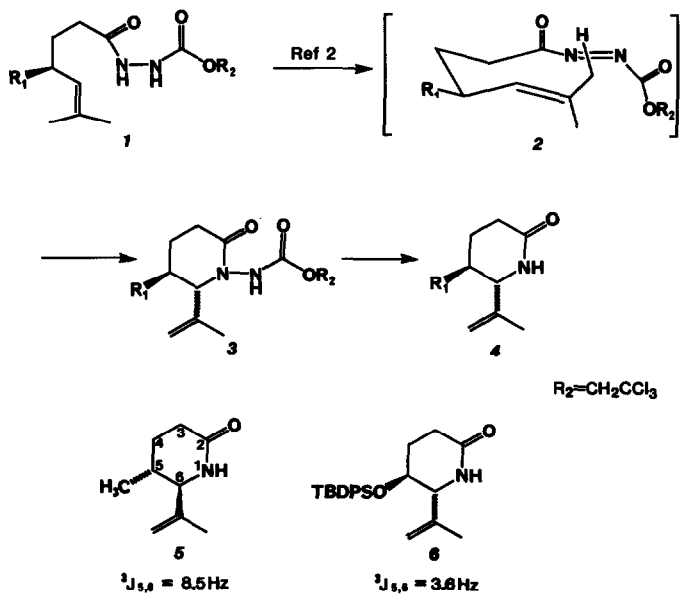
Summary: δ-lactams substituted at C-5 by an oxygen atom exist, in solution principally, in the axial conformation. This axial preferred form is also present in the solid state.

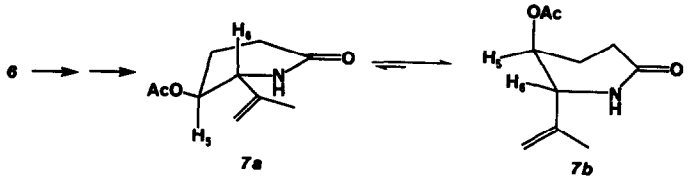
Lactams are useful precursors for the synthesis of a variety of alkaloids.[1] We have shown recently that γ- and δ-lactams can be efficiently prepared via an intramolecular ene reaction of an azodicarbonyl species (**2**) (Scheme 1).[2] For the case of six-membered rings, the reaction was highly stereoselective, especially with substrates having a stereogenic center adjacent to the new asymmetric center. Presumably, the reaction proceeds via a chair-like transition state to afford the trans isomer of the ene products (**3**). The corresponding lactams (**4**) were then easily obtained from the ene products (**3**) using our standard protocol for the conversion of 2,2,2-trichloroethyl hydrazides to free amines.[3]

Scheme 1



For the lactam **5**, the trans relationship between the C5 and C6 substituents was established based on the $^3J_{5,6}$ value in ^1H NMR (8.5 Hz, acetone-d_6). Surprisingly, the analogous coupling constant was lower than expected (3.6 Hz) for the lactam **6**, which is substituted at C5 by an oxygen atom. Therefore, at that time, the relative stereochemistry was uncertain. NOE experiments showed no significant enhancement of the H5 signal upon irradiation of H6 (trans isomer). The lactam **6** was then converted to the crystalline acetyl derivative **7** (Scheme 2) and the relative stereochemistry was confirmed by X-ray crystallographic analysis (Figure 1). In the crystalline form, the molecule adopts a half-chair conformation where the two substituents adopt a trans diaxial orientation (dihedral angle $OC_5C_6C = -162°$). Lactam **7** would be expected to undergo a fast conformational equilibrium between the X-ray form and the half-chair which places both substituents in the pseudoequatorial position (Scheme 2). Low temperature ^1H NMR experiments were conducted in order to determine the position of the equilibrium. Unfortunately, the coalescence temperature was not observed at T > 148 K (400 MHz). The barrier for ring reversal of six-membered ring containing an unsaturation is much lower than for cyclohexane.[4] Nevertheless, assuming that only the half-chair conformation **7a** and **7b** are present in solution, the position of the equilibrium could be estimated by comparison of the $^3J_{5,6}$ value calculated from the X-ray structure and the one observed by ^1H NMR (3.6 Hz). The method relies on a modified Karplus equation, parameterized for electronegative ring substituents.[5] The $^3J_{5,6}$ value calculated from the X-ray coordinates (**7b**) is 1.6 Hz. For conformer **7a**, the calculated $^3J_{5,6}$ value is 8.4 Hz. Therefore, using the weighed averaging method, the position of equilibrium was estimated to be 71/29 (**7b/7a**) ($\Delta G°_{298}$= -0.51 kcal/mol) in acetone-d_6.

Scheme 2



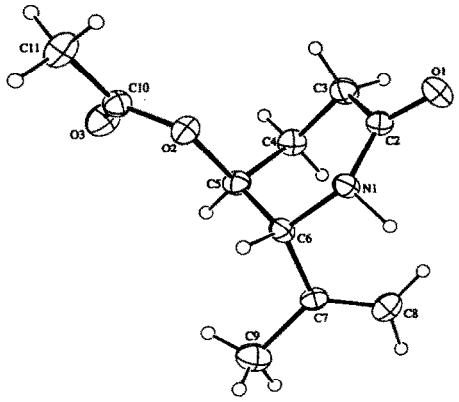


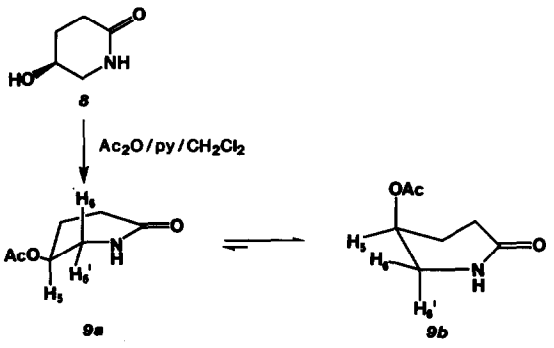
Figure 1. ORTEP representation of lactam 7 in orientation b

For 7b	$<OC_5C_6C$	−162°	
	$<H_5C_5C_6H_6$	76°	$^3J_{5,6}$ = 1.6 Hz
For 7a	$<H_5C_5C_6H_6$	−162°	$^3J_{5,6}$ = 8.4 Hz

Two hypotheses were considered in order to explain the preferred trans diaxial orientation of the C5 and C6 substituents in lactam **7** both in the solid state, and polar solution. Firstly, the gauche interaction between the vicinal substituent in the equatorial orientation might be responsible for the preferred axial conformation. This observation was made recently in six-membered lactones substituted vicinally by two bulky groups.[6] Such a trans diaxial conformation has been also observed in silylated 2-amino sugars, again presumably due to the gauche interaction of relatively bulky vicinal substituents.[7] Secondly, the trans diaxial orientation might be favoured due to the known tendency of two polar groups to adopt a gauche orientation.[8] This phenomenon is known as the gauche-effect and has been used by Jaime[9] to explain the conformation of 3- and 4-hydroxybutyrolactones. The gauche-effect has been estimated for 3-acetoxy and 3-acetamino-piperidine by Bernet and Vasella[10] and was shown to be an attractive force.

In order to define which of the two previous factors contribute to the axial conformation of lactam **7**, we have prepared the monosubstituted lactam **9** from the known alcohol **8**[11] (Scheme 3). As was the case for alcohol **8**, the acetyl derivative **9** shows two small coupling constant values ($^3J_{5,6}$ and $^3J_{5,6'}$ = 3.9 Hz). In the solid state structure of lactam **9**, the acetoxy group adopts an axial orientation; the dihedral angle $OC_5C_6H_6'$ being -177° (Figure 2). From the observed and calculated $^3J_{5,6}$ values, the position of the equilibrium was estimated at 92/8 (**9b/9a**) ($\Delta G°_{298}$ = -1.4 kcal/mol) in acetone-d_6. Therefore, the position of the equilibrium, in solution, of δ-lactams is largely controlled by the preferred axial orientation of the C5 oxygen substituent.

Scheme 3



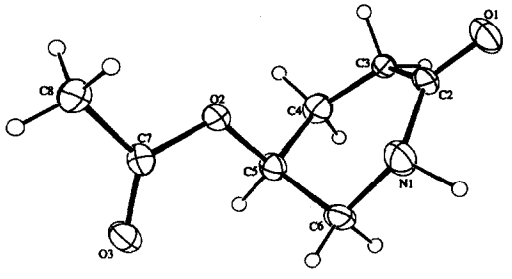
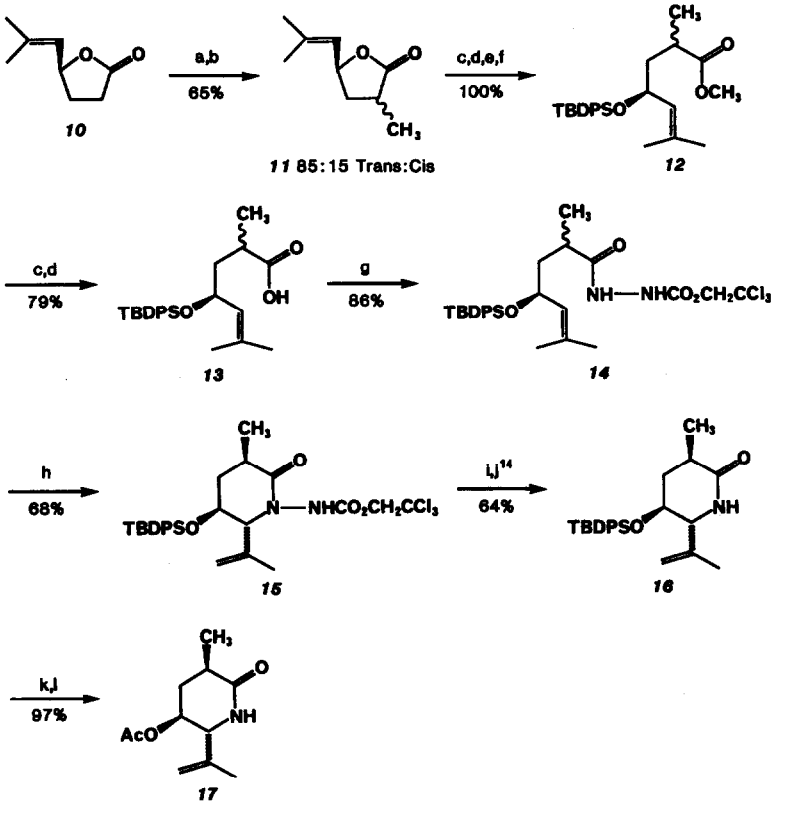


Figure 2. ORTEP representation of lactam 9 in orientation b

For 9b	$<OC_5C_6H_6'$	−177°	
	$<H_5C_5C_6H_6'$	−62°	$^3J_{5,6'}$ = 1.1 Hz
	$<H_5C_5C_6H_6$	58°	$^3J_{5,6}$ = 3.3 Hz
For 9a	$<H_5C_5C_6H_6$	−180°	$^3J_{5,6}$ = 10.3 Hz
	$<H_5C_5C_6H_6'$	−62°	$^3J_{5,6'}$ = 3.7 Hz

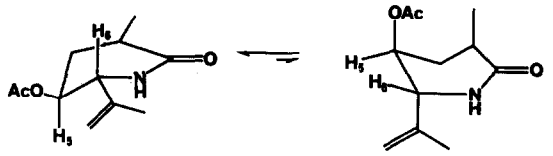
Hitherto we have observed that the position of the equilibrium for 5-, and 5,6-disubstituted lactams **7** and **9** favors the trans diaxial conformers. In principal, the introduction of a methyl group at C3 of lactam **7**, cis to the acetoxy unit, should increase the steric destabilization of the conformer having axial substituents, and displace the equilibrium toward the equatorial conformer. MMFF[12] calculations showed that the addition of a methyl substituent, cis to the oxygen atom, should have a destabilization effect of 2.4 kcal/mol. Consequently, lactam **17** should exist preferentially in the equatorial conformation **17b** (Scheme 5). This lactam has been prepared from lactone **10**[13] as outlined in Scheme 4. The $^3J_{5,6}$ value is 8.1 Hz in acetone-d_6. In this case, the equilibrium position was estimated by comparison of the observed value with those calculated for lactam **7**. Therefore, a 87/13 ratio (**17b/17a**) ($\Delta G°_{298}$ = +1.2 kcal/mol) was estimated for lactam **17** in acetone-d_6, and the steric factors now outweigh the gauche effect.

Scheme 4



a) LDA, 78°C; b) CH_3I, THF, HMPA; c) LiOH, H_2O_2, THF, H_2O; d) Na_2SO_3, H_2O; e) CH_2N_2, Et_2O; f) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0°C TO R.T.; g) $H_2NNHCO_2CH_2CCl_3$ *(18)*, DMAP, 1-HYDROXY-BENZOTRIAZOLE, 1-(3-DIMETHYLAMINOPROPYL)-3-ETHYLCARBODIIMIDE HCl, CH_2Cl_2; h) $Pb(OAc)_4$, CH_2Cl_2, -20°C 30 MIN. TO 0°C 30 MIN.; i) Zn, HOAc; j) Ph_2NNO, BENZENE, 80°C; k) TBAF, THF, 0°C TO R.T.; l) Ac_2O.

Scheme 5



17b 17a

In summary, the attractive gauche effect[10] influences the position of the equilibrium of C5 oxygen-substituted lactams. This effect overcomes, for lactams **7** and **9**, the gauche interaction resulting in axial conformers. The X-ray structures show a preferred axial conformation in the solid state and this conformer likely predominates in acetone-d_6 solutions. For lactam **17**, the equatorial conformer predominates in solution due to the steric constraints in the axial conformer.

ACKNOWLEDGEMENTS: The authors would like to thank D. Guay for helpful discussions regarding the gauche-effect and Professor White for discussions concerning the use of N-nitrosodiphenylamine for the conversion of hydrazides to amides.

EXPERIMENTAL

Crystal structure details for compound **7**: $C_{10}H_{15}NO_3$, M_r=197.24, orthorhombic, $P2_12_12_1$, a=11.770(3), b=12.279(2), c=7.3619(9)Å, V=1064Å^3, Z=4, D_x=1.231 g cm^{-3}, monochromatized radiation λ(Cu$K\alpha$)=1.541838Å, μ=0.713 mm^{-1}, F(000)=424, T=294 K. Data collected on a Rigaku AFC5R diffractometer to a θ limit of 70° with 818 observed, at $I \geq 3\sigma(I)$, reflections out of 1110 measured. Structure solved by direct methods and refined using full-matrix least-squares on F using 128 parameters. All non-hydrogen atoms refined with anisotropic thermal displacements. Final agreement statistics are: R=0.045, wR=0.045, S=2.06, $(\Delta/\sigma)_{max}$<0.01. Weighting scheme is $1/\sigma^2(F)$. Maximum peak height in final difference Fourier map is 0.16(4)eÅ^{-3} with no chemical significance. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

Crystal structure details for compound **9**: $C_7H_{11}NO_3$, M_r=157.171 monoclinic, $P2_1$, a=5.5729(6), b=6.5848(7), c=10.7715(7)Å, ß=93.629(7)°, V=394.5(1)Å^3, Z=2, D_x=1.323 g cm^{-3}, monochromatized radiation λ(CuK_α)=1.541838Å, μ=0.83 mm^{-1}, F(000)=168, T=294 K. Data collected on a Rigaku AFC5R diffractometer to a θ limit of 71° with 755 observed, at $I \geq 3\sigma(I)$, reflections out of 880 measured. Structure solved by direct methods and refined using full-matrix least-squares on F using 100 parameters. All non-hydrogen atoms refined with anisotropic thermal displacements. Final agreement statistics are: R=0.065, wR=0.080, S=5.61, $(\Delta/\sigma)_{max}$<0.01. Weighting scheme is $1/\sigma^2(F)$. Maximum peak height in final difference Fourier map is 0.34(6)eÅ^{-3} with no chemical significance. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(5S)-5-(Acetyloxy)-2-piperidinone (9) - To a solution of the alcohol **8**[11] (130 mg, 1.13 mmol) in CH_2Cl_2 (3.0 mL) was added an excess of pyridine (2.0 mL) and Ac_2O (250 μL). After a period of 18 hr, the solvents were evaporated under reduced pressure. The resulting residue was co-evaporated three times with toluene and chromatographed on silica gel to provide 100 mg (56%) of the title compound as a white solid: mp 107-109 °C (EtOAc-hexane); $[\alpha]^{20}_D$ - 39.0 (c, 0.27, $CHCl_3$); IR (KBr) 3456, 1725, 1645 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.97 to 2.07 (m, 2H, H_4 and $H_{4'}$), 2.02 (s, 3H), 2.16 to 2.21 (m, 1H, $H_{3'}$), 2.28 to 2.38 (m, 1H, $H_{3'}$), 3.51 (m, 2H, H_6 and $H_{6'}$, $J_{5,6}$ and $J_{5,6'}$=3.9 Hz, $J_{6,6'}$=12.0 Hz), 5.07 (quintet, 1H, H_5, J=3.9 Hz), 7.03 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.10, 25.00, 27.07, 46.08, 65.34, 170.34, 171.35. HRMS calcd for $C_7H_{12}NO_3$ $(M+H)^+$ 158.0817, found 158.0818.

(3R,5S)-Dihydro-3-methyl-5-(2-methyl-1-propenyl)-2(3H)furanone (11) - To freshly prepared LDA (10.8 mL, 3.78 mmole) in THF (0.35 M) at -78 °C was added HMPA (1.3 mL) followed by a THF solution (4.8 mL) of lactone **10**[13] (400 mg, 2.84 mmole). After a period of 15 minutes at -78 °C, MeI (354 μL, 5.68 mmole) was then added. The resulting mixture was allowed to warm slowly until -20 °C. The reaction was quenched by adding a 25% aqueous solution of NH_4OAc and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude mixture was purified by flash chromatography (20% ethyl acetate in hexane) to give a 10/1 mixture of lactone **11** (288 mg, 65%). An analytical sample was purified by HPLC (20% ethyl acetate in hexane): $[\alpha]_D^{20}$ + 124 (c, 013, acetone); ^{1}H NMR (500 MHz, acetone-d_6) δ 1.25 (d, 3H, CH_3), 1.73 (bs, 6H, 2 CH_3), 2.05 to 2.18 (m, 2H, CH_2), 2.75 (sextet, 1H, CH), 5.25 (m, 1H, CHO), 5.32 (m, 1H, CH=C$(CH_3)_2$); ^{13}C NMR (100 MHz, acetone-d_6) δ 15.83, 18.12, 25.68, 34.78, 37.33, 75.21, 124.47, 138.85, 179.89. HRMS calcd for $C_9H_{15}O_2$ $(M+H)^+$, 155.1072, found 155.1072.

(2R,4S)-4-[Tert-butyldiphenylsilyl)oxy]-2,6-dimethyl-5-heptenoic acid methyl ester (12) - To a solution of lactone **11** (1.20 g, 7.79 mmole) in THF (120 mL) - H_2O (36.0 mL) were added at 0 °C H_2O_2 60% (1.56 mL, 27.5 mmole) and LiOH (374 mg, 15.58 mmole). After a period of 24 h at room temperature, a H_2O solution (23.0 mL) of Na_2SO_3 (4.30 g, 34.1 mmole) was added. To the resulting mixture was added ether and AcOH (pH 5.5). After the addition of CH_2N_2, the organic phase was separated, washed with 25% aqueous solution of NH_4OAc, dried over Na_2SO_4 and evaporated under reduced pressure. The crude mixture was purified on silica gel (EtOAc) to afford the hydroxy ester which was then dissolved in CH_2Cl_2 (39.0 mL). At 0 °C were added Et_3N (2.15 mL, 15.5 mmol), t-butylchorodiphenylsilane (4.03 mL, 15.5 mmole) and DMAP (944 mg, 7.74 mmol). After a period of 18 h at room temperature, the reaction mixture was quenched by the addition

of 25% aqueous NH_4OAc solution, extracted with EtOAc and the organic phase dried over Na_2SO_4. The title compound was purified by flash chromatography (5% EtOAc in hexane); 3.30 g (100%) as a 83/17 mixture of diastereoisomer. Data for the major isomer: ^1H NMR (200 MHz, acetone-d_6) δ 1.03 (s, 9H, $(CH_3)_3C$), 1.08 (d, 3H, CH_3), 1.12 (d, 3H, CH_3), 1.48 (d, 3H, CH_3), 1.63 (m, 1H, CHH), 1.83 (m, 1H, CHH), 2.53 (sextuplet, 1H, CH), 3.56 (s, 3H, OCH_3), 4.44 (m, 1H, CHO), 5.09 (m, 1H, $CH=C(CH_3)_2$), 7.34 to 7.72 (m, 10H, 2Ph), ^{13}C NMR (100 MHz, acetone - d_6) δ 17.96, 18.26, 19.78, 25.61, 27.36, 36.47, 43.11, 51.61, 70.01, 128.16, 128.38, 128.88, 130.28, 133.68, 136.64, 176.89. HRMS calculated for $C_{22}H_{27}O_3Si$ (M - C_4H_9)$^+$ 367.1729, found 364.1730.

(2R,4S)-4-[(Tert-butyldiphenylsilyl)oxy]-2,6-dimethyl-5-heptenoic acid (13) - To a solution of the ester **12** (3.30 g, 5.82 mmole) in THF (121 mL) - H_2O (35.6 mL) were added H_2O_2 60% (1.6 mL, 28.2 mmol) and LiOH (394 mg, 16.4 mmole). After 3 days at 40 °C, a solution of Na_2SO_3 (4.59 g, 36.4 mmol) in H_2O (28.0 mL). A saturated solution of NH_4Cl was then added and the mixture extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The mixture was purified by flash chromatography (15% EtOAc in hexane) to provide the acid **13**; 2.57 g (79%) as a 82:18 mixture of diastereoisomer. Data for the major isomer: ^1H NMR (200 MHz, acetone-d_6) δ 1.03 (s, 9H, $(CH_3)_3C$), 1.04 (d, 3H, CH_3), 1.12 (d, 3H, CH_3), 1.47 (d, 3H, CH_3), 1.63 (m, 1H, CHH), 1.85 (m, 1H, CHH), 2.51 (sextuplet, 1H, CH), 4.50 (m, 1H, CHO), 5.13 (m, 1H, $CH=C(CH_3)_2$), 7.38 to 7.75 (m, 10H, 2Ph). ^{13}C NMR (100 MHz, acetone - d_6) δ 17.98, 18.12, 19.78, 25.59, 27.36, 36.15, 43.08, 69.98, 128.16, 128.36, 128.93, 130.26, 133.73, 136.63, 177.54. HRMS calcd for $C_{21}H_{25}O_3Si$ (M-C_4H_9)$^+$ 353.1572, found 353.1572.

1-Hydrazine carboxylic acid 2,2,2-trichloroethyl ester (18) - To a solution of hydrazine (22.5 mL, 0.703 mmol) in $CHCl_3$ (250 mL) at 0 °C was added a solution of 2,2,2-trichloroethyl chloroformate (20.9 mL, 0.151 mmol) in $CHCl_3$ (50.0 mL). After a period of 1 h at 0 °C, the reaction mixture was partitioned between EtOAc and H_2O. The organic phase was collected, dried over Na_2SO_4 and evaporated under reduced pressure. The hydrazide **18** was purified by flash chromatography (100% ethyl acetate), 25.6 g (82%), mp 42 °C (ether-hexane); ^1H NMR (300 MHz, $CHCl_3$) δ 3.82 (bs, 2H, NH_2), 4.75 (s, 2H, CH_2), 6.30 (bs, 1H). Anal calcd for $C_3H_5Cl_3N_2O_2$: C, 17.46; H, 2.43; N, 13.59. Found C, 17.70; H, 2.52; N, 13.51.

(2R,4S)-2-[2,6-Dimethyl-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-oxo-5-heptenyl]-hydrazinecarboxylic acid 2,2,2-trichloroethyl ester (14) - To the acid **13** (750 mg, 1.82 mmol) in CH_2Cl_2 (5.6 mL) was added the hydrazide **18** (760 mg, 3.67 mmole), DMAP (446 mg, 3.67 mmol) and 1-hydroxybenzotriazole (494 mg, 3.67 mmol). To the resulting mixture was added dropwise a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide•HCl (702 mg, 3.67 mmol) in CH_2Cl_2 (3.4 mL). After a period of 18 h at room temperature, the reaction mixture was partitioned between NH_4OAc 25% and EtOAc. The organic phase was separated, dried over Na_2SO_4, and evaporated under reduced pressure. The crude mixture was purified by flash chromatography (20% EtOAc in hexane) to afford the hydrazide **14** (940 mg, 80%) as a mixture of diastereoisomer. Data for the major isomer: ^1H NMR (200 MHz, acetone-d_6) δ 1.02 (s, 9H, $2(CH_3)_3C$), 1.06 (d, 3H, CH_3), 1.14 (d, 3H, CH_3), 1.48 (d, 3H, CH_3), 1.70 (m, 1H, CHH), 1.88 (m, 1H, CHH), 2.48 (m, 1H, CH), 4.52 (m, 1H, CHO), 4.80 (s, 2H, CH_2), 5.10 (m, 1H, $CH=C(CH_3)_2$), 7.34 to 7.75 (m, 10H, 2Ph), 8.60 (bs, 1H, NH), 8.88 (bs, 1H, NH), HRMS calcd for $C_{24}H_{28}Cl_3N_2O_4Si$ (M-C_4H_9)$^+$ 541.0884, found 541.0882.

(2R,3S,5R)-[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-5-methyl-2-(1-methylethenyl)-6-oxo-1-piperidinyl]-carbamic acid 2,2,2-trichloroethyl ester (15) - To the hydrazide **14** (450 mg, 0.755 mmol) in CH_2Cl_2 (3.5 mL) at -20 °C was added $Pb(OAc)_4$ (398 mg, 0.898 mmol). After a period of 30 min at -20 °C, the temperature was brought slowly to 0 °C and the reaction mixture was neutralized by the addition of NH_4OAc 25% in H_2O. After usual workup procedure (EtOAc), the cyclic hydrazide was purified by flash chromatography (20% EtOAc in hexane) to give 310 mg (68%) of an oil. $[\alpha]_D^{20}$ + 28.4° (c, 0.5 in acetone); ^1H NMR (300 MHz, acetone-d_6, 325 K) δ 1.06 (s, 9H, $(CH_3)_3C$), 1.11 (d, 3H, CH_3), 1.51 (bs, 3H, CH_3), 1.79 (m, 1H, H_4), 1.98 (m, 1H, H_4'), 2.24 (m, 1H, H_3), 4.14 (m, 1H, H_5), 4.27 (bd, 1H, H_6), 4.80 (bs, 2H, CH_2), 5.04 (m, 2H, CH_2=C), 7.40 to 7.79 (m, 10H, 2Ph), 8.34 (bs, 1H, NH). Anal. calcd for $C_{28}H_{35}Cl_3N_2O_4Si$; C, 56.28; H, 5.86; N, 4.69. Found C, 56.43; H, 6.07; N, 4.59. HRMS calcd for $C_{28}H_{36}Cl_3N_2O_4Si$: $(M+H)^+$ 597.1510, found 597.1508.

(3R,5S,6R)-5-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-3-methyl-6-(1-methylethenyl)-2-piperidinone (16) - To the hydrazide **15** (300 mg, 0.502 mmol) in AcOH (7.5 mL) was added portionwise zinc dust (900 mg). After a period of 4 hrs, the reaction mixture was filtered over celite and washed with CH_2Cl_2. The solvents were removed under reduced pressure and the mixture purified by flash chromatography (5% MeOH in CH_2Cl_2) to provide the mono hydrazide (210 mg). The hydrazide was then dissolved in benzene (7.5 mL) and N-nitrosodiphenylamine (343 mg) was then added. The brown mixture was then heated in a sealed tube at 80 °C for 4 h. The reaction was then directly chromatographed over silica gel (2.5% to 5% MeOH in CH_2Cl_2). After a second purification on silica gel (50% EtOAc in hexane) the lactam **16** was obtained as an oil (130 mg, 64%). $[\alpha]_D^{20}$ + 27.8 (c, 0.3 in acetone); ^1H NMR (400 MHz, acetone-d_6) δ 1.05 (s, 9H, $(CH_3)_3C$), 1.11 (d, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.68 (m, 1H, H_4), 1.91 (m, 1H, H_4'), 2.11 (m, 1H, H_3), 3.86 (d, 1H, H_6, $J_{6,5}$=6.9 Hz), 3.97 (m, 1H, H_5), 4.91 (m, 1H, C<u>H</u>H=C), 4.99 (m, 1H, CH<u>H</u>=C), 6.21 (bs, 1H, NH), 7.42 to 7.75 (m, 10H, 2Ph). ^{13}C NMR (100 MHz, acetone-d_6) δ 17.81, 18.41, 19.76, 27.30, 34.15, 37.15, 67.02, 69.36, 115.60, 128.54, 130.83, 134.04, 136.73, 144.34, 173.79. Anal. calcd for $C_{25}H_{33}NO_2Si$; C, 73.71, H, 8.11, N. 3.44. Found C, 73.32; H, 8.29; N, 3.39.

(3R,5S,6R)-5-(acetyloxy)-3-methyl-6-(1-methylethenyl)-2-piperidinone (17) - The lactam **16** (100 mg, 0.245 mmol) in THF (20 mL) at 0 °C was treated with nBu_4NF (490 μL, 0.490 mmol). After a period of 18 h at room temperature, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (5% MeOH in CH_2Cl_2). To the alcohol (50 mg) in CH_2Cl_2 (2.0 mL) was added Ac_2O (excess) and pyridine (100 μL). After a period of 8 h, the solvents were removed under reduced pressure and the title compound was purified by flash chromatography (100% ethyl acetate) (40.0 mg, 97%): $[\alpha]_D^{20}$ + 41.6° (c, 0.25 in acetone); ^1H NMR (400 MHz, acetone-d_6) δ 1.16 (d, 3H, CH_3), 1.68 (m, 1H, H_4), 1.72 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.13 (ddd, 1H, $H_{4'}$, $J_{4',5}$=3.8 Hz, $J_{4',3}$=6.0 Hz, $J_{4',4}$=12.7 Hz), 2.44 (m, 1H, $'H_3$,$J_{3,4'}$=6.0 Hz, $J_{3,4}$=10.9 Hz), 3.92 (d, 1H, H_6, $J_{6,5}$=8.1 Hz), 4.91 (m, 2H, C<u>H</u><u>H</u>=C), 5.03 (m, 1H, H_5, $J_{5,4'}$=3.8 Hz, $J_{5,4}$=10.4 Hz), 6.44 (bs, 1H, NH), ^{13}C NMR (100 MHz, acetone-d_6) δ 17.50 (2), 17.52, 20.86, 34.56, 64.22, 68.78, 115.35, 143.87, 170.13, 174.00. HRMS calcd for $C_{11}H_{18}NO_3$ $(M+H)^+$ 212.1287, found 212.1286.

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