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# Synthesis of Simplified Azasordarin Analogs as Potential Antifungal Agents

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# Synthesis of Simplified Azasordarin Analogs as Potential Antifungal Agents

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## Abstract

A new series of simplified azasordarin analogs was synthesized using as key steps a Diels–Alder reaction to generate a highly substituted bicyclo[2.2.1]heptane core, followed by a subsequent nitrile alkylation. Several additional strategies were investigated for the generation of the key tertiary nitrile or aldehyde thought to be required for inhibition at the fungal protein eukaryotic elongation factor 2. This new series also features a morpholino glycone previously reported in semisynthetic sordarin derivatives with broad spectrum antifungal activity. Despite a lack of activity against *Candida albicans* for these early de novo analogs, the synthetic route reported here permits more comprehensive modifications of the bicyclic core and structure–activity relationship studies that were not heretofore possible.

## Introduction

The development of resistance to the relatively small number of antifungal agents in clinical use for invasive fungal infections is now of great concern. It is estimated that more than 2 million people die annually of invasive fungal infections, which can have mortality rates of >50%.(1) Additionally, fungi are estimated to destroy approximately 20% of crops worldwide. With increasing resistance observed for both clinical and agricultural antifungals, the identification of new classes of antifungals is an urgent matter.(2−4) In 1965, Sigg and Stoll from Sandoz AG submitted a patent application first describing the natural product sordarin as an antibacterial and antifungal agent.(5) First isolated from the fungus *Sordaria araneosa*,(6) sordarin has a unique tetracyclic diterpene scaffold, with a [2.2.1]heptene at its core with adjacent aldehyde and acid groups (**1**, Figure 1). Attached to the core is an unusual carbohydrate glycone, which can be replaced with a multitude of substituents via semisynthesis, leading to derivatives such as **2** (GW 471558)(7) and **3**.(8)

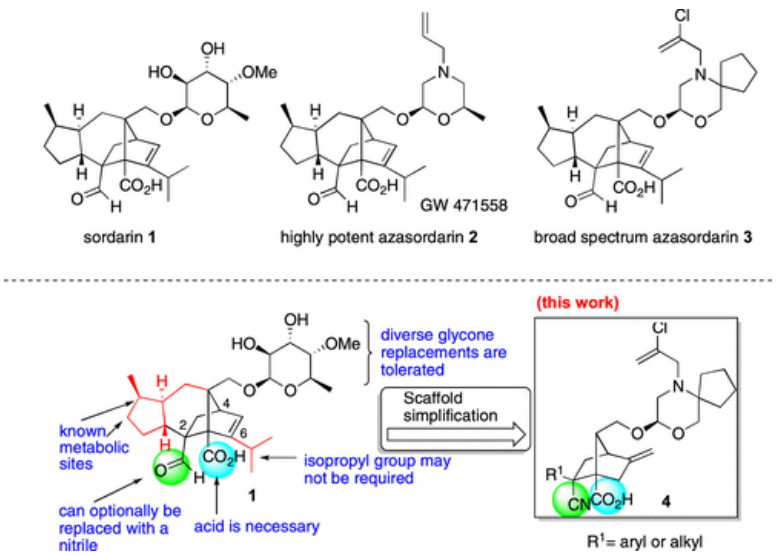



**Figure 1.** Sordarin and two representative azasordarin derivatives (top); known sordarin structure–activity relationship (SAR) and our plan for simplified analogs via scaffold simplification (bottom).

Importantly, the antifungal target of sordarin was later deduced by groups at Merck and Glaxo to be the ribosomal protein eukaryotic elongation factor 2 (eEF2),(9,10) a necessary component of protein synthesis which is a target presently unaddressed by current clinical antifungals. The high potency against fluconazole-resistant fungal strains and selectivity for sordarin derivatives over human eEF2 provided additional impetus for numerous pharmaceutical companies to pursue sordarin derivatives as antifungal agents. The complexity of sordarin as a synthetic target necessitated the near-exclusive pursuit of semisynthetic derivatives, since sordarin can be produced on large scales via fermentation,(11) and the natural glycone easily hydrolyzed and replaced with alternatives that imbue the derivatives with improved properties. Despite these efforts, to our knowledge, no fungal eEF2 inhibitors have reached clinical stages. This manuscript describes our efforts thus far to synthesize novel analogs possessing a simplified bicyclic [2.2.1] scaffold more amenable to systematic

modifications, which could lead to sordarin analogs with improved properties for clinical use. The strategy of identifying natural product pharmacophores and preparing structurally simpler compounds has been conceptualized by Wender (Function-Oriented Synthesis)(12) and has a long and successful history in medicinal chemistry. Important examples include the discovery of morphine-inspired opioids such as fentanyl,(13) synthetic statins such as atorvastatin inspired by the natural HMG-CoA reductase inhibitors compactin and lovastatin,(14,15) and the anticancer drug eribulin identified from the simplification of the sponge metabolite halichondrin B.(16) We believe that this underutilized approach could be fruitfully applied to sordarin.

## Design of Analogs

Semisynthetic replacement of the glycone of sordarin has led to several highly potent and orally active azasordarin analogs against *Candida albicans* such as **2** (Figure 1)(7) as well as a few analogs with a broader spectrum of antifungal activity (e.g., **3**).(8) One liability that has been identified with certain sordarin derivatives is their unsatisfactory metabolic stabilities. Sordarin and its aglycone sordaricin are hydroxylated on the cyclopentane (Figure 1, bottom left) by rat and mouse hepatic fractions.(17) We hypothesize that analogs with alternative scaffolds, particularly those with substituents at the "western" side that are resistant to cytochrome P-450-mediated oxidation, could maintain the pharmacophore for antifungal activity (Figure 1, bottom right) and possess improved pharmacokinetic (PK) profiles. Previous SAR studies have suggested that the key part of the sordarin pharmacophore is the vicinal aldehyde-carboxylic acid, held within the rigid bicyclic framework in a perpendicular orientation which precludes hemiacetal formation.(18) X-ray crystal structures of eEF2 complexed with sordarin have clarified the importance of the aldehyde and acid moieties, which form four hydrogen bonds with bound waters and two backbone amides of eEF2 (Figure 2).(19,20) It should be noted that several potent analogs have been reported where the aldehyde has been replaced with a nitrile.(18) We reasoned that a modified bicyclo[2.2.1]heptane core could maintain a similar dihedral angle between these moieties and permit the identification of novel analogs with comparable potencies to the natural product and its semisynthetic derivatives, but with the potential for improved PK properties. A simplified monocyclic cyclopentane with vicinal aldehyde and acid moieties was previously reported by Cuevas to possess only marginal antifungal activity.(17)

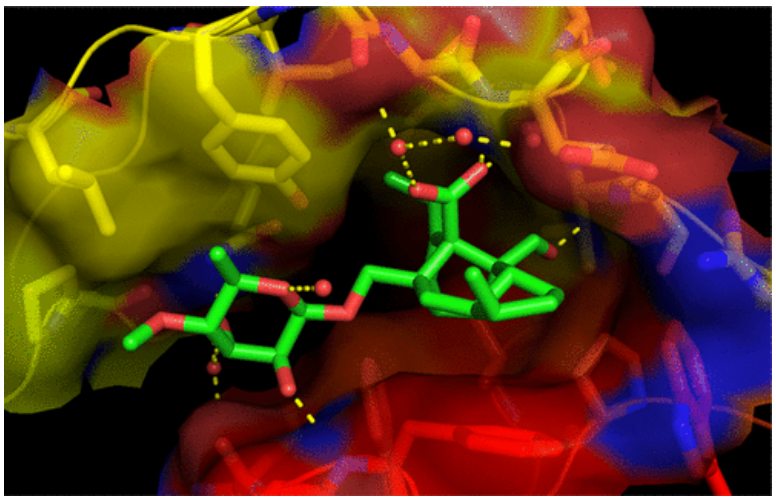
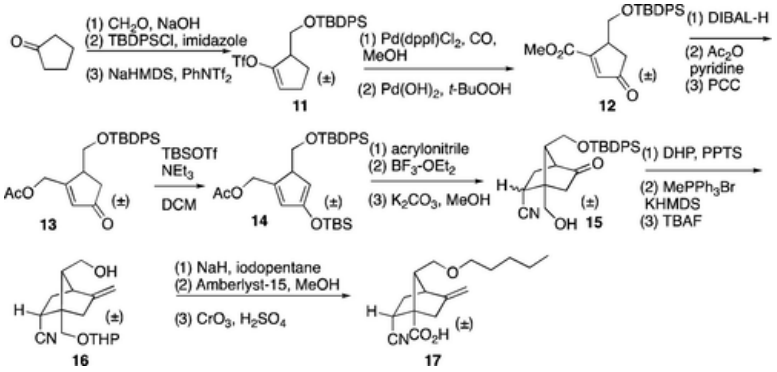


**Figure 2.** X-ray structure of eEF2-sordarin.(19)

Reasoning that the isopropyl group may not be required for activity, and its introduction would complicate the current synthetic routes under consideration, we initially pursued analogs without a substituent at C-6 of the bicycle. Alternatively, the crystal structure suggests that a small group at C-5 could be tolerated, which complements our current synthetic approach. Therefore, primarily for synthetic expediency, we have initially prepared the scaffold present in **4** (Figure 1) possessing an *exo*-methylene at C-5.

As described in our previous report,(21) we successfully established a synthetic route to simplified [2.2.1] bicyclic analogs of sordarin (Scheme 1). This route relied on chromatographic separation of endo/exo Diels–Alder adduct *rac*-**15** to give *endo*-**15**. Subsequent protecting group manipulation followed by Wittig reaction and Jones oxidation furnished simplified alkyl sordarin analog **17**. However, **17** failed to show antifungal activity against several strains of *C. albicans* at concentrations up to 8 μg/mL. We reasoned that this may be attributed to the lack of a complex glycone and/or the lack of a quaternary center at C-2. Therefore, we chose to append to our scaffold a morpholine glycone previously reported in sordarin derivatives showing broad and potent antifungal activity (**3**, Figure 1).(8)




**Scheme 1.** Synthesis of Our First-Generation Sordarin Analogs(21)

To construct the tertiary chiral center at C-2, we have thus far explored five strategies for the preparation of key intermediates **5** that are suitable for the elaboration to the desired analogs **4** (Figure 3). A Diels–Alder approach using 1,1-disubstituted alkenes could be the most convergent approach to **5**. Reactions using silyloxy diene **6** could avert undesired 1,5-hydride or alkyl shifts that are well known for cyclopentadienes(22) but are slowed down by electron-rich diene substituents.(23) The silyloxy group is also a versatile handle for subsequent transformations, and provides the desired regioselectivity for cycloadditions, with the aldehyde/nitrile and carboxylic acid precursors on vicinal carbons in the cycloadducts. The endo/exo diastereoselectivity could also be modified by using suitable Lewis acids. The second approach uses as the key step an asymmetric organocatalytic Diels–Alder reaction reported by Jørgensen,(24) which could also provide highly enantiomerically enriched products via the catalytic enamine intermediate **7**. This approach would also have the advantage of avoiding the need to preactivate the diene component via silylenol ether formation. The third approach also involves a formal [4 + 2] cycloaddition reaction, but one which could proceed via a double Michael addition mechanism. In this proposed reaction, enolate **8** could add to the dienophile to generate a second enolate, which could subsequently cyclize by adding back to the resulting enone. The fourth strategy, which depends on a prior cycloaddition reaction, is to install the nitrile on the endo face of the bicycle by the addition of cyanide to an intermediate carbocation **9**. The fifth strategy leverages our prior cycloaddition reactions with acrylonitrile,(21) but uses a subsequent $S_NAr$ or $S_N2$ substitution reaction to introduce the aryl or alkyl substituent via the exo face of the bicycle.

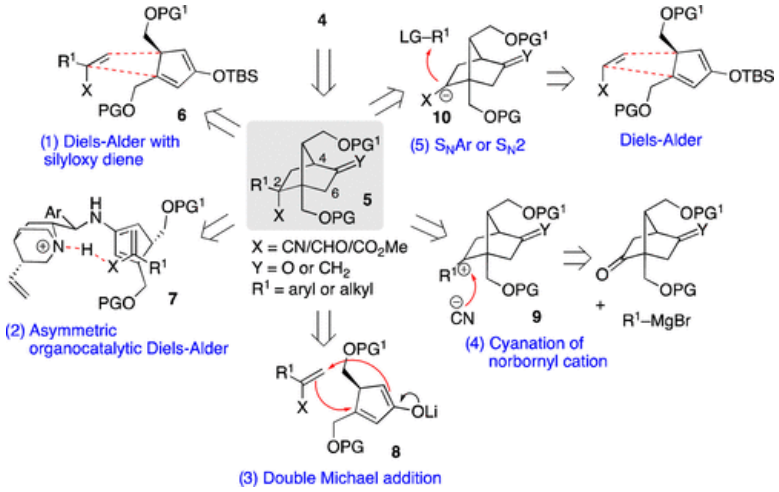
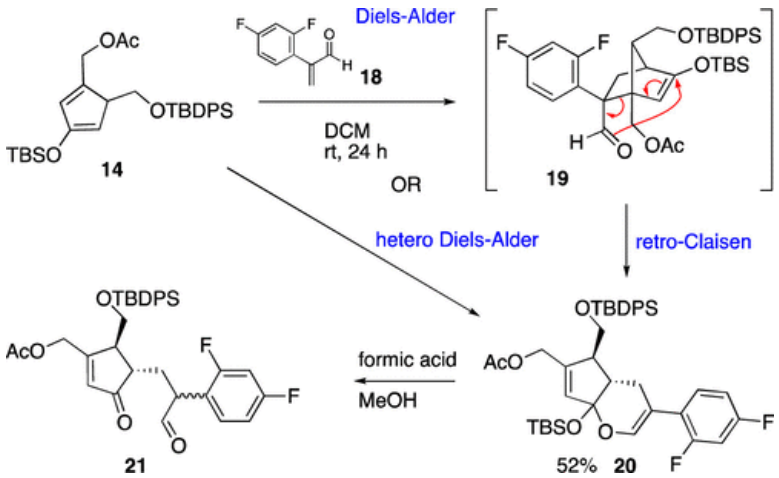



**Figure 3.** Proposed strategies for constructing the desired bicyclo[2.2.1]heptane core with quaternary center at C-2. PG = protecting group, LG = leaving group.

# Results and Discussion

## Diels–Alder with Silyloxy Diene

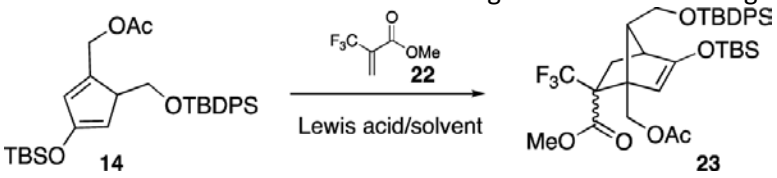
Our initial target compounds possess a fluorinated aryl group as $R^1$ (**4**, Figure 1), which we hypothesize should fit into the lipophilic portion of the eEF2 binding pocket occupied by the cyclopentane ring of sordarin. The installation of such aryl substituents has proven to be challenging thus far. Our initial attempt used the 2-aryl-acrolein **18**, but instead of the desired adduct **19**, the unexpected dihydropyran **20** was obtained (Scheme 2). This product could be generated from either a retro-Claisen rearrangement of **19** or an inverse electron demand, hetero Diels–Alder reaction. Davies reported that Lewis acid-catalyzed reactions of cyclopentadiene and 2-arylacroleins generated mixtures of bicyclo[2.2.1]heptenes and dihydropyrans analogous to **19** and **20**, with the heptenes able to convert to the dihydropyrans.(25) One notable difference in our case is that the dihydropyran was the only product observed. The aldehyde-containing Diels–Alder adduct and its rearranged product are expected to be in equilibrium, with the ratio determined in part by the ring strain and extent of conjugation of the α-substituent (in this case, a fluorinated arene).(26) Silyl ketal **20** is an unstable species that decomposed to racemic aldehyde **21** upon treatment with formic acid in methanol or after storage in the freezer (−20 °C) for a month dissolved in dichloromethane (DCM) under neutral conditions. The most straightforward way to circumvent the undesired hetero Diels–Alder reaction could be to use the nitrile or ester counterparts of **18**, but unfortunately these dienophiles failed to give any cycloadducts with **14**.



**Scheme 2.** Diels–Alder/Retro-Claisen or Hetero Diels–Alder Reaction of Enal **18**

To potentially circumvent the lack of Diels–Alder reactivity of acrylates, we turned our attention to the α,β-unsaturated ester **22** with a more highly activating trifluoromethyl methyl group to decrease the lowest unoccupied molecular orbital level of the dienophile. The trifluoromethyl group is also a desirable substituent for our medicinal chemistry studies due to its lipophilic but metabolically stable profile. After extensive screening of different solvents and Lewis acids, we learned that diene **14** was indeed not compatible with most Lewis or Brønsted acids (e.g., trifluoroethanol, Table1, entry 15), as reported by Gleason for a related OTBS-substituted cyclopentadiene.(23)Lewis acids that were compatible with **14** ($Mg(OTf)_2$, $Mg(ClO_4)_2$, and $Eu(hfc)_3$; entries 4, 18, and 19) did not give any endo selectivity. The diastereomers were tentatively assigned based on a report by Ishihara characterizing endo/exo isomers with the same dienophile.(27) The diastereoselectivity can be tilted slightly by using different solvents; the highest exo selectivity was achieved in DCM (Table1, entries 8 and 9), and the most endo-selective reaction was in hexanes (Table1, entry 11). Due to the low tolerance of **14** to Lewis acids, we did not pursue alternative dienophile/Lewis acid combinations to increase the proportion of the desired endo cycloadducts, though we anticipate that bulkier substituents than $CF_3$ may favor the desired endo cycloadducts.

**Table 1.** Solvent and Lewis Acid Screening for Diels–Alder Using 22a




| entry | solvent | temp. (°C) | Lewis acide | endo/exob | yieldc |
|---|---|---|---|---|---|
| **1** | **DCM** | **–78 to rt** | **$InCl_3$** | **N/A** | **decomp.** |
| **2** | **DCM** | **–78 to rt** | **$ZnBr_2$** | **N/A** | **decomp.** |
| **3** | **DCM** | **–78 to rt** | **$Yb(OTf)_3$** | **N/A** | **decomp.** |
| **4** | **DCM** | **–78 to rt** | **$Mg(OTf)_2$** | **0.75** | **68%** |
| **5** | **DCM** | **–78 to rt** | **$Zn(OTf)_2$** | **N/A** | **decomp.** |
| **6** | **DCM** | **–78 to rt** | **$Eu(OTf)_3$** | **N/A** | **decomp.** |
| **7** | **DCM** | **–78 to rt** | **K-10** | **N/A** | **decomp.** |
| **8** | **DCM** | **–78 to rt** | | **0.67** | **83%** |
| **9** | **DCM** | **rt** | | **0.71d** | **40%d** |
| **10** | **THF** | **rt** | | **0.82** | **85%** |
| **11** | **hexanes** | **rt** | | **1.04** | **96%** |
| **12** | **MeCN** | **rt** | | **0.85** | **91%** |
| **13** | **acetone** | **rt** | | **0.8** | **63%** |
| **14** | **MeOH** | **rt** | | **0.93** | **86%** |
| **15** | **$F_3CCH_2OH$** | **rt** | | **N/A** | **decomp.** |
| **16** | **$PhCF_3$** | **rt** | | **0.83** | **100%** |
| **17** | **EtOAc** | **rt** | | **0.78** | **74%** |
| **18** | **MeCN** | **rt** | **$Mg(ClO_4)_2$** | **0.87** | **98%** |
| **19** | **$CDCl_3$** | **rt** | **$Eu(hfc)_3$** | **0.62** | **trace** |

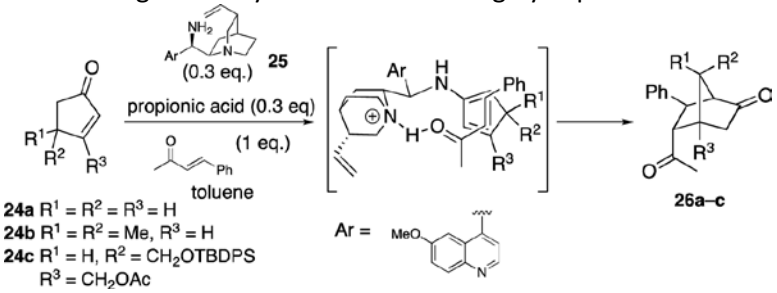
[a] Diene was washed with phosphate buffer (pH 7) before using; all experiments were run for 24 h.
[b] Diastereomers were assigned based on a previously reported analog,(27) and the ratio was determined with 19F NMR.
[c] NMR yield using pentachloroethane as an internal standard, unless otherwise specified.
[d] Isolated yield.

[e] 1 equiv except for entry 18 (0.9 equiv) and entry 19 (0.2 equiv). decomp. = diene decomposed to 13. K-10 = montmorillonite K-10. Eu(hfc)3 = europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. rt = room temperature (22–23 °C).

## Asymmetric Organocatalytic Diels–Alder

To achieve an endo-selective Diels–Alder reaction and avoid the acid sensitivity of diene **14**, we examined the organocatalytic asymmetric Diels–Alder reaction reported by Jørgensen.(24) The quinidine-derived amine catalyst **25** worked smoothly with cyclopentenone (Table2, entry 1), as was reported. However, we were not able to extend the scope to include 4-substituted cyclopentenones (entries 2 and 3). When the C-4 position of the cyclopentenone is disubstituted, the reaction did not proceed (entry 2), likely because the transition state is disrupted by the steric repulsion between the dienamine intermediate and the dienophile. When the C-4 position is monosubstituted (**24c**), the enone was consumed, but no cycloaddition products were observed (entry 3).

**Table 2.** Organocatalytic Diels–Alder using Cyclopentenones 24

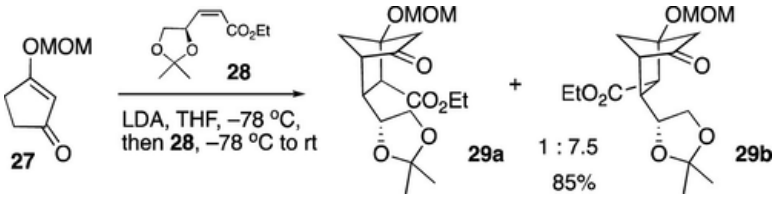



| entry | enone | *T*/*t* | result |
|---|---|---|---|
| **1** | **24a** | **60 °C, 3 days** | **100% conversion to 26a**[a] |
| **2** | **24b** | **60 °C, 3 days; 100 °C, 24 h** | **NR**[a] |
| **3** | **24c** | **60 °C, 2 days** | **decomposed 24c**[b] |

[a] Determined by gas chromatography–mass spectrometry.
[b] Determined by 1H NMR.

# Double Michael Addition

Inspired by Yamada's reports of stereoselective sequential Michael reactions using enolates generated from 3-alkoxy-cyclopentenones to generate [2.2.1] bicyclic adducts (Scheme 3),(28) we explored an analogous reaction starting from our enone **24c** and model enone **24b**. These were treated with lithium diisopropylamide (LDA) to give their corresponding lithium enolates, followed by the addition of an initial Michael acceptor. However, all enolates were unreactive in the presence of several Michael acceptors under a number of different conditions (Table3). Despite the fact that the cyclopentanone can be smoothly deprotonated, as demonstrated by $D_2O$ quench (entry 8), use of Michael acceptors with different reactivities ranging from methyl 2-(4-fluorophenyl)acrylate to acrylonitrile did not change the result. The addition of hexamethylphosphoramide (HMPA) (entries 2, 15, 11, 13) or heating (entries 10–13) was not able to initiate the desired reaction as well. Upon work up, the cyclopentenones **24b**–**c** were recovered. This inactivity could be explained by the lack of an electron-donating alkoxy group at C3 of **24b**–**c**. In the case of **24b**, the methyl group at C-4 proximal to the approaching Michael acceptor likely prevented its reaction due to steric hindrance (entries 9–11).




**Scheme 3.** Sequential Michael Reaction Reported by Yamada(28)

**Table 3.** Attempted Double Michael Addition

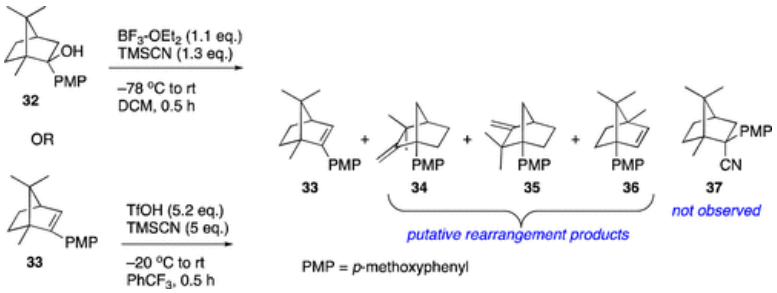

| entry | enone | Michael acceptor[b] | conditions[a] | additive | result[c] |
|---|---|---|---|---|---|
| **1** | **24c** | **$R^1$ = 4-FPh, $R^2$ = $CO_2Me$** | **A** | **none** | **NR** |
| **2** | **24c** | **$R^1$ = 4-FPh, $R^2$ = $CO_2Me$** | **A** | **HMPA (1 equiv)** | **NR** |
| **3** | **24c** | **$R^1$ = 4-FPh, $R^2$ = $CO_2Me$** | **A** | **none** | **NR** |
| **4** | **24c** | **$R^1$ = $CF_3$, $R^2$ = $CO_2Me$** | **A** | **none** | **NR** |
| **5** | **24c** | **$R^1$ = $CF_3$, $R^2$ = $CO_2Me$** | **A** | **HMPA (1 equiv)** | **NR** |
| **6** | **24c** | **$R^1$ = $CF_3$, $R^2$ = $CO_2Me$** | **A** | **none** | **NR** |
| **7** | **24c** | **acrolein** | **A** | **none** | **NR** |
| **8** | **24c** | **none, quenched with $D_2O$** | **A** | **none** | **deut.[d]** |
| **9** | **24c** | **$R^1$ = H, $R^2$ = $CO_2Et$** | **A** | **none** | **NR** |
| **10** | **24c** | **$R^1$ = 4-FPh, $R^2$ = $CO_2Me$** | **B** | **none** | **NR** |
| **11** | **24c** | **$R^1$ = 4-FPh, $R^2$ = $CO_2Me$** | **B** | **HMPA (1 equiv)** | **NR** |
| **12** | **24c** | **$R^1$ = $CF_3$, $R^2$ = $CO_2Me$** | **B** | **none** | **NR** |
| **13** | **24c** | **$R^1$ = $CF_3$, $R^2$ = $CO_2Me$** | **B** | **HMPA (1 equiv)** | **NR** |
| **14** | **24b** | **$R^1$ = H, $R^2$ = $CO_2Et$** | **A** | **none** | **NR** |
| **15** | **24b** | **acrylonitrile** | **A** | **none** | **NR** |
| **16** | **24b** | **$R^1$ = 4-FPh, $R^2$ = $CO_2Me$** | **A** | **none** | **NR** |

[a] Condition A: enones were deprotonated at −78 °C, followed by the addition of the Michael acceptor. All experiments except for entry 8 were kept at −78 °C for 2 h, then warmed up to rt and stirred for 22 h. Entry 8 was quenched at −78 °C after LDA deprotonation; condition B: enones were deprotonated at −78 °C, followed by the addition of the Michael acceptor, then warmed up to rt and refluxed for 3 h.
[b] 2 equiv of Michael acceptor were used in entries 1–13, each, and 1.2 equiv in entries 14–16.
[c] NR = no reaction.
[d] deut. = deuteration of α-carbon confirmed by 1H NMR.

## Hydrocyanation

We reasoned that the use of a bicyclic[2.2.1]ketone substrate could be advantageous, because it could permit the ready generation of varied aryl-containing analogs (e.g., **32**) via arylmetal 1,2-addition reactions, followed by the conversion of the resulting alcohols to nitriles via intermediate carbocations (**9**, Figure 3). However, one disadvantage of the tertiary alcohol to nitrile conversion is that it may only be high yielding for electron-rich arenes able to facilitate the $S_N1$-type transformation. Cyanation of a *p*-methoxylphenyl-stabilized tertiary cation has been reported with monocyclic substrates,(29−31) and there are also examples of trapping tertiary 2-norbornyl cations with nucleophiles,(32) without the extensive Wagner–Meerwein rearrangements of these nonclassical carbocations. We reasoned that an aryl substituent at the 2-position of the norbornane could inhibit rearrangements and permit trapping of the carbocation intermediate by a cyanide nucleophile at the 2-position. We examined this strategy using model systems formed by treating camphor with 4-methoxyphenyl

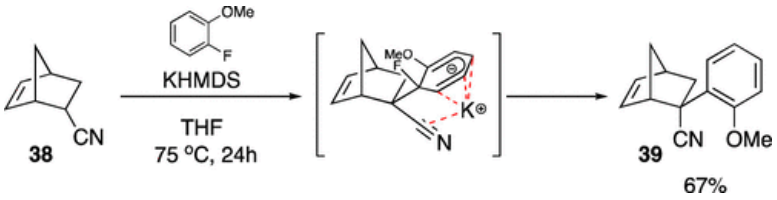
magnesium bromide to generate alcohol **32**, followed by acidic dehydration to generate **33**. These were separately reacted with two different acids and TMSCN (Scheme 4). Upon treatment with $BF_3$–$OEt_2$ and TMSCN, **32** quickly dehydrated and rearranged to give an inseparable mixture of dehydration product **33** and three other inseparable alkene products with GC–MS and NMR analysis consistent with Wagner–Meerwein and Nametkin rearrangements. The desired cyanation product **37** was not observed. Trapping of 2-norbornyl cation generated from **33** using TfOH and TMSCN(30)was also unsuccessful at a higher temperature (20 °C).




**Scheme 4.** Attempted Cyanation of Camphor-Derived Alcohol **32** and Alkene **33**

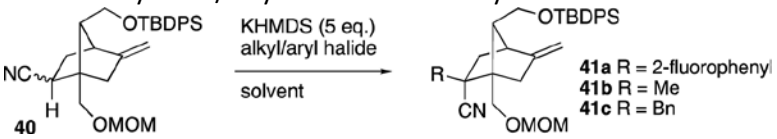
## $S_NAr$ and $S_N2$ Substitutions

An endo-selective $S_NAr$ reaction with 2-cyano-5-norbornene and aryl fluoride reported by Caron(33) suggested a promising path to desirable α-arylated nitriles (Scheme 5). In this approach, nitriles can be deprotonated with KHMDS and reacted with both electron-rich and electron-poor aryl fluorides, with **39** reported as a single (endo), presumably thermodynamic, diastereomer. We chose nitrile **40** to examine this approach for our application (Table4). Under Caron's optimal conditions, **40** did not undergo the $S_NAr$ substitution with 1,2-difluorobenzene (entry 1). When forcing conditions were applied (1,2-difluorobenzene as the solvent, 115 °C), only a trace amount of **41a** was observed via liquid chromatography–mass spectrometry (LC–MS), and most of **40** was decomposed, as followed by thin layer chromatography (TLC) (entry 2). We hypothesize that the substituted bridgehead next to the reaction center obstructed the approach of the arene electrophile. However, alkylation reactions were successful using iodomethane and benzyl bromide as electrophiles with quantitative conversion (entries 4 and 5). Single diastereomeric products were also characterized, which we presume are the endo products generated from the attack at the less hindered face of the nitrile anion, in accordance with Caron's report.(33)




**Scheme 5.** $S_NAr$ Reported by Caron(30) Using 2-Cyano-5-norbornene

**Table 4.** Arylation/alkylation of Secondary Nitrile 40



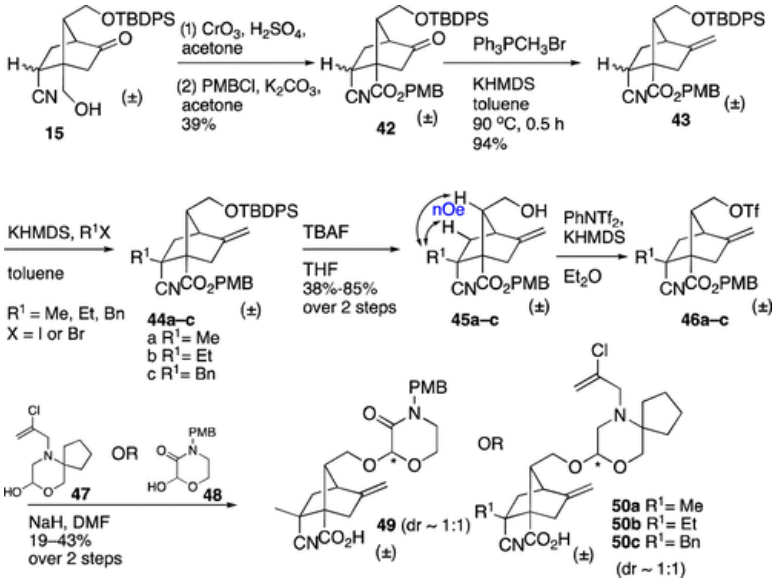

| entrya | electrophile | solvent | conditions | results |
|---|---|---|---|---|
| 1 | 1,2-difluorobenzene (4 equiv) | THF | 75 °C, 12 h | NRb |
| 2 | 1,2-difluorobenzene (excess) | neat | 90–115 °C, 24 h | trace 41ab |
| 3 | 1,2-difluorobenzene (50 equiv) | toluene | 18-crown-6 (1 equiv), 100 °C 12 h | NRb |
| 4 | MeI (45 equiv) | toluene | 55 °C, 12 h | quant. 41bc |

| | | | | |
|---|---|---|---|---|
| 5 | BnBr (5.5 equiv) | toluene | 55 °C, 12 h | quant. 41cc |

[a] To a solution of 40 (2 mg, 0.01 M) was added the indicated amount of electrophile followed by KHMDS.
[b] Observed by LC–MS.
[c] Estimated NMR yield using pentachloroethane as an internal standard. NR = no reaction.

## Synthesis of Azasordarin Analogs

We thus commenced our second-generation synthesis from the key intermediate **15**,(21) we reported previously (Scheme 6). First, the bridgehead primary alcohol of **15** was oxidized to the carboxylic acid and protected using PMBCl to provide ester **42**. In previous studies, deprotonation of the carbon α to the ketone in a compound similar to **42** caused ring opening through a retro-Michael pathway. In part to avoid this complication, **42** was subjected to a Wittig reaction to give olefin **43**. Normal Wittig conditions resulted in a very sluggish reaction, presumably due to steric hindrance from the TBDPS ether; however, generation and reaction of the required ylide at high temperature (90 °C) yielded alkene **43** in nearly quantitative yield. The nitrile α-carbon of **43** was deprotonated by KHMDS and alkylated with three different alkyl halides to give exclusively the desired *endo* nitrile products, thus eliminating a significant weakness of our first-generation synthesis which had to rely on chromatographic separation of endo/exo diastereomers. The resulting compounds **44a**–**c** were treated with TBAF to give primary alcohols **45a**–**c**. Stereochemistry was confirmed at this stage, with nOe observed between $R^1$and its two neighboring protons, as shown in Scheme 6. Protons were first assigned using a COSY experiment, then nOe signals were measured between H-10 and H-7 of **45a**–**c**, as depicted in the Supporting Information. In the case of **45a**, nOe between the *exo*-methyl protons and 5-$H_{exo}$ was also observed.




**Scheme 6.** Synthesis of Azasordarin Analogs

**45a**–**c** were then activated with $PhNTf_2$ to give triflates **46a**–**c**. The glycones **47** and **48** were prepared using modifications of a reported protocol;(34)though **48** has not previously been used in sordarin analogs, its ease of synthesis and similarity to other *N*-PMB morpholine-based glycones(7)inspired us to try it. Glycosidation(35) of triflates **46** with glycones **47** and **48**proceeded smoothly, and to our surprise, the PMB ester was also cleaved during these transformations to give the desired bridgehead carboxylic acids **49** and **50a**–**c.** These reactions proceeded in dimethylformamide (DMF) but did not work in tetrahydrofuran (THF). **50a**–**c** were obtained exclusively with what we assume to be the aglycones in the equatorial positions at the anomeric carbon. This is also consistent with the increased nucleophilicity of the β-anomer of 1-*O*-lithiated pyranoses in their reactions with alkyl triflates, leading to the highly selective formation of β-

glycosides.(36,37) The $^1$H NMR splitting of the anomeric proton of **47** in dry $CDCl_3$ (4.94 (ddd, *J* = 9.0, 3.9, 2.2 Hz)) is consistent with the hydroxyl group in the axial position due to the anomeric effect (the 9.0 Hz coupling is due to the splitting by OH). However, the diastereomeric anomeric protons in **50a** (see expansion in NMR spectrum in the Supporting Information) have larger coupling constants of 4.9 and 5.5 Hz (versus 3.9 Hz of **47**), which is more consistent with an equatorial disposition of the aglycone. Fuller and co-workers determined X-ray structures of triterpene natural product derivatives containing a morpholine-based glycone with an equatorial substitution at the anomeric position, with reported coupling constants of 4.1–6.8 Hz.(38) Ultimately, an X-ray structure may be needed with related azasordarin analogs in the future to confirm this assignment. Since we generated racemic intermediates via this synthetic route, the final compounds **49** and **50a**–**c** represent an approximate 1:1 mixture of racemic diastereomers, as observed by NMR.

### In Vitro Antifungal Testing

The isomeric mixtures **49** and **50a**–**c** were subjected to antifungal microdilution assays using Clinical and Laboratory Standards Institute methods M27-A3 and M38-A2 at the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio. No inhibition of fungal growth was observed at up to 8 or 4 μg/mL (**50c**), against *C. albicans*(isolate# CA1, CA2, CA3), *Aspergillus fumigatus* (isolate# AF1, AF2, AF3), *Candida parapsilosis* (CLSI QC), and *Paecilomyces variotii* (CLSI QC). Minimum inhibitory concentrations (MICs) were determined after 24 or 48 h (*A. fumigatus*), using fluconazole and voriconazole as positive controls. For comparison, sordarin itself has a reported MIC of 16 μg/mL vs wild type *C. albicans* (strain A28235),(39) and the azasordarin **3** was <0.008 μg/mL.(8)

## Conclusions

After examining numerous strategies to stereoselectively furnish the key tertiary nitrile on the bicyclo[2.2.1]heptane core, we have established a second-generation synthesis that enables the incorporation of substituents at the C-2 position. The key step was the highly endo-selective alkylation of bicyclic nitrile **43**, which was generated via the Diels–Alder reaction, as described in our previous report.(21) Additionally, our synthetic route facilitates the late stage incorporation of diverse glycones. Although the synthesized analogs **49** and **50a**–**c** failed to show activity as isomeric mixtures against several fungal species (at concentrations up to 8 μg/mL), this new synthetic route to azasordarin analogs will permit additional SAR studies not previously feasible.

## Experimental Section

### General Information

Unless otherwise noted, all reagents and solvents, including anhydrous solvents, were purchased from commercial vendors and used as received. Reactions were performed in ventilated fume hoods with magnetic stirring and heated in oil baths, unless otherwise noted. Reactions were performed in air, unless otherwise noted. Chilled reactions (below −10 °C) were performed in an acetone bath in a vacuum dewar, using a Neslab CC 100 immersion cooler. Unless otherwise specified, reactions were not run under $N_2$atmosphere. Deionized water was purified by charcoal filtration and used for reaction workups and in reactions with water. NMR spectra were recorded on Varian 300 or 400 MHz spectrometers as indicated. Proton and carbon chemical shifts are reported in parts per million (ppm; δ) relative to tetramethylsilane ($^1$H δ 0), or $CDCl_3$ ($^{13}$C δ 77.16), $(CD_3)_2CO$ ($^1$H δ 2.05, $^{13}$C δ 29.84), DMSO-$d_6$ ($^1$H δ 2.50, $^{13}$C δ 39.5), or $CD_3OD$ ($^1$H δ 3.31, $^{13}$C δ 49.00). NMR data are reported as follows: chemical shifts, multiplicity (obs = obscured, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex overlapping signals); coupling constant(s) in hertz; integration. Unless otherwise indicated, NMR data were collected at 25 °C. Filtration was performed by vacuum using VWR Grade 413 filter paper, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on Agela Technologies glass plates with 0.20 mm silica gel with F254 indicator. Visualization was accomplished with UV light (254 nm) and $KMnO_4$ stain, unless otherwise noted. Flash chromatography was

performed using Biotage SNAP cartridges filled with 40–60 μm silica gel on Biotage Isolera automated chromatography systems with photodiode array UV detectors. Unless otherwise mentioned, columns were loaded with crude compounds as DCM solutions. Tandem liquid chromatography/mass spectrometry (LC–MS) was performed on a Shimadzu LCMS-2020 with an autosampler, a photodiode array detector, and a single-quadrupole MS with ESI and APCI dual ionization, using a Peak Scientific nitrogen generator. Unless otherwise noted, a standard LC–MS method was used to analyze reactions and reaction products: Phenomenex Gemini C18 column (100 × 4.6 $mm^2$, 3 μm particle size, 110 A pore size); column temperature 40 °C; 5 μL of sample in MeOH or $CH_3CN$ at a nominal concentration of 1 mg/mL was injected, and peaks were eluted with a gradient of 25–95% $CH_3CN/H_2O$ (both with 0.1% formic acid) over 5 min, then 95% $CH_3CN/H_2O$ for 2 min. Purity was measured by UV absorbance at 210 or 254 nm. Preparative liquid chromatography was performed on a Shimadzu LC-20AP preparative high-performance liquid chromatography (HPLC) with autosampler, dual wavelength detector, and fraction collector. Samples purified by preparative HPLC were loaded as dimethyl sulfoxide (DMSO) solutions. Chemical names were generated, and selected chemical properties were calculated using either ChemAxon Marvin suite or ChemDraw Professional 15.1. NMR data were processed using either MestreNova or ACD/NMR Processor Academic Edition software. High-resolution mass spectra (HRMS) were obtained at the University of Cincinnati Environmental Analysis Service Center (EASC) with an Agilent 6540 Accurate-Mass with Q-TOF. Catalyst **25** was prepared according to a published protocol.(40)

### (7a-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-(2,4-difluorophenyl)-4,4a,5,7a-tetrahydrocyclopenta[b]pyran-6-yl)methyl acetate (20)

To a solution of enal **18** (49.7 mg, 0.296 mmol) in DCM (2.7 mL) was added cyclopentadiene **14** (94.6 mg, 176 μmol) in DCM (3 mL), and the mixture was stirred at rt for 24 h. TLC (10% EtOAc/hexanes) indicated complete consumption of the starting material, so the mixture was concentrated and purified on a 10 g $SiO_2$ column (30% DCM/hexanes) to give **20** (64.2 mg, 52%) as a yellow oil. $^1$H NMR (300 MHz, acetone-$d_6$) δ 7.76–7.60 (m, 4H), 7.52–7.33 (m, 6H), 7.26 (td, *J* = 9.0, 6.6 Hz, 1H), 7.06–6.90 (m, 2H), 6.78 (d, *J* = 1.7 Hz, 1H), 5.93 (d, *J* = 1.8 Hz, 1H), 4.77 (qt, *J* = 14.7, 1.4 Hz, 2H), 3.89 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.80 (dd, *J* = 10.7, 4.7 Hz, 1H), 2.83 (s, 1H), 2.74–2.61 (comp, 3H), 2.03 (s, 3H), 1.05 (s, 9H), 0.91 (s, 9H), 0.22 (s, 3H), 0.16 (s, 3H). $^{13}$C{$^1$H} NMR (75 MHz, acetone-$d_6$) δ 170.7, 144.8, 144.0, 143.9, 136.5, 136.4, 134.2 (d, *J* = 9.8 Hz), 132.0, 130.9, 130.9, 130.8, 130.7, 128.9, 128.8, 124.55 (t, *J* = 19.8 Hz), 112.16 (dd, *J* = 20.9, 3.6 Hz), 107.7, 105.06 (d, *J* = 25.9 Hz), 104.9, 64.1, 62.4, 50.3, 46.9, 27.4, 26.2, 23.6, 20.8, 20.0, 18.5, −2.8. Decomposed to give **21**under LC–MS conditions (formic acid/MeOH).

### (5-(((tert-Butyldiphenylsilyl)oxy)methyl)-4-(2-(2,4-difluorophenyl)-3-oxopropyl)-3-oxocyclopent-1-en-1-yl)methyl acetate (21)

To a solution of **20** (9.9 mg, 14 μmol) in MeOH (1 mL) in a 4 mL vial was added formic acid (50 μL, 1.2 mmol). After 5 min, TLC (10% EtOAc/hexanes) indicated the complete consumption of **21**, so the reaction mixture was concentrated and purified by chromatography on a silica gel-packed pipette (10–20% EtOAc/hexanes) to give aldehyde **21** (1:1 diastereomeric mixture, 6.0 mg, 73%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, *J* = 1.4 Hz, 1H), 9.58 (t, *J* = 1.0 Hz, 1H), 7.66–7.49 (comp, 8H), 7.48–7.33 (comp, 12H), 7.25–7.15 (m, 1H), 7.02 (td, *J* = 8.5, 6.2 Hz, 1H), 6.89–6.74 (comp, 4H), 6.11 (q, *J* = 1.7 Hz, 1H), 6.06 (q, *J* = 1.7 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 17.4 Hz, 1H), 4.83–4.73 (m, 2H), 4.27 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.95 (dd, *J* = 8.2, 5.6 Hz, 1H), 3.77 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.64 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.59 (d, *J* = 5.0 Hz, 3H), 2.73–2.58 (m, 3H), 2.38 (ddd, *J* = 13.9, 9.9, 5.3 Hz, 1H), 2.21–2.14 (m, 2H), 2.13 (s, 3H), 2.11 (s, 3H), 2.05–1.94 (m, 1H), 1.84 (ddd, *J* = 14.5, 9.4, 5.6 Hz, 1H), 1.01 (s, 9H), 0.97 (d, *J* = 2.6 Hz, 9H). $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 208.8, 208.5, 199.0, 198.5, 174.5, 172.0 (dd, *J* = 263.0, 2.6 Hz), 135.7, 135.7, 135.6, 135.6, 132.9, 132.6, 132.6 (dd, *J* = 18.6, 6.2 Hz), 131.2, 131.1, 130.2, 130.2, 130.2, 129.2 (d, *J* = 10.6 Hz), 128.0, 112.3 (dd, *J* = 21.3, 3.5 Hz), 112.1 (dd, *J* = 20.9, 4.0 Hz), 111.9, 104.64 (t, *J* = 25.7 Hz), 64.0, 63.5, 62.8, 62.5, 51.2, 51.0, 50.2, 49.3, 46.2, 45.5, 30.4, 30.0, 29.9, 26.9, 26.8, 20.8, 20.8, 19.3, 19.3. HRMS (ESI$^+$): calcd for $C_{34}H_{36}F_2NaO_5Si$ $[M + Na]^+$ 613.2198; found 613.2207.

### Methyl 1-(Acetoxymethyl)-5-((tert-butyldimethylsilyl)oxy)-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(trifluoromethyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (23)

To a solution of cyclopentadiene **14** (10 mg, 18.7 μmol) in DCM (0.4 mL) was added methyl 2-(trifluoromethyl)acrylate (**22**) (4.6 μL, 37.4 μmol) in 1 mL of DCM, and the mixture was stirred at rt for 24 h. TLC indicated the complete consumption of the starting material (20% EtOAc/hexanes), so the mixture was concentrated and purified by chromatography on a Pasteur pipette packed with silica gel (4% EtOAc/hexanes) to give cycloadduct **23** (1:1.4 diastereomeric mixture, 5.2 mg, 40%) as a yellow oil. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.67–7.55 (comp, 6H), 7.46–7.32 (comp, 8H), 4.56–4.02 (comp, 5H), 3.76 (s, 3H), 3.71 (s, 2H), 3.63 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.51 (dd, *J* = 10.1, 5.0 Hz, 1H), 2.92–2.76 (m, 3H), 2.59 (d, *J* = 13.0 Hz, 1H), 2.50 (ddd, *J* = 21.3, 9.2, 5.0 Hz, 2H), 2.19 (dd, *J* = 12.9, 3.5 Hz, 1H), 1.91 (d, *J* = 12.5 Hz, 1H), 1.77 (d, *J* = 2.0 Hz, 6H), 1.03 (d, *J* = 4.3 Hz, 18H), 0.93 (d, *J* = 3.1 Hz, 18H), 0.16 (d, *J* = 7.6 Hz, 5H), 0.12 (d, *J* = 13.8 Hz, 4H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −61.52, −64.24. $^{13}$C{$^{1}$H} NMR (75 MHz, $CDCl_3$) δ 170.7, 170.3, 169.8, 169.0, 162.6, 162.3, 135.7, 135.6, 133.9, 133.8, 133.8, 133.7, 129.7, 127.8, 99.6, 97.4, 62.9, 62.6, 61.8, 61.1, 60.5, 60.0, 59.5, 58.4, 52.9, 52.9, 47.4, 46.4, 34.6, 34.5, 27.0, 25.7, 20.6, 19.4, 18.1, 0.2, −4.5, −4.6. HRMS (ESI$^{+}$): calcd for $C_{36}H_{50}F_3O_6Si_2$ [M + H] 691.3098; found 691.3111.

### (1S,2S,4R)-2-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (32)(41) and (1S,4R)-2-(4-methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (33)(42)

To a solution of (*R*)-camphor (219 mg, 1.44 mmol) in THF (7 mL) was added anhydrous cerium(III) chloride (355 mg, 1.44 mmol). The mixture was sealed under $N_2$ and stirred for 0.5 h, then 0.5 M (4-methoxyphenyl)magnesium bromide in THF (3.2 mL, 1.58 mmol) was added. The resulting yellow solution was stirred for 0.5 h at rt, then quenched with $NH_4Cl$ (5 mL). GC–MS indicated that the organic layer contained a mixture of **32**, **33**, and unreacted starting material. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (25 g $SiO_2$ column, 0–7% EtOAc/hexanes) to give **32** (131 mg, 35%) as a colorless solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 2.28 (d, *J* = 13.8 Hz, 1H), 2.18 (ddd, *J* = 13.9, 4.2, 3.0 Hz, 1H), 1.89 (t, *J* = 4.3 Hz, 1H), 1.78 (s, 1H), 1.77–1.64 (m, 1H), 1.26 (s, 3H), 1.24–1.11 (m, 2H), 0.92–0.90 (m, 3H), 0.90 (s, 3H), 0.89–0.78 (m, 1H). **33** was also obtained (41 mg, 12%) as a yellow solid. $^{1}$H NMR ($CDCl_3$) δ 7.19 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 5.90 (d, *J* = 3.3 Hz, 1H), 3.80 (s, 3H), 2.36 (t, *J* = 3.5 Hz, 1H), 1.93 (ddt, *J* = 11.6, 8.7, 3.7 Hz, 1H), 1.70–1.61 (m, 1H), 1.33–1.22 (m, 1H), 1.13–1.05 (comp, 4H), 0.88 (s, 3H), 0.81 (s, 3H).

### 7-(((tert-Butyldiphenylsilyl)oxy)methyl)-1-((methoxymethoxy)methyl)-5-methylenebicyclo[2.2.1]heptane-2-carbonitrile (40)

To a solution of **15** (110 mg, 0.254 mmol) in $CHCl_3$ (5 mL) were added dimethoxymethane (224 μL, 2.54 mmol) and $P_2O_5$ (500 mg, 1.76 mmol).(43)The mixture was sealed under $N_2$ and stirred for 10 min. TLC (20% EtOAc/hexanes) indicated complete consumption of the starting material, the mixture was filtered through Celite and concentrated, and the intermediate MOM ether was used directly in the next step. To a solution of methyltriphenylphosphonium bromide (272 mg, 0.762 mmol) in toluene (5 mL) sealed under $N_2$ was added KHMDS (0.5 M in toluene, 1.52 mL, 0.762 mmol). The mixture was heated to 90 °C for 30 min, then the intermediate MOM ether was added (in toluene, 5 mL). The mixture was stirred at 90 °C for 10 min, after which time TLC (40% EtOAc/hexanes) indicated complete consumption of the starting material. The mixture was filtered through Celite, concentrated, and loaded as a toluene solution onto a 10 g $SiO_2$ column and purified by chromatography (5–10% EtOAc/hexanes) to give alkene **40** (1:0.7 diastereomeric mixture, 75 mg, 62%) as a colorless oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.73–7.58 (comp, 7H), 7.49–7.31 (comp, 10H), 4.98 (t, *J* = 2.5 Hz, 1H), 4.93–4.87 (m, 1H), 4.80 (s, 1H), 4.71 (s, 1H), 4.65–4.57 (m, 1H), 4.57–4.49 (m, 2H), 3.90 (d, *J* = 10.1 Hz, 1H), 3.73 (d, *J* = 10.1 Hz, 1H), 3.70–3.61 (m, 1H), 3.59–3.43 (comp, 4H), 3.35 (s, 2H), 3.24 (s, 3H), 3.09 (ddd, *J* = 12.0, 5.0, 2.5 Hz, 1H), 2.85 (d, *J* = 4.3 Hz, 1H), 2.75 (q, *J* = 5.8, 5.2 Hz, 1H), 2.47 (dd, *J* = 17.1, 2.1 Hz, 1H), 2.28 (dd, *J* = 12.3, 4.3 Hz, 1H), 2.23–1.96 (comp, 5H), 1.89 (dd, *J* = 12.6, 9.4 Hz, 1H), 1.69 (dd, *J* = 12.5, 5.0 Hz, 1H), 1.05 (s, 6H), 1.03

(s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 150.3, 149.5, 135.7, 135.7, 135.7, 135.6, 133.6, 133.5, 133.4, 133.2, 129.9, 129.8, 127.9, 127.8, 127.8, 127.8, 121.5, 121.1, 107.1, 106.6, 96.9, 96.6, 69.4, 66.3, 61.1, 61.1, 55.5, 55.4, 53.1, 52.9, 52.8, 47.6, 38.0, 35.4, 34.9, 34.5, 33.7, 32.4, 26.9, 19.3, 19.3. HRMS ($ESI^+$): calcd for $C_{29}H_{37}NNaO_3Si$ $[M + Na]^+$ 498.2440; found 498.2452.

## 4-Methoxybenzyl-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-cyano-5-oxobicyclo[2.2.1]heptane-1-carboxylate (42)

$CrO_3$ (525 mg, 5.25 mmol) was dissolved in $H_2O$ (2 mL). To the solution was added concentrated $H_2SO_4$ (0.45 mL), to give the Jones reagent (2.5 mL). To a solution of alcohol **15** (767 mg, 1.769 mmol) in acetone (20 mL) in a 50 mL round-bottom flask at 0 °C was added Jones reagent (1.77 mL, 4.42 mmol), and the mixture was stirred for 30 min at rt. TLC (40% EtOAc/hexanes) showed complete consumption of the starting material, so the mixture was quenched with MeOH (5 mL). $Na_2SO_4$ was added, and the mixture was filtered through Celite, and the mother liquor was condensed to a green residue. The crude was dissolved in DCM (10 mL) and passed through a 10 g silica gel pad, eluting with 80% EtOAc/hexanes. The resulting eluent was concentrated to give a crude yellow oil, which was dissolved in acetone (20 mL) in a 50 mL flask. To this solution were added PMBCl (360 µL, 2.65 mmol), $K_2CO_3$ (1.222 g, 8.84 mmol), and TBAI (13.1 mg, 0.0354 mmol). The mixture was stirred for 24 h at rt, after which time LC–MS indicated incomplete consumption of the starting material. Additional PMBCl (0.200 mL, 1.47 mmol) was added, and the mixture was stirred for another 24 h, after which time LC–MS showed complete conversion to the desired product. The mixture was filtered through Celite, concentrated, and purified by chromatography on a 10 g $SiO_2$ column (0–40% EtOAc/hexanes) to give ester **42** (388 mg, 39% over three steps) as a colorless oil (1:1 diastereomeric mixture). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.67–7.51 (comp, 8H), 7.48–7.31 (comp, 12H), 7.19 (dd, *J* = 14.1, 8.7 Hz, 4H), 6.81 (dd, *J* = 8.7, 1.8 Hz, 4H), 5.18–4.92 (comp, 4H), 3.89 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.78 (s, 6H), 3.60 (t, *J* = 6.2 Hz, 2H), 3.55–3.46 (m, 1H), 3.04–2.83 (comp, 4H), 2.82–2.75 (m, 2H), 2.69–2.59 (m, 2H), 2.46 (ddd, *J* = 13.7, 11.8, 4.9 Hz, 1H), 2.40–2.33 (m, 1H), 2.28 (dt, *J* = 13.8, 4.8 Hz, 1H), 2.16–2.06 (m, 2H), 1.79 (dd, *J* = 13.6, 5.4 Hz, 1H), 1.00 (d, *J* = 4.6 Hz, 18H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 209.8, 209.7, 169.6, 169.4, 159.9, 135.7, 135.6, 132.6, 132.5, 130.5, 130.2, 130.1, 130.0, 128.8, 128.0, 127.9, 127.0, 127.0, 119.9, 119.2, 114.2, 114.1, 67.7, 60.7, 60.5, 55.6, 55.4, 54.5, 52.4, 51.7, 51.3, 43.8, 39.7, 35.2, 33.9, 29.7, 29.0, 26.8, 19.2. HRMS ($ESI^+$): calcd for $C_{34}H_{37}$ $NNaO_5Si$ $[M + Na]^+$ 590.2339; found 590.2352.

## 4-Methoxybenzyl-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-cyano-5-methylenebicyclo[2.2.1]heptane-1-carboxylate (43)

To a solution of methyltriphenylphosphonium bromide (18.9 mg, 0.0528 mmol) in dry toluene (1 mL) sealed under $N_2$ atmosphere was added KHMDS (0.5 M in toluene, 106 µL, 0.0528 mmol), and the mixture was heated at 90 °C for 30 min. To the reaction was added **42** (5.0 mg, 8.8 µmol) in toluene (0.5 mL), and the mixture was stirred for 10 min. at the same temperature. TLC (20% EtOAc/hexanes) indicated complete consumption of the starting material, so the mixture was filtered through Celite and concentrated, then purified by chromatography on a silica gel-packed pipette (5–10% EtOAc/hexanes) to give alkene **43** (4.7 mg, 94%) as a colorless oil (1:1 diastereomeric mixture). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.68–7.53 (comp, 8H), 7.48–7.30 (comp, 12H), 7.17 (dd, *J* = 11.9, 8.7 Hz, 4H), 6.87–6.74 (comp, 4H), 5.14–4.90 (m, 6H), 4.82 (s, 1H), 4.78 (s, 1H), 3.99 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.79 (d, *J* = 1.1 Hz, 6H), 3.66 (dd, *J* = 10.6, 6.2 Hz, 1H), 3.56–3.35 (m, 3H), 3.06 (d, *J* = 4.2 Hz, 1H), 2.87 (d, *J* = 4.1 Hz, 1H), 2.83 (dd, *J* = 9.3, 5.1 Hz, 1H), 2.73 (s, 2H), 2.59 (dd, *J* = 10.3, 4.6 Hz, 1H), 2.47 (d, *J* = 17.1 Hz, 1H), 2.35 (dd, *J* = 12.3, 4.2 Hz, 1H), 2.30–2.11 (m, 3H), 1.97 (dd, *J* = 12.6, 9.3 Hz, 1H), 1.69 (dd, *J*= 12.5, 5.0 Hz, 1H), 1.03 (s, 18H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.1, 171.0, 159.9, 148.3, 147.9, 135.8, 135.7, 133.6, 133.4, 130.4, 130.2, 130.0, 129.9, 129.8, 127.9, 127.9, 127.8, 127.5, 127.5, 121.1, 120.6, 114.2, 114.1, 107.8, 67.3, 61.1, 60.9, 56.9, 56.5, 56.5, 55.5, 53.0, 48.4, 47.5, 38.3, 36.0, 35.5, 34.8, 34.5, 33.5, 29.9, 27.0, 19.5, 19.4. HRMS ($ESI^+$): calcd for $C_{35}H_{39}NNaO_4Si$ $[M + Na]^+$588.2546; found 588.2564.

### 4-Methoxybenzyl-2-cyano-7-(hydroxymethyl)-2-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylate (45a)

To a solution of **43** (57.3 mg, 101 µmol) in toluene (1 mL), sealed under $N_2$, was added iodomethane (63.0 µL, 1.01 mmol), followed by KHMDS (0.5 M in toluene, 0.61 mL, 0.30 mmol). The mixture was stirred at rt for 3 h, after which time TLC (10% EtOAc/hexanes) indicated complete consumption of the starting material. The mixture was quenched with saturated aqueous $NH_4Cl$ (1 mL), the organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 1 mL). The combined organics were dried over $Na_2SO_4$, filtered, concentrated, and used directly in the next step. To a solution of this intermediate (**44a**) (49.0 mg, 84.5 µmol) in THF (1 mL) was added a solution of TBAF (1.00 M in THF, 127 µL, 0.127 mmol) at 0 °C, and the mixture was removed from the ice bath and stirred at rt for 2 h. LC–MS indicated that some of the desired PMB ester products had been hydrolyzed to the carboxylic acid. The mixture was concentrated, then 1 N aqueous HCl (2 mL) was added, and the solution was extracted with EtOAc (3 × 2 mL). The combined organics were dried over $Na_2SO_4$, concentrated, and redissolved in acetone (3 mL). To the solution were added PMBCl (9.2 µL, 0.0676 mmol), $K_2CO_3$ (14.0 mg, 0.101 mmol), and 5–10 crystals of TBAI, and the mixture was stirred for 24 h at rt. TLC (100% EtOAc) indicated that the carboxylic acid was consumed. The mixture was filtered through Celite and concentrated, then purified by chromatography on a silica gel-packed Pasteur pipette, (30–40% EtOAc/hexanes), to give **45a** (15.9 mg, 55%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.26 (d, *J* = 11.9 Hz, 1H), 5.11 (d, *J* = 11.9 Hz, 1H), 5.01 (t, *J* = 2.6 Hz, 1H), 4.87 (t, *J* = 2.2 Hz, 1H), 3.81 (s, 3H), 3.76–3.63 (m, 1H), 3.60–3.44 (m, 1H), 3.10 (d, *J* = 8.4 Hz, 1H), 2.98 (dq, *J* = 17.5, 2.0 Hz, 1H), 2.68–2.54 (m, 2H), 2.32 (t, *J* = 6.4 Hz, 1H), 2.12–1.97 (m, 1H), 1.84 (dd, *J* = 12.4, 3.6 Hz, 1H), 1.25 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 172.5, 159.9, 147.1, 134.9, 130.5, 130.4, 129.7, 128.7, 127.8, 127.2, 123.4, 114.1, 114.1, 114.1, 114.0, 107.9, 67.4, 60.3, 60.2, 55.4, 50.8, 47.5, 45.0, 41.5, 36.2, 24.5. HRMS (ESI$^+$): calcd for $C_{20}H_{23}NNaO_4$ $[M + Na]^+$ 364.1525; found 364.1530.

### 4-Methoxybenzyl-2-cyano-2-ethyl-7-(hydroxymethyl)-5-methylenebicyclo[2.2.1]heptane-1-carboxylate (45b)

**43** (20.0 mg, 33.7 µmol) was treated following the procedure of **45a** using EtI instead of MeI. **45b** was obtained in 4.6 mg, 38% yield. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.22 (d, *J* = 11.9 Hz, 1H), 5.13 (d, *J* = 11.9 Hz, 1H), 5.02 (t, *J* = 2.6 Hz, 1H), 4.86 (t, *J* = 2.2 Hz, 1H), 3.81 (d, *J* = 0.5 Hz, 3H), 3.70 (dd, *J* = 11.7, 7.4 Hz, 1H), 3.60–3.43 (m, 1H), 3.12–2.94 (m, 2H), 2.70–2.52 (m, 2H), 2.31 (t, *J* = 6.4 Hz, 1H), 1.97–1.81 (m, 2H), 1.50–1.34 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 172.7, 159.9, 147.2, 130.4, 127.2, 122.2, 114.1, 107.9, 67.3, 60.7, 60.3, 55.4, 51.3, 47.8, 47.7, 41.8, 36.6, 29.3, 8.9. HRMS (ESI$^+$): calcd for $C_{21}H_{25}NNaO_4$ $[M + Na]^+$ 378.1681; found 378.1687.

### 4-Methoxybenzyl-2-benzyl-2-cyano-7-(hydroxymethyl)-5-methylenebicyclo[2.2.1]heptane-1-carboxylate (45c)

**43** (20.0 mg, 33.7 µmol) was treated following the procedure of **45a** using BnBr instead of MeI. **45c** was obtained in 12 mg, 85% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46–7.27 (comp, 5H), 7.23–7.13 (m, 2H), 6.96–6.82 (m, 2H), 5.28 (d, *J* = 11.8 Hz, 1H), 5.11 (d, *J* = 11.8 Hz, 1H), 4.97 (t, *J* = 2.6 Hz, 1H), 4.84 (t, *J* = 2.1 Hz, 1H), 3.77 (d, *J* = 0.9 Hz, 4H), 3.63–3.49 (m, 1H), 3.18 (s, 1H), 3.09 (d, *J* = 17.7 Hz, 1H), 2.75–2.55 (comp, 4H), 2.46 (t, *J* = 6.4 Hz, 1H), 2.07 (dd, *J*= 13.1, 4.3 Hz, 1H), 1.56 (d, *J* = 13.1 Hz, 1H). $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$) δ 172.5, 160.0, 147.0, 134.2, 130.6, 130.5, 128.6, 127.7, 127.2, 122.7, 114.2, 107.9, 67.4, 61.0, 60.3, 55.4, 51.4, 47.7, 47.1, 41.2, 41.0, 36.5. HRMS (ESI$^+$): calcd for $C_{26}H_{27}NNaO_4$ $[M + Na]^+$ 440.1838; found 440.1841.

### 6-(2-Chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-ol (47)

To a solution of (1-aminocyclopentyl)methanol(44) (3.10 g, 26.9 mmol) in EtOH (100 mL) was added 2,2-dimethoxyacetaldehyde (60% in water, 4.47 mL, 29.6 mmol). The mixture was stirred at rt for 18 h, after which time crude NMR indicated complete conversion to the intermediate imine. The mixture was quenched with 50 mL of 1 N aq. NaOH followed by 50 mL of $H_2O$, then extracted with DCM (3 × 100 mL). The combined organics

were dried over $Na_2SO_4$, filtered, concentrated, and redissolved in $Et_2O$ (100 mL) in a flask sealed under $N_2$. $LiAlH_4$ (1.02 g, 26.9 mmol) was added, and the mixture was stirred at rt for 30 min. The reaction was quenched by adding EtOAc (50 mL) and saturated aqueous Rochelle's salt (100 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organics were washed with brine (100 mL), dried over $Na_2SO_4$, filtered, and concentrated to give a colorless oil. The intermediate amine was dissolved in EtOH (60 mL), and 2,3-dichloroprop-1-ene (1.05 mL, 11.4 mol), $NaHCO_3$ (2.00 g, 23.8 mol), and NaI (114 mg, 0.763 mmol) were added. The mixture was heated to 80 °C under $N_2$ atmosphere for 18 h, after which time crude NMR indicated about 10% conversion to the desired product. Additional NaI (1.14 g, 7.63 mmol), $NaHCO_3$ (2.00 g, 23.8 mol), 5–10 crystals of TBAI and 2,3-dichloroprop-1-ene (0.1 mL, 1.09 mmol) were added. The mixture was refluxed at 87 °C under $N_2$ atmosphere for 24 h, after which time crude NMR indicated about 80% conversion. The mixture was heated to 100 °C for another 2 h, then filtered through Celite and concentrated to a yellow oil, which was dissolved in conc. HCl (60 mL). The mixture was then refluxed at 105 °C under $N_2$ atmosphere for 2 h, the solvent was evaporated, and 6 N NaOH (30 mL) was added. The mixture was extracted with EtOAc (3 × 30 mL), and the combined organics were washed with brine and dried over $Na_2SO_4$, filtered, concentrated, and purified by chromatography (10–40% EtOAc/hexanes) to give **47** (390 mg, 22% overall yield) as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.40 (app q, *J* = 1.2 Hz, 1H), 5.30 (app q, *J* = 1.0 Hz, 1H), 4.94 (ddd, *J*= 9.0, 3.9, 2.2 Hz, 1H), 3.82 (d, *J* = 9.1 Hz, 1H), 3.69 (dd, *J* = 11.4, 1.2 Hz, 1H), 3.25 (dd, *J* = 11.4, 0.7 Hz, 1H), 3.16 (dt, *J* = 15.0, 1.3 Hz, 1H), 2.96 (d, *J* = 14.8 Hz, 1H), 2.69 (dd, *J* = 11.6, 2.2 Hz, 1H), 2.46 (dd, *J* = 11.6, 3.9 Hz, 1H), 1.86–1.30 (comp, 8H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 140.2, 114.2, 91.5, 69.4, 66.0, 56.4, 52.8, 31.7, 28.4, 25.9, 25.8. HRMS (ESI$^+$): calcd for $C_{11}H_{19}ClNO_2$ [M + H] 232.1104; found 232.1106.

## 2-Hydroxy-4-(4-methoxybenzyl)morpholin-3-one (48)(34)

A solution of 50 wt % aqueous glyoxylic acid (9.14 g, 99.3 mmol) in THF (20 mL) was heated to reflux, then 2-(4-methoxybenzylamino)ethanol(45) (6.00 g, 33.1 mmol) was added over 30 min, and the reaction was refluxed for another 2 h. THF was distilled off under atmospheric pressure while maintaining a constant volume by simultaneous addition of water (20 mL). The mixture was cooled to rt, then placed in an ice bath for 30 min, where the product crystallized. The solids were filtered with a Buchner funnel, washed with water, and then dried under vacuum at 60 °C for 24 h to give **48** (3.6 g, 46%) as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.0 Hz, 2H), 6.86 (d, *J*= 7.0 Hz, 2H), 5.34 (s, 1H), 4.91 (s, 1H), 4.65 (d, *J* = 14.4 Hz, 1H), 4.44 (d, *J* = 14.4 Hz, 1H), 4.30–4.18 (m, 1H), 3.80 (s, 3H), 3.78–3.74 (m, 1H), 3.42 (td, *J* = 11.2, 10.6, 3.9 Hz, 1H), 3.11 (d, *J* = 12.4 Hz, 1H).

## 2-Cyano-7-(((-4-(4-methoxybenzyl)-3-oxomorpholin-2-yl)oxy)methyl)-2-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid (49)

**45a** (6.0 mg, 17.6 μmol) was treated following the same procedure of **50a**using **48** instead of **47**, **49** was obtained in 1.5 mg, 19% yield, as a diastereomeric mixture. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.18 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 5.10–4.95 (m, 1H), 4.94–4.80 (m, 1H), 4.63 (t, *J* = 15.7 Hz, 1H), 4.37 (t, *J* = 16.0 Hz, 1H), 4.24–3.89 (m, 2H), 3.72–3.60 (m, 1H), 3.42 (td, *J* = 12.4, 11.7, 4.8 Hz, 1H), 3.09 (d, *J* = 12.6 Hz, 1H), 2.93–2.75 (m, 2H), 2.44 (d, *J* = 17.8 Hz, 1H), 2.31 (d, *J* = 9.9 Hz, 1H), 2.03–1.82 (m, 2H), 1.58 (s, 0H), 1.45 (s, 3H), 1.36–1.13 (comp, 5H). $^{13}$C{$^1$H} NMR (151 MHz, $CD_3OD$) δ 174.1, 174.0, 166.3, 166.2, 160.9, 160.9, 150.0, 150.0, 130.7, 130.6, 129.2, 124.8, 124.8, 115.2, 115.1, 108.4, 108.2, 97.9, 97.0, 91.7, 67.8, 67.6, 67.0, 60.8, 57.9, 57.9, 50.0, 49.7, 46.6, 46.4, 46.1, 45.9, 42.6, 37.3, 33.1, 30.6, 30.5, 30.3, 30.2, 28.1, 26.9, 25.1, 25.0, 23.8. HRMS (ESI$^+$): calcd for $C_{24}H_{28}N_2NaO_6$ [M + Na]$^+$ 463.1845; found 463.1855, HPLC (Phenomenex Gemini $C_{18}$) (25% (0–1.5 min)–95% (3.5–10 min), MeCN/$H_2O$; flow rate, 1.0 mL/min). RT = 8.10 min.

## 7-(((-6-(2-Chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-yl)oxy)methyl)-2-cyano-2-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid (50a)

To a solution of **45a** (18.0 mg, 52.7 μmol) and $PhNTf_2$ (20.7 mg, 58.0 μmol) in $Et_2O$ (1 mL), sealed under $N_2$ and at −50 °C, was added KHMDS (0.5 M in toluene, 211 μL, 105 μmol), and the mixture was stirred at the same

temperature for 10 min. TLC indicated complete consumption of the starting material (40% EtOAc/hexane). The mixture was quenched with aq. $NH_4Cl$ (1 mL) at the same temperature, then extracted with EtOAc (3 × 1 mL). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated to give the crude triflate, which was used directly in the next step. To a solution of **47**(6.1 mg, 26 µmol) in DMF (0.2 mL) was added NaH (60% in mineral oil, 3.4 mg, 88 µmol) at 0 °C. The mixture was stirred at rt for 15 min, then a solution of the crude triflate in DMF (0.1 mL) was added. The mixture was stirred at rt for 1 h, after which time LC–MS indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous $NH_4Cl$ (3 mL) and extracted with EtOAc (3 × 3 mL). The combined organics were washed with brine, dried over $Na_2SO_4$, filtered, concentrated, and purified by preparative HPLC to give **50a** (3.3 mg, 43%) as a colorless oil (1.0:1.1 diastereomeric mixture). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.61–5.50 (m, 2H), 5.31 (d, *J* = 1.2 Hz, 2H), 5.11–5.02 (m, 2H), 4.94 (s, 2H), 4.59 (dd, *J* = 4.9, 2.7 Hz, 1H), 4.54 (dd, *J* = 5.5, 2.7 Hz, 1H), 4.08 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.68 (d, *J* = 7.8 Hz, 2H), 3.59 (dd, *J* = 11.1, 3.8 Hz, 2H), 3.38–3.17 (m, 3H), 3.04 (d, *J* = 5.5 Hz, 5H), 2.97 (s, 1H), 2.84 (d, *J* = 3.9 Hz, 1H), 2.79 (d, *J* = 4.0 Hz, 1H), 2.72–2.64 (comp, 3H), 2.60 (d, *J* = 2.7 Hz, 1H), 2.44 (ddd, *J* = 11.7, 9.3, 5.1 Hz, 2H), 2.16–2.30 (comp, 12H, presumably obs w/$H_2O$), 2.13 (dd, *J* = 12.6, 2.3 Hz, 2H), 1.89 (dt, *J* = 12.7, 3.8 Hz, 2H), 1.59 (d, *J* = 10.5 Hz, 6H), 1.51 (d, *J* = 1.0 Hz, 6H). $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$) δ 172.4, 172.4, 147.2, 147.1, 140.1, 140.0, 123.4, 123.3, 113.3, 113.1, 108.6, 108.5, 98.7, 98.2, 70.8, 70.3, 68.1, 65.6, 65.5, 65.5, 65.3, 59.5, 59.5, 57.0, 56.9, 52.1, 52.0, 48.2, 48.1, 47.7, 47.6, 44.9, 44.9, 41.9, 41.8, 41.0, 36.2, 36.2, 29.9, 29.8, 25.8, 25.7, 25.0, 25.0, 22.9, 14.3. HRMS (ESI$^+$): calcd for $C_{23}H_{32}ClN_2O_4$ [M + H] 435.2051; found 435.2060; HPLC (Phenomenex Gemini $C_{18}$) (25% (0–1.5 min)–95% (3.5–10 min), MeCN/$H_2O$; flow rate, 1.0 mL/min). RT = 7.30 min.

### 7-(((-6-(2-Chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-yl)oxy)methyl)-2-cyano-2-ethyl-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid (50b)

Following the same procedure of **50a** using **45b** (5.6 mg, 16 µmol) instead of **45a**, **50b** was obtained (1.5 mg, 20%) as a diastereomeric mixture (1.0:1.1). $^1$H NMR (400 MHz, $CDCl_3$) δ 5.60–5.52 (m, 2H), 5.30 (s, 2H), 5.10–5.05 (m, 2H), 4.94 (s, 2H), 4.61–4.56 (m, 1H), 4.54 (dd, *J* = 5.5, 2.7 Hz, 1H), 4.08 (dd, *J* = 9.7, 5.5 Hz, 1H), 3.81 (d, *J* = 1.0 Hz, 1H), 3.68 (d, *J* = 7.0 Hz, 2H), 3.58 (dd, *J* = 11.0, 4.5 Hz, 2H), 3.32 (t, *J* = 9.2 Hz, 1H), 3.23 (dd, *J* = 16.4, 11.1 Hz, 2H), 3.13–2.96 (comp, 6H), 2.86 (s, 1H), 2.80 (s, 1H), 2.71–2.56 (m, 2H), 2.49–2.35 (comp, 4H), 2.07–1.97 (m, 1H), 1.95 (t, *J* = 3.1 Hz, 5H), 1.92–1.78 (m, 2H), 1.69–1.45 (comp, 16H, presumably obs w/$H_2O$), 1.28 (s, 1H), 1.15–1.04 (m, 6H). $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$) δ 173.0, 147.2, 147.2, 140.1, 140.1, 133.8, 114.1, 113.3, 113.1, 108.6, 108.5, 98.8, 98.1, 76.9, 70.8, 70.2, 65.7, 65.5, 65.5, 65.3, 57.0, 56.9, 52.1, 52.0, 48.6, 48.0, 47.8, 47.8, 41.7, 41.6, 40.9, 37.1, 36.7, 36.7, 36.1, 32.1, 29.9, 29.8, 29.5, 29.5, 27.4, 25.8, 25.8, 25.8, 25.7, 22.9, 14.3. HRMS (ESI$^+$): calcd for $C_{24}H_{34}ClN_2O_4$ [M + H] 449.2207; found 449.2225; HPLC (Phenomenex Gemini $C_{18}$) (25% (0–1.5 min)–95% (3.5–10 min), MeCN/$H_2O$; flow rate, 1.0 mL/min). RT = 7.06 min.

### 2-Benzyl-7-(((-6-(2-chloroallyl)-9-oxa-6-azaspiro[4.5]decan-8-yl)oxy)methyl)-2-cyano-5-methylenebicyclo[2.2.1]heptane-1-carboxylic acid (50c)

Following the same procedure of **50a** using **45c** (7.8 mg, 19 µmol) instead of **45a**, **50c** was obtained (1.9 mg, 21%) as a diastereomeric mixture (1:1.0). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (comp, 10H), 5.57 (s, 1H), 5.53 (s, 1H), 5.30 (s, 2H), 5.01 (d, *J* = 7.5 Hz, 2H), 4.89 (s, 2H), 4.64–4.58 (m, 1H), 4.57–4.50 (m, 1H), 4.25–4.08 (m, 1H), 3.70 (dd, *J* = 20.1, 11.3 Hz, 2H), 3.59 (t, *J* = 10.7 Hz, 2H), 3.32 (t, *J* = 9.0 Hz, 1H), 3.26 (d, *J* = 11.1 Hz, 1H), 3.20 (dd, *J* = 12.3, 6.3 Hz, 2H), 3.14–2.96 (comp, 6H), 2.84 (s, 1H), 2.77 (s, 1H), 2.72 (d, *J* = 12.0 Hz, 1H), 2.69–2.63 (m, 2H), 2.62 (d, *J* = 0.7 Hz, 1H), 2.45 (ddd, *J* = 16.5, 12.8, 7.4 Hz, 5H), 2.14–2.02 (m, 2H), 1.57 (comp, 20H, presumably obs w/$H_2O$). HRMS (ESI$^+$): calcd for $C_{29}H_{35}ClN_2O_4$ [M + H] 511.2364; found 511.2370; HPLC (Phenomenex Gemini $C_{18}$) (25% (0–1.5 min)–95% (3.5–10 min), MeCN/$H_2O$; flow rate, 1.0 mL/min). RT = 8.27 min.

## General Procedure for Diels–Alder Reaction Using 22 (Table1)

A solution of the indicated amount of Lewis acid and methyl 2-(trifluoromethyl)acrylate (2.3 µL, 18.7 µmol) in the indicated solvent (0.5 mL) was sealed under $N_2$ and cooled to −78 °C. **14** (5.0 mg, 9.4 µmol) in the indicated solvent (0.2 mL) was then added by syringe, and the mixture was stirred and gradually warmed up to −30 °C over 1 h. In an aluminum foil-wrapped Dewar flask, the mixture was stirred for 24 h at rt. The mixture was filtered through a poly(tetrafluoroethylene) syringe filter, concentrated, and dissolved in 0.6 mL of $CDCl_3$ containing pentachloroethane (1.1 µL, 9.4 µmol). $^1H$ and $^{19}F$ NMR analysis was then conducted.

## Representative Procedure for Organocatalytic Diels–Alder Reaction Using Cyclopentanones (Table2)

To a solution of **25**(40) in toluene (0.2 M, 0.36 mL) and propionic acid (5.4 µL, 0.07 mmol) was added cyclopent-2-en-1-one (20 µL, 0.24 mmol). (*E*)-4-Phenylbut-3-en-2-one (17.5 mg, 0.12 mmol) was added, and the mixture was sealed under $N_2$ and heated to 60 °C The experiments were monitored by GC–MS after 24 h.

## General Procedure for Double Michael Addition (Table3)

**24a** or **24b** (14.0 µmol) was sealed under $N_2$, dissolved in THF (0.5 mL), and cooled to 0 °C. LDA (1.37 M in heptane, 10.2 µL, 14.0 µmol) was added, and HMPA (2.4 µL, 14 µmol) was optionally added. The mixture was cooled to −78 °C, and the indicated amount of Michael acceptor in THF (0.5 mL) was added by syringe. The mixture was stirred for 2 h, then warmed up to rt and stirred for another 22 h. The reaction was quenched with saturated $NH_4Cl$ solution (1 mL) and extracted with EtOAc (3 × 1 mL). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated prior to $^1H$ NMR and LC–MS analyses.

### Attempted Cyanation of Camphor-Derived Alcohol 32 and Alkene 33 (Scheme 4)

To a solution of **32** (17.4 mg, 66.8 µmol) in DCM (0.7 mL) sealed under $N_2$ and cooled to −78 °C was added TMSCN (10.6 µL, 84.9 µmol), followed by the addition of boron trifluoride etherate (8.8 µL, 72 µmol), which caused the colorless solution to turn yellow. The mixture was stirred at −78 °C for 15 min, then warmed to rt. The reaction was stirred for another 15 min, then it was quenched with sat. aq. $NaHCO_3$ (1 mL). The organic phase was separated, and the aqueous phase was extracted with DCM (3 × 1 mL). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated prior to GC–MS and $^1H$ NMR analyses.

Alternatively, $PhCF_3$ (0.5 mL) was sealed under $N_2$, cooled to −20 °C, and TfOH (18.8 µL, 0.21 mmol) and TMSCN (25.8 µL, 0.21 mmol) were added. After 5 min, **33** (10 mg, 0.04 mmol) in $PhCF_3$ (0.5 mL) was added dropwise at the same temperature. The mixture was allowed to warm to rt and stirred for 0.5 h. The reaction was quenched with aqueous NaOH (1 M, 1 mL), extracted with ethyl acetate (3 × 1 mL), dried over $Na_2SO_4$, filtered, and concentrated prior to GC–MS and $^1H$ NMR analyses.

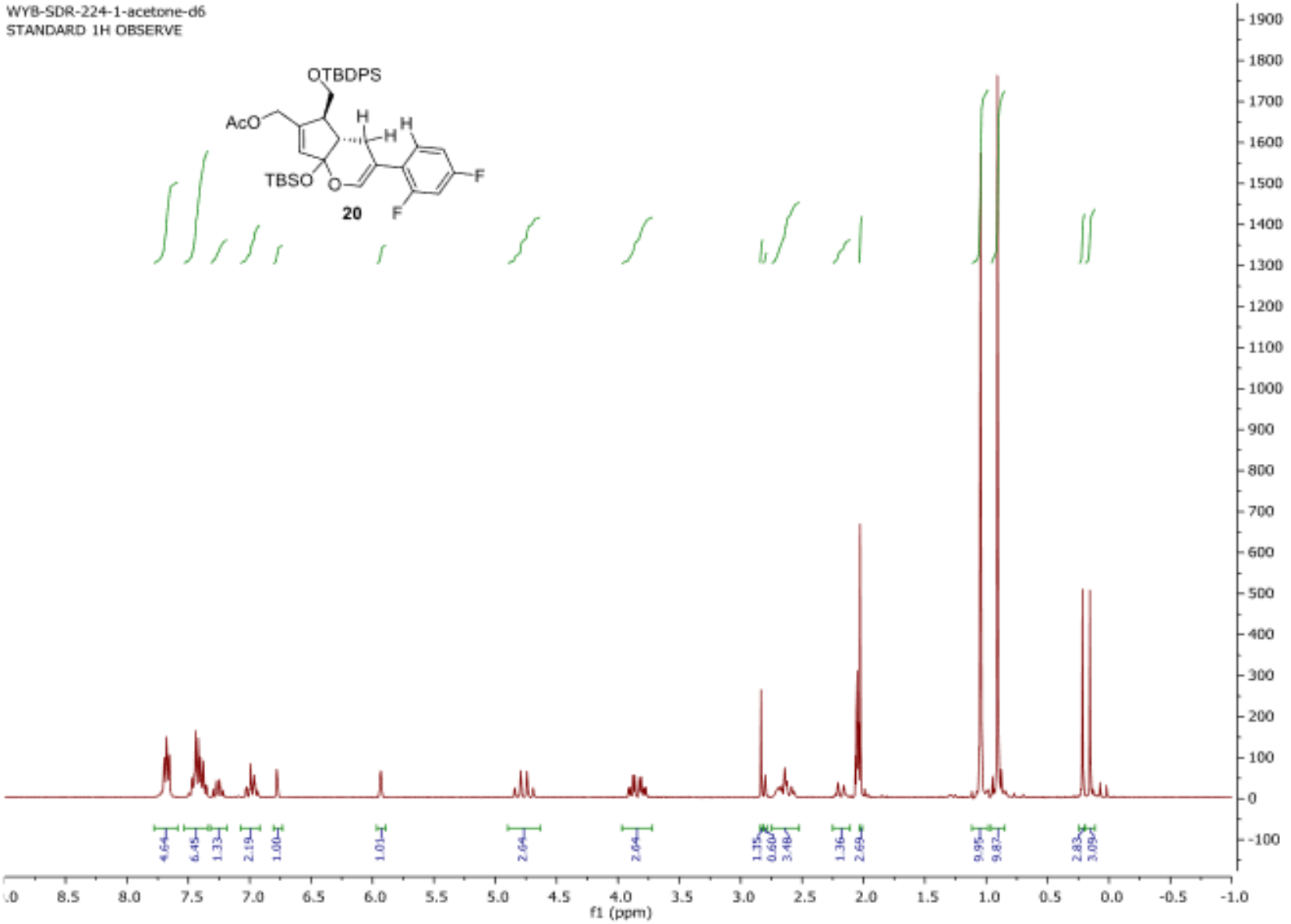
## General Procedure for Aryl/Alkylation of Secondary Nitrile 40 (Table4)

To a solution of **40** (2.5 mg, 5.3 µmol) in the indicated solvent (0.5 mL) sealed under $N_2$ was added the indicated amount of electrophile. KHMDS (0.5 M in toluene, 52.6 µL, 0.026 mmol) was then added. The mixture was heated at the indicated temperature for the indicated time. The reaction was worked up by washing with 1 N HCl (0.5 mL) and extracting with EtOAc (3 × 0.5 mL). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated to give a crude product which was dissolved in $CDCl_3$ containing pentachloroethane (5.26 µmol), prior to $^1H$ NMR analysis.

# Supporting Information

## Synthesis of Simplified Azasordarin Analogs as Potential Antifungal Agents

### 1H, 13C, COSY, and NOESY NMR spectra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TBSO
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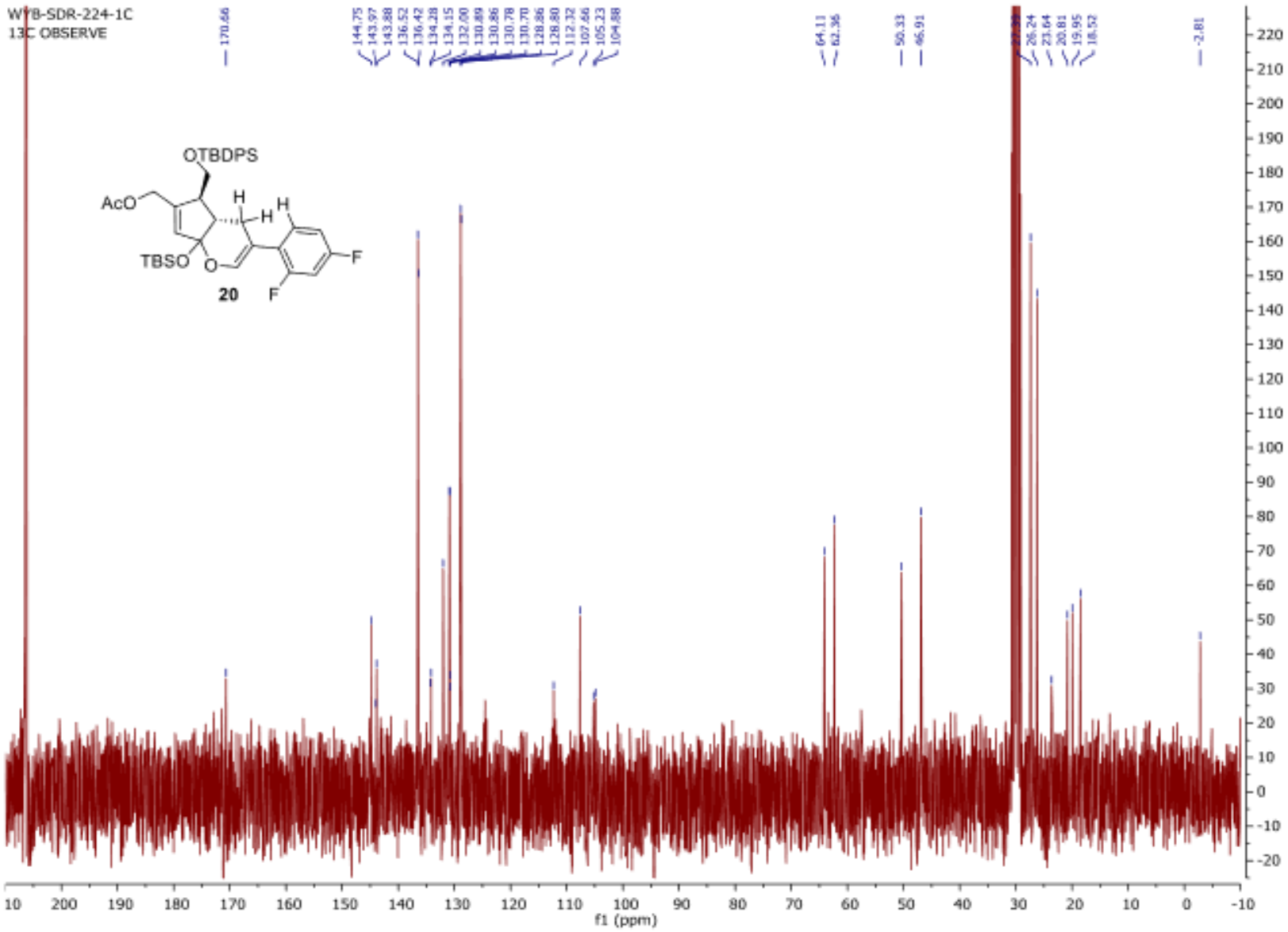
F
F
20
f1 (ppm)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130.78
130.70
128.86
128.80
112.32
107.66
105.23
104.88
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23.64
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H
H
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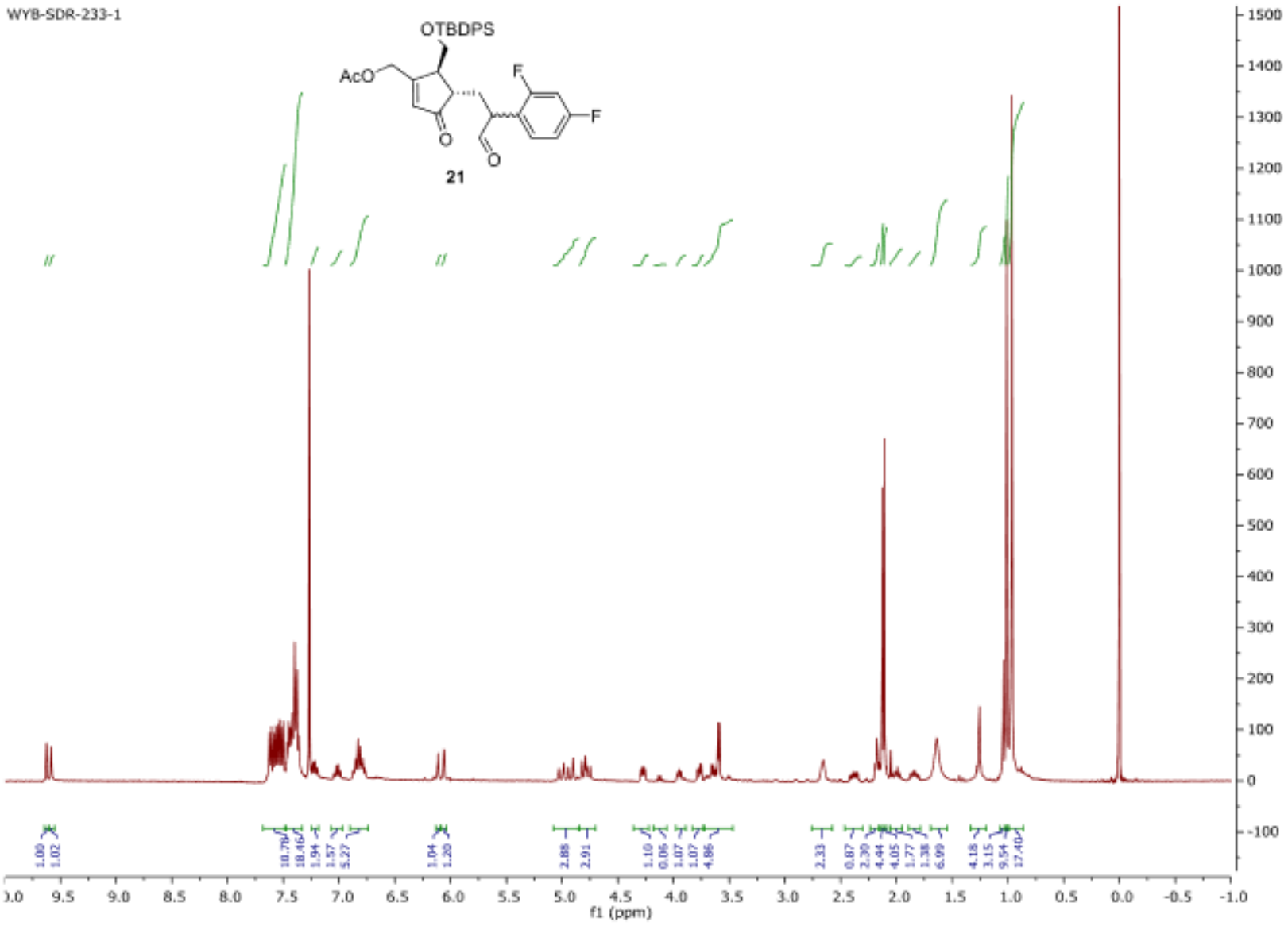
O
F
F
20
f1 (ppm)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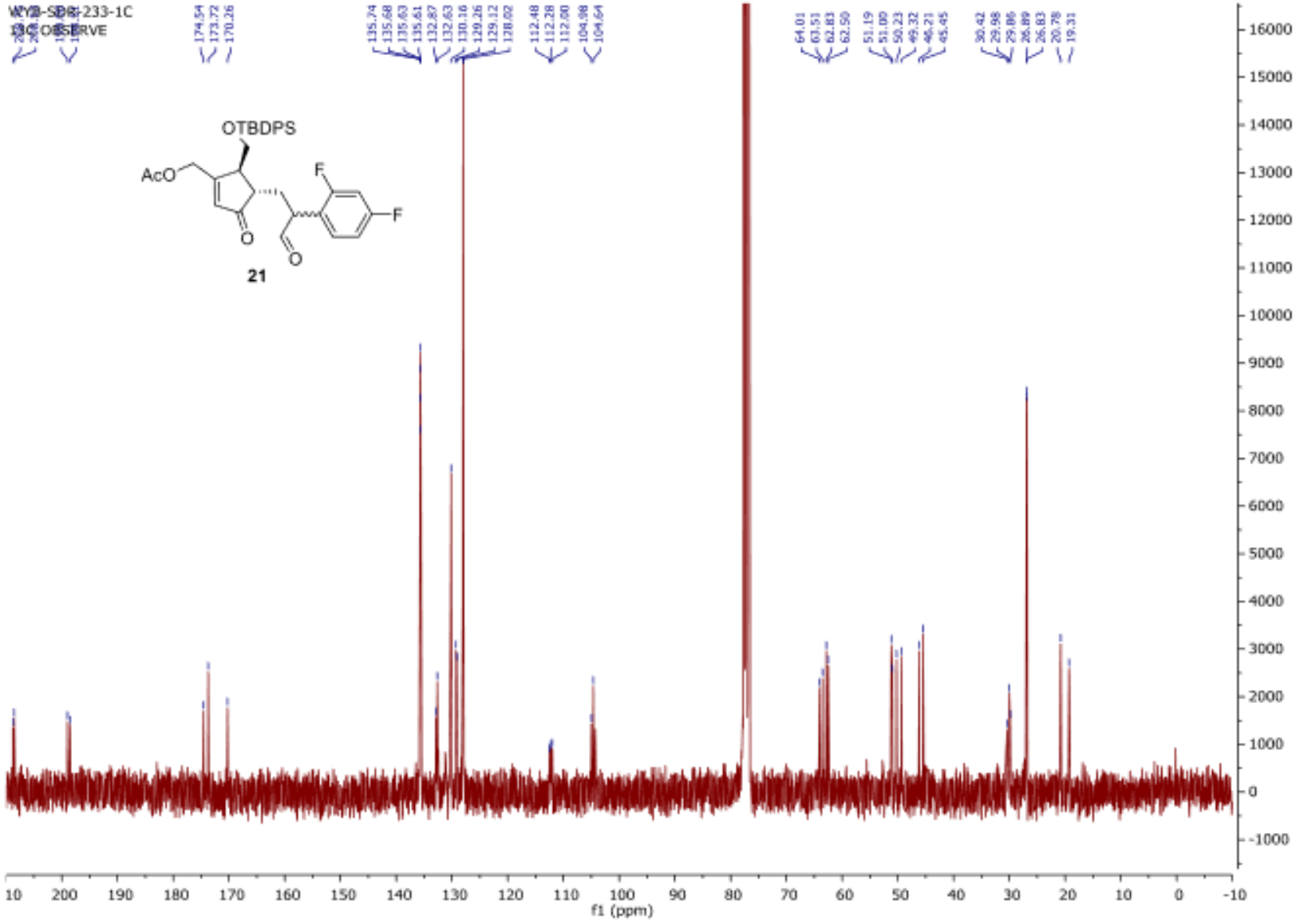
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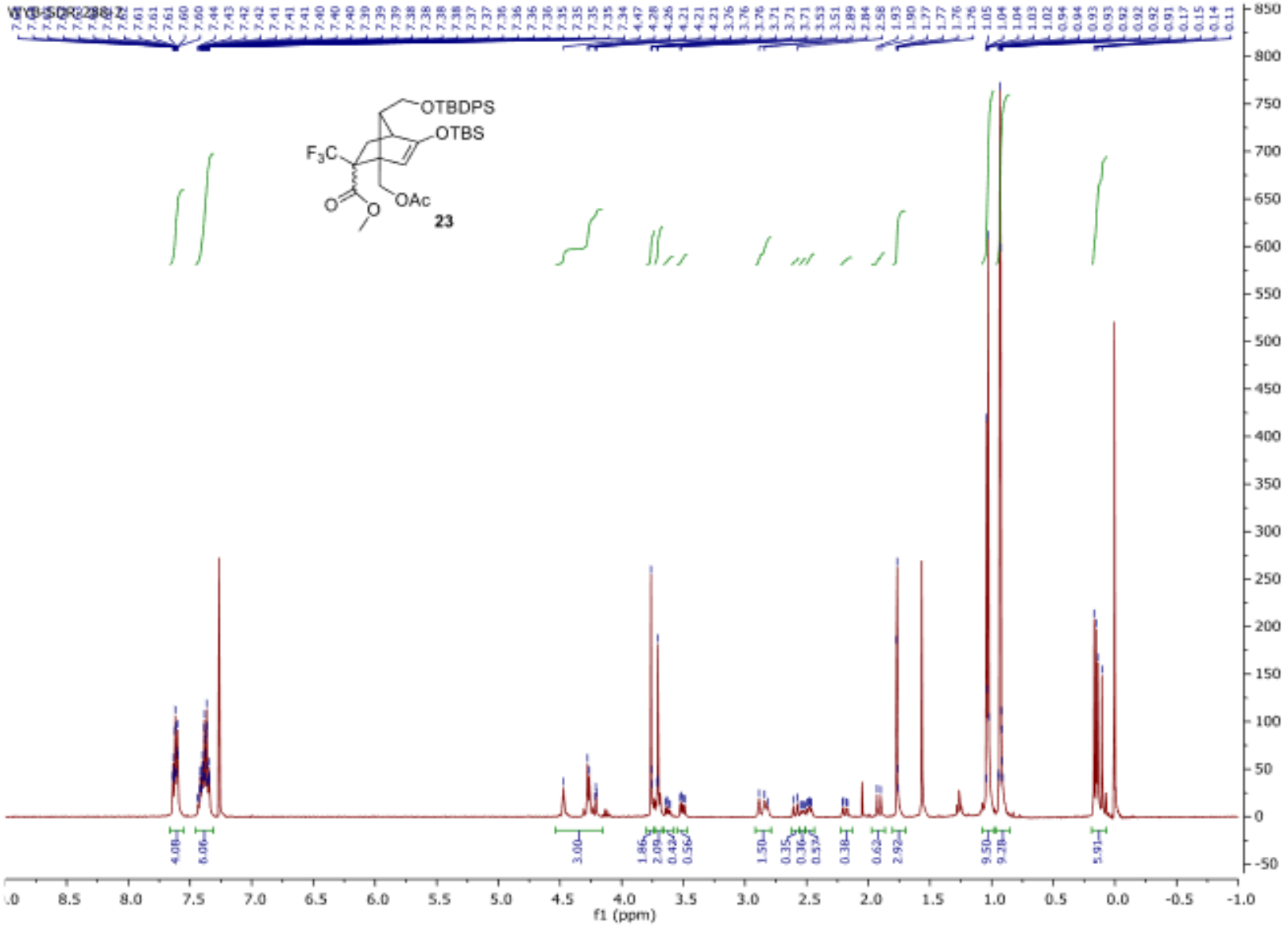
AcO
F
F
O
O
21
f1 (ppm)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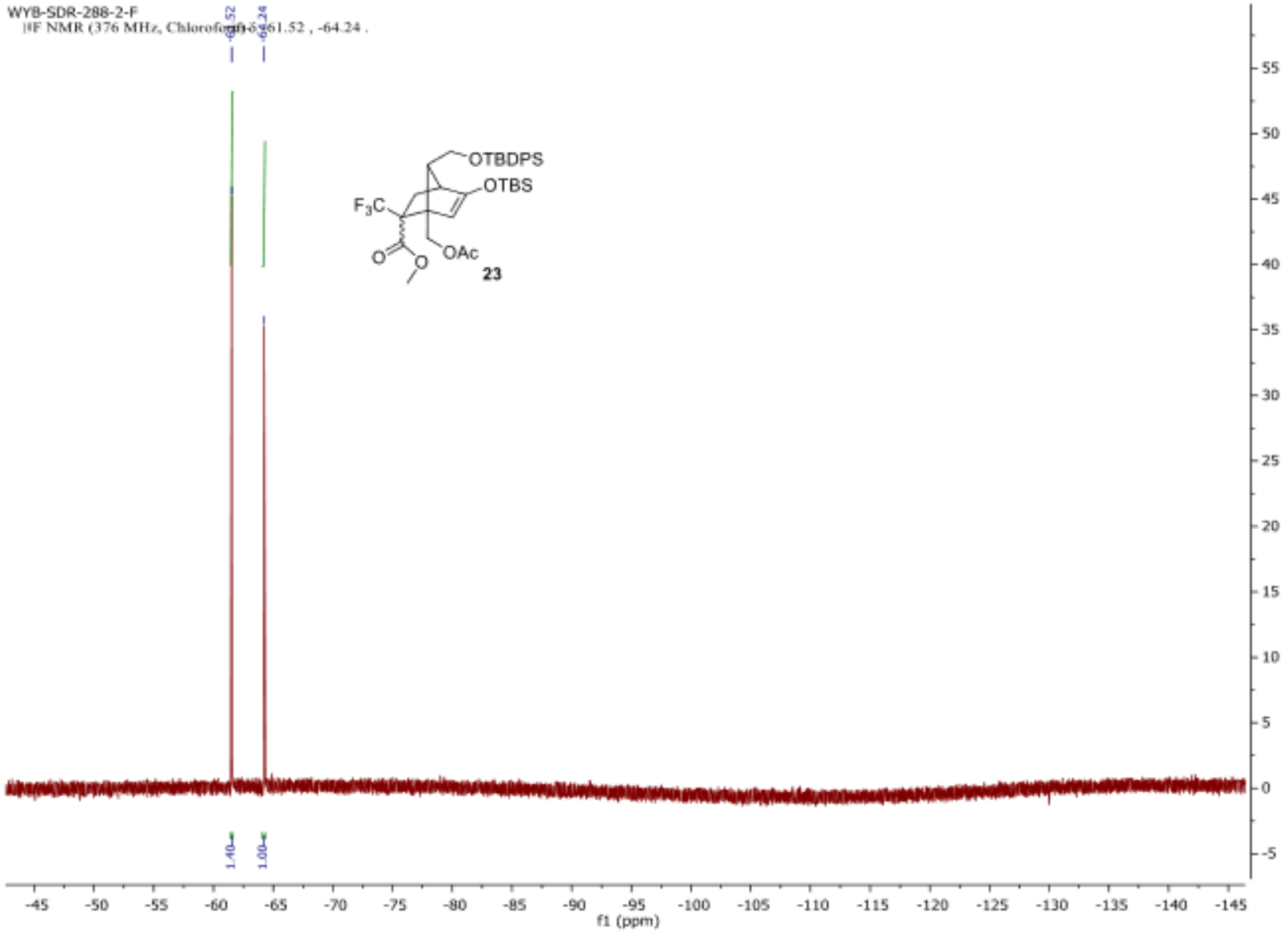
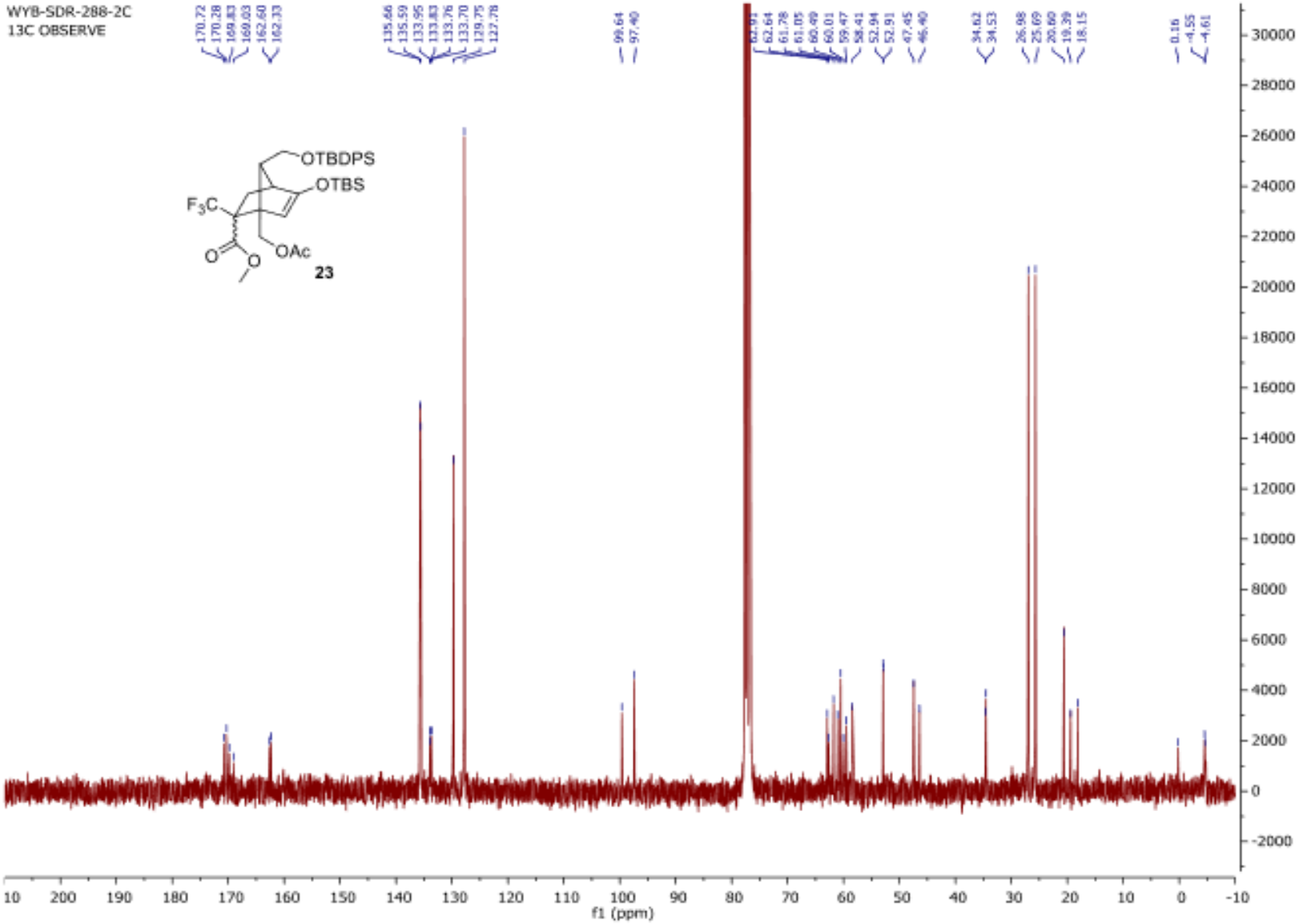
OTBS
F3C
OAc
O
O
23
f1 (ppm)

WYB-SDR-288-2-F

$^{19}$F NMR (376 MHz, Chloroform-d) δ -61.52 , -64.24 .

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62.64
61.78
61.05
60.49
60.01
59.47
58.41
52.94
52.91
47.45
46.40
34.62
34.53
26.98
25.69
20.60
19.39
18.15
0.16
-4.55
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OTBDPS
OTBS
F3C
O
O
OAc
23
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
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10
200
190
180
170
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60
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40
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20
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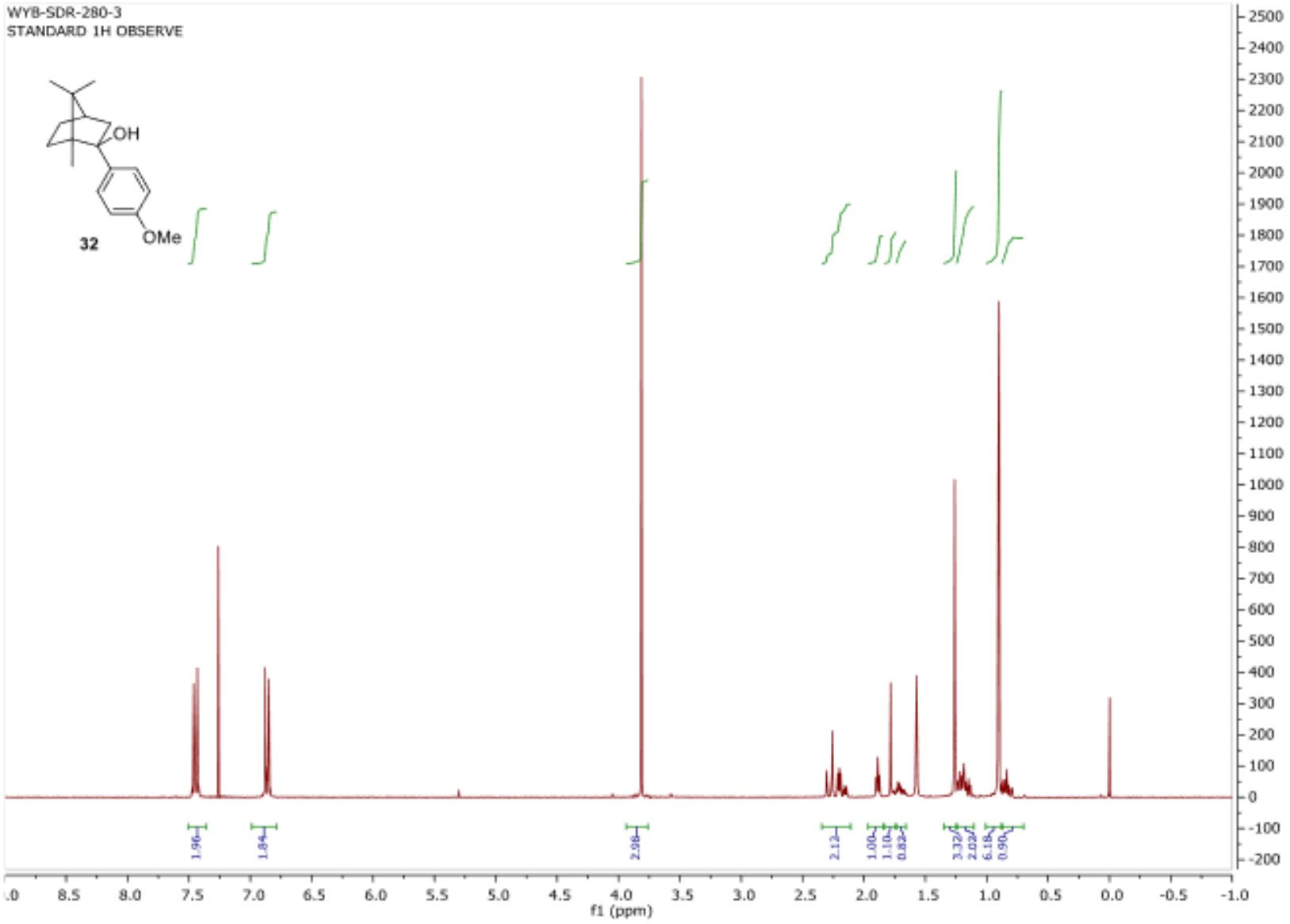
0
-10
f1 (ppm)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OMe
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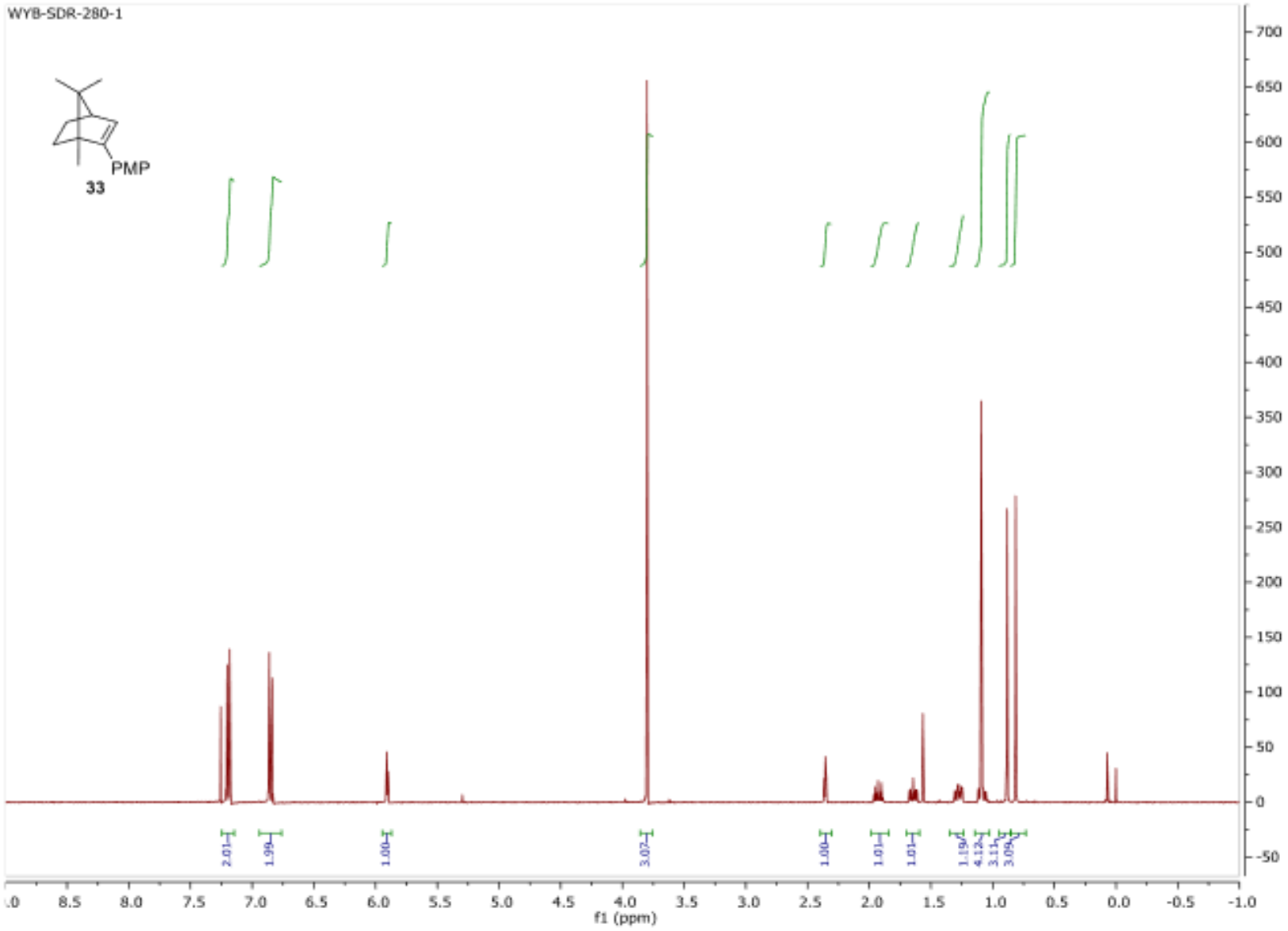
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33
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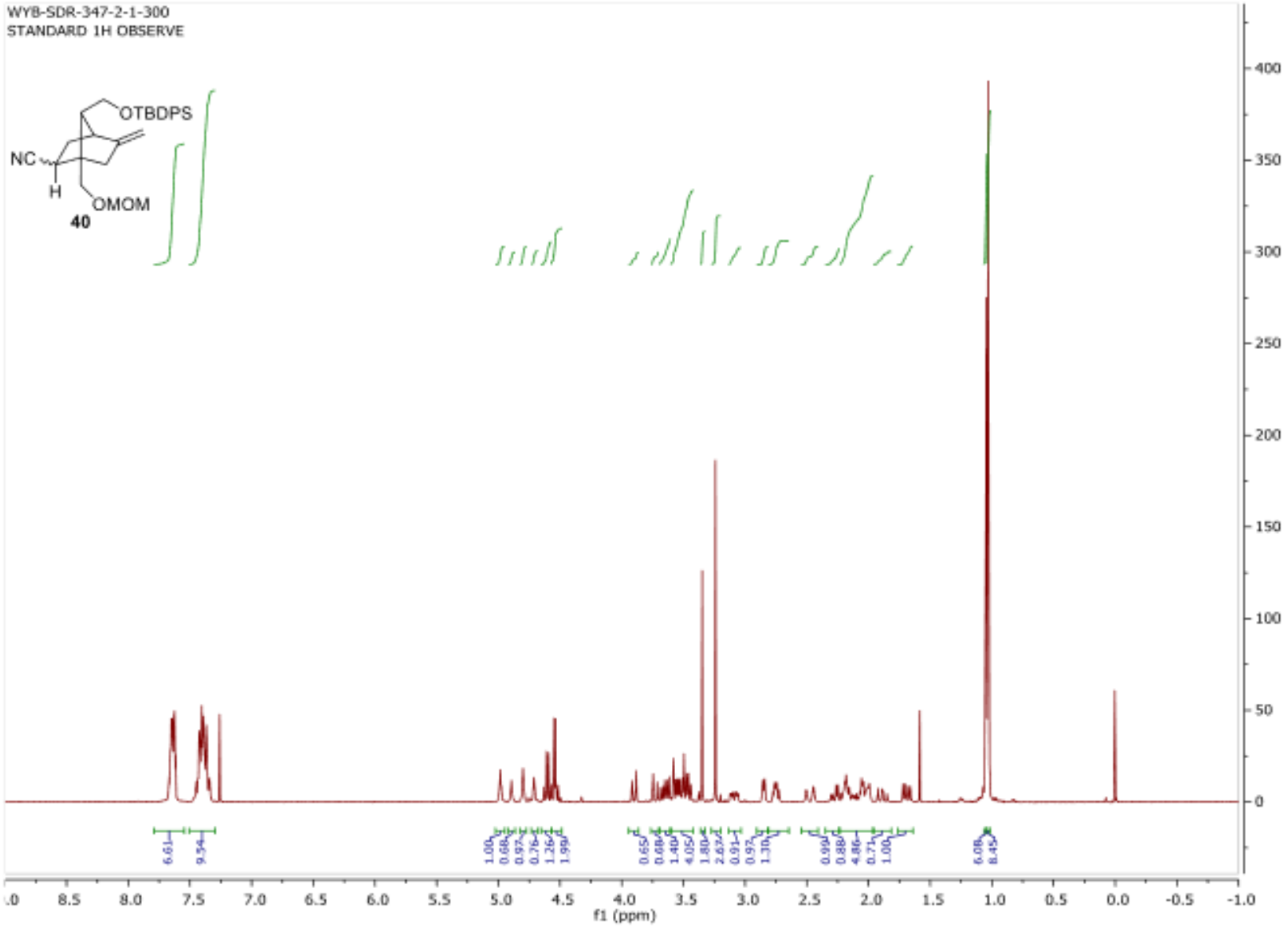
f1 (ppm)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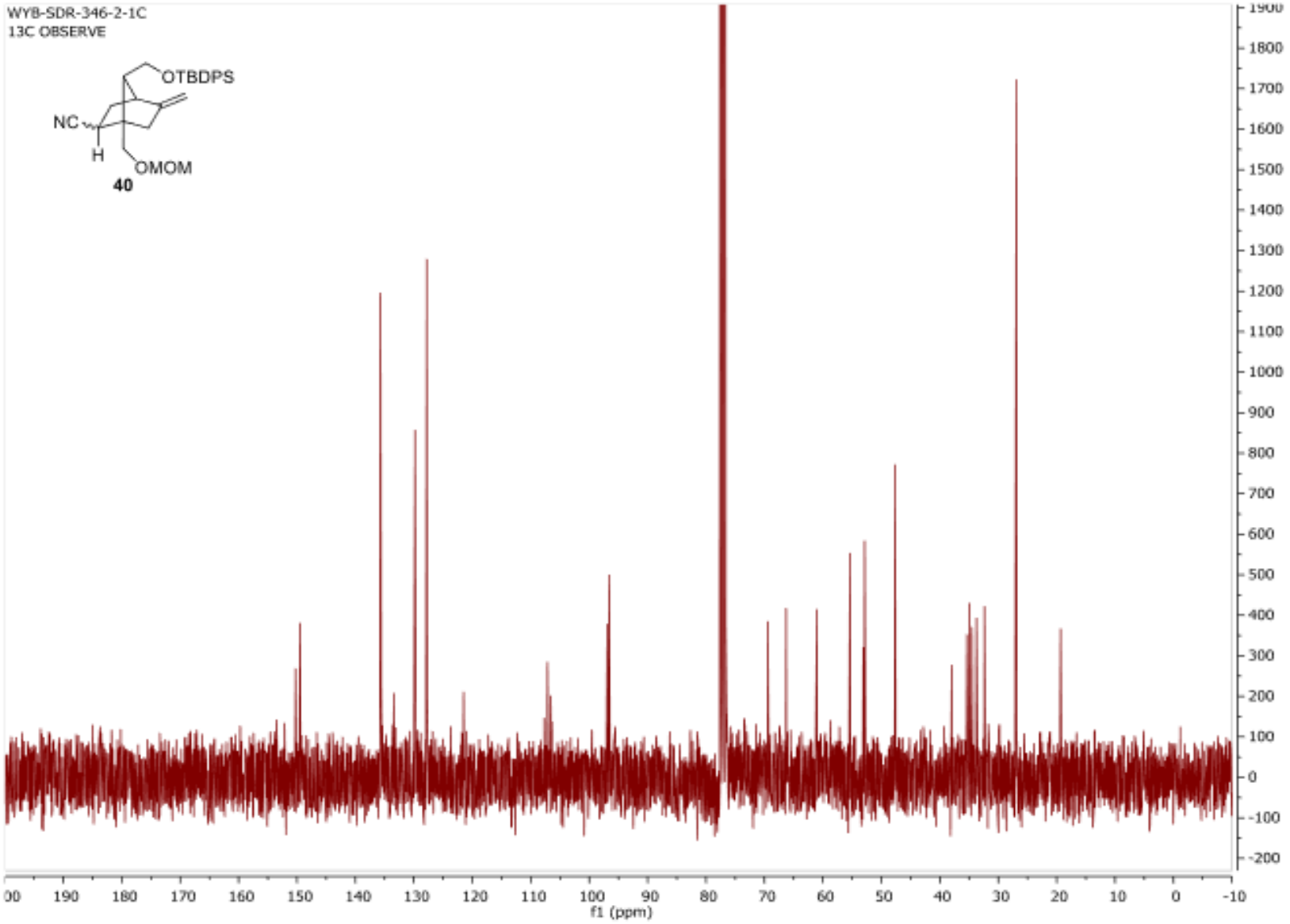
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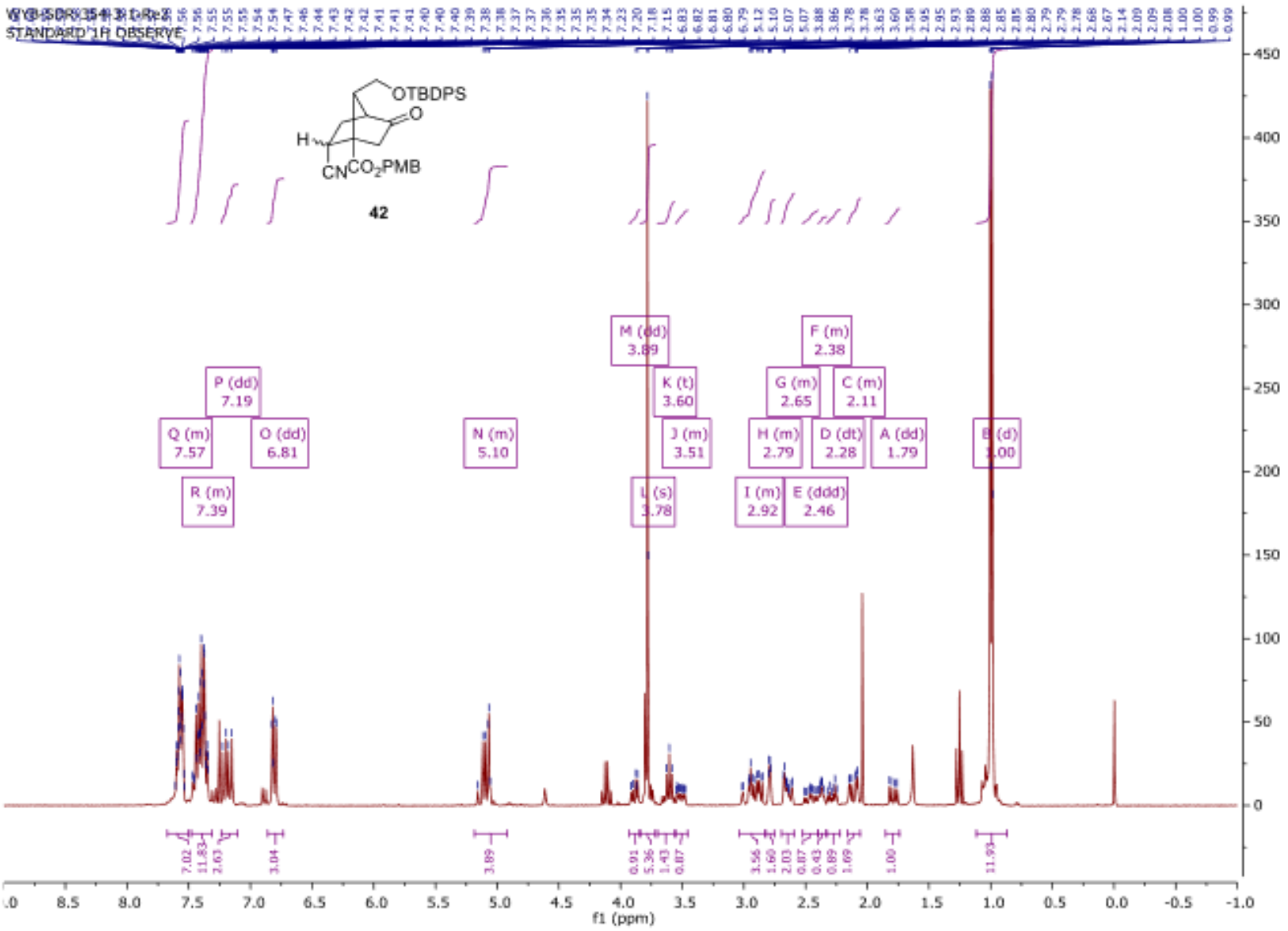
f1 (ppm)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J (m) 3.51
L (s) 3.78
F (m) 2.38
G (m) 2.65
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H (m) 2.79
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B (d) 1.00
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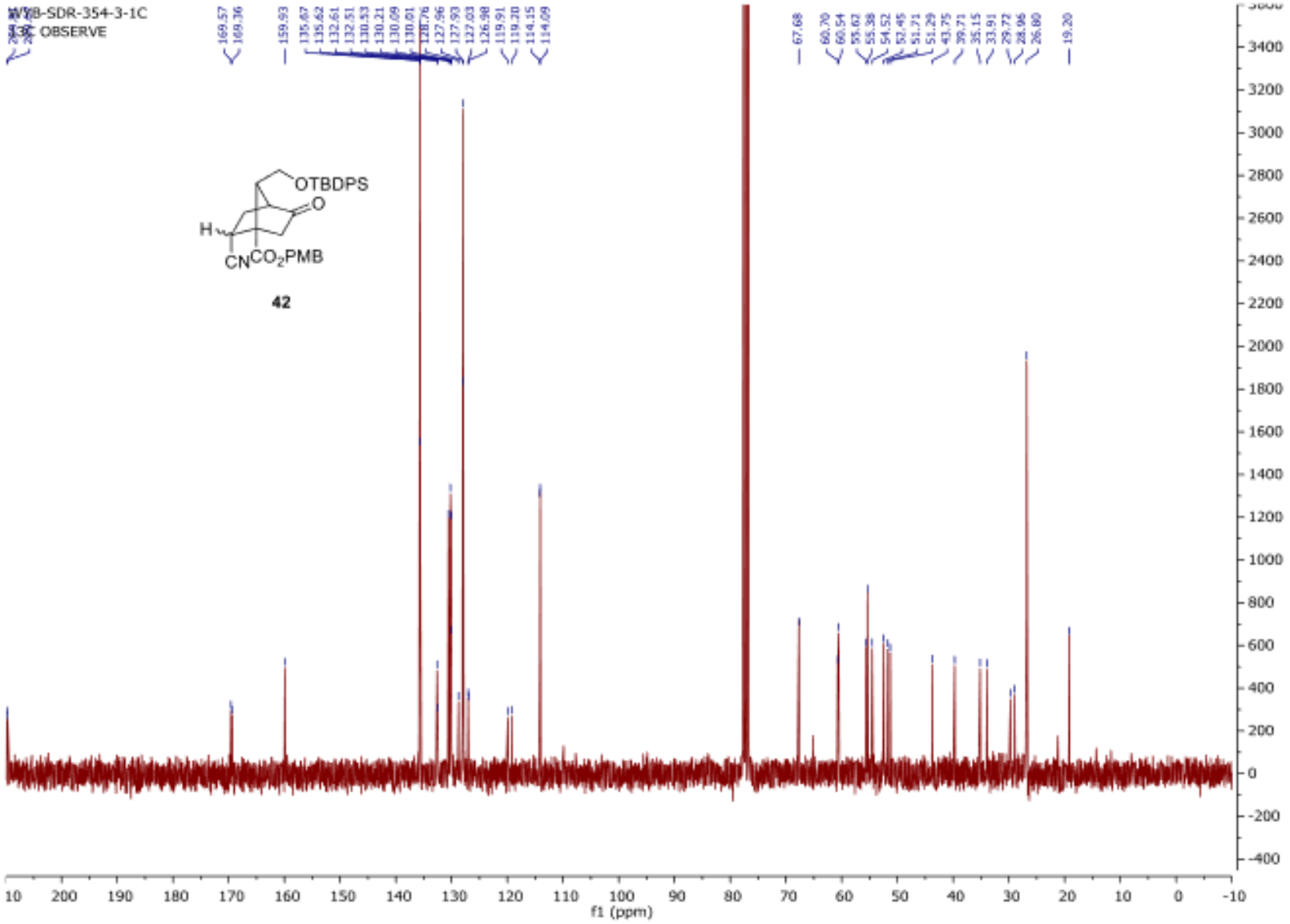
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CN
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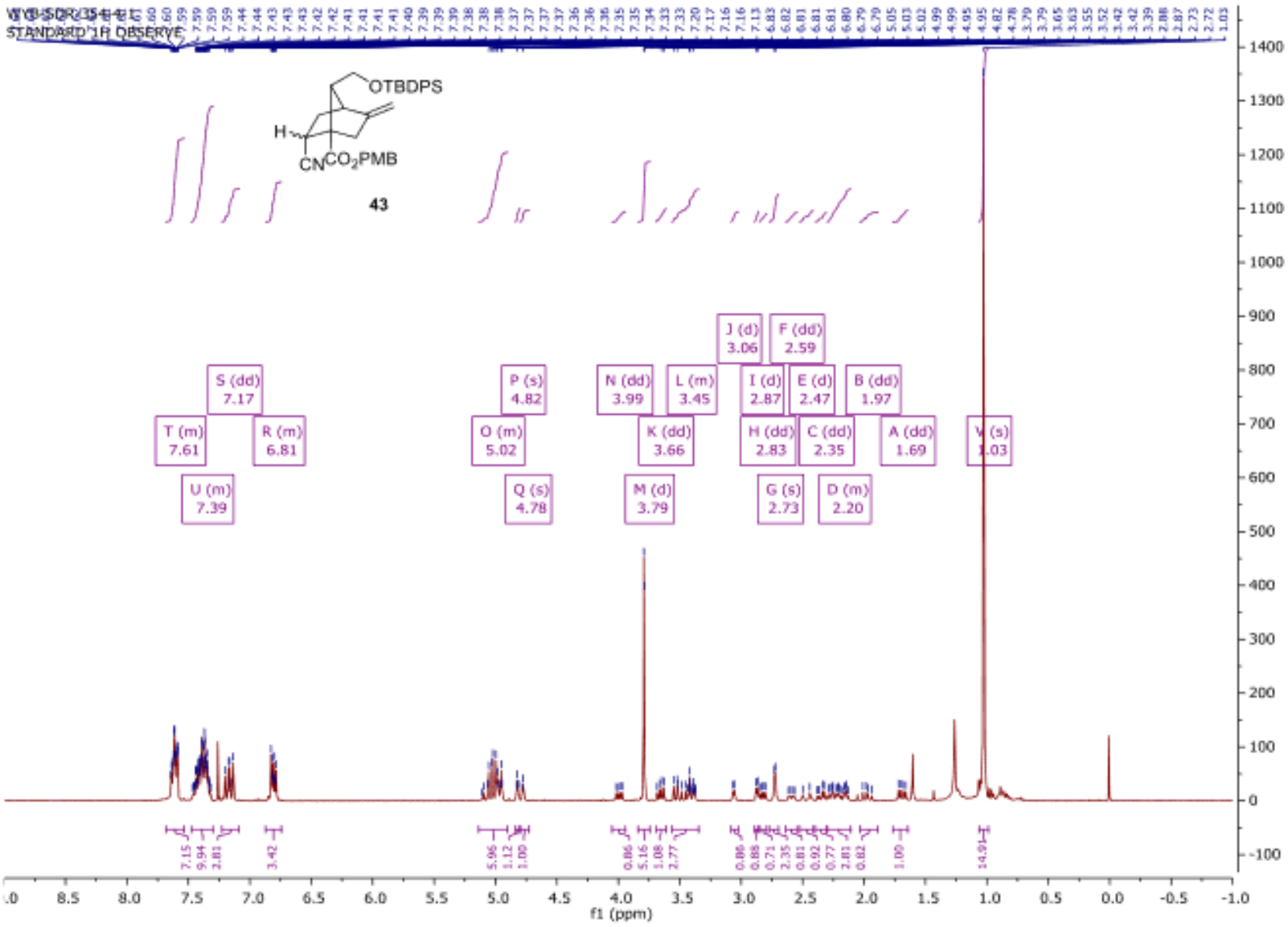
f1 (ppm)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L (m) 3.45
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M (d) 3.79
J (d) 3.06
F (dd) 2.59
I (d) 2.87
E (d) 2.47
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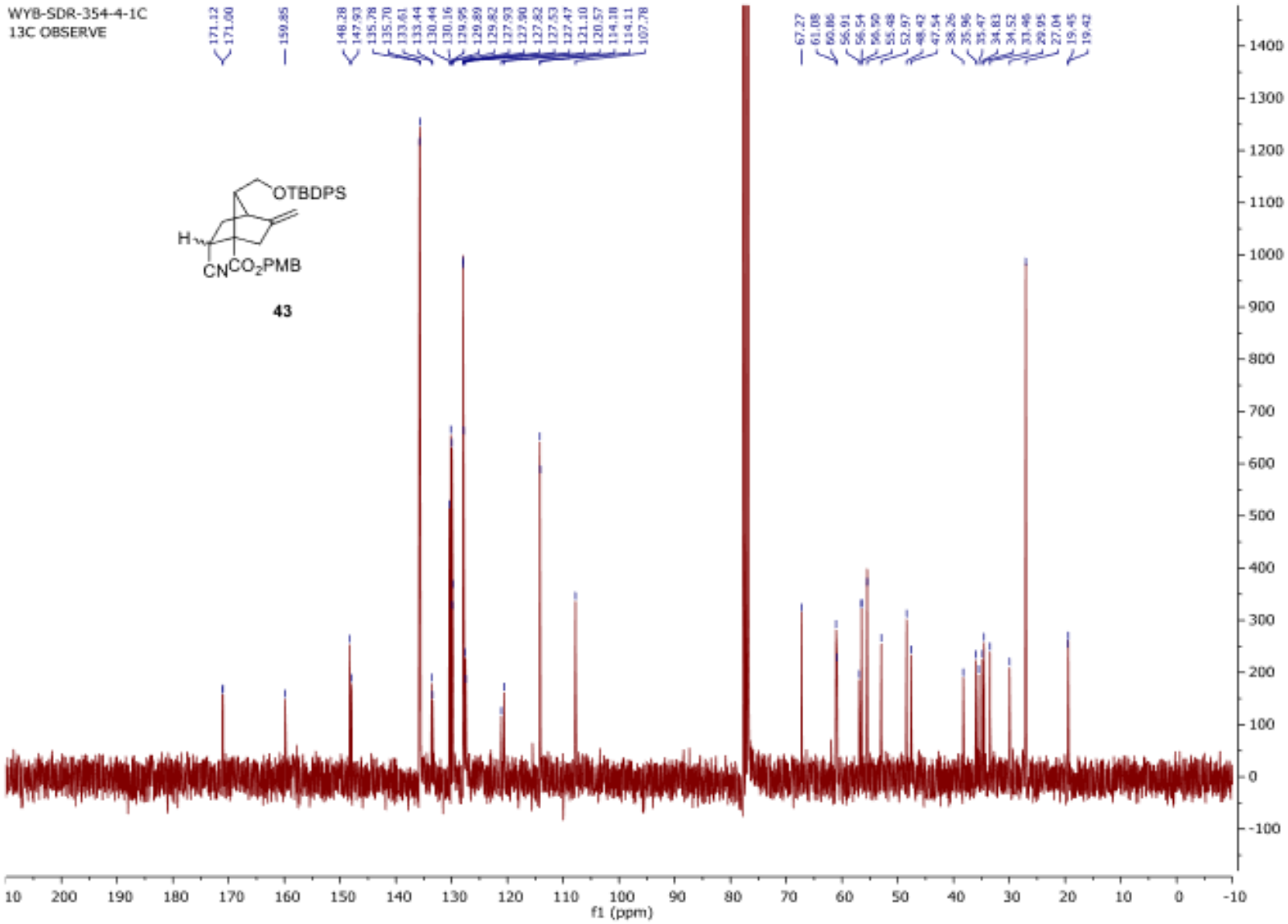
f1 (ppm)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127.53
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114.11
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67.27
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56.54
56.50
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CO2PMB
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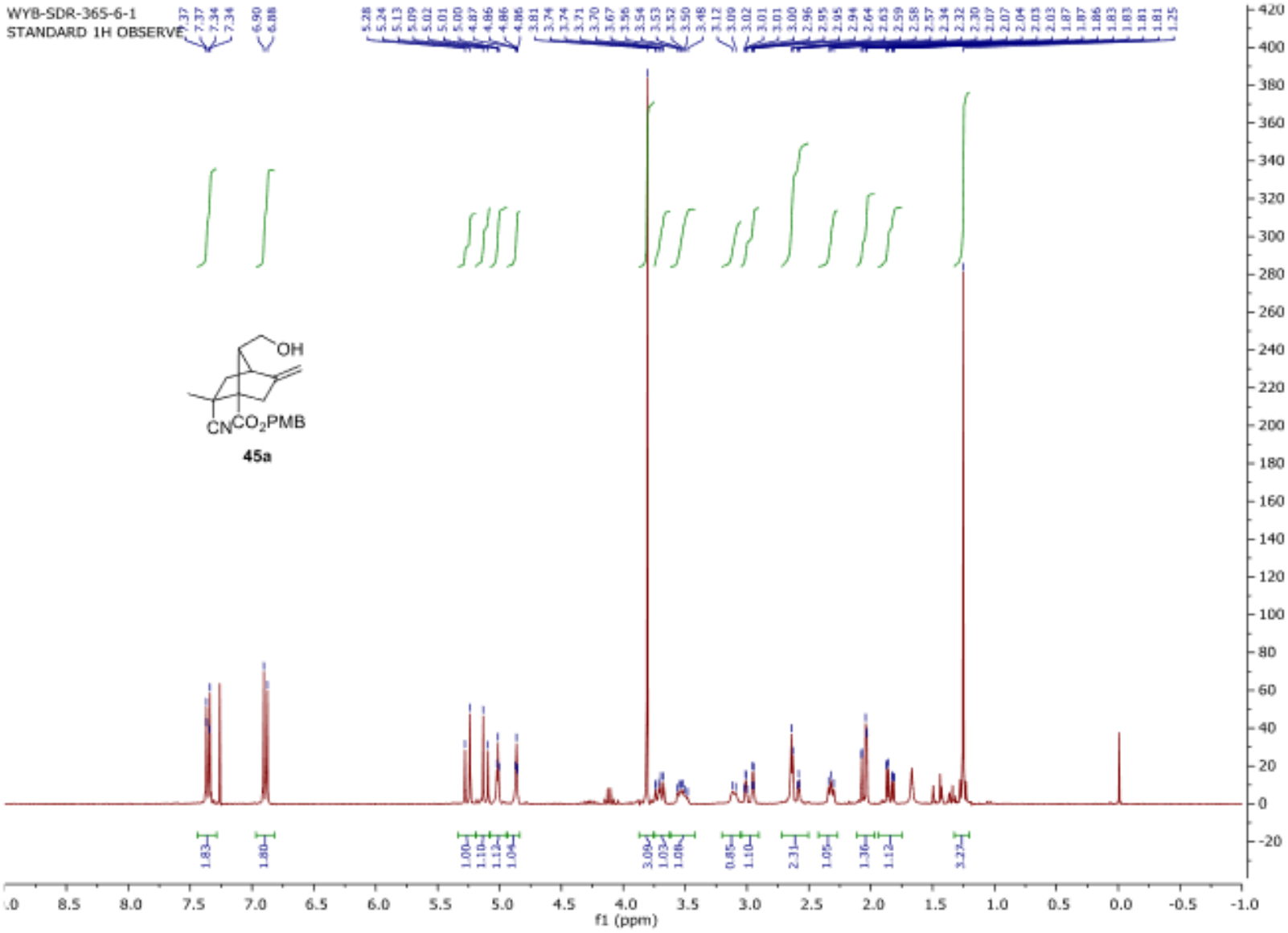
f1 (ppm)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CN
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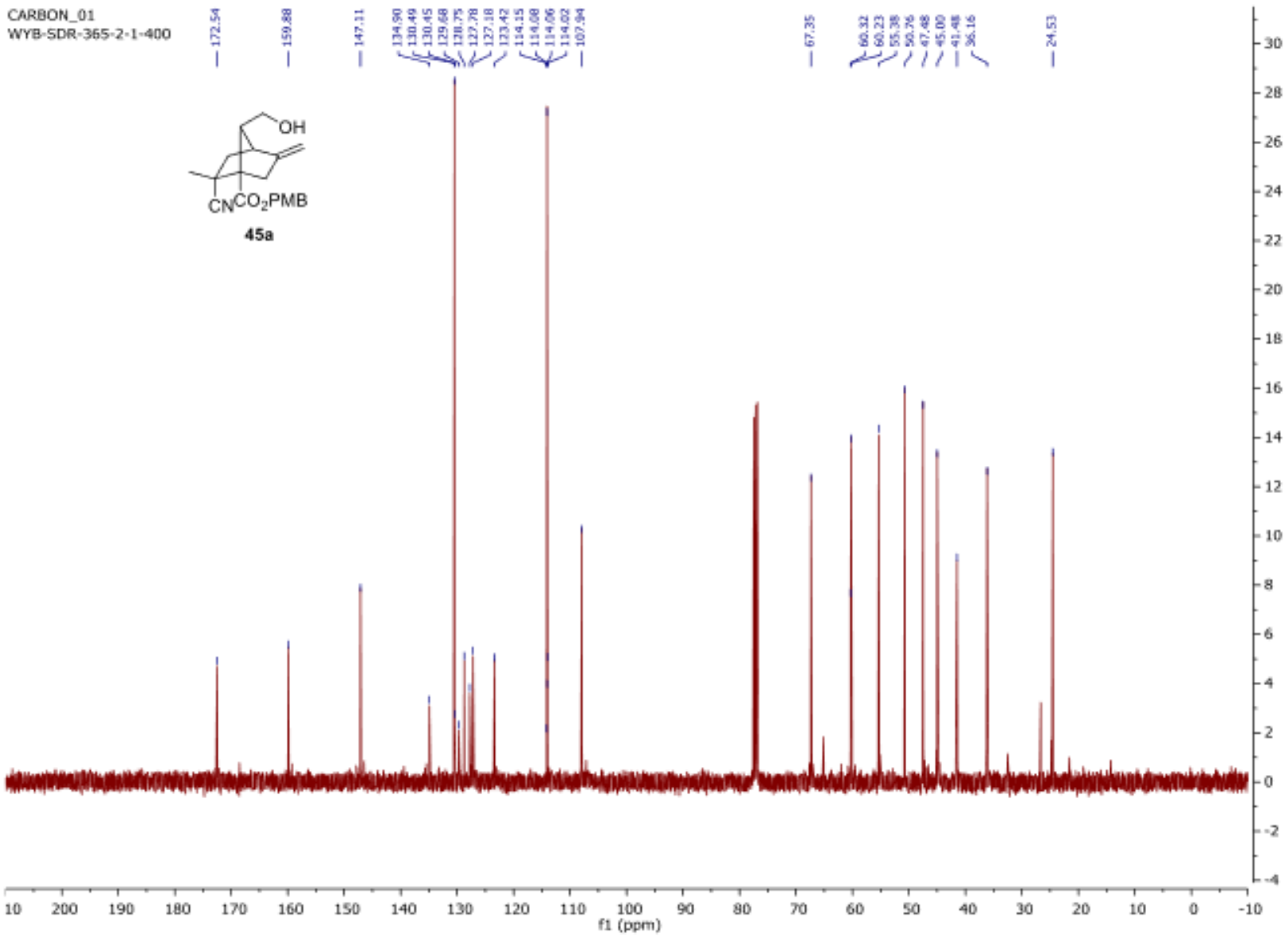
f1 (ppm)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127.78
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114.08
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114.02
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67.35
60.32
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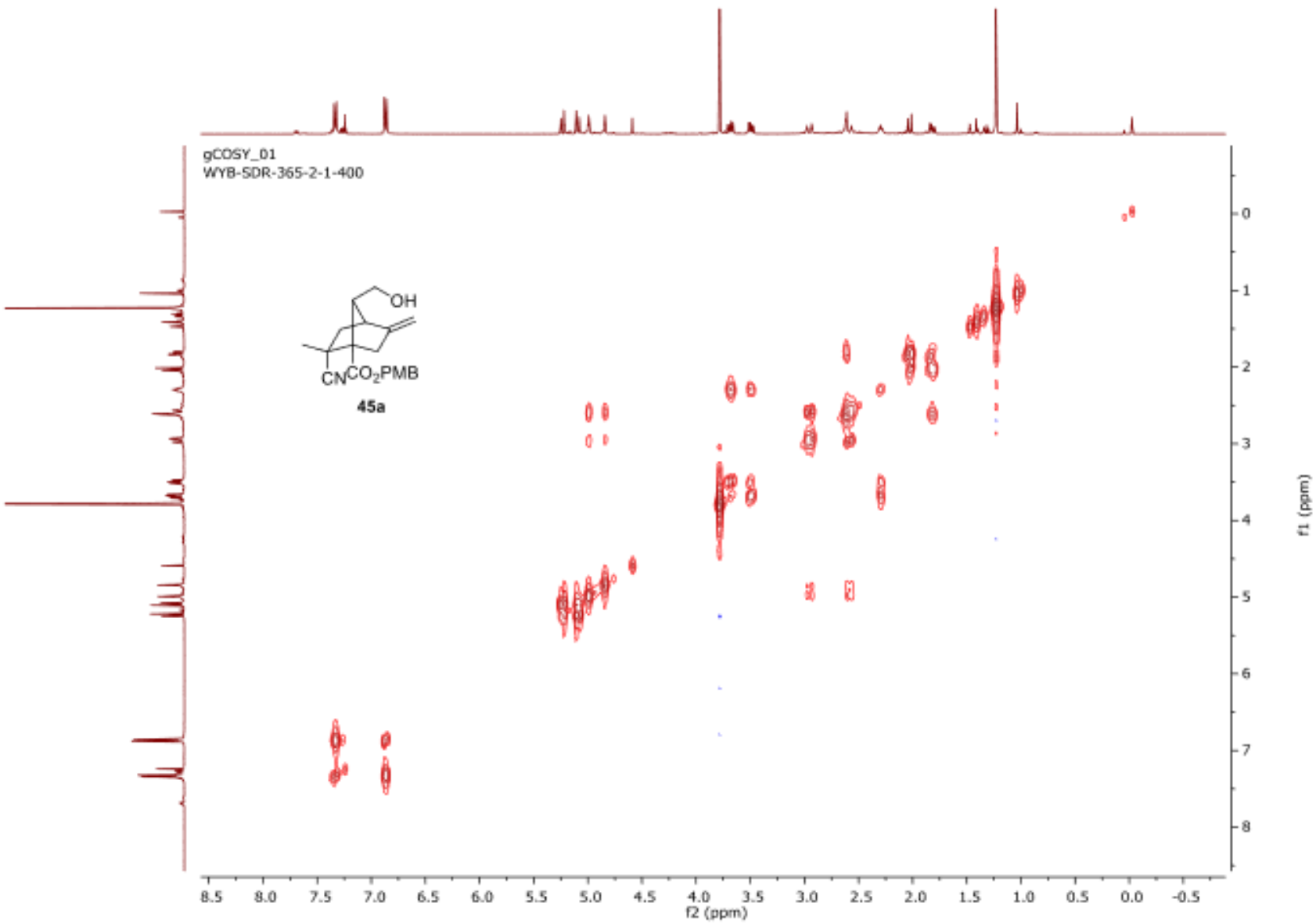
OH
CN
CO2PMB
45a
f1 (ppm)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CN
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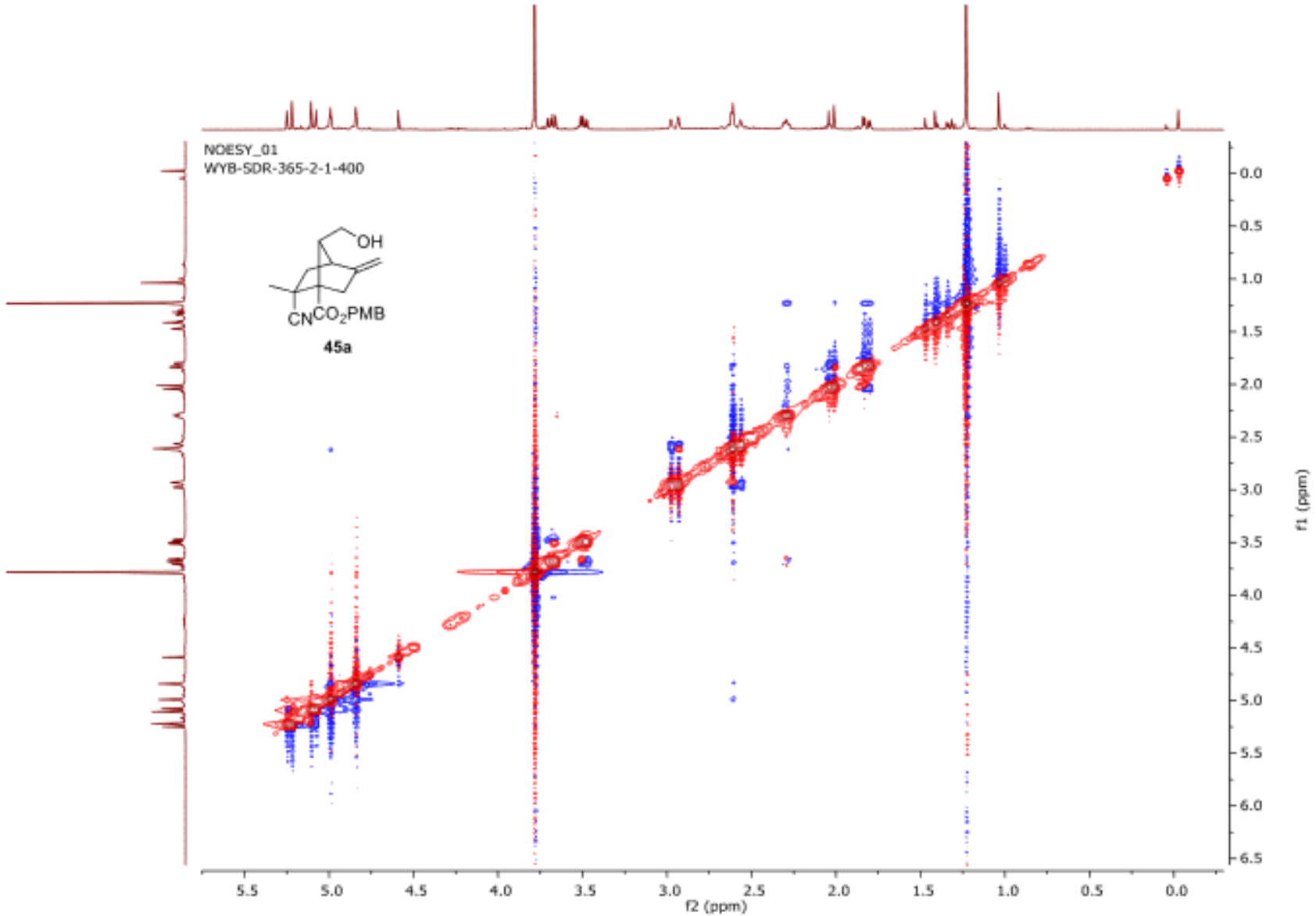
f2 (ppm)
f1 (ppm)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CN
CO2PMB
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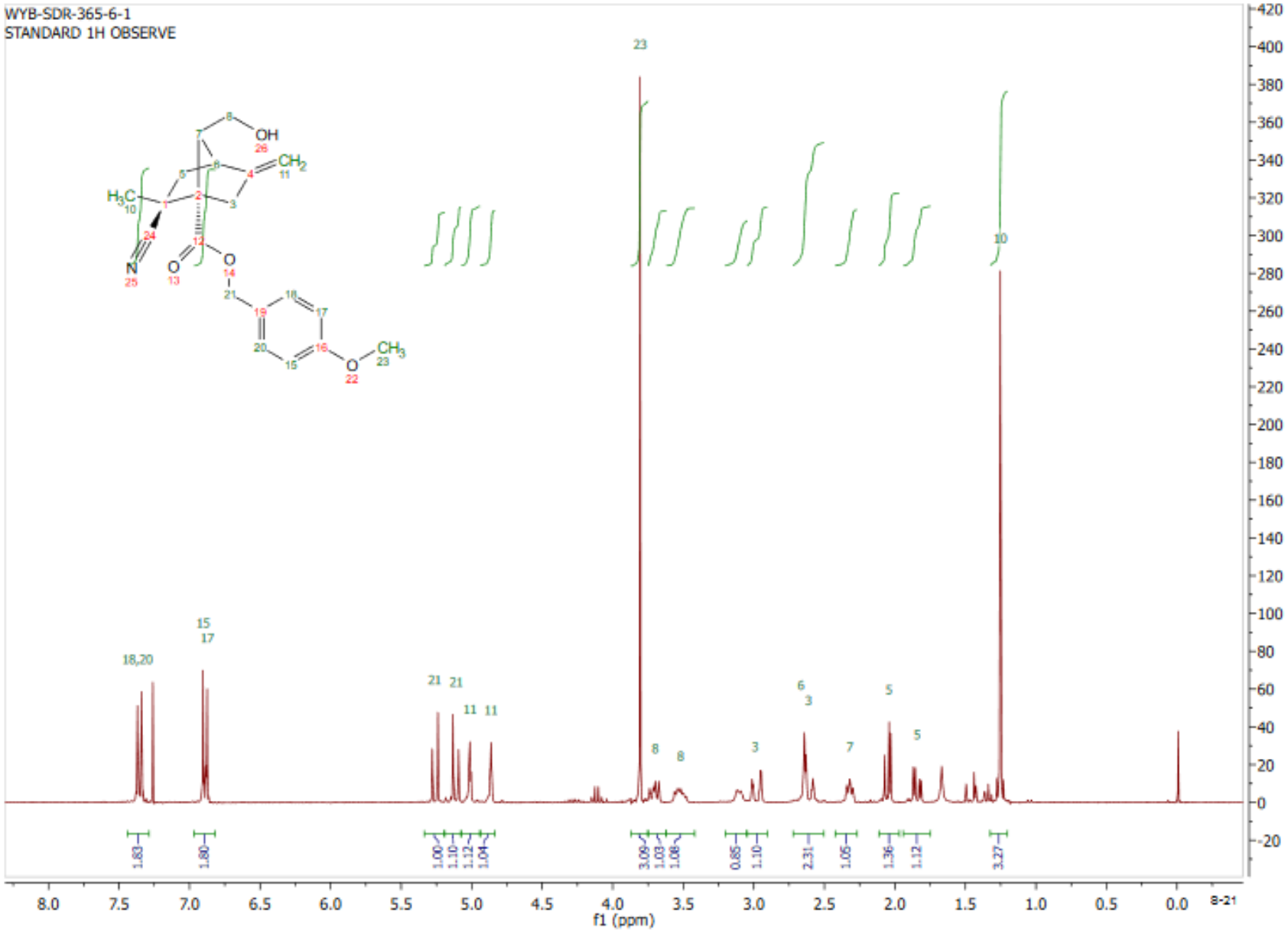
f2 (ppm)
f1 (ppm)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CH3
18,20
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21
21
11
11
23
8
8
3
6
3
7
5
5
10
1.83
1.80
1.00
1.10
1.12
1.04
3.09
1.03
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1.12
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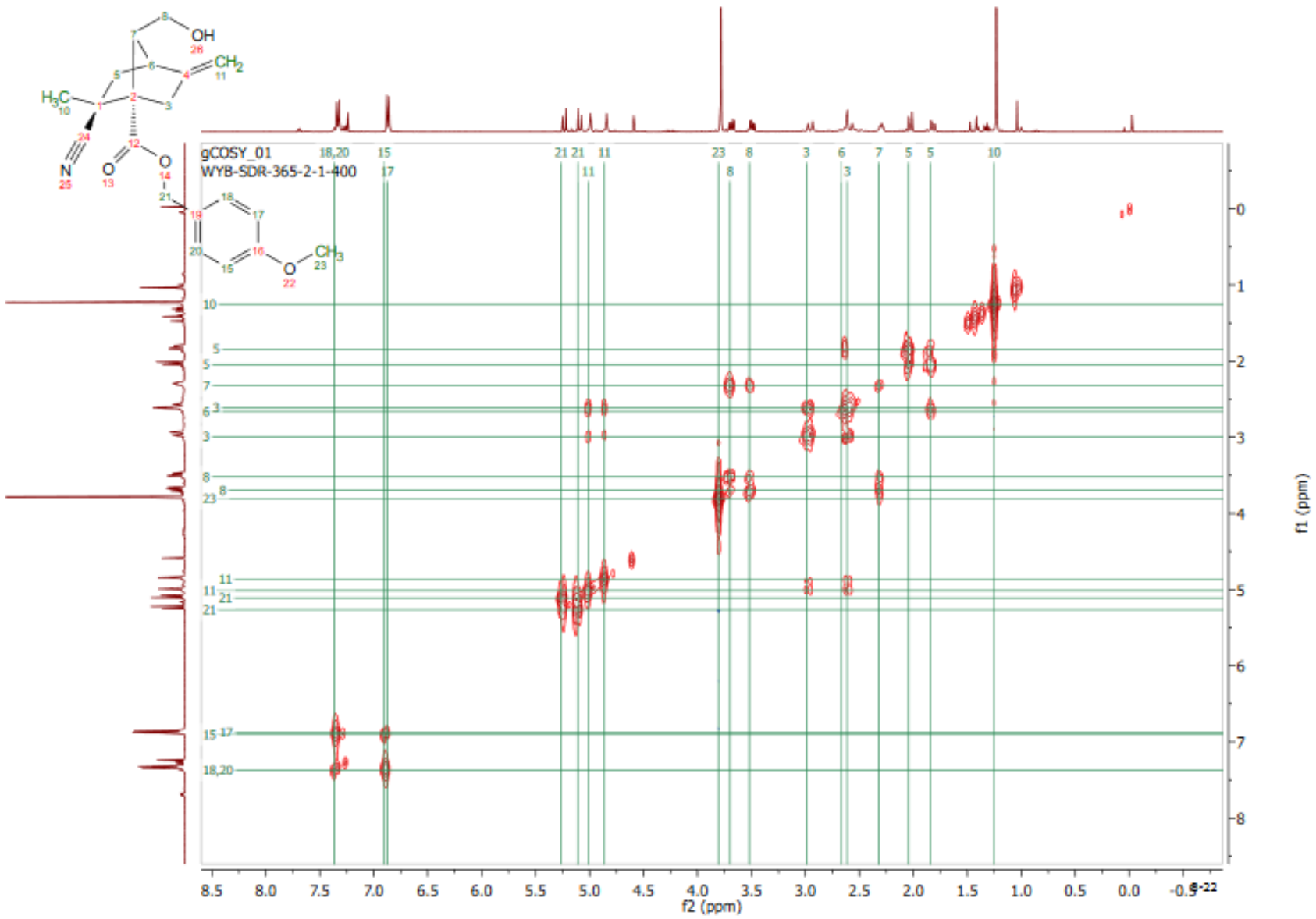
f1 (ppm)
8-21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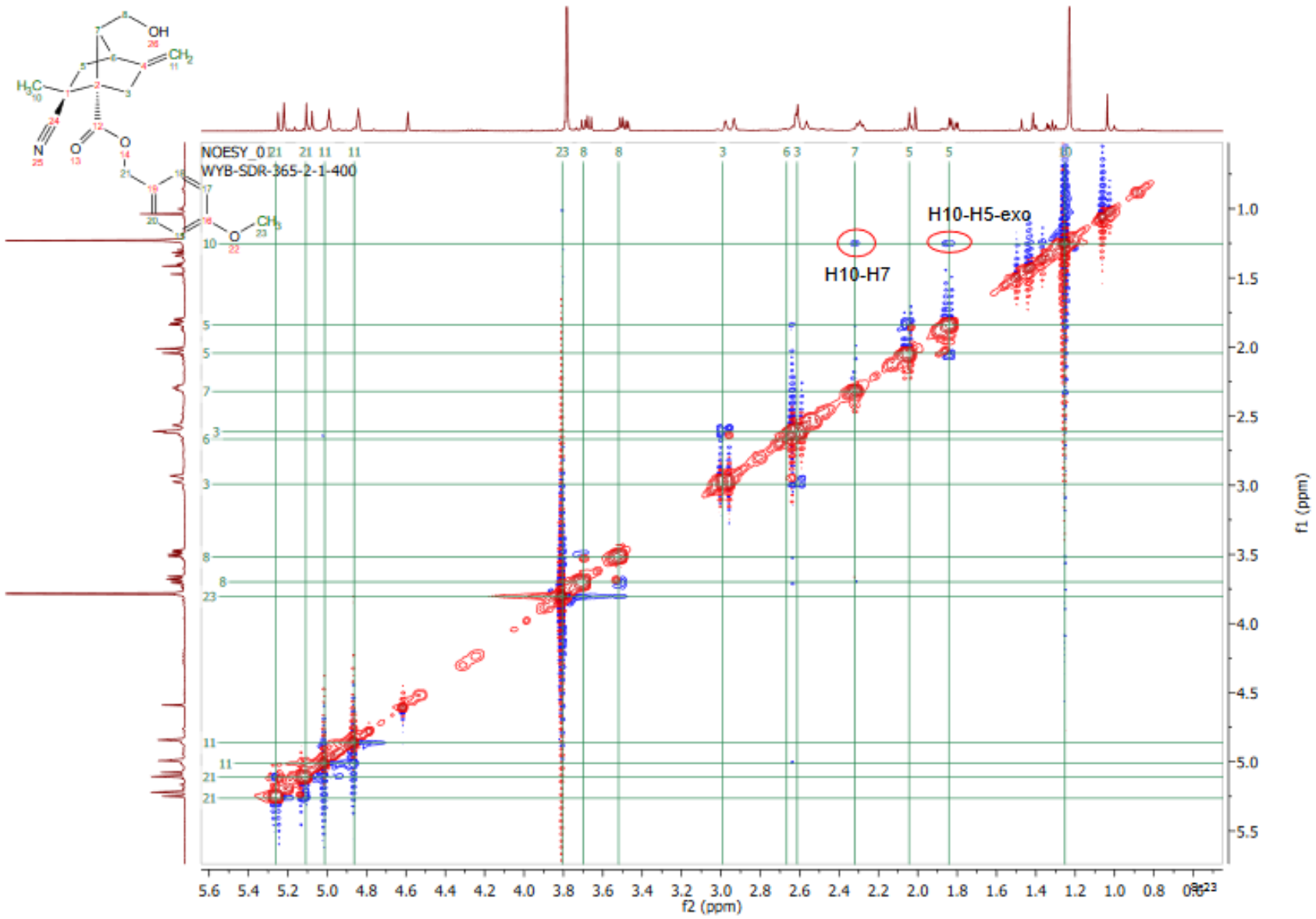
f1 (ppm)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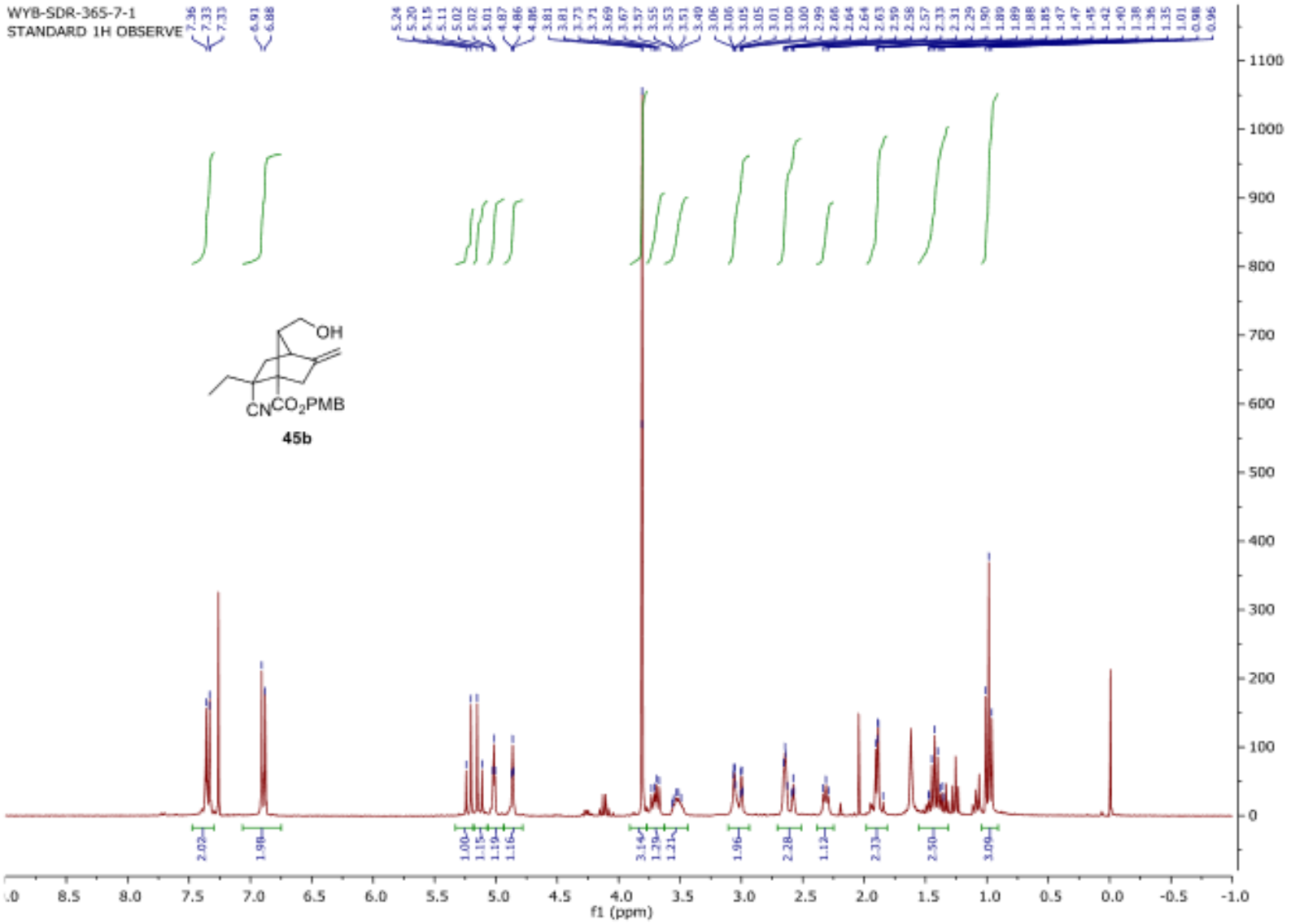
f2 (ppm)
f1 (ppm)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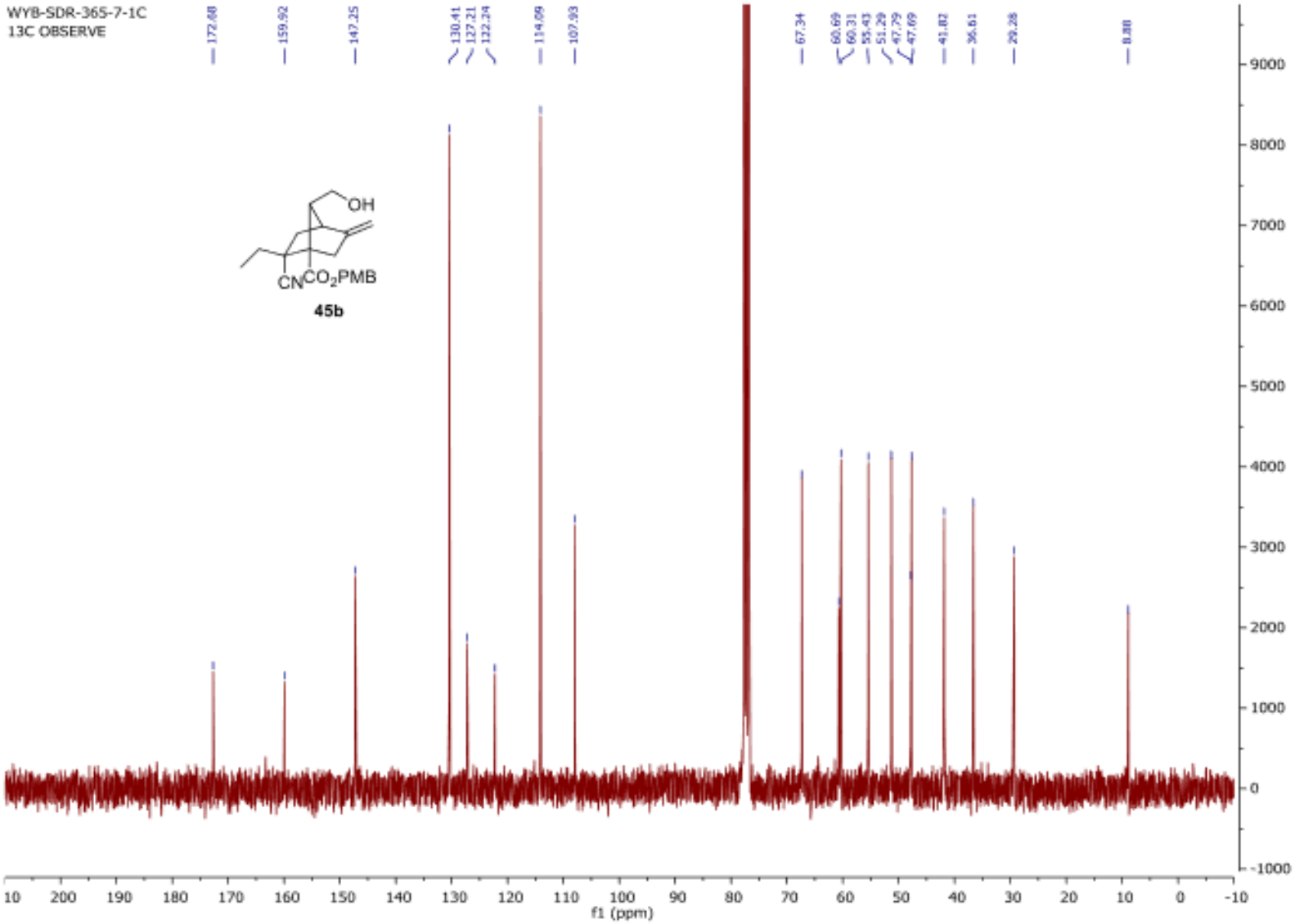
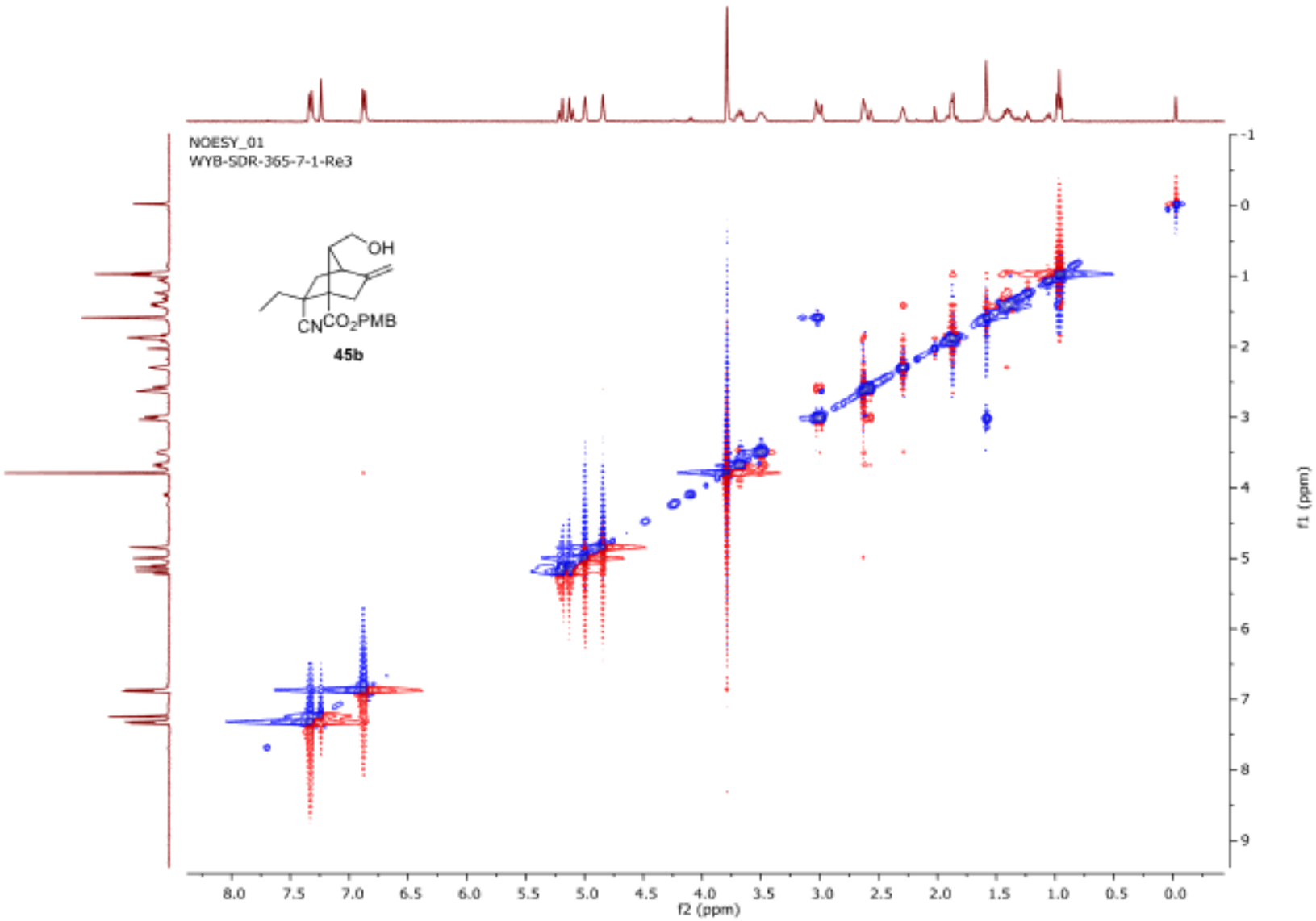
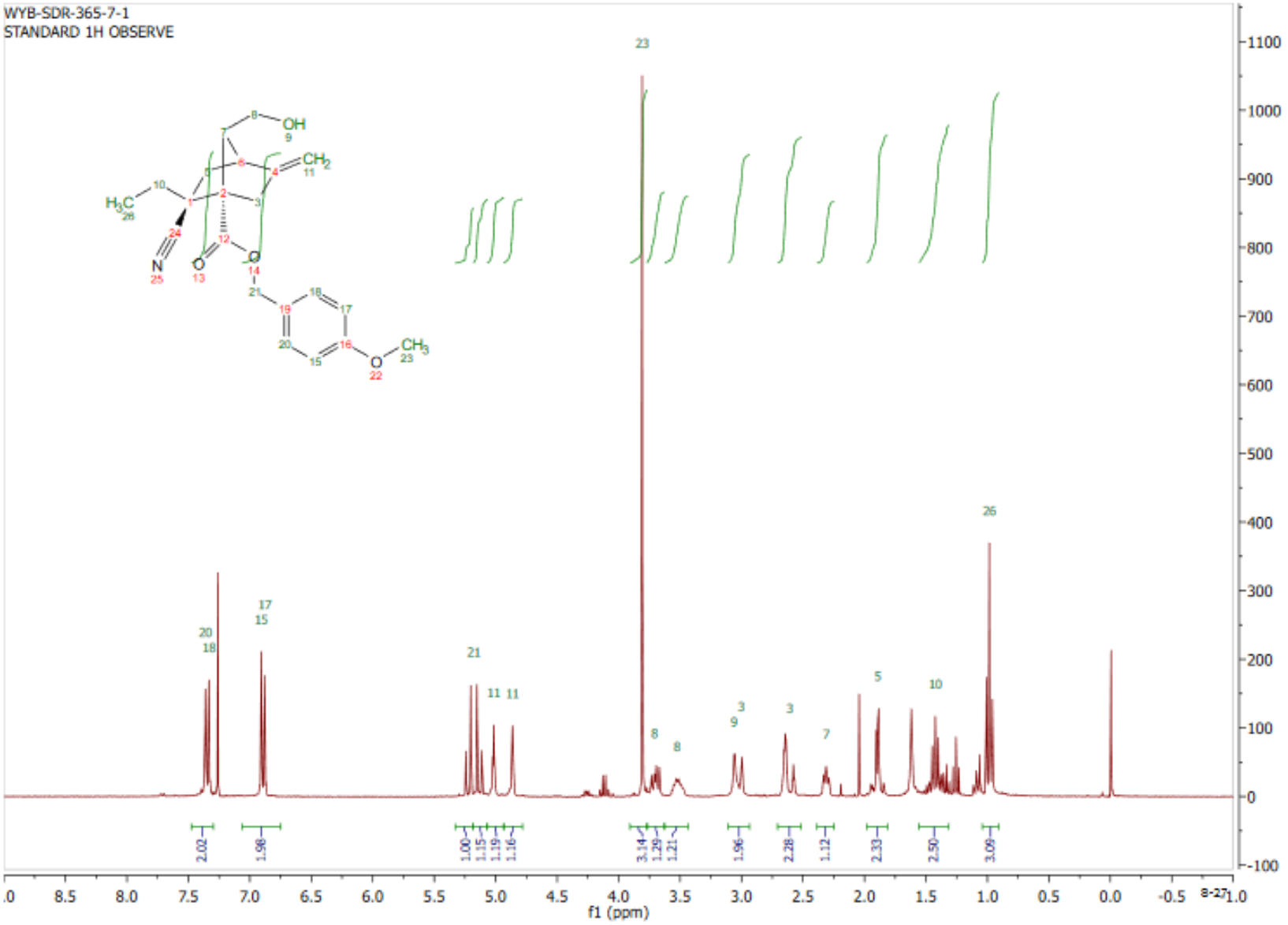
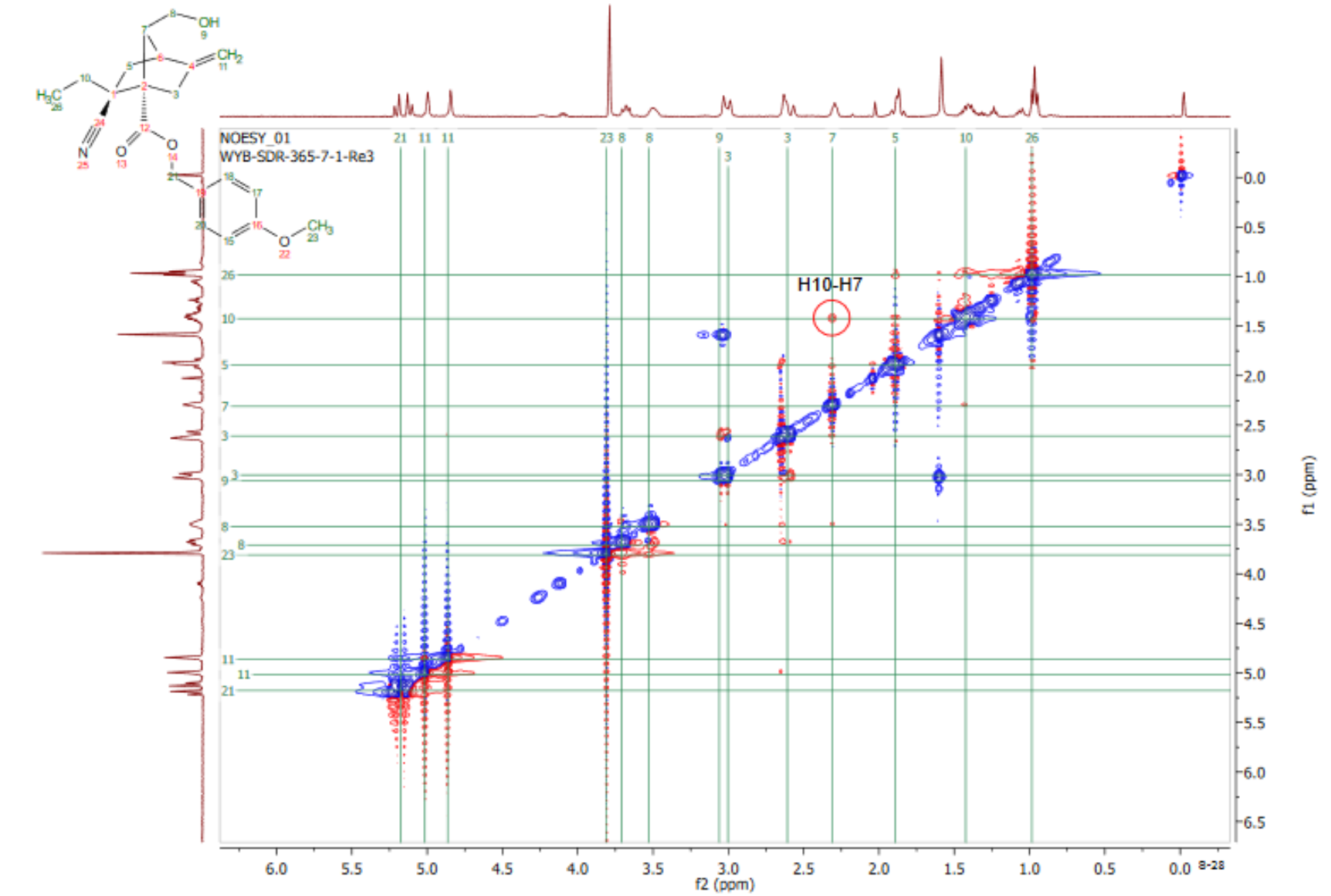
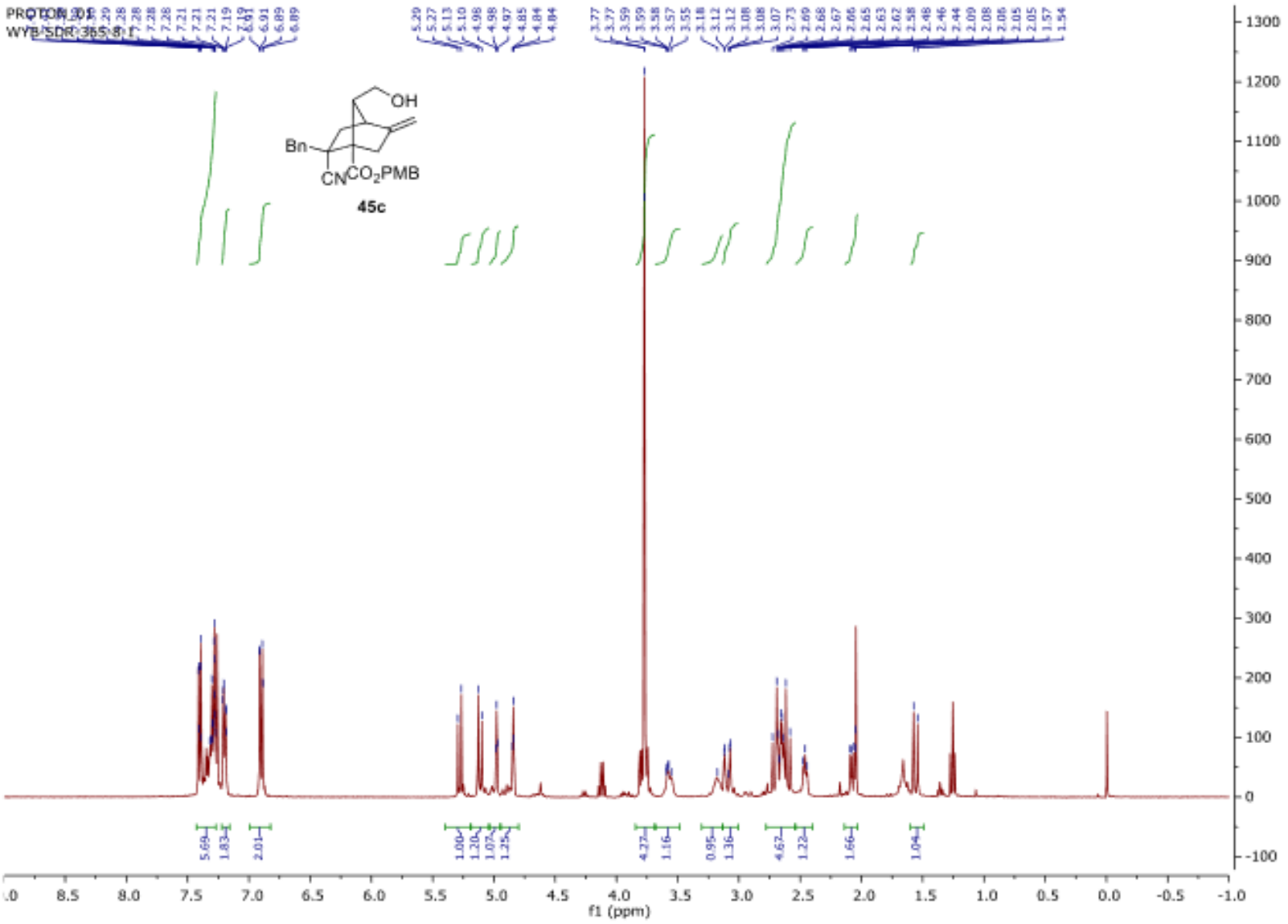
CN
CO2PMB
45b
f1 (ppm)

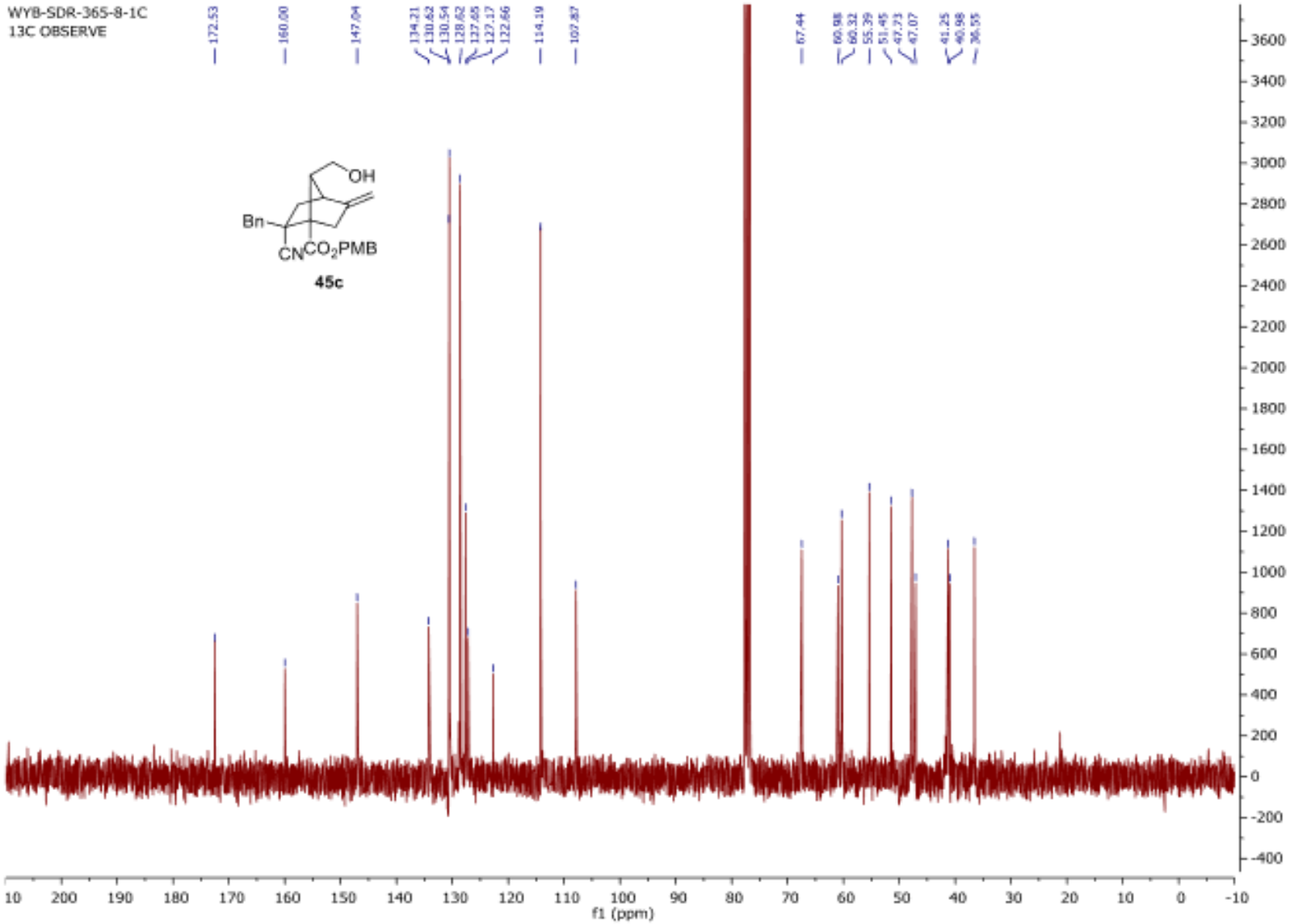

WYB-SDR-365-7-1C
13C OBSERVE
172.68
159.92
147.25
130.41
127.21
122.24
114.69
107.93
67.34
60.69
60.31
55.43
51.29
47.79
47.69
41.82
36.61
29.28
8.88
OH
CN
CO2PMB
45b
f1 (ppm)

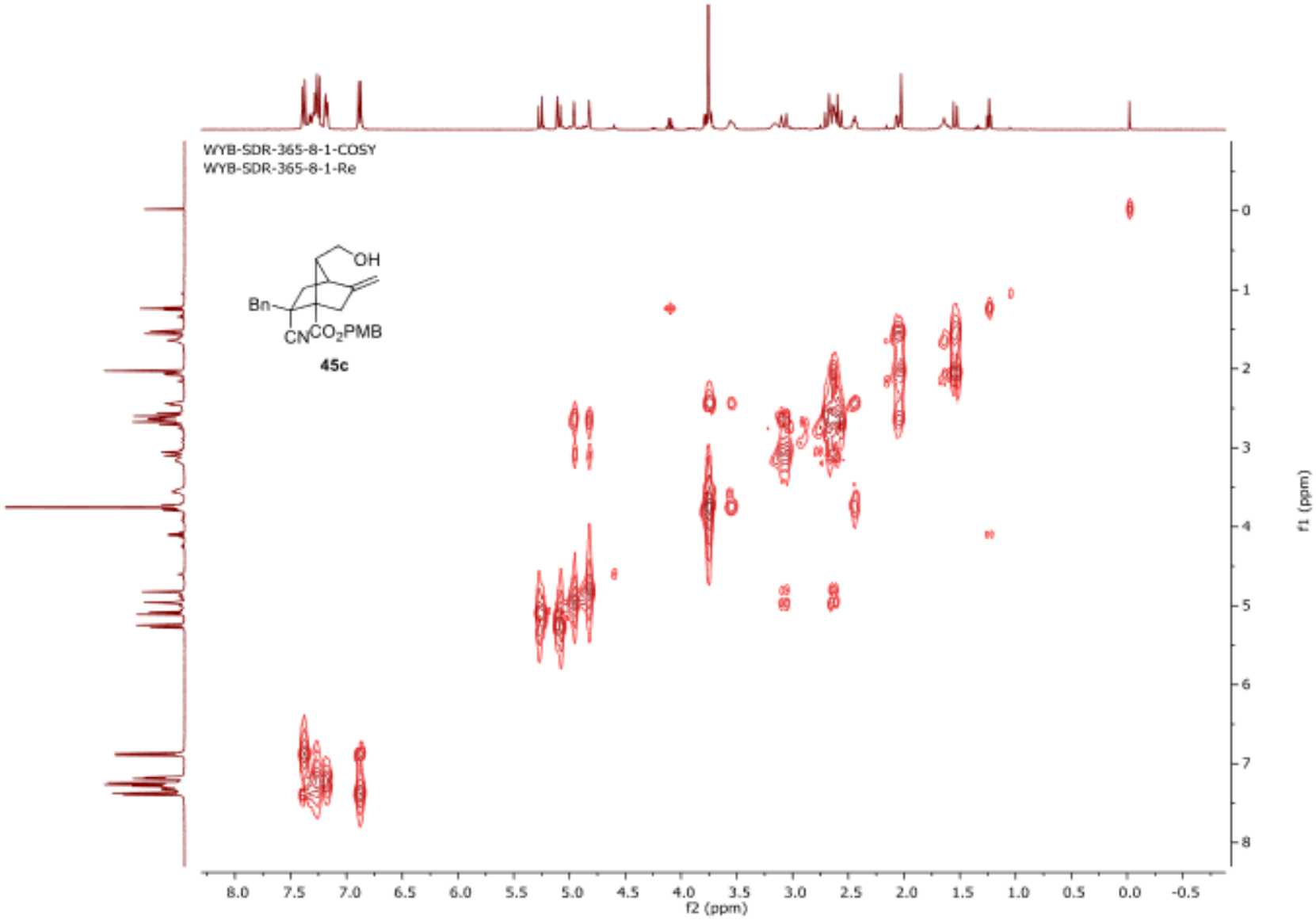

NOESY_01
WYB-SDR-365-7-1-Re3
OH
CN
CO2PMB
45b
f2 (ppm)
f1 (ppm)

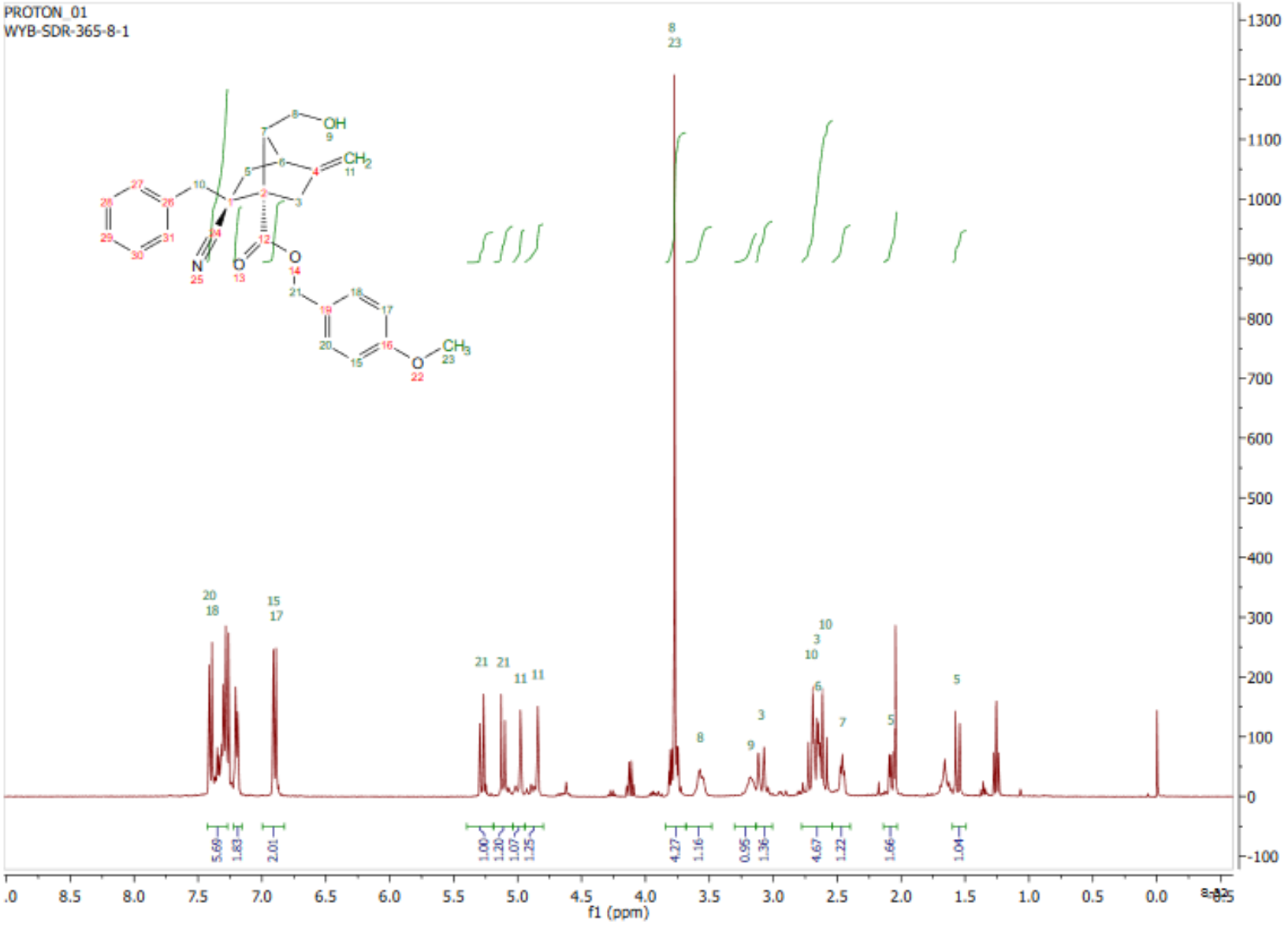

WYB-SDR-365-7-1
STANDARD 1H OBSERVE
f1 (ppm)

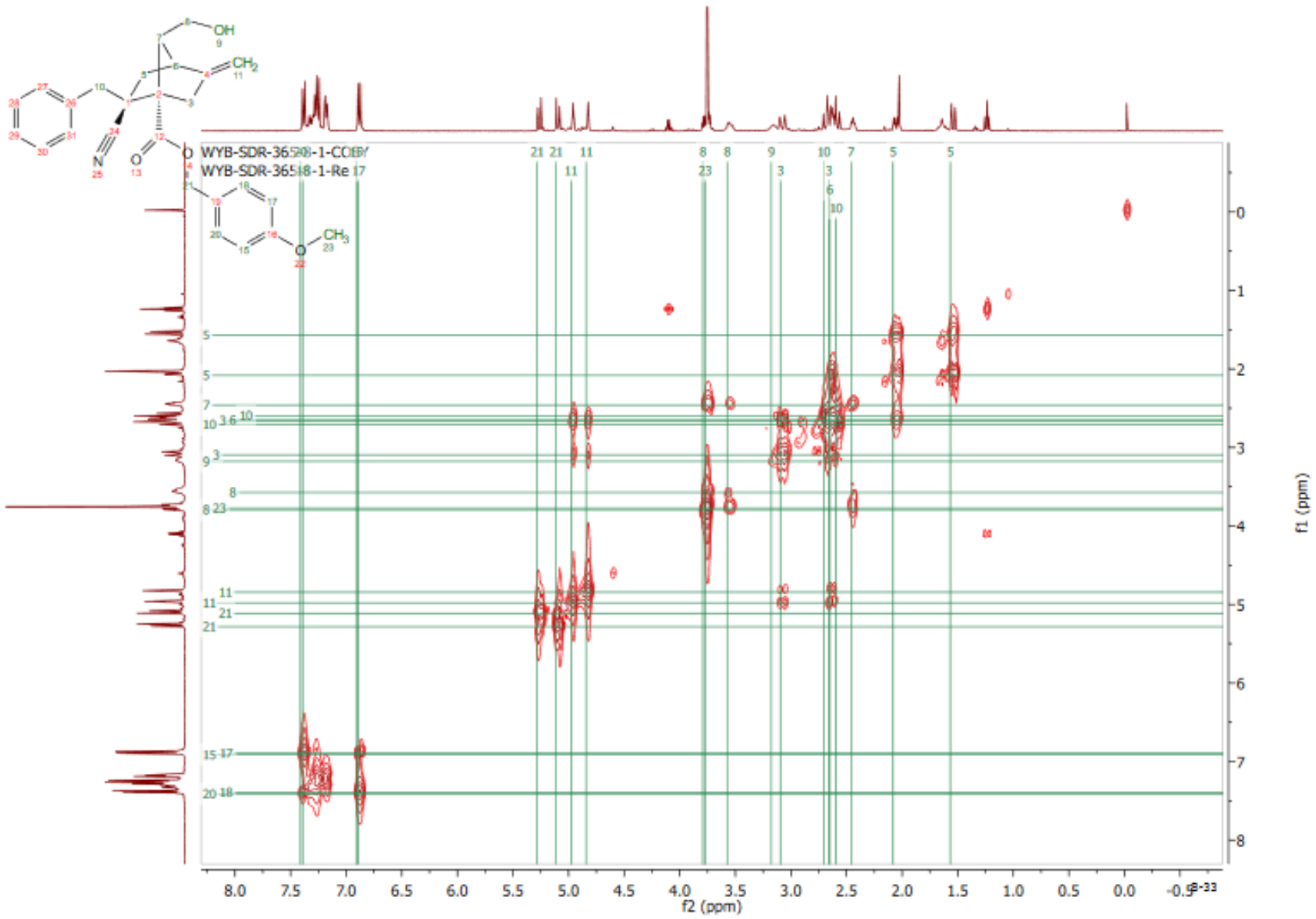

NOESY_01
WYB-SDR-365-7-1-Re3
H10-H7
f2 (ppm)
f1 (ppm)
8-28

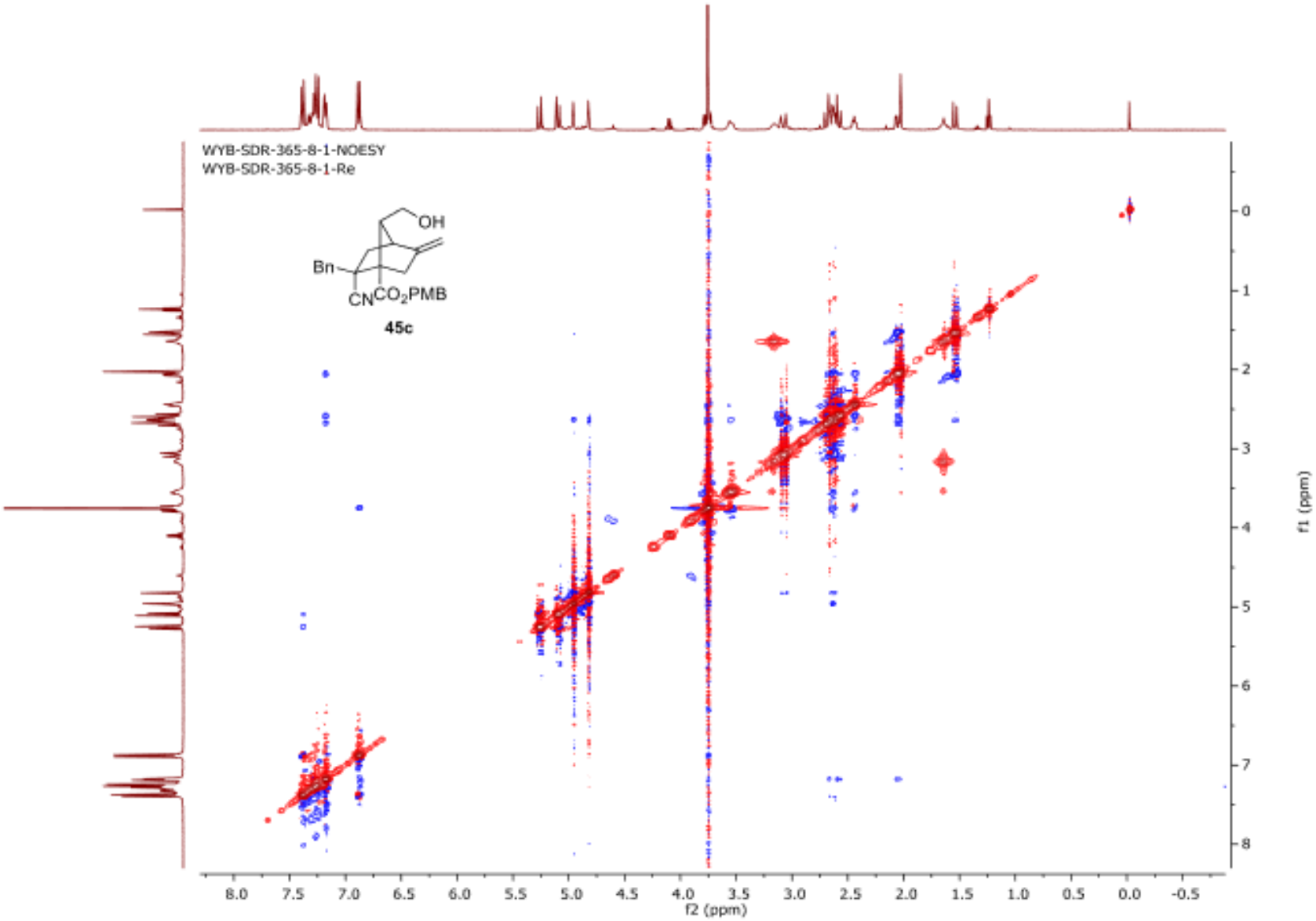

OH
Bn
CN
CO2PMB
45c
f1 (ppm)

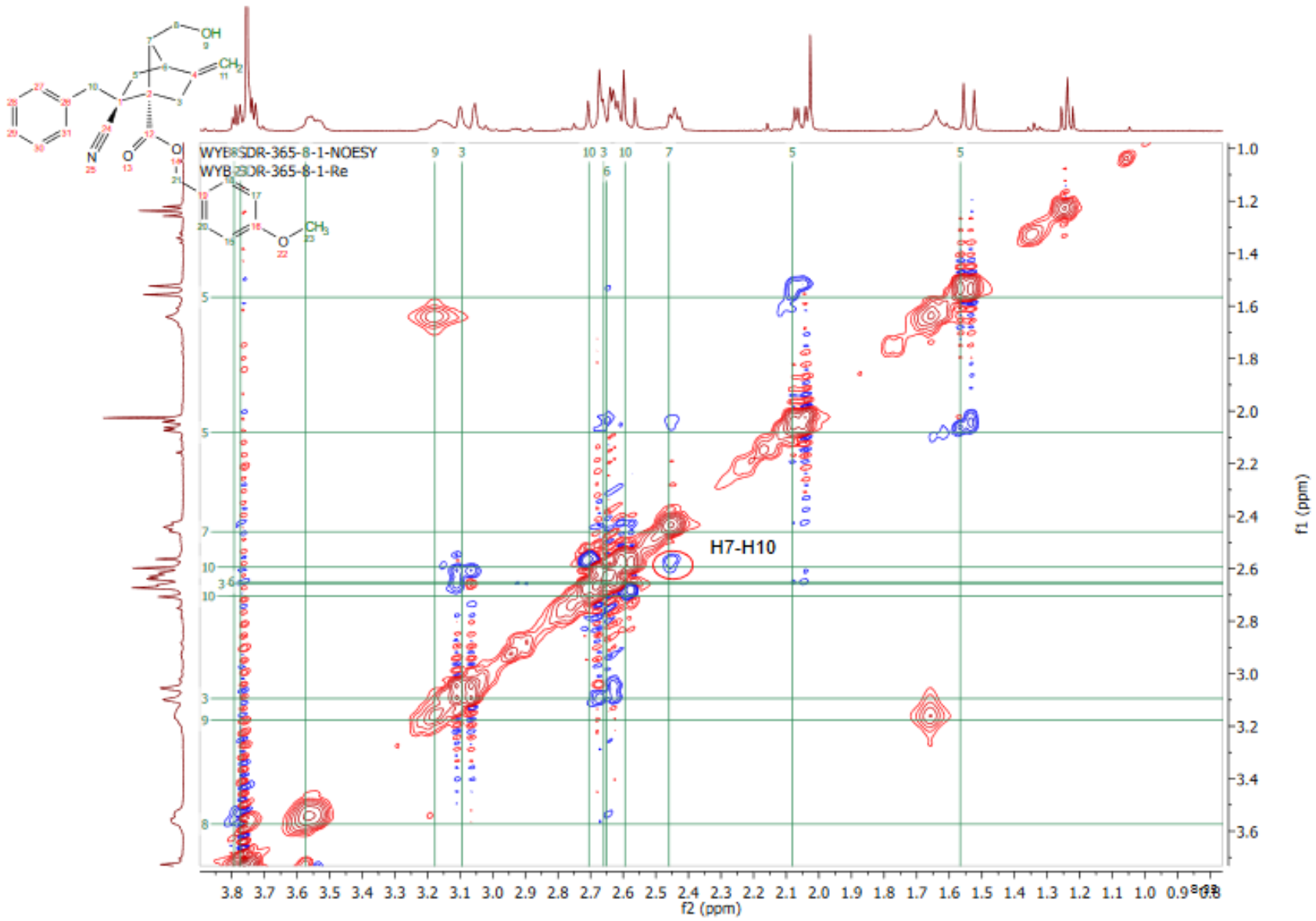

WYB-SDR-365-8-1C
13C OBSERVE
172.53
160.00
147.04
134.21
130.62
130.54
128.62
127.65
127.17
122.66
114.19
107.87
67.44
60.98
60.32
55.39
51.45
47.73
47.07
41.25
40.98
36.55
OH
Bn
CN
CO2PMB
45c
f1 (ppm)

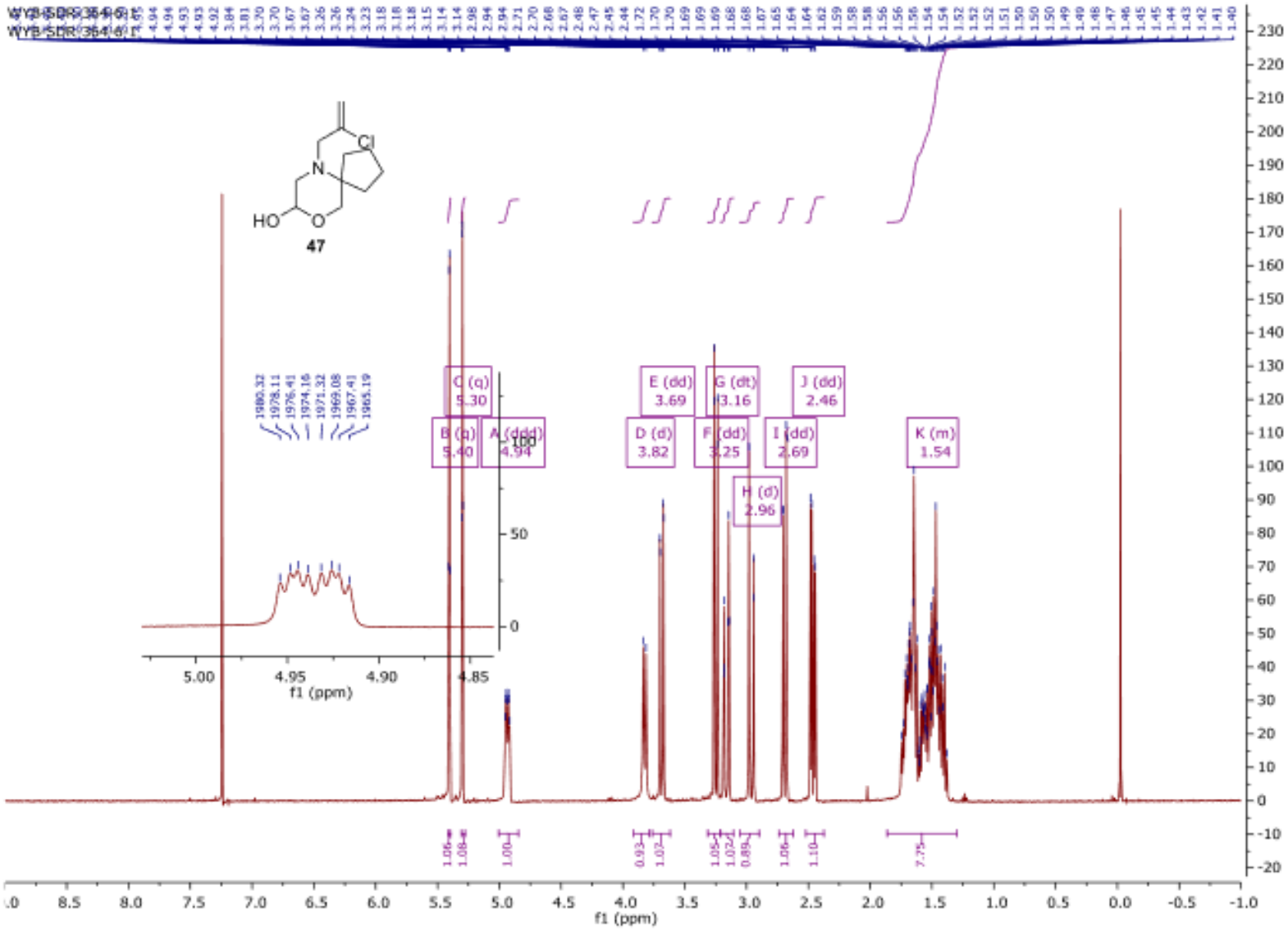

WYB-SDR-365-8-1-COSY
WYB-SDR-365-8-1-Re
OH
Bn
CN
CO2PMB
45c
f2 (ppm)
f1 (ppm)

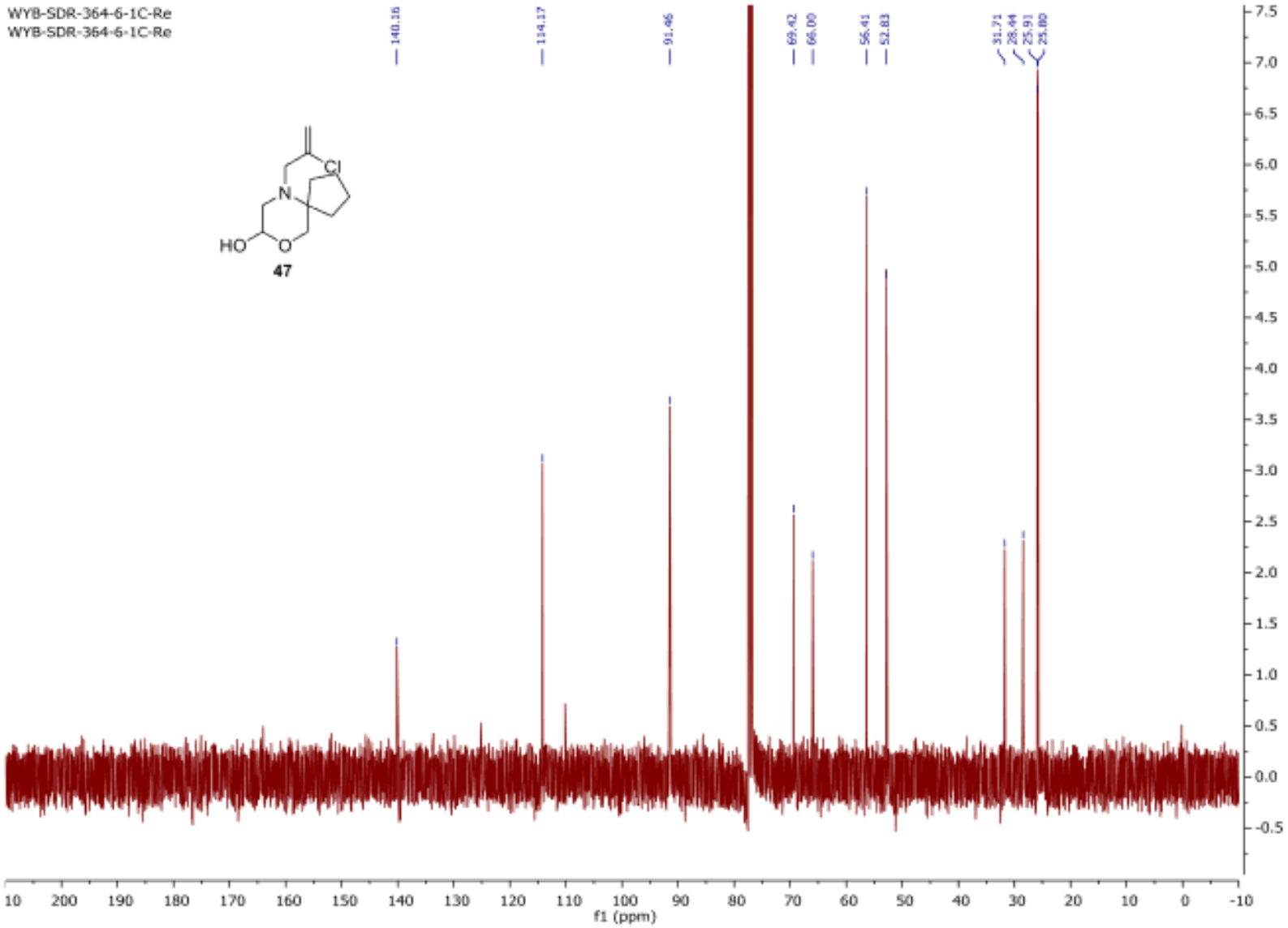

PROTON_01
WYB-SDR-365-8-1
f1 (ppm)

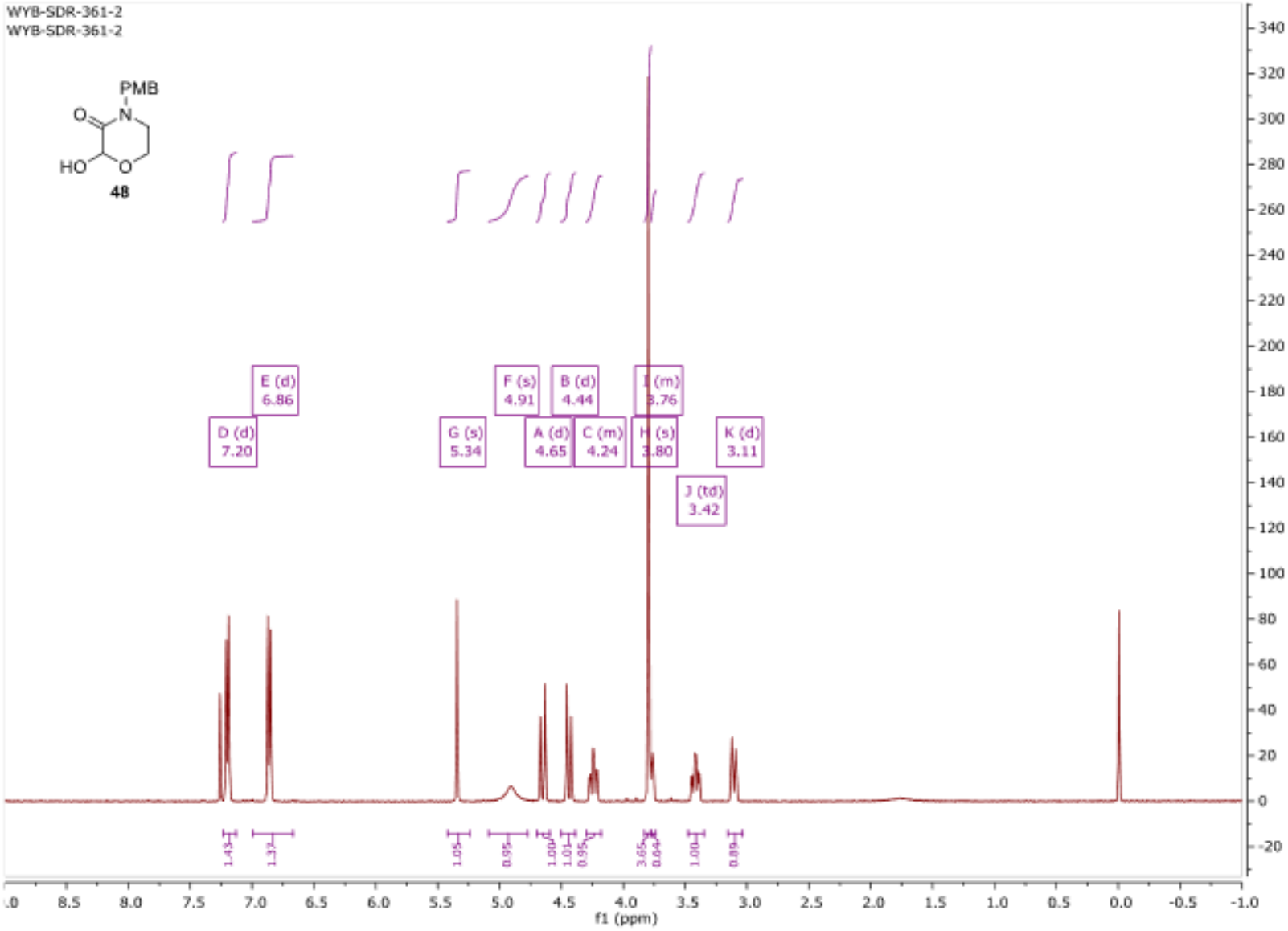

WYB-SDR-36520-1-COSY
WYB-SDR-36518-1-Re
f2 (ppm)
f1 (ppm)

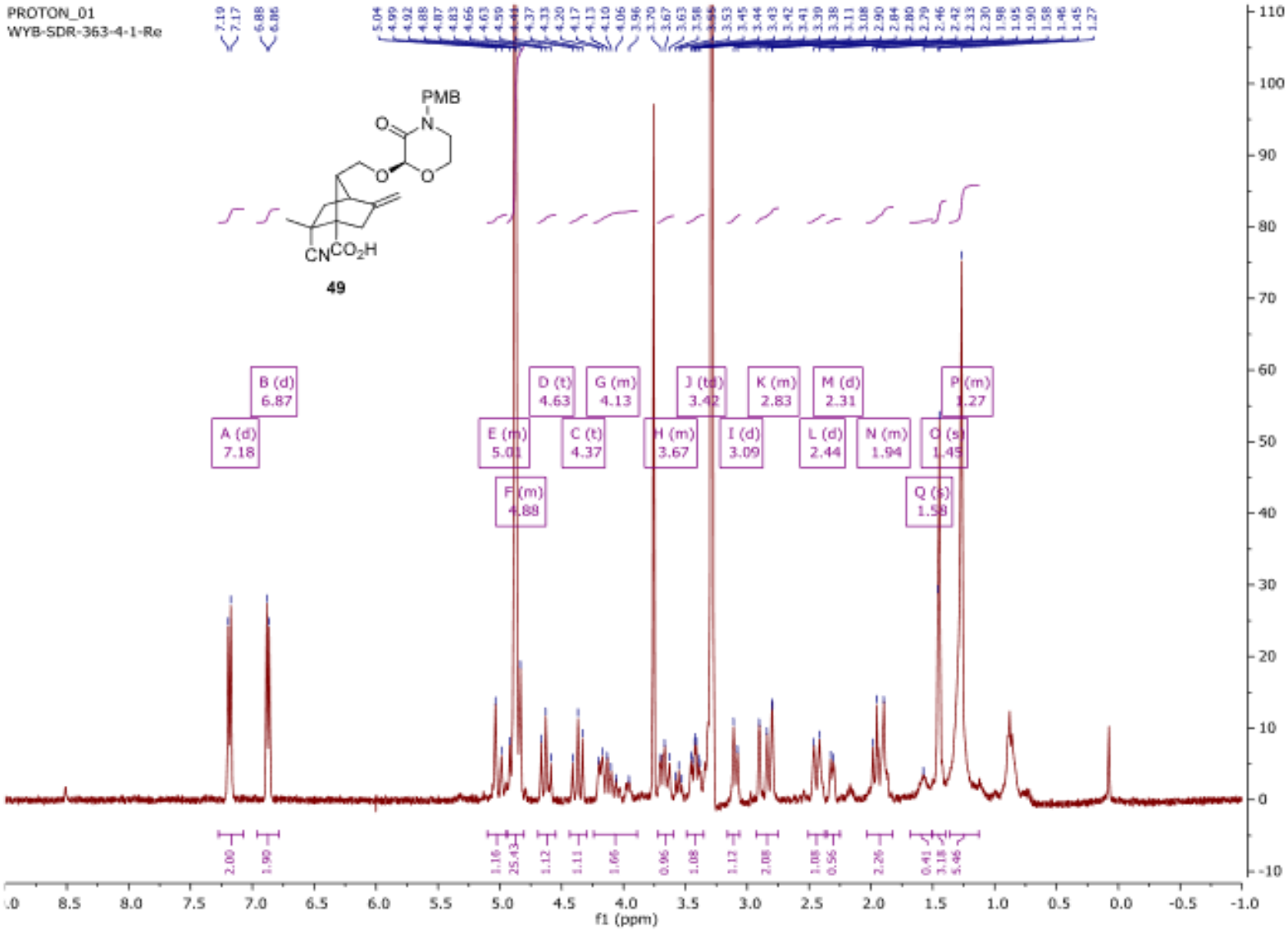

WYB-SDR-365-8-1-NOESY
WYB-SDR-365-8-1-Re
OH
Bn
CN
CO2PMB
45c
f2 (ppm)
f1 (ppm)

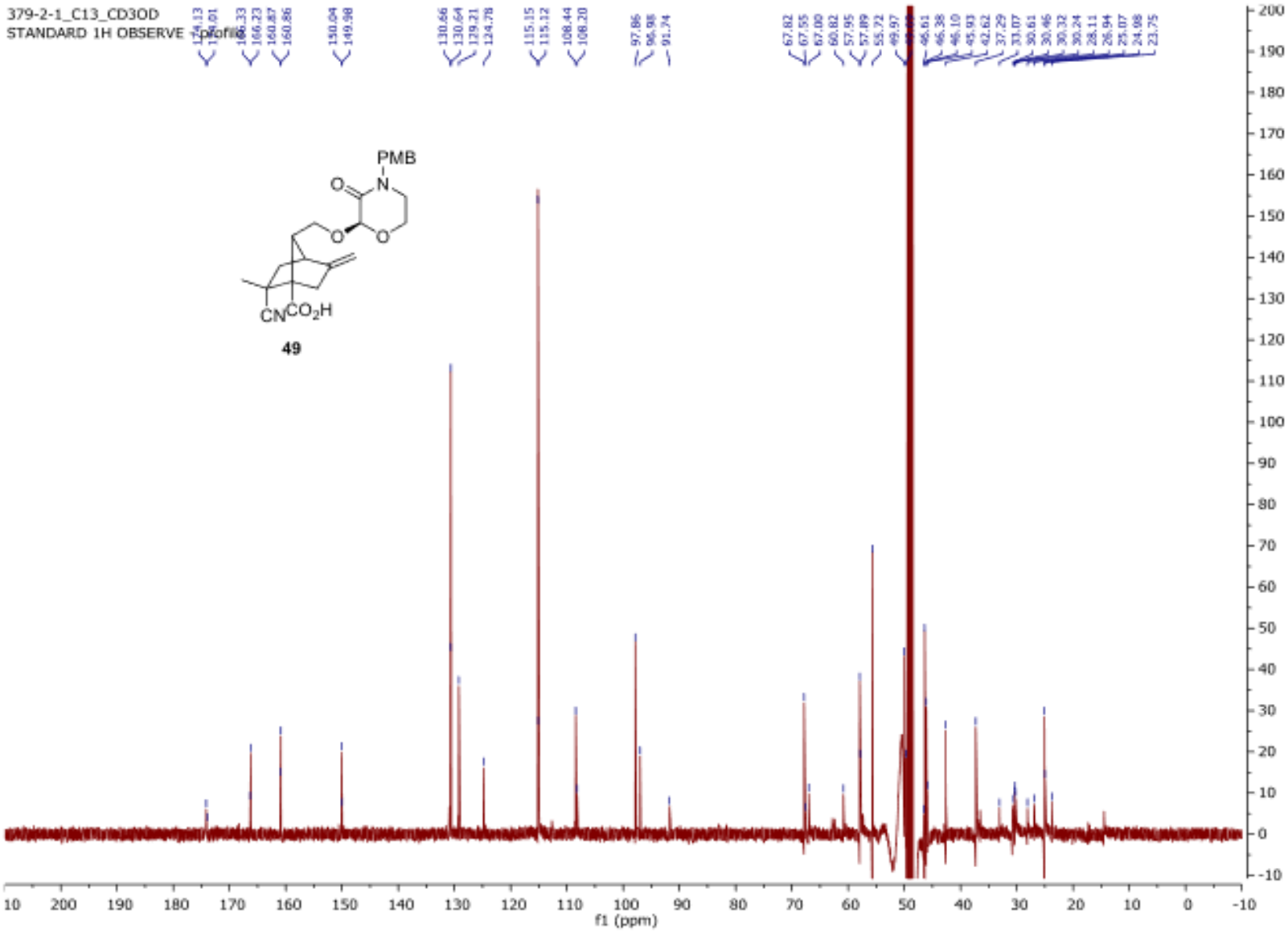

WYB-SDR-365-8-1-NOESY
WYB-SDR-365-8-1-Re
H7-H10
f2 (ppm)
f1 (ppm)

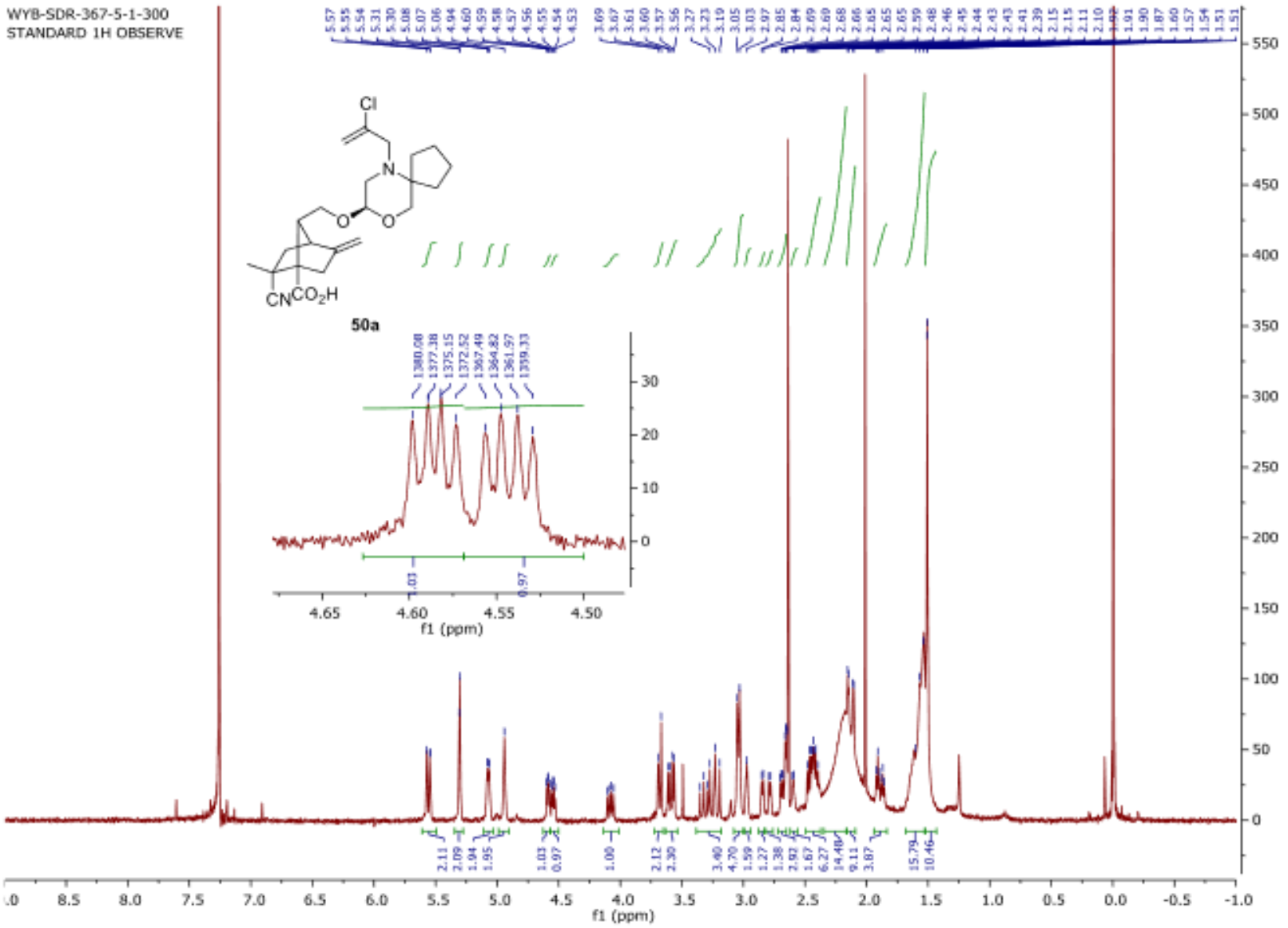

Cl
N
HO
O
47
C (q)
5.30
B (q)
5.40
A (ddd)
4.94
E (dd)
3.69
D (d)
3.82
G (dt)
3.16
F (dd)
3.25
H (d)
2.96
J (dd)
2.46
I (dd)
2.69
K (m)
1.54
f1 (ppm)
f1 (ppm)

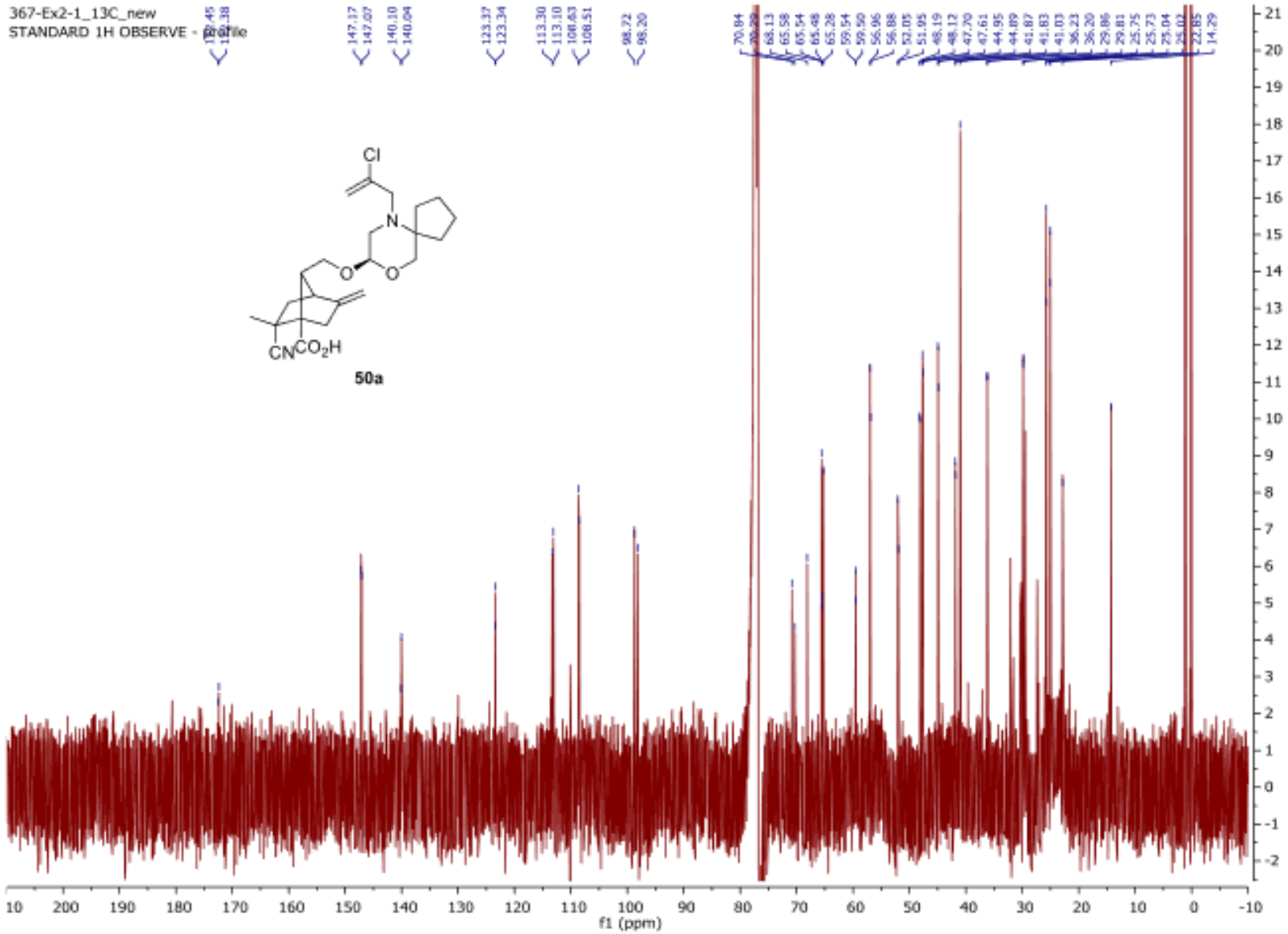

WYB-SDR-364-6-1C-Re
WYB-SDR-364-6-1C-Re
140.16
114.17
91.46
69.42
66.09
56.41
52.83
31.71
28.44
25.91
25.80
Cl
N
HO
O
47
f1 (ppm)

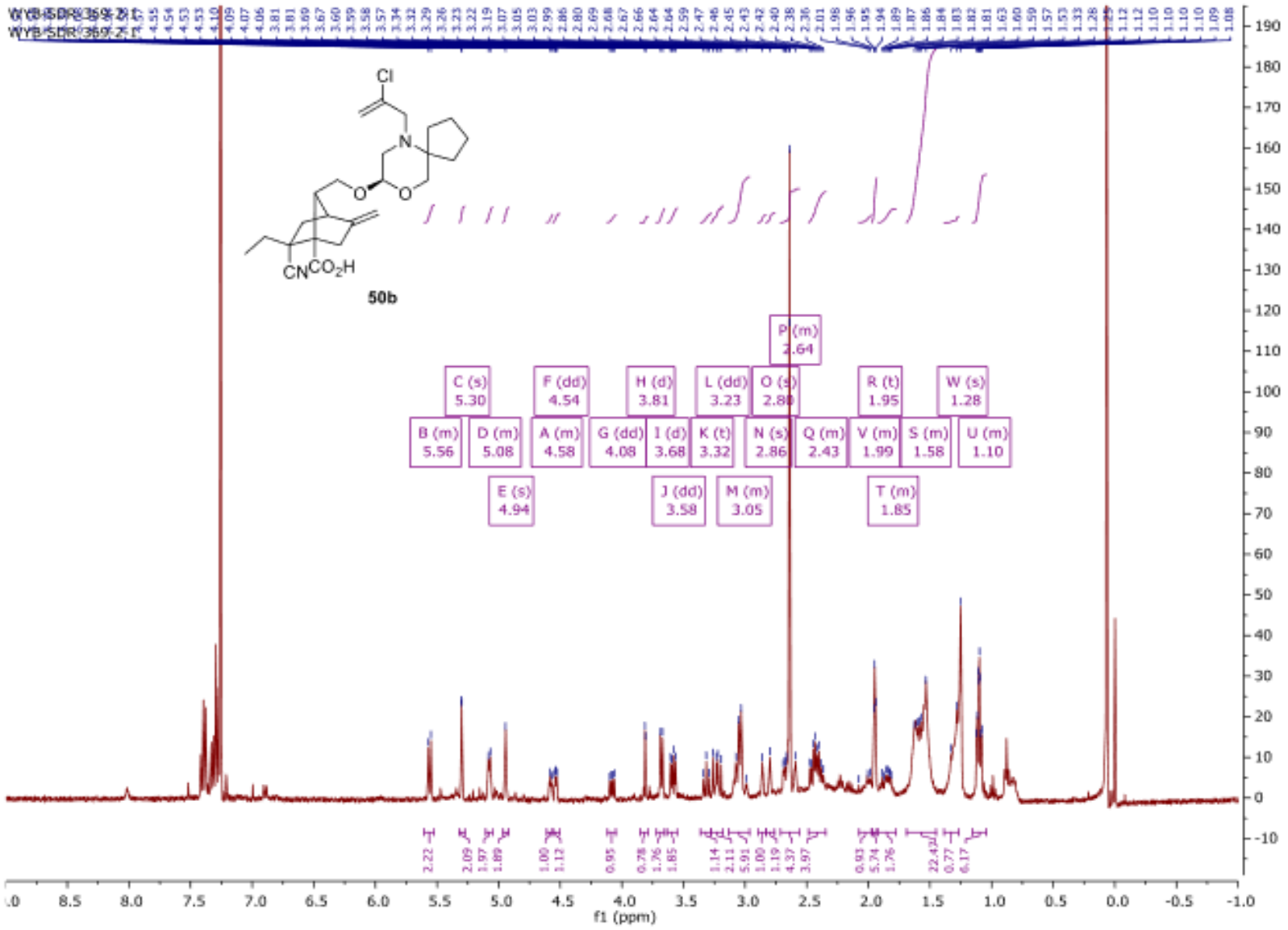

WYB-SDR-361-2
WYB-SDR-361-2
PMB
O
N
HO
O
48
E (d)
6.86
D (d)
7.20
F (s)
4.91
B (d)
4.44
I (m)
3.76
G (s)
5.34
A (d)
4.65
C (m)
4.24
H (s)
3.80
K (d)
3.11
J (td)
3.42
1.43
1.37
1.05
0.95
1.00
1.01
0.95
3.65
0.64
1.00
0.89
f1 (ppm)

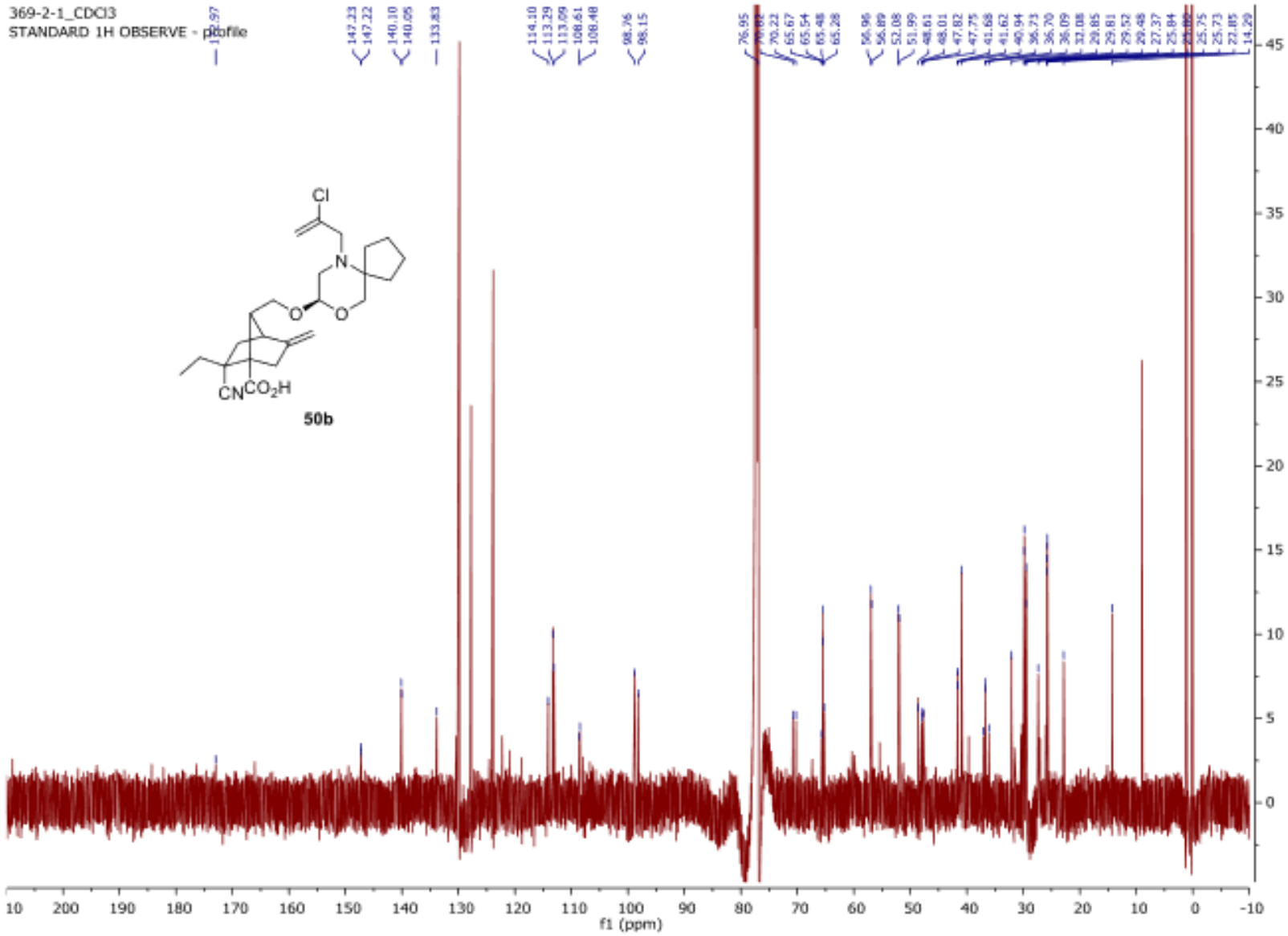

PROTON_01
WYB-SDR-363-4-1-Re
PMB
O
N
O
O
CN
CO2H
49
A (d) 7.18
B (d) 6.87
C (t) 4.37
D (t) 4.63
E (m) 5.01
F (m) 4.88
G (m) 4.13
H (m) 3.67
I (d) 3.09
J (td) 3.42
K (m) 2.83
L (d) 2.44
M (d) 2.31
N (m) 1.94
O (s) 1.45
P (m) 1.27
Q (s) 1.58
f1 (ppm)

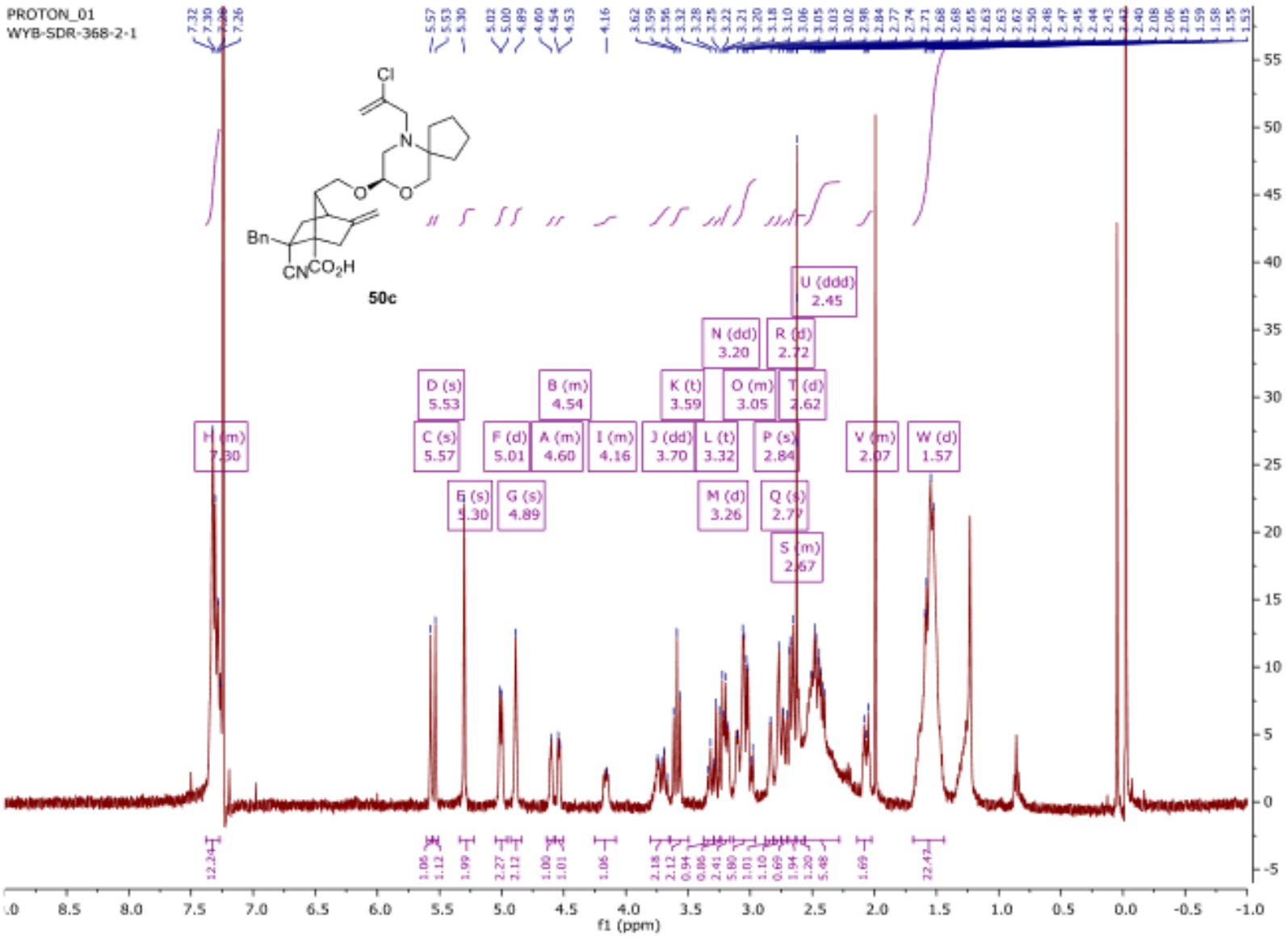

379-2-1_C13_CD3OD
STANDARD 1H OBSERVE - Default
PMB
O
N
O
O
CN
CO2H
49
f1 (ppm)


WYB-SDR-367-5-1-300
STANDARD 1H OBSERVE
Cl
N
O
O
CN
CO2H
50a
1380.08
1377.38
1375.15
1372.52
1367.49
1364.82
1361.97
1359.33
1.03
0.97
4.65
4.60
4.55
4.50
f1 (ppm)
2.11
2.09
1.94
1.95
1.03
0.97
1.00
2.12
2.30
3.40
4.70
1.59
1.27
1.38
2.93
1.67
6.27
14.48
9.11
3.87
15.79
10.46
f1 (ppm)


367-Ex2-1_13C_new
STANDARD 1H OBSERVE - Profile
Cl
N
O
O
CN
CO2H
50a
f1 (ppm)


Cl
N
O
O
CN
CO2H
50b
P (m) 2.64
C (s) 5.30
F (dd) 4.54
H (d) 3.81
L (dd) 3.23
O (s) 2.88
R (t) 1.95
W (s) 1.28
B (m) 5.56
D (m) 5.08
A (m) 4.58
G (dd) 4.08
I (d) 3.68
K (t) 3.32
N (s) 2.86
Q (m) 2.43
V (m) 1.99
S (m) 1.58
U (m) 1.10
E (s) 4.94
J (dd) 3.58
M (m) 3.05
T (m) 1.85
f1 (ppm)


369-2-1_CDCl3
STANDARD 1H OBSERVE - pbfile
147.23
147.22
140.10
140.05
133.83
114.10
113.29
113.09
108.61
108.48
98.76
98.15
76.95
70.22
65.67
65.54
65.48
65.28
56.96
56.89
52.08
51.99
48.61
48.01
47.82
47.75
41.68
41.62
40.94
36.73
36.70
36.09
32.08
29.85
29.81
29.52
29.48
27.37
25.84
25.75
25.73
22.85
14.29
Cl
N
O
O
CN
CO2H
50b
f1 (ppm)


PROTON_01
WYB-SDR-368-2-1
Cl
N
O
O
Bn
CN
CO2H
50c
U (ddd) 2.45
N (dd) 3.20
R (d) 2.72
D (s) 5.53
B (m) 4.54
K (t) 3.59
O (m) 3.05
T (d) 2.62
H (m) 7.30
C (s) 5.57
F (d) 5.01
A (m) 4.60
I (m) 4.16
J (dd) 3.70
L (t) 3.32
P (s) 2.84
V (m) 2.07
W (d) 1.57
E (s) 5.30
G (s) 4.89
M (d) 3.26
Q (s) 2.79
S (m) 2.67
f1 (ppm)

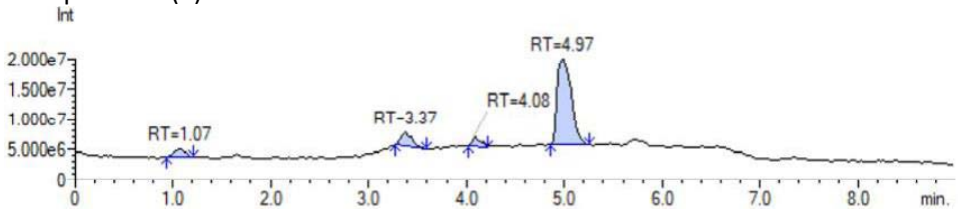
LC-MS traces of 49 and 50a–c

*Shimadzu Open Solution*

**Project:** Dockendorff Lab
**Experiment:** 6242wuy_20180803_05
**Experiment Description:** Wizard-generated sample plate
**Sample:** WYB-SDR-363-4-3
**Sample Description:** WYB-SDR-363-4-3
**Data File Name:** C:\Data\docken\yibiao\WYB-SDR-363-4-3.lcd
**Sample Location:** Plate Number: 1 - Position: 79
**Run By:** 6242wuy
**Run Started:** Friday, August 3, 2018 7:09:16 PM
**Run Finished:** Friday, August 3, 2018 7:19:15 PM
**Method:** 051817_Std_Gemini_25_MeCN

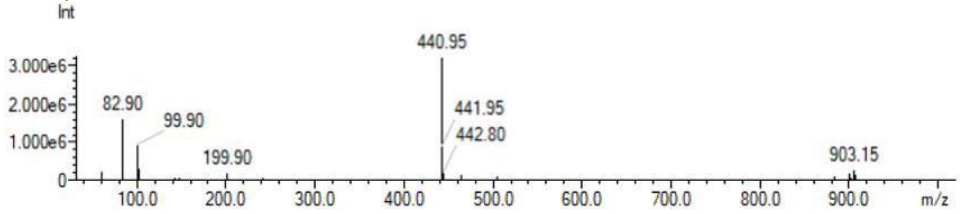
**MS Chromatogram**

Group#1 Scan(+) EI : TIC



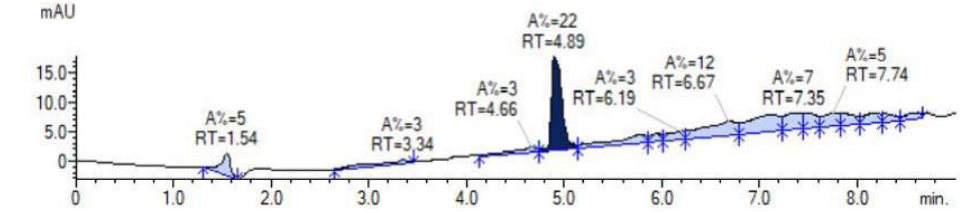

**MS Spectrum**

Group#1 - PDA Peak: 12, RT: 4.73 to 5.12 min



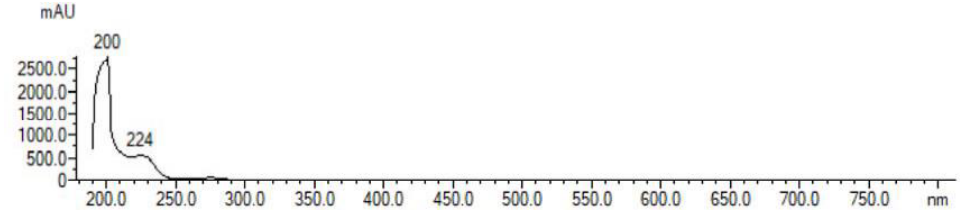

**PDA Chromatogram**

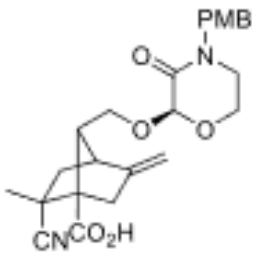
1: Wavelength 254 nm, Band Width 4 nm




**PDA Spectrum**

Peak: 12, RT: 4.89 min, 190 to 800 nm






**49**

Chemical Formula: $C_{24}H_{28}N_2O_6$
Exact Mass: 440.1947
Molecular Weight: 440.4960

**Sample:** WYB-SDR-363-4-3
**Run By:** 6242wuy
**Run Finished:** Friday, August 3, 2018 7:19:15 PM

**MS Peak Table**

| ID | RT | Scan Group | Purity | Purity Source | Area % |
|---|---|---|---|---|---|
| 1 | 1.07 | 1: TIC | 0.0 | | 5.7 |
| 2 | 3.37 | 1: TIC | 3.4 | PDA 3.34 min | 9.6 |
| 3 | 4.08 | 1: TIC | 3.4 | PDA 4.66 min | 5.0 |
| 4 | 4.97 | 1: TIC | 22.1 | PDA 4.89 min | 78.1 |
| 5 | 1.07 | 2: TIC | 0.0 | | 3.3 |
| 6 | 3.39 | 2: TIC | 3.4 | PDA 3.34 min | 3.2 |
| 7 | 4.95 | 2: TIC | 22.1 | PDA 4.89 min | 82.1 |
| 8 | 5.69 | 2: TIC | 6.6 | PDA 5.78 min | 10.3 |

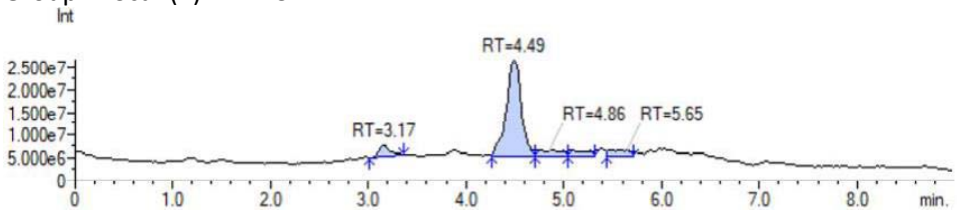
**PDA Peak Table**

| ID | RT | Multi-Chro Table Index | Area % |
|---|---|---|---|
| 9 | 1.54 | 1 | 5.1 |
| 10 | 3.34 | 1 | 3.4 |
| 11 | 4.66 | 1 | 3.4 |
| 12 | 4.89 | 1 | 22.1 |
| 13 | 5.78 | 1 | 6.6 |
| 14 | 5.93 | 1 | 2.0 |
| 15 | 6.19 | 1 | 3.2 |
| 16 | 6.67 | 1 | 11.5 |
| 17 | 7.09 | 1 | 12.2 |
| 18 | 7.35 | 1 | 6.6 |
| 19 | 7.49 | 1 | 4.4 |
| 20 | 7.74 | 1 | 4.7 |
| 21 | 7.87 | 1 | 3.8 |
| 22 | 8.14 | 1 | 3.6 |
| 23 | 8.29 | 1 | 2.1 |
| 24 | 8.56 | 1 | 2.3 |
| 25 | 1.01 | 2 | 4.8 |
| 26 | 1.35 | 2 | 3.3 |

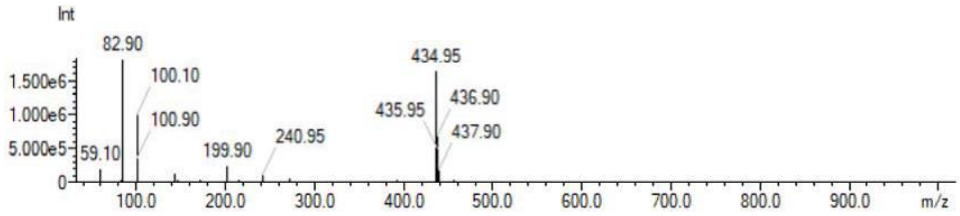
| | | | |
|---|---|---|---|
| 27 | 1.49 | 2 | 2.6 |
| 28 | 1.90 | 2 | 3.1 |
| 29 | 2.10 | 2 | 4.1 |
| 30 | 3.05 | 2 | 13.7 |
| 31 | 3.17 | 2 | 3.0 |
| 32 | 3.34 | 2 | 8.0 |
| 33 | 3.71 | 2 | 3.9 |
| 34 | 4.01 | 2 | 16.7 |
| 35 | 4.89 | 2 | 16.1 |
| 36 | 5.71 | 2 | 9.5 |
| 37 | 1.01 | 3 | 5.9 |
| 38 | 1.35 | 3 | 3.7 |
| 39 | 1.49 | 3 | 2.9 |
| 40 | 1.92 | 3 | 4.4 |
| 41 | 2.12 | 3 | 3.9 |
| 42 | 2.87 | 3 | 17.8 |
| 43 | 3.33 | 3 | 11.2 |
| 44 | 4.00 | 3 | 10.5 |
| 45 | 4.89 | 3 | 29.7 |
| 46 | 1.49 | 4 | 8.7 |
| 47 | 7.47 | 4 | 9.6 |
| 48 | 7.87 | 4 | 8.5 |
| 49 | 8.28 | 4 | 7.1 |

*Shimadzu Open Solution*
**Project:** Dockendorff Lab
**Experiment:** 6242wuy_20180906_02
**Experiment Description:** Wizard-generated sample plate
**Sample:** WYB-SDR-367-E8
**Sample Description:** WYB-SDR-367-E8
**Data File Name:** C:\Data\docken\yibiao\WYB-SDR-367-E8.lcd
**Sample Location:** Plate Number: 1 - Position: 94
**Run By:** 6242wuy
**Run Started:** Thursday, September 6, 2018 2:44:11 AM
**Run Finished:** Thursday, September 6, 2018 3:07:58 AM
**Method:** 051817_Std_Gemini_25_MeCN

**MS Chromatogram**
Group#1 Scan(+) EI : TIC

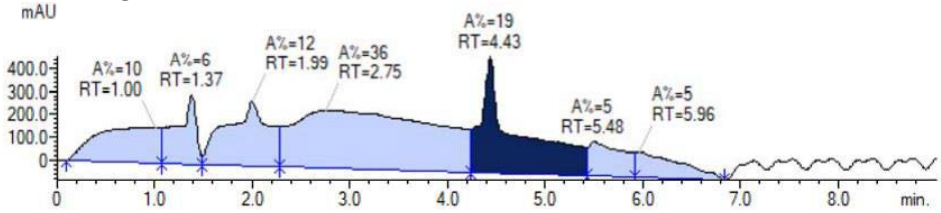



**MS Spectrum**
Group#1 - PDA Peak: 38, RT: 4.22 to 5.42 min



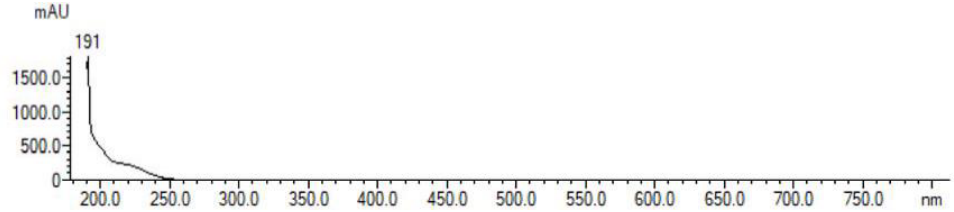

**PDA Chromatogram**

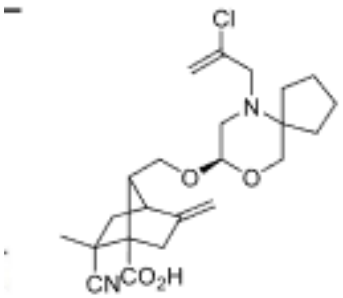
3: Wavelength 200 nm, Band Width 4 nm




**PDA Spectrum**

Peak: 38, RT: 4.43 min, 190 to 800 nm




**50a**

Chemical Formula: $C_{23}H_{31}ClN_2O_4$
Exact Mass: 434.1972
Molecular Weight: 434.9610

**Sample:** WYB-SDR-367-E8
**Run By:** 6242wuy
**Run Finished:** Thursday, September 6, 2018 3:07:58 AM

**MS Peak Table**

| ID | RT | Scan Group | Purity | Purity Source | Area % |
|---|---|---|---|---|---|
| 1 | 3.17 | 1: TIC | 0.0 | | 6.4 |
| 2 | 4.49 | 1: TIC | 0.0 | | 73.8 |
| 3 | 4.86 | 1: TIC | 2.0 | PDA 5.14 min | 7.2 |
| 4 | 5.08 | 1: TIC | 2.0 | PDA 5.14 min | 6.0 |
| 5 | 5.65 | 1: TIC | 3.1 | PDA 5.60 min | 6.6 |

| | | | | | |
|---|---|---|---|---|---|
| 6 | 4.47 | 2: TIC | 0.0 | | 85.5 |
| 7 | 5.53 | 2: TIC | 3.1 | PDA 5.60 min | 9.7 |
| 8 | 6.21 | 2: TIC | 8.6 | PDA 6.49 min | 2.1 |

**PDA Peak Table**

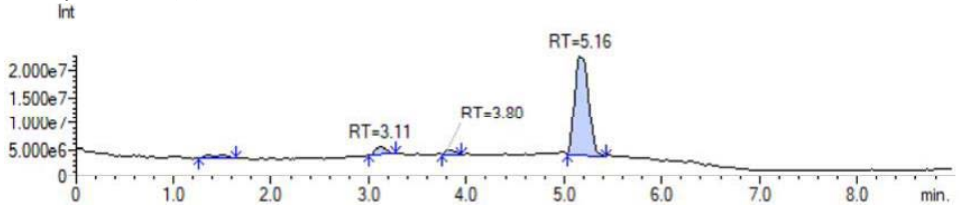
| ID | RT | Multi-Chro Table Index | Area % |
|---|---|---|---|
| 9 | 0.44 | 1 | 9.6 |
| 10 | 0.94 | 1 | 4.1 |
| 11 | 1.42 | 1 | 5.4 |
| 12 | 1.70 | 1 | 3.2 |
| 13 | 5.14 | 1 | 2.0 |
| 14 | 5.60 | 1 | 3.1 |
| 15 | 5.99 | 1 | 4.5 |
| 16 | 6.49 | 1 | 8.6 |
| 17 | 7.10 | 1 | 20.0 |
| 18 | 7.36 | 1 | 6.6 |
| 19 | 7.50 | 1 | 5.5 |
| 20 | 7.77 | 1 | 4.7 |
| 21 | 7.91 | 1 | 4.3 |
| 22 | 8.21 | 1 | 3.8 |
| 23 | 8.31 | 1 | 3.1 |
| 24 | 1.01 | 2 | 9.0 |
| 25 | 1.37 | 2 | 5.2 |
| 26 | 1.99 | 2 | 8.7 |
| 27 | 3.27 | 2 | 18.2 |
| 28 | 3.58 | 2 | 11.8 |
| 29 | 4.13 | 2 | 3.4 |
| 30 | 4.43 | 2 | 17.5 |
| 31 | 5.49 | 2 | 6.3 |
| 32 | 5.96 | 2 | 5.6 |
| 33 | 7.12 | 2 | 3.1 |
| 34 | 1.00 | 3 | 9.6 |
| 35 | 1.37 | 3 | 5.9 |
| 36 | 1.99 | 3 | 11.7 |
| 37 | 2.75 | 3 | 36.1 |
| 38 | 4.43 | 3 | 18.5 |
| 39 | 5.48 | 3 | 5.1 |
| 40 | 5.96 | 3 | 5.0 |
| 41 | 7.12 | 4 | 20.0 |
| 42 | 7.51 | 4 | 22.2 |
| 43 | 8.33 | 4 | 16.1 |

*Shimadzu Open Solution*

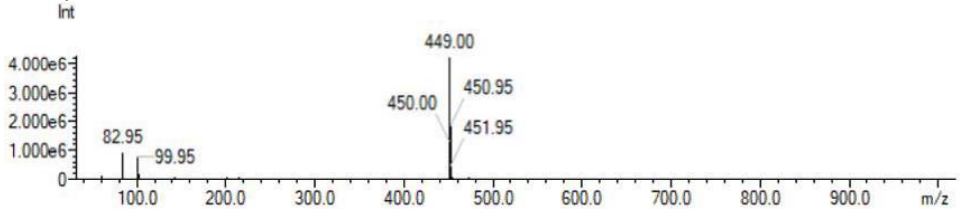
**Project:** Dockendorff Lab
**Experiment:** 6242wuy_20181006_01
**Experiment Description:** Wizard-generated sample plate
**Sample:** WYB-SDR-369-2-1-HPLC
**Sample Description:** WYB-SDR-369-2-1-HPLC

**Data File Name:** C:\Data\docken\yibiao\WYB-SDR-369-2-1-HPLC.lcd
**Sample Location:** Plate Number: 1 - Position: 95
**Run By:** 6242wuy
**Run Started:** Saturday, October 6, 2018 5:25:46 PM
**Run Finished:** Saturday, October 6, 2018 5:55:50 PM
**Method:** 051817_Std_Gemini_25_MeCN

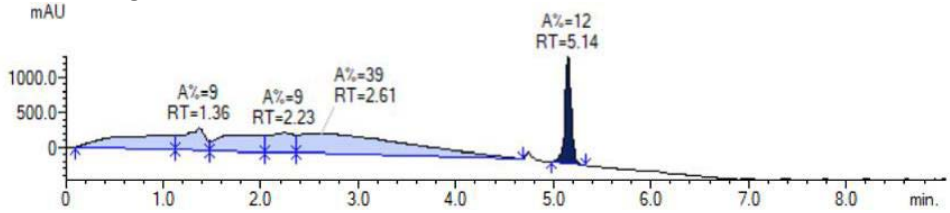
**MS Chromatogram**
Group#1 Scan(+) EI : TIC



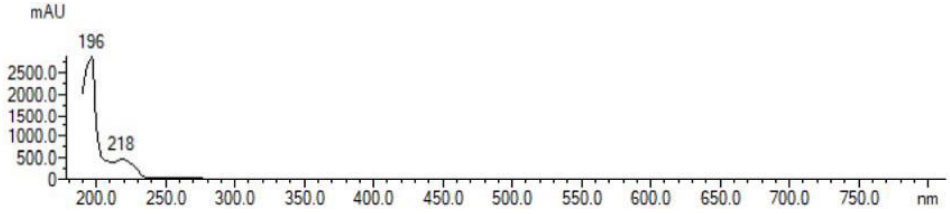

**MS Spectrum**
Group#1 - PDA Peak: 24, RT: 4.96 to 5.32 min

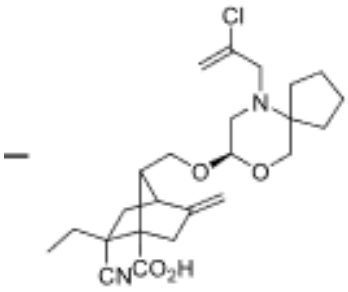



**PDA Chromatogram**
3: Wavelength 200 nm, Band Width 4 nm




**PDA Spectrum**
Peak: 24, RT: 5.14 min, 190 to 800 nm






**50b**

Chemical Formula: $C_{24}H_{33}ClN_2O_4$
Exact Mass: 448.2129
Molecular Weight: 448.9880

**Sample:** WYB-SDR-369-2-1-HPLC
**Run By:** 6242wuy
**Run Finished:** Saturday, October 6, 2018 5:55:50 PM

**MS Peak Table**

| ID | RT | Scan Group | Purity | Purity Source | Area % |
|---|---|---|---|---|---|
| 1 | 1.35 | 1: TIC | 15.1 | PDA 1.41 min | 4.2 |
| 2 | 3.11 | 1: TIC | 3.5 | PDA 3.16 min | 5.1 |
| 3 | 3.80 | 1: TIC | 0.0 | | 2.8 |
| 4 | 5.16 | 1: TIC | 38.9 | PDA 5.14 min | 86.7 |
| 5 | 5.18 | 2: TIC | 38.9 | PDA 5.14 min | 95.6 |

**PDA Peak Table**

| ID | RT | Multi-Chro Table Index | Area % |
|---|---|---|---|
| 6 | 0.56 | 1 | 20.5 |
| 7 | 1.11 | 1 | 5.3 |
| 8 | 1.41 | 1 | 15.1 |
| 9 | 2.81 | 1 | 7.6 |
| 10 | 3.16 | 1 | 3.5 |
| 11 | 4.72 | 1 | 5.8 |
| 12 | 5.14 | 1 | 38.9 |
| 13 | 1.06 | 2 | 17.0 |
| 14 | 1.37 | 2 | 9.1 |
| 15 | 1.95 | 2 | 13.4 |
| 16 | 2.23 | 2 | 9.5 |
| 17 | 2.62 | 2 | 43.6 |
| 18 | 5.14 | 2 | 5.5 |
| 19 | 1.07 | 3 | 15.8 |
| 20 | 1.36 | 3 | 8.8 |
| 21 | 1.96 | 3 | 13.0 |
| 22 | 2.23 | 3 | 9.3 |
| 23 | 2.61 | 3 | 39.1 |
| 24 | 5.14 | 3 | 12.0 |
| 25 | 1.27 | 4 | 5.9 |
| 26 | 1.37 | 4 | 13.8 |

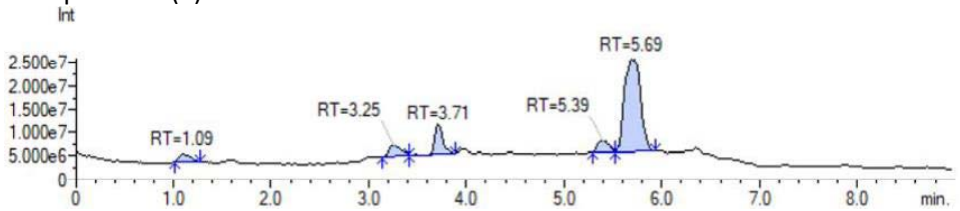
| | | | |
|---|---|---|---|
| 27 | 2.23 | 4 | 2.5 |
| 28 | 4.73 | 4 | 3.9 |

*Shimadzu Open Solution*

**Project:** Dockendorff Lab
**Experiment:** 6242wuy_20180924_01
**Experiment Description:** Wizard-generated sample plate
**Sample:** WYB-SDR-368-2-F4
**Sample Description:** WYB-SDR-368-2-F4
**Data File Name:** C:\Data\docken\yibiao\WYB-SDR-368-2-F4.lcd
**Sample Location:** Plate Number: 1 - Position: 84
**Run By:** 6242wuy
**Run Started:** Monday, September 24, 2018 1:49:12 AM
**Run Finished:** Monday, September 24, 2018 2:23:07 AM
**Method:** 051817_Std_Gemini_25_MeCN

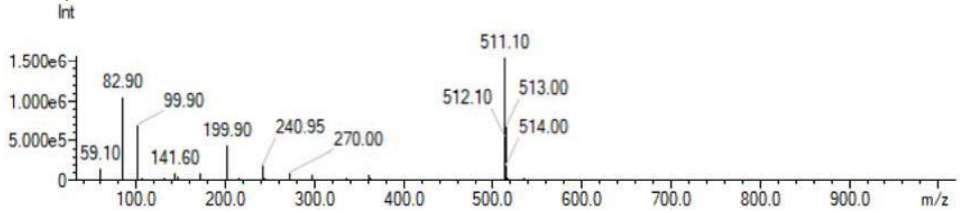
**MS Chromatogram**

Group#1 Scan(+) EI : TIC



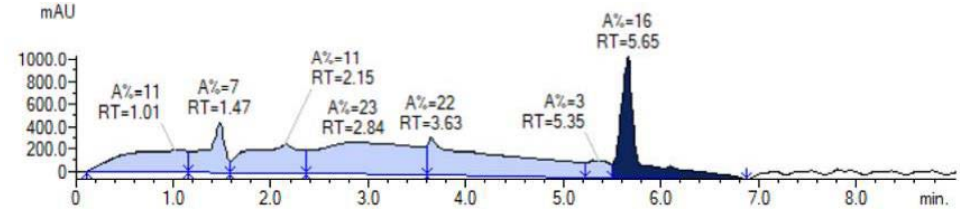

**MS Spectrum**

Group#1 - PDA Peak: 41, RT: 5.48 to 6.86 min



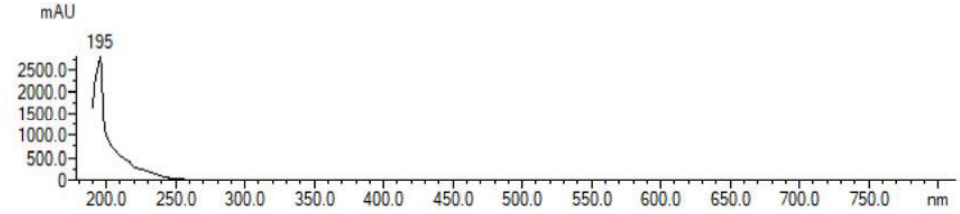

**PDA Chromatogram**

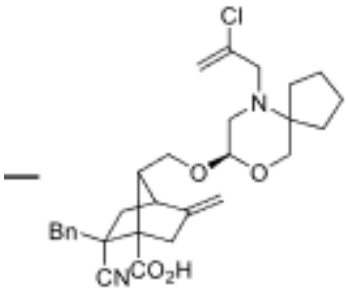
3: Wavelength 200 nm, Band Width 4 nm




**PDA Spectrum**

Peak: 41, RT: 5.65 min, 190 to 800 nm






**50c**

Chemical Formula: $C_{29}H_{35}ClN_2O_4$
Exact Mass: 510.2285
Molecular Weight: 511.0590

**Sample:** WYB-SDR-368-2-F4
**Run By:** 6242wuy
**Run Finished:** Monday, September 24, 2018 2:23:07 AM

**MS Peak Table**

| ID | RT | Scan Group | Purity | Purity Source | Area % |
|---|---|---|---|---|---|
| 1 | 1.09 | 1: TIC | 15.9 | PDA 0.48 min | 4.3 |
| 2 | 3.25 | 1: TIC | 0.0 | | 6.0 |
| 3 | 3.71 | 1: TIC | 0.0 | | 12.1 |
| 4 | 5.39 | 1: TIC | 16.1 | PDA 5.65 min | 5.7 |
| 5 | 5.69 | 1: TIC | 16.1 | PDA 5.65 min | 71.9 |
| 6 | 3.69 | 2: TIC | 0.0 | | 13.3 |
| 7 | 5.40 | 2: TIC | 16.1 | PDA 5.65 min | 9.8 |
| 8 | 5.70 | 2: TIC | 16.1 | PDA 5.65 min | 68.5 |
| 9 | 5.92 | 2: TIC | 2.8 | PDA 6.09 min | 3.3 |
| 10 | 6.13 | 2: TIC | 9.1 | PDA 6.61 min | 5.1 |

**PDA Peak Table**

| ID | RT | Multi-Chro Table Index | Area % |
|---|---|---|---|
| 11 | 0.48 | 1 | 15.9 |
| 12 | 1.49 | 1 | 5.7 |
| 13 | 1.79 | 1 | 4.3 |
| 14 | 5.65 | 1 | 16.1 |
| 15 | 5.86 | 1 | 2.2 |
| 16 | 6.09 | 1 | 2.8 |
| 17 | 6.61 | 1 | 9.1 |
| 18 | 7.12 | 1 | 14.7 |
| 19 | 7.51 | 1 | 10.3 |
| 20 | 7.77 | 1 | 4.0 |
| 21 | 7.91 | 1 | 3.6 |
| 22 | 8.18 | 1 | 2.9 |
| 23 | 8.33 | 1 | 2.5 |
| 24 | 1.01 | 2 | 9.4 |
| 25 | 1.46 | 2 | 6.1 |

| | | | |
|---|---|---|---|
| 26 | 2.15 | 2 | 9.4 |
| 27 | 3.22 | 2 | 15.1 |
| 28 | 3.43 | 2 | 2.2 |
| 29 | 3.63 | 2 | 8.6 |
| 30 | 4.03 | 2 | 18.0 |
| 31 | 5.35 | 2 | 3.4 |
| 32 | 5.65 | 2 | 7.6 |
| 33 | 6.08 | 2 | 4.0 |
| 34 | 7.13 | 2 | 2.3 |
| 35 | 1.01 | 3 | 11.1 |
| 36 | 1.47 | 3 | 7.3 |
| 37 | 2.15 | 3 | 11.5 |
| 38 | 2.84 | 3 | 23.3 |
| 39 | 3.63 | 3 | 22.3 |
| 40 | 5.35 | 3 | 2.8 |
| 41 | 5.65 | 3 | 15.8 |
| 42 | 1.47 | 4 | 14.4 |
| 43 | 7.14 | 4 | 12.1 |
| 44 | 7.80 | 4 | 12.8 |

## Author Contributions

Conceived the project: C.D. Designed compounds and synthetic routes: C.D., Y.W. Tested reactions, synthesized compounds, characterized products: Y.W. Wrote and edited the manuscript: Y.W., C.D. Prepared the Supporting Information: Y.W.

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The authors declare the following competing financial interest(s): A patent application has been submitted that includes some of the work in this publication.

## Notes

A preliminary version of this manuscript was submitted to the preprint server ChemRxiv.(46)

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