

New Building Block for Polyhydroxylated Piperidine: Total synthesis of 1,6-Dideoxynojirimycin

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SUPPORTING INFORMATION

1. General Procedures	S2
2. Synthesis and Spectroscopic Data	S2
3. NMR and Mass Spectrum	S5

General Procedures

All NMR spectra were obtained on a 300 MHz spectrometer. 2D experiments NOSEY and COSY were used to assist analysis of 1D spectra obtained on a 500 MHz spectrometer. All NMR experiments were run using standard routines. Flash column chromatography was performed using pre-packed silica gel columns. Thin layer chromatography was performed on commercially available glass-backed silica gel plates. Optical Rotations were measured using the Na-D line. All starting materials were dried in a vacuum for one day before use. All non-aqueous reactions were carried out under inert N₂ atmosphere, and reaction solvents were distilled according to standard procedures unless stated otherwise.

(S)-methyl 2-(tert-butoxycarbonylamino)propanoate (4). Prepared a suspension of L-alanine (5 g, 56.12 mmol) in (82.5 mL) of MeOH. Stirred, cooled to 0 °C. Carefully added (9 mL, 123.46 mmol) of SOCl₂ dropwise. The reaction mixture was then warmed to 40 °C. After 3.5 h, the reaction mixture was then cooled to rt. The solvent was removed by rotary evaporation to afford alanine ester hydrochloride (7.75 g, 99%) as a white solid. Dissolved (7 g, 50.15 mmol) of alanine ester hydrochloride in 1:1 mixture of THF/H₂O (167 mL), NaHCO₃ and Boc₂O were added consecutively stirred at room temperature for 7 h. The turbid solution was extracted with ether. The aqueous layer was acidified to pH = 4-5 by careful addition of sat. citric acid at 0 °C and then extracted with CH₂Cl₂. The combined organic phase was dried Na₂SO₄ and evaporated. The product was isolated by flash column chromatography (hexane: EtOAc = 80:20) to give 4 (9.3 g, 92%) as an yellow oil; [α]²⁰_D -3.4 (c 1, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 1.34 (3H, d, J = 7.2 Hz), 1.39 (9H, s), 3.69 (3H, s), 4.26 (1H, m), 5.26 (1H, brs, NH); ¹³C NMR (300 MHz; CDCl₃) δ 18.4, 28.2, 49.0, 52.1, 79.6, 155.0, 173.7; EI-MS (m/z) 203 (M⁺); HRMS calcd for C₉H₁₇NO₄ (M⁺) 203.1158, found 203.1159.

(S)-tert-butyl 1-hydroxypropan-2-ylcarbamate (5). To a suspension of (2.5 g, 66.40 mmol) LiAlH₄ in (128 mL) of dry THF. Stirred, cooled to 0 °C. Added a solution of **4** (9 g, 44.28 mmol) in (20 mL) of dry THF. After addition the reaction mixture was then brought to rt and quenched by the sequential addition

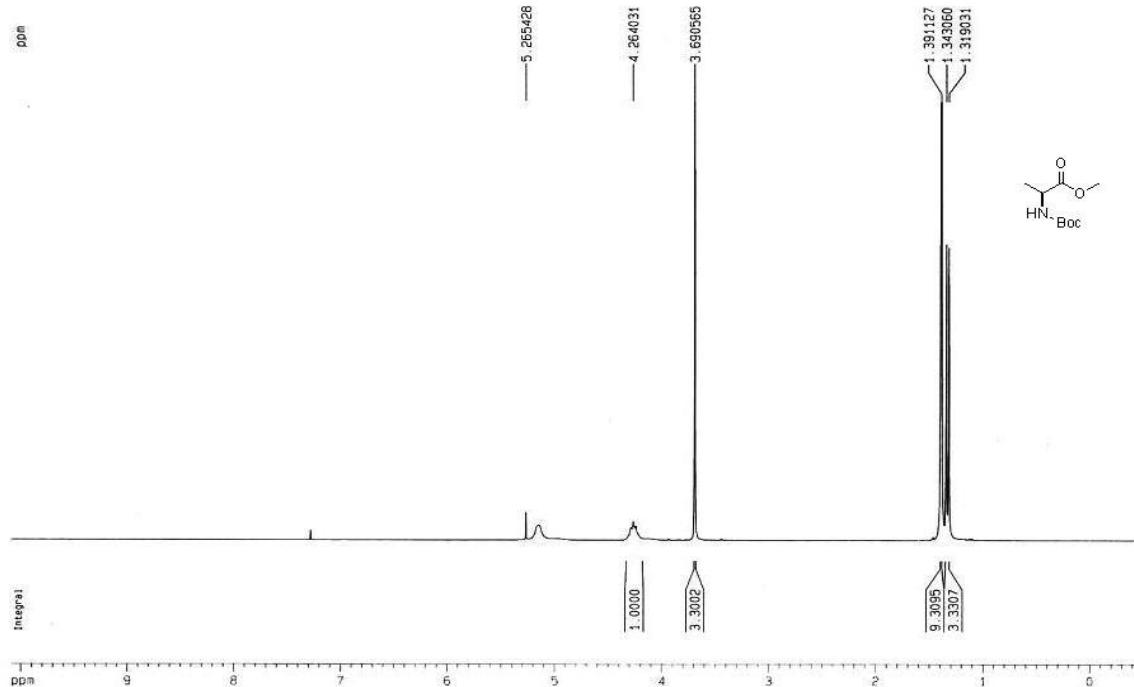
of 4.5 mL of H₂O, 4.5 mL of 15 % aq. NaOH and 12.5 mL of H₂O. The mixture was then poured into (150 mL) of Et₂O and stirred for 30 min. The insoluble material was removed by filtration through Celite and the solvent was removed from the filtrate by rotary evaporation dried over Na₂SO₄. The product was isolated by flash column chromatography on silica gel using (hexane: EtOAc = 70:30) to give **5** (7.50 g, 97%) as white solid; Mp 59-61 °C; [α]²⁰_D -9.3 (c 1, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 1.12 (3H, d, J = 6.7 Hz), 1.39 (9H, s), 3.48 (2H, m), 3.57 (1H, m), 5.0 (1H, brs, NH); ¹³C NMR (300 MHz; CDCl₃) δ 17.2, 28.3, 48.4, 66.5, 79.5, 156.3; EI-MS (m/z) (M⁺); HRMS calcd for C₈H₁₇NO₃ (M⁺) 175.1208, found 175.1209

(S)-tert-butyl 1-(tert-butyldimethylsilyloxy)propan-2-ylcarbamate (6). Dissolved (6 g, 34.24 mmol) of **5** and (6.99 g, 102.72 mmol) of imidazole in (114 mL) of CH₂Cl₂. Stirred at rt. Added (10.3 g, 68.48 mmol) of TBDMSCl and stirred overnight. After 16 h, quenched with sat aq. NH₄Cl Extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel using (hexane: EtOAc = 80:20) to give **6** (9.8 g, 99%) as colorless oil; [α]²⁰_D -20.2 (c 1, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 0.04 (6H, s), 0.89 (9H, s), 1.13 (3H, d, J = 6.6 Hz), 1.44 (9H, s), 3.52 (2H, m), 3.57 (1H, brs); ¹³C NMR (300 MHz; CDCl₃) δ -8.0, 15.0, 15.7, 23.3, 25.8, 45.1, 63.6, 76.4, 152.8; FAB-MS obsd 290.2832, calcd 290.2151 [(M+H)⁺, M = C₁₄H₃₁NO₃Si].

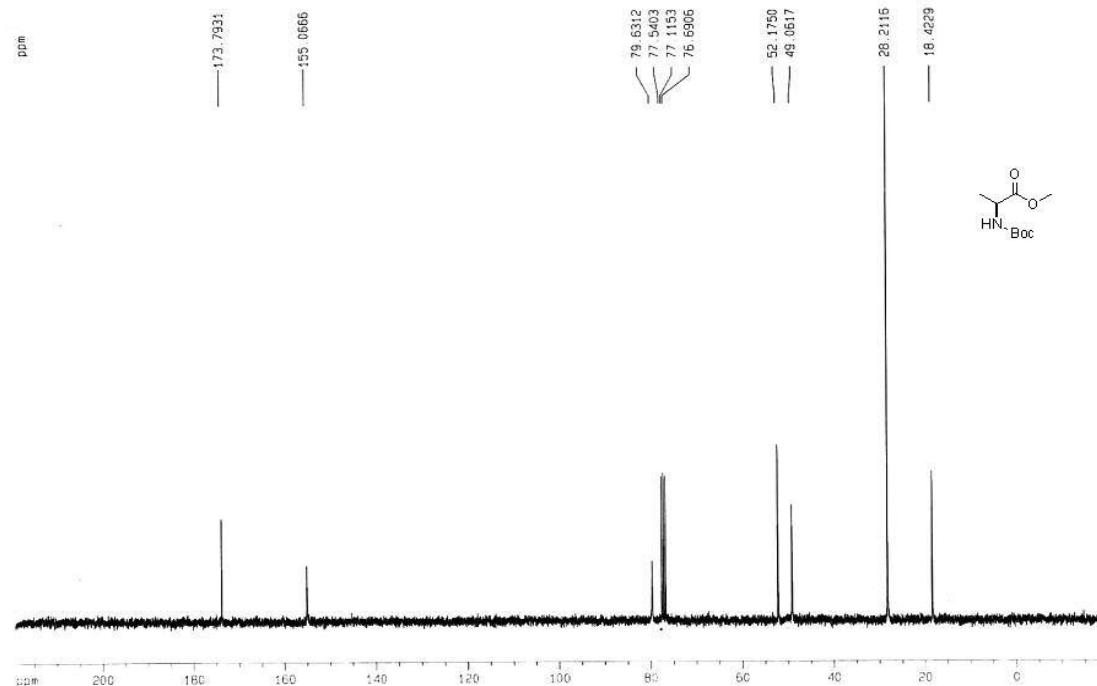
(S)-tert-butyl allyl(1-(tert-butyldimethylsilyloxy)propan-2-yl)carbamate (7). To a stirred solution of (0.99 g, 41.49 mmol) NaH in (118 mL) of dry DMF. Stirred, cooled to 0 °C. Added as solution of **6** (8 g, 27.66 mmol) in (20 mL) of dry DMF dropwise. Stirred for 15 min. Added (7.69 mL, 63.60 mmol) of allylbromide and allowed the reaction mixture to slowly warm to room temperature. After 24 h the reaction was quenched with H₂O, sat. aq. NH₄Cl and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered and the solvent was removed by rotary evaporation. The product was purified by flash column chromatography (hexane: EtOAc = 90:10) to give **7** (6.7 g, 74%) as colorless oil; [α]²⁰_D -

6.5 (c 1, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 0.06 (6H, s), 0.88 (9H, s), 1.13 (3H, d, J = 6.9 Hz), 1.44 (9H, s), 3.55 (2H, m), 3.37 (2H, brs), 5.06 (3H, m), 5.66 (1H, m), 3.84 (2H, m); ¹³C NMR (300 MHz; CDCl₃) δ 18.1, 25.8, 28.4, 65.2, 114.9, 117.1, 118.4, 135.5, 155.4; FAB-MS obsd 330.2508, calcd 330.2464 [(M+H)⁺, M = C₁₇H₃₅NO₃Si].

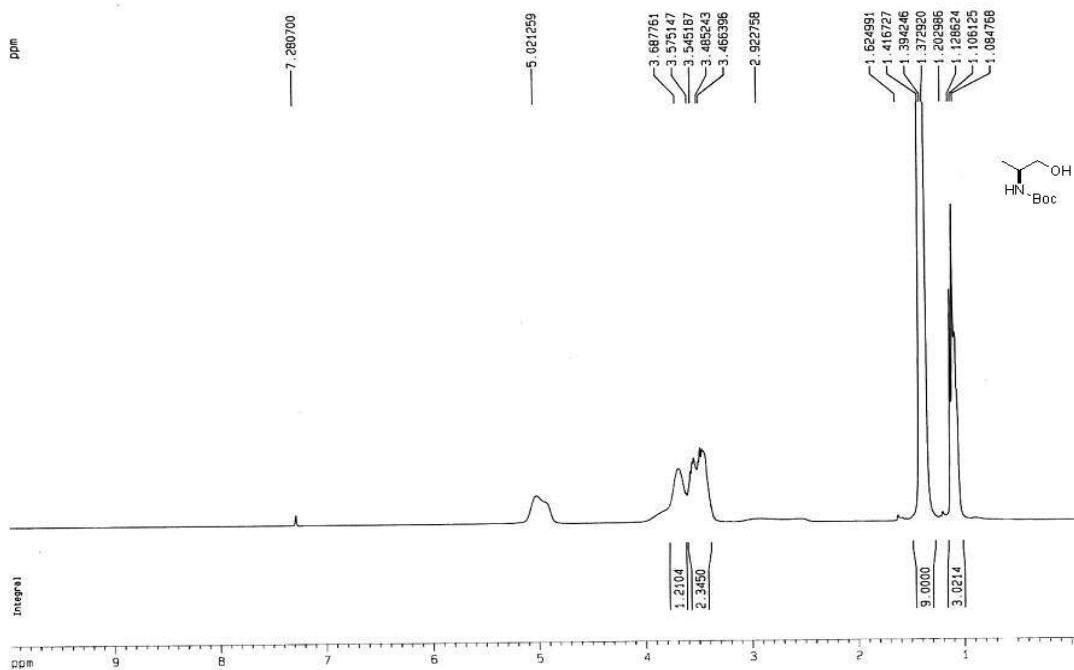
***tert*-butyl allyl(S)-1-hydroxypropan-2-ylcarbamate (8).** Dissolved (5.5 g, 16.68 mmol) of **7** in (10 mL) of THF. Added (33 mL, 33.36 mmol) of TBAF (1.0 M in THF). After 3 h, quenched with sat. aq. NH₄Cl. Extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered and the solvent was removed by rotary evaporation. The product was isolated by flash column chromatography on silica gel using (hexane: EtOAc = 70:30) to give **8** (3.38 g, 94%) as colorless oil; [α]²⁰_D +6.2 (c 1, CHCl₃); ¹H NMR (300 MHz; CDCl₃) δ 1.13 (3H, d, J = 6.9 Hz), 1.42 (9H, s), 3.56 (2H, brs), 3.72 (2H, brs), 3.99 (1H, brs), 5.09 (2H, m), 5.82 (1H, m); ¹³C NMR (300 MHz; CDCl₃) δ 14.7, 28.3, 46.9, 53.8, 65.0, 79.8, 115.7, 135.6, 156.2; EI-MS (m/z) 215 (M⁺); HRMS calcd for C₁₁H₂₁NO₃ (M⁺) 215.1521, found 215.1522.



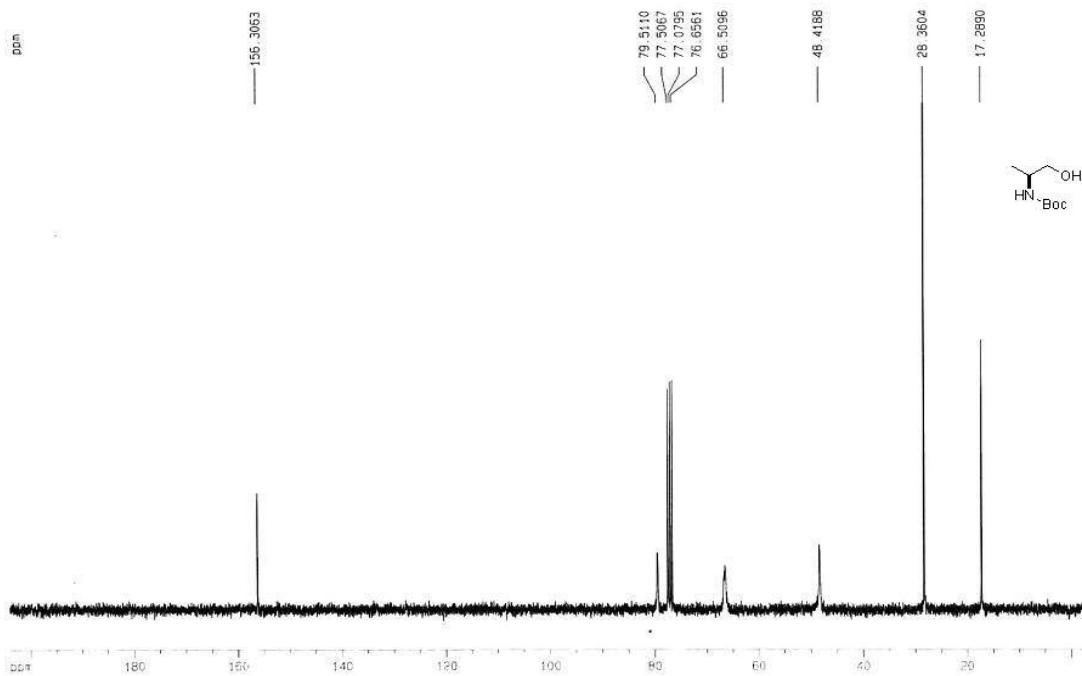
Spectra 1. ^1H NMR(300 MHz, CDCl_3) of (S)-methyl 2-(*tert*-butoxycarbonylamino)propanoate (4)



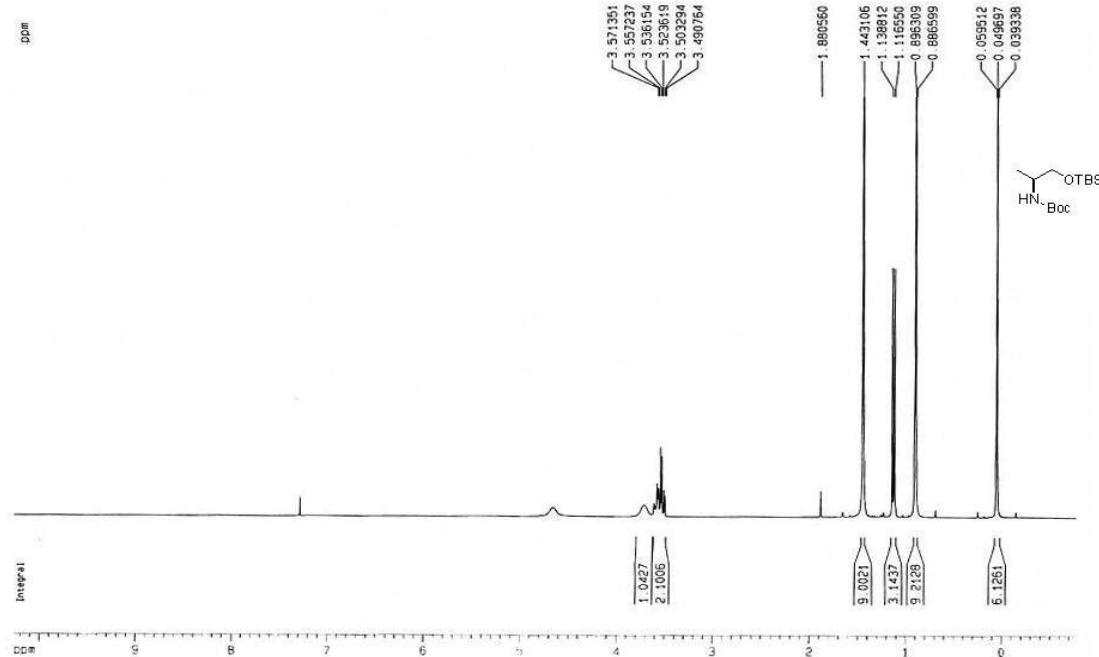
Spectra 2. ^{13}C NMR (300 MHz, CDCl_3) of (S)-methyl 2-(*tert*-butoxycarbonylamino)propanoate (4)



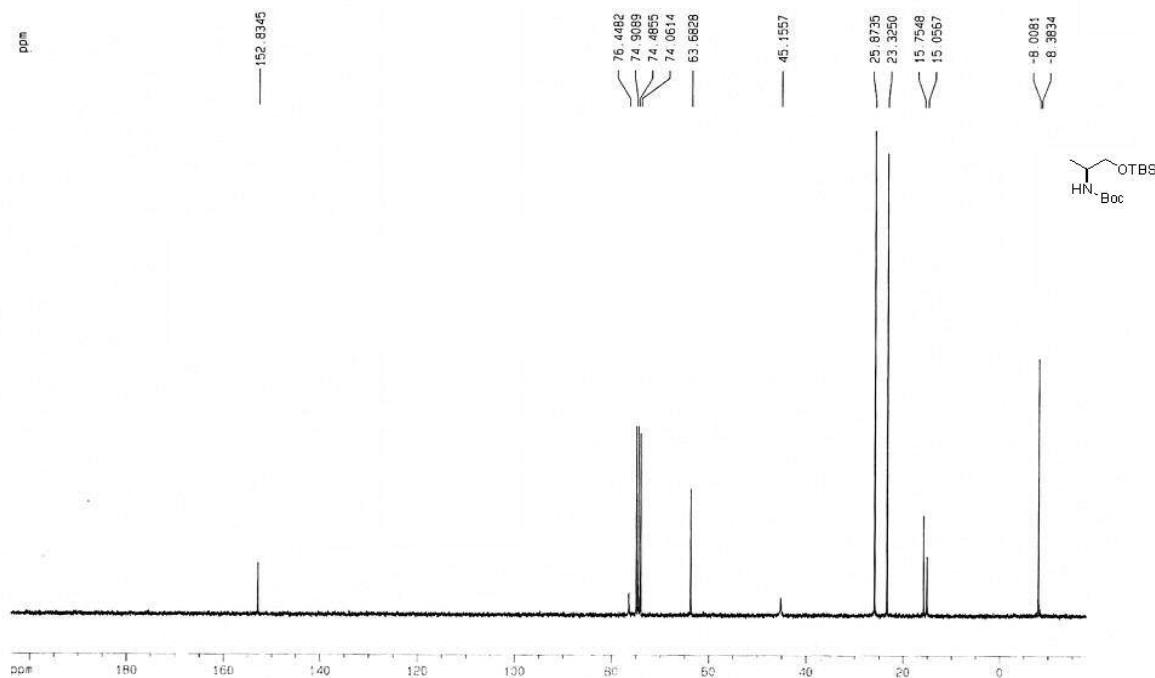
Spectra 3. ^1H NMR (300 MHz, CDCl_3) of (S)-*tert*-butyl 1-hydroxypropan-2-ylcarbamate (5)



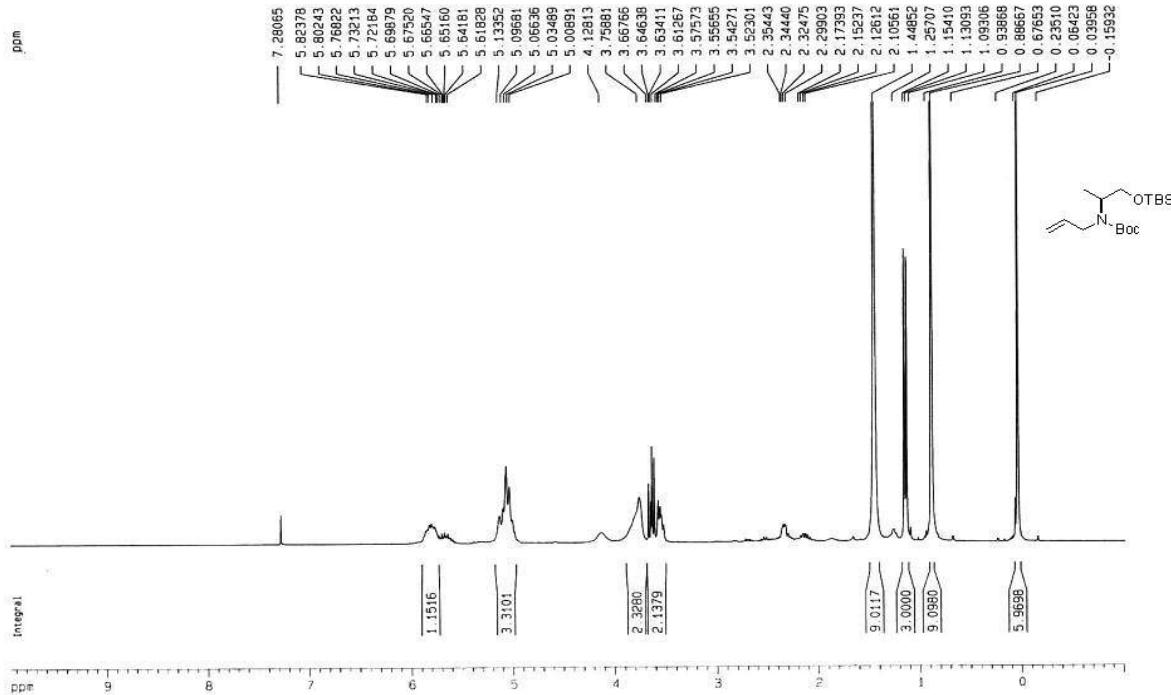
Spectra 4. ^{13}C NMR (300 MHz, CDCl_3) of (S)-*tert*-butyl 1-hydroxypropan-2-ylcarbamate (5)



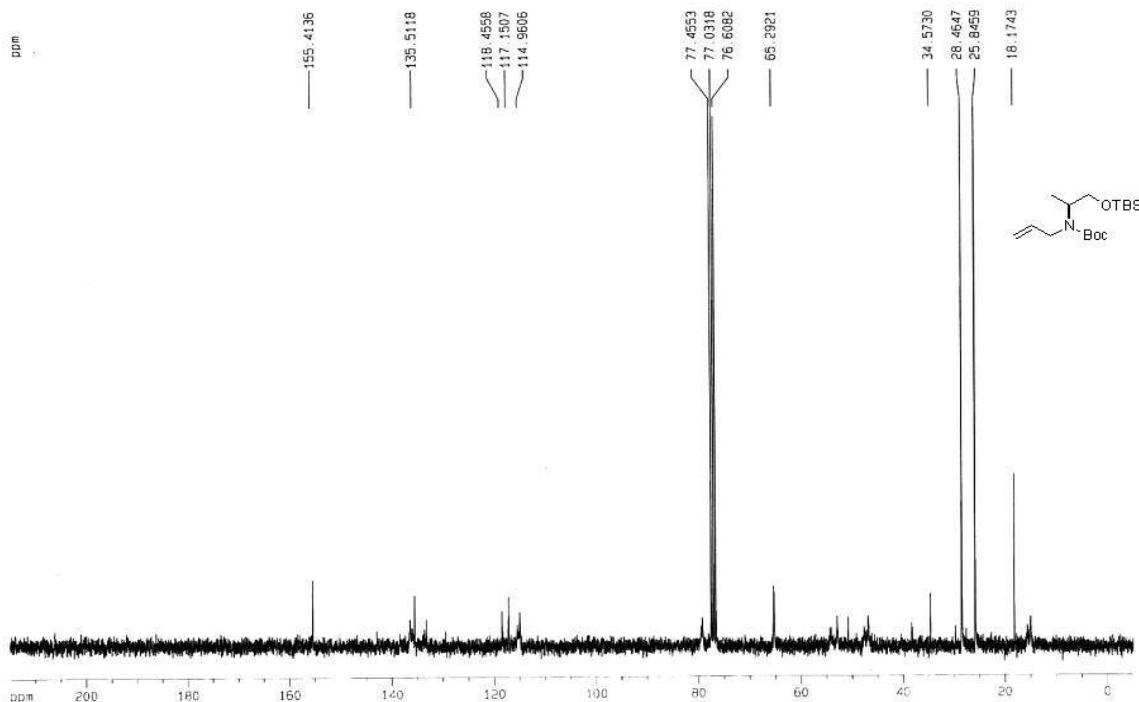
Spectra 5. ^1H NMR (300 MHz, CDCl_3) of (S)-*tert*-butyl 1-(*tert*-butyldimethylsilyloxy)propan-2-ylcarbamate (**6**)



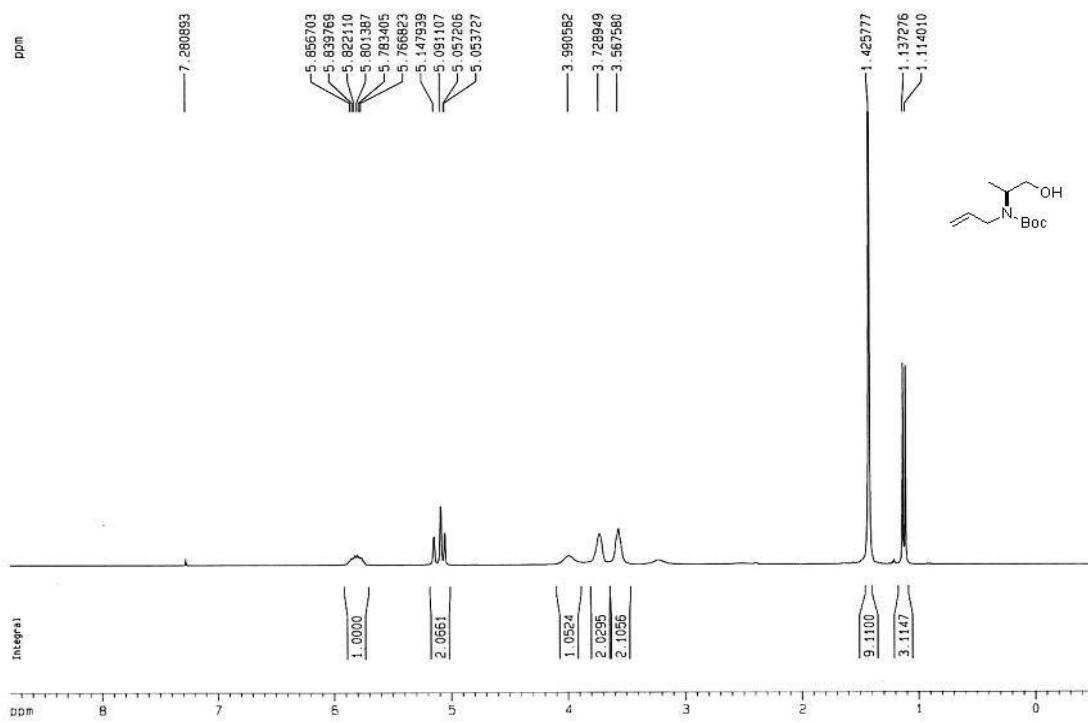
Spectra 6. ^{13}C NMR (300 MHz, CDCl_3) of (S)-*tert*-butyl 1-(*tert*-butyldimethylsilyloxy)propan-2-ylcarbamate (**6**)



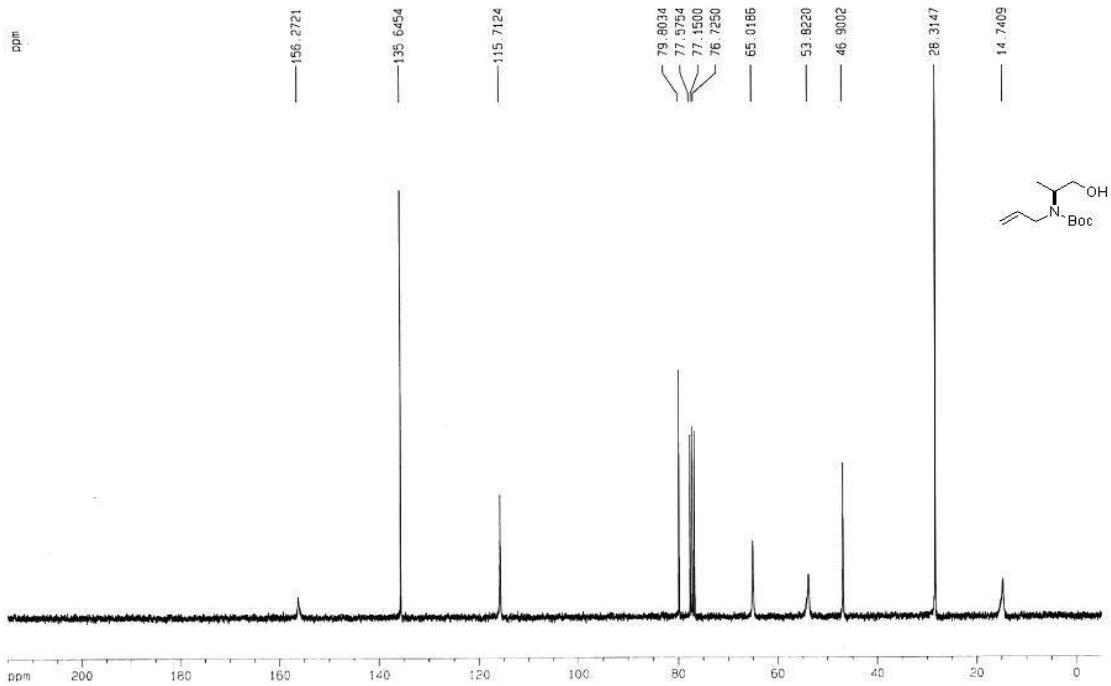
Spectra 7. ^1H NMR (300 MHz, CDCl_3) of (*S*)-*tert*-butyl allyl(1-(*tert*-butyldimethylsilyloxy)propan-2-yl)carbamate (7)



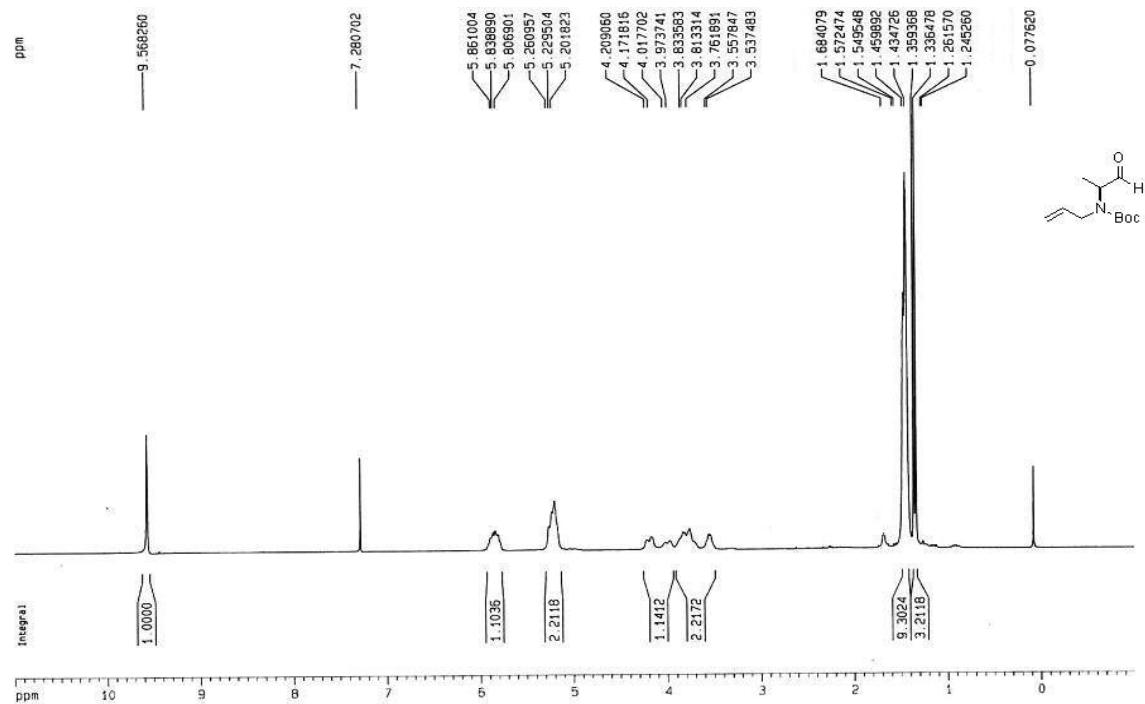
Spectra 8. ^{13}C NMR (300 MHz, CDCl_3) of (*S*)-*tert*-butyl allyl [1-(*tert*-butyldimethylsilyloxy)propan-2-yl] carbamate (7)



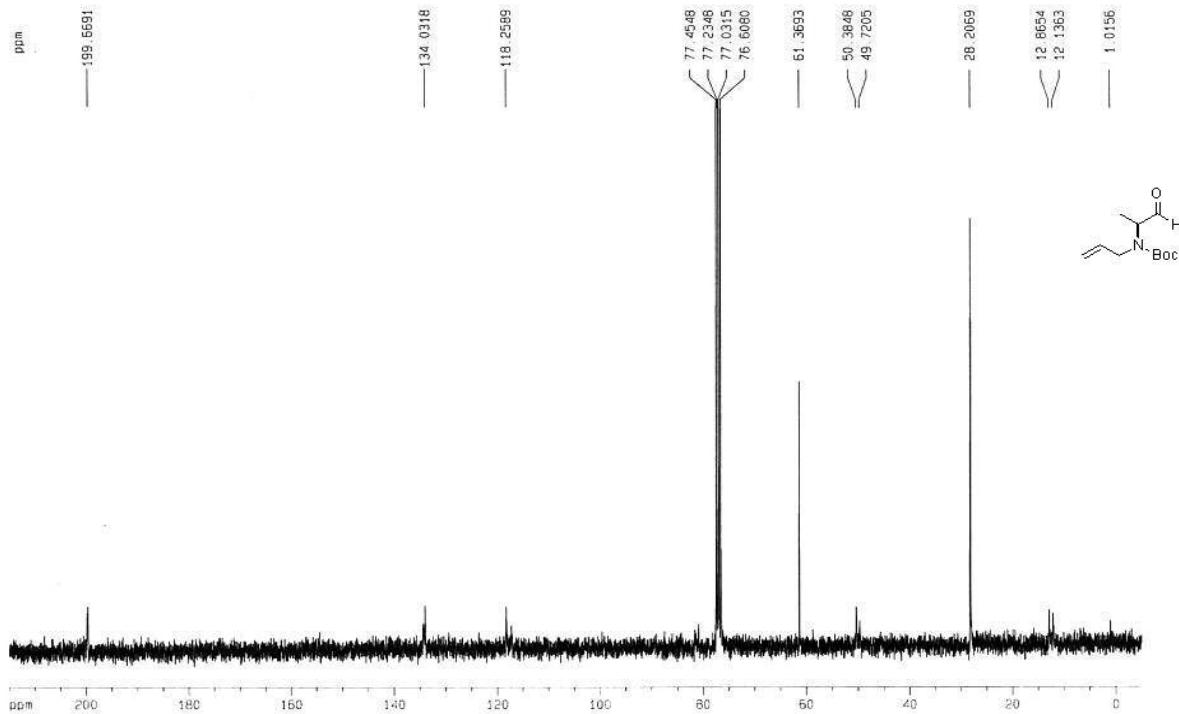
Spectra 9. ^1H NMR (300 MHz, CDCl_3) of (S)-*tert*-butyl allyl(1-hydroxypropan-2-yl)carbamate (8)



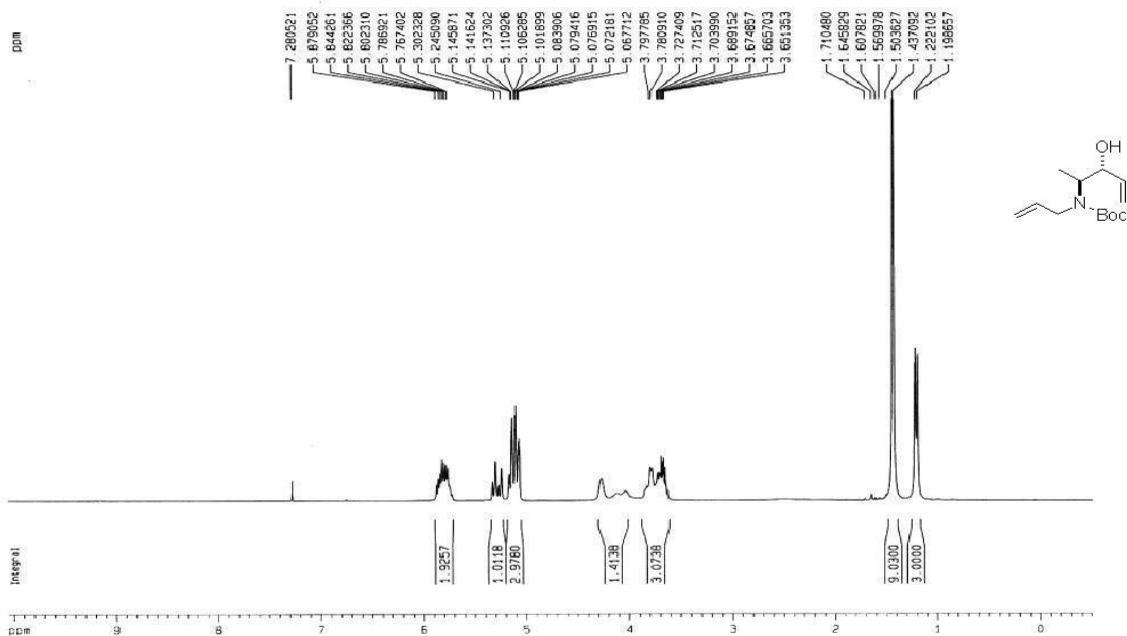
Spectra 10. ^{13}C NMR (300 MHz, CDCl_3) of (S)-*tert*-butyl allyl(1-hydroxypropan-2-yl)carbamate (8)



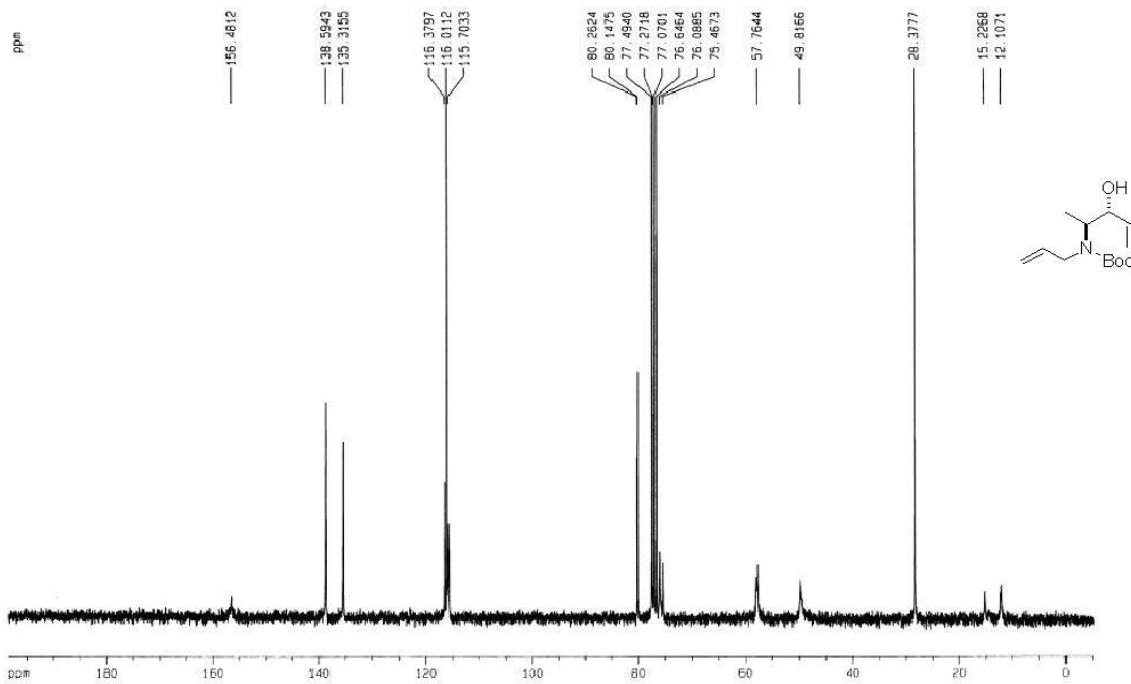
Spectra 11. ^1H NMR (300 MHz, CDCl_3) of (S)-*tert*-butyl allyl(1-oxopropan-2-yl)carbamate (9)



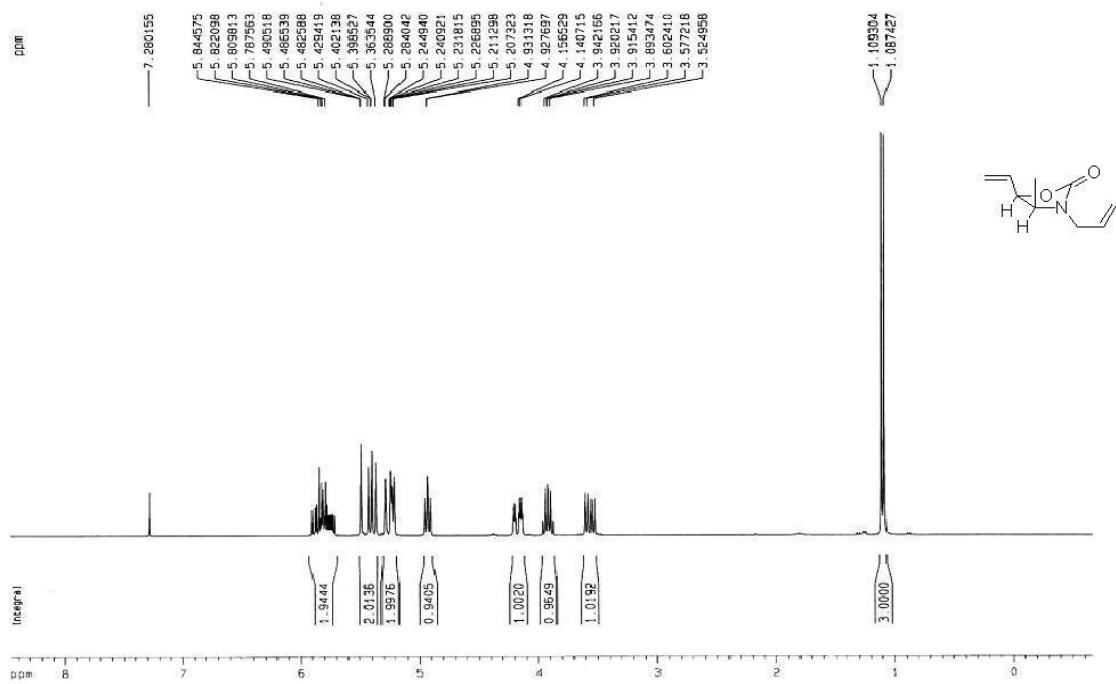
Spectra 12. ^{13}C NMR (300 MHz, CDCl_3) of (S)-*tert*-butyl allyl(1-oxopropan-2-yl)carbamate (9)



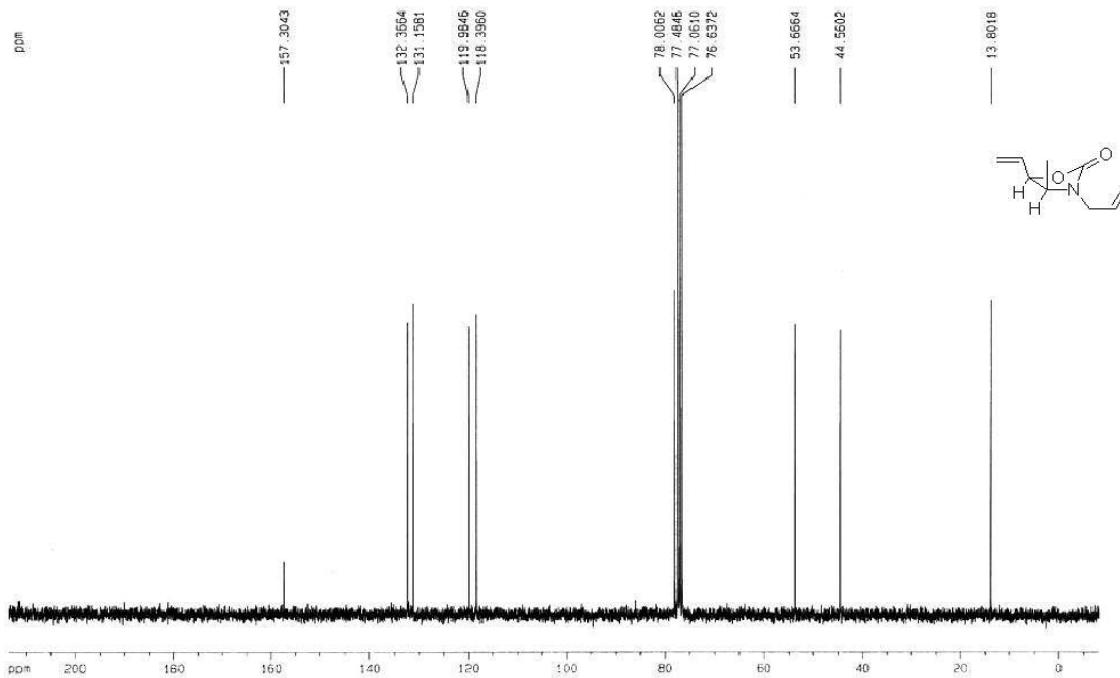
Spectra 13. ^1H NMR (300 MHz, CDCl_3) of *tert*-butyl allyl[(2*S*,3*R*)-3-hydroxypent-4-en-2-yl] carbamate (10)



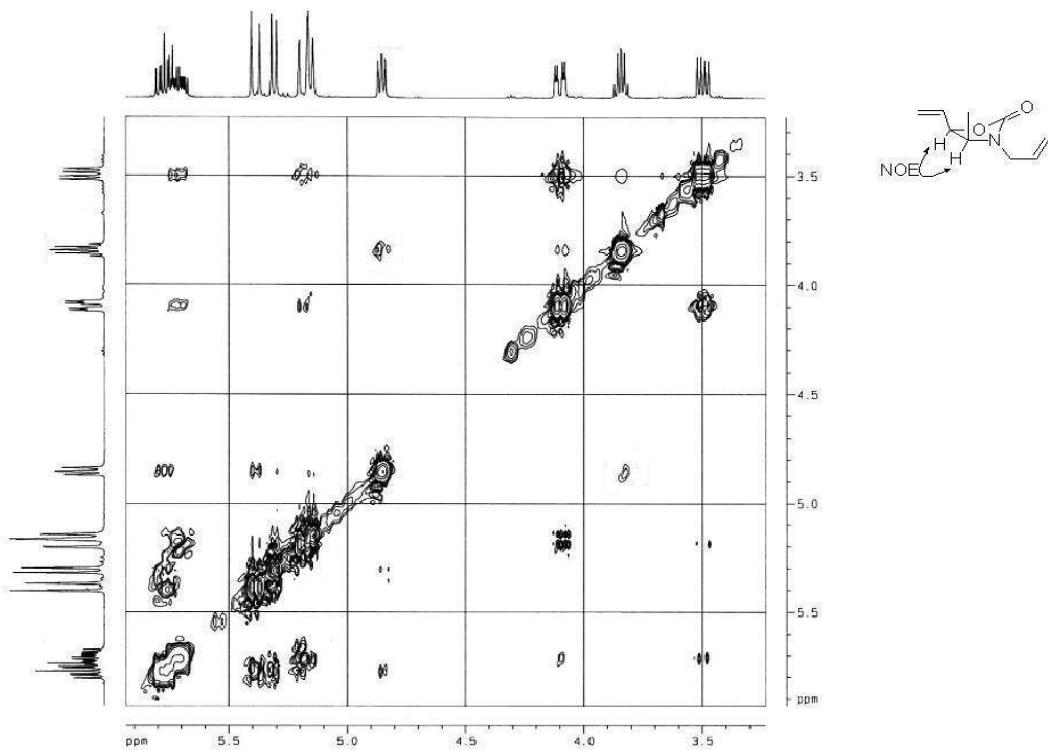
Spectra 14. ^{13}C NMR (300 MHz, CDCl_3) of *tert*-butyl allyl[(2*S*,3*R*)-3-hydroxypent-4-en-2-yl] carbamate (10)



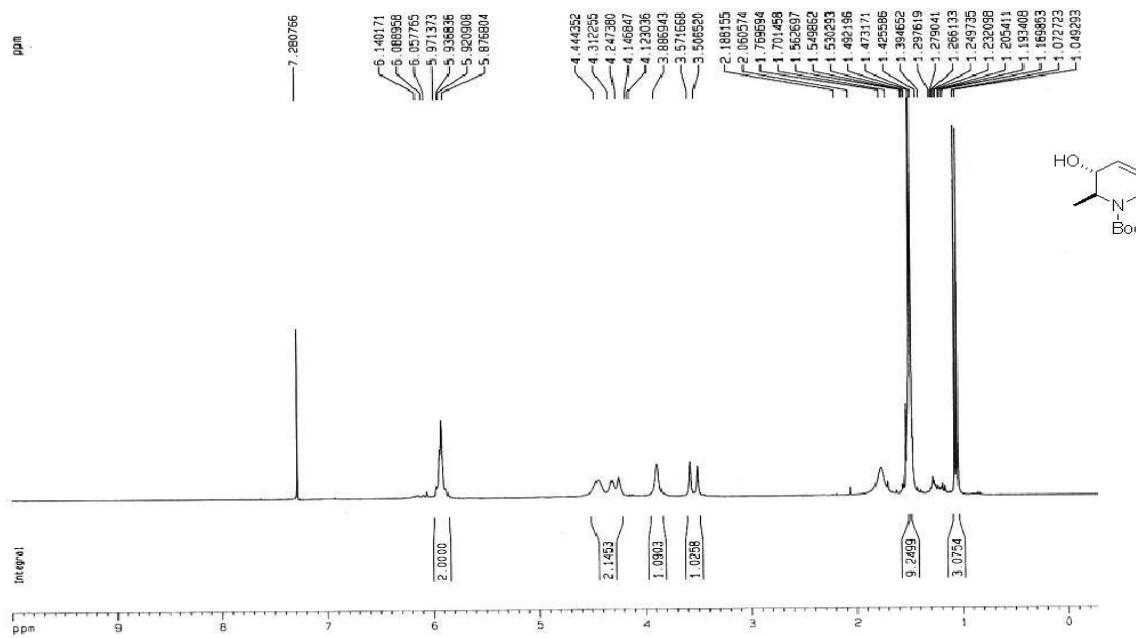
Spectra 15. ^1H NMR (300 MHz, CDCl_3) of (4S,5R)-3-allyl-4-methyl-5-vinyloxazolidin-2-one (11)



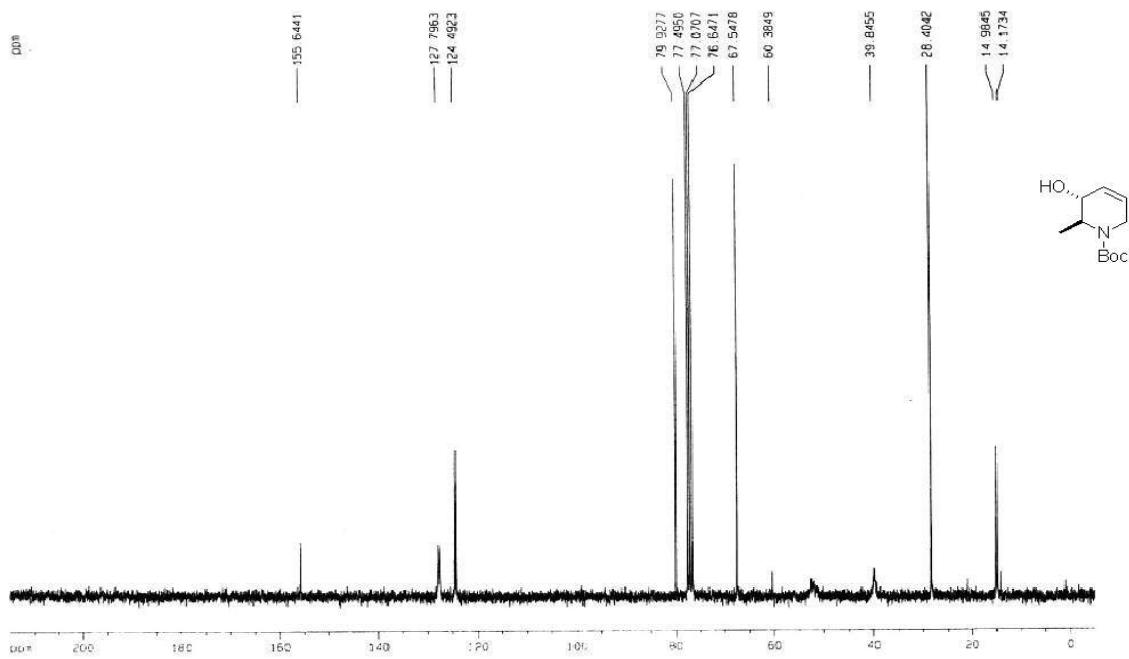
Spectra 16. ^{13}C NMR (300 MHz, CDCl_3) of (4S,5R)-3-allyl-4-methyl-5-vinyloxazolidin-2-one (11)



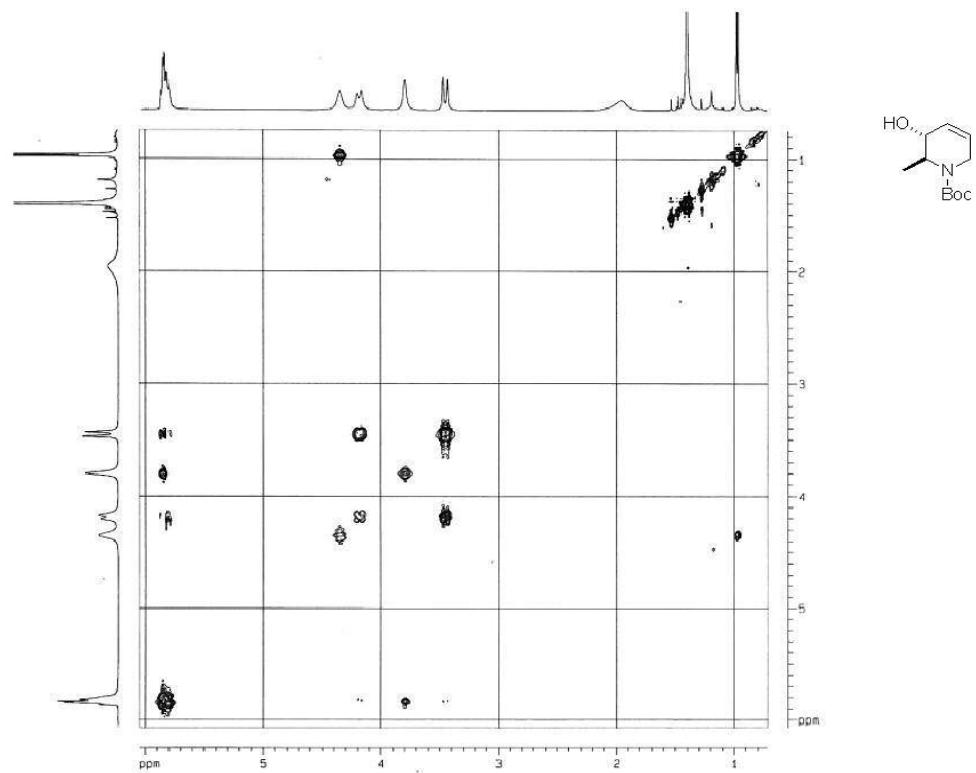
Spectra 17. NOESY (300 MHz, CDCl_3) of (4*S*,5*R*)-3-allyl-4-methyl-5-vinyloxazolidin-2-one (11)



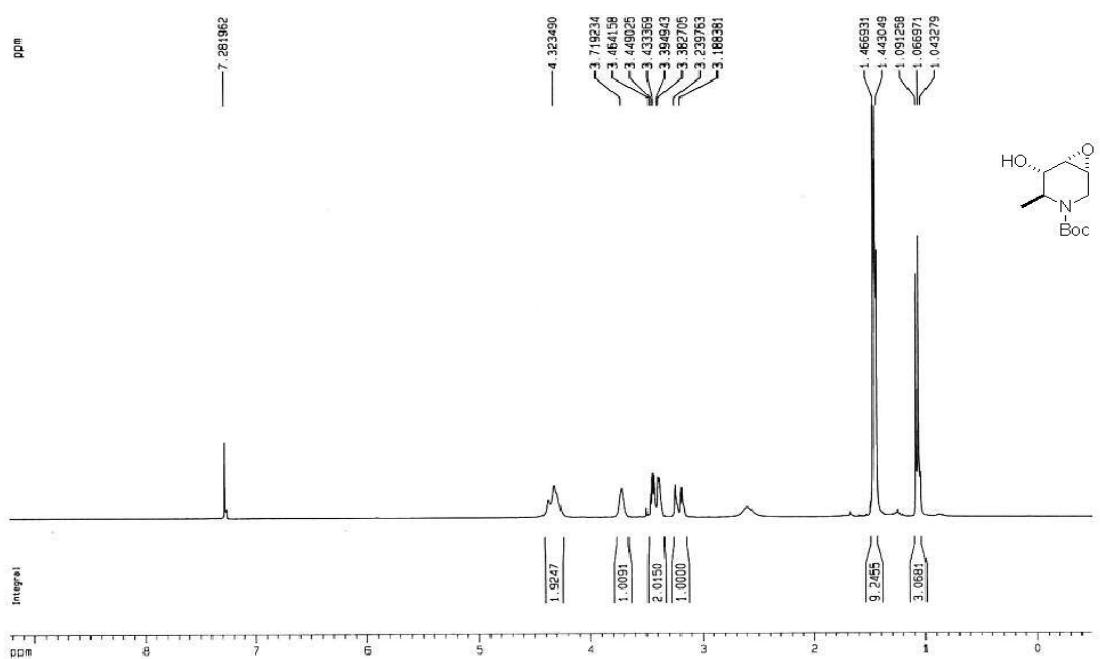
Spectra 18. ^1H NMR (300 MHz, CDCl_3) of (5*R*,6*S*)-*tert*-butyl-5-hydroxy-6-methyl-5,6-dihydropyridine-1(2*H*)-carbamate (13)



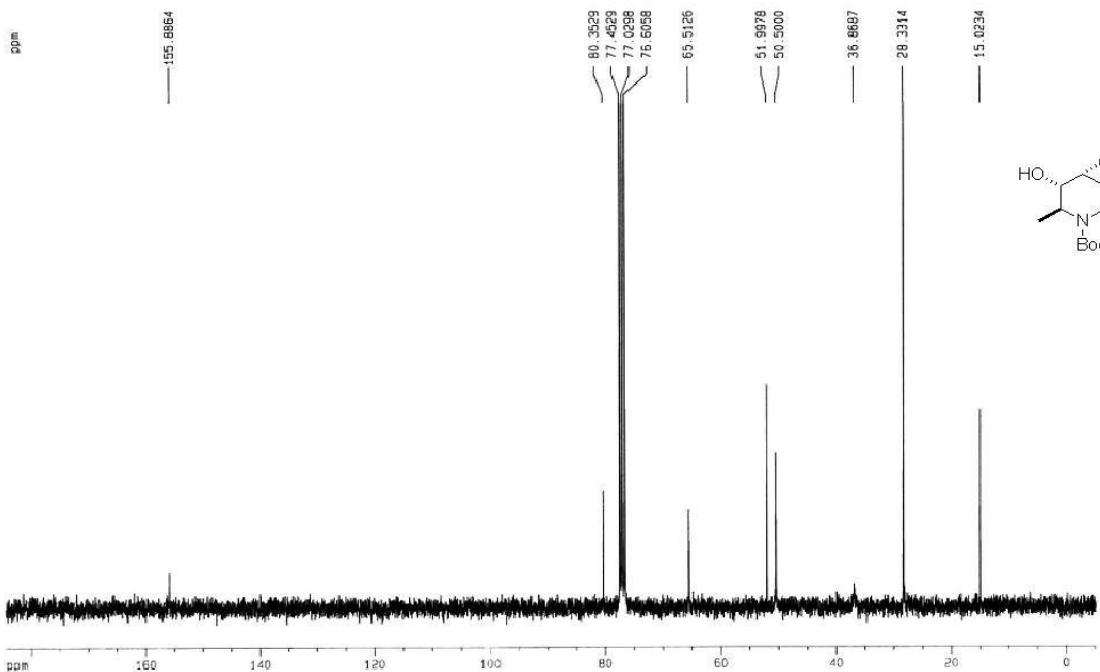
Spectra 19. ^{13}C NMR (300 MHz, CDCl_3) of (5*R*,6*S*)-*tert*-butyl 5-hydroxy-6-methyl-5,6-dihydropyridine-1(2*H*)-carbamate (13)



Spectra 20. HOMO COESY (300 MHz, CDCl_3) of (5*R*,6*S*)-*tert*-butyl 5-hydroxy-6-methyl-5,6-dihydropyridine-1(2*H*)-carbamate (13)



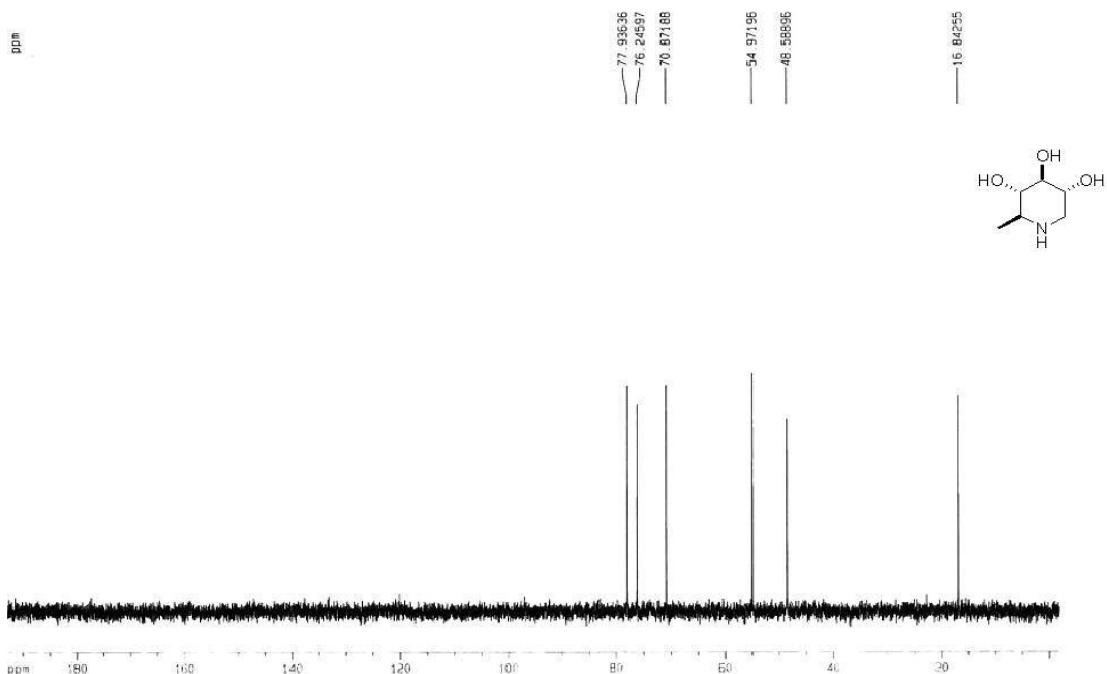
Spectra 21. ^1H NMR (300 MHz, CDCl_3) of (1*R*,4*S*,5*S*,6*S*)-*tert*-butyl-5-hydroxy-4-methyl-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carbamate (15)



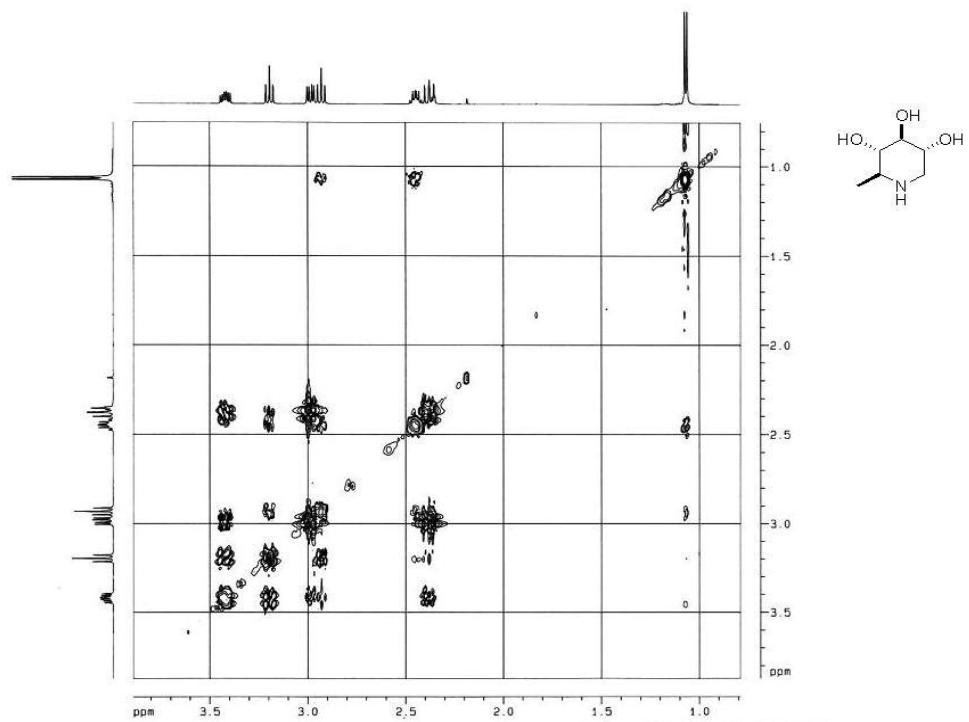
Spectra 22. ^{13}C NMR (300 MHz, CDCl_3) of (1*R*,4*S*,5*S*,6*S*)-*tert*-butyl-5-hydroxy-4-methyl-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carbamate (15)



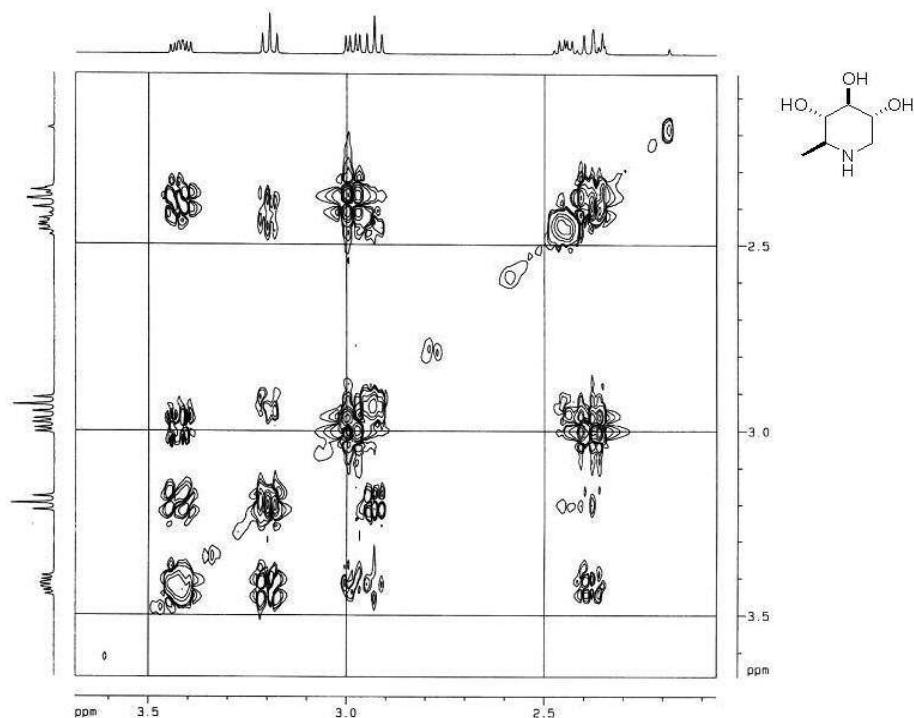
Spectra 23. ^1H NMR (300 MHz, D_2O) of (2*S*,3*S*,4*S*,5*R*)-2-methylpiperidine-3,4,5-triol (1)



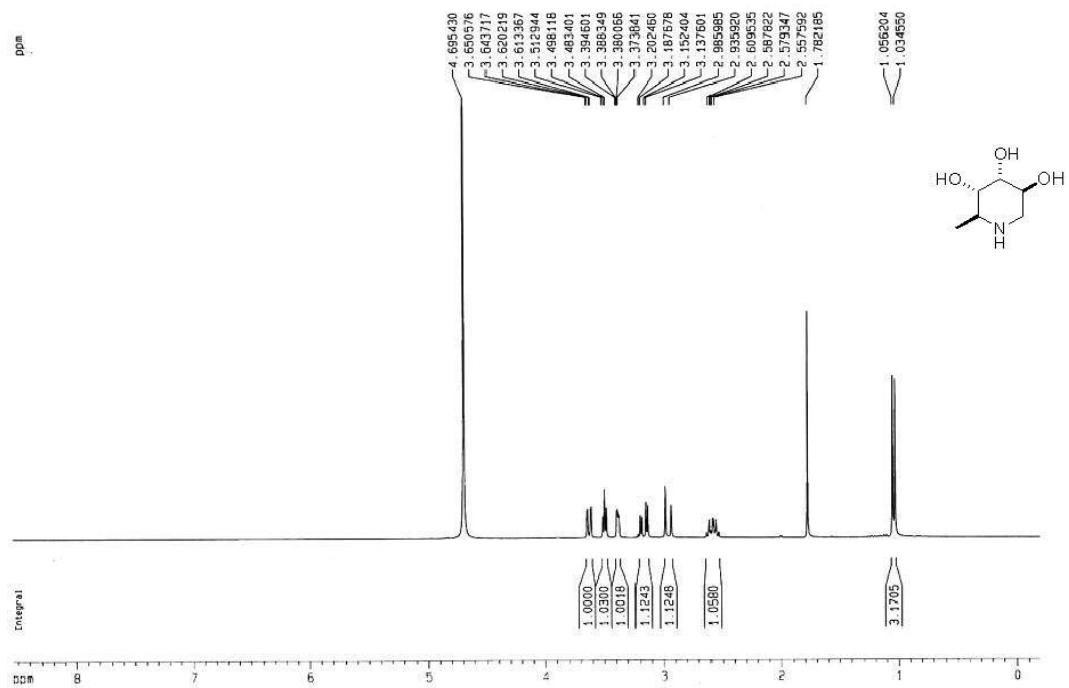
Spectra 24. ^{13}C NMR (300 MHz, D_2O) of (2*S*,3*S*,4*S*,5*R*)-2-methylpiperidine-3,4,5-triol (1)



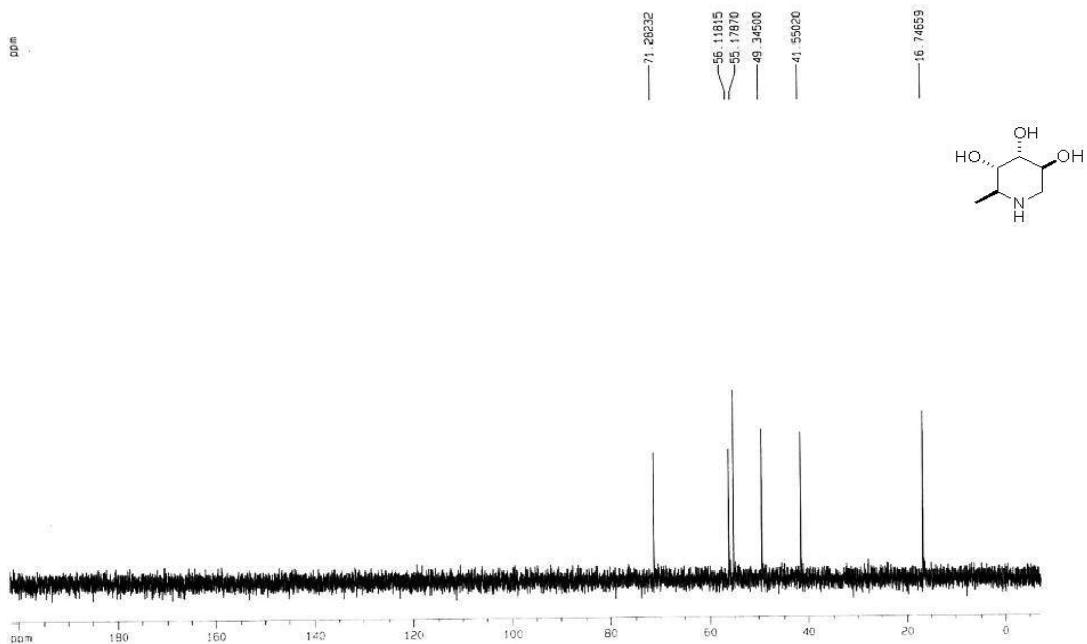
Spectra 25. NOESY (300 MHz, D_2O) of (2*S*,3*S*,4*S*,5*R*)-2-methylpiperidine-3,4,5-triol (1)



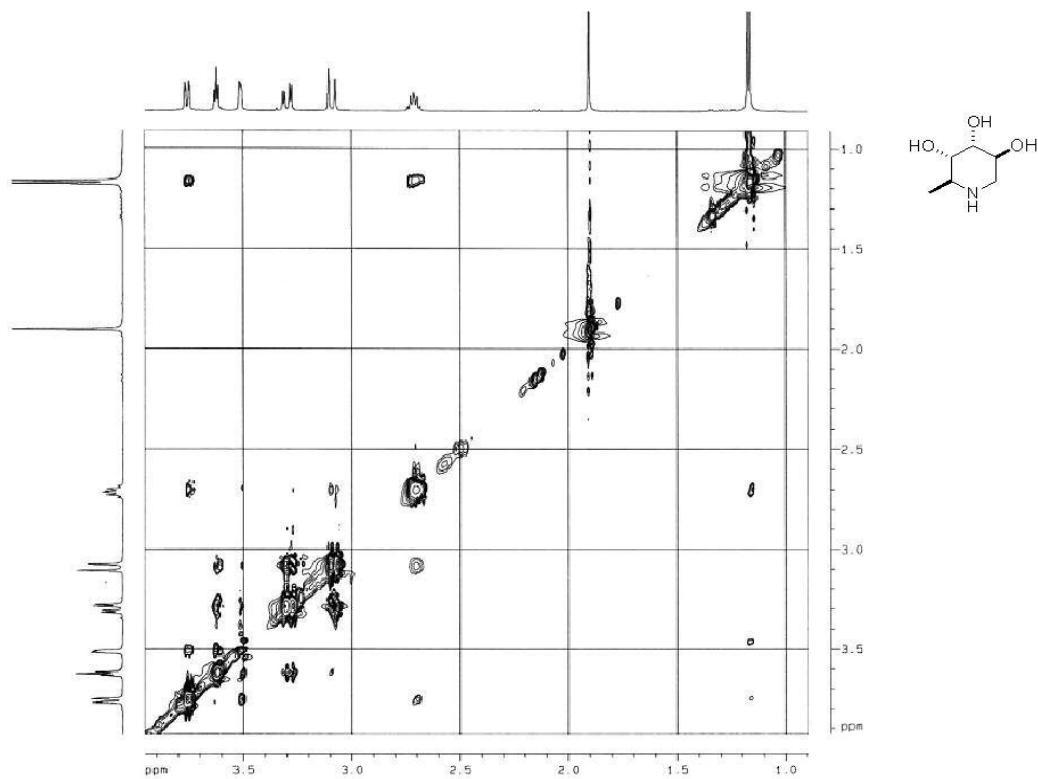
Spectra 26. Expanded NOESY (300 MHz, D_2O) of (2*S*,3*S*,4*S*,5*R*)-2-methylpiperidine-3,4,5-triol (1)



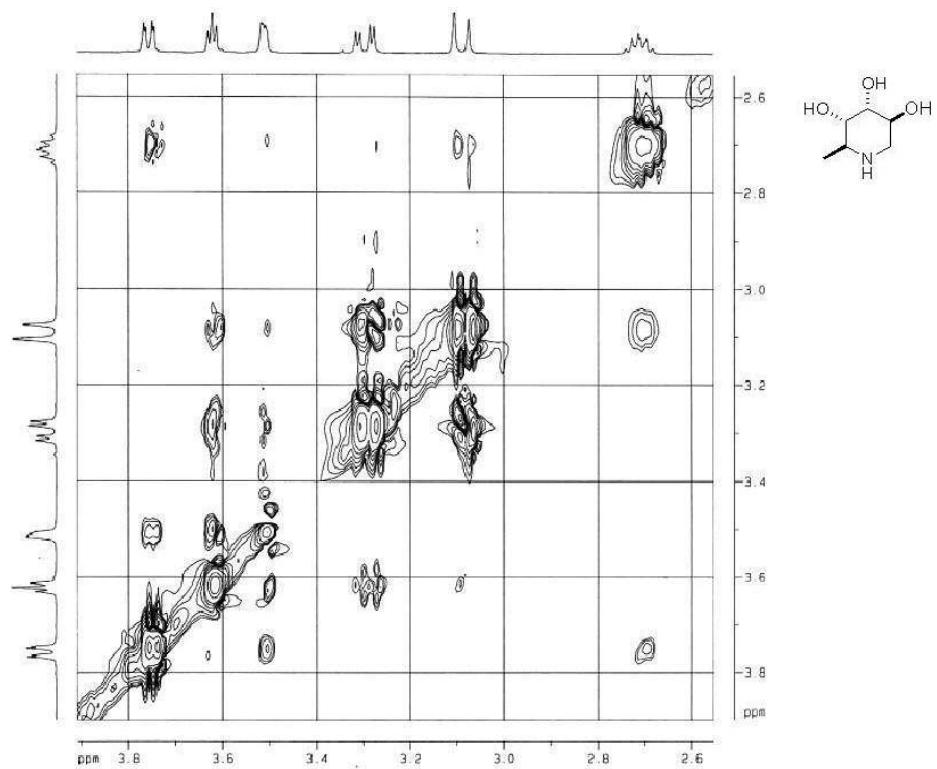
Spectra 27. ^1H NMR (300 MHz, D_2O) of (2*S*,3*S*,4*R*,5*S*)-2-methylpiperidine-3,4,5-triol (2)



Spectra 28. ^{13}C NMR (300 MHz, D_2O) of (2*S*,3*S*,4*R*,5*S*)-2-methylpiperidine-3,4,5-triol (2)



Spectra 29. NOESY (300 MHz, D₂O) of (2*S*,3*S*,4*R*,5*S*)-2-methylpiperidine-3,4,5-triol (2)



Spectra 30. Expanded NOESY (300 MHz, D₂O) of (2*S*,3*S*,4*R*,5*S*)-2-methylpiperidine-3,4,5-triol (2)

[Elemental Composition]

Data : A_triol

Date : 19-Sep-2007 15:19

Sample: -

Note : -

Inlet : Direct

Ion Mode : EI+

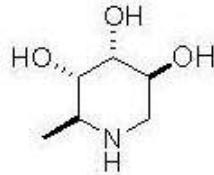
RT : 1.35 min

Scan#: 28

Elements : C 100/1, H 100/1, N 10/1, O 10/1

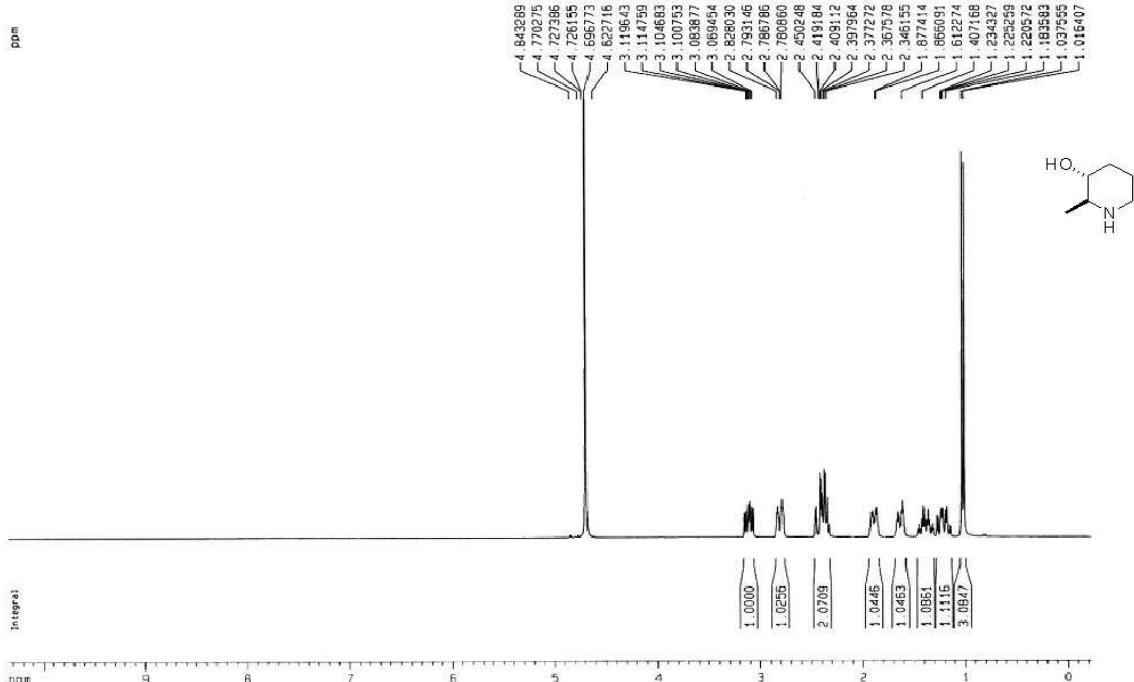
Mass Tolerance : 1000ppm, 5mmu if m/z > 5

Unsaturation (U.S.) : 0.0 - 30.0

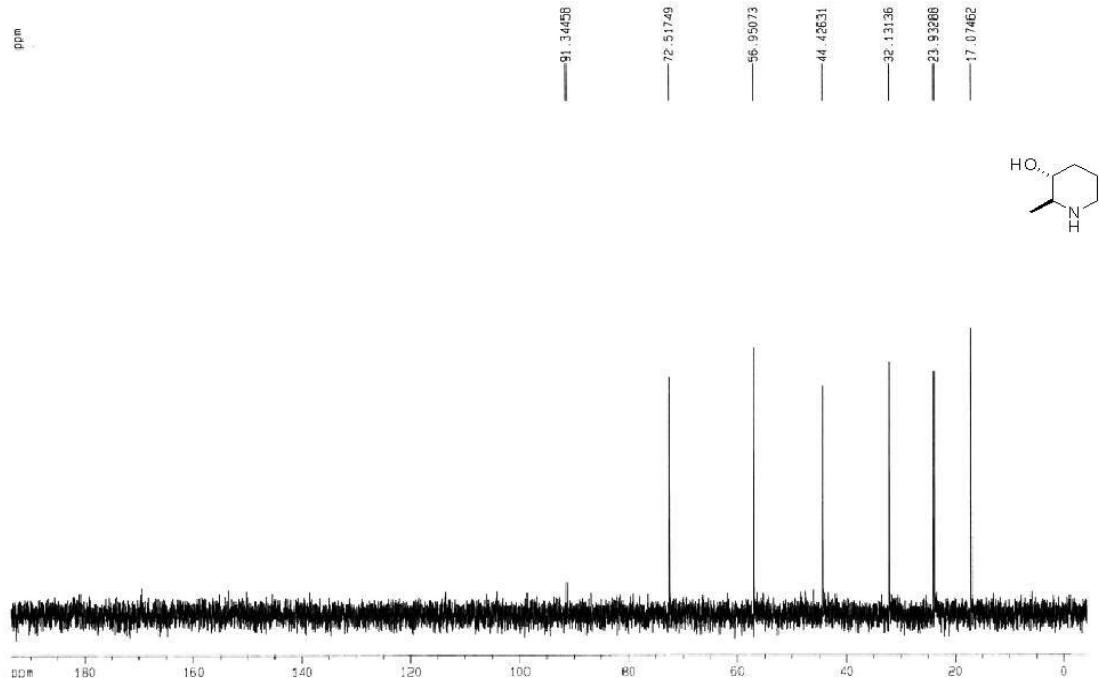


Observed m/z	Int%	Err [ppm / mmu]	U.S.	Composition
147.0895	100.0	+17.9 / +2.6	2.0	C 2 H 9 N 7 O
		+8.8 / +1.3	1.5	C 4 H 11 N 4 O 2
		→ -0.3 / -0.1	1.0	C 6 H 13 N O 3

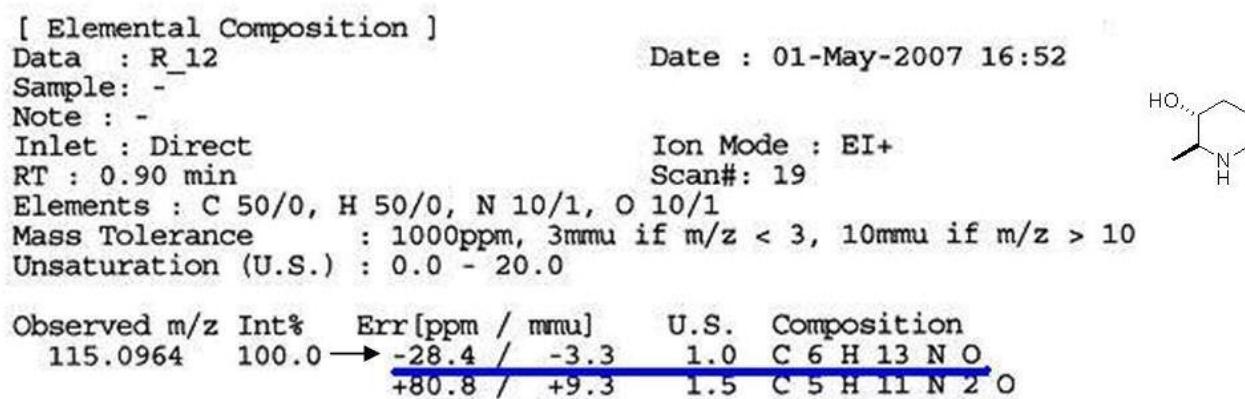
Spectra 31. HR mass of (2S,3S,4R,5S)-2-methylpiperidine-3,4,5-triol (2)



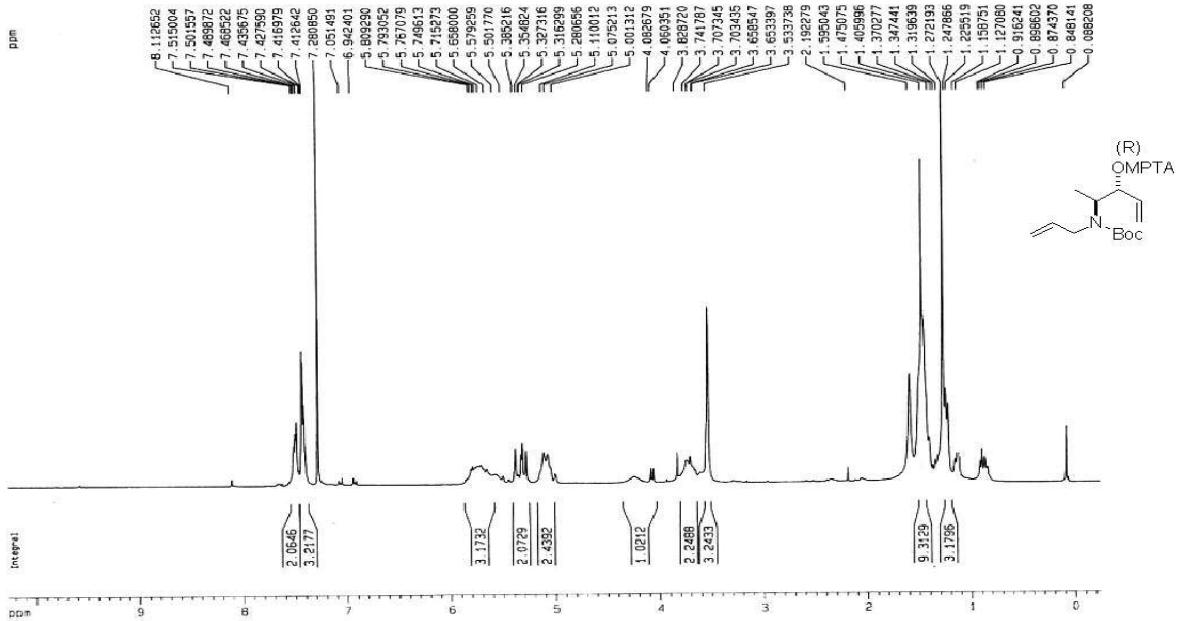
Spectra 32. ^1H NMR (300 MHz, D_2O) of (2S,3R)-2-methylpiperidin-3-ol (3)



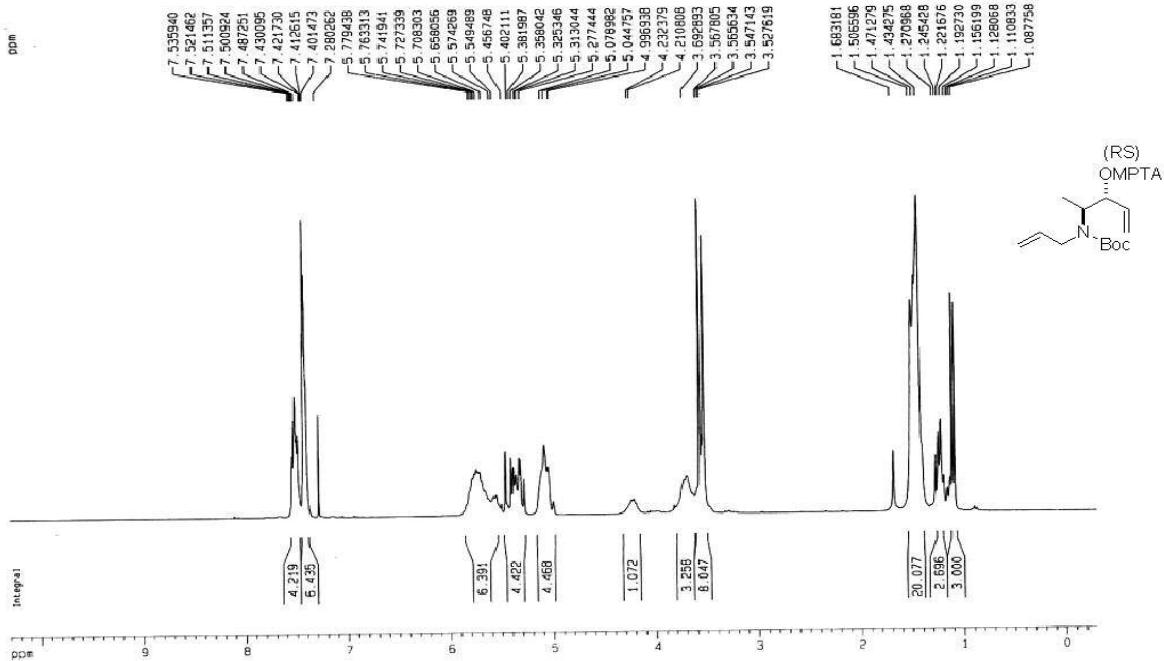
Spectra 33. ^{13}C NMR (300 MHz, D_2O) of (2*S*,3*R*)-2-methylpiperidin-3-ol (3)



Spectra 34. HR mass of (2*S*,3*R*)-2-methylpiperidin-3-ol (3)



Spectra 35. ^1H NMR (300 MHz, CDCl_3) of (3*R*,4*S*)-4-[allyl(*tert*-butoxycarbonyl)amino]pent-1-en-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (12)



Spectra 36. ^1H NMR (300 MHz, CDCl_3) of (3*R*,4*S*)-4-[allyl(*tert*-butoxycarbonyl)amino]pent-1-en-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (RS mixture) (12)

[Elemental Composition]

Data : B_tri_HR

Date : 13-Feb-2008 14:31

Page: 1

Sample: -

Note : -

Inlet : Direct

Ion Mode : FAB+

RT : 0.50 min

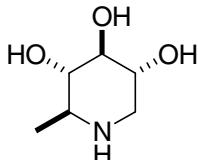
Scan#: 7

Elements : C 30/1, H 50/0, N 10/1, O 10/1

Mass Tolerance : 1000ppm, 3mmu if m/z < 3, 10mmu if m/z > 10

Unsaturation (U.S.) : -0.5 - 20.0

Observed m/z	Int%	Err [ppm / mmu]	U.S.	Composition
148.0970	0.3	+15.9 / +2.3	1.5	C 2 H 10 N 7 O
		+6.8 / +1.0	1.0	C 4 H 12 N 4 O 2
		-2.3 / -0.3	0.5	C 6 H 14 N O 3

Calcd [(M+H)⁺] : 148.0974**compound 1****Spectra 37. FAB-HRMS data of compound 1.**

[Elemental Composition]

Data : 4_DNJ_HR

Date : 13-Feb-2008 13:38

Page: 1

Sample: -

Note : -

Inlet : Direct

Ion Mode : FAB+

RT : 0.17 min

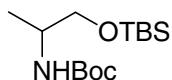
Scan#: 3

Elements : C 14/10, H 32/0, N 10/1, O 10/1, Si 5/1

Mass Tolerance : 1000ppm, 3mmu if m/z < 3, 100mmu if m/z > 100

Unsaturation (U.S.) : -0.5 - 10.0

Observed m/z	Int%	Err [ppm / mmu]	U.S.	Composition
290.2832	19.8	+234.4 / +68.1	0.5	C 14 H 32 N O 3 Si

Calcd [(M+H)⁺] : 290.2151**compound 6****Spectra 38. FAB-HRMS data of compound 6.**

[Elemental Composition]

Data : 5_DNJ_HR

Date : 13-Feb-2008 13:56

Page: 1

Sample: -

Note : -

Inlet : Direct .

Ion Mode : FAB+

RT : 0.09 min

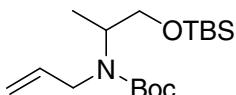
Scan#: 2

Elements : C 30/10, H 50/0, N 10/1, O 10/1, Si 5/1

Mass Tolerance : 1000ppm, 3mmu if m/z < 3, 10mmu if m/z > 10

Unsaturation (U.S.) : -0.5 - 10.0

Observed m/z	Int%	Err [ppm / mmu]	U.S.	Composition
330.2508	0.3	-16.8 / -5.5	2.0	C 14 H 34 N 6 O Si
		+21.3 / +7.0	2.5	C 13 H 32 N 7 O Si
		-20.9 / -6.9	1.5	C 16 H 36 N 3 O 2 Si
		+17.2 / +5.7	2.0	C 15 H 34 N 4 O 2 Si
		+13.2 / +4.3	1.5	C 17 H 36 N O 3 Si
		-4.5 / -1.5	1.0	C 16 H 38 N 2 O Si 2

Calcd [(M+H)⁺] : 330.2464

compound 7

Spectra 39. FAB-HRMS data of compound 7.

[Elemental Composition]

Data : 6_DNJ_HR

Date : 13-Feb-2008 14:11

Page: 1

Sample: -

Note : -

Inlet : Direct .

Ion Mode : FAB+

RT : 0.50 min

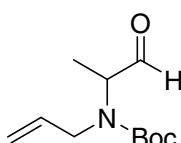
Scan#: 7

Elements : C 30/10, H 50/0, N 10/1, O 10/1

Mass Tolerance : 1000ppm, 3mmu if m/z < 3, 20mmu if m/z > 20

Unsaturation (U.S.) : -0.5 - 10.0

Observed m/z	Int%	Err [ppm / mmu]	U.S.	Composition
214.1526	0.2	-72.6 / -15.6	2.0	C 11 H 22 N 2 O 2
		-13.9 / -3.0	2.5	C 10 H 20 N 3 O 2
		+38.5 / +8.3	2.5	C 11 H 20 N O 3

Calcd [(M+H)⁺] : 214.1443

compound 9

Spectra 40. FAB-HRMS data of compound 9.

[Elemental Composition]
Data : HFAB-POS-080131003
Sample: A-7a

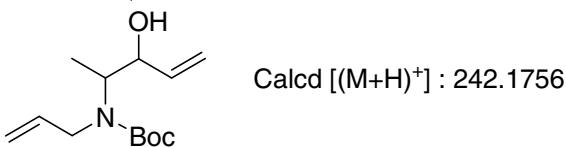
Date : 31-Jan-2008 15:20
Ion Mode : FAB+
Scan#: 30

Page: 1

Note : with PEG400
Inlet : Direct
RT : 4.07 min

Elements : C 13/0, H 24/0, O 3/0, N 1/0
Mass Tolerance : 5ppm, 5mmu if m/z > 1000
Unsaturation (U.S.) : 0.0 - 100.0

Observed m/z	Int%	Err [ppm / mmu]	U.S.	Composition
242.1764	0.6	+3.2 / +0.8	2.5	C 13 H 24 O 3 N



compound 10

Spectra 41. FAB-HRMS data of compound 10.

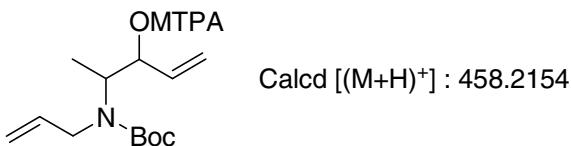
[Elemental Composition]
Data : HFAB-POS-080131004
Sample: MTPA
Note : with PEG400

Date : 31-Jan-2008 16:05

Page: 1

Inlet : Direct
RT : 0.33 min
Elements : C 23/0, H 31/0, O 5/0, N 1/0, F 3/0
Mass Tolerance : 5ppm, 5mmu if m/z > 1000
Unsaturation (U.S.) : 0.0 - 100.0

Observed m/z	Int%	Err [ppm / mmu]	U.S.	Composition
458.2156	1.5	+0.4 / +0.2	7.5	C 23 H 31 O 5 N F 3



compound 12

Spectra 42. FAB-HRMS data of compound 12.