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SELECTIVE IODINATION USING DIARYLIODONIUM SALTS

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SELECTIVE IODINATION USING DIARYLIODONIUM SALTS

by

William H. Miller IV

A THESIS

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SELECTIVE IODINATION USING DIARYLIODONIUM SALTS

William H. Miller

University of Nebraska, 2015

Advisor: Stephen G. DiMagno

Aryl iodides have become widely recognized as versatile synthetic intermediates, owing to aromatic iodine's excellent ability to participate in oxidative addition reactions. Iodoarenes readily undergo a variety of synthetic transformations including metal catalyzed cross-coupling reactions, diaryliodonium chemistry, formation of organometallics through reduction or metal-halogen exchange, as well as classical S_N2 type chemistry. Because a wide array of transformations are available for aryl iodides, organic molecules containing this moiety often serve as vital precursors to highly desirable pharmaceuticals.

This thesis describes a simple and selective two-step approach to the formation of aryl iodides. This method proceeds through an easily purified diaryliodonium salt intermediate, which is subsequently converted to the corresponding aryl iodide. This method is an effective and general process for the selective synthesis of a large variety of monoiodinated arenes that are difficult to access by other approaches.

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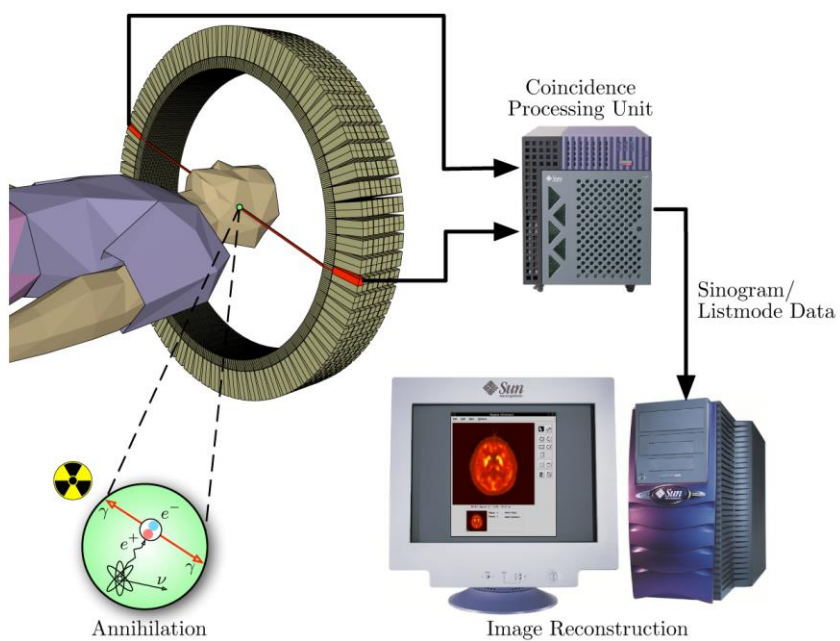
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CHAPTER ONE

POSITRON EMISSION TOMOGRAPHY



1.1 INTRODUCTION

1.1.1 Positron Emission Tomography

Positron Emission Tomography (PET) is a very powerful molecular imaging technique that is used to produce a three dimensional image of certain organs within the body.¹ This *in vivo* method allows for the non-invasive diagnosis of a wide range of diseases, making it a useful tool in biomedical research. Through PET, researchers gain valuable insight into vital physiological processes, which allows them to monitor the pharmacokinetics and circulation of various drugs throughout the body. In order to administer a PET scan, a drug labeled with a short-lived positron-emitting radioisotope is prepared and injected into the body. These drugs are commonly referred to as radiotracers. Once the radiotracer has become concentrated within the tissues or organs of interest and cleared from background tissues, the patient is placed into a device known as a scintillation detector (Figure 1.1).

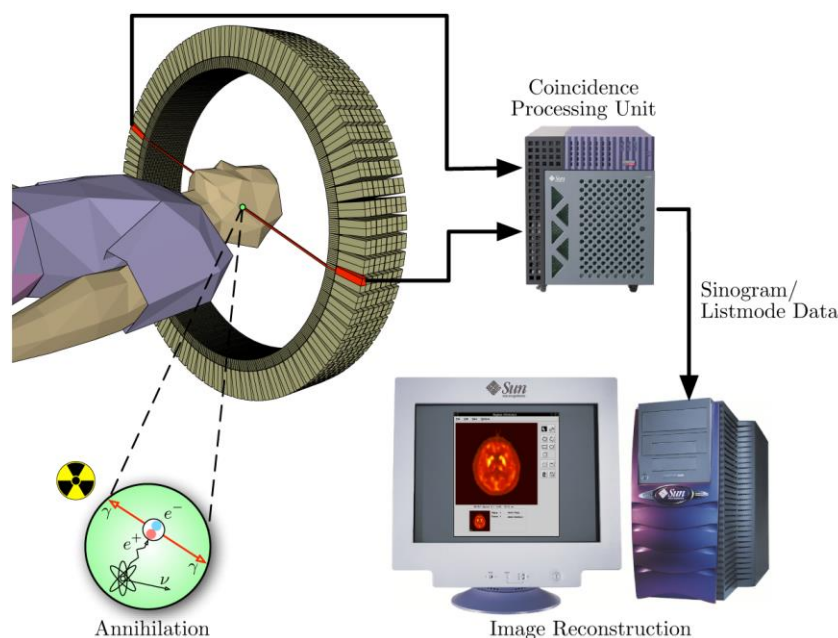


Figure 1.1 Diagram of a scintillation detector used in PET

The radionuclide of the labeled drug undergoes a process known as positive beta decay, in which a positron is emitted. This positron travels a short distance, (about 2-5 mm) which is dependent upon the average kinetic energy of the ejected positron. When the positron has lost enough energy to interact with an electron in the nearby tissues, an annihilation event consumes both particles and produces a pair of 511 keV gamma rays that radiate, at 180° angles, from the annihilation event. This coincident pair of photons is then detected by the scintillation detector, which defines a line along which the annihilation event occurred. Since the circular detector collects coincident events at many angles, a map of the defined lines shows intersection points that pinpoint where, and in what tissues, the radiotracer has become concentrated. The resolution of the image scales inversely with the distance the positron travels before interacting with an electron in an

annihilation event, and therefore radionuclides that emit positrons with low kinetic energy yield the highest resolution images.

1.1.2 PET Imaging using Fluorine-18 (^{18}F)

PET imaging has traditionally used radionuclides with relatively short half-lives, such as carbon-11, nitrogen-13, oxygen-15, and fluorine-18. However, there are certain considerations (Table 1.1) that must be taken into account when considering which radioisotope to use, including the average positron kinetic energy, the specific activity, and especially the half-life.

Table 1.1 Positron emitters commonly used in PET.

| Isotope | Half-life | Decay mode | $E_{\beta^+ \text{ Avg.}}$ (KeV) | Maximum (Average) Range in Tissue (mm) | Maximum Specific Activity (GBq/ μmol) |
|------------------|-------------|--|----------------------------------|---|--|
| ^{11}C | 20.39 min | β^+ (99.8%) EC (0.24%) | 385 | 3.8 (1) | 3.4×10^5 |
| ^{13}N | 9.965 min | β^+ (99.8%) EC (0.2%) | 491 | 5 (1.5) | 7.0×10^5 |
| ^{18}O | 122.24 sec | β^+ (99.9%) EC (0.1%) | 735 | 7.6 (2.7) | 3.4×10^6 |
| ^{18}F | 109.77 min | β^+ (96.73%) EC (3.3%) | 242 | 2.2 (0.3) | 6.3×10^4 |
| ^{124}I | 4.1760 days | β^+ (22.8%) EC (11.0%), e^- | 188 | 9.7 (3) | 1.2×10^3 |

Nuclear properties of commonly used positron emitting radionuclides used in PET. Data taken from Brown and Firestone 1986 and from Brookhaven National Laboratory internet database, BNL 2003

^{18}F -labeled imaging agents provide higher resolution images than those afforded by tracers labeled with the other radionuclides listed in Table 1.1. The reason for this is that ^{18}F emits a positron with relatively low kinetic energy, which is associated with an

annihilation event closer to the decay event. A short half-life is desirable for most diagnostic scans involving small molecule tracers that localize and clear quickly, but the synthetic routes used to synthesize many radiotracers preclude all but the most well-equipped hospitals from using novel PET diagnostic agents. Generally, a nearby cyclotron and an experimental radiochemistry laboratory are required in order to synthesize ^{18}F -labeled radiotracers. It is more common for hospitals to purchase standard ^{18}F -labeled tracers, such as fluorodeoxyglucose (FDG), from commercial radiopharmacies.

Generally, one desires a radiotracer to have the shortest possible half-life that is commensurate with obtaining a quality image. In practice this means that the radionuclide half-life must be sufficiently long to allow for synthesis of the radiotracer from the radionuclide, administration to the patient, localization in the tissue of interest, and clearance from background tissue. Toward these ends, fluorine-18 is the most commonly used radionuclide for incorporation into small molecule radiotracers,² as it can be synthesized off-site, incorporated into a radiotracer, and then shipped to diagnostic centers while still retaining a useful amount of radioactivity. In addition, the nuclear reaction which produces ^{18}F from H_2^{18}O yields several hundred times the amount of ^{18}F needed for a single human PET scan, and synthetic routes exist that give desirable radiotracers in high radiochemical yields.³

Choosing to use ^{18}F as the radiolabel on pharmaceutical provides additional benefits to those outlined above.⁴ The carbon-fluorine bond is one of the strongest in organic chemistry, owing to fluorine's high electronegativity. The dipolar nature of the C-F bond induces an electrostatic attraction between carbon and fluorine,⁵ which shortens

and strengthens the bond. Replacing hydrogen atoms with fluorine in pharmaceuticals⁶ also lends metabolic stability to the carbon framework, while introducing minimal structural perturbations. The small size of the fluorine atom makes it an appropriate replacement for hydrogen, thus, singly fluorinated organic compounds often behave very similarly to the corresponding hydrocarbon. While replacing hydrogen with fluorine in organic compounds changes little in the way of the physical structure of the compound, the fluorine is highly electronegative and alters the electronic properties of the molecule,^{7,8} making it a good bioisostere for a Lewis basic hydroxyl group.

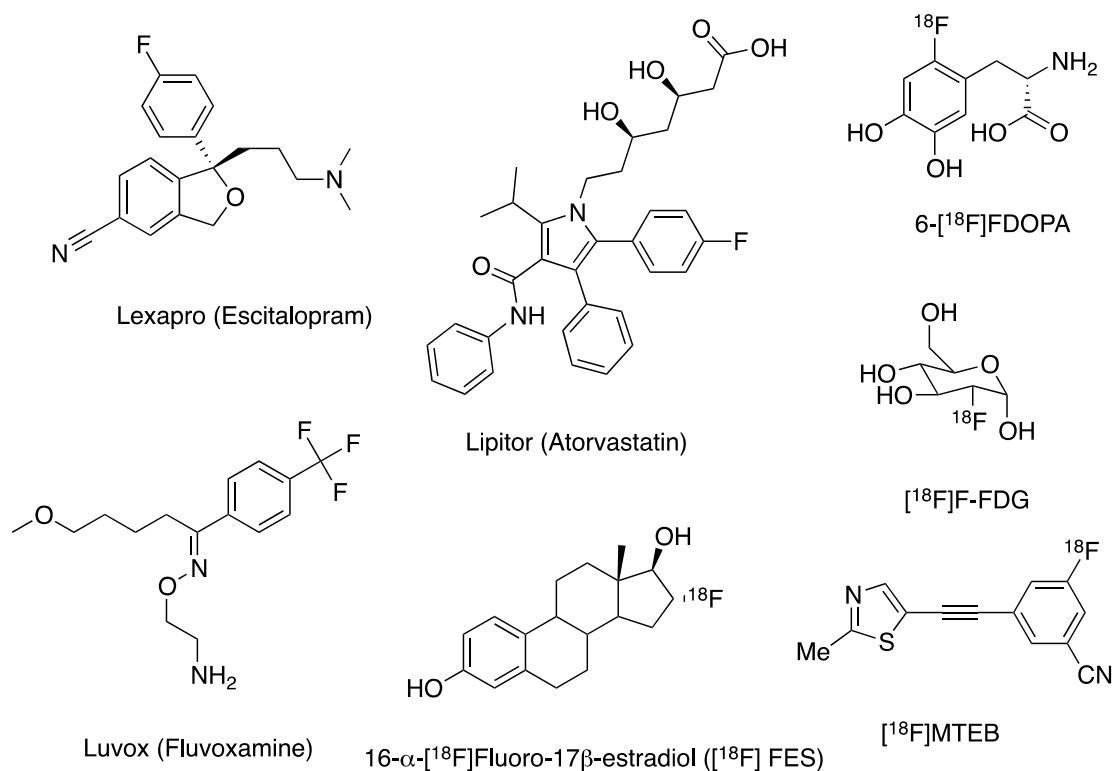


Figure 1.2 Common ¹⁸F and F labeled pharmaceuticals. Figure adapted from reference 90.

Because of these advantages, about one fifth of all pharmaceuticals contain at least one fluorine atom. Incorporation of fluorine into pharmaceuticals has been reported to increase the likelihood of creating a successful drug by a factor of ten^{9,10} (Figure 1.2). Fluorine substituted organic compounds often display increased lipophilicity over their corresponding hydrocarbons, which can be a desirable pharmacological property in some cases.¹¹ Additionally, replacing hydrogen with fluorine at a site of metabolic oxidation may extend the serum half-life of a drug in the body. This is an especially useful strategy to protect drugs that are susceptible to cytochrome P-450 catalyzed hydroxylation, a catabolic process that accounts for approximately 75% of all drug metabolites. Replacement of an aromatic hydrogen with fluorine stabilizes aromatic groups that are sensitive to this type of drug metabolism.¹²⁻¹⁸

1.1.3 Routes to ¹⁸F-labeled Radiotracers

While ¹⁸F is a highly desirable radiolabel, the introduction of ¹⁸F into pharmaceuticals poses a significant challenge for organic chemists. Elemental fluorine and hydrogen fluoride are difficult to handle and require specialized techniques and equipment, as they are highly reactive and very dangerous. Fluorine is one of the most reactive substances known, due to the strength of the bonds that fluorine forms with most other elements and the relative weakness of the fluorine-fluorine bond.

In order to accomplish the difficult task of fluorination, a variety of methods may be used. Electrophilic fluorination is a common method employed, and for this purpose elemental fluorine is commonly used in the form [¹⁸F]F₂. Radioactive fluorine [¹⁸F]F₂ used in electrophilic labeling techniques is generated in a cyclotron. The most common nuclear reaction used is ¹⁸O(p,n)¹⁸F in which the bombardment of [¹⁸O]-oxygen produces

$[^{18}\text{F}]\text{F}_2$, although a different, less common, reaction, $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ uses neon as the bombardment target. In the reaction using $[^{18}\text{O}]$ -oxygen, a trace amount of F_2 gas is sometimes added to extract the radioactive $[^{18}\text{F}]\text{F}_2$, which produces a mixture of $[^{18}\text{F}]\text{F}_2$ and $[^{19}\text{F}]\text{F}_2$ as the final product. This method is called “carrier added.” In practice, only a handful of cyclotron facilities in the world are able to produce $[^{18}\text{F}]\text{F}_2$ on a reliable basis.

When using elemental fluorine, the fluorine molecule is highly polarized, which allows electron-rich or Lewis basic substrates to act as nucleophiles. If this method is utilized, the upper limit of the radiochemical yield (RCY) is only 50%, due to the fact that 50% of the radioactivity is consumed in the chemical transformation and the other 50% is lost as the leaving group.² Electrophilic fluorination with F_2 also suffers from low specific activity of the final product, because a carrier gas (non-radioactive F_2) is added in order to extract the $[^{18}\text{F}]\text{F}_2$. Due to these limitations, the electrophilic fluorination method is only commonly used in applications that don't require a radiotracer with a high specific activity. When a higher specific activity product is necessary and electrophilic fluorination is the desired synthetic route, other fluorination reagents such as xenon difluoride, N-fluorinated amines, amides, and sulfonamides are used.² Because the source of electrophilic fluorine is contained within the reagent itself, instead of within diatomic fluorine (where one atom of radioactive fluorine is consumed in the transformation and the other half is converted to unusable radioactive fluoride) these reagents are able to provide a higher specific activity material.

The method used to obtain $[^{18}\text{F}]$ -fluoride for use in nucleophilic labeling reactions ($^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$) is similar to the reaction used to produce $[^{18}\text{F}]\text{F}_2$, except that the product is obtained as $[^{18}\text{F}]\text{HF}$ from an $[^{18}\text{O}]\text{-H}_2\text{O}$ target. This solution is then passed through an

ion-exchange resin, which traps the $[^{18}\text{F}]$ -fluoride. A solution containing K_2CO_3 and kryptofix 2.2.2 (Figure 1.3) is then used to elute radioactive fluoride (as $[^{18}\text{F}]\text{KF}$) from the ion-exchange resin into a reactor vial. Typically, the reagent is then mixed with acetonitrile and subject to azeotropic distillations to remove excess water to prepare a highly nucleophilic form of fluoride.²

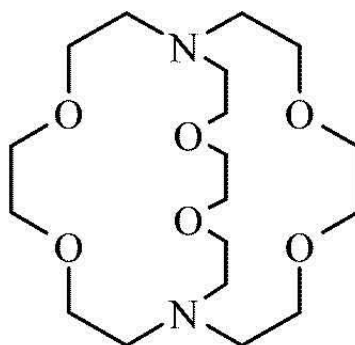


Figure 1.3 Kryptofix™ 2.2.2

Nucleophilic methods have been used to radiofluorinate a variety of compounds. These no carrier added (nca) nucleophilic methods, in which the cyclotron produced $[^{18}\text{F}]\text{F}^-$ is used directly, can result in very high specific activity products ($> 4 \times 10^3 \text{ GBq } \mu\text{mol}^{-1}$). Certain challenges are apparent if fluoride is to be used in nucleophile reaction, as fluoride is generally considered to be a poor nucleophile. However, fluoride is a moderate nucleophile, but only when it is desolvated, so every effort is made to eliminate potentially hydrogen bonding impurities (like water) to enhance the rates of reaction. Since alkyl fluorides are highly stable compounds, quite aggressive reaction conditions can generally be used for $\text{S}_{\text{N}}2$ reactions to form alkyl fluorides.

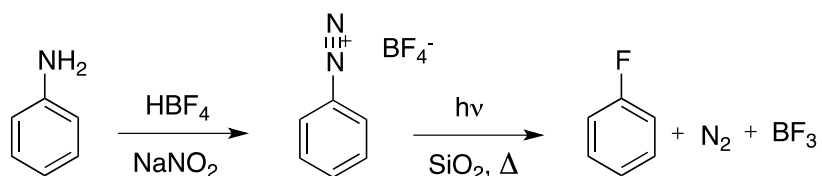
Regardless of whether an electrophilic or nucleophilic method of fluorination is used, there are certain constraints placed upon the method of synthesizing the radiotracer, due to the inherent properties of ^{18}F . The relatively short-half life of ^{18}F makes it desirable to minimize the number of post-labeling synthetic transformations as well as the length of any necessary purification processes. While many carrier added electrophilic fluorination methodologies seem attractive in this regard, they suffer from low selectivity during the labeling step, which translates into a low specific activity final product. Because high specific activity product is often required in imaging applications, radiochemists are often willing to use multistep syntheses and complex protecting group strategies so that $[^{18}\text{F}]$ -fluoride may be used to generate high specific activity products.

Some of the most desirable radiotracers contain fluoroarenes. Radiotracers incorporated onto electron-poor arenes may be synthesized using classical $\text{S}_{\text{N}}\text{Ar}$ reactions such as halogen exchange or fluorodenitration reactions. Strategies to prepare radiotracers that possess $[^{18}\text{F}]$ -fluorinated electron-rich aromatic groups include direct fluorination with $[^{18}\text{F}]\text{F}_2$ or electrophilic reagents derived from $[^{18}\text{F}]\text{F}_2$, or, more commonly fluorodestannylation. As outlined above, electrophilic methods generally provide tracers that have low specific activity. Due to this limitation, a method that is fast, high yielding, and highly selective, while affording the ability to radiolabel both activated and deactivated substrates using a no carrier added nucleophilic $[^{18}\text{F}]\text{F}^-$ is highly desirable. One objective of research in the DiMagno group is to provide a solution to this general problem.

1.1.4 Typical Aromatic Fluorination Methods

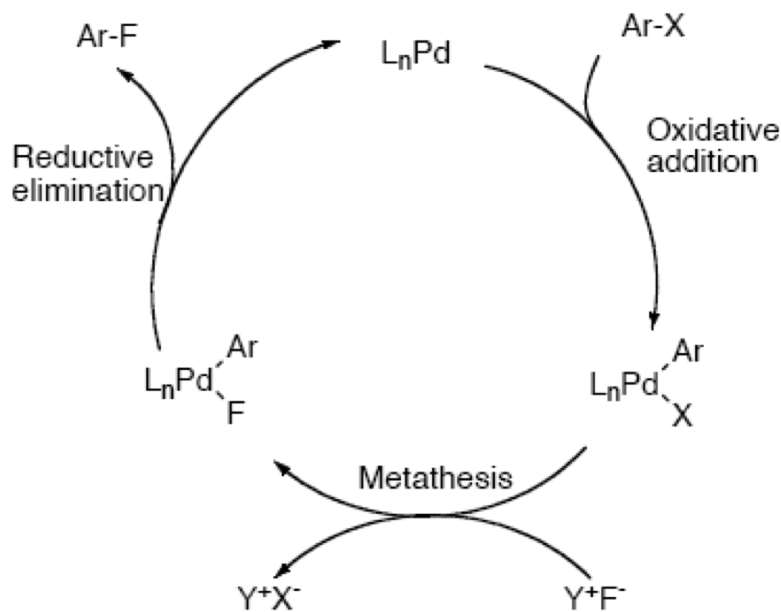
One very simple and straightforward method of obtaining aryl fluorides is to employ a S_NAr reaction to displace a leaving group with fluoride. These types of reactions often require high boiling solvents and high temperatures, which may not be compatible with sensitive functional groups. Also, owing to the miniscule amount of $[^{18}F]F^-$ present under no carrier added conditions (< 10 ng), a large excess of the desired halogenated arene precursor is required to drive the reaction to completion. For radiotracer synthesis, the S_NAr approach can lead to significant purification problems.

One of the most well-known reactions used to produce fluoroarenes is the Balz-Schiemann (Sandmeyer) reaction. In this method, anilines are converted to diazonium fluoroborates, which are subsequently converted to aryl fluorides (Scheme 1.1). This route has been used to produce several ^{18}F labeled radiotracers, including $[^{18}F]$ -F-DOPA, although the RCY suffers as a result of the use of BF_4^- , which limits the maximum radiochemical yield to only 25% since only one ^{18}F contained within the BF_4^- anion is transferred to the arene.² This method is also not tolerant to many acid-labile functional or protecting groups that may need to be used in the synthetic strategy, and as a result, fluoroborates are not generally used as a radiosynthetic strategy.²



Scheme 1.1 Balz-Schiemann reaction.

Another method that has been developed to fluorinate electron-rich aromatic compounds is based upon palladium-catalyzed cross coupling reaction, a strategy first developed by Buchwald (Scheme 1.2). A solution to this long-standing problem was noteworthy, because one would expect that the strength of the Pd-F bond would lead to relatively high barriers to reductive elimination of Pd⁰ to form the fluoroarene during the last catalytic step. However, this method is most effective when deactivated aromatics are the labeling target, as more electron rich compounds require a large excess of the fluorination reagent (6 equivalents of CsF), higher temperatures and longer reaction times (12 hours). This method suffers from less than perfect regioselectivity, and the toxicity of heavy metals is also a concern, as any potential pharmaceutical must remain metal-free, which limits its use as a synthetic strategy to obtain ¹⁸F radiolabeled drugs.¹⁹⁻²³

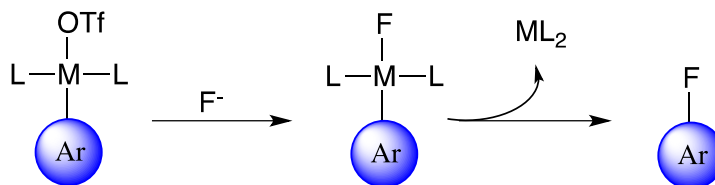


Scheme 1.2 Pd-catalyzed aromatic fluorination.

1.1.5 Diaryliodonium Salts as Precursors to Aryl Fluorides

In organometallic metal chemistry, it is well known that high-valent and/or electronegative transition metal ions are more prone to reductive elimination.²⁰ Using recent developments in palladium-catalyzed cross coupling reactions as an analogy, it was postulated that iodine should behave like a high-valent, highly electronegative transition metal ion in reductive elimination reactions. In addition, because the bond between fluorine and palladium is stronger than the bond between fluorine and iodine, reductive elimination reactions at I(III) centers should occur more readily than reductive elimination reactions at Pd(II) centers. Furthermore, $\text{Ar}_2\text{M}(\text{X})_n$ complexes usually give biaryl compounds upon reductive elimination, whereas Ar_2IX compounds generally form Ar-I and Ar-F compounds upon reductive elimination. Because of these properties, our group has explored reductive elimination reactions from I(III) centers to develop a potentially more facile route to fluoroarenes (Figure 1.4).

Pd-Catalyzed Arene Fluorination



Arene Fluorination via Diaryliodonium Salts

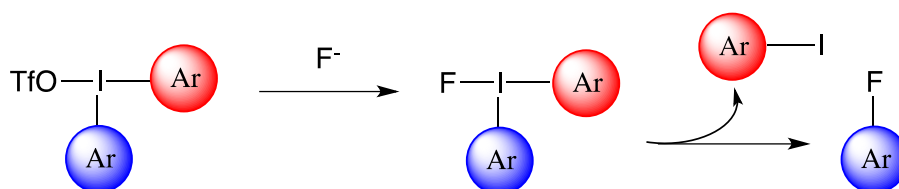
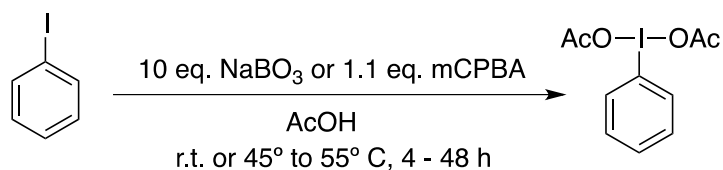


Figure 1.4 Iodine used as a transition metal.

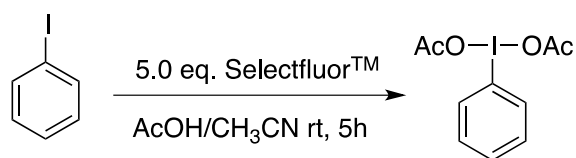
The decomposition of diaryliodonium salts (IUPAC: diaryl- λ^3 -iodanes) to aryl halides is a reaction that has been known for over one hundred years, but only recently has this type of chemistry come into the spotlight.⁸⁸ The current popularity of diaryliodonium chemistry in radiochemistry circles is due to the ability of this class of salts to rapidly undergo reductive elimination to form aryl fluorides.²⁴⁻²⁷ This property grants them special utility as radiotracer precursors. In most cases, the desired radiotracer can be obtained in one “hot” step after the desired diaryliodane is in hand. Developing especially high yielding radiolabeling strategies using this particular class of compounds is a primary focus of research in the DiMagno group.



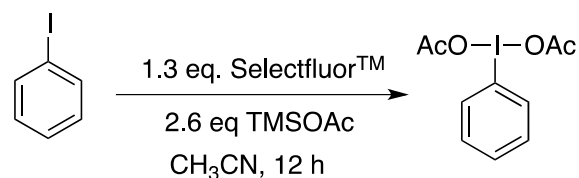
Scheme 1.3 Common strategies used to synthesize I(III) compounds.

A variety of methods allow one to synthesize iodonium salts from relatively simple arenes. However, in order for synthetic methods to be relevant to radiotracer synthesis, they must be general, have high functional group tolerance, and be compatible with any needed acid-labile protecting groups. (Nucleophilic radiofluorination reactions are generally performed with excess base present.) Two common strategies (Scheme 1.3) utilize oxidizing agents in the presence of acid, which would disqualify any drug containing acid-labile groups from being a candidate for diaryliodonium salt formation. A new strategy (Scheme 1.4), derived from the work of Shreeve,⁸⁹ circumvents this limitation by using the mild oxidant SelectfluorTM in the presence of TMS-acetate to give the diacetate in high yield under neutral conditions. Importantly, this process leaves acid-labile protecting groups intact.

Shreeve's Method



DiMagno's Method



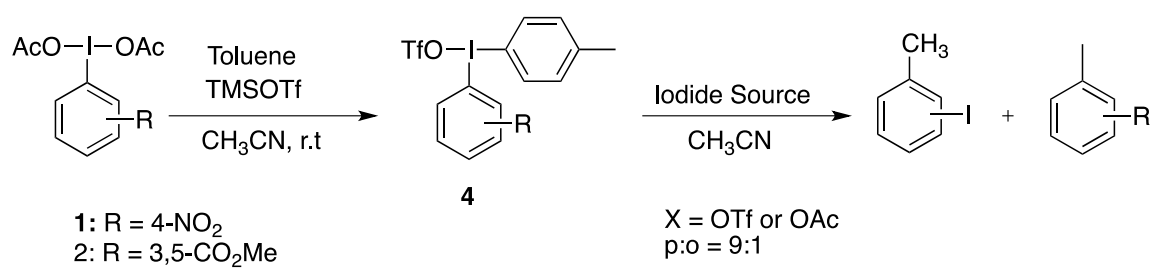
Scheme 1.4 Different methods used to synthesize I(III) compounds.

There are numerous literature examples describing the preparation of aryl fluorides from diaryliodonium salts. It has been suggested that the decomposition of diaryl- λ^3 -iodanes proceeds via an S_NAr mechanism, which directs the nucleophilic fluoride onto the *ipso* carbon of the less electron rich arene due to the ability of the electron poor ring to stabilize the negative charge that develops in the transition state.⁸⁷ Because of this, many diaryliodonium salts employ electron rich arenes such as 4-iodoanisole and 2-thienyl as the opposing arene.²⁸⁻³⁰ Because fluorination of diaryliodonium salts involves ionic reactants, this reaction was performed exclusively in polar media previously. However, work in our laboratory has shown that the use of nonpolar solvents, such as benzene or toluene, suppress detrimental side reactions and permit aryl fluorides to be prepared in greater yield.

With the ability to quickly synthesize a wide variety of diaryliodonium salts in high yield, and the capability to quickly and cleanly obtain the corresponding radiotracers from these compounds, my focus shifted to expanding the scope of the diaryliodonium salt method. In order to arrive at diaryliodonium salt precursors, however, it was necessary to develop a more general and selective method to iodinate compounds that would be later transformed into radiotracer precursors.

CHAPTER TWO

IODINATED COMPOUNDS IN RADIOSYNTHESIS



2.1 BACKGROUND

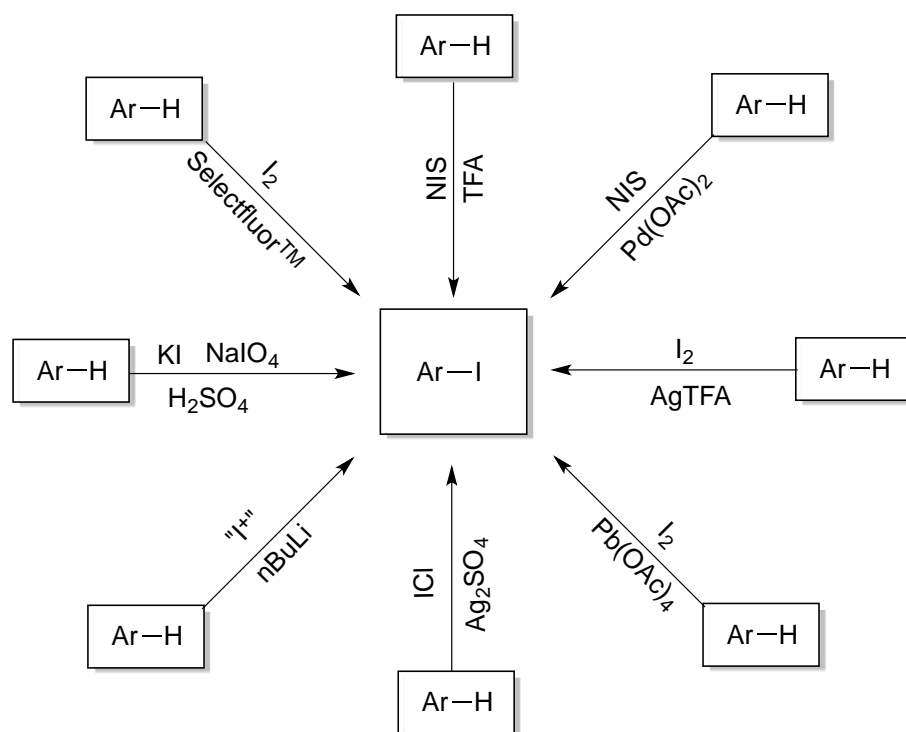
2.1.1 Aromatic Iodination

Aryl iodides have become widely recognized as versatile synthetic intermediates, owing to iodine's excellent ability to act as a leaving group. Iodoarenes readily undergo a variety of synthetic transformations including metal-catalyzed cross-coupling reactions, diaryliodonium salt chemistry, Grignard reactions, as well as classical S_NAr type chemistry. Because a wide array of transformations are available for aryl iodides, organic molecules containing this moiety often serve as vital precursors to highly desirable pharmaceuticals.

The wide array of methods that have been developed for iodoarene synthesis serves as evidence that the fabrication of these important pharmaceutical precursors is not straightforward, and that the reaction conditions must be carefully tuned to match the substrate. This complication arises from the fact that elemental iodine is the weakest electrophile of the halogens, and as a result, synthetic routes to aryl iodides often require harsh reaction conditions and highly activated reagents. Moreover, iodine is a relatively weak electron-withdrawing aryl substituent⁶³ (Hammett $\sigma_p = 0.18$, $\sigma_m = 0.35$, $\sigma^+ = 0.14$), so polyiodination is often a problem when very electron rich substrates or highly activated reagents are used. Activated substrates readily undergo electrophilic iodination, although often with poor selectivity. However, deactivated arenes are often difficult to iodinate, requiring powerful oxidants and long reaction times in concentrated acid. These problems limit the accessibility of iodinated intermediates as pharmaceutical precursors.

To arrive at these versatile iodoarene intermediates from the corresponding aromatic compounds, a variety of reagents may be used, including N-iodosuccinimide

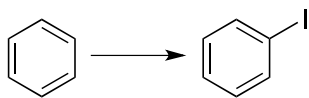
(NIS), iodine monochloride (ICl), sodium iodide or molecular iodine used in combination with a variety of oxidants, bis(pyridine)-iodonium(I) tetrafluoroborate (Py_2IBF_4), and silver or mercury salts combined with I_2 (Scheme 2.1). Iodoarenes may also be synthesized by various substitution reactions from compounds such as aryl amines, aryl halides, aryl boronic acids, aryl triflates and aryl silanes.³¹⁻⁶¹



Scheme 2.1 Various reactions used to synthesize aryl iodides.

Recently, a literature review describing various electrophilic aromatic iodination procedures was published.⁶⁴ Despite the range of reagent systems described in the review, there remains the need for a versatile, straightforward, and highly selective aromatic iodination method. For example, even the iodination of benzene is not straightforward; a

wide variety of the methods used failed to produce iodobenzene in quantitative yield (Table 1.2). The notable exception was molecular iodine and silver triflate in dichloromethane, however, for the purposes of pharmaceutical synthesis, this reaction is problematic.

Table 2.1 Iodination of benzene.

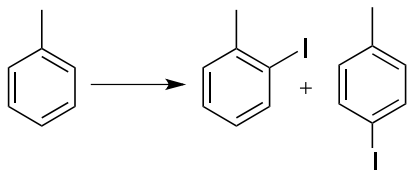
| Entry | Reagent | Conditions | Temp (°C) | Yield (%) | Reference |
|-------|---|---|-----------|-----------|-----------|
| 1 | I ₂ , CrO ₃ | AcOH, Ac ₂ O, H ₂ SO ₄ | 65 | 76 | 65 |
| 2 | I ₂ , SPC ^a | AcOH, Ac ₂ O, H ₂ SO ₄ | 40 | 40 | 66 |
| 3 | I ₂ , I ₂ O ₅ | AcOH, H ₂ SO ₄ | 60 | 56 | 67 |
| 4 | I ₂ /KI, PVP ^b -H ₂ O ₂ | H ₃ PW ₁₂ O ₄₀ , (cat.), CH ₂ Cl ₂ | reflux | 15-22 | 68 |
| 5 | I ₂ /NaI, Fe(NO ₃) ₃ •N ₂ O ₄ | CH ₂ Cl ₂ | r.t. | 74 | 69 |
| 6 | NaI, Ce(OH) ₃ OOH | aq. SDS | r.t. | 80 | 70 |
| 7 | KI, KBrO ₃ , H ⁺ | 60% AcOH/HCl | 80 | 91 | 71 |
| 8 | I ₂ , XeF ₂ | CH ₂ Cl ₂ | r.t. | 90 | 72 |
| 9 | I ₂ , Hg(NO ₃) ₂ | CH ₂ Cl ₂ | r.t. | 52 | 73 |
| 10 | I ₂ , AgOTf | CH ₂ Cl ₂ | r.t. | 100 | 74 |

*Data drawn from from reference 64.

^a SPC = Sodium percarbonate

^b PVP = polyvinylpyrrolidone

The results obtained from the iodination of alkylbenzenes are similarly disappointing. Toluene iodination ordinarily yields a mixture of 2- and 4-iodotoluene in systems using relatively harsh reaction conditions. Greater than average selectivity can be obtained under milder conditions at longer reaction times or in reactions that employ metal catalysts such as tungsten or vanadium (Table 1.3).

Table 2.2 Iodination of toluene.

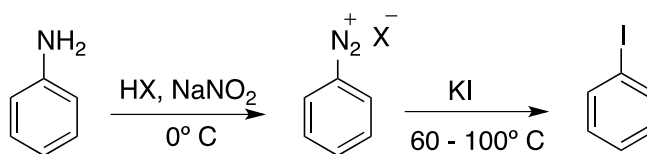
| Entry | Reagent | Conditions | Temp (°C) | Ratio (<i>o</i> : <i>p</i>) | Yield (%) | Reference |
|-------|---|--|-----------|-------------------------------|-----------|-----------|
| 1 | NaI or KI | Oleum | 60-120 | 0:100 | 76 | 75 |
| 2 | I ₂ , AgOTf | CH ₂ Cl ₂ | r.t. | 25:75 | 100 | 74 |
| 3 | I ₂ , Hg(NO ₃) ₂ | CH ₂ Cl ₂ | r.t. | 35:65 | 92 | 73 |
| 4 | I ₂ , Fe(NO ₃) ₃ | CH ₂ Cl ₂ ^a | 20 | 0:100 | 59 | 76 |
| 5 | I ₂ , Fe(NO ₃) ₃ •N ₂ O ₄ | CH ₂ Cl ₂ | r.t. | 40:60 | 93 | 69 |
| 6 | NaI, Ce(OH) ₃ OOH | aq. SDS | r.t. | 0:100 | 87 | 70 |
| 7 | I ₂ , H ₅ IO ₆ | EtOH | 60 | 8:92 | 44 | 77 |
| 8 | I ₂ , F-TEDA-BF ₄ | [bmim][PF ₆] | 80 | 35:65 | 40 | 78 |
| 9 | I ₂ , O ₂ | MeCN ^b | 80 | 15:85 | 99 | 79 |

*Data drawn from from reference 64.

^a Catalytic H₃PW₁₂O₄₀

^b H₅PV₂Mo₁₀O₄₀

In cases where the iodination of polysubstituted alkylbenzene derivatives was attempted, regioisomers and multiple iodination were observed in all but the most specific cases. This lack of selectivity is especially troublesome when attempting to iodinate compounds for which the sums of the substituent Hammett sigma values are similar. Furthermore, because the iodine substituent is not particularly deactivating, compounds that have already undergone iodination are susceptible to further iodination.



Scheme 2.2 Sandmeyer synthesis of iodoarenes.

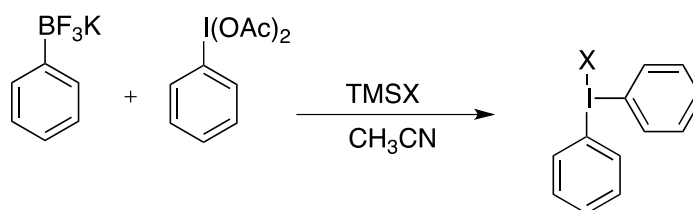
Iodination of relatively electron-poor arenes is a difficult task, conventionally accomplished by the indirect approach using the Sandmeyer reaction⁸⁰⁻⁸² (Scheme 1.6). The alternatives to the Sandmeyer reaction discussed within this section commonly employ harsh reaction conditions, use a large excess of the iodination reagent, concentrated acid, high temperatures and long reaction times, and/or strong oxidants in order to complete the transformation.⁸⁴⁻⁸⁶ Under these conditions, it is difficult to prevent multiple iodination, especially if there are two nearly equivalent positions at which iodination may occur. In addition, these harsh reaction conditions are often not compatible with functional or protective groups that may be necessary for the synthesis of complex pharmaceutical candidates.

2.1.2 Aromatic Iodination via Diaryliodonium Salt Decomposition

Because of the difficulty encountered during the iodination of both electron-rich and electron-poor aromatics, we sought a new method that would be selective and robust enough that the method could be used to iodinate a wide variety of aromatic substrates. In

order to solve this problem, we turned our attention once again to diaryliodonium chemistry.

In order to iodinate any given compound using iodane chemistry, the compound in question must first necessarily be transformed into the corresponding diaryliodonium salt. This procedure is not trivial, and introduces one or more additional steps into the reaction sequence. Typical procedures for preparing diaryliodonium salts involve electrophilic and nucleophilic partners, which condense to form the diaryliodonium salt. Naturally, this rather complex approach would require an arene already functionalized in the appropriate position, and would be a nonsensical method to prepare standard iodides. One such approach is shown in (Scheme 1.7).



Scheme 2.3 Synthesis of diaryliodonium salts.

A second issue is that the thermal decomposition of diaryliodonium salts leads to the formation of two different iodides (if $\text{X} = \text{I}$ in Figure 1.5), thus there could be a separations problem if the two iodoarenes are chemically similar.

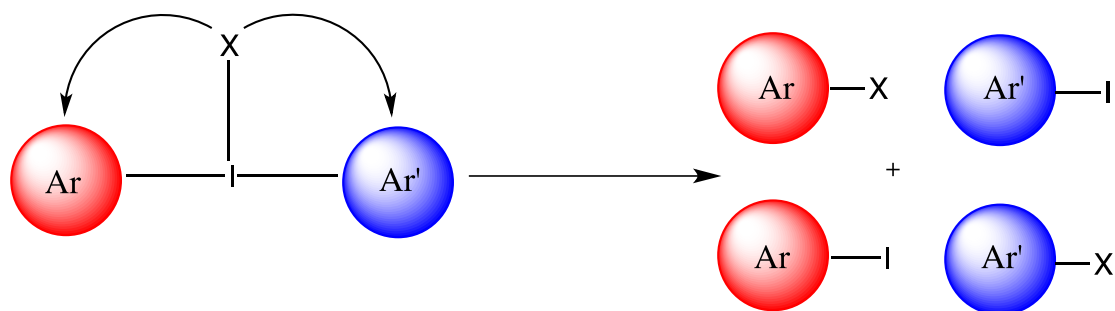


Figure 2.1 Products resulting from the reductive elimination of a diaryliodonium salt.

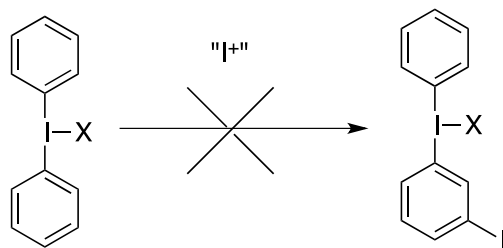
In summary, there are two main problems encountered when attempting to use iodane chemistry to introduce iodine into a pharmaceutical precursor. First, the typical methods used to obtain the necessary diaryliodonium salts employ precursors that could provide the aryl iodides directly; and second, the decomposition of the resulting iodonium salt step may give a mixture of products, which could require further costly and time-consuming purification steps.⁸³⁻⁸⁴ In the following section, I present a fairly general solution to the arene iodination problem, and show that it can be applied to a wide range of substrates.

2.2 RESULTS AND DISCUSSION

Portions of the rest of this section are drawn from a journal article on which I am a coauthor. Direct quotations are indicated with quotation marks. I have clearly attributed individual contributions.

In order to overcome the problems outlined previously, I developed a selective iodination methodology that can be used to functionalize a variety of electronically deactivated to activated arenes.

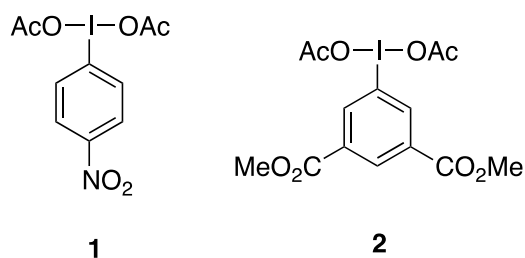
In order to address the problem of multiple iodine additions for compounds that contain several positions susceptible to electrophilic aromatic substitution, we developed a strategy that exploits a fundamental property of I(III) chemistry: the arylidonium substituent is very electron withdrawing ($\sigma_p = 1.37$, $\sigma_m = 1.35$ for $\text{PhI}(\text{BF}_4)$). To put this in context, the corresponding values for the nitro substituent are: $\sigma_p = 0.79$, $\sigma_m = 0.71$. Thus, any method that involves electrophilic substitution to form an Ar-I(III) intermediate effectively eliminates the possibility of any further electrophilic substitution by an “ I^+ ” species (Scheme 1.8)



Scheme 2.4 Resistance of diaryliodonium salts to further EAS

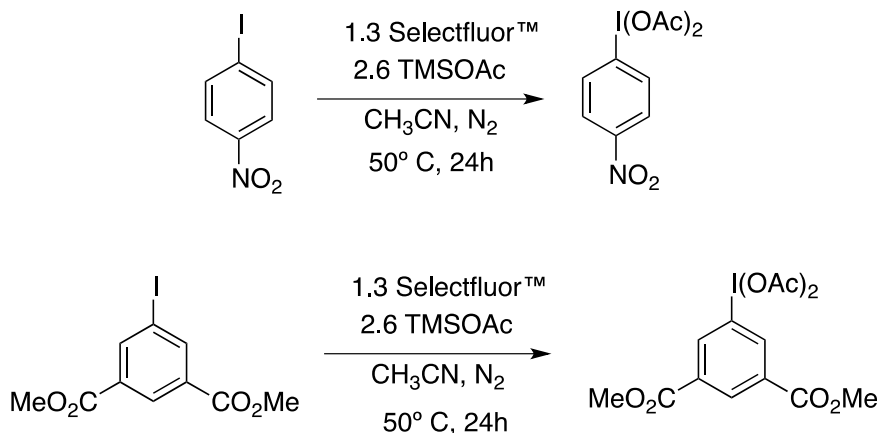
With this strategy in hand, I turned my attention toward developing a direct electrophilic substitution method that could be used with a variety of arenes. With my attention focused on developing a “one step addition” route to diaryliodonium salts, I envisioned a diacetoxyiodoarene that would be sufficiently electron-poor so that the I(III)

moiety would readily undergo electrophilic aromatic substitution with the desired substrates. To this end, I devised two reagents containing substituents of a sufficiently electron-withdrawing nature to facilitate the EAS reaction between arenes and the I(III) center of a diacetoxyiodoarene (Scheme 1.9).



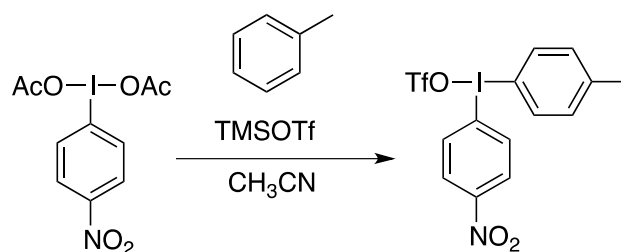
Scheme 2.5 Reagents used for “One Step Addition”

Reagent **1** ((4-nitrophenyl)iodonium diacetate) and reagent **2** ((3,5-dicarboxymethylphenyl)iodonium diacetate), were obtained in good yield by treating the corresponding iodides with 1.3 equivalents of Selectfluor™ and 2.6 equivalents of TMSOAc in acetonitrile (Scheme 1.10). These compounds are stable materials, and they are unreactive toward standard arenes in acetonitrile at room temperature.



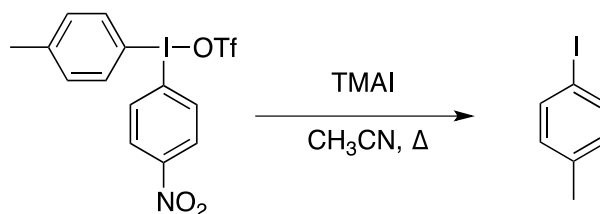
Scheme 2.6 Synthesis of aryliodonium diacetates

Upon electrophilic activation of **1** or **2** with trimethylsilyl triflate (TMSOTf), ligand exchange occurs and several different I(III) species (ArI(OAc)₂, ArI(OAc)(OTf), and ArI(OTf)₂) are observed. The evidence for this equilibration can be seen in the downfield shifts of signals in the aromatic region of the ¹H NMR spectrum, and by a signal consistent with generation of TMSOAc. The greater electrophilicity of the I(III) center, which is suggested by the downfield shifts of the signals in the ¹H NMR spectrum following treatment of ArI(OAc)₂ with TMSOTf, was confirmed when an arene such as toluene was added; the activated reagents participated in an EAS reaction to give the corresponding diaryliodonium salt at room temperature (Scheme 2.7).



Scheme 2.7 Activation of the aryliodination reagent and reaction with toluene.

With the diaryliodonium triflate in hand, the corresponding aryl iodide can be formed quickly and simply by treatment with tetramethylammonium iodide (TMAI) and heating (Scheme 2.8).

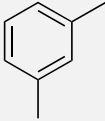
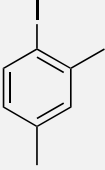
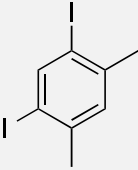
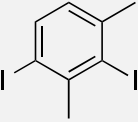
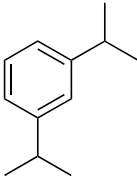
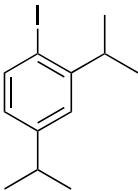
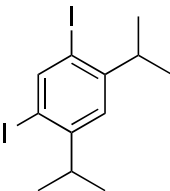
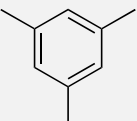
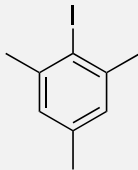
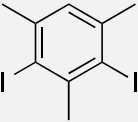
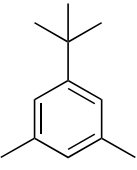
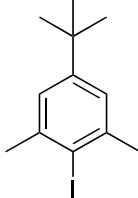


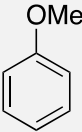
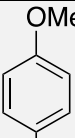
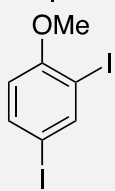
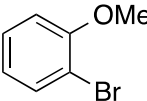
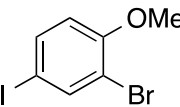
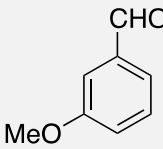
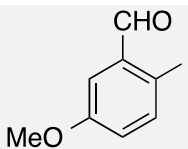
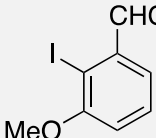
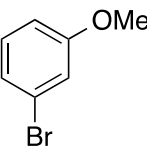
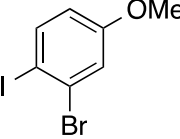
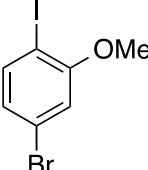
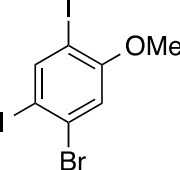
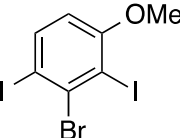
Scheme 2.8 Conversion of the diaryliodonium triflate to the iodoarene.

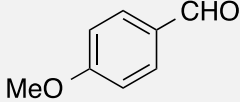
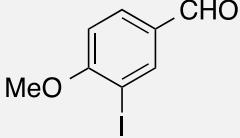
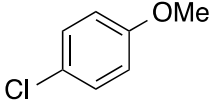
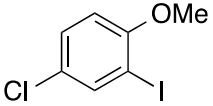
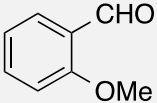
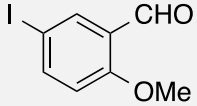
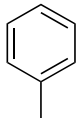
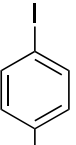
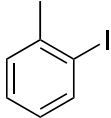
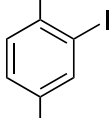
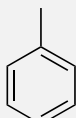
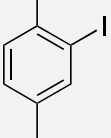
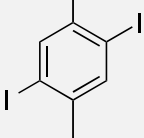
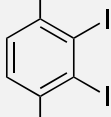
In order to determine the general scope of the reaction, I performed a comparison between traditional iodination strategies employing the use of N-iodosuccinimide (NIS) and SelectfluorTM and our methodology, which employs an I(III) substituted arene. For Method A and B, one and two equivalents of NIS were used to assess the selectivity and to attempt to drive the reaction to completion, respectively. Likewise, for Method C and D, one half and one equivalent of SelectfluorTM and I₂ were used for similar purposes.

For Method E, two equivalents of the aryliodination reagent **1** or **2** and four equivalents of trimethylsilyl triflate (TMSOTf) were used to ensure that all of the arene was consumed, and to ensure that multiple iodination did not occur. Because this was a preliminary survey of reactivity and scope, and because the decomposition of diaryliodonium salts is a thoroughly investigated topic and has been known for over a century, the yields listed column E refer only to the yields of the diaryliodonium salt intermediate. Even so, the results shown in Table 1.4 indicate that for a wide range of substrates, the aryliodination strategy promises to be superior in many regards.

Table 2.3. Comparison between standard iodination strategies and the diaryliodination strategy. For column E, I = I(OTf)(Ph(NO₂)).

| Entry | Reactant | Product(s) | Method & Yield ^{a,b} (%) | | | | E ^c |
|-------|---|---|-----------------------------------|------|------|------|------------------|
| | | | A | B | C | D | |
| 1 |  3 |  | 78.1 | 79.7 | 69.4 | 26.7 | >99 ^c |
| | |  | 0 | 0 | 16.0 | 57.2 | 0 |
| | |  | 0 | 0 | 4.2 | 16.1 | 0 |
| 2 |  4 |  | 63.7 | 100 | 100 | 50.7 | >99 ^c |
| | |  | 0 | 0 | 0 | 49.7 | 0 |
| 3 |  5 |  | 100 | 43.0 | 95.8 | 3.4 | >99 ^c |
| | |  | 0 | 57.0 | 1.6 | 96.6 | 0 |
| 4 |  6 |  | 100 | 100 | 100 | 100 | >99 |

| Entry | Reactant | Product(s) | Method & Yield ^{a,b} (%) | | | | E ^c |
|-------|---|---|-----------------------------------|------|------|------|----------------|
| | | | A | B | C | D | |
| 5 |  7 |  | - | 62.0 | 85.1 | 0 | >99 |
| | |  | - | 38.0 | 14.9 | 100 | 0 |
| 6 |  8 |  | 80.6 | 100 | 100 | 100 | >99 |
| 7 |  9 |  | 23.6 | 36.3 | 65.2 | 77.8 | >99 |
| | |  | 4.1 | 5.6 | 6.5 | 21.4 | 0 |
| 8 |  10 |  | 74.6 | 74.5 | 64.1 | 9.7 | 88 |
| | |  | 16.4 | 12.4 | 13.4 | 0 | 12 |
| | |  | 0 | 10.2 | 17.6 | 74.6 | 0 |
| | |  | 0 | 2.9 | 4.9 | 15.7 | 0 |

| Entry | Reactant | Product(s) | Method & Yield ^{a,b} (%) | | | | |
|-------|--|---|-----------------------------------|------|------|------|------------------|
| | | | A | B | C | D | E ^c |
| 9 |  11 |  | 22.5 | 35.3 | 76.1 | 84.3 | >99 |
| 10 |  12 |  | 30.8 | 55.2 | 76.9 | 100 | >99 |
| 12 |  13 |  | 34.6 | 88.5 | 88.0 | 94.5 | |
| 11 |  14 |  | 19.9 | 23.2 | 41.2 | 45.0 | 90 ^c |
| | |  | 21.5 | 20.9 | 44.5 | 48.6 | 10 |
| | |  | 0 | 0 | 0 | 6.3 | 0 |
| 12 |  15 |  | 64.1 | 82.1 | 90.7 | 45.1 | >99 ^c |
| | |  | 1.3 | 2.5 | 7.3 | 51.0 | 0 |
| | |  | 0 | 0 | 1.8 | 3.8 | 0 |

| Entry | Reactant | Product(s) | Method & Yield ^{a,b} (%) | | | | |
|-------|---------------|------------|-----------------------------------|------|------|----|----------------|
| | | | A | B | C | D | E ^c |
| 13 | 16 | | 24.8 | 19.8 | 66.6 | 81 | >99 |

^aYield determined by ¹H NMR, Full descriptions of methods A-F can be found in Appendix X

^bMethod A: 1.1 eq. NIS/TFA

Method B: 2.2 eq. NIS/TFA

Method C: 0.5 eq. SelectfluorTM/I₂

Method D: 1.1 eq. SelectfluorTM/I₂

Method E: 2.0 eq. **1** (Nitrophenyliodonium diacetate) & 4.0 eq TMSOTf

Method E: 2.0 eq. **2** (3,5-dicarboxymethyl)phenyliodonium diacetate & 4.0 eq TMSOTf

^cYield of diaryliodonium salt intermediate

For all of the alkyl substituted benzenes except toluene and 3-bromoanisole, the aryliodination strategy proceeded to 100% conversion within a 2 hours, and produced only a single regioisomer, while the N-iodosuccinimide and SelectfluorTM iodination method required overnight heating, and gave multiple regioisomers or multiply iodinated products.

Of special note is the comparison of the iodination of *p*-xylene. When treated with one equivalent of N-iodosuccinimide, only 64% of the monoiodination product was observed, accompanied by 1.5% of the doubly iodinated product. When subjected to 2 equivalents of N-iodosuccinimide, the reaction did not proceed to completion, but yielded only 82% of the desired mono-iodinated product, while also giving nearly 3% of the doubly-iodinated product. However, when *p*-xylene was treated with 2 equivalents of the aryliodination reagent **2**, the reaction proceeded to completion within one hour at room temperature, and gave the desired product in 99% yield. Similar results are observed for a wide range of molecules.

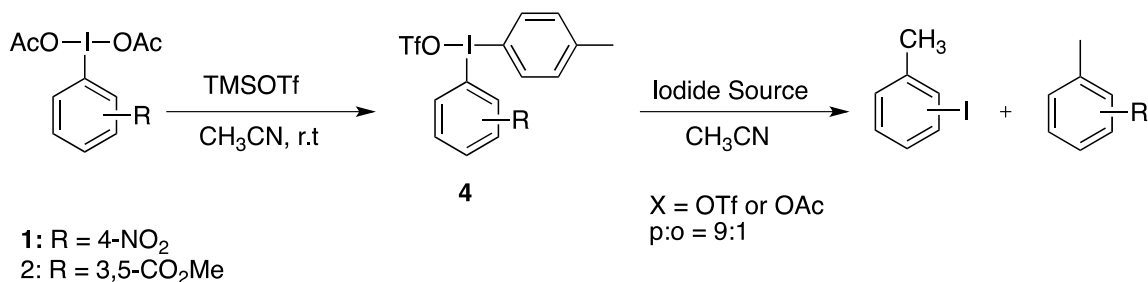
The aryliodination was also shown to be applicable to substrates ranging from benzaldehydes (electronically deactivated) to anilines (highly activated). In all cases where the aryliodination reagent was used, the starting material was completely consumed, regardless of electron-rich or poorness. This wide range of reactivity makes this iodination strategy particularly attractive as a robust, highly versatile alternative to other methods.

However, there are several drawbacks to the aryliodination approach. “The presence of free N-H bonds and phenolic hydroxyl groups were incompatible with the aryliodination reaction, although simple protecting group strategies *should* provide a workaround to this problem. Importantly, the presence of hydrogen bonding groups in the absence of a reducing functional group is tolerated. Highly reducing arenes (1,4-dimethylaminobenzene, 1,4-dimethoxybenzene) participated in redox reactions rather than EAS, indicating that reduction of the aryliodonium salt was the principal side reaction that limits the utility of this method.” For the iodination of particularly electron-rich aromatics, it is probable that a less activated aryliodonium reagent may be used. In these cases, it is likely that the reaction may be modified to suit these electron-rich substrates by simply using less potent activator such as trimethylsilyl trifluoroacetate (TMSTFA) or similar TMS-X reagent.

In order to determine the optimal conditions for the reaction, Bao Hu, a postdoctoral fellow in the DiMagno laboratory, surveyed the amounts of the aryliodination reagent and TMSOTf needed to generate the active electrophile in deuterated acetonitrile (CD_3CN). The activated aryliodonium species, prepared under a variety of conditions, was treated with one equivalent of toluene at room temperature.

Under the optimized conditions (Table 1.4), conversion of arene to the diaryliodonium salt was complete within one hour. Subsequent treatment with an excess (3 equivalents) of sodium iodide and heat (80° C) was sufficient to convert the diaryliodonium salt to the corresponding aryl iodides. Excess iodide was used for two reasons: it pushes the equilibrium for the intermediate diaryliodonium triflate to the iodide, and it also eliminates any unreacted ArIX₂ reagent remaining upon completion of the reaction by reduction ($2\text{I}^- \rightarrow \text{I}_2$).

Table 2.4 Optimization conditions for aryliodination



| Entry | Reagent | Ratio ^b | t (h) | conv. (%) ^c | Iodide source | eq. | T (°C) | t (h) | conv. (%) ^d |
|-------|---------|--------------------|-------|------------------------|---------------|-----|--------|-------|------------------------|
| 1 | 1 | 1.0/1.5/1.5 | 1 | 66 | – | – | – | – | – |
| 2 | 1 | 1.0/1.5/1.5 | 8 | 98 | TMAI | 2.0 | 80 | 13 | 68 |
| 3 | 1 | 1.0/2.0/4.0 | 0.5 | 95 | – | – | – | – | – |
| 4 | 1 | 1.0/2.0/4.0 | 1 | >99 | TMAI | 2.0 | 120 | 1 | 46 |
| 5 | 1 | 1.0/1.5/3.0 | 1 | >99 | TMAI | 2.0 | 120 | 1 | 71 |
| 6 | 1 | 1.0/1.5/3.0 | 1 | >99 | TMAI | 2.0 | 120 | 4 | 95 |
| 7 | 1 | 1.0/1.5/3.0 | 1 | >99 | TMAI | 4.0 | 80 | 1 | >99 |
| 8 | 1 | 1.0/1.5/3.0 | 1 | >99 | TMAI | 3.0 | 80 | 1 | >99 |

| | | | | | | | | | |
|-----|---|-------------|----|-----|------|-----|-----|----|------------------------|
| 91b | 1 | 1.0/1.5/3.0 | 1 | >99 | TBAI | 3.0 | 80 | 1 | >99 |
| 10 | 1 | 1.0/1.5/3.0 | 1 | >99 | NaI | 3.0 | 80 | 1 | >99 (>95) ^e |
| 11 | 2 | 1.0/1.5/1.5 | 1 | 30 | – | – | – | – | – |
| 12 | 2 | 1.0/1.5/1.5 | 29 | 97 | – | – | – | – | – |
| 13 | 2 | 1.0/1.5/3.0 | 1 | >99 | NaI | 3.0 | 120 | 22 | >99 (>95) ^e |

^aReaction conditions: 0.10 mmol scale, 1.5 mL of CD₃CN, N₂.

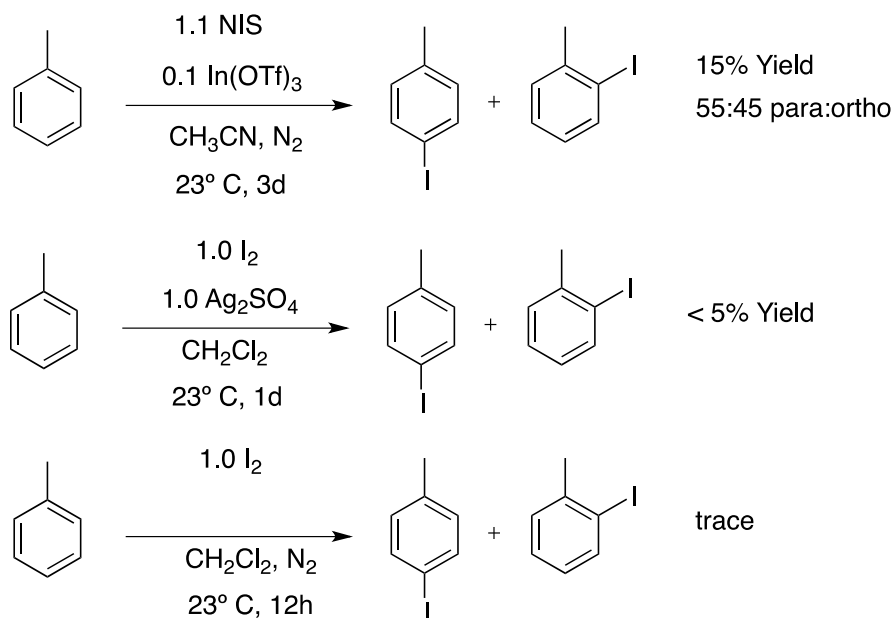
^bToluene/**1** (or **2**)/TMSOTf.

^cBased on toluene. ^dBased on **4**.

^eYields were determined by ¹H NMR spectroscopy.

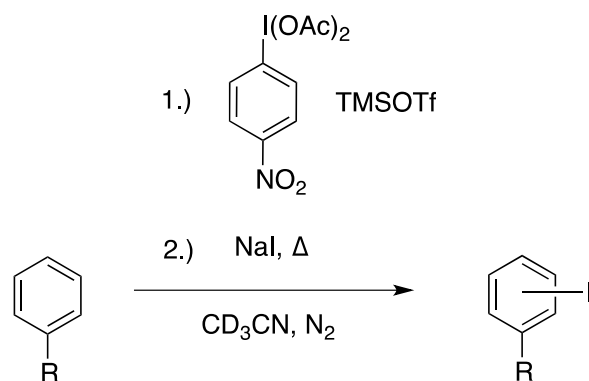
The mild (room temperature, no strong oxidant or protic acid) conditions under which this reaction takes place suggest that the I(III) electrophile is quite potent, yet the reaction proceeds with good regioselectivity. The 9:1 ratio of 4-iodotoluene to 2-iodotoluene indicates that the regioselectivity observed in the original diaryliodonium salt formation is carried through to the products during the decomposition step.

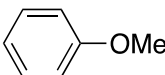
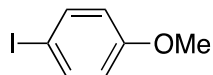
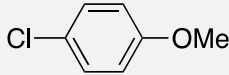
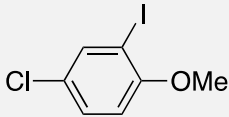
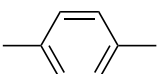
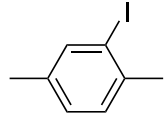
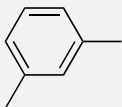
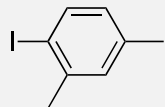
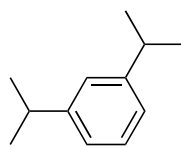
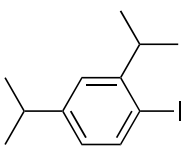
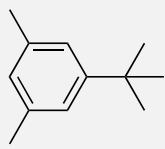
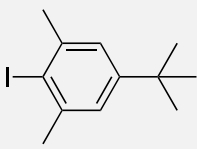
With the optimized reaction conditions in hand, Dr. Hu sought to further illustrate the benefits of using the diaryliodonium method of iodination in comparison to more common procedures. As a starting point, and because the aryliodination methodology proceeds quite mildly at room temperature, several common iodination strategies were performed on toluene *at room temperature*. These results are shown in Scheme 1.12.



Scheme 2.9 Comparison of toluene iodination.

Dr. Hu also performed a survey of the scope of the reaction for the decomposition of the diaryliodonium intermediate. For most of the arenes surveyed, the reaction proceeded to more than 99% conversion to the diaryliodonium intermediate within one hour at room temperature when 1.5 equivalents of the aryliodination reagent (**1** or **2**) and 3 equivalents of TMSOTf were used. The diaryliodonium intermediate was converted rapidly (within 1 hour) to the corresponding iodide when treated with 3 equivalents of sodium iodide in acetonitrile at 80° C. These results are compiled in Table 1.6. In no case were multiply iodinated products observed.

Table 2.5 Survey of the scope of the aryliodination reaction.

| Entry | Arene | Product | Yield (%) ^b |
|-------|---|--|--|
| 1 |  |  | 86 ^c |
| 2 |  |  | 75 ^d |
| 3 |  |  | 78 98 ^e 84 ^{e,f} |
| 4 |  |  | 93 |
| 5 |  |  | >95 |
| 6 |  |  | 79 |

| Entry | Arene | Product | Yield (%) ^b |
|-------|-------|---------|---|
| 7 | | | >95 |
| 8 | | | 84 ^g |
| 9 | | | >95 ^g >95 ^{e,g,h} 81 ^{e,g,h,i} |

^aReaction conditions: 0.10 mmol scale, arene/**1**/TMSOTf/NaI = 1:1.5:1.5:3.0, 1.5 mL of CD₃CN, N₂.

For details of operation, see the Supporting Information.

^bDetermined by ¹H NMR using an internal std.

^cThe iodination required 80 °C for 2 h.

^dThe iodination required 120 °C for 1 h.

^e**2** was instead of **1**.

^f1 mmol scale.

^gThe oxidation required 1 d.

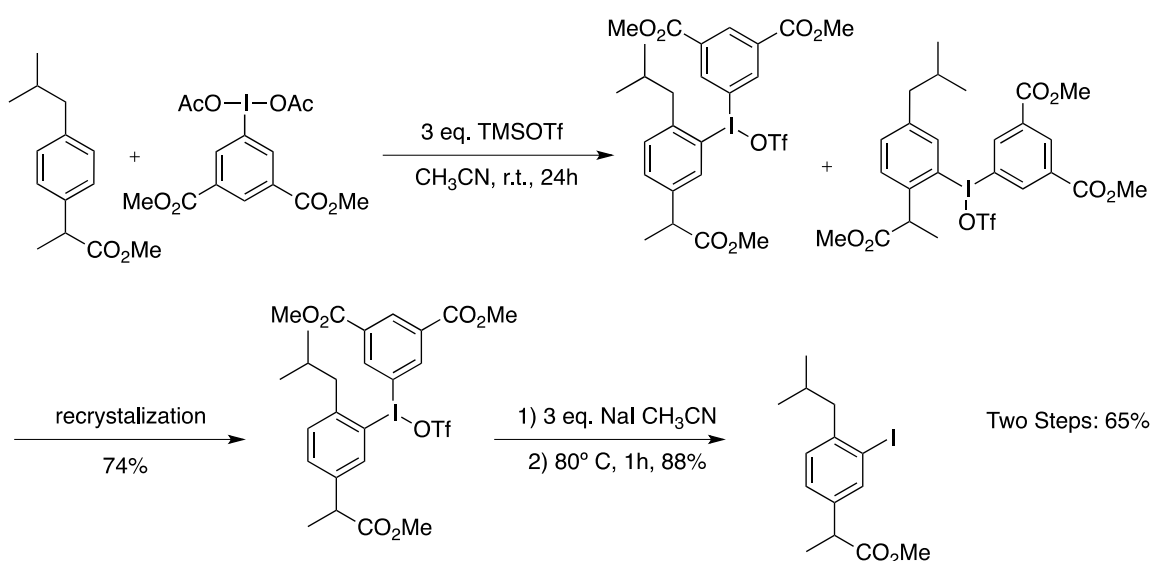
^hThe iodination required 120 °C for 40 min.

ⁱ6 mmol scale.

In order to demonstrate the utility of using this method in a synthetic strategy, I attempted to iodinate methyl 2-(4-isobutylphenyl)propanoate, also known as ibuprofen. Remarkably, this common material had not been selectively iodinated previously. It is difficult to selectively iodinate the methyl ester of ibuprofen, as the 2 and 3 position on the aromatic ring are very electronically similar, and conventional electrophilic aromatic substitution methods give a mixture of the two possible regioisomers, which are especially difficult to separate using normal phase silica gel chromatography.

When the ibuprofen methyl ester was subjected to the standard conditions for aryliodination using our method, a 9:1 mixture of the two possible regioisomeric

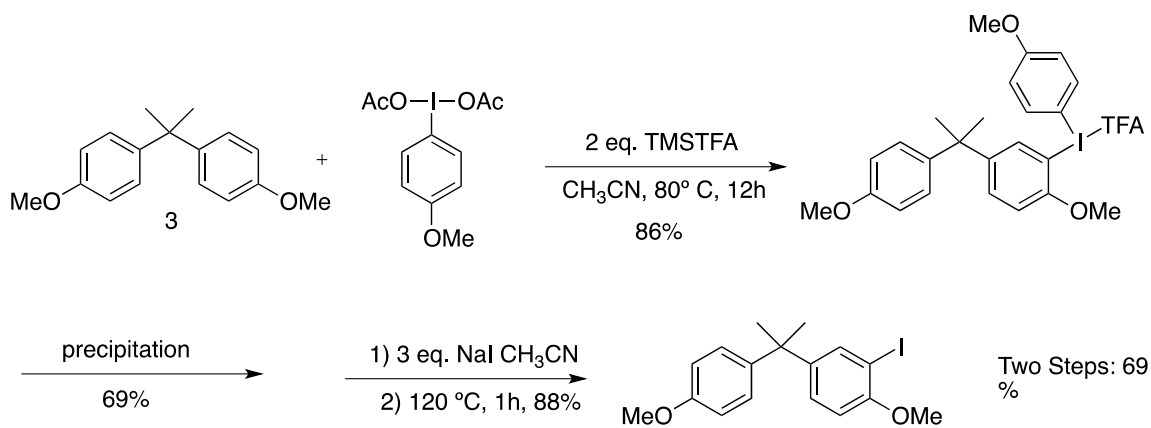
diaryliodonium products were obtained (Scheme 1.14). Recrystallization gave the desired, regioisomerically pure diaryliodonium salt intermediate product in good yield. Dr. Hu then treated the diaryliodonium salt intermediate with 3 equivalents of sodium iodide in acetonitrile at 80° C to form the corresponding iodide. Silica gel chromatography (1:40 EtOAc:Hexanes) removed 5-iodoisophthalate to provide methyl 2-(3-iodo-4-isobutylphenyl)propanoate in 65% overall yield.



Scheme 2.10 Iodination of ibuprofen methyl ester

Additionally, I attempted to iodinate bisphenol A dimethyl ether (BPAD) using this new diaryliodonium salt approach. Initial experiments indicated that the strategy was indeed viable, but reagents **1** and **2**, when combined with TMSOTf as the activator, proved to be overly electrophilic reagents, and reduction of the aryliodonium triflate was a predominant side reaction. Dr. Hu, however, was able to use the aryliodination method

to produce monoiodinated BPAD in good yield. He used a less aggressive aryliodination reagent, (4-methoxypheny)iodonium diacetate in place of **1** or **2**, to form product in good yield, as is shown in Scheme 1.14.



Scheme 2.11 Iodination of bisphenol A dimethyl ether (BPAD)

The iodination of BPAD is especially remarkable; every other common iodination methods that we explored (NIS/TFA, Ag₂SO₄/I₂, ICl) gave inseparable mixtures of starting material and singly and multiply iodinated BPAD, even when a large excess of BPAD was used. However, aryliodination was capable of forming a single diaryliodonium salt, even when only a slight excess of BPAD was used. More surprising is that this non-statistical preference for mono-substitution seems to be originate from a through-bond electronic effect, since the T-shaped structure of the diaryliodonium salt intermediate seems to preclude any through space aryl-aryl interaction of the 4-methoxyphenyl ring with the unsubstituted ring of BPAD. The singly-substituted diaryliodonium salt was readily separated from the unreacted BPAD by precipitation

from ethyl acetate with hexanes, and iodination with excess KI was performed in excellent yield.

2.3 CONCLUSIONS

In comparison to the Sandmeyer reaction, the preparation of aryl iodides using aryliodination is functionally simpler and retains many of the advantages of the Sandmeyer reaction. The formation of a polar, diaryliodonium salt intermediate that is readily purified makes it quite simple to obtain good yields of single regioisomer aryl iodides. In addition, the diaryliodonium salt intermediate possesses solubility characteristics that make it possible to obtain good yields of iodinated arenes when the reaction is carried out at low conversion. The aryliodination reagents' reactivity may also be tuned to match a range of electron-rich arenes, and the polarity of the aryliodination reagents can be modified to simplify product isolation by silica gel chromatography. Using this method, iodoarenes that cannot normally be synthesized regioselectively by electrophilic aromatic substitution may now be prepared. The two step process also provides a method to isolate iodoarenes that would otherwise be extremely challenging to separate from their unsubstituted parent compounds. Finally, these reagents are characterized by a unique combination of reactivity and selectivity—they are simultaneously more aggressive, regioselective, and chemoselective than standard reagents for electrophilic aromatic iodination.

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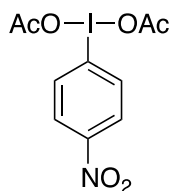
2.4 EXPERIMENTAL

2.4.1 Materials

The chemicals were obtained from Aldrich Chemical Company and used as received unless otherwise noted. Acetonitrile and acetonitrile- d_3 (Cambridge Isotope Laboratories) were dried over P_2O_5 , distilled under reduced pressure into flame-dried storage tubes, and stored under dry nitrogen. TMSOTf (trimethylsilyl trifluoromethanesulfonate) was distilled prior to use. SelectfluorTM (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) (Oakwood Chemical Company) was dried *in vacuo* for 2 days at room temperature before use. All other reagents were used as received. 1H NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer in the NMR Laboratory at the University of Nebraska-Lincoln.

2.4.2 Synthetic Procedures

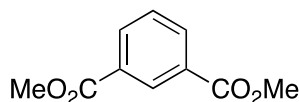
Synthesis of 1-(diacetoxyiodo)-4-nitrobenzene, **1**



To a 500 mL oven dried Schlenk flask in a nitrogen charged glovebox was added dry acetonitrile (250 mL), 1-iodo-4-nitrobenzene (0.08 mol, 19.92 g), 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (0.104 mol, 36.84 g) and trimethylsilyl acetate (0.208 mol, 27.50 g). The reaction vessel was sealed, removed from the glovebox, and heated at 50 °C for 24 hours with stirring. The reaction was allowed to cool to room temperature and the acetonitrile was removed *in vacuo*. The orange solid

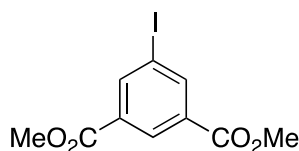
was dissolved in dichloromethane (250 mL) washed with pH 5 acetate buffer (3 x 100 mL), dried over sodium sulfate, filtered, and the solvent was removed by rotary evaporation. The orange solid was dissolved in dichloromethane (50 mL), and triturated with a 10% diethyl ether/hexanes solution (250 mL) to give a pale yellow solid after filtration. The solid was dried at room temperature *in vacuo* for 24 hours to obtain the product in 85% yield. ^1H NMR (CD_3CN , 400 MHz, 25 °C): δ 8.337 (q, J = 7.97 Hz, 4H), 1.949 (s, 6H).

Synthesis of dimethyl isophthalate



To a 500 mL round bottom flask was added methanol (250 mL) and isophthaloyl dichloride (0.1 mol, 20.30 g). The reaction mixture was heated at reflux for 3 hours, cooled to 0 °C, and filtered to afford dimethyl isophthalate as a white solid in 96% yield.

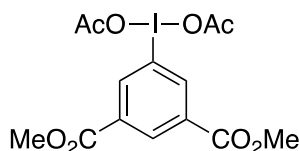
Synthesis of dimethyl 5-iodoisophthalate



To a 96% sulfuric acid solution was added iodine (0.056 mol, 7.11 g) and sodium periodate (0.019 mol, 4.06 g). The reaction mixture was heated at 30 °C for 45 minutes, at which point the reaction mixture became dark purple and dimethyl isophthalate (0.075 mol, 14.56 g) was added. After heating for another 12 hours at 30 °C, The reaction mixture was poured over crushed ice, neutralized with sodium bicarbonate, filtered, and rinsed with water. The purple solid was then dissolved in dichloromethane (100 mL),

washed with a saturated sodium bicarbonate solution (1x 100 mL), water (3 x 100 mL), and a saturated sodium bisulfite solution (3x 50 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The resulting white solid was then recrystallized from boiling methanol to afford dimethyl 5-iodoisophthalate as a white solid. The solid was dried at room temperature *in vacuo* for 24 hours to obtain the product in 73% yield. ^1H NMR (CDCl_3 , 400 MHz, 25 $^\circ\text{C}$): δ 8.634 (s, 1H), 8.5505 (d, J = 1.87 Hz, 2H), 3.957 (s, 6H).

Synthesis of 1-(diacetoxyiodo)-3,5-dicarboxymethylbenzene, 2



To a 500 mL oven dried Schlenk flask in a nitrogen charged glovebox was added dry acetonitrile (250 mL), 5-iodoisophthalate (0.02 mol, 8.76 g), 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (0.026 mol, 9.21 g) and trimethylsilyl acetate (0.052 mol, 6.88 g). The reaction vessel was sealed, removed from the glovebox, and heated at 50 $^\circ\text{C}$ for 24 hours with stirring. The reaction was allowed to cool to room temperature and the acetonitrile was removed *in vacuo*. The white solid was dissolved in dichloromethane (250 mL) washed with pH = 5 acetate buffer (3 x 100 mL), dried over sodium sulfate, and concentrated *in vacuo*. The orange solid was dissolved in dichloromethane (50 mL), and triturated with a 10% diethyl ether/hexanes solution (250 mL) to give a white solid after filtration. The solid was dried at room temperature *in vacuo* for 24 hours to obtain the product in 80% yield. ^1H NMR (CDCl_3 , 400 MHz, 25 $^\circ\text{C}$): δ 8.898 (d, J = 1.76 Hz, 2H), 8.866 (d, J = 1.79 Hz, 1H), 4.010 (s, 6H), 2.024 (s, 6H).

Method A: Synthesis of iodoarenes using NIS and TFA (1 equivalent)

A solution of arene (0.1 mmol) in dry acetonitrile- d_3 (0.5 mL) was prepared. To this mixture was added a solution of 1-iodo-2,5-pyrrolidinedione (N-iodosuccinimide) and 2,2,2-trifluoroacetic acid in dry acetonitrile- d_3 (1 mL, 1.1 M each in NIS and TFA). The reaction vial was sealed and heated at 50 °C for 12 hours. Yields of iodinated arenes were determined by ^1H NMR spectroscopy.

Method B: Synthesis of iodoarenes using NIS and TFA (2 equivalents)

A solution of arene (0.1 mmol) in dry acetonitrile- d_3 (0.5 mL) was prepared. To this mixture was added a solution of N-iodosuccinimide and 2,2,2-trifluoroacetic acid in dry acetonitrile- d_3 (1 mL, 2.1 M each in NIS and TFA). The reaction vial was sealed and heated at 50 °C for 12 hours. Yields of iodinated arenes were determined by ^1H NMR spectroscopy.

Method C: Synthesis of iodoarenes using SelectfluorTM and I₂ (1 equivalent)

To a solution of arene (0.1 mmol) in dry acetonitrile- d_3 (0.5 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (0.06 mmol, 22 mg). To this mixture was added a solution of iodine in dry acetonitrile- d_3 (1 mL, 0.6 M). The reaction vial was sealed and heated at 50 °C for 12 hours. Yields of iodinated arenes were determined by ^1H NMR spectroscopy.

Method D: Synthesis of iodoarenes using SelectfluorTM and I₂ (2 equivalents)

To a solution of arene (0.1 mmol) in dry acetonitrile- d_3 (0.5 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (0.11 mmol, 39 mg). To this mixture was added an iodine solution in dry acetonitrile- d_3 (1 mL,

1.1 M). The reaction vial was sealed and heated at 50 °C for 12 hours. Yields of iodinated arenes were determined by ^1H NMR spectroscopy.

Method E: Synthesis of iodoarenes using 1-(diacetoxyiodo)-4-nitrobenzene (2 equivalents)

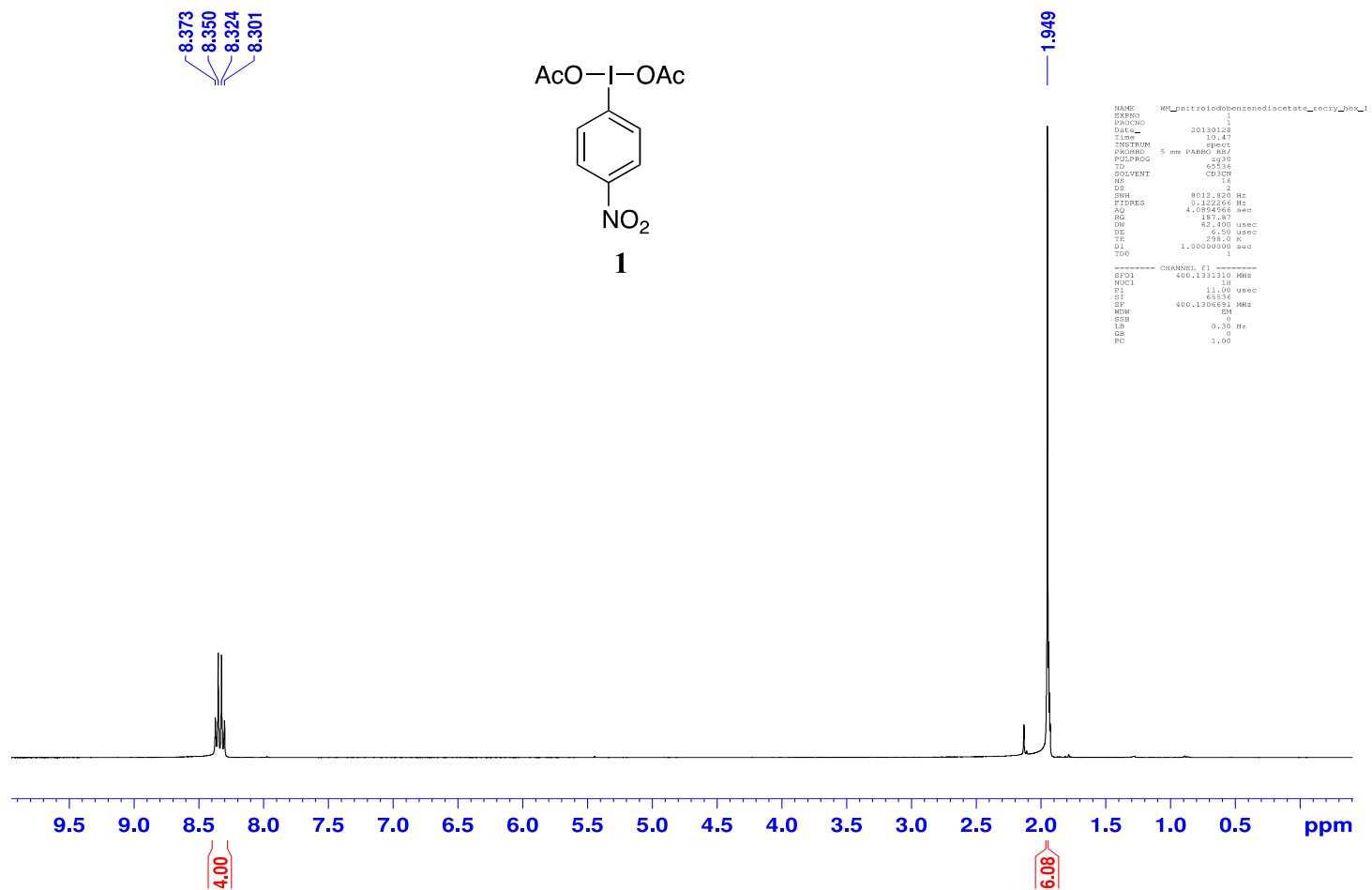
In a glovebox under nitrogen, trimethylsilyl trifluoromethanesulfonate (0.4 mmol, 89 mg) was added to a solution of 1-(diacetoxyiodo)-4-nitrobenzene (0.2 mmol, 73 mg) in dry acetonitrile- d_3 (1 mL). The solution was transferred to a 5 mm NMR tube, fitted with a rubber septum, removed from the glovebox and sealed with paraffin film. To the sealed NMR tube was added a solution of arene (0.1 mmol) dissolved in dry acetonitrile- d_3 (0.5 mL). The reaction mixture was kept at room temperature for 3 hours, then tetrabutylammonium iodide (0.15 mmol, 56 mg) was added and the reaction mixture was diluted with 50 mL dichloromethane. The organic layer was washed with water (3 x 50 mL), dried over sodium sulfate, and concentrated *in vacuo*.

Method F: Synthesis of iodoarenes using 1-(diacetoxyiodo)-3,5-dicarboxymethylbenzene (2 equivalents)

In a glovebox under nitrogen, trimethylsilyl trifluoromethanesulfonate (0.4 mmol, 89 mg) was added to a solution of dimethyl 1-(diacetoxyiodo)-3,5-dicarboxymethylbenzene (0.2 mmol, 88 mg) in dry acetonitrile- d_3 (1 mL). The solution was transferred to a 5 mm NMR tube, fitted with a rubber septum, removed from the glovebox and sealed with paraffin film. To the sealed NMR tube was added a solution of arene (0.1 mmol) dissolved in dry acetonitrile- d_3 (0.5 mL). The reaction mixture was kept at room temperature for 3 hours, then tetrabutylammonium iodide (0.15 mmol, 56 mg)

was added and the reaction mixture was diluted with 20 mL dichloromethane. The organic layer was washed with water (3 x 10 mL), dried over sodium sulfate, and concentrated *in vacuo*.

4.1 APPENDIX A: NMR Data

Figure S1. ¹H NMR spectrum of **1** in CD₃CN.

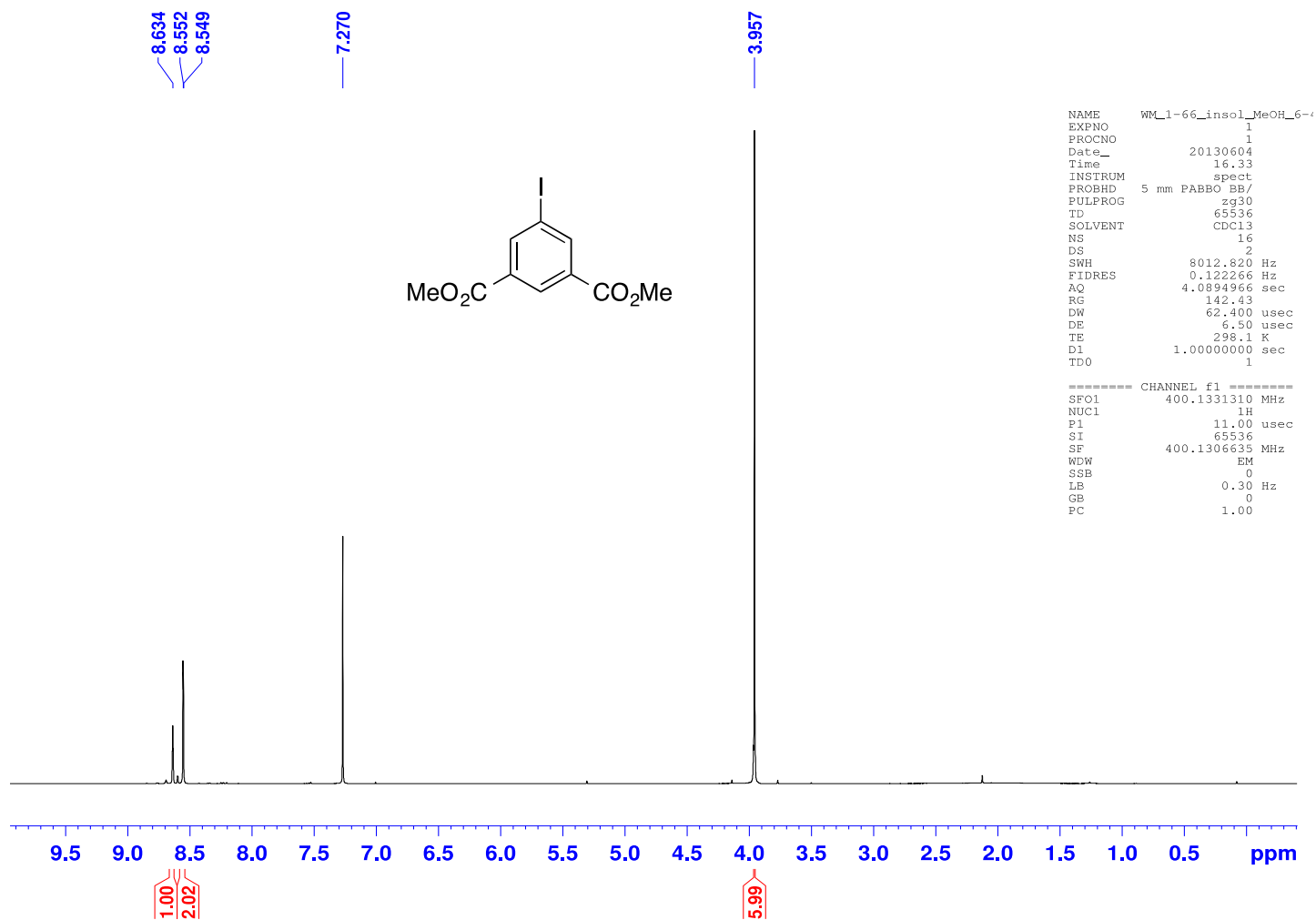


Figure S2. ¹H NMR spectrum of 5-iododimethylisophthalate in CDCl₃

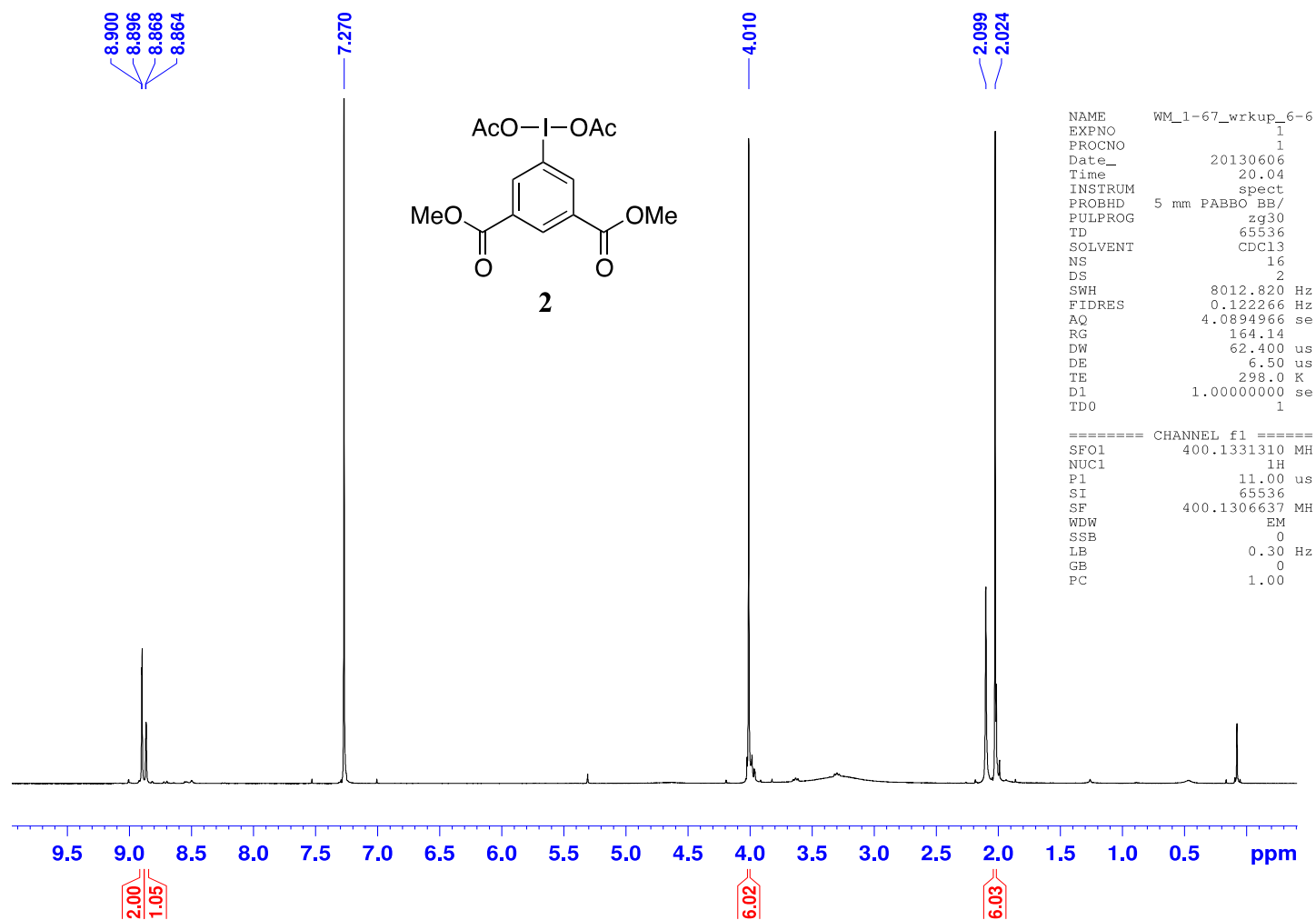


Figure S3. ¹H NMR spectrum of **2** in CD₃CN.

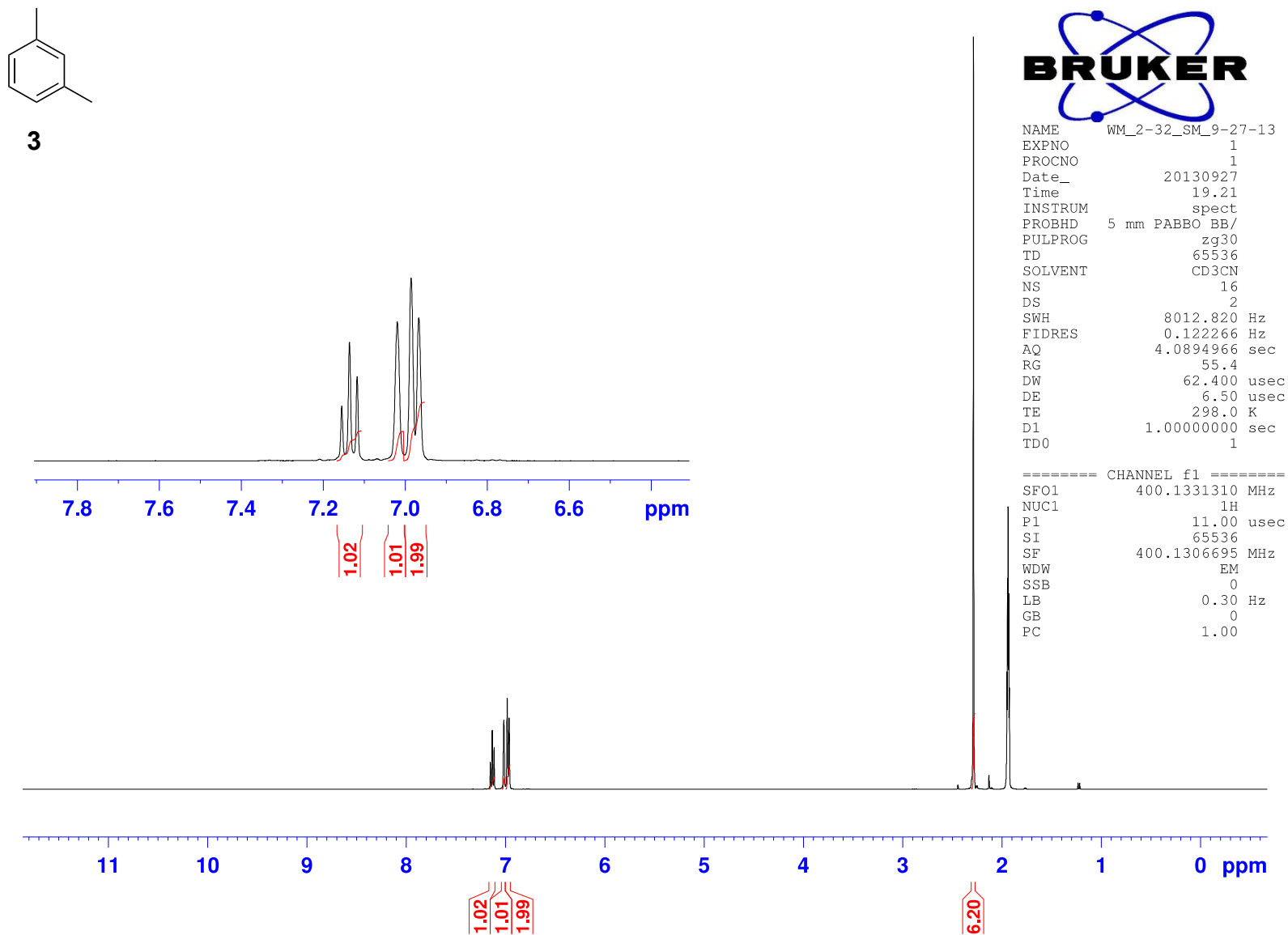


Figure S4. ^1H NMR spectrum of **3** in CD_3CN .

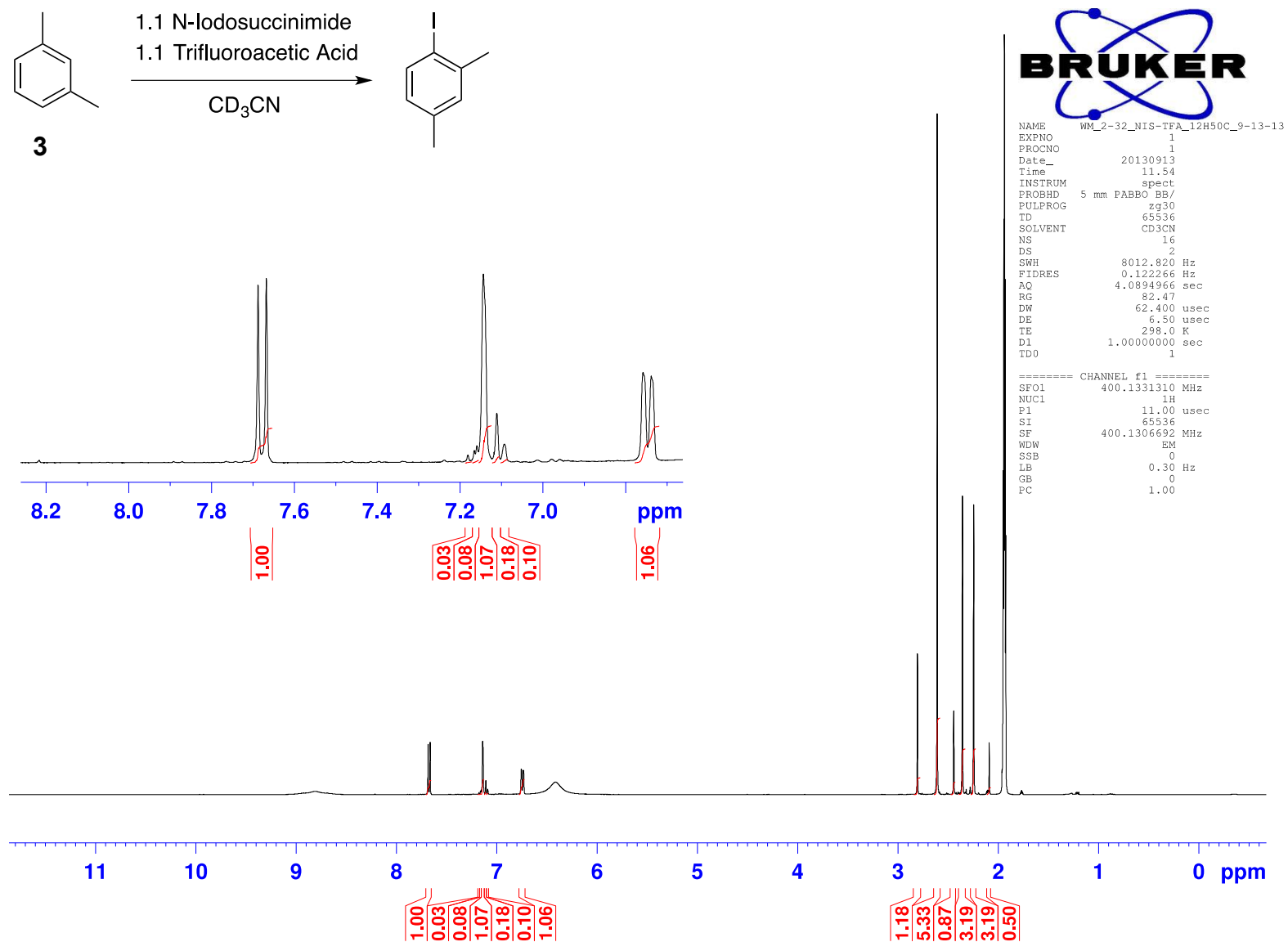


Figure S5. ^1H NMR spectrum of the iodination of **3** by Method A in CD_3CN .

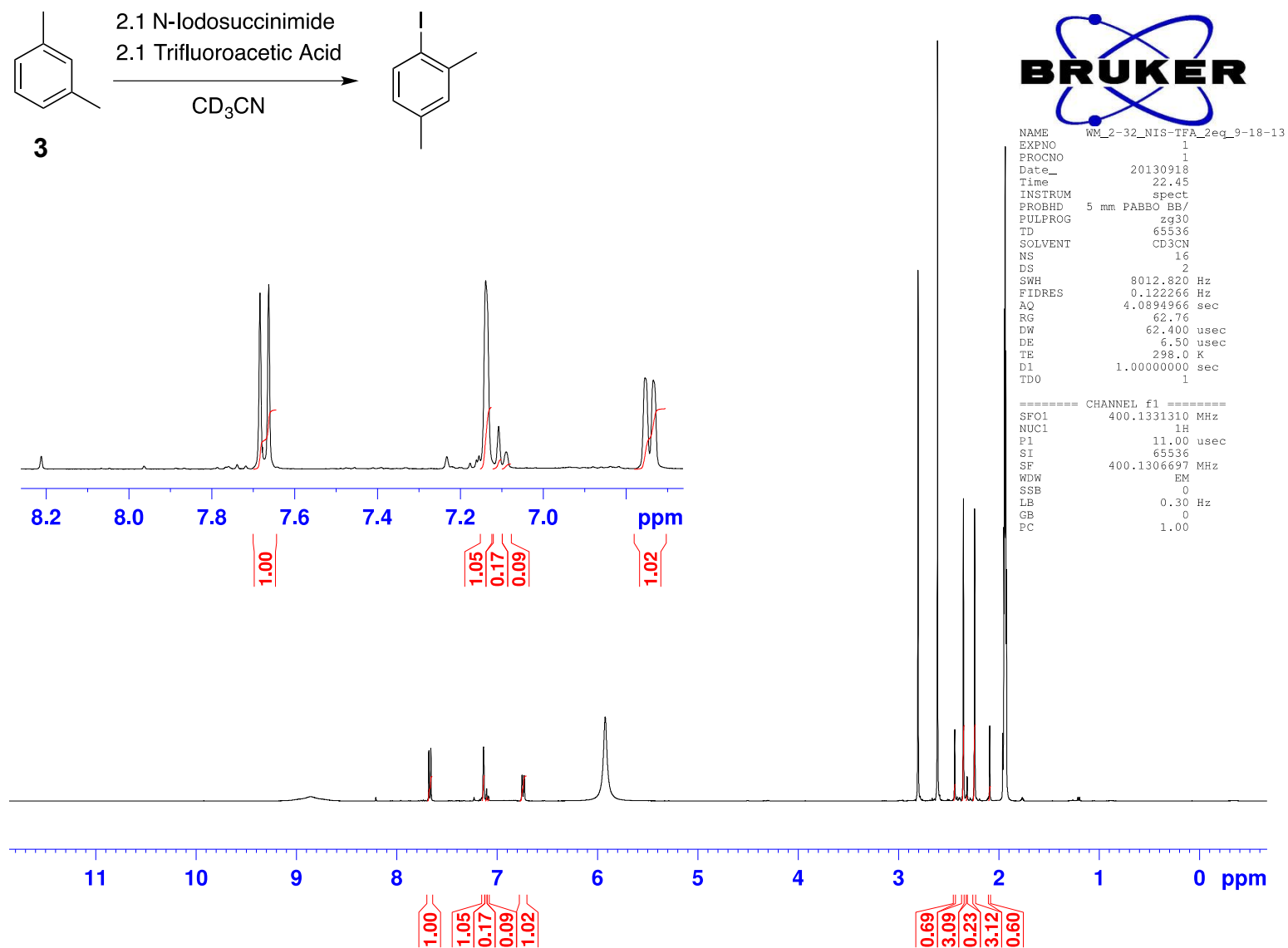


Figure S6. ¹H NMR spectrum of the iodination of **3** by Method B in CD₃CN.

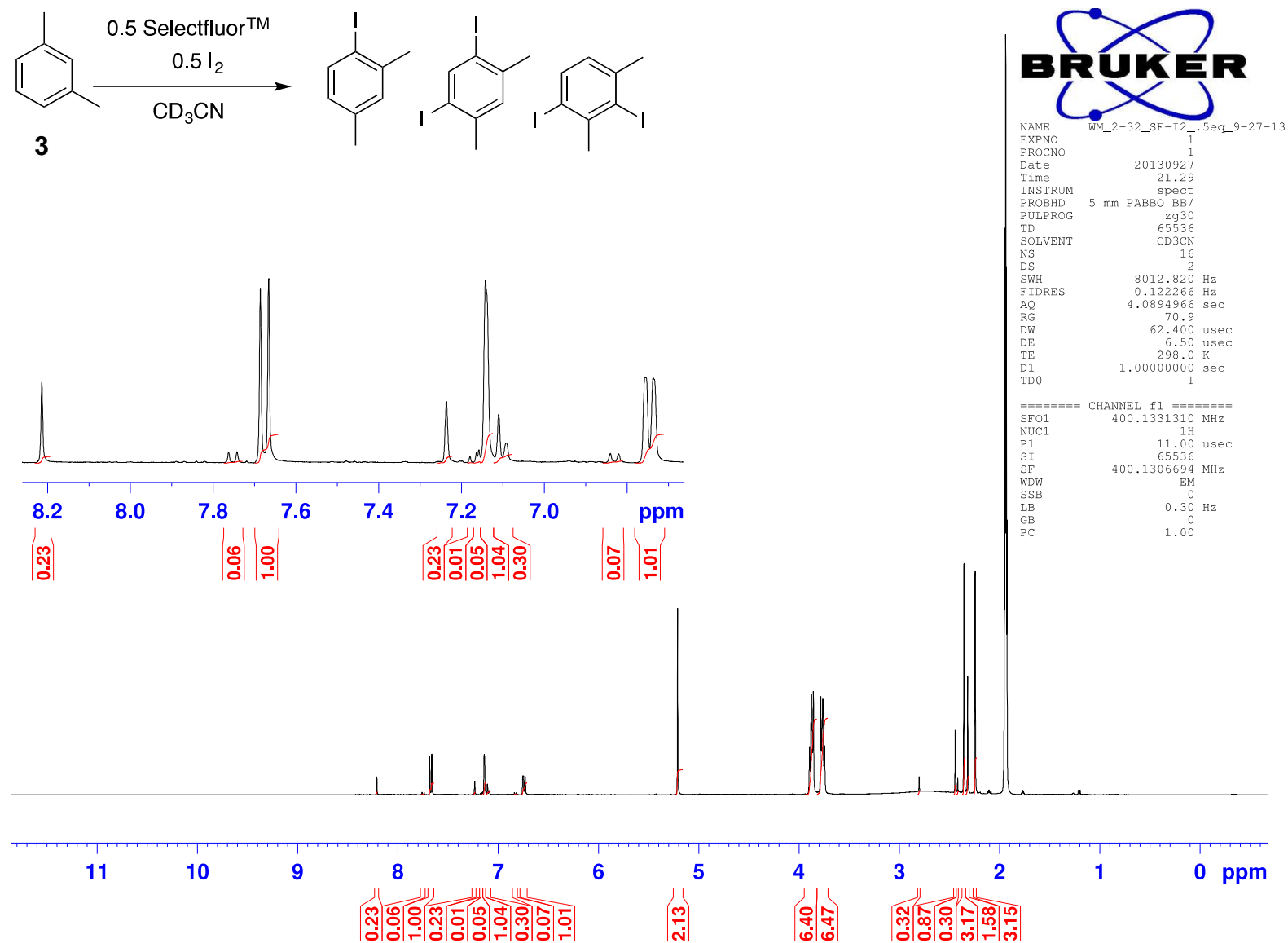


Figure S7. ¹H NMR spectrum of the iodination of **3** by Method C in CD₃CN.

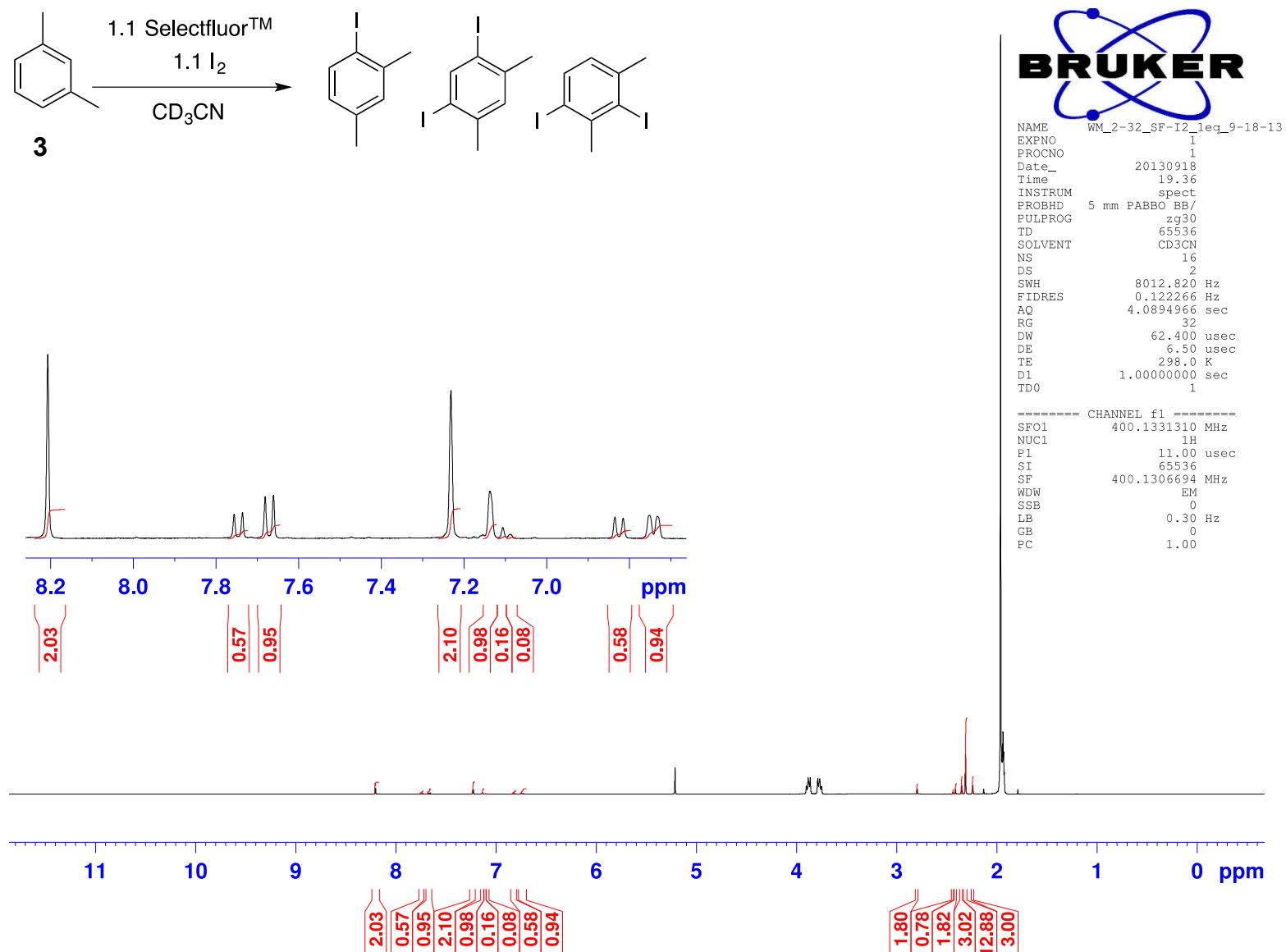


Figure S8. ¹H NMR spectrum of the iodination of **3** by Method D in CD₃CN.

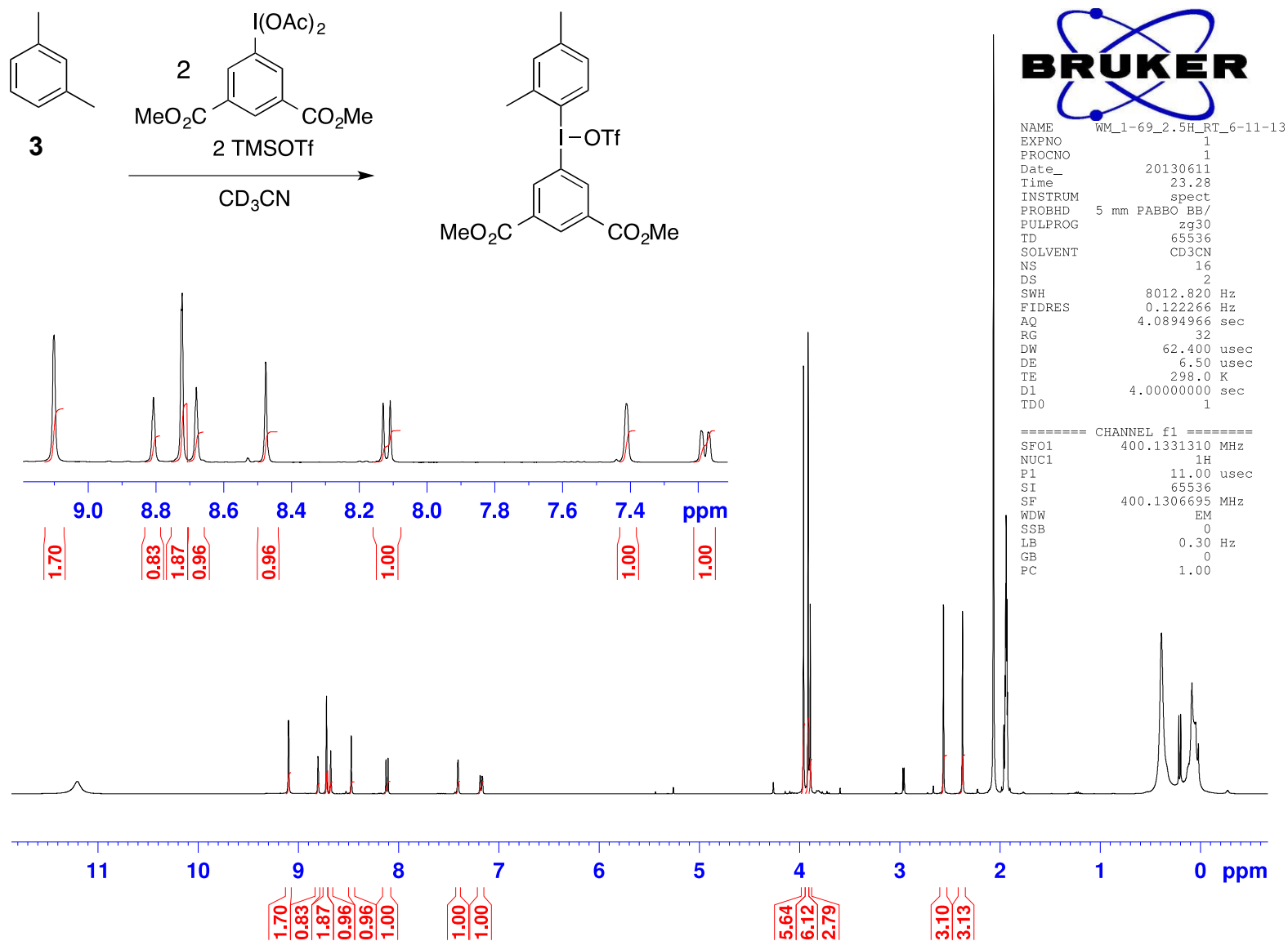


Figure S9. ¹H NMR spectrum of the iodination of **3** by Method F in CD₃CN.

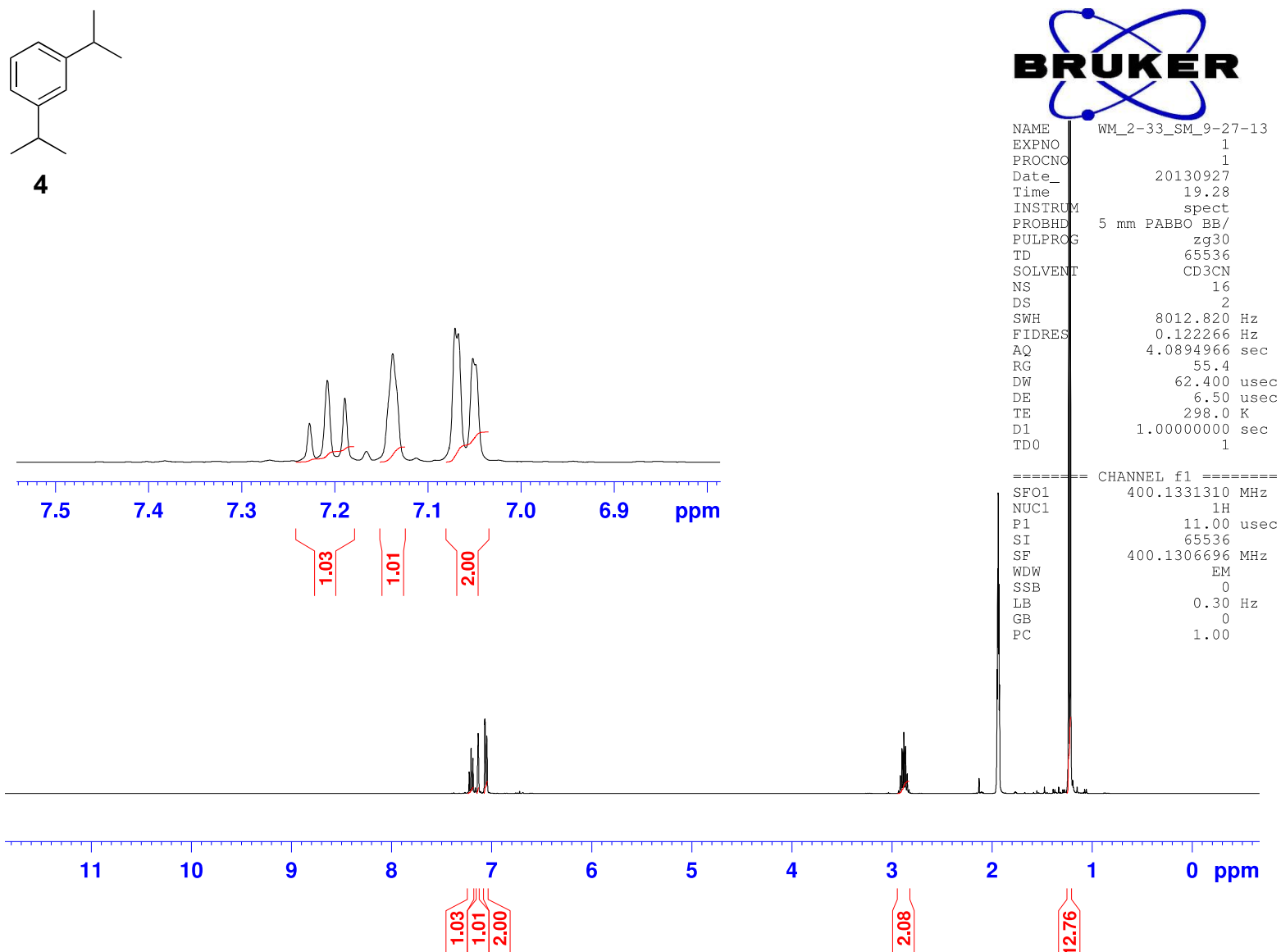


Figure S11. ^1H NMR spectrum of **4** in CD_3CN .

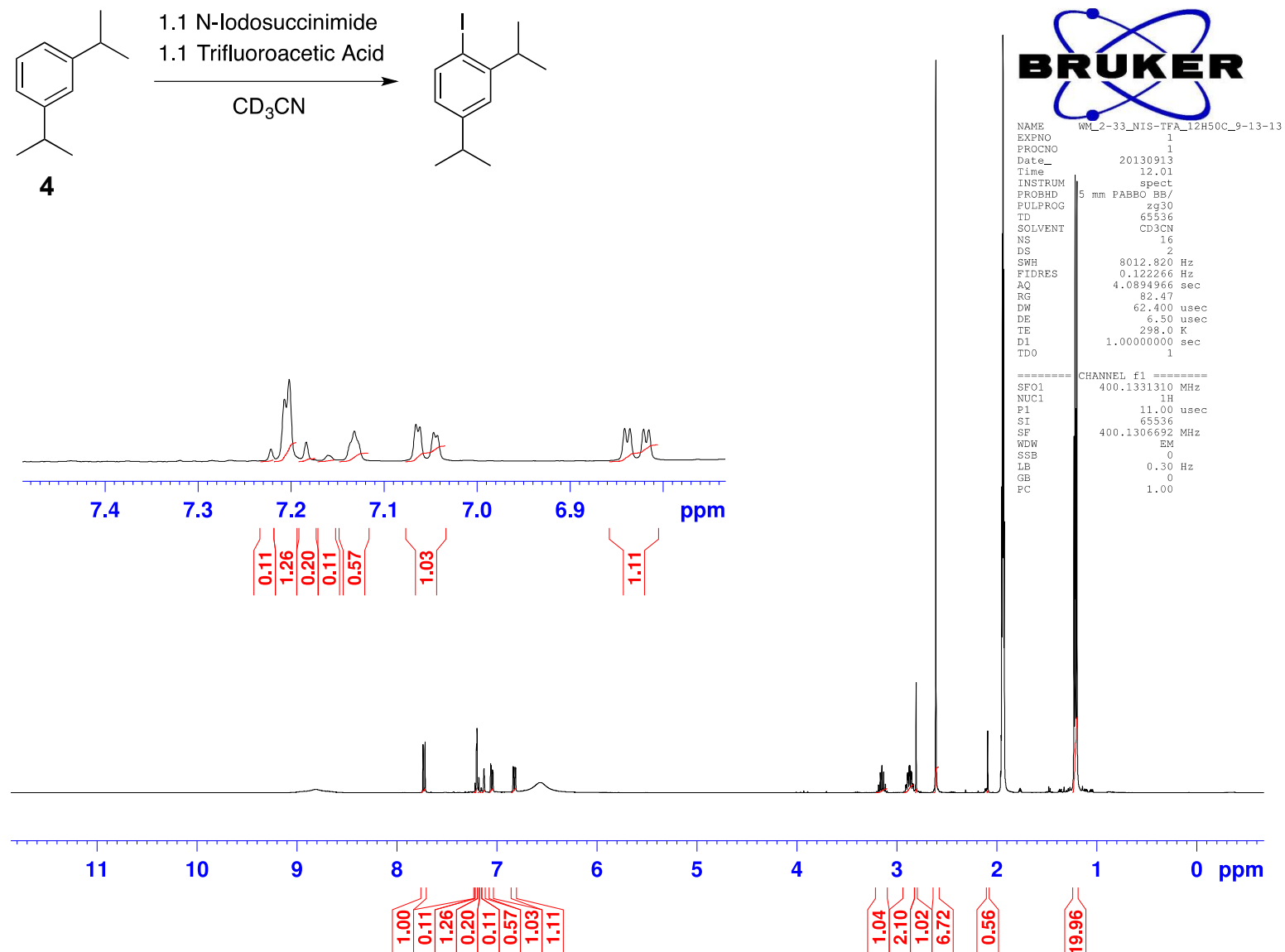


Figure S12. ¹H NMR spectrum of the iodination of **4** by Method A in CD₃CN.

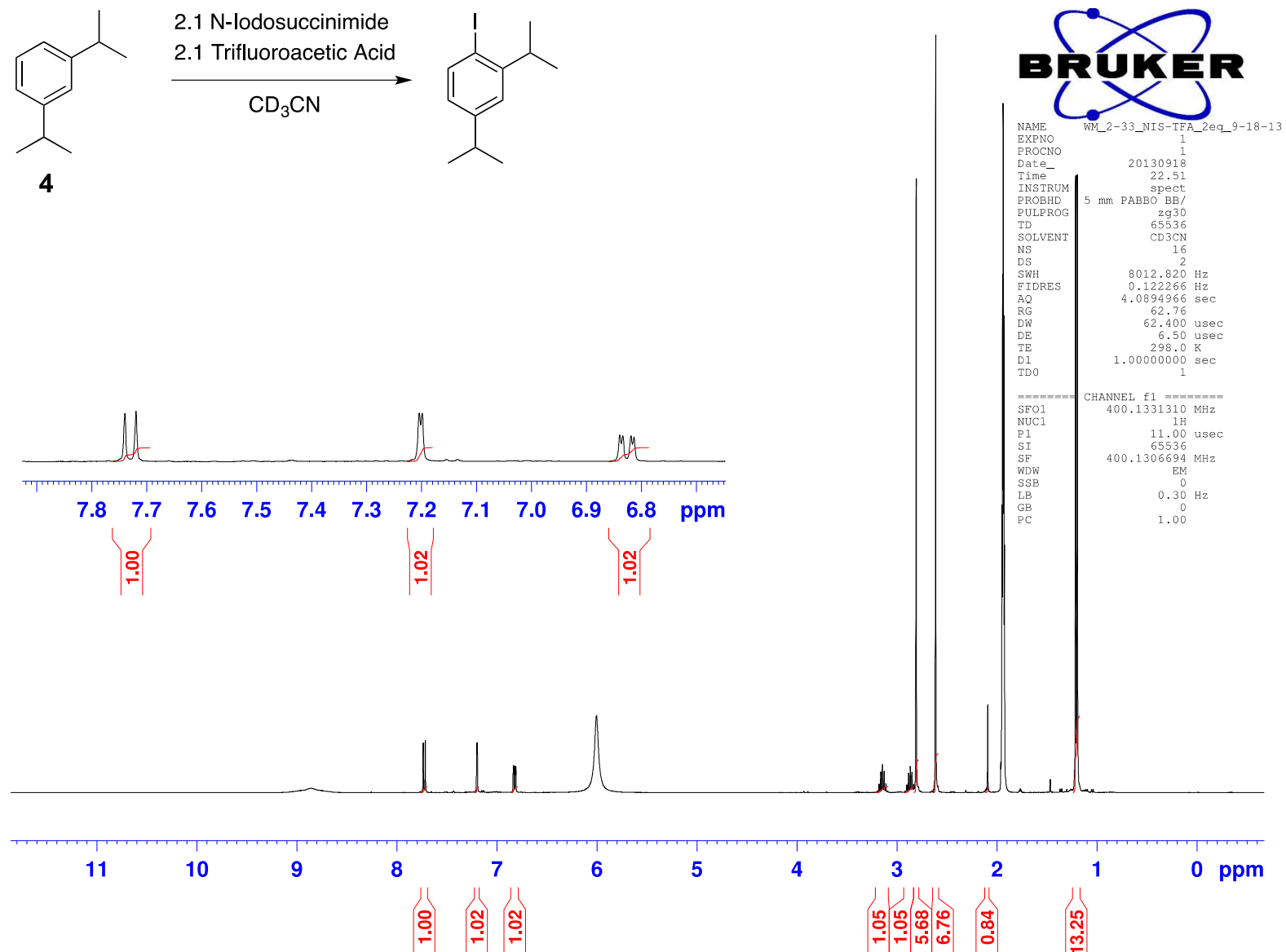


Figure S13. ^1H NMR spectrum of the iodination of **4** by Method B in CD_3CN .

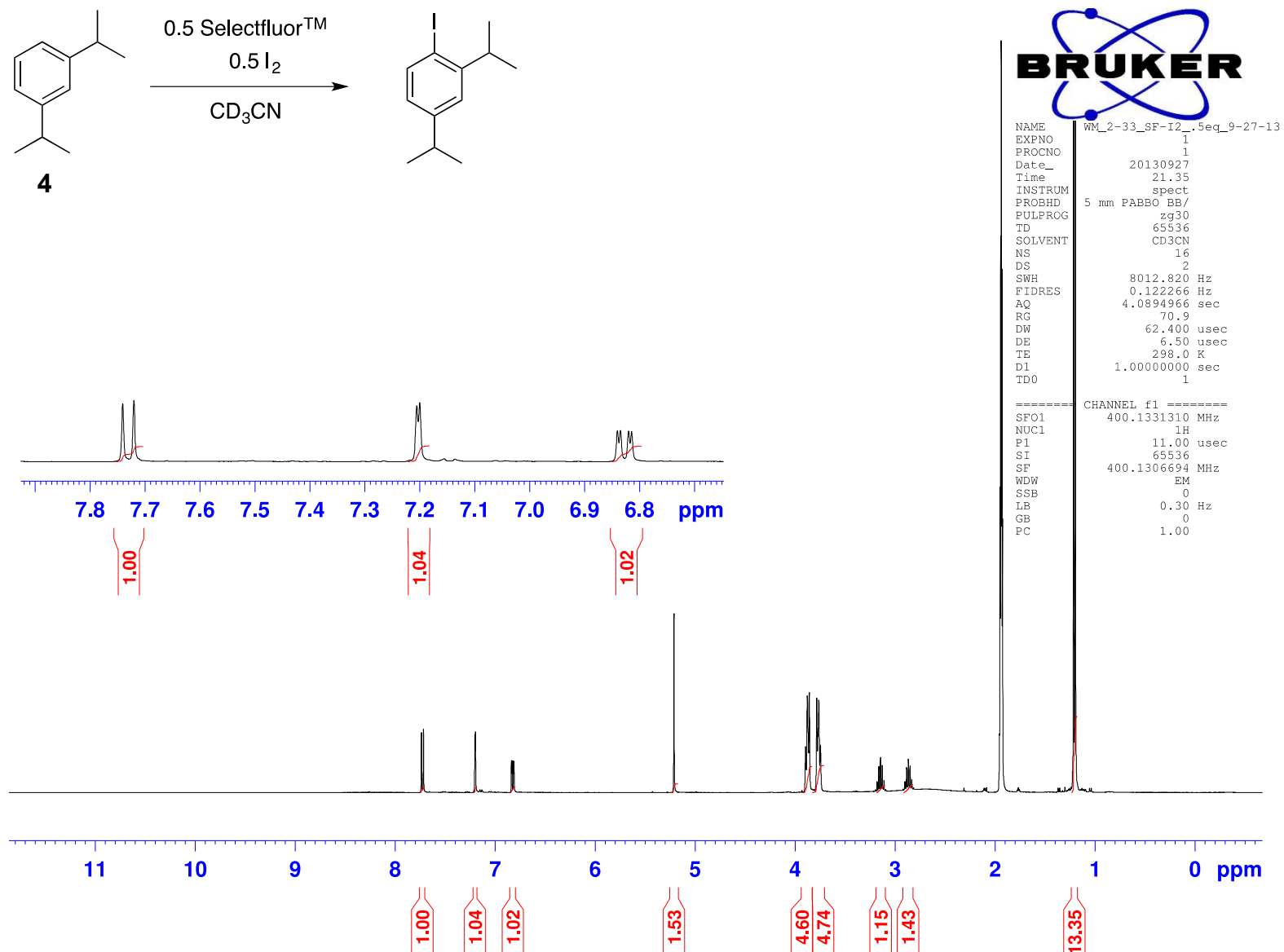


Figure S14. ¹H NMR spectrum of the iodination of **4** by Method C in CD₃CN.

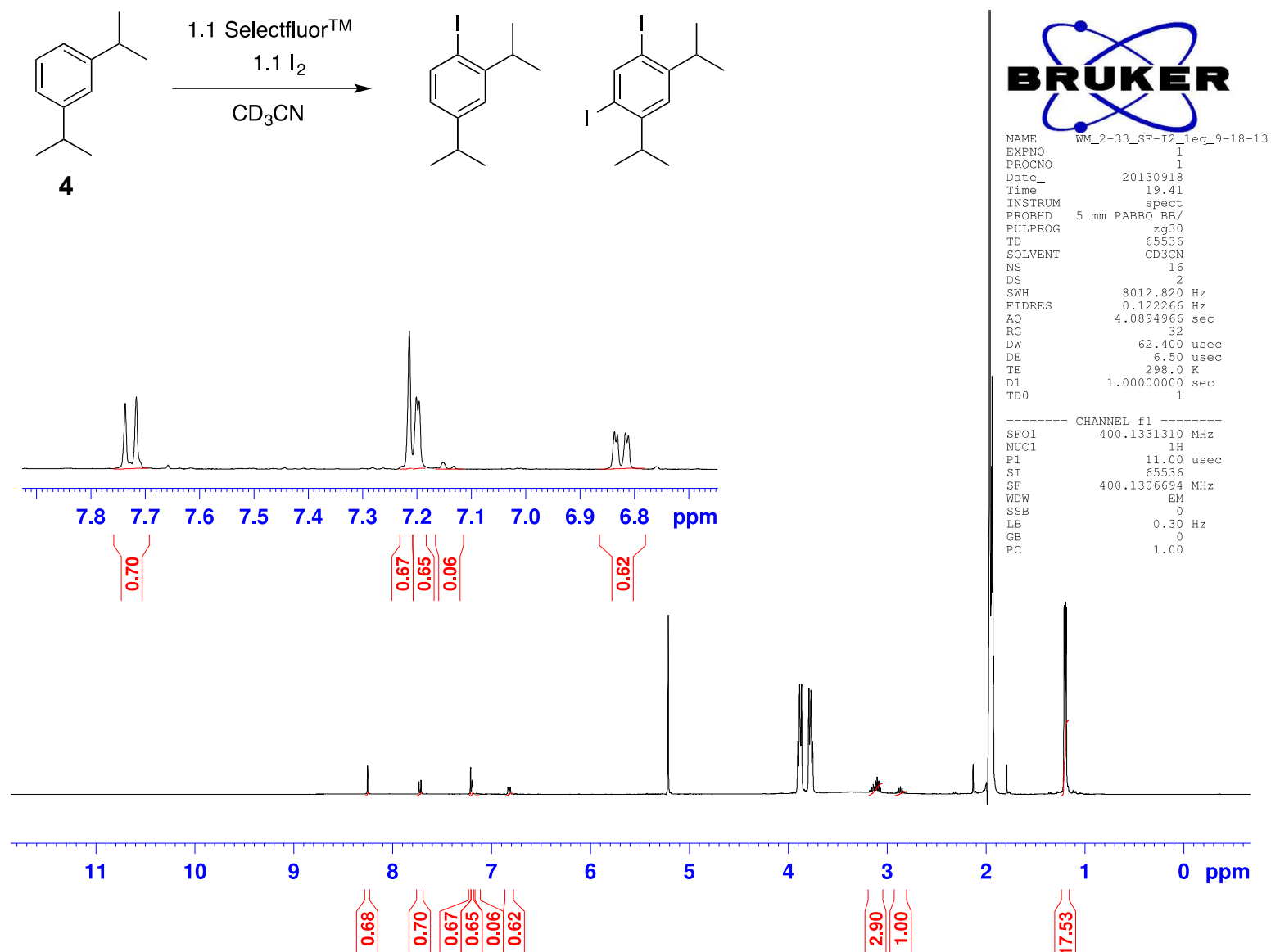


Figure S15. ¹H NMR spectrum of the iodination of **4** by Method D in CD₃CN.

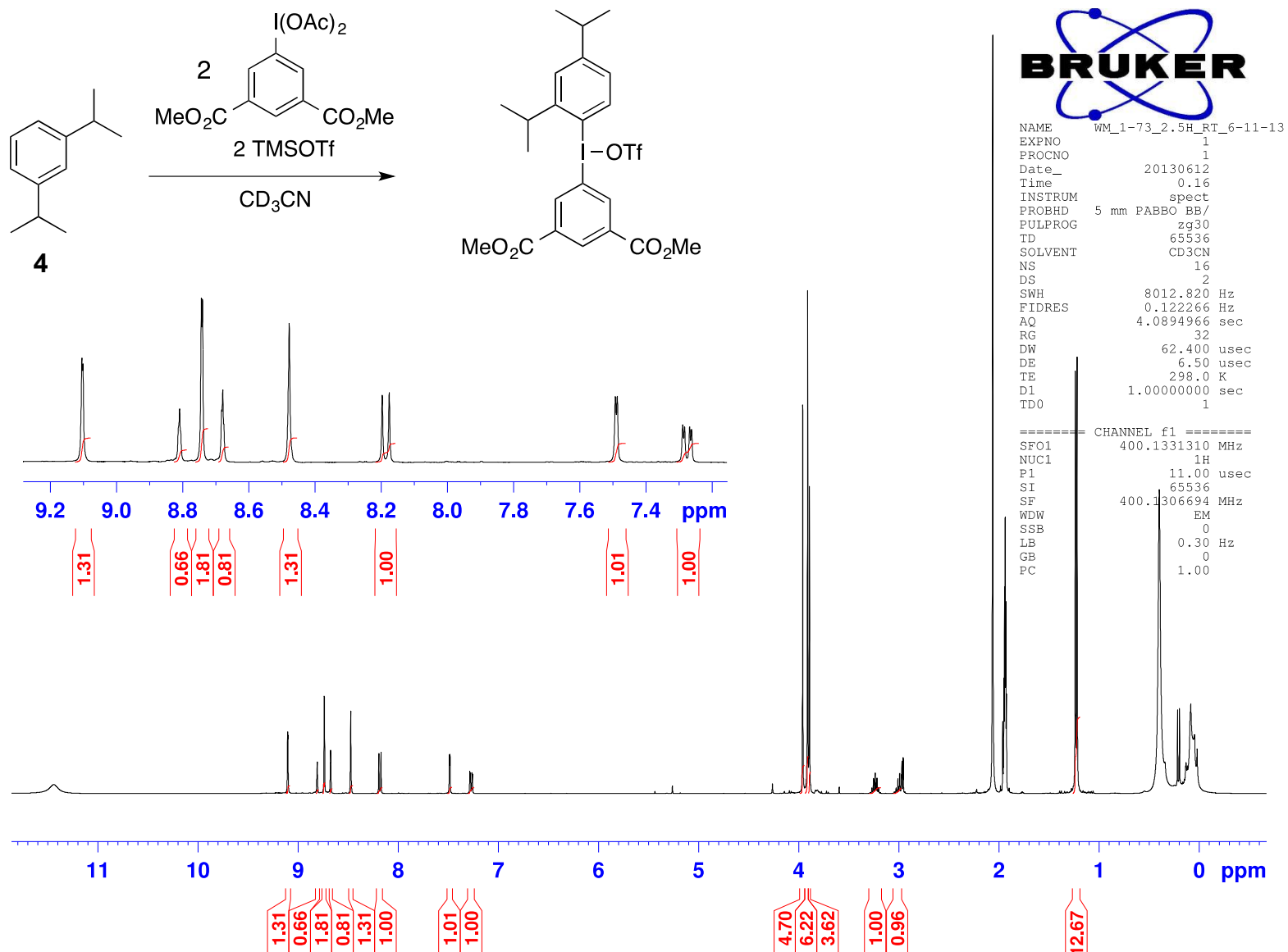


Figure S16. ¹H NMR spectrum of the iodination of **4** by Method F in CD₃CN.

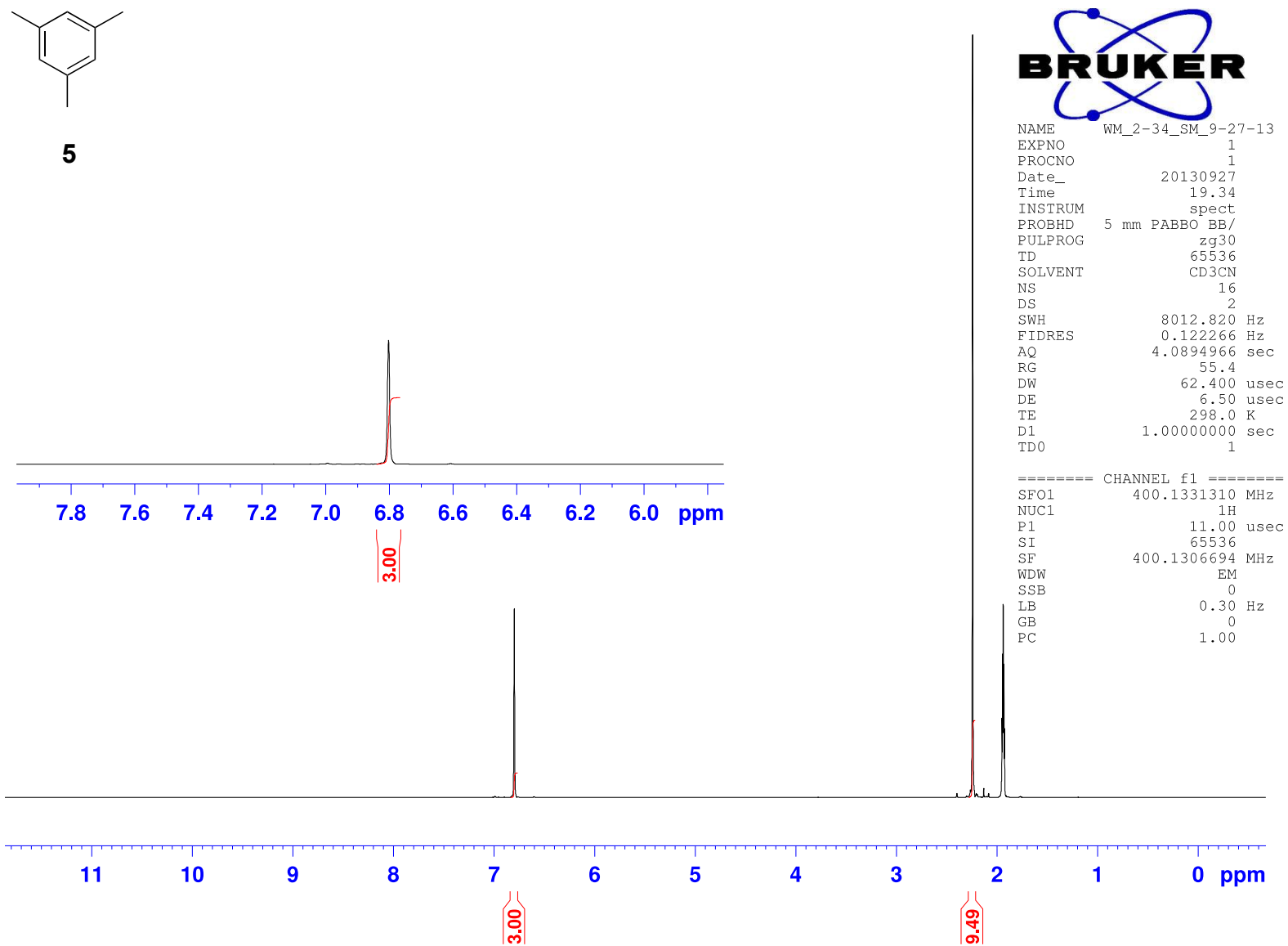


Figure S17. ^1H NMR spectrum of **5** in CD_3CN .

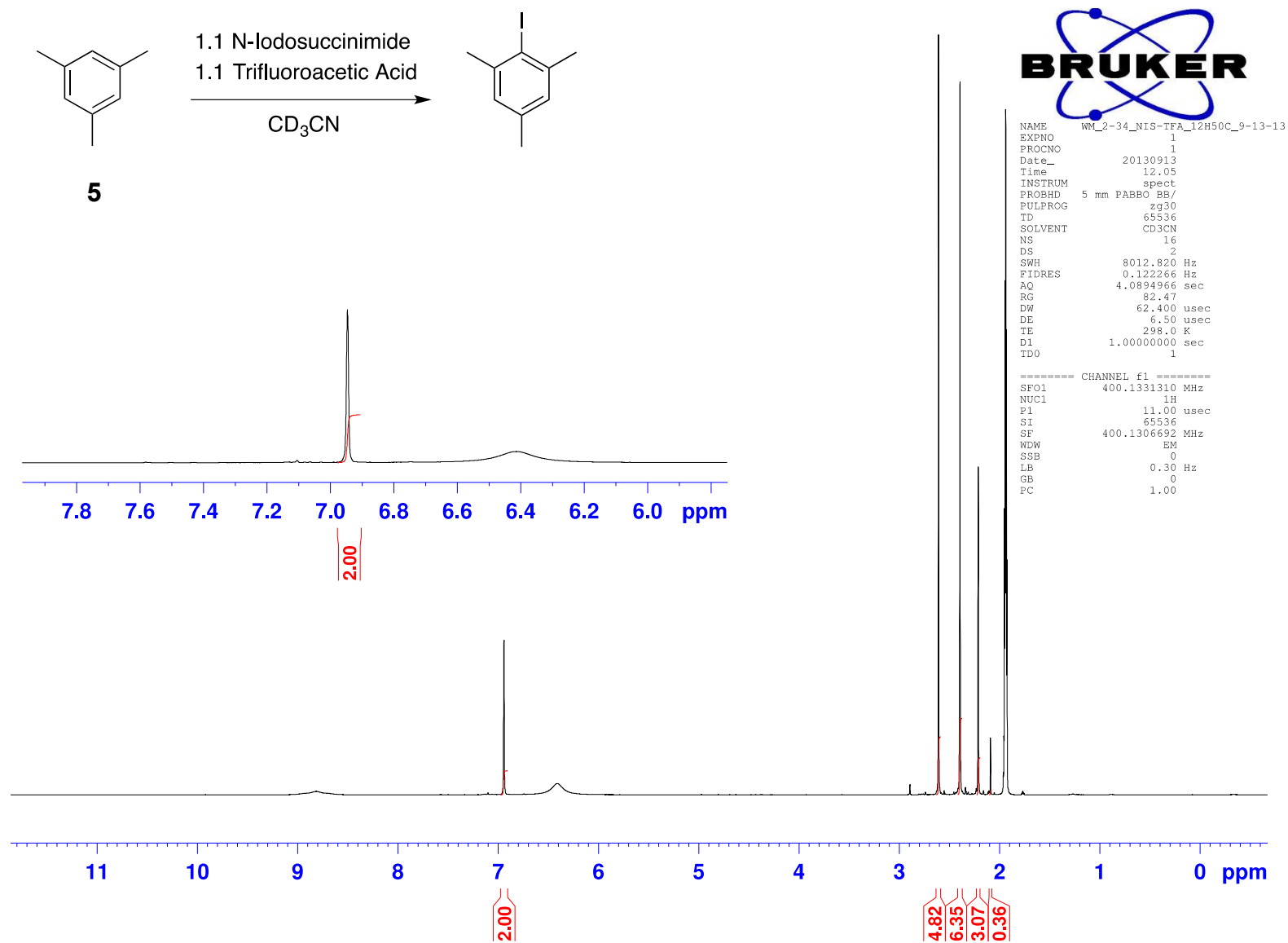


Figure S18. ^1H NMR spectrum of the iodination of **5** by Method A in CD_3CN .

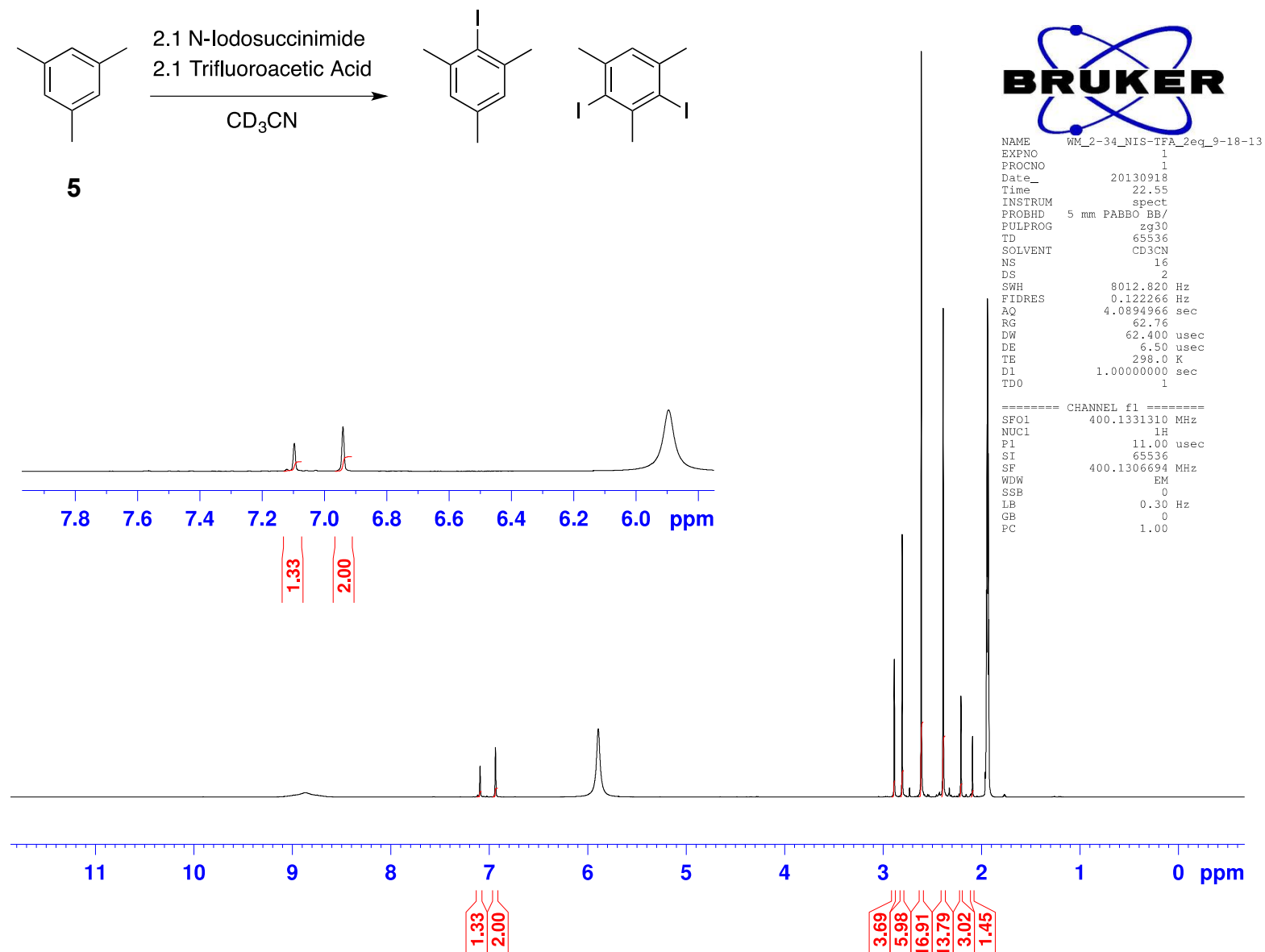


Figure S19. ^1H NMR spectrum of the iodination of **5** by Method B in CD_3CN .

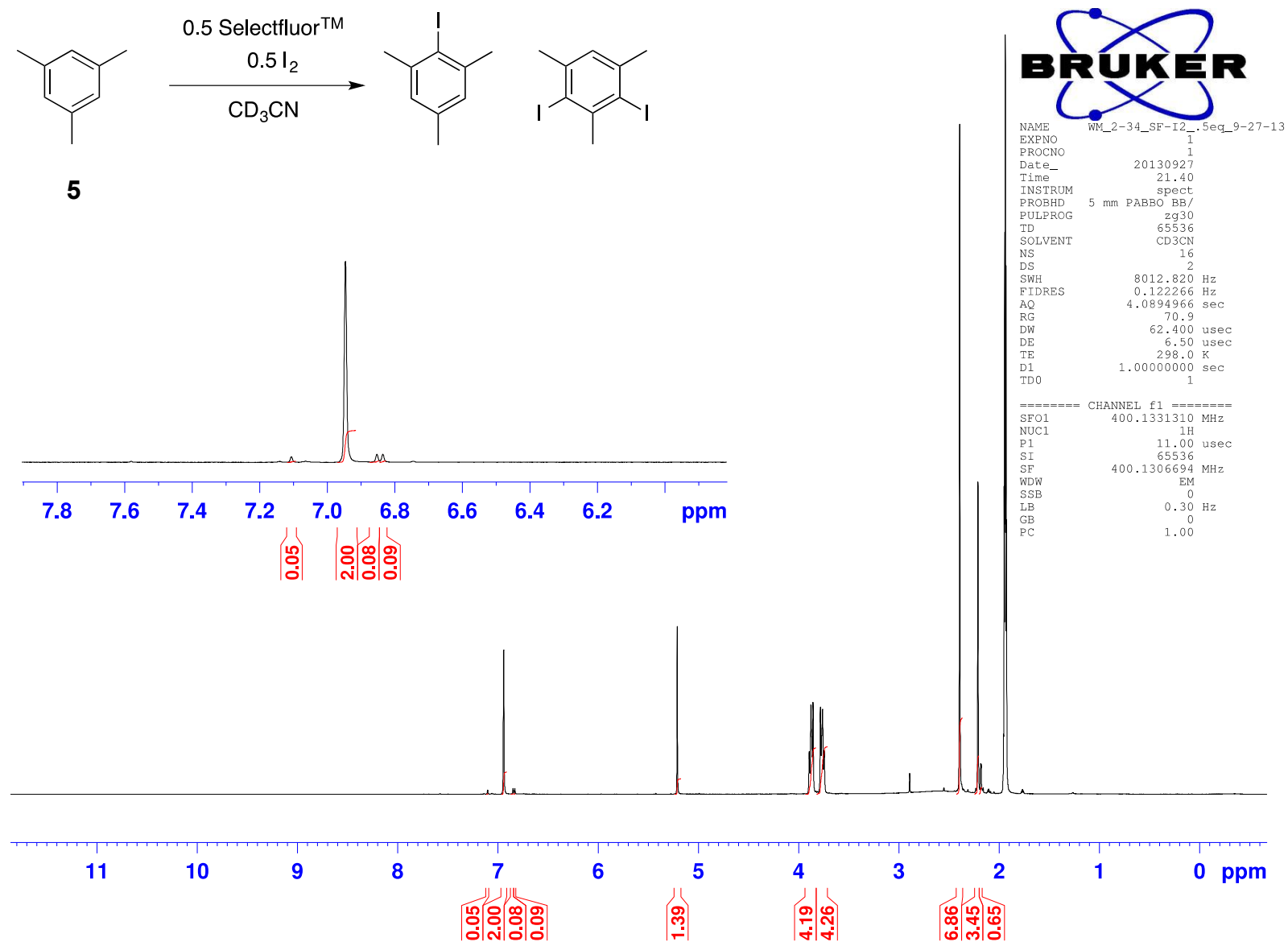


Figure S20. ¹H NMR spectrum of the iodination of **5** by Method C in CD₃CN.

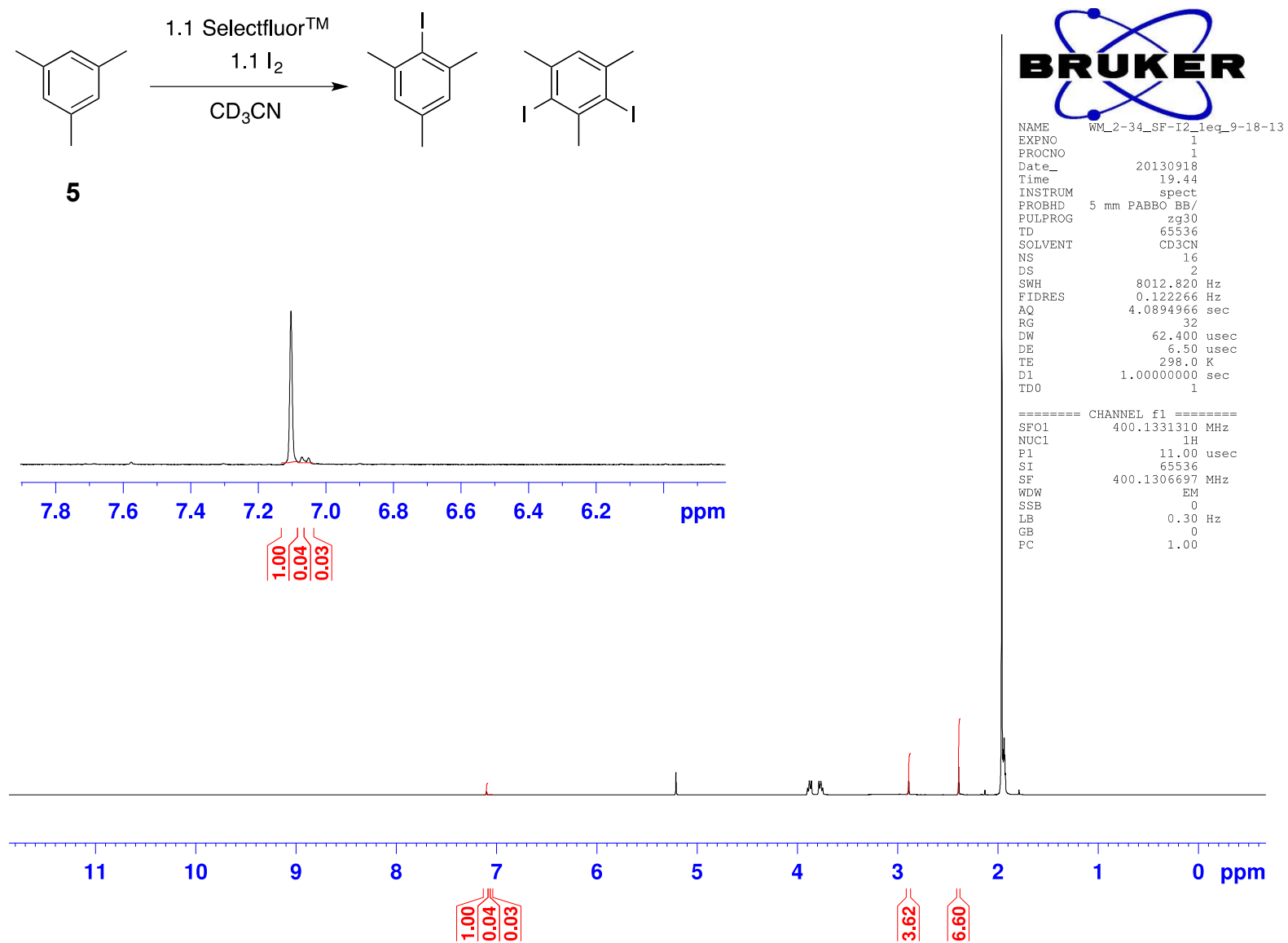


Figure S21. ¹H NMR spectrum of the iodination of **5** by Method D in CD₃CN.

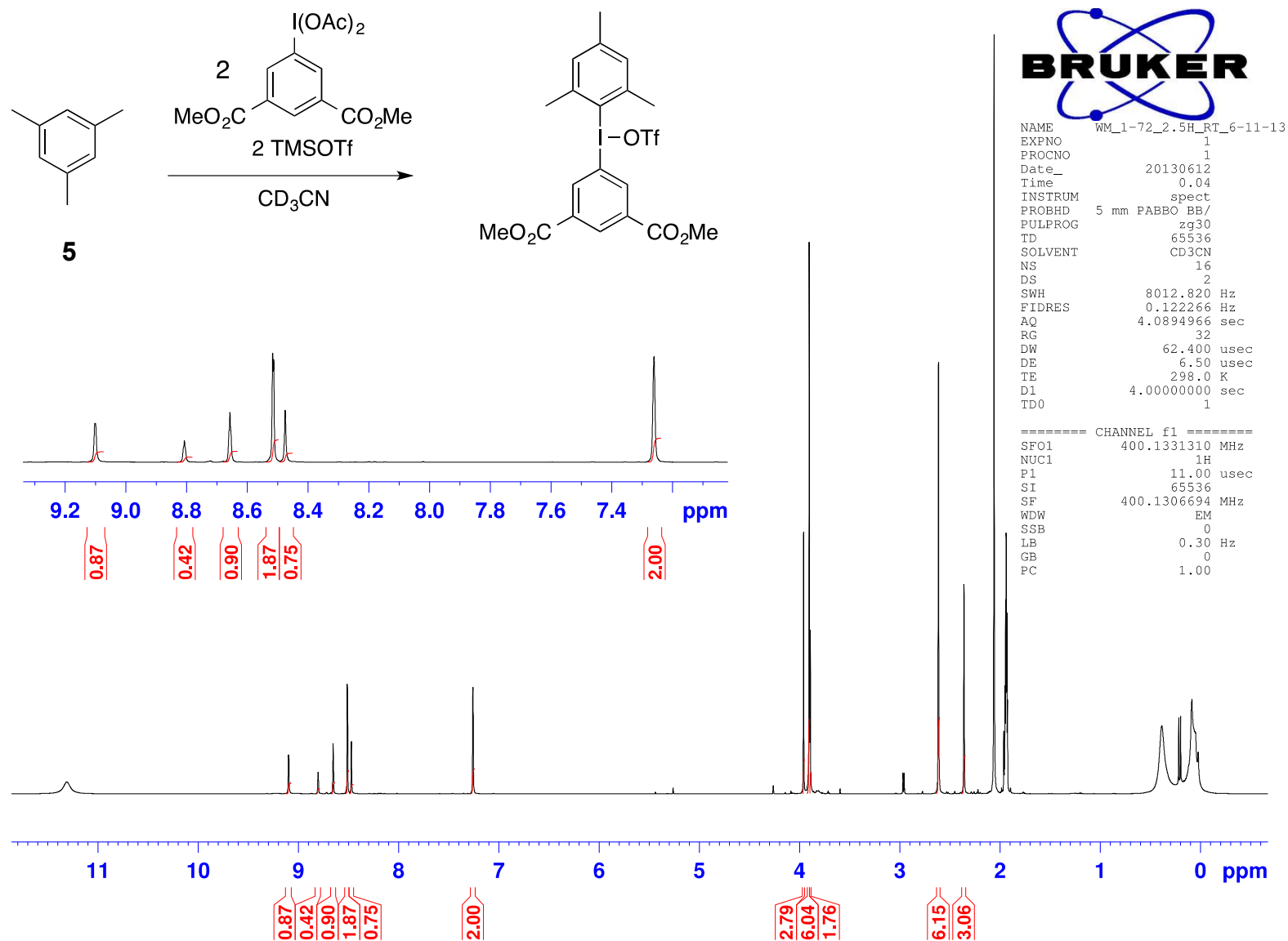


Figure S22. ¹H NMR spectrum of the iodination of **5** by Method f in CD₃CN.

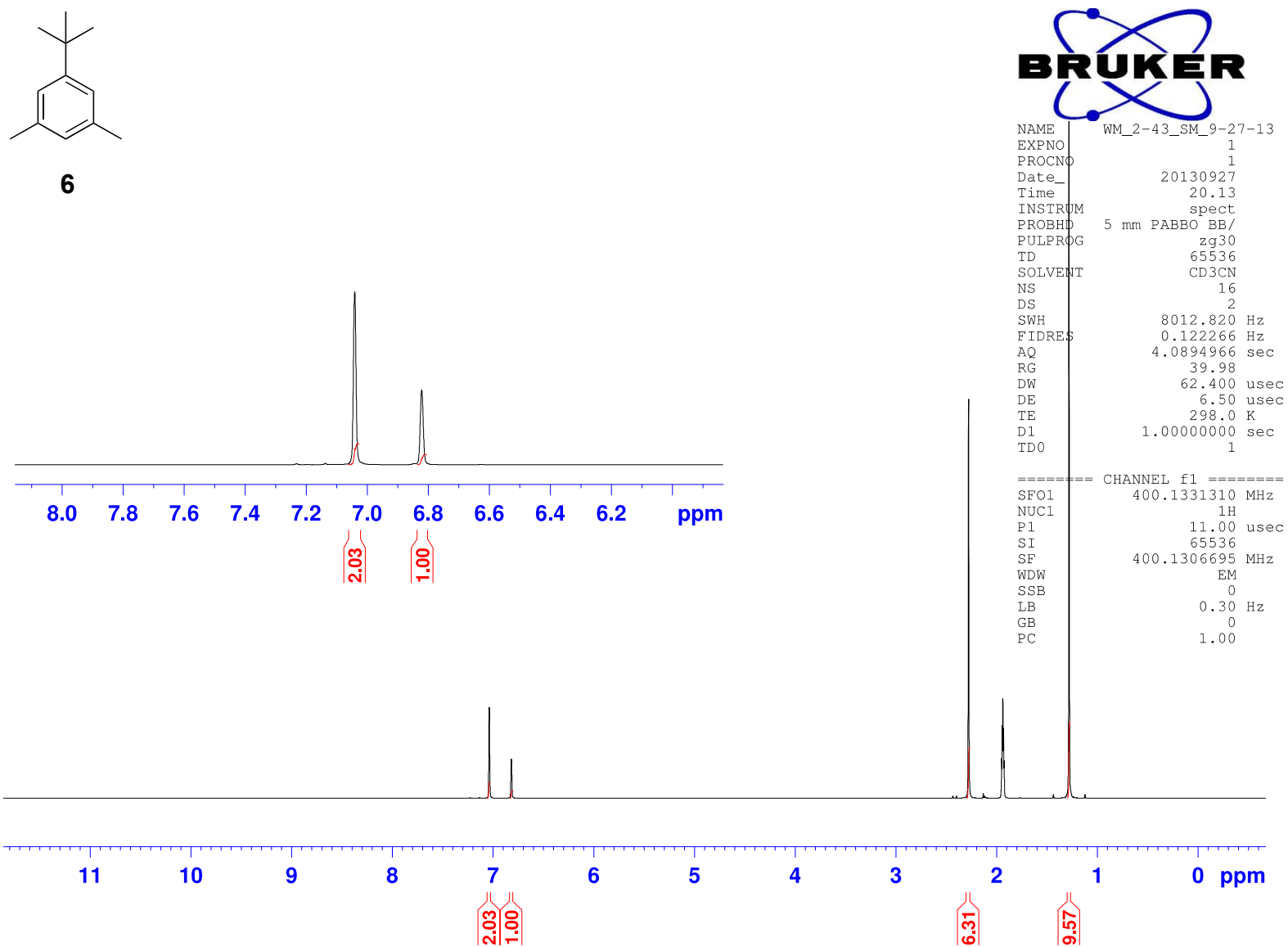


Figure S23. ^1H NMR spectrum of **6** in CD_3CN .

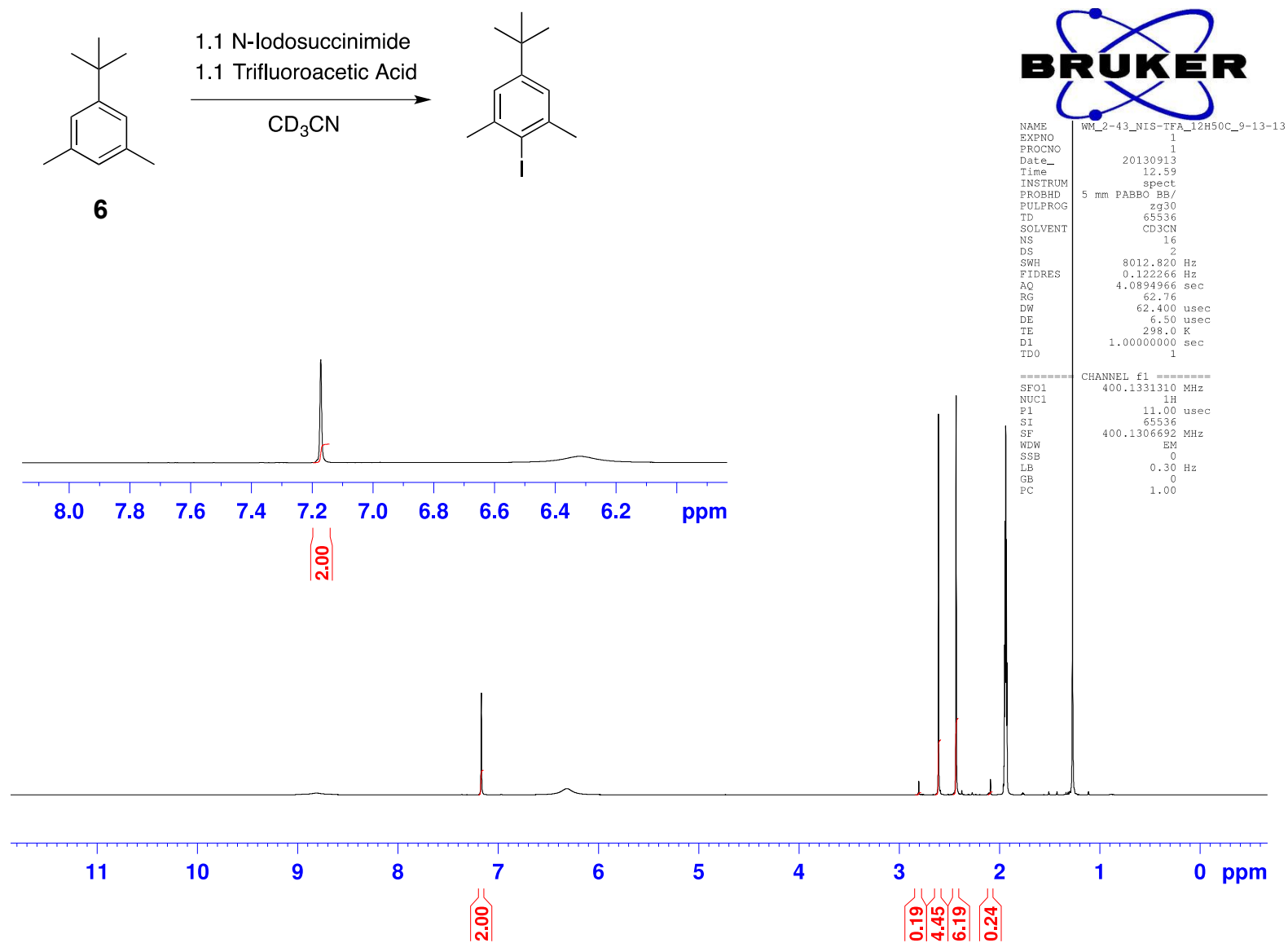


Figure S24. ¹H NMR spectrum of the iodination of **6** by Method A in CD₃CN.

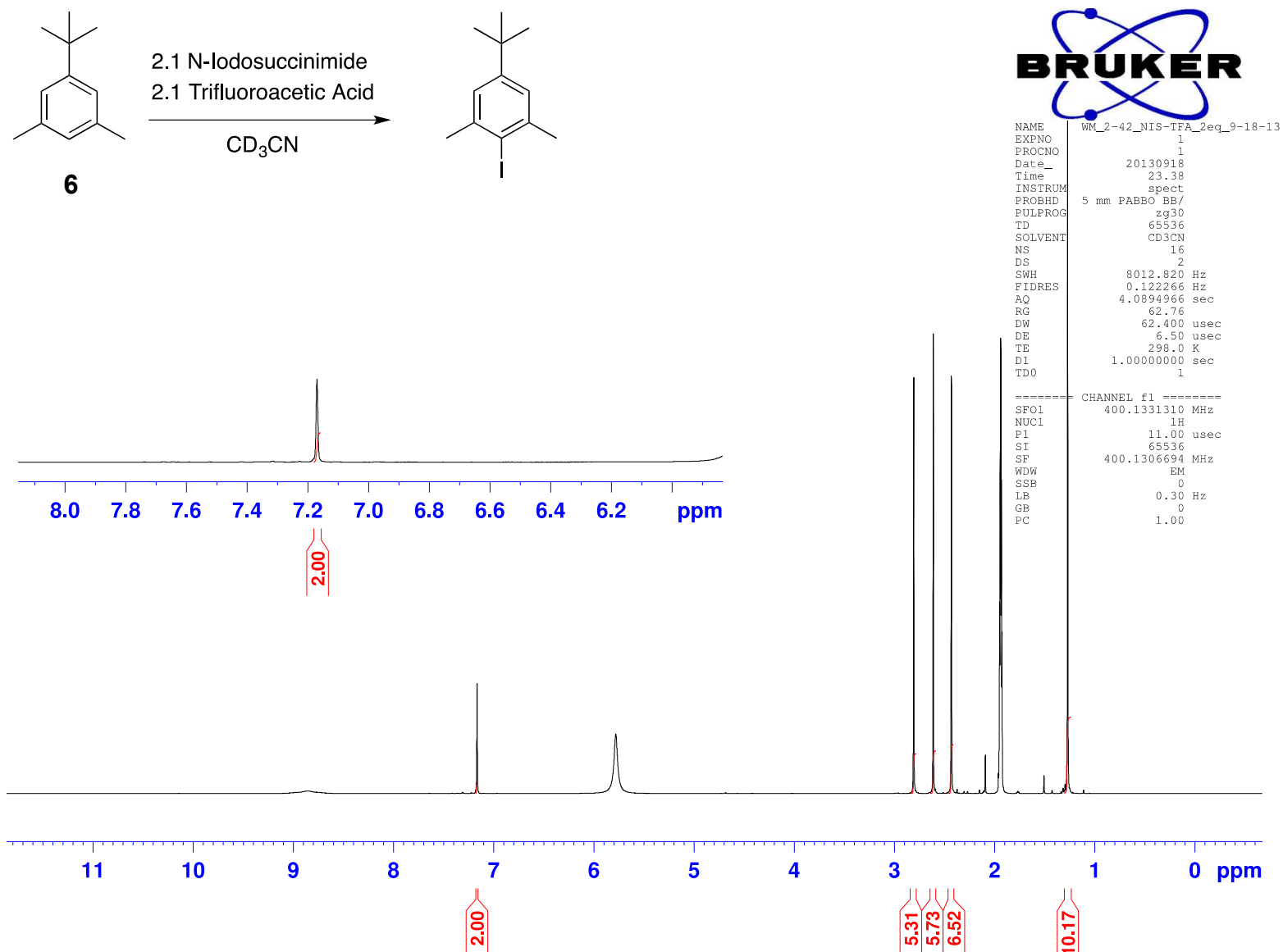


Figure S25. ¹H NMR spectrum of the iodination of **6** by Method B in CD₃CN.

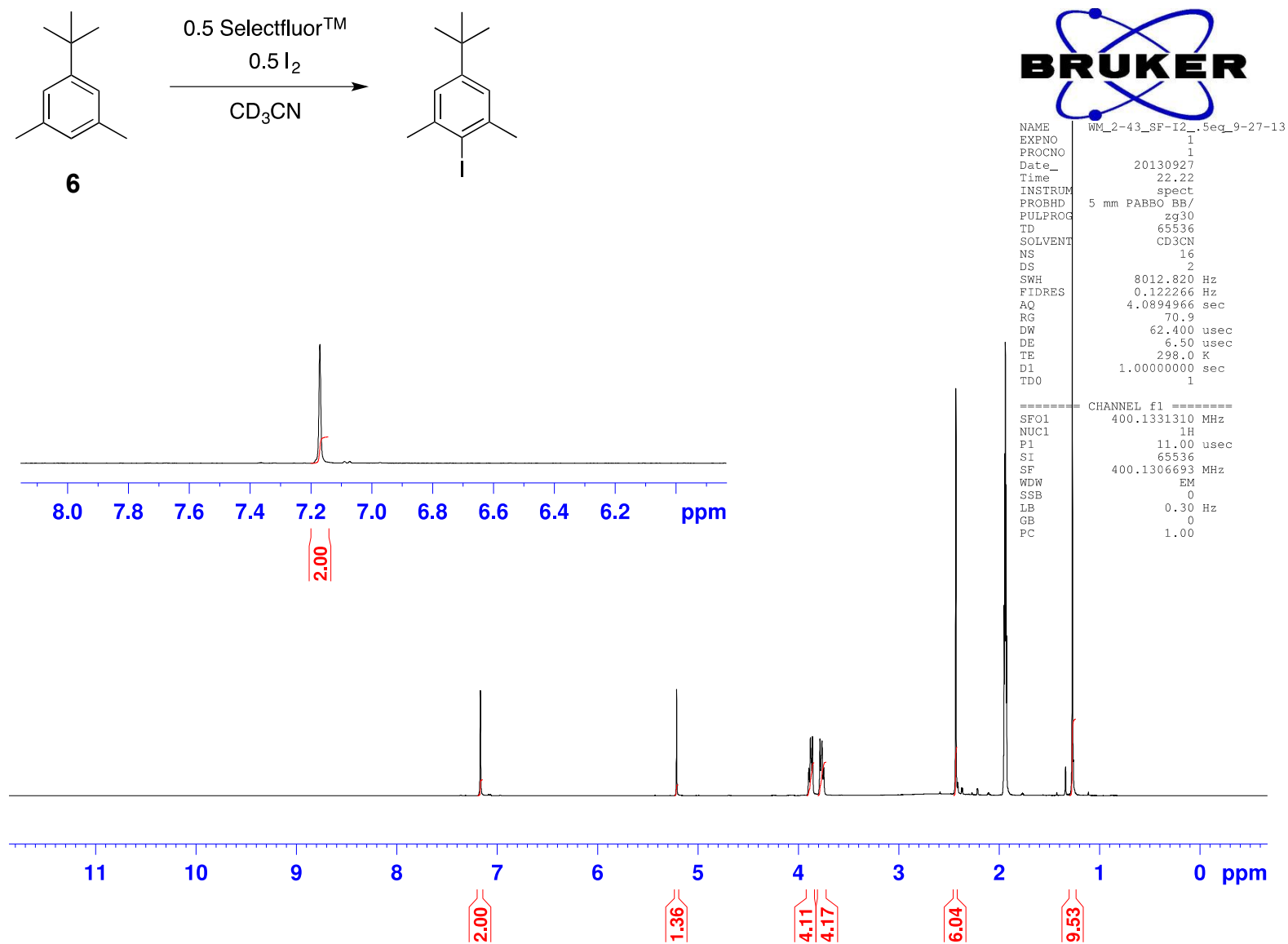


Figure S26. ¹H NMR spectrum of the iodination of **6** by Method C in CD₃CN.

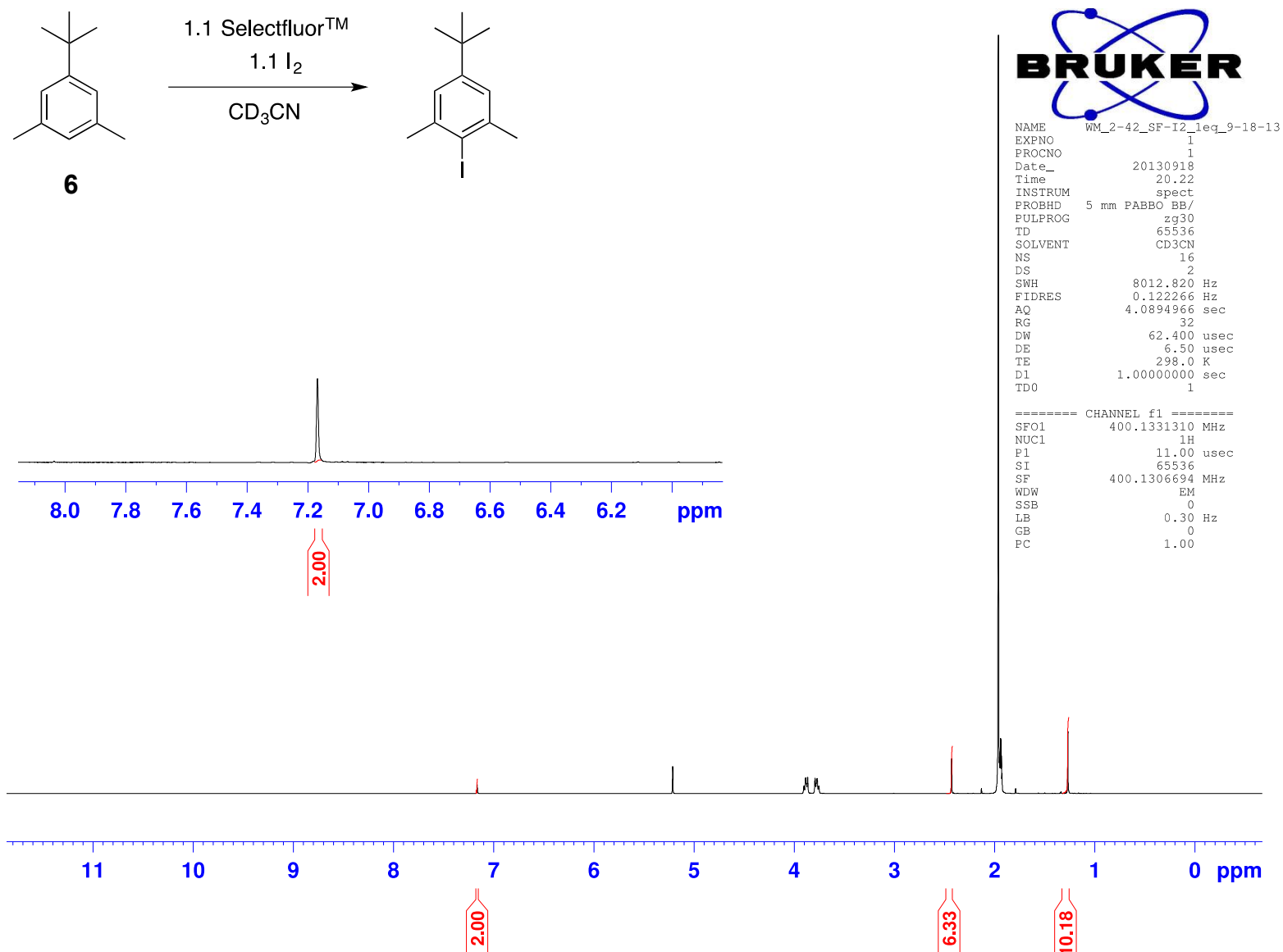


Figure S27. ¹H NMR spectrum of the iodination of **6** by Method D in CD₃CN.

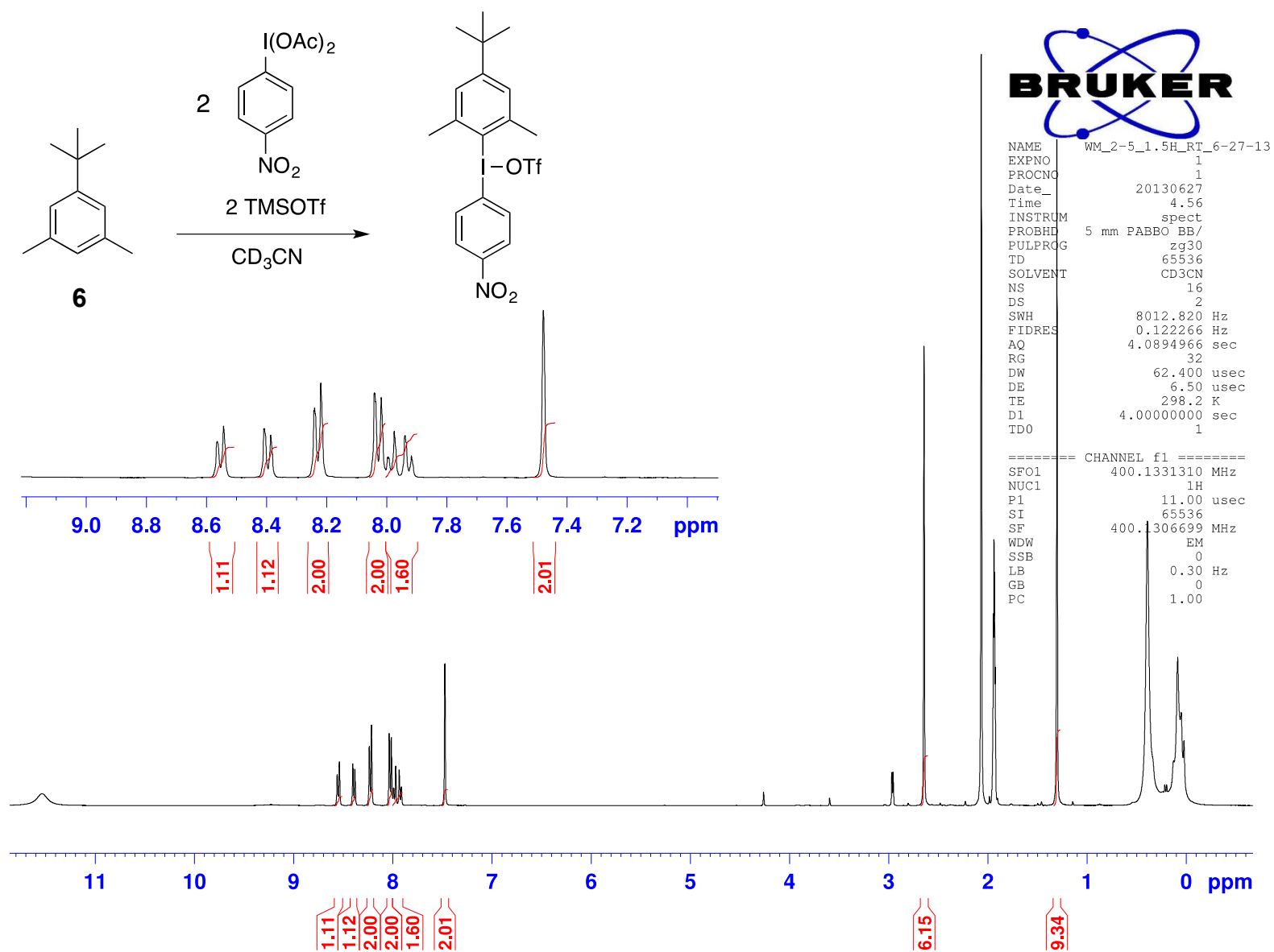


Figure S28. ¹H NMR spectrum of the iodination of **6** by Method E in CD_3CN .

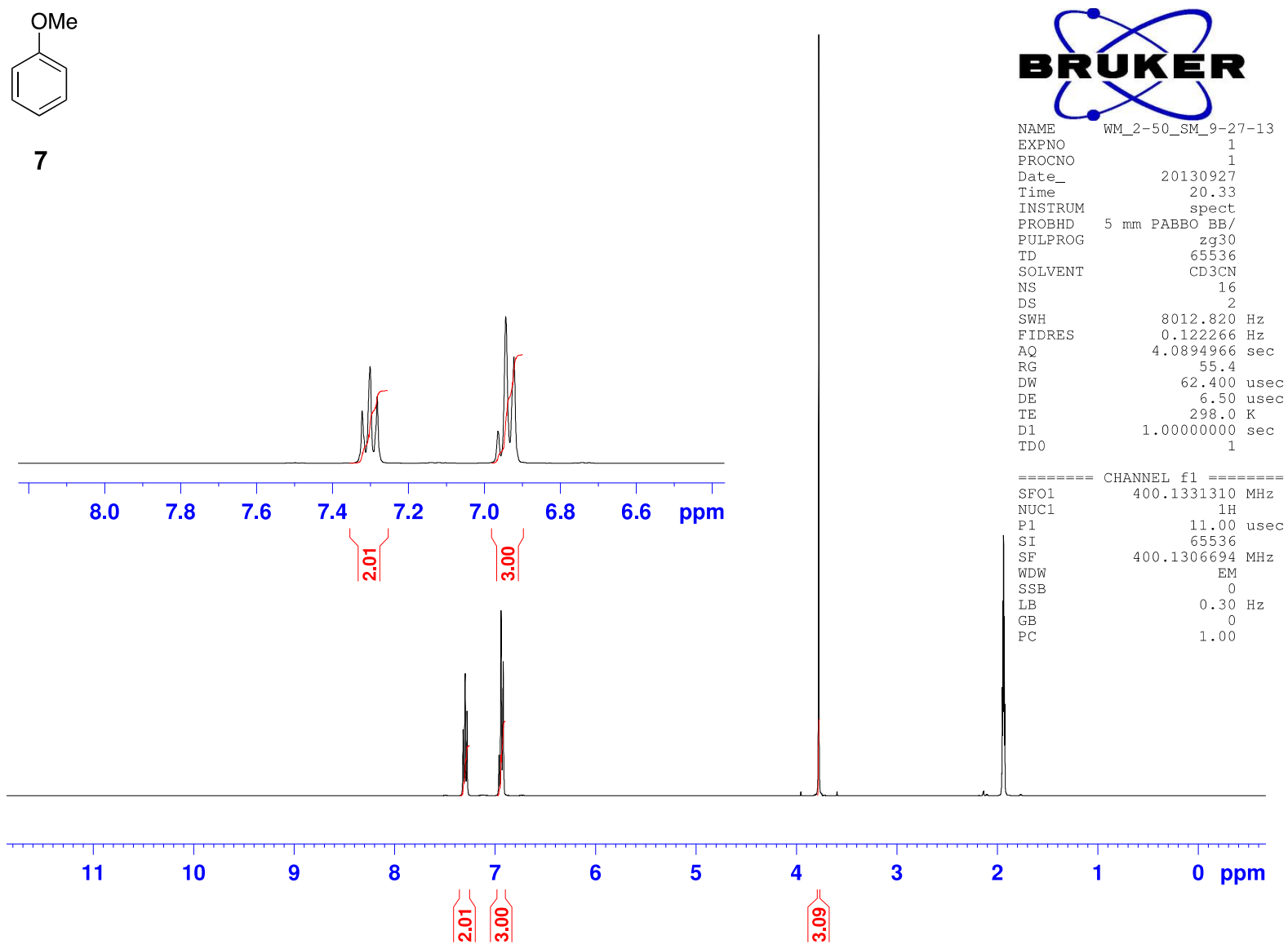


Figure S29. ^1H NMR spectrum of **7** in CD_3CN .

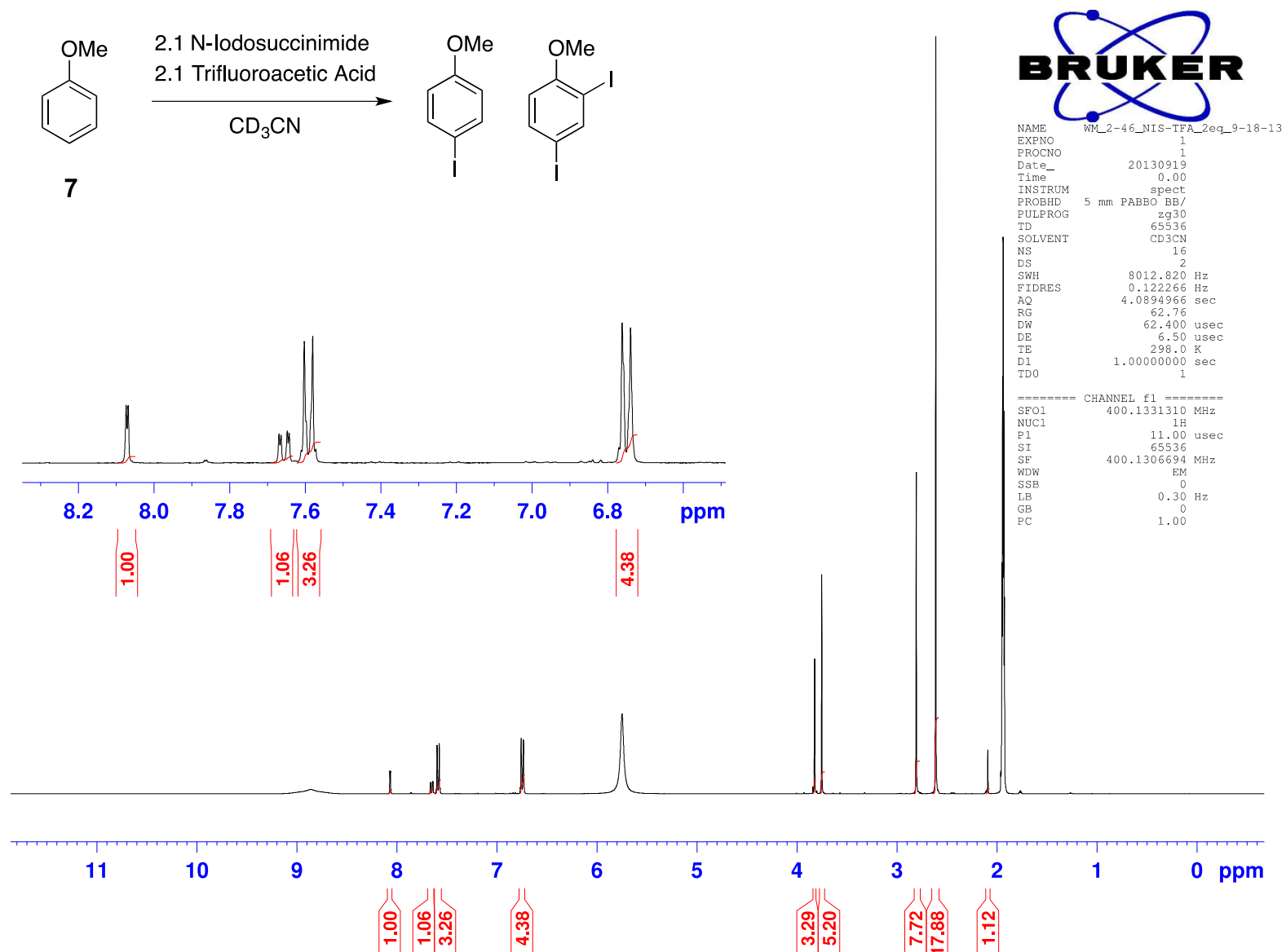


Figure S31. ^1H NMR spectrum of the iodination of **7** by Method B in CD_3CN .

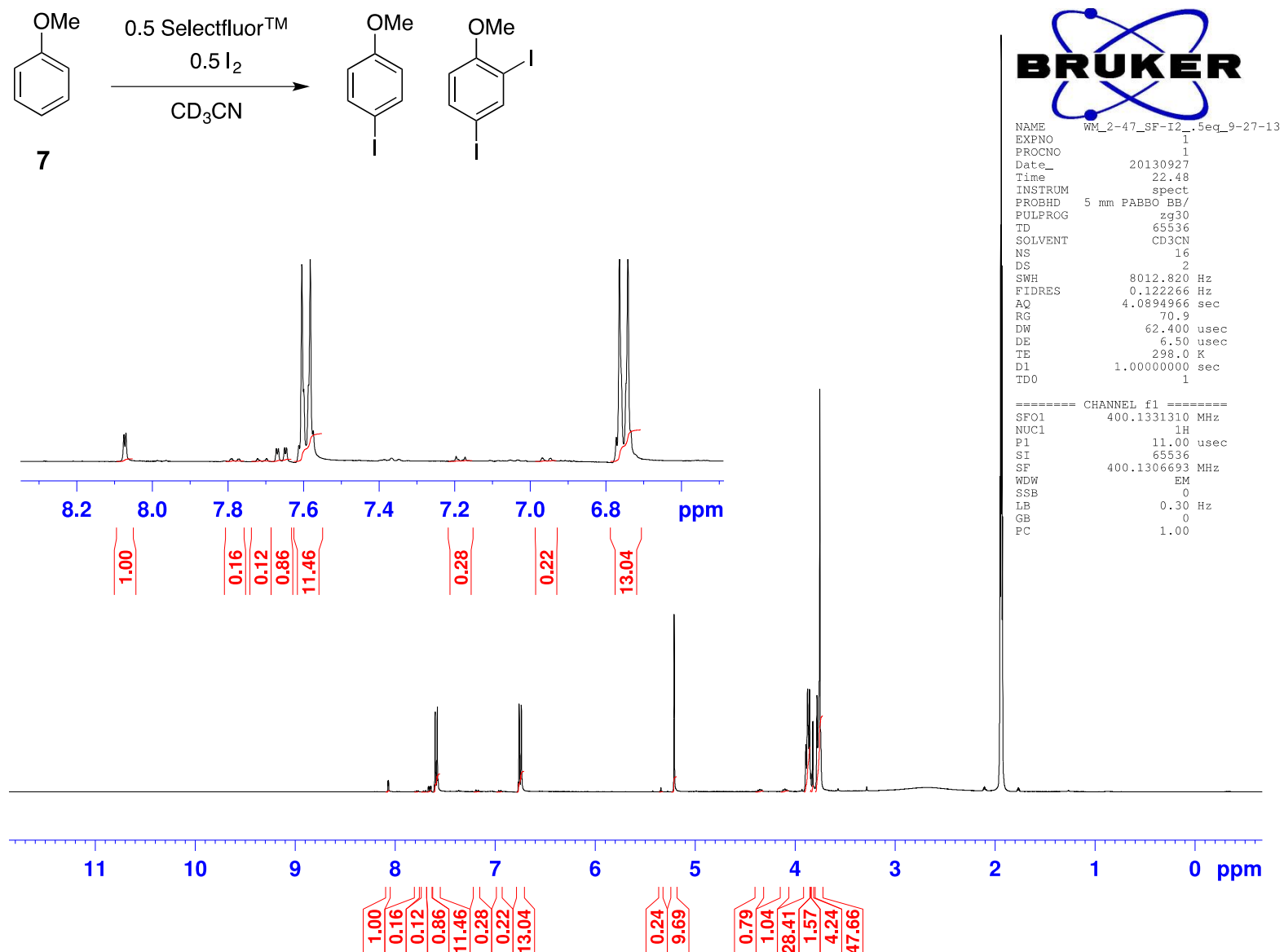


Figure S32. ¹H NMR spectrum of the iodination of **7** by Method C in CD₃CN.

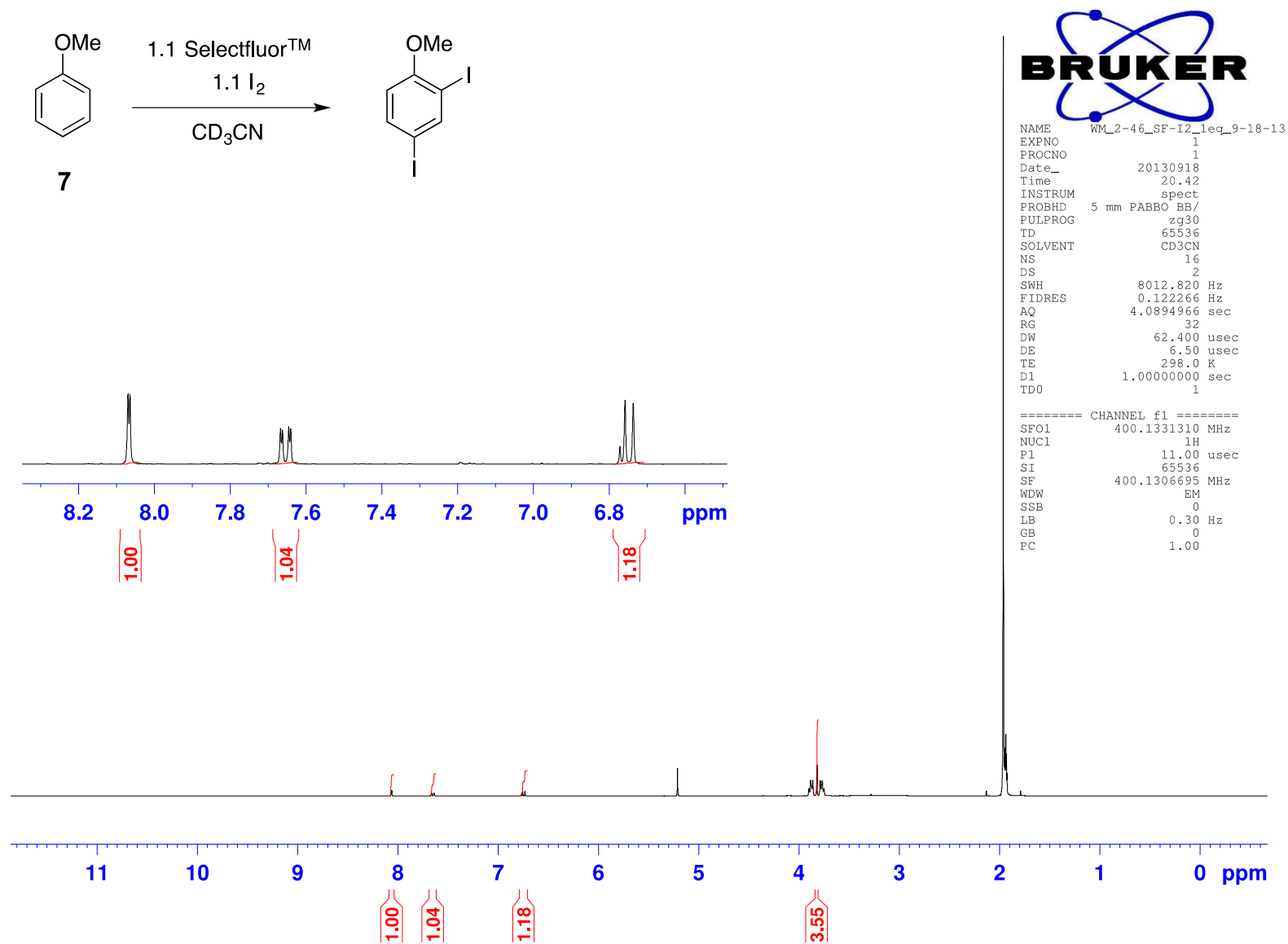


Figure S33. ¹H NMR spectrum of the iodination of **7** by Method D in CD₃CN.

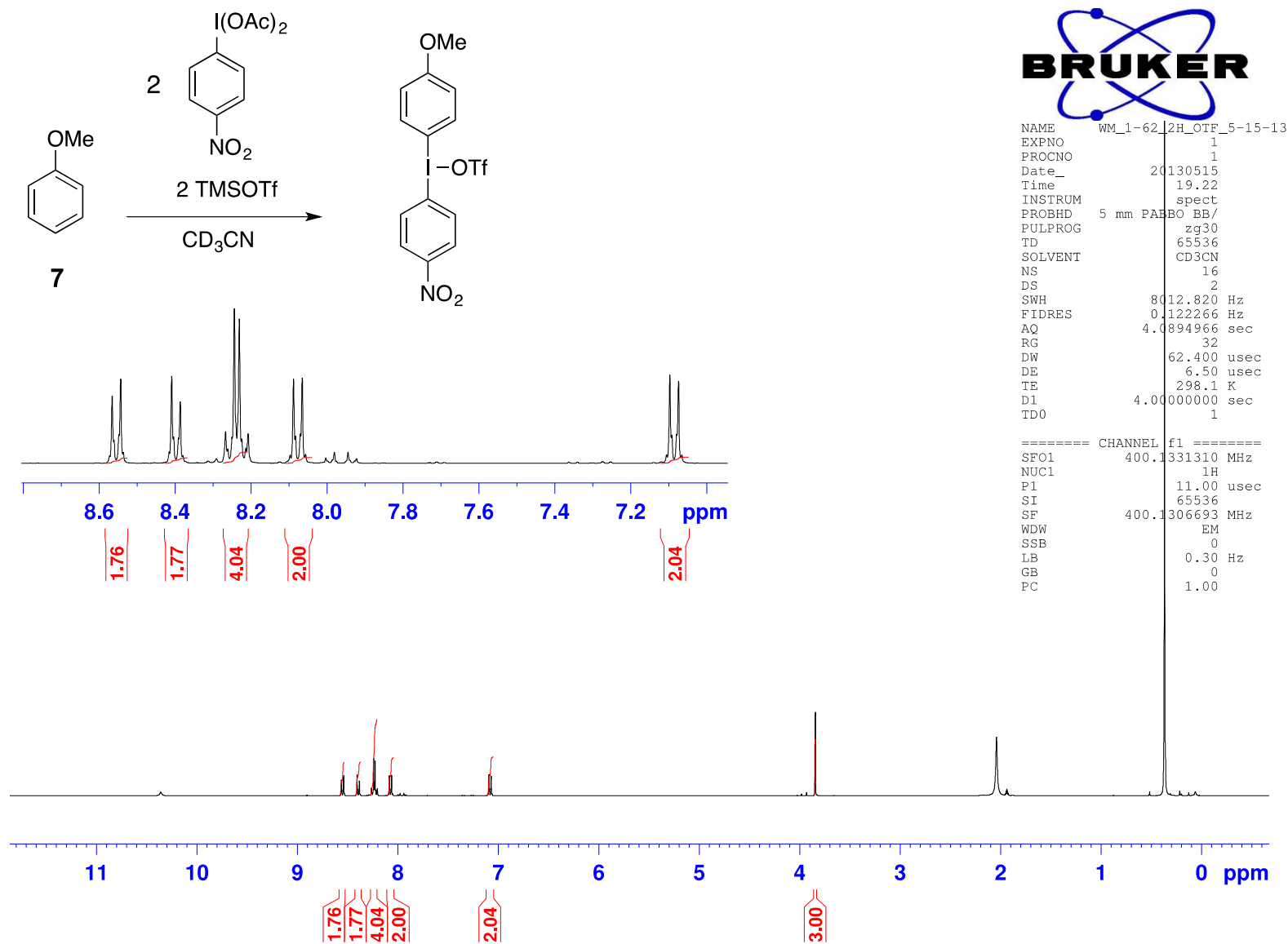


Figure S34. ^1H NMR spectrum of the iodination of **7** by Method E in CD_3CN .

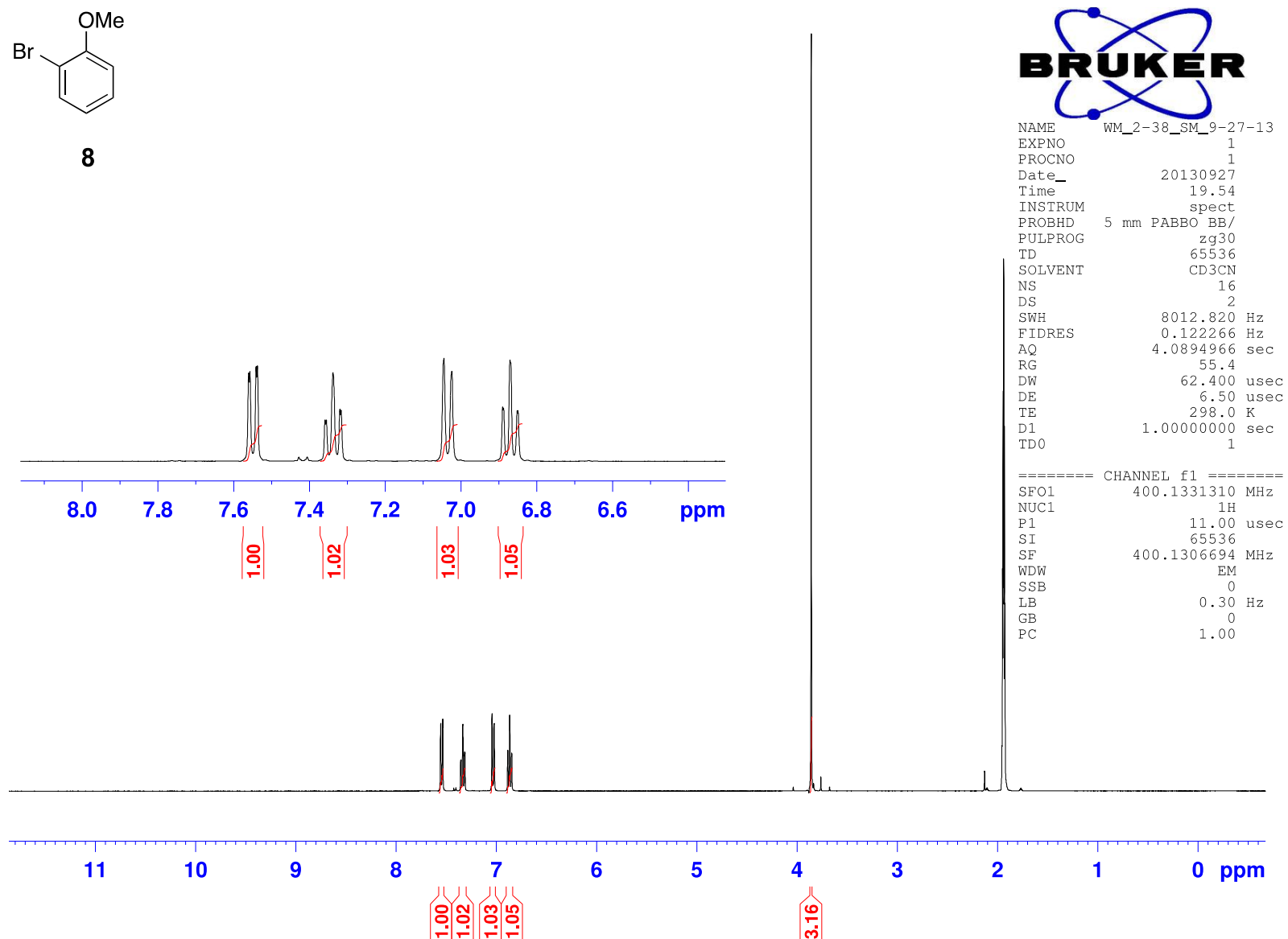


Figure S35. ^1H NMR spectrum of **8** in CD_3CN .

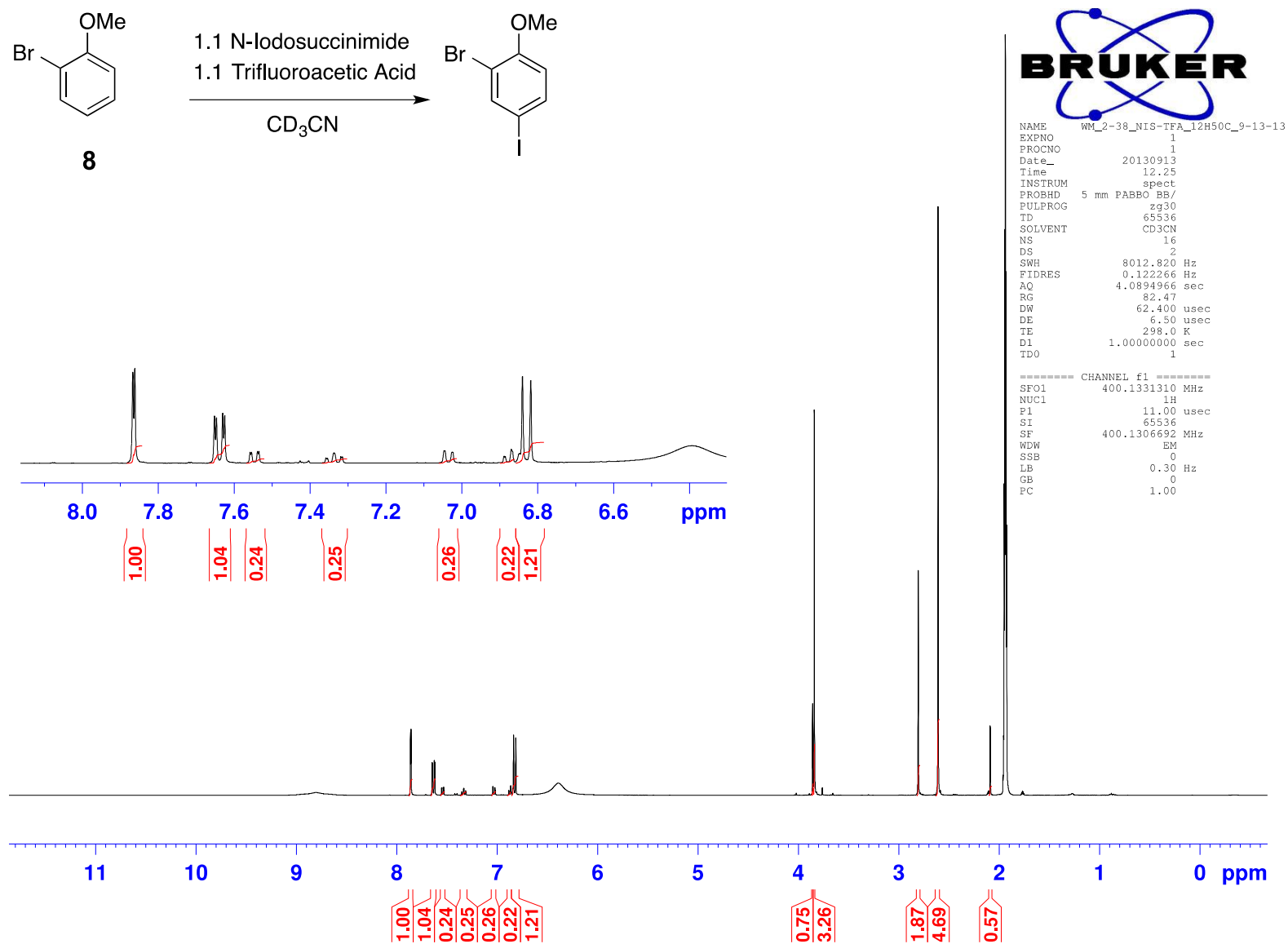


Figure S36. ^1H NMR spectrum of the iodination of **8** by Method A in CD_3CN .

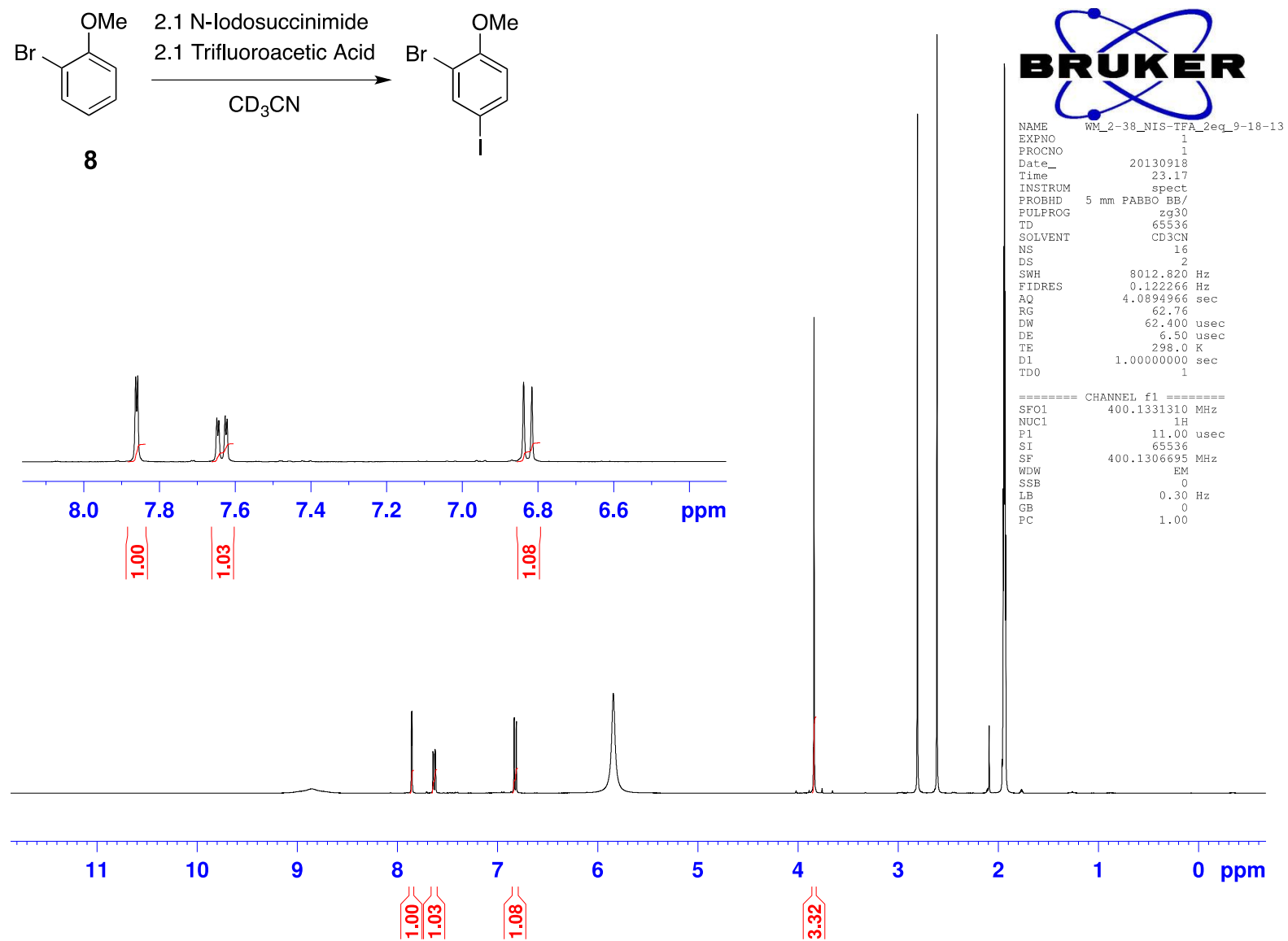


Figure S37. ¹H NMR spectrum of the iodination of **8** by Method B in CD₃CN.

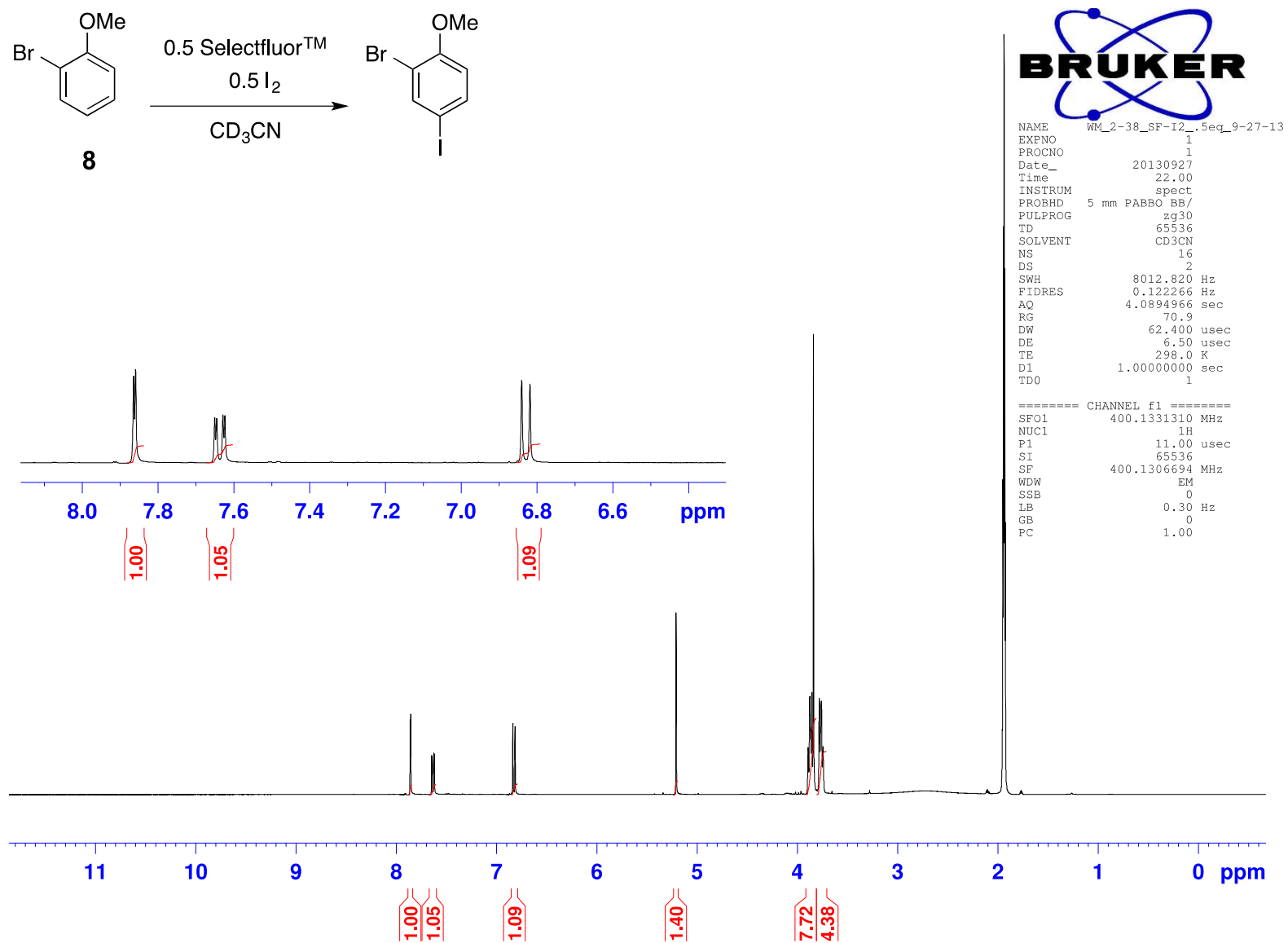


Figure S38. ¹H NMR spectrum of the iodination of **8** by Method C in CD₃CN.

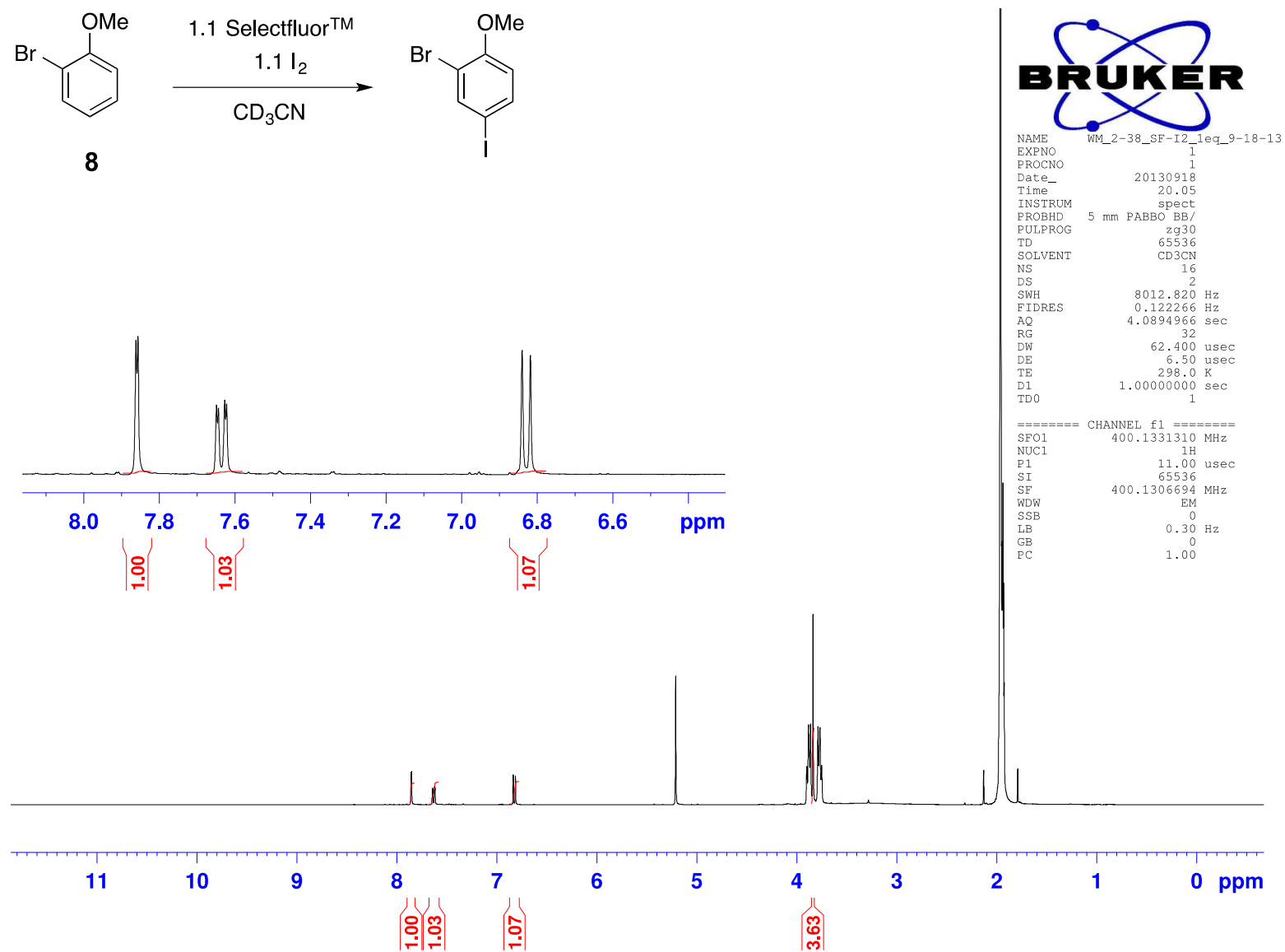


Figure S39. ¹H NMR spectrum of the iodination of **8** by Method D in CD₃CN.

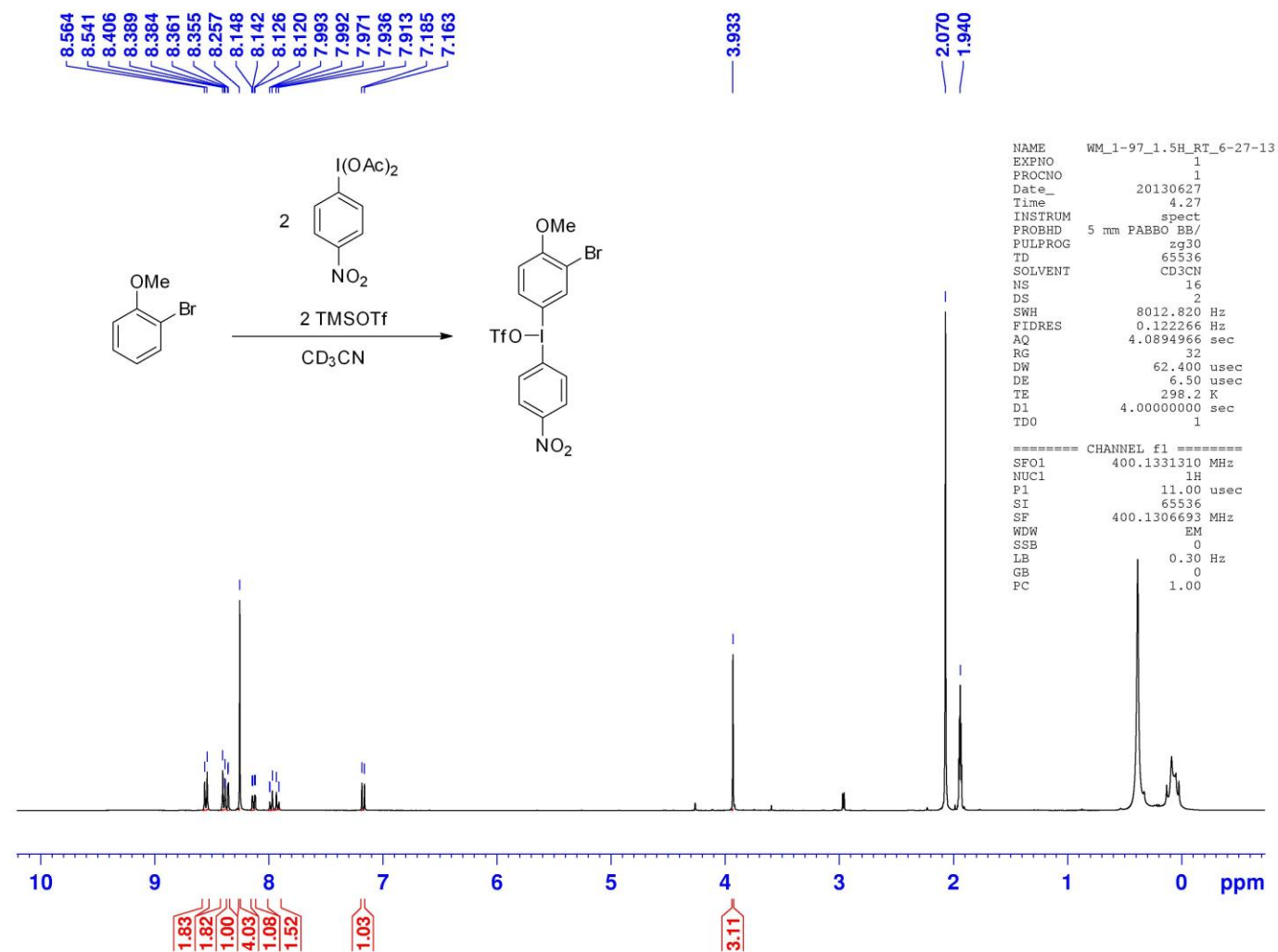


Figure S40. ^1H NMR spectrum of the iodination of **8** by Method E in CD_3CN .

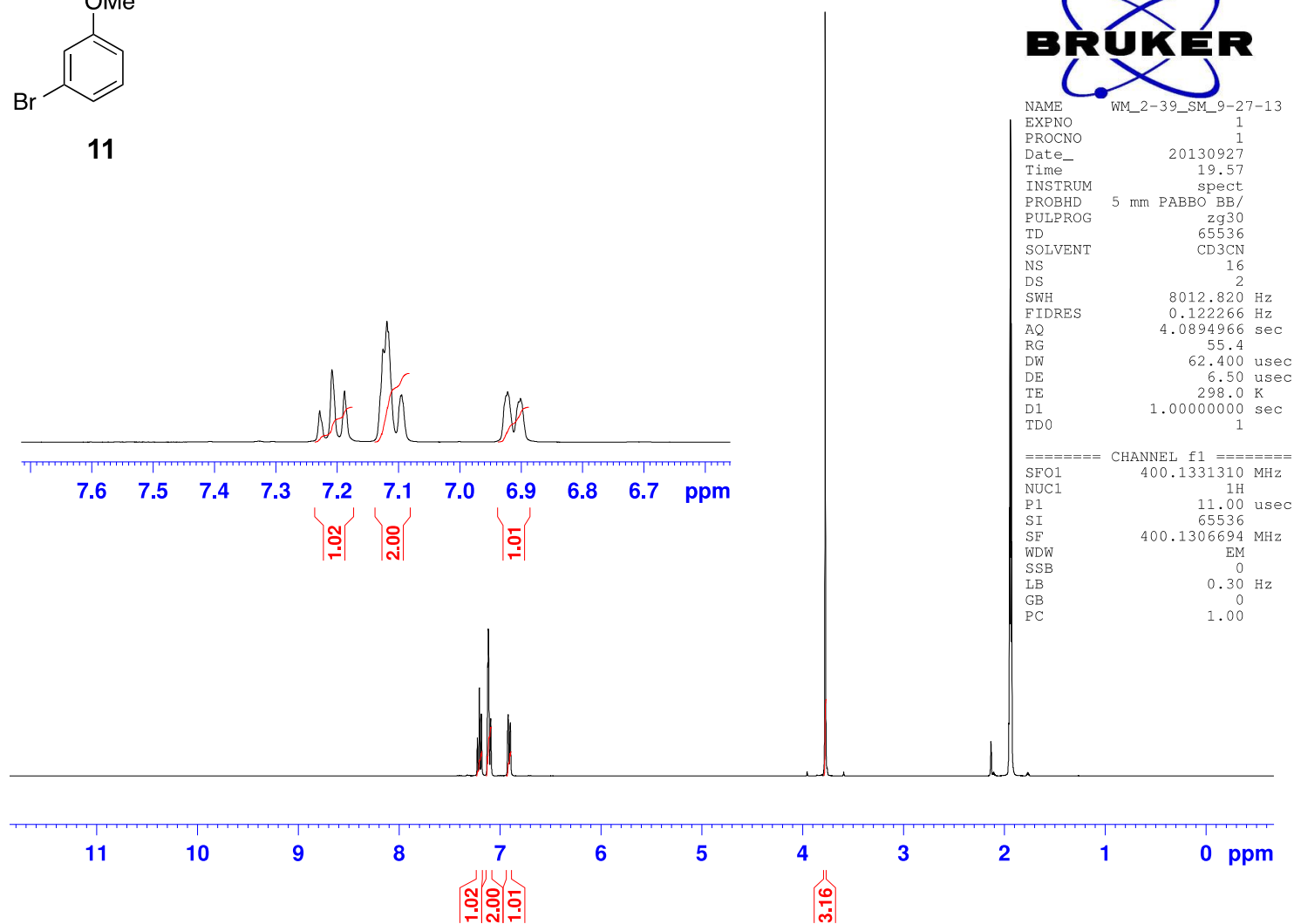
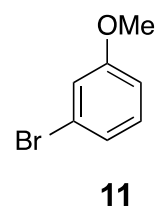


Figure S53. ^1H NMR spectrum of **11** in CD_3CN .

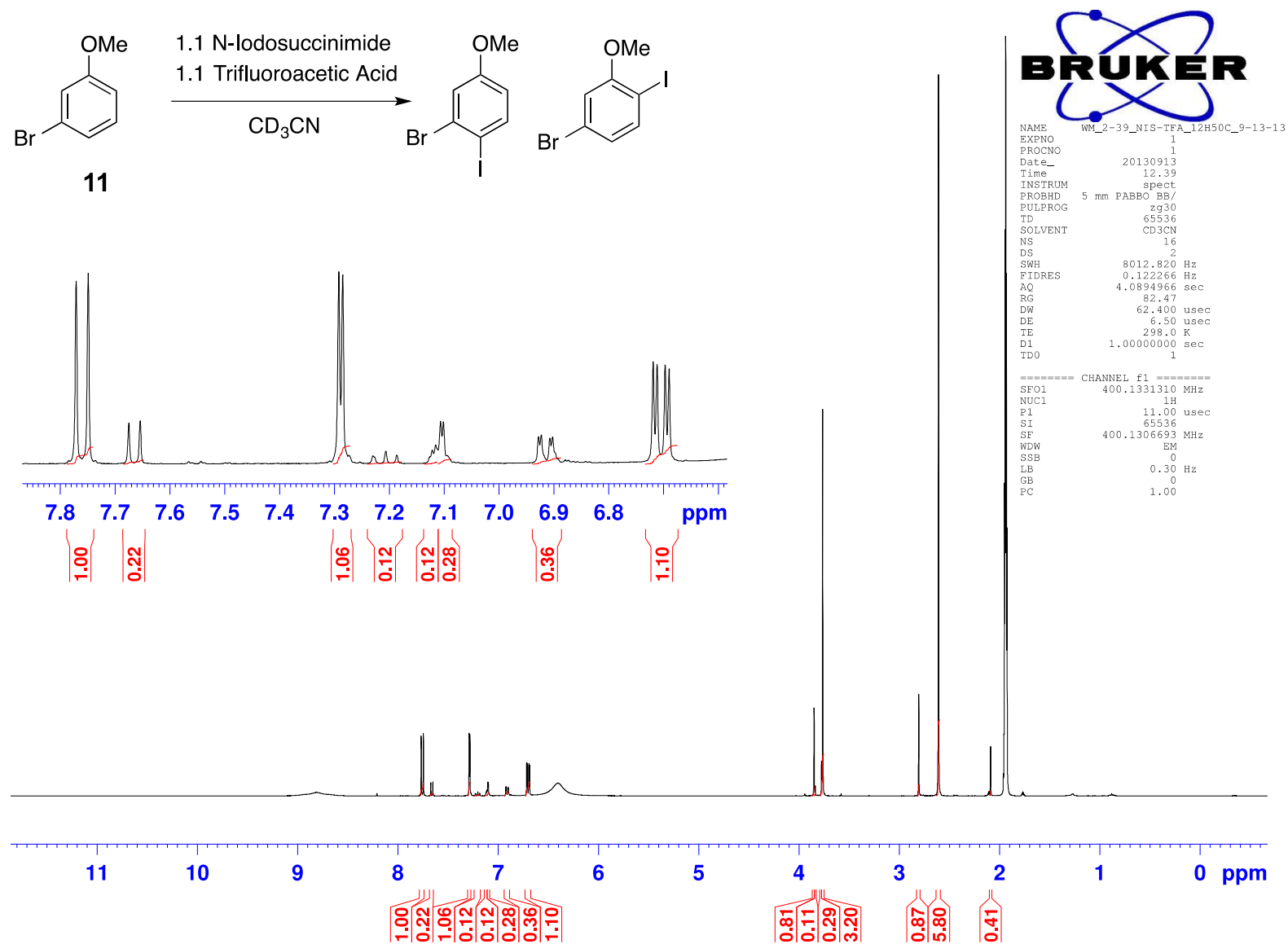


Figure S54. ^1H NMR spectrum of the iodination of **11** by Method A in CD_3CN .

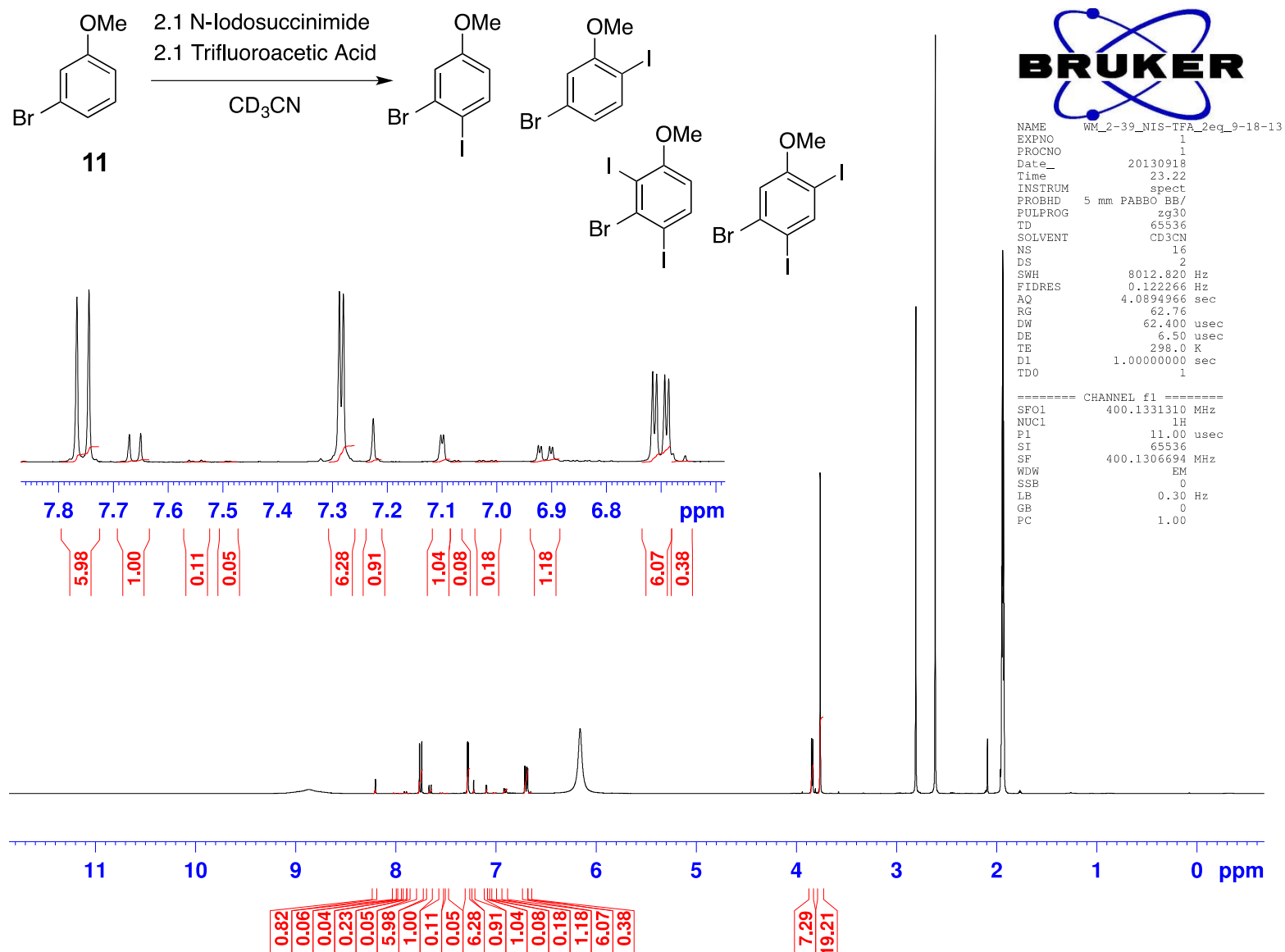


Figure S55. ^1H NMR spectrum of the iodination of **11** by Method B in CD_3CN .

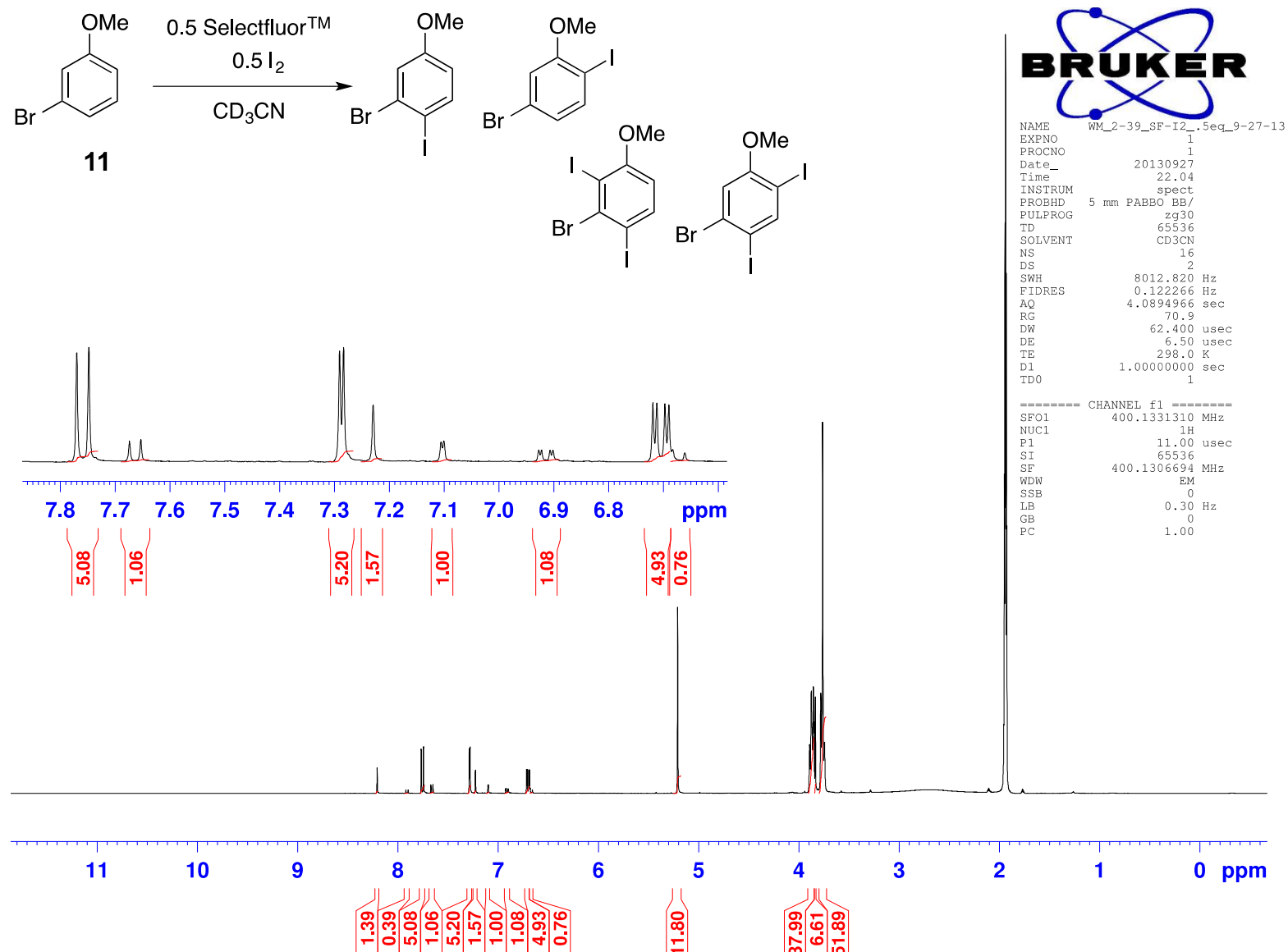


Figure S56. ¹H NMR spectrum of the iodination of **11** by Method C in CD₃CN.

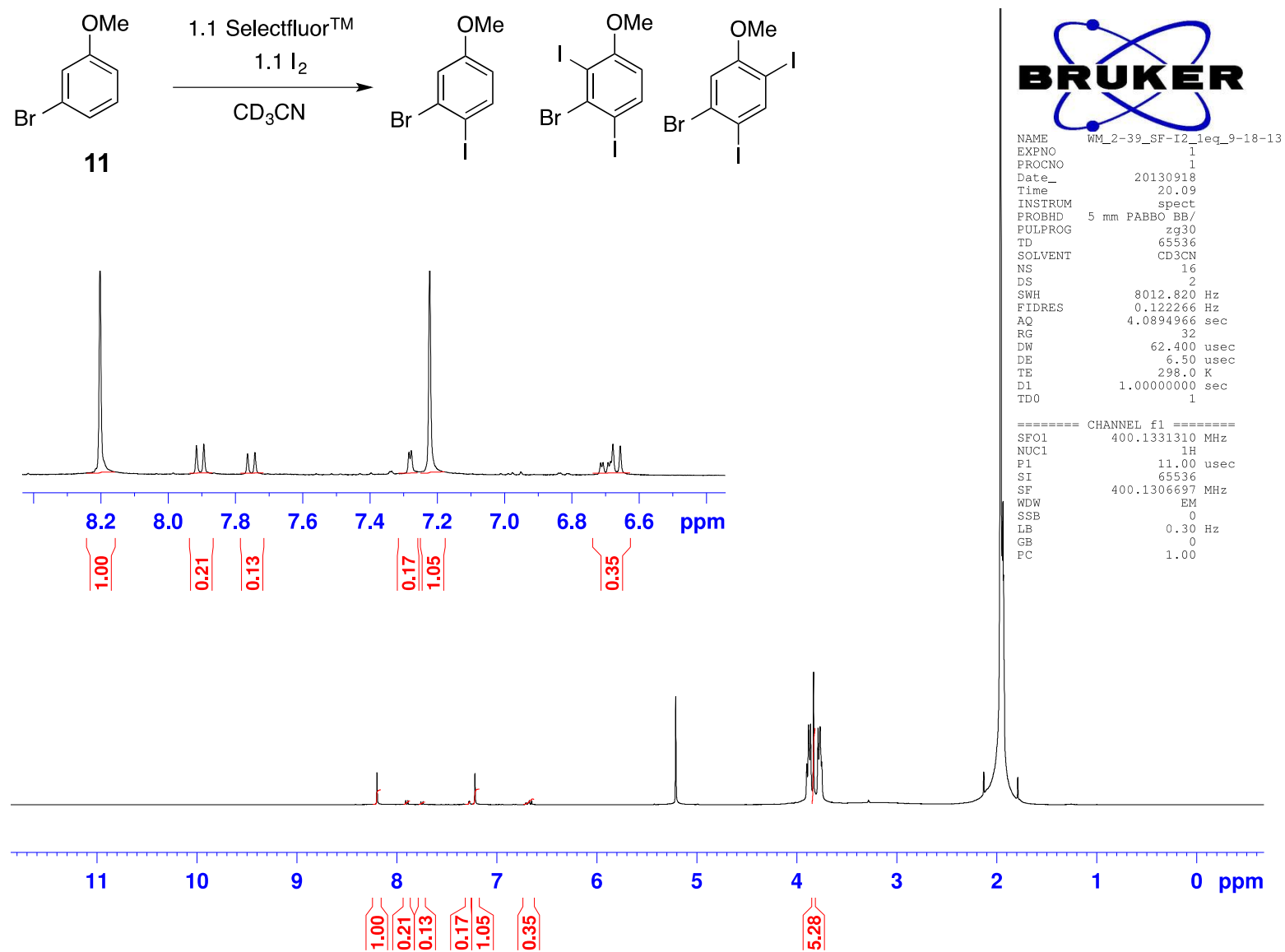


Figure S57. ¹H NMR spectrum of the iodination of **11** by Method D in CD₃CN.

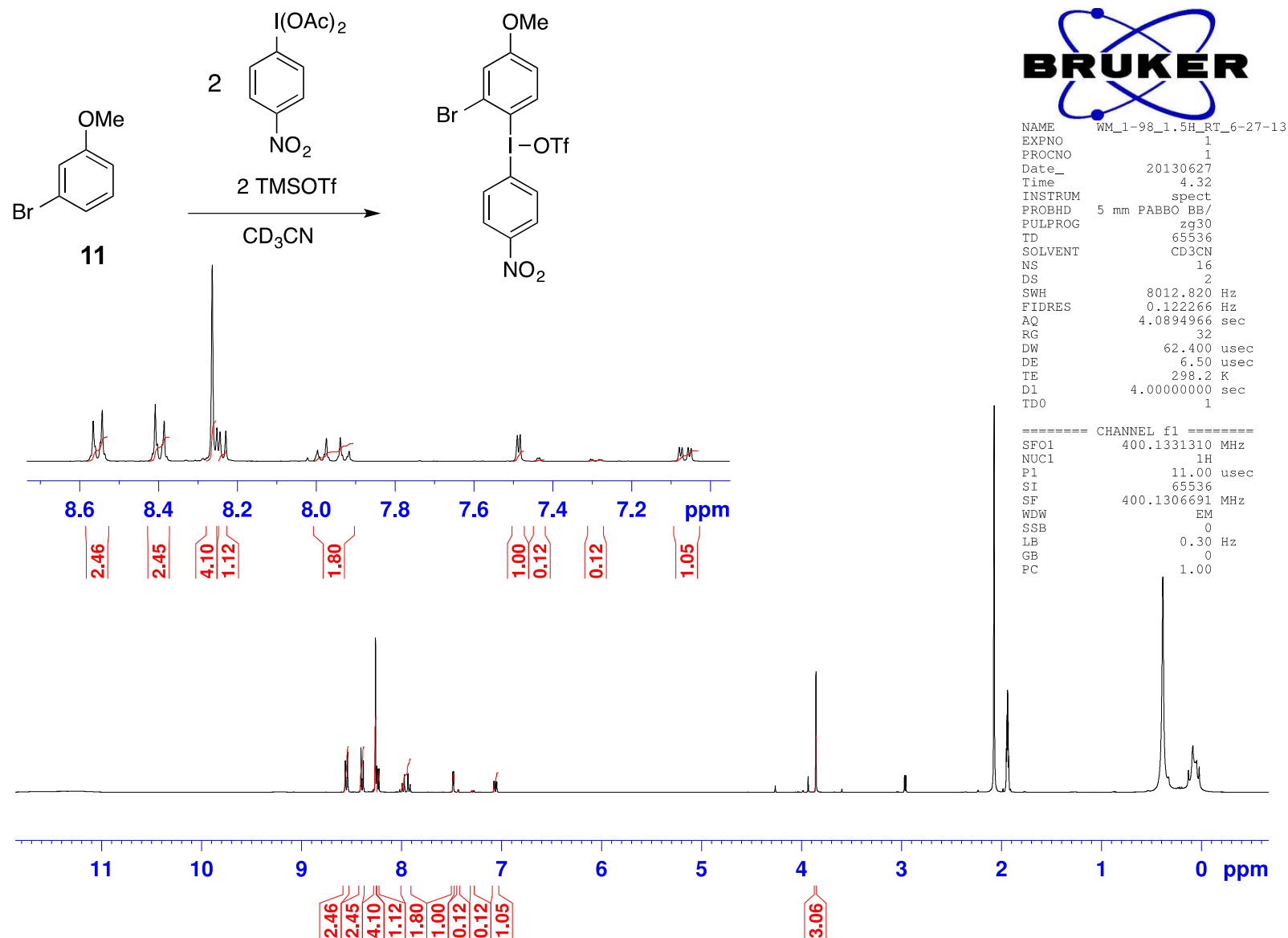
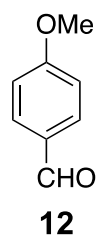


Figure S58. ¹H NMR spectrum of the iodination of **11** by Method E in CD₃CN.



NAME WM_2-36_SM_9-27-13
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PROCNO 1
Date_ 20130927
Time 19.43
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CD3CN
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894966 sec
RG 55.4
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

===== CHANNEL f1 =====
SF01 400.1331310 MHz
NUC1 1H
P1 11.00 usec
SI 65536
SF 400.1306695 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

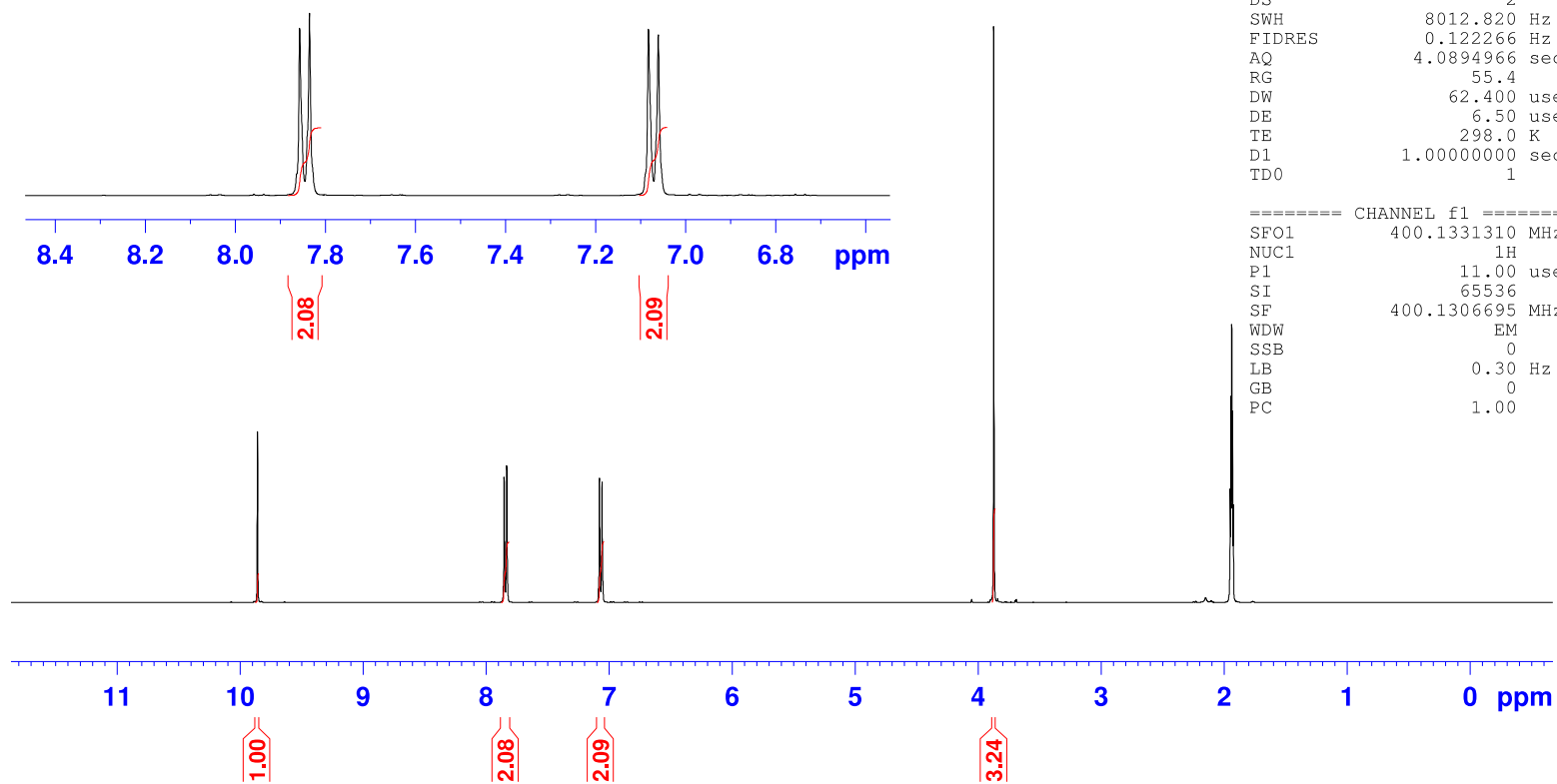


Figure S59. ¹H NMR spectrum of **12** in CD₃CN.

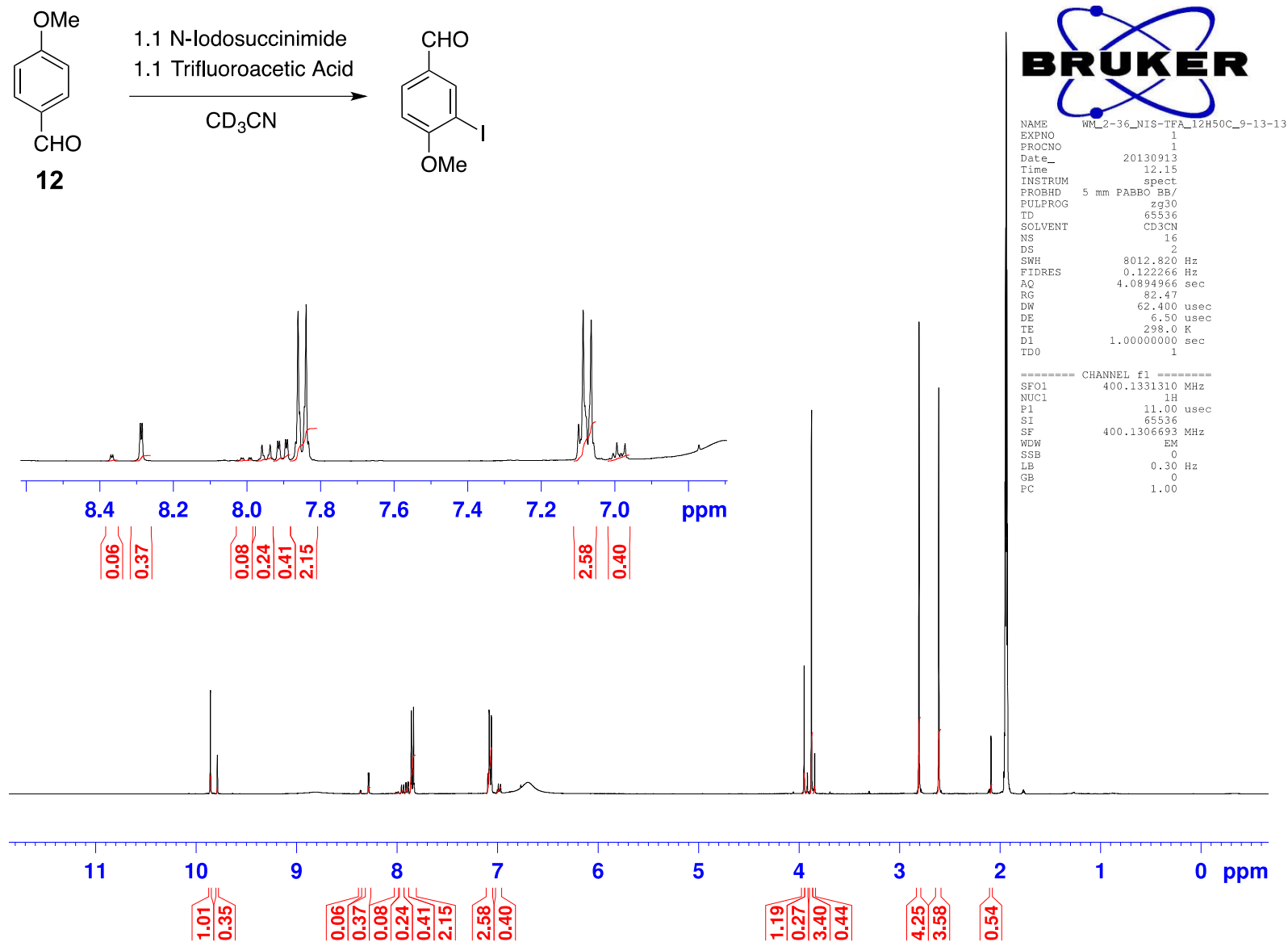


Figure S60. ¹H NMR spectrum of the iodination of **12** by Method A in CD₃CN.

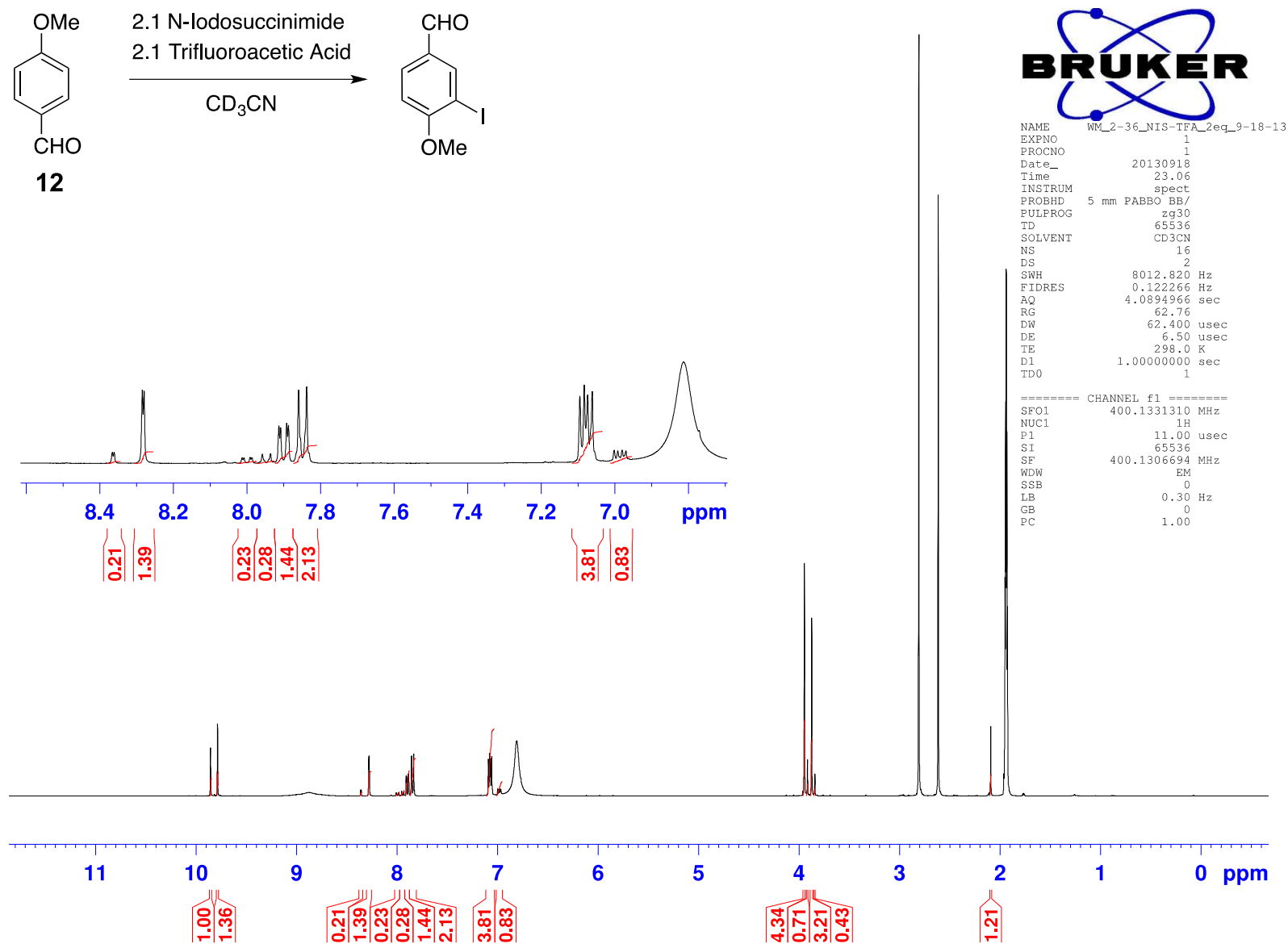


Figure S61. ^1H NMR spectrum of the iodination of **12** by Method B in CD_3CN .

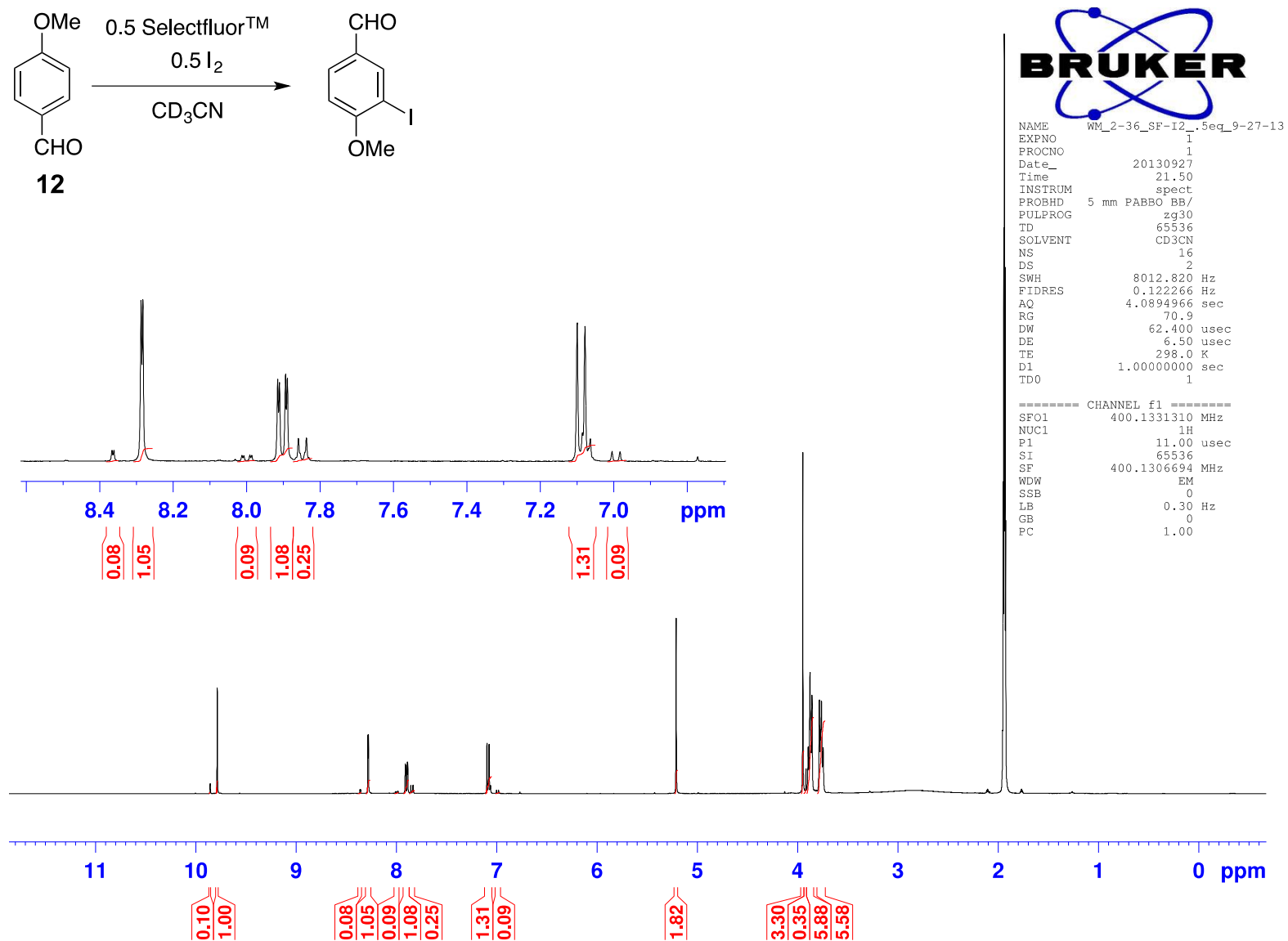


Figure S62. ¹H NMR spectrum of the iodination of **12** by Method C in CD₃CN.

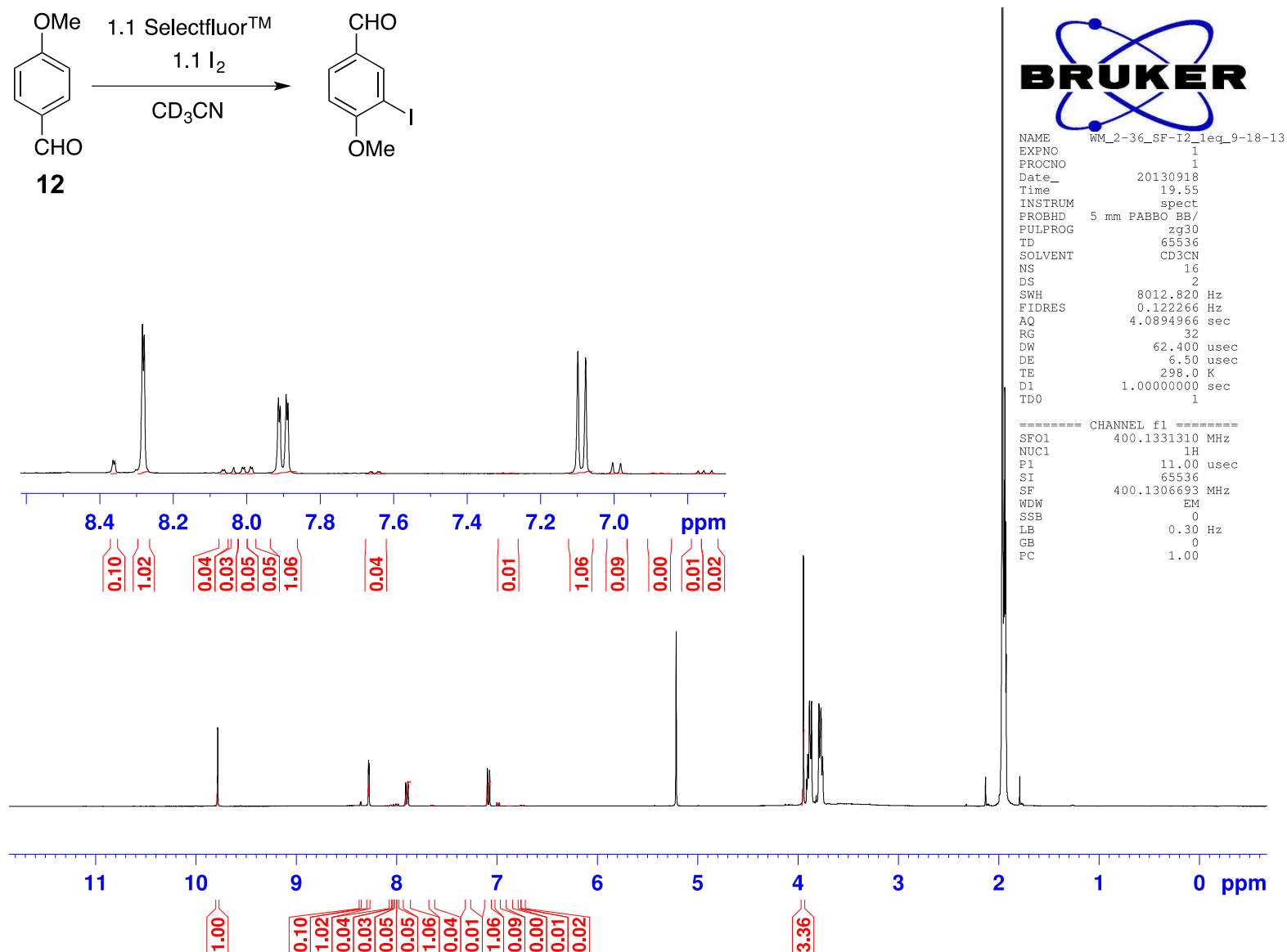


Figure S63. ¹H NMR spectrum of the iodination of **12** by Method D in CD₃CN.

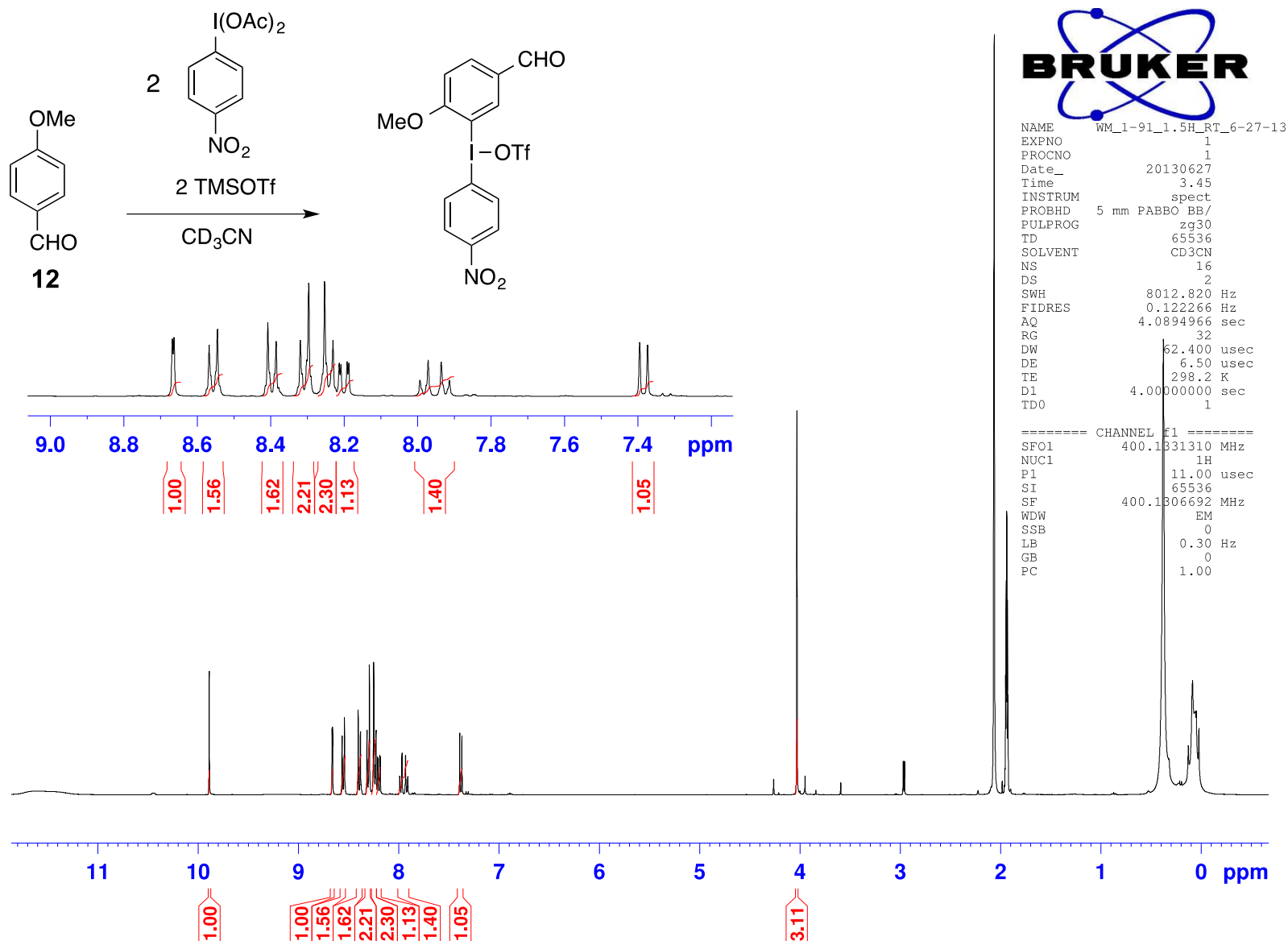


Figure S64. ¹H NMR spectrum of the iodination of **12** by Method E in CD₃CN.

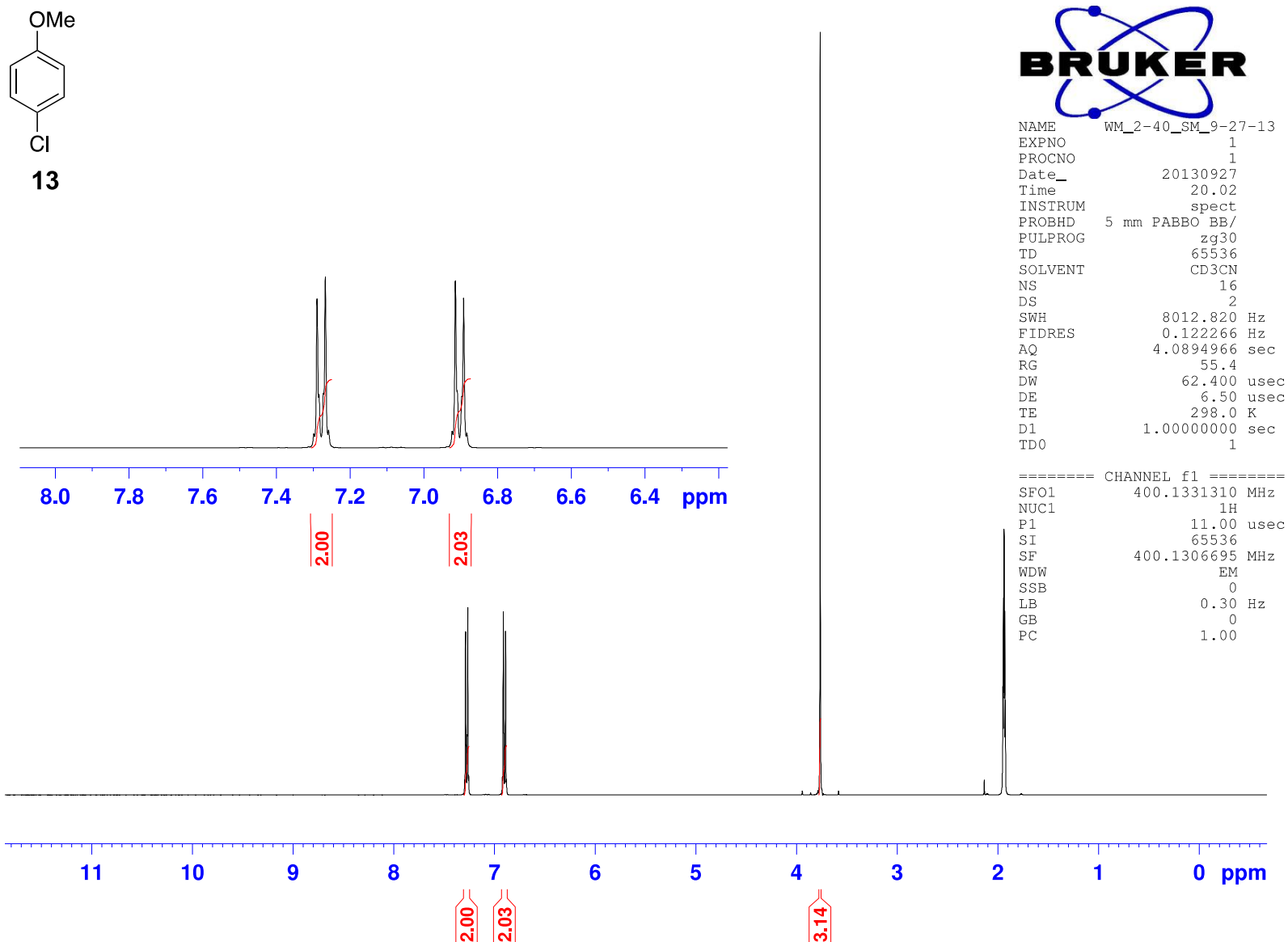


Figure S65. ^1H NMR spectrum of **13** in CD_3CN .

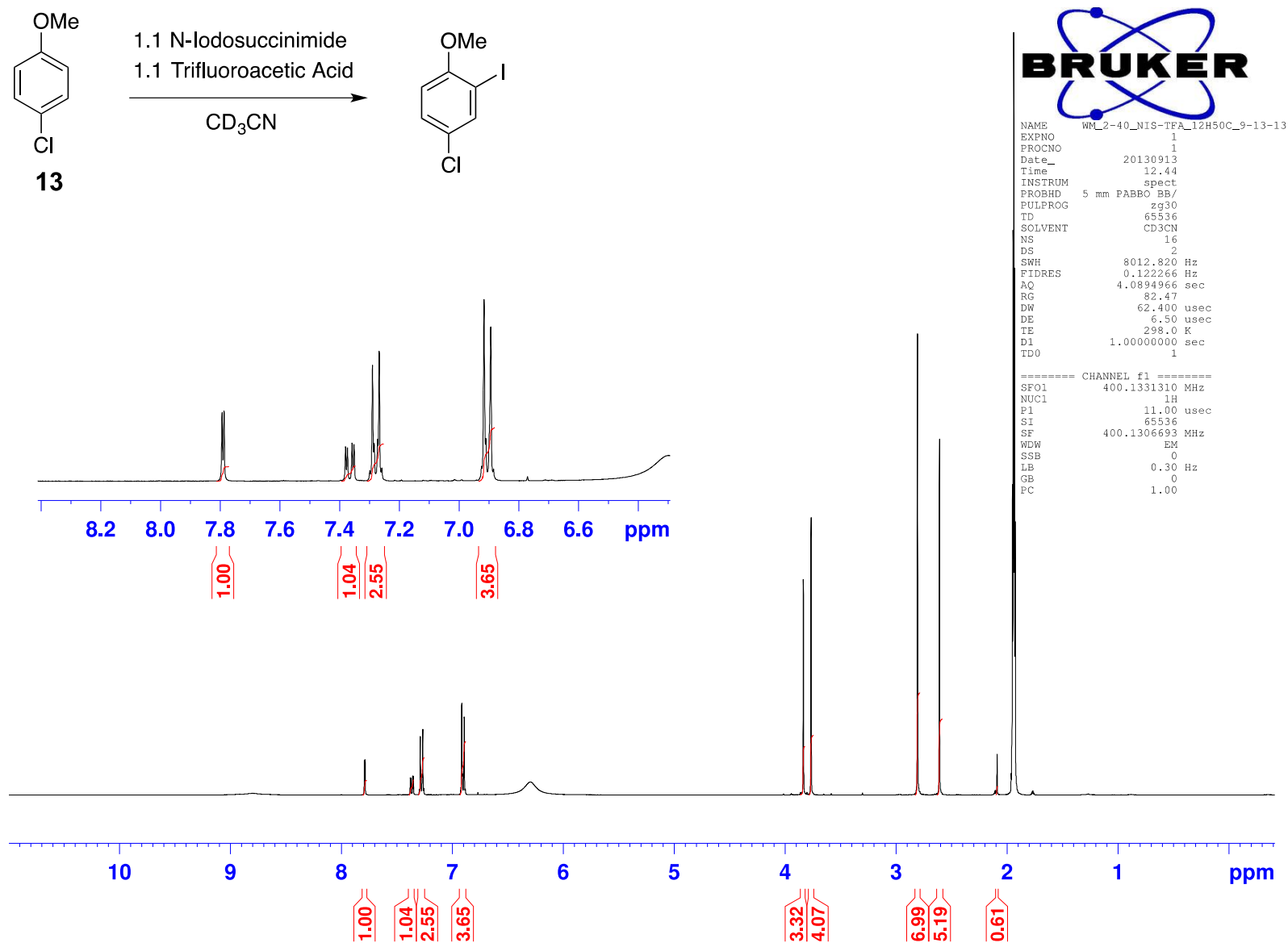


Figure S66. ¹H NMR spectrum of the iodination of **13** by Method A in CD₃CN.

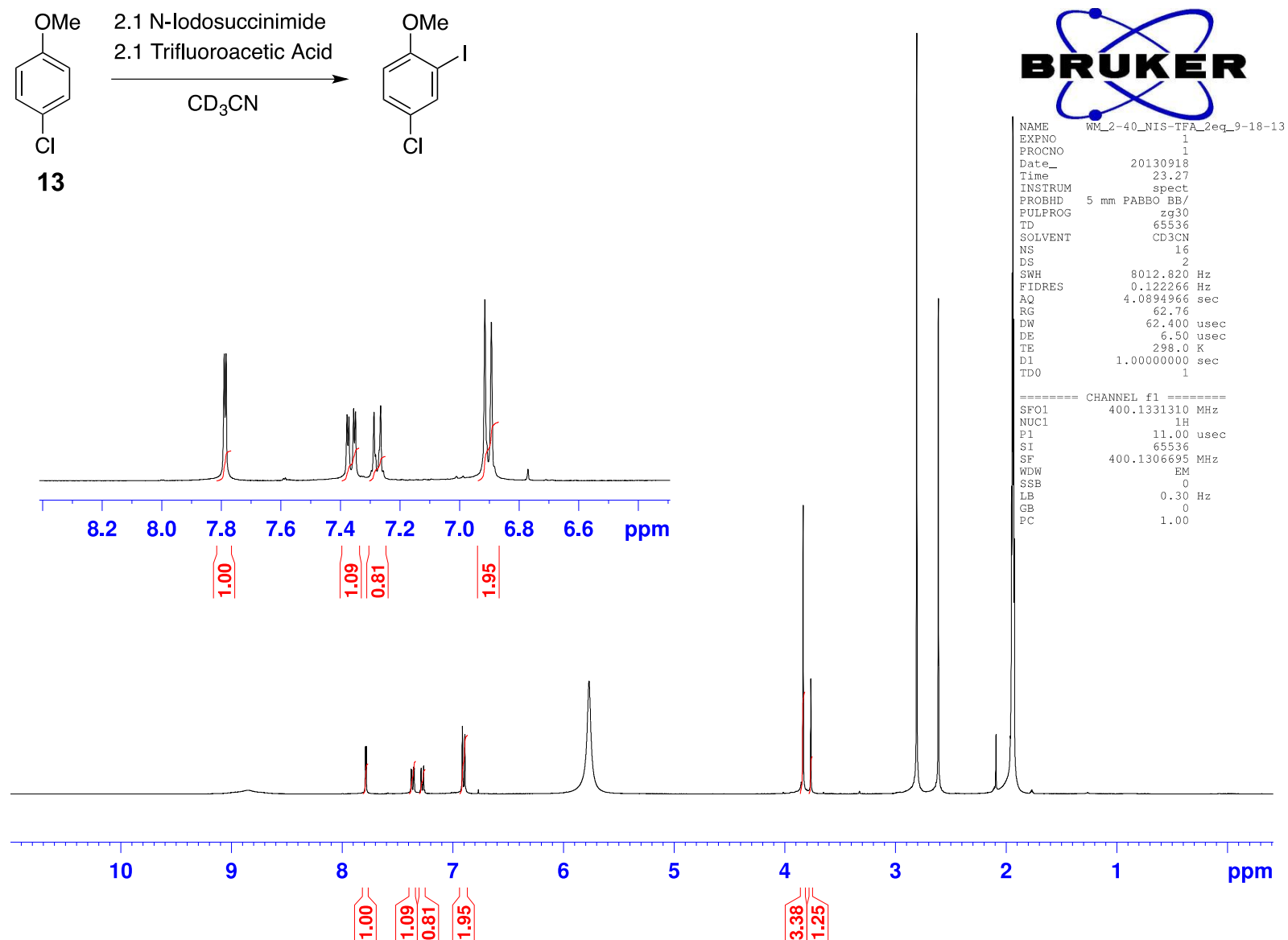


Figure S67. ¹H NMR spectrum of the iodination of **13** by Method B in CD₃CN.

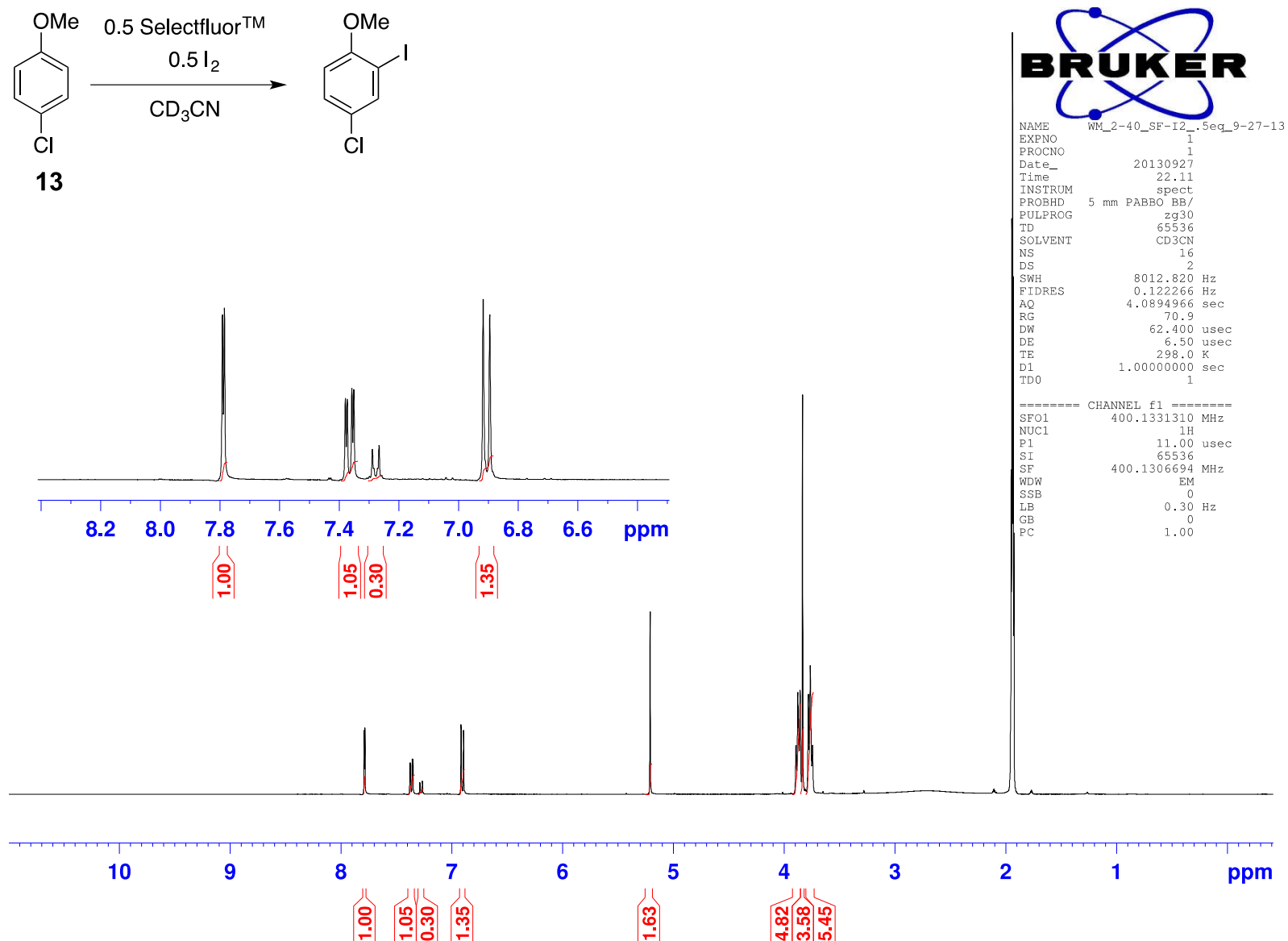


Figure S68. ¹H NMR spectrum of the iodination of **13** by Method C in CD₃CN.

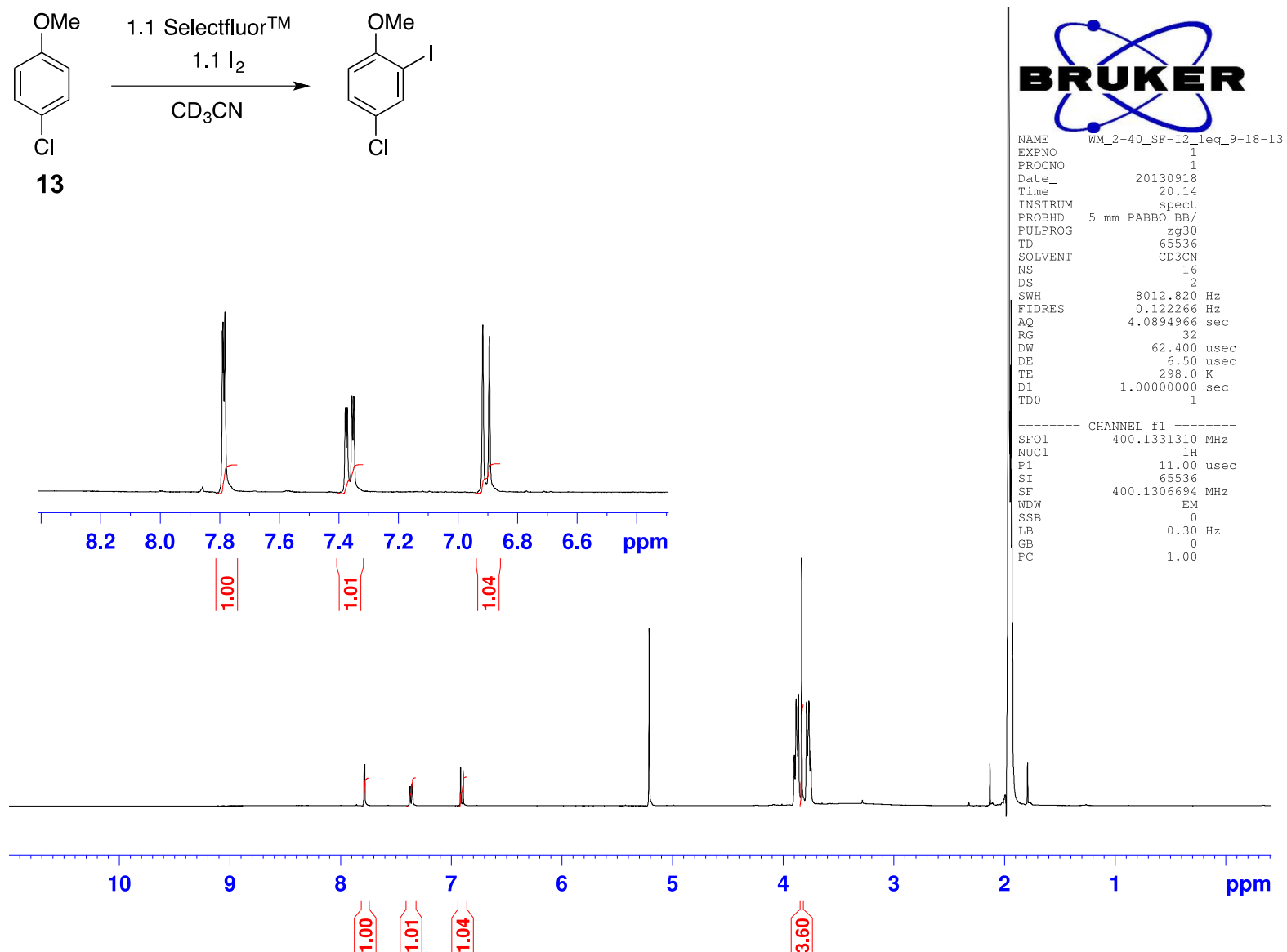


Figure S69. ¹H NMR spectrum of the iodination of **13** by Method D in CD₃CN.

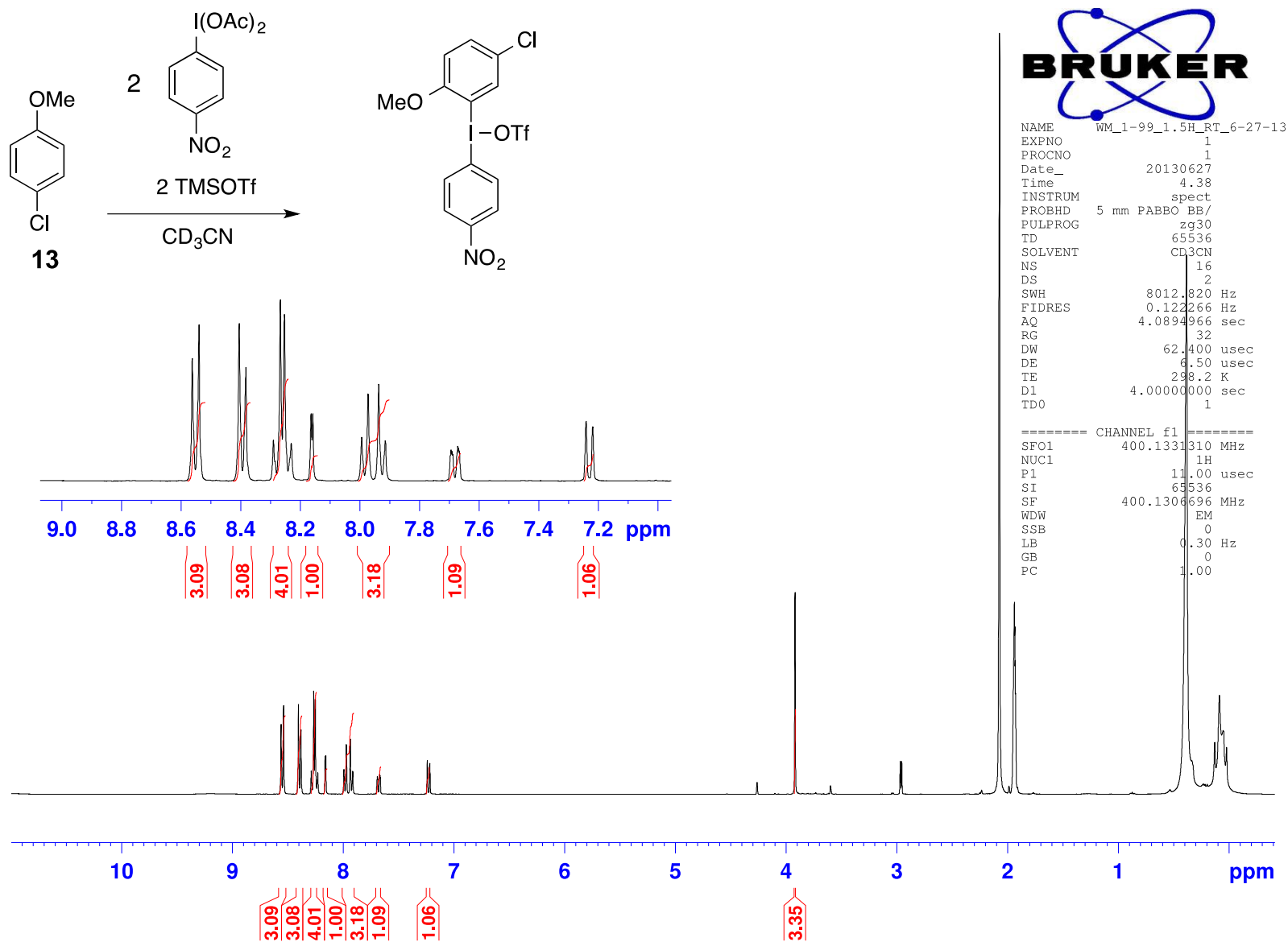


Figure S70. ¹H NMR spectrum of the iodination of **13** by Method E in CD₃CN.

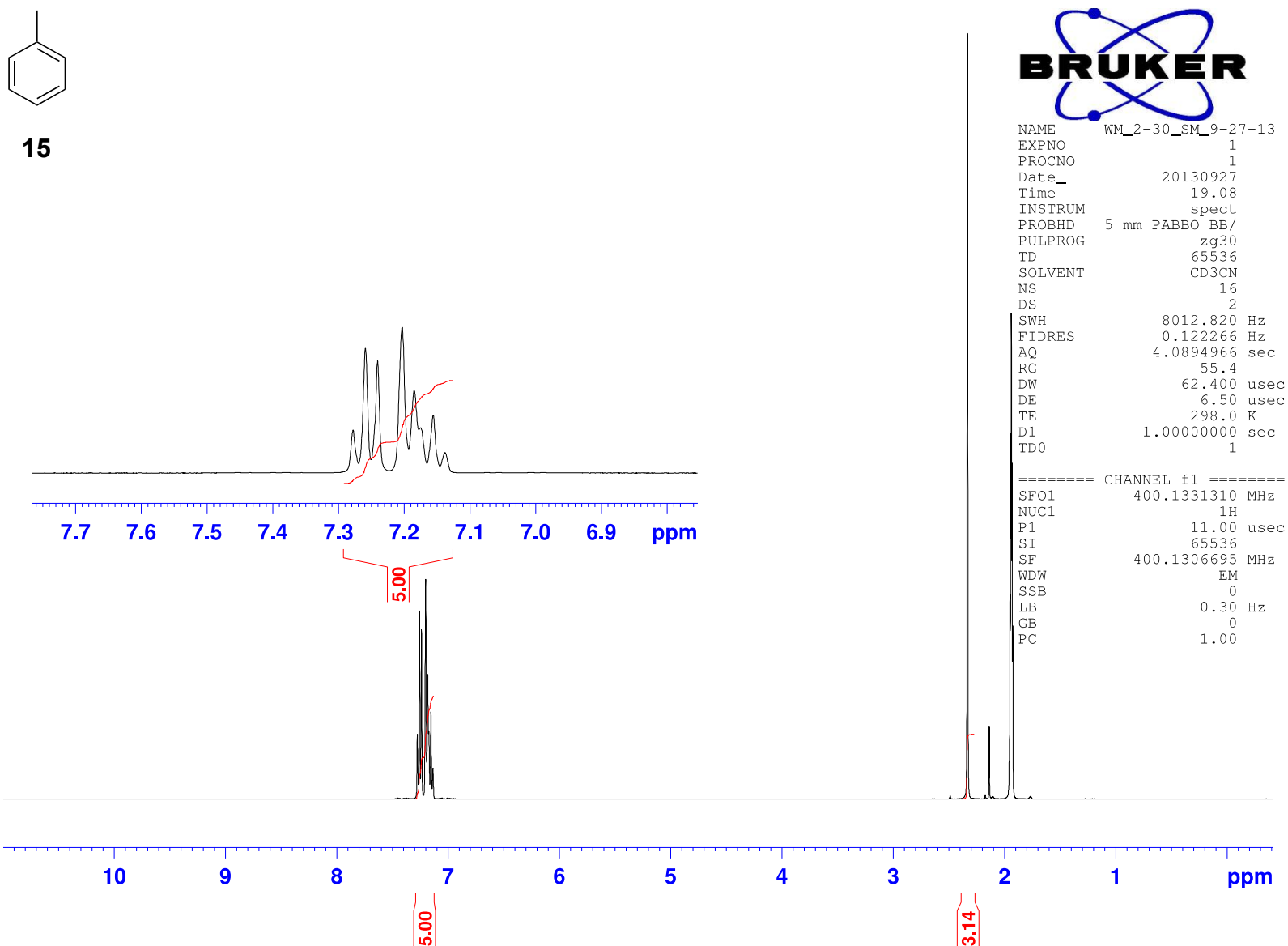


Figure S77. ^1H NMR spectrum of **15** in CD_3CN .

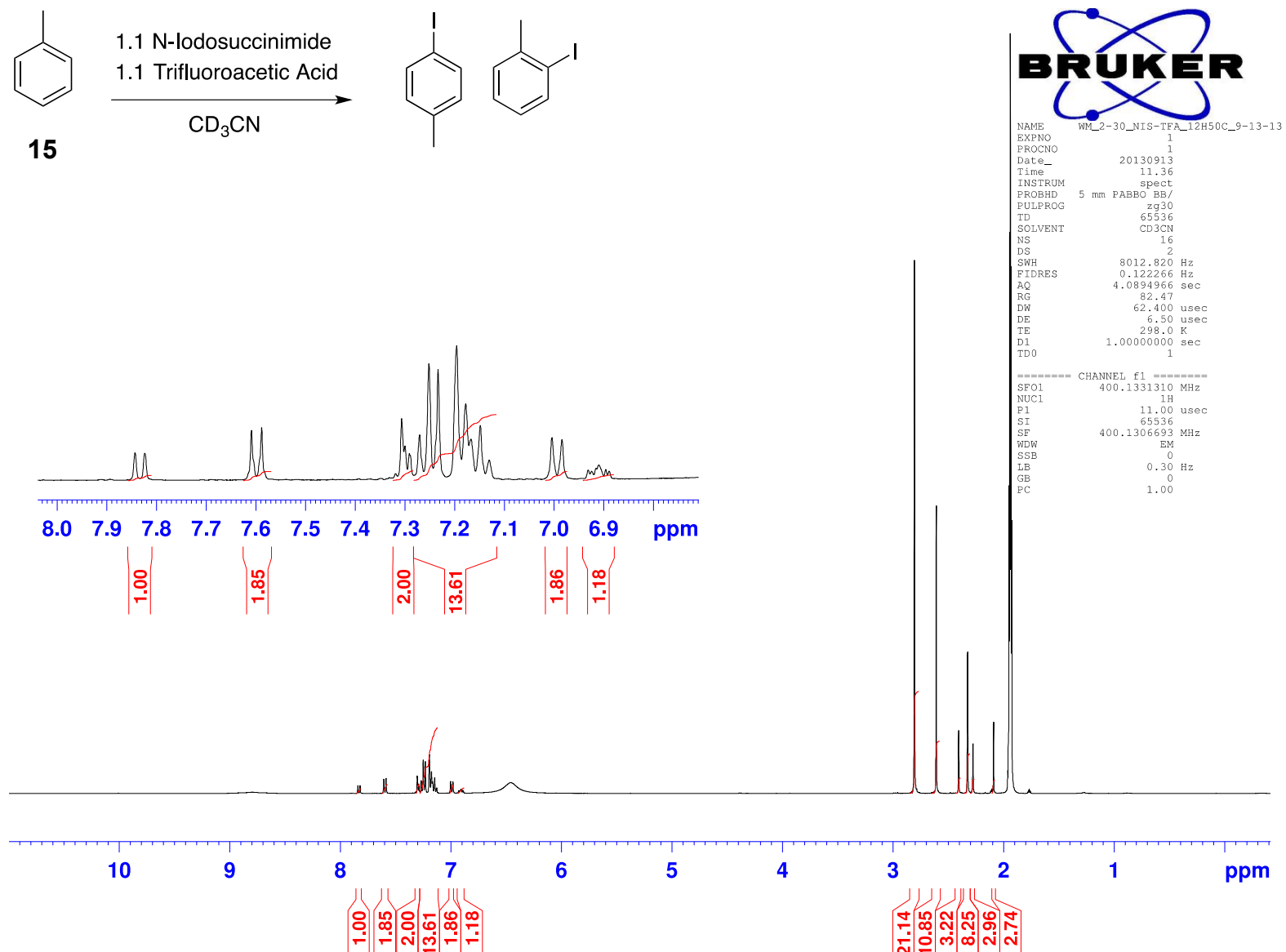


Figure S78. ^1H NMR spectrum of the iodination of **15** by Method A in CD_3CN .

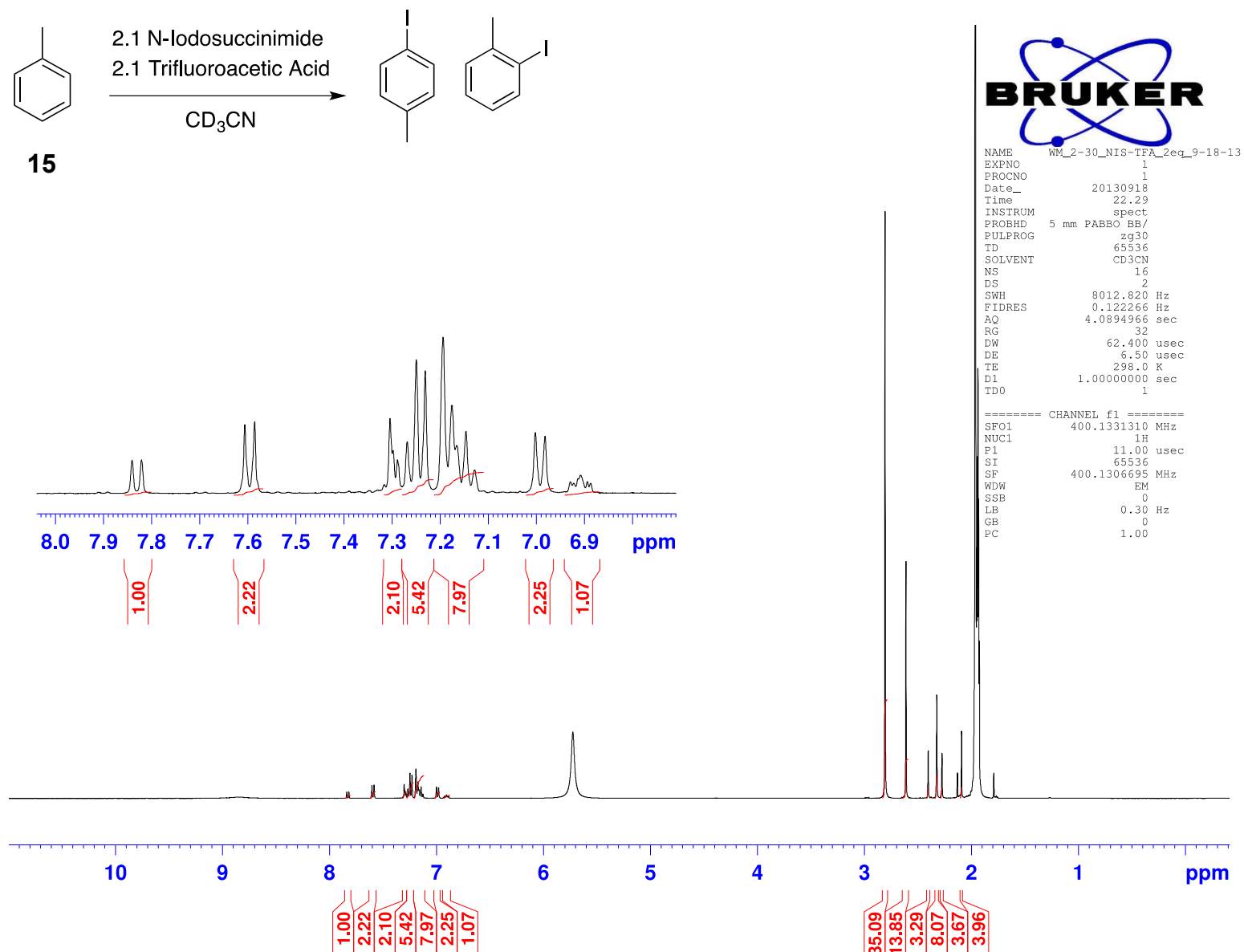


Figure S79. ^1H NMR spectrum of the iodination of **15** by Method B in CD_3CN .

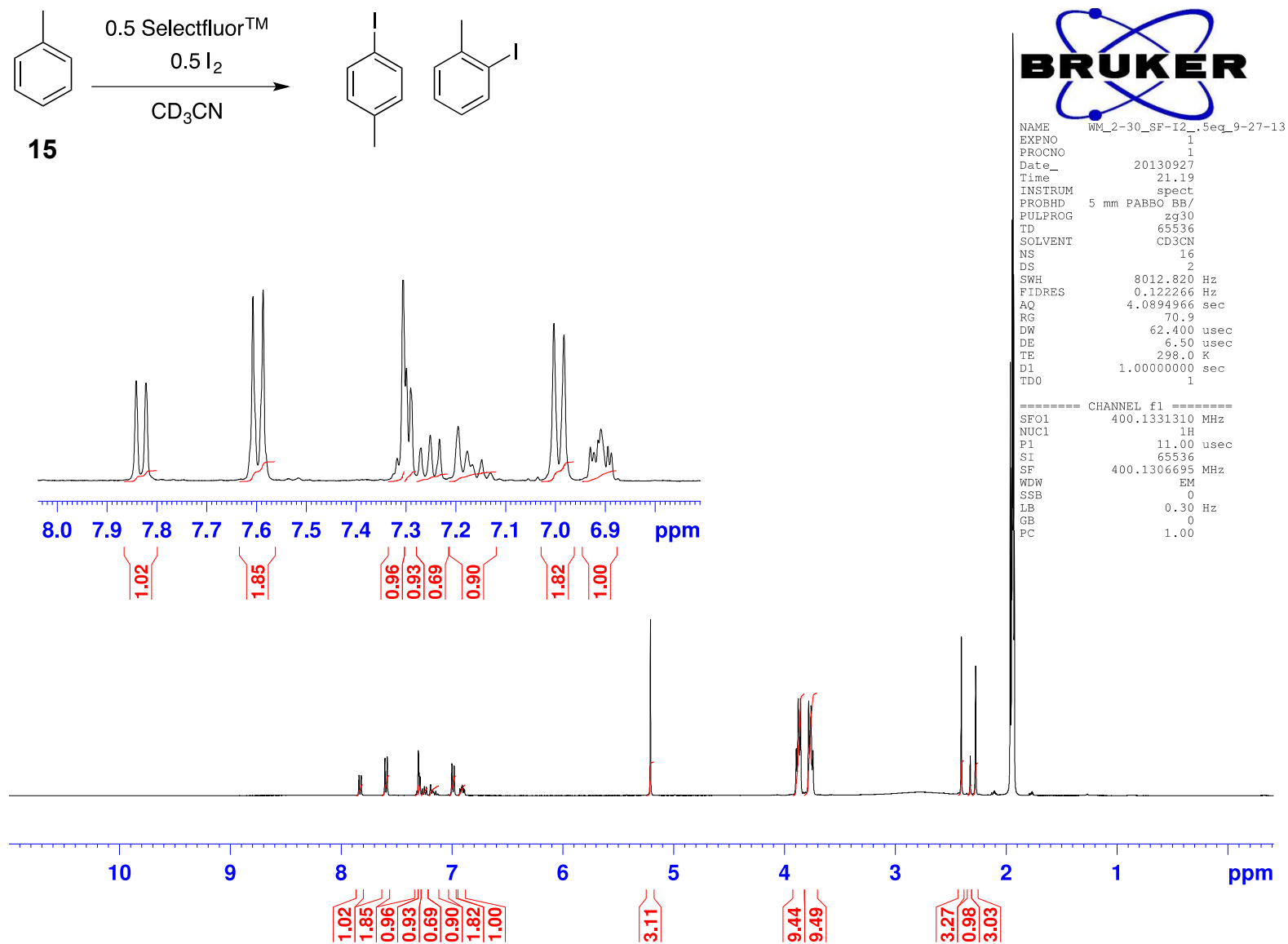


Figure S80. ¹H NMR spectrum of the iodination of **15** by Method C in CD₃CN.

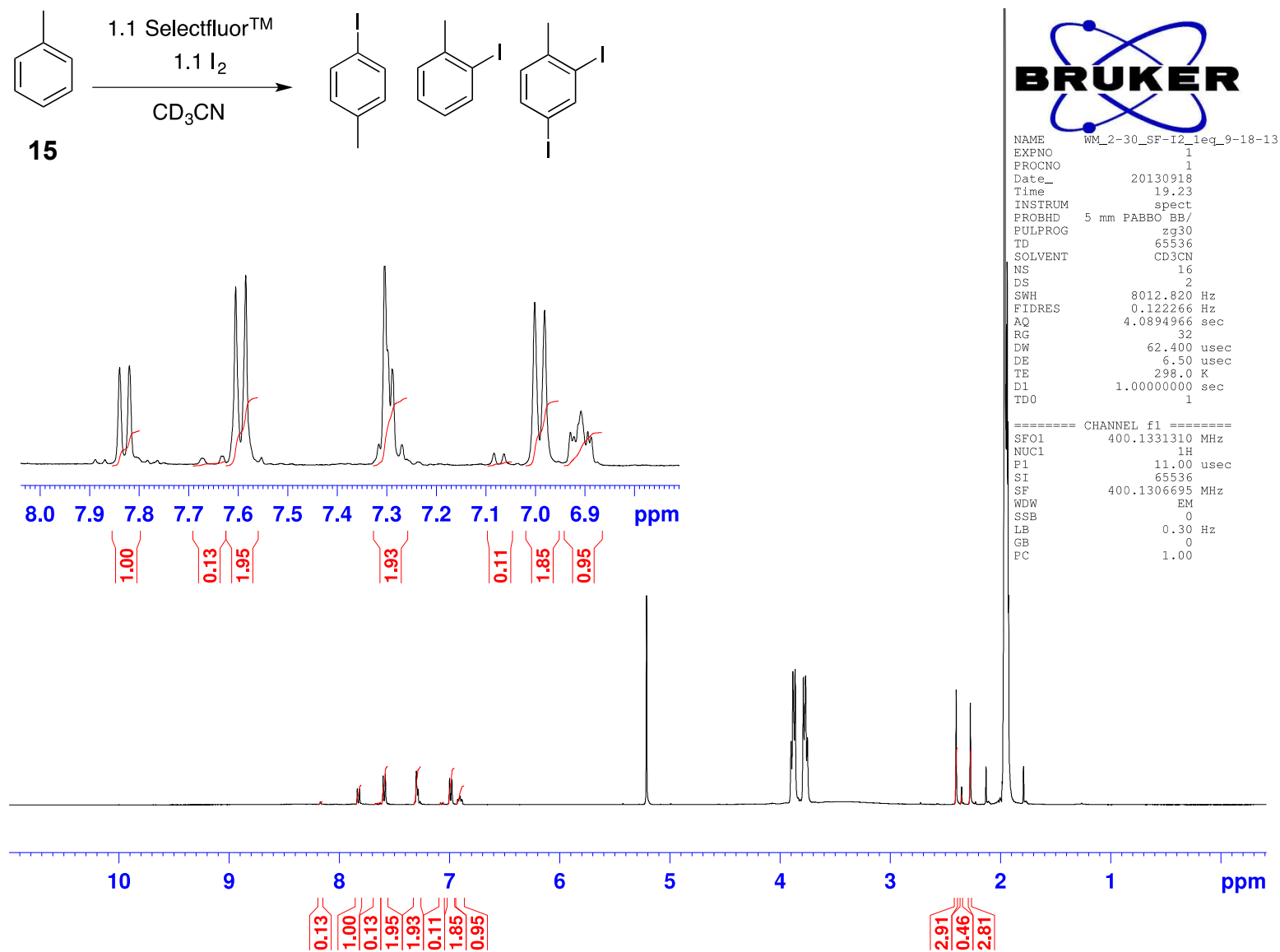


Figure S81. ¹H NMR spectrum of the iodination of **15** by Method D in CD₃CN.

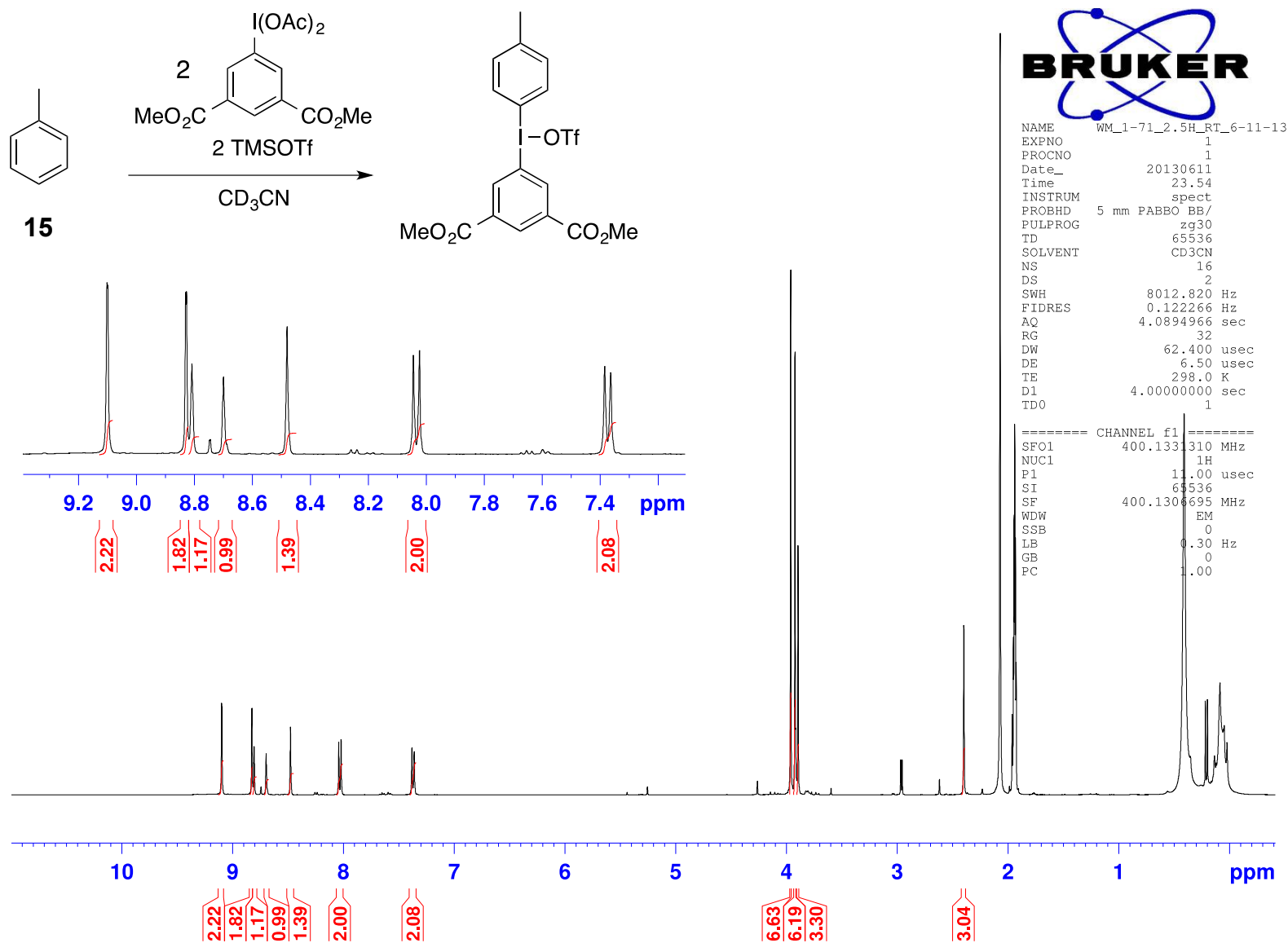


Figure S82. ¹H NMR spectrum of the iodination of **15** by Method F in CD₃CN.

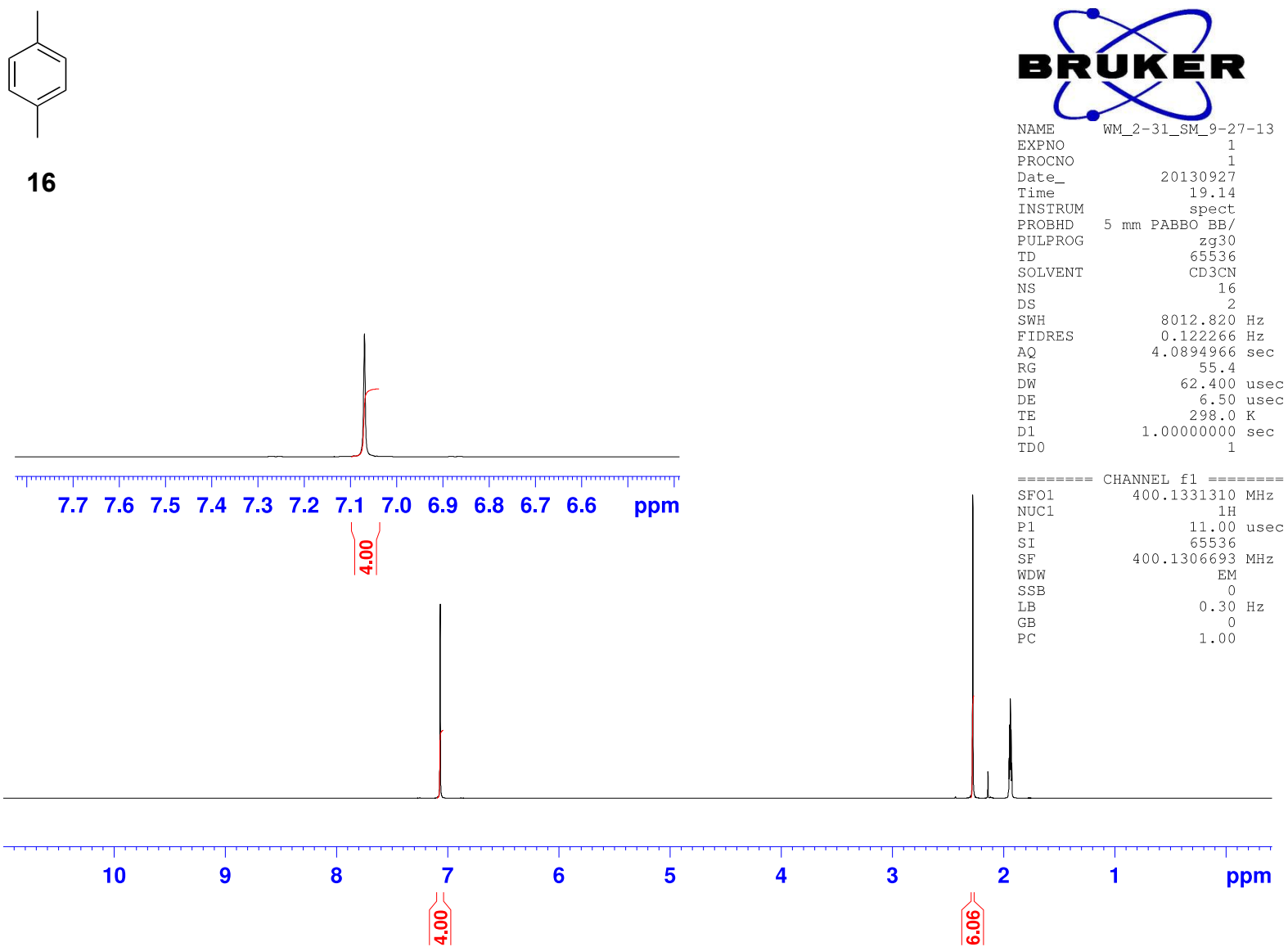


Figure S83. ^1H NMR spectrum of **16** in CD_3CN .

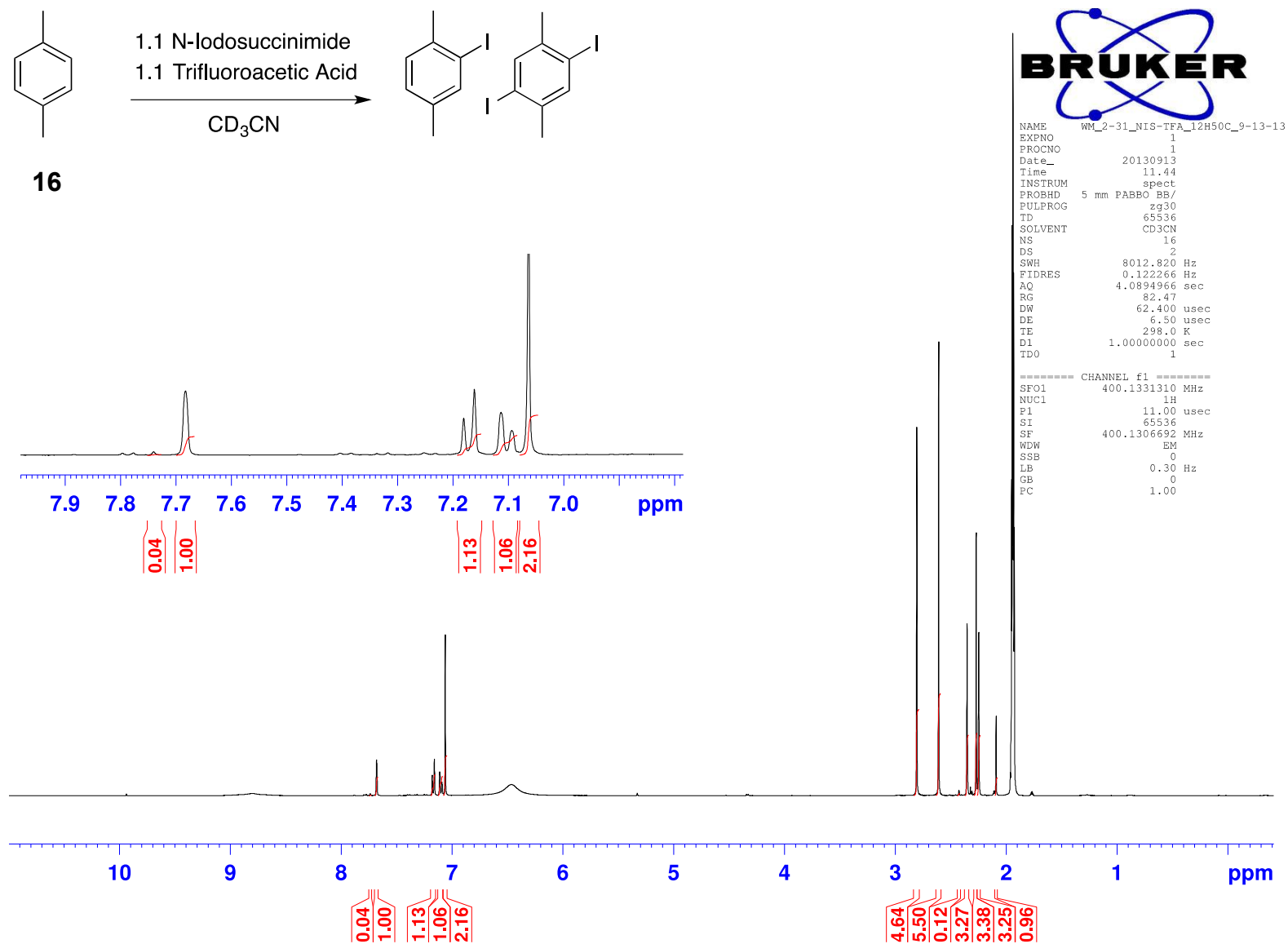


Figure S84. ^1H NMR spectrum of the iodination of **16** by Method A in CD_3CN .

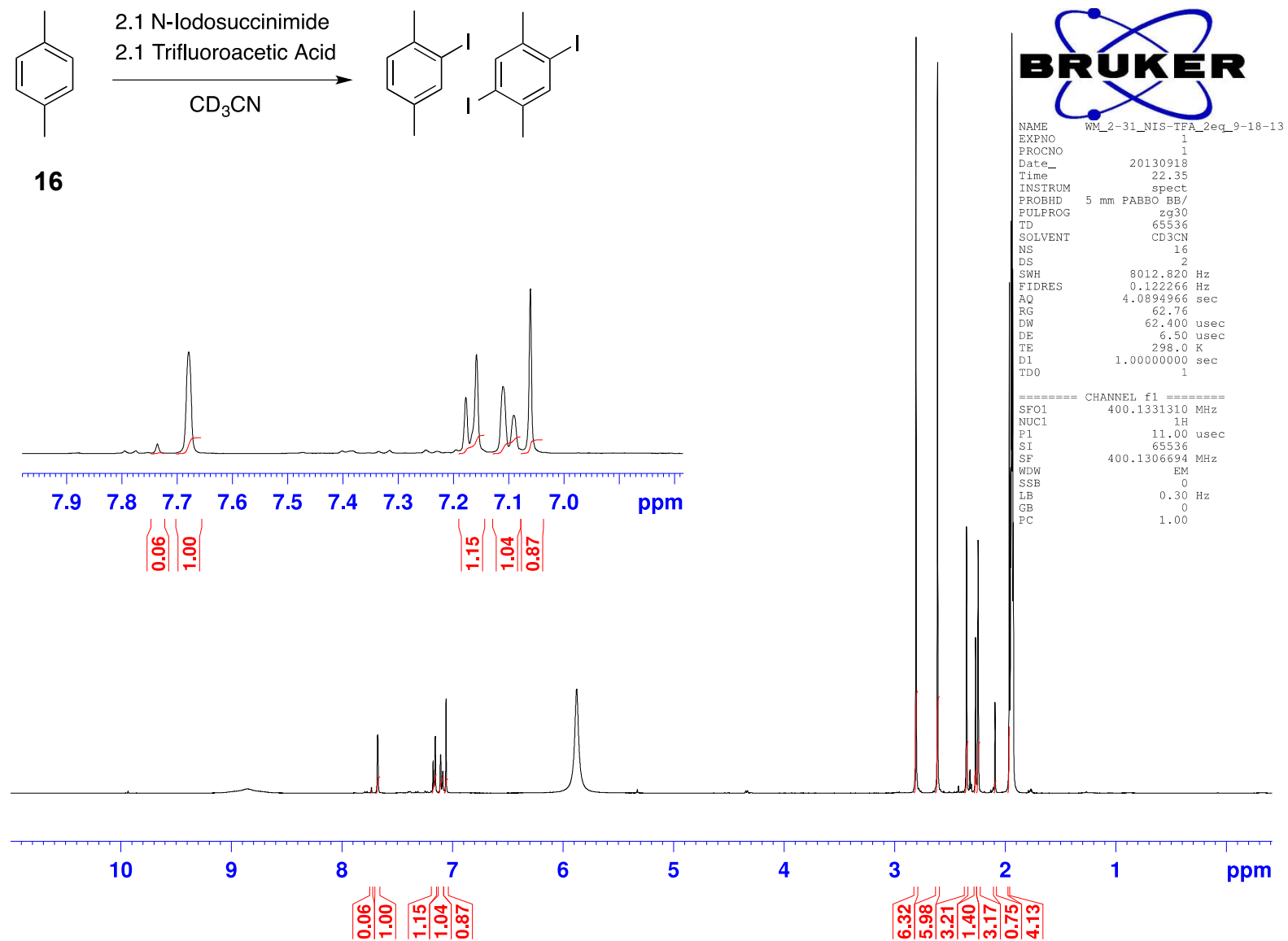


Figure S85. ^1H NMR spectrum of the iodination of **16** by Method B in CD_3CN .

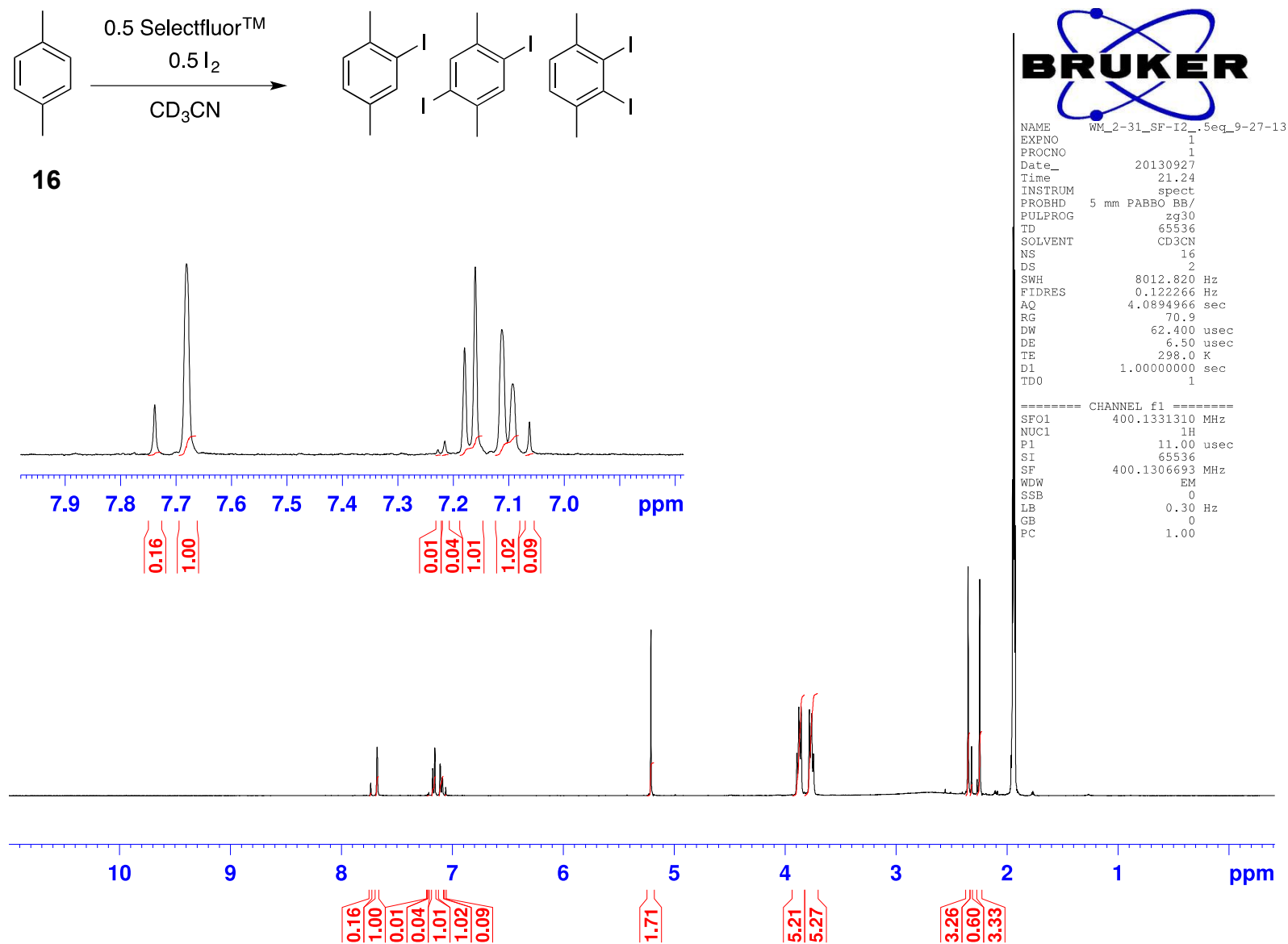


Figure S86. ¹H NMR spectrum of the iodination of **16** by Method C in CD₃CN.

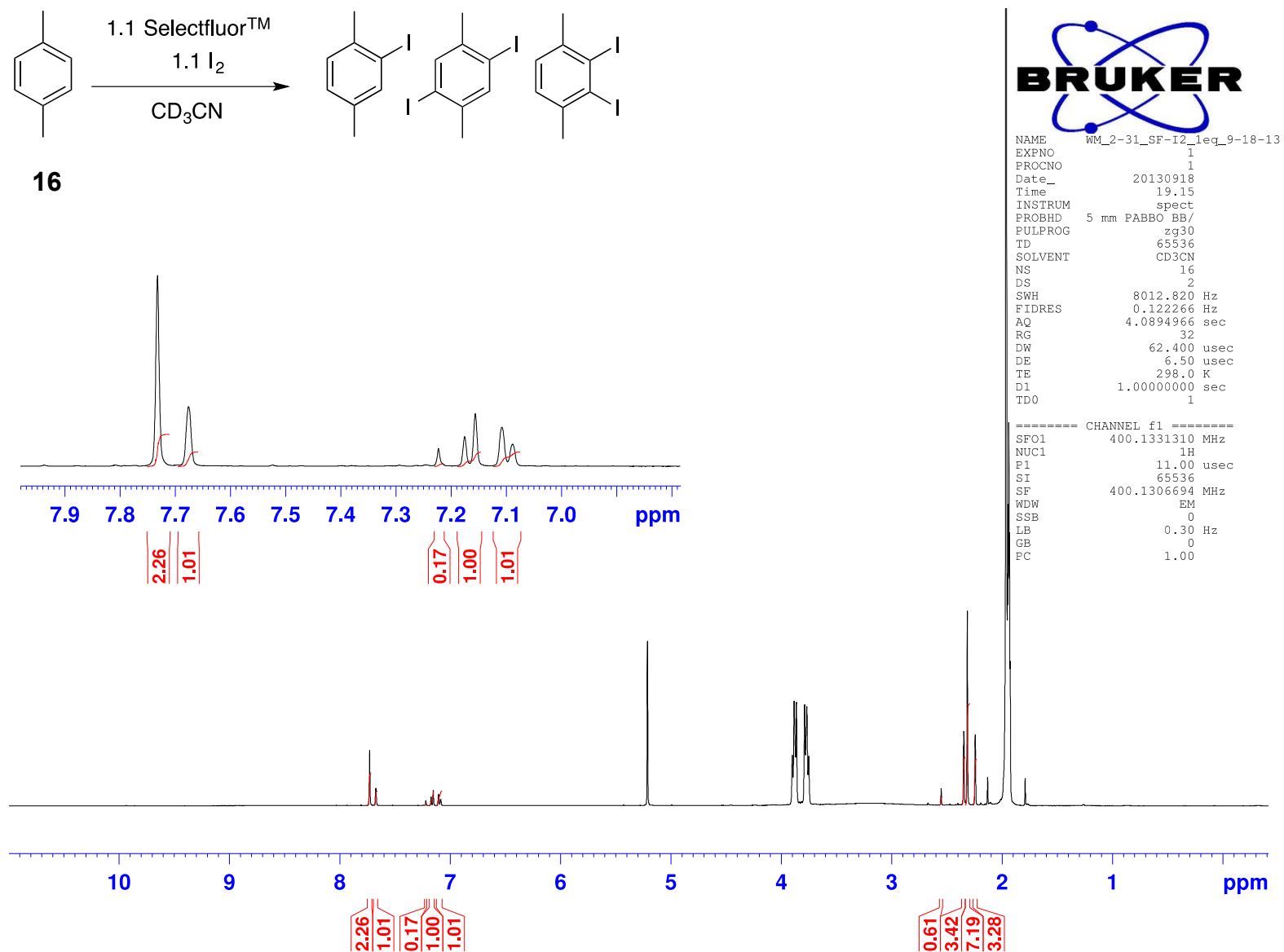


Figure S87. ¹H NMR spectrum of the iodination of **16** by Method D in CD₃CN.

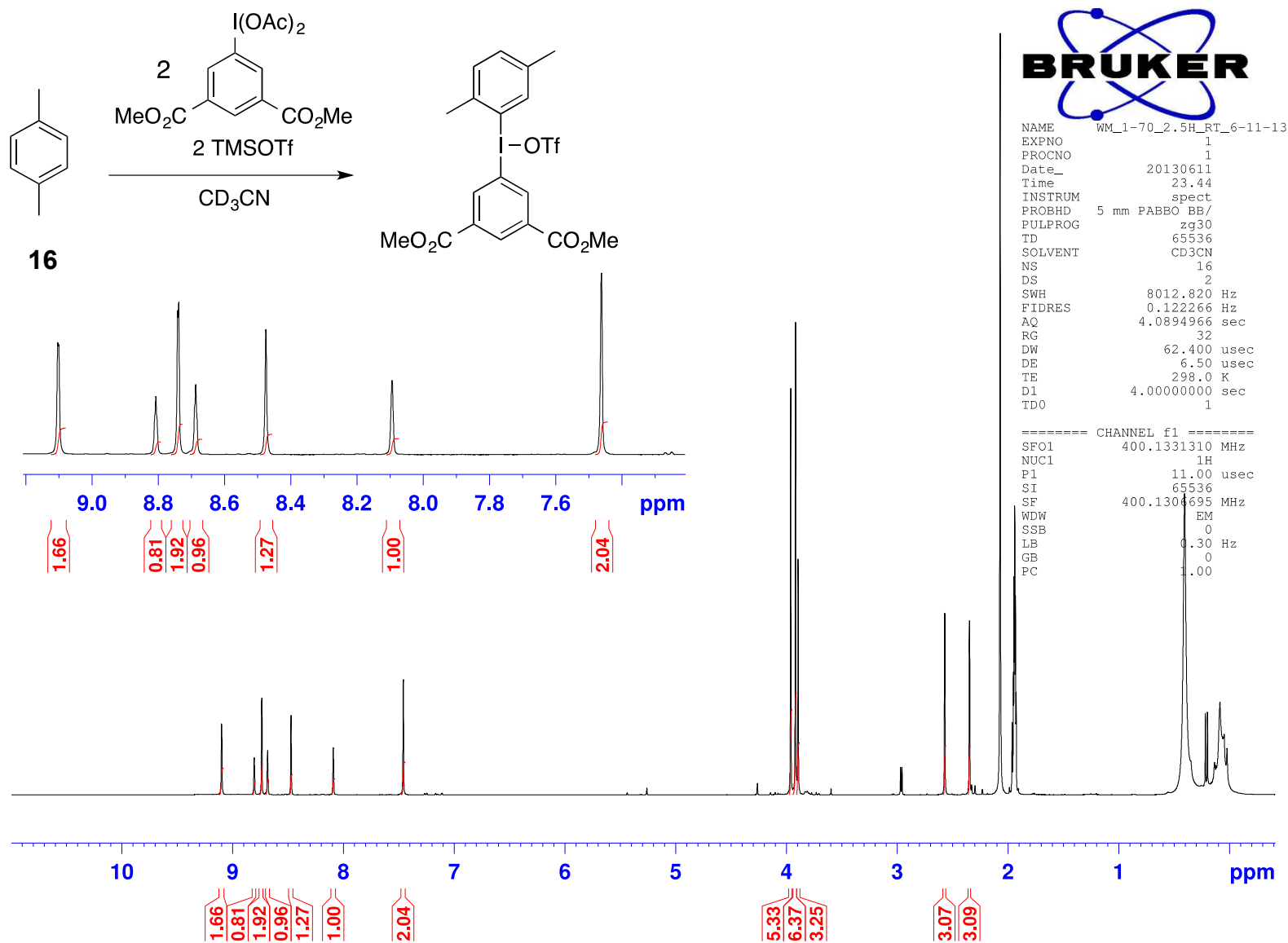


Figure S88. ¹H NMR spectrum of the iodination of **16** by Method F in CD₃CN.

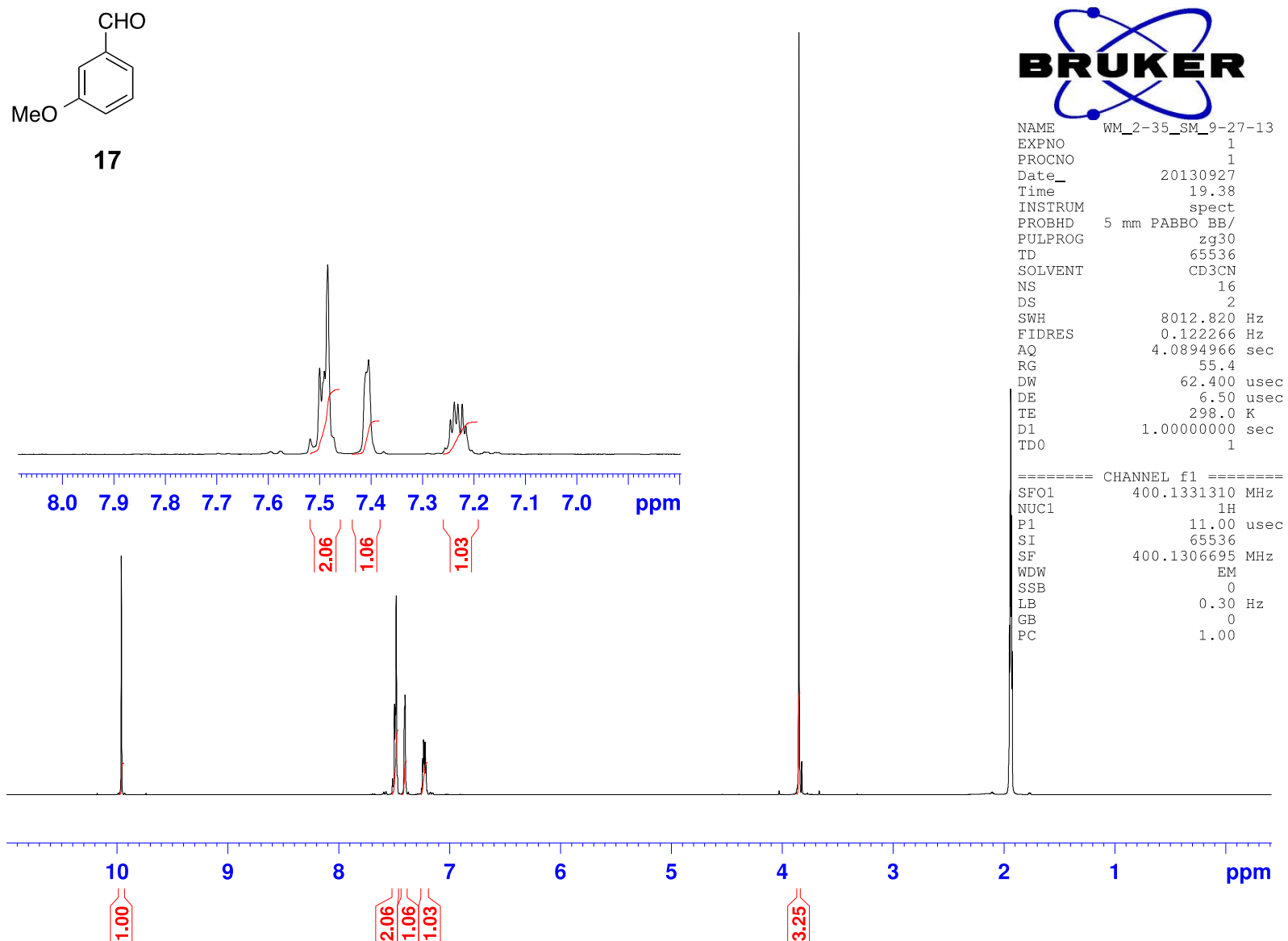


Figure S89. ^1H NMR spectrum of **17** in CD_3CN .

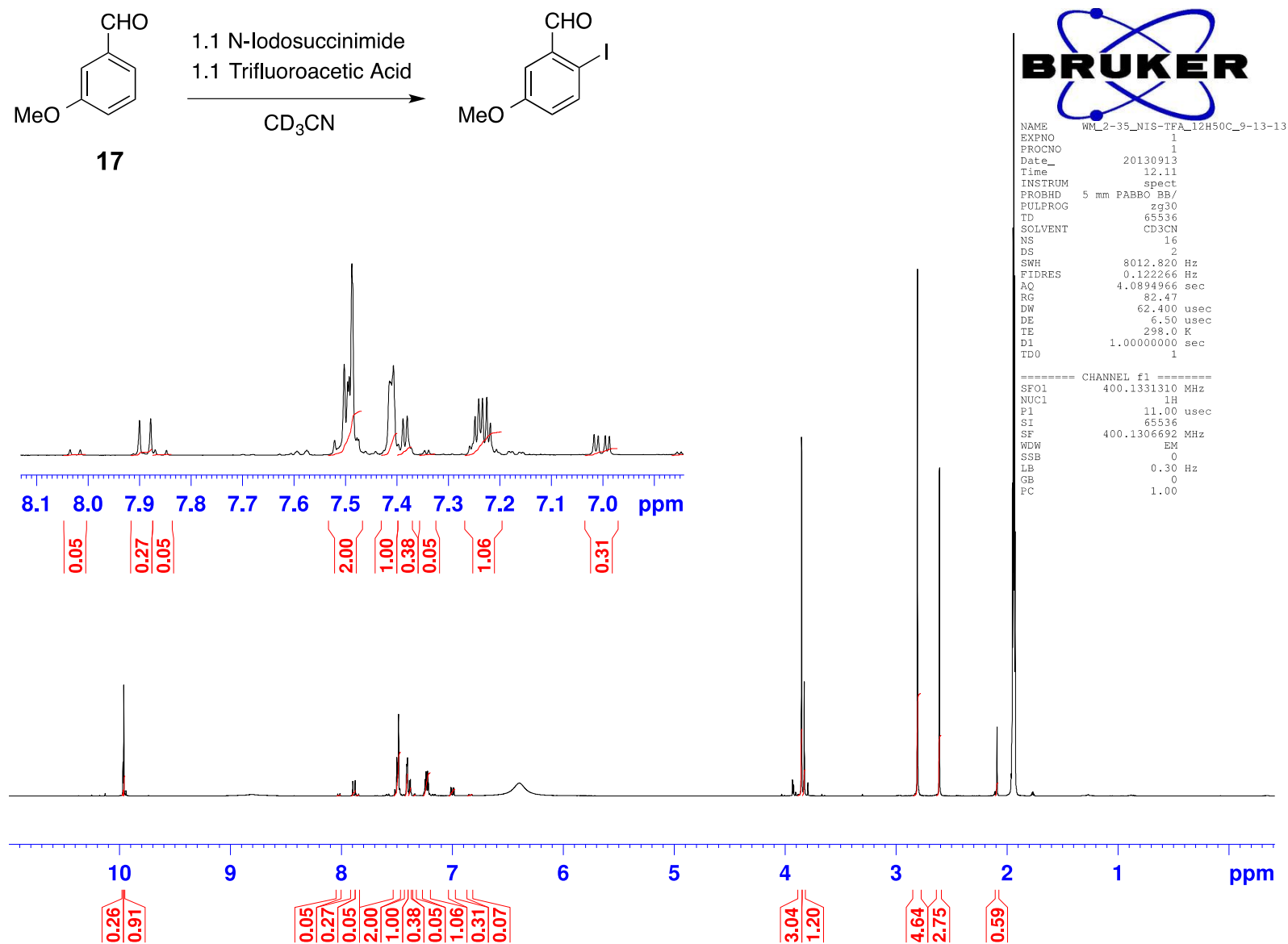


Figure S90. ¹H NMR spectrum of the iodination of **17** by Method A in CD₃CN.

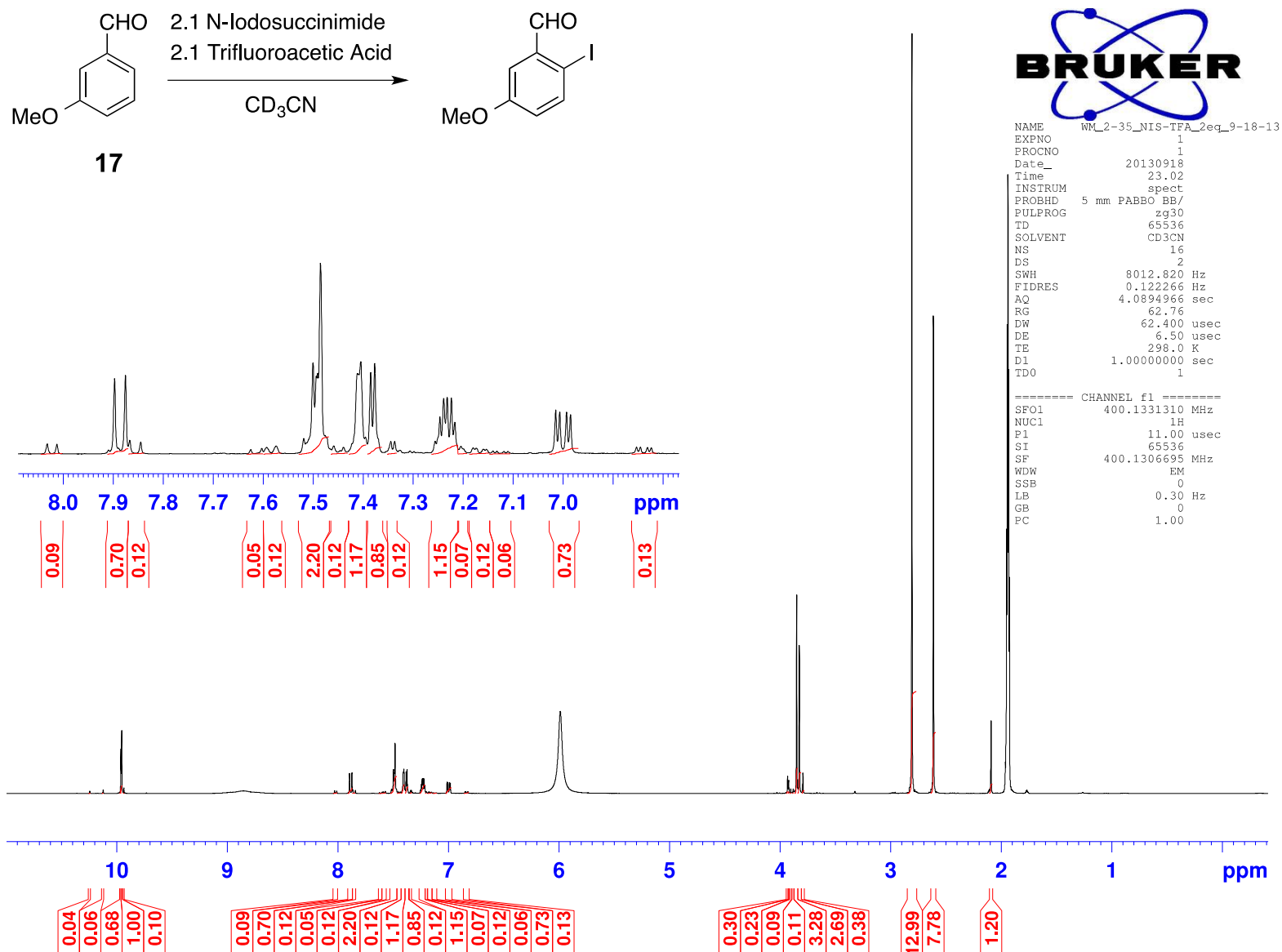


Figure S91. ^1H NMR spectrum of the iodination of **17** by Method B in CD_3CN .

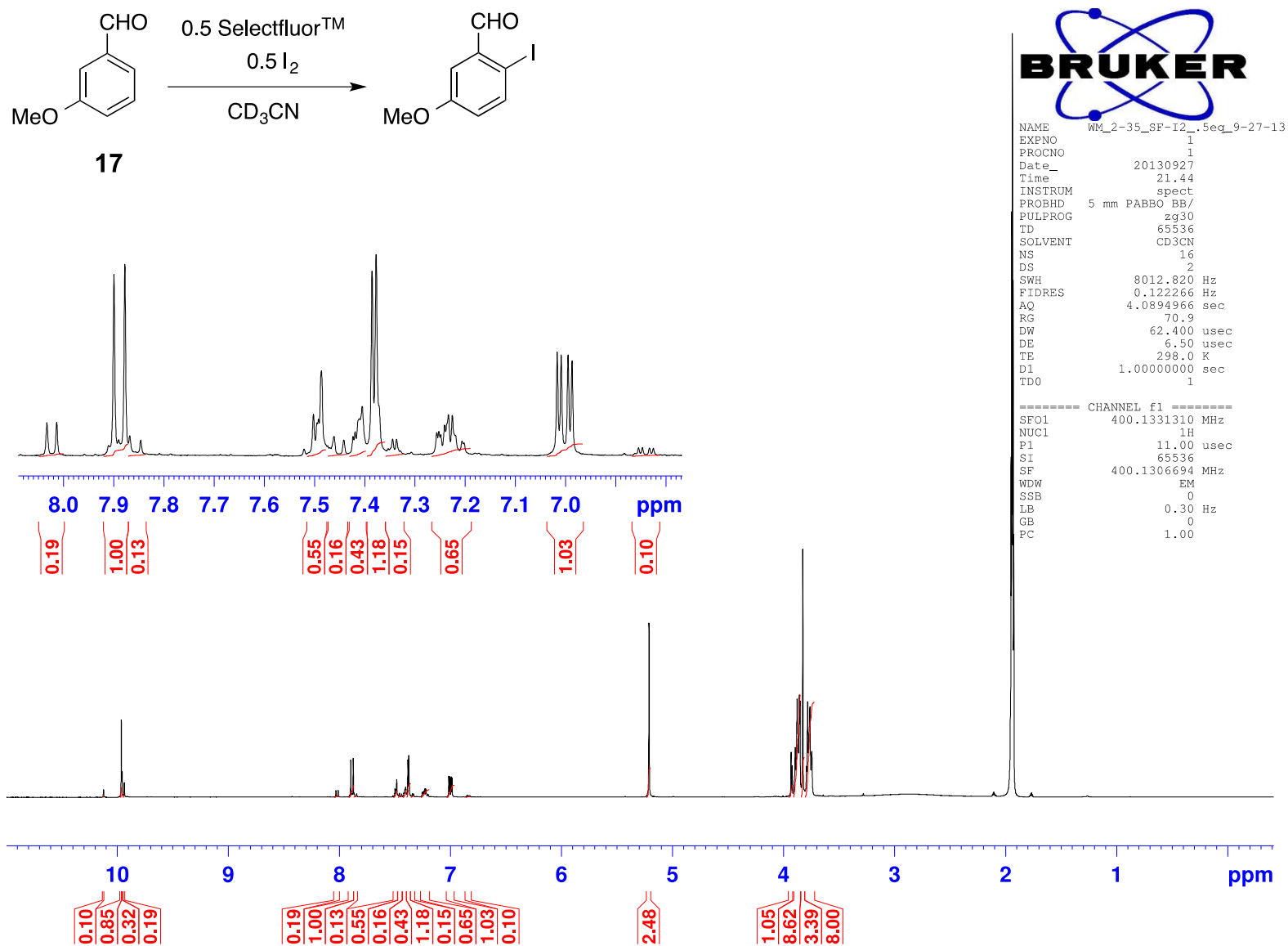


Figure S92. ¹H NMR spectrum of the iodination of **17** by Method C in CD₃CN.

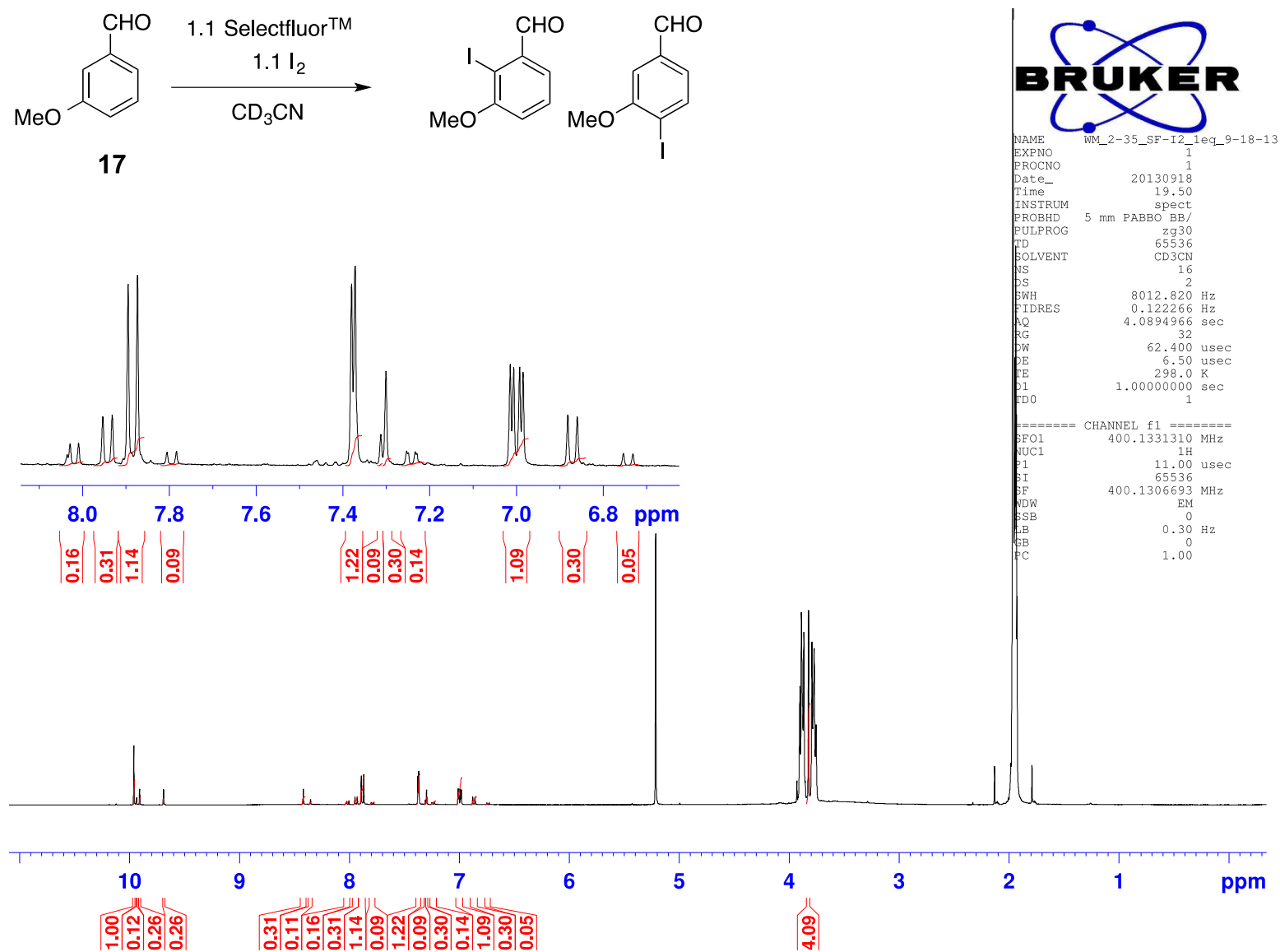


Figure S93. ¹H NMR spectrum of the iodination of **17** by Method D in CD₃CN.

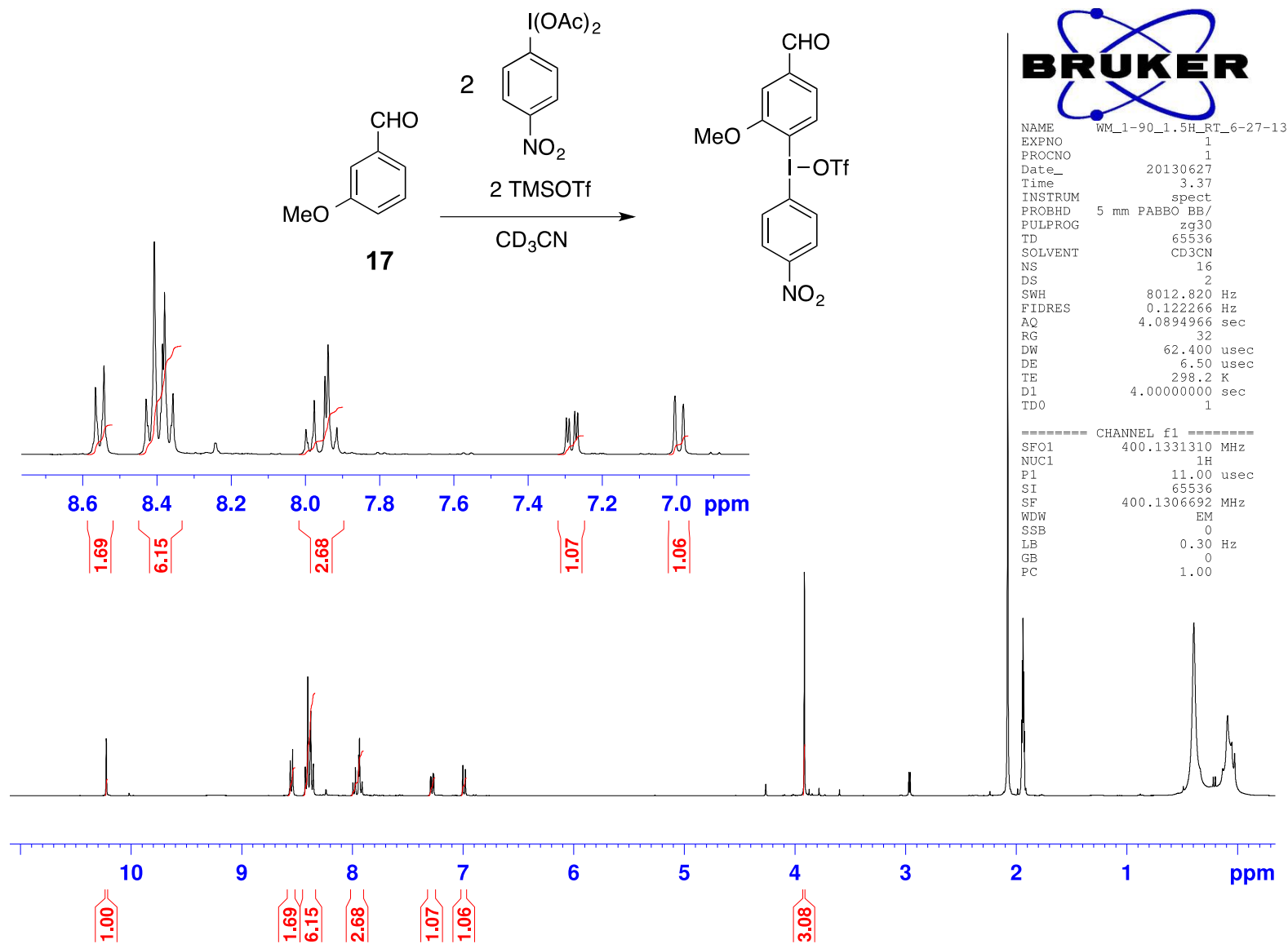


Figure S94. ¹H NMR spectrum of the iodination of **17** by Method E in CD₃CN.

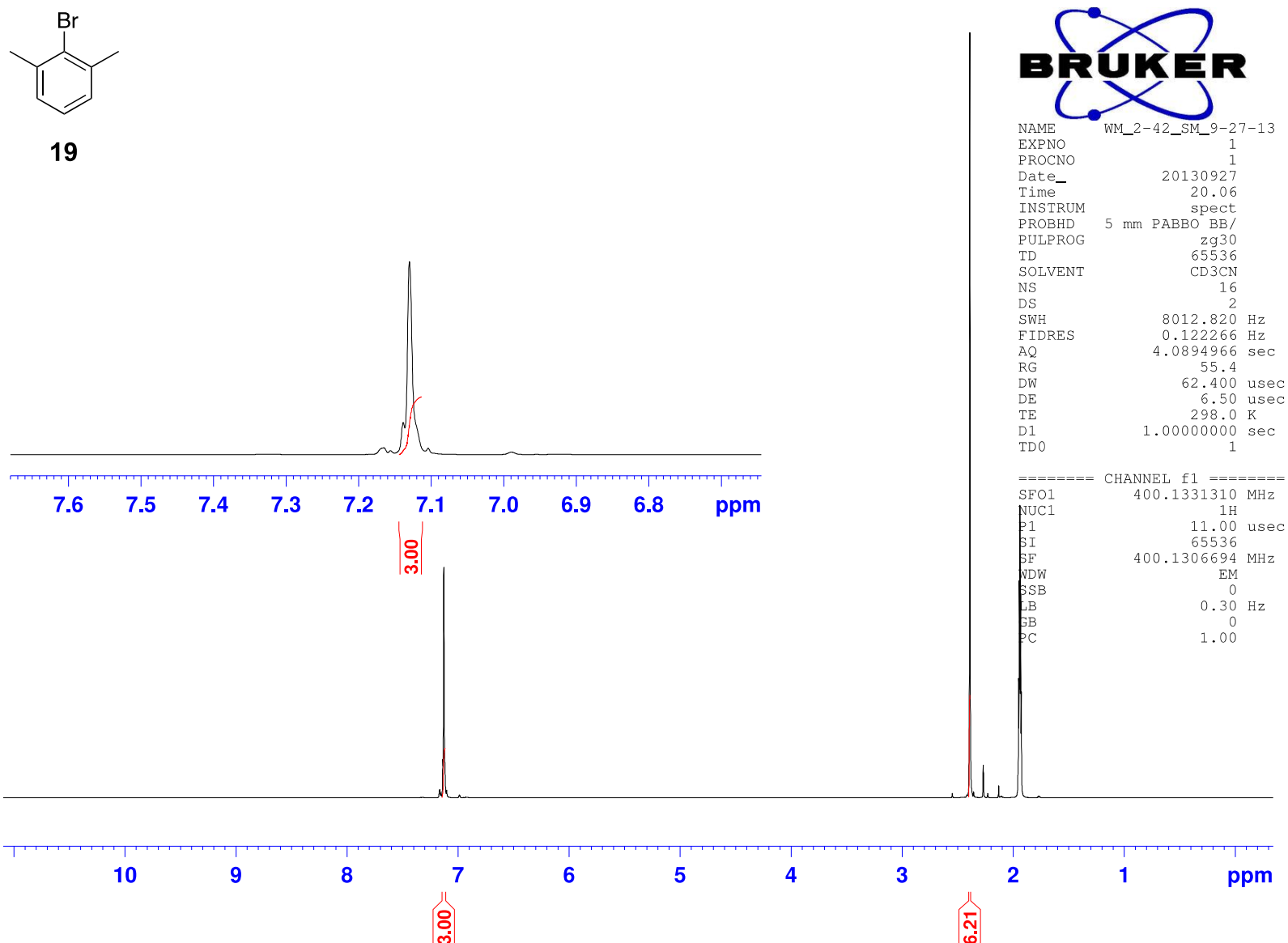


Figure S107. ^1H NMR spectrum of **20** in CD_3CN .

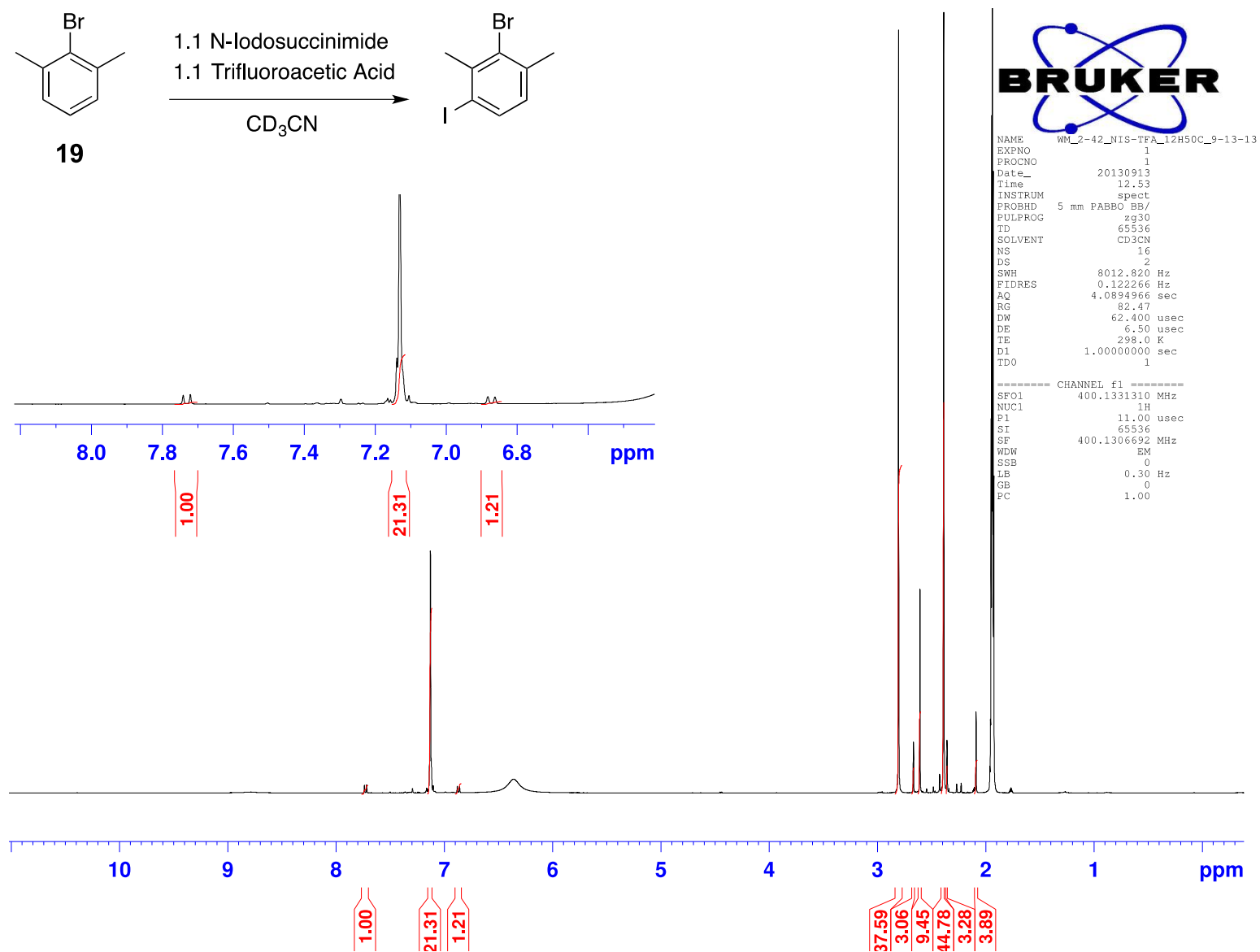


Figure S108. ^1H NMR spectrum of the iodination of **20** by Method A in CD_3CN .

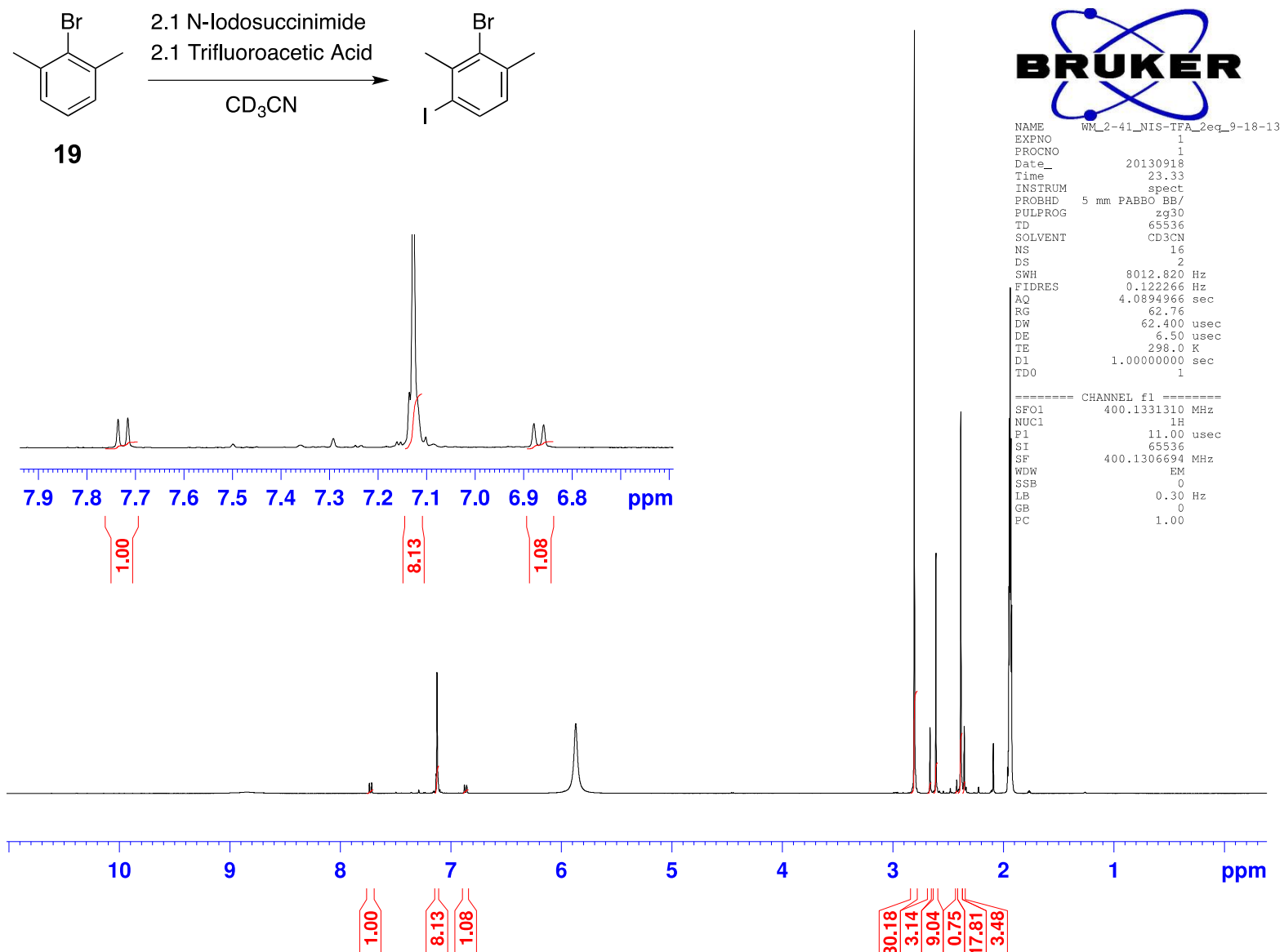


Figure S109. ^1H NMR spectrum of the iodination of **20** by Method B in CD_3CN .

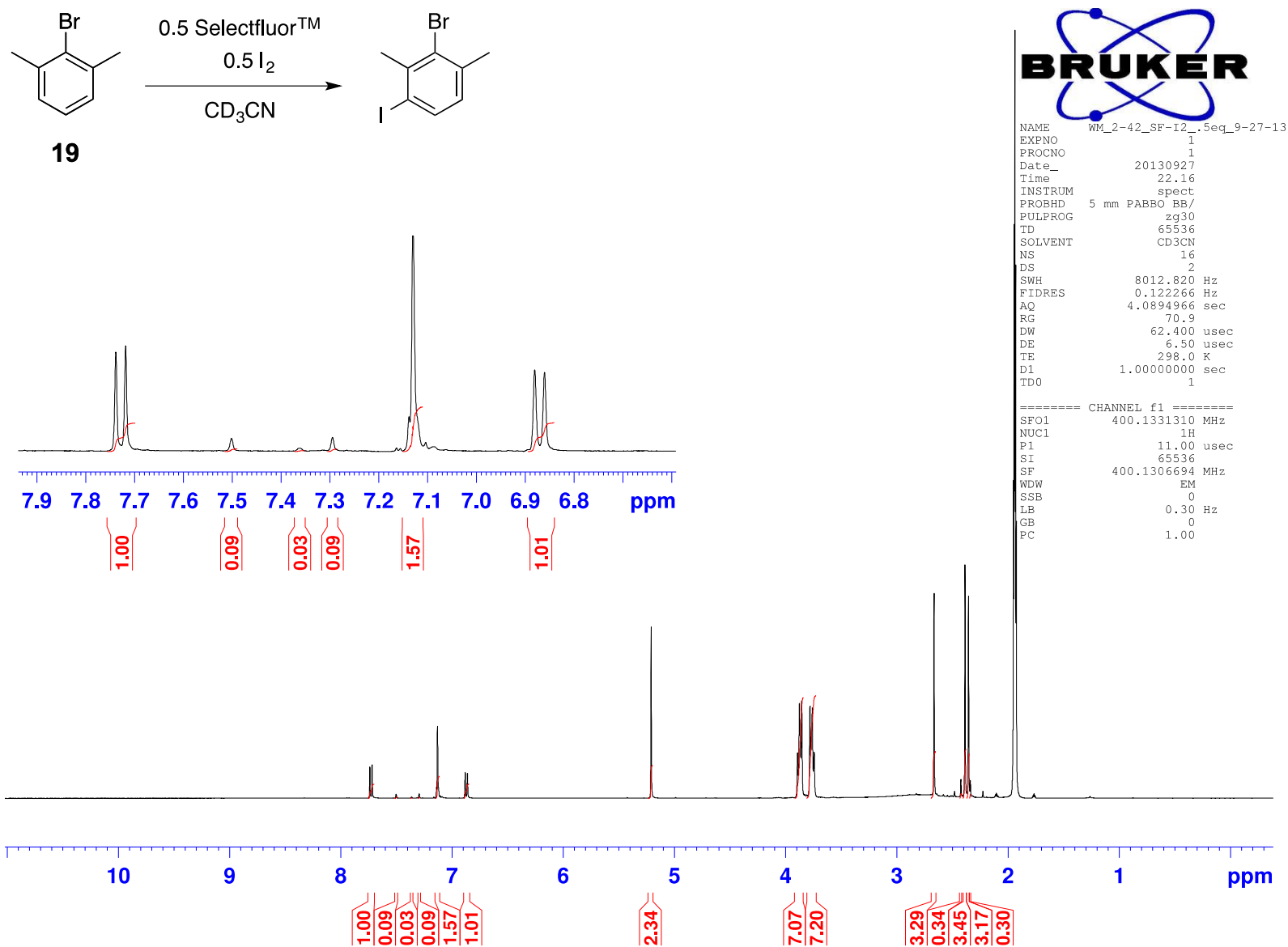


Figure S110. ¹H NMR spectrum of the iodination of **20** by Method C in CD₃CN.

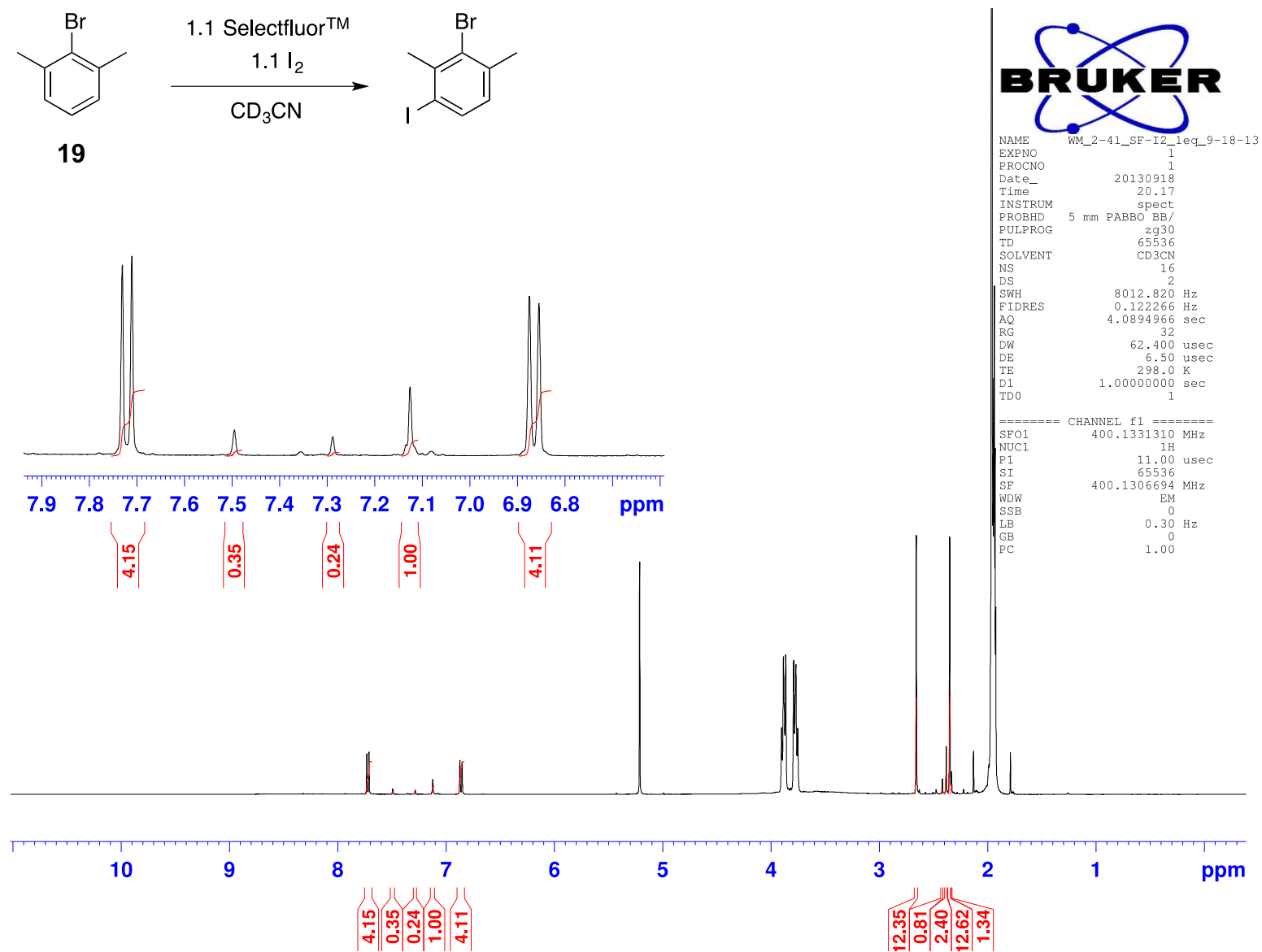


Figure S111. ¹H NMR spectrum of the iodination of **20** by Method D in CD₃CN.

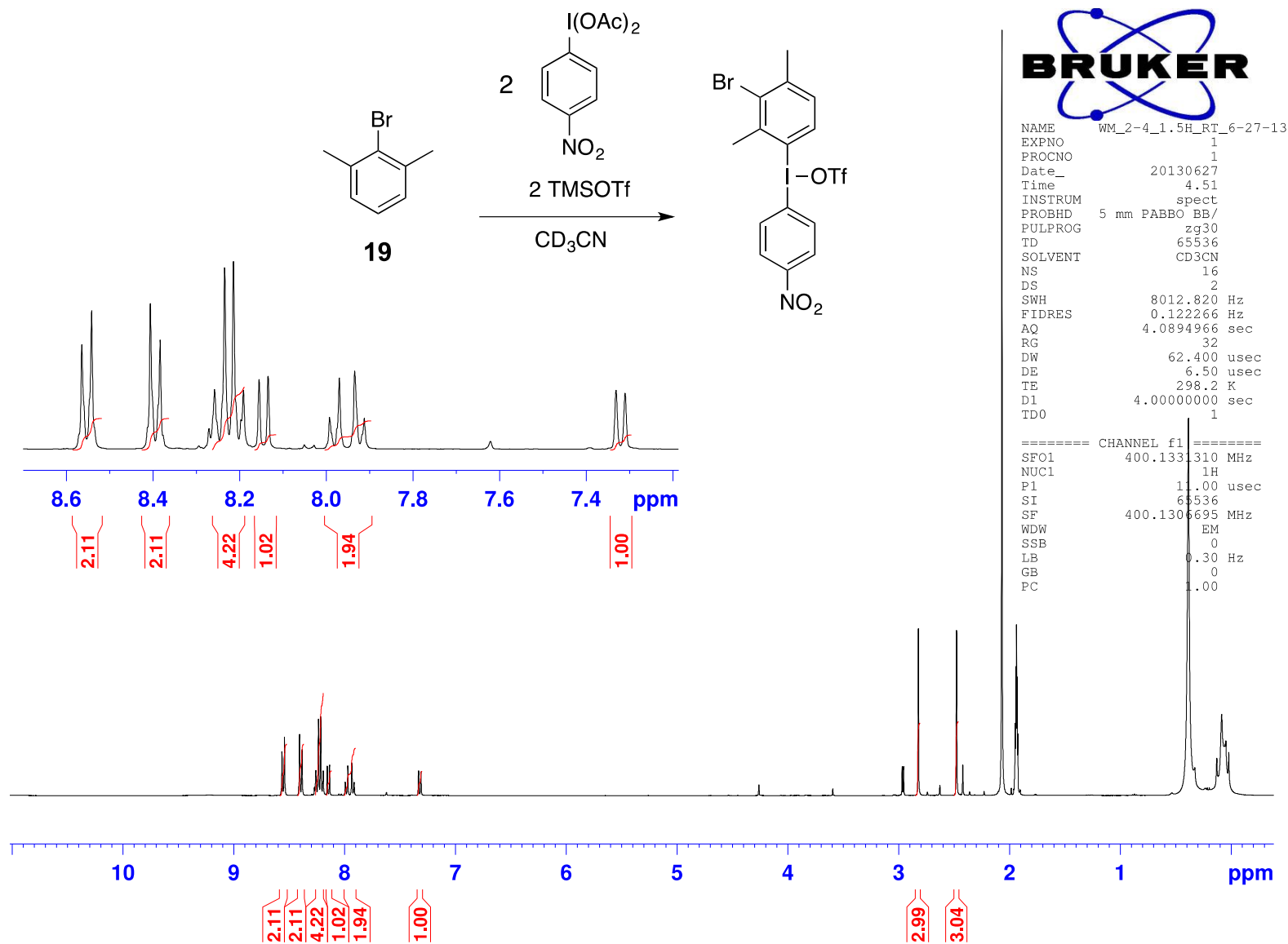


Figure S112. ¹H NMR spectrum of the iodination of **20** by Method E in CD₃CN.

