Supplementary Material (ESI) for Chemical Communications

Supporting Information

A Highly Efficient Synthesis of Telaprevir by Strategic Use of Biocatalysis and Multicomponent Reactions

Anass Znabet, Marloes M. Polak, Elwin Janssen, Frans J. J. de Kanter, Nicholas J. Turner, Romano V. A. Orru and Eelco Ruijter*

Department of Chemistry & Pharmaceutical Sciences
Vrije Universiteit Amsterdam
De Boelelaan 1083, 1081 HV Amsterdam, the Netherlands

and

School of Chemistry
University of Manchester,
Manchester Interdisciplinary Biocentre
131 Princess Street, Manchester, M1 7DN, United Kingdom

Table of Contents

General Information

Commercially available starting materials and solvents were used as received. Dry CH_2Cl_2 was dried and distilled from CaH_2 prior to use.

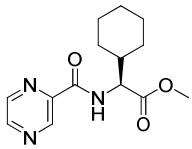
^1H and ^{13}C NMR spectra measured at 250.13, 400.13, or 500.23 MHz for ^1H and at 62.90, 100.61, or 125.78 MHz for ^{13}C in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in δ values (ppm) downfield from tetramethylsilane.

Column chromatography was performed on silica gel. Chromatographic purification refers to flash chromatography using the indicated solvent (mixture) and silica (40-63 μm, 60 Å). Thin Layer Chromatography was performed using silica plates (silica on aluminum with fluorescence indicator). Compounds on TLC were visualized by UV detection unless stated otherwise.

Electrospray Ionisation (ESI) mass spectrometry was carried out using a TOF-Quadrupole instrument in positive ion mode (capillary potential of 4500 V). Infrared (IR) spectra were recorded neat, and wavelengths are reported in cm^{-1}. Optical rotations were measured with a sodium lamp and are reported as follows: $[\alpha]_D^{20}$ (c = g/100 mL, solvent).

Experimental details and characterization of new compounds

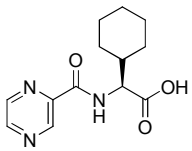
Bicyclic imine 3. Imine **3** was synthesized according to literature procedure[1] with minor adjustments as follows: 2.5 g of freeze-dried MAO-N D5 *E. coli* were rehydrated for 30 min. in 20 ml of KPO_4 buffer (100 mM, pH = 8.0) at 37 °C. Subsequently 1 mmol amine **5** in 30 ml of KPO_4 buffer (100 mM, pH = 8,0) was prepared. The pH of the solution was adjusted to 8.0 by addition of NaOH and then added to the rehydrated cells. After 16-17 h the reaction was stopped (conversion was > 95 %) and worked up. For workup the reaction mixture was centrifuged at 4000 rpm and 4°C until the supernatant had clarified (40 – 60 min.). The pH of the supernatant was then adjusted to 10-11 by addition of aq. NaOH and the supernatant was subsequently extracted with *t*-butyl methyl ether (4 × 70 mL). The combined organic phases were dried with Na_2SO_4 and concentrated at the rotary evaporator.



(*S*)-Methyl 2-cyclohexyl-2-(pyrazine-2-carboxamido)acetate (**9**). Pyrazinecarboxylic acid (2.72 g, 21.9 mmol) was added to a solution of L-cyclohexylglycine methyl ester (4.13 g, 19.9 mmol) in CH_2Cl_2 (100 ml) at room temperature under N_2, forming a white suspension. Triethylamine (6.33 ml, 4.62 g, 45.8 mmol) was added, followed by benzotriazol-1-yloxy-*tris*-(dimethylamino)phosphonium hexafluorophosphate (BOP; 9.69 g, 21.9 mmol), which turned the reaction mixture from purple to an orange solution. After two days of stirring at room temperature the reaction mixture was washed two times with 50

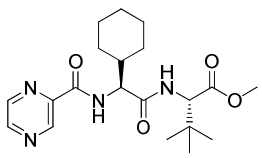
ml saturated Na_2CO_3, followed by the washing of the aqueous layers with CH_2Cl_2 (2 x 50 ml). The organic layers were collected and dried with $MgSO_4$, followed by concentration in *vacuo*. Purification by silica gel flash chromatography (*c*-Hex:EtOAc = 2:1 with 0.5% triethylamine) afforded **9** (5.28 g, 19.03 mmol, 96%) as a yellow oil that solidified upon standing to give a white solid.

$[\alpha]_D^{20}$ = +42.5 (c= 1.13, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ = 9.39 (d, *J*= 1.25 Hz, 1H), 8.76 (d, *J* = 2.5 Hz, 1H), 8.57 (t, *J* = 1.5 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 4.74 (dd, *J* = 5.5, 9.3 Hz, 1H), 3.78 (s, 3H), 1.96 (m, 1H), 1.77 (m, 5H), 1.24 (m, 5H); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ= 172.0 (C), 162.8 (C), 147.4 (CH), 144.5 (CH), 144.1 (C), 142.7(CH), 57.0 (CH), 52.3 (CH_3), 41.2 (CH), 29.7 (CH_2), 28.4 (CH_2), 26.0 (CH_2); IR (neat): ν_{max} (cm^{-1}) = 3374 (m), 2920 (s), 2845 (w), 1740 (s), 1665 (s); HRMS (ESI, 4500 V): m/z calcd. for $C_{14}H_{19}N_3O_3Na^+$ ($[M + Na]^+$) 300.1319, found 300.1319.



(*S*)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetic acid (**10**). A solution of 1 M NaOH (12 ml, 12 mmol) was added to a solution of **9** (2.77 g, 10 mmol) in THF (25 ml) at 0˚C. MeOH was added to the formed suspension, to give a clear, colorless solution. The reaction mixture was stirred overnight at room temperature, followed by concentration in *vacuo*. The pH of the aqueous layer was set on 3.5 with a 1 M $KHSO_4$ solution and was extracted with EtOAc (2 x 25 ml). The mixture was dried with Na_2SO_4, filtered, and concentrated in *vacuo*, to give **10** (2.49 g, 9.45 mmol, 95%) as a white solid.

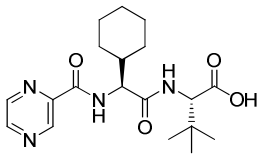
$[\alpha]_D^{20}$ = +50.9 (c= 1.06, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 9.38 (d, *J* = 1.5 Hz, 1H), 8.78 (d, *J* = 2.5 Hz, 1H), 8.58 (dd, *J* = 1.5, 2.5 Hz, 1H), 8.27 (d, *J* = 9.0, 1H), 4.77 (dd, *J* = 4.3, 5.0 Hz, 1H), 2.00 (m, 1H), 1.76 (m, 5H), 1.37 (m, 5H); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 175.7 (C), 163.0 (C), 147.2 (CH), 144.3 (CH), 144.2 (C), 142.0 (CH), 56.9 (CH), 40.9 (CH), 29.7 (CH_2), 28.1 (CH_2), 25.9 (CH_2); IR (neat): ν_{max} (cm^{-1}) = 3383 (m), 2928 (s), 2852 (w), 1713 (m), 1676 (s), 1518 (s); HRMS (ESI, 4500 V): m/z calcd. For $C_{13}H_{17}N_3O_3Na^+$ ($[M + Na]^+$) 286.1162, found 286.1158.



(S)-methyl 2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)-acetamido)-3,3-dimethylbutanoate (**11**). **10** (0.653 g, 4.5 mmol) was added to a solution of H-Tle-OMe (0.653 g, 4.5 mmol) in DMF (40 ml). 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide-HCl (EDC•HCl; 0.919 g, 6.75 mmol) was added to this colorless solution followed by 1-hydroxy-7-azabenzotriazole (HOAt; 1.035 g, 5.4 mmol) giving a bright yellow solution. The reaction mixture was stirred for 3 days and afterwards concentrated in *vacuo*. The formed yellow solid was dissolved in EtOAc, washed with 40 ml saturated aqueous ammonium chloride solution and 40 ml of saturated aqueous $NaHCO_3$ solution. The

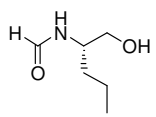
organic layers were collected, dried with $MgSO_4$ and concentrated in *vacuo* to give **11** (1.48 g, 3.78 mmol, 84%) as a white solid.*

$[\alpha]_D^{20}$ = -2.0 (c= 1.0, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 9.39 (d, *J* = 1.5 Hz, 1H), 8.76 (d, *J* = 2.3 Hz, 1H), 8.55 (dd, *J* = 2.4, 1.8 Hz, 1H), 8.29 (d, *J* = 8.1, 1H), 6.40 (d, *J* = 9.3 Hz, 1H), 4.46 (m, 2H), 3.74 (s, 3H), 1.81 (m, 1H), 1.76 (m, 4H), 1.24 (m, 6H), 0.96 (s, 12H); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 171.7 (C) , 170.4 (C), 163.0 (C), 147.5 (CH), 144.5 (CH), 144.2 (C), 142.7 (CH), 60.2 (CH_3), 58.4 (CH), 51.9 (CH), 40.5 (CH), 31.7 (C), 29.7 (CH_2), 28.7 (CH_2), 26.6 (CH_3), 25.9 (CH_2); IR (neat): ν_{max} (cm^{-1}) = 3350 (m), 2928 (m), 2853 (w), 1738 (s), 1686 (s), 1640 (s), 1520 (s); HRMS (ESI, 4500 V): m/z calcd. for $C_{20}H_{30}N_4O_4Na^+$ ($[M + Na]^+$) 413.2159, found 413.2169.



(S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoic acid (**2**)**.** A solution of 1 M NaOH (0.94 ml, 0.94 mmol) was added to a solution of **11** (0.31 g, 0.78 mmol) in THF (3 ml) at 0˚C. MeOH was added to the formed suspension, to give a clear and colourless solution. The reaction mixture was stirred overnight at room temperature, followed by concentration in *vacuo*. The pH of this aqueous layer was set to 3.5 with 1 M $KHSO_4$ and subsequently extracted with EtOAc (2 x 10ml). The mixture was dried with Na_2SO_4, filtered, and concentrated in *vacuo*, to give **2** (0.28 g, 0.75 mmol, 95%) as a white solid.

$[\alpha]_D^{20}$ = +21.7 (c= 1.015, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 9.39 (d, *J* = 1.3 Hz, 1H), 8.77 (d, *J* = 2.5 Hz, 1H), 8.57 (dd, *J* = 1.5, 2.5 Hz, 1H), 8.35 (d, *J* = 9 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 1H), 4.45 (t, *J* = 8.8 Hz, 1H), 4.42 (d, *J* = 9.2 Hz, 1H), 1.94 (m, 1H), 1.71 (m, 5H), 1.20 (m, 5H), 1.01 (s, 9H); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 173.4 (C), 170.5 (C), 163.3 (C), 147.4 (CH), 144.4 (CH), 144.2 (C), 142.8 (CH), 58.4 (CH), 51.9 (CH), 40.4 (CH), 34.7 (C), 29.8 (CH_2), 28.6 (CH_2), 26.6 (CH_3), 25.8 (CH_2); IR (neat): ν_{max} (cm^{-1}) = 3335 (w), 2930 (m), 1726 (m), 1663 (s), 1514 (s); HRMS (ESI, 4500 V): m/z calc. for $C_{19}H_{29}N_4O_4Na^+$ ($[M + Na]^+$) 399.2003, found 399.2013.

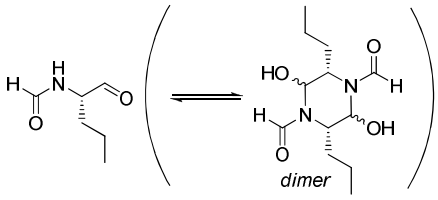


(*S*)-2-formamido-1-pentanol (12). (*S*)-2-amino-1-pentanol (1.00 g, 9.7 mmol) was dissolved in ethylformate (7.84 ml, 7.19 g, 97 mmol). This reaction mixture was refluxed at 80 ˚C for 4 hours, followed by stirring overnight at room temperature. The colourless solution was concentrated in *vacuo* and stirred for 1 hour in a 10 mol% K_2CO_3 in MeOH (25 ml). Afterwards, the pH was set to 7

* Racemization of activated **10** was ruled out by the diastereomeric composition of **11** (single diastereomer).

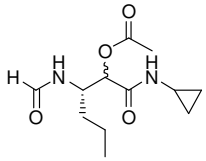
with DOWEX 50wx8, followed by filtration and concentration in *vacuo* to give **12** (1.26 g, 9.61 mmol, 99%).

$[\alpha]_D^{20}$ = -29.6 (c = 1.15, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 8.20 (s, 1H), 5.81 (bs, 1H), 4.04 (m, 1H), 2.11 (b, 1H), 1.47 (m, 4H), 0.94 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (62.90 MHz, $CDCl_3$): 161.8 (C), 65.1 (CH_2), 50.6 (CH), 33.2 (CH_2), 19.2 (CH_2), 13.9 (CH_3); IR (neat): ν_{max} (cm^{-1}) = 3248 (s), 2957 (m), 1651 (s), 1528 (m), 1381 (m); HRMS (ESI, 4500 V): m/z calcd. for $C_6H_{13}NO_2Na^+$ ([M + Na]$^+$) 154.0838, found 154.0835.



(*S*)-2-formamidopentanal. **(7).** Dess-Martin periodinane (5.514 g, 13 mmol) was added to a solution of (*S*)-2-formamido-1-pentanol (**12**, 1.31 g, 10 mmol) in CH_2Cl_2 (100 ml) at room temperature. The white suspension was stirred for 2 days and subsequently 35 ml MeOH was added and stirred for 30 minutes. The resulting suspension was filtrated and the filtrate was concentrated in *vacuo*. The crude product was purified by silica gel flash chromatography (*c*Hex:EtOAc = 1:4) to give **7** (1.08 g, 8.29 mmol, 83%) as a white solid. NMR analysis indicates that **7** is in equilibrium with its cyclic dimer.[†]

$[\alpha]_D^{20}$ = +37.6 (c= 0.745, $CHCl_3$); ^{1}H NMR assigned to the monomer (250.13 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 7.84 (s, 1H), 7.10 (m, 1H), 5.31 (m, 1H), 1.52 (m, 4H), 0.95 (m, 3H); ^{13}C NMR assigned to the monomer (100.61 MHz, CDCl3): 198.8 (CH), 161.7 (CH), 57.4 (CH), 30.8 (CH_2), 18.4 (CH_2), 13.7 (CH_3); ^{1}H NMR assigned to the dimer (400.13 MHz, $CDCl_3$) 8.22 (s, 2H), 5.26 (m, 2H), 3.72 (m, 2H) 1.52 (m, 8H), 0.95 (m, 6H;) ^{13}C NMR (100.61 MHz, $CDCl_3$) assigned to the dimer: 161.7 (CH), 89.8 (CH), 63.1 (CH), 30.8 (CH2), 18.4 (CH2), 13.7 (CH3); IR (neat): ν_{max} (cm^{-1}): 3325 (s), 2959 (s), 1649 (s), 1530 (s), 1381 (m), 1123 (w); HRMS (ESI, 4500 V): m/z calc. for $C_6H_{12}NO_2^+$ ([M + H]$^+$) 130.0863, found 130.0858.



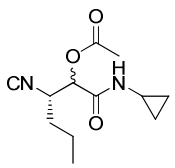
(3*S*)-2-acetoxy-*N*-cyclopropyl-3-formamidohexanoyl amide (**13**). *From 7:* Aldehyde **7** (0.892 g, 6.91 mmol) was added to a solution of cyclopropyl isocyanide (0.410 g, 6.12 mmol) in CH_2Cl_2 (110 ml) and stirred for 5 minutes at room temperature. Acetic acid (0.711 ml, 0.747 g, 12.44 mmol) was added and the yellow reaction mixture was stirred for 3 days at room

[†] Compound **7** is in dynamic equilibrium with its cyclic dimer. This dimer contains two additional stereocenters and therefore exists as a mixture of four diastereomers. All five compounds (monomer + four dimer diastereomers) appear as mixtures of rotamers in NMR due to restricted rotation around the formamide bond. Moreover, the reversible dimerization severely complicated chromatographic purification and prevented removal of traces of Dess-Martin periodinane and/or its degradation products, which accounts for the aromatic impurities observed in the ^{1}H NMR spectrum.

temperature. The reaction mixture was washed twice with 100 ml saturated Na_2CO_3, followed by drying with Na_2SO_4 and concentration in *vacuo*. The crude was purified by silica gel flash chromatography (5% MeOH in CH_2Cl_2, 1% triethylamine). (3*S*)-2-acetoxy-*N*-cyclopropyl-3-formamidohexanoyl amide (0.99 g, 3.87 mmol, 56%) was obtained as a white solid as a 78:22 mixture of diastereomers.

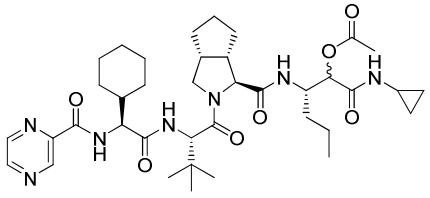
*From **12**:* Dess Martin periodinane (5.66 g, 12.3 mmol) was added to a solution of (*S*)-*N*-(1 hydroxypentan-2-yl)formamide (1.15 g, 8.8 mmol) in CH_2Cl_2 (12 ml) at room temperature. The white suspension was stirred for 60 minutes and subsequently cyclopropyl isocyanide (0.74 g, 10.0 mmol) was added and stirred for 48 hours. The resulting suspension was filtrated and washed twice with 10 ml saturated Na_2CO_3, followed by drying with Na_2SO_4 and concentration in *vacuo*. The crude product was purified by silica gel flash chromatography (5% MeOH in CH_2Cl_2, 1% triethylamine) to give **13** (1.34 g, 5.22 mmol, 60%) as a pale yellow solid as a 78:22 mixture of diastereomers.

^{1}H NMR (130 °C, 400.13 MHz, DMSO-d_6): δ = 8.03 (s, 1H), 7.52 (m, 1H), 7.30 (m, 1H), 4.89 (d, *J* = 4.4, 1H), 4.28 (m, 1H), 2.65 (m, 1H), 2.17(s, 3H), 1.27-1.47 (m, 4H), 0.89 (t, *J* = 7.2, 3H), 0.63 (m, 2H), 0.48 (m, 2H); ^{13}C NMR (125.78 MHz, DMSO-d_6): δ = 169.8 (C), 168.5 (C), 160.6 (CH), 74.4 (CH), 47.5 (CH), 22.2 (CH), 18.4 (CH_3), 13.6 (CH_3), 5.7 (CH_2); IR (neat): ν_{max} (cm^{-1}) 3283 (s), 2961 (w), 1744 (m), 1661 (s), 1530 (s), 1238 (s); HRMS (ESI, 4500 V): m/z calcd. for $C_{12}H_{20}N_2O_4Na^+$ ([M + Na]$^+$) 279.1315, found 279.1325.

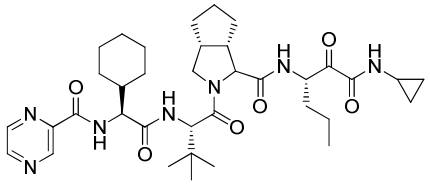


(3*S*)-2-acetoxy-*N*-cyclopropyl-3-isocyano-hexanoyl amide (4). *N*-methylmorpholine (0.57 ml, 0.562 g, 5.56 mmol) was added to a solution of (*S*)-1-(cyclopropylamino)-3-formamido-1-oxohexan-2-yl acetate (0.713 g, 2.78 mmol) in CH_2Cl_2 (40 ml) at room temperature. The reaction mixture was cooled to -78 ˚C and triphosgene (0.289 g, 0.97 mmol) was quickly added and stirred for 5 minutes at this temperature. The resulting yellow solution was warmed up to -30 ˚C and was stirred for another 3 h. Subsequently, the reaction was quenched with water and extracted twice with CH_2Cl_2 (40 ml). The organic layers were collected, dried with Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by silica gel flash chromatography (2% MeOH in CH_2Cl_2) to give **4** (0.578 g, 2.42 mmol, 87%) as a white solid.

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 6.28 (s, 1H), 5.25 (d, *J* = 2.5 Hz, 1H), 4.2 (m, 1H), 2.74 (m, 1H), 2.24 (s, 3H), 1.55 (m, 4H), 0.96 (m, 3H), 0.84 (m, 2H), 0.60 (m, 2H); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ= 169.7 (C), 168.3 (C), 74.4 (CH), 47.5 (CH), 22.0 (CH), 20.6 (CH_3), 18.5 (CH_2), 13.5 (CH_3), 5.5 (CH_2); IR (neat): ν_{max} (cm^{-1}): 3267 (s), 2959 (m), 1745 (m), 1643 (s), 1512 (m), 1221 (s); HRMS (ESI, 4500 V): m/z calcd. for $C_{12}H_{18}N_2O_3Na^+$ ([M + Na]$^+$) 261.1210, found 261.1214.



Compound 14. Isocyanide **4** (0.549 g, 2.3 mmol) was dropwise added to a solution of imine **3** (0.252 g, 2.3 mmol) and carboxylic acid **2** (0.602 g, 1.60 mmol) in CH_2Cl_2 (5 ml) at room temperature. This yellow solution was stirred for 72 hours and afterwards diluted with 5 ml CH_2Cl_2. The reaction mixture was washed twice with saturated Na_2CO_3 solution (10 ml) and twice with saturated NH_4Cl. The organic layers were collected, dried with $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by silica gel flash chromatography (5% MeOH in CH_2Cl_2) to give **14** (0.876 g, 1.21 mmol, 76%) as a mixture of diastereomers.
^{1}H NMR (500.23 MHz, $CDCl_3$): δ = 9.50 (s, 1H), 8.75 (d, *J* = 2.5, 1H), 8.59 (s, 1H), 8.35 (d, *J* = 9.0, 1H), 6.84 (d, *J* = 9.0, 1H), 6.44 (s, 1H), 5.20 (d, *J* = 3.0, 1H), 4.74 (d, *J*= 9.5, 1H), 4.58 (t, *J* = 7.5, 1H), 4.38 (m, 1H), 3.37 (d, *J*= 6.0, 1H), 2.82 (m, 1H), 2.69 (m, 1H), 2.11 (s, 3H), 1.26 (s, 2H), 0.97 (s, 9H), 0.86 (m, 3H), 0.84-2.00 (m, 21H), 0.76 (m, 2H), 0.51 (m, 2H); ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 170.5 (C), 169.3 (C), 162.9 (C), 147.4 (CH), 144.6 (CH), 144.2 (C), 142.8 (CH), 74.4 (CH), 66.6 (CH), 58.3 (CH), 56.6 (CH), 54.5 (CH_2), 44.9 (CH), 43.0 (CH), 41.3 (CH), 35.5 (C), 26.4 (CH_3), 20.8 (CH_3), 19.1 (CH_2), 13.8 (CH_3), 6.6 (CH_2); ν_{max} (cm^{-1}): 3306 (m), 2928 (m), 2931 (m), 1743 (w), 1655 (s), 1520 (m), 1219 (m); HRMS (ESI, 4500 V): m/z calcd. for $C_{38}H_{57}N_7O_7Na^+$ ([M + Na]$^+$) 746.4212, found 746.4107.



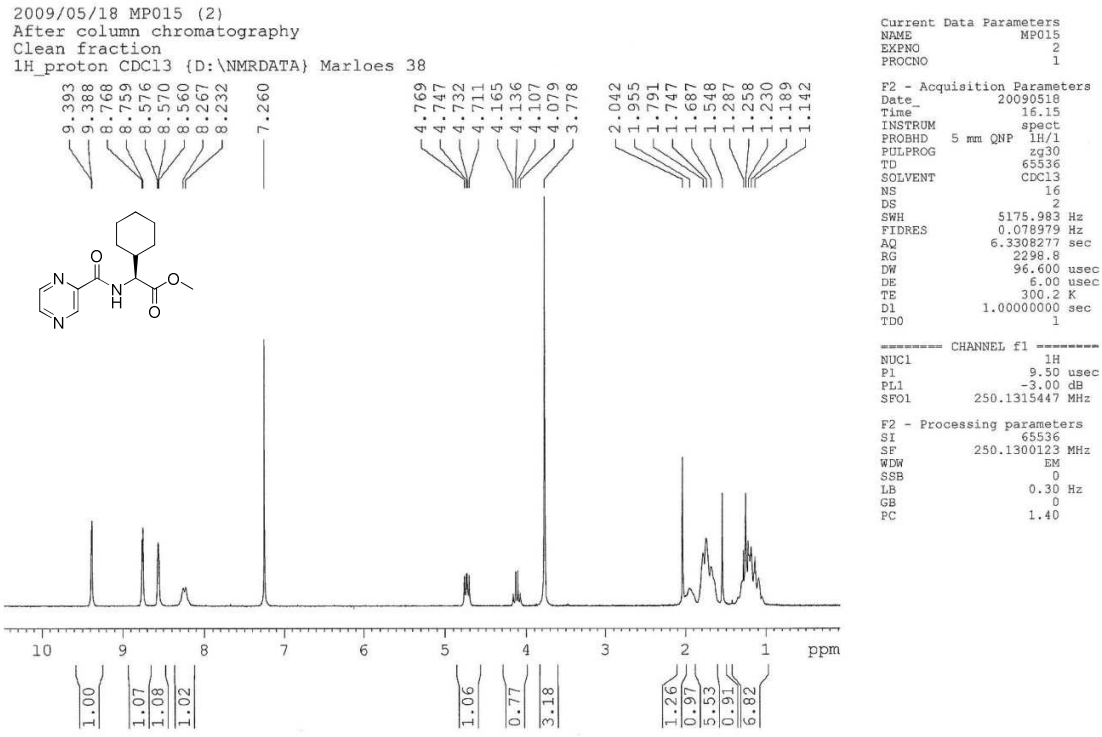
Telaprevir (1). 250 µl of saturated K_2CO_3 was added to a solution of **14** (0.514 g, 0.75 mmol) in MeOH (20 ml) at room temperature. The reaction mixture was stirred for 30 minutes at room temperature resulting in a pale yellow suspension. After full conversion (as judged by TLC analysis), the reaction mixture was washed with 20 ml brine, the aqueous layer was washed again with 10 ml CH_2Cl_2 (2x). The organic layers were collected, dried with $MgSO_4$ and concentrated *in vacuo*, to yield a pale yellow solid. The yellow solid was dissolved in CH_2Cl_2 (10 ml) and Dess-Martin periodinane (0.650 g, 1.532 mmol) was added at room temperature. The reaction mixture was stirred overnight before adding saturated $NaHCO_3$ solution (10 ml) and saturated $Na_2S_2O_3$ solution (10 ml). This mixture was stirred for 10 minutes, separated and the aqueous layers were washed with EtOAc (2 x 10 ml). The organic layers were collected, dried with $MgSO_4$ and concentrated in *vacuo* to give the crude product as an 83:13:4 mixture of diastereomers. After silica gel flash chromatography (1% MeOH in CH_2Cl_2), **1** (0.412 mg, 0.61 mmol, 80%) was obtained as a white solid.
^{1}H NMR (500.23 MHz, DMSO-d_6): δ = 9.19 (d, *J* = 1.4 Hz, 1H), 8.91 (d, *J* = 24.5 Hz, 1H), 8.76 (dd, *J* = 1.5, 2.5 Hz, 1H), 8.71 (d, *J* = 5.3 Hz, 1H), 8.49 (d, *J* = 9.2 Hz, 1H),

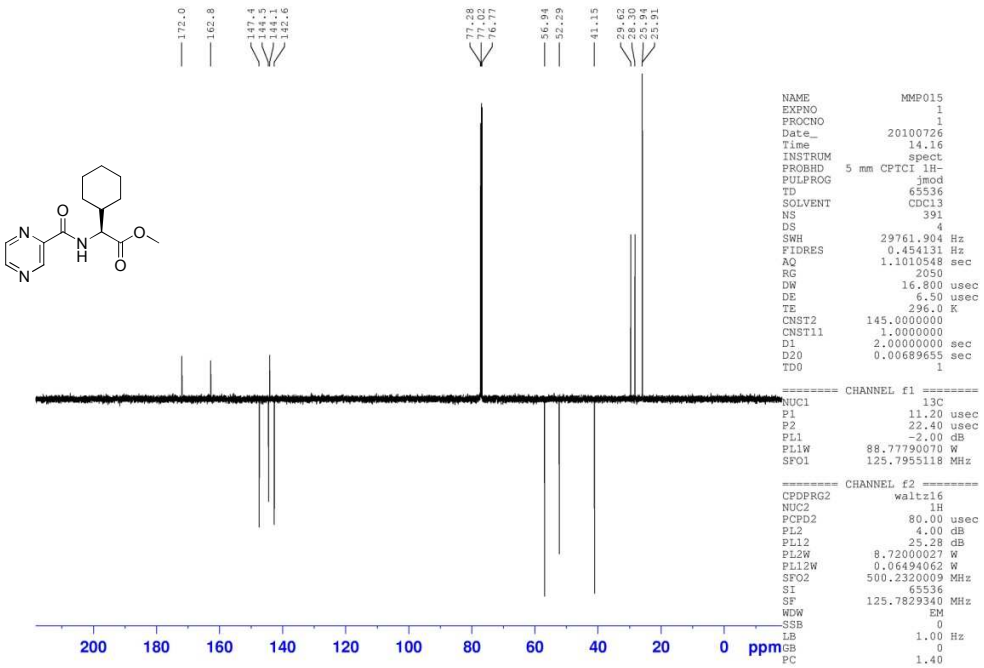
8.25 (d, *J* = 6.8 Hz, 1H), 8.21 (d, *J* = 8.9 Hz, 1H), 4.94 (m, 1H), 4.68 (dd, *J* = 6.5, 9.0 Hz, 1H), 4.53 (d, *J* = 9.0 Hz, 1H), 4.27 (d, *J* = 3.5 Hz, 1H), 3.74 (dd, *J* = 8.0, 10 Hz, 1H), 2.74 (m, 1H), 3.64 (d, *J* = 3.5 Hz, 1H), 0.92 (s, 9H), 0.87 (t, 3H), 0.84-1.40 (m, 23H), 0.65 (m, 2H), 0.56 (m, 2H); ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 197.0 (C), 171.8 (C), 170.4 (C), 169.0 (C), 162.1 (C), 161.9 (C), 147.9 (CH), 144.0 (C), 143.4 (CH), 56.4 (CH), 56.3 (CH), 54.2 (CH), 53.4 (CH), 42.3 (CH), 41.3 (CH), 32.1 (CH), 31.8 (CH), 31.6 (CH), 29.1 (CH), 28.0 (CH), 26.4 (CH_3); ν_{max} (cm^{-1}): 3302 (m), 2928 (m), 2858 (w), 1658 (s), 1620 (s), 1561 (s), 1442 (m); HRMS (ESI, 4500 V): m/z calcd. for $C_{36}H_{53}N_7O_6Na^+$ ([M + Na]$^+$) 702.3950, found 702.3941.

References:

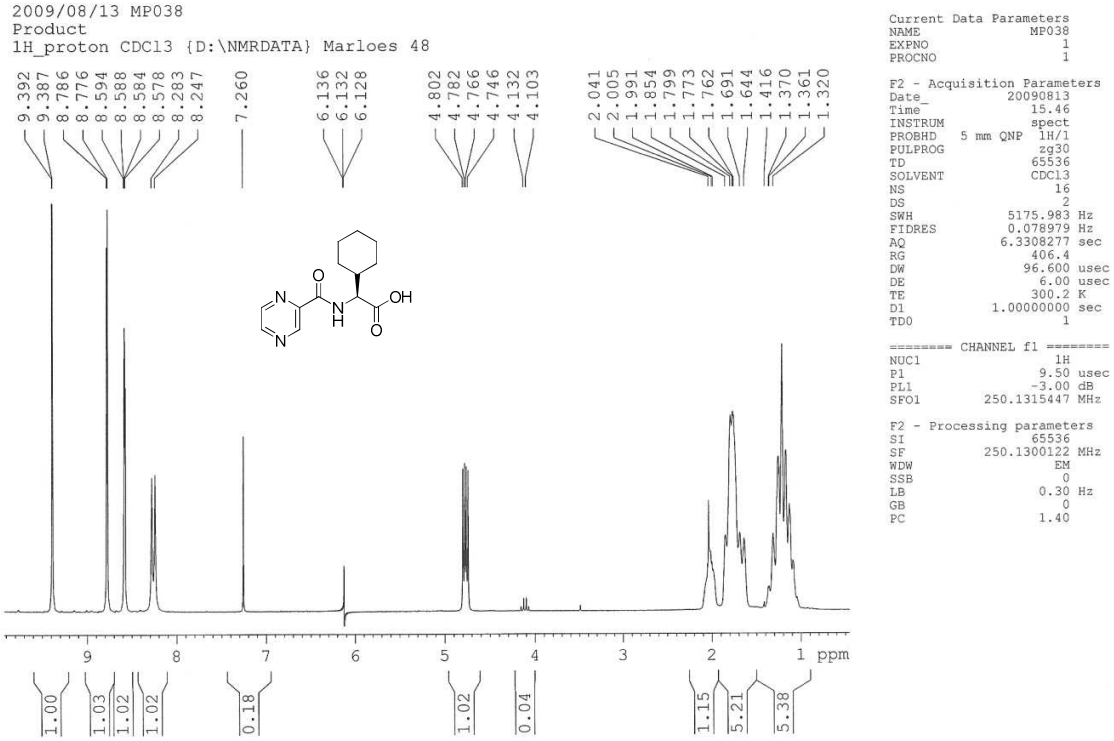
1. V. Köhler, K. R. Bailey, A. Znabet, J. Raftery, M. Helliwell and N. J. Turner, *Angew. Chem. Int. Ed.* 2010, **49**, 2182.

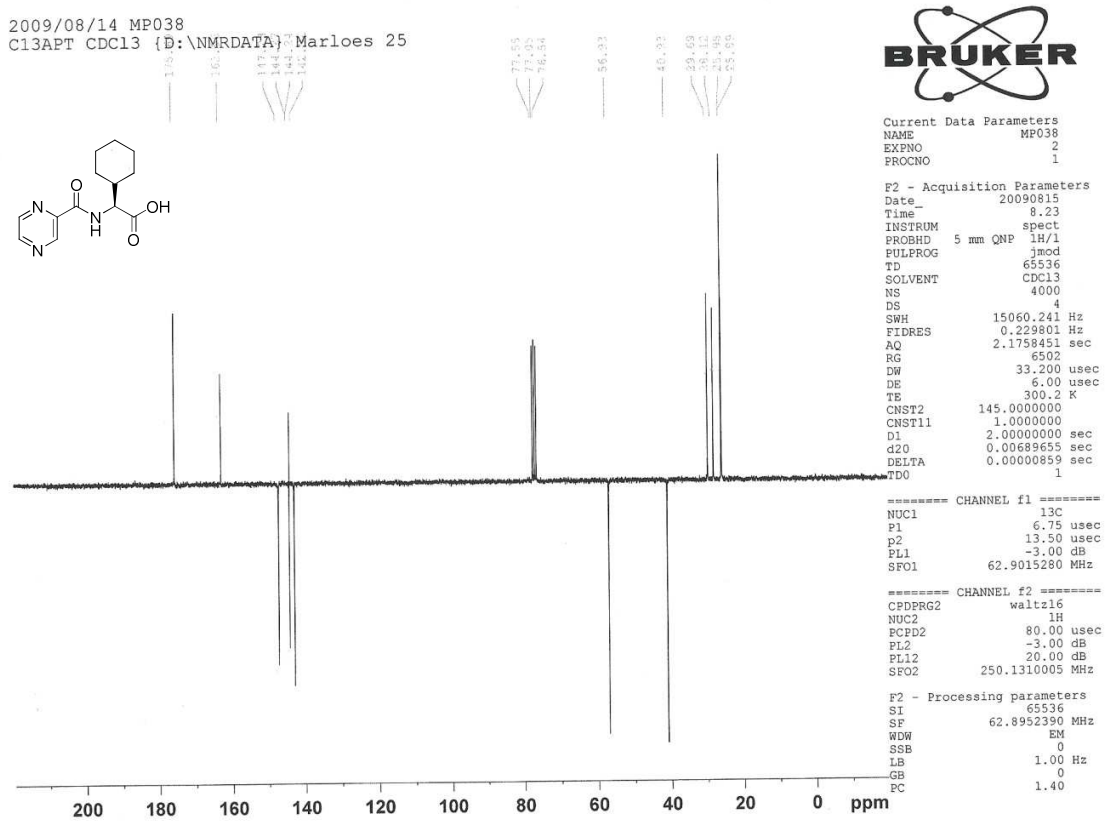
(*S*)-Methyl 2-cyclohexyl-2-(pyrazine-2-carboxamido)acetate (9).



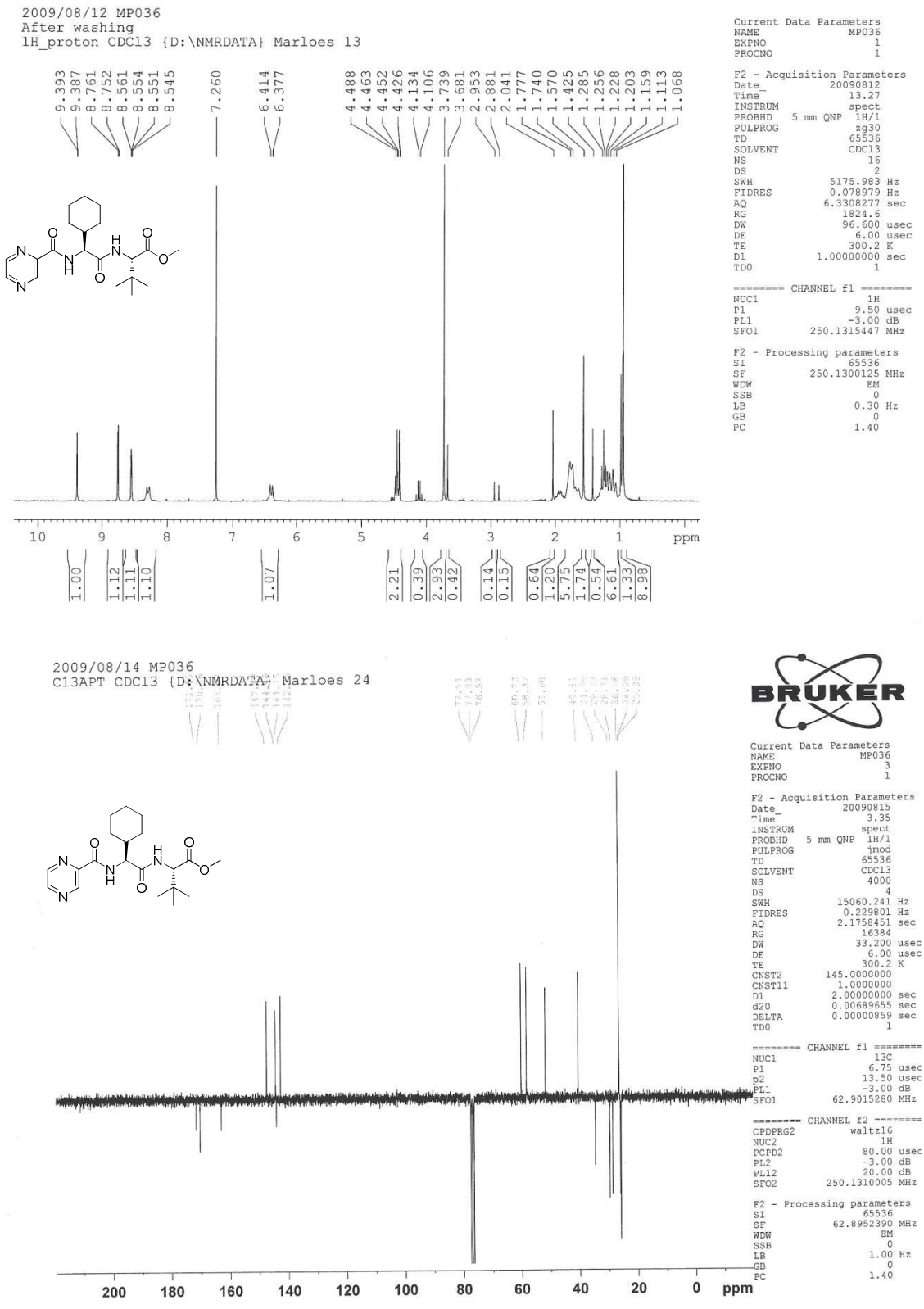


(*S*)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetic acid (10).

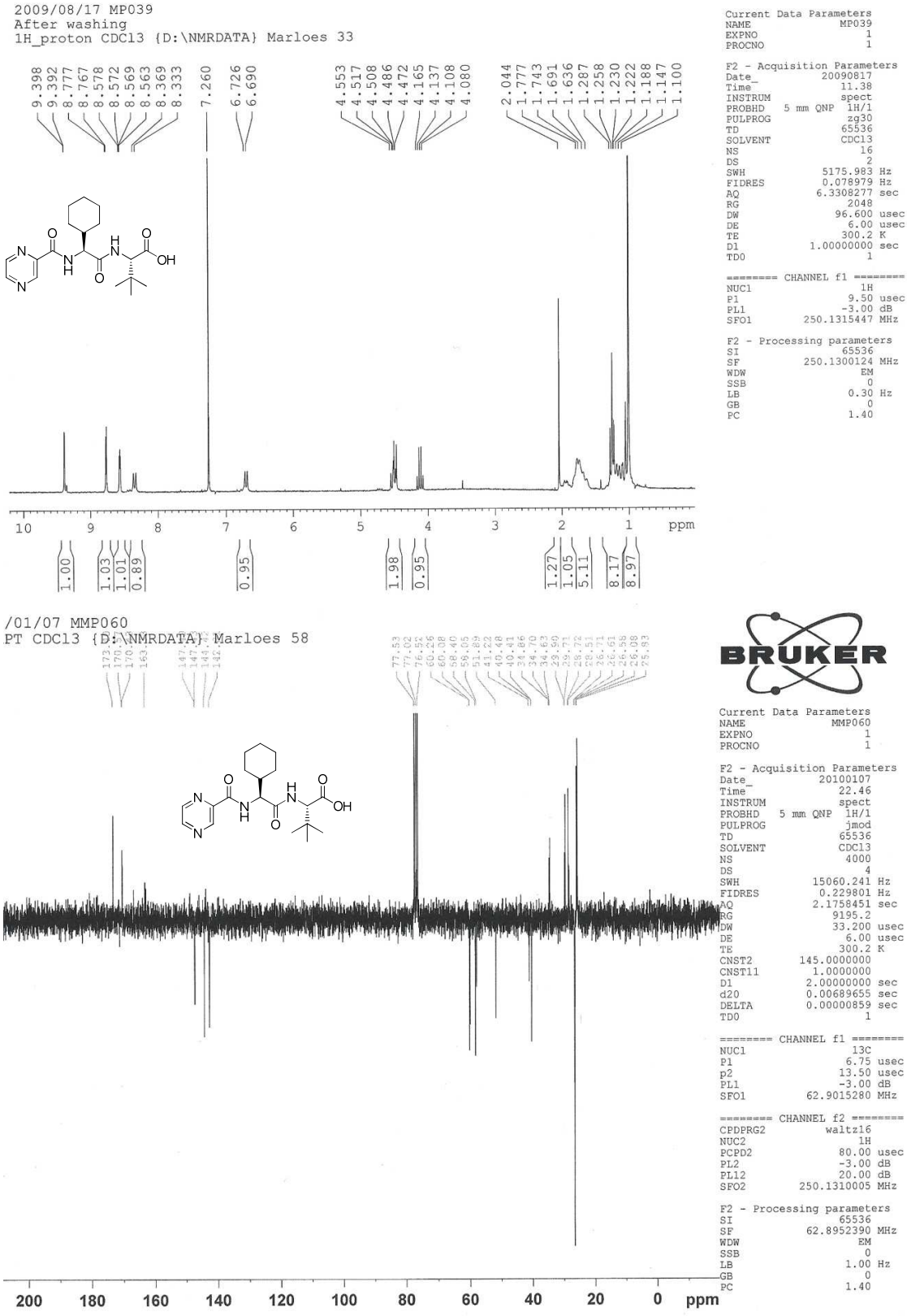




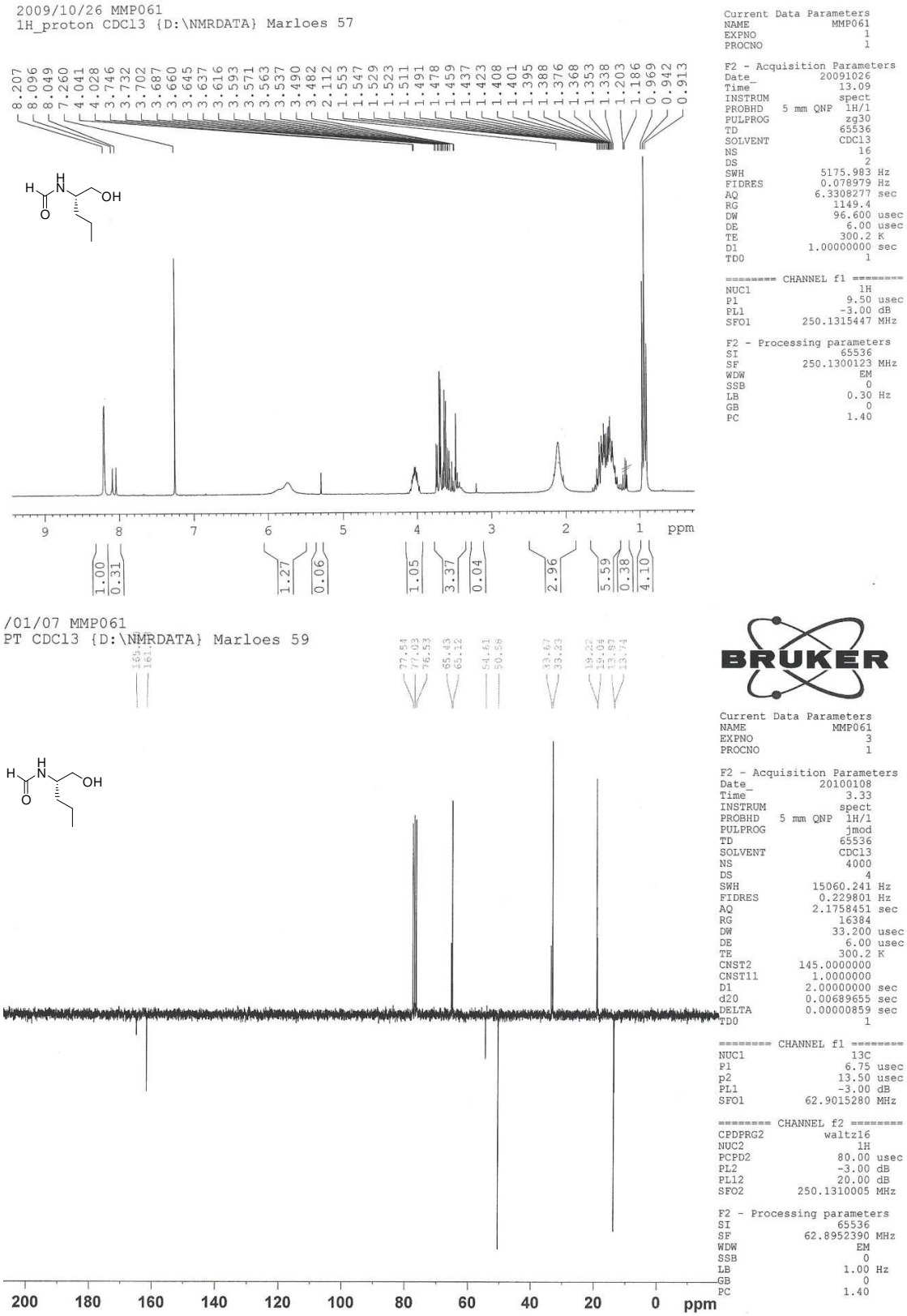
(*S*)-methyl 2-((*S*)-2-cyclohexyl-2-pyrazine-2carboxamido) acetamido)-3,3-dimethylbutanoate (11).



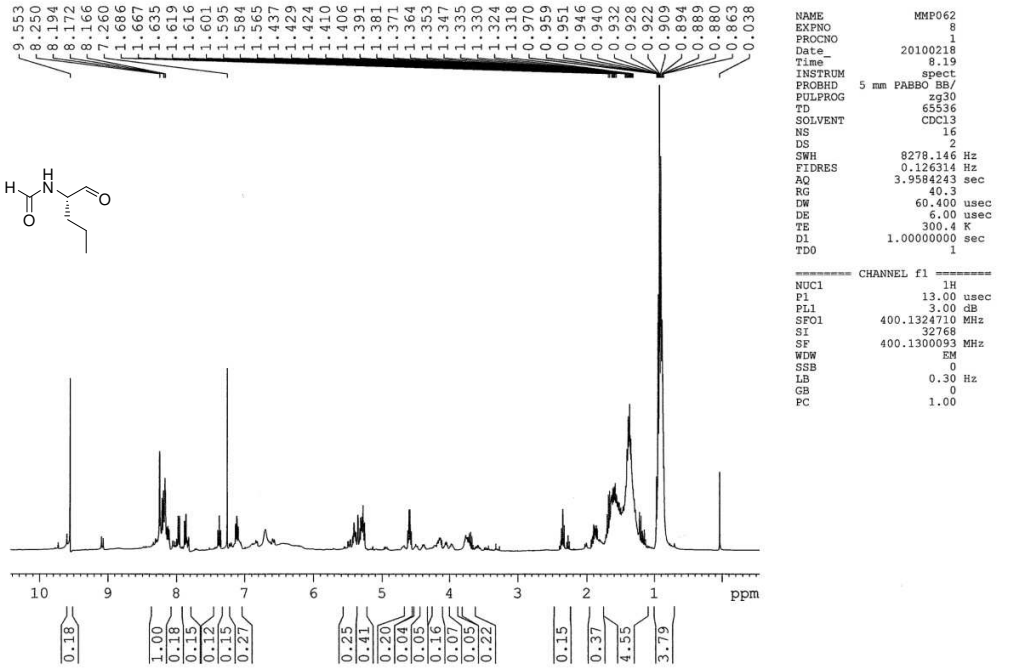
(*S*)-2-((*S*)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3 dimethylbutanoic acid (2).



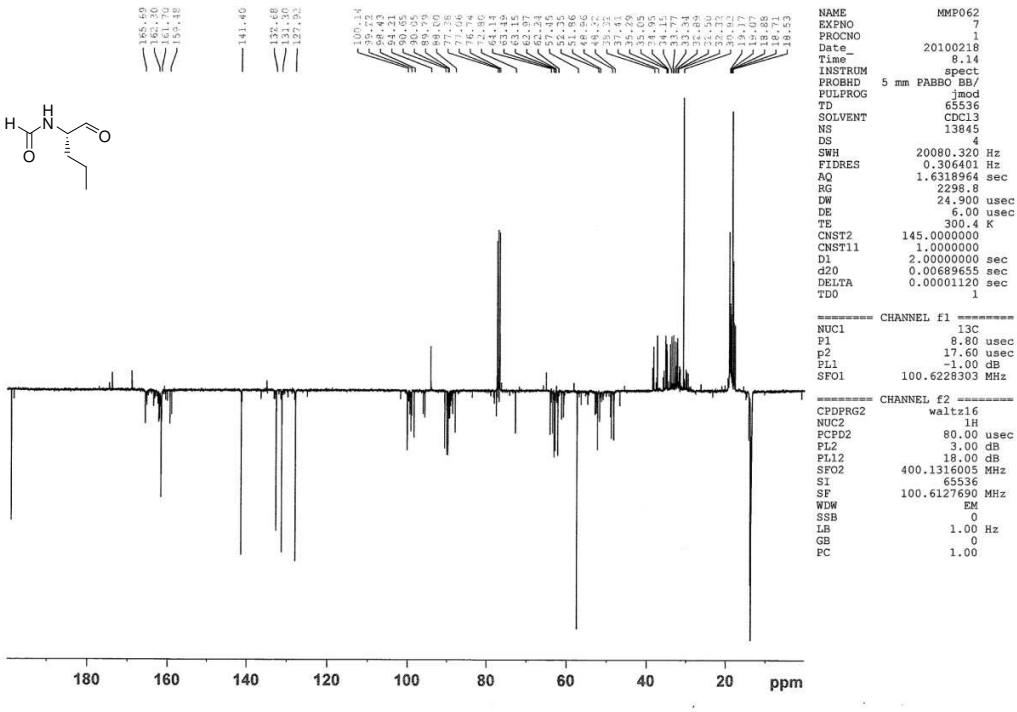
(*S*)-2-formamido-1-pentanol (12).



(*S*)- 2-formamidopentanal (7).

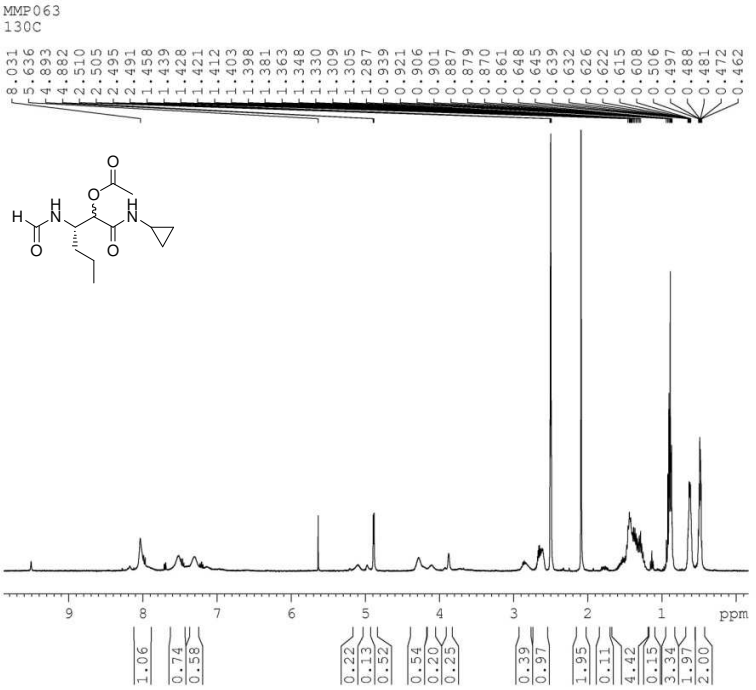


NAME	MMP062
EXPNO	8
PROCNO	1
Date_	20100218
Time_	8.19
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	40.3
DW	60.400 usec
DE	6.00 usec
TE	300.4 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	13.00 usec
PL1	3.00 dB
SFO1	400.1324710 MHz
SI	32768
SF	400.1300093 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

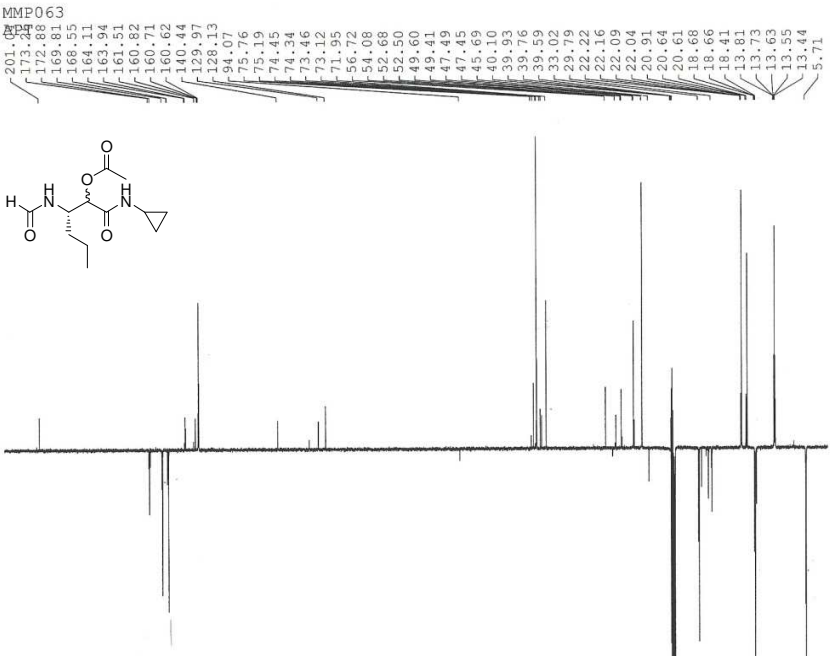


NAME	MMP062
EXPNO	7
PROCNO	1
Date_	20100218
Time	8.14
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	jmod
TD	65536
SOLVENT	CDCl3
NS	13845
DS	4
SWH	20080.320 Hz
FIDRES	0.306401 Hz
AQ	1.6318964 sec
RG	2298.8
DW	24.900 usec
DE	6.00 usec
TE	300.4 K
CNST2	145.0000000
CNST11	1.0000000
D1	2.00000000 sec
d20	0.00689655 sec
DELTA	0.00001120 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	8.80 usec
p2	17.60 usec
PL1	-1.00 dB
SFO1	100.6228303 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	3.00 dB
PL12	18.00 dB
SFO2	400.1316005 MHz
SI	65536
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

(3*S*)-2-acetoxy-*N*-cyclopropyl-3-formamido-hexanoyl amide (13).

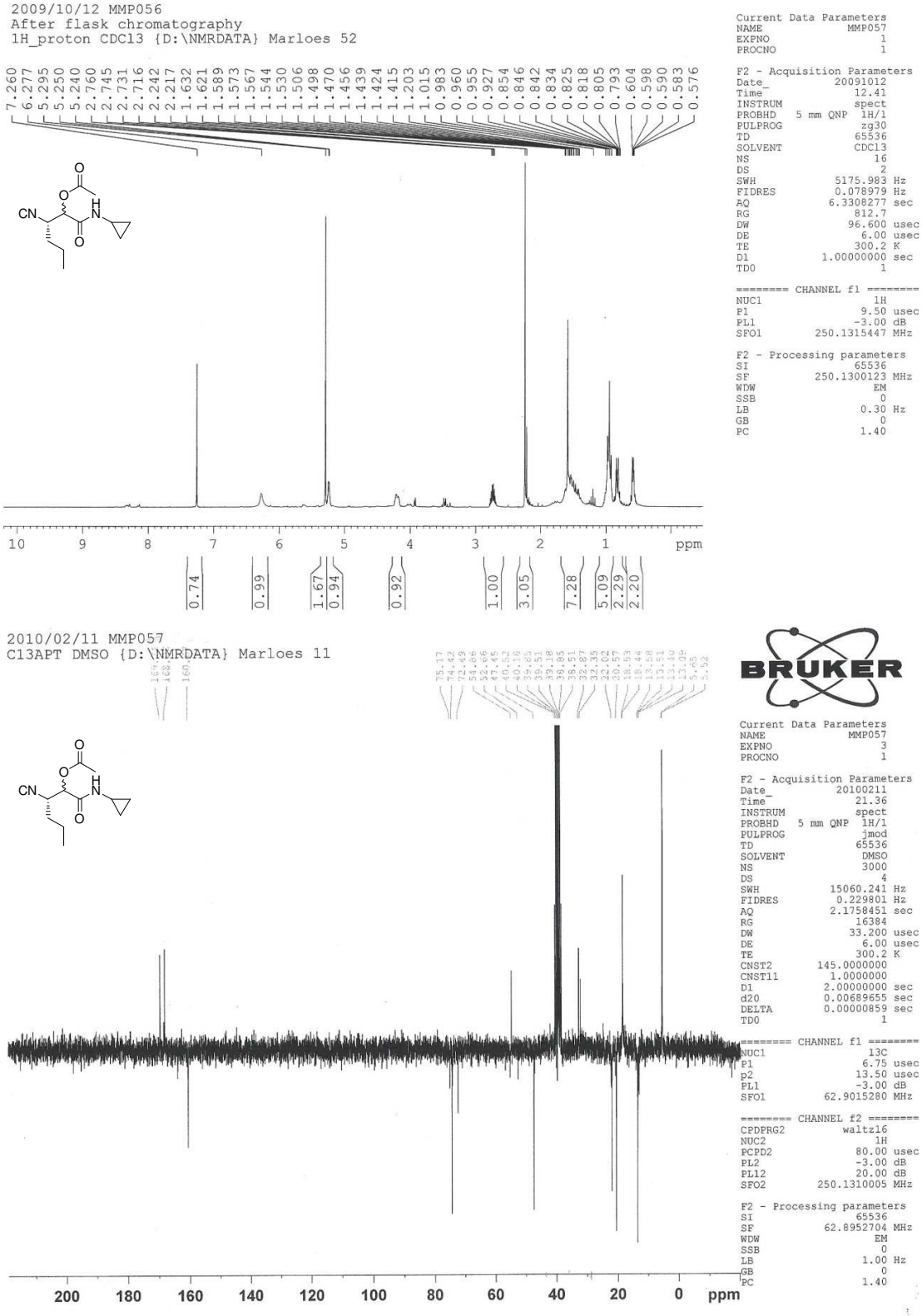


NAME	MMP063
EXPNO	3
PROCNO	1
Date_	20100111
Time	10.29
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	32768
SOLVENT	DMSO
NS	8
DS	2
SWH	5592.841 Hz
FIDRES	0.170680 Hz
AQ	2.9295092 sec
RG	228.1
DW	89.400 usec
DE	6.00 usec
TE	403.4 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	13.00 usec
PL1	3.00 dB
SFO1	400.1320007 MHz
SI	65536
SF	400.1300022 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	0.50

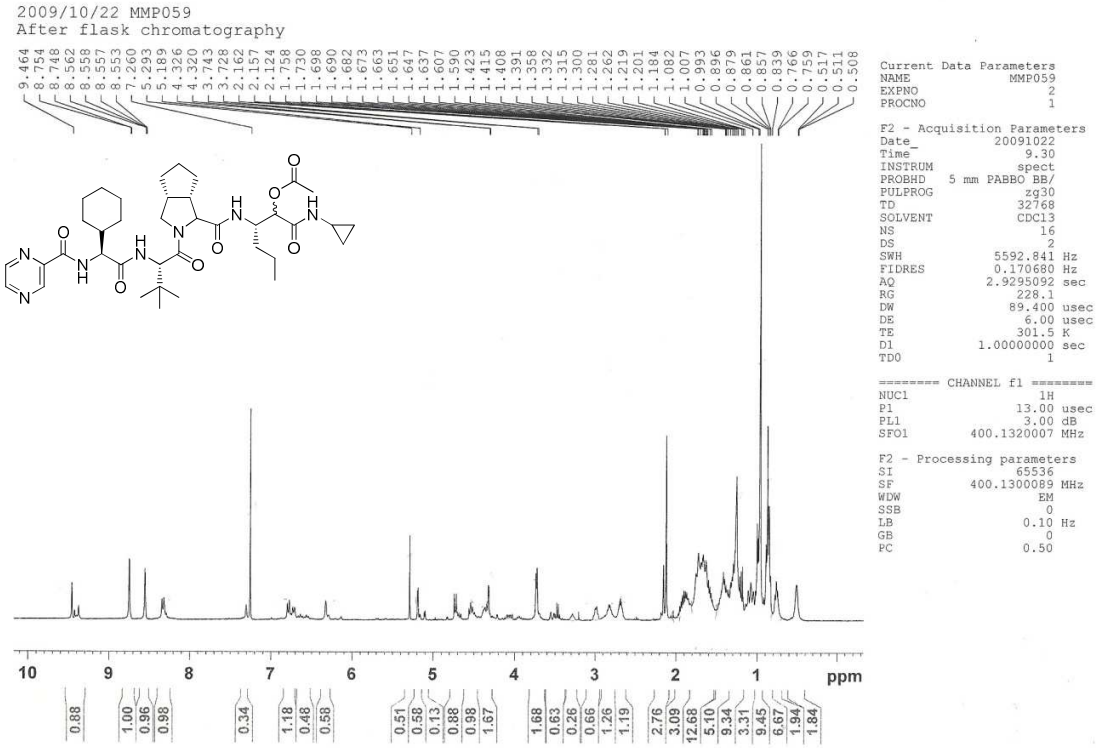


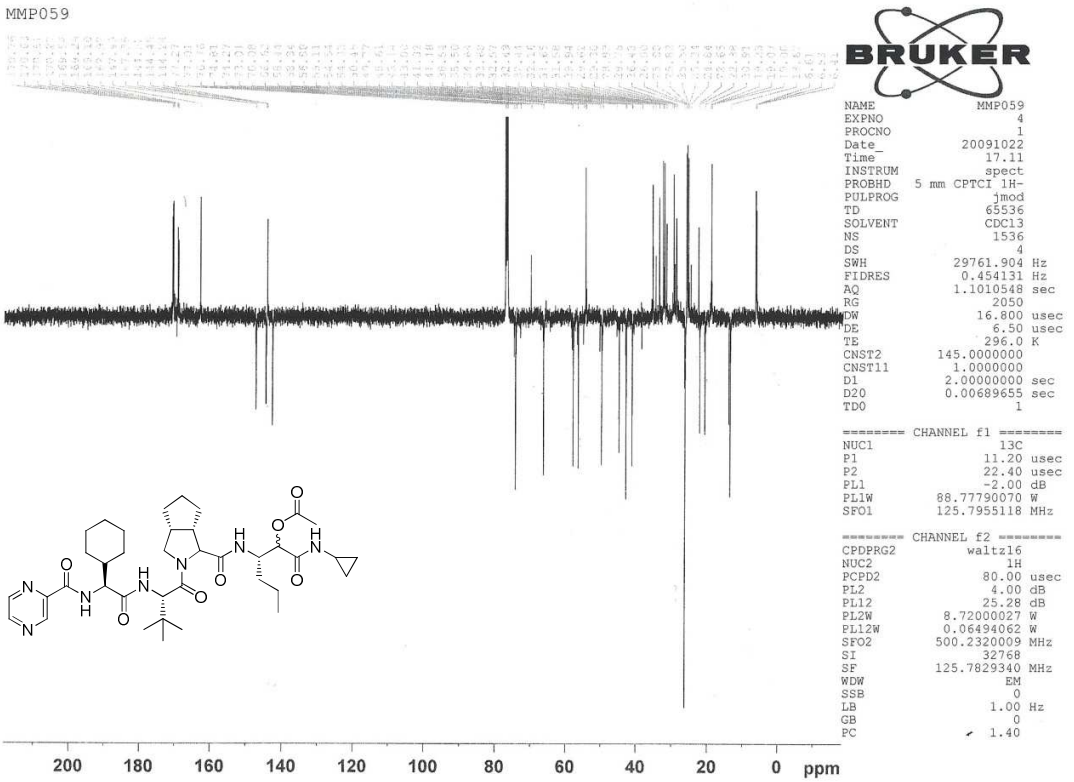
NAME	MMP063
EXPNO	7
PROCNO	1
Date_	20100111
Time	22.58
INSTRUM	spect
PROBHD	5 mm CPTCI 1H-
PULPROG	jmod
TD	65536
SOLVENT	DMSO
NS	4096
DS	4
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	2050
DW	16.800 usec
DE	6.50 usec
TE	296.1 K
CNST2	145.0000000
CNST11	1.0000000
D1	2.00000000 sec
D20	0.00689655 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.20 usec
P2	22.40 usec
PL1	-2.00 dB
PL1W	88.77790070 W
SFO1	125.7967701 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	4.00 dB
PL12	25.28 dB
PL2W	8.72000027 W
PL12W	0.06494062 W
SFO2	500.2325012 MHz
SI	131072
SF	125.7829925 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

(3*S*)-2-acetoxy-*N*-cyclopropyl-3-isocyano-hexanoyl amide (**4**)



Compound 14.


2009/10/22 MMP059
After flask chromatography
Current Data Parameters
NAME MMP059
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20091022
Time 9.30
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 32768
SOLVENT CDC13
NS 16
DS 2
SWH 5592.841 Hz
FIDRES 0.170680 Hz
AQ 2.9295092 sec
RG 228.1
DW 89.400 usec
DE 6.00 usec
TE 301.5 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 13.00 usec
PL1 3.00 dB
SFO1 400.1320007 MHz
F2 - Processing parameters
SI 65536
SF 400.1300089 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 0.50
10 9 8 7 6 5 4 3 2 1 ppm
0.88 1.00 0.96 0.98 0.34 1.18 0.48 0.58 0.51 0.58 0.13 0.88 0.98 1.67 1.68 0.63 0.26 0.66 1.26 1.19 2.76 3.09 12.68 5.10 9.34 3.31 9.45 6.67 1.94 1.84


MMP059
BRUKER
NAME MMP059
EXPNO 4
PROCNO 1
Date_ 20091022
Time 17.11
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG jmod
TD 65536
SOLVENT CDC13
NS 1536
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 2050
DW 16.800 usec
DE 6.50 usec
TE 296.0 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
D20 0.00689655 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 11.20 usec
P2 22.40 usec
PL1 -2.00 dB
PL1W 88.77790070 W
SFO1 125.7955118 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 4.00 dB
PL12 25.28 dB
PL2W 8.72000027 W
PL12W 0.06494062 W
SFO2 500.2320009 MHz
SI 32768
SF 125.7829340 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 180 160 140 120 100 80 60 40 20 0 ppm

Telaprevir (1).