Efforts toward a stereocontrolled synthesis of CYP3A4 inhibitor GF-I-1 and stereoisomers

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Abstract

Several furocoumarin compounds that show significant inhibition of the main human metabolic enzyme CYP3A4 have been isolated from grapefruit juice. The most potent of these is GF-I-1, an asymmetrical homodimer whose stereochemistry remains unknown. We sought to synthesize GF-I-1 and its three stereoisomers in a stereocontrolled fashion to unambiguously determine the absolute stereochemistry of natural GF-I-1. We were also interested in comparing the biological activities of the four synthetic isomers, following work that showed that CYP3A4 is not sensitive to the absolute configuration of a simpler grapefruit furocoumarin.

We have achieved the synthesis of a key dimeric intermediate in racemic form on the route towards GF-I-1. In doing so, we assessed the efficiencies of $BiCl_3$ and $Cu^{II}(BF_4)_2$, two newly-discovered Lewis acid catalysts, for promoting the condensation of precious alcohols and epoxides. $Cu^{II}(BF_4)_2$ appears to be a promising catalyst for these transformations, for which well-established synthetic protocols have been notably absent.

We also progressed along the stereocontrolled route towards GF-I-1 and its stereoisomers, with the stereospecific synthesis of all required chiral

precursors in greater than 96% enantiomeric excess. While the total synthesis was not completed due to a transformation that could not be efficiently accomplished during the allotted time for the project, we have laid the groundwork for the rapid stereocontrolled synthesis of GF-I-1 in the future.

Chapter 1

Introduction and Background

In 1989, a drug interaction between grapefruit (*Citrus paradisii*) and felodipine, a dihydropyridine calcium channel antagonist, was serendipitously discovered by Bailey et al. They were investigating the interaction of felodipine and ethanol, using grapefruit juice as the delivery vehicle.[1] When felodipine was ingested with grapefruit juice, the plasma concentrations of the drug were more than five-fold greater than when taken with water. It was known that the bioavailability of felodipine typically averages only 15% due to exhaustive first-pass metabolism.[2] This, coupled with the observation that grapefruit juice has no effect on the elimination of plasma felodipine,[3] suggested that regulation of the first-pass enzyme by compounds in the grapefruit juice may be responsible for the observed drug interaction. A search for that first-pass enzyme yielded cytochrome P450 3A4.[4]

Cytochrome P450 enzymes are a class of heme-containing proteins that generally catalyze the oxidation of their substrates. Of the many cytochrome P450 isoforms present, cytochrome P450 3A4 (CYP3A4) is the most abundant in the liver and epithelial tissue of the small intestine.[5] It has been implicated in metabolizing approximately 50% of the clinical drugs on the market as well as a broad range of xenobiotics.[6] For example, it is known

that CYP3A4 catalyzes the conversion of polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HAs) to reactive electrophiles. These metabolites from PAHs, often referred to as diol epoxides, react with DNA, and thus exert carcinogenic and mutagenic effects.[7]

Once the target metabolic enzyme CYP3A4 was identified, work ensued in identifying the compounds present in grapefruit that are responsible for altering its biological activity. A series of furocoumarins and furocoumarin dimers were isolated and their structures characterized from fractions of organic extracts of grapefruit juice that showed inhibition of CYP3A4.[8] Of these, the most potent inhibitor was determined to be GF-I-1 (recently renamed: Paradisin A), a furocoumarin dimer that is a mechanism-based competitive inhibitor of CYP3A4, with an IC_{50} on the order of 10 nM.[9]

It should be mentioned that neither do the grapefruit furocoumarins inhibit CYP3A4 exclusively nor are they the only known inhibitors of CYP3A4. The furocoumarins present in grapefruit have been shown to inhibit several other P450 isoforms.[9] They recently have also been observed to interact with P-glycoprotein, a membrane-localized drug transporter, thus inhibiting the cellular efflux of its targets.[10] CYP3A4 has long been known to be inhibited by Ketoconazole,[11] an anti-fungal drug, and recently a new class of bisalkaloids from white pepper that also possess moderate CYP3A4 inhibitory activity has been isolated.[12]

While the structures of the furocoumarins present in grapefruit have been identified, the stereochemical properties of these chiral molecules have not been unambiguously elucidated. Previously, through a total stereocontrolled synthesis, our laboratory has unambiguously determined the absolute stereochemistry of natural 6,7-dihydroxybergamottin (DHB), another CYP3A4 inhibitor from grapefruit that is somewhat less potent but more synthetically accessible than GF-I-1 (**Figure 1**).[13] Furthermore, the CYP3A4 inhibition activity of the two stereoisomers of DHB were compared against each other as well as racemic DHB, revealing that all three activities are nearly equivalent. This suggested that the portion of DHB containing the stereocenter does not interact with the CYP3A4 active site.
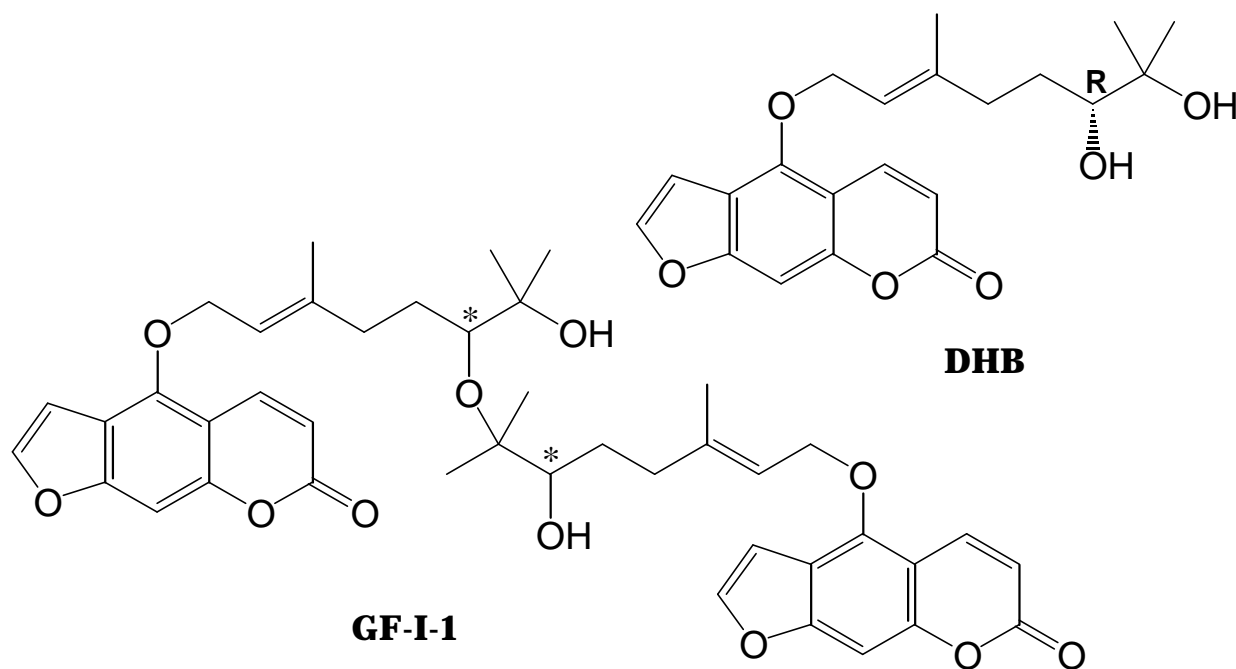
Figure 1. Synthetic target.

We now turned our attention towards the more potent GF-I-1 furocoumarin dimer. The absolute stereochemistry of this compound has been proposed to be (6R, 6'R) through ^{1}H NMR studies of the corresponding Mosher esters,[14] however this method has been known to give erroneous results.[15,16] We decided to unambiguously determine the absolute stereochemistry of GF-I-1 using a synthetic approach. We were also interested in comparing the inhibition activities of the four GF-I-1 diastereomers. In this dissertation, we describe our efforts toward the stereocontrolled total synthesis of GF-I-1 and its stereoisomers.

Chapter 2

Synthesis of Racemic Model System

The greatest challenge that we anticipated in the synthesis of GF-I-1 was the coupling of the two geranyl chains to form the ether-linked dimer. In fact, prior to the very recent work by Barluenga et al.,[17] the literature was void of any systematic protocol for opening precious epoxides with precious alcohols. Cognizant of this difficulty, we synthesized a racemic model system for conducting epoxide-opening trials.

Starting with the commercially available geraniol (**1**), the racemic epoxide (**3**) and diol (**4**) were readily prepared (**Scheme 1**). The primary alcohol of geraniol (**1**) was protected with the pivaloate ester to prevent competition with the secondary alcohol of the diol (**4**) in opening the epoxide (**3**). The geranyl pivaloate (**2**) was oxidized with *m*CPBA to form the epoxide (**3**), which was hydrolyzed with strong aqueous acid to make the diol (**4**).

With a generous supply of racemic epoxide (**3**) and diol (**4**) in hand, we began a series of experiments to identify a suitable Lewis acid catalyst for their complexation to form the ether-linked dimer. We first tried BiCl$_3$, a Lewis acid catalyst which had been reported to promote efficient epoxide opening under mild conditions (**Scheme 2**).[18] Although high yields of cleaved

Scheme 1[a]
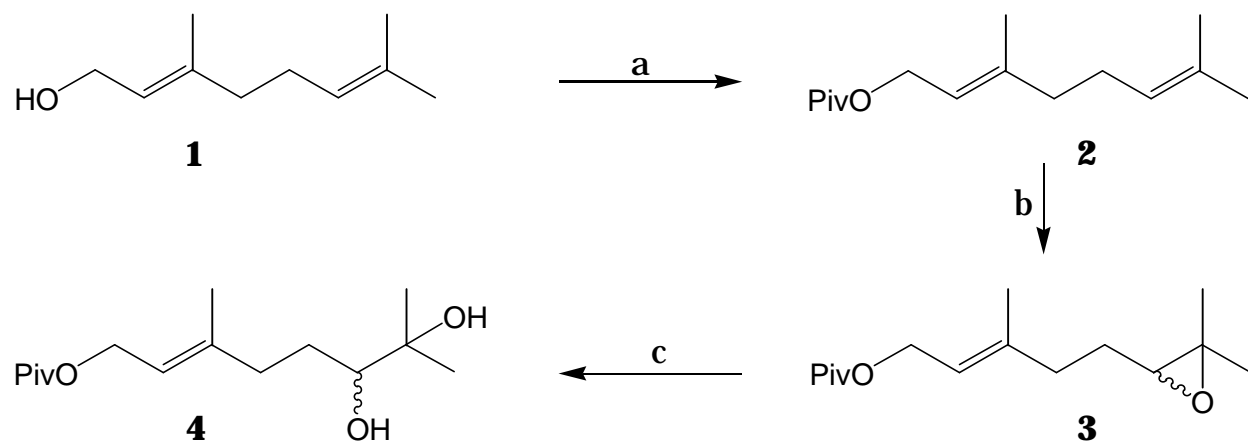
[a] Reagents and Conditions: (a) PivCl, py, CH_2Cl_2, 0 °C, 3 h, 88%; (b) *m*CPBA, CH_2Cl_2, 0 °C, 2 h, 65%; (c) H_2SO_4, THF, rt, 45 m, 62%.

epoxide had been reported using $BiCl_3$, when we tried the reaction between styrene oxide (**5**) and isopropanol, we observed only partial formation of the resulting α-alkoxy alcohol (**6**). Furthermore, the trial was conducted using isopropanol as both a reagent and the solvent simultaneously, a luxury we could not afford with the precious diol (**4**). When this experiment was repeated without using a large excess of the alcohol (8 mol eq), no product (**6**) was observed, even when the reaction mixture was heated to reflux and the amount of catalyst increased five-fold. To conclusively verify that these results apply to our system, racemic epoxide (**3**) and diol (**4**) were subjected to the $BiCl_3$ catalyst and no product was observed. Thus, $BiCl_3$ is not a suitable catalyst for promoting the condensation of precious alcohols and epoxides.

Scheme 2[a]
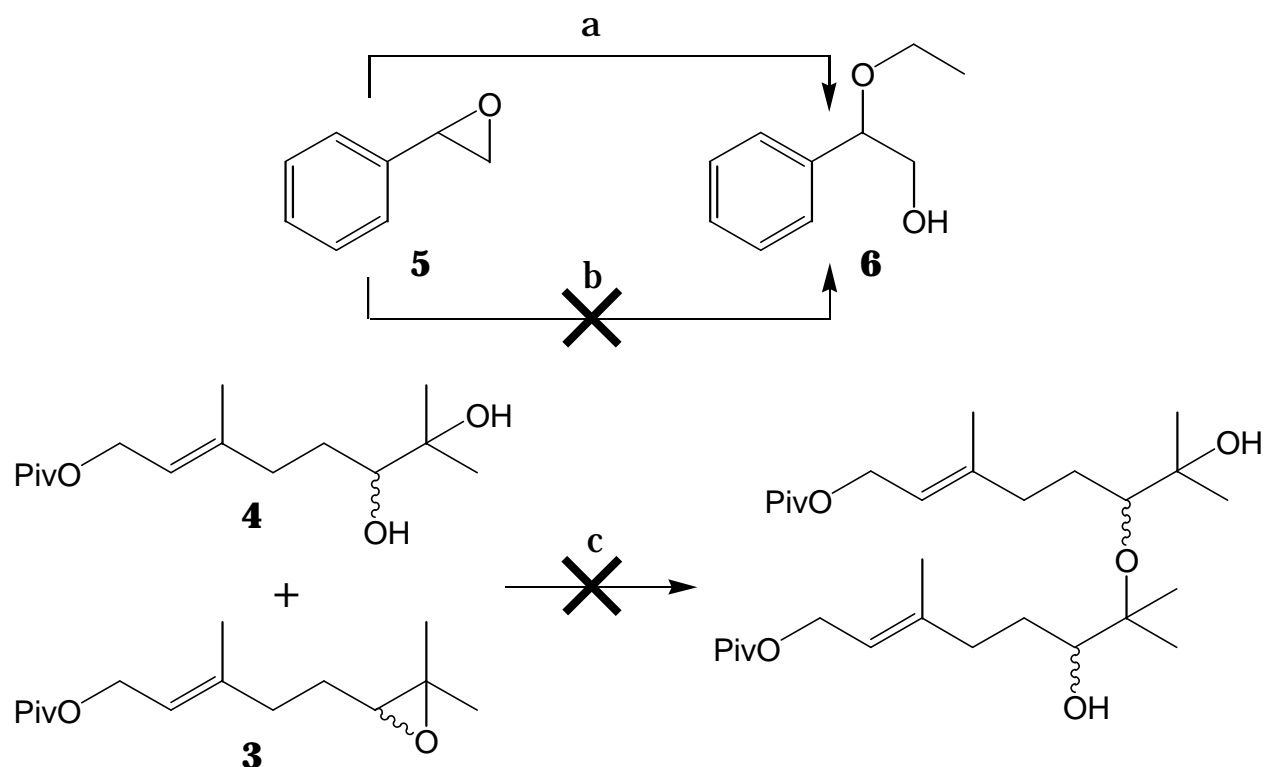
[a] Reagents and Conditions: (a) BiCl$_3$ (0.1 mol eq), isopropanol, rt, 2 h, 39%; (b) BiCl$_3$ (0.5 mol eq), isopropanol (8 mol eq), benzene, reflux, 4 h; (c) BiCl$_3$ (0.25 mol eq), hexafluoroisopropanol, rt, 48 h.

We next turned our attention towards the newly reported Cu^{II}(BF$_4$)$_2$ Lewis acid catalyst.[17] Based on a reported epoxide opening using only 4 mole equivalents of methanol to afford the opened epoxide product in 99% yield, it looked to be very promising for our purposes. The first trial of Cu^{II}(BF$_4$)$_2$ with our racemic system (**Scheme 3**) afforded the desired product, which was confirmed to be the sought-after dimer (**7**) by ^{1}H and ^{13}C NMR spectroscopy and electrospray mass spectrometry. Further work showed that the yield of

Scheme 3[a]
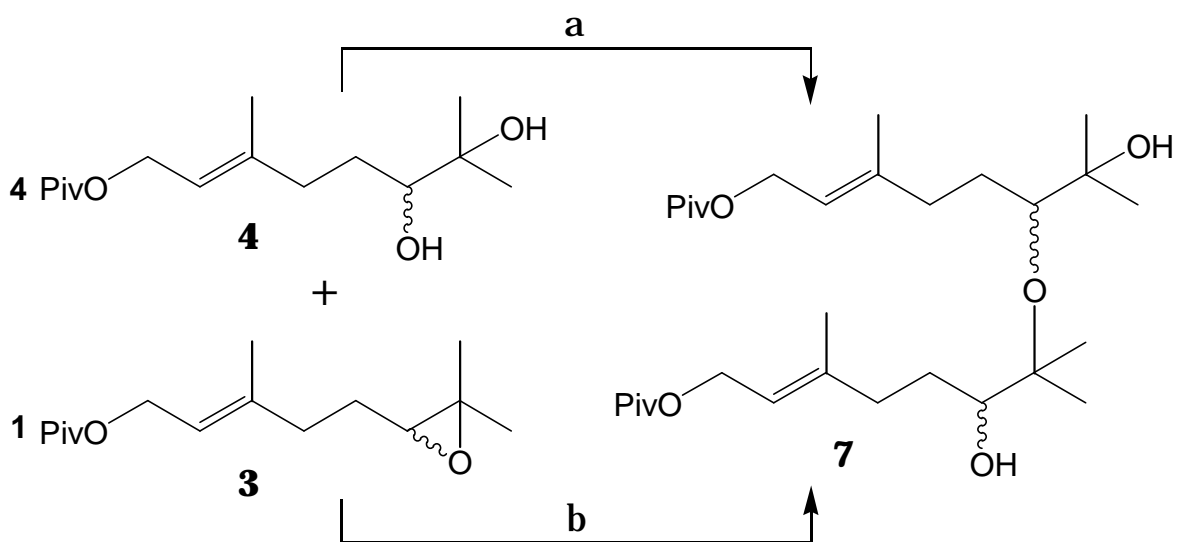
[a] Reagents and Conditions: (a) $Cu^{II}(BF_4)_2$ (0.1 mol eq), CH_2Cl_2, rt, 20 h, 9%; (b) $Cu^{II}(BF_4)_2$ (0.3 mol eq), CH_2Cl_2, reflux, 24 h, 28%.

product (**7**) could be increased by raising the temperature of the reaction and increasing the mole equivalent of $Cu^{II}(BF_4)_2$ catalyst used. Thus, we had identified $Cu^{II}(BF_4)_2$ to be a suitable Lewis acid catalyst for promoting the formation of the ether-linked dimer (**7**) from the epoxide (**3**) and the diol (**4**).

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Chapter 3

Stereocontrolled Synthesis

Having identified a reliable method for synthesizing the ether-linked dimer with the racemic model system, we concentrated our efforts on a stereocontrolled synthesis. The protected geranyl pivaloate (**2**) already on hand was oxidized to the corresponding (S)-diol (**8**) and (R)-diol (**9**) using the Sharpless method of asymmetric dihydroxylation (**Scheme 4**).[19]   It is noteworthy that both in these oxidations as well as in the oxidation of **2** to **3**, the reactions are cleanly regioselective towards the terminal alkene. The other alkene is thought to avoid oxidation due to the proximity of the electronegative ester, which reduces the nucleophilicity of that alkene.[20]

Scheme 4[a]

$[\alpha]_D^{rt} = -22.4$ (*c* 0.0125, MeOH) $[\alpha]_D^{rt} = +23.2$ (*c* 0.0125, MeOH)
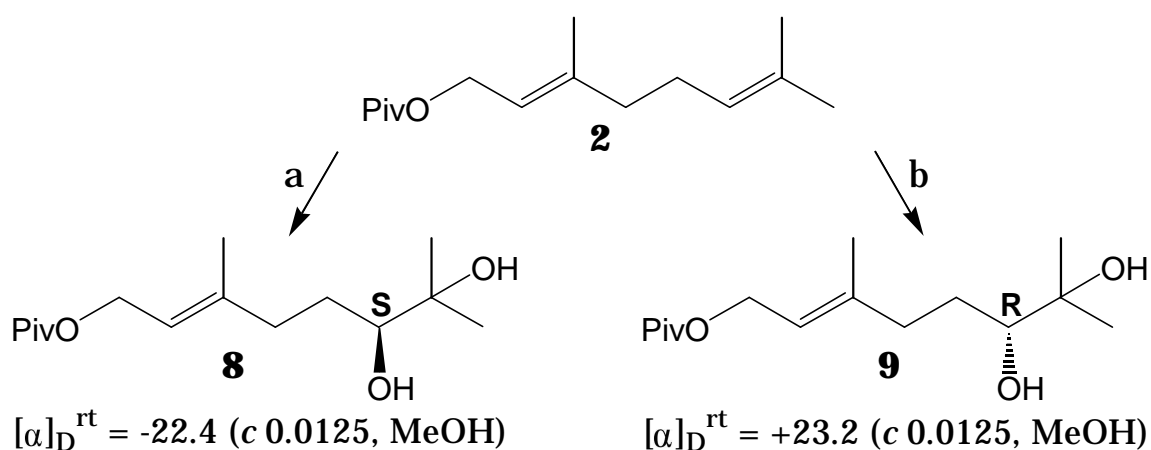
[a] Reagents and Conditions: (a) AD-mix-α, MeSO$_2$NH$_2$, 1:1 (v/v) H$_2$O:*t*-BuOH, 0 °C, overnight, 95%; (b) AD-mix-ß, MeSO$_2$NH$_2$, 1:1 (v/v) H$_2$O:*t*-BuOH, 0 °C, overnight, 62%.

The optical rotations of diols **8** and **9** were found to be opposite of each other and of approximately the same magnitude as the optical rotations of the corresponding diols of geranyl acetate,[13] suggesting the possibility of optical purity. However, optical rotation data can be unreliable, and we were interested in quantitatively determining the enantiomeric excesses of the desired diol isomers.

The first strategy for determining the enantiomeric excess was to transform the secondary alcohol of the diol into the corresponding Mosher ester and analyze the ratio of diastereomers thus formed with NMR spectroscopy.[21] However, this method proved to be unsuccessful. Due to the small reaction scales and losses during purification, ^{1}H NMR could not detect the minor stereoisomers. ^{19}F NMR seemed promising due to its greater sensitivity in this case, however the signal peaks were transient and thus could not be correlated to specific stereoisomers. Furthermore, ^{19}F NMR analysis of Mosher esters has been demonstrated to be unreliable.[16]

The next strategy was to allow the diols to complex to the chiral lanthanide NMR shift reagent Eu(hfc)$_3$ and then analyze these formed complexes by ^{1}H NMR.[22] Diols **8** and **9** were combined in an NMR tube in mole ratios of 1:2 and 1:1 with 0.8 mole equivalents of Eu(hfc)$_3$ and analyzed by ^{1}H NMR. Two sets of signals with integration ratios very similar to the known mole ratios of diols **8** and **9** were readily identified in each spectrum

recorded. Then, diols **8** and **9** were individually analyzed by ^{1}H NMR in the presence of 0.8 mole equivalents of Eu(hfc)$_3$ and the integrations of the major and minor stereoisomer signals were used to determine the enantiomeric excess. For both **8** and **9**, the enantiomeric excess of the major stereoisomer was found to be greater than 96%.

Having established the high enantiomeric purity of the first stereospecific synthetic intermediates **8** and **9**, we attempted to convert these diols to their corresponding epoxides. This seemingly facile transformation presented a synthetic challenge which we had not anticipated. All reactions we tried shared the common strategy of making the secondary alcohol a better leaving group and then promoting S$_N$2 attack with the tertiary alcohol, thus displacing the derivatized secondary alcohol and forming the epoxide ring. However, significant steric bulk around both alcohols prevented an efficient reaction.

Once the supply of racemic diol (**4**) was exhausted, stereopure diols **8** and **9** were alternated in these epoxidation trials (**Scheme 5**). Racemic diol (**4**) was converted into the secondary tosylate and treated with the mild base TEA. No epoxide product was observed from this reaction despite letting it run overnight. (S)-diol (**8**) was also converted to the corresponding tosylate; when treated with the strong base NaH, a small amount of epoxide (**10**) was observed to form. Furthermore, when (R)-diol (**9**) was converted to the

Scheme 5[a]
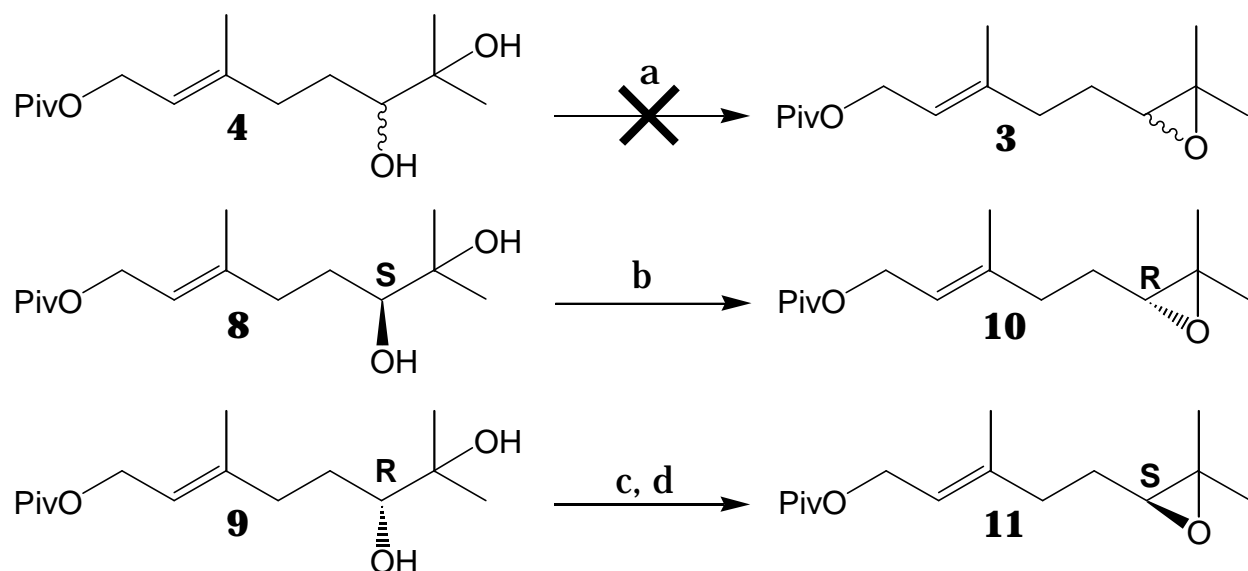
[a] Reagents and Conditions: (a) TsCl, TEA, CH₂Cl₂, rt, overnight; (b) TsCl, NaH, benzene, rt, overnight, 22%; (c) MsCl, py, THF, 0 °C, overnight; (d) NaH, rt, 5 h, 26%.

corresponding mesylate and NaH was introduced as a second step, the yield of epoxide (**11**) was observed to increase. Even so, the largest yield obtained was only 26%, which did not provide enough material to allow making the stereospecific ether-linked dimers. Time did not permit us to discover an efficient method of transforming the diol into the epoxide, though if greater amounts of starting material were used, this challenge could potentially be disregarded.

Chapter 4

Future Directions

We have determined a suitable method for achieving the key dimer intermediate **7** and progressed along the stereocontrolled synthetic route toward GF-I-1. Once optimal reaction conditions are worked out for the formation of epoxides **10** and **11**, they can be easily opened by diols **8** and **9** (**Scheme 6**, shown for the 6S,6'R diastereomer of GF-I-1), as has already been done with the racemic system. The coupling of the two stereopure diols with the two stereopure epoxides will lead to the formation of all four possible

Scheme 6
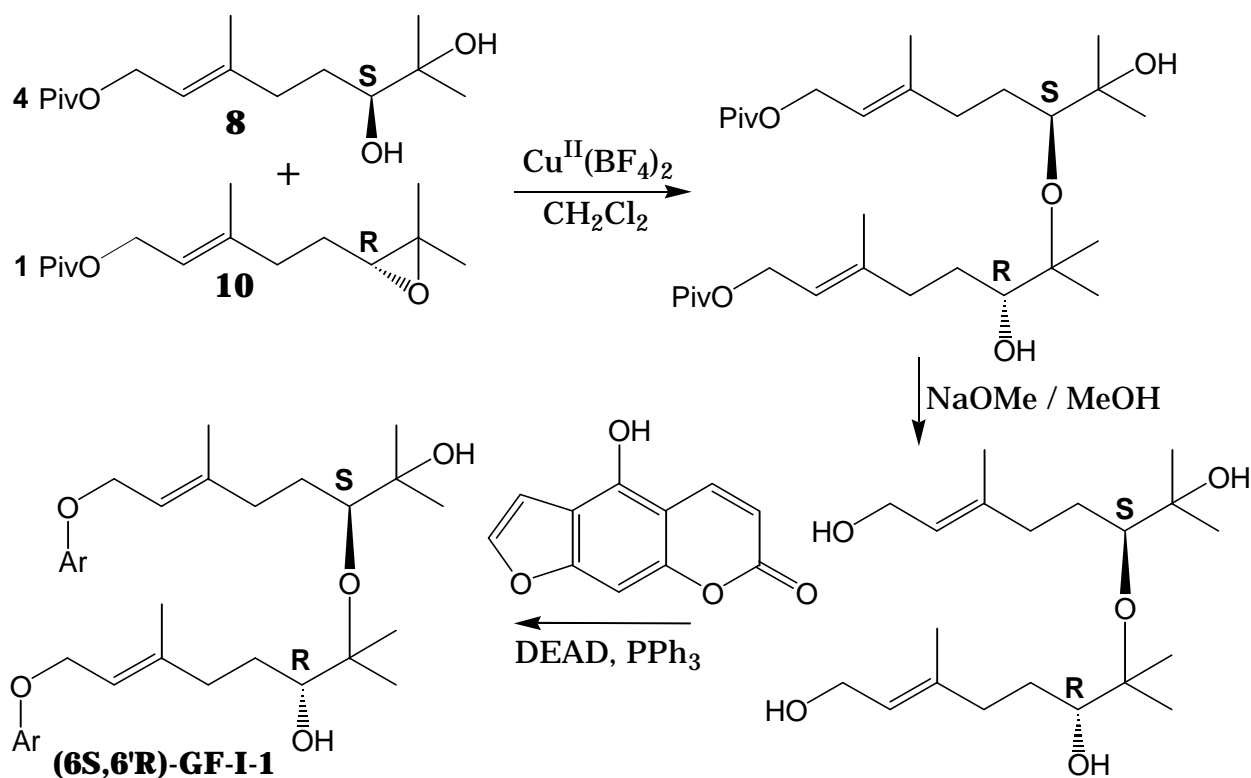
diastereomers of the ether-linked dimer. Each of these four diastereomeric dimers can then be deprotected with mild base to return the primary alcohols, followed by Mitsunobu coupling[23] to the psoralen heterocycle to form GF-I-1.

Comparisons of optical rotation data and ^{1}H NMR spectroscopic data of the four diastereomers with those of the natural GF-I-1 should result in the unequivocal assignment of the absolute stereochemistry of natural GF-I-1. The four diastereomers can then be bioassayed on their inhibition of CYP3A4 to determine the sensitivity of the enzyme to the different stereoisomers of GF-I-1.

Experimental Section

General Methods. All moisture and air sensitive reactions were performed in oven dried glassware equipped with rubber septa under a positive pressure of nitrogen or argon. When necessary, solvents were distilled prior to use. Reaction mixtures were magnetically stirred. Thin layer chromatography was performed on Merck precoated silica gel 5534-3 plates (0.2 mm). Concentration in vacuo was generally performed using a Büchi rotary evaporator and a high vacuum oil pump. Flash column chromatography was performed on Merck 70–230 mesh silica gel under a positive pressure of nitrogen. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Nuclear magnetic resonance spectra were recorded with Varian model Mercury 300 or UnityINOVA 400 instruments. ^{1}H NMR spectra were obtained with $CDCl_3$ as solvent using TMS as an internal standard (0 ppm). ^{13}C NMR spectra were recorded in ppm relative to the solvent signal: $CDCl_3$ (77 ppm). Electrospray mass spectra were recorded on a Micromass model LCT spectrometer and are reported in units of mass to charge (m/z).

Geranyl pivaloate (2). To a stirred solution of **1** (6.47 g, 42 mmol) and pyridine (6.4 mL, 84 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added pivaloyl chloride (7.8 mL, 63 mmol). The solution was stirred for 3 h at that

temperature. The reaction was quenched with sat. NH_4Cl (80 mL) and extracted with CH_2Cl_2 (40 mL). The organic layer was washed with sat. NH_4Cl (2 x 80 mL) and sat. $CuSO_4$ successively. The combined organic layers were dried with Na_2SO_3, filtered, and the solvent was removed in vacuo. Column chromatography (50:1 hexane:ethyl acetate) afforded **2** in 88% yield (8.77 g). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.32 (tq, J = 7.0, 1.5 Hz, 1H), 5.08 (tt, J = 6.9, 1.5 Hz, 1H), 4.57 (d, J = 7.0 Hz, 2H), 2.06 (m, 4H), 1.68 (d, J = 7.5 Hz, 6H), 1.60 (s, 3H), 1.20 (s, 9H).

Racemic 6,7-epoxygeranyl pivaloate (3). To a stirred solution of **2** (4.66 g, 19.6 mmol) in CH_2Cl_2 (117 mL) at 0 °C was added *m*CPBA (5.83 g). The solution was stirred for 2 h at that temperature. The reaction mixture was filtered, washed with 10% aq. Na_2SO_3 (100 mL) and 10% aq. Na_2CO_3 (100 mL), dried with $MgSO_4$, and filtered. The solvent was removed in vacuo and column chromatography (100:6 hexane:ethyl acetate) afforded **3** in 65% yield (3.24 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (tq, J = 7.0, 1.1 Hz, 1H), 4.58 (d, J = 6.9 Hz, 2H), 2.70 (t, J = 6.2 Hz, 1H), 2.19 (m, 2H), 1.73 (s, 3H), 1.66 (m, 2H), 1.31, (s, 3H), 1.27 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.50, 140.63, 119.36, 63.84, 61.17, 58.30, 38.70, 36.13, 27.17, 24.81, 22.61, 18.72, 16.43, 14.07.

Racemic 6,7-dihydroxygeranyl pivaloate (4). To a stirred solution of **3** (2.5 g, 9.84 mmol) in THF (180 mL) was added 5M H_2SO_4 dropwise (8.4 mL).

The solution was stirred for 45 m at room temperature. The reaction mixture was poured onto brine (200 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried with Na_2SO_4, filtered, and the solvent was removed in vacuo. Column chromatography (15:1 hexane: ethyl acetate) afforded **4** in 62% yield (1.57 g). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.38 (tq, J = 7.0, 1.1 Hz, 1H), 4.58 (d, J = 6.6 Hz, 2H), 3.33 (dd, J = 10.4, 1.8 Hz, 1H), 2.48 (br, 1H), 2.32 (m, 1H), 2.14 (m, 1H), 1.72 (s, 3H), 1.61 (m, 1H), 1.46 (m, 1H), 1.21 (s, 3H), 1.19 (s, 9H), 1.17 (s, 3H).

1-phenyl-1-isopropoxyethanol (6). To a stirred solution of **5** (360 mg, 3 mmol) in isopropanol (15 mL) at reflux was added BiCl$_3$ (95 mg, 0.1 mol eq). The solution was stirred for 2 h at reflux. The solvent was removed in vacuo and the crude reaction mixture was dissolved in diethyl ether (15 mL) and poured onto H_2O (15 mL). The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 x 15 mL). The combined organic layers were dried with MgSO$_4$, filtered, and the solvent was removed in vacuo. Column chromatography (1:1 hexane:ethyl acetate) afforded **6** in 39% yield (209 mg). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 (m, 5H), 4.53 (dd, J = 8.0, 4.7 Hz, 1H), 3.60 (m, 3H), 2.33 (br, 1H), 1.19 (d, J = 6.2 Hz, 3H), 1.13 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 128.41, 127.89, 126.79, 79.92, 69.54, 67.49, 23.45.

Racemic dimer (7). To a stirred solution of **3** (60 mg, 0.236 mmol) and **4** (244 mg, .897 mmol) in CH_2Cl_2 (1 mL) was added $Cu^{II}(BF_4)_2$ catalyst (15 mg, .30 mol eq). The solution was stirred for 24 h at reflux. The reaction mixture was quenched with H_2O (20 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (60 mL), dried with Na_2SO_4, filtered, and the solvent was removed in vacuo. Column chromatography (15:1 hexane:ethyl acetate) afforded **7** in 28% yield (40 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (td, J = 6.9, 1.2 Hz, 2H), 4.58 (d, J = 6.9 Hz, 4H), 3.53 (tq, J = 11.2, 2.2 Hz, 2H), 2.34 (m, 2H), 2.14 (m, 2H), 2.07 (m, 2H), 1.72 (s, 6H), 1.66 (s, 6H), 1.56 (m, 2H), 1.45 (m, 2H), 1.37 (s, 6H), 1.31 (s, 6H), 1.19 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.59, 141.17, 119.33, 98.74, 97.10, 76.26, 76.04, 61.21, 38.72, 36.07, 29.14, 29.09, 27.18, 23.65, 23.40, 21.37, 21.14, 16.45; ES MS found: m/z 531.4, calcd for $[C_{30}H_{54}O_7 + Na^+ - H_2O]$: m/z 531.

(S)-6,7-dihydroxygeranyl pivaloate (8). To a stirred solution of H_2O (80 mL) and t-BuOH (80 mL) at 0 °C were added the AD-mix-α very slowly (20.6 g), $MeSO_2NH_2$ (1.40 g), and **2** (3.97 mL, 14.7 mmol), successively. The solution was stirred overnight at that temperature. The reaction mixture was quenched with Na_2SO_3 (22.0 g). The organic layers were extracted with ethyl acetate (3 x 80 mL), washed with 2M KOH (2 x 200 mL), dried with $MgSO_4$, and filtered. The solvent was removed in vacuo and column

chromatography (20:1 CH$_2$Cl$_2$:MeOH) afforded **8** in 95% yield (3.81 g). [α]$_D^{rt}$ -22.4 (*c* 0.0125 in MeOH); ^{1}H NMR (400 MHz, CDCl3) δ 5.39 (tq, *J* = 6.7, 1.1 Hz, 1H), 4.58 (dd, *J* = 7.0, 0.7 Hz, 2H), 3.35 (dd, *J* = 10.5, 1.8 Hz, 1H), 2.31 (m, 2H), 2.13 (m, 2H), 1.72 (s, 3H), 1.66 (m, 3H), 1.46 (m, 1H), 1.21 (s, 3H), 1.20 (s, 9H), 1.17 (s, 3H).

(R)-6,7-dihydroxygeranyl pivaloate (9). To a stirred solution of H$_2$O (80 mL) and *t*-BuOH (80 mL) at 0 °C were added the AD-mix-ß very slowly (20.6 g), MeSO$_2$NH$_2$ (1.40 g), and **2** (2.50 mL, 9.26 mmol), successively. The solution was stirred overnight at that temperature. The reaction mixture was quenched with Na$_2$SO$_3$ (22.0 g). The organic layers were extracted with ethyl acetate (3 x 80 mL), washed with 2M KOH (2 x 200 mL), dried with MgSO$_4$, and filtered. The solvent was removed in vacuo and column chromatography (20:1 CH$_2$Cl$_2$:MeOH) afforded **9** in 62% yield (1.56 g). [α]$_D^{rt}$ +23.2 (*c* 0.0125 in MeOH); ^{1}H NMR (400 MHz, CDCl3) δ 5.37 (tq, *J* = 6.8, 1.1 Hz, 1H), 4.58 (d, *J* = 6.9 Hz, 2H), 3.34 (d, *J* = 10.4 Hz, 1H), 2.46 (br, 1H), 2.32 (m, 1H), 2.21 (br, 1H), 2.12 (m, 1H), 1.72 (s, 3H), 1.61 (m, 1H), 1.46 (m, 1H), 1.21 (s, 3H), 1.19 (s, 9H), 1.17 (s, 3H).

(R)-6,7-epoxygeranyl pivaloate (10). To a stirred solution of **8** (200 mg, 0.736 mmol) and tosyl chloride (74 mg, 0.772 mmol) in benzene (16 mL) was added NaH slowly (58 mg). The solution was stirred overnight at room temperature. The reaction mixture was quenched with H$_2$O (32 mL) and

extracted with ethyl acetate (16 mL). The organic layer was washed with H_2O (2 x 32 mL), dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. Column chromatography (10:1 hexane:ethyl acetate) afforded **10** in 22% yield (42 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (tq, J = 7.0, 1.5 Hz, 1H), 4.58 (d, J = 6.9 Hz, 2H), 2.71 (t, J = 6.2 Hz, 1H), 2.17 (m, 2H), 1.73 (s, 3H), 1.68 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) d 178.49, 140.61, 119.44, 119.18, 63.99, 63.68, 61.41, 61.14, 60.86, 60.31, 58.31, 38.66, 36.09, 27.25, 27.01, 24.90, 24.67, 20.99, 20.95, 18.80, 18.56, 16.49, 16.32, 14.24, 14.01.

(S)-6,7-epoxygeranyl pivaloate (11). To a stirred solution of **9** (200 mg, 0.736 mmol) and pyridine (1 mL) in THF (5 mL) at 0 °C was added the mesyl chloride dropwise (91 μL). The solution was stirred overnight at that temperature. NaH (210 mg) and additional THF (5 mL) were added to the reaction mixture, and it was allowed to stir for an additional 5 h. The reaction was quenched with H_2O (15 mL). The organic layer was extracted with ethyl acetate (15 mL) and washed with sat. $CuSO_4$ (2 x 20 mL) and brine (20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and the solvent was removed in vacuo. Column chromatography (10:1 hexane: ethyl acetate) afforded **11** in 26% yield (49 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (tq, J = 6.9, 1.5 Hz, 1H), 4.58 (d, J = 6.8 Hz, 2H), 2.71 (t, J = 6.2 Hz, 1H), 2.17 (m, 2H), 1.73 (s, 3H), 1.70 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H), 1.19 (s, 9H).

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Geranyl pivaloate - 2

Pulse Sequence: s2pul

Solvent: CDC13
Ambient temperature
File: SG29-Ester
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 40.0 degrees
Acq. time 2.666 sec
Width 6000.6 Hz
112 repetitions
OBSERVE   H1, 399.9649446 MHz
DATA PROCESSING
FT size 32768
Total time 5 min, 42 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	2129.493	5.324	31.3
2	2128.394	5.321	32.8
3	2033.897	5.085	20.7
4	2032.432	5.082	26.8
5	2030.967	5.078	21.0
6	1832.082	4.581	97.8
7	1825.123	4.563	93.5
8	844.618	2.112	24.1
9	837.293	2.093	42.7
10	830.700	2.077	30.9
11	823.375	2.059	65.3
12	816.416	2.041	38.7
13	679.064	1.698	244.8
14	672.472	1.681	205.3
15	671.373	1.679	205.9
16	640.972	1.603	219.6
17	506.551	1.266	58.6
18	479.447	1.199	217.5
19	478.349	1.196	2000.0
20	-0.000	-0.000	27.7

INDEX	FREQUENCY	PPM	HEIGHT
1	2148.539	5.372	35.8
2	2147.441	5.369	36.3
3	1835.012	4.588	102.4
4	1828.053	4.571	98.4
5	1087.822	2.720	35.6
6	1081.595	2.704	70.4
7	1075.368	2.689	37.7
8	875.751	2.190	30.1
9	867.327	2.169	30.9
10	690.785	1.727	270.1
11	677.966	1.695	30.5
12	671.373	1.679	46.5
13	669.541	1.674	33.5
14	668.076	1.670	32.6
15	666.978	1.668	33.9
16	665.146	1.663	39.4
17	662.949	1.658	46.2
18	660.751	1.652	33.1
19	659.286	1.648	29.5
20	522.301	1.306	513.6
21	506.551	1.266	538.6
22	477.250	1.193	2000.0
23	353.450	0.884	43.1
24	0.000	0.000	61.1

ppm

3.05 2.19

2.06

0.95

2.09

1.00

Racemic 6,7-epoxygeranyl pivaloate - 3

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: SGZ16-13C
INOVA-500 "Ni"

PULSE SEQUENCE
Relax. delay 0.900 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
504 repetitions
OBSERVE C13, 100.5712662 MHz
DECOUPLE H1, 399.9969644 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 35 min, 58 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	17951.666	178.497	6.7
2	14142.956	140.626	19.6
3	12004.371	119.362	35.9
4	7776.032	77.319	36.1
5	7743.987	77.000	37.3
6	7711.943	76.681	34.9
7	6420.247	63.838	37.5
8	6151.684	61.167	39.2
9	5863.284	58.300	10.5
10	3891.789	38.697	15.7
11	3633.144	36.125	47.3
12	3172.315	31.543	5.9
13	2732.848	27.173	125.0
14	2723.693	27.082	56.3
15	2495.567	24.814	42.8
16	2273.545	22.606	4.4
17	1882.145	18.715	33.1
18	1652.493	16.431	27.5
19	1415.212	14.072	4.7

Racemic 6,7-dihydroxygeranyl pivaloate - 4

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
INOVA-400 "Zr"

PULSE SEQUENCE
Pulse 40.0 degrees
Acq. time 2.666 sec
Width 6000.6 Hz
120 repetitions
OBSERVE H1, 399.9649402 MHz
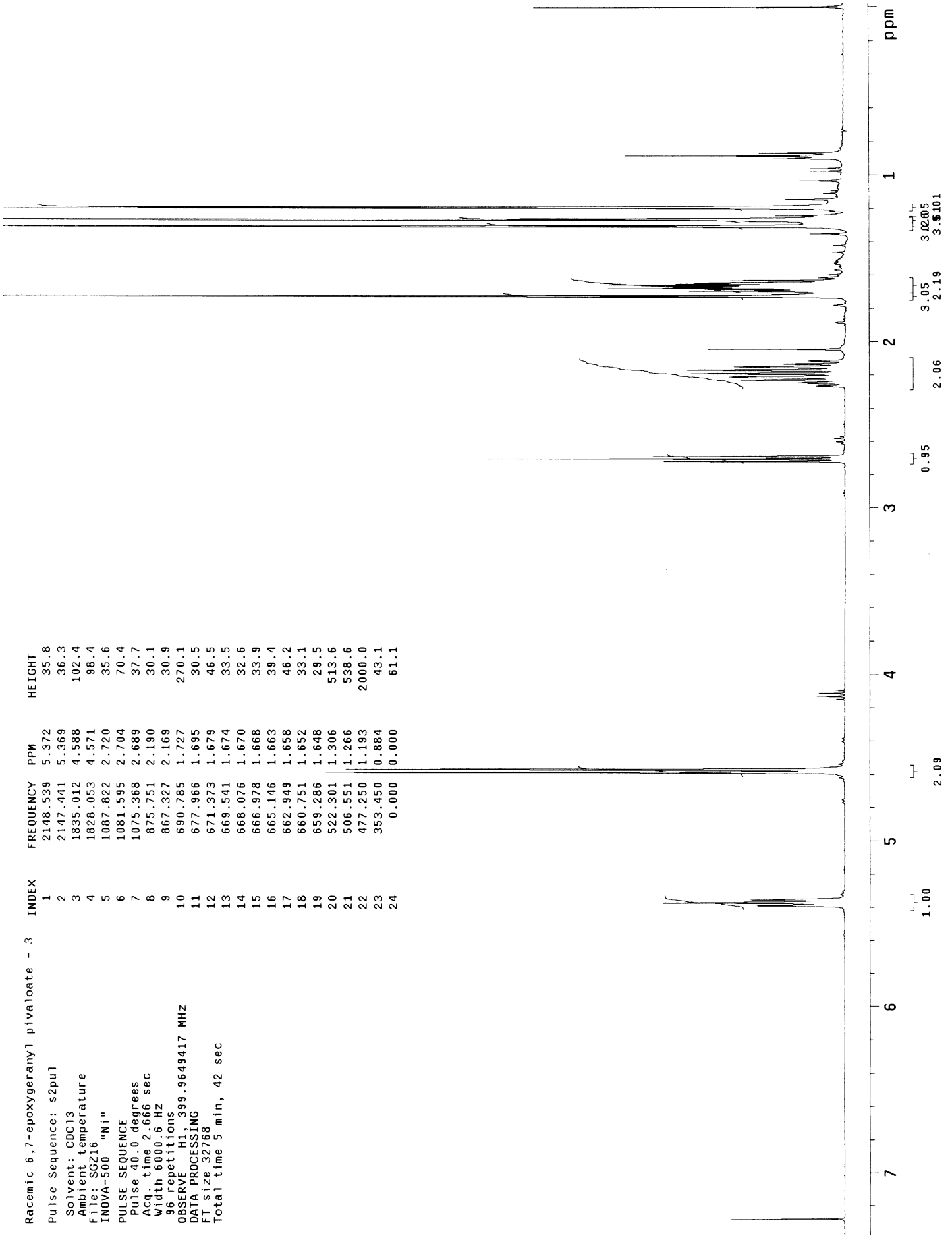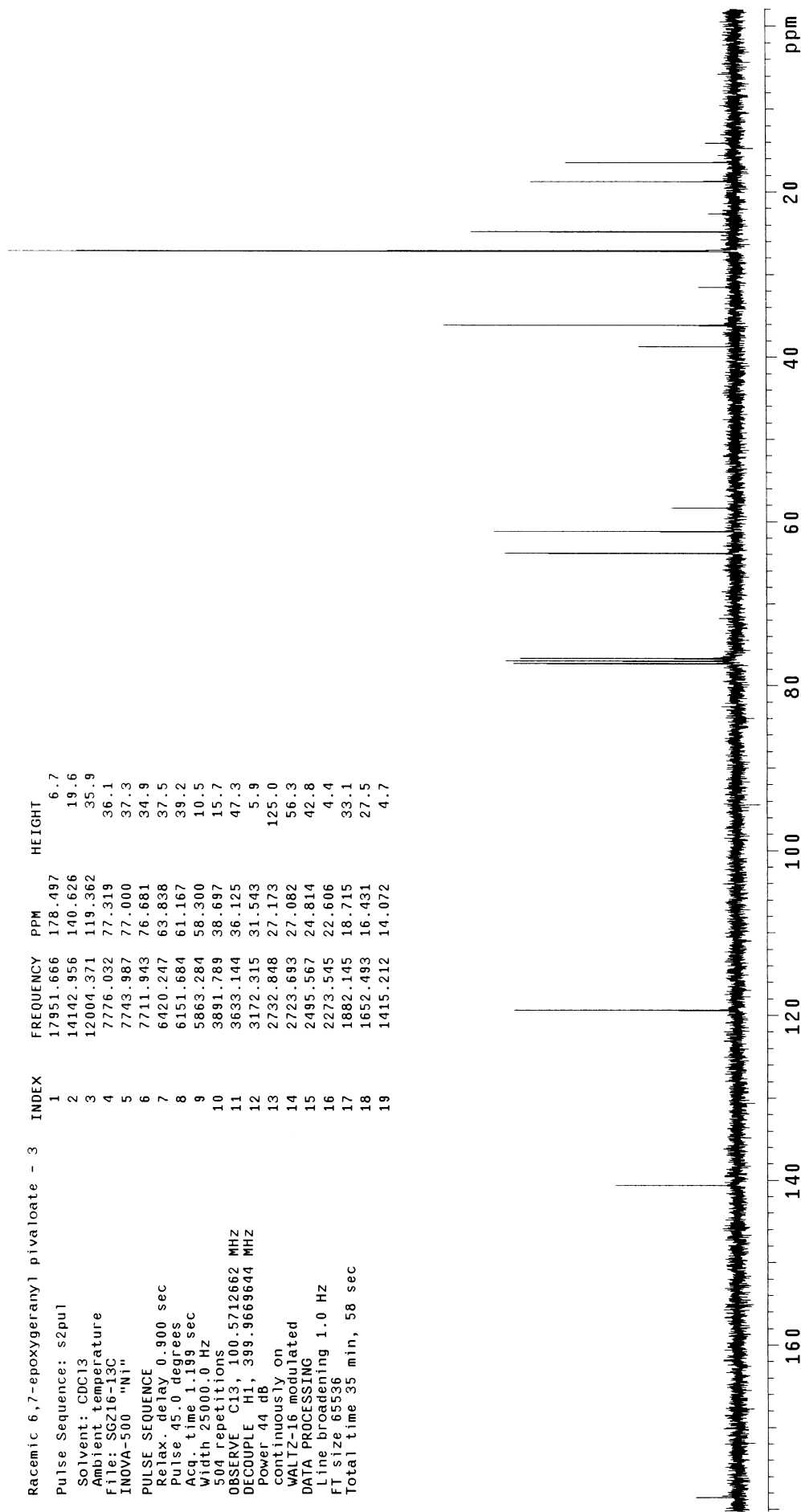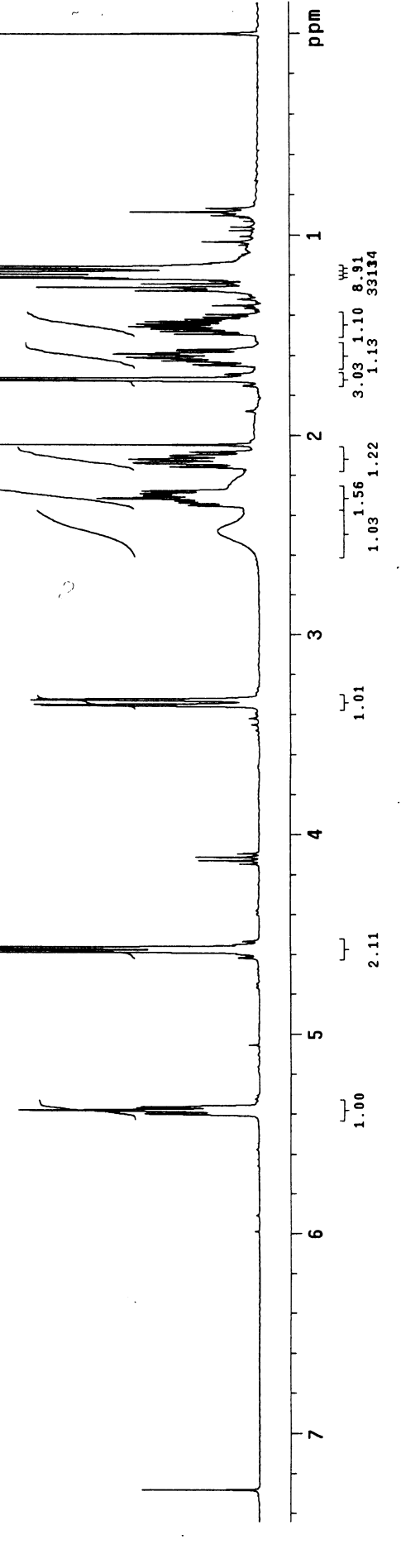DATA PROCESSING
FT size 32768
Total time 5 min, 42 sec

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2	2159.894	5.400	17.8
3	2158.795	5.397	18.5
4	2154.400	5.386	24.3
5	2153.301	5.384	36.9
6	2151.836	5.380	38.7
7	2150.737	5.377	23.0
8	2147.441	5.369	13.7
9	2146.342	5.366	19.8
10	2144.877	5.363	19.2
11	2143.778	5.360	11.6
12	1833.547	4.584	86.5
13	1832.815	4.582	85.5
14	1826.588	4.567	84.6
15	1820.361	4.551	4.4
16	1652.244	4.131	9.9
17	1644.918	4.113	10.4
18	1341.647	3.354	34.9
19	1339.815	3.350	36.1
20	1331.025	3.328	36.6
21	1329.560	3.324	35.7
22	992.591	2.482	6.8
23	940.215	2.351	11.5
24	935.087	2.338	13.1
25	931.058	2.328	13.7
26	925.930	2.315	26.1
27	920.803	2.302	18.7
28	917.140	2.293	19.2
29	911.646	2.279	18.9
30	863.298	2.158	14.5
31	854.874	2.137	20.3
32	847.915	2.120	21.0
33	840.589	2.102	14.5
34	833.264	2.083	11.3
35	821.177	2.053	4.9
36	818.980	2.048	52.1
37	688.587	1.722	277.5
38	677.599	1.694	5.6
39	659.652	1.649	9.6
40	657.821	1.645	10.7
41	653.059	1.633	11.6
42	650.862	1.627	15.7
43	648.298	1.621	12.9
44	646.100	1.615	17.9
45	643.903	1.610	21.2
46	641.705	1.604	13.3
47	639.141	1.598	17.8
48	637.310	1.593	23.4
49	634.746	1.587	16.6
50	629.984	1.575	13.3
51	627.787	1.570	13.1
52	597.386	1.494	13.6
53	591.892	1.480	15.8
54	588.229	1.471	17.4
55	586.764	1.467	17.2
56	582.735	1.457	20.9
57	581.637	1.454	18.5
58	577.974	1.445	19.6
59	574.311	1.436	14.9
60	572.480	1.431	18.3
61	568.817	1.422	10.7
62	567.718	1.419	12.0
63	563.689	1.409	9.0
64	558.562	1.397	8.7
65	540.248	1.351	7.6
66	511.313	1.278	19.9
67	510.214	1.276	19.2
68	508.383	1.271	8.6
69	505.819	1.265	12.2
70	503.987	1.260	35.6
71	499.592	1.249	4.4
72	497.028	1.243	18.9
73	496.296	1.241	14.8
74	491.900	1.230	5.7
75	490.802	1.227	8.0
76	487.139	1.218	27.8
77	483.476	1.209	438.7
78	479.447	1.199	192.3
79	477.250	1.193	2000.0
80	469.895	1.165	443.1
81	455.006	1.140	8.1
82	413.152	1.033	9.3
83	389.711	0.974	4.9
84	383.118	0.958	4.6
85	361.043	0.900	7.7
86	354.084	0.883	20.7
87	345.125	0.865	8.6
88	0.000	0.000	62.8

1.00   2.11   1.01   1.03   1.56   1.22   3.03   1.10   1.13   8.91   33134

ppm

1-phenyl-1-isopropoxyethanol - 6

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: SGZ20-6
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 44.0 degrees
Acq. time 2.666 sec
Width 6000.6 Hz
128 repetitions
OBSERVE H1, 399.9649490 MHz
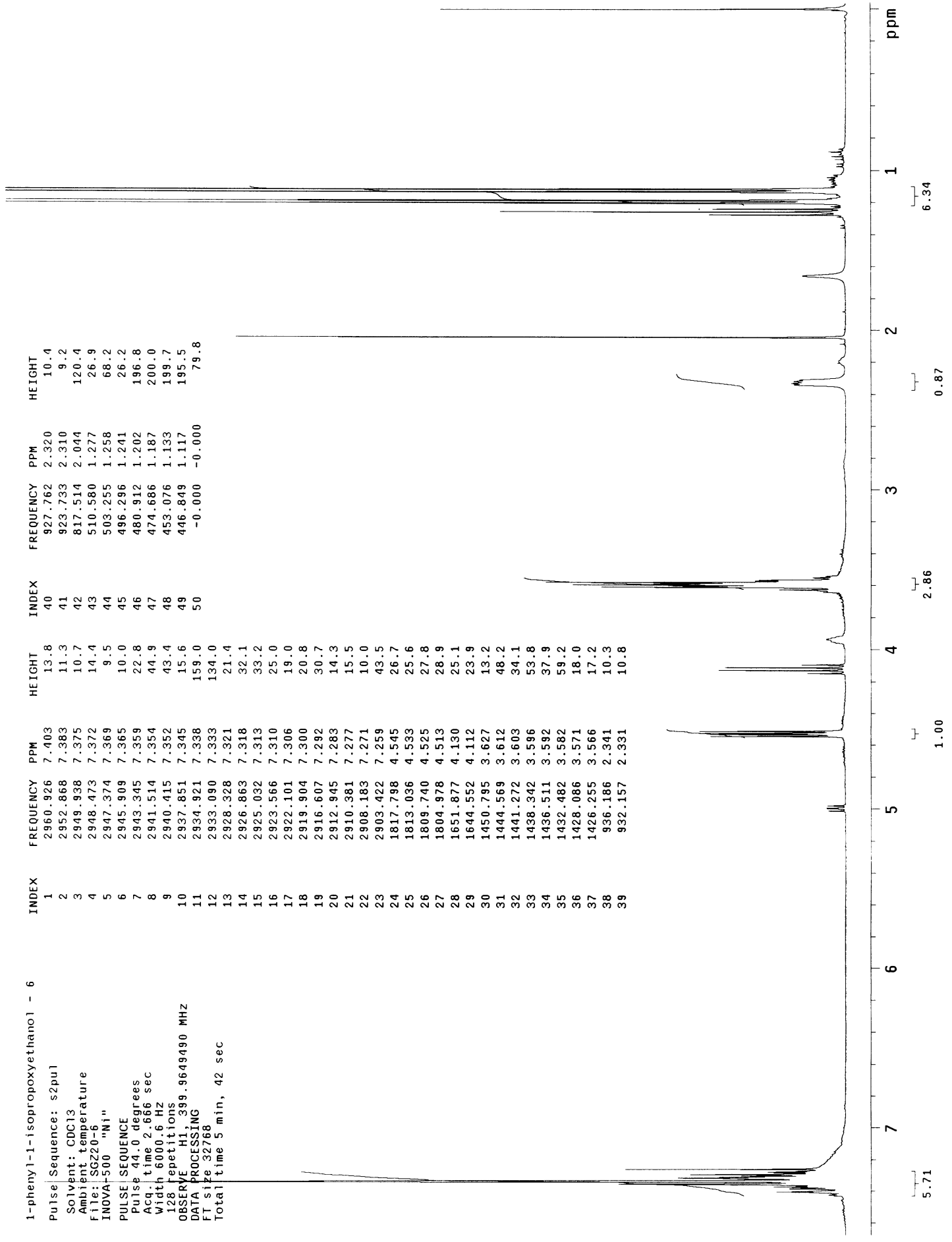DATA PROCESSING
FT size 32768
Total time 5 min, 42 sec

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1	2960.926	7.403	13.8
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3	2949.938	7.375	10.7
4	2948.473	7.372	14.4
5	2947.374	7.369	9.5
6	2945.909	7.365	10.0
7	2943.345	7.359	22.8
8	2941.514	7.354	44.9
9	2940.415	7.352	43.4
10	2937.851	7.345	15.6
11	2934.921	7.338	159.0
12	2933.090	7.333	134.0
13	2928.328	7.321	21.4
14	2926.863	7.318	32.1
15	2925.032	7.313	33.2
16	2923.566	7.310	25.0
17	2922.101	7.306	19.0
18	2919.904	7.300	20.8
19	2916.607	7.292	30.7
20	2912.945	7.283	14.3
21	2910.381	7.277	15.5
22	2908.183	7.271	10.0
23	2903.422	7.259	43.5
24	1817.798	4.545	26.7
25	1813.036	4.533	25.6
26	1809.740	4.525	27.8
27	1804.978	4.513	28.9
28	1651.877	4.130	25.1
29	1644.552	4.112	23.9
30	1450.795	3.627	13.2
31	1444.569	3.612	48.2
32	1441.272	3.603	34.1
33	1438.342	3.596	53.8
34	1436.511	3.592	37.9
35	1432.482	3.582	59.2
36	1428.086	3.571	18.0
37	1426.255	3.566	17.2
38	936.186	2.341	10.3
39	932.157	2.331	10.8

INDEX	FREQUENCY	PPM	HEIGHT
40	927.762	2.320	10.4
41	923.733	2.310	9.2
42	817.514	2.044	120.4
43	510.580	1.277	26.9
44	503.255	1.258	68.2
45	496.296	1.241	26.2
46	480.912	1.202	196.8
47	474.686	1.187	200.0
48	453.076	1.133	199.7
49	446.849	1.117	195.5
50	-0.000	-0.000	79.8

ppm

5.71   1.00   2.86   0.87   6.34

1-phenyl-1-isopropoxyethanol - 6

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: SG220-6C
INOVA-500 "Ni"

PULSE SEQUENCE
Relax. delay 0.900 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
152 repetitions
OBSERVE C13, 100.5712670 MHz
DECOUPLE H1, 399.9669644 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 22 min, 14 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	12914.586	128.412	37.7
2	12861.942	127.889	20.4
3	12751.312	126.789	38.4
4	8037.728	79.921	9.8
5	7776.032	77.319	47.6
6	7743.988	77.000	50.0
7	7711.943	76.681	49.9
8	6993.232	69.535	13.0
9	6787.995	67.494	17.8
10	2358.234	23.448	14.0
11	2145.367	21.332	12.1
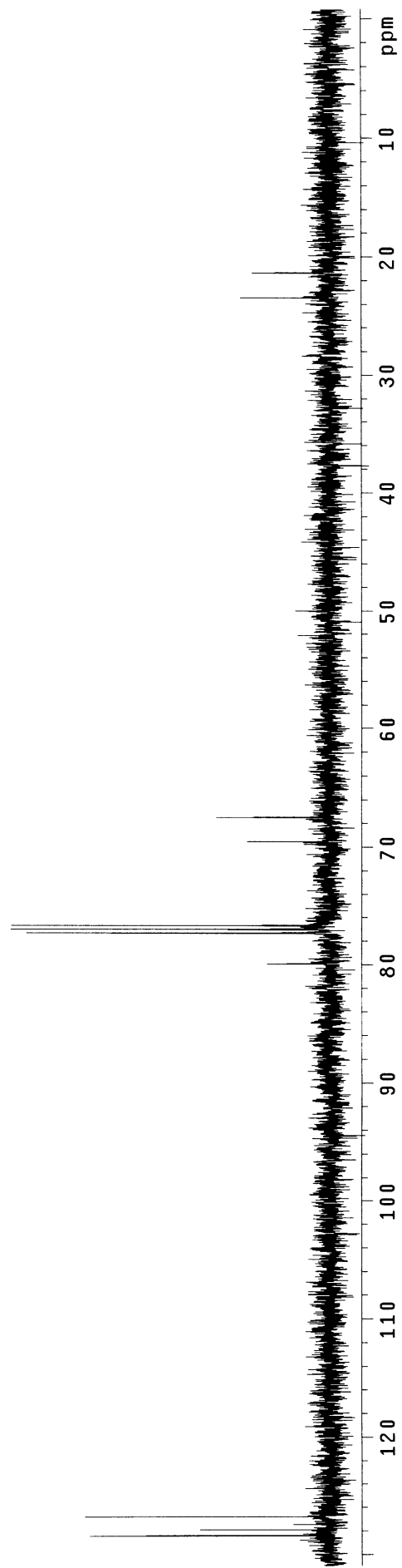
INDEX	FREQUENCY	PPM	HEIGHT
1	2907.817	7.270	32.0
2	2158.429	5.397	19.8
3	2151.469	5.379	40.3
4	2150.371	5.376	38.3
5	2144.877	5.363	21.3
6	2143.412	5.359	19.6
7	1834.646	4.587	133.1
8	1827.687	4.570	126.4
9	1417.465	3.544	19.7
10	1415.633	3.539	22.5
11	1413.436	3.534	22.9
12	1411.604	3.529	20.8
13	933.988	2.335	24.8
14	858.903	2.147	21.9
15	851.944	2.130	22.9
16	831.433	2.079	28.5
17	830.334	2.076	30.9
18	827.404	2.069	51.8
19	824.840	2.062	30.9
20	818.613	2.047	50.2
21	687.855	1.720	333.6
22	664.414	1.661	104.3
23	623.758	1.560	23.5
24	586.032	1.465	23.4
25	581.637	1.454	24.2
26	576.509	1.441	19.8
27	571.381	1.429	22.3
28	546.108	1.365	537.3
29	523.766	1.310	529.9
30	503.987	1.260	44.3
31	502.522	1.256	23.7
32	477.616	1.194	2500.0
33	-0.000	-0.000	106.0
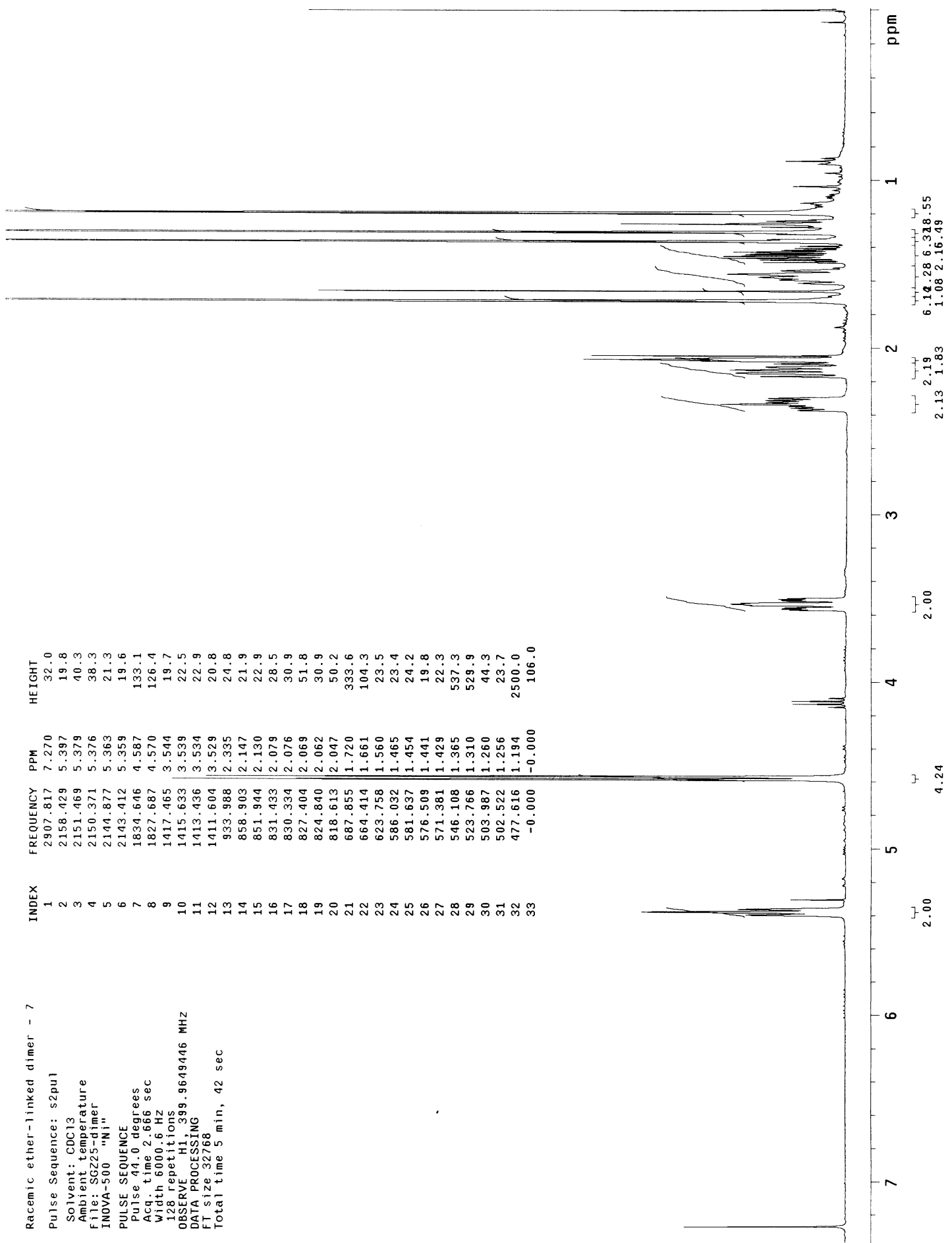
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1.08 2.16.49
2.19
2.13 1.83
2.00
4.24
2.00

ppm
7 6 5 4 3 2 1

Racemic ether-linked dimer - 7

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: SGZ25-dimer
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 44.0 degrees
Acq. time 2.666 sec
Width 6000.6 Hz
128 repetitions
OBSERVE H1, 399.9649446 MHz
DATA PROCESSING
FT size 32768
Total time 5 min, 42 sec

INDEX	FREQUENCY	PPM	HEIGHT
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2	1426.255	3.566	90.2
3	1424.424	3.561	88.7
4	1422.226	3.556	85.6
5	1417.465	3.544	137.7
6	1415.633	3.539	157.2
7	1413.436	3.534	160.0
8	1411.604	3.529	145.6
9	1406.476	3.516	87.9
10	1404.645	3.512	90.0
11	1402.448	3.506	94.5
12	1400.250	3.501	81.6

2.00
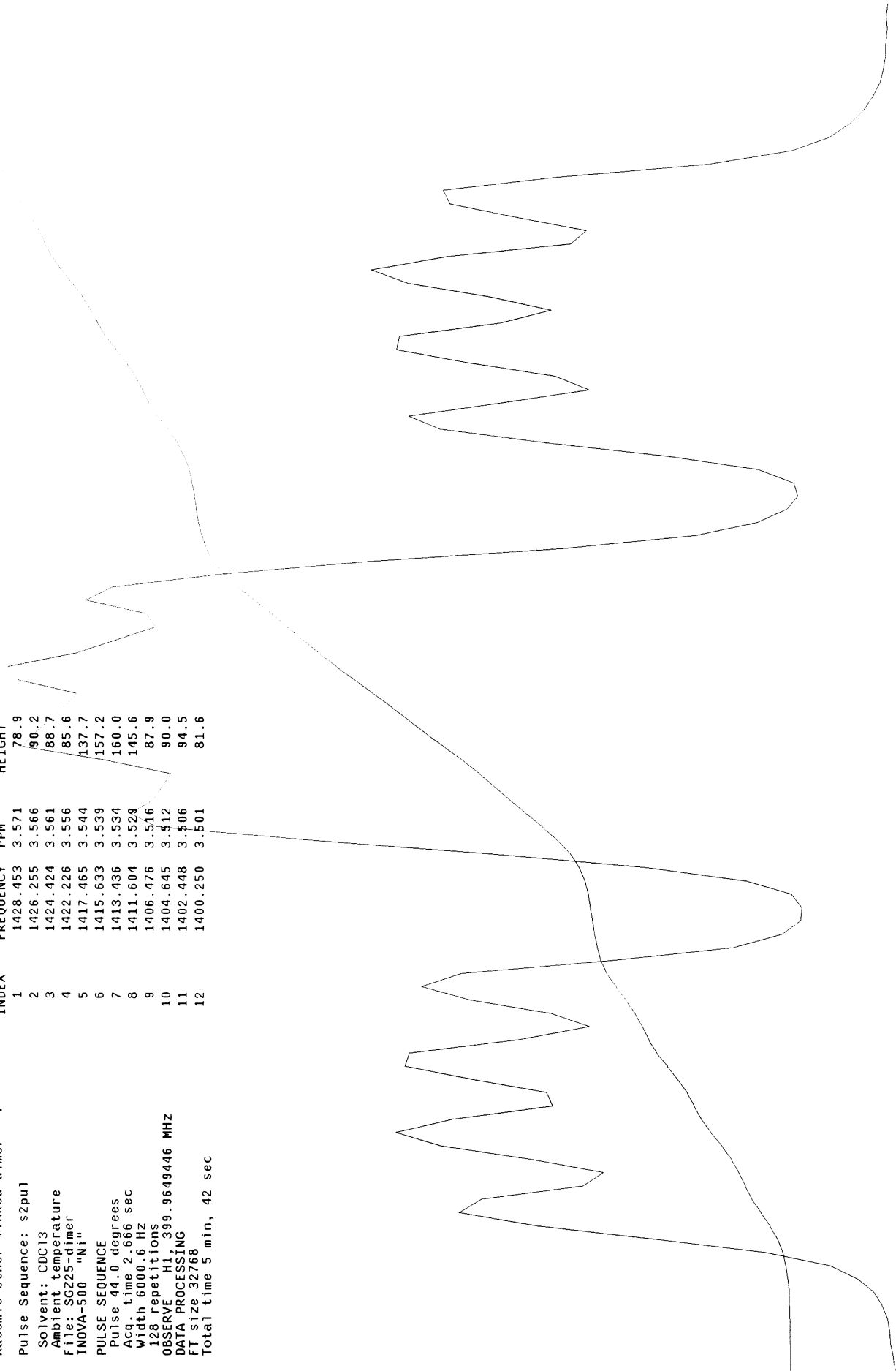
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INDEX	FREQUENCY	PPM	HEIGHT
1	933.988	2.335	24.8
2	858.903	2.147	21.9
3	851.944	2.130	22.9
4	831.433	2.079	28.5
5	830.334	2.076	30.9
6	827.404	2.069	51.8
7	824.840	2.062	30.9
8	818.613	2.047	50.2
9	687.855	1.720	333.6
10	664.414	1.661	104.3
11	623.758	1.560	23.5
12	586.032	1.465	23.4
13	581.637	1.454	24.2
14	571.381	1.429	22.3
15	546.108	1.365	537.3
16	523.766	1.310	529.9
17	503.987	1.260	44.3
18	502.522	1.256	23.7
19	477.616	1.194	2500.0
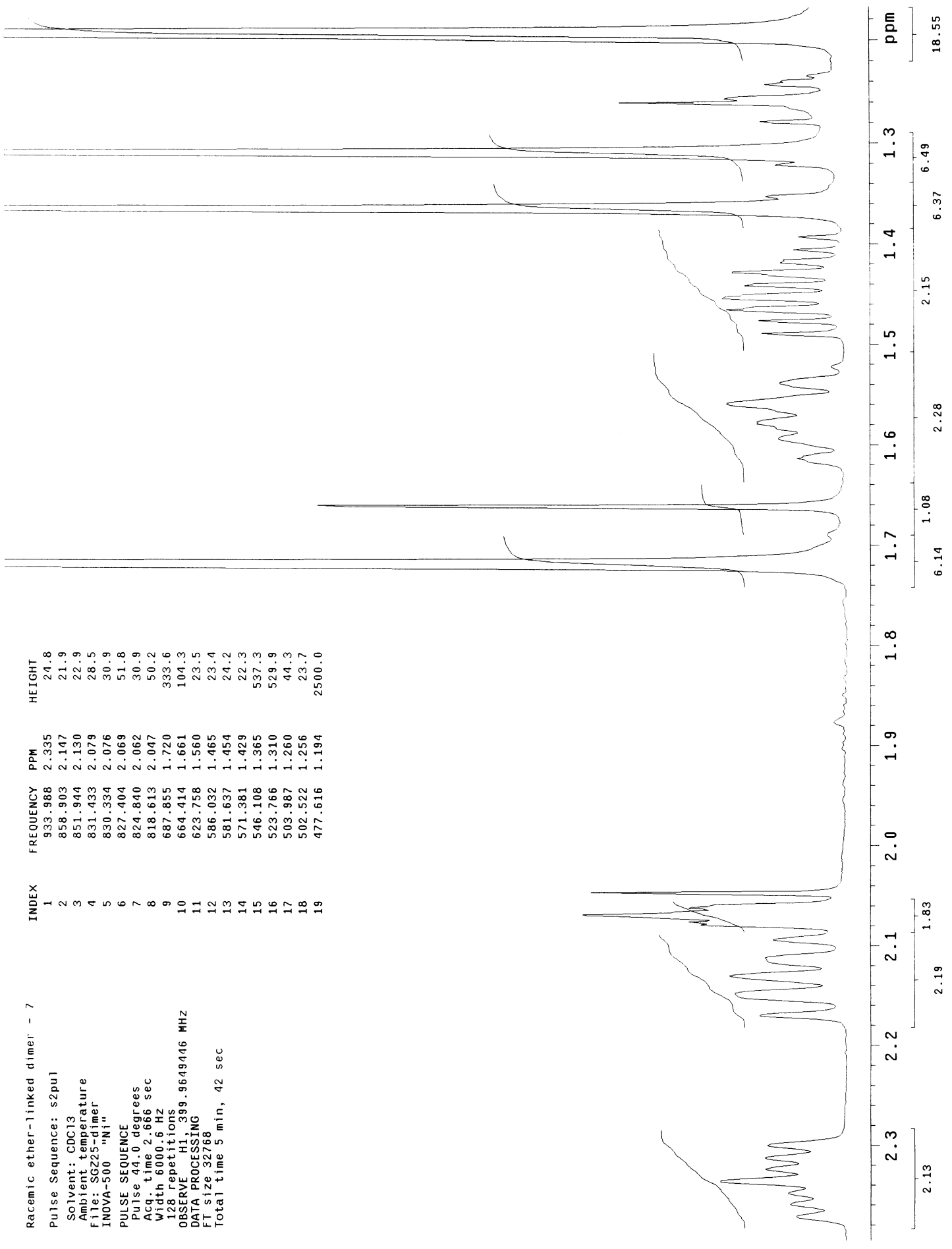
ppm

18.55

1.3   6.49

6.37

1.4   2.15

1.5

1.6   2.28

1.08

1.7   6.14

1.8

1.9

2.0   1.83

2.1   2.19

2.2

2.3   2.13

Racemic ether-linked dimer - 7

Pulse Sequence: s2pul

Solvent: CDC13
Ambient temperature
INOVA-400 "Zr"

PULSE SEQUENCE
Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
99999 repetitions
OBSERVE C13, 100.5712662 MHz
DECOUPLE H1, 399.9669644 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 75 hr, 13 min, 38 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	17960.822	178.588	9.4
2	14197.126	141.165	27.0
3	12001.320	119.331	29.3
4	9930.639	98.742	11.7
5	9765.839	97.104	8.1
6	7776.032	77.319	130.2
7	7743.987	77.000	132.6
8	7711.943	76.681	125.5
9	7669.980	76.264	26.8
10	7647.091	76.037	25.7
11	6155.499	61.205	45.7
12	3894.078	38.720	20.8
13	3627.804	36.072	62.2
14	2930.456	29.138	29.3
15	2925.115	29.085	25.6
16	2733.611	27.181	141.2
17	2378.071	23.646	22.3
18	2353.656	23.403	20.7
19	2149.182	21.370	19.0
20	2125.530	21.135	19.5
21	1654.019	16.446	32.9

semyon-3 65 (1.138) Cm (59:80)

26-Aug-200213:12:55

TOF MS ES+
6.67e3
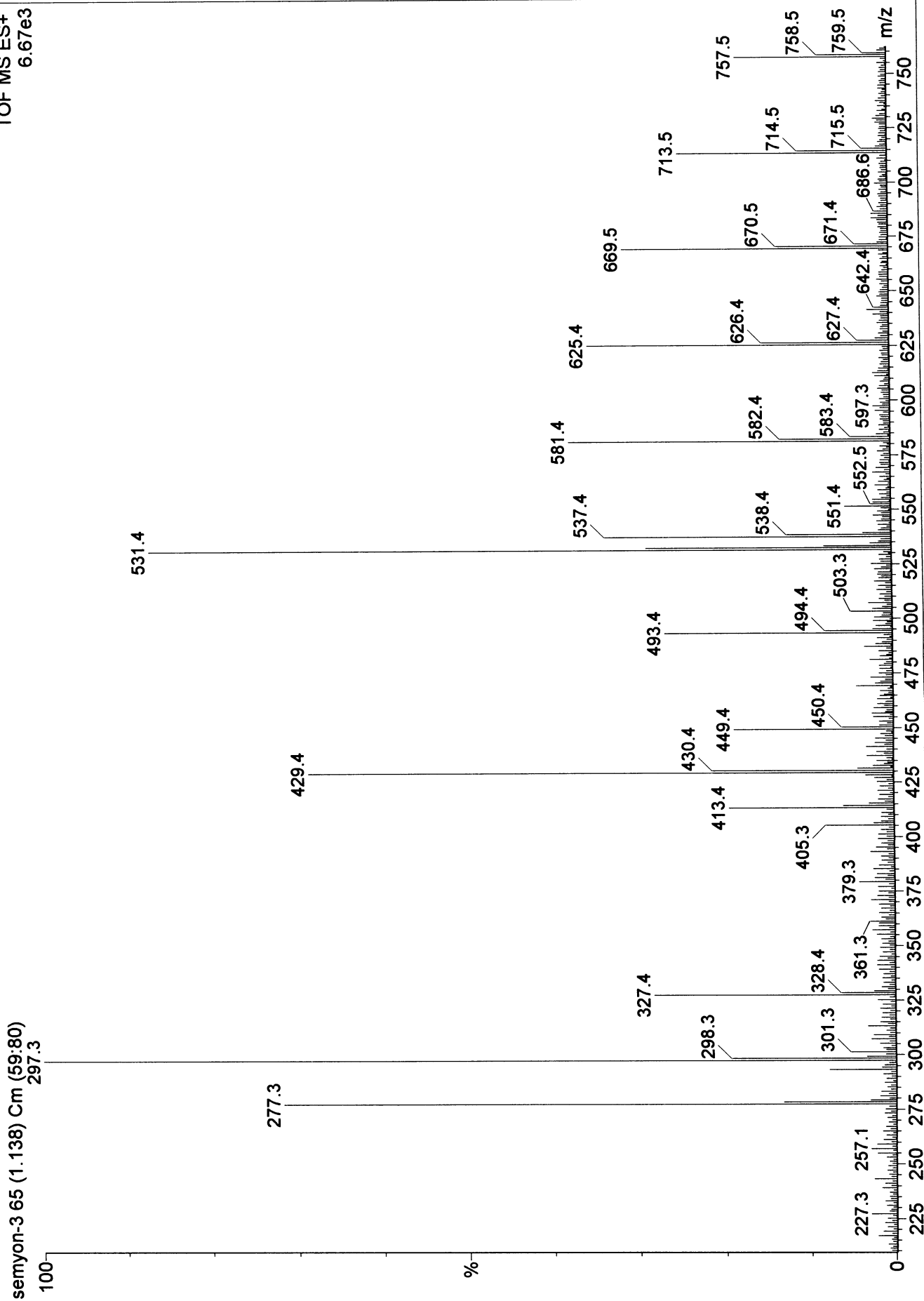
(S)-6,7-dihydroxygeranyl pivaloate - 8

Pulse Sequence: s2pul

Solvent: CDC13
Ambient temperature
File: SGZ2-cp1
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 40.0 degrees
Acq. time 2.666 sec
Width 6000.6 Hz
72 repetitions
OBSERVE   H1, 399.9649457 MHz
DATA PROCESSING
FT size 32768
Total time 5 min, 42 sec
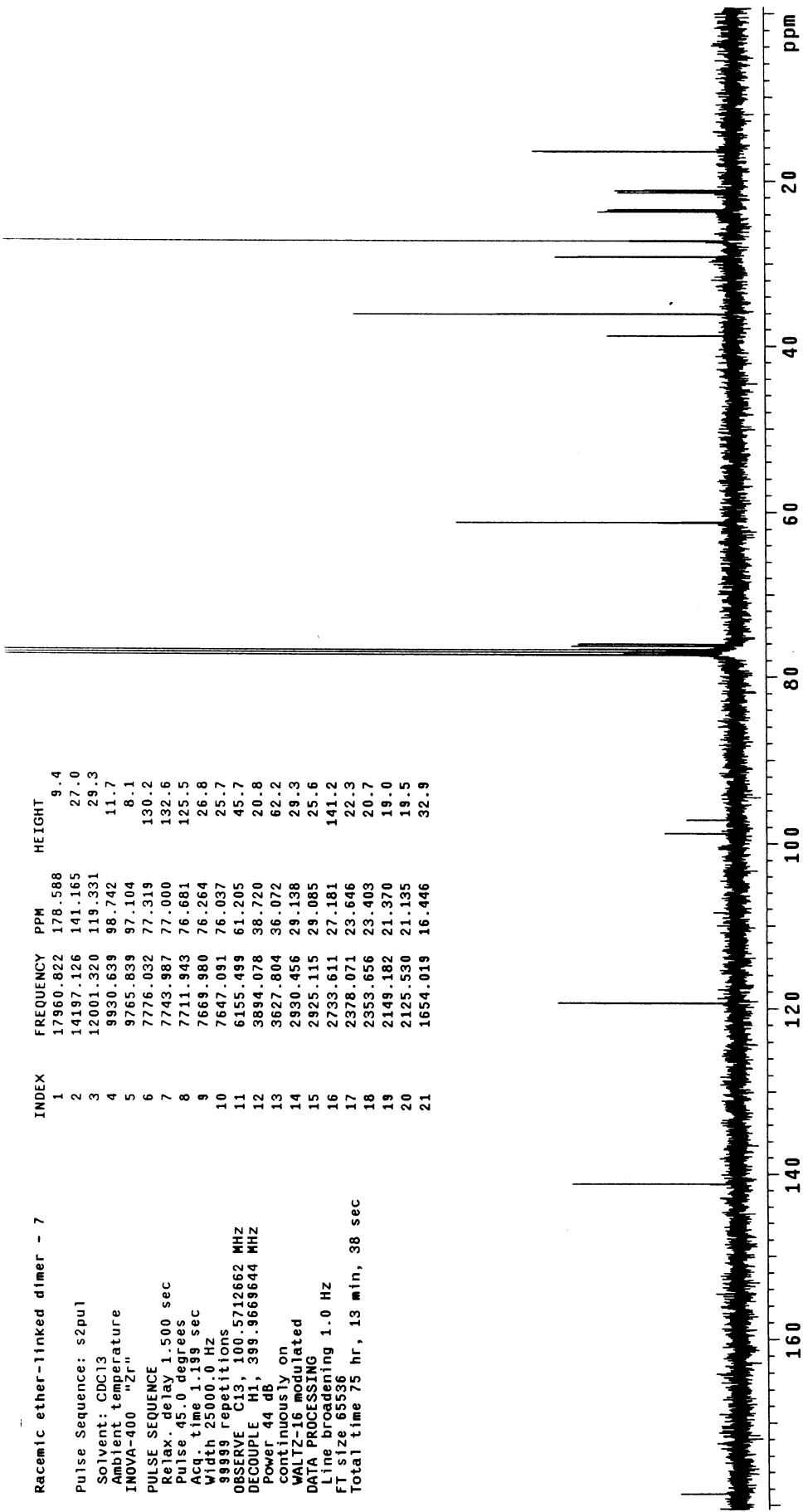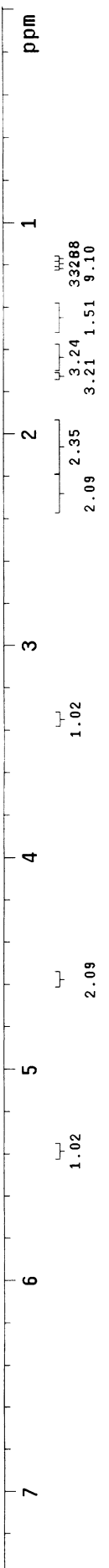
INDEX	FREQUENCY	PPM	HEIGHT
1	2906.718	7.267	182.1
2	2155.498	5.389	20.5
3	2154.033	5.386	35.2
4	2152.935	5.383	35.7
5	2121.802	5.305	78.1
6	1834.280	4.586	69.2
7	1833.547	4.584	68.0
8	1827.321	4.569	68.0
9	1826.588	4.567	66.9
10	1396.221	3.491	27.3
11	1344.211	3.361	32.4
12	1342.379	3.356	33.6
13	1333.589	3.334	33.5
14	1331.757	3.330	32.2
15	924.465	2.311	21.6
16	857.804	2.145	19.6
17	850.845	2.127	20.8
18	689.320	1.723	255.7
19	668.809	1.672	21.9
20	665.879	1.665	21.3
21	661.850	1.655	29.9
22	660.018	1.650	27.9
23	654.891	1.637	22.9
24	653.059	1.633	26.9
25	650.495	1.626	21.4
26	647.931	1.620	25.0
27	646.100	1.615	29.0
28	641.339	1.603	23.3
29	638.775	1.597	29.0
30	636.577	1.592	19.7
31	589.328	1.473	20.3
32	583.834	1.460	22.6
33	582.369	1.456	20.3
34	578.706	1.447	23.4
35	573.579	1.434	19.9
36	494.464	1.236	47.9
37	491.168	1.228	43.2
38	488.604	1.222	23.7
39	484.941	1.212	468.2

INDEX	FREQUENCY	PPM	HEIGHT
40	477.982	1.195	2000.0
41	475.418	1.189	105.4
42	466.994	1.168	454.7
43	457.837	1.145	32.7
44	0.000	0.000	185.7

ppm

1.02   2.09   1.02   2.09   2.35   3.24   3288
                                     3.21 1.51 9.10

7   6   5   4   3   2   1   ppm

(R)-6,7-dihydroxygeranyl pivaloate - 9

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: SGZ5-cp2main
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 45.0 degrees
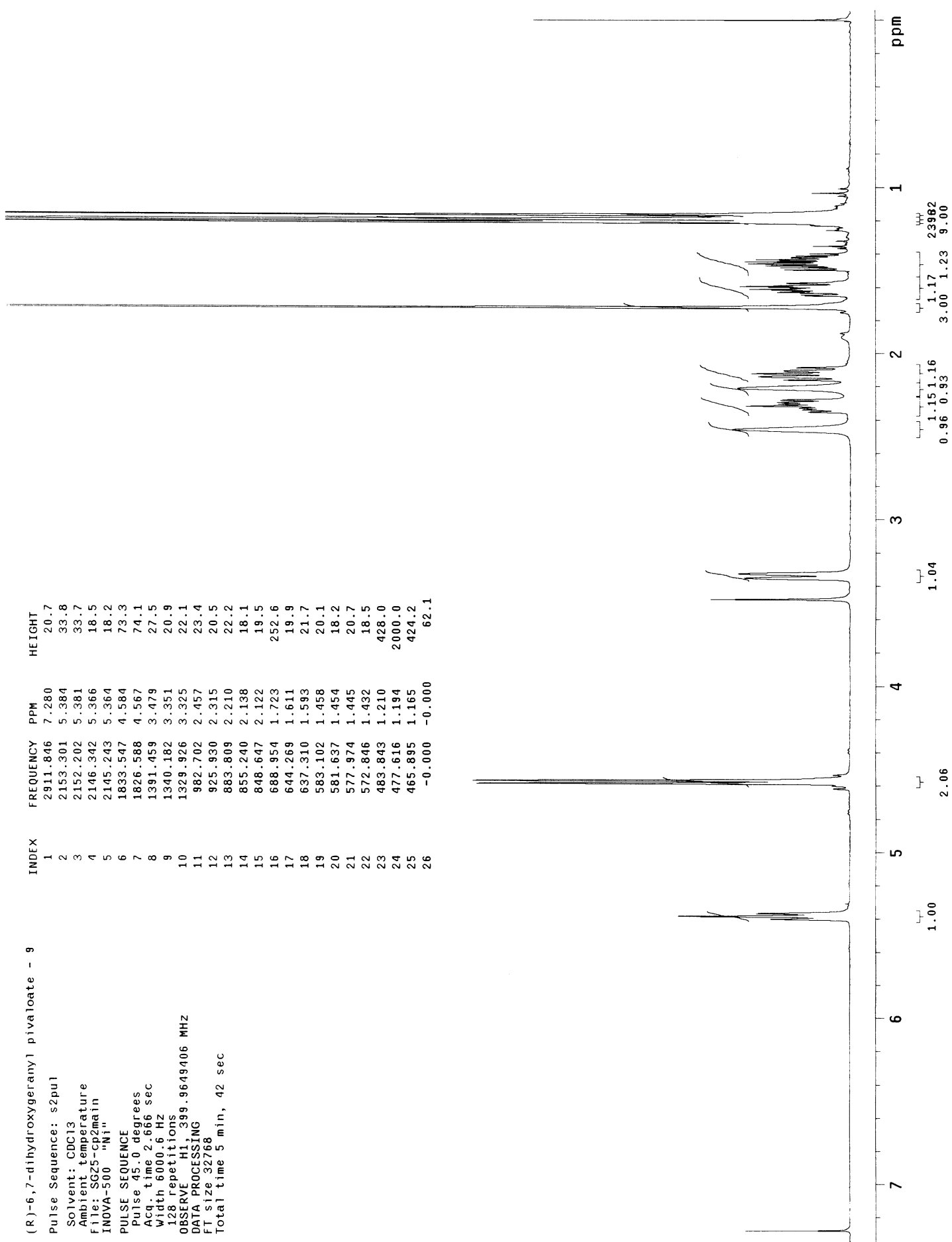Acq. time 2.666 sec
Width 6000.6 Hz
128 repetitions
OBSERVE   H1, 399.9649406 MHz
DATA PROCESSING
FT size 32768
Total time 5 min, 42 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	2911.846	7.280	20.7
2	2153.301	5.384	33.8
3	2152.202	5.381	33.7
4	2146.342	5.366	18.5
5	2145.243	5.364	18.2
6	1833.547	4.584	73.3
7	1826.588	4.567	74.1
8	1391.459	3.479	27.5
9	1340.182	3.351	20.9
10	1329.926	3.325	22.1
11	982.702	2.457	23.4
12	925.930	2.315	20.5
13	883.809	2.210	22.2
14	855.240	2.138	18.1
15	848.647	2.122	19.5
16	688.954	1.723	252.6
17	644.269	1.611	19.9
18	637.310	1.593	21.7
19	583.102	1.458	20.1
20	581.637	1.454	18.2
21	577.974	1.445	20.7
22	572.846	1.432	18.5
23	483.843	1.210	428.0
24	477.616	1.194	2000.0
25	465.895	1.165	424.2
26	-0.000	-0.000	62.1

ppm
1 2 3 4 5 6 7

23962 9.00
1.17 1.23
3.00
1.15 1.16
0.96 0.93
1.04
2.06
1.00

Diols 8 and 9 with 0.8 mol eq Eu(hfc)3, 1:1

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: diols-1-11.8
INOVA-500 "N1"

PULSE SEQUENCE
Pulse 35.0 degrees
Acq. time 3.833 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0732252 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 7 min, 7 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	3006.343	10.019	157.5
2	2884.650	9.613	149.4
3	2550.612	8.500	55.5
4	2466.004	8.218	51.0

ppm

0.74

0.75

2.15

2.00

Diols 8 and 9 with 0.8 mol eq Eu(hfc)3, 1:2

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: diols-2-1-18
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 35.0 degrees
Acq. time 3.333 sec
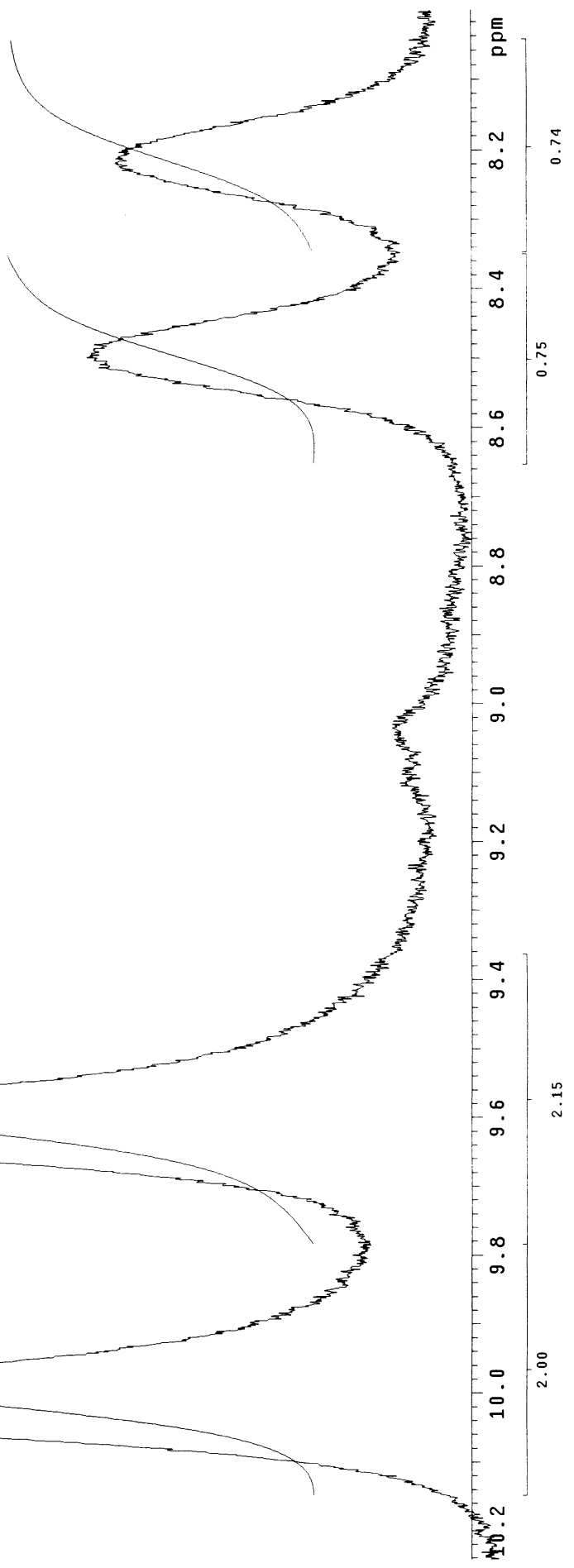Width 4500.5 Hz
96 repetitions
OBSERVE   H1, 300.0732213 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 7 min, 7 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	2737.684	9.123	157.1
2	2627.254	8.755	77.9
3	2374.803	7.914	46.7

2.00   1.00   0.78   0.57

Diol 8 with 0.8 mol eq Eu(hfc)3

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: diol-3eealtint
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 35.0 degrees
Acq. time 3.333 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0732271 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 7 min, 7 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	3229.951	10.764	17.3
2	3106.335	10.352	421.5
3	2914.868	9.714	20.3
4	2831.633	9.436	-14.9
5	2779.714	9.263	-15.0
6	2611.596	8.703	165.9

Diol 9 with 0.8 mol eq Eu(hfc)3

Pulse Sequence: s2pul

Solvent: CDC13
Ambient temperature
File: sgz-10eealtin
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 35.0 degrees
Acq. time 3.383 sec
Width 4500.5 Hz
40 repetitions
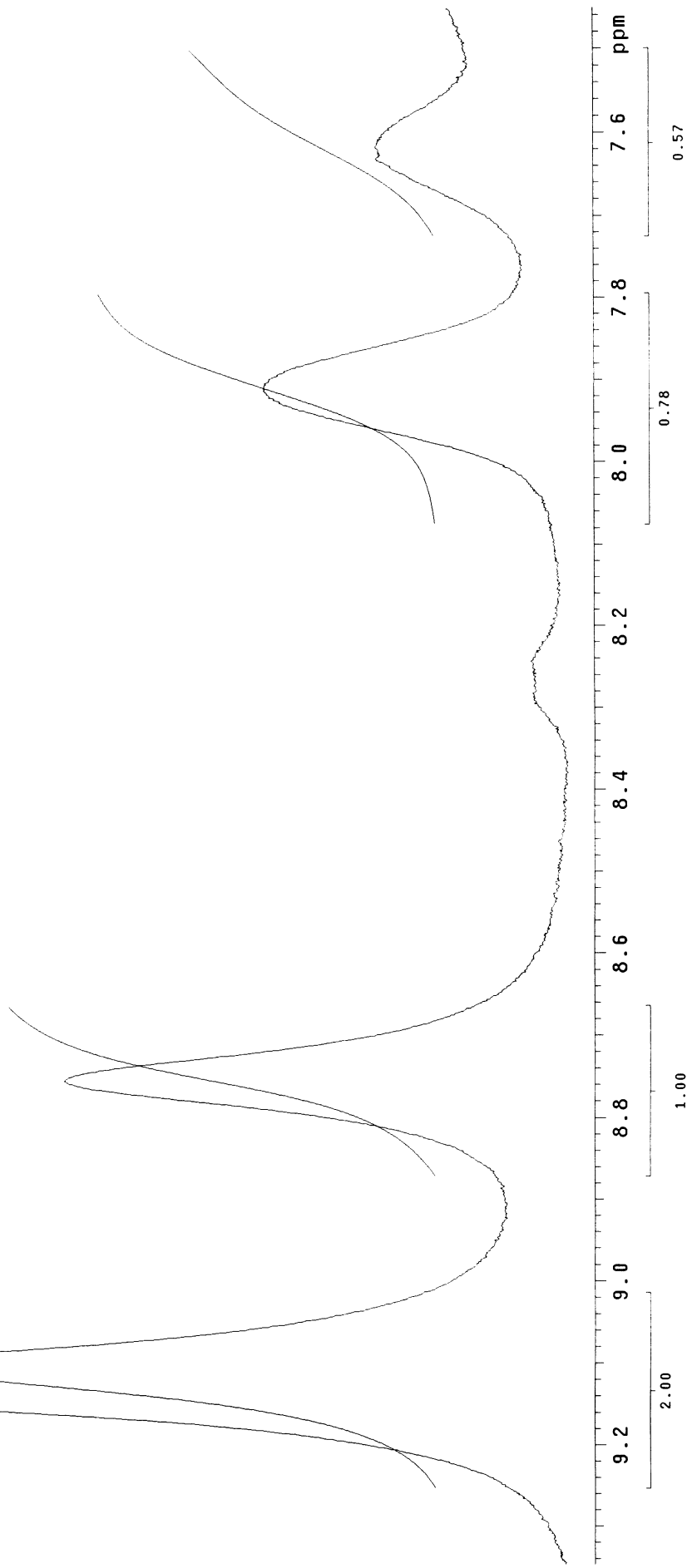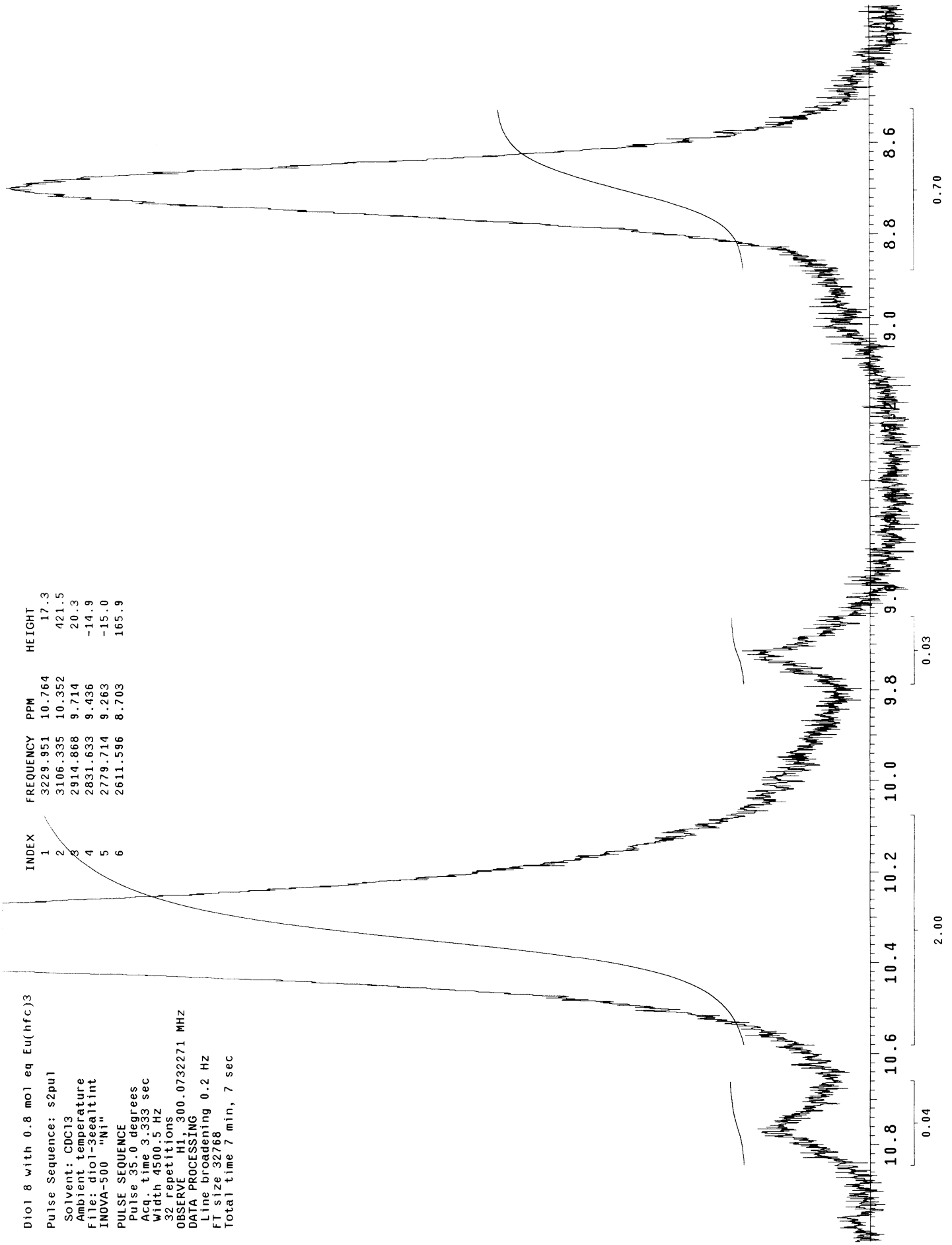OBSERVE   H1, 300.0732271 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 7 min, 7 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	3338.184	11.125	411.9
2	3079.140	10.261	13.4
3	2865.971	9.551	-16.2
4	2772.297	9.239	166.1

2.00   0.04   0.58

(R)-6,7-epoxygeranyl pivaloate - 10
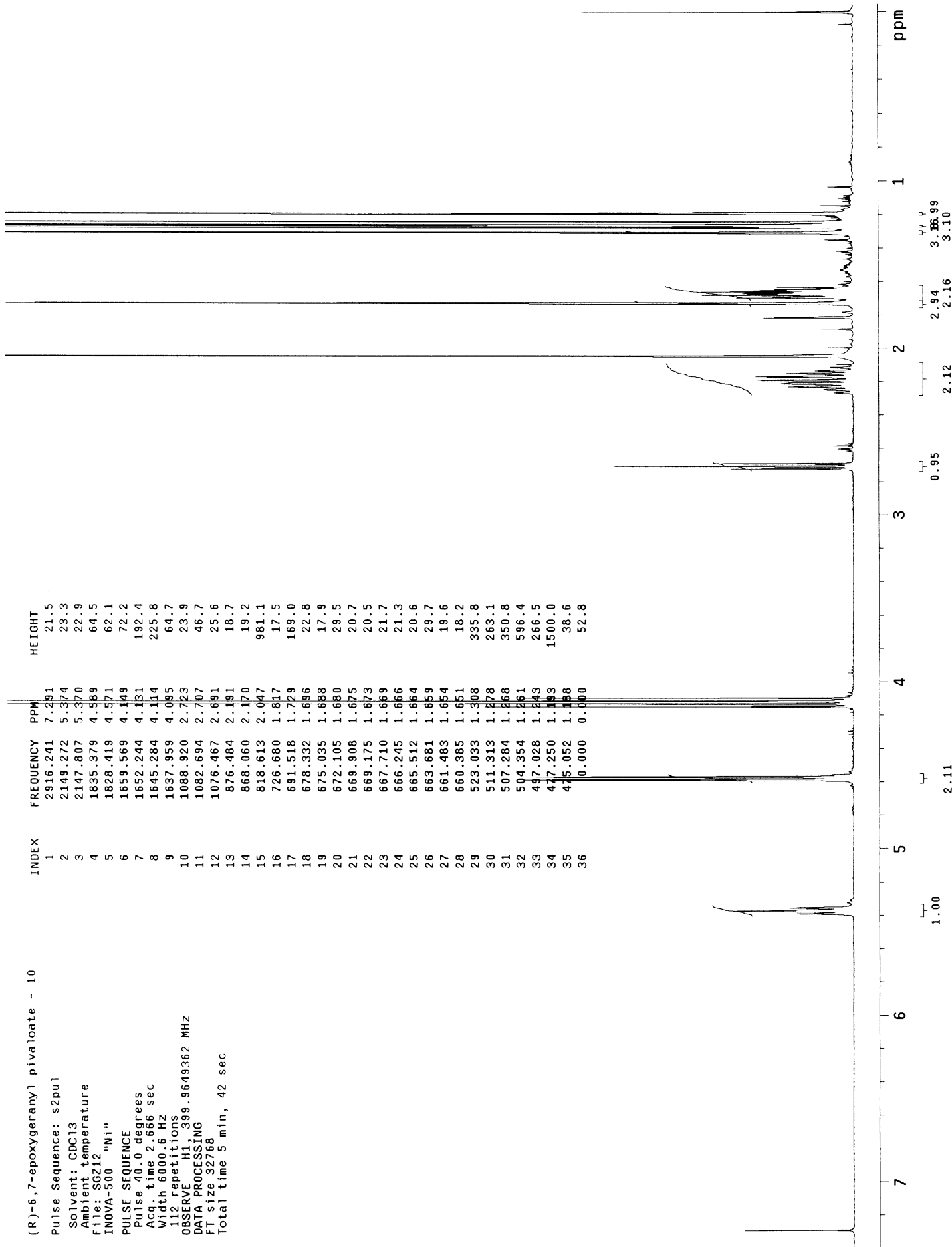
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: SGZ12
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 40.0 degrees
Acq. time 2.666 sec
Width 6000.6 Hz
112 repetitions
OBSERVE H1, 399.9649362 MHz
DATA PROCESSING
FT size 32768
Total time 5 min, 42 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	2916.241	7.291	21.5
2	2149.272	5.374	23.3
3	2147.807	5.370	22.9
4	1835.379	4.589	64.5
5	1828.419	4.571	62.1
6	1659.569	4.149	72.2
7	1652.244	4.131	192.4
8	1645.284	4.114	225.8
9	1637.959	4.095	64.7
10	1088.920	2.723	23.9
11	1082.694	2.707	46.7
12	1076.467	2.691	25.6
13	876.484	2.191	18.7
14	868.060	2.170	19.2
15	818.613	2.047	981.1
16	726.680	1.817	17.5
17	691.518	1.729	169.0
18	678.332	1.696	22.8
19	675.035	1.688	17.9
20	672.105	1.680	29.5
21	669.908	1.675	20.7
22	669.175	1.673	20.5
23	667.710	1.669	21.7
24	666.245	1.666	21.3
25	665.512	1.664	20.6
26	663.681	1.659	29.7
27	661.483	1.654	19.6
28	660.385	1.651	18.2
29	523.033	1.308	335.8
30	511.313	1.278	263.1
31	507.284	1.268	350.8
32	504.354	1.261	596.4
33	497.028	1.243	266.5
34	477.250	1.193	1500.0
35	475.052	1.188	38.6
36	0.000	0.000	52.8

ppm

1   3.16.99
    3.10

2.94
2.16

2.12

0.95

3

4

2.11

5

1.00

6

7

(R)-6,7-epoxygeranyl pivaloate - 10

Pulse Sequence: s2pul

Solvent: CDC13
Ambient temperature
File: SGZ12-13C
INOVA-500 "Ni"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 40.0 degrees
Acq. time 1.706 sec
Width 18761.7 Hz
952 repetitions
OBSERVE C13, 75.4534754 MHZ
DECOUPLE H1, 300.0746975 MHZ
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 3 hr, 5 min, 18 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	13467.601	178.489	5.7
2	12907.618	171.067	19.1
3	10609.282	140.607	16.8
4	9011.784	119.435	14.1
5	8992.317	119.177	22.0
6	5841.982	77.425	97.8
7	5809.918	77.000	99.6
8	5777.853	76.575	96.2
9	4827.943	63.986	11.1
10	4805.040	63.682	10.8
11	4633.838	61.413	8.3
12	4613.226	61.140	41.1
13	4592.040	60.859	8.5
14	4550.814	60.313	40.0
15	4399.653	58.309	12.9
16	2917.244	38.663	10.4
17	2723.139	36.090	34.9
18	2073.834	27.485	15.4
19	2056.084	27.250	43.1
20	2038.906	27.022	51.9
21	2020.584	26.779	8.5
22	1879.156	24.905	12.1
23	1861.407	24.670	12.9
24	1583.705	20.989	17.5
25	1581.415	20.959	16.2
26	1418.230	18.796	10.0
27	1400.480	18.561	11.8
28	1244.165	16.489	7.3
29	1231.569	16.322	6.8
30	1091.859	14.471	6.6
31	1074.682	14.243	21.6
32	1056.932	14.008	21.6
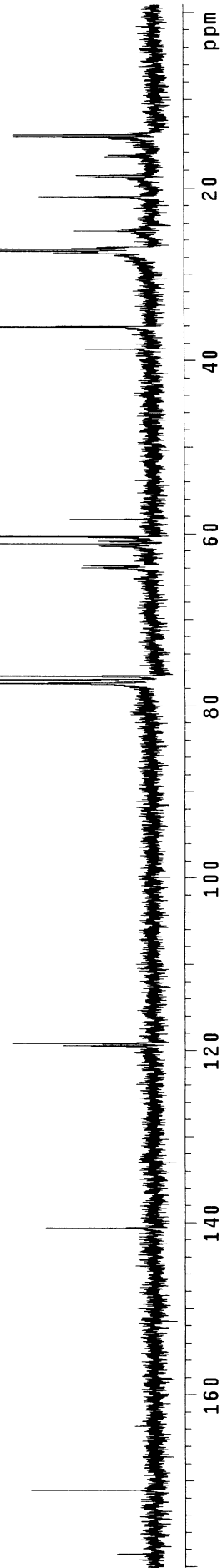
(S)-6,7-epoxygeranyl pivaloate - 11

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: SGZ14-1
INOVA-500 "Ni"

PULSE SEQUENCE
Pulse 40.0 degrees
Acq. time 2.666 sec
Width 6000.6 Hz
80 repetitions
OBSERVE   H1, 399.9649413 MHz
DATA PROCESSING
FT size 32768
Total time 5 min, 42 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	2148.539	5.372	31.6
2	2147.074	5.368	32.5
3	1834.646	4.587	94.2
4	1827.687	4.570	90.5
5	1088.920	2.723	34.9
6	1082.694	2.707	67.9
7	1076.467	2.691	37.1
8	875.751	2.190	26.1
9	867.327	2.169	27.5
10	818.613	2.047	27.9
11	690.053	1.725	249.6
12	677.966	1.695	32.5
13	674.303	1.686	25.7
14	671.739	1.679	42.3
15	669.908	1.675	29.2
16	668.443	1.671	28.5
17	667.344	1.669	30.0
18	665.512	1.664	39.6
19	663.315	1.658	43.0
20	661.117	1.653	28.6
21	659.652	1.649	26.3
22	522.667	1.307	467.0
23	506.918	1.267	498.8
24	504.354	1.261	35.9
25	477.250	1.193	2000.0
26	0.000	-0.000	59.7