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Facile Synthetic Route to Diazepinone Derivatives via Ring Closing Metathesis (RCM) and Its Application for Human Cytidine Deaminase Inhibitors

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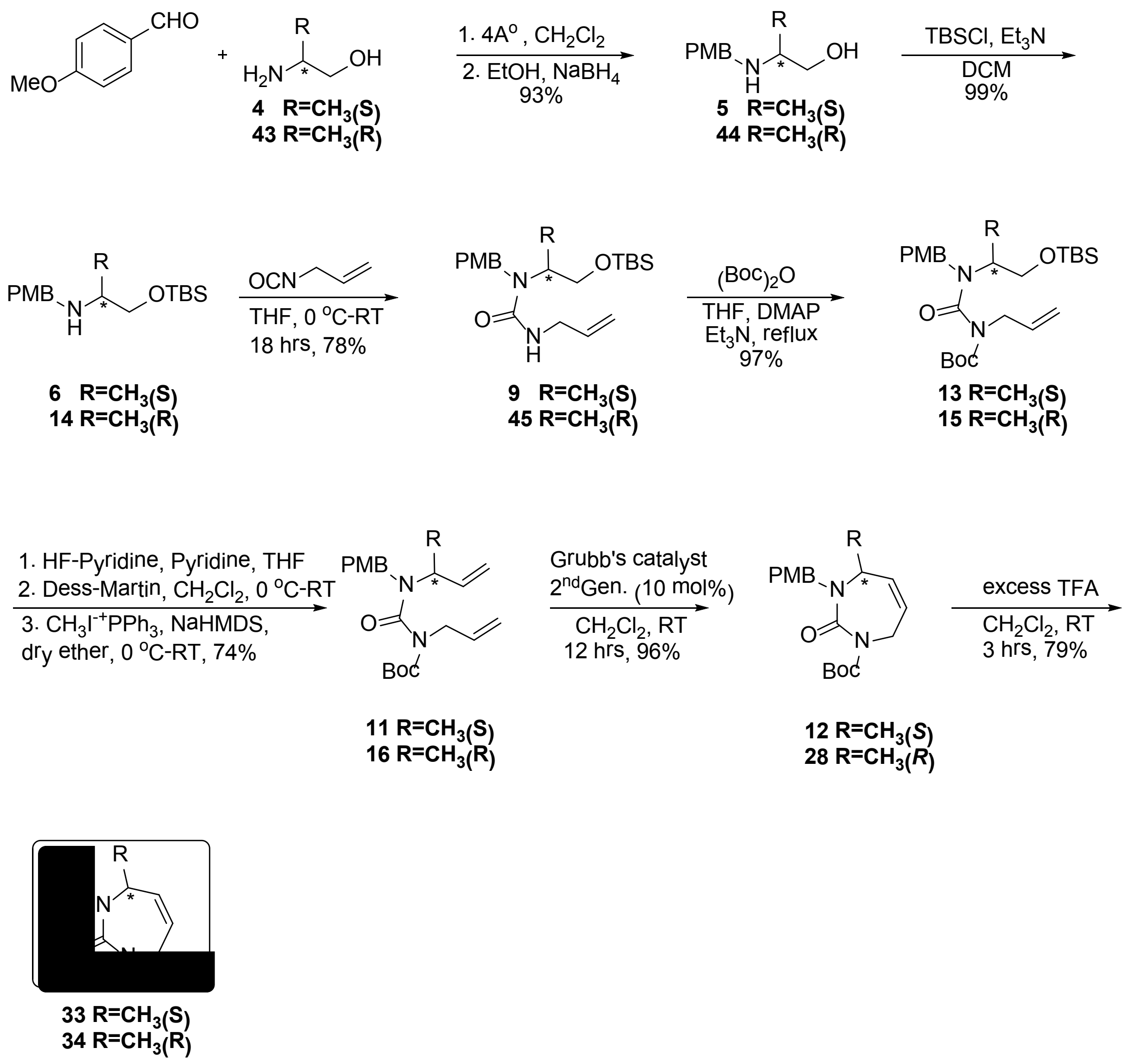
Ⅰ. General Information

Chemical reagents were obtained from Aldrich chemical company. All reaction solvents were dried before use following the literature method. Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate. Subsequent to elution, plates were detection of UV radiation (254 nm). Further visualization was possible by staining with basic solution of phosphomolybdic acid. Column chromatography was performed using E. Merck silica gel 230-400mesh.

Melting points were determined on a Fisher scientific melting point apparatus. Nuclear magnetic resonance (NMR) spectra were recorded on a VARIAN 500 (500 MHz). Chemical shifts (δ) in $CDCl_3$ were reported in the scale relative to $CDCl_3$ (7.26 ppm), CD_3OD (4.87 ppm) for ^1H NMR, and to $CDCl_3$ (77.0 ppm), CD_3OD (49.1 ppm) for ^{13}C NMR. NMR spectra are reported as: s = singlet, d = doublet, dd = doublet of doublets, m = multiplet, brs = broad; coupling constant (s) in Hz; integration. The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz.

LRMS(ESI) spectra were recorded on Shimadzu LCMS 2010 and HRMS(FAB) spectra on JMS-700 Matation.

Ⅱ. Experimental Procedures



General procedure for the synthesis of 5 and 44: To a solution of the optically pure amino-1-propanol (3.92 g, 52.2 mmol) in CH_2Cl_2 (100 mL) was added 4A° molecular sieves (10.0 g) and *p*-methoxybenzaldehyde (7.11 g, 52.2 mmol). The solution was then stirred at room temperature for 3 h, after the reaction mixture was filtered through the cellite and residue was concentrated under reduced pressure. The solution of residue in EtOH (100 mL) was reacted with $NaBH_4$ (2.37 g, 62.6 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was addition of a sat. NH_4Cl solution and concentrated under reduced pressure. The solution was neutralized with 1*N* NaOH, and extracted with CH_2Cl_2 (3 x 75.0 mL). The combined organic extracts were washed with brine and concentrated under vacuum to get as white solid. This compound was used without further purification.

(*S*)-2-(4-Methoxybenzylamino)propan-1-ol (5): Yield = 9.48 g, 93.0%; mp = 72 °C; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.23 (2H, d, J = 8.3 Hz), 6.85 (2H, d, J = 8.6 Hz), 4.58 (1H, brs), 3.82 (1H, s), 3.78 (3H, s), 3.67 (1H, d, *J* = 12.7 Hz), 3.57 (1H, dd, *J* = 3.9, 10.8 Hz), 3.28 (1H, dd, *J* = 7.0, 10.6 Hz), 2.82 (1H, m), 2.43 (1H, brs), 1.07 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.7, 129.3, 128.5, 113.9, 65.4, 55.2, 53.9, 50.4, 16.9; LRMS (ESI) m/z 196 $[M + H]^+$.

(*R*)-2-(4-Methoxybenzylamino)propan-1-ol (44): Yield = 9.44 g, 92.6%; mp = 70 °C; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.24 (2H, d, *J* = 8.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 4.59 (1H, brs), 3.83 (1H, s), 3.78 (3H, s), 3.68 (1H, d, *J* = 13.0 Hz), 3.58 (1H, dd, *J* = 4.2, 10.8 Hz), 3.30 (1H, dd, *J* = 6.9, 10.8 Hz), 2.84 (1H, m), 2.70 (1H, brs), 1.09 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.8, 129.4, 128.5, 113.9, 65.3, 55.2, 53.7, 50.2, 16.8; LRMS (ESI) m/z 196 $[M + H]^+$.

General procedure for the synthesis of 6 and 14: A solution of *tert*-butyldimethylsilyl chloride (5.47 g, 36.3 mmol) in CH_2Cl_2 (50.0 mL) was added dropwise to a stirred solution of **5** or **44** (6.44 g, 33.0 mmol) and Et_3N (9.18 mL, 66.0 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 12 h, then sat. NH_4Cl solution (50.0 mL) was added, and extracted with CH_2Cl_2 (3 x 100 mL) and washed with brine. The organic fraction was dried over $MgSO_4$, filtered, and solvent was evaporated under reduced pressure giving relatively pure oil.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-*N*-(4-methoxybenzyl)propan-2-amine (6): Yield = 10.1 g, 99.0%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.26 (2H, d, *J* = 8.6 Hz), 6.85 (2H, d, *J* = 8.6 Hz), 3.84 (1H, d, *J* = 13.0 Hz), 3.78 (3H, s), 3.71 (1H, d, *J* = 13.2 Hz), 3.57 (1H, dd, *J* = 4.6 Hz), 3.49 (1H, dd, *J* = 7.2, 9.9 Hz), 2.79 (1H, m), 1.05 (3H, d, *J* = 6.6 Hz), 0.89 (9H, s), 0.04 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.7, 129.4, 127.5, 113.8, 66.8, 55.3, 53.8, 50.3, 25.9, 18.2, 16.4, -5.4; LRMS (ESI) m/z 310 $[M + H]^+$.

(*R*)-1-(*tert*-Butyldimethylsilyloxy)-*N*-(4-methoxybenzyl)propan-2-amine (14): Yield = 10.1 g, 99.4%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.24 (2H, d, *J* = 8.3 Hz), 6.85 (2H, d, *J* = 8.8 Hz), 3.83 (1H, s), 3.79 (3H, s), 3.68 (1H, d, *J* = 13.0 Hz), 3.55 (1H, dd, *J* = 4.7, 9.8 Hz), 3.45 (1H, dd, *J* = 7.3, 10.0 Hz), 2.80 (1H, m), 1.02 (3H, d, *J* = 6.4 Hz), 0.89 (9H, s), 0.04 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si): δ 158.6, 129.2, 127.5, 113.8, 67.1, 55.2, 53.8, 50.5, 25.9, 18.2, 16.7, -5.4; LRMS (ESI) m/z 310 $[M + H]^+$.

General procedure for the synthesis of 9 and 45: To a THF (60.0 mL) solution of crude **6** or **14** (9.48 g, 30.0 mmol) in an ice bath, the allyl isocyanate (3.23 mL, 36.8 mmol) was added dropwise. The reaction temperature was allowed to room temperature over the 18 h. The solvent was removed under vacuum and the residue was purified by column chromatography (8% EtOAc in hexane) to afford compound.

(*S*)-3-Allyl-1-(1-(*tert*-butyldimethylsilyloxy)propan-2-yl)-1-(4-methoxybenzyl)urea (9): Yield = 9.15 g, 76.1%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.22 (2H, d, *J* = 8.6 Hz), 6.85 (2H, d, *J* = 8.6 Hz), 5.76 (1H, m), 4.98 (2H, m), 4.50 (1H, d, *J* = 17.1 Hz), 4.35 (1H, d, *J* = 16.9 Hz), 4.26 (1H, m), 3.81 (2H, m), 3.79 (3H, s), 3.56 (2H, m), 1.17 (3H, d, *J* = 6.9 Hz), 0.87 (9H, s), 0.02 (6H, s); ^{13}C

NMR (125 MHz; $CDCl_3$; Me_4Si) δ 159.0, 158.7, 135.8, 131.3, 127.9, 115.0, 114.1, 66.5, 55.3, 53.1, 46.7, 43.3, 25.9, 18.2, 15.2, -5.6; LRMS (ESI) m/z 393 $[M + H]^+$.

(*R*)-3-Allyl-1-(1-(*tert*-butyldimethylsilyloxy)propan-2-yl)-1-(4-methoxybenzyl)urea (45): Yield = 9.38 g, 78.0%; ^1H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.22 (2H, d, J = 8.3 Hz), 6.85 (2H, d, J = 8.3 Hz), 5.80 (1H, m), 5.00 (2H, m), 4.50 (1H, d, J = 17.1 Hz), 4.35 (1H, d, J = 16.9 Hz), 4.28 (1H, m), 3.81 (2H, m), 3.79 (3H, s), 3.61 (2H, m), 1.17 (3H, d, J = 7.1 Hz), 0.88 (9H, s), 0.02 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 159.0, 158.7, 135.8, 131.3, 127.8, 115.0, 114.1, 66.5, 55.3, 53.1, 46.7, 43.3, 25.8, 18.2, 15.2, -5.6; LRMS (ESI) m/z 393 $[M + H]^+$.

General procedure for the synthesis of 13 and 15: To a solution of protected urea **9** or **45** (9.38 g, 23.9 mmol), Et_3N (4.32 mL, 31.1 mmol) and DMAP (1.46 g, 11.9 mmol) in 50.0 mL of dry THF at 0 ^oC was added dropwise di-*tert*-butyl dicarbonate (6.79 g, 31.1 mmol) in 20.0 mL THF. The reaction mixture was refluxed under N_2 for 24 h. The reaction mixture was quenched with water (20.0 mL) and extracted with EtOAc (3 x 50.0 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography (6% EtOAc in hexane) to afford as an oil.

(*S*)-*tert*-Butylallyl((1-(*tert*-butyldimethylsilyloxy)propan-2-yl)(4-methoxybenzyl)carbamoyl)carbamate (13): Yield = 10.3 g, 87.8%; ^1H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.23 (2H, m), 6.84 (2H, d, J = 8.6 Hz), 5.87(1H, m), 5.22 (1H, m), 5.13 (1H, d, J = 10.3 Hz), 4.40 (1H, d, J = 16.6 Hz), 4.12(1H, d, J = 16.6 Hz), 3.97 (1H, m), 3.80 (3H, s), 3.63 (2H, m), 3.49 (2H, d, J = 5.4 Hz), 1.49 (9H, s), 1.49 (3H, d, J = 6.8 Hz), 0.87 (9H, s), 0.01 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 152.9, 131.2, 128.7, 119.0, 117.7, 113.8, 81.7, 65.3, 55.7, 55.3, 49.4, 45.0, 28.3, 25.9, 18.2, -5.5; LRMS (ESI) m/z 515 $[M + Na]^+$.

(*R*)-*tert*-Butylallyl((1-(*tert*-butyldimethylsilyloxy)propan-2-yl)(4-methoxybenzyl)carbamoyl)carbamate (15): Yield = 11.3 g, 96.6%; ^1H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.23 (2H, m), 6.83 (2H, d, J = 8.3 Hz), 5.87 (1H, m), 5.22 (1H, d, J = 17.1 Hz), 5.12 (1H, d, J = 10.0 Hz), 4.44 (2H, m), 4.02 (3H, m), 3.79 (3H, s), 3.61 (2H, m), 1.49 (9H, s), 1.20 (3H, d, J = 6.8 Hz), 0.87 (9H, s), 0.01 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.8, 152.9, 133.9, 128.7, 117.6, 113.8, 81.7, 65.2, 55.7, 55.3, 49.4, 28.3, 25.9, 18.2, -5.5; LRMS (ESI) m/z 515 $[M + Na]^+$.

General procedure for the synthesis of 11 and 16: The compound **13** or **15** (11.3 g, 22.9 mmol) was dissolved in 100 mL of THF and pyridine solution, after added HF-pyridine (70% as hydrogen fluoride). The reaction mixture was stirred at room temperature for 3 h. Then, the reaction mixture was concentrated under reduce pressure. The crude product was purified by column chromatography (30% EtOAc in hexane) to afford alcohol. The free alcohol (6.63 g, 17.5 mmol) was dissolved in a CH_2Cl_2 (100 mL) reacted with Dess-Martin periodiane (65.0 mL, 15% in CH_2Cl_2, 22.8 mmol), initially stirred for 5 min at 0 ^oC, and then stirred for 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$, and the organic material was extracted with CH_2Cl_2 (3 x 50.0 mL). Combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The product was purified by column chromatography (10% EtOAc in hexane) to afford aldehyde as an oil. Finally, the solution of methyltriphenylphosphonium iodide (9.05 g, 22.4 mmol) in anhydrous diethyl ether (200 ml) at 0 °C, NaHMDS (1.0 M in THF, 19.4 mL, 19.4 mmol) was added dropwise and stirred for 30 min under N_2. The aldehyde (5.62 g, 14.9 mmol) in dry ether (100 ml) was added dropwise at 0 °C and stirred for 1 h. The reaction was quenched with sat. NH_4Cl solution and the mixture was extracted with EtOAc (3 x 50.0 mL) and dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (6% EtOAc in hexane) to afford as an oil.

(*S*)-*tert*-Butylallyl(but-3-en-2-yl(4-methoxybenzyl)carbamoyl)carbamate (11): Yield = 4.08 g, 73.0%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.19 (2H, d, J = 7.1 Hz), 6.82 (2H, d, J = 8.8 Hz), 5.89 (1H, m), 5.81 (1H, m), 5.15 (4H, m), 4.67 (1H, m), 4.43 (2H, s), 3.93 (2H, m), 3.78 (3H, s), 1.48 (9H, s), 1.27 (3H, d, J = 6.8 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.7, 156.9, 152.8, 138.2, 133.7, 130.3, 128.6, 118.0, 116.2, 113.7, 81.8, 55.2, 49.3, 28.3, 17.2; LRMS (ESI) m/z 397 $[M + Na]^+$.

(*R*)-*tert*-Butylallyl(but-3-en-2-yl(4-methoxybenzyl)carbamoyl)carbamate (16): Yield = 4.16 g, 74.4%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.19 (2H, d, J = 6.6 Hz), 6.82 (2H, d, J = 8.6 Hz), 5.95 (1H, m), 5.81 (1H, m), 5.16 (4H, m), 4.67 (1H, m), 4.24 (2H, s), 3.91 (2H, m), 3.79 (3H, s), 1.47 (9H, s), 1.27 (3H, d, J = 6.8 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.7, 156.9, 152.8, 138.3, 133.7, 130.3, 128.7, 118.0, 116.2, 113.7, 81.8, 55.2, 49.3, 28.3, 17.2; LRMS (ESI) m/z 397 $[M + Na]^+$.

General procedure for the synthesis of 12 and 28: A round bottomed flask charged with the Grubb's catalyst 2nd generation (623 mg, 10.0 mol%) was evacuated and filled with argon three times before the addition of the diene **11** or **16** (2.75 g, 7.30 mmol) in CH_2Cl_2 (130 mL). The resulting solution was stirred under argon for 12 h, after 4 h stirred in air. Then, removed the solvent *in vacuo* gave a black oil residue. The crude product was purified by column chromatography (23% EtOAc in hexane) to afford as light black oil.

(*S*)-*tert*-Butyl-3-(4-methoxybenzyl)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (12): Yield = 2.43 g, 95.9%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.25 (2H, d, J = 8.8 Hz), 6.84 (2H, d, J = 8.6 Hz), 5.63 (2H, m), 4.59 (1H, d, , J = 14.4 Hz), 4.56 (1H, d, J = 4.8 Hz), 4.47 (1H, d, J = 15.1 Hz), 3.79 (3H, s), 3.75 (1H, d, J = 7.3 Hz), 3.73 (1H, m), 1.50 (9H, s), 1.19 (3H, d, J = 7.1 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 159.0, 157.3, 152.8, 129.6, 129.2, 125.9, 113.9, 81.4, 55.1, 54.6, 52.2, 42.6, 28.1, 20.5; LRMS (ESI) m/z 369 $[M + Na]^+$.

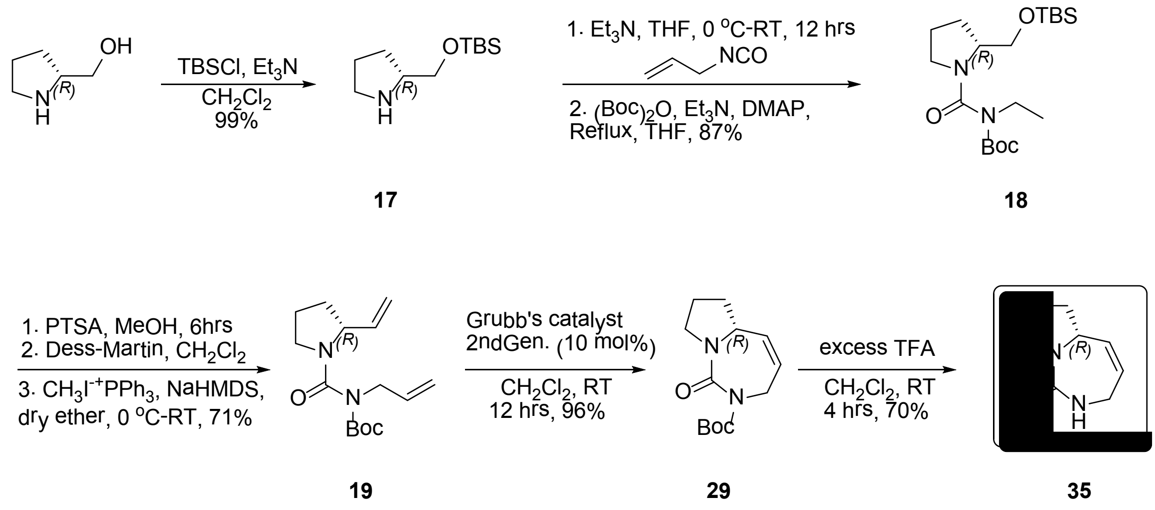
(*R*)-*tert*-Butyl-3-(4-methoxybenzyl)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (28): Yield = 2.44 g, 96.0%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.24 (2H, d, J = 8.6 Hz), 6.85 (2H, d, J = 8.6 Hz), 5.64 (2H, m), 4.59 (1H, d, J = 4.8 Hz), 4.47 (2H, d, J = 15.1 Hz), 3.80 (3H, s), 3.75 (1H, d, J = 7.3 Hz), 3.73 (1H, m), 1.59 (3H, d, J = 7.1 Hz), 1.50 (9H, s); ^{13}C NMR (125

MHz; $CDCl_3$; Me_4Si) δ 159.1, 157.3, 152.9, 129.7, 129.2, 125.9, 113.9, 81.5, 55.2, 54.6, 52.2, 42.6, 28.2, 20.6; LRMS (ESI) m/z 369 $[M + Na]^+$.

General procedure for the synthesis of 33 and 34: A solution of **12** or **28** (2.12 g, 6.12 mmol) in 40.0 mL of CH_2Cl_2 was reacted with 10.0 ml of trifluoroacetic acid at room temperature for 3 h. The reaction mixture was concentrated and the residual trifluoroacetic acid was removed by co-evaporation with several portion of CH_2Cl_2. The residue was neutralized with 1*N* NaOH, extracted with CH_2Cl_2 (3 x 75.0 mL) and washed with brine. The organic extracts were dried over $MgSO_4$ and concentrated under vacuum to get crude product as black solid. The residue was purified by column chromatography (3% MeOH in CH_2Cl_3) to afford as a black oil.

(*S*)-4-Methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (33): Yield = 610 mg, 79.0%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 5.76 (1H, m), 5.65 (1H, m), 5.26 (1H, brs), 4.90 (1H, brs), 4.14 (1H, m), 3.80 (1H, dd, , J = 16.6, 3.4 Hz), 3.63 (1H, dd, , J = 15.1, 3.5 Hz), 1.30 (3H, d, J = 7.8 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 164.1, 133.3, 125.7, 47.1, 40.9, 22.3; LRMS (ESI) m/z 127 $[M + H]^+$; HRMS (FAB) m/z calcd for $C_6H_{11}N_2O$ $[M+H]^+$ 127.0793, found 127.0871.

(*R*)-4-Methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (34): Yield = 610 mg, 79.0%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 5.79 (1H, m), 5.68 (1H, m), 5.44(1H, brs), 5.06 (1H, brs), 4.18 (1H, m), 3.82 (1H, dd, , J = 16.6, 4.9 Hz), 3.65 (1H, dd, , J = 16.5, 4.8 Hz), 1.31 (3H, d, J = 7.1 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 163.8, 133.4, 125.8, 47.0, 40.7, 22.2; LRMS (ESI) m/z 127 $[M + H]^+$; HRMS (FAB) m/z calcd for $C_6H_{11}N_2O$ $[M+H]^+$ 127.0793, found 127.0871.



(*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)pyrrolidine (17): A solution of *tert*-butyldimethylsilane chloride (3.27 g, 21.8 mmol) in CH_2Cl_2 (50.0 mL) was added dropwise to a stirred solution of (*R*)-pyrrolidin-2-ylmethanol (2.00 g, 19.8 mmol) and Et_3N (3.58 mL, 25.7 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 12 h, then washed with brine and extracted with

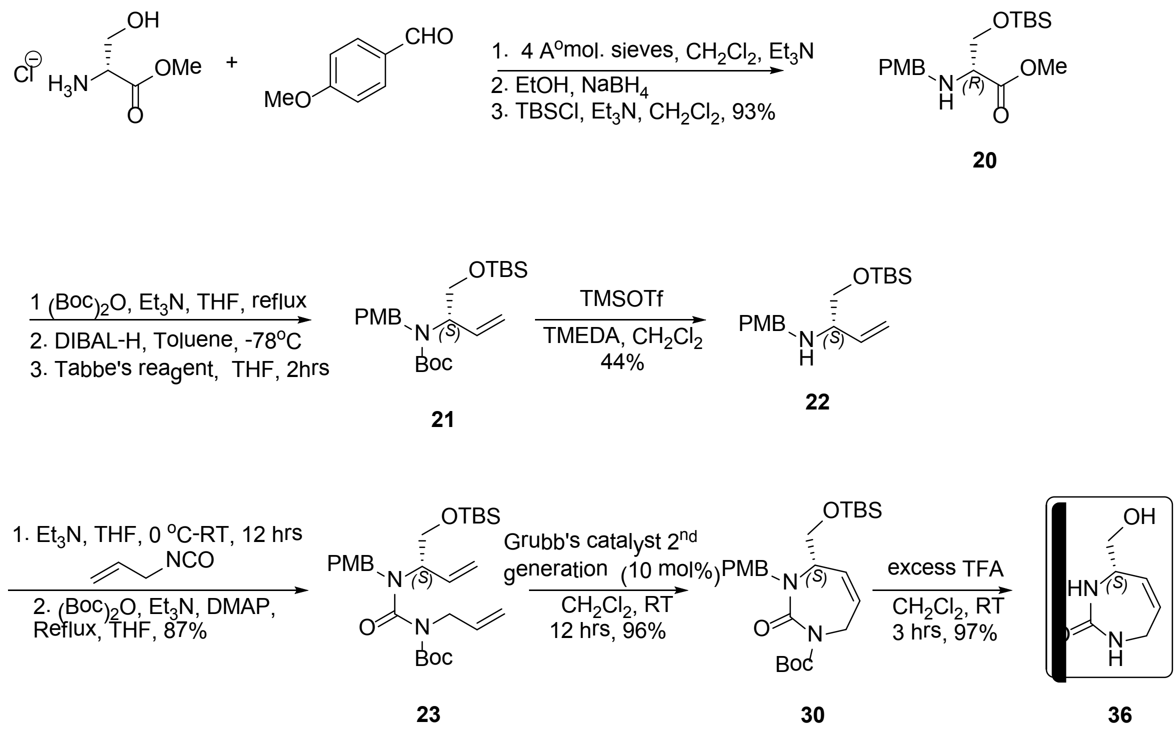
CH_2Cl_2 (3 x 100 mL). The organic fraction was dried over $MgSO_4$, filtered, and solvent was evaporated under reduced pressure to afford a crude oil (4.54 g, 99.9%). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 3.59 (1H. m), 3.52 (1H, m), 3.17 (1H, m,), 2.98 (1H, m), 2.84 (1H, m), 2.36 (1H, brs), 1.75 (3H, m), 1.44 (1H, m), 0.89 (9H, m), 0.04 (6H, m); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 65.6, 60.0, 46.4, 28.6, 27.4, 25.9, 25.3, 23.2, 18.3, -5.4; LRMS (ESI) m/z 216 $[M + H]^+$.

(*R*)-*tert*-Butylallyl(2-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidine-1-carbonyl)carbamate (18): The TBS protected product **17** (4.50 g, 20.9 mmol) was dissolved in 60.0 mL of dried THF and the solution was cooled in an ice bath. After the allyl isocyanate (2.04 mL, 23.2 mmol) was added quickly dropwise. The solution was then stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (10% EtOAc in hexane) to afford a white solid. To the solution of the protected urea (3.40 g, 11.5 mmol) and DMAP (700 mg, 5.75 mmol) in 30.0 mL of dry THF was added Et_3N (42.40 mL, 17.3 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 0.5 h and was then added dropwise a solution of di-*tert*-butyl dicarbonate (5.01 g, 23.0 mmol) in THF (20.0 ml). The reaction mixture was then refluxed under N_2 for 24 h. The reaction mixture was quenched with water (10.0 mL) and extracted with EtOAc (3 x 30.0 mL). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo,* and purified by column chromatography (10% EtOAc in hexane) to afford **18** (3.99 g, 87.0%) as a yellowish oil. ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 5.86 (1H, m), 5.19 (1H, dd, *J*=17.12, 0.98 Hz), 5.11 (1H, d, *J*=9.54 Hz), 4.03 (3H, m), 3.86 (1H, brs), 3.42 (4H, m), 1.95 (4H, m), 1.77 (1H, brs), 1.46 (9H, s), 0.87 (9H, s), 0.03 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 154.9, 133.8, 117.5, 81.3, 62.7, 59.4, 48.6, 28.2, 25.8, 23.9, 18.2, 5.5; LRMS (ESI) m/z 421 $[M + Na]^+$.

(*R*)-*tert*-Butylallyl(2-vinylpyrrolidine-1-carbonyl)carbamate (19): Compound **18** (982 mg, 3.50 mmol) was dissolved in 10.0 mL of MeOH and to the solution was added catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then concentrated *in vacuo*. The residue was extracted with EtOAc (3 x 20.0 ml) and the extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to afford an alcohol. The free alcohol (343 mg, 1.20 mmol) was dissolved in CH_2Cl_2 (10 mL) and to this was added Dess-Martin periodiane (7.4 mL 15.0% in CH_2Cl_2, 2.60 mmol) under N_2. The reaction mixture was stirred for 5 min at 0 °C and then stirred for 1 h at room temperature. The reaction was quenched by addition of sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15.0 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc in hexane) to afford aldehyde as an oil. Finally, To the solution of methyltriphenylphosphonium iodide (199 mg, 0.49 mmol) in anhydrous diethyl ether (10.0 ml) at 0 °C was added dropwise NaHMDS (1.0 M solution in THF, 0.43 mL, 0.43 mmol) and the mixture was stirred for 30 min under N_2. Then the aldehyde (92.7 mg, 0.33 mmol) in dry ether (5.00 ml) was added dropwise to the above solution at 0 ^{o}C and stirred for 1 h. The reaction was quenched with a sat. NH_4Cl solution, and extracted with EtOAc (3 x 15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (33% EtOAc in hexane) to afford **19** (65.8 mg, 71.2%) as an oil.; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 5.86 (1H, m), 5.69 (1H, brs), 5.13 (4H, m), 4.46 (1H, ,brs), 4.02 (2H, brs), 3.46 (2H, brs), 2.07 (1H, m), 1.78 (3H, m), 1.43 (9H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si): δ 154.8, 152.3, 140.0, 134.0, 117.5, 115.0, 81.5, 60.2, 48.8, 47.7, 31.1, 28.2, 23.8; LRMS (ESI) m/z 303 $[M + Na]^{+}$.

(*R*)-*tert*-Butyl 1-oxo-5,6,7,8-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]diazepine-2(3*H*)-carboxylate (29): A round bottomed flask charged with the Grubb's catalyst 2nd generation (44.0 mg, 10.0 mol%) was evacuated and filled with argon three times before the addition of the diene (**19**) (72.7 mg, 0.26 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred under argon for 12 h and then stirred for 4 h exposed to the air, removed the solvent to get black oil residue. The crude product was purified by column chromatography (25% EtOAc in hexane) to afford **29** (71.4 mg, 98.0%) as colorless oil. ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 5.59 (1H, m), 5.52 (1H, m), 4.48 (2H, m), 3.68 (1H, d, *J*=18.10 Hz), 3.62 (1H, m), 3.40 (1H, m), 2.22 (1H, m), 1.80 (4H, m), 1.43 (9H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 155.0, 152.8, 129.2, 127.5, 81.3, 55.5, 47.2, 43.2, 33.8, 28.2, 23.5; LRMS (ESI) m/z 275 $[M + Na]^{+}$.

(*R*)-2,3,5,6,7,8-Hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]diazepin-1-one (35): To the solution of (*R*)-*tert*-butyl-1-oxo-5,6,7,8-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]diazepine-2(3*H*)-carboxylate (**29**) (71.4 mg, 0.28 mmol) in 5.00 mL of CH_2Cl_2 was added 3.50 ml of trifluroacetic acid and stirred at room temperature for 3 h. The reaction mixture was concentrated and the residual trifluroacetic acid was removed by co-evaporation with several portion of CH_2Cl_2. The residue was neutralized with 1*N* NaOH, and extracted with CH_2Cl_2 (3 x 20 mL), washed with brine and concentrated under vacuum to get crude product. The residue was purified by column chromatography (5% MeOH in CH_2Cl_3) to afford 3**5** (29.8 mg, 70.0%) as a black oil.; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 5.64 (2H, m), 4.96 (1H, brs), 4.26 (1H, s), 3.60 (3H, m), 3.26 (1H, m), 2.11 (1H, s), 1.66 (3H, m); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 162.7, 131.0, 126.7, 55.8, 47.6, 42.2, 34.2, 22.6; LRMS (ESI) m/z 153 $[M + H]^{+}$; HRMS (FAB) m/z calcd for $C_8H_{13}N_2O$ $[M+H]^{+}$ 153.0950, found 153.1028.



(*R*)-Methyl-3-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzylamino)propanoate (20): To a solution of the D-serine methyl ester hydrochloride (3.50 g, 22.9 mmol) in CH_2Cl_2 (100 mL) was added 4 A° molecular sieves (10.0 g), Et_3N (3.83 mL, 27.5 mmol) and *p*-methoxybenzaldehyde (3.11 g, 22.9 mmol). After 3 h at room temperature without stirring, then suspension was filtered through the cellite and filtrate was concentrated under reduced pressure. Further, the residue was dissolved in EtOH (50 mL) and reacted with $NaBH_4$ (1.02 g, 27.0 mmol) at room temperature for 2 h. The reaction mixture was addition of a sat. NH_4Cl solution and concentrated under reduced pressure to remove the EtOH. The aqueous solution was neutralized with 1*N* NaOH, and extracted with CH_2Cl_2 (3 x 75.0 mL), washed with brine and concentrated under vacuum to get crude product as a white solid (5.55 g, 90.2%). This compound was used further without purification. Next, a solution of *tert*-butyldimethylsilane chloride (4.20 g, 27.8 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a stirred solution of (*R*)-methyl-3-hydroxy-2-(4-methoxybenzylamino)propanoate (5.50 g, 23.2 mmol) and Et_3N (3.87 mL, 27.83 mmol) in CH_2Cl_2 (70.0 mL). The mixture was stirred at room temperature for 12 h, then sat. NH_4Cl solution (50.0 mL) was added, and extracted with CH_2Cl_2 (3 x 100 mL) and combined extracts were washed with brine. The organic fraction was dried over $MgSO_4$, filtered, and solvent was evaporated under reduced pressure to obtain oil (7.47 g, 92.7%). This product was used for next reaction without further purification.; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.24 (2H, d, J = 8.31 Hz), 6.86 (2H, d, J = 6.35 Hz), 3.83 (5H, m), 3.72 (3H, s), 3.66 (1H, dd, J = 14.67 Hz), 3.61 (1H, m), 3.55(1H, m, J = 4.89 Hz), 0.87 (9H, s), 0.03 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ

173.8, 158.7, 132.0, 129.4, 113.8, 64.6, 62.1, 55.3, 51.6, 51.3, 25.7, 18.2, -5.6; LRMS (ESI) m/z 376 $[M + Na]^+$.

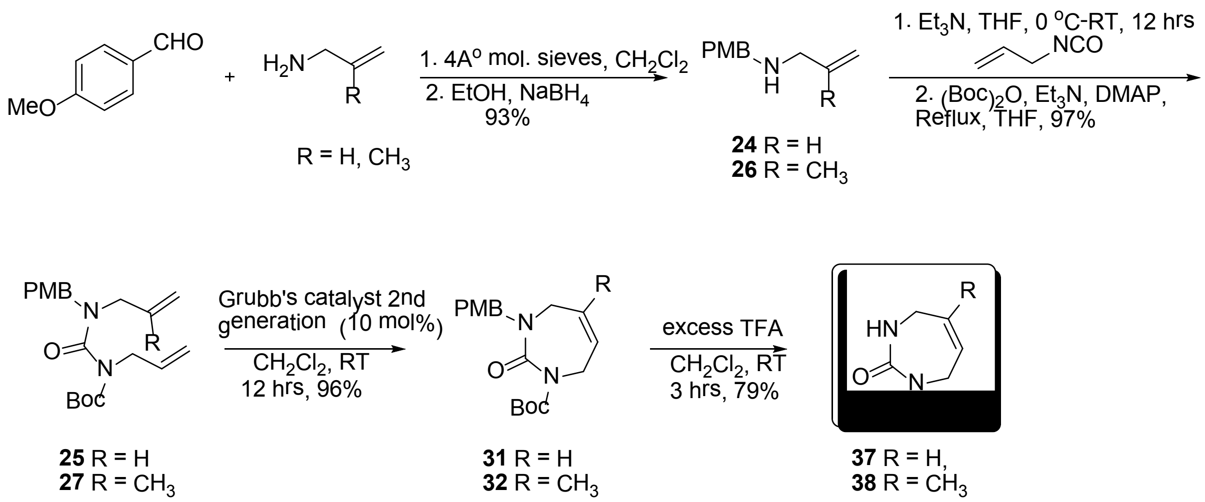
(*S*)-*tert*-Butyl-1-(*tert*-butyldimethylsilyloxy)but-3-en-2-yl(4-methoxybenzyl)carbamate (21): To the solution of protected urea **20** (4.26 g, 12.0 mmol) in 25.0 mL of dry THF at 0 °C was added Et_3N (2.52 mL, 18.1 mmol) and stirred at same temperature for 0.5 h, then added dropwise 20.0 mL solution of di-*tert*-butyldicarbonate (3.94 g, 18.1 mmol) in THF. After addition the reaction mixture was refluxed under N_2 for 24 h. The reaction mixture was quenched with water (10.0 mL) and extracted with EtOAc (3 x 30.0 mL). The combined extracts were washed with brine, the organic layer was dried over anhydrous $MgSO_4$ concentrated *in vacuo* and purified by column chromatography (10% EtOAc in hexane) to afford an oil. Then, diisobutyl aluminum hydride, 1.0 M in toluene (4.40 mL, 4.40 mmol,) was added to slurry of crude compound (1.00 g, 2.20 mmol) in water (15.0 mL) at -78 °C under vigorous stirring. After addition the reaction mixture was stirred at -78°C for 15 min. The reaction mixture was quenched with water (10.0 mL) and extracted with EtOAc (3 x 20.0 mL). The combined extracts were washed with brine, the organic layer was dried over anhydrous $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (12% EtOAc in hexane) to afford a colorless oil. Finally, the aldehyde compound (53.0 mg, 0.12 mmol) was dissolved in 3.00 mL of THF, and added Tabbe's reagent (0.5 M in toluene in Toluene, 0.30 ml, 0.15 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with 1*N* NaOH aqueous solution and extracted with ether (3 x 20 mL). The combined extracts were washed with brine, the organic layer was dried over anhydrous $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (13% ethyl acetate in hexane) to afford a colorless oil **21** (38.0 mg, 72.1%).; ^1H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.24 (2H, m), 6.86 (2H, m), 5.94 (1H, m), 5.11 (2H, brs), 4.31 (3H, m), 4.12 (1H, m), 3.80 (3H, s), 3.73 (1H, brs), 1.48 (9H, m), 0.88 (9H, s), 0.02 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.5, 135.3, 128.6, 113.6, 79.1, 60.3, 55.2, 49.5, 28.4, 25.8, 21.0, 18.2. 14.2, -5.4; LRMS (ESI) m/z 444 $[M + Na]^+$.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-N-(4-methoxybenzyl)but-3-en-2-amine (22): To a solution of **21** (30.0 mg, 0.07 mmol) in CH_2Cl_2 (3.00 mL) was added TMEDA (9.92 mg, 0.08 mmol) and TMSOTf (0.01 mL, 0.08 mmol). The mixture was stirred at room temperature for 24 h, then water (10.0 mL) was added, and mixture was extracted with CH_2Cl_2 (3 x 10.0 mL) and washed with brine. The organic fraction was dried over $MgSO_4$, filtered, and solvent was evaporated under reduced pressure and purified by column chromatography (5% EtOAc in hexane) to afford an oil **22** (20.0 mg, 87.7%). ^1H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.24 (2H, d, J = 8.3 Hz), 6.86 (2H, d, J = 8.3 Hz), 5.65 (1H, m), 5.22 (2H, m), 3.80 (3H, s), 3.72 (1H, m), 3.60 (2H, m), 3.53 (2H, m), 3.21 (1H, m), 0.89 (9H, s), 0.04 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.5, 132.8, 129.2, 117.6, 113.8, 66.2, 62.4, 55.3, 50.5, 25.9, 18.2, -5.4; LRMS (ESI) m/z 322 $[M + H]^+$.

(*S*)-*tert*-Butylallyl((1-(*tert*-butyldimethylsilyloxy)but-3-en-2-yl)(4-methoxybenzyl)carbamoyl)carbamate (23): The TBS product **22** (20.0 mg, 30.0 mmol) was dissolved in of dried THF and the solution was cooled in an ice bath. After the allyl isocyanate (6.00 ml, 0.06 mmol) was added quickly dropwise. The solution was then stirred at room temperature for 18 h. The solvent was removed in vacuum and the residue was purified by column chromatography (5% EtOAc in hexane) to afford urea compound. To the solution of protected urea (20.0 mg, 0.04 mmol) and DMAP (3.00 mg, 0.02 mmol) in 3.00 mL of dry THF was added Et_3N (10.4 ml, 0.07 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 0.5 h and was added dropwise solution of di-*tert*-butyl dicarbonate (16.2 mg, 0.07 mmol) in THF. The reaction mixture was then refluxed under N_2 for 24 h. The reaction mixture was quenched with water (5.00 mL) and extracted with EtOAc (3 x 10.0 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (10% EtOAc in hexane) to afford an oil **23** (10.3 mg, 51.5%).; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.23 (2H, d, J = 8.3 Hz), 6.83 (2H, d, J = 8.6 Hz), 5.91 (2H, brs), 5.17 (4H, m), 4.47 (3H, brs), 3.78 (7H, m), 1.48 (9H, s), 0.86 (9H, s), 0.02 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.8, 152.8, 134.2, 133.9, 128.9, 118.2, 117.5, 113.7, 81.8, 64.3, 62.3, 55.3, 49.4, 28.3, 25.8, 18.2, -5.5; LRMS (ESI): m/z 527 $[M + Na]^+$.

(*S*)-*tert*-Butyl-4-((*tert*-butyldimethylsilyloxy)methyl)-3-(4-methoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (30): A round bottomed flask charged with the Grubb's catalyst 2nd generation (373 mg, 10 mol%) was evacuated and filled with argon three times before the addition of the diene (**23**) (1.10 g, 2.20 mmol) in degassed CH_2Cl_2 (55.0 mL). The resulting solution was stirred under argon for 12 h and then stirred for 4 h exposed to the air, removed the solvent *in vacuo* to obtain a black oil residue. The crude product was purified by column chromatography (15% EtOAc in hexane) to afford **30** (988 mg, 95.1%) as colorless oil.; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.18 (2H, d, J = 8.6 Hz), 6.83 (2H, d, J = 8.6 Hz), 5.74 (1H, m), 5.62 (1H, m), 4.93 (2H, d, J = 14.9 Hz), 4.61 (1H, m), 4.33 (1H, d, J = 14.9 Hz), 4.11 (1H, d, J = 7.3 Hz), 3.78 (3H, s), 3.68(2H, m), 1.51 (9H, s), 0.87 (9H, s), 0.00 (6H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 159.1, 157.2, 153.2, 129.1, 127.8, 128.0, 114.0, 81.6, 66.1, 61.0, 55.2, 53.4, 42.7, 28.2, 25.8, 18.1, -5.3; LRMS (ESI) m/z 499 $[M + Na]^+$.

(*S*)-4-(Hydroxymethyl)-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (36): To the solution of (*S*)-*tert*-butyl-4-((*tert*-butyldimethylsilyloxy)methyl)-3-(4-methoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (**30**) (930 mg, 1.95 mmol) in 40.0 mL of CH_2Cl_2 was added 10.0 ml of trifluroacetic acid and stirred at room temperature for 3 h. The reaction mixture was concentrated and the residual trifluroacetic acid was removed by co-evaporation with several portion of CH_2Cl_2. The residue was neutralized with 1*N* NaOH, and extracted with CH_2Cl_2 (3 x 30.0 mL), washed with brine, dried over $MgSO_4$ and concentrated under vacuum to get crude product. The residue was purified by column chromatography (3% MeOH in CH_2Cl_3) to afford **36** (106 mg, 38.2%) as a colored solid. mp 120 °C; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 6.04(1H, brs), 5.87 (1H, m), 5.63 (1H, m), 4.59 (1H, brs), 4.00 (1H, s), 4.82 (1H, d, J = 18.6 Hz), 3.68 (1H, m), 3.59 (1H, m), 3.46 (1H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 164.5, 127.6, 64.9, 54.1, 40.7; LRMS (ESI) m/z 143 $[M + H]^+$; HRMS (FAB) m/z calcd for $C_6H_{11}N_2O_2$ $[M+H]^+$ 143.0742, found 143.0821.



General procedure for the synthesis of 24 and 26: To a solution of amine Hydrochloride (5.00 g, 53.4 mmol) in CH_2Cl_2 (100 mL) was added 4 A° molecular sieves (10.0 g) and *p*-methoxybenzaldehyde (7.27 g, 53.4 mmol). The solution was then stirred at room temperature for 3 h, after the reaction mixture was filtered through the cellite and residue was concentrated under reduced pressure. The solution of residue in EtOH (100 mL) and reacted with $NaBH_4$ (1.68 g, 64.1 mmol) at room temperature for 2 h. The reaction mixture was addition of a sat. NH_4Cl solution and concentrated under reduced pressure to remove EtOH. Further, the solution was neutralized with 1*N* NaOH, and extracted with CH_2Cl_2 (3 x 75.0 mL), washed with brine and concentrated under vacuum to get product as an oil.

***N*-(4-Methoxybenzyl)prop-2-en-1-amine (24):** Yield = 8.60 g, 90.7%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.23 (2H, d, J = 8.3 Hz), 6.87 (2H, m), 5.59 (1H, m), 5.18 (1H, dd, J = 17.1, 1.2 Hz), 5.10 (1H, dd, J = 10.3, 1.1 Hz), 4.59 (1H, brs), 3.79 (3H, s), 3.71 (2H, s), 3.25 (2H, d, J = 5.9 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 158.8, 136.7, 129.3, 128.5, 115.9, 113.8, 55.2, 52.6, 51.6; LRMS (ESI) m/z 178 $[M + H]^+$.

***N*-(4-Methoxybenzyl)-2-methylprop-2-en-1-amine (26):** Yield = 9.47 g, 99.9%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.24 (2H, d, J = 8.8 Hz), 6.86 (2H, d, J = 8.6 Hz), 4.48 (2H, d, J = 20.5 Hz), 3.77 (3H, s), 3.68 (2H, s), 3.16 (2H, s), 2.31 (1H, brs), 1.77 (3H, s); ^{13}C NMR (125 MHz; $CDCl_3$;

Me_4Si) δ 158.4, 132.1, 129.1, 128.1, 113.5, 111.6, 63.9, 54.9, 52.1, 20.5; LRMS (ESI) m/z 192 $[M + H]^+$.

General procedure for the synthesis of 25 and 27: The amine product **24** or **26** (8.60 g, 48.0 mmol) was added 60.0 mL of dried THF and the solution was cooled in an ice bath. After the allyl isocyanate (5.11 mL, 58.0 mmol) was added quickly dropwise. The solution was allowed to stir and gradually equilibrate to room temperature over the course of 18 h. The solvent was removed under vacuum and the residue was purified by column chromatography (20 % ethyl acetate in hexane) to afford urea compound. Next, To the solution of protected urea (6.32 g, 24.0 mmol) and DMAP (1.48 g, 12.0 mmol) in 50.0 mL of dry THF at 0 °C was added Et_3N (7.00 mL, 48.0 mmol) and stirred at same temperature for 0.5 h. Then add dropwise di-*tert*-butyldicarbonate (20.9 g, 96.0 mmol) in 20.0 mL of THF. After addition, the reaction mixture was refluxed under N_2 for 24 h. After the reaction mixture was quenched with water (20.0 mL) and extracted with EtOAc (3 x 50.0 mL). The combined extracts were washed with brine, the organic layer was dried over anhydrous $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (8% EtOAc in hexane) to afford an oil **25** or **27**.

***tert*-Butylallyl(allyl(4-methoxybenzyl)carbamoyl) (25):** Yield = 8.22 g, 93.9%; ^1H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.17 (2H, m), 6.84 (2H, d, J = 8.6 Hz), 5.87 (1H, m), 5.74 (1H, m), 5.25 (2H, d, J = 5.1 Hz), 5.18 (2H, m), 5.14 (2H, d, J = 5.1 Hz), 4.45 (2H, m), 4.06 (2H, d, J = 6.4 Hz), 3.78 (3H, s), 1.44 (9H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 159.1, 156.6, 152.7, 133.6, 129.5, 128.4, 118.1, 113.9, 81.8, 55.2, 49.1, 28.2; LRMS (ESI) m/z 383 $[M + Na]^+$.

***tert*-Butylallyl((4-methoxybenzyl)(2-methylallyl)carbamoyl)carbamate) (27):** Yield = 8.32 g, 95.0%; ^1H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.19 (2H, m), 6.84 (2H, d, J = 8.3 Hz), 5.90 (1H, m), 5.24 (2H, dd, J = 17.1, 1.5 Hz), 5.15 (2H, dd, J = 10.3, 1.2 Hz), 4.94 (2H, s), 4.85 (2H, s), 4.05 (2H, d, J = 6.4 Hz), 3.78 (3H, s), 1.69 (3H, s), 1.47 (9H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 159.1, 157.1, 152.7, 140.1, 133.8, 129.7, 128.5, 117.9, 113.9, 105.0, 81.9, 55.2, 49.5, 28.2, 20.2; LRMS (ESI) m/z 397 $[M + Na]^+$.

General procedure for the synthesis of 31 and 32: A round bottomed flask charged with the Grubb's catalyst 2nd generation (470 mg, 10 mol%) was evacuated and filled with argon three times before the addition of the diene **25** or **27** (2.00 g, 5.50 mmol) in CH_2Cl_2 (130 mL). The resulting solution was stirred under argon for 12 h and then stirred for 4 h exposed to the air, removed the solvent *in vacuo* to get a black oil. The crude product was purified by column chromatography (15% EtOAc in hexane) to afford as a colorless oil.

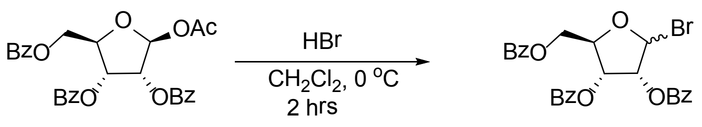
***tert*-Butyl-3-(4-methoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (31):** Yield = 1.86g, 99.9%; ^1H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.23 (2H, d, J = 8.3 Hz), 6.85 (2H, d, J = 8.6 Hz), 5.70 (2H, d, J = 1.7 Hz), 4.55(2H, s), 4.20 (1H, s), 3.80 (3H, s), 3.79 (2H, m), 3.68 (1H, s), 1.50 (9H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 159.2, 157.6, 152.7, 129.1, 128.5, 123.6, 114.0, 81.6, 55.2, 51.8, 45.0, 43.3, 28.3; LRMS (ESI) m/z 355 $[M + Na]^+$.

***tert*-Butyl-3-(4-methoxybenzyl)-5-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (32):** Yield = 1.77 g, 95.0%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.15 (2H, m), 6.77 (2H, m), 5.25 (1H, m), 4.46 (2H, d, J = 3.7 Hz), 4.06 (2H, m), 3.71 (3H, s), 3.51 (2H, m), 1.94 (3H, s), 1.46 (9H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 159.0, 157.4, 152.5, 131.7, 128.9, 128.4, 121.4, 113.7, 81.1, 54.9, 51.6, 49.4, 42.9, 28.0, 23.2; LRMS (ESI) m/z 369 $[M + Na]^+$.

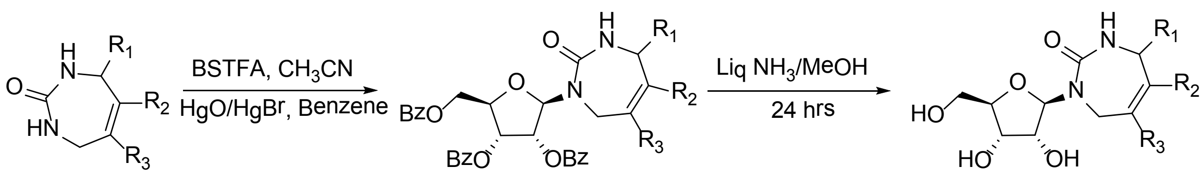
General procedure for the synthesis of 37 and 38: A solution of **31** or **32** (685 mg, 2.10 mmol) in 20.0 mL of CH_2Cl_2 was taken and then added 15.0 mL of trifluroacetic acid followed by stirring at room temperature for 3 h. The reaction mixture was concentrated and the residual trifluroacetic acid was removed by co-evaporation with several portion of CH_2Cl_2. The residue was neutralized with 1*N* NaOH, and extracted with CH_2Cl_2 (3 x 30.0 mL), washed with brine and concentrated under vacuum to get crude product as a black solid. The residue was purified by column chromatography (3% MeOH in CH_2Cl_3) to afford **37** or **38**.

3,4-Dihydro-1*H*-1,3-diazepin-2(7*H*)-one (37): Yield = 222 mg, 96.0%; mp 72 °C; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 5.88 (2H, m), 5.44 (1H, brs), 3.74 (4H, m); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 165.2, 128.9, 41.3; LRMS (ESI) m/z 113 $[M + H]^+$; HRMS (FAB) m/z calcd for $C_5H_9N_2O$ $[M+H]^+$ 113.0637, found 113.0715.

5-Methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (38): Colored Oil; Yield = 208 mg, 90.0%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 10.71 (1H, brs), 6.94 (1H, brs), 5.87 (1H, m), 3.79 (4H, m), 1.97 (3H, s); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 163.9, 137.1, 122.1, 44.8, 40.0, 22.5; LRMS (ESI) m/z 127 $[M + H]^+$; HRMS (FAB) m/z calcd for $C_6H_{11}N_2O$ $[M+H]^+$ 127.0793, found 127.0874.



39



37 R_1=R_2=R_3=H
33 R_1 = (S) CH_3, R_2=R_3 = H
34 R_1 = (R) CH_3, R_2=R_3 = H

40 R_1=R_2=R_3=H
41 R_1 = (S) CH_3, R_2=R_3 = H
42 R_1 = (R) CH_3, R_2=R_3 = H

1 R_1=R_2=R_3=H
2 R_1 = (S) CH_3, R_2=R_3 = H
3 R_1 = (R) CH_3, R_2=R_3 = H

Ribofuranosyl bromide (39): Hydrogen bromide gas ($KBr+H_2SO_4$) was bubbled in to an ice cold solution of 1-*O*-acetyl-2,3,5-tribenzoyl-*β*-D-ribofuranose (252 mg, 5.00 mmol) in CH_2Cl_2 (15.0 mL) for 15 min. After the reaction mixture had been stirred at 0 °C for 2 h and at room temperature for 30 min, it was concentrated under vacuum to thin syrup. Then 3 times with 3.00 mL of CH_2Cl_2 and 3.00 mL of toluene were successively distilled in vacuum from the syrup which was then used immediately for the condensation reaction.

General procedure e for the synthesis of 40, 41 and 42: **37** or **33** or **34** (90.0 mg, 0.70 mmol) was dissolved in 5.00 mL of CH_3CN and treated with an excess of BSTFA (2.50 mL) at room temperature for 1 h. After the completion of reaction the solvent and excess reagent were removed under vacuum. The residue was dissolved in anhydrous benzene (5.00 mL). The solution was slowly added to a mixture of HgO (263 mg, 1.20 mmol) and $HgBr_2$ (265 mg, 0.73 mmol) in refluxing benzene 5.00 mL. Immediately a benzene solution containing ribofuranosyl bromide (**39**) was added dropwise to the refluxing mixture and heating and stirring were continued for 12 h. After cooling the reaction mixture was filtered through cellite, the organic filtrate was washed twice with sat. $NaHCO_3$ solution and H_2O. The organic layer was dried over $MgSO_4$, concentrated under vacuum and the residue was purified by column chromatography (50% EtOAc in hexane) to afford **40** or **41** or **42**.

(2*R*,3*R*,4*R*,5*R*)-2-(Benzoyloxymethyl)-5-(2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (40): Colored Oil; Yield = 204 mg, 50.0%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 8.14 (2H, dd, J=8.2, 0.9 Hz), 7.94 (4H, m), 7.59 (1H, m), 7.51 (4H, m), 7.35 (4H, m), 6.13 (1H, d, J=7.1 Hz), 5.79 (1H, dd, J=6.0, 3.3 Hz), 5.65 (1H, m), 5.58 (2H, m), 4.93 (1H, brs), 4.80 (1H, m), 4.57 (2H, m), 3.86 (1H, d, J=15.9 Hz), 3.74 (2H, m), 3.57 (1H, d, J=18.8 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 166.0, 165.4, 165.3, 165.2, 133.4, 133.3, 133.2, 133.0, 129.7, 129.6, 129.5, 128.9, 128.8, 128.6, 128.3, 128.2, 126.9, 125.5, 83.3, 78.7, 71.5, 70.8, 64.3, 60.3, 43.0, 41.2, 20.9, 14.1

(2*R*,3*R*,4*R*,5*R*)-2-(Benzoyloxymethyl)-5-((*S*)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (41): Colored Oil; Yield = 163 mg, 40.0%; mp: 88 °C; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 8.15 (2H, m), 7.96 (4H, m), 7.61 (2H, m), 7.53 (3H, m), 7.36 (4H, m), 6.16 (1H, d, J=7.3 Hz), 5.78 (1H, dd, J=6.1, 3.4 Hz), 5.64 (1H, dd, J=7.1, 6.4 Hz), 5.48 (2H, m), 4.81 (1H, dd, J=3.9 Hz), 4.57 (2H, m), 4.28 (1H, s), 3.86 (1H, m), 3.69 (1H, m), 1.22 (3H, d, J=6.8 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 166.1, 165.5, 165.3, 164.4, 133.5, 133.4, 133.3, 132.8, 129.8, 129.8, 129.7, 129.6, 129.0, 128.9, 128.6, 128.4, 128.3, 124.7, 88.2, 78.9, 71.5, 70.9, 64.3, 48.9, 41.0, 22.5; LRMS (ESI) m/z 571 $[M + H]^+$.

(2*R*,3*R*,4*R*,5*R*)-2-(Benzoyloxymethyl)-5-((*R*)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (42): Colored Oil; Yield = 175 mg, 43.0%; ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si) δ 8.16 (2H, m), 7.94 (4H, m), 7.61 (2H, m), 7.53 (3H, m), 7.36 (4H, m), 6.19

(1H, d, *J*=8.1 Hz), 6.05 (1H, d, J=7.3 Hz), 5.79 (1H, m), 5.63 (1H, m), 5.52 (2H, s), 4.80 (1H, dd, *J*=4.6 Hz), 4.57 (3H, m), 3.86 (1H, m), 3.67 (1H, dd, *J*=16.4, 4.2 Hz), 1.14 (3H, d, *J*=6.8 Hz); ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si) δ 166.0, 165.4, 165.2, 164.1, 133.4, 133.3, 132.6, 129.8, 129.7, 129.6, 129.5, 128.9, 128.8, 128.6, 128.4, 128.3, 124.2, 87.6, 79.0, 71.6, 70.7, 64.4, 49.9, 40.5, 22.7, 14.1; LRMS (FAB) m/z 571 $[M + H]^+$.

General procedure for the synthesis of 1, 2 and 3: The compound **40** or **41** or **42** (95.0 mg, 0.16 mmol) was dissolved in 20.0 mL of sat. methanolic ammonia and stirred at room temperature for 30 h, then remove of the solvent under vaccum gave a white foam. The residue was purified by column chromatography (12% MeOH in CH_2Cl_3) to afford **1** or **2** or **3**.

1-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one *(*1): Colored Oil*;* Yield = 41.7 mg, 97.0%; ^{1}H NMR (500 MHz, CD_3OD) δ 5.89 (2H, m), 5.53 (1H, m), 4.04 (2H, m), 3.88 (4H, m), 3.77 (1H, m), 3.72 (1H, m), 3.68 (2H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 167.6, 128.9, 127.9, 92.7, 95.0, 73.1, 71.8, 63.5, 43.4, 42.8

(*S*)-1-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (2): Colored Oil*;* Yield = 40.9 mg, 95.0%; ^{1}H NMR (500 MHz, CD_3OD) δ 5.83 (1H, m), 5.66 (1H, m), 5.52 (1H, d, *J*=5.6 Hz), 4.13 (1H, m), 4.02 (3H, m), 3.83 (2H, m), 3.74 (2H, dd, *J*=4.6, 3.2 Hz), 3.66 (1H, dd, *J*=5.4 Hz), 1.30 (3H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 166.7, 134.6, 126.5, 92.7, 85.0, 73.1, 71.9, 63.4, 50.3, 42.6, 22.8; LRMS (FAB) m/z 259 $[M + H]^+$; HRMS (FAB) m/z calcd for $C_{11}H_{19}N_2O_5$ $[M+H]^+$ 259.1216, found 259.1294.

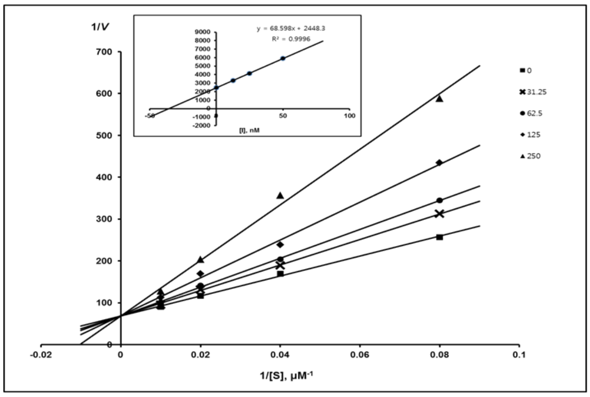
(*R*)-1-((2*R*,3*R*,4*S*,5*R*)-3,4-Bihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (3): Colored Oil*;* Yield = 43.0 mg, 99.9%; ^{1}H NMR (500 MHz, CD_3OD) δ 5.86 (1H, m), 5.73 (1H, m), 5.55 (1H, d, *J*=5.6 Hz), 4.01 (3H, m), 3.87 (2H, m), 3.77 (2H, m), 3.68 (1H, dd, *J*=12.0, 4.2 Hz), 1.35 (3H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 167.1, 134.2, 128.1, 92.2, 85.0, 73.3, 71.8, 63.5, 51.2, 42.3, 23.1; LRMS (FAB) m/z 259 $[M + H]^+$; HRMS (FAB) m/z calcd for $C_{11}H_{19}N_2O_5$ $[M+H]^+$ 259.1216, found 259.1294.

Ⅲ. Enzyme assay

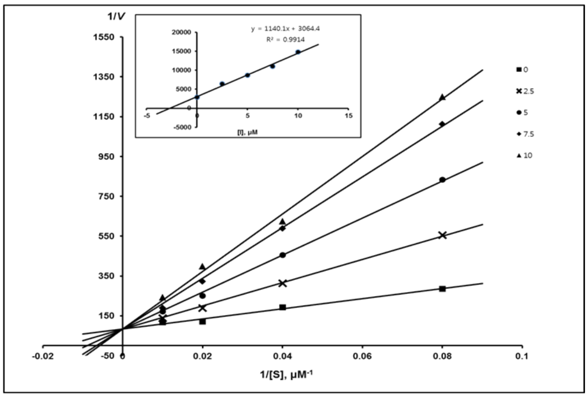
Cloning and purification of human CDA: Human CDA gene **(**IMAGE consortium) was amplified by PCR with synthetic primer set (5′ primer: gga att cca tat gaa gcc tga gtg tgt cca gca gct (NdeI site marked in bold type letter), 3′ primer: tgg tgc tcg agt tat ttt tgt aaa tct ata ata tcg (XhoI site marked in bold type letter)). Human CDA gene encoding amino acid sequence 11-146 was cloned into *pET28a* vector (Novagen) with NdeI/XhoI cleavage site. The resulting *N*-terminal His-tagged hCDA construct was transformed into *E. coli* Rosetta (DE3) (Novagen). Cells were grown at 37 °C in LB medium until the optical density at A_{600} reached to 0.6-0.8 and hCDA protein was expressed by adding 1 mM IPTG at 18 °C for 18 h. Cells were harvested, washed with buffer A (50 mM Tris pH 7.5, 250 mM NaCl, 5% glycerol, 1 mM β-mercaptoethanol) and lysed using ultrasonication. After centrifugation (29,820*g* for 30 min), the supernatant was incubated with a cobalt affinity resin (TALON®, Clontech) on a rocker for 1 h at 4 °C and washed with buffer A containing 10 mM imidazole. The proteins were eluted from the metal affinity resin by buffer A supplemented with 100 mM imidazole, concentrated to 2 mg/ml, and stored -80 °C.

Inhibitory assay of compounds 1, 2 and 3 against cytidine deamination by human CDA: Cytidine deaminase activity was monitored by the loss of absorbance of cytidine at 282 nm ($\Delta\varepsilon$ = -3600) during the deamination reaction. hCDA (12.5 nM of final concentrations) was added to cytidine (0, 12.5, 25, 50, 100 and 200 μM of the final concentration) in pH 7.4 PBS buffer and the absorbance change was monitored at 282 nm on a DU 800 UV-VIS Spectrophotometer (Beckman Coulter). K_m value was calculated to be 26 μM using Hyper32 (version 1.0.0 http://homepage.ntlworld.com/john.easterby/hyper32.html). The synthetic inhibitors (**1** and **3**: 31.25, 62.5, 125, 250 nM of the final concentrations; **2**: 1.25, 2.5, 5, 10 μM of the final concentrations) were added to hCDA (12.5 nM of final concentration) in pH 7.4 PBS buffer. The enzyme reaction was started by addition of substrate solution (cytidine: 2.5, 25, 50, 100 μM of final concentrations). Each initial velocity was measured by monitoring disappearance of cytidine and analyzed by Lineweaver-Burk plot and secondary plot to determine inhibition constant (K_i) (Figure S1).

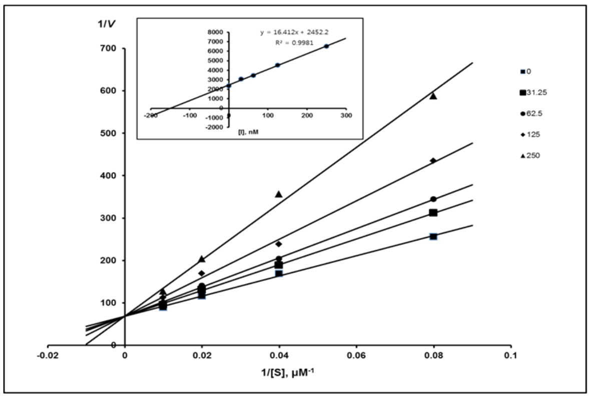
(a) Compound **1**



(b) Compound **2**



(c) Compound **3**

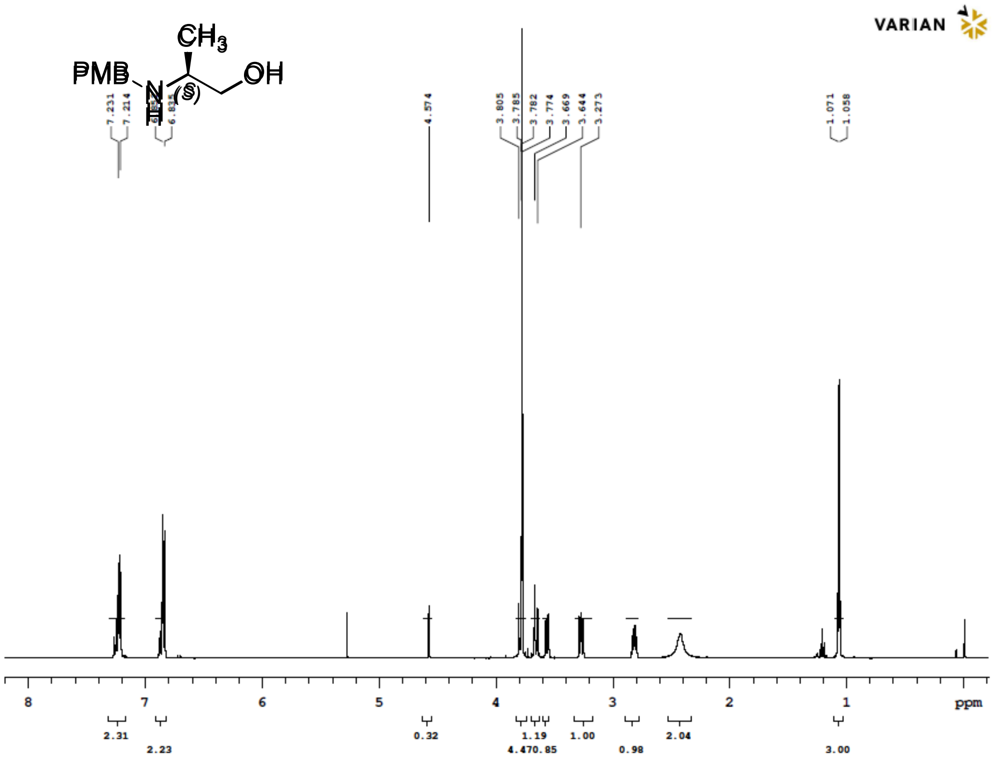


Inhibition constants (K_i)

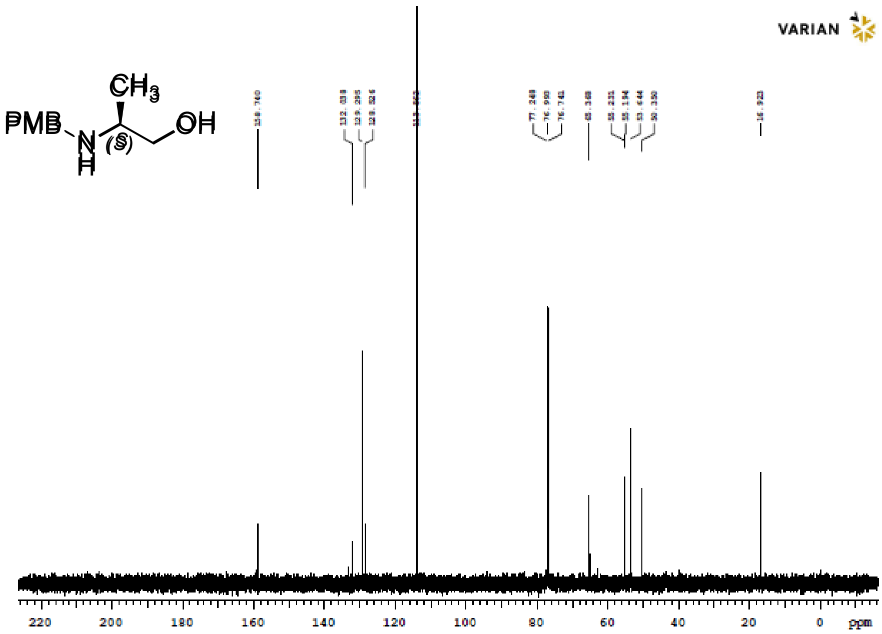
Compound	**1**	**2**	**3**
K_i	35.33 ± 0.49 nM	2.56 ± 0.18 μM	145.97 ± 4.87 nM

Figure S1. The initial velocities were analyzed by Lineweaver-Burk plot, and the resulting slopes of the grapes were plotted against the corresponding inhibitor concentrations (secondary plots), where x-intercept corresponds to - K_i. (a) Compound **1**; (b) Compound **2**; (c) Compound **3**

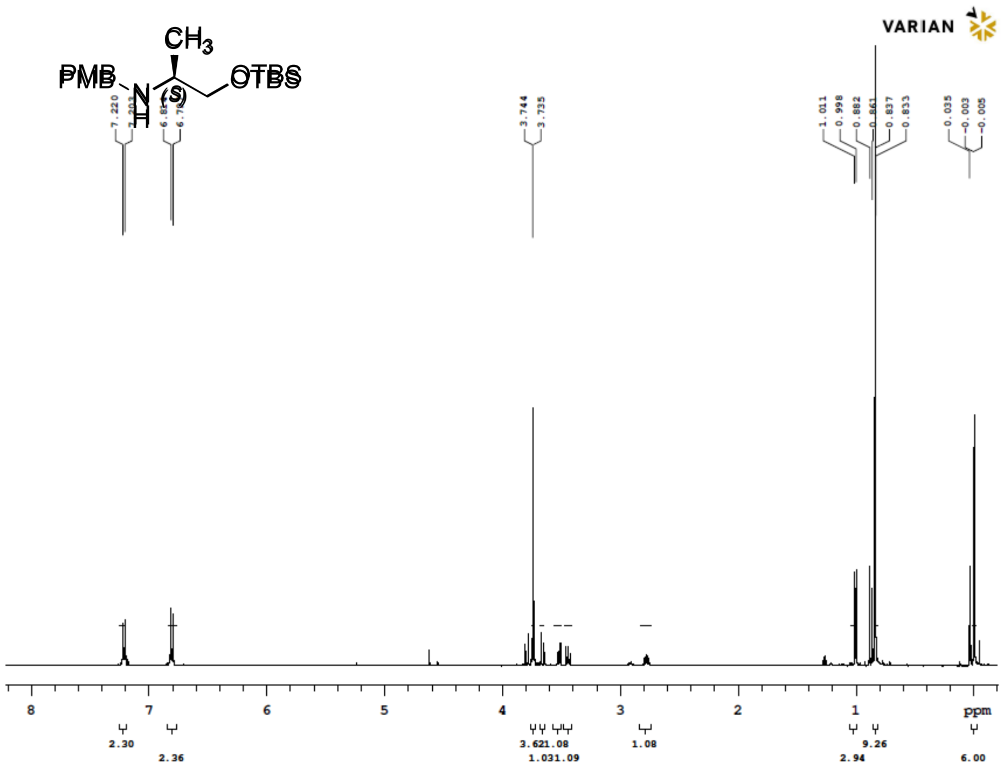
Ⅳ NMR spectra



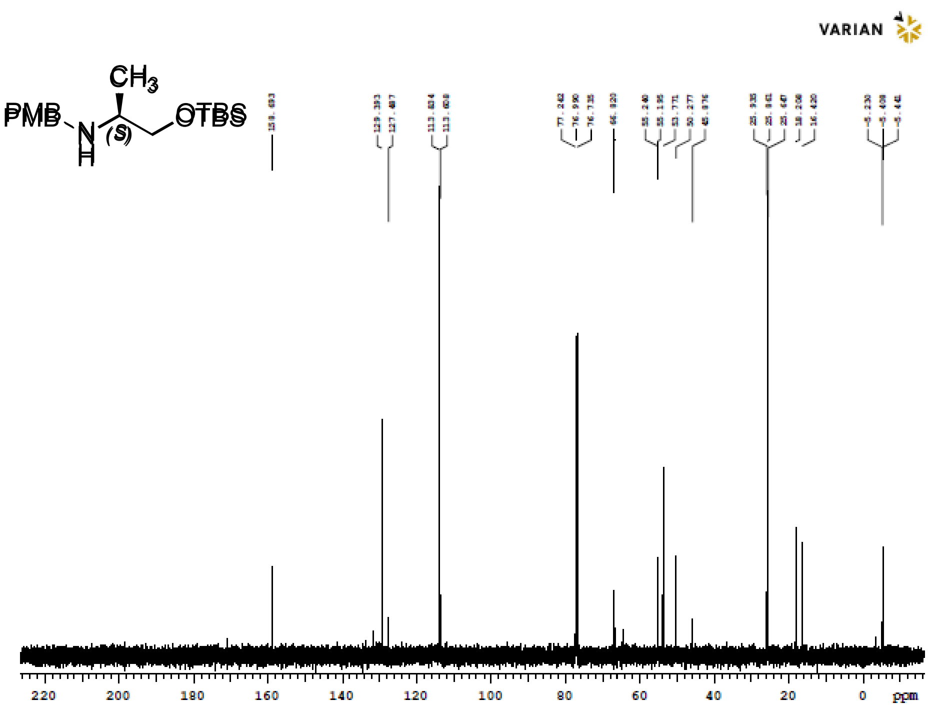
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-2-(4-methoxybenzylamino)propan-1-ol (5)



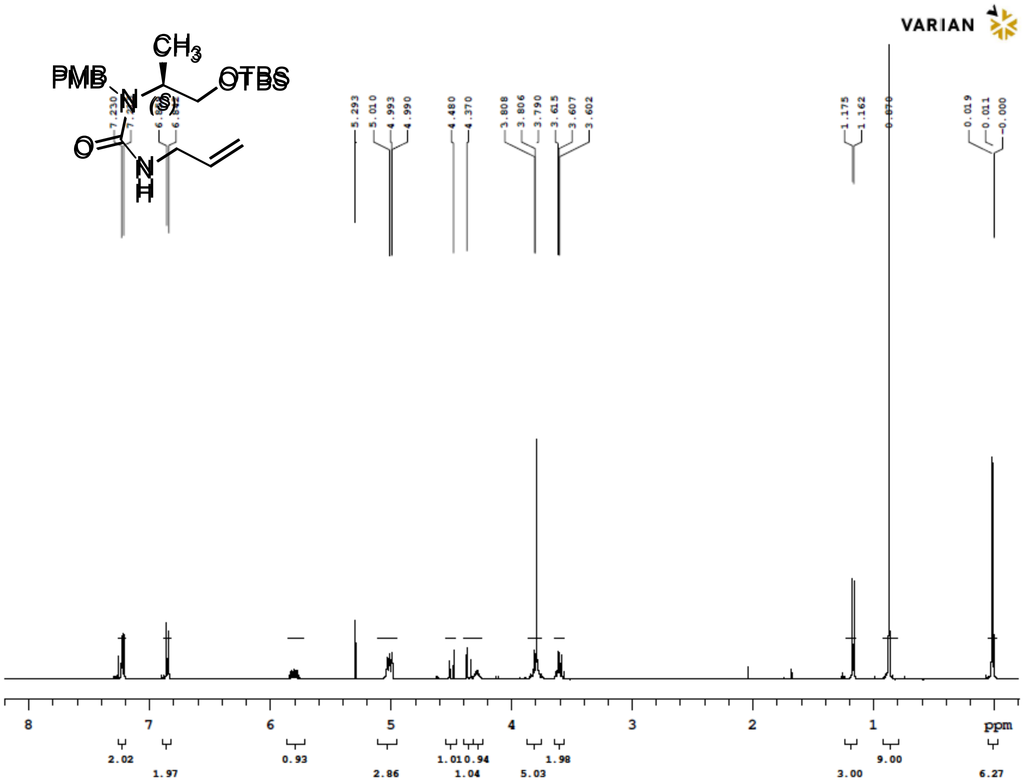
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-2-(4-methoxybenzylamino)propan-1-ol (5)



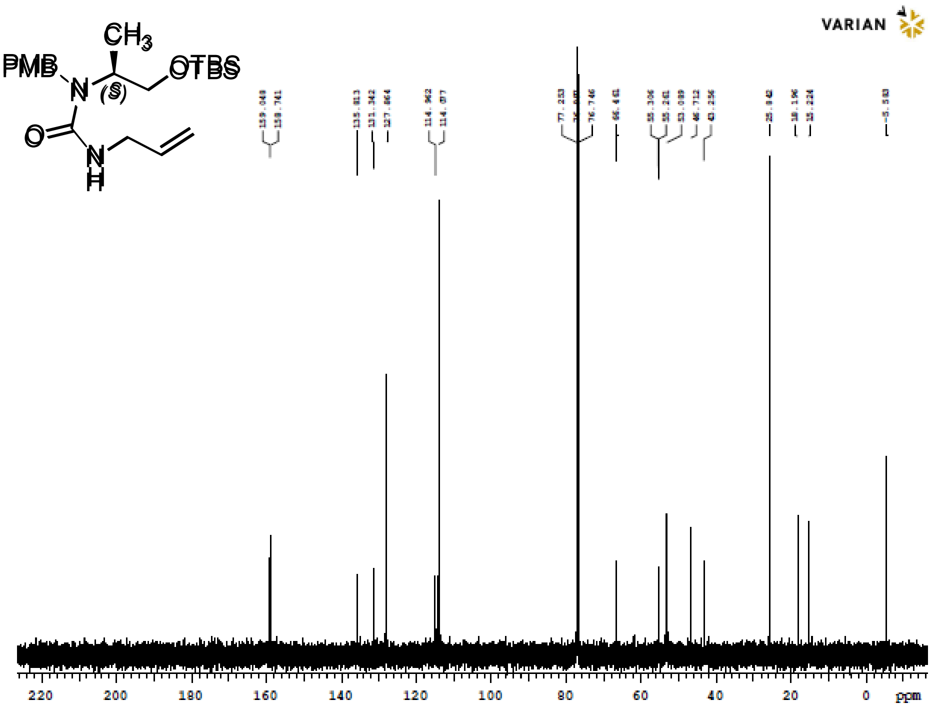
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-1-(tert-butyldimethylsilyloxy)-*N*-(4-methoxybenzyl)propan-2-amine (6)



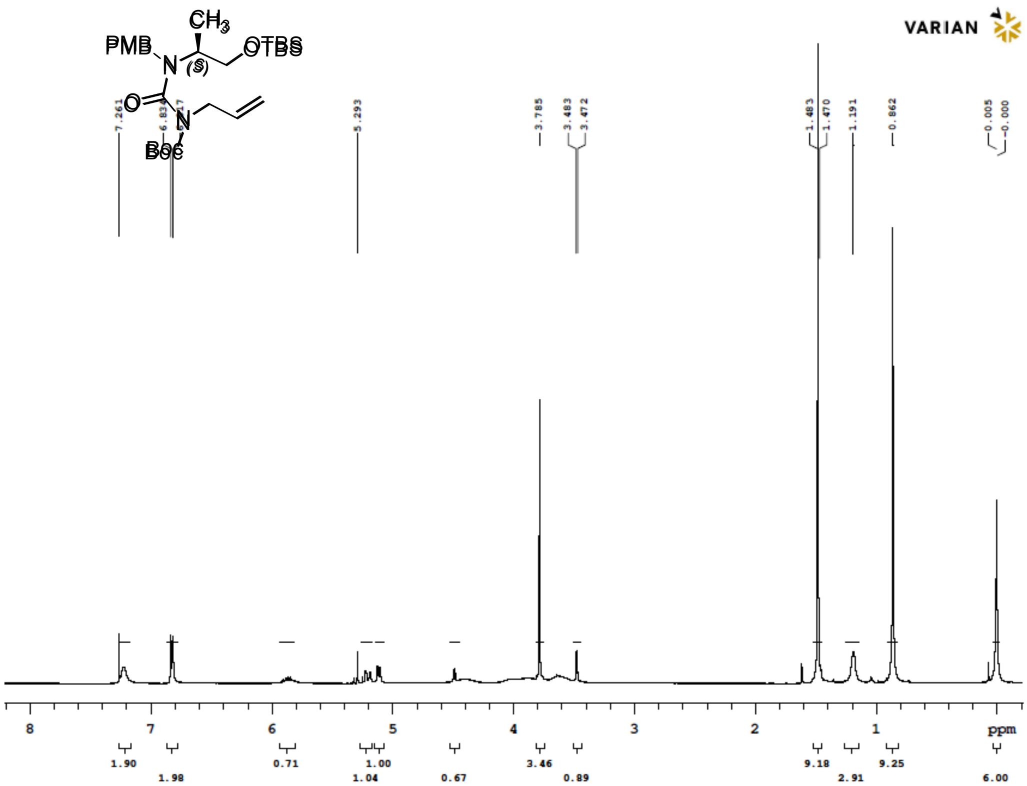
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-1-(tert-butyldimethylsilyloxy)-*N*-(4-methoxybenzyl)propan-2-amine (6)



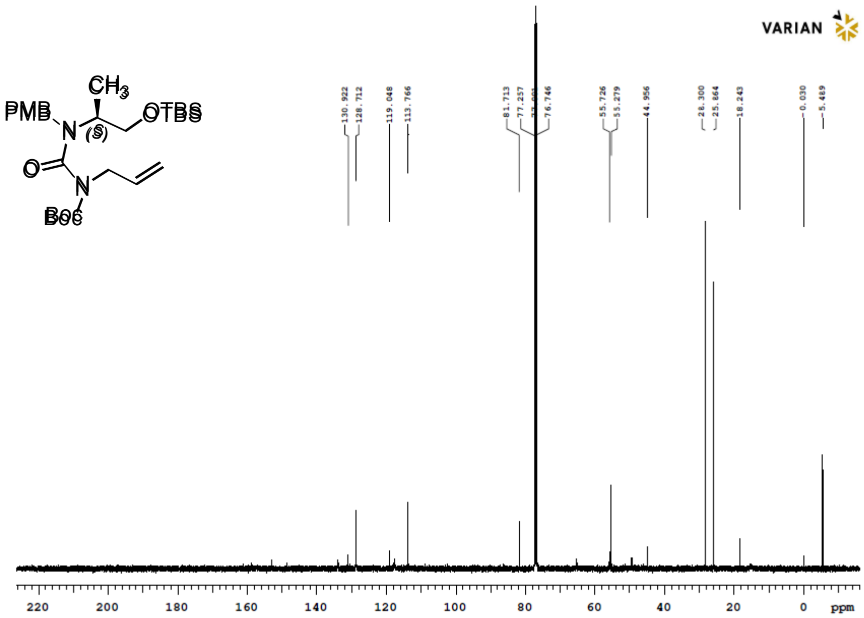
[1]H-NMR ($CDCl_3$, 500 MHz):
(*S*)-3-allyl-1-(1-(*tert*-butyldimethylsilyloxy)propan-2-yl)-1-(4-methoxybenzyl)urea (9)



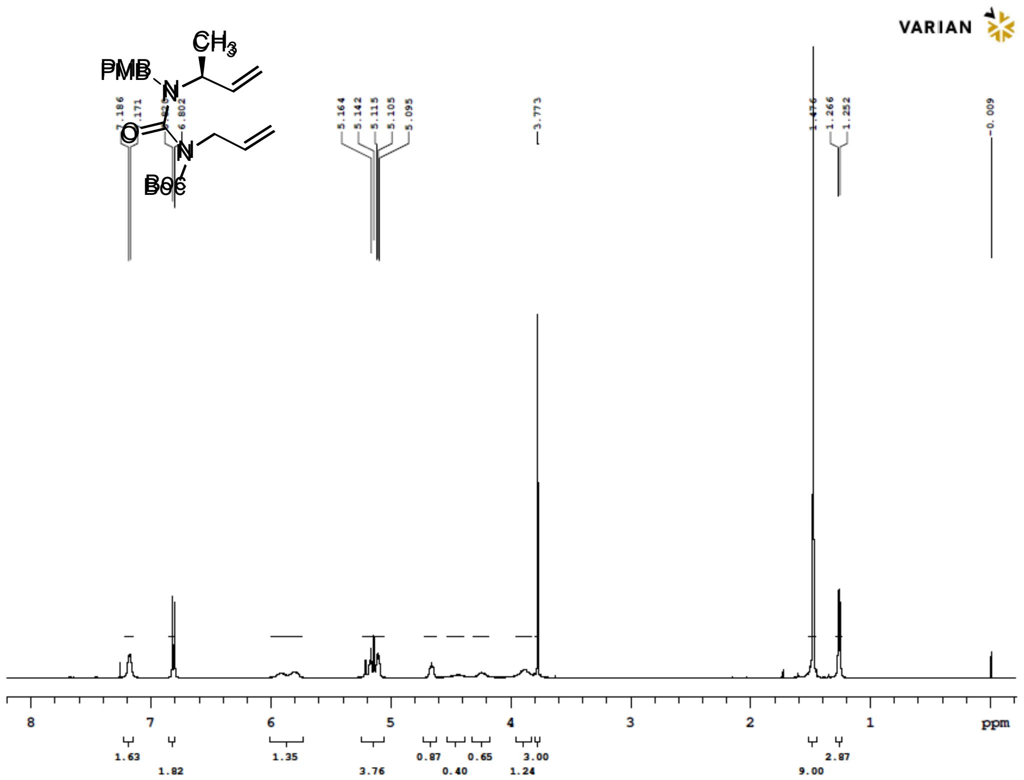
[13]C-NMR ($CDCl_3$, 125 MHz):
(*S*)-3-allyl-1-(1-(*tert*-butyldimethylsilyloxy)propan-2-yl)-1-(4-methoxybenzyl)urea (9)



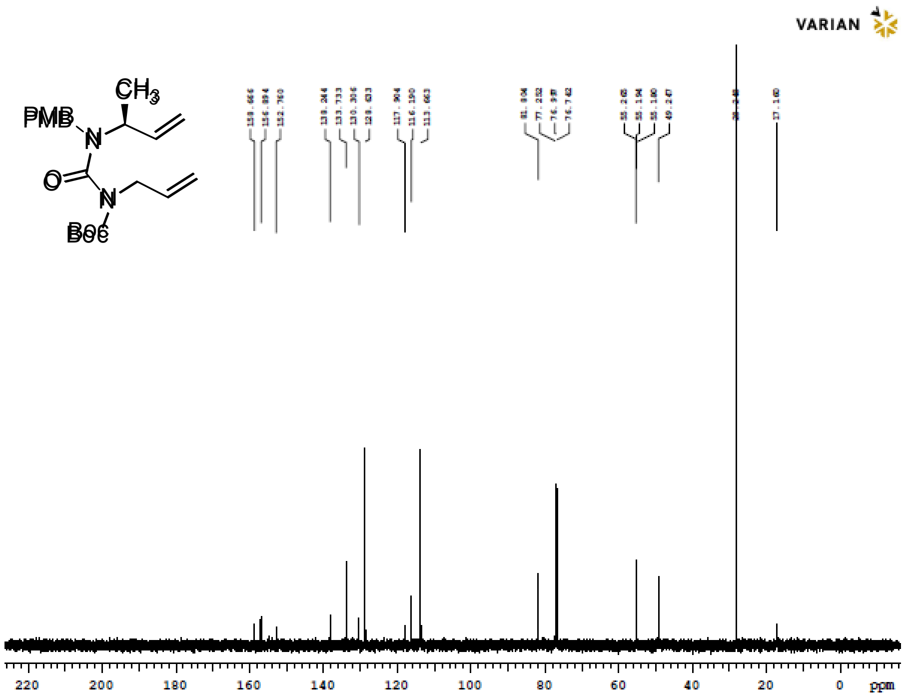
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-*tert*-butyl allyl((1-(*tert*-butyldimethylsilyloxy)propan-2-yl)(4-methoxybenzyl)carbamoyl)carbamate (13)



^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-*tert*-butyl allyl((1-(*tert*-butyldimethylsilyloxy)propan-2-yl)(4-methoxybenzyl)carbamoyl)carbamate (13)

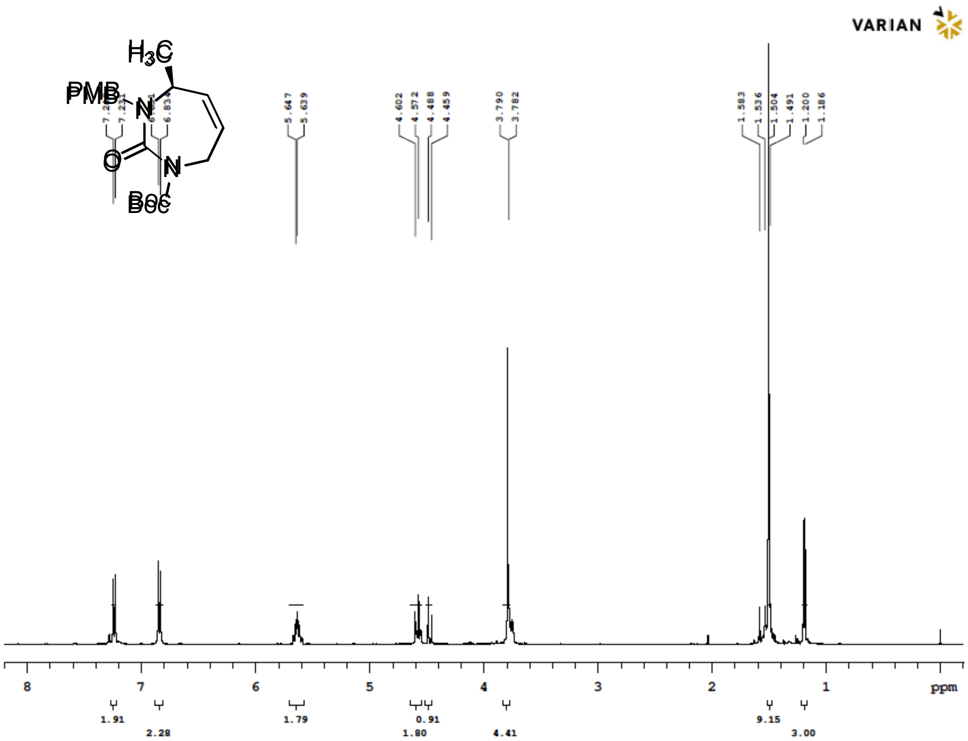


^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-*tert*-butyl allyl(but-3-en-2-yl(4-methoxybenzyl)carbamoyl)carbamate (11)

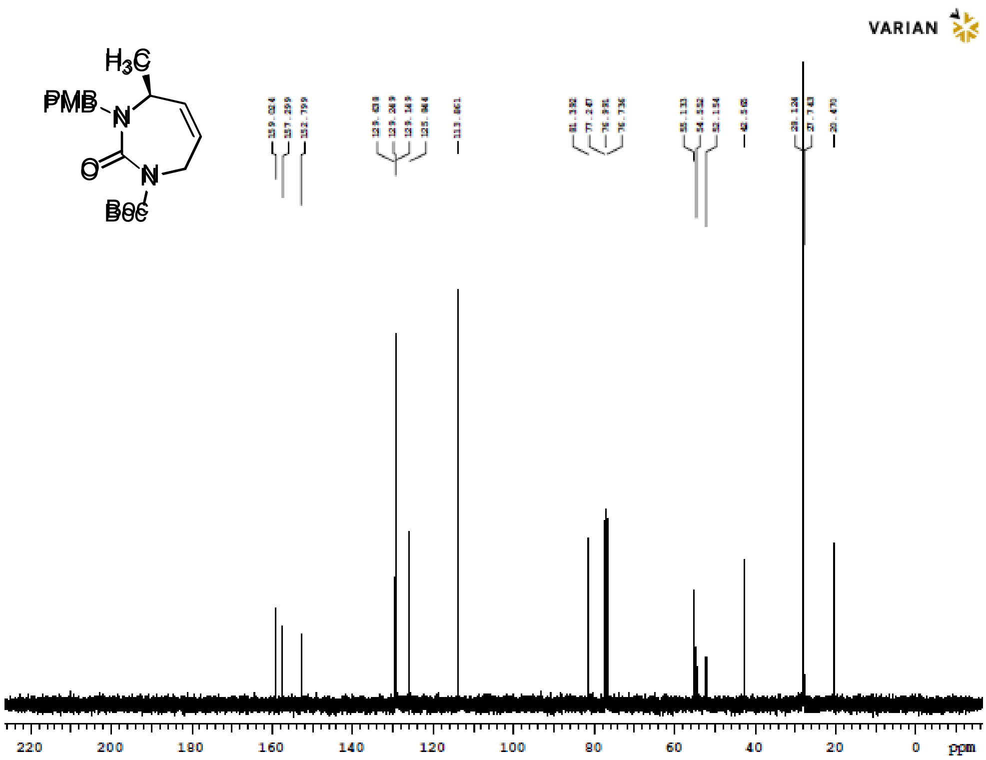


^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-*tert*-butyl allyl(but-3-en-2-yl(4-methoxybenzyl)carbamoyl)carbamate (11)

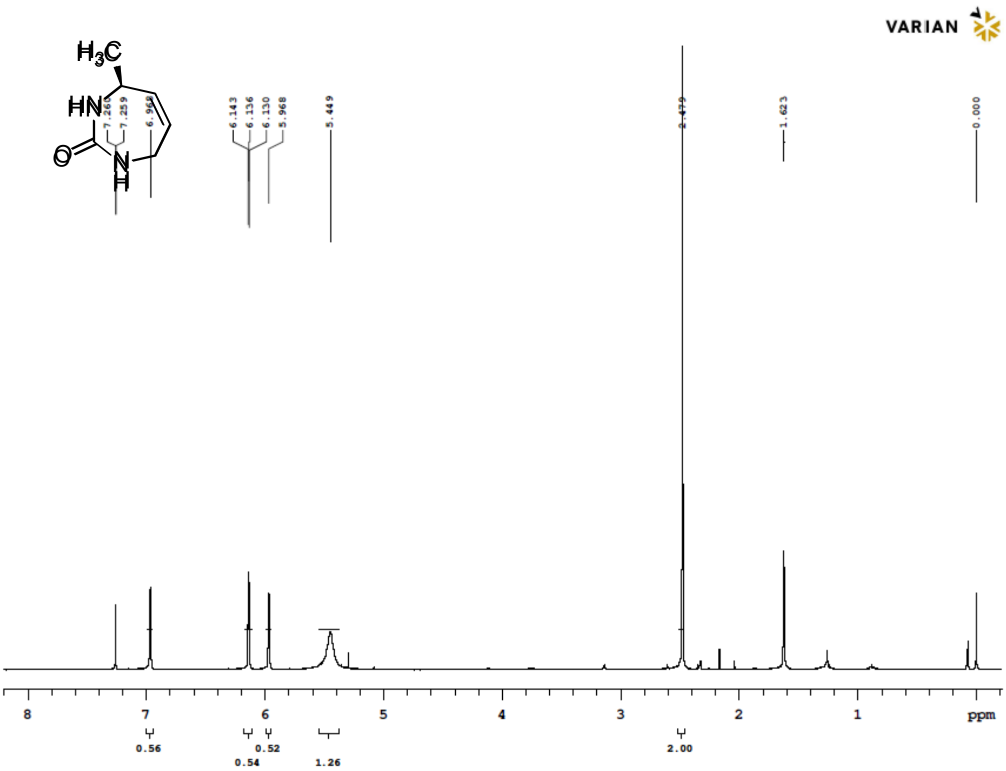
Electronic Supplementary Material (ESI) for Chemical Communications



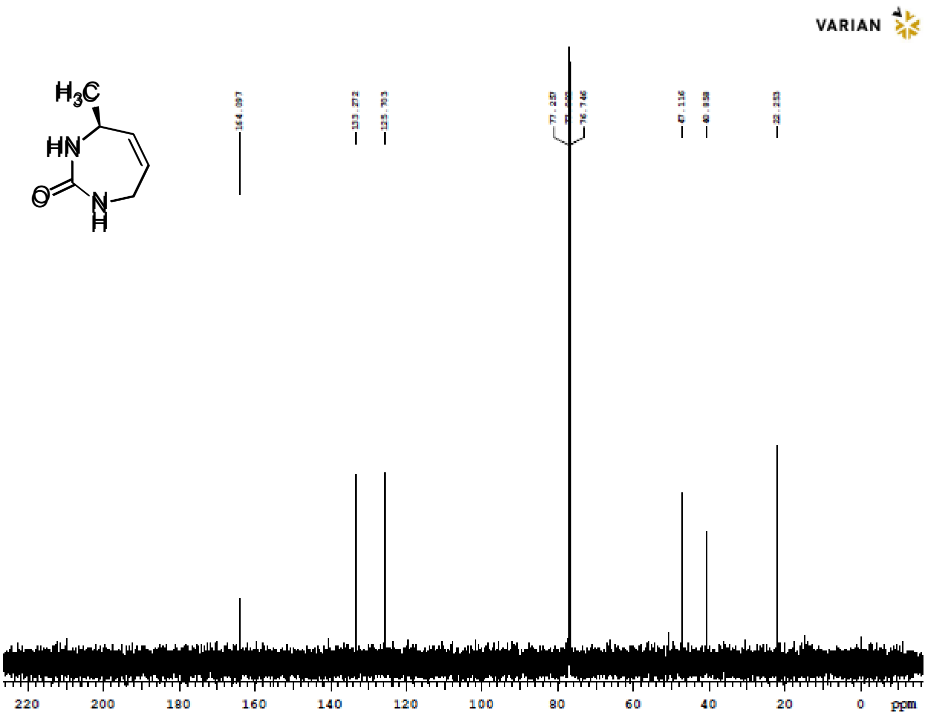
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-*tert*-butyl 3-(4-methoxybenzyl)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (12)



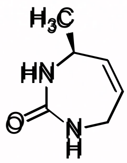
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-*tert*-butyl 3-(4-methoxybenzyl)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (12)

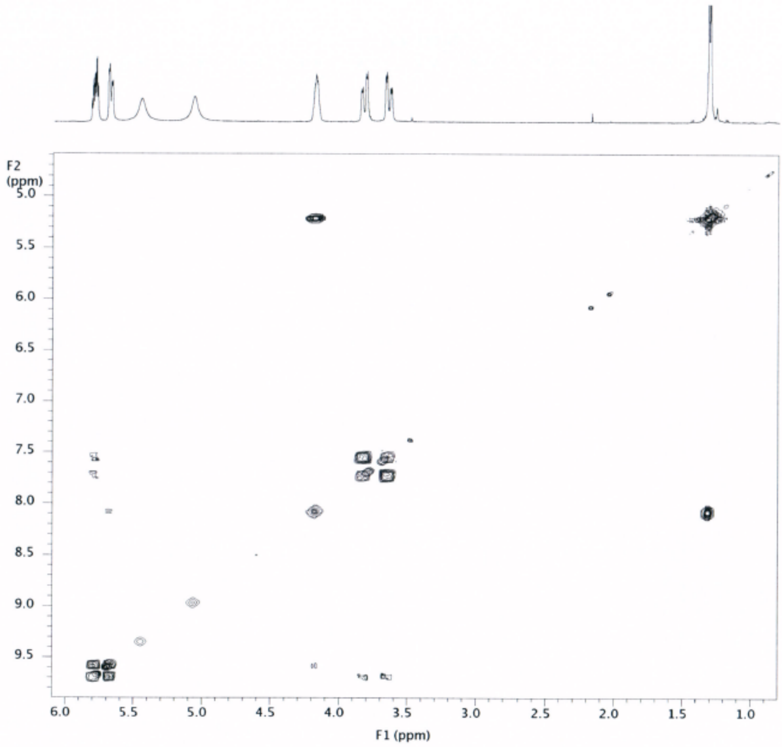


[1]H-NMR ($CDCl_3$, 500 MHz):
(*S*)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (33)

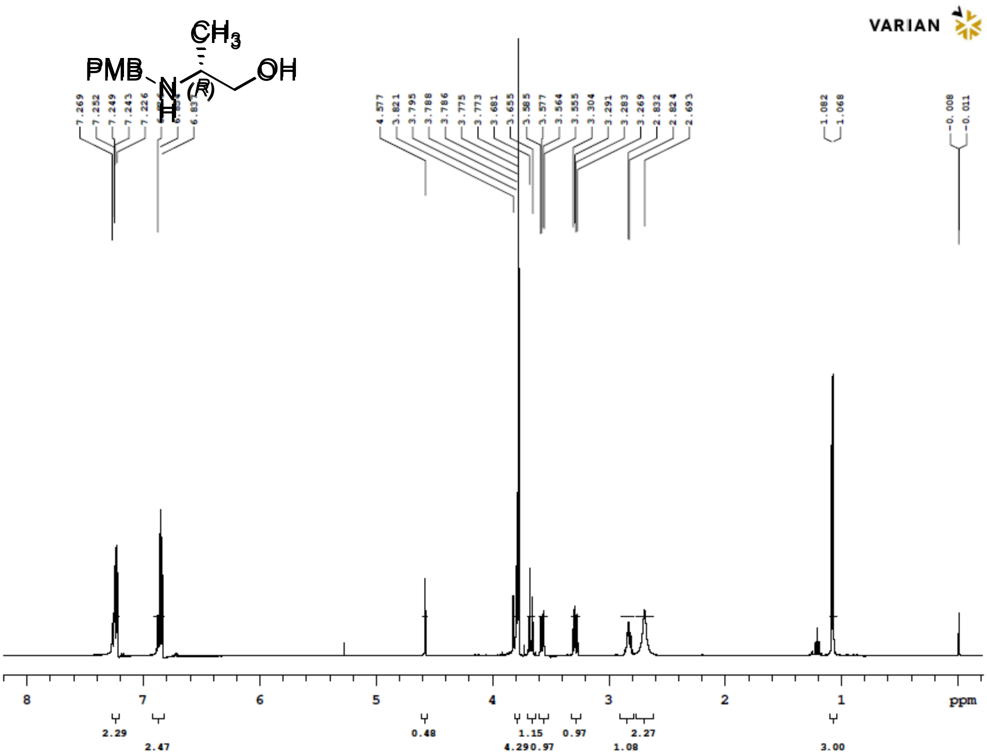


[13]C-NMR ($CDCl_3$, 125 MHz):
(*S*)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (33)



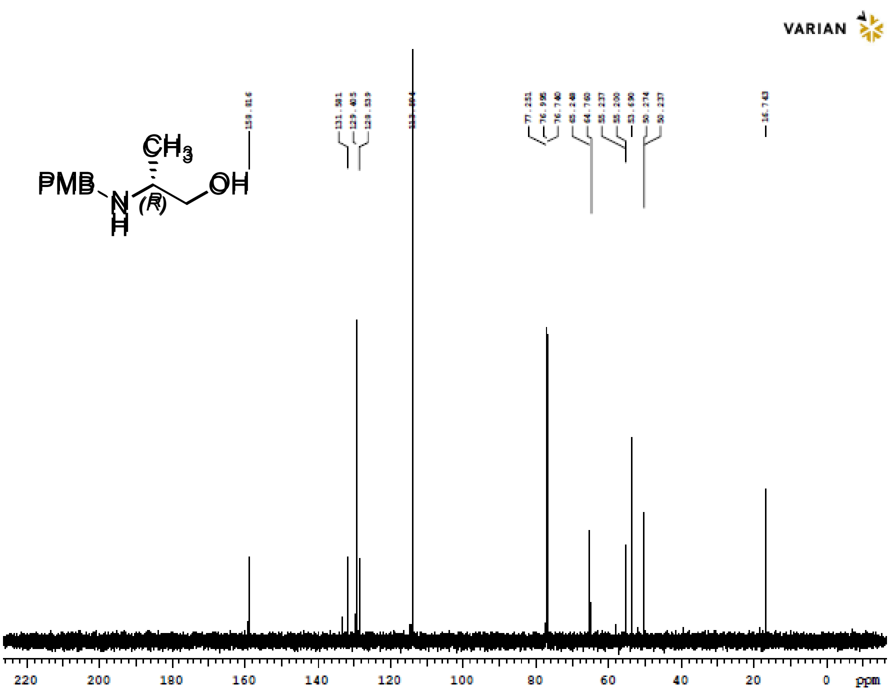


COSY-Spectrum ($CDCl_3$, 500 MHz):
(*S*)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (33)

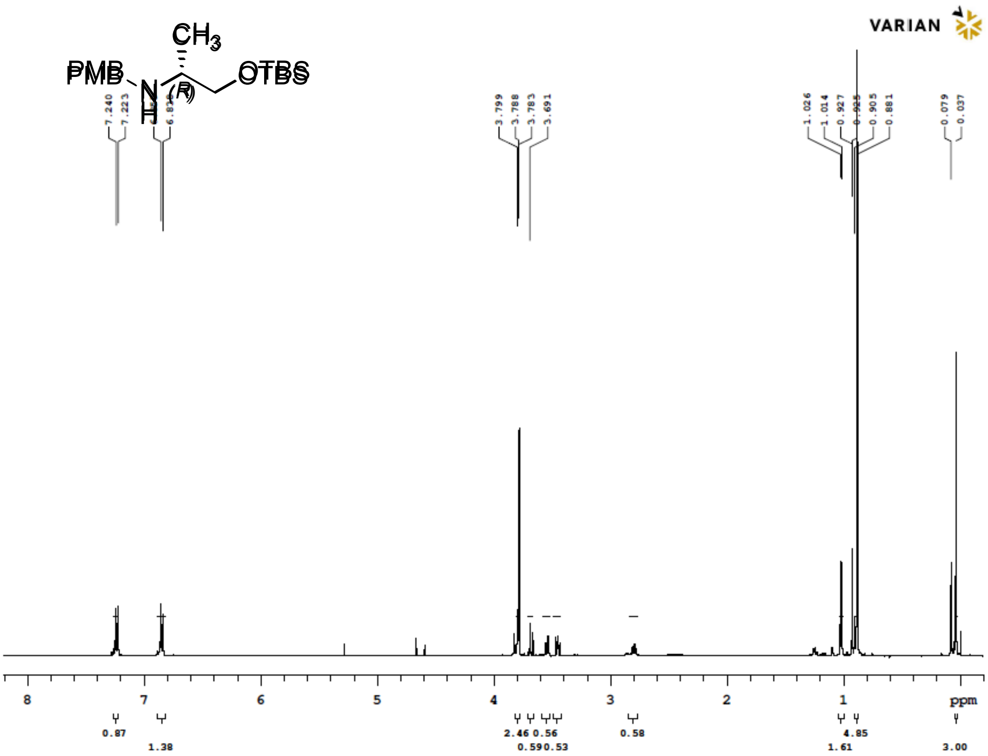


^{1}H-NMR ($CDCl_3$, 500 MHz):

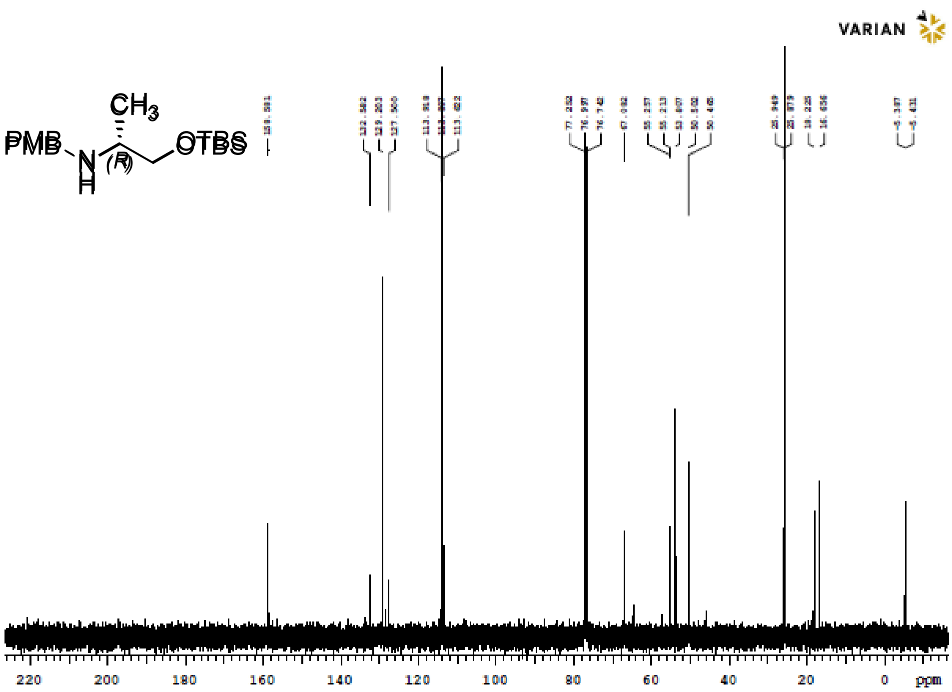
(*R*)-2-(4-methoxybenzylamino)propan-1-ol (44)



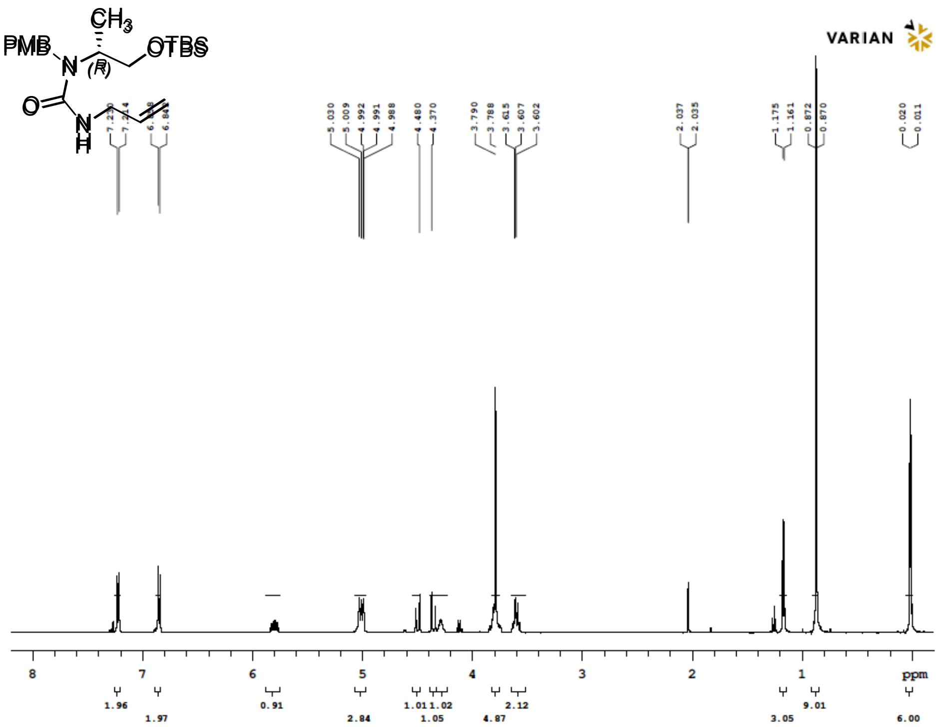
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-2-(4-methoxybenzylamino)propan-1-ol (44)



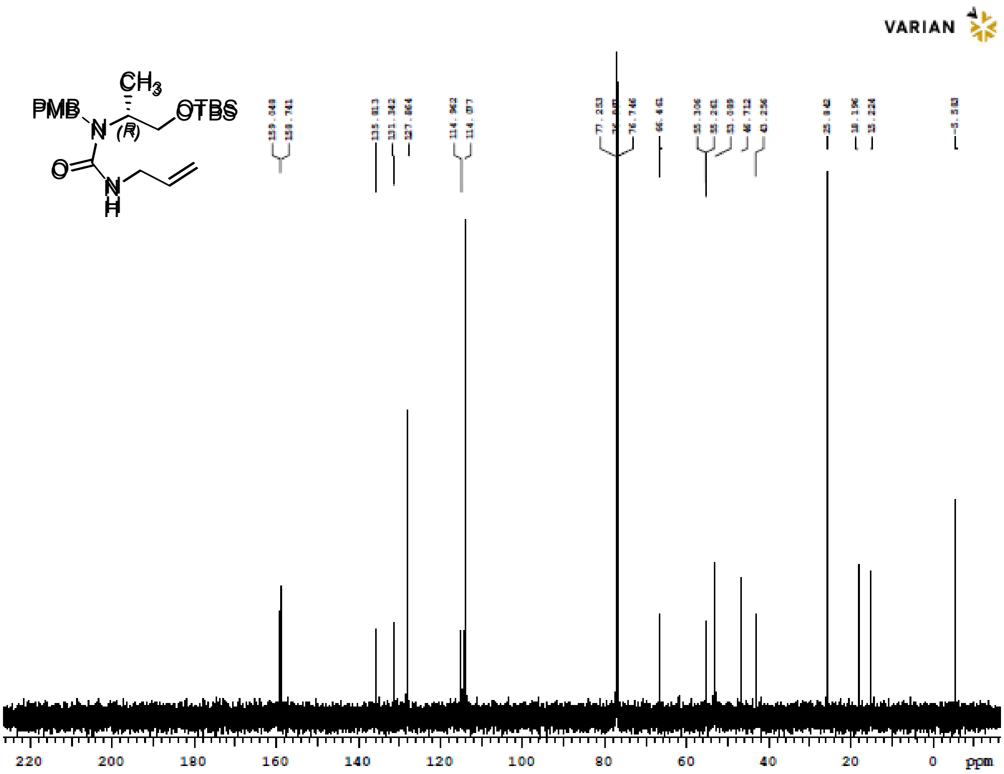
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*R*)-1-(*tert*-butyldimethylsilyloxy)-*N*-(4-methoxybenzyl)propan-2-amine (14)



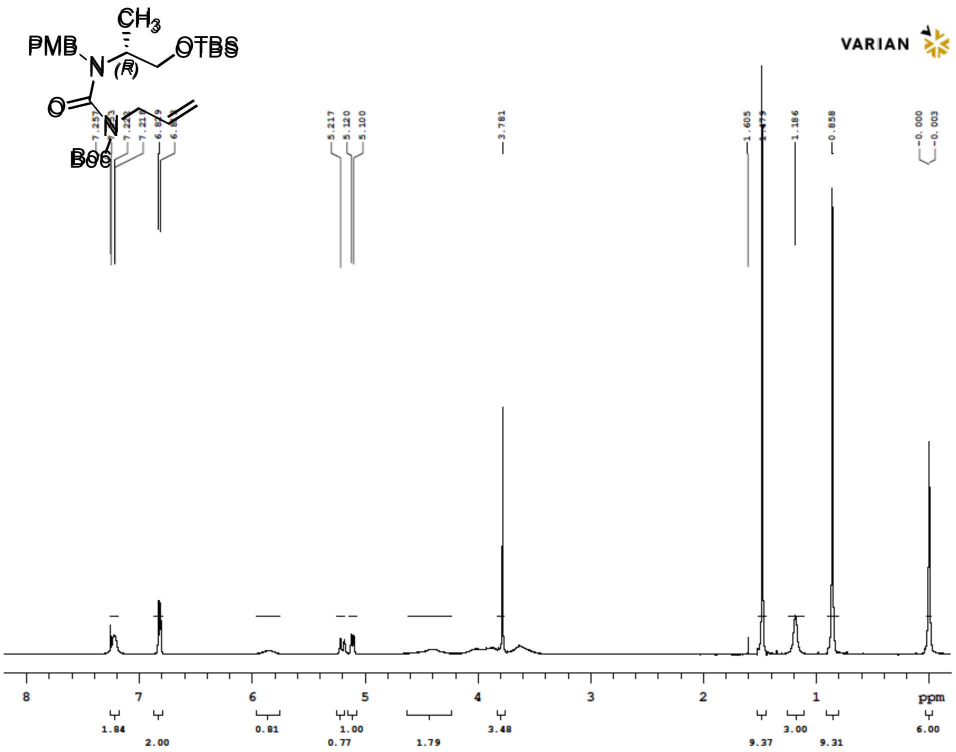
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-1-(*tert*-butyldimethylsilyloxy)-*N*-(4-methoxybenzyl)propan-2-amine (14)



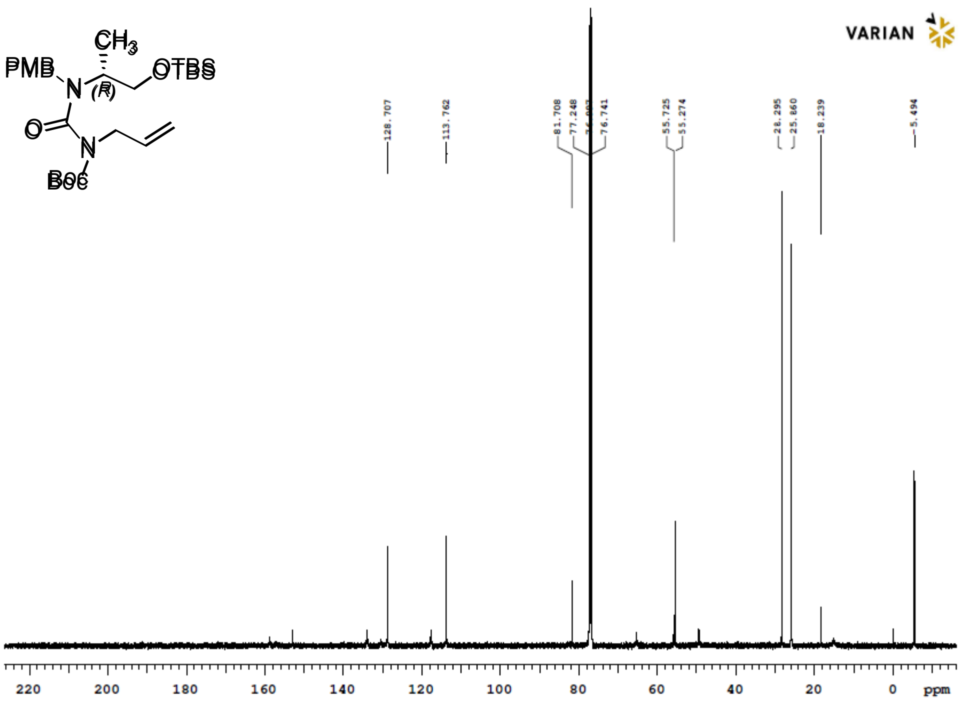
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*R*)-3-allyl-1-(1-(*tert*-butyldimethylsilyloxy)propan-2-yl)-1-(4-methoxybenzyl)urea (45)



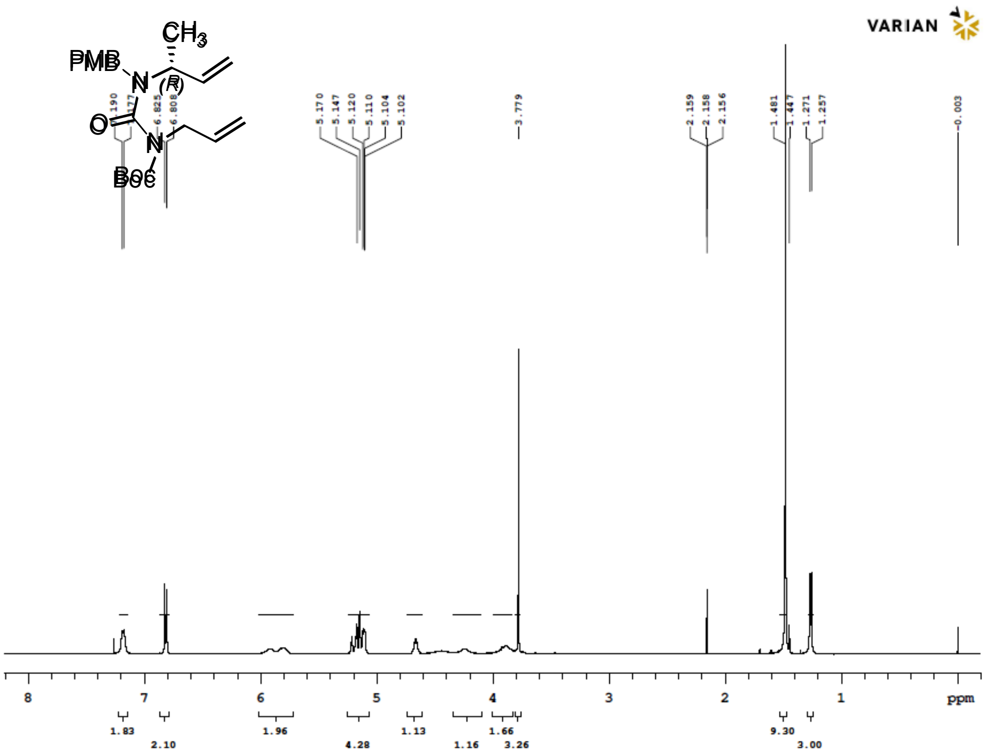
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-3-allyl-1-(1-(*tert*-butyldimethylsilyloxy)propan-2-yl)-1-(4-methoxybenzyl)urea (45)



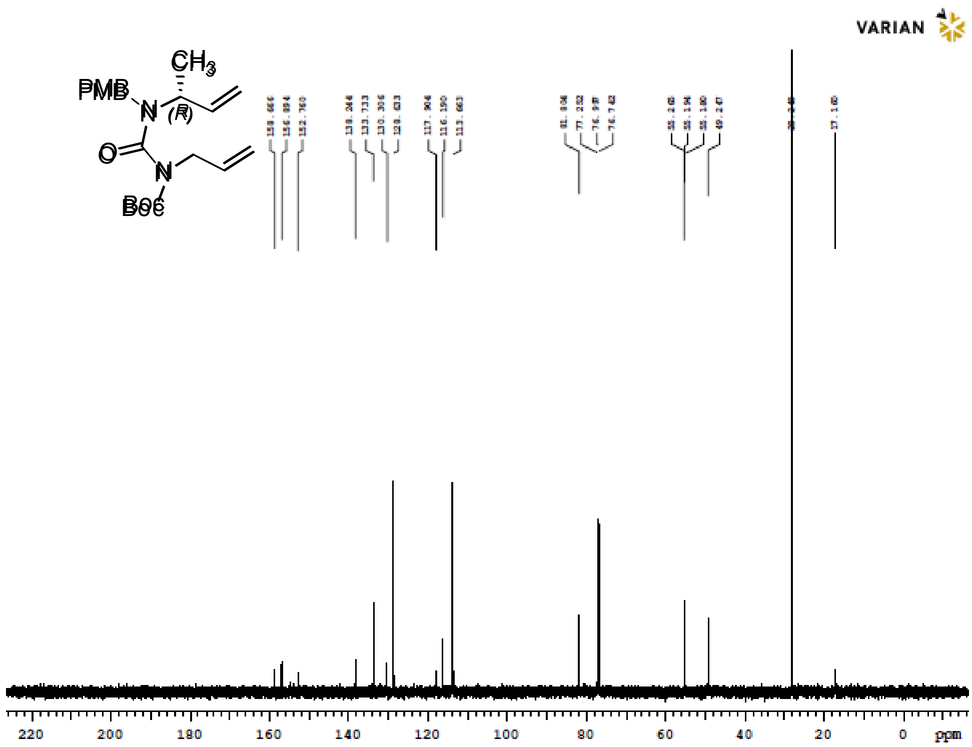
[1]H-NMR ($CDCl_3$, 500 MHz):
(*R*)-*tert*-butyl allyl((1-(*tert*-butyldimethylsilyloxy)propan-2-yl)(4-methoxybenzyl)carbamoyl)carbamate (15)



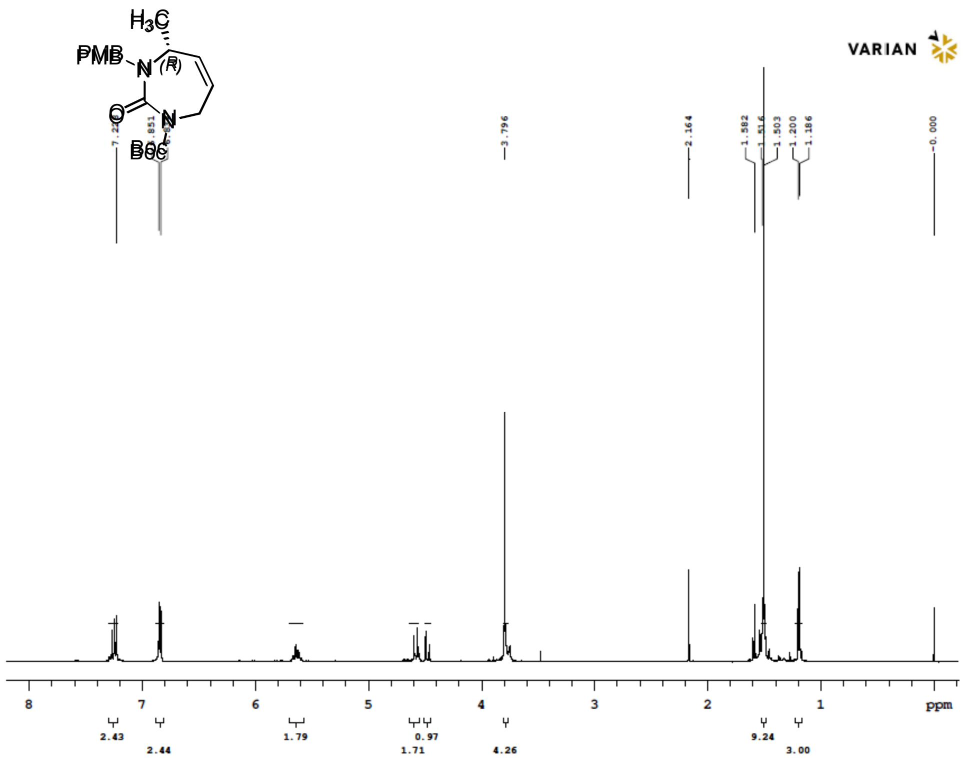
[13]C-NMR ($CDCl_3$, 125 MHz):
(*R*)-*tert*-butyl allyl((1-(*tert*-butyldimethylsilyloxy)propan-2-yl)(4-methoxybenzyl)carbamoyl)carbamate (15)



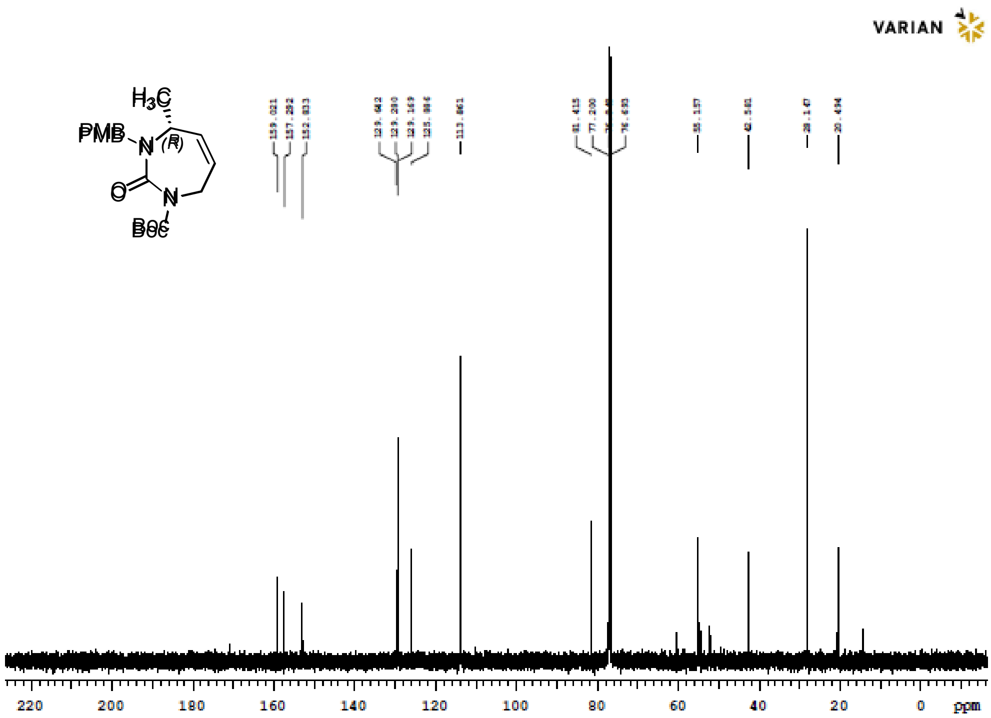
[1]H-NMR ($CDCl_3$, 500 MHz):
(*R*)-*tert*-butyl allyl(but-3-en-2-yl(4-methoxybenzyl)carbamoyl)carbamate (16)



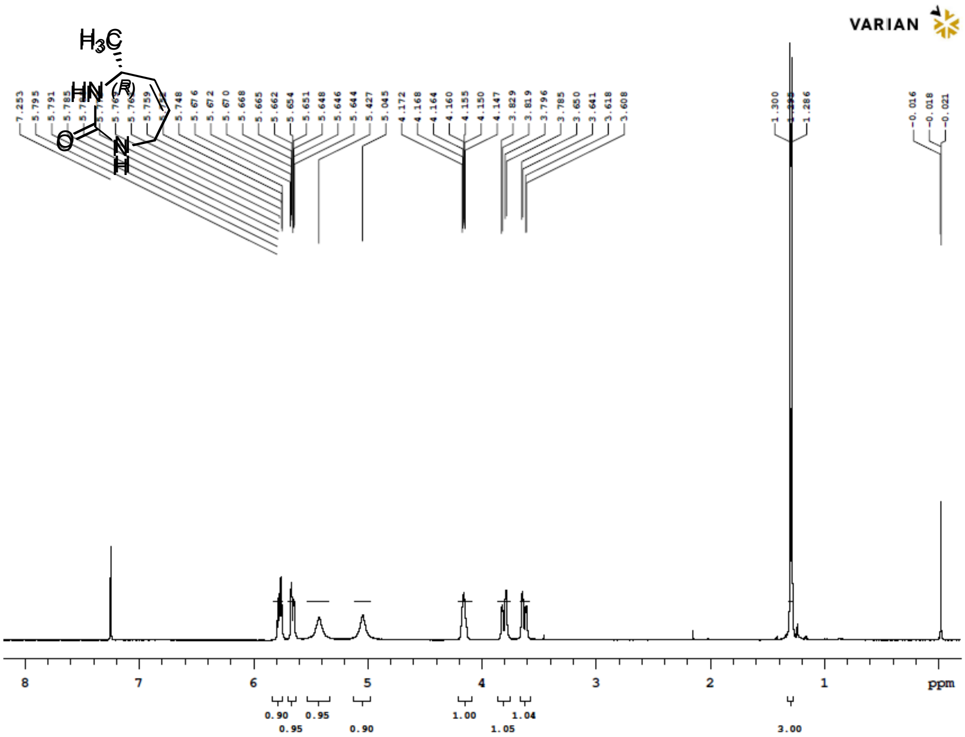
[13]C-NMR ($CDCl_3$, 125 MHz):
(*R*)-*tert*-butyl allyl(but-3-en-2-yl(4-methoxybenzyl)carbamoyl)carbamate (16)



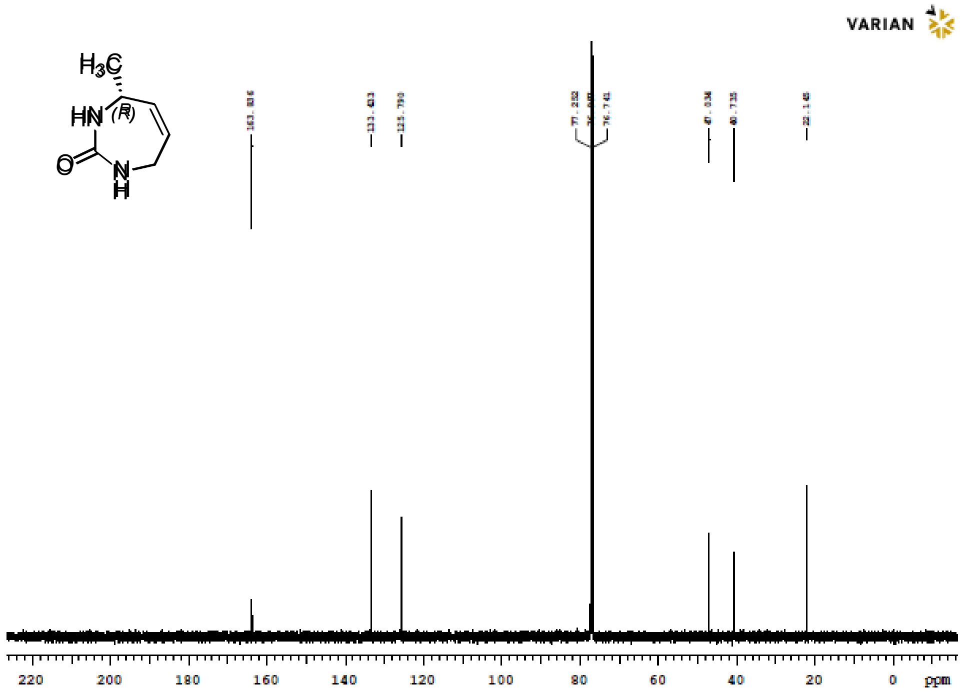
[1]H-NMR ($CDCl_3$, 500 MHz):
(*R*)-*tert*-butyl 3-(4-methoxybenzyl)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (28)



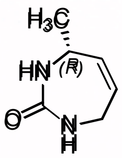
[13]C-NMR ($CDCl_3$, 125 MHz):
(*R*)-*tert*-butyl 3-(4-methoxybenzyl)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (28)

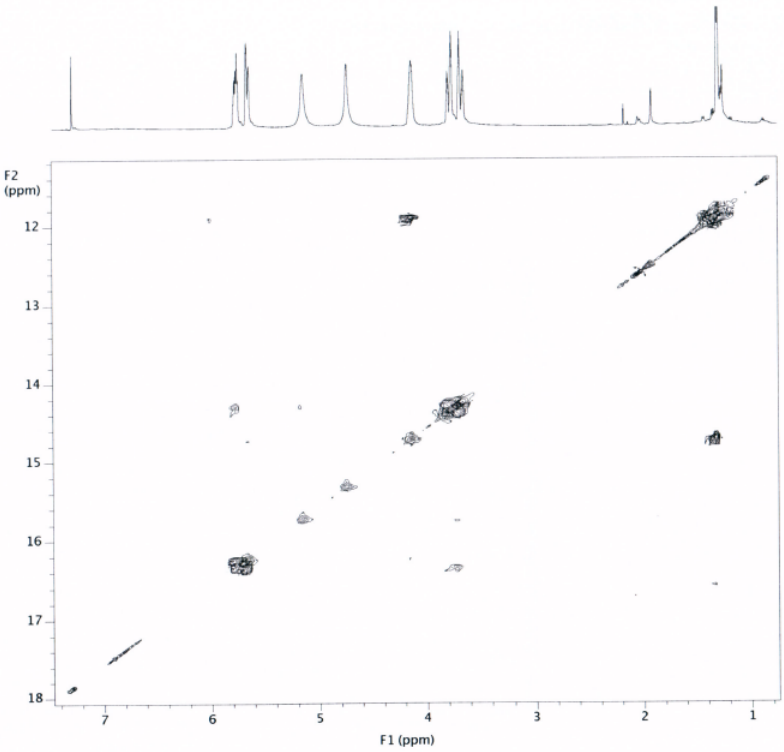


^{1}H-NMR ($CDCl_3$, 500 MHz):
(*R*)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (34)

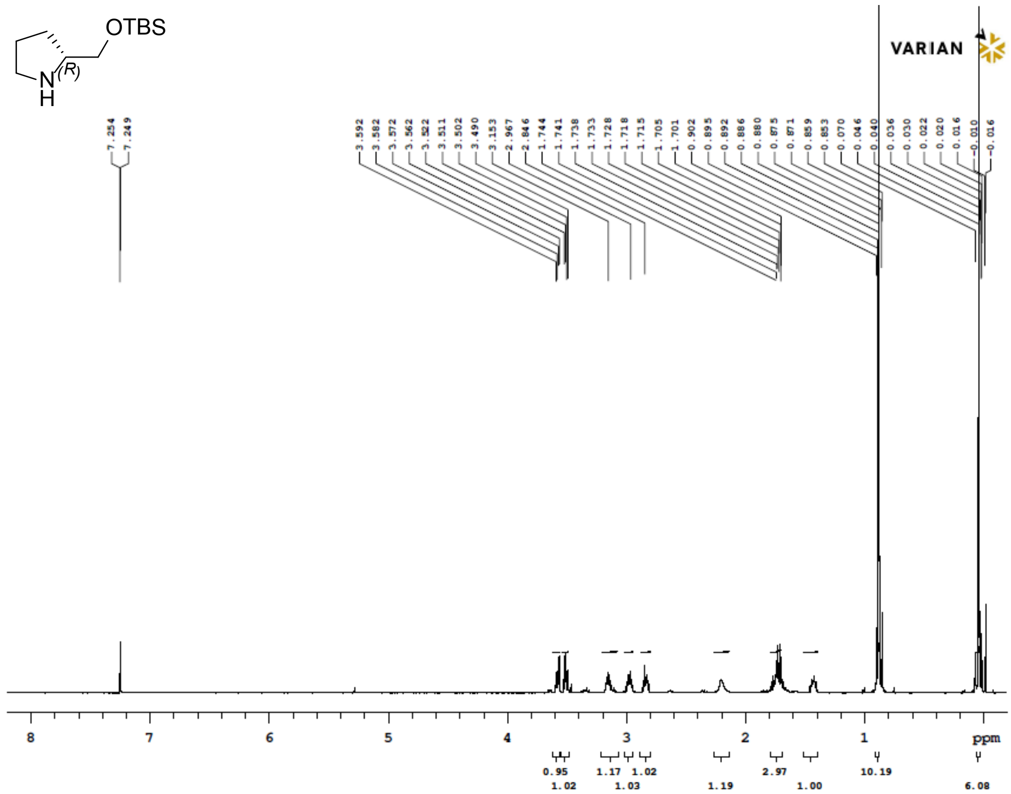


^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (34)

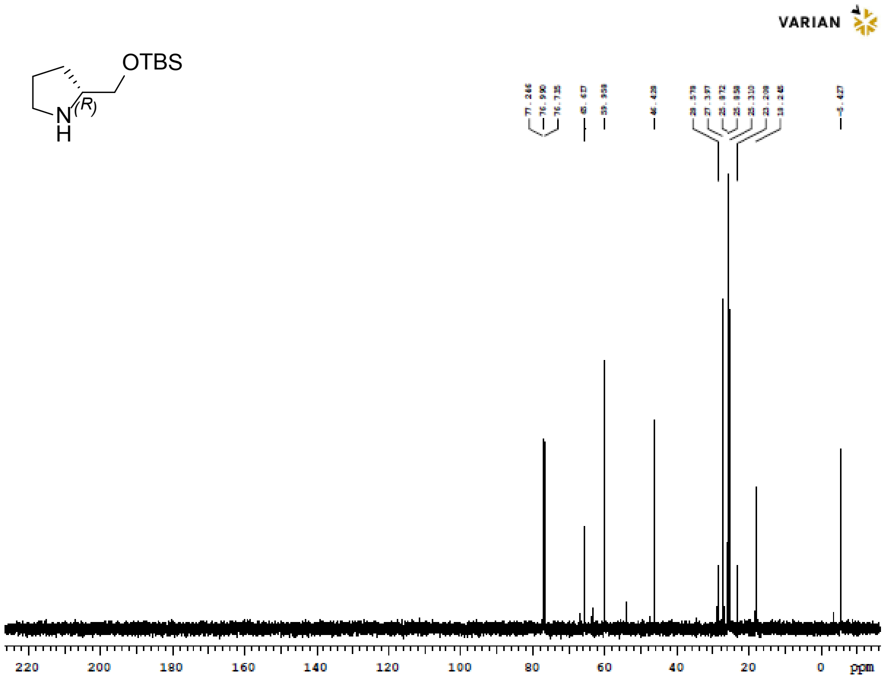




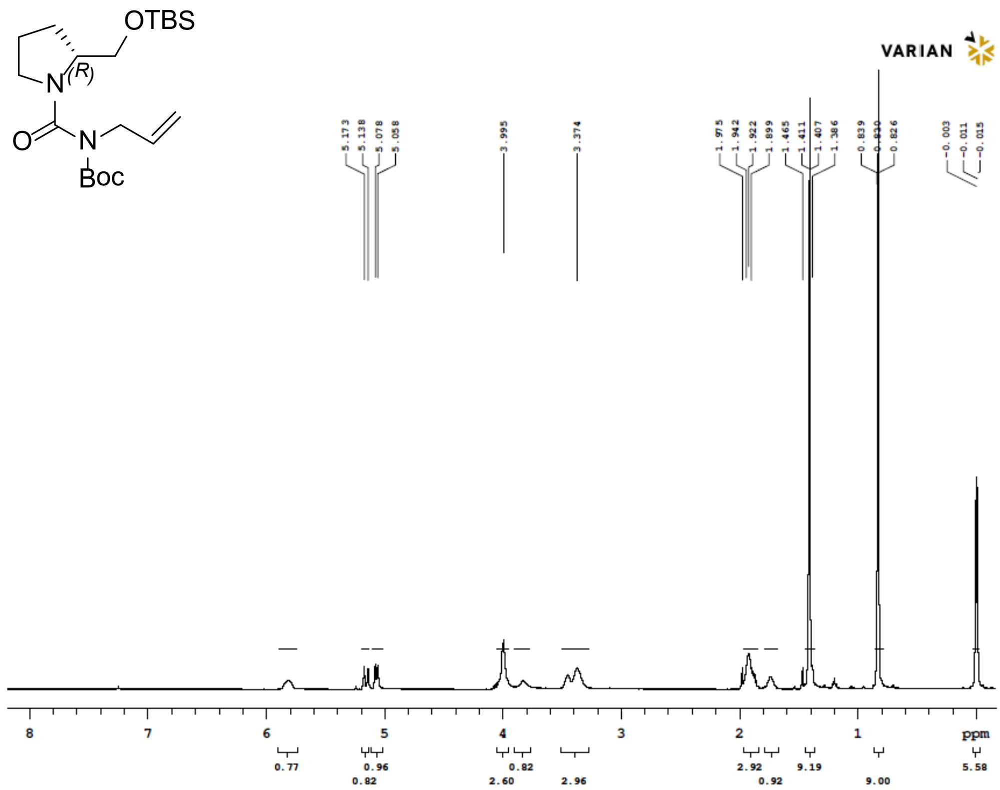
COSY- Spectrum ($CDCl_3$, 500 MHz):
(*R*)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (34)



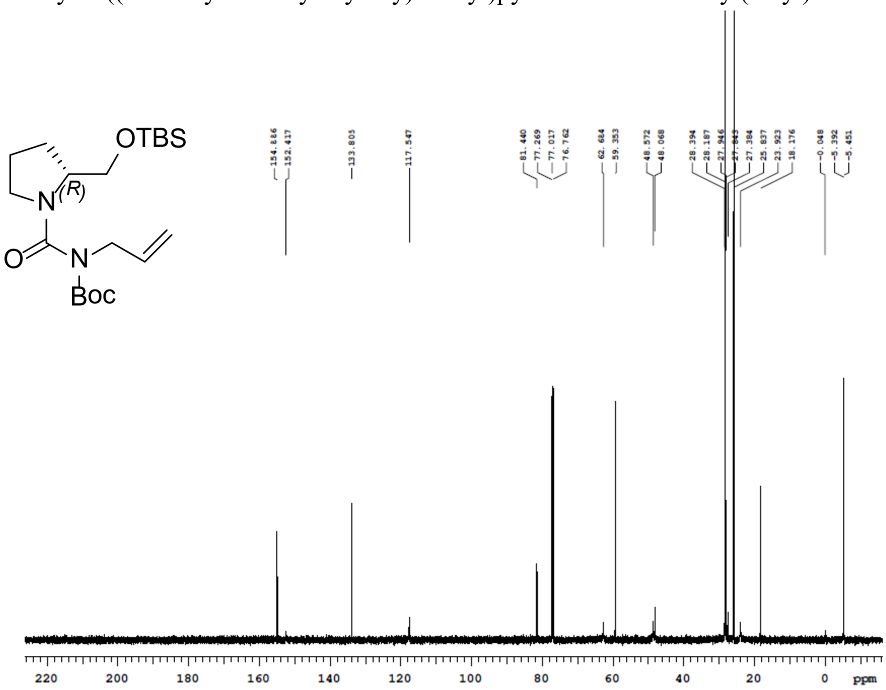
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*R*)-2-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidine (17)



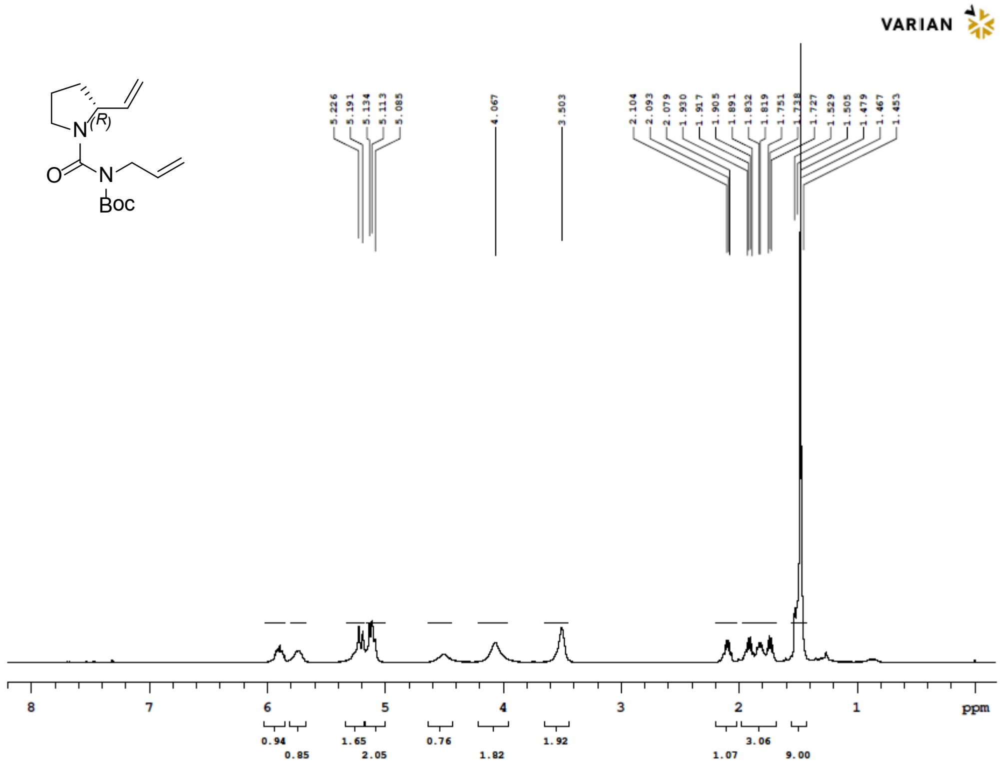
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-2-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidine (17)



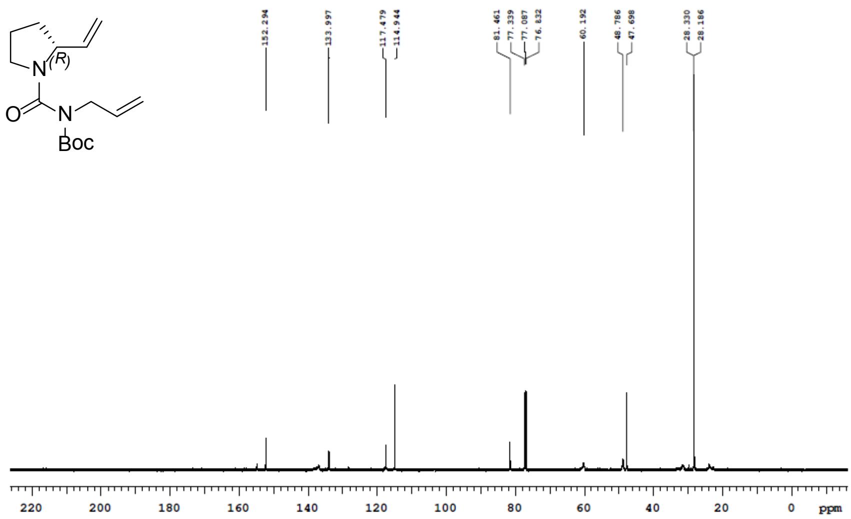
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*R*)-*tert*-butyl 2-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidine-1-carbonyl(ethyl)carbamate (18)



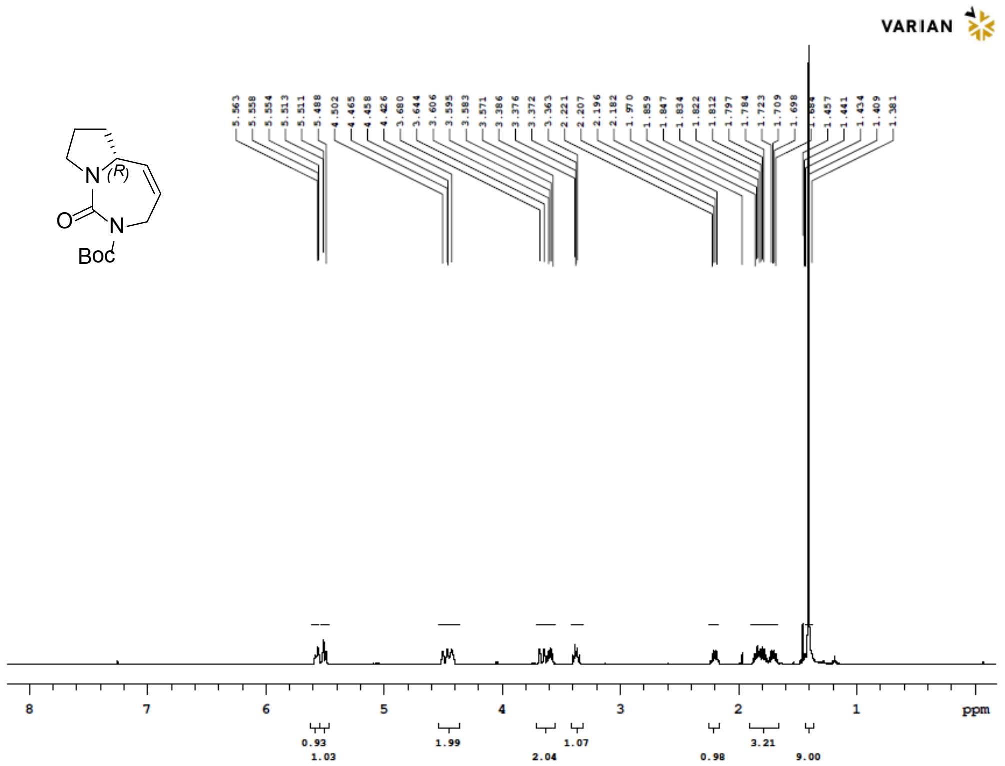
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-*tert*-butyl 2-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidine-1-carbonyl(ethyl)carbamate (18)



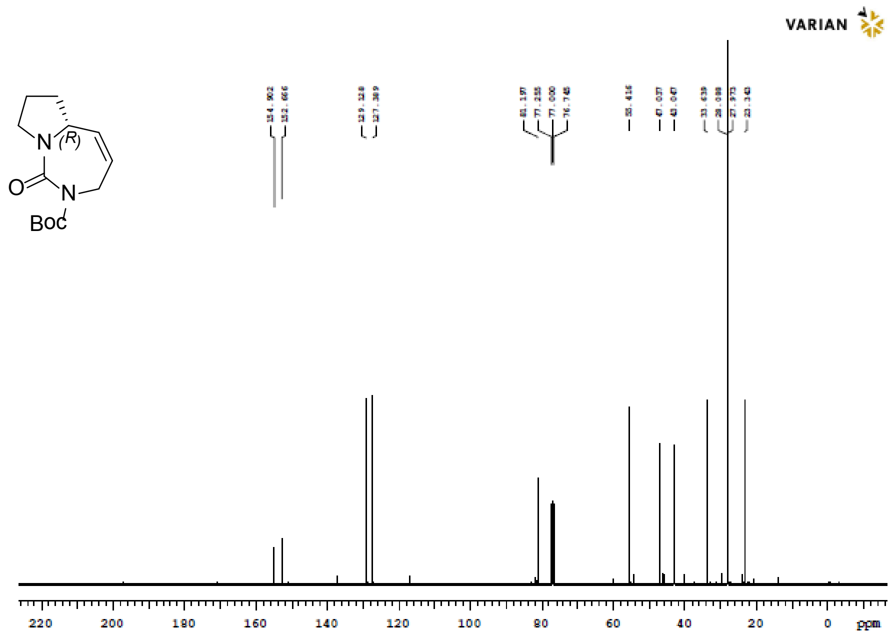
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*R*)-*tert*-butyl allyl(2-vinylpyrrolidine-1-carbonyl)carbamate (19)



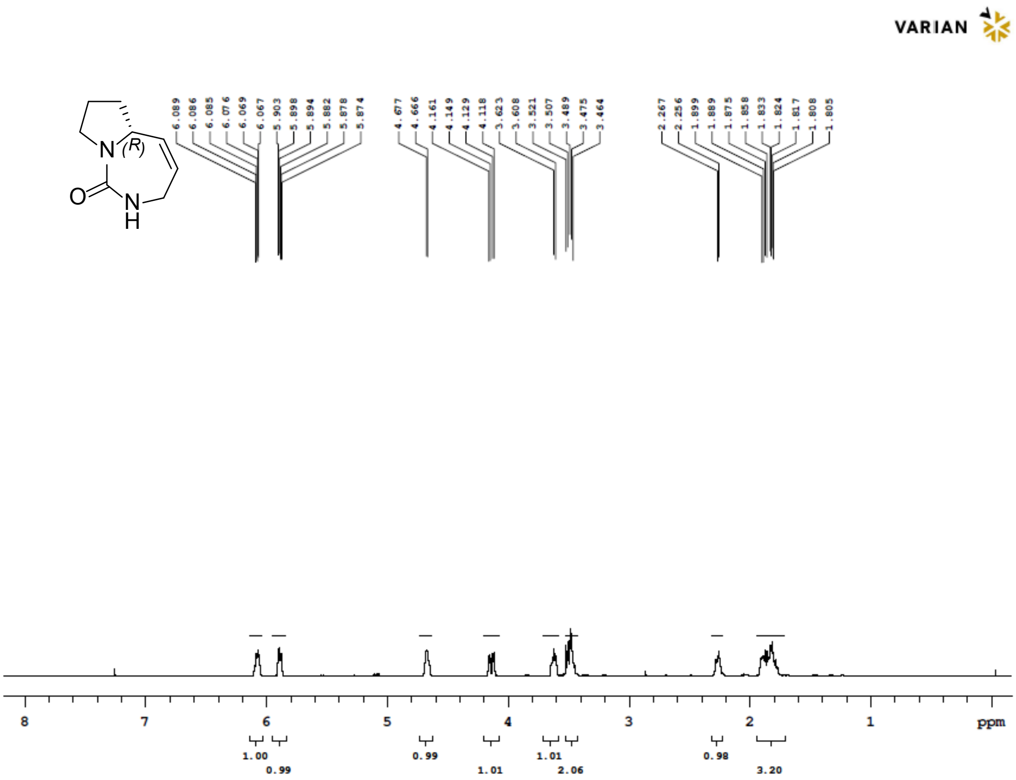
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-*tert*-butyl allyl(2-vinylpyrrolidine-1-carbonyl)carbamate (19)



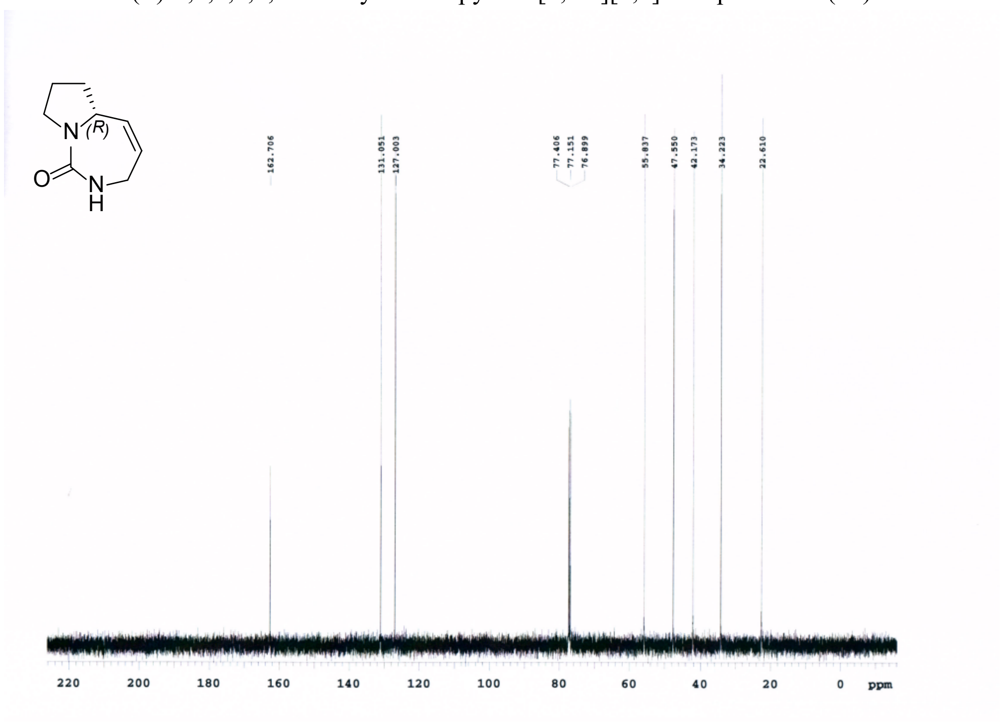
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*R*)-*tert*-butyl 1-oxo-5,6,7,8-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]diazepine-2(3*H*)-carboxylate (29)



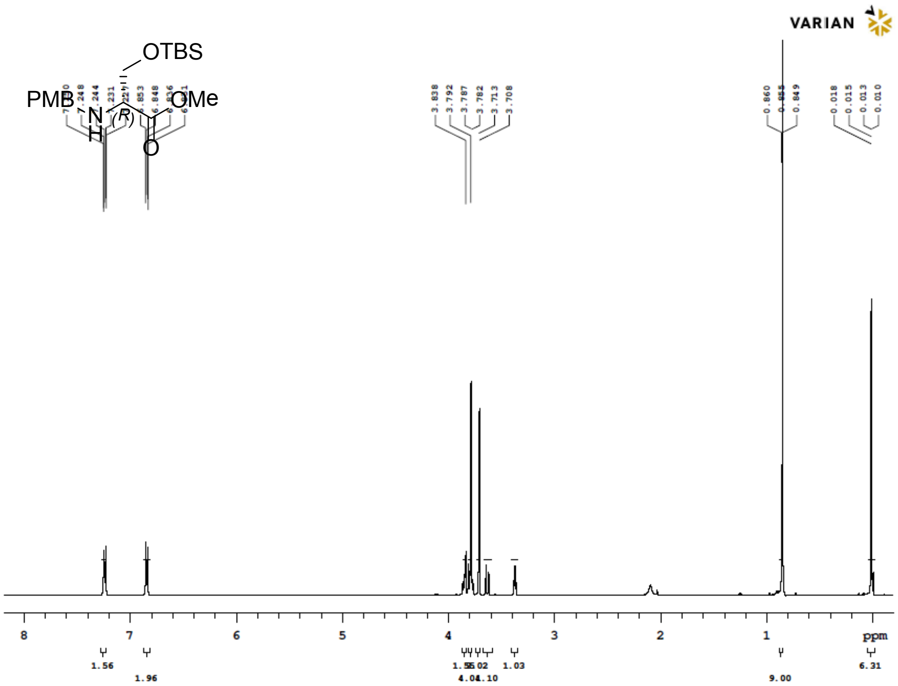
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-*tert*-butyl 1-oxo-5,6,7,8-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]diazepine-2(3*H*)-carboxylate (29)



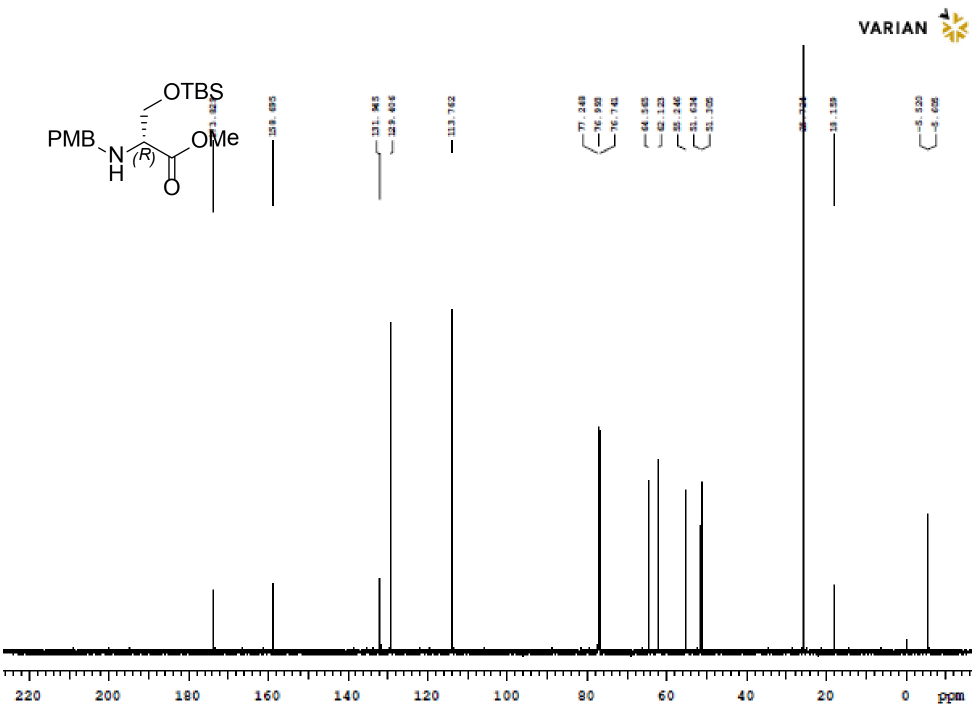
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*R*)-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]diazepin-1-one (35)



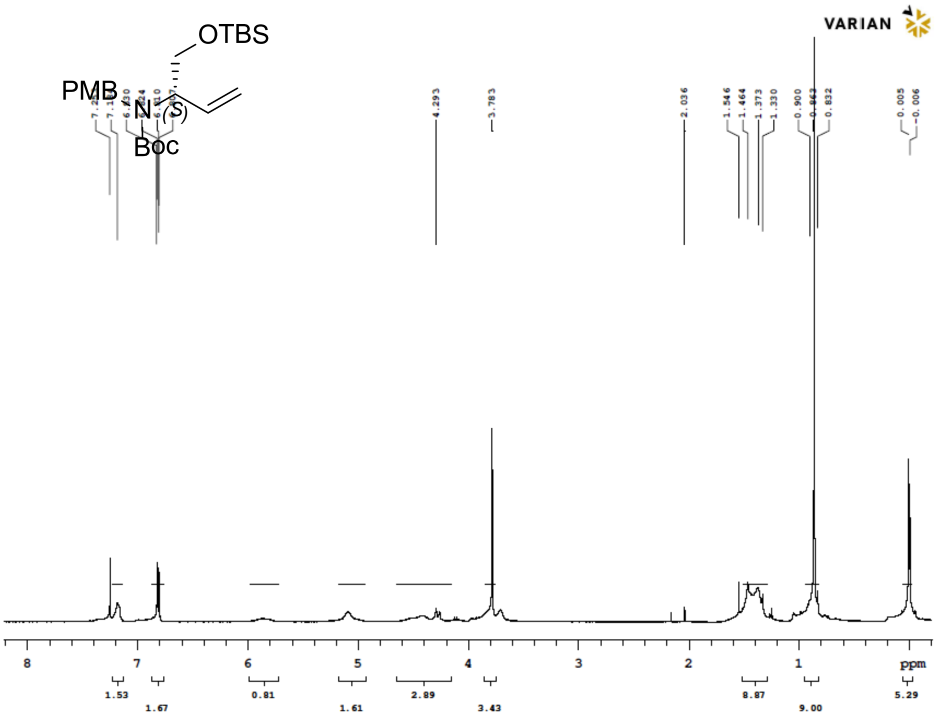
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]diazepin-1-one (35)



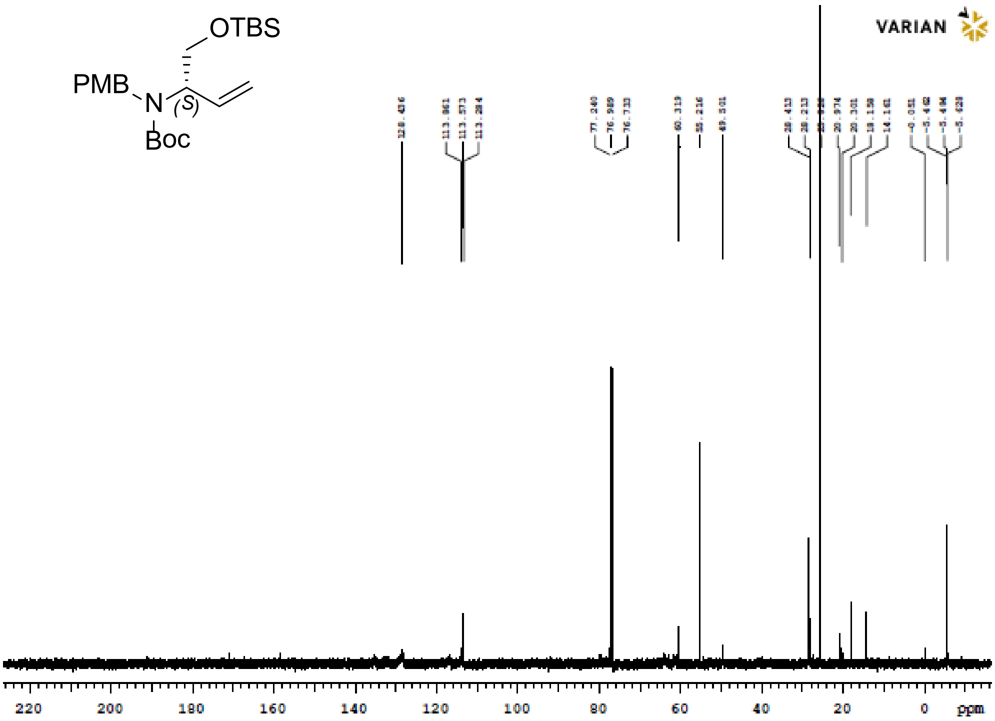
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*R*)-methyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzylamino)propanoate (20)



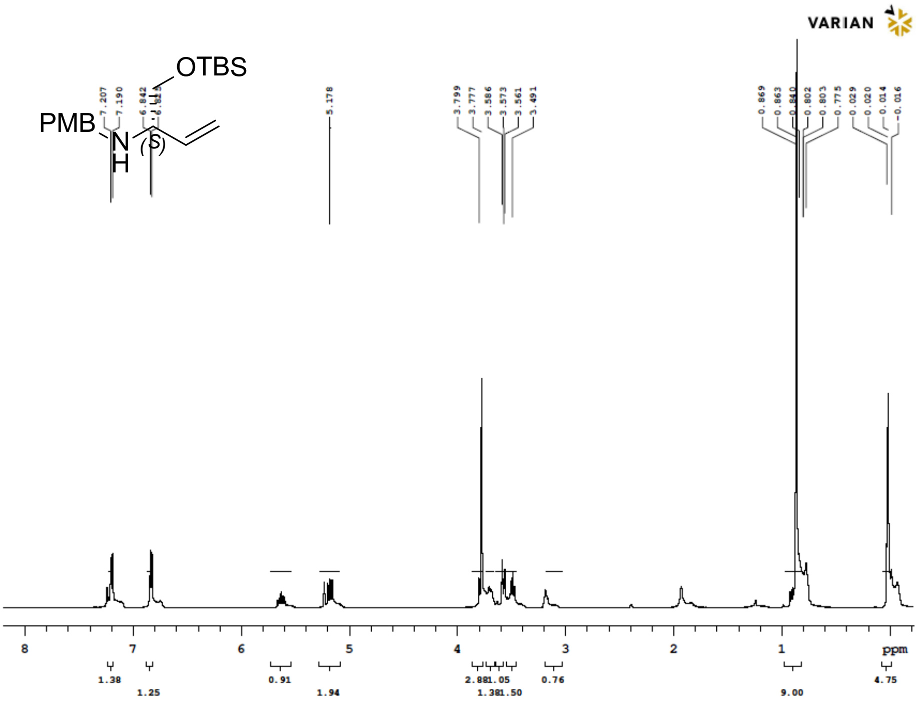
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*R*)-methyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzylamino)propanoate (20)



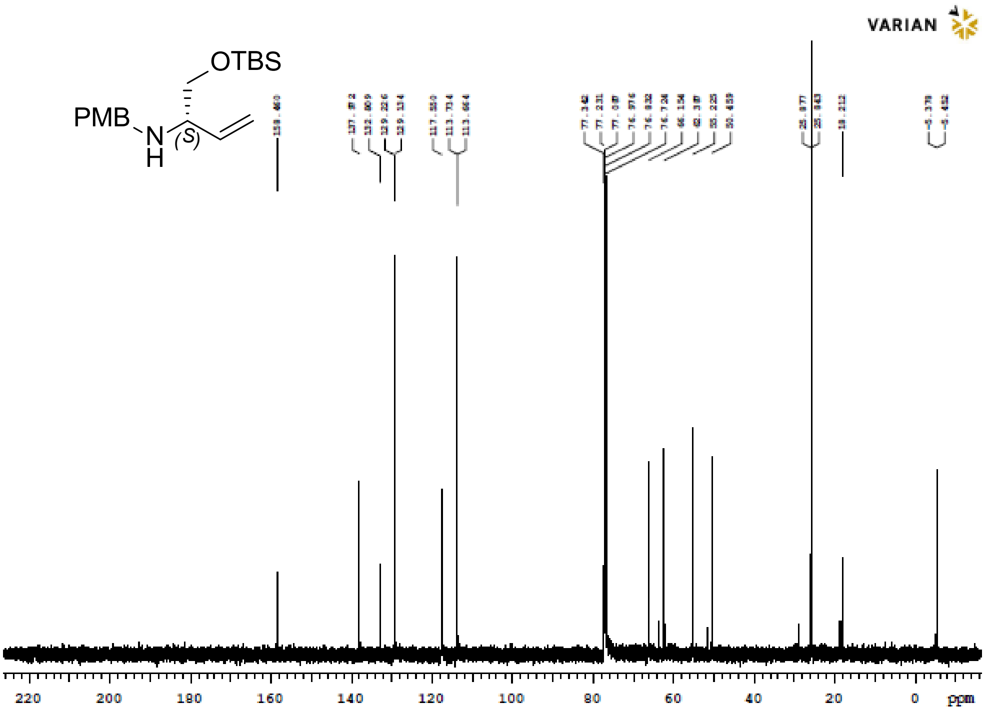
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-*tert*-butyl 1-(*tert*-butyldimethylsilyloxy)but-3-en-2-yl(4-methoxybenzyl)carbamate (21)



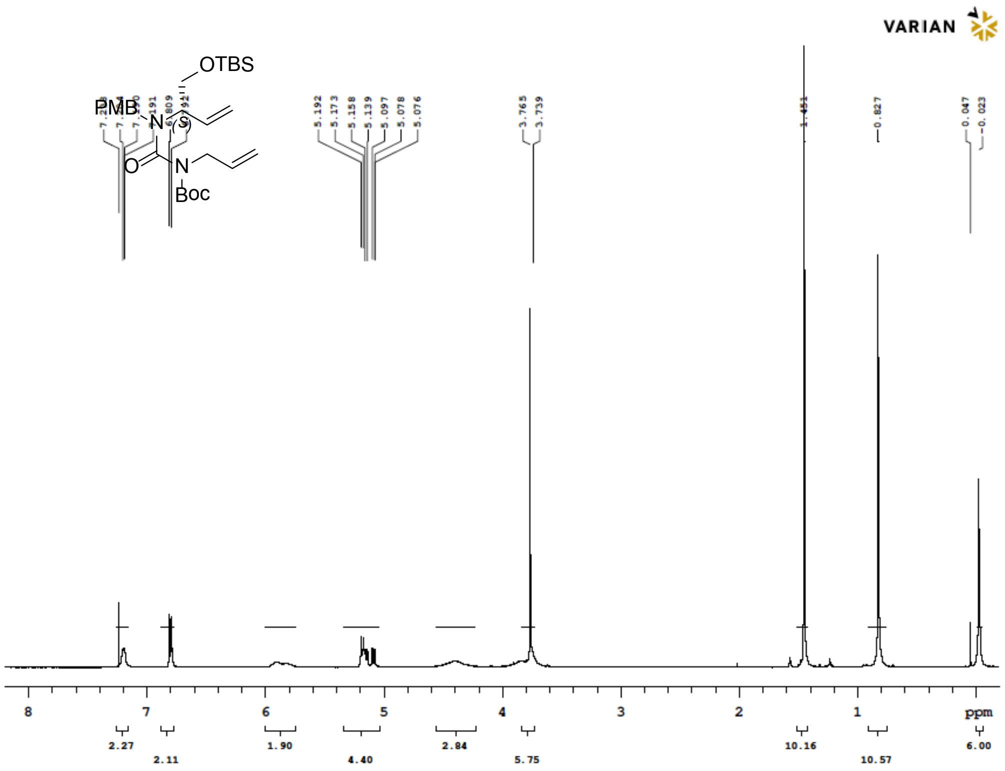
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-*tert*-butyl 1-(*tert*-butyldimethylsilyloxy)but-3-en-2-yl(4-methoxybenzyl)carbamate (21)



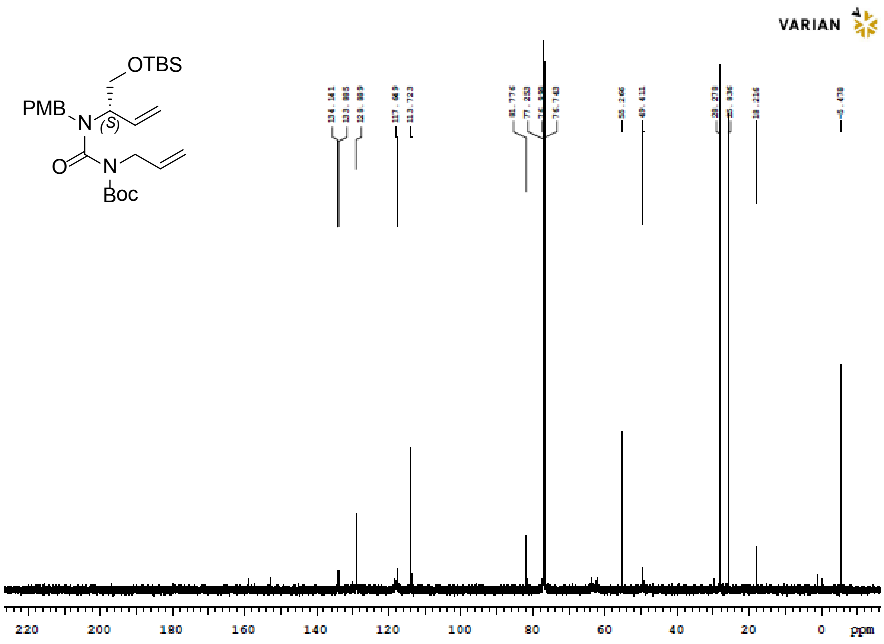
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-1-(*tert*-butyldimethylsilyloxy)-*N*-(4-methoxybenzyl)but-3-en-2-amine (22)



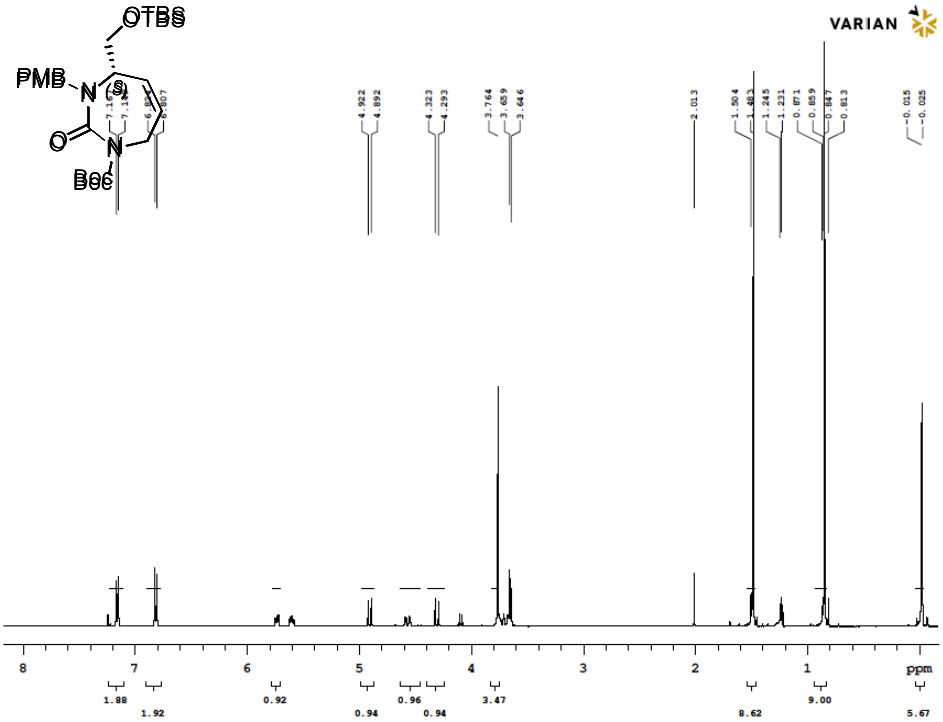
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-1-(*tert*-butyldimethylsilyloxy)-*N*-(4-methoxybenzyl)but-3-en-2-amine (22)



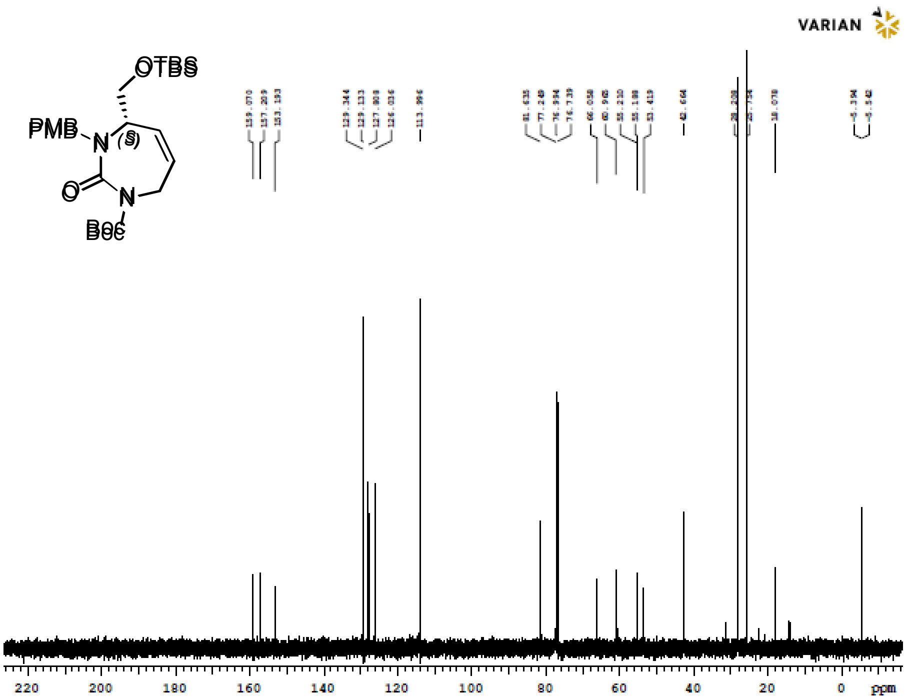
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-*tert*-butyl allyl((1-(*tert*-butyldimethylsilyloxy)but-3-en-2-yl)(4-methoxybenzyl)carbamoyl)carbamate (23)



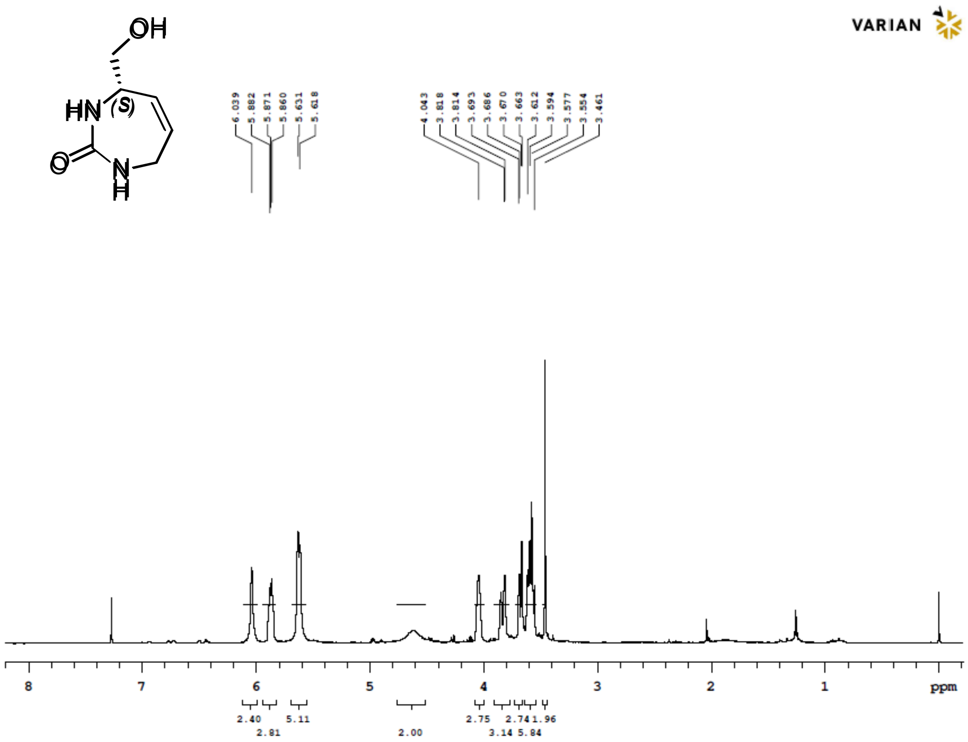
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-*tert*-butyl allyl((1-(*tert*-butyldimethylsilyloxy)but-3-en-2-yl)(4-methoxybenzyl)carbamoyl)carbamate (23)



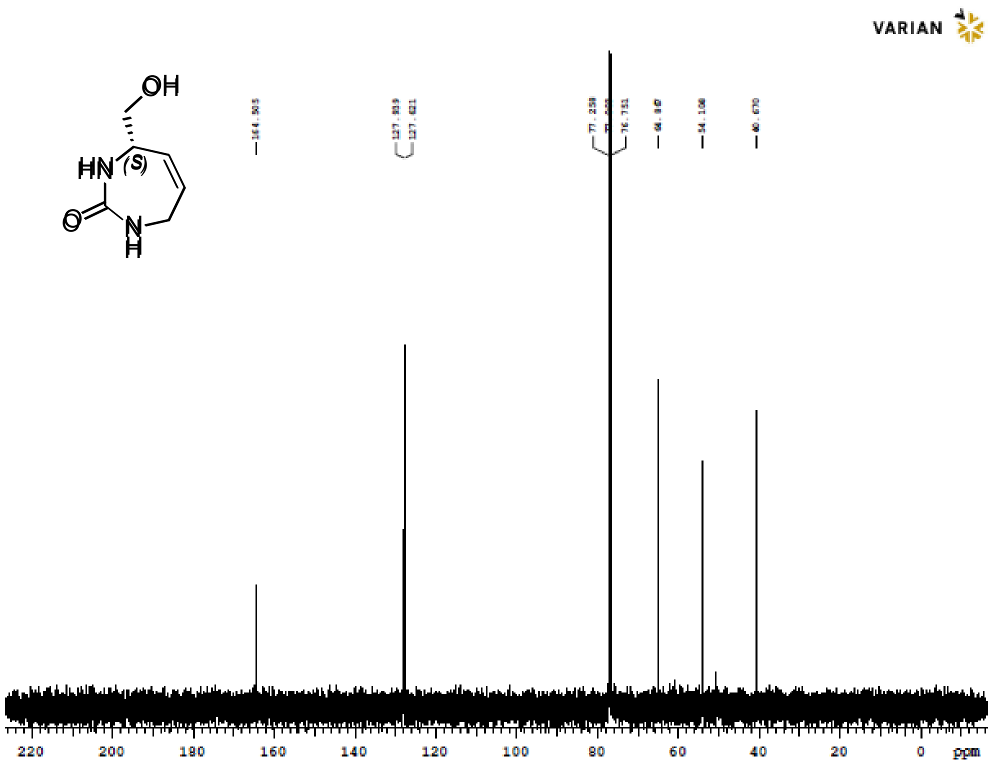
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyloxy)methyl)-3-(4-methoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (30)



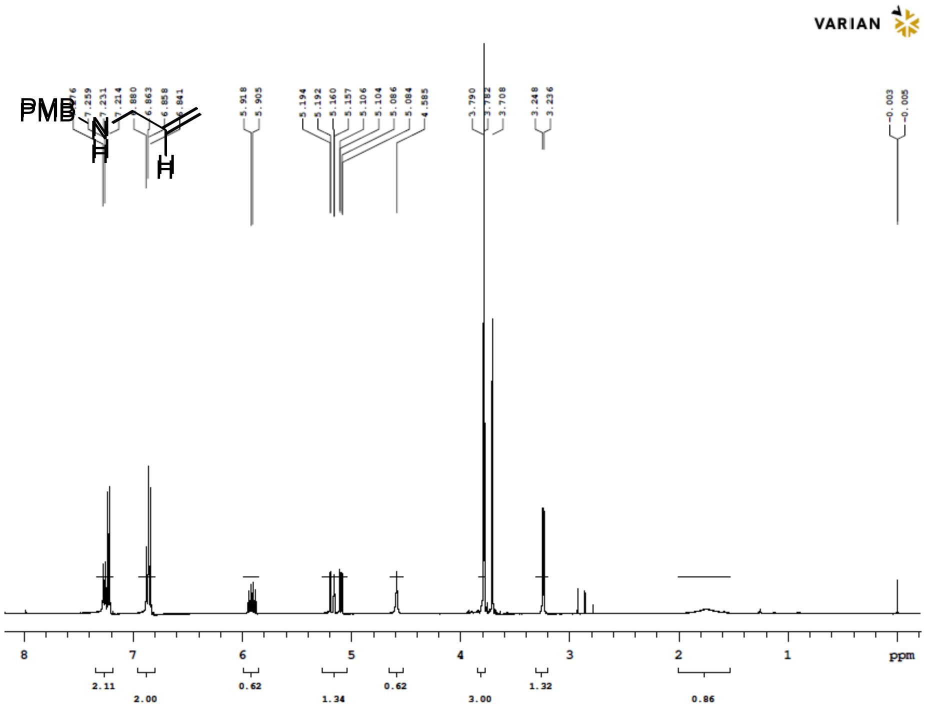
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyloxy)methyl)-3-(4-methoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (30)



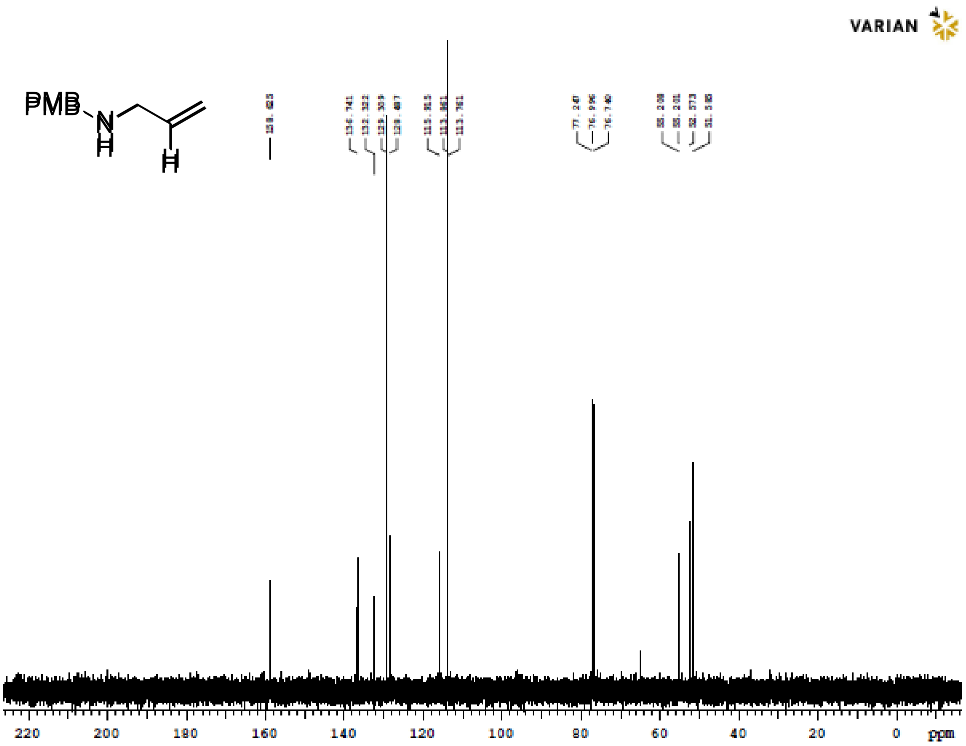
^{1}H-NMR ($CDCl_3$, 500 MHz):
(*S*)-4-(hydroxymethyl)-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (36)



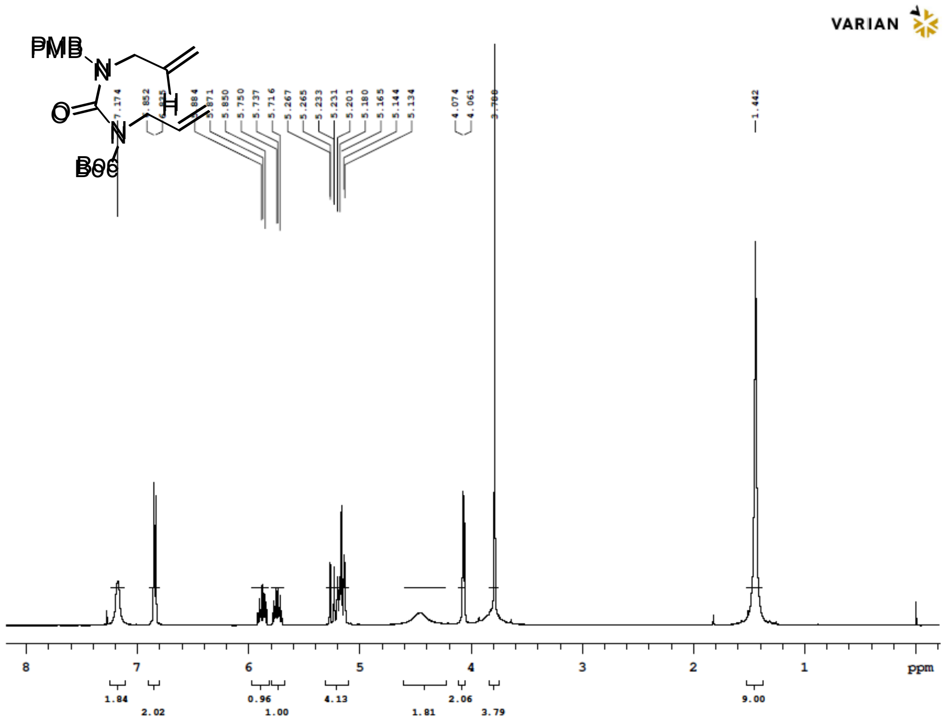
^{13}C-NMR ($CDCl_3$, 125 MHz):
(*S*)-4-(hydroxymethyl)-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (36)



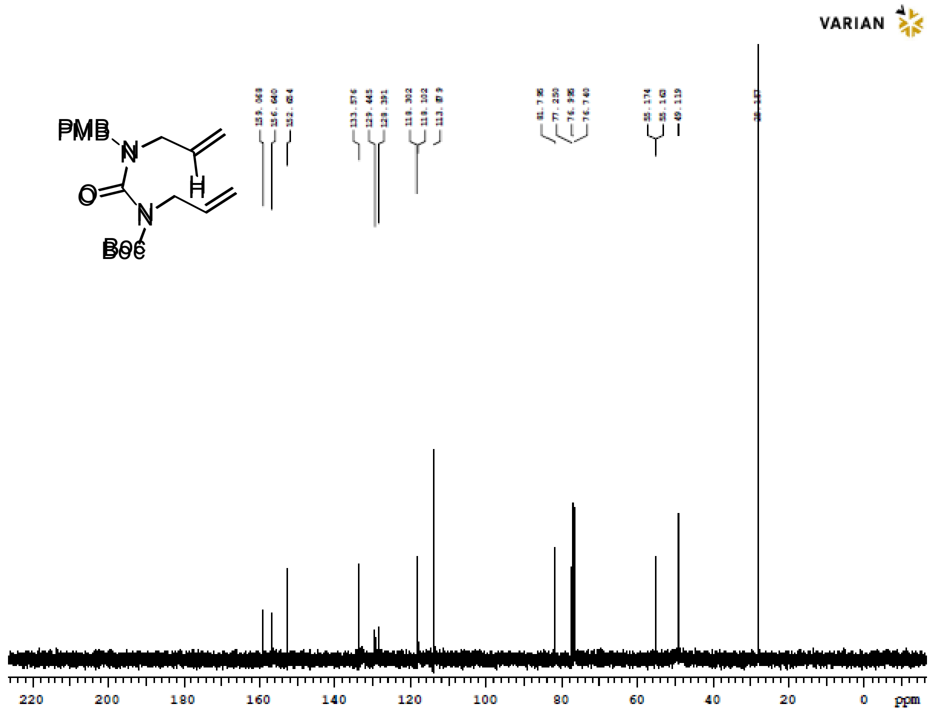
^{1}H-NMR ($CDCl_3$, 500 MHz):
N-(4-methoxybenzyl)prop-2-en-1-amine (24)



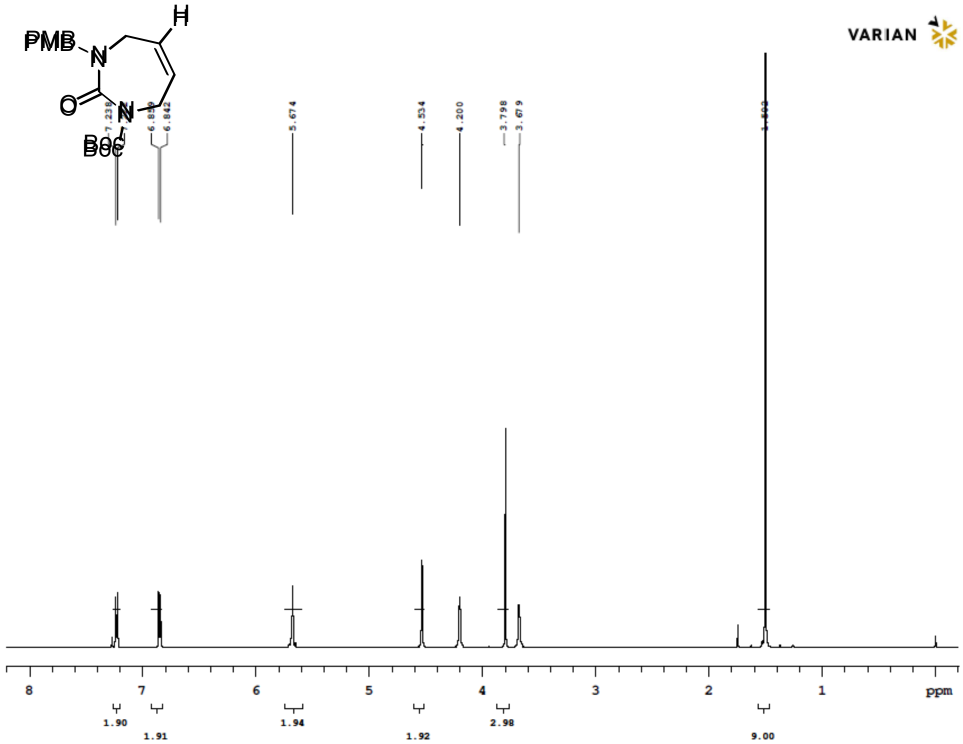
^{13}C-NMR ($CDCl_3$, 125 MHz):
N-(4-methoxybenzyl)prop-2-en-1-amine (24)



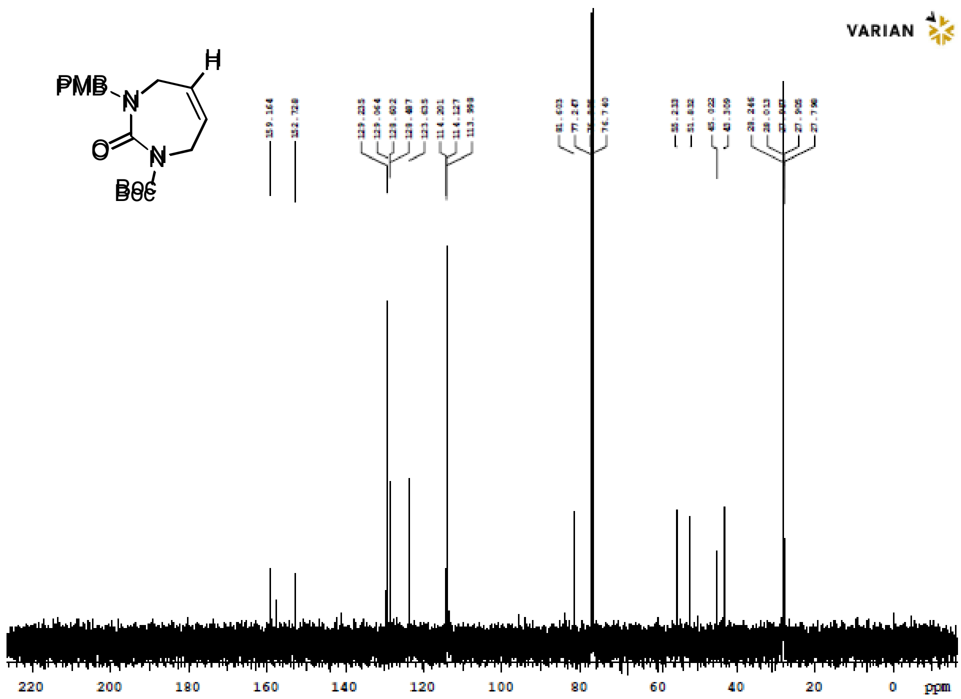
^{1}H-NMR ($CDCl_3$, 500 MHz):
tert-butyl allyl(allyl(4-methoxybenzyl)carbamoyl)carbamate (25)



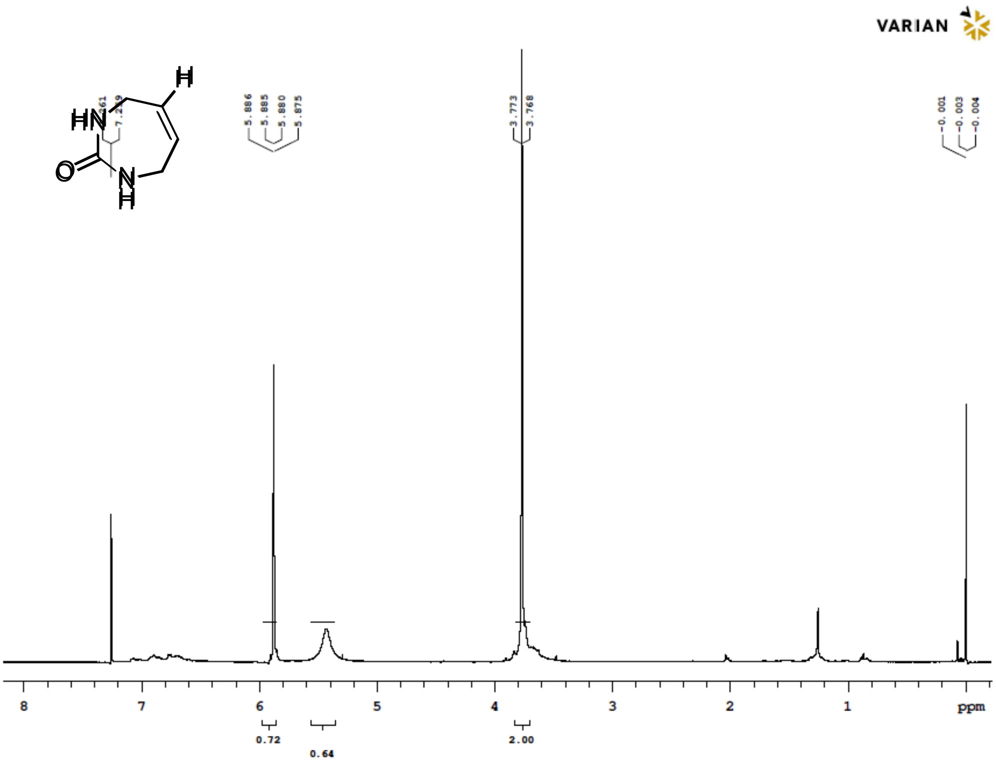
^{13}C-NMR ($CDCl_3$, 125 MHz):
tert-butyl allyl(allyl(4-methoxybenzyl)carbamoyl)carbamate (25)



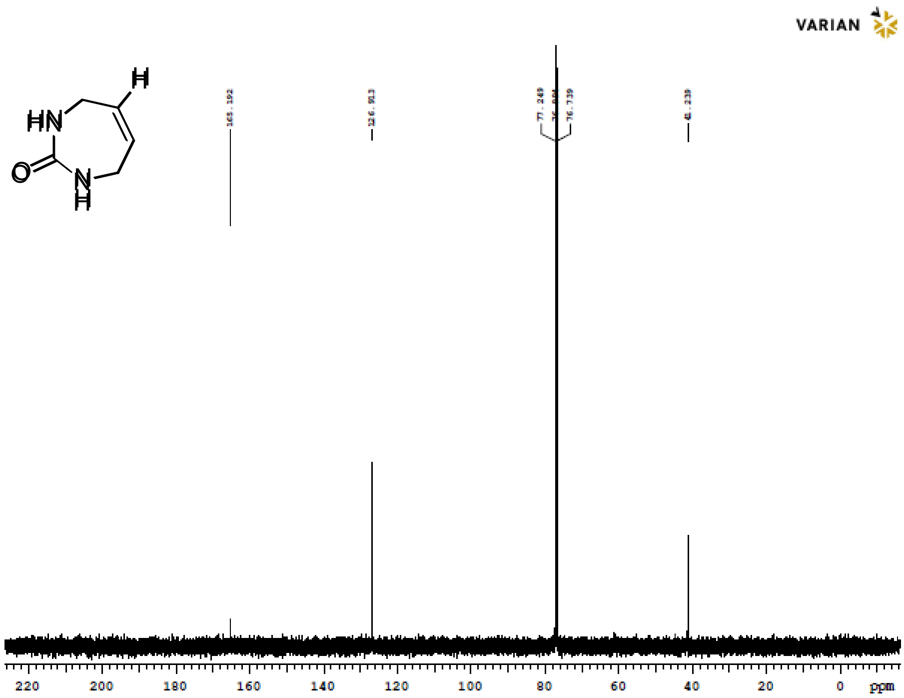
^{1}H-NMR ($CDCl_3$, 500 MHz):
tert-butyl 3-(4-methoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (31)



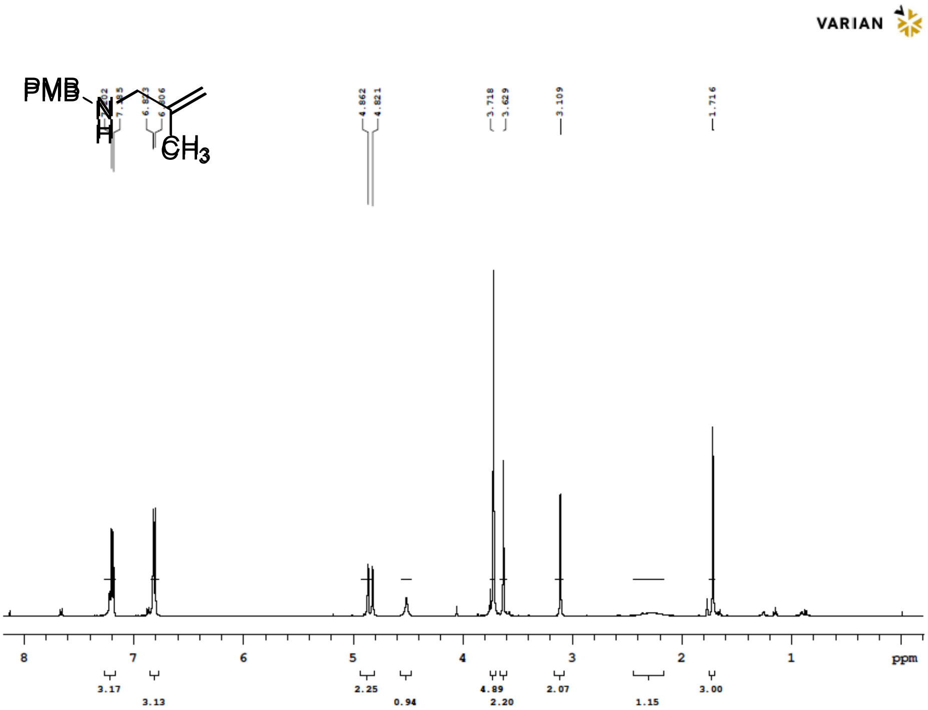
^{13}C-NMR ($CDCl_3$, 125 MHz):
tert-butyl 3-(4-methoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (31)



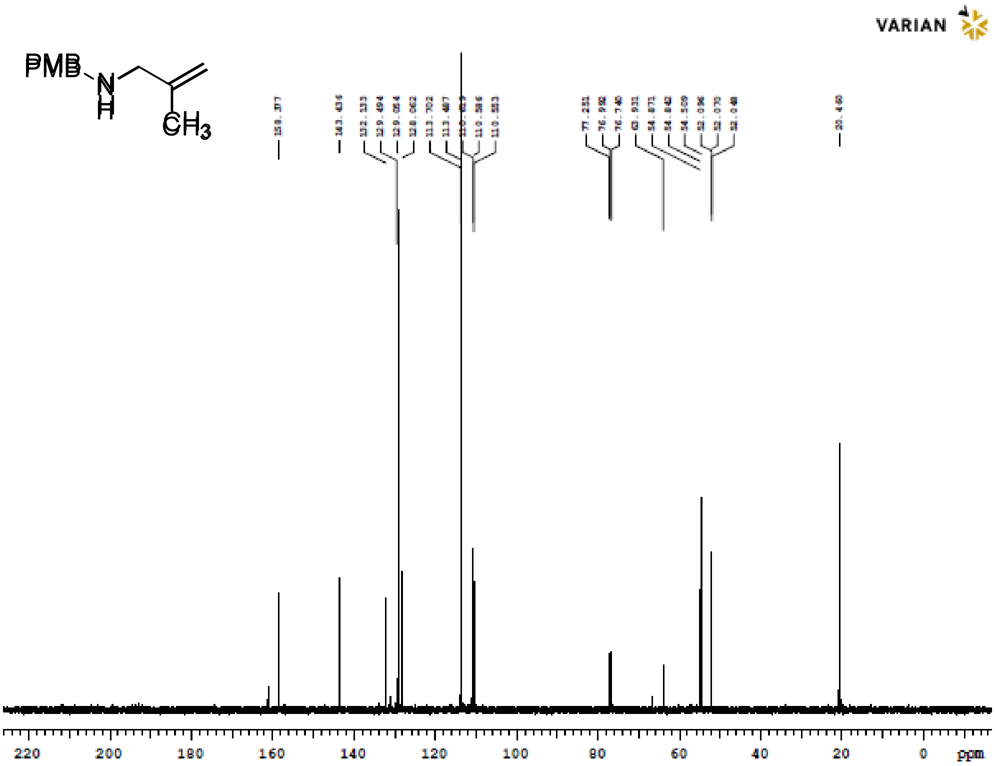
^{1}H-NMR ($CDCl_3$, 500 MHz):
3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (37)



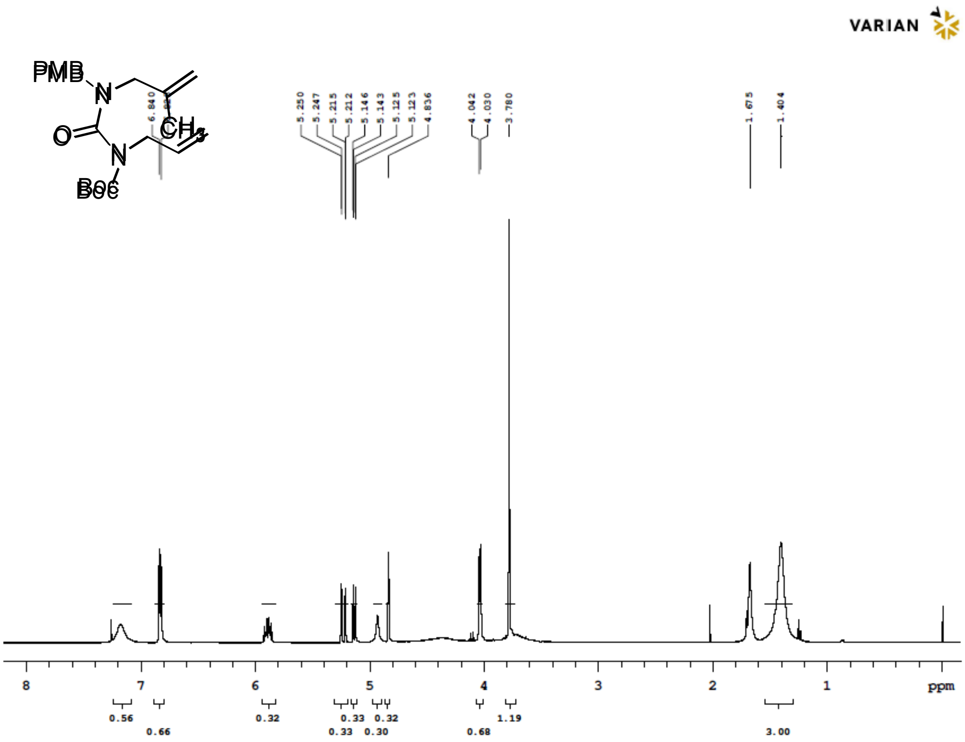
^{13}C-NMR ($CDCl_3$, 125 MHz):
3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (37)



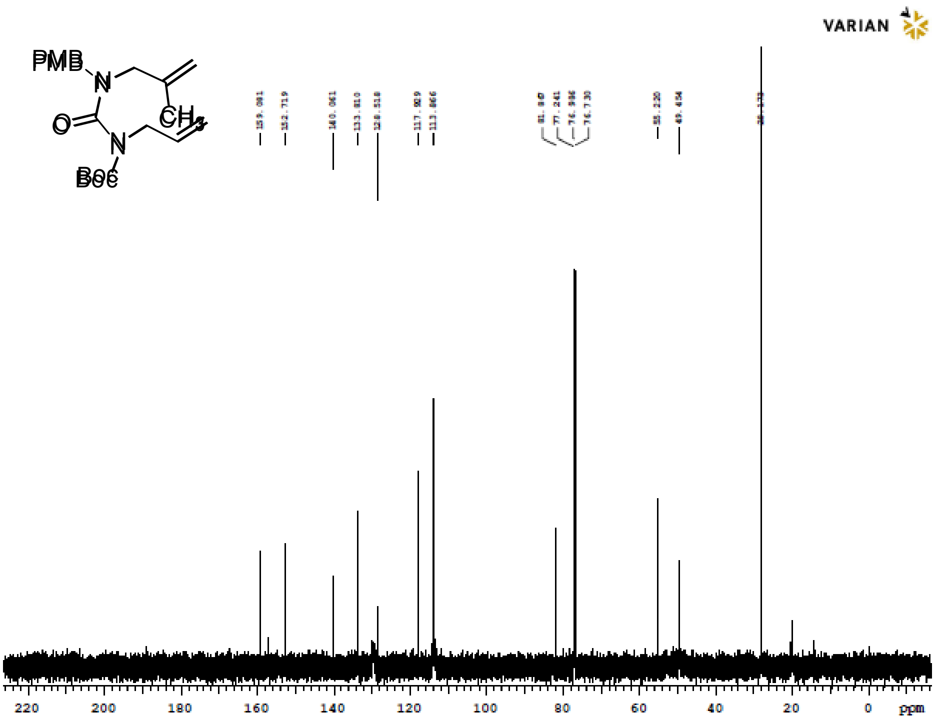
^{1}H-NMR ($CDCl_3$, 500 MHz):
N-(4-methoxybenzyl)-2-methylprop-2-en-1-amine (26)



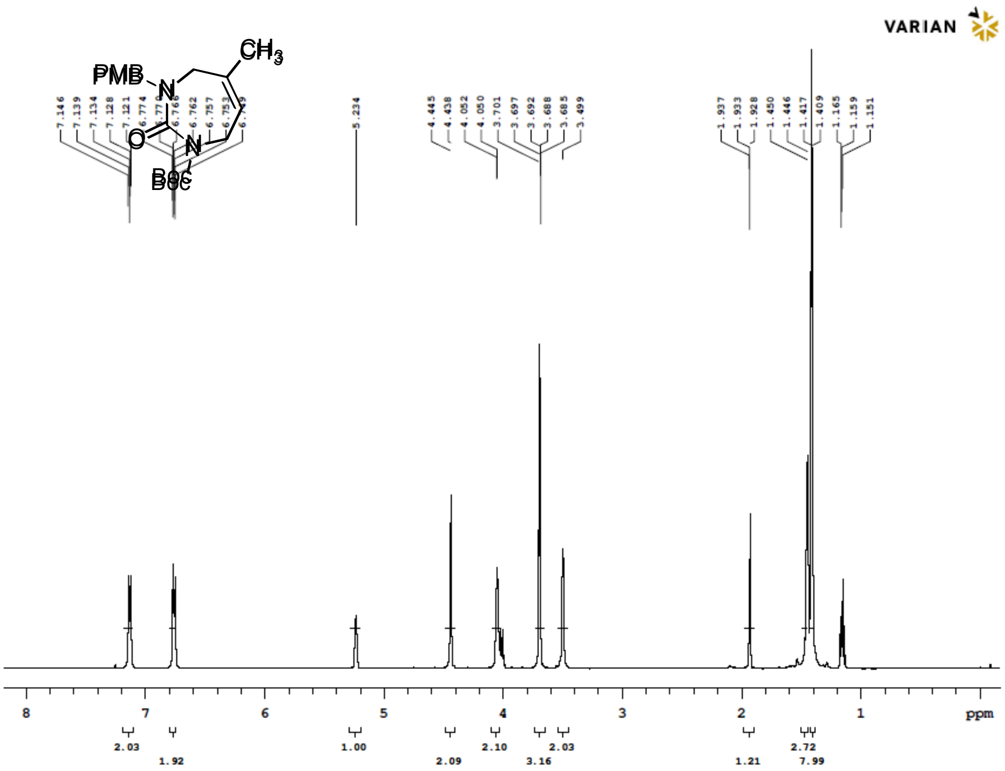
^{13}C-NMR ($CDCl_3$, 125 MHz):
N-(4-methoxybenzyl)-2-methylprop-2-en-1-amine (26)



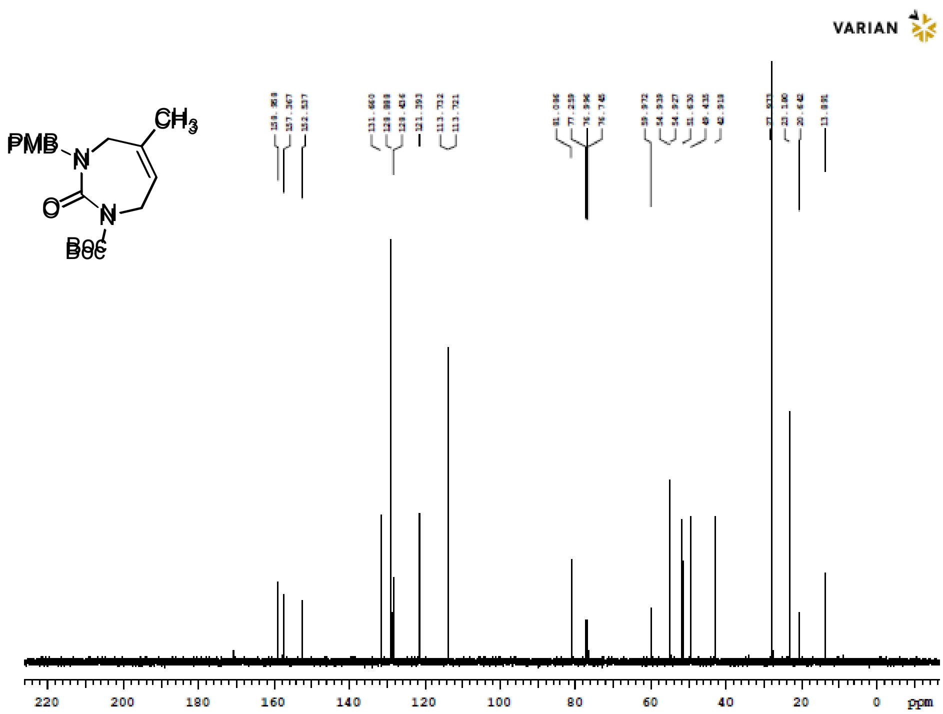
^{1}H-NMR ($CDCl_3$, 500 MHz):
tert-butyl allyl((4-methoxybenzyl)(2-methylallyl)carbamoyl)carbamate (27)



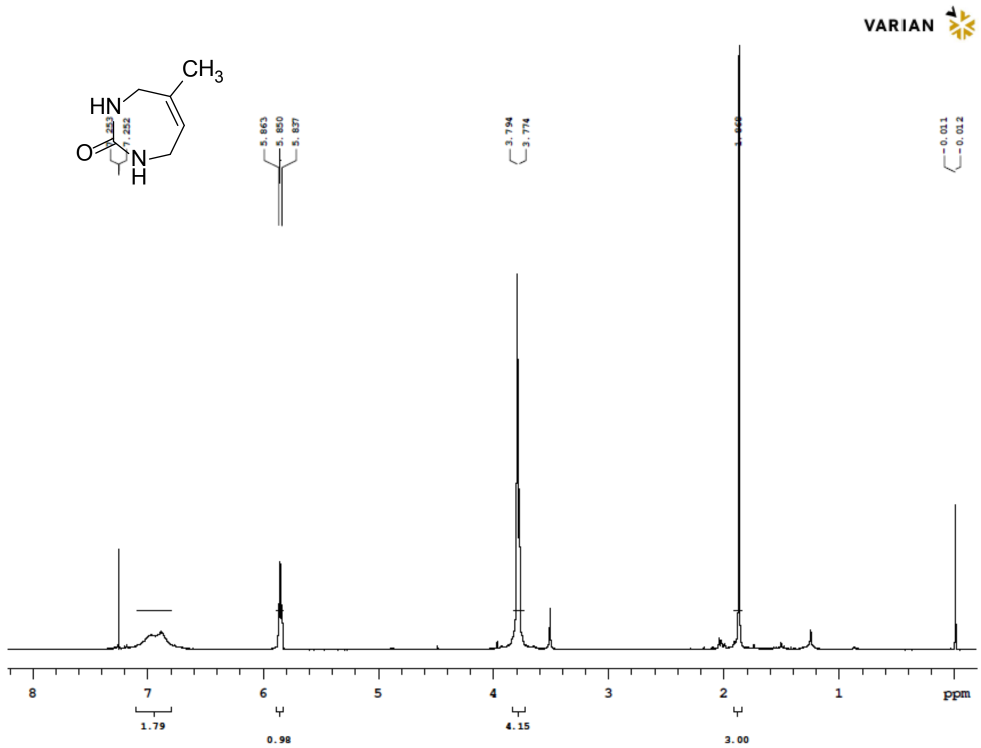
^{13}C-NMR ($CDCl_3$, 125 MHz):
tert-butyl allyl((4-methoxybenzyl)(2-methylallyl)carbamoyl)carbamate (27)



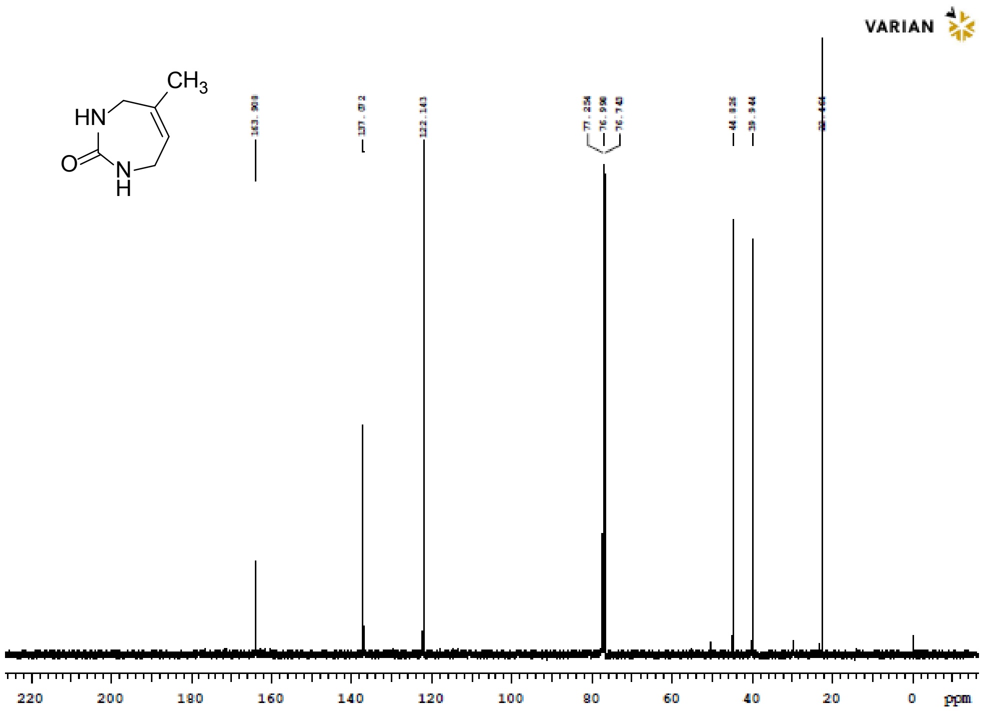
^{1}H-NMR ($CDCl_3$, 500 MHz):
tert-butyl 3-(4-methoxybenzyl)-5-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (32)



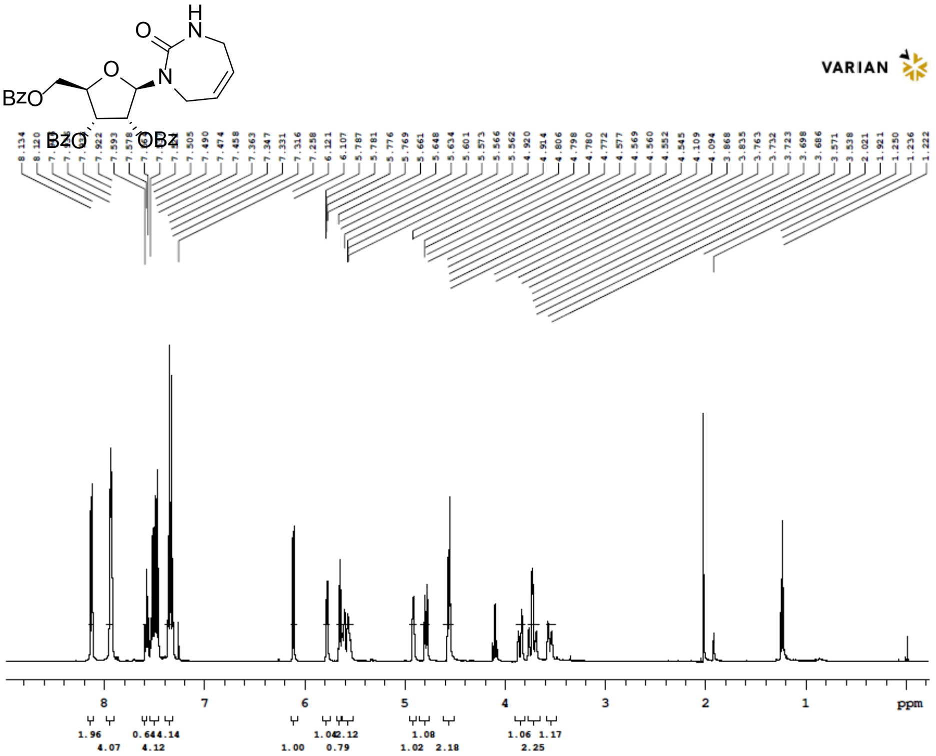
^{13}C-NMR ($CDCl_3$, 125 MHz):
tert-butyl 3-(4-methoxybenzyl)-5-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepine-1-carboxylate (32)



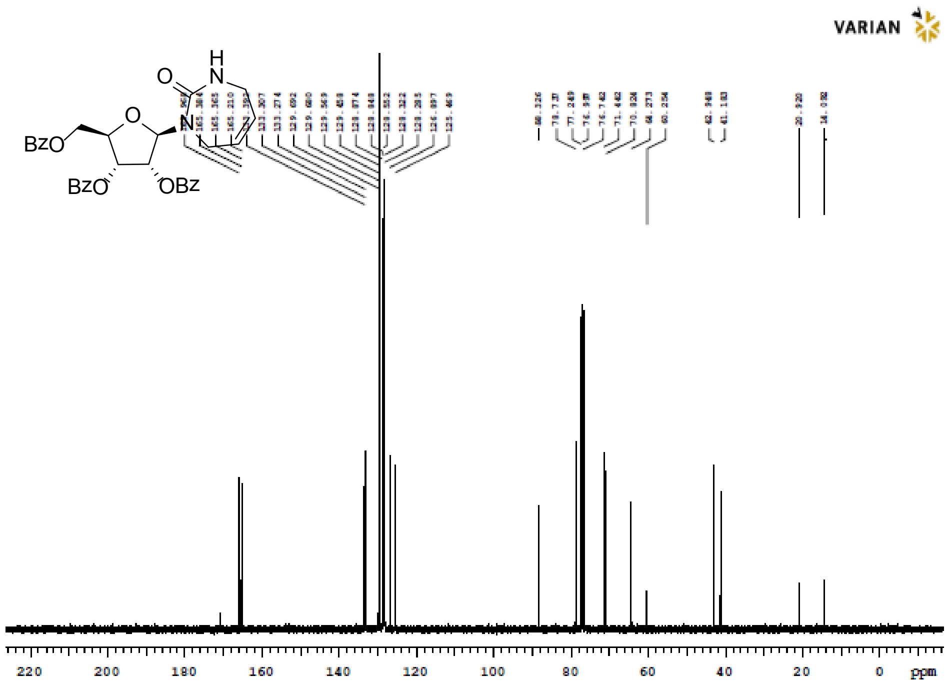
[1]H-NMR ($CDCl_3$, 500 MHz):
5-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (38)



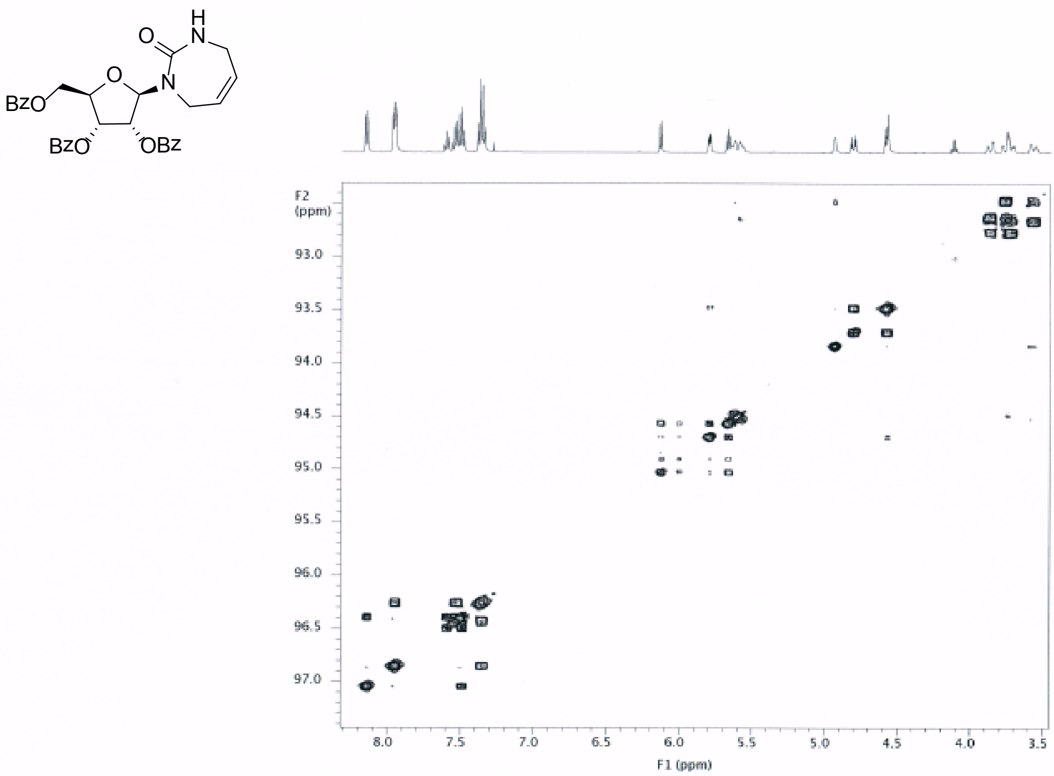
[13]C-NMR ($CDCl_3$, 125 MHz):
5-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (38)



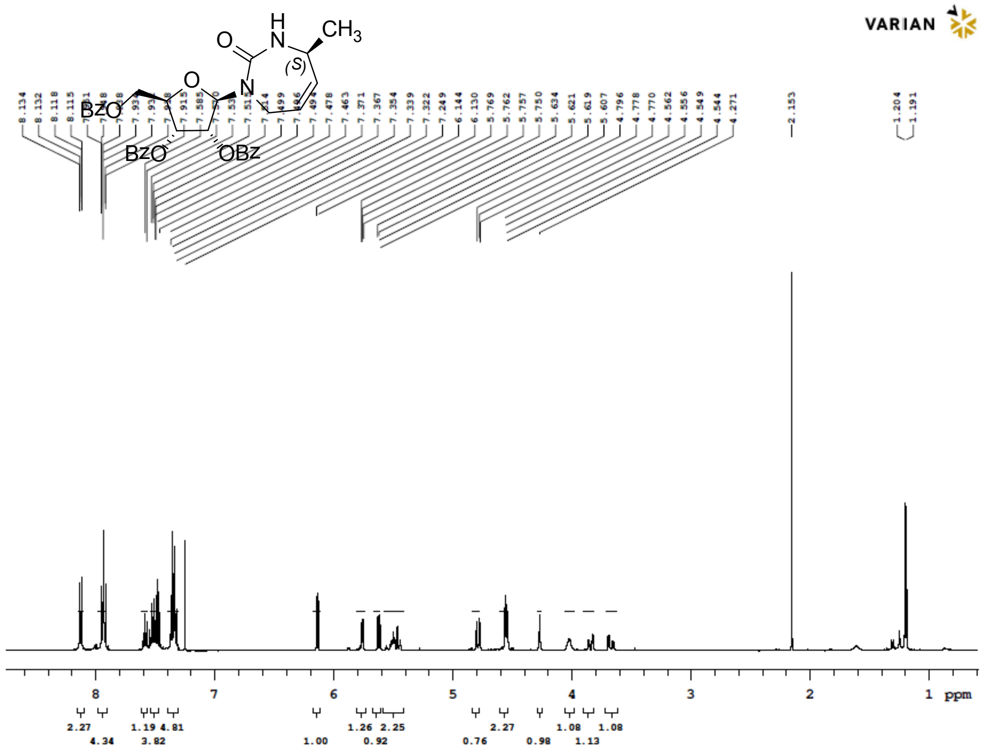
^{1}H-NMR ($CDCl_3$, 500 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-(2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (40)



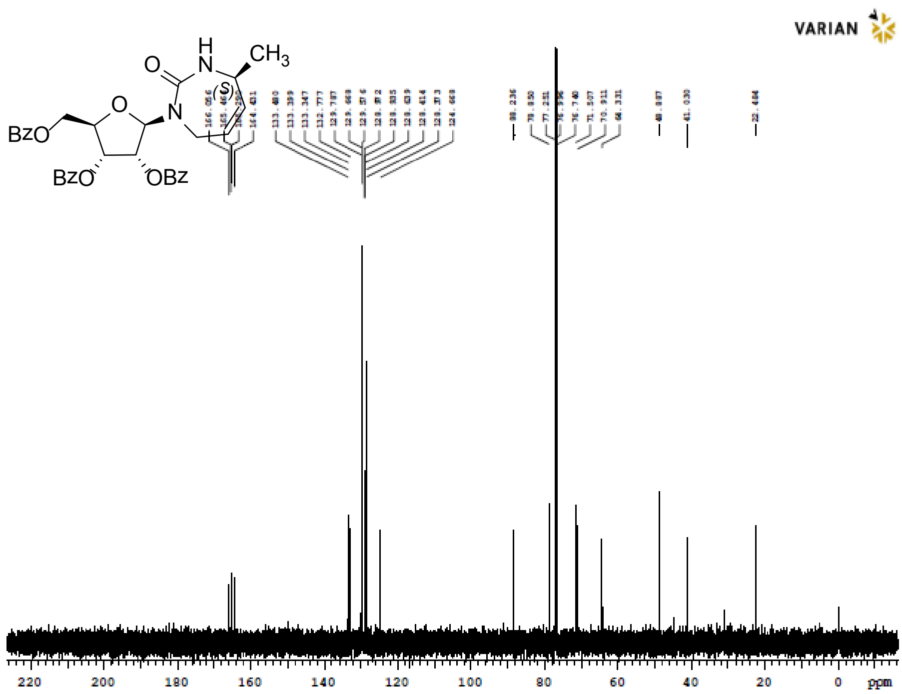
^{13}C-NMR ($CDCl_3$, 125 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-(2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (40)



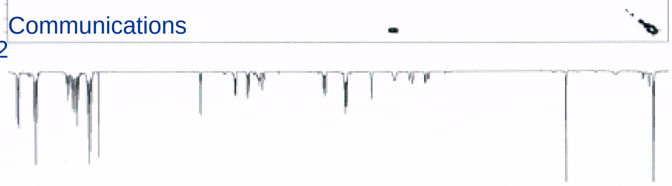
COSY-Spectra ($CDCl_3$, 500 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-(2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (40)

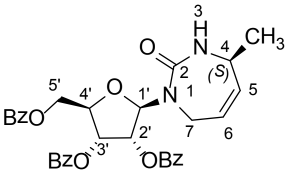


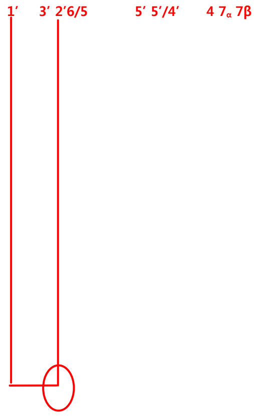
^{1}H-NMR ($CDCl_3$, 500 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-((*S*)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (41)



^{13}C-NMR ($CDCl_3$, 125 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-((*S*)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (41)

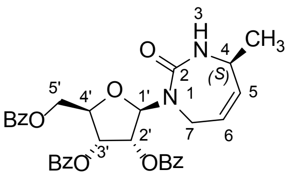


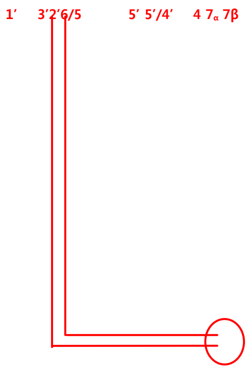


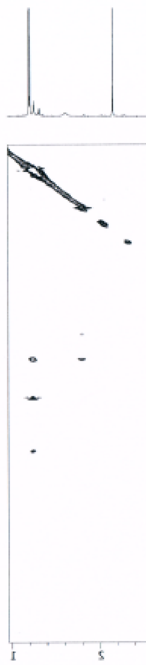


correlation between signals of 1’H (6.16 ppm)-2’H (5.64 ppm).

COSY-Spectra ($CDCl_3$, 500 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-((*S*)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (41)

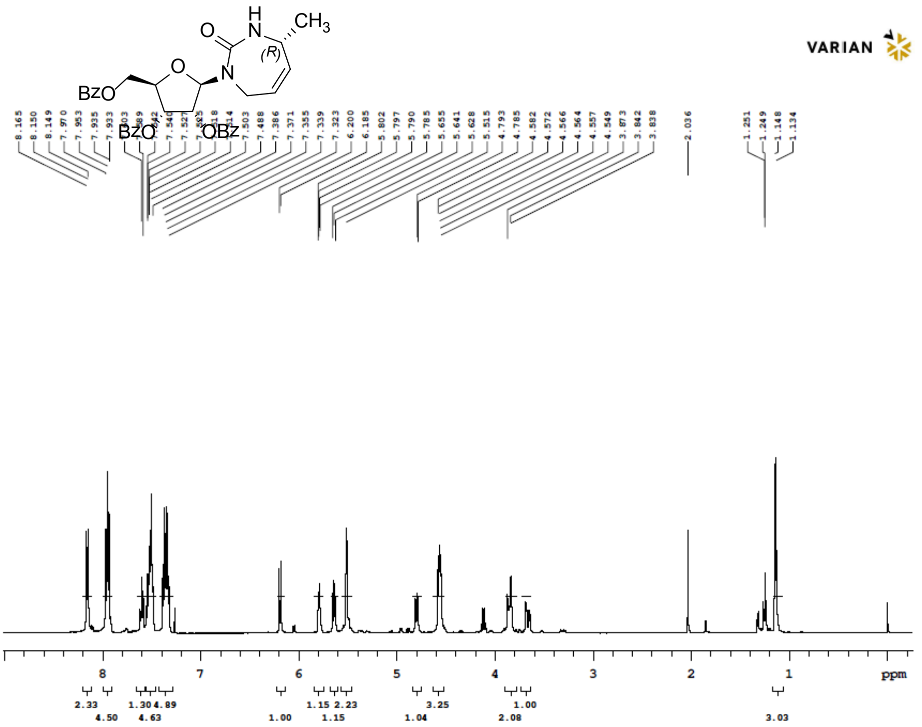




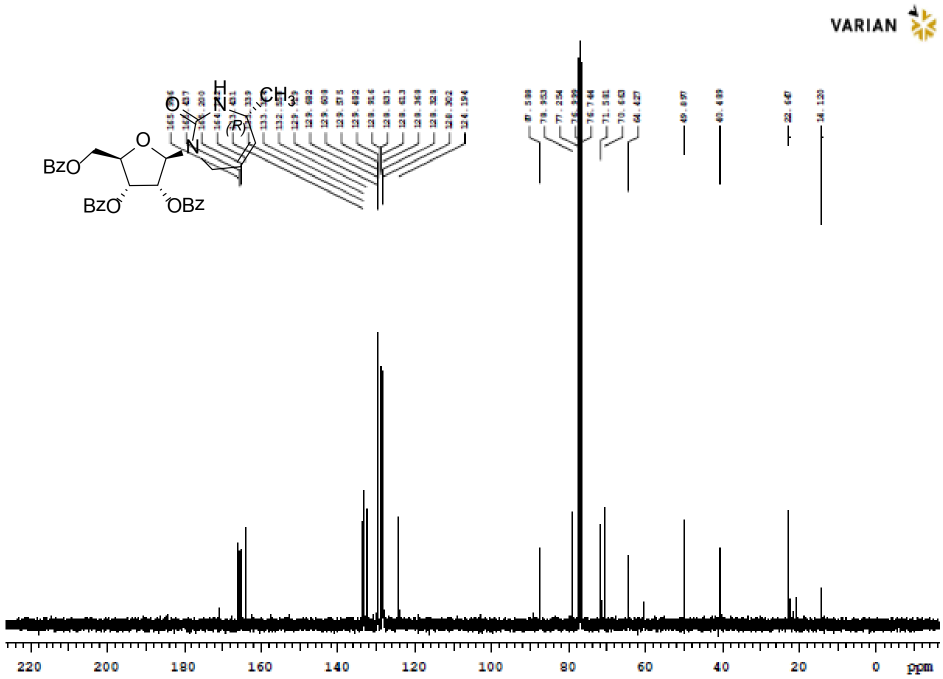


correlation between signals of 2’H (5.64 ppm)-7H$_\beta$ (3.69 ppm) and 6H (5.48 ppm) and)- 7H$_\beta$ (3.69 ppm).

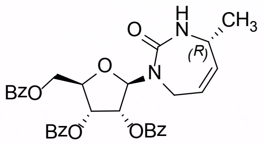
NOESY- Spectra ($CDCl_3$, 500 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-((*S*)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (41)

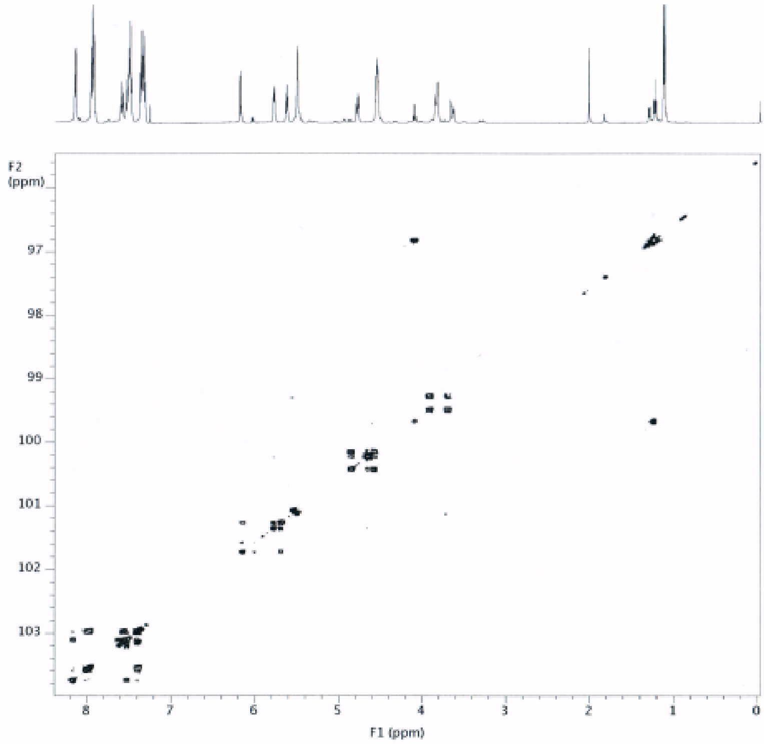


[1]H-NMR ($CDCl_3$, 500 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-((*R*)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (42)

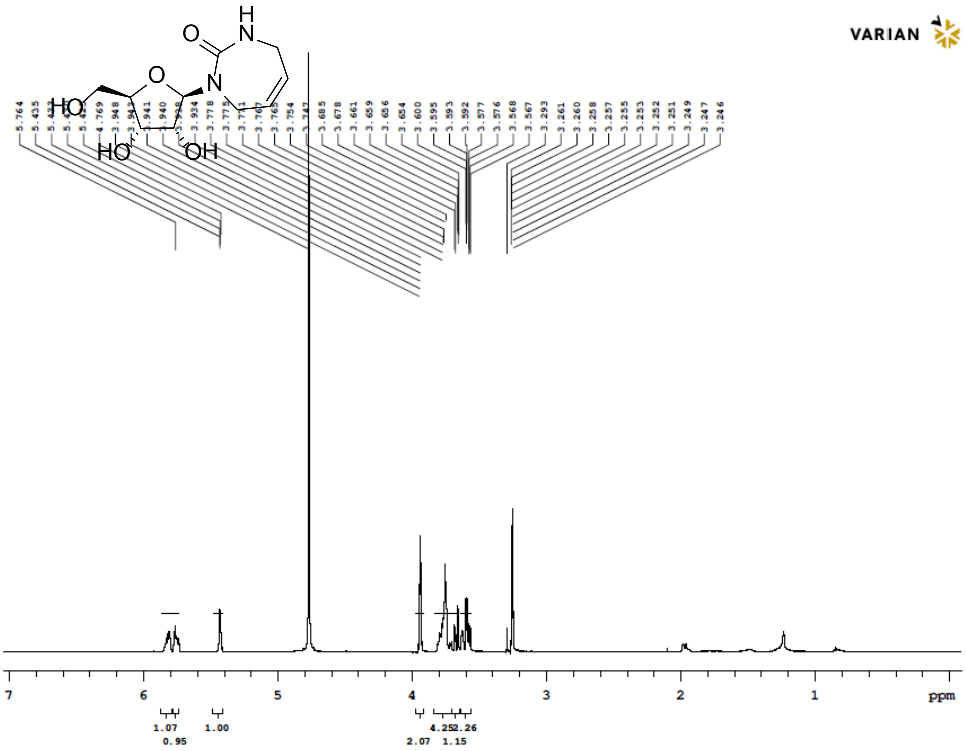


[13]C-NMR ($CDCl_3$, 125 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-((*R*)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (42)

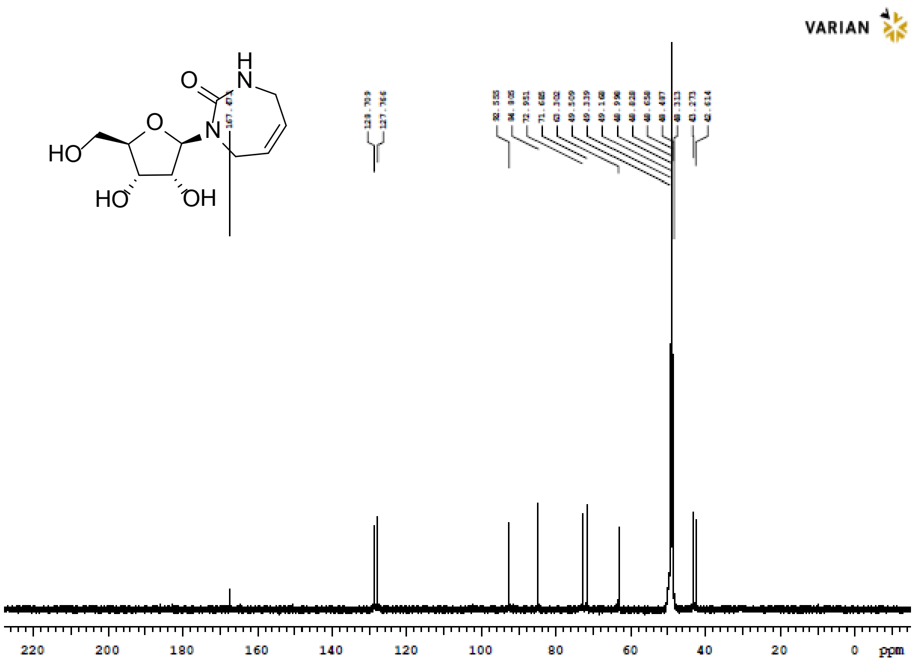




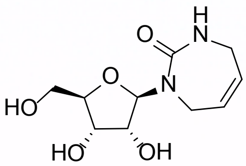
COSY- Spectra ($CDCl_3$, 500 MHz):
(2*R*,3*R*,4*R*,5*R*)-2-(benzoyloxymethyl)-5-((*R*)-4-methyl-2-oxo-2,3,4,7-tetrahydro-1*H*-1,3-diazepin-1-yl)tetrahydrofuran-3,4-diyl dibenzoate (42)

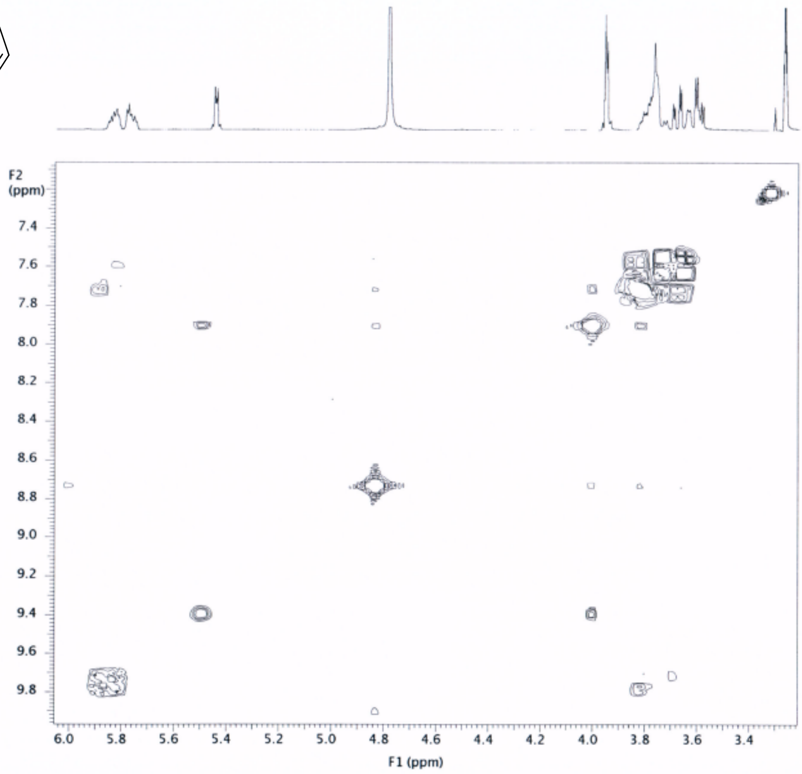


^{1}H-NMR (CD_3OD, 500 MHz):
1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (1)

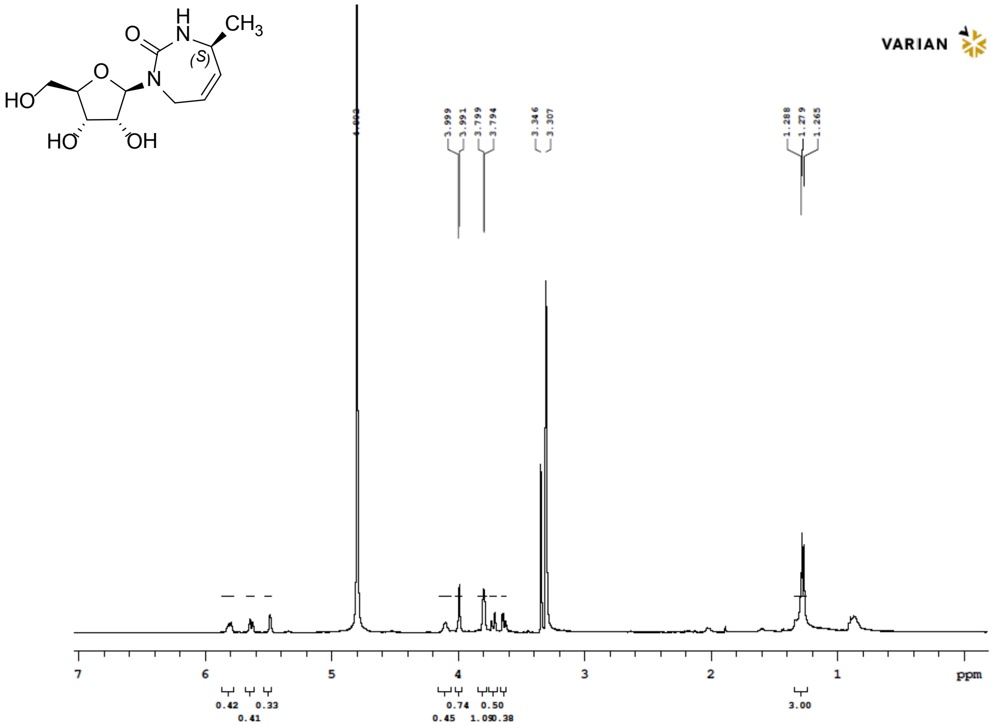


^{13}C-NMR (CD_3OD, 125 MHz):
1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (1)

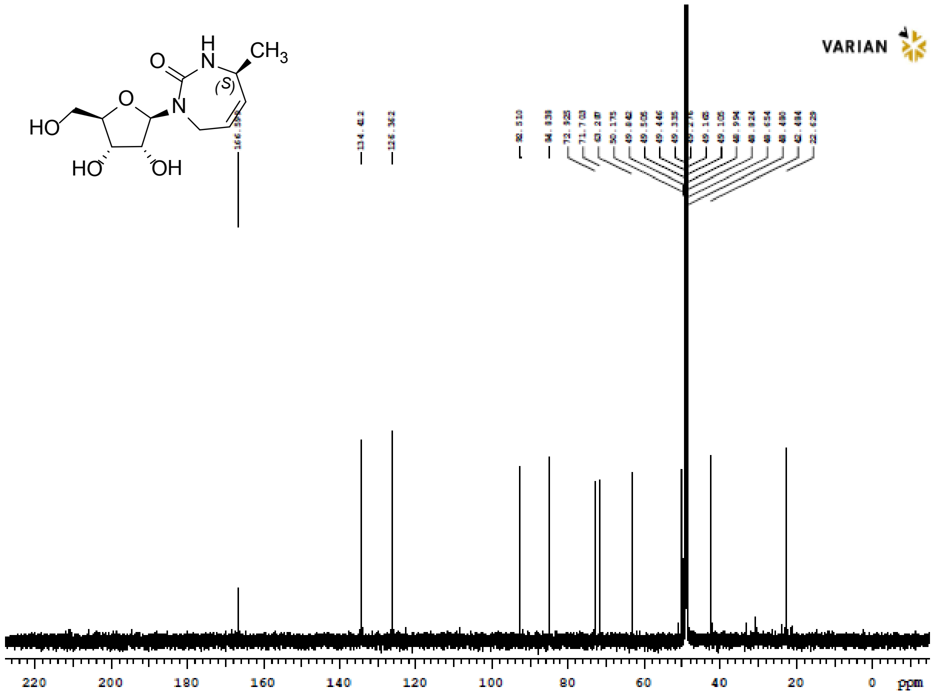




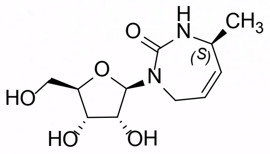
COSY- Spectra (CD_3OD, 500 MHz):
1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (1)

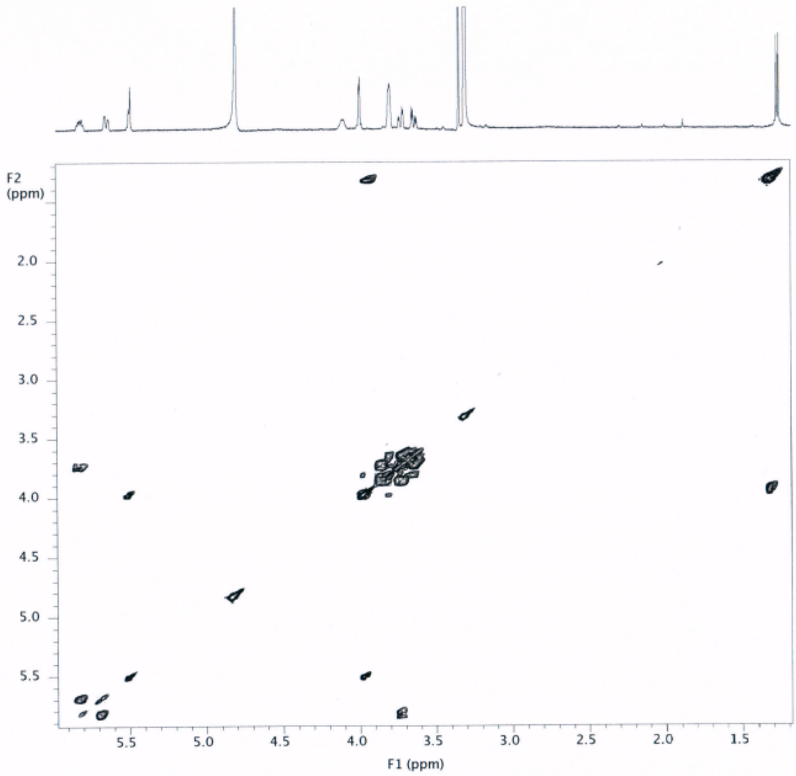


[1]H-NMR (CD_3OD, 500 MHz):
(*S*)-1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (2)

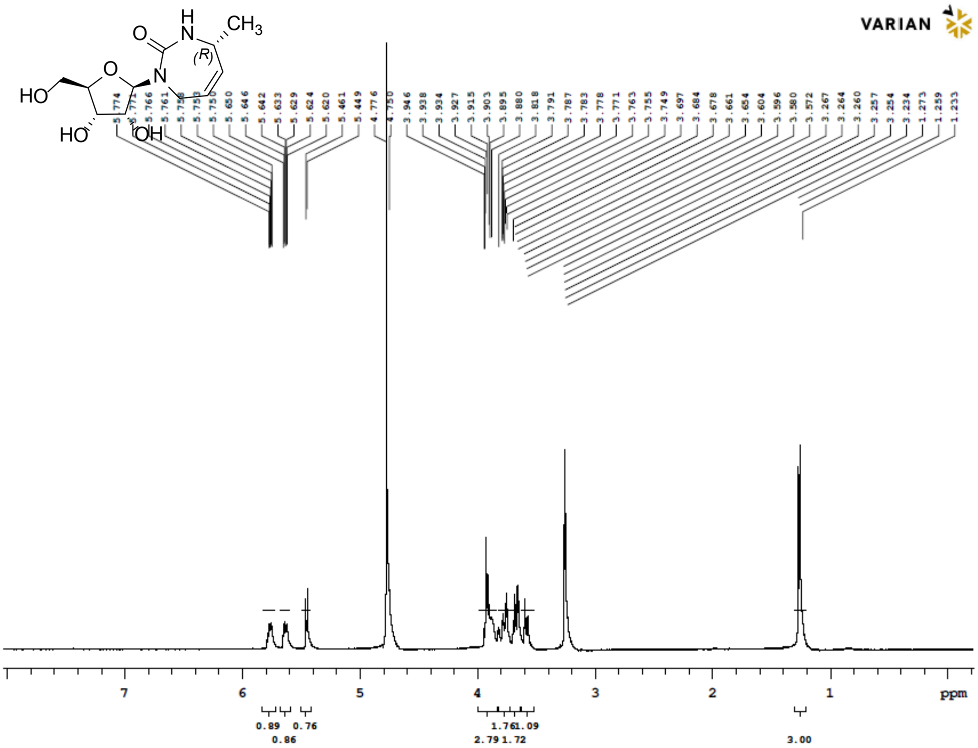


[13]C-NMR (CD_3OD, 125 MHz):
(*S*)-1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (2)

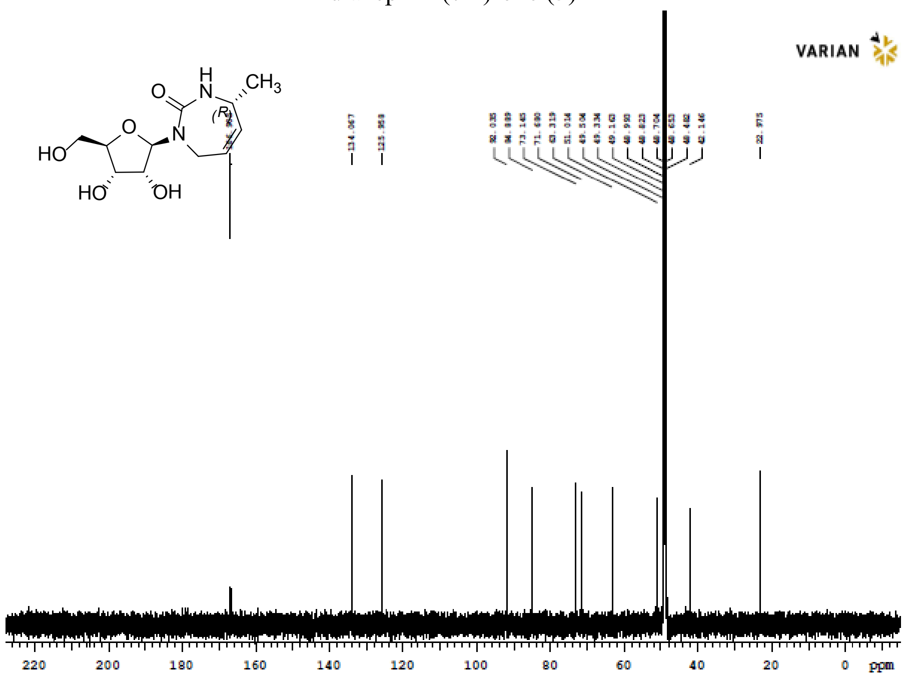




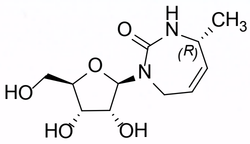
COSY- Spectra (CD_3OD, 500 MHz):
(*S*)-1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (2)

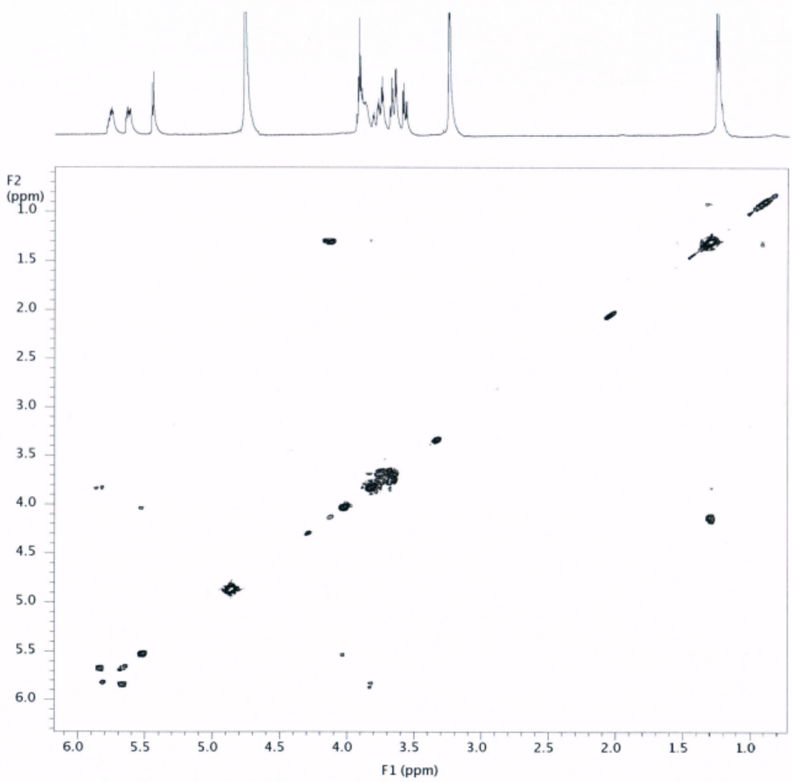


[1]H-NMR (CD_3OD, 500 MHz):
(*R*)-1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (3)



[13]C-NMR (CD_3OD, 125 MHz):
(*R*)-1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (3)





COSY- Spectra (CD_3OD, 500 MHz):
(*R*)-1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (3)