TOWARDS THE SYNTHESIS OF THE NEUROFURANS

by

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ABSTRACT

Derived from endogenous docosahexaenoic acid, neurofurans (nFs) are produced in mammalian brain tissue through nonenzymatic free radical oxidation pathways, culminating in 512 enantiomerically pure diastereomers. To achieve enantioselective syntheses of individual nFs, a strategy involving a tunable tetrahydrofuran intermediate was developed. The four stereocenters of the THF core were set by choice of ligands during the Sharpless epoxidation and dihydroxylation steps. Subsequent cascade cyclization delivered the key tetrahydrofuran intermediate as a single enantiomer. The THF core's design also allows for diversity in upper and lower sidechain construction, thus being flexible enough to allow the synthesis of each of the many different nFs. This strategy was applied towards the synthesis of AC-Δ^9-5-NeuroF and its C-11 epimer.

Chapter 1

INTRODUCTION

The goal of this project was to develop a general synthetic route to a recently discovered class of compounds, the neurofurans. My specific goal was to synthesize AC-Δ^9-5-NeuroF[1] (**2**) (Figure 1.1). Derived from endogenous docosahexaenoic acid (DHA, **1**), neurofurans (nFs) are produced through nonenzymatic free radical oxidation pathways, culminating in 512 enantiomerically pure diastereomers.[2] Although these metabolites are produced in quantity *in vivo*, their physiological activity has not been assessed. The total synthesis outlined here will make the nFs available for further evaluation.

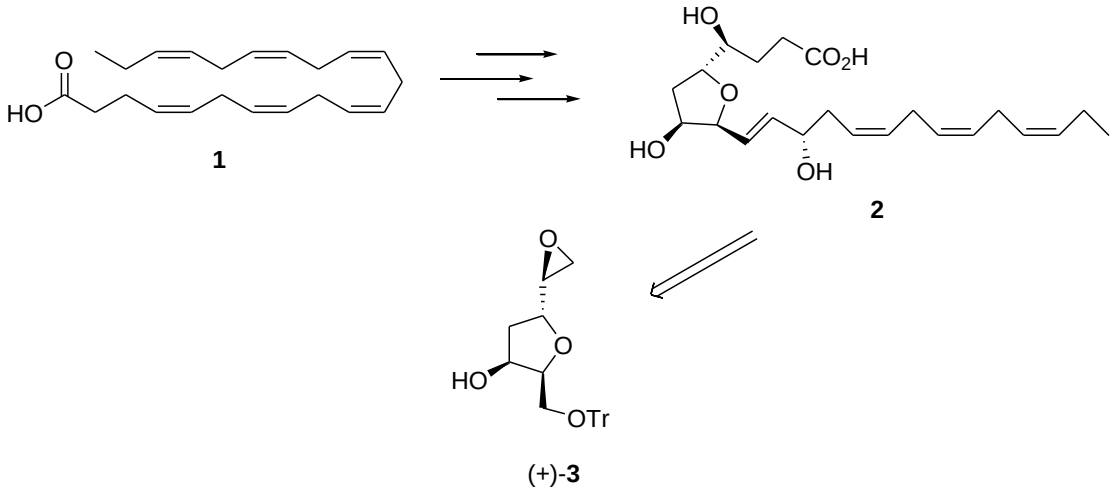


Figure 1.1 Biological and synthetic precursors to nF 2.

Metabolites of arachidonic acid (AA) have been known for quite some time. Prostaglandins, enzymatic products derived from AA, were discovered in 1935 by von Euler[3] and Goldblatt,[4] working independently. It has since been shown that these highly reactive molecules exert significant control on a variety of cells through the nine currently known prostaglandin receptors.

More recently, Roberts et al. found that there are other derivatives of AA present in biological systems. Unlike the prostaglandins, these compounds, deemed isoprostanes[5] and isofurans[6,7], are formed through nonenzymatic free radical oxidation pathways. Analogous to the isofurans, neurofurans, derived from 22 carbon DHA, were suspected to exist in rat liver and brain tissue.[7] By analyzing derivatives of the tissue extracts with LC/MS instrumentation, Fitzgerald et al. confirmed the existence of compounds analogous to the isofurans.[2] Through their study, it was found that all of these compounds had 22 carbon atoms, 3 hydroxyl groups, 4 double bonds, and a carboxylic acid moiety. Epoxide or carbonyl groups were excluded from proposed structures after treatment with HCl or methoxyamine HCl failed to alter the mass chromatogram.[2]

Pathways similar to isofuran formation are proposed for the biosynthesis of the neurofurans. There are two, nonenzymatic pathways that lead to a total of 16 regioisomers. Since each compound contains five stereocenters, there are a total of 512 enantiomerically pure neurofurans, existing *in vivo* as a statistically determined,

complex mixture that also contains iso- and neuroprostanes and isofurans. The cyclic peroxide cleavage pathway leads to eight classes of nFs (Figure 1.2).

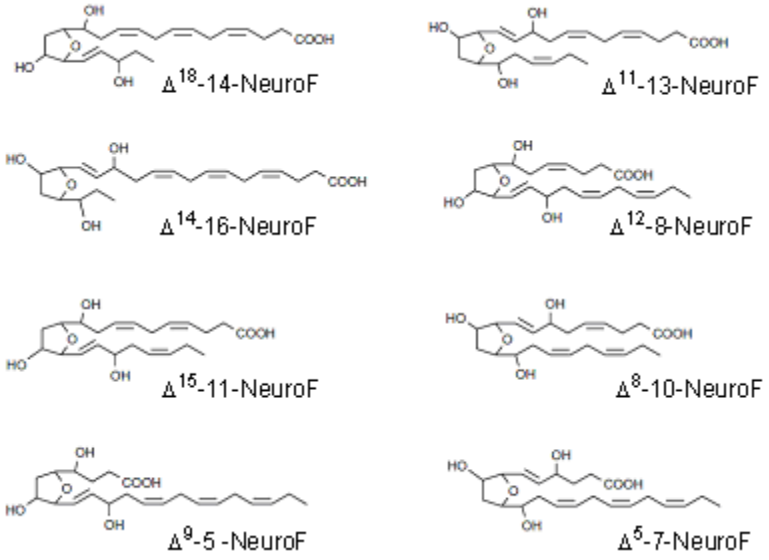


Figure 1.2 The cyclic peroxide cleavage pathway of nF formation.

The epoxide hydrolysis pathway leads to all sixteen classes, but only the remaining eight are shown in Figure 1.3.

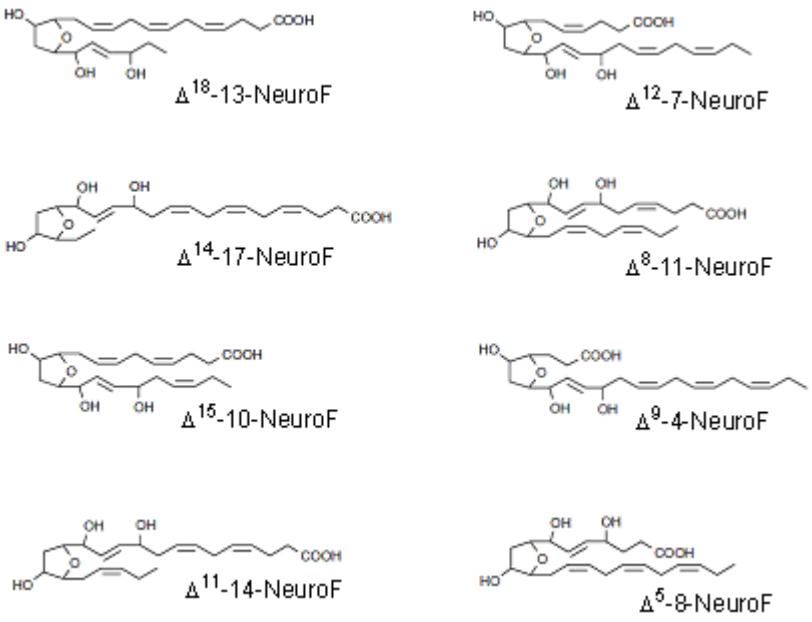


Figure 1.3 The epoxide hydrolysis pathway of nF formation.

Data from LC/MS/MS parent-daughter ion analyses supports these proposed structures.[2]

Comparing brain tissue extracts of normal mice with their Tg 2576 littermates (a widely used model for Alzheimer's disease), Fitzgerald made a few observations. First, he found that nFs existed in significantly higher concentration than the other eicosanoids in both types of mice (Figure 1.4). Secondly, the concentration of all eicosanoids in the transgenic mice cortex were significantly greater than the control. This was not the case in the cerebellum.

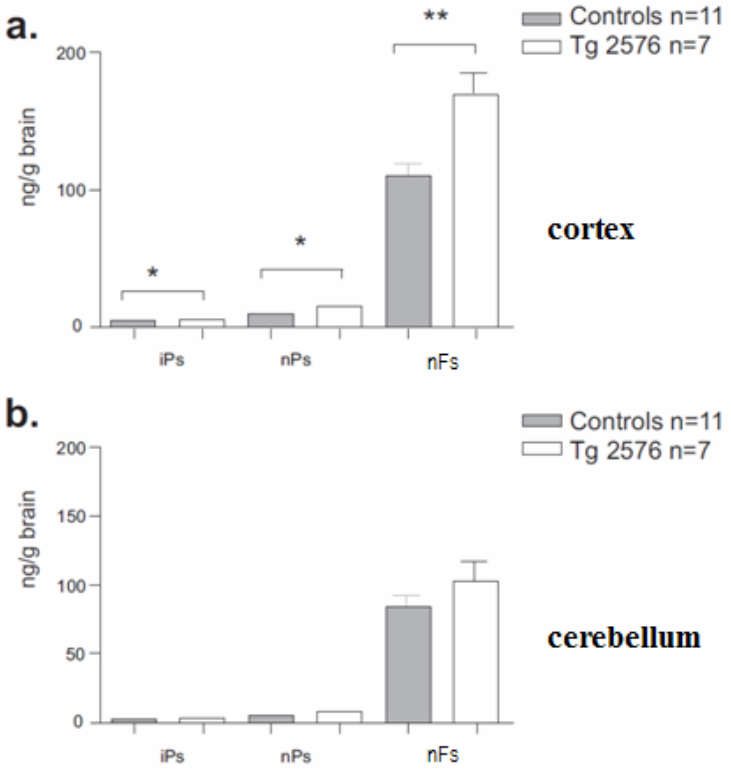


FIGURE 14. **Relative amounts of iPs, nPs, and nFs in the brain cortex of Tg 2576 transgenic mice and nontransgenic littermates (controls) (SRM analysis of *m/z* 393 → 193 and 377 → 101).** *a*, all three classes of peroxidation compounds were significantly elevated in AD brain cortex. *, $p < 0.05$; **, $p < 0.01$. *b*, no significant difference was noted in levels of iPs, nPs, and nFs in the cerebellum of Tg 2576 *versus* control mice.

Figure 1.4 Eicosanoids in the cortex of Tg2576 transgenic mice.

There are no synthetic samples of neurofurans currently available. This project aimed to remedy this, enabling further studies which would provide valuable insight into the pathophysiology of oxidant stress in the central nervous system.

Chapter 2

SYNTHESIS OF THE TETRAHYDROFURAN CORE

The strategy used in this synthesis improves upon a previous route to the isofurans.[8] In his efforts to make 32 enantiomerically pure isofurans, Dr. Peiming Gu of the Taber group developed this strategy to eliminate the regioselectivity problem the previous route had during the dihydroxylation step.[9] The advantage of this plan is that one can access four, enantiomerically pure tetrahydrofuran intermediates from the monotrityl ether shown below depending on the choice of reagents in the SAE and SAD reactions (Figure 2.1). When I began working with Dr. Gu, I set out to make (+)-**3**, which had not yet been synthesized.

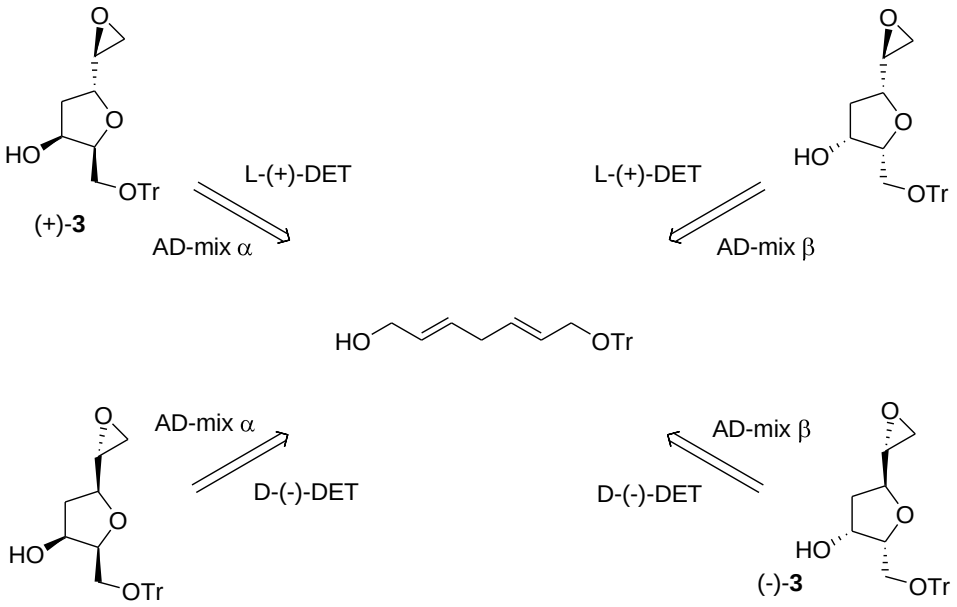


Figure 2.1 Tuning the stereocenters.

The synthesis of the tetrahydrofuran core began with methyl 4-bromocrotonate (Figure 2.2). The ester was reduced to the alcohol with $LiAlH_4$ in dry ether on a 60 g scale in 54% yield. Next, this alcohol was coupled with propargyl alcohol by treatment with NaI, CuI, and K_2CO_3, completing the seven carbon framework of the tetrahydrofuran intermediate. This reaction resulted in a 2:1 ratio of linear and branched compounds in 62% yield, coming from competing S_N2 and S_N2' reaction pathways. The mixture was purified by flash chromatography, but the two compounds were not separated at this point. Separation would be much easier if these diols were made less polar, so the separation was postponed until one hydroxyl was protected as the trityl ether.

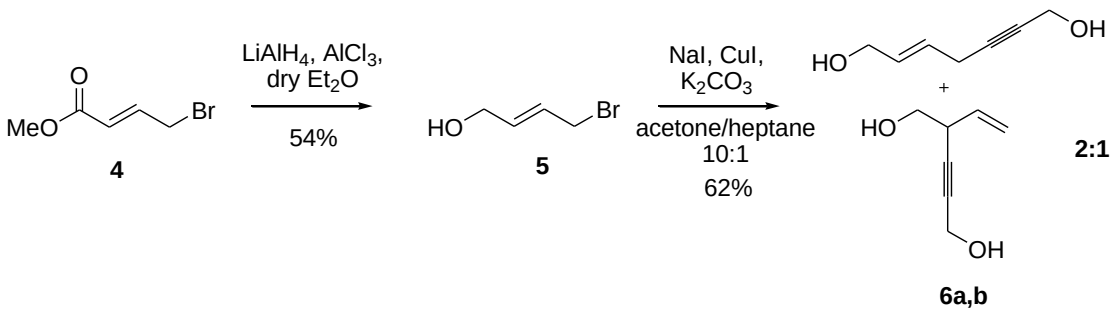


Figure 2.2 Synthesis of diols 6a,b.

The diol mixture was then subjected to reducing conditions (5 eq. $LiAlH_4$, 9 eq. methanol in THF), delivering the desired skipped diene along with the branched compound (Figure 2.3). This mixture of diols was treated with trityl chloride, triethylamine, and DMAP (cat.) in dry methylene chloride. The desired product of this reaction was the linear, monotrityl ether **8a**. Separation via flash chromatography afforded **8a** in 42% isolated yield.

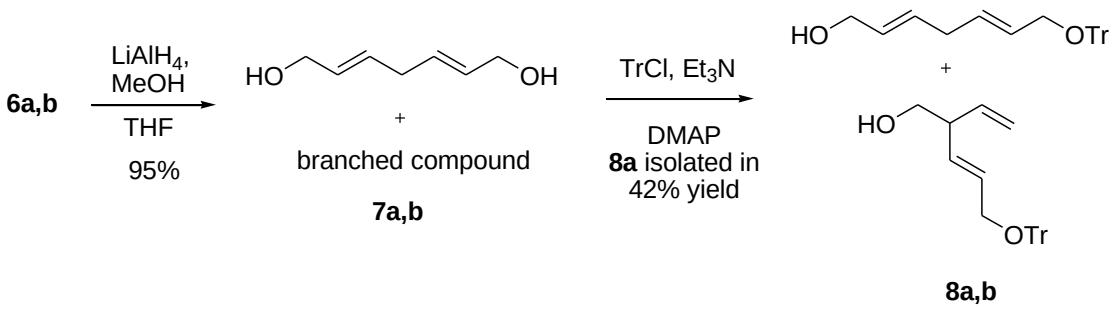


Figure 2.3 Synthesis of monotrityl ether 8a.

With pure **8a** in hand, regio- and enantioselective epoxidation was effected via the Sharpless protocol.[10] This reaction provided allylic epoxy alcohol **9** in 81% yield. The remaining free hydroxyl was then converted to the benzenesulfonate in preparation for the cascade cyclization reaction.

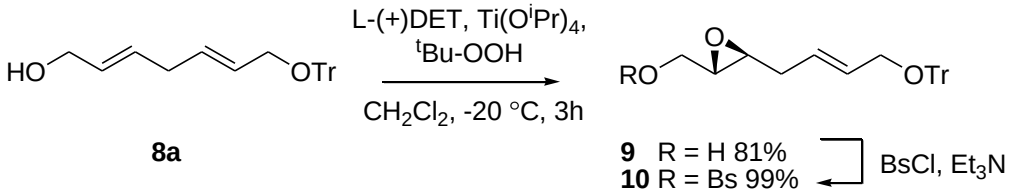


Figure 2.4 Synthesis of sulfonate 10.

Sulfonate **10** was treated with AD-mix α and methane sulfonamide to effect the asymmetric dihydroxylation[11] of the remaining alkene, delivering diol **11**.

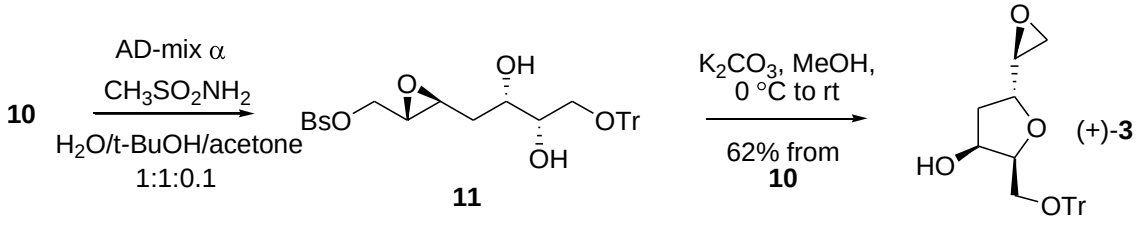


Figure 2.5 Synthesis of enantiopure tetrahydrofuran core.

The cascade cyclization of crude diol **11** to form tetrahydrofuran (+)-**3** was performed in methanol. Potassium carbonate deprotonated the hydroxyl groups of **11**, which allowed for 5-exo-tet ring closure preferentially over other possible pathways. The oxyanion formed in the epoxide opening then displaced benzenesulfonate, forming the terminal epoxide with (*R*)-configuration. Using chiral high-performance liquid chromatography, (+)-**3** was found to have greater than 99% ee.[12]

The simultaneous generation of a terminal epoxide along with a functionalized THF core with control over absolute configuration is a powerful tool in organic synthesis. The configuration of the terminal epoxide in **3** was previously set by the asymmetric epoxidation, then transferred through the cascade cyclization reaction. Besides cascade reactions like these, the current, best method to access enantiopure terminal epoxides is by hydrolytic kinetic resolution of a racemic mixture.[13] The advantage of the method described herein is that useful bonds are being formed in the process as well.

Chapter 3

TOWARDS THE SYNTHESIS OF THE LOWER SIDECHAIN

The sixteen classes of neurofurans (see Figure 1.2 and 1.3) contain the same THF core with varying upper and lower sidechains. The functionalized THF intermediate (**3**) was chosen for this project for its ability to accommodate these various sidechains. The trityl ether of **3** can be deprotected, then oxidized to the aldehyde, thus opening the possibility of installing lower sidechains with the requisite trans alkene through a Wittig reaction (**13** + **14**, Figure 3.1). With THF **3** in hand, I set out to make the 13 carbon lower sidechain synthon (**14**) of the target neurofuran (**2**). It was found that a similar all *cis*- skipped triene was reported in previous work done by You and Taber.[14] This prior work guided my steps towards **14**.

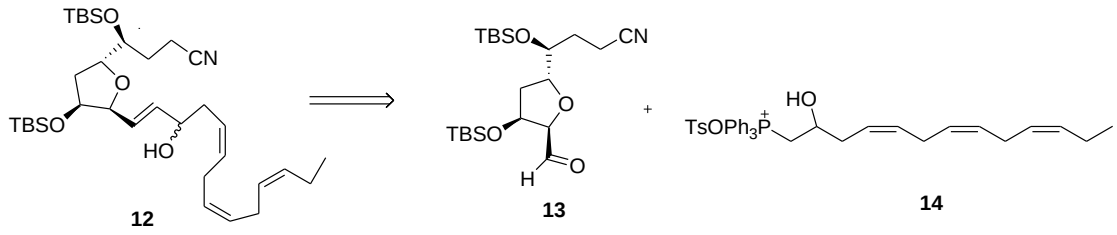


Figure 3.1 Planned union of the complex coupling partners.

The synthesis of **14** began with the coupling of propargyl alcohol with allyl bromide on a 3 gram scale (Figure 3.2). The product of this reaction was purified by bulb-to-bulb distillation at 89 °C, delivering the product alcohol.

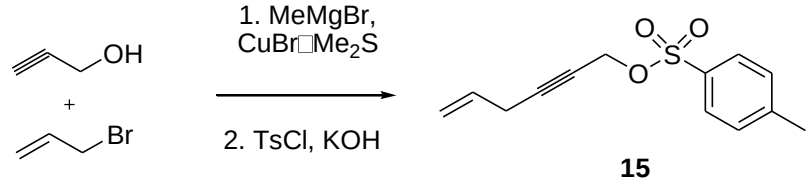


Figure 3.2 Synthesis of tosylate 15.

The resulting alcohol was then tosylated to give **15**, which was purified by flash chromatography. An unknown amount of tosyl chloride contaminated the product, however, so a yield was not calculated for this reaction. Coupling partner **16** was made from the protection of 4-butynol as the THP ether (Figure 3.3). Then, **16** was added to tosylate **15** by treatment with methyl Grignard reagent and a copper(I) catalyst, delivering THP ether **17**. An impurity in the product of this reaction proved difficult to separate, preventing a calculation of the yield.

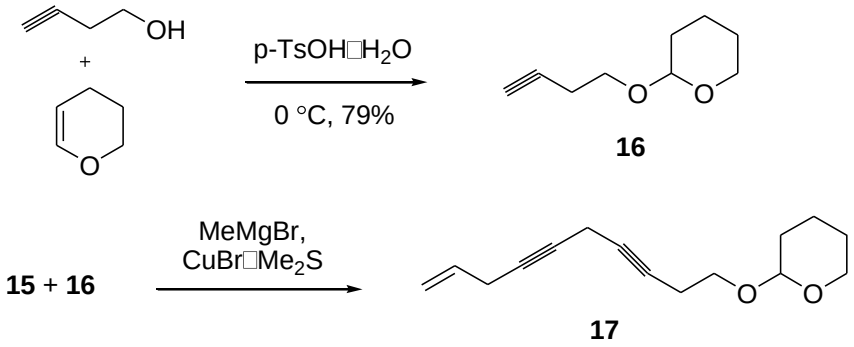


Figure 3.3 Synthesis of THP ether 17.

After obtaining poor yields and product contamination with the use of methyl magnesium bromide, the choice of Grignard reagent was altered. Instead, freshly prepared ethyl magnesium bromide was used to deprotonate propargyl alcohol, and

upon addition of allyl bromide and the copper catalyst, the six carbon alcohol was obtained in 66% yield (Figure 3.4). Tosylation of the alcohol proceeded in 10% yield. This poor yield could be due to the fact that impure tosyl chloride was used. The tosyl chloride was subsequently purified, but the reaction was not repeated.

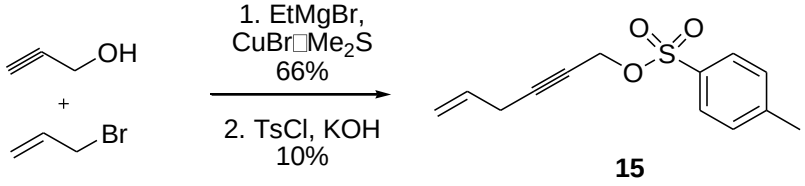


Figure 3.4 Synthesis of tosylate 15 using EtMgBr.

Compound **17** could be dihydroxylated[11] (Figure 3.4) using AD-mix α to install the functionality necessary for further development. The crude diol could be treated with Dowex 50x8-100 ion exchange resin to remove the THP protecting group, revealing the free alcohol.

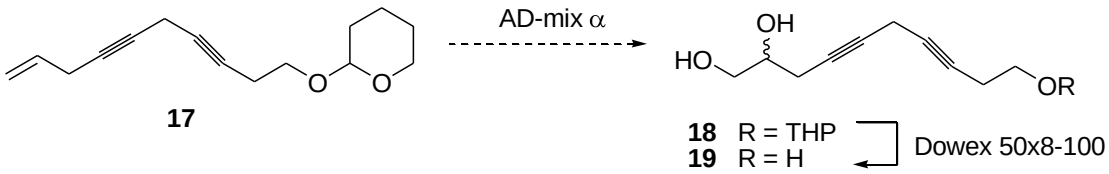


Figure 3.5 Proposed synthesis of the 10 carbon triol (19).

The next step would be to protect **19** as the acetonide (**20**, Figure 3.5), using acetone, catalytic sulfuric acid, anhydrous sodium sulfate, and 4 Å molecular sieves. With **20** in hand, it would be possible to reduce the triple bonds, using a sodium borohydride reduced nickel catalyst.[15] This would give **21**, which could then be tosylated to give **22**. Displacing the tosyl group with triphenylphosphine would offer

phosphonium salt **23**, which could then be coupled with propanal in a Wittig reaction to give the all *cis*- skipped triene **24**.

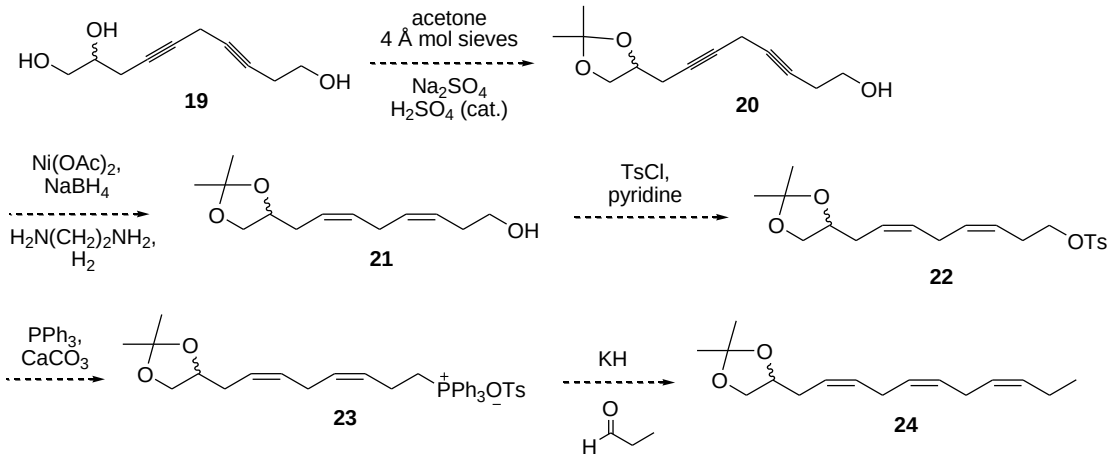


Figure 3.6 Proposed route to skipped triene 24.

Removal of the acetonide followed by selective tosylation[16] should give tosylate **25**. Treating **25** with triphenylphosphine should give Wittig coupling partner **14**.

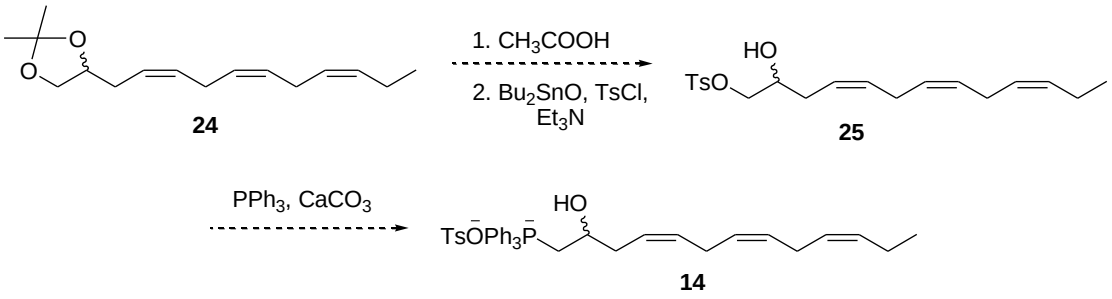


Figure 3.7 Proposed route to Wittig coupling partner 14.

Chapter 4

TOWARDS THE SYNTHESIS OF THE NEUROFURANS

With **3** in hand, it was necessary to protect the free hydroxyl before the upper sidechain could be constructed. *tert*-Butyldimethylsilyl chloride and imidazole with catalytic DMAP effected the transformation of **3** to **26** in 97% yield.

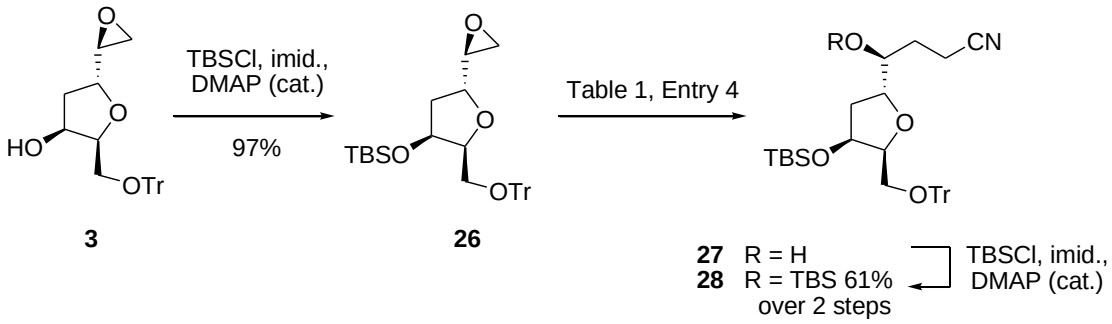
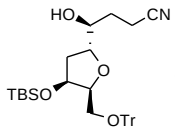
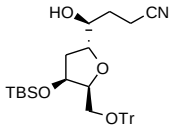


Figure 4.1 Installation of the upper sidechain.

It was thought that a nucleophile such as lithioacetonitrile could open epoxide **26**, installing the four carbon upper chain as well as the equivalent of a masked carboxylic acid. To achieve this goal, various experiments were performed, summarized in Table 4.1.

Table 4.1 Development of the lithioacetonitrile epoxide opening reaction.

Entry	Conditions	Results
1	1. $(^{i}Pr)_2NH$, nBuLi -78 °C, 40 min 2. CH_3CN, 30 min; then **26** -78 °C 1 hr, 75 °C 1 hr; then rt overnight	No reaction
2	1. CH_3CN, nBuLi -78 °C, 1 hour and 15 min 2. **26** added, -78 °C to rt over 2 hrs; then left to react overnight	Decomposition of starting material
3	1. CH_3CN, nBuLi -78 °C, 45 minutes 2. BF_3 OEt_2, then **26**, -78 °C, 1 hr	 minor + **26** remained + new polar compound
4	1. CH_3CN, nBuLi -78 °C, 1.5 hours 2. **26** added over 10 min period, 75 min at -78 °C, 30 min at 0 °C	 major

In the first experiment, I attempted to deprotonate diisopropylamine by adding 2 equivalents of n-BuLi by syringe to the stirring mixture of 2 equiv i-Pr_2NH in THF at -78 °C. This was allowed to stir for 40 minutes before 1.5 equiv acetonitrile was added. This stirred for another 30 minutes before 1 equiv of epoxide **26** was added. After 1 hour at -78 °C, according to TLC analysis, no reaction had occurred. The reaction mixture was then heated to 75 °C for 1 hour, but still no reaction had occurred. The mixture was left to react overnight, but once again, only starting material remained in the flask.

Next, I tried n-BuLi as the only base. To a solution of 1.7 ml CH_3CN in 1 ml THF at -78 °C was added 0.24 mL 2.47 M n-BuLi (3 equiv). After 1 hour and 15 minutes of stirring, **26** was added. After two hours of stirring at -78 °C, no reaction had occurred. It was left to react overnight, and one product was isolated in 31% yield. This product however, did not contain any of the oxygenated carbons present in **27**, and was not synthetically useful.

Next, a Lewis acid was utilized to promote the opening of the epoxide. 0.31 ml of 2.47 M n-BuLi (3 equiv) was added to a stirring solution of 0.1 ml CH_3CN in 0.1 ml THF at -78 °C. After 45 minutes of stirring, 0.01 ml 48% $BF_3{\cdot}OEt_2$ and **26** were added sequentially. After 1 hour at -78 °C, the mixture was worked up with distilled water. It was found that the reaction mixture contained a mixture of unreacted starting material, nitrile **27**, and a new polar compound.

Lastly, drawing upon a procedure for a similar nucleophilic addition of lithioacetonitrile,[17] a reaction using only n-BuLi was performed. This time, the base was allowed to stir with acetonitrile for a longer period of time. To a solution of 0.04 ml CH_3CN in 0.10 ml THF was added 0.31 ml 2.47 M n-BuLi at -78 °C. This was allowed to stir for 1.5 hours before epoxide **26** was added. 1.25 hours of stirring at -78 °C was followed by 30 minutes at 0 °C. The reaction was quenched with distilled water and extracted with ethyl acetate. By TLC, only one product was formed with an R_f matching that of previously characterized nitrile **27**. The concentrated, crude reaction mixture was used in the protection step, delivering **28** in 61% over two steps.

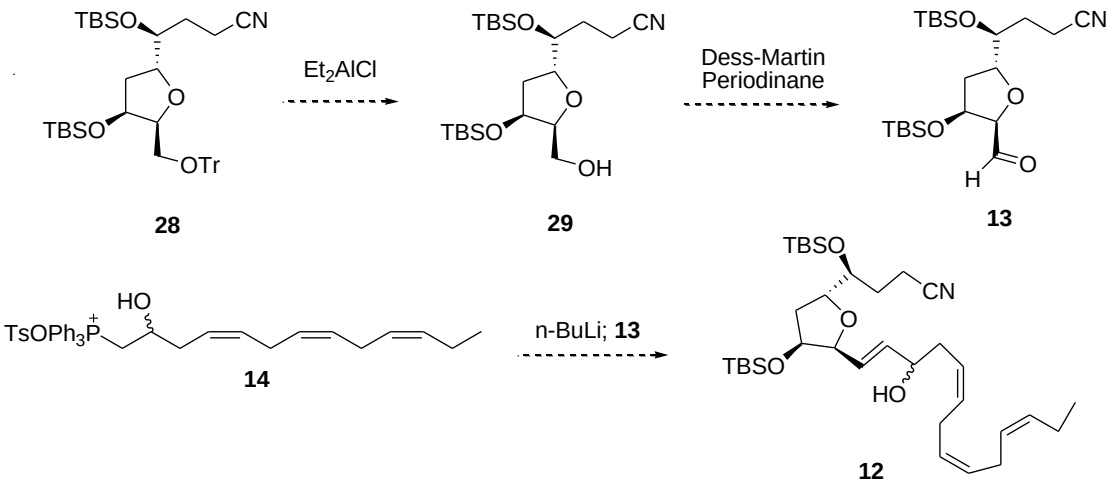


Figure 4.2 Planned incorporation of the lower sidechain.

With **28** in hand, it is possible to remove the trityl group by treatment with diethylaluminum chloride. Dess-Martin periodinane can oxidize the primary alcohol to the aldehyde (**13**), preparing the substrate for a Wittig coupling with phosphonium salt **14**. It has been shown[18] that α-hydroxy phosphonium salts react to give (*E*) alkenes, thus we expect **12** to be formed selectively. This reaction sequence was not attempted because **14** has not yet been synthesized.

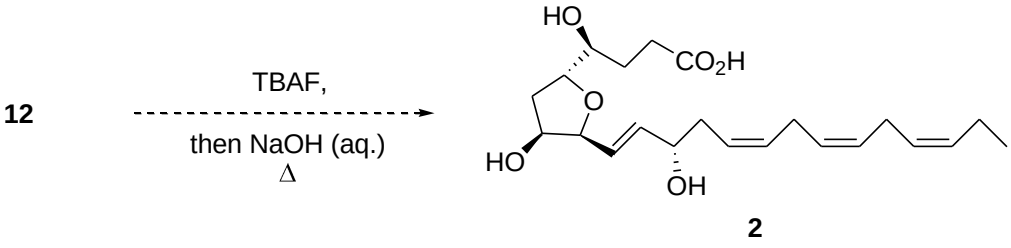


Figure 4.3 Proposed conversion of advanced intermediate 12 to nF 2.

After the Wittig coupling of the two complex fragments (**13 + 14**), the only action left would be the global deprotection of the alcohols and hydrolysis of the

nitrile[8] to give AC-Δ^9-NeuroF (**2**) along with its C-11 epimer. Previous experience[19] with similar compounds suggests that the epimers may be separable by chromatographic methods.

Chapter 5

CONCLUSION

In conclusion, the tetrahydrofuran core of AC-Δ^9-5-NeuroF with its upper sidechain (**28**) was synthesized in 5.2% yield (over 10 steps) in greater than 99% ee. The design of the THF core allows for a lower sidechain to be appended via a Wittig reaction. Due to the convergent nature of this synthesis, neurofuran **2** can be synthesized in large enough quantities for further biological study.

Key reactions of this project include sequential Sharpless asymmetric epoxidation and asymmetric dihydroxylation reactions that set the stereocenters of the substrate. The stereochemical information was then translated through a cascade cyclization to deliver (+)-**3** in greater than 99% ee. As current methods of synthesizing enantiopure terminal epoxides are limited, this cascade reaction sequence is a significant contribution that can deliver a specific enantiomer in greater than 50% yield. The opening of the terminal epoxide by lithiated acetonitrile is a useful method for installing a latent carboxylic acid moiety while forming a carbon to carbon bond seen in the natural product.

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APPENDIX

Towards the Synthesis of the Neurofurans

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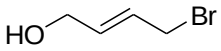
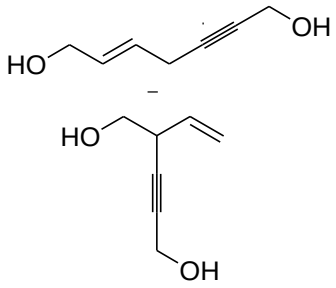
General Experimental Protocol

Unless otherwise noted, reaction solvents were distilled and reagents were used without additional purification. All reagents used were of commercial quality. All reactions were stirred using a magnetic stir bar under a nitrogen atmosphere and heated using a silicon oil bath unless otherwise noted. Thin-layer chromatography (TLC) was performed on Analtech pre-scored 2.5 x 10 cm, 250 μm silica gel plates. NMR spectra were obtained using a Bruker AV400 instrument. $CDCl_3$ was used as the solvent in each NMR experiment, with tetramethylsilane included as the reference for the chemical shifts reported. A JVERT program was used when obtaining ^{13}C NMR spectra in order to aid in structure determination. Methyl and methine peaks are labeled "down" while methylene and quaternary carbons are labeled "up." Infrared spectra were obtained neat using an FTIR spectrometer with a NaCl plate. High resolution mass spectra were obtained by John Dykins of the University of Delaware Mass Spectrometry Lab. High performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1090 chromatograph equipped with a Chiralcel-OD column.

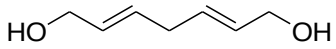
Experimental Procedures



(2*E*)-4-Bromo-2-buten-1-ol (5) To a 3-necked, 3 L flask was added 10.64 g LAH (280.3 mmol), then 700 ml distilled Et_2O was added slowly, with stirring. The mixture was brought to -78 °C, then 12.47 g of $AlCl_3$ (93.54 mmol) was added slowly. After being allowed to return to room temperature for 30 minutes, the mixture was brought back down to -78 °C. At this time, methyl 4-bromocrotonate (50.16 g, 280.2 mmol in 100 ml dry Et_2O) was added dropwise over 25 minutes using an addition funnel. The reaction mixture was then stirred at -78 °C for 2.5 hours. The reaction was slowly brought to room temperature, quenched with 400 ml 3 N HCl solution, and extracted with ethyl acetate (2 × 500 ml). The combined organic fractions were washed with saturated aqueous sodium bicarbonate, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (15% MTBE/PE) afforded the title compound as a yellow oil (22.80 g, 151 mmol, 54%). TLC R_f = 0.26 (30% MTBE/PE).

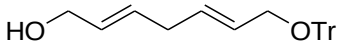


(2*E*)-7-Hydroxy-2-hepten-5-yn-1-ol (6a) and its branched isomer (6b) To a stirring solution of **5** (8.97 g, 59.4 mmol) in acetone (200 ml) at room temperature were added propargyl alcohol (3.36 g, 59.9 mmol), K_2CO_3 (16.45 g, 119 mmol), NaI (18.75 g, 125 mmol), CuI (12.49 g, 65.6 mmol), and heptane (20 ml). The reaction was stirred for 51 hours, then filtered through a pad of celite. The filtrate was concentrated *in vacuo*, then purified by flash chromatography (50% MTBE/PE, then MTBE) to afford the title compounds as a yellow oil (4.656 g, 36.96 mmol, 62%, roughly 2:1 linear:branched). TLC R_f = 0.32 (80% MTBE/PE).

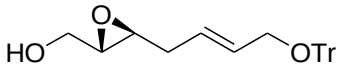


(2*E*,5*E*)-7-Hydroxy-2,5-heptadien-1-ol (7a) and its branched isomer (7b) To a stirring solution of $LiAlH_4$ in THF (3.20 g, 84.4 mmol in 55 ml) at -50 °C was added methanol (8.1 ml) dropwise. After 25 minutes of stirring, a solution of **6a/6b** in THF (2.01 g, 15.9 mmol in 10 ml) was added dropwise. The reaction was stirred at -50 °C for another 30 minutes before allowing it to slowly return to room temperature over a period of 5.5 hours. At this point, 45 ml of THF was added, followed by 7 ml

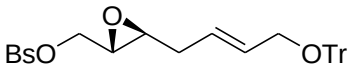
of H_2O. The reaction mixture was then filtered through a pad of celite. The pad was washed with 40 ml THF and 40 ml EtOH. The filtrate was then concentrated *in vacuo*. Purification by flash chromatography (50% MTBE/PE, then MTBE) afforded the title compounds as a yellow oil (1.94 g, 15.2 mmol, 95%, roughly 2:1 linear : branched). TLC R_f = 0.24 (80% MTBE/PE).



(2*E*,5*E*)-7-Triphenylmethylmethoxy-hepta-2,5-dien-1-ol (8a) To a stirring solution of **7a/7b** (12.63 g, 98.54 mmol in 400 ml CH_2Cl_2) at -70 °C was added Et_3N (9.14 g, 90.3 mmol in 10 ml CH_2Cl_2). Then, trityl chloride (22.4 g, 80.4 mmol in 10 ml CH_2Cl_2) was added dropwise. After 15 minutes of stirring, the reaction was slowly warmed to room temperature. After 3 hours, H_2O (50 ml) was added to the reaction mixture, followed by extraction with CH_2Cl_2 (2 × 100ml). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (15 – 20% MTBE/PE) afforded the title compound as a yellow oil (15.44 g, 41.70 mmol, 42%, linear only). TLC R_f = 0.38 (30% MTBE/PE).

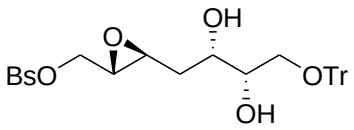


(2*R*,3*S*)-2,3-Epoxy-7-triphenylmethylmethoxy-5-hepten-1-ol (9) A stirring solution of L-DET (257.5 mg, 1.25 mmol) and $Ti(O^iPr)_4$ (344.1 mg, 1.21 mmol) in CH_2Cl_2 (3 ml) was kept at -20 to -30 °C for 30 minutes before a solution of **8a** in CH_2Cl_2 (405.6 mg, 1.10 mmol in 4 ml) was added. After another 30 minutes -20 to -30 °C, 1.2 ml of 4.71 M *t*-BuOOH in CH_2Cl_2 was added dropwise. After 3 hours of stirring at this temperature range, 1 M aq. NaOH (6 ml) was added. The reaction was allowed to stir for 40 minutes before being extracted with CH_2Cl_2 (3 × 40 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (30% MTBE/PE) afforded the title compound as a clear oil (338.9 mg, 0.878 mmol, 81%). TLC R_f = 0.24 (50% MTBE/PE).

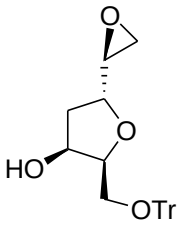


(2*R*,3*S*)-1-Benzenesufonyl-2,3-epoxy-7-triphenylmethylmethoxy-5-heptene (10) To a stirring solution of **9** in CH_2Cl_2 (1.438 g, 3.73 mmol in 26 ml) at 0 °C were added DMAP (21.1 mg, 0.173 mmol), Et_3N (1.471 g, 14.54 mmol), and a solution of benzenesulfonyl chloride in CH_2Cl_2 (1.873 g, 10.60 mmol in 4 ml). The reaction was allowed to stir at 0 °C for 50 minutes before it was quenched with H_2O and extracted

with CH_2Cl_2 (3 × 50 ml). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (30 - 50% MTBE/PE) afforded the title compound as a yellow oil (1.932 g, 3.673 mmol, 99%). TLC R_f = 0.49 (30% MTBE/PE).

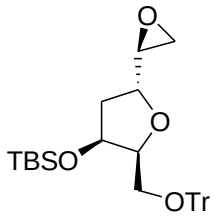


(5*S*,6*R*)-2,3-Dihydroxy-5,6-epoxy-7-benzenesulfonyl-1-triphenylmethylmethoxyheptane (11) To a stirring 10:10:1 solution of t-BuOH : H_2O : acetone (11 ml, 11 ml, 1.1 ml) was added **10** (0.751 g, 1.43 mmol). The flask was cooled to 0 °C, followed by addition of AD-mix α (2.86 g). After 15 minutes of stirring $CH_3SO_2NH_2$ (166.4 mg, 1.75 mmol) was added. The reaction was then allowed to slowly return to room temperature. After 3 days, 6 hours, and 35 minutes, $NaHSO_4$ (2.38 g, 19.82 mmol) was added to the reaction mixture. After an additional 1 hour of stirring, the reaction mixture was extracted ethyl acetate (3 × 50 ml). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was taken directly to the next step. TLC R_f = 0.09 (50% MTBE/PE).

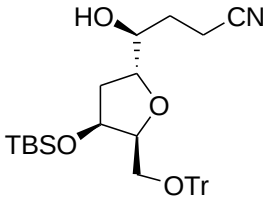


(2*S*,3*S*,5*R*)-5-((*S*)-Oxiran-2-yl)-2-(trityloxymethyl)-tetrahydrofuran-3-ol

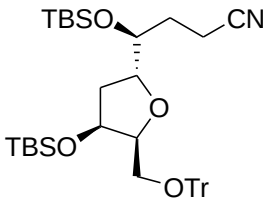
(3) To a stirring solution of crude **11** in methanol (25 ml) was added K_2CO_3 (0.601 g, 4.35 mmol) at 0 °C. The reaction was maintained at 0 °C for 130 minutes, then brought to room temperature for 80 minutes. The reaction was then brought back down to 0 °C for another 80 minutes before being extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 – 50% MTBE/PE) afforded the title as white crystals (323.5 mg, 0.884 mmol, 62% from **10**). TLC R_f = 0.28 (50% MTBE/PE); ^{1}H NMR (400 MHz) δ 7.36 (m, 6 H), 7.16-7.26 (m, 9 H), 4.50 (m, 1 H), 4.22 (m, 1 H), 4.08 (m, 1 H), 3.42 (dd, 1 H), 3.24 (dd, 1 H), 3.02 (m, 1 H), 2.72 (m, 1 H), 2.49 (dd, 1 H), 2.41 (d, 1 H), 1.98 (ddd, 1 H), 1.87 (m 1 H); HRMS *m/z* calcd. for $C_{26}H_{26}O_4Na$ (M+Na), 425.1729; found 425.1722.



tert-Butyldimethyl((2*S*,3*S*,5*R*)-5-((*S*)-oxiran-2-yl)-2-(trityloxymethyl)-tetrahydrofuran-3-yloxy)silane (26) To a stirring solution of **3** in CH_2Cl_2 (272.2 mg, 0.744 mmol in 3 ml) were added imidazole (355 mg, 5.21 mmol), TBSCl (449 mg, 2.98 mmol), and DMAP (14.5 mg, 0.119 mmol) at room temperature. The reaction was stirred for 1 hour 50 minutes before being quenched with distilled water (10 ml). The reaction mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (100% PE, 10% MTBE/PE, 20% MTBE/PE) afforded the title compound as a yellow oil (373.2 mg, 0.723 mmol, 97%). TLC R_f = 0.56 (30% MTBE/PE); ^{1}H NMR (400 MHz) δ 7.34-7.37 (m, 6 H), 7.09-7.20 (m, 9 H), 4.29 (m, 1H), 4.08 (q, 1 H), 3.95 (q, 1 H), 3.25 (m, 1 H), 2.96-3.05 (m, 2 H), 2.72 (m, 1 H), 2.49 (m, 1 H), 1.79-1.81 (m, 2 H), 0.60 (s, 9 H), -0.14 (s, 3 H), -0.28 (s, 3 H).

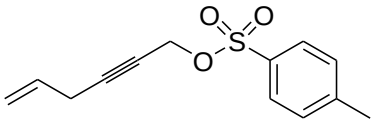


(*S*)-4-((2*R*,4*S*,5*S*)-4-(tert-Butyldimethylsilyloxy)-5-(trityloxymethyl)-tetrahydrofuran-2-yl)-4-hydroxybutanenitrile (27) To a stirring solution of CH_3CN (0.04 ml, 0.766 mmol) in THF (0.10 ml) at -78 °C under an argon atmosphere (balloon) was added 2.47 M *n*-BuLi (0.31 ml) by syringe. The reaction was stirred at -78 °C for 1.5 hours. To this mixture was added **26** (157 mg, 0.304 mmol in 0.15 ml THF) by syringe over a period of 10 minutes. The reaction stirred at -78 °C for 1 hour, then was allowed to warm to 0 °C. After 30 minutes at this temperature, the reaction was quenched with distilled water (5 ml) and extracted with ethyl acetate (3 × 40 ml). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was carried on to the next step. TLC R_f = 0.52 (50% MTBE/PE); ^{1}H NMR (400 MHz) δ 7.49-7.52 (m, 6 H), 7.24-7.35 (m, 9 H), 4.39 (s, 1 H), 4.14-4.18 (m, 2 H), 3.98 (m, 1 H), 3.39-3.43 (m, 1 H), 3.14-3.17 (dd, 1 H), 2.62-2.50 (m, 2 H), 1.96-2.03 (m, 1 H), 1.80-1.88 (m, 1 H), 1.61-1.77 (m, 2 H), 1.30 (1 H), 0.75 (s, 9 H), -0.04 (s, 3 H), -0.18 (s, 3 H); ^{13}C NMR (100 MHz) δ u: 144.2, 119.7, 86.9, 64.1, 35.3, 28.4, 17.9, 14.4, d: 128.8, 127.8, 126.9, 83.1, 80.1, 73.1, 70.3, 25.7, -4.8, -5.3; IR (film) 3447 broad, 3061, 2350, 2245, 1714, 1253 cm^{-1}.

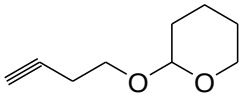


(*S*)-4-(tert-Butyldimethylsilyloxy)-4-((2*R*,4*S*,5*S*)-4-(tert-butyldimethylsilyloxy)-5-(trityloxymethyl)-tetrahydrofuran-2-yl)butanenitrile (28) To a stirring solution of crude **27** in dry CH_2Cl_2 (2.17 ml), were added TBSCl (213 mg. 1.41 mmol), imidazole (134 mg, 1.97 mmol), and DMAP (6.9 mg, 0.056 mmol). After stirring for 3 hours, the reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 × 50 ml). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (100% PE, 6% MTBE/PE, 23.5% MTBE/PE) afforded the title compound as a yellow oil (123.4 mg, 0.1844 mmol, 61% from **26**). TLC R_f = 0.81 (50% MTBE/PE); ^{1}H NMR (400 MHz) δ 7.46 (m, 6 H), 7.18-7.30 (m, 9 H), 4.32 (m, 1 H), 4.13 (m, 1 H), 4.02 (m, 1 H), 3.92 (m, 1 H), 3.31 (dd, 1 H), 3.04 (dd, 1 H), 2.47 (m, 2 H), 1.72-1.95 (m, 4 H), 0.91 (s, 9 H), 0.70 (s, 9 H), 0.17 (s, 3 H), 0.14 (s, 3 H), -0.06 (s, 3 H), -0.20 (s, 3 H); IR (film) 2248, 1598, 1448, 1254 cm^{-1}; HRMS *m/z* calcd. for $C_{40}H_{57}NO_4Si_2Na$ (M+Na), 694.3724; found 694.3707.

Hex-5-en-2-yn-1-ol To a mixture of finely ground magnesium turnings in THF (2.6 g, 107 mmol in 10 ml) was added a solution of ethyl bromide in THF (11.66 g, 107 mmol in 10 ml) dropwise. This was allowed to stir until most of the magnesium was consumed (~20 minutes). The reaction was chilled to 0 °C, then propargyl alcohol in THF (3.0 g, 54 mmol in 35 ml) was added dropwise. The reaction was then heated to 50 °C for 30 minutes, then cooled to 0 °C again. At this point, addition of $CuBr{\cdot}Me_2S$ (0.88 g, 4.28 mmol) was followed by dropwise addition of allyl bromide (7.83 g, 64.2 mmol). The reaction was allowed to stir at 0 °C for 5 hours. The reaction was quenched with 10 ml H_2O, 50 ml sat. aq. NH_4Cl, then 8 ml HCl (3 M). After extraction with Et_2O, the combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Bulb-to-bulb distillation at 89 °C afforded the title compound as a clear liquid contaminated with some impurities (3.95 g total, ^{1}H NMR indicates 86% purity: 3.4 g product, 35 mmol, ~66% yield). TLC R_f = 0.37 (30% MTBE/PE); ^{1}H NMR (400 MHz) δ 5.8-5.9 (m, 1 H) compared to 6.0 (m, 0.16 H - impurity); ^{13}C NMR (100 MHz) δ u: 23.0, 50.9, 80.8, 82.6, 116.2, d: 132.3.

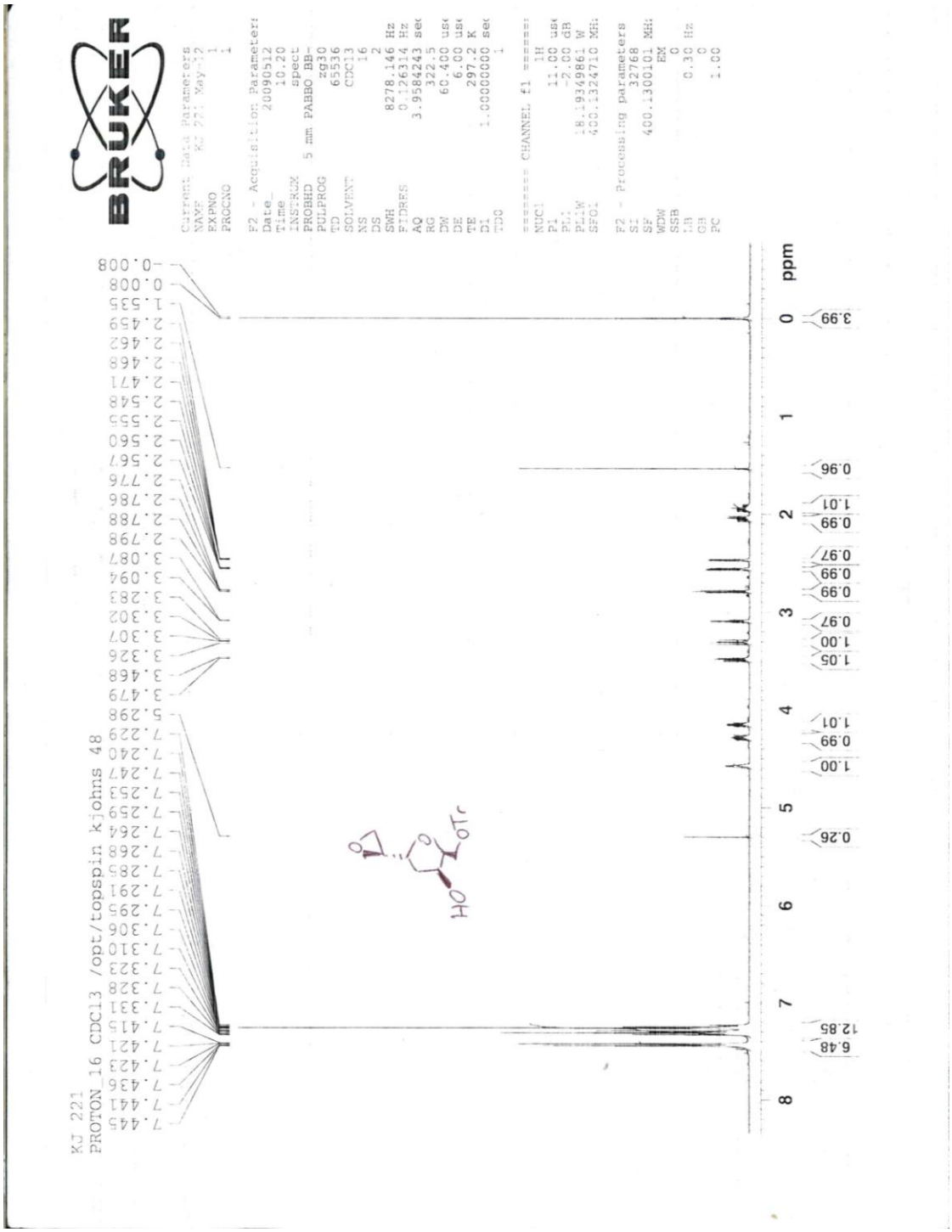


Hex-5-en-2-ynyl 4-methylbenzenesulfonate (15) To a stirring solution of KOH (2.96 g, 52.7 mmol) and tosyl chloride (8.11g, 42.5 mmol, impure) in Et_2O (114 ml) was added hex-5-en-2-yn-1-ol (3.4 g, 35 mmol) at -78 °C. After 4 hours and 45 minutes of stirring at this temperature, the reaction was quenched with sat. aq. NH_4Cl. The reaction mixture was extracted with Et_2O (3 × 50 ml). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5-15% MTBE/PE) afforded the title compound as a cloudy oil (868 mg, 3.47 mmol, 10%). TLC R_f = 0.53 (30% MTBE/PE); ^{1}H NMR (400 MHz) δ 2.45 (s, 3 H), 2.87 (m, 2 H), 4.75 (t, 2 H), 5.05-5.29 (m, 2 H), 5.60-5.78 (m, 1 H), 7.38 (d, 2 H), 7.78 (d, 2 H); ^{13}C NMR (100 MHz) δ u: 22.9, 58.5, 74.2, 86.9, 116.6, 133.3, 144.9, d: 21.6, 128.5, 129.5, 131.2.



2-(But-3-ynyloxy)-tetrahydro-2H-pyran (16) To a stirring solution of 2,3-dihydropyran in CH_2Cl_2 (28.78 g, 342 mmol in 134 ml) was added 3-butyn-1-ol (11.26 g, 161 mmol) and p-toluenesulfonic acid monohydrate (3.71 g, 19.5 mmol) at 0 °C. The reaction stirred at 0 °C for 12 hours before being quenched with sat. aq. $NaHCO_3$.

After extraction with CH_2Cl_2, the combined organic fractions were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Bulb-to-bulb distillation at 85-90 °C afforded the title compound as a clear liquid (19.37 g, 125.8 mmol, 79%). TLC R_f = 0.64 (30% MTBE/PE); ^{13}C NMR (100 MHz) δ u: 19.5, 19.9, 25.4, 30.7, 62.2, 65.5, 69.2, 81.4, d: 98.7.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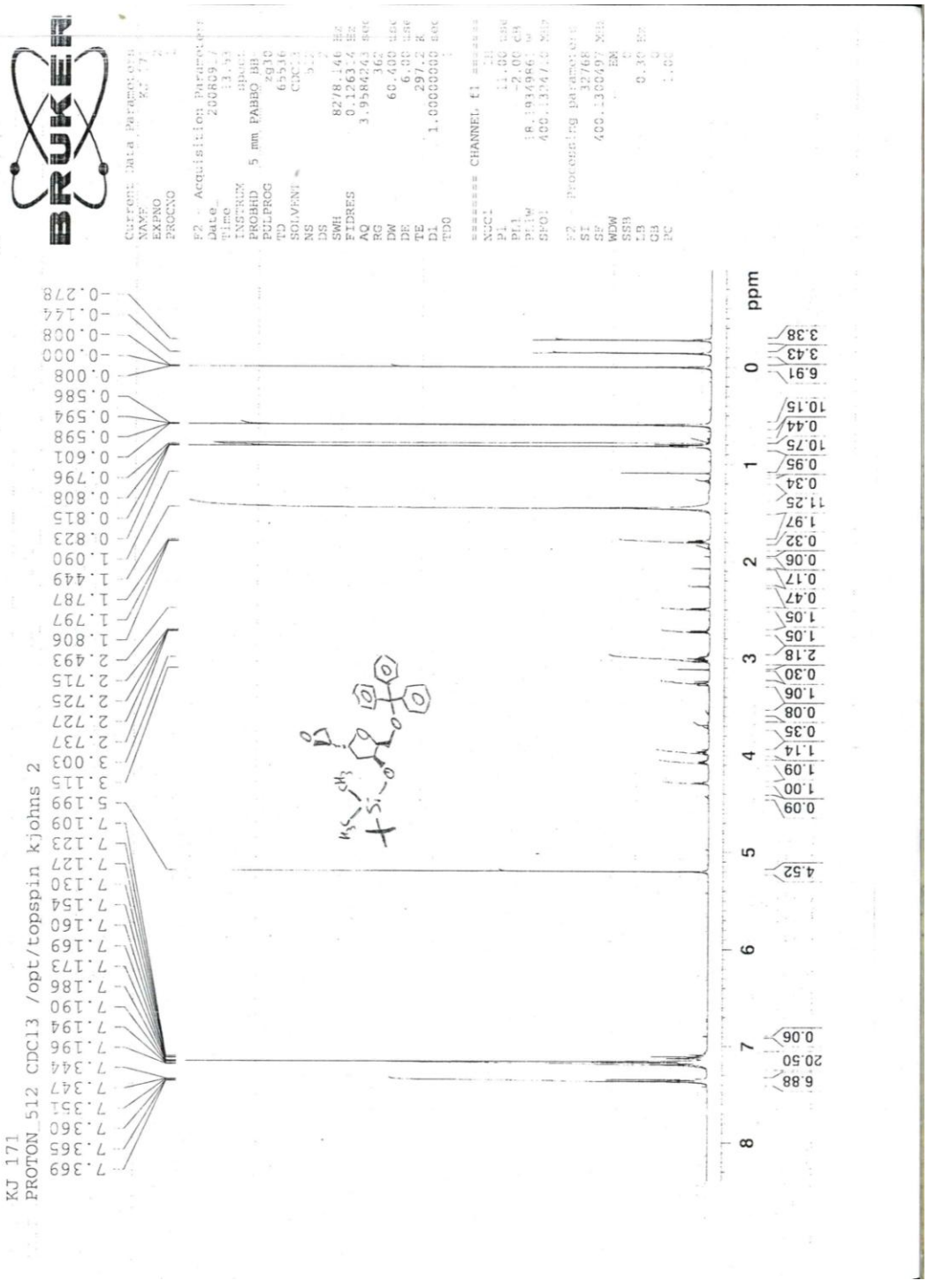
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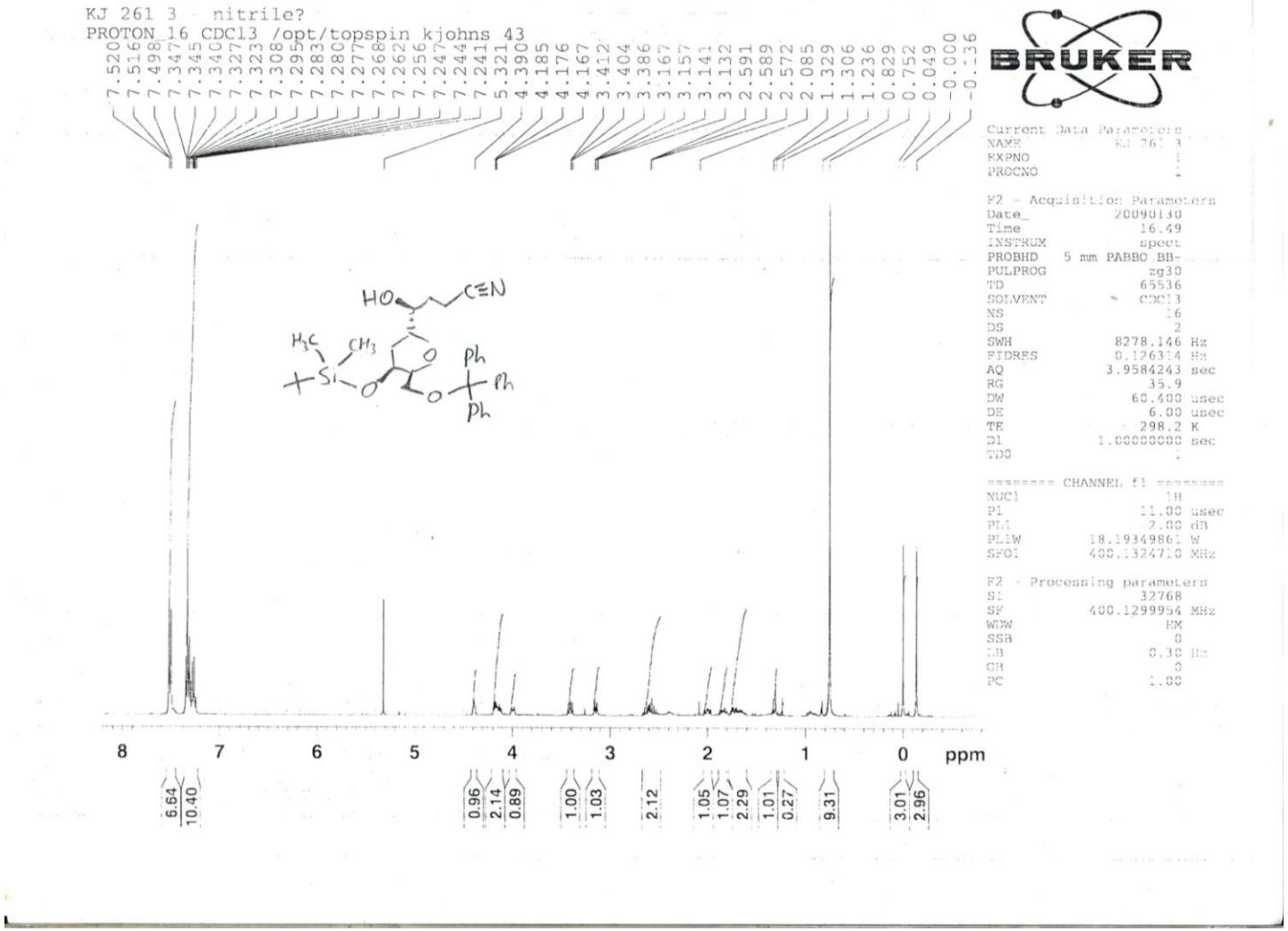
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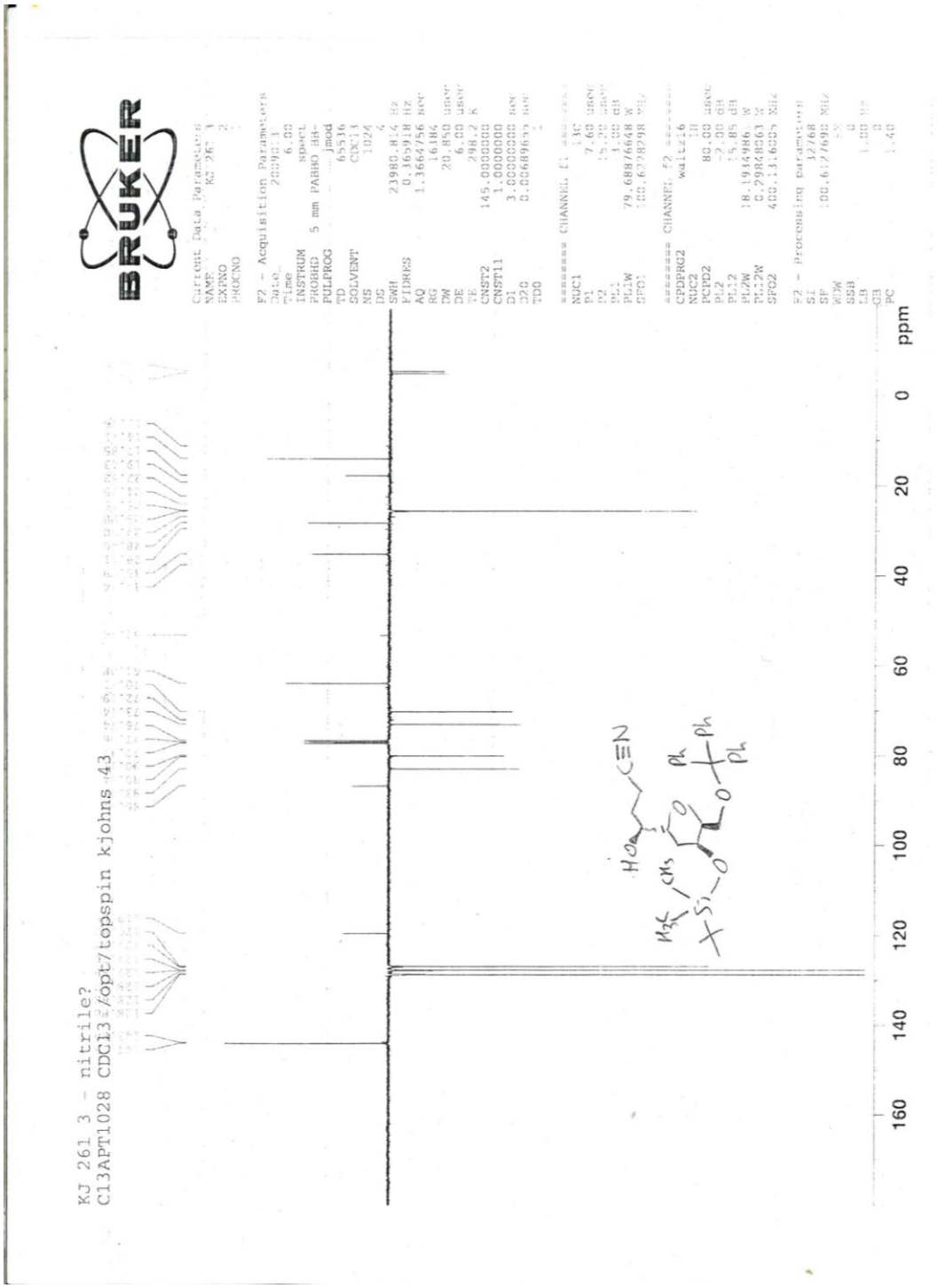
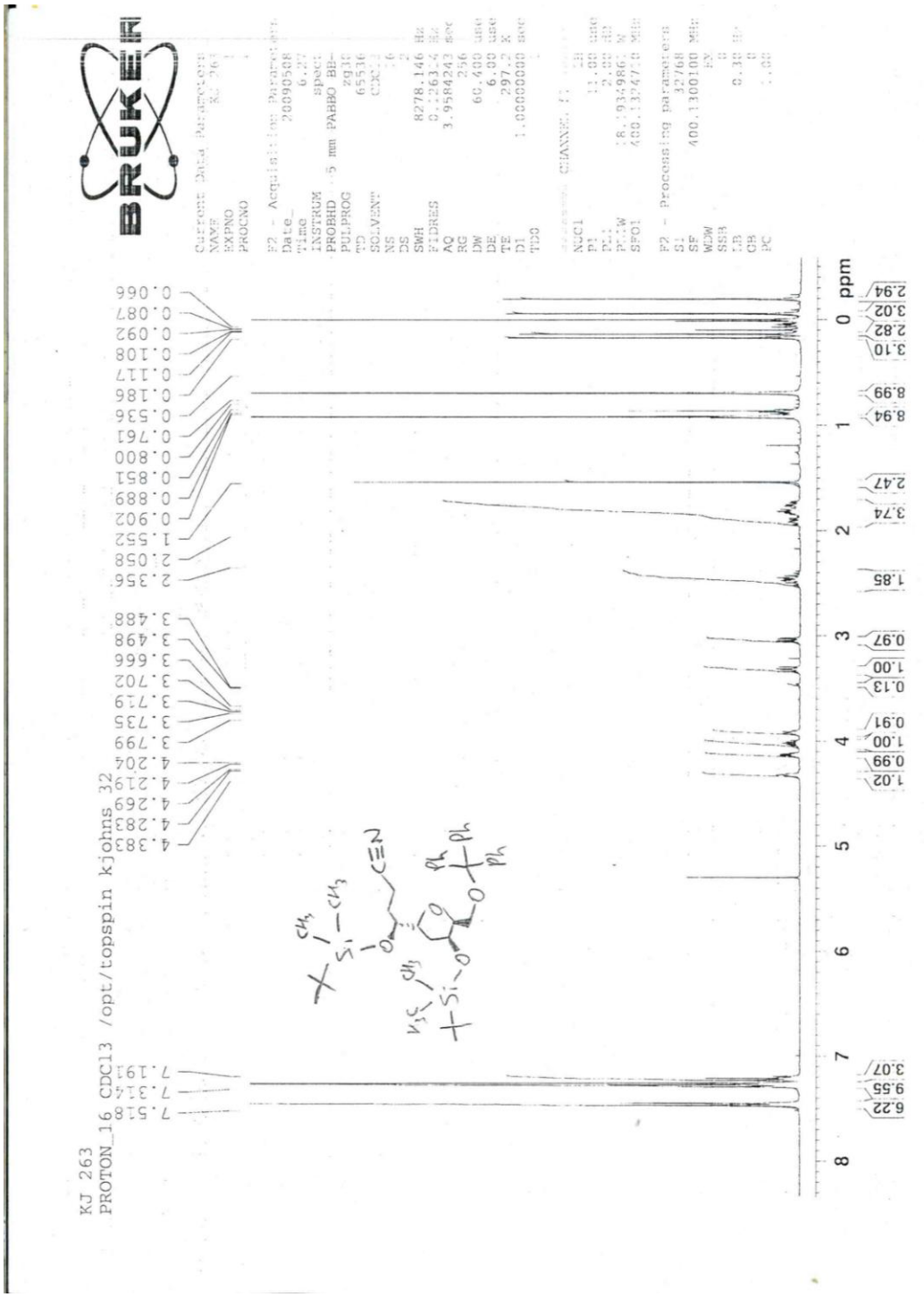
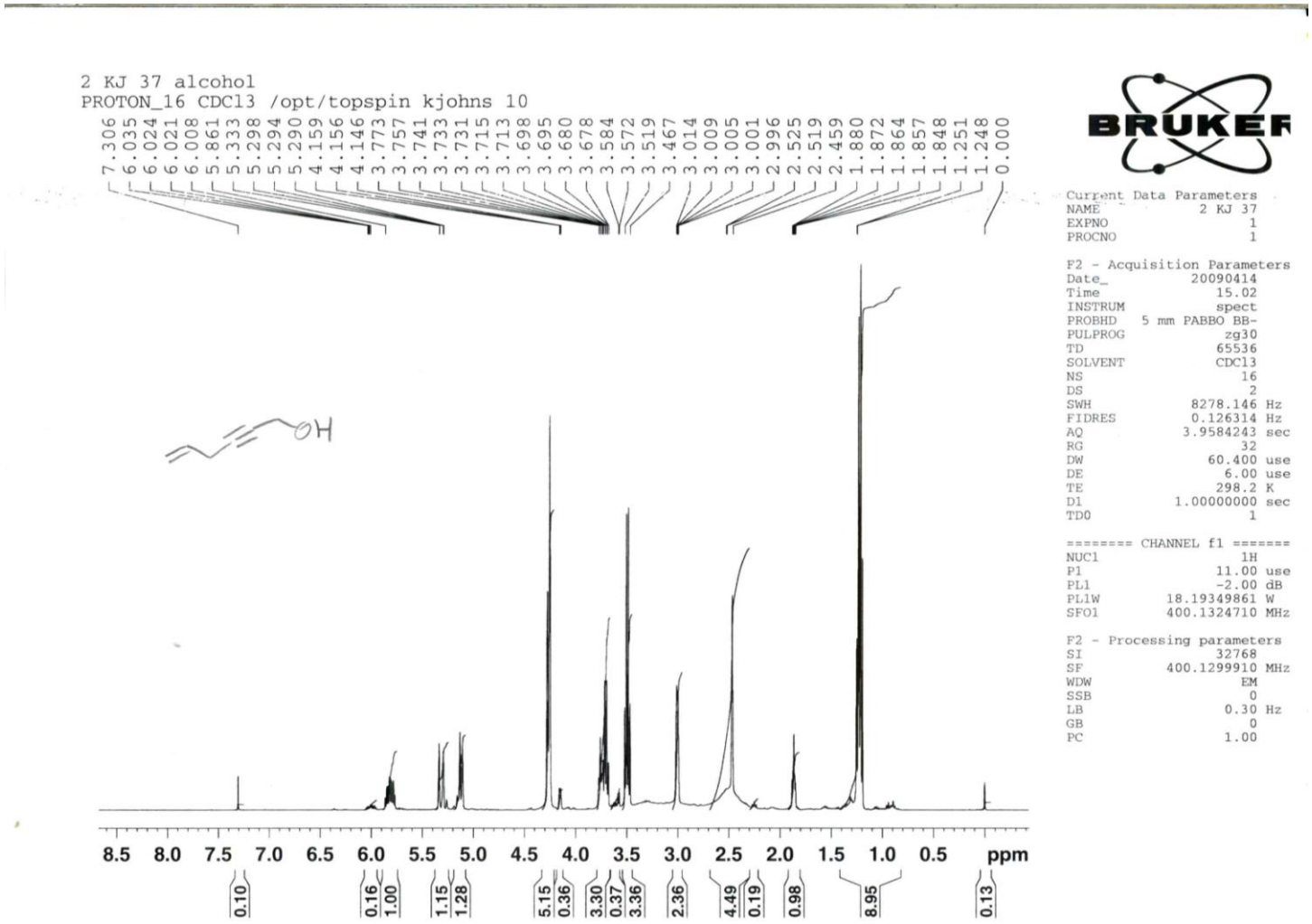
7.516
7.498
7.347
7.345
7.340
7.327
7.323
7.308
7.295
7.283
7.280
7.277
7.268
7.262
7.256
7.247
7.244
7.241
5.321
4.390
4.185
4.176
4.167
3.412
3.404
3.386
3.167
3.157
3.141
3.132
2.591
2.589
2.572
2.085
1.329
1.306
1.236
0.829
0.752
0.049
-0.000
-0.136
HO
C≡N
H3C
CH3
Si
O
Ph
Ph
Ph
8
7
6
5
4
3
2
1
0
ppm
6.64
10.40
0.96
2.14
0.89
1.00
1.03
2.12
1.05
1.07
2.29
1.01
0.27
9.31
3.01
2.96
BRUKER
Current Data Parameters
NAME KJ 261 3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090130
Time 16.49
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 35.9
DW 60.400 usec
DE 6.00 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 11.00 usec
PL1 2.00 dB
PL1W 18.19349861 W
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1299954 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


KJ 261 3 - nitrile?
C13APT1028 CDCl3 /opt/topspin kjohns 43
BRUKER
160
140
120
100
80
60
40
20
0
ppm


KJ 263
PROTON_16 CDCl3 /opt/topspin kjohns 32
ppm



BRUKER

Current Data Parameters

NAME	2 KJ 37
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

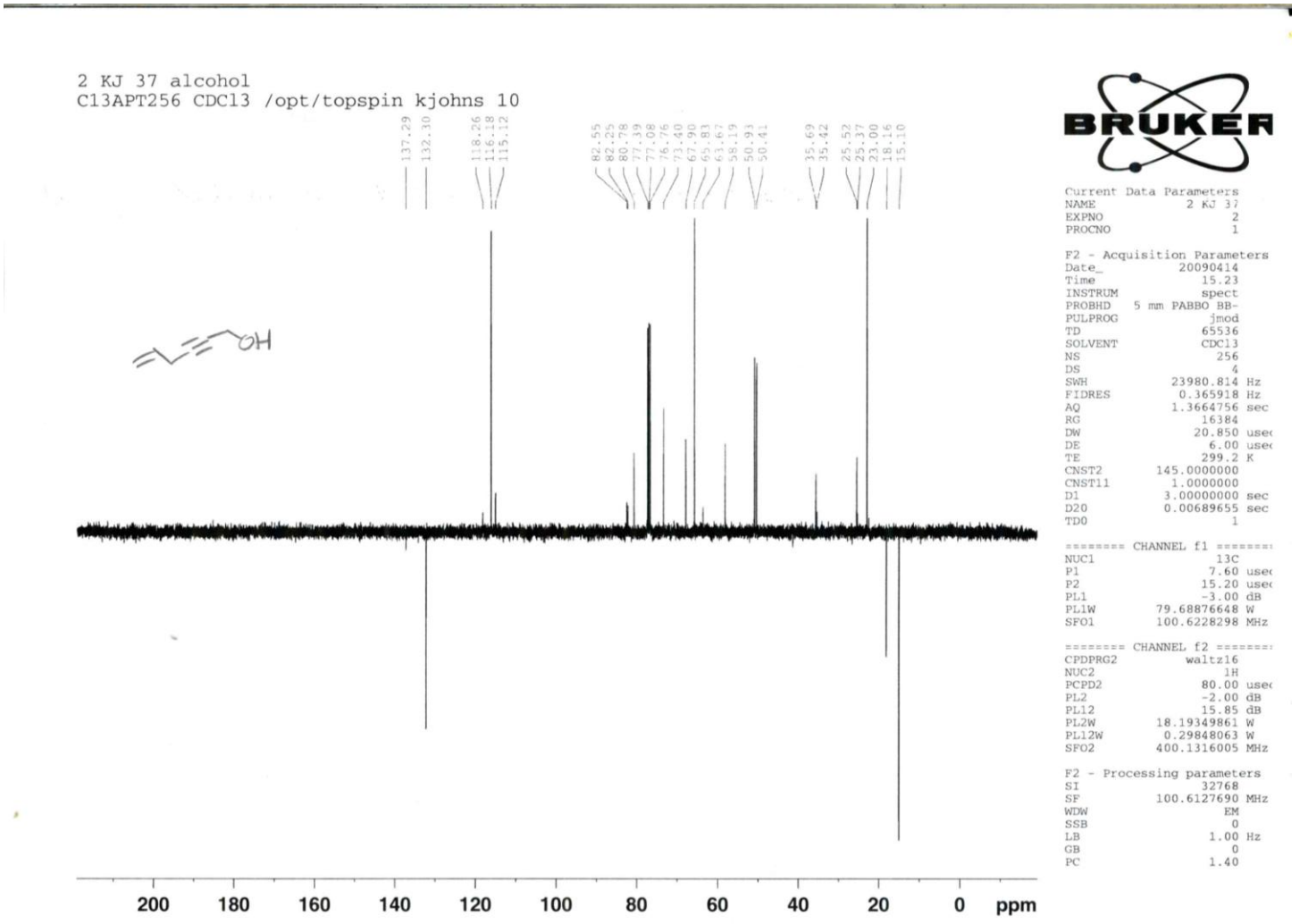
Date_	20090414
Time	15.02
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	32
DW	60.400 use
DE	6.00 use
TE	298.2 K
D1	1.00000000 sec
TD0	1

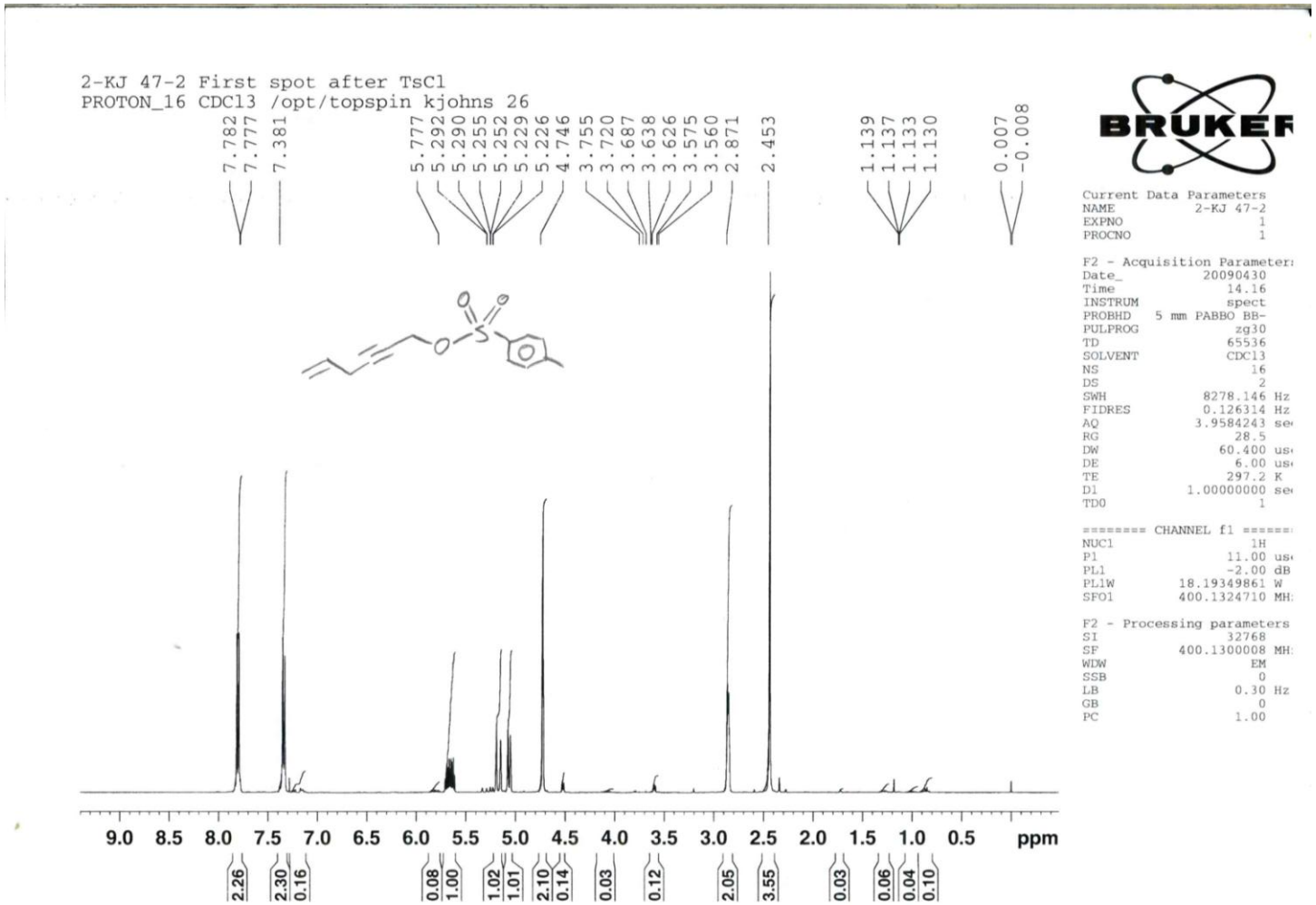
======== CHANNEL f1 =======

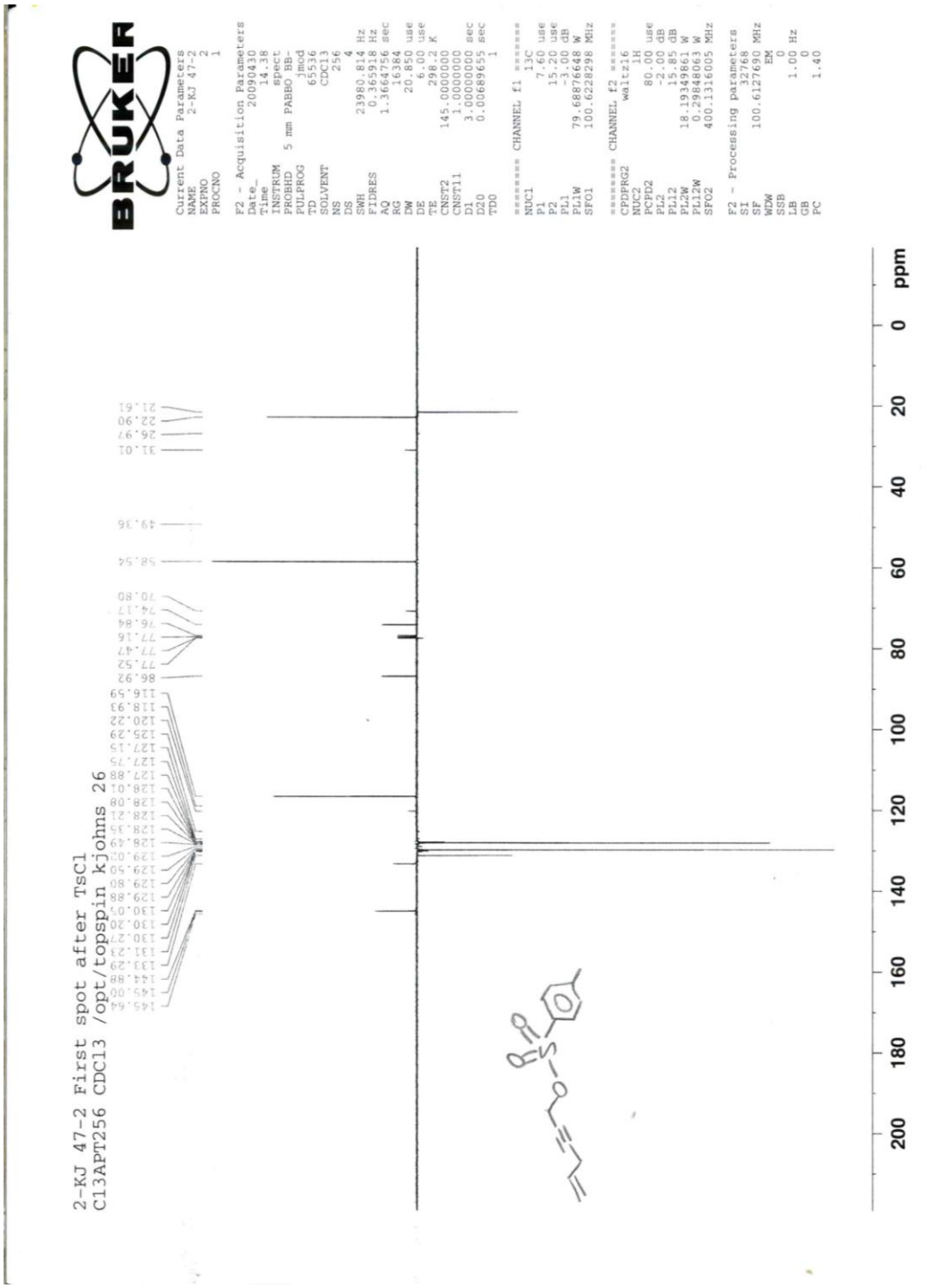
NUC1	1H
P1	11.00 use
PL1	-2.00 dB
PL1W	18.19349861 W
SFO1	400.1324710 MHz

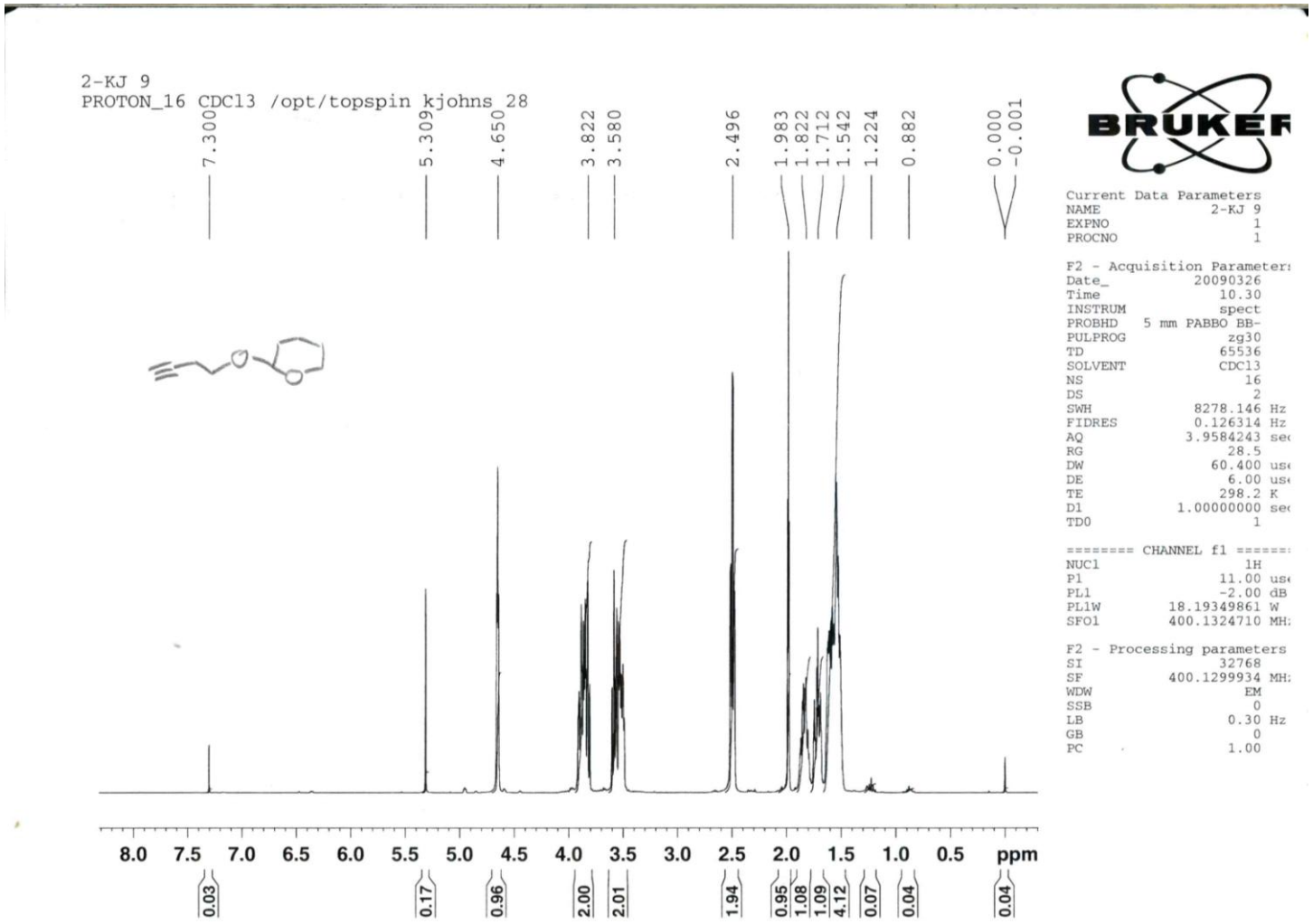
F2 - Processing parameters

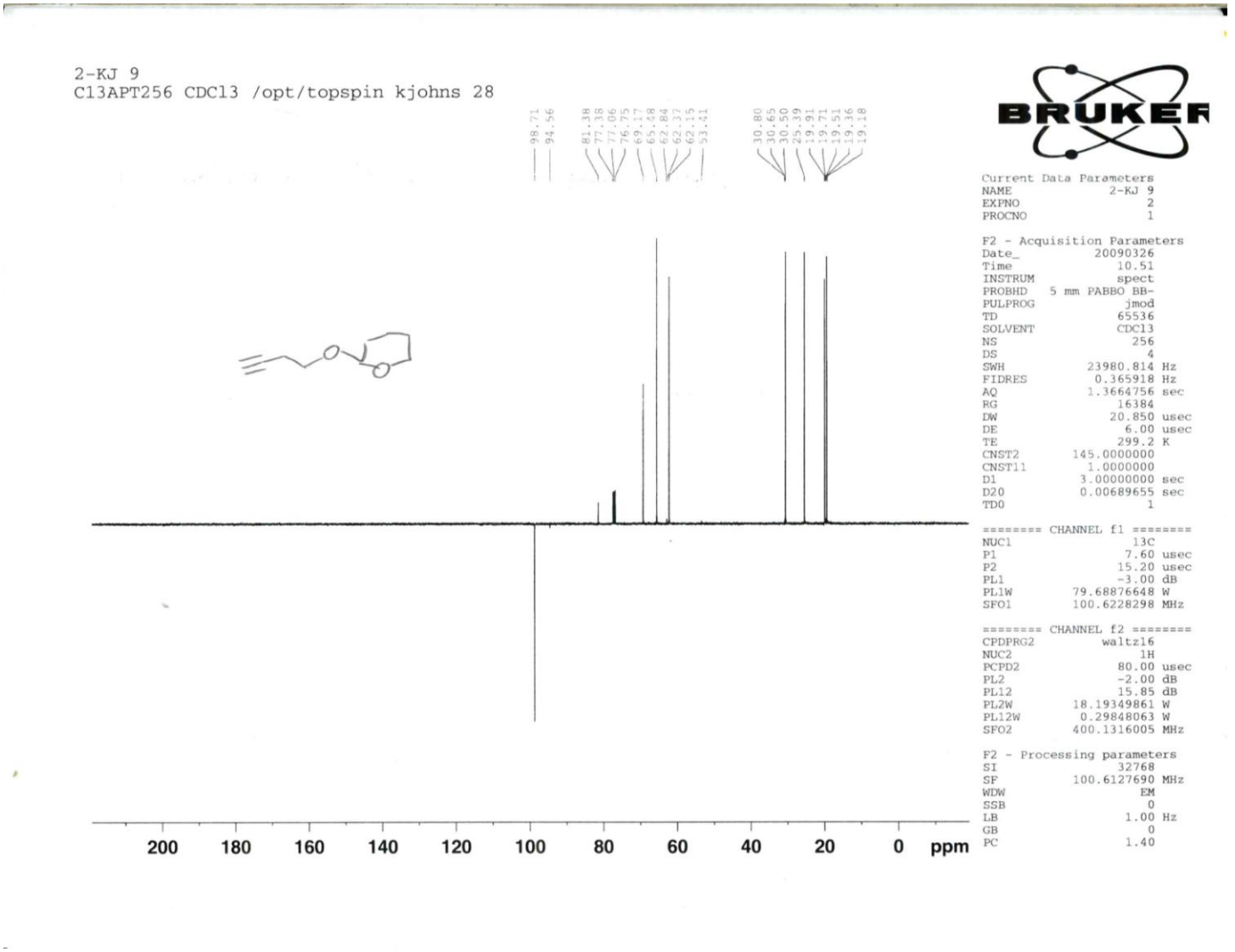
SI	32768
SF	400.1299910 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00


2 KJ 37 alcohol
C13APT256 CDCl3 /opt/topspin kjohns 10
137.29
132.30
118.26
116.18
115.12
82.55
82.25
80.78
77.39
77.08
76.76
73.40
67.90
65.83
63.67
58.19
50.93
50.41
35.69
35.42
25.52
25.37
23.00
18.16
15.10
OH
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
Current Data Parameters
NAME 2 KJ 37
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090414
Time 15.23
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 16384
DW 20.850 use
DE 6.00 use
TE 299.2 K
CNST2 145.0000000
CNST11 1.0000000
D1 3.00000000 sec
D20 0.00689655 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 7.60 use
P2 15.20 use
PL1 -3.00 dB
PL1W 79.68876648 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 use
PL2 -2.00 dB
PL12 15.85 dB
PL2W 18.19349861 W
PL12W 0.29848063 W
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


2-KJ 47-2 First spot after TsCl
PROTON_16 CDCl3 /opt/topspin kjohns 26
7.782
7.777
7.381
5.777
5.292
5.290
5.255
5.252
5.229
5.226
4.746
3.755
3.720
3.687
3.638
3.626
3.575
3.560
2.871
2.453
1.139
1.137
1.133
1.130
0.007
-0.008
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.26
2.30
0.16
0.08
1.00
1.02
1.01
2.10
0.14
0.03
0.12
2.05
3.55
0.03
0.06
0.04
0.10
BRUKER
Current Data Parameters
NAME 2-KJ 47-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameter
Date_ 20090430
Time 14.16
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 se
RG 28.5
DW 60.400 us
DE 6.00 us
TE 297.2 K
D1 1.00000000 se
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 11.00 us
PL1 -2.00 dB
PL1W 18.19349861 W
SFO1 400.1324710 MH
F2 - Processing parameters
SI 32768
SF 400.1300008 MH
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


2-KJ 47-2 First spot after TsCl
C13APT256 CDCl3 /opt/topspin kjohns 26
Current Data Parameters
NAME 2-KJ 47-2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090430
Time 14.38
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 16384
DW 20.850 use
DE 6.00 use
TE 298.2 K
CNST2 145.0000000
CNST11 1.0000000
D1 3.00000000 sec
D20 0.00689655 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 7.60 use
P2 15.20 use
PL1 3.00 dB
PL1W 79.68876648 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 use
PL2 -2.00 dB
PL12 15.85 dB
PL2W 18.19349861 W
PL12W 0.29848063 W
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
21.61
22.90
26.97
31.01
49.36
58.54
70.80
74.17
76.84
77.16
77.47
77.52
86.92
116.59
118.93
120.22
125.29
127.15
127.75
127.88
128.01
128.08
128.21
128.35
128.49
129.07
129.50
129.80
129.88
130.05
130.20
130.23
131.23
133.29
144.88
145.08
145.64
200
180
160
140
120
100
80
60
40
20
0
ppm


2-KJ 9
PROTON_16 CDCl3 /opt/topspin kjohns 28
7.300
5.309
4.650
3.822
3.580
2.496
1.983
1.822
1.712
1.542
1.224
0.882
0.000
-0.001
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.03
0.17
0.96
2.00
2.01
1.94
0.95
1.08
1.09
4.12
0.07
0.04
0.04
BRUKER
Current Data Parameters
NAME 2-KJ 9
EXPNO 1
PROCNO 1
F2 - Acquisition Parameter
Date_ 20090326
Time 10.30
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 se
RG 28.5
DW 60.400 us
DE 6.00 us
TE 298.2 K
D1 1.00000000 se
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 11.00 us
PL1 -2.00 dB
PL1W 18.19349861 W
SFO1 400.1324710 MH
F2 - Processing parameters
SI 32768
SF 400.1299934 MH
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


2-KJ 9
C13APT256 CDCl3 /opt/topspin kjohns 28
98.71
94.56
81.38
77.38
77.06
76.75
69.17
69.18
62.84
62.37
62.15
53.41
30.80
30.65
30.50
25.39
19.91
19.71
19.51
19.36
19.18
200
180
160
140
120
100
80
60
40
20
0
ppm
Current Data Parameters
NAME 2-KJ 9
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20090326
Time 10.51
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 16384
DW 20.850 usec
DE 6.00 usec
TE 299.2 K
CNST2 145.0000000
CNST11 1.0000000
D1 3.00000000 sec
D20 0.00689655 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 7.60 usec
P2 15.20 usec
PL1 -3.00 dB
PL1W 79.68876648 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 15.85 dB
PL2W 18.19349861 W
PL12W 0.29848063 W
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40