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Graphical Abstract

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An asymmetric substrate-controlled Morita-Baylis-Hillman reaction as approach to the synthesis of poly-hydroxylated pyrrolizidinones and pyrrolizidines

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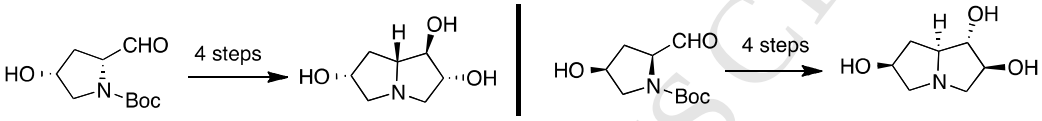

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An asymmetric substrate-controlled Morita-Baylis-Hillman reaction as approach for the synthesis of pyrrolizidinones and pyrrolizidines

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ABSTRACT

We describe herein an approach to the total synthesis of functionalized pyrrolizidinones and pyrrolizidines. The synthetic sequence is based on a highly stereoselective substrate-controlled Morita-Baylis-Hillman (MBH) reaction between a chiral amino-aldehyde and methyl acrylate. The selectivity attained in this reaction was controlled by the presence of a hydroxyl group adequately placed in the structure of the amino-aldehyde used as the nucleophilic component of the MBH reaction. The MBH adducts were used as substrate for an efficient total synthesis of pyrrolizidinones and pyrrolizidines in good overall yield.

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1. Introduction

The mammalian chemical machinery uses highly specialized paths to obtain the substances necessary to keep its homeostasis. Enzymes play an important role as part of essential biochemical pathways, many of them being of fundamental importance for maintenance of life of living organisms, particularly, our species.

Among the families of enzymes, glycosidases (EC 3.2.1) deserve special attention. Chemically, this group of enzymes catalyzes the hydrolysis of a bond joining a sugar of a glycoside to an alcohol or another sugar unit. They are responsible for regulating a great variety of biological processes, including the catalysis, degradation and biosynthesis of oligosaccharides and glycoconjugates, which are involved in variety of mechanisms, including different pathologies.[1] Glycosidases are also closely related to the preservation of the mammalian species, since it is generally accepted that some acid glycosidases are related to spermatozoa maturation and to the fusion of spermatozoon and ovum during fertilization.[2]

Efficient inhibitors of these enzymes may be applied to the treatment of several diseases or metabolic dysfunctions such as lysosomal storage diseases,[3] diabetes,[4] cancers,[5] malaria[6] and viral infections,[7] including influenza[8] and HIV.[9]

Alkaloids are good candidates as glycosidases inhibitors, specially those structurally related to carbohydrates (Figure 1).[10]

Polyhydroxylated pyrrolizidines are iminosugars of particular interest because of their selectivity, although their stereoselective syntheses remain challenging issues.

The biological activity of synthetic and naturally occurring polyhydroxylated pyrrolidizines has attracted attention in recent years leading to the development of new and more efficient approaches for the synthesis of compounds belonging to this class of heterocycles.[11-13]

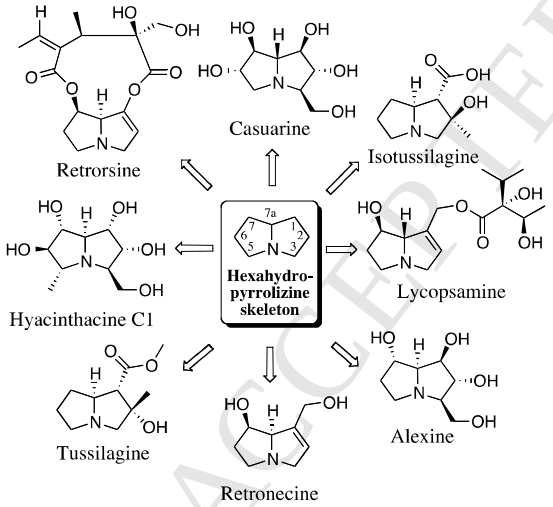


Figure 1. Representative examples of pyrrolizidine alkaloids

Pyrrolizidinones are compounds closely related to pyrrolizidines, which can be used, for example, as valuable substrates for the total synthesis of modified iminosugars,[12a] as catalysts,[14] and as prototypes for the development of new drugs for the treatment of inflammation.[14] Pyrrolizidinone **1** (Figure 2) was used by Barrett *et al.*[14] as a chiral auxiliary for the development of an asymmetric version for the Morita-Baylis-Hillman reaction, while pyrrolizidinone **2** is an inhibitor for the interaction of LFA-1 and its ligands. These compounds are involved in relevant biological events, such as cell adhesion, migration and activation. Selective LFA-1 inhibitors are drug candidates for the treatment of inflammation and autoimmune diseases.[15]

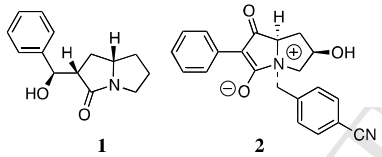
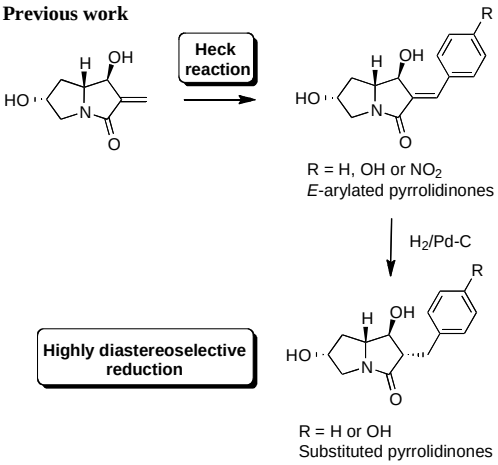


Figure 2. Examples of substituted pyrrolizidinones

In spite of the importance of substituted pyrrolizidinones, only a few approaches have been reported dealing with their total synthesis.[16]

As a result of ongoing research efforts directed to the development of new synthetic applications for the Morita-Baylis-Hillman reaction, some years ago we developed a simple and direct two-step approach to the preparation of the hexahydro-pyrrolizine skeleton (Scheme 1), which it is the basic structural motif of pyrrolizidine alkaloids.[17]

The Morita-Baylis-Hillman (MBH) reaction is an amazing organocatalyzed chemical transformation which presents a high atom-economy.[18,19] This sustainable transformation provides simple and rapid access to highly substituted small molecules which can be used as valuable starting materials for the syntheses of natural products, heterocyclic compounds and drugs.[20] The biological relevance of pyrrolizidines and pyrrolizidinones justifies the need to develop new synthetic alternatives for the preparation of these important classes of heterocycles. This goal, combined with our interest in exploring the synthetic potentiality of MBH products and their adducts, allowed us to extend our original approach focused now on the total synthesis of some new arylated pyrrolizidinone analogs (Scheme 1).[17,21]

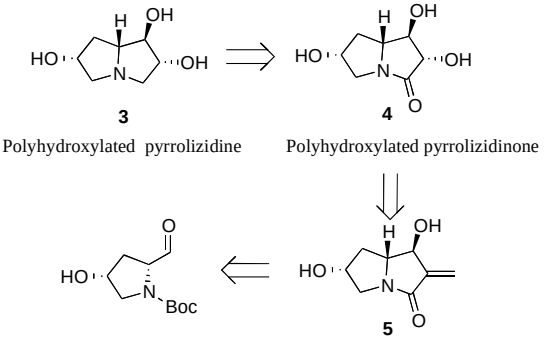


Scheme 1. Asymmetric synthesis of substituted pyrrolidinones from asymmetric Morita-Baylis-Hillman adduct

During the development of our most recent work,[21] we observed that the stereochemistry of the new stereogenic center formed during the Morita-Baylis-Hillman reaction was controlled by the hydroxyl group at C4. When this hydroxyl was oriented to the same side of the aldehyde carbonyl (*cis* orientation), an

intramolecular hydrogen bond occurs, decreasing the energy of this isomer when compared with the *trans* isomer (hydroxyl group placed in opposite side of the aldehyde carbonyl). Several experimental evidences were collected in order to demonstrate unambiguously this control.[22]

In this paper, we disclosed the results of a study focused on evaluating the generality of this effect and on the preparation of some key intermediates to the asymmetric synthesis of polyhydroxylated pyrrolizidinones and pyrrolizidines. To achieve our target a retrosynthetic analysis was conceived using chiral hydroxylated *cis*-prolinals **6** and **10** (Scheme 2) as substrates for the MBH reaction. The required heterocyclic compounds can be synthetized according to the retrosynthetic sequence disclosed below.

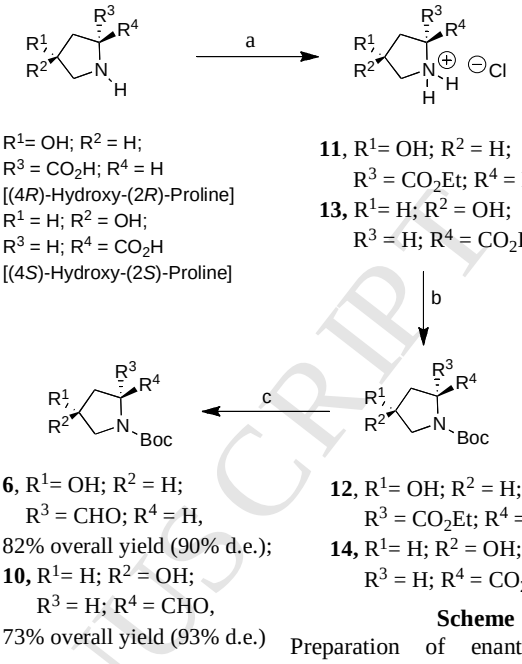


Scheme 2. Retrosynthetic sequence for the synthesis of pyrrolizidinones and pyrrolizidines

Based on the sequence shown in scheme 2, the synthesis of pyrrolizidinones **4** and **8** and pyrrolizidine **3** and **7** can be accomplished from intermediates **5** and **9,** which contain all functional groups required for the proposed chemical transformations. In fact, compounds **5** and **9** can be seen as a conformationally restricted MBH adduct, being itself a valuable tool to control the stereochemistry of new asymmetric centers formed during synthetic sequences. This rationale proved to be flexible and extremely efficient for the asymmetric total synthesis of the new highly substituted pyrrolizidinones and pyrrolizidines reported in this work.

2. Results and Discussion

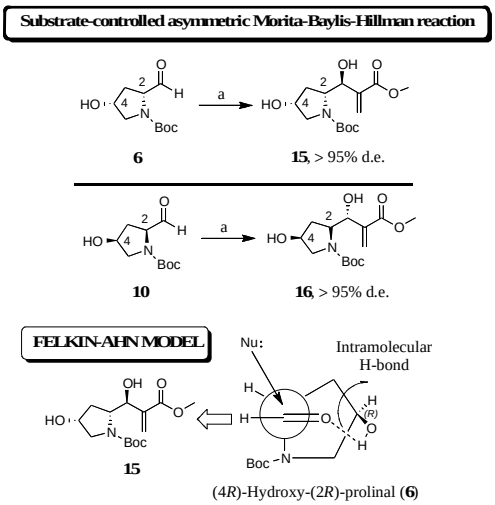
We began our work by transforming commercial (4*R*)-hydroxy-(2*R*)-proline into amino-aldehyde **6**, using a straightforward three step protocol already described in literature,[23] in 82% overall yield (Scheme 3). The same protocol was used to synthesize amino-aldehyde **9**, in 73% overall yield, from the enantiomeric commercial (4*S*)-hydroxy-(2*S*)-proline.



Scheme 3. Preparation of enantiomeric *cis*-prolinals **6** and **10** Reagents and conditions: a) $SOCl_2$, EtOH, reflux, 6h, 98% (both cases); b) $(Boc)_2O$, $NaHCO_3$, MeOH, ultrasound, 91%(**12**), 85% (**14**); c) DIBAL-H (1.0 mol.L^{-1}), CH_2Cl_2, -84 ºC, 30 min. 92% (**6**), 86%(**10**).

After confirmation of the enantiomeric purity by chiral gas chromatography, both aldehydes were treated with an excess of methyl acrylate and DABCO (0.65 equiv.) for 96h to give the corresponding MBH adducts **15** and **16**, in 70% and 67% yield, respectively. In both reactions, we were able to detect the presence of an unique diastereoisomer by chiral GC (Scheme 4).

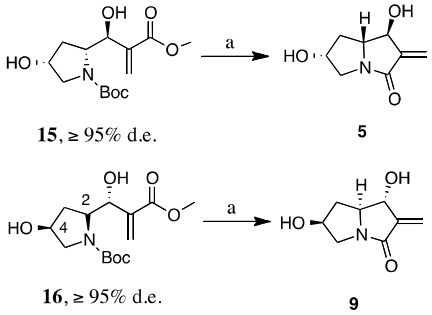
The intramolecular hydrogen bond described above can explain the high diastereoselectivity observed.[21,22] A*cyclic* intermediate exposes preferentially the face *Si* for aldehyde **6**, leading to the Felkin product **15**.[24]



Scheme 4. Highly diastereoselective preparation of Morita-Baylis-Hillman adducts **15** and **16**. Reagents and conditions: a) methyl acrylate, DABCO, 96h, r.t., 70% (**15**), 67% (**16**).

The hydroxyl group controls efficiently the aza-enolate attack when the *cis*-prolinal is used as substrate for this type of MBH reaction. After chromatographic filtration, adducts **15** and **16** were submitted to a cyclisation reaction in order to determined the relative configuration of them.

MBH adducts **15** and **16** were treated separately with conc. HCl in toluene, at 0 ºC for 5 min., followed by treatment with a 35% solution of NaOH to give cyclic compounds **5** and **9**, in 56% and 50% yield, respectively. All attempts we performed to optimize these experimental conditions failed (Scheme 5).



Scheme 5. Cyclisation of MBH adducts. Reagents and conditions: a) conc. HCl, toluene, 0 ºC, 5 min., then 35% NaOH, 0 ºC, 30 min., 56% (**5**), 50% (**9**)

Diastereoisomeric pyrrolizidinones **5** was analyzed through NMR experiments (nOe) aimed at confirming their relative stereochemistry.[25]When pyrrolizidinone **5** was irradiated at 4.51 ppm (H_6, Figure 3), we observed increments of 1.5% and 1.86 % on the hydrogen atoms at 2.35 ppm (H_{7B}) and 3.17 ppm (H_{5B}), respectively. This observation indicates that these hydrogens have a *cis* relationship with H_6. The irradiation of the hydrogen at 1.67 ppm (H_{7A}) showed increments of 1.50% and 0.49% on the hydrogen atoms at 4.61 ppm (H_1) and at 4.51 ppm (H_6), respectively. The hydrogen at 1.67 ppm was supposed to have a *cis* relationship with H_1. In order to collect more data on the relative stereochemistry of compound **5**, we irradiated the hydrogen at 2.35 ppm (H_{7B}) (Figure 3).

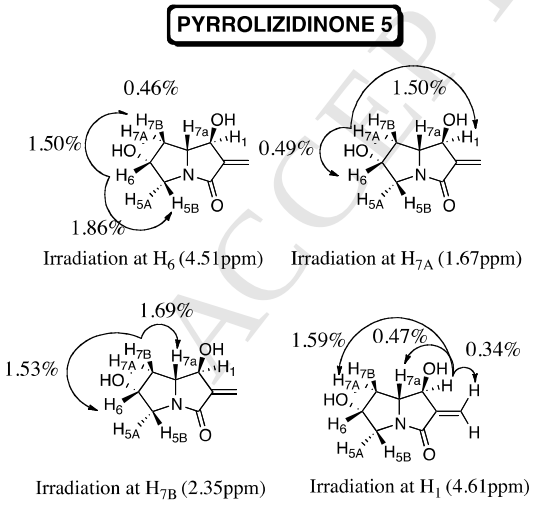
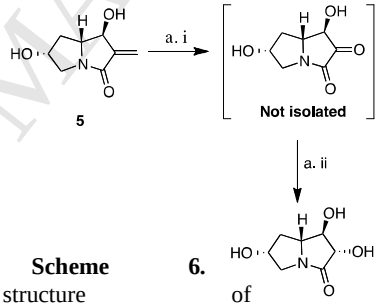


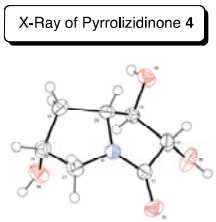
Figure 3. Determining the relative stereochemistry of pyrrolizidinone **5** by nOe experiments.

We observed an increment of 1.53% on the hydrogen at 4.51 ppm (H_6) and 1.69% on the hydrogen at 3.61 ppm, attributed to the hydrogen at the ring junction (H_{7a}). These data also indicated that hydrogens H_6 and H_{7a} have a *cis* relationship in regard to H_{7B}. Finally, we irradiated the carbinolic hydrogen at 4.61 ppm (H_1). This irradiation showed the same tendency, since we observed an increment of 1.59% on the hydrogen at 1.67 ppm (H_{7A}) and a low increment (0.47%) on the hydrogen at 3.61 ppm (H_{7a}).[23] Based on this data, there is a *cis* relationship between the hydrogen at H_{7a} (ring junction), the carbinolic proton at 4.51 (H_6) and the hydrogens at 2.35 ppm (H_{7B}) and at 3.17 ppm (H_{5B}), as well as a *trans* relationship with the carbinolic hydrogen at 4.61 ppm (H_1). These data led us to confirm the relative stereochemistry proposed for pyrrolizidinone **5** (Figure 3).

A nOe study was also performed with the pyrrolizidinone **9** and confirmed unambiguously its the relative stereochemistry.

Searching to collect more information about these pyrrolizidinones we tried to crystallize them. We intend to get a monocrystal in order to collect R-X crystallographic data. Unfortunately, all attempts to crystallize them failed. As an attempt to circumvent this issue and obtain a crystalline solid compound, we decided to go further with our synthetic planning. Then, a solution of pyrrolizidinone **5** in a mixture dichloromethane: methanol (8:2) was treated with ozone at -78 °C for 10 min. The intermediate ozonide was then treated *in situ* with $NaBH_4$ at -78 °C to provide, after chromatographic filtration, the trihydroxylated pyrrolizidinone **4**, as a single isomer, in 80% yield (Scheme 6).





Scheme 6. Synthesis and X-ray structure of trihydroxylated pyrrolizidinone **4**. Reagents and conditions: a) i. O_3, CH_2Cl_2: MeOH (8:2), -78 ºC, 10 min. ii) $NaBH_4$, - 78 ºC to r.t., 4h, 83%.

Pleasingly, **4** was a solid and, after recrystallization (ethanol : ethyl ether),[26] good diffractive crystals were obtained. X-ray diffraction data confirmed the relative stereochemistry of pyrrolizidinone **4** and consequently the stereochemistry of the MBH adduct **15** (Scheme 6).[27, 28, 29, 30]

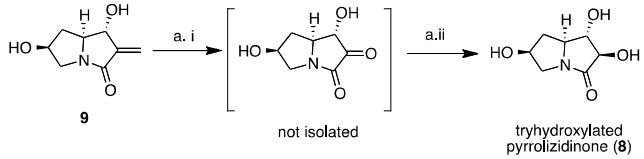
We have tried the same crystallization procedure to obtain a crystal of pyrrolizidinone **9**, however we did not succeed.

Interestingly, for both pyrrolizidinones we obtained a high selectivity in the reduction step with $NaBH_4$. The release of the hydride in both cases seems to have been directed by the hydroxyl group at C1, probably through a complex formed between the hydride and hydroxyl group.

At this point it was necessary to get information about the relative stereochemistry of pyrrolizidinone **8**. Mono- and bi-dimensional NMR data (^{1}H and COSY) has allowed us to have some information about the relative stereochemistry of **8**. Initially, the analysis of both spectra allowed the correct attribution of each hydrogen atom of the structure. So, the signal at 4.77 ppm was attributed to H_2, while that centered at 4.17 ppm

was attributed to H_1. Both hydrogens show a coupling constant of 8.4Hz, which suggest a *trans* relationship between them.

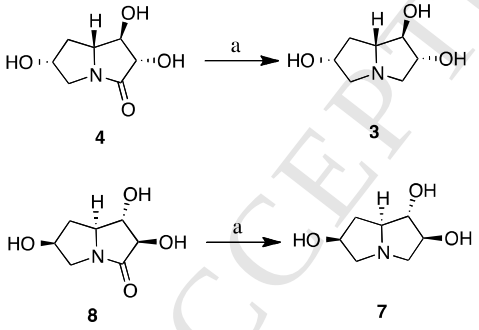
To also obtain crystallographic data for the enantiomeric pyrrolizidinone **9**, an analogous experimental sequence was employed. A solution of **9** in a mixture of dichloromethane : MeOH (7 : 3) was treated with a flow of O_3 at – 78 °C for 10 min. and the reaction medium was then quenched with $NaBH_4$ to furnish the trihydroxylatedpyrrolizidinone**8** in 80% yield, as a white solid. Recrystallization of **8** in a mixture ethanol : chloroform[26] failed and we were unable to get crystal good enough to collect crystallographic data (Scheme 7).[27, 28, 30, 31]



Scheme 7. Synthesis of trihydroxylated pyrrolizidinone **8**. Reagents and conditions: a) i. O_3, CH_2Cl_2 : MeOH (8 : 2), -78 ºC, 10 min. ii) $NaBH_4$, - 78 ºC to r.t., 4h, 80%.

The enantiomeric purity of pyrazolidinone **8** was confirmed by chiral gas chromatography.

Pyrrolizidinones **4** and **8** were synthesized for the first time in three steps from aldehydes **6** and **10** with an overall yield of 32% and 27%, respectively. At this stage of our work we have established an easy and efficient way to prepare these compounds starting from a chiral Morita-Baylis-Hillman adduct. After ascertaining the stereochemical data for these compounds, we proceed towards the total synthesis of hydroxylated pyrrolizidines. This aim was accomplished by treating the trihydroxylated pyrrolizidinone **4** and **8** with alane (AlH_3)[32] to provide the trihydroxylated pyrrolizidines **3** and **7**, in 4 steps, with an overall yield of 26 and 21%, respectively (Scheme 8). It is worth noting that the first synthesis reported for compound **4** was accomplished in 11 steps with an overall yield of 4%.[33] Besides, no protecting group was required in our sequence after cyclization of the MBH adducts.



Scheme 8. Synthesis of the trihydroxylated pyrrolidines **3** and **7** from a MBH adduct. Reagents and conditions: a) AlH_3 (17 equiv.) ($AlCl_3$: $LiAlH_4$, 1 mol/L), THF, reflux, 3 h, 80% (for both reactions)

In order to confirm the relative stereochemistry of pyrrolidine **7**, nOe experiments were performed. The results are summarized in the Figure 4. When signal at 4.56 ppm (attributed to H_6) was irradiated, increments in hydrogen atoms H_{7A}, H_{5A} and H_{7a} were observed (1.58, 1.46 and 0.46%, respectively). These results show that all these hydrogen atoms are in the same side of the molecule. Otherwise, the irradiation of H_1, centered at 4.31, showed an increment of 1.52% on hydrogen atom H_{7B} and another of 0.72% on hydrogen atom at H_{3B}. A similar procedure was done and signal at 4.27 ppm (H_2) was irradiated, and increments of 1.22% on hydrogen atom at H_{3A} and another of 0.46% at H_{7a} were observed. Finally, when hydrogen H_{7a} was irradiated, increments of 2.14% in H_{7A}, of 0.45% for H_6 and of 0.48% for H_2 were detected.

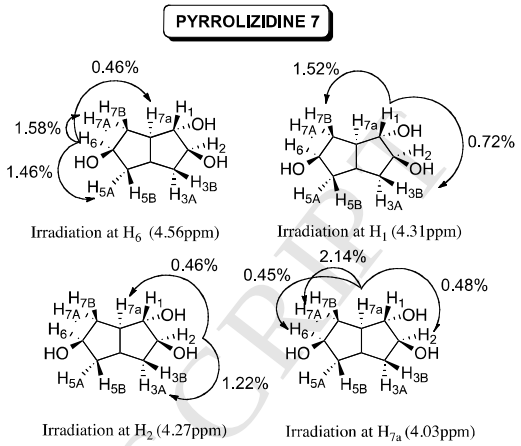


Figure 4. nOe data for pyrrolizidine **7**.

These data confirmed unambiguously the relative stereochemistry of pyrrolizidine **7**, and consequently that of pyrrolizidinone **9**.

3. Conclusion

In summary, we have described the total synthesis of polyfunctionalized pyrrolizidinones and pyrrolizidines using Morita-Baylis-Hillman products as substrates, in a few steps and in moderated to good overall yields. This approach has allowed for the asymmetric total synthesis of two new pyrrolizidinones and two trihydroxylated pyrrolizidines. The relative stereochemistries of the compounds were confirmed by spectroscopic data. Thanks to the control exerted by the hydroxyl group adequately placed on the structure of the prolinal used as starting material, it was possible to perform a substrate-controlled asymmetric Morita-Baylis-Hillman with a high diastereoselective control. This simple approach allows for the preparation of the hexahydro-pyrrolizine skeleton in two steps and presents great potentiality to be used in the total synthesis of pyrrolizidines isolated from natural sources. Efforts towards the generalization of this method to the synthesis of pyrrolizidines with different substitutions patterns are ongoing and will be disclosed in due time.

4. Experimental section

General information: The ^1H spectra were recorded at 250 MHz, 400 MHz, 500 MHz and 600 MHz. The ^{13}C spectra were recorded at 62.5 MHz, 125 MHz, 250 MHz. The high resolution mass spectra were recorded at the Analytical Central of Institute of Chemistry. Manipulations and reactions were not performed under dry atmospheres or employing dry solvents, unless otherwise specified. In those cases CH_2Cl_2, DMF, and triethylamine were dried over CaH_2 and distilled. Purification and separations by column chromatography were performed on silica gel, using normal or flash chromatography. TLC visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. All Morita-Baylis-Hillman reactions were sonicated in an ultrasonic cleaner (81W, 40 MHz).

*4.1. tert-butyl (2R,4R)-2-formyl-4-hydroxypyrrolidine-1-carboxylate **(6)**:*

A stirred solution of 1-*tert*-butyl 2-ethyl(2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate **12** (0.25 g, 0.96 mmol) in anhydrous dichloromethane (5 mL), at -84 ºC and under argon atmosphere, was slowly added (during 5 minutes) to a toluene solution of DIBAL-H (1.0 mol/L solution, 1.9 mL, 2.89 mmol). The mixture was stirred for 20 min at the same temperature. TLC followed reaction evolution. The cooling bath was removed and a saturated solution of sodium acetate (5 mL) was added. The reaction medium was poured into a stirred mixture of ethyl ether (50 mL) and saturated ammonium chloride (10 mL). After 2h, the gel formed was filtered over a pad of Celite® and the aqueous filtrate was extracted again with ethyl ether. The organic phases were combined, dried over anhydrous Na_2SO_4 and evaporated. The residue was quickly filtered over a tiny amount of silica gel (hexane : EtOAc 40 : 60 to 20 : 80), to provide amino aldehyde **6**, as colorless oil (0.188 g) in 91 % yield. Hydroxy-aldehyde **6** should be stored at -20 ºC or used immediately after being prepared. $[\alpha]_D^{20}$ +45 (c 1.5; MeOH); IR (film, ν_{max}): 3377, 2974, 2931, 2838, 1728, 1646, 1428, 1370, 1279 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6, 90 ºC) δ 1.42 (9H, s), 1.89 (1H, m), 2.23 (1H, ddd, *J* = 13.5, 9.6, 4.1 Hz), 3.31 (1H, dt, *J* = 11.2, 1.7 Hz); 3.42 (1H, dd, *J* = 11.2, 4.2 Hz), 4.04 (1H, dt, *J* = 9.6, 2.5 Hz), 4.27 (1H, m), 9.47 (1H, s); ^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) δ 28.5, 38.1, 55.2, 64.1, 68.7, 79.7, 154.7, 202.8; HRMS (ESI-TOF): Calcd. for $C_{10}H_{18}NO_4$ $[M + H]^+$ 216.1236. Found 216.1245. GC conditions: β-cyclodextrin chiral column, flow 1.5 mL/min; 100 °C; 10 °C/min up to 230 ºC; pos run: 230 °C/15 min); T_R = 15.57 min (**2**); 90 % d.e.

*4.2. tert-butyl (2S,4S)-2-formyl-4-hydroxypyrrolidine-1-carboxylate **(10)**:*

Following the general procedure for the preparation of **6**, the ester **14** (0.25 g, 0.96 mmol) was submitted to reduction to afford 0.190 g of the amino aldehyde **10** (92 %), as a colorless oil, after quick filtration over a tiny amount of flash silica gel (hexane : EtOAc 40 : 60 to 20 : 80). Amino aldehyde **10** should be stored at -20 ºC or used immediately after preparation. $[\alpha]_D^{20}$ -42 (c 1.5; MeOH); IR (film, ν_{max}): 3377, 2974, 2931, 2838, 1728, 1646, 1428, 1370, 1279 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6, 90 ºC) (250 MHz, DMSO-d_6, 90 ºC) δ 1.42 (9H, s), 1.9 (1H, m), 2.23 (1H, m), 3.31 (1H, dd), 3.46 (1H, dd), 4.04 (1H, m), 4.28 (1H, m), 9.49 (1H, s).^{13}C NMR (250 MHz, DMSO-d_6, 90 ºC) δ 28.5, 37.7, 55.2, 64.2, 68.8, 79.8, 154.4, 201.8; HRMS (ESI-TOF): Calcd. for $C_{10}H_{18}NO_4$ $[M + H]^+$ 216.1236. Found 216.1245; GC conditions: β-cyclodextrin chiral column, flow 1.5 mL/min; 100 °C; 10 °C/min up to 230 ºC; pos run: 230 °C/15 min); T_R = 15.57 min (**2**); 90 % d.e.

*4.3. Diastereoisomeric MBH adducts **(15)** and **(16)**.*

Hydroxy-aldehyde **6** and **10** (0.23 g, 1.069 mmol), DABCO (0.12 g, 1.069 mmol) and ethyl acrylate (2 mL) was sonicated for 96 h (followed by GC). Then, the excess of methyl acrylate was removed under reduced pressure (**CAUTION**: this operation should be performed under an efficient fume hood). The residue was diluted with dichloromethane (20 mL). The organic phase was washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4 and evaporated. The crude residue was purified by flash silica gel column chromatography (hexane : CH_2Cl_2 : EtOAc – 3.0:5.0:3.0) to provide adducts **15** (0.206 g) as colorless oils, in 70 % yield, and **16** (0.193 g) as colorless oils, in 67 % yield.

*4.3.1. tert-butyl (2R,4R)-4-hydroxy-2-[(1S)-1-hydroxy-3-methoxy-2-methylidene-3-oxopropyl]pyrrolidine-1-carboxylate **(15)**:*

$[\alpha]_D^{20}$-2 (c 1.5; MeOH); IR (film, ν_{max}): 3387, 2970, 2958, 2933, 2355, 2332, 1715, 1666, 1413, 1368, 1155, 1090 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6, 90 °C) δ 1.43 (s, 9H), 1.74 (dt, *J* = 13.9, 4.3 Hz, 1H), 1.92 (m, 1H), 3.10 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.57 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.71 (s, 3H), 4.05 (m, 2H), 4.94 (m, 1H), 5.87 (t, *J* = 1.6 Hz, 1H), 6.17 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) δ 27.8, 32.9, 50.8, 54.8, 58.6, 67.4, 68.0, 78.0, 124.0, 142.2, 153.2, 165.6; HRMS (ESI-TOF): Calcd. for $C_{14}H_{24}NO_6$ $[M + H]^+$ 302.1604. Found 302.1631; GC conditions: β-cyclodextrin chiral column, flow 1.5 mL/min; 100 °C; 10 °C/min up to 230 ºC; pos run: 230 °C/15 min); T_R = 22.97 min.

*4.3.2. tert-butyl (2S,4S)-4-hydroxy-2-[(1R)-1-hydroxy-3-methoxy-2-methylidene-3-oxopropyl]pyrrolidine-1-carboxylate **(16)**:*

$[\alpha]_D^{20}$ +1 (c 1.5; MeOH); IR (film, ν_{max}): 3402, 2879, 2952, 1720, 1670, 1417, 1368, 1273, 1163, 1092 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6, 90 °C) δ 1.44 (s, 9H), 1.78 (dt, *J* = 13.7, 4.3 Hz, 1H), 1.93 (m, 1H), 3.11 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.58 (dd, *J* = 11.3, 5.9 Hz, 1H), 3.71 (s, 3H), 4.06 (m, 2H), 4.93 (m, 1H), 5.84 (t, *J* = 1.7 Hz, 1H), 6.12 (d, *J* = 1.2 Hz, 1H);^{13}C NMR (250 MHz, DMSO-d_6, 90 ºC) δ 28.7, 34.1, 51.6, 55.9, 59.8, 68.6, 69.5, 79.1, 124.6, 143.4, 154.3, 166.7. HRMS (ESI-TOF): Calcd. for $C_{14}H_{24}NO_6$ $[M + H]^+$ 302.1604. Found 302.1634; GC conditions: β-cyclodextrin chiral column, flow 1.5 mL/min; 100 °C; 10 °C/min up to 230 ºC; pos run: 230 °C/15 min); T_R = 22.09 min.

*4.4. (1S,6R,7aR)-1,6-dihydroxy-2-methylidene-hexahydro-1H-pyrrolizin-3-one **(5)**:*

To a stirred solution of the Morita-Baylis-Hillman adduct **15** (0.20 g, 0.66 mmol) in toluene (3 mL), at 0 °C, it was added concentrated HCl (0.1 mL, 3.31 mmol). The resulting mixture was further stirred for 5-7 min. Then, a 35% solution of NaOH was added (0.46 mL, 4 mmol) and the reaction was further stirred for 30 min, at room temperature. The medium was neutralized to pH 7 (10% HCl solution) and the solvents were removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography (CH_2Cl_2 : MeOH– 95 : 05) to give pyrrolizidinone **5** (0.06 g) as a white solid, in 57 % yield. $[\alpha]_D^{20}$ -5 (c 2; EtOH); M.p. 93-94° C; IR (KBr): ν 3396, 3205, 2985, 2946, 2883, 1654, 1442 cm^{-1};^1H NMR (500 MHz, $(CD_3)_2CO$) δ 1.67 (m, *J* = 13.4, 6.4, 4.4 Hz, 1H, H-7A), 2.35 (ddd, *J* = 13.4, 7.3, 5.6 Hz, 1H, H-7B), 3.17 (dd, *J* = 12.2, 5.2 Hz, 1H, H-5B), 3.57 (dd, *J* = 12.2, 2.9 Hz, 1H, H-5A), 3.62 (ddd, *J* = 7.3, 6.4, 5.2 Hz, 1H, H-7a), 4.51 (m, *J* = 5.2, 3.2 Hz, 1H, H-6), 4.61 (m, *J* = 5.2, 2.9 Hz, 1H, H-1), 5.47 (d, *J* = 2.6 Hz, 1H, CH_2), 5.82 (d, *J* = 3.0 Hz, 1H, CH_2); ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) δ 38.3, 51.6, 65.7, 71.9, 75.7, 114.8, 148.4, 168.3; HRMS (ESI-TOF): Calcd. for $C_8H_{12}NO_3$ $[M + H]^+$ 170.0817. Found 170.0844.

*4.5. (1R,6S,7aS)-1,6-dihydroxy-2-methylidene-hexahydro-1H-pyrrolizin-3-one **(9)**:*

Following the general procedure for the preparation of **5**, the Morita-Baylis-Hillman adduct **16** (0.05 g, 0.165 mmol) was submitted to cyclization to afford 0.012 g of the pyrrolizidinone **9** (55%), as a colorless oil, after flash silica gel column chromatography (CH_2Cl_2 : MeOH– 95 : 05). $[\alpha]_D^{20}$ +4.2 (c 2; EtOH); M.p. 93-94° C; IR (KBr): ν 3396, 3205, 2985, 2946, 2883, 1654, 1442 cm^{-1};^1H NMR (400 MHz, (CD_3CN) δ 1.64 (m, *J* = 12.4, 6.0 Hz, 1H, H-7B), 2.35 (ddd, *J* = 13.2, 6.8 Hz, 1H, H-7A), 3.20 (dd, *J* = 12.4, 5.2 Hz, 1H, H-5A), 3.52 (dd, *J* = 12.4, 2.8 Hz, 1H, H-5B), 3.63 (dd, *J* = 7.2, Hz, 1H, H-7a), 4.49 (m, *J* =

5.2 Hz, 1H, H-6), 4.59 (m, *J* = 5.2, 2.4 Hz, 1, H-1), 5.51 (d, *J* = 2.4 Hz, 1H, CH_2), 5.87 (d, *J* = 2.8 Hz, 1H, CH_2); ^{13}C NMR (400 MHz, (CD_3CN) δ 36.3, 49.5, 64.1, 70.3, 73.6, 114.4, 145.0, 167.0. HRMS (ESI-TOF): Calcd. for $C_8H_{12}NO_3$ $[M + H]^+$ 170.0817. Found 170.0844.

*4.6. (1R,2S,6R,7aR)-1,2,6-trihydroxy-hexahydro-1H-pyrrolizin-3-one **(4)**:*

A solution of pyrrolizidinone **5** (0.08 g, 0.47 mmol) in a mixture MeOH : CH_2Cl_2 (2:8, 15mL) was cooled to -72 ^{0}C and a flow of ozone (0.4% in a flow of oxygen) was bubbled into the solution for 8-10 min. Then, $NaBH_4$ (0.089 g, 2.36 mmol, 5 equiv.) was added to the reaction medium at -72 ºC, and the resulting mixture was stirred, at room temperature, for 6 h. The reaction was initially acidified to pH 2-3 with a solution of HCl in MeOH, and afterwards was neutralized to pH 6-7 with solid Na_2CO_3. The mixture was filtered over a pad of Celite®, and the solid was washed with MeOH. The combined organic phases were removed under reduced pressure. The residue was purified by silica gel (230-400 mesh) column chromatography using a mixture CH_2Cl_2 : MeOH (95:05), to provide pyrrolizidinone **4** in 80% yield (0.06 g), as a white solid. $[\alpha]^D_{20}$ + 4º (c 1, MeOH); mp: 151-152° C; IR (KBr, ν_{max}): 3411, 2916, 2849, 1685, 1442, 1206 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.93 (m, *J* = 13.1, 5.5 and 3.7 Hz, 1H, H-7A), 2.57(ddd, *J* = 13.8, 5.5 and 5.5 Hz, 1H, H-7B), 3.34 (ddd, *J* = 12.4, 4.9 and 1.6 Hz, 1H, H-5B), 3.73 (d, *J* = 12.4, 1H, H-5A), 3.85 (td, $J_{1,7a}$ = 7.9, *J* = 5.5 Hz, 1H, H-7a), 4.17 (dd, $J_{1,2}$ = 8.9, $J_{1,7a}$ = 7.9 Hz, 1H, H-1), 4.66 (dd, $J_{1,2}$ = 8,9, *J* = 1.3 Hz, 1H, H-2), 4.71(m, 1H, H-6); ^{13}C NMR (62.5 MHz, MeOD) δ 38.7, 52.5, 62.6, 72.4, 78.8, 83.8, 175.7; HRMS (ESI-TOF, *m/z*): Calc. for $C_7H_{11}NO_4Na$ [M + Na]+: 196.0586. Found: 196.0579.

*4.7. (1S,2R,6S,7aS)-1,2,6-trihydroxy-hexahydro-1H-pyrrolizin-3-one **(8)**:*

Following the general procedure for the preparation of **4**, pyrrolizidinone **9** (0.10 g, 0.59 mmol) in a mixture of MeOH : CH_2Cl_2 (3 : 7, 15mL) was submitted to ozonolysis and reduction to afford 0.08 g of the pyrrolizidinone **8** (83 %), as a white solid, after flash silica gel (230-400 mesh) column chromatography (CH_2Cl_2 : MeOH – 95:05). $[\alpha]^D_{20}$ - 3.8º (c 1, MeOH); M.p. 150-152 °C; IR (KBr, ν_{max}): 3411, 2916, 2849, 1685, 1442, 1206 cm^{-1}.^{1}H NMR (400 MHz, CD_3CN)) δ 1.96 (m, *J* = 12.4, 3.2, 1.2 Hz, 1H, H-7B), 2.50 (ddd, *J* = 13.6, 6.4, 3.2 Hz, 1H, H-7A), 3.25 (ddd, *J* = 11.6, 4.4, 1.2 Hz, 1H, H-5A), 3.76 (td, $J_{1,7a}$ = 7.6, *J* = 4.8 Hz, 1H, H-7a), 3.84 (d, *J* = 12.0, Hz, 1H, H-5B), 4.12 (dd, $J_{1,2}$ = 8.4, $J_{1,7a}$ = 7.6 Hz, 1H, H-1), 4.50 (dd, $J_{1,2}$ = 8.4,*J* = 1.2 Hz, 1, H-2), 4.62 (m, 1H, H-6); ^{13}C NMR (250 MHz, MeOD) δ 35.7, 49.5, 59.5, 69.4, 75.7, 80.8, 172.7;HRMS (ESI-TOF, *m/z*): Calc. for $C_7H_{12}NO_4$[M + H]$^+$: 174.0761. Found 174.0754.

*4.8. (1R,2R,6R,7aR)-hexahydro-1H-pyrrolizine-1,2,6-triol **(3)**:*

To a solution of pyrrolizidinone **4** (0.08 g, 0.49 mmol) in anhydrous THF (5 mL) was added a THF solution of AlH_3 (1 mol/L, 10 equiv., 4.9 mmol, 4.9 mL; prepared from a mixture of $LiAlH_4$ (9 mmol) with $AlCl_3$(1 mmol) in anhydrous THF). After addition, the reaction medium was stirred for 3h at reflux. Then, the reaction was quenched with a saturated solution of Na_2SO_4, filtered over a pad of Celite® and the solvents were evaporated. The residue was diluted in distilled water and purified with an ion exchange column (Dowex® 50WX8, 200-400 mesh, pre-washed with deionized H_2O). Initially the column was eluted with deionized H_2O and then with a 30% solution of NH_4Cl to give hydroxylated pyrrolizidine **3** (0.06 g), as a colorless solid, in 80 % yield. $[\alpha]_D^{20}$ +10 (c 0.82, MeOH); IR (film, ν_{max}): 3349, 2931, 1650, 1607, 1568, 1443, 1401, 1119 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 2.01 (m, 1H, H-7A), 2.33 (ddd, *J* = 13.8, 8.6, 5.6 Hz, 1H, H-7B), 2.95 (ddd, *J* = 11.6, 4.8, 0.9 Hz, 1H, H-5B), 3.02 (dd, *J* = 10.9, 7.5 Hz, 1H, H-3A), 3.26 (dd, *J* = 11.6, 5.0 Hz, 1H, H-5A), 3.46 (dd, *J* = 10.9, 5.1 Hz, 1H, H-3B), 3.53 (m, *J* = 8.3, 6.1 Hz, 1H, H-7a), 4.16 (t, *J* = 6.1 Hz, 1H, H-1), 4.19 (ddd, *J* = 7.5, 6.1, 5.1 Hz, 1H, H-2), 4.49 (m, 5.1, 5.0, 4.8, 1H, H-6); ^{13}C NMR (125 MHz, D_2O/CCl_4) δ 36.6, 56.6, 60.4, 67.5,71.8, 75.9, 80.3; HRMS (ESI-TOF, *m/z*): Calcd. for $C_7H_{14}NO_3$ $[M + H]^+$ 160.0974. Found 160.0958.

*4.9. (1S,2S,6S,7aS)-1,2,6-trihydroxy-hexahydro-1H-pyrrolizin-3-one **(7)**:*

The same experimental procedure described for pyrrolizidine **3** was used to obtain pyrrolizidine **7** (0.048 g), as a colorless solid, in 73 % yield. $[\alpha]_D^{20}$ -9 (c 0.82, MeOH), IR (film, ν_{max}): 3349, 2931, 1650, 1607, 1568, 1443, 1401, 1119 cm^{-1}; ^{1}H NMR (600 MHz, D_2O) δ 2.18 (m, 1H, H-7B), 2.43 (ddd, *J* = 12.7, 5.0, 3.7 Hz, 1H, H-7A), 3.28 (dd, *J* = 10.4, 3.6, 1.2 Hz, 1H, H-5A), 3.35 (dd, *J* = 10.6, 5.5 Hz, 1H, H-3B), 3.64 (dd, *J* = 11.6, 5.0 Hz, 1H, H-5B), 3.84 (dd, *J* = 10.2, 5.3 Hz, 1H, H-3A), 4.0 (m, *J* = 8.1, 6.3Hz, 1H, H-7a), 4.27 (t, *J* = 6.0 Hz, 1H, H-1), 4.30 (ddd, *J* = 7.8, 6.4, 5.3 Hz, 1H, H-2), 4.55 (m, *J* = 5.2, 4.8, 4.9, 1H, H-6); ^{13}C NMR (600 MHz, D_2O) δ 35.7, 58.0, 60.7, 70.5, 70.7, 75.0, 78.6; HRMS (ESI-TOF, *m/z*): Calcd. for $C_7H_{14}NO_3$ $[M + H]^+$ 160.0974. Found 160.0958.

*4.10. X-ray crystallographic analysis for pyrrolizidinone **(4)**:*

The X-ray diffraction data for compound **4** as measured using a Bruker Kappa CCD diffractometer (LdrX-UFF), equipped with graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å) at room temperature. The structures were solved by direct methods and refined by full-matrix least square methods on F^2 using the package SHELX-97.[41] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. The hydrogen atoms were added geometrically and refined according to the riding model.

4 (CCDC 802113): $C_7H_{11}NO_4$, Fw = 173.17, orthorhombic, $P2_12_12_1$, *a*=7.3837(14) Å,*b*=9.984(4) Å,*c*=10.069(1) Å, V = 742.3(3) Å^3, *Z* = 4, D_c = 1.550 mg/m^3, μ = 0.128 mm^{-1}, *F*(000) =368, R(reflections)= 0.0317(925), wR2(reflections)= 0.0811(1004), S = 1.106 Npar= 113

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22. Previously we demonstrated that the protection of C4 hydroxyl group led to the formation of a diastereoisomeric mixture associated with the inversion of the diastereoisomeric ratio (see reference 21).
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25. nOe experiments were also performed using a solution, which was previously degassed. The results obtained are similar, although the intensity of the nOe increments were slightly bigger.
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27. Crystallographic data for compound **4** have been deposited with the Cambridge Crystallographic Data Centre (deposition number

CCDC 802113). Tables with crystal data and selected geometric parameters are presented as supplementary information.)
28. Crystallographic data were collected and analyzed by Dr. Jackson A. L. C. Resende from the Inorganic Chemistry Department of Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil.
29. For details concerning the crystallographic data of compound **14**, see: Oliveira, F. L.; Freire, K. R. L.; Aparicio, R.; Coelho, F. *Acta Crystallogr., Sect. E: Struct. Rep. Online.* **2012**, *68*, o586.
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Supplementary Material

Supplementary material containing all spectroscopic data for compounds prepared in this work is available at

SUPPORTING INFORMATION

An asymmetric substrate-controlled Morita-Baylis-Hillman reaction as approach for the synthesis of pyrrolizidinones and pyrrolizidines

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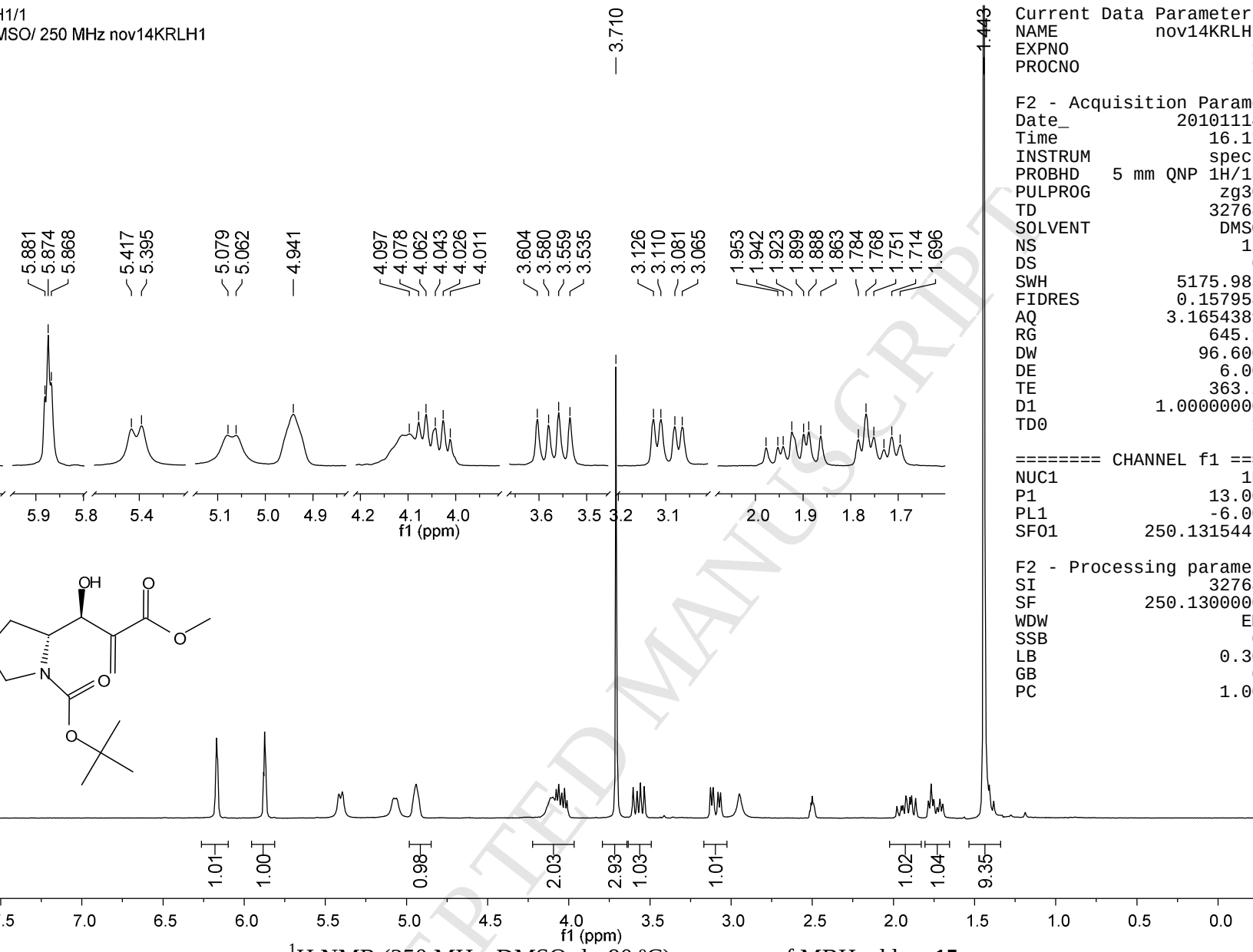
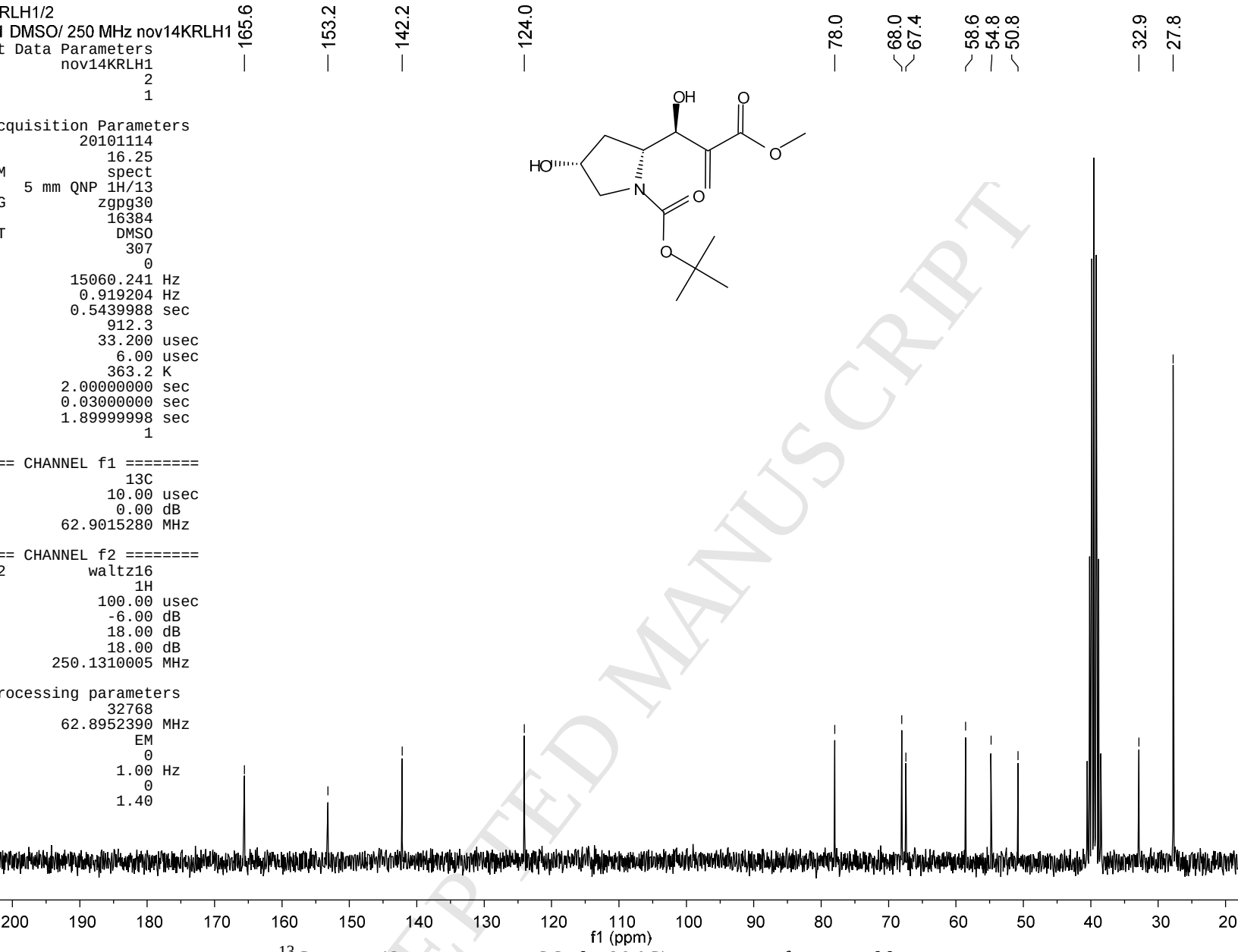
a. University of Campinas, Institute of Chemistry – PO Box 6154 – 13083-970 – Campinas, SP – Brazil; b. X-ray diffraction Laboratory - Institute of Chemistry/UFF – Campus do Valonginho – 24020-150, Niterói, RJ – Brazil.
coelho@iqm.unicamp.br

Table of spectra



^{1}H NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of MBH adduct **15**.



^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) spectrum of MBH adduct 15.

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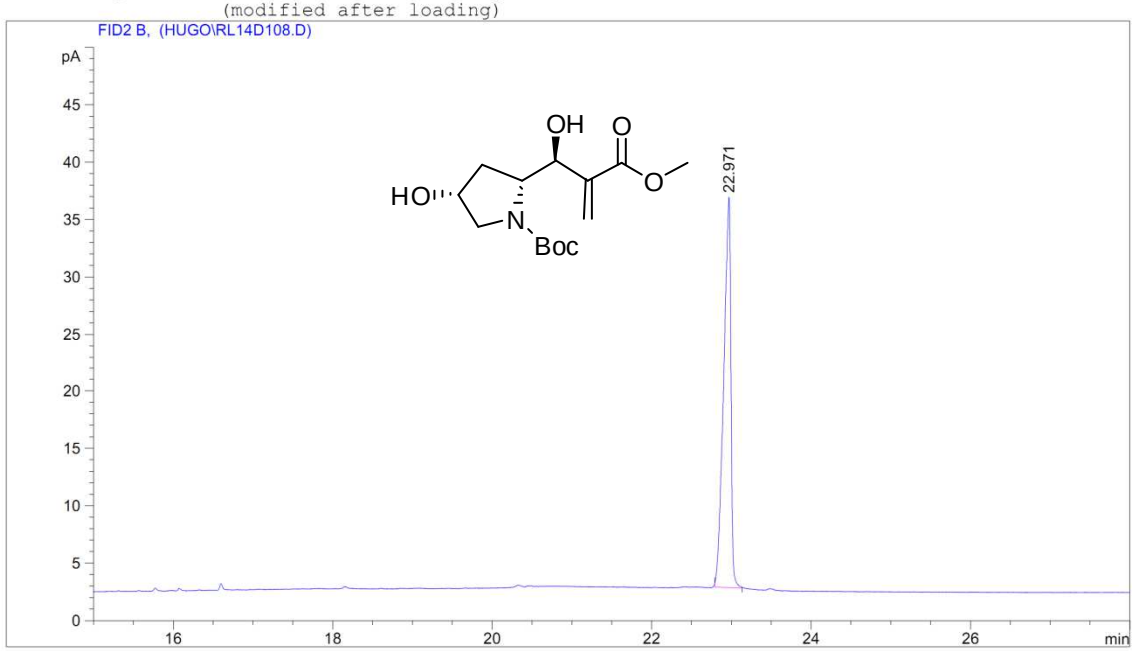

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Area Percent Report
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Results obtained with enhanced integrator!
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*** End of Report ***

GC chromatogram of MBH adduct **15**.

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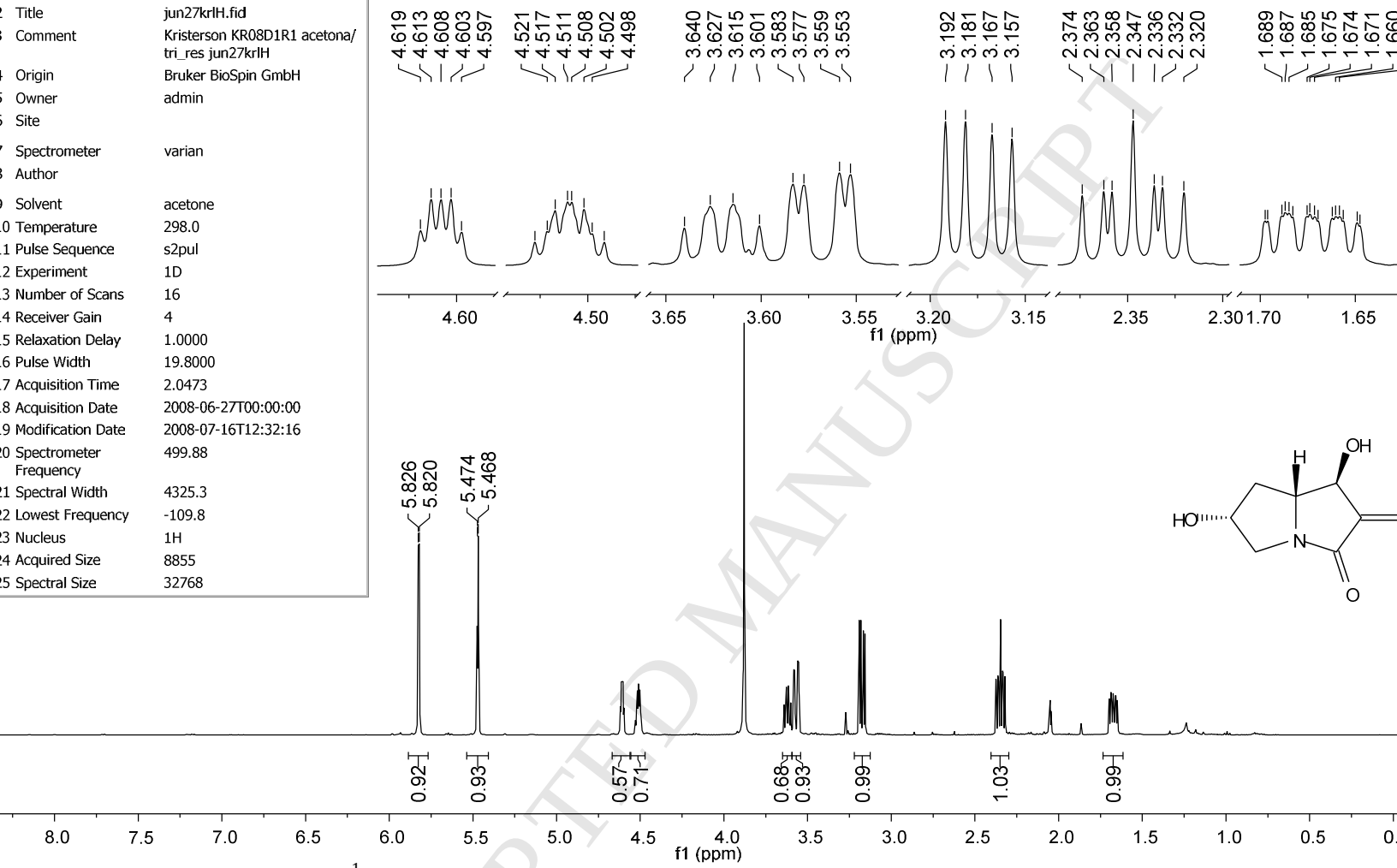
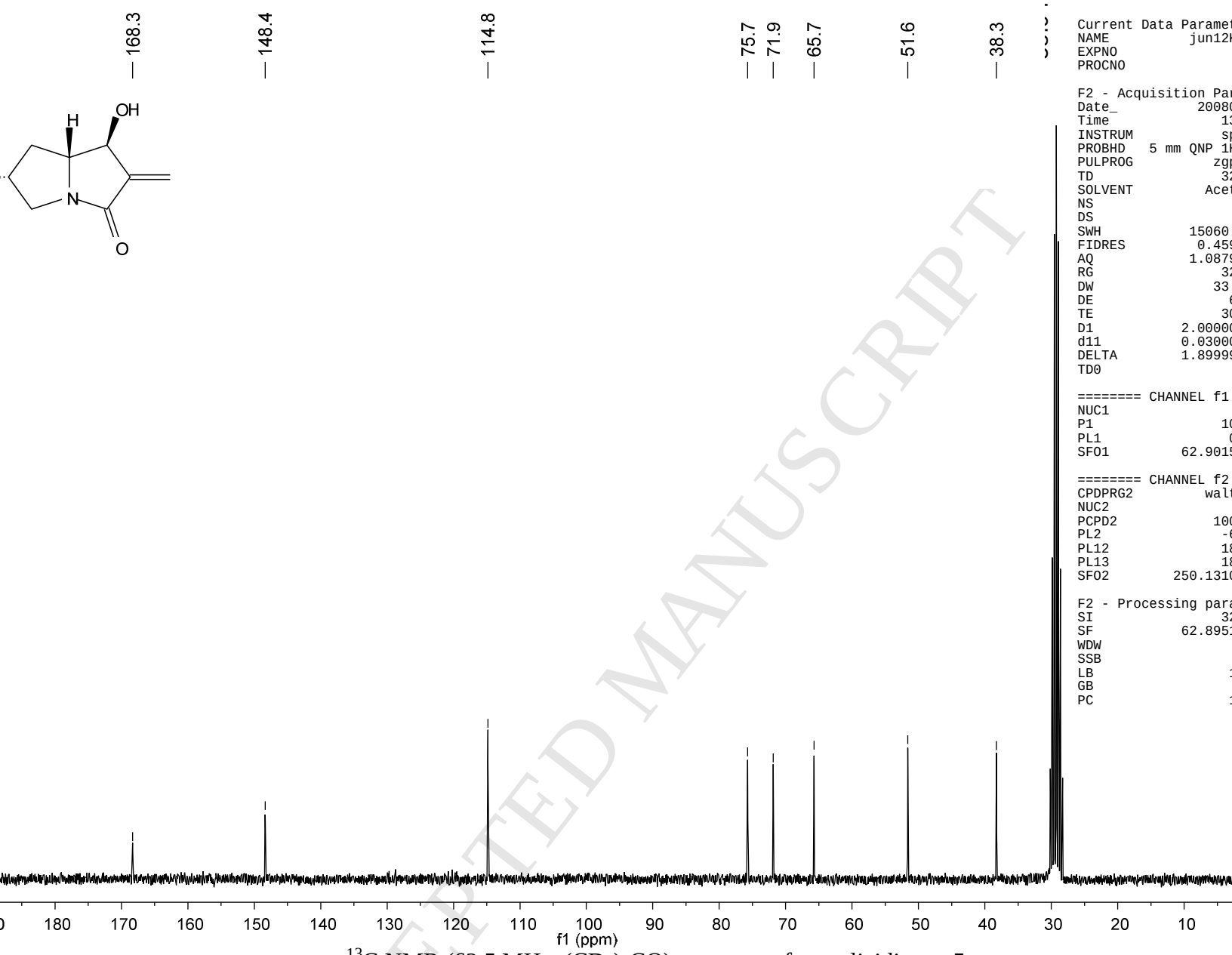


^{1}H NMR (500 MHz, $(CD_3)_2CO$) spectrum of pyrrolizidinone **5**.



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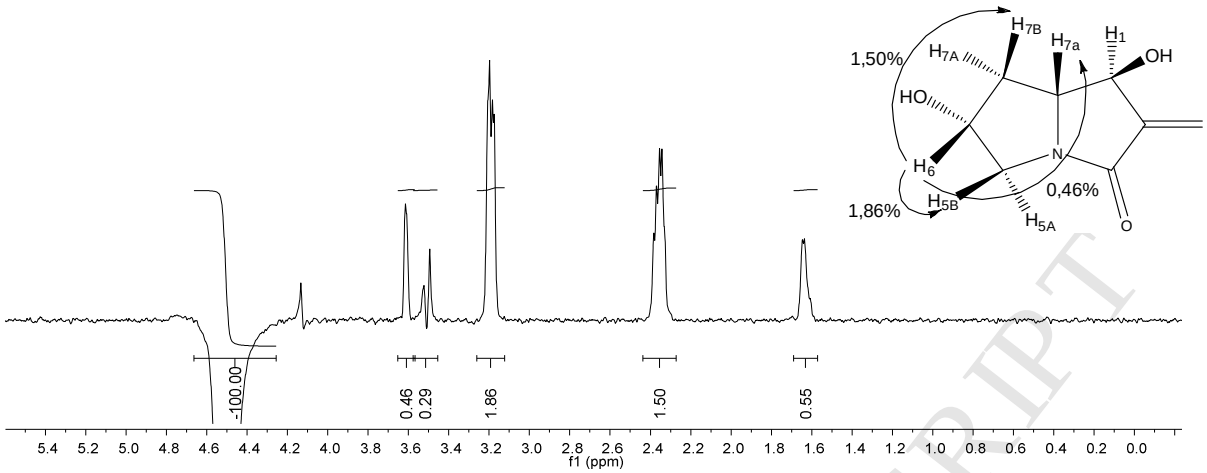

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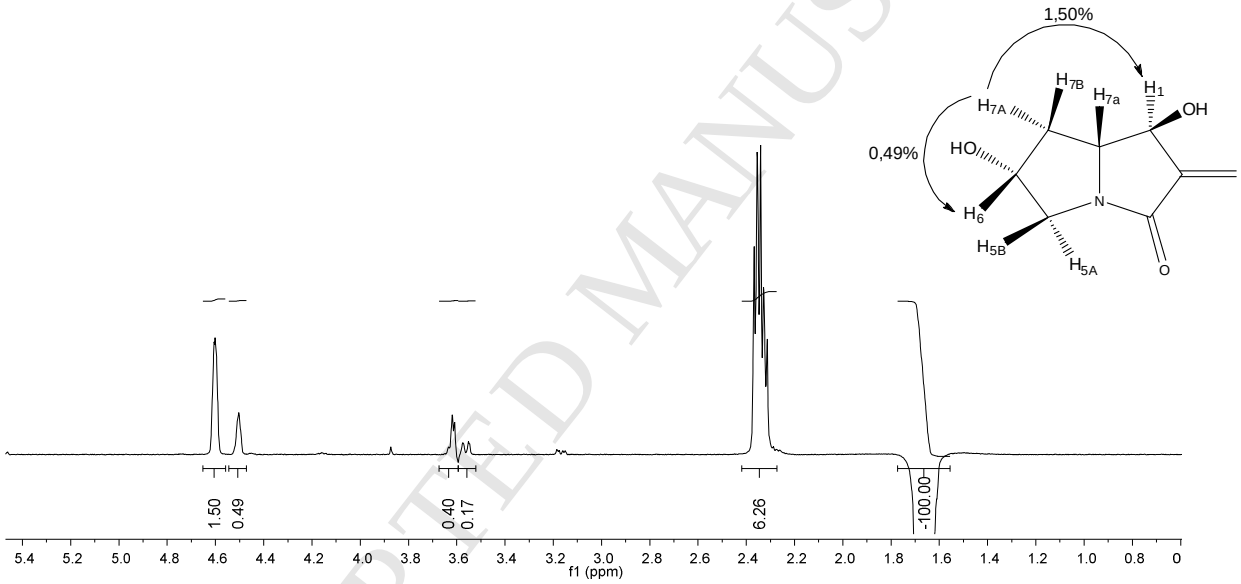

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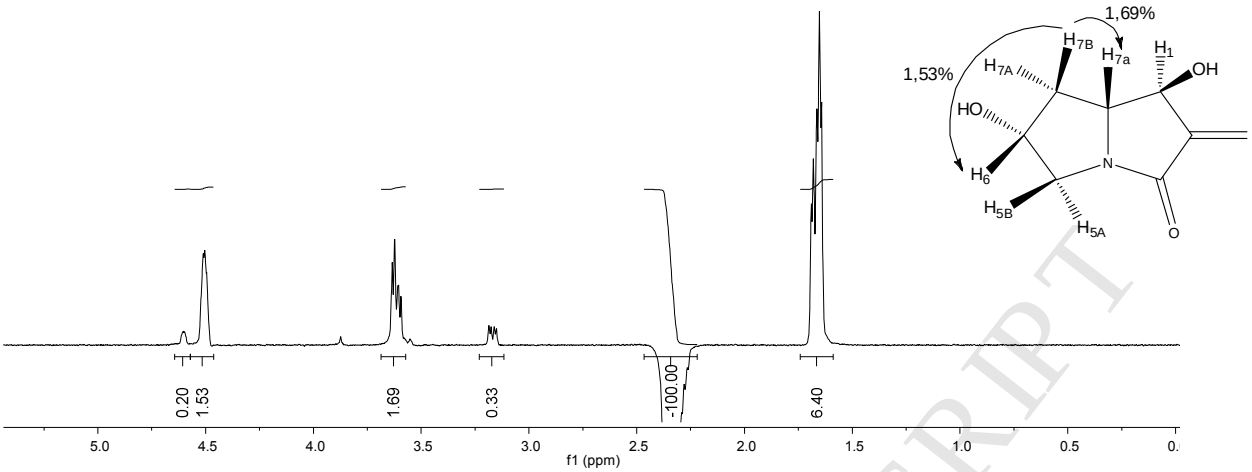

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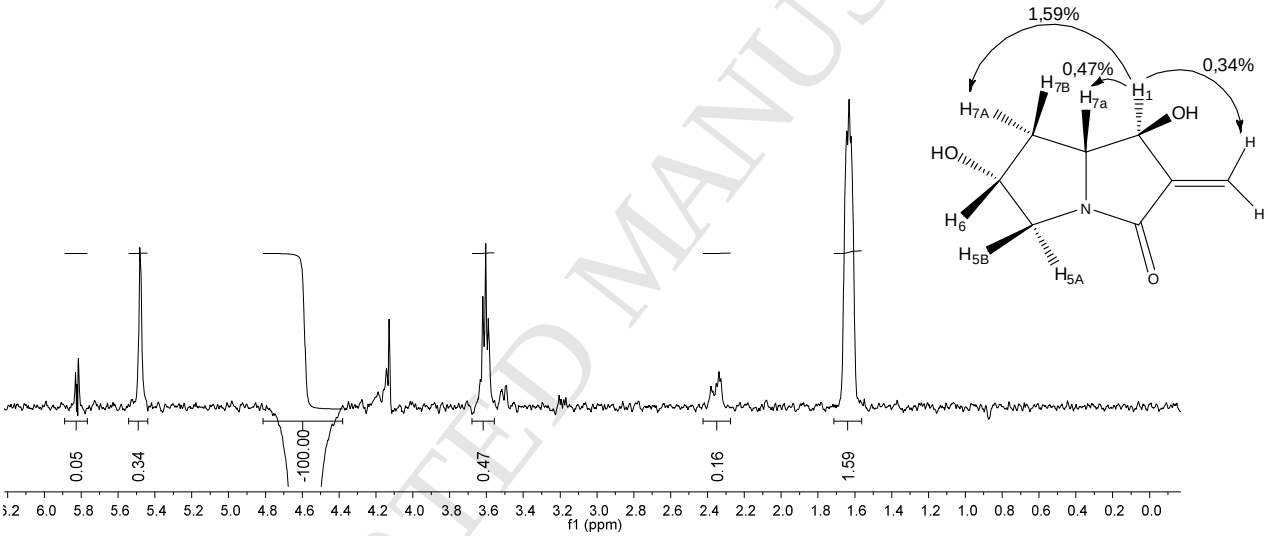

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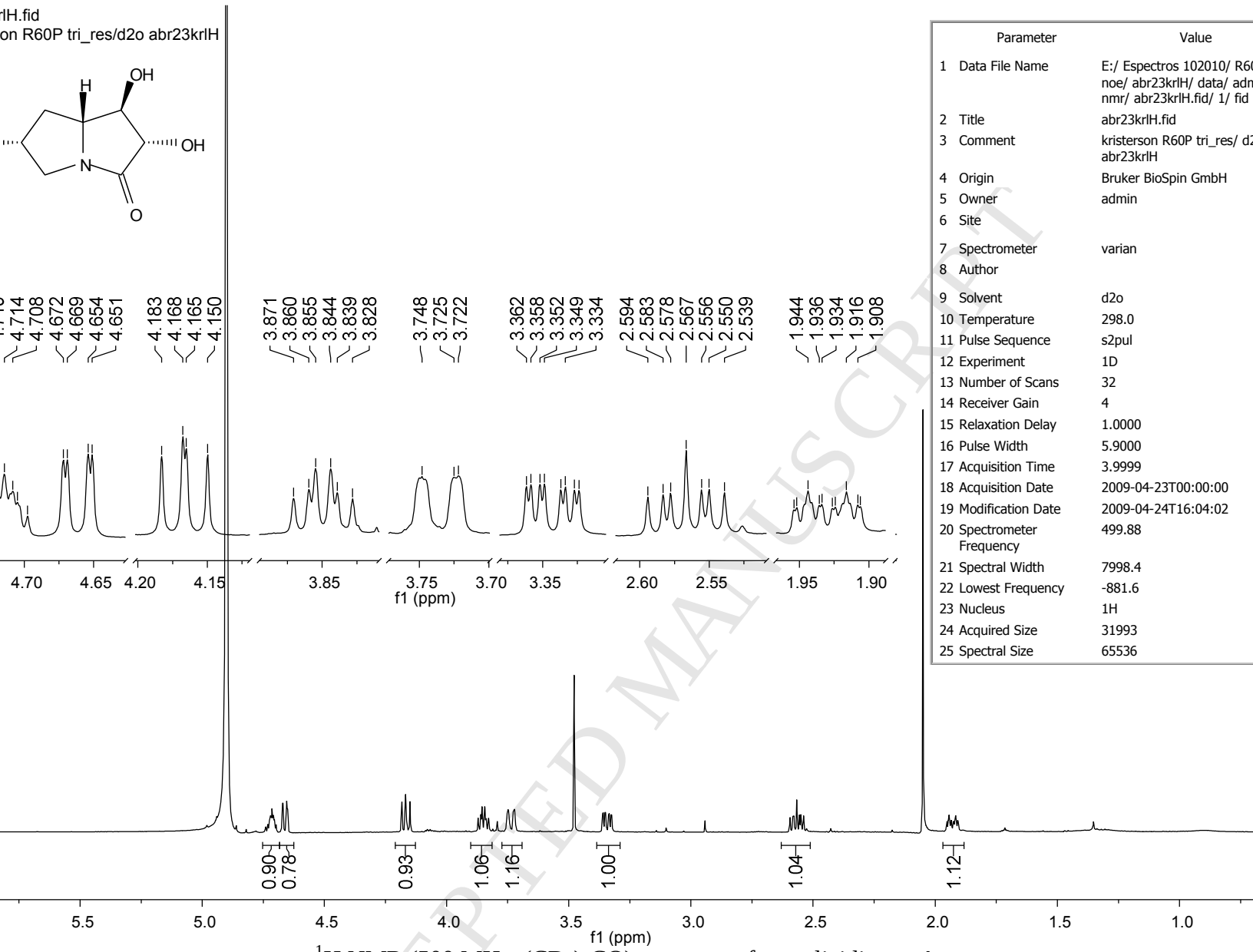

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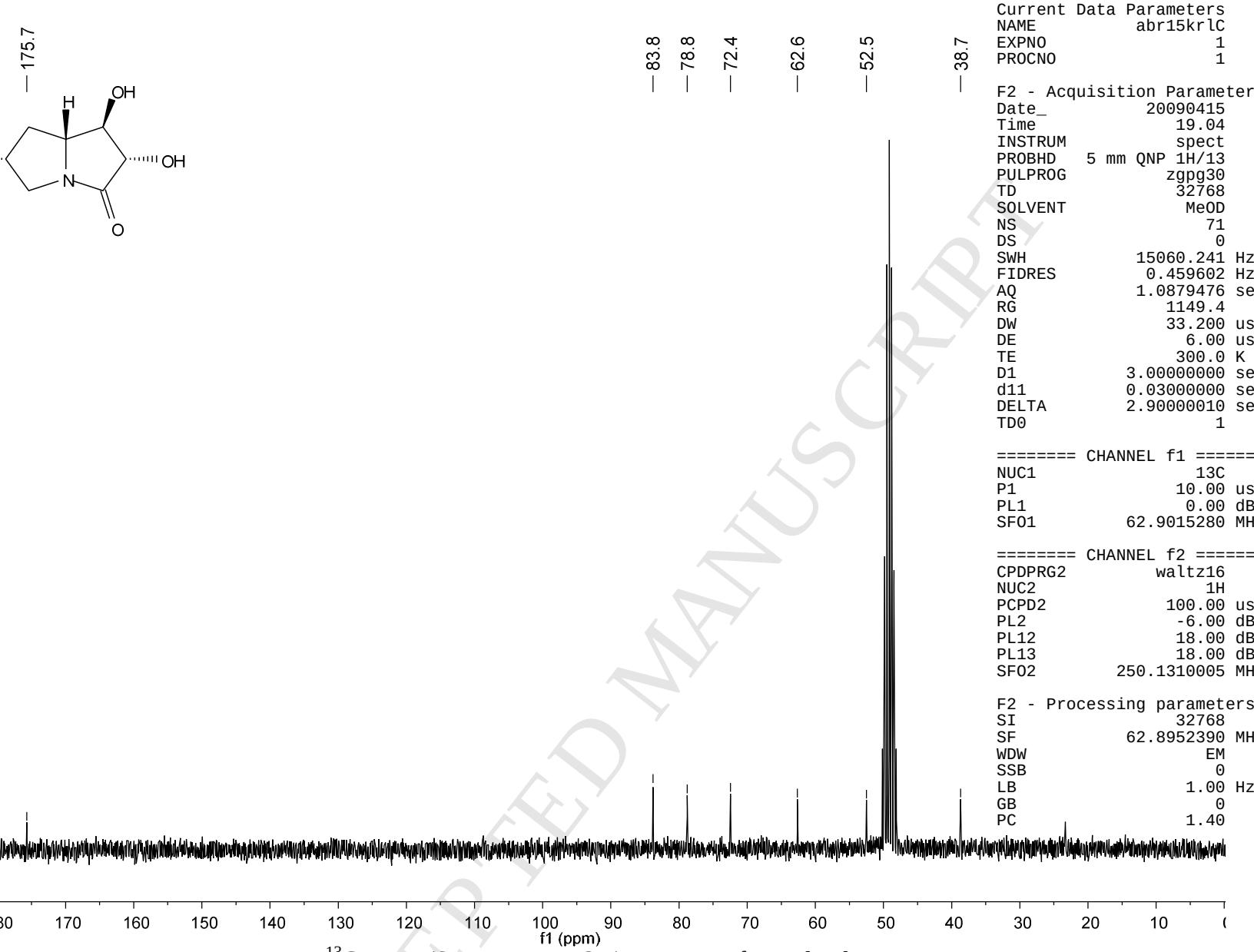
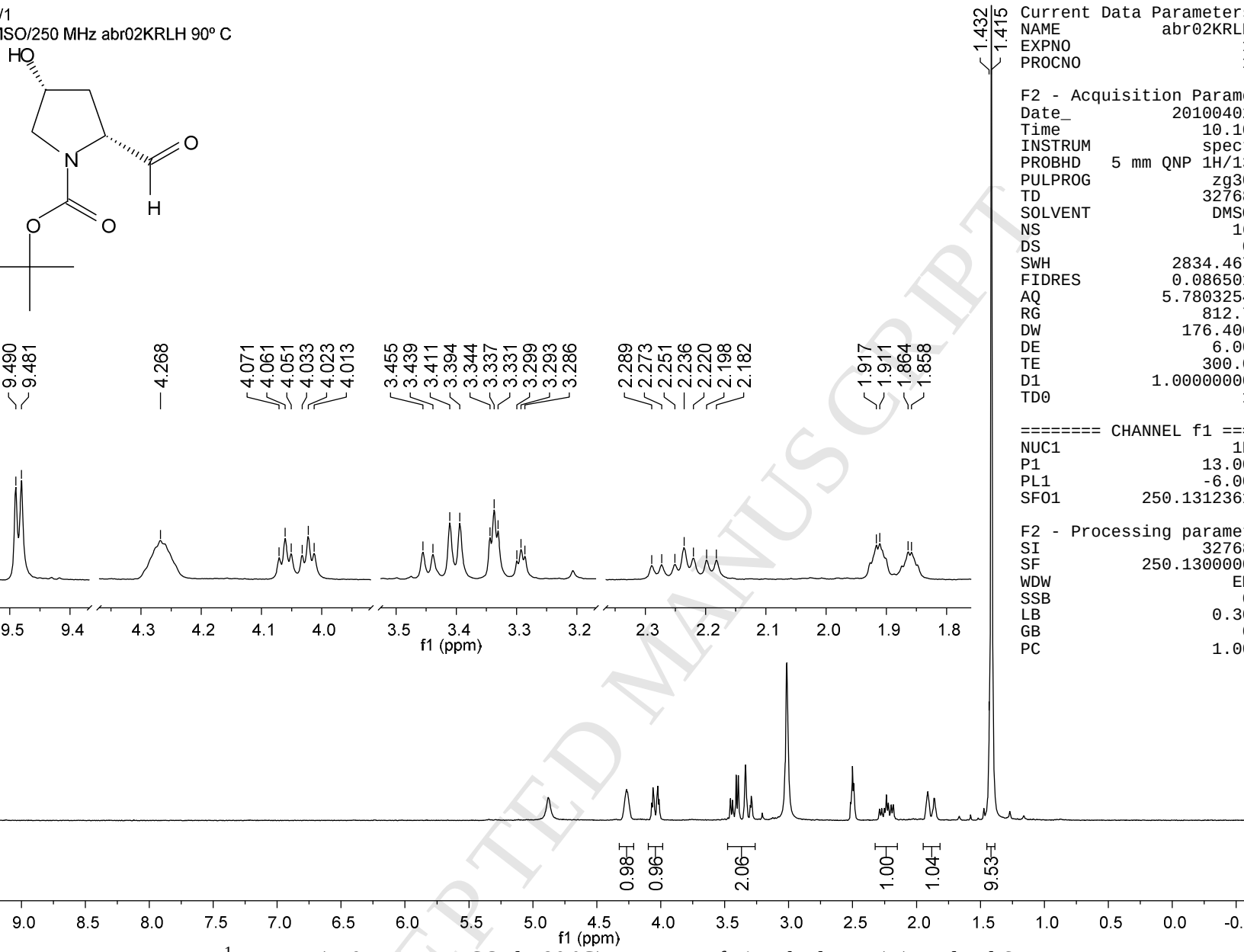
^{1}H NMR (500 MHz, $(CD_3)_2CO$) spectrum of pyrrolizidinone **4**.



^{13}C NMR (62.5 MHz, MeOD) spectrum of pyrrolizidinone **4**.



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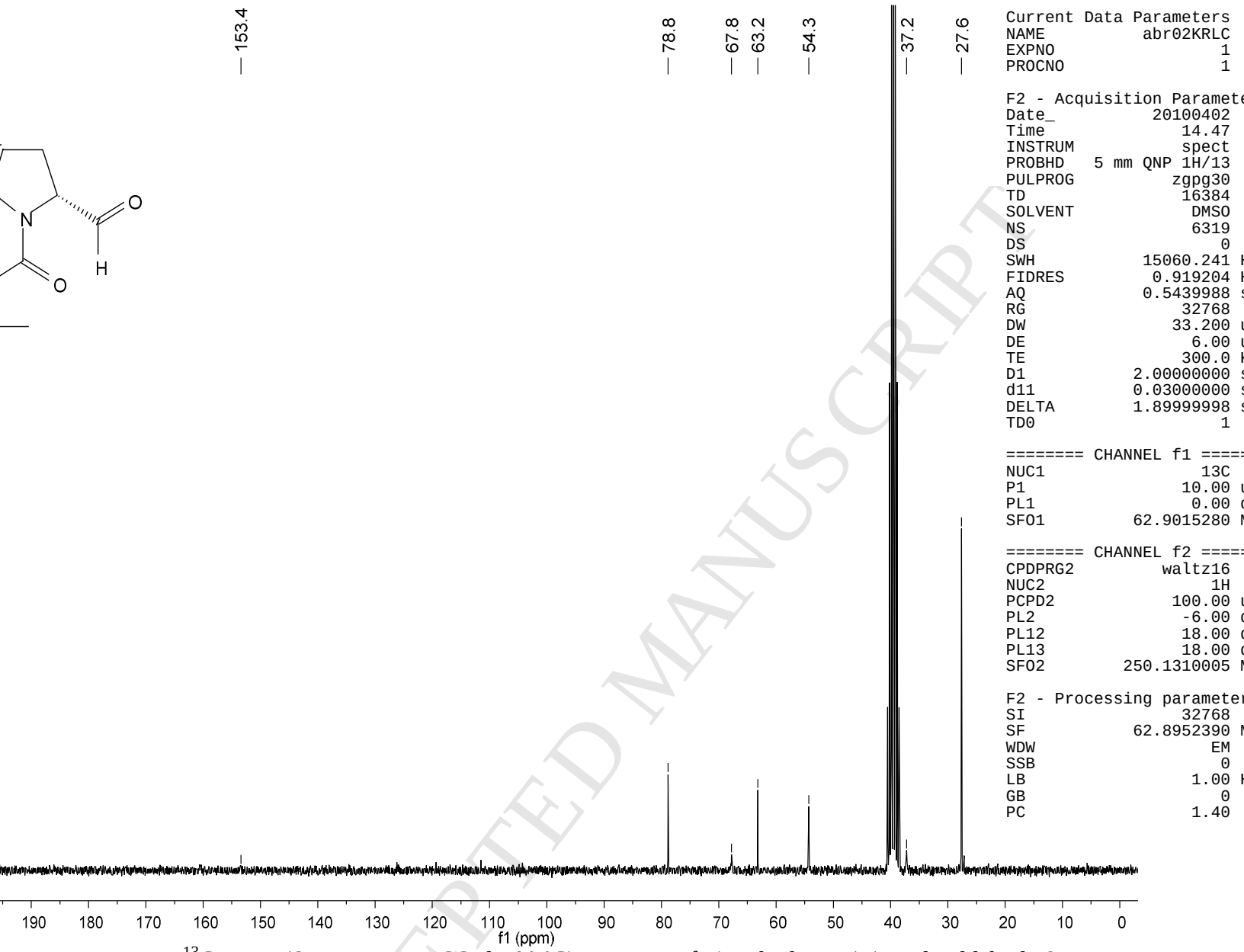

^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) spectrum of *cis*-4-hydroxy-(*D*)-prolinaldehyde **6**.

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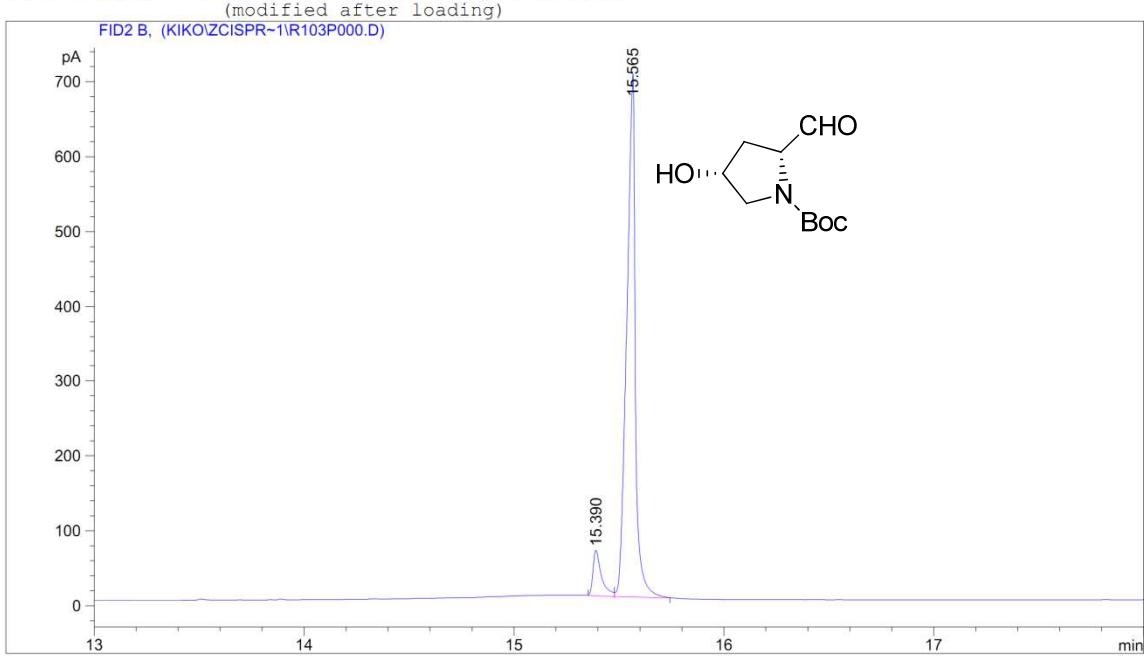


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 Results obtained with enhanced integrator!
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GC chromatogram of *cis*-4-hydroxy-(*D*)-prolinal **6**.

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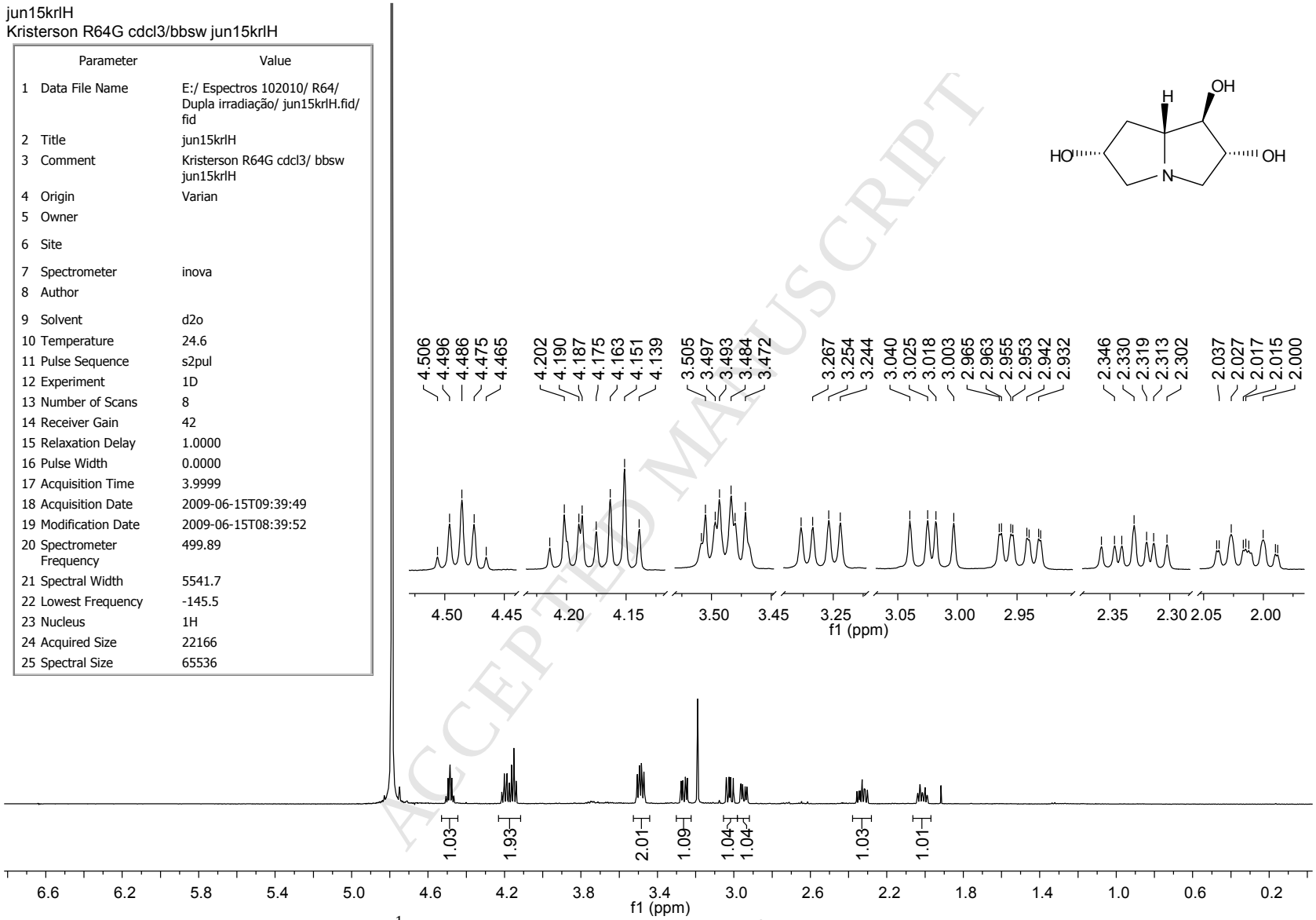

^{1}H NMR (500 MHz, D_2O) spectrum of pyrrolizidine **3**.

jun03krlC1
Kristerson "R64P" D2O/BBSW jun03krlC1

	Parameter	Value
1	Data File Name	G:/ Espectros 102010/ R64/ jun03krlC1.fid/ fid
2	Title	jun03krlC1
3	Comment	Kristerson "R64P" D2O/ BBSW jun03krlC1
4	Origin	Varian
5	Owner	
6	Site	
7	Spectrometer	inova
8	Author	rmn
9	Solvent	d2o
10	Temperature	24.6
11	Pulse Sequence	s2pul
12	Experiment	1D
13	Number of Scans	4370
14	Receiver Gain	30
15	Relaxation Delay	1.0000
16	Pulse Width	0.0000
17	Acquisition Time	1.3005
18	Acquisition Date	2009-06-03T07:43:08
19	Modification Date	2009-06-03T11:00:04
20	Spectrometer Frequency	125.71
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22	Lowest Frequency	-1860.1
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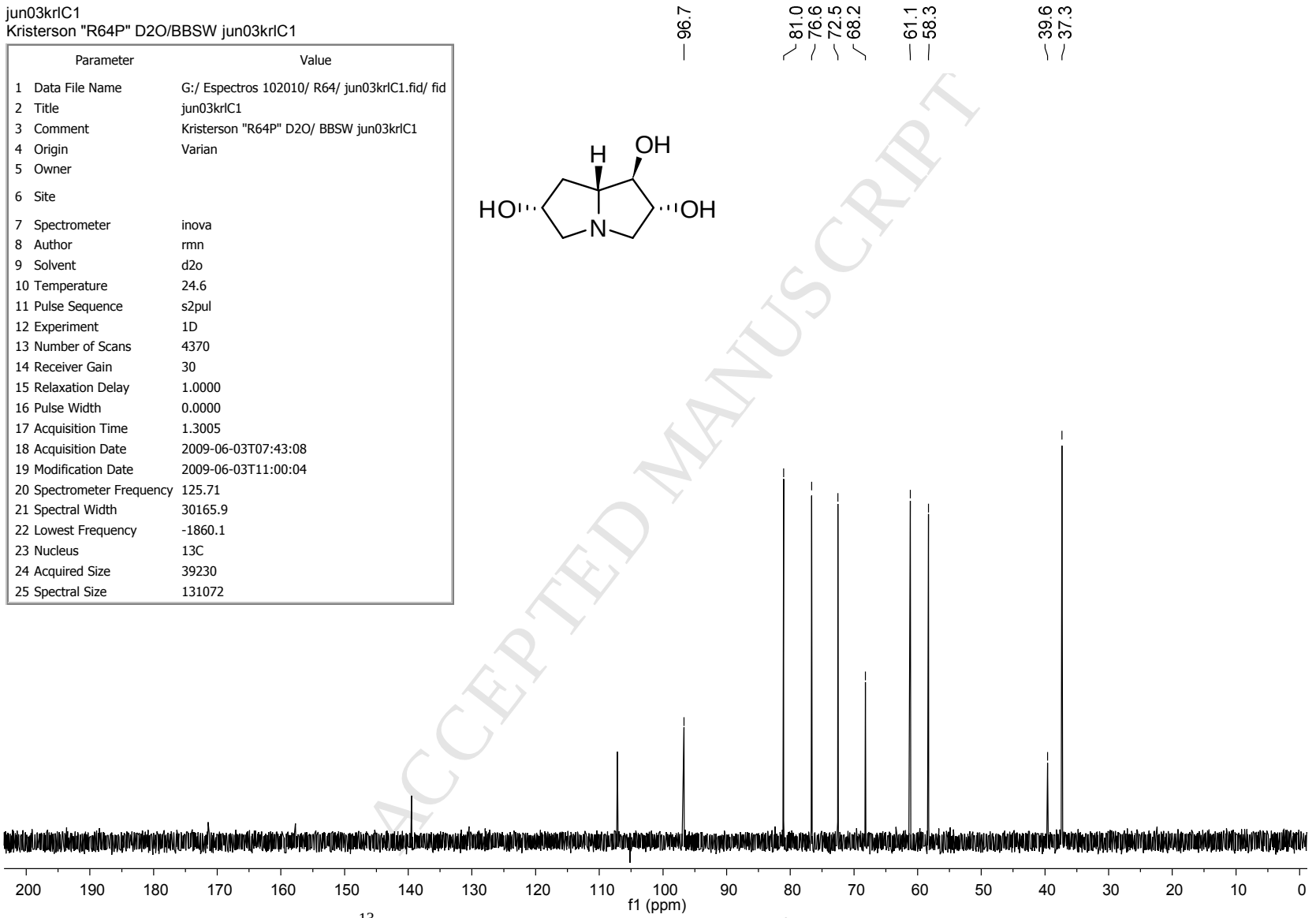
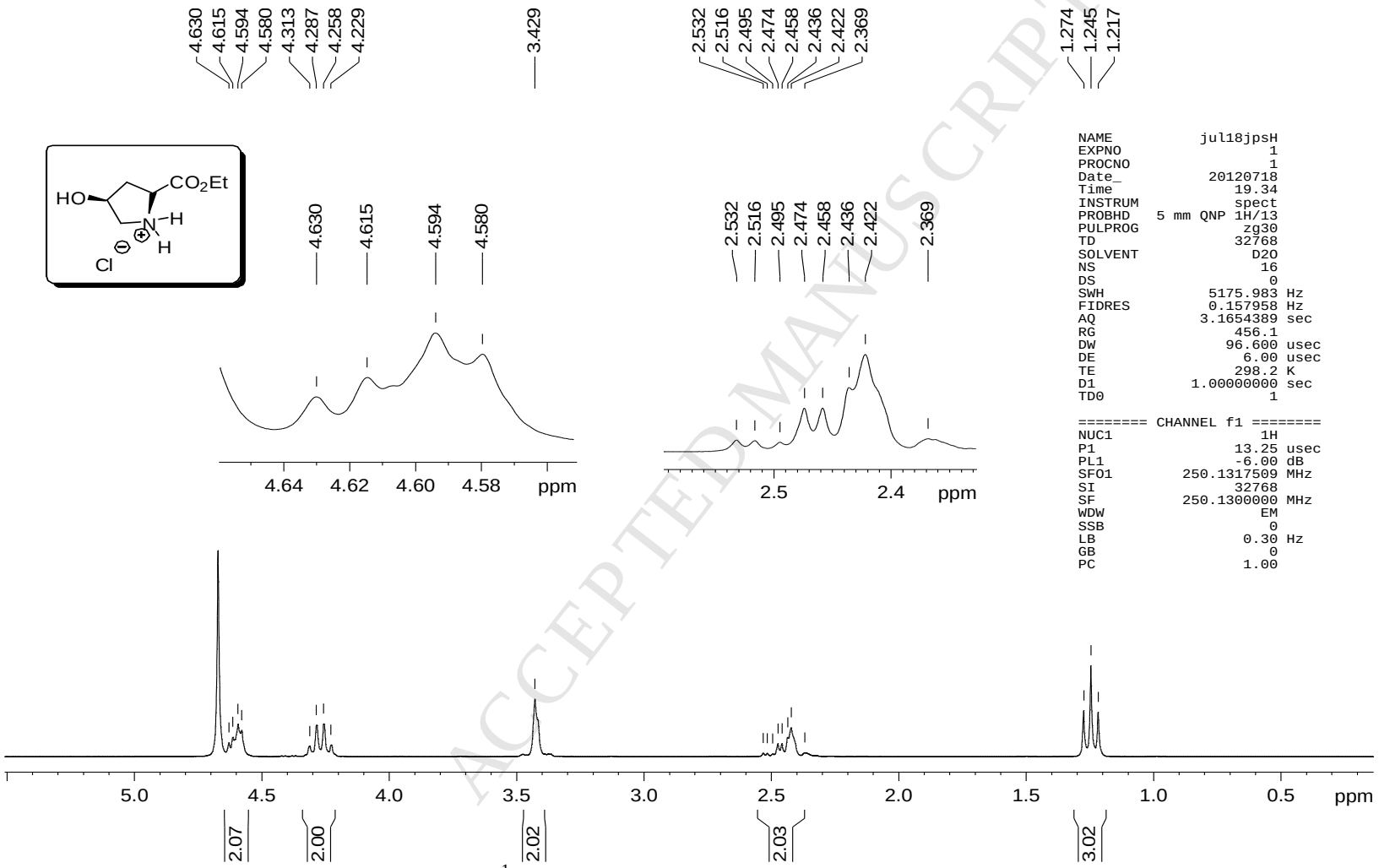
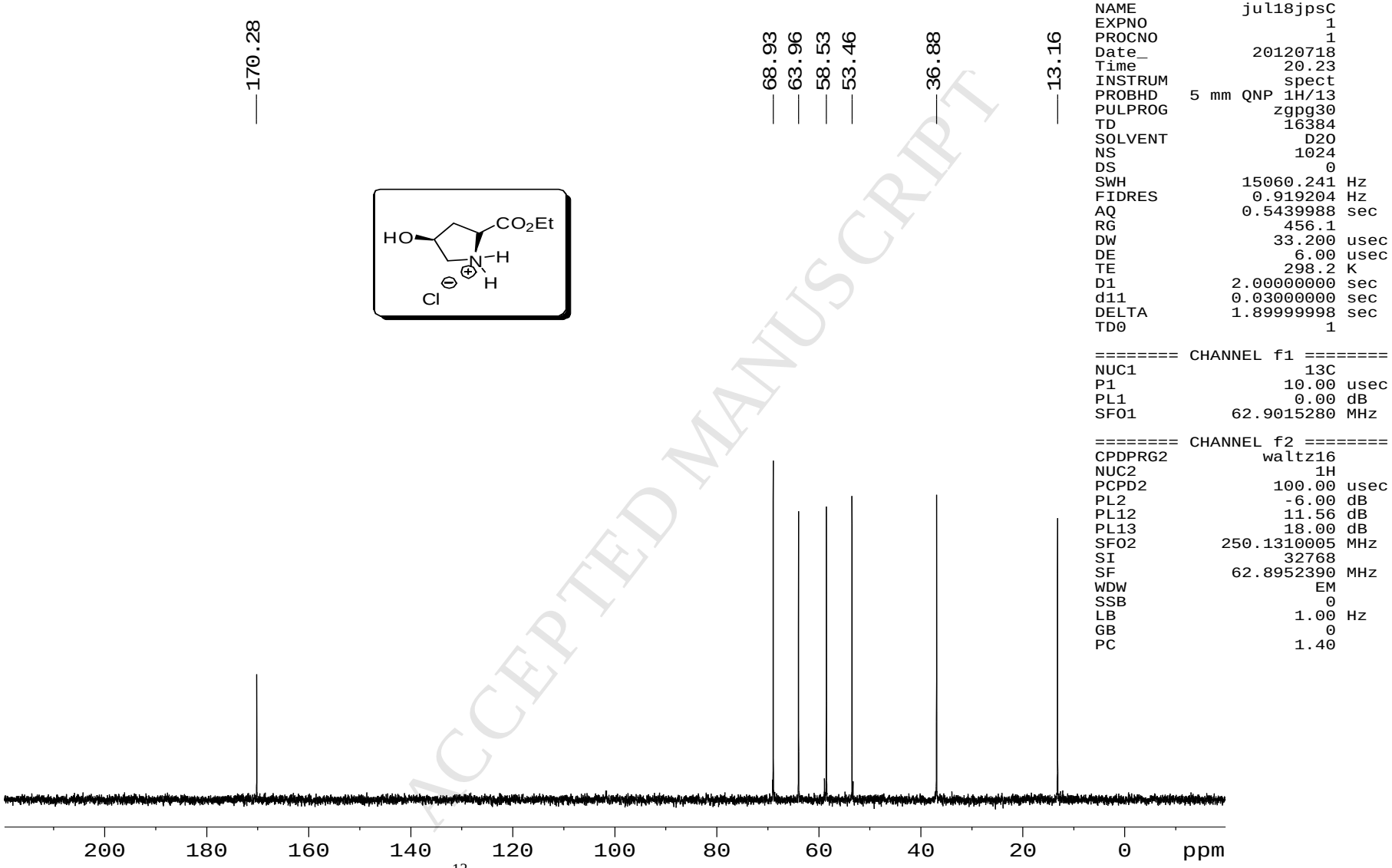


^{13}C NMR (125 MHz, $D_2O\backslash CCl_4$) spectrum of pyrrolizidine **3**.



^{1}H NMR (250 MHz, D_2O) spectrum of ester **13**.

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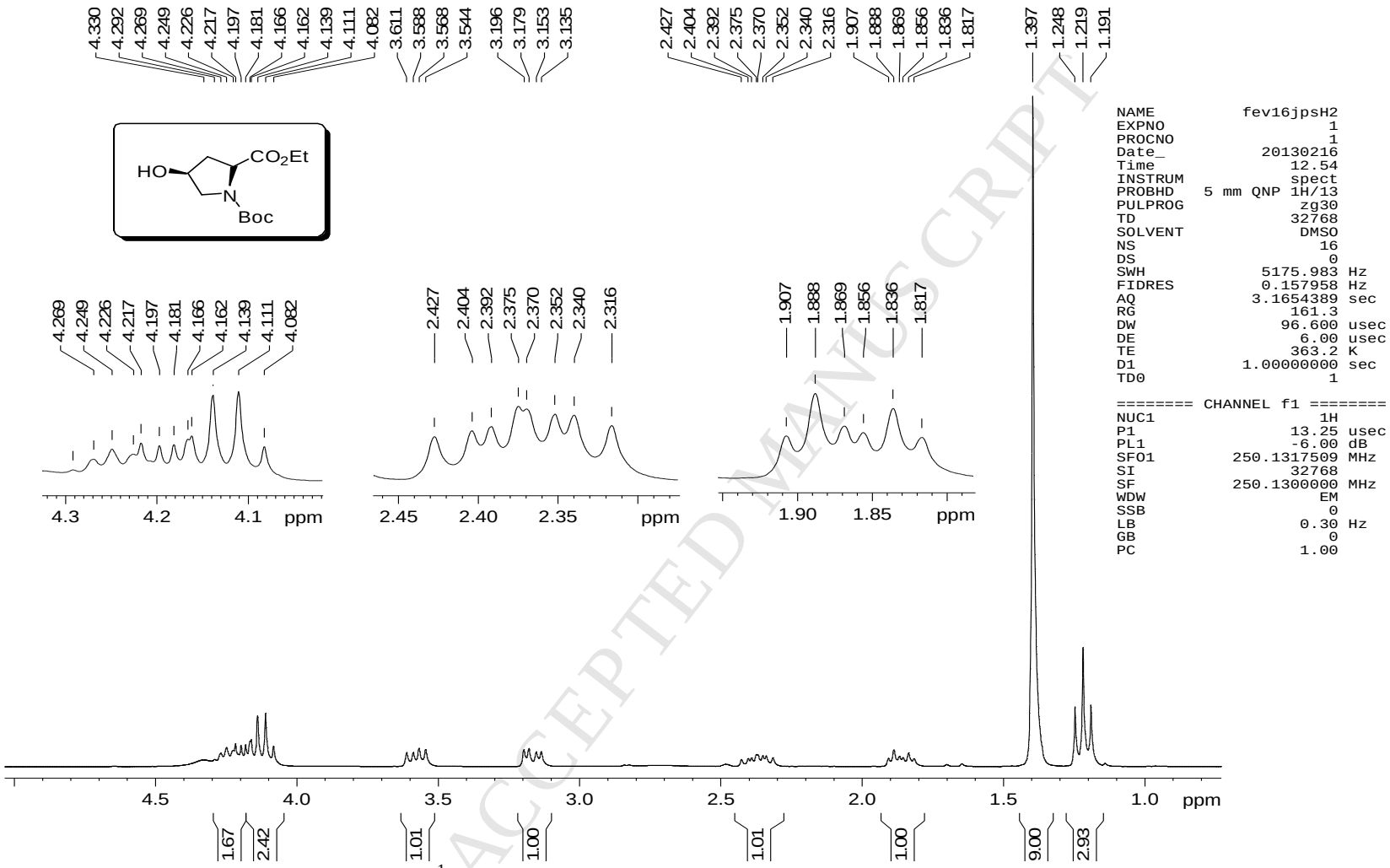
EXPNO                  1
PROCNO                 1
Date_           20120718
Time               20.23
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                16384
SOLVENT             D2O
NS                 1024
DS                    0
SWH           15060.241 Hz
FIDRES         0.919204 Hz
AQ             0.5439988 sec
RG                456.1
DW               33.200 usec
DE                6.00 usec
TE                298.2 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

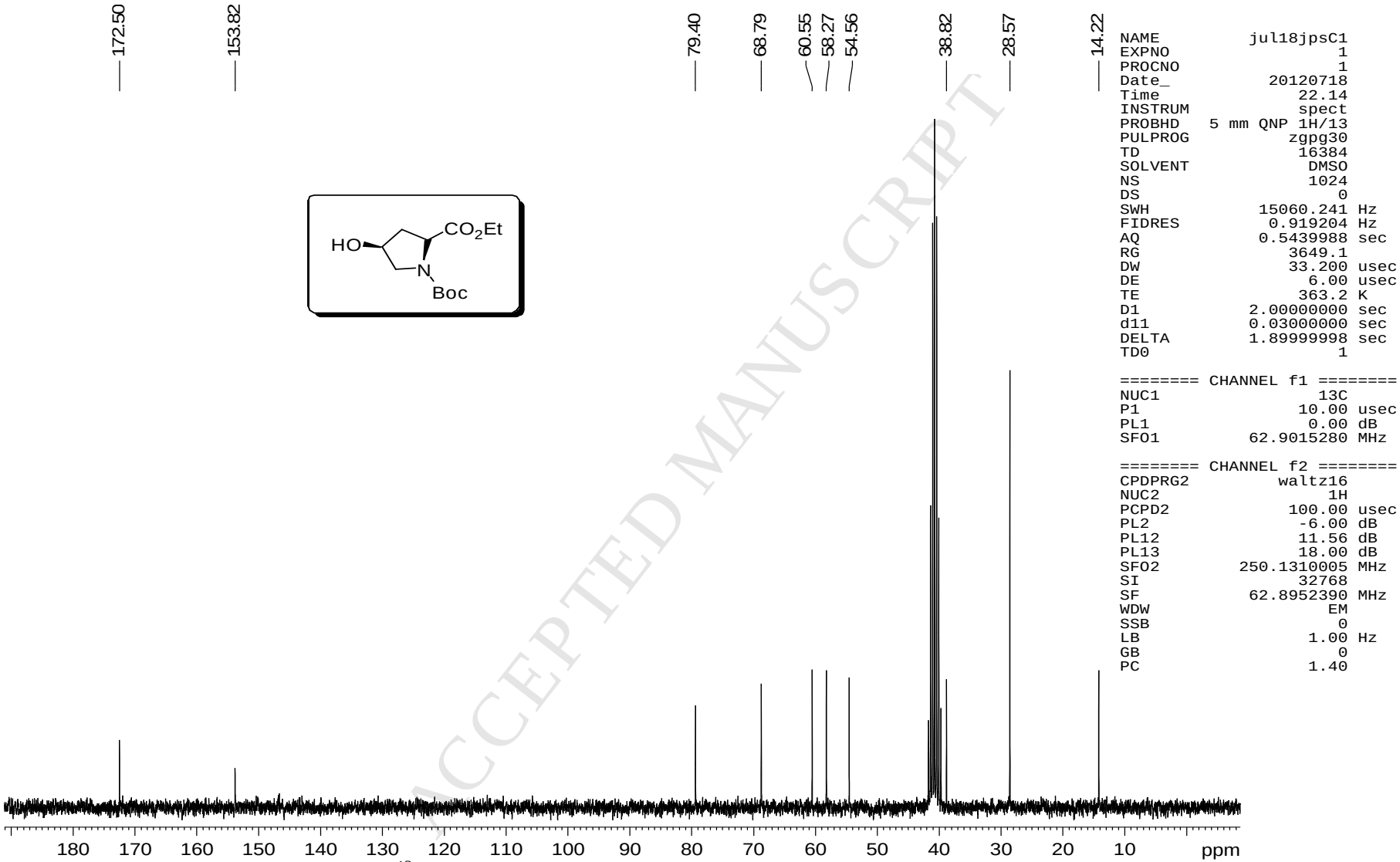
======== CHANNEL f1 ========
NUC1                  13C
P1                 10.00 usec
PL1                 0.00 dB
SFO1          62.9015280 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                -6.00 dB
PL12               11.56 dB
PL13               18.00 dB
SFO2         250.1310005 MHz
SI                 32768
SF            62.8952390 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

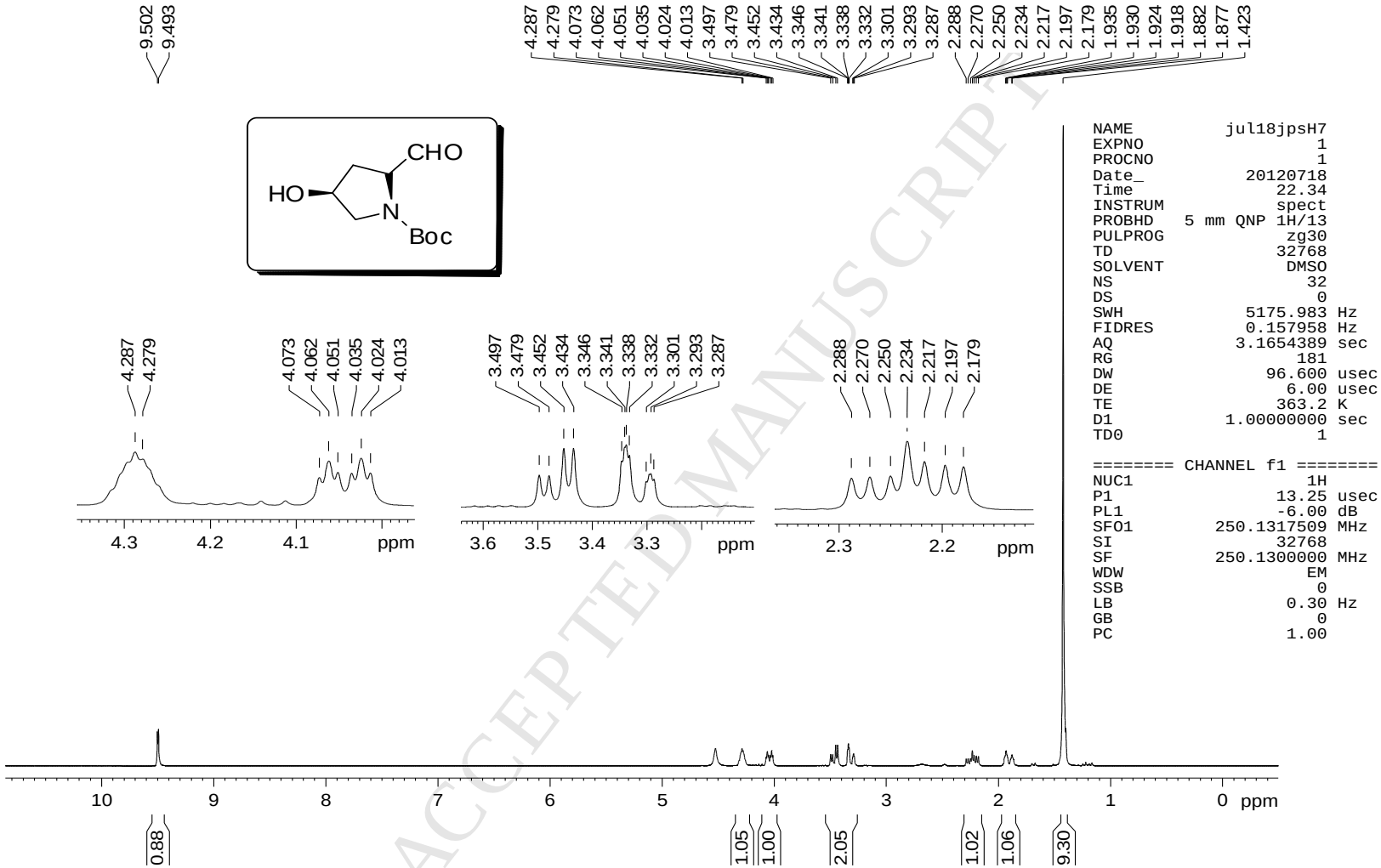
^{13}C NMR (250 MHz, D_2O) spectrum of ester **13.**



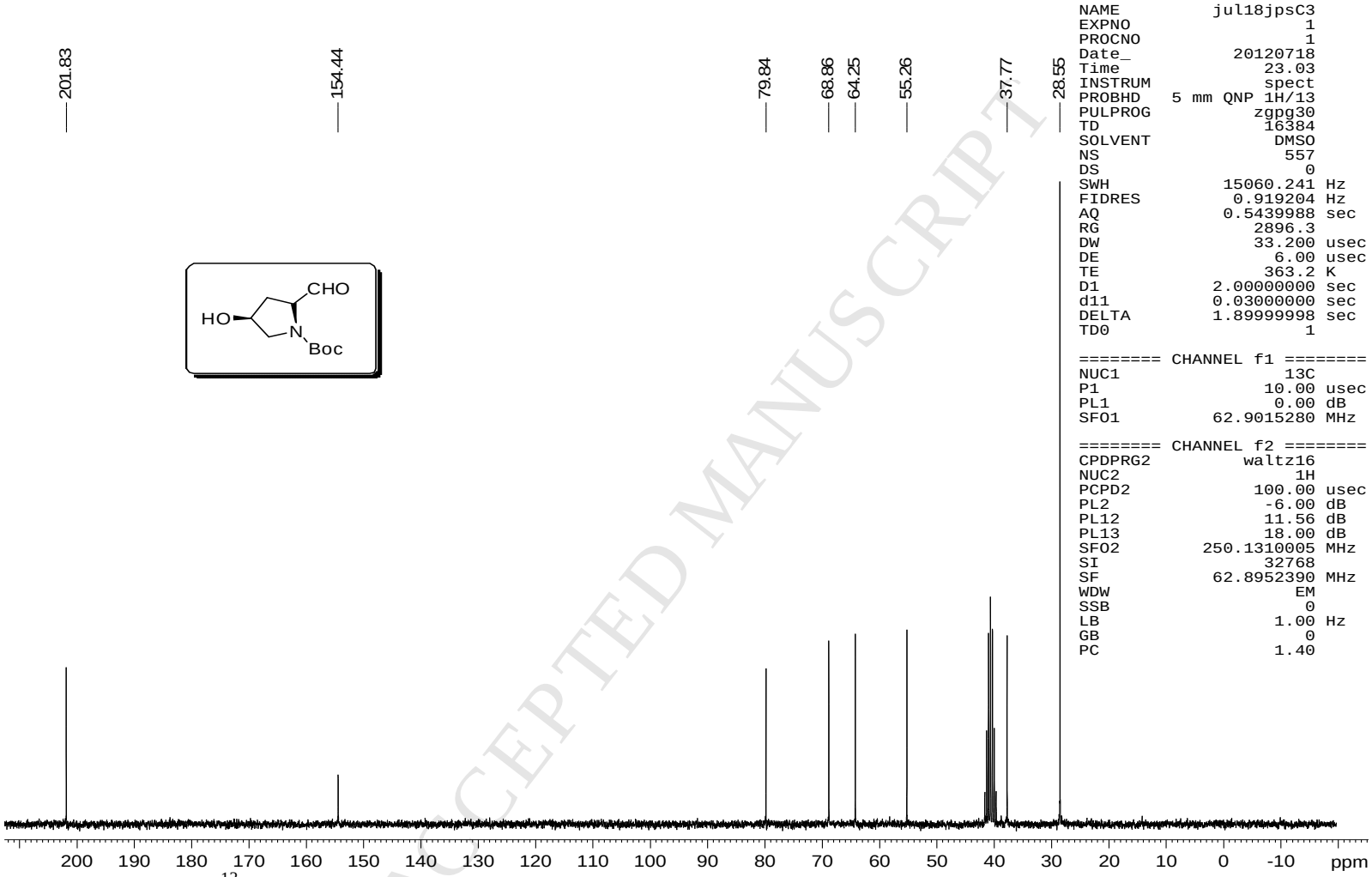
^{1}H NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of ester **14.**



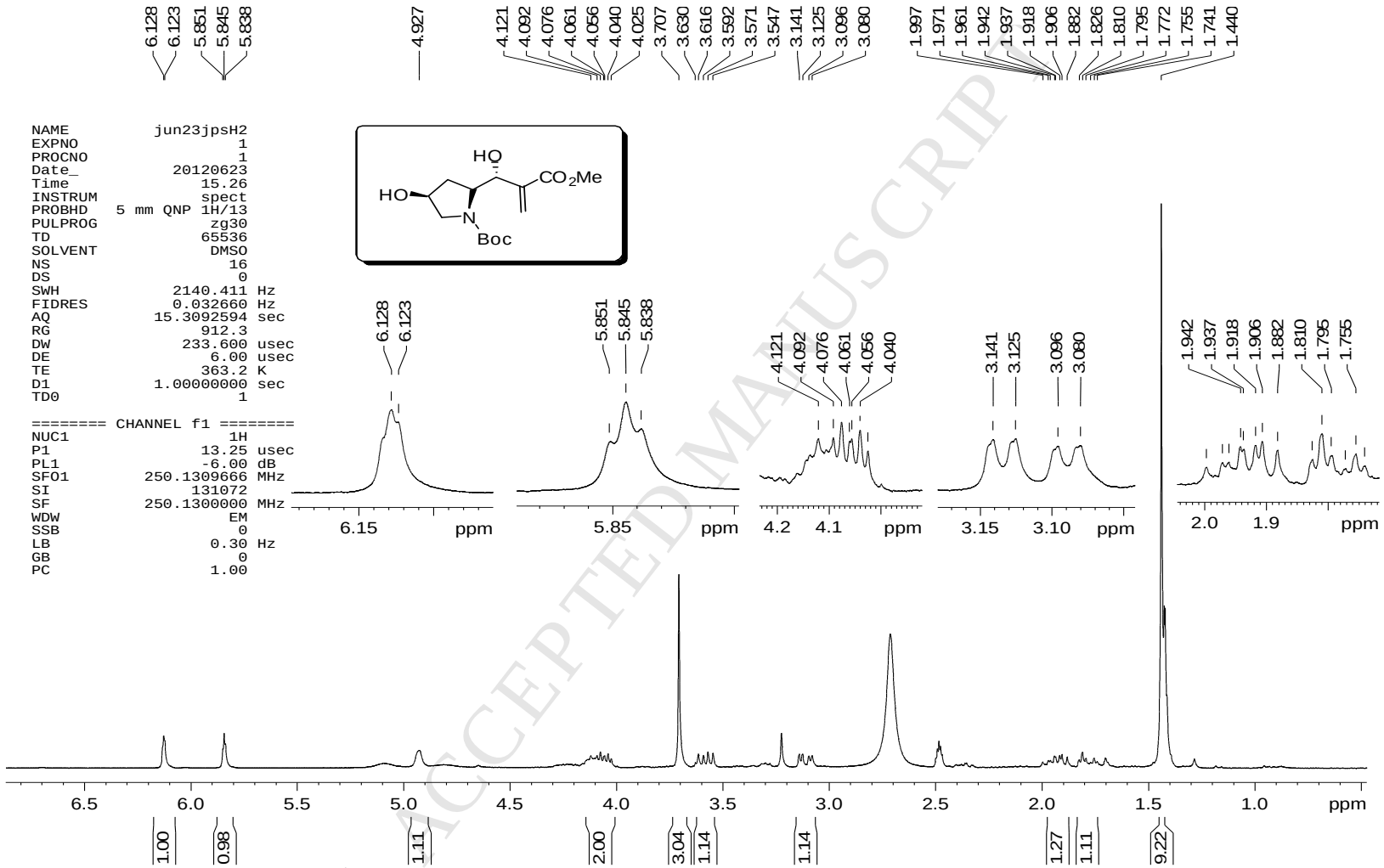
^{13}C NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of ester **14**.



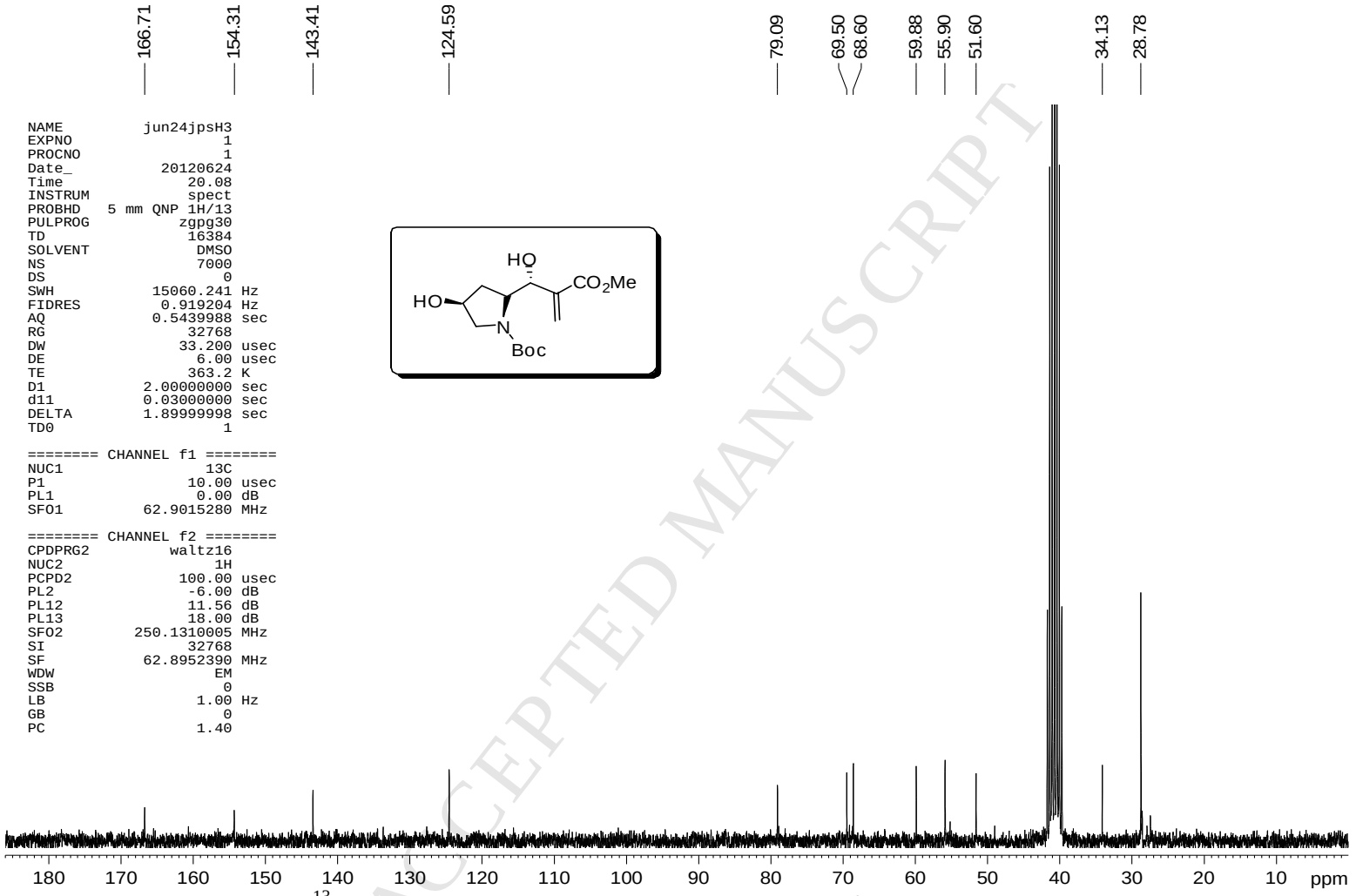
^{1}H NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of *cis*-4-hydroxy-(*L*)-prolinal **10.**



^{13}C NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of *cis*-4-hydroxy-(*L*)-prolinaldehyde **10.**



^{1}H NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of MBH adduct **16.**



^{13}C NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of MBH adduct **16**.

Data File C:\HPCHEM\1\DATA\JP_ART\MBH00402.D Sample Name: MBH JP004

MBH JP004 4dia + aduto puro

==========

Injection Date : 10/9/2012 1:16:48 PM
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Acq. Operator : jp Inj : 1
Inj Volume : Manually

Acq. Method : C:\HPCHEM\1\METHODS\JPB.M
Last changed : 10/9/2012 12:40:04 PM by jp
(modified after loading)
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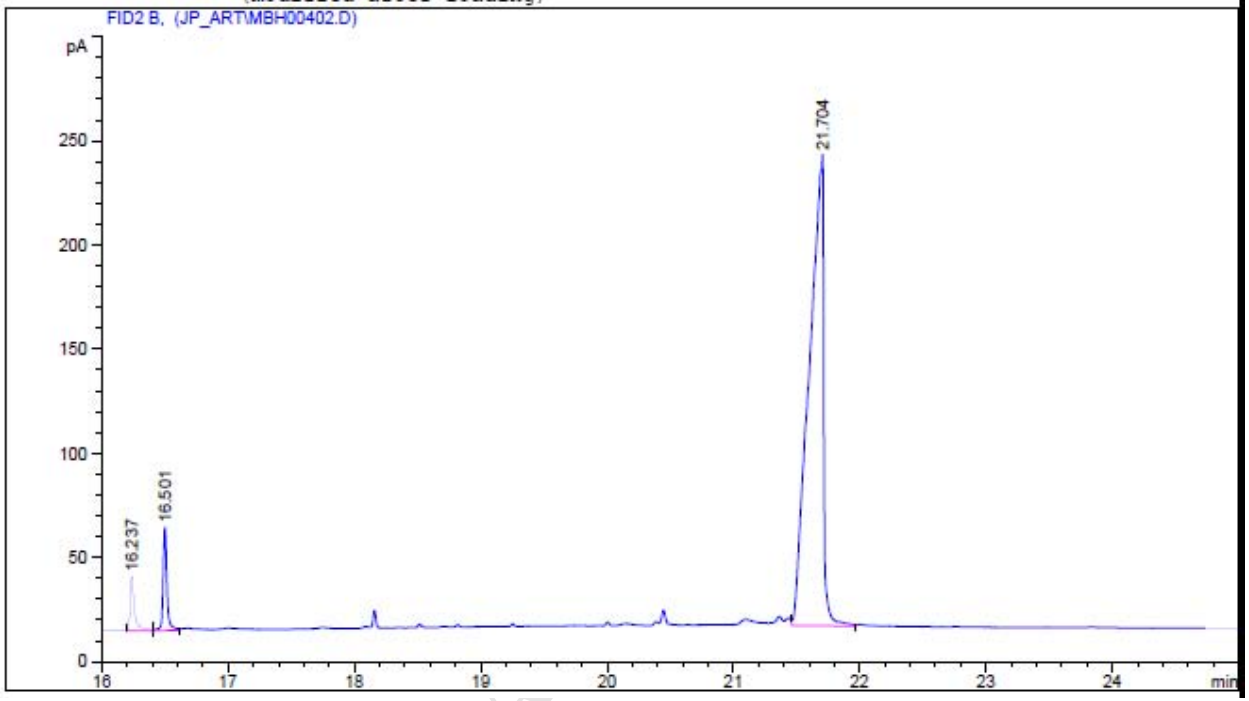
Last changed : 4/5/2013 12:52:26 PM by Tiago
(modified after loading)



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=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Calib. Data Modified  :      Wednesday, September 12, 2007 6:50:37 PM
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: FID2 B,

Peak RetTime  Type    Width     Area      Area    Name
  #   [min]           [min]   [pA*s]       %
  16  10.385 PB      0.0354 6.59603e-1  0.00015 ?
  17  11.014 PP      0.0334 2.53880e-1 5.693e-5 ?
  18  12.719 PB      0.0419 6.40237e-1  0.00014 ?
  19  13.639 BP      0.0323    2.07570  0.00047 ?
  20  14.698 PB      0.0512 7.60013e-1  0.00017 ?
  21  14.846 BP      0.0286 2.47091e-1 5.541e-5 ?
  22  14.915 VV      0.0879   15.06341  0.00338 ?
  23  15.114 VV      0.0400   57.82418  0.01297 ?
  24  15.319 VB      0.0439   42.43530  0.00952
  25  15.556         0.0000    0.00000  0.00000
  26  16.237 BV      0.0349   63.14836  0.01416 ?
  27  16.501 VV      0.0319  105.96007  0.02376 ?
  28  21.704 VV      0.0968 1786.30078  0.40055 ?

Totals :                   4.45962e5
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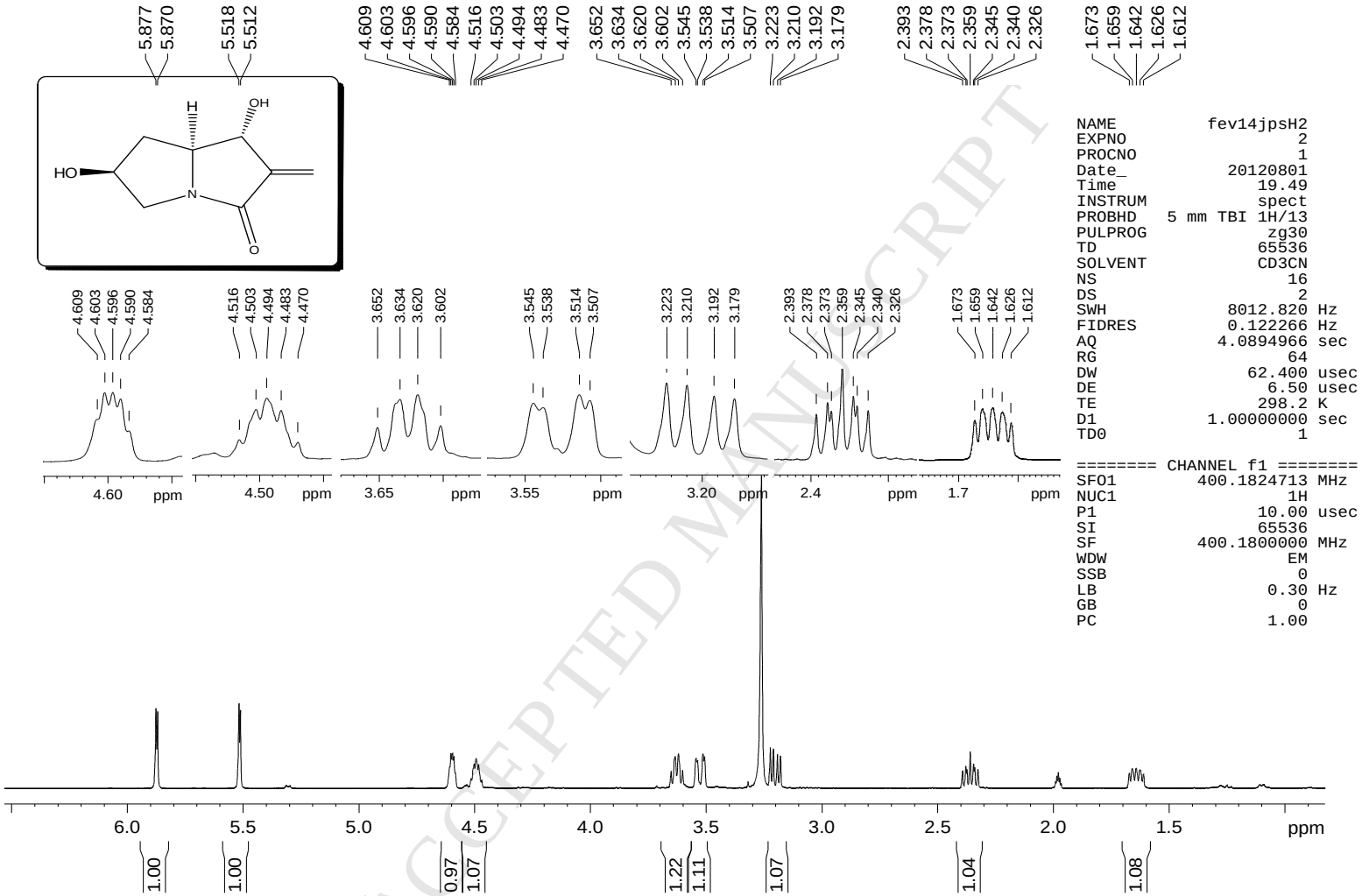
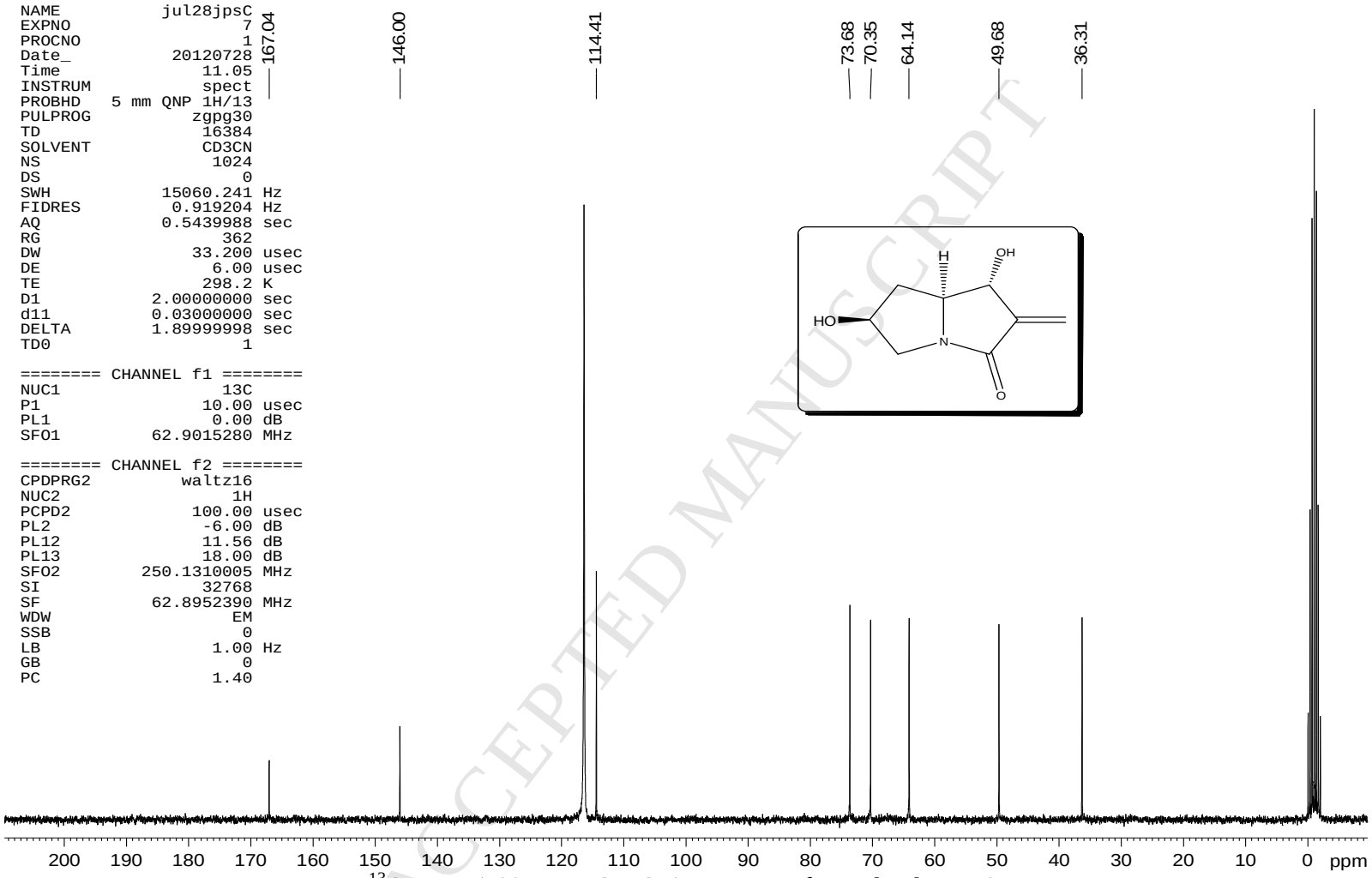
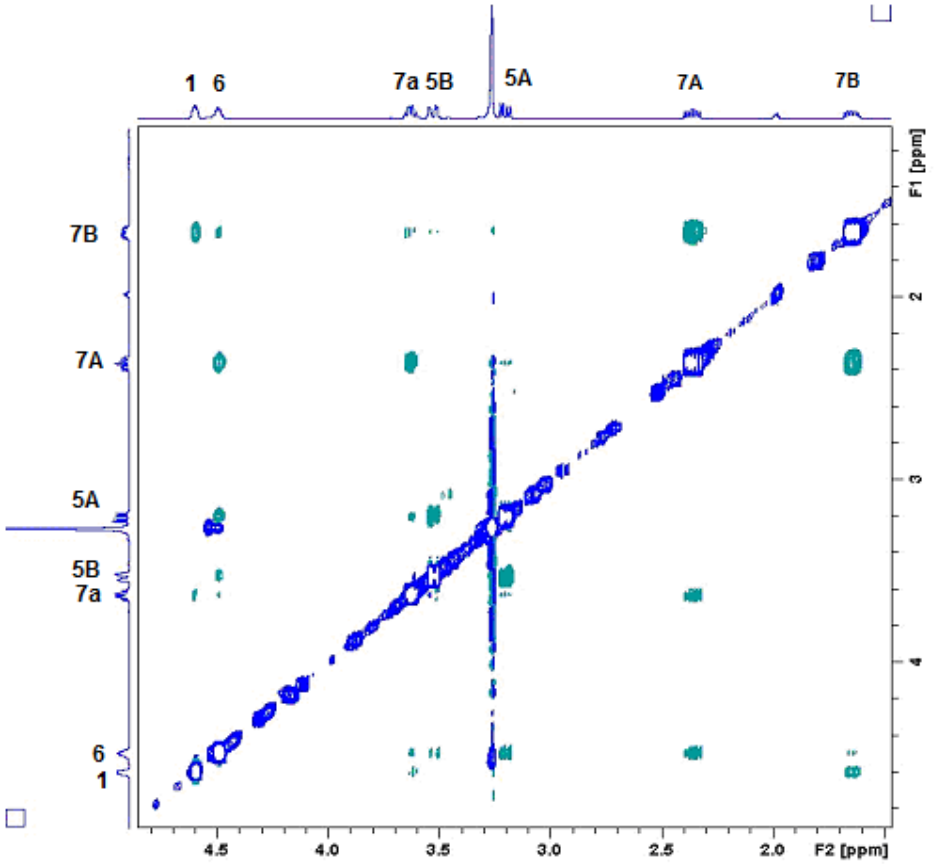
GC chromatogram of MBH adduct **16.**



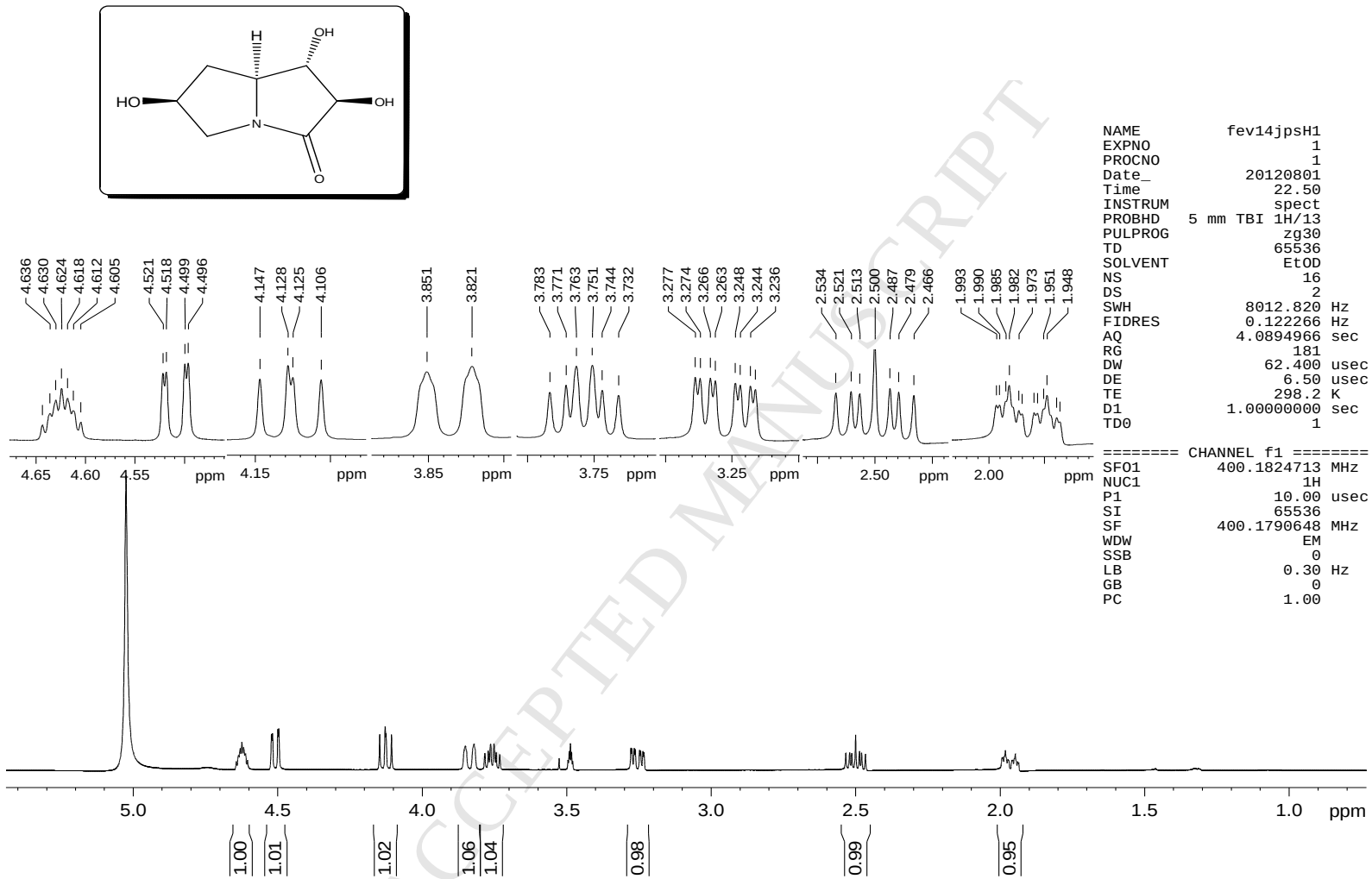
^{1}H NMR (400 MHz, CD_3CN) spectrum of pyrrolizidinone **9.**



^{13}C NMR (400 MHz, CD_3CN) spectrum of pyrrolizidinone **9.**



2D-COSY (400 MHz, CD_3CN) spectrum of pyrrolizidinone **9.**

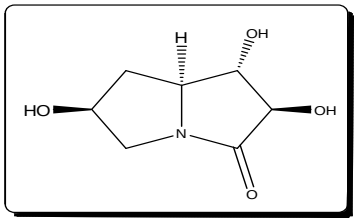


^{1}H NMR (400 MHz, CD_3CN) spectrum of pyrrolizidinone **8**.

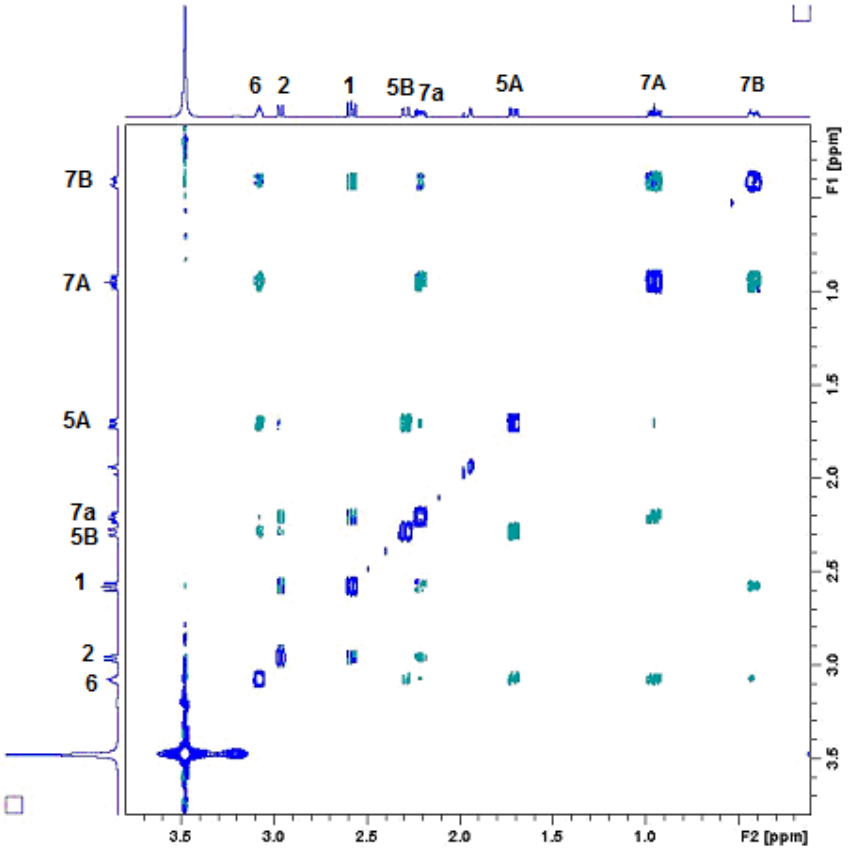
```
NAME          jul28jpsC1
EXPNO                  7
PROCNO                 1
Date_           20120728
Time                12.28
INSTRUM          spect
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                 16384
SOLVENT             MeOD
NS                  1024
DS                     0
SWH           15060.241 Hz
FIDRES         0.919204 Hz
AQ             0.5439988 sec
RG                 724.1
DW                33.200 usec
DE                 6.00 usec
TE                298.2 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 10.00 usec
PL1                 0.00 dB
SFO1          62.9015280 MHz

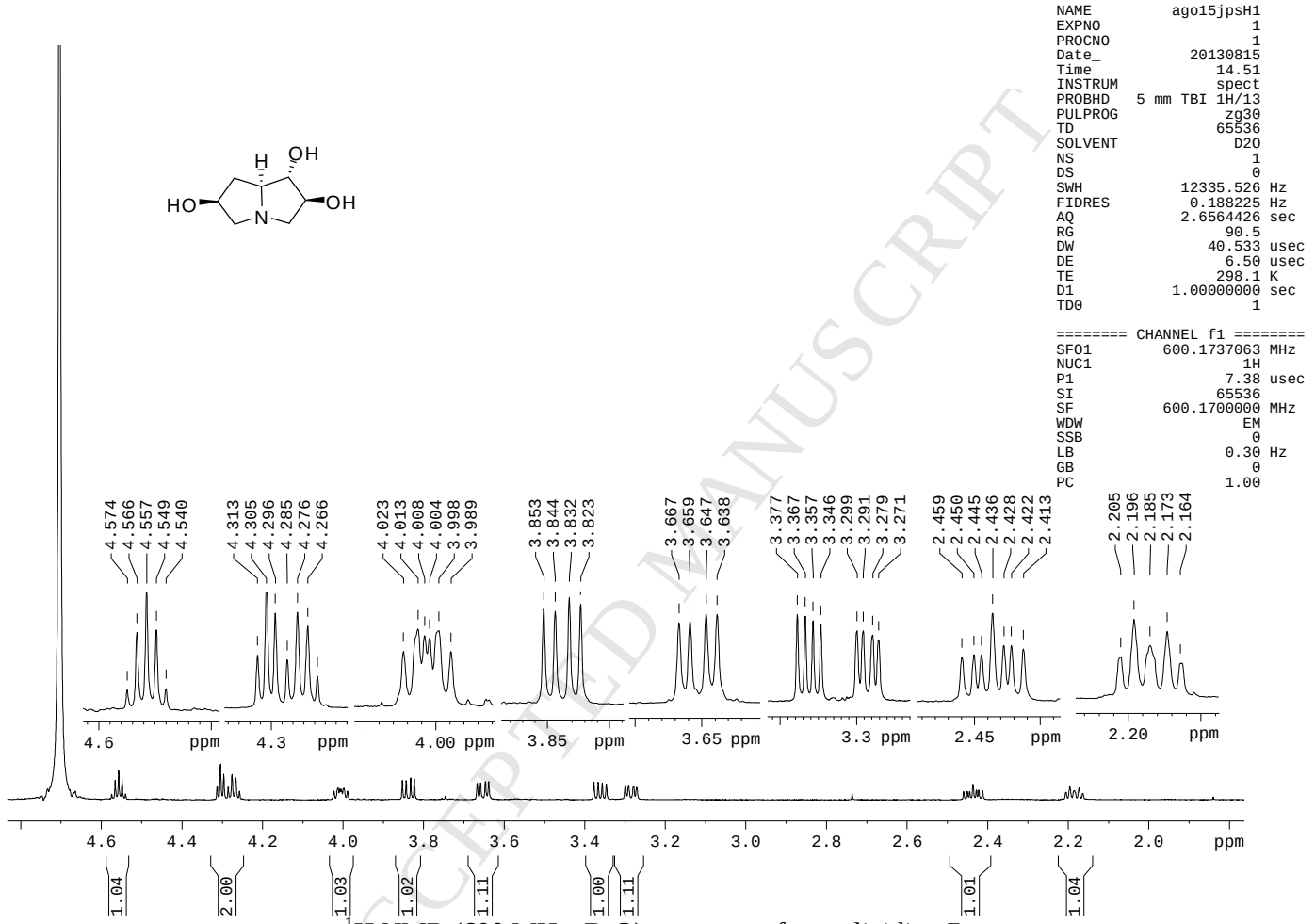
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                -6.00 dB
PL12               11.56 dB
PL13               18.00 dB
SFO2         250.1310005 MHz
SI                 32768
SF            62.8952390 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



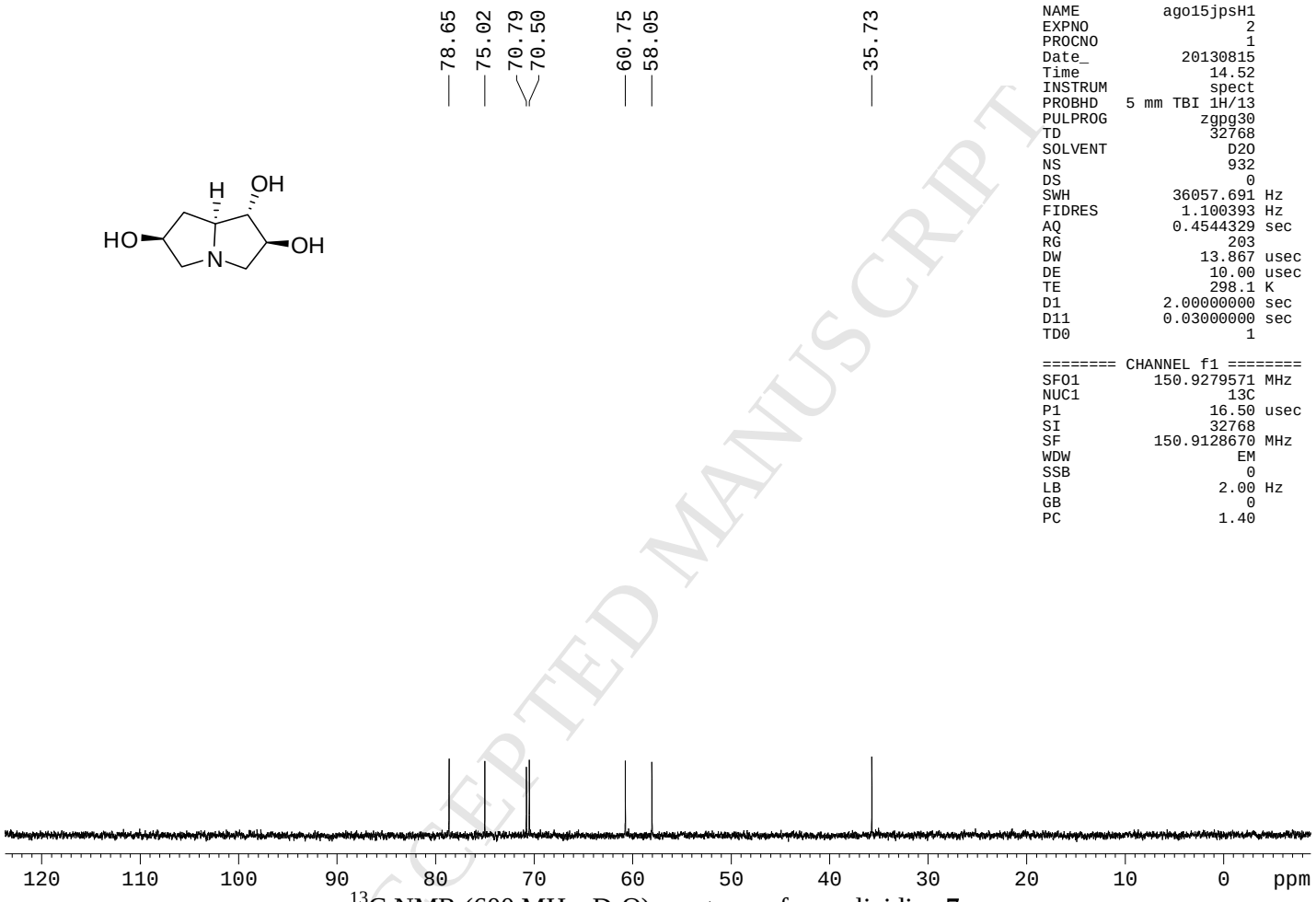
^{13}C NMR (250 MHz, MeOD) spectrum of pyrrolizidinone **8**.



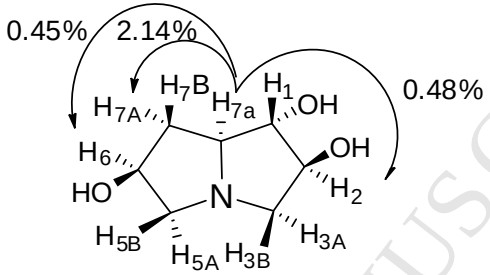
2D-COSY (400 MHz, CD_3CN) spectrum of pyrrolizidinone **8.**



^{1}H NMR (600 MHz, D_2O) spectrum of pyrrolizidine 7**.**



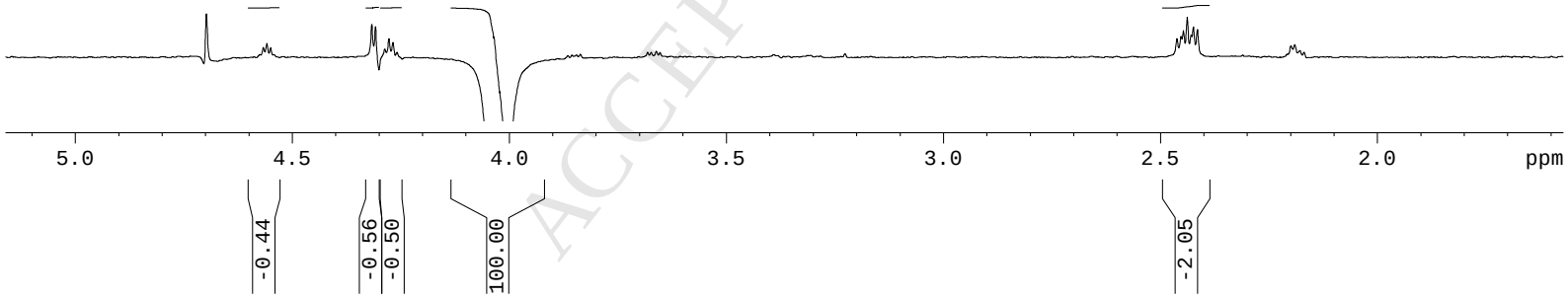
^{13}C NMR (600 MHz, D_2O) spectrum of pyrrolizidine **7**.



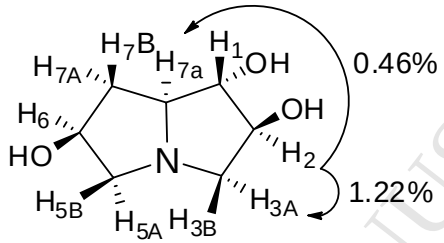
Irradiated at H_{7a} (4.03 ppm)

```
NAME          set21jpsH
EXPNO                 9
PROCNO                1
Date_          20130921
Time              20.04
INSTRUM           spect
PROBHD   5 mm TBI 1H/13
PULPROG         selnogp
TD                32768
SOLVENT             D2O
NS                 1024
DS                    4
SWH            7812.500 Hz
FIDRES        0.238419 Hz
AQ            2.0972021 sec
RG                  203
DW               64.000 usec
DE                6.50 usec
TE                298.2 K
D1           5.00000000 sec
D8           0.60000002 sec
D16          0.00020000 sec
D20          0.29879999 sec
TD0                   1
ZGOPTNS

======== CHANNEL f1 ========
SFO1         600.1724161 MHz
NUC1                 1H
P1                7.90 usec
P2               15.80 usec
P12           71883.00 usec
SI                65536
SF           600.1700021 MHz
WDW                 EM
SSB                  0
LB                2.00 Hz
GB                   0
PC                1.00
```



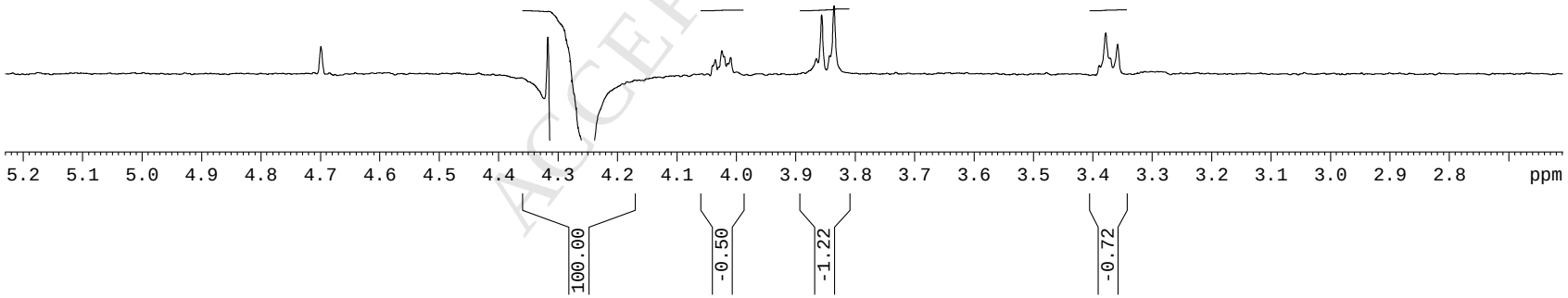
NOE [600 MHz, (D_2O)] spectrum of pyrrolizidine **7**, irradiation at 4.03 ppm, H-7a.



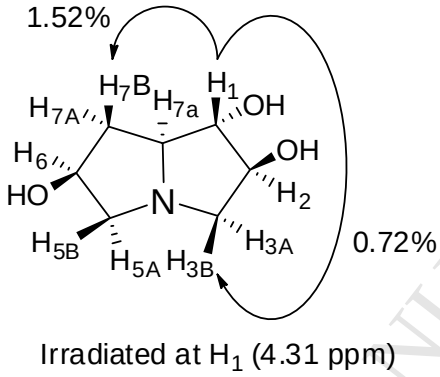
Irradiated at H_2 (4.27 ppm)

```
NAME          set21jpsH
EXPNO                 8
PROCNO                1
Date_          20130921
Time              17.50
INSTRUM           spect
PROBHD   5 mm TBI 1H/13
PULPROG         selnogp
TD                32768
SOLVENT             D2O
NS                 1024
DS                    4
SWH            7812.500 Hz
FIDRES        0.238419 Hz
AQ           2.0972021 sec
RG                  203
DW               64.000 usec
DE                6.50 usec
TE               298.1 K
D1           5.00000000 sec
D8           0.60000002 sec
D16          0.00020000 sec
D20          0.29879999 sec
TD0                   1
ZGOPTNS

======== CHANNEL f1 ========
SFO1         600.1725646 MHz
NUC1                 1H
P1                 7.90 usec
P2                15.80 usec
P12            81685.00 usec
SI                65536
SF           600.1700021 MHz
WDW                  EM
SSB                   0
LB                 2.00 Hz
GB                    0
PC                 1.00
```



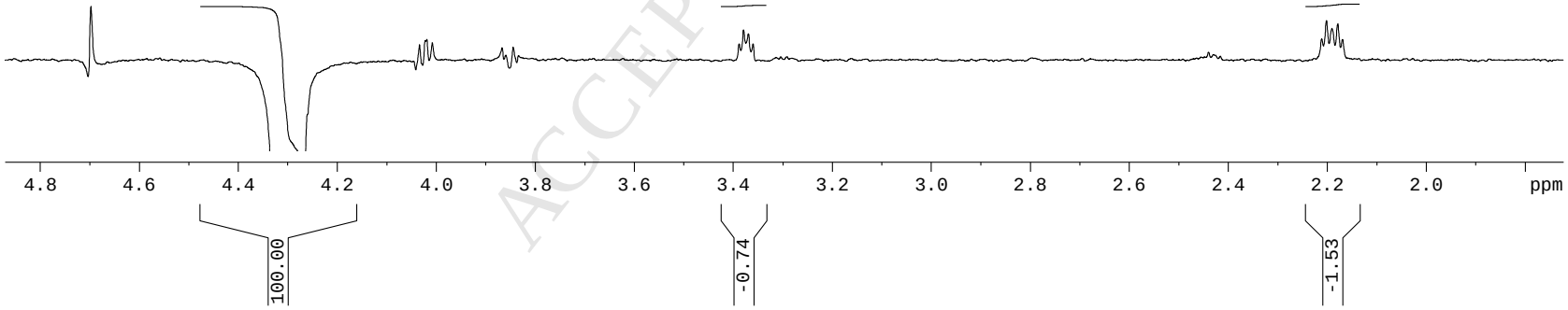
NOE [600 MHz, (D_2O)] spectrum of pyrrolizidine **7**, irradiation at 4.27 ppm, H-2



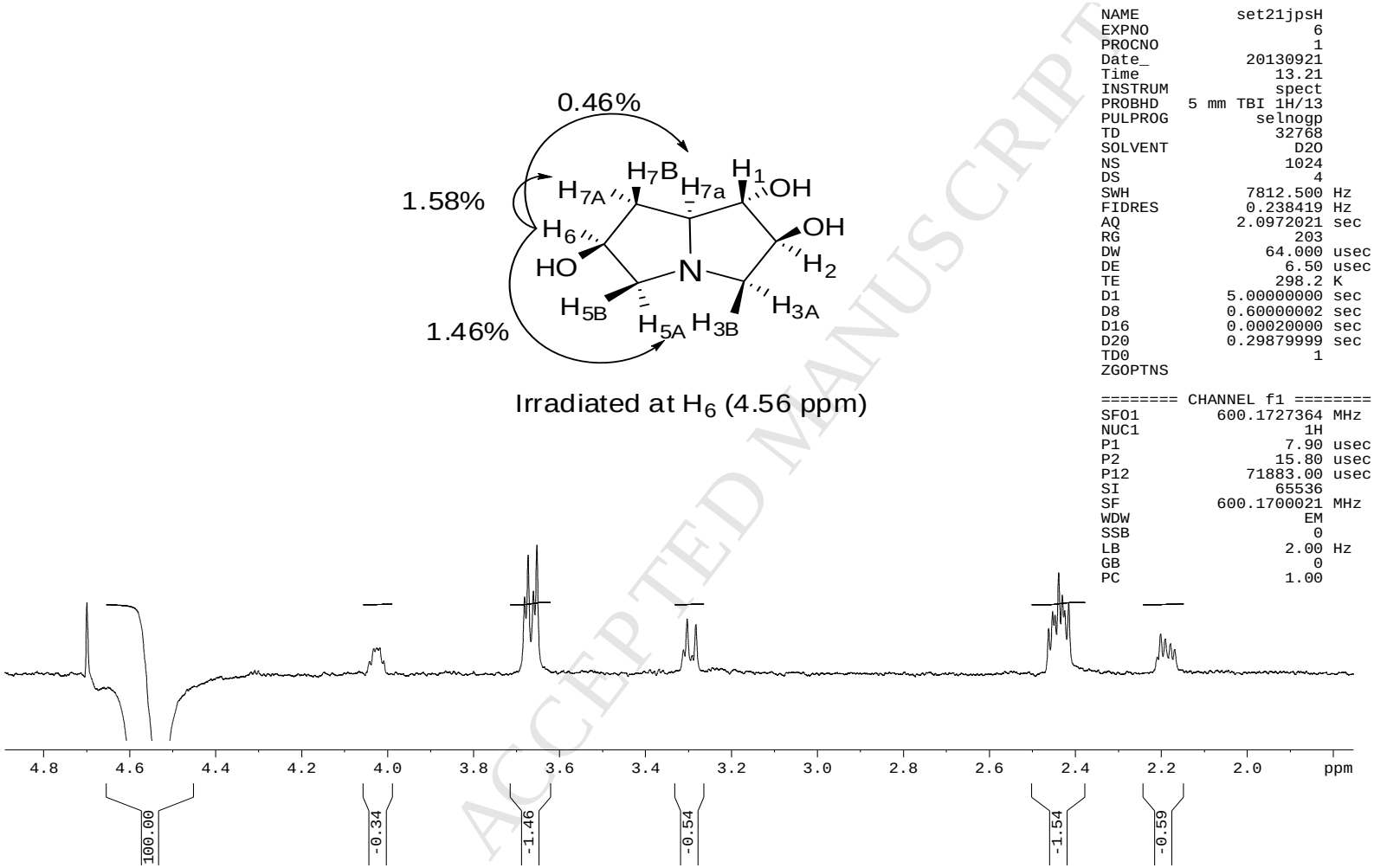
Irradiated at H_1 (4.31 ppm)

```
NAME           set21jpsH
EXPNO                  7
PROCNO                 1
Date_           20130921
Time               15.36
INSTRUM            spect
PROBHD   5 mm TBI 1H/13
PULPROG          selnogp
TD                 32768
SOLVENT              D2O
NS                  1024
DS                     4
SWH             7812.500 Hz
FIDRES          0.238419 Hz
AQ              2.0972021 sec
RG                   203
DW                64.000 usec
DE                 6.50 usec
TE                298.1 K
D1             5.00000000 sec
D8             0.60000002 sec
D16            0.00020000 sec
D20            0.29879999 sec
TD0                    1
ZGOPTNS

======== CHANNEL f1 ========
SFO1          600.1725865 MHz
NUC1                  1H
P1                  7.90 usec
P2                 15.80 usec
P12            140000.00 usec
SI                 65536
SF            600.1700021 MHz
WDW                  EM
SSB                   0
LB                 2.00 Hz
GB                    0
PC                 1.00
```



NOE [600 MHz, (D_2O)] spectrum of pyrrolizidine **7**, irradiation at 4.31 ppm, H-1



NOE [600 MHz, (D_2O)] spectrum of pyrrolizidine **7**, irradiation at 4.56 ppm, H-6