AN ABSTRACT OF THE THESIS OF

Patrick Salvo for the degree of Master of Science in Chemistry presented on June 12, 2015.

Title: Progress Towards the Total Synthesis of Bazzanin K.

Abstract approved:

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Christopher M. Beaudry

Molecular chirality plays a critical role in chemistry, biology, and medicine. To study and better understand conformational chirality, it is necessary to obtain structurally interesting molecules that exhibit this form of chirality. Our lab utilizes total synthesis and methodological development to obtain conformationally chiral natural products of interest. We believe that bazzanin K is a chiral molecule although it lacks sp^3 hybridized stereocenters. To test this hypothesis, we set out to synthesize bazzanin K, separate the potential enantiomers, and measure the energy barrier of racemization. The progress towards the total synthesis of bazzanin K is described herein.

Progress Towards the Total Synthesis of Bazzanin K

by
Patrick Salvo

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APPROVED:

Major Professor, representing Chemistry

Chair of the Department of Chemistry

Dean of the Graduate School

I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

Patrick Salvo, Author

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Progress Towards the Total Synthesis of Bazzanin K

Chapter 1: Introduction and background

1.1 Cyclophanes

Cyclophanes are a class of bridged aromatic compounds that have been of interest to organic chemists since their discovery in 1949. The original definition applied to compounds having two *p*-phenylene groups held face-to-face by alkyl bridges. This definition has been extended to include aromatic rings bridged by unsaturated carbon tethers and/or heteroatoms within the macrocyclic system.[1] These rigidified and highly strained macrocycles have inspired organic chemists to develop novel methods for synthesizing such unusual molecular structures.[2] The first cyclophanes synthesized were [2.2]metacyclophane **1** and [2.2]paracyclophane **2**.[3,4] These simple cyclophanes were studied

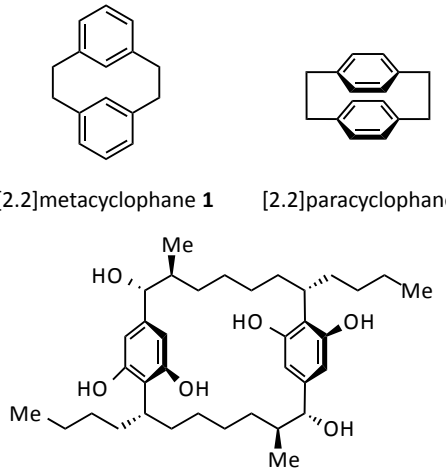
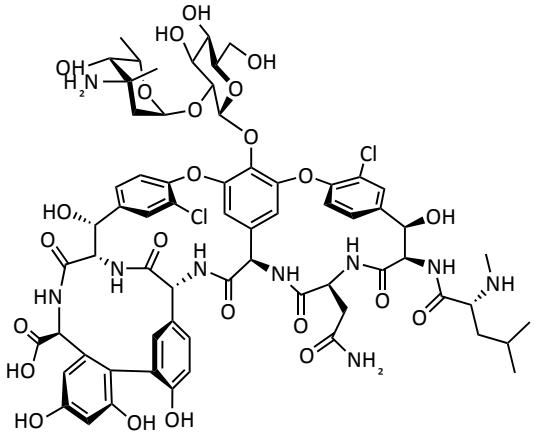


Figure 1.1 Metacyclophane, Paracyclophane, and Cyclindrocyclophane A

for their molecular strain and "bent and battered" benzene rings. The first cyclophane natural product to satisfy the original definition was cyclindrocyclophane A **3**, isolated in 1990.[5] The [7.7]paracyclophane architecture of cyclindrocyclophane A attracted significant interest from the synthetic community leading to a number of successful total syntheses.[6-8] However, under the expanded definition of cyclophanes exists a wealth of natural products that are intriguing not only for their structural complexity but also for the potent biological activity. Vancomycin (**4**) is a polycyclic cyclophane with potent antibacterial activity against Gram-positive bacteria. It is often referred to as the "antibiotic of last resort" against methicillin-resistant *Staphylococcus aureus* (MRSA).[9] The total syntheses of the vacomycin aglycon by the Nicolaou, Evans, and Boger groups represent great achievements in modern organic synthesis.[10-12]



vancomycin **4**

Figure 1.2 Vancomycin

1.2 Conformational Chirality

Molecular chirality plays a critical role in chemistry, biology, and medicine.[13] Molecules containing sp^3 hybridized stereocenters are readily identified as chiral molecules unless S-type symmetry exists. However, for molecules that are chiral due to restricted rotation of sigma bonds, or conformational chirality, there are no predictive methods available. In addition, experimental determination of chirality in molecules devoid of stereocenters is not trivial. Differentiating between a racemic mixture of enantiomers and an achiral molecule using experimental techniques can be challenging.

A long term goal of the Beaudry research group is to develop methods for predicting and understanding conformational chirality.[14] To this end, conformationally chiral natural products of interest will be obtained by total synthesis for stereochemical studies.

1.3 The Macrocyclic Bisbibenzyls

The macrocyclic bisbibenzyls are a class of approximately one hundred cyclophane natural products isolated from species of liverworts and other bryophytes.[15] Each member is biosynthesized from two molecules of lunularin (**5)** which undergo a series of oxidative couplings to form biphenyl or diaryl ether linkages between the aromatic rings. Marchantin A (**6)**, isoriccardin C (**7)**, and bazzanin S (**8)** are representative of the "O—O", "C—O", and

"C–C" type connectivity found among the macrocyclic bisbibenzyls, respectively.

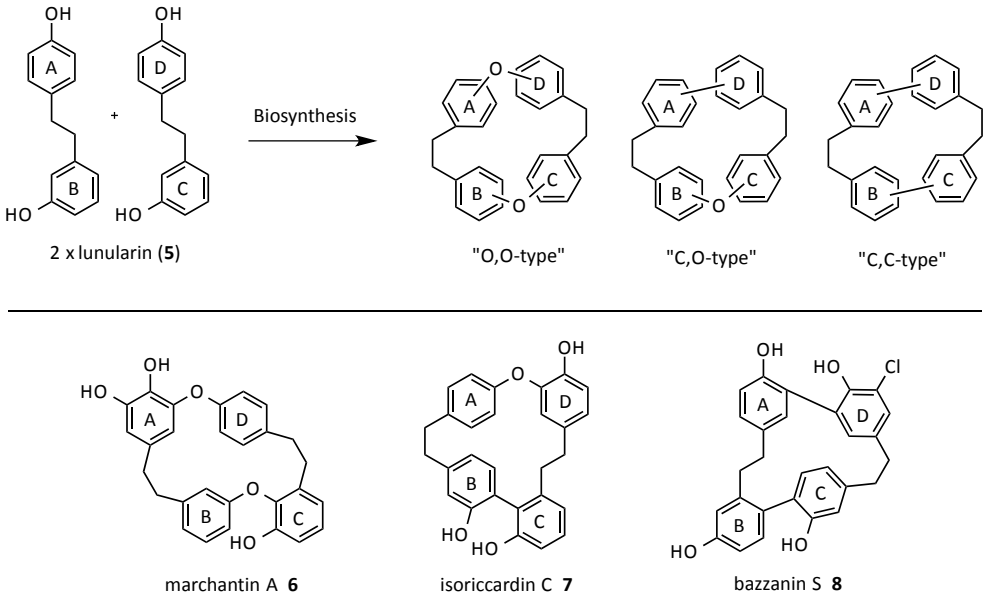


Figure 1.3 Biosynthesis of Macrocyclic Bisbibenzyls; Marchantin A, Isoriccardin C, and Bazzanin S.

This class of natural products is especially interesting when further oxidative couplings occur in the biosynthesis to form new ring systems within the macrocyclic structure. Asterelin A **9** was isolated from the liverwort species *Asterella angusta* and has been shown to exhibit anti-fungal activity.[16] Asterelin A contains a biphenyl and diaryl ether linkage between the B and C rings to form a substituted dibenzofuran within the macrocycle. Cavicularin **10** displays an additional biphenyl bond between the C and D rings forming a dihydrophenanthrene moiety. This intriguing structure causes significant molecular strain evidenced in the x-ray crystallography study where the A ring is distorted 15 degrees from planarity.[17] Cavicularin is a conformationally chiral

molecule and exists as a single enantiomer in nature. Bazzanin K (**11)** was isolated from the liverwort species *Bazzania trilobata* in 1997.[18] Bazzanin K contains an additional biphenyl bond between the C and D rings and the bibenzyl bond is unsaturated forming a phenanthrene. In contrast to cavicularin, bazzanin K contains a biphenyl bond between the A and D ring and is classified as a "C—C" type macrocycle. Moreover, the B and D rings of bazzanin K contain aryl chlorides.

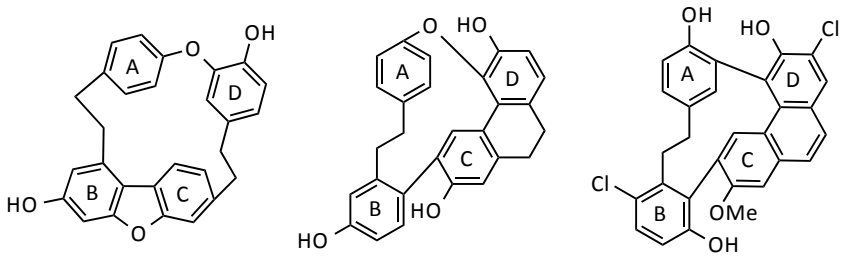


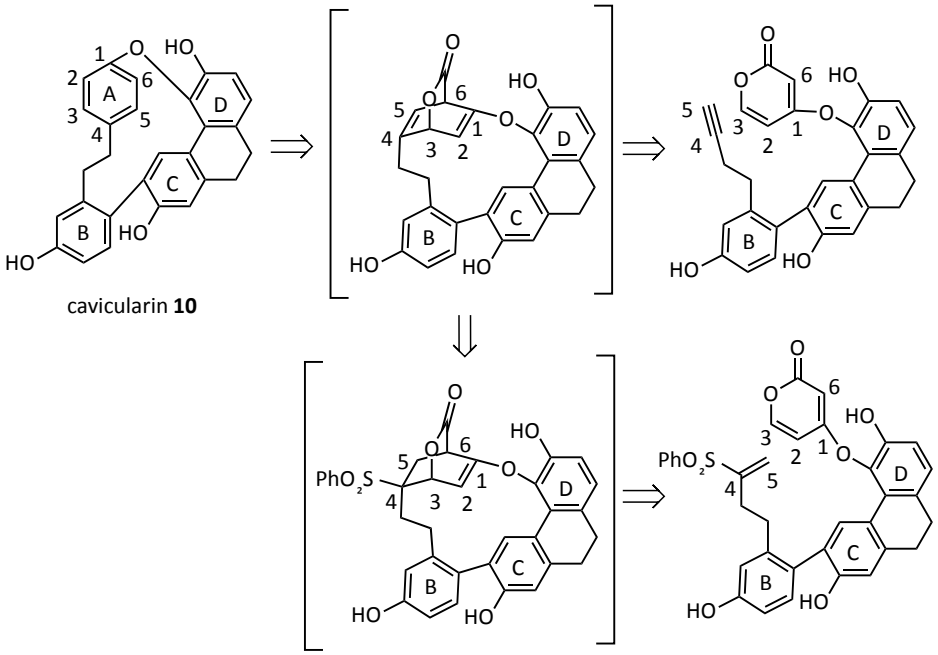
Figure 1.4 Asterelin A, Cavicularin, and Bazzanin K

Whether or not bazzanin K is a conformationally chiral molecule is yet to be determined. The isolation paper for bazzanin K reported an optical rotation of +180, indicating that bazzanin K is a chiral molecule which exists in an enantioenriched form. However, our group has demonstrated that optical rotation is not always a reliable method for identifying conformational chirality due to the possibility of impurities in the isolation sample giving rise to false positive values.[19] In the ^{1}H NMR spectrum of **11**, the geminal methylene protons are reported to be chemical shift inequivalent. This result indicates that the rigidified macrocyclic structure interconverts slowly on the NMR time scale. In combination with the structural similarities to cavicularin, we believe that bazzanin K

is a chiral molecule that exists in stable enantiomeric conformations. To test this hypothesis, we are currently working towards the total synthesis of bazzanin K.

1.4 The Total Synthesis of Cavicularin

Cavicularin has attracted significant interest from the synthetic community for its structural complexity and severe molecular strain. The total synthesis of cavicularin has been achieved by the groups of Harrowven, Baran, Fukuyama, Suzuki, and Beaudry.[20-24] The inspiration for our synthetic strategy towards bazzanin K draws heavily upon the elegant total synthesis of cavicularin completed by Peng Zhao and Chris Beaudry.

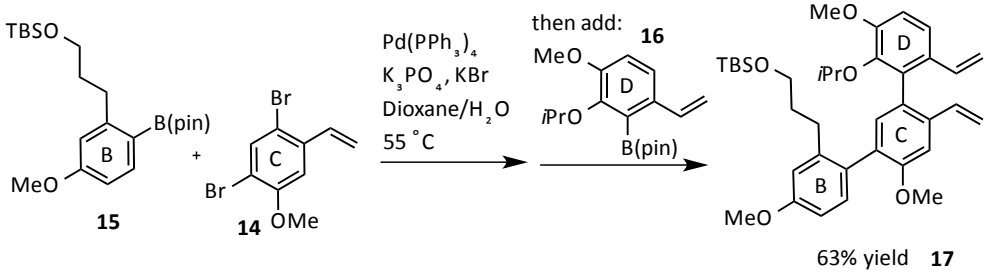


Scheme 1.1 Retrosynthesis of the cavicularin A ring

Zhao and Beaudry envisioned that the A ring of cavicularin could

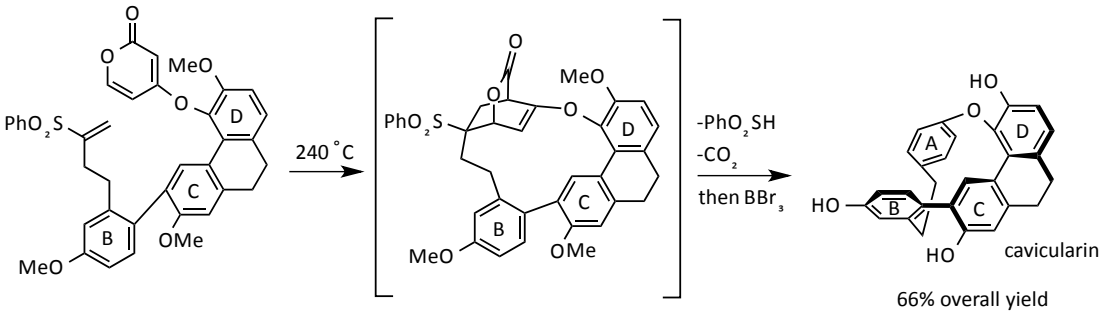
be constructed via an intramolecular Diels–Alder cascade between an α-pyrone and a terminal alkyne. In order to achieve the *para* substitution of the A ring, the nucleophilic carbon 6 of the pyrone must bond with the terminal carbon 5 of the alkyne in the initial [4+2] cycloaddition. To circumvent the issue of regioselectivity in the Diels–Alder event, an alkyne equivalent was employed, specifically, a vinyl sulfone. The vinyl sulfone serves as an electron deficient dienophile with the terminal carbon 5 being especially electrophilic to control the regioselectivity of the Diels–Alder cascade.

To access the Diels–Alder precursor, a double Suzuki coupling was developed. Zhao and Beaudry discovered that dibromostyrene **14** would preferentially couple with boronic esters to the bromine *ortho* to the methoxy group. The regioselectivity of dibromostyrene **14** led to the development of a one-pot, three-component Suzuki coupling. After completion of the initial Suzuki coupling by TLC analysis between dibromostyrene **14** and the B ring boronic ester **15**, the D ring boronic ester **16** was added to give the terphenyl **17** in good yield. Terphenyl **17** was then advanced to



Scheme 1.2 One-Pot, Three-Component Suzuki Coupling

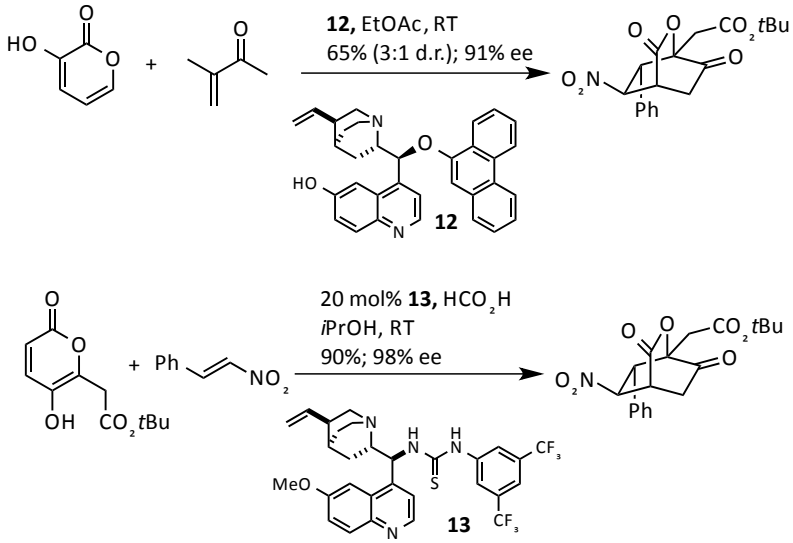
the Diels—Alder substrate to investigate the efficacy of this synthetic strategy.



Scheme 1.3 Intramolecular Diels—Alder Casade

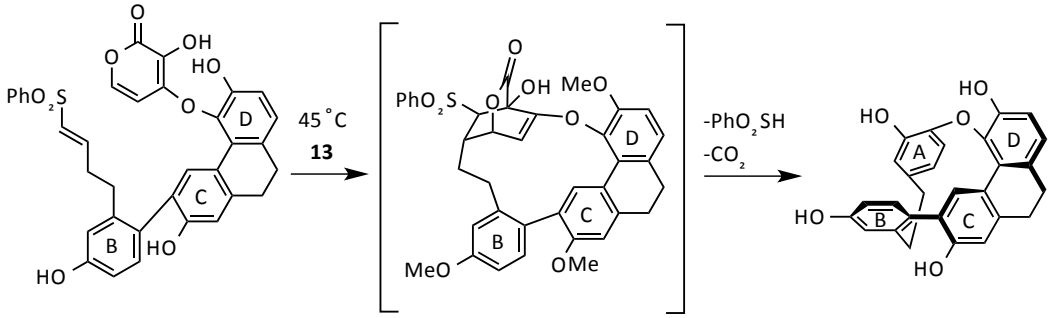
At 240 °C, the initial [4+2] cycloaddition occurs to give an oxabicyclo[2.2.2]octene with the aryl ether and the alkyl tether being in a 1,4-relationship. After loss of phenylsulfinic acid, a retro—Diels—Alder occurs to give the A ring with the desired *para* substitution observed in the natural product. With the development of this powerful strategy, Zhao and Beaudry next investigated the possibility of an enantioselective synthesis of cavicularin.

Enantioselective Diels—Alder reactions with α-pyrones are known in the literature but have never been used for the enantioselective synthesis of cyclophanes. Cinchona-based chiral catalysts have been used to control enantioselective Diels—Alder reactions involving hydroxypyrones with good selectivity.[25,26]



Scheme 1.4 Enantioselective Diels–Alder of Hydroxypyrones

To explore the efficacy of such catalysts, a 3-hydroxypyrone was installed on the substrate en route to cavicularin. It was discovered that the resulting 3,4-dioxygenated α-pyrone gave the wrong regiochemical outcome in the Diels–Alder event, leading exclusively to a *meta* substituted A ring which did not correspond to the natural product. By switching to a 1,2-disubstituted vinyl sulfone, the regiochemical outcome was corrected to achieve the desired *para* substitution. In the presence of the cinchona alkaloid derivative **13** at 45 °C, the Diels–Alder cascade yielded the desired macrocycle in 89:11 e.r. This discovery represents the first



Scheme 1.5 Enantioselective Intramolecular Diels–Alder Cascade

enantioselective intramolecular Diels–Alder reaction involving an α-pyrone.

The elegant total synthesis of cavicularin developed by Zhao and Beaudry has inspired us to pursue a similar strategy towards the total synthesis of bazzanin K.

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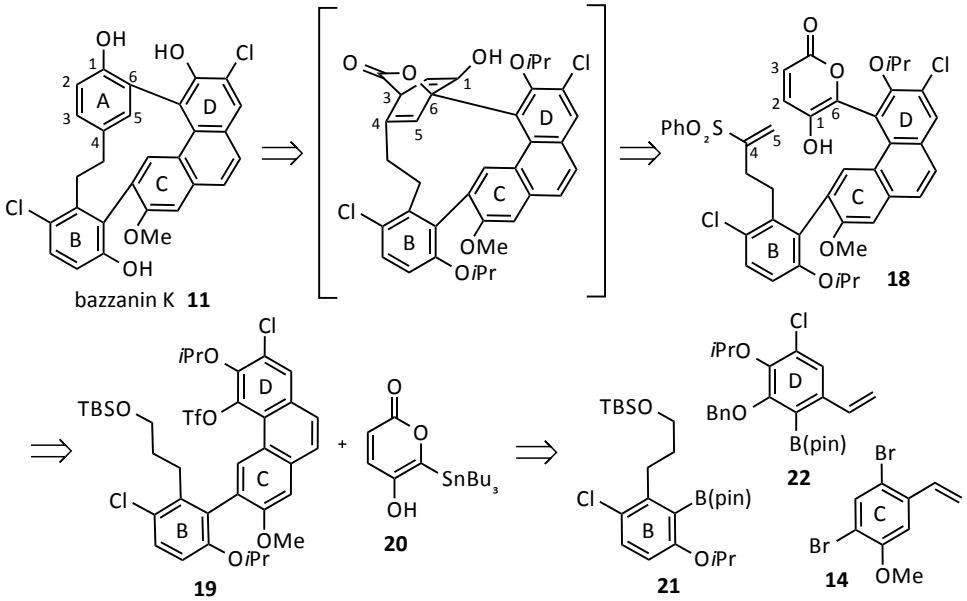
Chapter 2: Progress Towards the Total Synthesis of Bazzanin K: 1st Generation Approach

2.1 Retrosynthetic Analysis of Bazzanin K

Our retrosynthetic analysis of bazzanin K is inspired by that of our group's synthesis of cavicularin but there are significant differences between these intriguing natural products that makes the total synthesis of bazzanin K a more ambitious target.

The A ring of bazzanin K is a *meta*-substituted aromatic ring with respect to the alkyl tether and the biphenyl bond. This substitution pattern gives rise to a twelve membered macrocyle, two carbons smaller than that of cavicularin. The A ring will be accessed through a retro—Diels—Alder reaction from the



Scheme 2.1 Retrosynthetic Analysis of Bazzanin K

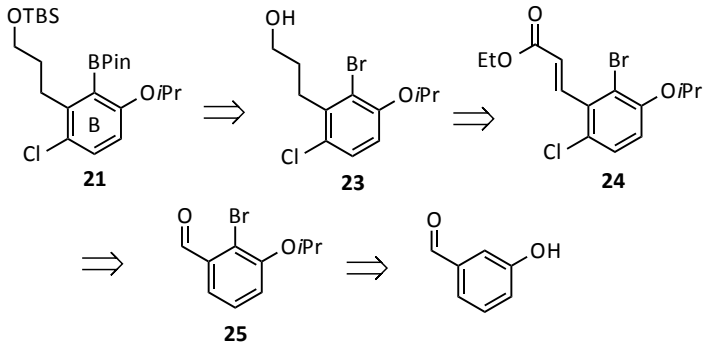
oxabicyclo[2.2.2]octene intermediate in which the alkyl tether and the D ring are in a 1,3-relationship. The bicyclic intermediate will be accessed through an intramolecular Diels–Alder reaction between the 5-hydroxypyrone and the vinyl sulfone substituents of compound **18**. It's worth noting that employing a 5-hydroxypyrone in the Diels–Alder cascade would set the correct functionality of the phenolic A ring and would also make an enantioselective variant possible with the use of the chincona-based chiral catalyst **13**. In contrast to cavicularin, bazzanin K has a biaryl carbon-carbon bond between the A and D rings and a phenol at carbon 1 of the A ring. Thus, we will introduce a 5-hydroxypyrone, via a Stille coupling between between aryl triflate **19** and pyrone-stannane **20**. The substituted phenanthrene moiety will be constructed using a double Suzuki cross coupling between aryl boronic esters **21** and **22** and dibromostyrene **14**.

*2.2 Retrosynthesis of Aryl Boronic Ester **21***

Aryl boronic ester **21** is *ortho,ortho*-disubstituted. Not only will this substitution pattern make the Suzuki couplings more hindered but it will also make installing the boronic ester a challenge. Boronic esters are commonly installed from the corresponding aryl bromide. Thus, finding an efficient protocol to perform a regioselective bromination is critical. In addition, aryl boronic ester **21** contains an aryl chloride. A regioselective chlorination will also have to be performed either before or after the bromination step. Regioselectively halogenating aromatics rings

with more than one type of halogen is not trivial. Additionally, issues of chemoselectivity may arise when trying to selectively react with bromine over chlorine in the installation of the boronic esters and in the Suzuki cross couplings.

We envisioned that boronic ester **21** could be accessed from the corresponding aryl bromide **23** after TBS protection of the primary alcohol. The propanol side chain could be obtained from the enone **24** which in turn could be accessed by a Horner-Wadsworth-Emmons olefination and a regioselective chlorination *para* to isopropoxy group of bromobenzaldehyde **25**. Bromobenzaldehyde



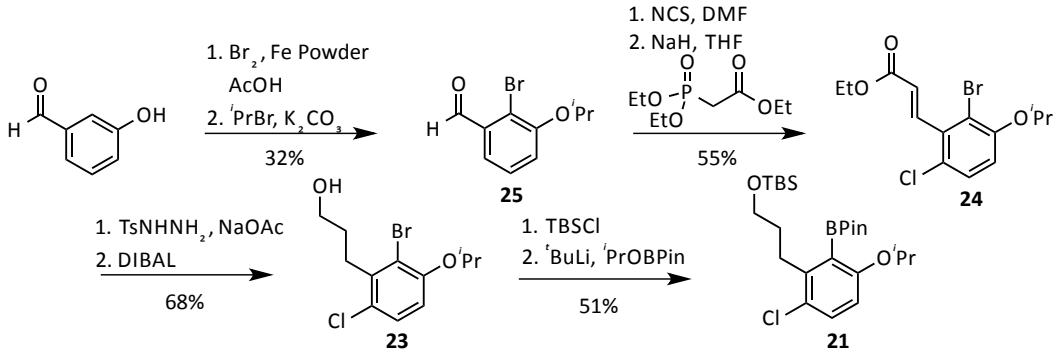
Scheme 2.2 Retrosynthetic analysis of aryl boronic ester **21**

25 could then be obtained by a regioselective bromination of commercially available 3-hydroxybenzaldehyde.

*2.3 Synthesis of Aryl Boronic Ester **21***

Starting from the inexpensive and commercially available 3-hydroxybenzaldehyde, we regioselectively brominate the 2-position according to a known literature procedure.[27] After

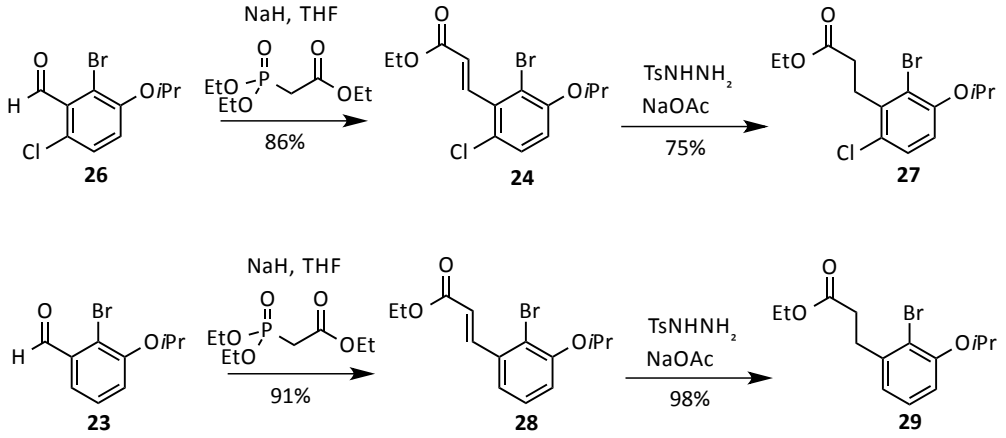
isopropyl protection of the phenol, a regioselective chlorination is performed. We believe the origin of the observed regioselectivity arises from the bulky isopropoxy group blocking the remaining *ortho* position. A Horner-Wadsworth-Emmons olefination of the halogenated benzaldehyde yielded enone **24** in 55% over two steps. To reduce the enone to the saturated ester, Pd/C and H_2 was initially used in a hydrogenation reaction. Unfortunately, the major product isolated was the desired saturated ester but the aryl bromide had also been reduced. This problem was circumvented by using tosyl hydrazine and sodium acetate to generate *in-situ* diimide which reduced the enone in good yield via a group transfer reaction. No loss of the aryl bromide was observed under these reaction conditions. The saturated ester was reduced to the primary alcohol **25** with diisobutyl aluminum hydride in excellent yield. After TBS protection of the primary alcohol, a chemoselective lithium halogen exchange was performed using *t*BuLi to obtain the B ring aryl boronic ester **21** in 52% yield.



Scheme 2.3 First Generation Synthesis of Aryl Boronic Ester **21**

When comparing the yields of the Horner-Wadsworth-Emmons olefination and diimide reduction to those commonly found in the

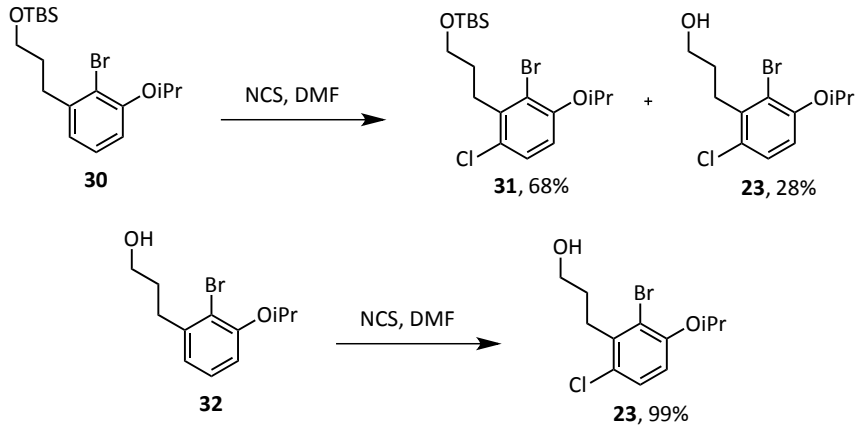
literature, we concluded that the dihalogenated benzaldehyde was not the optimal substrate for olefination and diimide reduction chemistry. As the nucleophilic Horner-Wadsworth-Emmons substrate approaches the aldehyde at the Burgi-Dunitz angle, a steric penalty could be experienced for approaching over one or more of the halogens. The diimide reduction could also be inhibited by steric hinderance with one or more halogens. To test this hypothesis, we attempted the Horner-Wadsworth-Emmons olefination and diimide reduction on the mono-halogenated benzaldehyde, reserving the chlorination for a later stage in the synthesis. Only a minor improvement was observed for the olefination reaction but a significant improvement was observed for the diimide reduction, delivering a 98% yield. With these improvements in hand, we shifted our focus towards the optimization of the regioselective chlorination reaction.



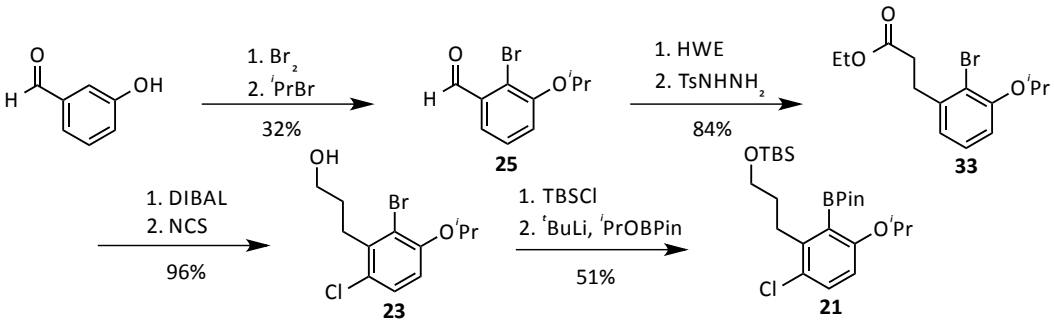
Scheme 2.4 Optimization of Olefination and Reduction Reactions

We predicted that the optimal substrate for the chlorination reaction would be the TBS-protected ether **30**. The isopropoxy

group and the alkyl tether would serve as *ortho*/*para* directing groups and the alcohol would be restrained from interfering with the desired reaction. In addition, we would expect the chlorine to react at the less hindered position, *para* to the isopropoxy group. After synthesizing compound **30**, the chlorination reaction was attempted under identical conditions. Unexpectedly, a mixture of chlorinated products was obtained with the TBS ether being cleaved. The only literature precedent for similar reactivity is the deprotection of TMS ethers using *N*-bromosuccinimide.[28] Based on this result, it was decided to attempt the chlorination on the free alcohol. To our delight, the chlorination reaction proceeded in a nearly quantitative yield. With significant improvements made to the olefination, conjugate reduction, and chlorination steps, a second generation approach to aryl boronic ester **21** was developed.



Scheme 2.5 Optimization of Chlorination Reaction

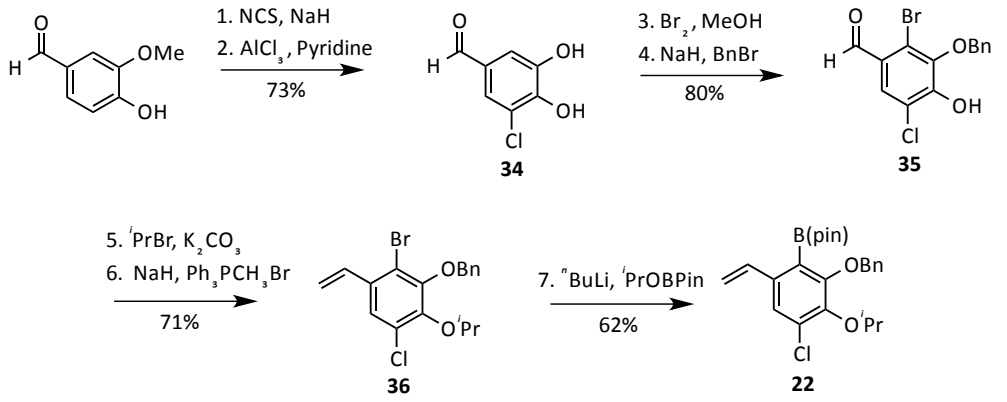


Scheme 2.6 Second Generation Synthesis of Aryl Boronic Ester **21**

With bromobenzaldehyde **25** in hand, we perform a Horner-Wadsworth-Emmons olefination and diimide reduction to deliver the saturated ester **33** in 84% over two steps. The ester is reduced to the free alcohol and the regioselective chlorination is completed to deliver **23** is 96% over two steps. After TBS protection of the primary alcohol and installation of the boronic ester, we obtain aryl boronic ester **21** in 51% yield over two steps. With the second generation approach, aryl boronic ester **21** can be accessed in 8 steps with a 16% overall yield, a three-fold improvement in yield from the first generation synthesis.

*2.4 Synthesis of Aryl Boronic Ester **22***

My colleague Dr. Frank Dyer, a recent post-doc in our lab, developed a synthetic route to aryl boronic ester **22**. Starting from vanillin, a regioselective chlorination *ortho* to the phenol is

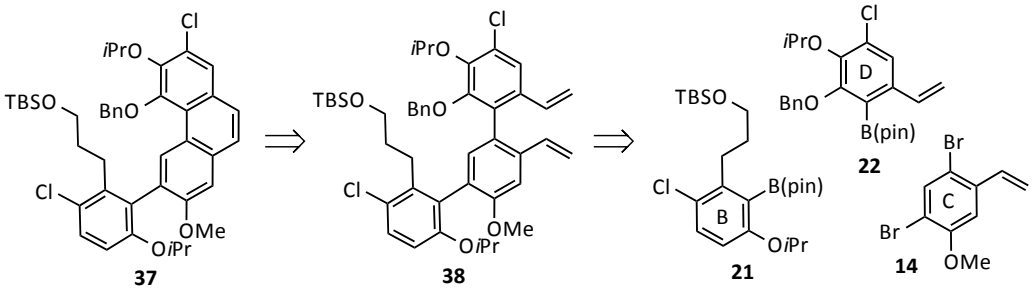


Scheme 2.7 Synthesis of Aryl Boronic Ester **22**

achieved with sodium hydride and *N*-chlorosuccinimide. Demethylation with aluminum trichloride delivers the chloro-diphenol **34** in 73% over two steps. A regioselective bromination followed by benzyl protection delivers the dihalogenated benzaldehyde **35** in 80% over two steps. After isopropyl protection of the remaining phenol, a Wittig olefination yields the substituted styrene **36** in 71% over two steps. Finally, a lithium halogen exchange and treatment with *i*PrOBPin delivers the aryl boronic ester **22** in 62% yield. Over 7 steps, this synthetic sequence yields **22** is 25% overall yield. With arylboronic esters **21** and **22** in hand, the Suzuki cross coupling with dibromostyrene **14** could now be investigated.

*2.5 Suzuki Cross Couplings of Aryl Boronic Esters **21** and **22** with Dibromostyrene **14***

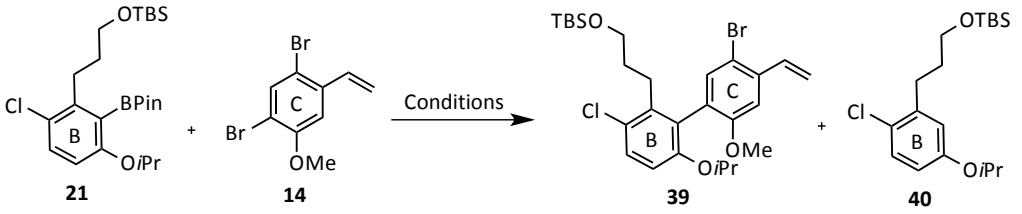
We envisioned that a double Suzuki reaction with dibromostyrene **14** would give efficient access to terphenyl **38** which would enable



Scheme 2.8 Retrosynthesis of Phenanthrene **37**

us to access the phenanthrene subunit **37** of the natural product after Grubb's ring closing metathesis. Our group has already demonstrated that dibromostyrene **14** will react regioselectively in Suzuki cross couplings, with the bromine atom *ortho* to the methoxy group being more reactive. However, it was not known if the desired regioselectivity would be achieved in cross couplings with more complex and sterically hindered boronic esters. Also, the presence of aryl chlorides and aryl bromides demands that the cross coupling must be chemoselective for bromine over chlorine to deliver the desired biphenyl.[29] To test if the desired region- and chemoselectivity could be achieved, we first investigated the cross coupling of aryl boronic ester **21** and dibromostyrene **14**.

Under typical Suzuki cross coupling conditions, only poor yields of the desired product were obtained (entry 1). The major byproduct observed was the decomposition of aryl boronic ester **21**, commonly referred to as hydrolytic doboronation, to give compound **40**. Hydrolytic deboronation of boronic acids and esters is common in sterically hindered Suzuki cross couplings.[30] However, a number of methods have been developed in an effort to



Entry	Conditions	Yield of **39**
1	$Pd(PPh_3)_4$, K_3PO_4 KBr, Dioxane/H_2O, 55 °C	17%
2	$Pd(PPh_3)_4$, Cs_2CO_3 DMF, 55 °C	10%
3	$Pd(PPh_3)_4$, NaOH KBr, 5% H_2O/DME, 65 °C	57%
4	$Pd(PPh_3)_4$, $Ba(OH)_2$ KBr, 5% H_2O/DME, 65 °C	32%
5	$Pd(PPh_3)_4$, KO*t*Bu KBr, 5% H_2O/DME, 65 °C	35%
6	$Pd_2(dba)_3$, P(*t*Bu)$_3$, KF THF, r.t. to 100 °C	0%

Scheme 2.9 Optimization of Suzuki Cross Coupling

overcome this problem. One such method, developed by Suzuki and coworkers, involves the use of $Pd(PPh_3)_4$ as the active catalyst, aq. sodium hydroxide as a base, and dimethoxyethane as the solvent.[31] Using these optimized conditions in our system delivered the desired coupling product in 57% yield. Although the hydrolytic deboronation product **40** was still observed as the major byproduct, we were pleased with this initial result. Other alkoxide bases such as barium hydroxide and potassium *tert*-butoxide have also been shown to be useful in sterically demanding Suzuki cross couplings.[32] Unfortunately, both of these bases proved to be less effective than sodium hydroxide in carrying out our desired cross coupling. The Fu group reported anhydrous reaction conditions delivering sterically hindered biaryls in good yield using potassium

fluoride as a base and the *in situ* generation of a highly reactive $Pd(P(tBu)_3)_2$ catalyst.[33] Unfortuantely, no reaction was observed under these conditions.

The Suzuki coupling between aryl boronic ester **21** and dibromostyrene **14** delivered a single biaryl product, indicating the cross coupling was indeed regioselective. However, we did not know which bromine the cross coupling was selective for. We set out to determine this issue using NMR spectroscopy. Using common 1D and 2D NMR experiments, such as HSQC, HMBC, and NOESY, we were not able to able to unequivocally determine which regioisomer was present. This determination is complicated by the fact that only four of the twelve aromatic carbons bear a hydrogen atom. In addition, the aromatic hydrogens of the C ring are equidistant to the biaryl bond in either regioisomer. Thus, the only experiment that confirmed the structure of our desired coupling product was ^{13}C-^{13}C INADEQUATE.

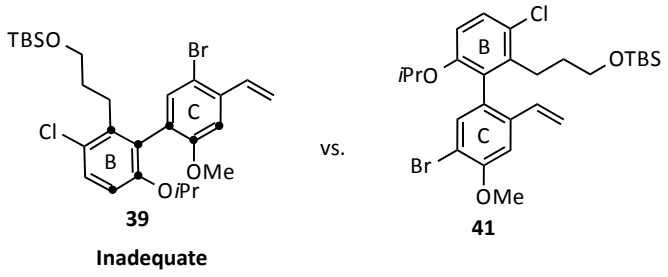
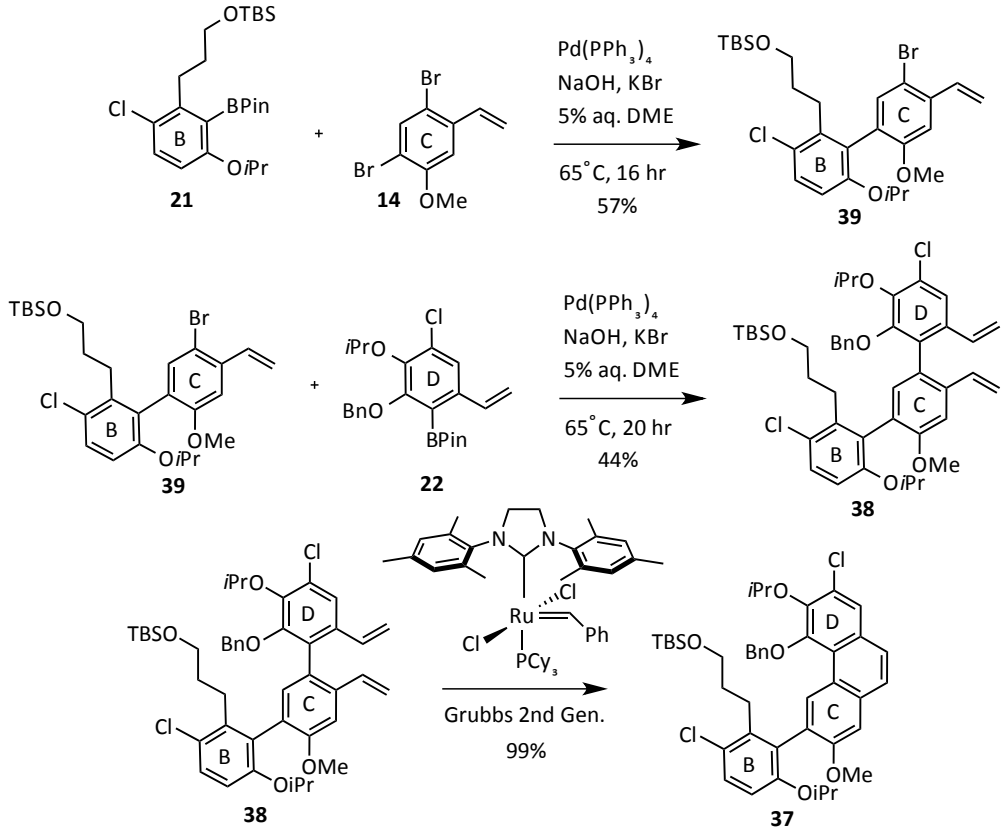


Figure 2.1 Spectroscopic Determination of Suzuki Cross Coupling Product Using INADEQUATE

With biphenyl **39** in hand, aryl boronic ester **22** was then coupled to the remaining bromide in 44% yield. Pleasingly, this result

indicates that a one-pot, three-component Suzuki coupling may be possible. Investigations into the one-pot, three-component coupling are currently underway. Terphenyl **38** was treated with Grubbs 2nd generation catalyst to form the substituted phenanthrene **37** in excellent yield.

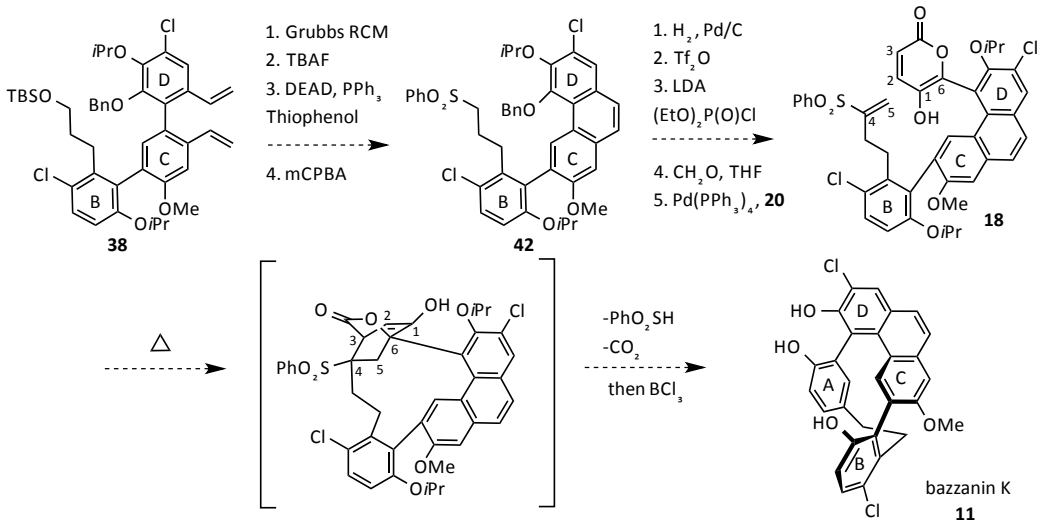


Scheme 2.10 Synthesis of Phenanthrene **37**

2.6 Future Work Towards the Total Synthesis of Bazzanin K

To complete the total synthesis of bazzanin K, phenanthrene **37** will first be advanced to the to the Diels–Alder precursor **18** to investigate the intramolecular Diels–Alder cascade to install the A ring of the natural product. Thus, the TBS ether side chain must

converted into a vinyl sulfone and the benzyl ether of the D ring must be converted into a carbon-carbon bond with a 5-hydroxypyrone.



Scheme 2.11 Future Work Towards The Total Synthesis of Bazzanin K

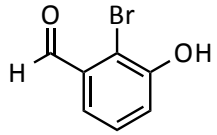
First, the TBS ether will be deprotected and a Mitsunobu reaction with thiophenol followed by oxidation with mCPBA, should afford the alkyl sulfone **42**. The benzyl ether of the D ring will then be deprotected and converted into the corresponding aryl triflate. The α-position of the sulfone will be deprotonated and treated with diethyl chlorophosphate to deliver the corresponding phosphonate. A Horner-Wadsworth-Emmons olefination with formaldehyde will afford the vinyl sulfone to act as an electron deficient dienophile in the Diels–Alder cascade. Next, the 5-hydroxypyrone will be introduced via a Stille coupling with the aryl triflate of the D ring, setting the stage for the Diels–Alder event. At elevated temperature, we anticipate the initial [4+2] cycloaddition will take

place with the nucleophilic carbon 6 of the pyrone bonding with the electrophilic carbon 5 of the vinyl sulfone, delivering a [2.2.2] bicycle with the alkyl tether and D ring in a 1,3-relationship. After loss of phenylsulfinic acid, a retro—Diels—Alder should occur to deliver bazzanin K after global deprotection.

2.7 Experimental Section

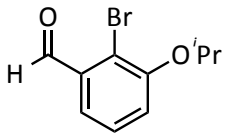
General Experimental Details:

All reactions were carried out under inert Ar atmosphere in oven-dried glassware. Flash column chromatography (FCC) was carried out with SilicaFlash P60, 60 Å silica gel. Reactions and column chromatography were monitored with EMD silica gel 60 F254 plates and visualized with potassium permanganate, iodine, or vanillin stains. Tetrahydrofuran (THF) was dried by passage through an activated alumina column. DMF was stored over 3 Å molecular sieves. All other reagents and solvents were used without further purification from commercial sources. Instrumentation: FT-IR spectra were obtained on NaCl plates with a PerkinElmer Spectrum Vision spectrometer. Proton and carbon NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker 700 MHz Avance III with carbon-optimized cryoprobe and a Bruker 400 MHz DPX-400 spectrometer. Multiplicites are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet. Melting points were determined with a Cole-Parmer instrument and are uncorrected.



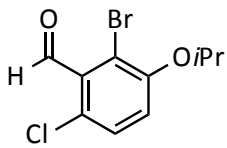
2-bromo-3-hydroxybenzaldehyde. A 250 mL flask was charged with 3-hydroxybenzaldehyde (16.1 g, 0.132 mol), NaOAc (21.6 g, 0.264 mol), iron powder (0.56 g, 10 mmol), and 120 mL of AcOH (0.9 M). The suspension was heated (~60 °C) until a clear solution was obtained and allowed to slowly cool to room temperature. A solution of bromine (23.2 g, 0.145 mol) in 25 mL of AcOH was added dropwise over 15 min. After one hour, the reaction was poured onto 800 mL of ice water and extracted with DCM (3x200 mL). The organic layer was dried over $MgSO_4$, filtered through a pad of silica gel, and concentrated. Recrystallized (DCM/Hexanes) to yield 2-bromo-3-hydroxybenzaldehyde (6.23 g, 0.031 mol, 23%) as a light brown solid. Flash column chromatography (5:1 Hexanes : EtOAc). Recrystallized (DCM/Hexanes) to yield 2-bromo-3-hydroxybenzaldehyde (3.97 g, 0.020 mol, 15%) as a light brown solid.

Data for 2-bromo-3-hydroxybenzaldehyde: R_f 0.57 (2:1 Hexanes:EtOAc); m.p. 148-149 °C; IR (thin film) 3139, 1658, 1566, 1295, 781 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 10.31 (s, 1 H), 7.54 (d, J = 7.7 Hz, 1 H), 7.38 (t, J = 7.7 Hz, 1 H), 7.31 (d, J = 8.4 Hz, 1 H), 6.03 (bs, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 191.3, 152.9, 133.8, 128.9, 122.7, 121.7, 114.0; HRMS (TOF MS ES+) cald for $C_7H_5O_2Br$: 199.94729, found 199.94835.



2-bromo-3-isopropoxybenzaldehyde (25). 2-bromo-3-hydroxybenzaldehyde (4.15 g, 20.6 mmol), K_2CO_3 (5.70 g, 41.3 mmol), and DMF (42 mL, 0.5 M) were stirred under argon for five minutes before the addition of *i*PrBr (3.80 g, 30.9 mmol) and the reaction was heated to 55 °C. After 6 hours, the reaction was cooled to room temp. and quenched with aq. LiCl and extracted with Et_2O (3 x 90 mL). The organic layer was washed with aq. LiCl (40 mL), H_2O (40 mL), and brine (40 mL). Dried over Na_2SO_4, filtered, and concentrated to yield 2-bromo-3-isopropoxybenzaldehyde (4.98 g, 20.4 mmol, 99%) as a yellow oil.

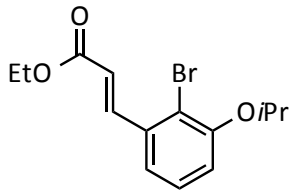
Data for 2-bromo-3-isopropoxybenzaldehyde: R_f 0.76 (3:1 Hexanes:EtOAc); IR (thin film) 3070, 2978, 2933, 2871, 1690, 1567, 1267, 1237, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 4.61 (sept, *J* = 6.0 Hz,1 H), 1.43 (d, *J* = 6.0 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 192.6, 155.0, 135.0, 128.1, 121.5, 121.7, 120.5, 119.0, 72.7, 21.9; HRMS (TOF MS ES+) cald for $C_{10}H_{11}O_2Br$: 241.99424, found 241.99408.



2-bromo-6-chloro-3-isopropoxybenzaldehyde (26). 2-bromo-3-isopropoxybenzaldehyde (1.55 g, 6.3 mmol), pTsOH-H_2O (2.43 g,

12.7 mmol), and CH_3CN (32 mL, 0.2 M) were stirred under argon and heated to 70 °C before the addition of *N*-chlorosuccinimide (0.85 g, 6.3 mmol). After 5 hours, the reaction was cooled to room temp. and quenched with aq. $Na_2S_2O_3$ and extracted with Et_2O (3 x 60 mL). The organic layer was washed twice with aq. $Na_2S_2O_3$, twice with H_2O, and once with brine. Dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (12:1 Hexanes:EtOAc) to yield 2-bromo-6-chloro-3-isopropoxybenzaldehyde (1.13 g, 4.0 mmol, 64%) as a yellow oil.

Data for 2-bromo-6-chloro-3-isopropoxybenzaldehyde: R_f 0.38 (12:1 Hexanes:EtOAc); IR (thin film) 3075, 2978, 2932, 2872, 1704, 1557, 1445, 1285, 1108, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1 H), 7.36 (d, J = 8.8 Hz, 1 H), 7.01 (d, J = 8.8 Hz, 1 H), 4.58 (sept, J = 6.0 Hz,1 H), 1.42 (d, J = 6.0 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 190.5, 153.9, 133.2, 130.3, 126.2, 118.8, 116.4, 73.0, 21.8; HRMS (TOF MS ES+) cald for $C_{10}H_{11}O_2ClBr$: 276.9631, found 276.9630.

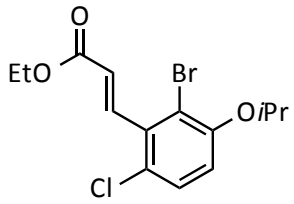


Ethyl (*E*)-3-(2-bromo-3-isopropoxyphenyl)acrylate (28)

Triethylphosphonoacetate (0.69 g, 3.1 mmol) and THF (4 mL, 0.5 M) were stirred under argon and cooled to 0 °C before the addition of NaH (123 mg, 3.1 mmol). After stirring for 1 hour, 2-bromo-3-

isopropoxybenzaldehyde was added (0.50 g, 2.1 mmol). After slowly warming to room temp. over 4 hours, the reaction was quenched with aq. NH_4Cl and extracted with Et_2O (3 x 15 mL). The organic layer was washed twice with H_2O and once with brine. Dried over Na_2SO_4, filtered, and concentrated to yield Ethyl (*E*)-3-(2-bromo-3-isopropoxyphenyl)acrylate (0.59 g, 1.9 mmol, 91%) as a colorless oil.

Data for ethyl (*E*)-3-(2-bromo-3-isopropoxyphenyl)acrylate: R_f 0.45 (2:1 DCM:Hexanes); IR (thin film) 3075, 2978, 2931, 2872, 1704, 1265, 1108, 805; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 16.0 Hz, 1 H), 7.23 (m, 2 H), 6.93 (dd, *J* = 6.8, 1.2 Hz, 1 H), 6.37 (d, *J* = 16.0 Hz, 1 H), 4.57 (sept, *J* = 6.0 Hz,1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 1.40 (d, *J* = 6.0 Hz, 6 H), 1.36 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.4, 155.0, 143.6, 136.3, 127.8, 121.1, 119.8, 116.9, 116.2, 72.3, 60.6, 22.0, 14.3; HRMS (TOF MS ES+) cald for $C_{14}H_{18}O_3Br$: 313.0439, found 313.0442.

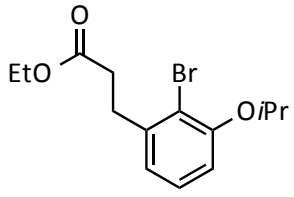


Ethyl (*E*)-3-(2-bromo-6-chloro-3-isopropoxyphenyl)acrylate (24)

Triethylphosphonoacetate (1.83 g, 8.1 mmol) and THF (16 mL, 0.25 M) were stirred under argon and cooled to 0 °C before the addition of NaH (0.33 g, 8.1 mmol). After stirring for 1 hour, 2-

bromo-6-chloro-3-isopropoxybenzaldehyde was added (1.13 g, 4.0 mmol). After slowly warming to room temp. over 6 hours, the reaction was quenched with aq. NH_4Cl and extracted with Et_2O (3 x 30 mL). The organic layer was washed twice with H_2O and once with brine. Dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (12:1 Hexanes:EtOAc) to yield Ethyl (*E*)-3-(2-bromo-6-chloro-3-isopropoxyphenyl)acrylate (1.22 g, 3.5 mmol, 86%) as a colorless oil.

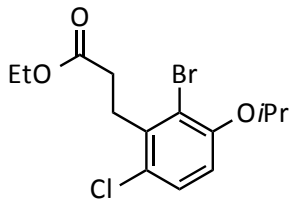
Data for ethyl (*E*)-3-(2-bromo-6-chloro-3-isopropoxyphenyl)acrylate: R_f 0.21 (10:1 Hexanes:Et_2O); IR (thin film) 2978, 2935, 1715, 1444, 1268, 1176, 1105, 803; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 16.4 Hz, 1 H), 7.33 (d, *J* = 8.8 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 1 H), 6.44 (d, *J* = 16.4 Hz, 1 H), 4.55 (sept, *J* = 6.0 Hz,1 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 1.40 (d, *J* = 6.0 Hz, 6 H), 1.37 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.1, 153.7, 140.9, 135.0, 129.2, 126.7, 125.1, 116.2, 115.6, 72.7, 60.8, 21.9, 14.3; HRMS (TOF MS ES+) cald for $C_{14}H_{16}O_3ClBr$: 345.99713, found 345.99809.



Ethyl 3-(2-bromo-3-isopropoxyphenyl)propanoate Ethyl (*E*)-3-(2-bromo-3-isopropoxyphenyl)acrylate (4.52 g, 14.4 mmol), $TsNHNH_2$ (13.44 g, 72.2 mmol), and THF (58 mL, 0.25 M) were

stirred under argon and heated to 65 °C. A solution of NaOAc (5.92 g, 72.2 mmol) in H_2O (44 mL, 0.33 M) was added over 15 min. After 12 hours, the reaction was cooled to room temperature and extracted with EtOAc (2 x 120 mL), washed with H_2O (3 x 60 mL), washed with brine (60 mL), dried over Na_2SO_4, and filtered through a pad of silica gel. Filtered through a pad of celite (Hexanes) to yield ethyl 3-(2-bromo-3-isopropoxyphenyl)propanoate (4.44 g, 14.1 mmol, 98%) as a colorless oil.

Data for ethyl 3-(2-bromo-3-isopropoxyphenyl)propanoate: R_f 0.10 (10:1 Hexanes:Et_2O)); IR (thin film) 2978, 2936, 1731, 1462, 1264, 1114, 778; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.0 Hz, 1 H), 6.85 (d, *J* = 8.0 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz,1 H), 4.53 (sept, *J* = 6.0 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 3.08 (t, *J* = 7.6 Hz, 2 H), 2.63 (t, *J* = 7.6 Hz, 2 H), 1.37 (d, *J* = 6.0 Hz, 6 H), 1.24 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.8, 154.8, 141.7, 127.6, 122.4, 115.8, 113.5, 72.1, 60.4, 34.1, 31.9, 22.1, 14.2; HRMS (TOF MS ES+) cald for $C_{14}H_{20}O_3Br$: 315.0596, found 315.0601.

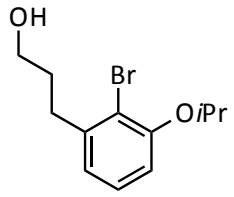


Ethyl 3-(2-bromo-6-chloro-3-isopropoxyphenyl)propanoate

Ethyl (*E*)-3-(2-bromo-6-chloro-3-isopropoxyphenyl)acrylate (361

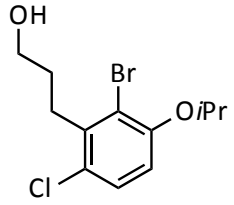
mg, 1.04 mmol), $TsNHNH_2$ (3.55 g, 20.8 mmol), and THF (4.2 mL, 0.25 M) were stirred under argon and heated to 65 °C. A solution of NaOAc (1.70 g, 20.8 mmol) in H_2O (3.1 mL, 0.33 M) was added via syringe pump over 6 hours. After 16 hours, the reaction was diluted with EtOAc (40 mL), washed with H_2O (4 x 20 mL), washed with brine (20 mL), dried over Na_2SO_4, and filtered through a pad of silica gel. Flash column chromatography (14:1 Hexanes:EtOAc) to yield ethyl 3-(2-bromo-6-chloro-3-isopropoxyphenyl)propanoate (272 mg, 0.77 mmol, 75%) as a colorless oil.

Data for ethyl 3-(2-bromo-6-chloro-3-isopropoxyphenyl)propanoate: R_f 0.33 (14:1 Hexanes:Et_2O)); IR (thin film) 2978, 2929, 1732, 1447, 1270, 1180, 1109, 798; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 1 H), 6.75 (d, *J* = 8.8 Hz, 1 H), 4.52 (sept, *J* = 6.0 Hz,1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 3.33 (m, 2 H), 2.57 (m, 2 H), 1.39 (d, *J* = 6.0 Hz, 6 H), 1.29 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 172.5, 153.7, 139.0, 128.4, 126.1, 117.0, 114.0, 72.4, 60.6, 32.2, 30.0, 22.0, 14.2; HRMS (TOF MS ES+) cald for $C_{14}H_{19}O_3ClBr$: 349.0206, found 349.0205.



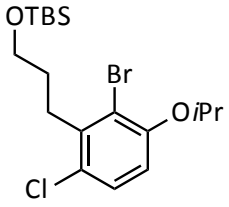
3-(2-bromo-3-isopropoxyphenyl)propan-1-ol Ethyl 3-(2-bromo-3-isopropoxyphenyl)propanoate (4.44 g, 14.1 mmol) and THF (70 mL, 0.2 M) are stirred under argon at room temp. before the addition of a 1.2 M solution DIBAL in hexanes (35 mL, 42.3 mmol) over 10 min. After 3 hours, the reaction is diluted with EtOAc (50 mL) followed by an aq. solution of Rochelle's salt (50 mL). After 30 min. of stirring, the reaction was transferred to a seperatory funnel where the layers were separated. The aqueous layer was extracted with EtOAc (150 mL) and the combined organic extracts were washed with aq. Rochelle's salt (2 x 100 mL), H_2O (100 mL), and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 3-(2-bromo-3-isopropoxyphenyl)propan-1-ol (3.74 g, 13.7 mmol, 97%).

Data for 3-(2-bromo-3-isopropoxyphenyl)propan-1-ol: R_f 0.22 (3:1 Hexanes:EtOAc); IR (thin film) 3342, 2978, 2932, 2870, 1569, 1462, 1116, 1025, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.0 Hz, 1 H), 6.86 (d, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 4.56 (sept, *J* = 6.0 Hz, 1 H), 3.72 (t, *J* = 6.4 Hz, 2 H), 2.88 (m, 2 H), 1.92 (m, 2 H), 1.40 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.7, 140.5, 128.4, 126.1, 117.2, 113.8, 72.5, 62.5, 31.2, 31.0, 22.0; HRMS (TOF MS ES+) cald for $C_{12}H_{17}O_2Br$: 272.04119, found 272.03981.



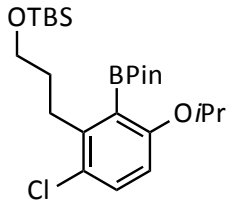
3-(2-bromo-6-chloro-3-isopropoxyphenyl)propan-1-ol 3-(2-bromo-3-isopropoxyphenyl)propan-1-ol (3.74 g, 13.7 mmol) and DMF (46 mL, 0.3 M) were stirred under argon at room temp. before the addition of *N*-chlorosuccinimide (2.01 g, 15.1 mmol) and the reaction was heated to 40 °C. After 2.5 hours, the reaction was diluted with aq. LiCl (50 mL) and extracted with Et_2O (3 x 100 mL). The organic layer was washed with aq. $Na_2S_2O_3$ (2 x 50 mL) and aq. LiCl (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude mixture was filtered through a pad of celite (3:1 Hexanes:EtOAc at 0 °C) to yield 3-(2-bromo-6-chloro-3-isopropoxyphenyl)propan-1-ol (4.2 g, 13.6 mmol, 99%) as a colorless oil.

Data for 3-(2-bromo-6-chloro-3-isopropoxyphenyl)propan-1-ol: R_f 0.42 (3:1 Hexanes:EtOAc); IR (thin film) 3342, 2978, 2932, 2870, 1569, 1462, 1116, 1025, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 1 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 4.53 (sept, *J* = 6.3 Hz, 1 H), 3.77 (t, *J* = 6.3 Hz, 2 H), 3.09 (t, *J* = 8.4 Hz, 2 H), 1.88 (m, 2 H), 1.40 (d, *J* = 6.3 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.6, 140.4, 128.4, 126.1, 117.1, 113.7, 72.4, 62.5, 31.1, 31.0, 22.0; HRMS (TOF MS ES+) cald for $C_{12}H_{16}O_2ClBr$: 306.00221, found 306.00175.



(3-(2-bromo-6-chloro-3-isopropoxyphenyl)propoxy)(*tert*-butyl)dimethylsilane 3-(2-bromo-6-chloro-3-isopropoxyphenyl)propan-1-ol (245 mg, 0.80 mmol), imidazole (136 mg, 1.99 mmol), and DMF (4 mL, 0.2 M) were stirred under argon at room temp. before the addition of TBSCl (144 mg, 0.96 mmol). After 2 hours, the reaction was quenched with aq. $NaHCO_3$ and extracted with Et_2O (2 x 20 mL). Washed once with aq. $NaHCO_3$ and once with brine. Dried over Na_2SO_4, filtered, and concentrated to yield (3-(2-bromo-6-chloro-3-isopropoxyphenyl)propoxy)(*tert*-butyl)dimethylsilane (330 mg, 0.78 mmol, 98%).

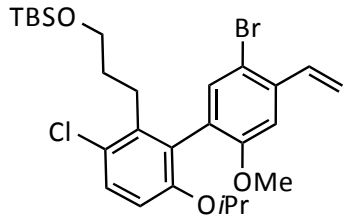
Data for (3-(2-bromo-6-chloro-3-isopropoxyphenyl)propoxy)(*tert*-butyl)dimethylsilane: R_f 0.43 (2:1 Hexanes:DCM); IR (thin film) 2957, 2928, 2895, 2856, 1446, 1256, 1095, 1010, 795; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.8 Hz, 1 H), 6.72 (d, J = 8.8 Hz, 1 H), 4.51 (sept, J = 6.0 Hz, 1 H), 3.75 (t, J = 6.4 Hz, 2 H), 3.03 (m, 2 H), 1.80 (m, 2 H), 1.39 (d, J = 6.0 Hz, 6 H), 0.94 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.6, 141.0, 128.3, 126.2, 117.2, 113.7, 72.5, 62.9, 31.4, 31.2, 25.9, 22.0, 18.3, -5.2; HRMS (TOF MS ES+) cald for $C_{18}H_{31}O_2SiClBr$: 421.0965, found 421.0986.



***tert*-butyl(3-(6-chloro-3-isopropoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propoxy)dimethylsilane** (3-(2-bromo-6-chloro-3-isopropoxyphenyl)propoxy)(*tert*-butyl)dimethylsilane (200 mg, 0.47 mmol) and THF (2.4 mL, 0.2 M) were stirred under and argon and cooled to -78 °C before the dropwise addition of *t*BuLi (0.63 mL, 1.04 mmol) over 10 min. After stirring for 20 min., *i*PrOBPin (353 mg, 1.90 mmol) was added. After 2 hours of stirring, the reaction was diluted with EtOAc, filtered through a pad of celite, and concentrated. Flash column chromatography (3:2 DCM:Hexanes) to yield *tert*-butyl(3-(6-chloro-3-isopropoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propoxy)dimethylsilane (113 mg, 0.24 mmol, 51%) as a colorless oil.

Data for *tert*-butyl(3-(6-chloro-3-isopropoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propoxy)dimethylsilane: R_f 0.18 (3:2 DCM:Hexanes); IR (thin film) 2977, 2955, 2929, 2856, 1331, 1254, 1142, 1100, 832, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.8 Hz, 1 H), 6.62 (d, J = 8.8 Hz, 1 H), 4.49 (sept, J = 6.0 Hz, 1 H), 3.70 (t, J = 6.4 Hz, 2 H), 2.71 (m, 2 H), 1.82 (m, 2 H), 1.40 (s, 12 H), 1.31 (d, J = 6.0 Hz, 6 H), 0.92 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.4, 143.9, 136.5, 134.7, 130.7, 125.3, 118.6, 111.2,

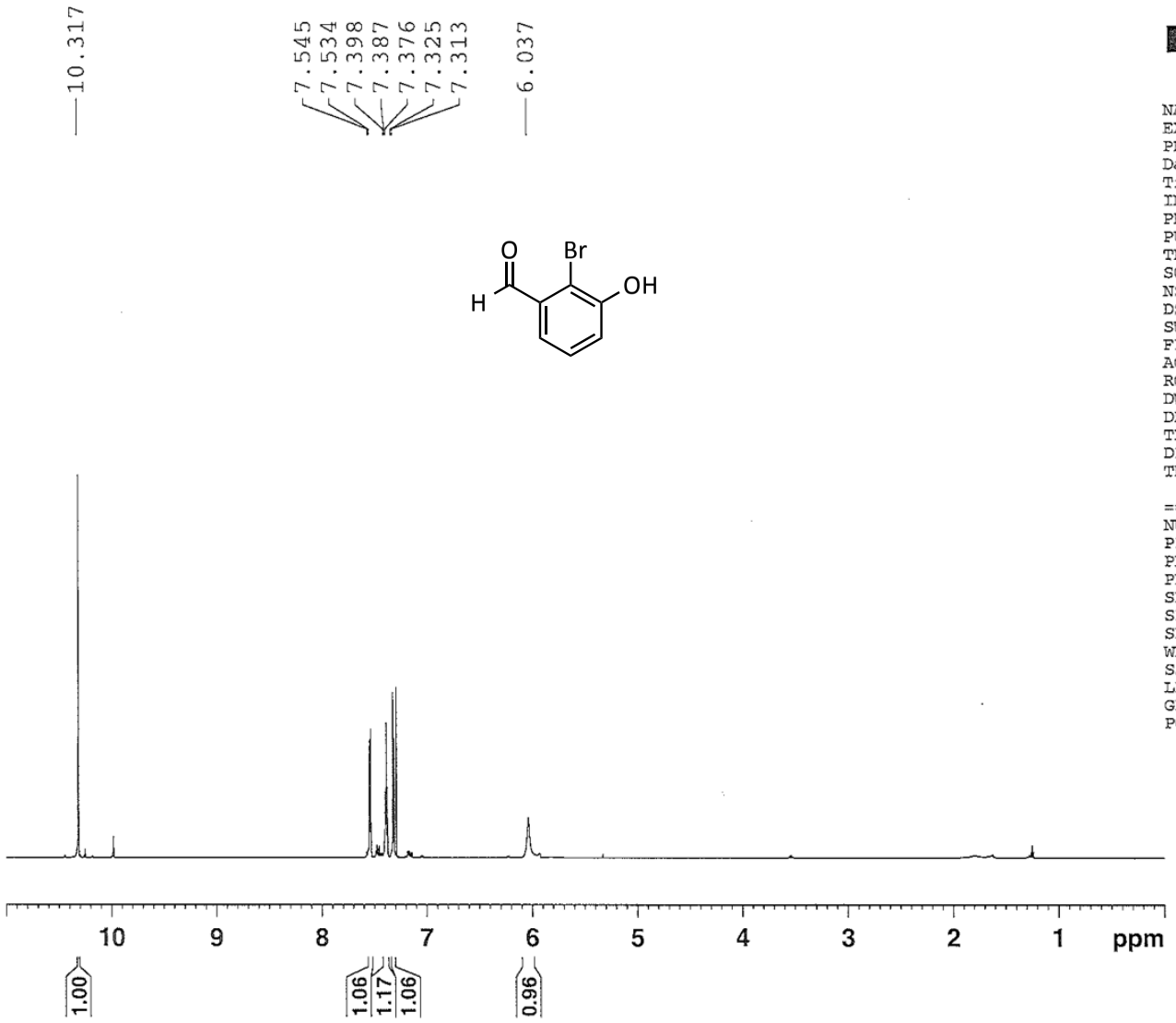
84.0, 70.3, 63.4, 33.5, 31.9, 26.0, 24.9, 22.1, 18.4, -5.1; HRMS (TOF MS ES+) cald for $C_{24}H_{42}O_4SiClB$: 468.26340, found 468.26158.



(3-(5'-bromo-3-chloro-6-isopropoxy-2'-methoxy-4'-vinyl-[1,1'-biphenyl]-2-yl)propoxy)(*tert*-butyl)dimethylsilane 1,5-dibromo-2-methoxy-4-vinylbenzene (120 mg, 0.41 mmol), $Pd(PPh_3)_4$ (24 mg, 0.02 mmol), NaOH (66 mg, 1.65 mmol), KBr (196 mg, 1.65 mmol), dimethoxyethane (2.1 mL, 0.2 M), and H_2O (0.2 mL, 5% v/v) are stirred under argon and heated to 65 °C. A solution of *tert*-butyl(3-(6-chloro-3-isopropoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propoxy)dimethylsilane (193 mg, 0.41 mmol) in dimethoxyethane (2.0 mL, 0.2 M) added at 65 °C. After 18 hours, the reaction was diluted with H_2O (25 mL) and extracted with EtOAc (3 x 25 mL). The organic layer was washed once with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (30:1 Hexanes:Et_2O) to yield (3-(5'-bromo-3-chloro-6-isopropoxy-2'-methoxy-4'-vinyl-[1,1'-biphenyl]-2-yl)propoxy)(*tert*-butyl)dimethylsilane (131 mg, 0.24 mmol, 57%) as a white solid.

Data for (3-(5'-bromo-3-chloro-6-isopropoxy-2'-methoxy-4'-vinyl-[1,1'-biphenyl]-2-yl)propoxy)(*tert*-butyl)dimethylsilane: R_f 0.18

(20:1 Hexanes:Et_2O); IR (thin film) 2977, 2954, 2930, 2855, 1462, 1373, 1264, 1090, 833, 772; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 1 H), 7.13 (s, 1 H), 7.13 (dd, *J* = 11.2 Hz, 6.3 Hz, 1 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 5.79 (d, *J* = 16.8 Hz, 1 H), 5.44 (d, *J* =10.5 Hz, 1 H), 4.35 (m, 1 H), 3.78 (s, 3 H), 3.53 (t, *J* = 6.3 Hz, 2 H), 2.62 (m, 1 H), 2.47 (m, 1 H), 1.63 (m, 2 H), 1.16 (dd, *J* = 10.5 Hz, 6.3 Hz, 6 H), 0.85 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 156.5, 154.5, 140.1, 137.0, 136.1, 135.1, 129.3, 129.0, 128.1, 126.1, 116.0, 113.9, 113.2, 108.4, 71.3, 63.1, 55.5, 32.1, 28.3, 25.9, 22.1, 21.9, 18.2, -5.3; HRMS (TOF MS ES+) cald for $C_{27}H_{39}O_3SiClBr$: 553.1540, found 553.1555.



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TD	65536
SOLVENT	CDCl3
NS	10
DS	0
SWH	14423.077 Hz
FIDRES	0.220079 Hz
AQ	2.2719646 sec
RG	16
DW	34.667 usec
DE	6.50 usec
TE	298.4 K
D1	1.00000000 sec
TD0	1
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PL1W	33.59817505 W
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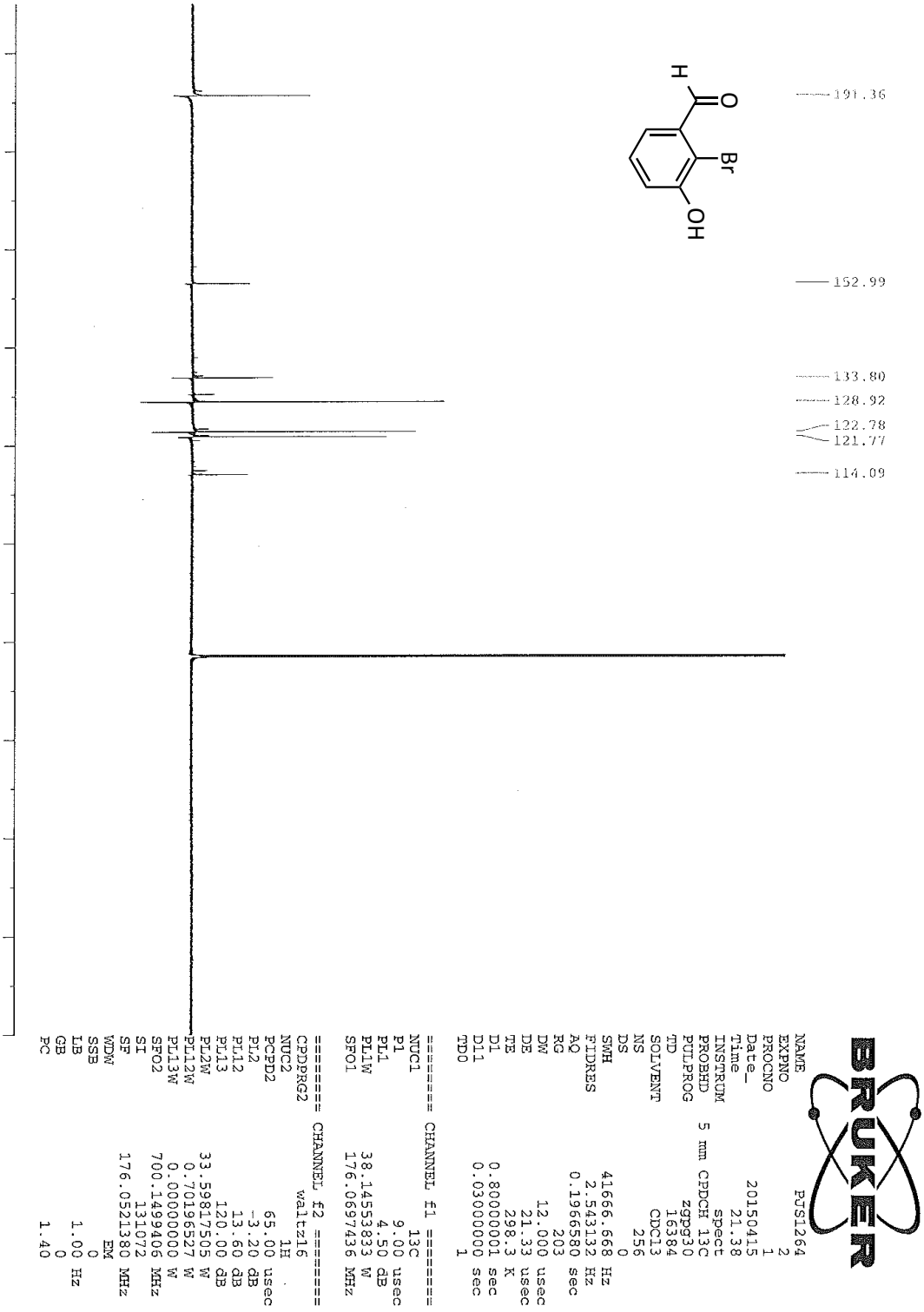
SI	131072
SF	700.1471400 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00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40
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ppm
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PROCNO 1
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Time 21.38
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DS 0
SWH 41666.668 Hz
FIDRES 2.543132 Hz
AQ 0.1966580 sec
RG 203
DW 12.000 usec
DE 21.33 usec
TE 298.3 K
D1 0.80000001 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 4.50 dB
PL1W 38.14553833 W
SFO1 176.0697436 MHz
======== CHANNEL f2 ========
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NUC2 1H
PCPD2 65.00 usec
PL2 -3.20 dB
PL12 13.60 dB
PL13 120.00 dB
PL2W 33.59817505 W
PL12W 0.70196527 W
PL13W 0.00000000 W
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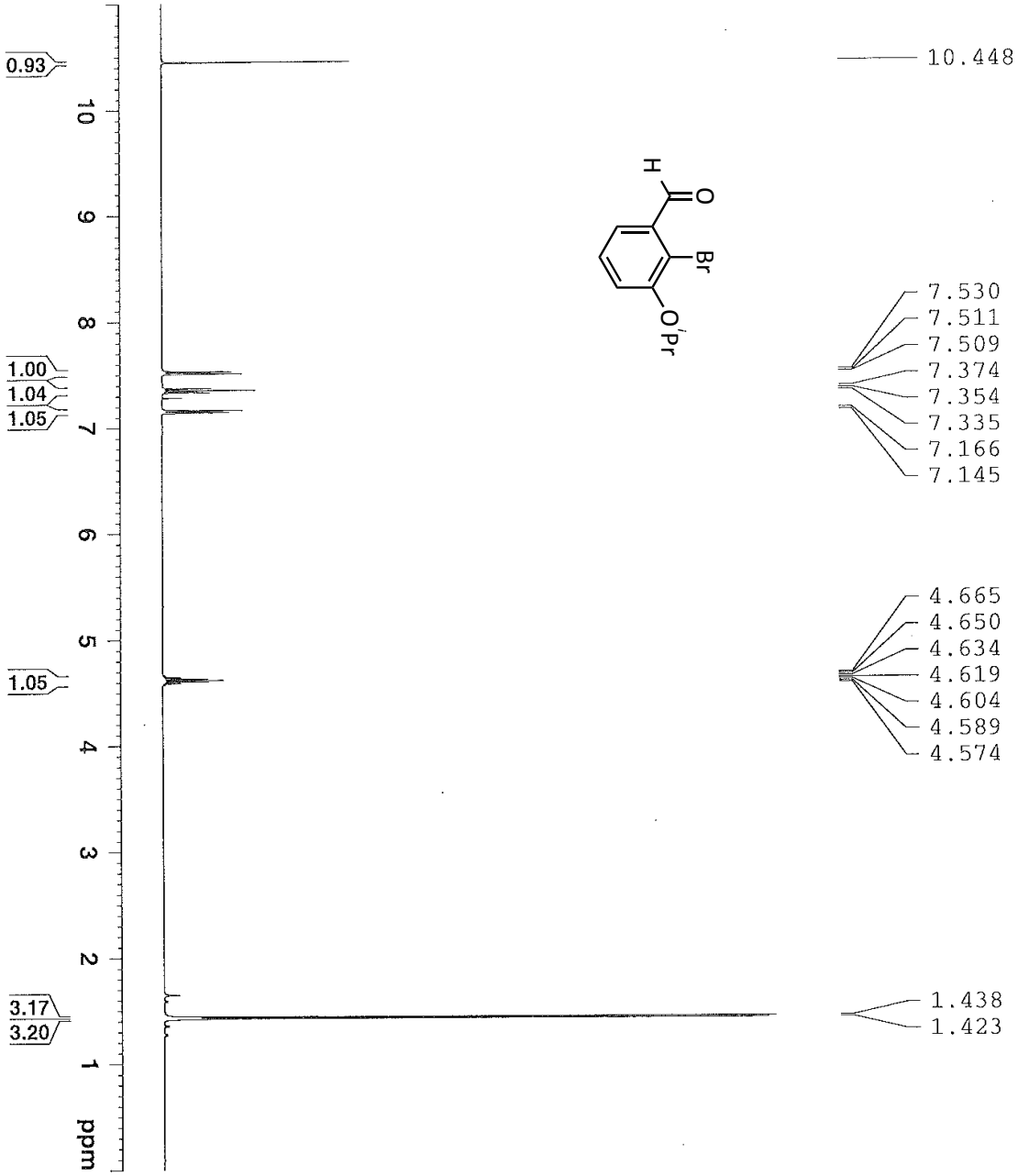
SI 131072
SF 176.0521380 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

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EXPNO                      3
PROCNO                     1

F2 - Acquisition Parameters
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PROBHD     5 mm PABBO BB-
PULPROG            zg30
TD                 32768
SOLVENT            CDCl3
NS                 8
DS                 0
SWH                7183.908 Hz
FIDRES             0.219235 Hz
AQ                 2.2807028 sec
RG                 90.5
DW                 69.600 usec
DE                 6.50 usec
TE                 298.2 K
D1                 2.00000000 sec
TD0                1

======== CHANNEL f1 ========
NUC1               1H
P1                 11.20 usec
PL1                0.00 dB
SFO1               400.1428010 MHz

F2 - Processing parameters
SI                 16384
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WDW                EM
SSB                0
LB                 0.00 Hz
GB                 0
PC                 1.00
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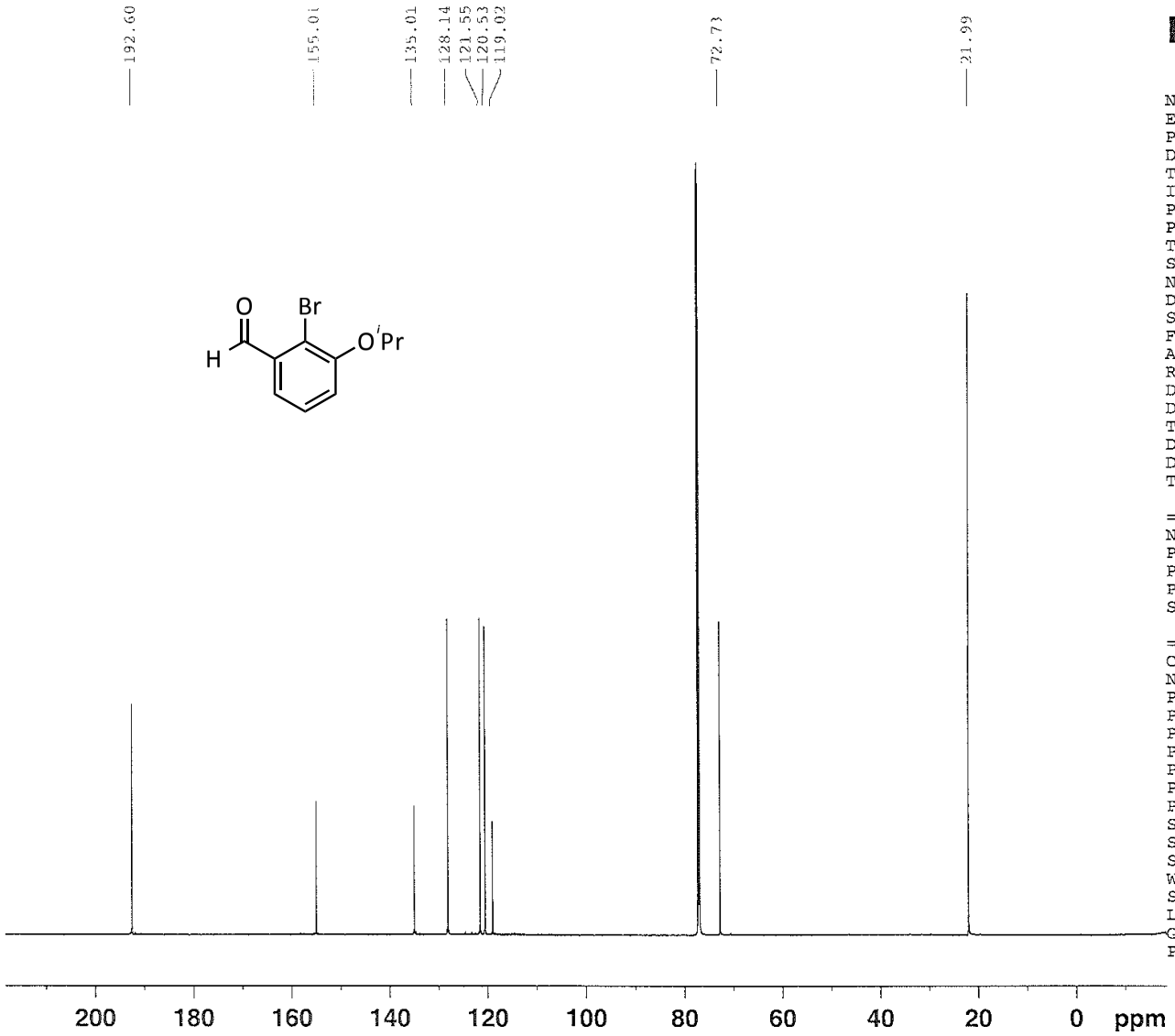
PJS1188-C



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PROCNO	1
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INSTRUM	spect
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PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	736
DS	4
SWH	41666.668 Hz
FIDRES	0.635783 Hz
AQ	0.7864820 sec
RG	203
DW	12.000 usec
DE	16.50 usec
TE	298.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.00 usec
PL1	4.50 dB
PL1W	38.14553833 W
SFO1	176.0697436 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	65.00 usec
PL2	-3.20 dB
PL12	13.60 dB
PL13	120.00 dB
PL2W	33.59817505 W
PL12W	0.70196527 W
PL13W	0.00000000 W
SFO2	700.1499406 MHz
SI	32768
SF	176.0521380 MHz
WDW	EM
SSB	0
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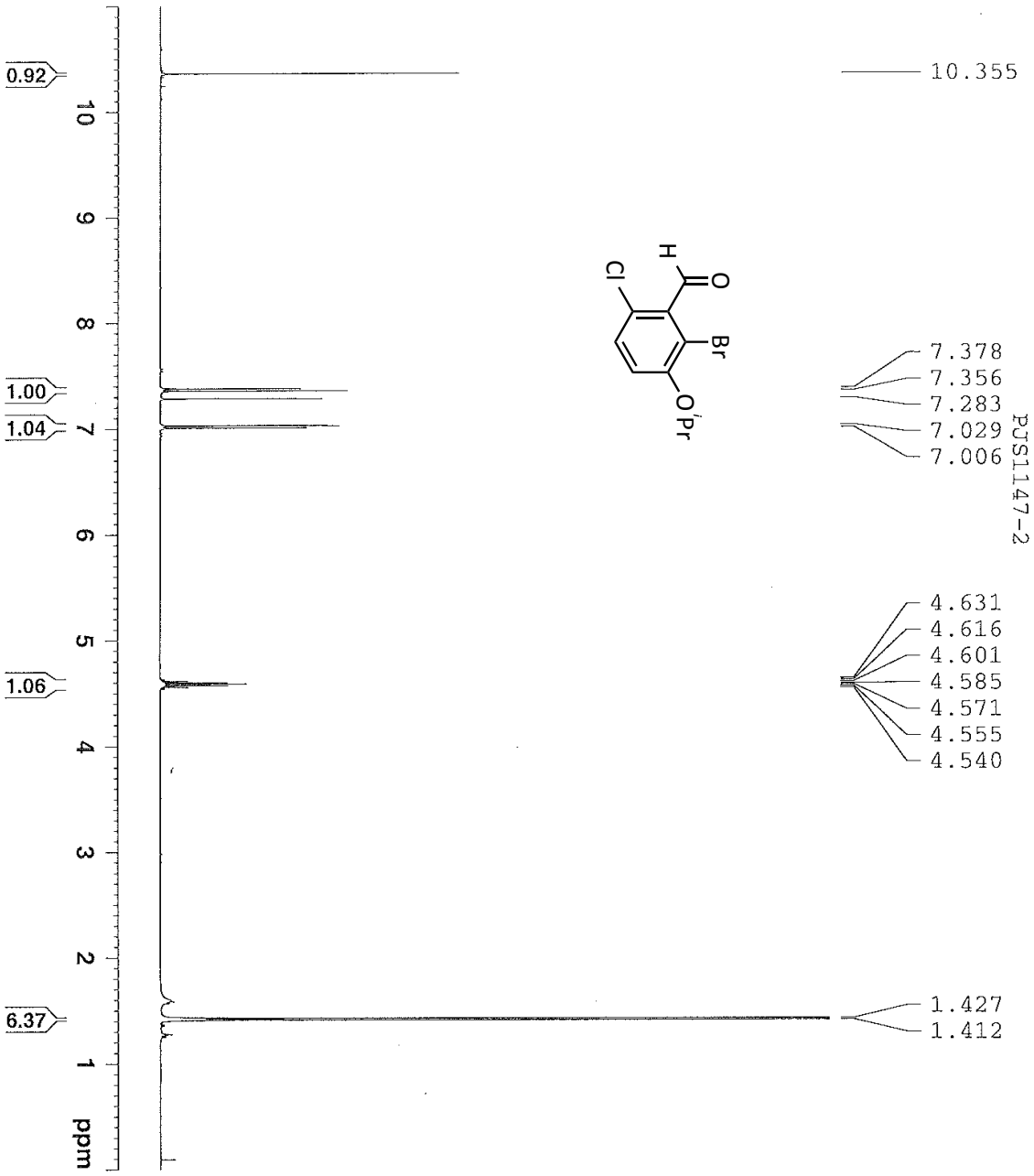
GB	0
PC	1.40

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Current Data Parameters
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EXPNO                       3
PROCNO                      1

F2 - Acquisition Parameters
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Time               16.44
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PROBHD     5 mm PABBO BB-
PULPROG            zg30
TD                 32768
SOLVENT            CDCl3
NS                 16
DS                 0
SWH                7183.908 Hz
FIDRES             0.219235 Hz
AQ                 2.2807028 sec
RG                 228.1
DW                 69.600 usec
DE                 6.50 usec
TE                 298.2 K
D1                 2.00000000 sec
TD0                1

======== CHANNEL f1 ========
NUC1               1H
P1                 11.20 usec
PL1                0.00 dB
SFO1               400.1428010 MHz

F2 - Processing parameters
SI                 16384
SF                 400.1400000 MHz
WDW                EM
SSB                0
LB                 0.00 Hz
GB                 0
PC                 1.00
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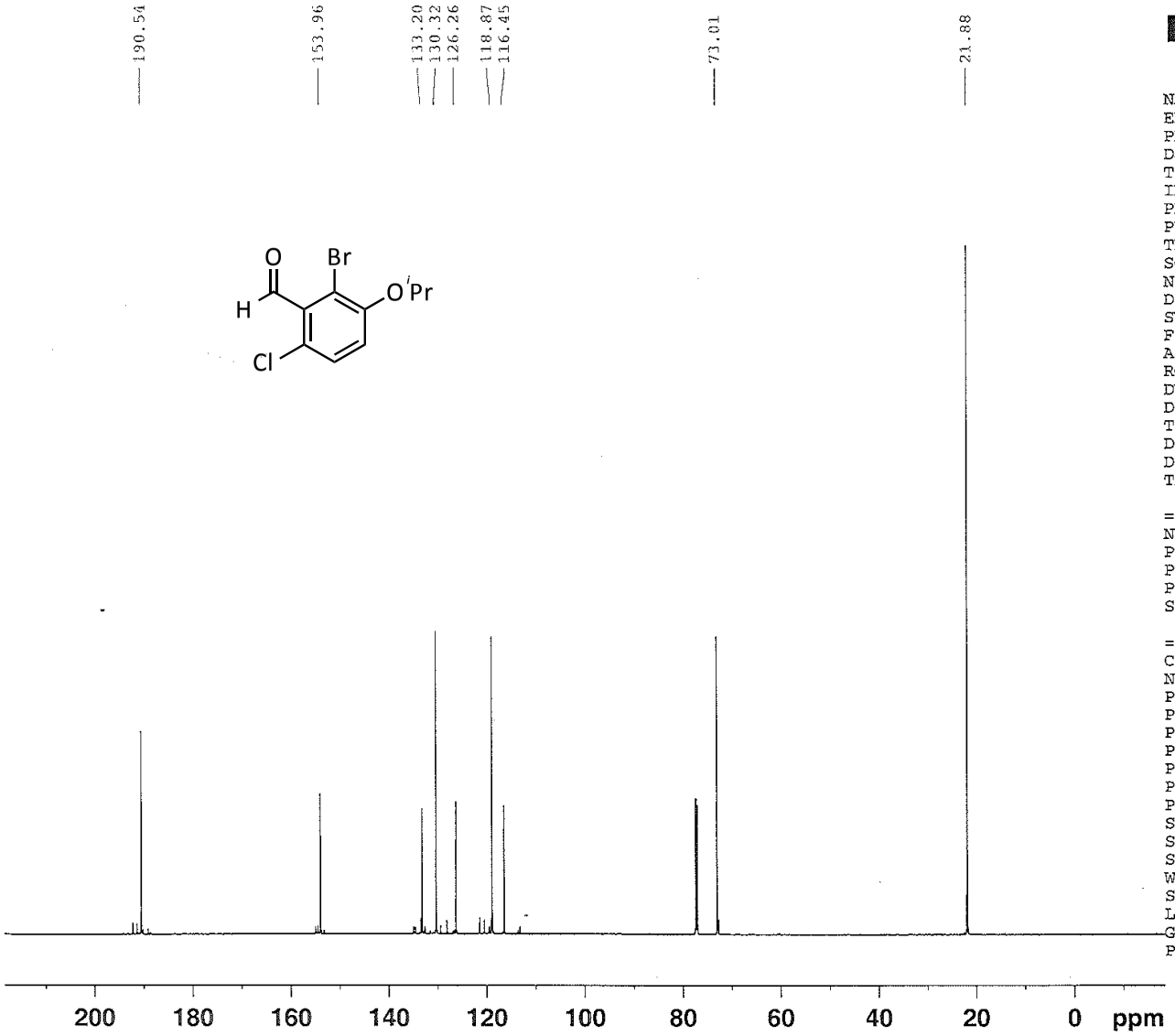
PJS1173-Carbon



BRUKER

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EXPNO	2	
PROCNO	1	
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INSTRUM	spect	
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PULPROG	zgpg30	
TD	65536	
SOLVENT	CDCl3	
NS	106	
DS	4	
SWH	41666.668	Hz
FIDRES	0.635783	Hz
AQ	0.7864820	sec
RG	203	
DW	12.000	usec
DE	16.50	usec
TE	298.3	K
D1	2.00000000	sec
D11	0.03000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	13C	
P1	9.00	usec
PL1	4.50	dB
PL1W	38.14553833	W
SFO1	176.0697436	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	65.00	usec
PL2	-3.20	dB
PL12	13.60	dB
PL13	120.00	dB
PL2W	33.59817505	W
PL12W	0.70196527	W
PL13W	0.00000000	W
SFO2	700.1499406	MHz
SI	32768	
SF	176.0521380	MHz
WDW	EM	
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LB	3.00	Hz
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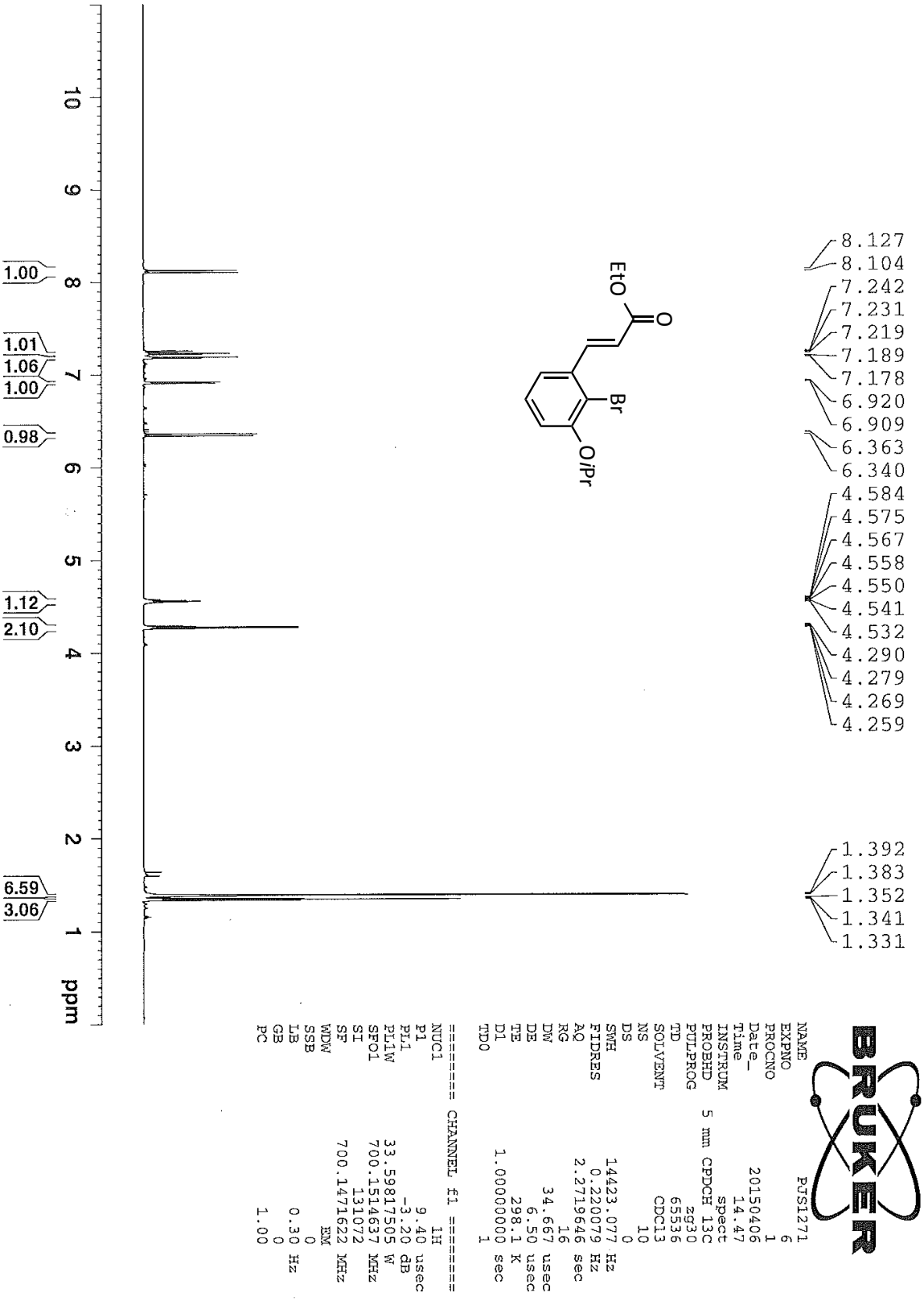
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8
7
6
5
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3
2
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EXPNO 6
PROCNO 1
Date_ 20150406
Time_ 14.47
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 10
DS 0
SWH 14423.077 Hz
FIDRES 0.220079 Hz
AQ 2.2719646 sec
RG 16
DW 34.667 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.40 usec
PL1 -3.20 dB
PL1W 33.59817505 W
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SI 131072
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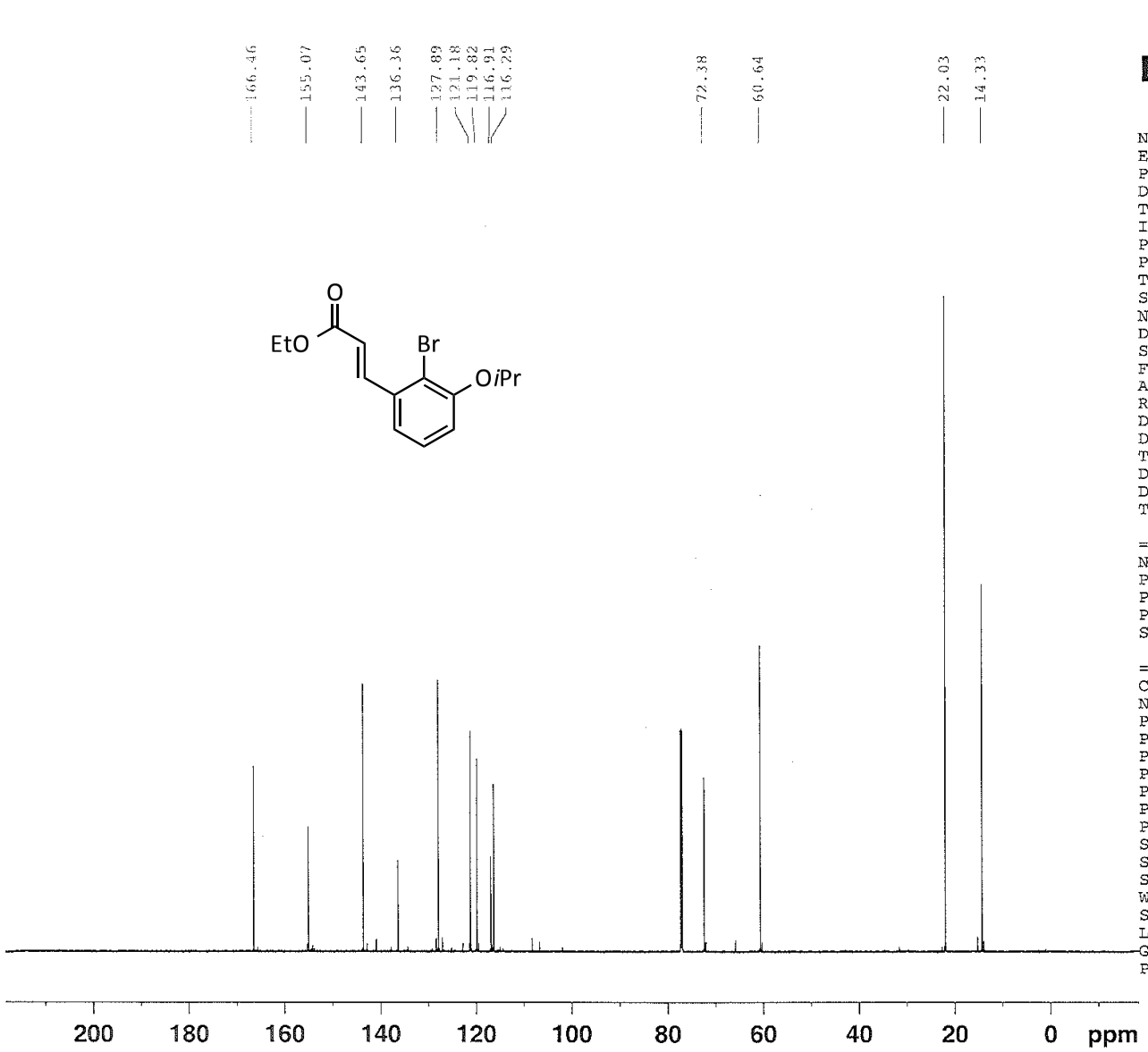
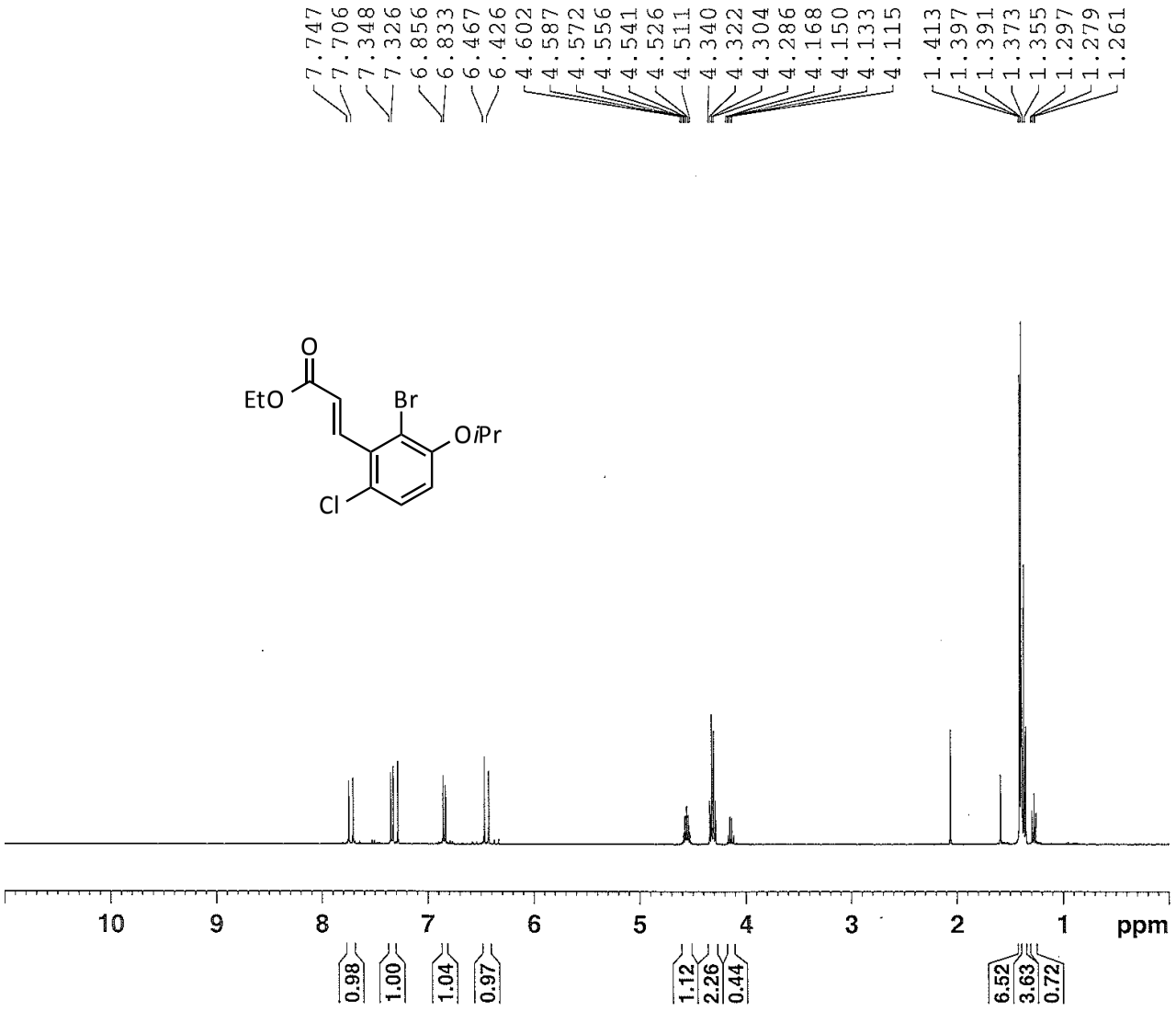
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



BRUKER

NAME	PJS1271
EXPNO	9
PROCNO	1
Date_	20150406
Time	18.23
INSTRUM	spect
PROBHD	5 mm CPDCH 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	27
DS	4
SWH	41666.668 Hz
FIDRES	0.635783 Hz
AQ	0.7864820 sec
RG	203
DW	12.000 usec
DE	21.33 usec
TE	298.3 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.00 usec
PL1	4.50 dB
PL1W	38.14553833 W
SFO1	176.0697436 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	65.00 usec
PL2	-3.20 dB
PL12	13.60 dB
PL13	120.00 dB
PL2W	33.59817505 W
PL12W	0.70196527 W
PL13W	0.00000000 W
SFO2	700.1499406 MHz
SI	131072
SF	176.0521380 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

PJS1175-1



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PROCNO	1
Date_	20140226
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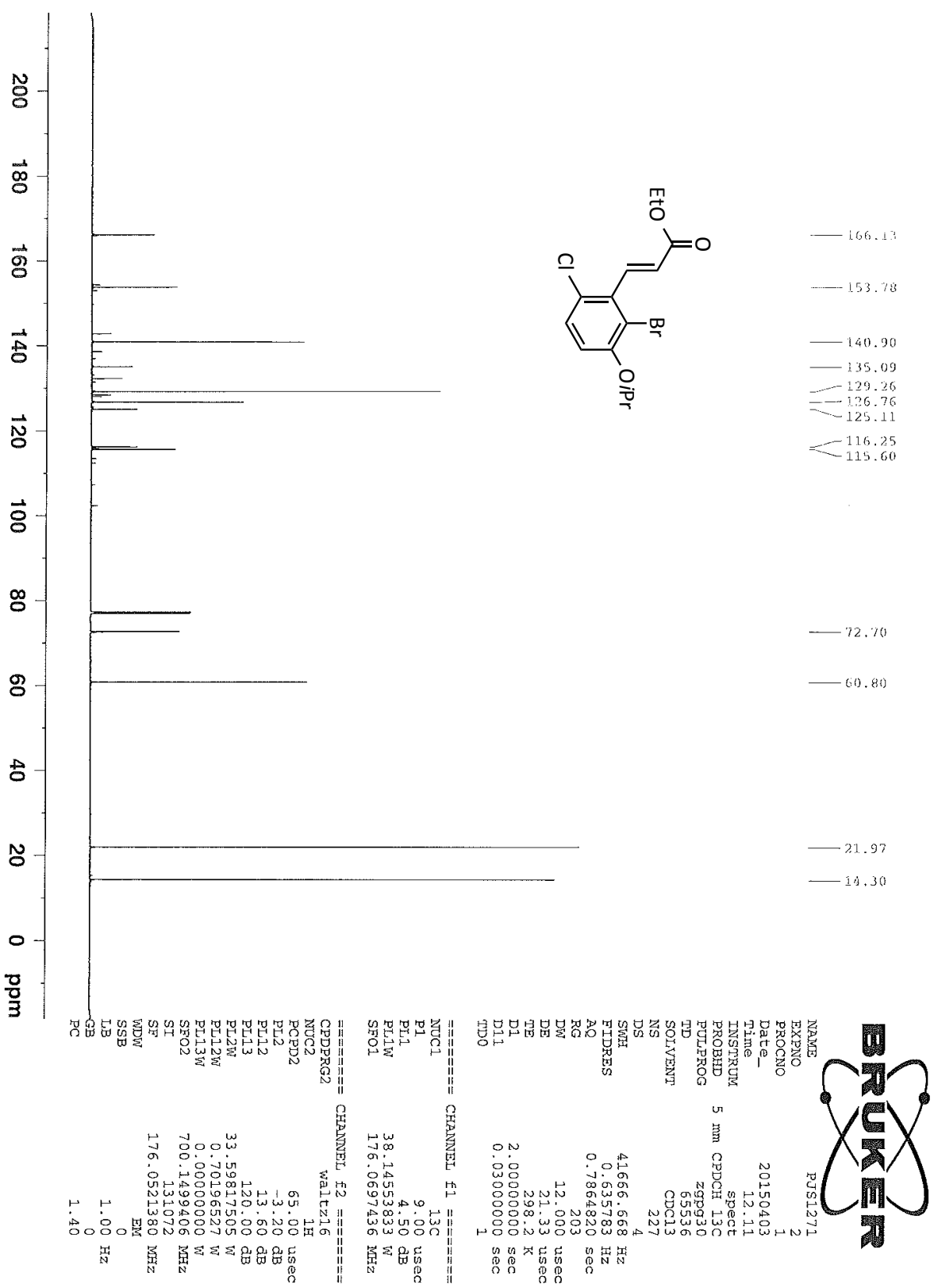
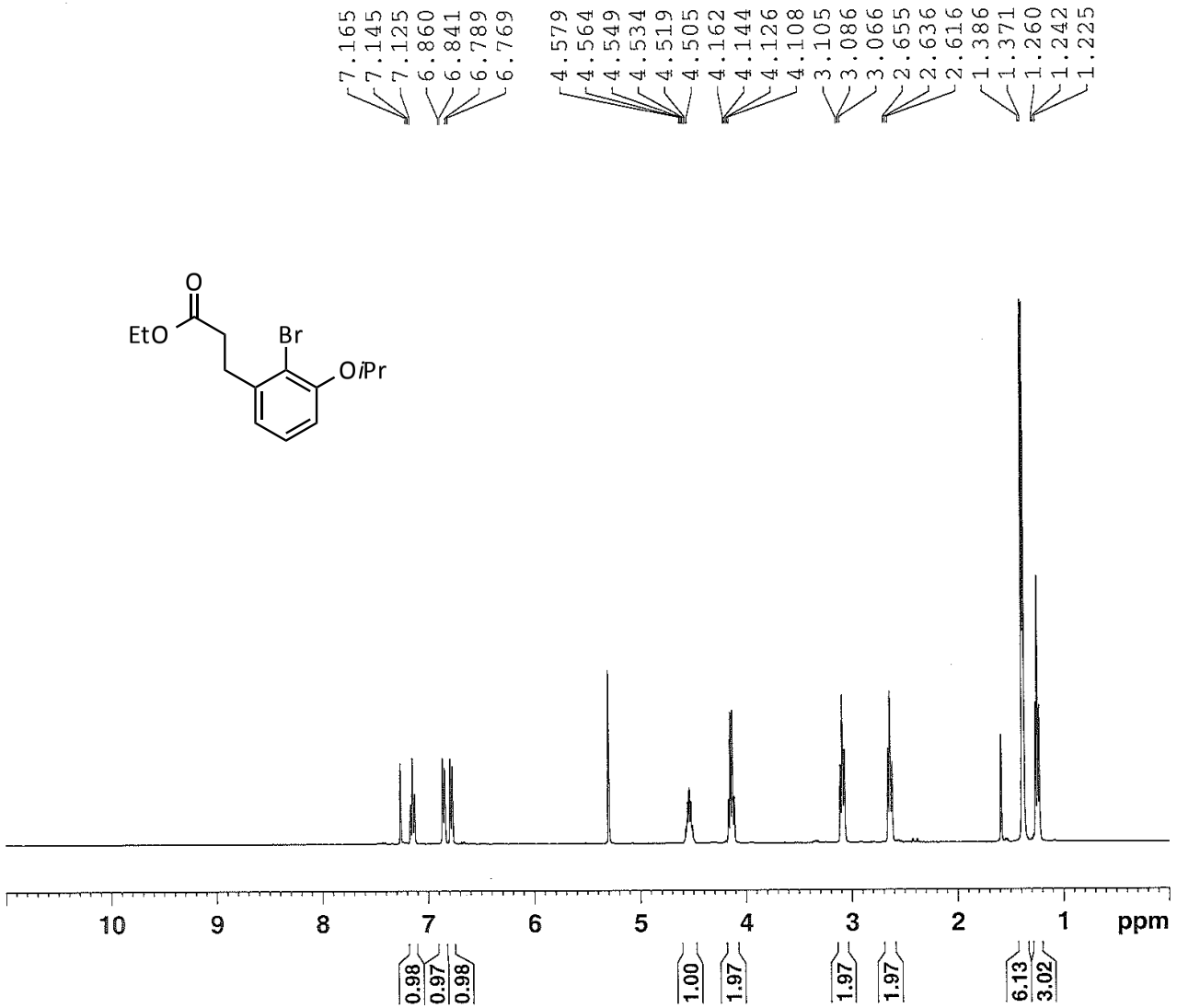
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	12
DS	0
SWH	7183.908 Hz
FIDRES	0.219235 Hz
AQ	2.2807028 se
RG	128
DW	69.600 us
DE	6.50 us
TE	298.3 K
D1	2.00000000 se
TD0	1
========	CHANNEL f1 ======
NUC1	1H
P1	11.20 us
PL1	0.00 dB
SFO1	400.1428010 MH
SI	16384
SF	400.1400000 MH
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

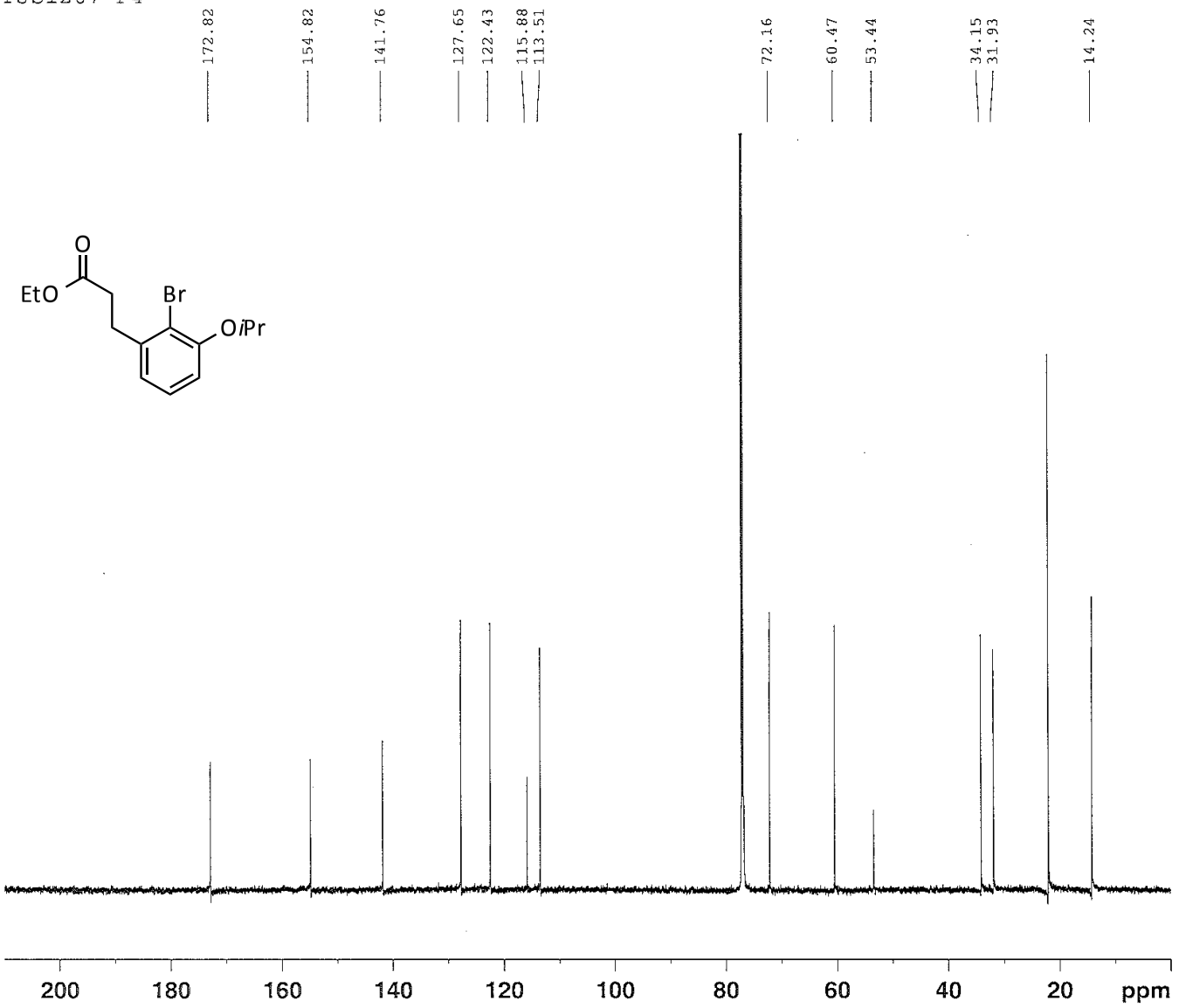

EtO
O
Cl
Br
OiPr
166.13
153.78
140.90
135.09
129.26
126.76
125.11
116.25
115.60
72.70
60.80
21.97
14.30
200
180
160
140
120
100
80
60
40
20
0
ppm
NAME PJS1271
EXPNO 2
PROCNO 1
Date_ 20150403
Time 12.11
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 227
DS 4
SWH 41666.668 Hz
FIDRES 0.635783 Hz
AQ 0.7864820 sec
RG 203
DW 12.000 usec
DE 21.33 usec
TE 298.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
========== CHANNEL f1 ==========
NUC1 13C
P1 9.00 usec
PL1 4.50 dB
PL1W 38.14553833 W
SFO1 176.0697436 MHz
========== CHANNEL f2 ==========
CPDPRG2 waltz16
NUC2 1H
PCPD2 65.00 usec
PL2 -3.20 dB
PL12 13.60 dB
PL13 120.00 dB
PL2W 33.59817505 W
PL12W 0.70196527 W
PL13W 0.00000000 W
SFO2 700.1499406 MHz
SI 1311072
SF 176.0521380 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

PJS1207-F4



NAME	PJS1207
EXPNO	4
PROCNO	1
Date_	20141006
Time	0.38
INSTRUM	robinson
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	12
DS	0
SWH	7183.908 Hz
FIDRES	0.219235 Hz
AQ	2.2807028 se
RG	128
DW	69.600 us
DE	6.50 us
TE	297.3 K
D1	2.00000000 se
TD0	1
======== CHANNEL f1 =======	
NUC1	1H
P1	11.20 us
PL1	0.00 dB
SFO1	400.1428010 MH
SI	16384
SF	400.1400090 MH
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

PJS1207-F4



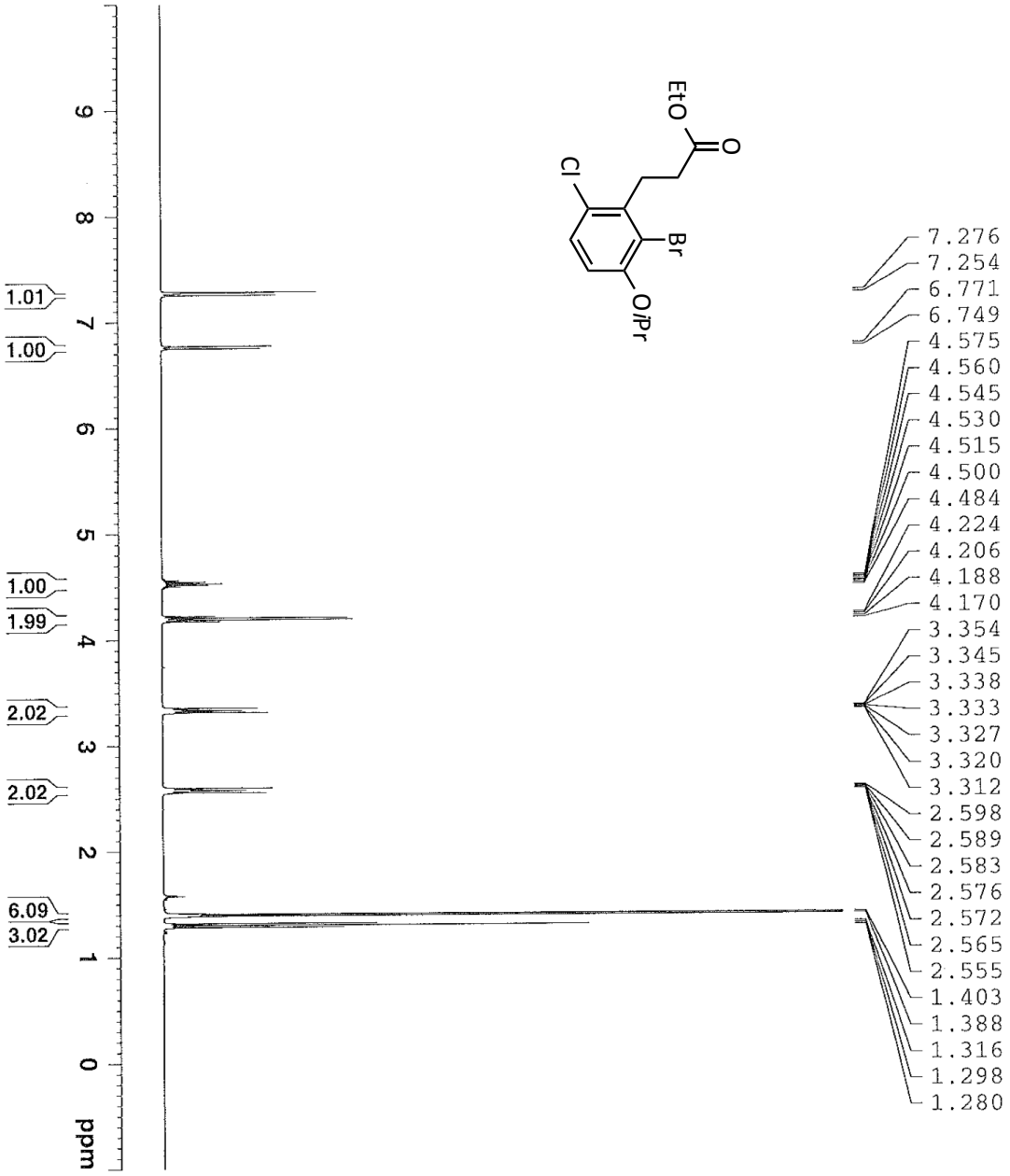

```
Current Data Parameters
NAME                  PJS1207
EXPNO                       2
PROCNO                      1

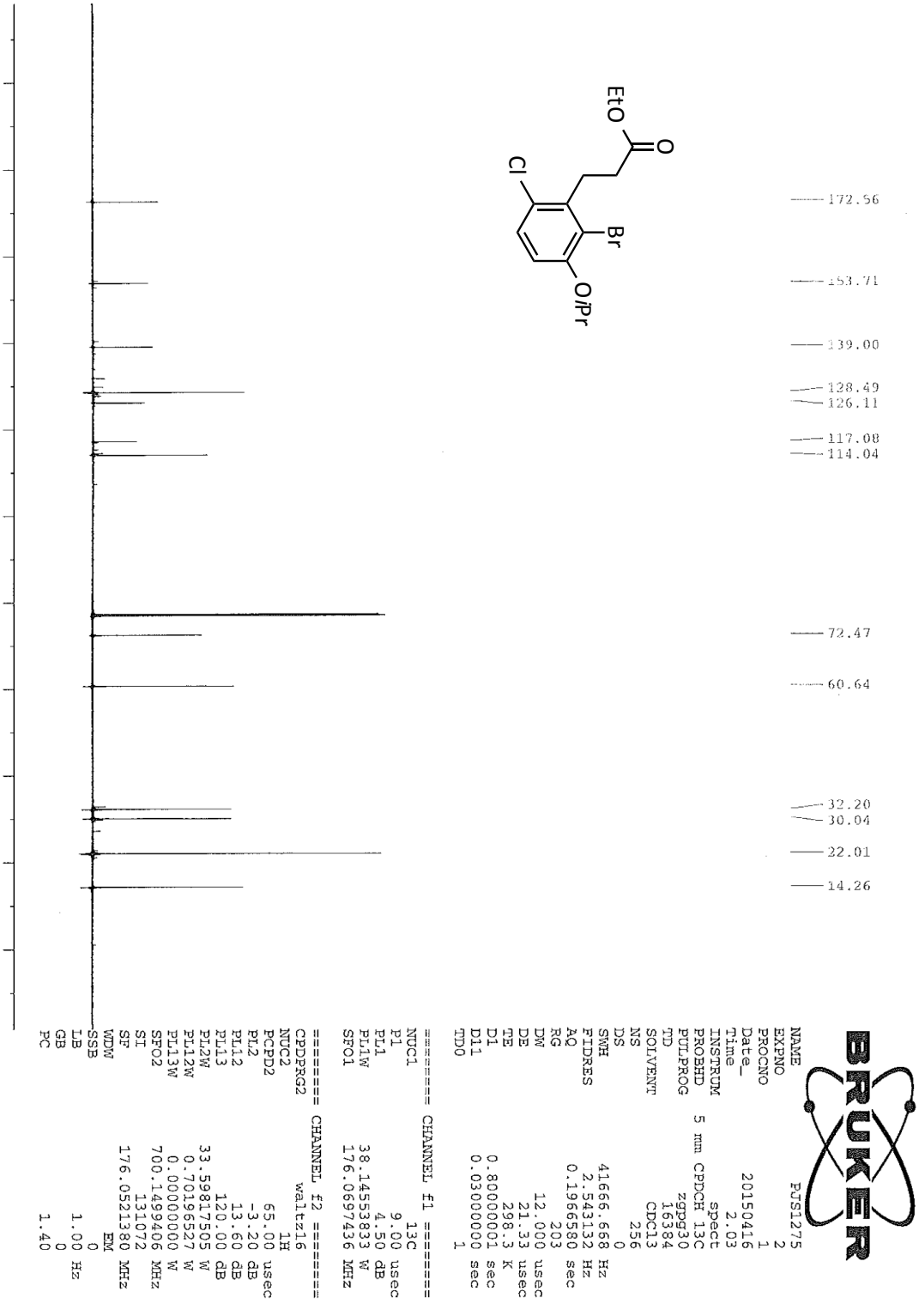
F2 - Acquisition Parameters
Date_              20141006
Time                   1.05
INSTRUM               spect
PROBHD   5 mm CPDCH 13C
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1024
DS                       4
SWH             41666.668 Hz
FIDRES          0.635783 Hz
AQ              0.7864820 sec
RG                     203
DW                12.000 usec
DE                16.50 usec
TE                298.1 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1

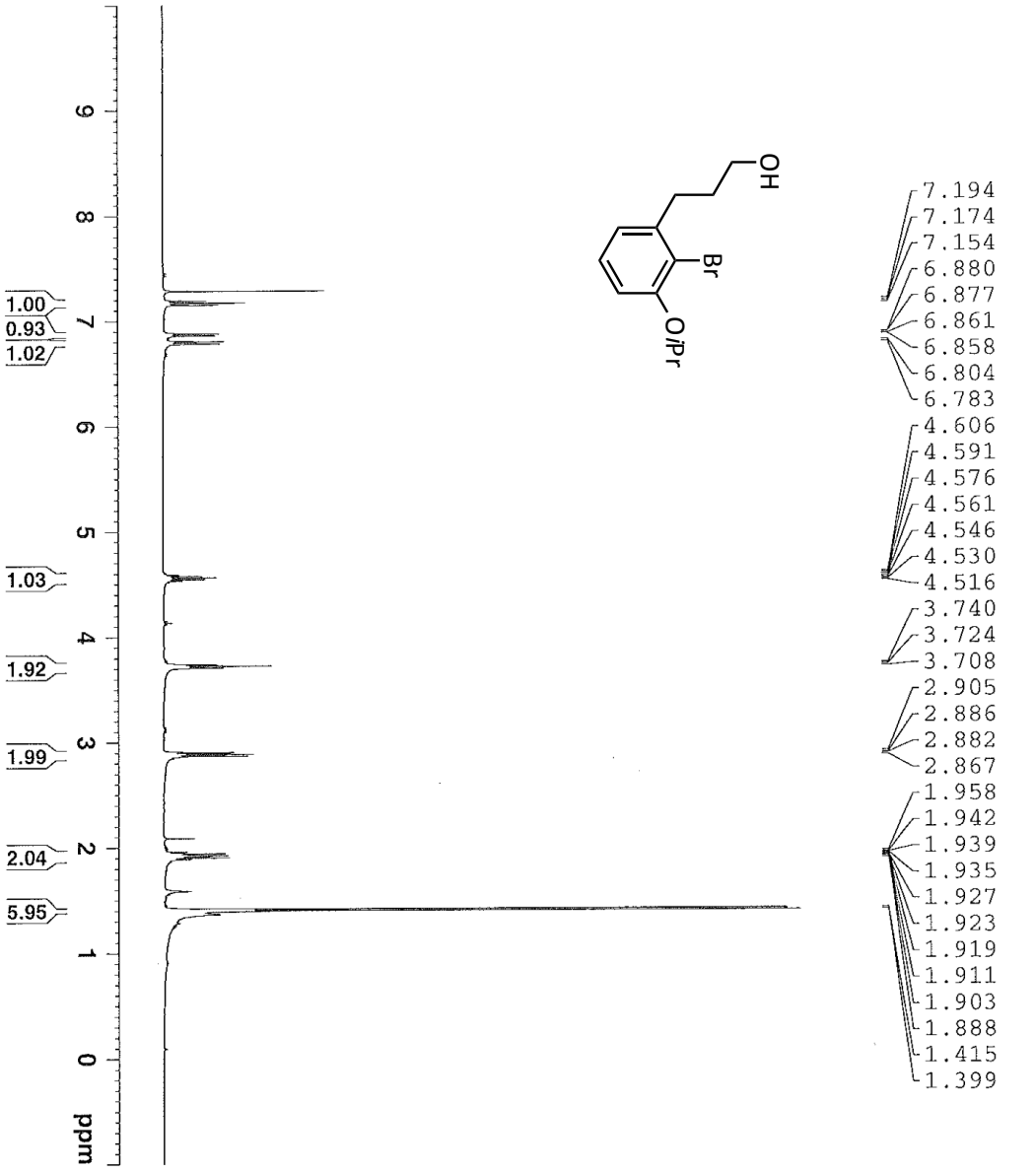
======== CHANNEL f1 ========
NUC1                   13C
P1                  9.00 usec
PL1                 4.50 dB
PL1W         38.14553833 W
SFO1        176.0697436 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2              65.00 usec
PL2                -3.20 dB
PL12               13.60 dB
PL13              120.00 dB
PL2W         33.59817505 W
PL12W         0.70196527 W
PL13W         0.00000000 W
SFO2        700.1499406 MHz

F2 - Processing parameters
SI                   32768
SF          176.0521380 MHz
WDW                    EM
SSB                     0
LB                 3.00 Hz
GB                      0
PC                   1.40
```

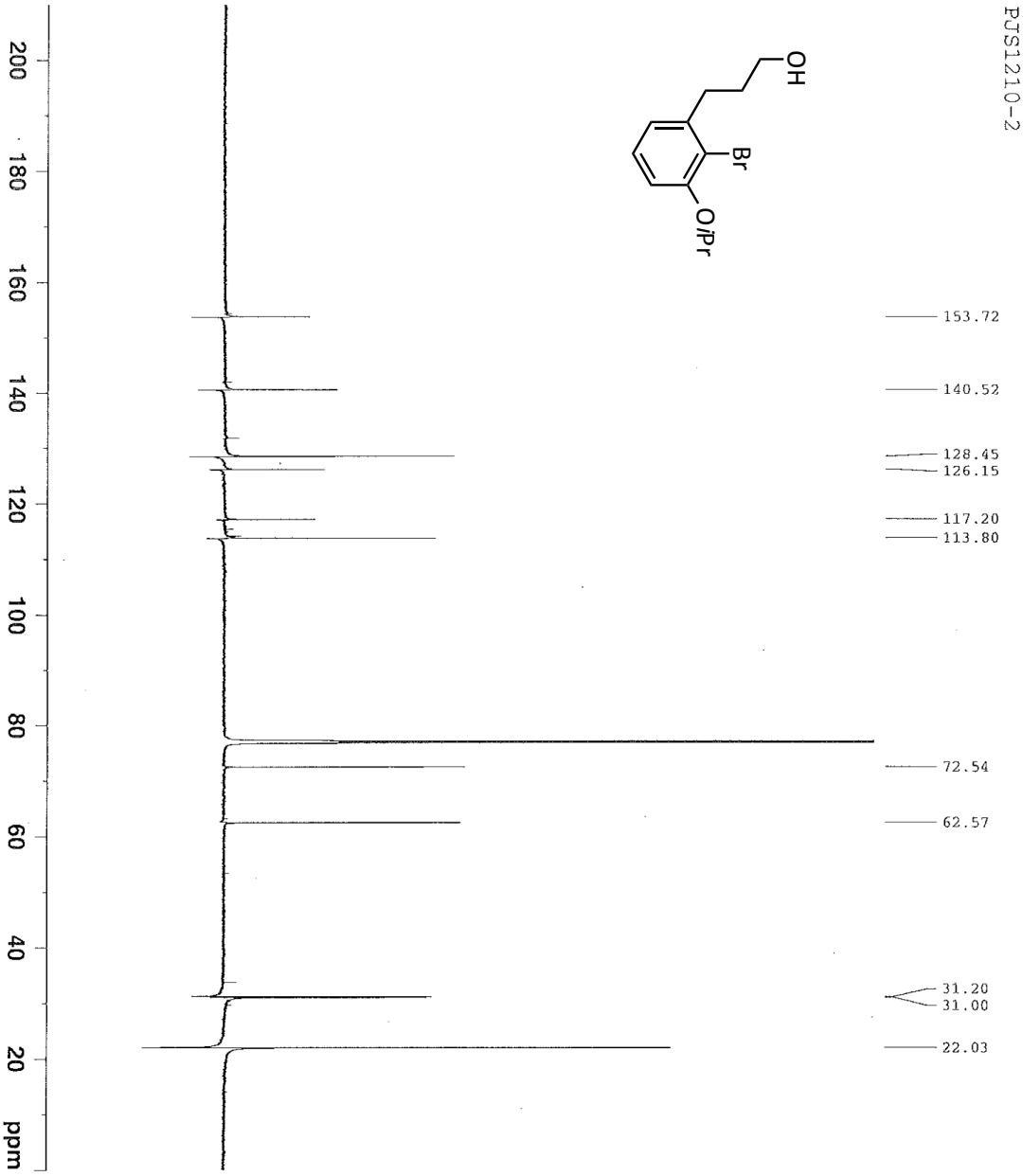

PJS1176-Fractions 42-48
7.276
7.254
6.771
6.749
4.575
4.560
4.545
4.530
4.515
4.500
4.484
4.224
4.206
4.188
4.170
3.354
3.345
3.338
3.333
3.327
3.320
3.312
2.598
2.589
2.583
2.576
2.572
2.565
2.555
1.403
1.388
1.316
1.298
1.280
EtO
O
Cl
Br
O/Pr
1.01
1.00
1.00
1.99
2.02
2.02
6.09
3.02
9
8
7
6
5
4
3
2
1
0
ppm
Current Data Parameters
NAME PJS1176
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140304
Time 12.10
INSTRUM robinson
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 12
DS 0
SWH 7183.908 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 181
DW 69.600 usec
DE 6.50 usec
TE 298.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 11.20 usec
PL1 0.00 dB
SFO1 400.1428010 MHz
F2 - Processing parameters
SI 16384
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0
PC 1.00


EtO
O
Cl
Br
OiPr
172.56
153.71
139.00
128.49
126.11
117.08
114.04
72.47
60.64
32.20
30.04
22.01
14.26
BRUKER
NAME PJS1275
EXPNO 2
PROCNO 1
Date_ 20150416
Time 2.03
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 16384
SOLVENT CDCl3
NS 256
DS 0
SWH 41666.668 Hz
FIDRES 2.543132 Hz
AQ 0.1966580 sec
RG 203
DW 12.000 usec
DE 21.33 usec
TE 298.3 K
D1 0.80000001 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 4.50 dB
PL1W 38.14553833 W
SFO1 176.0697436 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 65.00 usec
PL2 -3.20 dB
PL12 13.60 dB
PL13 120.00 dB
PL2W 33.59817505 W
PL12W 0.70196527 W
PL13W 0.00000000 W
SFO2 700.1499406 MHz
SI 131072
SF 176.0521380 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 180 160 140 120 100 80 60 40 20 0 ppm




```
NAME                  PJS1210
EXPNO                       1
PROCNO                      1
Date_              20150423
Time                   23.36
INSTRUM                robinson
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       10
DS                        0
SWH               8278.146 Hz
FIDRES               0.126314 Hz
AQ                3.9584243 sec
RG                    228.1
DW                   60.400 usec
DE                    6.50 usec
TE                   299.0 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      1H
P1                    11.20 usec
PL1                    0.00 dB
SFO1          400.1424710 MHz
SI                     131072
SF            400.1400000 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```



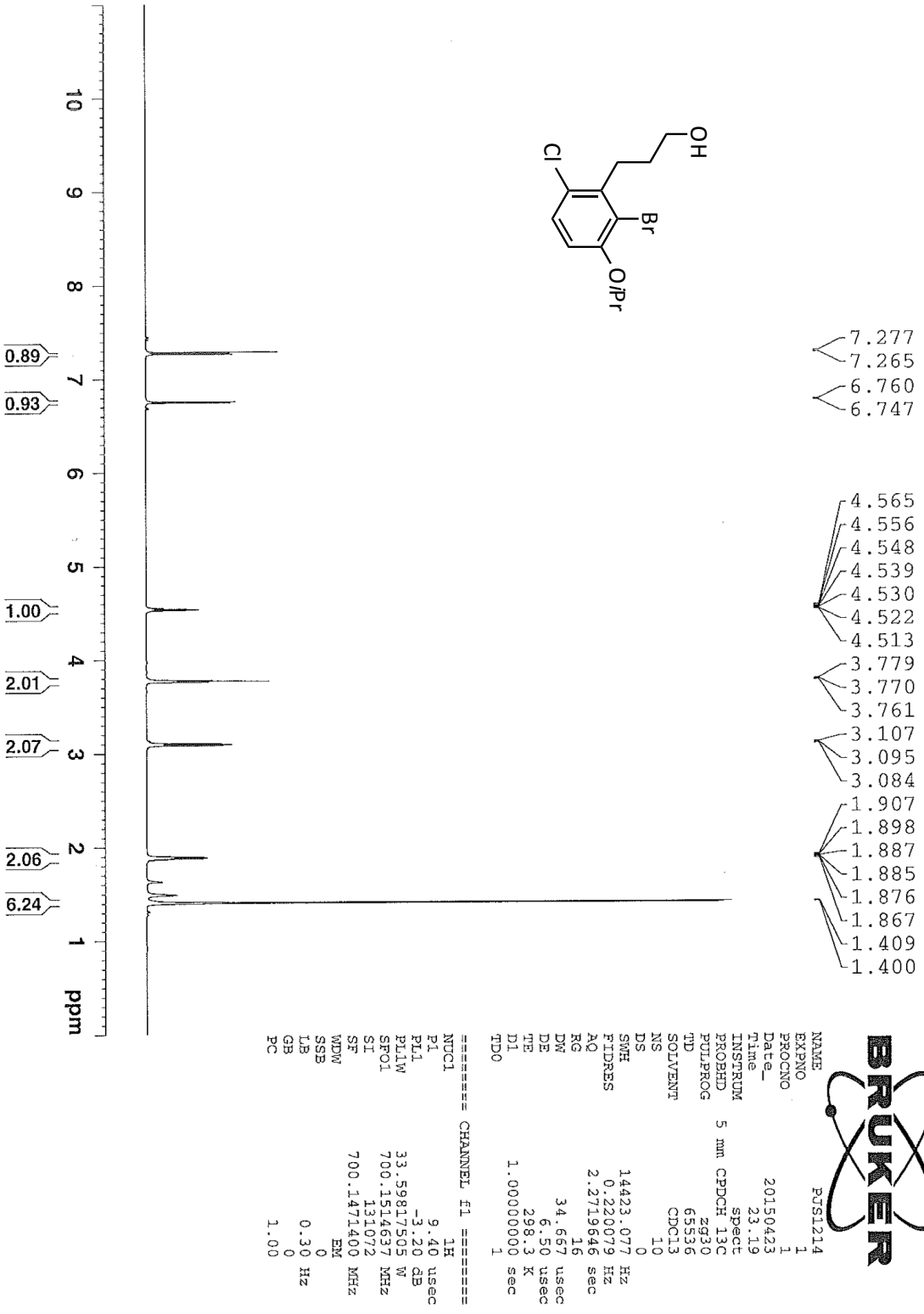

```
Current Data Parameters
NAME                  PJS1210
EXPNO                       2
PROCNO                      1

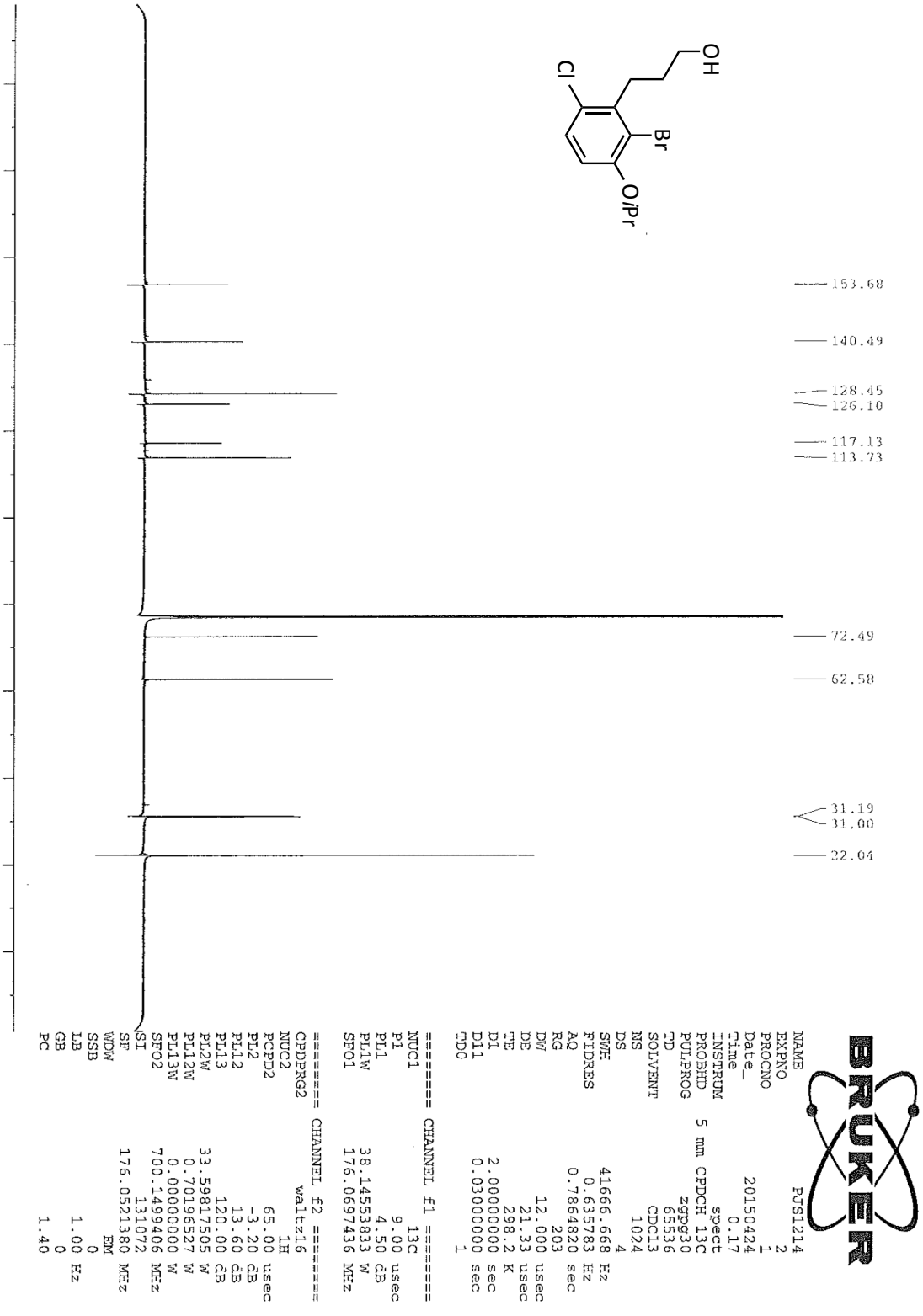
F2 - Acquisition Parameters
Date_              20141009
Time                   20.06
INSTRUM                spect
PROBHD   5 mm CPDCH 13C
PULPROG             zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    598
DS                      4
SWH              41666.668 Hz
FIDRES               0.635783 Hz
AQ                   0.7864820 sec
RG                    203
DW                   12.000 usec
DE                   16.50 usec
TE                   298.3 K
D1                   2.00000000 sec
D11                  0.03000000 sec
TD0                         1

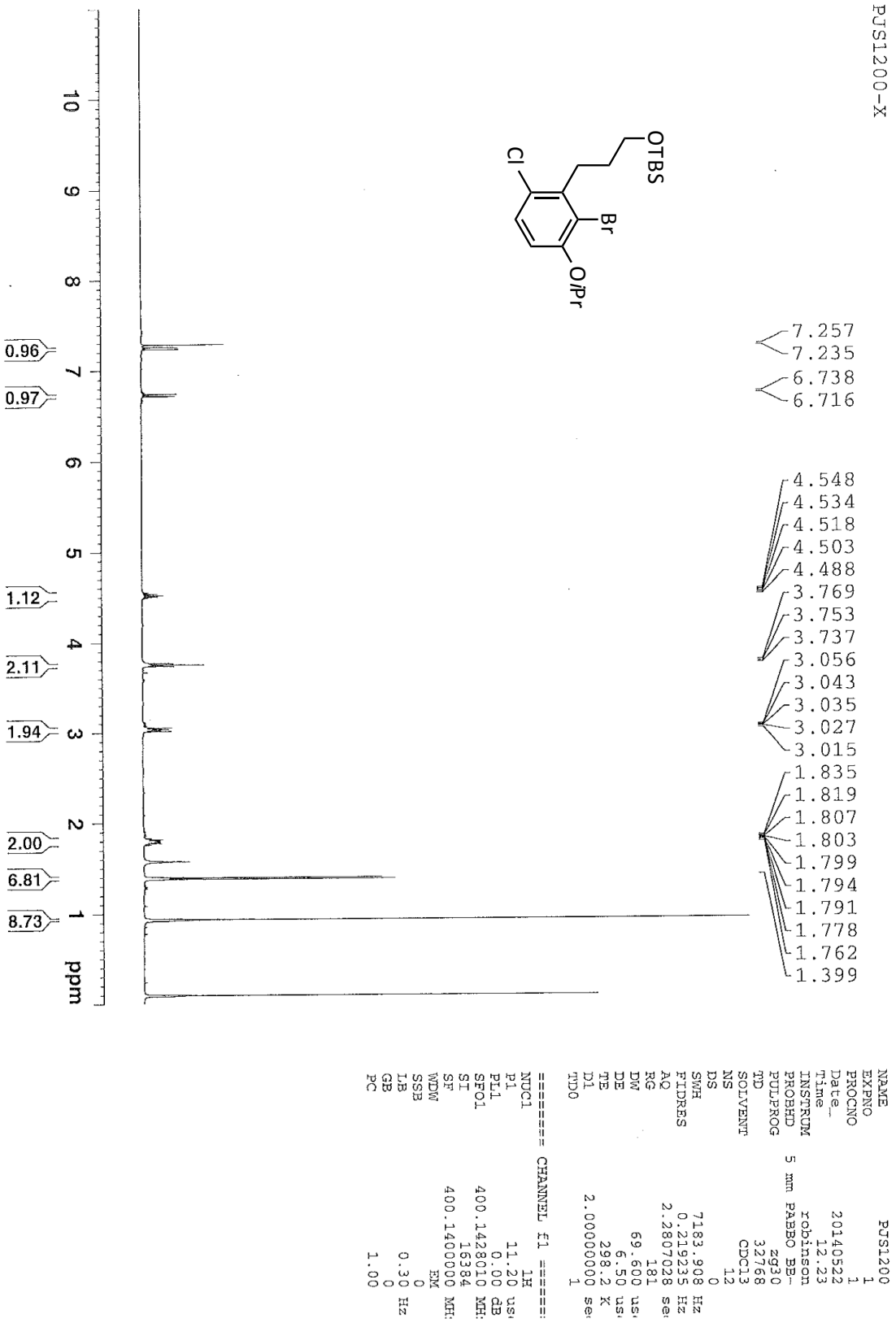
========== CHANNEL f1 ========
NUC1                   13C
P1                    9.00 usec
PL1                   4.50 dB
PL1W            38.14553833 W
SFO1           176.0697436 MHz

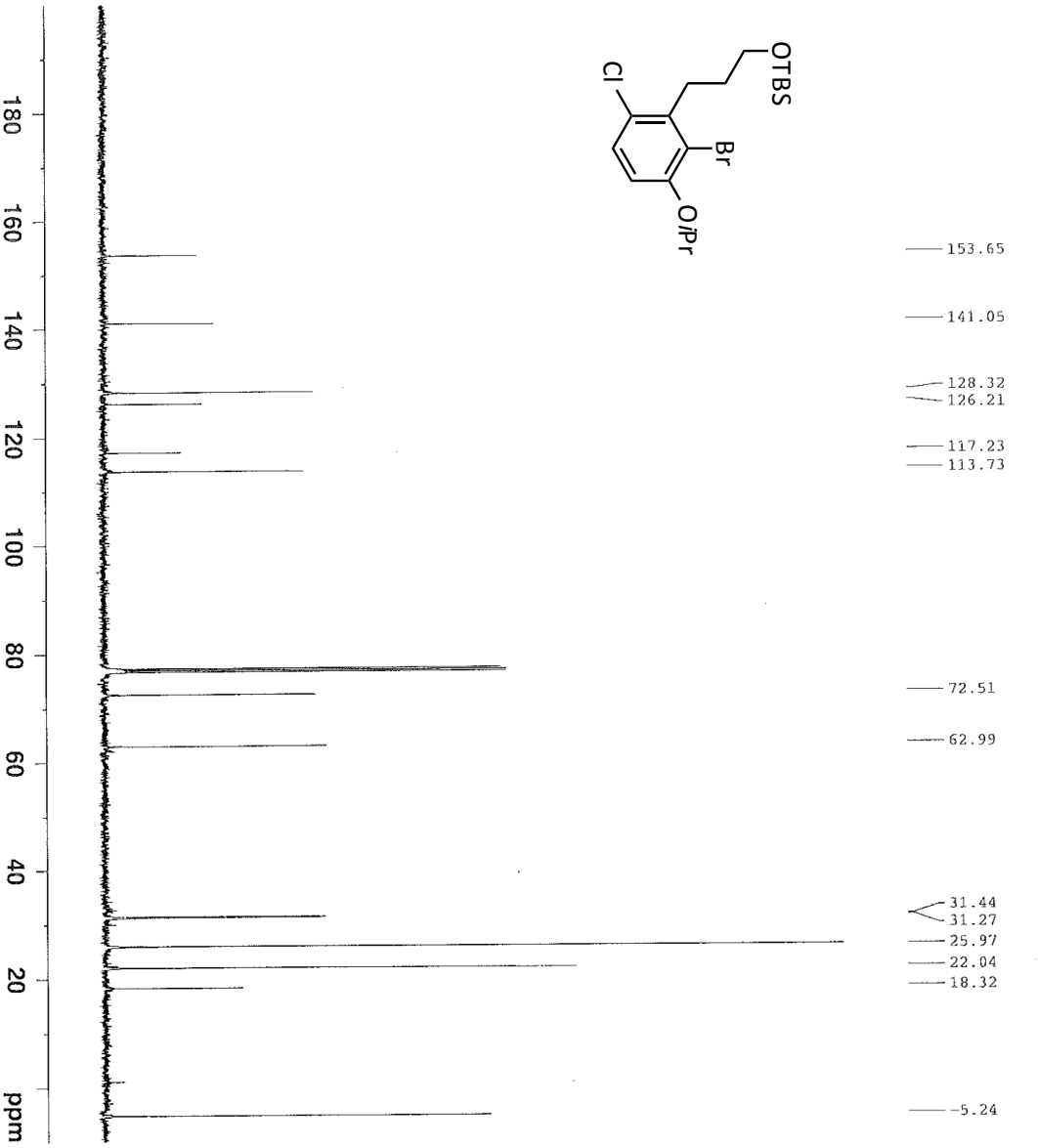
========== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                    1H
PCPD2                65.00 usec
PL2                  -3.20 dB
PL12                 13.60 dB
PL13                120.00 dB
PL2W            33.59817505 W
PL12W            0.70196527 W
PL13W            0.00000000 W
SFO2           700.1499406 MHz

F2 - Processing parameters
SI                     32768
SF             176.0521380 MHz
WDW                       EM
SSB                        0
LB                      3.00 Hz
GB                         0
PC                      1.40
```


OH
Cl
Br
O/Pr
7.277
7.265
6.760
6.747
4.565
4.556
4.548
4.539
4.530
4.522
4.513
3.779
3.770
3.761
3.107
3.095
3.084
1.907
1.898
1.887
1.885
1.876
1.867
1.409
1.400
0.89
0.93
1.00
2.01
2.07
2.06
6.24
10
9
8
7
6
5
4
3
2
1
ppm
BRUKER
NAME PJS1214
EXPNO 1
PROCNO 1
Date_ 20150423
Time 23.19
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 10
DS 0
SWH 14423.077 Hz
FIDRES 0.220079 Hz
AQ 2.2719646 sec
RG 16
DW 34.667 usec
DE 6.50 usec
TE 298.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.40 usec
PL1 -3.20 dB
PL1W 33.59817505 W
SFO1 700.1514637 MHz
SI 131072
SF 700.1471400 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


OH
Cl
Br
OiPr
153.68
140.49
128.45
126.10
117.13
113.73
72.49
62.58
31.19
31.00
22.04
200
180
160
140
120
100
80
60
40
20
0
ppm
BRUKER
NAME FOS1214
EXPNO 2
PROCNO 1
Date_ 20150424
Time 0.17
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 41666.668 Hz
FIDRES 0.635783 Hz
AQ 0.7864820 sec
RG 203
DW 12.000 usec
DE 21.33 usec
TE 298.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 4.50 dB
PL1W 38.14553833 W
SFO1 176.0697436 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 65.00 usec
PL2 -3.20 dB
PL12 13.60 dB
PL13 120.00 dB
PL2W 33.59817505 W
PL12W 0.70196527 W
PL13W 0.00000000 W
SFO2 700.1499406 MHz
SI 131072
SF 176.0521380 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

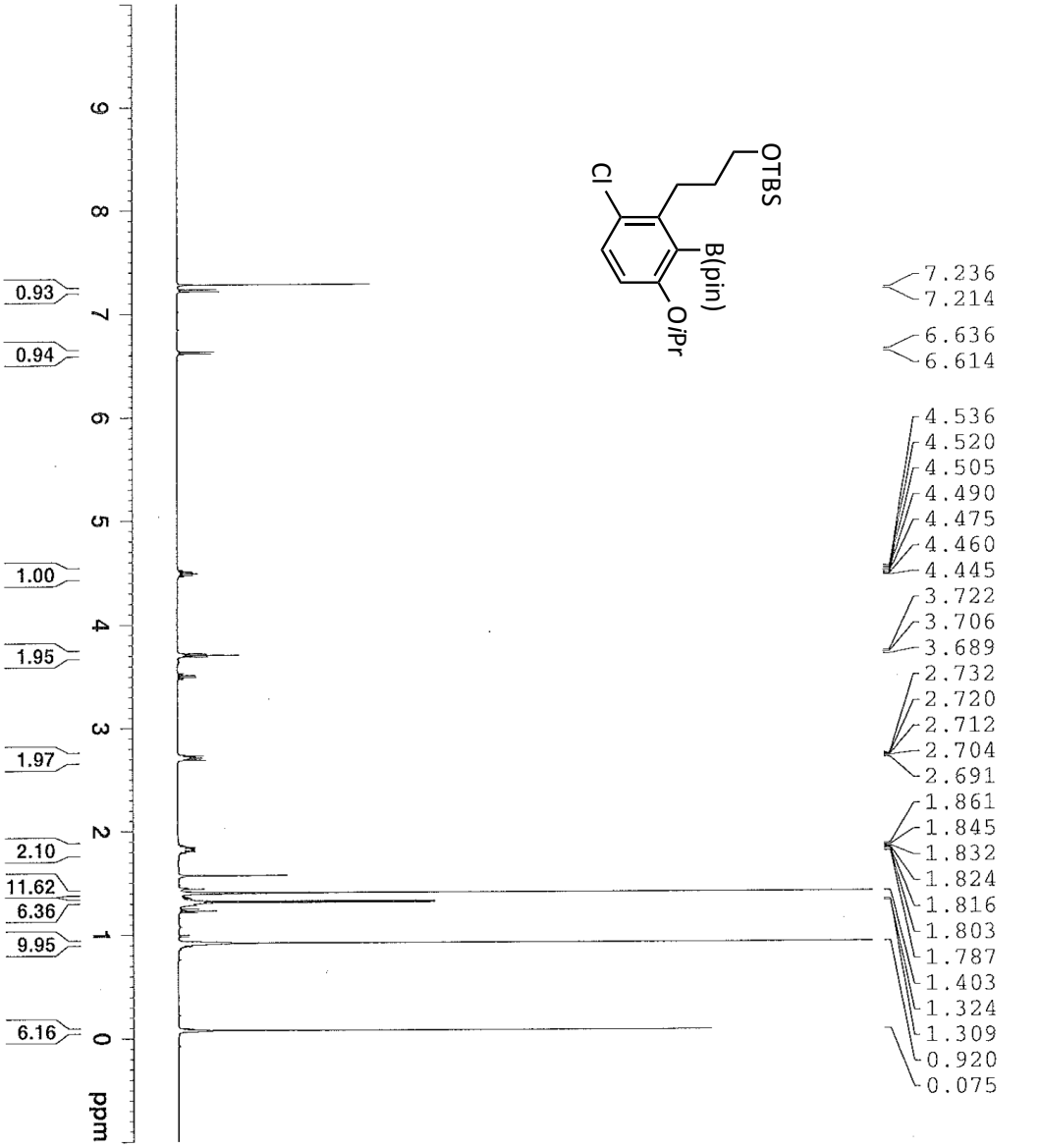

PJS1200-X
OTBS
Cl
Br
OiPr
7.257
7.235
6.738
6.716
4.548
4.534
4.518
4.503
4.488
3.769
3.753
3.737
3.056
3.043
3.035
3.027
3.015
1.835
1.819
1.807
1.803
1.799
1.794
1.791
1.778
1.762
1.399
0.96
0.97
1.12
2.11
1.94
2.00
6.81
8.73
ppm
NAME PJS1200
EXPNO 1
PROCNO 1
Date_ 20140522
Time 12.23
INSTRUM robinson
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 12
DS 0
SWH 7183.908 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 se
RG 181
DW 69.600 us
DE 6.50 us
TE 298.2 K
D1 2.00000000 se
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 11.20 us
PL1 0.00 dB
SFO1 400.1428010 MH
SI 16384
SF 400.1400000 MH
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00




```
NAME                                    PJS1248
EXPNO                                         2
PROCNO                                        1
Date_                                20150603
Time_                                    2.13
INSTRUM                                robinson
PROBHD                 5 mm PABBO BB-
PULPROG                             zgpg30
TD                                       65536
SOLVENT                                  CDCl3
NS                                         269
DS                                           4
SWH                                  24154.590 Hz
FIDRES                                0.368570 Hz
AQ                                    1.3566452 sec
RG                                         9195.2
DW                                       20.700 usec
DE                                        6.50 usec
TE                                       298.6 K
D1                                    2.70000005 sec
D11                                   0.03000000 sec
TD0                                           1

========== CHANNEL f1 ========
NUC1                                        13C
P1                                        7.60 usec
PL1                                      -2.00 dB
SFO1                       100.6263507 MHz

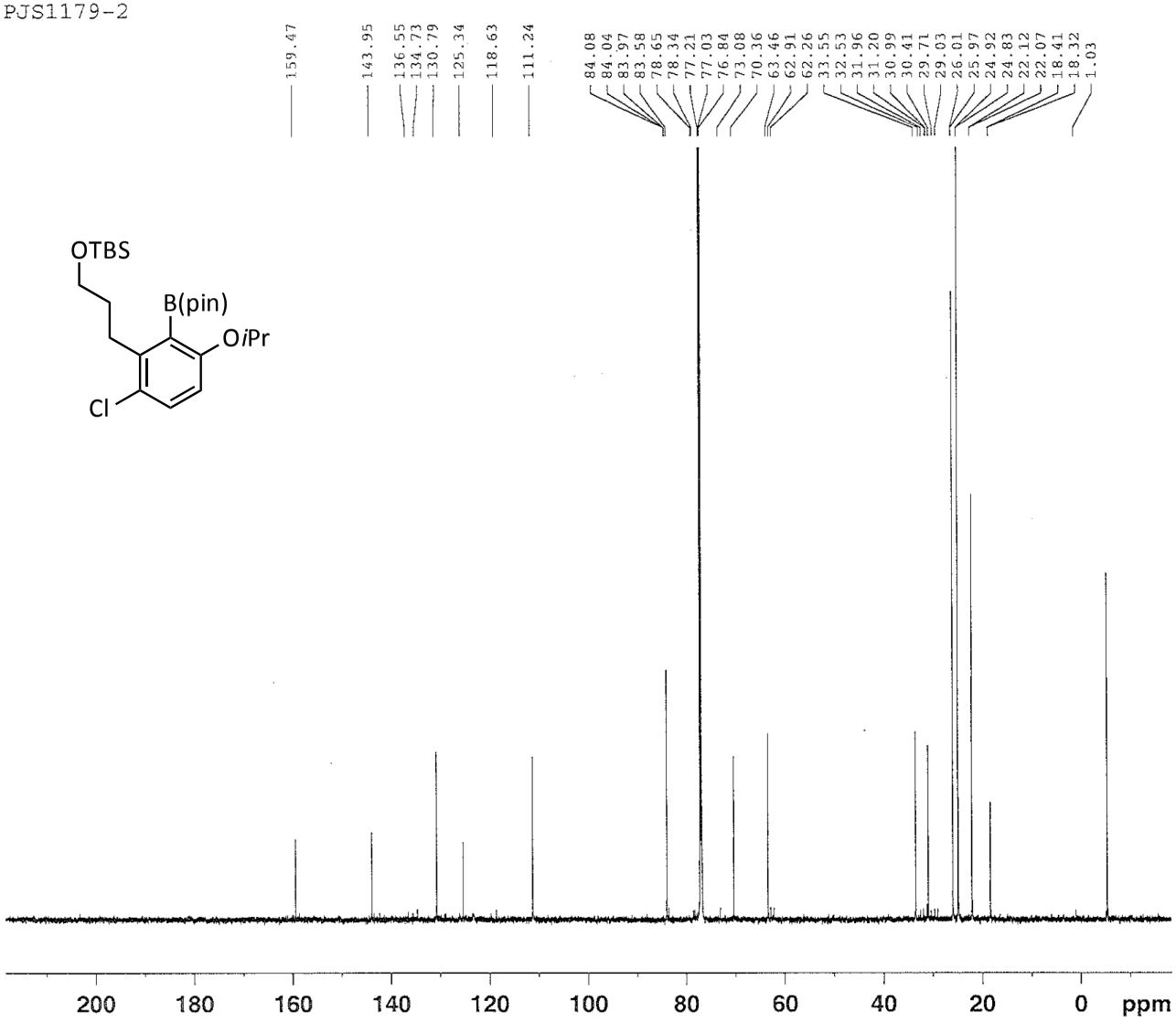
========== CHANNEL f2 ========
CPDPRG2                               waltz16
NUC2                                        1H
PCPD2                                 90.00 usec
PL2                                    0.00 dB
PL12                                  18.10 dB
PL13                                  17.00 dB
SFO2                       400.1416006 MHz
SI                                      131072
SF                         100.6152830 MHz
WDW                                        EM
SSB                                         0
LB                                       3.00 Hz
GB                                          0
PC                                       1.40
```




```
NAME                                    PJS1268
EXPNO                                         1
PROCNO                                        1
Date_                                20150306
Time                                    23.26
INSTRUM                                robinson
PROBHD                 5 mm PABBO BB-
PULPROG                              zg30
TD                                  65536
SOLVENT                             CDCl3
NS                                     10
DS                                      0
SWH                              8278.146 Hz
FIDRES                           0.126314 Hz
AQ                               3.9584243 se
RG                                    256
DW                                 60.400 us
DE                                  6.50 us
TE                                 298.2 K
D1                               1.00000000 se
TD0                                     1

======== CHANNEL f1 ========
NUC1                                   1H
P1                                  11.20 us
PL1                                  0.00 dB
SFO1                        400.1424710 MH
SI                                  131072
SF                          400.1400000 MH
WDW                                    EM
SSB                                     0
LB                                   0.30 Hz
GB                                      0
PC                                   1.00
```

PJS1179-2



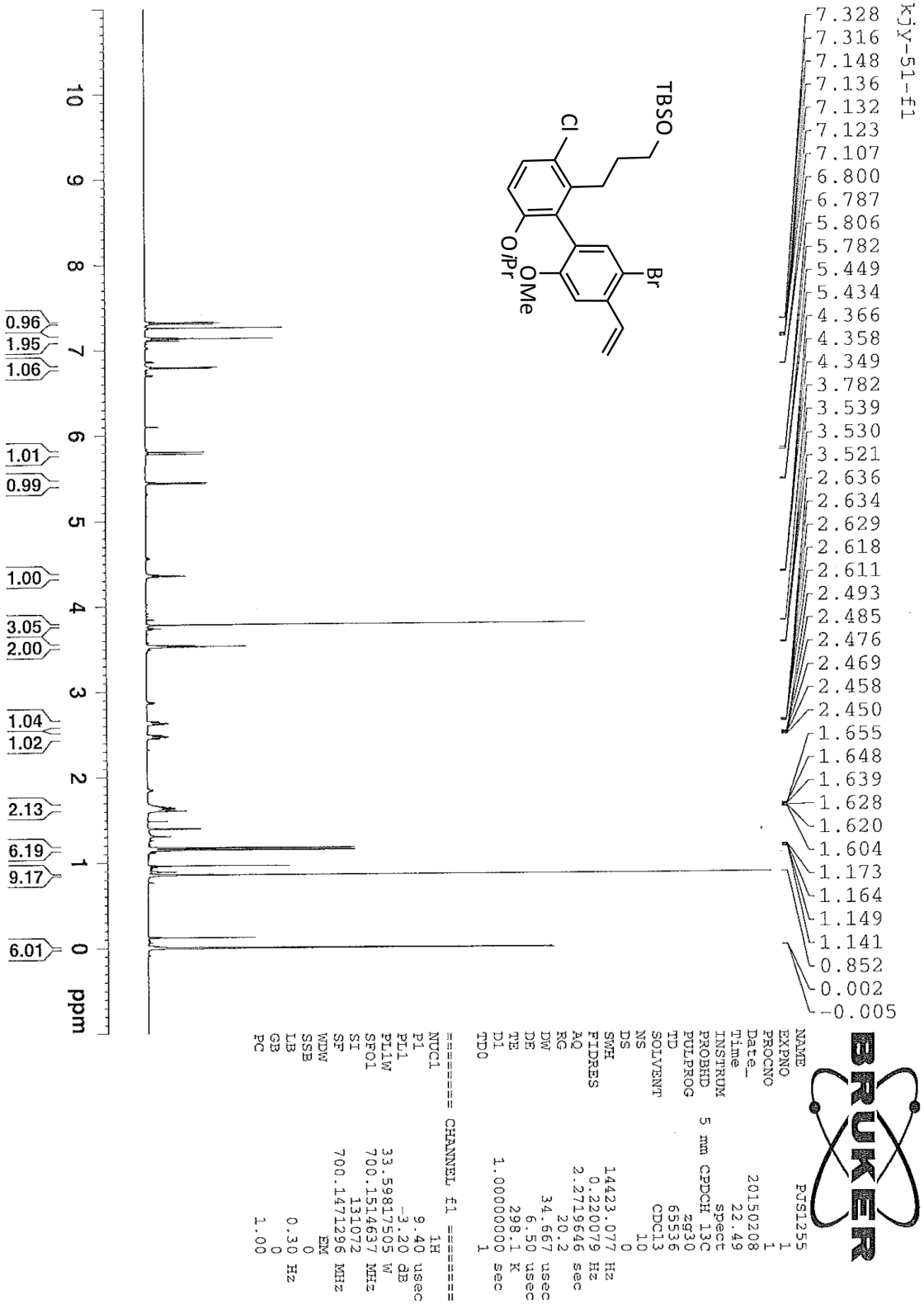

```
Current Data Parameters
NAME                  PJS1179
EXPNO                       2
PROCNO                      1

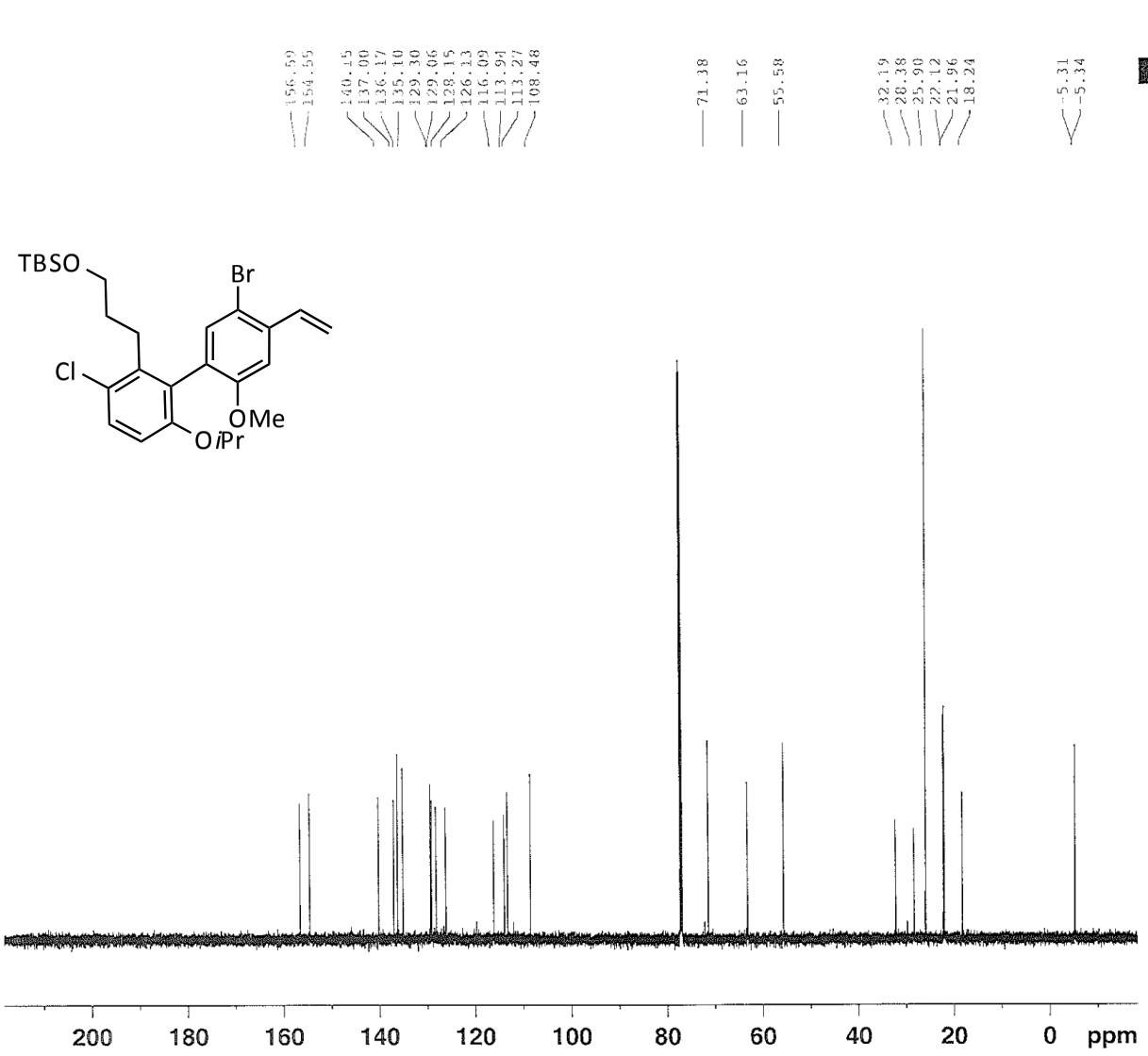
F2 - Acquisition Parameters
Date_              20140313
Time                  22.18
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        4
SWH              41666.668 Hz
FIDRES           0.635783 Hz
AQ               0.7864820 sec
RG                      203
DW                 12.000 usec
DE                 16.50 usec
TE                 298.4 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                   9.30 usec
PL1                  2.00 dB
PL1W          67.83342743 W
SFO1         176.0697436 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2               80.00 usec
PL2                 -3.00 dB
PL12                12.30 dB
PL13                12.30 dB
PL2W          32.08600616 W
PL12W          0.94692516 W
PL13W          0.94692516 W
SFO2         700.1499406 MHz

F2 - Processing parameters
SI                      32768
SF           176.0521380 MHz
WDW                        EM
SSB                         0
LB                   3.00 Hz
GB                          0
PC                   1.40
```


kjy-51-f1
TBSO
Cl
Br
OiPr
OMe
7.328
7.316
7.148
7.136
7.132
7.123
7.107
6.800
6.787
5.806
5.782
5.449
5.434
4.366
4.358
4.349
3.782
3.539
3.530
3.521
2.636
2.634
2.629
2.618
2.611
2.493
2.485
2.476
2.469
2.458
2.450
1.655
1.648
1.639
1.628
1.620
1.604
1.173
1.164
1.149
1.141
0.852
0.002
-0.005
0.96
1.95
1.06
1.01
0.99
1.00
3.05
2.00
1.04
1.02
2.13
6.19
9.17
6.01
10 9 8 7 6 5 4 3 2 1 0 ppm
NAME PJS1255
EXPNO 1
PROCNO 1
Date_ 20150208
Time 22.49
INSTRUM spect
PROBHD 5 mm CPDCH 13C
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 10
DS 0
SWH 14423.077 Hz
FIDRES 0.220079 Hz
AQ 2.2719646 sec
RG 20.2
DW 34.667 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.40 usec
PL1 -3.20 dB
PL1W 33.59817505 W
SFO1 700.1514637 MHz
SI 131072
SF 700.1471296 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



BRUKER

NAME	PJS1255+1259
EXPNO	2
PROCNO	1
Date_	20150225
Time	17.11
INSTRUM	spect
PROBHD	5 mm CPDCH 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1
DS	4
SWH	41666.668 Hz
FIDRES	0.635783 Hz
AQ	0.7864820 sec
RG	203
DW	12.000 usec
DE	21.33 usec
TE	298.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.00 usec
PL1	4.50 dB
PL1W	38.14553833 W
SFO1	176.0697436 MHz
======== CHANNEL f2 ========	
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PL2	-3.20 dB
PL12	13.60 dB
PL13	120.00 dB
PL2W	33.59817505 W
PL12W	0.70196527 W
PL13W	0.00000000 W
SFO2	700.1499406 MHz
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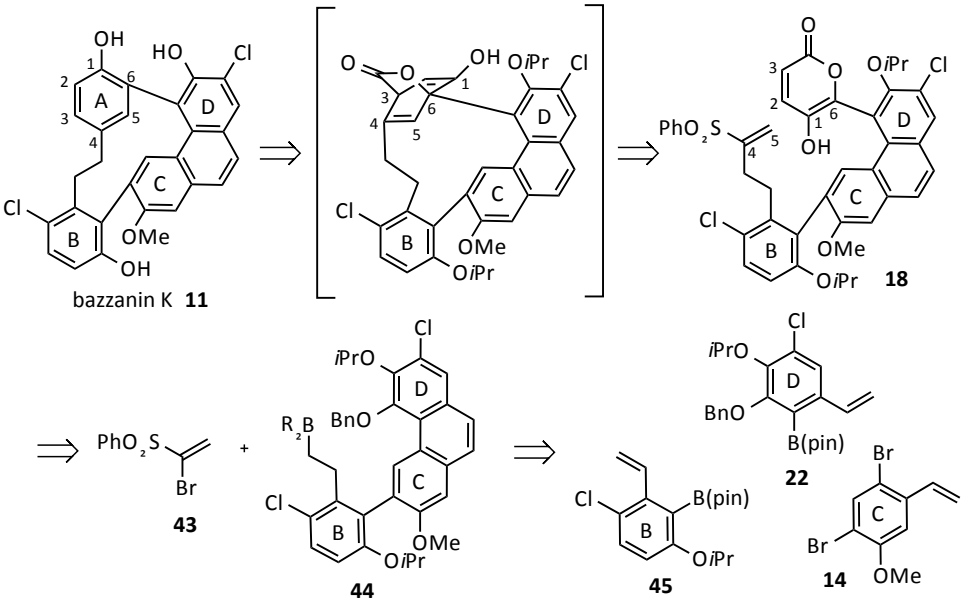
Chapter 3: Progress Towards the Total Synthesis of Bazzanin K: 2st Generation Approach

3.1 2nd Generation Retrosynthetic Analysis of Bazzanin K

In an attempt to reduce the number of functional group manipulations in the 1st generation route, a 2nd generation approach towards the total synthesis of bazzanin K was investigated. The A ring of bazzanin K is disconnected in an identical fashion to that of the 1st generation route. However, the vinyl sulfone of compound **18** will be installed via a B-alkyl Suzuki coupling between vinyl bromide **43** and alkyl borane **44**. The phenanthrene moiety will be constructed from the Suzuki cross couplings of aryl boronic esters **22** and **45** with dibromostyrene **14**. The B ring aryl boronic ester

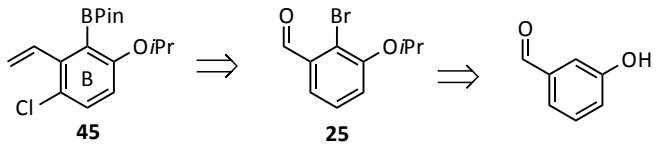


Scheme 3.1 2nd Generation Retrosynthetic Analysis of Bazzanin K

45 now contains a vinyl group which will undergo hydroboration after formation of the phenanthrene moiety.

*3.2 Retrosynthesis of Aryl Boronic Ester **45***

The B ring aryl boronic ester **21**, from the 1st generation route, required sequential reduction steps and TBS protection of the subsequent primary alcohol before the Suzuki cross coupling could take place. By simplifying the B ring coupling partner to a styrene compound, we would avoid the need for reduction chemistry and TBS protection.



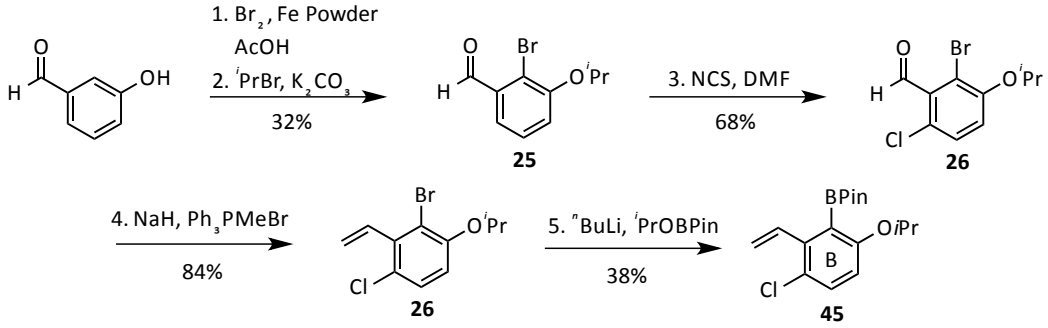
Scheme 3.2 Retrosynthesis of Aryl Boronic Ester **45**

We envisioned that aryl boronic ester **45** could be accessed from the corresponding aryl bromide. The vinyl group will be constructed in a Wittig olefination of the related benzaldehyde which will in turn be accessed by the regioselective chlorination of **25**. Bromo-benzaldehyde **25** will be access from commercially available 3-hydroxybenzaldehyde.

*3.3 Synthesis of Aryl Boronic Ester **45***

Starting from commercially available 3-hydroxybenzaldehyde, we regioselectively brominate the 2-position of the aromatic ring.

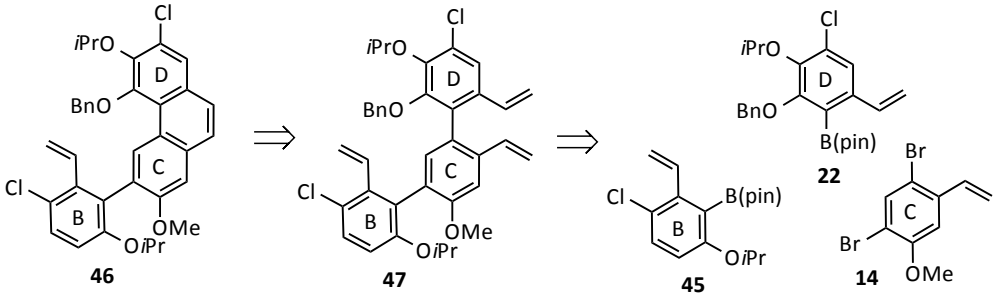
After isopropyl protection of the phenol, a regioselective chlorination is performed *para* to the bulky isopropoxy group. A Wittig olefination converts the benzaldehyde to the corresponding styrene. A lithium-halogen exchange and treatment with *i*PrOBPin completes the aryl boronic ester **45**.



Scheme 3.3 Synthesis of Aryl Boronic Ester **45**

*3.4 Suzuki Cross Coupling of Aryl Boronic Ester **45** with Dibromostyrene **14***

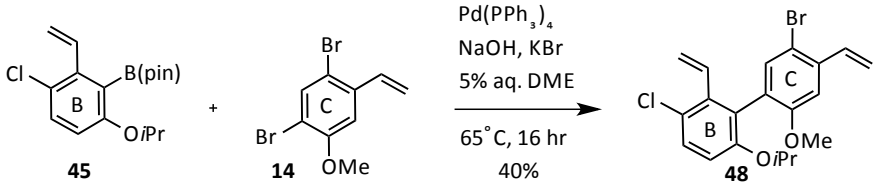
In order to access the substituted phenanthrene **46**, Grubbs ring-closing metahesis of terphenyl **47** was envisioned. To construct the terphenyl **47,** a double Suzuki reaction with dibromostyrene **14** was again chosen as the ideal strategy. We first investigated the



Scheme 3.4 Retrosynthetic Analysis of Phenanthrene **46**

efficiency of the Suzuki coupling between aryl boronic ester **45** Scheme 3.4 Retrosynthetic Analysis of Phenanthrene **46** with dibromostyrene **14**.

Using the optimized reaction conditions from the first generation route, the Suzuki coupling between aryl boronic ester **45** and dibromostyrene **14** proceeded in 40% yield to deliver biphenyl **48**. Confirmation of the regioselectivity by INADEQUATE analysis is currently underway. In an attempt to increase the yield of the coupling reaction, a screening of alternate reaction conditions will be carried out in the near future.

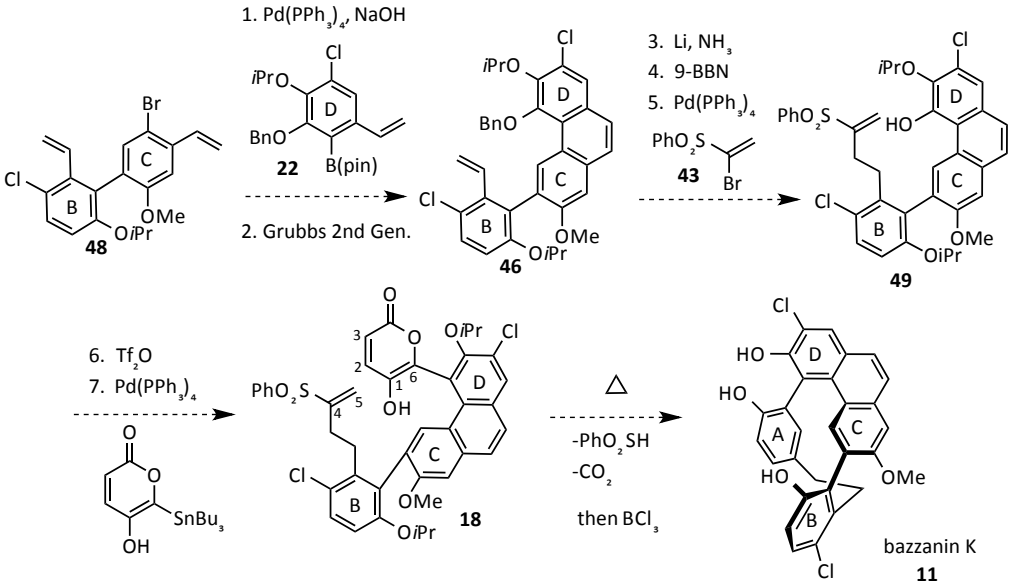


Scheme 3.5 Suzuki Coupling of Aryl Boronic Ester **45** and Dibromostyrene **14**

3.5 Future Work Towards The Total Synthesis of Bazzanin K

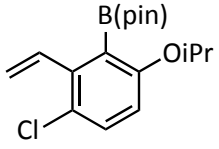
To complete the total synthesis of bazzanin K using the 2nd generation approach, biphenyl **48** will next be coupled with aryl boronic ester **22** to deliver terphenyl **47**. Treatment with Grubbs 2nd generation catalyst will construct the phenanthrene **46**. 9-BBN will be used to perform a hydroboration of the vinyl group to form the alkyl borane **44**. Vinyl bromide **43**, which is synthesized in two steps following a known literature procedure,[34] will be coupled

in a B-alkyl Suzuki reaction with alkyl borane **44** to form the vinyl sulfone **49**. Benzyl deprotection, conversion to the aryl triflate, and Stille coupling with pyrone-stannane **20** will construct the Diels—Alder precursor. At elevated temperature, we anticipate that the Diels—Alder cascade will proceed in a regioselective manner to yield the A ring of the natural product with the desired meta substitution with respect to the alkyl tether and the D Ring. After isopropyl deprotection with boron trichloride, we expect to obtain bazzanin K.



Scheme 3.6 Completion of Bazzanin K: 2nd Generation Route

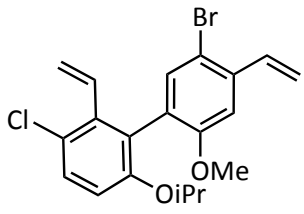
3.6 Experimental Section



2-(3-chloro-6-isopropoxy-2-vinylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2-bromo-4-chloro-1-isopropoxy-3-

vinylbenzene (32 mg, 0.12 mmol) and THF (1.2 mL, 0.1 M) are stirred under argon and cooled to -78 °C. *t*BuLi is added dropwise over 10 min. After 15 min, *i*PrOBPin is added slowly. After 2 hours, the reaction was diluted with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL). Dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (10:1 Hexanes:Et_2O) to yield 2-(3-chloro-6-isopropoxy-2-vinylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14 mg, 0.04 mmol, 36%) as a white solid.

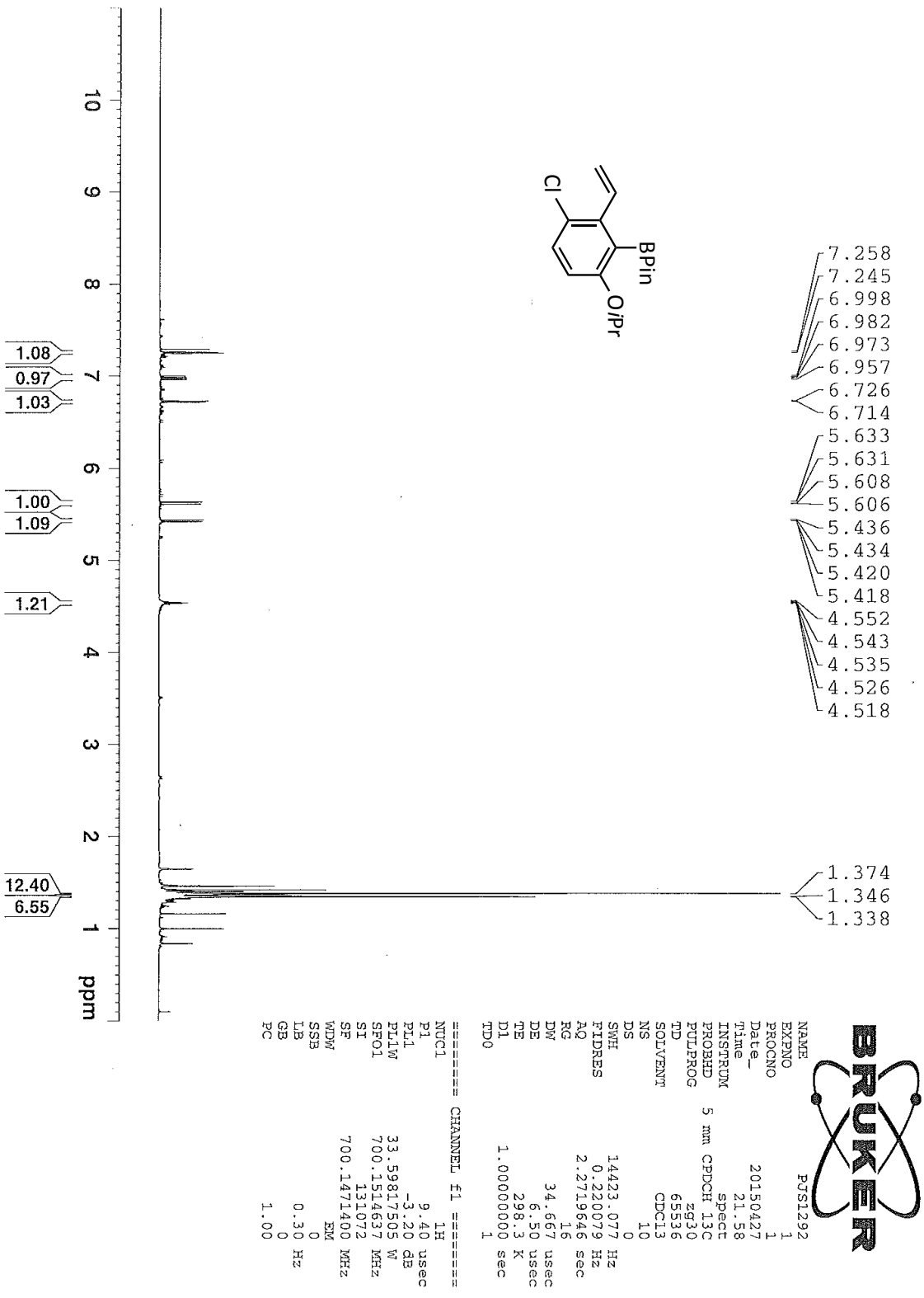
Data for 2-(3-chloro-6-isopropoxy-2-vinylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: R_f 0.27 (10:1 Hexanes:Et_2O); IR (thin film) 2977, 2930, 1578, 1442, 1312, 1248, 1138, 987, 862; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 1 H), 6.97 (dd, *J* = 11.2 Hz, 6.3 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 5.63 (d, *J* = 14 Hz, 1 H), 5.42 (d, *J* =11.2 Hz, 1 H), 4.53 (sept, *J* = 6.3 Hz, 1 H), 1.37 (s, 12 H), 1.34 (d, *J* = 5.6 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 159.6, 141.3, 135.8, 130.3, 124.3, 119.7, 112.4, 83.9, 70.4, 24.9, 22.1; HRMS (TOF MS ES+) cald for $C_{17}H_{25}O_3ClB$: 323.1585, found 323.1602.



5'-bromo-3-chloro-6-isopropoxy-2'-methoxy-2,4'-divinyl-1,1'-biphenyl 1,5-dibromo-2-methoxy-4-vinylbenzene (9 mg, 0.03 mmol), $Pd(PPh_3)_4$ (2 mg, 0.002 mmol), NaOH (5 mg, 0.12 mmol), KBr (15 mg, 0.12 mmol), dimethoxyethane (0.15 mL, 0.2 M), and H_2O (0.02 mL, 5% v/v) are stirred under argon and heated to 65 °C. After 15 min., a solution of 2-(3-chloro-6-isopropoxy-2-vinylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (193 mg, 0.41 mmol) in dimethoxyethane (0.16 mL, 0.2 M) is added. After 9 hours, the reaction is cooled to room temp., diluted with H_2O (1 mL), and extracted with EtOAc (2 x 5 mL). The organic layer was washed with H_2O (2 mL) and brine (2 mL). Dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (10:1 Hexanes:Et_2O) to yield 5'-bromo-3-chloro-6-isopropoxy-2'-methoxy-2,4'-divinyl-1,1'-biphenyl (5 mg, 0.012 mmol, 40%) as a white solid.

Data for 5'-bromo-3-chloro-6-isopropoxy-2'-methoxy-2,4'-divinyl- 1,1'-biphenyl: R_f 0.33 (10:1 Hexanes:Et_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 1 H), 7.25 (s, 1 H), 7.10 (dd, *J* = 11.2 Hz, 6.3 Hz, 1 H), 7.09 (s, 1 H), 6.50 (dd, *J* = 11.2 Hz, 6.3 Hz, 1 H), 5.77 (dd, *J* = 10.5 Hz, 0.7 Hz, 1 H), 5.41 (dd, *J* = 10.5 Hz, 0.7 Hz,1 H), 5.26 (dd, *J* = 11.9 Hz, 1.4 Hz, 1 H), 5.16 (d, *J* = 2.1 Hz, 1 H), 5.13 (d, *J* = 1.4 Hz, 1 H), 4.35 (sept, *J* = 6.3 Hz, 1 H), 3.77 (s, 3 H), (m, 1 H), 1.18 (d, *J* = 6.3 Hz, 3 H), 1.15 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 156.5, 154.4, 137.2, 136.8, 136.1, 135.5, 132.9, 129.4, 128.2, 128.1, 124.8, 120.8, 116.0, 114.5, 113.8, 108.4,

71.5, 55.6, 22.0, 21.9; HRMS (TOF MS ES+) cald for $C_{20}H_{20}O_2ClBr$: 406.03351, found 406.03454.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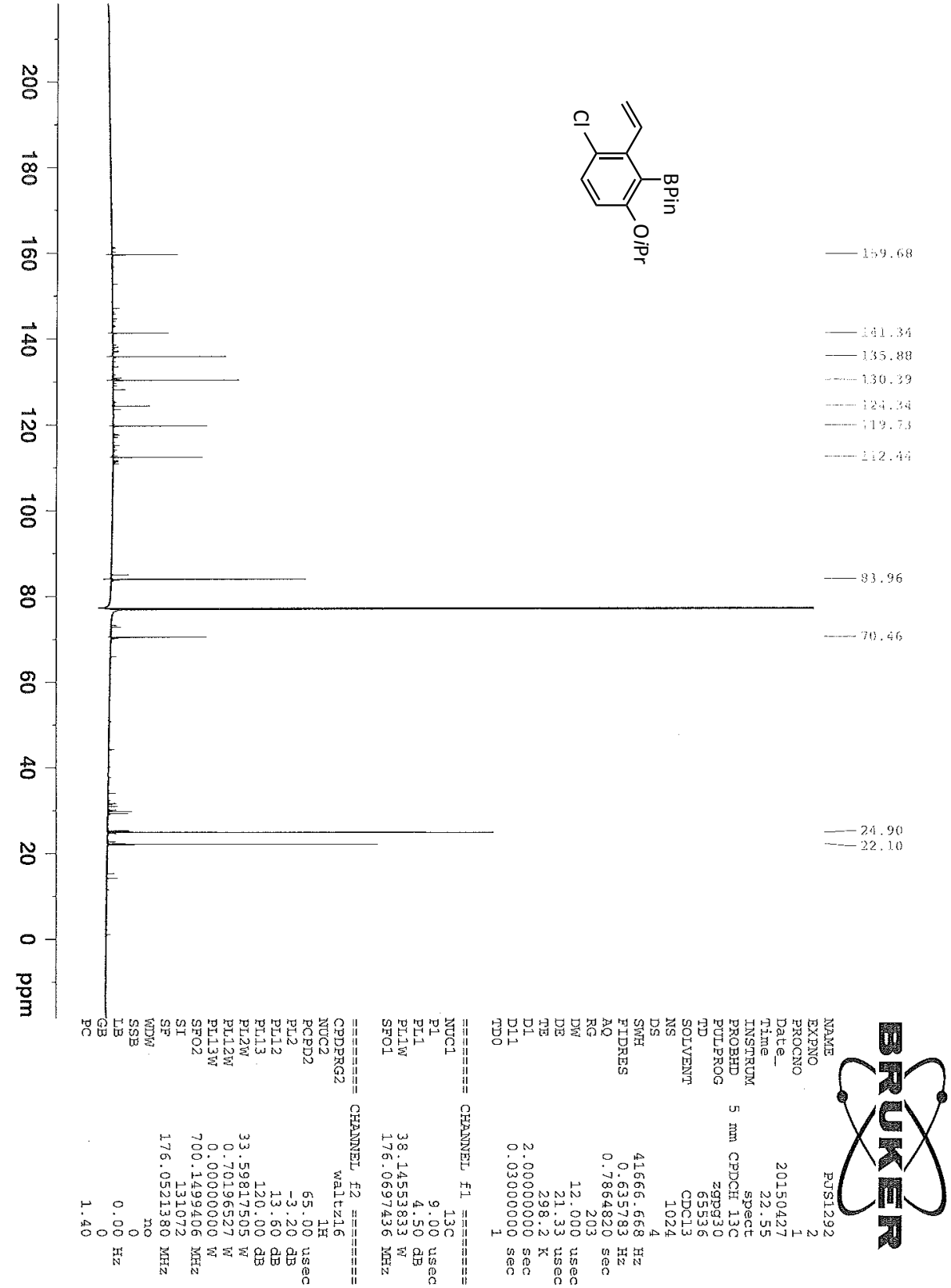


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PL12                     13.60 dB
PL13                    120.00 dB
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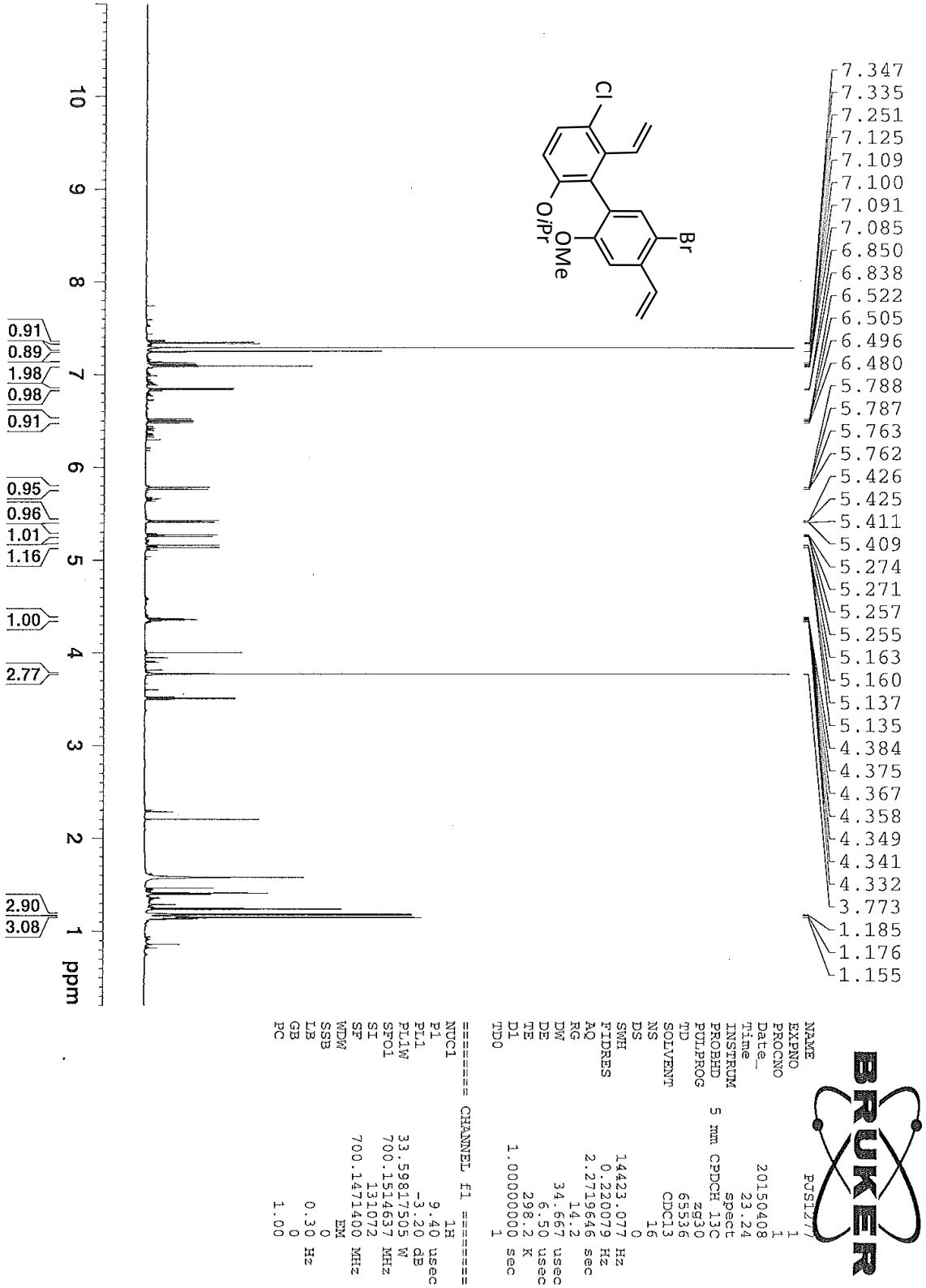
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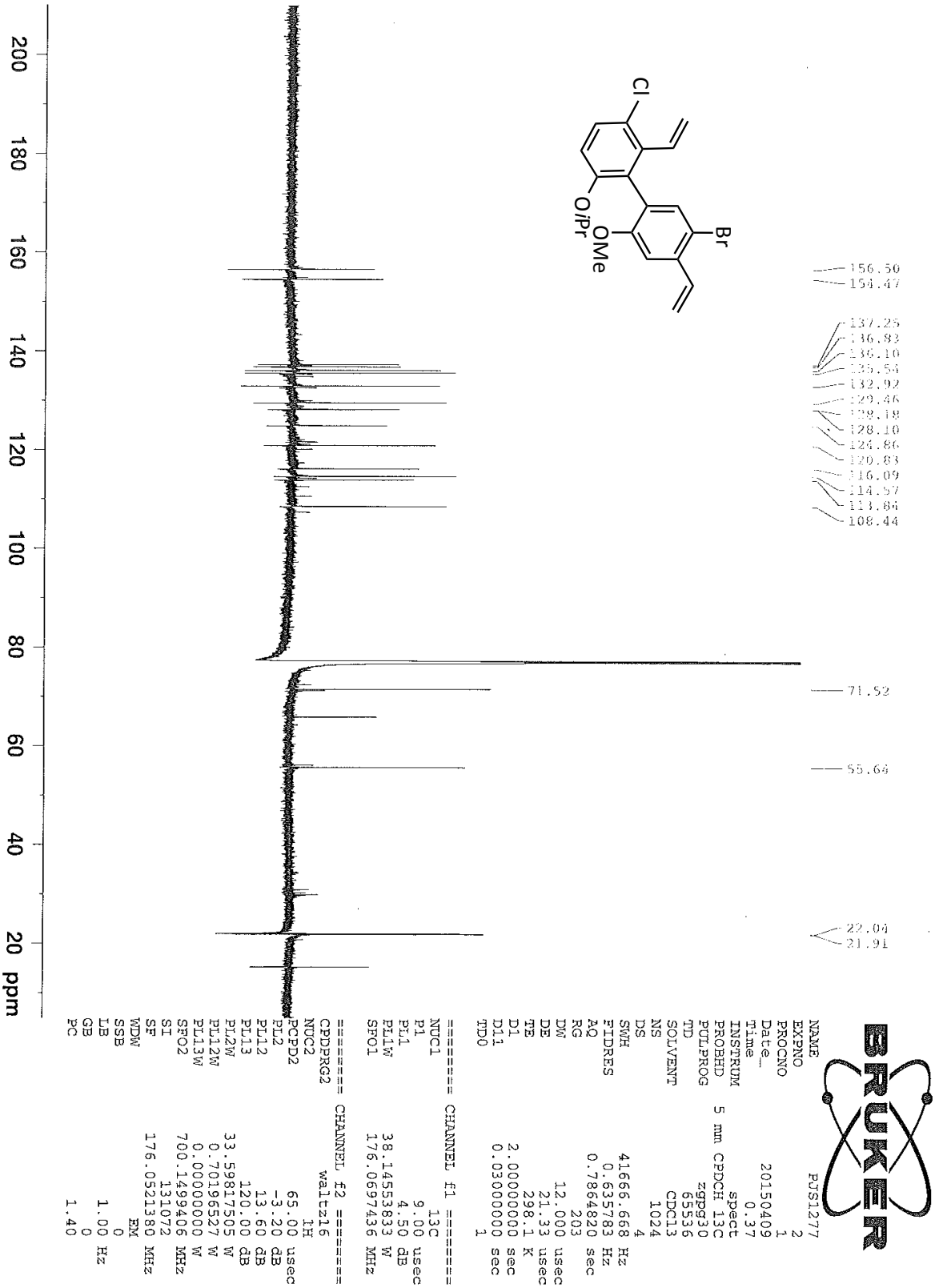


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TD0                       1

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PL1                  4.50 dB
SFO1          176.0697436 MHz

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WDW                     EM
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LB                    1.00 Hz
GB                       0
PC                    1.40
```

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Chapter 4: Conclusion

4.1 Conclusion

The study of cyclophanes began in 1949 with the synthesis of [2.2]paracyclophane by Brown and Farthing. Simple cyclophanes were studied for their molecular strain and non-planar benzene rings. The field grew as novel cyclophanes were applied in supramolecular chemistry and even used at chiral auxiliaries. The isolation of cyclophane natural products attracted significant interest from the synthetic community for their interesting molecular structures and biological activity.

The rigidified macrocylic structure of many cyclophanes can give rise to molecules that exist in stable enantiomeric conformations due to restricted rotation. We believe that conformational chirality is more widespread than previously thought. Thus, our group's long-term goal is to develop methods for identifying conformational chirality in molecules devoid of the sp^3 hybridized stereocenters. To this end, total synthesis and stereochemical study are the means by which we hope to achieve this goal.

Our group's total synthesis of cavicularin showed that the natural product exists in stable enantiomeric conformations at room temperature. Interestingly, the natural product is biosynthesized as a single enantiomer in nature. The dihydrophenanthrene moiety

imparts significant molecular strain on the macrocyclic structure. To access cavicularin, a regioselective double Suzuki cross coupling was developed to access the dihydrophenanthrene structure. The first enantioselective intramolecular Diels-Alder reaction involving an α-pyrone was discovered as a method for macrocyclization. A vinyl sulfone was found to be an efficient alkyne equivalent in the Diels-Alder, retro-Diels-Alder cascade. Inspired by the synthetic strategy used to synthesize cavicularin, we set out to develop a total synthesis of bazzanin K.

Chapter 2 describes the 1st generation synthetic strategy towards bazzanin K and the progress made thus far. We first set out to develop efficient syntheses of aryl boronic esters **21** and **22**. After optimization of the Horner-Wadworth-Emmons olefination, diimide reduction, and chlorination steps, I was able to access aryl boronic ester **21** in 8 steps with 16% overall yield. My colleague Dr. Frank Dyer developed a route to access aryl boronic ester **22** in 7 steps and 25% overall yield. With both aryl boronic esters in hand, we investigated the efficacy of the Suzuki cross couplings with dibromostyrene **14**. The first regioselective coupling proceeded in 57% yield to form biphenyl **39**. The second Suzuki coupling gave terphenyl **38** in 44% yield and subsequent ring closing metathesis provided the phenanthrene moiety of the natural product. Investigations into a one-pot, three-component Suzuki coupling are currently underway.

In chapter 3 we describe a 2nd generation synthetic strategy towards bazzanin K. To reduce the number of steps requiring functional group manipulations, we envisioned installing the vinyl sulfone in B-alkyl Suzuki cross coupling. This strategy reduces the number of steps to install the vinyl sulfone and allows for the synthesis of the simpler aryl boronic ester **45** to be employed in the Suzuki cross coupling. The coupling between aryl boronic ester **45** and dibromostyrene **14** proceeded in 40% yield to give biphenyl **48**. Determination of the regioselectivity of the cross coupling will be carried out by INADEQUATE analysis. The subsequent Suzuki cross coupling to access terphenyl **47** is currently being investigated.

With the successful total synthesis of bazzanin K, we will separate the potential enantiomers using chiral HPLC and the measure the energy barrier of racemization. This will allow us to calculate a half-life of racemization for the natural product. Based on the structural similarities to cavicularin, the diastereotopic methylene protons reported in the isolation paper, and a non-zero optical rotation, we believe that bazzanin K is a chiral molecule by virtue of its conformation.