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New technologies in green chemistry; Atroposelective synthesis towards korupensamine D

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New technologies in green chemistry;
Atroposelective synthesis towards korupensamine D

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Chemistry

by

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- Highly skilled in small molecule separation and purification by traditional and modern methods (preparative LC, flash chromatography, etc.)
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- Served as project manager for several research endeavors, while interpreting, writing, presenting the results for publication

Agere Pharmaceuticals, Inc., Bend, OR
Pharmaceutical Chemist, 2009-2011

- Experienced in developing analytical methods, design and implementation of stability studies, excipient compatibility, and performance assessment
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ABSTRACT

New technologies in green chemistry;
Atroposelective synthesis towards korupensamine D
by

James Carl Fennewald

Chemists and chemical companies alike are well aware of the large amounts of waste they generate, although until recently little attention has been paid to the waste flow in terms of cost and environmental consequences. By most estimates (roughly 85%) of organic waste produced comes in the form of organic solvents. Thus, our goal continues to be the reduction of waste by focusing on organic solvents, and getting those solvents out of reactions via replacement by micellar catalysis, as quantified by E Factors.

Fluorinated compounds have blossomed in the pharmaceutical industry due to the better bioavailability through an increase in membrane permeability when compared to their non-fluorinated analogues. Micellar catalysis has been found to be amenable to radical-based trifluoromethylation of various heterocyclic compounds. Nanoreactors

composed of the designer surfactant TPGS-750-M enable these substitution reactions to be performed in water at room temperature in modest to good yields in combination with Langlois' reagent ($NaSO_2CF_3$) and *t*-BuOOH, negating the need for pre-functionalization. Trifluoromethylation of several heterocyclic arrays has been accomplished, including heteroaromatics.

Aromatic halogens have long served as excellent handles for transition metal catalysis and directing groups in synthesis, with subsequent need for removal. Current protocols for such dehalogenations are cost prohibitive at scale, energy intensive, and generally call for harsh reaction conditions. The new surfactant, SPGS-550-M, ('Nok') in water with Fu's catalyst and a mild hydride source is used for facile debromination of aromatic compounds. These reactions take place at ambient temperatures. Furthermore, the aqueous mediums can be recycled, thus greatly reducing our dependence on organic solvents while furthering technologies in green chemistry.

Chiral compounds and their syntheses have been an intellectual curiosity of organic chemists since the first chiral resolution of tartaric acid in 1848 by Louis Pasteur. We have taken on the challenge to induce axial chirality for the natural product korupensamine D with use of an internal aromatic auxiliary blocking one face of the coupling partner via π-stacking. Korupensamine D has yet to be synthesized in its natural form, due to the inherent instability of the *cis* tetrahydroisoquinoline ring presenting an exciting, challenging exercise in stereo control.

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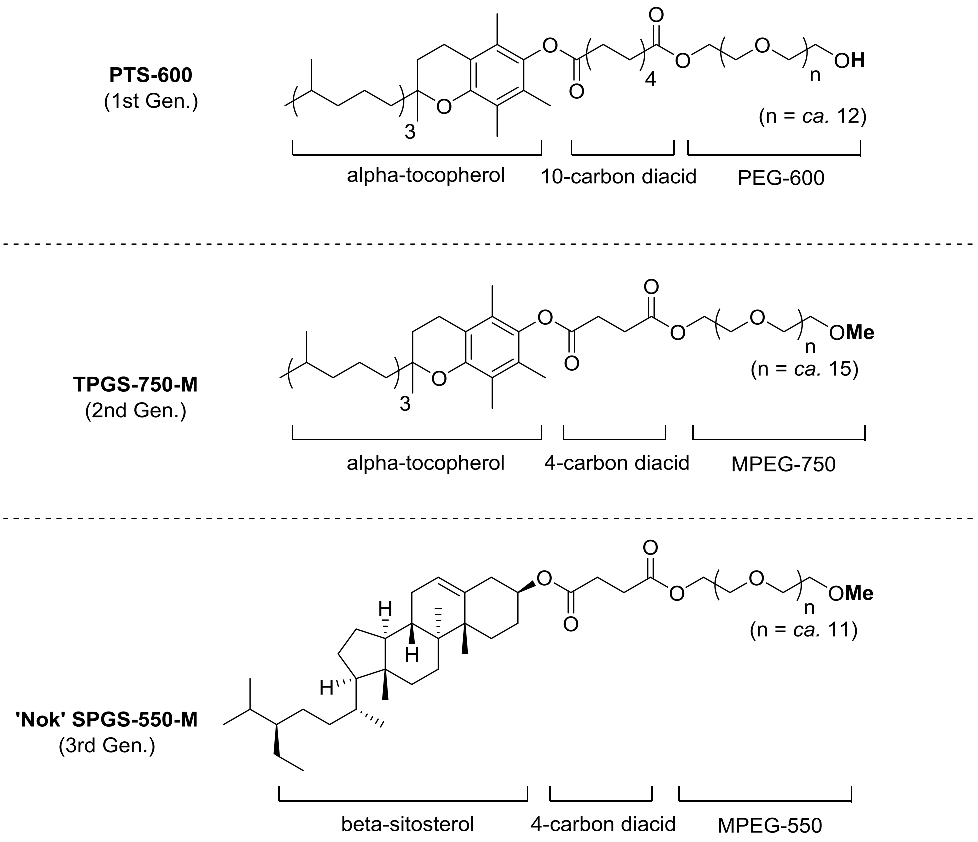
I. *Introduction to green chemistry and its quantification*

1.1 Introduction

Academic and industrial chemists alike have been pushing the fields of modern medicines and materials to the limits for decades, saving and improving billions of lives worldwide. While this may sound very heartwarming and well intentioned, which it is, this continuous drive forward has come at a tremendous cost, affecting many more than we have helped. This cost, is in terms of organic waste production that has been, historically, simply poured down the drain, to today's standard of incineration, sending millions of metric tons of toxic pollutants into our atmosphere, oceans, and ultimately our own food sources through the trophic pyramid. Thus, the burden is on the backs on the next generation of chemists to cease the use of high energy input, high waste generating 'old' methodologies, and to look for new technologies that are sustainable for the responsible stewardship of our world.

With this insight is has been a pleasure to join the Lipshutz research group with my passion for sustainable practices and become an integral player in the green chemistry arena. As we have enabled many traditional organic reactions thought to be intolerant to moisture, to be ran in … water…yes, water with the aid of designer surfactants PTS-600,[1] TPGS-750-M,[2] and SPGS-550-M[3] 'Nok', as shown in Figure 1. These surfactants spontaneously self-assemble in water forming micelles with their hydrophobic portions in the interior. As the saying goes 'like dissolves like' such that the organic hydrophobic reagents and starting materials partition into the hydrophobic pocket or core of these designer surfactants dubbed ‘nanoreactors,’ This enables very high localized concentrations within the nanoreactors themselves, thus allowing chemistry to proceed at ambient temperatures (rt) with no external energy source other than stirring. Because there is little surfactant by weight (2 wt. %) in water, there is a truly minimal resource investment for micellar catalysis, even more so when the aqueous medium is recycled. For the past decade we have been leaders of the green chemistry movement, showcasing the sheer number of transformation facilitated by these nanoreactors. Some of these transformations include, but are not limited to the following; Pd catalyzed cross couplings (Suzuki, Heck, Negishi, Stille, Sonagashira), aminations, borylations, cross metathesis, Cu catalyzed 1,2- and 1,4-asymmetric additions, nitro reductions, hydroformylations, and allylic alcohol oxidations to name a few. Our recent review in *Green Chemistry*[4] provides an excellent encompassing historical perspective and current uses of our groups’ surfactants technology.

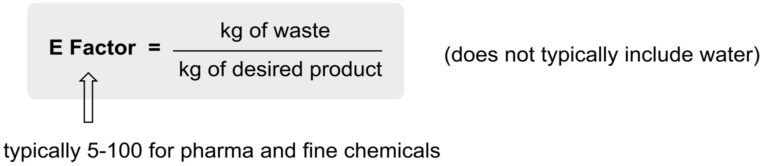
Figure 1. Lipshutz Group surfactants for enabling green chemistry



Up until the past few decades little attention has been paid to the waste flow in terms of cost and environmental consequences.[5] Even with Anastas' and Warners development of the "12 Principles of Green Chemistry" in the late 1990's,[6] the specific aims of which call for; waste prevention, atom economy, non-hazardous synthesis, design of safer chemicals, use of renewable solvents and feedstocks, and catalytic or recyclable systems. Since the inception of the green chemistry movement several metrics have been developed as a way to gauge its 'greeness' using comparative analyses[7,8] (*vide infra*).

These metrics include, effective mass yield (EMY), as it defines yield in the terms of what proportion of the final product mass was produced from non-toxic, benign, and renewable materials. As the EMY reaches ‘1’ the process can be assumed sustainable.[9] Atom economy (AE), one of the original metrics developed by Trost, is measured as the mass of desired product divided by the mass of all reagents used, an AE of 1 signifies that all atoms used in the synthesis appear in the final product.[10] While more recently many pharmaceutical and fine chemical companies have used process mass intensity (PMI) as a measuring stick, as this metric takes into account reagent stoichiometry, reaction media, work-up, and purification conditions thus painting a more accurate picture of the mass of waste generated for given amount of product, although it does not include water.[11] One of the most encompassing metrics is the life cycle assessment (LCA), a method commonly dubbed ‘cradle to grave’ which takes into account all materials and energy from the processes from inception to disposal.[12] Although it is an extremely time consuming costly metric that is commonly discarded by smaller outfits that opt to use either the PMI metric or the far more appropriate environmental factor (E Factor) both are reliable comparing various processes solely from the waste generated in the form of solvents used for the reaction medium and associated work-up.

E Factors were developed as one of the most effective metrics to quantify the ‘greenness’ of any given process and its relative waste generated. The E Factor metric was orginated by Sheldon.[13] By most estimates (ca 85%) of chemical waste produced comes in the form of organic solvents.[14] Thus, E Factors provide a simple metric for all chemists to measure reactions based solely on solvent usage. While E Factors tend to focus only on the first use of any medium, all subsequent reactions involving recycled solvent lead to a large reduction in E Factors. Secondly the E Factor is often reported with and without its aqueous components to allow for a more uniform metric independent of work up and purification procedures.



Scheme 1. Definition of an E Factor

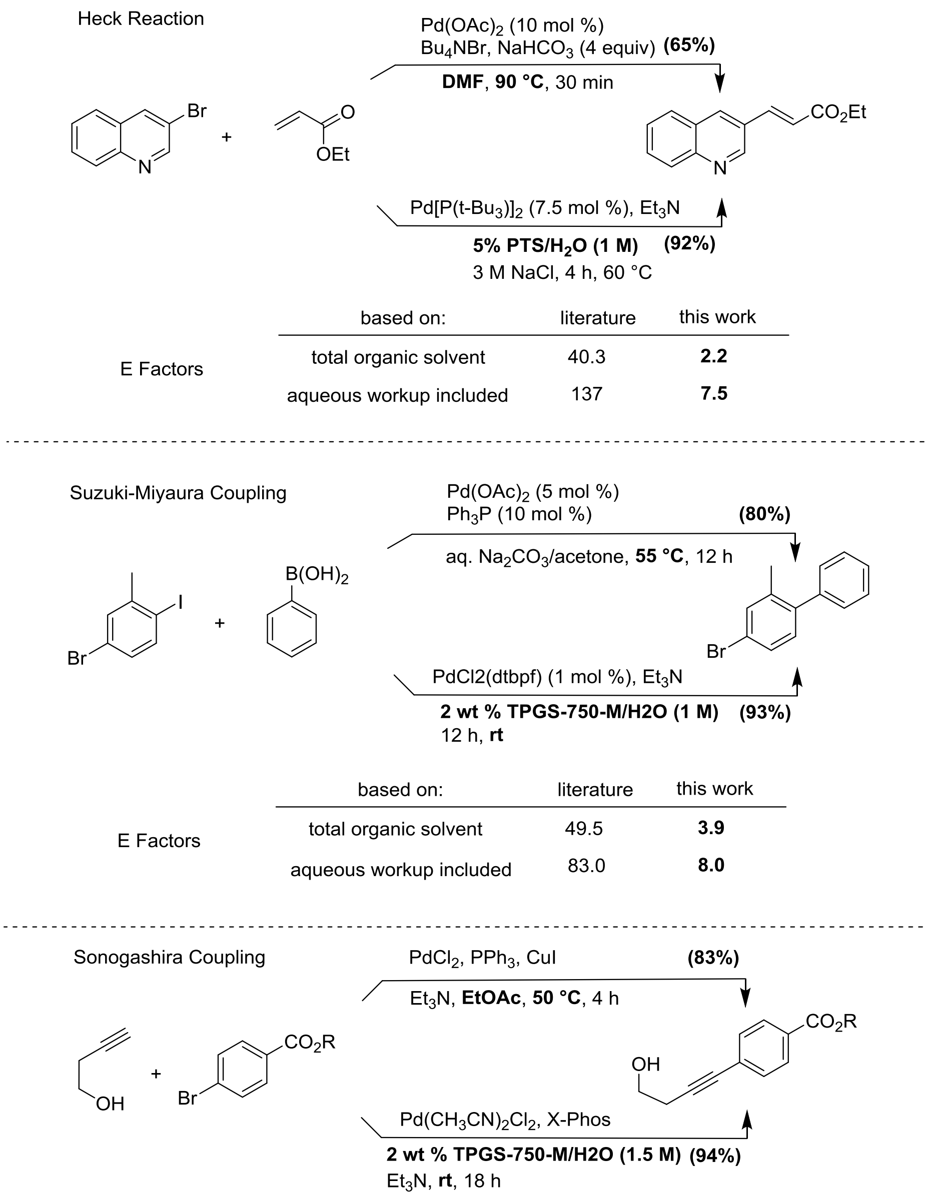
The E factor metric is quantified as the amount of waste generated (kg) divided by the amount of pure product obtained (kg), as shown in Scheme 1. A smaller E Factor translates into less waste production. It should be noted that while the E Factor is inclusive of the major waste component of organic synthesis (solvents) the calculation ignores some parameters such as; catalyst systems, recyclable solvents, atom economy, and energy input. A breakdown of E Factors by industry,[15] shown in Table 1, shows that the pharmaceutical companies are by far the largest waste generators with typical E Factors ranging from 25 to 100 due their complexity, while the petroleum industry is the least waste producing by its nature of converting crude oils directly to commodity chemicals and fuels with an E Factor of generally as low as ~0.1.

Table 1. Breakdown of E Factors by industry

Industry	E-factor
Petroleum	0.1
Bulk Chemicals	<1-5
Fine Chemicals	5-50
Pharmaceuticals	25-100

Thus, our recent goal has been to reduce E Factors by focusing on organic solvents and getting those solvents out of reactions. To showcase our micellar catalysis several current large scale Pd catalyzed cross coupling E Factors were calculated both with and without their aqueous work ups. Then, the same reactions using PTS or TPGS-750-M were run to replace the organic solvent, which allowed us to access the 'greenness' or E Factors of the given process.

As the cross coupling examples in Scheme 2 illustrate, involving Heck,[16] Suzuki,[17] and Sonagashira[18] reactions, E Factors associated with each type can be reduced dramatically, in many cases by greater than an order of magnitude. Since these were run in water on a far smaller, academic scale relative to those in the published studies, the corresponding drop in E Factor would likely be even more pronounced at larger scales where small loses are of little consequence. Moreover, in most cases, the hydrophobic effect[19] characteristic of aqueous micellar catalysis allows for cross-coupling to take place at room temperature, while in traditional organic media heating might well be needed to initiate and/or drive reactions to completion.



Heck Reaction – E Factors

based on:	literature	this work
total organic solvent	40.3	**2.2**
aqueous workup included	137	**7.5**

Suzuki-Miyaura Coupling – E Factors

based on:	literature	this work
total organic solvent	49.5	**3.9**
aqueous workup included	83.0	**8.0**

Scheme 2. Comparison of three of the ‘named’ coupling reactions of E Factors from industry verse our micellar catalysis

The key to lowering E Factors in these reactions is the application of environmentally benign surfactants that spontaneously self-assemble in water into nanomicelles of a particularly engineered shape and size. Cross-coupling and related reactions run within their lipophilic cores, especially at ambient temperatures, are typically clean and thus, can oftentimes be more efficient than those run in organic media and once complete, product can be extracted with the minimal amount of organic solvent. Opportunities for recycling of these aqueous reaction mixtures serve to further reduce dependence on organic solvents. New industrial processes, therefore, that begin green are very likely to remain green for the lifetime of a given process; *i.e.,* years, translating into a potential economic and environmental windfall for each green step in a synthesis. For an in depth review of E Factors, please see our recent mini review.[20]

In conclusion, micellar catalysis has been found to be amenable to a plethora of various couplings, oxidations, reductions, etc. Nanoreactors composed of the designer surfactants enable these reactions to be performed in water at room temperature in good yields. The aqueous reaction mixtures are readily recycled, and given the limited amounts of organic solvent needed for product isolation, the associated E Factors imply that a considerably enhanced level of greenness is characteristic of these reactions.

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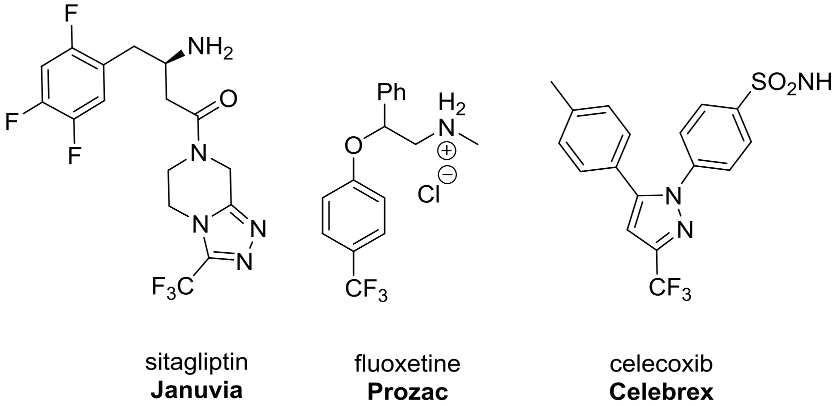
II. *Aqueous trifluoromethylation of heterocycles at room temperature*

2.1 Introduction

Recent research methods for introduction of the trifluoromethyl group onto aromatic and especially heteroaromatic ring systems has blossomed, as this moiety imparts several physiological advantages. But is also plagued by its problematic and harsh conditions, with little to no regard for waste production.



sitagliptin **Januvia**

fluoxetine **Prozac**

celecoxib **Celebrex**

Figure 1. Top selling drug examples containing F or CF_3

From the latest statistics thirty percent of the top ten selling drugs in 2011 (Figure 1) contained fluorine atoms, as do 7 of the 35 newly approved pharmaceutics.[1] For these physiologically active compounds the most common fluorine source is a CF_3 group on arene units.[2,3] Fluorinated compounds display better bioavailability through an increase in membrane permeability when compared to their non-fluorinated analogues; due to the change in their enhanced solubility and lipophillicity. They are also more difficult to oxidize leading to an increase in metabolic stability.[1] Fluorinated compounds are used heavily throughout the pesticide and agrochemical industries.[4] This large amount of fluorinated chemicals necessitates the need for a new, greener, and higher yielding methodology for C-CF_3 bond formation.

Although in the medicinal chemistry and fine chemicals arenas there is a rich history of using super stoichiometric CF_3Br or more commonly CF_3I as precursors to CF_3 radicals for synthetic targets.[5] opportunities remain not only for improvements in existing technologies and development of new reagents, but also for new processes that are more environmentally benign. Most recent methods leading to insertion of this valued appendage rely on transition metal-mediated C-CF_3 bond constructions, and while these typically offer good yields, they tend to require tedious pre-functionalization.

2.2 Previous Work in Trifluoromethylation

The present day industrial process for trifluoromethylated homo and hetero aromatics involves exhaustive chlorination of the methyl group appended to an aryl ring[6] followed by the Swarts reaction of the resulting $ArCCl_3$ with hydrofluoric acid.[7] This current process is substantially limited in its functional group tolerance and thus must be performed early in the synthesis. It is also environmentally offensive, requiring large amounts of Cl_2 and HF while generating excessive quantities of acid (HCl) waste.[8]

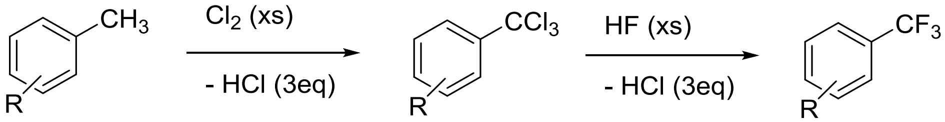
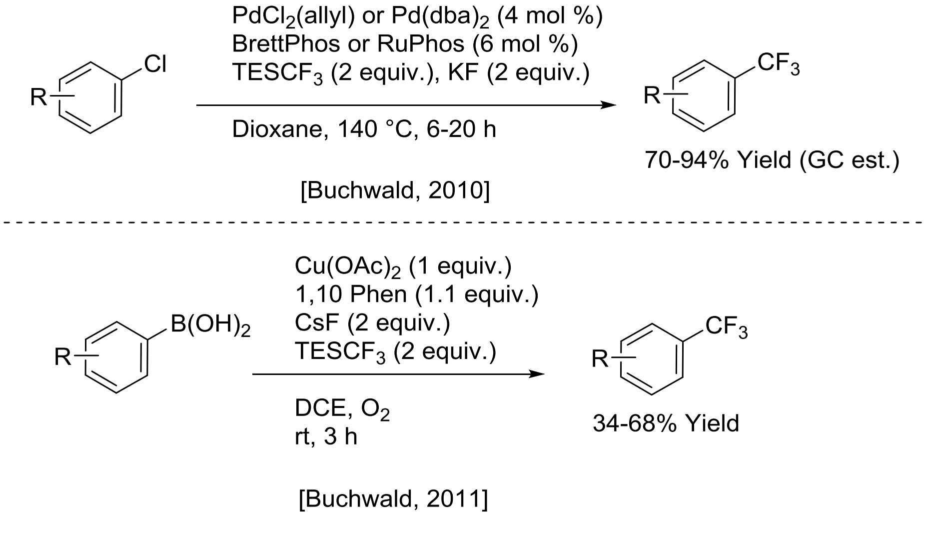


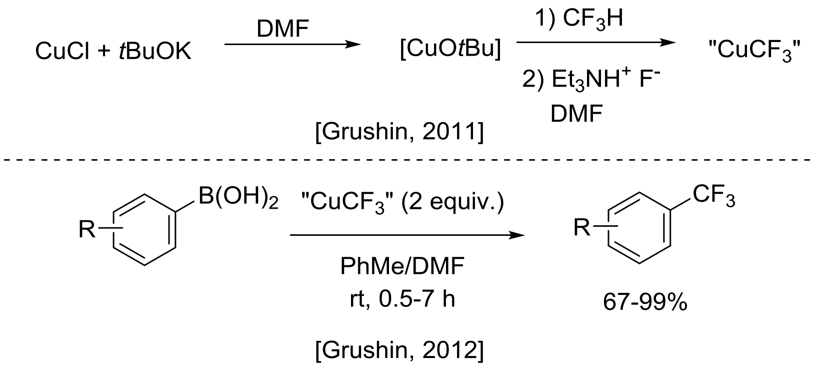
Figure 2. Current industrial process for trifluoromethyaltions

Over the past few years, reports on installation of the trifluoromethyl group have skyrocketed, with over 100 detailed reviews and books published over the last two years alone, and seemingly more reports published daily. Some of the more relevant detailed historical reviews of aliphatic[9] and aromatic[8] trifluoromethylations are worth noting by Ma and Grushin, respectively. While we wish to provide a thorough examination of prior art, the sheer number of growing publications makes it impossible. Thus we have listed the more commonly employed cases utilizing more traditional CF_3 sources, such as Cu/Unemotos reagent (*S*-(trifluoromethyl)thiophenium salts),[10-12] Re/Togni's reagent (3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole),[13,14] Pd/$TESCF_3$,[15,16] Cu/Rupperts reagent ($TMSCF_3$),[17-18] Ru/CF_3SO_2Cl,[19,20] Ag/$NaSO_2CF_3$[21] and Ag/CF_3I.[22] Some of the more recent methods developed in fluorine chemistry such as from the labs of Buchwald, Grushin, and Sanford are shown in Schemes 1-3, respectively.

The Buchwald group has pursued directed trifluoromethylation via Pd catalyzed couplings, with use of $TESCF_3$, (Scheme 1, top) using aryl chlorides in refluxing dioxane. Aryl bromides and triflates are also amenable to these reaction conditions, although with depressed yields compared to the chlorides.[23] A year later Buchwald *et al*. followed up their earlier work, again with the CF_3 source $TESCF_3$, except this time they utilized boronic acids, copper, a phenanthroline ligand, and ran the reactions at room temperature instead of refluxing conditions. They had obtained modest yields, with lower yields being that of theses hindered *ortho*-substituted aryl rings making the copper mediated coupling difficult.[24] (Scheme 1, bottom)

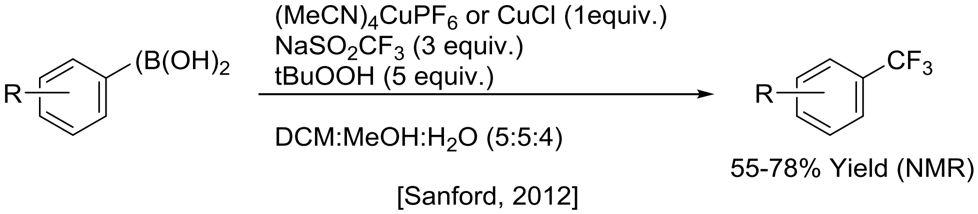


Scheme 1. Highlighted works by Buchwald *et al.* in trifluoromethylations



Scheme 2. Highlighted works by Grushin *et al.* in trifluoromethylations

An effort toward minimization of the use of additional reagents (i.e., base, ligand, atom inefficient CF_3 sources, etc.) was enabled by the preparation of an inexpensive ‘bottled’ $CuCF_3$ species (Scheme 2, top) by Grushin *et al.* The ready to use $CuCF_3$ reagent in DMF was found to be stable at room temperature for up to three days.[25] Whereas the same workers shortly followed up with application of their cheap fluoroform prepared $CuCF_3$ reagent in DMF, with the substrate (boronic acid) dissolved in PhMe to which was added two equivalents of $CuCF_3$ at room temperature while open to air thus avoiding additional costly and dangerous O_2 or Ag^I oxidants.[6] The mild conditions enable yields up to 99%, with excellent functional group compatibilities (Scheme 2, bottom).



Scheme 3. Highlighted work by Sandford *et al.* in trifluoromethylations

Boronic acids were used again for installation of the CF_3 group by Sandford *et al.,* by *in-situ* formation of $CuCF_3$ from Langlois' reagent[26] ($NaSO_2CF_3$), 'Cu', and radical initiator *t*-butyl peroxide.[27] They observed that for electron deficient boronic acids, CuCl gave very low yields (~20%), and later found the copper^I salt $(MeCN)_4CuPF_6$ to furnish modest yields in the 55-70% range, determined via NMR.

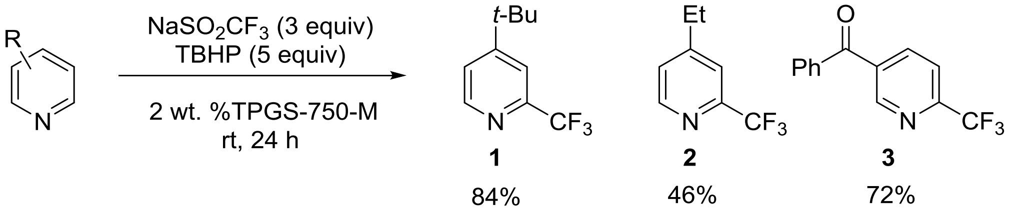
While these prior methods mentioned above offer good opportunities for synthesis of trifluoromethylated medicinal and agrochemical compounds for discovery research, their costs deem their use at scale unlikely. The key problem with scaling up a majority of the reported trifluoromethylation reactions is the prohibitive cost of the CF_3 source.[27] Another drawback of many current methodologies is the reliance on transition metals or more often times (super)stoichiometric quantities of transition metal complexes which may present limitations in terms of both waste disposal and cost.[6]

Most, if not all, methods for trifluoromethylation reported thus far have been optimized without consideration of their environmental impact. Likewise, no efforts have been made towards consideration of the twelve guiding principles of green chemistry.[28] There are currently no known methods for trifluoromethylation in green solvents. As well, virtually zero procedures have reduced organic and/or aqueous waste being generated, as quantified via E Factors.

Hence, we have set out to develop a procedure that addresses three main elements of green chemistry (a) in a green medium (i.e., water); (b) recyclability, and (c) minimization of waste being generated (organic and aqueous).

2.3 Results and Discussion

We had decided to target substitution at the C-H bond rather than the C-X bond of heterocycles for trifluoromethylation. This will enhance atom economy and help reduce waste by avoiding pre-functionalization. From this perpective, the impressive method reported by Baran[29] involving CF_3 radicals seemed especially attractive, utilizing commercially available Langlois' reagent ($NaSO_2CF_3$) as the source of these radicals, where no transition metal is needed.

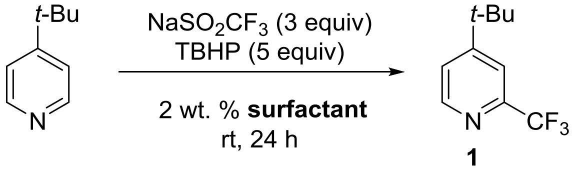


Scheme 4. Initial GC conversion results for trifluoromethylation in water

As a test case using aqueous micellar conditions based on our designer surfactant TPGS-750-M[30], three substituted pyridine systems were treated with $NaSO_2CF_3$ and then *t*-butylhydroperoxide (TBHP), leading to good levels of conversion to the anticipated trifluoromethylated products **1**, **2**, and **3** of 84, 46, and 72%, respectively, after 24 hours (Scheme 4). These initial results were encouraging due to the fact that we obtained a much higher rate of conversion than previously cited reports for the same substrates, [29] while achieving a greener process due to use of an aqueous medium, no metals, no energy input, and high concentrations enabling shortened reaction times. It was observed that reaction preparation was key to a high yield; solid substrates must be ground to a fine powder via mortar and pestle and form a uniform suspension in the surfactant before subsequent reagents are added. Failure to do so causes clumping, and/or rapid release of sulfur dioxide and quenching of the CF_3 radical to fluoroform (CF_3H).

A screening of alternative surfactants that we have used for previous micellar catalysis chemistry was performed at the commercially available concentrations of two weight percent (2 wt. %) as shown in Table 1 for the conversion of *t*-butylpyridine to **1** in the same manner as our initial results at a global concentration of 0.5 M. The top performing surfactants, TPGS-750-M (entry 1) and PTS-600[31] (entry 2) led to 84% and 54% conversion to **1**, respectively. Both commercial amphiphillic surfactants were developed by our research group for cross coupling reactions, although have now been shown to have a wide variety of synthetic applications. The excellent performance by TPGS-750-M (entry 1), can be attributed to its larger particles that provide greater amounts of lipophilic material within their inner cores, thus, increasing organic solubility and leading to enhanced levels of conversion. This is further substantiated by Scheme 1 as **1** had the best levels of conversion and being the most lipophilic. The corresponding water reactions (i.e., on water) gave the lowest level of conversion (entry 8).

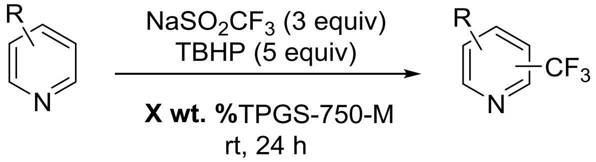
Table 1. Screening of surfactants for the production of **1**



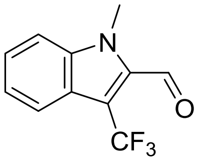
entry	surfactant	GC conv. (%)
1	TPGS-750-M	84
2	PTS-600	54
3	Cremophor EL	36
4	Triton X 100	22
5	Brij-30	22
6	TPGS-1000	19
7	PQS	18
8	none (water)	17

With the determined optimal surfactant, TPGS-750-M, we varied its concentration from zero (only water) to five weight percent as shown in Table 2 for the conversion towards **1** and **4**. For the example of **1**, three weight percent (entry 4) performed slightly better than two weight percent (entry 3), although two weight percent was chosen to be used for the remainder of the study because of the fact that it is commercially available, thus making our process more user friendly. We had also further confirmed that the surfactant was indeed playing a pivotal role for these trifluoromethylations as compound **4** was converted from its starting indole in 46% conversion using TPGS-750-M (entry 3) versus the water control of only 7% (entry 1).

Table 2. Screening of TPGS-750-M concentration for the production of **1** and **4**



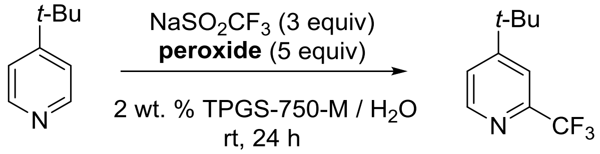
		GC conv. (%)	
entry	weight (%)	**1**	**4**
1	0	17	7
2	1	37	-
3	2	80	46
4	3	83	-
5	5	60	-



4

Various peroxide sources were screened as radical initiators for the reaction shown in Table 3. We first investigated cumene hypdroperoxide (CHP) as its clogP of 2.44 is much higher than that of TBHP of 1.05; from our previous work with micellar catalysis and surfactants a significant hydrophobic effect was observed, meaning that as the lipophillicity of compound and/or reagent(s) increased the yields tend to follow.[32] Ultimately, due to the high viscosity of CHP, we observed difficulties in maintaining a homogeneous reaction medium without significant clumping. Benzoyl peroxide gave no reaction as it failed to give **1**, presumably due to it gelling providing poor dissolution of the reagent. Our proposed hydrophobic effect theory was further supported by the fact that hydrogen peroxide was not incorporated into the micelles for a reaction to occur. The preferred peroxide was determined to be TBHP providing **1** in 88% isolated yield.

Table 3. Screening of peroxide radical initiators for the production of **1**

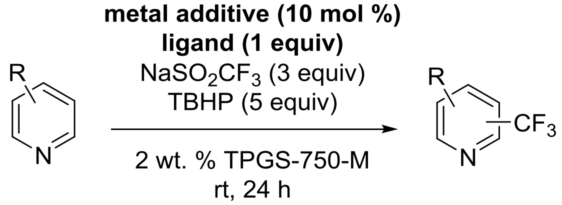


1

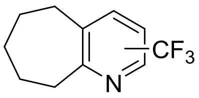
entry	peroxide	Yield (%)
1	TBHP	88
2	CHP	72
3	Bz_2O_2	0
4	H_2O_2	0

From previous analysis of Langlois' reagent, various amounts of trace metals were discovered.[29] From these known metal contaminants we chose to screen for those in the highest concentrations such as zinc, copper, and nickel, all of which are also known to facilitate single electron transfer from the CF_3 source as shown for products **5** and **6** (Table 4). Zinc(II), copper(I), and nickel(II) salts bearing various counterions appeared in all cases to decrease the yields (entries 2-9) obtained in both examples, with annulated pyridine **5** and substituted indole **6**, when compared to reactions without added metal (entry 1). From previous work using zinc with surfactants, TMEDA or 1,1- phenalthroline (1,10-Phen) is needed to coordinate zinc, thus making it more lipophilic and shuttle it into the micelle.[30] Although, interestingly, 1,10-Phen completely inhibited the reactions (entry 3). Initially we presumed that the ligand itself had been trifluoromethylated but GC-MS analysis did not support this and it is still difficult to explain.

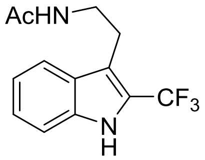
Table 4. Screening for metal enhancement for the trifluoromethylations **5** and **6**



entry	metal	ligand	Yield (%) **5**	Yield (%) **6**
1	-	-	73	64
2	$ZnCl_2$	TMEDA	51	42
3	$ZnCl_2$	1,10-Phen	0	0
4	CuI	-	53	49
5	CuOAc	-	54	52
6	$CuBr\text{-}SMe_2$	-	52	47
7	$NiCl_2$	-	42	-
8	$NiI_2(Ph_3)_2$	-	47	-
9	$Ni(COD)_2$		45	-



5 (C2:C3 1:3.8)



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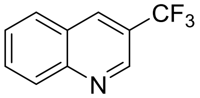
In efforts to further enhance the yield of our aqueous trifluoromethylation we investigated the effects of portion-wise versus single addition, and an increase of Langlois's reagent and TBHP for the production of **1**. Our attempt at employing portion-wise addition, by adding one third of the reagents every hour to overcome possible slow reaction kinetics led to the same conversion as a single addition within experimental error. Increasing the equivalents of Langlois and TBHP reagents to 5 and 8.5 from 3 and 5 respectively caused a large reduction in converted substrate due to the unproductive formation of fluoroform. Heating the reaction had the same effect.

With our results from these optimization studies completed, the procedure that emerged involved use of Langlois' reagent (3 equiv) in combination with TBHP (5 equiv), in 2 weight percent TPGS-750-M at room temperature. Several heterocyclic and heteroaromatic substrates were tested in an effort to establish the scope and utility of this new process. Also, many of the examples were directly compared to previously reported syntheses, and to our overwhelming pleasure, our aqueous trifluoromethylations furnished products in higher yields than prior methodology for all substrates (Table 5).

Table 5. Initial substrate scope for aqueous trifluoromethylations with literature comparisons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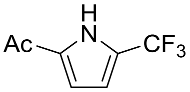
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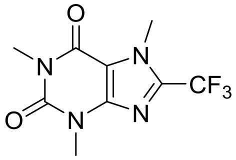
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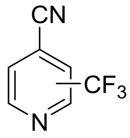
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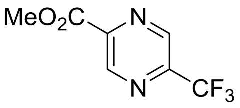
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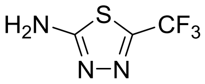
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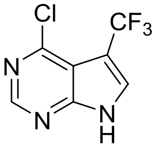
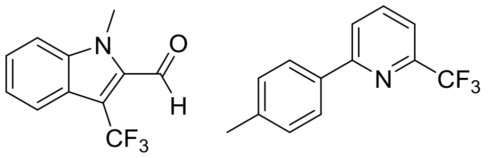

13

		this work[a]	literature
entry	compound	yield (%)	yield (%)
1	**3**	66	40[c]
2	**5**	73	43[d,e]
3	**6**	64	51[d]
4	**7**	71[b]	59,[c] 38[f]
5	**8**	62	57[d]
6	**9**	84	78[d]
7	**10**	55	48[d,e]
8	**11**	54	50[d,e]
9	**12**	43	33[d,e]
10	**13**	47	43[d]

[a] conditions: substrate (1 mmol), $NaSO_2CF_3$ (3 equiv), TBHP (5 equiv), 2 wt. % TPGS-750-M (0.5 M), [b] NMR yield, [c] see ref. 33, [d] see ref. 29, [e] required double addition of reagents, [f] see ref. 24

The compound 3-phenone-pyridine used in early stages of testing was subjected to the optimized conditions forming **3** in 66% yield (entry 1). Makosza *et al.* had previously reported the formation of **3** over three steps in 40%[33] via production of a pyridyl protected PMB bromide azinium salt, followed by trifluoromethylation with triphenyltin fluoride, KF, and TMSCF$_3$ in DCM forming a dihydroazine intermediate, then oxidized with CAN. Additionally Makosza *et al.* used this same strategy producing **7** in 59% overall yield[33] verse our yield of 71% of **7** (entry 3). Buchwald *et al.* also produced **7** in 38% yield [24] using Cu (II) salts with TESCF$_3$ in DCE under an oxygen atmosphere as described above in Scheme 1. Examples from Baran and co-workers[29] were also directly compared as his method is most similar in respects to the reagents utilized, as demonstrated in Table 5 for compounds **5**, **6**, and **8-13** (entries 2,3,5-10); again all yields had been improved. It is worth noting that for compounds **5**, and **10-12** Baran required additional NaSO$_2$CF$_3$ and TBHP reagents (3-6 equiv; 5-10 equiv, respectively) to achieve modest yields. In no case did we find it necessary to use more than our optimized amounts of NaSO$_2$CF$_3$ and TBHP.

Two additional compounds **4** and **14** were also subjected to the reaction conditions and provided isolated yields of 42 and 68%, respectively. The yield of compound **4** is presumably low and not an accurate representation of the quality of bond formation, caused by aldehyde oxidation to the water soluble carboxylic acid by the peroxide.



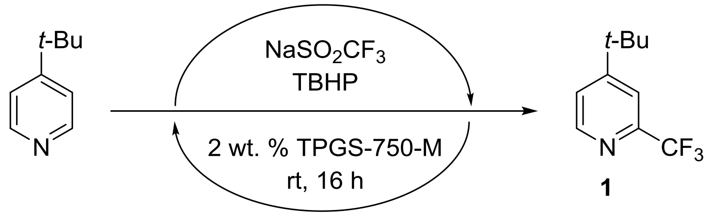
4, 42%[a] **14**, 68%[a]

Figure 3. Additional examples of aqueous trifluoromethylation

[a] conditions: substrate (1 mmol), NaSO$_2$CF$_3$ (3 equiv), TBHP (5 equiv), 2 wt. % TPGS-750-M (0.5 M)

Workup of these trifluoromethylations is quite simple; a minimum amount of EtOAc is added directly to the reaction vessel, slowly stirred and extracted. This technique allows the isolation of crude product generally in >85% purity, while the remaining aqueous mixture retains the TPGS-750-M and hence, can be recycled several times. The reuse of the aqueous media and no need for additional water during the work up, drastically reduced our waste output. Results from a recycling study for the synthesis of **1** are shown in Table 6. The drop in isolated yields associated with 4th and 5th recycle is likely due to continuous buildup of *t*-butanol in the reaction mixture, which would help solubilize the product in the aqueous layer. Although the yields tended to decrease over time, the TLC analysis of each recycle suggests that the extent of conversion is also dropping, and the reactions are not any less clean than those done earlier in the sequence.

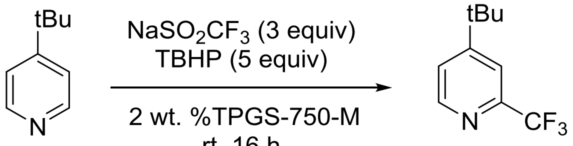
Table 6. Surfactant recycling study for the of **1**



entry	cycle[a]	yield (%)
1	1	78
2	2[b]	79
3	3[b]	73
4	4[b]	68
5	5[b]	62

[a] conditions: substrate (1 mmol), $NaSO_2CF_3$ (3 equiv), TBHP (5 equiv), 2wt% TPGS-750-M (0.5 M), [b] extracted with EtOAc and subjected the aqueous medium to the next reaction

Table 7. Calculated E Factors for production of **1**



1

	based on:	this work	with recycling
E Factors	total organic solvent	5.6	6.1
	aqueous media included	18.2	8.9

One of the ways to measure the environmental impact or “greenness” of any specific reaction is by means of an E Factor.[34] While as the rules from Sheldon[35] state only the first use of any medium need be calculated in the E Factor, all subsequent reactions may ignore the recycled solvent thus causing a large reduction in E Factor. As shown in Table 7, trifluoromethylation reactions carried out in nanomicelles led to an E Factor of only 5-6, given the complete absence of any organic solvent in the reaction medium. An E Factor calculated on inclusion of water raises this value to only 18.2, but with a single recycle this value is cut in half, in line with our previous observations relating to cross-coupling reactions performed within these recyclable nanoreactors.

In conclusion, micellar catalysis has been found to be amenable to radical-based trifluoromethylation of various hetercyclic and heteroaromatic compounds. Nanoreactors composed of the designer surfactant TPGS-750-M enable these substitution reactions to be performed in water at room temperature in modest to good yields. The aqueous reaction mixtures are readily recycled, and given the limited amounts of organic solvent needed for product isolation, the associated E Factors imply that a considerably enhanced level of greenness is characteristic of these reactions. Thus completing our goals of (1) eliminated use of a mixed aqueous solvent system that included a chlorinated solvent (DCM); (2) reducing the amounts of reagents involved; (3) improve yields; (4) be amenable to recycling of the purely aqueous reaction medium, and (5) reduce the level of organic waste being created.

2.4 Experimental and compound data

General information

The water for this study was HPLC grade and was degassed prior to use by bubbling a flow of argon through the mixture for several hours. All commercially available reagents were used without further purification unless otherwise stated. The surfactant TPGS-750-M is commercially available from Sigma-Aldrich but can be synthesized through a previously published procedure.[30] Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). The developed chromatogram was analyzed by UV lamp (254 nm) and/or aqueous potassium permanganate ($KMnO_4$), and developed by applying heat with a heat gun. Flash chromatography was performed in glass columns using Silica Flash® P60 (SiliCycle, 40-63 μm). ^{1}H and ^{13}C spectra were recorded at 23 °C on a Varian UNITY INOVA 500 MHz. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. GC/MS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). As capillary column a HP-5MS cross-linked 5% phenylmethyl-polysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min.

Standard Procedures

Surfactant screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1x5mm) with septum. Added 2 wt% surfactant ([0.5], 0.2 mL, Table 1), 4-*tert* butyl pyridine (0.10 mmol, 15uL), sodium trifluoromethanesulfinate (0.30 mmol, 47 mg) then cooled to ~ 5 °C. Then via syringe added 70wt% TBHP (0.50 mmol, 68uL). Allowed to stir at room temperature (~ 23°C) for 24 hours, quenched with saturated $NaHCO_3$ (1 mL), extracted with EtOAc (1 mL) and percent conversion determined by GC.

Surfactant strength screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1x5mm) with septum. Added TPGS-750-M ([0.5], 0.2 mL, Table 2), 4-*tert* butyl pyridine (0.10 mmol, 15uL), sodium trifluoromethanesulfinate (0.30 mmol, 47 mg) then cooled to ~ 5 °C. Then via syringe added 70wt% TBHP (0.50 mmol, 68uL). Allowed to stir at room temperature (~ 23°C) for 24 hours, quenched with saturated $NaHCO_3$ (1 mL), extracted with EtOAc (1 mL) and percent conversion determined by GC.

Peroxide screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1x5mm) with septum. Added 2wt% TPGS-750-M ([0.5], 0.2 mL), 4-*tert* butyl pyridine (0.10 mmol, 15uL), sodium trifluoromethanesulfinate (0.30 mmol, 47 mg) then cooled to ~ 5 °C. Then added the peroxide (Table 3) drop wise for liquid reagents and slow addition for solids, 70 wt% TBHP (0.50 mmol, 68uL), 80% CHP (0.5mmol, 94uL), benzoyl peroxide (0.5 mmol, 121 mg), and 30% hydrogen peroxide (0.5 mmol, 40 uL). Allowed to stir at room temperature (~ 23°C) for 24 hours then quenched with saturated $NaHCO_3$ (2 mL)), extracted with EtOAc (3 mL), concentrated under reduced pressure. Isolated via column chromotagraphy eluting with EtOAc:Hex.

Metal additive screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1x5mm) with septum. Added 2wt% TPGS-750-M ([0.5], 0.3 mL), substrate (0.15 mmol), sodium trifluoromethanesulfinate (0.45 mmol, 70 mg), various metal salts at 10 mol% and associated ligands at 1 equiv (Table 4) then cooled to ~ 5 °C. Then added 70 wt% TBHP (0.75 mmol, 103uL) drop wise. Allowed to stir at room temperature (~ 23°C) for 24 hours, then quenched with saturated $NaHCO_3$ (2 mL)), extracted with EtOAc (3 mL), concentrated under reduced pressure. Isolated via column chromotagraphy eluting with EtOAc:Hex.

Portion wise addition

To a 5 mL microwave vial equipped with a PTFE stir bar (1x5mm) with septum. Added 2wt% TPGS-750-M ([0.5], 0.5 mL), caffeine (0.25 mmol). The sodium trifluoromethanesulfinate and TBHP were then added in one third portions per hour over three hours. Sodium trifluoromethanesulfinate (0.75 mmol, 117 mg), 70 wt% TBHP (1.25

mmol, 171uL) drop wise. Allowed to stir at room temperature (~ 23°C) for 48 hours, then quenched with saturated $NaHCO_3$ (2 mL)), extracted with EtOAc (3 mL), concentrated under reduced pressure. Isolated via column chromotagraphy eluting with EtOAc:Hex to provide the trifluoromethylated caffeine analog **6** in 81% yield as a white crystalline solid.

Representative procedure

To a 5 mL round bottom flask with a PTFE stir bar (1x5mm) with septum. Added 2wt% TPGS-750-M ([0.5], 2.0 mL), heterocycle (1.00 mmol) sodium trifluoromethanesulfinate (3.0 mmol, 468 mg) then cooled to ~ 5 °C. Then added 70 wt% TBHP (5.00 mmol, 690uL) drop wise . Allowed to stir at room temperature (~ 23°C) until complete by TLC, then quenched with saturated $NaHCO_3$ (2 mL)), extracted with EtOAc (3 mL), concentrated under reduced pressure. Passed through a bed a silica gel with EtOAc to provide the trifluoromethylated heterocycle analog.

Note: highly crystalline solids must be ground to a fine powder (mortar and pestle) thereby forming a uniform suspension in the aqueous medium prior to introduction of reagents. As well as slow addition of the TBHP is necessary. Failure to do so causes clumping, and/or rapid release of sulfur dioxide and ultimately quenching of the CF_3 radical to form fluoroform (CHF_3).[29]

Recycling study

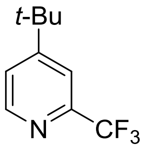
To a 5 mL round bottom flask with a PTFE stir bar (1x5mm) with septum. Added 2wt% TPGS-750-M ([0.5], 2.0 mL), 4-*tert* butyl pyridine (1.0 mmol, 148uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg) then cooled to ~ 5 °C. Then added 70 wt% TBHP (5.00 mmol, 690uL) drop wise (~100uL/min) Allowed to stir at room temperature (~ 23°Cfor 24 hours then extracted with EtOAc (1 mL), concentrated under reduced pressure.

Isolated via column chromotagraphy eluting with EtOAc:Hex.to provide the trifluoromethylated 4-*tert* butyl pyridine analog **1**. The aqueous reaction media was then subjected to a subsequent reaction and repeated four more times as shown in Table 5.

Surfactant solution preparation

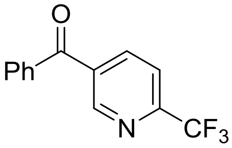
The water for this study was HPLC grade and was degassed prior to use by bubbling a flow of argon through the mixture for several hours. Then each solution prepared weight by weight for the desired concentration with the previously degassed HPLC grade water and subjected to an addition sparging with argon for an hour. All surfactants were stored under an argon atmosphere prior to use. Surfactants PTS and TPGS-750-M are both commercially available from Sigma-Aldrich but can be synthesized through a previously published procedures.[30,31]

Compound data



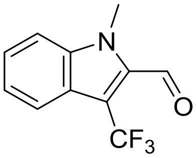
1

4-*t*-Butyl-2-trifluoromethylpyridine (1, JF-004-205). The representative procedure was followed using 4-*t* butylpyridine (1.0 mmol, 148 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). Reaction was complete after 15 h by TLC. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex. (R_f = 0.55, 20% EtOAc:hex) to yield **1** 161 mg, 79% of faint yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.19 Hz, 1H), 7.66 (s, 1H), 7.47 (d, J = 5.19 Hz, 1H), 1.35 (s, 9H). GC/MS m/z: 203.09. Compound data matches that of previously reported. [29]



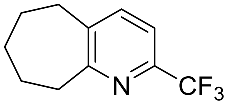
3

phenyl(6-(trifluoromethyl)pyridin-3-yl)methanone (3, JF-003-117). The representative procedure was followed using phenyl(pyridin-3-yl)methanone (1.0 mmol, 183 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The crude product was isolated by passage through a bed a silica gel with 15% EtOAc:hex (R_f = 0.35, 20% EtOAc:hex) to yield **3**, 166 mg, 66%, of a clear solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 1.97 Hz, 1H), 8.19 (d, *J* = 8.22 Hz, 2H), 8.13 (dd, *J* = 0.96, 7.85 Hz, 1H), 7.94 (m, 1H), 7.75 (d, *J* = 8.15 Hz, 2H), 7.53 (m, 1H). GC/MS m/z: 251.23. Compound data matches that of previously reported.[24]

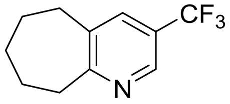


4

1-Methyl-3-(trifluoromethyl)-1H-indole-2-carbaldehyde (4, JF-003-116). The representative procedure was followed using 1-methyl-1H-indole-2-carbaldehyde (1.0 mmol, 159 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The crude product was isolated by passage through a bed a silica gel with 20% EtOAc:hex (R_f = 0.55, 10% EtOAc:hex) to yield **4**, 96 mg, 42%, of an off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.91 (d, *J* = 8.32 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.32 (ddd, *J* = 1.22, 6.66, 8.08 Hz, 1H), 4.15 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 182.62, 154.30, 131.87, 130.72, 127.49, 122.96, 121.88, 110.78, 96.12, 92.77, 32.49. HREIMS calcd for $C_{11}H_8F_3NO$: 227.0558. Found: 227.0560

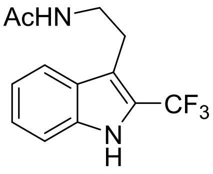


5-C2



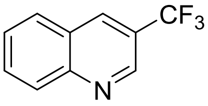
5-C3

2-(Trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (5-C2, JF-002-182) and **3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (5-C3, JF-002-182)**. The representative procedure was followed using 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (1.0 mmol, 156 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete after 43 h by TLC. Crude product by purified by passage through a bed a silica gel with 20% EtOAc:hex to yield 394 mg, 73%, (1:3.8 **5-C2:5-C3)** of faint yellow liquid. Data for **(5-C2)** (105 mg), (R_f = 0.60, 20% EtOAc:hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.68 Hz, 1H) 7.38 (d, *J* = 7.70 Hz, 1H), 3.14 – 3.08 (m, 2H), 2.88 – 2.81 (m, 2H), 1.95 – 1.86 (m, 2H), 1.79 – 1.64 (m, 4H), GC/MS m/z: 215.1. Data for **(5-C3)** (289 mg), (R_f = 0.55, 20% EtOAc:hex).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.20 Hz, 1H), 7.33 (d, *J* = 5.19 Hz, 1H), 3.21 – 3.11 (m, 2H), 2.98 – 2.90 (m, 2H), 1.92 – 1.83 (m, 2H), 1.74 – 1.62 (m, 4H). GC/MS m/z: 215.09. Compound data matches that of previously reported.[29] Note: Minor region-isomer impurities observed in ^{1}H NMR.



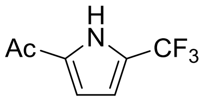
6

2-Trifluoromethyl melatonin (6, JF-002-189). The representative procedure was followed using melatonin (1.0 mmol, 232 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). Reaction was complete as judged by TLC in 44 h. Crude product was purified by passage through a bed a silica gel with EtOAc (R_f = 0.70, 100% EtOAc) to yield **6**, 192 mg, 64% of off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.54 (d, *J* = 9.04 Hz, 1H), 7.06 (d, *J* = 9.06 Hz, 1H), 5.72 (t, J = 5.36 Hz, 1H), 3.89 (s, 3H), 3.47 (m, 2H), 3.10 (t, *J* = 6.93 Hz, 2H), 1.95 (s, 3H). GC/MS m/z: 300.11. Compound data matches that of previously reported.[29]



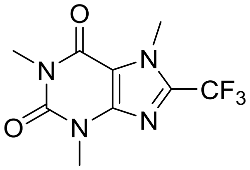
7

3-(Trifluoromethyl)quinolone (7, JF-002-210). The representative procedure was followed using quinoline (1.0 mmol, 129 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was stopped after 36 h (no additional conversion passed this point). The crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex (R_f = 0.25, 20% EtOAc:hex) to yield **7**, 140 mg of product and starting material. The yield was determined by NMR to be 71%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, *J* = 4.15 Hz, 1H), 8.24 (d, *J* = 8.30 Hz, 1H), 8.10 (d, *J* = 7.27 Hz, 1H), 8.04 (d, *J* = 8.28 Hz, 1H), 7.61 (t, *J* = 7.32 Hz, 1H), 7.52 (m, 1H). GC/MS m/z: 197.16. Compound data matches that of previously reported.[29]



8

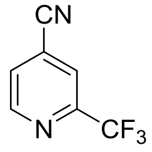
1-(5-(Trifluoromethyl)-1H-pyrrol-2-yl)ethan-1-one (8, JF-004-185). The representative procedure was followed using 1-(1H-pyrrol-2-yl)ethan-1-one (1.0 mmol, 109 mg), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 28 h. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex (R_f = 0.45, 20% EtOAc:hex) to yield **8**, 110 mg, 62% of an off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (brs, 1H), 6.87 (s, 1H), 6.61 (s, 1H), 2.48, (s, 3H). GC/MS m/z: 177.04. Compound data matches that of previously reported.[29] Note: Minor regio-isomer impurities observed in ^{1}H NMR.



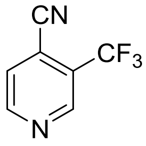
9

Trifluoromethylated caffeine (9, JF-002-134). The representative procedure was followed using caffeine (1.0 mmol, 194 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 23 h. The crude product was purified by passed through a bed a silica gel with 20%

EtOAc:hex (R_f = 0.25, 20% EtOAc:hex) to yield **9**, 222 mg, 84% of white crystalline solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (s, 3H), 3.58 (s, 3H), 3.40 (s, 3H). GC/MS m/z: 264.08. Compound data matches that of previously reported.[29]

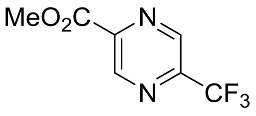


10-C2



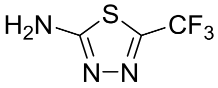
10-C3

2-Trifluoromethyl-4-cyano-pyridine (10-C2, JF-002-187) and **3-trifluoromethyl-4-cyano-pyridine (7-C3, JF-004-187)**. The representative procedure was followed using 4-cyano-pyridine (1.0 mmol, 104 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 44 h. The crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex to yield 97 mg, 55% (1.6:1 **10-C2:10-C3**) of a colorless oil. **Data for 10-C2** (61 mg), (R_f = 0.50, 20% EtOAc:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (d, *J* = 4.93 Hz, 1H), 7.92 (s, 1H), 7.76 (d, *J* = 4.92 Hz, 1H). GC/MS m/z: 172.02; **Data for (10-C3)** (35 mg), (R_f = 0.30, 20% EtOAc:hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 9.03 (d, *J* = 4.93 Hz, 1H), 7.74 (d, *J* = 4.94 Hz, 1H). GC/MS m/z: 172.02. Compound data matches that of previously reported.[29] Note: Minor regio-isomer impurities observed in ^{1}H NMR.



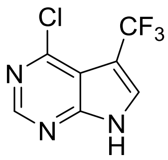
11

Methyl 5-(trifluoromethyl)pyrazine-2-carboxylate (11, JF-002-193). The representative procedure was followed using methyl pyrazine-2-carboxylate (1.0 mmol, 138 uL), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete by TLC in 51 h. The crude product by passed through a bed a silica gel with 20% EtOAc:hex (R_f = 0.35, 20% EtOAc:hex) to yield **11**, 112 mg, 54%, as an off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 9.07 (s, 1H), 4.10 (s, 3H). GC/MS m/z: 206.03. Compound data matches that of previously reported.[29]



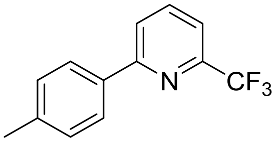
12

5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (12, JF-004-110). The representative procedure was followed using 1,3,4-thiadiazol-2-amine (1.0 mmol, 101.mg), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete by TLC in 38 h. The crude product by passed through a bed a silica gel with 50% EtOAc:hex (R_f = 0.73, 75% EtOAc:hex) to yield **12**, 73 mg, 43%, as an off white solid; ^{1}H NMR (500 MHz, MeOD) δ 4.88 (s, 2H), GC/MS m/z: 169.12. Compound data matches that of previously reported.[29]



13

4-chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidine (13, JF-003-116). The representative procedure was followed using 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (1.0 mmol, 154.mg), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete by TLC in 52 h. The crude product by passed through a bed a silica gel with 40% EtOAc:hex (R_f = 0.70, 50% EtOAc:hex) to yield **13**, 73 mg, 47%, as an off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.67 (br s, 1H), 8.81 (s, 1H), 7.09 (s, 1H). GC/MS m/z: 221.54. Compound data matches that of previously reported.[29]

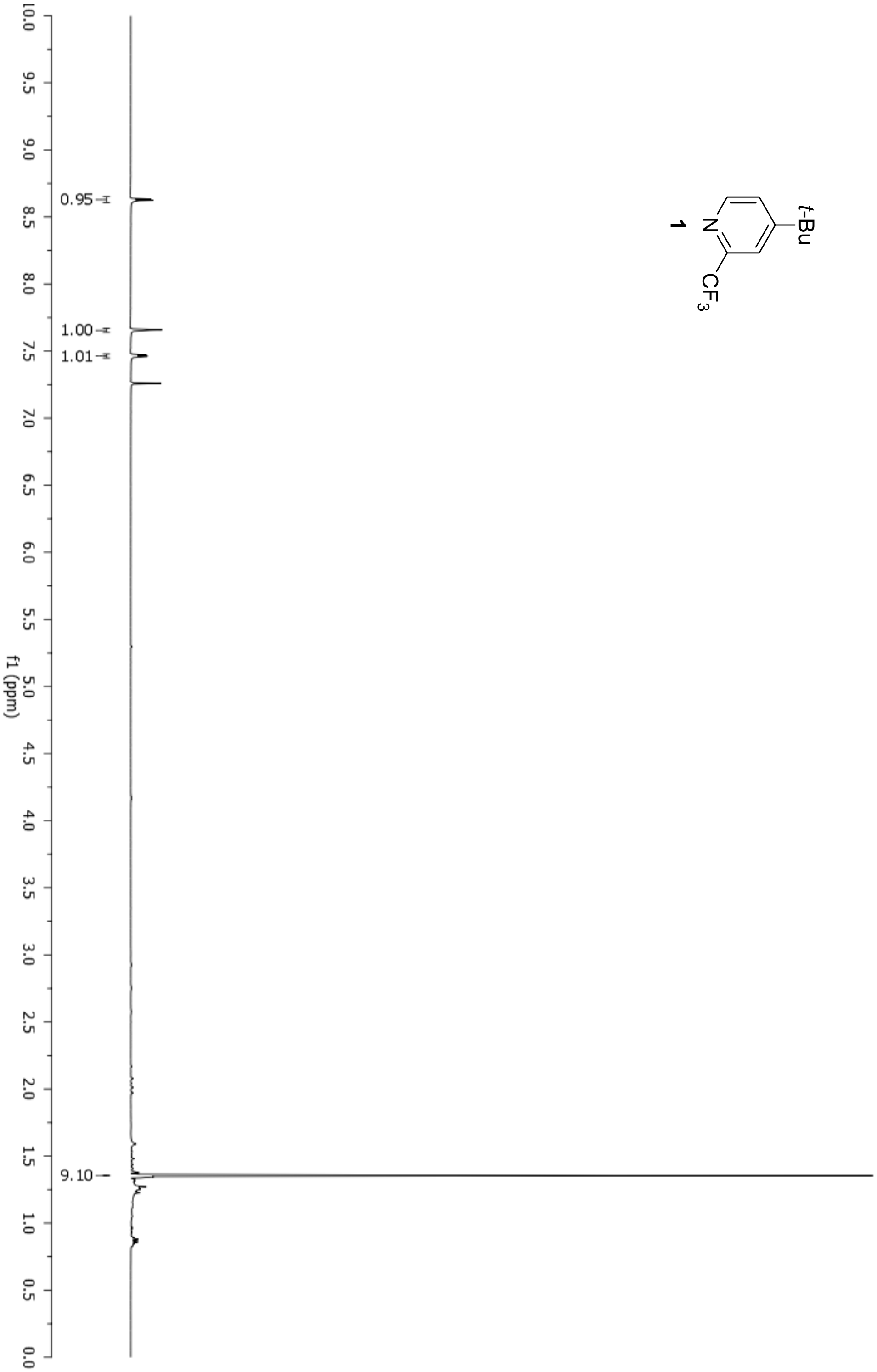


14

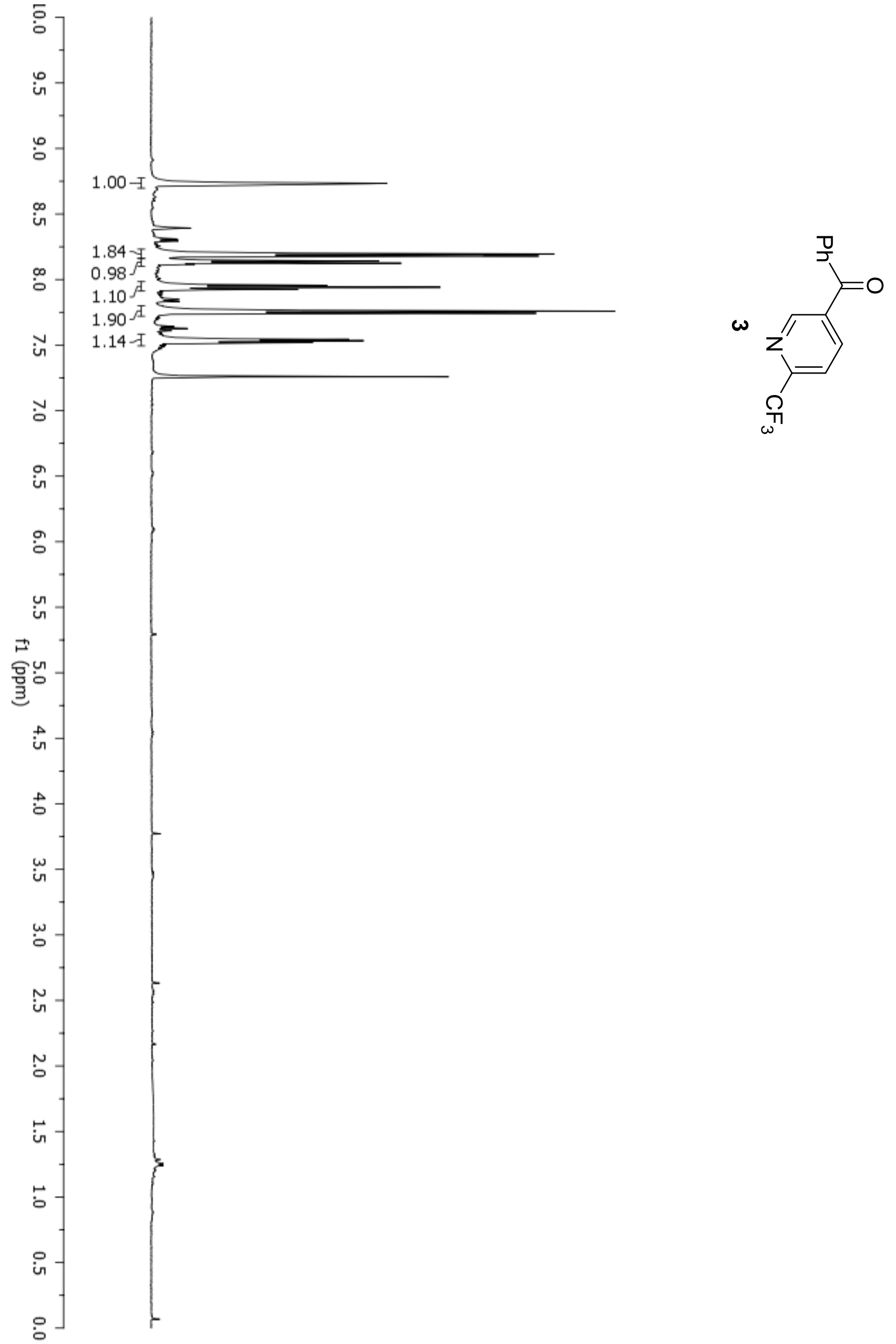
2-(*p*-Tolyl)-6-(trifluoromethyl)pyridine (14, JF-002-214). The representative procedure was followed using 2-(*p*-tolyl)pyridine (1.0 mmol, 169 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 18 h. The crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex (R_f = 0.35, 10% EtOAc:hex) to yield **14**, 161 mg, 68%, as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.13 Hz, 2H), 7.89 (d, J = 4.61 Hz, 2H), 7.57 (t, J = 3.89 Hz, 1H), 7.30 (d, J = 8.05 Hz, 2H), 2.42 (s, 3H). GC/MS m/z: 237.08. Compound data matches that of previously reported.[36]

2.5 Spectral Data

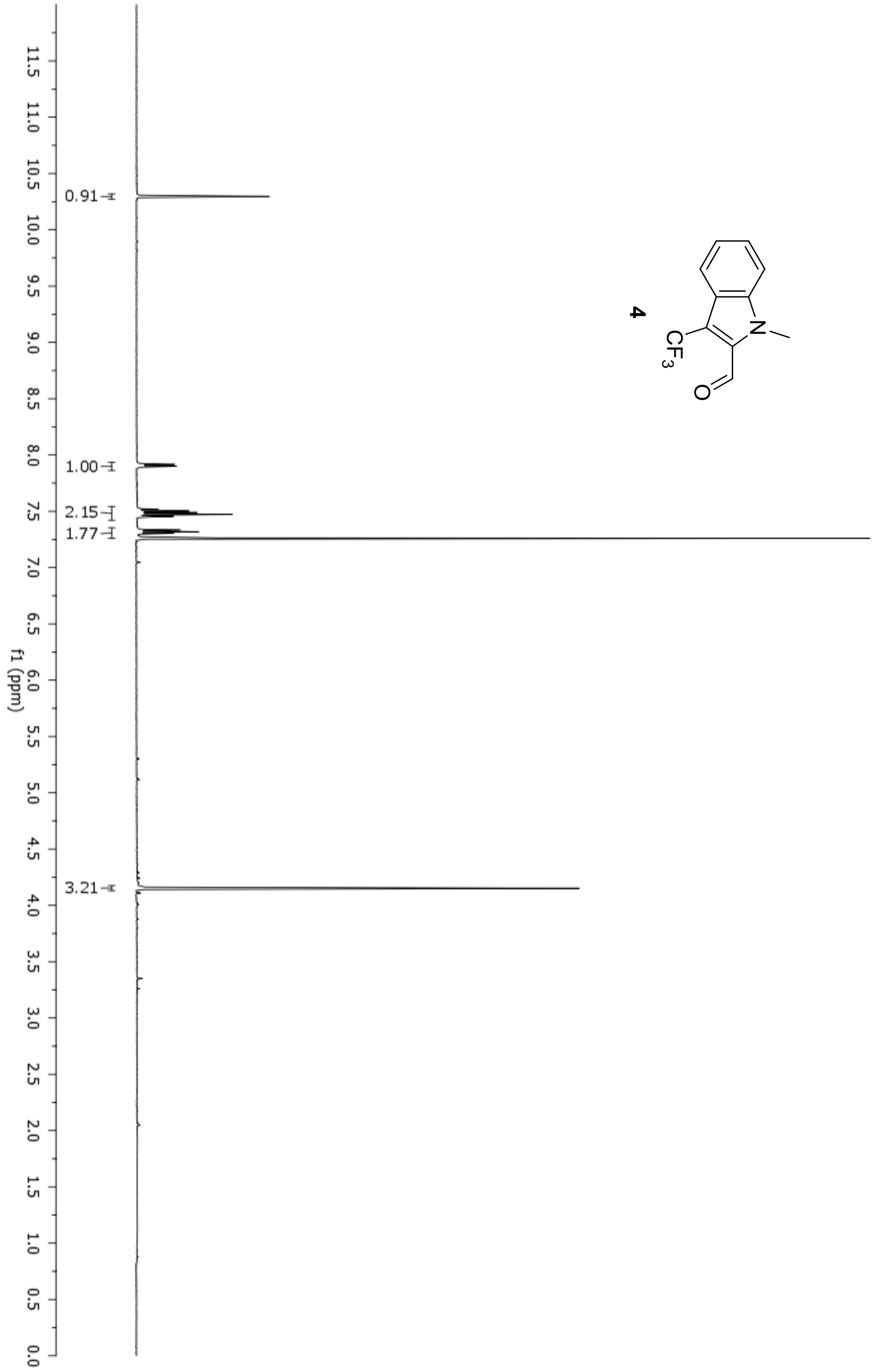
4-*tert* butyl-2-trifluoromethyl pyridine **1**; Proton NMR ($CDCl_3$)



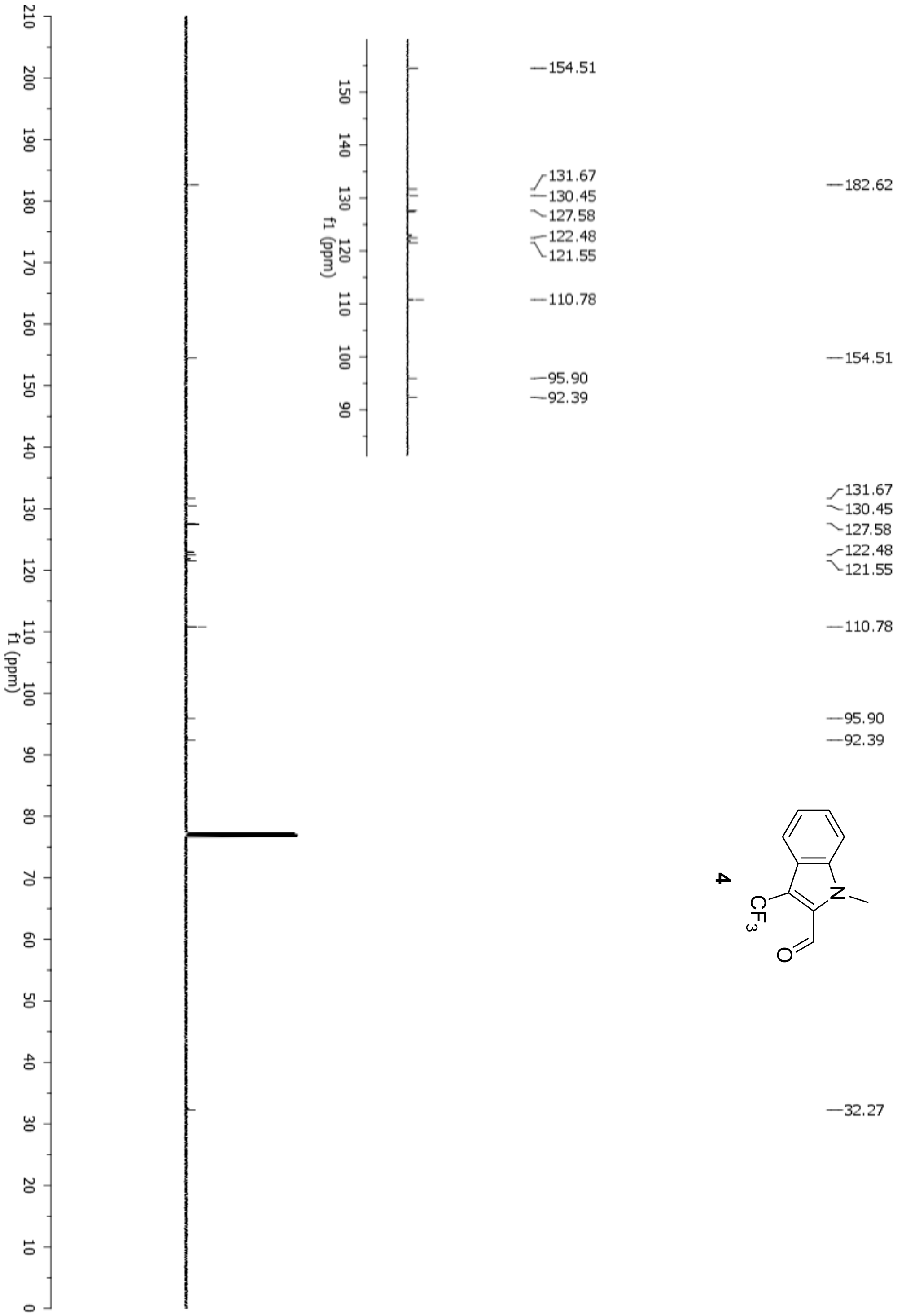
phenyl(6-(trifluoromethyl)pyridin-3-yl)methanone **3**; Proton NMR ($CDCl_3$)



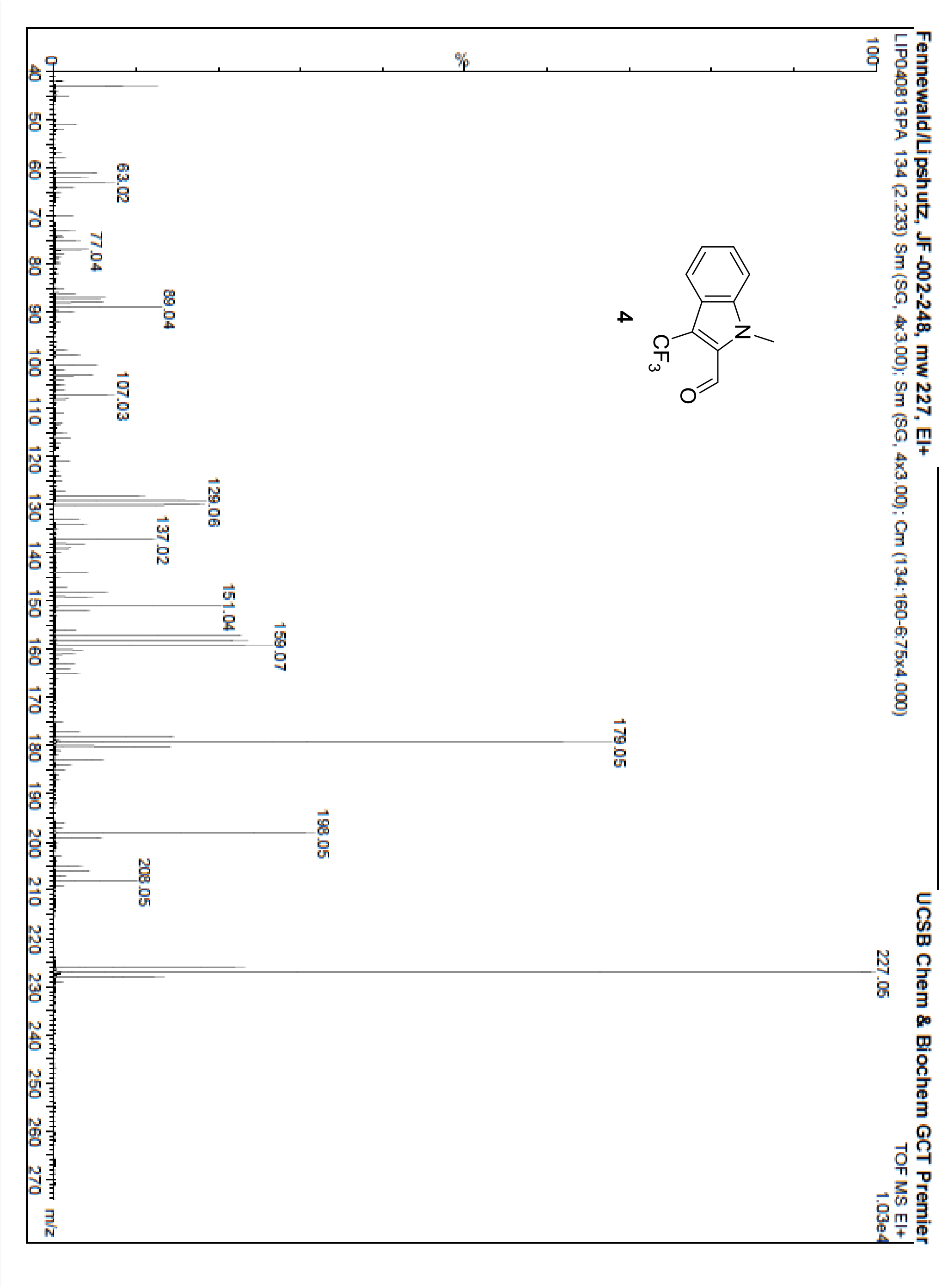
1-methyl-3-(trifluoromethyl)-1H-indole-2-carbaldehyde **4**; Proton NMR ($CDCl_3$)



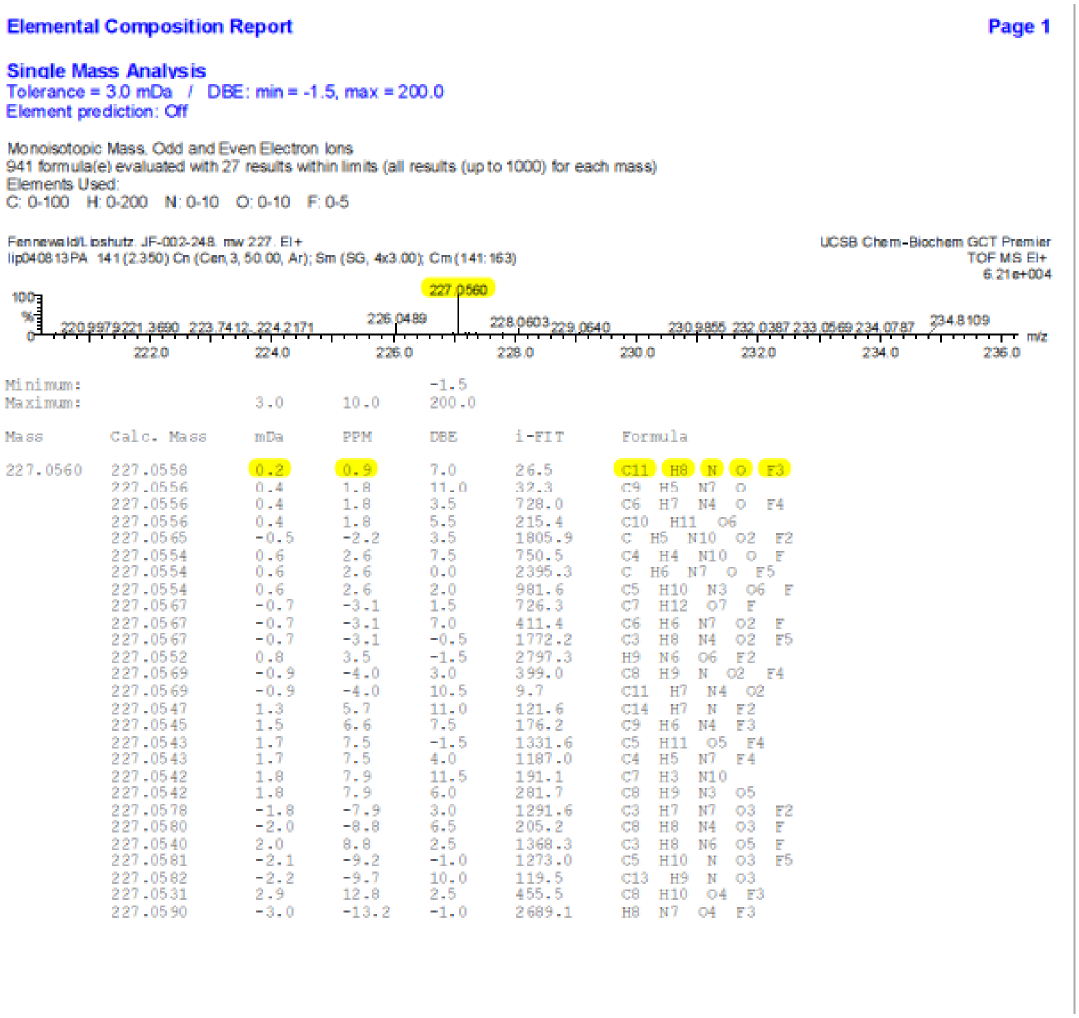
1-methyl-3-(trifluoromethyl)-1H-indole-2-carbaldehyde **4**; Carbon NMR (CDCl$_3$)



1-methyl-3-(trifluoromethyl)-1H-indole-2-carbaldehyde **4**; LREIMS



1-methyl-3-(trifluoromethyl)-1H-indole-2-carbaldehyde **4**; HREIMS



Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 mDa / DBE: min = -1.5, max = 200.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
941 formula(e) evaluated with 27 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-200 N: 0-10 O: 0-10 F: 0-5

Fennewald/Lipshutz JF-002-248 mw 227 EI+
lip040813PA 141 (2.350) Cn (Cen,3, 50.00, Ar); Sm (SG, 4x3.00); Cm (141:163)

UCSB Chem-Biochem GCT Premier
TOF MS EI+
6.21e+004

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Minimum:                               -1.5
Maximum:                3.0     10.0   200.0

Mass      Calc. Mass    mDa     PPM    DBE     i-FIT     Formula

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          227.0556      0.4     1.8    3.5     728.0     C6   H7   N4   O    F4
          227.0556      0.4     1.8    5.5     215.4     C10  H11  O6
          227.0565      -0.5    -2.2   3.5     1805.9    C  H5  N10  O2   F2
          227.0554      0.6     2.6    7.5     750.5     C4   H4   N10  O    F
          227.0554      0.6     2.6    0.0     2395.3    C  H6  N7  O  F5
          227.0554      0.6     2.6    2.0     981.6     C5   H10  N3   O6   F
          227.0567      -0.7    -3.1   1.5     726.3     C7   H12  O7   F
          227.0567      -0.7    -3.1   7.0     411.4     C6   H6   N7   O2   F
          227.0567      -0.7    -3.1   -0.5    1772.2    C3   H8   N4   O2   F5
          227.0552      0.8     3.5    -1.5    2797.3    H9   N6   O6   F2
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          227.0569      -0.9    -4.0   10.5    9.7       C11  H7   N4   O2
          227.0547      1.3     5.7    11.0    121.6     C14  H7   N    F2
          227.0545      1.5     6.6    7.5     176.2     C9   H6   N4   F3
          227.0543      1.7     7.5    -1.5    1331.6    C5   H11  O5   F4
          227.0543      1.7     7.5    4.0     1187.0    C4   H5   N7   F4
          227.0542      1.8     7.9    11.5    191.1     C7   H3   N10
          227.0542      1.8     7.9    6.0     281.7     C8   H9   N3   O5
          227.0578      -1.8    -7.9   3.0     1291.6    C3   H7   N7   O3   F2
          227.0580      -2.0    -8.8   6.5     205.2     C8   H8   N4   O3   F
          227.0540      2.0     8.8    2.5     1368.3    C3   H8   N6   O5   F
          227.0581      -2.1    -9.2   -1.0    1273.0    C5   H10  N    O3   F5
          227.0582      -2.2    -9.7   10.0    119.5     C13  H9   N    O3
          227.0531      2.9     12.8   2.5     455.5     C8   H10  O4   F3
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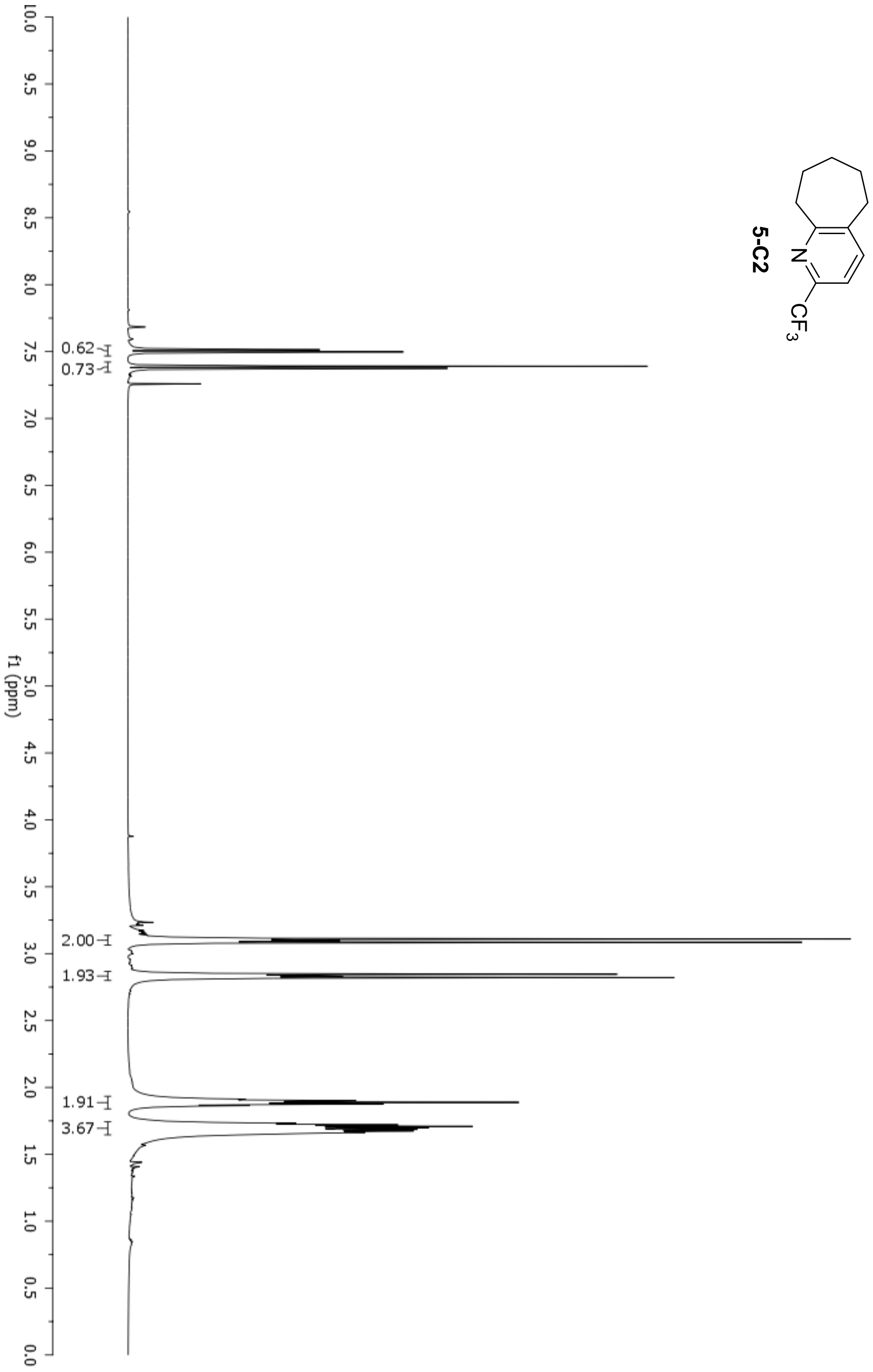
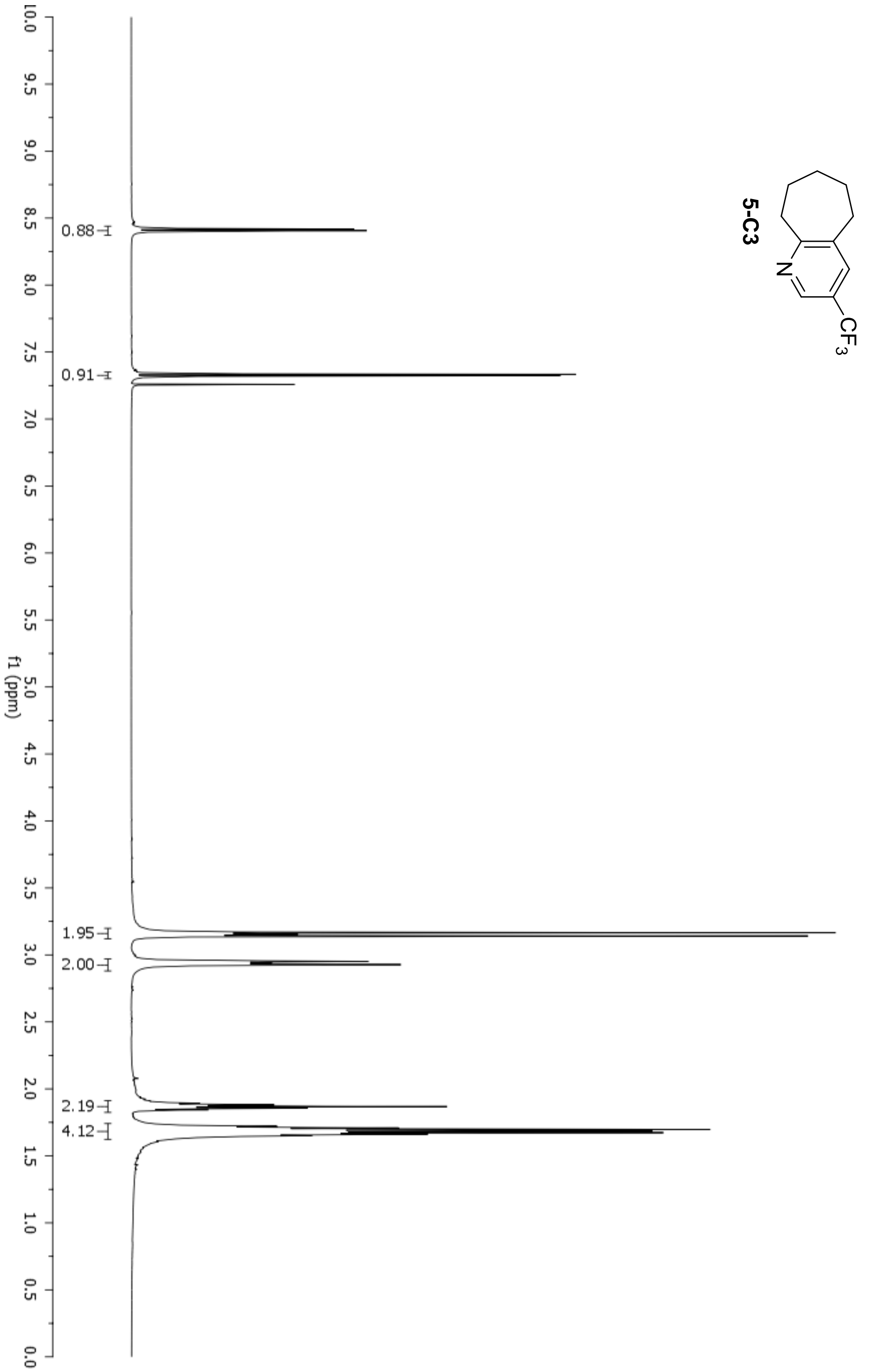
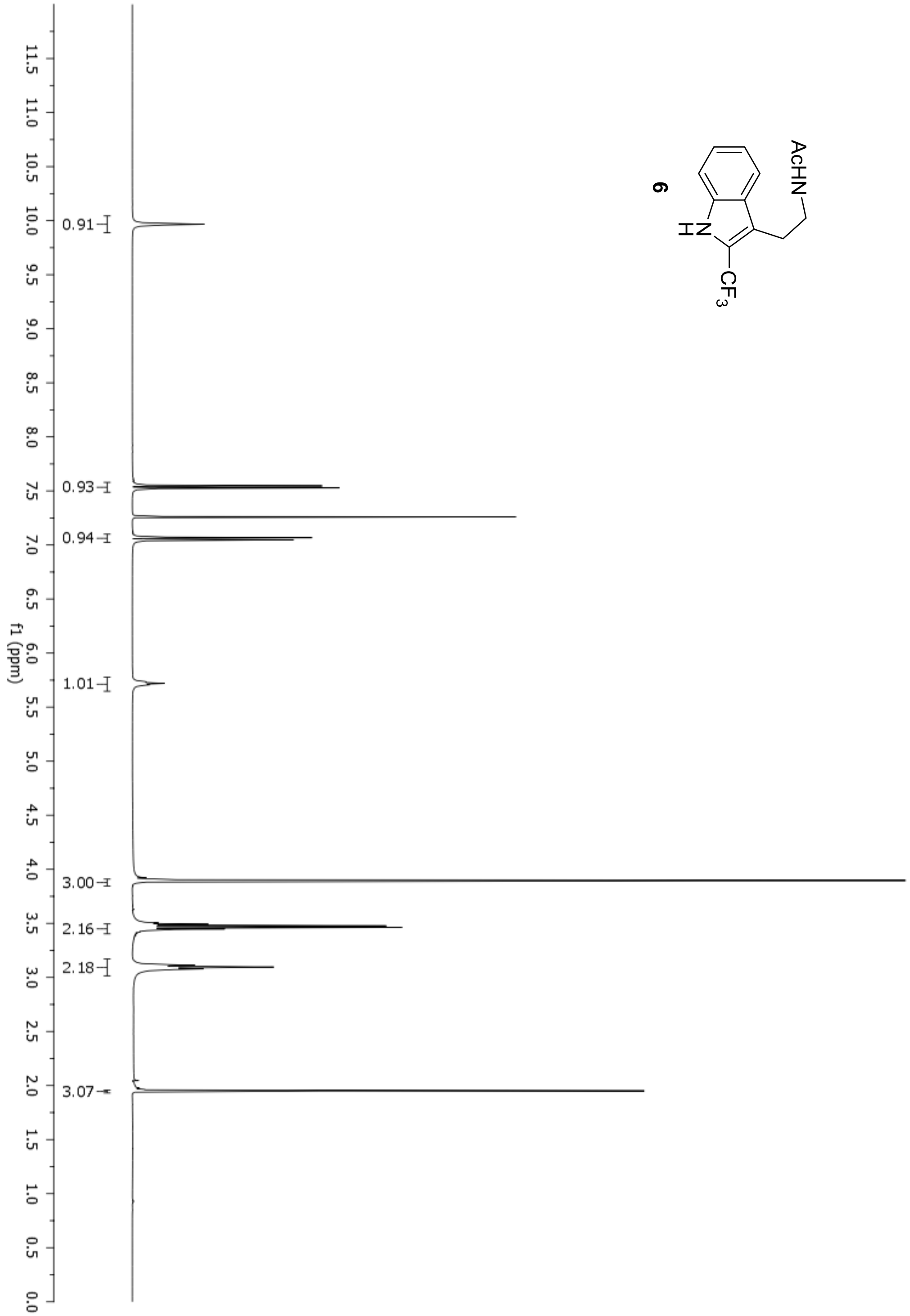
2-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine **5-C2**; Proton NMR ($CDCl_3$)



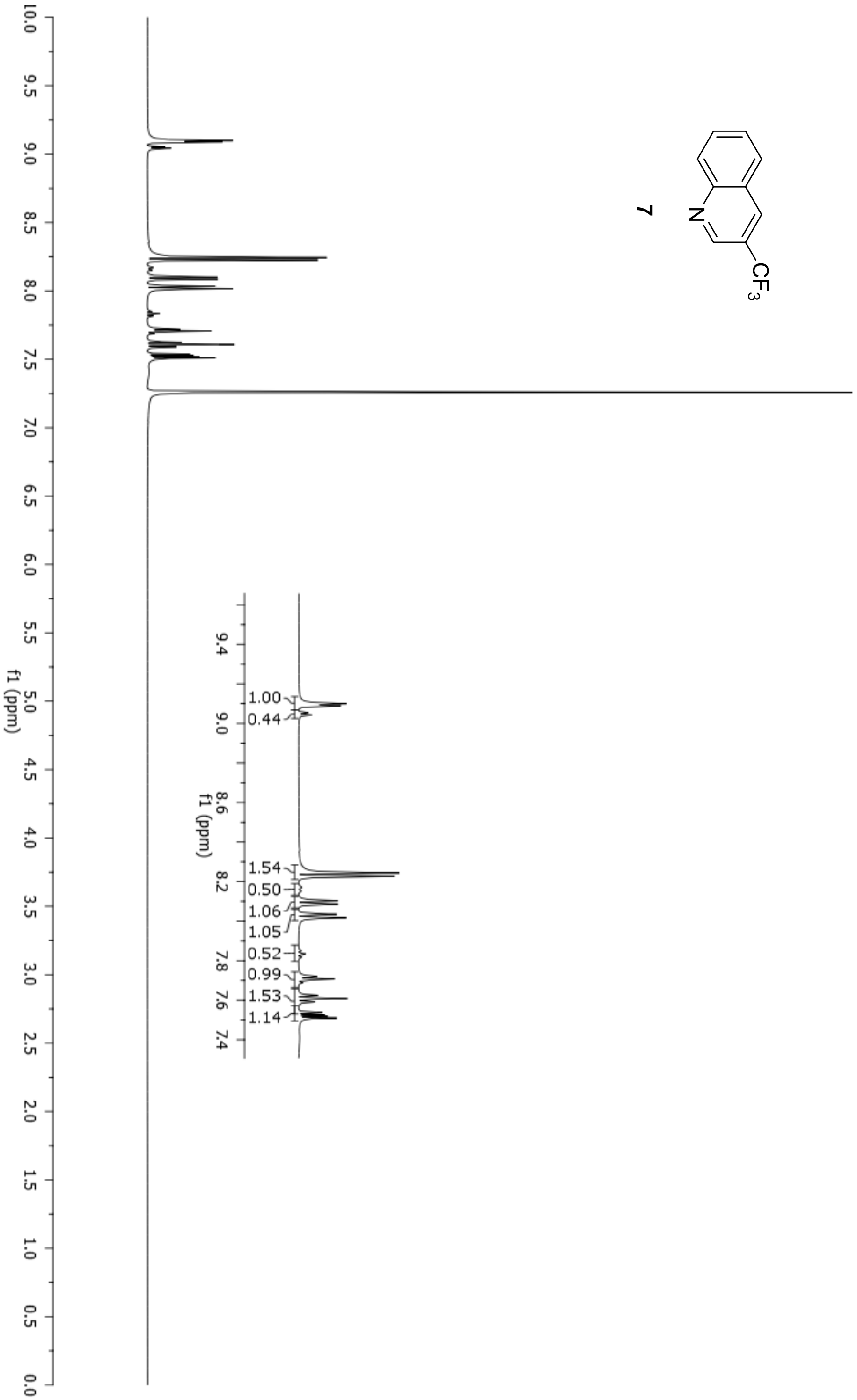
3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine **5-C3**; Proton NMR ($CDCl_3$)



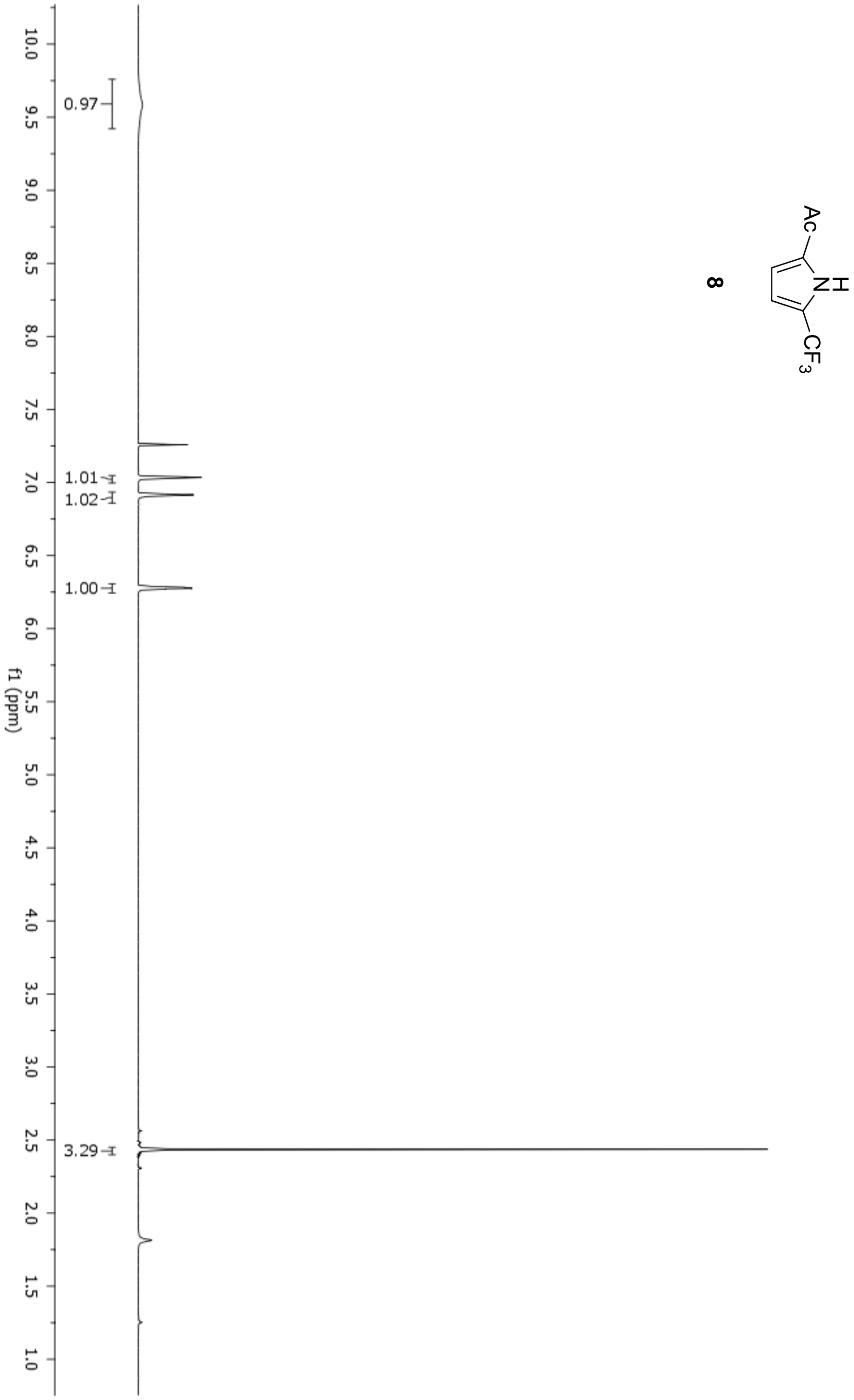
2-trifluoromethyl melatonin **6**; Proton NMR ($CDCl_3$)



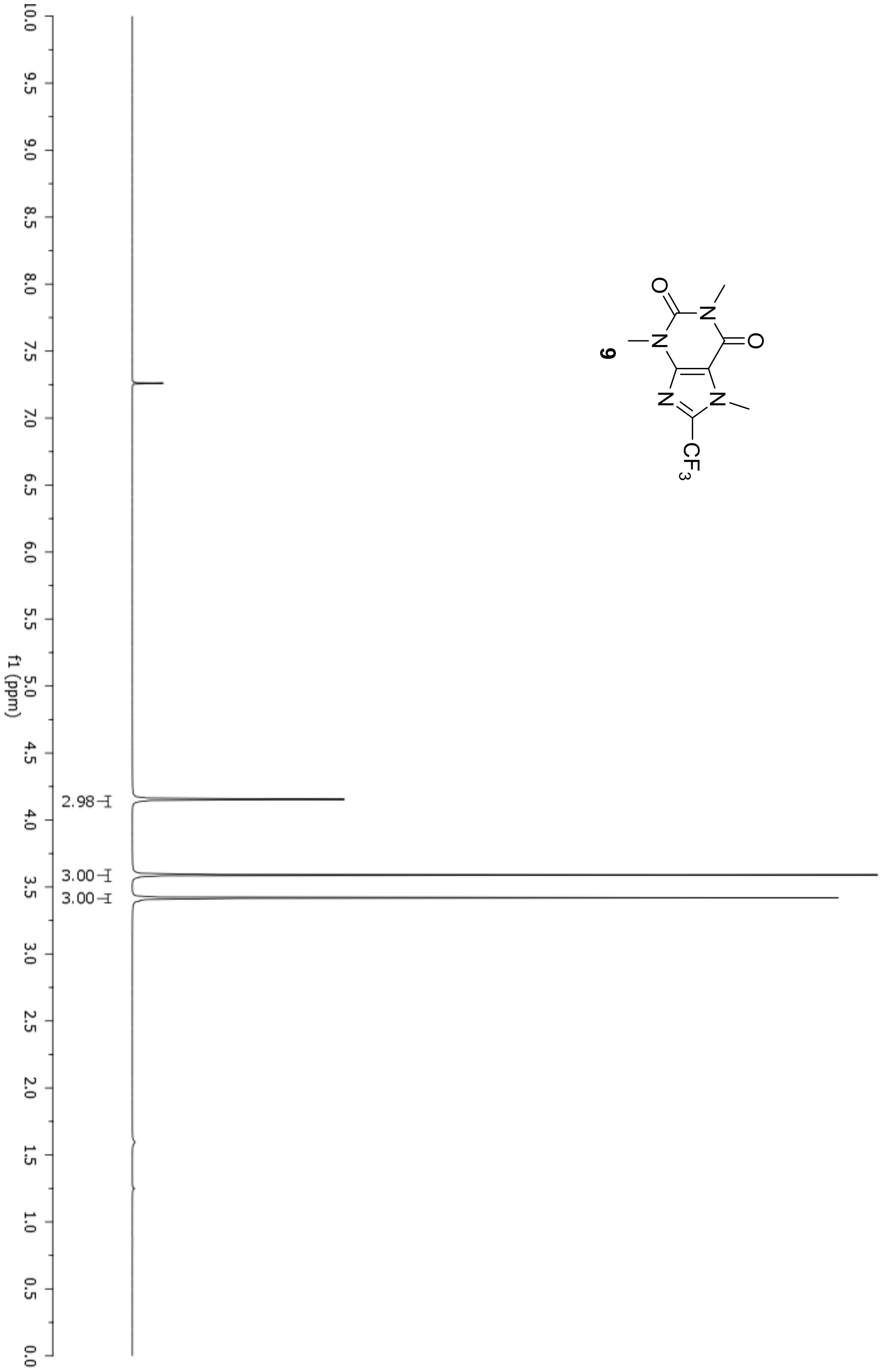
3-(trifluoromethyl)quinolone **7**; Proton NMR ($CDCl_3$)



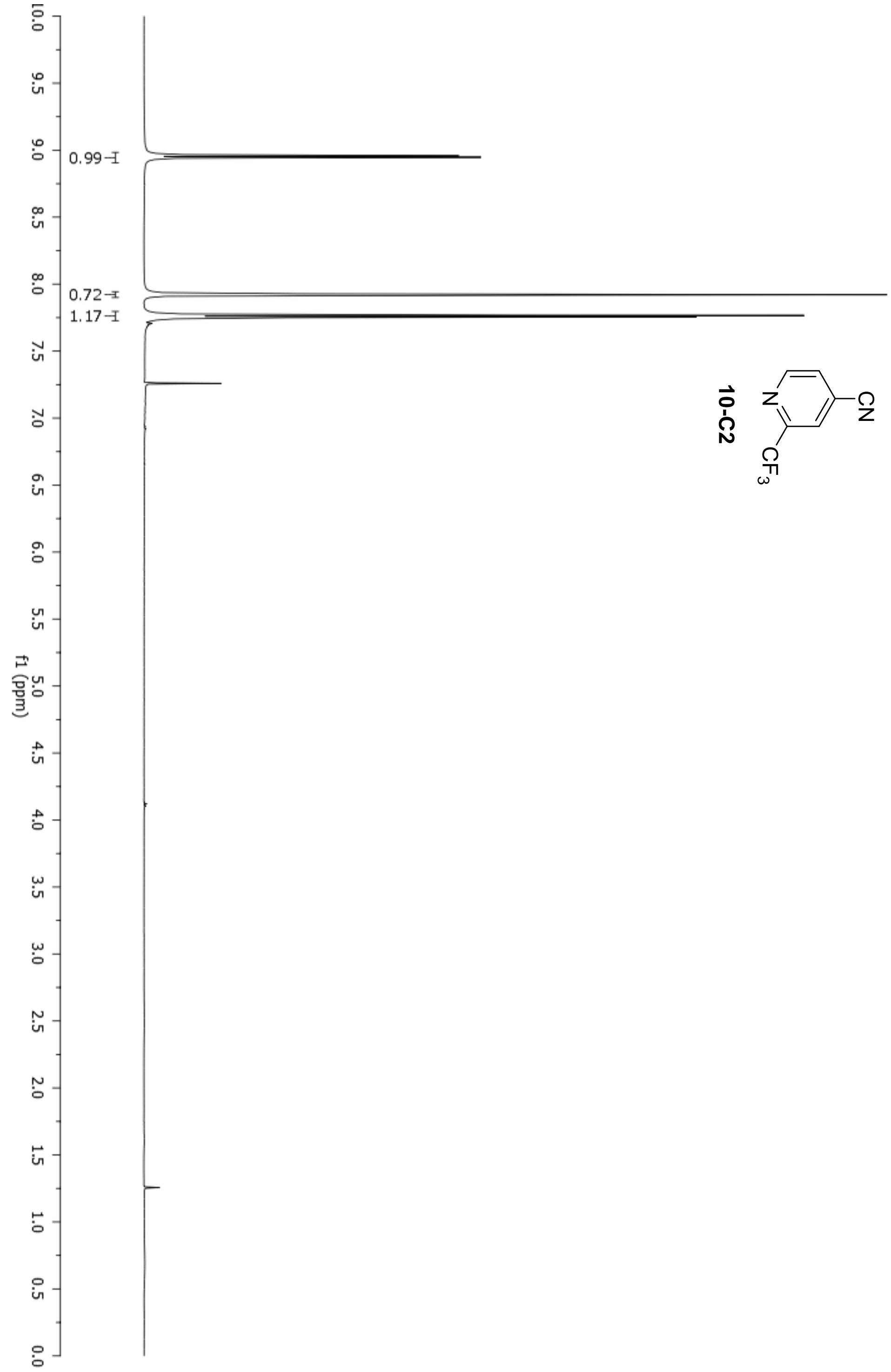
1-(5-(trifluoromethyl)-1H-pyrrol-2-yl)ethan-1-one **8**; Proton NMR ($CDCl_3$)



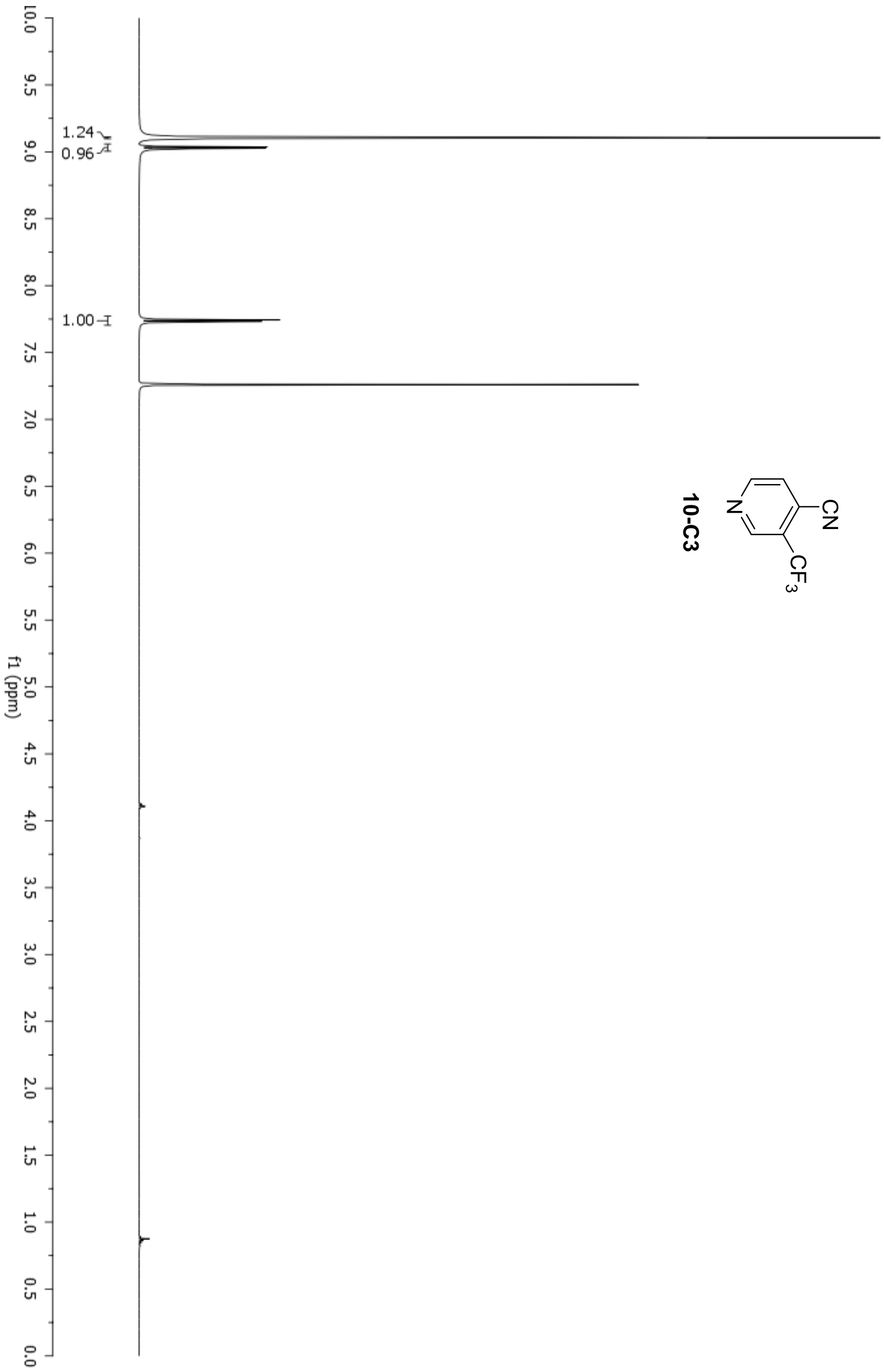
Trifluoromethylated caffeine **9**; Proton NMR ($CDCl_3$)



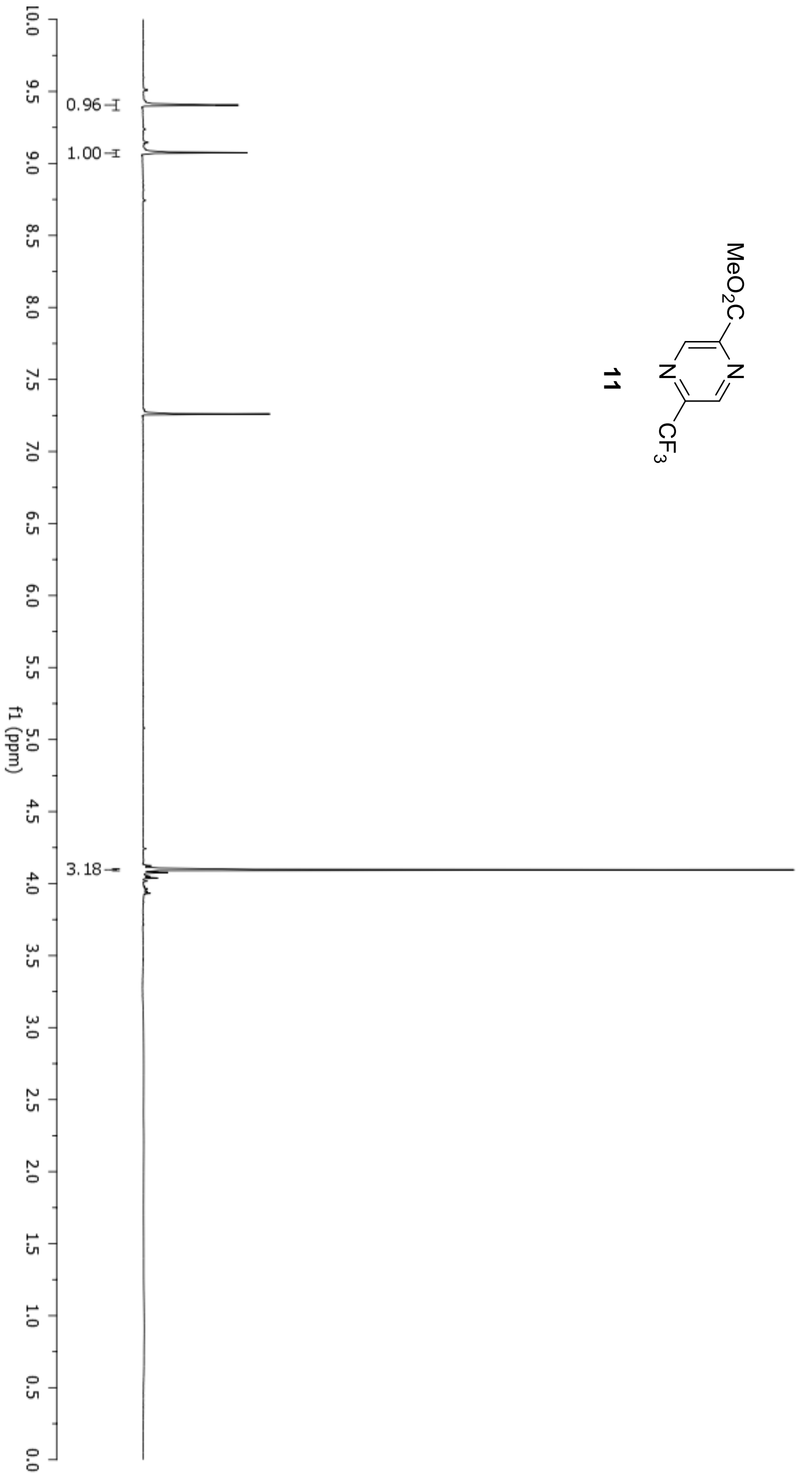
2-trifluoromethyl-4-cyano-pyridine **10-C2**; Proton NMR ($CDCl_3$)



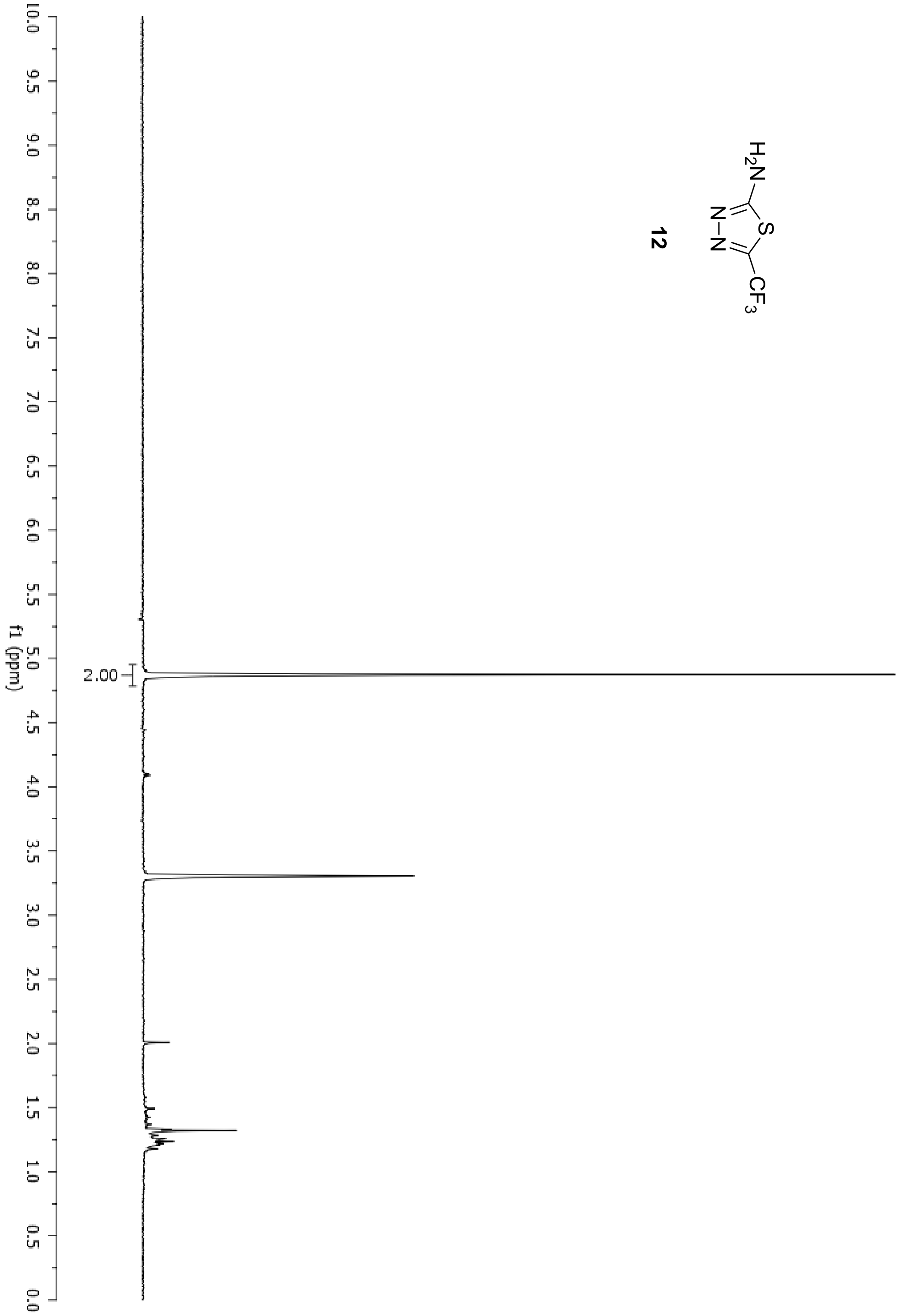
3-trifluoromethyl-4-cyano-pyridine **10-C3**; Proton NMR ($CDCl_3$)



methyl 5-(trifluoromethyl)pyrazine-2-carboxylate **11**; Proton NMR ($CDCl_3$)



5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine **12**; Proton NMR (MeOD)



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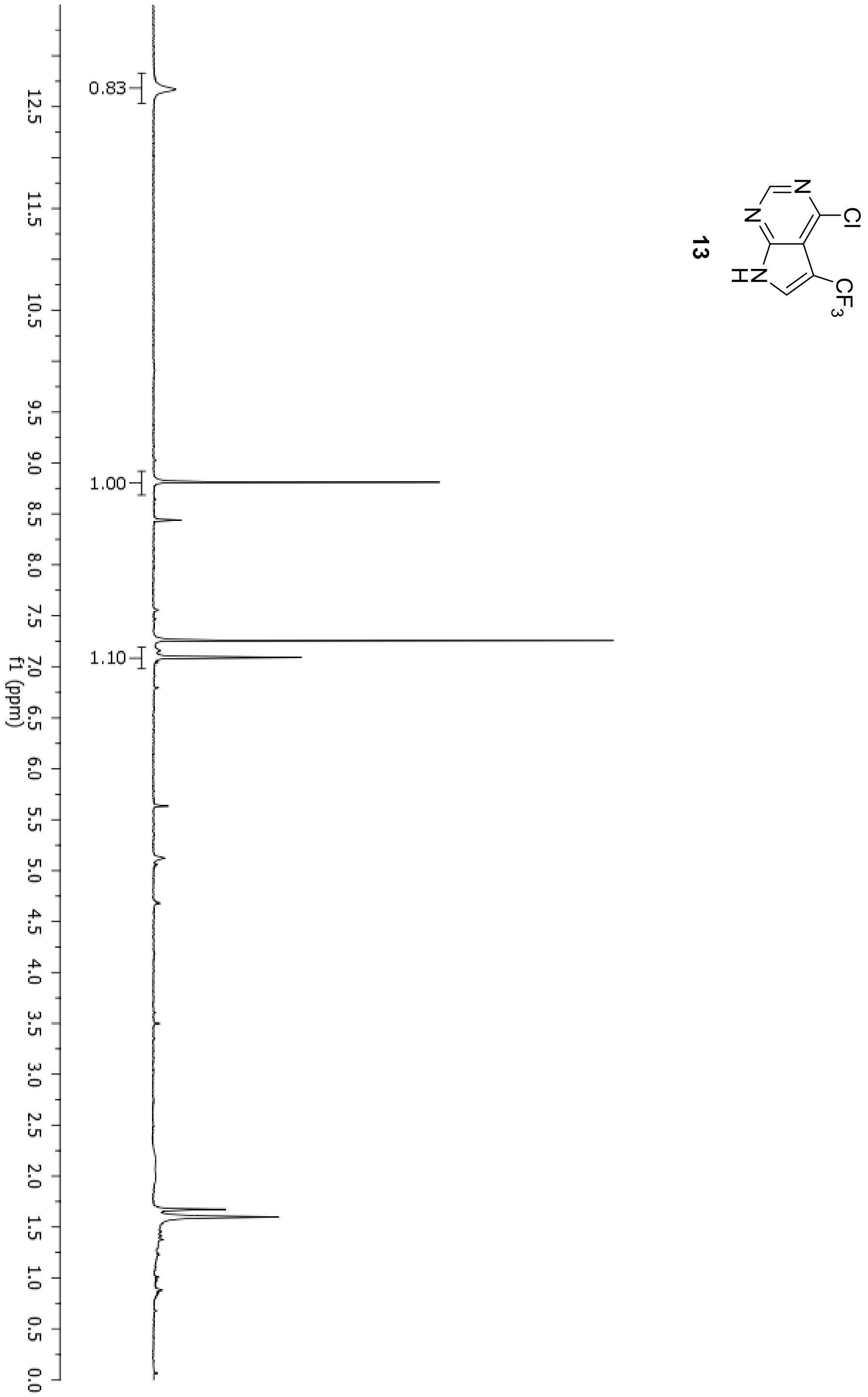
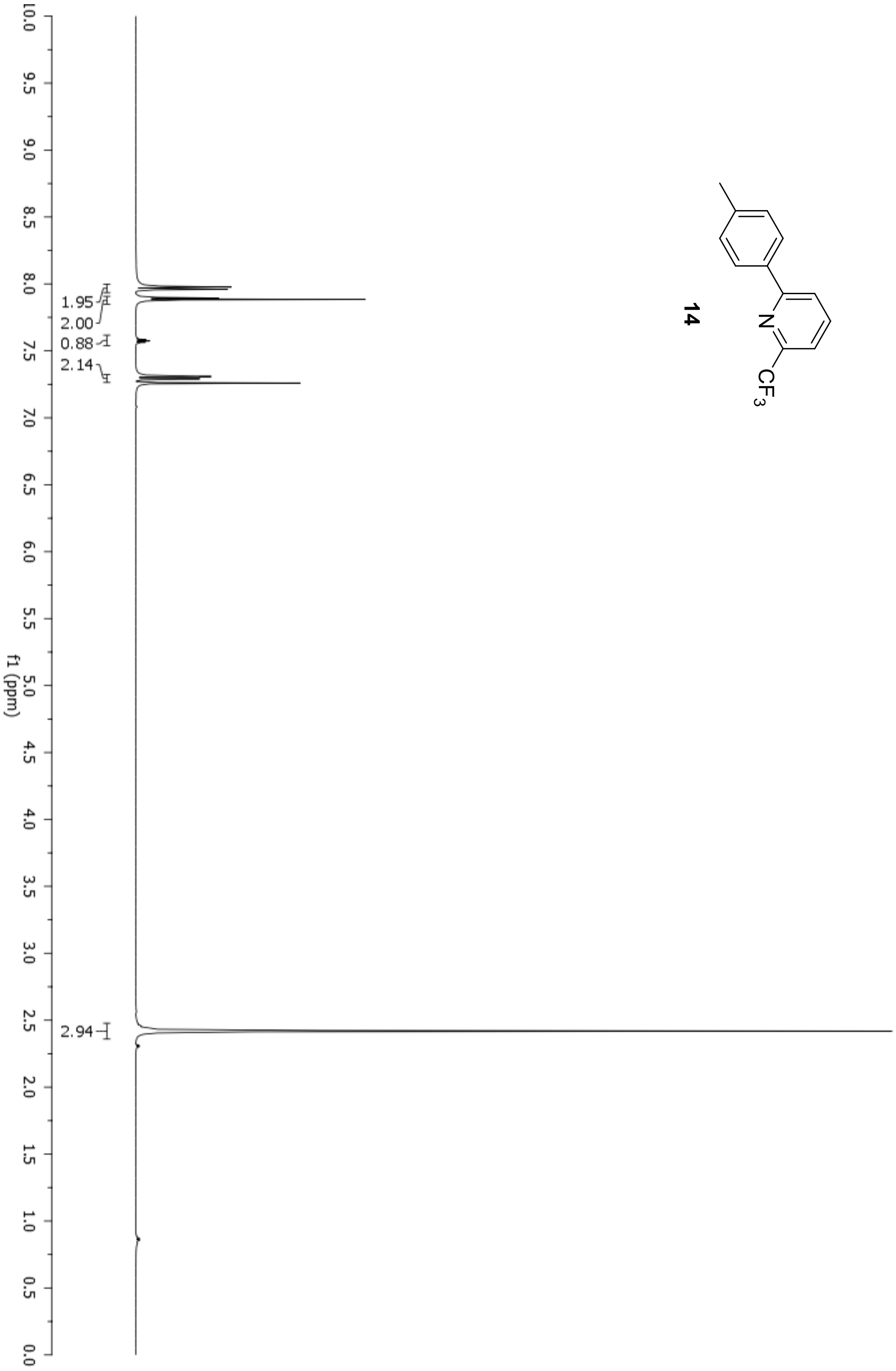
4-chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidine **13**; Proton NMR ($CDCl_3$)



2-(p-tolyl)-6-(trifluoromethyl)pyridine **14**; Proton NMR ($CDCl_3$)



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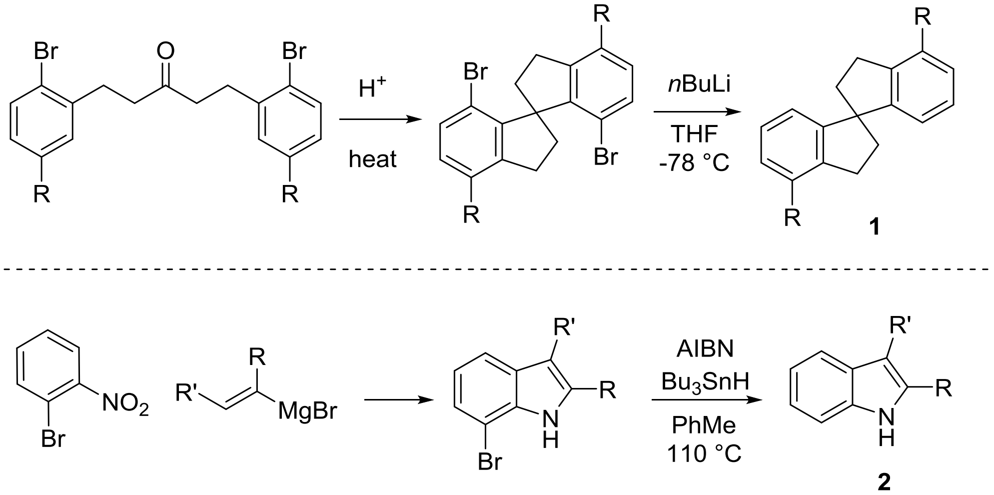
III. *Aqueous aromatic dehalogenation at room temperature*

3.1 Introduction

From a synthetic chemist's point of view, aromatic halogen substituents are often valuable handles enabling facile access towards transition metal catalysis, for the production of pharmaceuticals, agrichemicals, perfumes, and materials.[1] Historically, aromatic halogens were precursors for the construction of aryl-aryl bonds via S_EAr reactions long before the discovery of modern cross couplings,[2] and as directing or protecting groups in the construction of aromatic systems.[3] Examples of halides serving as blocking or directing groups have been explored,[4] which oftentimes necessitates their subsequent removal, as shown in Scheme 1. Lam *et al.* used this method for the synthesis of chiral spiro-biindane ligands[5] (Scheme 1, top) and Dobbs for his directed Bartoli indole **2** synthesis.[6] (bottom)

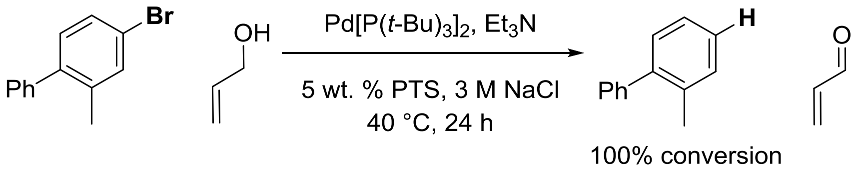


Scheme 1. Examples of bromides used as a directing group and subsequent removal

The high demand placed upon aryl halides en route to modern medicines, agrichemicals, and materials, has come at a cost. Their disposal has historically been an afterthought, resulting in improper disposal. Due to the high toxicity of many halogenated aromatics and their long term stability there continues to be a need for new dehalogenation protocols, aside from their applications in synthetic research. Ideally, dehalogenation would proceed in a recyclable aqueous medium rather than in organic solvent, involves a recyclable catalyst, mild hydride source, be highly functional group tolerant, and occur under mild conditions such that little-to-no investment of energy is required beyond that provided at ambient temperatures. Such a process would then adhere to many of the '*12 Principles of Green Chemistry'* and thus, might be viewed not only as synthetically useful, but also as environmentally attractive.[7]

3.2 Initial discovery

The discovery of our method for aromatic dehalogenation in aqueous media was found serendipitously during prior work with comparisons between literature examples of Pd-catalyzed cross couplings performed by pharmaceutical companies. Typically, such reactions are run in refluxing organic solvents rather than the identical couplings done in the hydrophobic core of aqueous nanoreactors composed of our designer surfactants.[8]



Scheme 2. Discovery conditions for aromatic dehalogenation

The intent was to originally perform a tandem cross coupling sequence, Suzuki followed by Heck; the second coupling (Heck) with allyl alcohol was unsuccessful and led solely to dehalogenated intermediate. (Scheme 2)

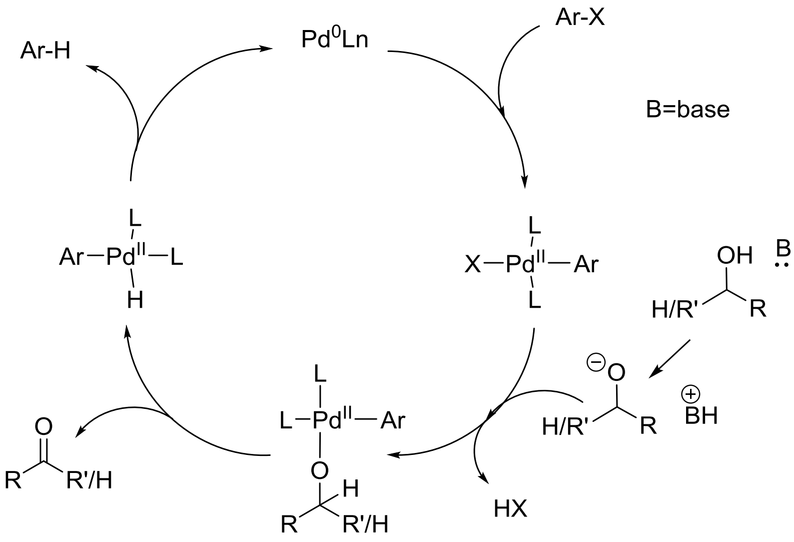
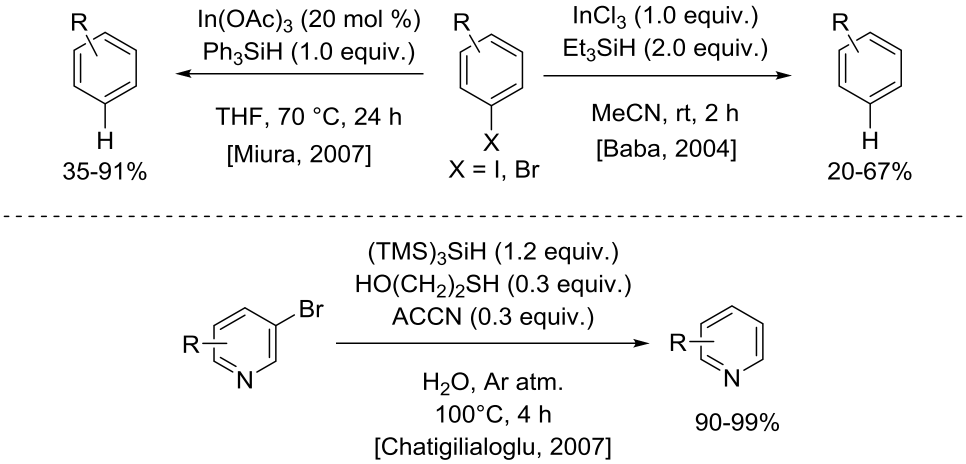


Figure 1. Proposed catalytic cycle for aromatic dehalogenation using alcohols

This dehalogenation process was originally discovered by Heck almost 40 years earlier from works attributed to his cross-couplings[9] with allylic and aromatic hydrocarbons as by-products. His work was later confirmed by Helquist *et al*. as a viable route for the reduction of aryl halides with methanol as the reductant;[10] while the proposed mechanism is displayed above (Figure 1).

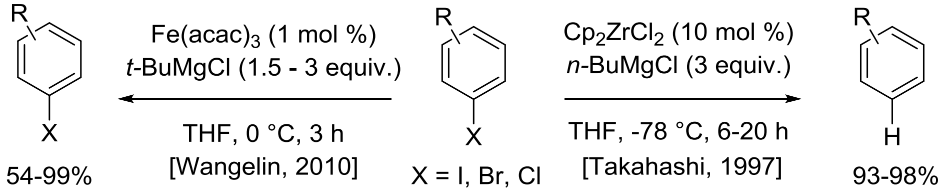
3.3 Prior Work on Aromatic Dehalogenation

Due to our wide use of various halogenated aromatic compounds, we have seen a surge in protocols for the dehalogenation of these toxic substrates to their more benign hydrocarbon analogs. Even more useful for synthesis is the need for their removal when used as directing or protecting groups. As the methods for dehalogenation and hydride sources are numerous and ever expanding, we have chosen a small subset that has received the most attention recently, mainly from the dehalogenation of environmental toxins. Silyl hydrides have enjoyed use as a mild hydride source for utilization of radical initiated silyl hydride dehalogenation methodology.



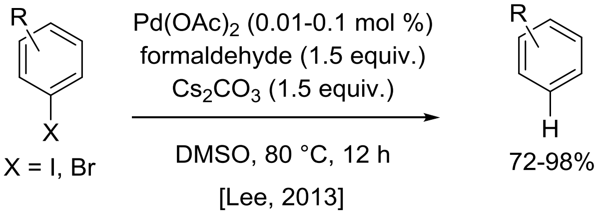
Scheme 3. Methods for radical initiated silyl hydride dehalogenations

While one method includes the unattractive use of stoichiometric indium chloride with two equivalents of Et_3SiH (Scheme 3, top right) from Baba *et al.*, this wasteful process gave dehalogenated product in mediocre yields along with large amounts of homocoupled side products were detected.[11] They had previously employed similar conditions for their studies with $NaBH_4/InCl_3$ systems for simple non-substituted aromatic dehalogenations and enyne cyclizations.[12] In 2007, dehalogenation via catalytic use of indium was reported, a large improvement over the work of Baba, Miura *et. al.*, (Scheme 3, top left), lowering the precious metal use fivefold to 20 mol %. Their use of indium acetate and triphenylsilane in refluxing THF, noting that esters were compatible with the reaction conditions but ketones are generally reduced.[13] Methodology developed by Chatgilialoglu *et al.* for the dehalogenation of heterocycles is easily appreciable as an example of clean, environmentally friendly chemistry. Their method utilizes water as the reaction medium with the radical initiator azobiscyclohexylcarbononitrile (ACCN) and TMS_3SiH, albeit at elevated reaction temperatures. A broad diverse range of functionalized substrates was also noted[14] (Scheme 3, bottom).



Scheme 4. Grignard reagents as a hydride source

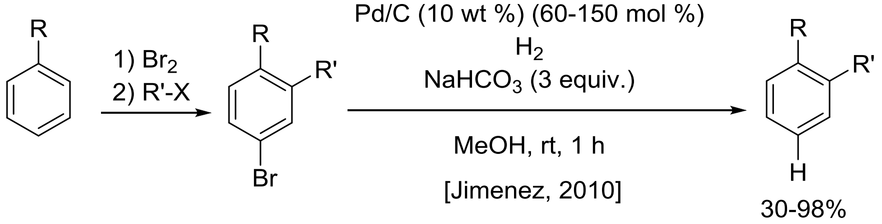
Others hydride sources include alkyl magnesium reagents (Grignards) capable of β-hydride elimination in the presence of transition metals. Takahashi had reported very high yields of unwanted dehalogenated starting material from his original work with Zr-Negeshi like reagents to be used for cross-coupling.[15] This led to their reinvestigation of the reaction conditions and through screening of various Grignard reagents had helped prove the hydride hypothesis, it was concluded that the reduction was, in fact, due to β-hydride elimination as simple methylmagnesium bromide gave no reaction while detection of *n*-butene was observed when researchers used *n*-BuLi.[16] While they had readily achieved yields in excess of 90% (Scheme 4, right) little can be said in regards to functional group compatibility but one could assume that the typical groups known to be incompatible with Grignards would apply here as well. Replacing expensive, precious zirconocene with cheap abundant iron and therefore reducing the environmental footprint was performed by Wangelin *et al.* in conjunction with mechanistic studies. They formed deuterated Grignard ($Et_{d6}MgBr$) that when the halogen was replaced by deuterium forming ethane (Et_{d4}), this further reinforced beta-hydride delivery mechanism[2] (Scheme 4, left). With impressive yields even including heteroaromatics, they stated that these dehalogenations are functional group tolerant; although the only labile example is that of a *t*-butylester, a group that would normally survive reaction conditions with the bulky *t*-BuMgBr Grignard utilized.



Scheme 5. Formaldehyde hydride source

Lee and workers utilized formaldehyde as the hydride source. After attack by the base (Cs_2CO_3) there is a β-hydride ready for delivery, ultimately producing the dehalogenated product. The assumed notion that formaldehyde was oxidized *in-situ* to formate following hydride delivery by release if CO_2 in the typical fashion, was disproven as benzaldehyde also provided dehalogenated product. Lee *et. al.* had also employed a novel detection technique of paper based colorimetric sensors (PBCS) developed for the pharmaceutical industry to aide in the facile detection of aryl halides and metals from industrial cross couplings. This enabled them to rapidly screen hundreds of reaction conditions, saving countless hours of GC or LC time.[17] The final reaction conditions are shown in Scheme 5.

With very low levels of Pd (<0.1 mol%) they were able to achieve modest yields, although the examples are all fairly simple. They did perform a dehalogenation of an aryl methyl ester where only the aryl halide bond was reduced and the ester remained intact.



Scheme 6. Dehalogenation via traditional hydrogenation

..

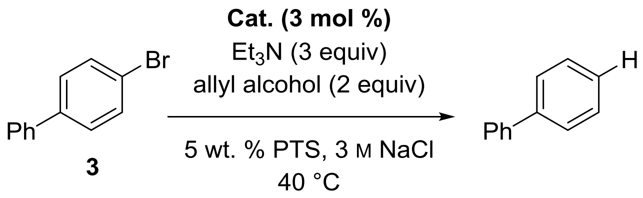
The use of traditional hydrogenation conditions (i.e., H_2, Pd/C, and alcoholic solvent) were employed by Jimenez *et al.*[4] Using bromide as a *para* blocking group as shown in Scheme 6, removal of the halogen would be required with sensitive functional groups present. High yields were obtained when electron-withdrawing groups were appended to the ring, but the opposite is true for electron-rich systems. One of their most significant draw backs is the need for stoichiometric Pd but, in principle, it could be recovered and reused.

Even with all the recent advances in methodology for aromatic dehalogenation, they appear to be cost prohibitive at scale, energy intensive, make use of H_2 gas, toxic reagents, harsh conditions, and in general, have limited substrate scope with little functional group tolerance. These limitations have placed further pressure on green chemists to develop benign processes, with little-to-no production of waste other than dehalogenated product.

3.4 Results and Discussion

Excited from our initial findings (Scheme 2) by the prospects of developing an aqueous aromatic dehalogenation protocol, we set out to further explore and optimize the reaction conditions. Using similar conditions illustrated in Scheme 2, we began to screen various catalysts known for their facile oxidative addition into aryl halide bonds. Our initial hit led us to Fu's catalyst, $\mathrm{Pd(P[tBu]_3)_2}$ (entry 1, Table 1).

Table 1. Catalyst screening for the dehalogenation of **3** using allyl alcohol



entry	Catalyst	Time (h)	GC Conv. (%)
1	$\mathrm{Pd[P(}t\mathrm{\text{-}Bu_3)]_2}$	6	>99
2	$\mathrm{Pd(PCy_3)_2}$	24	14
3	$\mathrm{Pd[PPh(}t\mathrm{\text{-}Bu)_{2]2}}$	24	9
4	$\mathrm{Ni(COD)_2}$	48	<1
5	$\mathrm{NiBr_2(PPh_3)_2}$	48	<1
6	$\mathrm{NiCl_2(P}n\mathrm{\text{-}Bu_3)2}$	48	<1
7	$\mathrm{NiCl_2(P}i\mathrm{\text{-}Bu_3)_2}$	48	<1
8	Pd/C (10wt %)	24	<1
9	$\mathrm{Pd(PPh_3)_4}$	24	<1

Next, we turned our efforts towards determining the number of equivalents of allyl alcohol necessary for complete conversion of 4-bromobiphenyl **3** as a model substrate. As shown in Table 2, only require 1.5 equivalents are needed (entry 2).

Table 2. Screen for equivalents needed of allyl alcohol for dehalogenation of **3**

$$\mathbf{3} \xrightarrow[\substack{\text{5 wt. \% PTS, 3 M NaCl} \\ \text{40 °C, 24 h}}]{\substack{\text{Pd[P(}t\text{-Bu}_3\text{)]}_2\text{ (3 mol \%)} \\ \text{Et}_3\text{N (3 equiv)} \\ \textbf{allyl alcohol (X equiv)}}} \text{Ph-Ph}$$

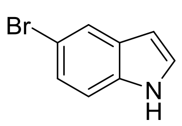
entry	allylOH (equiv.)	Time (h)	GC Conv. (%)
1	2.0	6	>99
2	1.5	23	>99
3	1.0	23	88
4	0.5	23	59
5	0.0	6	<1

With our results beginning to turn towards a promising method for a mild and green protocol, we had overlooked our waste production. We soon realized that throughout the course of the reaction, acrolein is produced in stoichiometric amounts, a compound associated with high toxicity for humans with respiratory difficulties.[18] Thus, we performed a thorough screening of mild hydride sources that have been previously employed for dehalogenation on a range of substrates. (Table 3) The plan was to reduce the reductant to a 1:1 ratio (hydride:substrate) over previous experiments, using the original allyl alcohol reduction as a metric.

Table 3. Screening of hydride sources for the dehalogenation of **3-6**

$$\text{Ar-X} \xrightarrow[\substack{\text{5 wt. \% PTS, 3 M NaCl} \\ \text{40 °C, 18 h}}]{\substack{\text{Pd[P(}t\text{-Bu}_3\text{)]}_2\text{ (3 mol \%)} \\ \text{Et}_3\text{N (1.5 equiv)} \\ \textbf{Reductant (1.0 equiv)}}} \text{Ar-H}$$

		GC conversion (%)			
entry	reductant	**3**	**4**	**5**	**6**
1	$NaBH_4$	98	>99	66	>99
2	allyl alcohol	69	50	82	>99
3	cinnamyl alcohol	45	63	2	-
4	$PhMe_2SiH$	80	-	16	62
5	H_2	23	59	<1	-
6	formic acid	3	11	-	-
7	ammonium formate	<1	<1	-	-
8	isopropanol	<1	<1	-	-



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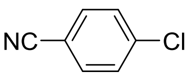

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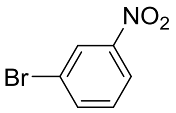
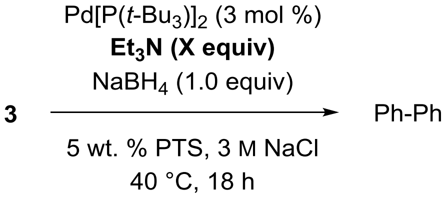


6

Substrates 4-bromobiphenyl **3**, 5-bromoindole **4**, *p*-chlorobenzonitrile **5**, and 3-bromo nitrobenzene **6** were used as model substrates for hydride screening (Table 3). Although our goal was focused on bromide reductions we included **5** as the increased strength of the aryl chloride bond might lead to a more robust method. Sodium borohydride (entry 1) clearly afforded the best results, while allyl alcohol (entry 2) was superior for the reduction of **5** and comparable to us of $NaBH_4$ on educt **6**. In the case of cinnamyl alcohol (entry 3) a lower conversion was observed than with allyl alcohol, but was tested to determine if cinnamaldehyde was produced in order to confirm that the hydride was being supplied from the alcohol precursor. This would be in agreement with prior observations by Yoshida.[19] As expected, cinnamaldehyde was produced, as detected by GCMS to the same extent of conversion from cinnamyl alcohol as the substrate to product. Triphenylsilyl hydride was tested (entry 4) although gave mediocre levels of conversion were observed, and thus, it was not tested on the remaining substrates as it would be considered poor atom economy if taken forward. Reductants H_2, formic acid, NH_4 formate, and *i*-PrOH (entries 5-8) did not lead to any appreciable amounts of product.

Focusing on $NaBH_4$, as the stoichiometric reductant, we chose to optimize the required stoichiometry of Et_3N and $NaBH_4$, shown in Tables 4 and 5, respectively. The base (Et_3N), was reduced from two to one and a half equivalents without impacting conversion, and adjustments in the amount of hydride included lowering from one to a half equivalent; although in reality it is still 4 equivalents of hydride.

Table 4. Effect of the equivalents of trimethylamine for the conversion of **3**



entry	Et_3N (equiv)	GC conv. (%)
1	2.0	98
2	1.5	>99
3	1.0	67
4	0.5	16

Table 5. Effect of the equivalents of $NaBH_4$ on the conversion of **3** to biphenyl

$$\mathbf{3} \xrightarrow[\substack{\text{5 wt. \% PTS, 3 M NaCl} \\ \text{40 °C, 18 h}}]{\substack{\text{Pd[P(}t\text{-Bu}_3\text{)]}_2\text{ (3 mol \%)} \\ \text{Et}_3\text{N (1.5 equiv)} \\ \mathbf{NaBH_4\ (X\ equiv)}}} \text{Ph-Ph}$$

entry	$NaBH_4$ (equiv)	GC conv. (%)
1	2.0	>99
2	1.5	>99
3	1.0	>99
4	0.5	>99
5	0.0	<1

From efforts to reduce the loading of Pd catalyst, we found that one could go from 3 to 2 mol % Pd,, although mild heating of the reaction mixture to 30 °C was required. Nonetheless we decided to remain at the 3 mol % to minimize reaction times (Table 6).

Table 6. Effect of the catalyst loading for the conversion of **3**

$$\mathbf{3} \xrightarrow[\substack{\text{5 wt. \% PTS, 3 M NaCl} \\ \text{30 °C, 18 h}}]{\substack{\mathbf{Pd[P(}\boldsymbol{t}\mathbf{\text{-}Bu)_3]_2}\text{ (}\mathbf{X}\text{ mol \%)} \\ \text{Et}_3\text{N (1.5 equiv)} \\ \text{NaBH}_4\text{ (1.0 equiv)}}} \text{Ph-Ph}$$

entry	catalyst loading	GC conv. (%)
1	1%	57
2	2%	>99
3	3%	98

From our groups' previous work utilizing micellar catalysis we have found that inclusion of salt (NaCl) can greatly affect the size of the micelle, thus enhancing rates of reactions.[20] Using the optimal amounts of reductant and base, the effect of NaCl was screened, again for the dehalogenation of **3**, with the results shown in Table 7. The optimized concentration of NaCl in the aqueous medium was found to 3 M. (entry 4)

Table 7. Effect of the salt concentration for the conversion of **3**

$$\mathbf{3} \xrightarrow[\substack{\text{5 wt. \% PTS, } \mathbf{X\ M\ NaCl} \\ \text{40 °C, 18 h}}]{\substack{\text{Pd[P(}t\text{-Bu}_3\text{)]}_2\text{ (3 mol \%)} \\ \text{Et}_3\text{N (1.5 equiv)} \\ \text{NaBH}_4\text{ (0.5 equiv)}}} \text{Ph-Ph}$$

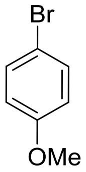
entry	[NaCl]	GC conv. (%)
1	0	61
2	1	76
3	2	87
4	3	>99

Screening of alternative surfactants that might facilitate micellar catalysis at the standard two weight percent showed that SPGS-550-M ('Nok')[21] (entry 1) our latest (3rd) generation surfactant enabled the highest levels of conversion for all substrates **3**, **5**, **7**, and **8** (Table 8). Curiously the reactions run in the absence of surfactant (i.e., on water), (entry 5) was very competitive with Nok and PTS-600 for substrates **3**, **5**, and **7**. Fortunately, substrate **8** displayed a moderate discrepancy between Nok and the 'on water' control with 98 and 72% conversion, respectively. Although the 'on water' reaction performed almost as well for three of the substrates, we had chosen to use the surfactant Nok due to the anticipated recycling of the aqueous medium.

Table 8. Impact of the surfactant on dehalogenation of **3**, **5**, **7**, and **8**

$$\text{Ar-X} \xrightarrow[\text{2 wt. \% \textbf{surfactant}, 3 M NaCl; 30 °C, 18 h}]{\text{Pd[P(}t\text{-Bu}_3\text{)]}_2\text{ (3 mol \%); Et}_3\text{N (1.5 equiv); NaBH}_4\text{ (0.5 equiv)}} \text{Ar-H}$$

		GC conv. (%)			
entry	surfactant	**3**	**5**	**7**	**8**
1	SPGS-550-M (Nok)	>99	32	97	98
2	PTS-600	>99	8	95	-
3	TPGS-750-M	59	12	72	-
4	cremophor	70	26	64	-
5	none (water)	97	31	93	72



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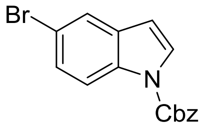
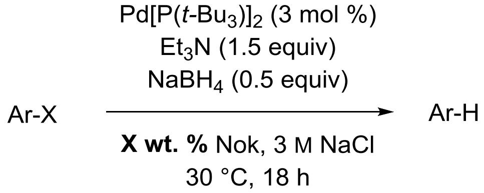


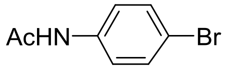
8

It has been shown during earlier cross coupling studies by our research group that the weight percent of surfactant can play a pivotal role in the success or failure of certain reactions under micellar catalysis.[20] As we varied the concentration of Nok from one up to five weight percent for substrates **3**, **5**, **7**, and **9**, (Table 9), substrates **3**, **7**, and **9** all performed essentially the same regardless of surfactant strength. Compound **5** seemed to suggest that as the level of surfactant increased, so did the extent of conversion. Given this information two weight percent was chosen for all remaining screenings and determination of substrate scope, for reasons mentioned *vide infra*. In addition, this concentration also corresponds to material that is commercially available.

Table 9. Impact of the surfactant strength (Nok) for dehalogenation of **3**, **5**, **7**, and **9**



		GC conv. (%)			
entry	weight %	**3**	**5**	**7**	**9**
1	1	96	21	98	94
2	2	95	32	98	96
3	5	96	40	94	95



9

With the optimal choices of reducing agent, surfactant, and its strength made, we next revisited various sources of palladium (Table 10). The bisphosphino-ferrocenyl ligated Pd^{II} (entry 5) performed equally as well as Fu's catalyst (entry 1) for **1** and **7**, and provided even better conversion in the case of **5**. The catalyst Pd[P(Cy$_3$)]$_2$ (entry 4) had also displayed somewhat useful levels of conversion. It was tempting for us to change the catalyst at this point with this data but in hand; however, we chose to move forward with Fu's catalyst as we have already observed excellent conversion with other substrates described above. We opted to keep the possibility of using Pd[P(Cy$_3$)]$_2$ and Pd(dtbpf)Cl$_2$ in the future in case of any un foreseen complications.

Table 10. Catalyst screening for dehalogenation of **3**, **5**, and **7**

$$\text{Ar-X} \xrightarrow[\substack{\text{2 wt. \% Nok, 3 M NaCl} \\ \text{30 °C, 18 h}}]{\substack{\textbf{Cat. (3 mol \%)} \\ \text{Et}_3\text{N (1.5 equiv)} \\ \text{NaBH}_4\text{ (0.5 equiv)}}} \text{Ar-H}$$

		GC conv. (%)		
entry	catalyst	**3**	**5**	**7**
1	Pd[P(*t*-Bu)$_3$]$_2$	>99	29	>99
2	PdCl$_2$(TMEDA)	65	7	>99
3	PdCl$_2$[P(Cy)$_3$]$_2$	12	<1	25
4	Pd[P(Cy)$_3$]$_2$	96	83	46
5	Pd(dtbpf)Cl$_2$	>99	89	>99
6	Pd[PPh$_3$)]$_4$	39	5	20

Additional reaction parameters, such as temperature and global substrate concentration, were investigated (Table 11). Results obtained appear to be independent of both temperature (22-30 °C) and concentration (0.5 to 1.0 M). We had determined that conditions C (rt, 1.0 M) (Table 11), provided the greenest method since no additional nvestment of energy as well no organic solvent is needed. Further increasing the global concentration past 1.0 M led to difficulty in stirring the reaction due to substantial clumping of the reagents and substrate, and thus, was abandoned.

Table 11. Concentration and temperature dependence for the debromination of **3**

$$\mathbf{3}\ \xrightarrow[\text{2 wt. \% Nok, 3 M NaCl, 24 h}\\ \textbf{conditions}]{\text{Pd[P(}t\text{-Bu}_3\text{)]}_2\text{ (3 mol \%)}\\ \text{Et}_3\text{N (1.5 equiv)}\\ \text{NaBH}_4\text{ (0.5 equiv)}}\ \text{Ph-Ph}$$

conditions

A = 30 °C, 0.5 M
B = rt, 0.5 M
C = rt, 1.0 M

	GC Conv. (%)		
time (h)	A	B	C
3	45	48	59
5	58	57	62
7	64	61	64
17	>99	>99	98

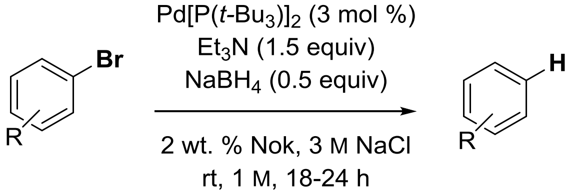
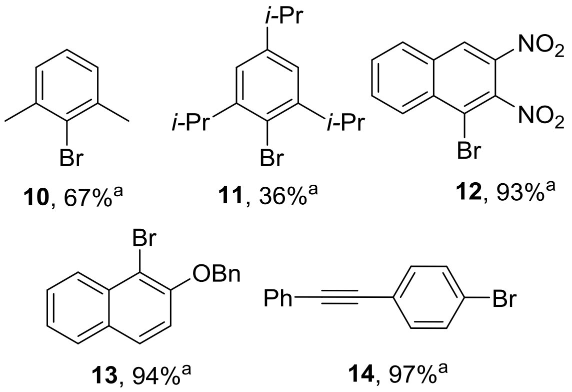


Figure 2. Optimized reaction conditions reduction of aryl bromides in water

With our newly optimized conditions for the reduction of aryl bromides in water (Figure 2), we set out to determine the substrate scope and feasibility of the methodology. When the steric bulk of the *ortho* positions relative to the bromide was increased, for substrates 2,5-bromoxylene **10** and 2,4,6-bromoisoproylmesityl **11** (Figure 3), the conversion was drastically reduced to 67% and 36%, respectively. Groups sensitive to hydrogenation conditions were examined next, as we had observed evolution of hydrogen gas during the process. Compounds **12**, **13**, and **14** all achieved high rates of conversion. The highly activating nitro groups of **12** were not reduced to the respective amines. Likewise, the benzyl protecting group in **13** was not cleaved by the dehalogenation conditions. Brominated diphenyl acetylene **14** was tested as, our group recently studied selective alkyne hydrogenation from *in-situ* formed Pd nanoparticles, H_2 from $NaBH_4$ and $Pd(OAc)_2$ in water,[22] we obtained 97% conversion to desired debrominated product from **14** with only 2% of reduced alkyne.



10, 67%[a] **11**, 36%[a] **12**, 93%[a]

13, 94%[a] **14**, 97%[a]

Figure 3. Initial substrate scope and feasablity screening
[a] percent conversions determined by GC-MS

Additional substrates were examined, with isolated yields found to be high, and with equal levels of functional group tolerance (Figure 4), as suggested by ketone **19**, that could be debrominated without carbonyl group reduction. This was a pleasant surprise assuming the ketone functionality would be lost due the $NaBH_4$ used in the reaction. The pseudo-halide, tosylate **15**, was debrominated in 91% yield. The benzyl protecting group of **20**, again remained intact, as previously demonstrated. The polyhalogenated amide **17** led solely to debromination allowing one to selectively remove bromine in the presence of aryl chlorides. The product from indole **21** was obtained in 89%, a result that compliments previous work in indole syntheses by Dobbs[6] (Scheme 1). Dibromide **22** gave the corresponding doubly reduced aromatic product in a modest 66% yield, although the yield may likely increase if repeated with stoichiometric $NaBH_4$. Since naphthol derivative **23** afforded the expected product in 91% yield, this result displays the robustness of the method given the acidic nature of this substrate. The phenyl acetamide **9** also smoothly furnished its debrominated product in 89% yield

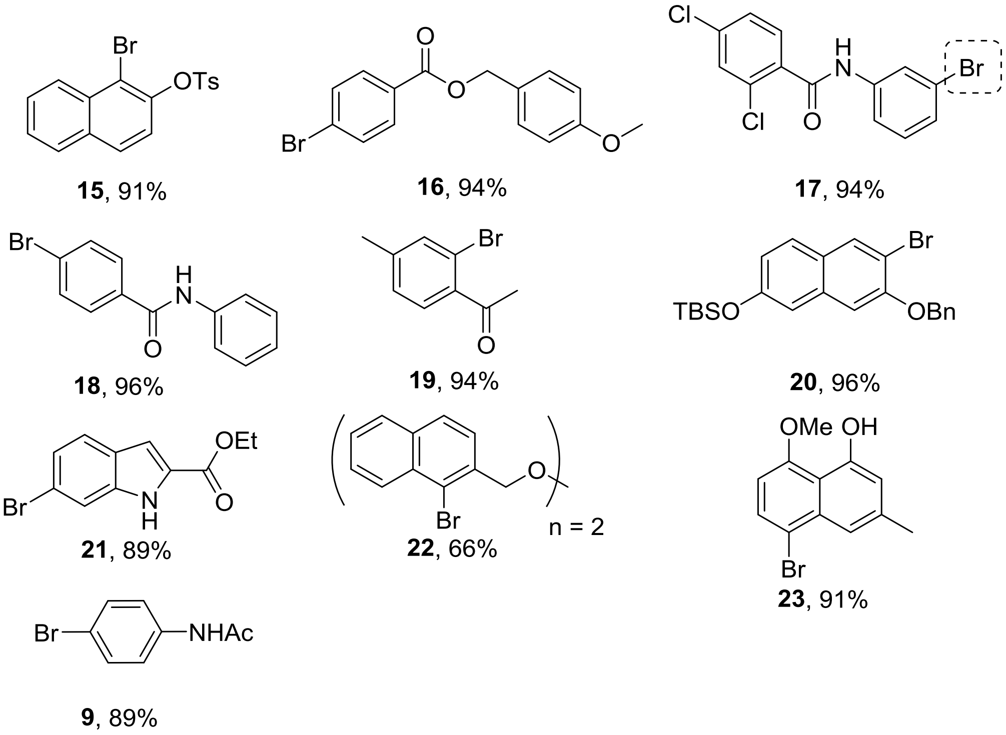
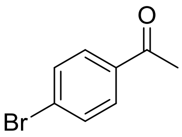


Figure 4. Representative examples of our debrominations with isolated yields

In further validation of our green methodology, we performed a comparison study of several substrates in the literature, as shown in Table 12. The model compound **3** used for all optimizations was previously dehalogenated by MacArthur[23] *et al*. in 77% isolated yield using CuI (20 mol %), NaI (2 equiv), and racemic *N,N'*-dimethylcyclohexane-1,2-diamine (1.5 equiv) in CH_3CN under microwave irradiation. The compound *p*-bromoacetophenone **24** was previously dehalogenated in the ionic liquid 1-butyl-3-methyl-imidazolium bromide (bmim Br), and stoichiometric nanoindium. Only a 20% isolated yield was achieved[24] compared to our 92% yield, also noting that the ketone remained intact, as shown above. In work reported by Birman *et al.*, spirocyclic ligand precursor **25**, where bromine was used as a directing group (Scheme 1) and required its subsequent removal by *n*-BuLi in THF at – 78 °C giving a 93% yield.[5] While their method was efficient, there is no functional group compatibility in contrast to our method that provides a 91% yield for the same compound. Impressively brominated piperonal **26** was successfully debrominated in 87% yield, with <5% of the corresponding reduced aldehyde being observed. Previously, **26** was dehalogentated by Chen and co-workers using $Pd(OAc)_2$ with triphenylphosphine in *n*-butanol at 100 °C.[25]

Table 12. Direct comparisons with literature methodology.



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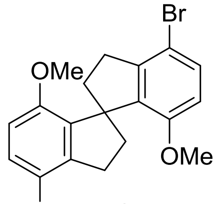

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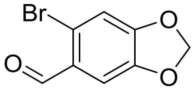
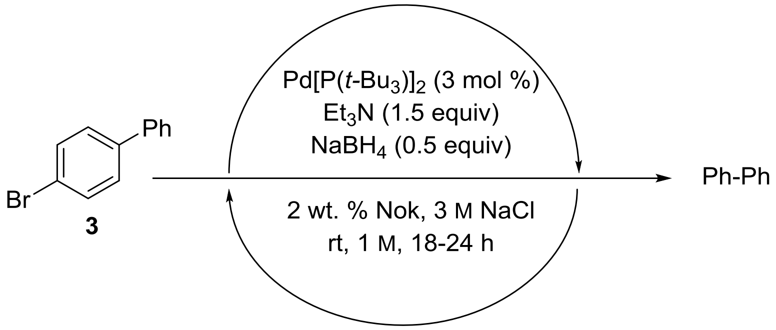


26

		this work	literature
entry	compound	isolated yields (%)	
1	**3**	97	77[23]
2	**24**	92	20[24]
3	**25**	91	93[5]
4	**26**	87	98[25]

We also endeavored to recycle our reaction medium leading to a ‘greener’ process; hence, we conducted the study outlined in Table 13. The workup of these dehalogenation reactions consists of the addition of a small amount of organic solvent (EtOAc) (~1 mL / g product), directly to the reaction vessel with slow stirring, then extraction and the product is then subjected to further purification. The total amount of water invested in the entire process is truly minimal, as reactions are run at 1.0 M and no additional water is used for the workup. Because the aqueous layer retains the surfactant, the reaction mixture can be recycled. Results from a recycling study for the dehalogenation of **3** are shown in Table 8. For recycles 2-5 it was necessary to add 1.5 mol % of catalyst in order to reach full conversion, most likely due to the labile catalyst being oxidized during handling. In hindsight, we may have been able to circumvent the need for excess catalyst if we had chosen one of the more stable alternatives discovered to work equally as well (Table 10) such as Pd(dtbpf)Cl_2.

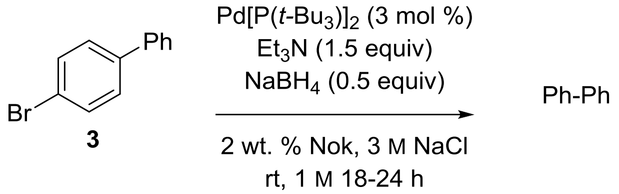
Table 13. Recycling the aqueous medium for the debromination of **3**



entry	cycle[a]	yield (%)
1	1	99
2	2[b]	96
3	3[b]	98
4	4[b]	98
5	5[b]	96

[a] extracted with EtOAc; aqueous medium used for next reaction. [b] for cycle 2-5 1.5 mol % catalyst was used.

To further assess the "greenness" of this process, E Factors were calculated based on organic solvent usage, since most organic waste from organic reactions is attributable to this reaction variable,[26] as previously described (Chapter 1). As shown in Figure 5, these dehalogenation reactions lead to E Factors that are quite low given the absence of any organic solvent in the reaction medium. An E Factor calculated inclusive of water raises this value to only 8.9, but upon recycling this value drops dramatically to 3.7.



	based on:	single run	with recycling
E Factors	total organic solvent	**2.4**	**2.4**
	aqueous media included	**8.9**	**3.7**

Figure 5. E Factors associated with debromination of **3**

In an effort to gain insight as to the source of the hydrogen in the product, a series of experiments were performed, as outlined in Figure 6. As expected, $NaBH_4$ promotes formation of a hydrido-palladium species that delivers hydrogen to the aromatic ring, rather than involvement by water. This was supported by the use of $NaBD_4$ in H_2O leading to 100% deuterium incorporation, while $NaBH_4$ in D_2O gave no deuterium incorporation.

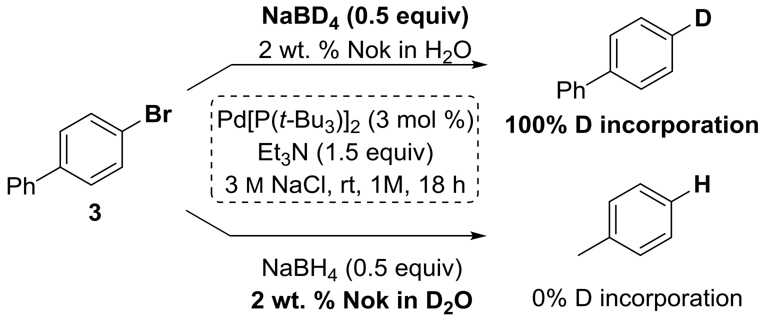


Figure 6. Source of hydrogen for the debromination of **3**

In conclusion, we have developed a mild, and environmentally friendly aromatic debromination prcedure. Because reagent formation takes place *in-situ*, the method is functional group tolerant. This methodology relies on the use of a designer surfactant that forms nanoreactors in water within which the reductions take place. As for observed limitations of this methodology, attempts to remove bromine from either an aromatic ring bearing a thioether residue or in a brominated pyridine led to no reaction. By contrast, yields in all cases utilizing this nanomicellar technology afforded each product in high isolated yield.

3.5 Experimental and Compound Data

General Information

The water used in this study was HPLC grade and was degassed prior to use by bubbling a flow of argon through the mixture for several hours. All commercially available reagents were used without further purification unless otherwise stated. The surfactants SPGS-550-M (Nok) and TPGS-750-M are commercially available from Sigma-Aldrich. (Catalog #'s 776033 and 733857) Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). The developed chromatogram was analyzed by UV lamp (254 nm) and/or aqueous potassium permanganate ($KMnO_4$), and developed by applying heat with a heat gun. Flash chromatography was performed in glass columns using Silica Flash® P60 (SiliCycle, 40-63 μm). ^{1}H and ^{13}C spectra were recorded at 23 °C on a Varian UNITY INOVA 500 MHz. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s =

singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. GC/MS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). As capillary column a HP-5MS cross-linked 5% phenylmethyl-polysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min.

Standard Procedures

Hydride screening

To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) under argon with septum was added substrate (0.25 mmol), $Pd[P(t\text{-}Bu)_3]_2$ (0.008 mmol, 3.8 mg, 3 mol %), reductant (0.25 mmol, 1.0 equiv), triethylamine (0.375 mmol, 52 uL, 1.5 equiv.), then 5 wt. % PTS with 3M NaCl ([0.5], 0.5 mL). The mixture was allowed to stir in an oil bath at 40 °C for 18 h then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Triethylamine screening

To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) under Ar with a septum was added **3** (0.2 mmol, 47 mg), $Pd[P(t\text{-}Bu)_3]_2$ (0.006 mmol, 3.1 mg, 3 mol %), $NaBH_4$ (0.2 mmol, 7.6 mg, 1.0 equiv), triethylamine (see above), then 5 wt. % PTS with 3 M NaCl ([0.5], 0.4 mL). The mixture was allowed to stir in an oil bath at 40 °C for 20 h and then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Sodium borohydride screening

To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) under Ar with a septum was added **3** (0.2 mmol, 47 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.006 mmol, 3.1 mg, 3 mol %), NaBH$_4$ (see above), triethylamine (0.3 mmol, 42 uL, 1.5 equiv), then 5 wt. % PTS with 3 M NaCl ([0.5], 0.4 mL). The mixture was allowed to stir in an oil bath at 40 °C for 20 h then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Salt effect on dehalogenations

To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) under Ar with septum was added **3** (0.25 mmol, 58 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.008 mmol, 3.8 mg, 3 mol %), NaBH$_4$ (0.125 mmol, 4.7 mg, 0.5 equiv), triethylamine (0.38 mmol, 52 uL, 1.5 equiv), then 5 wt. % PTS with NaCl ([0.5], 0.5 mL). The mixture was allowed to stir in an oil bath at 40 °C for 18 h and then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Surfactant screening

To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) under Ar with a septum was added substrate (0.25 mmol, see above), Pd[P(*t*-Bu)$_3$]$_2$ (0.008 mmol, 3.8 mg, 3 mol %), NaBH$_4$ (0.125 mmol, 4.7 mg, 0.5 equiv), triethylamine (0.38 mmol, 52 uL, 1.5 equiv), then 2 wt. % surfactant with 3 M NaCl ([0.5], 0.5 mL, see above). The mixture was allowed to stir in an oil bath at 30 °C for 18 h then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Screening of surfactant strength

To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5mm) under Ar with a septum was added substrate (0.25 mmol, see above), Pd[P(*t*-Bu)$_3$]$_2$ (0.008 mmol, 3.8 mg, 3 mol %), NaBH$_4$ (0.125 mmol, 4.7 mg, 0.5 equiv), triethylamine (0.38 mmol, 52 uL, 1.5 equiv), then X wt. % surfactant with 3 M NaCl ([0.5], 0.5 mL, see above). The mixture was allowed to stir in an oil bath at 30 °C for 18 h then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Catalyst screening

To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) under Ar with a septum was added substrate (0.25 mmol, see above), catalyst (0.008 mmol, 3.8 mg, 3 mol %), NaBH$_4$ (0.125 mmol, 4.7 mg, 0.5 equiv), triethylamine (0.38 mmol, 52 uL, 1.5 equiv), and then 2 wt. % Nok with 3 M NaCl ([0.5], 0.5 mL, see above). The mixture was allowed to stir in an oil bath at 30 °C for 18 h then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Temperature and concentration dependence

To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5mm) under Ar with a septum was added **3** (1.00 mmol, 233 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), triethylamine (01.50 mmol, 209 uL, 1.5 equiv), then 2 wt. % Nok with 3 M NaCl (see above). The mixture was allowed to stir (Figure 1) for 18 h then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Recycling study

To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) under Ar with a septum was added **3** (1.00 mmol, 233 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), triethylamine (01.50 mmol, 209 uL, 1.5 equiv), then 2 wt. % Nok with 3 M NaCl ([1.0], 1.0 mL,). The mixture was allowed to stir at RT for 24 h then extracted with EtOAc (2 x 0.2 mL) and then concentrated under reduced pressure. Passage through a bed a silica gel with 5% EtOAc:hexanes provided dehalogenated **3**. The aqueous reaction medium was then subjected to a subsequent identical reaction, and the cycle repeated four more times, as summarized above.

Representative procedure

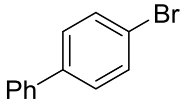
To a dry 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) under Ar with a septum was added Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaCl (3 mmol, 175 mg, [3.0]), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), substrate (1.00 mmol), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt. % Nok ([1.0], 1.0 mL). The mixture allowed to stir at rt (~ 23 °C) until complete as judged by TLC or GC-MS. It was, extracted with EtOAc (2 x 2 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with EtOAc:hexanes provided the desired dehalogenated analog.

Note: Highly crystalline solids must be ground to a fine powder (mortar and pestle) thereby forming a uniform suspension in the aqueous medium.

Surfactant solution preparation

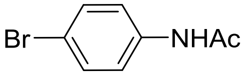
The water used in this study was HPLC grade and was degassed prior to use by bubbling Ar through for several hours.Then each solution was prepared by weight percent for the desired surfactant concentration with degassed HPLC grade water and subjected to an additional sparging with Ar for 1 h. All aqueous solutions containing surfactants were stored under an Ar atmosphere prior to use. Surfactants PTS and TPGS-750-M are both commercially available from Sigma-Aldrich but can be synthesized through previously published procedures.

Compound Data



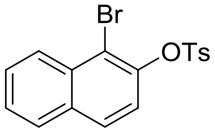
3

Reduction product from 4-bromobiphenyl (3, JF-003-012). The representative procedure was followed using 4-bromobiphenyl (1.00 mmol, 233.3 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv) NaCl (3 mmol, 175 mg), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 1.0 mL). The reaction was complete after 18 h by GC-MS. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hexanes to yield 149 mg, 97% **3** a white crystalline solid; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.59 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.36, 128.88, 127.37, 127.28; GC/MS m/z: 154.2. Compound data matched those previously reported.[23]



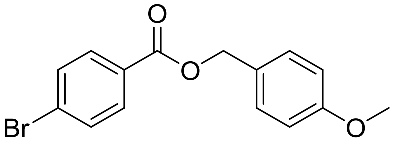
9

Reduction product from *N*-(4-bromophenyl)acetamide (9, JF-002-259). The representative procedure was followed using *N*-(4-bromophenyl)acetamide (0.70 mmol, 150 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.02 mmol, 10.7 mg, 3 mol %), NaCl (2.1 mmol, 123 mg), NaBH$_4$ (0.70 mmol, 13 mg, 1.0 equiv), triethylamine (1.05 mmol, 146 uL, 1.5 equiv), and then 2 wt % Nok with ([1.0], 0.70 mL). The reaction was complete after 24 h by TLC. Crude product was purified by passage through a bed a silica gel with EtOAc (R_f = 0.30, 3% EtOAc:hexanes) to yield 84.3 mg, 89% **9** a white crystalline solid; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.49 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.15 (s, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 169.01, 138.07, 128.88, 124.26, 120.17, 24.39; GC/MS m/z: 135.1. Compound data matched those previously reported.[27]



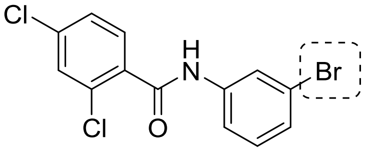
15

Reduction product from 1-bromonaphthalen-2-tosylate (15, JF-004-096). The representative procedure was followed using 1-bromonaphthalen-2-tosylate (1.00 mmol, 377.3 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), NaCl (3 mmol, 175 mg, [3.0]), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 1.0 mL). The reaction was complete after 8 h by GC-MS. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hexanes to yield 272 mg, 91% **15** a white crystalline solid; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84 – 7.78 (m, 1H), 7.74 (dd, *J* = 9.9, 9.0 Hz, 4H), 7.50 – 7.45 (m, 3H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.10 (dd, *J* = 8.9, 2.4 Hz, 1H), and 2.44 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 147.19, 145.35, 133.43, 132.45, 131.87, 129.76, 129.72, 128.55, 127.87, 127.73, 126.82, 126.35, 121.17, 119.94, and 21.71. GC/MS m/z: 298.4. HREIMS calcd for $C_{17}H_{14}O_3S$: 298.0664, found = 298.0670



16

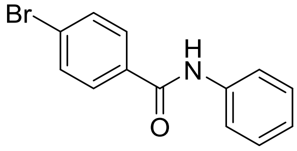
Reduction product from 4-methoxybenzyl 4-bromobenzoate (16, JF-002-254). The representative procedure was followed using 4-methoxybenzyl-4-bromo benzoate (1.00 mmol, 321.2 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), NaCl (3 mmol, 175 mg, [3.0]), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 1.0 mL). The reaction was complete after 16 h by GC-MS. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hexanes to yield 228 mg, 94% of a clear waxy solid; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.07 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.42 (dd, *J* = 17.0, 8.3 Hz, 4H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.31 (s, 2H), and 3.81 (s, 3H); ^{1}H NMR (126 MHz, CDCl$_3$) δ 166.49, 159.66, 132.94, 130.07, 129.66, 128.33, 128.17, 127.21, 113.97, 66.54, and 55.29; GC-MS m/z: 242.3. Compound data matched those previously reported.[28]



17

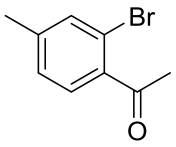
Reduction product from *N*-(3-bromophenyl)-2,4-dichlorobenzamide (17, JF-004-008). The representative procedure was followed using *N*-(3-bromophenyl)-2,4-dichlorobenzamide (1.00 mmol, 345.1 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), NaCl (3 mmol, 175 mg, [3.0]), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 1.0 mL). The reaction was complete after

18 h by TLC. Crude product was purified by passage through a bed a silica gel with 10% EtOAc:hexanes (R_f = 0.45, 20% EtOAc:hexanes) to yield 249 mg, 94% **17** as a white crystalline solid ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.44 (s, 1H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.32 (dd, *J* = 8.3, 1.6 Hz, 1H), and 7.18 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.54, 137.35, 137.15, 133.56, 131.48, 131.29, 130.14, 129.13, 127.65, 125.05, and 120.22; HREIMS calcd for $C_{13}H_9Cl_2NO$: 265.0061, found 265.0063.



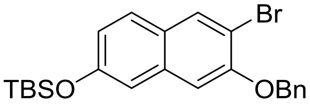
18

Reduction product from 4-bromo-*N*-phenylbenzamide (18, JF-004-010). The representative procedure was followed using 4-bromo-*N*-phenylbenzamide (1.00 mmol, 276.1 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), $NaBH_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), NaCl (3 mmol, 175 mg, [3.0]), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 1.0 mL). Added The second portion of $NaBH_4$ was added after 18 h. The reaction was complete after 37 h by TLC. Crude product was purified by passage through a bed a silica gel with 0% EtOAc:hexanes (R_f = 0.15, 10% EtOAc:hexanes) to yield 189 mg, 96% **18** as a white crystalline solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.1 Hz, 2H), 7.85 (s, 1H),7.65 (d, *J* = 8.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.71, 137.91, 135.01, 131.83, 129.09, 128.79, 127.00, 124.57, and 120.19. HREIMS calcd for $C_{13}H_{11}NO$: 197.0841, found 197.0842.



19

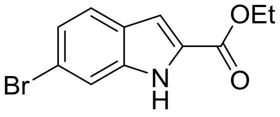
Reduction product from 2-bromo-4-methylacetophenone (19, JF-004-014). The representative procedure was followed using 2-bromo-4-methylacetophenone (1.00 mmol, 213.4 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), NaCl (3 mmol, 175 mg, [3.0]), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 1.0 mL). The reaction was complete after 14 h by TLC. Crude product was purified by passage through a bed a silica gel with 5% EtOAc:hexanes (R_f = 0.22, 5% EtOAc:hexanes) to yield 126 mg, 94% of waxy white solid; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.57 (s, 3H), and 2.40 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 197.81 143.84, 134.71, 129.21, 128.41, 26.49, and 21.60; HREIMS calcd for $C_9H_{10}O$: 134.0732, found 134.0731.



20

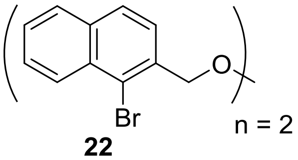
Reduction product from ((7-(benzyloxy)-6-bromonaphthalen-2-yl)oxy) (*t*-butyl)dimethyl-silane (20, JF-004-015). The representative procedure was followed using ((7-(benzyloxy)-6-bromo-naphthalen-2-yl)oxy) (*t*-butyl)dimethylsilane (1.00 mmol, 443.4 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), NaCl (3 mmol, 175 mg, [3.0]), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), and then 2 wt % Nok ([1.0], 1.0 mL). The reaction was complete after 15 h by TLC. Crude product was purified by passage through a bed a silica gel with 3% EtOAc:hexanes (R_f =

0.40, 3% EtOAc:hexanes) to yield 351 mg, 96% **20** as a faint yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 14.0, 8.7 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.12 (s, 2H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.18 (s, 2H), 1.05 (s, 9H), and 0.27 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.18, 155.11, 137.96, 136.89, 130.16, 130.02, 129.58, 128.96, 128.55, 127.97, 120.64, 117.78, 115.22, 107.18, 70.96, 26.73, 19.26, and -3.31; HREIMS calcd for $C_{23}H_{28}O_2Si$: 364.1859, found 364.1866.



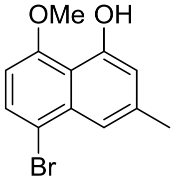
21

Reduction product from ethyl 6-bromo-1H-indole-2-carboxylate (21, JF-004-034). The representative procedure was followed using ethyl 6-bromo-1H-indole-2-carboxylate (1.00 mmol, 268.1 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), $NaBH_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), NaCl (3 mmol, 175 mg, [3.0]), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 1.0 mL). The reaction was complete after 20 h by TLC. Crude product was purified by passage through a bed a silica gel with 10% EtOAc:hexanes (R_f = 0.22, 10% EtOAc:hexanes) to yield 168 mg, 89% of **21** a white crystalline solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.16 (dd, *J* = 7.8, 7.2 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), and 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.96, 136.76, 127.51, 125.33, 123.56, 122.58, 120.78, 111.81, 108.62, 61.00, and 14.39; GC/MS m/z: 189.2. Compound data matched those previously reported.[29]



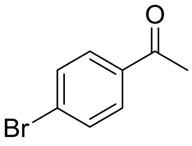
22

Reduction product from 2,2'-(oxybis(methylene))bis(1-bromonaphthalene) (22, EL-lnb). The representative procedure was followed using 2,2'-(oxybis(methylene))-*bis*-(1-bromonaphthalene) (0.70 mmol, 319 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.02 mmol, 10.7 mg, 3 mol %), NaCl (2.1 mmol, 123 mg [3.0]), NaBH$_4$ (0.70 mmol, 13 mg, 1.0 equiv), triethylamine (1.05 mmol, 146 uL, 1.5 equiv), then 2 wt % Nok with ([1.0], 0.70 mL). The reaction was complete after 24 h by TLC. Crude product was purified by passage through a bed a silica gel with EtOAc (R_f = 0.30, 3% EtOAc:hexanes) to yield 138 mg, 66% of **22** a white crystalline solid; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 – 7.82 (m, 4H), 7.55 – 7.51 (m, 1H), 7.48 (p, *J* = 5.8 Hz, 2H), 4.77 (s, 2H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 135.87, 133.43, 133.14, 128.33, 128.00, 127.83, 126.65, 126.21, 125.97, 125.94, 72.32. Compound data matched those previously reported.[30]



23

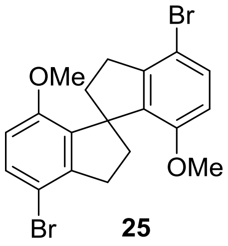
Reduction product from 5-bromo-8-methoxy-3-methylnaphthalen-1-ol (23, EL-lnb). The representative procedure was followed using 5-bromo-8-methoxy-3-methylnaphthalen-1-ol (0.5mmol, 133 mg), Pd[P(t-Bu)3]2 (0.015 mmol, 7.7 mg, 3 mol %), NaCl (1.5 mmol, 88 mg, [3.0]), NaBH$_4$ (0.55 mmol, 20.8 mg, 1.1 equiv), triethylamine (0.75 mmol, 76 uL, 1.5 equiv), then 2 wt % Nok with ([1.0], 0.50 mL). The reaction was complete after 20 h by GC. The reaction was treated with HCl (1.5 ml, [2.0]) and the crude was passed through a bed of silica gel with 10% EtOAc:hexanes (R_f 0.27, 10% EtOAc:hexanes). The product was dissolved in Et_2O (2 mL) and washed twice with HCl ([1.0], 1.5mL). The product was purified by passing through through a bed of silica gel with 10% EtOAc:hexanes (Rf 0.27, 10% EtOAc:hexanes) to yield 85.5 mg, 91% of **23** a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.26 (t, J = 7.9 Hz, 1H), 7.09 (s, 1H), 6.74 (s, 1H), 6.70 (d, J = 7.6 Hz, 1H), 4.04 (s, 3H), 2.42 (s, 3H). 13C NMR (126 MHz, $CDCl_3$) δ 156.29, 154.30, 137.99, 137.03, 125.80, 121.39, 118.40, 113.40, 112.39, 103.23, 56.14, 21.75. GC/MS mz: 188.1. Compound data matched those previously reported.[31]



24

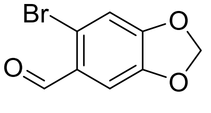
Reduction product from 4-bromoacetophenone (24, JF-003-012). The representative procedure was followed using 4-bromoacetophenone (1.00 mmol, 199.1 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), $NaBH_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), NaCl (3 mmol, 175 mg, [3.0]), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 1.0 mL). The reaction was complete after 16 h by TLC. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hexanes (R_f = 0.70, 30% EtOAc:hexanes) to yield 111 mg, 92% of **24** a clear liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 2.59 (s, 3H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 198.11, 137.12, 133.07, 128.54, 128.28, 26.58; GC/MS m/z: 120.1. Compound data matched those previously reported.[24]



25

Reduction product from *bis*-bromospirobiindane (25,). The representative procedure was followed using *bis*-bromospirobiindane (0.35 mmol, 153 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.01 mmol, 5.4 mg, 3 mol %), $NaBH_4$ (0.35 mmol, 13 mg, 1.0 equiv), NaCl (0.53 mmol, 61 mg, [3.0]), triethylamine (0.53 mmol, 73 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 0.35 mL). The reaction was complete after 20 h by TLC. Crude product was purified by passage through a bed a silica gel with 5% EtOAc:hexanes (R_f = 0.30, 5% EtOAc:hexanes) to yield 89 mg, 91% **25** as a white crystalline solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.7 Hz, 2H), 6.85 (d, *J* = 7.4 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 2H), 3.53 (s, 3H), 3.06 (m, 2H), 3.00 (m, 2H), 2.33 (m, 2H), and 2.16 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.53, 145.35, 136.64, 127.52, 116.79, 108.64, 59.22, 55.18, 38.81, and 31.61; GC/MS m/z: 280.4. Compound data matched those previously reported.[5]



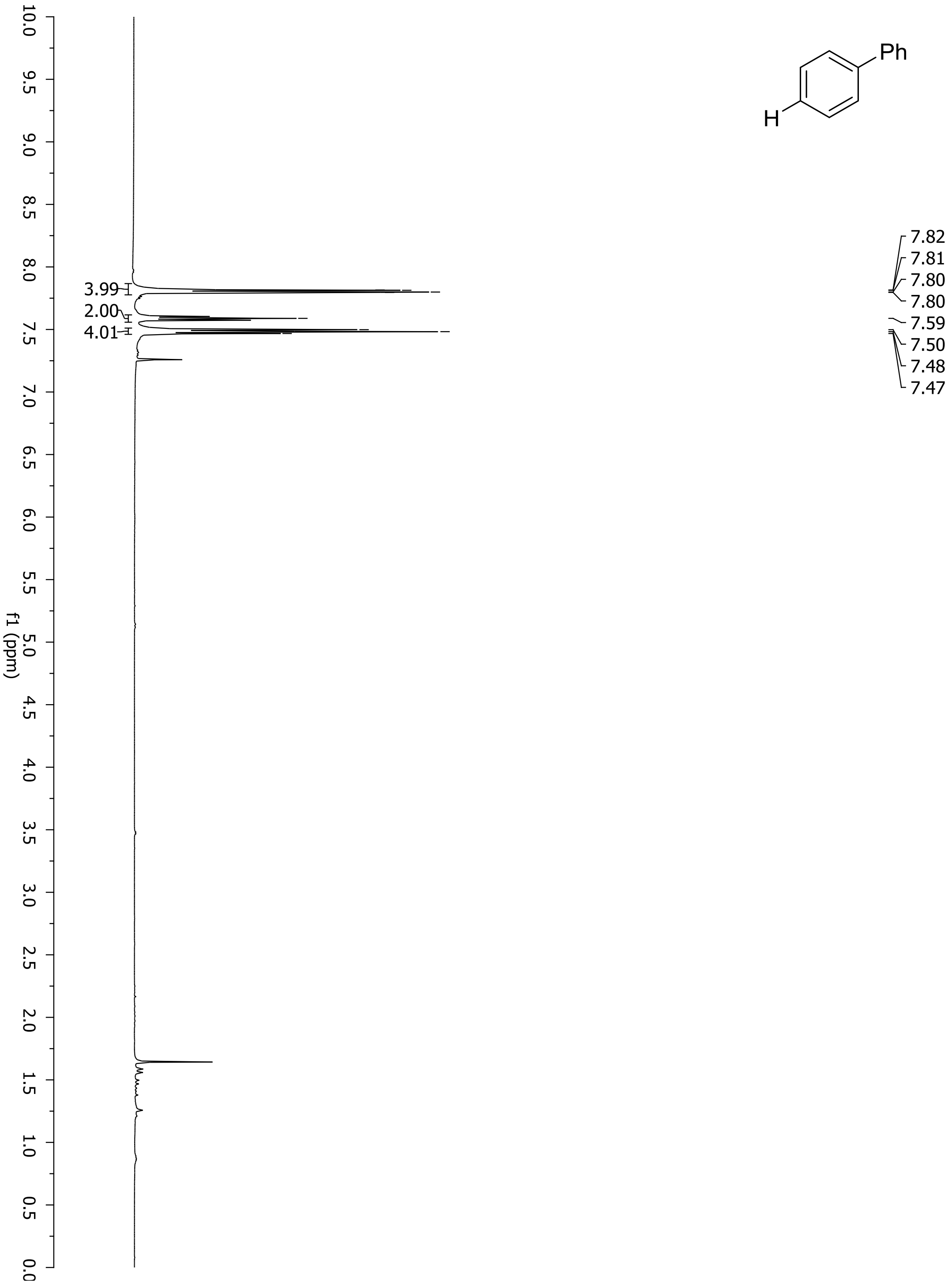
26

Reduction product from 6-bromobenzo[1,3]dioxole-5-carbaldehyde (26, JF-004-031). The representative procedure was followed using 6-bromobenzo[1,3]dioxole-5-

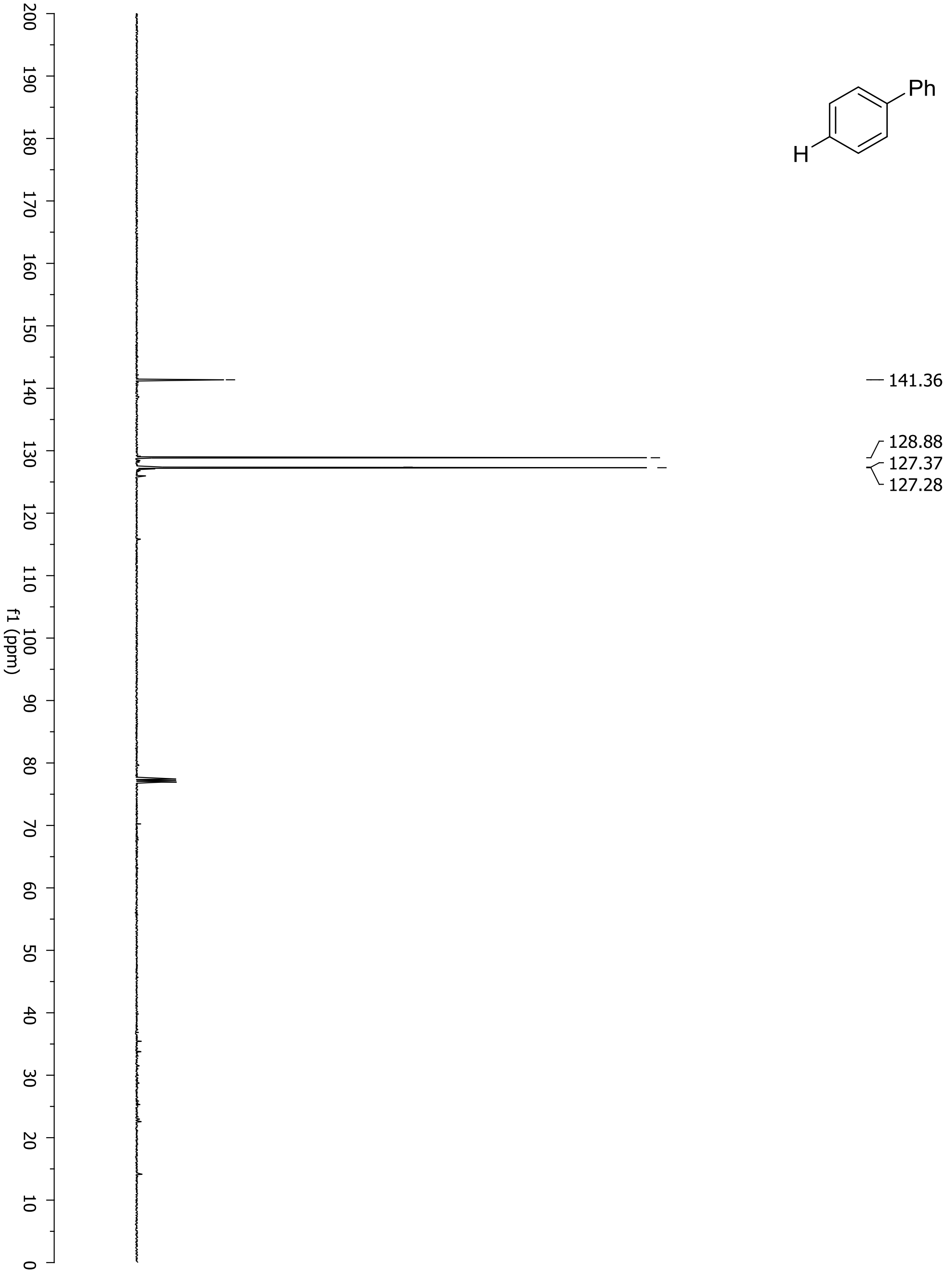
carbaldehyde (1.00 mmol, 229.1 mg), Pd[P(*t*-Bu)$_3$]$_2$ (0.03 mmol, 15.3 mg, 3 mol %), NaBH$_4$ (0.50 mmol, 18.9 mg, 0.5 equiv), NaCl (3 mmol, 175 mg, [3.0]), triethylamine (1.50 mmol, 209 uL, 1.5 equiv), then 2 wt % Nok ([1.0], 1.0 mL). The reaction was complete after 22 h by TLC. Crude product was purified by passage through a bed a silica gel with 10% EtOAc:hexanes (R_f = 0.60, 10% EtOAc:hexanes) to yield 131 mg, 87% of **26** a clear oil; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.81 (s, 1H), 7.41 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.33 (d, *J* = 1.6 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), and 6.07 (s, 2H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 190.23, 153.08, 148.70, 131.89, 128.61, 108.34, 106.92, and 102.08; GC/MS m/z: 150.1. Compound data matched those previously reported.[25]

3.6 Spectral Data

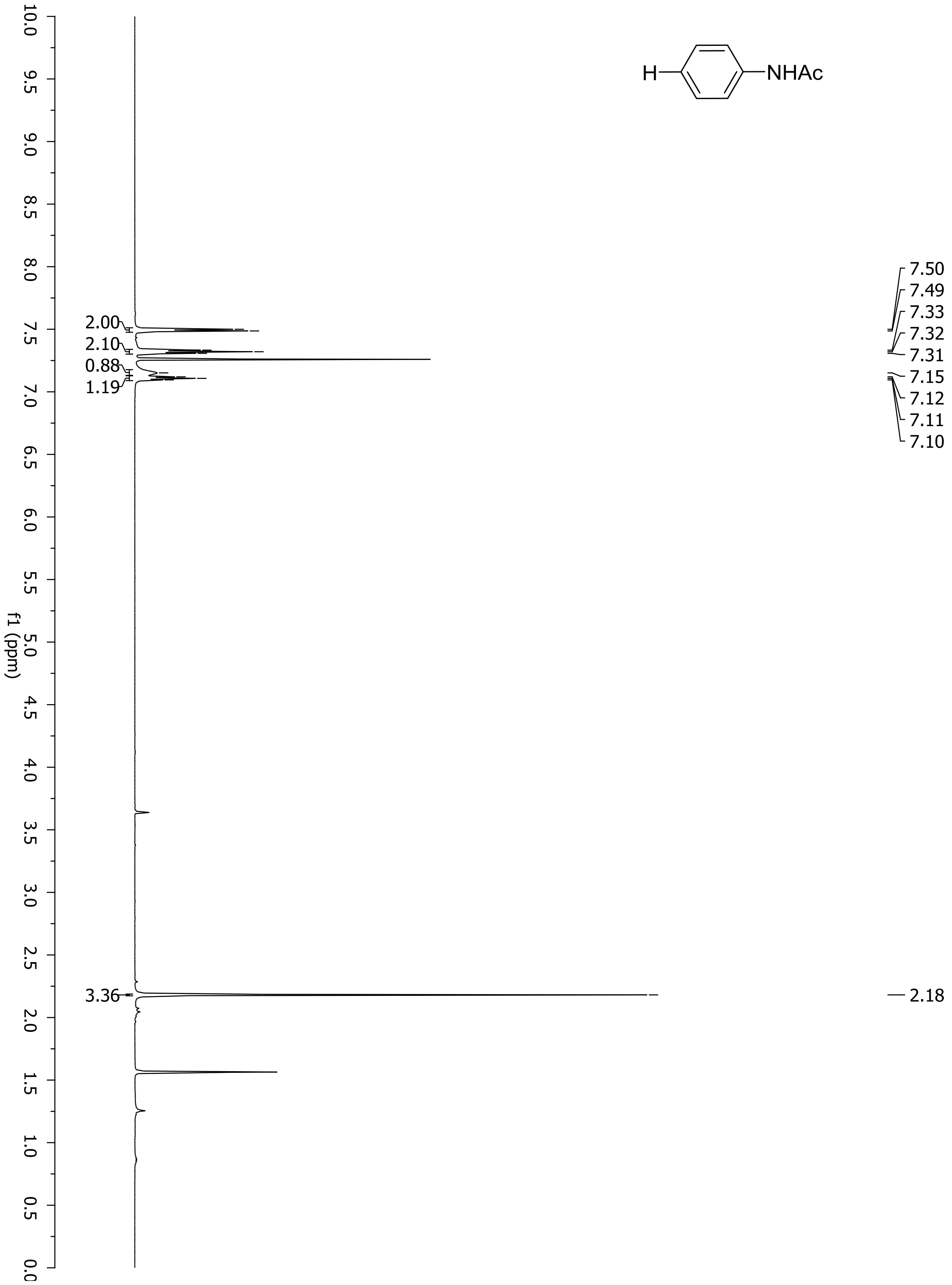
Reduced 4-bromobiphenyl **3** Proton NMR ($CDCl_3$)



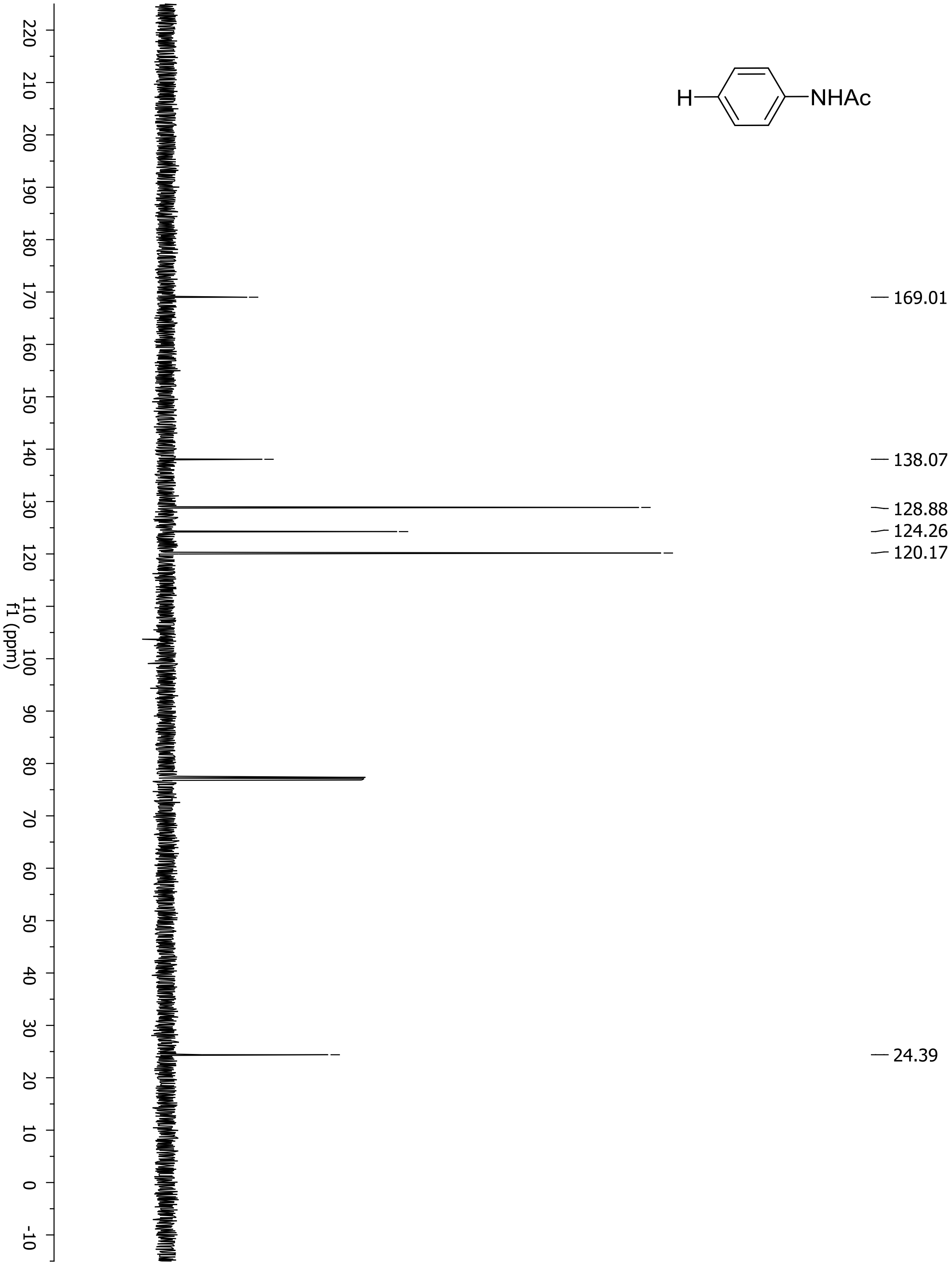
Reduction product from 4-bromobiphenyl **3**; Carbon NMR ($CDCl_3$)



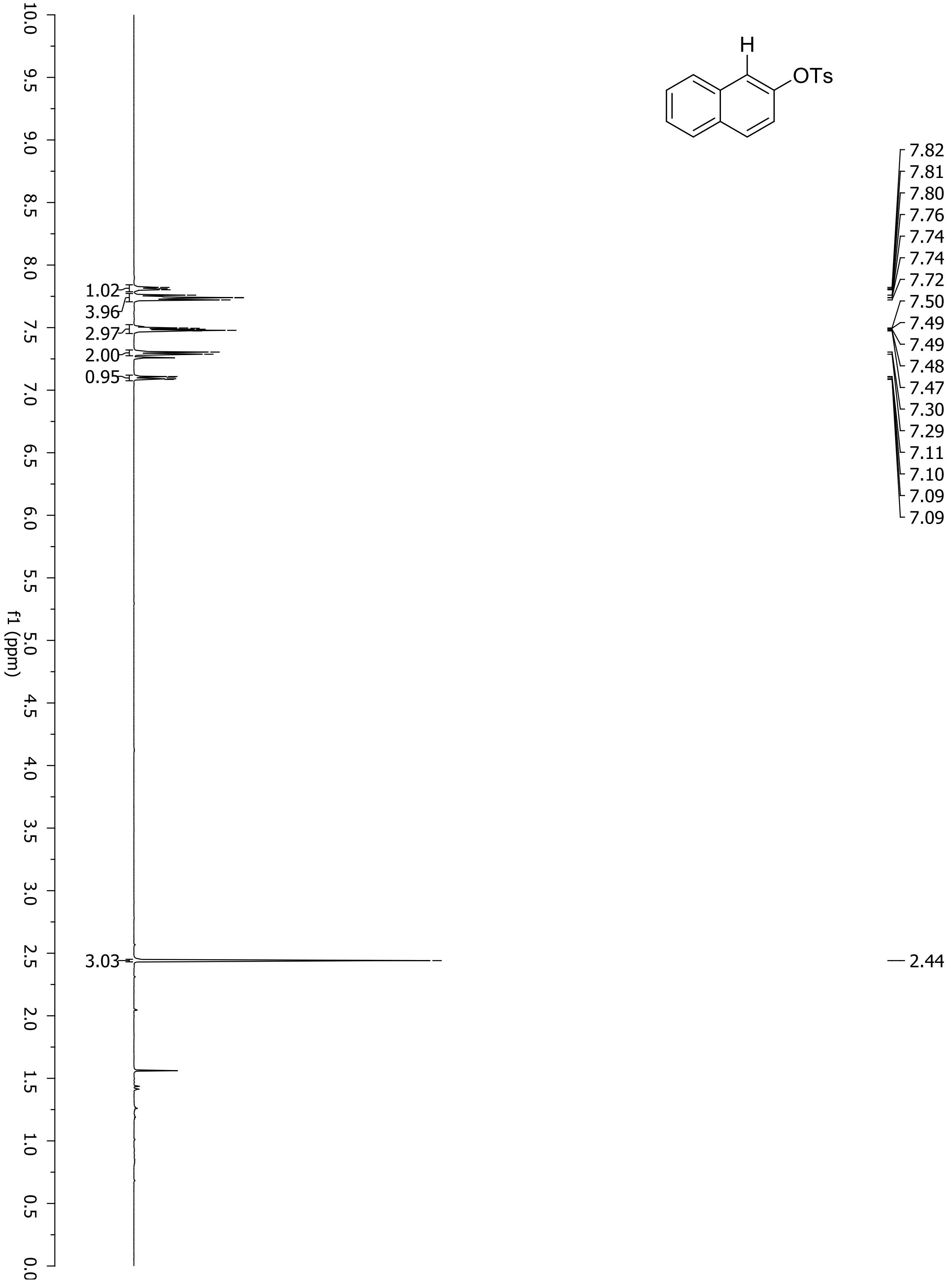
Reduction product from *N*-(4-bromophenyl)acetamide **9**; Proton NMR ($CDCl_3$)



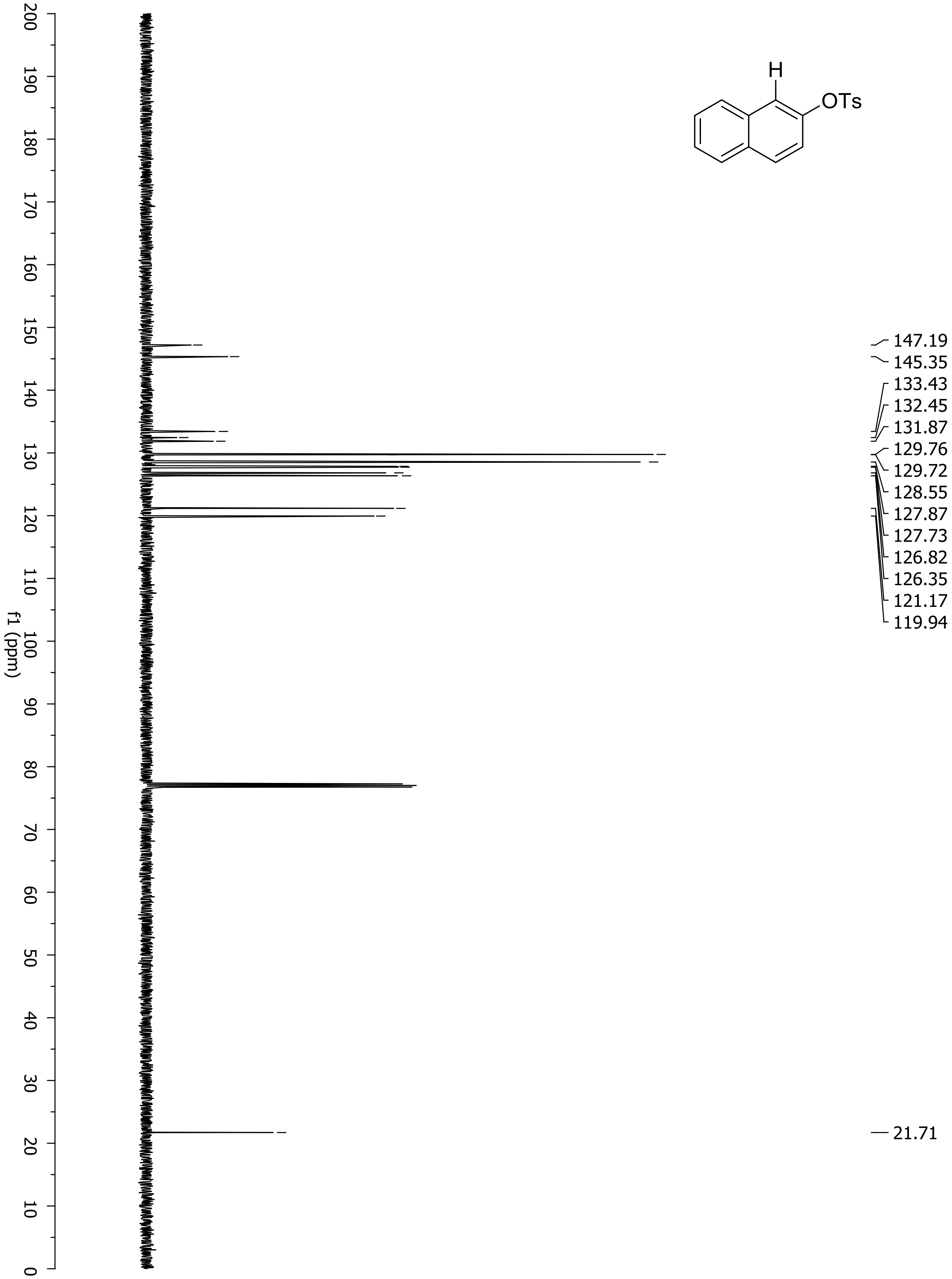
Reduction product from *N*-(4-bromophenyl)acetamide **9**; Carbon NMR ($CDCl_3$)



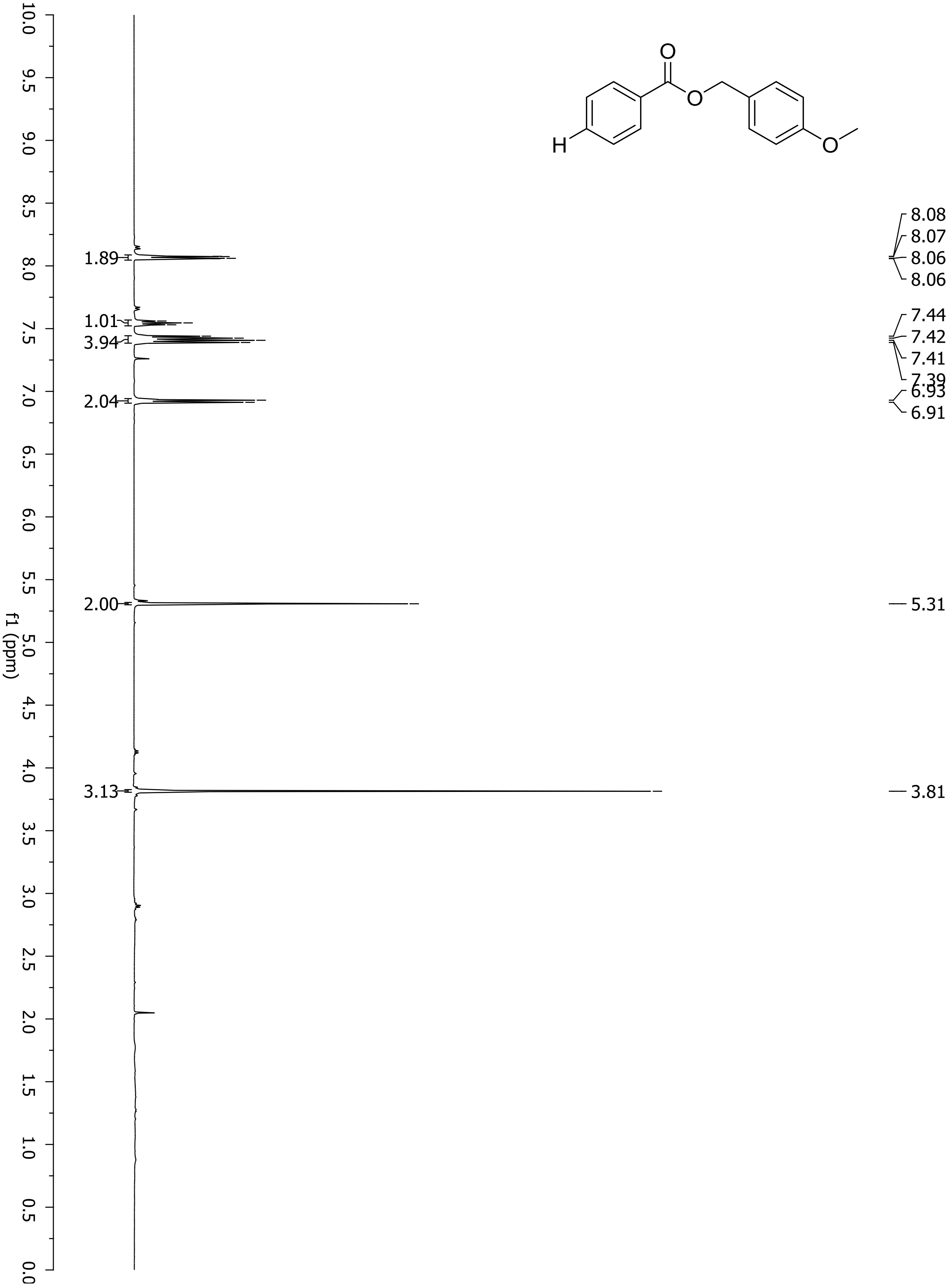
Reduction product from 1-bromonaphthalen-2-tosylate **15**; Proton NMR ($CDCl_3$)



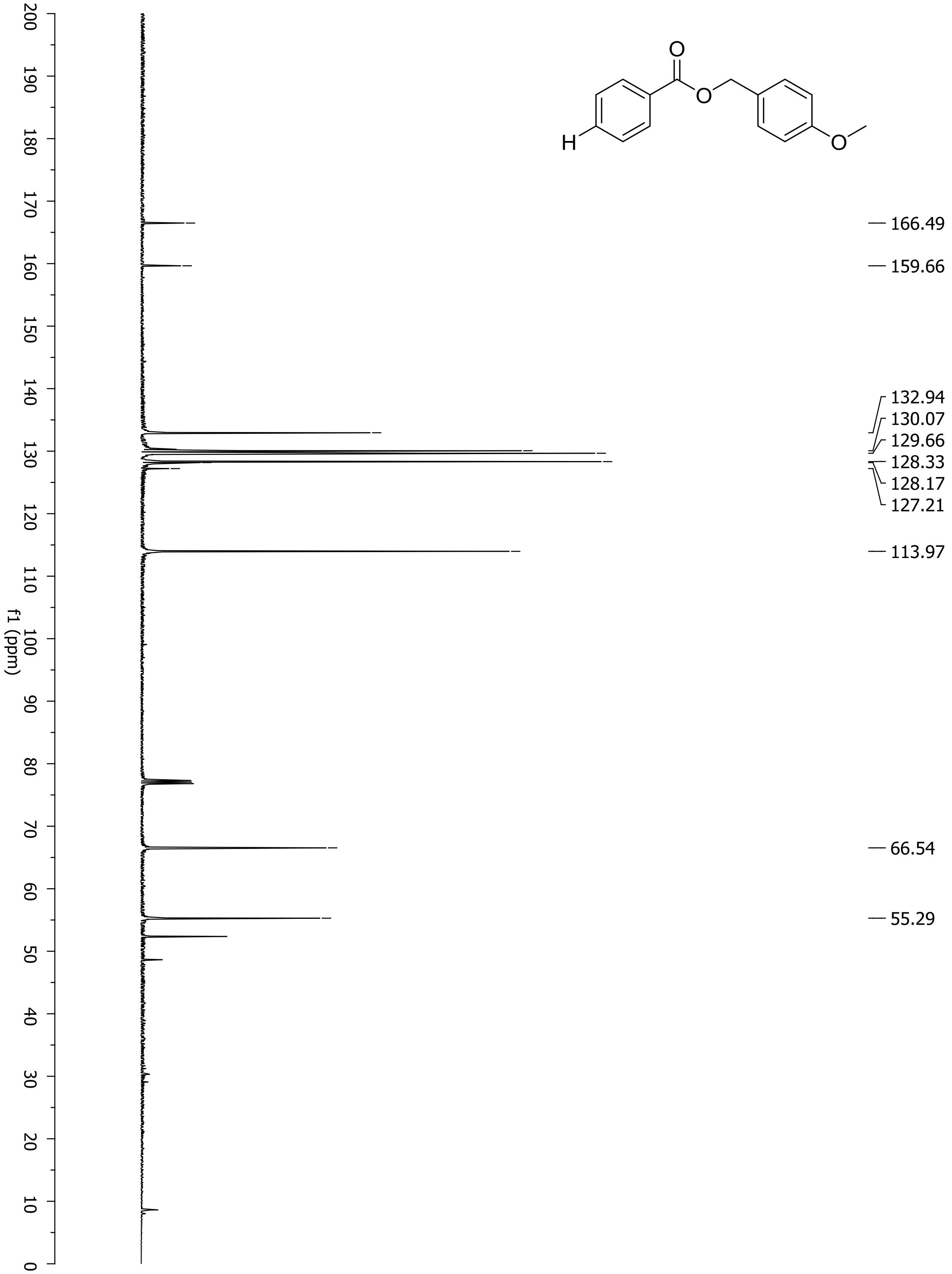
Reduction product from 1-bromonaphthalen-2-tosylate **15**; Carbon NMR ($CDCl_3$)



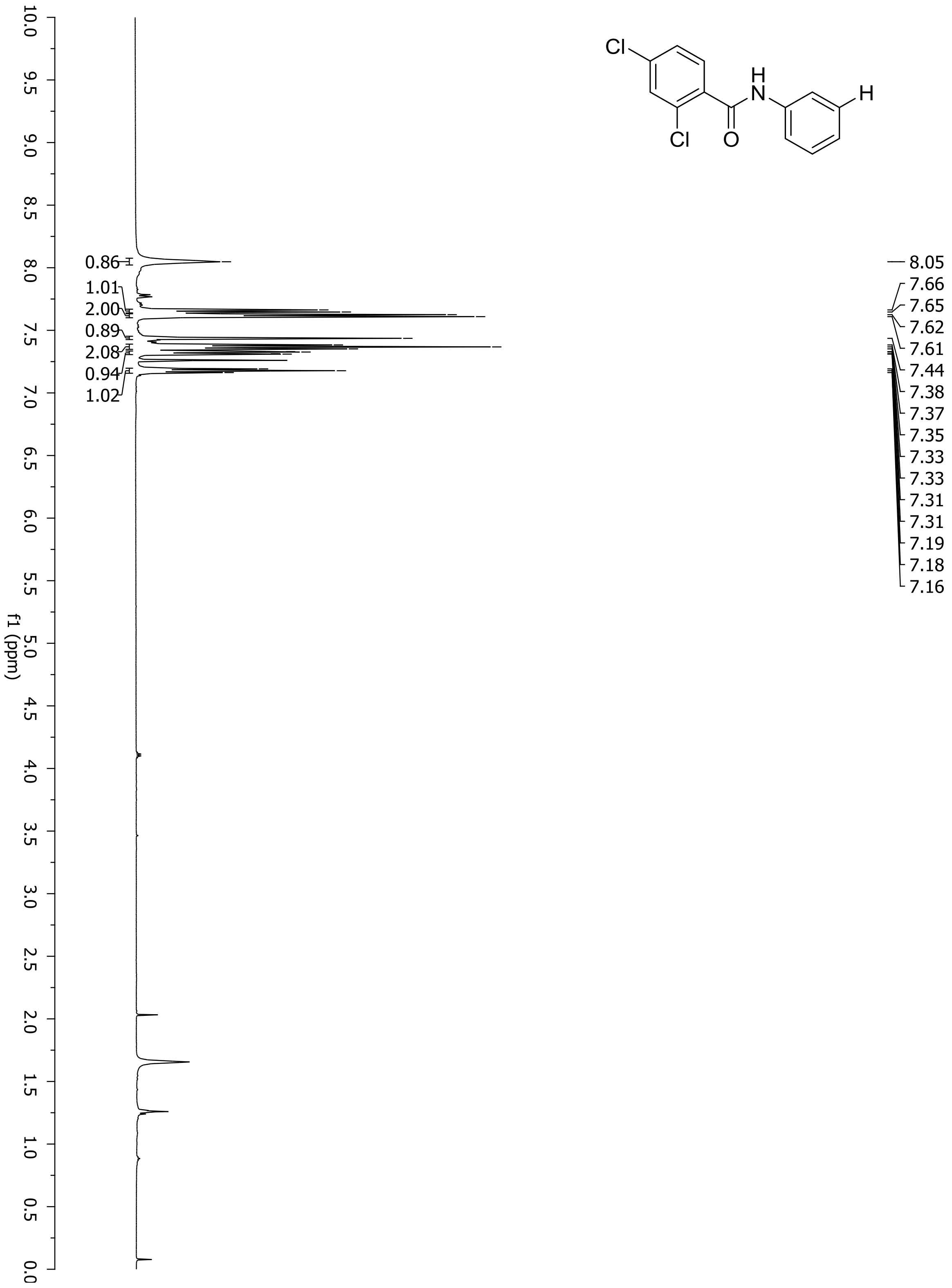
Reduction product from 4-methoxybenzyl 4-bromobenzoate **16**; Proton NMR ($CDCl_3$)



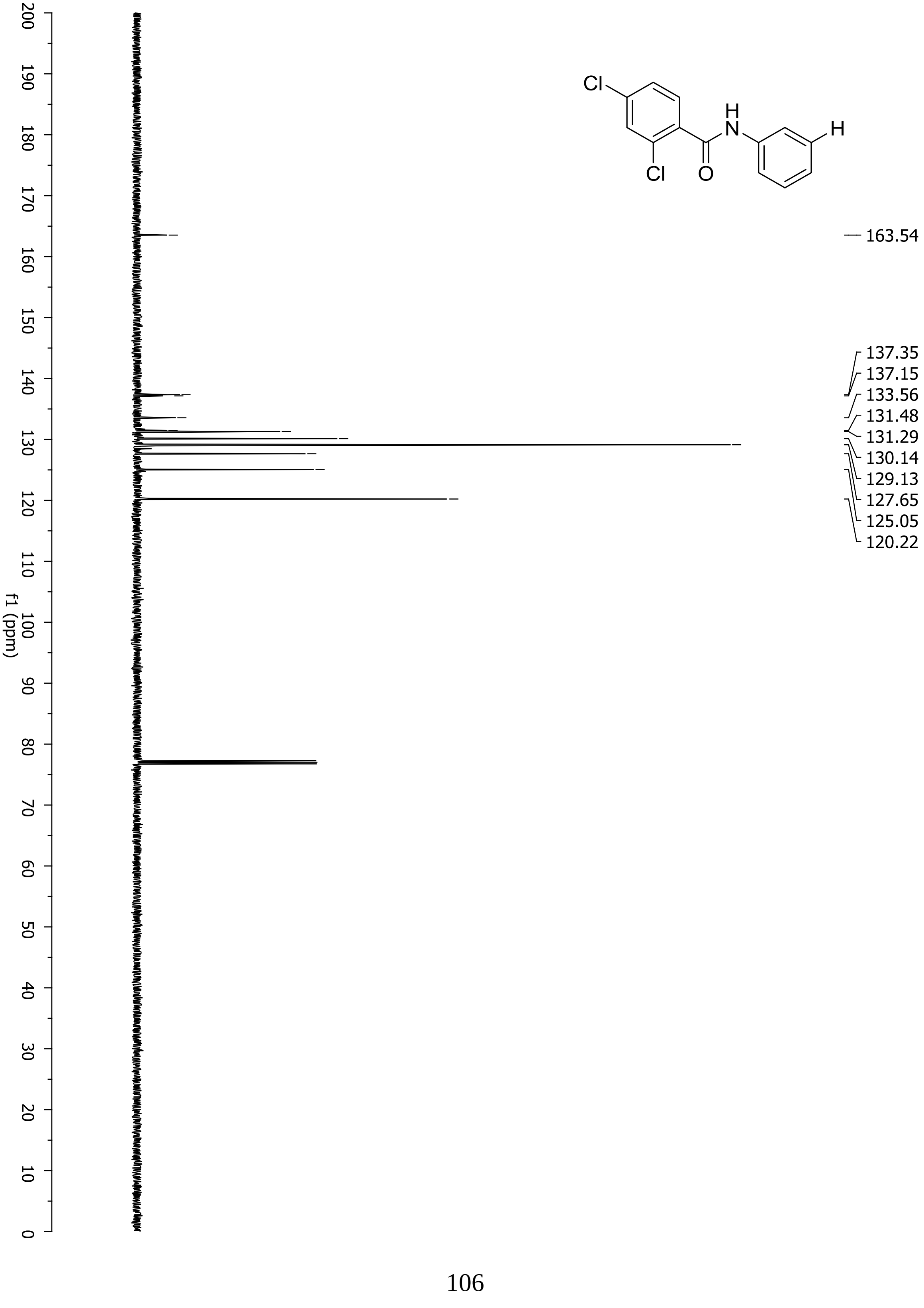
Reduction product from 4-methoxybenzyl 4-bromobenzoate **16**; Carbon NMR ($CDCl_3$)



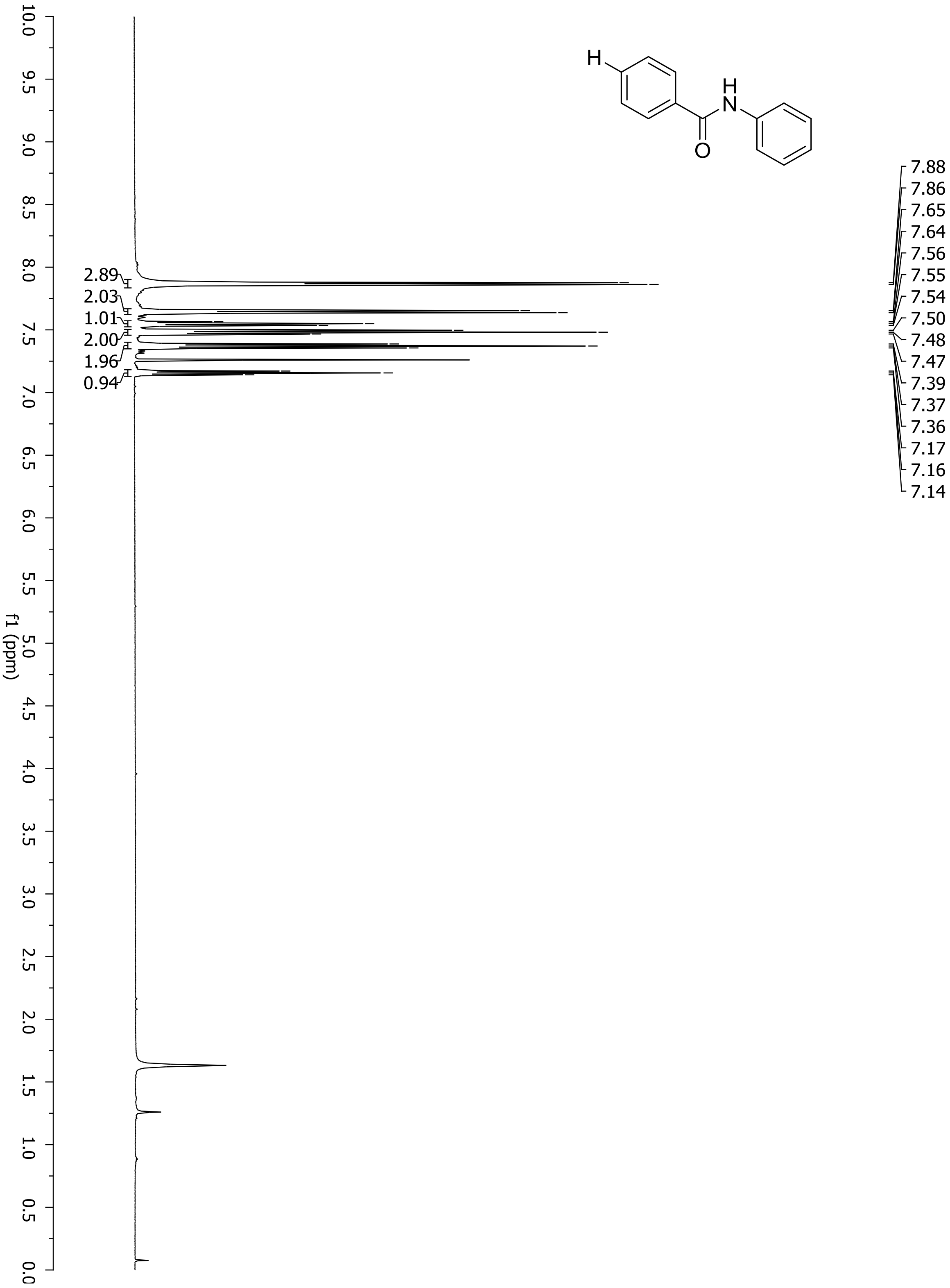
Reduction product from *N*-(3-bromophenyl)-2,4-dichlorobenzamide **17**; Proton NMR ($CDCl_3$)



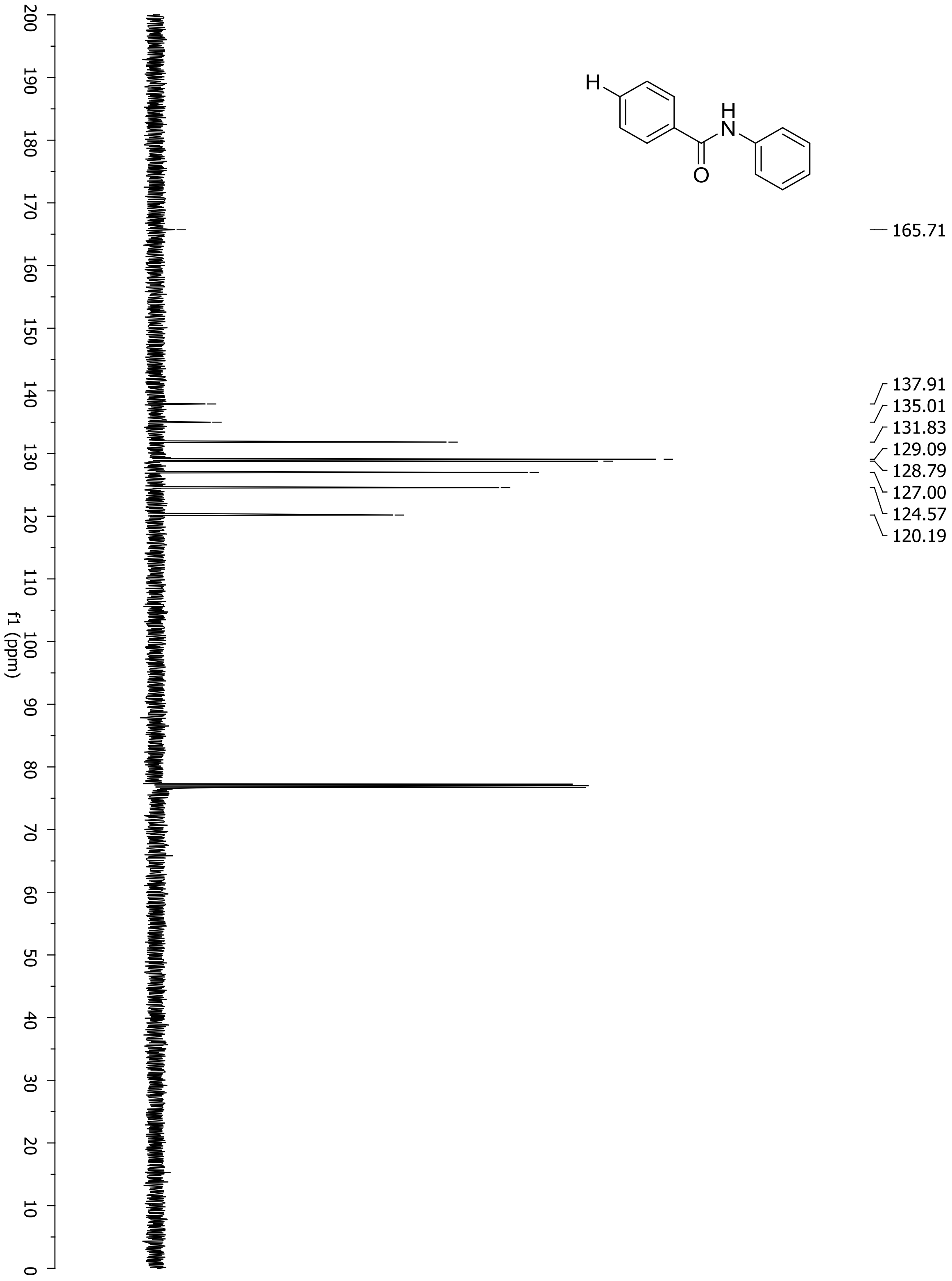
Reduction product from *N*-(3-bromophenyl)-2,4-dichlorobenzamide **17**; Carbon NMR ($CDCl_3$)



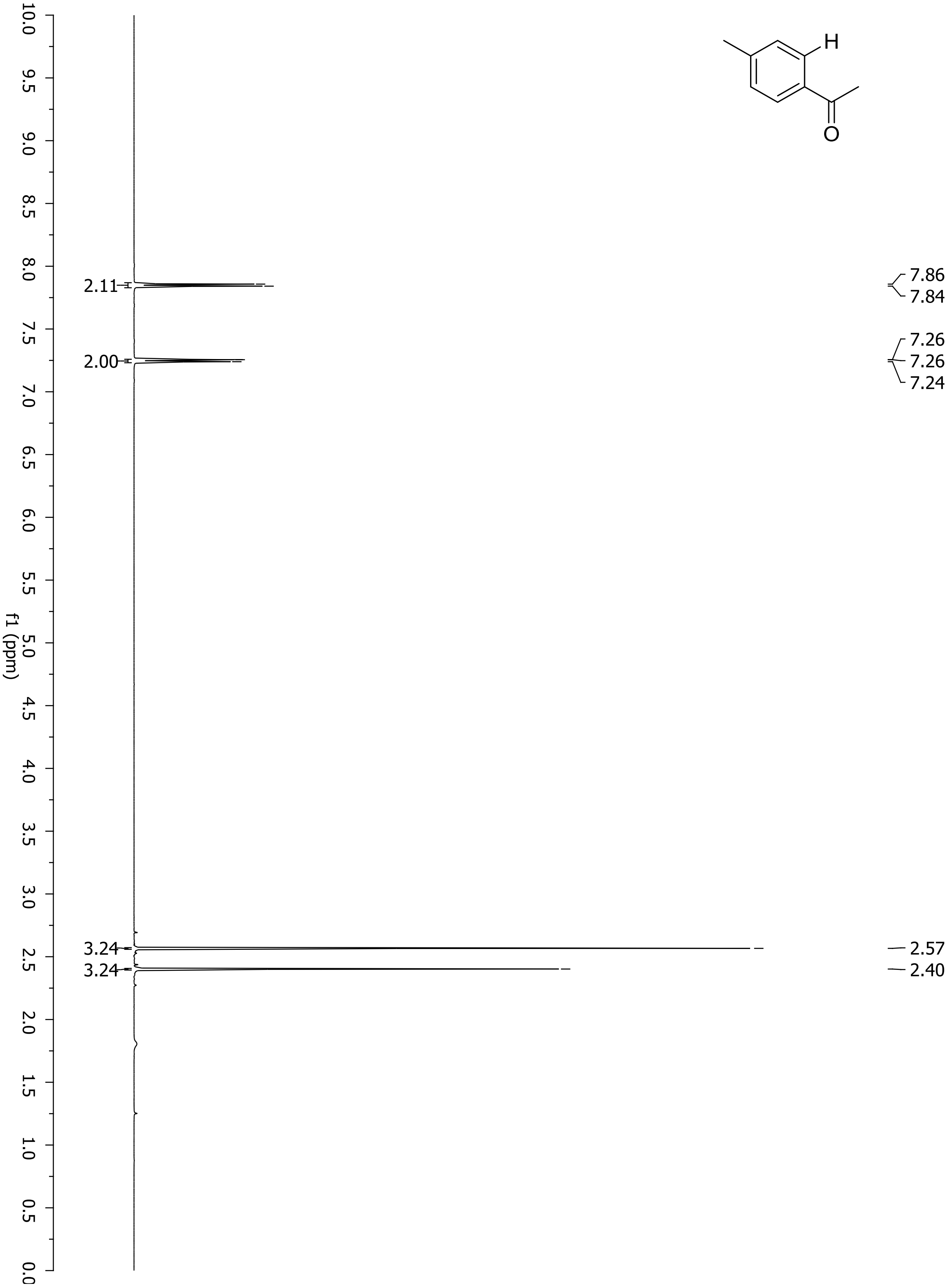
Reduction product from 4-bromo-*N*-phenylbenzamide **18**; Proton NMR ($CDCl_3$)



Reduction product from 4-bromo-*N*-phenylbenzamide **18**; Carbon NMR ($CDCl_3$)



Reduced 2-bromo-4-methyl acetophenone **19**; Proton NMR ($CDCl_3$)



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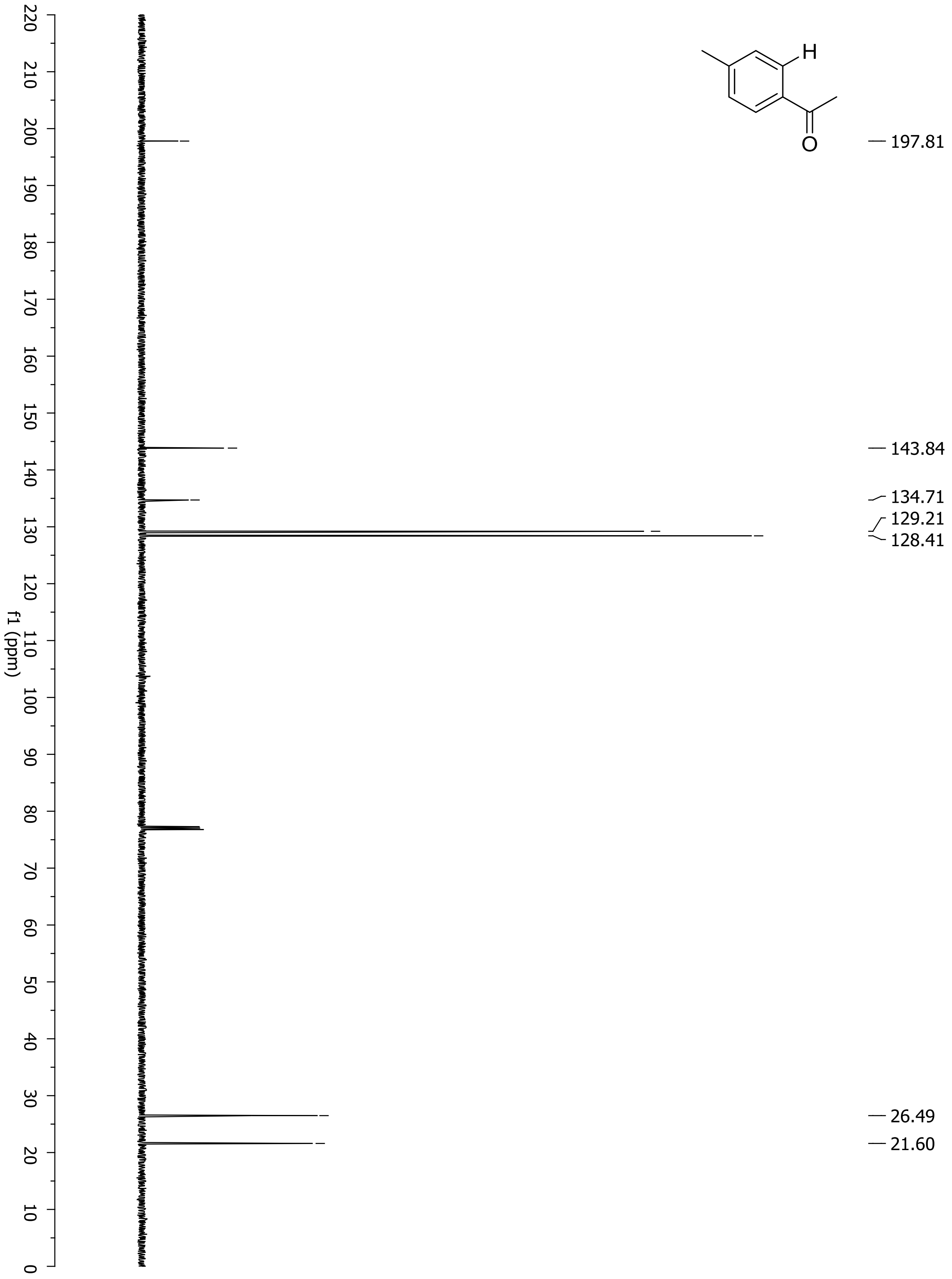
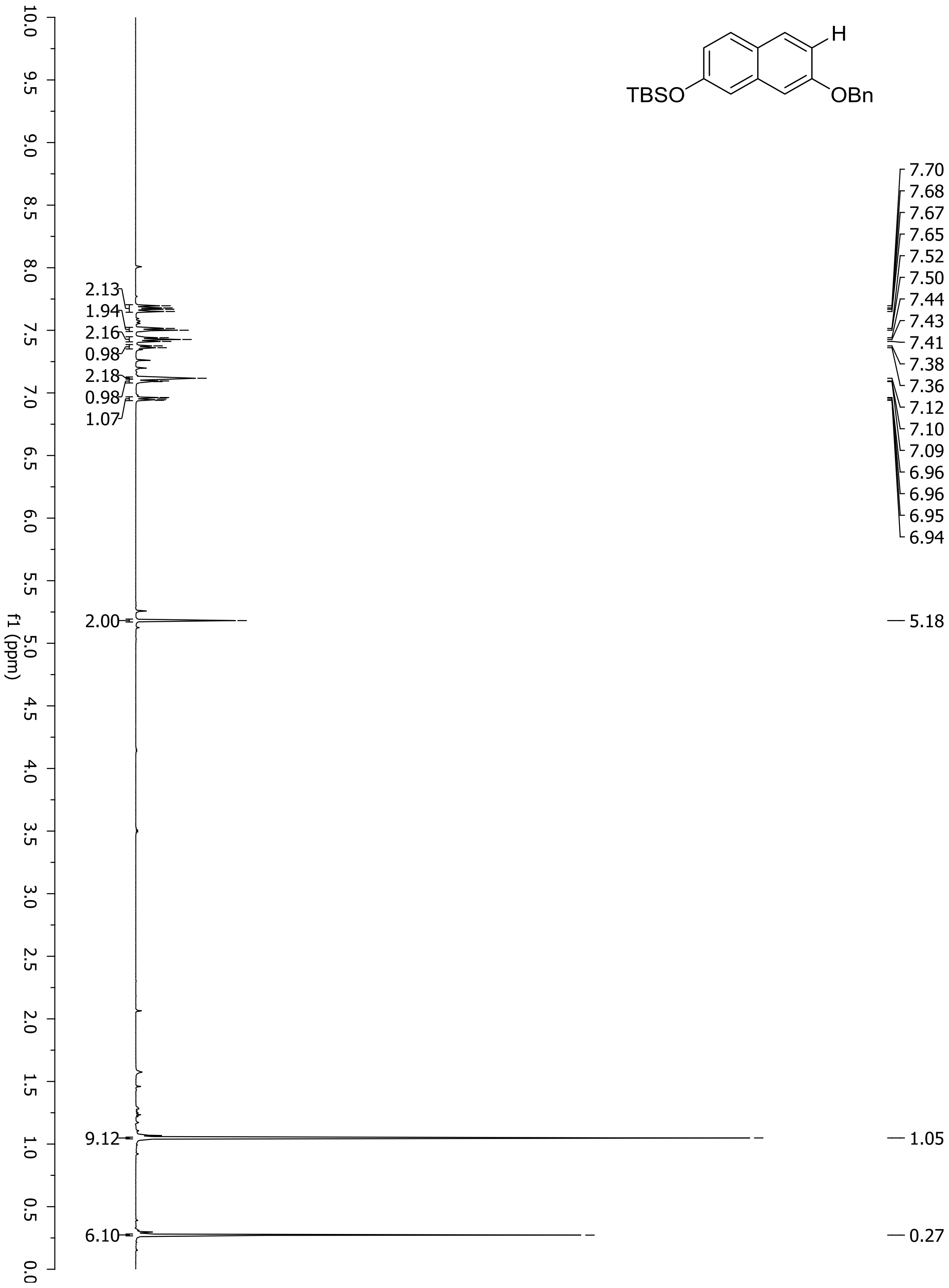


Reduction product from ((7-(benzyloxy)-6-bromonaphthalen-2-yl)oxy) (*t*-butyl)dimethylsilane **20**; Proton NMR ($CDCl_3$)



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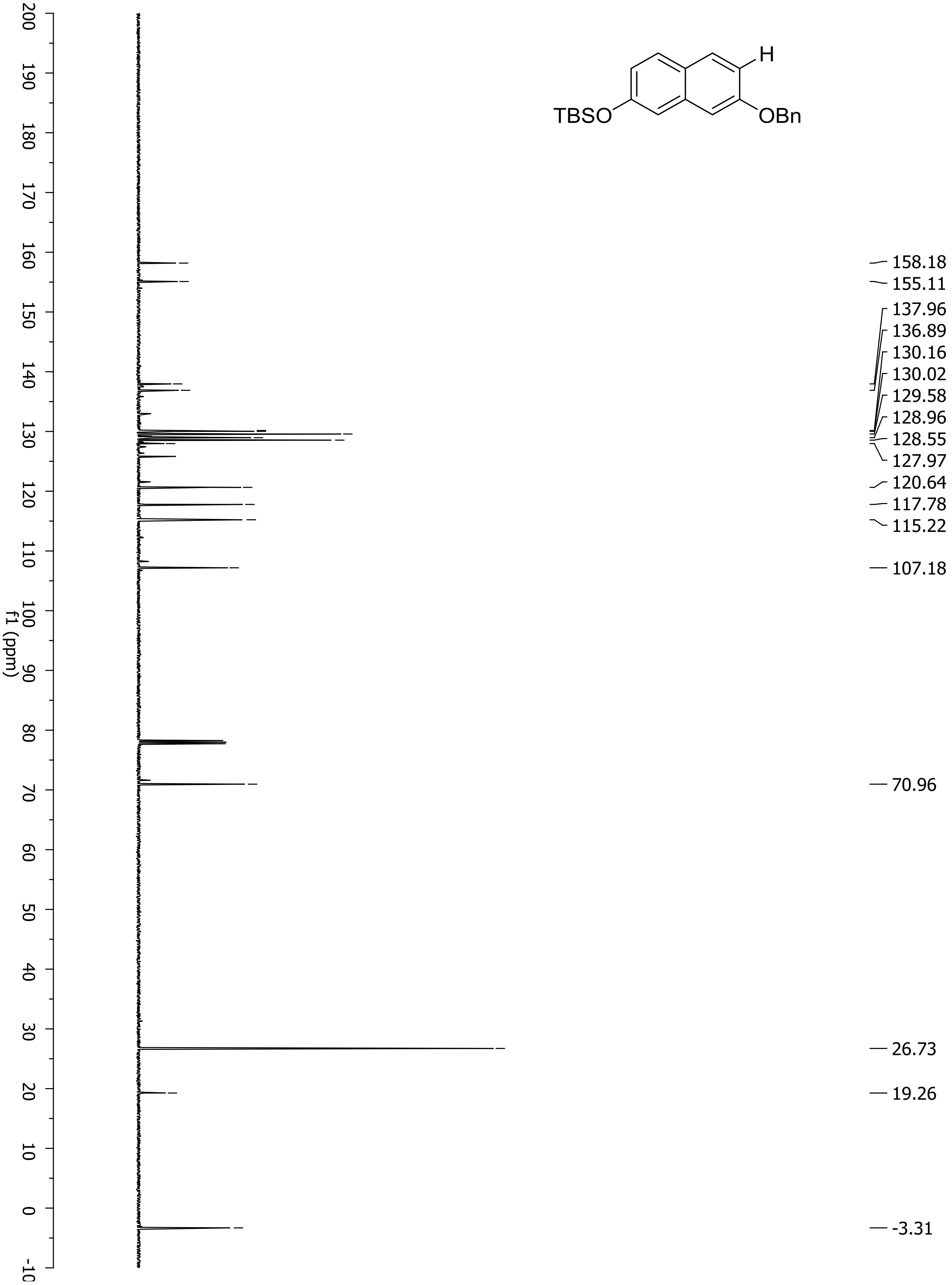
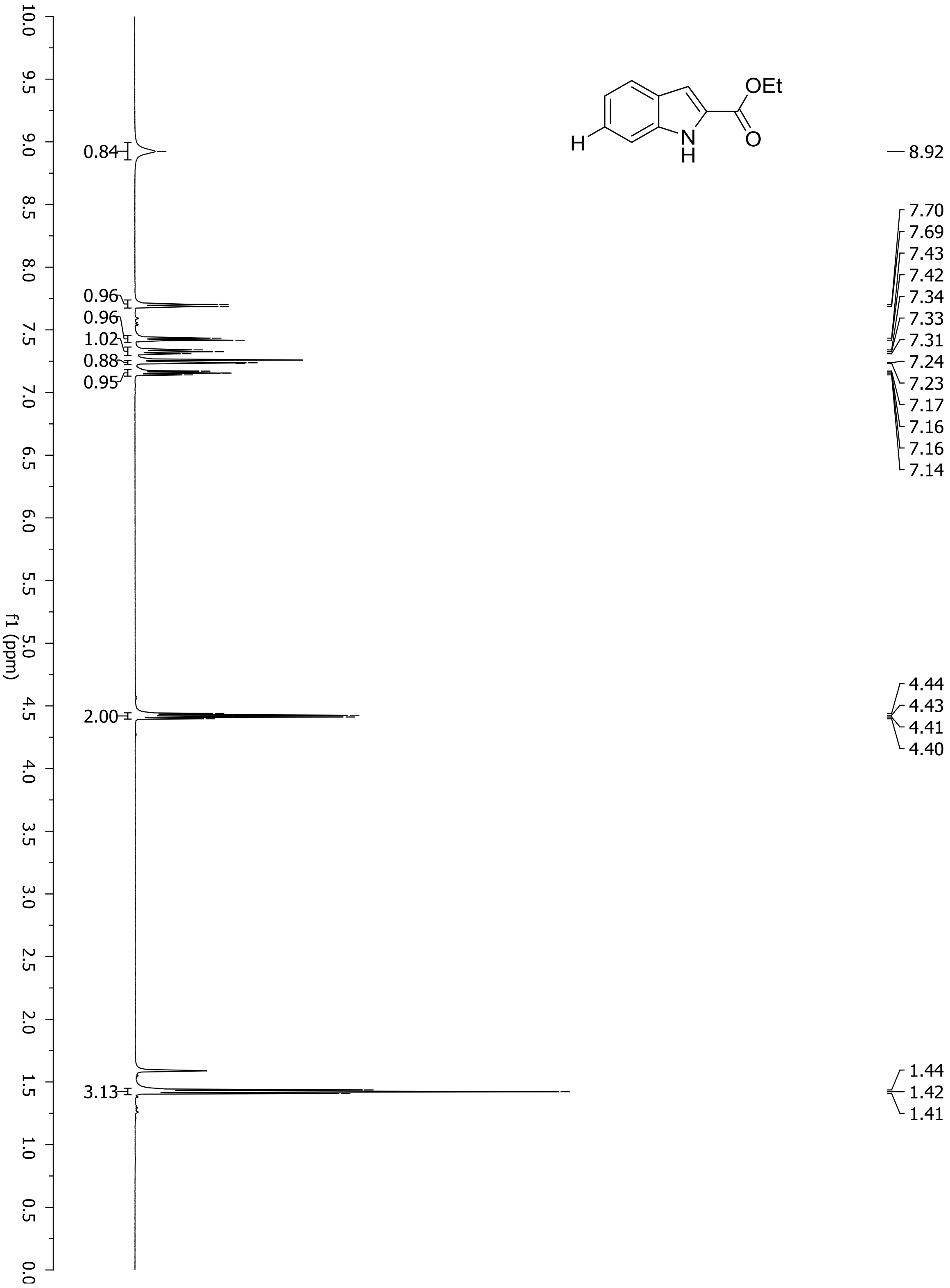


Reduction product from ethyl 6-bromo-1H-indole-2-carboxylate **21**; Proton NMR ($CDCl_3$)



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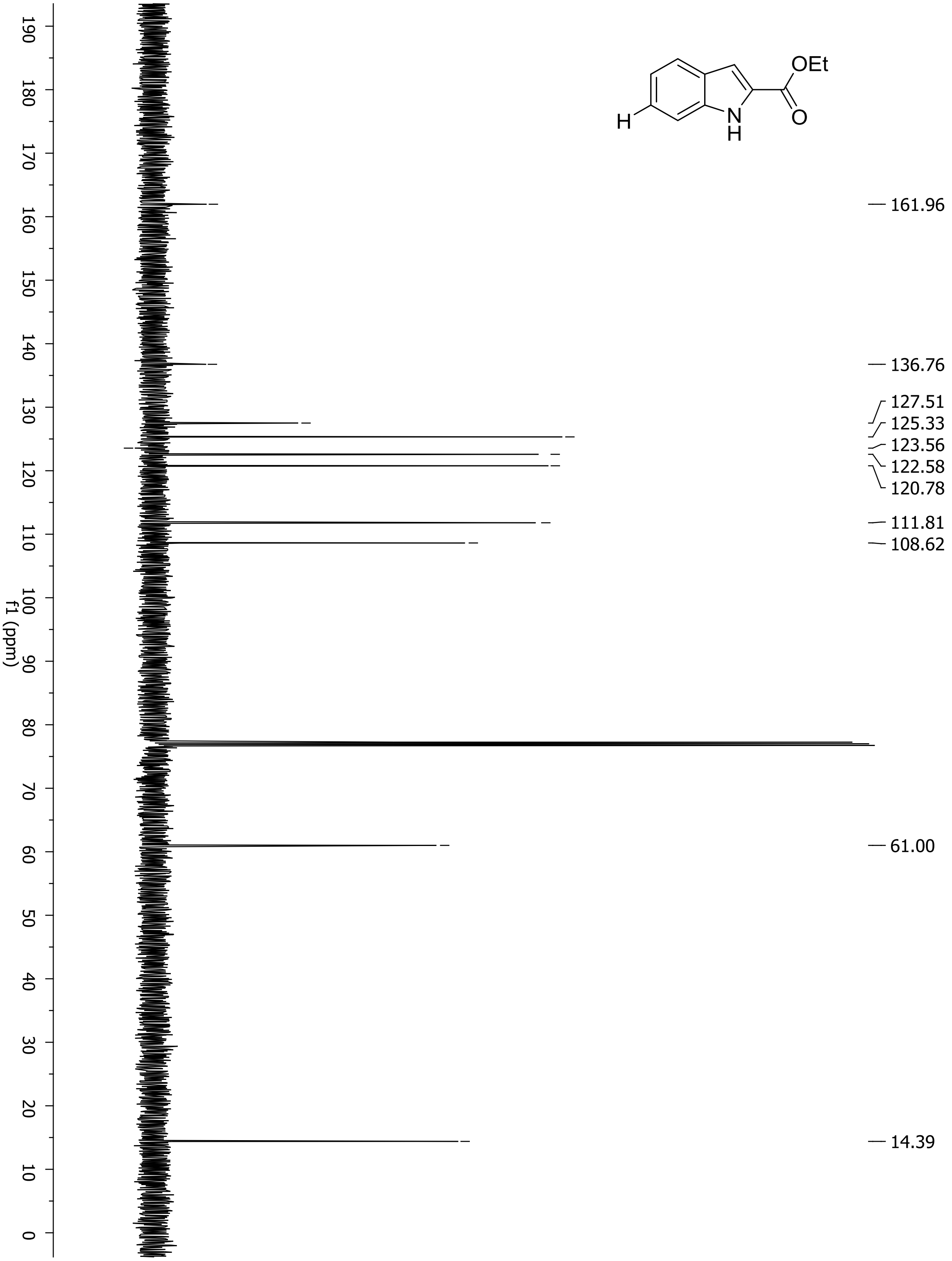

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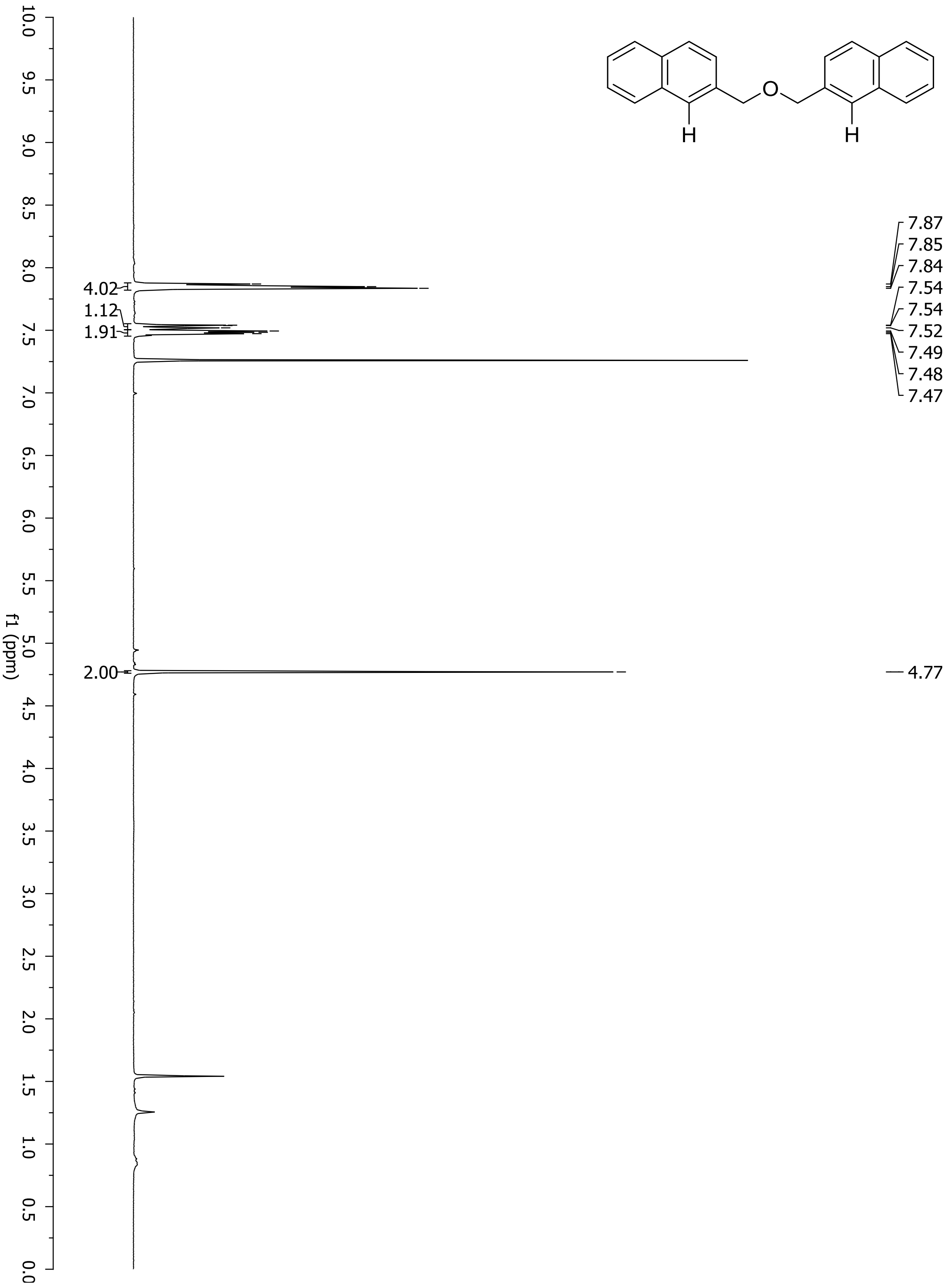

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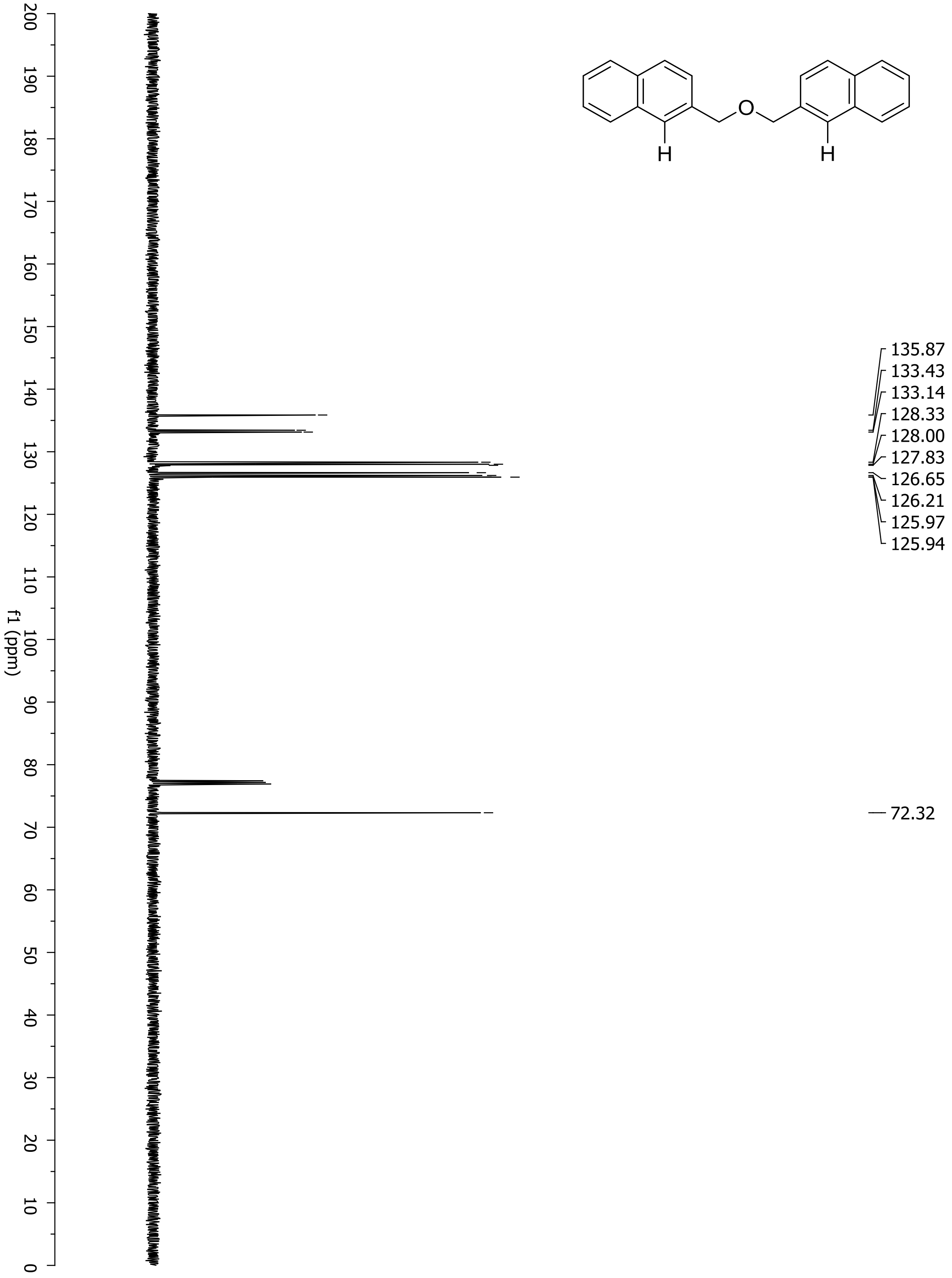
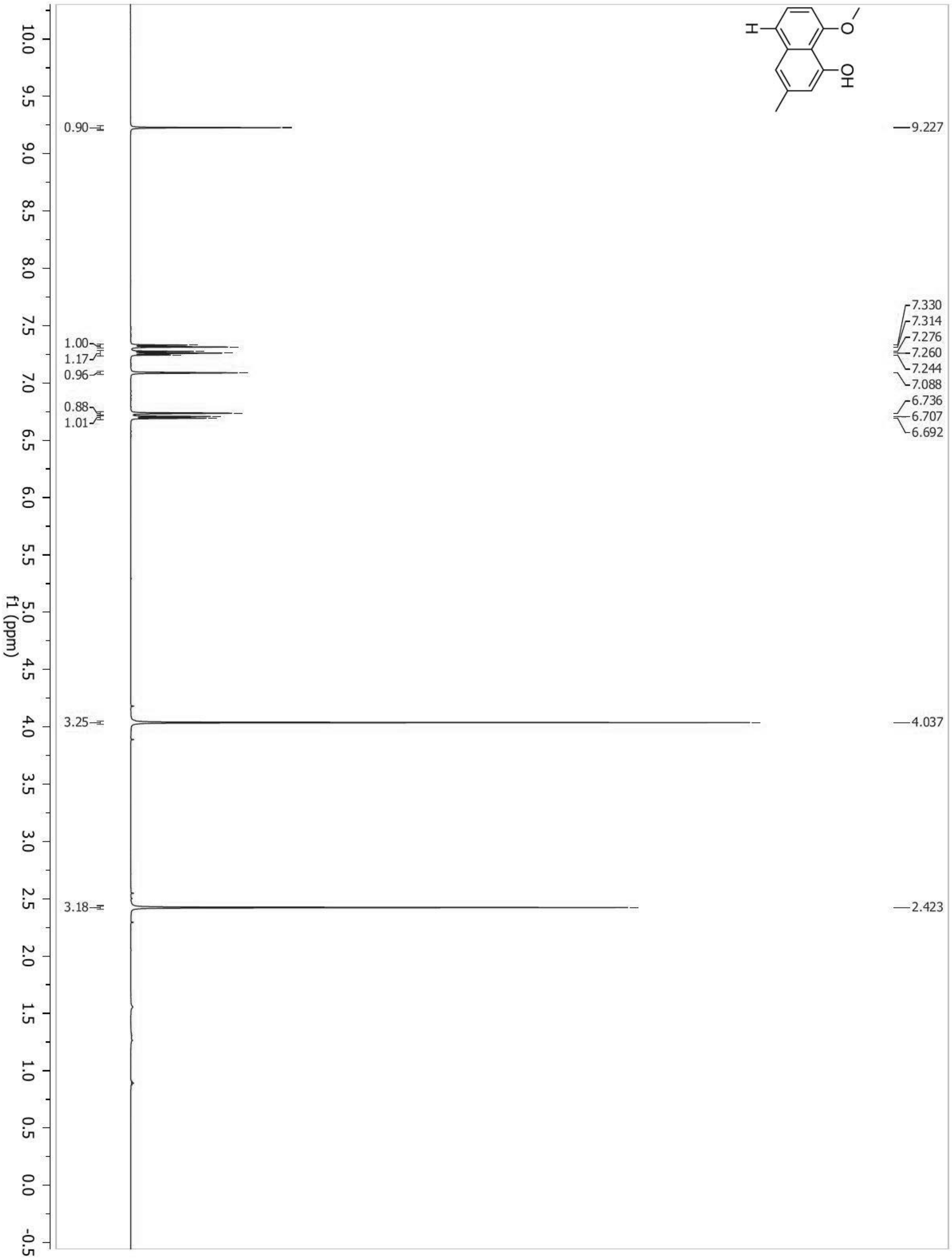


Reduction product from 1-bromo-2-((1-bromonaphthalen-2-yl)methoxy)naphthalene **23**;

Proton NMR



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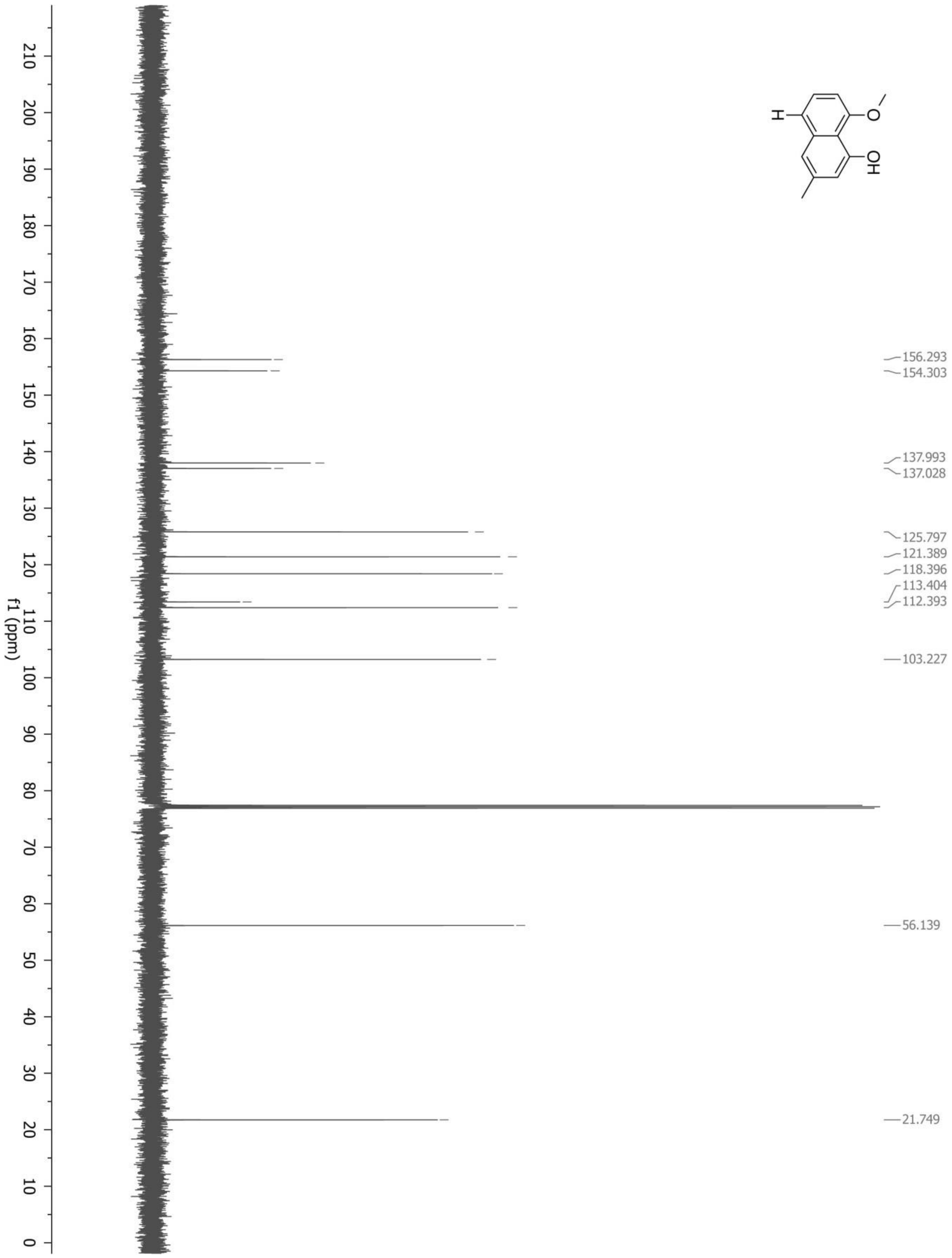
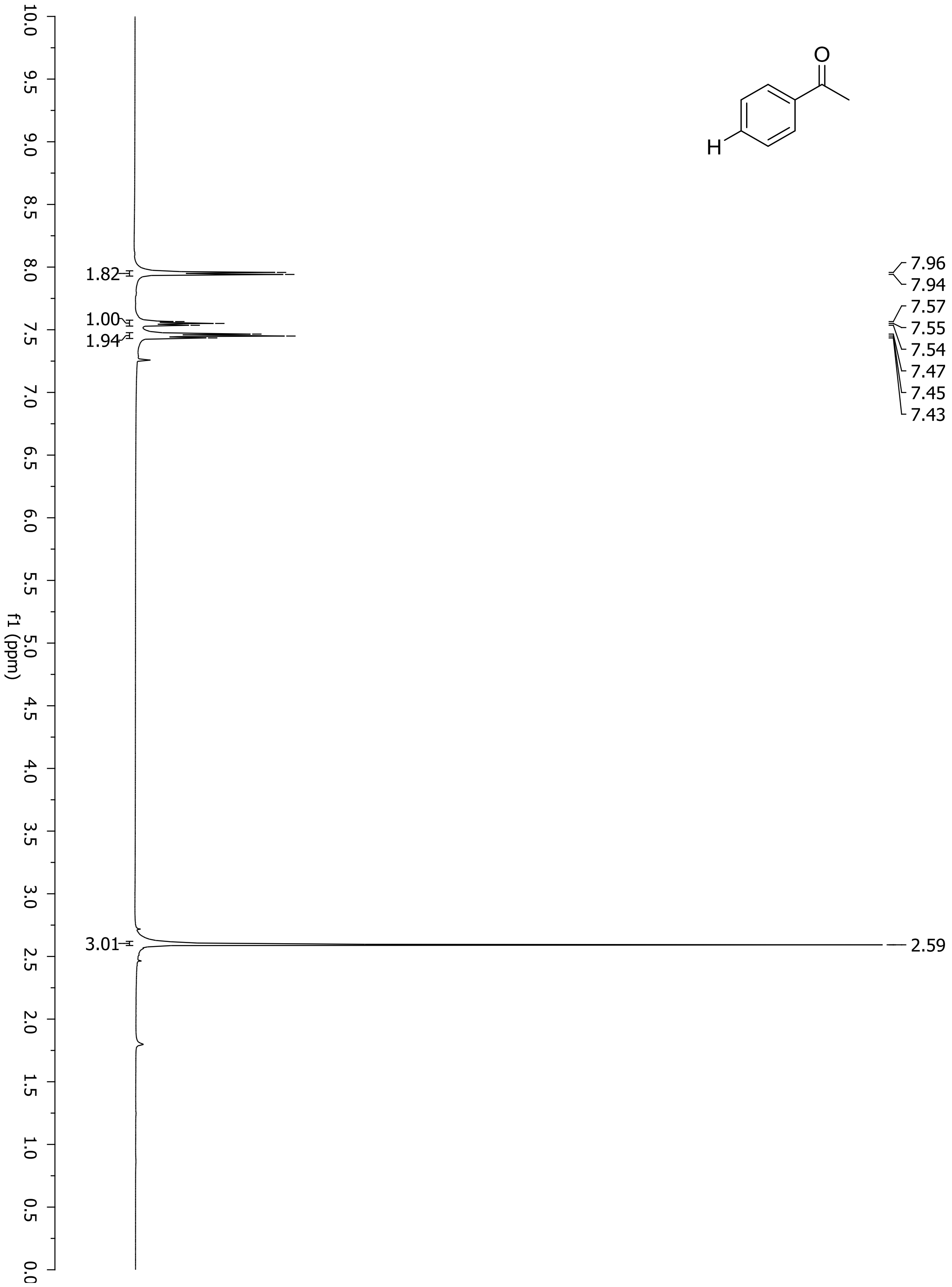
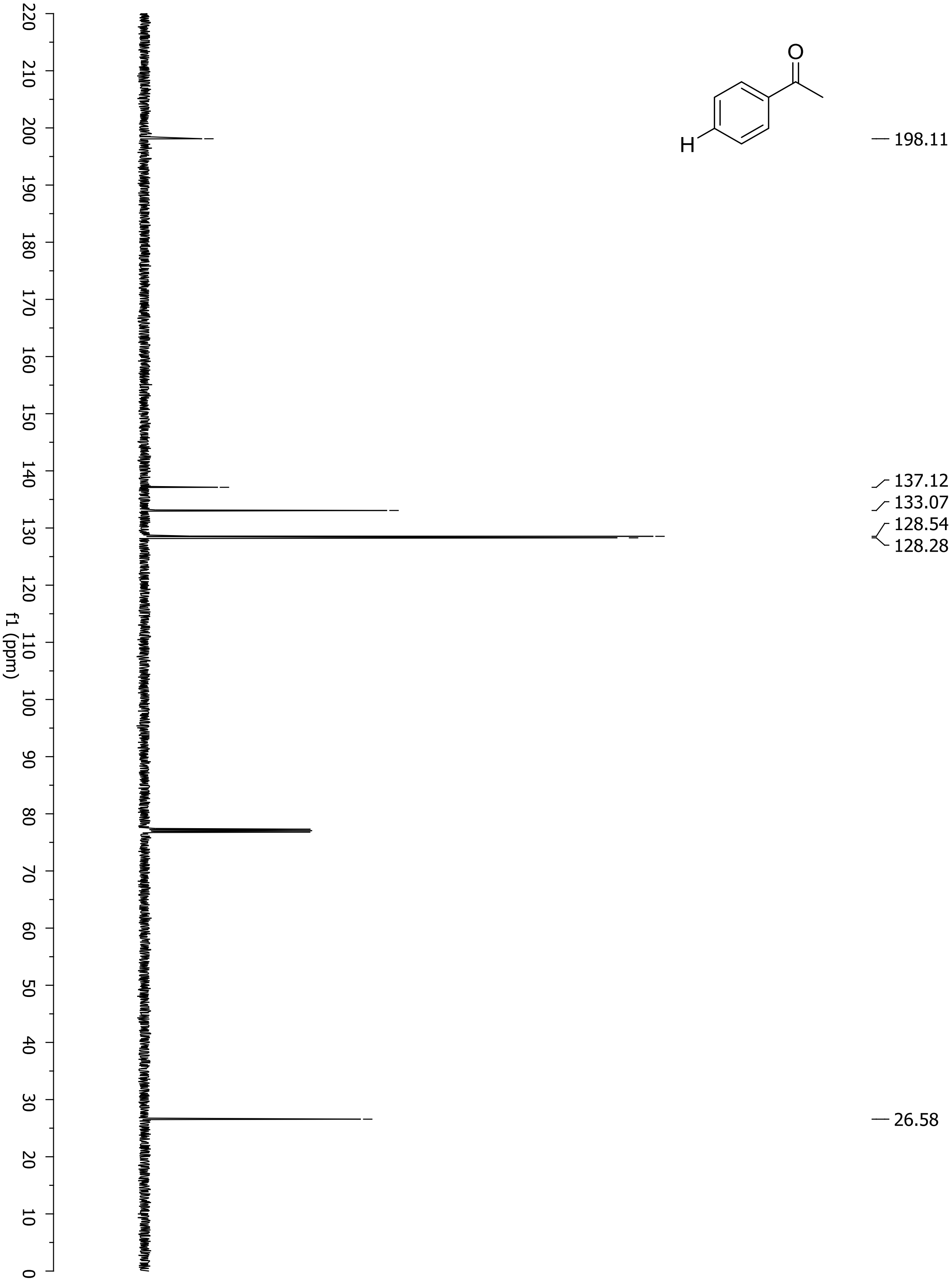
Carbon NMR



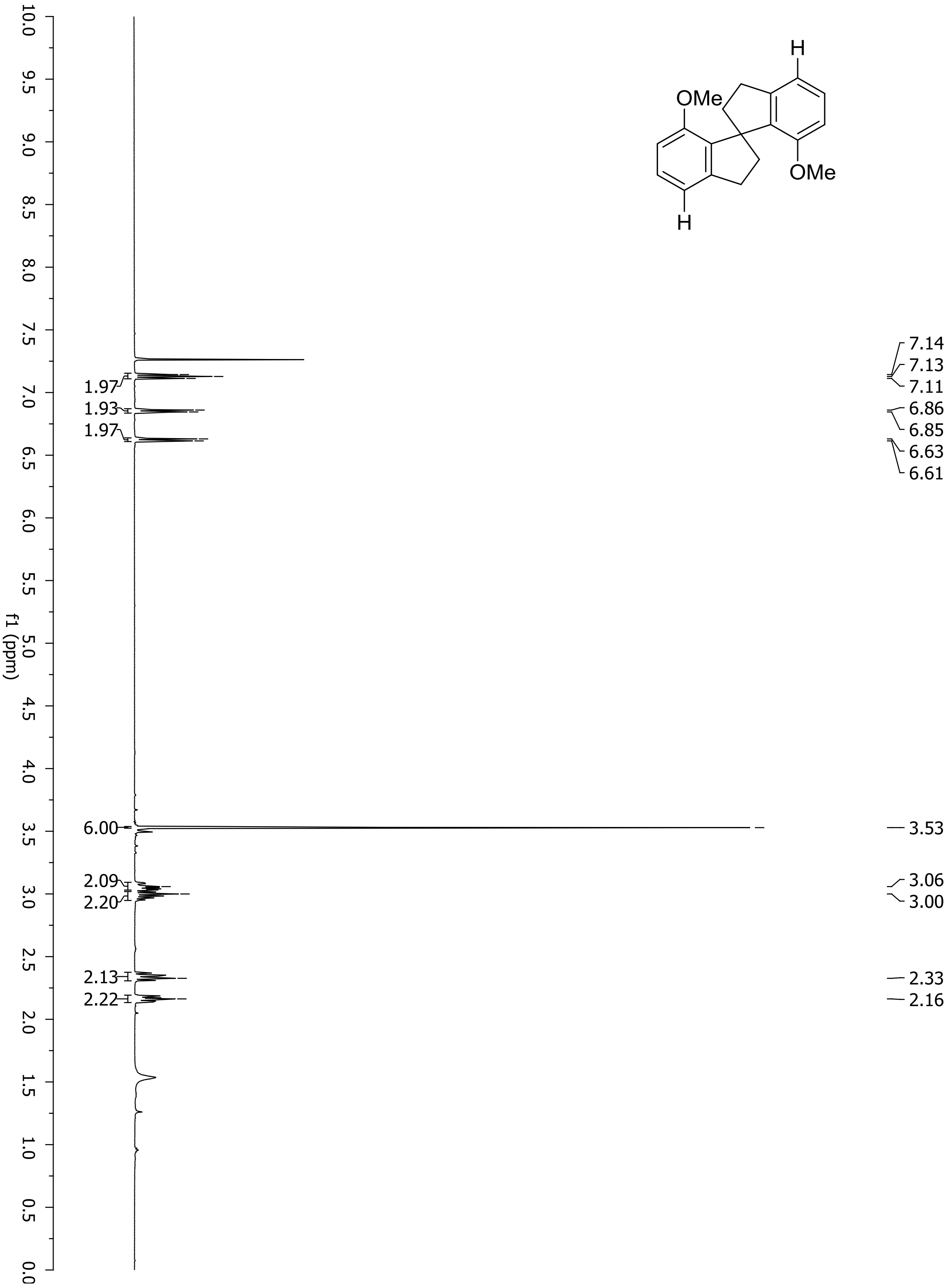
Reduction product from 4-bromoacetophenone **24**; Proton NMR ($CDCl_3$)



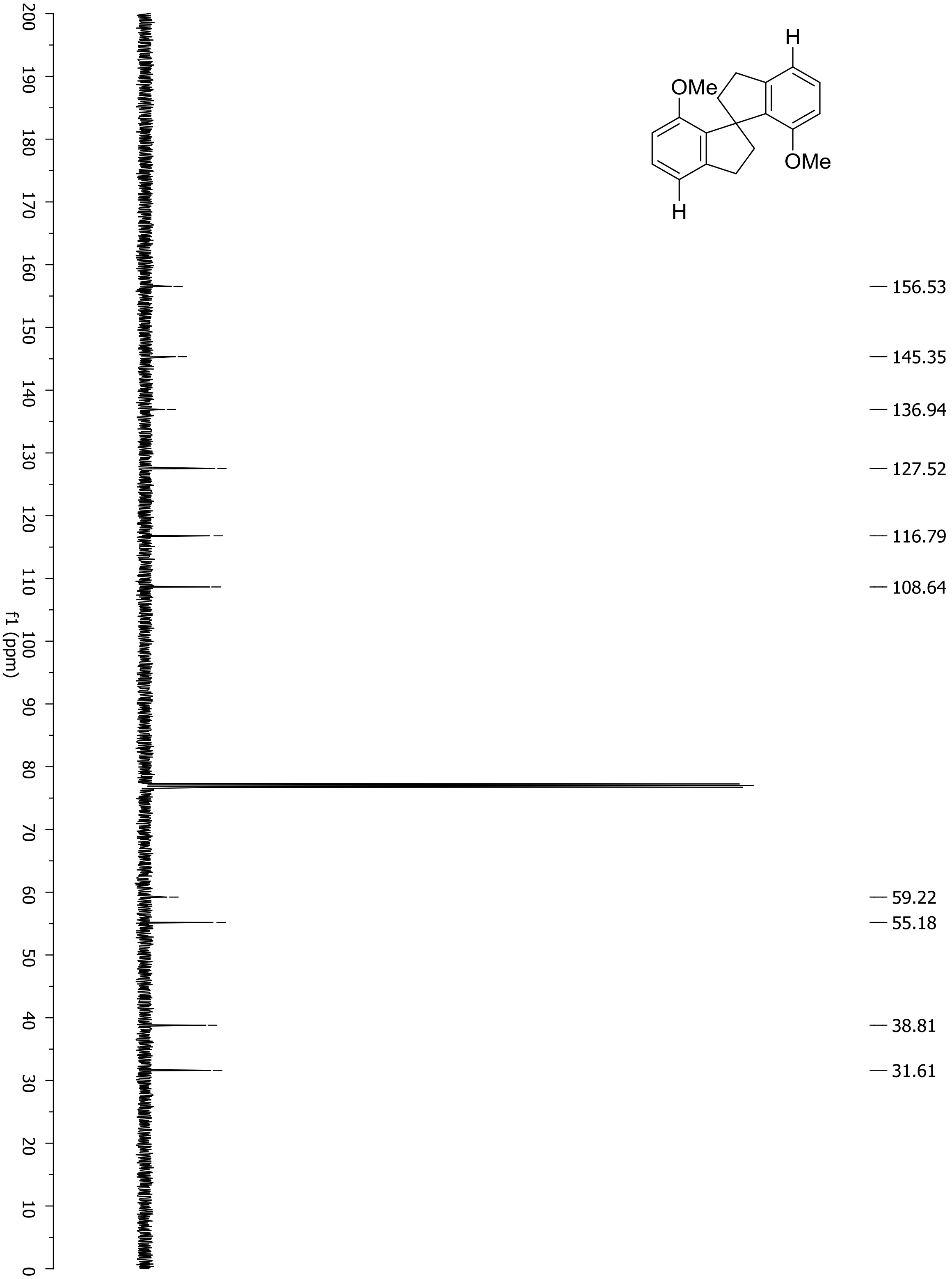
Reduction product from 4-bromoacetophenone **24**; Carbon NMR ($CDCl_3$)



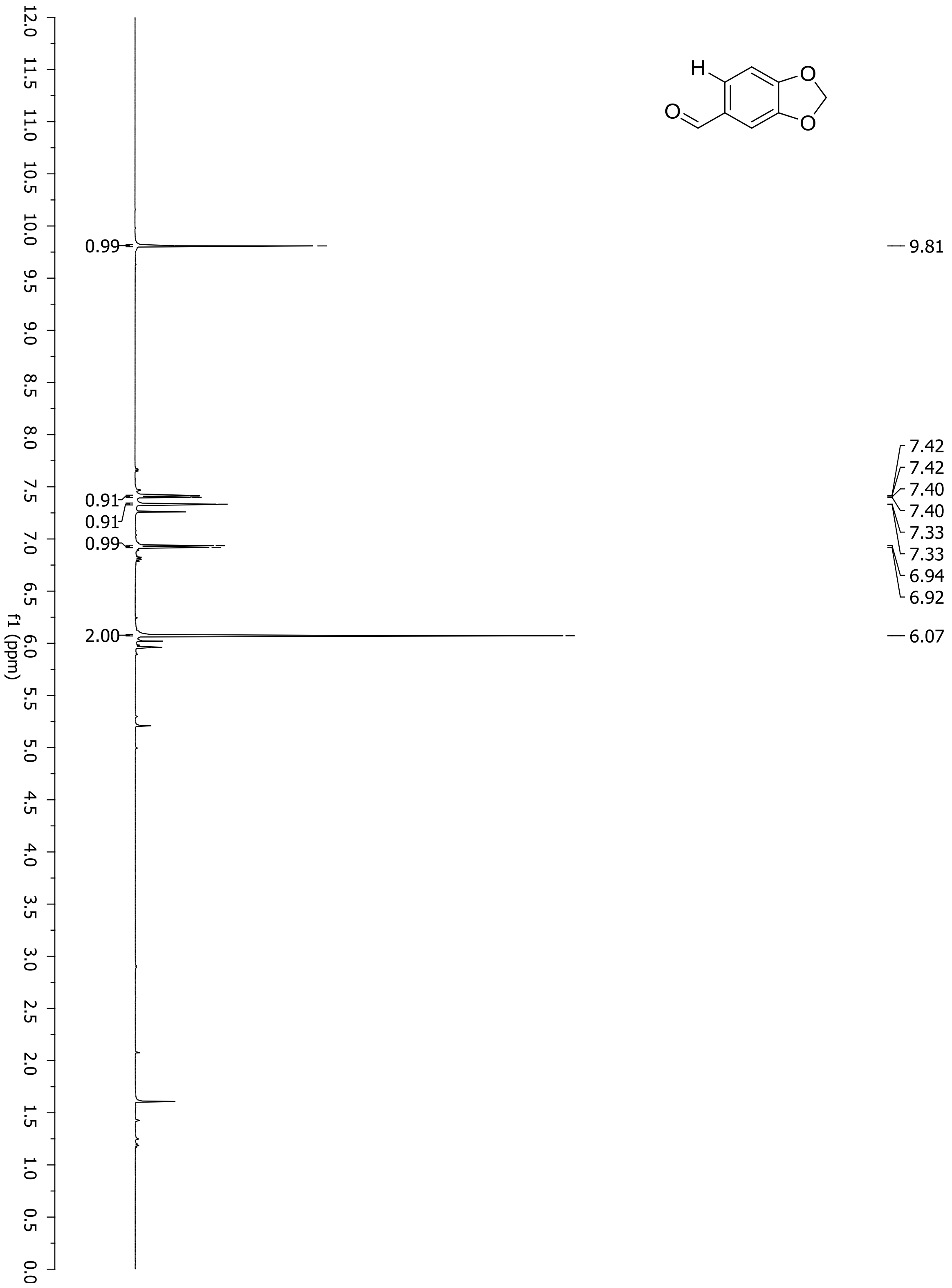
Reduction product from *bis*-bromospirobindane **25**; Proton NMR ($CDCl_3$)



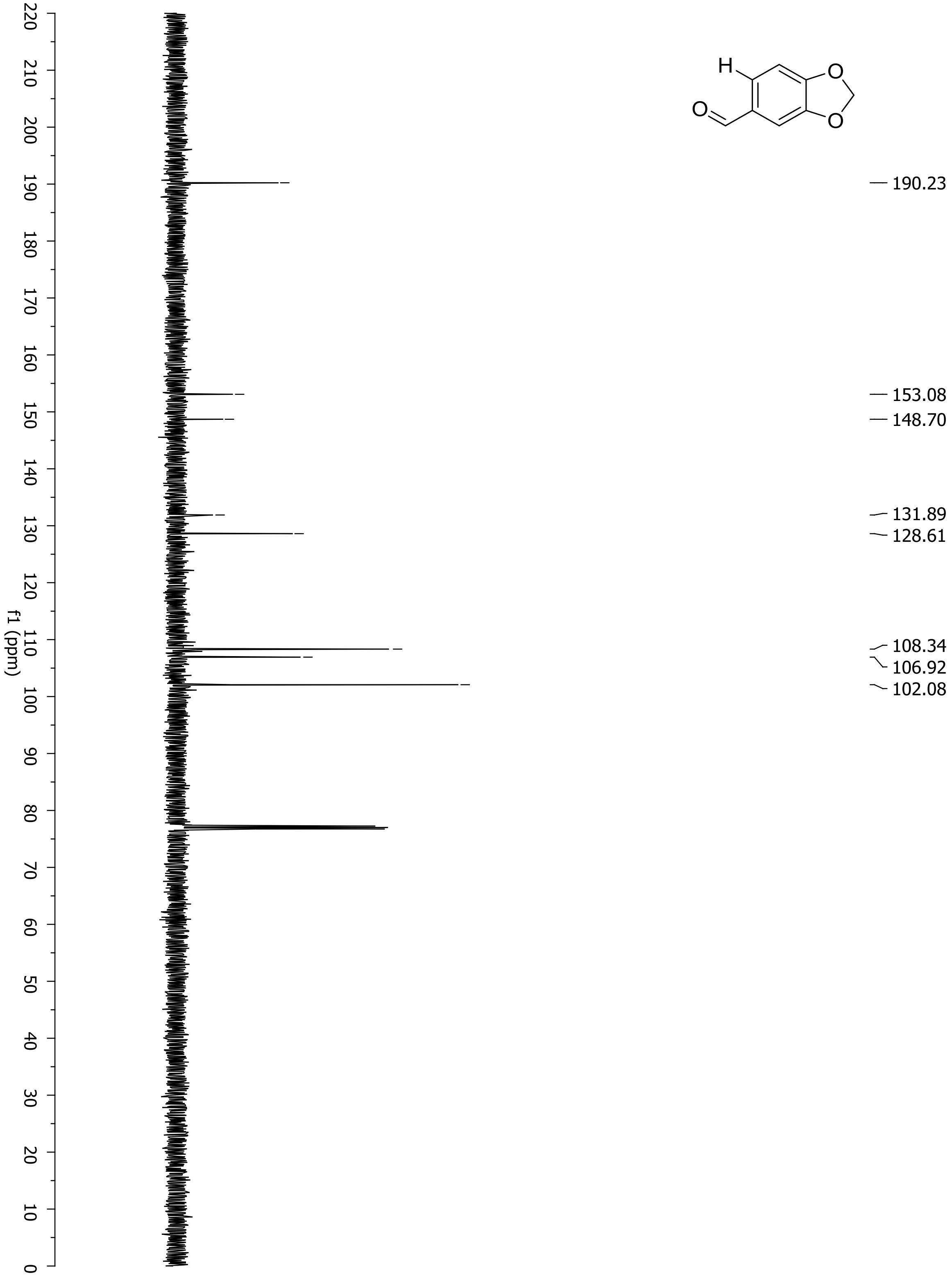
Reduction product from *bis*-bromospirobindane **25**; Carbon NMR ($CDCl_3$)



Reduction product from 6-bromobenzo[1,3]dioxole-5-carbaldehyde **26**; Proton NMR ($CDCl_3$)



Reduction product from 6-bromobenzo[1,3]dioxole-5-carbaldehyde **26**; Carbon NMR ($CDCl_3$)



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IV. *Atroposelective Synthesis Towards korupensamine D*

4.1 Introduction

Chiral compounds and their syntheses have been an intellectual curiosity of organic chemists since the first chiral resolution of tartaric acid in 1848 by Louis Pasteur.[1] This has provided a challenge to synthetic chemists, creating chirality like mother nature has elegantly done over the millennia. Although many of us take chirality of sp^3 centers for granted, it has taken almost 60 years since chemists developed an appreciation for the importance of axially chiral compounds that possess hindered rotation about an aryl – aryl bond thus giving rise to atropisomers.

Optical chirality due to atropisomers were first reported in 1922 by Christie and Kenner[2] through crystal formation of *P*-6,6'-dinitro-[1,1'-biphenyl]-2,2'-dicarboxylic acid **1**. Although at first glance **1** seems symmetrical, it is not due to hindered rotation about the biaryl bond leads to optical rotation of polarized light (Figure 1). This led to the discovery of this unique form of stereoisomerism. The term 'atropisomer' was not coined until almost a decade later by Nobel laureate Kuhn, coming from the Greek words of 'a' and 'tropos' meaning not and to turn, respectively.[3]

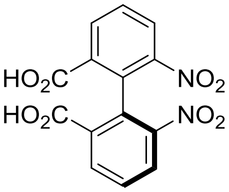

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Figure 1. The first structure **1** to be recognized as having axial chirality

This newly found phenomenon of atropisomers via hindered rotation of a seemingly symmetric aryl – aryl bond was unfortunately given little industrial attention. Only a small number of scientists in the pursuit of academic research were interested until the early 1980's with development of the enantiopure biaryls *bis*-diphenylphosphine binaphthalene (BINAP) (Figure 3). These biaryls represent a valuable class of ligands capable of inducing stereochemical control for a vast number of synthetic transformations. Secondly, the understanding that the configuration of a given biaryl axis is a decisive factor for a molecules physiological properties of biological active pharmacophores[1] and has recently helped further the exploration in atroposelective syntheses.

The assignment of stereochemistry for these atropisomers can be made by viewing down either biaryl axis. Group priority is given identically to that of central carbon sp^3 chirality by atomic number, while the priority along the ring is *ortho* > *meta.* The chiral descriptors *M* and *P* are used for the way they each rotate polarized light, minus or plus, respectively, as shown in Figure 2.

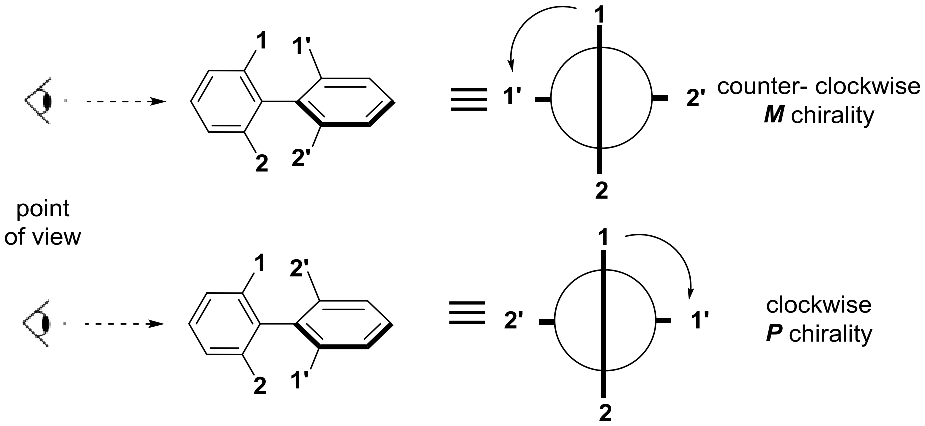


Figure 2. Assignment of atropisomer chirality

From one of the axis the viewer assigns priority to each group as 1 or 2, then the ring out of plane is assigned in the same fashion but using 1’ and 2’ instead. Once the assignment has been made, if 1’ is counter clockwise (left) with respect to 1, then the compound is labeled the *M* atropisomer, while the opposite is true for the *P* atropisomer. (Figure 2)

As well for atropisomers the nomenclature of *R* and *S* become *M* (minus) and *P* (plus), respectively, as shown with **2** and **3** in Figure 3 with the commonly used ligand BINAP.

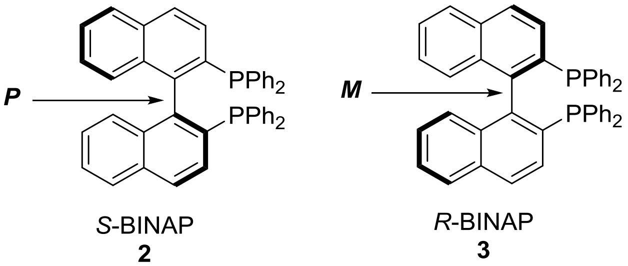


Figure 3. Nomenclature relationship between *R/S* and *M/P* of the BINAP **2** and **3**

Atropisomers can be subdivided into two low level groups; non-bridged and bridged (Figure 4). They can be further classified into isocyclic, fused heterocycles, and hetero biaryls for non-bridged cases (Figure 5) Bridged atropisomers contain lactones, peptides, lignans, and all carbon biaryl[4] (Figure 6).

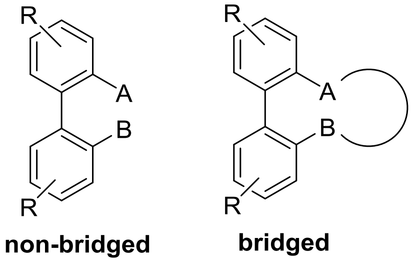


Figure 4. Classification of the two forms of atropisomers

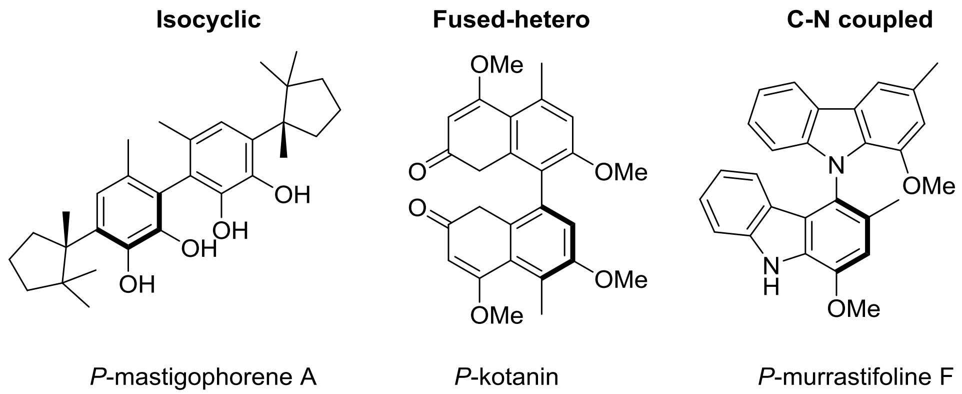


Figure 5. Selected examples of non-bridged biaryls

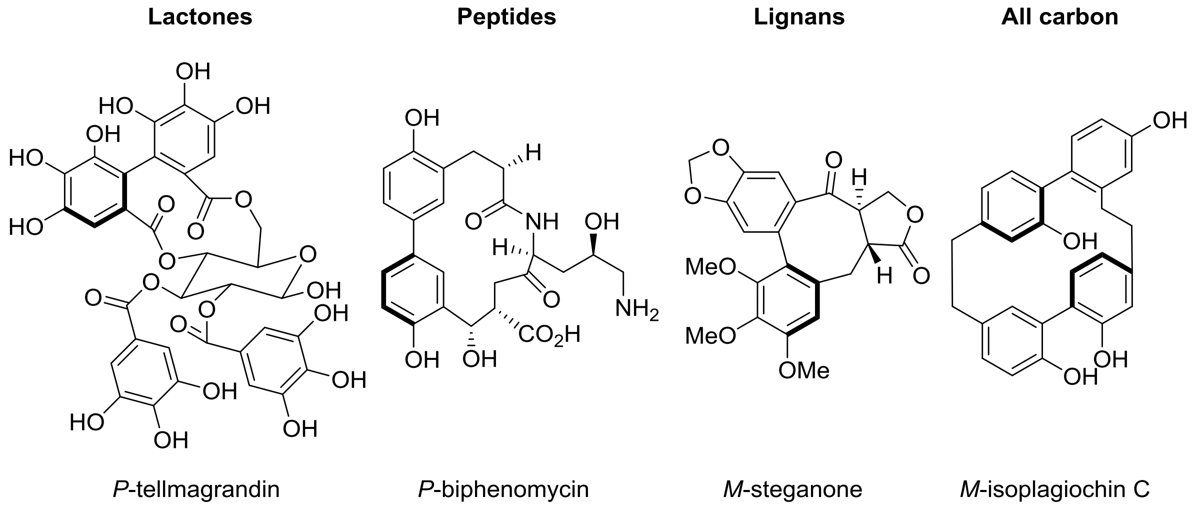


Figure 6. Selected examples of bridged biaryls

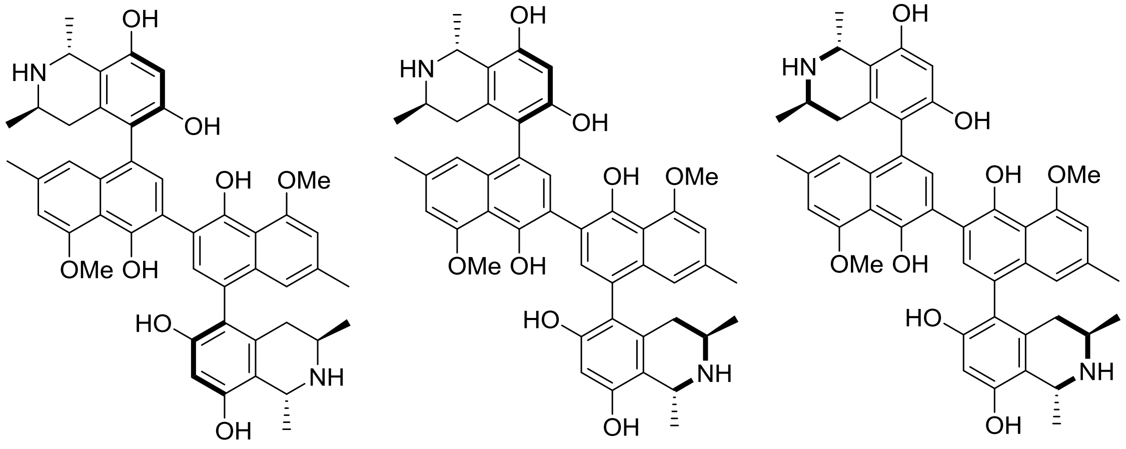
While a vast quantity (>1000) of biaryls with configurationally stable axis have been isolated and identified from nature, only a few have been prepared atroposelectively via total synthesis. That such a small number have been synthesized in an atroposelective manner despite their excellent biological activities for a number of ailments, is due to the high complexity and difficulty of controlling the configuration of the biaryl bond.[5]

4.2 Discovery and Biological Activity

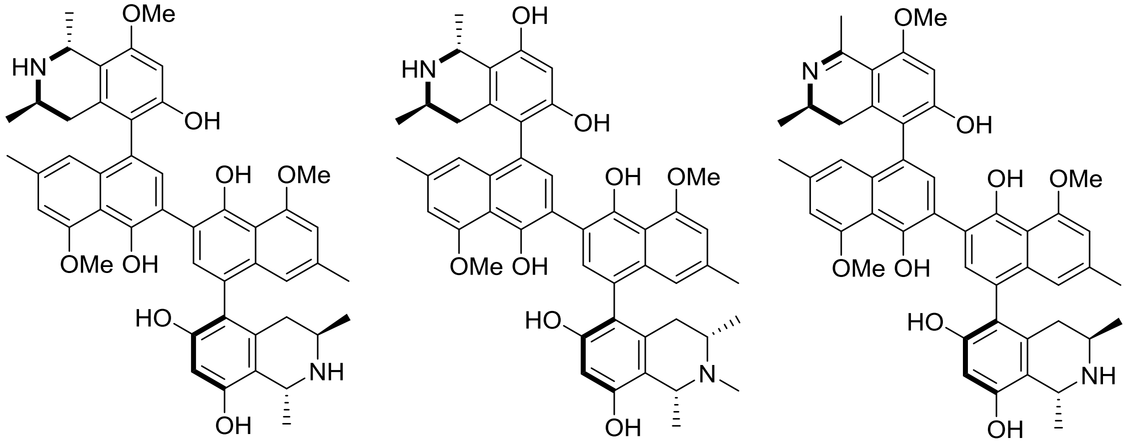
In 1991 Boyd *et al.* discovered a novel atropisomeric pair of compounds that were found to exhibit anti HIV activity, michellamines A **4** and B **5 (**Figure 7) from Korup, Cameroon.[6] These two michellamines are dimers of two naphthyl-tetrahydroisoquinolines linked at the C5 to C8 positions, isolated from the plant source of *Ancistrocladus abbreviatus* collected in 1987. Their connectivity and relative stereochemistry was established through extensive nOe and HMQC NMR studies and found to only differ in their biaryl configurations.[6] Later, the absolute configurations at C1 and C3 were determined by Bringmann *et al.*[7] via ruthenium catalyzed degradation of the tetrahydroisoquinoline ring to its respective simple amino acids alanine and 3-aminobutaric acid; they had previously employed this technique to determine the absolute stereochemistry of an unrelated monomeric naphthyl-tetrahydroisoquinoline dioncophylline A.[8]

Shortly after, the same researchers discovered a third compound, michellamine C **6**.[9] Soon thereafter michellamines D-F **7-9**[10] (Figure 7) were isolated, completing the known michellamine series, along with a new monomer korupensamine E **14**[10] (Figure 8), the structure for which was determined using the same techniques as previously employed.[9] While the michellamine series displayed biological activity against HIV, michellamine B was more effective against HIV-1 and 2 and thus selected as a preclinical drug candidate, although later it was abandoned due to its high toxicity in the liver.[10]

Upon reinvestigation of the original plant source *Ancistrocladus abbreviates* from additional locations in Cameroon, it became apparent that there were subtle differences in the taxonomy from the first reported herbaceous isolation of michellamines,[11] this was later confirmed when the newly collected specimens all disappointingly lacked the presence of michellamines A-F **4-9**. This revealed that the first isolation was from an unknown plant species and prompted a new investigation for the true source of michellamines. Again, from Cameroon the authentic michellamine-containing species was identified and aptly named *Ancistrocladus kourpensis* after the new class of alkaloids discovered from them.



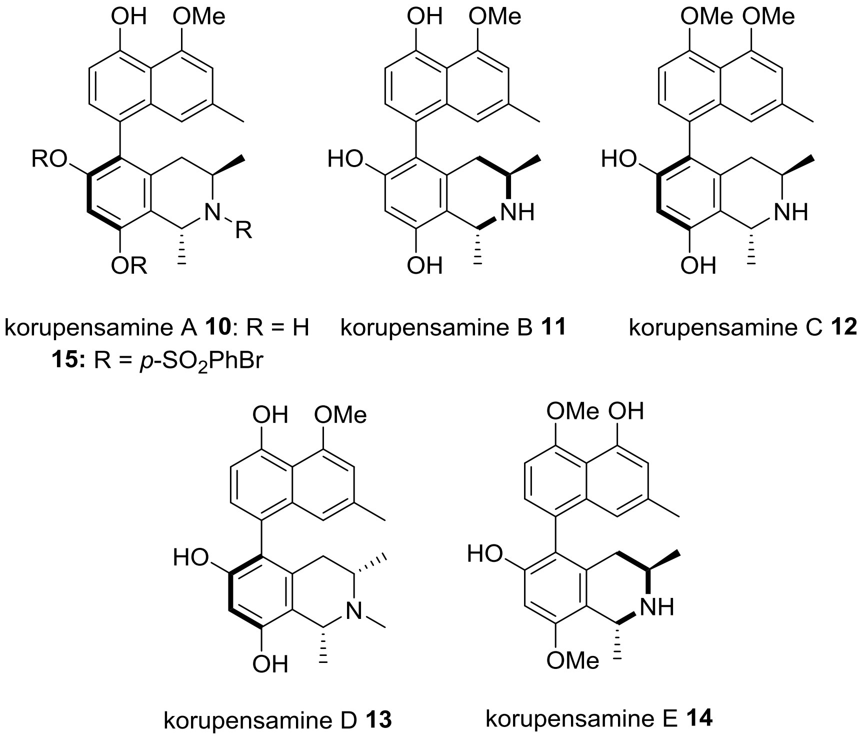
michellamine A **4** michellamine B **5** michellamine C **6**



michellamine D **7** michellamine E **8** michellamine F **9**

Figure 7. michellamines A-F **4-9**

Once the corrected plant species had been identified by Hallock *et al.*, who had scaled up a subsequent isolation for additional michellamines, when several closely related monomeric alkaloids were discovered in 1994.[12] The new alkaloids named kourpensamine A-D (**10-13**) were found to be biosynthetic precursors towards the michellamine series (Figure 8). While these newly discovered natural products did not display anti-HIV properties they showed promising efficacy against malarial parasites in vitro,[13] but their low concentrations in the plant and extreme difficulty in their atroposelective synthesis caused them to be abandoned for other more cost effective drugs.



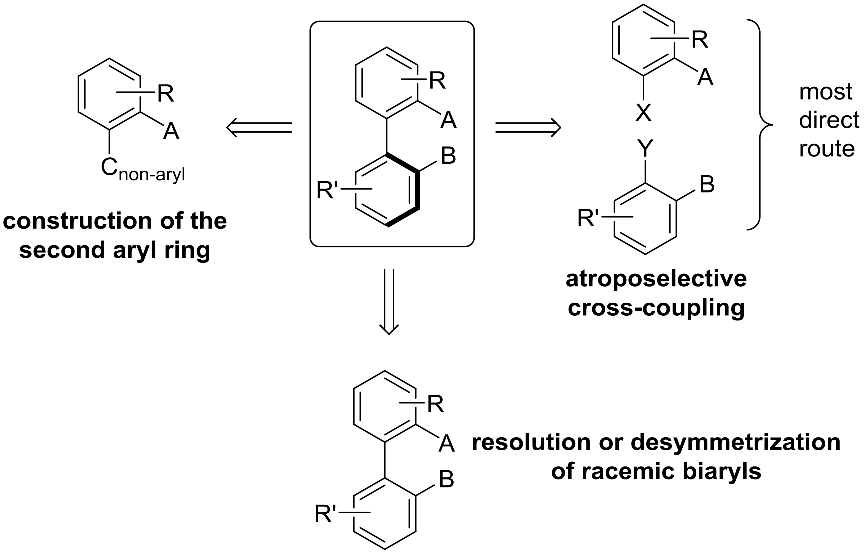
korupensamine A **10**: R = H
15: R = *p*-SO_2PhBr
korupensamine B **11**
korupensamine C **12**
korupensamine D **13**
korupensamine E **14**

Figure 8. korupensamines A-E **10-14**

The absolute configuration of the korupensamine A-E (**10-14**), was determined via nOE and HMBC NMR correlations with comparisons against the previously isolated michellamines A-F[7,10] and further confirmed via ruthenium degradation.[7] Further elucidation was performed on korupensamine A (**10**) as its brosylate derivative (**15**) via single crystal X-ray spectroscopy.[12]

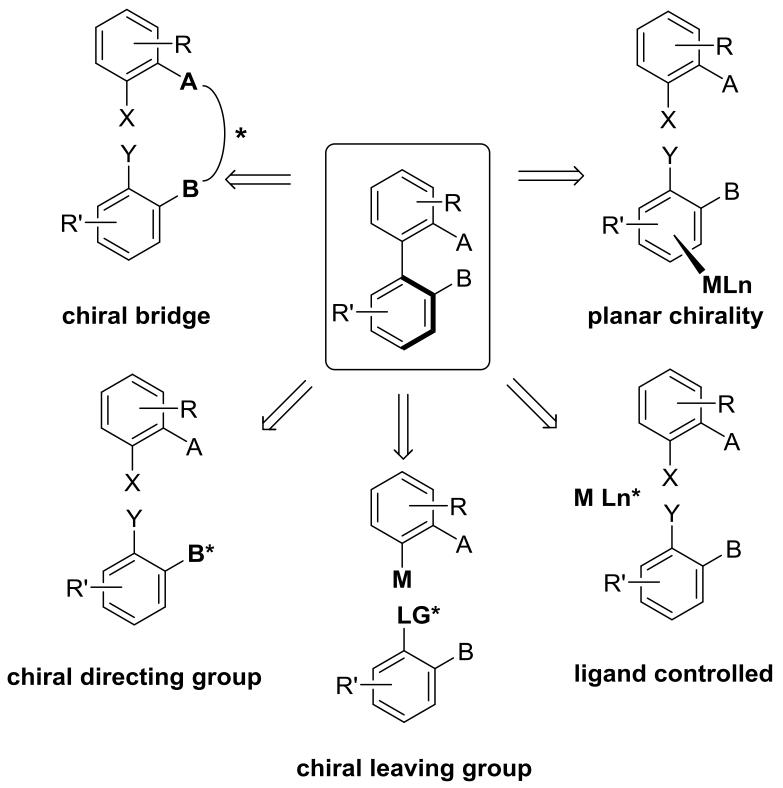
4.3 Prior Work in Atroposelective Syntheses

Currently there are three main methodologies commonly employed for the synthesis of atropisomers: (1) atroposelective biaryl cross coupling; (2) desymmetrization or resolution of atropisomers; and (3) atropisomer via construction of the second aryl ring. Of these three only one efficiently constructs the appropriate atropisomer in the key cross coupling step while the other two rely upon further modification and synthetic effort (Scheme 1).



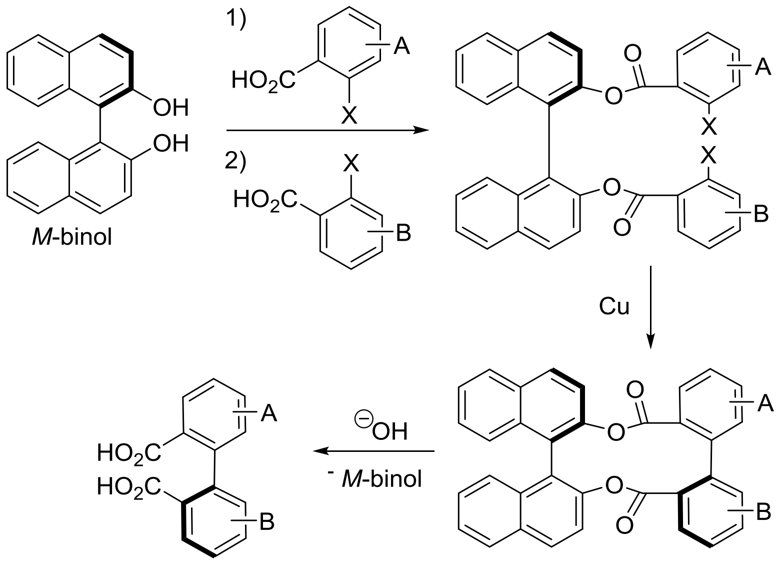
Scheme 1. Three strategies commonly employed in atropisomer synthesis

Atroposelective cross couplings can be subdivided into five categories for bond formation: (1) intramolecular chiral bridges; (2) intermolecular chiral directing groups; (3) chiral leaving groups; (4) ligand control; and (5) planar chirality (Scheme 2).



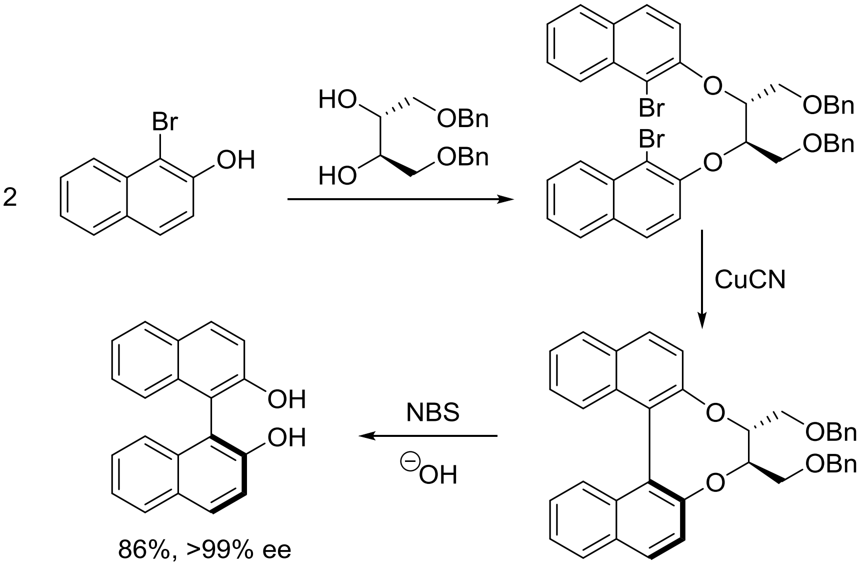
Scheme 2. Five strategies for atroposelective couplings

The use of intermolecular chiral bridges was developed in large part by Miyano *et. al.* in the early 1980's by utilizing ester linkages to *M*-BINOL. This chiral bridge induced the desired atropisomer using a copper-mediated Ullmann coupling and became widely established by the end of the decade[14,15] (Scheme 3). The advantages of this method are the high yields, ability to form both homo- and hetero-coupled products, and the excellent distereoselectivity (>99%) that makes this an extremely versatile method for biaryl formation, especially considering that the bridge may remain intact or cleaved for the final product. A potential drawback is the need for CO_2H groups to append the BINOL bridge which many natural products lack.



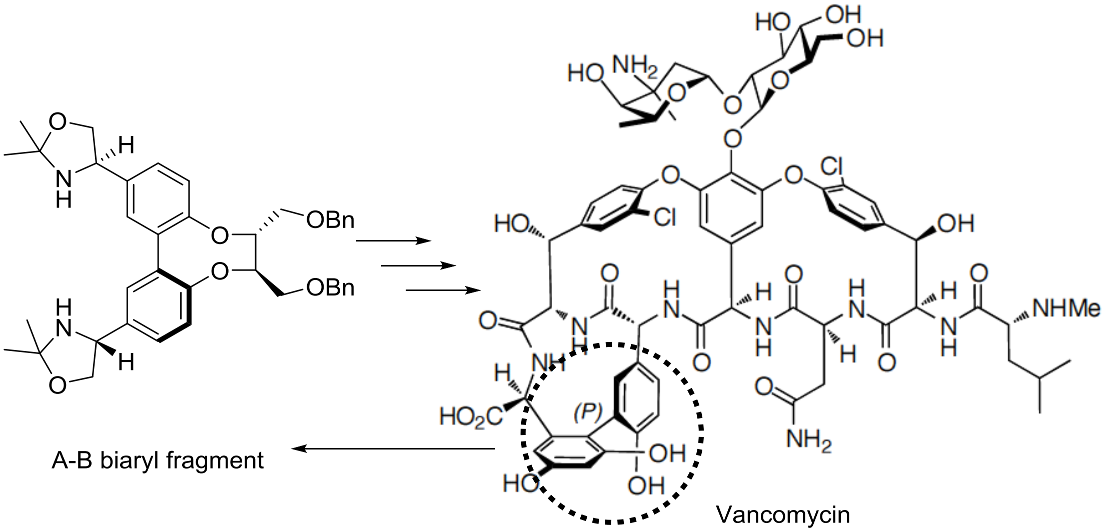
Scheme 3. Miyano's use of chiral bridges

The use of bridges was greatly advanced by our group in the mid 1990's with use of a tartaric acid derived linkage which bears two stereogenic centers further increasing the atroposelectivity (>90%), whereas bridges with only a single stereogenic center typically provide selectivity in the range of 66-90%. The tartaric acid derivative was installed via a double Mistunobu then coupled via Ullmann coupling. The chiral bridge was cleaved with NBS in the presence of hydroxide[16] (Scheme 4).



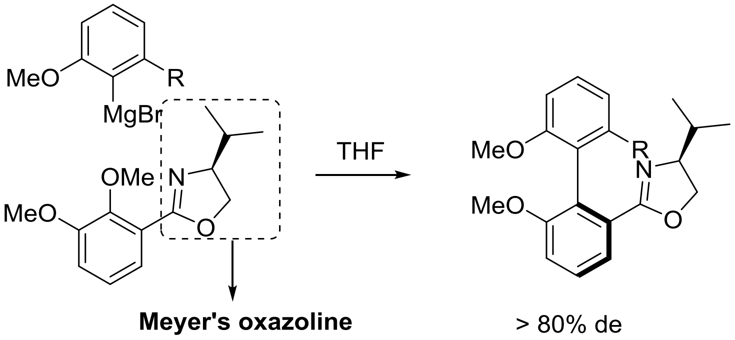
Scheme 4. Lipshutz's derivatized tartaric acid chiral bridge

This tartaric acid derivative method was used for the atroposelective nickel catalyzed synthesis of the AB biaryl system of vancomycin[17] (Scheme 5), possibly one of the most well-known of all atropisomers.



Scheme 5. Lipshutz's atroposelective synthesis of the AB fragment of vancomycin

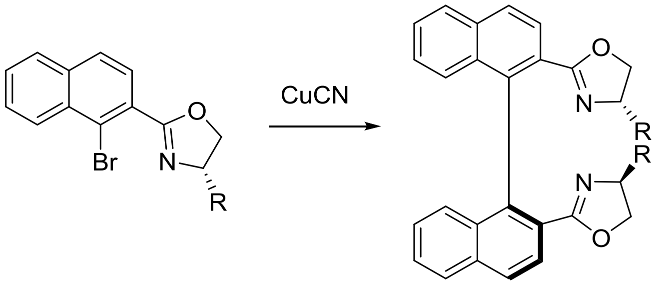
The employment of intermolecular chiral directing groups has also enjoyed a broad substrate scope where only one of the coupling partners needs a chiral auxiliary in order to induce high diastereoselectivity of the biaryl coupling reaction. This chiral information can be transmitted from the *ortho* and *meta* positions. Meyers *et. al.* may have pushed this method further than any other researcher by the development and use of his chiral oxazolines to induce axial chirality through a S_N2Ar reactions with aryl Grignards and a methoxy leaving group (Scheme 6).



Scheme 6. Use of Meyer's chiral oxazoline directing group

The atroposelectivity of this reaction is strongly dependent upon the electron donating character of the R group appended to the aryl Grignard coupling partner.[18] Meyers *et. al.* noted that for substituents with a greater donating ability than that of methoxy, selectivity of > 80% could readily be achieved due to chelation control from the lone pair of electrons of oxygen with the incoming aryl Grignard species.[19] The general requirement of an *ortho* methoxy substituent should not be seen as a limitation considering that many of the biaryl natural products contain a methoxy group in this position or an alkoxy group that is readily accessible through well-known demethylation and etherification methods. This methodology was applied by Bringmann *et al.* for the total synthesis of a number of naphthyl tetrahydroisoquinoline alkaloids. (*vide infra*)

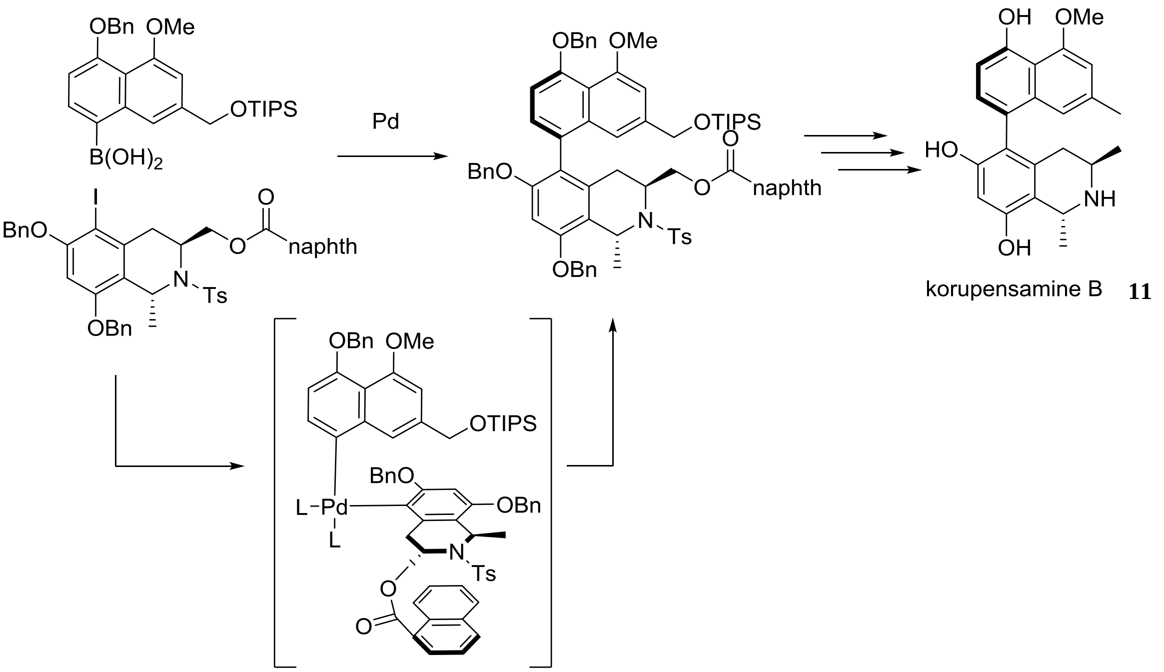
Meyers later expanded this work to the more facile Ullmann coupling (Scheme 7) negating the need to protect functional groups known to be sensitive towards Grignard reagents. The need for *ortho* methoxy groups was replaced by increasing the steric bulk of the oxazoline rings leading to high distereoselectivity (> 80%).[20] One of the large draw backs of this method is the high price and synthetic effort needed to install the *t*-butyl oxazoline chiral auxiliary.



R	% de
Ph	34
*i*Pr	60
*t*Bu	94

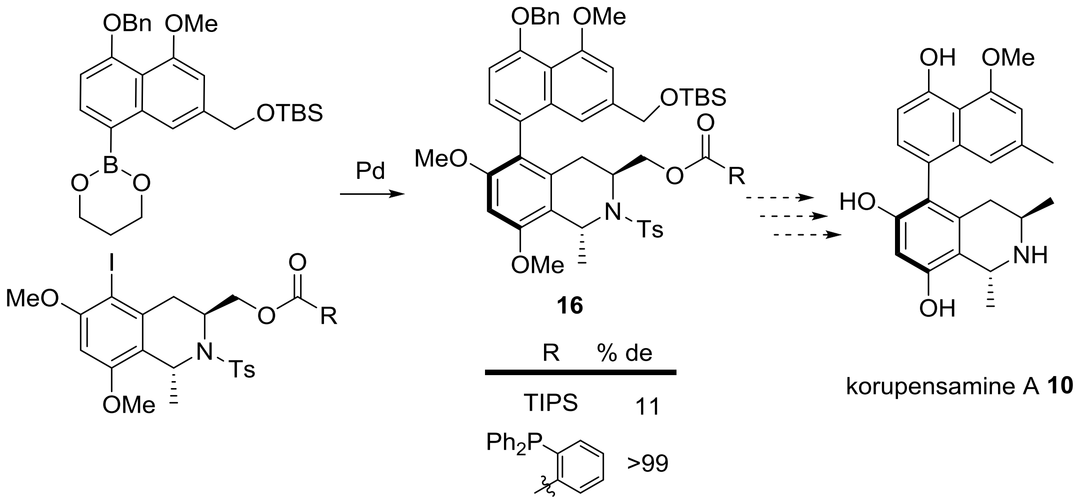
Scheme 7. Meyer's atroposelective Ullmann coupling with chiral oxazolines

Our research group has also been active in the development of atroposelective biaryl ring formation in the arena of intramolecular chiral induction with work in naphthyltetrahydroisoquinoline syntheses. Most recently we have utilized π-stacking (Scheme 8). By taking advantage of the chiral methyl group at C3, a naphthyl unit was installed blocking one face of the aryl iodide coupling partner inducing selectivity of 9:1 for the synthesis of korupensamine B (**11**).[21] This technique allowed for an improvement over the previous synthesis of **11** 1.5:1 by Bringmann *et. al.*[22, 23]



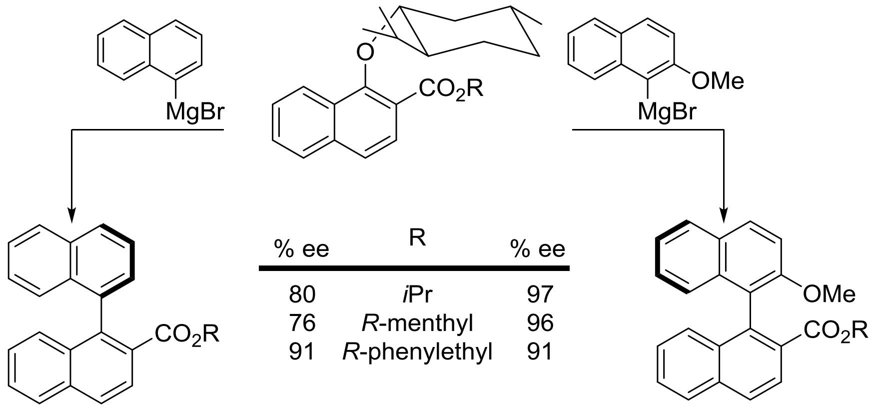
Scheme 8. Lipshutz’s atroposelective route of korupensamine B **11** via π-stacking

We previously employed a similar strategy (Scheme 9) for the synthesis **16** an analogue of korupensamine A **10**. A chelating phosphine was appended in the same fashion as the π-stacking unit for the synthesis of **11**. The effect of the chelating phosphine was confirmed via the exchange of a TIPS silyl ether leading to only a 11% de in contrast to the completely selective >99% de coupling achieved with the diphenylphosphinyl auxiliary.[24] Our two methods of chiral directing groups (pi stacking and chelation control) should allow one to access all of the korupensamines regardless of the axial and C3 chirality.



Scheme 9. Lipshutz’s work in atroposelectivity via chiral chelation control for synthesis of a korupensamine A analog **16**

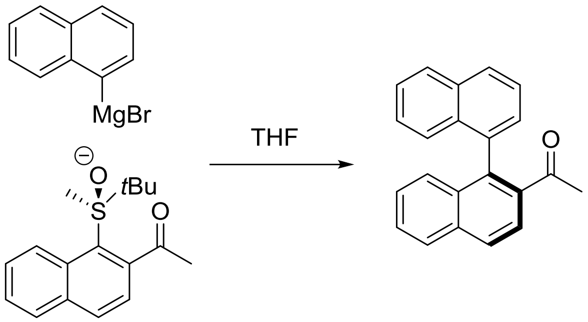
The third method of accessing atroposelective biaryl coupling is enabled by a chiral leaving group used to direct the incoming coupling partner. The advantage of this technique is that in S_NAr reactions the chiral auxiliary introduces the atroposelectivity while automatically displacing the chiral leaving group negating the need for further manipulation in order to remove the auxiliary. In the early 1980’s Cram and Wilson noted that non-racemic *R*-menthol was suitable as a leaving group inducing the desired atroposelectivity for direct cross coupling with aryl Grignards.[25] Less than a decade later Miyano *et al.* developed a complimentary method to that of Cram and Wilson’s by the addition of *ortho* carboxylate groups to the *R*-menthol (Scheme 10) although steric effects did not play a pivotal role as one may have suspected (Scheme 7). As the steric bulk was increased from iso-propyl to phenyl ethyl the % ee remained largely unaffected. It was fascinating that with the addition of the *ortho* methoxy group could completely invert the atroposelectivity from *M* to *P* via chelation control.[26] This same observation was noted by Meyers *et al.* in their work with oxazolines.[20]



% ee	R	% ee
80	*i*Pr	97
76	*R*-menthyl	96
91	*R*-phenylethyl	91

Scheme 10. Atroposelective biaryls via chiral *R*-menthol leaving group

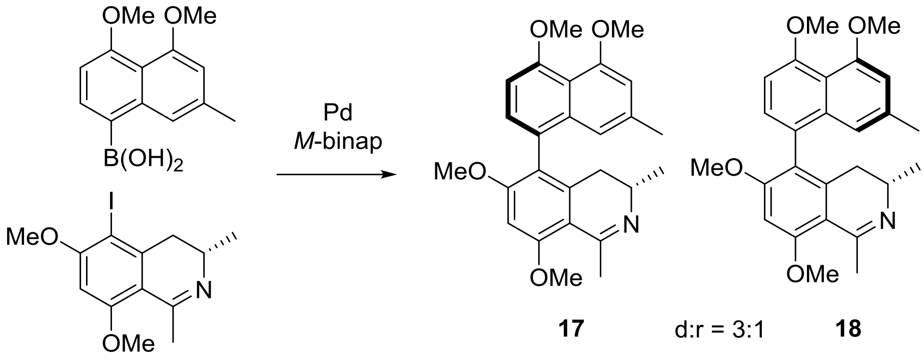
Non ethereal based chiral leaving groups such as sulfoxides were utilized by Baker[27] and Sargent,[28] again in an aryl Grignard S_NAr reaction pathway. (Sheme 11)



Scheme 11. Chiral sulfoxide leaving group for atroposelectivity

Although this method offers stereoselectivity (>90%ee) there are several shortcomings; if the steric bulk *ortho* to the aryl Grignard partner is greater than hydrogen (i.e., any group), no cross coupling reaction was observed; if the *t*-butyl group appended to the sulfoxide contains less steric bulk the atroposelectivity is greatly reduced to <75% ee due to racemization at sulfur; lastly, accessing the enantiopure starting material is very labor intensive, and it is prone to racemization upon purification.[29, 30]

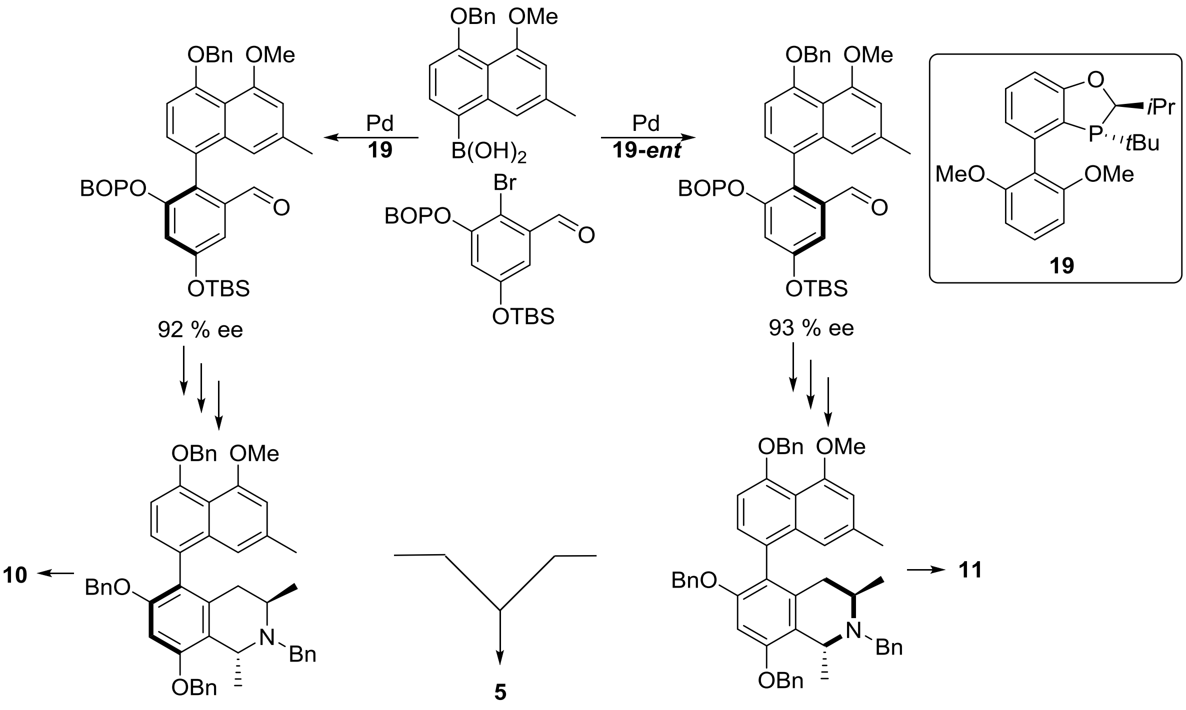
Ligand-controlled synthesis of biaryls has some of the largest advantages in comparison with the other four methods described herein. These key benefits include: the biaryls can be constructed in a single step with all functionalities present, negating the need for further modification; generally proceed under mild conditions, and the chiral information of the ligand is transferred directly to the product in a catalytic nature leading to high atom economy. Despite these promising features the field is still in its infancy due to the complexity and limited generality found among biaryl natural products. Some of the initial attempts by Kumada *et. al.* in the early 1970's with aryl Grignards, *M*-BINAP, and nickel catalysis led to low selectivity (10-25% ee) for the cross coupling of *ortho* substituted naphthalene's.[31] The work by the Kumada group led to an academic investigation for furthering the selectivity of these ligand controlled atroposelective cross couplings to more relevant examples, such as vancomycin.[32]



Scheme 12. Bringmann's ligand-controlled atroposelective approach to **17** and **18**

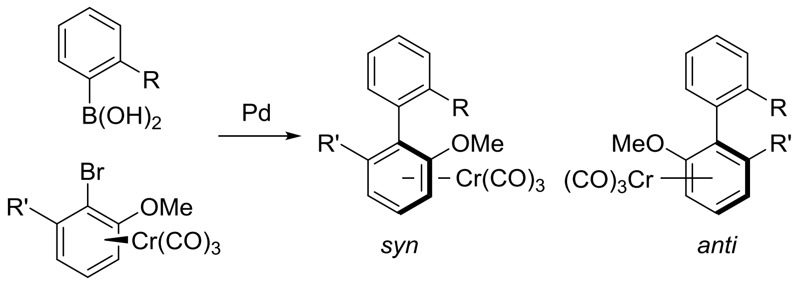
More recently, Bringmann *et al.* have utilized this technique, with *M*-BINAP for the synthesis of ancistrotanzanine B **17** and ancistroealaine A **18,** which differ only in their biaryl configuration (Scheme 12) in modest atroposelectivity (3:1).[33] Although the atroposelectivity is low, it is valuable to note that the cross coupling was the last reaction in the total synthesis, allowing access to the natural product without further de-protection or modification.

The work performed by Tang *et. al.* for the total synthesis of korupensamines A **10** and B **11**, with subsequent dimerization to form michellamine B **5**, was performed in an elegant series of atroposelective reactions. Their design of the chiral monophosphine ligand **19** enabled effective atroposelectivity through numerous biaryl substrates, all with % ee greater than 90%, via the internal coordinating highly polarized BOP group (Scheme 13). Although the THIQ ring was constructed post-Suzuki coupling, an astonishing 93% ee was obtained from the simple coupling partners all enabled by the ligand![34]



Scheme 13. Tang's work for atroposelective synthesis of **10**, **11**, and **5** via chiral ligand **19**

Control of atropisomer induction via a fixed but not covalently bound element of planar chirality, is the fifth main method. It likens its strategy to that of ligand controlled in regards that it is viewed as a traceless stereogenic center capable of inducing atroposelective cross couplings, shown in the generic coupling reactions in Scheme 2. This novel idea was pursued by Uemura *et. al.*[35] with the use of $Cr(CO)_3$ catalyst for the Pd catalyzed Suzuki couplings to generate the *syn* or *anti* products relative to the chromium and *ortho* substituents (Scheme 14). The distribution of *syn* vs *anti* products were obtained in excellent atroposelectivity (>99%) and interestingly, led more to the *syn* atropisomer, with greater steric congestion. They noted if the *ortho* group had a carbonyl present the opposite product (*anti*) could be obtained although at the time researchers were unable to determine a trend from the limited screening data.[35] From their later work it was determined that the reversal in selectivity was due to the racemization of benzaldehyde derivatives to the more stable *anti* isomer under the reaction conditions.[37,38]

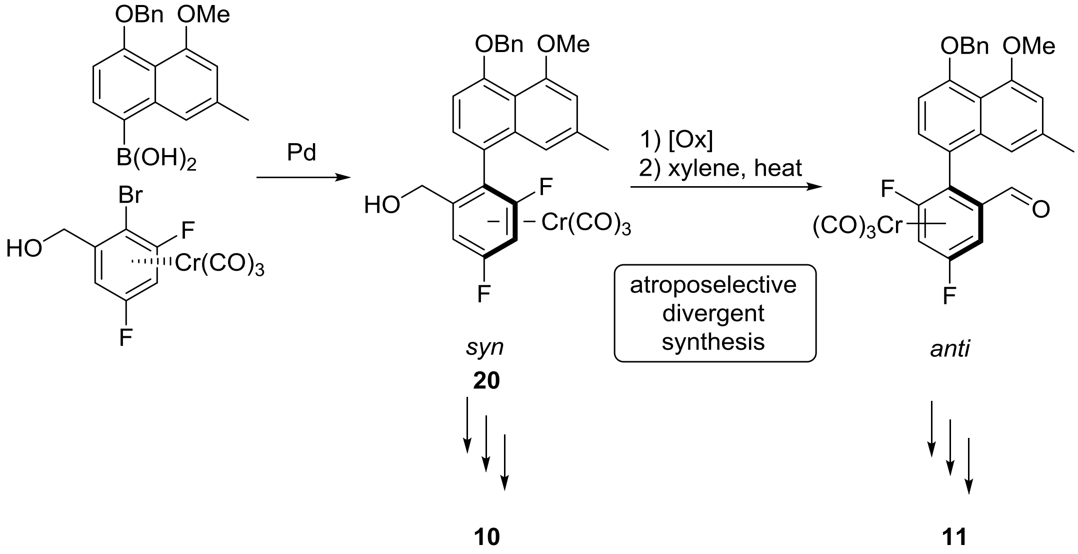


R	R'	*syn:anti*
Me	Me	99:1
Me	CH_2OH	99:1
CHO	Me	1:99
CHO	CHO	1:99

Scheme 14. Uemura’s early work in atroposelective cross coupling with chiral planarity

It was observed that the electron deficient $Cr(CO)_3$ must be placed on the aryl halide coupling partner to facilitate a more facile oxidative addition by Pd. The placement of $Cr(CO)_3$ onto the aryl boronic acid led to low yields and virtually no atroposelectivity.[36]

The same researchers have also developed conditions for isomerization of the aryl-aryl bond of benzaldehyde derivatives to the desired *anti* isomer via heating in an aromatic (toluene) solvent, leading to the more thermodynamically stable isomer.[37,38] This isomerization towards the more stable atropisomer was utilized again by Uemura *et. al.* for the total synthesis of korupensamines A (**10**) and B (**11**). The same late stage intermediate **20** was used for both natural products, as shown in Scheme 15, where **20** was thermally isomerized to the appropriate atropisomer after oxidation of the benzyl alcohol functionality. The most obvious advantage to the use of chiral metal complexes is that both atropisomers can be produced from a single chiral planar precursor, as the work shown in Scheme 15 elegantly displays.



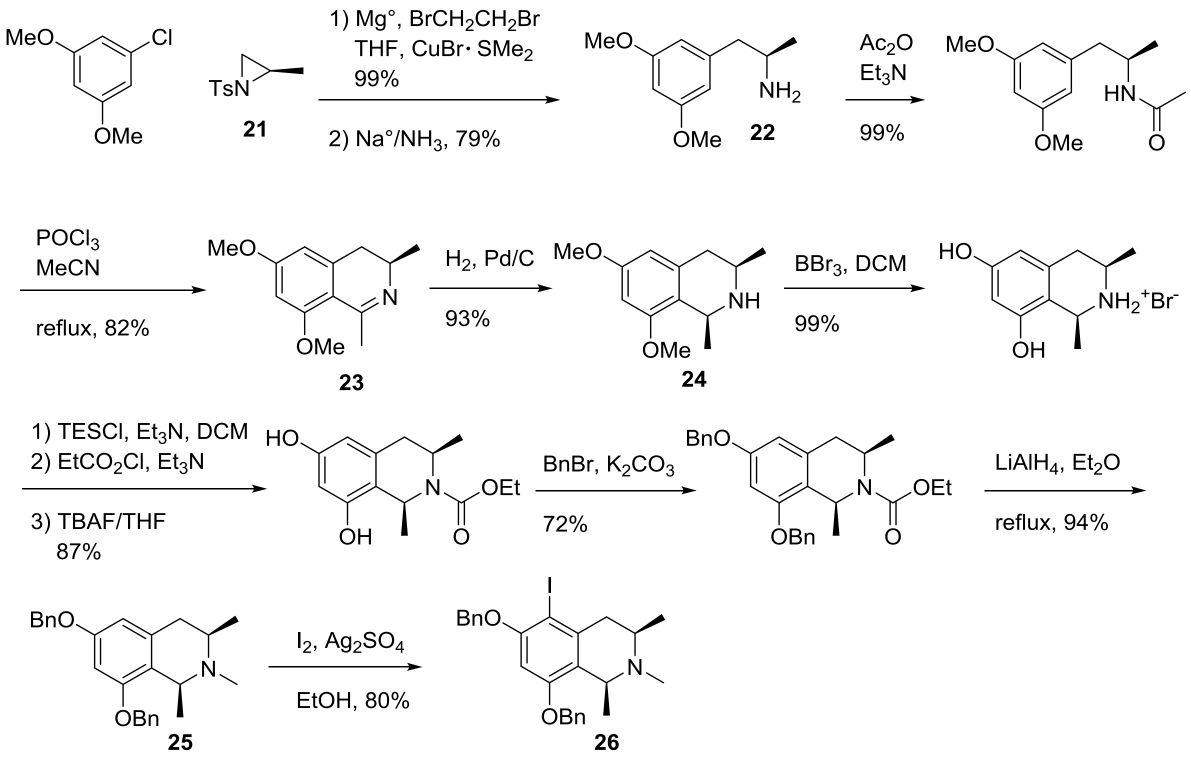
Scheme 15. Uemura's atroposelective divergent synthesis of **10** and **11**

4.4 Prior Work in Total Synthesis of korupensamine D

Korupensamine D is unique in the fact that, (1) of all the korupensamines it is the only one containing both methyl substituents of the tetrahydroisoquinoline ring in a 1, 3- *cis* equatorial relationship, and (2) features a methylated amine (Figure 8). The promising initial anti-HIV properties of michellamine B and recently discovered anti-malarial features of the korupensamines have provided a desire for access to korupensamine D, along with its dimerization to michellamine analogs for biological screenings has fostered need its synthesis. The preparation of authentic korupensamine D has yet to be seen due to its conformation about the tetrahydroisoquinoline ring. The conformation of having both hydrogens in the 1, 3 axial positions has been proven unstable, the easily accessible axial hydrogen is prone to oxidation with atmospheric oxygen as the free base, mild acid-base catalyzed epimerization, Hoffmann rearrangement, and retro-Mannich ring opening epimerization events (*vide infra*) to relive stress at the ‘1’ position forming the *trans* isomer discovered from related works of *cis*-1, 3 dimethyl- tetrahydroisoquinoline ring systems.

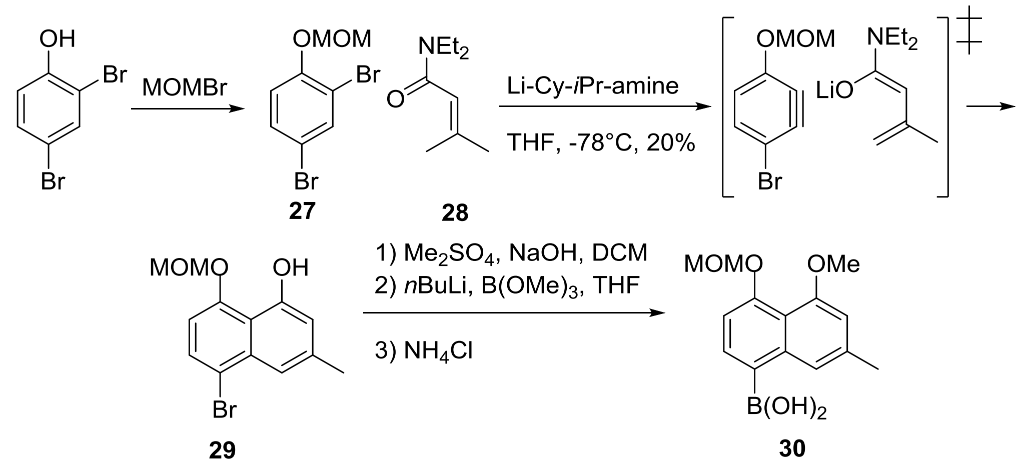
4.4.1 Hoye’s 1st Attempted Synthesis of korupensamine D

After korupensamine D (**13**) had been isolated and identified,[12] the laboratory of Hoye *et al.* pursued the total synthesis of **13** (Schemes 16-18) in enantiopure form in 1996.[39] They presented a new synthetic scheme (Scheme 16) to access the asymmetric tetrahydroisoquinoline from the chiral aziridine **21** readily obtained from D or L valine in three steps[40] allowing access to both *R* and *S* isomers at the C3 center. Asymmetric ring opening via Grignard addition followed by detoslylation formed the enantiopure primary amine **22**, confirmed by Mosher amide analysis. This method of stereo assignment was developed by Bringmann *et al.* in a number of his nonracemic tetrahydroisoquinoline syntheses.[41] After formation of the amide, Bischler-Napieralski cyclization led to cyclic imine **23**. Although the known reduction with $NaBH_4$ had been established, they decided to subject **23** to traditional hydrogenation conditions to give the *cis* configured compound **24** as the only diastereomer (via ^{1}H NMR). Exchange of the methoxy groups for benzyloxy was performed to avoid the late stage use of harsh BBr_3 demethylation procedures, followed by carboamination with concurrent reduction using $LiAlH_4$ afforded the N-methylated *cis* configured tetrahydroisoquinoline compound **25**. Simple iodination with I_2 and Ag_2SO_4 gave the ready to use coupling partner **26**, (Scheme 16) although the enantiomer of the tetrahydroisoquinoline portion of **13**. They had placed both methyl groups in the axial positions unlike the natural product **13** with both methyl groups in equatorial positions very well likely due to its known instability *vide infra* as had later confirmed with our work in tetrahydroisoquinoline ring synthesis.



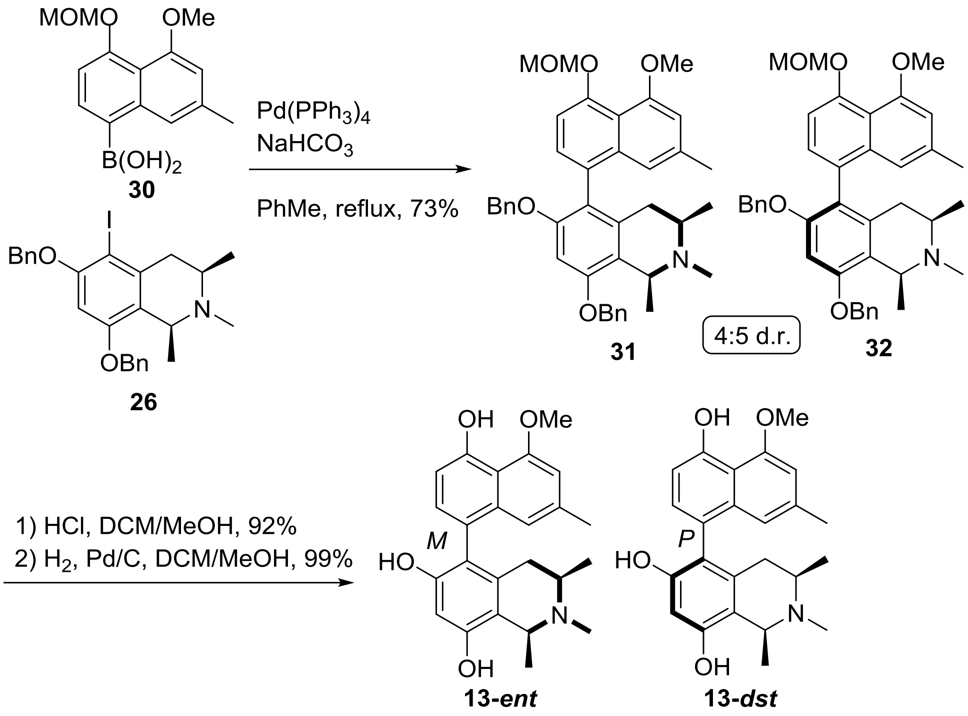
Scheme 16. Hoye’s original tetrahydroisoquinoline synthesis en route toward korupensamine D **13**

They obtained their naphthylene coupling partner in a short four step route previously utilized for the synthesis of michellamines A-C, **4-6**.[42] (Scheme 17) The MOM protected dibromide **27** was easily prepared from 2,4-dibromophenol. They had hypothesized that **29** was formed from the benzyne intermediate of **27**, formed with lithium cyclohexylisopropylamide and N,N-diethylseneciamide that underwent a Diels Alder transformation with the enolate of **28**. Although only a 20% yield of **29** was achieved, the procedure is very reproducible with similar overall yields compared to previous naphthylene syntheses. Facile O-methylation followed by borylation affords their naphthylene partner **30**.



Scheme 17. Hoye's general naphthylene synthesis for korupensamines and michellamines

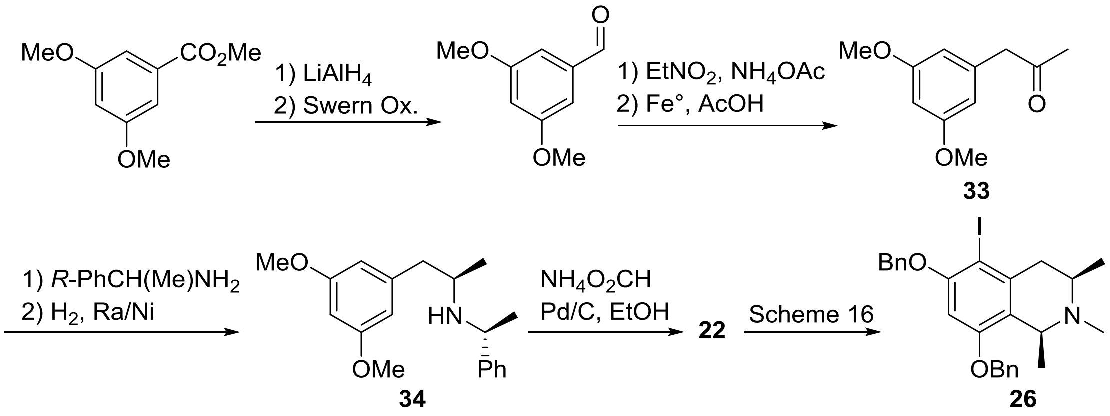
With both coupling partners now in hand they carried out a routine Suzuki coupling (Scheme 18) to obtain korupensamine analogs **31** and **32** in a combined 73% yield, although with essentially no atroposelectivity (4:5). Both analogs were subjected to hydrolysis of the MOM ether and hydrogenation of the benzyl groups which provided the two atropisomers **13-*ent*** and **13-*dst***. Researchers determined compound **13-*dst*** to be the diastereomer, and while **13-*ent*** had identical ^{1}H NMR to **13** the specific rotation had the opposite sign but same magnitude confirming it as an enantiomer. Nevertheless, their work can be applied to the synthesis of structural and analogs of the korupensamines and their respective dimeric michellamines.



Scheme 18. Hoye's first attempt to synthesize kourpenamine D **13**

4.4.2 Hoye's 2nd Attempt: Synthesis of korupensamine D

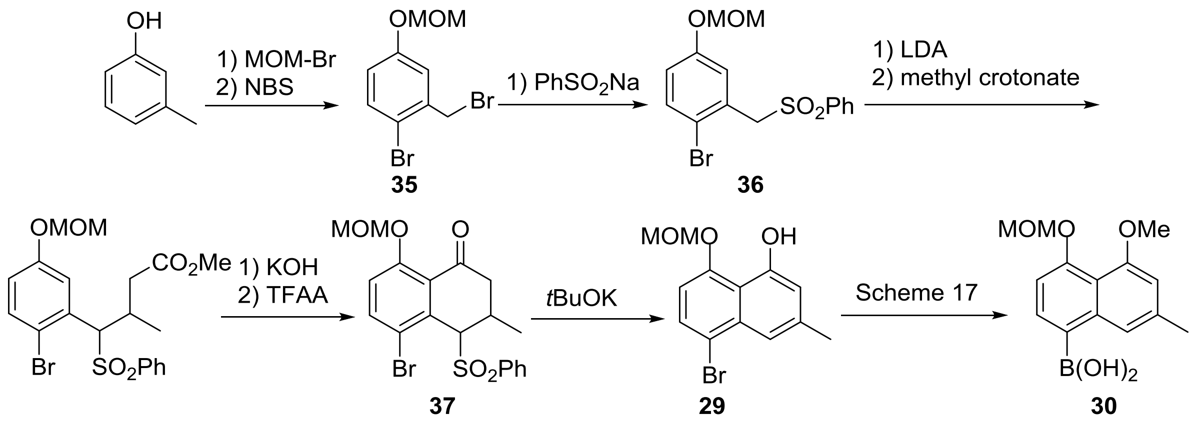
Since Hoye's first attempt of the total synthesis of korupensamine D[39] which yielded its enantiomer **13-*ent*** and its diastereomer **13-*dst***, they have reinvestigated the synthesis in efforts of a more efficient tetrahydroisoquinoline synthesis.[13] Instead of utilizing the previously used chiral aziridine **21**, they employed a chiral reductive amination as developed by Bringmann *et al.*[43] on the phenyl-2-propanone (P2P) derivative **33** (Scheme 19) with *R*-1-phenylethyl amine to yield the C3 chiral intermediate **34**. Upon hydrogenation with ammonium formate the chiral amine **22** was obtained. Compound **22** underwent further manipulation as shown in Scheme 16 to yield the same tetrahydroisoquinoline coupling partner **26**. I find it odd that Hoye would synthesize the same intermediate **26** knowing that is was indeed a *cis* relationship but the unnatural isomer, other than the novelty of a more efficient synthesis to arrive at **26** over their previous publication,[39] and leads to the enantiomer (**13-*ent***) of korupensamine D (**13**).



Scheme 19. Hoye's modified tetrahydroisoquinoline synthesis in route toward korupensamine D **13**

This new naphthylene coupling partner strategy (Scheme 20) was more efficient over the first in the sense that compounds prepared were crystalline and could be purified via recrystallization allowing for preparation at larger scales where column chromatography is prohibitive.[44] Compound **35** was prepared after a simple MOM protection of the starting tolulylol with NBS in the presence of a 100W tungsten incandescent bulb, which they had noted without the intense irradiation multiple bromination would occur making purification a daunting task. Displacement of the benzylic bromide with sodium phenylsulfinite yielded **36** that in turn formed the sulfone. Deprotonation with LDA and addition of methyl crotonate formed an adduct which following saponification, was cyclized to ketosulfone **37**. Aromatization of **37** via elimination of the sulfone with *t*BuOK efficiently afforded **29**.

Subjection of **29** to the conditions outlined in Scheme 17 arrive at the naphthylene coupling partner **30**.



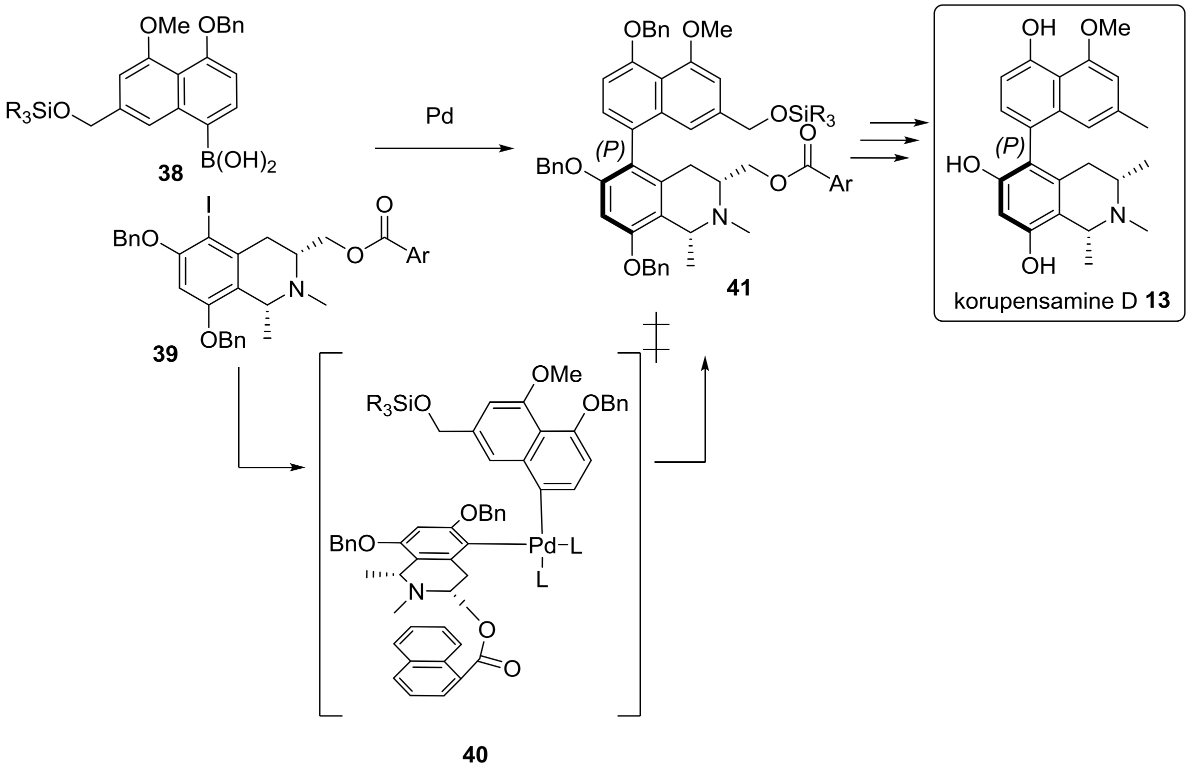
Scheme 20. Hoye’s modified naphthylene synthesis for korupensamines and michellamines

Again, with both coupling partners they performed a Suzuki coupling (Scheme 18) to obtain korupensamine analogs **31** and **32** in the same 73% yield that they had previously obtained. They then transformed both into the unprotected korupensamine D analogs in the same fashion displayed in Scheme 18. The selectivity was the same as previously seen, with little selectivity with respects to the aryl-aryl bond of 4:5 for **31**:**32**. The same compounds **13-*ent*** and **13-*dst*** were obtained from their second approach, being the enantiomer and diastereomer of korupensamine D **13**.

4.5 Results and Discussion

Inducing atroposelective biaryl bond formation has been described above, along with the two racemic syntheses of korupensamine D **13** having been outlined. Previously, we have pursued atroposelective cross coupling of an analog of korupensamine A (**10**, Scheme 9) and korupensamine B (**11**, Scheme 8) with atroposelectivities of 99:1 and 9:1, respectively, via chiral directing groups.

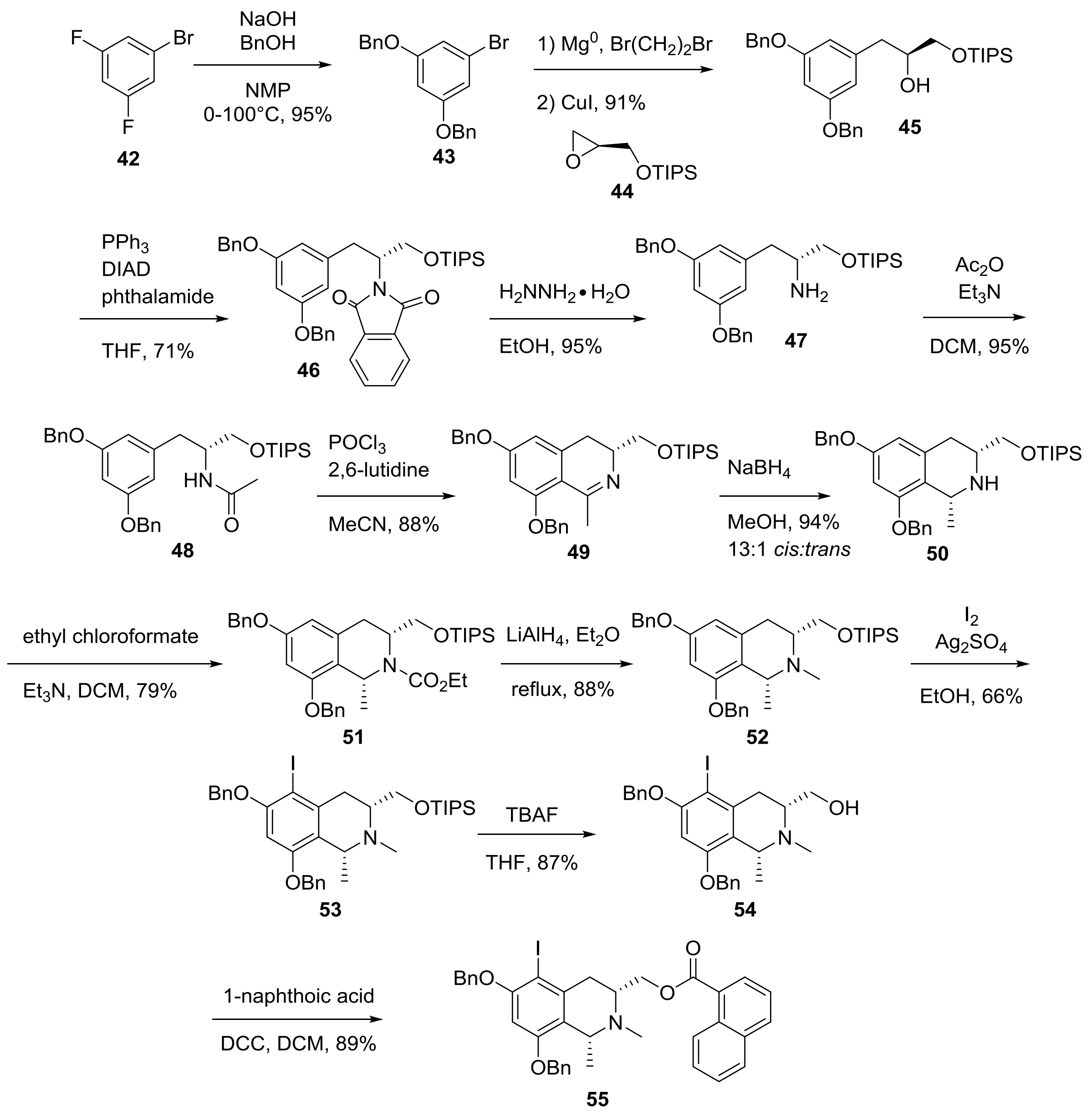
Firstly, in efforts to further our methodology of atroposelective biaryl bond formation, we have pursued improvement of key literature cross couplings to korupensamine D **13**, or an analog and, secondly, transforming the biaryl product to authentic **13** with the known unstable tetrahydroisoquinoline ring. We have invoked a similar strategy (Scheme 21) to that previously employed by our research group[21] for synthesis of **11**. That is, we utilized a π-stacking phenomenon to block one face of the tetrahydroisoquinoline coupling partner to force the 'long' side of the naphthylene partner away from the π-stacking unit, as well the bulky silyl ether of **38** that further encourages the direction of coupling to avoid a steric clash with the π-stacking unit, as shown in intermediate **40**. These features should aid in the formation of the *P* isomer of **41** which could be further manipulated to korupensamine D **13** (Scheme 21).



Scheme 21. Proposed pi-stacking phenomena for atroposelective formation of **41**

4.5.1 Synthesis of the cis-tetrahydroisoquinoline coupling partner

Synthesis of the tetrahydroisoquinoline coupling partner is loosely related to the work performed by Keith in his atroposelective cross coupling towards korupensamine A **10** analog **16.**[45] We have chosen to work with the benzyl protected analog to avoid the late stage use of BBr_3 to access the free phenols of **13**. Starting with commercially available 3,5-difluorobromobenzene **42**, we performed a double nucleophilic aromatic substitution with benzyl alcohol to provide the benzylated aryl bromide derivative **43** (Scheme 22). The TIPS protected *R*-glycidol **44** was formed from routine silylation chemistry to give the TIPS protected alcohol in nearly quantitative yield; assignment of stereochemistry matches that of previously synthesized material.[46]



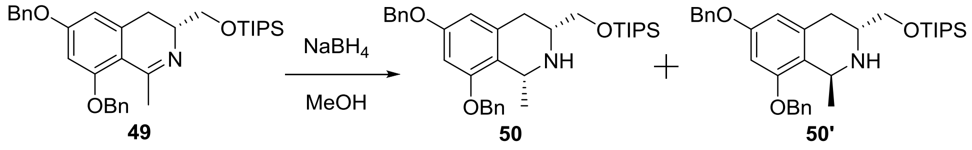
Scheme 22. Tetrahydoisoquinoline coupling partner synthesis

The known[47] regioselective copper catalyzed epoxide ring opening was performed initially with CuBr·SMe$_2$ yielding **45** in a disappointing 22% yield, with the remaining mass being homocoupled Grignard starting material. From careful re-inspection of the literature we found that CuI is better suited with our aryl bromide **43**. With the new catalyst we were able to readily achieve yields in excess of 85%. Transformation of the free alcohol of **45** to the phthalimide derivative **46** with inversion of stereochemistry was carried out by Mitsunobu conversion,[48] followed by hyrdrazinolysis to afford primary amine **47**. Acetimidation was performed with acetic anhydride to give **48**. This route was chosen as we have found from previous work that installation of the chiral methyl group in a *cis* relationship post-cyclization proved to be difficult. From acetamide **48** ring closure was performed via a Bischler-Napieralski reaction[21,49] forming imine **49** in excellent yield.

It is important to note that formation of **49** requires care with respect to reaction time, temperature, and work-up. If the reaction is allowed to continue reflux after completion (~3 h), the yield was generally depressed due to degradation from in situ phosphoric acid formation. The issue becomes much worse at elevated temperatures. Also, the work-up must be completed quickly by pouring the reaction mixture into a mixture of cold 1:1 ethers : triethylamine and stirred immediately, followed by basic work-up and purification.

With imine **49** in hand it was decided to carry out a diastereoselective sodium borohydride reduction to **50**, as previously used by Bringmann for similar *cis* selective reductions of 1,3 dimethyltetrahydroisoquinolines.[41] This route was chosen over the widely used hydrogenation on Pd/C, which would lead to concurrent debenzylation. This unwanted deprotection could give material that might prove too difficult to solely methylate or reprotect the phenols vs the amine. Although this procedure proved selective to obtain **50**, our initial attempt led to a disappointing 3:1 *cis*:*trans* (entry 1) selectivity at 5 °C (Table 1). Further optimization led to the current condition (entry 5) providing a 13:1 *cis*:*trans* selectivity. Although superior selectivities (entries 3 and 4) were achieved at colder temperatures, reaction rates dropped precipitously along with yields.

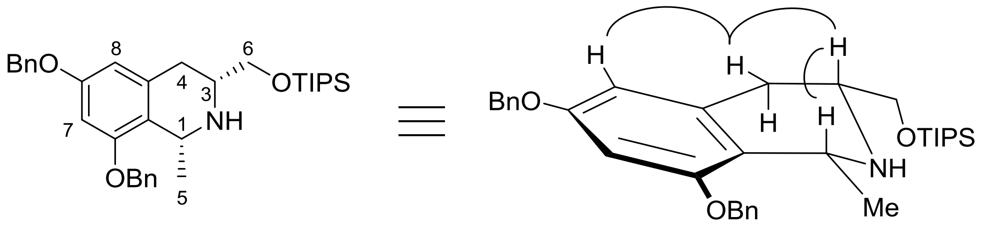
Table 1. Optimization for the formation of the *cis* secondary amine **50**



entry	temp. (°C)	time (h)	yield (%)	**50** : **50'**
1	5	0.5	99	3:1
2	0	1.5	99	4:1
3	-39	8	41[a]	14:1
4	-30	6	58[a]	14:1
5	-15	2	94	13:1

[a] incomplete conversion and no further progress

Proton and carbon NMR assignments were made at the two stereogenic centers, C1 and C3 of **50** with the use of HMQC, ^{1}H, and ^{13}C NMR (Figure 9). These assignments were necessary as the diastereotopic methylene protons tend to be quite misleading if one were to only rely on simple proton NMR. Using this information we observed a strong nOe effect between the 1-3, and 4eq-8 hydrogens of **50** with 2-D NOSEY NMR experiments, this assignment confirms the *cis* relationship as originally reported when korupensamine D **13** was first isolated.[12] Importantly, there is an absence of an nOe between hydrogens 5-3 which would be present in the *trans* isomer.

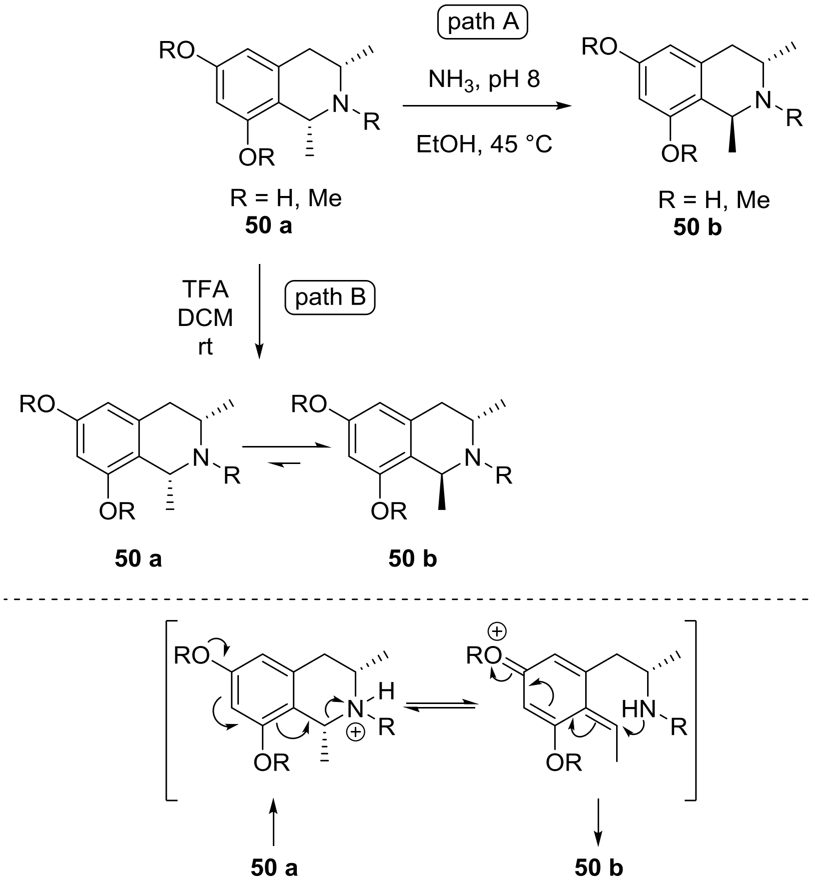


50

position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	4.37 (q, 6.1, 1H)	49.03
3	2.93 (m, 1H)	54.36
4_{ax}	2.58 (dd, 15.2, 11.2, 1H)	33.95
4_{eq}	2.72 (dd, 15.2, 2.5, 1H)	33.95
5	1.51 (d, 6.3, 3H)	23.20
6_{a}	3.85 (dd, 9.6, 4.4, 1H)	67.11
6_{b}	3.79 (dd, 9.6, 5.5, 1H)	67.11
7	6.48 (d, 2.2, 1H)	98.62
8	6.38 (d, 2.1, 1H)	106.15

Figure 9. Stereochemical assignment of **50** from key nOe interactions

Special care must be taken from this point on in the synthesis, as 1,3-*cis*-dimethyl tetrahydroisoquinolines with axial hydrogens are known to epimerize to the more stable *trans* isomer under both mildly basic and acidic conditions (Scheme 23). They have also been found to rapidly oxidize at room temperature in the presence of atmospheric oxygen furthering the need for cautious handling.[41] This epimerization was used by Bringmann to convert their unwanted *cis* byproducts **50a** from a Pictect-Spengler reaction with ammonia/EtOH (pH 8), as shown in Scheme 23 (Path A) in nearly quantitative yield to the *trans* isomer **50b**.[41] While Bringmann was able to use this epimerization to his advantage, Amat *et al.*[50] were not so fortunate. They had set out to synthesize the tetrahydroisoquinoline portion of **13**, and unexpectedly realized this epimerization when performing a N-Boc deprotection with TFA (Scheme 23, Path B) which was overcome by using TMSOTf and 2,6-lutidine. A proposed mechanism is drawn (Scheme 23, bottom) for the plausible retro-Michael ring opening and closure. With this insight the utmost attention must be paid throughout the remainder of the synthesis as to avoid this potential dead end.

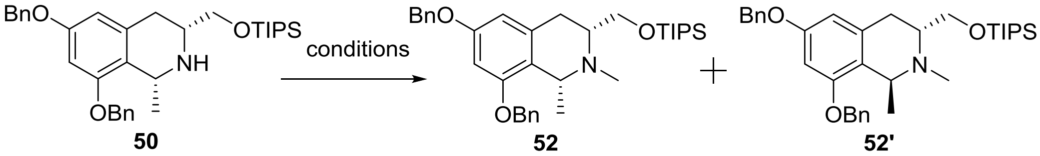


Scheme 23. Pathways for the known epimerization of *cis* configured compounds like **50 a**

Formation of N-methylated amine **52** initially proved difficult as we wished to use traditional single step methylation procedures over the known two step methods, from carbamate installation followed by reduction as used by Hoye *et al.*[51] We soon discovered why…

From screening of the electrophilic methyl sources; methyl iodide (MeI), Meerweins salt (Me_3O^+ $^-BF_4$), and dimethyl sulfate (Me_2SO_4). Shown in Table 2, use of MeI at room temperature (entry 1) led to no reaction after being left overnight. When the reaction was heated (entry 2) three products were obtained: N-methyl **52** (*cis)*/**52’** (*trans),* amine salt **52a**, similar to the Hoffmann rearrangement products of the natural product gentrymine B synthesized by Bringmann *et. al.*[52] (Scheme 24), and epimerized starting material.

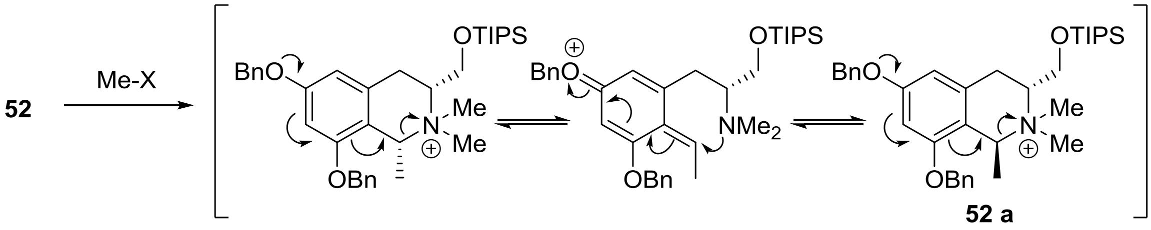
Table 2. Screening for N-methylation of **50** to **52**



entry	conditions	Yield	**52** or **52'**^{e}
1	2 equiv MeI, K_2CO_3, acetone, rt	n.r.	-
2	1.3 equiv MeI, K_2CO_3, acetone, 50 °C	21%^{a,b}	nd
3	1.3 equiv $Me_3O^+BF_4$, DCM, 0 °C	44%^{a,f}	**52**
4	1.3 equiv Me_2SO_4, Et_3N, acetone, 50 °C	12%^{c}	nd
5	CHO_2H, CH_2O, MeOH, 40 °C	34%^{b,c}	nd
6	CHO_2H, CH_2O, MeOH, 60 °C	94%^{f}	**52'**
7	EtOCOCl, Et_3N, DCM, 0°C^e, then $LiAlH_4$, Et_2O, reflux	70%^{d,f}	**52**

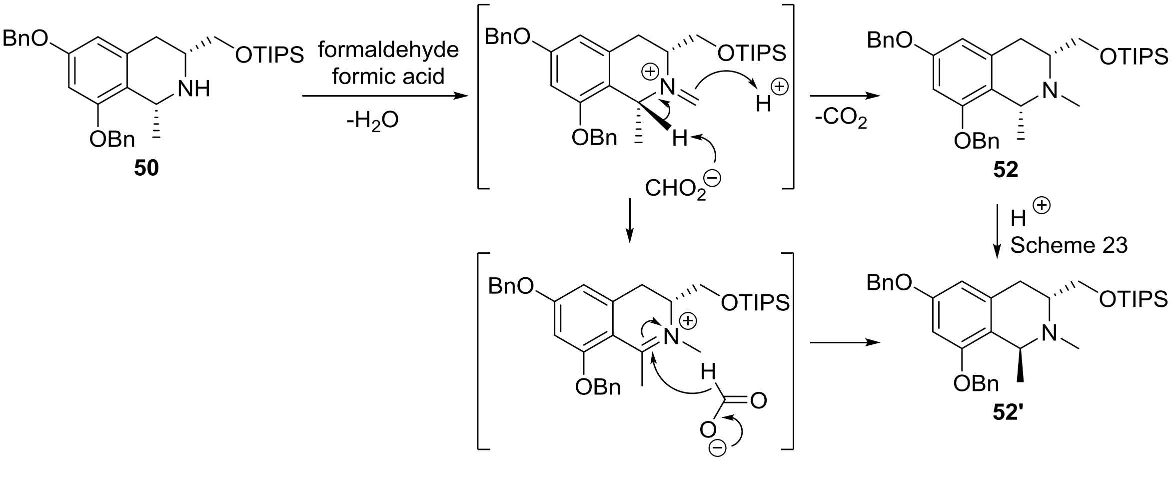
[a] degradation products mostly recovered, [b] epimierized starting material [c] incomplete conversion, [d] overall yield,[e] determined by 2D Nosey, [f] anhydrous reaction conditions

Meerwiens salt (entry 3, Table 2) afforded the N-methylated product **52** in the correct stereochemistry, although in a rather poor yield of 51%. Dimethyl sulfate gave incomplete reaction with a 12% yield (entry 4). We chose not to further pursue the use of Me_3O^+ $^-BF_4$ or Me_2SO_4 from our lesson learned with unwanted byproduct formation with heating electrophilic MeI (Scheme 24).



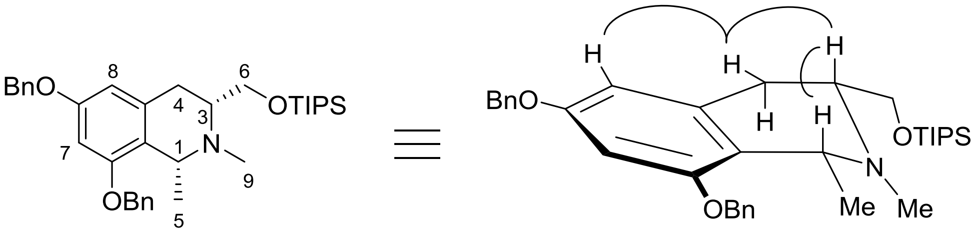
Scheme 24. Formation of unwanted gentrymine B analog **52 a**

Efforts using reductive amination with formaldehyde and formic acid led solely to the *trans* isomer **52’**, which could be formed from presumably two pathways shown in Scheme 25. Either the preferred product may be formed which then undergoes acid catalyzed epimerization (Scheme 23), or the reactive imine my lower the pK_a of the benzylic proton such that formate can serve as a base at 60 °C, resulting in a new imine with the C1 position sp^2 hybridized center available for hydride delivery to form the more stable product **52’**.



Scheme 25. Formation of **52’** from reductive amination of **50**

After quickly realizing we were exhausting precious *cis* dimethyl amine **50** we resorted to using the two step procedure by first formation of a ethyl carbamate **51** (Scheme 22) followed by reduction using $LiAlH_4$ in dry refluxing ether, which afforded the N-methyl amine **52** in 70% overall yield. Its stereochemistry was assigned again with ^{1}H, ^{13}C, HMQC and Noesy NMR as shown in Figure 10. Key nOe correlations observed were the hydrogen signals of 1-3, 4eq-8, 3-4eq, and again the lack of 5-3.

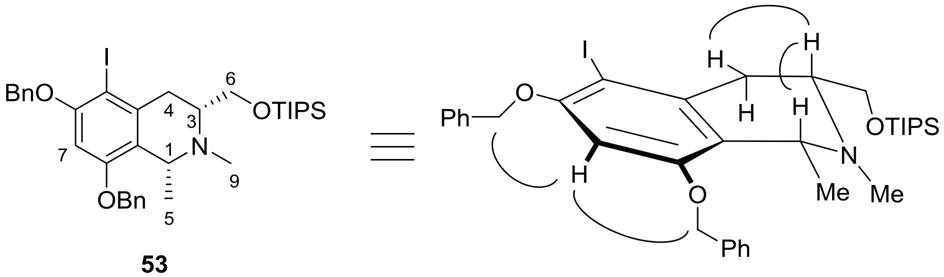


52

position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	3.91 (dd, 6.0, 6.4, 1H)	55.36
3	2.61 (br s / m, 1H)	62.21
4_{ax}	2.67 (dd, 12.3, 3.8, 1H)	32.53
4_{eq}	2.94 (dd, 12.2, 3.2, 1H)	32.53
5	1.35 (d, 5.8, 3H)	22.70
6_{a}	4.00 (dd, 5.7, 3.3, 1H)	67.01
6_{b}	3.60 (t, 8.3, 1H)	67.01
7	6.48 (d, 1.7, 1H)	98.37
8	6.43 (d, 1.7, 1H)	105.42
9	2.50 (s, 3H)	43.43

Figure 10. Stereochemical assignment of **52** from key nOe interactions

Now with a reliable means to produce N-methylated **52** in a diastereomericly pure fashion we moved on to installation of the halogen for cross coupling. Iodination of **52** with I_2 and Ag_2SO_4 in ethanol proceeded smoothly affording aryl iodide **53** in 66% yield. Although exposure to UV light should be avoided, an impromptu stability sample was placed in an NMR tube and left on the window sill in direct sunlight for ~8 h a day. Impressively after two weeks the sample had retained ~80% of the iodide. The regiochemistry of the iodine atom and the stereochemistry of the C1 and C3 hydrogens were determined via 2D Noesy assigned again from HMQC, ^{1}H, and ^{13}C as shown in Figure 11. The observed nOe's of proton 7 with both benzylic protons and the loss of the 4eq-8 nOe determined the regiochemistry of the iodine, if the iodine were in the 7 position only one of the benzyls would show an nOe. The stereochemistry of **53** was found from the nOe of 1-3, and proton 3 was assigned from its nOe with the 4eq proton. It appears there may be a small nOe of 3-5 although only a single diastereomer is resolved with the ^{1}H NMR, and the following desilylation to **54** did not contain a nOe for 3-5, only 1-3 and 3-4eq hydrogens suggesting that we still have the labile *cis* configuration.

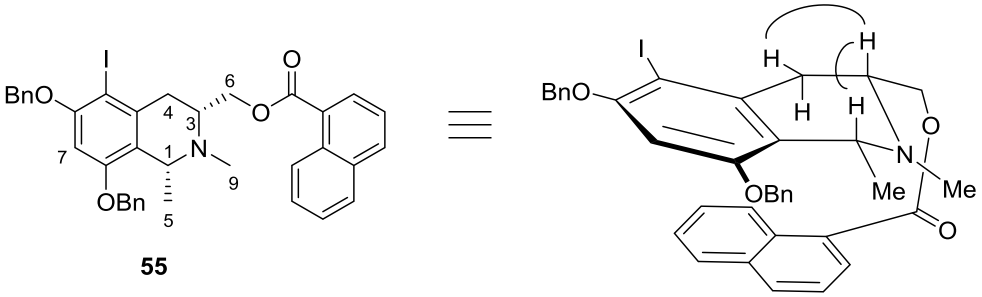


53

position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	3.91 (d, 6.3, 1H)	55.59
3	2.55 (br s / m, 1H)	62.58
4_{ax}	2.60 (d, 7.9, 1H)	37.68
4_{eq}	3.31 (dd, 12.2, 2.4, 1H)	37.68
5	1.31 (d, 5.9, 3H)	22.70
6_a	4.01 (d, 7.7, 1H)	66.82
6_b	3.62 (t, 7.3, 1H)	66.82
7	6.48 (d, 1.7, 1H)	98.37
Bn	5.09 (s, 2H); 5.03 (s, 2H)	71.35; 70.26
9	2.48 (s, 3H)	43.24

Figure 11. Regio and stereochemical assignment of **53** from key nOe interactions

Desilylation of **53** proceeded uneventfuly giving 87% yield of alcohol **54**, 2D NMR suggests that the *cis* configuration is still in place from the nOe correlations of 1-3, 3-4eq hydrogens, and noting the lack of the *trans* 5-3 hydrogens nOe. (See SI) Alcohol **54** was carried into a DCC coupling with 1-naphthoic acid to cleanly produce the tetrahydroisoquinoline coupling partner **55** (Scheme 22). Structural assignment shown in Figure 12 of **55** was performed with ^{1}H, ^{13}C, HMBC, HMQC, and NOESY NMR. The observed nOe for the *cis* compound was found for 1-3, 3-4eq, and 5-4ax as well the ^{1}H NMR indicated there to be only a single diastereomer.



55

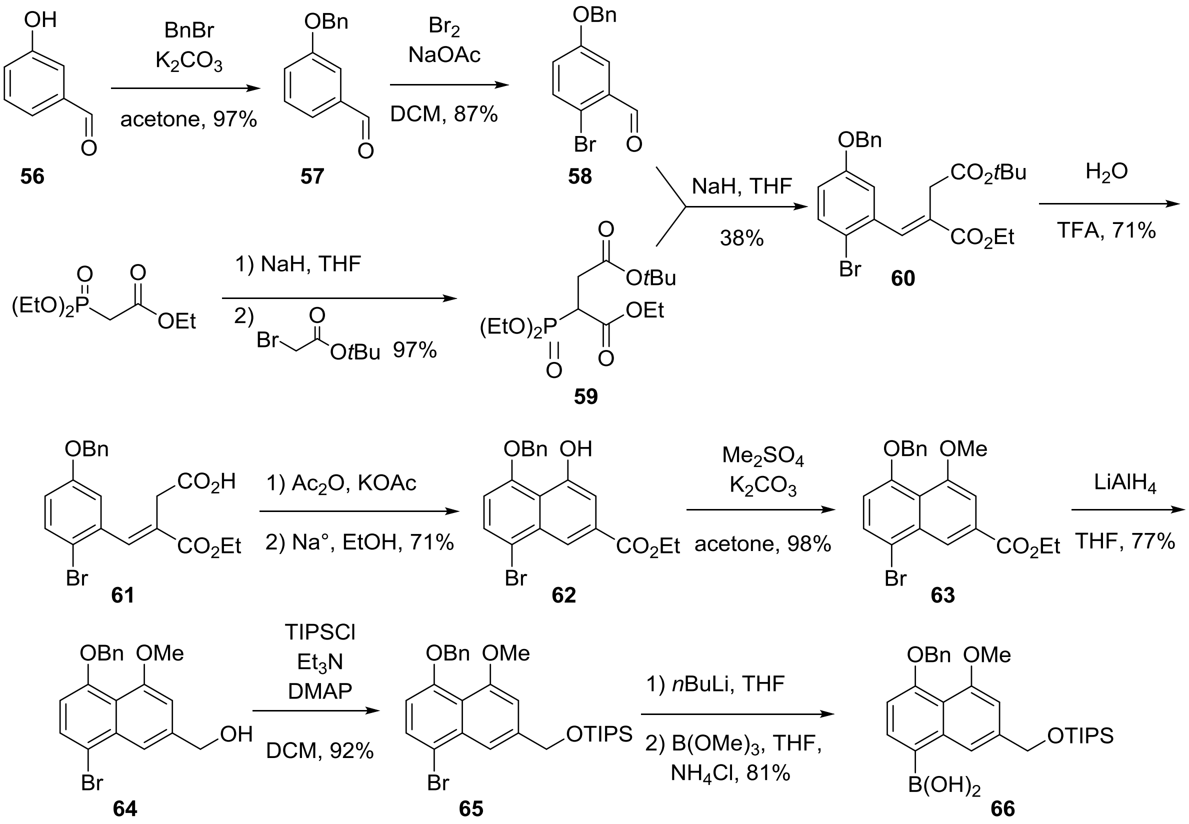
position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	4.00 (q, 6.6, 1H)	55.39
3	2.91 (m, 1H)	59.24
4_{ax}	2.84 (dd,15.4, 9.8, 1H)	38.04
4_{eq}	3.29 (dd,15.4, 3.6, 1H)	38.04
5	1.37 (d, 6.6, 3H	22.73
6_{a}	4.64 (dd, 11.1, 4.1, 1H)	67.33
6_{b}	4.48 (dd, 11.1, 6.3, 1H)	67.33
7	6.45 (s, 1H)	97.47
Bn	5.09 (s, 2H); 5.05 (d, 3.6, 2H)	71.38; 70.30
9	2.58 (s, 3H)	43.05

Figure 12. Regio and stereochemical assignment of **55** from key nOe interactions

4.5.2 Synthesis of the naphthylene coupling partner

Synthesis of the naphthylene coupling partner (Scheme 26) was far more straightforward as most of the details and pitfalls had been previously worked through by Keith,[45] Petersen,[53] and utilized by Bringmann[23] for his work with michelleamines A-C.

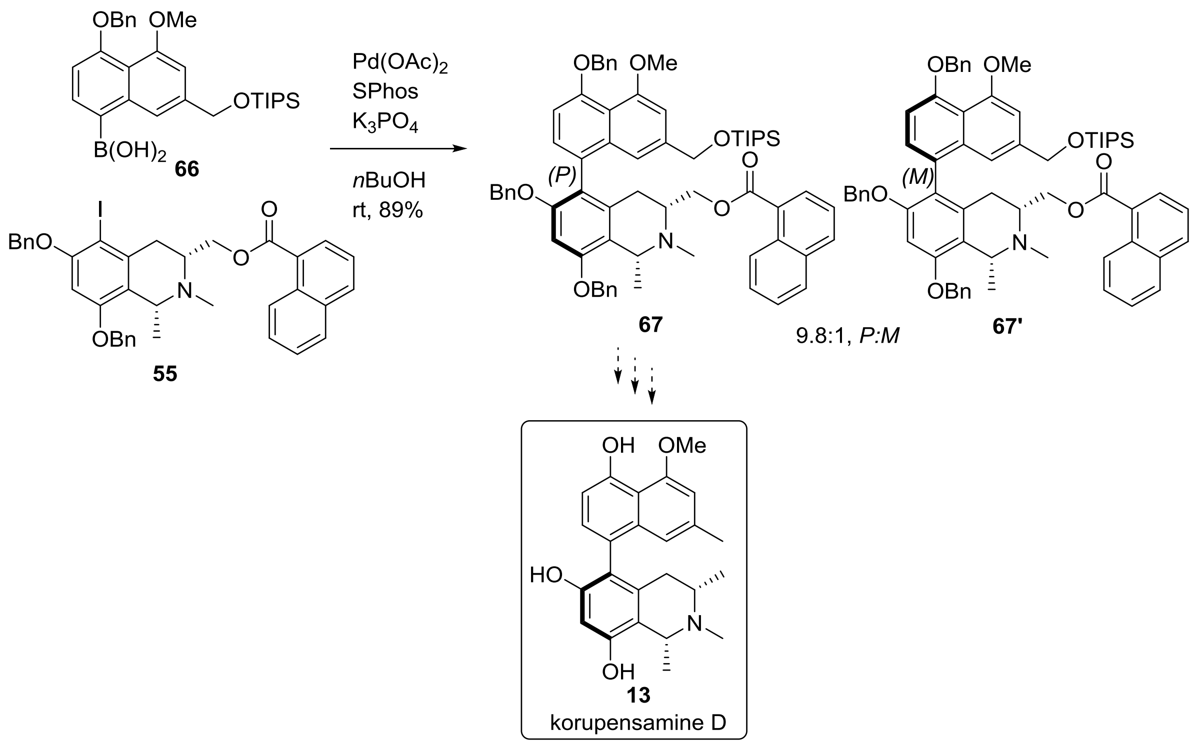
Commercially available 3-hydroxybenzaldehyde **56** was benzylated in 97% yield to afford **57**, which was subjected to bromination conditions with NBS and sodium acetate giving the brominated aldehyde derivative **58**. Preparation of **59** resulted from *t*-butyl bromoacetate and diethylphosphonate ethyl ester in 97% yield,[54] which was and used in the Horner-Wadsworth-Emmons reaction forming **60**. We typically see much higher yields, although it was noted after addition that the THF still had become contaminated with water: product **60** was obtained in 38% yield. The *t*-butyl ester was cleaved under acid hydrolysis conditions to give **61** that was cyclized using acetic anhydride, and then aromatized with sodium ethoxide furnishing **62** in 71% overall yield. Methylation followed by ester reduction gave the alcohol **64**. At this point we could have removed the alcohol via mesylation and reduction, but decided to silylate the free alcohol to the TIPS ether increasing the steric bulk on the 'long' side of the naphthylene ring of **65**. Typical borylation chemistry gave the final product **66** in 81% yield.



Scheme 26. Naphthylene coupling partner synthesis

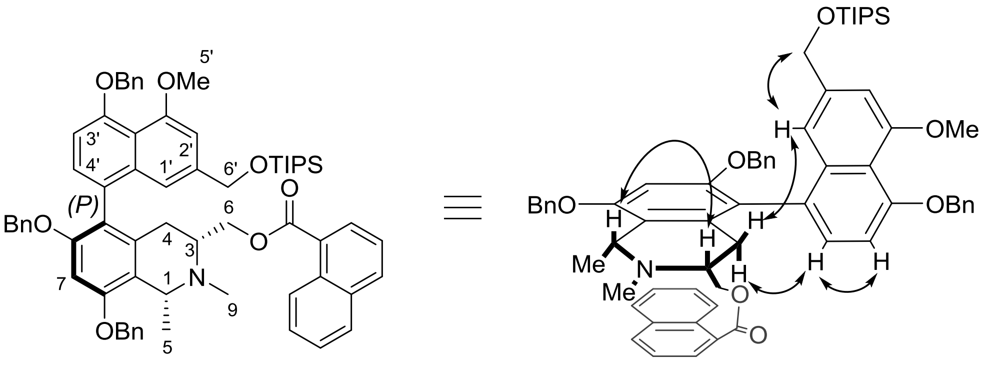
4.5.3 Atroposelective cross-coupling en route towards korupensamine D

With successful completion of both coupling partners **55** and **66** we were able to carry out the much anticipated atroposelective cross coupling towards korupensamine D analog **67** (Scheme 27). We accomplished the selective formation of **67** in a yield of 89% with excellent selectivity of 9.8:1 (**67**:**67'**) for the *P:M* diastereomers by ^{1}H NMR, better than the related cross coupling reactions in prior art towards **13**.[13,39] Identification of the *P* and *M* diastereomers was performed in the same fashion using the diastereotopic protons appended to the naphthylene unit, and 4ax/4eq positions of the tetrahydroisoquinoline ring as previously reported in work towards related korupensamine analogs discussed below.[13,54,56]



Scheme 27. Atroposelective cross coupling of korupensamine D **13** analog **67**

Further structural information was gathered through extensive ^{1}H, ^{13}C, HMQC, and Noesy NMR studies with comparison to related *cis* korupensamines. They key nOe hydrogen correlations leading to an assignment of axial chirality for **67**, were 1-3, 4eq-1’, 4ax-4’, 6’-1’, and the lack of 3-5, these correlations were also observed by Hallock *et al.*[10,12] and shown in Figure 13. The specific rotation was also positive like that of **13**, thus providing further evidence of the *P* isomer.



67

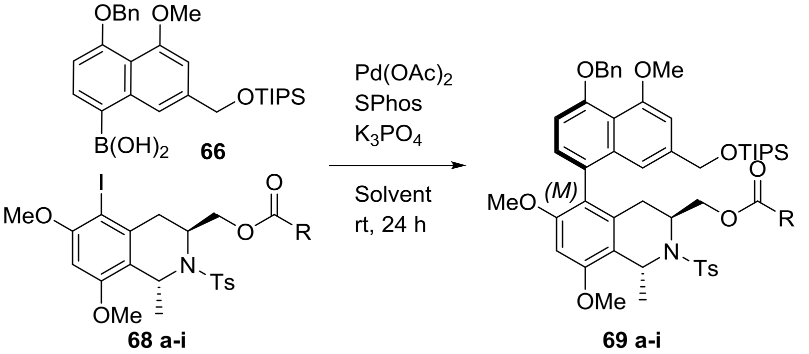
position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	4.12 (dd, 12.8, 6.2, 1H)	55.22
3	2.82 (m, 1H)	59.07
4_{ax}	2.34 (dd, 15.6, 9.9, 1H)	29.41
4_{eq}	2.67 (dd, 15.8, 3.6, 1H)	29.41
5	1.46 (d, 6.2, 3H)	23.05
6_{a}	4.54 (dd, 10.7, 3.7, 1H)	67.53
6_{b}	4.08 (dd, 10.2, 7.9, 1H)	67.53
7	6.60 (s, 1H)	97.67
9	2.59 (s, 3H)	43.61
1'	7.17 (d, 1.2, 1H)	128.19
2'	7.16 (d, 1.2, 1H)	127.59
3'	7.15 (d, 1.2, 1H)	127.57
4'	7.10 (s, 1H)	114.66
5'	3.95 (s, 3H)	56.13
6'	4.80 (m, 2H)	65.04

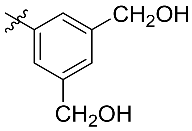
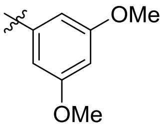
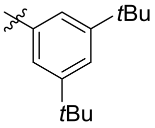
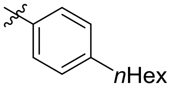
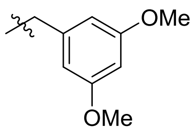
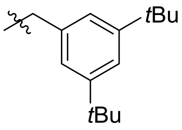
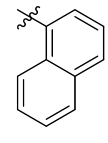
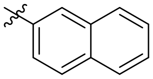
Figure 13. Key nOe correlations for the assignment of **67**

Our choice of atropisomer induction via the π-stacking unit had been previously developed by Petersen[21,54]and Huang.[21,56] From their optimization studies (Table 3) that involved varying sterics, hydrogen bonding, and levels of conjugation, 1-naphthoate ester **68g** proved best giving atroposelectivity of 9:1 for **69g** in *n*BuOH as measured by the diastereotopic protons via ^{1}H NMR as confirmed by HPLC.[21] The effect of π-stacking was confirmed with substrate **68i** bearing a simple methyl ester, lacking the aryl π-stacking interactions leading to cross coupled product **69i** in a 1:1 ratio.

Although they had worked towards the *M* isomer, our modeling would suggest that the P isomer selectivity should be similar if not higher than previous efforts. This was suggested given that the naphthylene unit is in closer proximity to the aryl ring of the tetrahydroisoquinoline ring when placed in the equatorial position, such as in **55**. By contrast **68g** contains both, a large sterically crowding N-tosyl protecting group and the π-unit in the axial-like positions.

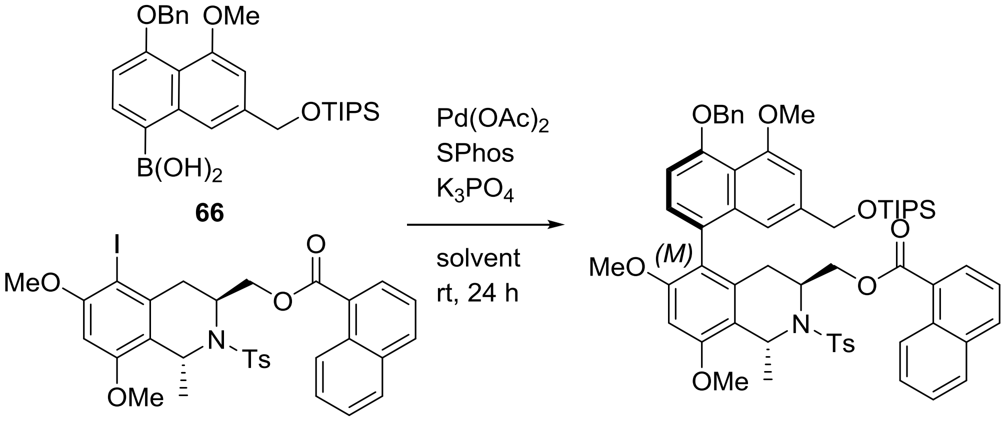
Table 3. Effect of the pi-stacking unit for the atroposelectivity of **69 a-i** by Petersen and Huang



entry	R =	solvent	*M* / *P*
69 a		*n*BuOH	5:1
69 b		$MeNO_2$ *n*BuOH	7:1 6:1
69 c		*n*PrOH	4:1
69 d		$MeNO_2$ *n*BuOH	8:1 3:1
69 e		$MeNO_2$	7:1
69 f		*n*BuOH	6:1
69 g		$MeNO_2$ *n*BuOH	8:1 9:1
69 h		*n*BuOH	3:1
69 i	CH_3	*n*BuOH	1:1

With the optimal π-stacking unit selected; their efforts to further increase atroposelectivity moved towards solvent selection[45] in hopes of increasing the stability of intermediate **40** (Scheme 21). As shown in Table 4, from work by Petersen,[54] toluene displayed a modest selectivity due to its aromaticity, which perturbs the desired π-stacking of **40**. More polar solvents were investigated in order to induce the π-stacking effect and, as shown, *n*-butanol led to an impressive 9:1 atropisomer selectivity.

Table 4. The effect of solvent for the atroposelectivity of **69 g** by Petersen

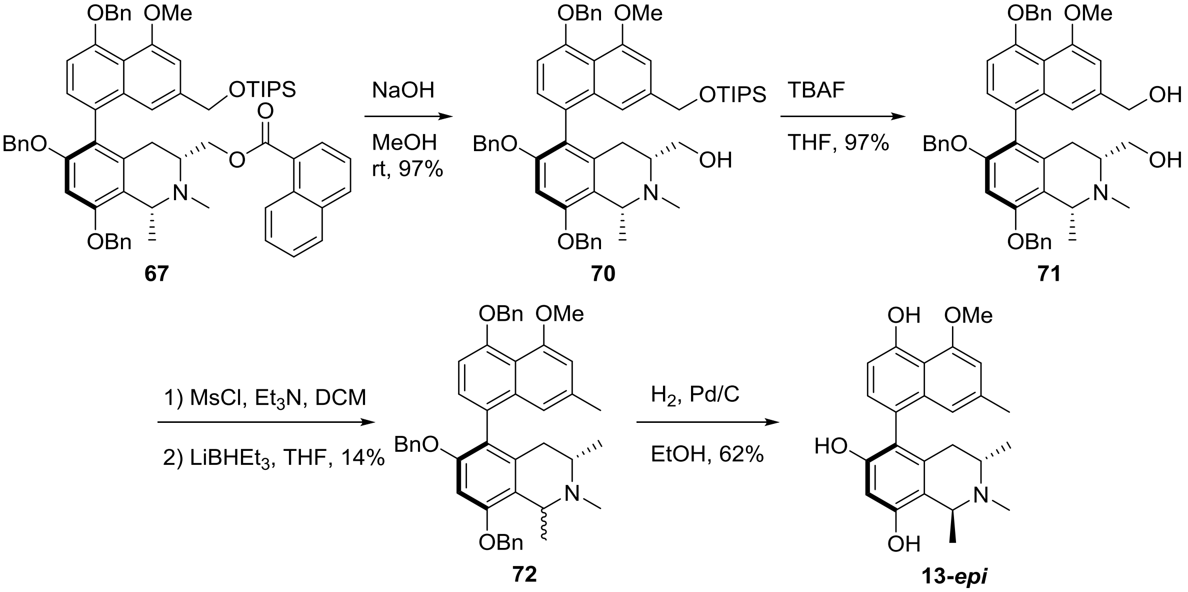


68 g **69 g**

entry	solvent	*M* / *P*
1	toluene	1.6:1
2	THF	3:1
3	1-hexanol	4.5:1
4	*n*PrOH	7.7:1
5	*n*BuOH	9:1

4.5.4 Auxiliary and protecting group removal towards korupensamine D

Accomplishing the first project goal of expanding our groups' capabilities towards atroposelective bond formations with the formation of **67** in 9.8:1 selectivity, an analog of the natural product **13** had been achieved. Previous work suggested that we could easily transform korupensamine D analog **67** to **13** in relatively high yields, as performed by Huang,[56] to complete the synthesis of extremely labile *cis* configured **13** that has been shown to epimerize under mild conditions (*vide infra).* Saponification of the naphthyl unit with sodium hydroxide in dry MeOH:THF gave compound **70** in 97% yield (Scheme 28). Stereochemical assignments for **70** proved to be inconclusive due to overlapping proton signals for the expected nOe correlation of 1-3 hydrogens. In contrast, it is important to note that the *trans* isomer was not observed, indicated by the lack of a nOe correlation for signal 3-5 (See SI). The known facile base-catalyzed isomerization described above (Scheme 23) was not observed, although desilyated **70** (**71**) was produced after extended reaction times.

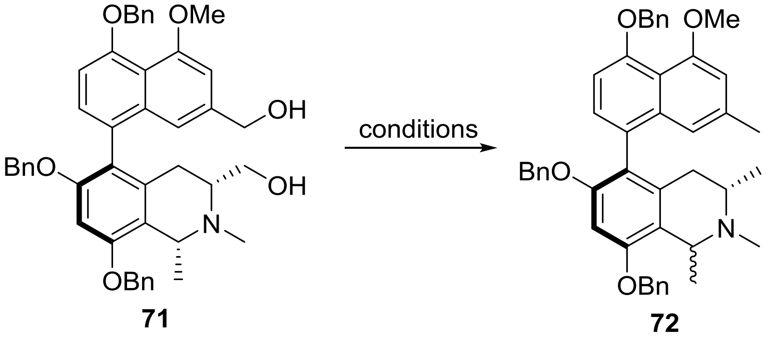


Scheme 28. Works toward natural product **13** from analog **67**

The routine desilylation of **70** proceeded without incedent to afford **71** in 97% yield. Stereochemical assignments for **71** were again found to be difficult due to the overlap of the N-methyl, position 3, and position 4ax protons, thus the conclusive assignment is not certain. An alternative method that may be employed, involves ruthenium catalyzed degradation to the respective chiral amino acids as previously performed for structure elucidation.[7,8]

The transformation of **71** to **13** using Appel-like reaction conditions followed by $LiAlH_4$ reduction then global debenzylation was used in the known analogous synthesis of korupensamine B **11**.[21] In our hands, despite our best attempts to reproduce the literature procedure, we could not obtain **13**, but did make **72** in a 3% yield (entry 1, Table 5) with a large amount of dimerization, as shown in Figure 12. The dimerization event occurs from the highly electrophilic benzylic alcohol intermediate being transformed into its derived halide or mesylate, and then being displaced in an S_N2 fashion by the more nucleophilic aliphatic alcohol.

Table 5. Screening of deoxygenation methods for the formation of **72**



entry	conditions	Yield (%)
1	$(Cl_2BrC)_2$, PPh_3, KOAc, DCM, then $LiAlH_4$/Zn, THF	3[a]
2	I_2, PPh_3, ImH, DCM, then $LiAlH_4$, THF	7[a]
3	PBr_3, DCM then $LiAlH_4$, THF	0[b]
4	MsCl, Et_3N, THF, then $LiAlH_4$, THF	0[a]
5	MsCl, Et_3N, DCM [0.1 M], then $LiAlH_4$, THF	5
6	MsCl, Et_3N, DCM [0.05 M], then $LiEt_4BH$, THF	14

[a] dimerization/polymerzation prouct mainly recovered, [b] degradation

In search of other means of halogen installation followed by reduction we had turned to the tried and true Appel reaction[57] (entry 2), but this route led largely to dimerized starting material, presumably due to the more reactive iodo intermediate (Figure 14). Disappointed that neither the previous deoxygenation conditions nor the Appel reaction had provided the desired product **72**, we turned to PBr_3, well known for its ability to exchange oxygen for bromine that could then be removed with $LiAlH_4$. Several attempts with PBr_3 (entry 3) through varying the addition rate and temperature routinely led to the degradation products BnBr and **71**-PO_4H as detected by GC-MS by the reaction of the benzylic oxygen and PBr_3.

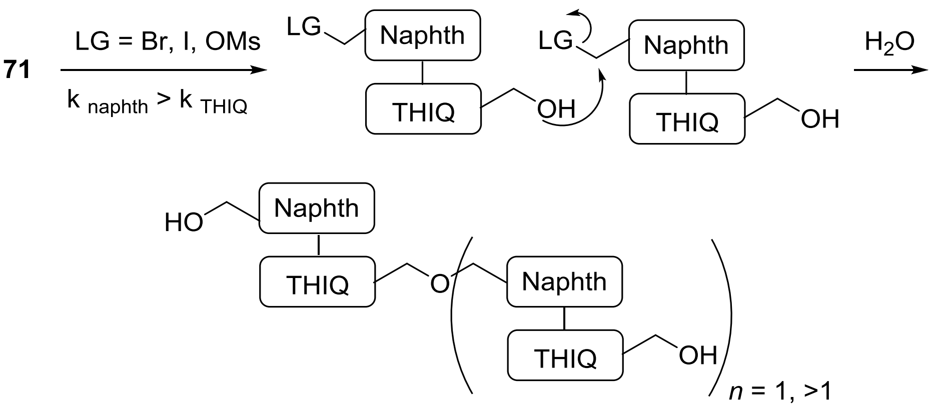


Figure 14. Plausible route for the dimerization of **71**

Reviewing the literature for alternative methods en route to **72**, the traditional method of mesylation followed by mild reduction using $LiEt_3BH$ (super hydride) of aliphatic alcohols seemed plausible.[58,59] With this new procedure we set out to obtain a sample of **72** (entry 4) although our first attempt led only to dimerized starting material with a viscous white precipitate hypothesized to be polymerized THF. The use of THF for the installation of the mesylate should be avoided, with efforts to perform the reduction in the same pot as we had done. Literature methods called for initial mesylation in DCM, filtration, and solvent evaporation then running the reduction in THF with superhydride. We followed the literature procedure closely using DCM and then THF (entries 5 and 6) at 0.1 and 0.05 molarities, respectively, and the exchange of $LiAlH_4$ for $LiEt_3BH$. The reaction ran at 20 fold less concentration (entry 6) afforded **72** in only 14% yield, the ^{1}H NMR was nearly identical to an intermediate of **13-*ent*** by the works Hoye,[13] and was quickly moved to the next step due to its known stability issues.

From **72**, the last transformation!, debenzylation with H_2 over Pd/C catalyst in EtOH led disappointingly not to **13**, but to a new product ***13-epi*** in 42% yield which is the product we had feared would surface from the unstable *cis* conformation of the 1,3-dimethyl's of **13**. The product was assigned from the characteristic relationship of the C1 and C3 protons for the *cis* vs *trans* configurations of the korupensamine series.[12] Chemical shift values for the *cis* C1 and C3 protons are always are at 3.8-3.7 and 2.4-2.3 ppm, respectively, whereas the *trans* position of the C1 and C3 protons are also all within a close range for the entire korupensamine series at 4.5-4.3 and 3.3-2.9 ppm, respectively. As the new compound obtained ***13-epi*** has the characteristic chemical shifts of the *trans* isomer of 4.26 and 2.88 ppm for C1 and C3, respectively, versus the relative shifts of *cis* **13.**[12] The accurate atomic mass measurement indicated a mass precisely like that of compound **13** giving further evidence that ***13-epi*** was produced

In conclusion, the epimerization event as outlined in Scheme 23 very likely occurred at some point during the last few transformations of saponification (basic), or deoxygenation (*in situ* acid formation), although the exact timing could not be confirmed due to inconclusive 2D NMR analysis. In order to circumvent this issue in the future one could perform the previously mentioned ruthenium catalyzed oxidative degradation of the tetrahydroisoquinoline ring to its respective chiral alanine and 3-aminobutyric acid residues as performed for prior structure elucidation of closely related structures.[7,8]

Noted from previous total syntheses of *cis*-naphthyl-tetrahydroisoquinoline alkaloids bearing both hydrogens in the axial positions, the last step is almost always a facile, mild cross coupling, global debenzylation, or N-methylation reaction providing the desired material albeit, generally in racemic form, thus limiting the exposure of the unstable *cis* isomer to additional reaction sequences.[13,60-61] Our use of the chiral pi-stacking unit and silyl ether with their need to removal followed by deoxygenation may not be amenable to the synthesis of **13** due to its inherent instability (*vide supra*).

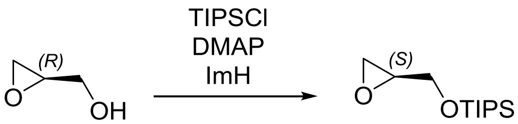
An alternative strategy to access authentic **13** would be to deoxygenate the naphthylic oxygen prior to coupling, thus enabling a much more facile deoxygenation of the tetrahydroisoquinoline ring by preventing the observed dimerization. A potential drawback of this alternative could be decreased atroposelectivity, but would still enable the investigation of our π-stacking atroposelective cross coupling methodology. While the option of deoxygenating in a step wise fashion may increase yields, the end result might still depend on instability issues as we had discovered. Thus these *cis* compounds are amenable to our methodology, as evidenced by the high atroposelectivity of 9:8:1, yet are plagued by their intrinsic unstable configuration as still preventing the total synthesis of natural korupensamine D **13**.

4.6 Experimental and Compound Data

General Information

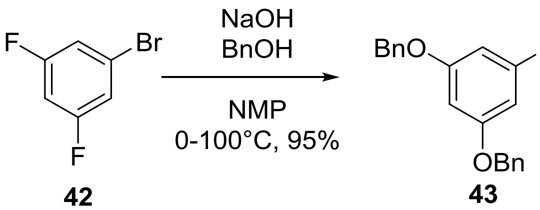
All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. THF, diethyl ether, and DCM were all purified via Innovative Technologies Pure-Sol SPS-400-5 purification system. Et_3N, $POCl_3$, MeCN, 2,6 Ltd was distilled prior to use. MeOH, EtOH, acetone, and n-BuOH were purchased in anhydrous form purged with argon for ~30 min. and stored over activated 4Å molecular sieves.

Reagents were purchased and used without further purification. Thin layer chromatography was performed using EM Science 60-F254 (250 nm) silica gel precoated plates; EM Science cat. No. 5714-3. Flash chromatography was performed using 200–425 mesh silica gel (Type 60A Grade 633) available from Fisher Scientific. HRMS spectra were recorded at the UCSB mass spectrometry facility by Dr. James Pavlovich using a Micromass VG 70e magnetic sector by standard methods on a PE Sciex Qstar quadrapole/time-of-flight tandem mass spectrometer. NMR spectra were recorded using Varian Inova spectrometers either at 500, or 600 MHz for 1H, and 125, or 150 MHz for 13C and 2-D experiments in $CDCl_3$ or CD_3OD. Chemical shifts are referenced to chloroform solvent residual peaks (1H = 7.26 ppm, 13C = 77.23 ppm). Optical rotations were measured on a Perkin Elmer model 341 polarimeter



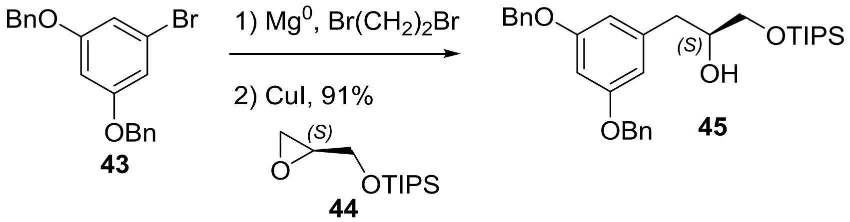
44

(*S*)-triisopropyl(oxiran-2-ylmethoxy)silane (44, JF-004-155) To a dry 500 mL round bottom flask charged with magnetic a stir bar and argon, added (R)-gycidol (11.11 g, 9.92 mL, 150 mmol, 1 equiv.), and DCM (200 mL, 0.75M) then cooled to -5°C. Added DMAP (21.99 g, 180 mmol, 1.20 equiv.) and ImH (11.23 g, 165 mmol, 1.10 equiv.) in one portion, followed by dropwise addition of TIPS-Cl (34.70 g, 38.52 mL, 180 mmol, 1.20 equiv.) via syringe at -5°C. The reaction was allowed to stir and warm to RT overnight (14h). Solid residue was removed via filtration then diluted with DCM (200 mL) and washed with sat. NH_4Cl (2 x 100 mL), brine (1 x 100 mL), dried over Na_2SO_4 and concentrated in vacuuo. Crude product was purified via flash chromatography with silica gel (50 x 150 mm) eluted with 5:95 EtOAc:Hex (R_f = 0.43, 1:9 EtOAc:Hex, developed with $KMnO_4$) to yield 26.26 g, 76 % **44** a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.75 (dd, *J* = 11.7, 4.7 Hz, 1H), 3.11 (m, 1H), 2.77 (dd, *J* = 5.1, 4.2 Hz, 1H), 2.66 (dd, *J* = 5.2, 2.7 Hz, 1H), and 1.07 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.92, 52.55, 44.43, 17.89, and 11.94. $[\alpha]^{23}_{D}$=-3.62° ; $CHCl_3$. HREIMS calc'd for $C_{12}H_{26}O_2Si$: 230.1702, Found: 187.1154 $[M–C_3H_7]^+$. Compound data matches that of previously reported.[47]



42 **43**

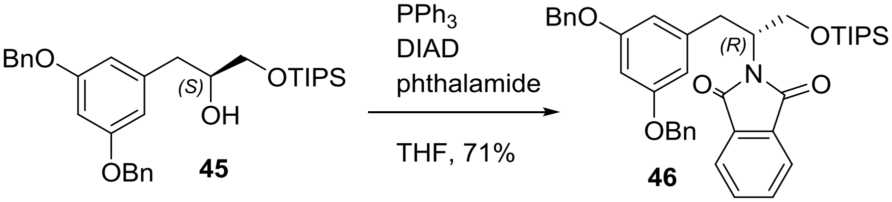
(((5-bromo-1,3-phenylene)bis(oxy))bis(methylene))dibenzene (43, JF-004-156) To a dry 250 mL three neck round bottom flask fitted with water condenser was charged with magnetic stir bar and argon, added NaH (50 wt. %, 3.92 g, 81.6 mmol, 2.33 equiv.), and suspended in NMP (44 mL, 1.85M) then cooled to 0°C (Note: formed pink suspension). Added a solution of BnOH (8.71 g, 8.34 mL, 80.5 mmol, 2.30 equiv.) in NMP (27mL, 3.0M) drop wise at 0°C then removed the ice bath and stirred at RT for 1 h (Note: reaction turned dark purple) Cooled to 0°C and added a solution of **42** (6.75 g, 4.03 mL, 35 mmol, 1.00 eqiuv.) in NMP (17 mL, 2.0M) drop wise at 0°C then removed the ice bath and heated to 100°C for 2 h (Note: reaction now dark green). Once cooled to room temperature the reaction was partitioned into 1:1 Et_2O:H_2O (250 mL) and separated. Extracted with Et_2O (5 x 100 mL), the combined organic extracts were washed with 10 wt% KOH:H_2O (2 x 200 mL), brine (1 x 100 mL), dried over $MgSO_4$, and concentrated invacuuo to afford a yellow solid. Crude product was purified via flash chromatography with silica gel (50 x 175 mm) eluted with 3:97 EtOAc:Hex ($R_f = 0.33$, 3:97 EtOAc:Hex) to yield 12.27 g, 95 % **43** a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.32 (m, 10H), 6.78 (d, *J* = 2.1 Hz, 2H), 6.55 (t, *J* = 2.1 Hz, 1H), and 5.01 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.37, 136.31, 128.64, 128.16, 127.52, 122.93, 111.06, 101.36, and 70.30. HREIMS calc'd for $C_{20}H_{17}O_2Br$: 368.0412, Found: 368.0408



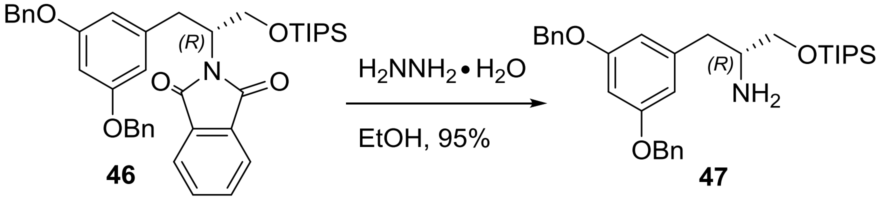
(*S*)-1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-ol (45, JF-004-167)

To a dry 500 mL three neck round bottom flask fitted with water condenser was charged with a magnetic stir bar and argon, added Mg turnings (18.23 g, 750 mmol, 7.50 equiv) then flamed dried under high vac and backfilled with argon thrice. Dissolved **43** (55.39 g, 150 mmol, 1.50 equiv.) in THF (200 mL, 0.75M) and added approximately 10 % of the solution to the Mg turnings via addition funnel followed by ethylene bromide (1.30 mL, 2.82 g, 15 mmol, 0.02 equiv.) (Note solution began to reflux without applied heat) then the rest of the aryl bromide solution was added dropwise at a rate (~30 min.) to maintain reflux with additional heat. Upon complete addition of the aryl bromide the solution was heated to reflux for 1.5 h then cooled to room temperature. To a second flask, a 1 L mL round bottom flask charged with magnetic stir bar and argon suspended CuI (2.38 g, 12.5 mmol, 0.13 equiv.) in THF (30 mL) at -40°C then added the Grignard solution and allowed to stir for approximately 15 min followed by dropwise addition of **44** in THF (60 mL). The reaction was stirred at -40°C until complete as judged by TLC (2.25 h). Diluted the reaction with Et_2O (250 mL) and washed with sat. NH_4Cl (3 x 200 mL) then extracted the aqueous with Et_2O (2 x 100 mL). The combined organics were washed with sat. $NaHCO_3$ (2 x 150 mL) and brine (2 x 100mL), dried over $MgSO_4$ and concentrated in vaccuo to afford a yellow oil. The crude product was purified via flash chromatography with silica gel (75 x 250 mm) eluted with 0 to 20% Et_2O:Hex (R_f = 0.16, 1:9 Et_2O:Hex) to yield 47.16 g, 91 % **45** a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.37 (m, 8H). 7.35-7.31 (m, 2H), 6.52 (s, 2H), 6.51

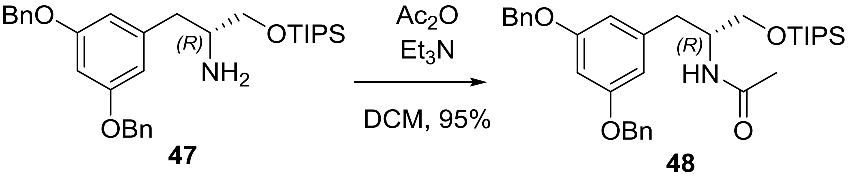
(d, J = 1.7 Hz, 1H), 5.03 (s, 4H), 3.94-3.88 (m, 1H), 3.71 (dd, J = 9.8, 4.0 Hz, 1H), 3.62 (dd, J = 9.8, 6.6 Hz, 1H), 2.75 (s, 1H), 2.74 (s, 1H), 2.36 (br s, 1H), and 1.16-1.03 (m, 21H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.98, 140.70, 136.95, 128.55, 127.94, 127.52, 108.49, 100.11, 72.76, 70.02, 66.64, 39.98, 17.99, and 11.94. $[\alpha]^{20}_D$=+1.67° ; $CHCl_3$. HREIMS calc'd for $C_{32}H_{44}O_4Si$: 520.3009, Found: 520.3016



(*R*)-2-(1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-yl)isoindoline-1,3-dione (46, JF-004-169) To a dry 2 L round bottom flask charged with magnetic stir bar and argon, dissolved PPh_3 (25.97 g, 99 mmol, 1.50 equiv.) and phthalimide (12.14 g, 82.5 mmol, 1.25 equiv.) in THF (660 mL, 0.1M) and cooled to 0°C. Added DIAD (19.49 mL, 20.02 g, 99mmol, 1.50 equiv.) dropwise and stirred for 15 min (Note: formed a bright yellow suspension) then added **45** (34.37 g, 66 mmol, 1.0 equiv.) in THF (100 mL) and allowed to warm to room temperature and stir overnight until complete at judged by TLC (10.5 h). Added 1:1 celite:silica gel (75 g) and removed solvent invaccuo. Crude product was purified via flash chromatography with silica gel (75 x 250 mm) eluted with 5:95 to 1:9 EtOAc:Hex (R_f = 0.22, 1:9 EtOAc:Hex developed with 2,4 dinitrophenyl hydrazine) to yield 30.52 g, 71 %, **46** a faint yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 5.3, 3.2 Hz, 2H), 7.67 (dd, J =, 5.5, 3.0 Hz, 2H), 7.37-7.28 (m, 10H), 6.46 (d, J = 2.0 Hz, 2H), 6.40 (t, J = 2.1 Hz, 1H), 4.93 (d, J = 11.6 Hz, 2H), 4.89 (d, J = 11.6 Hz, 2H) 4.73-4.68 (m, 1H) 4.19 (dd, J = 9.7, 8.7 Hz, 1H), 4.01 (dd, J = 9.8, 6.2 Hz, 1H), 3.28 (dd, J = 14.0, 10.5 Hz, 1H), 3.11 (dd, *J* = 14.1, 5.6 Hz, 1H), and 1.06-0.93 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.55, 159.92, 140.28, 136.90, 133.72, 131.91, 128.49, 127.87, 127.48, 123.00, 107.94, 100.61, 69.97, 62.98, 54.79, 34.76, 17.85, and 11.86. $[\alpha]^{20}_D$=+67.50°; $CHCl_3$.HREIMS calc'd for $C_{40}H_{47}NO_5Si$: 649.3224, Found: 649.3218

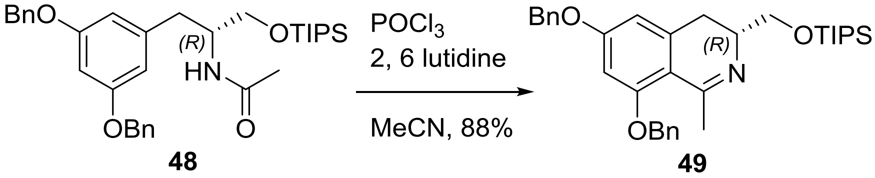


(*R*)-1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-amine (47, JF-004-170) To a 1 L round bottom flask fitted with reflux condenser and charged with a magnetic stir bar dissolved **46** (30.06 g, 46.25 mmol, 1.0 equiv.) in EtOH (460 mL, 0.1M) followed by hydrazine hydrate (115.74 g, 112.48 mL, 2.31 mol, 50 equiv.) and heated to reflux until complete as judged by TLC (1 h, R_f = 0.06, 1:9 EtOAc:Hex). Cooled to ~ 0°C and filtered the crystallized phenylhydrazide then concentrated in vacuo. Dissolved the resulting oil in Et_2O (250 mL), added water (200 mL) and extracted with Et_2O (5 x 250 mL). Washed combined organics with 2N NaOH (2 x 400 mL), brine (2 x 150 mL), dried over $MgSO_4$ and concentrated in vacuo to afford a yellow oil. The crude oil was passed over a pad of silica gel (75 x 75mm) and eluted with 1:1 EtOAc:Hex to yield 27.24 g, 95%, **47** a faint yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.36 (m, 8H), 7.35-7.31 (m, 2H), 6.51-6.49 (m, 1H), 6.49 (d, *J* = 1.9 Hz, 2H), 5.02 (s, 4H), 3.69 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.58 (dd, 9.6, 6.5 Hz, 1H), 3.17-3.11 (m, 1H), 2.79 (dd, *J* = 13.3, 5.2 Hz, 1H), 2.51 (dd, *J* = 13.2, 8.5 Hz, 1H), 1.81 (br s, 2H), and 1.16-1.01 (m, 21H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.99, 141.51, 136.94, 128.55, 127.93, 127.50, 108.48, 100.09, 70.03, 67.67, 54.53, 40.56, 33.02, 18.045and 11.98. $[\alpha]^{20}_{D}$=+1.90°; HREIMS calc'd for $C_{32}H_{45}NO_3Si$: 519.3169, Found: 476.2617 $[M–C_3H_7]^+$.



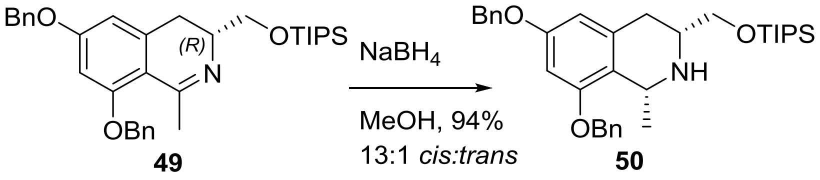
(*R*)-N-(1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-yl)acetamide (48, JF-004-172) To a 500 mL round bottom flask charged with argon and a magnetic stir bar dissolved **47** (22.35 g, 43 mmol, 1.0 equiv.) in DCM (287 mL, 0.15M) followed by Et_3N (27.19 g, 37.61 mL, 269 mmol, 6.25 equiv.), DMAP (0.534 g, 4.3 mmol, 0.10 equiv.), and ~1 g 4Å molecular sieves and stirred for ~ 15 min. Then added Ac_2O (43.90 g, 40.65 mL, 430 mmol, 10 equiv.) dropwise and allowed to stir at room temperature until complete as judged by TLC (66 h). Diluted with water (100 mL) and separated, extracted with Et_2O (3 x 100 mL) to the combined organic extracts wshed with sat. NH_4Cl (1 x 100 mL), sat. $NaHCO_3$ (2 x 100 mL), brine (100 mL), dried $MgSO_4$ and concentrated in vacuo. Passed over a pad of silica (50 50 mm) eluted with 1:1 EtOAc:Hex (R_f = 0.19, 2:8 EtOAc:Hex) to yield 23.02 g, 95%, **48** a faint yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.36 (m, 8H), 7.34-7.30 (m, 2H), 6.51 (d, *J* = 2.1 Hz, 2H), 6.49 (t, *J* = 2.1 Hz, 1H), 5.76 (d, *J* = 8.3 Hz, 1H), 5.01 (s, 4H), 4.26-4.19 (m, 1H), 3.66 (dd, *J* = 10.2, 3.2 Hz, 1H), 3.64 (dd, *J* = 10.2, 4.3 Hz, 1H, 2.86 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.82 (dd, *J* = 13.4, 8.3 Hz, 1H), 1.95 (s, 3H), and 1.15-1.03 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.36, 159.98, 140.43, 136.93, 128.53, 127.91, 127.47, 108.51, 100.34, 69.98, 63.04, 51.54, 37.26, 23.45, 18.02, and 11.95.

$[\alpha]^{20}_{D}$=+17.45°, $CHCl_3$. HREIMS calc'd for $C_{34}H_{47}NO_4Si$: 561.3274, Found: 518.2728 $[M–C_3H_7]^+$.



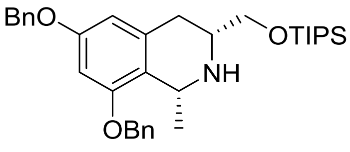
(*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-3,4-dihydroisoquinoline (49, JF-004-180) To a 500 mL three neck round bottom flask charged with argon, magnetic stir bar and water condensor dissolved **48** (11.24 g, 20 mmol, 1.0 equiv.) in MeCN (200 mL, 1.0M) followed by 2, 6-lutidine (5.36 g, 5.79 mL, 50 mmol, 2.5 equiv.), and drop wise addition of freshly distilled $POCl_3$ (6.13 g, 3.73 mL, 40 mmol, 2.0 equiv.), and heated at 80°C until complete as judged by TLC (2.75 h). Cooled to room temperature then poured into a seperatory funnel with Et_2O (250 mL), water (50 mL), and Et_3N (25 mL) then quickly shook and separated. Quickly extracted the aqueous with Et_2O (2 x 100 mL), to the combined organics washed with 1N NaOH (2 x 100 mL) and brine (1 x 100 mL), dried $MgSO_4$ and concentrated in vacuo to afford a dark orange oil. Crude product was purified via flash chromatography with silica gel (90 x 225 mm) eluted with 20:80:1 EtOAc:Hex:Et_3N, (R_f = 0.08, 2:8 EtOAc:Hex, Product appears blue with long wave UV) to yield 9.54 g, 88 %, **49** a viscous yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.34 (m, 10H), 6.52 (d, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 5.08 (d, *J* = 3.9 Hz, 2H), 5.07 (d, *J* = 2.6 Hz, 2H), 4.19 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.73 (t, *J* = 9.8 Hz, 1H), 3.38 (m, 1H), 2.93 (dd, *J* = 15.7, 4.4 Hz, 1H), 2.43 (s, 3H), 2.39 (d, *J* = 14.4 Hz, 1H), and 1.10-1.02 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.36, 136.41, 136.23, 128.67, 128.63, 128.20, 128.16, 127.65, 127.55, 105.84, 103.73, 99.18, 70.77, 70.17, 67.58, 57.96, 31.07, 27.79, 18.05, and 11.96. $[\alpha]^{20}_D$=-1.63°; $CHCl_3$. HREIMS calc'd for $C_{34}H_{45}NO_3Si$: 543.3169, Found: 543.3145.

(*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-3,4-dihydroisoquinoline (49b, JF-004-188) Followed the procedure for formation of **49**. Used **48** (10.11 g, 18 mmol, 1.0 equiv.), MeCN (180 mL, 1.0M) followed by 2, 6-lutidine (4.82g, 5.21 mL, 45 mmol, 2.5 equiv.), and $POCl_3$ (5.52 g, 3.36 mL, 36 mmol, 2.0 equiv.) to yield an additional 9.06 g, 93%, **49** labeled as **49b** a viscous yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.34 (m, 10H), 6.52 (d, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 5.08 (d, *J* = 3.9 Hz, 2H), 5.07 (d, *J* = 2.6 Hz, 2H), 4.19 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.73 (t, *J* = 9.8 Hz, 1H), 3.38 (m, 1H), 2.93 (dd, *J* = 15.7, 4.4 Hz, 1H), 2.43 (s, 3H), 2.39 (d, *J* = 14.4 Hz, 1H), and 1.10-1.02 (m, 21H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 142.36, 136.41, 136.23, 128.67, 128.63, 128.20, 128.16, 127.65, 127.55, 105.84, 103.73, 99.18, 70.77, 70.17, 67.58, 57.96, 31.07, 27.79, 18.05, and 11.96. $[\alpha]^{20}_D$=-1.44°; $CHCl_3$. Compound data matched that of previously synthesized.



(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline (50, JF-004-185) To a 1L round bottom flask charged with a stir bar, dissolved **49** (8.16 g, 15 mmol, 1.0 equiv.) in MeOH (500 mL, 0.03M) and cooled to -15 °C. Added $NaBH_4$ (1.13 g, 30 mmol, 2.0 equiv.) in one portion and allowed to stir at -15°C until complete as judged by TLC (2 h). Added basic Al_2O_3 (~20 g) and removed solvent in vacuuo. Crude product was purified via flash chromatography with silica gel (90 x 250 mm) eluted with 10:90:1 EtOAc:Hex:Et_3N, (R_f = 0.39, 2:8 EtOAc:Hex) to yield 7.68 g, 94 %, **50** labeled as **50a** 13:1 *cis:trans*, of a faint viscous yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.37 (m, 8H), 7.35-7.31 (m, 2H), 6.48 (d, *J* = 2.2 Hz, 1H), 6.38 (d, *J* = 2.1 Hz, 1H), 5.04 (d, *J* = 7.3 Hz, 2H), 5.03 (d, *J* = 7.0 Hz, 2H), 4.37 (q, *J* = 6.1 Hz, 1H), 3.85 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.79 (dd, *J* = 9.6, 5.5 Hz, 1H), 2.96-2.91 (m, 1H), 2.72 (dd, *J* = 15.2, 2.5 Hz, 1H) 2.58 (dd, *J* = 15.2, 11.2 Hz, 1H), 1.95 (br s, 1H), 1.51 (d, 6.27 Hz), and 1.20-1.06 (m, 21H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.64, 157.05, 137.99, 137.11, 137.08, 128.58, 128.53, 127.95, 127.77, 127.57, 127.13, 127.00, 106.15, 98.62, 70.10, 69.94, 67.11, 54.36, 49.03, 33.95, 23.20, 18.05, and 11.98.

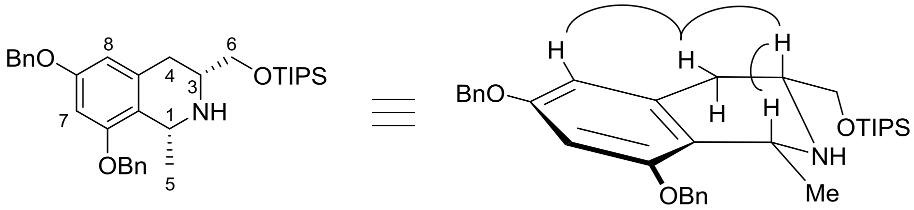
(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline (50b, JF-004-190) Followed the procedure for **50**. Used **49b** (8.97 g, 16.5 mmol, 1.0 equiv.), MeOH (550 mL, 0.03M), and $NaBH_4$ (1.25 g, 33 mmol, 2.0 equiv) to yield an additional 7.83 g, 87 %, **50** labeled as **50b** 13:1 *cis:trans*, of a faint viscous yellow oil. Compound data matches that of previously synthesized **50a**.



50

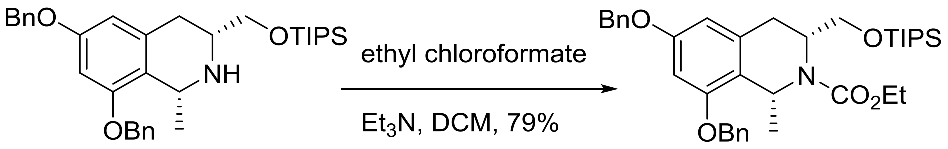
(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline (50, JF-004-191) Combined **50a** and **50b** (15.51 g) in effort to increase purity via flash chromatography with silica gel (90 x 250 mm) eluted with 5:95:1 EtOAc:Hex:Et_3N, (R_f = 0.39, 2:8 EtOAc:Hex) to recover 12.193 g, 79 %, of **50** in a 14:1 *cis:trans*, of a faint viscous yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.37 (m, 8H), 7.35-7.31 (m, 2H), 6.48 (d, *J* = 2.2 Hz, 1H), 6.38 (d, *J* = 2.1 Hz, 1H), 5.04 (d, *J* = 7.2 Hz, 2H), 5.03 (d, *J* = 7.0Hz, 2H), 4.37 (q, *J* = 6.1 Hz, 1H), 3.85 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.79 (dd, *J* = 9.6, 5.5 Hz, 1H), 2.96-2.91 (m, 1H), 2.72 (dd, *J* = 15.2, 2.5 Hz, 1H) 2.58 (dd, *J* = 15.2, 11.2 Hz, 1H), 1.95 (br s, 1H), 1.51 (d, 6.3 Hz, 3H), and 1.20-1.06 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.64, 157.05, 137.99, 137.11, 137.08, 128.58, 128.53, 127.95, 127.77, 127.57, 127.13, 127.00, 106.15, 98.62, 70.10, 69.94, 67.11, 54.36, 49.03, 33.95, 23.20, 18.05, and 11.98. $[\alpha]^{20}_D$= +45.24°; $CHCl_3$. HRCIMS calc'd for $C_{34}H_{47}NO_3Si$: 545.3325, Found: 546.405 $[M+H]^+$. THIQ stereochemistry determined by ^{1}H, ^{13}C, HMQC, and 2-D Noesy analysis.

Key nOe interactions of **50**



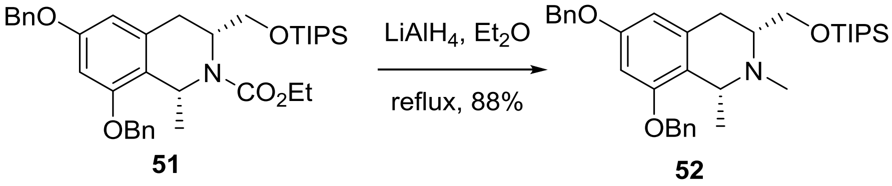
50

position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	4.37 (q, 6.1, 1H)	49.03
3	2.93 (m, 1H)	54.36
4_{ax}	2.58 (dd, 5.2, 11.2, 1H)	33.95
4_{eq}	2.72 (dd, 15.2, 2.5, 1H)	33.95
5	1.51 (d, 6.3, 3H)	23.20
6_a	3.85 (dd, 9.6, 4.4, 1H)	67.11
6_b	3.79 (dd, 9.6, 5.5, 1H)	67.11
7	6.48 (d, 2.2, 1H)	98.62
8	6.38 (d, 2.1, 1H)	106.15



50 **51**

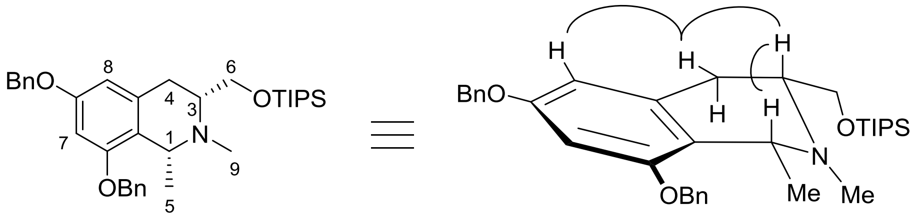
Ethyl-(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-3,4-dihydroisoquinoline-2 (1H)-carboxylate (51, JF-004-192) To a 500 mL round bottom flask charged with argon and magnetic stir bar dissolved **50** (11.05 g, 20.25 mmol, 1.0 equiv.) in DCM (203 mL, 0.1M) followed by Et_3N (8.81 g, 12.14 mL, 87 mmol, 4.3 equiv.), then cooled to 0°C followed by drop wise addition of ethyl chloroformate (4.18 g, 3.68 mL, 38.5 mmol, 1.9 equiv.), removed ice bath and stirred at room temperature until complete as judged by TLC (2.25 h). Washed with H_2O (1 x 50 mL) and brine (1 x 50 mL), dried over Na_2SO_4 and concentrated in vacuo to afford a yellow oil. Crude product was purified via flash chromatography with silica gel (70 x 225 mm) eluted with 4:95:1 EtOAc:Hex:Et_3N, (R_f = 0.41, 1:9 EtOAc:Hex) to yield 9.883 g, 79 %, **51** a clear viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.37 (m, 8H), 7.36-7.32 (m, 2H), 6.48 (d, *J* = 2.2 Hz, 1H), 6.43 (s, 1H), 5.62 (d, *J* = 49 Hz, 1H), 5.07 (s , 2H), 5.03 (s, 2H), 4.32 (br s, 1H), 4.18 (dd, *J* = 15.8, 8.9 Hz, 2H), 3.88 (s, 1H), 3.77 (s, 1H), 3.12 (d, *J* = 4.8 Hz, 1H), 2.99 (dd, *J* = 18.3, 14.1 Hz, 1H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.29 (t, *J* = 6.5, 3H), and 1.15-1.06 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.36, 155.94, 155.37, 137.01, 135.41, 134.70, 128.60, 128.00, 127.79, 127.55, 127.03, 120.82, 105.67, 98.56, 70.17, 69.98, 65.81, 64.60, 61.21, 52.64, 45.74, 30.25, 22.08, 18.05, 14.73, and 12.00. $[\alpha]^{20}_D$= +12.26°; $CHCl_3$. HREIMS calc'd for $C_{37}H_{51}NO_5Si$: 617.3537, Found: 574.2998 $[M–C_3H_7]^+$.



(1*R*,3*R*)-6,8-bis(benzyloxy)-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline (52, JF-004-193) To a 1 L round bottom flask charged with argon, magnetic stir bar, and reflux condenser, suspended $LiAlH_4$ (2.35 g, 62 mmol, 5.1 equiv.) in Et_2O (150 mL) then dissolved **51** (7.49 g, 12 mmol, 1.0 equiv.) in Et_2O (150 mL), 0.04M global concentration and heated to relfux until complete as judged by TLC (5.25 h). Cooled to 0°C and slowly quenched with H_2O (6 mL), 15 wt% NaOH:H_2O (8 mL), then additional H_2O (100 mL), filtered off salts, washed with brine (50 mL), dried over $MgSO_4$, absorbed onto basic Al_2O_3 (~20 g) and concentrated in vacuo. Crude product was purified via flash chromatography with silica gel (90 x 200 mm) eluted with 5:95:1 EtOAc:Hex:Et_3N, (R_f =

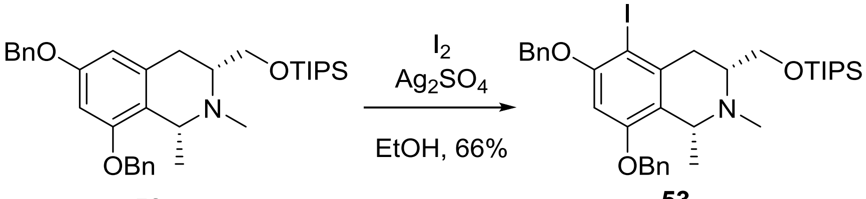
0.18, 1:9 EtOAc:Hex) to yield 6.03 g, 88 %, **52** a clear viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.37 (m, 8H), 7.36-7.31 (m, 2H), 6.48 (d, *J* = 1.7 Hz, 1H), 6.43 (d, *J* = 1.3 Hz, 1H), 5.04 (m, 4H), 4.00 (dd, *J* = 5.7, 3.3 Hz, 1H), 3.91 (dd, *J* = 6.0, 6.4 Hz, 1H), 3.60 (t, *J* = 8.3 Hz, 1H), 2.94 (dd, 12.2, 3.2 Hz, 1H), 2.67 (dd, *J* = 12.3, 3.8 Hz, 1H), 2.61 (br s / m, 1H), 2.50 (s, 3H), 1.35 (d, *J* = 5.8 Hz, 3H), and 1.18-1.03 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.85, 155.94. 137.18, 137.12, 128.56, 128.54, 127.95, 127.79, 127.63, 127.16, 105.42, 98.37, 70.14, 69.93, 67.01, 62.21, 55.36, 43.43, 32.53, 22.70, 18.06, and 11.98. $[\alpha]^{20}_{D}$= +27.34°; $CHCl_3$. HREIMS calc'd for $C_{35}H_{49}NO_3Si$: 559.3482, Found: 516.2944 $[M–C_3H_7]^+$. THIQ stereochemistry determined by ^{1}H, ^{13}C, HMQC, and 2-D Noesy analysis.

Key nOe interactions of **52**



52

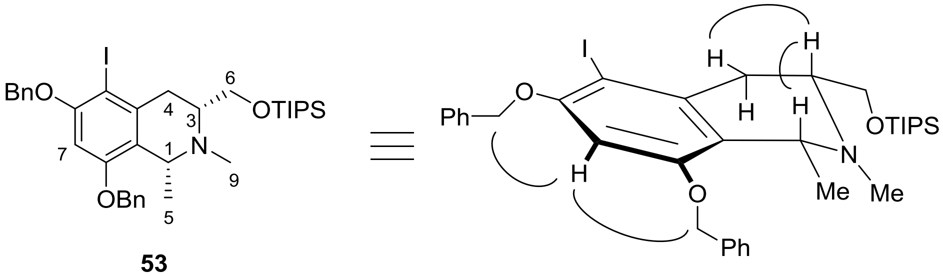
position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	3.91 (dd, 6.0, 6.4, 1H)	55.36
3	2.61 (br s / m, 1H)	62.21
4_{ax}	2.67 (dd, 12.3, 3.8, 1H)	32.53
4_{eq}	2.94 (dd, 12.2, 3.2, 1H)	32.53
5	1.35 (d, 5.8, 3H)	22.70
6_a	4.00 (dd, 5.7, 3.3, 1H)	67.01
6_b	3.60 (t, 8.3, 1H)	67.01
7	6.48 (d, 1.7, 1H)	98.37
8	6.43 (d, 1.7, 1H)	105.42
9	2.50 (s, 3H)	43.43



52 **53**

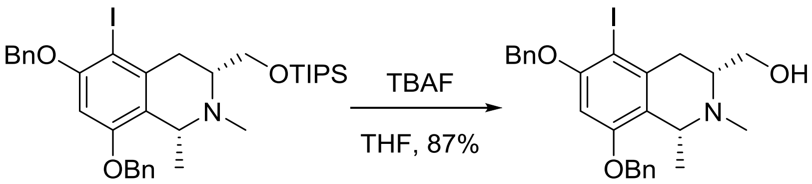
(1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline (53, JF-004-196) To a 150 mL round bottom flask charged with a stir bar added I_2 (3.02 g, 11.90 mmol, 6.60 equiv.) and Ag_2SO_4 (3.62 g, 11.61 mmol, 6.45 equiv.), dissolved in EtOH (18 mL) then wrapped in Al foil. Added **52** in EtOH (18 mL), 0.05M global concentration dropwise, stirred at room temperature until complete as judged by TLC (4.75h). Filtered to remove salts, absorbed onto basic Al_2O_3 (~10 g) and concentrated in vacuo. Crude product was purified via flash chromatography with silica gel (40 x 150 mm) eluted with 1:9:1 EtOAc:Hex:Et_3N, (R_f = 0.41, 1:9 EtOAc:Hex) to yield 2.43 g, 66 %, **53** a foamy white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.5 Hz, 2H), 7.41-7.32 (m, 8H), 6.43 (s, 1H), 5.09 (s, 2H), 5.03 (d, *J* = 3.7 Hz, 2H), 4.01 (d, *J* = 7.7 Hz, 1H), 3.91 (d, *J* = 6.3 Hz, 1H), 3.62 (t, *J* = 7.3 Hz, 1H), 3.31 (dd, 12.2, 2.4 Hz, 1H), 2.60 (d, *J* = 7.9 Hz, 1H), 2.55 (br s / m, 1H), 2.48 (s, 3H), 1.31 (d, *J* = 5.9 Hz, 3H), and 1.17-1.08 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.95, 155.84, 140.13, 136.80, 136.76, 128.64, 128.53, 127.98, 127.83, 127.11, 127.07, 97.27, 83.41, 71.35, 70.26, 66.82, 62.58, 55.59, 43.24, 37.68, 22.70, 18.10, and 12.01. $[\alpha]^{20}_D$= +33.01°; $CHCl_3$. HRCIMS calc'd for $C_{35}H_{48}NO_3SiI$: 685.2448, Found: 686.2522 $[M+H]^+$. THIQ regio and stereochemistry determined by ^{1}H, ^{13}C, HMQC, and 2-D Noesy analysis.

Key nOe interactions of **53**



53

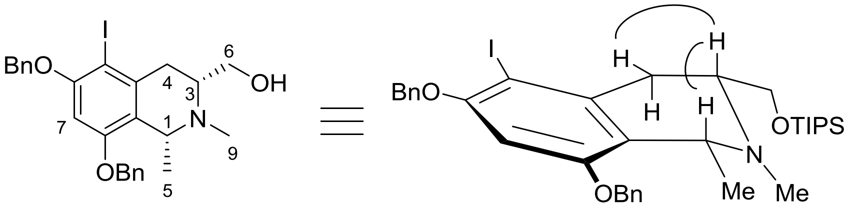
position	^{1}H (ppm, J Hz, Int)	^{13}C (ppm)
1	3.91 (d, 6.3, 1H)	55.59
3	2.55 (br s / m, 1H)	62.58
4_{ax}	2.60 (d, 7.9, 1H)	37.68
4_{eq}	3.31 (dd, 12.2, 2.4, 1H)	37.68
5	1.31 (d, 5.9, 3H)	22.70
6_a	4.01 (d, 7.7, 1H)	66.82
6_b	3.62 (t, 7.3, 1H)	66.82
7	6.48 (d, 1.7, 1H)	98.37
Bn	5.09 (s, 2H); 5.03 (s, 2H)	71.35; 70.26
9	2.48 (s, 3H)	43.24



53 **54**

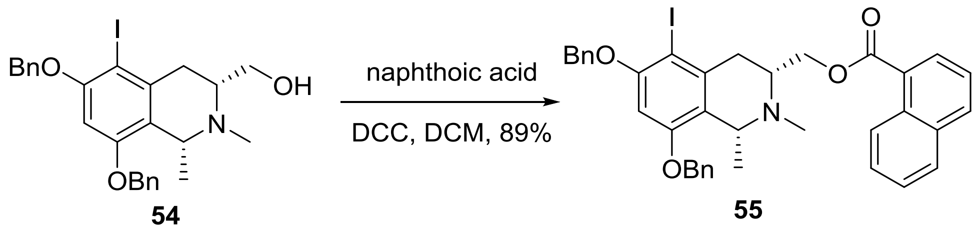
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (54, JF-004-198) To a 25 mL round bottom flask charged with a stir bar dissolved **53** (1.71 g, 2.50 mmol, 1.0 equiv.) in THF (7.5 mL, 0.2M), cooled to 0°C, the added TBAF (0.91 g, 3.25 mmol, 1.30 equiv.) in THF (3.25 mL, 1.0M) and stirred at room temperature until complete as judged by TLC (3 h). Diluted with EtOAc (150 mL), washed with sat. $NaHCO_3$ (2 x 25 mL) and brine (1 x 25 mL). Dried over $MgSO_4$, absorbed onto basic Al_2O_3 (~5 g) and concentrated in vacuo. Crude product was purified via flash chromatography with silica gel (70 x 200 mm) eluted with 2 to 5% MeOH:DCM with 1% Et_3N (R_f = 0.09, 2:98 MeOH:DCM) to yield 1.16 g, 87 %, **54** a foamy white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.42-7.31 (m, 8H), 6.45 (s, 1H), 5.09 (s, 2H), 5.04 (s, 2H), 4.04 (q, *J* = 6.8 Hz, 1H), 3.78 (dd, *J* = 10.6, 4.2 Hz, 1H), 3.50 (dd, *J* = 10.7, 3.2 Hz, 1H), 3.05 (dd, *J* = 16.2, 4.5 Hz, 1H), 2.81 (dd, *J* = 16.2, 10.7 Hz, 1H), 2.59 (m, 2), 2.59 (m OH), 2.44 (s, 3H), and 1.31 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.11, 155.72, 139.97, 136.68, 136.64, 128.68, 128.57, 128.07, 127.90, 127.14, 127.07, 123.33, 97.29, 82.98, 71.36, 70.31, 62.95, 61.21, 54.87, 43.49, 36.40, and 23.77. $[\alpha]^{20}_D$= +33.01°; $CHCl_3$. HRCIMS calc'd for $C_{26}H_{28}NO_3I$: 529.1114, Found: 530.1194 $[M+H]^+$. THIQ regio and stereochemistry determined by ^{1}H, ^{13}C, HMQC, and 2-D Noesy analysis.

Key nOe interactions of **54**



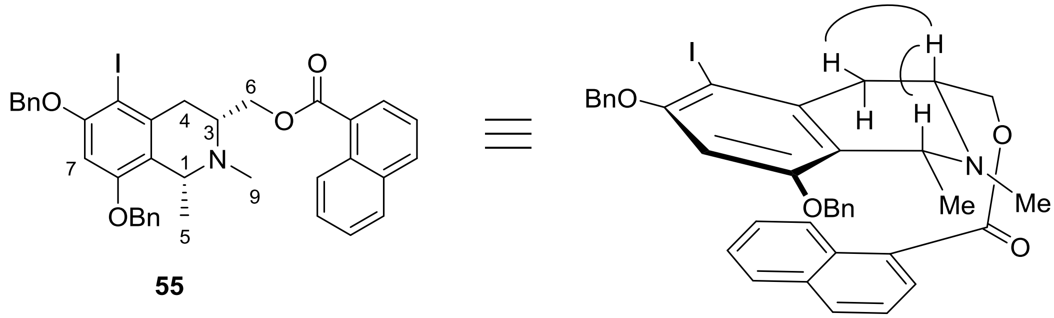
54

position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	4.04 (q, 6.8, 1H)	54.87
3	2.59 (m, 1H)	61.21
4_{ax}	2.81 (dd,16.2, 10.7, 1H)	36.40
4_{eq}	3.05 (dd, 16.2, 4.5, 1H)	36.40
5	1.31 (d, 6.8 Hz, 3H)	23.77
6_a	3.78 (dd, 10.6, 4.2, 1H)	62.95
6_b	3.50 (dd, 10.7, 3.2, 1H)	62.95
7	6.45 (s, 1H)	97.29
Bn	5.09 (s, 2H); 5.04 (s, 2H)	71.36; 70.31
9	2.44 (s, 3H)	43.49



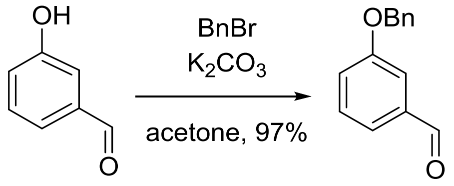
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl 1-naphthoate (55, JF-004-200) To a 50 mL round bottom flask charged with argon and magnetic stir bar, dissolved **54** (635 mg, 1.2 mmol, 1.0 equiv.), DCC (322 mg, 1.56 mmol, 1.3 equiv.), DMAP (29 mg, 0.24 mmol, 0.2 equiv.), and 1-naphthoic acid (413 mg, 2.4 mmol, 2.0 equiv.) in DCM (16 mL, 0.08M) then stirred at room temperature until complete as judged by TLC (15 h). Diluted with DCM (50 mL), washed with sat. $NaHCO_3$ (25 mL), brine (25 mL), dried over $MgSO_4$, absorbed onto basic Al_2O_3 (~5 g) and concentrated in vacuo. Crude product was purified via flash chromatography with silica gel (25 x 150 mm) eluted with 1:9 EtOAc:Hex with 1% Et_3N, (R_f = 0.15, 1:9 EtOAc:Hex) to yield 731 mg, 89 %, **55** a white foamy solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, *J* = 8.6 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.63 (ddd, *J* = 8.6, 6.8, 1.4 Hz, 1H), 7.56-7.47 (m, 4H), 7.41-7.31 (m, 8H), 6.45 (s, 1H), 5.09 (s, 2H), 5.05 (d, *J* = 3.6 Hz, 2H), 4.64 (dd, *J* = 11.1, 4.1 Hz, 1H), 4.48 (dd, *J* = 11.1, 6.3 Hz, 1H), 4.00 (q, *J* = 6.6 Hz, 1H), 3.29 (dd, *J* = 15.4, 3.6 Hz, 1H), 2.96-2.88 (m, 1H), 2.84 (dd, *J* = 15.4, 9.8 Hz, 1H), 2.58 (s, 3H), and 1.37 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.52, 156.05, 155.90, 139.17, 136.65, 133.37, 130.36, 128.67, 128.55, 128.50, 128.04, 127.88, 127.80, 127.12, 127.08, 126.17, 125.99, 124.54, 97.47, 83.16, 71.38, 70.30, 67.33, 59.24, 55.39, 43.05, 38.04, and 22.73. $[\alpha]^{20}_D$= +37.19°; $CHCl_3$. HREIMS calc'd for $C_{37}H_{34}NO_4I$: 683.1533, Found: 684.1631 $[M + H]^+$. THIQ regio and stereochemistry determined by ^{1}H, ^{13}C, HMQC, and 2-D Noesy analysis.

Key nOe interactions of **55**



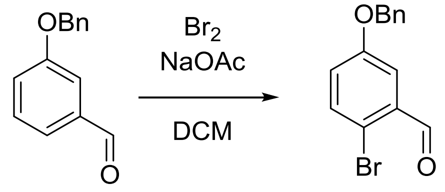
55

position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	4.00 (q, 6.6, 1H)	55.39
3	2.91 (m, 1H)	59.24
4_{ax}	2.84 (dd,15.4, 9.8, 1H)	38.04
4_{eq}	3.29 (dd,15.4, 3.6, 1H)	38.04
5	1.37 (d, 6.6, 3H	22.73
6_a	4.64 (dd, 11.1, 4.1, 1H)	67.33
6_b	4.48 (dd, 11.1, 6.3, 1H)	67.33
7	6.45 (s, 1H)	97.47
Bn	5.09 (s, 2H); 5.05 (d, 3.6, 2H)	71.38; 70.30
9	2.58 (s, 3H)	43.05



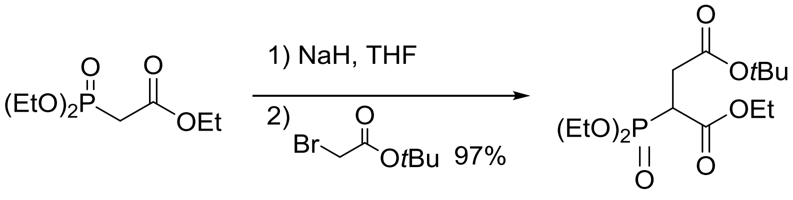
56 **57**

3-benzyloxy benzaldehyde (57, JF-004-153) To a 250mL round bottom flask charged with a magnetic stir bar, 3-hydroxybenzaldehyde **56** (30.53 g, 250 mmol, 1.0 equiv.), K_2CO_3 (41.46 g, 300 mmol, 1.20 equiv.) and dissolved in acetone (100 mL, 2.5M). Cooled to ~0°C and added via syringe benzyl bromide (49.17 g, 34.15 mL, 287.5 mmol, 1.15 equiv.). The reaction was allowed to stir and warm to RT overnight (16 h). Solid residue was removed via vacuum filtration and filtrate was concentrated in vacuuo. The resulting oil was dissolved in Et_2O (500 mL) and washed with 1N NaOH (2 x 200 mL), brine (1 x 100 mL), dried over $MgSO_4$, and concentrated. The crude product was purified via recrystallization from hot Et_2O and cold *n*-Pentane, the filtrate was concentrated in vacuuo and subjected to flash chromatography with silica gel (50 x 150 cm) eluted with 1:9 EtOAc:Hex (R_f = 0.34, 1:9 EtOAc:Hex) Combined yield from recrystallization and flash chromatography was 51.23 g, 97 %, **57** a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.47 (m, 5H), 7.40 (m, 2H), 7.35 (m, 1H), 7.26 (m, 1H), and 5.13 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.01, 159.32, 137.84, 136.31, 130.11, 128.67, 128.19, 127.53, 123.65, 122.17, 113.31, and 70.24. HREIMS calc'd for $C_{14}H_{12}O_2$: 212.0837, Found: 212.0838



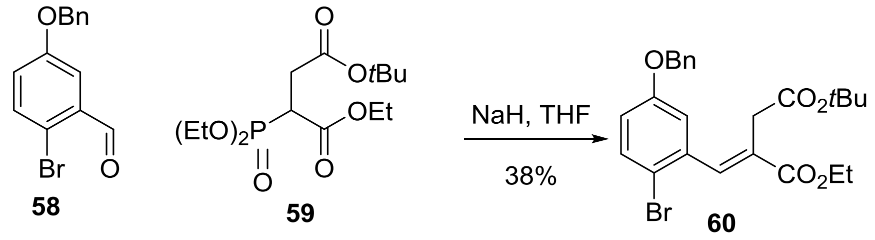
57 58

5-(benzyloxy)-2-bromobenzaldehyde (58, JF-004-171) To a 2 L three neck round bottom flask charged with a magnetic stir bar, argon, and addition funnel, dissolved **57** (49.88 g, 235 mmol, 1.0 equiv) in DCM (712 mL, 0.33M) followed by NaOAc (131.08 g, 1.6 mol, 6.80 equiv.) then cooled to ~0°C. Added Br_2 (187.8 g, 60.2 mL, 1.18 mol, 5.0 equiv.) via addition funnel over ~ 45 min, then removed ice bath and allowed to stir at room temperature for until complete as judged by TLC (5.25 h). Quenched with ice (~ 0.5 kg) and water (0.5 L), added sodium thiosulfate (250 g) and stirred until the bromine color had faded then separated. Extracted with DCM (4 x 250 mL), washed with sat. $NaHCO_3$ (2 x 250 mL) and brine (2 x 250 mL), dried over $MgSO_4$ and removed solvent in vaccuo to afford a yellow solid. The crude produict was purified via flash chromatography with silica gel (90 x 225 cm) eluted with 3:97 EtOAc:Hex (R_f = 0.33, 5:95 EtOAc:Hex) to yield 59.26 g, 87 %, **58** as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 3.2 Hz, 1H), 7.44-7.33 (m, 5H), 7.10 (dd, *J* = 8.8, 3.2 Hz, 1H), and 5.10 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.65, 158.37, 135.90, 134.63, 134.01, 128.69, 128.30, 127.54, 123.69, 118.15, 113.88, and 70.46. HREIMS calc'd for $C_{14}H_{11}BrO_2$: 289.9942, Found: 289.9944



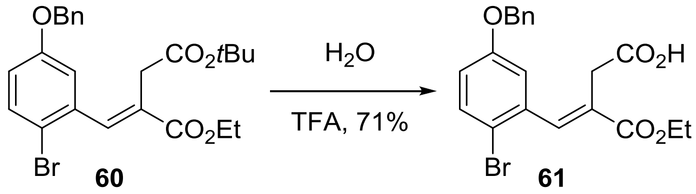
59

4-(*t*-butyl) 1-ethyl 2-(diethoxyphosphoryl)succinate (59, JF-004-163) To a dry 1 L round bottom flask charged with a stir bar and argon, suspended NaH (55 wt%, 13.2 g, 275 mmol, 1.10 equiv.) in THF (111 mL) and cooled to 0°C. To a dry 500 mL round bottom flask charged with argon, dissolved ethyl 2-(diethoxyphosphoryl)acetate (56.05 g, 49.60 mL, 250 mmol, 1.00 equiv.) in THF (222 mL) and transferred via cannula to the NaH suspension over 30 min then stirred for 1 h at 0°C. To a dry 250 mL round botton flask charged with argon dissolved *t*-butyl bromoacetate (52.42 g, 39.68 mL, 267.5 mmol, 1.07 equiv.) in THF (167 mL, 1.6M) and transferred via cannula over 30 min, allowed to stir and warm to room temperature until complete as judged by TLC (13 h) (Note: reaction turned cloudy white suspension). Quenched reaction with ice / H_2O (150 mL) then extracted with EtOAc (5 x 100 mL), washed with brine (2 x 100 mL), dried over $MgSO_4$ and concentrated in vaccuo to afford a pale yellow oil. Crude product was purified via flash chromatography with silica gel (75 x 250 mm) eluted with 1:1 EtOAc:Hex (R_f = 0.22, 1:1 EtOAc:Hex, developed with $KMnO_4$) to yield 81.79 g, 97 %, **59** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37-3.98 (m, 6H), 3.37 (ddd, J = 24.0, 11.6, 3.4 Hz, 1H), 2.96 (ddd, J = 17.5, 11.6, 7.1 Hz, 1H), 2.70 (ddd, J = 17.4, 9.1, 3.4 Hz, 1H), 1.40 (s, 9H), and 1.35-1.22 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.27 (d, J_{CP} = 6.05 Hz), 16.36 (d, J_{CP} = 6.25 Hz), 32.50 (d, J_{CP} = 2.64 Hz), 41.41 (d, J_{CP} = 131.13 Hz), 61.57, 62.84 (d, J_{CP} = 6.94 Hz), 63.27 (d, J_{CP} = 7.17 Hz), 168.26 (d, J_{CP} = 5.52 Hz), and 170.07 (d, J_{CP} = 19.43 Hz). HREIMS calc'd for $C_{14}H_{27}O_7P$: 338.1494, Compound data matches that of previously reported.[54]



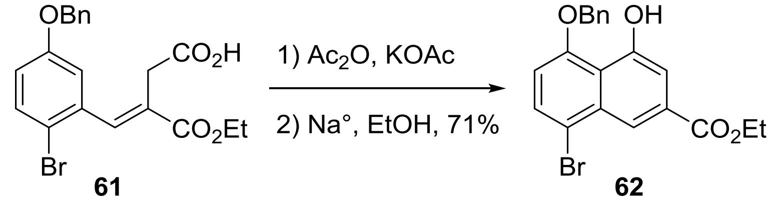
4-(*t*-butyl) 1-ethyl (E)-2-(5-(benzyloxy)-2-bromobenzylidene)succinate (60, JF-004-174) To a dry 1 L round bottom flask charged with a stir bar and argon, suspended NaH (50 wt%, 9.76 g, 203 mmol, 1.07 equiv.) in THF (50 mL) and cooled to 0°C. To a dry 500 mL round bottom flask charged with argon, dissolved **59** (68.78 g, 203 mmol, 1.07 equiv.) in THF (200 mL, 1M) and transferred via cannula to the NaH suspension over 30 min at 0°C then stirred for 6 h at room temperature. (Note: solution turned dark yellow). Recooled to 0°C and to a dry 250 mL round bottom flask charged with argon dissolved **58** (55.32 g, 190 mmol, 1.0 equiv.) in THF (190 mL, 1M) and transferred via cannula over 30 min, allowed to stir and warm to room temperature until complete as judged by TLC (13 h) (Note: reaction turned dark brown). Reduced reaction volume by ~50% in vacuuo before diluting with Et_2O

(200 mL), water (300 mL) and separated. Extracted with Et_2O (4 x 250 mL), washed with sat $NaHCO_3$ (2 x 200 mL), and brine (2 x 200 mL). Dried over $MgSO_4$ and removed solvent in vaccuo to afford a dark brown oil. Crude product was purified via flash chromatography with silica gel (90 x 250 mm) eluted with 5:95 EtOAc:Hex (R_f = 0.24, 1:9 EtOAc:Hex, developed with $KMnO_4$) to yield 33.93 g, 38 %, **60** as a faint yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s,1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.41-7.34 (m, 5H), 7.04 (d, *J* = 3.0 Hz, 1H), 6.84 (dd, *J* = 8.8, 3.0 Hz, 1H), 5.01 (s, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.32 (s, 2H), 1.46 (s, 9H), and 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.17, 166.86, 157.84, 140.53, 136.42, 136.26, 133.40, 128.61, 128.41, 128.15, 127.44, 117.39, 116.08, 114.63, 81.10, 70.25, 61.18, 35.13, 28.00, and 14.23. HREIMS calc'd for $C_{24}H_{27}O_5Br$: 474.1042, Found: 474.1034



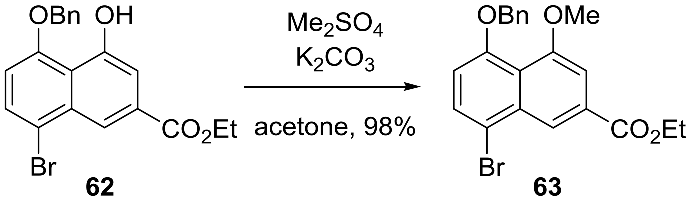
(E)-4-(5-(benzyloxy)-2-bromophenyl)-3-(ethoxycarbonyl)but-3-enoic acid (61, JF-004-176) To a 250 mL round bottom flask charged with a stir bar dissolved **60** (33.28 g, 70 mmol, 1.0 equiv.) in trifluoroacetic acid (106 g, 71 mL, 928 mmol, 13.25 equiv.) then added water (7.7 mL,427 mmol, 6.10 equiv.) and stirred at room temperature open to the atmosphere until complete as judged by TLC (3h). Removed TFA invaccuo and dissolved the resulting oil in DCM (500 mL), washed with H_2O (3 x 150 mL) and brine (2 x 150 mL). Dried over $MgSO_4$ and concentrated in vaccuo to afford a yellow solid. Crude product was purified via flash chromatography with silica gel (90 x 175 mm) eluted with 25:75:1

EtOAc:Hex:AcOH (R_f = 0.13, 1:3 EtOAc:Hex) to yield 20.79 g, 71 %, **61** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s,1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.38-7.28 (m, 5H), 6.95 (d, *J* = 3.0 Hz, 1H), 6.87 (dd, *J* = 8.8, 3.0 Hz, 1H), 5.04 (s, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.36 (s, 2H), and 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.46, 166.80, 157.83, 141.63, 136.19, 135.91, 133.58, 128.65, 128.10, 127.21, 127.13, 117.81, 115.93, 114.49, 70.18, 61.55, 33.69, and 14.12. HREIMS calc'd for $C_{20}H_{19}O_5Br$: 418.0416, Found: 418.0412.

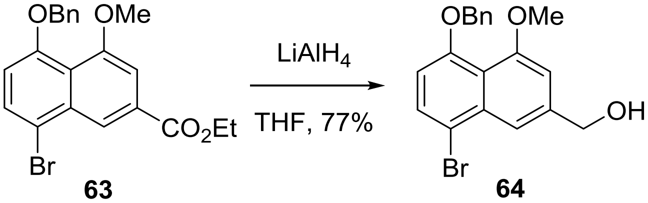


ethyl 5-(benzyloxy)-8-bromo-4-hydroxy-2-naphthoate (62, JF-004-182) To a dry 1 L round bottom flask charged with argon, stir bar, and a water condenser dissolved **61** (20.54 g, 49 mmol, 1.0 equiv.) in acetic anhydride (490 mL, 0.1M) then added KOAc (5.39 g, 54.9 mmol, 1.12 equiv.). Heated to and maintained reflux until complete as judged by TLC (~15 min.) (R_f = 0.38, 1:3 EtOAc:Hex). Poured reaction over ice with K_2CO_3 (200 g) and stirred. Extracted with DCM (4 x 250 mL), washed with brine (250 mL) and dried over Na_2SO_4. Removed solvent invaccuo and azeotoped the remaining acetic acid with toluene (4 x 150 mL) to afford a brown solid. To a dry 2 L round bottom flask charged with argon and a stir bar dissolved Na° (19.26 g, 17.1 equiv.) in EtOH (700 mL, 0.07M) followed by slow addition of the intermediate dissolved in EtOH (50 mL) allowed reaction to stir at room temperature until complete as judged by TLC (14 h). The reaction was acidified with 2N

HCl (400 mL) and extracted with EtOAc (5 x 250 mL), washed with 2N HCl (2 x 250 mL) and brine (250 mL), dried over $MgSO_4$ and concentrated in vacuuo to afford a brown solid. Crude product was purified via flash chromatography with silica gel (90 x 225 mm) eluted with 15:85 EtOAc:Hex:AcOH (R_f = 0.46, 1:3 EtOAc:Hex) to yield 14.15 g, 71 %, **62** as an off white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.44 (d, *J* = 1.5 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.51-7.40 (m, 6H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.28 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), and 1.44 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.17, 15.08, 154.90, 134.45, 133.96, 130.83, 130.18, 129.1, 128.03, 120.89, 118.26, 116.52, 111.19, 107.71, 72.17, 61.33, and 14.33. HREIMS calc'd for $C_{20}H_{17}O_4Br$ 400.0310, Found: 400.0286

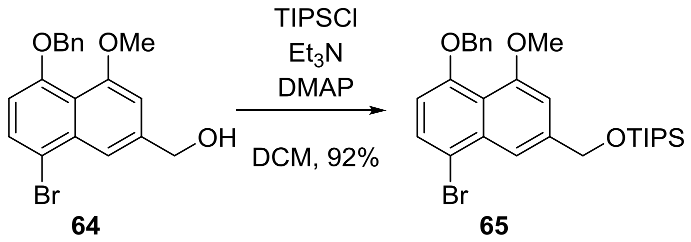


ethyl 5-(benzyloxy)-8-bromo-4-methoxy-2-naphthoate (63, JF-004-189) To a 500 mL round bottom flask charged with a stir bar and reflux condenser dissolved **62** (14.04 g, 35 mmol, 1.0 equiv.) in acetone (233 mL, 0.15M) followed by addition of K_2CO_3 (12.58 g, 91 mmol, 2.60 equiv.) and Me_2SO_4 (12.58 g, 9.46 mL, 99.8 mmol, 2.85 equiv.) at room temperature. Heated to reflux until complete as judged by TLC (14 h). Diluted with EtOAC (200 mL) and reduced volume by 50% , repeated thrice times. Diluted with EtOAc (250 mL) and washed with sat $NaHCO_3$ (2 x 150 mL), brine (1 x 150 mL), dried over $MgSO_4$ and concentrated to afford a white solid. Crude product was passed over a bed of silica gel (75 x 75mm) eluted with 1:9 EtOAc:Hex (R_f = 0.33, 1:9 EtOAc:Hex) to yield 14.29 g, 98 %, **63** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.48 (s, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.14 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), and 1.45 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.43, 157.74, 155.95, 136.87, 134.27, 131.09, 129.43, 128.43, 127.75, 126.91, 122.52, 121.25, 115.32, 110.81, 105.69, 71.58, 61.38, 56.39, and 14.38. HREIMS calc'd for $C_{21}H_{19}O_4Br$ 414.0467, Found: 414.0451.

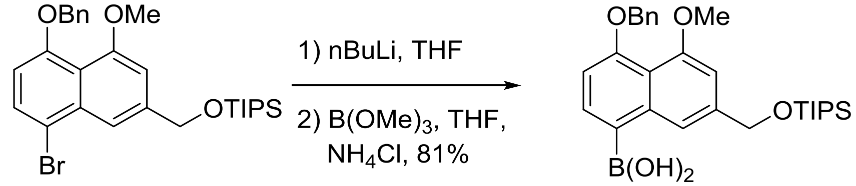


63 **64**

(5-(benzyloxy)-8-bromo-4-methoxynaphthalen-2-yl)methanol (64, JF-004-195) To a dry 500 mL round bottom flask charged with argon and a stir bar suspended $LiAlH_4$ (1.92 g, 50.63 mmol, 1.5 equiv.) in THF (85 mL) then cooled to 0°C. Added **63** (14.02 g, 34 mmol, 1.0 equiv.) in THF (85 mL) drop wise then stirred and allowed to warm to room temperature until complete as judged by TLC (14 h, R_f = 0.12, 1:4 EtOAc:Hex). Cooled o 0°C and slowly quenched with MeOH (~25 mL), diluted with EtOAc (300 mL) and washed with 10 wt% KF:H_2O (2 x 200 mL), brine (1 x 100 mL), dried over $MgSO_4$ and concentrated to afford an off white solid (4:1 brominated:debrominated by GCMS) Recrystallized form EtOH to yield 9.67 g, 77 %, **64** as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 7.1 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.4Hz, 1H), 6.93 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.17 (s, 2H), 4.83 (s, 2H), 3.95 (s, 3H), and 1.86 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.84, 156.04, 140.63, 137.15, 134.78, 130.67, 128.40, 127.68, 126.95, 118.64, 117.27, 114.16, 108.88, 105.66, 71.54, 65.45, and 56.32. HREIMS calc'd for $C_{19}H_{17}O_3Br$ 372.0361, Found: 372.0352.

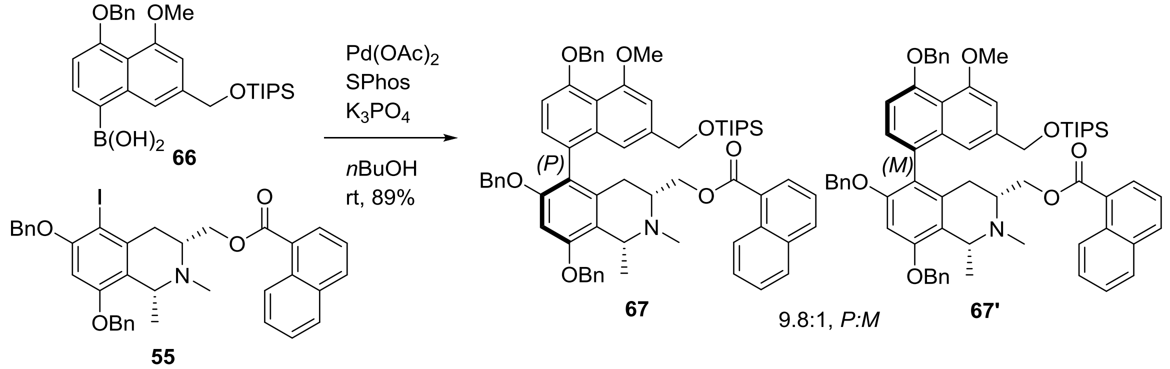


((5-(benzyloxy)-8-bromo-4-methoxynaphthalen-2-yl)methoxy)triisopropylsilane (65, JF-004-197) To a dry 250 mL round bottom flask charged with argon and a stir bar dissolved **64** (9.33 g, 25 mmol, 1.0 equiv.), DMAP (0.31 g, 2.5 mmol, 0.1 equiv.) and Et_3N (2.78g, 3.83 mL, 27.5 mmol, 1.1 equiv.) in DCM (50 mL, 0.5M) and cooled to 0°C. Added TIPSCl (7.23 g, 8.02 mL, 37.5 mmol, 1.5 equiv.) drop wise, stirred and allowed to warm to room temperature until complete as judged by TLC (15.5h). Partioned into sat $NaHCO_3$ (100 mL) and separated, extracted with DCM (4 x 50 mL), washed with brine (50 mL), dried over $MgSO_4$ and concentrated to afford an off white solid. R_f = 0.12, 1:4 EtOAc:Hex). Cooled o 0°C and slowly quenched with MeOH (~25 mL), diluted with EtOAc (300 mL) and washed with 10 wt% KF:H_2O (2 x 200 mL), brine (1 x 100 mL), dried over $MgSO_4$ and concentrated to afford an off white solid Crude product was purified via flash chromatography with silica gel (90 x 250 mm) eluted with 5:95 EtOAc:Hex, (R_f = 0.47, 1:9 EtOAc:Hex) to yield 12.14 g, 92 %, **65** as a white solid.. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.7Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 2H), 5.02 (s, 2H), 3.96 (s, 3H), 1.29-1.20 (m, 3H), and 1.17-1.12 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.50, 156.06, 141.63, 137.28, 134.87, 130.39, 128.38, 127.61, 126.95, 118.32, 116.03, 114.29, 108.44, 105.03, 71.54, 65.01, 56.26, 18.09, and 12.11. HREIMS calc'd for $C_{28}H_{37}O_3BrSi$ 528.1695, Found: 528.1700.



65 **66**

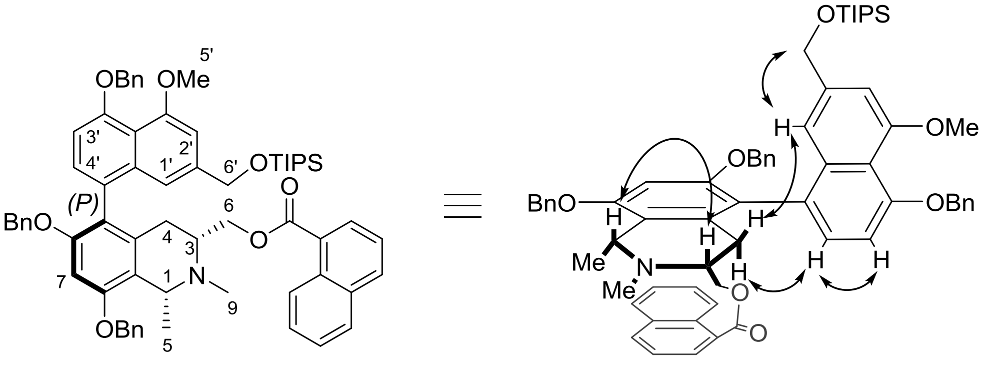
(4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy)methyl)naphthalen-1-yl)boronic acid (66, JF-004-199) To a dry 500 mL round bottom flask charged with argon and a stir bar dissolved **65** (8.21 g, 15.5 mmol, 1.0 equiv.), in THF (155 mL, 0.1M) and cooled to -78°C. Added *n*BuLi (1.09 g, 7.93 mL, 17.05 mmol, 1.1 equiv., 2.15M) drop wise and allowed to stir for ~ 15 min. at -78°C. (Note: formed yellow solution) then added $B(OMe)_3$ (8.05 g, 8.64 mL, 77.5 mmol, 5.0 equiv.) quickly (Note: reaction turned clear) stirred and allowed to warm to room temperature overnight. Diluted with EtOAc (300 mL), washed with sat. $NaHCO_3$ (3 x 150 mL) and brine (2 x 100 mL). Dried over $MgSO_4$ and removed solvent in vacuuo to afford a pink solid. Recrystallized from PhMe and *n*Pent to yield 6.23 g, 81%, **66** as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, *J* = 1.1 1H), 8.58 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.1 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 1.0 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 5.31 (s, 2H), 5.02 (s, 2H), 4.01 (s, 3H), 1.21-1.12 (m, 3H), and 1.10-1.05 (d, *J* = 6.6 Hz, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.30, 157.90, 141.75, 140.82, 139.21, 137.26, 128.41, 127.61, 126.85, 117.35, 117.04, 106.17, 104.93, 70.65, 65.72, 56.08, 18.09, and 12.08. CIMS calc'd for $C_{28}H_{39}O_5BSi$ 494.2660, Found: 451.28 $[M–C_3H_7]^+$.



((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy) methyl) naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl1-naphthoate (67 and 67', JF-004-202) To a dry 25 mL round bottom flask charged with argon and magnetic stir bar, added **55** (273 mg, 0.4 mmol, 1.0 equiv.), **66** (297 mg, 0.6 mmol, 1.5 equiv.), $Pd(OAc)_2$ (3.6 mg, 0.016 mmol, 0.04 equiv.), SPhos (13 mg, 0.032 mmol, 0.08 equiv.), and K_3PO_4 (272 mg, 1.3 mmol, 3.2 equiv.) then evacuated and backfilled with argon thrice times. Added *n*BuOH (11.4 mL, 0.04M), wrapped in Al foil then stirred at room temperature until complete as judged by TLC (21 h). Diluted with brine (25 mL) and extracted with DCM (4 x 25 mL), washed combined organics with sat. $NaHCO_3$ (2 x 25 mL) and brine (1 x 25 mL), dried over $MgSO_4$, absorbed onto basic Al_2O_3 (~5 g) and concentrated in vacuo. Crude product was purified via flash chromatography with silica gel (50 x 150 mm) eluted with 2:8 EtOAc:Hex with 1% Et_3N, (R_f = 0.24, 2:8 EtOAc:Hex) to yield 357 mg, 89 %, **67/67'** as a white foamy solid, (9.8:1 *P/M)* as inseparable isomers. Data for *P* atropisomer **67**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, *J* =

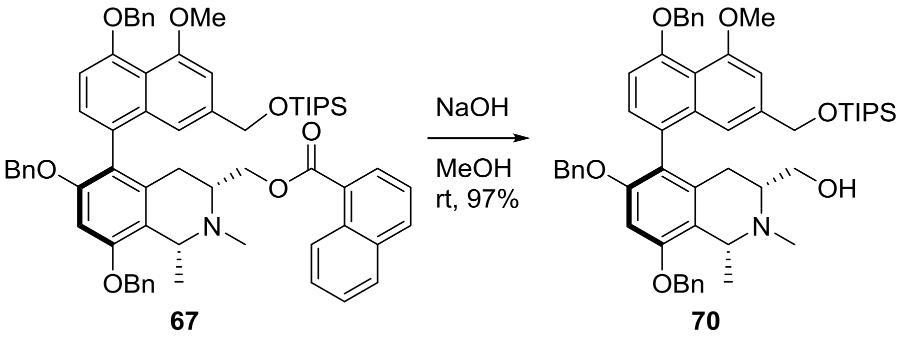
8.1 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 6.2 Hz, 1H), 7.67 (d, *J* = 7.18 Hz, 2H), 7.53-7.34 (m, 13H), 7.17 (dd, *J* = 1.2 Hz, 1H), 7.16 (d, *J* = 1.2 Hz, 1H), 7.15 (d, *J* = 1.2 Hz, 1H), 7.10 (s, 1H), 6.97-6.94 (m, 2H), 6.83 (d, *J* = 9.0 Hz, 1H), 6.60 (s, 1H), 5.19-5.09 (m, 4H), 4.90-4.83 (m, 2H), 4.82-4.76 (m, 2H), 4.54 (dd, *J* = 10.7, 3.7 Hz, 1H), 4.12 (dd, *J* = 12.8, 6.2 Hz, 1H), 4.08 (dd, *J* = 10.2, 7.9 Hz, 1H), 3.95 (s, 3H), 2.82 (m, 1H), 2.67 (dd, *J* = 15.8, 3.6 Hz, 1H), 2.59 (s, 3H), 2.34 (dd, *J* = 15.6, 9.9 Hz, 1H), 1.46 (d, *J* = 6.2 Hz, 3H), 1.10-1.01 (m, 3H), and 0.99-0.95 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.16, 157.41, 155.67, 155.51, 154.95, 139.90, 137.97, 137.49, 137.30, 136.79, 136.06, 133.69, 133.02, 131.28, 130.11, 128.63, 128.51, 128.33, 128.19, 127.91, 127.59, 127.57, 127.42, 127.28, 127.26, 126.92, 126.67, 126.06, 125.83, 124.49, 122.02, 121.91, 117.30, 114.66, 107.76, 104.22, 97.67, 71.32, 70.96, 70.18, 67.53, 65.04, 59.07, 56.13, 55.22, 43.61, 29.41, 23.05, 18.03, and 11.99. $[\alpha]^{20}_{D}$= +8.45°; $CHCl_3$. $[M + H]^+$. Key nOe were observed in agreement with literature observed nOe shown below, assignments made by use of ^{1}H, ^{13}C, HMQC, HMBC, COSY and NOESY NMR. Data for *M* atropisomer **67'**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (d, *J* = 7.7 Hz, 1H), 8.22 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 7.1Hz, 1H), 7.77 (d, *J* = 6.9 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.53-7.49 (m, 12H), 7.22 (d, *J* = 4.5 Hz, 1H), 7.03-7.00 (m, 2H), 6.92 (d, *J* = 4.3 Hz, 2H), 6.78 (s, 1H), 6.57 (s, 1H), 6.49 (s, 1H), 6.41 (s, 1H), 5.17 (m, *2*H), 5.03 (m, 2H), 4.75 (m, 2H), 4.65, (m, 2H), 4.41 (dd, *J* = 11.0, 4.2 Hz, 1H), 4.20 (d, *J* = 7.1 Hz, 1H), 4.18 (d, *J* = 7.2 Hz, 1H), 3.98 (s, 3H), 2.90 (m, 1H), 2.61 (s, 3H), 2.48 (m, 2H), 1.40 (d, *J* = 6.6 Hz, 3H), 1.10-1.01 (m, 3H), and 0.99-0.95 (m, 18H)

Key nOe interactions of **67**



67

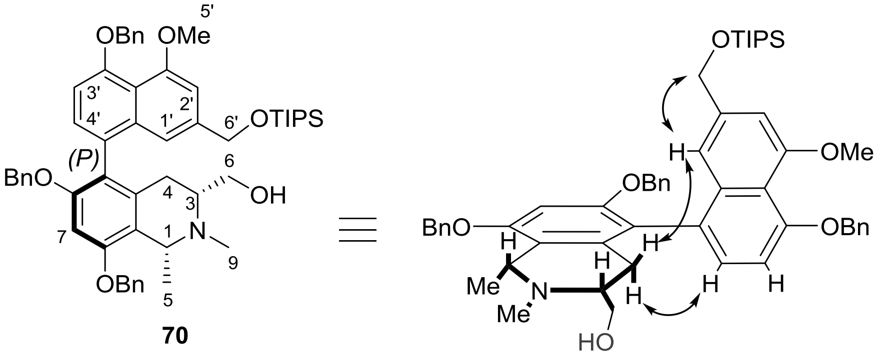
position	^{1}H (ppm, *J* Hz, Int)	^{13}C (ppm)
1	4.12 (dd, 12.8, 6.2, 1H)	55.22
3	2.82 (m, 1H)	59.07
4_{ax}	2.34 (dd, 15.6, 9.9, 1H)	29.41
4_{eq}	2.67 (dd, 15.8, 3.6, 1H)	29.41
5	1.46 (d, 6.2, 3H)	23.05
6_{a}	4.54 (dd, 10.7, 3.7, 1H)	67.53
6_{b}	4.08 (dd, 10.2, 7.9, 1H)	67.53
7	6.60 (s, 1H)	97.67
9	2.59 (s, 3H)	43.61
1'	7.17 (d, 1.2, 1H)	128.19
2'	7.16 (d, 1.2, 1H)	127.59
3'	7.15 (d, 1.2, 1H)	127.57
4'	7.10 (s, 1H)	114.66
5'	3.95 (s, 3H)	56.13
6'	4.80 (m, 2H)	65.04



((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy) methyl naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (70, JF-004-206) To a dry 100 mL round bottom flask charged argon, ~0.2 g 4Å molecular sieves, and a magnetic stir bar, added dissolved **67** (302 mg, 0.3 mmol, 1.0 equiv.) in dry THF:MeOH (30 mL, 0.01M) followed by NaOH (600 mg, 15 mmol, 50 equiv.) then stirred at room temperature until complete as judged by TLC (4 h). Note: aide in absorbing any residual moisture, prevent the aq. Base catalyzed epimerization, and may not be left in solution once complete) Diluted with Et_2O (50 mL) and washed with sat. $NaHCO_3$ (1 x 25 mL), extracted aqueous with Et_2O (3 x 25 mL), washed combined organics with brine (1 x 25 mL), dried over $MgSO_4$, absorbed onto basic Al_2O_3 (~1 g) and concentrated in vacuo. Crude product was purified via flash chromatography with silica gel (50 x 150 mm) eluted with 5:95 MeOH:DCM with 1% Et_3N, (R_f = 0.28, 7:93 MeOH:DCM) to yield 248 mg, 97 %, **70** as a white foamy solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.40 (m, 6H), 7.35 (dt, *J* = 15.0, 9.6 Hz, 3H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.15-7.13 (m, 3H), 7.00 (s, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.93 (dd, *J* = 6.2, 3.0 Hz, 2H), 6.85 (s, 1H), 6.56 (s, 1H), 5.25 (s, 2H), 5.07 (q, *J* = 11.8 Hz, 2H), 4.84 (d, *J* = 12.4 Hz, 2H), 4.79 (dd, *J* = 13.0, 6.1 Hz, 2H), 4.15 (dd, *J* = 13.4, 6.7 Hz, 1H), 3.97 (s, 3H), 3.55 (dd, *J* = 10.5, 3.8 Hz, 1H), 3.14 (d, *J* = 9.2 Hz, 1H), 2.65 (br s, 1H), 2.46 (dd, *J* = 10.8, 3.4 Hz, 1H), 2.43 (s, 3H), 2.33

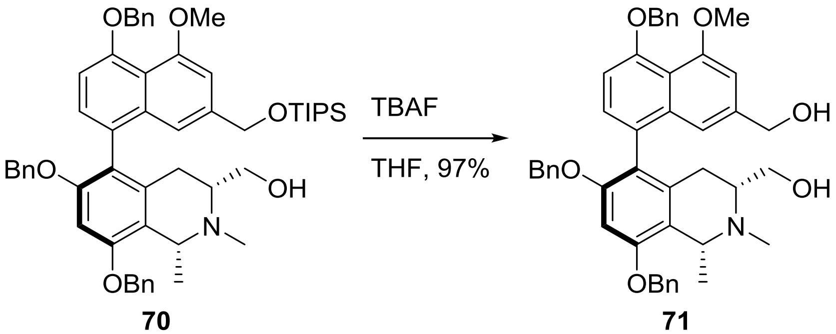
(dd, J = 15.8, 11.0 Hz, 1H), 2.24 (dd, J = 15.9, 4.5 Hz, 1H), 1.39 (d, J = 6.6 Hz, 3H), 1.08-1.05 (m, 3H), and 0.98 (d, J = 6.2 Hz, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.40, 155.79, 155.54, 154.79, 139.91, 137.91, 137.47, 137.26, 136.84, 128.63, 128.38, 128.33, 128.20, 128.17, 127.94, 127.65, 127.44, 127.29, 127.27, 127.01, 126.65, 126.55, 122.04, 117.36, 114.66, 107.96, 104.28, 97.48, 71.54, 70.98, 70.17, 65.09, 62.83, 56.21, 54.80, 46.16, 43.87, 27.95, 23.89, 18.04, and 12.01. $[\alpha]^{20}_{D}$= +18.93°; $CHCl_3$. HRCIMS calc'd for $C_{54}H_{65}NO_6Si$: 854.4581, Found: 852.4647 $[M + H]^+$.

Key nOe correlations for **70**



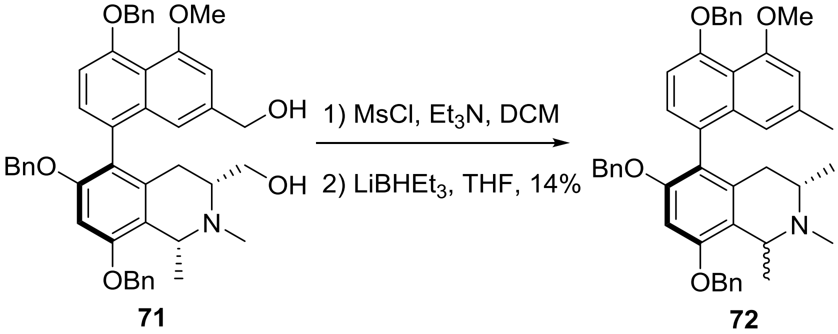
70

position	^{1}H (ppm, J Hz, Int)	^{13}C (ppm)
1	4.15 (dd, 13.4, 6.7, 1H)	54.80
3	2.46 (dd, 10.8, 3.4, 1H)	56.21
4_{ax}	2.24 (dd, 15.9, 4.5, 1H)	27.95
4_{eq}	2.33 (dd, 15.8, 11.0, 1H)	27.95
5	1.39 (d, 6.6, 3H)	23.89
6_a	3.55 (dd, 10.5, 3.8, 1H)	62.83
6_b	3.14 (d, 9.2, 1H)	62.83
7	6.56 (s, 1H)	97.48
9	2.43 (s, 3H)	46.16
1'	6.96 (d, 7.9, 1H)	127.01
2'	6.94 (m, 1H)	126.65
3'	6.93 (m, 1H)	126.55
4'	7.16 (s, 1H)	136.84
5'	3.97 (s, 3H)	56.21
6'	4.80 (m, 2H)	65.09



((*P*)-5-(benzyloxy)-8-((1*R*,3*R*)-6,8-bis(benzyloxy)-3-(hydroxymethyl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-methoxynaphthalen-2-yl)methanol (71, JF-004-209) To a dry 10 mL round bottom flask charged a magnetic stir bar, dissolved **70** (234 mg, 0.28 mmol, 1.0 equiv.) in THF (3 mL, 0.1M) followed by dropwise addition of TBAF (85 mg, 0.3 mmol, 1.1 equiv.) then stirred at room temperature until complete as judged by TLC (30 min). Diluted with Et_2O (25 mL) and washed with sat. $NaHCO_3$ (1 x 10 mL), extracted aqueous with Et_2O (3 x 10 mL), washed combined organics with brine (1 x 10 mL), dried over $MgSO_4$, absorbed onto basic Al_2O_3 (~1 g) and concentrated in vacuo. Crude product was purified via flash chromatography with silica gel (50 x 150 mm) eluted with 7:93 MeOH:DCM with 1% Et_3N, (R_f = 0.19, 7:93 MeOH:DCM) to yield 186 mg, 97 %, **71** as a white foamy solid. *Cis* by 2-D Noesy. ^1H NMR (500 MHz, $CDCl_3$) δ ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 2H), 7.47 – 7.41 (m, 6H), 7.37 (ddd, *J* = 19.1, 10.1, 4.6 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.18 – 7.16 (m, 3H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.97 (dd, *J* = 6.1, 2.5 Hz, 1H), 6.93 (s, 1H), 6.89 (s, 1H), 6.60 (s, 1H), 5.26 (s, 2H), 5.10 (q, *J* = 11.8 Hz, 2H), 4.85 (dd, *J* = 31.9, 12.5 Hz, 2H), 4.63 (s, 2H), 4.17 (dd, *J* = 13.2, 6.5 Hz, 1H), 3.99 (s, 3H), 3.57 (dd, *J* = 10.8, 3.1 Hz, 1H), 3.18 (d, *J* = 10.3 Hz, 1H), 2.78 (br s, 1H), 2.51 – 2.46 (m, 1H), 2.45 (s, 3H), 2.41 (d, *J* = 10.8 Hz, 1H), 2.19 (d, *J* = 12.2 Hz, 1H), 1.42 (d, *J* = 6.7 Hz, 3H), and 1.16 (br s, 1H). ^{13}C NMR (125MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ

^{13}C NMR (126 MHz, CDCl$_3$) δ 157.93, 155.68, 155.60, 154.81, 139.22, 137.77, 137.34, 137.10, 136.82, 136.59, 128.98, 128.65, 128.36, 128.23, 128.22, 127.99, 127.50, 127.41, 127.30, 126.99, 126.72, 126.60, 121.79, 117.74, 116.18, 108.37, 105.09, 97.73, 71.55, 70.97, 70.23, 65.68, 62.53, 56.26, 54.97, 43.48, 28.29, and 23.75. $[\alpha]^{20}_D$= +24.23°; CHCl$_3$. HCIMS calc'd for $C_{45}H_{45}NO_6$: 695.3247, Found: 696.3352 $[M + H]^+$.



(3S)-6,8-bis(benzyloxy)-5-((S)-4-(benzyloxy)-5-methoxy-7-methylnaphthalen-1-yl)-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (72, JF-004-211) To a dry 25 mL round bottom flask charged with argon and a stir bar dissolved **71** (44 mg, 0.07 mmol, 1.0 equiv.), in DCM (7 mL, 0.01M), followed by Et$_3$N (50 uL, 36 mg, 0.35 mmol, 5.0 equiv.) then cooled to 0 °C and stirred (~ 15 min). Added MsCl (32 mg, 21 uL, 0.28 mmol, 4.0 equiv.) in DCM (0.3 mL, 1 M) allowed to stir at ~0 °C for 15 min. then removed ice bath and stirred at rt until complete as judged by TLC (3 h) (R_f = 0.85, 7:93 MeOH:DCM; deactivated TLC plate with Et$_3$N) Note: the mesylate intermediate will decompose on silica gel) Diluted with DCM (25 mL) and quickly washed with sat. NH$_4$Cl (1 x 10 mL), and brine (1 x 10 mL), dried over MgSO$_4$, concentrated in vaccuo to afford an orange oil. To the mesylate intermediate in a 25 mL RBF with stir bar dissolved in dry THF (7 mL, 0.01M) followed by 4Å molecular sieves (10 beads) then cooled to 0 °C and stirred (~ 15 min). Added LiEt$_3$BH

(111 mg, 1.1 mL, 1.1 mmol, 15 equiv.) in THF (1 M) allowed to stir at 0 °C for 15 min. then removed ice bath and stirred at rt. Reaction was incomplete as judged by TLC (7 h) with little product formed and still mainly mesylate intermediate, recooled to 0 °C. Added additional $LiEt_3BH$ (111 mg, 1.1 mL, 1.1 mmol, 15 equiv.) in THF (1 M) allowed to stir at 0 °C for 15 min. then removed ice bath and stirred at rt until complete as judged by TLC (12 h). Cooled to 0 °C and slowly quenched with sat. NH_4Cl (10 mL) then extracted with Et_2O (3 x 10 mL), washed with brine (1 x 10 mL), dried over $MgSO_4$, and concentrated in vaccuo. Crude product was purified via prep-TLC, developed withh 7:93 MeOH:DCM with 1% Et_3N, (R_f = 0.34, 7:93 MeOH:DCM) to yield 6.4 mg, 14 %, **72** as a tan solid. [58,59] ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 2H), 7.43 (dd, *J* = 8.0, 4.8 Hz, 6H), 7.36 (m, 2H), 7.19 – 7.17 (m, 3H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.01 – 6.97 (m, 2H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.81 (s, 1H), 6.70 (s, 1H), 6.61 (d, *J* = 5.3 Hz, 1H), 5.26 (s, 2H), 5.08 (dd, *J* = 26.0, 11.7 Hz, 2H), 4.84 (dd, *J* = 29.6, 12.4 Hz, 2H), 4.06 (dd, *J* = 12.4, 8.0 Hz, 1H), 3.97 (s, 3H), 3.65 – 3.58 (m, 1H), 2.58 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.51 (s, 3H), 2.34 (s, 3H), 2.27 (dd, *J* = 14.2, 9.6 Hz, 1H), 1.61 (d, *J* = 6.1 Hz, 3H), and 1.09 (d, *J* = 5.8 Hz, 3H). $[\alpha]^{20}_{D}$= +13.04°; $CHCl_3$. HREIMS calc'd for $C_{45}H_{45}NO_4$: 663.3497, Found: 664.3409 $[M + H]^+$.

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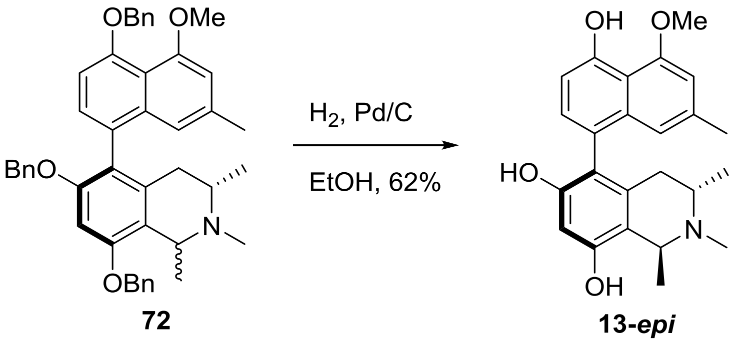
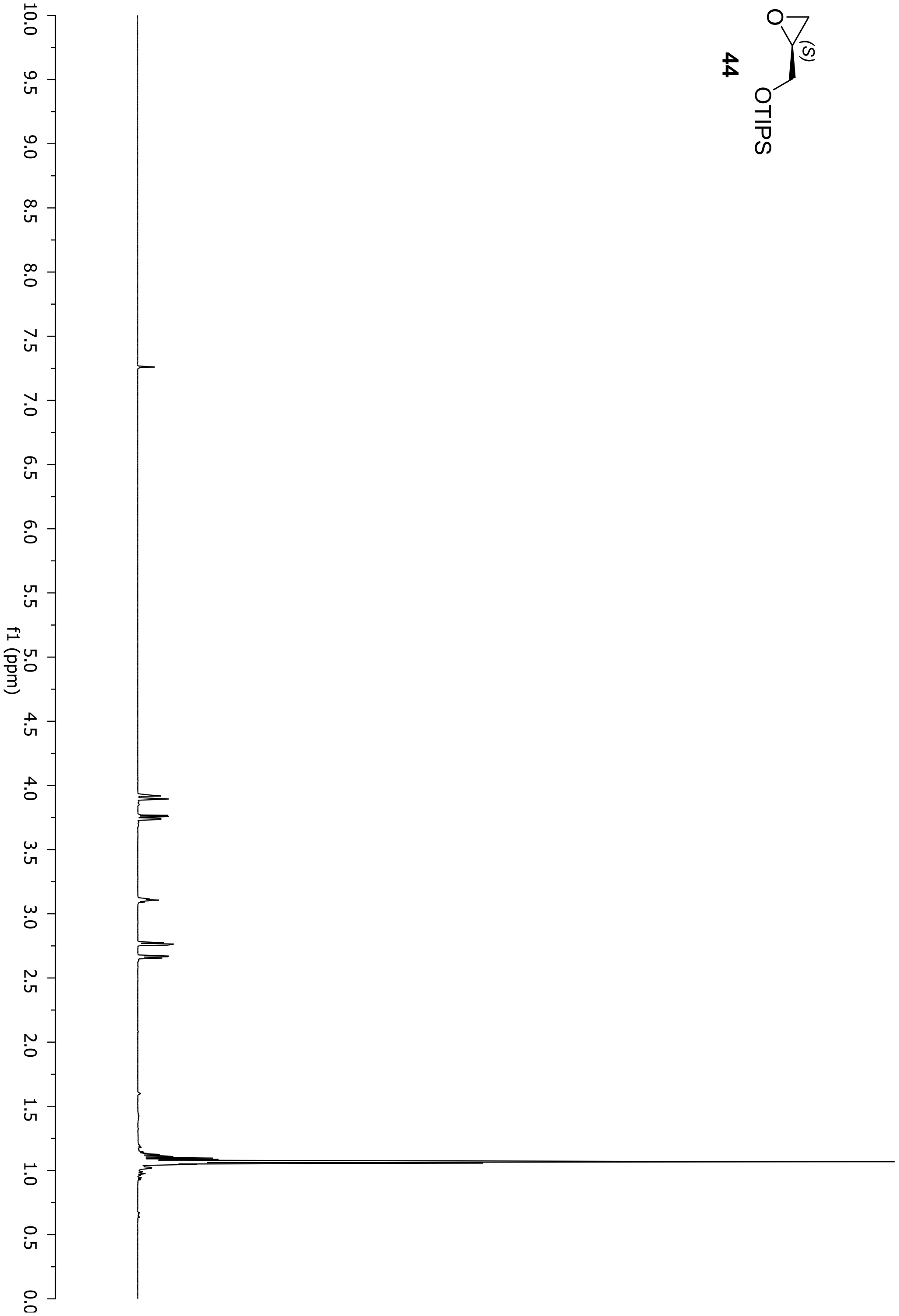


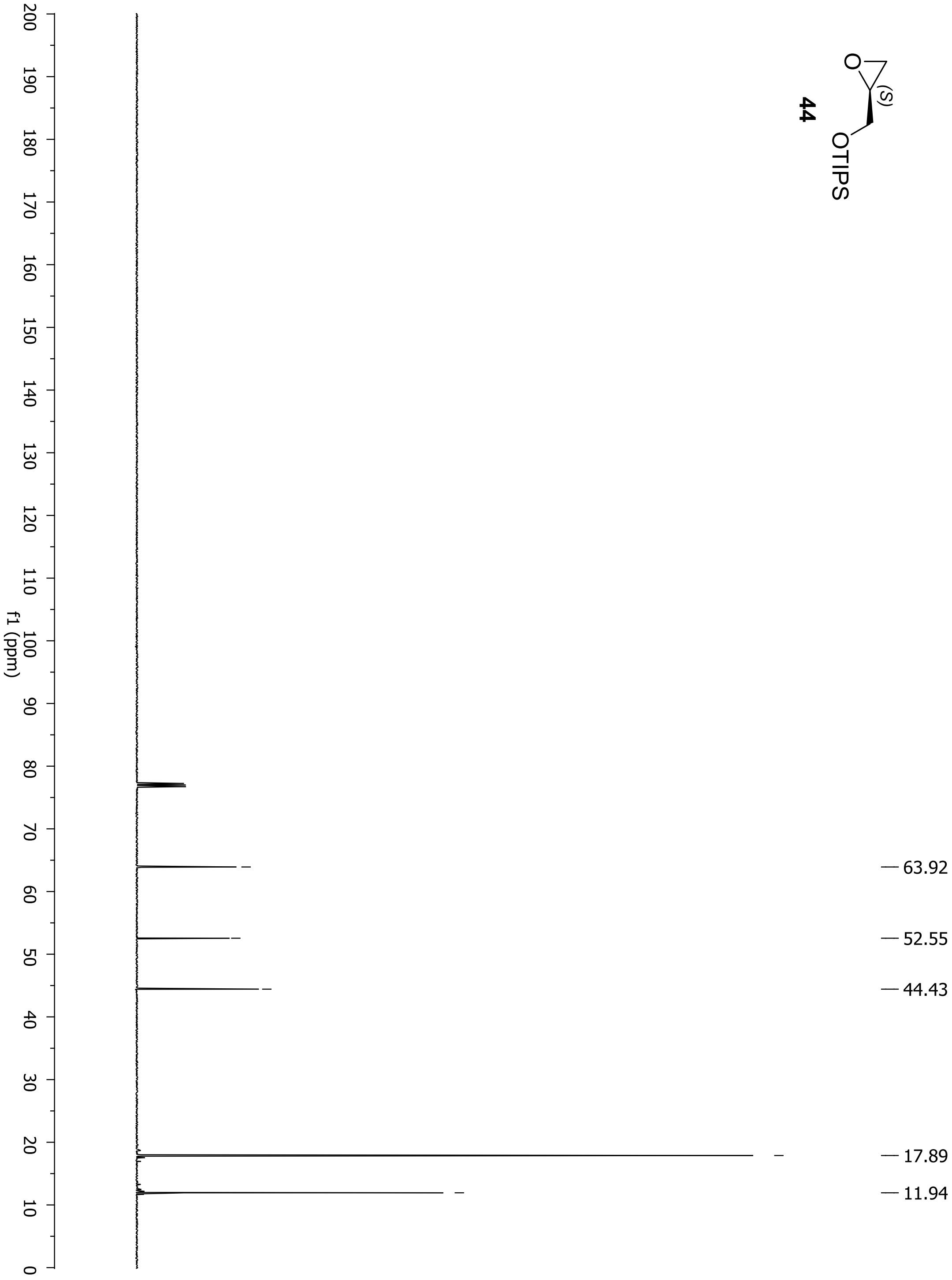
(1*S*,3*S*)-5-((*P*)-4-hydroxy-5-methoxy-7-methylnaphthalen-1-yl)-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline-6,8-diol (13-*epi*, JF-004-213) and (1*R*,3*S*)-5-((*P*)-4-hydroxy-5-methoxy-7-methylnaphthalen-1-yl)-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline-6,8-diol (13, JF-004-213) To a 25 mL round bottom flask charged with a stir bar, dissolved **72** (6.4 mg, 0.01mmol, 1.0 equiv.) in MeOH:DCM, 2:1 (5 mL, 2 mM), added Pd/C (10 wt%, 33 mg, 0.03 mmol, 3.0 equiv.), then fixed an H_2 balloon and stirred at rt until complete as judged by TLC (8 h). Filtered reaction through a pad of celite and concentrated filtrate in vaccuo Crude product was purified via prep-TLC, developed withh 1:9 MeOH:DCM with 1% Et_3N, (R_f = 0.16, 1:9 MeOH:DCM) to yield 2.4 mg, 62 %, **13-*epi*** as a tan solid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.07 (d, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 7.4 Hz, 3H), 6.42 (s, 1H), 4.25 (d, *J* = 5.1 Hz, 1H), 4.06 (s, 3H), 3.06 (dd, *J* = 14.5, 7.3 Hz, 1H), 2.87 (s, 1H), 2.74 (s, 3H), 2.31 (s, 3H), 2.27 (d, *J* = 2.7 Hz, 1H), 2.17 (dd, *J* = 16.8, 10.3 Hz, 1H), 1.67 (d, *J* = 6.4 Hz, 3H), and 1.14 (d, *J* = 6.3 Hz, 3H). HREIMS calc'd for $C_{24}H_{28}NO_4$: 393.2018, Found: 394.2032 $[M + H]^+$.

4.7 Spectral Data

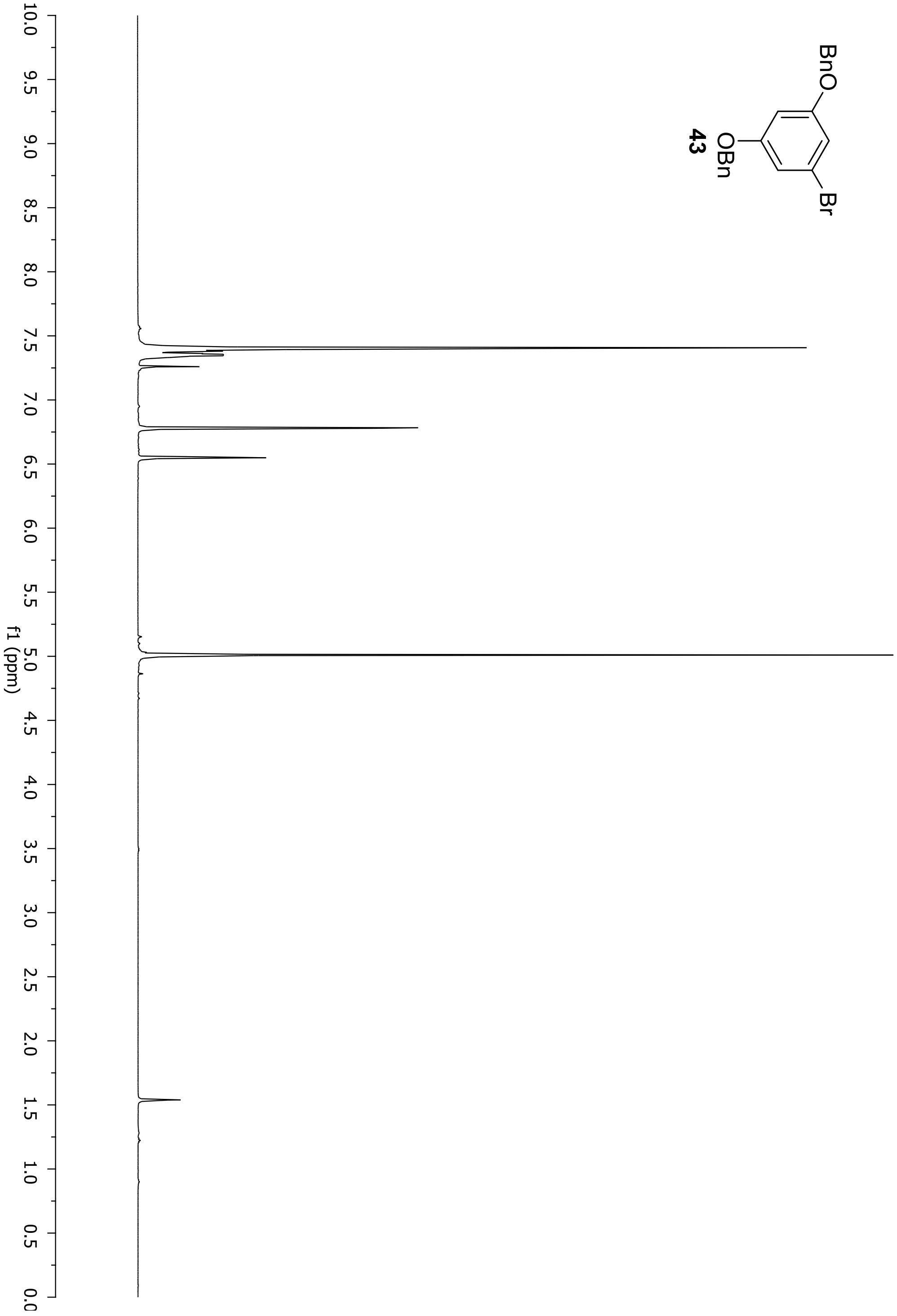
(*S*)-triisopropyl(oxiran-2-ylmethoxy)silane **44**; Proton NMR, $CDCl_3$



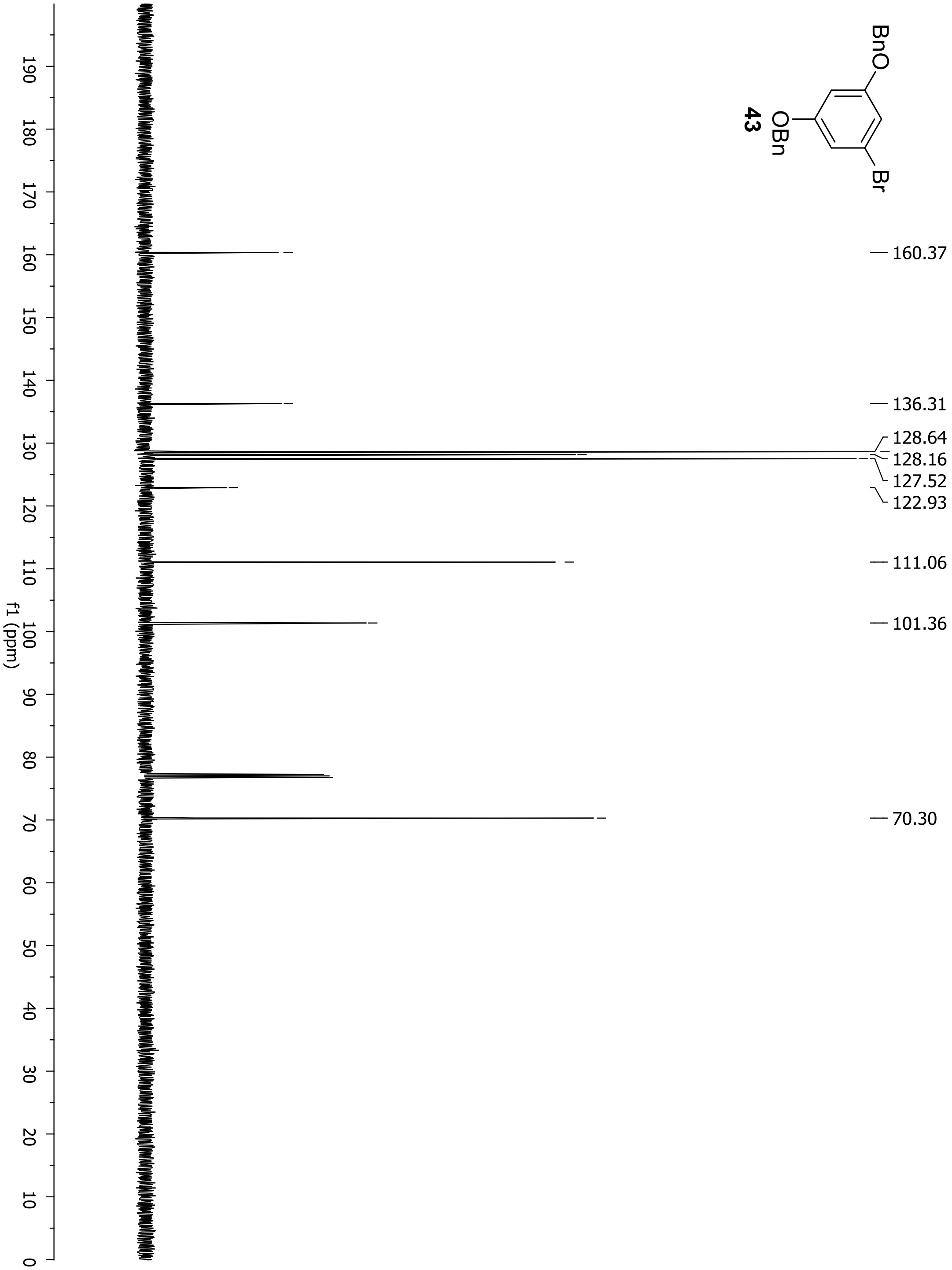
(*S*)-triisopropyl(oxiran-2-ylmethoxy)silane **44**; Carbon NMR, $CDCl_3$



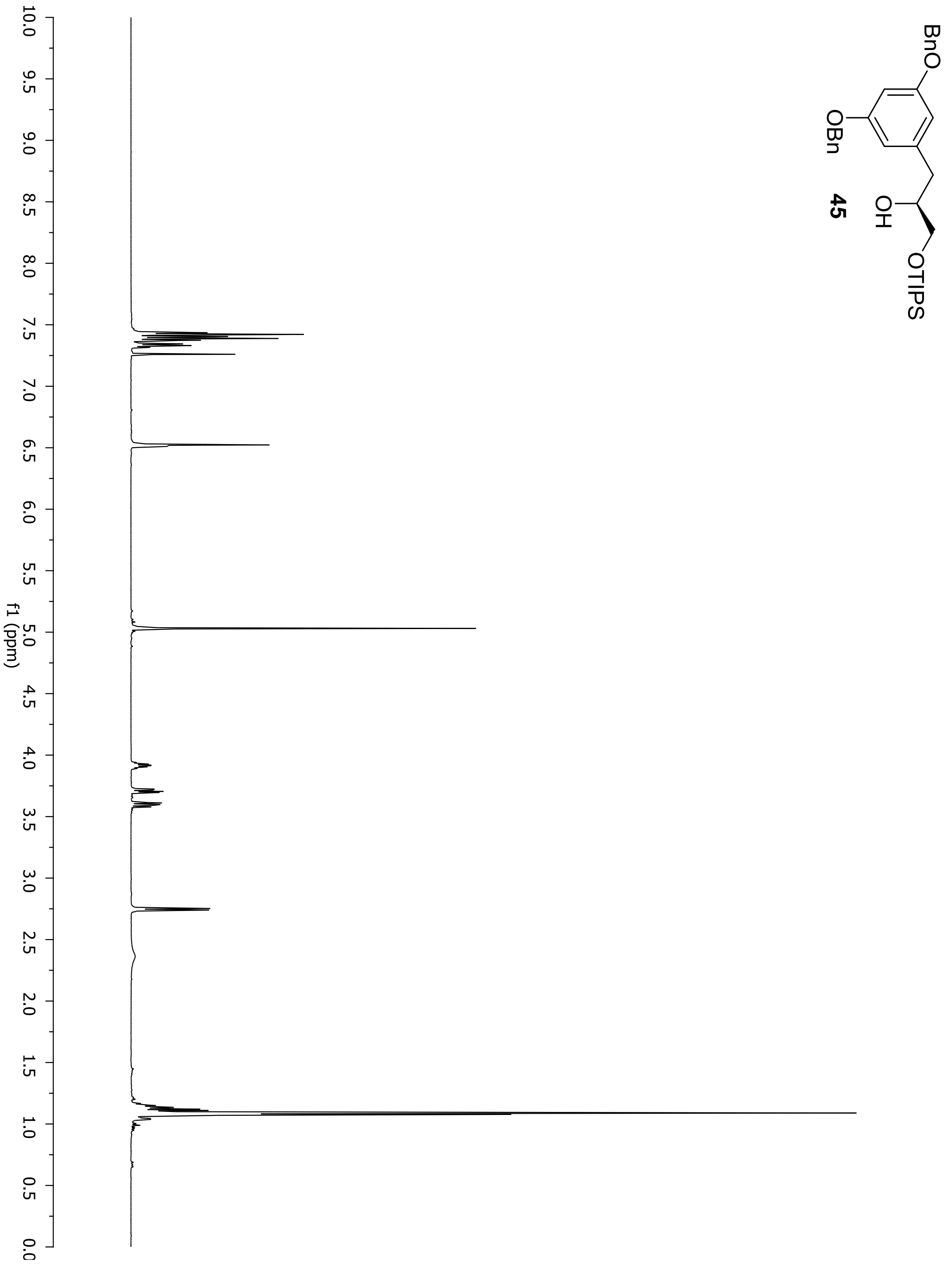
(((5-bromo-1,3-phenylene)bis(oxy))bis(methylene))dibenzene **43**; Proton NMR, CDCl$_3$



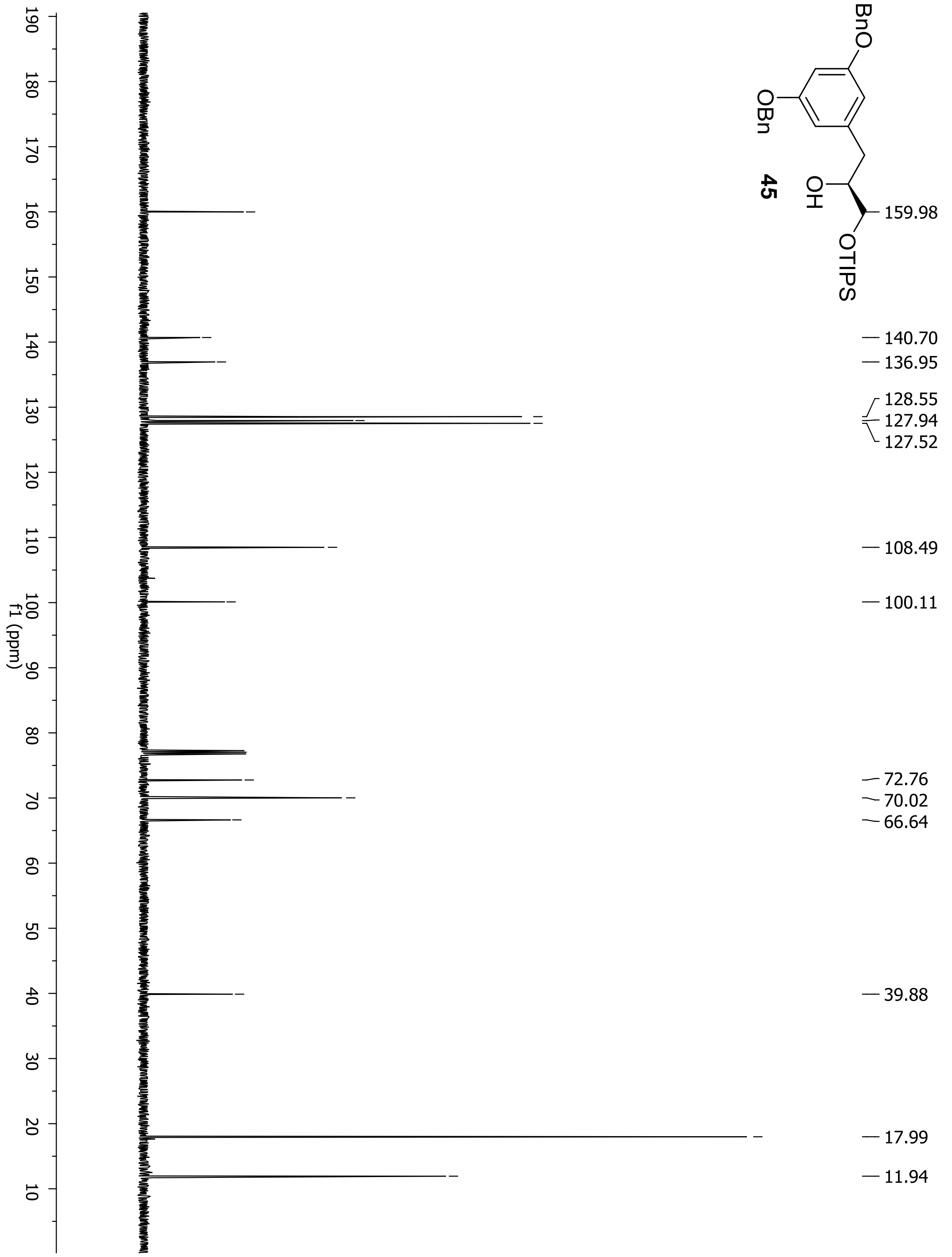
(((5-bromo-1,3-phenylene)bis(oxy))bis(methylene))dibenzene **43**; Carbon NMR, $CDCl_3$



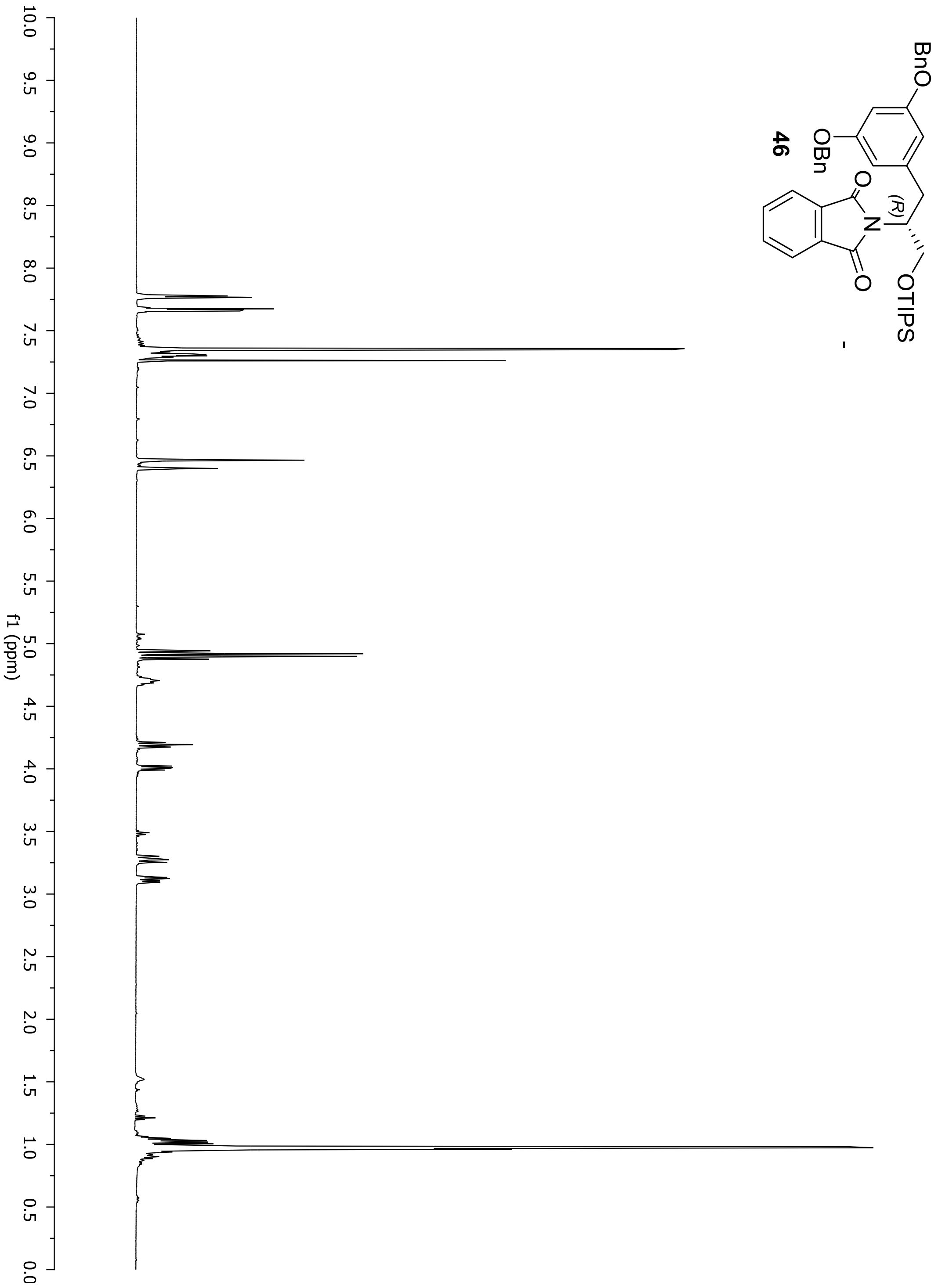
(*S*)-1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-ol **45**; Proton NMR, $CDCl_3$



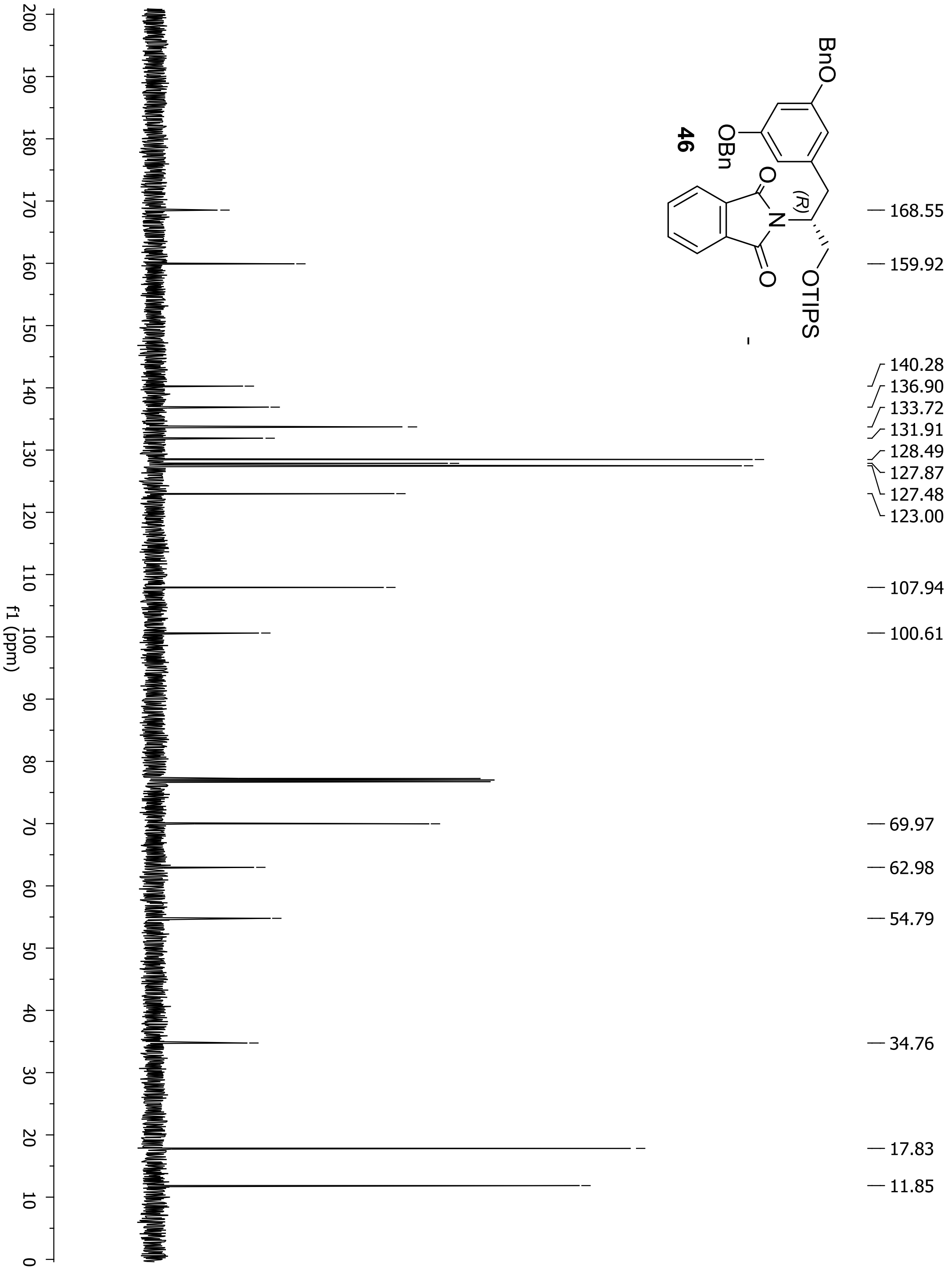
(*S*)-1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-ol **45**; Carbon NMR, $CDCl_3$



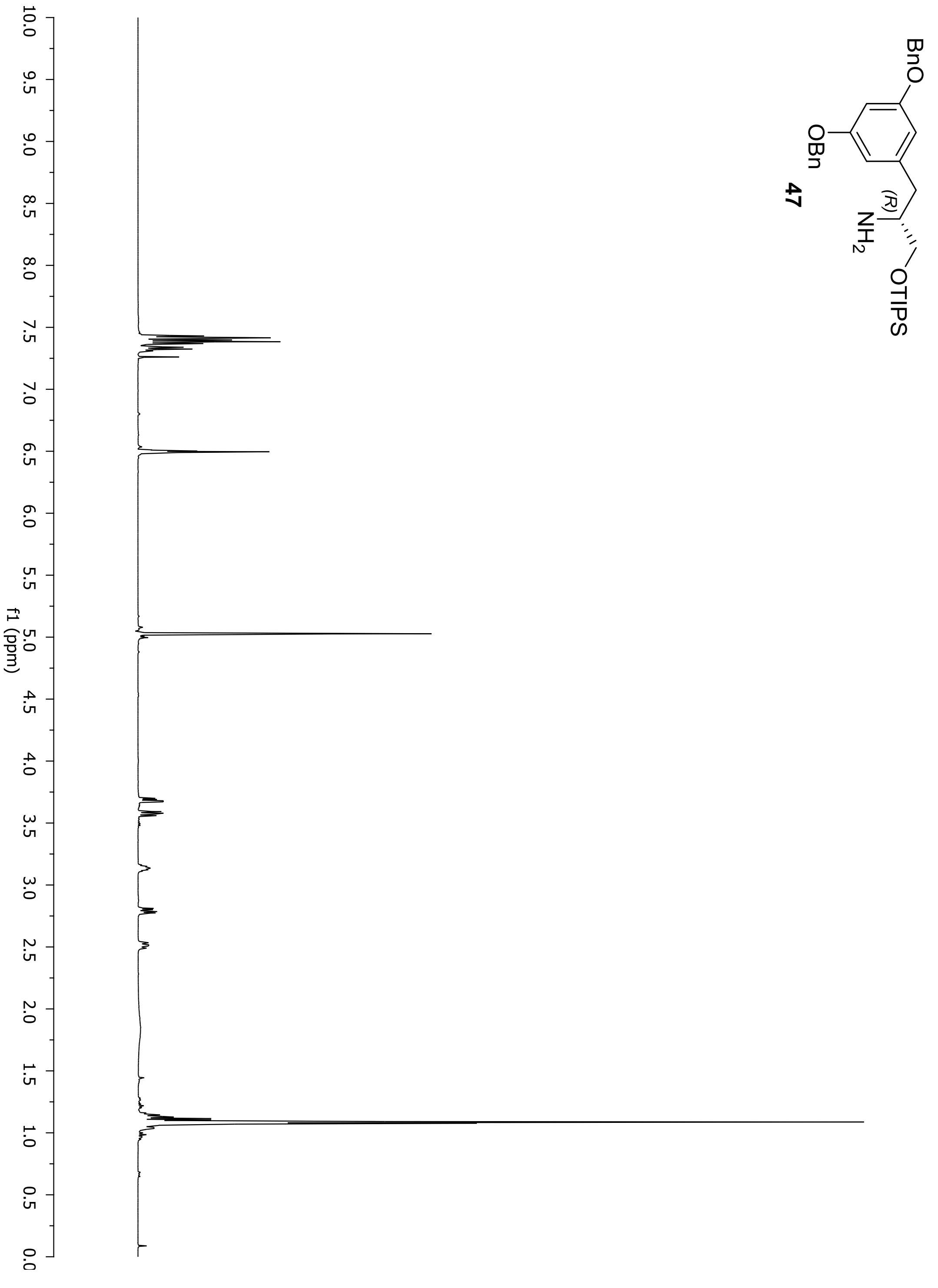
(*R*)-2-(1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-yl)isoindoline-1,3-dione **46**; Proton NMR, $CDCl_3$



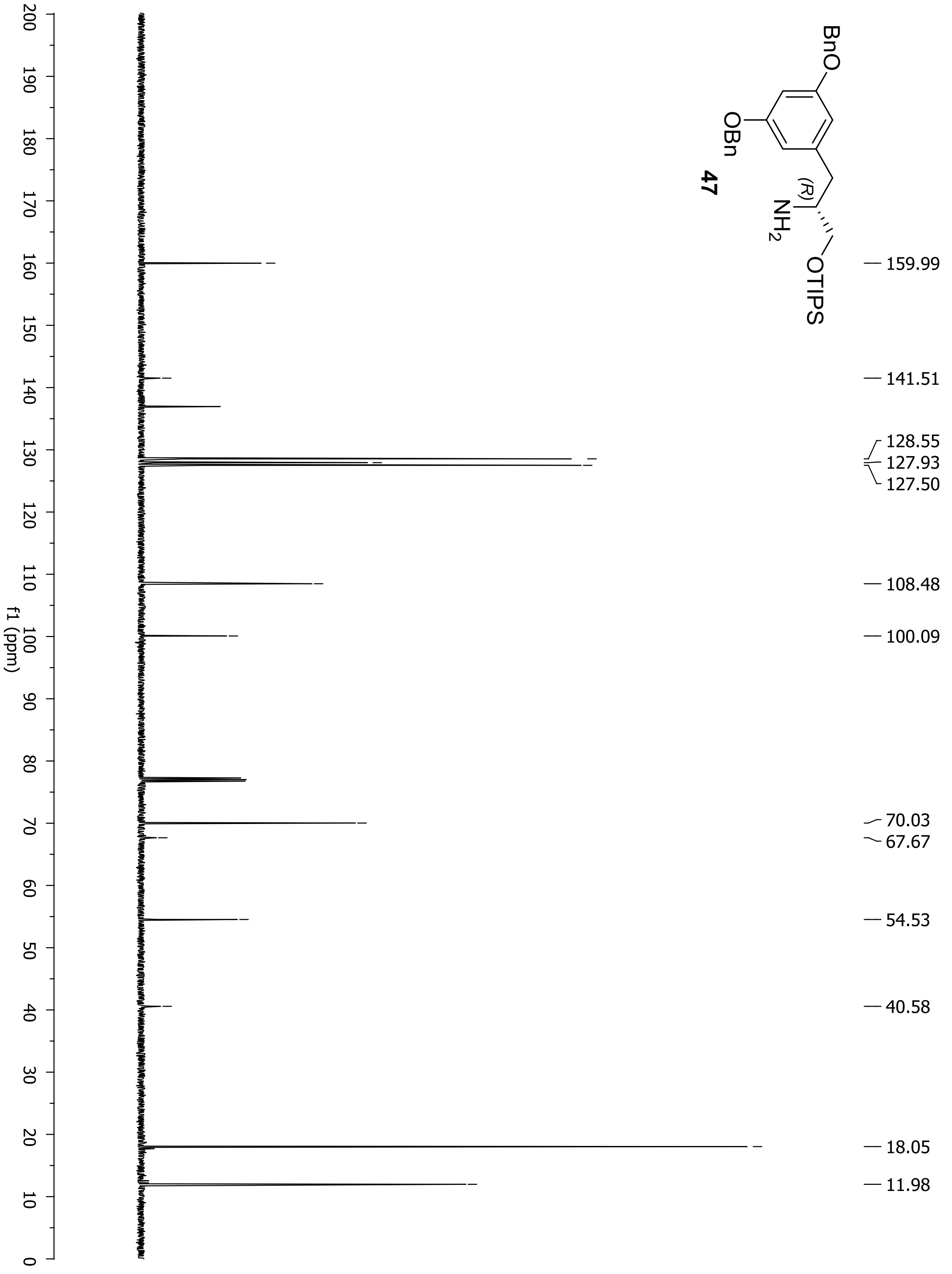
(*R*)-2-(1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-yl)isoindoline-1,3-dione **46**; Carbon NMR, $CDCl_3$



(*R*)-1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-amine **47**; Proton NMR, $CDCl_3$

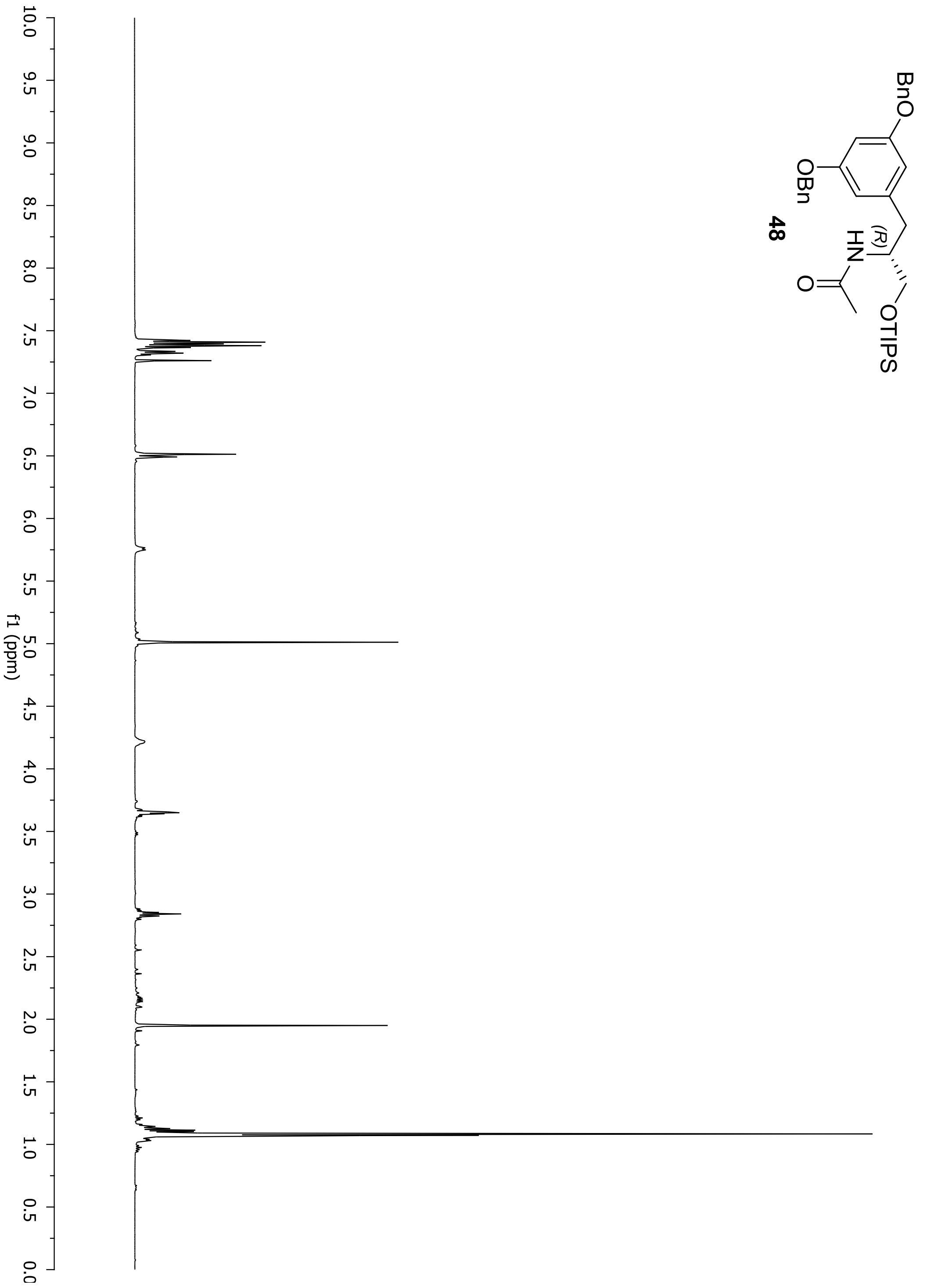


(*R*)-1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-amine **47**; Carbon NMR, $CDCl_3$



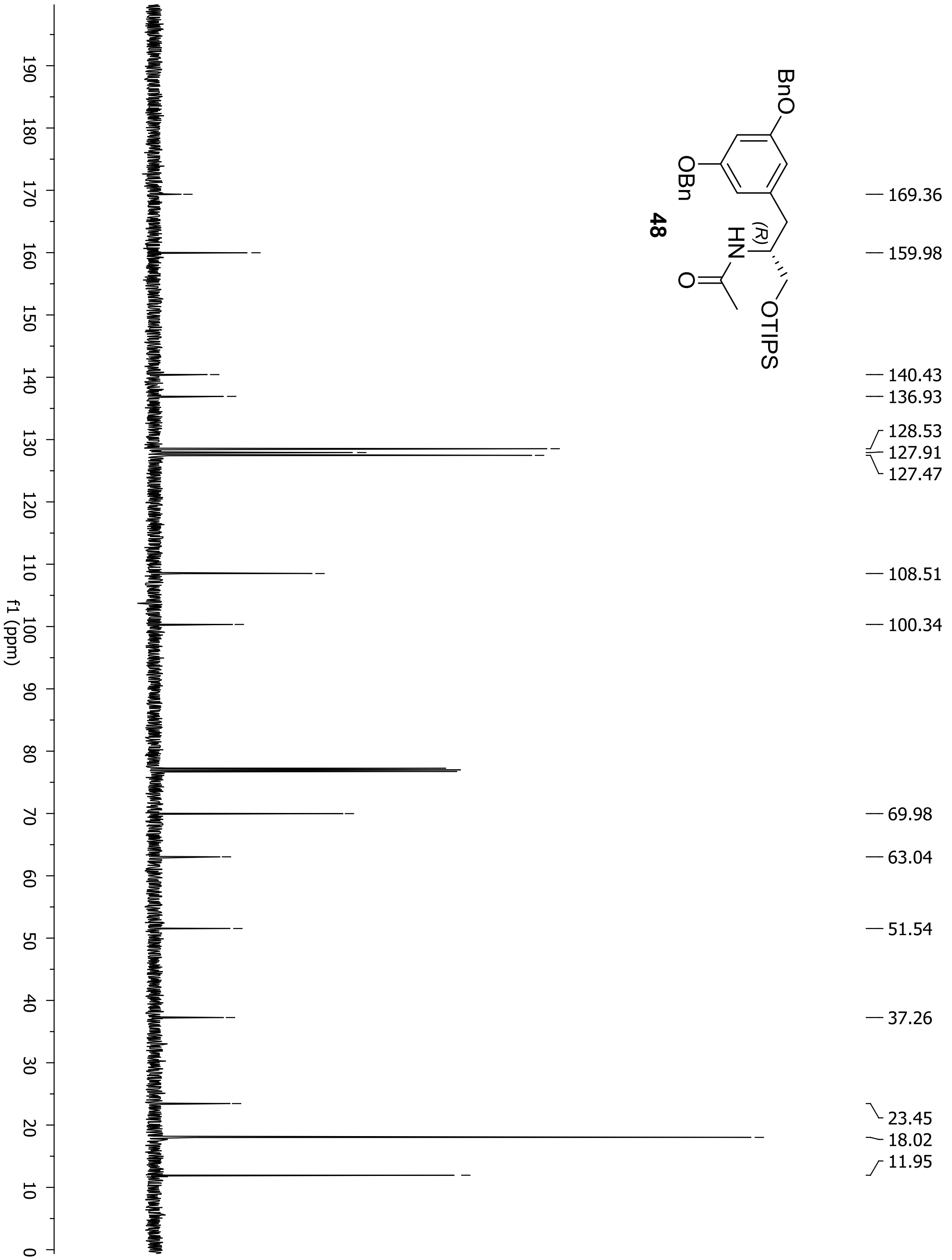
(*R*)-N-(1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-yl)acetamide **48**;

Proton NMR, $CDCl_3$

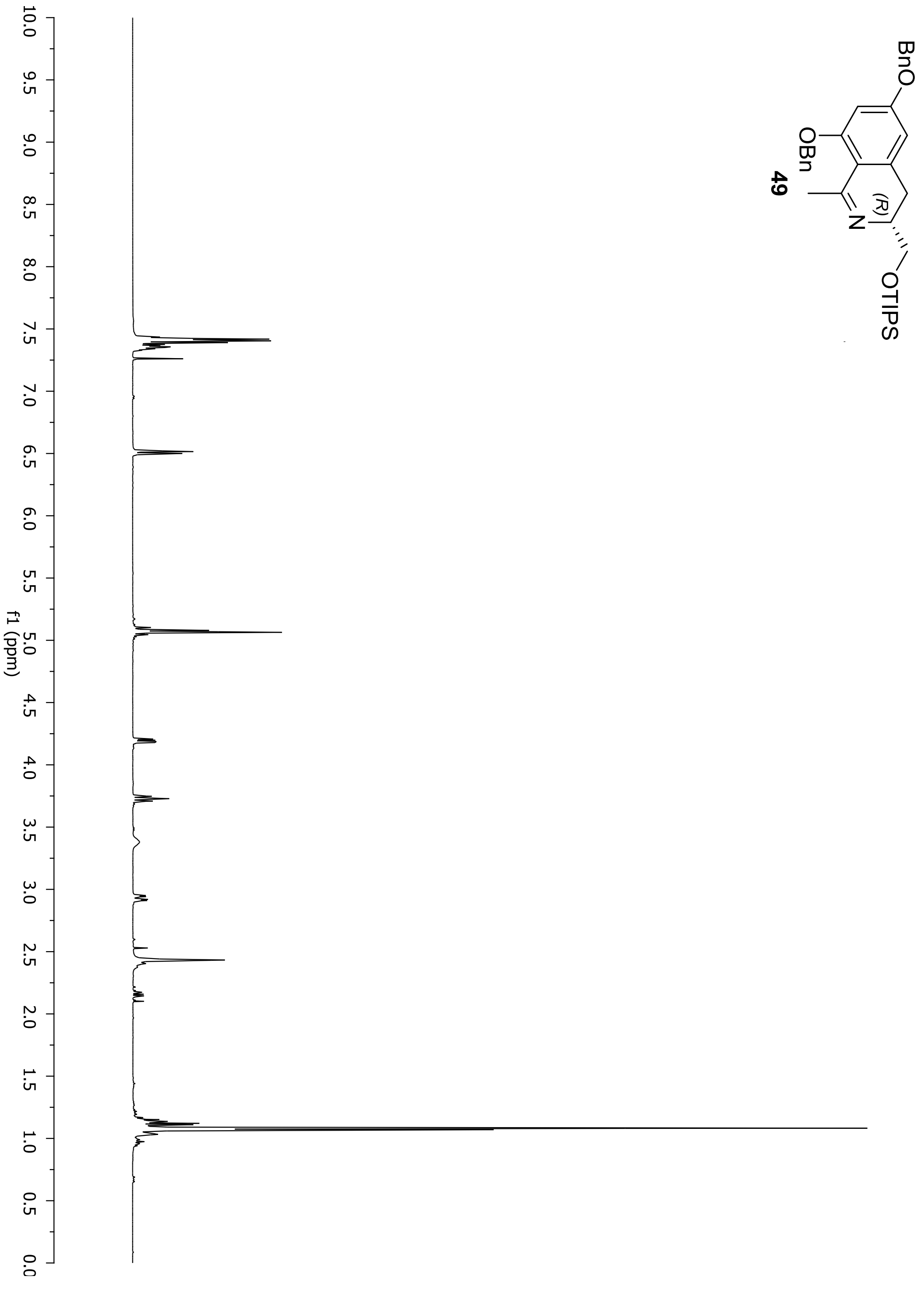


(*R*)-N-(1-(3,5-bis(benzyloxy)phenyl)-3-((triisopropylsilyl)oxy)propan-2-yl)acetamide **48**;

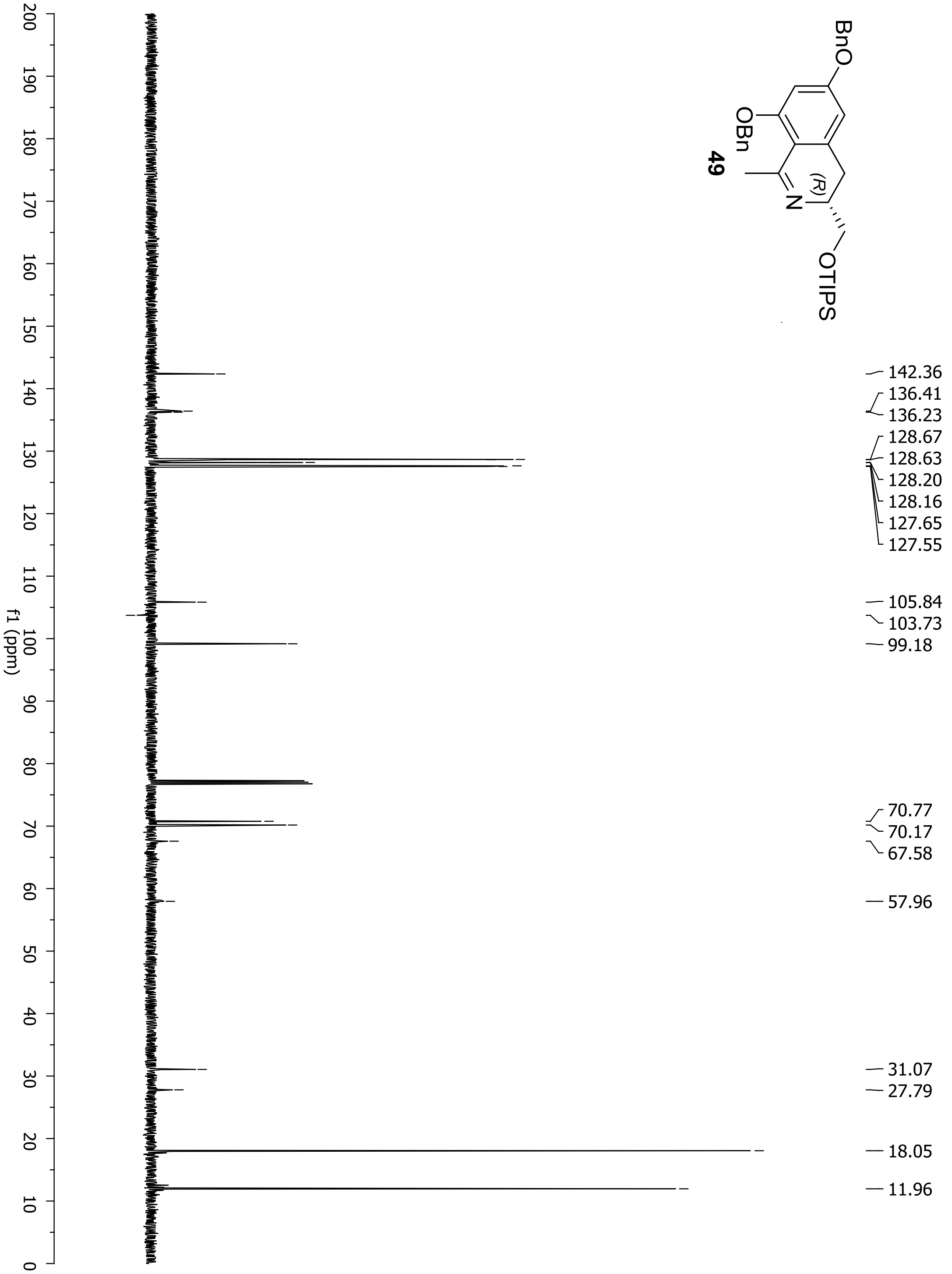
Carbon NMR, $CDCl_3$



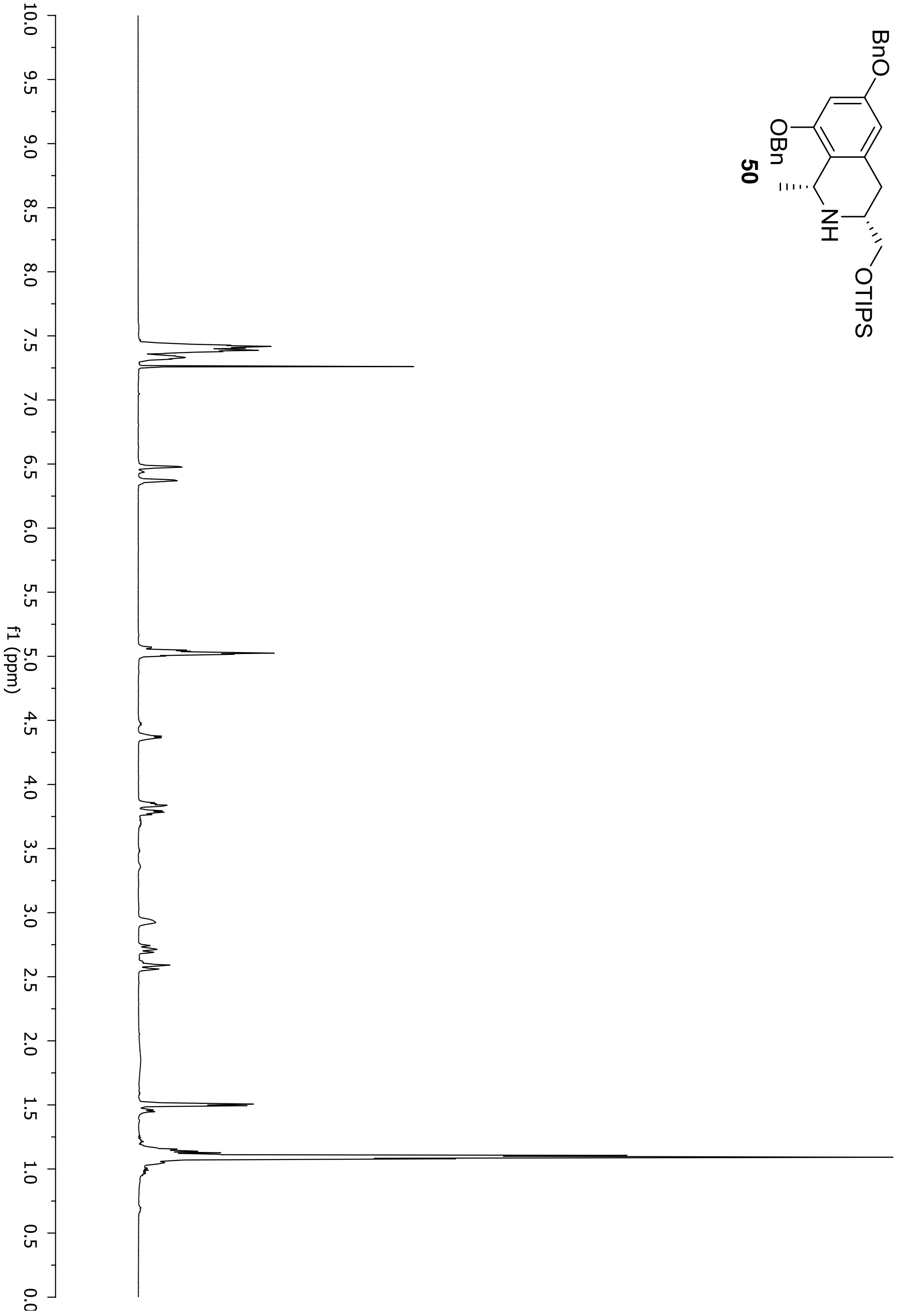
(*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-3,4-dihydroisoquinoline **49**; Proton NMR, $CDCl_3$



(*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-3,4-dihydroisoquinoline **49**; Carbon NMR, $CDCl_3$

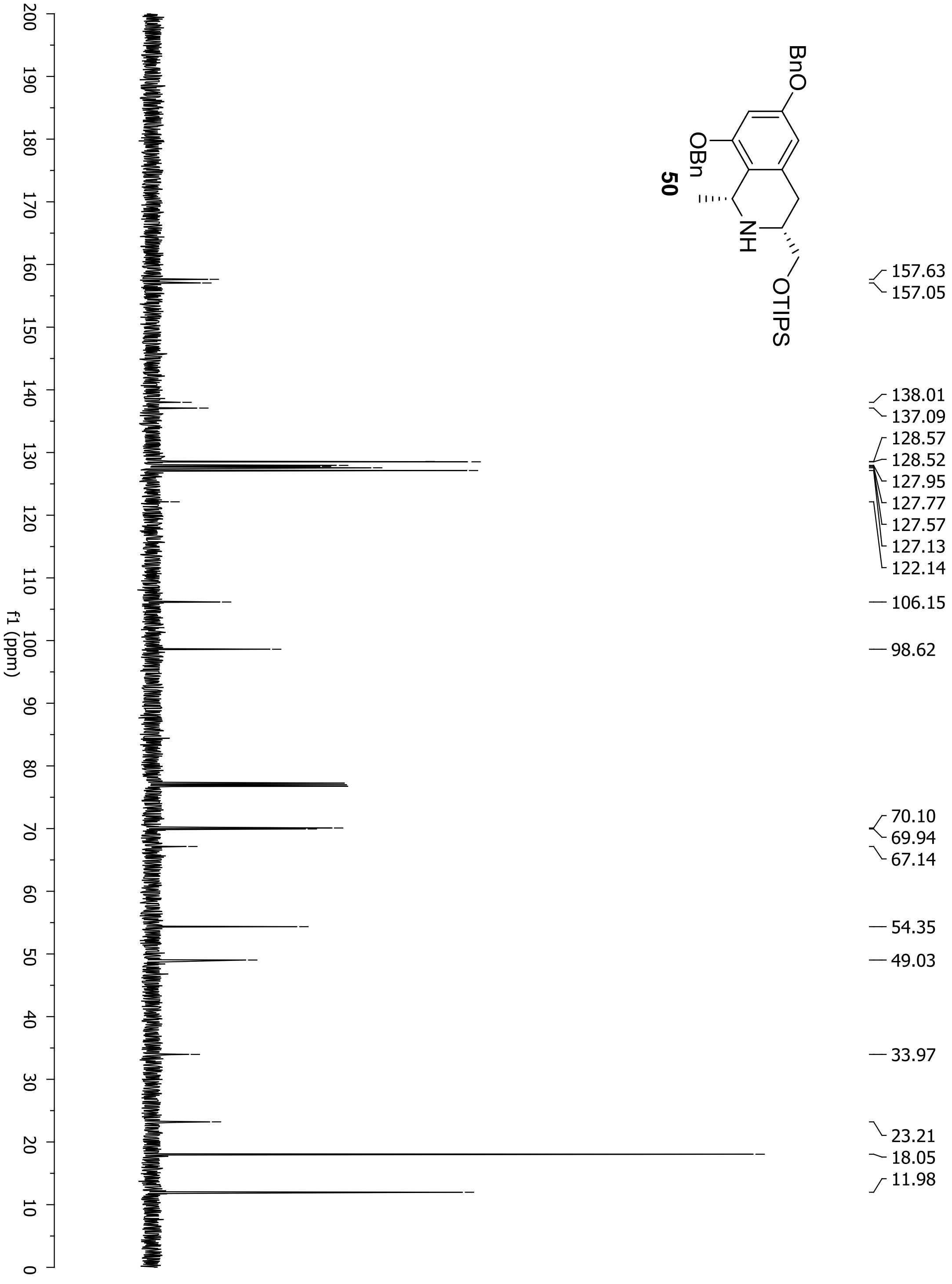


(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **50**; Proton NMR, $CDCl_3$

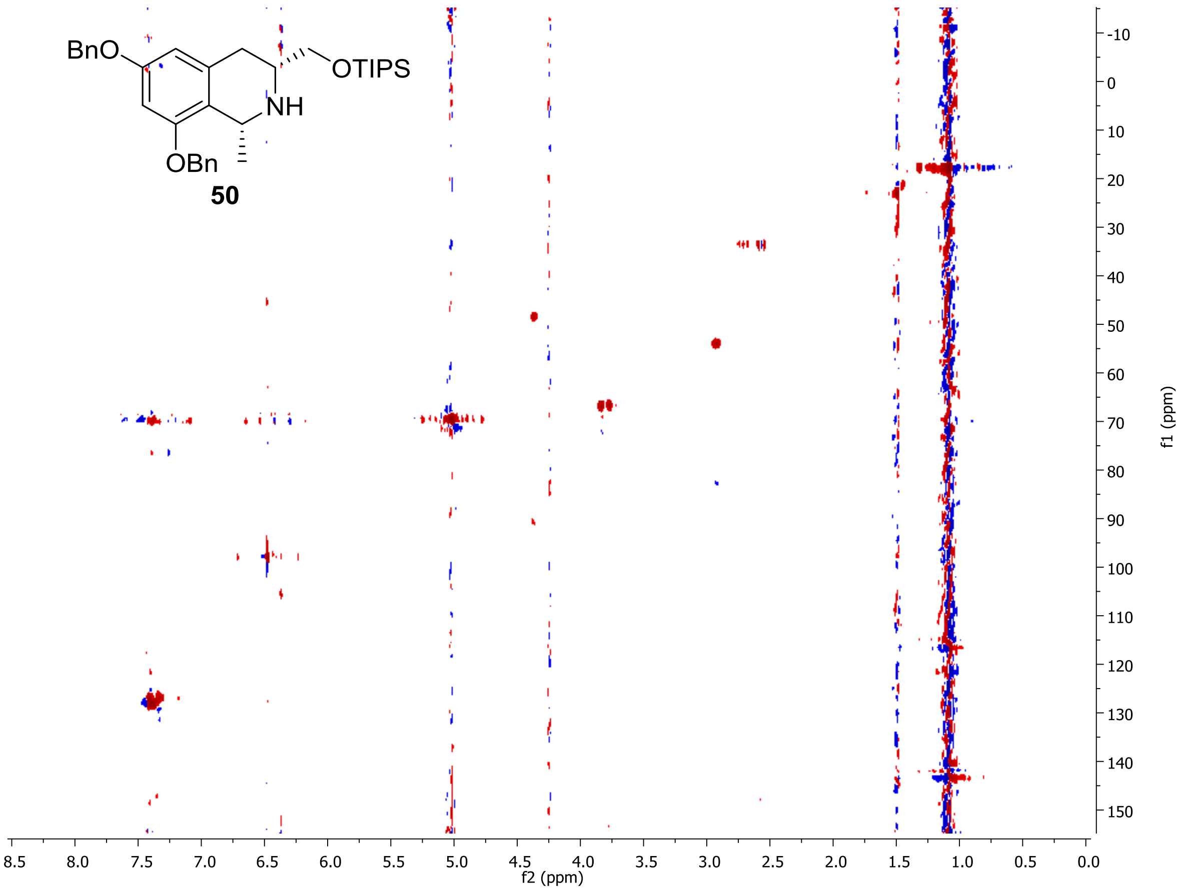


50

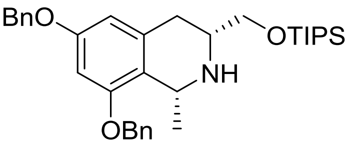
(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **50**; Carbon NMR, $CDCl_3$



(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **50**; HMQC NMR, $CDCl_3$



(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **50**; Noesy NMR, $CDCl_3$



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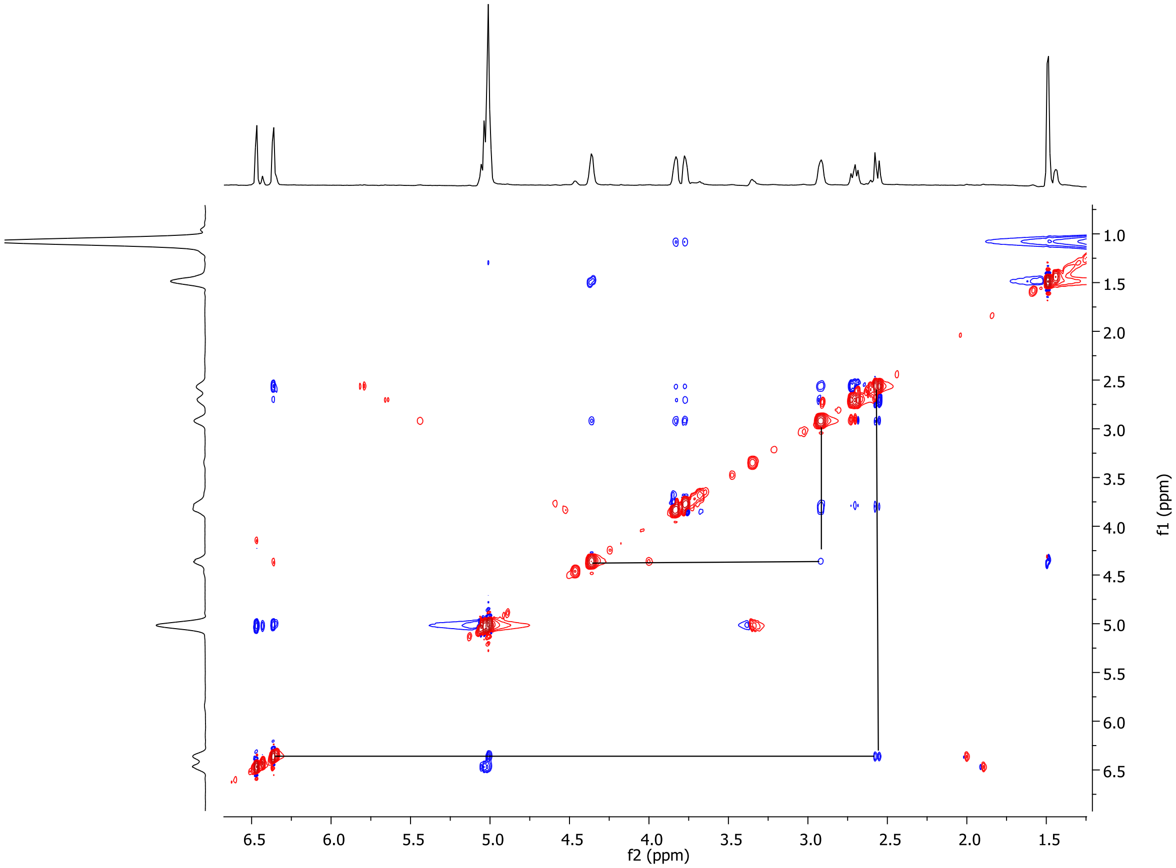
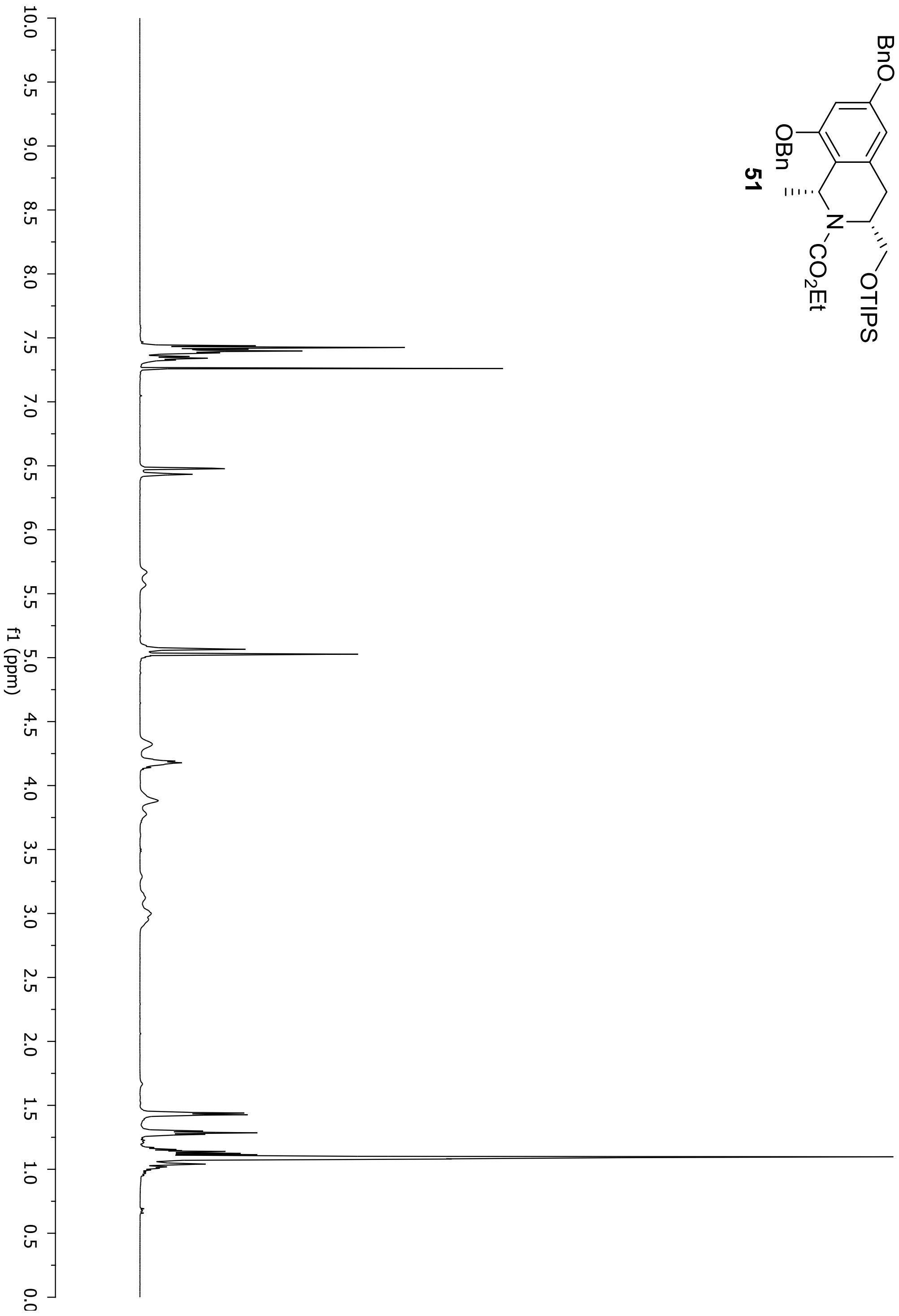
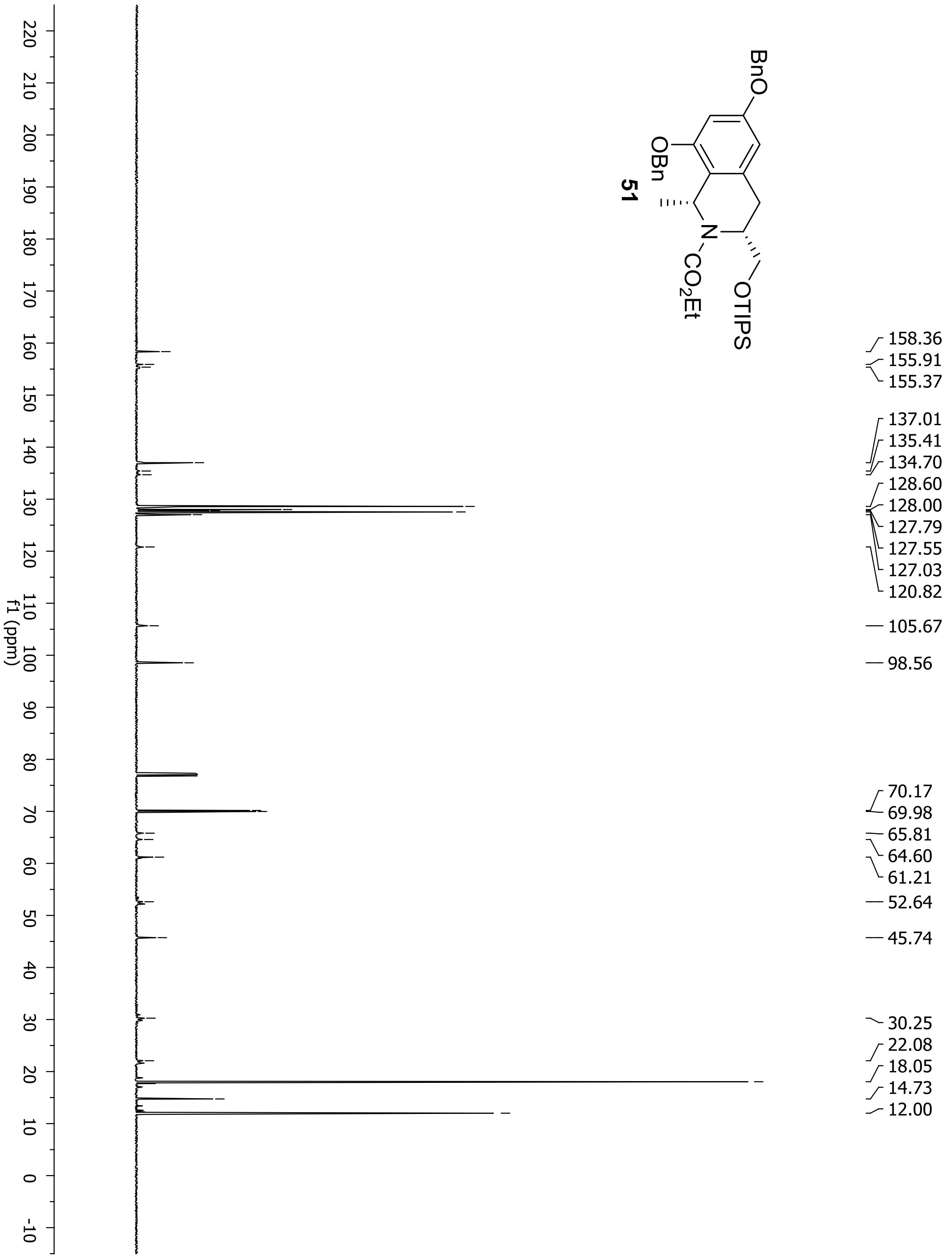


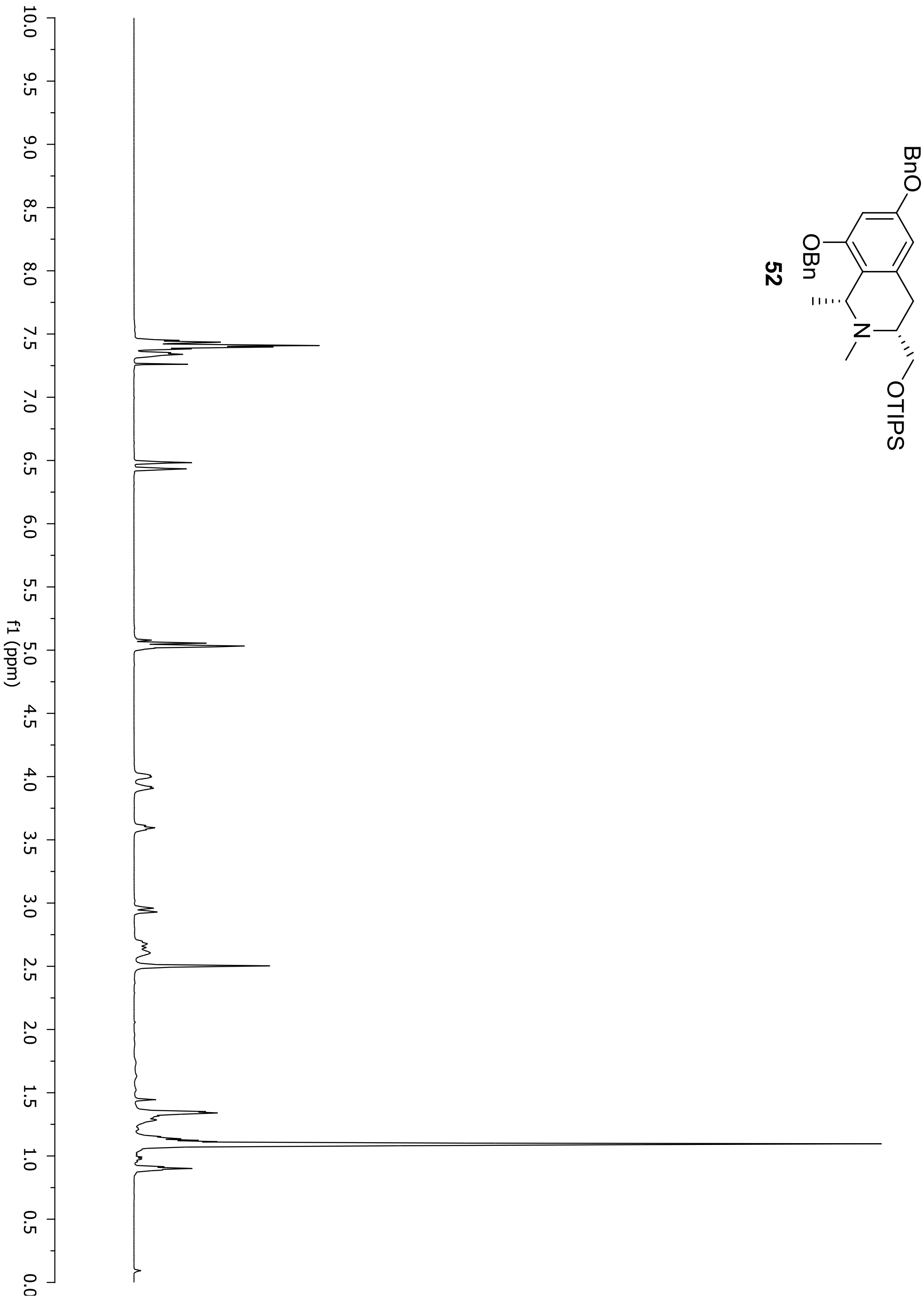
Ethyl-(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-3,4-dihydroisoquinoline-2 (1H)-carboxylate **51**; Proton NMR, $CDCl_3$



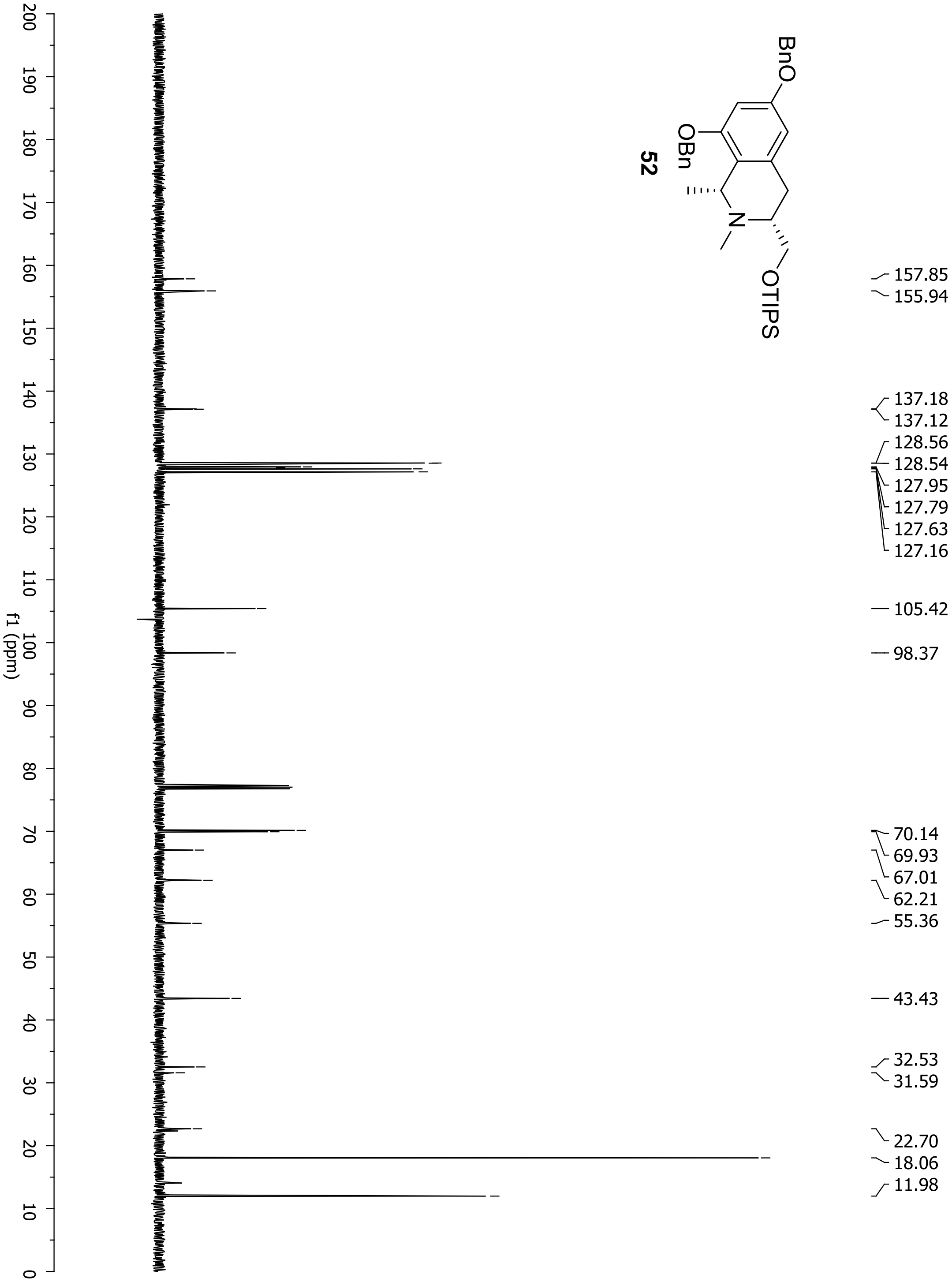
Ethyl-(1*R*,3*R*)-6,8-bis(benzyloxy)-1-methyl-3-(((triisopropylsilyl)oxy)methyl)-3,4-dihydroisoquinoline-2 (1H)-carboxylate **51**; Carbon NMR, $CDCl_3$



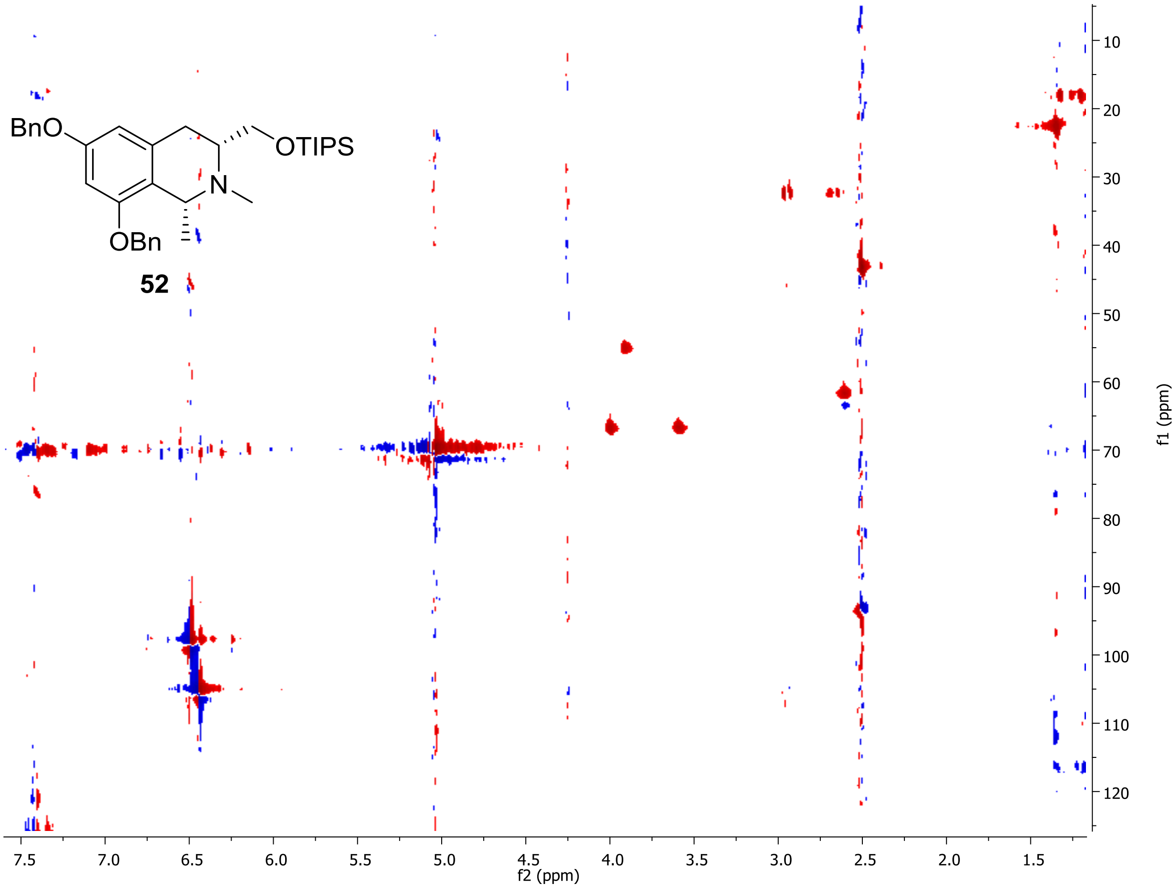
(1*R*,3*R*)-6,8-bis(benzyloxy)-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **52**; Proton NMR, $CDCl_3$



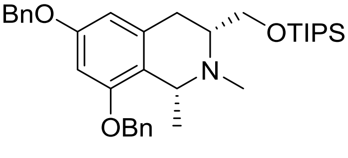
(1*R*,3*R*)-6,8-bis(benzyloxy)-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **52**; Carbon NMR, $CDCl_3$



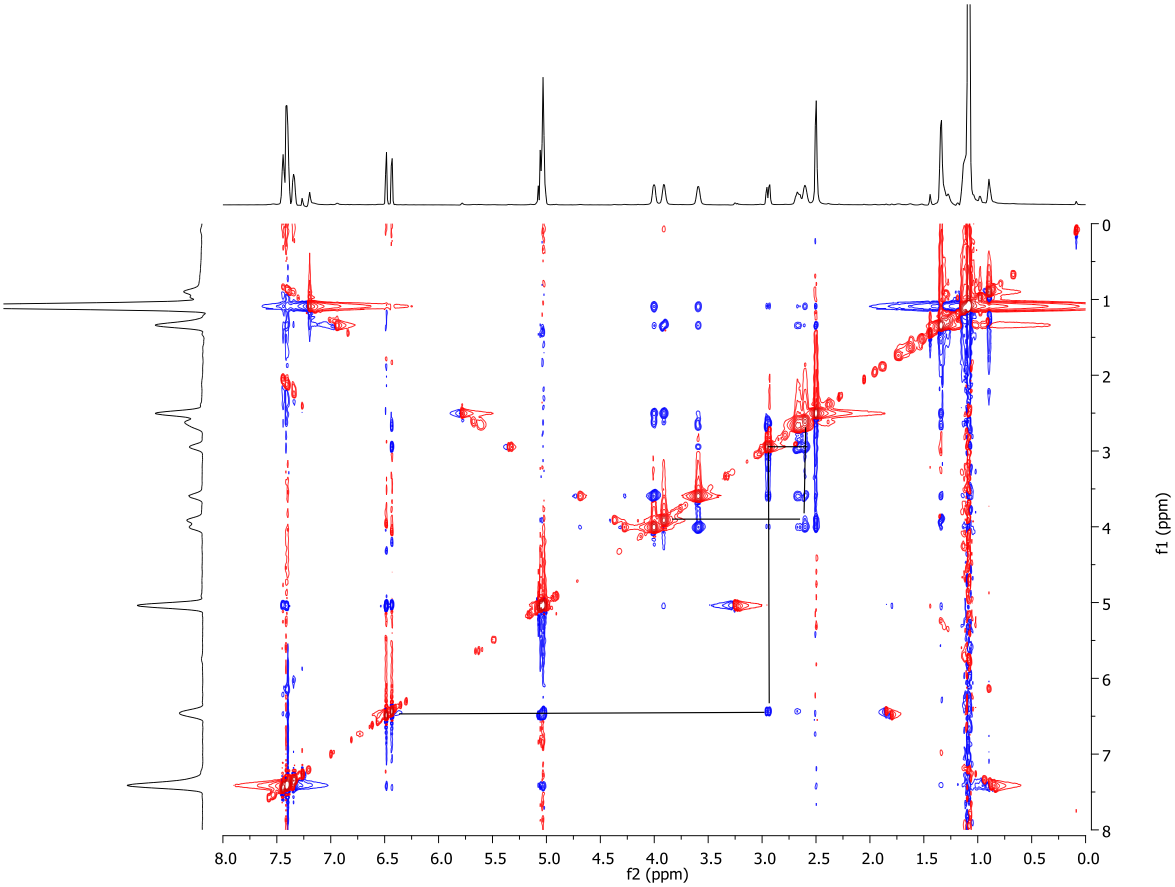
(1*R*,3*R*)-6,8-bis(benzyloxy)-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **52**; HMQC NMR, CDCl$_3$



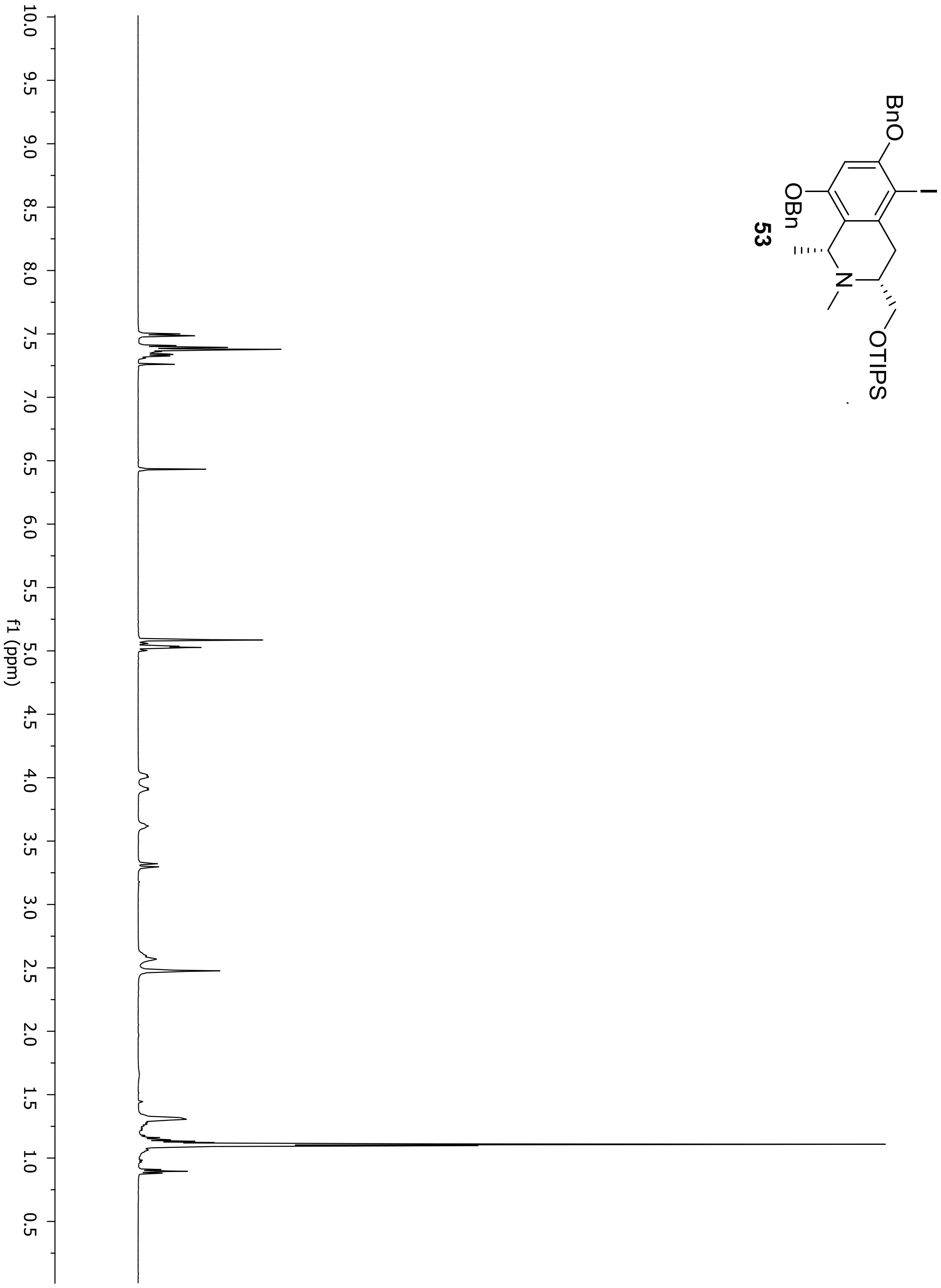
(1*R*,3*R*)-6,8-bis(benzyloxy)-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **52**; 2D Noesy NMR, $CDCl_3$



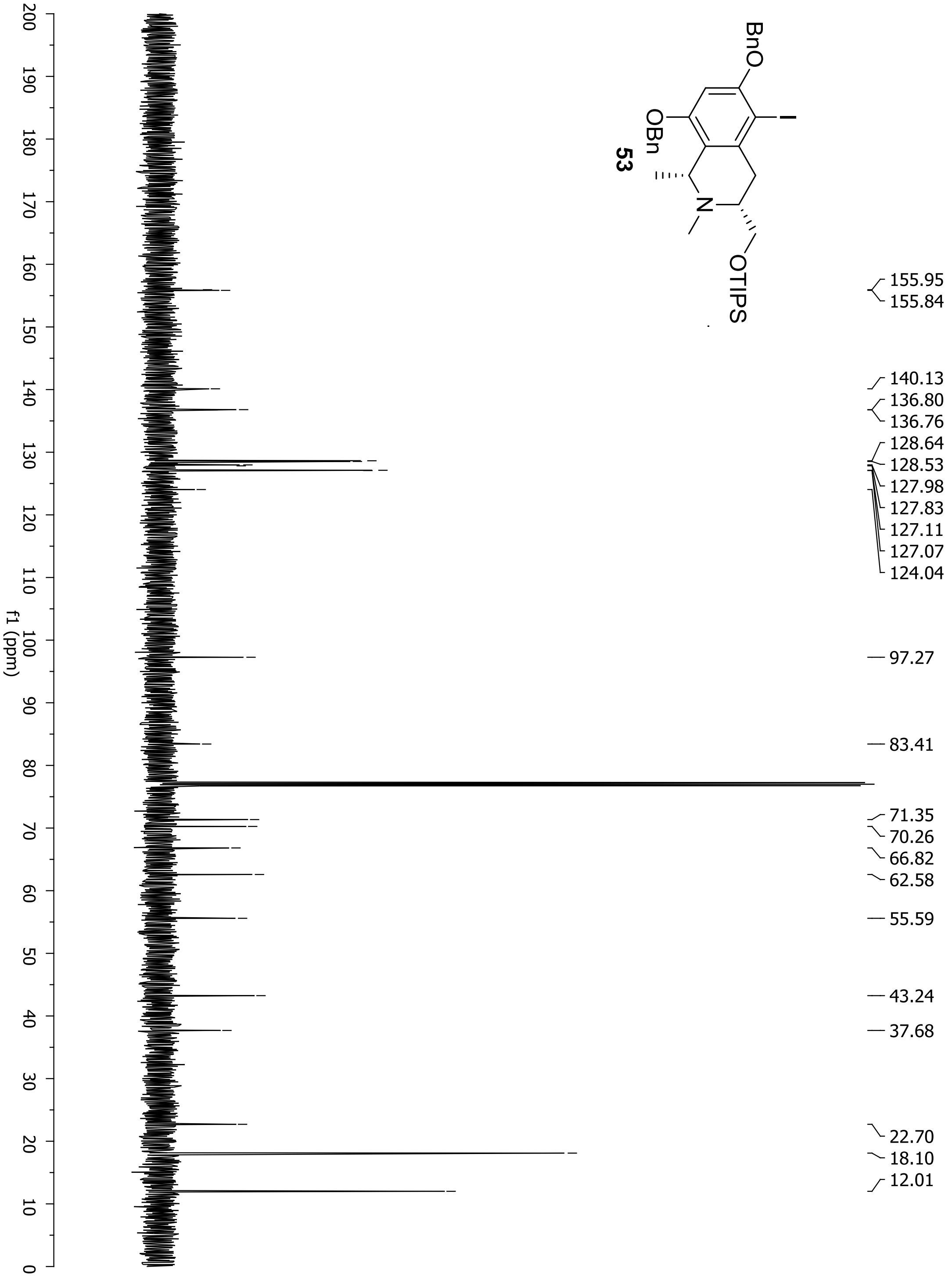
52



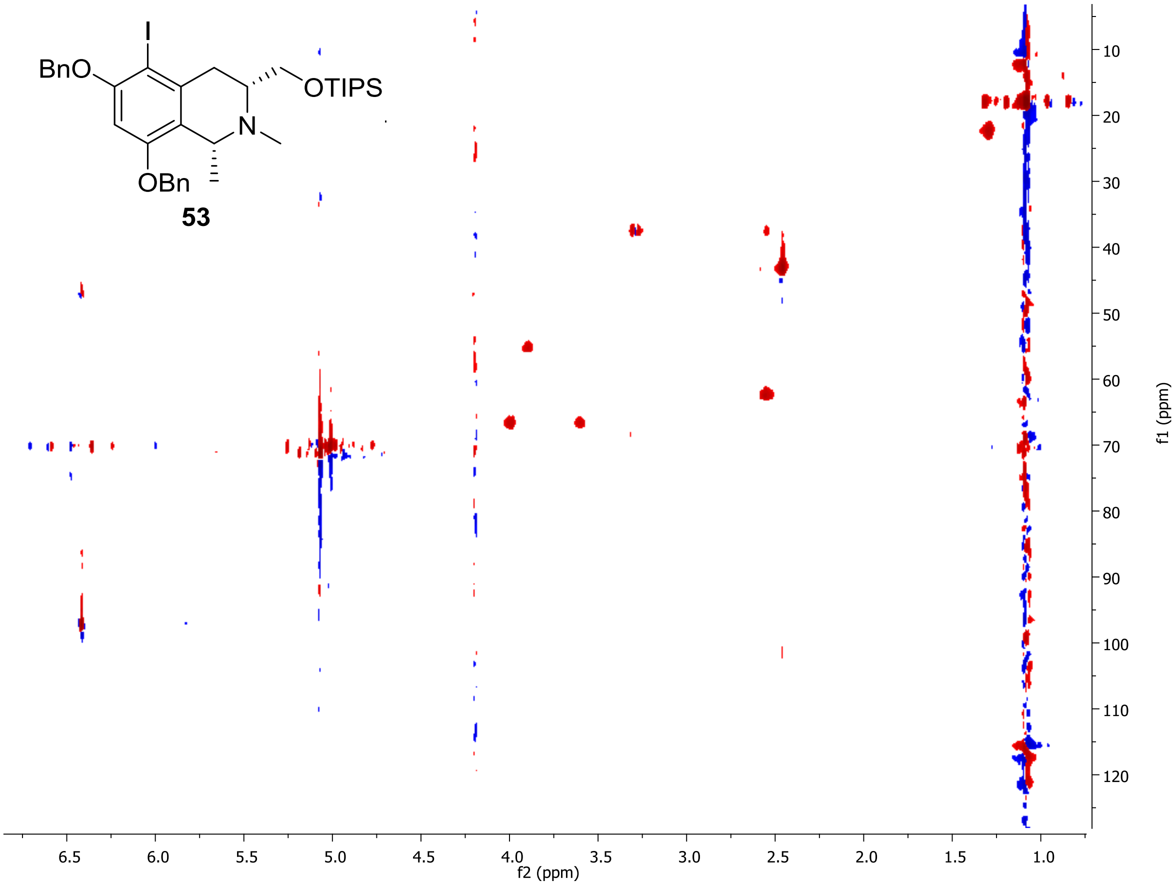
(1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **53**; Proton NMR, $CDCl_3$



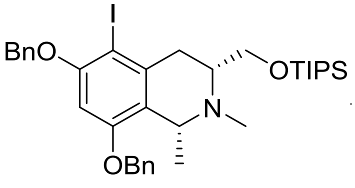
(1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **53**; Carbon NMR, $CDCl_3$



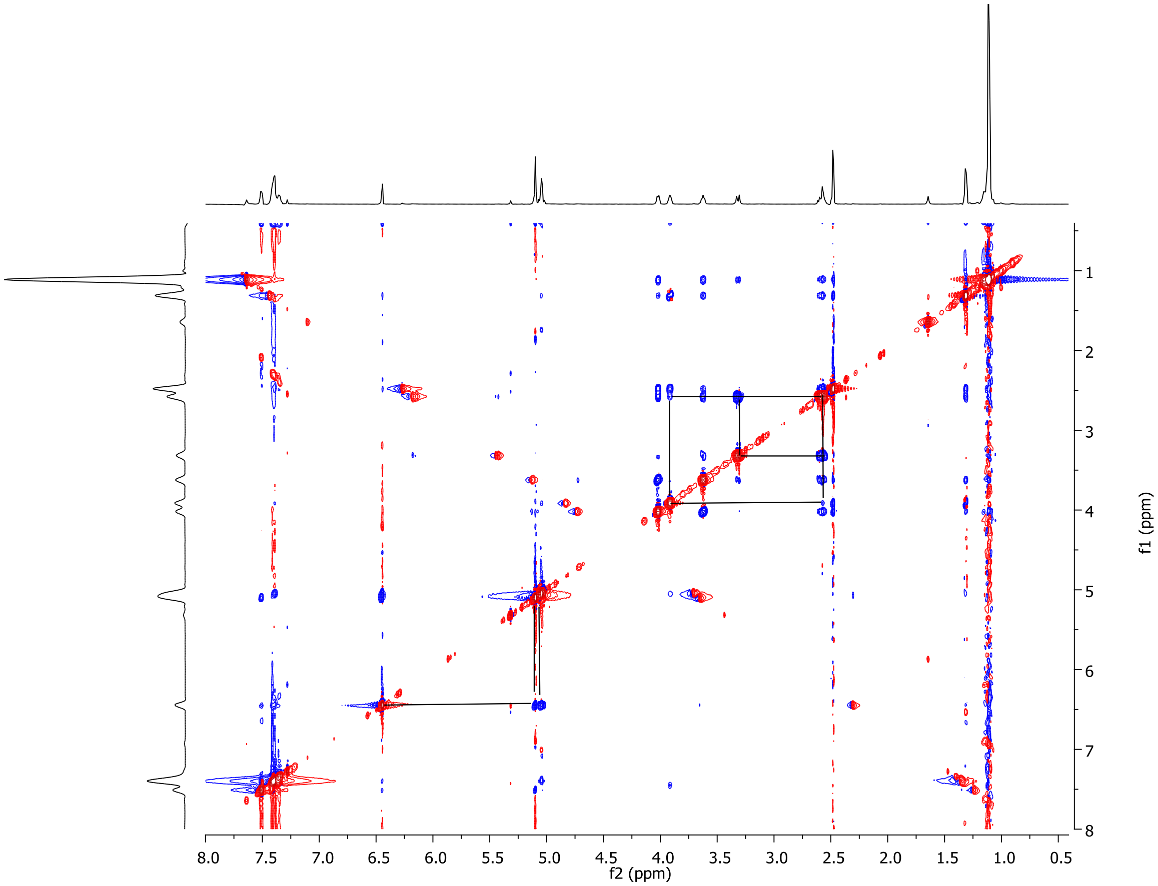
(1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **53**; HMQC NMR, $CDCl_3$



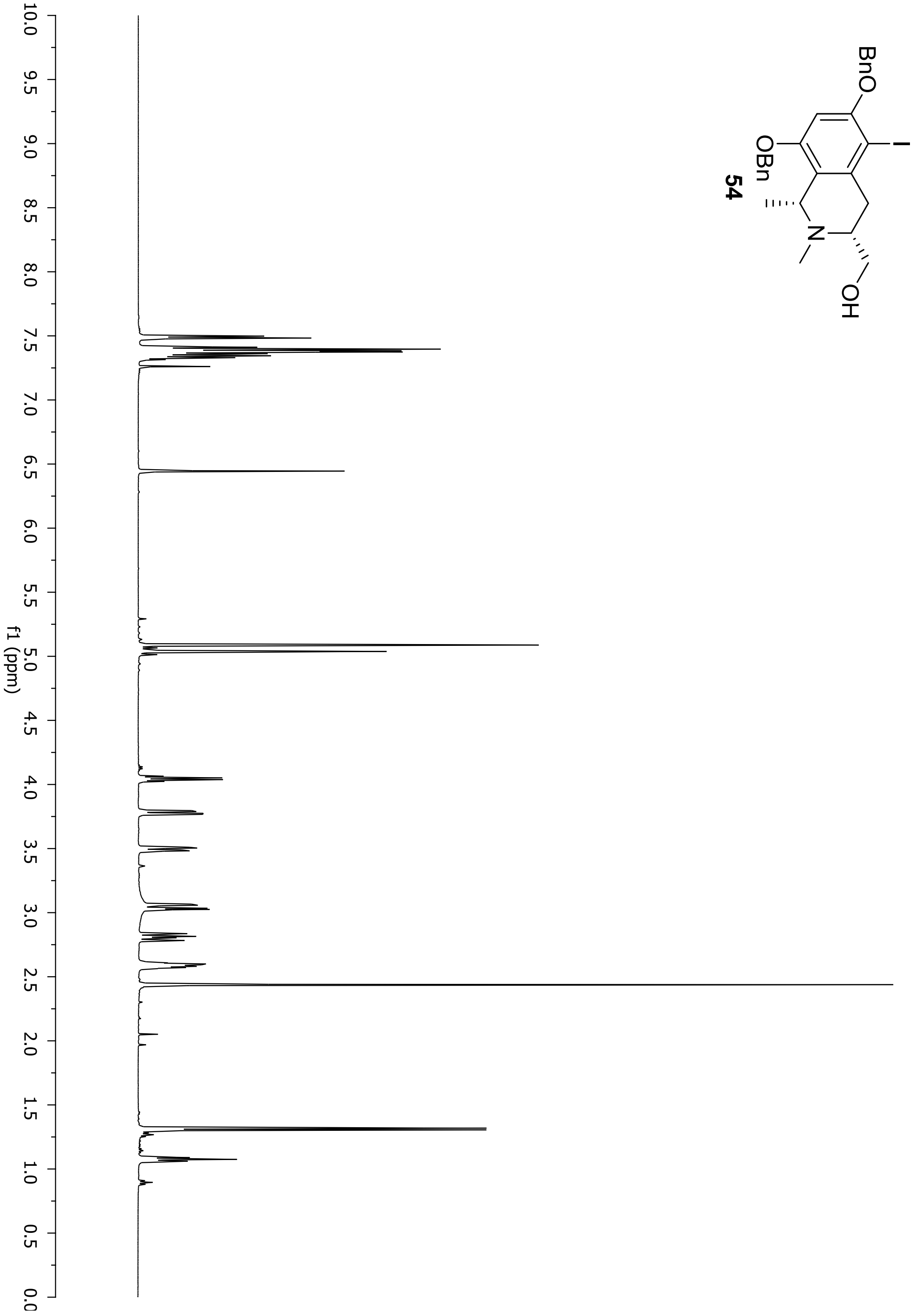
(1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline **53**; 2D Noesy NMR, $CDCl_3$



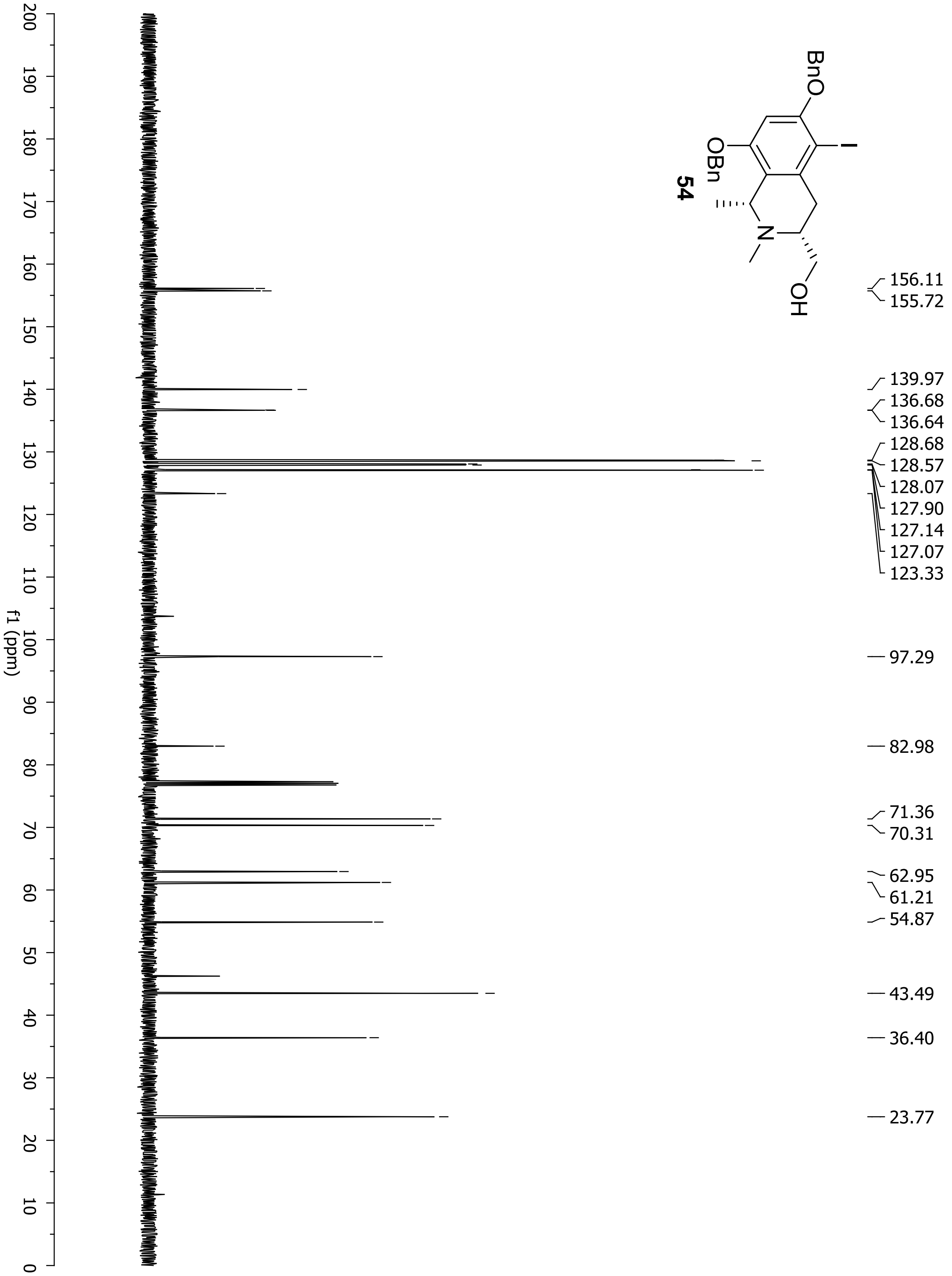
53



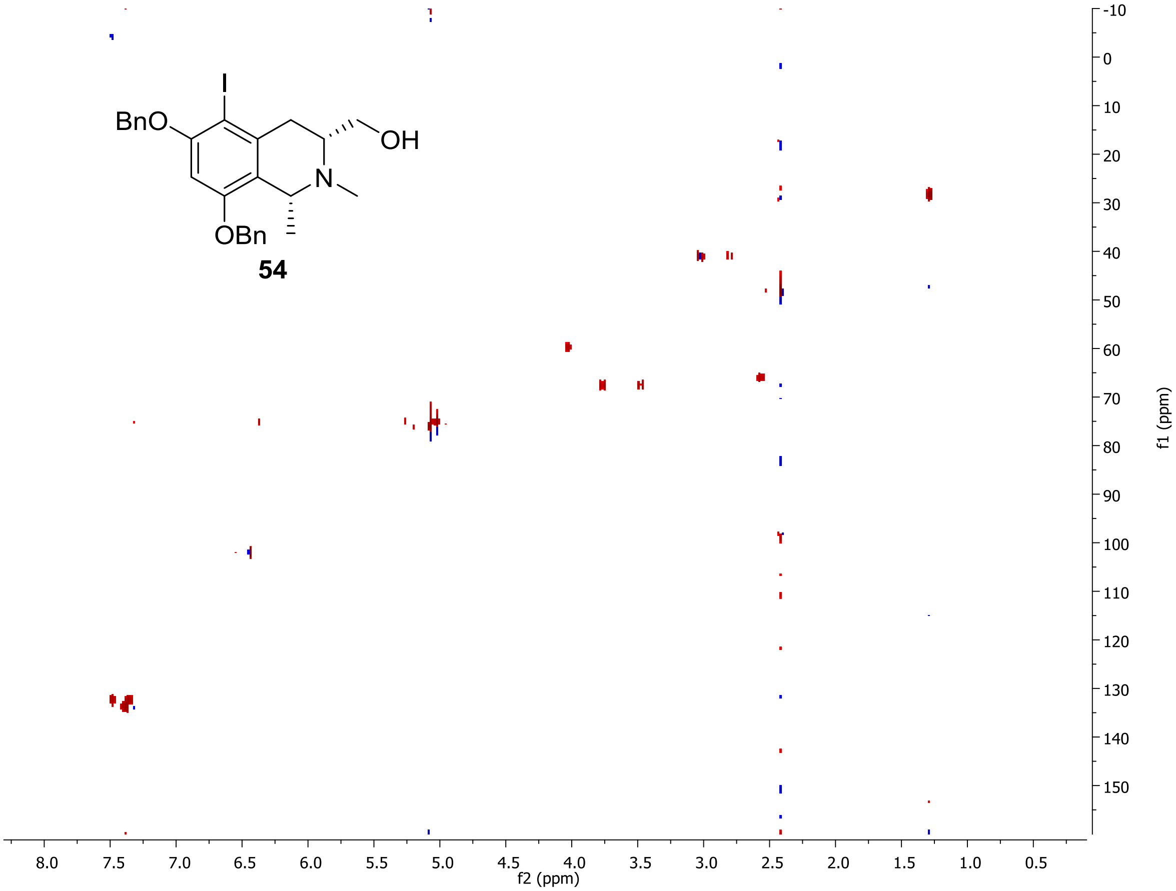
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **54**; Proton NMR, $CDCl_3$



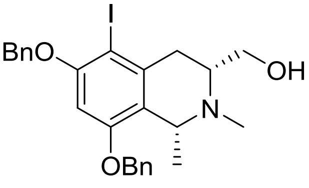
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **54**; Carbon NMR, $CDCl_3$



((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **54**; HMQC NMR, CDCl$_3$



((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **54**; 2D Noesy NMR, $CDCl_3$



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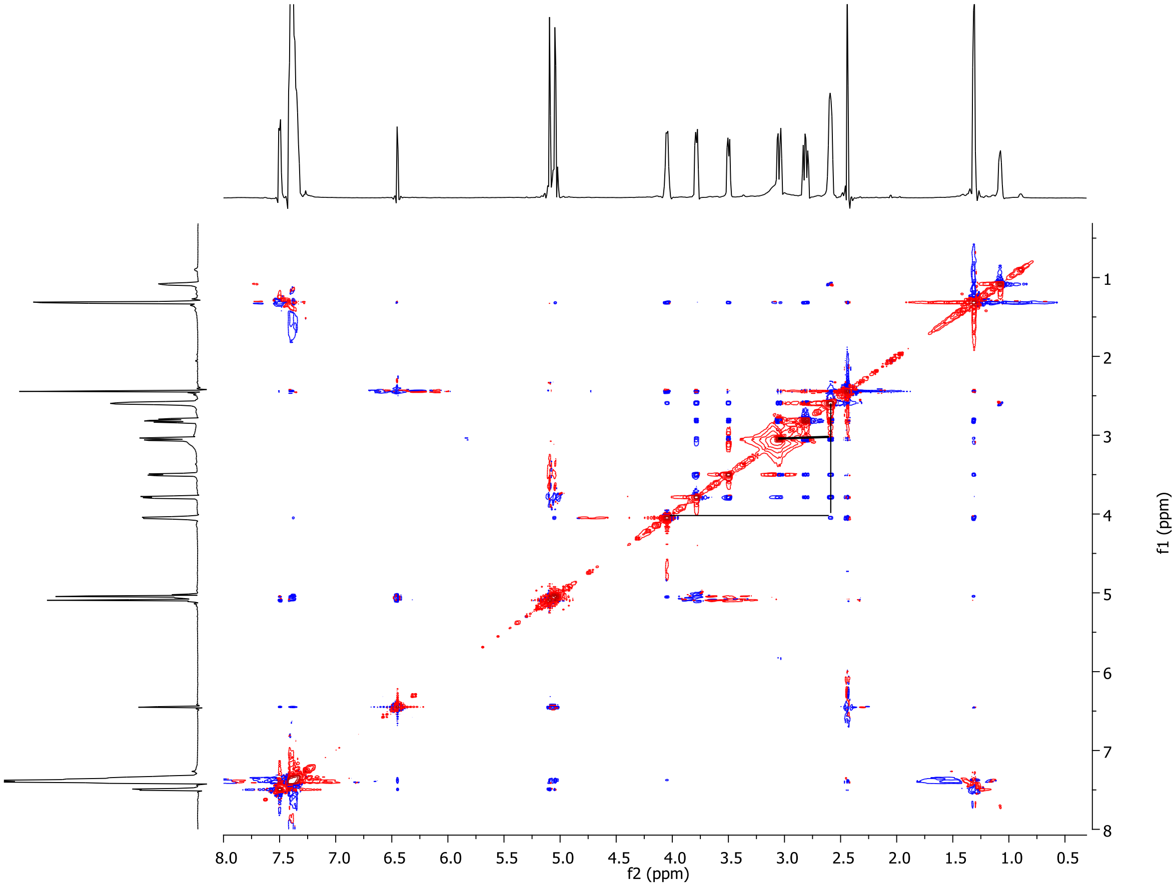
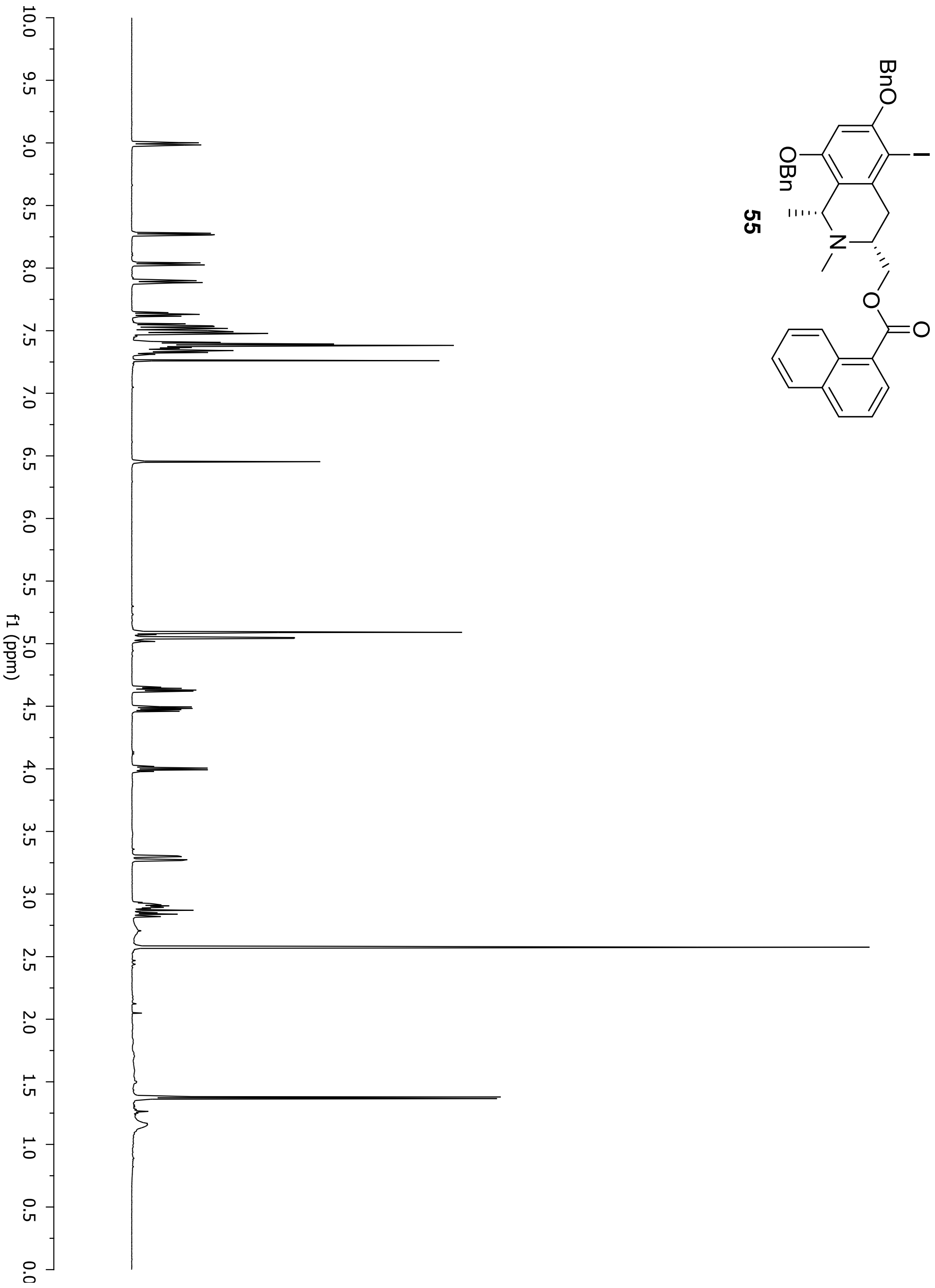
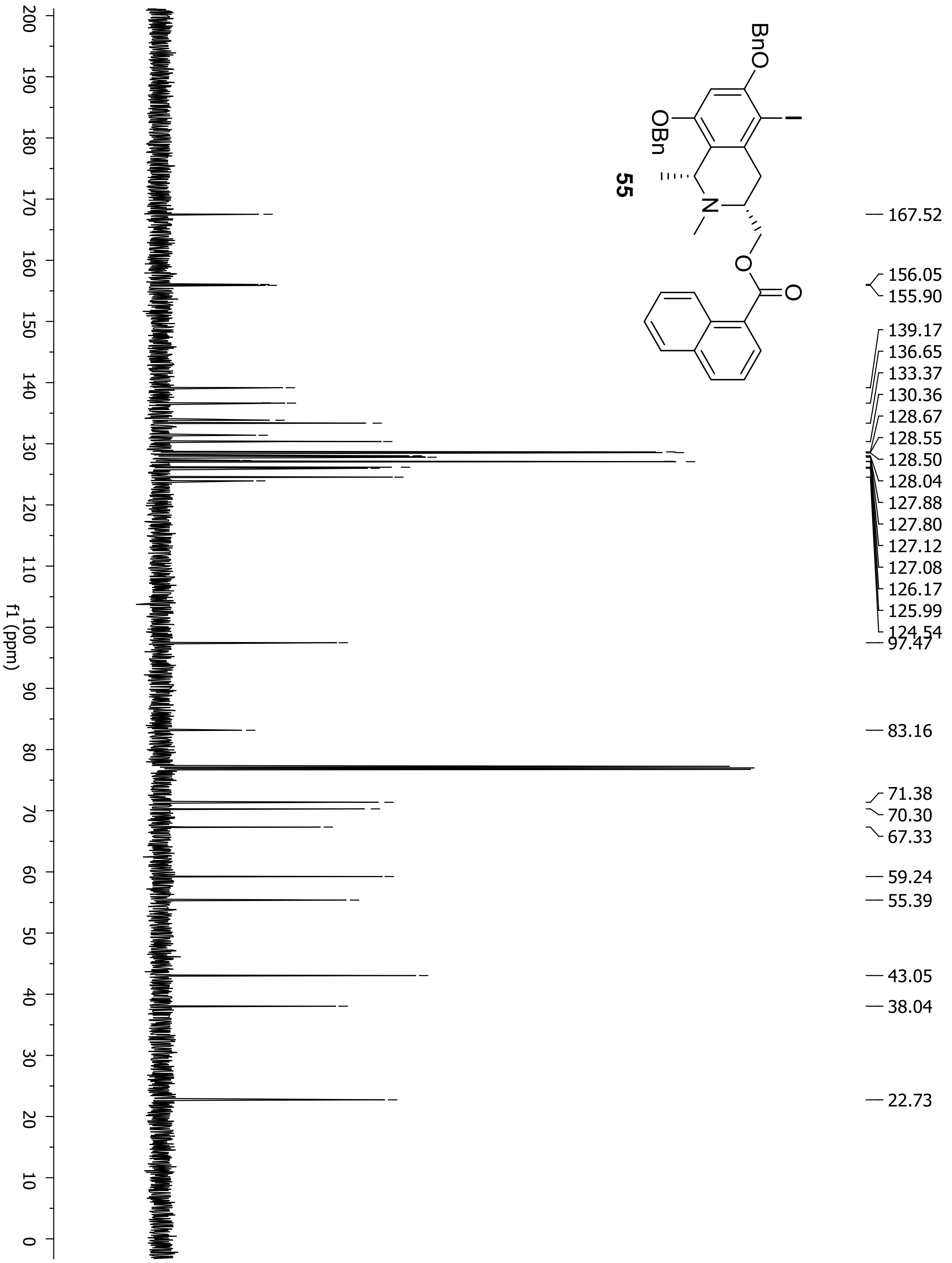


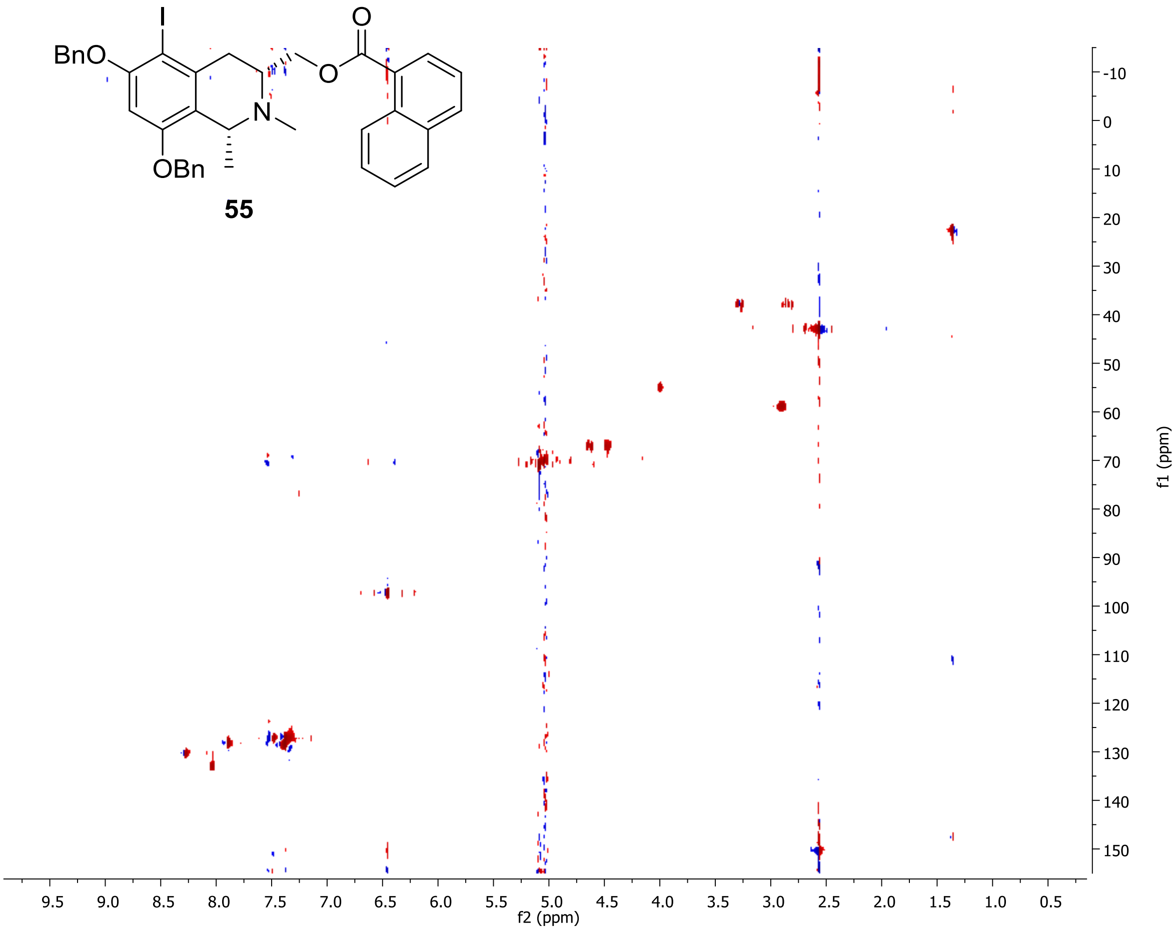
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl 1-naphthoate **55**; Proton NMR, CDCl$_3$



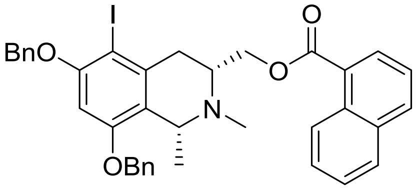
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl 1-naphthoate **55**; Carbon NMR, $CDCl_3$



((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl 1-naphthoate **55**; HMQC NMR, $CDCl_3$



((1*R*,3*R*)-6,8-bis(benzyloxy)-5-iodo-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl 1-naphthoate **55**; 2D Noesy NMR, $CDCl_3$



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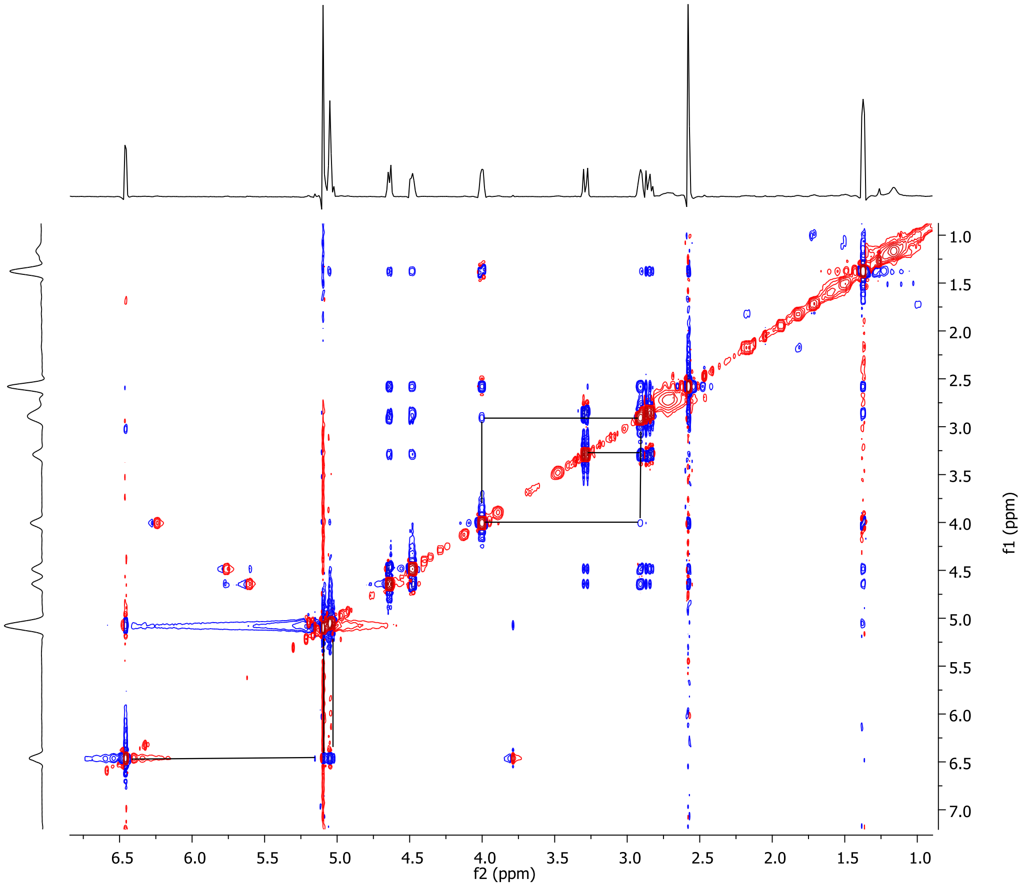
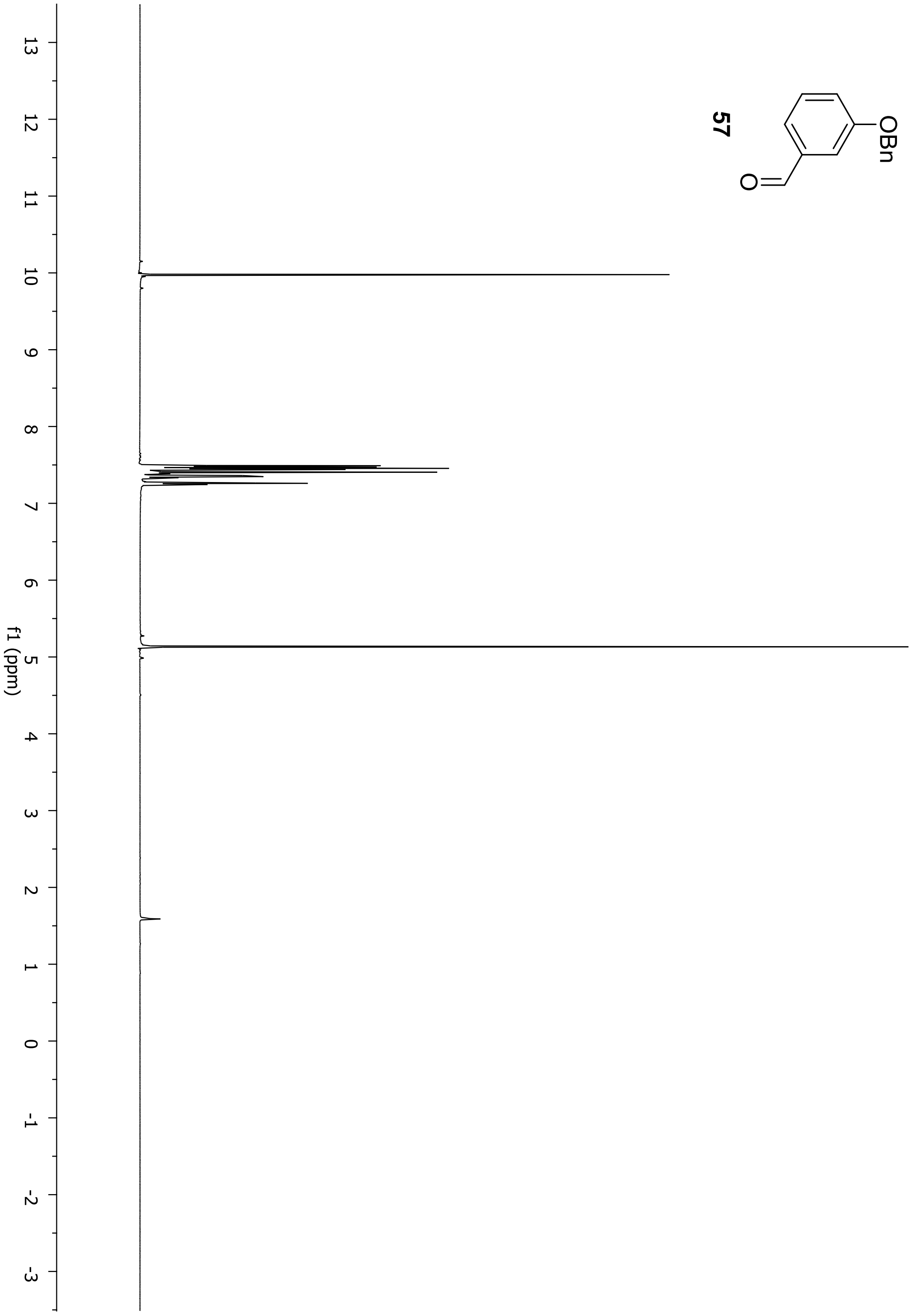
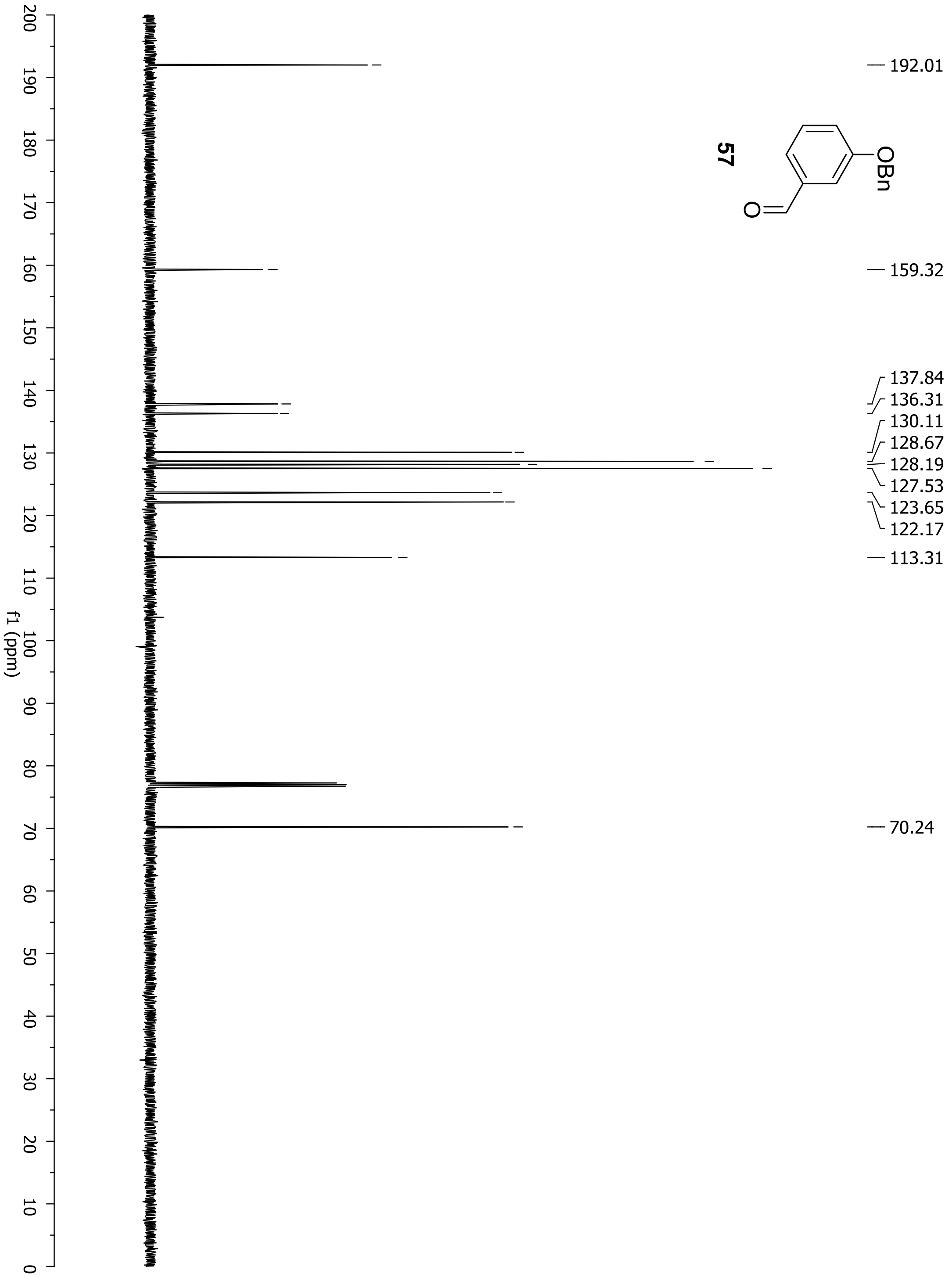


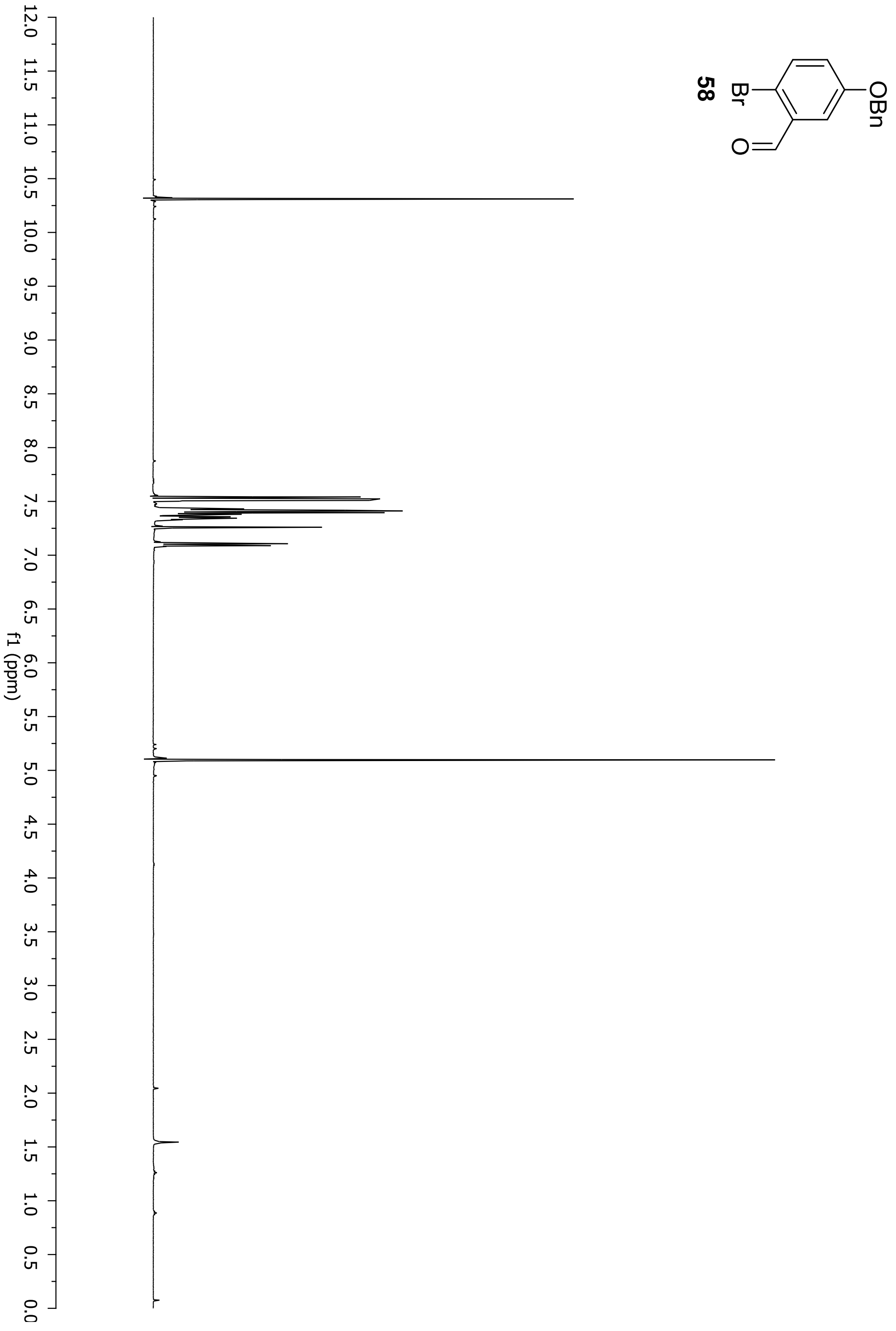
3-benzyloxy benzaldehyde **57**; Proton NMR, $CDCl_3$



3-benzyloxy benzaldehyde **57**; Carbon NMR, $CDCl_3$

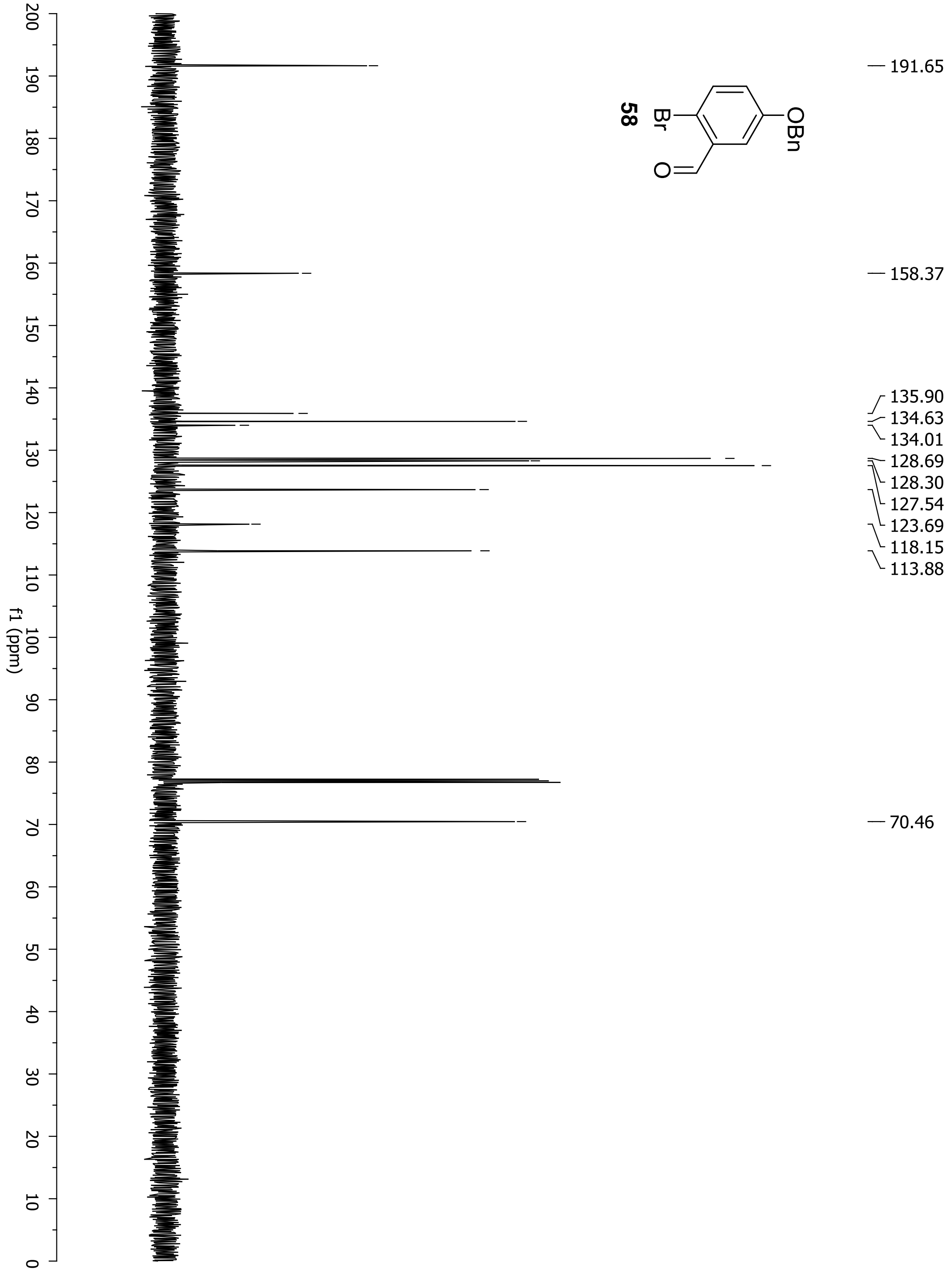


5-(benzyloxy)-2-bromobenzaldehyde **58**; Proton NMR, $CDCl_3$

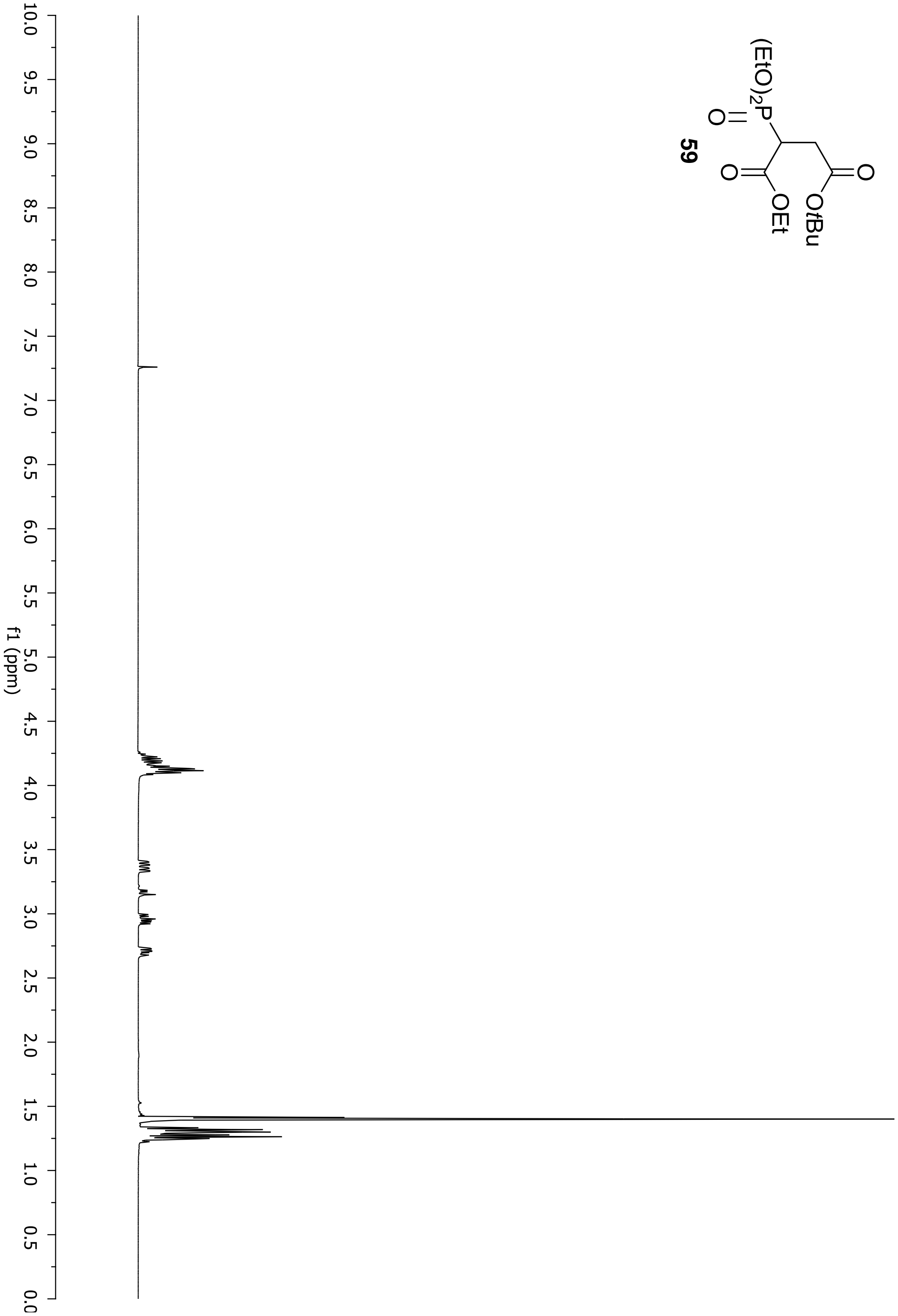


58

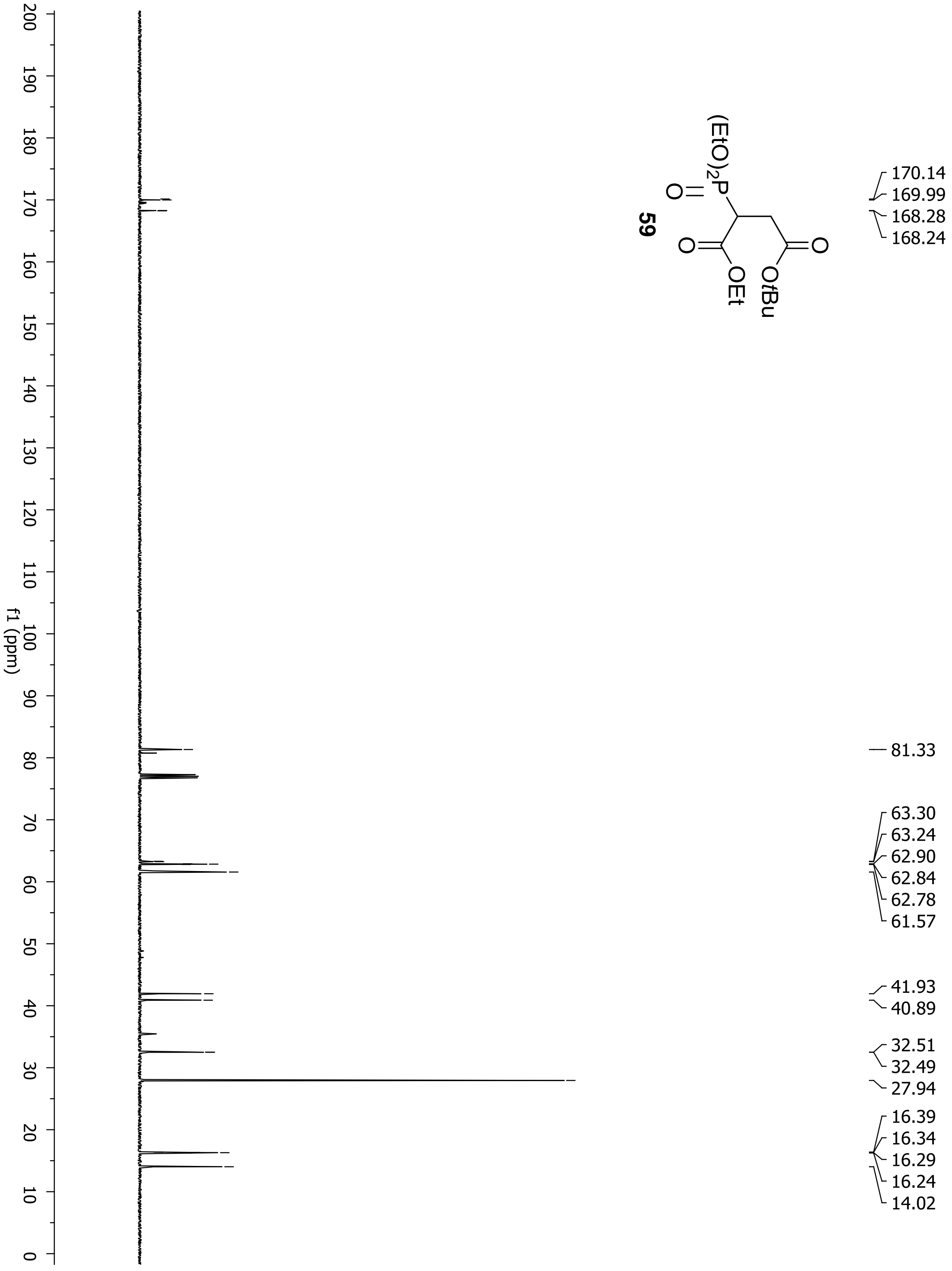
5-(benzyloxy)-2-bromobenzaldehyde **58**; Carbon NMR, CDCl$_3$



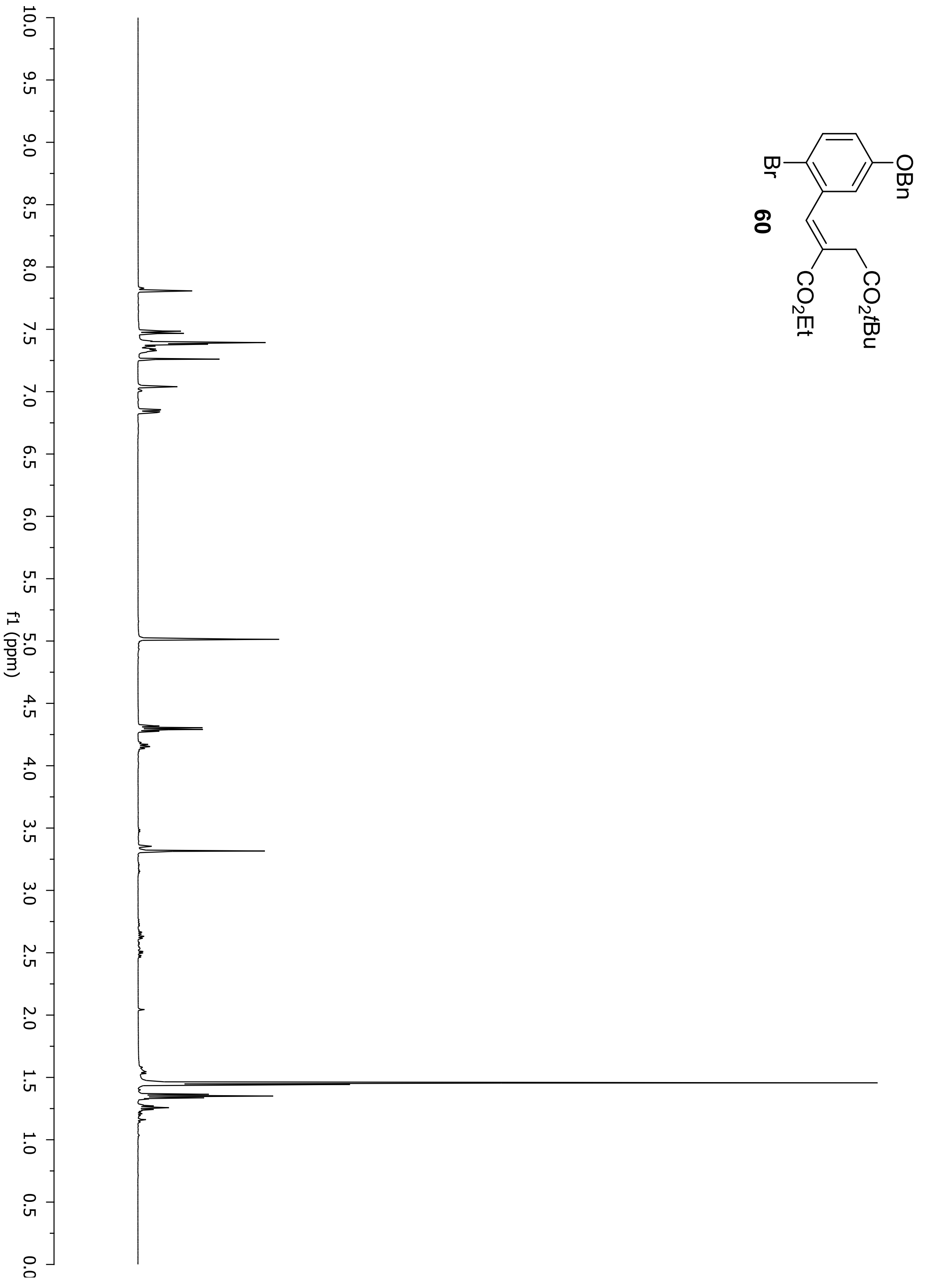
4-(*t*-butyl) 1-ethyl 2-(diethoxyphosphoryl)succinate **59**; Proton NMR, $CDCl_3$



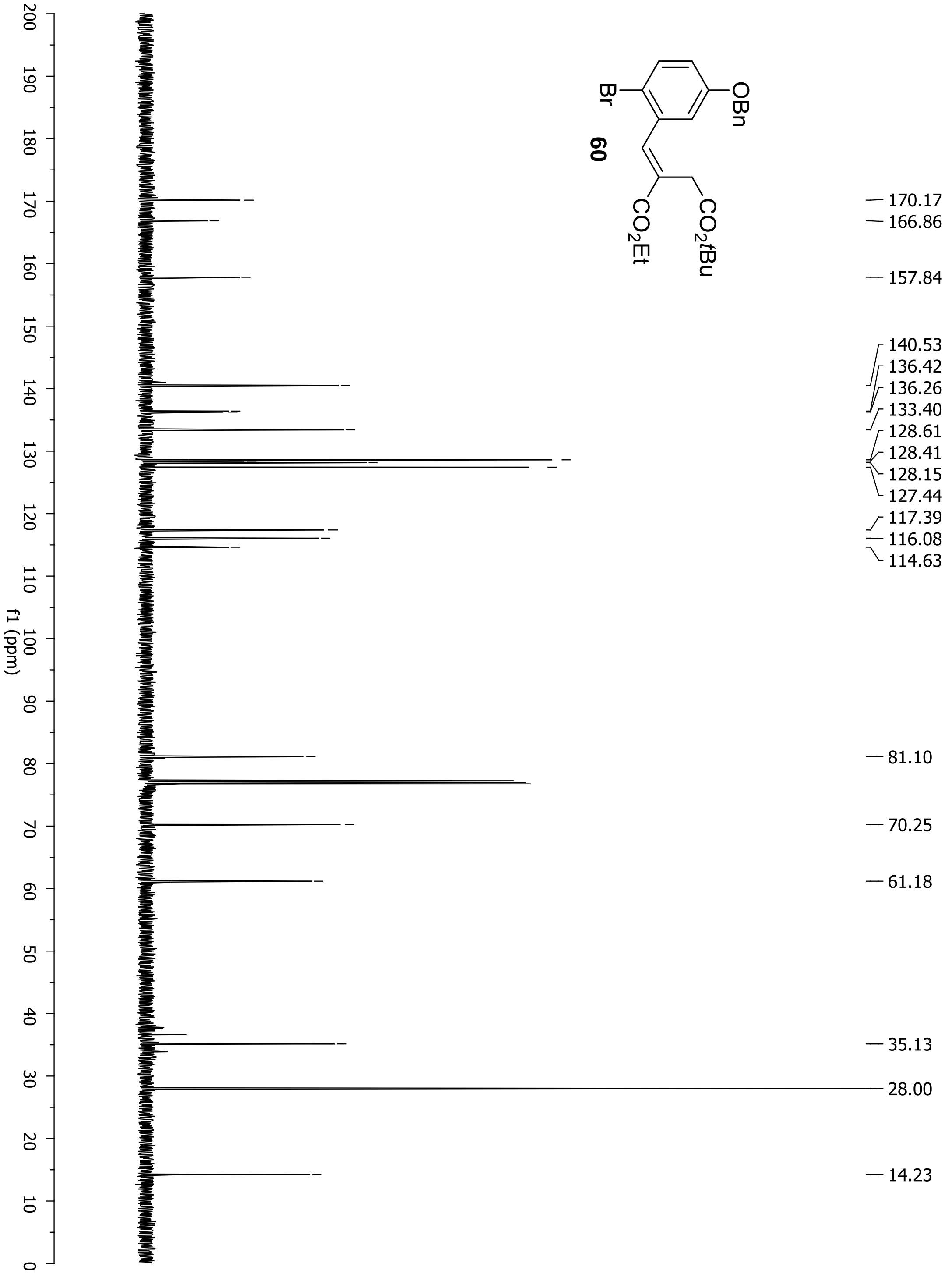
4-(*t*-butyl) 1-ethyl 2-(diethoxyphosphoryl)succinate **59**; Carbon NMR, $CDCl_3$



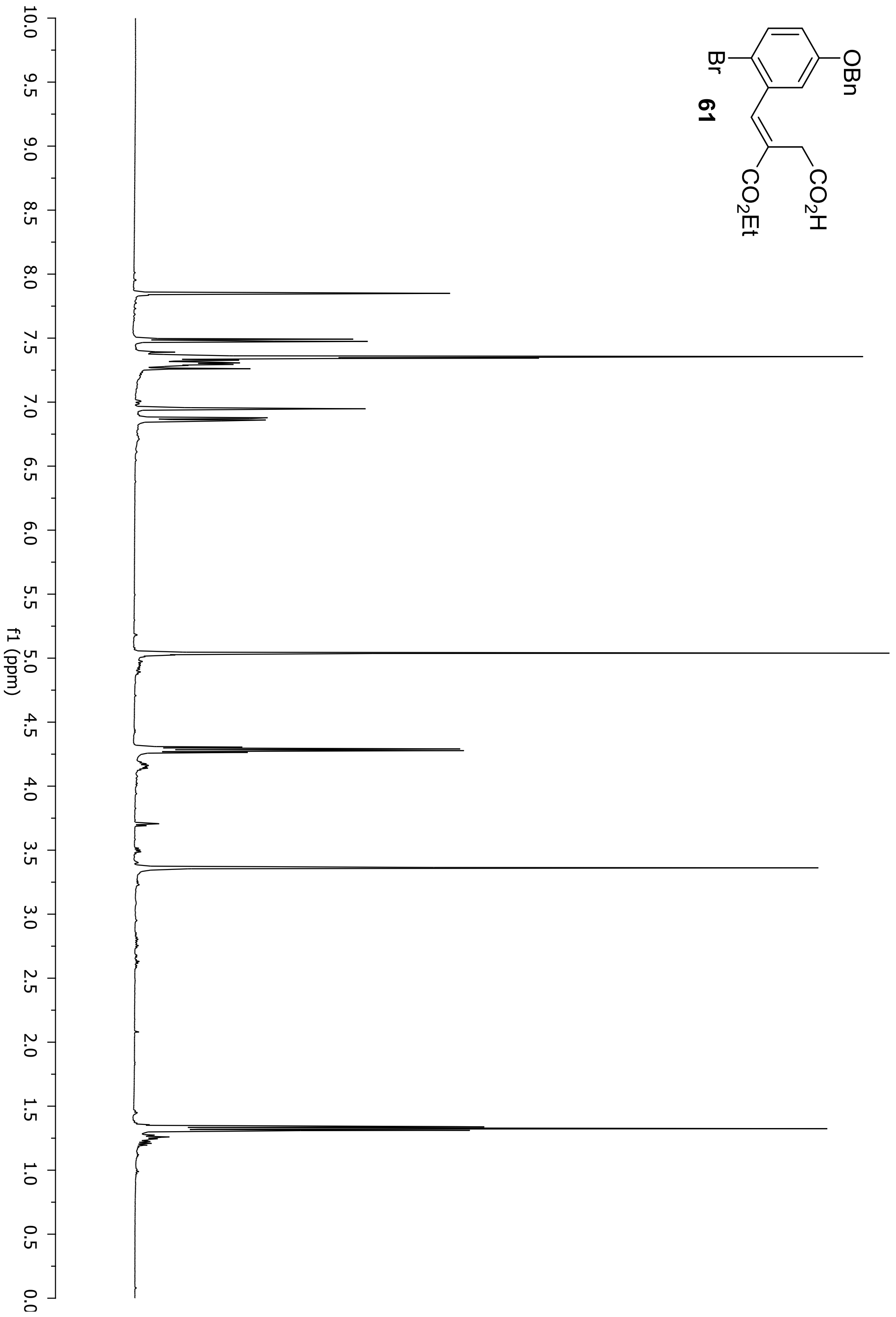
4-(*t*-butyl) 1-ethyl (E)-2-(5-(benzyloxy)-2-bromobenzylidene)succinate **60**; Proton NMR, $CDCl_3$**)**



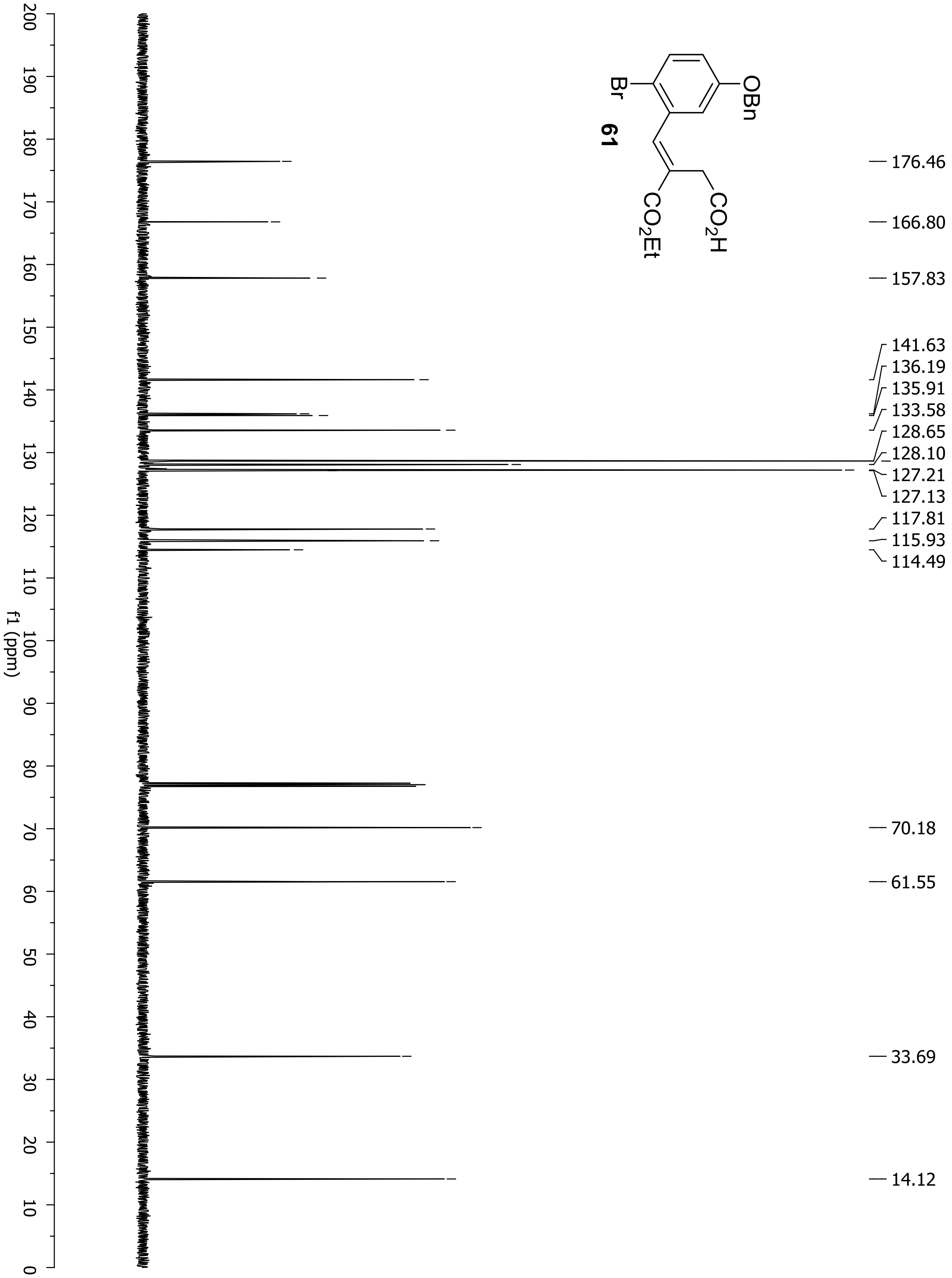
4-(*t*-butyl) 1-ethyl (E)-2-(5-(benzyloxy)-2-bromobenzylidene)succinate **60**; Carbon NMR, $CDCl_3$



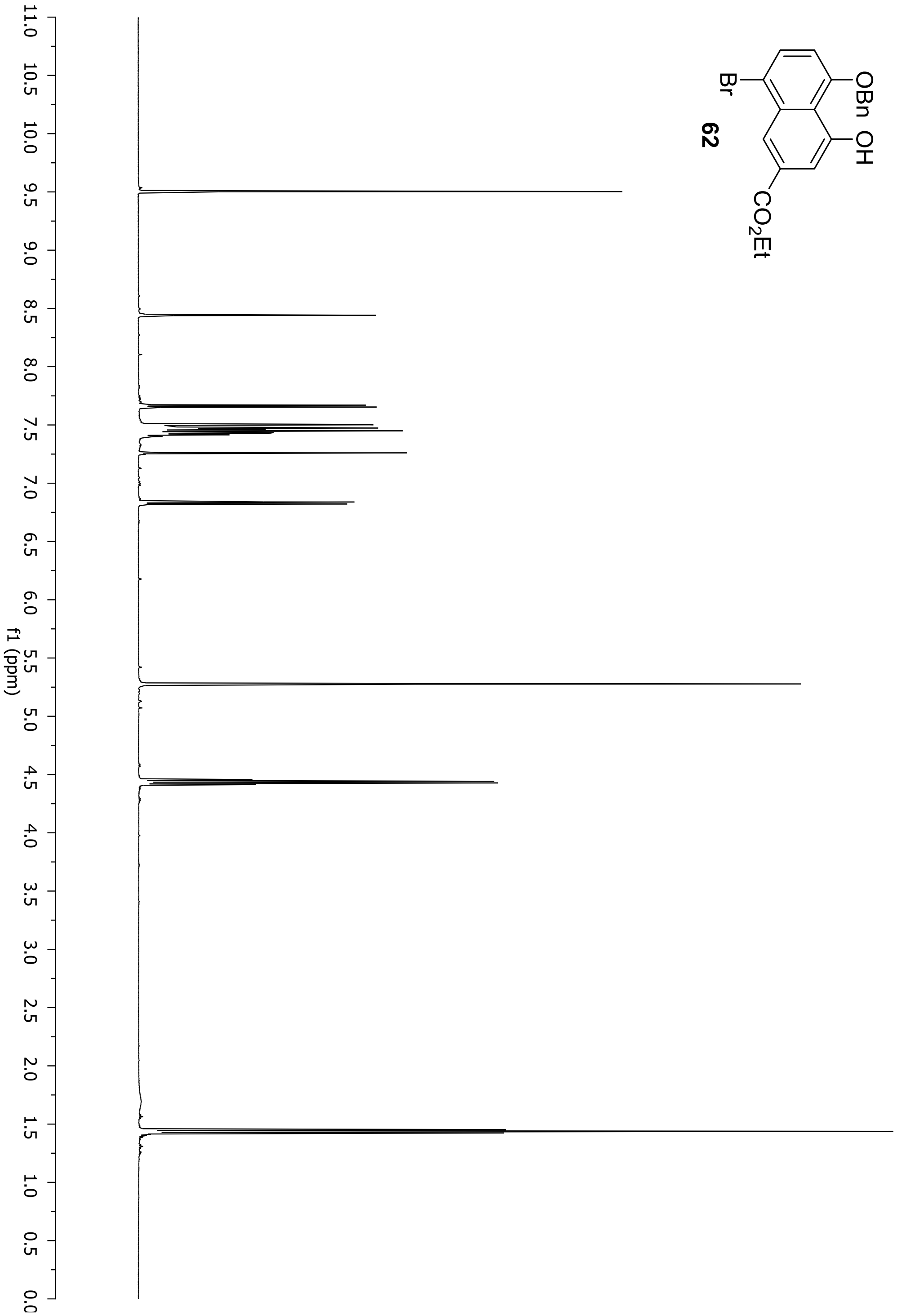
(E)-4-(5-(benzyloxy)-2-bromophenyl)-3-(ethoxycarbonyl)but-3-enoic acid **61**; Proton NMR, $CDCl_3$



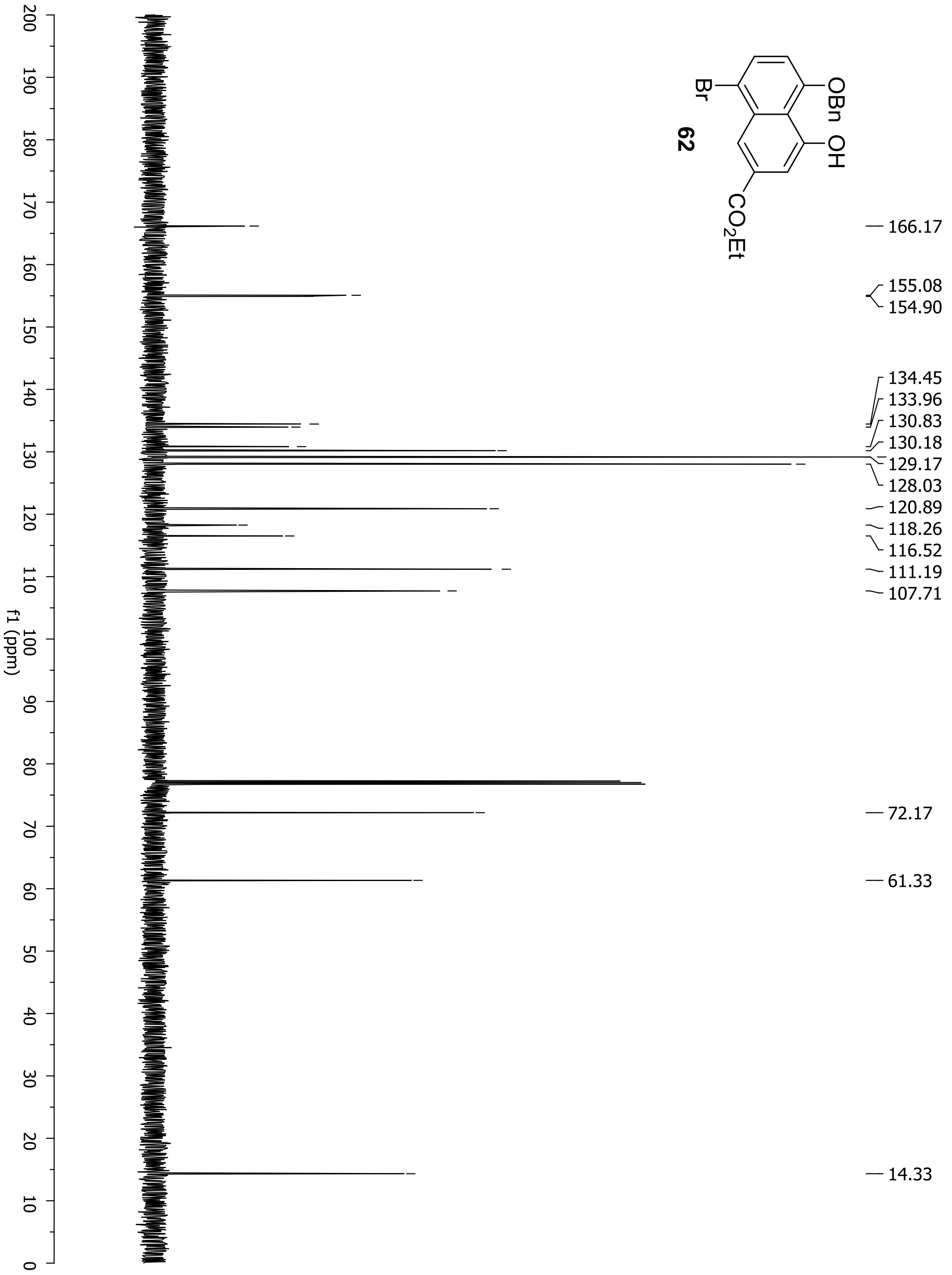
(E)-4-(5-(benzyloxy)-2-bromophenyl)-3-(ethoxycarbonyl)but-3-enoic acid 61; Carbon NMR, $CDCl_3$



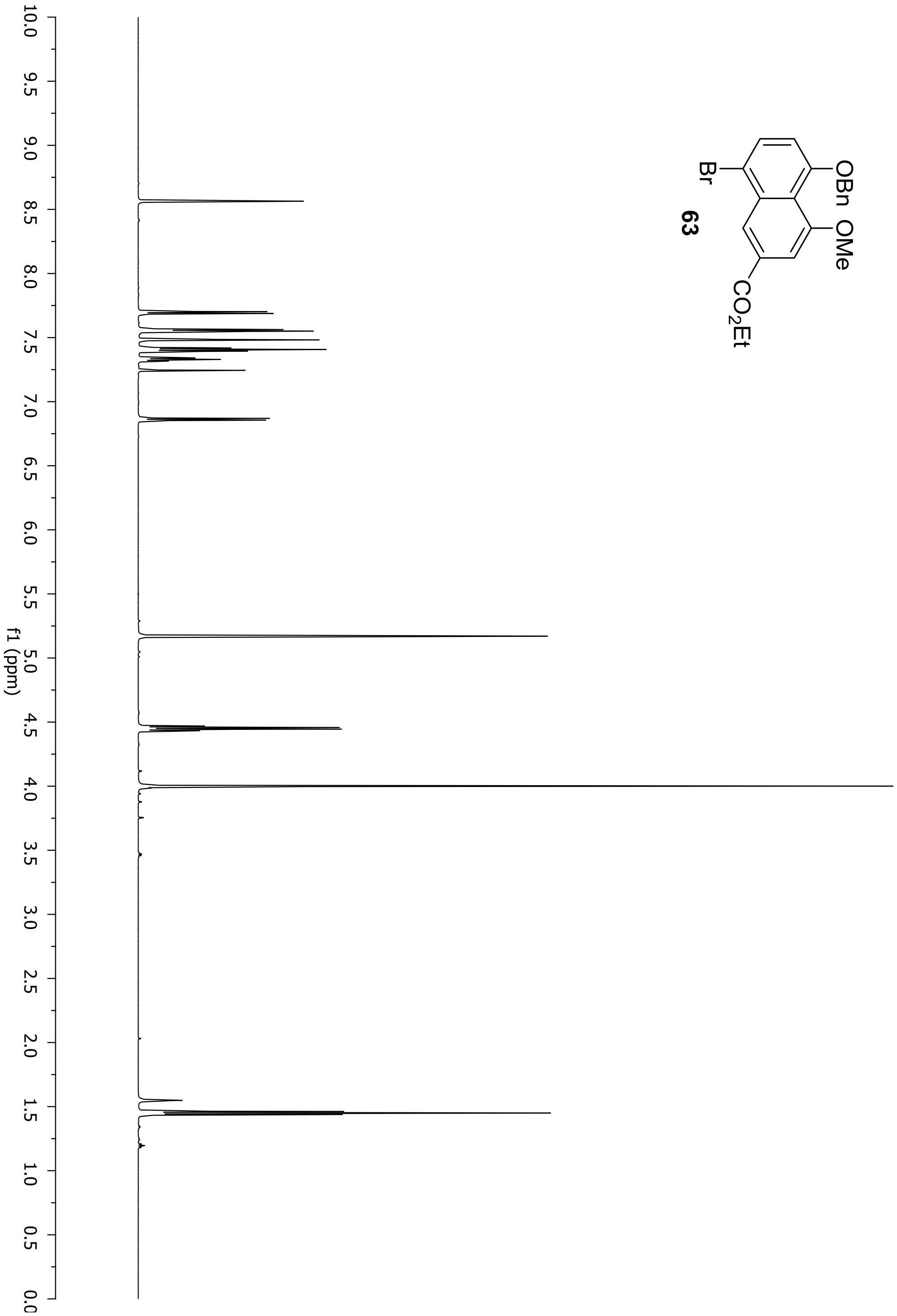
Ethyl 5-(benzyloxy)-8-bromo-4-hydroxy-2-naphthoate **62**; Proton NMR, $CDCl_3$



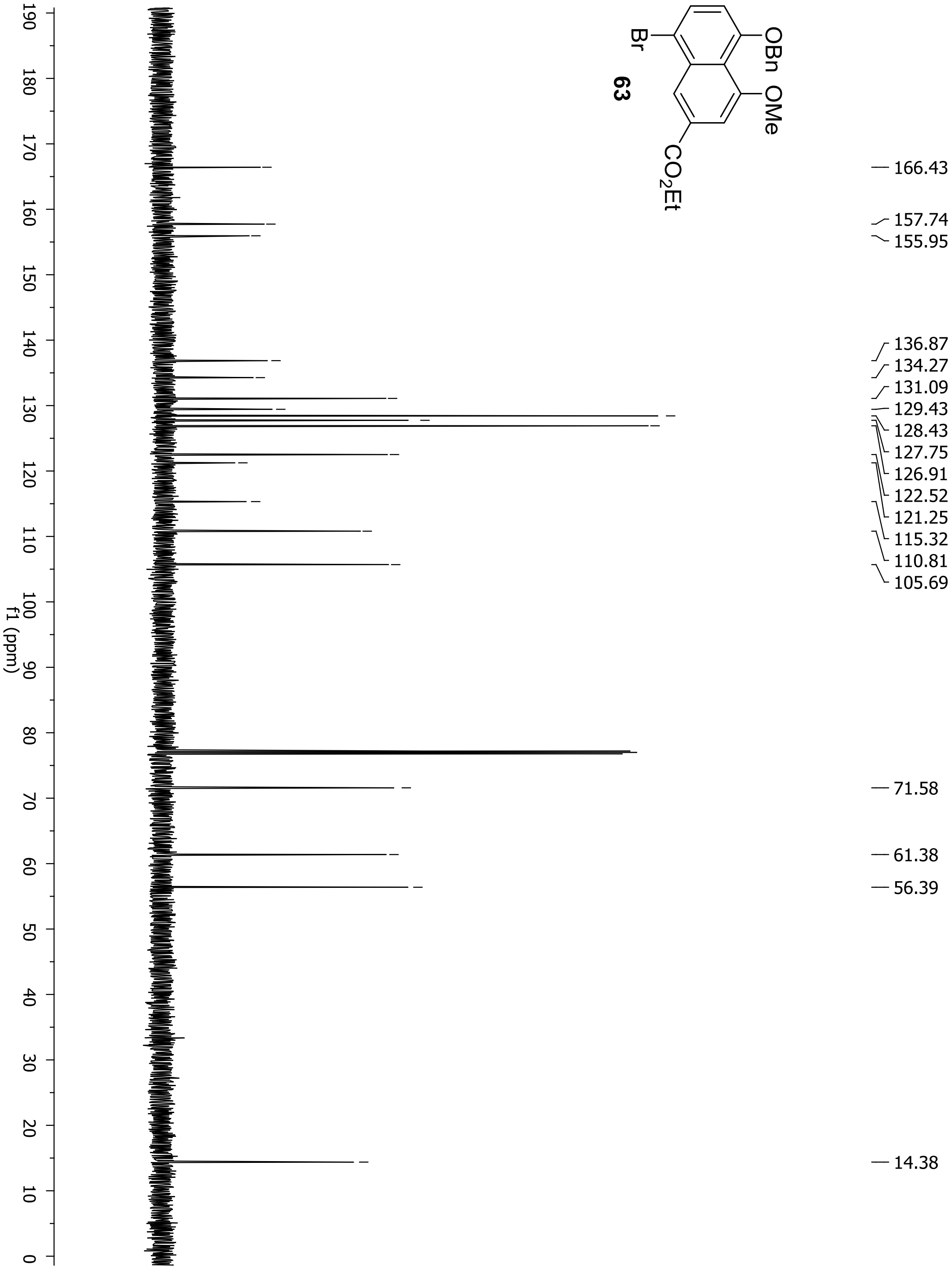
Ethyl 5-(benzyloxy)-8-bromo-4-hydroxy-2-naphthoate **62**; Carbon NMR, $CDCl_3$



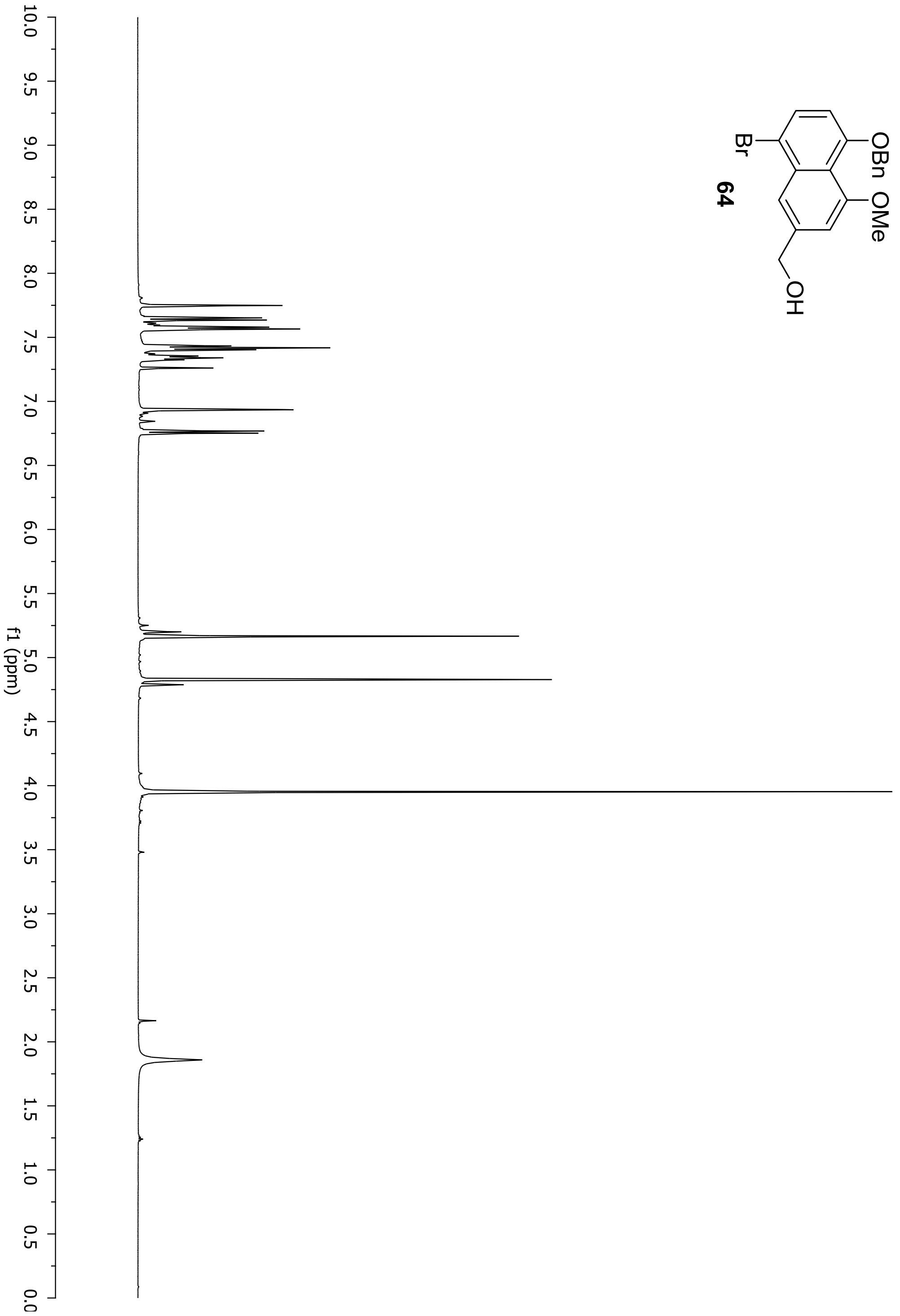
Ethyl 5-(benzyloxy)-8-bromo-4-methoxy-2-naphthoate **63**; Proton NMR, $CDCl_3$



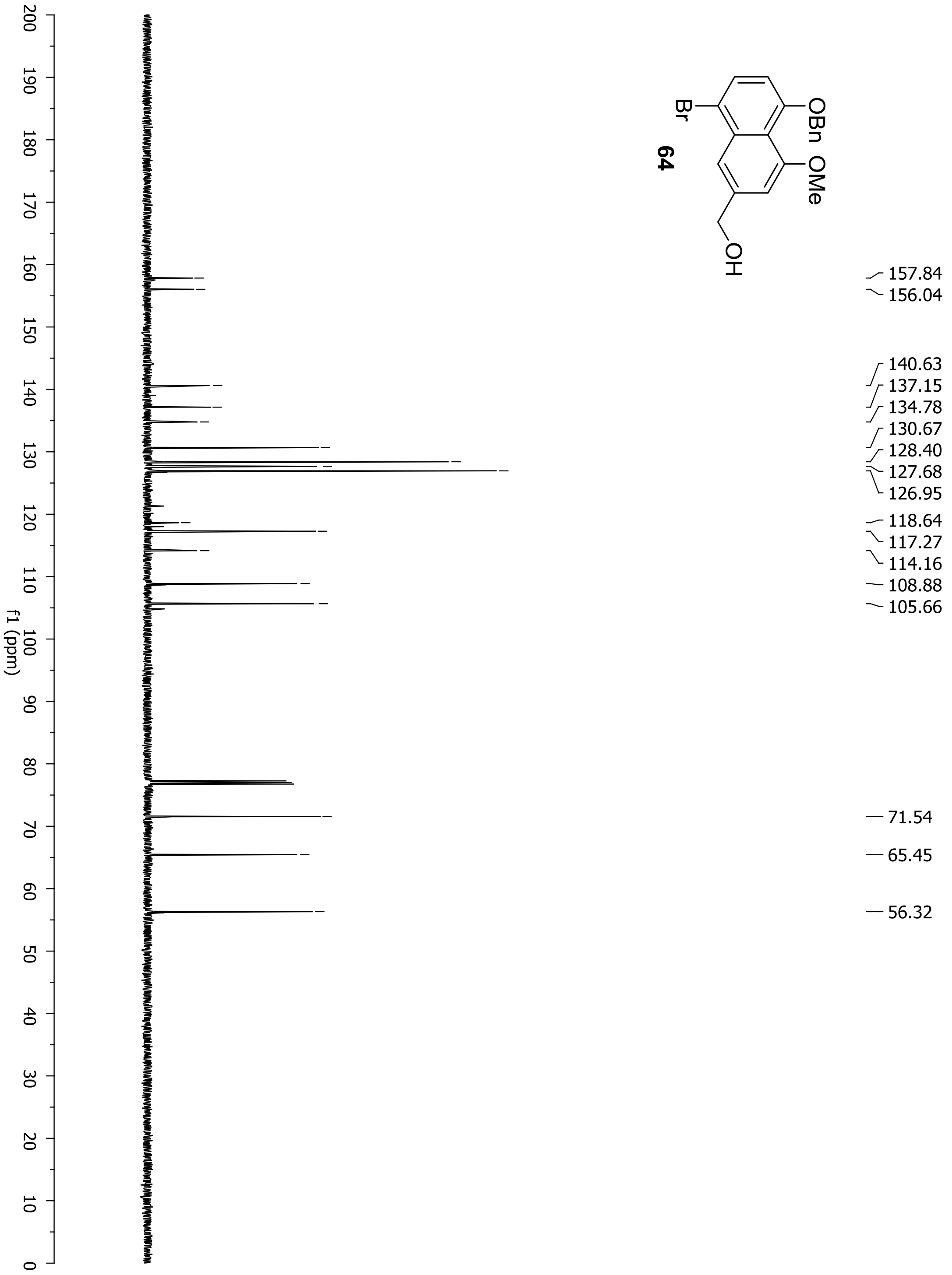
Ethyl 5-(benzyloxy)-8-bromo-4-methoxy-2-naphthoate **63**; Carbon NMR, $CDCl_3$



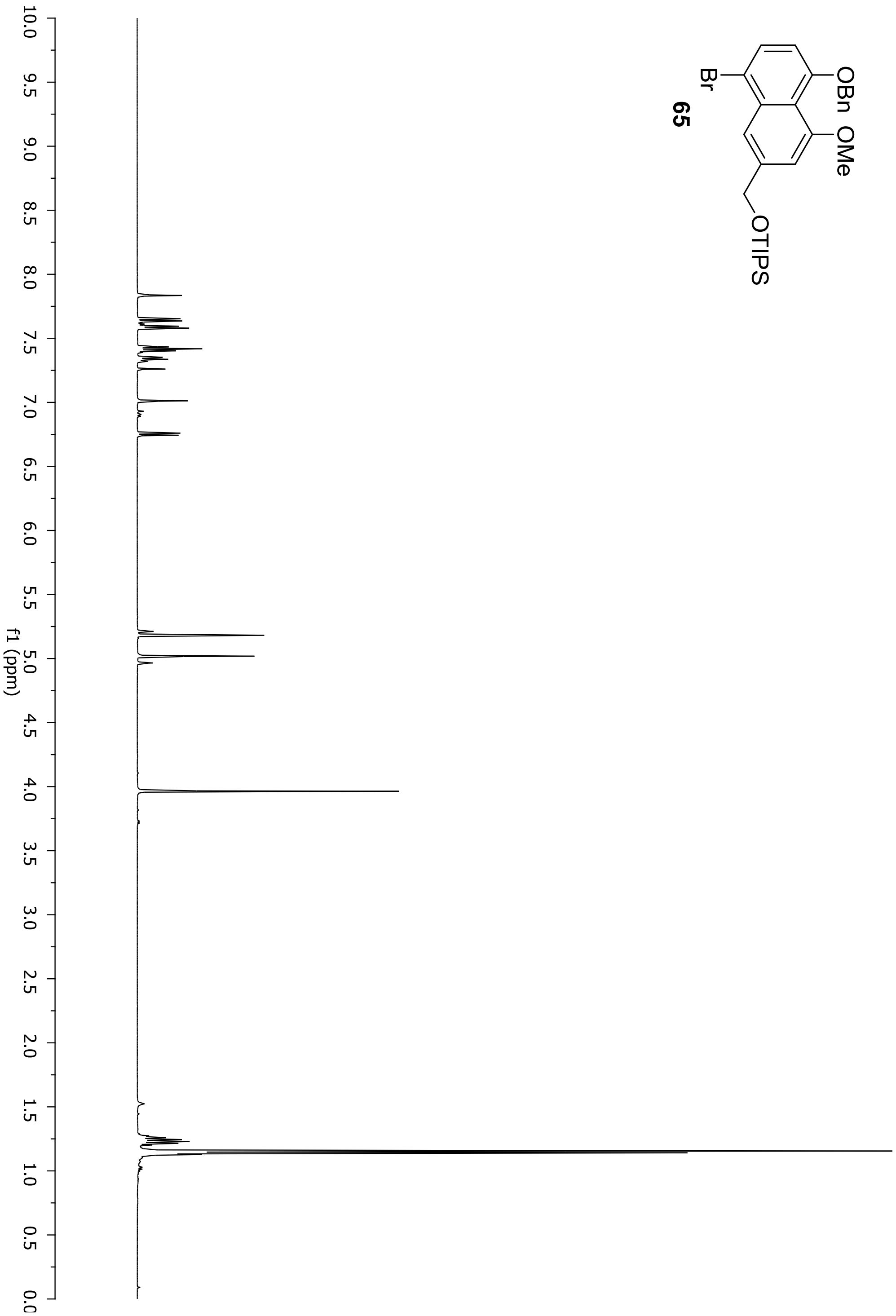
(5-(benzyloxy)-8-bromo-4-methoxynaphthalen-2-yl)methanol **64**; Proton NMR, $CDCl_3$



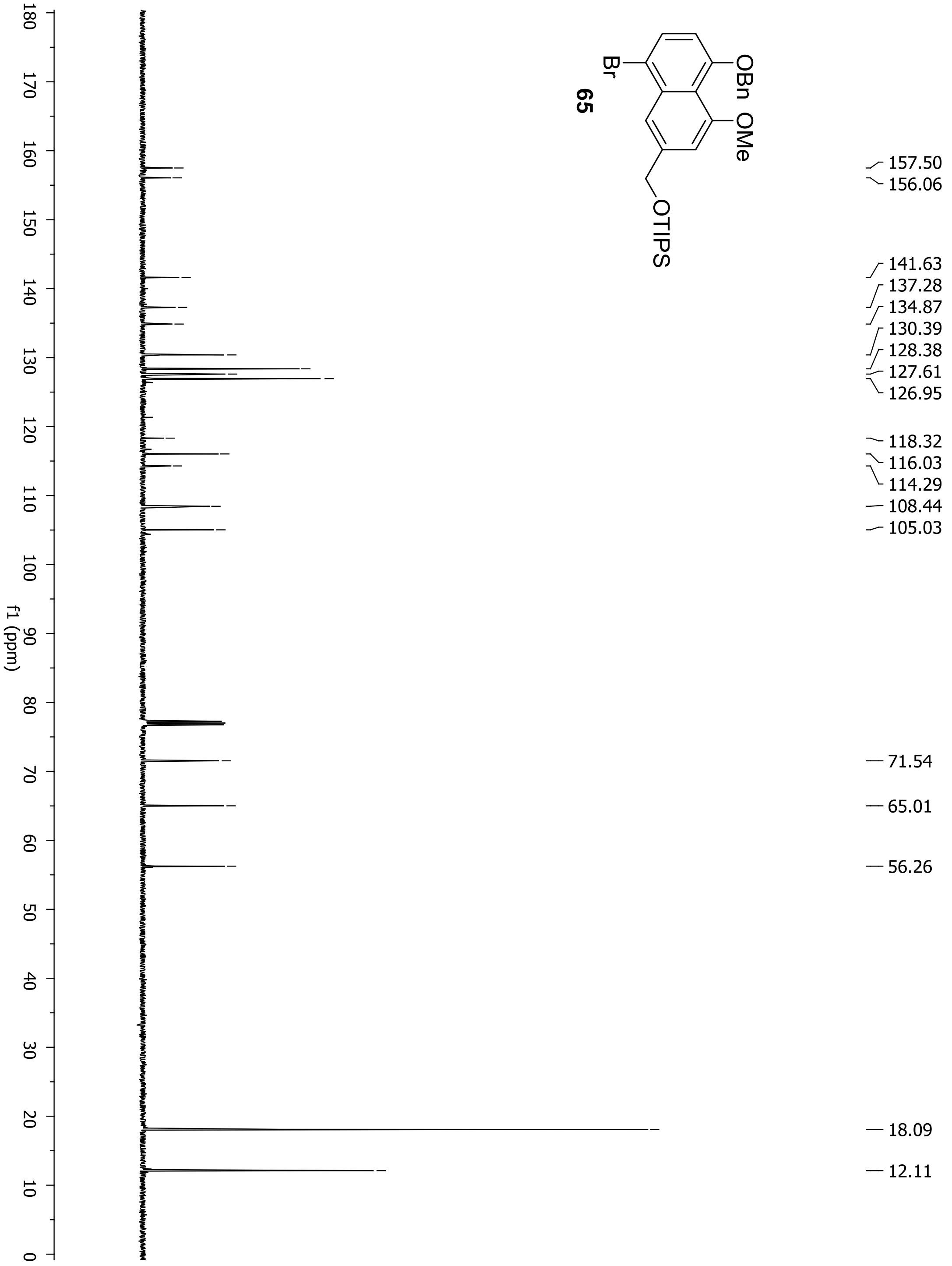
(5-(benzyloxy)-8-bromo-4-methoxynaphthalen-2-yl)methanol **64**; Carbon NMR, $CDCl_3$



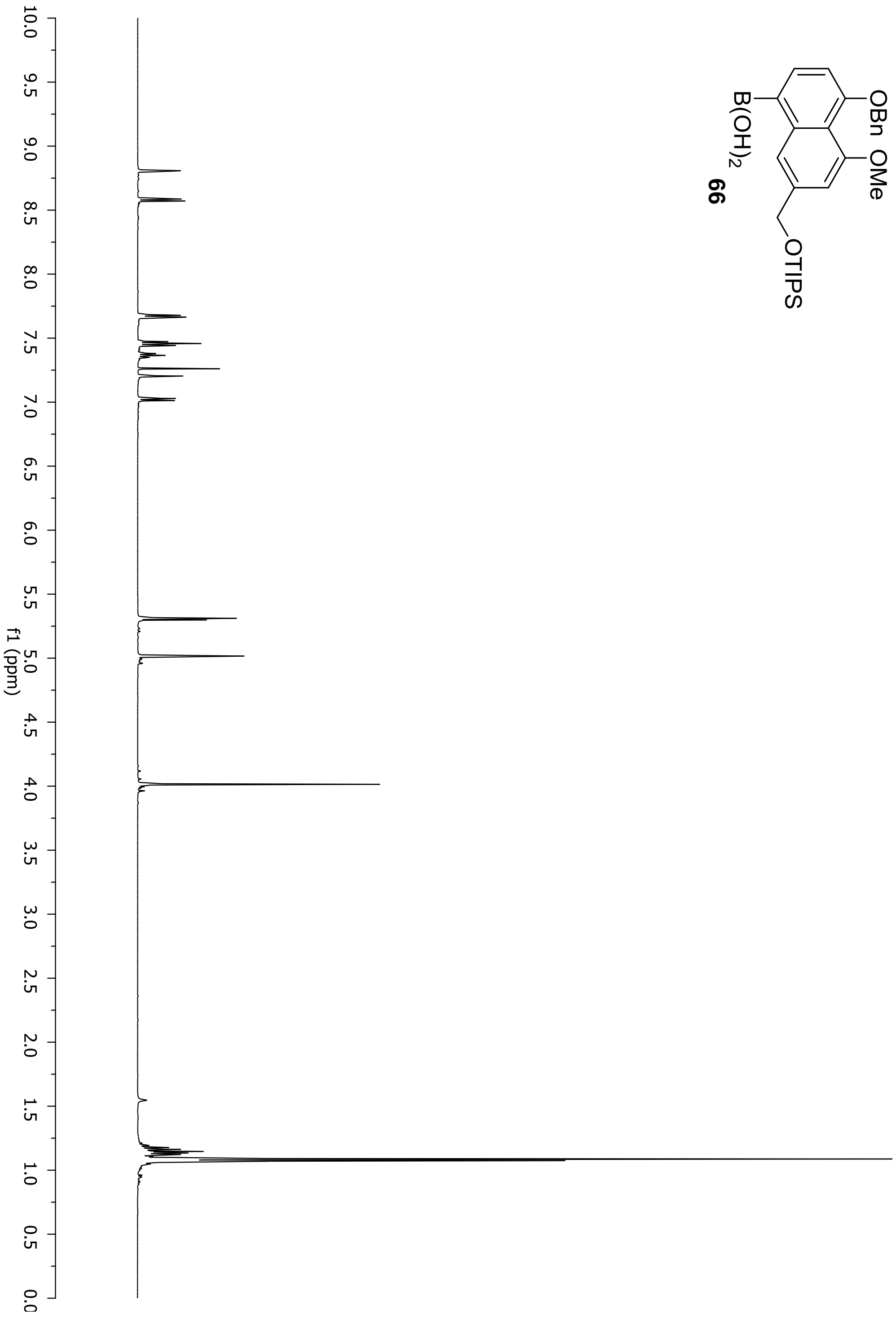
((5-(benzyloxy)-8-bromo-4-methoxynaphthalen-2-yl)methoxy)triisopropylsilane **65**; Proton NMR, $CDCl_3$



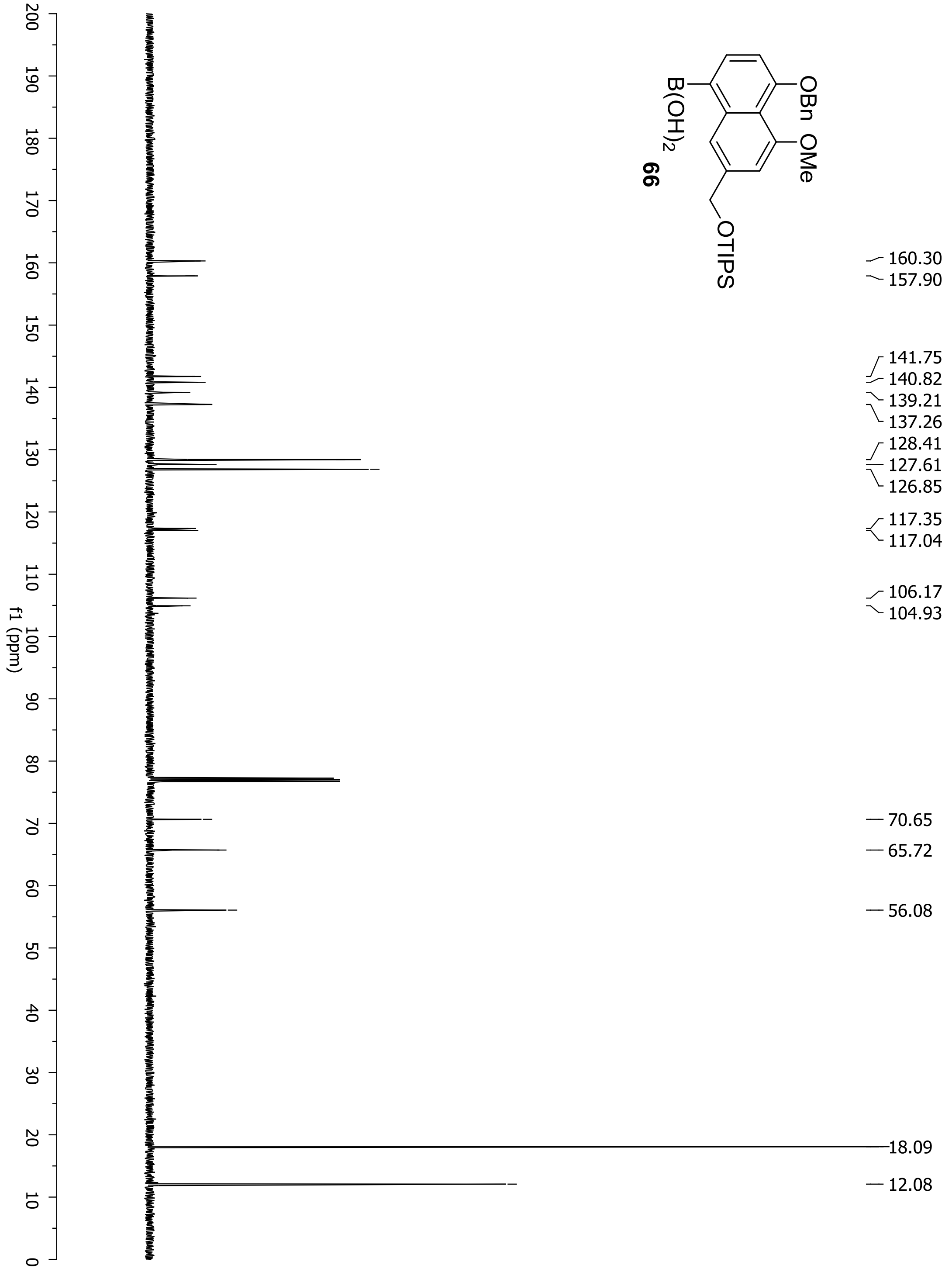
((5-(benzyloxy)-8-bromo-4-methoxynaphthalen-2-yl)methoxy)triisopropylsilane **65**; Carbon NMR, $CDCl_3$



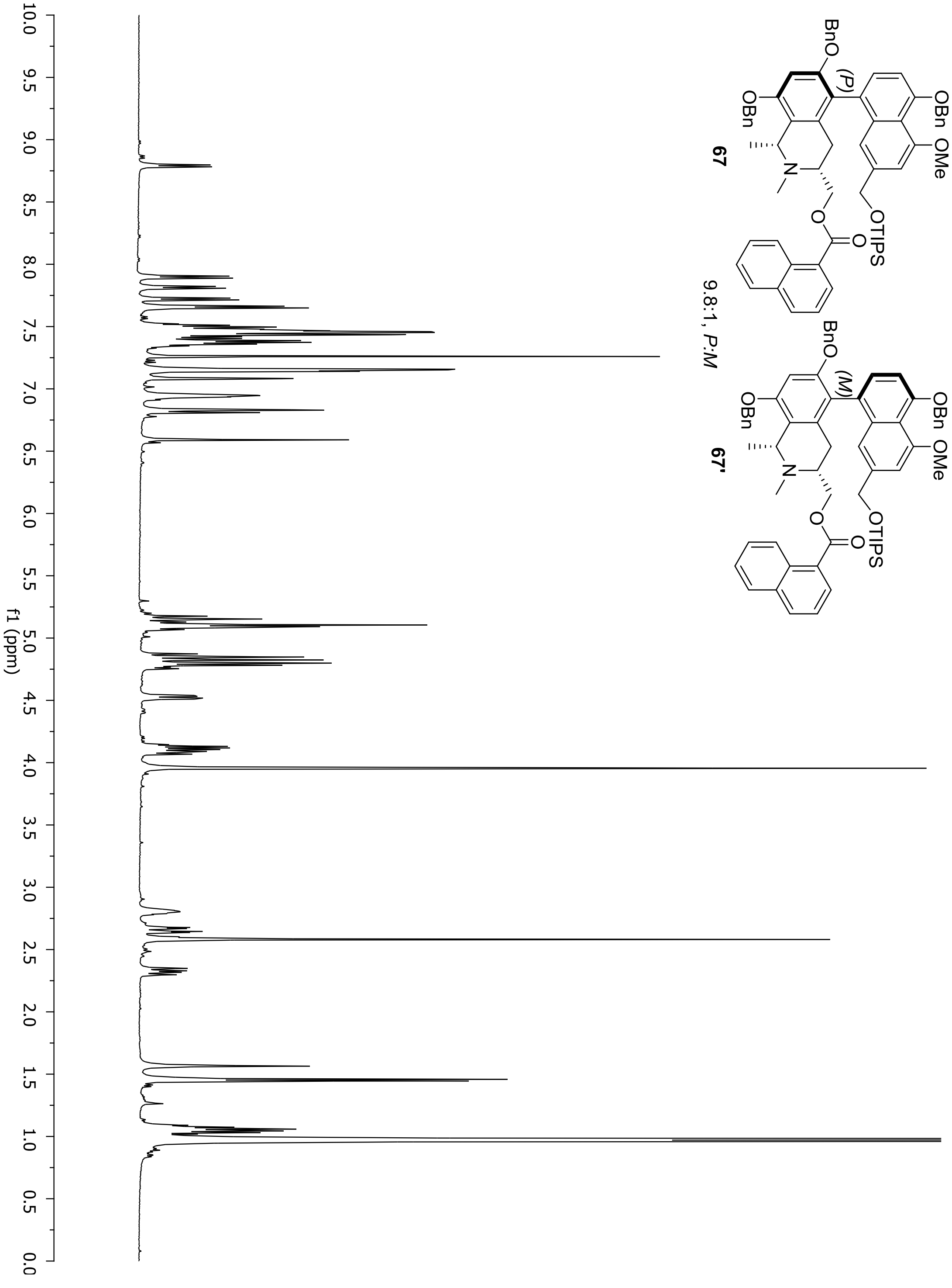
(4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy)methyl)naphthalen-1-yl)boronic acid **66**; Proton NMR, $CDCl_3$



(4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy)methyl)naphthalen-1-yl)boronic acid **66**; Carbon NMR, $CDCl_3$



((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy)methyl) naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl1-naphthoate **67** and **67’**; Proton NMR, CDCl$_3$

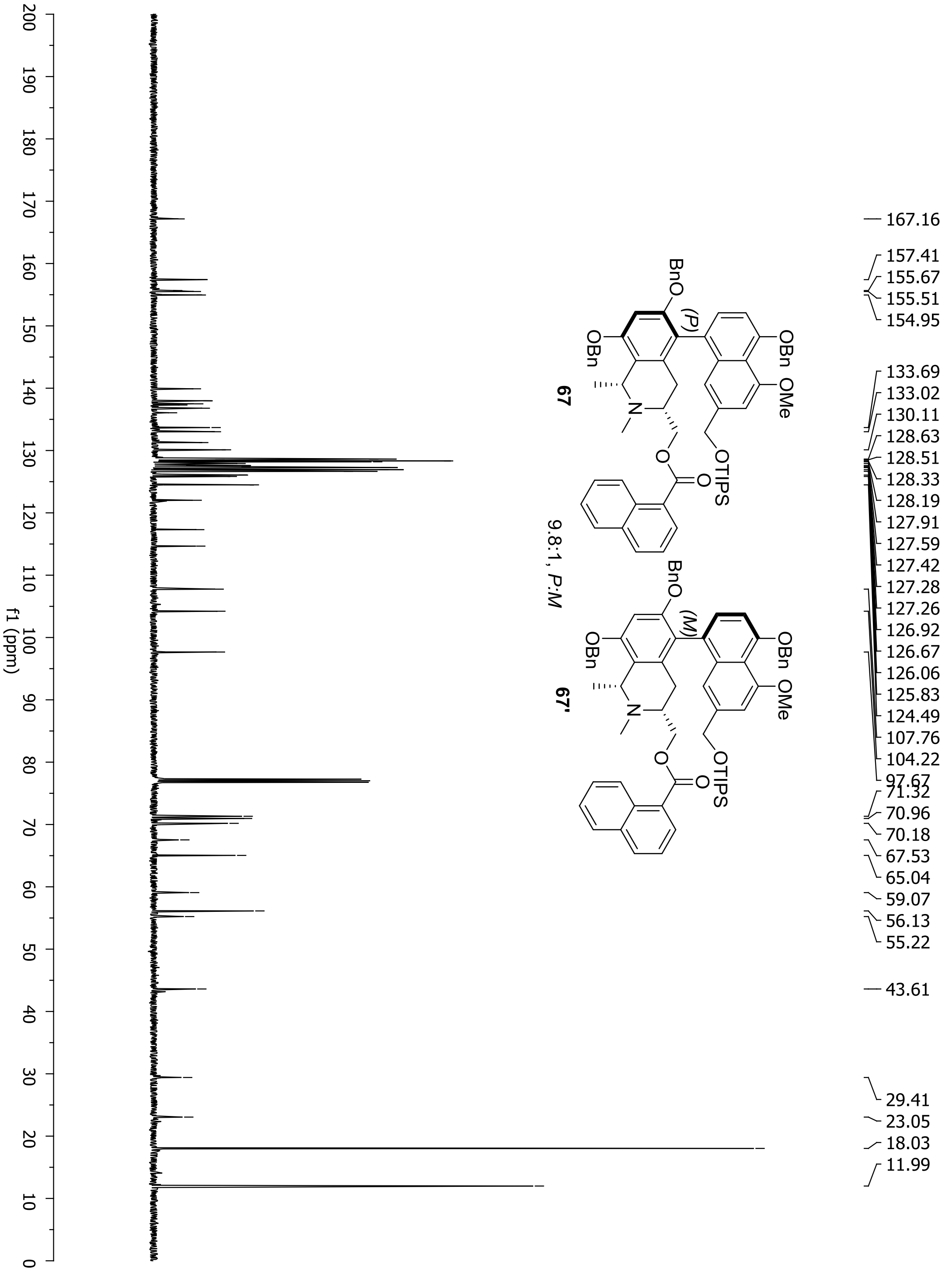


67

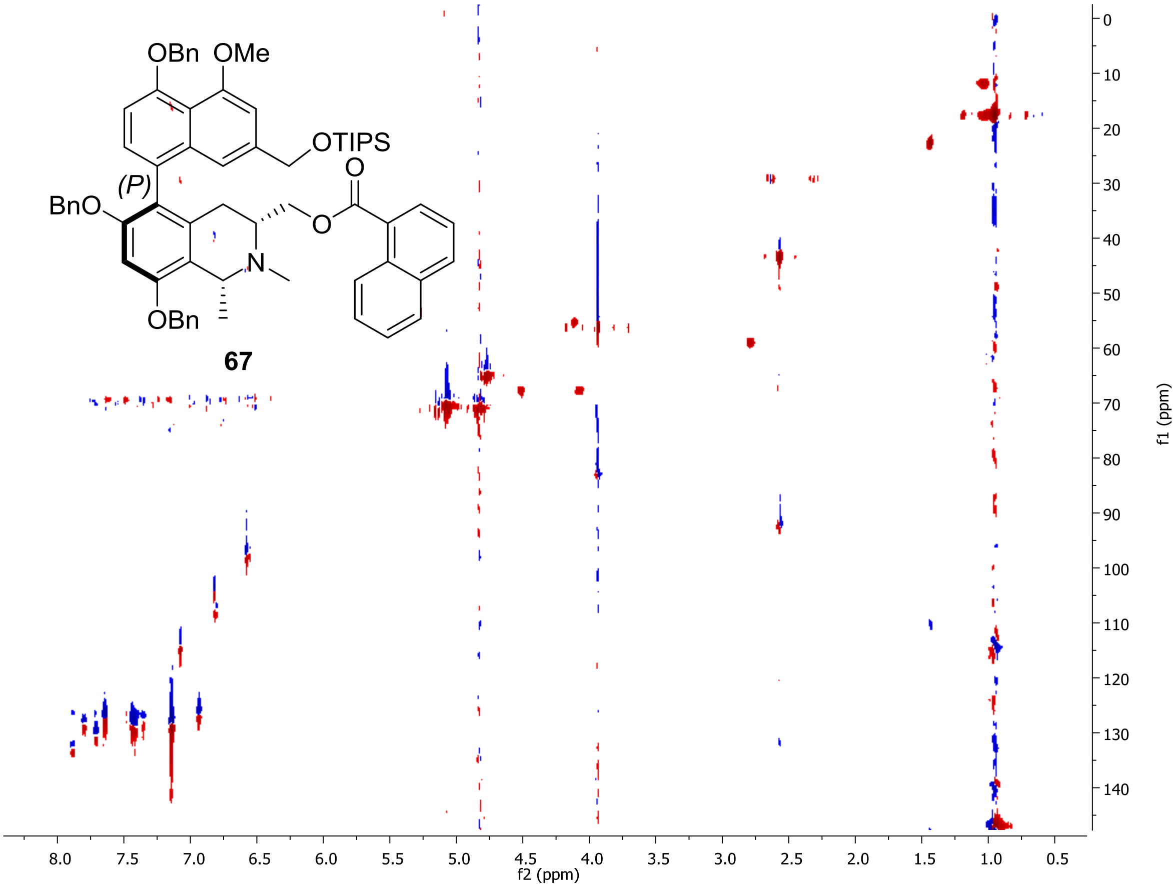
9.8:1, *P*:*M*

67'

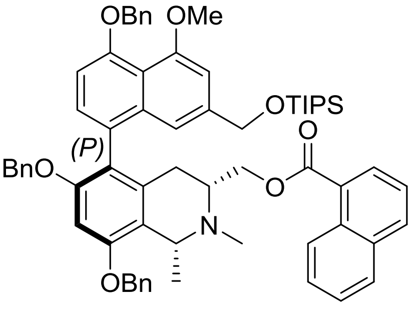
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy) methyl) naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl1-naphthoate **67** and **67'**; Carbon NMR, $CDCl_3$



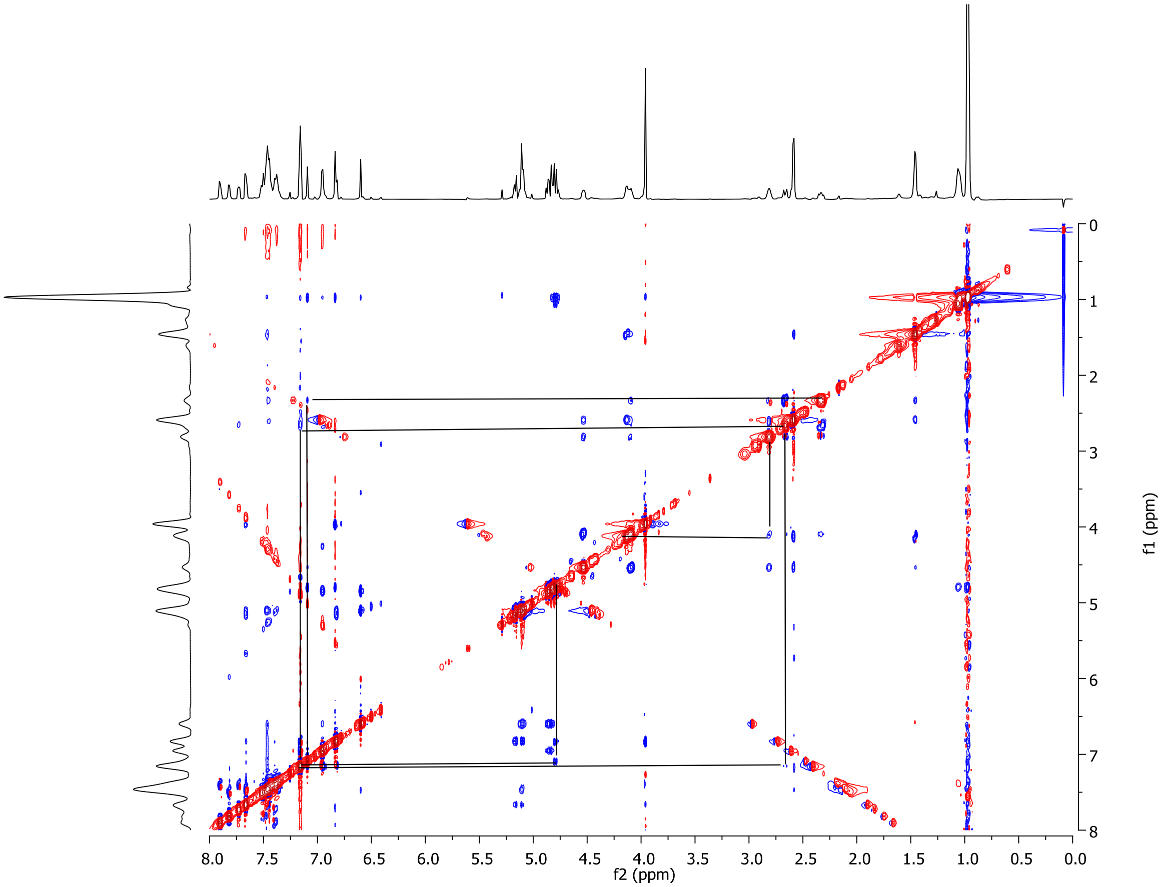
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy) methyl) naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl1-naphthoate **67**; HMQC NMR, CDCl$_3$



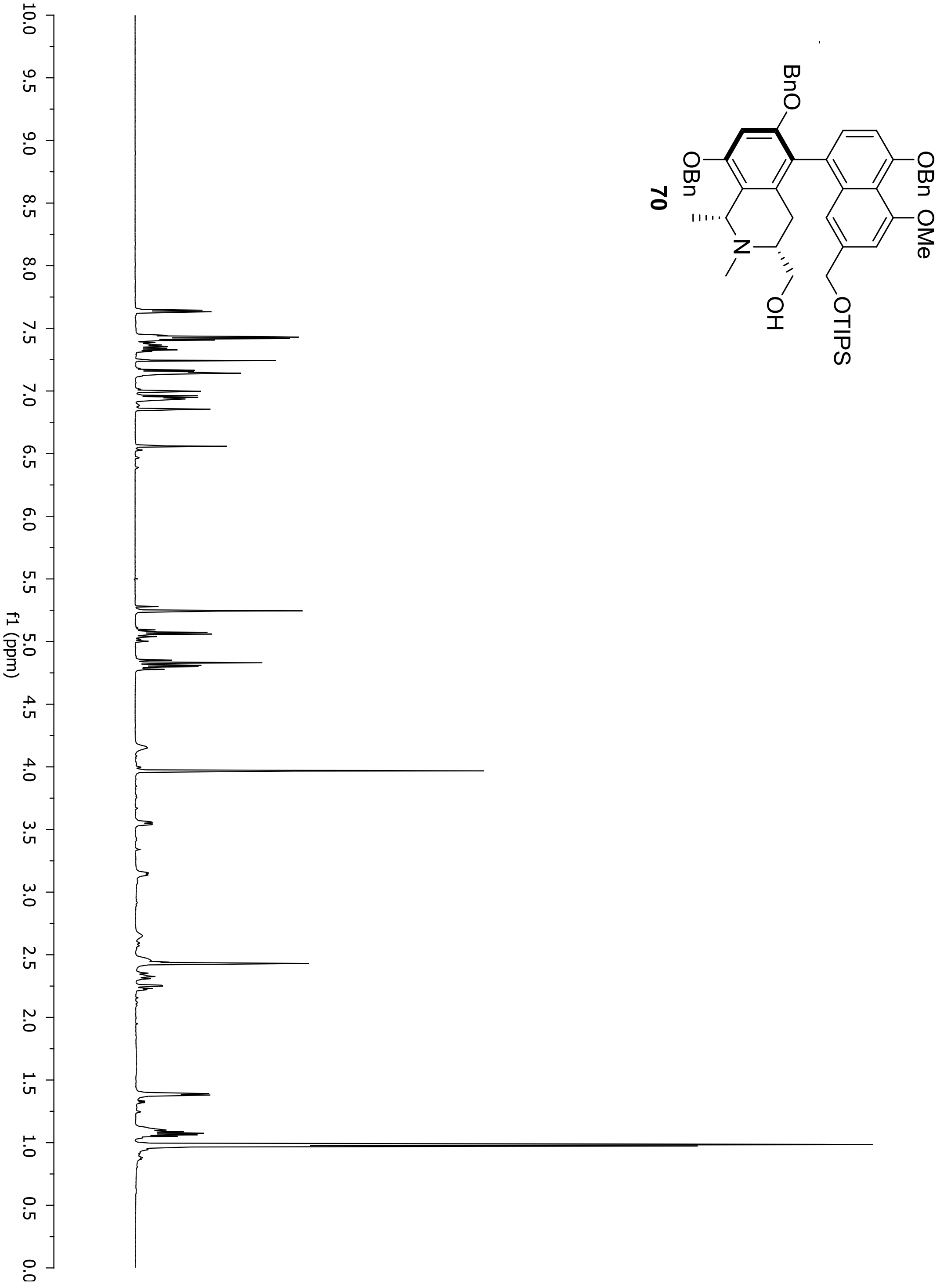
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy)methyl) naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl1-naphthoate **67**; 2D Noesy NMR, $CDCl_3$



67

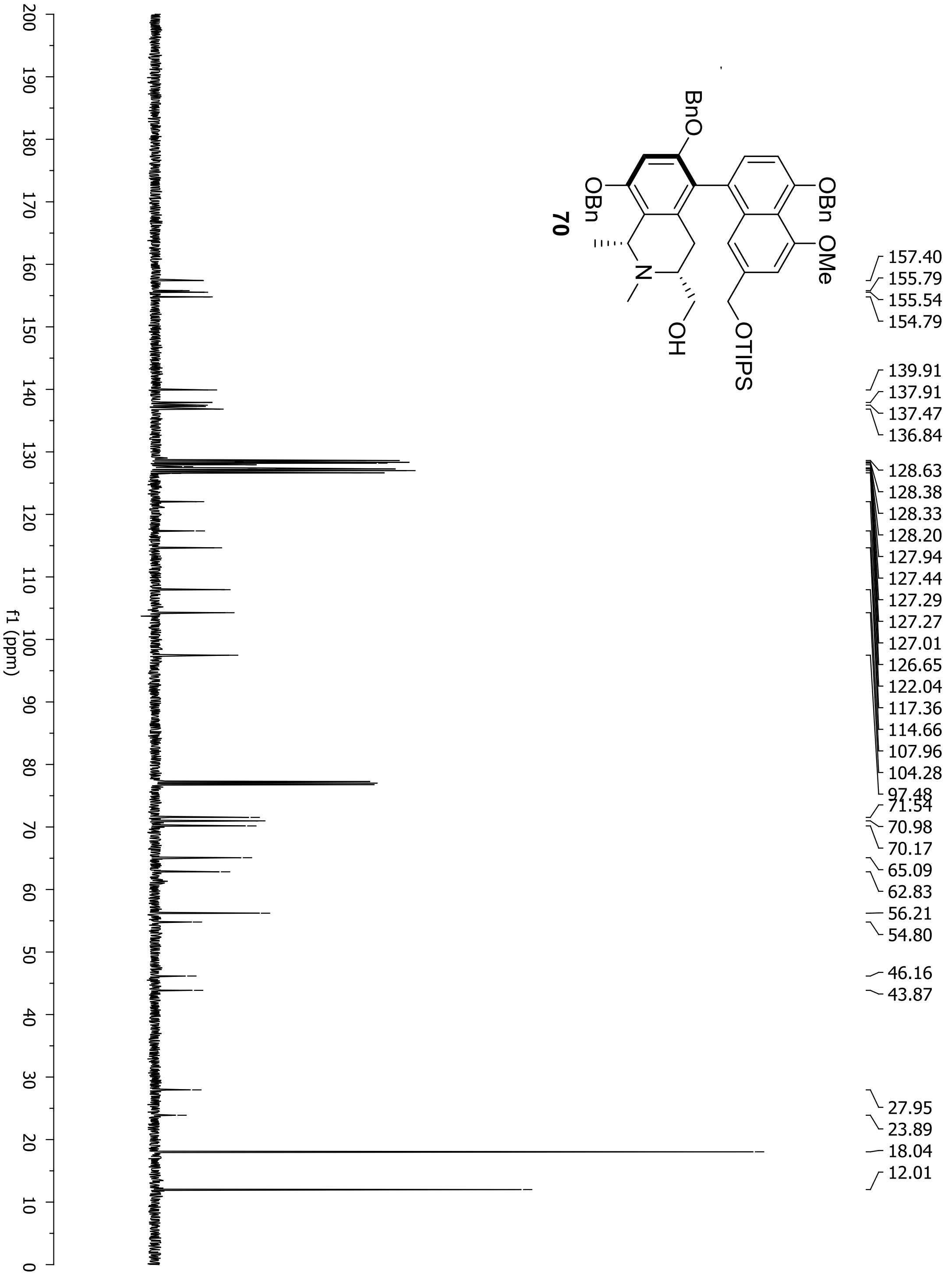


((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy) methyl naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **70**; Proton NMR, $CDCl_3$

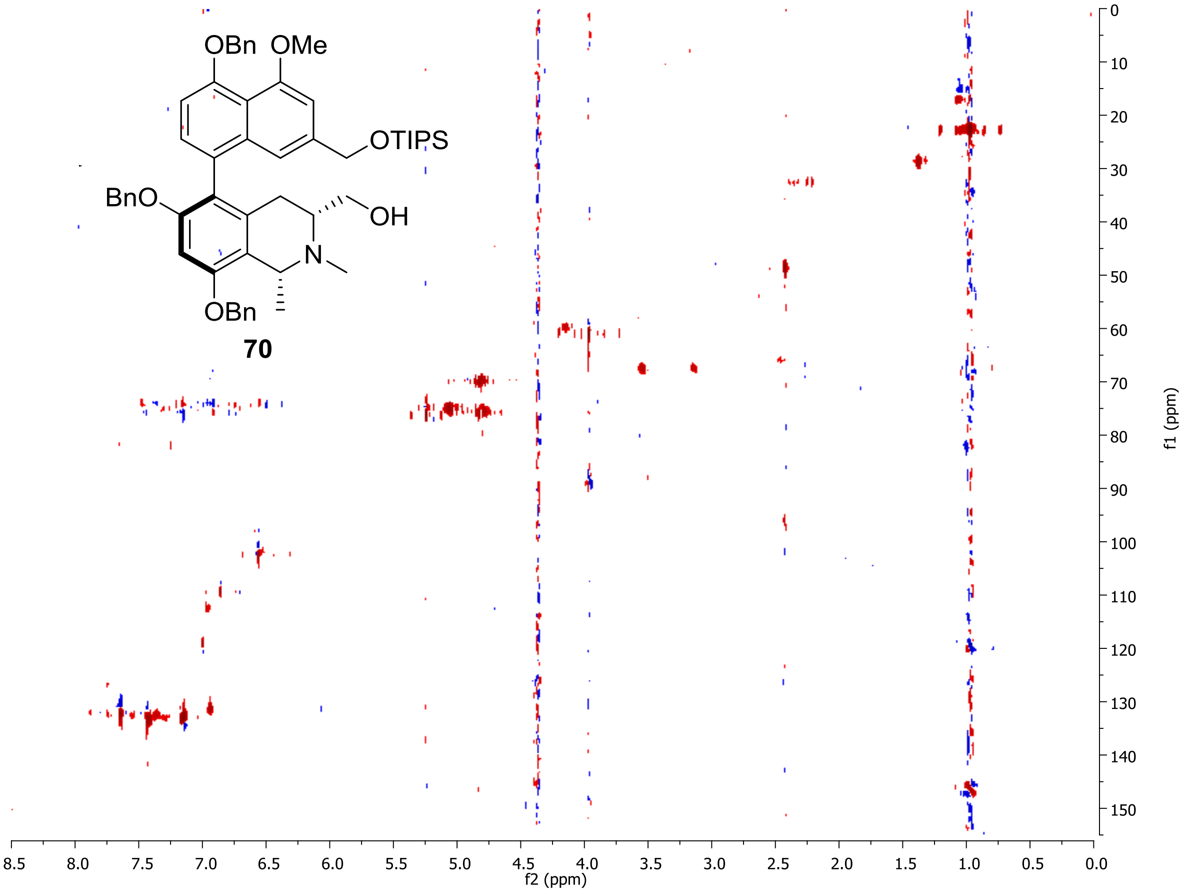


((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy) methyl naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **70**;

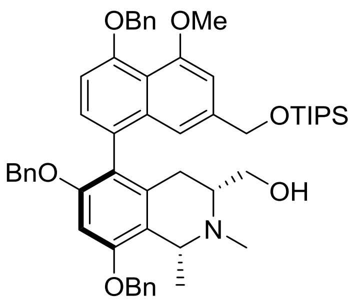
Carbon NMR, $CDCl_3$



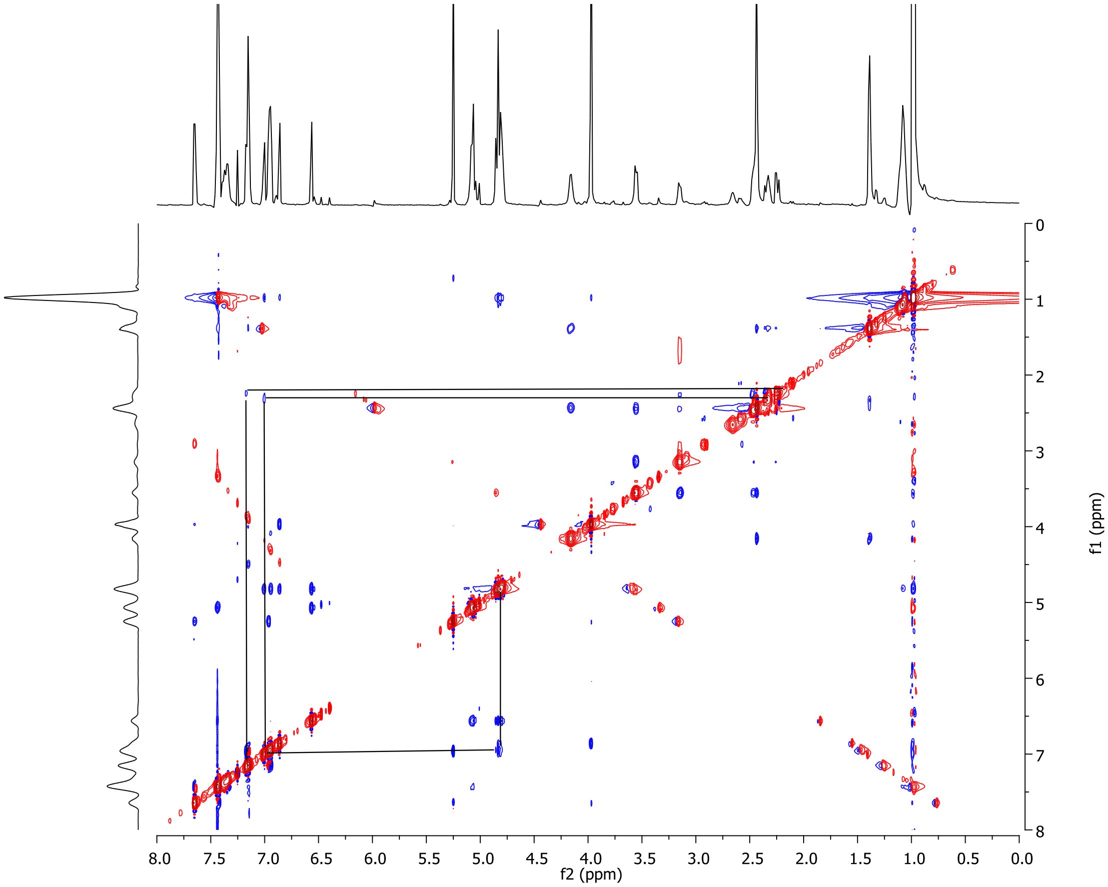
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy)methyl naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **70**; HMQC NMR, $CDCl_3$



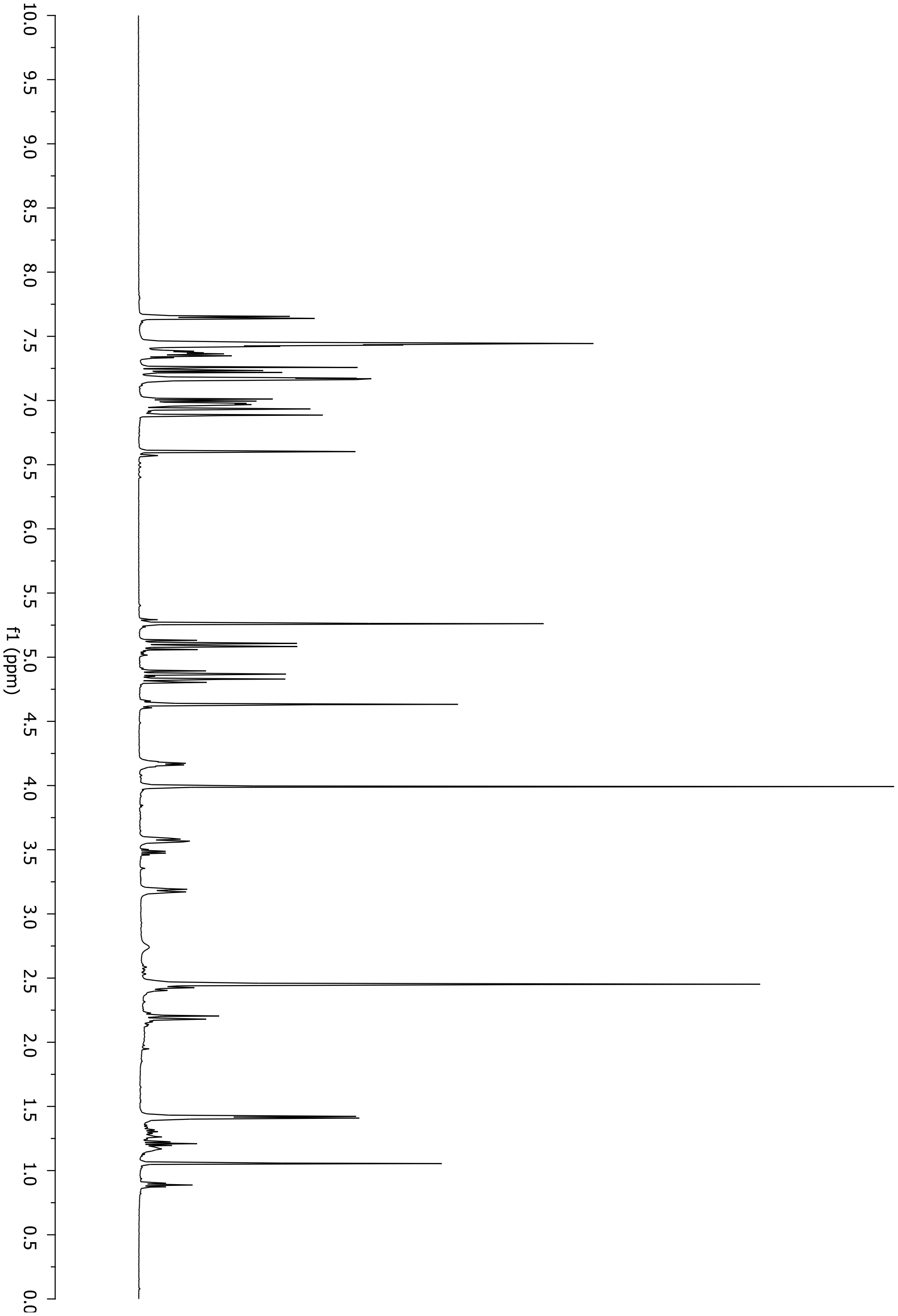
((1*R*,3*R*)-6,8-bis(benzyloxy)-5-((*P*)-4-(benzyloxy)-5-methoxy-7-(((triisopropylsilyl)oxy)methyl naphthalen-1-yl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **70**; 2D Noesy NMR, $CDCl_3$



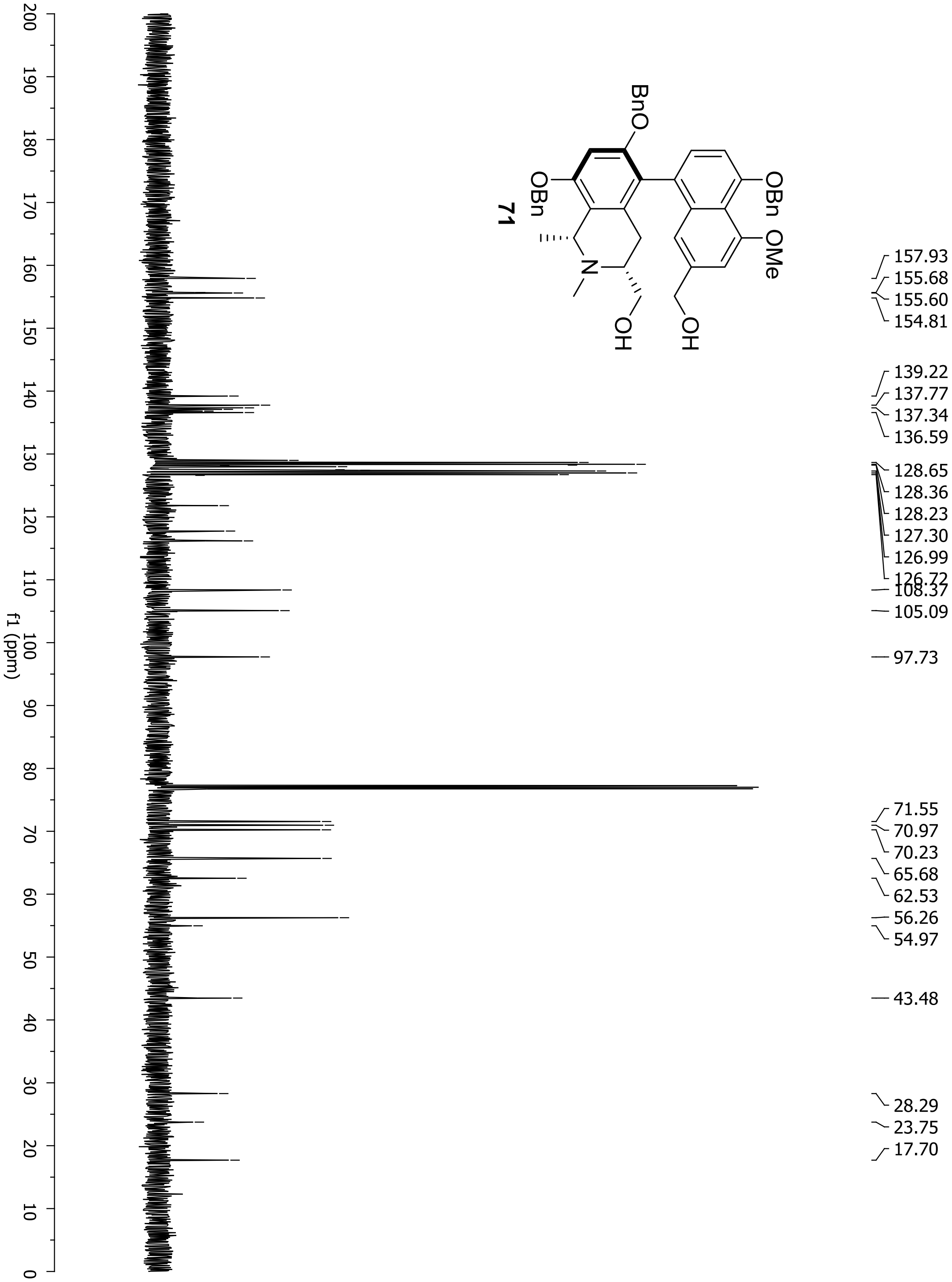
70



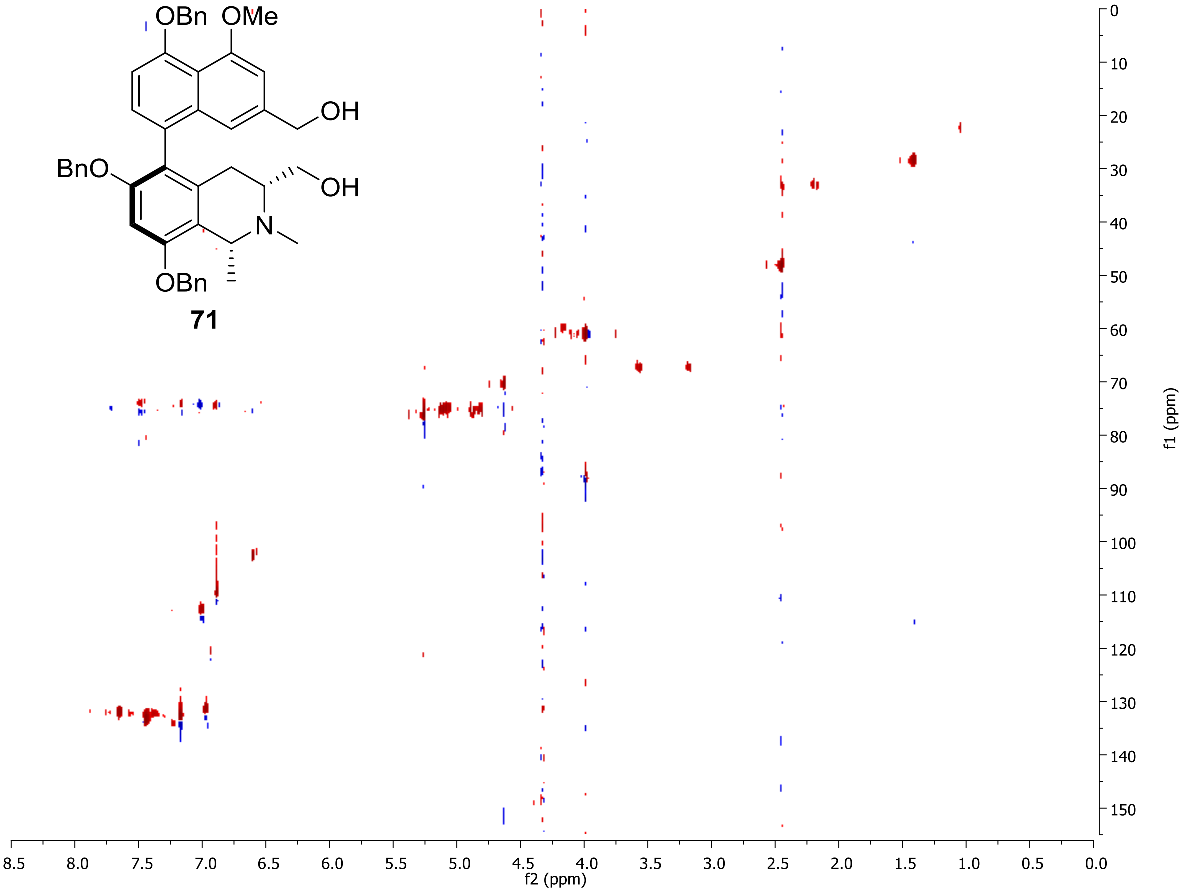
((*P*)-5-(benzyloxy)-8-((1*R*,3*R*)-6,8-bis(benzyloxy)-3-(hydroxymethyl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-methoxynaphthalen-2-yl)methanol **71**; Proton NMR, $CDCl_3$



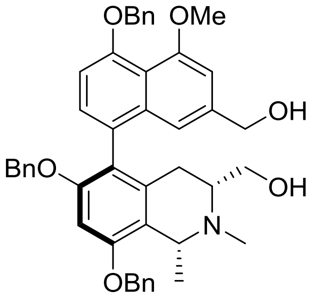
((*P*)-5-(benzyloxy)-8-((1*R*,3*R*)-6,8-bis(benzyloxy)-3-(hydroxymethyl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-methoxynaphthalen-2-yl)methanol **71**; Carbon NMR, $CDCl_3$



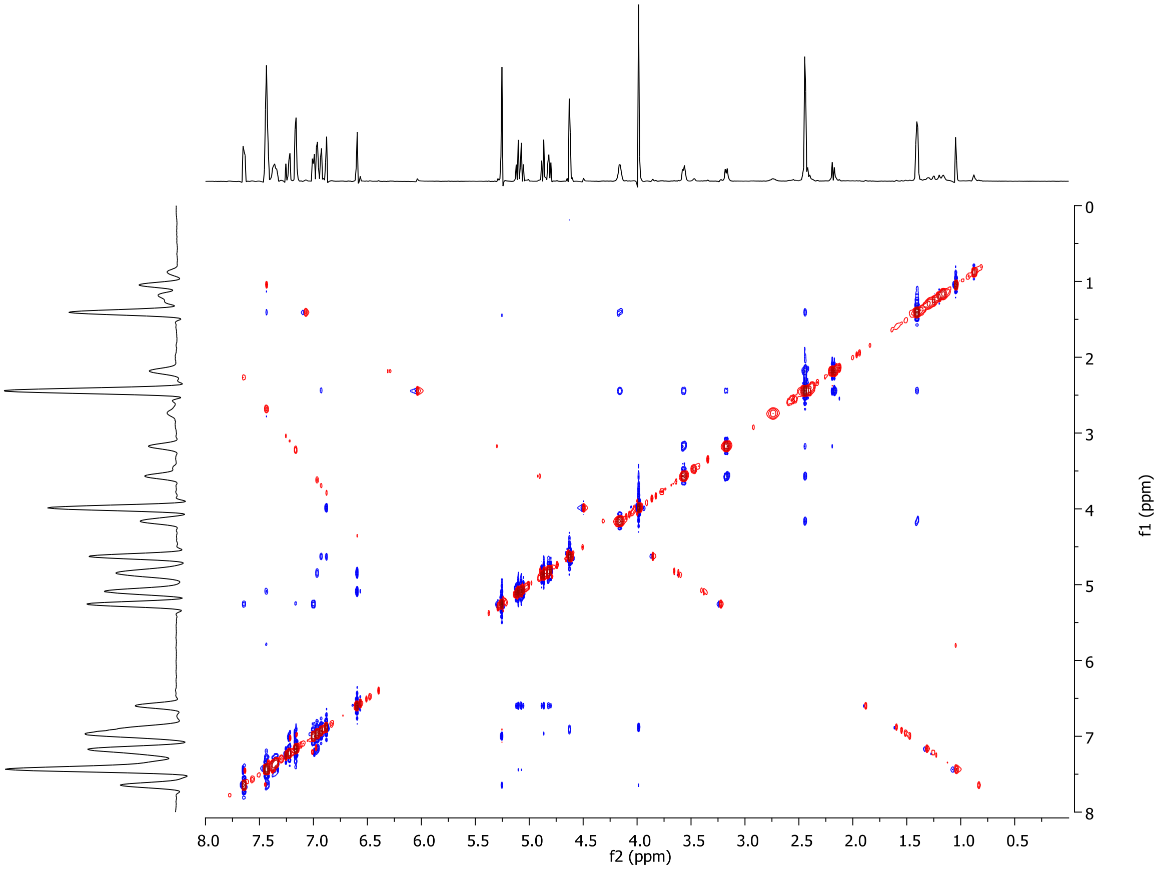
((*P*)-5-(benzyloxy)-8-((1*R*,3*R*)-6,8-bis(benzyloxy)-3-(hydroxymethyl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-methoxynaphthalen-2-yl)methanol **71**; 2D Noesy NMR, $CDCl_3$



((*P*)-5-(benzyloxy)-8-((1*R*,3*R*)-6,8-bis(benzyloxy)-3-(hydroxymethyl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-methoxynaphthalen-2-yl)methanol **71**; 2D Noesy NMR, $CDCl_3$



71



(3S)-6,8-bis(benzyloxy)-5-((S)-4-(benzyloxy)-5-methoxy-7-methylnaphthalen-1-yl)-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline **72**; Proton NMR, $CDCl_3$

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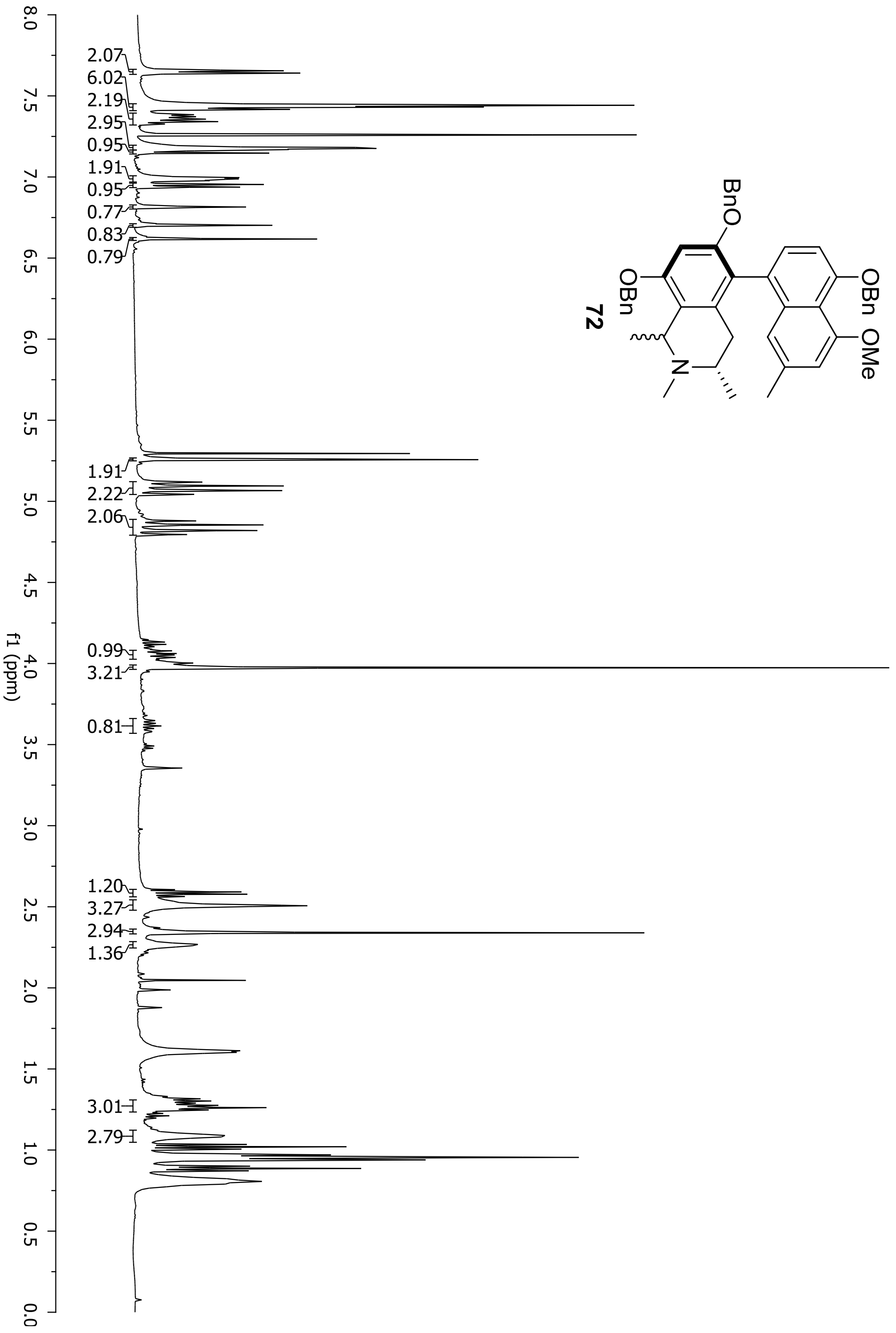
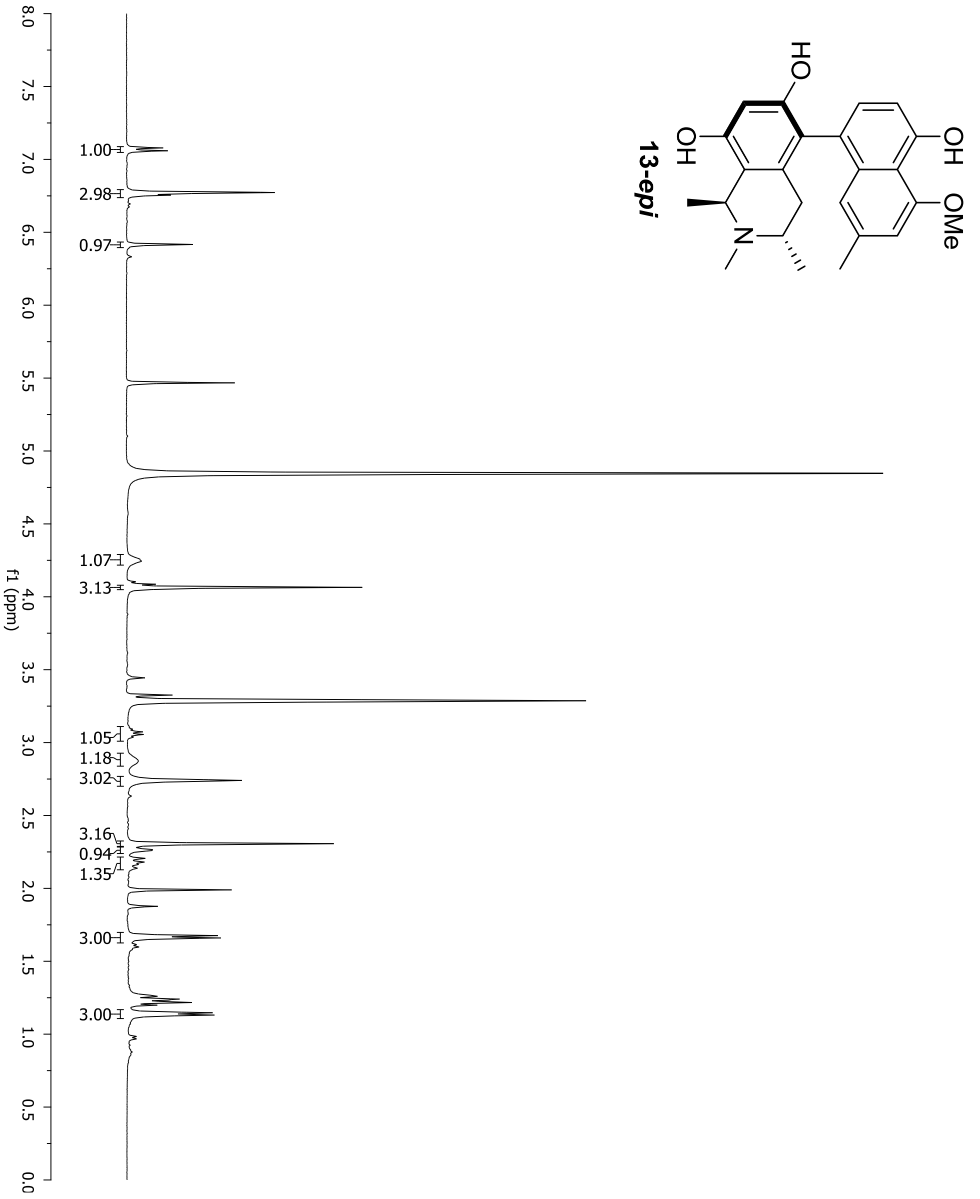


(1*S*,3*S*)-5-((*P*)-4-hydroxy-5-methoxy-7-methylnaphthalen-1-yl)-1,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline-6,8-diol **13-*epi***; Proton NMR, $CDCl_3$



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