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SÍNTESIS ESTEREOSELECTIVA DE *cis*-DECAHIDROQUINOLINAS: INTERMEDIOS AVANZADOS PARA EL ACCESO A LAS LEPADINAS

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Model studies in the lepadin series: synthesis of enantiopure decahydroquinolines by aminocyclization of 2-(3-aminoalkyl)cyclohexenones

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Abstract—Syntheses of enantiopure 3-acetoxy-2-methyldecahydroquinolines are accomplished by coupling cyclohexenyllithium **3** with α-amino epoxides and an aminocyclization of 2-(3-aminoalkyl)cyclohexenones (i.e., **5** and **9**) as the key steps. The procedure allows the incorporation of alkyl substituents at C(5) to give enantiopure 2,3,5-trisubstitued decahydroquinolines.

1. Introduction

Lepadin alkaloids are structurally characterized by the presence of a 2,3,5-trisubstituted *cis*-fused decahydroquinoline ring. The substitution pattern, which has a methyl group at C(2), a hydroxyl group, free or acylated, at C(3), and an eight carbon side chain at C(5), shows a variety of stereochemical arrangements, as shown in Figure 1. Eight lepadins (A–H) have been isolated from marine sources since 1991,[1–4] of which lepadins A–C have been found to possess significant in vitro cytotoxicity against several human cancer cell lines, whereas lepadins D–F have shown low cytotoxicity but significant and selective antiplasmodial and antitrypanosomal activity.

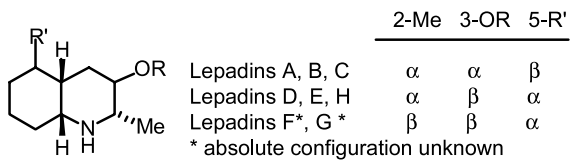

Figure 1.

Total enantioselective syntheses of lepadins A,[5] B,[5–7] C,[5] D–E,[7] and H,[7] as well as a formal route to *rac*-lepadin B[8] have been reported. The strategies described for the construction of 5-substituted 3-hydroxy-2-methyldecahydroquinolines in these synthetic approaches involve the elaboration of a polyfunctionalized piperidine followed by carbocyclic ring closure through aldol processes[5,6] or the construction of the piperidine ring from cyclohexanone derivatives either by an intramolecular enamine alkylation[7] or using a xanthate-mediated radical cyclization[8] (Scheme 1).

In this work, we report our studies on a new synthetic entry to the azabicyclic core of lepadins, either those that show a *cis* or *trans* relationship between the respective methyl and hydroxyl substituents at C(2) and C(3) of the decahydroquinoline ring (see Fig. 1). In our approach, we envisaged enantiopure cyclohexenones of type **I** ($R'=H$) as potential intermediates as they would bring about ring closure by forming the N–C(8a) bond. Here, we present the synthesis of these building blocks and the results obtained by their aminocyclization, either when $R'=H$ or $R'=$alkyl.

2. Results and discussion

2.1. Synthetic aspects

The required starting materials are 2-bromocyclohex-2-enone ethylene acetal (**1**) and the (*S*) and (*R*) isomers of [(*S*)-1′-(dibenzylamino)ethyl]oxirane (**2a** and **2b**). The cyclohexenone derivative **1**, reported by Smith,[9] is a precursor of the α-ketovinyl anion equivalent **3**, often used in the formation of C–C bonds, for example, in reactions with alkyl halides,[9,10] ketones,[11] ethyl chloroformate,[9] and DMF.[12] Moreover, this vinyllithium derivative has been

Keywords: Lepadin alkaloids; Decahydroquinolines; Epoxides; Organolithiums; Nitrogen heterocycles.
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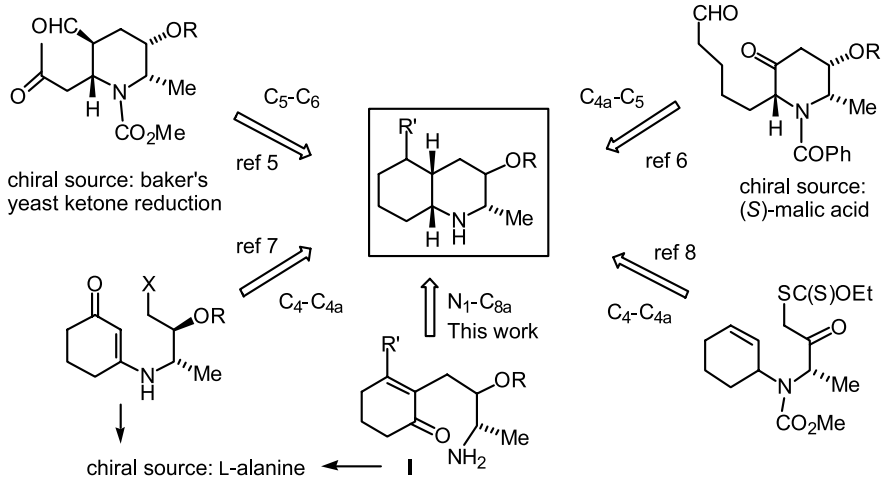
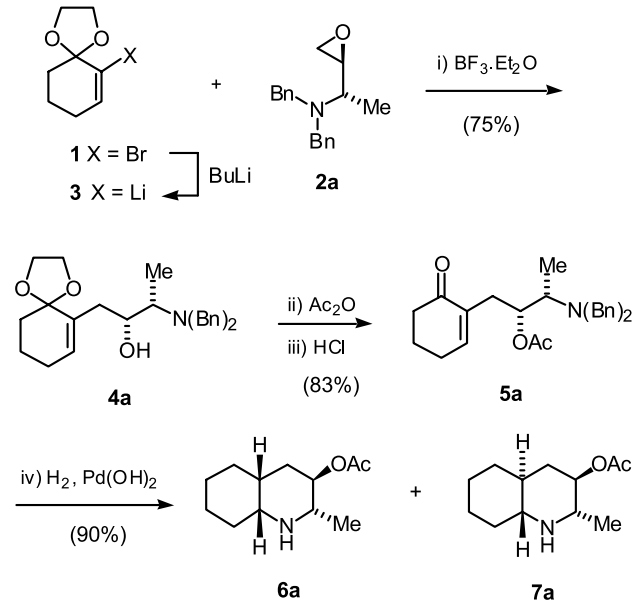


Scheme 1. Synthetic approaches to lepadin alkaloids.

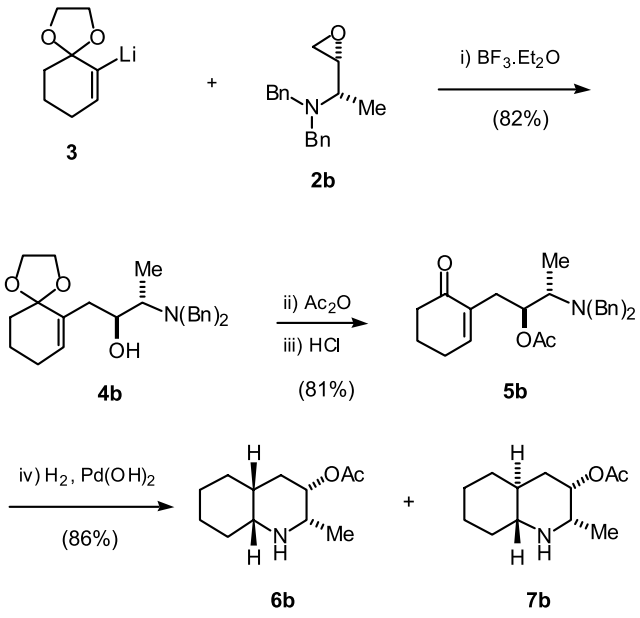
transmetallated with copper,[13] tin,[14] and palladium[15] reagents and then used in coupling processes. Finally, the lithium compound **3** reacts with TMSCl[16] and sulfinates to give vinylsilane and vinylsulfoxide[17] derivatives, respectively. To our knowledge, this versatile lithium derivative has not been used in reactions with epoxides, such as described in the present work. On the other hand, epoxides **2**[18] have been described by Reetz,[19] Barluenga and Concellón[20] and Beaulieu,[21] but there are no examples of their reactions with organolithium derivatives.[22]

The vinyllithium **3** formed on treatment of bromoacetal **1** with *n*-BuLi in THF reacted with epoxide **2a**[20] in presence of $BF_3 \cdot Et_2O$ (Ganem's conditions)[23,24] to give enantiopure alcohol **4a** (Scheme 2). After protection of the hydroxyl group as an acetate and subsequent deprotection of the acetal, the resulting cyclohexenone **5a** was submitted to a hydrogenation reaction, which involves a reduction of the double bond, a double debenzylation of the tertiary amine and an intramolecular reductive amination, to give the decahydroquinoline ring. In this process, in which two new



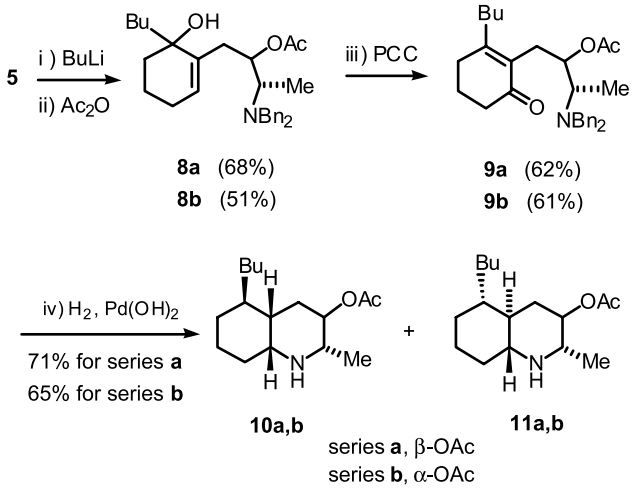
Scheme 2.

stereogenic centers are formed, the bicyclic compounds **6a** and **7a** were isolated in a 2:1 ratio. We then carried out the same sequence of reactions but starting from epoxide **2b**[20] (Scheme 3). In this series, the aminocyclization step starting from cyclohexenone **5b** gave a nearly equimolecular mixture of decahydroquinolines **6b** and **7b**. Thus, 5-dealkyllepadin derivatives with the same absolute configuration as lepadins D, E, and H (i.e., compound **6a**), and lepadins A, B, and C (i.e., compound **6b**) were achieved.



Scheme 3.

At this point, we explored the usefulness of cyclohexenones **5** as precursors of 5-alkylsubstituted decahydroquinolines (Scheme 4). Treatment of **5a** with *n*-BuLi gave a tertiary alcohol as an epimeric mixture, which was reacetylated upon the hydroxyl of the side chain, and the resulting **8a** was oxidized[25] to give the rearranged enone **9a**. The multi-step tranformation of **9a** under a hydrogen atmosphere (hydrogenation, debenzylation, and reductive aminocyclization) gave a mixture of trisubstituted decahydroquinolines **10a**



Scheme 4.

and **11a** in a nearly equimolecular ratio (71% overall yield), in which three new stereogenic centers were formed. Working with the epimeric epoxide **5b**, and following the same reaction sequence, decahydroquinolines **10b** and **11b** were formed in a 1:4 ratio (65% overall yield).

In all the cyclization processes (**5**→**6**+**7** and **9**→**10**+**11**), both in series **a** (3*R* configuration) and series **b** (3*S* configuration), the isolated decahydroquinolines show an *R* configuration at C(8a) (see Fig. 2). The configuration at C(4a) is controlled by the configuration of C(3) as well as by the presence or absence of a substituent at C(5). From the β-unsubstituted cyclohexenones (i.e., compounds **5**), the aminocyclization takes place with some diastereoselection if the acetoxy substituent can adopt a pseudo-equatorial disposition in the transition state leading to the reduced product, as occurs in **6a**, whereas in the epimeric series no stereocontrol was observed in the formation of the C(4a) stereocenter. Since it has not been established if the course of the reaction follows a pathway through an enimine intermediate or if there is a reduction of the double bond prior to the cyclization step, a clear understanding of the stereochemical course is not possible at this stage. More intriguing is the pathway of the aminocyclization leading to 2,3,5-trisubstituted decahydroquinolines **10** and **11**. The configuration at C(4a) and C(5) in all cases showed a trans relationship between the hydrogen atoms of these stereocenters suggesting that the double bond underwent a trans hydrogenation, as has been reported in some tetrasubstituted alkenes,[26] or, after a cis hydrogenation and formation of the subsequent imine, an epimerization took place at C(4a) through an enamine intermediate. Again, as occured in the 5-unsubstituted series, the ratio of trans decahydroquinolines (i.e., **11b**) to the cis epimers was higher in compounds with a 3*S* rather than 3*R* configuration.

2.2. NMR studies of decahydroquinolines 6, 7, 10, and 11 (series a and b)

The cis (**6** and **10**) and trans decahydroquinolines (**7** and **11**) are clearly differentiated by two NMR features: (i) the ^{1}H NMR chemical shift of H-8a, which appears more deshielded (δ 2.95) in the *cis*-than in the trans-derivatives (δ 2.20); (ii) the ^{13}C chemical shift of C(7) is more deshielded (~4–5 ppm) in the trans than in the cis derivatives.[27] In all cases, the preferred conformation of the cis decahydroquinolines has the H-8a axial with respect to the *N*-containing ring (*N-endo* conformer).

The absolute configuration of **6a** was deduced considering that: (a) the coupling constants for H-2 (dq, J=10, 6.5 Hz) and H-3 (td, J=10.5, 4.8 Hz) determined their axial location and hence, fixed the methyl at C(2) and the acetoxy at C(3) to an equatorial disposition; (b) the multiplicity of H-8a (br s) implied an equatorial relationship with respect to the cyclohexane ring, which discarded not only a trans junction of the decaline ring but also, taking into account the preferred conformation, implied an *R* configuration for C(8a). The ^{13}C chemical shifts also agree with this elucidation since the value of δ 20.3 for C(7) is diagnostic of a cis decahydroquinoline in a *N-endo* conformation. For trans compound **7a**, the axial proton H-8a is strongly coupled to two adjacent axial protons and one equatorial proton. Hence, its resonance signal appears as a deceptively simple triplet (J=10.4 Hz) of doublets (J=3.2 Hz) centered at δ 2.19. The NMR data for compounds **6b** and **7b** follow the same pattern of signals as that of their corresponding epimers at C(3), the major differences being in the chemical shift for H-3, which is now more deshielded since it is located in an equatorial arrangement, and in C-3 and C-4a, which resonate at a lower field, due to the axially

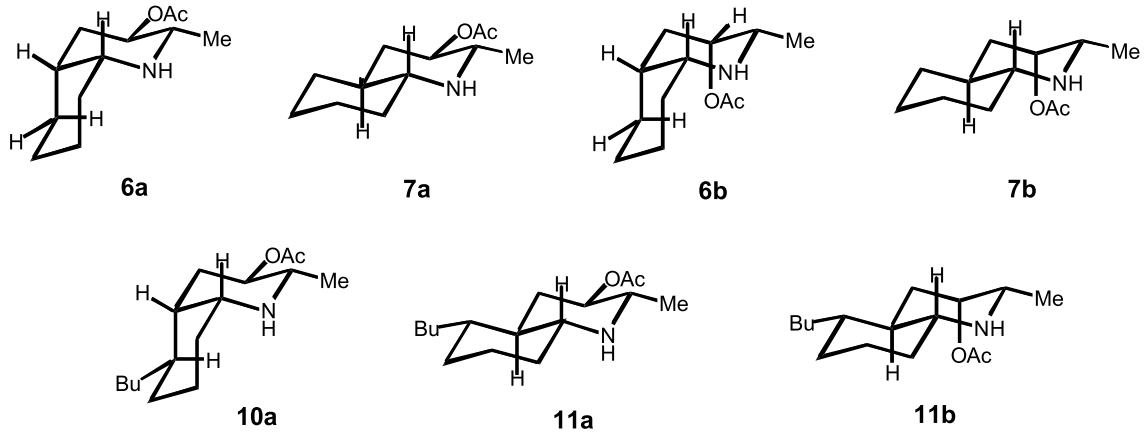


Figure 2. Preferred conformation of decahydroquinolines **6**, **7**, **10**, and **11**.

Table 1. ^{13}C NMR data for decahydroquinolines **6**, **7**, **10**, and **11**

	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9	C-1′	C-2′	C-3′	C-4′	OAc
6a	56.5	73.0	36.4	36.8	26.5	26.1	20.3	31.9	54.3	18.9	—	—	—	—	170.6/21.3
6b	55.0	70.3	35.0	33.5	27.5	26.8	20.8	32.6	54.6	18.2	—	—	—	—	170.8/21.4
7a	55.7	75.7	37.5	41.6	31.8	25.6	25.3	32.6	60.9	18.5	—	—	—	—	170.4/21.2
7b	54.0	71.6	36.6	36.9	31.9	26.0	25.5	33.2	61.4	18.3	—	—	—	—	171.0/21.3
10a	56.5	72.7	32.5	41.8	33.0	29.7	21.3	32.7	55.5	18.8	31.9	28.1	23.1	14.1	170.5/21.1
11a	55.4	76.4	34.4	46.3	40.8	31.3	24.7	33.1	60.8	18.7	32.1	28.5	23.1	14.1	170.5/21.3
11b	53.7	71.6	33.5	40.9	40.7	31.9	24.9	33.4	61.1	18.2	31.7	28.4	23.1	14.1	171.0/21.3

All spectra were recorded at 100 MHz in $CDCl_3$ and the assignments were aided by HSQC experiments.

located acetoxy group (Table 1). For trisubstituted cis decahydroquinoline **10a**, the butyl substituent at C(5) controls the preferred conformation of the bicyclic ring, which agrees with the conformation showed for lepadins where the substituent at C(5) is always equatorially located. The stereochemistry at C(5) for the butyl substituted products (**10** and **11**) was determined considering that the equatorially located butyl side chain exerts a steric crowding on H-4*eq*, due to their 1,3-synperiplanar relationship, which is reflected in the ^{13}C and ^{1}H NMR spectra by an upfield chemical shift (~3 ppm) for C(4) and a downfield chemical shift (δ 2.25±0.05) for H-4*eq* as compared to the NMR data for compounds **6** and **7**.

In summary, a new synthetic entry to enantiopure polysubstituted decahydroquinolines has been reported. Although the observed stereoselectivity does not allow lepadin-type stereochemistries to be achieved, further studies in aminocyclization processes, starting from cyclohexenones of type **5**, are in progress with the aim of achieving the required stereochemistry of lepadin derivatives. Interestingly, the reported methodology could be applied to the synthesis of another type of natural decahydroquinolines, such as *trans*-195A,[28] 5-*epi*-*trans*-243A,[29] and related alkaloids isolated from dendrobatid frogs,[27c] which show the same pattern of relative configuration as compounds **11a** and **11b** in their four stereocenters.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel $60F_{254}$, Merck) or Al_2O_3 (ALOX N/UV_{254}, Polygram), and the spots were located with iodoplatinate reagent (compounds **4**, **5**, **8**, and **9**) or 1% aqueous $KMnO_4$ (compounds **6**, **7**, **10**, and **11**). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–240 mesh ASTM) or Al_2O_3 (aluminium oxide 90, Merck). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or 300, or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

3.1.1. 2-[(2*R*,3*S*)-3-Dibenzylamino-2-hydroxybutyl] cyclohex-2-enone ethylene acetal (4a). A solution of 6-bromo-1,4-dioxaspiro[4.5]dec-6-ene (**1**, 1.04 g, 4.75 mmol) in THF (3 mL) was added to a solution of *n*-BuLi (1.6 M in hexanes, 3.2 mL, 5.11 mmol) in THF (7 mL) at −78 °C. The reaction mixture was stirred for 90 min, treated with a solution of (2*S*)-[1′(*S*)-(dibenzylamino)ethyl]oxirane (**2a**, 489 mg, 1.83 mmol) in THF (6 mL) and $BF_3 \cdot Et_2O$ (0.64 mL, 5.11 mmol), and continuously stirred at −78 °C for 2 h prior to being quenched with saturated $NaHCO_3$ solution (10 mL) and warmed to rt. The

product was extracted with Et_2O (3×20 mL), the combined organic layers were dried, concentrated, and the residue was chromatographed (SiO_2, elution with 9:1 hexane/EtOAc) to give 560 mg (75%) of **4a** as a colorless oil: R_f=0.31 (SiO_2, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +10.0 (*c* 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.15 (d, *J*=6.3 Hz, 3H), 1.60–1.80 (m, 5H), 1.95–2.05 (br, 2H), 2.52–2.61 (m, 1H), 2.85 (dm, *J*=14 Hz, 1H), 3.25 (br, 1H), 3.45 (d, *J*=13.8 Hz, 2H), 3.66–3.73 (m, 1H), 3.77 (d, *J*=13.8 Hz, 2H), 3.84–3.90 (m, 2H), 3.91–3.97 (m, 2H), 5.76 (t, *J*=3 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 8.4 (CH_3), 20.6 (CH_2), 25.4 (CH_2), 33.2 (CH_2), 36.2 (CH_2), 54.3 (CH_2), 57.7 (CH), 64.6 (CH_2), 64.7 (CH_2), 74.1 (CH), 107.5 (C), 126.7 (CH), 128.1 (CH), 128.7 (CH), 133.6 (CH), 140.3 (C). HRFABMS calcd for $C_{26}H_{34}NO_3$ (M^++1) 408.2539, found 408.2516.

3.1.2. 2-[(2*S*,3*S*)-3-Dibenzylamino-2-hydroxybutyl] cyclohex-2-enone ethylene acetal (4b). Operating as above, starting from 881 mg (4.02 mmol) of **1** and using (2*R*)-[1′(*S*)-(dibenzylamino)ethyl]oxirane (**2b**, 414 mg, 1.55 mmol), and after chromatography (SiO_2, 9:1 hexane/EtOAc) **4b** (518 mg, 82%) was isolated as an oil: R_f=0.28 (SiO_2, 9:1 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 1.05 (d, *J*=6.6 Hz, 3H), 1.62–1.72 (m, 5H), 1.95–2.05 (br, 2H), 2.17–2.25 (m, 1H), 2.52–2.62 (m, 1H), 3.33 (d, *J*=13.6 Hz, 2H), 3.64–3.76 (m, 1H), 3.88 (d, *J*=13.6 Hz, 2H), 3.90–3.98 (m, 4H), 5.93 (t, *J*=2 Hz, 1H), 7.16–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 8.6 (CH_3), 20.6 (CH_2), 25.3 (CH_2), 33.6 (CH_2), 34.3 (CH_2), 53.6 (CH_2), 58.2 (CH), 64.7 (CH_2), 64.8 (CH_2), 70.8 (CH), 107.8 (C), 127.0 (CH), 128.3 (CH), 128.9 (CH), 131.5 (CH), 139.2 (C).

3.1.3. 2-[(2*R*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl] cyclohex-2-enone (5a). To a solution of **4a** (101 mg, 0.25 mmol) in pyridine (0.8 mL) and Ac_2O (0.24 mL, 2.5 mmol) was added DMAP (5 mg, 0.04 mmol). The reaction mixture was stirred overnight at rt. A saturated $NaHCO_3$ solution (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The dried organic extracts were concentrated to give the corresponding acetate, which was used directly in the following acetal hydrolysis step. The above crude acetal was dissolved in 1:1 H_2O/THF (4 mL) and stirred at rt for 1 h. The reaction mixture was basified with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3×10 mL), and the resulting organic extracts were dried and concentrated. The residue was purified by chromatography (SiO_2, hexane/EtOAc 8:2) to give **5a** as an oil (80 mg, 83%): R_f=0.27 (SiO_2, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +7.8 (*c* 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.08 (d, *J*=6.6 Hz, 3H), 1.75–1.83 (m, 1H), 1.83–1.93 (m, 2H), 1.94 (s, 3H), 2.16–2.28 (m, 2H), 2.31–2.38 (m, 2H), 2.75 (quint, *J*=6 Hz, 1H), 3.18 (dm, *J*=14 Hz, 1H), 3.41 (d, *J*=13.6 Hz, 2H), 3.78 (d, *J*=13.6 Hz, 2H), 5.17 (ddd, *J*=9.6, 7.6, 3.4 Hz, 1H), 6.53 (t, *J*=4 Hz, 1H), 7.17–7.41 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 8.8 (CH_3), 21.2 (CH_3), 22.9 (CH_2), 26.2 (CH_2), 33.2 (CH_2), 38.2 (CH_2), 53.9 (CH_2), 55.1 (CH), 74.3 (CH), 126.7 (CH), 128.1 (CH), 129.0 (CH), 136.4 (C), 139.9 (C), 146.4 (CH), 170.4 (C), 198.7 (C). Anal. Calcd for $C_{26}H_{31}NO_3$: C, 77.00; H, 7.70; N, 3.45. Found C, 76.75; H, 7.85; N, 3.39.

3.1.4. 2-[(2*S*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl] cyclohex-2-enone ethylene acetal (5b). Operating as above, starting from 263 mg (0.64 mmol) of alcohol **4b**, and after chromatography (SiO_2, 8:2 hexane/EtOAc), acetate **5b** (196 mg, 81%) was isolated as an oil: R_f=0.25 (SiO_2, hexane/EtOAc, 8:2); $[\alpha]_D^{20}$ −32 (*c* 1.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.09 (d, *J*=7.2 Hz, 3H), 1.86–1.94 (m, 3H), 2.01 (s, 3H), 2.16–2.30 (m, 3H), 2.33–2.40 (m, 1H), 2.60 (dm, *J*=14 Hz, 1H), 2.89 (quint, *J*=7 Hz, 1H), 3.37 (d, *J*=13.8 Hz, 2H), 3.87 (d, *J*=13.8 Hz, 2H), 5.06 (ddd, *J*=10.2, 6.2, 2.6 Hz, 1H), 6.60 (t, *J*=4.2 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): 9.7 (CH_3), 21.2 (CH_3), 22.9 (CH_2), 26.1 (CH_2), 33.0 (CH_2), 38.2 (CH_2), 54.3 (CH_2), 55.4 (CH), 74.7 (CH), 126.6 (CH), 128.1 (CH), 128.8 (CH), 136.3 (C), 140.3 (C), 146.3 (CH), 170.3 (C), 198.8 (C). HRFABMS calcd for $C_{26}H_{32}NO_3$ (M^++1) 406.2382, found 406.2339.

3.1.5. Aminocyclization of 5a. A suspension of enone **5a** (50 mg, 0.12 mmol) and activated[30] $Pd(OH)_2$ in EtOH (2 mL) was stirred overnight under hydrogen. The catalyst was removed by filtration through Celite, and the solvent was evaporated to give a residue, which was purified by chromatography (Al_2O_3, 9:1 hexane/EtOAc) to give **6a** (13 mg, 54%) and **7a** (9 mg, 36%), both as oils.

(2*S*,3*R*,4a*R*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline (**6a**). R_f=0.51 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −20.7 (*c* 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.08 (d, *J*=6.4 Hz, 3H, Me), 1.20 (m, H-5*ax*), 1.40 (m, 3H, H-6*ax* and H-7), 1.45 (m, H-4*ax*), 1.55 (m, H-8), 1.70 (m, H-8), 1.74 (m, 3H, H-4a, H-5*eq*, H-6*eq*), 1.87 (ddd, *J*=11.0, 3.6, 1.2 Hz, H-4*eq*), 2.05 (s, 3H, OAc), 2.70 (dq, *J*=10.0, 6.5 Hz, H-2*ax*), 2.95 (br s, H-8a), 4.58 (td, *J*=10.5, 4.8 Hz, H-3*ax*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{12}H_{22}NO_2$ (M^++1) 212.1651, found 212.1646.

(2*S*,3*R*,4a*S*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline (**7a**). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.02 (qd, *J*=10.4, 3.2 Hz, H-5*ax*), 1.10 (masked, H-4*ax*), 1.12 (d, *J*=6.4 Hz, 3H, Me), 1.20–1.30 (m, 2H, H-8*ax* and H-4a), 1.35 (m, 2H, H-6*ax* and H-7*ax*), 1.65 (m, 2H, H-7*eq* and H-5*eq*), 1.8 (m, 2H, H-8*eq* and H-6*eq*), 2.04 (s, 3H, OAc), 2.05 (masked, H-4*eq*), 2.19 (td, *J*=10.4, 3.2 Hz, H-8a), 2.76 (dq, *J*=10, 6.4 Hz, H-2*ax*), 4.45 (td, *J*=10.4, 4.4 Hz, H-3*ax*); ^{13}C NMR see Table 1.

3.1.6. Aminocyclization of 5b. Operating as above, starting from 49 mg (0.12 mmol) of enone **5b**, and after chromatography (Al_2O_3, from 9:1 to 7:3 hexane/EtOAc), 11 mg (43%) of **6b** and 11 mg (43%) of **7b**, both as colorless oils, were isolated.

(2*S*,3*S*,4a*R*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline (**6b**). R_f=0.30 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +10.8 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.08 (d, *J*=6.6 Hz, 3H, Me), 1.20 (m, H-5*ax*), 1.40 (m, 3H, H-6*ax*, H-7), 1.50 (m, 2H, H-8*ax*, H-4*ax*), 1.72 (m, 4H, H-4a, H-5*eq*, H-6*eq*, H-8*eq*), 1.87 (ddd, *J*=12, 3.6, 1.5 Hz, H-4*eq*), 2.09 (s, 3H, OAc), 2.90 (qd, *J*=6.8, 2 Hz, H-2*ax*), 2.92 (br, H-8a), 4.75 (ddd, *J*=3.2, 3.2, 1.6 Hz, H-3*eq*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{12}H_{22}NO_2$ (M^++1) 212.1651, found 212.1648.

(2*S*,3*S*,4a*S*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline

(**7b**). R_f=0.23 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +28.6 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.94 (qd, *J*=12, 3 Hz, H-5*ax*), 1.06 (dd, *J*=6.8 Hz, 3H, Me), 1.21–1.34 (m, 5H, H-4*ax*, H-4a, H-6*ax*, H-7*ax*, H-8*ax*), 1.54 (dm, *J*=12 Hz, H-5*eq*), 1.69 (dm, *J*=12 Hz, H-6*eq*), 1.77 (dm, 2H, *J*=12 Hz, H-7*eq*, H-8*eq*), 1.88 (dd, *J*=10.8, 3.2 Hz, H-4*eq*), 2.12 (s, 3H, OAc), 2.22 (td, *J*=10, 3.2 Hz, H-8a), 2.92 (qd, *J*=6.4, 1.6 Hz, H-2*ax*), 4.88 (ddd, *J*=3.2, 3.2, 1.6 Hz, H-3*eq*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{12}H_{22}NO_2$ (M^++1) 212.1651, found 212.1648.

3.1.7. 2-[(2*R*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-1-butylcyclohex-2-en-1-ol (8a). To a cooled (−78 °C) solution of **5a** (105 mg, 0.258 mmol) in THF (3 mL) was added *n*-BuLi (1.6 M in hexanes, 0.8 mL, 1.29 mmol) and the reaction mixture was stirred for 4 h, the temperature slowly rising to rt. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The dried organic extracts were concentrated and the residue was dissolved in pyridine (1 mL) and treated with Ac_2O (0.25 mL, 2.58 mmol) and DMAP (5 mg, 0.04 mmol). The reaction mixture was stirred overnight at rt, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 15 mL). The dried organic extract was concentrated and purified by chromatography (SiO_2, hexane/EtOAc 8:2) to give the epimeric alcohols **8a** and 1-*epi*-**8a** (81 mg, 68%), in a 1:1 ratio according to the NMR spectrum, which were used directly in the next step.*Compound* **8a**. R_f=0.82 (SiO_2, 8:2 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 0.92 (t, *J*=6.8 Hz, 3H), 1.11 (d, *J*=7.0 Hz, 3H), 1.18–1.38 (m, 4H), 1.49–1.80 (m, 7H), 1.82–1.93 (m, 2H), 1.98 (s, 3H), 2.75 (quint, *J*=7 Hz, 1H), 2.95 (dm, *J*=12 Hz, 1H), 3.44 (d, *J*=13.6 Hz, 2H), 3.75 (d, *J*=13.6 Hz, 2H), 5.29–5.40 (m, 2H), 7.18–7.40 (m, 10H). *Compound* 1-*epi*-**8a**. R_f=0.64 (SiO_2, 8:2 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 0.89 (t, *J*=6.6 Hz, 3H), 1.06 (d, *J*=6.6 Hz, 3H), 1.18–1.38 (m, 4H), 1.40–1.70 (m, 7H), 1.74–1.88 (m, 2H), 2.00 (s, 3H), 2.44–2.54 (m, 1H), 2.85 (quint, *J*=7 Hz, 1H), 3.48 (d, *J*=13.6 Hz, 2H), 3.73 (d, *J*=13.6 Hz, 2H), 5.30 (m, 1H), 5.39 (t, *J*=3.9 Hz, 1H), 7.18–7.40 (m, 10H).

3.1.8. 2-[(2*S*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-1-butylcyclohex-2-enol (8b). Operating as above, starting from 147 mg (0.36 mmol) of cyclohexenone **5b**, and after chromatography (SiO_2, hexane/EtOAc 8:2), 85 mg (51%) of **8b** was obtained: R_f=0.58 (SiO_2, 8:2 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 0.91 (t, *J*=6.8 Hz, 3H), 1.09 (d, *J*=7 Hz, 3H), 1.20–1.40 (m, 5H), 1.42–1.78 (m, 6H), 1.84–1.96 (m, 2H), 2.05 (s, 3H), 2.18–2.28 (m, 1H), 2.85 (quint, *J*=7 Hz, 1H), 3.37 (d, *J*=13.5 Hz, 2H), 3.90 (d, *J*=13.5 Hz, 2H), 5.13–5.22 (m, 1H), 5.45 (t, *J*=3.7 Hz, 1H), 7.18–7.40 (m, 10H).

3.1.9. 2-[(2*R*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-3-butylcyclohex-2-enone (9a). To a solution of epimeric alcohols **8a** (81 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) were added PCC (57 mg, 0.26 mmol) and SiO_2 (57 mg), and the mixture was stirred overnight at rt. The residue obtained after evaporation of the solvent was purified by chromatography (SiO_2, hexane/EtOAc 9:1) to give **9a** as a viscous oil (50 mg, 62%): R_f=0.36 (SiO_2, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −5.3 (*c* 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 0.91 (t, *J*=6.8 Hz, 3H), 1.11 (d, *J*=6.4 Hz, 3H), 1.20–1.50 (m, 4H), 1.70–1.8 (m, 2H), 1.92 (s, 3H), 1.98–2.33 (m, 6H), 2.34–2.42 (m, 1H), 2.71 (quint, *J*=6.8 Hz, 1H), 3.08 (dd, *J*=13.6, 4.4 Hz, 1H), 3.45 (d, *J*=13.6 Hz, 2H), 3.75 (d, *J*=13.6 Hz, 2H), 5.20 (ddd, *J*=8.8, 6.8, 5.2 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$, HSQC) 8.9 (CH_3), 14.1 (CH_3), 21.2 (CH_3), 22.4 (CH_2), 22.9 (CH_2), 28.3 (CH_2), 30.1 (CH_2), 30.8 (CH_2), 34.7 (CH_2), 37.7 (CH_2), 54.0 (CH_2), 55.2 (CH), 75.0 (CH), 126.7 (CH), 128.1 (CH), 128.9 (CH), 131.3 (C), 140.1 (C), 160.9 (C), 170.4 (C), 198.7 (C). Anal. Calcd for $C_{30}H_{39}NO_3\cdot H_2O$: C, 75.12; H, 8.62; N, 2.92. Found C, 75.48; H, 9.02; N, 2.58.

3.1.10. 2-[(2*S*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-3-butylcyclohex-2-enone (9b). Operating as above, starting from 71 mg (0.15 mmol) of alcohol **8b** and after chromatography (SiO_2, 9:1 hexane/EtOAc), enone **9b** (41 mg, 61%) was isolated as a viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) 0.89 (t, *J*=7.2 Hz, 3H), 1.10 (d, *J*=6.8 Hz, 3H), 1.20–1.32 (m, 2H), 1.32–1.44 (m, 2H), 1.81–1.88 (m, 2H), 1.96 (s, 3H), 1.96–2.03 (m, 2H), 2.16–2.42 (m, 6H), 2.34–2.42 (m, 1H), 2.68 (dd, *J*=13.8, 11.0 Hz), 2.89–2.96 (m, 1H), 3.39 (d, *J*=13.6 Hz), 3.90 (d, *J*=13.6 Hz), 5.08 (ddd, *J*=11.0, 5.8, 2.4 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$, HSQC) 9.7 (CH_3), 14.1 (CH_3), 21.1 (CH_3), 22.4 (CH_2), 23.0 (CH_2), 28.4 (CH_2), 30.1 (CH_2), 30.9 (CH_2), 34.8 (CH_2), 37.8 (CH_2), 54.5 (CH_2), 55.8 (CH), 75.9 (CH), 126.7 (CH), 128.1 (CH), 128.7 (CH), 131.7 (C), 140.22 (C), 160.1 (C), 170.1 (C), 198.8 (C).

3.1.11. Aminocyclization of 9a. Following the above procedure for the aminocyclization of **5a** using enone **9a** (38 mg, 0.08 mmol) and carrying out the hydrogenation process for 36 h, the crude product was purified by chromatography (Al_2O_3, from 9:1 to 7:3 hexane/EtOAc) to give 7 mg (33%) of **10a** and 8 mg (38%) of **11a**, both as colorless oils.

(2*S*,3*R*,4a*S*,5*R*,8a*R*)-3-Acetoxy-5-butyl-2-methyldecahydroquinoline (**10a**). R_f=0.59 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −34.5 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.90 (m, 1H, H-1′), 0.90 (t, *J*=6.8 Hz, 3H, H-4′), 1.10 (d, *J*=6.4 Hz, Me), 1.12 (masked, H-8*ax*), 1.20 (m, 4H, H-6 and H-2′), 1.25 (m, 2H, H-3′), 1.30 (m, H-4*ax*), 1.40 (m, H-4a), 1.48 (m, 2H, H-7), 1.5 (m, H-8*eq*), 1.70 (m, 2H, H-5*ax*, H-1′), 2.04 (s, 3H, OAc), 2.27 (ddd, *J*=12.4, 3.6, 2.8 Hz, H-4*eq*), 2.76 (dq, *J*=10, 6.5 Hz, H-2*ax*), 2.97 (br s, H-8a), 4.49 (td, *J*=10.4, 4.4 Hz, H-3*ax*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{16}H_{30}NO_2$ (M^++1) 268.2198, found 268.2202.

(2*S*,3*R*,4a*R*,5*S*,8a*R*)-3-Acetoxy-5-butyl-2-methyldecahydroquinoline (**11a**). R_f=0.28 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −4.3 (*c* 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.88 (t, *J*=6.8 Hz, 3H, H-4′), 0.90 (masked, 1H, H-6*ax*), 0.94 (m, 2H, H-4*ax*, H-4a), 1.05 (masked, 2H, H-5 and H-1′), 1.07 (d, *J*=6.4 Hz, 3H, Me), 1.15 (m, 1H, H-8*ax*), 1.25 (m, 4H, H-2′, H-3′), 1.30 (m, 1H, H-7*ax*), 1.45 (m, 1H, H-1′), 1.75 (m, 3H, H-6, H-7, H-8), 2.05 (s, 3H, OAc), 2.20 (ddd, *J*=11, 9, 3 Hz, H-8a), 2.29 (dm, *J*=12 Hz, H-4*eq*), 2.70 (dq, *J*=10.4, 6.4 Hz, H-2*ax*), 4.41 (td, *J*=10.4, 4.8 Hz, H-3*ax*); ^{13}C NMR see Table 1.

HRFABMS calcd for $C_{16}H_{30}NO_2$ ($M^+ +1$) 268.2198, found 268.2203.

3.1.12. Aminocyclization of 9b. Operating as in the cyclization of **9a**, from enone **11** (22 mg, 0.05 mmol) was obtained **11b** as an oil (6 mg, 52%) after chromatography (Al_2O_3, from 9:1 to 7:3 hexane/EtOAc).[31]

(2*S*,3*S*,4a*R*,5*S*,8a*R*)-3-Acetoxy-5-butyl-2-methyldecahydroquinoline (**11b**). R_f=0.13 (Al_2O_3, 8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.87 (t, J=6.8 Hz, 3H, H′-4), 0.98 (m, 4H, H-4a, H-5, H-6, H-1′), 1.06 (d, J=6.8 Hz, 3H, Me), 1.15 (m, 2H, H-4*ax*, H-8*ax*), 1.25 (m, 4H, H-2′ and H-3′), 1.30 (m, H-7*ax*), 1.45 (m, 1H, H-1′), 1.77 (m, 3H, H-8*eq*, H-7*eq*, H-6*eq*), 2.11 (s, 3H, OAc), 2.20 (dt, J=10, 3.2 Hz, H-4*eq*), 2.27 (td, J=10, 3 Hz, H-8a), 2.90 (qd, J=6.4, 1.6 Hz, H-2*ax*), 4.91 (ddd, J=3.2, 3.2, 1.6 Hz, H-3*eq*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{16}H_{30}NO_2$ ($M^+ +1$) 268.2198, found 268.2194.

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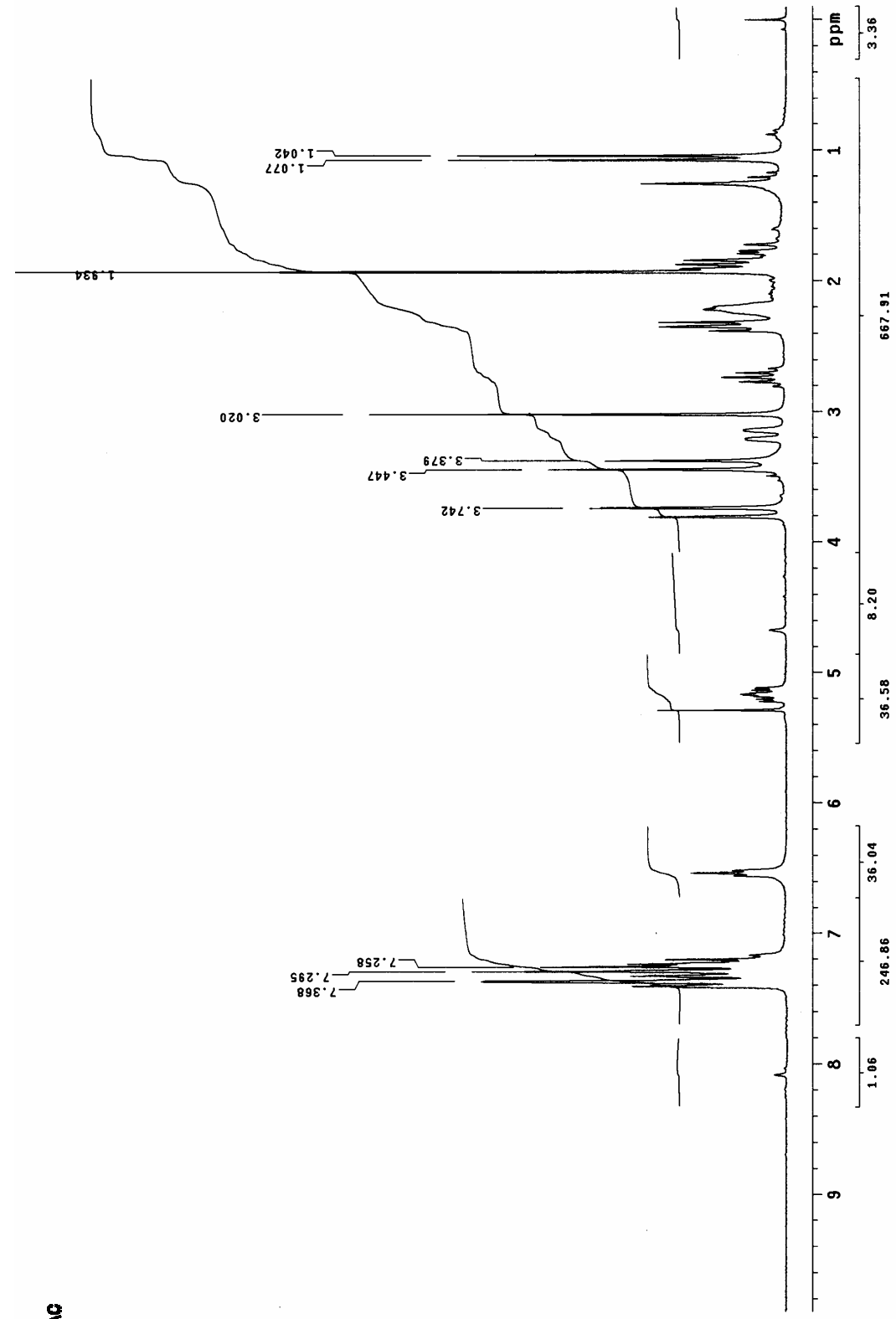
31. Minor signals (approximately in a 1:3 ratio with respect to the major compound isolated **11b**) in the NMR of the crude reaction mixture at δ 4.76 (ddd, J=3.2, 3.2, 1.6 Hz, H-3*eq*), 2.96 (m, H-8a), 2.66 (qd, J=6.4, 3.2 Hz, H-2*ax*), and 2.16 (dm, J=12 Hz, H-4*eq*) were observed. They could be attributed to the isomer **10b**, which cannot be isolated in pure form. The isolated decahydroquinoline **11b** remains partially contaminated by this compound even after repeating the chromatography.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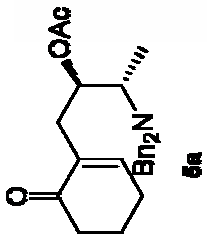
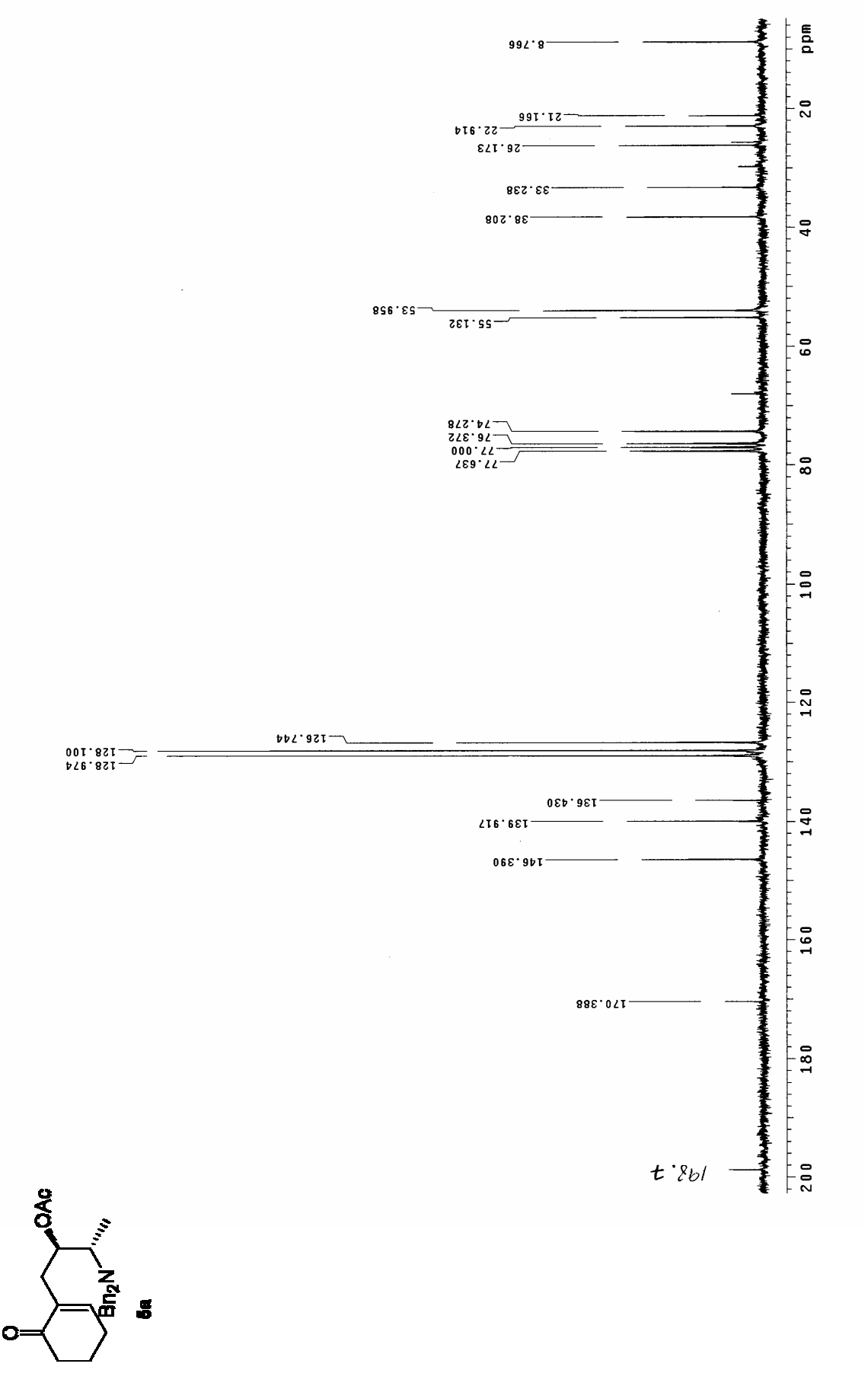
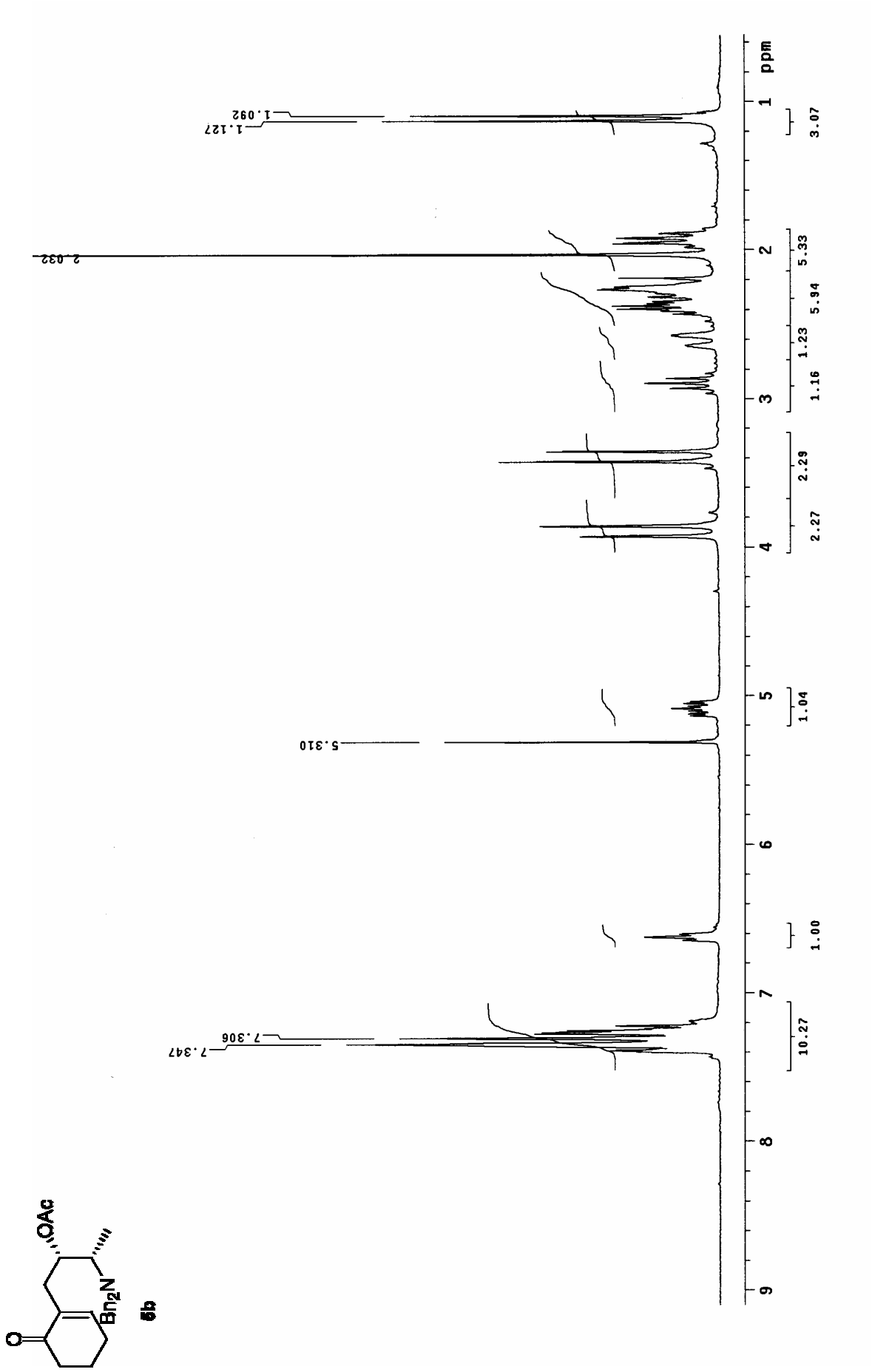
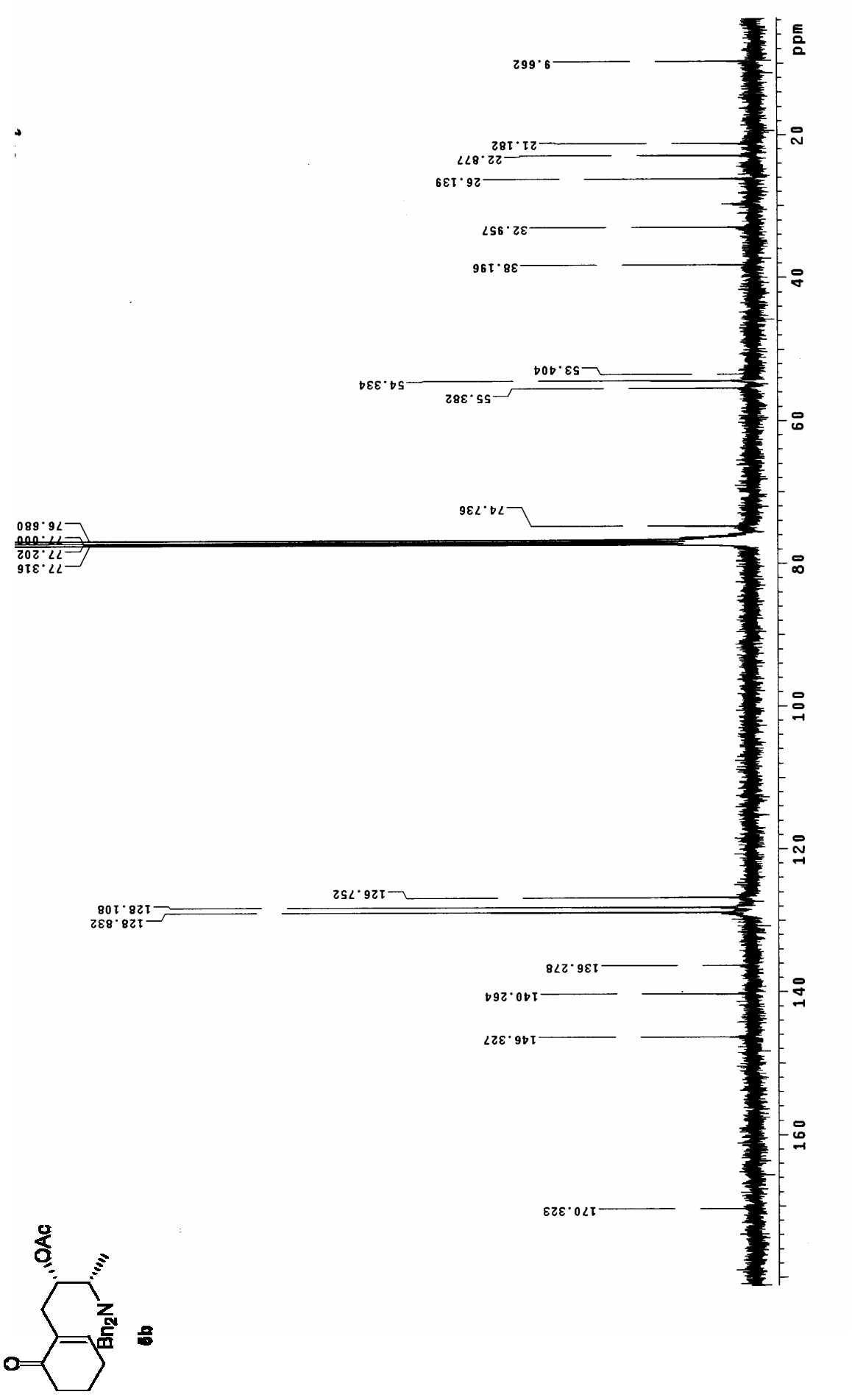
246.86
1.06


OAc
Bn2N
O

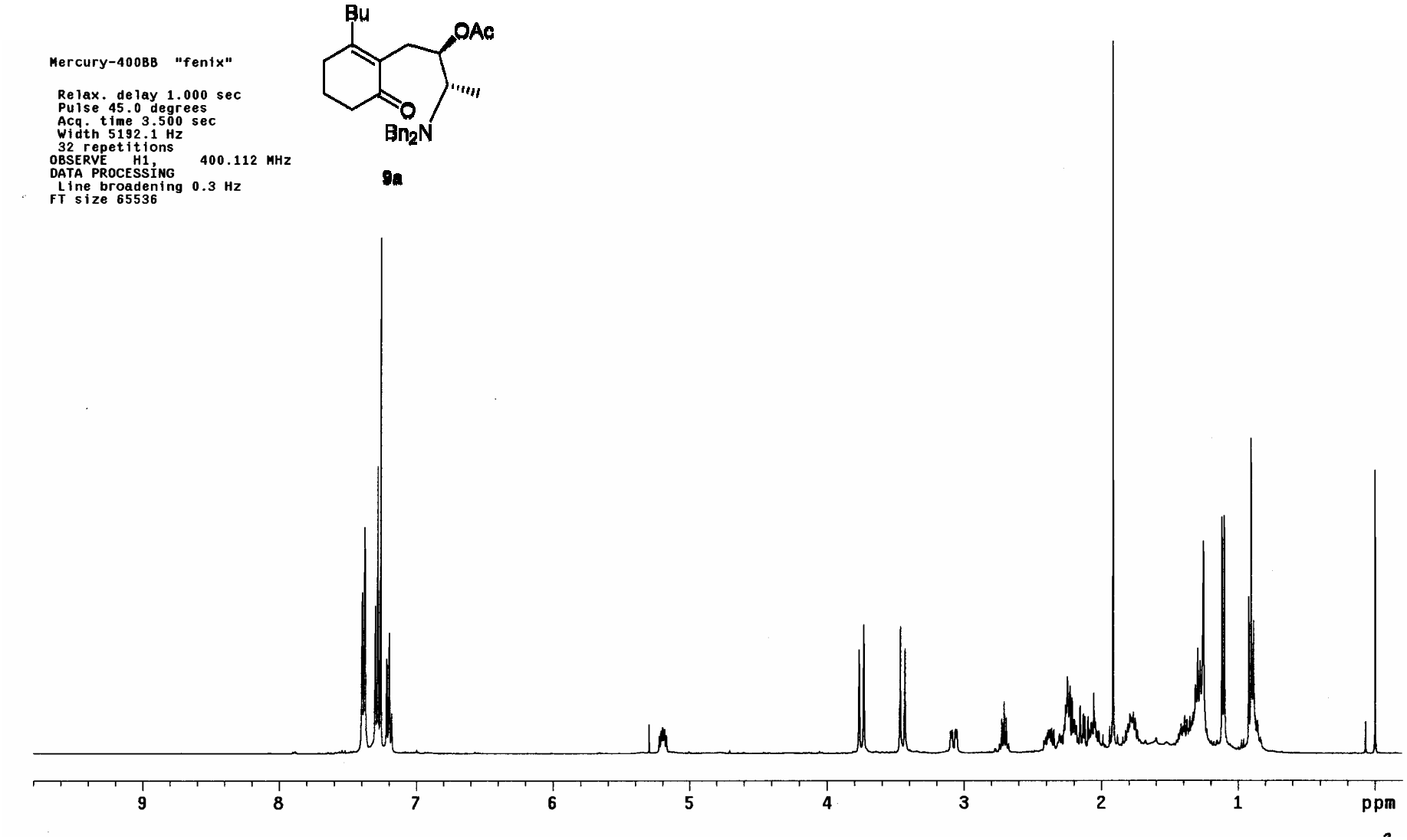
6a

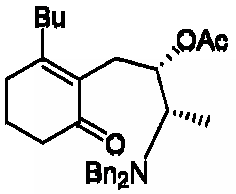

OAc
Bn2N
O
5a
170.388
146.390
139.917
136.430
128.974
128.100
126.744
77.637
77.000
76.372
74.278
53.958
55.132
38.208
33.238
26.173
22.914
21.166
8.766
ppm


OAc
Bn2N
O
6b
7.347
7.306
5.310
2.032
1.127
1.092
ppm
1
2
3
4
5
6
7
8
9
3.07
5.33
5.94
1.23
1.16
2.29
2.27
1.04
1.00
10.27

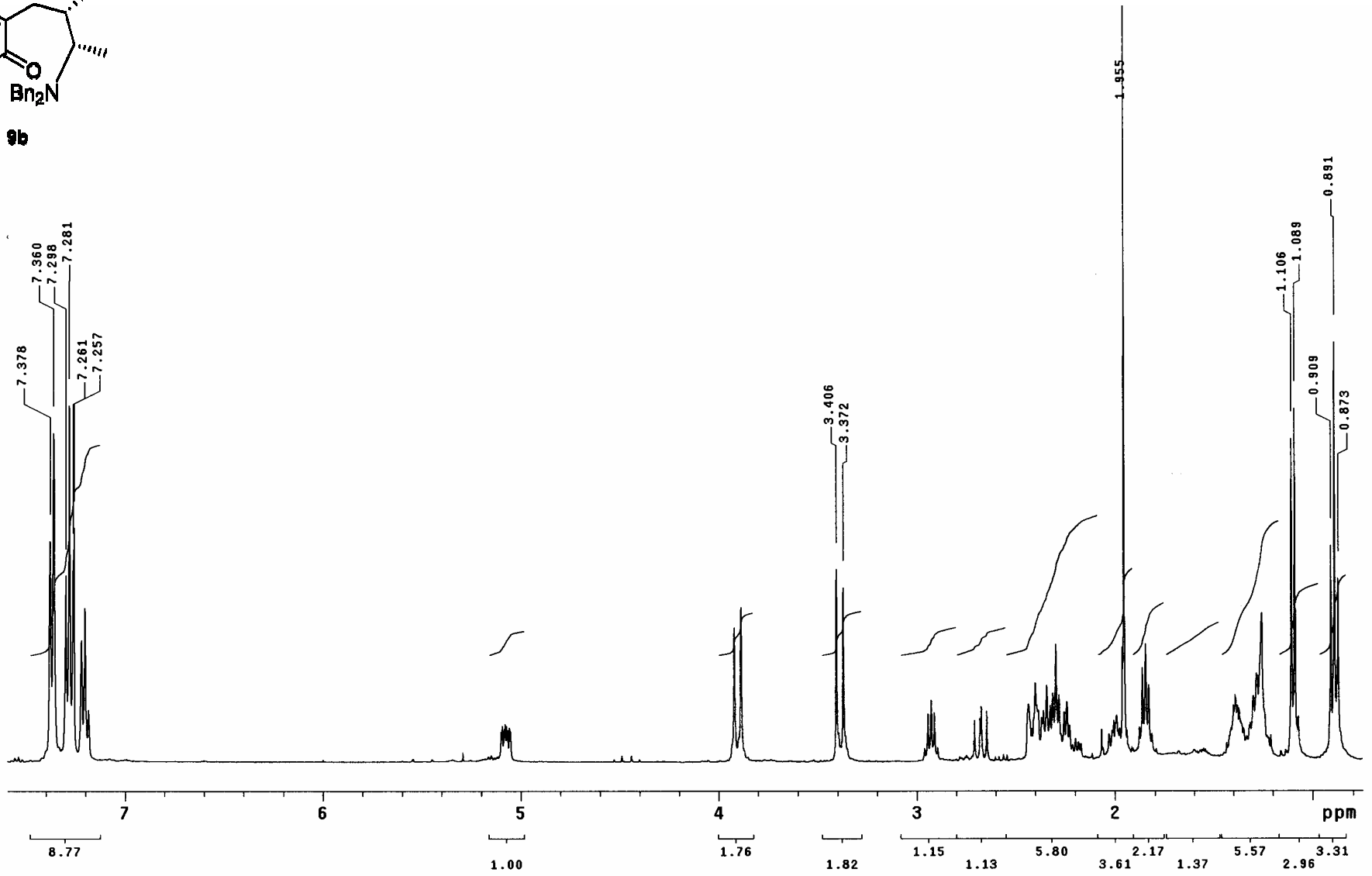

9.662
21.182
22.877
26.139
32.957
38.196
53.404
54.334
55.382
74.736
76.680
77.000
77.202
77.316
126.752
128.108
128.832
136.278
140.264
146.327
170.323
ppm
20
40
60
80
100
120
140
160
OAc
Bn2N
O

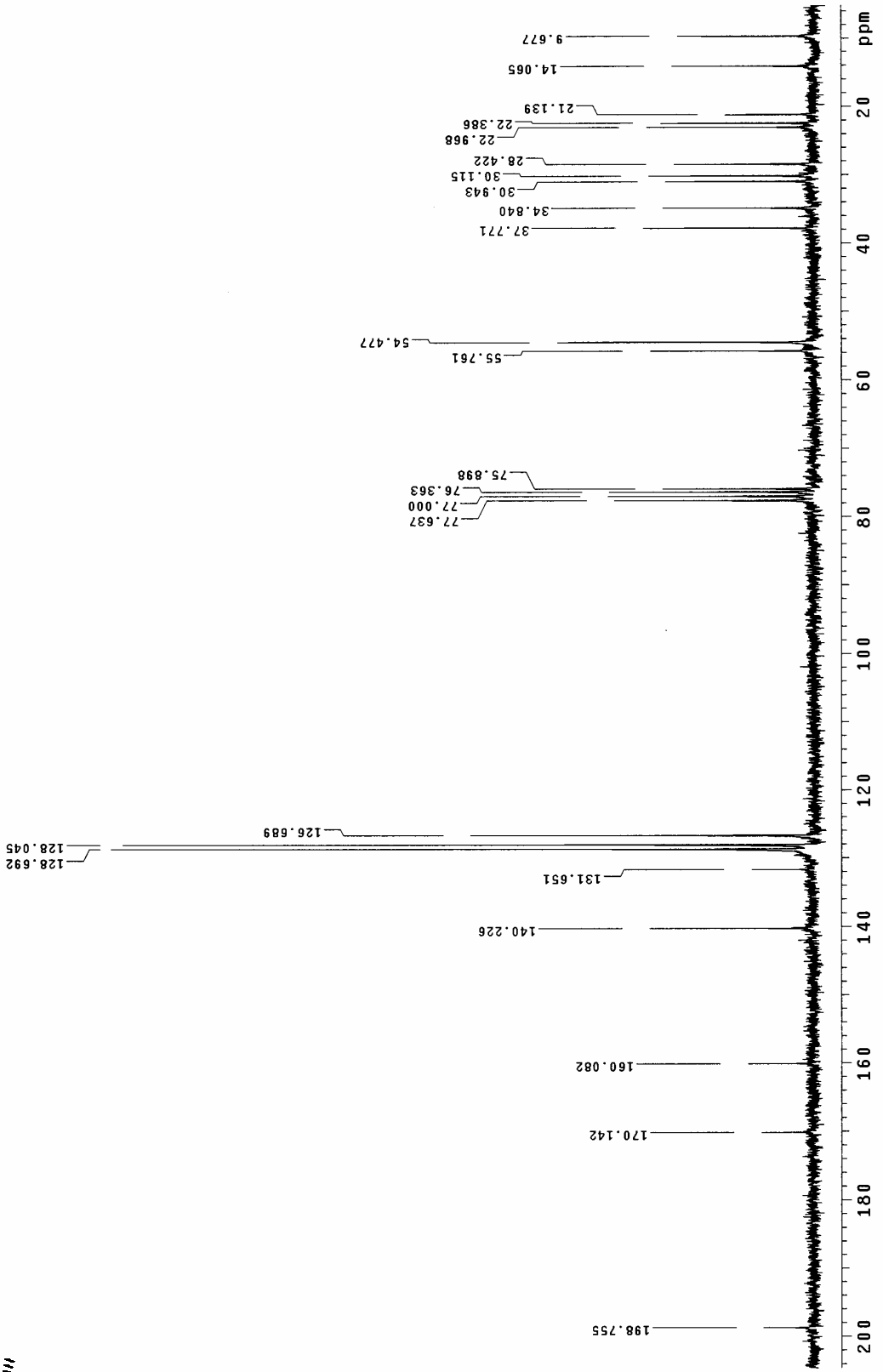
4b

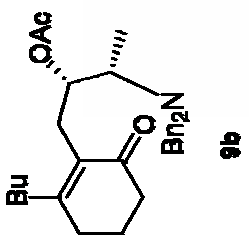

Mercury-400BB "fenix"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.500 sec
Width 5192.1 Hz
32 repetitions
OBSERVE H1, 400.112 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Bu
OAc
O
Bn2N
9a
9
8
7
6
5
4
3
2
1
ppm


Bu
OAc
O
Bn2N

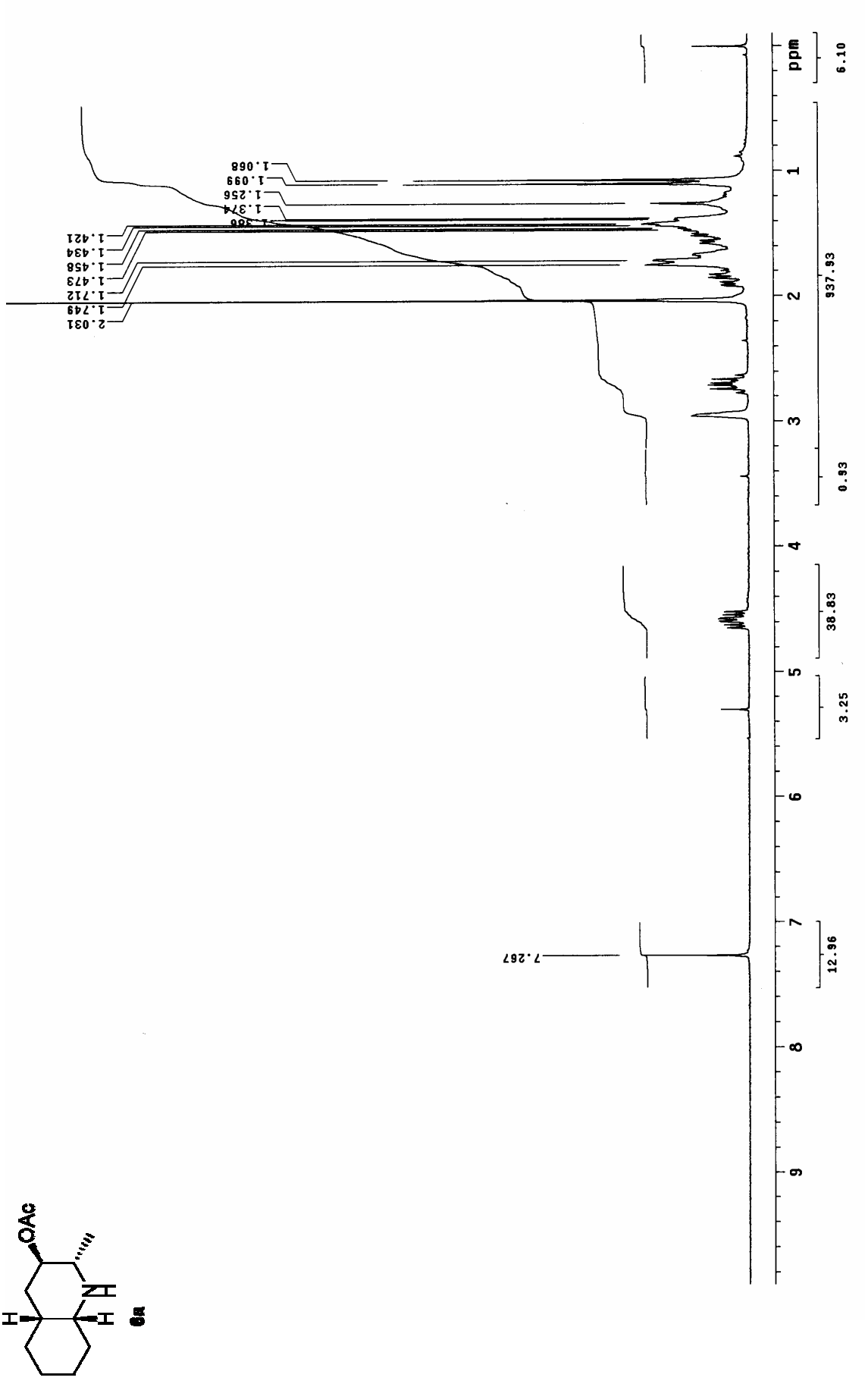
9b

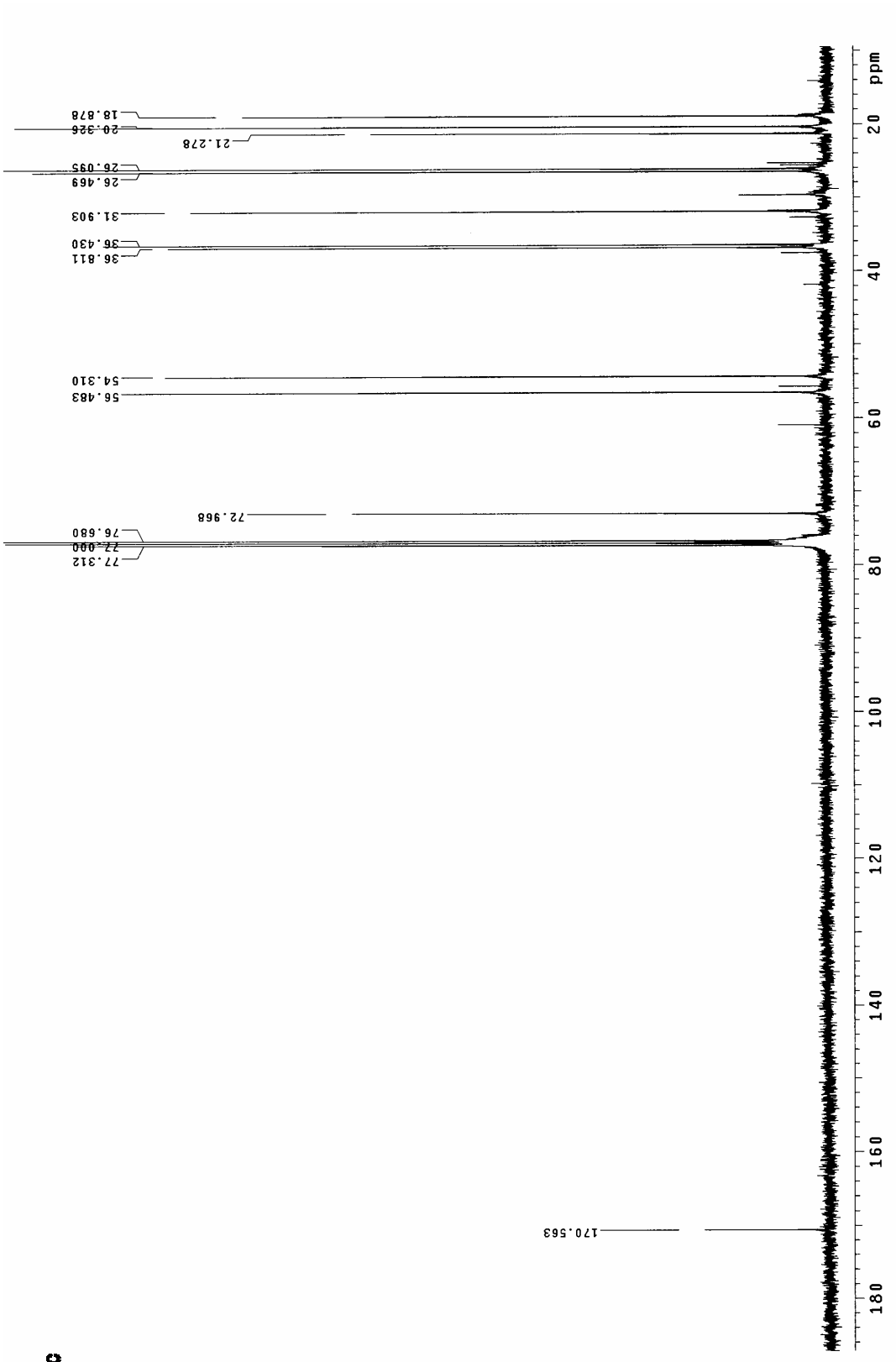

7.378
7.360
7.298
7.281
7.261
7.257
3.406
3.372
1.955
1.106
1.089
0.909
0.891
0.873
7
6
5
4
3
2
ppm
8.77
1.00
1.76
1.82
1.15
1.13
5.80
3.61
2.17
1.37
5.57
2.96
3.31

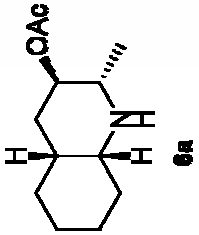

198.755
170.142
160.082
140.226
131.651
128.692
128.045
126.689
77.637
77.000
76.363
75.898
55.761
54.477
37.771
34.840
30.943
30.115
28.422
22.968
22.386
21.139
14.065
9.677
ppm
20
40
60
80
100
120
140
160
180
200

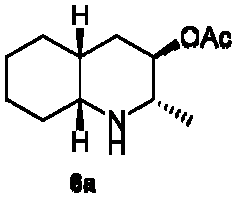

OAc
Bn2N
O
Bu

9b

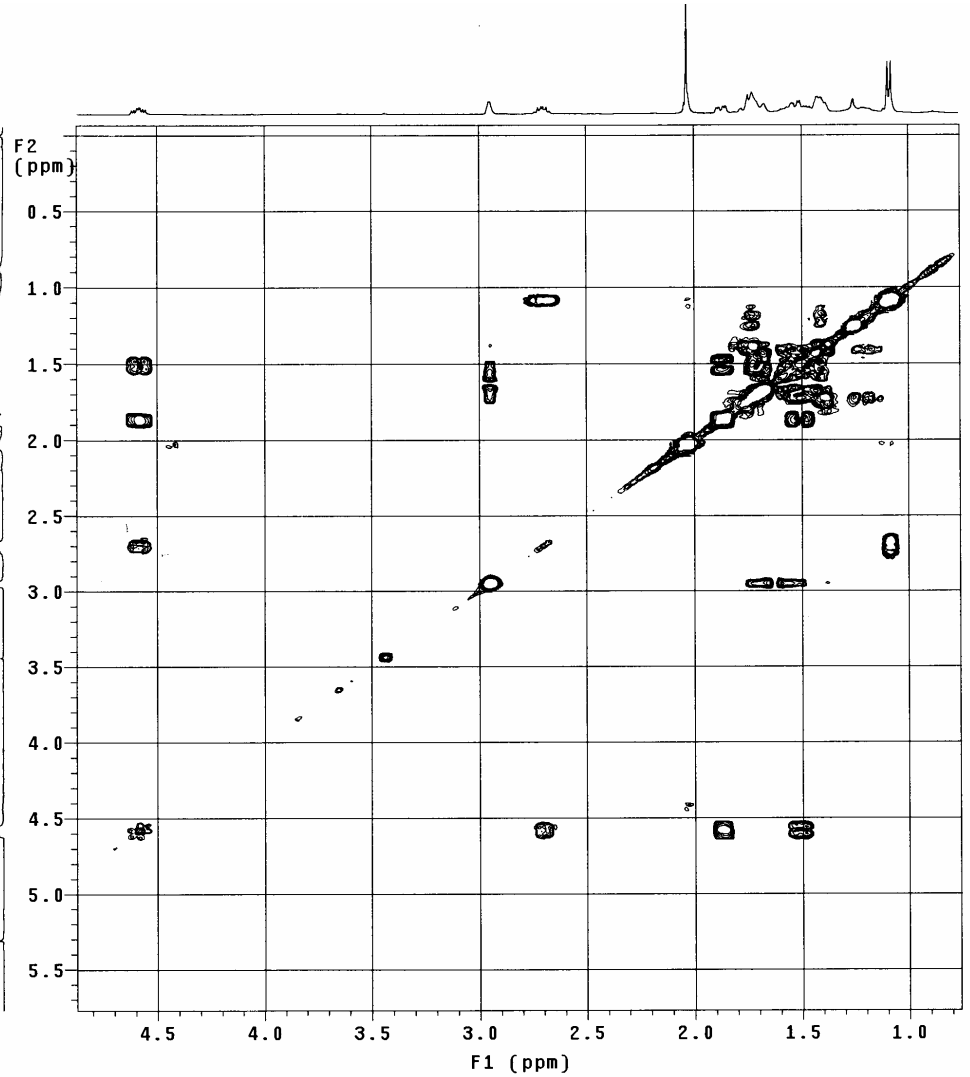

OAc
H
H
H
6a
ppm
1
2
3
4
5
6
7
8
9
6.10
937.93
0.93
38.83
3.25
12.96
7.267
2.031
1.749
1.712
1.473
1.458
1.434
1.421
1.360
1.374
1.256
1.099
1.068

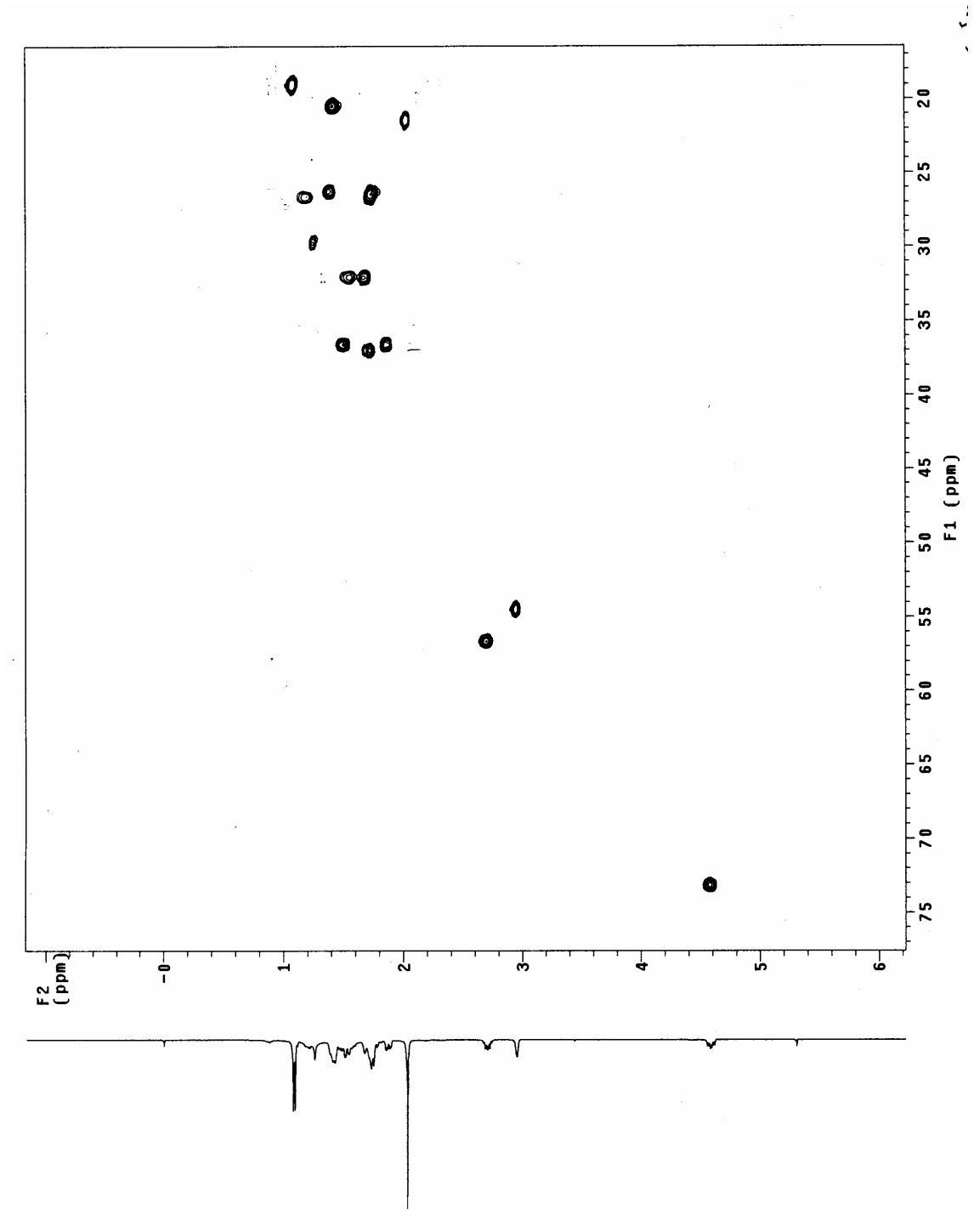

170.563
72.968
77.312
77.000
76.680
56.483
54.310
36.811
36.430
31.903
26.469
26.095
21.278
20.326
18.878
ppm
20
40
60
80
100
120
140
160
180

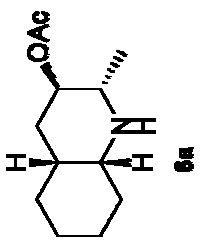

OAc
H
H
N
6a

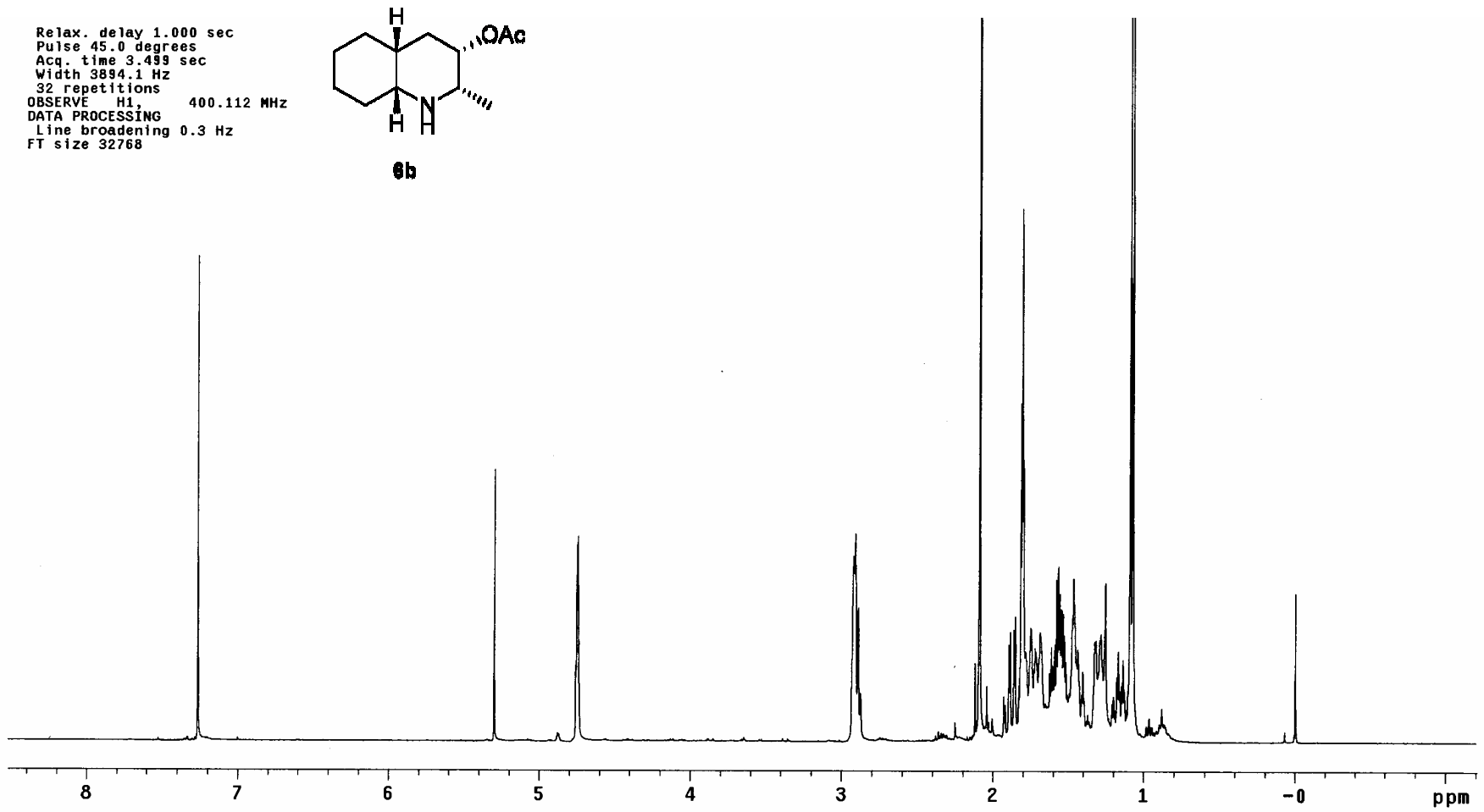


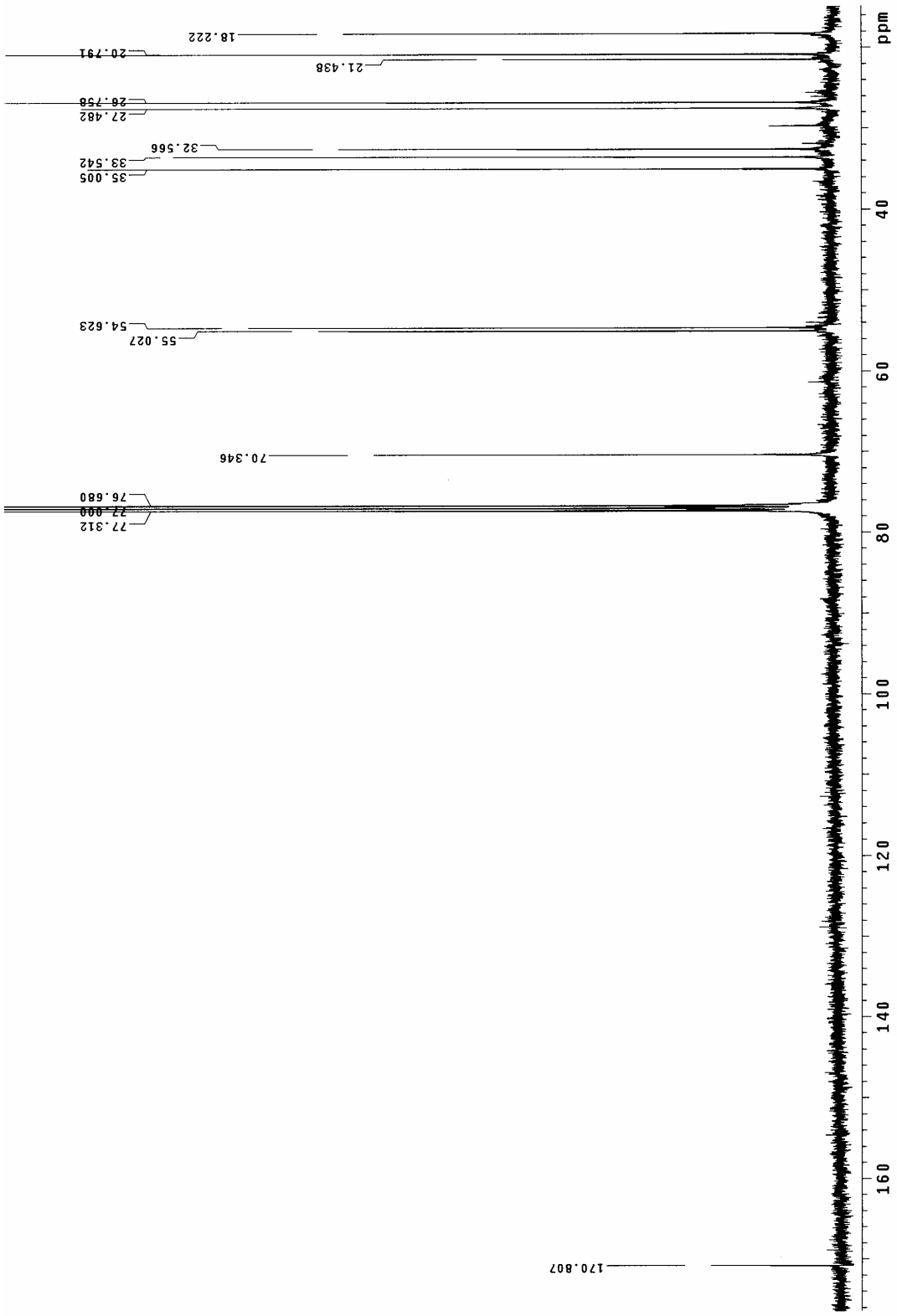

```
H1 / gCOSY / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-1388
Usuari: san / Mostra: mmc365p
Nom: MARISA MENA CERVIGON
Data:25/01/05 / Sist automatic

exp2  gCOSY

      SAMPLE              FLAGS
date   Jan 25 2005  hs               nn
solvent      cdcl3  sspul             n
sample auto_Custom~ hsglvl         1002
       Q_25Jan2005        SPECIAL
   ACQUISITION       temp           25.0
sw          3876.0   gain             10
at           0.150   spin              0
np            1162     F2 PROCESSING
fb        not used   sb            -0.075
ss              16   sbs        not used
d1           1.000   fn              2048
nt               4     F1 PROCESSING
  2D ACQUISITION     sb1           -0.066
sw1         3876.0   sbs1       not used
ni             256   proc1            lp
  PRESATURATION      fn1             2048
satmode          n        DISPLAY
satfrq           0   sp             -25.3
satdly           0   wp            2333.9
satpwr           0   sp1            304.3
   TRANSMITTER       wp1           1644.4
tn              H1   rf1            483.8
sfrq       400.113   rfp                0
tof         -568.6   rf11           483.8
tpwr            61   rfp1               0
pw           9.800          PLOT
     GRADIENTS       wc             153.0
gzlvl1         1002  sc               6.2
gt1       0.001000   wc2            153.0
gstab     0.000500   sc2                0
    DECOUPLER        vs               363
dn              C13  th                 5
dm              nnn  al  cdc  av
```

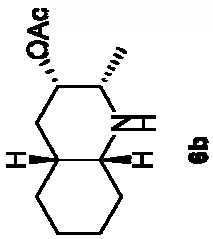



F2 (ppm)
F1 (ppm)

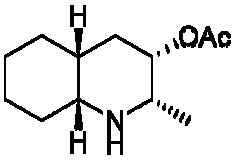

OAc
H
H
N
H


Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.499 sec
Width 3894.1 Hz
32 repetitions
OBSERVE H1, 400.112 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
H
OAc
N
H
H
9b
8
7
6
5
4
3
2
1
-0
ppm


18.222
20.791
21.438
26.758
27.482
32.566
33.542
35.005
54.623
55.027
70.346
76.680
77.000
77.312
170.807
ppm
40
60
80
100
120
140
160

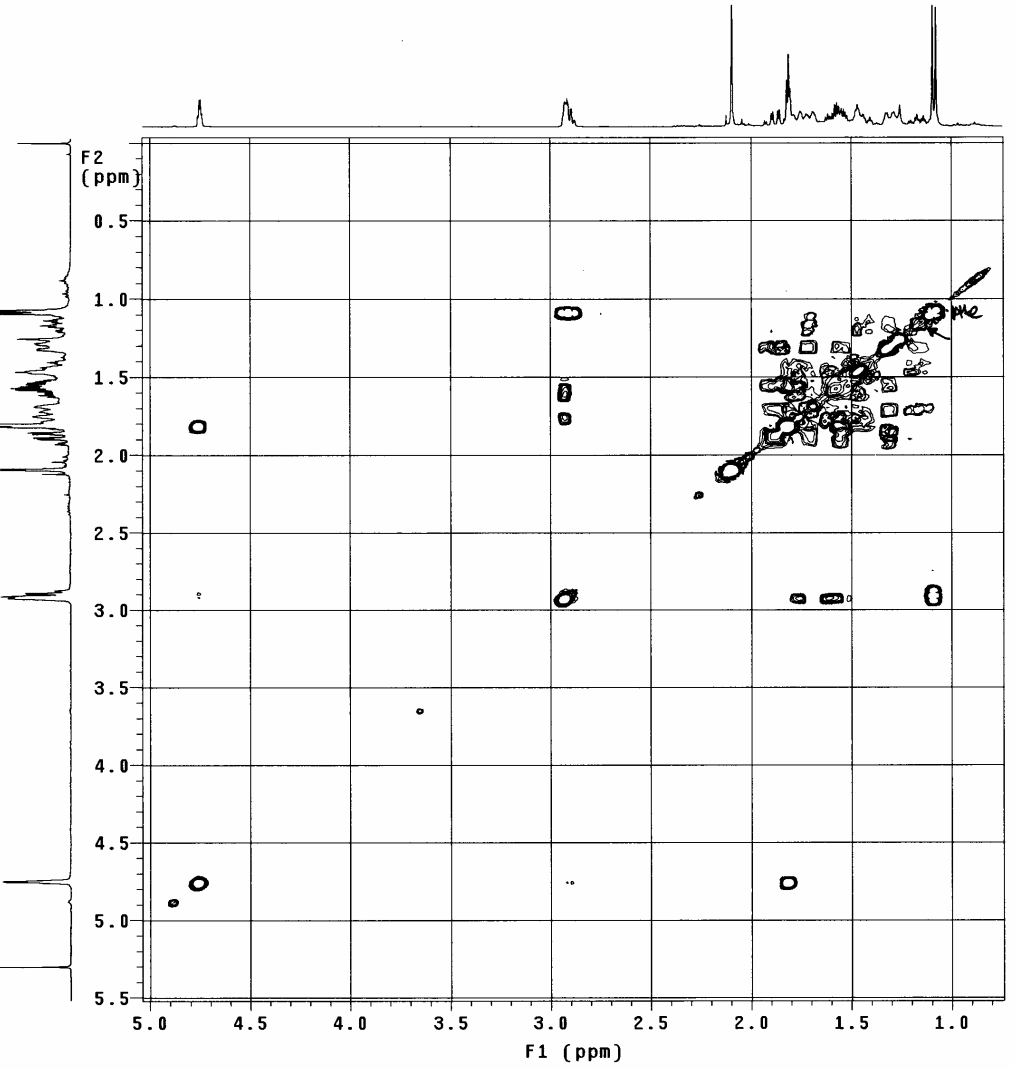

OAc
H
H
N

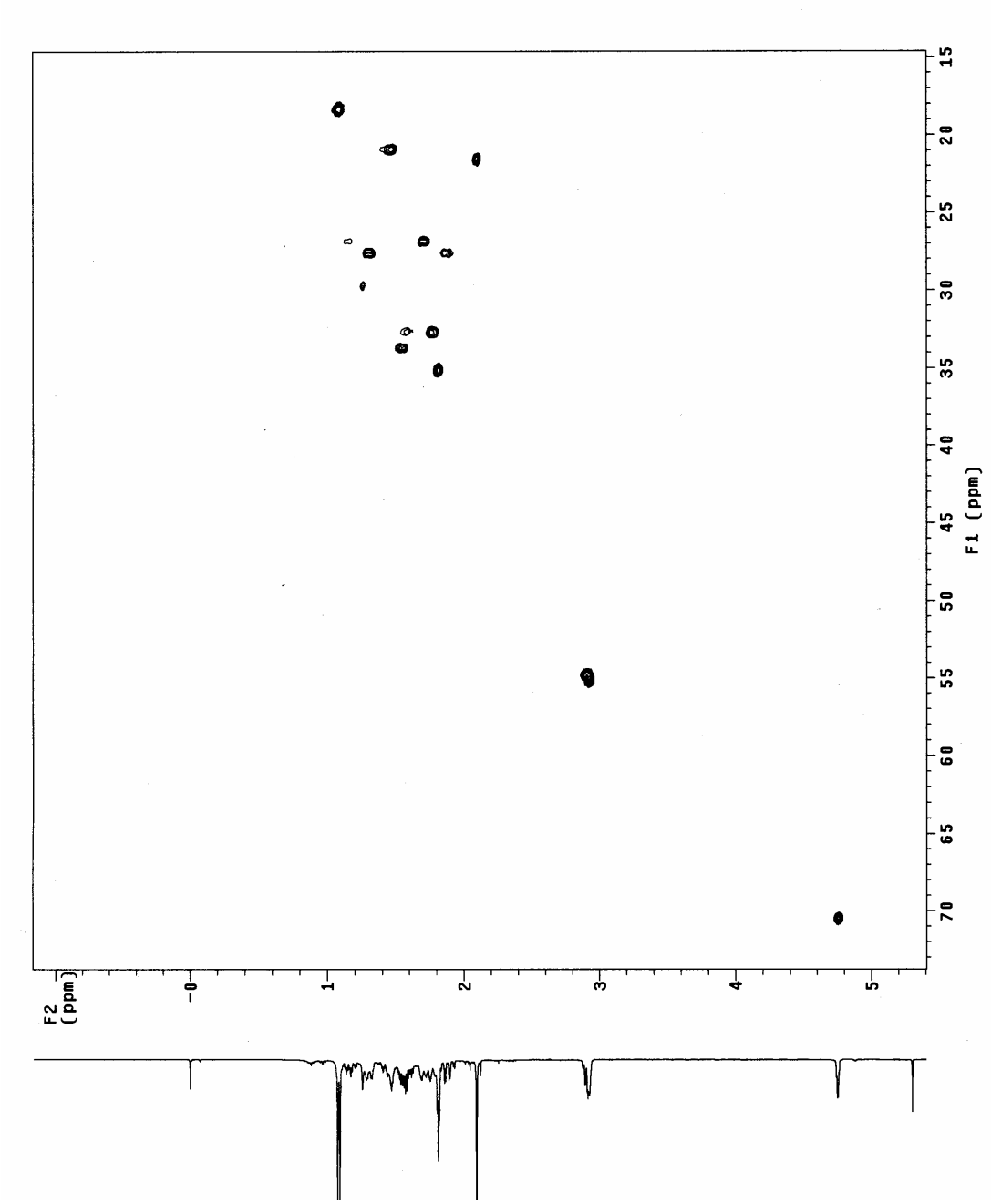
6b

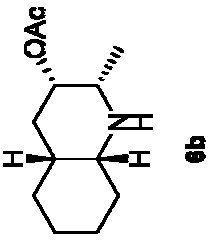


6b

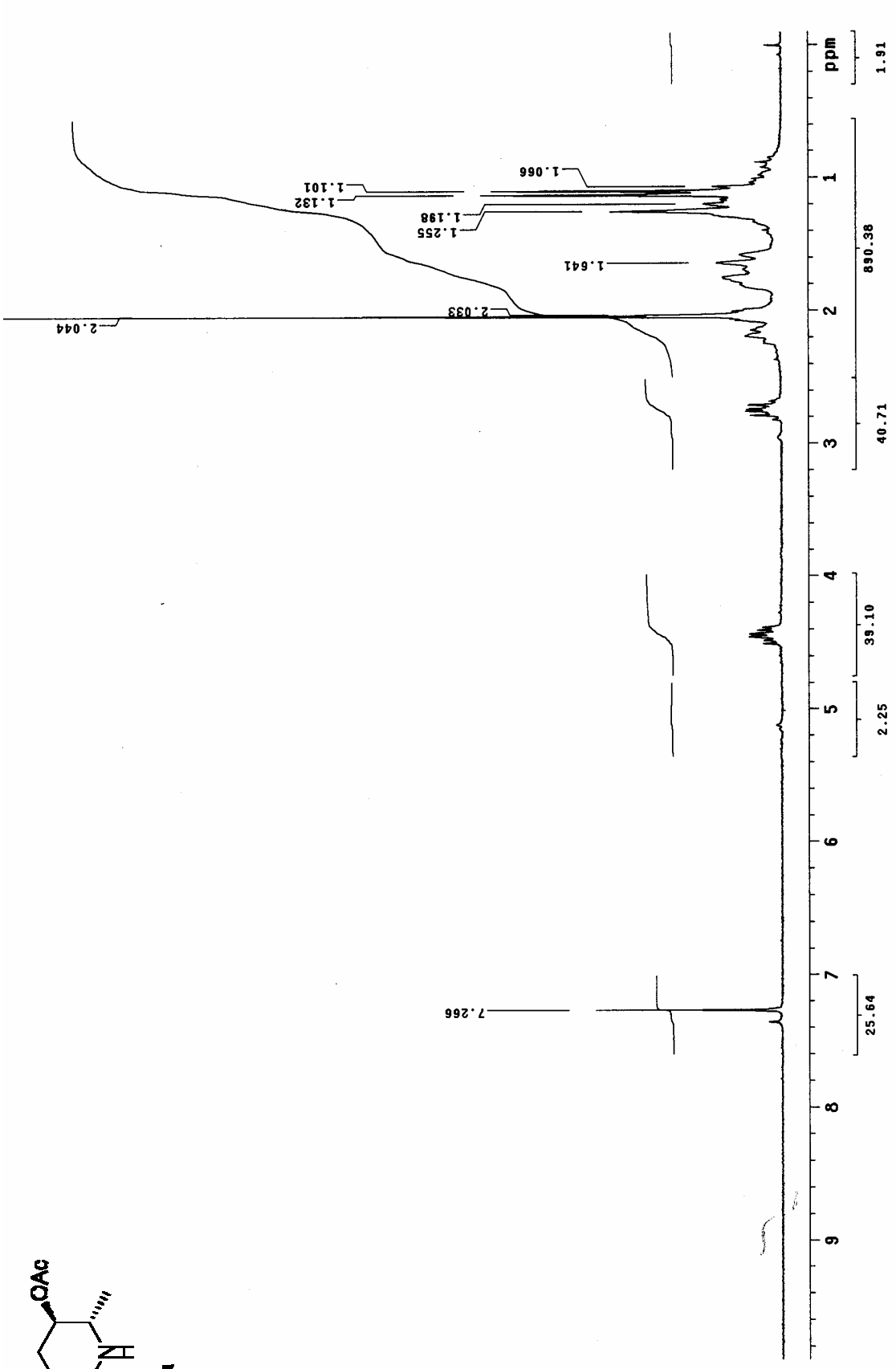
```
H1 / gCOSY / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-1744
Usuari: san / Mostra: ammc442
Nom: MARISA MENA CERVIGON
Data:05/02/05 / Sist automatic

exp4  gCOSY

      SAMPLE                FLAGS
date   Feb  5 2005   hs                 nn
solvent       cdcl3  sspul               n
sample auto_Custom~  hsglvl          1005
       Q_04Feb2005         SPECIAL
   ACQUISITION       temp            25.0
sw          3906.2   gain              16
at           0.150   spin               0
np            1172     F2 PROCESSING
fb        not used   sb             -0.075
ss              16   sbs         not used
d1           1.000   fn                2048
nt               4     F1 PROCESSING
  2D ACQUISITION     sb1            -0.066
sw1         3906.2   sbs1        not used
ni             256   proc1             lp
  PRESATURATION      fn1               2048
satmode          n          DISPLAY
satfrq           0   sp              -13.3
satdly           0   wp            2222.3
satpwr           0   sp1            296.0
   TRANSMITTER       wp1           1718.3
tn              H1   rf1            483.0
sfrq       400.113   rfp                0
tof        -557.9    rfl1           483.0
tpwr            61   rfp1               0
pw           9.300          PLOT
    GRADIENTS        wc             153.0
gzlvl1         1005   sc                 6.2
gt1       0.001000   wc2            153.0
gstab     0.000500   sc2                0
    DECOUPLER        vs                492
dn              C13   th                 7
dm              nnn   ai  cdc  av
```





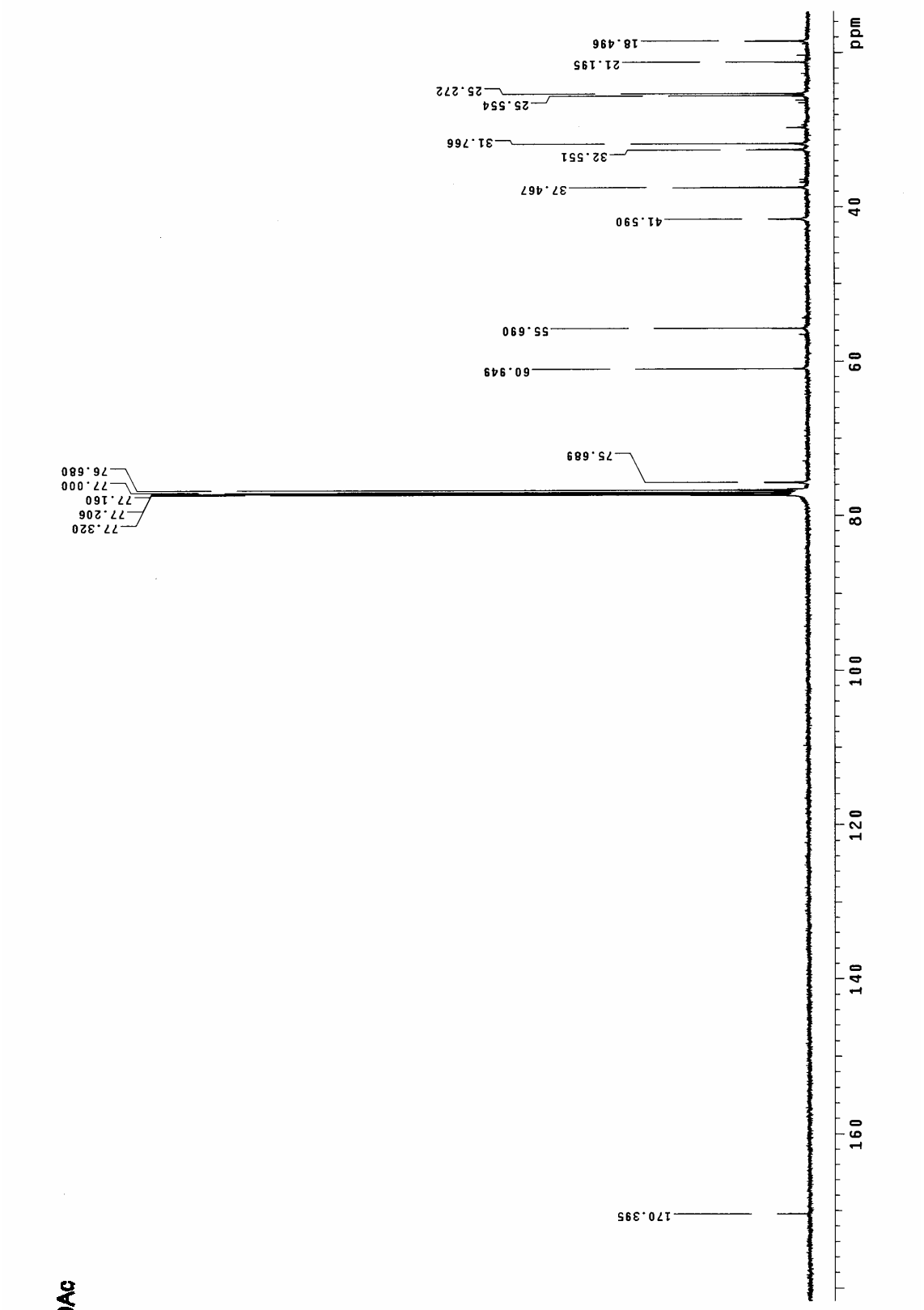


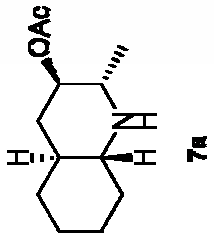
6b

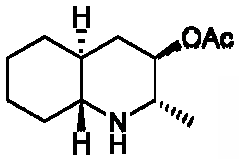

7.266
2.044
2.033
1.641
1.255
1.198
1.132
1.101
1.066
ppm
1.91
890.38
40.71
39.10
2.25
25.64

OAc
H
N
H

7a


170.395
77.320
77.206
77.160
77.000
76.680
75.689
60.949
55.690
41.590
37.467
32.551
31.766
25.554
25.272
21.195
18.496
ppm
160
140
120
100
80
60
40


OAc
H
H
H
7a

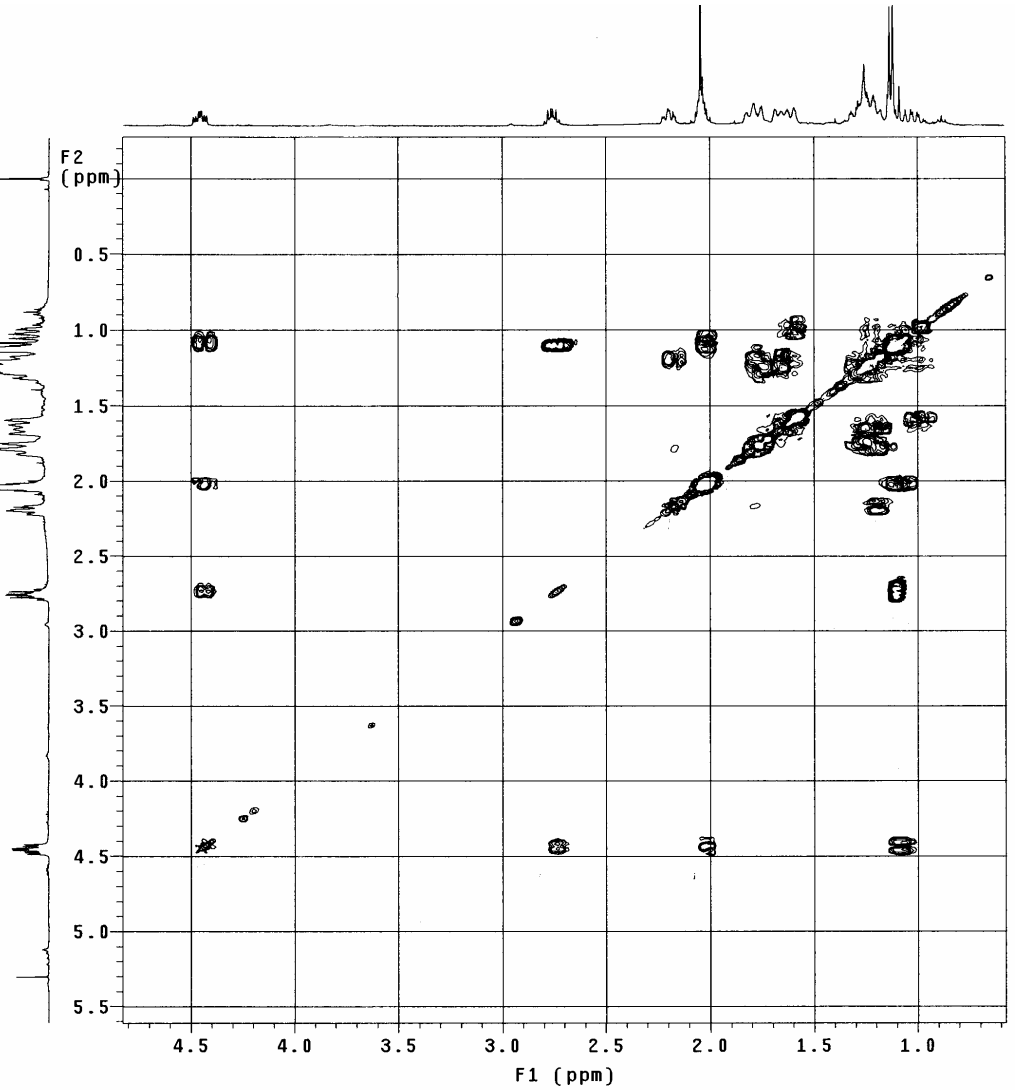


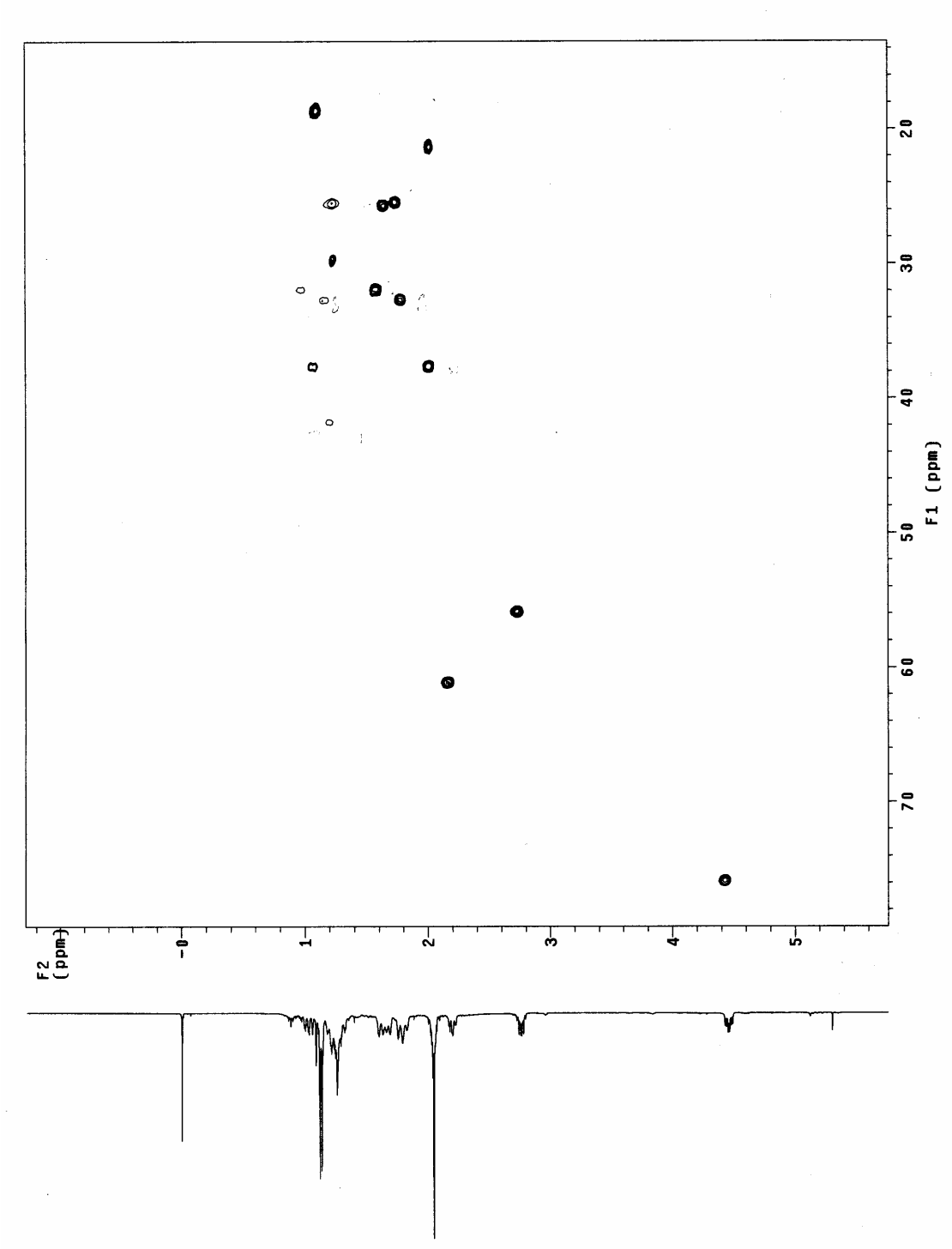
7a

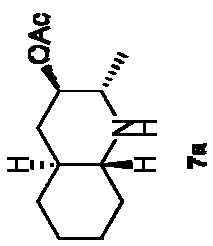
H1 / gCOSY / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-1991
Usuari: san / Mostra: bmmc449
Nom: M.MAR BORREGAN PRATS
Data:04/03/05 / Sist automatic

exp3 gCOSY

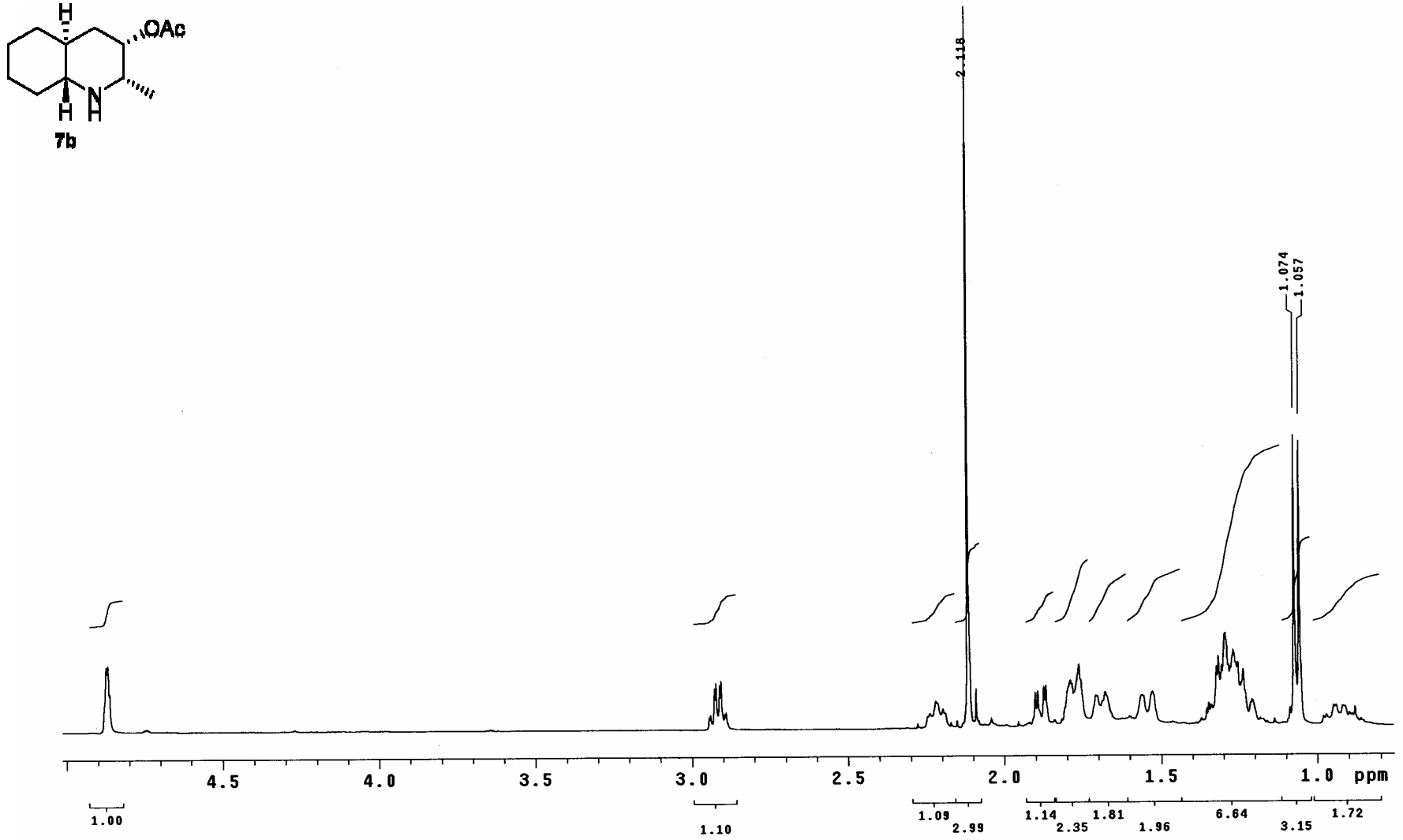
SAMPLE		FLAGS	
date	Mar 4 2005	hs	nn
solvent	cdcl3	sspul	n
sample	auto_Custom~ Q_03Mar2005	hsglvl	997
ACQUISITION		SPECIAL	
sw	3968.3	temp	25.0
at	0.150	gain	16
np	1190	spin	0
fb	not used	F2 PROCESSING	
ss	16	sb	-0.075
d1	1.000	sbs	not used
nt	8	fn	2048
2D ACQUISITION		F1 PROCESSING	
sw1	3968.3	sb1	-0.065
ni	256	sbs1	not used
PRESATURATION		proc1	qf
satmode	n	fn1	2048
satfrq	0	DISPLAY	
satdly	0	sp	-110.3
satpwr	0	wp	2354.6
TRANSMITTER		sp1	231.1
tn	H1	wp1	1699.0
sfrq	400.113	rfl	544.7
tof	-575.6	rfp	0
tpwr	62	rfl1	544.7
pw	8.700	rfp1	0
GRADIENTS		PLOT	
gzlvl1	997	wc	153.0
gt1	0.001000	sc	6.2
gstab	0.000500	wc2	153.0
DECOUPLER		sc2	0
dn	C13	vs	646
dm	nnn	th	6
		ai cdc av	

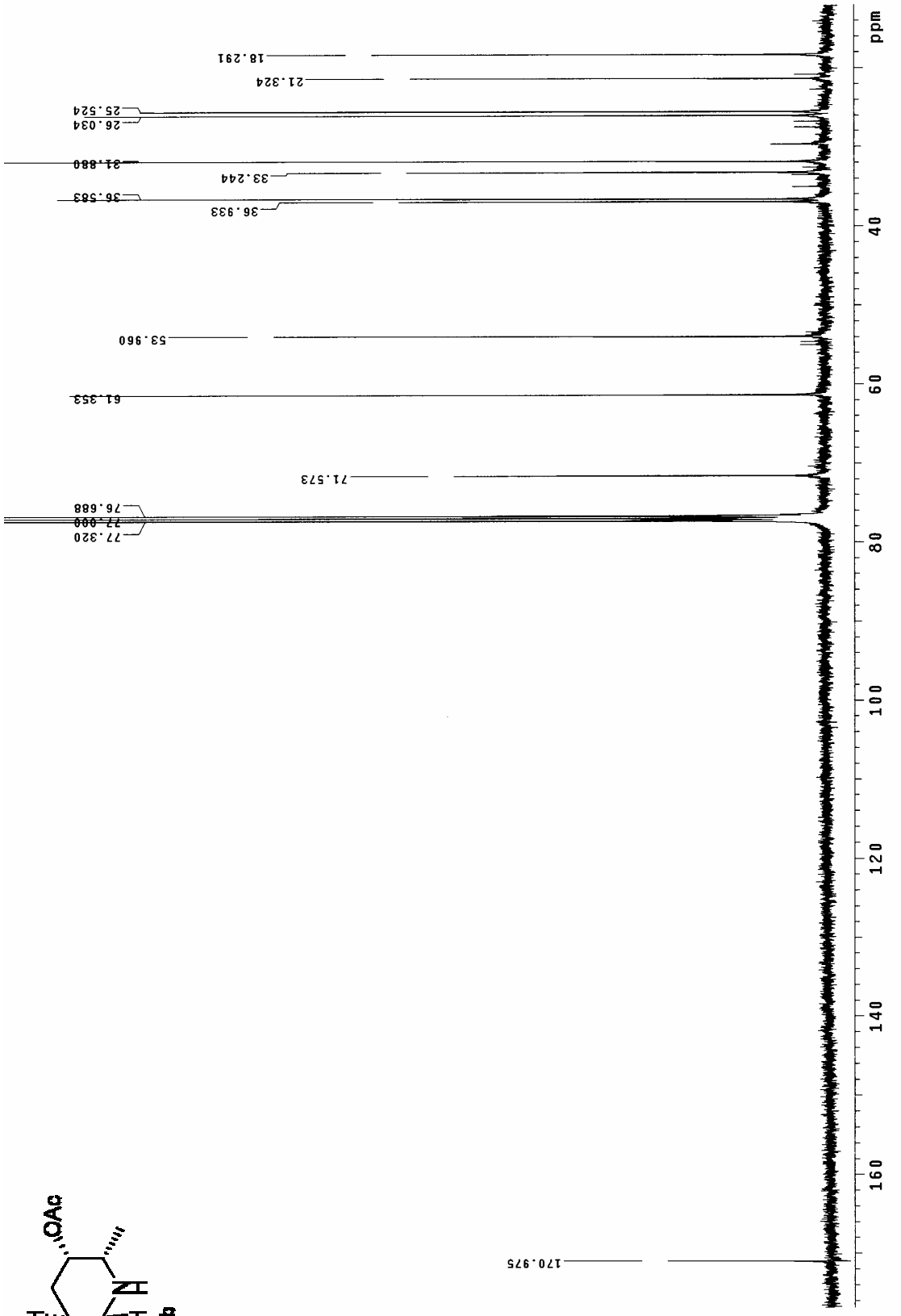


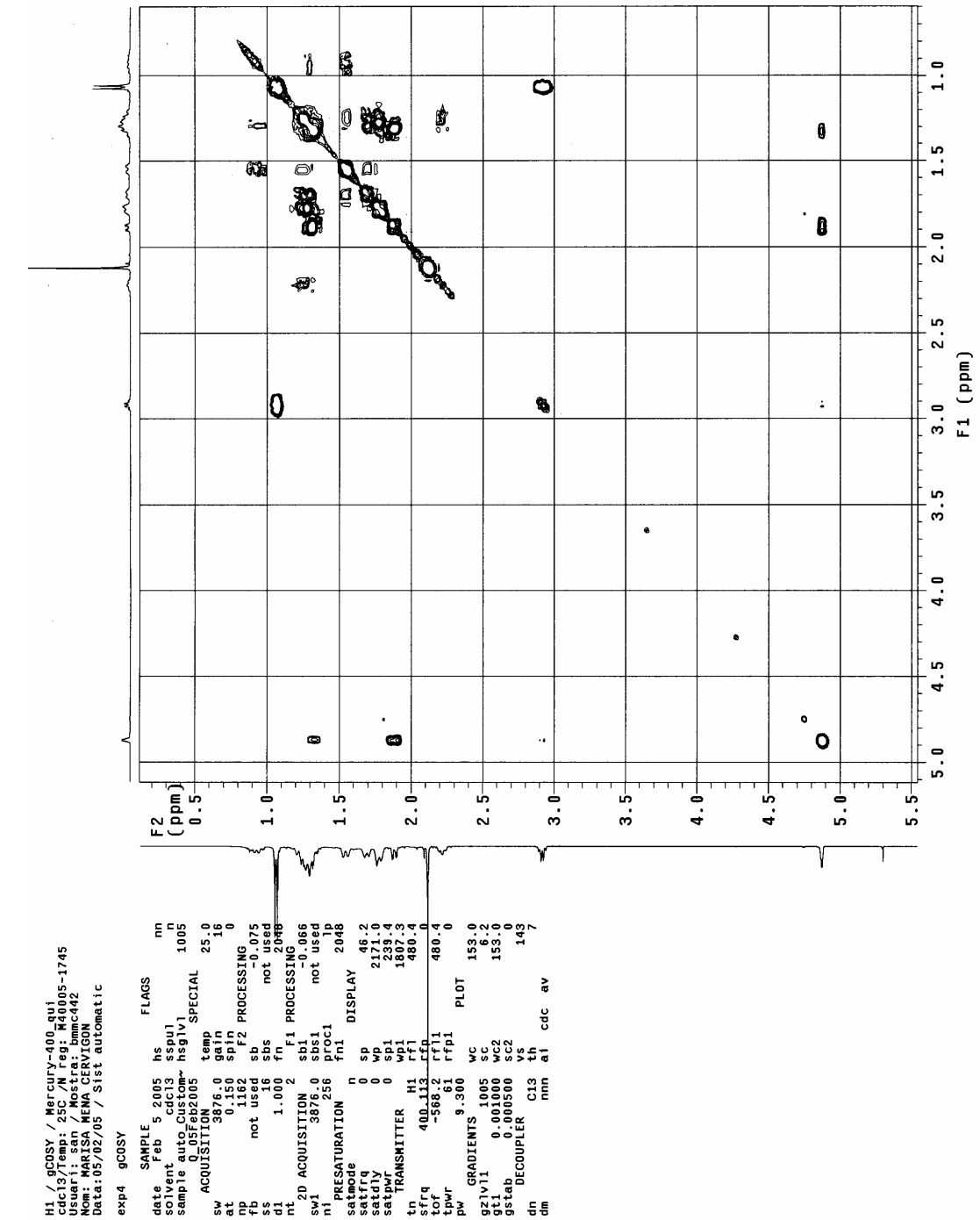




7a


OAc
H
N
H
7b
2.118
1.074
1.057
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.10
1.09
2.99
1.14
2.35
1.81
1.96
6.64
3.15
1.72


170.975
77.320
76.688
71.573
61.353
53.960
36.933
33.244
31.880
26.034
25.524
21.324
18.291
ppm
7b


H1 / gCOSY / Mercury-400_gui
cdcl3/Temp: 25C/N reg: M40105-1745
Usuari/Lsn: 2/Mostra: mmc442
Nom: MARISA MENA CERVIGON
Data:05/02/05 / Sist automatic
exp4 gCOSY
SAMPLE FLAGS
date Feb 5 2005 hs nn
solvent cdcl3 sspul n
sample auto_Custom~ hsglvl 1005
0_05Feb2005 SPECIAL
ACQUISITION temp 25.0
sw 3876.0 gain 16
at 0.150 spin 0
np 1162 F2 PROCESSING
fb not used sb -0.075
ss 16 sbs not used
d1 1.000 fn 2048
nt 2 F1 PROCESSING
2D ACQUISITION sb1 -0.066
sw1 3876.0 sbs1 not used
ni 256 proc1 lp
PRESATURATION fn1 2048
satmode n DISPLAY
satfrq 0 sp 46.2
satdly 0 wp 2171.0
satpwr 0 sp1 239.4
TRANSMITTER wp1 1807.3
tn H1 rf1 480.4
sfrq 400.113 rfp 0
tof -568.2 rf11 480.4
tpwr 61 rfp1 0
pw 9.300 PLOT
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gzlvl1 1005 sc 6.2
gt1 0.001000 wc2 153.0
gstab 0.000500 sc2 0
DECOUPLER vs 143
dn C13 th 7
dm nnn al cdc av
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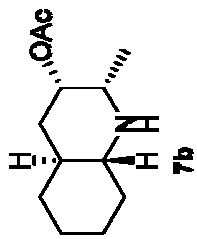
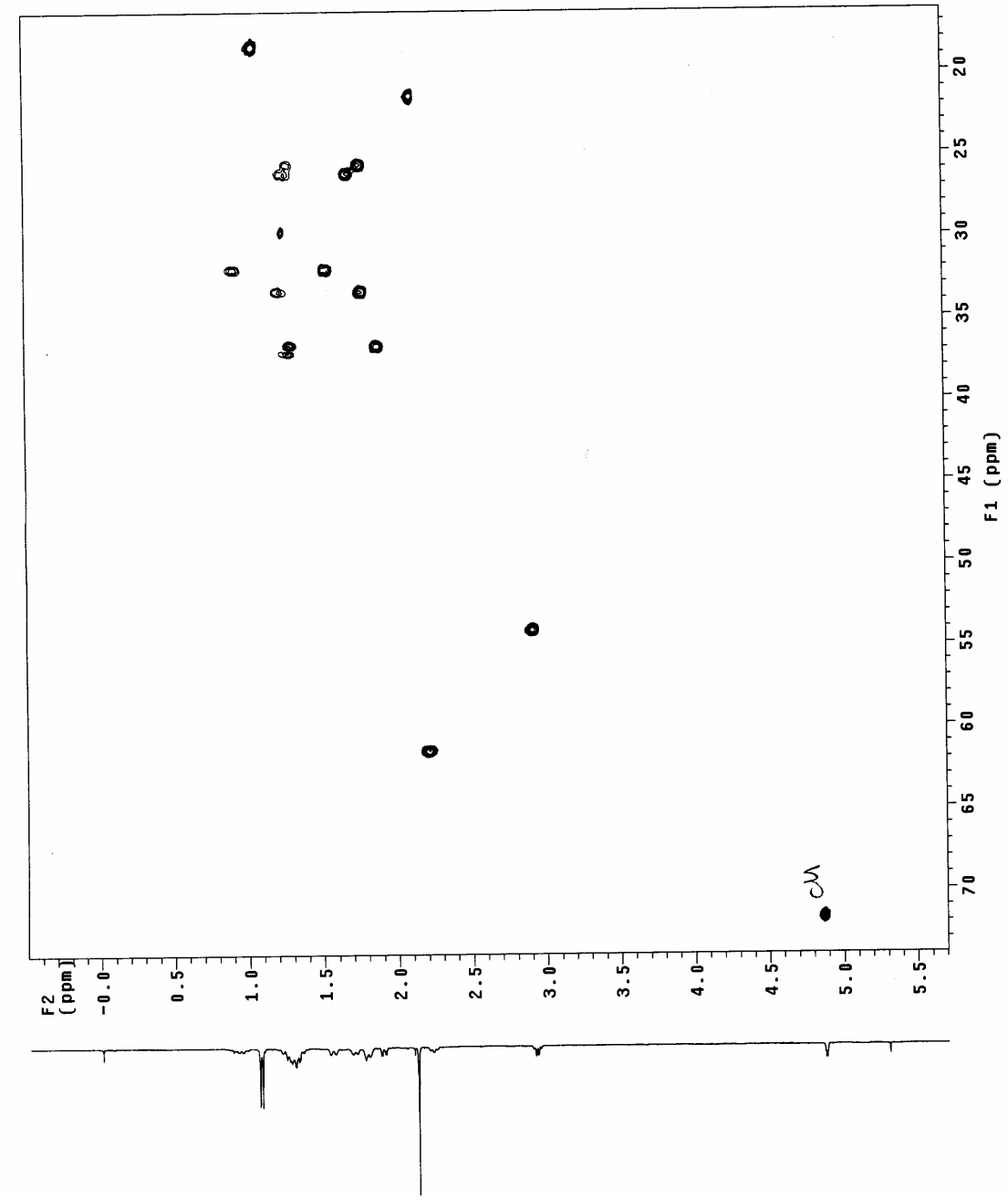
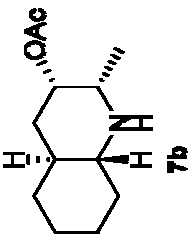
F1 (ppm)


OAc
H
H
N
H

7b





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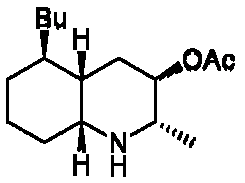
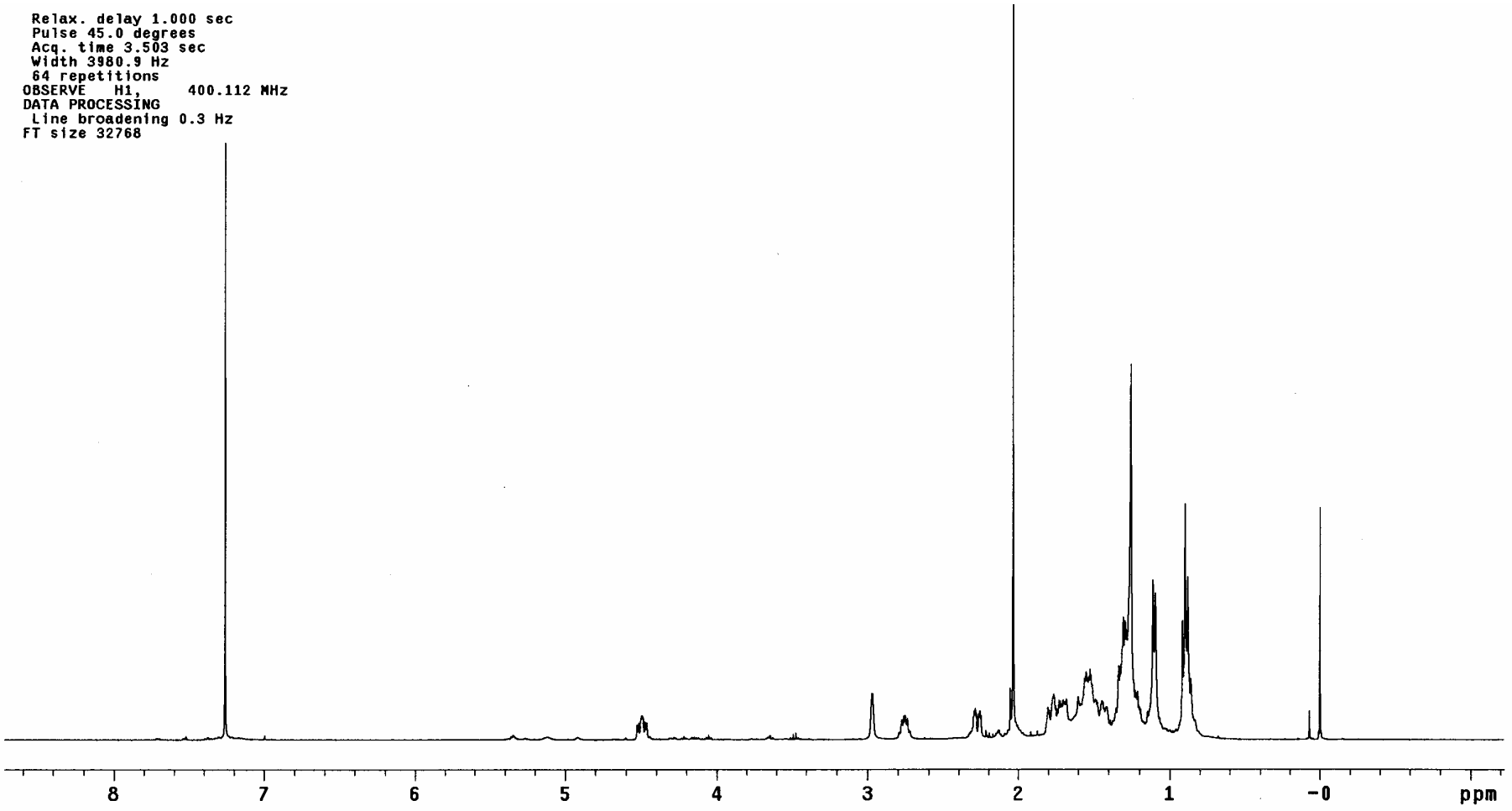

Bu
H
OAc
N
H
H

10a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Pulse 45.0 degrees
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DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
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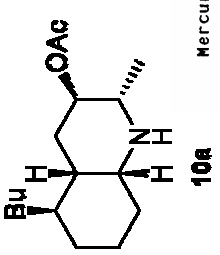
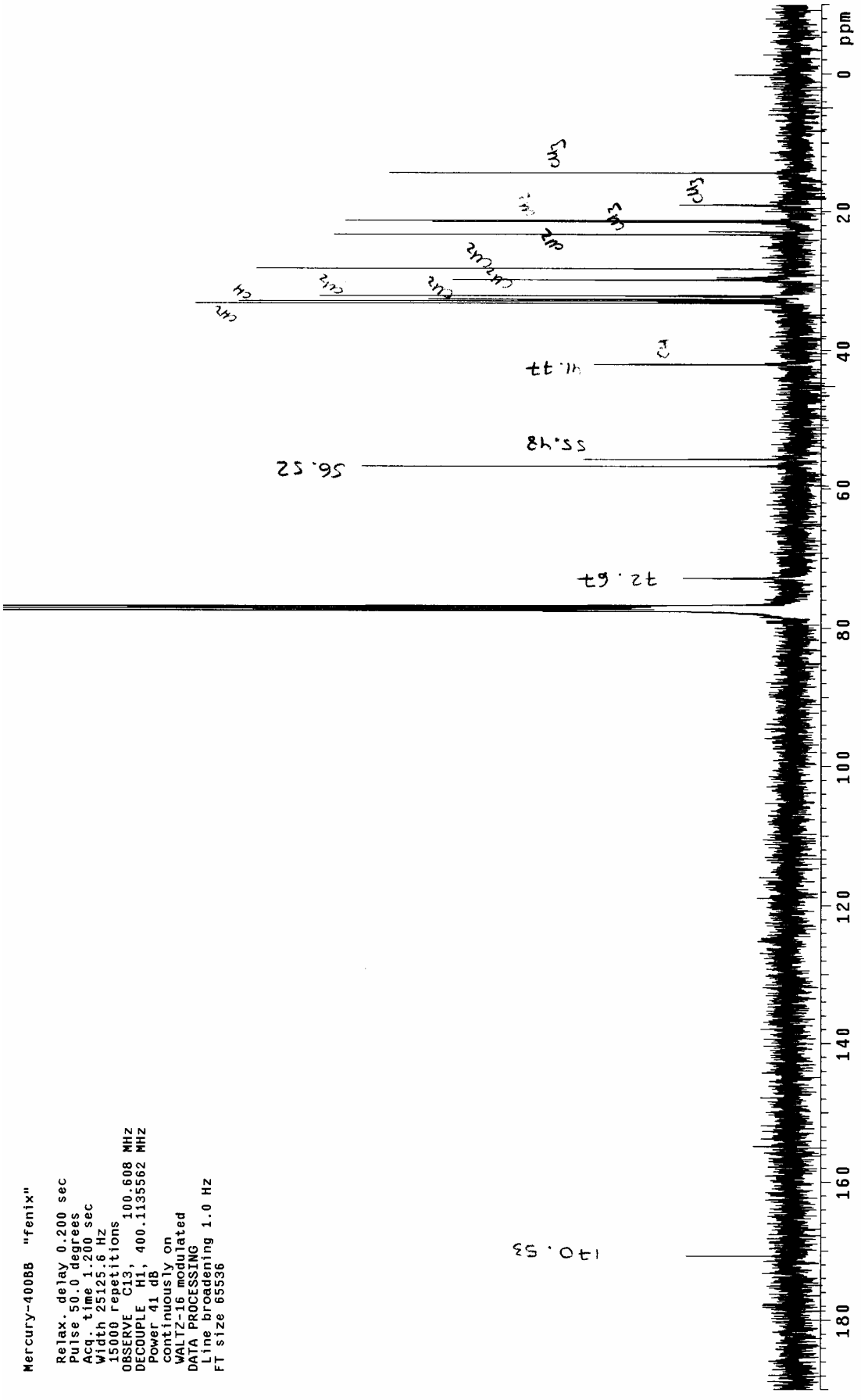
7
6
5
4
3
2
1
-0
ppm

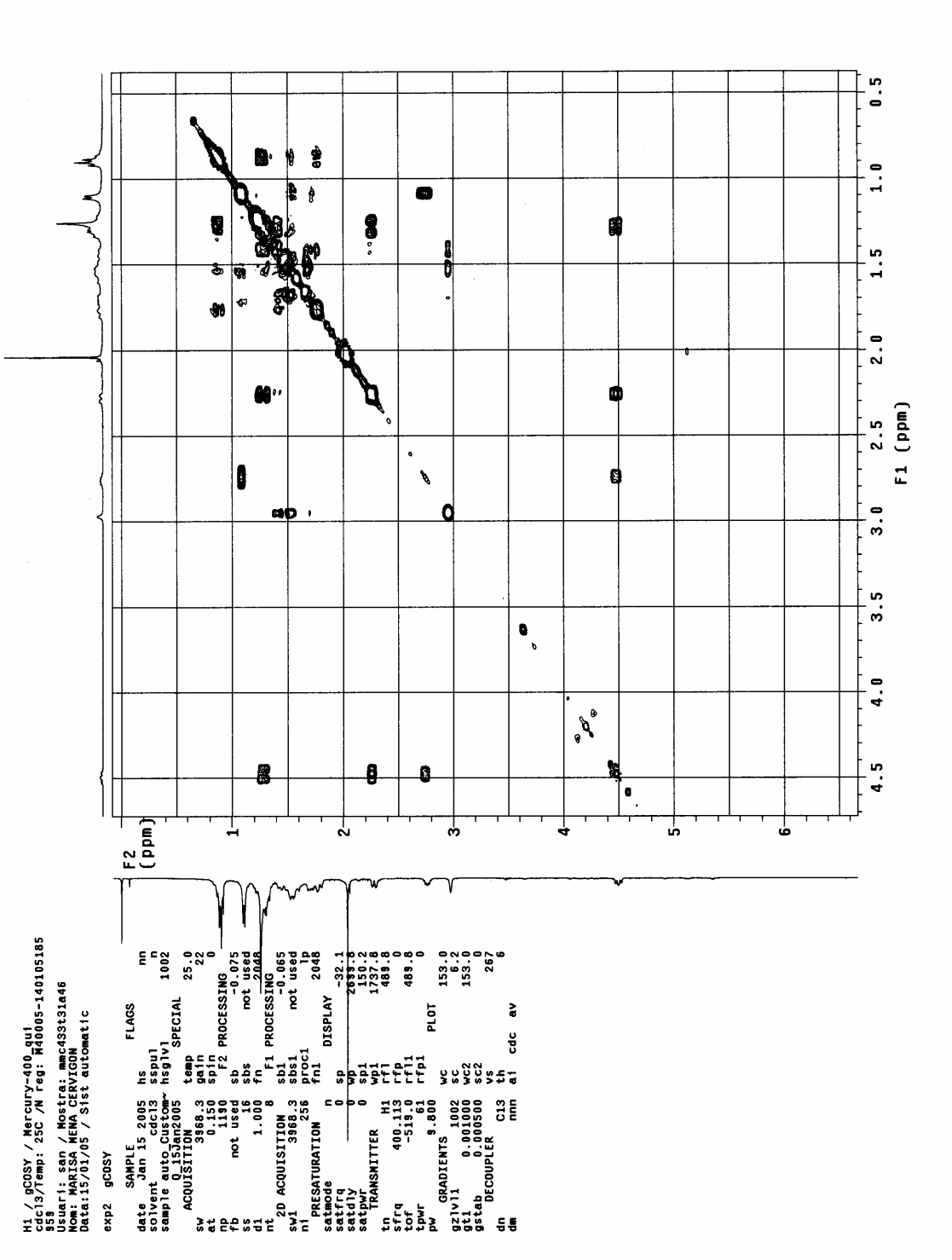


10a

Mercury-400BB "fenix"

Relax. delay 0.200 sec
Pulse 50.0 degrees
Acq. time 1.200 sec
Width 25125.6 Hz
15000 repetitions
OBSERVE C13, 100.608 MHz
DECOUPLE H1, 400.1135562 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536

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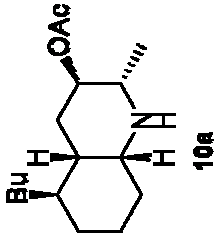
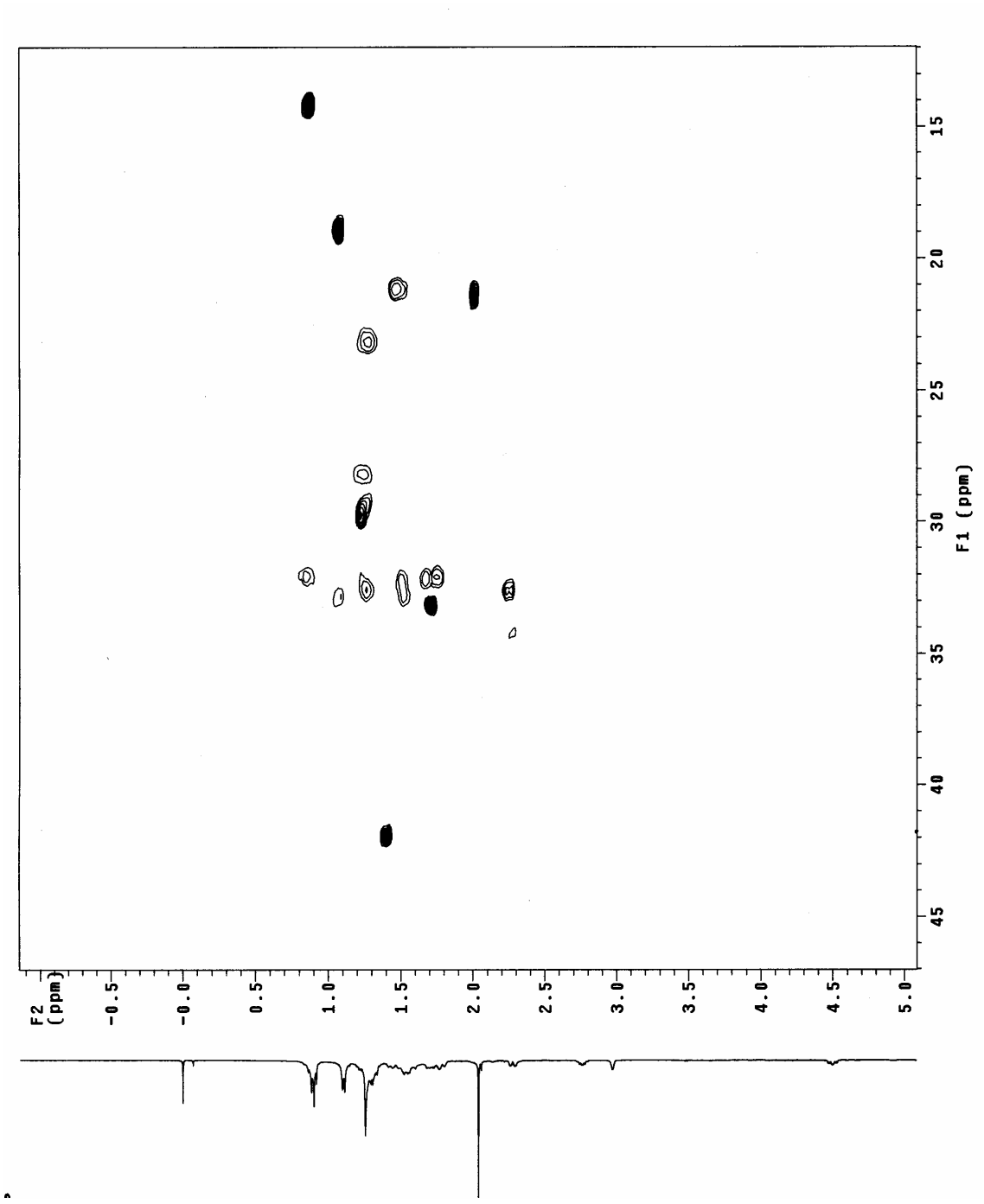
sfrq
Usuari: san / Nostra: mmc433t31a46
Nom: MARISA MENA CERVIGON
Data:15/01/05 / Sist automatic
exp2 gCOSY
SAMPLE FLAGS nn
date Jan 15 2005 hs n
solvent cdcl3 sspul n
sample auto_Custom~ hsglvl 1002
0_15Jan2005 SPECIAL
ACQUISITION
sw 3968.3 temp 25.0
at 0.150 gain 22
np 1190 spin 0
fb not used F2 PROCESSING
ss 16 sb -0.075
d1 1.000 sbs not used
nt 8 fn 2048
2D ACQUISITION F1 PROCESSING
sw1 3968.3 sb1 -0.065
n1 256 sbs1 not used
PRESATURATION proc1 lp
satmode n fn1 2048
satfrq 0 sp DISPLAY -32.1
satdly 0 wp 2699.8
satpwr sp1 150.2
TRANSMITTER wp1 1737.8
tn H1 rf1 489.8
sfrq 400.113 rfp 0
tof -519.0 rfl1 489.8
tpwr 61 rfp1 0
pw 9.800 PLOT
GRADIENTS wc 153.0
gzlvl1 1002 sc 153.2
gt1 0.001000 wc2 153.0
gstab 0.000500 sc2 0
DECOUPLER vs 267
dn C13 th 6
dm nnn at cdc av
F2 (ppm)
F1 (ppm)


OAc
Bu
H
N
H
H

10a


F2 (ppm)
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-0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
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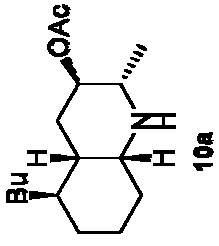
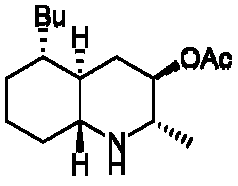
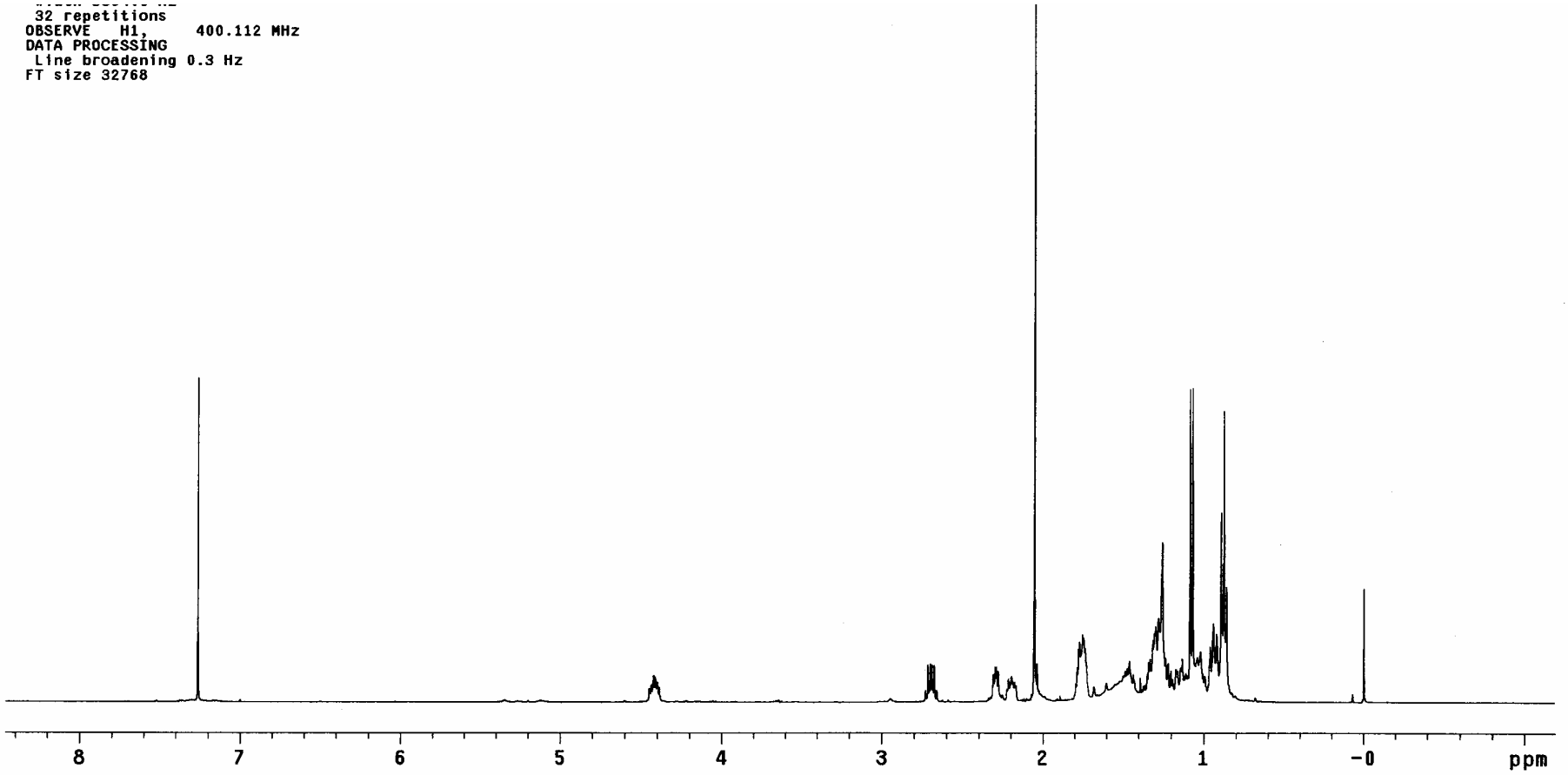
F1 (ppm)
15
20
25
30
35
40
45


OAc
Bu
H
N
H
H

10a


Bu
H
OAc
N
H
H

11a


32 repetitions
OBSERVE H1, 400.112 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
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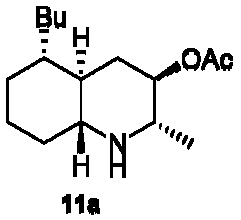
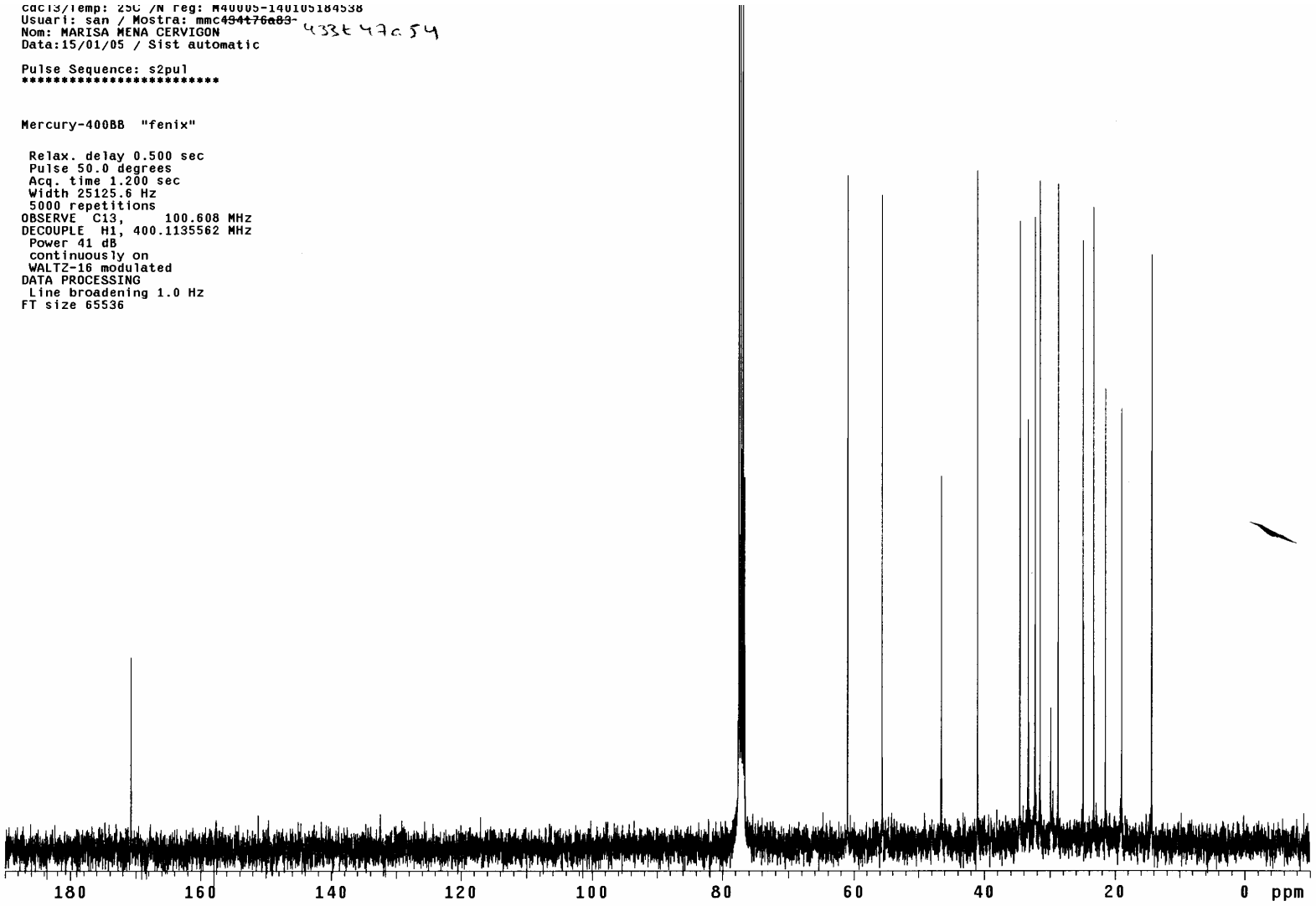
7
6
5
4
3
2
1
-0
ppm


Bu
H
OAc
N
H
H

11a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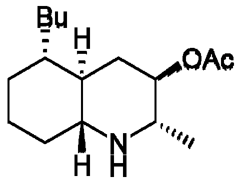
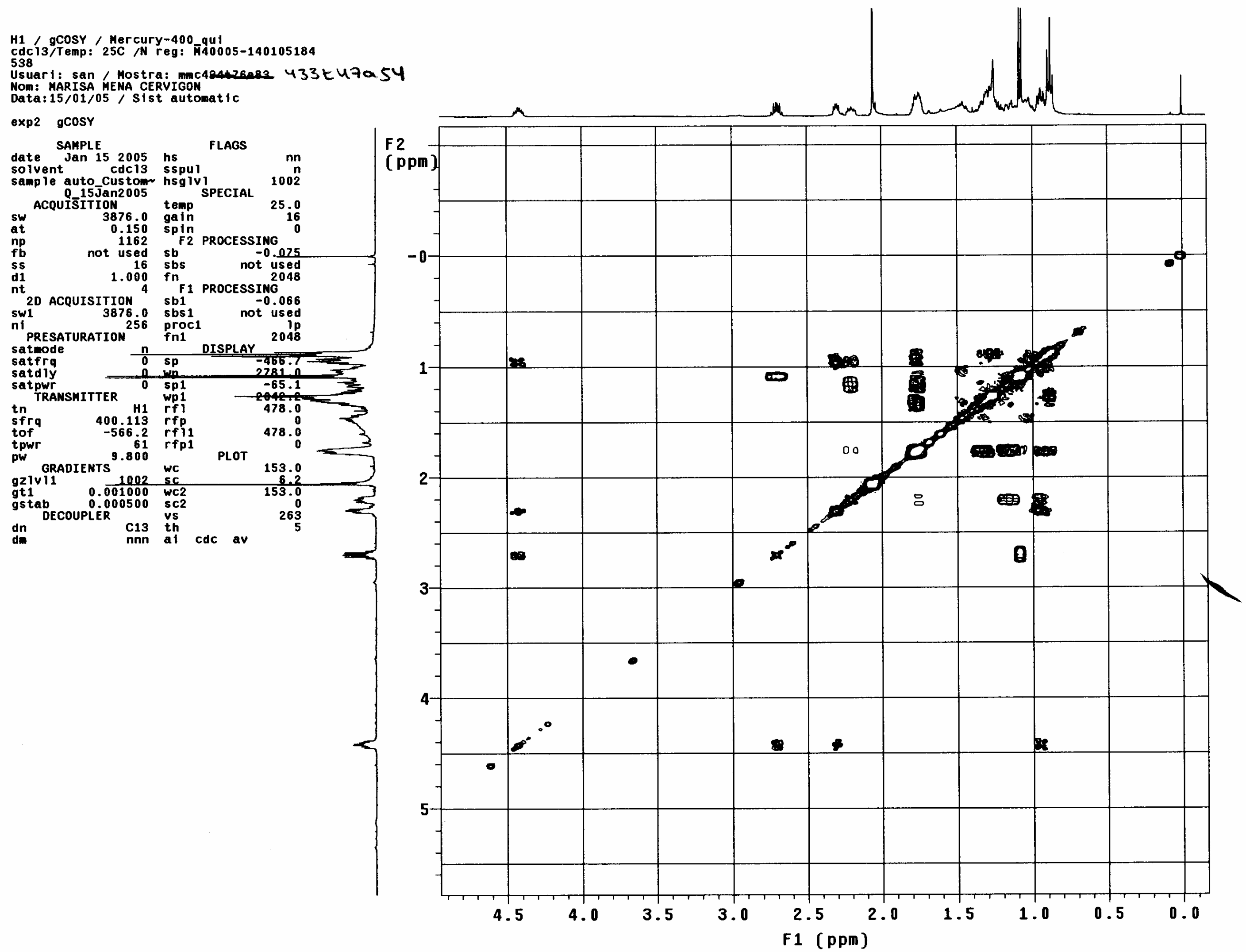
Usuari: san / Mostra: mmc4344t76a83-
Nom: MARISA MENA CERVIGON
Data:15/01/05 / Sist automatic
4336 47c 54
Pulse Sequence: s2pul
****
Mercury-400BB "fenix"
Relax. delay 0.500 sec
Pulse 50.0 degrees
Acq. time 1.200 sec
Width 25125.6 Hz
5000 repetitions
OBSERVE C13, 100.608 MHz
DECOUPLE H1, 400.1135562 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
180
160
140
120
100
80
60
40
20
0
ppm



11a



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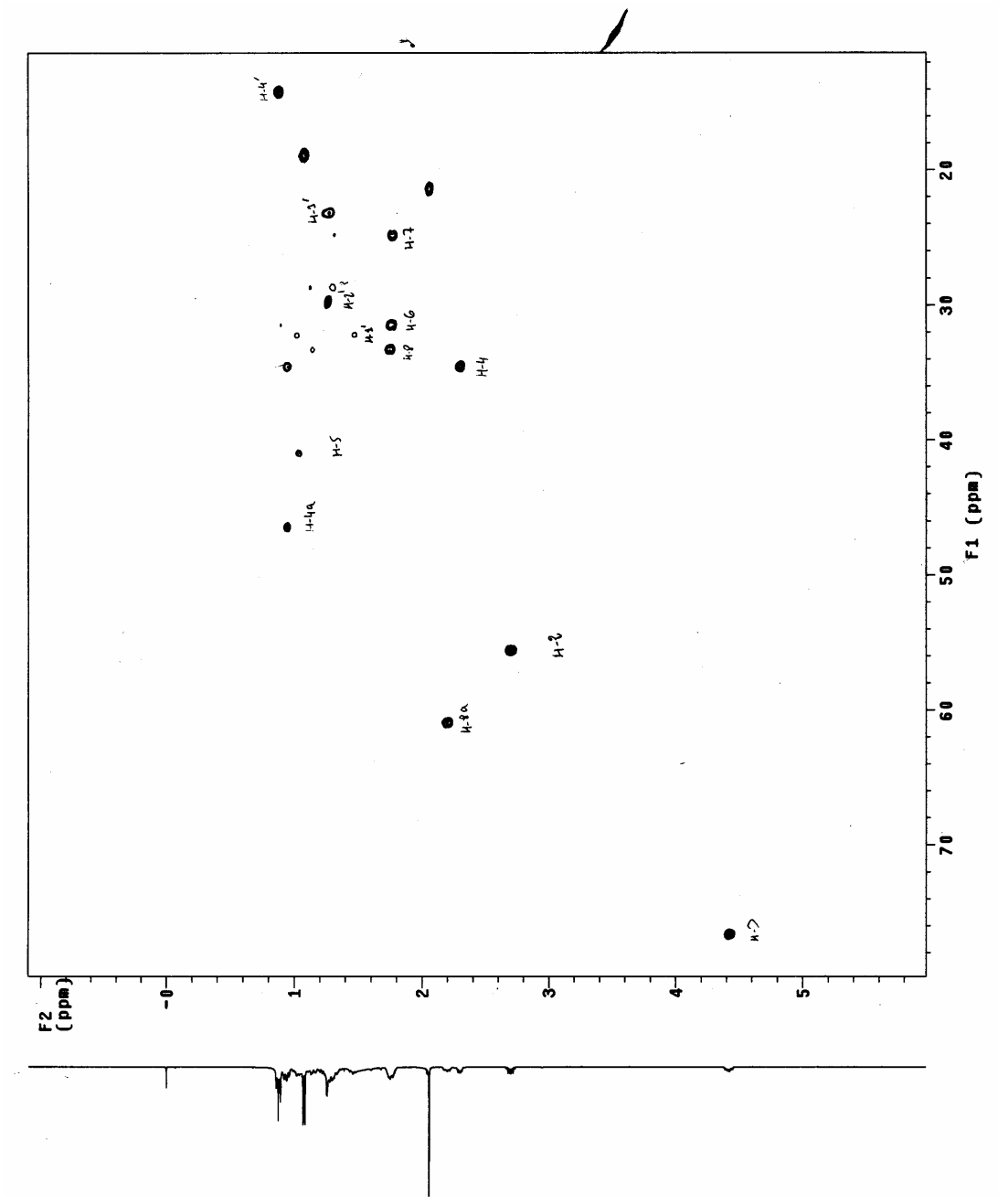
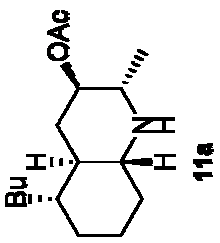
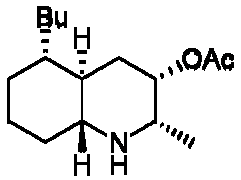
538
Usuari: san / Mostra: mmc4 433t47a54
Nom: MARISA MENA CERVIGON
Data:15/01/05 / Sist automatic
exp2 gCOSY
SAMPLE
date Jan 15 2005
solvent cdcl3
sample auto_Custom~
Q_15Jan2005
ACQUISITION
sw 3876.0
at 0.150
np 1162
fb not used
ss 16
d1 1.000
nt 4
2D ACQUISITION
sw1 3876.0
ni 256
PRESATURATION
satmode n
satfrq 0
satdly 0
satpwr 0
TRANSMITTER
tn H1
sfrq 400.113
tof -566.2
tpwr 61
pw 9.800
GRADIENTS
gzlvl1 1002
gt1 0.001000
gstab 0.000500
DECOUPLER
dn C13
dm nnn
FLAGS
hs nn
sspul n
hsglvl 1002
SPECIAL
temp 25.0
gain 16
spin 0
F2 PROCESSING
sb -0.075
sbs not used
fn 2048
F1 PROCESSING
sb1 -0.066
sbs1 not used
proc1 lp
fn1 2048
DISPLAY
sp -466.7
wp 2781.0
sp1 -65.1
wp1 2042.2
rfl 478.0
rfp 0
rfl1 478.0
rfp1 0
PLOT
wc 153.0
sc 6.2
wc2 153.0
sc2 0
vs 263
th 5
ai cdc av
F2 (ppm)
-0
1
2
3
4
5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
F1 (ppm)

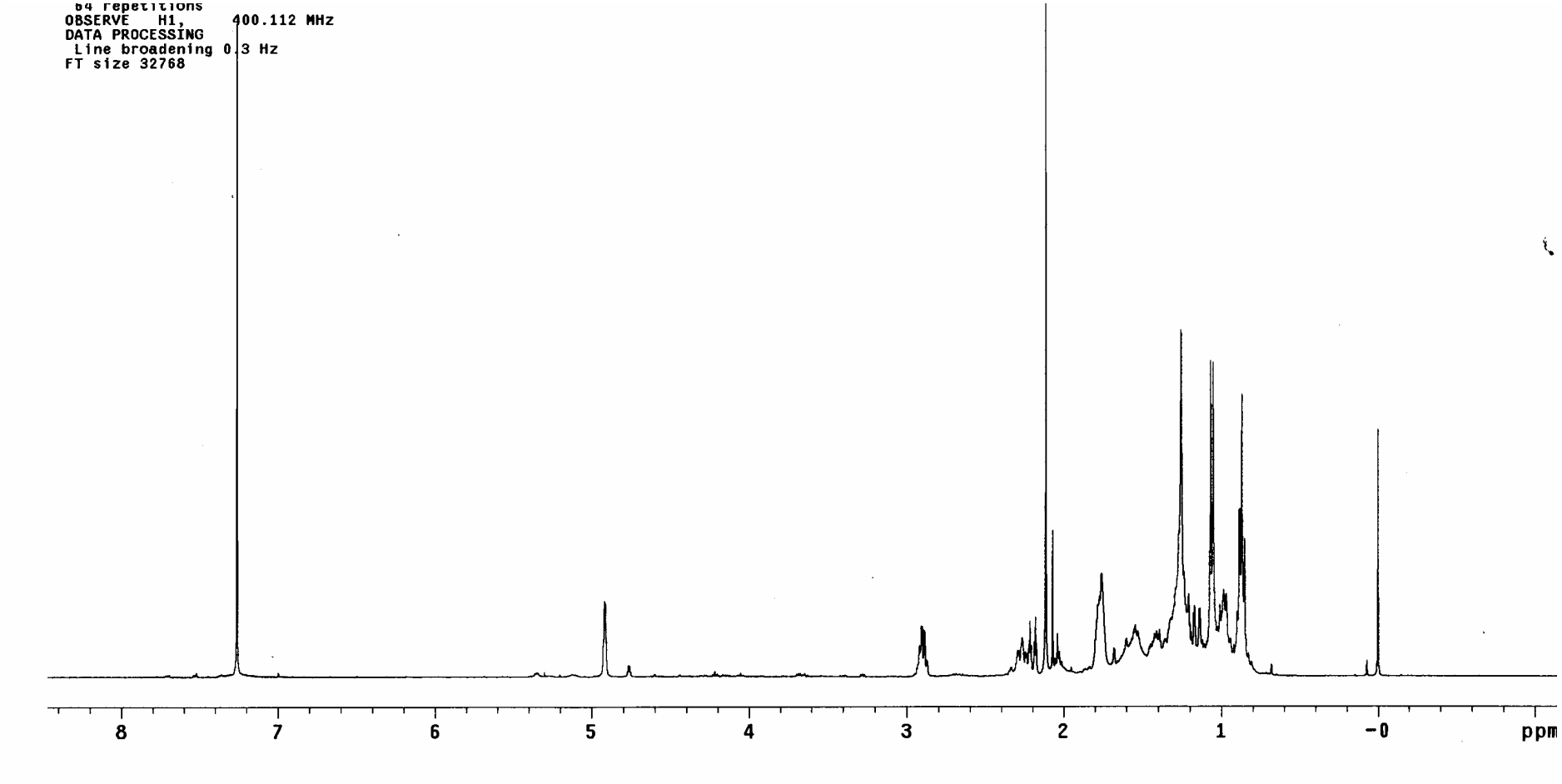


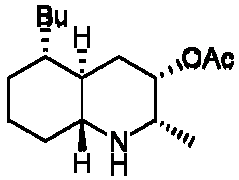


11a

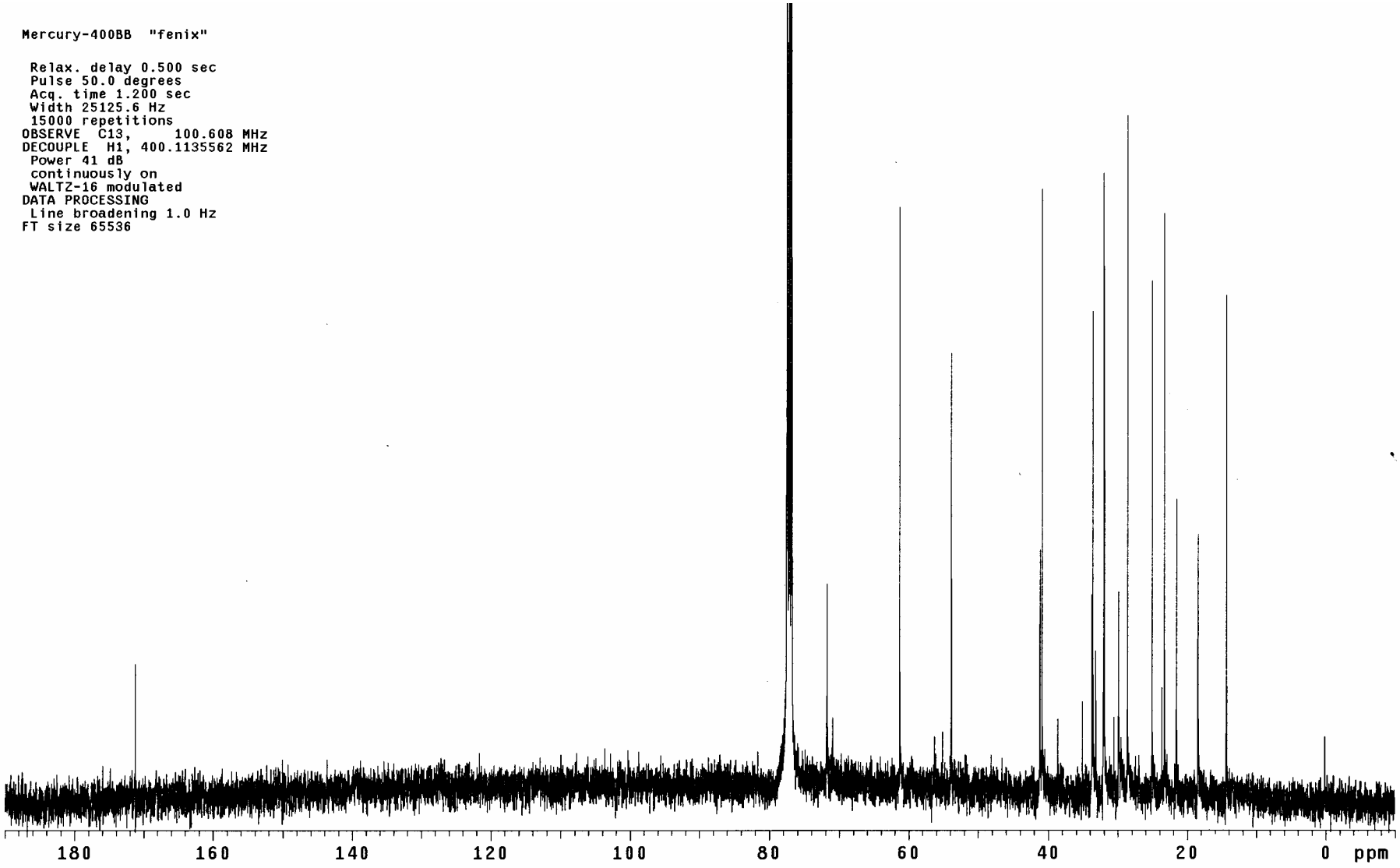

Bu
H
OAc
N
H
H

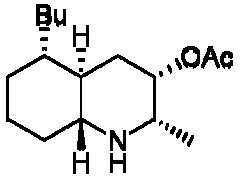
11b


64 repetitions
OBSERVE H1, 400.112 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
8
7
6
5
4
3
2
1
-0
ppm


Bu
H
OAc
N
H
H

11b


Mercury-400BB "fenix"
Relax. delay 0.500 sec
Pulse 50.0 degrees
Acq. time 1.200 sec
Width 25125.6 Hz
15000 repetitions
OBSERVE C13, 100.608 MHz
DECOUPLE H1, 400.1135562 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
180
160
140
120
100
80
60
40
20
0
ppm



11b

```
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404
Usuari: san / Mostra: mmc434tub76a
Nom: MARISA MENA CERVIGON
Data:15/01/05 / Sist automatic

exp2  gCOSY

      SAMPLE                FLAGS
date    Jan 15 2005   hs                nn
solvent         cdcl3   sspul             n
sample auto_Custom~   hsglvl          1002
        Q_15Jan2005         SPECIAL
    ACQUISITION       temp             25.0
sw           3876.0   gain               22
at            0.150   spin                0
np             1162     F2 PROCESSING
fb         not used   sb              -0.075
ss               16   sbs          not used
d1            1.000   fn                2048
nt                8     F1 PROCESSING
  2D ACQUISITION     sb1             -0.066
sw1          3876.0   sbs1         not used
ni              256   proc1              lp
  PRESATURATION      fn1               2048
satmode           n         DISPLAY
satfrq            0   sp               64.4
satdly            0   wp             1405.4
satpwr            0   sp1              204.6
   TRANSMITTER        wp1              844.9
tn               H1   rfl              481.1
sfrq        400.113   rfp                 0
tof          -566.0   rfl1             481.1
tpwr             61   rfp1                0
pw            9.800         PLOT
     GRADIENTS        wc               153.0
gzlvl1         1002   sc                 6.2
gt1       0.001000   wc2              153.0
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dn              C13   th                  4
dm              nnn   ai  cdc  av
```

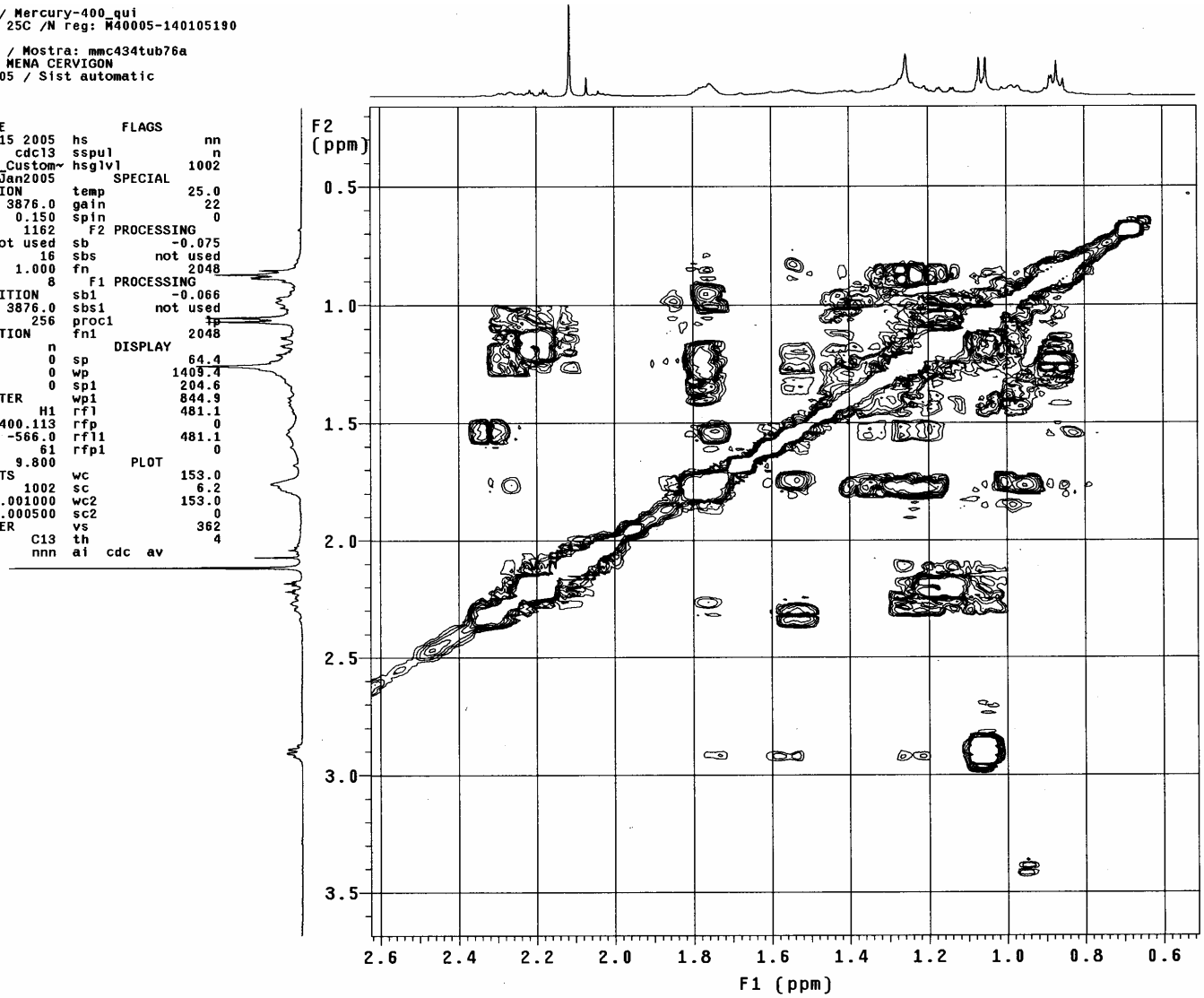

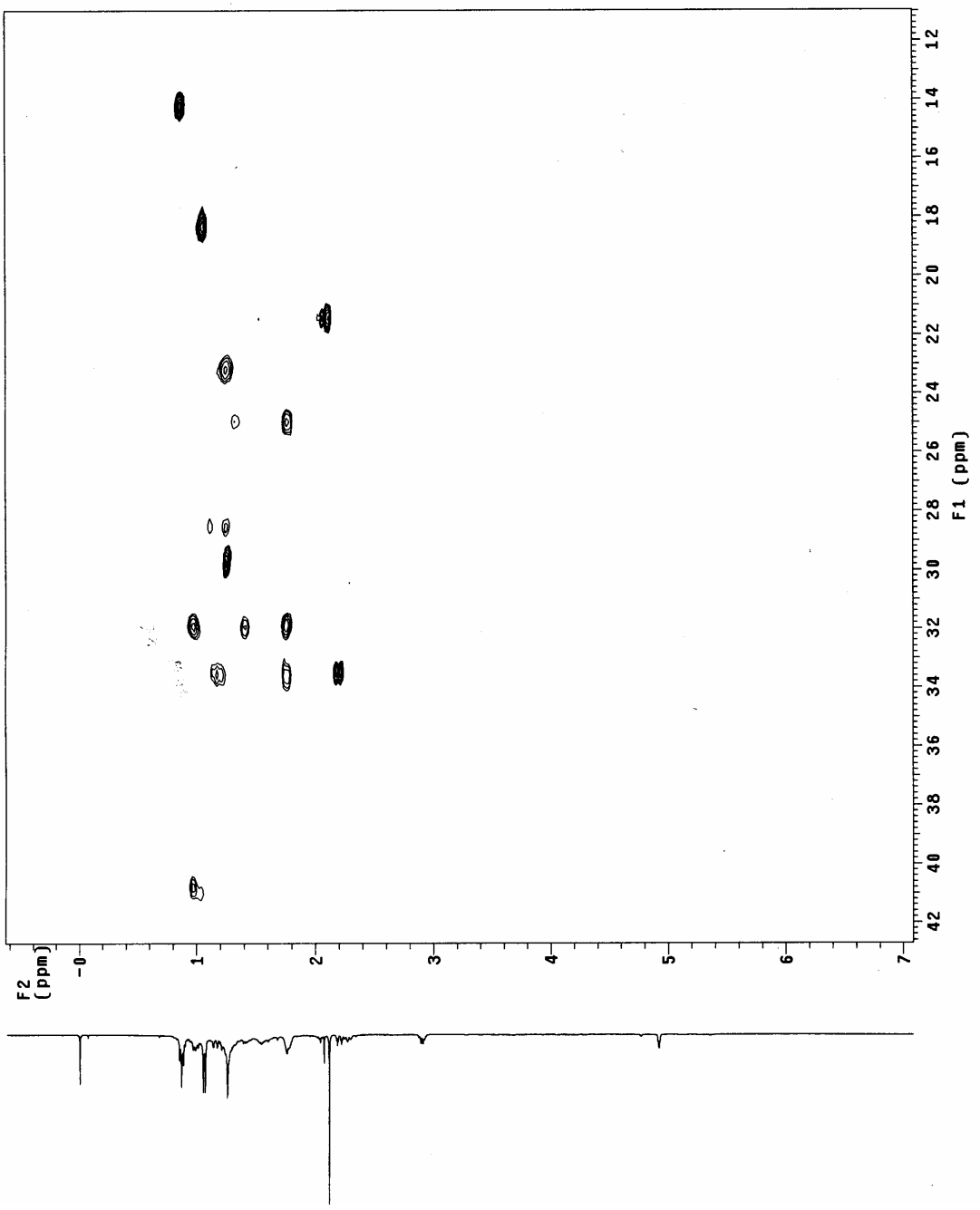

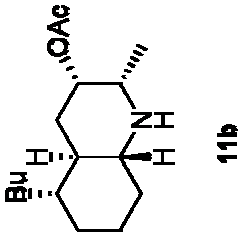

11b

6.2

Ring expansion of Functionalized Octahydroindoles to Enantiopure *cis*-decahydroquinolines

Marisa Mena y Josep Bonjoch

Domingo Gomez-Pardo y Janine Cossy

J. Org. Chem. **2006**, *71*, 0000.

Ring Expansion of Functionalized Octahydroindoles to Enantiopure *cis*-Decahydroquinolines†

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Domingo Gomez Pardo and Janine Cossy

Laboratoire de Chimie Organique, associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

josep bonjoch@ub edu

RECEIVED DATE

TITLE RUNNING HEAD: Ring expansion of octahydroindoles to *cis*-decahydroquinolines

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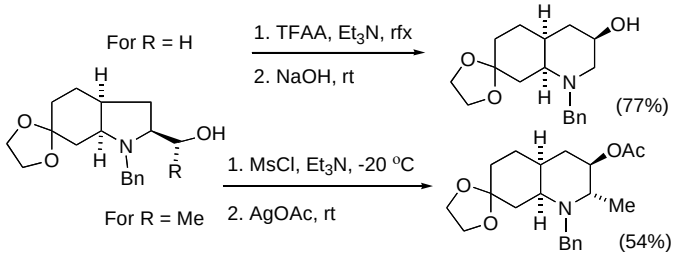


ABSTRACT A new synthetic entry to enantiopure *cis*-decahydroquinolines is reported *Endo* and *exo* derivatives of *cis*-1-benzyl-2-(hydroxymethyl)octahydroindol-6-one ethylene acetal undergo ring-enlargement upon treatment with TFAA and then Et_3N (thermodynamic conditions) to give enantiopure 1-benzyl-3-hydroxydecahydroquinolin-7-one derivatives in 77% and 82% yield, respectively For 2-(1-hydroxyethyl) analogs, the best synthetic result is obtained from the (2*S*,1'*R*) *endo* isomer, which under kinetic reaction conditions (MsCl, THF, -20 °C, then AgOAc at rt) gives the expanded product in 54% yield

---

cis-Decahydroquinoline constitutes the azabicyclic skeleton of natural products such as lepadins[1] and several amphibian alkaloids,[2] as well as some pharmacologically interesting synthetic compounds [3] Moreover, this heterocyclic motif occurs as a subunit of other azapolycyclic natural products (*e.g.* gephyrotoxins,[4] cylindricines,[5] and pseudoaspidopermidine and pandoline alkaloids[6]) (Figure 1) The extensive occurrence of this azabicyclic ring has stimulated the implementation of new procedures to gain access to functionalized enantiopure *cis*-decahydroquinolines that can be used as advanced intermediates in the synthesis of compounds embodying this skeleton-type [7]

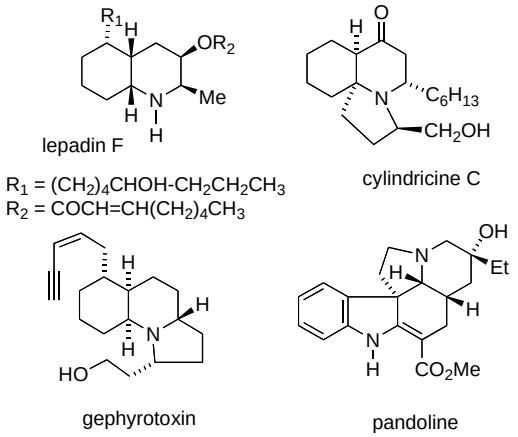
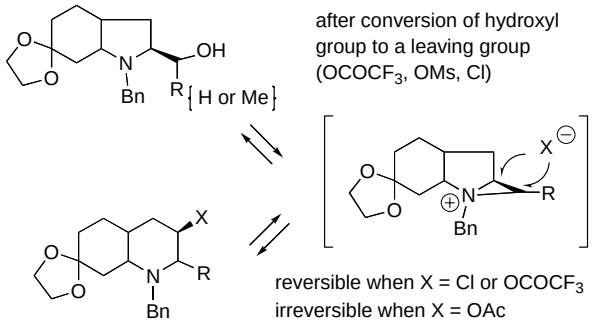


FIGURE 1. Natural and synthetic compounds embodying the *cis*-decahydroquinoline framework

In this paper we report the studies devoted to the ring-enlargement of *cis*-octahydroindole derivatives to *cis*-decahydroquinolines The diastereoselective ring expansion of monocyclic amines (azetidines,[8] pyrrolidines,[9,10] pyrrolines,[11] piperidines[12]) and bicyclic amines (2-azabicyclo[3 3 0]octanes,[13] 1-azabicyclo[2 2 2]octanes,[14] indolizidines,[15] indolines,[16] hexahydropyrrolo[3,4-d]isoxazoles[17]) with a hydroxymethyl substituent adjacent to the nitrogen atom is a well known process,[18,19] but it is unprecedented in octahydroindole compounds Considering the precedents, we envisaged that the transformation (Scheme 1) would occur via aziridinium intermediates,[20] once the hydroxyl group is converted into a good leaving group A ring opening at the fused carbon atom would then lead to a new heterocyclic derivative with an expanded ring If the leaving group were a chloride or trifluoroacetate, in absence of another nucleophile in the reaction medium, the process would be reversible and the ratio of the expanded and non-expanded compounds would reflect their thermodynamic stability On the contrary, if X^- were an acetate and the

chloride ion were taken out of the reaction medium using silver acetate, the ring opening of the aziridinium ion would be irreversible and the ratio of the formed compounds would arise from a kinetic control

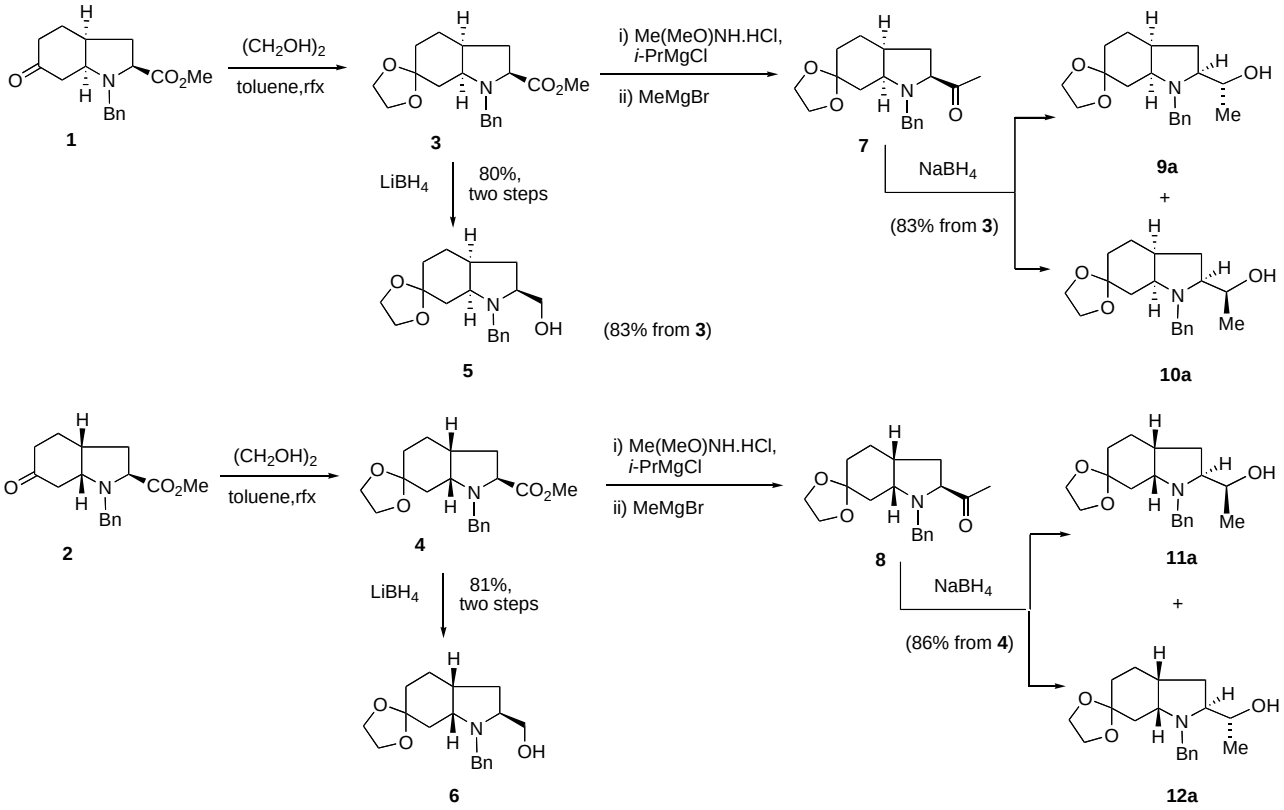
SCHEME 1. The synthetic approach to enantiopure *cis*-decahydroquinolines



Our study of the stereospecific rearrangement of 2-hydroxymethyl- and 2-(α-hydroxyethyl)octahydroindoles to 3-substituted and 2,3-disubstituted decahydroquinolines began with the preparation of the rearrangement precursors (Scheme 2) The starting materials were the azabicyclic esters *endo* **1** and *exo* **2**, which were available from *O*-methyltyrosine in three steps (Birch reduction, aminocyclization promoted by MeOH-HCl, and benzylation) [21] Both esters were protected to give acetals **3** and **4**, which, in turn, were reduced with $LiBH_4$ to the corresponding primary alcohols **5** and **6** in 80% overall yield in each series On the other hand, the preparation of the secondary alcohols was carried out as follows: esters **3** and **4** were transformed to methyl ketones **7** (*endo*) and **8** (*exo*), respectively, in a two-step sequence involving the formation of their corresponding Weinreb amides,[22] followed by coupling with methylmagnesium bromide Then, ketones **7** and **8** were both reduced with $NaBH_4$ to give a mixture of secondary alcohols **9a** and **10a** (55:45 ratio)[23] in the *endo* series and **11a** and **12a** (63:37 ratio) in the *exo* series At this point, improving the

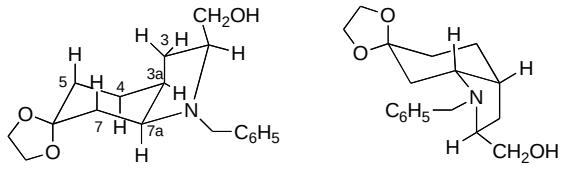
diastereoselectivity of the reduction was not a priority since the availability of all the diastereomers would help evaluate the scope and limitations of the enlargement process

SCHEME 2. Synthesis of *cis*-2-hydroxymethyl- and 2-(α-hydroxyethyl)octahydroindole derivatives



Two ^{13}C NMR features clearly differentiate the *endo* and *exo* series of *cis*-2-substituted octahydroindol-6-ones (Table 1, Supporting Information): (i) the chemical shift of the benzylic carbon resonates at a higher field in *exo* compounds (δ 51 5-54 0) than in the *endo* compounds (δ 59-63); (ii) the C-7 signal appears at lower values in the *exo* compounds (δ 29-32) than in the *endo* isomers (δ 37-39) It is worth noting that the stereochemistry at C-1' for alcohols **9a**-**12a** was only unequivocally established after the stereochemical elucidation of the expanded decahydroquinolines (*cf.* vide infra) The conformationally mobile *cis*-octahydroindole system[21] has two conformers (*N*-outside

and *N*-inside) in which H-7a is axial or equatorial, respectively, with respect to the carbocyclic ring NMR studies allowed us to assign the conformational preference of the described *cis*-2-substituted octahydroindol-6-one derivatives, in which the coupling constants H7-H7a (one of them of 11 Hz) are consistent with antiperiplanar couplings, indicating that the H-7a proton[24] is axially located with respect to the carbocyclic ring (Figure 2)



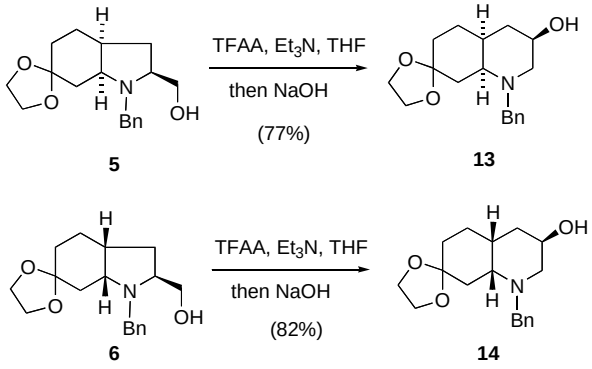
5 **6**

FIGURE 2. Preferred conformation of *endo* and *exo* compounds **5** and **6**

Treatment of 2-(hydroxymethyl)octahydroindole derivative **5** with TFAA in THF followed by the addition of triethylamine[9] led to the ring-expanded product, which after a hydrolytic work-up (aqueous NaOH) allowed the isolation of decahydroquinoline **13** (Scheme 3) The NMR data (see below) of this compound proves that the configuration of C-3 in (-)-**13** is *R*, which supports the mechanism depicted in Scheme 1 (stereocontrolled process during the nucleophilic attack at C-2 of the aziridinium intermediate) The same protocol (TFAA/Et_3N/NaOH) was also applied to the *exo* isomer **6**, decahydroquinoline (+)-**14** being isolated as a single isomer in 82% yield Both decahydroquinolines show the same preferred conformation according to their NMR spectra Thus, the coupling constants of H-4a and H-8a in each diastereomer are in accordance with an axial and an equatorial relationship, respectively, with respect to the *N*-containing ring (*N*-exo conformation) [25] The ^{13}C NMR data corroborate the above stereochemical elucidation since both **13** and **14** show a relative upfield for C-2 and C-

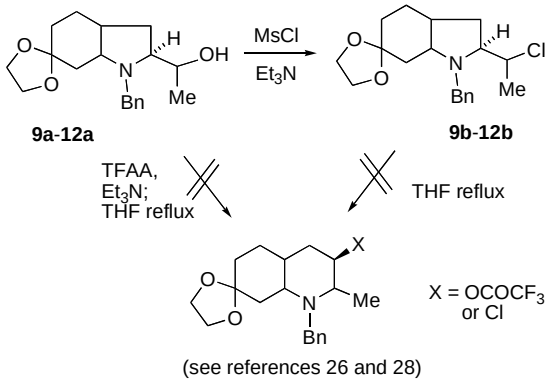
8, a characteristic feature of *cis*-decahydroquinolines in the *N*-exo conformation (see Figure 3)

SCHEME 3 Synthesis of 3-hydroxydecahydroquinolines



When we applied the same procedure (TFAA, THF, then Et_3N) to the secondary alcohols **9a**-**12a**, i e under thermodynamic reaction conditions, the results were disappointing since after long reaction times (4-5 days at reflux temperature) only the starting material and degradation products were obtained [26,27] The next attempt to expand the ring involved converting alcohols **9a**-**12a** to the secondary chlorides **9b**-**12b**, which were then heated in refluxing THF In all cases, the unexpanded 2-(α-chloroethyl)octahydroindoles **9b**-**12b** were isolated (Scheme 4) [28] Since the configuration at C-1' was retained, these results show that the process occurred through an aziridinium salt intermediate and that chlorides **9b**-**12b** were either directly formed by opening of an aziridinium by the chloride ion or by a reversion process from an initially expanded product Thus, under thermodynamic reaction conditions, we were unable to achieve 2,3-disubstituted decahydroquinolines from octahydroindoles **9a**-**12a** [29]

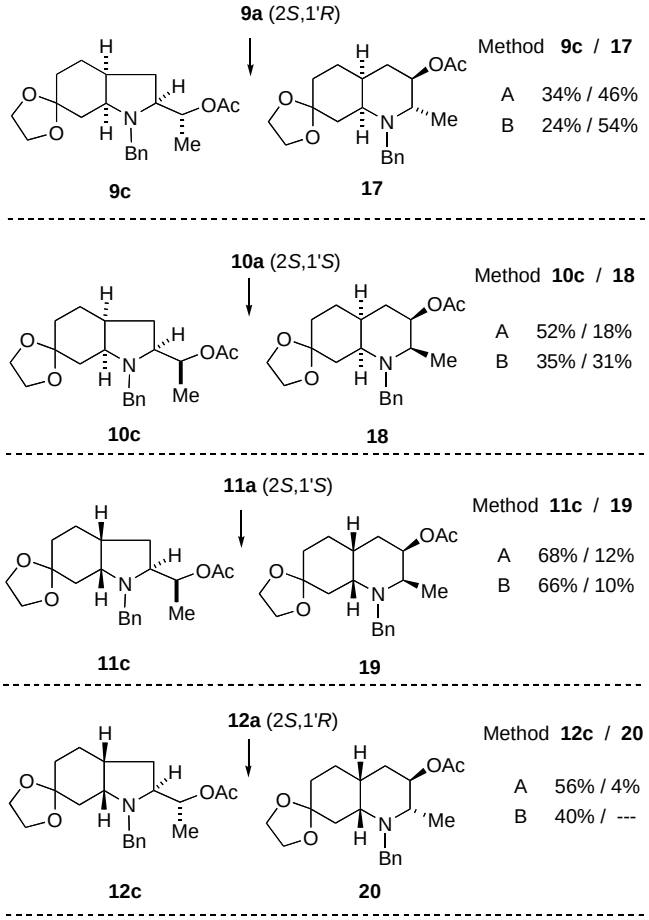
SCHEME 4. Attempted ring expansion under thermodynamic conditions



In order to have an irreversible ring opening of the aziridinium intermediate, the chlorides **9b**-**12b** were treated with AgOAc in a THF solution at reflux temperature (Method A) Under these kinetic conditions, the ring expanded decahydroquinolines **17**-**19** were formed in variable yields (Scheme 5), and **20** was only detected in the GC-MS analysis The non-enlarged acetates **9c**-**12c** formed by the acetate attack on the carbon linked to the methyl group in the aziridinium intermediate, were also isolated [30] The best results from a synthetic point of view were obtained for the *endo* compound **9b**, since it was only in this series that the decahydroquinoline derivative was isolated as the main product We then decided to carry out the process starting from alcohols **9a**-**12a**, working at -20 °C to avoid the formation of the corresponding chlorides,[10c] and promoting the ring opening of the aziridinium with AgOAc at room temperature (Method B) This decrease in temperature led to a slight increase in the ratio of the thermodynamically unfavoured decahydroquinolines (see Scheme 5) Not unexpectedly, in the *endo* series of 2-(α-hydroxyethyl)octahydroindoles the best result was obtained from alcohol **9a**, which was transformed into the decahydroquinoline **17** in 54-58% yield [31,32] The reason was that the aziridinium intermediate was formed and opened without generating steric repulsion due to the antiperiplanar relationship between the methyl group and the C(2)-C(3) bond On the contrary, the reason for the poor yields

observed in the ring-expanded compounds in the *exo* series (**11a** and **12a**) is unclear, even taking into consideration that the transition states between **12a** and decahydroquinoline **20** are likely to be the most sterically demanding of the four pathways leading to expanded compounds Figure 3 depicts the preferred conformation of all the synthesized 3-oxygenated *cis*-decahydroquinolines

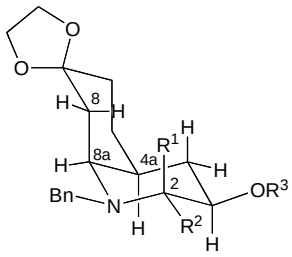
SCHEME 5. Ring expansion under kinetic conditions



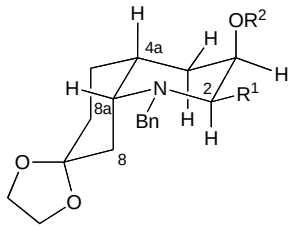
Method A: (i) MsCl, Et_3N, THF reflux, 4h

(**9b**-**12b** formed); (ii) AgOAc, THF reflux, 4 h

Method B: (i) MsCl, Et_3N, THF, -20 °C; (ii) AgOAc, rt, 1h



13 $R^1 = R^2 = H$; $R^3 = H$
17 $R^1 = H$; $R^2 = Me$; $R^3 = Ac$
18 $R^1 = Me$; $R^2 = H$; $R^3 = Ac$
21 $R^1 = H$; $R^2 = Me$; $R^3 = H$

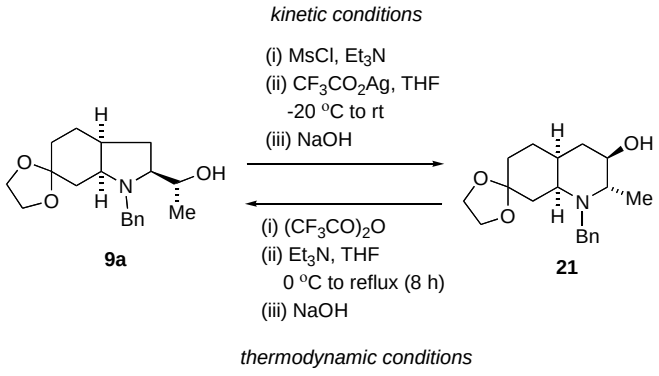


14 $R^1 = R^2 = H$
15 $R^1 = Me$; $R^2 = H$
19 $R^1 = Me$; $R^2 = Ac$

FIGURE 3 Stereochemistry of *cis*-decahydroquinolines

Finally, to obtain a better understanding of the ring enlargement process, decahydroquinoline **21** (obtained under kinetic conditions from **9a**)[31] was submitted to the thermodynamic conditions of the aziridinium ring formation and opening (TFAA, then Et_3N followed by heating at reflux for 8 h, and ending with an aqueous NaOH treatment) Under these conditions, octahydroindole **9a** was formed, albeit as the only product (Scheme 6) This result confirms that 2-(α-hydroxyethyl)octahydroindoles are more stable than 2-methyl-3-hydroxyquinolines in the series of compounds examined (**9**-**12** *vs* **17**-**20**)

SCHEME 6



In summary, the study of the ring enlargement of *cis*-octahydroindole derivatives has given access to valuable functionalized enantiopure *cis*-decahydroquinolines (**13** and **14**, in excellent yields, and **17** in good yield), which could be used as building blocks in the synthesis of natural products Moreover, it has been shown that subtle stereochemical differences in the octahydroindoles studied can have a significant impact on the ring-expansion pathway when the process is carried out under thermodynamic or kinetic conditions

Experimental Section

(3*R*,4aS,8aS)-1-Benzyl-3-hydroxy-7-oxodecahydroquinoline ethylene acetal (13). To a solution of alcohol **5** (223 mg, 0 74 mmol) in THF (2 mL) cooled to -78 ºC was added TFAA (0 21 mL, 1 47 mmol, 2 equiv) and the reaction mixture was stirred for 3 h at this temperature Et_3N (0 5 mL, 3 68 mmol, 5 equiv) was added and after 15 min, the reaction mixture was heated at reflux for 20 h The mixture was cooled to 25 ºC, and 2 5 N NaOH (15 mL, 50 equiv) was added After stirring for 3 h, the reaction mixture was extracted with CH_2Cl_2 (3x20 mL) The organic extracts were dried and concentrated to give an oil, which was purified by chromatography (SiO_2, 1% to 5% MeOH in CH_2Cl_2) to give 173 mg (77%) of **13** as a colorless oil: R_f = 0 35 (SiO_2, CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ - 44 (*c* 0 3, $CHCl_3$); ^{1}H NMR (500 MHz, gCOSY, $CDCl_3$) 1 45 (dm, *J* = 10 5 Hz, 1H, H-5eq), 1 47 (m, 1H, H-6eq), 1 50 (q, *J* = 10 5 Hz, 1H, H-4ax), 1 55 (m, 1H, H-6ax), 1 58 (m, 1H, H-4eq), 1 61 (ddd, *J* = 12 5, 4 5, 2 0 Hz, 1H, H-8eq), 1 73 (tt, *J* = 13 5, 5 0 Hz, 1H, H-5ax), 1 82 (t, *J* = 12 5 Hz, 1H, H-8ax), 1 97 (dm, *J* = 10 5 Hz, 1H, H-4a), 2 10 (t, *J* = 10 5 Hz, 1H, H-2ax), 2 62 (ddd, *J* = 10 5, 5 0, 1 5 Hz, 1H, H-2eq), 3 00 (dt, *J* = 12 5, 4 5 Hz, 1H, H-8a), 3 45 and 3 66 (2d, *J* = 12 5 Hz, 1H each, NCH_2Ar), 3 68 (dddd, *J* = 10 5, 10 5, 5 0, 5 0, 1H, H-3ax), 3 80-3 90 (m, 4H, OCH_2),

7 20-7 30 (m, 5H, ArH); ^{13}C NMR (75 MHz, gHSQC) 26 9 (C-5), 27 0 (C-8), 29 9 (C-6), 32 8 (C-4a), 33 1 (C-4), 52 0 (C-2), 57 0 (C-8a), 58 3 (NCH_2), 64 1 and 64 2 (OCH_2), 68 1 (C-3), 109 9 (C-7), 126 8, 128 1, 129 5, 139 3 (Ar) Anal Calcd for $C_{18}H_{25}NO_3$: C 71 26, H 8 31, N 4 62 Found: C 70 86, H 8 03, N 4 38

(3*R*,4a*R*,8a*R*)-1-Benzyl-3-hydroxy-7-oxodecahydroquinoline ethylene acetal (14). Operating as above, alcohol **6** (464 mg, 1 53 mmol) in THF (4 mL) was treated with TFAA (0 43 mL, 3 04 mmol, 2 equiv), and then with Et_3N (1 07 mL, 7 65 mmol, 5 equiv) After work-up, the crude material was purified by chromatography (SiO_2, 1% to 5% MeOH in CH_2Cl_2) to give **14** (380 mg, 82%) as a white solid: R_f = 0 40 (SiO_2, CH_2Cl_2/MeOH 95:5); mp 101-103 °C; $[\alpha]_D^{20}$ + 39 (*c* 1 0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1 47 (m, 1H, H-6eq), 1 52 (m, 1H, H-5eq), 1 55 (m, 1H, H-4), 1 60 (m, 1H, H-6ax), 1 68 (m, 2H, H-4, H-8eq), 1 80 (tt, *J* = 13 5, 5 0 Hz, 1H, H-5ax), 1 87 (t, *J* = 12 5 Hz, 1H, H-8ax), 2 31 (dm, *J* = 10 5 Hz, 1H, H-4a); 2 52 and 2 57 (2d, *J* = 12 0 Hz, 1H each, H-2), 3 15 (dt, *J* = 12 5, 4 5 Hz, 1H, H-8a), 3 48 and 3 71 (2d, *J* = 13 0 Hz, 1H each, NCH_2Ar), 3 84 (br s, 1H, H-3eq), 3 90-3 95 (m, 4H, OCH_2), 7 20-7 35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), 25 6 (C-8), 26 6 (C-5), 29 8 (C-6), 28 8 (C-4a), 30-5 (C-4), 50 6 (C-2), 57 7 (C-8a), 58 5 (NCH_2), 64 1 and 64 3 (OCH_2), 65 4 (C-3), 109 8 (C-7), 127 2, 128 4, 128 7, 139 0 (Ar) Anal calcd for $C_{18}H_{25}NO_3$: C 71 26, H 8 31, N, 4 62 Found: C 70 89, H 8 50, N 4 44

Ring expansion of alcohol 9a. A solution of alcohol **9a** (50 mg, 0 16 mmol) in THF (1 mL) was treated with MsCl (16 μL, 0 19 mmol, 1 2 equiv) and Et_3N (90 μL, 0 64 mmol, 4 equiv) under an argon atmosphere at – 20 ºC for 1 h AgOAc was added (80 mg, 0 48 mmol, 3 equiv) and the resulting mixture was warmed to rt over a period of 1 h The reaction mixture was filtered through a bed of Celite and diluted with CH_2Cl_2 The organic layer was washed with saturated $NaHCO_3$ (10 mL), dried and concentrated

to give a mixture of acetates **9c** and **17** Purification and separation of the compounds was performed by chromatography (SiO_2, CH_2Cl_2/EtOAc 9:1) to afford 14 mg (24%) of **9c** (for analytical data, see Supporting Information) and 31 mg (54%) of **17**

(2*S*,3a*S*,7a*S*)-1-Benzyl-2-[(1'*R*)-(1-acetoxyethyl)]octahydroindol-6-one ethylene acetal (9c): Colourless oil R_f = 0 38 (SiO_2, CH_2Cl_2/EtOAc 8:2); $[\alpha]_D^{20}$ - 10 7 (*c* 0 4, $CHCl_3$); IR 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 1 23 (d, *J* = 6 4 Hz, 3H, CH_3), 1 26 (m, 2H, H-5), 1 44 (d, *J* = 8 4 Hz, 2H, H-7), 1 60 (m, 2H, H-4), 1 76 (m, 2H, H-3), 2 07 (s, 3H, OAc), 2 20 (m, 1H, H-3a), 2 90 (q, *J* = 8 4 Hz, 1H, H-7a), 2 91 (ddd, *J* = 8 4, 8 0, 4 0 Hz, 1H, H-2), 3 63 and 3 86 (2d, *J* = 14 0 Hz, 1H each, NCH_2Ar), 3 66-3 83 (m, 4H, OCH_2), 5 05 (qd, *J* = 6 4, 4 0 Hz, 1H, H-1'), 7 20-7 35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), see Table 1 HRFABMS: calcd for $C_{21}H_{30}NO_4$ 360 2175 (MH^+), found 360 2170

(2*S*,3*R*,4a*S*,8a*S*)-3-Acetoxy-1-benzyl-2-methyl-7-oxodecahydroquinoline ethylene acetal (17): Colourless oil R_f = 0 84 (SiO_2, CH_2Cl_2/EtOAc 8:2) $[\alpha]_D^{20}$ - 37 (*c* 1 0, $CHCl_3$); IR 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 1 03 (d, *J* = 6 4 Hz, 3H, Me), 1 45-1 74 (m, 7H, H-4, H-5, H-6, and H-8eq), 1 91 (t, *J* = 12 4 Hz, 1H, H-8ax), 2 06 (s, 3H, OAc), 2 10 (dm, *J* = 12 0 Hz, 1H, H-4a), 2 84 (dq, *J* = 10 0, 6 0 Hz, 1H, H-2ax), 2 93 (dt, *J* = 12 4, 4 4 Hz, 1H, H-8a), 3 63 and 3 90 (2d, *J* = 14 8 Hz, 1H each, NCH_2Ar), 3 81-3 94 (m, 4H, OCH_2), 4 60 (td, *J* = 11 0, 5 2 Hz, 1H, H-3ax), 7 18-7 35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, gHSQC) 16 8 (Me), 21 3 (OAc), 26 6 (C-5), 28 1 (C-8), 29 6 (C-4), 29 7 (C-6), 31 4 (C-4a), 52 6 (NCH_2), 53 0 (C-2), 55 8 (C-8a), 64 0 and 64 1 (OCH_2), 75 5 (C-3), 109 8 (C-7), 126 5, 127 7, 128 2, 141 2 (Ar), 170 6 (CO) HRFABMS: calcd for $C_{21}H_{30}NO_4$ 360 2175 (MH^+), found 360 2171

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S**upporting Information Available** Experimental and NMR data for all compounds reported, including Tables of ^{13}C NMR chemical shifts of octahydroindoles and decahydroquinolines reported Copies of ^{1}H and ^{13}C NMR spectra of all new compounds as well as COSY and HSQC spectra when available This material is available free of charge via the Internet at http://pubs acs org

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24 The chemical shift of H-3a and H-7a appears more deshielded in the *exo*-derivatives than in the *endo* compounds, due to the *syn* relationship of the nitrogen lone pair with both protons in the *exo* series (Figure 2)

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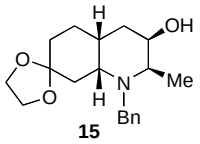
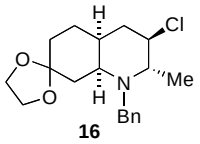
26 Decahydroquinoline **15** was isolated in one run working from alcohol **11a**, although only in 5% yield For ^{13}C NMR data see Table 2 (Supporting Information)



15

27 The use of microwave conditions did not give satisfactory results either

28 Together with chloride **9b**, the expanded product **16** was formed according to the ^{13}C NMR spectrum of the reaction mixture For NMR data of **9b**-**12b**, see Supporting Information



16

29 There are scarcely any examples of ring enlargement via aziridinium ions from secondary alcohols and they are always of the benzylic type: see references 9b and 10b-c

30 It was confirmed in two series that the configuration at C-1' of the side chain was identical to that of the starting alcohol Treatment of **10a** and **11a** with acetic anhydride gave the same acetates **10c** and **11c** as those obtained through sequential treatment with MsCl and Et_3N, then AgOAc

31 The use of silver trifluoroacetate instead of silver acetate slightly increased the yield of the expanded compound, which after a basic work-up gave alcohol **21** (58%), see Scheme 6

32 The use of tetrabutylammonium acetate did not improve the course of the reaction From **9a**, a mixture of acetates **17** (38%) and **9c** (34%) were isolated, whereas from **10a**-**12a** more complex reaction mixtures were formed, the decahydroquinolines **18**, **19**, and **20** being obtained in a yield lower than 10%

Supporting Information

Ring Expansion of Functionalized Octahydroindoles to Enantiopure *cis*-Decahydroquinolines

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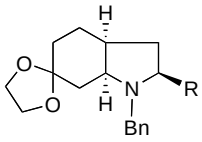
Contents

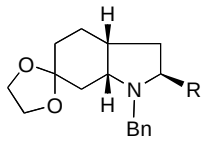
Table 1. ^{13}C NMR Chemical shifts of octahydroindoles 3-12[a]

	3	4	5	6	7	8	9a	10a	11a
C2	66.2	62.9	66.2	61.7	74.9	70.8	71.0	72.5	66.1
C3	33.6	31.7	32.1	30.5	33.3	30.6	30.6	32.2	25.4
C3a	35.7	35.2	35.0	35.6	35.6	35.6	34.6	34.8	35.6
C4	24.0	23.3	24.3	22.8	24.2	22.8	23.9	22.7	22.9
C5	31.0	29.9	31.0	28.9	31.0	29.2	27.5	29.3	28.9
C6	109.1	109.3	108.9	109.4	108.8	109.2	108.9	109.0	109.4
C7	37.5	31.9	37.8	30.6	38.2	30.9	38.2	38.8	30.4
C7a	62.5	59.5	63.0	59.3	63.0	59.4	62.9	63.3	58.9
NCH_2	58.8	53.4	58.8	51.7	60.0	53.4	58.9	63.2	51.4
***ips*-Ar**	139.1	139.0	139.2	139.3	139.2	138.5	140.0	140.0	139.4
***o*-Ar**	129.1	128.8	128.9	128.4	129.4	128.7	129.1	128.3	128.4
***m*-Ar**	127.9	128.1	128.3	128.3	128.1	128.2	128.4	128.3	128.2
***p*-Ar**	126.8	126.9	127.2	127.0	127.1	127.1	127.2	127.0	127.0
C-1'	175.0	174.2	61.2	62.4	213.2	216.4	63.5	71.9	64.7
Me	51.6	51.6	---	---	24.9	24.9	18.2	20.8	18.2
OCH_2	64.3	64.3	64.1	64.3	64.0	64.3	64.0	64.1	64.1
	64.0	64.0	63.9	63.9	64.0	63.9	64.0	63.9	63.8

[a] Values for compounds **3**, **5**, **9a, 10a** and **11a** were assigned on the basis of gHSQC spectra.



3 R = CO_2Me
5 R = CH_2OH
7 R = $COCH_3$
9a R = (*R*)-$CHOHCH_3$
10a R = (*S*)-$CHOHCH_3$

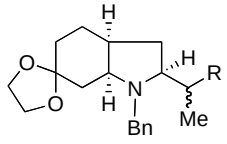


4 R = CO_2Me
6 R = CH_2OH
8 R = $COCH_3$
11a R = (*S*)-$CHOHCH_3$

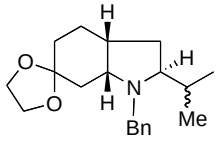
Table 1 continued). ^{13}C NMR Chemical shifts of octahydroindoles 3-12[b]

	12a	9b	10b	11b	12b	9c[c]	10c[c]	11c[c]	12c[c]
C2	66.5	72.1	71.6	66.7	66.4	69.1	68.8	64.4	62.9
C3	30.3	29.7	30.4	28.2	27.1	30.1	31.0	27.7	27.4
C3a	35.3	34.5	34.5	34.6	35.0	34.4	34.6	34.8	35.2
C4	22.7	23.0	23.3	22.8	22.8	23.3	23.2	22.9	22.8
C5	29.0	29.5	29.9	29.7	29.0	29.8	29.7	29.1	29.0
C6	109.4	109.2	109.1	109.5	109.4	109.2	109.1	109.5	109.5
C7	31.2	39.2	39.1	31.0	30.9	39.1	39.3	30.2	30.6
C7a	58.8	62.5	63.7	58.9	58.3	62.2	63.8	58.2	58.4
NCH_2	53.9	61.4	61.3	52.2	52.7	60.4	61.8	52.0	52.5
***ips*-Ar**	139.5	140.6	140.7	139.9	139.8	139.2	141.2	139.8	140.0
***o*-Ar**	128.2	128.3	128.6	128.2	128.2	129.4	128.2	128.1	128.1
***m*-Ar**	127.8	128.1	128.2	128.2	128.1	128.1	128.0	128.0	128.0
***p*-Ar**	126.7	126.6	126.8	126.7	126.8	127.1	126.5	126.6	126.6
C-1'	71.1	63.4	60.6	60.9	59.8	71.1	75.2	70.7	72.3
Me	20.6	22.9	19.8	22.3	17.7	17.1	16.5	16.7	14.5
OCH_2	64.2	64.1	64.0	64.2	64.3	63.9	64.0	64.1	64.2
	63.8	63.8	63.9	63.9	63.9	63.8	63.8	63.8	63.9

[b] Values for compounds **12a**, **10b**, **11b**, **9c, 11c,** and **12c** were assigned on the basis of gHSQC spectra.
[c] OAc: 170.6 / 170.7 and 21.3 /21.5.



9b R = Cl (1'*R*)
10b R = Cl (1'*S*)
9c R = OAc (1'*R*)
10c R = OAc (1'*S*)

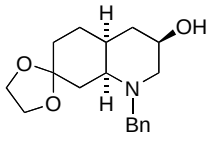


12a R = OH (1'*R*)
11b R = Cl (1'*S*)
12b R = Cl (1'*R*)
11c R = OAc (1'*S*)
12c R = OAc (1'*R*)

Table 2. ^{13}C NMR Chemical shifts of decahydroquinolines 13-21[a]

	13	14	15	16[b]	17	18	19[c]	21
C2	52.0	50.6	57.1	56.0	53.0	51.9	53.2	55.7
C3	68.1	65.4	69.7	61.4	75.5	73.2	73.1	73.6
C4	33.1	30.5	26.8	33.1	29.6	27.0	24.2	33.3
C4a	32.8	28.8	28.3	35.5	31.4	33.6	28.4	32.0
C5	26.9	26.6	26.4	26.7	26.6	25.0	26.8	26.9
C6	29.9	29.8	30.2	32.4	29.7	30.2	30.0	29.9
C7	109.9	109.8	109.3	109.6	109.8	109.4	109.3	109.9
C8	27.0	25.6	33.5	28.9	28.1	34.1	34.7	27.6
C8a	57.0	57.7	56.6	56.2	55.8	56.1	56.9	56.5
Me	---	---	14.9	18.4	16.8	11.5	15.7	16.9
NCH_2	58.3	58.5	55.3	52.7	52.6	55.7	55.9	52.8
Ar	126.8	127.2	127.1	126.5	126.5	126.9	140.2	126.5
	128.1	128.4	128.3	127.6	127.7	128.2	128.3	127.9
	129.5	128.7	128.5	128.1	128.2	128.2	127.9	128.1
	139.3	139.0	n.o.	141.1	141.2	139.8	126.6	140.6
OCH_2	64.2	64.3	63.9	64.0	64.1	64.2	64.2	64.1
	64.1	64.1	64.2	63.7	64.0	63.9	63.9	64.0
Other					170.6	170.4	170.7	
					21.3	21.3	21.4	

[a] Values for compounds **13**, **17**, **18**, **19** and **21** were assigned on the basis of gHSQC spectra [b] Values taken from an NMR spectrum of a mixture of **9b** and **16**. [c] Values taken from an NMR spectrum of a mixture of **11c** and **19**.



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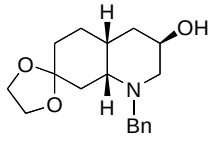

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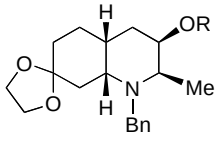
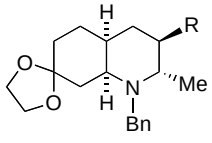
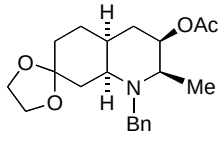


15 R = H
19 R = Ac



16 R = Cl
17 R = OAc
21 R = OH



18

Experimental Section

General: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical thin-layer chromatography was performed on SiO_2 (silica gel 60 F_{254}) or Al_2O_3 (ALOX N/UV_{254}), and the products were located with iodoplatinate spray. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, 230-240 mesh ASTM) or Al_2O_3 (aluminium oxide 90). Drying of organic extracts was performed over anhydrous Na_2SO_4. Evaporation of solvent was accomplished with a rotatory evaporator. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. Only noteworthy IR absorptions (cm^{-1}) are listed.

Methyl 2*S*,3a*S*,7a*S*)-1-Benzyl-6-oxooctahydroindole-2-carboxylate ethylene acetal 3). To a solution of ketone **1** (3.28 g, 11 mmol) in toluene (350 mL) were added a catalytic amount of TsOH and ethyleneglycol (1.84 mL, 33 mmol), and the reaction mixture was heated at reflux temperature for 4 h in a flask incorporating a Dean-Stark apparatus. The cooled solution was diluted with CH_2Cl_2 and washed with aqueous saturated $NaHCO_3$ (100 mL). The organic phase was dried and concentrated to give 3.64 g of **3** as a yellowish oil, which was used in the next step without further purification. An analytical sample was obtained by chromatography (SiO_2, 1% MeOH in CH_2Cl_2). R_f = 0.37 (SiO_2, hexane/EtOAc 3:2); $[\alpha]_D^{20}$ -41 (*c* = 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 1.46-1.58 (m, 1H), 1.64-1.85 (m, 5H), 1.87-1.95 (m, 1H), 2.02-2.11 (m, 1H), 2.13 -2.26 (m, 1H), 2.99 (q, *J* = 7.5 Hz, 1H, H-7a), 3.41 (dd, *J* = 9.1, 7.7 Hz, 1H, H-2), 3.54 (s, 3H, OCH_3), 3.74-3.92 (m, 6H), 7.18-7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, gHSQC), see Table 1. Anal. Calcd for $C_{19}H_{25}NO_4$: C 68.86, H 7.60, N 4.22. Found: C 68.48, H 7.55, N 4.20.

Methyl 2*S*,3a*R*,7a*R*)-1-Benzyl-6-oxooctahydroindole-2-carboxylate ethylene acetal 4). Operating as above, from ketone **2** (1.03 g, 3.6 mmol), acetal **4** was obtained (1.12 g) as yellowish crystals and used in the next step without further purification. An analytical sample was obtained by chromatography (SiO_2, 1% MeOH in CH_2Cl_2): R_f = 0.24 (SiO_2, hexane/EtOAc 3:2); mp 64-66 °C;

$[\alpha]_D^{20}$ -53 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.44-1.72 (m, 4H), 1.79-1.94 (m, 3H), 2.12 (dt, *J* = 12.9, 10.7 Hz, 1H), 2.46 -2.58 (m, 1H), 3.37 (dt, *J* = 10.5, 5.3 Hz, 1H, H-7a), 3.50 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2), 3.55 (s, 3H, OCH_3), 3.74 (d, *J* = 13.2 Hz, 1H), 3.81 (d, *J* = 13.2 Hz, 1H), 3.83 -3.96 (m, 4H), 7.18-7.40 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1. Anal. calcd for $C_{19}H_{25}NO_4$: C 68.86, H 7.60, N 4.22. Found: C 68.56, H 7.85, N 4.24.

2*S*,3a*S*,7a*S*)-1-Benzyl-2-hydroxymethyl-6-oxooctahydroindole ethylene acetal 5). Ester **3** (603 mg, 1.82 mmol) was dissolved in THF (9 mL) and then cooled to 0 ºC. $LiBH_4$ (2 M in THF, 2.8 mL, 5.46 mmol, 3 equiv) was slowly added, and the reaction mixture was stirred at rt for 24 h. The reaction was quenched by adding H_2O (5 mL) and the organic layer was dried and concentrated to give a residue, which was purified by chromatography (SiO_2, 1% MeOH in CH_2Cl_2) to afford 441 mg (80% from **1**) of **5** as a colourless oil: R_f = 0.31 (SiO_2, CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ -15 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.49 (dddd, *J* = 12.0, 5.0, 5.0, 1.2 Hz, 1H, H-5eq), 1.65 (m, 3H, H-5 and H-7), 1.75 (m, 3H, H-3 and H-4), 1.85 (dd, *J* = 12.4, 7.2 Hz, 1H, H-3), 2.20 (m, 1H, H-3a), 2.40 (brs, 1H, OH), 2.98 (dddd, *J* = 8.0, 7.5, 5.4, 1.8 Hz, 1H, H-2), 3.02 (q, *J* = 7.2 Hz, 1H, H-7a), 3.33 (dd, *J* = 11.0, 1.2 Hz, 1H, CH_2OH), 3.42 (dd, *J* = 11.0, 3.6 Hz, 1H, CH_2OH), 3.69-3.88 (m, 6H, OCH_2 and NCH_2), 7.26-7.32 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1. HRFABMS calcd for $C_{18}H_{26}NO_3$ 304.1906 (MH^+), found 304.1913.

2*S*,3a*R*,7a*R*)-1-Benzyl-2-hydroxymethyl-6-oxooctahydroindole ethylene acetal 6). Operating as above from ester **4** (627 mg, 1.89 mmol), alcohol **6** (464 mg, 81% from **2**) was obtained after chromatography (SiO_2, 1% MeOH in CH_2Cl_2), as white crystals: R_f = 0.40 (SiO_2, CH_2Cl_2/MeOH 95:5); mp 72-74 °C; $[\alpha]_D^{20}$ -72 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, COSY, $CDCl_3$) 1.46 (t, *J* = 12.0 Hz, 1H, H-7ax), 1.52 (dq, *J* = 12.5, 2.5 Hz, 1H, H-4eq), 1.63 (dm, *J* = 12.0 Hz, 1H, H-5eq), 1.64 (td, *J* = 10.0, 3.2 Hz, 1H, H-5ax), 1.78 (m, 1H, H-4ax), 1.80 (m, 1H, H-3β), 1.83 (dd, *J* = 12.0, 5.5 Hz, 1H, H-7eq), 2.05 (q, *J* = 12.0 Hz, 1H, H-3α), 2.30 (m, 1H, H-3a), 2.99 (dt, *J* = 10.0, 3.2 Hz, 1H, H-2), 3.24 (ddd, *J* = 12.0, 5.5, 5.5 Hz, 1H, H-7a), 3.38 (dm *J* = 10.8 Hz, 1H, CH_2OH), 3.55 (dd, *J* = 10.8, 3.2 Hz, 1H, CH_2OH), 3.64 and 3.71 (2d, *J* = 13.6 Hz, 1H each,

NCH_2), 3.77-3.93 (m, 4H, OCH_2), 7.26-7.32 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT), see Table 1. Anal. Calcd for $C_{18}H_{25}NO_3$: C 71.26, H 8.31, N 4.62. Found: C 71.05, H 8.20, N 4.57.

2*S*,3a*S*,7a*S*)-2-Acetyl-1-benzyloctahydroindol-6-one ethylene acetal 7). To a solution of ester **3** (2.45 g, 7.4 mmol) in THF (140 mL) cooled to -20 ºC was added Me(MeO)NH.HCl (1.82 g, 18.5 mmol, 2.5 eq) and then over 30 min was added a solution of *i*-PrMgCl in THF (18.5 mL, 2.0 M, 5 equiv) maintaining the temperature at -10 °C. The mixture was stirred for 40 min and quenched with saturated aqueous NH_4Cl solution (50 mL). The organic layer was dried and concentrated to afford 2.65 g of the corresponding Weinreb amide as a yellow oil, which was used without purification: R_f = 0.21 (SiO_2, CH_2Cl_2/MeOH 96:4). To a solution of the aforementioned Weinreb amide (2.65 g, 7.4 mmol) in THF (95 mL) cooled to 0 ºC was added dropwise MeMgBr in Et_2O (6.4 mL, 3 M, 19.24 mmol, 2.6 eq). The reaction mixture was stirred at 0 ºC for 1 h and quenched with saturated aqueous NH_4Cl solution (50 mL). The organic layer was dried and concentrated to give ketone **7** (2.32 g) as an oil, which was used without further purification. R_f = 0.52 (SiO_2, CH_2Cl_2/MeOH 95:5); ^1H NMR (300 MHz, $CDCl_3$) 1.53 (m, 1H), 1.61-1.85 (m, 6H), 2.02 (dt, *J* = 12.3, 7.2 Hz, 1H), 2.04 (s, 3H, CH_3), 2.25 (m, 1H, H-3a), 3.02 (q, *J* = 6.9 Hz, 1H, H-7a), 3.29 (dd, *J* = 9.3, 7.8 Hz, 1H, H-2), 3.63 and 3.83 (2d, *J* = 13.5 Hz, 1H each, NCH_2Ar), 3.75-3.95 (m, 4H, OCH_2), 7.20- 7.35 (m, 5H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

2*S*,3a*R*,7a*R*)-2-Acetyl-1-benzyloctahydroindol-6-one ethylene acetal 8). The above procedure was applied to ester **4** (1.12 g) to afford the corresponding Weinreb amide (1.30 g): R_f = 0.16 (SiO_2, CH_2Cl_2/MeOH 95:5). The Weinreb amide was treated with MeMgBr in Et_2O (3.12 mL, 3 M, 9.36 mmol, 2.6 eq) and operating as in the formation of ketone **7**, 1.21 g of ketone **8** was isolated, which was used without further purification. R_f = 0.49 (SiO_2, CH_2Cl_2/MeOH 95:5); ^1H NMR (300 MHz, $CDCl_3$) 1.40 (t, *J* = 12.0 Hz, 1H, H-5ax), 1.50-1.70 (m, 3H), 1.75-1.90 (m, 3H), 2.07 (s, 3H, CH_3), 2.16 (dt, *J* = 13.5, 11.4 Hz, 1H), 2.50 (m, 1H, H-3a), 3.36 (ddd, *J* = 11.4, 5.7, 5.7 Hz, 1H, H-7a), 3.35 (dd, *J* = 11.0, 1.5 Hz, 1H, H-2), 3.57 and 3.71 (2d, *J* = 13.2 Hz, 1H each, CH_2Ar), 3.75-3.94 (m, 4H, OCH_2), 7.20- 7.35 (m, 5H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT), see Table 1.

Reduction of ketone 7. To a solution of amino ketone **7** (2.29 g, 7.25 mmol) in MeOH (85 mL) at -20 °C was added $NaBH_4$ (571 mg, 14.5 mmol) in small portions. The resulting mixture was maintained at this temperature for 6 h. Then, water (25 mL) was added and the mixture was extracted with Et_2O (3x50 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by chromatography (SiO_2, hexane to hexane/EtOAc 1:1) provided 1.05 g (46%) of alcohol **9a** as a colourless oil and 862 mg (37%) of alcohol **10a** as a colorless oil, after two succesive purifications. Overall yield for three steps (**3** → **9a** + **10a**): 83%; 1.2:1 ratio of alcohols **9a**:**10a**.

2*S*,3a*S*,7a*S*)-1-Benzyl-2-[1'*R*)- 1-hydroxyethyl)]octahydroindol-6-one ethylene acetal 9a): R_f = 0.30 (SiO_2, CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ - 41 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, *g*COSY) 1.09 (d, *J* = 6.6 Hz, 3H, CH_3), 1.43-1.81 (m, 8H, H-3, H-4, H-5, and H-7), 2.20 (m, 1H, H-3a), 2.80 (ddd, *J* = 9.3, 6.9, 3.3 Hz, 1H, H-2), 3.02 (q, *J* = 7.2 Hz, 1H, H-7a), 3.66-3.85 (m, 7H, H-1', NCH_2Ar, and OCH_2), 7.26-7.32 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1. HRFABMS: calcd for $C_{19}H_{28}NO_3$ 318.2069 (MH^+), found 318.2070.

2*S*,3a*S*,7a*S*)-1-Benzyl-2-[1'*S*)- 1-hydroxyethyl)]octahydroindol-6-one ethylene acetal 10a): R_f = 0.30 (SiO_2, CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ - 32 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.16 (d, *J* = 6.4 Hz, 3H, CH_3), 1.50 (m, 2H, H-5 and H-7), 1.60 (m, 2H, H-3 and H-5), 1.63 (t, *J* = 12.0 Hz, 1H, H-7ax), 1.77 (m, 2H, H-4), 1.88 (ddd, *J* = 12.0, 8.0, 7.0 Hz, 1H, H-3), 2.34 (m, 1H, H-3a), 2.82 (q, *J* = 7.5 Hz, 1H, H-2), 2.97 (dt, *J* = 12.0, 6.0 Hz, 1H, H-7a), 3.54 (quint, *J* = 6.2 Hz, 1H, H-1'), 3.74-3.86 (m, 6H, OCH_2, NCH_2Ar), 7.20-7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1. HRFABMS: calcd for $C_{19}H_{28}NO_3$ 318.2069 (MH^+), found 318.2074.

Reduction of ketone 8. The above procedure was followed using ketone **8** (1.06 g, 3.36 mmol). Purification by chromatography (SiO_2, hexane to hexane-EtOAc 1:1) afforded 622 mg (54%) of alcohol **11a** as a white solid and then 365 mg (32%) of alcohol **12a** as a white solid. Overall yield for three steps (**4** → **11a** + **12a**): 86%; 1.7:1 ratio of alcohols **11a** and **12a**.

2*S*,3a*R*,7a*R*)-1-Benzyl-2-[1'*S*)- 1-hydroxyethyl)]octahydroindol-6-one ethylene acetal 11a): R_f = 0.22 (SiO_2, CH_2Cl_2/MeOH 98:2); mp 73-75 °C; $[\alpha]_D^{20}$ -100 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.13 (d, *J* = 6.4 Hz, 3H, CH_3), 1.41 (t, *J* = 12.0 Hz, 1H, H-7ax), 1.50 (dm, *J* = 12.0 Hz, 1H), 1.60-1.68 (m, 2H), 1.73-1.90 (m, 4H), 2.21 (m, 1H, H-3a), 2.76 (dq, *J* = 10.0, 2.4 Hz, 1H, H-2), 3.21 (ddd, *J* = 12.0, 5.5, 5.5 Hz, 1H, H-7a), 3.61 and 3.77 (2d, *J* = 14.0 Hz, 1H each, NCH_2Ar), 3.78-3.93 (m, 5H, OCH_2 and H-1'), 7.20-7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1. HRFABMS: calcd for $C_{19}H_{28}NO_3$ 318.2069 (MH^+), found 318.2074.

2*S*,3a*R*,7a*R*)-1-Benzyl-2-[1'*R*)- 1-hydroxyethyl)]octahydroindol-6-one ethylene acetal 12a): R_f = 0.11 (SiO_2, CH_2Cl_2/MeOH 98:2); mp 91-93 °C; $[\alpha]_D^{20}$ - 36 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, *g*COSY) 1.22 (d, *J* = 6.6 Hz, 3H, CH_3), 1.43 (t, *J* = 12.0 Hz, 1H, H-7ax), 1.50-1.75 (m, 4H, H-3, H-4, H-5, H-7), 1.80 (m, 2H, H-4 and H-5), 2.15 (m, 1H, H-3), 2.32 (m, 1H, H-3a), 2.88 (ddd, *J* = 9.8, 4.8, 2.2 Hz, 1H, H-2), 3.22 (ddd, *J* = 11.0, 5.4, 5.4 Hz, 1H, H-7a), 3.69 (m, 1H, H-1'), 3.73-3.92 (m, 6H, NCH_2 and OCH_2), 3.96 (br s, 1H, OH), 7.20-7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1. HRFABMS: calcd for $C_{19}H_{28}NO_3$ 318.2069 (MH^+), found 318.2063.

Conversion of alcohols 9a-12a to their corresponding chlorides 9b-12b.

Compounds **9b**-**12b** were prepared according to the following procedure: to a solution of alcohol (**9a**-**12a**, 50 mg, 0.16 mmol) in THF (1 mL) at 0 ºC was added MsCl (0.014 mL, 0.18 mmol, 1.1 equiv), followed by Et_3N (0.09 mL, 0.64 mmol, 4.0 equiv). After 4 h at reflux, the reaction mixture was poured into an aqueous 2.5 M NaOH solution (1 mL). After extraction with CH_2Cl_2 (3 x 2 mL), the organic phase was dried and concentrated to afford compounds **9b**-**12b**, which were used without further purification.

2*S*,3a*S*,7a*S*)-1-Benzyl-2-[1'*R*)- 1-chloroethyl)]octahydroindol-6-one ethylene acetal 9b). This compound was obtained together with the expanded chloride **16**; ^{1}H NMR (300 MHz, $CDCl_3$) 1.53 (d, *J* = 6.6 Hz, 3H, CH_3), 1.40-2.10 (m, 8H), 2.25 (m, 1H), 2.85-3.00 (m, 2H), 3.80-4.00 (m,

7H), 7.20-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), see Table 1. HRFABMS calcd for $C_{19}H_{27}{}^{35}ClNO_3$ 336.1730 (MH^+), found 336.1731.

2*S*,3a*S*,7a*S*)-1-Benzyl-2-[1'*S*)- 1-chloroethyl)]octahydroindol-6-one ethylene acetal 10b): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.49 (d, *J* = 6.8 Hz, 3H, CH_3), 1.55-1.65 (m, 4H, H-5 and H-7), 1.70-1.80 (m, 3H, H-3, H-4), 1.88 (ddd, *J* = 12.0, 8.0, 7.0 Hz, 1H, H-3), 2.25 (m, 1H, H-3a), 2.94 (dt, *J* = 10.5, 6.8 Hz, 1H, H-7a), 3.15 (dt, *J* = 9.2, 6.4 Hz, 1H, H-2), 3.73 and 3.87 (2d, *J* = 13.5 Hz, 1H each, NCH_2Ar), 3.70-3.84 (m, 4H, OCH_2), 3.95 (dq, *J* = 11.5, 6.4 Hz, 1H, H-1'), 7.20-7.38 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1) . HRFABMS calcd for $C_{19}H_{27}{}^{35}ClNO_3$ 336.1730 (MH^+), found 336.1727.

2*S*,3a*R*,7a*R*)-1-Benzyl-2-[1'*S*)- 1-chloroethyl)]octahydroindol-6-one ethylene acetal 11b): white solid; ^{1}H NMR (400 MHz, $CDCl_3$, *g*COSY) 1.39 (t, *J* = 12.0 Hz, 1H, H-7ax), 1.44 (d, *J* = 6.8 Hz, 3H, CH_3) 1.50-1.65 (m, 4H, H-3 and H-4), 1.75-1.95 (m, 3H, H-7eq and H-5), 2.42 (m, 1H, H-3a), 2.96 (dt, *J* = 10.0, 3.0 Hz, 1H, H-2), 3.23 (ddd, *J* = 11.6, 5.6, 5.6 Hz, 1H, H-7a), 3.72 and 3.84 (2d, *J* =14 Hz, 1H each, NCH_2), 3.78-3.90 (m, 4H, OCH_2), 4.05 (qd, *J* = 6.8, 3.2 Hz, 1H, H-1'), 7.20-7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, *g*HSQC), see Table 1. HRFABMS calcd for $C_{19}H_{27}{}^{35}ClNO_3$ 336.1730 (MH^+), found 336.1741.

2*S*,3a*R*,7a*R*)-1-Benzyl-2-[1'*R*)- 1-chloroethyl)]octahydroindol-6-one ethylene acetal 12b): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 1.48 (d, *J* = 6.6 Hz, CH_3), 1.40-2.05 (m, 8H), 2.25 (m, 1H), 3.20 (m, 2H), 3.6-4.0 (m, 7H), 7.20-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), see Table 1.

Ring expansion of chlorides 9b-12b

Method A. A solution of the appropriate chloride derivative **9b**-**12b** (0.16 mmol) in THF (1 mL) was treated with AgOAc (0.48 mmol, 3 equiv) at reflux for 4 h. The reaction mixture was filtered through a bed of Celite and diluted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ (10 mL), dried and concentrated to afford the corresponding mixture of acetates **9c-12c** and **17-20**. (See Table 1 in the main paper for results in each series and below for the NMR data of formed acetates).

- From **9b**, a mixture of acetates **9c** and **17** was obtained (80% overall yield) in a 1:1.3 ratio according to the NMR spectrum. Purification and separation of the compounds was performed by chromatography (SiO_2, CH_2Cl_2/EtOAc; 9:1).
- From **10b**, a mixture of acetates **10c** and **18** was obtained (70 % overall yield) in a 2.9:1 ratio according to the NMR spectrum. Purification and separation of the compounds was performed by chromatography (SiO_2, CH_2Cl_2/EtOAc; 9:1).
- From **11b**, a non-separable mixture of acetates **11c** and **19** was obtained (80 % overall yield) in a 5.7:1 ratio according to the NMR spectrum and GC-MS analysis. Purification of the mixture of compounds was performed by chromatography (SiO_2, CH_2Cl_2/EtOAc 9:1).
- From **12b**, a non-separable mixture of acetates **12c** and **20** was formed (60 % overall yield) in a 13:1 ratio according to the NMR spectrum. Purification of the mixture of compounds was performed by chromatography (SiO_2, CH_2Cl_2/EtOAc 9:1).

Ring expansion of alcohols 9a-12a

***Method B*.** A solution of the appropriate alcohol derivative **9a** – **12a** (0.16 mmol) in THF (1 mL) was treated with MsCl (0.19 mmol, 1.2 equiv) and Et_3N (0.64 mmol, 4 equiv) under an argon atmosphere at – 20 ºC for 1 h. AgOAc (0.48 mmol, 3 equiv) was added and the resulting mixture was warmed to rt over a period of 1 h. The reaction mixture was filtered through a bed of Celite and diluted with CH_2Cl_2. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (10 mL), dried and concentrated to afford the corresponding mixture of acetates.

From 9a. A mixture of acetates **9c** and **17** was obtained in a 1:2.2 ratio according the NMR spectrum in 78 % yield. Purification and separation of the compounds was performed by chromatography (SiO_2, CH_2Cl_2/EtOAc 9:1). For analytical data of **9c** and **17**, see the main text and Tables 1 and 2.

From 10a. A mixture of acetates **10c** and **18** was obtained in a 1.1:1 ratio according the NMR spectrum in 66 % yield. Purification and separation of the compounds was performed by chromatography (SiO_2, CH_2Cl_2/EtOAc 9:1).

2*S*,3a*S*,7a*S*)-1-Benzyl-2-[1'*S*)- 1-acetoxyethyl)]octahydroindol-6-one ethylene acetal 10c): Colourless oil. R_f = 0.26 (SiO_2, CH_2Cl_2/EtOAc 9:1). $[\alpha]_D^{20}$ - 57 (*c* 0.2, $CHCl_3$); IR 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 1.21 (d, *J* = 6.0 Hz, 3H, CH_3), 1.50 (t, *J* = 11.0 Hz, 1H, H-5), 1.50-1.80 (m, 7H), 1.90 (s, 3H, OAc), 2.25 (m, 1H, H-3a), 2.85 (dt, *J* = 11.0, 6.4 Hz, 1H, H-7a), 3.00 (dt, *J* = 10.0, 7.0 Hz, 1H, H-2), 3.70 and 3.94 (2d , *J* = 14.0 Hz, 1H each, NCH_2Ar), 3.74-3.86 (m, 4H, OCH_2), 4.91 (quint, *J* = 6.2 Hz, 1H, H-1'), 7.20-7.35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), see Table 1. HRFABMS: calcd for $C_{21}H_{30}NO_4$ 360.2175 (MH^+), found 360.2163.

2*R*,3*R*,4a*S*,8a*S*)-3-Acetoxy-1-benzyl-2-methyl-7-oxodecahydroquinoline ethylene acetal 18): Colourless oil. R_f = 0.58 (SiO_2, CH_2Cl_2/EtOAc 9:1). $[\alpha]_D^{20}$ - 24 (*c* 1.0, $CHCl_3$); IR 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 1.10 (d, *J* = 7.0 Hz, 3H, CH_3), 1.48 (m, 1H, H-5), 1.52 (m, 1H, H-4), 1.59 (m, 2H, H-6), 1.72 (t, *J* = 12.4 Hz, 1H, H-8ax), 1. 80 (m, 1H, H-5), 1.87 (brt, *J* = 13.0 Hz, 1H, H-4ax), 1.94 (dm, *J* = 12.4 Hz, 1H, H-8eq), 2.00 (s, 3H, OAc), 2.08 (m, 1H, H-4a), 3.00 (dt, *J* = 12.8, 4.4 Hz, 1H, H-8a), 3.20 (q, *J* = 6.5 Hz, 1H, H-2); 3.78 and 3.84 (2d, *J* = 14.4 Hz, 1H each, NCH_2Ar), 3.86-3.95 (m, 4H, OCH_2), 4.99 (ddd, *J* = 12.0, 5.6, 4.4 Hz, 1H, H-3), 7.20-7.35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 2 HRFABMS: calcd for $C_{21}H_{30}NO_4$ 360.2175 (MH^+), found 360.2171.

From 11a. **11c** and **19** were obtained in a 2.2:1 ratio according the NMR spectrum in 76 % yield as a unseparable mixture. Purification of the mixture of compounds was performed by chromatography (SiO_2, CH_2Cl_2/EtOAc 9:1).

2*S*,3a*R*,7a*R*)-1-Benzyl-2-[1'*S*)- 1-acetoxyethyl)]octahydroindol-6-one ethylene acetal 11c): Colourless oil. R_f = 0.31 (SiO_2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 1.23 (d, *J* = 6.4 Hz, 3H, CH_3), 1.35 (t, *J* = 12.4 Hz, 1H, H-7ax), 1.45-2.05 (m, 7H), 2.07 (s, 3H, OAc), 2.25 (m, 1H, H-3a), 2.89 (dt, *J* = 10.0, 2.8 Hz, 1H, H-2), 3.08 (dt, *J* = 12.0, 6.0 Hz, 1H, H-7a), 3.52 and 3.88 (2d, *J* = 13.6 Hz, 1H each, NCH_2), 3.80-4.00 (m, 4H, OCH_2), 5.14 (qd, *J* = 6.4, 2.4 Hz, 1H, H-1'), 7.15-7.35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1. HRFABMS: calcd for $C_{21}H_{30}NO_4$ 360.2175 (MH^+), found 360.2158.

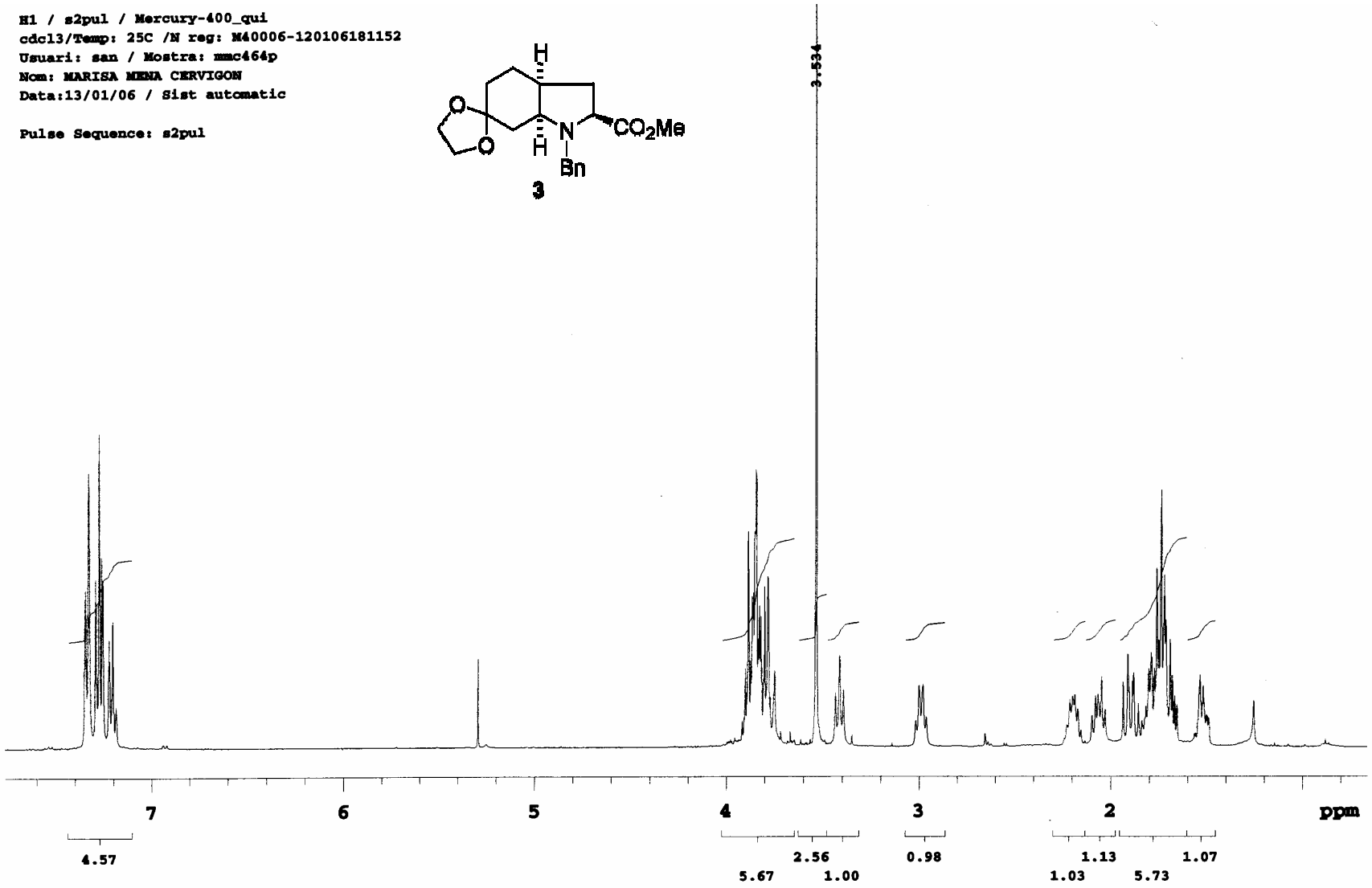
2*R*,3*R*,4a*R*,8a*R*)-3-Acetoxy-1-benzyl-2-methyl-7-oxodecahydroquinoline ethylene acetal 19): Colourless oil. R_f = 0.31 (SiO_2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 1.04 (d, *J* = 7.2 Hz, 3H, CH_3), 1.45-2.05 (m, 8H), 2.07 (s, 3H, OAc), 2.34 (m, 1H, H-4a), 2.89 (qd, *J* = 7.2, 1.2 Hz, 1H, H-2ax), 3.09 (dt, *J* = 11.5, 4.4 Hz, 1H, H-8a), 3.68-3.80 (m, 6H, NCH_2Ar and OCH_2), 4.82 (q, *J* = 2.8 Hz, 1H, H-3eq), 7.15-7.30 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), see Table 2. HRFABMS: calcd for $C_{21}H_{30}NO_4$ 360.2175 (MH^+), found 360.2158.

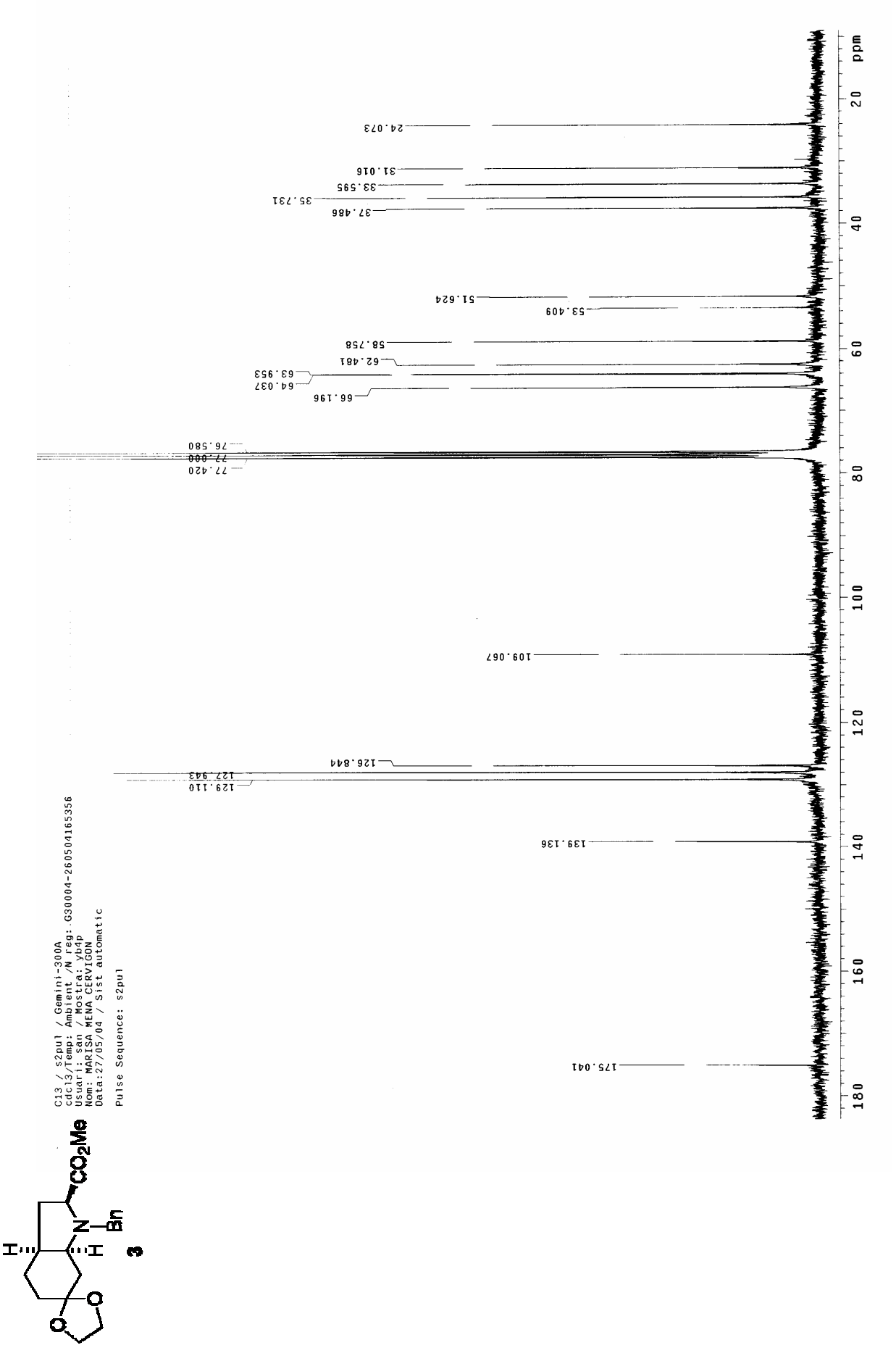
From 12a. Acetate **12c** and traces of **20** were formed in a 13:1 ratio, according the NMR spectrum and GC-MS analysis, in 40% yield as a unseparable mixture. Purification of the mixture of compounds was performed by chromatography (SiO_2, CH_2Cl_2/EtOAc 9:1).

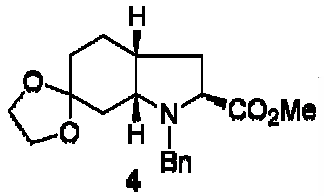
2*S*,3a*R*,7a*R*)-1-Benzyl-2-[1'*R*)- 1-acetoxyethyl)]octahydroindol-6-one ethylene acetal 12c): White Solid. R_f = 0.31 (SiO_2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.24 (d, *J* = 6.4 Hz, 3H, CH_3), 1.37 (t, *J* = 12.0 Hz, 1H, H-7ax), 1.49 (dm, *J* = 12.0 Hz, 1H, H-5eq), 1.60-1.70 (m, 3H, H-5 and H-4), 1.75 (m, 1H, H-3),1.80-1.90 (m, 2H, H-3 and H-7eq), 1.96 (s, 3H, OAc), 2.28 (m, 1H, H-3a), 3.05 (ddd, *J* = 8.8, 6.4, 2.8 Hz, 1H, H-2), 3.15 (ddd, *J* = 11.2, 5.6, 5.6 Hz, 1H, H-7a), 3.69 and 3.88 (2d, *J* = 14.4 Hz, 1H each, NCH_2Ar), 3.73-3.90 (m, 4H, OCH_2), 4.95 (quint, *J* = 6.4 Hz, 1H, H-1'), 7.20-7.35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), see Table 1. HRFABMS: calcd for $C_{21}H_{30}NO_4$ 360.2175 (MH^+), found 360.2163.

Ring expansion of octahydroindole 9a using silver trifluoroacetate. A solution of alcohol **9a** (62 mg, 0.2 mmol) in THF (1.4 mL) was treated with MsCl (0.019 mL, 0.24 mmol, 1.2 equiv) and Et_3N (0.11 mL, 0.8 mmol, 4 equiv) under argon atmosphere at – 20 ºC for 1 h. CF_3CO_2Ag was added (221 mg, 1 mmol, 5 equiv) and the resulting mixture was warmed to room temperature over a period of 1 h. The mixture was treated with 2.5 N NaOH (1 mL) and stirred for 3 h. The reaction mixture was filtered through a bed of Celite and diluted with CH_2Cl_2. The organic layer was dried and concentrated to afford a mixture of **9a** and **21**, which was purified by chromatography (Al_2O_3, hexane/EtOAc 9:1) to give 16 mg (26%) of **9a** and 36 mg (58%) of (2*S*,3*R*,4a*S*,8a*S*)-1-Benzyl-3-hydroxy-2-methyl-7-oxodecahydroquinoline ethylene acetal (**21**): Colourless oil. R_f = 0.10 (Al_2O_3,

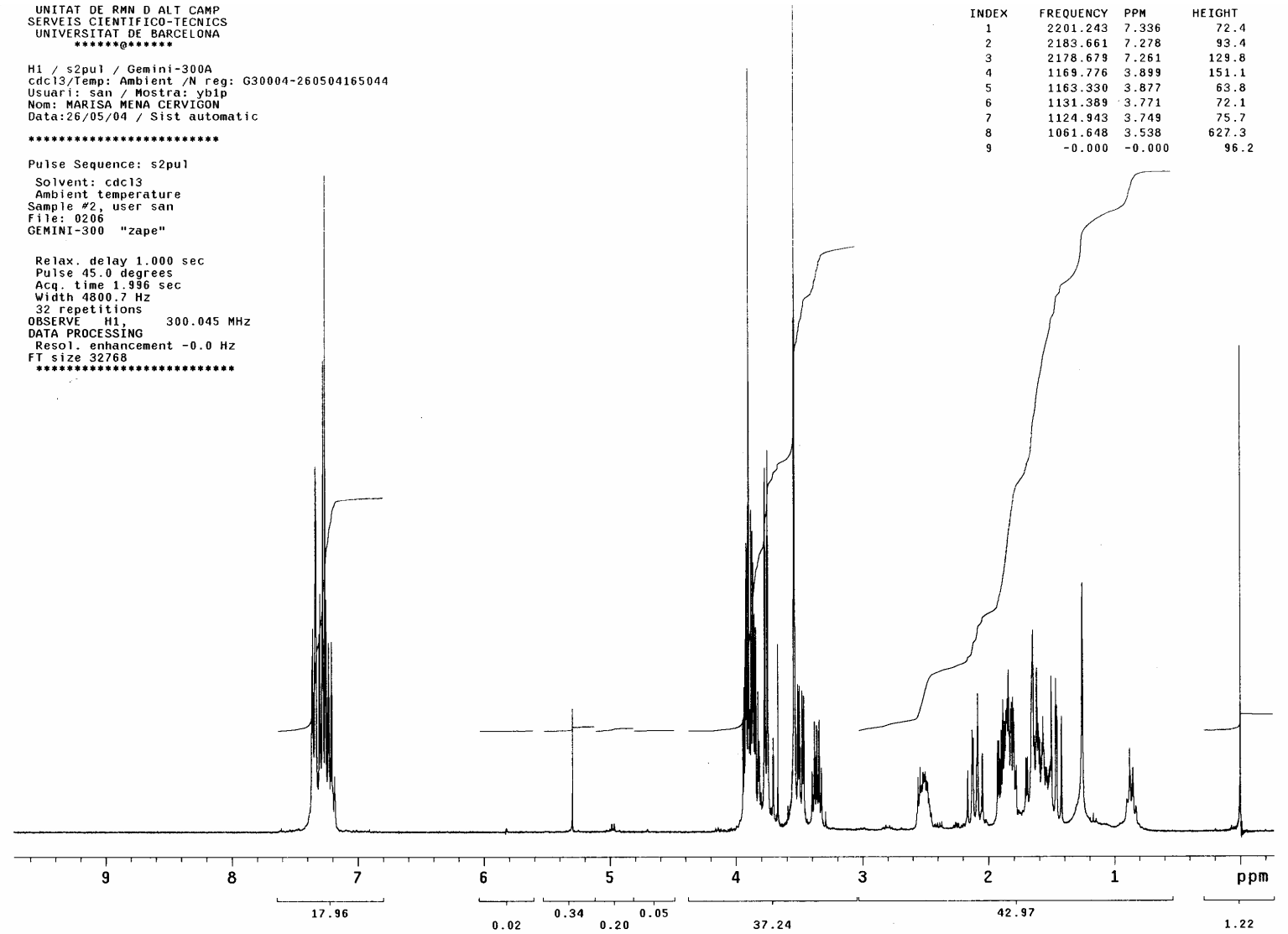
Hexane/EtOAc 8:2). $[\alpha]_D^{20}$ +1.5 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, COSY) 1.17 (d, *J* = 6.0 Hz, 3H, CH_3), 1.43-1.49 (m, 2H, H-5 and H-6), 1.55-1.74 (m, 5H, H-4, H-5, H-6, and H-8eq), 1.88 (t, *J* = 12.6 Hz, 1H, H-8ax), 2.04 (m, 1H, H-4a), 2.57 (dq, *J* = 9.0, 6.0 Hz, 1H, H-2ax), 2.93 (dt, *J* = 12.6, 4.5 Hz, 1H, H-8a), 3.36 (td, *J* = 9.0, 7.2 Hz, 1H, H-3ax), 3.57 and 3.90 (2d, *J* = 14.4 Hz each, NCH_2Ar), 3.79-3.94 (m, 4H, OCH_2), 7.18-7.35 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, gHSQC), see Table 2. HRFABMS: calcd for $C_{19}H_{28}NO_3$ 318.2069 (MH^+), found 318.2064.

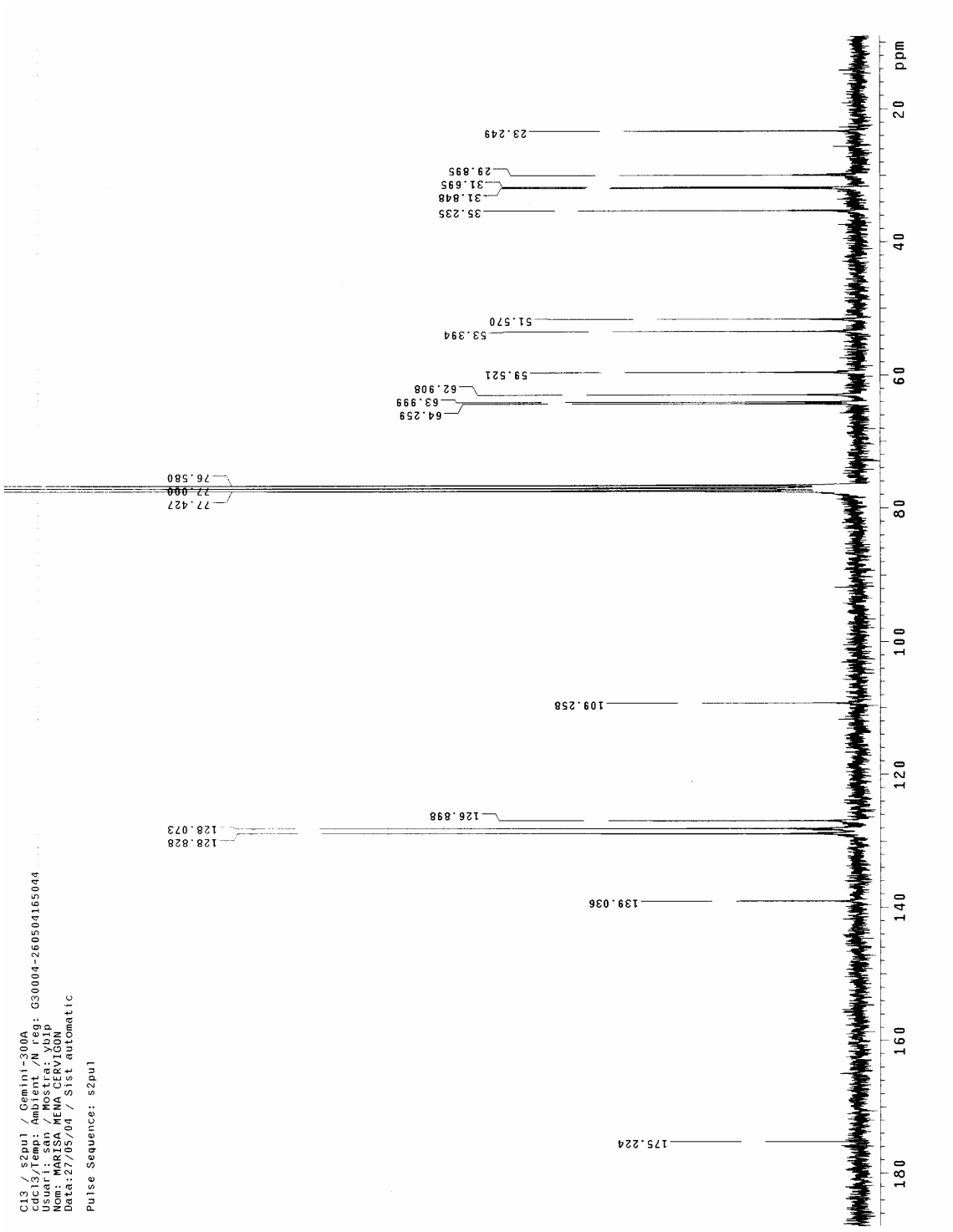

H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40006-120106181152
Usuari: san / Mostra: mmc464p
Nom: MARISA MENA CERVIGON
Data:13/01/06 / Sist automatic
Pulse Sequence: s2pul
H
O
O
H
N
Bn
CO2Me
3
3.534
7
6
5
4
3
2
ppm
4.57
5.67
2.56
1.00
0.98
1.03
1.13
5.73
1.07

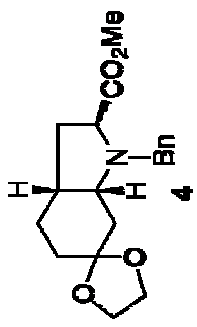

C13 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: G30004-260504165356
Usuario:san /Mostra:.yd4p
Nom: MARISA MENA CERVIGON
Data:27/05/04 / Sist automatic
Pulse Sequence: s2pul
24.073
31.016
33.595
35.731
37.486
51.624
53.409
58.758
62.481
63.953
64.037
66.196
76.580
77.000
77.420
109.067
126.844
127.943
129.110
139.136
175.041
ppm
20
40
60
80
100
120
140
160
180
CO2Me
N
Bn
H
H
O
O
3

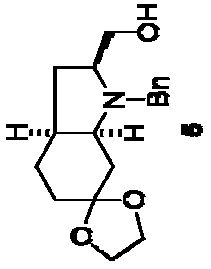

H
O
O
H
N
Bn
CO2Me

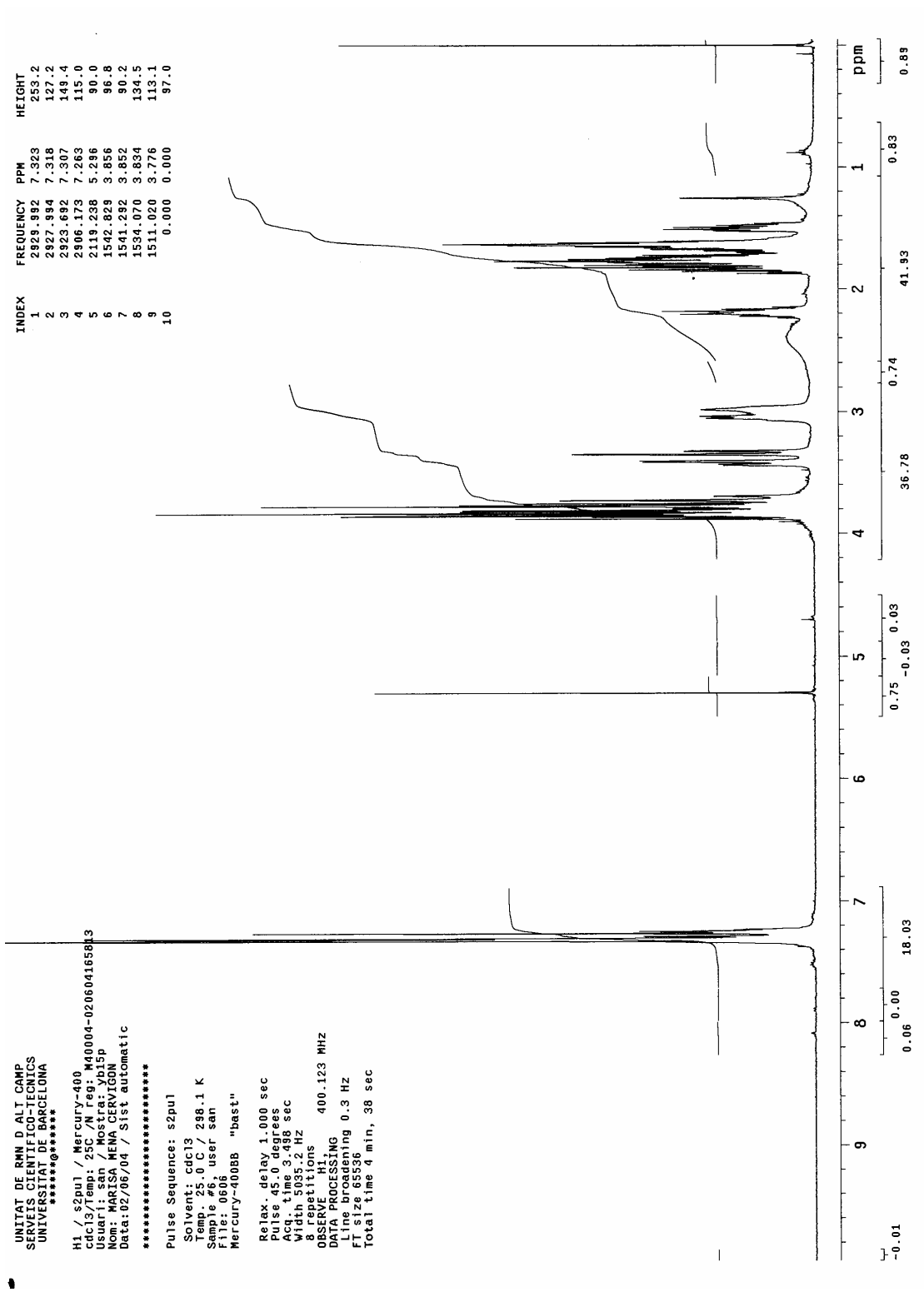
4

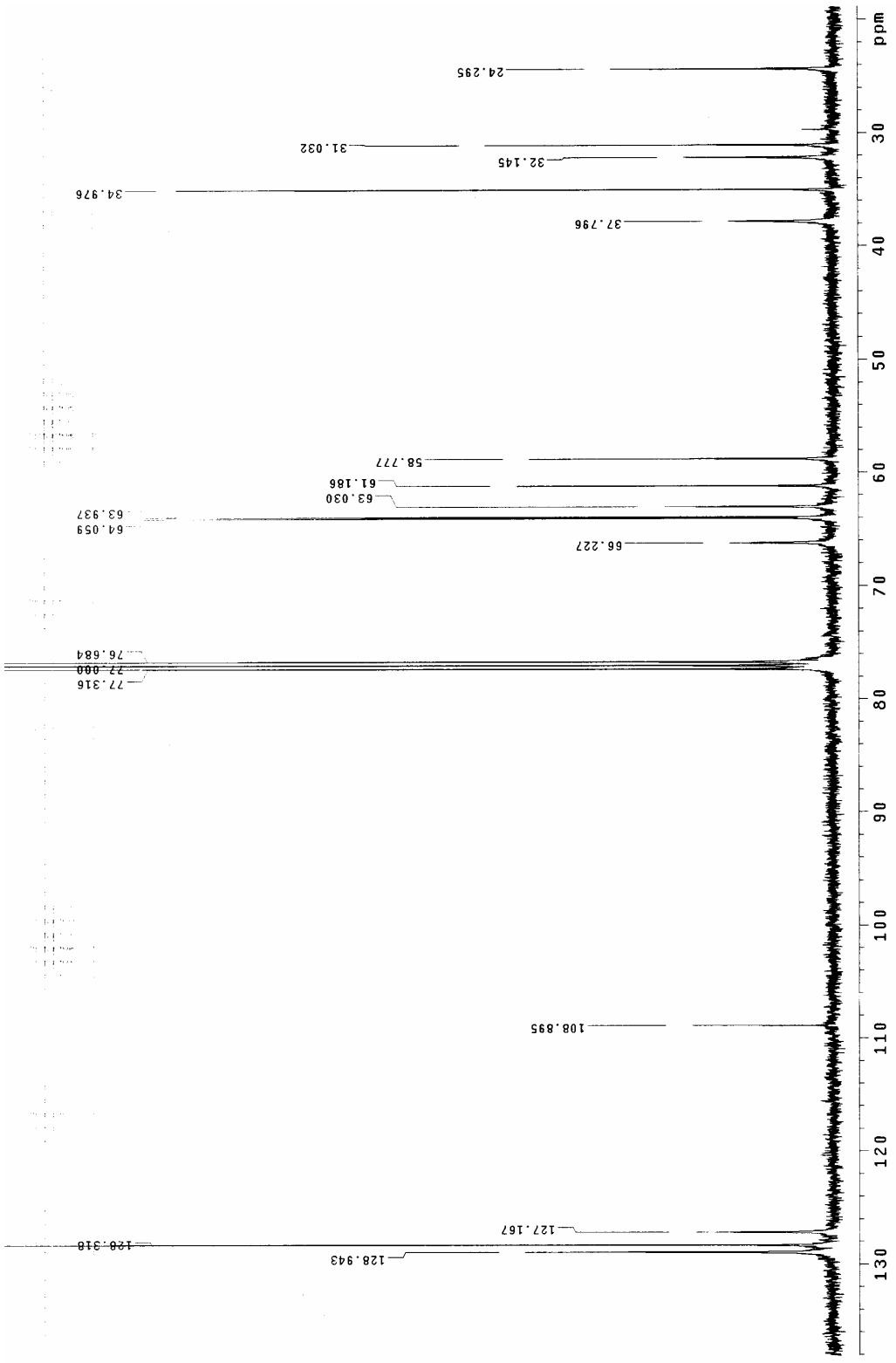

UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
******@******
H1 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: G30004-260504165044
Usuari: san / Mostra: yb1p
Nom: MARISA MENA CERVIGON
Data:26/05/04 / Sist automatic
****
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #2, user san
File: 0206
GEMINI-300 "zape"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.996 sec
Width 4800.7 Hz
32 repetitions
OBSERVE H1, 300.045 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 32768
****
INDEX FREQUENCY PPM HEIGHT
1 2201.243 7.336 72.4
2 2183.661 7.278 93.4
3 2178.679 7.261 129.8
4 1169.776 3.899 151.1
5 1163.330 3.877 63.8
6 1131.389 3.771 72.1
7 1124.943 3.749 75.7
8 1061.648 3.538 627.3
9 -0.000 -0.000 96.2
9
8
7
6
5
4
3
2
1
ppm
17.96
0.02
0.34
0.20
0.05
37.24
42.97
1.22

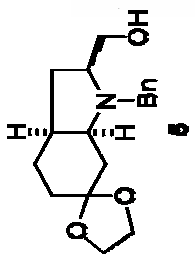

C13 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: G30004-26050416504 4
Usuari: san / Mostra: ybip
Nom: MARISA MENA CERVIGON
Data:27/05/04 / Sist automatic
Pulse Sequence: s2pul
23.249
29.895
31.695
31.848
35.235
51.570
53.394
59.521
62.908
63.999
64.259
76.580
77.000
77.427
109.258
126.898
128.073
128.828
139.036
175.224
ppm

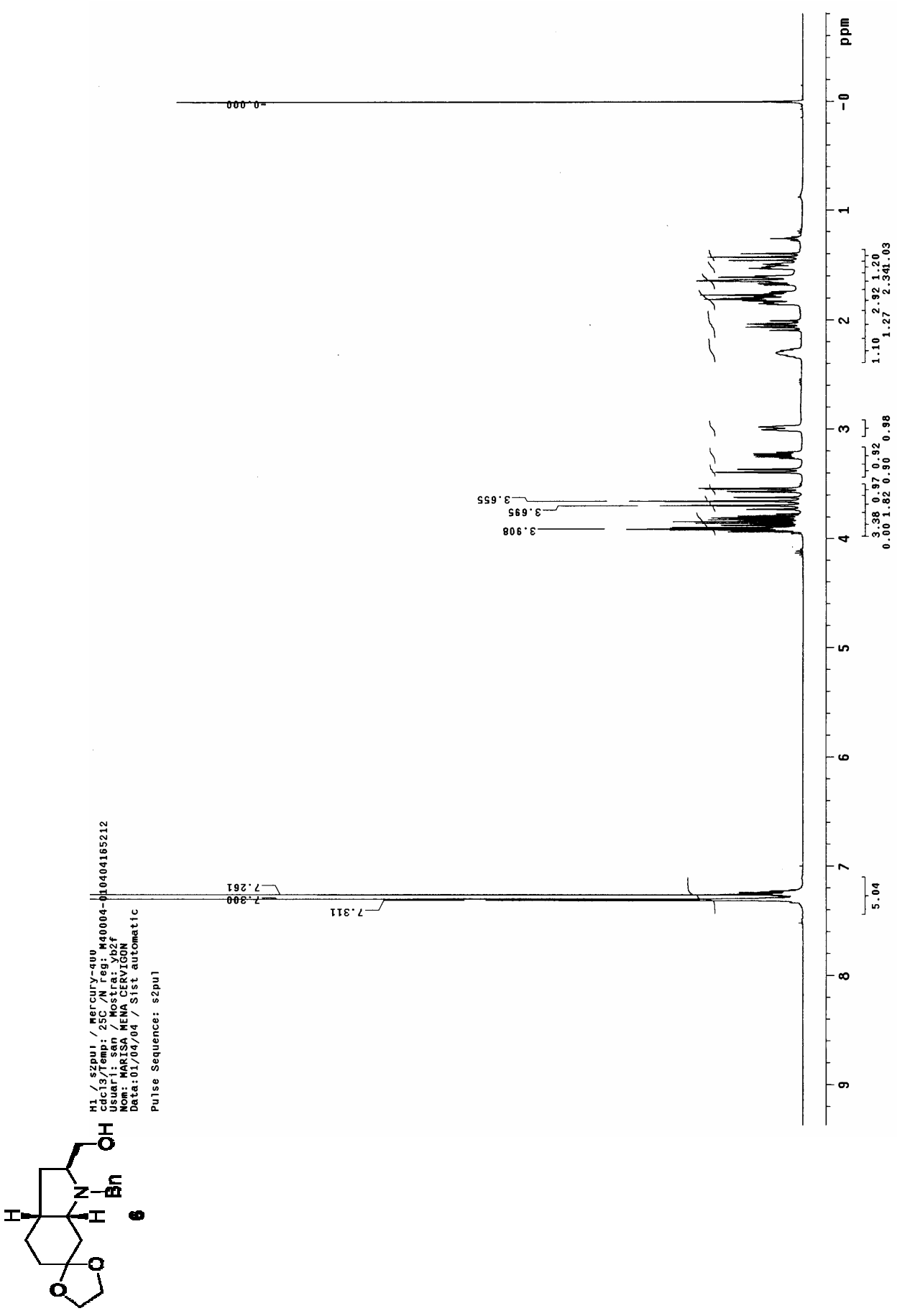

CO2Me
N
Bn
H
H
O
O
4

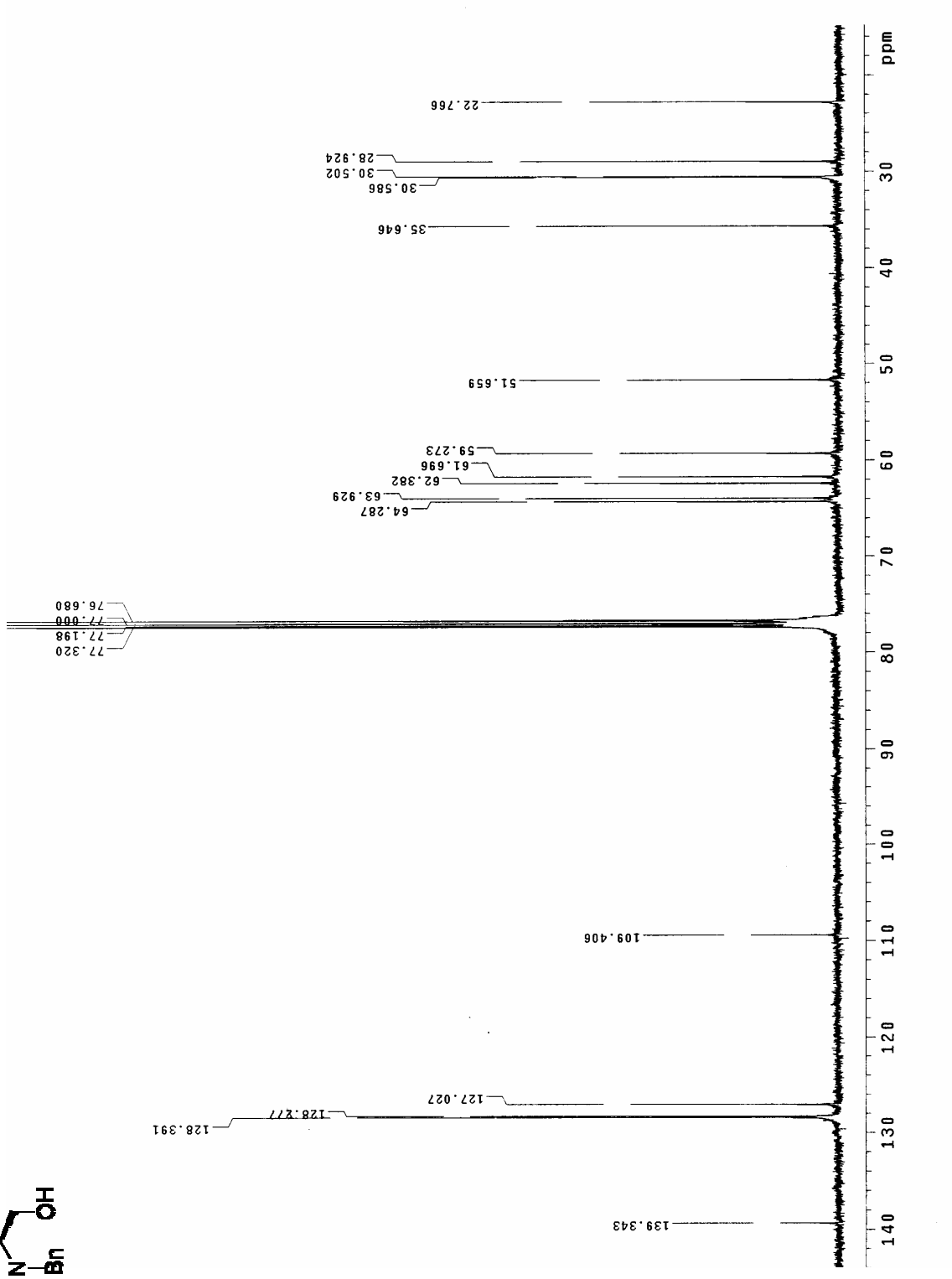


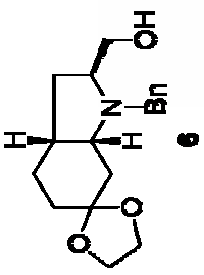

UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #6, user san
File: 0606
Mercury-400BB "bast"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.498 sec
Width 5035.2 Hz
8 repetitions
OBSERVE H1 400.123 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
Total time 4 min, 38 sec
INDEX FREQUENCY PPM HEIGHT
1 2929.992 7.323 253.2
2 2927.994 7.318 127.2
3 2923.692 7.307 149.4
4 2906.173 7.263 115.0
5 2119.238 5.296 90.0
6 1542.829 3.856 96.8
7 1541.282 3.852 90.2
8 1534.070 3.834 134.5
9 1511.020 3.776 113.1
10 0.000 0.000 97.0
ppm


24.295
31.032
32.145
34.976
37.796
58.777
61.186
63.030
63.937
64.059
66.227
76.684
77.000
77.316
108.895
127.167
128.318
128.943
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130

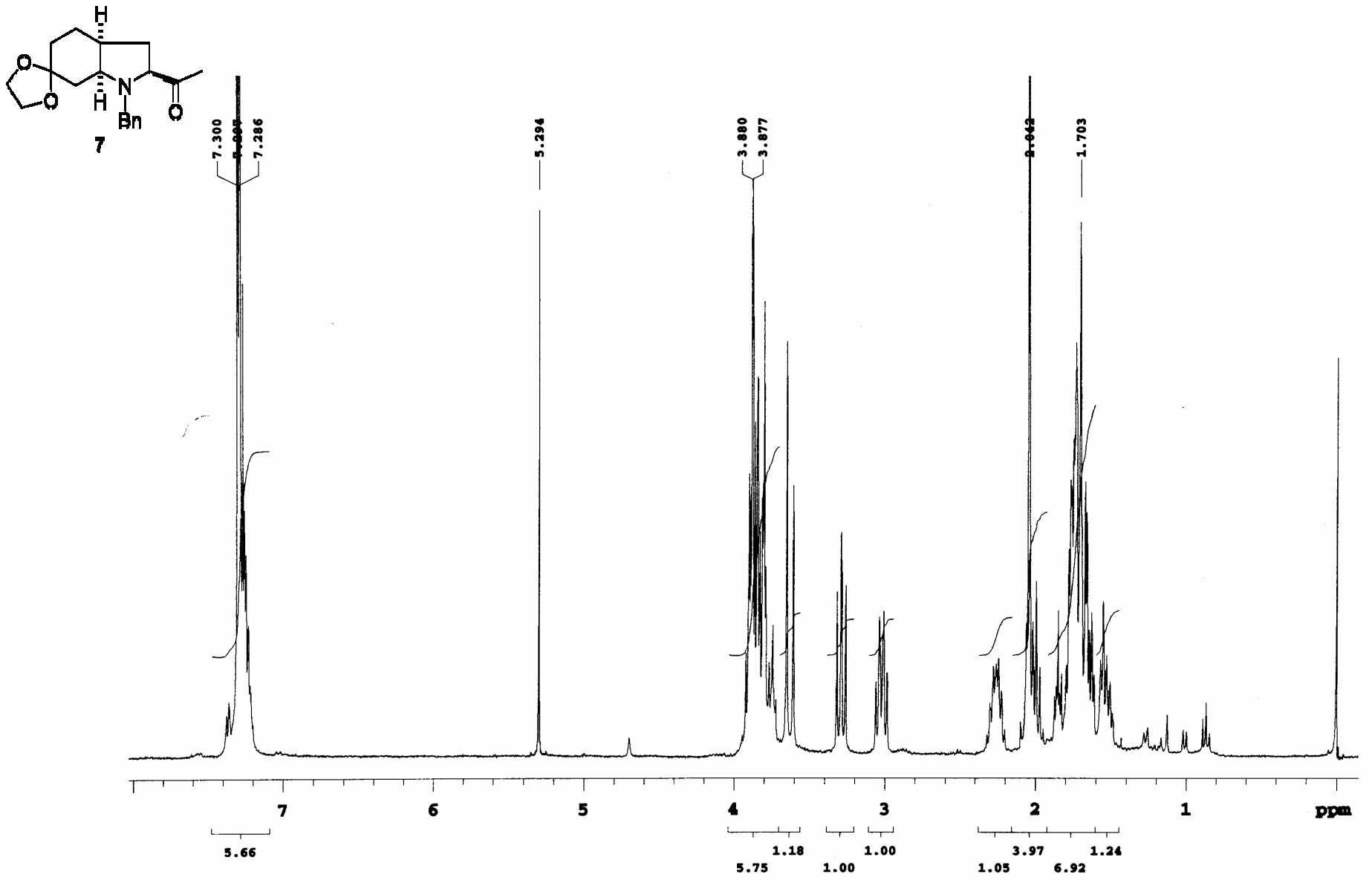

OH
N
Bn
H
H
O
O

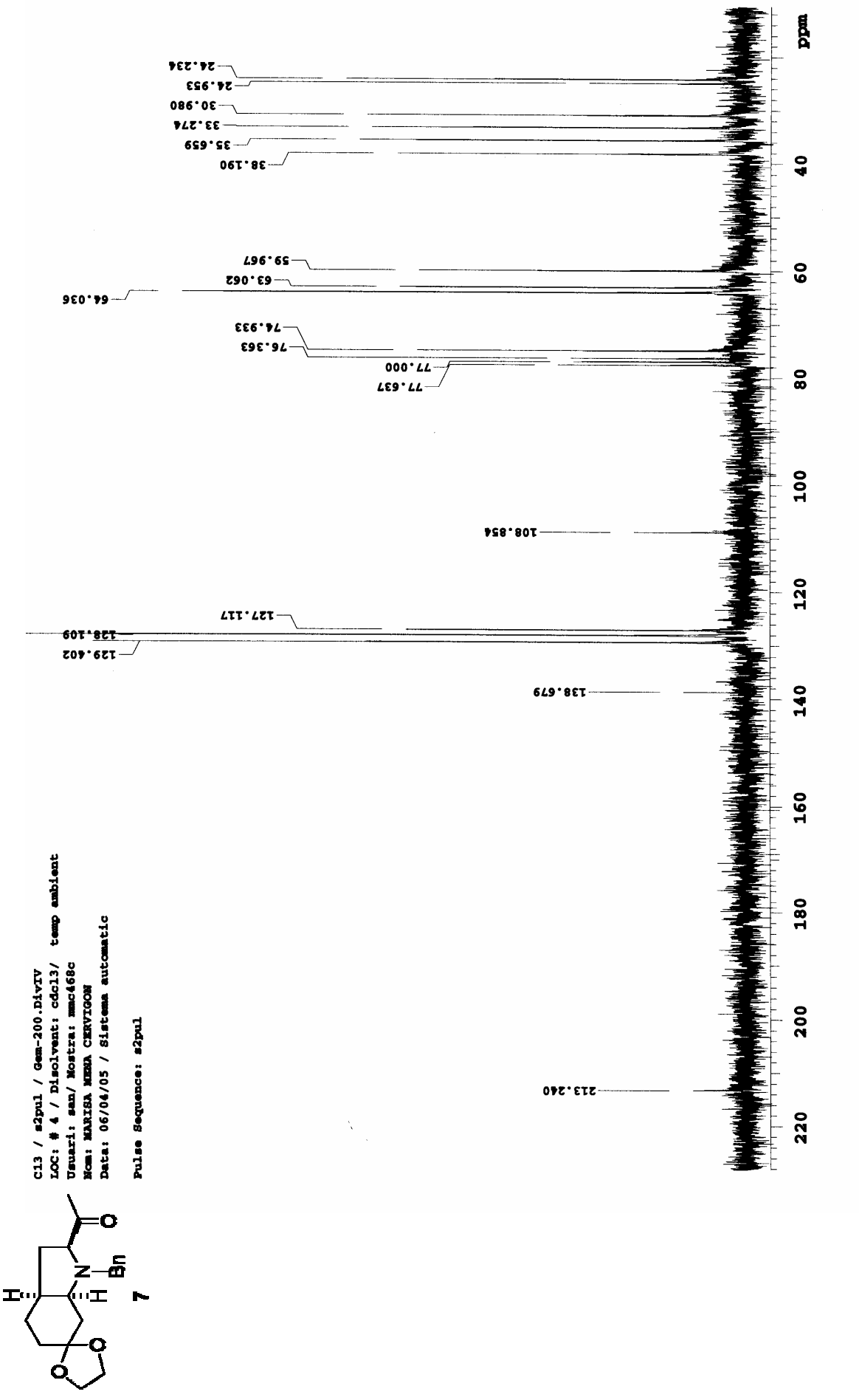

H1 / s2pul / Mercury-400
cdcl3/Temp: 25C /N reg: M40004-010404165212
Usuari: san / Mostra: yb2f
Nom: MARISA MENA CERVIGON
Data:01/04/04 / Sist automatic
Pulse Sequence: s2pul
7.311
7.300
7.261
3.908
3.695
3.655
0.000
ppm
5.04
3.38 0.97 0.92
0.00 1.82 0.90 0.98
1.10 2.92 1.20
1.27 2.34 1.03
OH
N
Bn
H
H
O
O
6

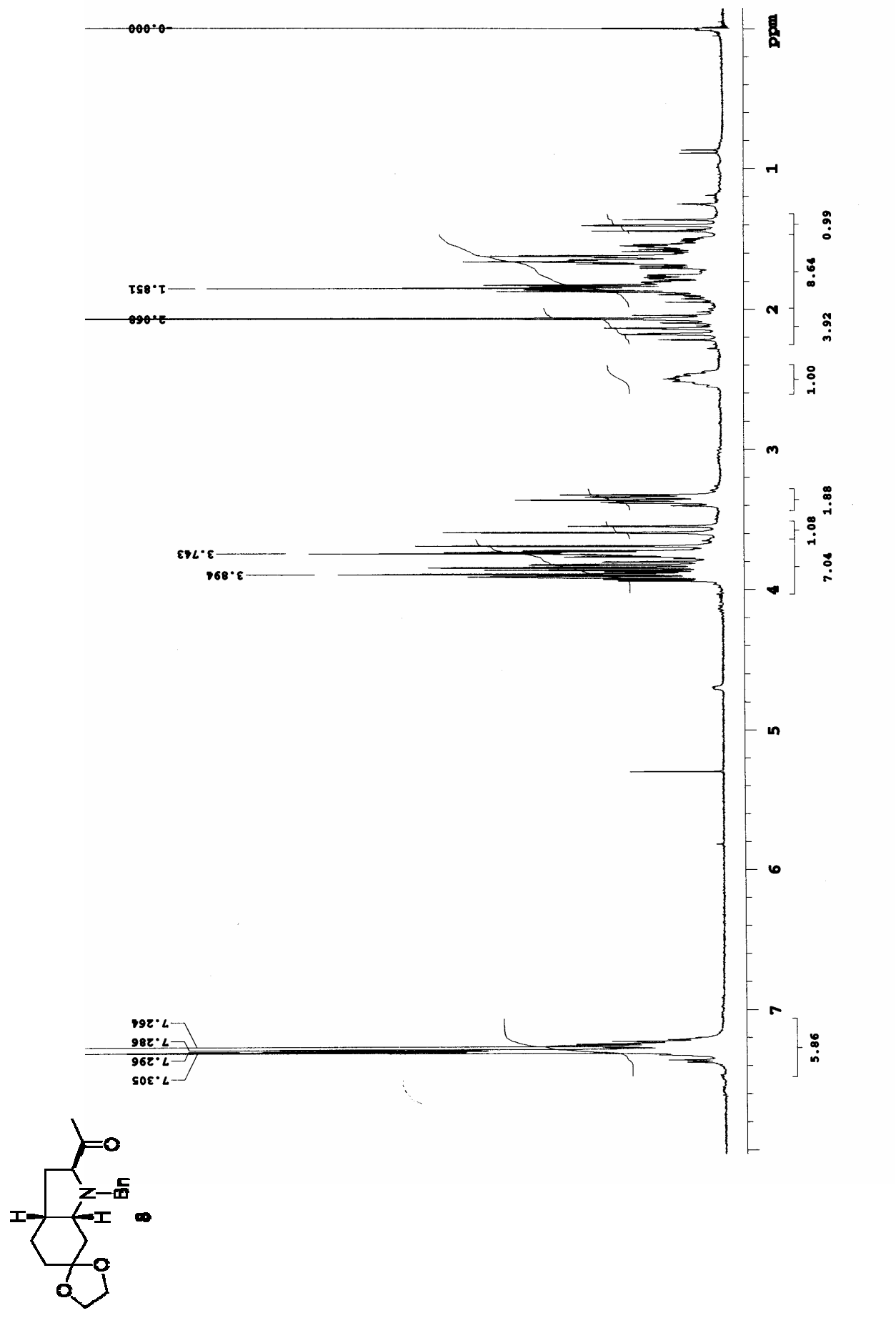

22.766
28.924
30.502
30.586
35.646
51.659
59.273
61.696
62.382
63.929
64.287
76.680
77.000
77.198
77.320
109.406
127.027
128.277
128.391
139.343
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140

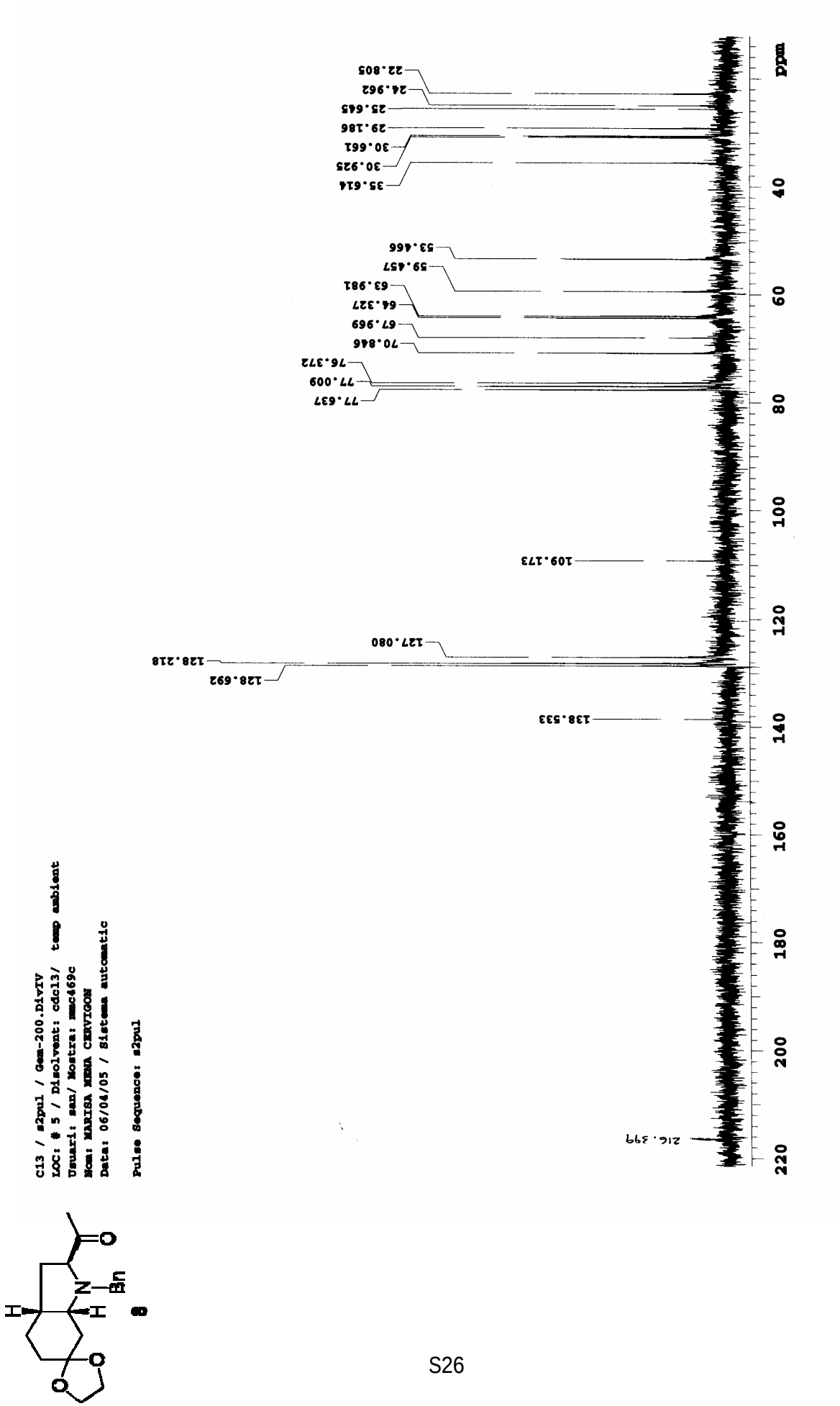

OH
N
Bn
H
H
O
O
O

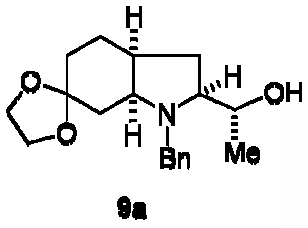
9


7
7.300
7.286
5.294
3.880
3.877
2.042
1.703
7
6
5
4
3
2
1
ppm
5.66
5.75
1.18
1.00
1.00
1.05
3.97
6.92
1.24

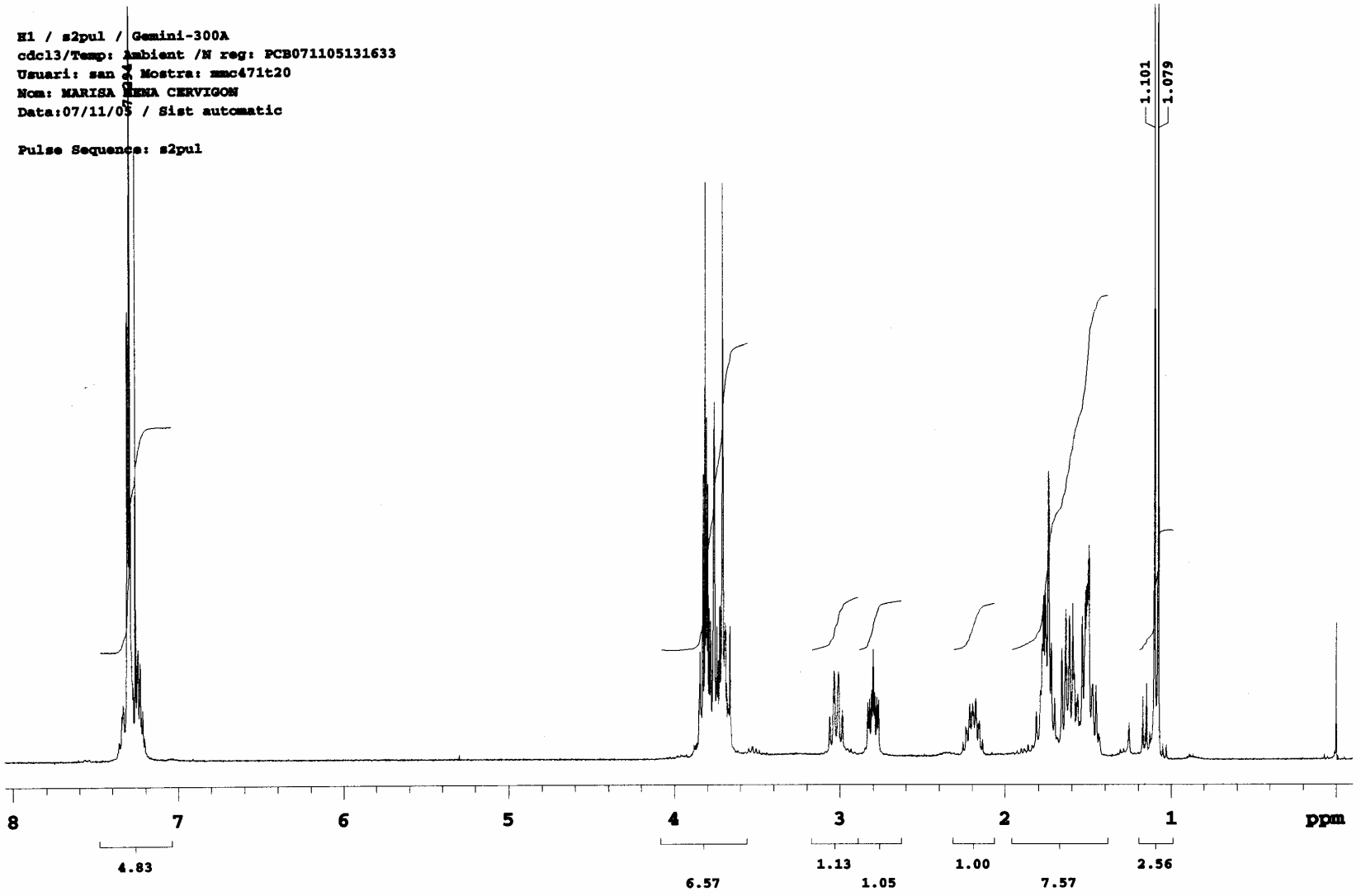

C13 / s2pul / Gem-200.DivIV
LOC: # 4 / Disolvent: cdcl3/ temp ambient
Usuari: san/ Mostra: mmc468c
Mem: MARISA MEMA CERVIGON
Data: 06/04/05 / Sistema automatic
Pulse Sequence: s2pul
213.240
138.679
129.402
128.109
127.117
108.854
77.637
77.000
76.363
74.933
64.036
63.062
59.967
38.190
35.659
33.274
30.980
24.953
24.234
ppm
220
200
180
160
140
120
100
80
60
40
H
H
N
Bn
O
O
O
O
7

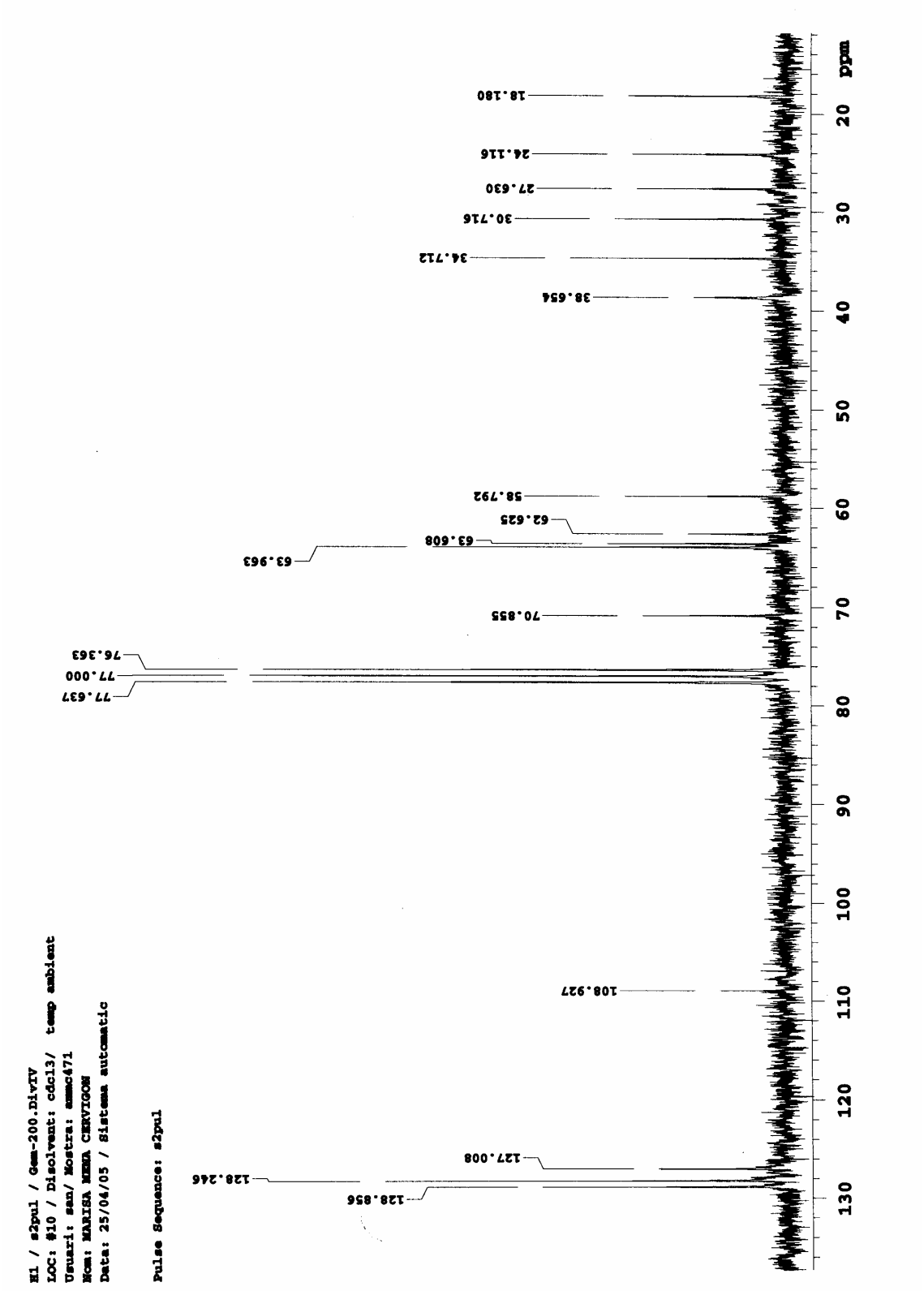

0.000
1.851
2.060
3.743
3.894
7.264
7.286
7.296
7.305
ppm
1
2
3
4
5
6
7
0.99
8.64
3.92
1.00
1.88
1.08
7.04
5.86
O
N—Bn
H
H
O
O
O

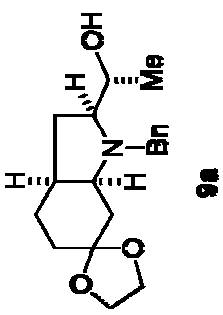

C13 / s2pul / Gem-200.DivIV
LOC: # 5 / Disolvent: cdcl3/ temp ambient
Usuari: san/ Mostra: mmc469c
Nom: MARISA MENA CERVIGON
Data: 06/04/05 / Sistema automatic
Pulse Sequence: s2pul
212.399
138.533
128.692
128.218
127.080
109.173
77.637
77.009
76.372
70.846
67.969
64.327
63.981
59.457
53.466
35.614
30.925
30.661
29.186
25.645
24.962
22.805
ppm
220
200
180
160
140
120
100
80
60
40
H
N
Bn
H
O
O
O
6


H
O
H
OH
O
N
H
Bn
Me

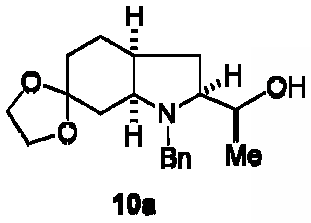
9a


H1 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB071105131633
Usuari: san Mostra: mmc471t20
Nom: MARISA MENA CERVIGON
Data:07/11/05 / Sist automatic
Pulse Sequence: s2pul
1.101
1.079
8
7
6
5
4
3
2
1
ppm
4.83
6.57
1.13
1.05
1.00
7.57
2.56


E1 / s2pul / Gem-200.DirTV
LOC: #10 / Disolvent: cdcl3/ temp ambient
Usuari: san/ Mostra: smmc471
Nom: MARIA MERA CERVIGON
Data: 25/04/05 / Sistema automatic
Pulse Sequence: s2pul
18.180
24.116
27.630
30.716
34.712
38.654
58.792
62.625
63.608
63.963
70.855
76.363
77.000
77.637
108.927
127.008
128.246
128.856
ppm


OH
H
Me
N
Bn
H
H
O
O
O

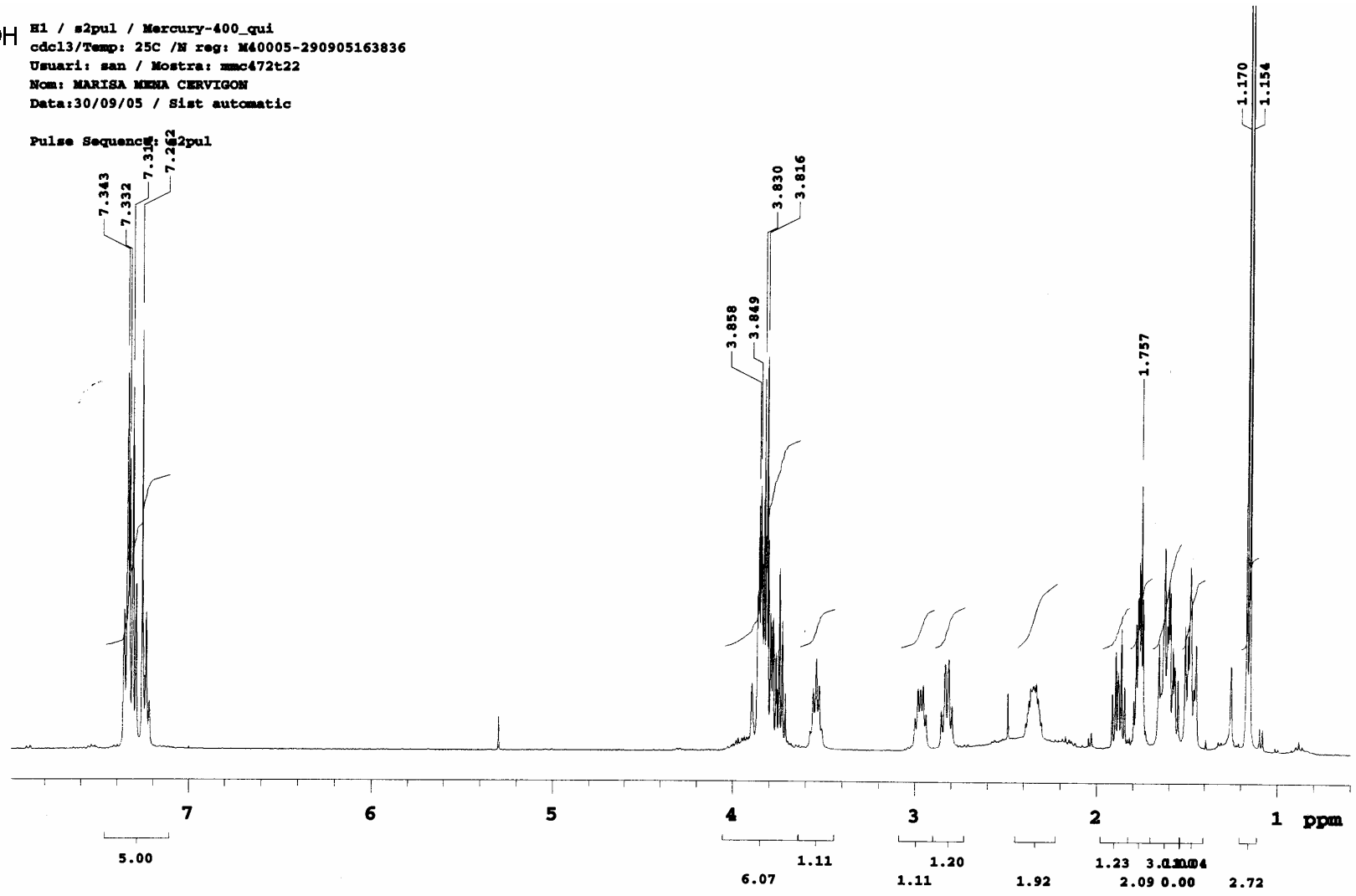
9a

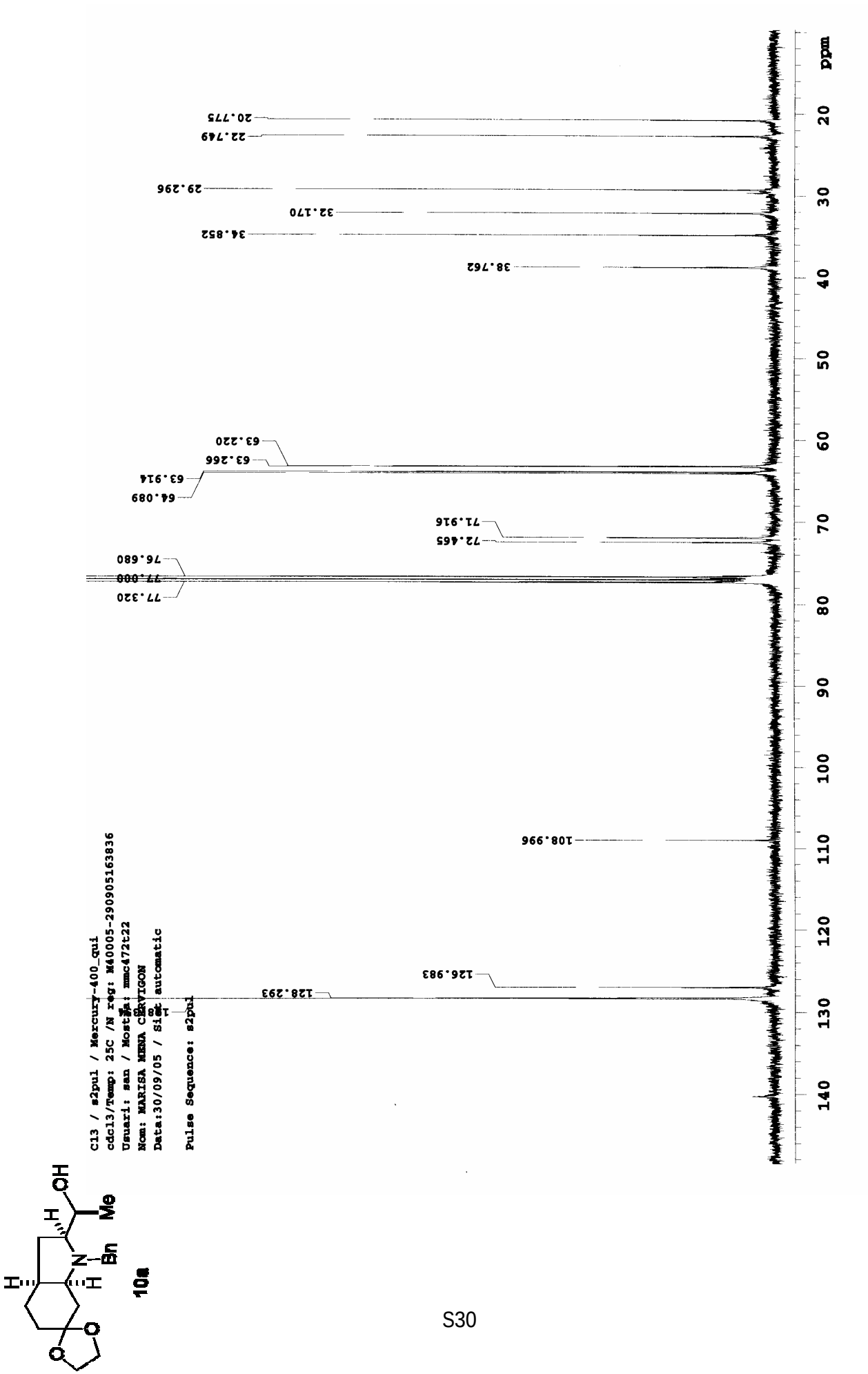


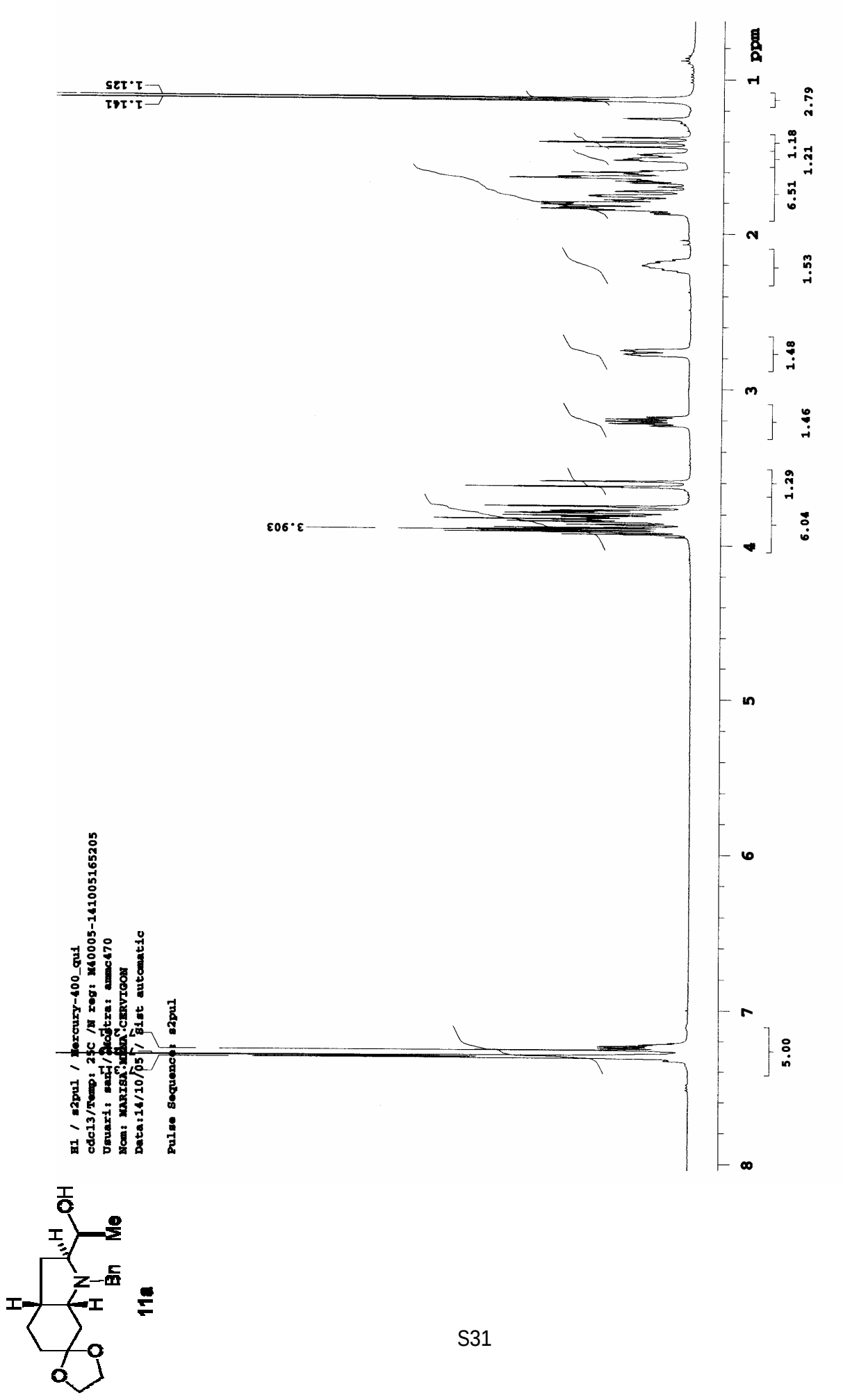
10a

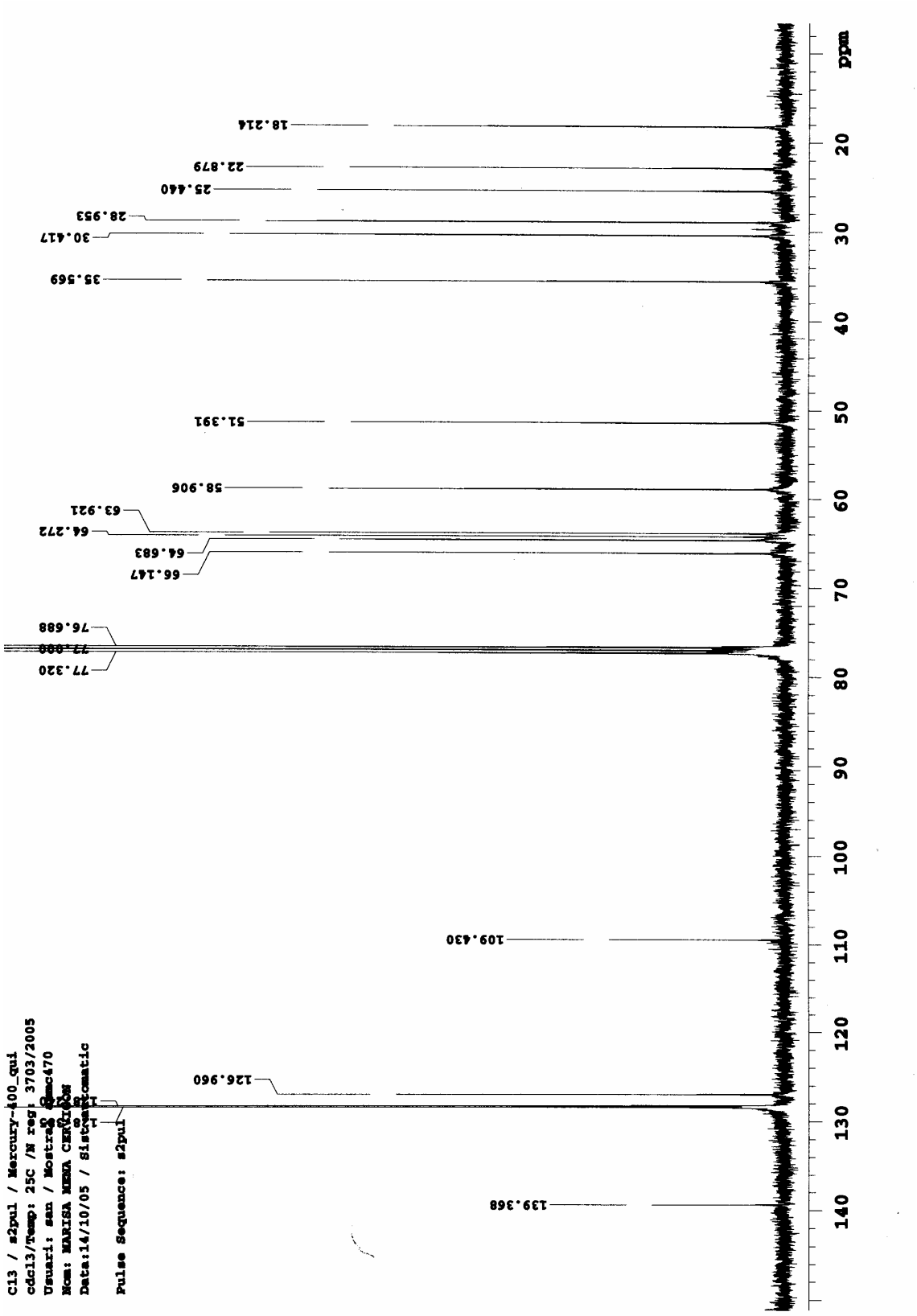
H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-290905163836
Usuari: san / Mostra: mmc472t22
Nom: MARISA MENA CERVIGON
Data:30/09/05 / Sist automatic

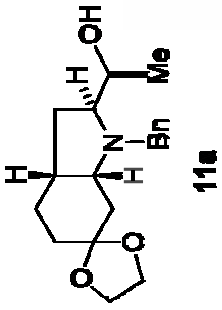
Pulse Sequence: s2pul



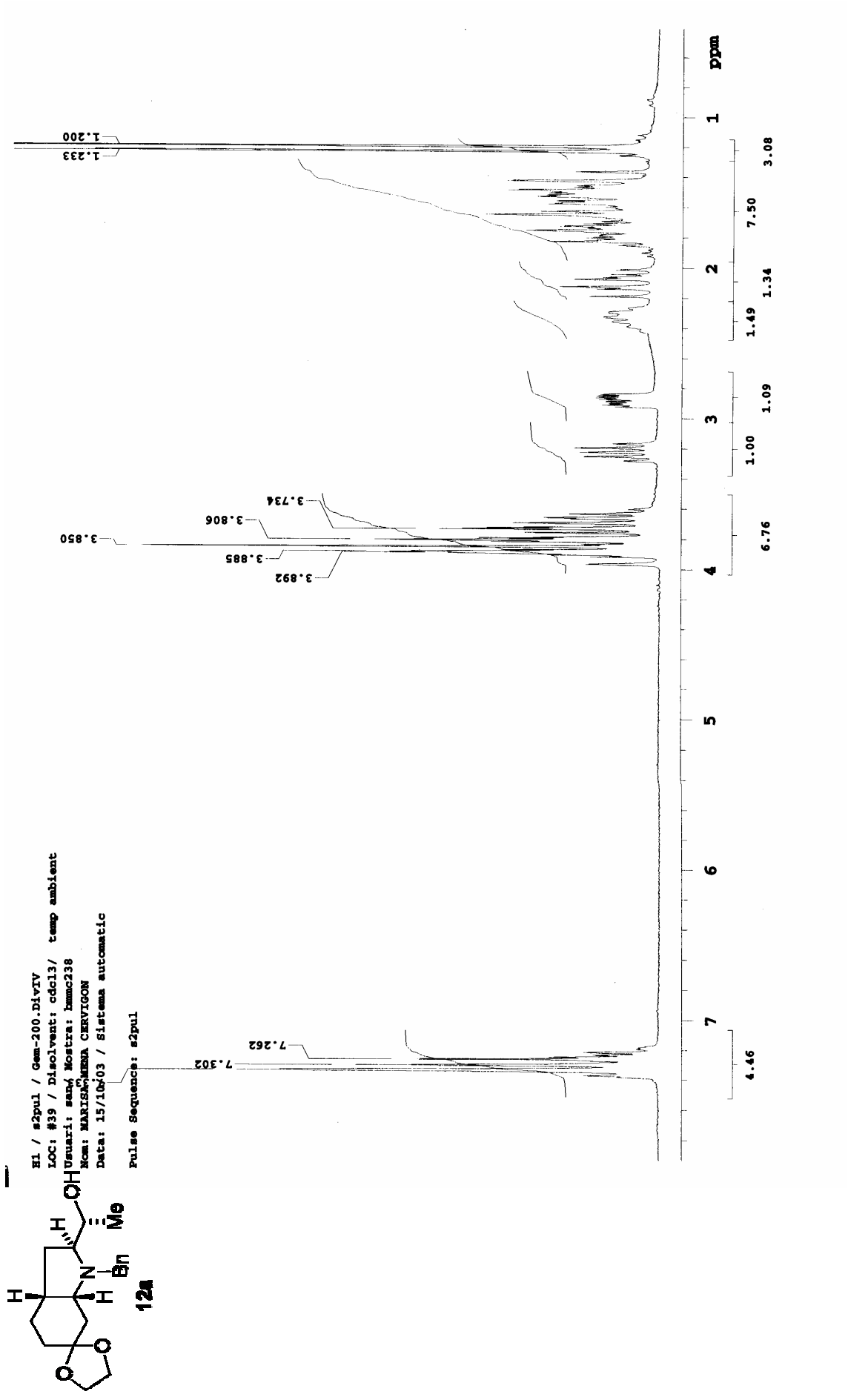

C13 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-29090516836
Usuari: san / Most#: mmc472t22
Ncm: MARISA MEMA CERVIGON
Data:30/09/05 / Sist: automatic
Pulse Sequence: s2pul
77.320
77.000
76.680
72.465
71.916
64.089
63.914
63.266
63.220
38.762
34.852
32.170
29.296
22.749
20.775
128.293
126.983
108.996
ppm
10a

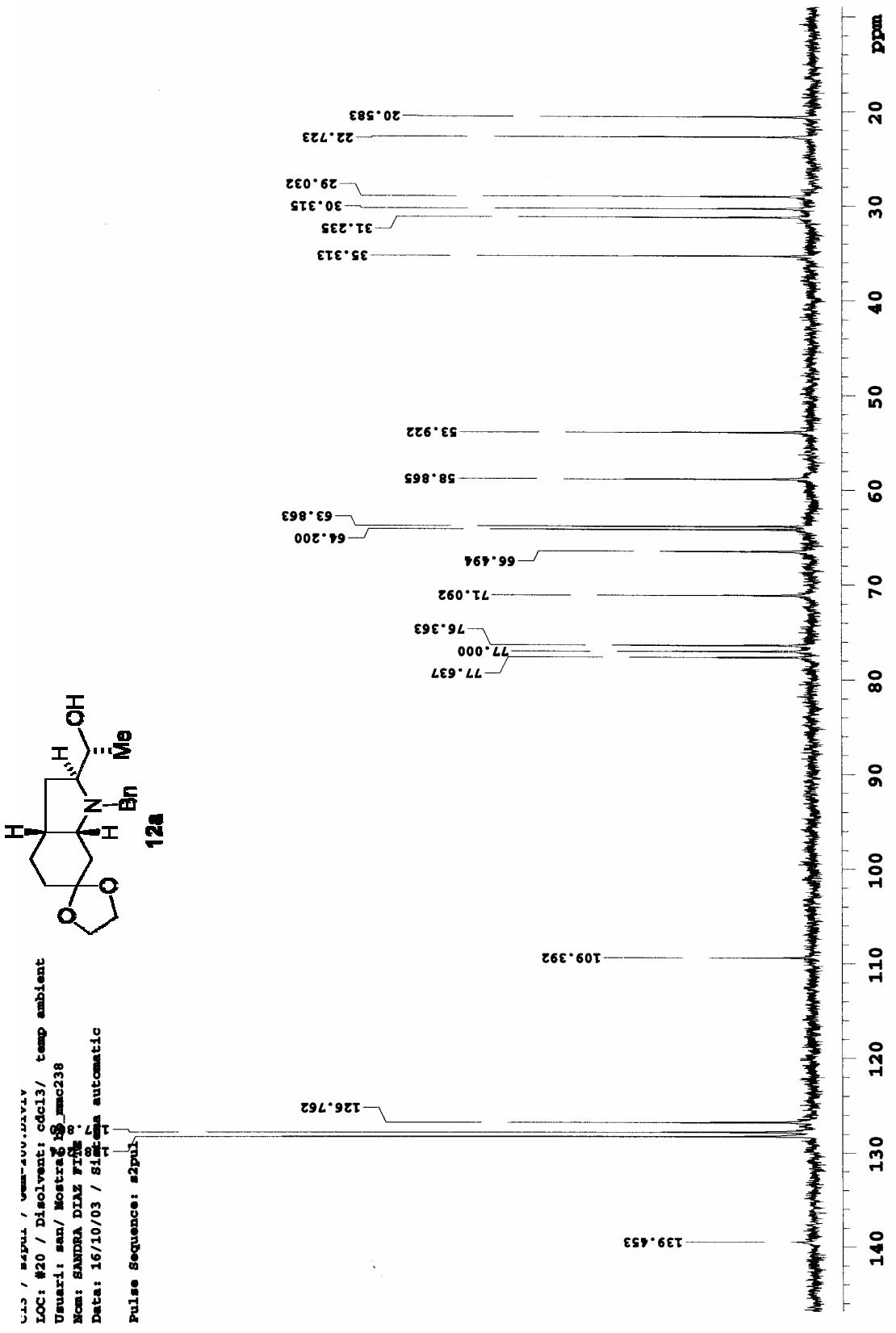

11a
H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-14100516520S
Usuari: sau/Espectra: ammc470
Nom: MARISA, MARI CERVIGON
Data:14/10/05 / 21st automatic
Pulse Sequence: s2pul
1.125
1.141
3.903
1 ppm
2.79
1.18
1.21
6.51
1.53
1.48
1.46
1.29
6.04
5.00

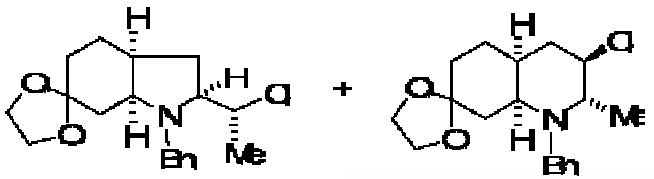

C13 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: 3703/2005
Usuari: sam / Mostra: Qmc470
Nom: MARISA MENA CERVERON
Data:14/10/05 / Sistema:Automatic
Pulse Sequence: s2pul
18.214
22.879
25.440
28.953
30.417
35.569
51.391
58.906
63.921
64.272
64.683
66.147
76.688
77.320
109.430
126.960
139.368
ppm


OH
H
Me
N
Bn
H
H
O
O
O

11a

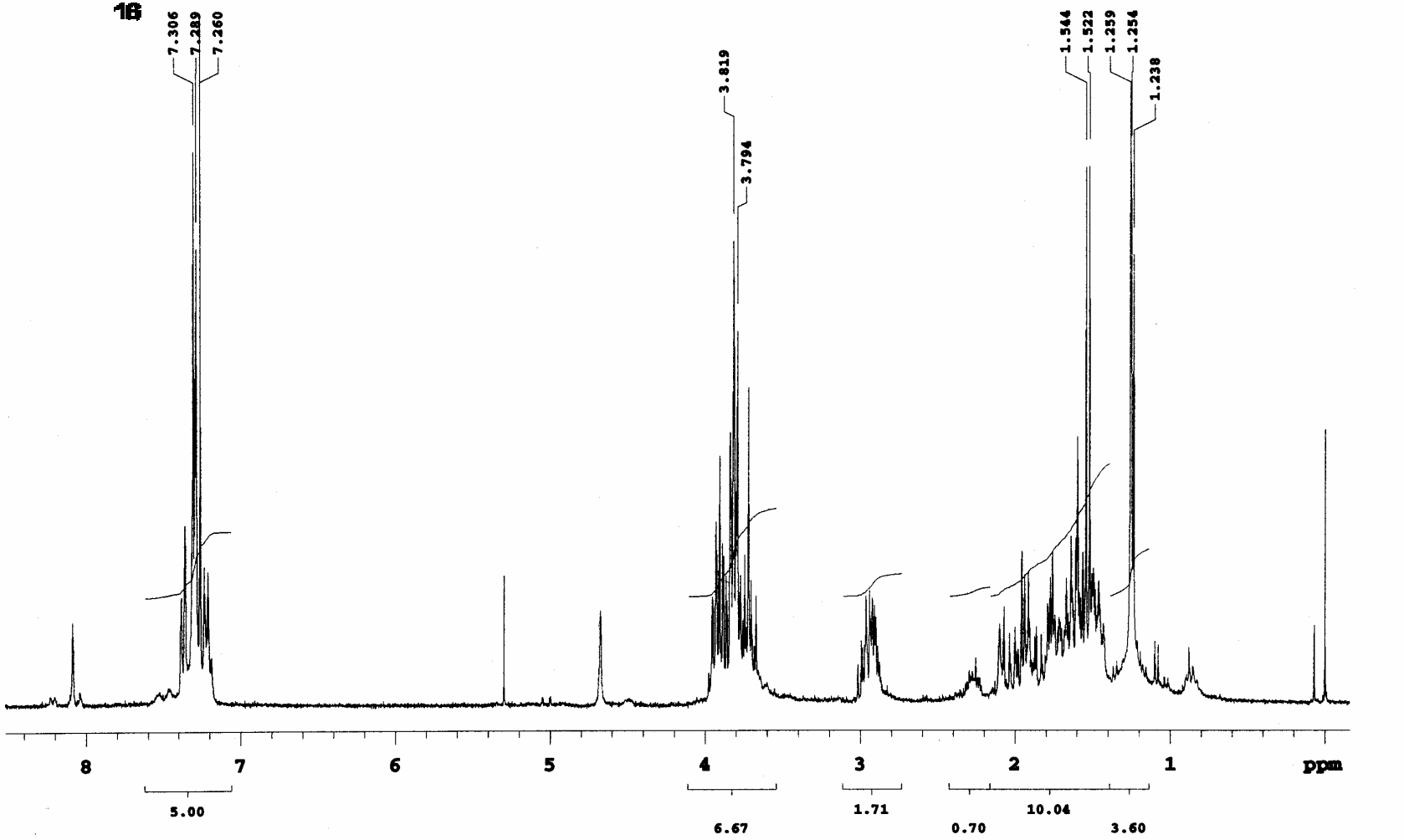

E1 / s2pul / Gem-200.DivIV
LOC: #39 / Disolvent: cdcl3/ temp ambient
Usuari: sam/ Mostra: hmmc238
Nom: MARISA MENA CERVIGON
Data: 15/10/03 / Sistema automatic
Pulse Sequence: s2pul
12a
7.302
7.262
3.892
3.885
3.850
3.806
3.734
1.233
1.200
ppm
4.46
6.76
1.00
1.09
1.49
1.34
7.50
3.08

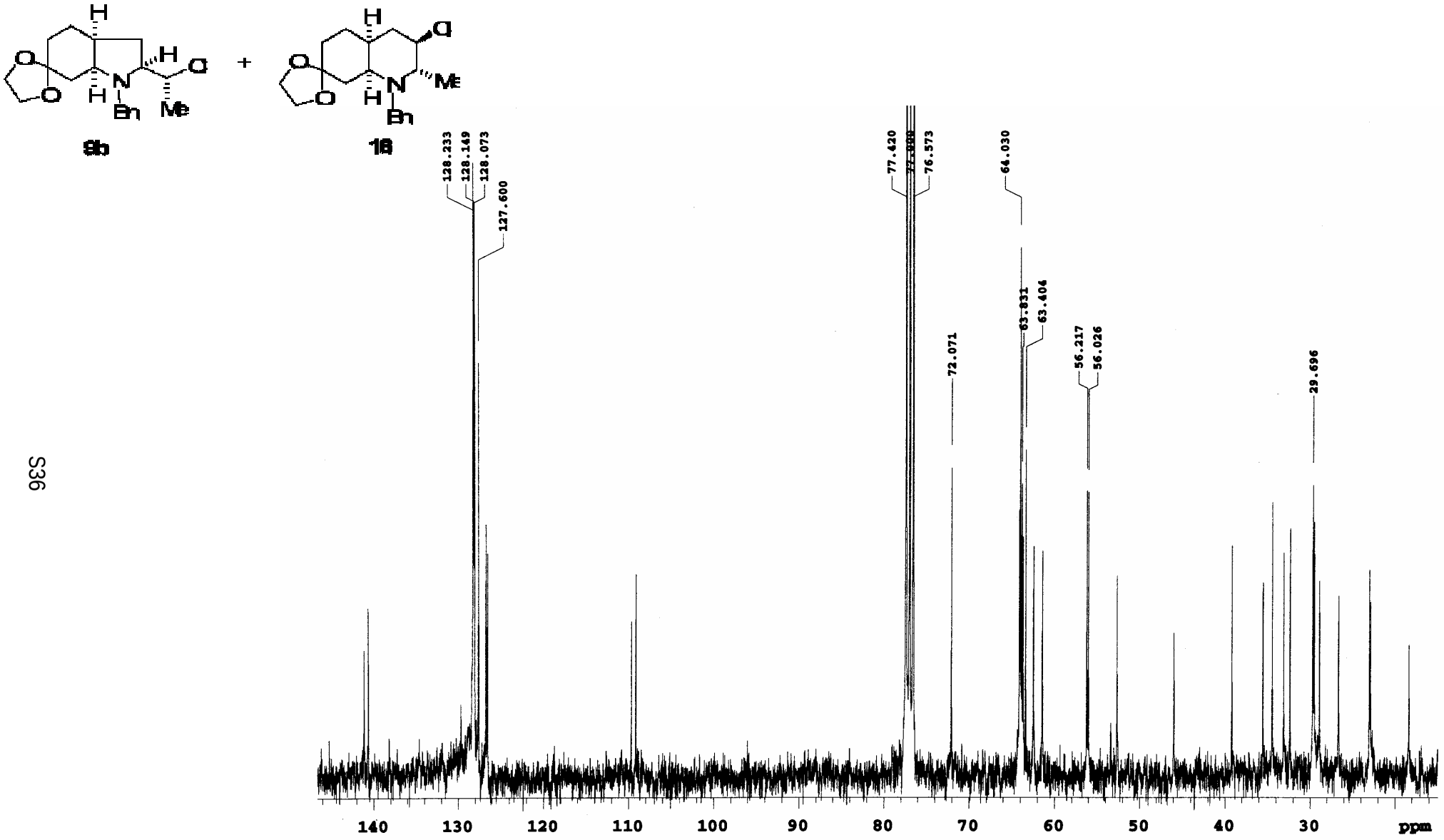

20.583
22.723
29.032
30.315
31.235
35.313
53.922
58.865
63.863
64.200
66.494
71.092
76.363
77.000
77.637
109.392
126.762
139.453
ppm
OH
Me
Bn
N
H
O
12a

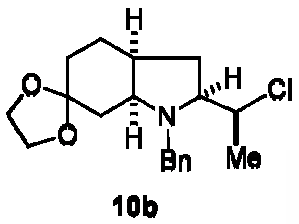


9b

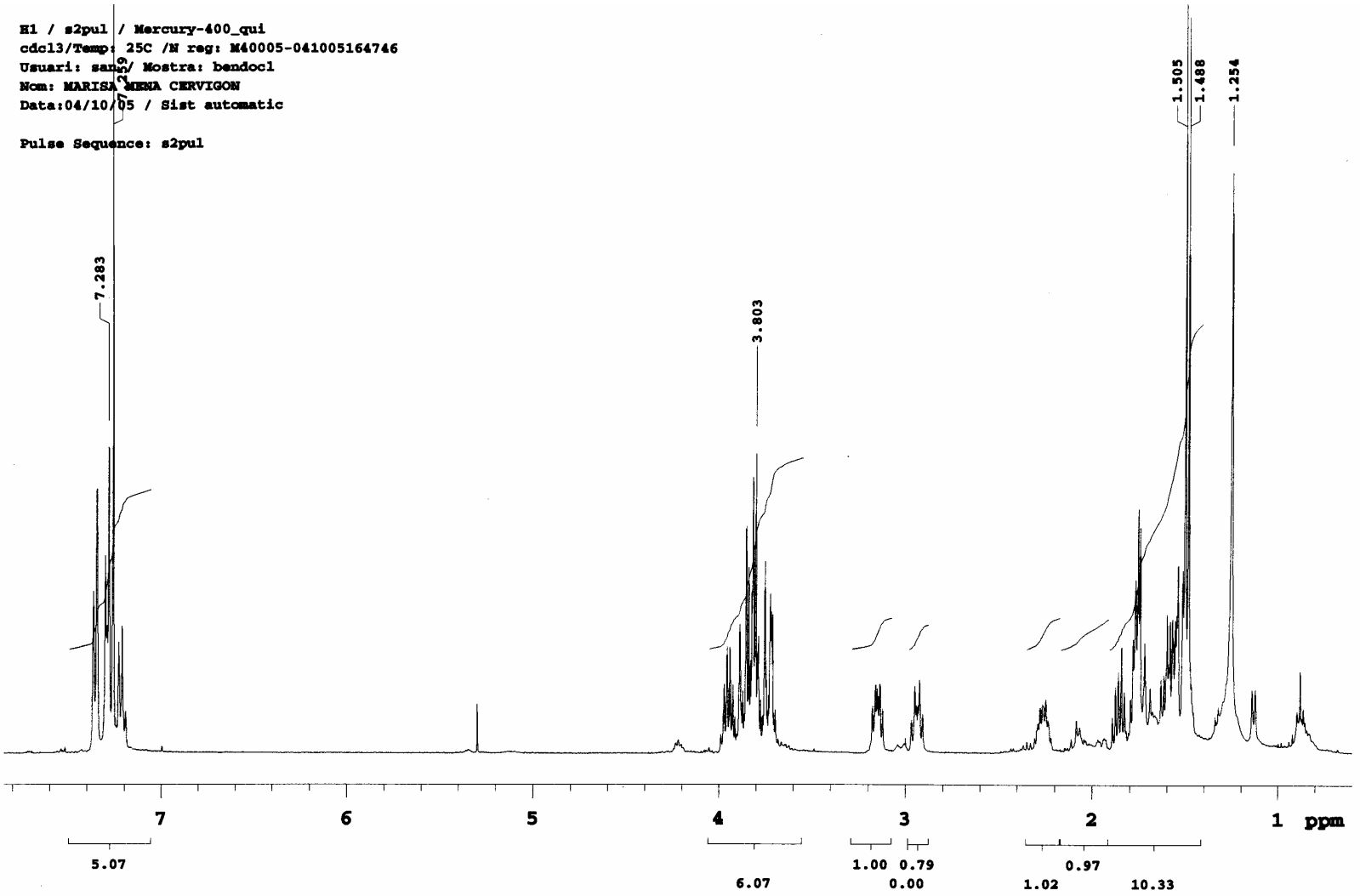
16

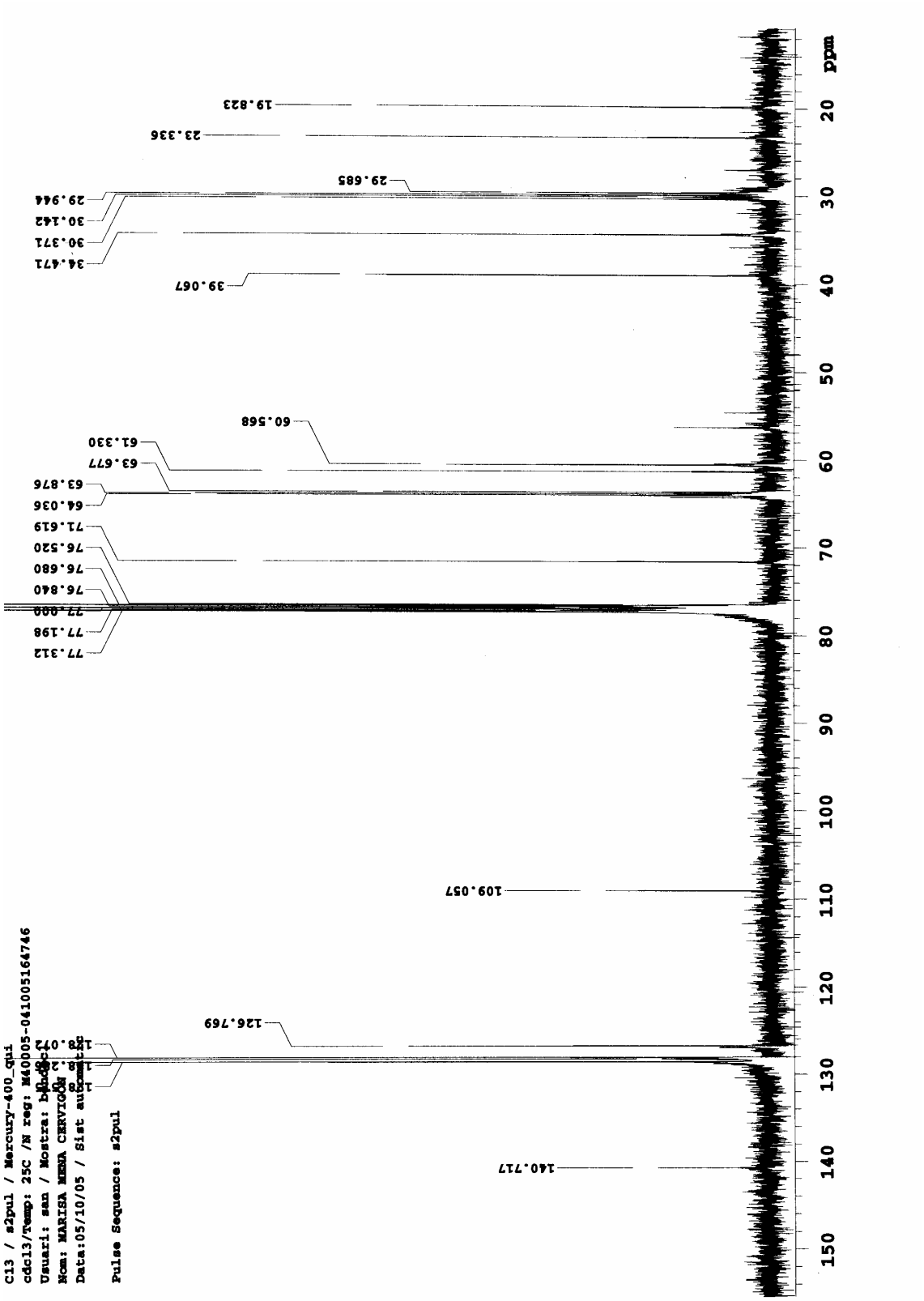

7.306
7.289
7.260
3.819
3.794
1.544
1.522
1.259
1.254
1.238
8
7
6
5
4
3
2
1
ppm
5.00
6.67
1.71
0.70
10.04
3.60

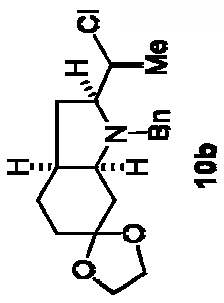

9b
16
128.233
128.149
128.073
127.600
77.420
76.573
72.071
64.030
63.831
63.404
56.217
56.026
29.696
140
130
120
110
100
90
80
70
60
50
40
30
ppm


H
O
O
H
N
Bn
H
Cl
Me

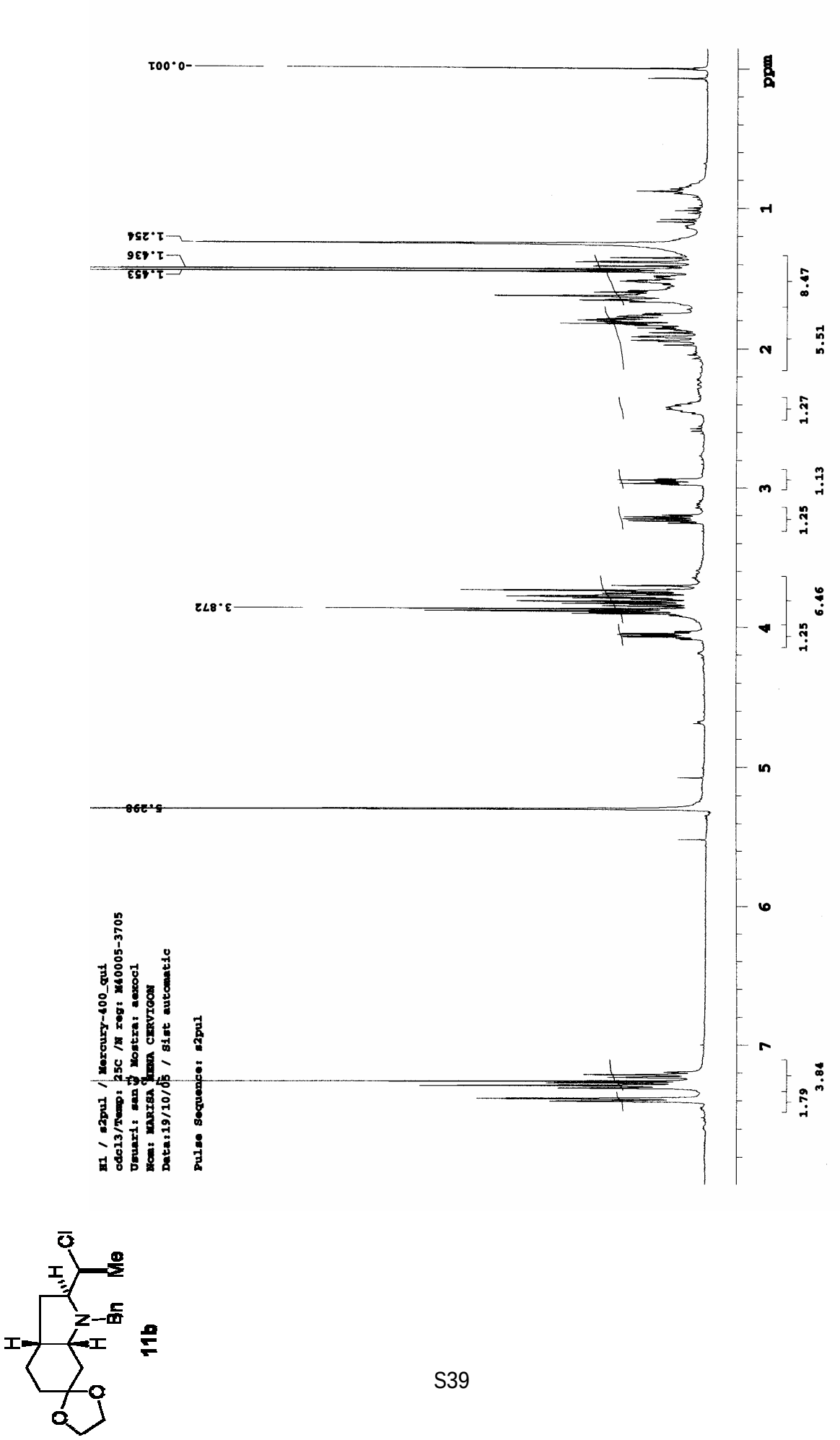
10b

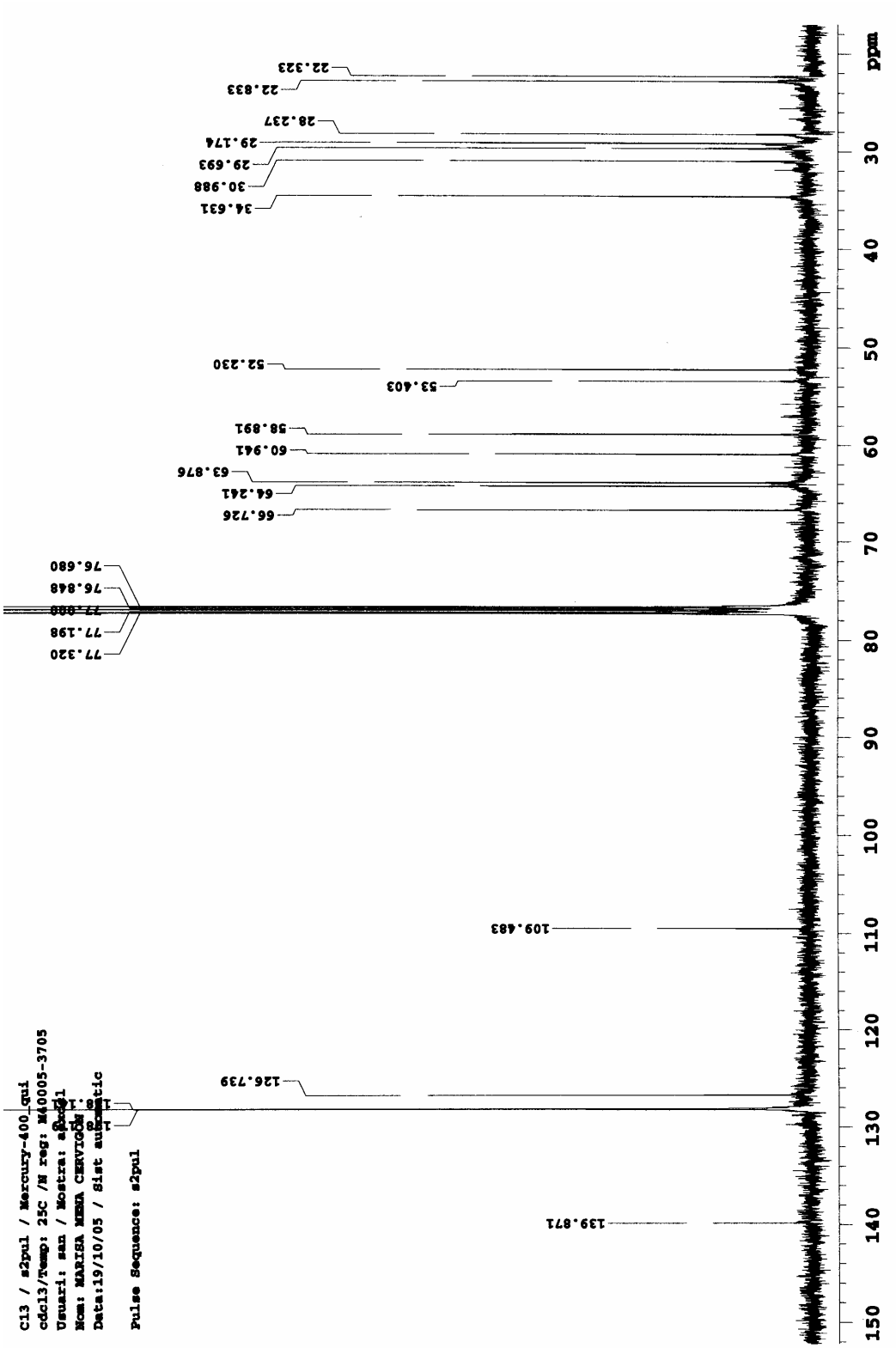

H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-041005164746
Usuari: sam / Mostra: bendocl
Nom: MARISA MENA CERVIGON
Data:04/10/05 / Sist automatic
Pulse Sequence: s2pul
7.283
7.269
3.803
1.505
1.488
1.254
7
6
5
4
3
2
1
ppm
5.07
6.07
1.00
0.79
0.00
0.97
1.02
10.33

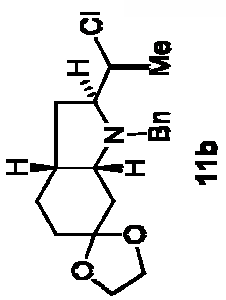

C13 / s2pul / Mercury-400_qui
cdc13/Temp: 25C /N reg: M40005-041005164746
Usuari: san / Mostra: b
Mem: MARISA MENA CERVIGON
Data:05/10/05 / Slst auto
Pulse Sequence: s2pul
19.823
23.336
29.685
29.944
30.142
30.371
34.471
39.067
60.568
61.330
63.677
63.876
64.036
71.619
76.520
76.680
76.840
77.000
77.198
77.312
109.057
126.769
128.072
140.717
ppm


Cl
H
Me
N
Bn
H
H
O
O

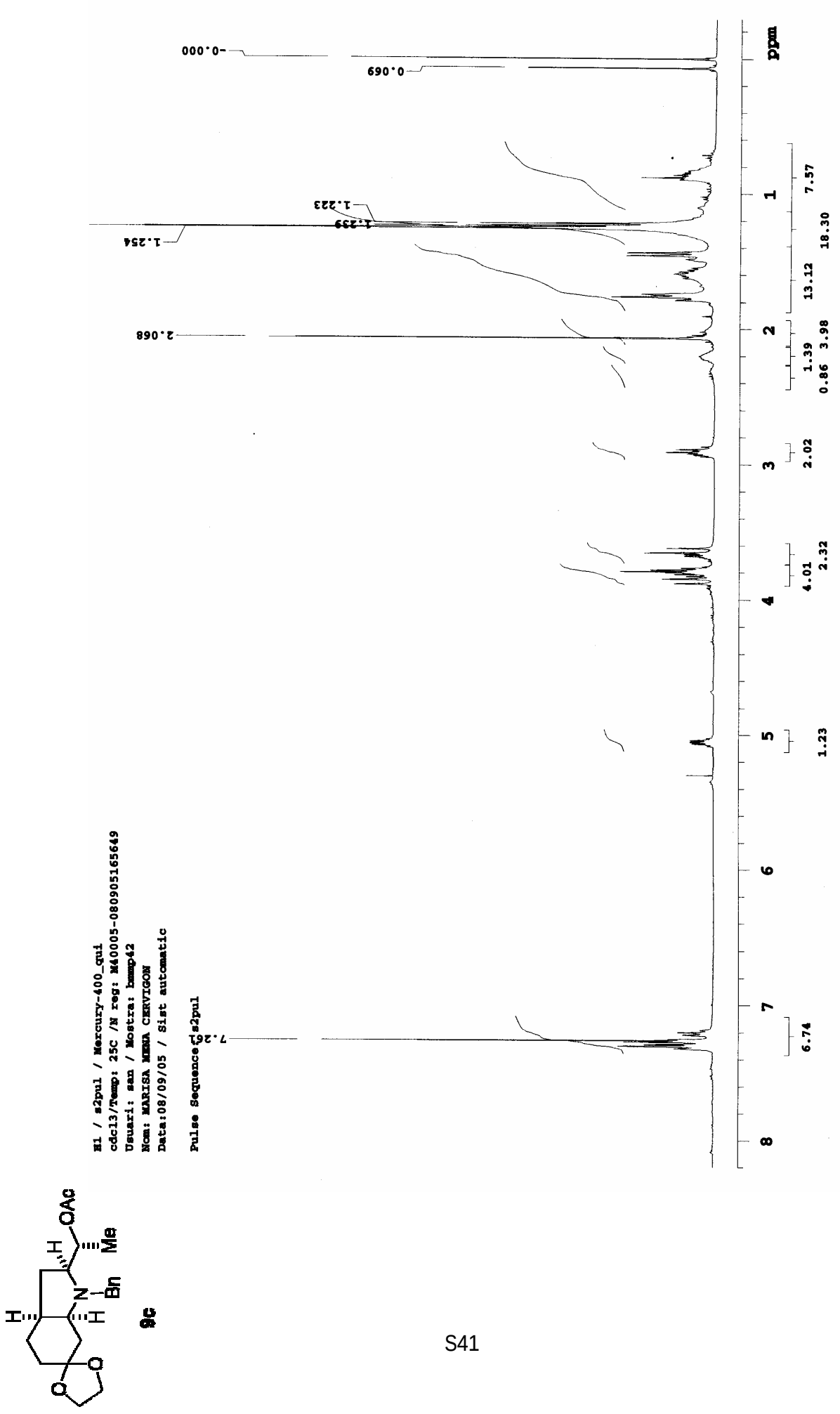
10b

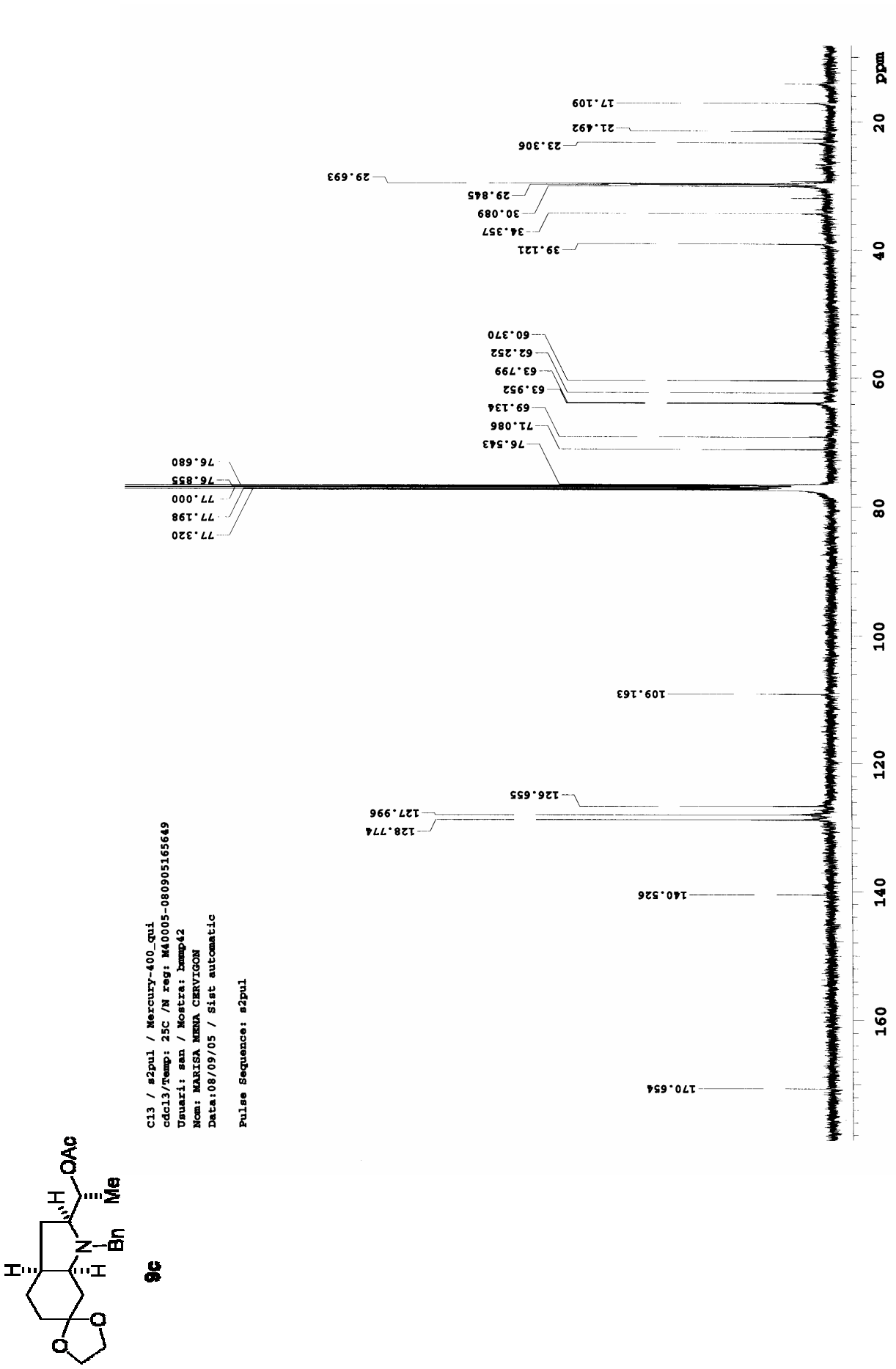

11b
Bn
Me
Cl
H
H
O
O
O
N
-0.001
1.254
1.436
1.453
3.872
5.298
ppm
1
2
3
4
5
6
7
8.47
5.51
1.27
1.13
1.25
6.46
1.25
1.79
3.84

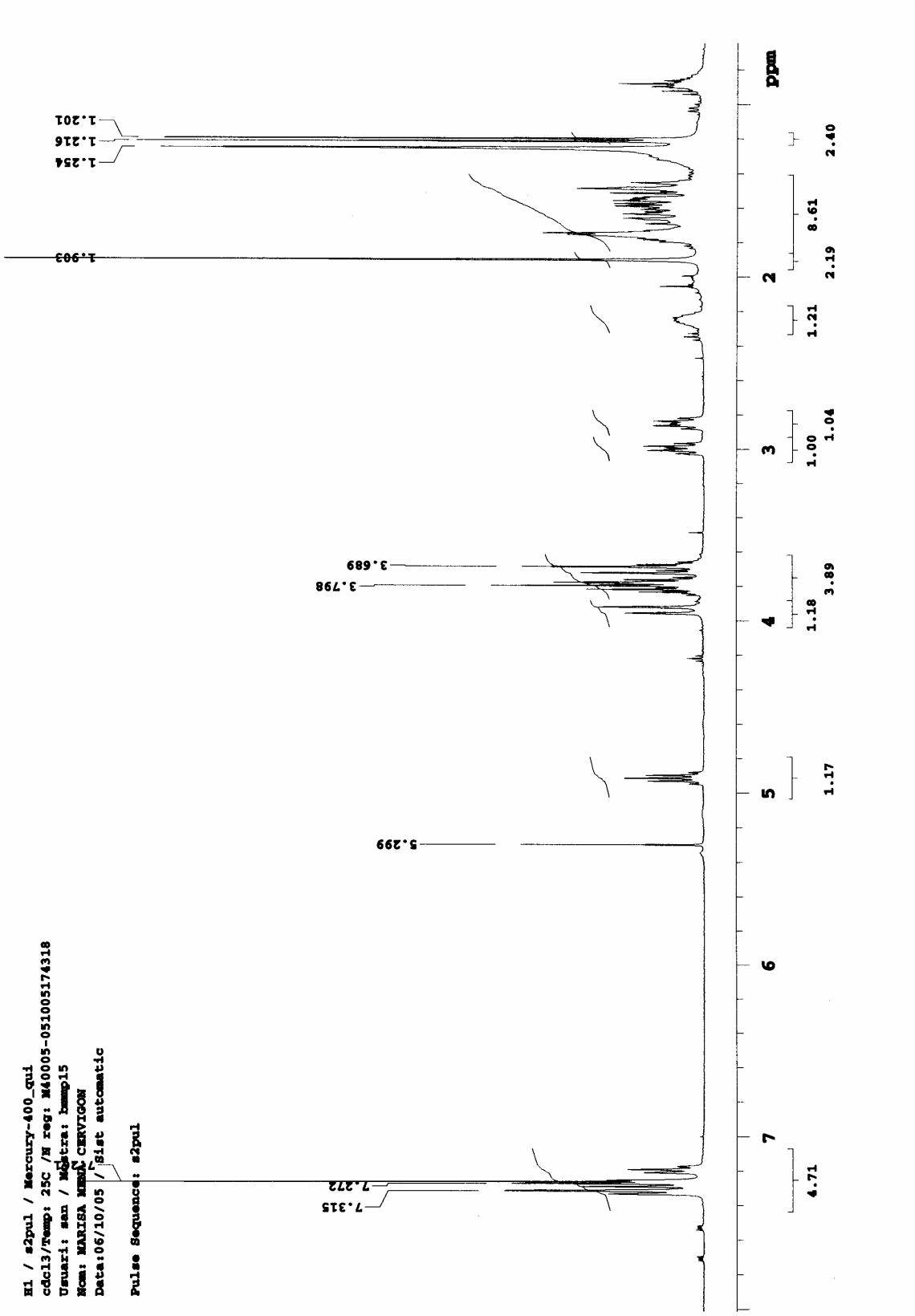

22.323
22.833
28.237
29.174
29.693
30.988
34.631
52.230
53.403
58.891
60.941
63.876
64.241
66.726
76.680
76.848
77.320
77.398
109.483
126.739
139.871
ppm
C13 / s2pul / Mercury-400.qui
cdcl3/Temp: 25C /N reg: M40005-3705
Pulse Sequence: s2pul

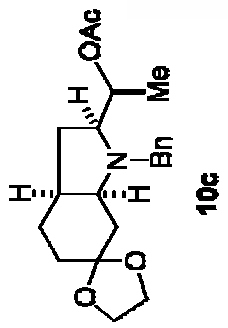

Cl
H
Me
N
Bn
H
H
O
O

11b

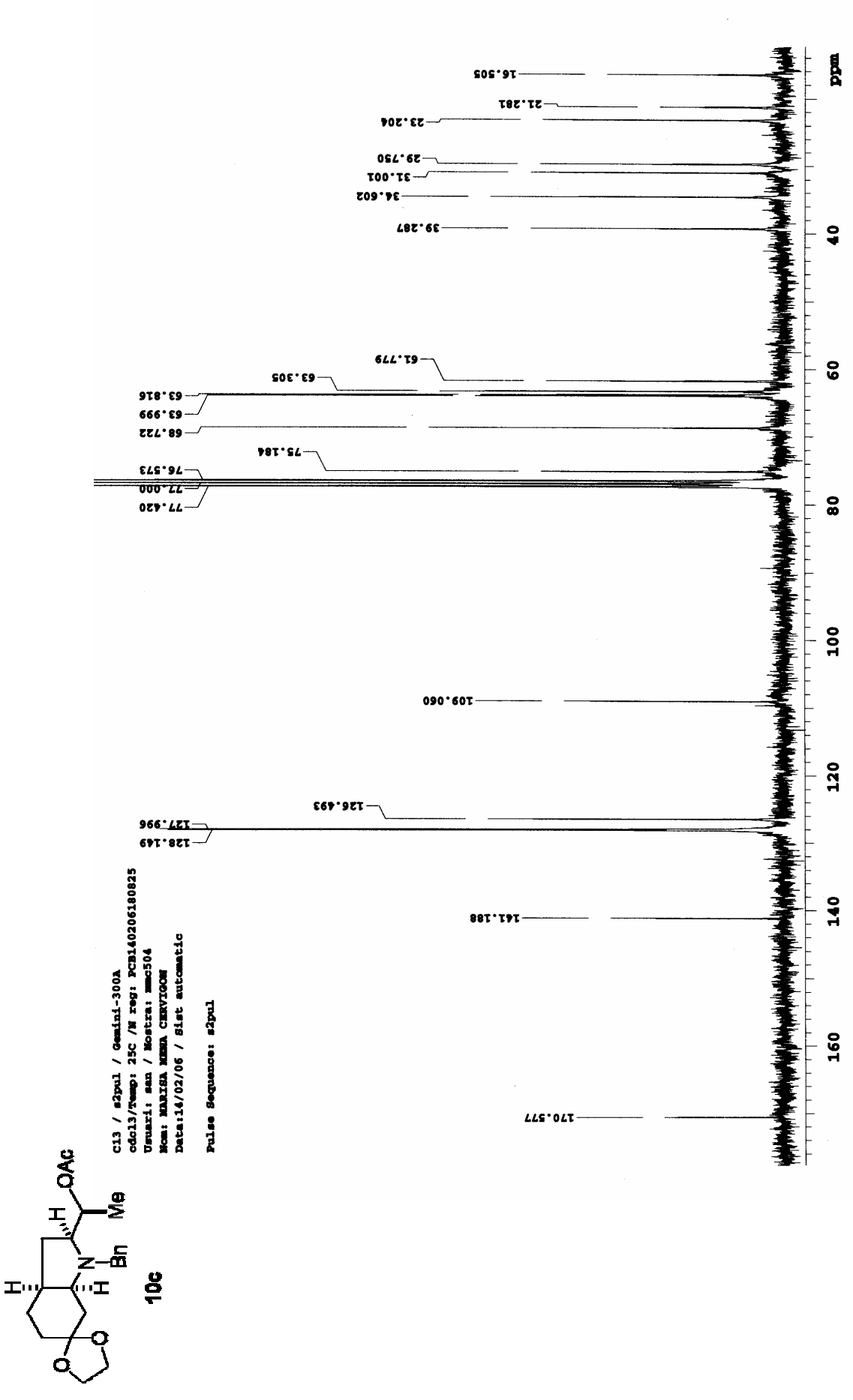

OAc
H
Me
N
Bn
H
H
O
O
9c
H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-080905165649
Usuari: sam / Mostra: hmmp42
Nom: MARISA MENA CERVIGON
Data:08/09/05 / Slst automatic
Pulse Sequence: s2pul
7.26
2.068
1.254
1.239
1.223
0.069
-0.000
ppm
1
2
3
4
5
6
7
8
7.57
18.30
13.12
1.39
0.86
3.98
2.02
4.01
2.32
1.23
6.74

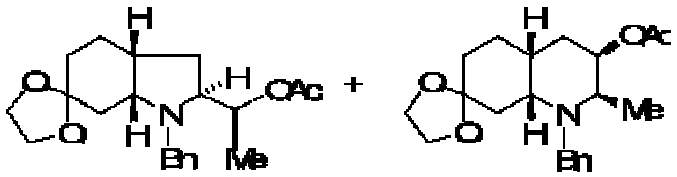

C13 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-080905165649
Usuari: san / Mostra: hmmp42
Mem: MARISA MENA CERVIGON
Data:08/09/05 / Slet automatic
Pulse Sequence: s2pul
170.654
140.526
128.774
127.996
126.655
109.163
77.320
77.198
77.000
76.855
76.680
76.543
71.086
69.134
63.952
63.799
62.252
60.370
39.121
34.357
30.089
29.845
29.693
23.306
21.492
17.109
ppm
20
40
60
80
100
120
140
160
OAc
Me
Bn
H
N
O
9c


H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-051005174318
Usuari: san / Master: bamp15
Nom: MARISA MMF CERVIGON
Data:06/10/05 / 8ist automatic
Pulse Sequence: s2pul
1.201
1.216
1.254
1.903
3.689
3.798
5.299
7.272
7.315
ppm
1.17
4.71
1.18
3.89
1.00
1.04
1.21
2.19
8.61
2.40


OAc
H
Me
N
Bn
H
H
O
O
O

10c

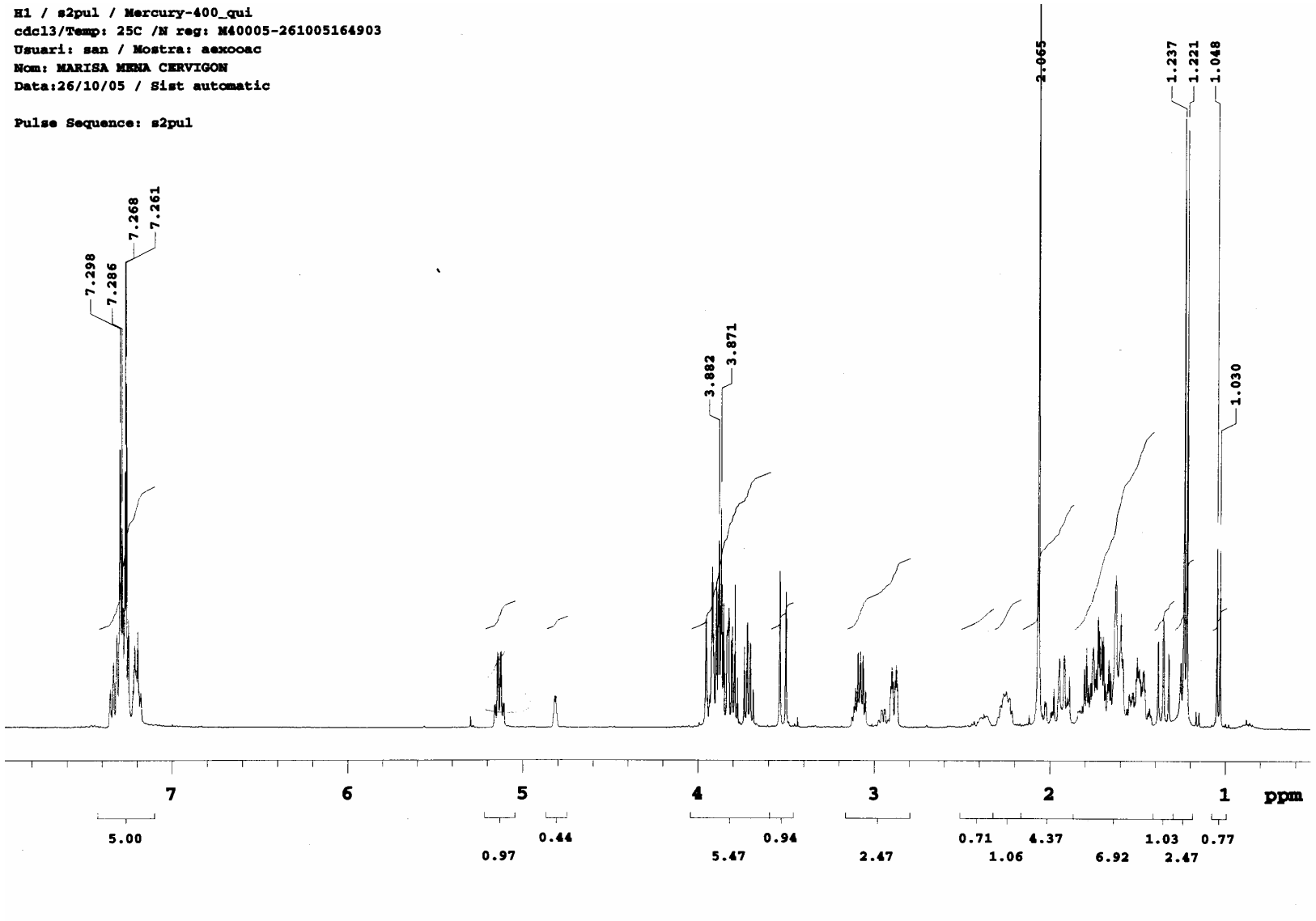

C13 / s2pul / Gemini-300A
cdcl3/Temp: 25C /N reg: PCB140206180825
Uzuari: sm / Mostra: mm0504
Mem: MARISA MEMA CERVIGON
Data:14/02/06 / Slst automatic
Pulse Sequence: s2pul
16.505
21.281
23.304
29.750
31.001
34.602
39.287
61.779
63.305
63.816
63.999
68.722
75.184
76.573
77.000
77.420
109.060
126.493
127.996
128.149
141.188
170.577
ppm
OAc
Me
H
N
Bn
H
H
O
O
10c

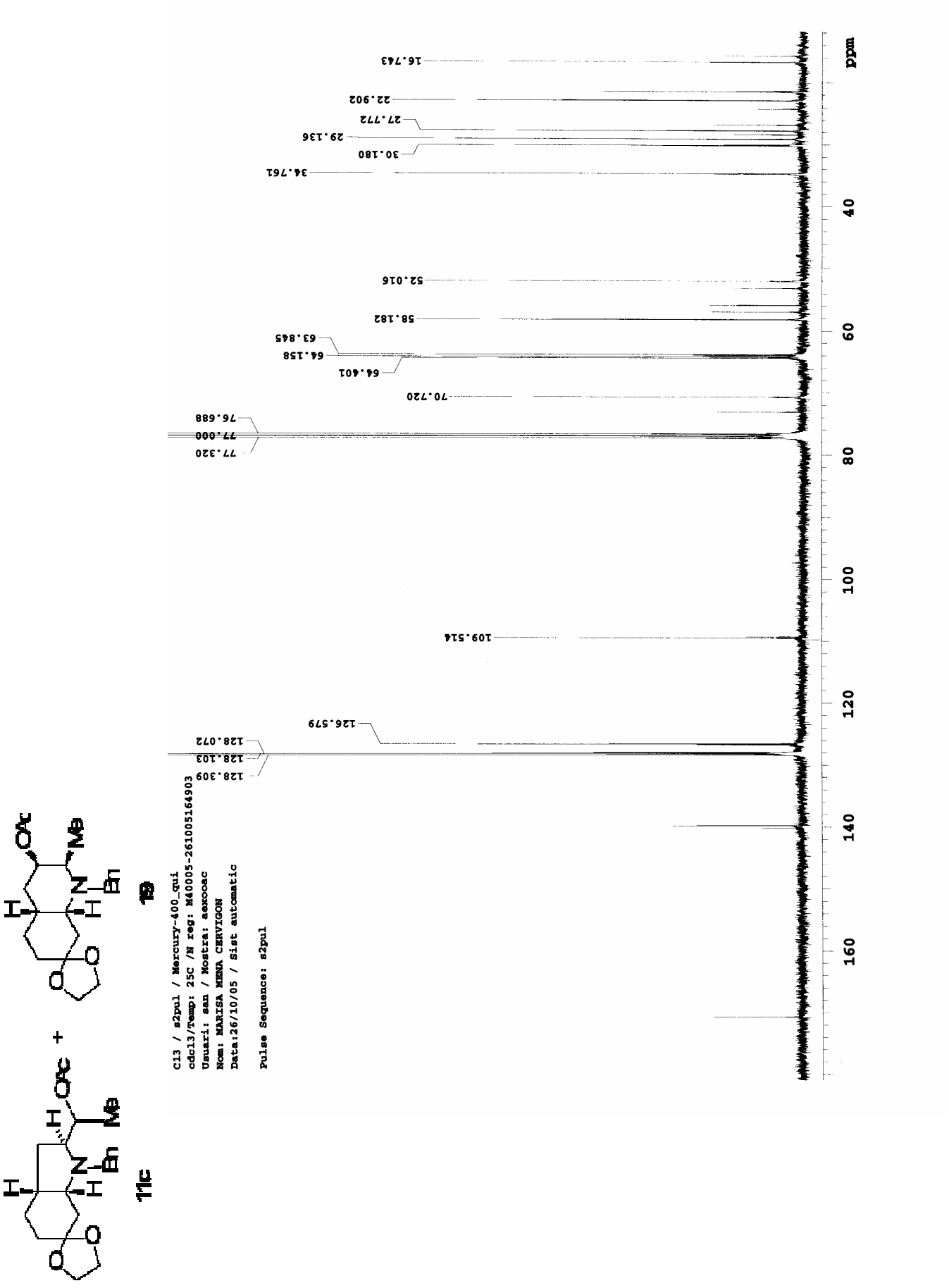


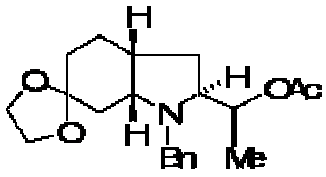
11c 19

H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-261005164903
Usuari: san / Mostra: aexooac
Nom: MARISA MENA CERVIGON
Data:26/10/05 / Sist automatic

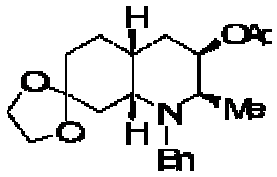
Pulse Sequence: s2pul




11c
11b
C13 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-261005164903
Usuari: san / Mostra: aexcoac
Nom: MARISA MENA CERVIGON
Data:26/10/05 / Sist automatic
Pulse Sequence: s2pul
128.309
128.103
128.072
126.579
109.514
77.320
77.000
76.688
70.720
64.401
64.158
63.845
58.182
52.016
34.761
30.180
29.136
27.772
22.902
16.743
ppm
160
140
120
100
80
60
40

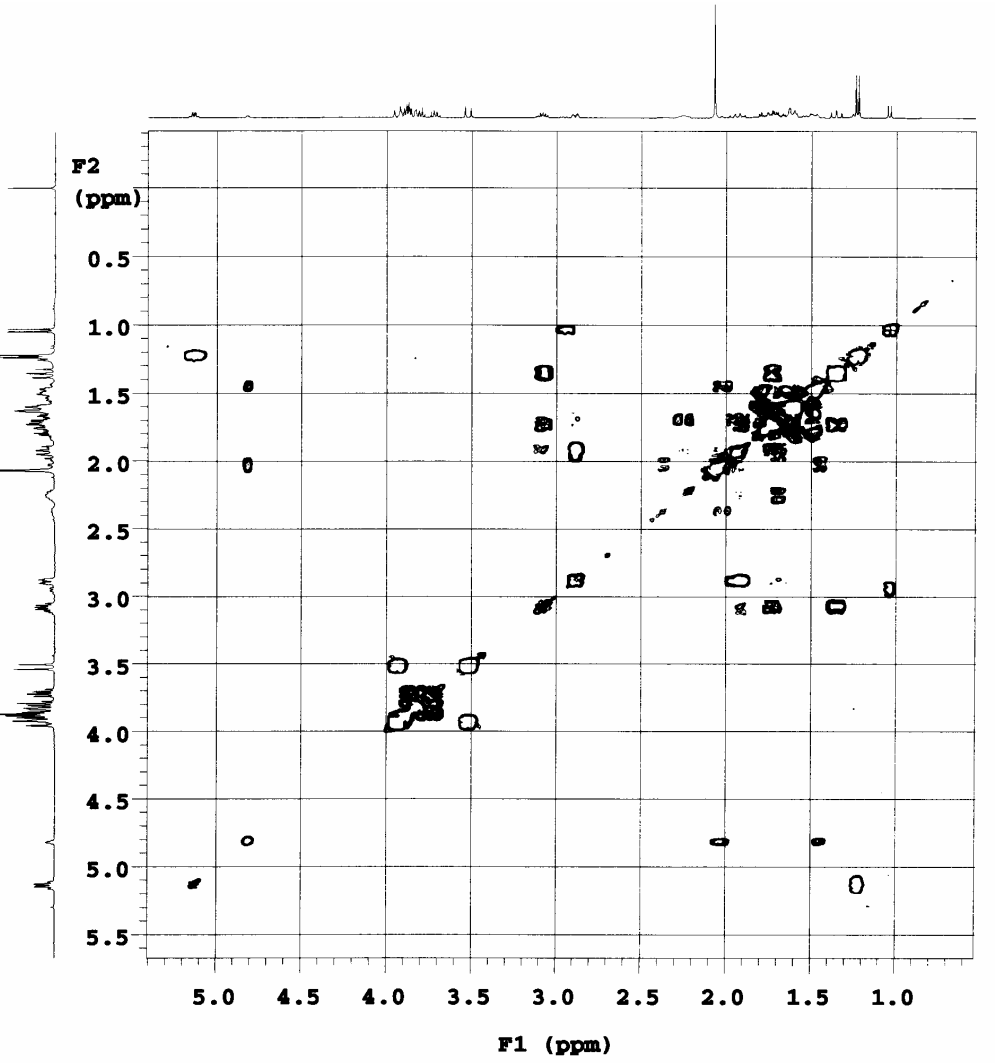


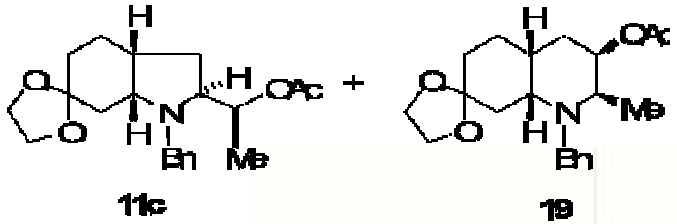
11c



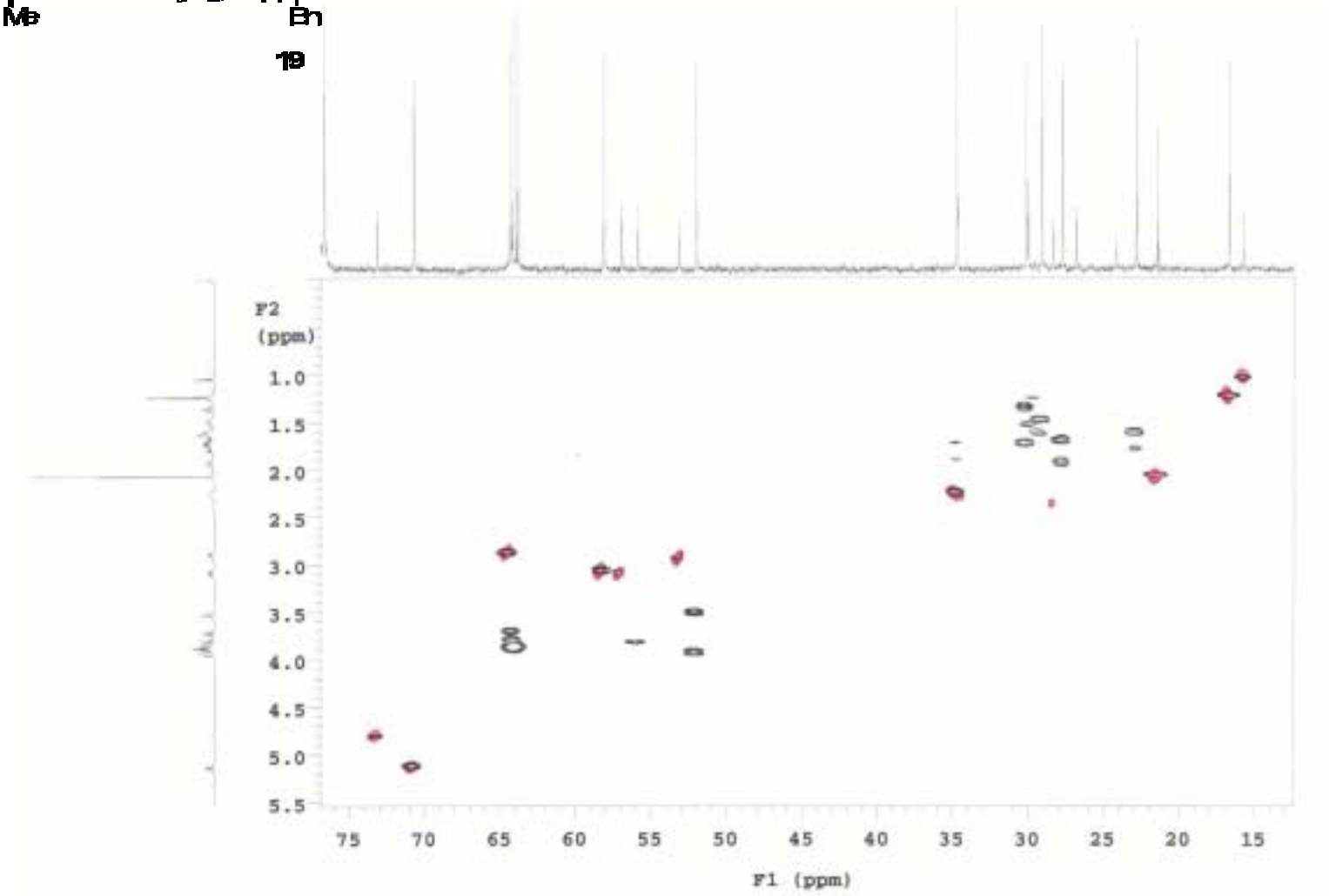
19

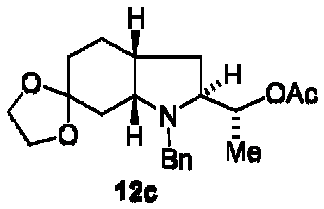
```
H1 / gCOSY / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-261005164
903
Usuari: san / Mostra: aexooac
Nom: MARISA MENA CERVIGON
Data:26/10/05 / Sist automatic

exp3  gCOSY

      SAMPLE                FLAGS
date    Oct 26 2005   hs                nn
solvent       cdcl3   sspul              n
sample auto_Custom~   hsglvl          1000
       Q_26Oct2005          SPECIAL
   ACQUISITION        temp            25.0
sw          3906.2    gain              22
at           0.150    spin               0
np            1172      F2 PROCESSING
fb         not used    sb            -0.075
ss              16    sbs          not used
d1           1.000    fn                2048
nt               4      F1 PROCESSING
  2D ACQUISITION      sb1           -0.066
sw1         3906.2    sbs1         not used
ni              256    proc1             lp
  PRESATURATION       fn1               2048
satmode           n         DISPLAY
satfrq            0   sp             -164.0
satdly            0   wp            2432.3
satpwr            0   sp1            214.0
   TRANSMITTER        wp1           1947.4
tn               H1   rf1            484.7
sfrq        400.113    rfp                0
tof          -547.3    rf11           484.7
tpwr             58    rfp1               0
pw           12.300           PLOT
    GRADIENTS         wc             131.8
gzlvl1         1000    sc                 6.2
gt1        0.001000    wc2            131.8
gstab      0.000500    sc2                0
    DECOUPLER         vs               200
dn               C13   th                 6
dm               nnn   ai  cdc  av
```



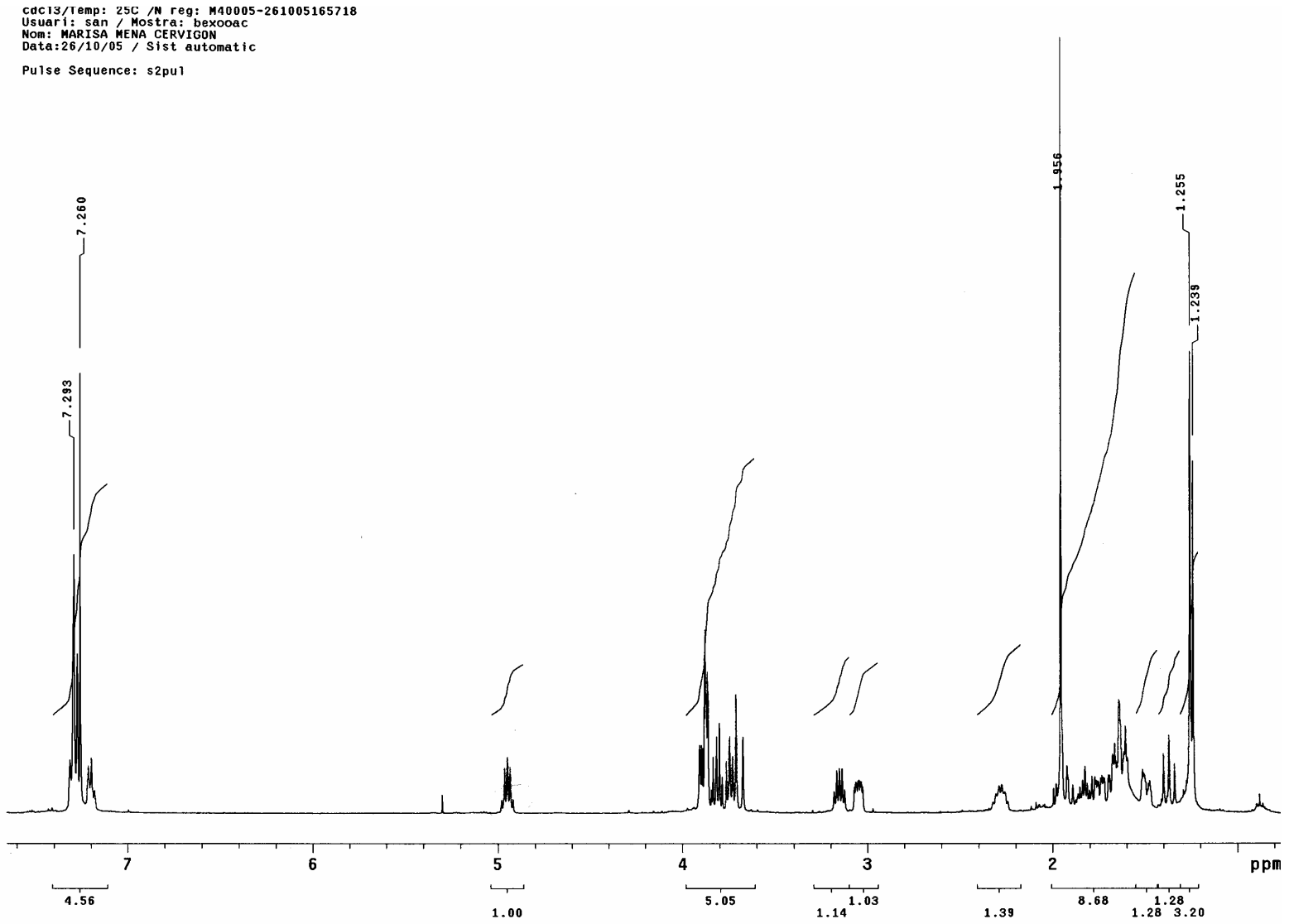

H
O
H
OAc
O
N
H
Bn
Me

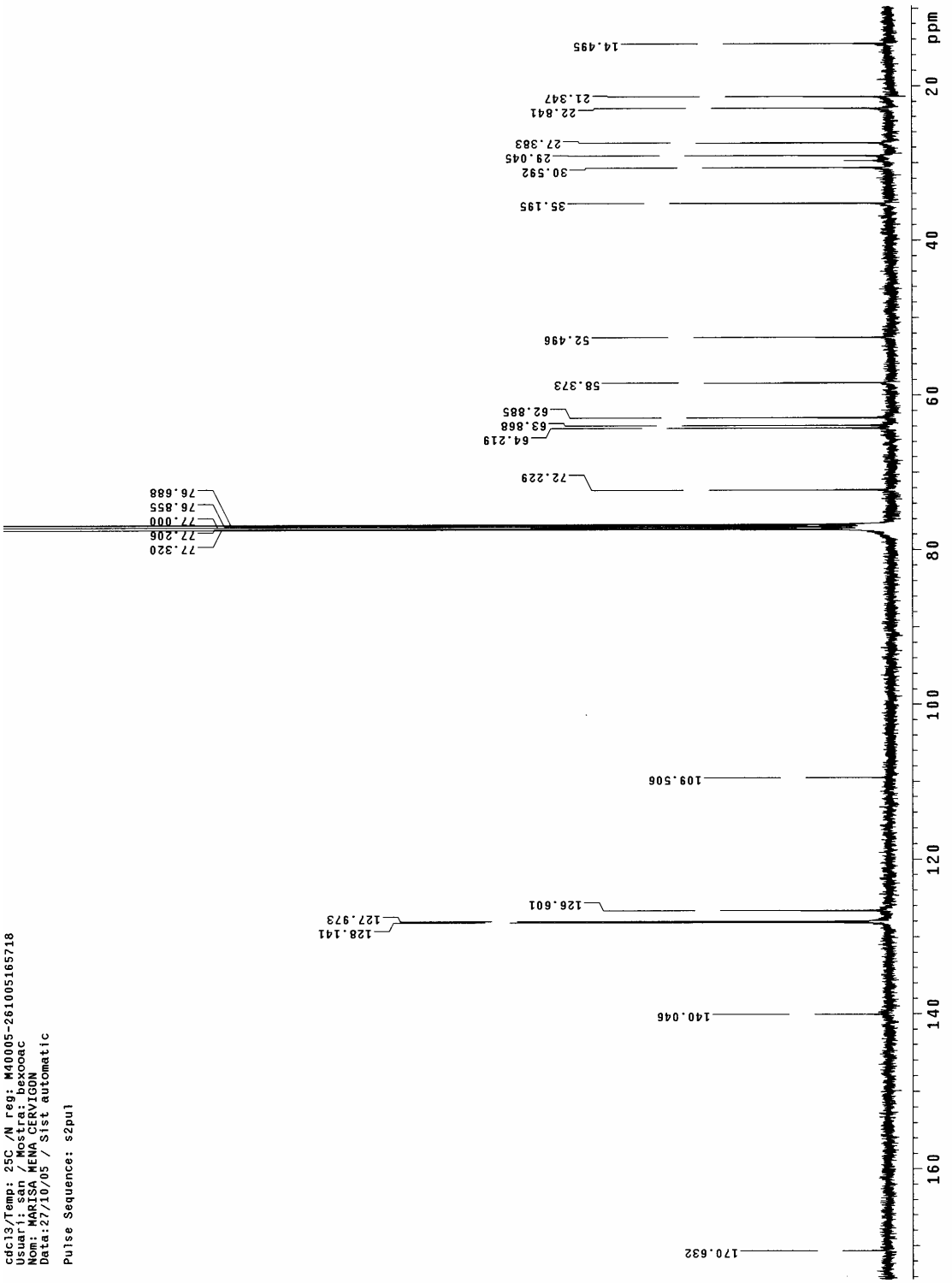
11c + 19

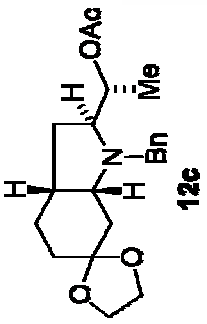

F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
75
70
65
60
55
50
45
40
35
30
25
20
15
F1 (ppm)

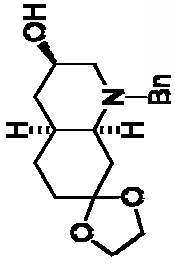

H
O
H
OAc
O
H
N
Bn
Me

12c

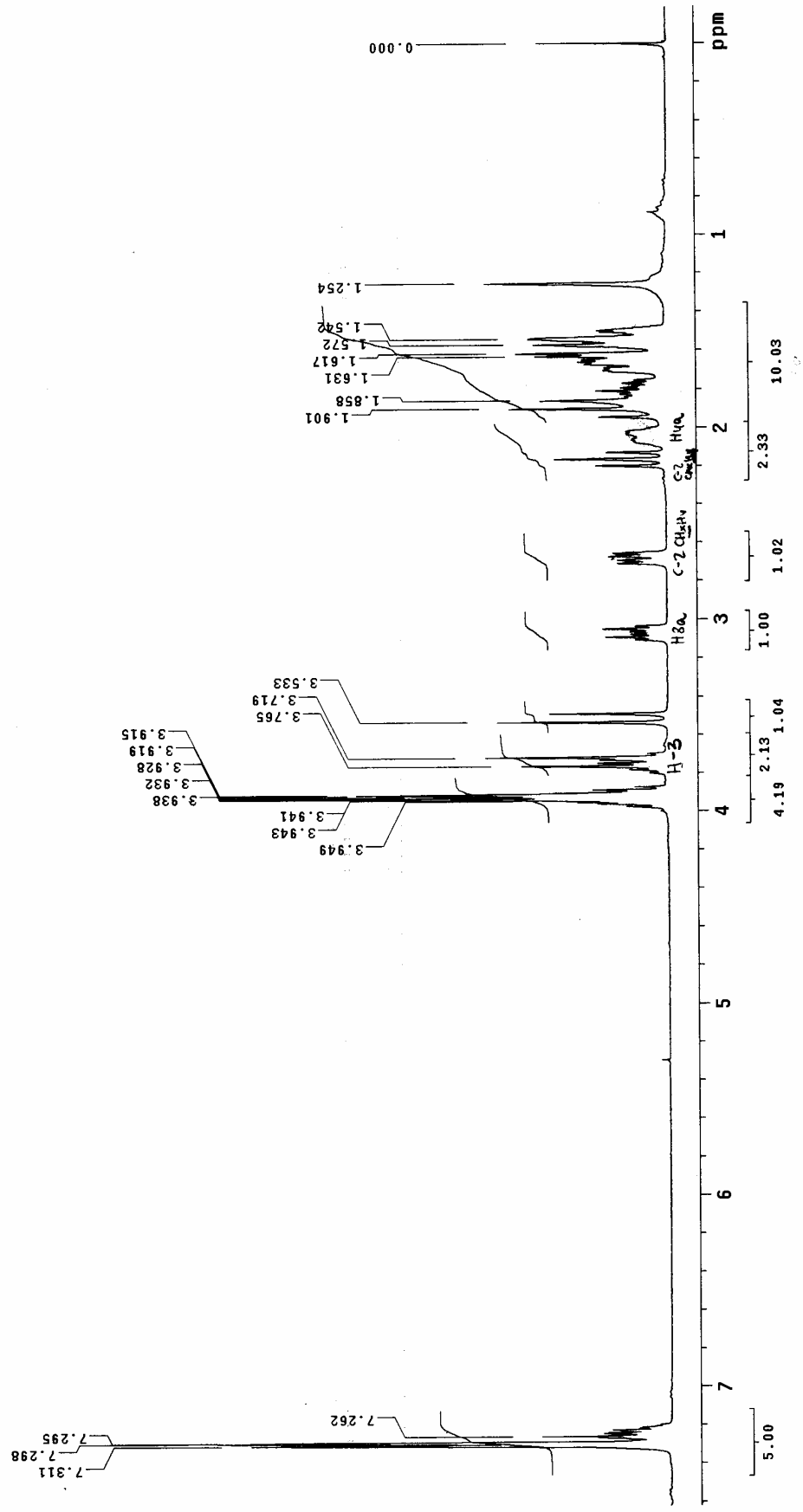

cdcl3/Temp: 25C /N reg: M40005-261005165718
Usuari: san / Mostra: bexooac
Nom: MARISA MENA CERVIGON
Data:26/10/05 / Sist automatic
Pulse Sequence: s2pul
7.260
7.293
1.956
1.255
1.239
7
6
5
4
3
2
ppm
4.56
1.00
5.05
1.14
1.03
1.39
8.68
1.28
1.28
3.20

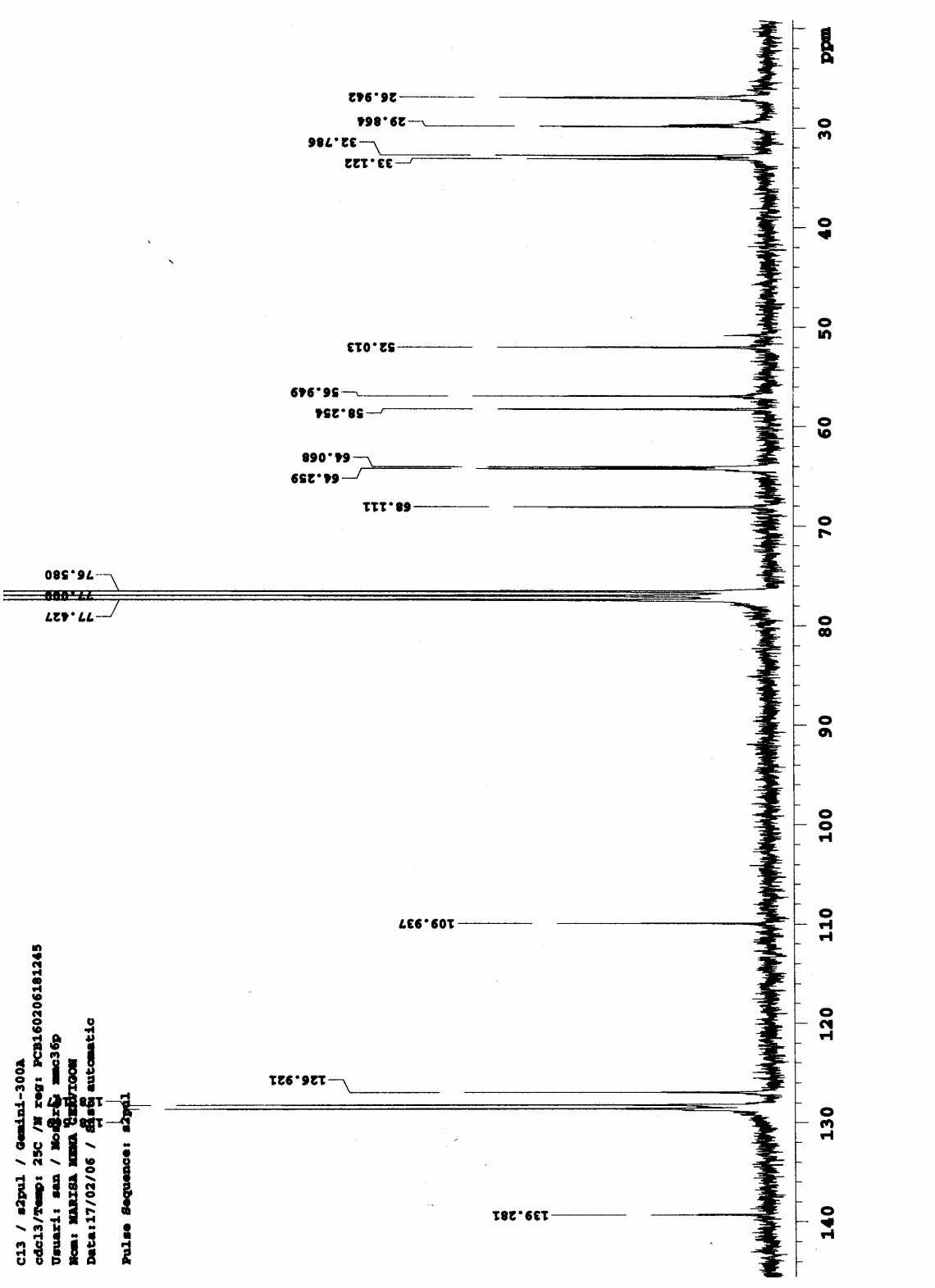

cdcl3/Temp: 25C /N reg: M40005-261005165718
Usuari: san / Mostra: bexooac
Nom: MARISA MENA CERVIGON
Data:27/10/05 / Sist automatic
Pulse Sequence: s2pul
14.495
21.347
22.841
27.383
29.045
30.592
35.195
52.496
58.373
62.885
63.868
64.219
72.229
76.688
76.855
77.000
77.206
77.320
109.506
126.601
127.973
128.141
140.046
170.632
ppm
20
40
60
80
100
120
140
160

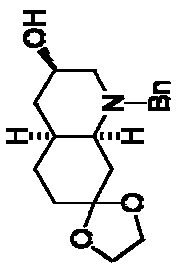

OAc
H
Me
N
Bn
H
H
O
O
12c


OH
N
Bn
H
H
O
O

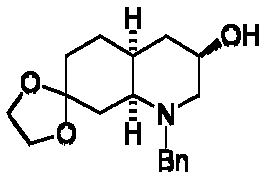
13


ppm
0.000
1.254
1.542
1.572
1.617
1.631
1.858
1.901
3.533
3.719
3.765
3.915
3.919
3.928
3.932
3.938
3.941
3.943
3.949
7.262
7.295
7.298
7.311
H-3
H3a
C-2 CH2Ph
C-2 CH2Ph
H4a
5.00
4.19
2.13
1.04
1.00
1.02
2.33
10.03


C13 / s2pul / Gemini-300A
cdcl3/Temp: 25C /N reg: PCB160206181245
Usuari: san / Mo
Nom: MARSA MMA
Data:17/02/06 /
Pulse Sequence: s2pul
139.281
126.921
109.937
77.427
76.580
68.111
64.259
64.068
58.254
56.949
52.013
33.122
32.786
29.864
26.942
ppm


OH
N
Bn
H
H
O
O

13



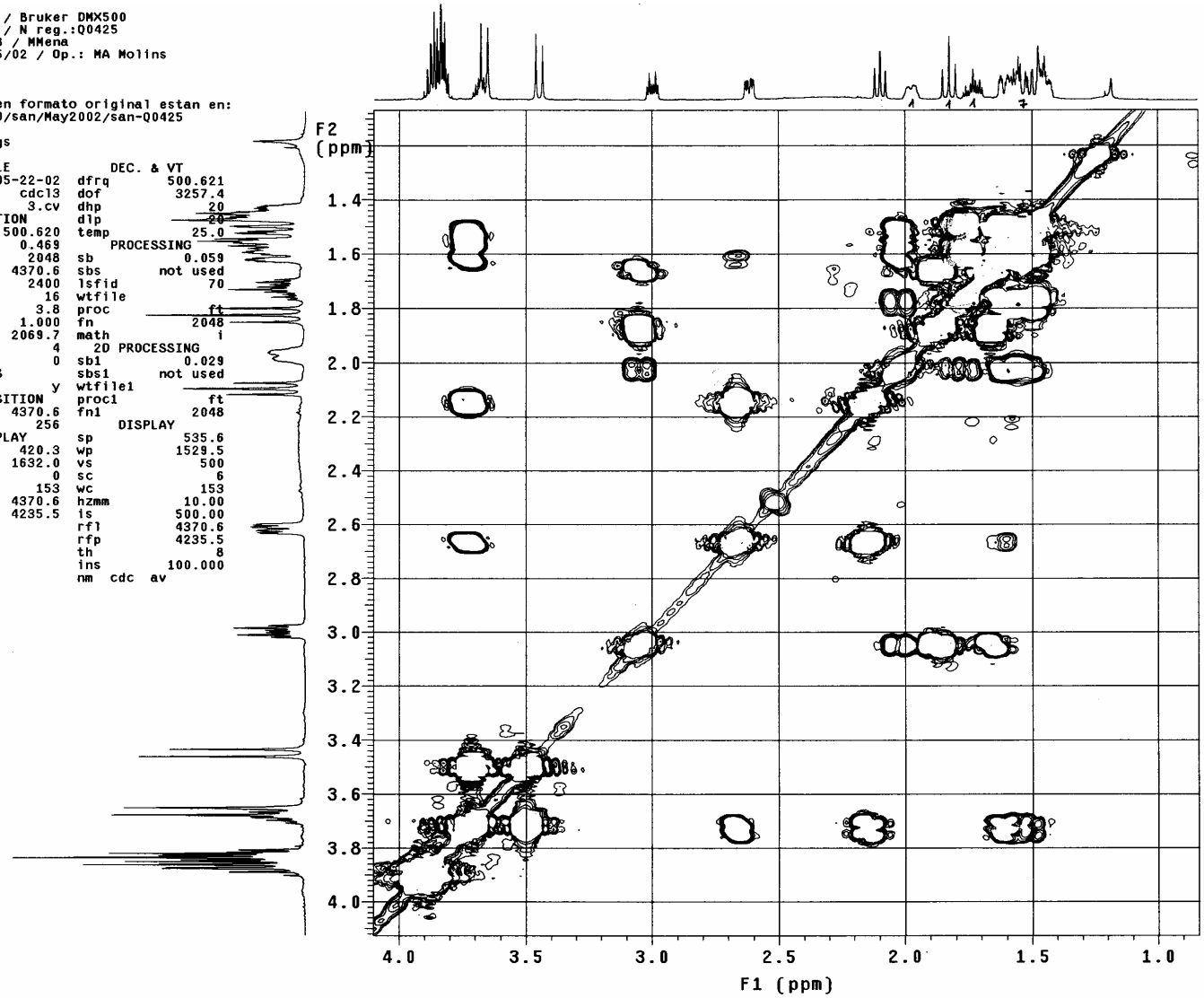
13

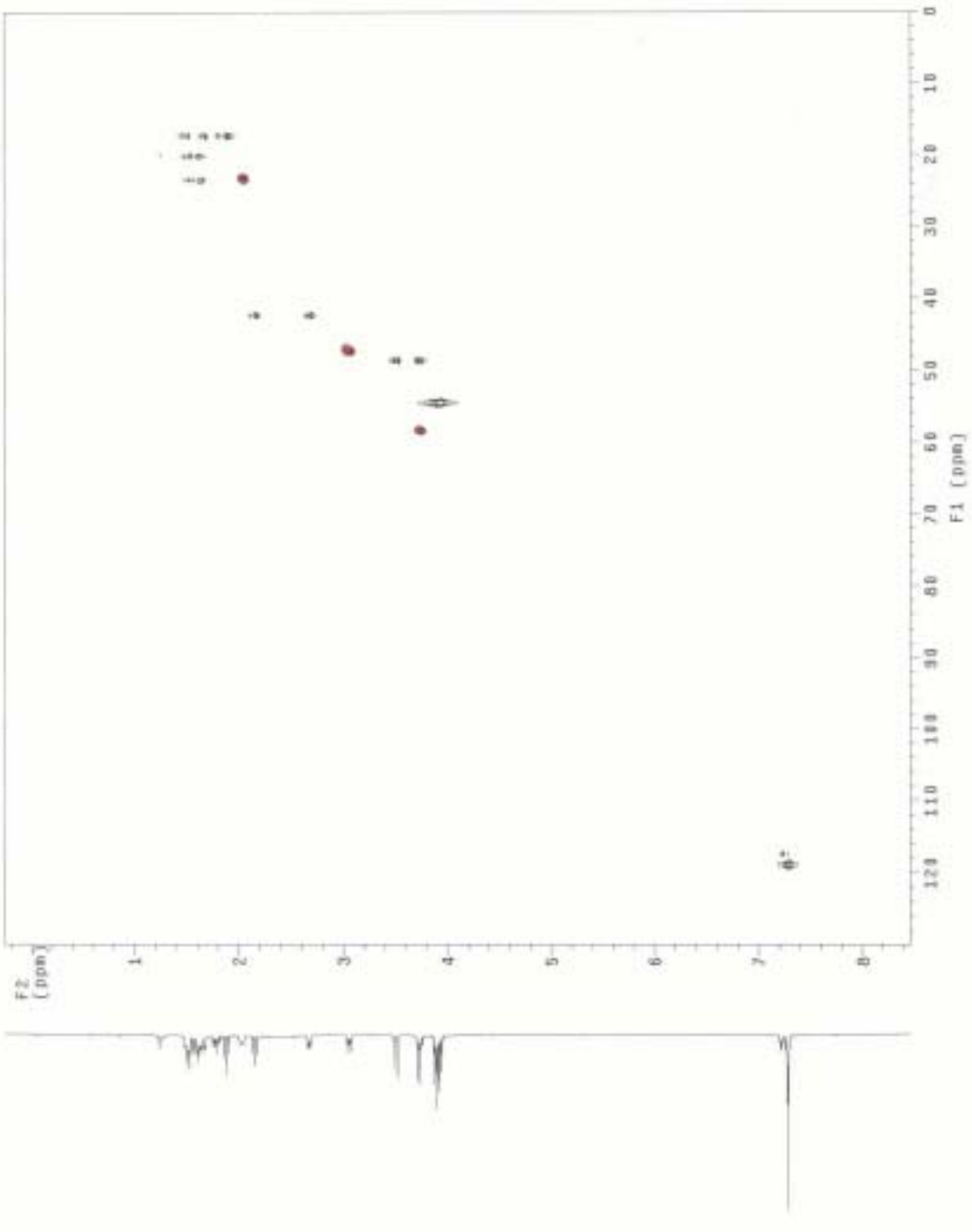
H1 / gcosy / Bruker DMX500
cdcl3/ 25C / N reg.:Q0425
san/ mmc038 / MMena
Data: 22/05/02 / Op.: MA Molins

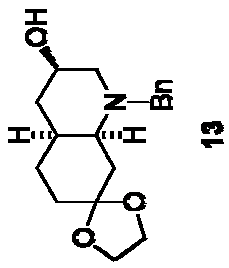
los datos en formato original estan en:
/data3/B500/san/May2002/san-Q0425

exp1 cosygs

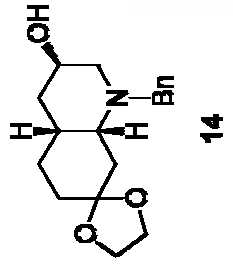
SAMPLE		DEC. & VT	
date	05-22-02	dfrq	500.621
solvent	cdcl3	dof	3257.4
file	3.cv	dhp	20
ACQUISITION		dlp	20
sfrq	500.620	temp	25.0
at	0.469	PROCESSING	
np	2048	sb	0.059
sw	4370.6	sbs	not used
fb	2400	lsfid	70
ss	16	wtfile	
pw	3.8	proc	ft
rd	1.000	fn	2048
tof	2069.7	math	i
nt	4	2D PROCESSING	
ct	0	sb1	0.029
FLAGS		sbs1	not used
dp	y	wtfile1	
2D ACQUISITION		proc1	ft
sw1	4370.6	fn1	2048
ni	256	DISPLAY	
2D DISPLAY		sp	535.6
sp1	420.3	wp	1529.5
wp1	1632.0	vs	500
sc2	0	sc	6
wc2	153	wc	153
rfl1	4370.6	hzmm	10.00
rfp1	4235.5	is	500.00
		rfl	4370.6
		rfp	4235.5
		th	8
		ins	100.000
		nm cdc av	



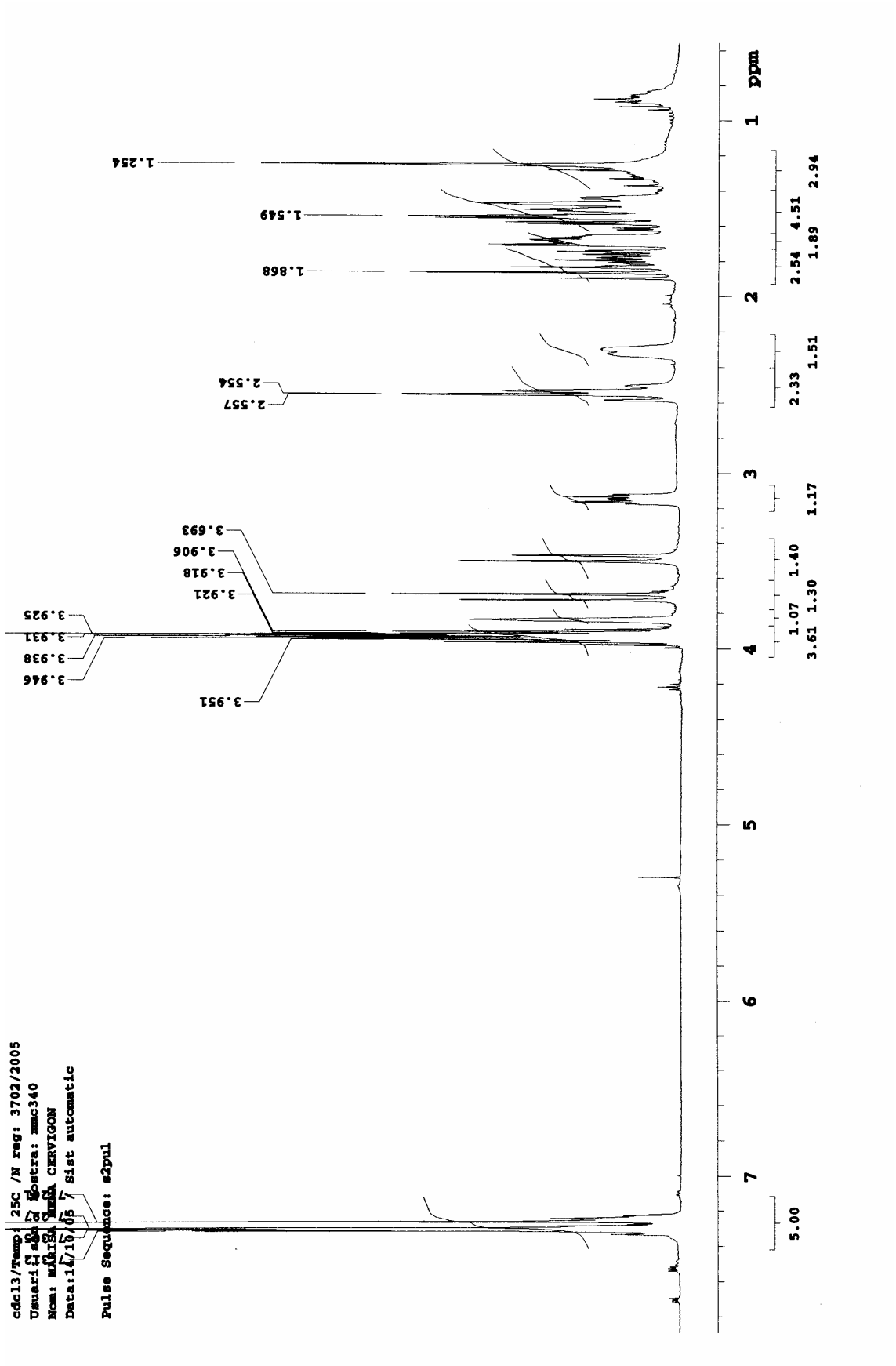


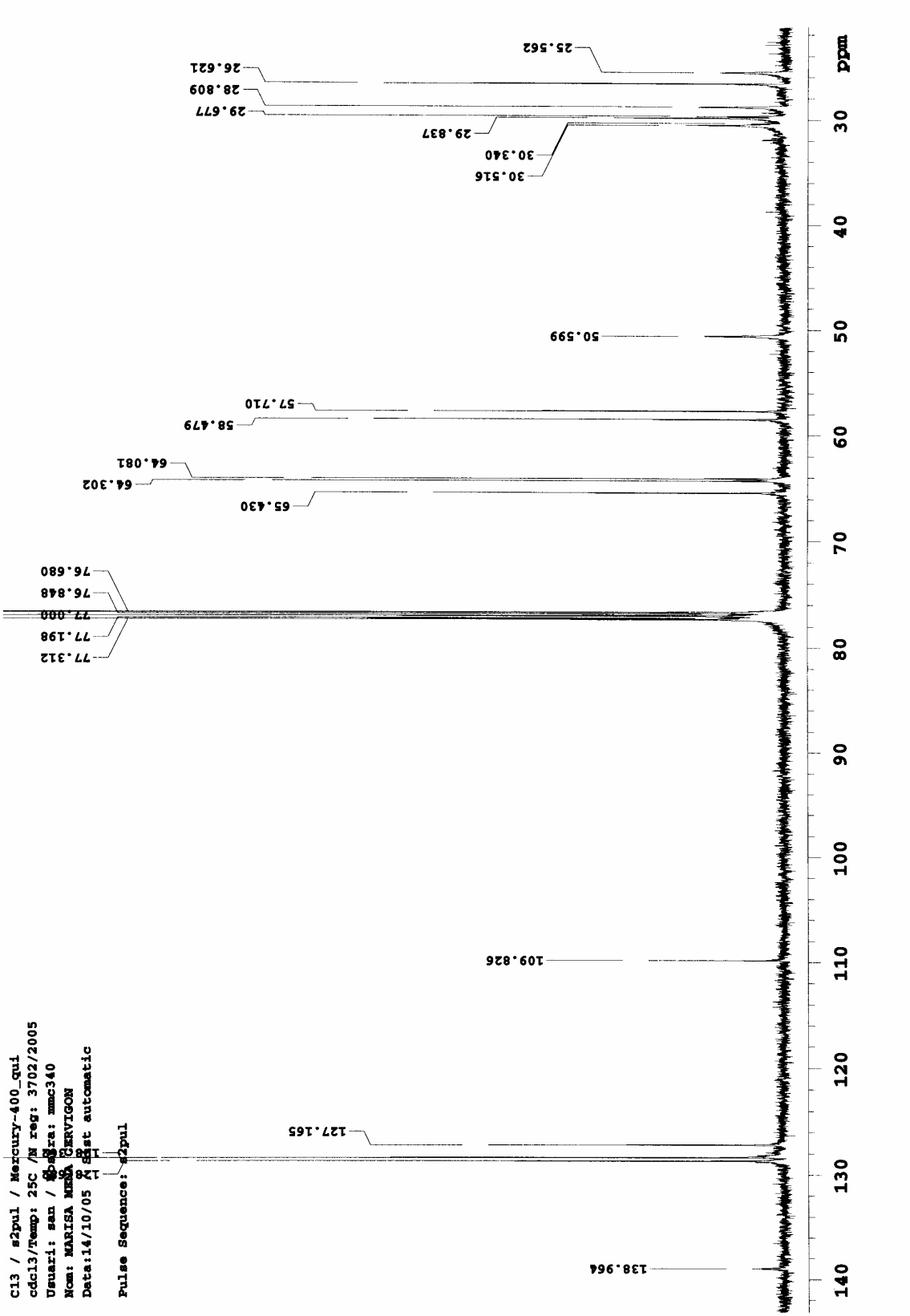


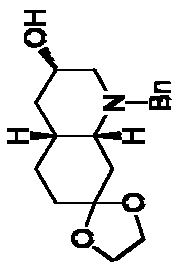
13


OH
N
Bn
H
H
O
O

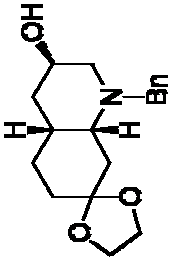
14


cdcl3/Temp: 25C /N reg: 3702/2005
Pulse Sequence: s2pul
1.254
1.549
1.868
2.554
2.557
3.693
3.906
3.918
3.921
3.925
3.931
3.938
3.946
3.951
ppm
5.00
1.07
1.40
3.61
1.30
1.17
2.33
1.51
2.54
4.51
1.89
2.94

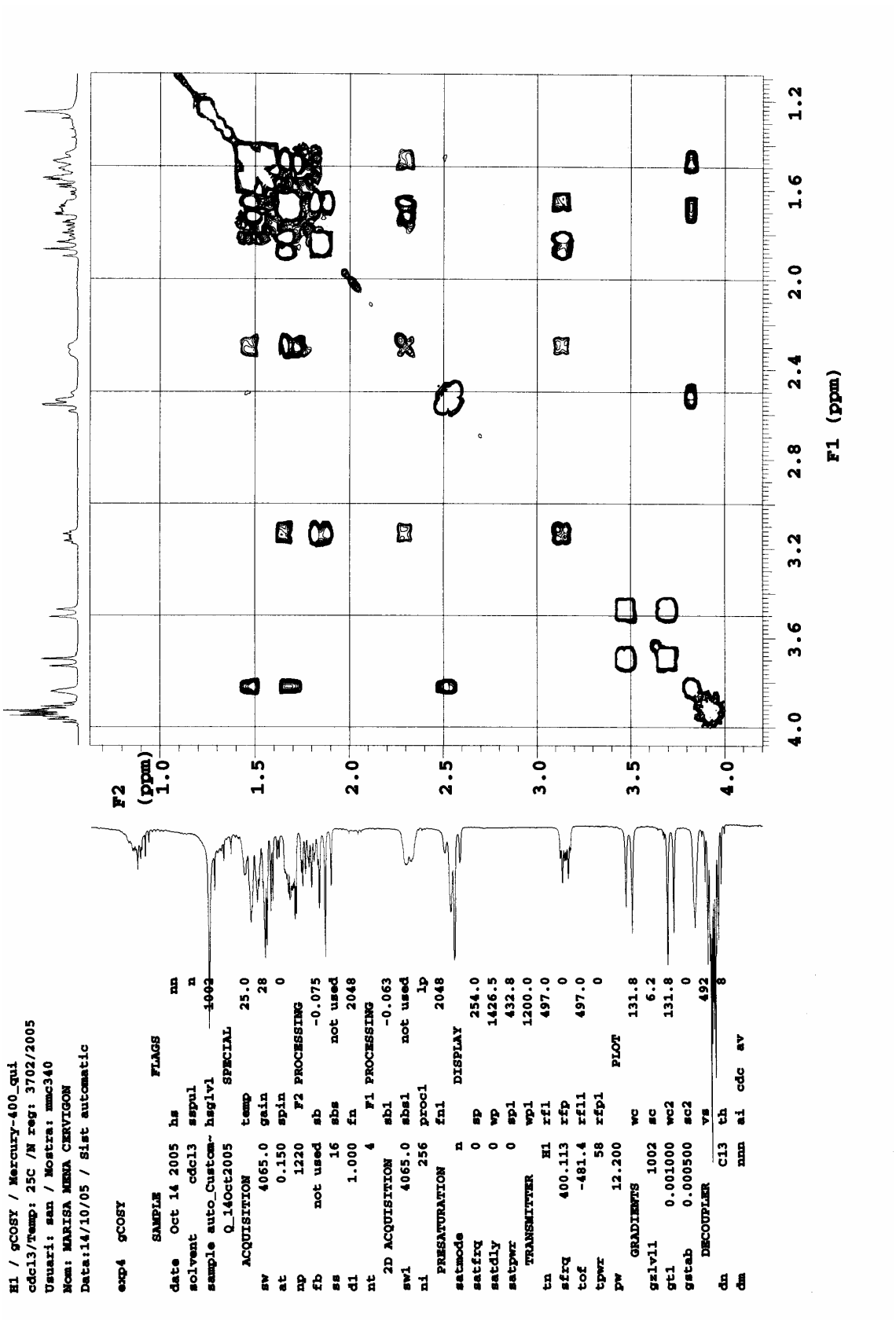

C13 / s2pul / Mezcury-400_qui
cdcl3/Temp: 25C /N rep: 3702/2005
Usuari: san / Spectra: mmc340
Nom: MARISA MERA SERVIGON
Data:14/10/05 Sist automatic
Pulse Sequence: s2pul
138.964
127.165
109.826
77.312
77.198
77.000
76.848
76.680
65.430
64.302
64.081
58.479
57.710
50.599
30.516
30.340
29.837
29.677
28.809
26.621
25.562
ppm

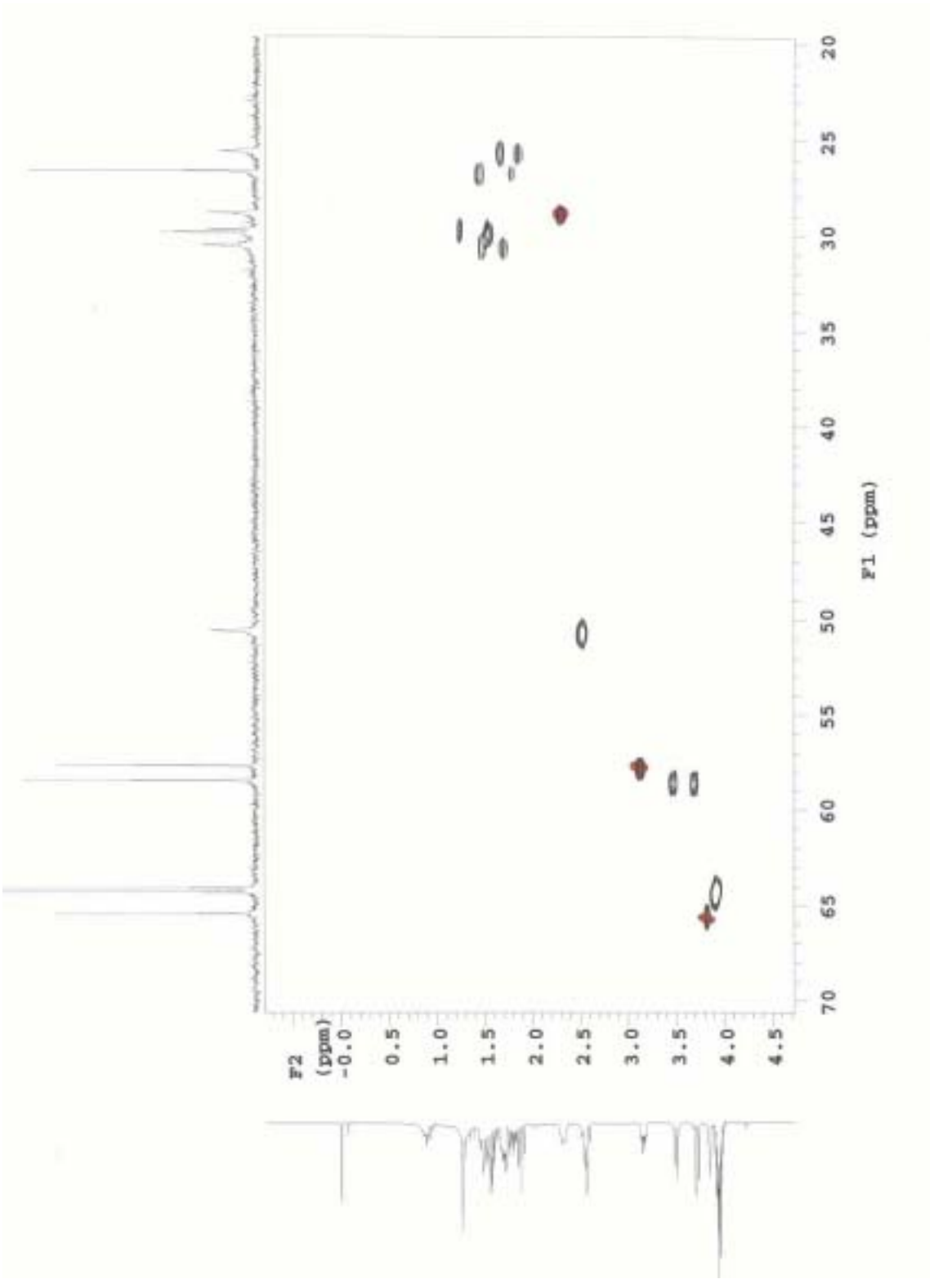

OH
N
Bn
H
H
O
O

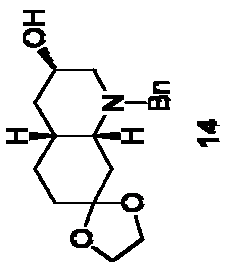
14


OH
N
Bn
H
H
O
O

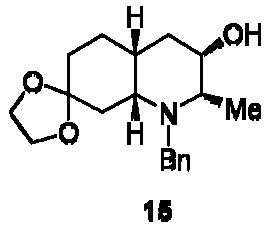
14


H1 / gCOSY / Mercury-400_qui
cdcl3/Temp: 25C /N reg: 3702/2005
Usuari: san / Mostra: mmc340
Nom: MARISA MESA CERVIGON
Data:14/10/05 / Sist automatic
exp4 gCOSY
SAMPLE FLAGS
date Oct 14 2005 hs nn
solvent cdcl3 sspul n
sample auto_Custom~ hsglvl 1002
Q_14Oct2005 SPECIAL
ACQUISITION temp 25.0
sw 4065.0 gain 28
at 0.150 spin 0
np 1220 F2 PROCESSING
fb not used sb -0.075
ss 16 sbs not used
dl 1.000 fn 2048
nt 4 F1 PROCESSING
2D ACQUISITION sb1 -0.063
sw1 4065.0 sbs1 not used
ni 256 procl lp
PRESATURATION fn1 2048
satmode n DISPLAY
satfrq 0 sp 254.0
satdly 0 wp 1426.5
satpwr 0 sp1 432.8
TRANSMITTER wp1 1200.0
tn H1 rf1 497.0
sfrq 400.113 rfp 0
tof -481.4 rfl1 497.0
tpwr 58 rfp1 0
pw 12.200 PLOT
GRADIENTS wc 131.8
gzlvl1 1002 sc 6.2
gt1 0.001000 wc2 131.8
gstab 0.000500 sc2 0
DECOUPLER vs 492
dn C13 th 8
dm nnn ai cdc av
F2 (ppm)
F1 (ppm)

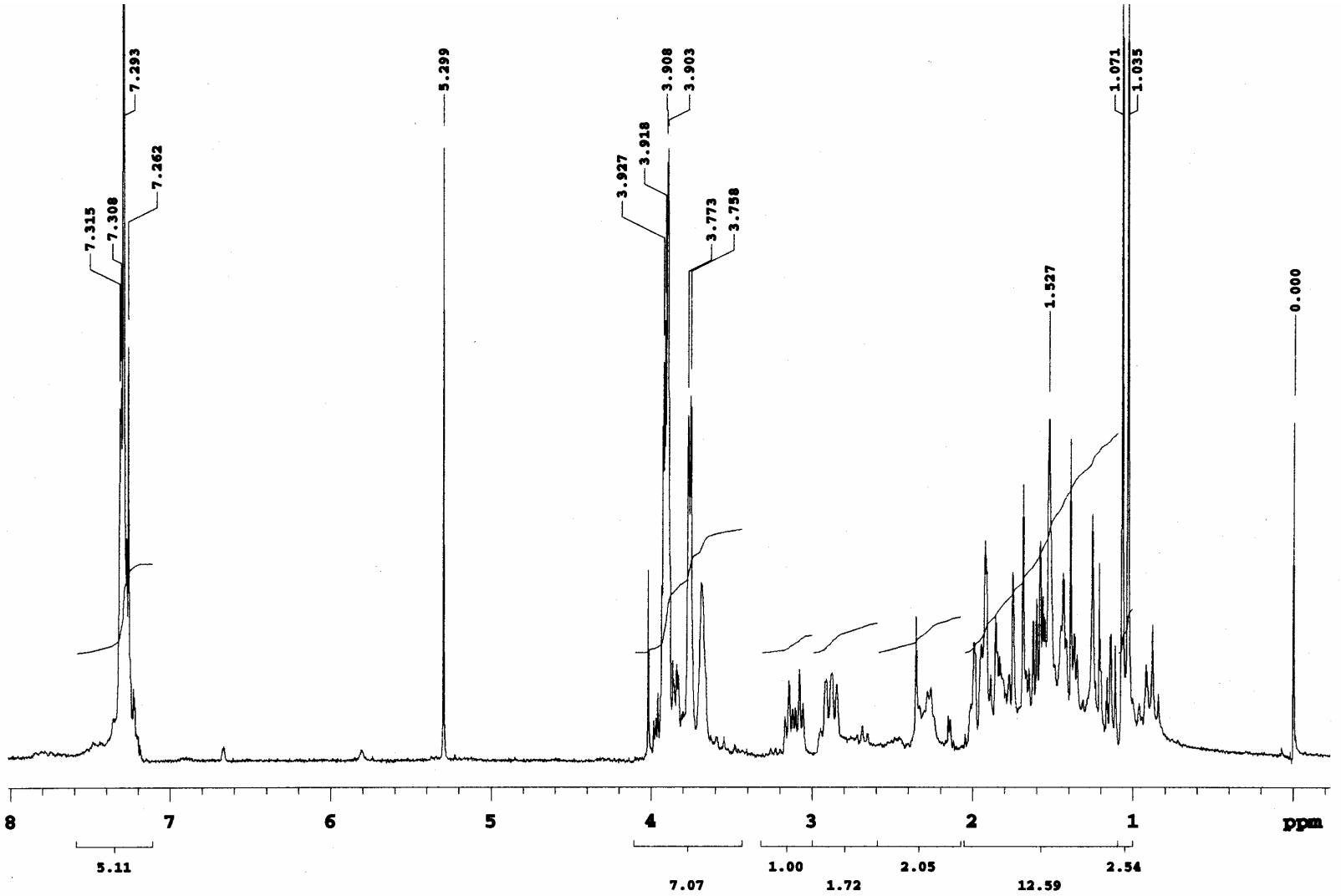


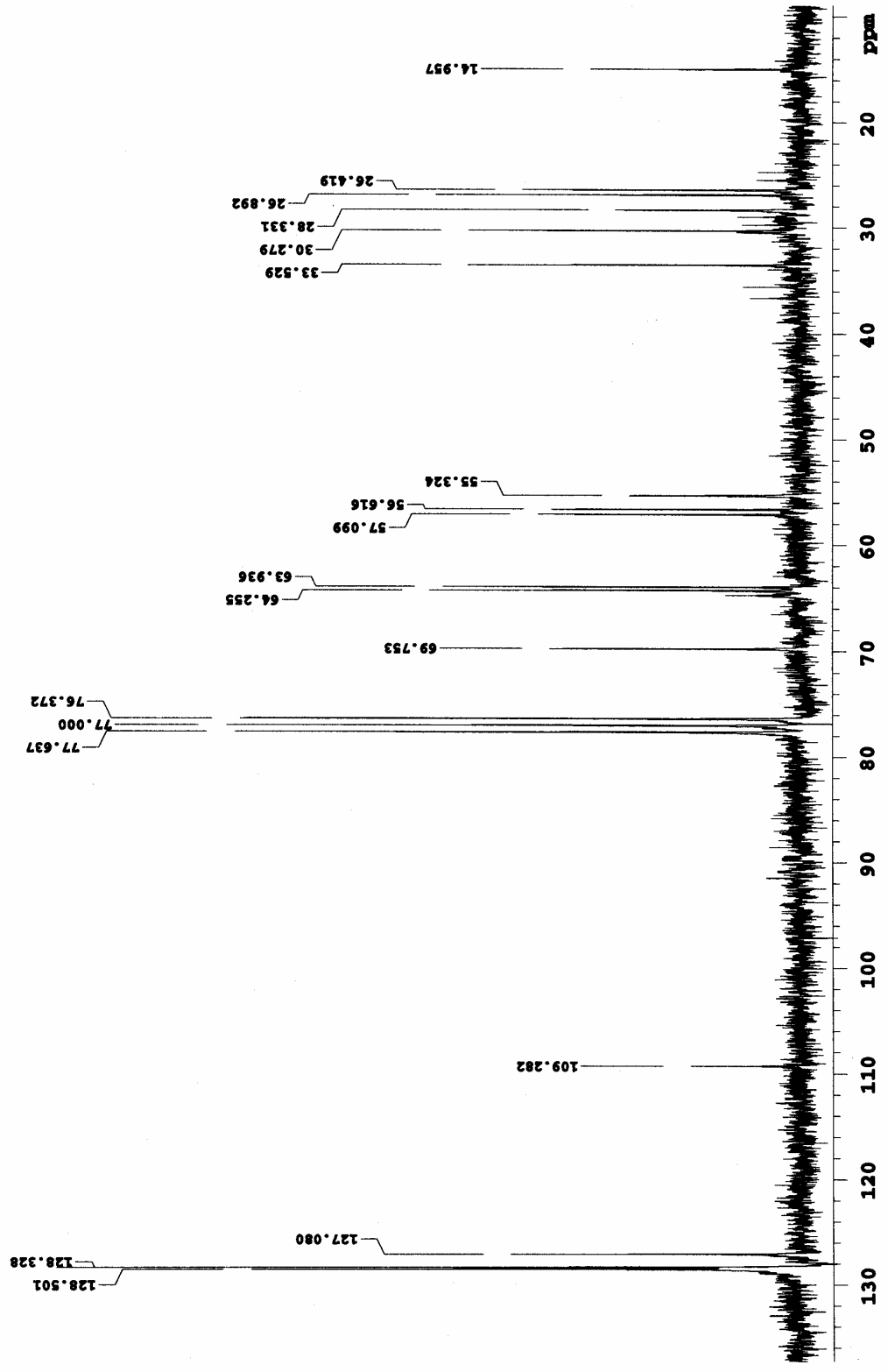


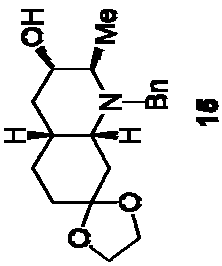
14


H
OH
O
O
N
H
Me
Bn

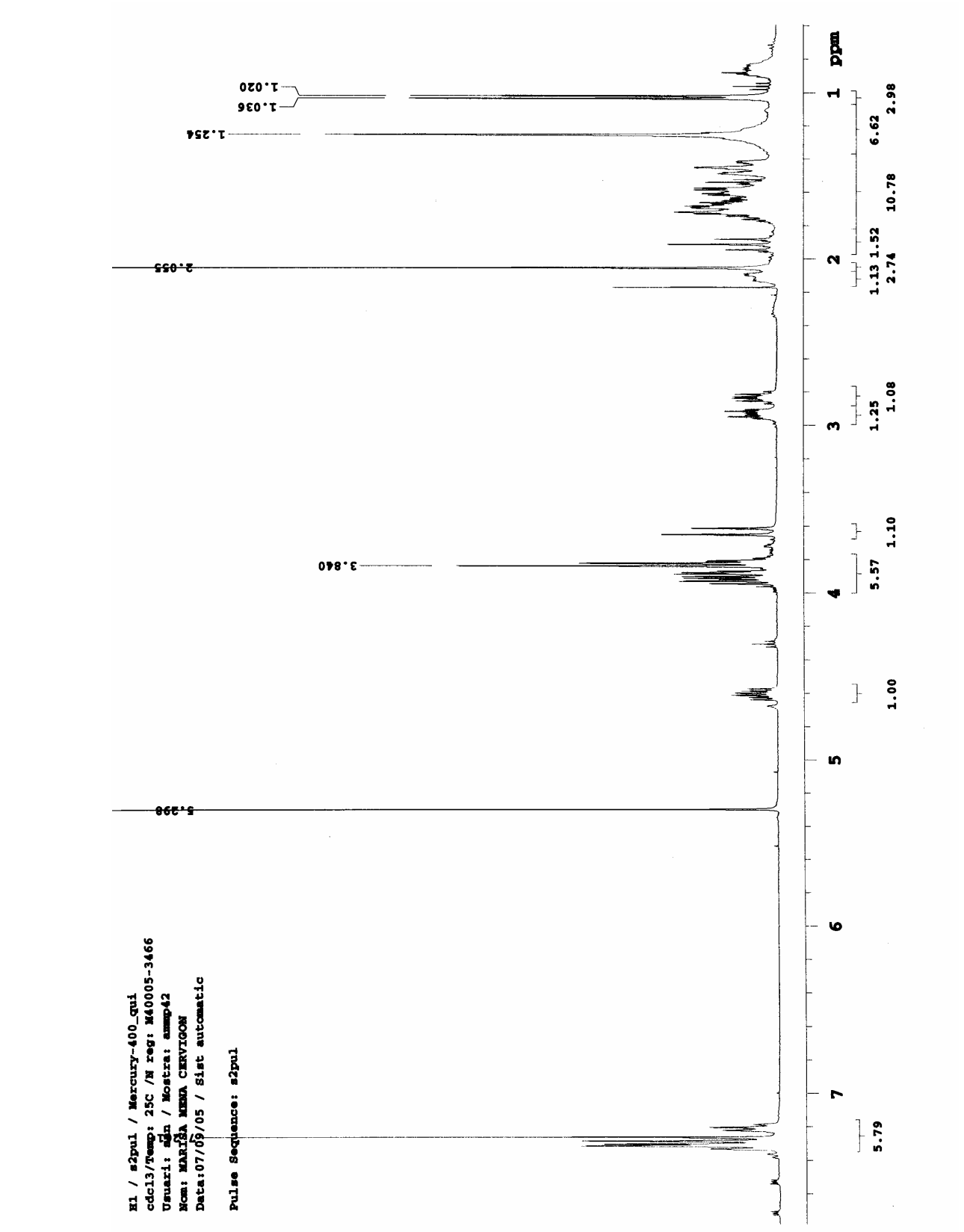
15

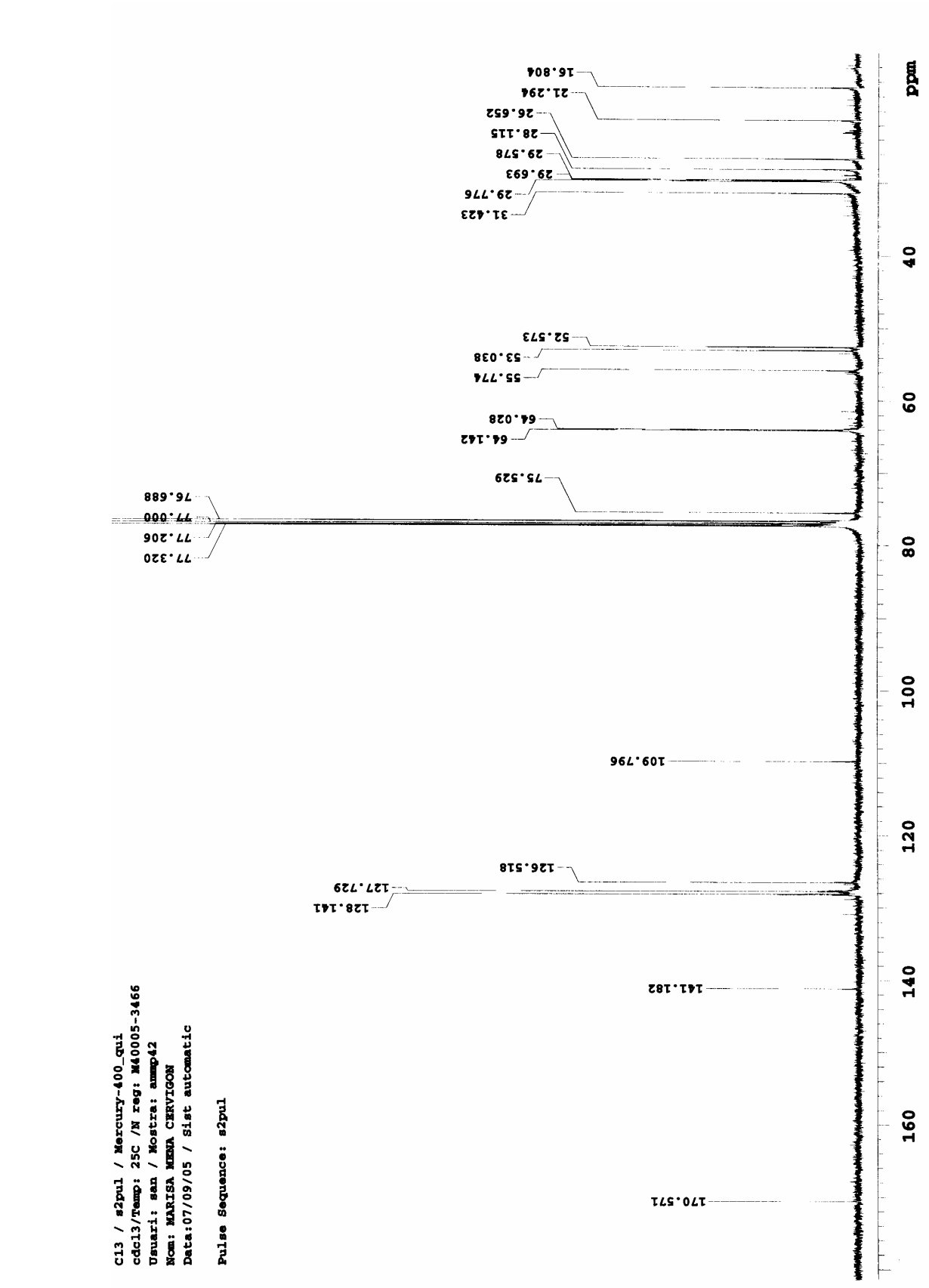

7.315
7.308
7.293
7.262
5.299
3.927
3.918
3.908
3.903
3.773
3.758
1.527
1.071
1.035
0.000
8
7
6
5
4
3
2
1
ppm
5.11
7.07
1.00
1.72
2.05
12.59
2.54

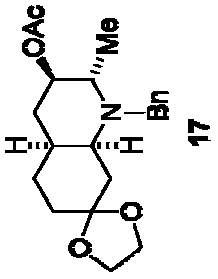

14.957
26.419
26.892
28.331
30.279
33.529
55.324
56.616
57.099
63.936
64.255
69.753
76.372
77.000
77.637
109.282
127.080
128.328
128.501
ppm
20
30
40
50
60
70
80
90
100
110
120
130


OH
Me
N
Bn
H
H
O
O

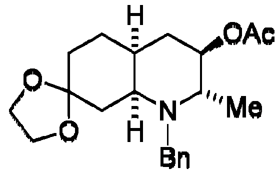
15


H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-3466
Usuari: sdn / Mostra: amnp42
Nom: MARTA MERA CERVIGON
Data:07/09/05 / Sist automatic
Pulse Sequence: s2pul
5.398
3.840
2.055
1.254
1.036
1.020
ppm
OAc
Me
Bn
17


C13 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-3466
Usuari: san / Mostra: ammp42
Nom: MARISA MENA CERVIGON
Data:07/09/05 / Sist automatic
Pulse Sequence: s2pul
170.571
141.182
128.141
127.729
126.518
109.796
77.320
77.206
77.000
76.688
75.529
64.142
64.028
55.774
53.038
52.573
31.423
29.776
29.693
29.578
28.115
26.652
21.294
16.804
ppm
160
140
120
100
80
60
40

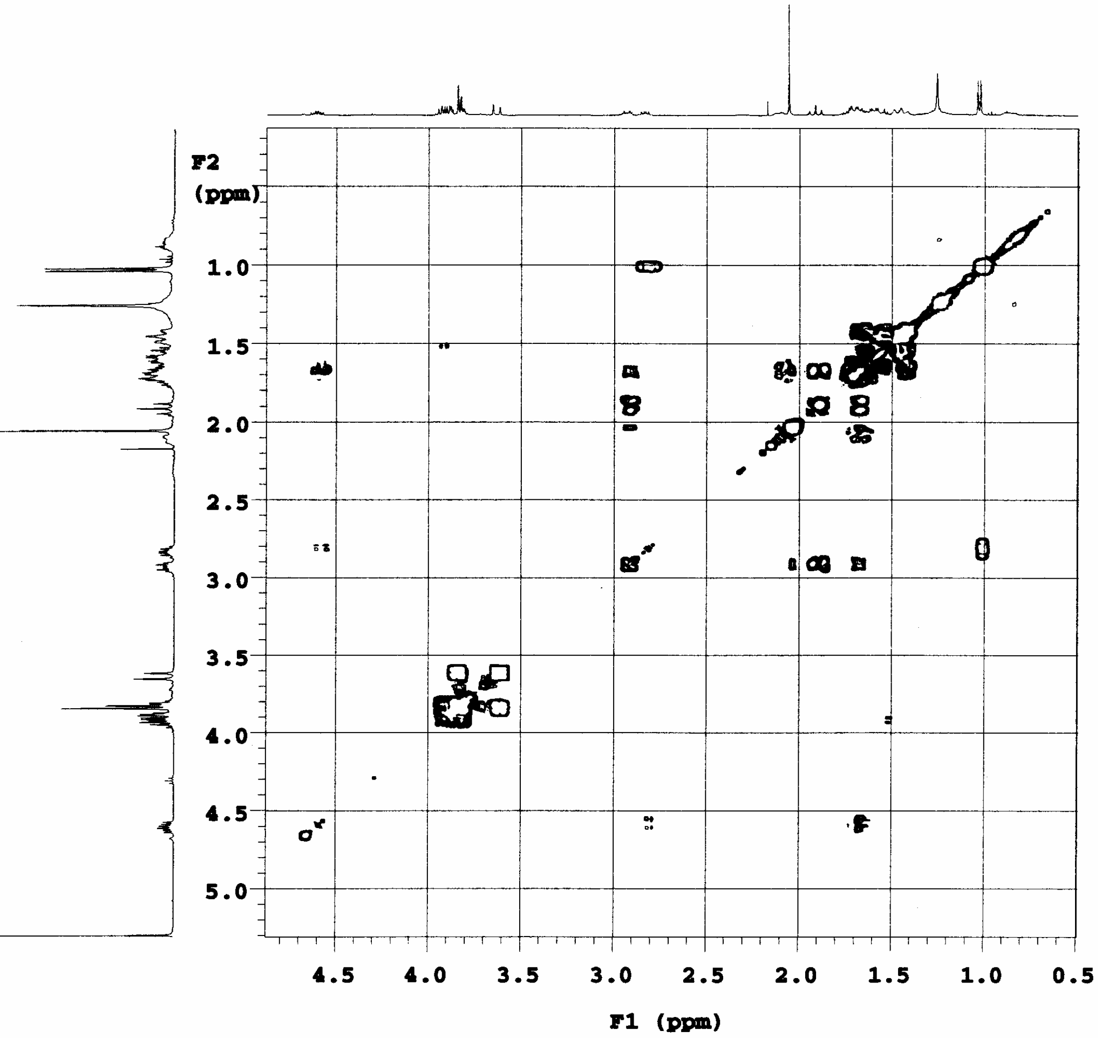

OAc
Me
N
Bn
H
H
O
O

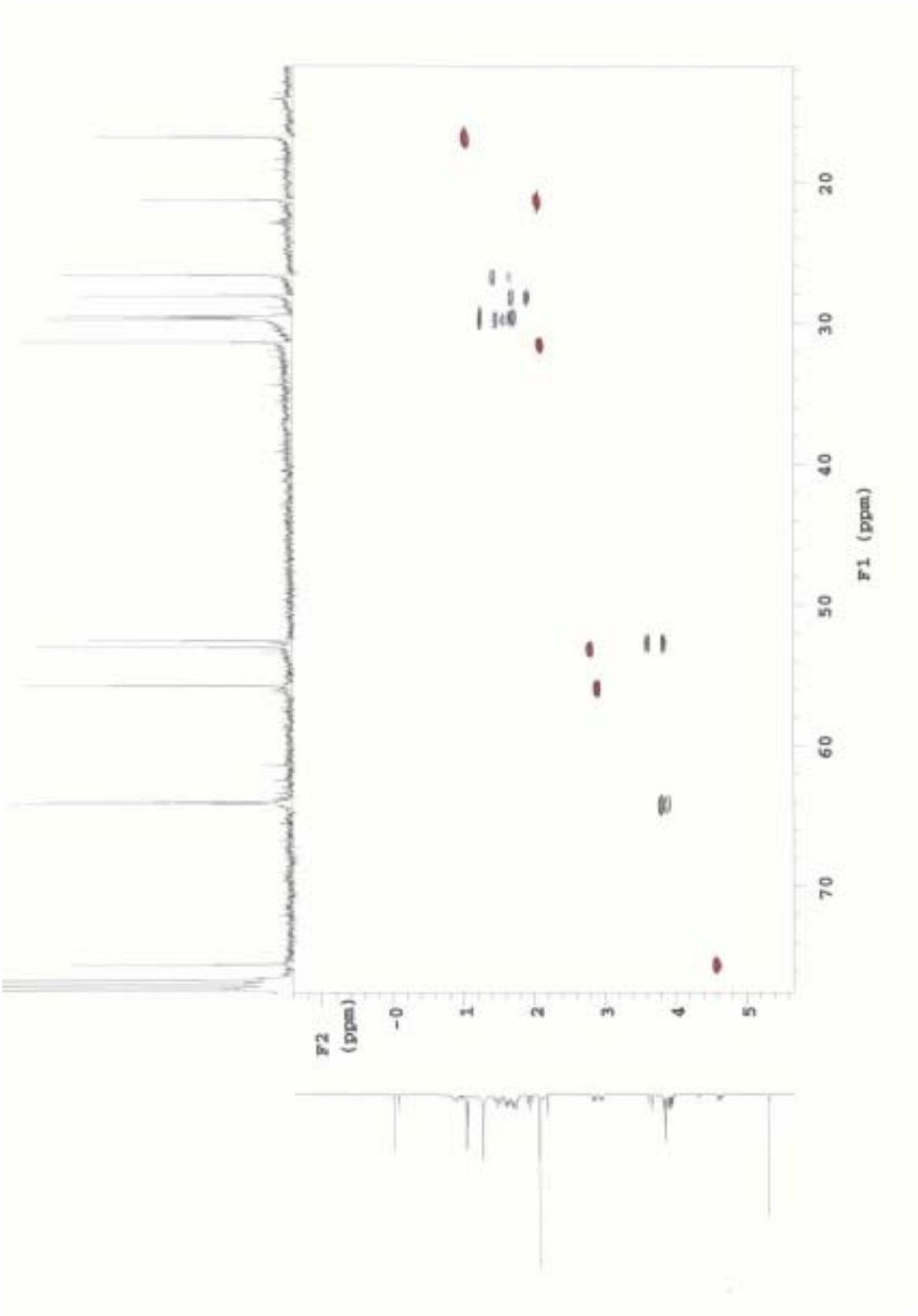
17

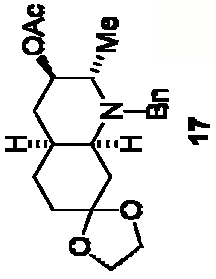


17

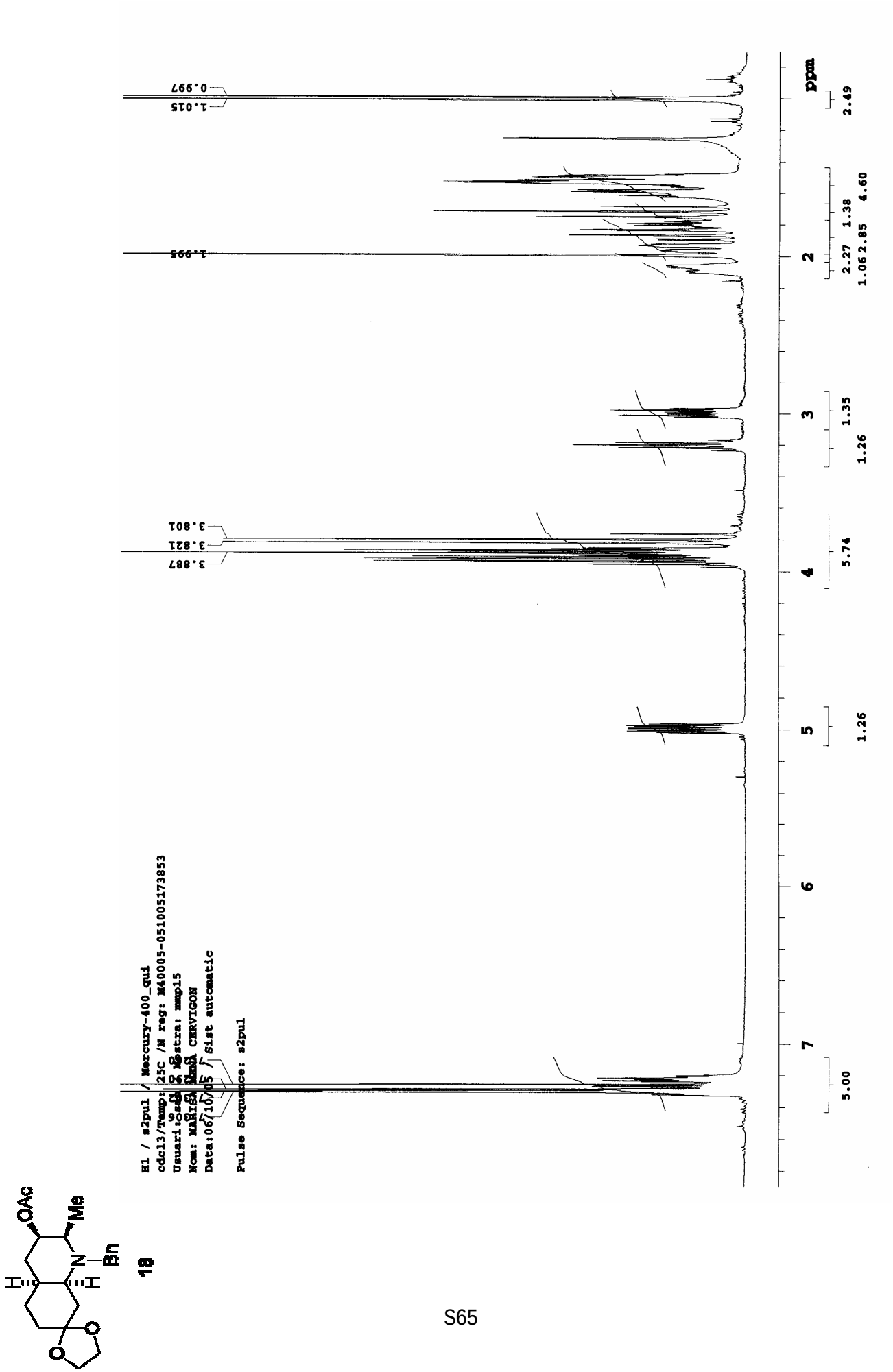
```
H1 / gCOSY / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-3466
Usuari: san / Mostra: ammp42
Nom: MARISA MENA CERVIGON
Data:07/09/05 / Sist automatic

exp3  gCOSY

      SAMPLE                FLAGS
date    Sep  7 2005  hs              nn
solvent       cdcl3  sspul            n
sample auto_Custom-  hsglvl        1002
       Q_07Sep2005        SPECIAL
  ACQUISITION        temp          25.0
sw           4310.3  gain            28
at            0.150  spin             0
np             1294     F2 PROCESSING
fb         not used  sb          -0.075
ss               16  sbs       not used
d1            1.000  fn            2048
nt                4     F1 PROCESSING
  2D ACQUISITION     sb1         -0.059
sw1          4310.3  sbs1      not used
ni              256  proc1           lp
  PRESATURATION      fn1           2048
satmode           n       DISPLAY
satfrq            0  sp            54.4
satdly            0  wp          2068.8
satpwr            0  sp1          197.7
  TRANSMITTER        wp1         1752.8
tn               H1  rfl          573.4
sfrq        400.113  rfp              0
tof          -430.2  rfl1         573.4
tpwr             58  rfp1             0
pw           12.200        PLOT
  GRADIENTS          wc           131.8
gzlvl1         1002  sc             6.2
gt1        0.001000  wc2          131.8
gstab      0.000500  sc2              0
  DECOUPLER          vs             171
dn              C13  th               7
dm              nnn  ai  cdc  av
```

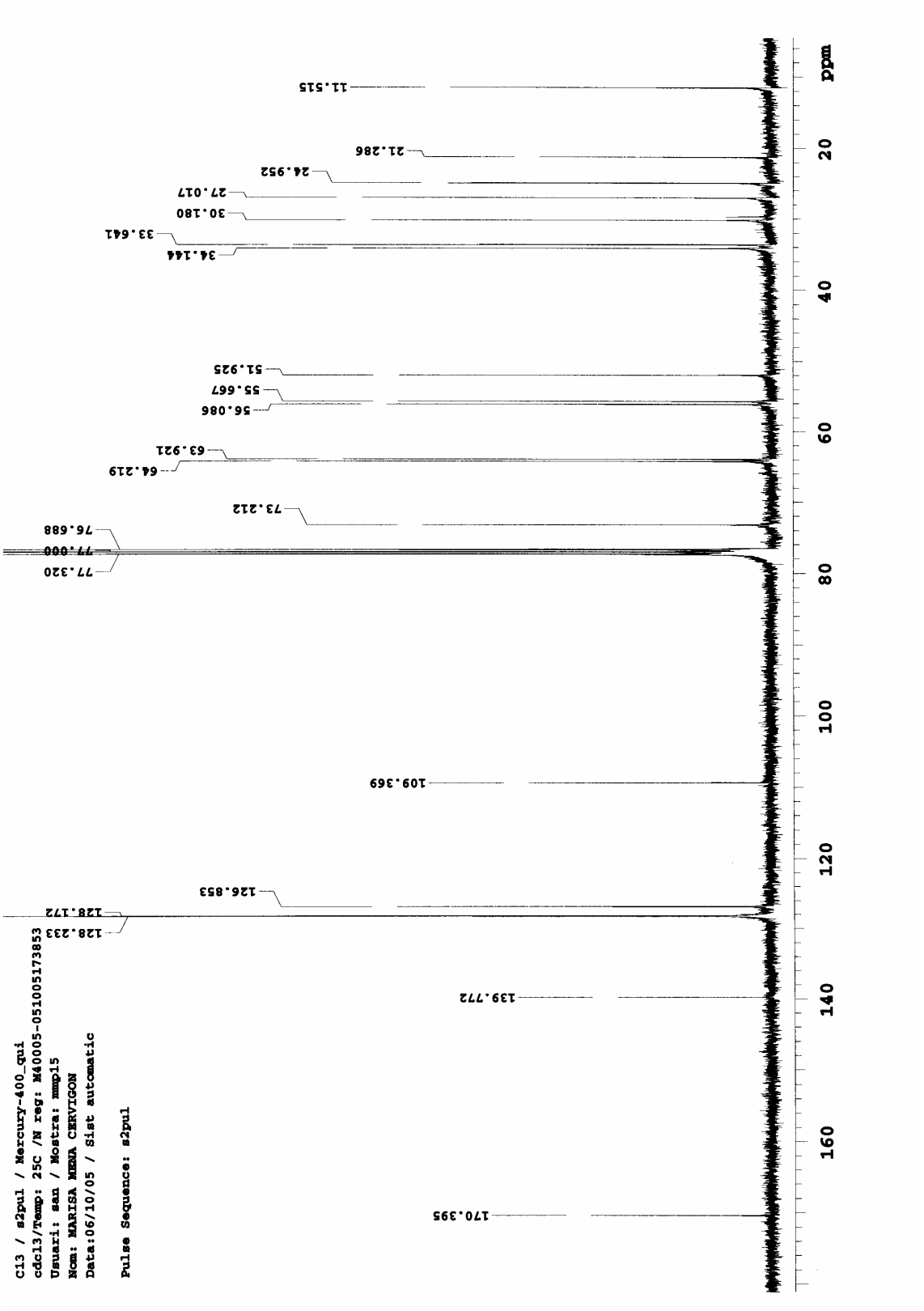


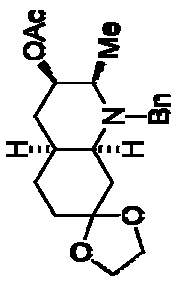




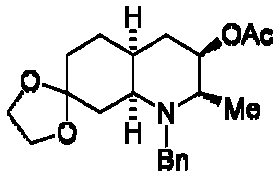
17


OAc
Me
N
Bn
H
H
O
O
18
E1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-051005173853
Usuari:
Nom: MARIA CERVIGON
Data:06/10/05 / 51st automatic
Pulse Sequence: s2pul
0.997
1.015
1.995
3.801
3.821
3.887
ppm
2.49
2.27 1.38
1.06 2.85 4.60
1.35
1.26
5.74
1.26
5.00


C13 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-051005173853
Usuari: san / Mostra: mmp15
Nom: MARISA MENA CERVIGON
Data:06/10/05 / Sist automatic
Pulse Sequence: s2pul
11.515
21.286
24.952
27.017
30.180
33.641
34.144
51.925
55.667
56.086
63.921
64.219
73.212
76.688
77.000
77.320
109.369
126.853
128.172
128.233
139.772
170.395
ppm
20
40
60
80
100
120
140
160

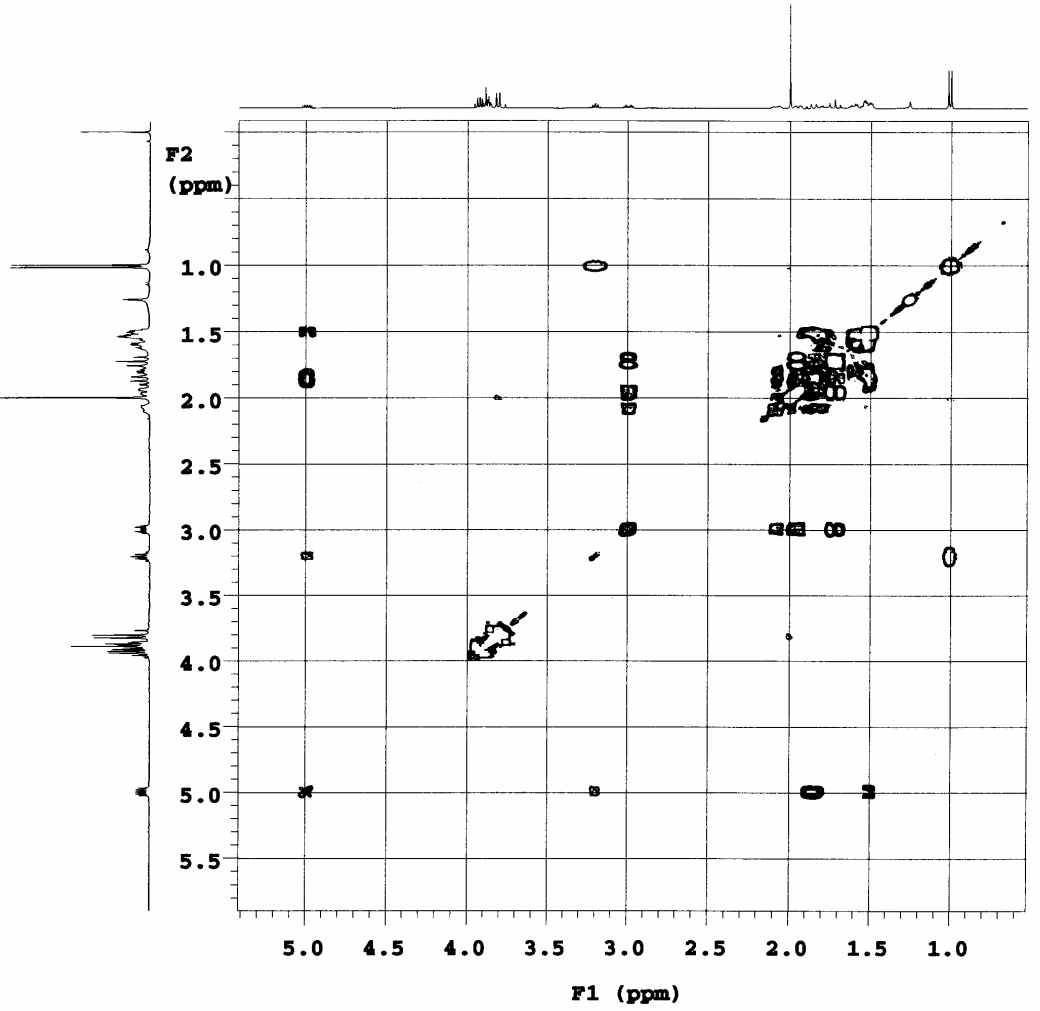

OAc
Me
N
Bn
H
H
O
O
O

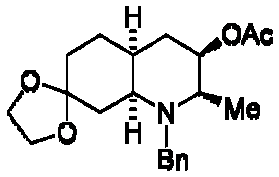
18



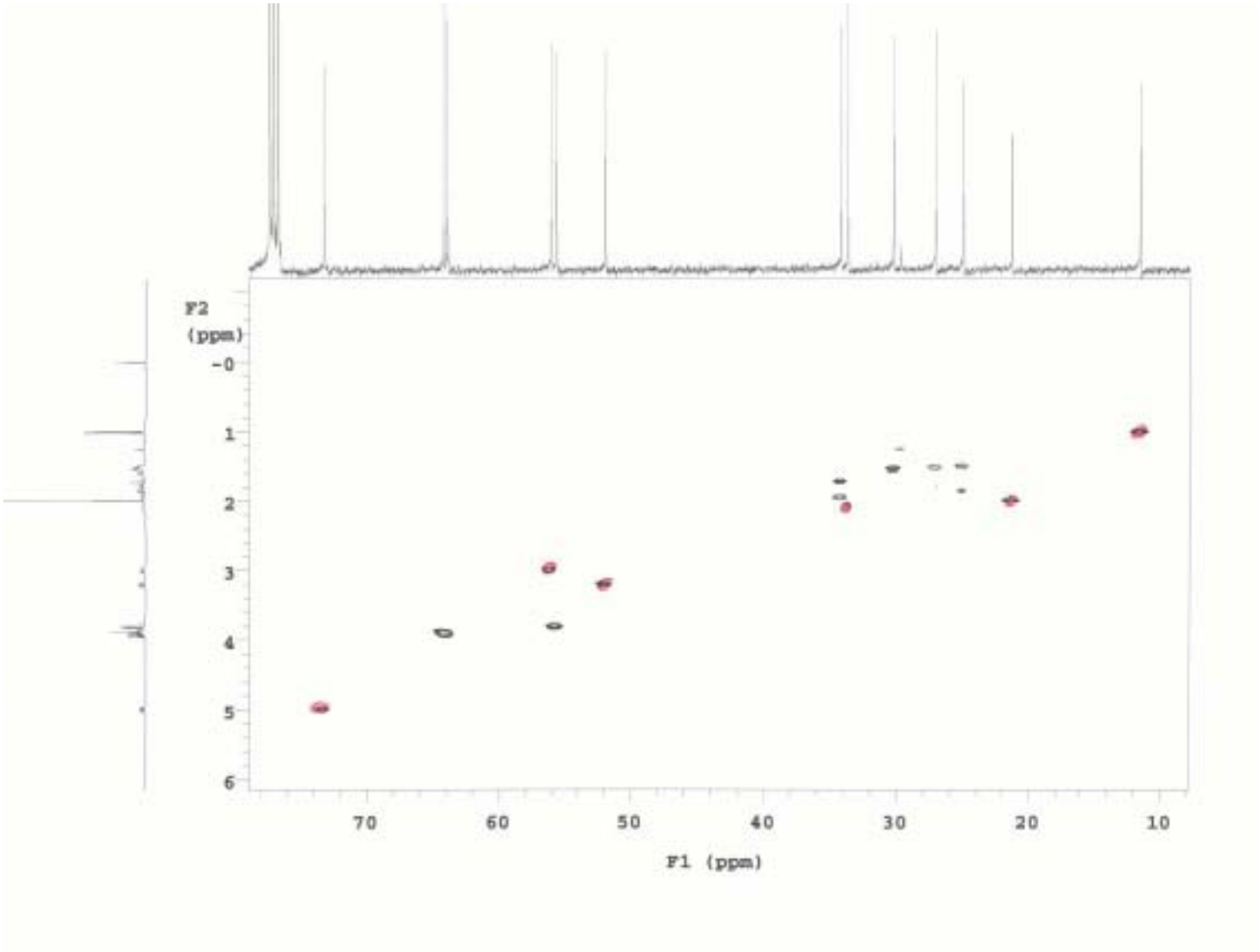
18

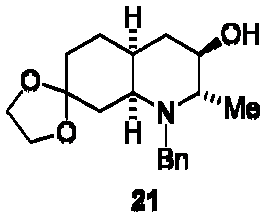
```
H1 / gCOSY / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-051005173
853
Usuari: san / Mostra: mmp15
Nom: MARISA MENA CERVIGON
Data:06/10/05 / Sist automatic

exp22  gCOSY

      SAMPLE                FLAGS
date    Oct  6 2005   hs                nn
solvent       cdcl3   sspul              n
sample auto_Custom~   hsglvl          1002
       Q_06Oct2005          SPECIAL
   ACQUISITION        temp            25.0
sw          3937.0    gain              26
at           0.150    spin               0
np           1182       F2 PROCESSING
fb        not used     sb             -0.075
ss             16      sbs          not used
d1          1.000      fn              2048
nt             4        F1 PROCESSING
  2D ACQUISITION      sb1            -0.065
sw1         3937.0    sbs1         not used
ni           256      proc1             lp
  PRESATURATION       fn1             2048
satmode          n          DISPLAY
satfrq           0    sp              -31.7
satdly           0    wp             2389.9
satpwr           0    sp1             210.7
   TRANSMITTER        wp1            1955.0
tn              H1    rf1             485.8
sfrq       400.113    rfp                0
tof         -540.4    rf11            485.8
tpwr            58    rfp1               0
pw          12.200           PLOT
    GRADIENTS         wc              131.8
gzlvl1         1002   sc                6.2
gt1       0.001000    wc2             131.8
gstab     0.000500    sc2                0
    DECOUPLER         vs                139
dn              C13   th                 6
dm              nnn   ai  cdc  av
```



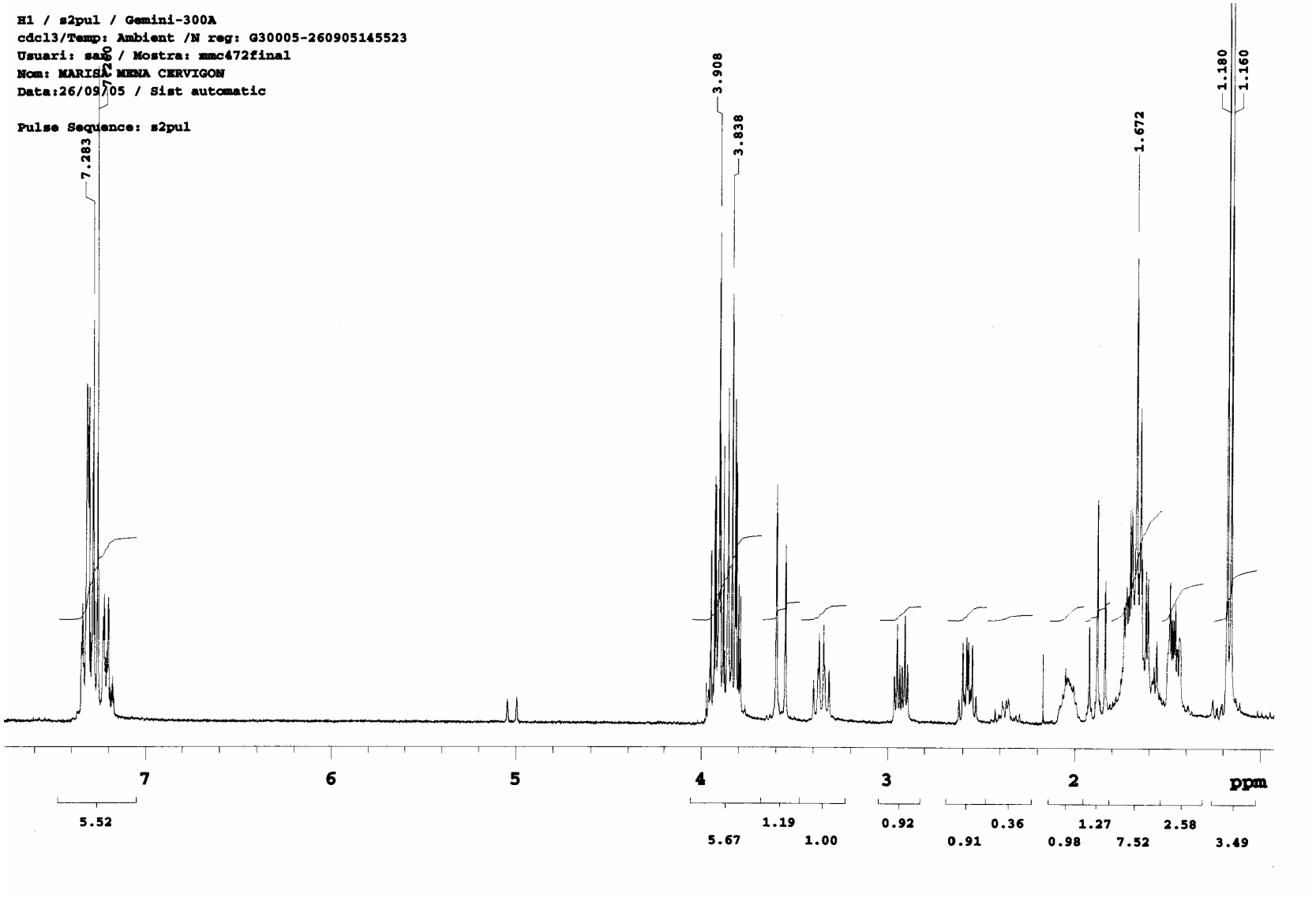


18




H
OH
O
N
Me
H
O
Bn

21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Data:26/09/05 / Sist automatic
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3.838
1.672
1.180
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7
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5
4
3
2
ppm
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5.67
1.19
1.00
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0.36
0.98
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7.52
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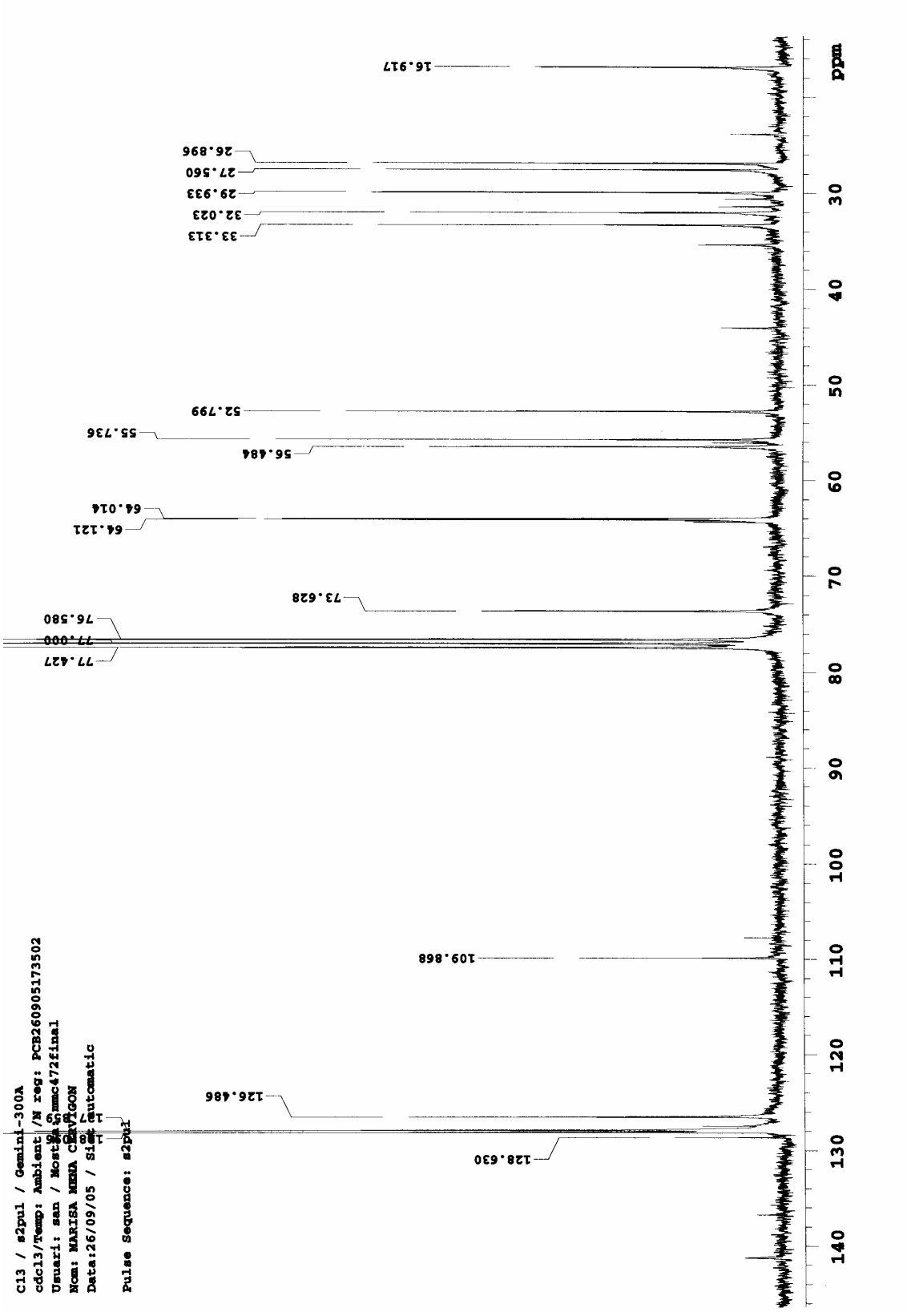
3.49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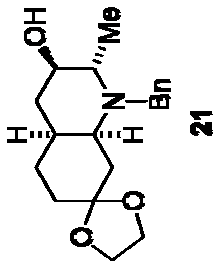
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Bn
H
H
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O

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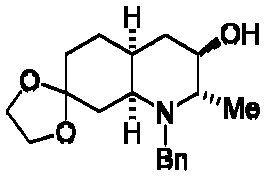

21

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sample auto_26Sep2~  spin             0
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at           0.180  hsgt       0.005000
np            1024    F2 PROCESSING
fb            2250  sb           -0.090
ss               2  sbs        not used
d1           1.000  fn             2048
nt               4    F1 PROCESSING
  2D ACQUISITION    sb1          -0.090
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sfrq       300.046  sp           -299.4
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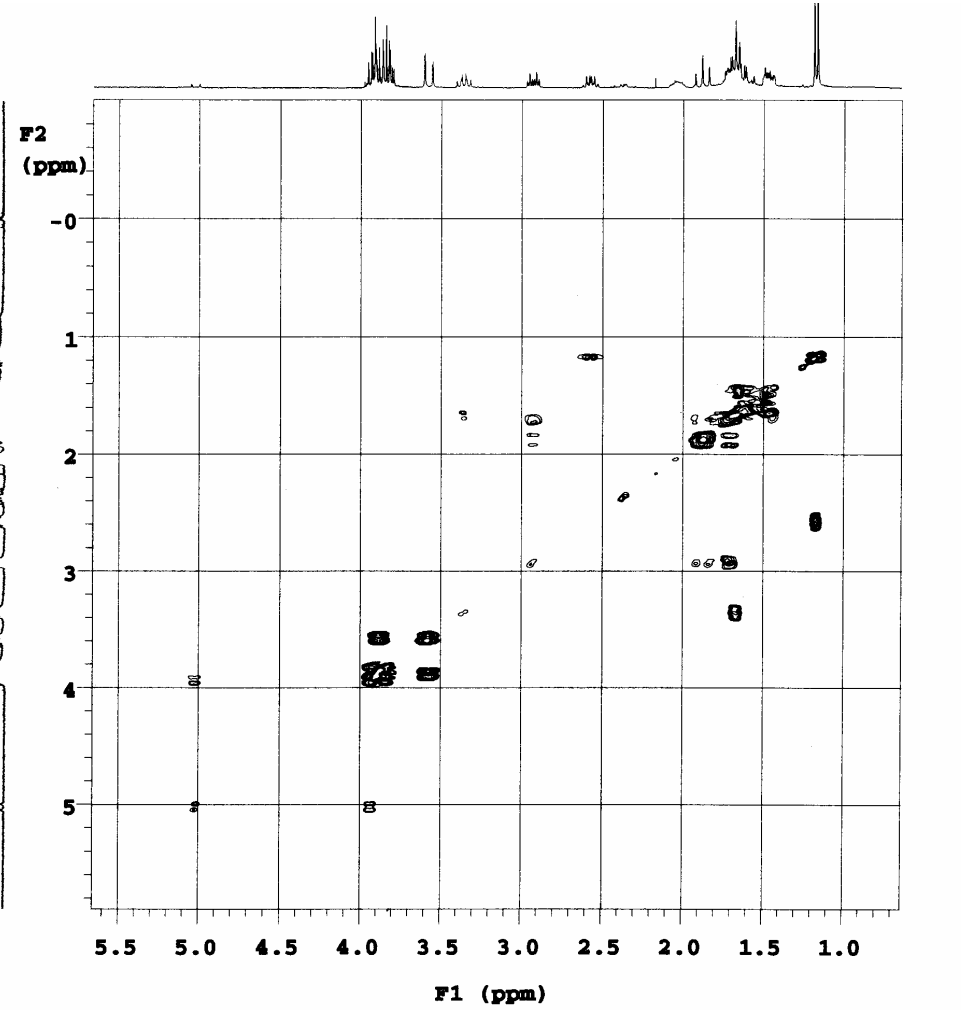

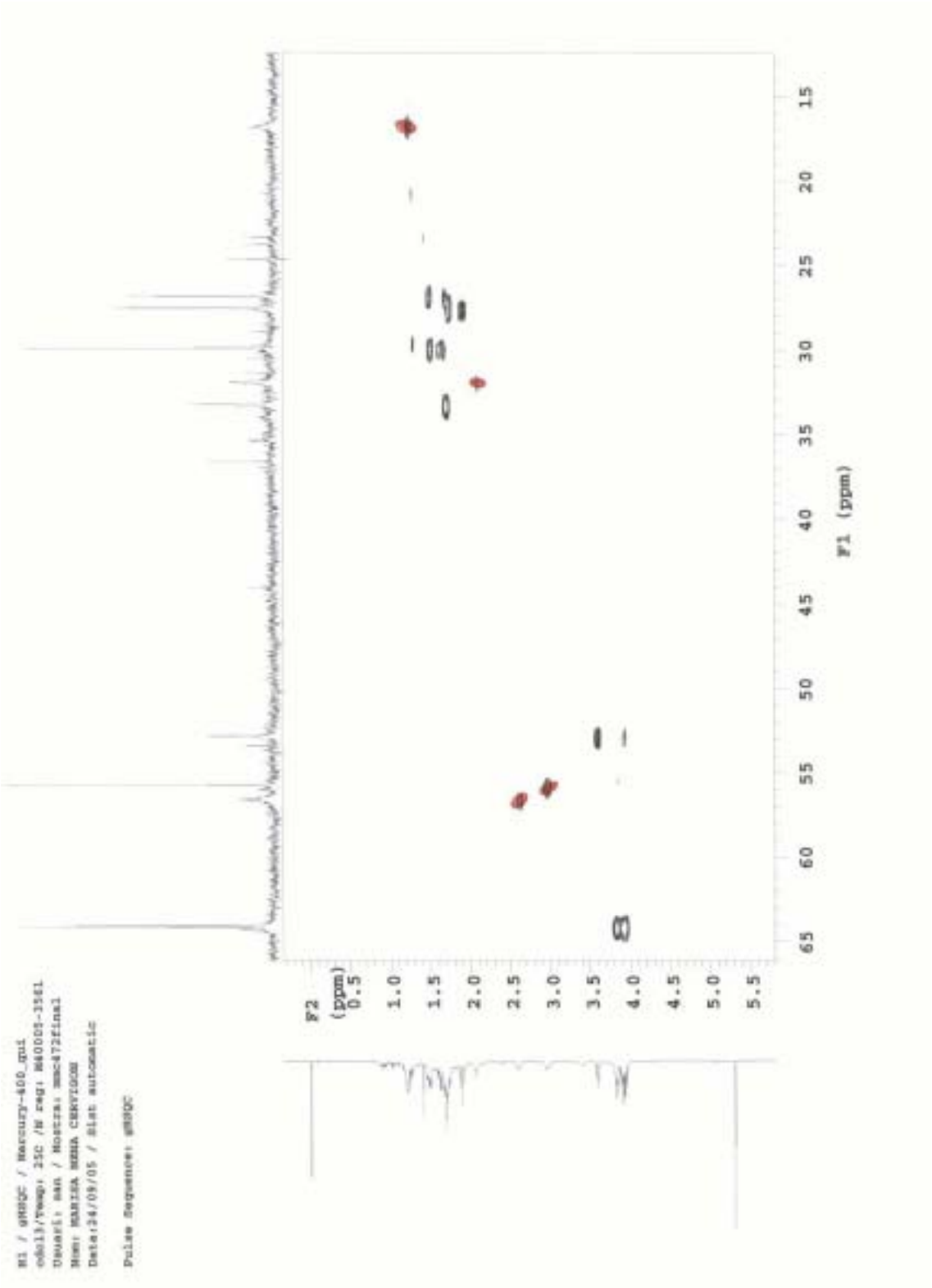

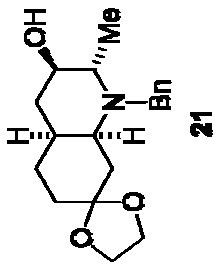

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6.3

Synthesis of enantiopure *cis*-decahydroquinolines from homotyramines by Birch reduction and aminocyclization

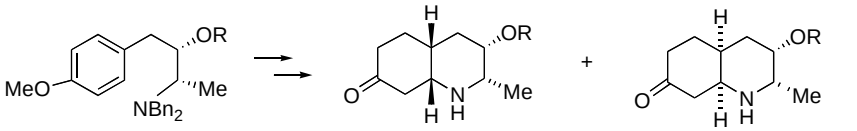
Marisa Mena, Nativitat Valls, Mar Borregán y Josep Bonjoch

Tetrahedron. **2006**, remitido

Graphical Abstract

Synthesis of enantiopure *cis*-decahydroquinolines from homotyramines by Birch reduction and aminocyclization

Marisa Mena, Nativitat Valls, Mar Borregán and Josep Bonjoch*



7b

major, when R = H
(43%)

8b

major, when R = Me
(39%, after benzoylation)

Synthesis of enantiopure *cis*-decahydroquinolines from homotyramines by Birch reduction and aminocyclization

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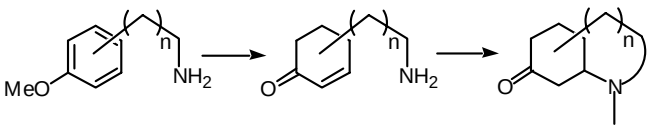
Av. Joan XXIII s/n, 08028-Barcelona, Spain

Abstract –Birch reduction of homotyramines with a *syn*-β-amino alcohol unit followed by acid treatment of formed dihydroanisole derivatives gives polysubstituted enantiopure *cis*-decahydroquinolines. The stereoselectivity of the process differs if the hydroxyl group is free or protected. The procedure allows the synthesis of 7-oxodecahydroquinolines embodying four stereogenic centers with the same relative configuration as that of lepadins F and G.

1. Introduction

The use of (ω-aminoalkyl)methoxybenzene derivatives (*e.g*. tyrosine and tyramine compounds) as starting materials to elaborate azabicyclic compounds through a Birch reduction followed by an intramolecular cyclization of the resulting amino-tethered cyclohexenone (Scheme 1) is well-precedented in the literature. Following this methodology, octahydroindoles,[1,2] azaspiroundecanes,[3] 6-azabicyclo[3.2.1]octanes,[4] 2-azabicyclo[3.3.1]nonanes,[5] and decahydroquinolines[6] have been prepared, but, apart from of our work on the synthesis of enantiopure octahydroindoles,[2] all described processes lead to racemic compounds.

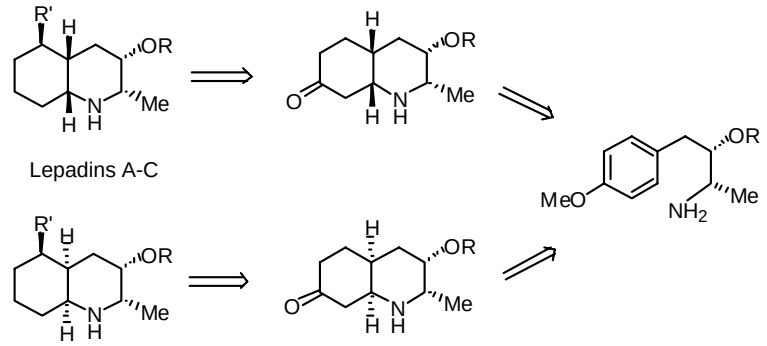


Scheme 1. The Birch reduction-aminocyclization process leading to azabicyclic compounds

* *Keywords*: Lepadin alkaloids; ecahydroquinolines; poxides; Conformational analysis; Nitrogen heterocycles

* Corresponding author. Tel.: 34-934024540; fax: 34-934024539; e-mail: josep.bonjoch@ub.edu

In this paper, we describe the synthesis of enantiopure polysubstituted decahydroquinolines from homotyramine precursors following the aforementioned Birch reduction/aminocyclization sequence.[7] The interest of this work, aside from the studying the stereocontrol of the process, lies in the possible usefulness of the resulting compounds in the synthesis of lepadin alkaloids. These natural products are structurally characterized by the presence of a 2,3,5-trisubstituted cis-fused decahydroquinoline ring. The substitution pattern, which has a methyl group at C(2), a hydroxyl group, free or protected, at C(3), and a functionalized side chain at C(5), shows a variety of stereochemical arrangements.[8] Total enantioselective syntheses of lepadins A,[9] B,[9-11] C,[9] - ,[11] and H,[11] as well as a formal route to *rac*-lepadin B[12] have been reported.



* absolute configuration unknown

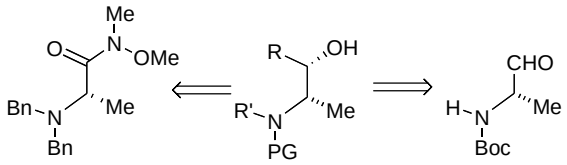
Scheme 2. Retrosynthetic approach to lepadin alkaloids

We focused our attention on the synthesis of *cis*-decahydroquinolines incorporating a methyl at C(2) and a hydroxyl at C(3), with an *S* configuration at both stereogenic centers, as occurs in lepadins A, B, and C. In lepadins F and G both substituents also have a cis relationship, although their absolute configuration is unknown (see Scheme 2). The strategies described for the construction of 3-hydroxy-2-methyldecahydroquinolines involve the elaboration of a polyfunctionalized piperidine followed by carbocyclic ring closure through aldol processes [9,10] or the construction of the piperidine ring from cyclohexanone derivatives either by an intramolecular enamine alkylation[11] or using a xanthate-mediated radical cyclization.[12] In our approach, we envisaged enantiopure anisole derivatives of type **I** (R = H or Me) as potential intermediates for the aforementioned *cis*-decahydroquinolines, as they would bring about ring closure by forming the N-C(8a) bond.[13]

RESULTS AND DISCUSSION

Synthetic aspects

For the proposed studies of Birch reduction of homotyramines followed by an aminocyclization process to achieve *cis*-decahydroquinolines of interest in the lepadine field, α-methyl-β-aminoalcohol **I** was required. The synthesis of *syn* α-methyl-β-amino alcohols (**II**, Scheme 3) is well-precedented not only by the methodological studies of the reactivity of alanine derivatives but also by the presence of this structural motif in several natural products other than the aforementioned lepadins, such as various piperidine alkaloids[14] (*i.e.* carpamic acid, azimic acid, julifloridine, and cassine *inter alia*). The most suitable procedures for *syn* amino alcohols of type **II** are the orgamometallic addition upon the Weinreb amide of *N*,*N*-dibenzylalanine[15] followed by hydride reduction of the resulting α-amino ketone[16] or the organometallic addition upon the *N*-Boc-alaninal.[17,18] To our knowledge, none of these versatile approaches have been used in reactions involving p-methoxybenzylmagnesium bromide, as was required in the present work. We decided to use the protocol involving the Weinreb amide of *N*,*N*-dibenzylalanine and, in addition, introduced a new approach based on the ring-opening of a suitable epoxide with a lithium reagent is introduced to achieve aminoalcohol **I**.



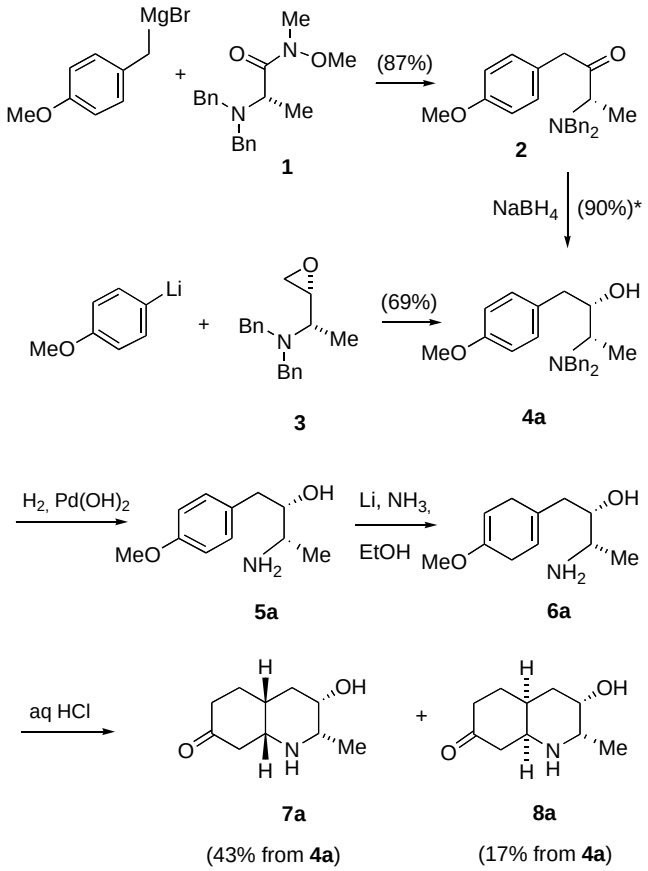
II

(**I**, when R = 4-OMeC$_6$H$_4$CH$_2$; R' = PG = H)

Scheme 3. Synthesis of enantiopure *syn*-α-methyl-β-aminoalcohols

Coupling of either the *p*-methoxybenzylmagnesium bromide with Weinreb amide **1**[19,20] or the *p*-methoxyphenyllithium with the (*R*) isomer of [(*S*)-1'-(dibenzylamino)ethyl]oxirane (**3**)[21] in presence of BF_3. t_2O (Ganem's conditions)[22,23] gave synthetic access to the required aminoalcohol **4a**, a diastereoselective reduction of the initially formed β-amino ketone **2** being necessary in the former sequence (Scheme 4, * denotes that 10% of the epimer of **4a**[24] was additionally isolated in this route, see experimental part). This sequence (**1** → **4a**) seemed to result in some loss of enantiopurity[25] as determined by optical rotations in comparison with the sample

obtained through enantiopure epoxide **3**. Since the goal was to study the course of the aminocyclization of the dihydroanisole derivatives, optimizing the described protocol to minimize any racemization was not pursued at this stage.

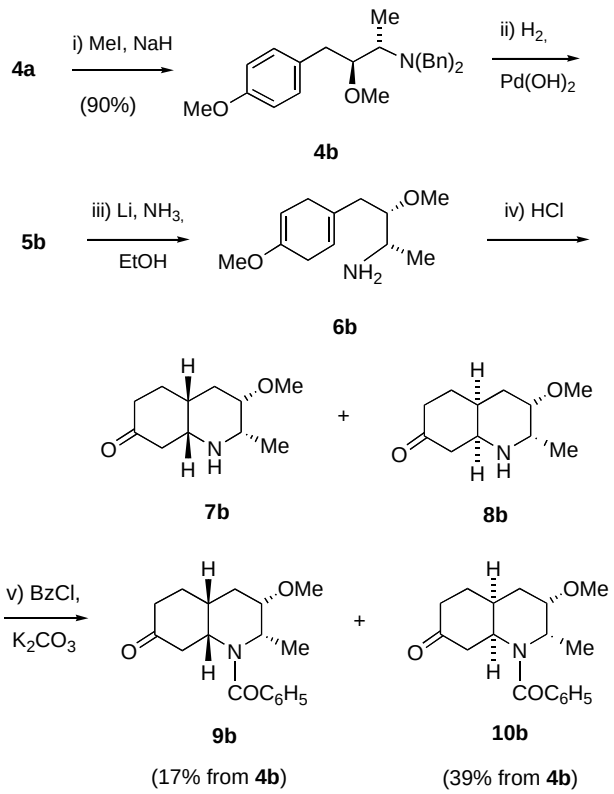


Scheme 4. Synthesis of *cis*-decahydroquinolines.

ebenzylation of **4a** gave the primary amine **5a**, which was submitted to the Birch reduction conditions (Li/NH_3) to allow the formation of dihydroanisole **6a**. This was treated with a 2 N HCl solution at 75 ºC, and the decahydroquinoline ring was formed after enol ether hydrolysis, double bond isomerization, and an intramolecular 1,4-addition of the amino group across the cyclohexenone intermediate. The process is stereoselective, with the exlusive formation of cis isomers of the decahydroquinoline ring. olysubstituted decahydroquinolines **7a** (43%) and **8a** (17%) were isolated in a 2.5:1 ratio and a overall yield of 60% from the sequence **4a** → **7a** + **8a**.

We then carried out the same sequence of reactions but starting from *syn*-amino ether **4b**, which was obtained by *O*-methylation of aminoalcohol **4a** (Scheme 5). In this series, the aminocyclization step starting from dihydroanisole **6b** gave a 1:2.3 mixture

of decahydroquinolines **7b** and **8b**, which were only partially separated. However, when the reaction mixture was basified and treated with benzoyl chloride after aminocyclization, the corresponding amides **9b** and **10b** were isolated in 17% and 39% overall yield (four steps from **4b**).

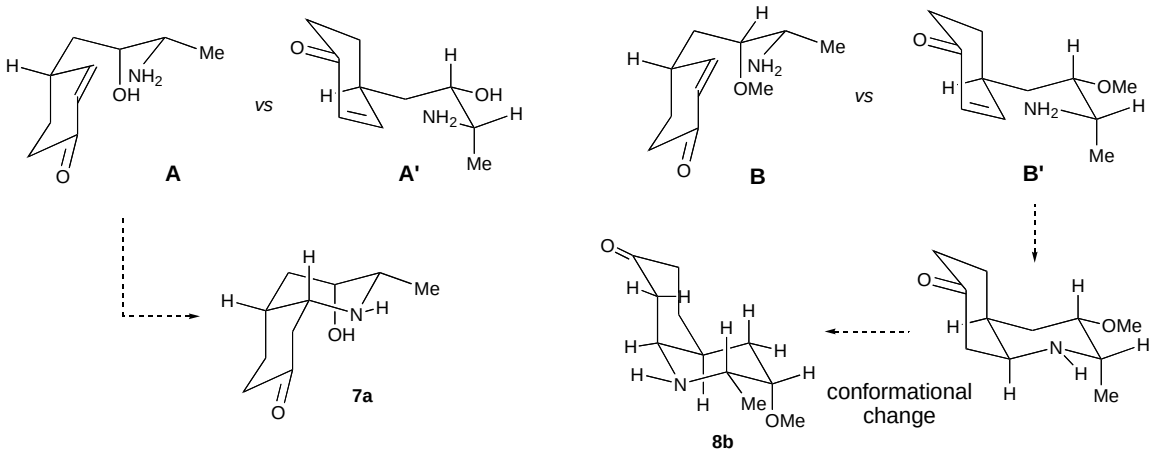


Scheme 5.

In the cyclization processes (**6** → **7** + **8**), both in series **a** (3-OH) and series **b** (3-OMe), the isolated decahydroquinolines showed a *cis*-fused relationship. The major compound of series **a** (i.e. **7a**) showed the same pattern of absolute configuration in its four stereocentres as lepadins A-C, while that of series **b** (i.e. **8b**) matched the relative configuration of lepadins F and G, allowing them to be considered as advanced building blocks for elaborating the aforementioned alkaloids.

The stereoselective *cis*-perhydroquinoline formation through a 6-*exo* process agreed with the stereochemical outcome observed in related cyclizations,[6] and with both the steric and electronic preference for a pseudo axial addition of the nucleophilic species to the cyclohexenone moiety. Interestingly, the configuration of the new methine carbons (i.e. C-4a and C-8a) is controlled to some extent by the oxygenated function. Why does the decalin ring formation change diastereoselectivity if there is a free or protected

hydroxyl group?. Considering that the axial attack proceeds through a chair-like transition state, in the hydroxyl series perhaps a hydrogen bonding favours the formation of enone **A** with respect to the epimeric enone **A'**, which could be in equilibrium by means of a tautomeric process through their corresponding dienol ether. On the contrary in series **b**, in which the hydroxyl group is protected as methyl ether, the steric factors (a 1,3-diaxial relationship between the C3-OMe and C4a-C5 bonds) prevent to some extent the formation of epimer **B**, the formation of **B'** being favoured (Scheme 6). Thus, the ratio of cis decahydroquinoline with an *S* configuration at the two new stereogenic centers formed in the aminocylization to the diastereoisomers with an *R* configuration was higher in compounds with a methoxy rather than hydroxyl substituent.



Scheme 6.

NMR studies of decahydroquinolines 7-10 (series a and b)

The stereochemistry of the synthesized azabicyclic compounds was elucidated by 2 NMR spectra (COSY, HSQC). The *N*-inside (**7a** and **7b**) and *N*-outside (**8a** and **8b**) *cis*-decahydroquinoline isomers[26] in the amino series are clearly differentiated by two NMR features: (i) the ^{1}H NMR chemical shift of H-2, which appears more deshielded (δ 3.1) in the *N*-outside than in the *N*-inside derivatives (δ 2.8), due to the compression upon H-2 of the C8-C8a bond, which has a 1,3-cis relationship, on the *N*-outside derivatives; (ii) the ^{13}C chemical shift of C(2) is more upfielded (~ 10 ppm) in compounds with the *N*-outside conformation than those with the *N*-inside conformation; moreover the signals given by the carbon atoms at C-4, C-6, and C-8 also appear in a higher field in the *N*-outside derivatives.

The key evidence for the conformational elucidation of **7a** was found in the ^{1}H NMR coupling pattern for the methylene protons at C-8, which appear as dd (J =14.6 and 5.4 Hz). The relative configuration for methoxy derivative **7b** is the same as that observed in **7a** and their NMR data follows the same pattern of chemical shifts. (Scheme 2). The absolute configuration of **7a** was deduced by considering that: a) the coupling constants for H-2 (qd, J = 6.6, 2 Hz) and H-3 (q, J = 2.4 Hz) determined their location and hence fixed the methyl at C(2) and the hydroxyl at C(3) to an equatorial and axial disposition, respectively; b) the multiplicity of H-8a (br s) implied an equatorial relationship with respect to the cyclohexane ring, which discarded not only a trans junction of the decaline ring but also, taking into account the preferred conformation, implied an R configuration for C(8a). For the major component in the methoxy series **8b**, the axial proton H8a is strongly coupled to one adjacent axial. Hence, its resonance signal appears as a deceptively simple doublet (J = 10.4 Hz) of triplets (J = 4.8 Hz) centered at δ 3.43.

In summary, the twin chair conformation with the nitrogen axially substituting the carbocyclic ring is the lowest energy conformation for **7a**, whereas the twin chair conformation with the nitrogen equatorially substituting the carbocyclic ring is the lowest energy conformation for **8b**.

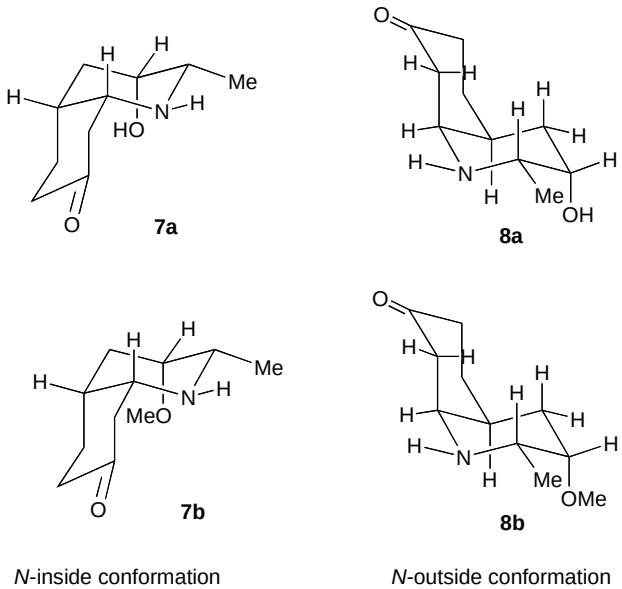


Figure 2. referred conformation of decahydroquinolines **7**and **8**.

Interestingly, the *N*-benzoyl derivatives **9a**, prepared from amine **7a** in quantitative yield, and **10b** (Figure 3) showed a different preferred conformation to that of their precursors **7a** and **8b**, respectively, as has been observed in synthetic intermediates in lepadin synthesis[9-11] when the amino group is converted to a carbamate or amide group.

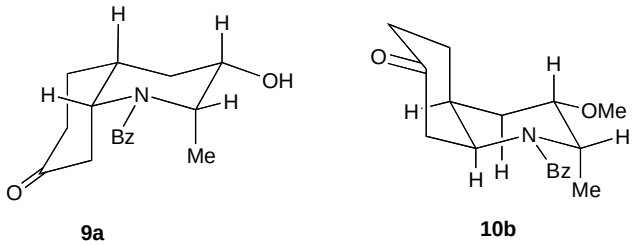


Figure 3. referred conformation of decahydroquinolines **9** and **10**.

In summary, a new synthetic entry to enantiopure polysubstituted *cis*-decahydroquinolines has been reported. Since the observed stereoselectivity allows lepadin-type stereochemistries to be achieved, further studies using decahydroquinolines **9a** and **10b** as advanced synthetic intermediates are in progress with the aim of achieving lepadins A-C and F-G, respectively.

3. Experimental

3.1. General. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) or Al_2O_3 (ALOX N/UV_{254}, olygram), and the spots were located with iodoplatinate reagent (compounds **1**-**8**) or 1% aqueous $KMnO_4$ (compounds **9** and **10**). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, S S, 230-240 mesh ASTM) or Al_2O_3 (aluminium oxide 90, Merck). rying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Optical rotations were recorded with a erkin- lmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or 300, or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy.

3.1.1. (*S*)-(*N*,*N*-Dibenzyl)amino-*N*-methoxy-*N*-methylpropionamide (1). To a solution of benzyl (S)-2-(*N*,*N*-dibenzylamino)propionate (2.15 g, 6 mmol), which was prepared from L-alanine (BnBr, K_2CO_3, tOH) by the previously reported procedure,[28] and HCl.HN(OMe)Me (3.0 g, 30 mmol) in THF (90 mL) at –20 ºC, ^{i} rMgCl 2 M in THF (30 mL, 60 mmol) was added dropwise over a period of 30 min. The reaction mixture was stirred for 2 h at this temperature and then warmed to rt for 2.5 h. NH_4Cl (20 mL) was added and the product was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was dried and concentrated to an oil which contained **1** and BnOH. The latter was removed under vacuum to afford compound **1** (1.94 g), which was used without further purification. The ^{1}H NMR data were identical to those previously reported.[20] R_f = 0.1 (SiO_2, 9:1 hexane/ tOAc); ^{13}C NMR (50 MHz, C Cl_3) 14.9 (CH_3), 54.4 (CH_2), 56.1 (CH), 60.1 (CH_2), 126.8 (CH), 127.4 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 139.8 (C), 173.9 (C).

3.1.2. (3*S*)-3-(*N*,*N*-Dibenzyl)amino-1-(4-methoxyphenyl)butan-2-one (2). To a solution of **1** (1.81 g, 5.8 mmol) in THF (50 mL) at 0 ºC, 2-methoxybenzylmagnesium chloride 0.25 M in THF (46 mL, 11.6 mmol) was added dropwise. The reaction mixture was stirred 1 h at 0 ºC and then quenched with NH_4Cl. The organic layer was dried and concentrated to an oil, which was purified by chromatography (SiO_2, 9:1 hexane/ tOAc) to give **2** as a colourless oil (2.17 g, 87%): R_f = 0.5 (SiO_2, 9:1 hexane/AcO t); $[\alpha]^{25}$ -2.4 (*c* 1.0 , $CHCl_3$); IR (KBr) 1715, 1611 cm^{-1}; ^{1}H NMR (300 MHz, C Cl_3) 1.15 (d, *J* = 6.6 Hz, 3H), 3.47 (d, *J* = 13.2 Hz, 2H), 3.52 (q, *J* = 6.6 Hz, 1H), 3.72 (d, *J* = 15.0 Hz, 1H), 3.74 (d, *J* = 13.2 Hz, 2H), 3.76 (s, 3H), 3.88 (d, *J* = 15.3 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.20-7.40 (m, 10H); ^{13}C NMR (75 MHz, C Cl_3) 7.1 (CH_3), 45.3 (CH_2), 54.6 (CH_2), 55.2 (CH_3), 60.6 (CH), 113.8 (CH), 126.5 (C), 127.2 (CH), 128.4 (CH), 128.9 (CH), 130.3 (CH), 139.2 (C), 158.3 (C). Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.40; H, 7.29; N, 3.75. Found: 80.00; H, 7.29; N, 3.67**.**

3.1.3. (2*S*,3*S*)-3-(*N*,*N*-Dibenzyl)amino-1-(4-methoxyphenyl)butan-2-ol (4a)

Method A (from ketone **2**). To a solution of **2** (2.15 g, 5.75 mmol) in MeOH (68 mL) at -20 ºC $NaBH_4$ (453 mg, 11.5 mmol) was added. The reaction mixture was stirred for 1 h at this temperature, and then quenched with brine (30 mL). The product was extracted with CH_2Cl_2 (3 x 30 mL), dried and concentrated to give a mixture of

alcohols **4a** and *epi*-**4a**[25] in a 9:1 ratio according to the NMR spectrum. urification by chromatography (SiO_2, 9:1 hexane/ tOAc) gave **4a** (1.94 g, 90 %) and *epi*-**4a** (216 mg, 10 %).

4a: colourless oil. R_f = 0.24 (SiO_2, 9:1 hexane/AcO t); $[\alpha]^{25}$ -2.0 (*c* 0.4, $CHCl_3$); IR (KBr) 3600-3100, 1611 cm^{-1}; ^1H NMR (300 MHz, C Cl_3) 1.07 (d, *J* = 6.6 Hz, 3H), 2.38 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.60 (dq, *J* = 9.3, 6.6 Hz, 1H), 2.78 (dd, J_1 = 14.3, 3.0 Hz, 1H), 3.30 (d, *J* = 13.5 Hz, 2H), 3.68 (m, 1 H), 3.77 (s, 3H), 3.82 (d, *J* = 13.5 Hz, 2H), 6.77 (d, *J* = 9 Hz, 2H), 7.11 (d, *J* = 9 Hz, 2H), 7.20-7.40 (m, 10H); ^{13}C NMR (75 MHz, C Cl_3) 8.3 (CH_3), 39.1 (CH_2), 53.2 (CH_2), 55.2 (CH_3), 57.7 (CH), 71.9 (CH), 113.5 (CH), 127.1 (CH), 128.4 (CH), 128.9 (CH), 130.1 (CH), 131.0 (C), 138.7 (C), 157.8 (C). Anal. Calcd for $C_{25}H_{29}NO_2.1/2H_2O$: C, 78.12; H, 7.81; N, 3.64. Found : C, 77.84; H, 8.16; N, 3.34.

epi-**4a:** colourless oil. R_f = 0.14 (SiO_2, 9:1 hexane/AcO t); IR (KBr) 3600-3100, 1611 cm^{-1}; ^1H NMR (300 MHz, C Cl_3) 1.17 (d, *J* = 6.6 Hz, 3H), 2.30 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.75 (quint, *J* = 6.9 Hz, 1H), 3.21 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.50 (*J* = 13.8 Hz, 2H), 3.73-3.81 (m, 1H), 3.80 (d, *J* = 14.1 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.20-7.40 (m, 10H); ^{13}C NMR (75 MHz, C Cl_3) 8.6 (CH_3), 40.6 (CH_2), 54.7 (CH_2), 55.3 (CH_3), 57.2 (CH), 74.7 (CH), 113.9 (CH), 126.8 (CH), 128.2 (CH), 128.8 (CH), 130.2 (CH), 131.0 (C), 140.0 (C), 158.1 (C).

Method B (from epoxide **3**). To a solution of *n*-BuLi (1.6 M in hexanes, 1.05 mL, 1.68 mmol) in THF (3.5 mL) at -78 ºC was added 4-bromoanisole (0.2 mL, 1.56 mmol). The reaction mixture was stirred for 90 min, treated with a solution of (2*R*)-[1'(*S*)-(dibenzylamino)ethyl]oxirane[21] (162 mg, 0.6 mmol) in THF (2 mL) and BF_3. t_2O (0.21 mL, 1.68 mmol), and continuously stirred at -78 ºC for 2 h prior to being quenched with saturated NH_4Cl (4 mL) and warmed to rt. The product was extracted with CH_2Cl_2 (3 X 10 mL), and the organic layer was dried and concentrated to give an oil, which was purified by chromatography (SiO_2, 9:1 hexane/AcO t) to give **4a** as a colourless oil (153 mg, 69 %). The spectroscopic data were identical with the product obtained by *method A*, but its rotatory power was higher: $[\alpha]^{25}$ **=** -5.6 (*c* 1.4, $CHCl_3$).

3.1.4. (2*S*,3*S*)-*N*,*N*-Dibenzyl-3-methoxy-4-(4-methoxyphenyl)-2-butanamine (4b). To a suspension of NaH (195 mg, 4.89 mmol) in dry THF (2 mL) at 0 ºC under argon atmosphere a solution of **4a** (1.22 g, 3.26 mmol) in dry THF was transferred (1 mL + 1

mL). The reaction mixture was warmed over 20 min to rt and then MeI (2 mL, 32.6 mmol) was added. The reaction was sealed and stirred for 48 h. NH_4Cl was added (10 mL) and the product was extracted with CH_2Cl_2 (3 X 20 mL). The resulting organic layer was washed with H_2O (15 mL), brine (15 mL), dried, and concentrated to give an oil, which was purified by chromatography (SiO_2, 9:1 hexane/AcO t) to give **4b** as a colourless oil. (1.14 g, 90%): R_f = 0.42 (SiO_2, 9:1 hexane/AcO t); $[\alpha]^{25}$ –4.6 (*c* 1.0, $CHCl_3$); IR (KBr) 1611 cm^{-1}; ^1H NMR (300 MHz, C Cl_3) 1.13 (d, *J* = 6.9 Hz, 3H), 2.74-2.88 (m, 3H), 3.13 (s, 3H), 3.22 (dt, *J* = 7.2, 4.8 Hz, 1H), 3.43 (d, *J* = 13.5 Hz, 2H), 3.77 (s, 3H), 4.01 (d, *J* = 13.5 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.20-7.32 (m, 6H), 7.39-7.41 (m, 4H); ^{13}C NMR (75 MHz, C Cl_3) 10.1 (CH_3), 37.4 (CH_2), 55.1 (CH), 55.2 (CH_2), 55.2 (CH_3), 59.2 (CH_3), 88.1 (CH), 113.5 (CH), 126.6 (CH), 128.1 (CH), 128.9 (CH), 130.2 (CH), 132.3 (C), 140.9 (C), 157.7 (C). Anal. Calcd for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02; N, 3.60. Found: C, 80.07; H, 8.31; N, 3.40.

3.1.5. (2*S*,3*S*)-3-Amino-1-(4-methoxyphenyl)butan-2-ol (5a). A suspension of **4a** (2.16 g, 5.75 mmol) and d(OH)$_2$/C (20%, 210 mg) in tOH (110 mL) was stirred at rt under hydrogen atmosphere overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated to give **5a** as an oil (1.12 g), which was used directly in the next step. An analytical sample was obtained by chromatography (Al_2O_3, CH_2Cl_2 saturated with NH_3); $[\alpha]^{25}$ -15.5 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, C Cl_3) 1.12 (d, *J* = 6.6 Hz, 3H), 2.56 (dd, *J* = 14.0, 8.6 Hz, 1H), 2.74-2.86 (m, 2H), 3.40-3.46 (m, 1H), 3.78 (s, 3H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, C Cl_3) 20.5 (CH_3), 39.6 (CH_2), 50.3 (CH), 54.7 (CH_2), 55.2 (CH_3), 76.4 (CH), 113.7 (CH), 130.1 (C), 130.2 (CH), 158.0 (C).

3.1.6. (2*S*,3*S*)-3-Methoxy-4-(4-methoxyphenyl)-2-butanamine (5b). Operating as above, starting from **4b** (1.14 g, 2.92 mmol), **5b** was obtained (615 mg) as an oil which was used directly in the next step; ^1H NMR (200 MHz, C Cl_3) 1.11 (d, *J* = 6.3 Hz, 3H), 2.56 (dd, *J* = 14.3, 6.5 Hz, 1H), 2.90-2.81 (m, 2H), 3.07, dt, *J* = 6.6, 5.4 Hz, 1H), 3.30 (s, 3H), 3.79 (s, 3H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (50 MHz, C Cl_3) 20.1 (CH_3), 35.8 (CH_2), 49.2 (CH), 55.2 (CH_3), 58.8 (CH_3), 87.6 (CH), 113.7 (CH), 130.4 (CH), 130.8 (C), 158.0 (C).

3.1.7. (2*S*,3*S*)-3-Amino-1-(4-methoxy-2,5-dihydrophenyl)butan-2-ol (6a). To a solution of **5a** (1.12 g, 5.75 mmol) in tOH (6 mL) at -78 ºC, ammonia (46 mL) was added. Small chips of lithium (280 mg, 40 mmol) were added until the solution was a persistent deep blue for 1.5 h. The cooling bath was removed, the ammonia was allowed to evaporate overnight, and the reaction mixture was evaporated. The dried extract was dissolved in brine (15 mL) and the product was extracted with CH_2Cl_2 (3 X 15 mL), dried with Na_2SO_4 and concentrated to give **6a** (1.112 g) as an oil which was used directly in the next step; ^{1}H NMR (200 MHz, C Cl_3) 1.11 (d, *J* = 6.3 Hz, 3H), 2.08 (dd, *J* = 14.1, 9.0 Hz, 1H), 2.21 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.69-2.84 (m, 6H), 3.33-3.40 (m, 1H), 3.55 (s, 3H), 4.63 (m, 1H), 5.51 (m, 1H); ^{13}C NMR (75 MHz, C Cl_3) 20.2 (CH_3), 29.1 (CH_2), 29.4 (CH_2), 41.6 (CH_2), 50.8 (CH), 53.7 (CH_3), 73.1 (CH), 90.2 (CH), 120.2 (CH), 132.4 (C), 152.6 (C).

3.1.8. (2*S*,3*S*)-3-Methoxy-4-(4-methoxy-2,5-dihydrophenyl)-2-butanamine (6b). Operating as above, starting from **5b** (611 mg, 2.92 mmol), **6b** was obtained (620 mg) as an oil which was used directly in the next step; ^{1}H NMR (200 MHz, C Cl_3) 1.09 (d, *J* = 6.6 Hz, 3H), 2.14-2.29 (m, 2H), 2.74-2.84 (m, 3H), 2.87-2.96 (m, 1H), 3.02-3.07 (m, 1H), 3.40 (s, 3H), 3.55 (s, 3H), 4.62 (m, 1H), 5.49 (m, 1H); ^{13}C NMR (50 MHz, C Cl_3) 20.1 (CH_3), 29.2 (CH_2), 30.0 (CH_2), 37.9 (CH_2), 49.3 (CH), 53.9 (CH_3), 58.4 (CH_3), 84.7 (CH), 90.4 (CH), 120.1 (CH), 132.6 (C), 152.9 (C).

3.1.9. Aminocyclization of 6a. A solution of **6a** (95 mg, 0.48 mmol) in 2 N HCl (1.6 mL) was stirred for 3.5 h at 70 ºC. The mixture was basified with NaOH (1N, 10 mL) and the solution was extracted with CH_2Cl_2 (4 x 10 mL) and $CHCl_3$/MeOH (4 x 10 mL), dried, and concentrated to give a brown oil. urification by chromatography (Al_2O_3, CH_2Cl_2 saturated with NH_3) gave a partially separated 2.5:1 mixture of **7a** (37 mg, 43%) and **8a** (15 mg, 17%).

(2*S*,3*S*,4a*R*,8a*R*)-3-Hydroxy-2-methyloctahydroquinolin-7-one (7a): white solid; mp 112-114 ºC. R_f = 0.17 (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH); ^{1}H NMR (400 MHz, C Cl_3, gCOSY) 1.11 (d, *J* = 6.8 Hz, 3H, Me), 1.81 (ddd, J = 14.8, 5.6, 3.6 Hz, H-4eq), 1.87 (dm, *J* = 14 Hz, H-5eq), 1.95 (dt, *J* = 14.4, 2 Hz, H-4ax), 2.05 (m, H-4a), 2.24 (dt, J = 14.4, 2 Hz, H-6eq), 2.29 (dd, *J* = 14.4, 5.6 Hz, H-8ax), 2.32 (m, H-6ax), 2.50 (qd, *J* = 13.6, 4.8 Hz, H-5ax), 2.65 (ddd, *J* = 14.8, 4.8, 0.8 Hz, H-8eq), 2.80 (qd, *J*

= 6.6, 2 Hz, H-2ax), 3.35 (brs, H-8a), 3.58 (q, *J* = 2.4 Hz, H-3eq); ^{13}C NMR (100 MHz, C Cl_3, gHSQC) 18.1 (Me), 28.8 (C-5), 33.5 (C-4a), 36.4 (C-4), 41.6 (C-6), 47.5 (C-8), 56.8 (C-8a), 59.3 (C-2), 68.2 (C-3), 210.8 (C-7). HRMS (SI-TOF) calcd for $C_{10}H_{18}NO_2$ (M^++1) 184.1332, found 184.1337.

(2*S*,3*S*,4a*S*,8a*S*)- 3-Hydroxy-2-methyloctahydroquinolin-7-one (8a): Colourless oil. R_f = 0.14 (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH); ^{1}H NMR (300 MHz, C Cl_3) 1.10 (d, *J* = 6.6 Hz, 3H, Me), 1.72-1.98 (m, 4H), 2.15-2.44 (m, 4H), 2.93 (t, *J* = 12.6, H-8ax), 3.06 (qd, *J* = 6.5, 1,8 Hz, H-2ax), 3.39 (dt, *J* = 11.7, 4.8 Hz, H-8a), 3.76 (brs, H-3eq;^{13}C NMR (75 MHz, C Cl_3, T) 17.7 (Me), 28.0 (C-5), 28.1 (C-4a), 31.9 (C-4), 36.6 (C-6), 42.6 (C-8), 47.5 (C-2), 55.9 (C-8a), 68.2 (C-3), 210.9 (C-7). HRMS (SI-TOF) calcd for $C_{10}H_{18}NO_2$ (M^++1) 184.1332, found 184.1331.

3.1.10. Aminocyclization of 6b. Following the above procedure for the aminocyclization of **6a** using methoxy derivative **6b** (225 mg, 1.07 mmol), heating at 70 ºC for 3 h, and purifying by chromatography (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH), a partially separated mixture of **7b** (36 mg, 17%) and **8b** (50 mg, 22%) was obtained.

(2*S*,3*S*,4a*R*,8a*R*)-3-Methoxy-2-methyldecahydroquinolin-7-one (7b): white solid, mp 45-47 ºC; R_f = 0.25 (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH); $[\alpha]^{25}$ +14.6 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, C Cl_3, gCOSY) 1.12 (d, *J* = 6.8 Hz, 3H, Me), 1.62 (ddd, J = 14.8, 5.6, 3.2 Hz, H-4eq), 1.74 (m, H-5eq), 2.00 (dm, *J* = 12 Hz, H-4a), 2.13 (dt, *J* = 14.8, 2.2 Hz, H-4ax), 2.23 (td, *J* = 14, 6 Hz, H-6ax), 2.26 (dm, *J* = 14.8 Hz, H-8), 2.32 (dddd, *J* = 14, 4.8, 2.4, 2.4 Hz, H-6eq), 2.61 (dd, *J* = 14.8, 5.6 Hz, H-8), 2.63 (qd, *J* = 14, 4.2 Hz, H-5ax), 2.78 (qd, *J* = 6.5, 2.4 Hz, H-2ax), 3.05 (q, *J* = 2.7 Hz, H-3eq), 3.30 (masked, H-8a), 3.31 (s, 3H, OMe); ^{13}C NMR (100 MHz, C Cl_3, gHSQC) 18.1 (Me), 26.9 (C-5), 30.9 (C-4), 33.4 (C-4a), 41.4 (C-6), 47.6 (C-8), 56.3 (C-2), 56.9 (OMe), 58.7 (C-8a), 76.9 (C-3), 210.6 (C-7). HRMS (SI-TOF) calcd for $C_{11}H_{20}NO_2$ (M^++1) 198.1489, found 198.1487.

(2*S*,3*S*,4a*S*,8a*S*)-3-Methoxy-2-methyldecahydroquinolin-7-one (8b): colourless oil, R_f = 0.19 (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH); ^{1}H NMR (400 MHz, C Cl_3, gCOSY) 1.11 (d, *J* = 6.8 Hz, 3H, Me), 1.75-2.00 (m, 4H, H-4 and H-5), 2.20-2.30 (m, 3H, H-4a, H-6), 2.39 (ddd, *J* = 14.4, 4.4, 1.5 Hz, H-8eq), 2.62 (dd, *J* = 14.4, 10 Hz, H-8ax), 3.13 (qd, *J* = 6.5, 3.2 Hz, H-2ax), 3.34 (masked, H-3eq), 3.36 (s, 3H, OMe), 3.43 (ddd, *J* = 10, 4.8, 4.8 Hz, H-8a); ^{13}C NMR (100 MHz, C Cl_3, gHSQC) 16.0 (Me), 27.6

(C-5), 27.8 (C-4), 29.6 (C-4a), 37.7 (C-6), 43.7 (C-8), 48.1 (C-2), 53.3 (C-8a), 56.7 (OMe), 76.4 (C-3), 210.9 (C-7). HRMS (SI-TOF) calcd for $C_{11}H_{20}NO_2$ (M^++1) 198.1489, found 198.1487.

3.1.11. (2*S*,3*S*,4a*R*,8a*R*)-1-Benzoyl-3-hydroxy-2-methyloctahydroquinolin-7-one (9a). A solution of **7a** (12 mg, 0.07 mmol) was dissolved in THF (0.2 mL) and H_2O (0.2 mL) was added. Then, K_2CO_3 (39 mg, 0.28 mmol) and BzCl (8.4 μL, 0.074 mmol) were added. The reaction mixture was stirred for 2 h at rt, extracted with CH_2Cl_2 (4 x 15 mL), dried, and concentrated to give a brown oil. urification by column chromatography (Al_2O_3, from CH_2Cl_2 saturated with NH_3 to 98:2 CH_2Cl_2 saturated with NH_3/MeOH) gave **9a** (19 mg, 99%): R_f = 0.44 (Al_2O_3, 98:2 CH_2Cl_2 saturated with NH_3); ^{1}H NMR (300 MHz, C Cl_3, mixture of rotamers) 1.20 and 1.30 (2 brd, CH_3), 1.70-2.20 (m, 6H), 2.34 (br, 1H), 2.75 (m, 1H), 3.85-4.15 (br, 2H), 5.07 (br, 1H), 7.25-7.45 (m, 5H, ArH); ^{13}C NMR (75 MHz, C Cl_3) 14.1 and 15.7 (CH_3), 27.5 and 28.6 (C.4), 29.7 (C-5), 31.9 (C-4a), 36.2 (C-6), 49.1 (C-8), 53.4 (C-2), 55.3 (C-8a), 74.6 (C-3), 125.9, 128.8, 129.5, 136.5 (Ar), 171.6 and 172.2 (NCO), 208.0 (C-7). HRMS (SI-TOF) calcd for $C_{17}H_{22}NO_3$ (M^++1) 288.1594, found 288.1585.

3.1.12. (2*S*,3*S*,4a*R*,8a*R*)-1-Benzoyl-3-methoxy-2-methyloctahydroquinolin-7-one (9b). Operating as above, starting from **7b** (16 mg, 0.08 mmol) and after purification by chromatography (Al_2O_3, CH_2Cl_2 saturated with NH_3), amide **9b** (24 mg, 99%) was obtained as a white solid: mp 100-102 ºC; R_f = 0.52 (Al_2O_3, CH_2Cl_2 saturated with NH_3); ^{1}H NMR (300 MHz, C Cl_3, mixture of rotamers) 1.05 and 1.25 (2 brd, CH_3), 1.70-2.20 (m, 6H), 2.35 (br, 1H), 2.75 (m, 1H), 3.20 and 3.40 (2s, 3H, OCH_3), 3.25-3.45 (masked, 2H), 3.95 (br, 0.5H), 4.15 (br, 0.5 H), 5.0 (br, 0.5H), 5.20 (br, 0.5H), 7.20-7.65 (m, 4H, ArH), 8.20 (d, J = 7.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, C Cl_3) 15.0 and 16.0 (CH_3), 25.3 and 25.7 (C-4), 27.6 (C-5), 32.6 and 33.5 (C-4a), 36.0 and 36.4 (C-6), 43.6 and 45.2 (C-8), 45.4, 49.4, 51.2, and 56.2 (C-2 and C-8a), 55.6 and 56.6 (OCH_3), 77.9 and 78.4 (C-3), 125.7, 128.7, 129.4, 136.6 (Ar), 171.6 (NCO), 207.4 and 207.9 (C-7). HRMS (SI-TOF) calcd for $C_{18}H_{24}NO_3$ (M^++1) 302.1751, found 302.1752.

3.1.13. (2*S*,3*S*,4a*R*,8a*R*)- and (2*S*,3*S*,4a*S*,8a*S*)-1-Benzoyl-3-methoxy-2-methyloctahydro-quinolin-7-one (9b and 10b). A solution of **6b** (90 mg, 0.42 mmol)

in HCl 2 N (2 mL) was stirred for 3 h at 75 ºC. The mixture was basified with K_2CO_3 (464 mg, 3.36 mmol) and BzCl (0.06 ml, 0.5 mmol) in THF (2 mL) was added. The reaction mixture was stirred for 2 h at rt, concentrated and extracted with CH_2Cl_2 (4 x 20 mL). The dried organic layers were concentrated to give a brown oil, which was purified by chromatography (SiO_2, from Hexane/AcO t 7:3 to AcO t) to give a 1:2.3 mixture of **9b** (22 mg, 17% from **4b**) and **10b** (50 mg, 39% from **4b**). For data of **9a**, see above.

Compound **10b**: Colourless oil. R_f = 0.14 (SiO_2, 1:1 Hexane/AcO t); $[\alpha]^{25}$ +16 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, C Cl$_3$, gCOSY) 1.25 (d, *J* = 6.8 Hz, 3H, Me), 1.80 (m, H-5), 1.87 (m, H-4), 1.99 (dt, *J* = 14, 5.2 Hz, H-4eq), 2.11 (dddd, *J* = 12, 11, 9.4, 4.4 Hz, H-5ax), 2.25 (ddd, J = 15.4, 10, 5.4 Hz, H-6ax), 2.36 (m, H-4a), 2.64 (masked, 1H, H-6), 2.59 and 2.67 (2dd, *J* = 16.8, 5.6 Hz, 1H each, H-8), 3.20 (s, 3H, OMe), 3.51 (ddd, *J* = 10.8, 5.4, 5.4 Hz, H-3ax), 4.12 (ddd, *J* = 5.6, 5.6, 2.8 Hz, H-8a), 4.24 (quint, *J* = 6.4 Hz, H-2eq), 7.40 (s, 5H, ArH); ^{13}C NMR (100 MHz, C Cl$_3$, gHSQC) 12.5 (Me), 26.5 (C-5), 28.5 (C-4), 33.3 (C-4a), 38.5 (C-6), 43.0 (C-8), 51.9 (C-8a), 52.8 (C-2), 56.2 (OMe), 75.0 (C-3), 126.8, 128.6, 130.0, 136.6 (Ar), 173.2 (NCO), 205.4 (C-7). HRMS (SI-TOF) calcd for $C_{18}H_{24}NO_3$ (M^++1) 302.1751, found 302.1750.

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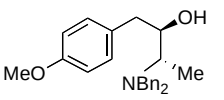
24.  *epi*-**4a**
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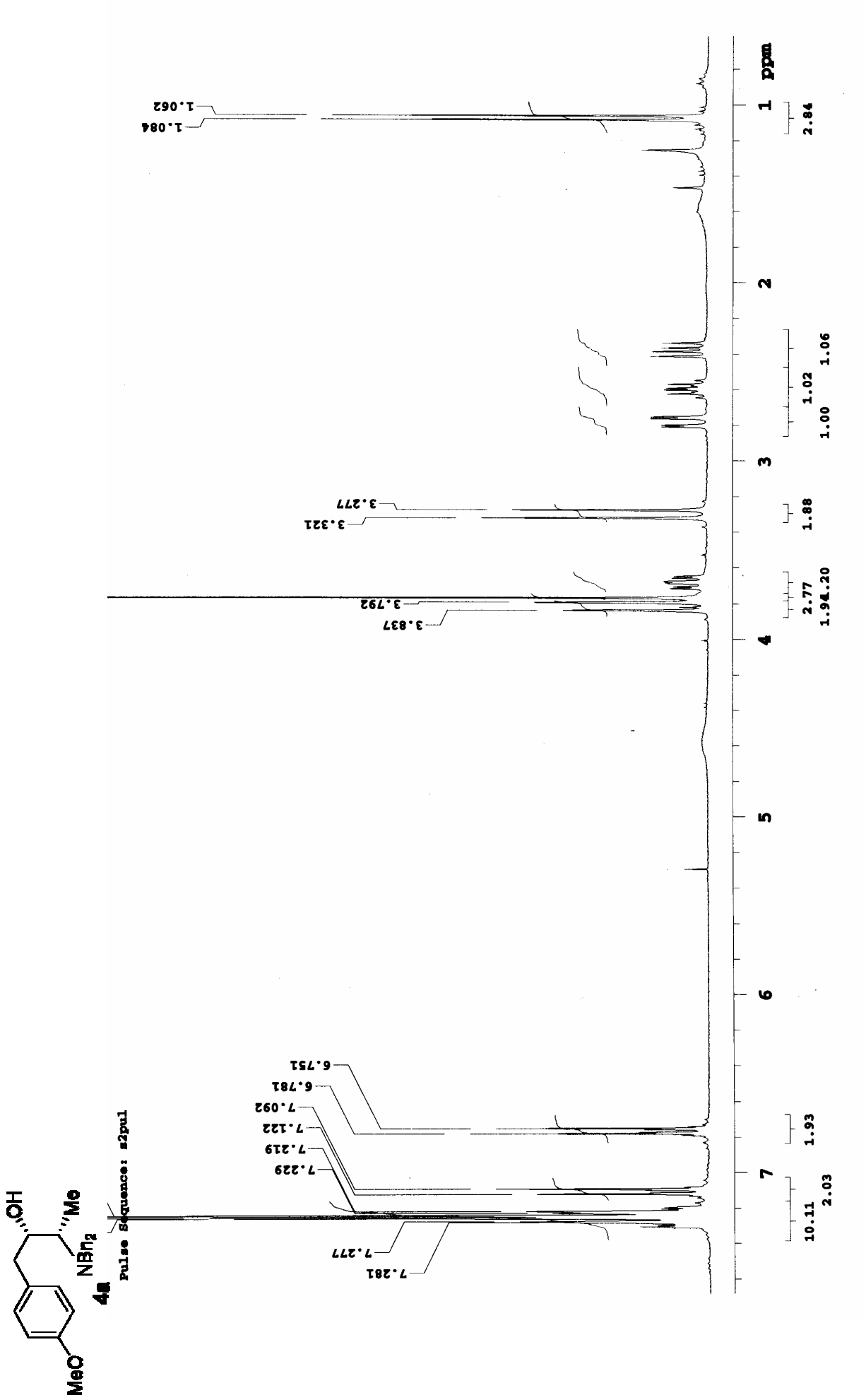
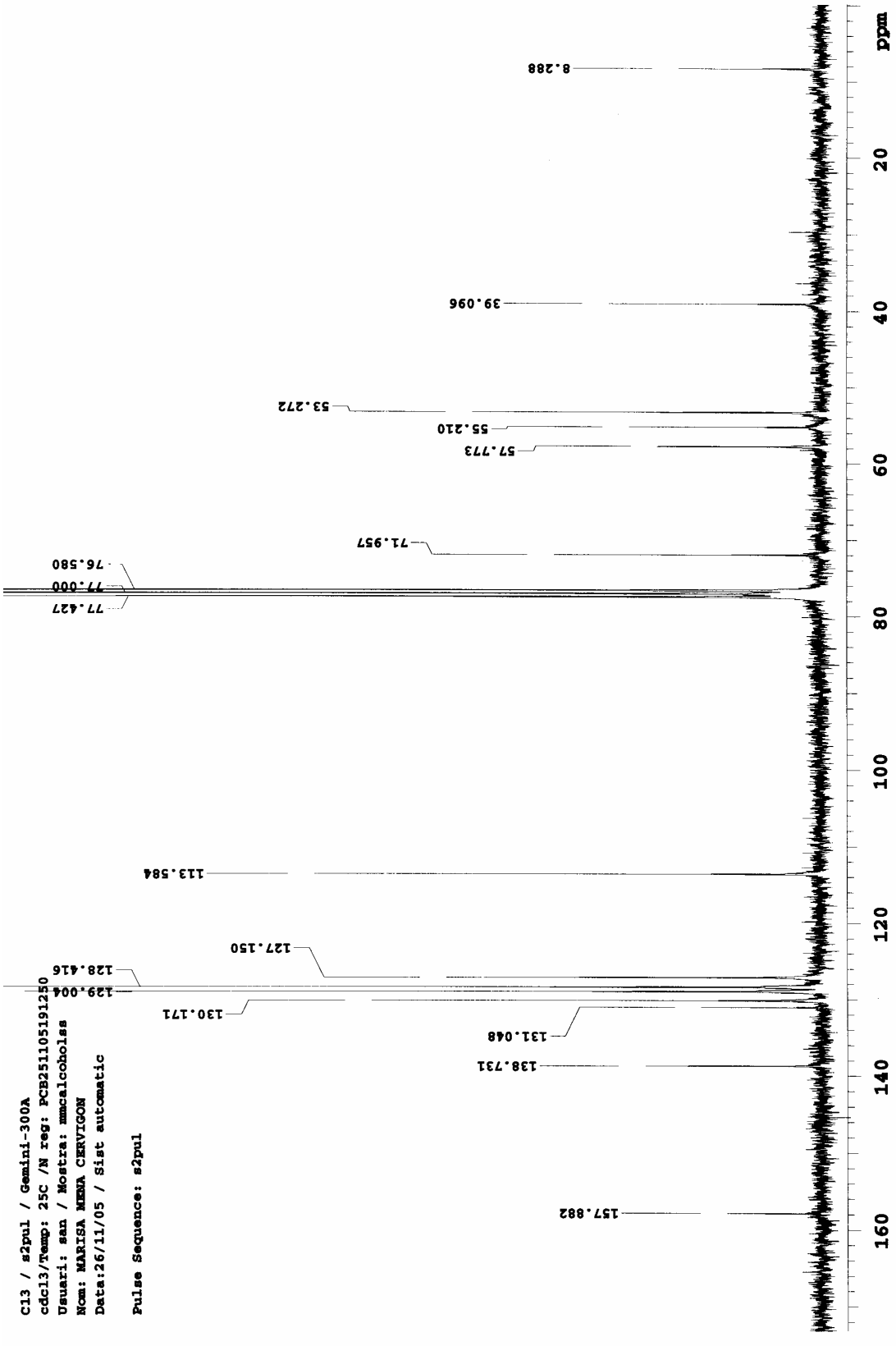

OH
Me
NBn2
MeO
4a
Pulse Sequence: s2pul
7.281
7.277
7.229
7.219
7.122
7.092
6.781
6.751
3.837
3.792
3.321
3.277
1.084
1.062
ppm
1
2
3
4
5
6
7
2.84
1.06
1.02
1.00
1.88
2.77
1.94
4.20
1.93
10.11
2.03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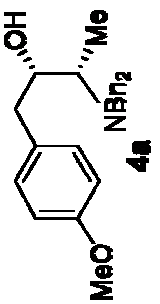
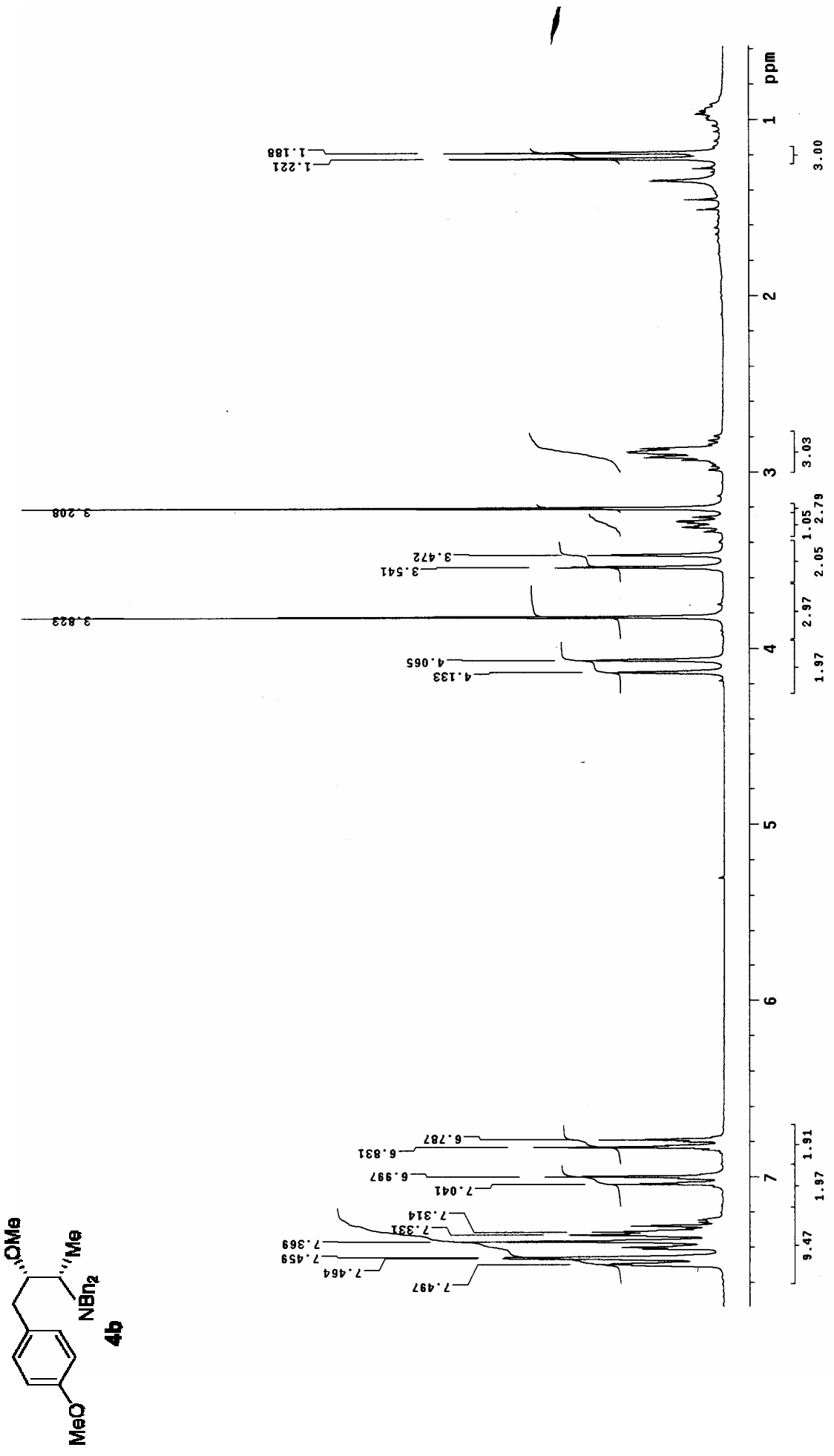
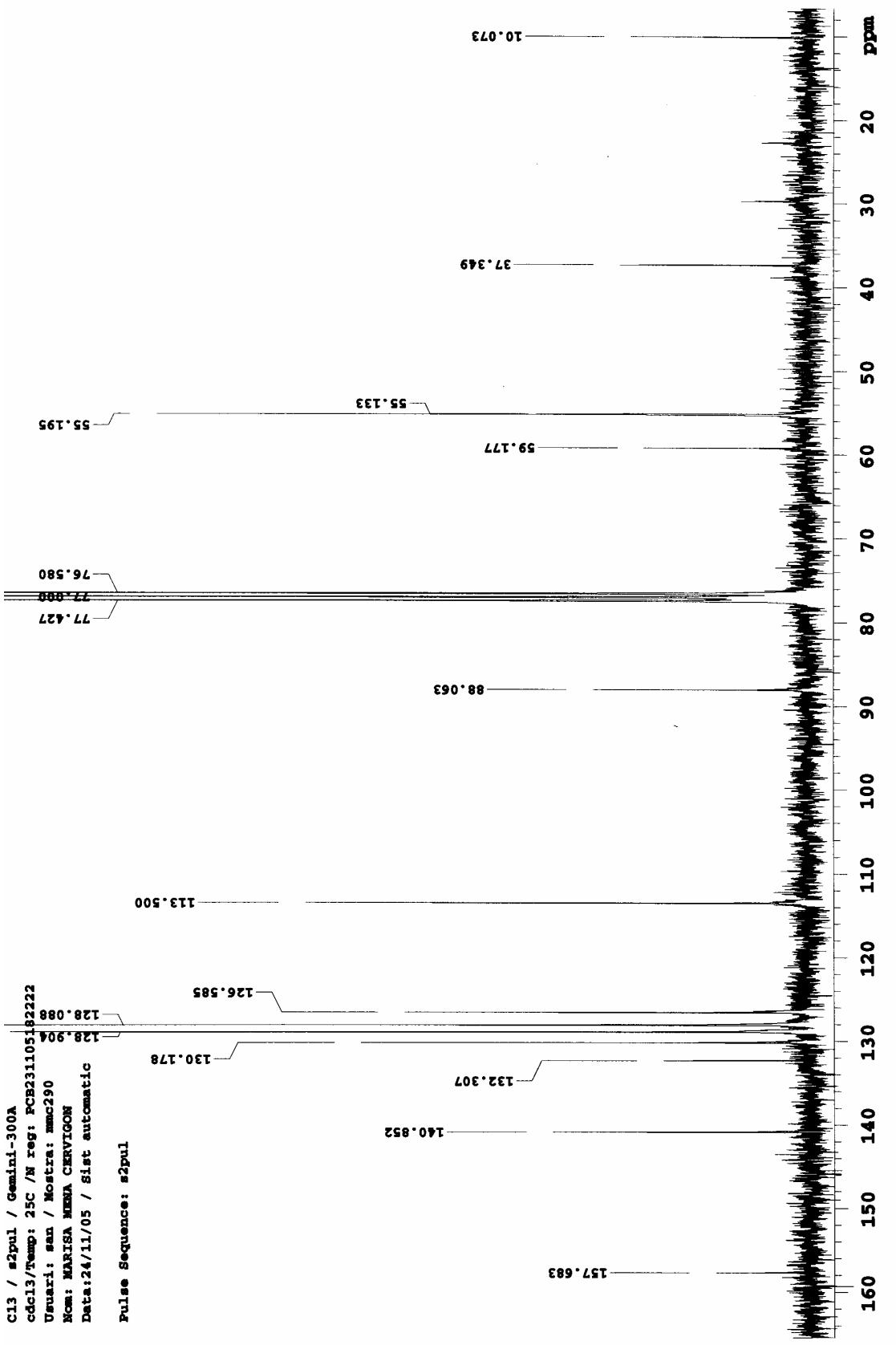
Usuari: san / Mostra: mmcalcobolss
Nom: MARISA MENA CERVIGON
Data:26/11/05 / Sist automatic
Pulse Sequence: s2pul
8.288
39.096
53.272
55.210
57.773
71.957
76.580
77.000
77.427
113.584
127.150
128.416
129.004
130.171
131.048
138.731
157.882
ppm
20
40
60
80
100
120
140
160


OH
Me
NBn2
MeO

4a


OMe
Me
NBn2
MeO
4b
7.497
7.464
7.459
7.369
7.331
7.314
7.041
6.997
6.831
6.787
4.133
4.065
3.823
3.541
3.472
3.208
1.221
1.188
ppm
9.47
1.97
1.91
1.97
2.97
2.05
1.05
2.79
3.03
3.00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37.349
55.133
55.195
59.177
76.580
77.088
77.427
88.063
113.500
126.585
128.088
128.904
130.178
132.307
140.852
157.683
ppm
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Usuari: san / Mostra: mmc290
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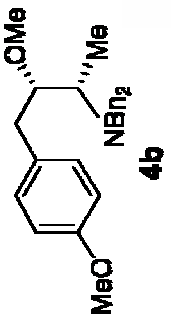
Data:24/11/05 / Sist automatic
Pulse Sequence: s2pul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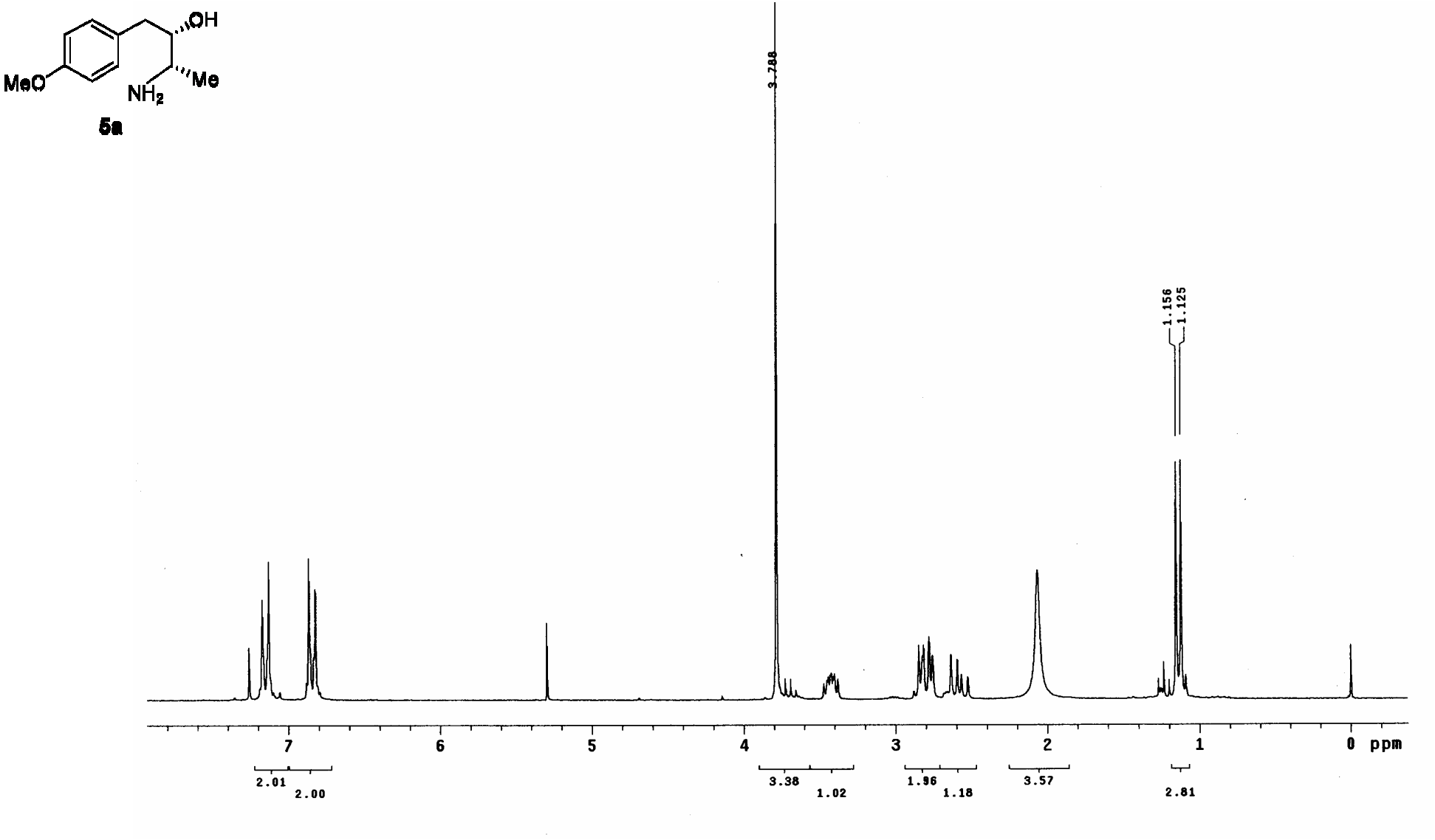
Me
NBn2
MeO

4b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MeO
Me
NH2
5a
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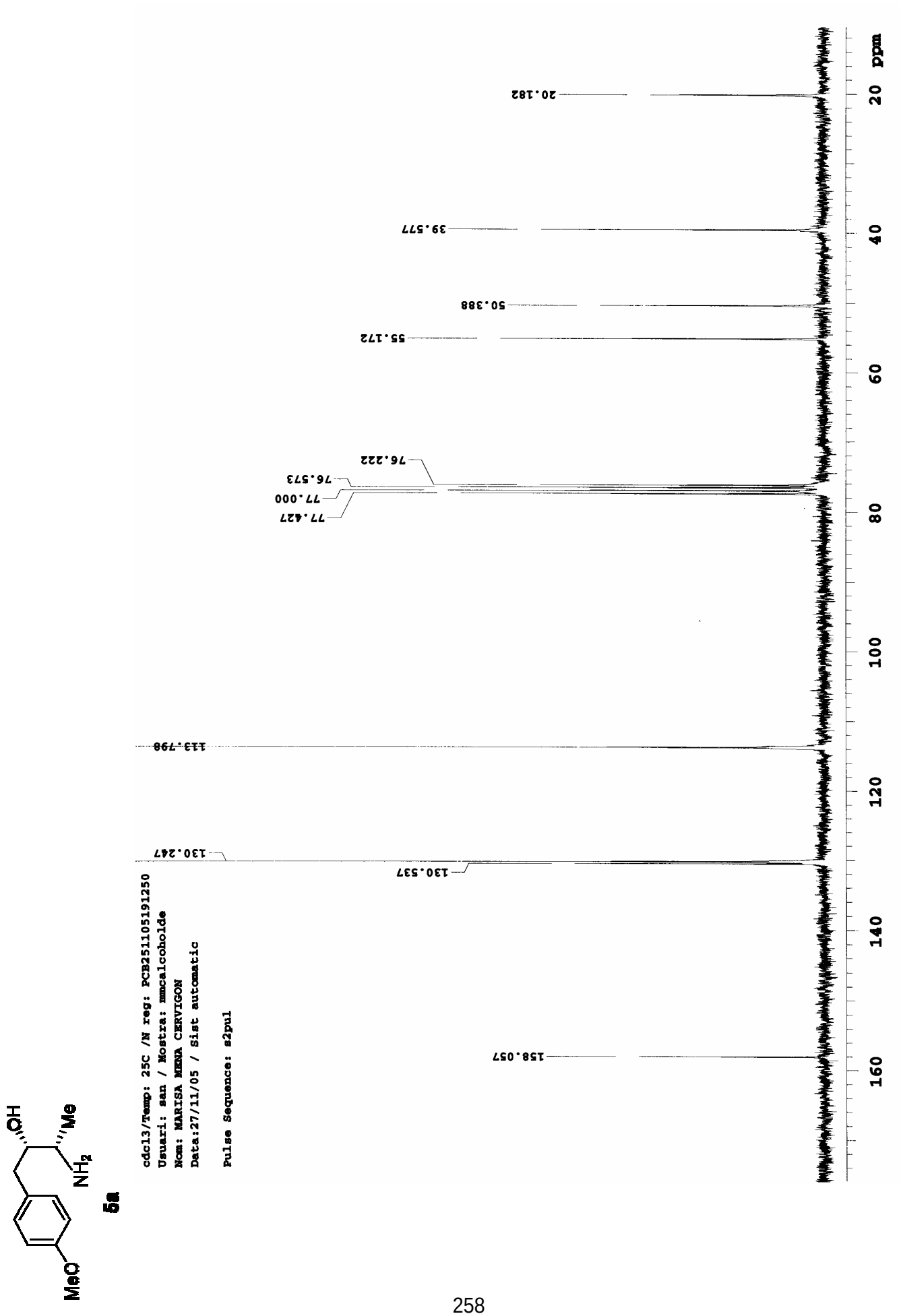
1.156
1.125
7
6
5
4
3
2
1
0 ppm
2.01
2.00
3.38
1.02
1.96
1.18
3.57
2.81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Me
NH2
MeO
5a
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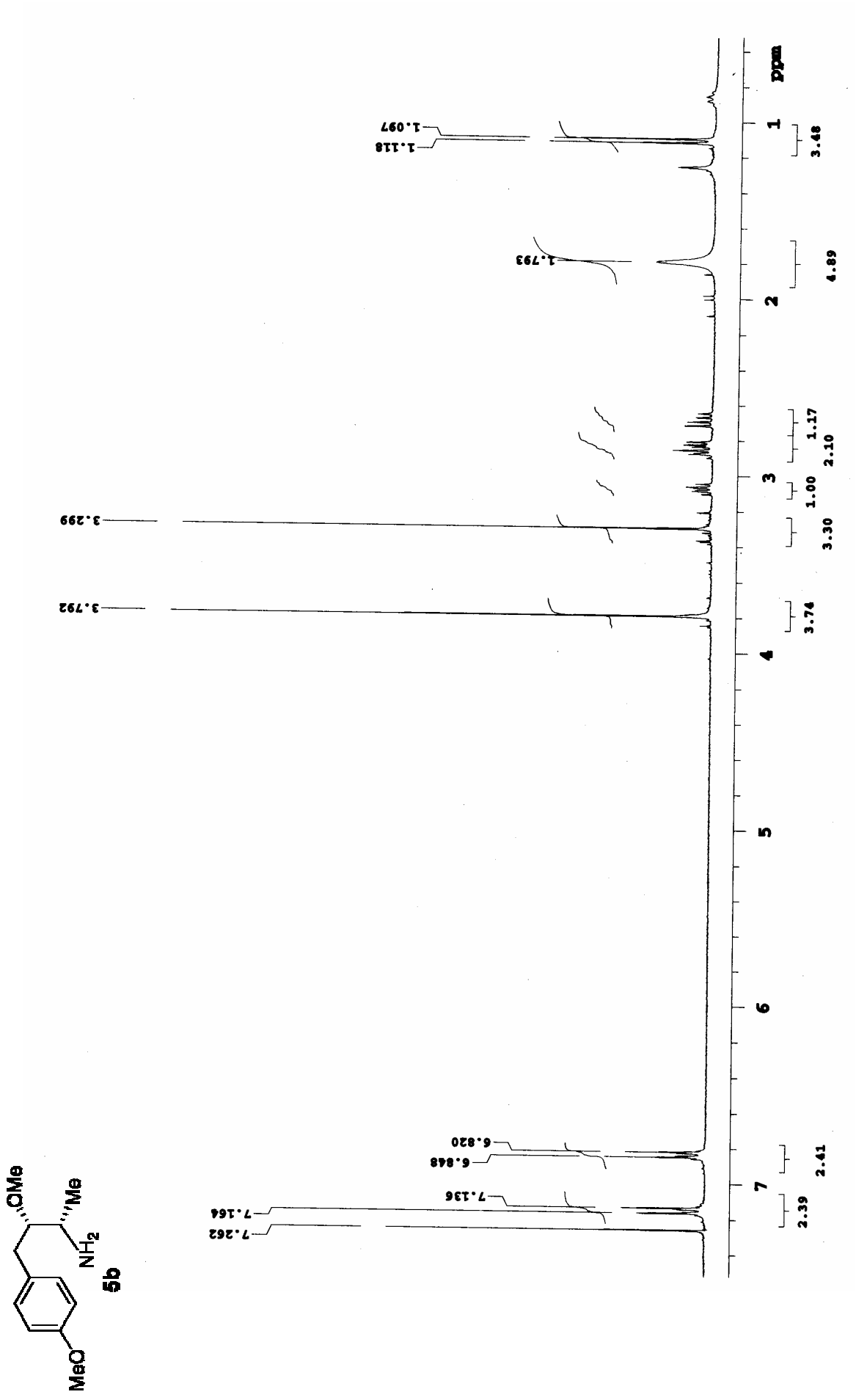
Usuari: san / Mostra: mmcalcohols
Nom: MARISA MENA CERVIGON
Data:27/11/05 / Sist automatic
Pulse Sequence: s2pul
158.057
130.537
130.247
113.798
77.427
77.000
76.573
76.222
55.172
50.388
39.577
20.182
ppm
20
40
60
80
100
120
140
160


OMe
Me
NH2
MeO
5b
7.262
7.164
7.136
6.848
6.820
3.792
3.299
1.793
1.118
1.097
ppm
1
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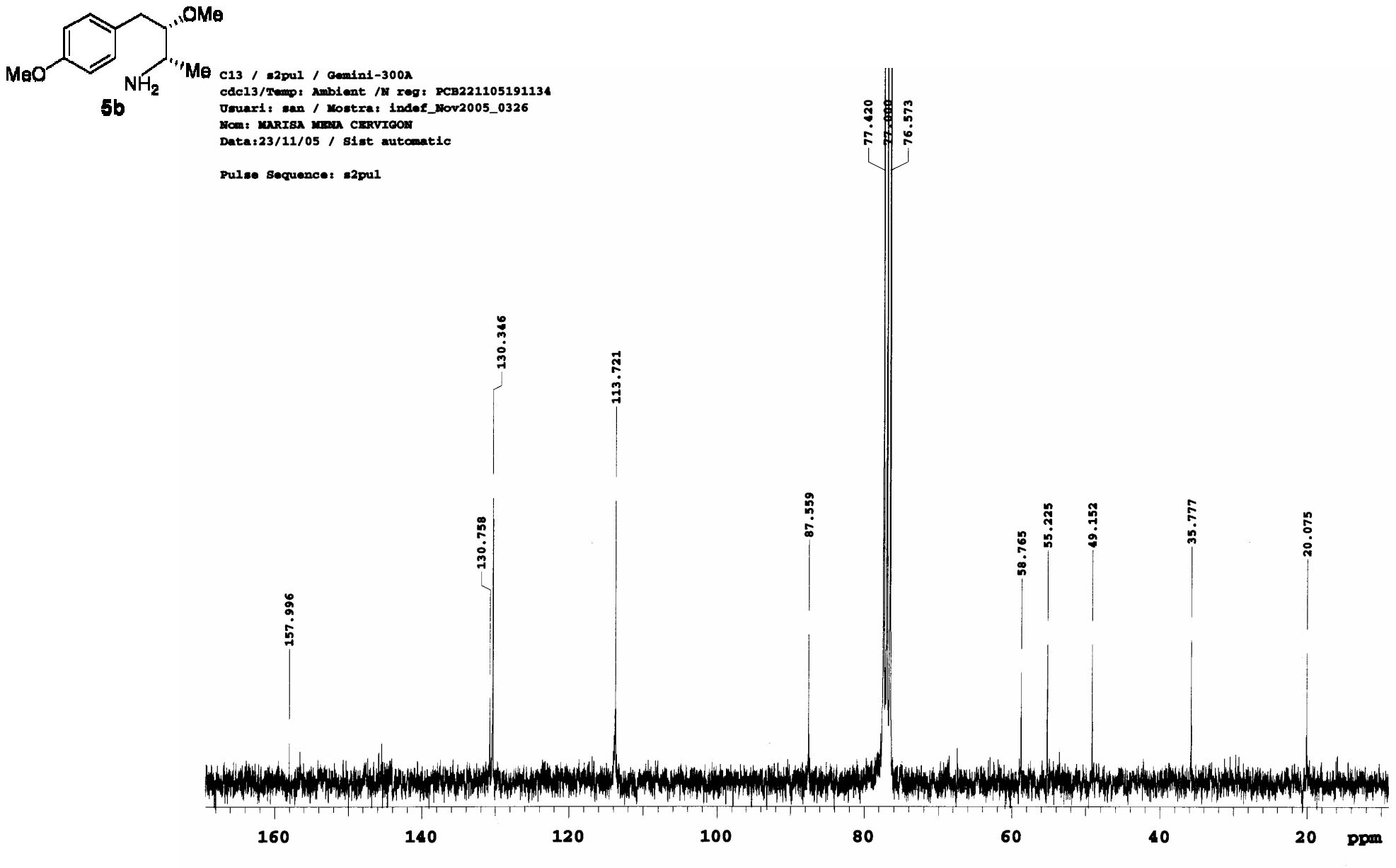
2.10
1.00
3.30
3.74
2.41
2.39


OMe
MeO
Me
NH2
5b
C13 / s2pul / Gemini-300A
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Usuari: san / Mostra: indef_Nov2005_0326
Nom: MARISA MENA CERVIGON
Data:23/11/05 / Sist automatic
Pulse Sequence: s2pul
157.996
130.758
130.346
113.721
87.559
77.420
76.573
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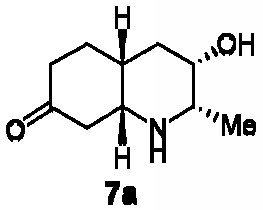
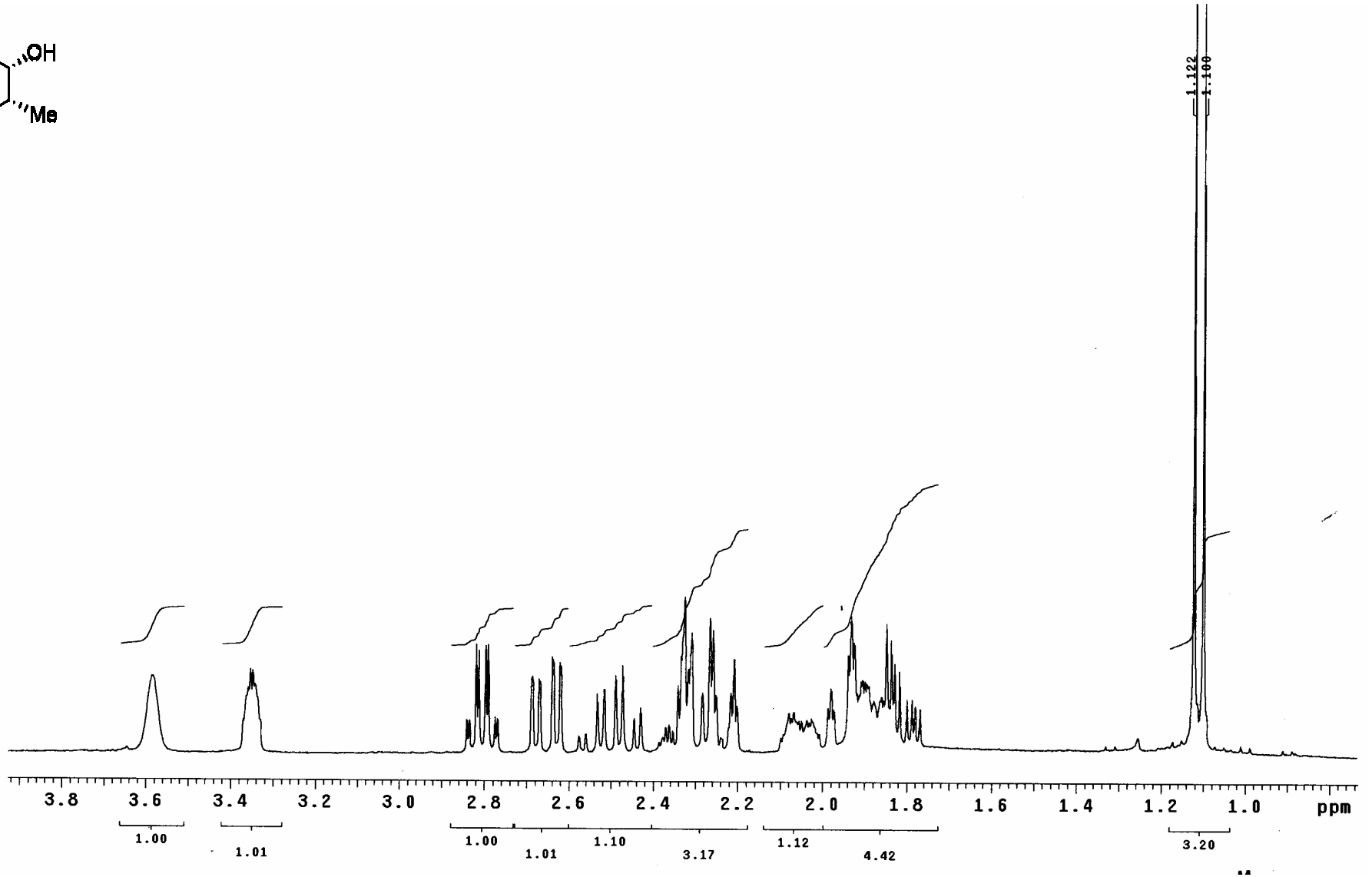
55.225
49.152
35.777
20.075
160
140
120
100
80
60
40
20
ppm


H
OH
O
N
H
Me
H

7a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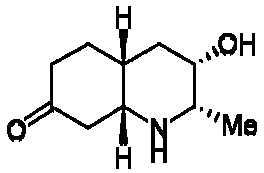
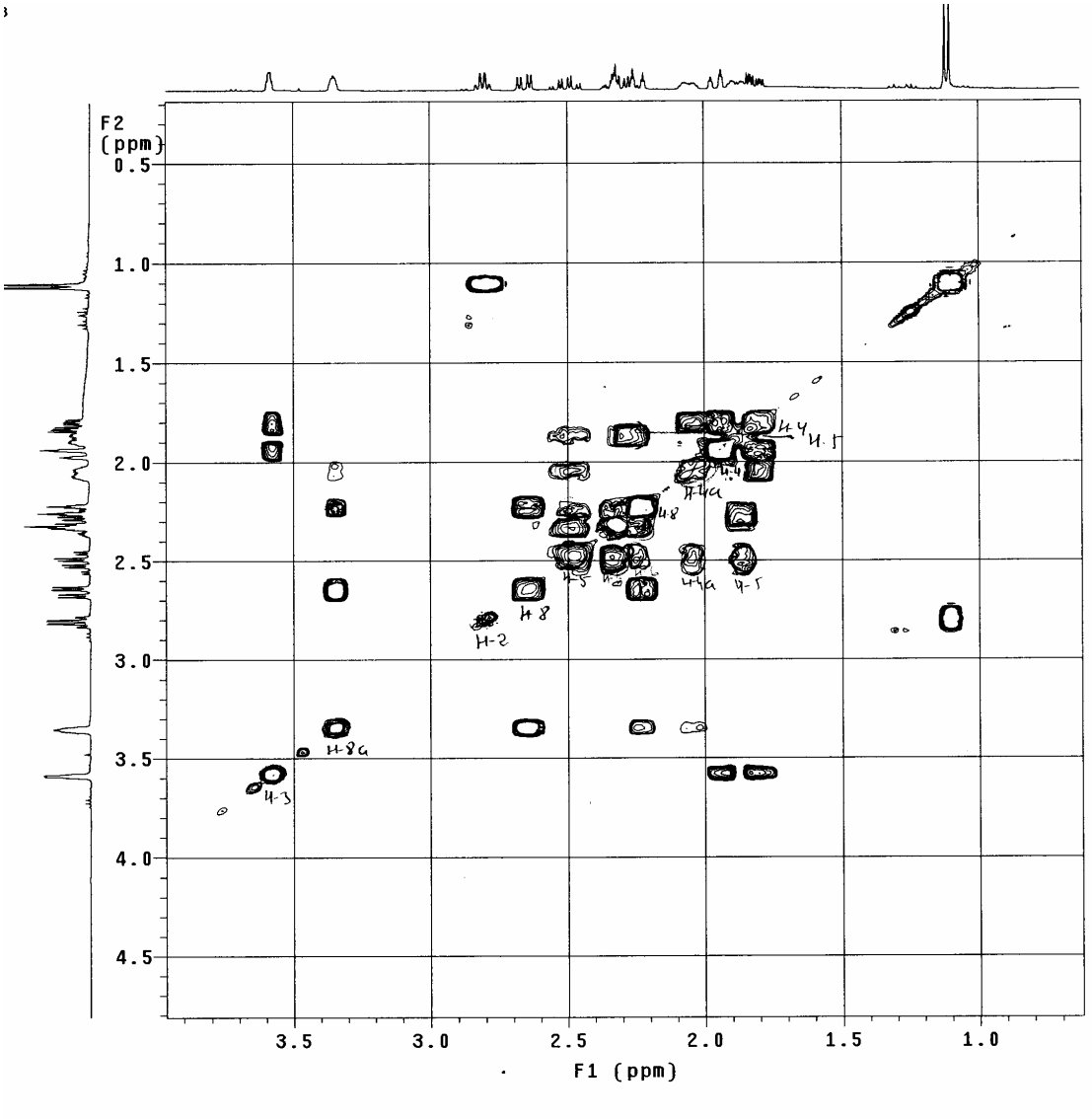
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
ppm
1.00
1.01
1.00
1.01
1.10
3.17
1.12
4.42
3.20

18.064
28.840
33.467
36.393
41.553
42.543
56.811
59.318
68.228
76.680
77.000
77.312
20
30
40
50
60
70
80
OH
Me
H
N
H
O
7a


H
OH
O
N
H
Me
H

7a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(ppm)
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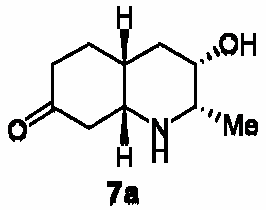
1.5
2.0
2.5
3.0
3.5
4.0
4.5
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)
H-2
H-3
H-8a
H-8
H-4
H-4a
H-5

2 x 256 increments
OBSERVE H1, 400.1226026 MHz
DECOUPLE C13, 100.6184326 MHz
Power 45 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.063 sec
F1 DATA PROCESSING
Gauss apodization 0.014 sec
FT size 1024 x 2048
Total time 1 hr, 23 min, 27 sec



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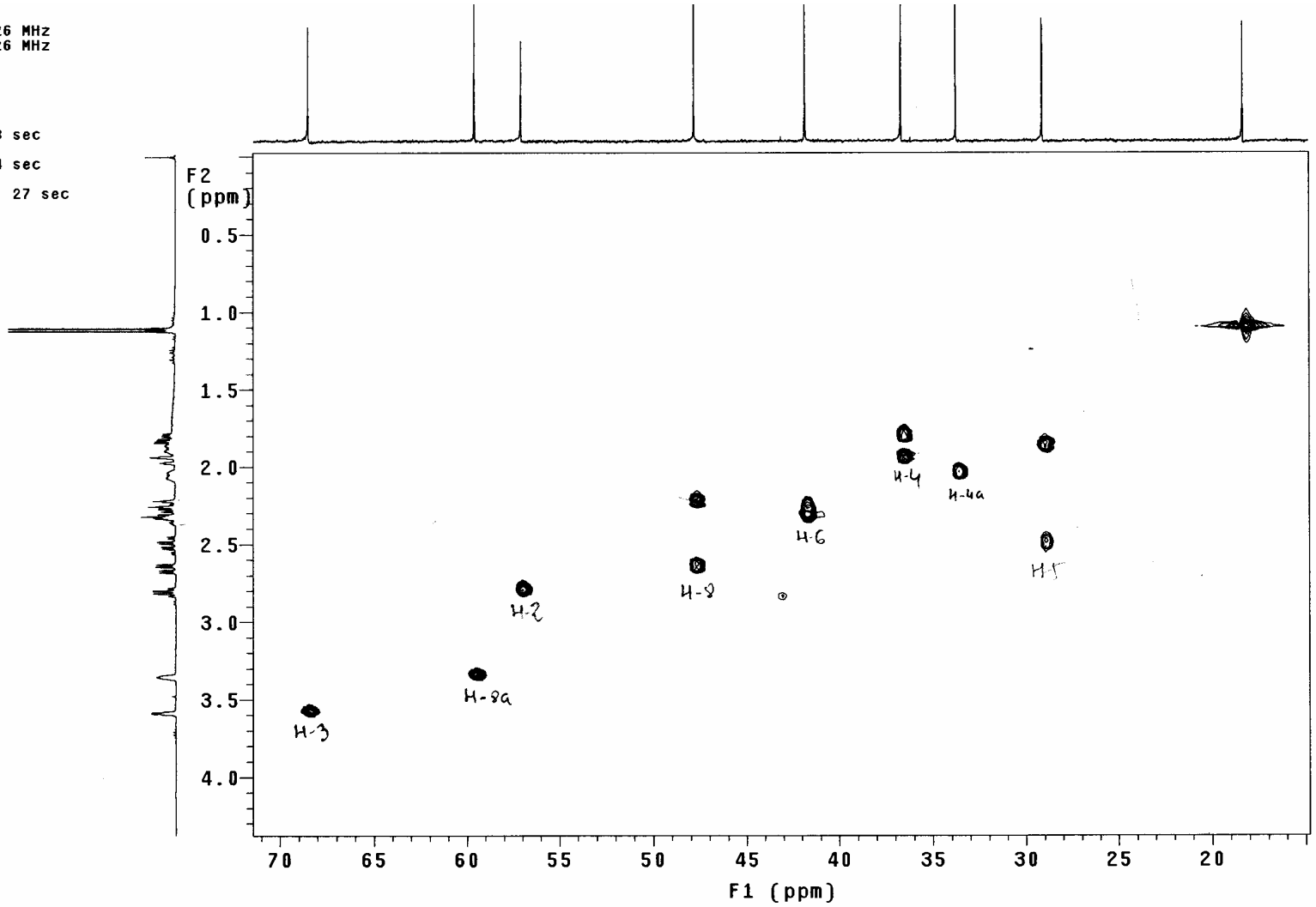
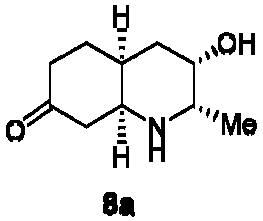
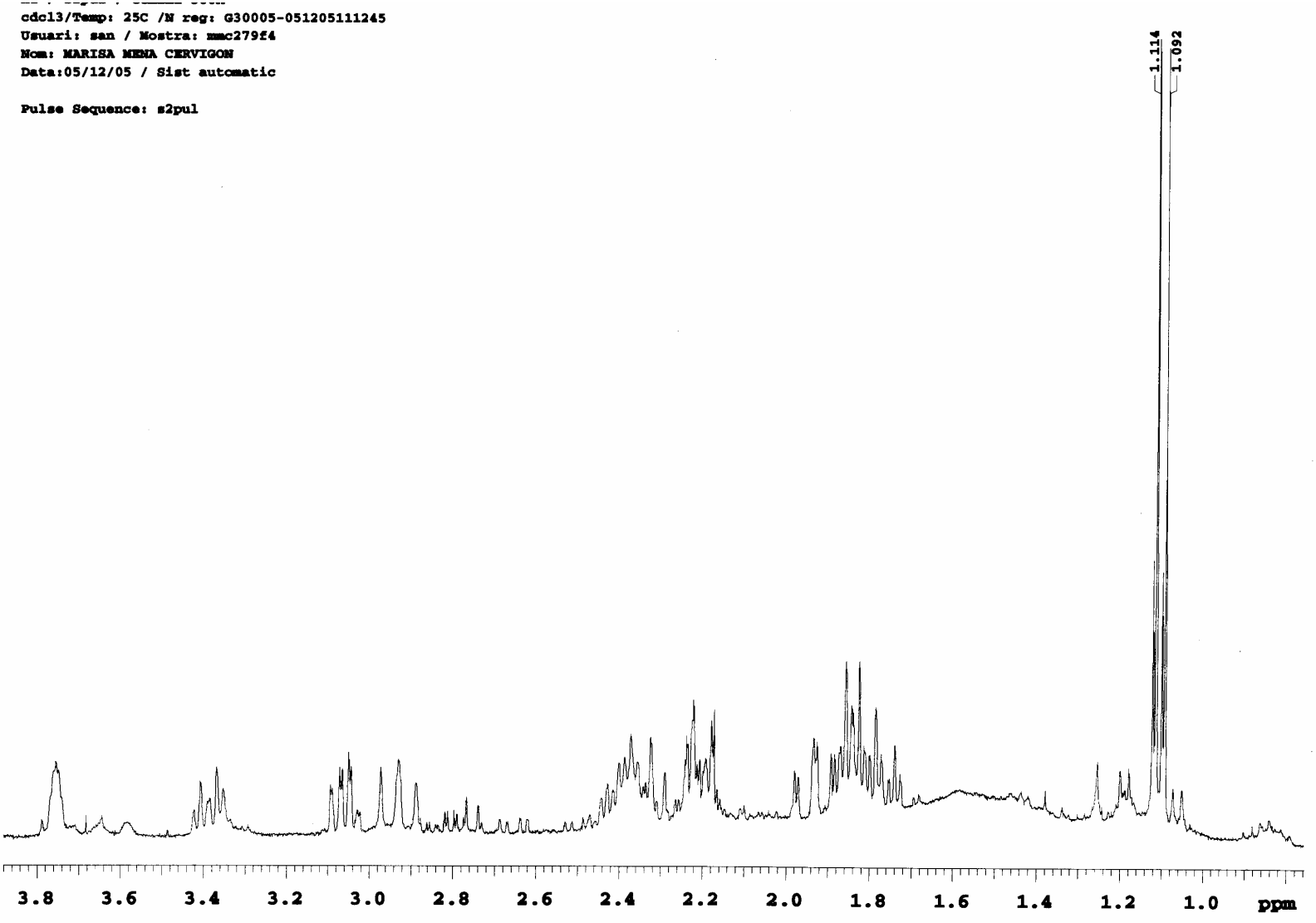



H
OH
O
N
H
Me
H

8a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Data:05/12/05 / Sist automatic
Pulse Sequence: s2pul
1.114
1.092
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
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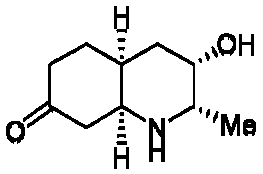
1.8
1.6
1.4
1.2
1.0
ppm



8a

C13 / s2pul / Gemini-300A
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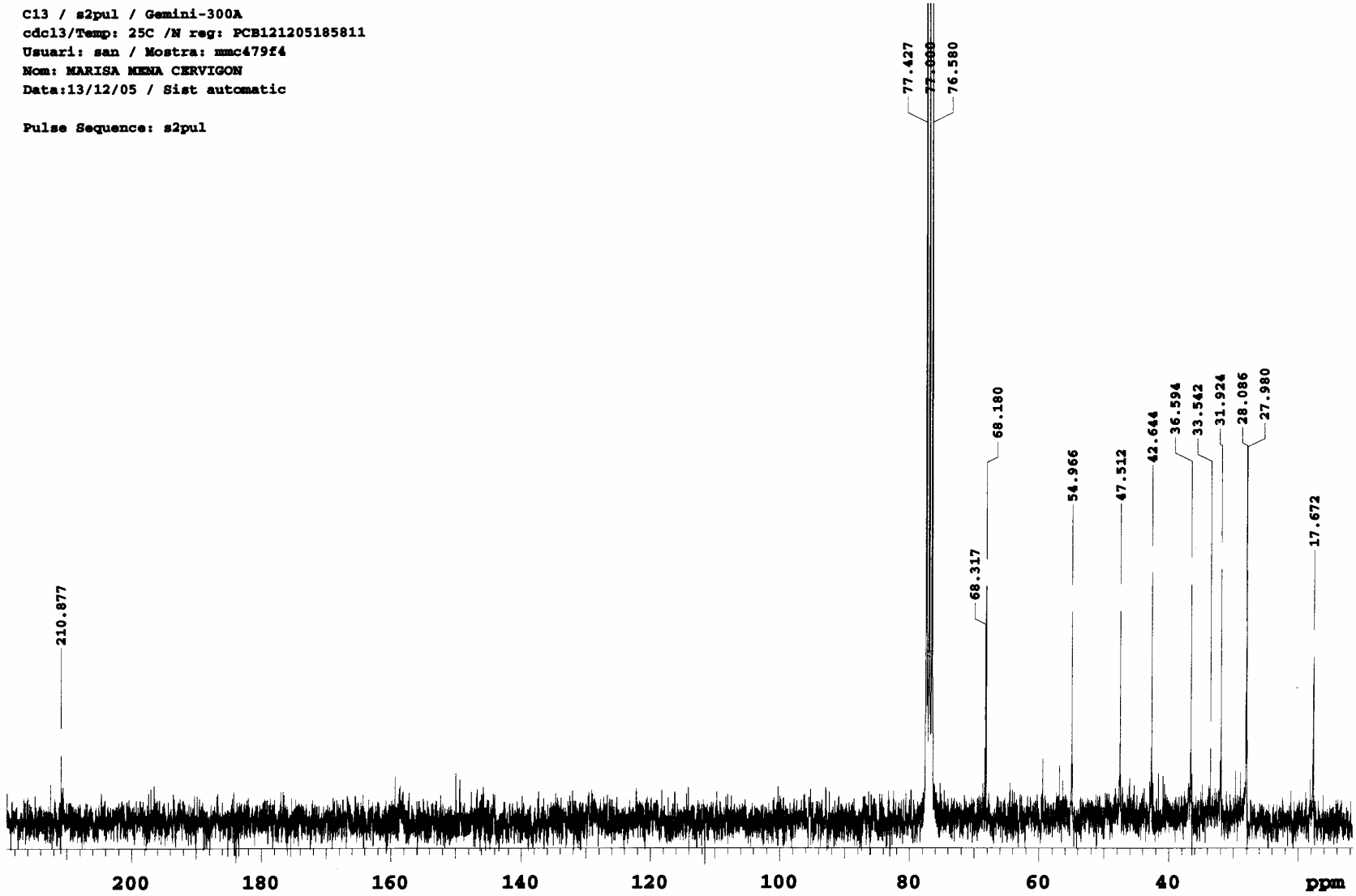
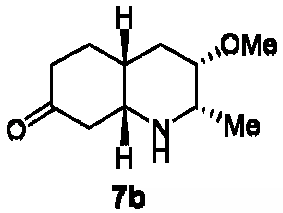
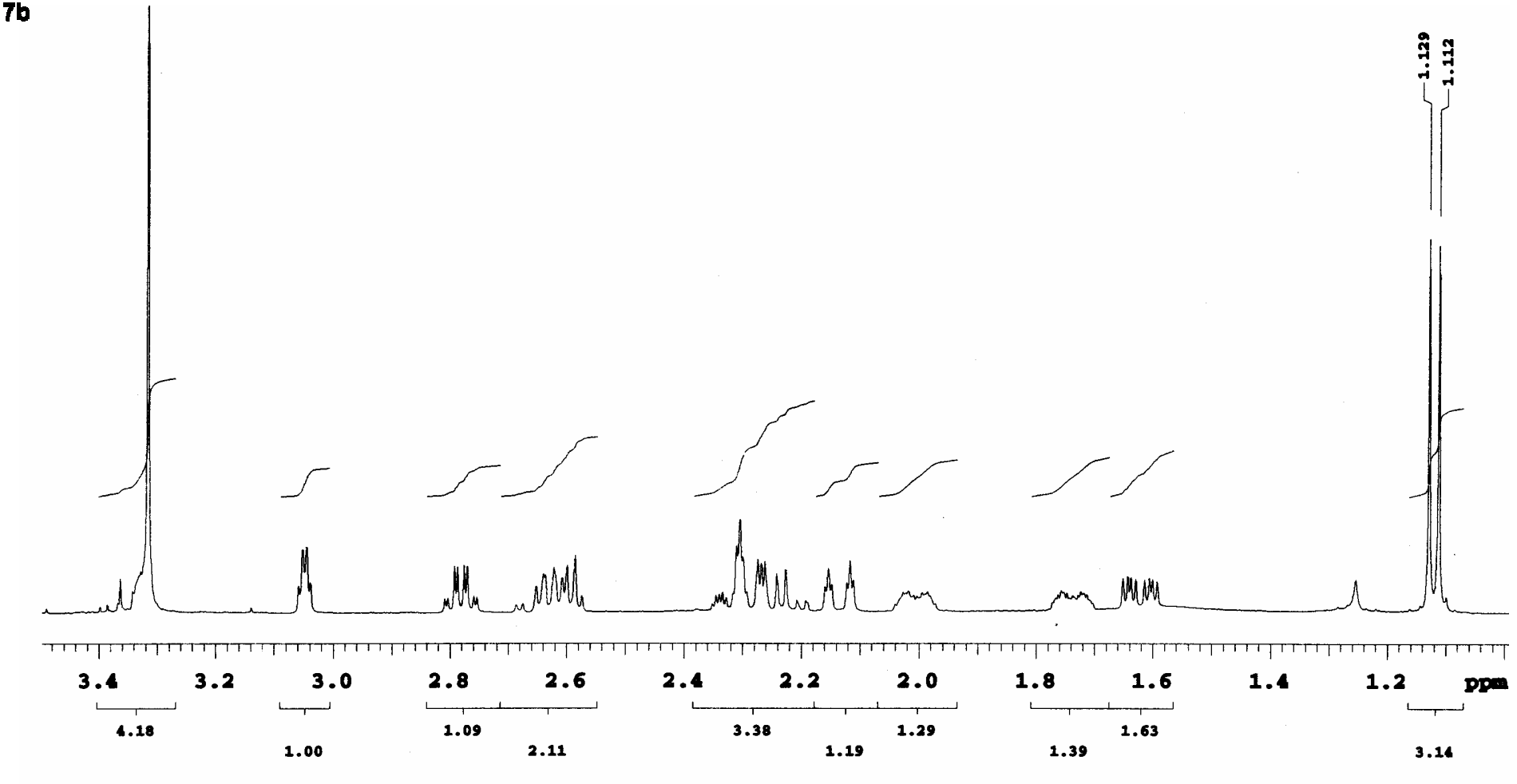
Data:13/12/05 / Sist automatic

Pulse Sequence: s2pul




H
OMe
O
Me
N
H
H

7b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3.0
2.8
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2.4
2.2
2.0
1.8
1.6
1.4
1.2
ppm
4.18
1.00
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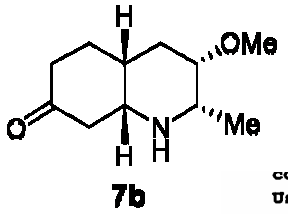
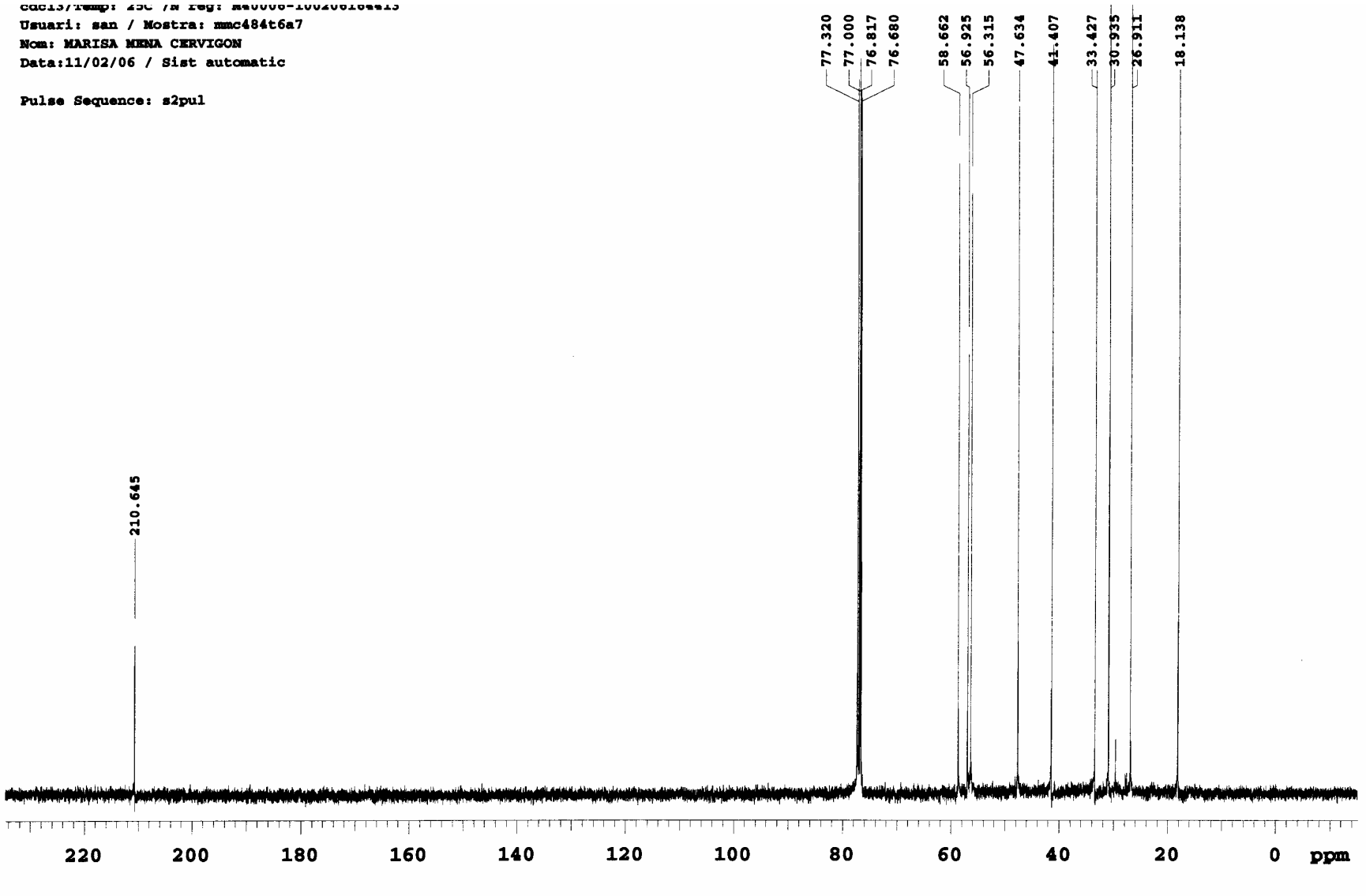
2.11
3.38
1.19
1.29
1.39
1.63
3.14


H
OMe
O
N
H
Me
H

7b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Data:11/02/06 / Sist automatic
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76.817
76.680
58.662
56.925
56.315
47.634
41.407
33.427
30.935
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18.138
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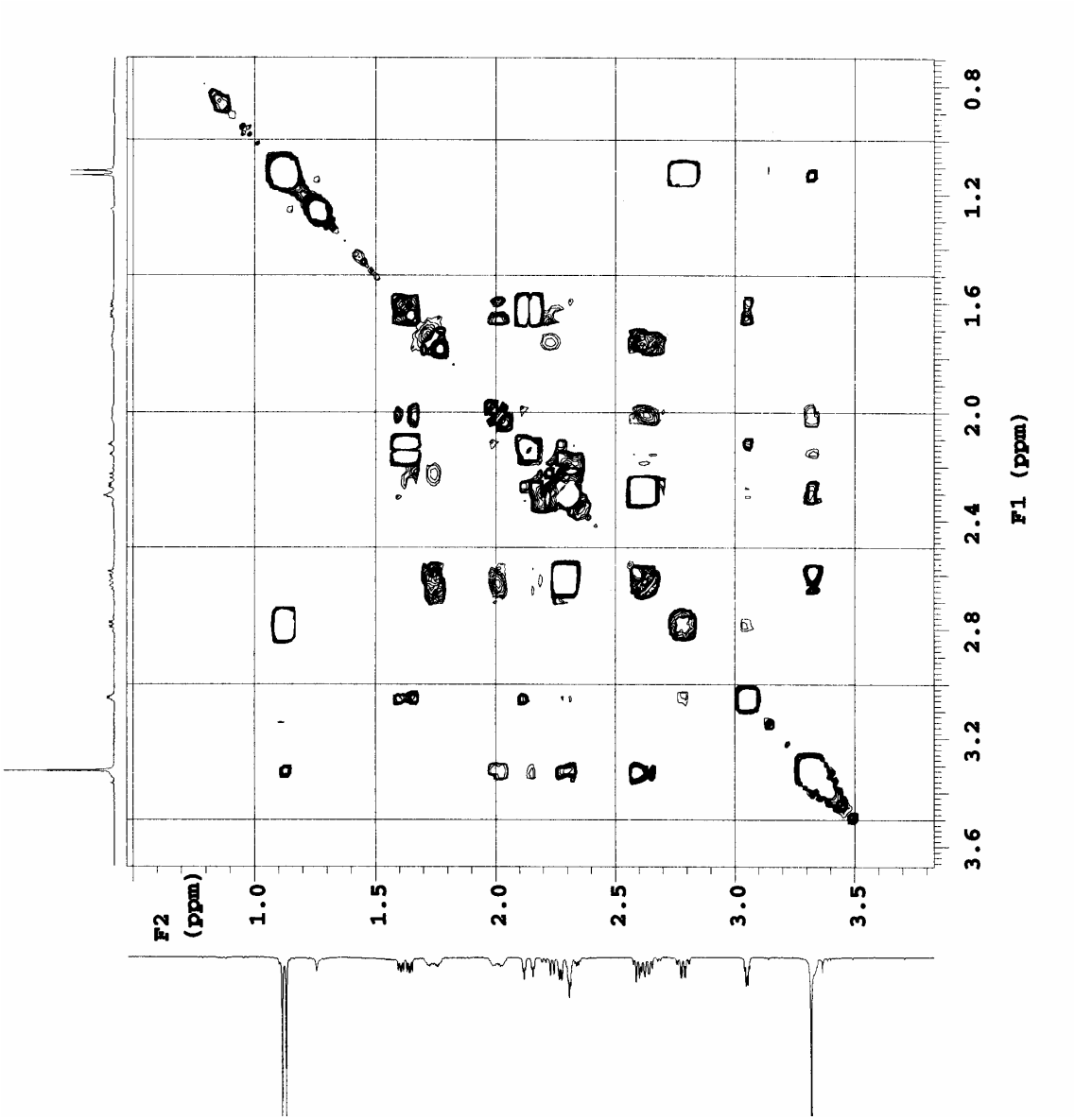
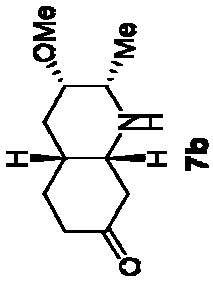
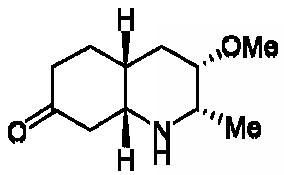
220
200
180
160
140
120
100
80
60
40
20
0
ppm

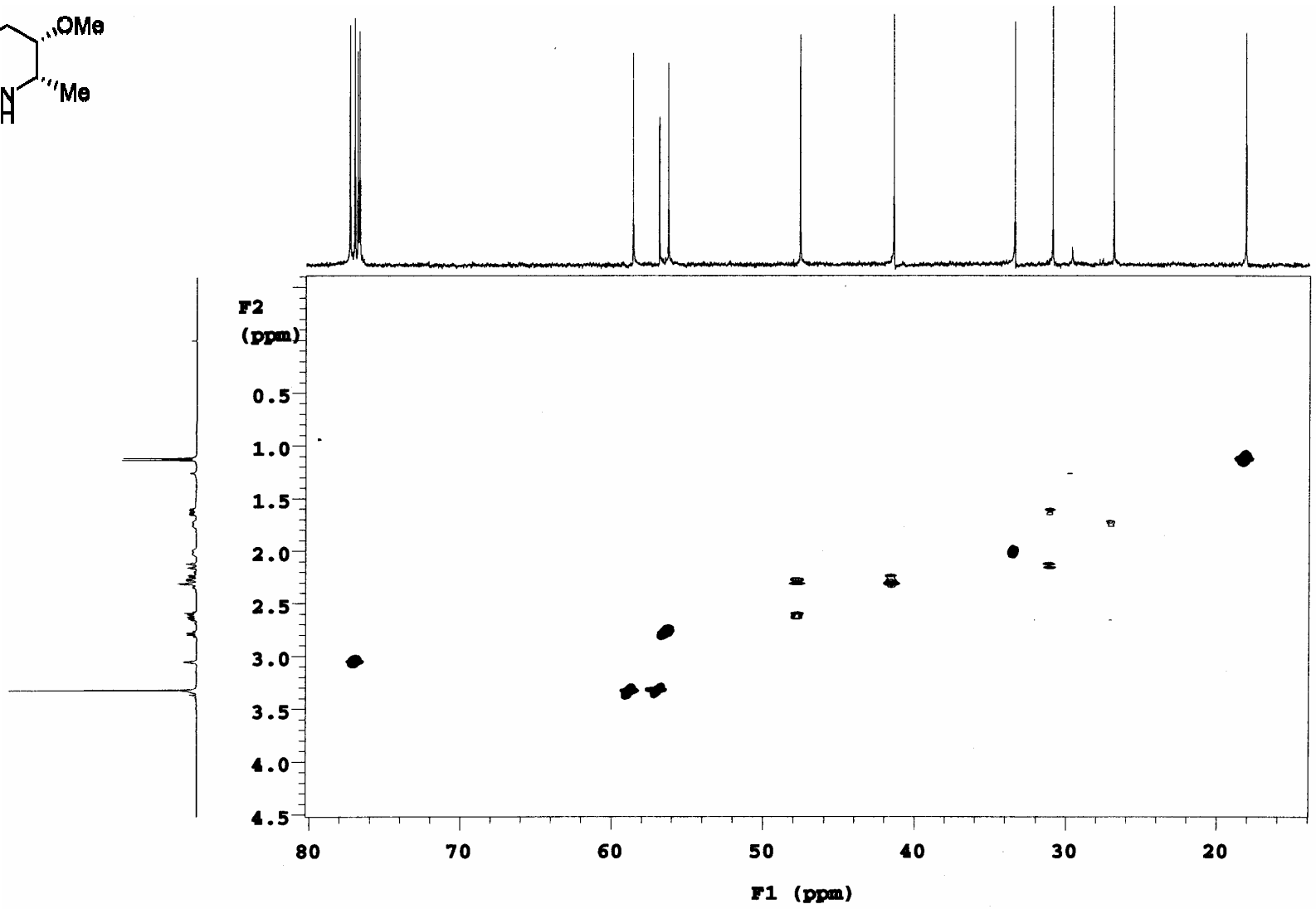


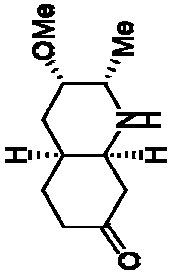


7b

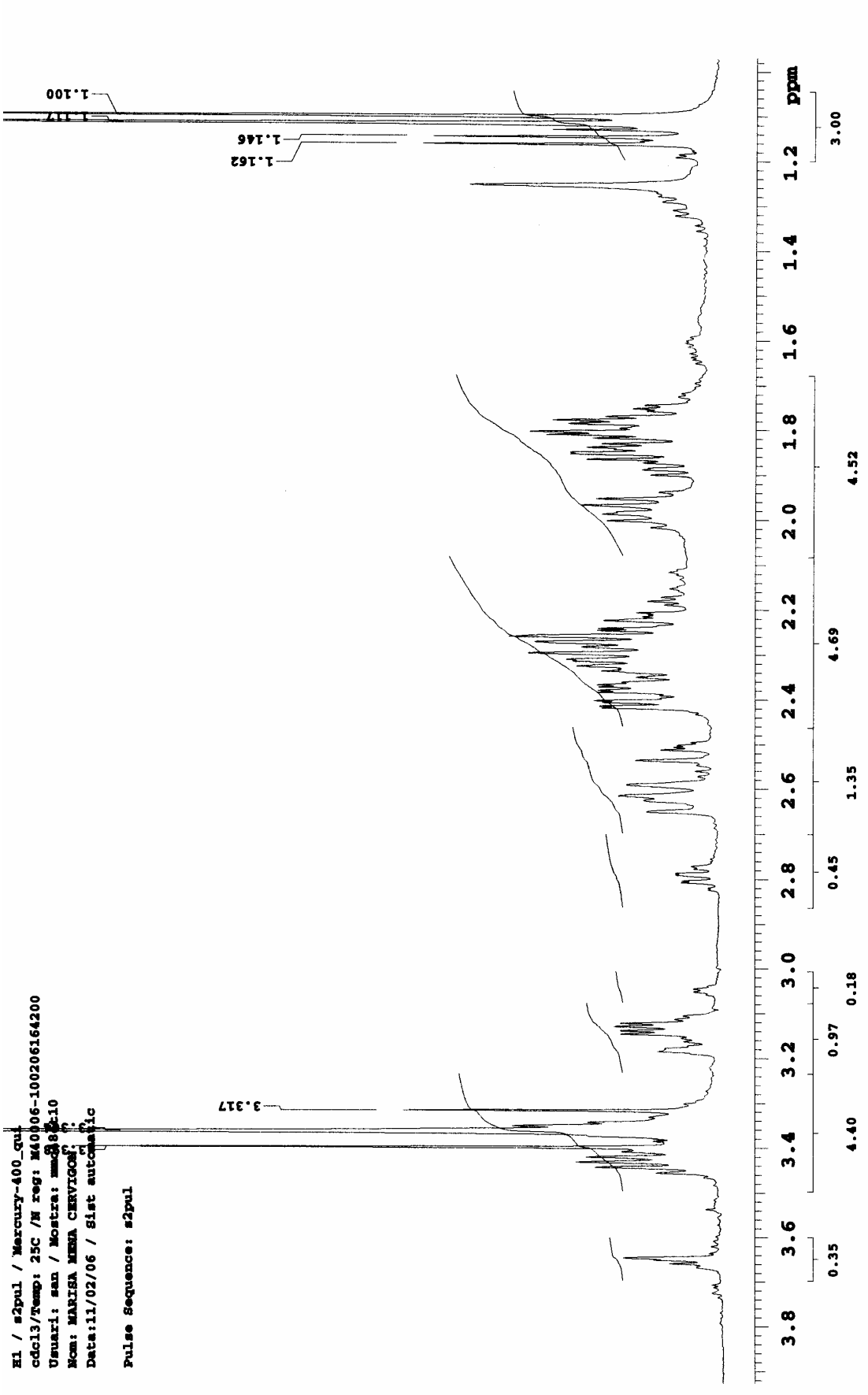

H
OMe
O
N
H
Me
H

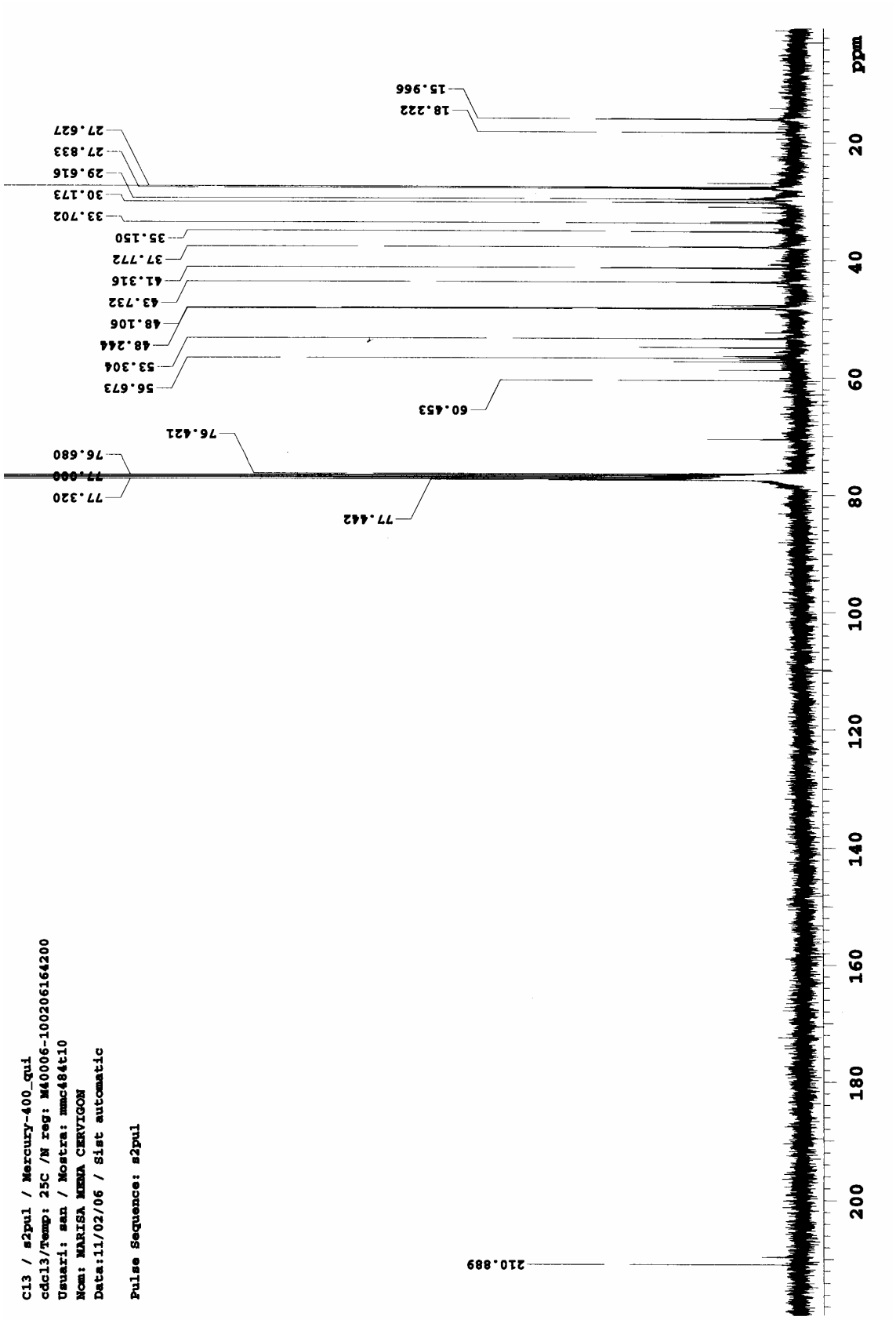
7b

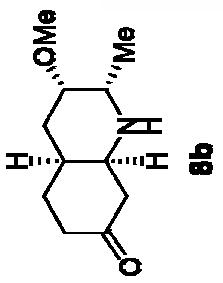

F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
80
70
60
50
40
30
20
F1 (ppm)


OMe
Me
H
N
H
H
O

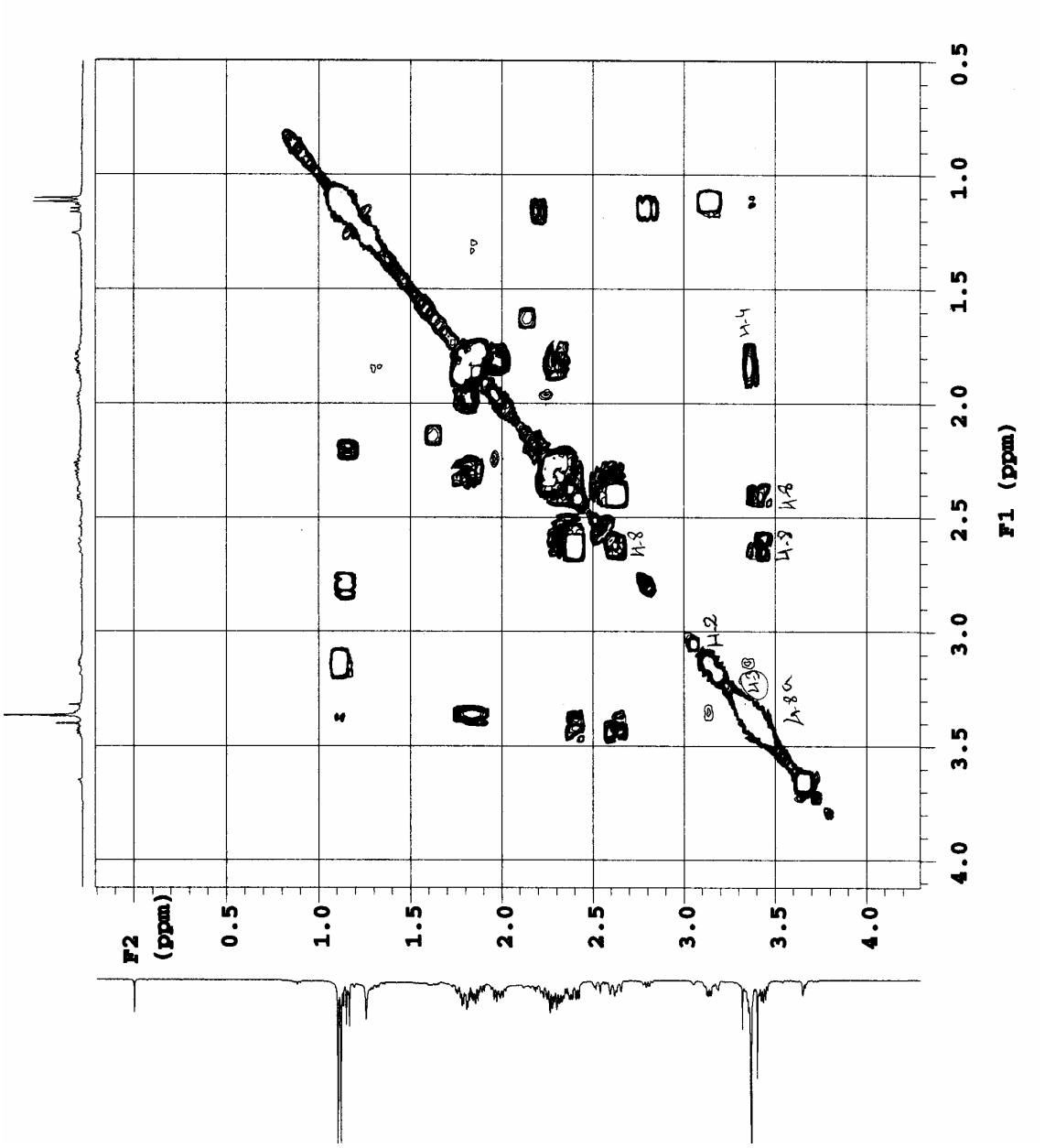
8b

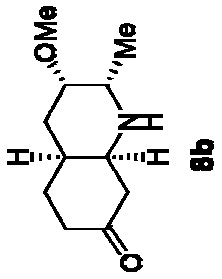

E1 / s2pul / Mercury-400_qul
cdcl3/Temp: 25C /N reg: M40006-10020616200
Usuari: san / Mostra:
Nom: MARISA MEMA CERVIGON
Data:11/02/06 / Sist automatic
Pulse Sequence: s2pul
3.317
1.162
1.146
1.100
ppm
0.35
4.40
0.97
0.18
0.45
1.35
4.69
4.52
3.00

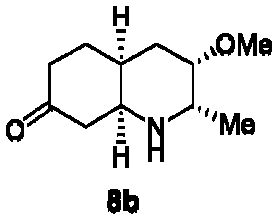

C13 / s2pul / Mercury-400_gui
cdcl3/Temp: 25C /N reg: M40006-100206164200
Usuari: san / Mostra: mmc484t10
Nom: MARISA MENA CERVIGON
Data:11/02/06 / Sist automatic
Pulse Sequence: s2pul
210.889
77.442
76.421
60.453
56.673
53.304
48.244
48.106
43.732
41.316
37.772
35.150
33.702
30.173
29.616
27.833
27.627
18.222
15.966
ppm


OMe
Me
H
N
H
O

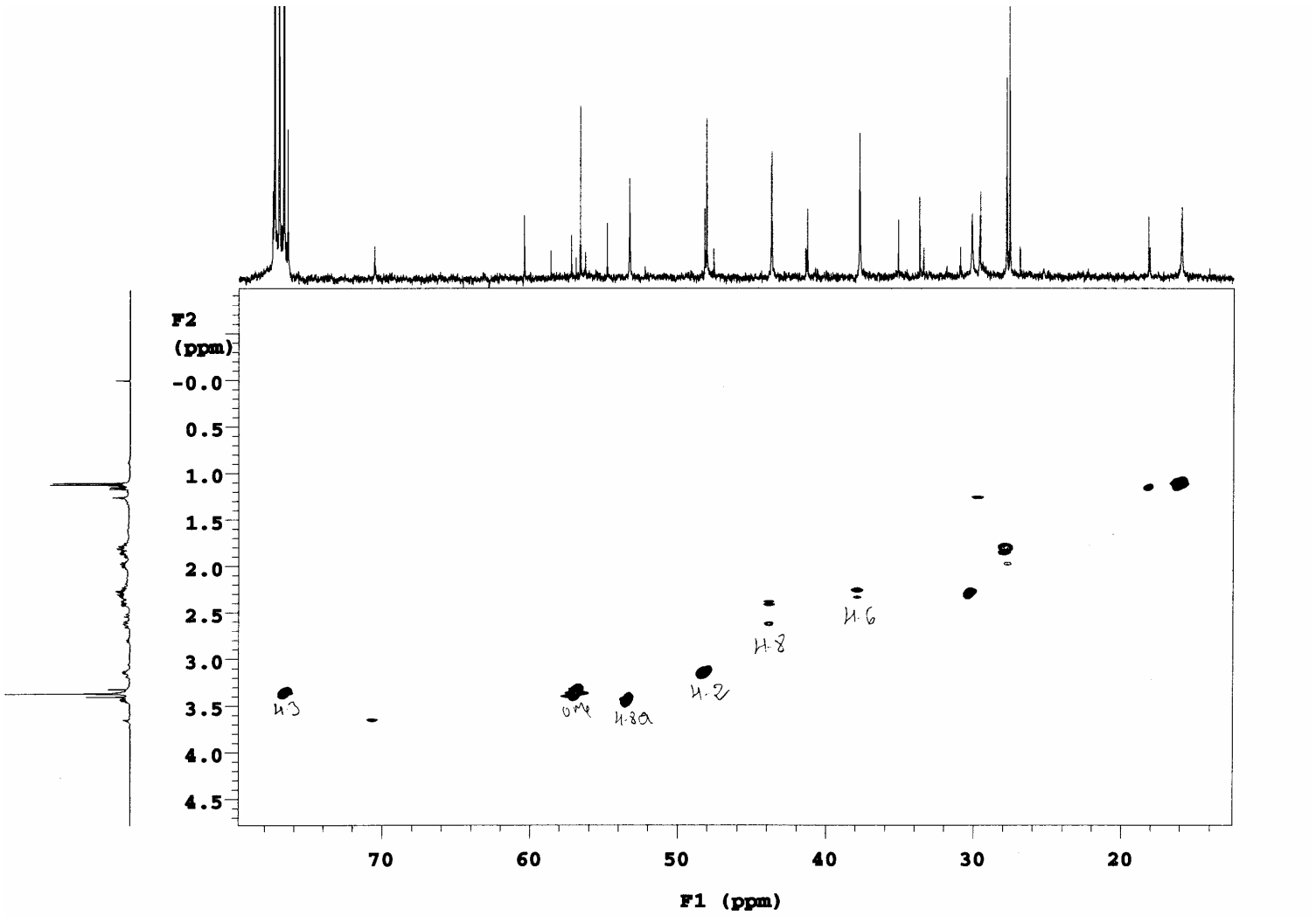
8b


F2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
F1 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
H-4
H-8
H-8
H-12
H-13
H-8a

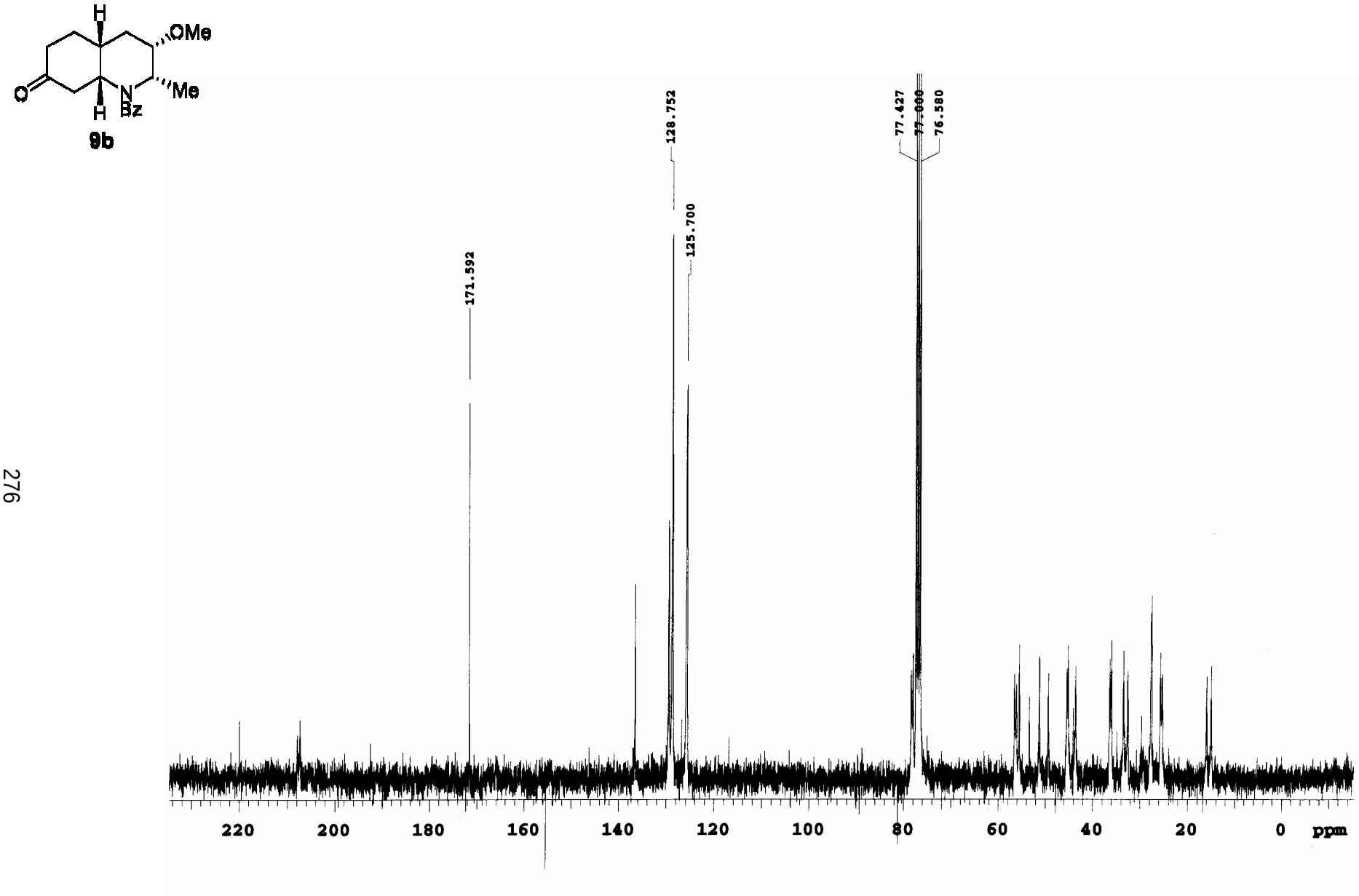

OMe
Me
H
N
H
O
8b

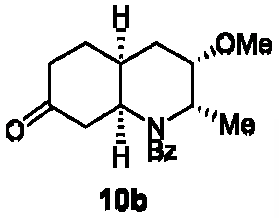

H
OMe
O
N
H
Me
H

8b

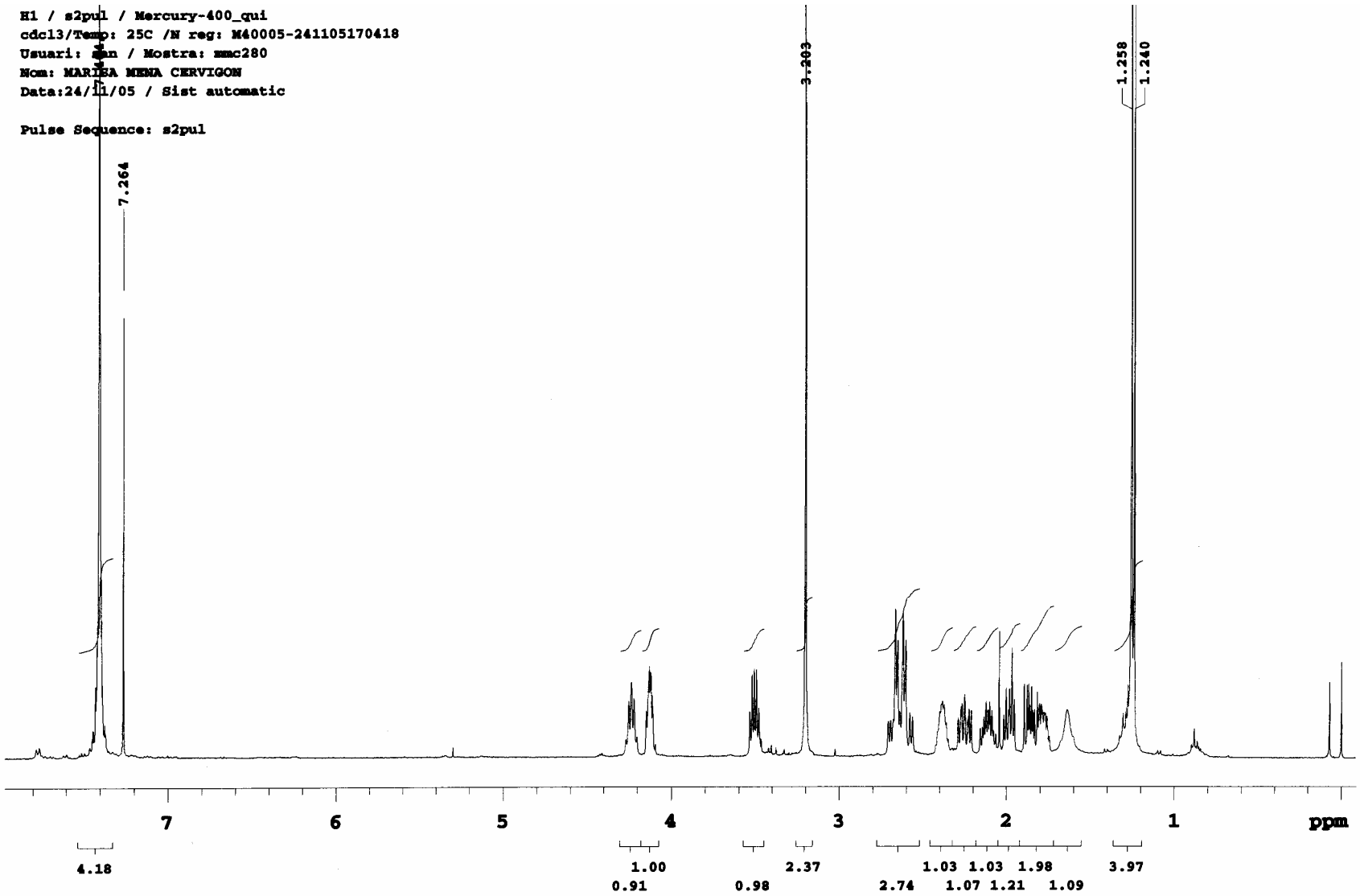

F2
(ppm)
-0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
70
60
50
40
30
20
F1 (ppm)
H-3
OMe
H-8a
H-2
H-8
H-6

7.754
7.408
7.314
7.317
7.267
5.299
5.296
3.455
3.246
1.300
1.254
1.152
1.137
-0.000
ppm
1
2
3
4
5
6
7
8
OMe
Me
N
Bz
H
H
O
9b


H
OMe
O
N
Me
H
Bz
9b
171.592
128.752
125.700
77.427
77.000
76.580
220
200
180
160
140
120
100
80
60
40
20
0
ppm

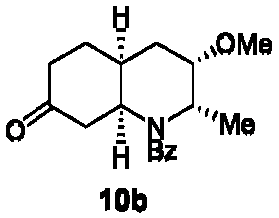

H
OMe
O
N
Me
Bz
H

10b

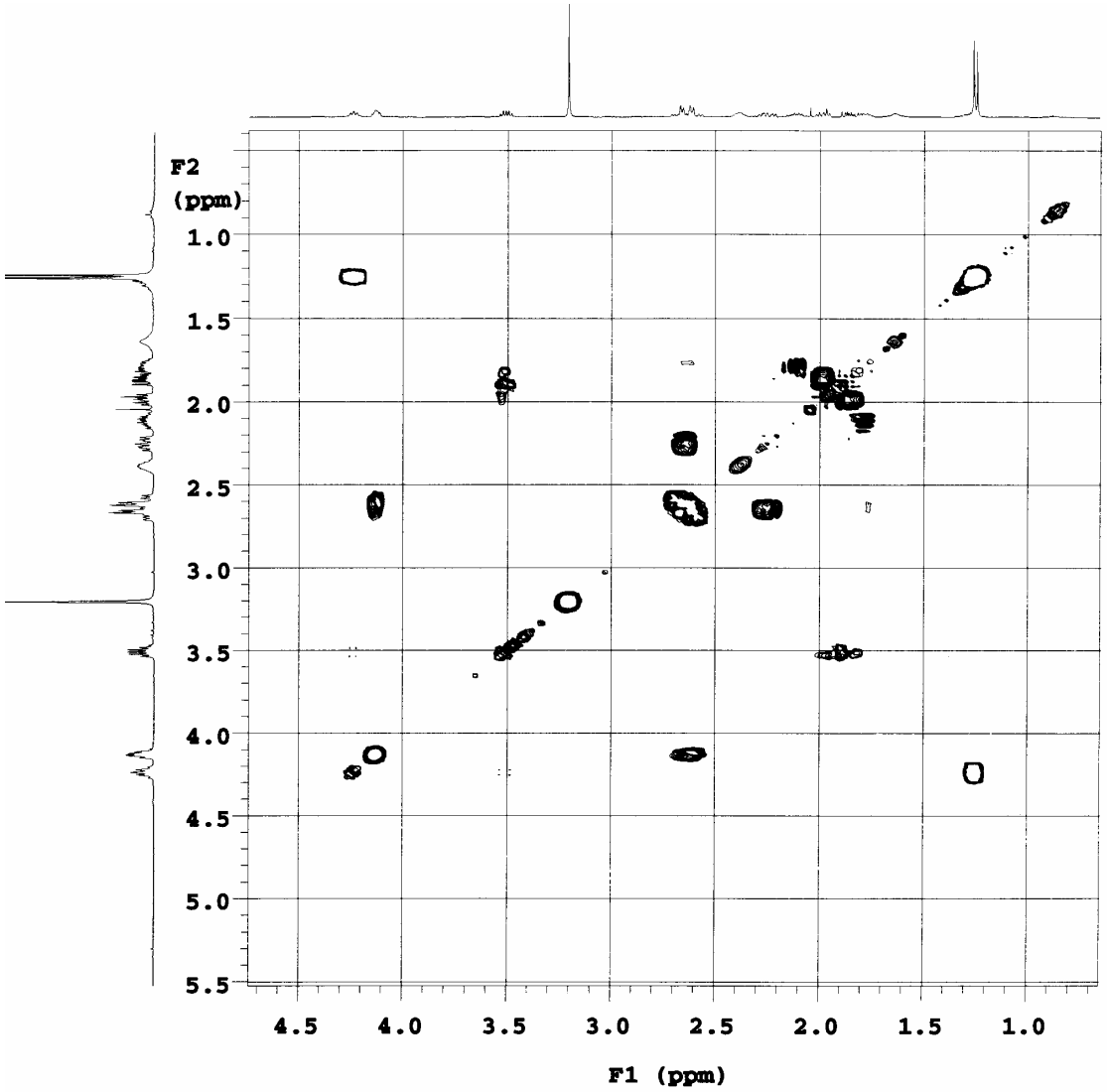

H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40005-241105170418
Usuari: san / Mostra: mmc280
Nom: MARIBA MENA CERVIGON
Data:24/11/05 / Sist automatic
Pulse Sequence: s2pul
7.264
3.203
1.258
1.240
7
6
5
4
3
2
1
ppm
4.18
1.00
0.91
0.98
2.37
2.74
1.03
1.07
1.03
1.21
1.98
1.09
3.97

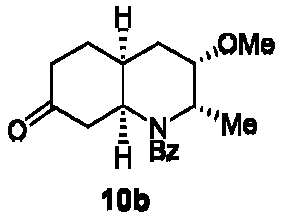
12.506
26.469
28.504
29.677
33.351
38.534
43.503
51.902
52.824
56.254
75.018
76.688
76.840
77.000
77.206
77.320
126.784
128.568
130.016
136.639
173.208
205.417
20
40
60
80
100
120
140
160
180
200
ppm

OMe
Me
N
Bz
H
H
O
10b

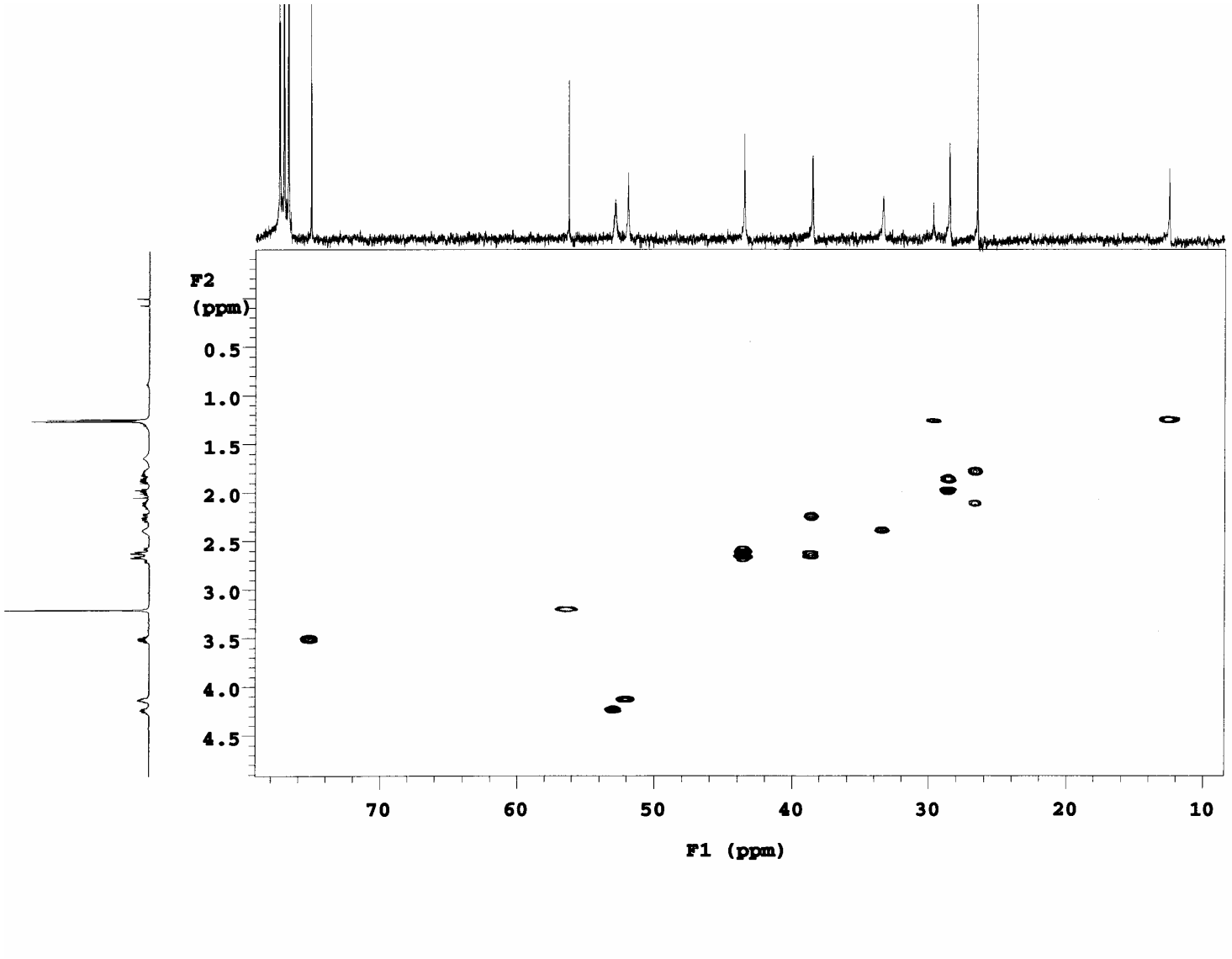

H
OMe
O
N
Me
Bz
H

10b


F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)


H
OMe
O
N
Me
H
Bz

10b


F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
70
60
50
40
30
20
10
F1 (ppm)