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Mn-mediated radical coupling toward synthesis of alpha, alpha-disubstituted alpha-amino esters and formal synthesis of quinine

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MN-MEDIATED RADICAL COUPLING TOWARD SYNTHESIS OF α,α-DISUBSTITUTED α-AMINO ESTERS AND FORMAL SYNTHESIS OF QUININE

by

An Ji

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Chemistry
in the Graduate College of
The University of Iowa

July 2011

Thesis Supervisor: Associate Professor Gregory K. Friestad

ABSTRACT

Chiral α-branched amines are common substructures of bioactive synthetic targets such as alkaloids and amino acids. Direct asymmetric amine synthesis by addition to the C=N bond of carbonyl imino derivatives is promising and efficient to introduce the stereogenic center and carbon-carbon bond in one step. Furthermore, disconnection of either C-C bond at the amine stereogenic center would be the most versatile method to achieve this objective; we could make the choice depending on the different synthetic strategies, such as the availability of precursors and the presence of complicating structural features.

In our group, we disclosed that manganese carbonyl mediates stereoselective photolytic radical addition of alkyl iodides to chiral imino acceptors, which is a powerful tool to form a new C-C bond and generate a chiral center. Qualitative mechanistic studies confirm the importance of free radicals, imply that this is a nonchain (or short chain length) free-radical process, and reveal that organomanganese compounds are not a viable source of alkyl radical for the addition reactions under the conditions in our lab. In my thesis, we have extended the application of our methodology.

At the beginning of my research, our Mn-mediated addition methodology was first applied to accomplish the couplings of iodides and ketone *N*-acylhydrazones, generating quaternary carbon stereocenters and offering access to a variety of α-alkylated alanine analogs. These radical additions complement enolate alkylation methodologies, as they occur under nonbasic conditions and permit introduction of both primary and secondary alkyl groups with relative ease. The versatility with respect to the iodide is a distinguishing feature of the Mn-mediated coupling that foreshadows application to more complex targets.

Secondly, a Mn-mediated radical–ionic annulation strategy was validated as a synthetic route to quinine. Intermolecular radical addition to C=N bonds has rarely been

applied as a strategic bond construction in natural product synthesis; this synthesis of quinine offers the strongest demonstration yet of the utility of such reactions in application toward complex multifunctional targets.

Abstract Approved: _____
Thesis Supervisor

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Title and Department

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Graduate College
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CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph.D. thesis of

An Ji

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
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Edward G. Gillan

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To Peixun Ji and Guilan You

I am a slow walker, but I never walk backwards.

Abraham Lincoln

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First and foremost I offer my sincere gratitude to my professor, Dr. Greg Friestad, who has supported me throughout my graduate work with his patience and knowledge whilst allowing me the room to work in my own way.

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I would also like to thank my wife, Yong You, who's being very helpful both in my study and everyday life. My thanks also go to my twin boys, Austin Yongqi Ji and Daniel Yonglin Ji, who are the cutest boys I ever know. They are the greatest achievements in my life.

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CHAPTER 1

INTRODUCTION

Significance of α,α-Disubstituted α-Amino Acids

Natural and unnatural compounds with α,α-disubstituted α-amino acids have attracted chemists‟ attention over decades, due to their significant structural complexity and potent biological activity.[1-3] At the α position of the amino acids, there is an additional substituent, which sterically constrains the free rotation of the side chain or restricts conformation of a carbo- or heterocylic ring. In nature, α,α-disubstituted α-amino acids are often found either in their free form or as components of biologically active natural products that are well-known as enzyme inhibitors, agonists and/or antagonists of neuronal acceptors, and antibiotics.[4]

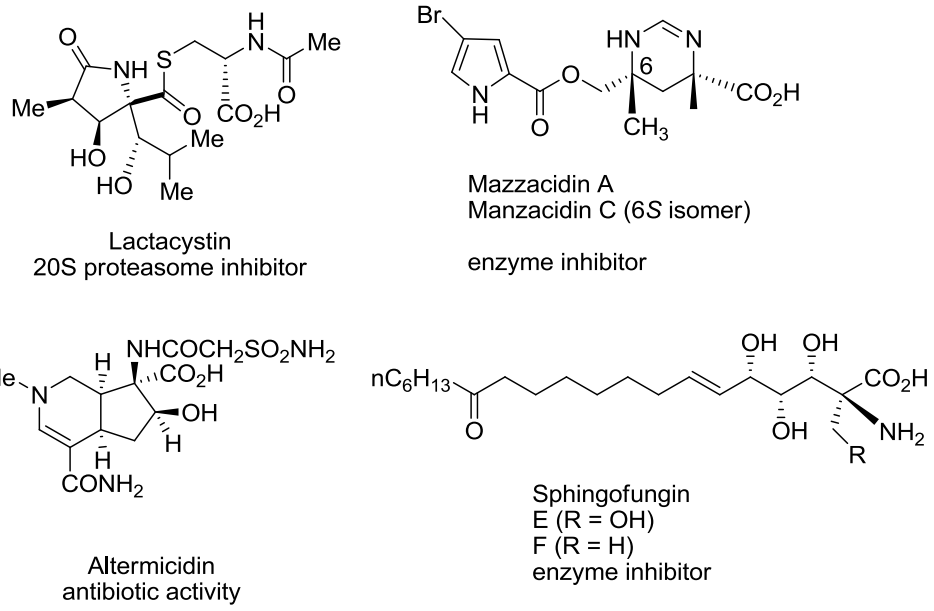


Figure 1. Examples of natural compounds possessing α,α-disubstituted α-amino acids.

For example, lactacystin (Figure 1),[5,6] first isolated from *Streptomyces sp*. OM6591, is the inhibitor of 20S proteosome, which is very important in removing damaged,

misfolded, and mistranslated proteins. Manzacidin A and C (Figure 1), which were first isolated from the Okinawan *sponge Hymeniacidon sp.*, have activities as α-adenoceptor blockers, antagonists of serotogenic receptors, and actomyosin ATPase activators.[7] Naturally occurring sulfonamide altemicidin (Figure 1), was first isolated from the actinomycete strain *Streptomyces sioyaensis* SA-1758, and possesses strong inhibitory activity against tumor cell growth as well as potent acarcidal activity.[8] Sphingofungin E and F,[9] isolated from fungi, are known to exhibit potent antifungal activity and inhibitory activity against serine palmitoyltransferase, which is an essential enzyme for sphingosin biosynthesis (Figure 1).[10]

For these reasons, interest has been growing in the synthesis of α,α-disubstituted α-amino acids. Recent efforts to synthesize these amino acids are mainly asymmetric construction based on alkylation of enolates from different precursors, cyanide addition to ketimines, carbene insertion, nitrene insertion, Diels-Alder reaction, Hatakeyama epoxide opening, enolate rearrangement, and Overman rearrangement. This indicates that asymmetric synthesis of these amino acids is a great challenge and still requires methodological advances.[11,12]

Significance of Quinine

Since the Jesuits first recorded use of powdered "Peruvian bark" in religious writing in 1633, the component of the cinchona bark has been a powerful therapeutic agent in the treatment of malaria over three centuries, which is described as "*the most significant disease for world civilization over the past three millennia*".[13] After nearly two centuries" studies, quinine was discovered to be the active component in the cinchona bark and first isolated in 1820 by Pelletier and Caventou.[13] The right connection of quinine was first suggested by Rabe in 1908, who reconstructed quinine by degradation, proving his structural assignment in 1918.[13]

Quinine (Figure 2), as a longstanding challenge, has inspired synthetic efforts since 1800s. The first total synthesis of quinine was reported by Woodward in 1944.[14] A "formal total synthesis", Woodward"s approach relies on the preparation of quinotoxine (Figure 2), which was converted to quinine in three operations by Rabe.[15,16] Recently, Williams and coworkers proved Rabe"s three manipulations for the conversion of quinotoxine to quinine by experimental data, which ended the controversy surrounding the Woodward-Doering claim of the first "total synthesis" of quinine.[17] Even with practical developments led by Uskokovic,[18-22] Taylor,[23,24] and Gates [25] in the 1970s for access to quinine and quinidine (Figure 2), there was still no total synthesis with complete configurational control until 2001. Quinine finally yielded to the first asymmetric total synthesis as reported by Stork in 2001.[26] Syntheses by Jacobsen [27] and Kobayashi [28] appeared in 2004. In 2008, Krische published concise formal synthesis of (±) quinine in 16 steps in accordance with his strategy, achieved by the merged Morita-Baylis-Hillman-Tsuji-Trost catalytic enone cycloallylation.[29] The newest route to synthesis of quinine was accomplished by Aggarwal, mediated by selective reactions of sulfur ylides in 2010.[30]

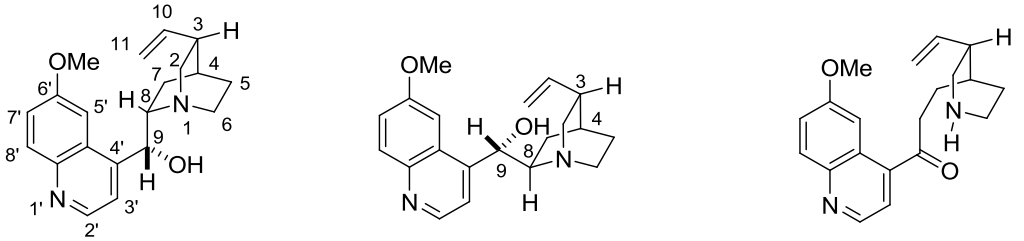


Figure 2. Structure of quinine, quinidine and quinotoxine.

Quinine attracted our interest in the course of our program to develop new C–C bond construction approaches to chiral amines.[31] Asymmetric preparation of amines presents challenges in the synthesis of nitrogen-containing natural products, particularly

alkaloids and peptides derived from unusual amino acids. While numerous indirect methods involving C–N bond construction are available, an attractive alternative is a C–C bond construction via addition to the C=N bond of carbonyl imino derivatives.[32-39] We have introduced Mn-mediated free radical additions to chiral *N*-acylhydrazones, achieving excellent acyclic stereocontrol under mild reaction conditions compatible with complex multifunctional precursors. Quinine presented an ideal challenge to the applicability of these Mn-mediated coupling reactions to synthetic problems in a multifunctional molecular setting.

Statement of Purpose

The first work in this thesis is to develop new, improved and efficient methods to synthesize α,α-disubstituted α-amino acid derivatives. Our solution for this synthetic challenge is to apply Mn-mediated radical coupling of diverse alkyl iodides with ketone-derived hydrazones in a route to α,α-disubstituted α-amino esters. The second work is to achieve total synthesis of quinine via Mn-mediated free radical additions to chiral *N*-acylhydrazones. These two projects will help us understand radical chemistry in more depth, specifically intermolecular radical addition to C=N bonds, and prove the applicability of these Mn-mediated coupling reactions toward unnatural and natural products.

CHAPTER 2

BACKGROUND

Previous Methods Toward α,α-Disubstituted α-Amino Acids

Introduction

α,α-Disubstituted α-amino acids are important non-proteinogenic amino acids which play a role in the inhibition of enzyme activities and in the design of conformationally modified bioactive peptides.[40-54] They have received significant attention in the synthetic approach. Many methods have been developed for the enantio- and diastereoselective synthesis of α,α-disubstituted α-amino acids. The efforts continue to be the focus of methodology advancements because of their unique biological activities.

Recently, the mainly asymmetric transformation of α,α-disubstituted α-amino acids has been based on alkylation of different precursors, such as bis-lactims, oxazinones, and imidazolidinones.[55-99]

The addition of nucleophiles to the C=N bond of chiral compounds is a useful tool for asymmetric C–C bond construction.[123-136] This methodology is based upon the introduction of the carboxylic acid moiety by the Strecker synthesis or the side chain of the amino acid by the addition of organometallic reagents. For intermolecular radical addition to C=N bond, the Takemoto group reported inspiring results, which will be discussed in Chapter 3.[163,290]

Other efficient asymmetric routes to α,α-disubstituted α-amino acids have been sigmatropic rearrangements,[120-122] rearrangement of β-carbonyl carboxylic acid derivatives,[100-119] diastereoselective cycloaddition,[99] and diastereoselective S_N2‟ substitution.[112-117] In addition to diastereoselective and enantioselective syntheses, it is also possible to obtain enantiomerically pure compounds from racemic mixtures by

enzymatic procedures, separation of diastereoisomers and chiral chromatography. A general review will be given which is focused on diastereoselective and enantioselective syntheses of α,α-disubstituted α-amino acids in the following.

Alkylation of Enolates

Seebach has developed a successful synthetic route by stereoselective alkylation of *cis*- or *trans*-imidazolidinones (Figure 3).[55-58] Deprotonation of imidazolidinones **2** or **5** with lithium diisopropylamide (LDA) to form non-racemic lithium enolates, after addition of the electrophile, afforded α-alkylamino acid precursors with a high stereoselectivity. Then, severe hydrolysis is necessary to get the free α-alkylamino acids, which limits this methodology to amino acids without acid-sensitive fragments.

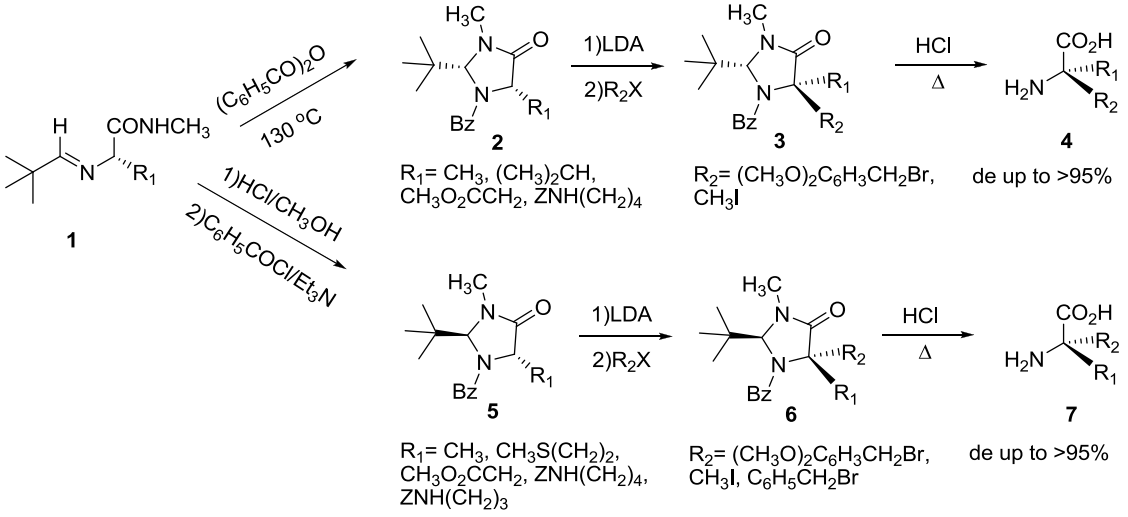


Figure 3. Synthetic route reported by Seebach.

Hruby applied similar alkylation by use of racemic (1-bromoethyl)benzene as the electrophile to yield all the isomers of α,β-dimethylphenylalanine from (*S*)- and (*R*)-alanine *N*-methylamide (Figure 4). [59]

Zhang synthesized the cis-oxazolidinone **19** by cyclisation of the Schiff base of (*R*)-tryptophan and pivalaldehyde in the presence of ethyl chloroformate (Figure 5).[60] Methylation of this compound can be done without protection of the indole moiety by treatment with two equivalents of LDA followed by one equivalent of methyl iodide. The reaction works only on the α carbon in good yield and proceeds with excellent diastereoselectivity.

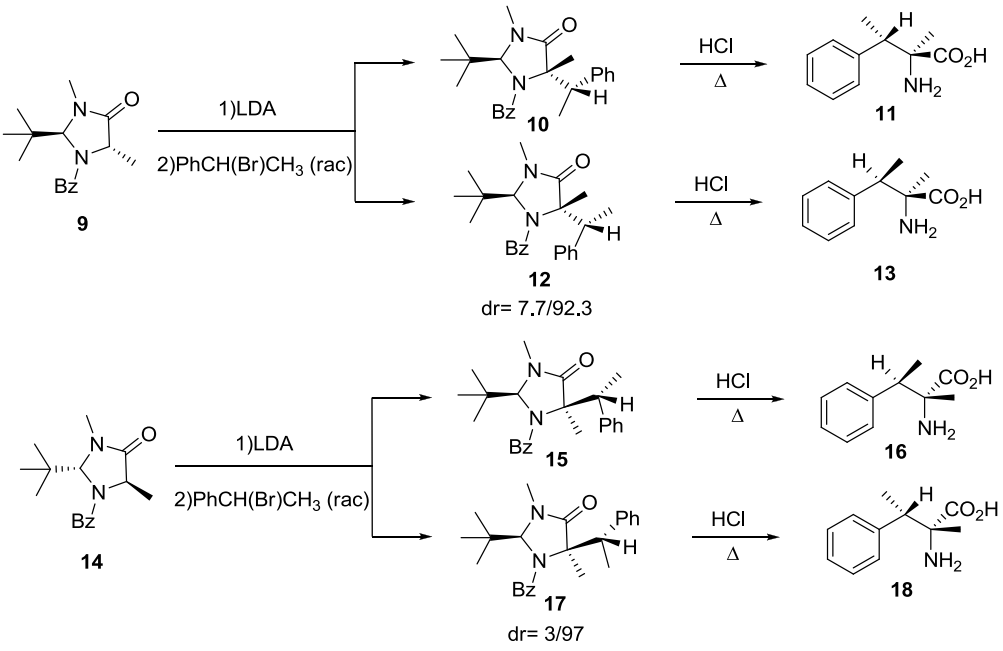


Figure 4. Synthetic route reported by Hruby.

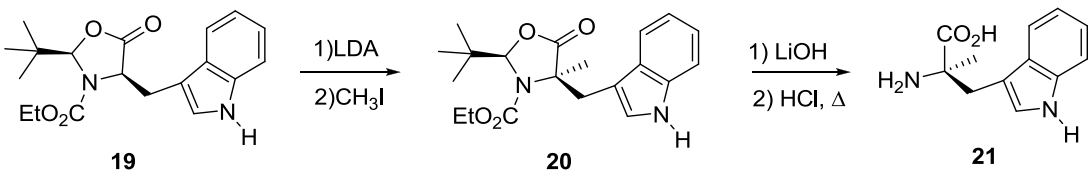


Figure 5. Synthetic route reported by Zhang.

Hirschmann obtained some α-(3,3-dimethylallyl)amino esters through use of allyl chloroformate to modify cis-oxazolidinone through Seebach protocol (Figure 6).[61,62] After alkylation with high diastereoselectivity, the final amino esters were afforded by basic hydrolysis to the alloc-protected amino acids, transformation of the amino acids to the corresponding amino esters and removal of the alloc protecting group with a catalytic amount of $Pd(PPh_3)_4$.

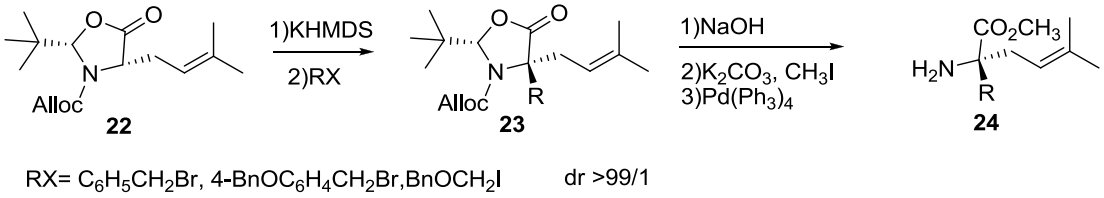


Figure 6. Synthetic route reported by Hirschmann.

Zydowsky developed a tricyclic version of Seebach"s oxazolidinone (Figure 7).[63] Alkylation of these compounds with alkyl halide using lithium bis(trimethylsilyl)amide as a base proceeded in good yields and excellent diastereoselectivity. The free amino acids were given by hydrolysis of alkylation products with lithium hydroxide.

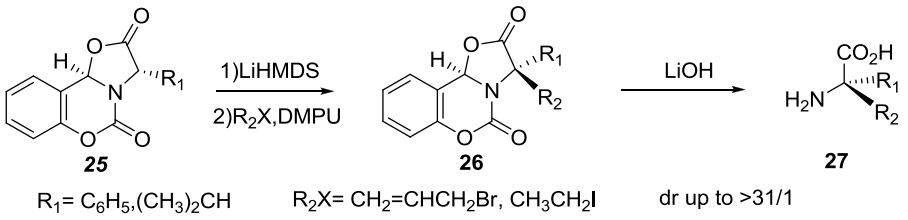


Figure 7. Synthetic route reported by Zydowsky.

Crich applied the Seebach protocol based upon the reactivity of the indole group in tryptophan (Figure 8).[64,65] The substrate can be deprotonated at -78°C with LDA and then reacts with different electrophiles to give excellent yields and complete diastereoselectivity. The alkylation products can be converted to free amino acids after several steps.

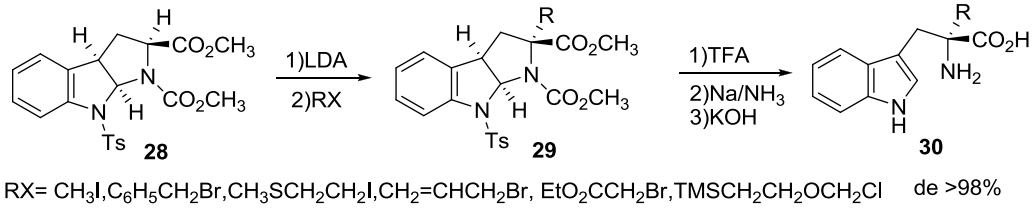


Figure 8. Synthetic route reported by Crich.

The chiral oxazinone **31** was obtained by Nájera to go through Seebach concept (Figure 9).[66] It can react with various electrophiles in the presence of potassium carbonate and tetra *n*-butylammonium bromide (TBAB), affording the corresponding alkylated oxazinones **32** or **34** with good yields and diastereoselectivities. The alkylation can also occur between oxazinone and allylic carbonates in the presence of $Pd(PPh_3)_4$ and 1,2-bis(diphenylphsphino)ethane as a catalyst. Final hydrolysis afforded the desired amino acids.

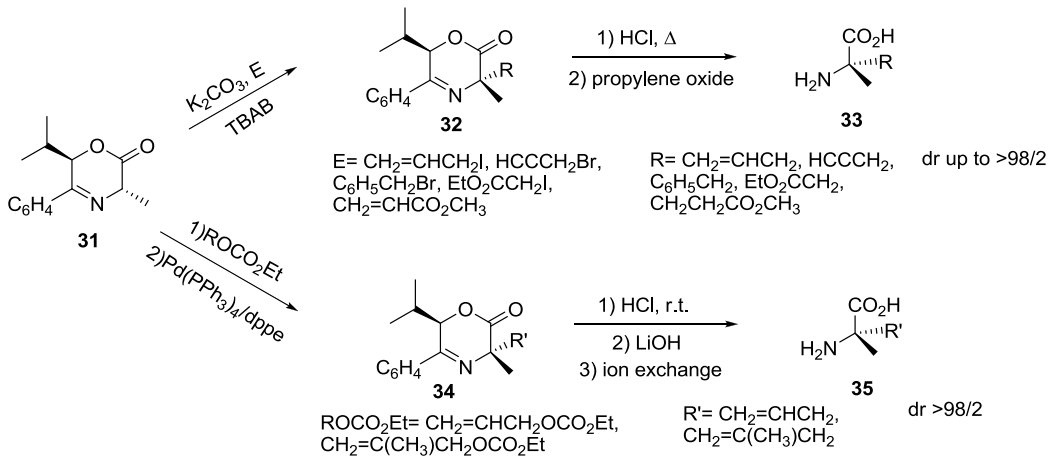


Figure 9. Synthetic route reported by Nájera.

Schöllkopf developed the bis-lactim ether methodology (Figure 10).[67-72] These bis-lactim ethers (**36**) can be alkylated after deprotonation by butyllithium, with different electrophiles with high diastereoselectivity.

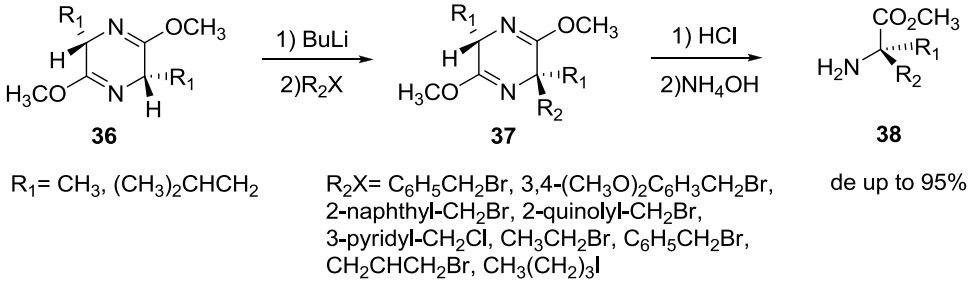


Figure 10. Synthetic route from **36** reported by Schöllkopf.

Chiral *N*-tert-butoxycarbonyl or *N*-benzyloxycarbonyl 5,6-diphenyltetrahydro-1,4-oxazin-2-ones have proven to be good starting materials for the syntheses of α,α-disubstituted α-amino acids (Figure 11). Baldwin has improved on the results described by Williams for the synthesis of dialkylation products.[73-75] Further, Remuzon and Sandri successfully developed related approaches to desired alkylation compounds.[76-78]

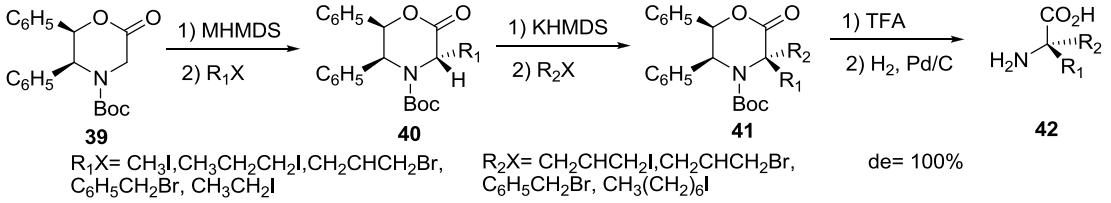


Figure 11. Synthetic route reported by Baldwin, Remuzon and Sandri.

Kolb and Barth have used chiral amidine esters in alkylation reactions which give moderate yields and low diastereoselectivities (Figure 12).[79-81]

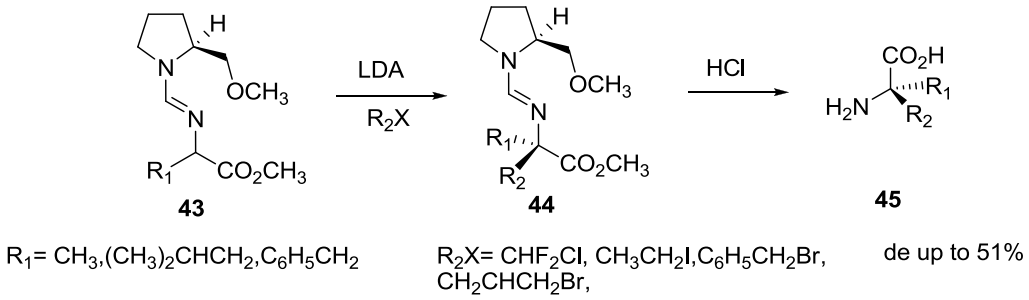


Figure 12. Synthetic route reported by Kolb and Barth.

Schöllkopf reported one of the first examples describing the synthesis of α-alkylamino acids using a chiral Schiff base (Figure 13).[82] Viallefont has used Schiff bases derived from 2-hydroxypinan-3-one to prepare α-alkyl amino acids (Figure 14).[83,84] Lavergne synthesized α-substituted arylamino acids through the addition of fluorobenzene tricarbonyl chromium complexes to α-imino esters derived from 2-hydroxypinan-3-one (Figure 15). Lavielle has approached to diastereoselective alkylation of aldimines derived from 4-chlorobenzaldehyde and sultam-derived amino acids (Figure 16).[85] Chiral nickel complexes of Schiff base are also efficient starting materials to afford α-alkyl amino acid precursors (Figure 17).[86-88] A different route was reported by Berkowitz and Smith by the diastereoselective double alkylation of the dianion derived from a chiral *N*-benzoyl α-alkyl amino ester (Figure 18).[89]

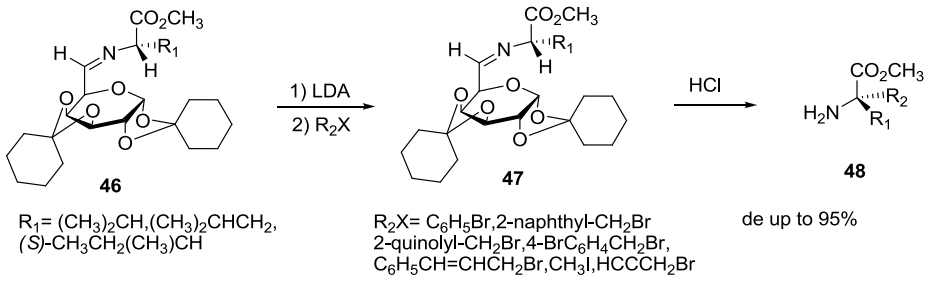
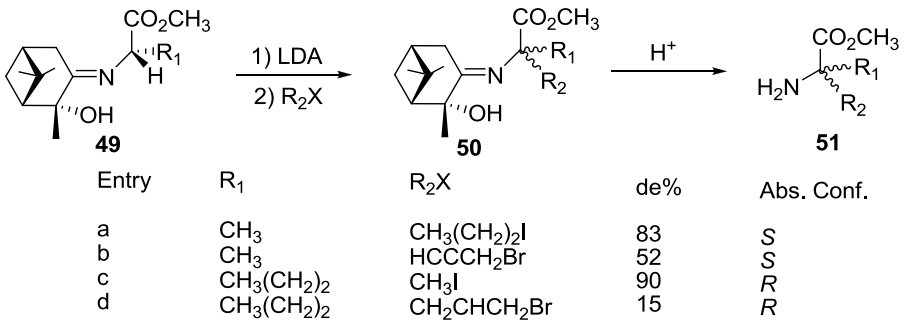


Figure 13. Synthetic route from **46** reported by Schöllkopf.



Entry	R_1	R_2X	de%	Abs. Conf.
a	CH_3	$CH_3(CH_2)_2I$	83	*S*
b	CH_3	$HCCCH_2Br$	52	*S*
c	$CH_3(CH_2)_2$	CH_3I	90	*R*
d	$CH_3(CH_2)_2$	CH_2CHCH_2Br	15	*R*

Figure 14. Synthetic route reported by Viallefont.

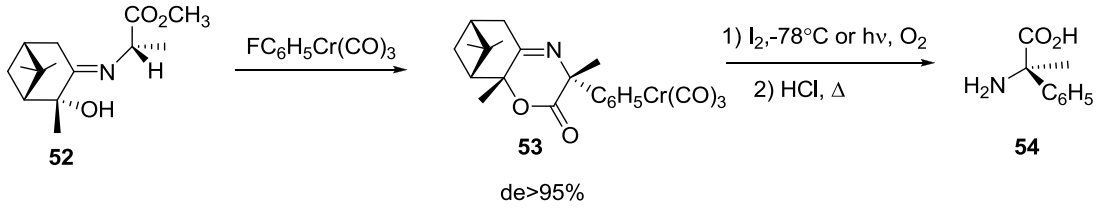


Figure 15. Synthetic route reported by Lavergne.

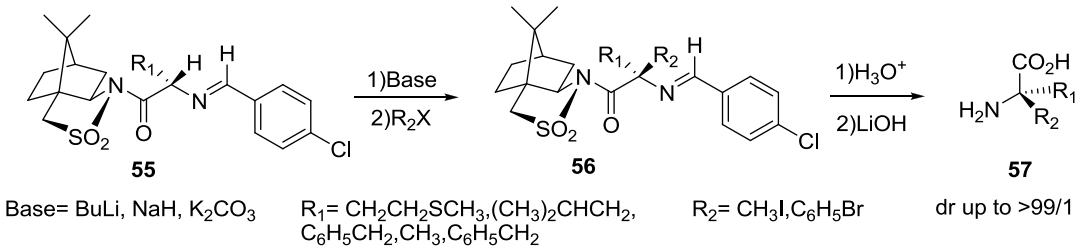


Figure 16. Synthetic route reported by Lavielle.

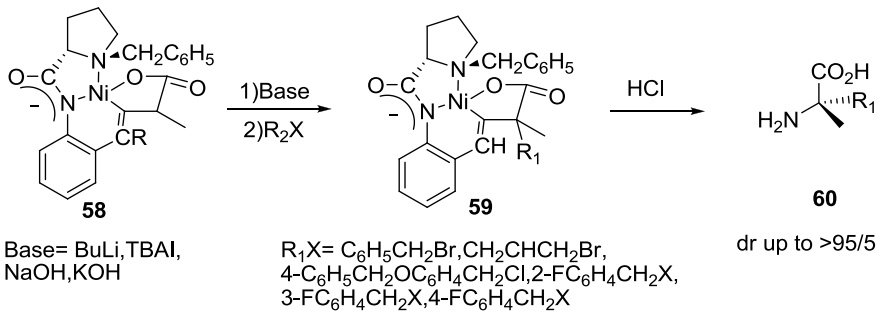


Figure 17. Synthetic route by chiral nickel complexes of Schiff base.

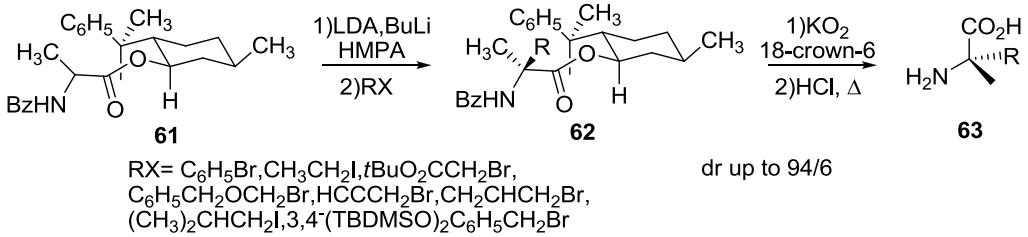


Figure 18. Synthetic route reported by Berkowitz and Smith.

Chiral β-Lactams as Chiral Auxiliary

Chiral β-lactams are useful in the synthesis of a variety of compounds of biological interest, which is called β-lactam synthon method.[90,91]

The asymmetric ketene-imine [2+2] cycloaddition with a chiral auxiliary to the ketene provides asymmetric 3-amino β-lactams **65** (Figure 19).[92-94] Treatment of a β-lactam with base followed by reaction with methyl iodide gives methylation at the C_3 carbon from the opposite side to the C_4 aryl group, which builds a quaternary center.

Hegedus developed a chiral hindered bicyclic β-lactam, which is alkylated at C_3 with complete retention of configuration, although this reaction is limited to very reactive electrophiles (Figure 20).[95,96] Hydrolysis of the methylated compound affords an aldehyde, which is a key intermediate to synthesize different α-methylamino acids.

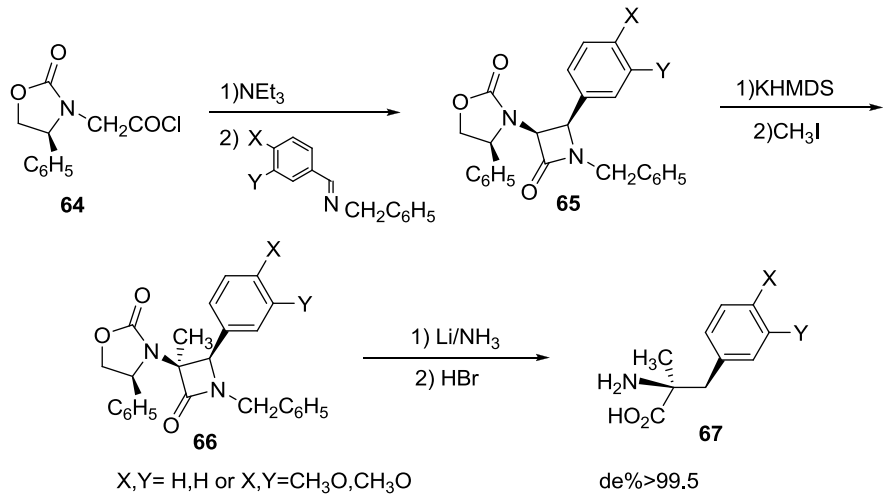


Figure 19. Synthetic route by use of asymmetric 3-amino β-lactams.

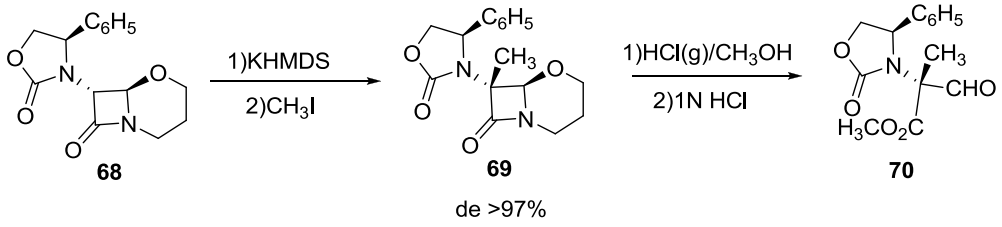


Figure 20. Synthetic route reported by Hegedus.

β-Lactams can be also stereoselectively alkylated on the side chain bonded to the N atom (Figure 21).[92,93,97] For this example, the β-lactam enolate formed by treatment with LDA, is alkylated with almost complete stereoselectivity and good yield.

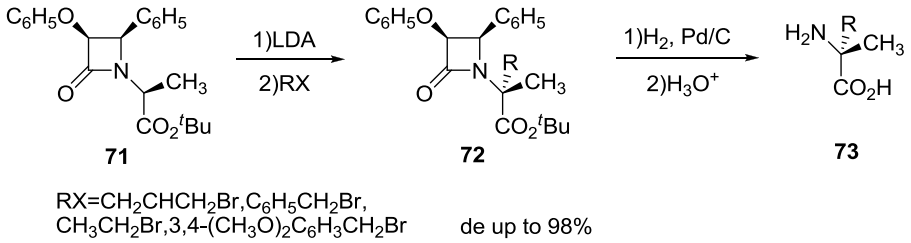


Figure 21. Synthetic route from β-lactam **71**.

The β-Lactam obtained from the [2+2] cycloaddition of chiral (*S*)-(4-phenyloxazolidi-nyl)ketene with *tert*-butyl *N*-benzylidenealaninate can be alkylated with extremely high stereoselectivity (Figure 22).[92,93] Amino acids were provided after deprotection and reduction.

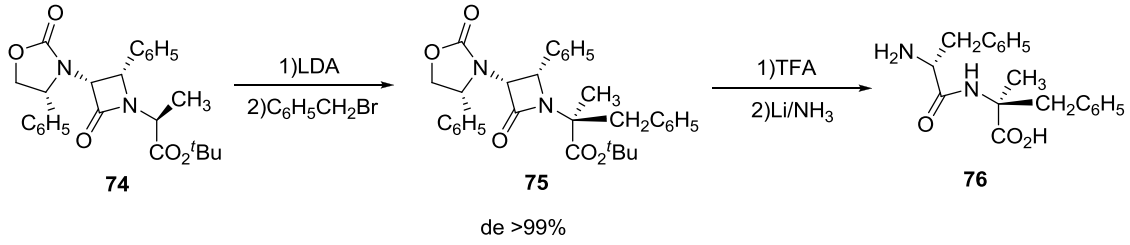


Figure 22. Synthetic route from β-lactam **74**.

Palomo used the stereoselective [2+2] cycloaddition of imines (**77**), derived from a chiral α-alkoxyketone, with (benzyloxy)ketene and transformation of the chiral β-lactam **78** in an amino acid *N*-carboxy anhydride.[98,99] *N*-Benzylimines were converted to β-lactams with (benzyloxy)ketene as single diastereoisomers (Figure 23). These compounds can be transformed to *N*-carboxy anhydrides of α-methyl β-alkylserines (**80**), which can be coupled with amino acid benzyl esters to yield dipeptides **81**.

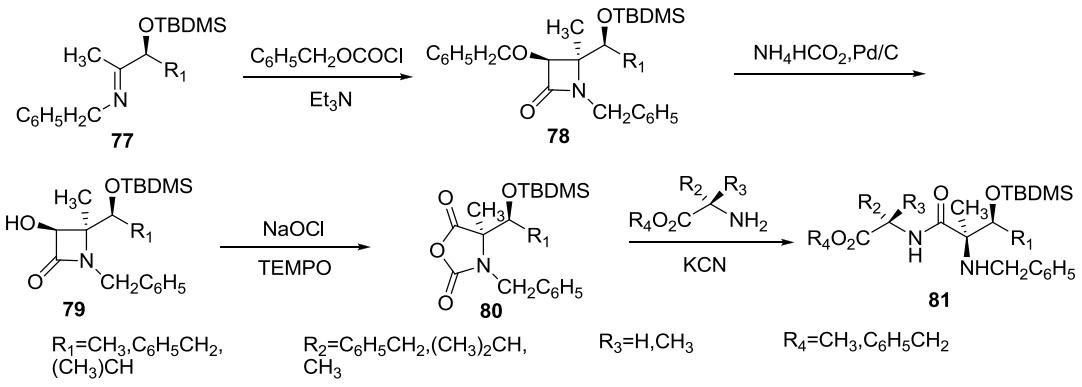


Figure 23. Synthetic route reported by Palomo.

β-Lactam **83** formed from [2+2] cycloaddition of (benzyloxy)ketene and *N*-benzylimine incorporates a masked formyl group at C_4, and this formyl group may be revealed by hydrolysis of the isopropylidene group and cleavage of the diol with sodium periodate. Wittig olefination was followed by hydrogenolysis of the benzyl group with concomitant hydrogenation of the double bond of this 4-formyl-β-lactam (Figure 24).[99] Then it can be converted to the *N*-carboxy anhydrides of the corresponding α-methylamino acid, which can be coupled with amino acid esters.

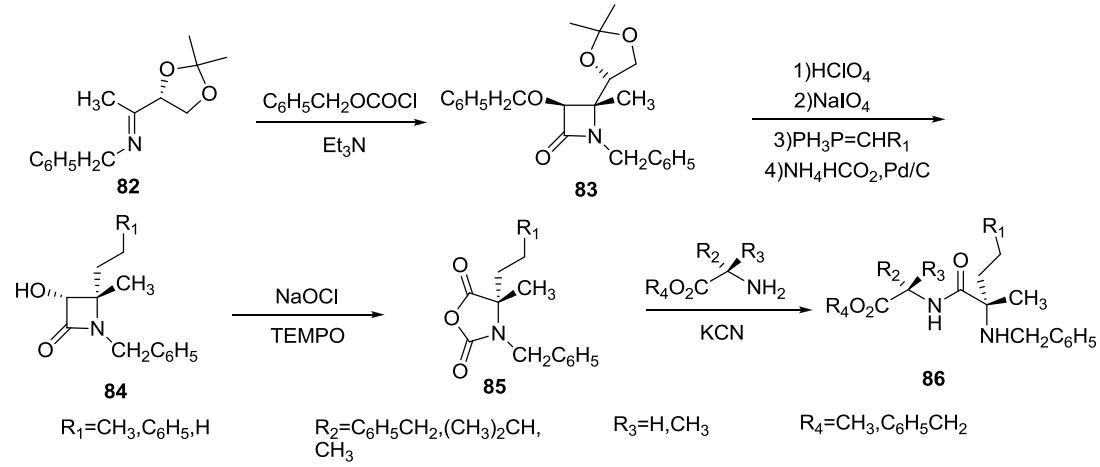


Figure 24. Synthetic route from β-lactam **83** reported by Palomo.

Rearrangement of β-Carbonyl Carboxylic Acid Derivatives

Rearrangement of β-dicarbonyl compounds is another approach to α-alkylamino acids. Fukumoto synthesized chiral 8-phenylmenthyl α,α-dialkylmonomalonic esters by diastereoselective alkylation 8-phenylmethyl α-alkylmonomalonic esters (Figure 25).[100,101] The major compound goes through Curtius rearrangement followed by hydrogenolysis. Then hydrolysis provided the corresponding α-alkylamino acid.

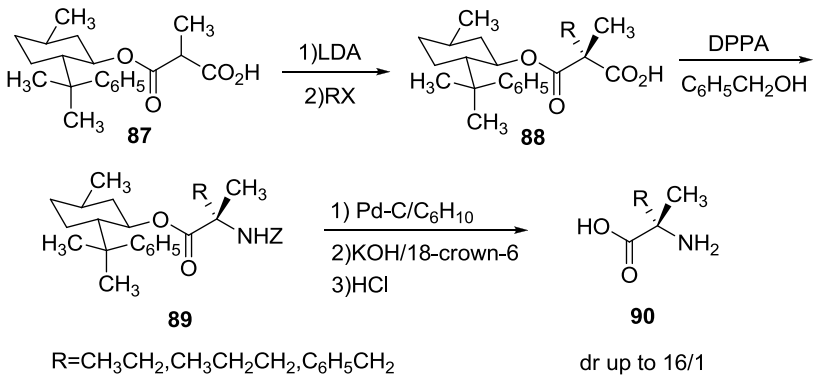


Figure 25. Synthetic route reported by Fukumoto.

Cativiela developed diastereoselective alkylation of chiral cyanoesters derived from (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisoborneol as key intermediates in the synthesis of α-alkylamino acids.[102-109] Curtius rearrangement or Hofmann rearrangement can be applied to the corresponding amino acid derivatives (Figure 26).

Enantiomerically pure α,α-disubstituted-β-ketoesters obtained from asymmetric alkylation of chiral enamines are submitted to Schmidt rearrangement.[110] After acidic hydrolysis, the desired amino acids were afforded (Figure 27).

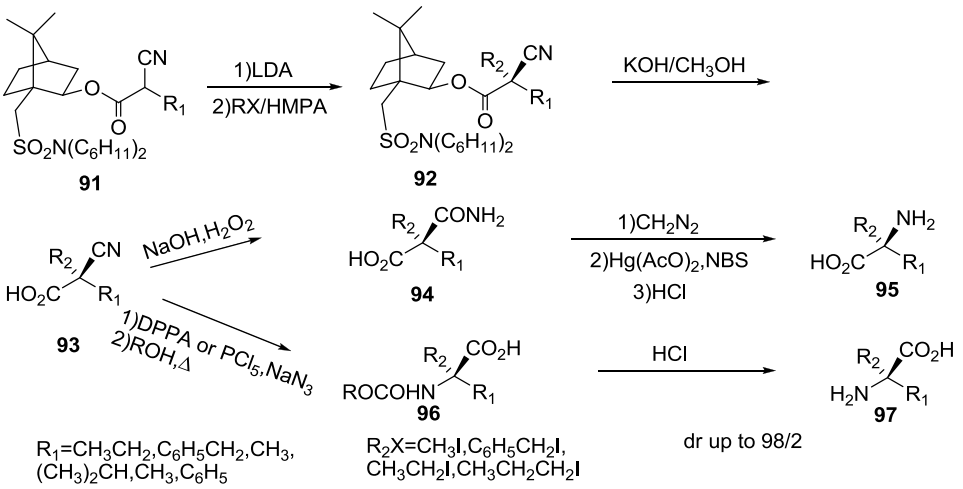


Figure 26. Synthetic route reported by Cativiela.

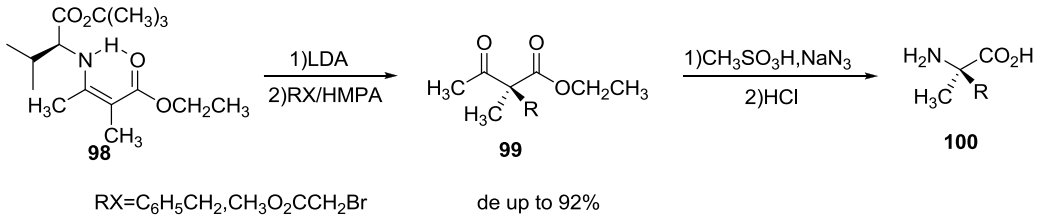


Figure 27. Synthetic route from α,α-disubstituted-β-ketoesters.

Frutos used α,α-disubstituted-β-ketoesters to yield oximes, which are submitted to Beckmann rearrangement.[111] After being *N*-tosylated, the corresponding amino esters were furnished (Figure 28).

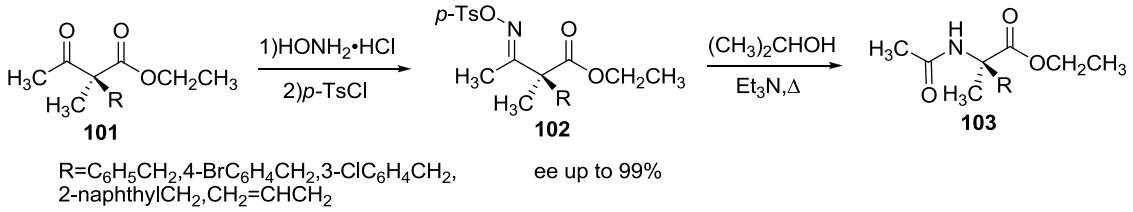


Figure 28. Synthetic route reported by Frutos.

Chiral 2*H*-Azirines and Aziridines as Building Blocks

The „aziridine/oxazolone method" developed by Heimgartner was known for peptide synthesis and can also be regarded as an asymmetric synthesis of α,α-dialkylamino acid moiety (Figure 29).[112] In this route, chiral amide **104** can be converted to azirine **105**. Then, ring opening affords the corresponding dipeptide **106**.

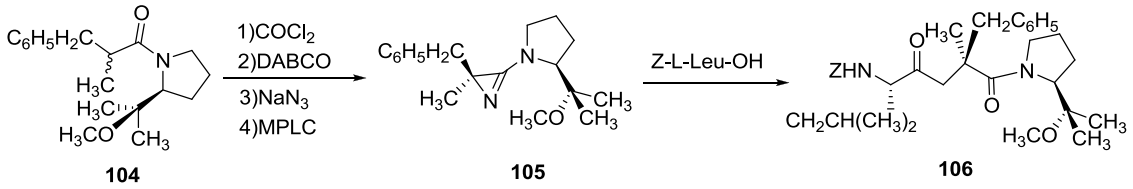


Figure 29. Synthetic route reported by Heimgartner.

Chiral 2-aziridine carboxylates are also used as synthetic intermediates. The ring opening of aziridine leads to unusual amino acids.

Goodman obtained benzyl (*S*)-2-methyl-2-oxirane carboxylate, which can be converted to enantiomerically pure benzyl (*R*)-2-methyl-2-aziridine carboxylate.[113] Lewis acid catalyzed ring opening of the aziridine affords α-methylcysteines (Figure 30).

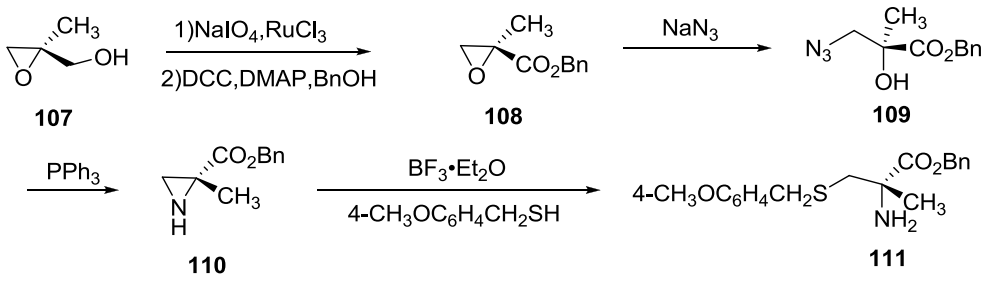


Figure 30. Synthetic route reported by Goodman.

Wipf obtained an activated aziridine **118** by *N*-sulfonylation that allows the smooth regioselective opening with sodium benzyloxide (Figure 31).[114,115]

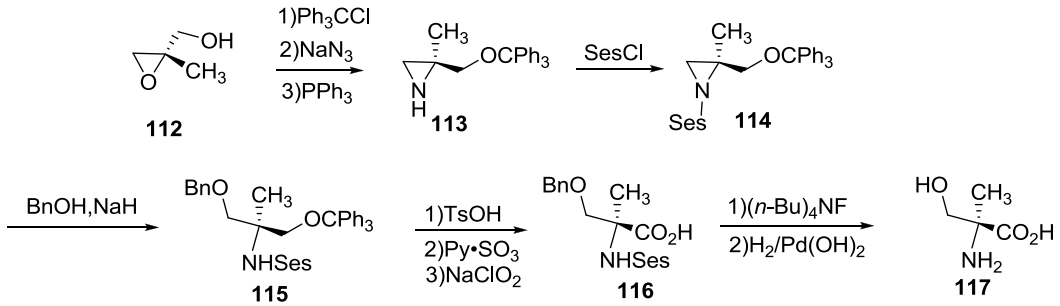


Figure 31. Synthetic route reported by Wipf.

Pritchard activated aziridine **118** by *N*-tosylation. Ring opening with carbon nucleophiles provides precursors of α-methylamino acids (Figure 32).[116]

Davis synthesized chiral 2-methyl-2-aziridinecarboxylic acid derivative by a Darzens-type condensation (Figure 33).[117] Acidic hydrolysis of *N*-sulfinylaziridine affords (2*R*,3*R*)-α-methyl-β-phenylserine methyl ester. On the other hand, *N*-sulfinylaziridine **124** was converted to the activated *N*-tosylaziridine **126** by treatment of *meta*-chloroperbenzoic acid. Hydrogenation of this compound yields an (*R*)-α-methylphenylalanine derivative **127**.

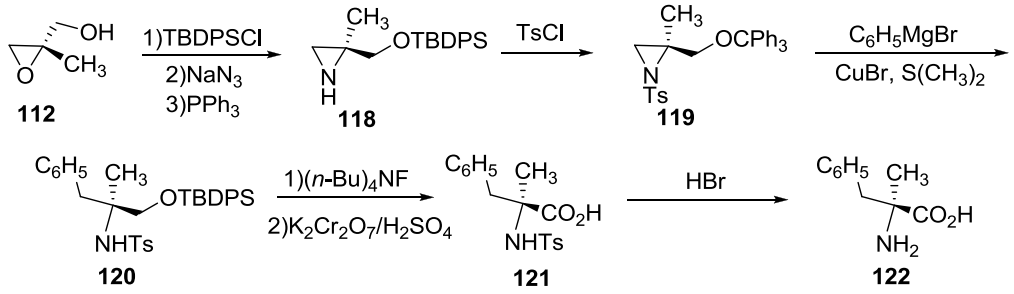


Figure 32. Synthetic route reported by Pritchard.

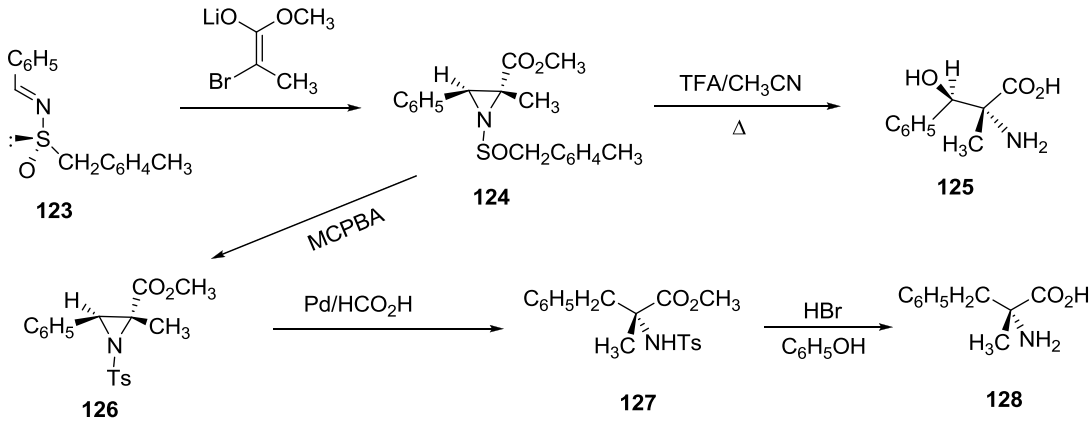


Figure 33. Synthetic route reported by Davis.

Chiral methyl (*R*)-2*H*-azirine-2-carboxylate **130** was afforded from *N*-tosylaziridine **129** by treatment with LDA.[118] This compound yields more substituted azirine-2-carboxylate **131** by addition of Grignard reagents (Figure 34). Then, hydrogenolysis of aziridine provides the corresponding amino esters.

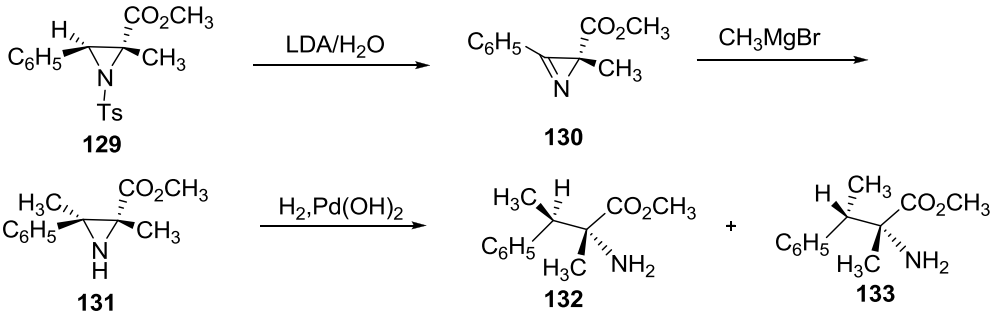


Figure 34. Synthetic route from compound **130**.

2-Substituted aziridines **135** from chiral 2-sulfinylaziridines **134** with *tert*-butyllithium and ethyl chloroformate can be further elaborated to precursors of α-methylamino acids (Figure 35).[119]

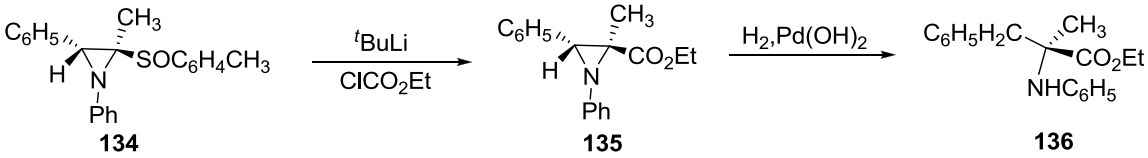


Figure 35. Synthetic route from compound **134**.

Sigmatropic Rearrangements

Steglich first reported the synthesis of allylic amino acids by the Claisen rearrangement[291] and later Barlett did.[292] However, the general application of this method to generate γ,δ-unsaturated amino acid derivatives has been developed by Kazmaier. Allylic esters of *N*-protected amino acids are deprotonated with LDA and then undergo a Claisen rearrangement to give α-allylic amino acids (Figure 36).[120,121]

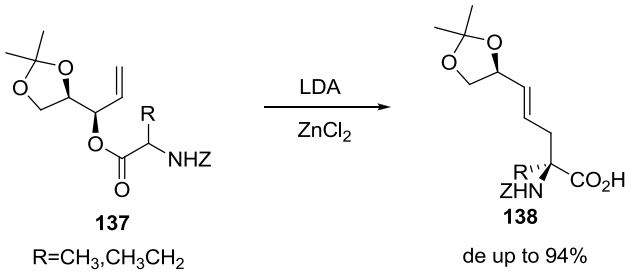


Figure 36. Synthetic route reported by Kazmaier.

Larchevêque used trichloroacetimidates, which are precursors of α-allylic amino acids, to make desired allylic amines by sigmatropic rearrangement under heating (Figure 37).[122]

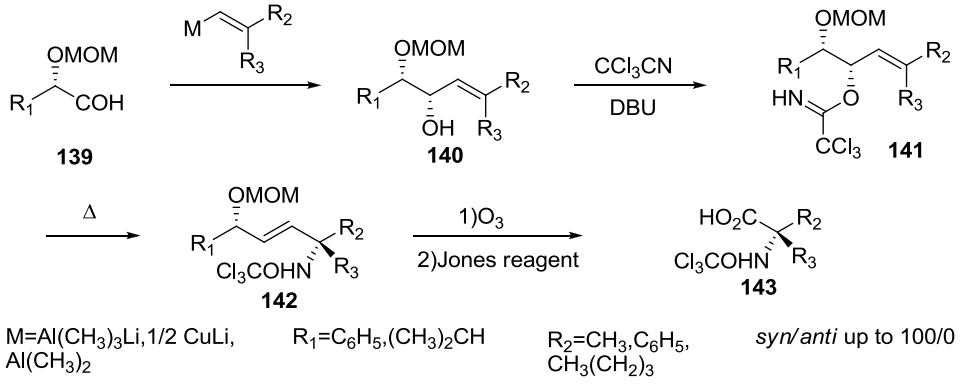


Figure 37. Synthetic route reported by Larchevêque.

Addition to the C=N Bond

The Strecker synthesis is known as procedure for preparation of α-amino acids. The first examples in synthesis of α-alkyl amino acids were reported by Weinges.[123-127] They obtained α-methylamino nitriles in high yield and with excellent

diastereoselectivity, which can be transformed to the corresponding amino acids (Figure 38).

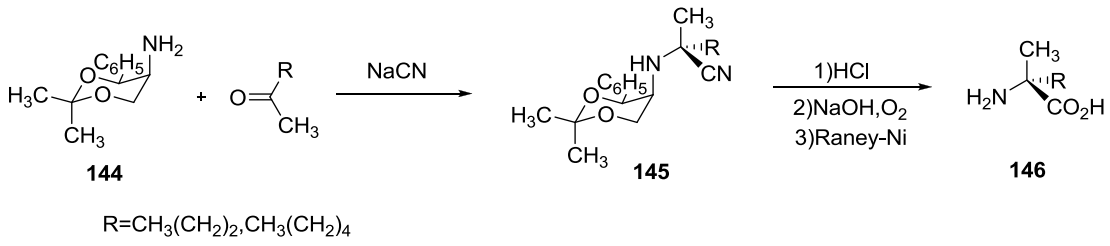


Figure 38. Synthetic route reported by Weinges.

Ohfune applied the Strecker synthesis to provide α-methyl-β-hydroxyamino acids (Figure 39).[128,129] Esterification of α-hydroxyketones with chiral *N*-*tert*-butoxycarbonylamino acids gives an intermediate. After removal of the *N*-Boc protecting group with trifluoroacetic acid and treatment of the resulting trifluoroacetate salt with sodium cyanide, a mixture of diastereomeric amino nitriles is afforded, from which the major diastereoisomer has been isolated. These amino nitriles can be converted to the corresponding α-methyl-β-hydroxyamino acids.

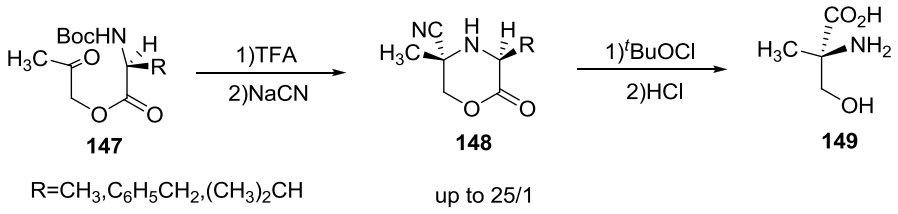


Figure 39. Synthetic route reported by Ohfune.

Chiral *N*-carbobenzyloxy-α-fluoroalkyl-β-sulfinylenamines **150** also have been used as starting materials in the asymmetric Strecker synthesis to afford *N*-benzyloxycarbonyl-α-amino-β-sulfinyl nitriles **151** in excellent yields with only modest

diastereoselectivity.[130] Compounds such as nitrile **151** are precursors of amino acids (Figure 40).

Stereoselective addition of organometallic reagents to the C=N bond of a chiral compound is a useful methodology to the asymmetric synthesis of α-alkylamino acids (Figure 41).[131] Hua reported that the chiral sufinimine **155** goes through a stereoselective addition reaction with allylmagnesium bromide.

(5*R*)-5-Phenyl-3-methyl-3,4-dehydromorpholinone undergoes a stereoselective addition with organomagnesium reagents in the presence of a Lewis acid.[132] These addition compounds are precursors of α-alkylamino acids (Figure 42).

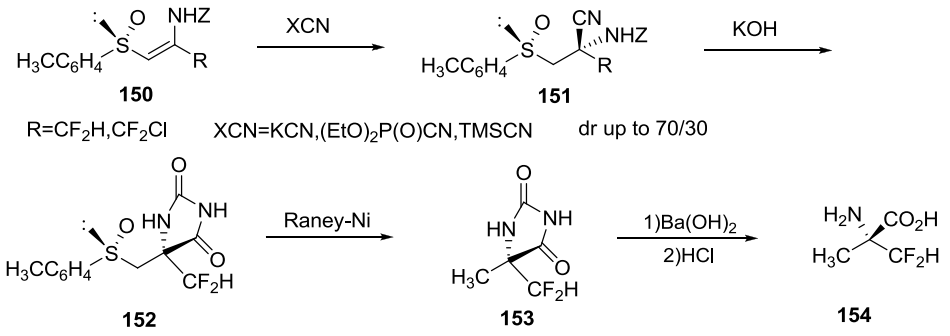


Figure 40. Synthetic route from compound **150**.

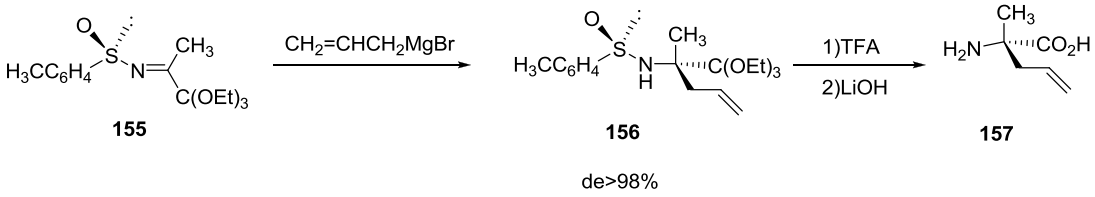


Figure 41. Synthetic route reported by Hua.

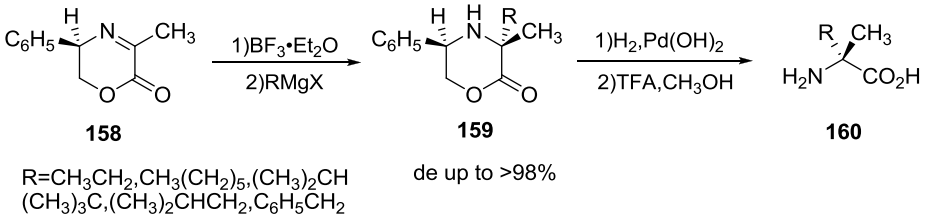


Figure 42. Synthetic route from compound **158**.

E-Configured ketoximes **161** obtained from protected erythrulose and *O*-benzylhydroxylamine pass through the addition with organolithium reagents stereoselectively (Figure 43).[133-135] The addition products can be converted to the corresponding amino acids.

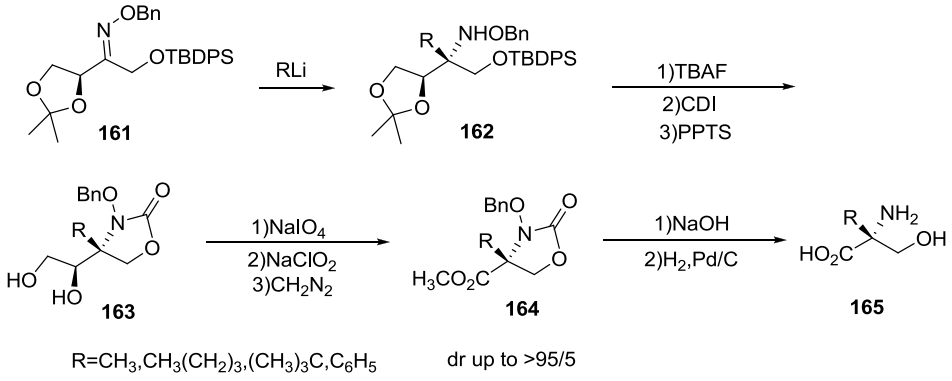


Figure 43. Synthetic route from compound **161**.

Diastereoselective addition of butyllithium to chiral (*E*)-*O*-[(*R*)-1-phenylbutyl] ketoxime **166** affords the corresponding hydroxylamine in moderate yield and with about 80% diastereomeric excess (Figure 44).[136] Cleavage of the N-O bond, acylation and oxidative cleavage of double bond provide α-alkylamino acid derivatives.

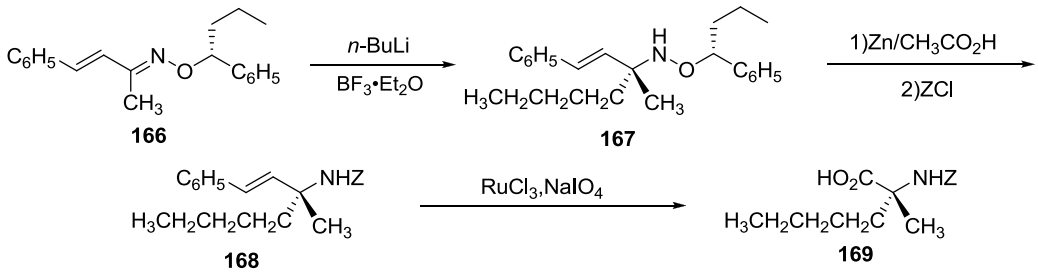


Figure 44. Synthetic route from compound **166**.

Enantioselective Syntheses

Ito developed an enantioselective synthesis of α-alkylserines through a gold(I)-catalysed asymmetric aldol reaction of α-isocyanocarboxylates with formaldehyde, using (aminoalkyl)ferrocenylphosphines as chiral ligands (Figure 45).[137]

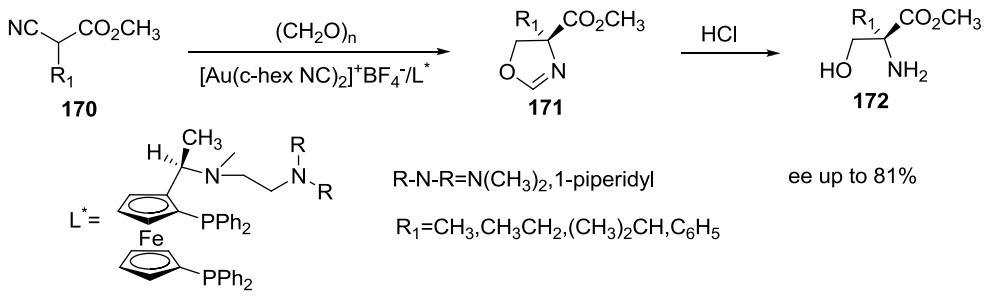


Figure 45. Synthetic route from compound **170**.

O'Donnell used cinchonine and cinchonidine as a chiral catalyst to do asymmetric synthesis of α-methylamino acids by phase-transfer catalytic alkylation of Schiff bases (Figure 46).[138,139]

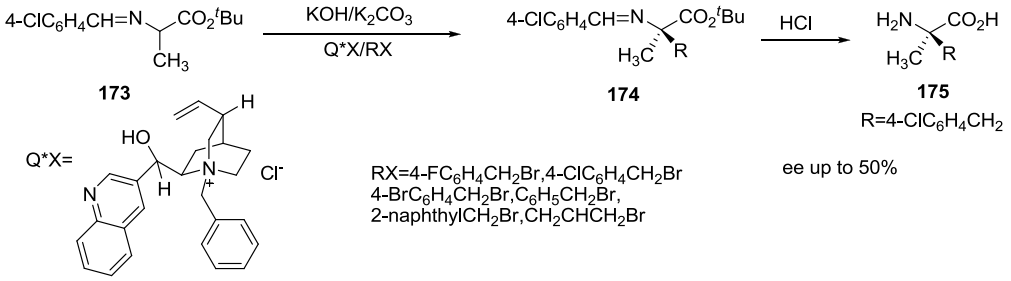


Figure 46. Synthetic route reported by O'Donnell.

Belokon applied *C*-alkylation of Schiff bases under phase-transfer catalysis using (4*R*,5*R*)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol, TADDOL, as the chiral promoter. Deprotection of the alkylation compounds furnishes the corresponding amino acids (Figure 47).[140]

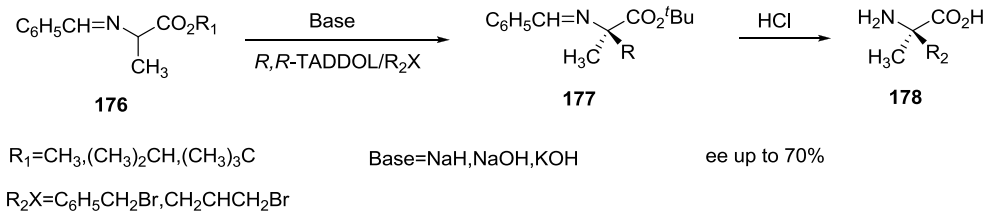


Figure 47. Synthetic route by reported Belokon.

Allylation of azlactones in the presence of chiral palladium catalysts gave the desired alkylation product in high yield, with a good stereoselectivity and a high enantioselectivity.[141] They can be transformed to α,α-dialkylamino acid (Figure 48).

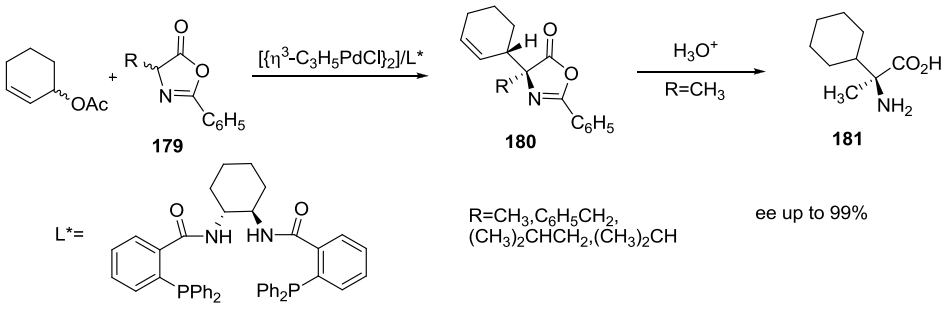


Figure 48. Synthetic route from compound **179**.

Asymmetric Michael addition between α-cyanocarboxylates and vinylketones, catalyzed by rhodium complexes with a diphosphine as a chiral ligand, affords optically active Michael adducts in high yield (Figure 49). The Michael adduct finally can be converted to α-alkylamino acids after Wittig olefination, hydrogenation and Hofmann rearrangement.[142]

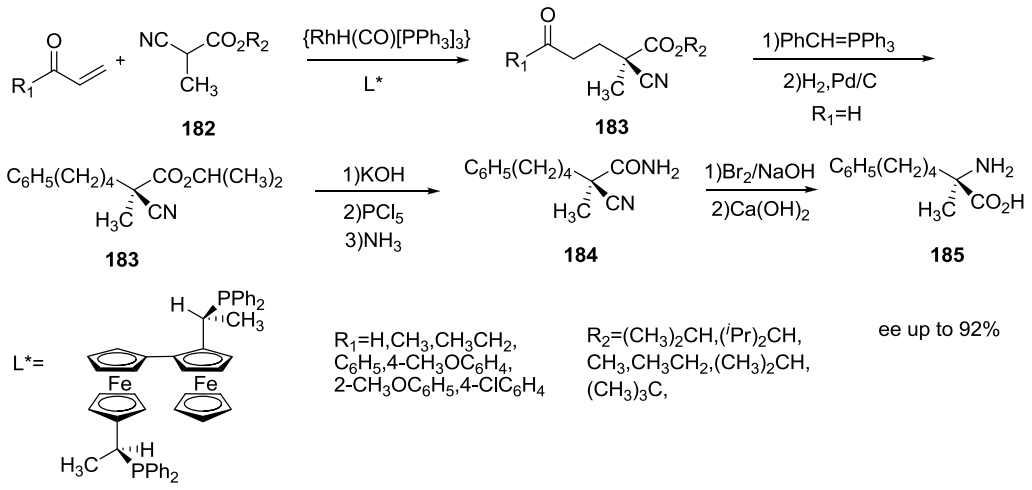


Figure 49. Synthetic route from compound **182**.

α,α-Disubstituted α-amino acids have very important bioactivities. As we have showed above, widely synthetic approaches to these compounds has been developed.

However, asymmetric radical addition to C=N bond has been rarely achieved to obtain these amino acids. My work in Chapter 2 is going to exhibit success on our asymmetric radical synthetic route.

Previous Studies on Mn-Mediated Radical Intermolecular Coupling

Chiral α-branched amines are common substructures of bioactive synthetic targets such as alkaloids and amino acids. Direct asymmetric amine synthesis by addition to the C=N bond of carbonyl imino derivatives[32-39] is a promising and efficient route to introduce the stereogenic center and carbon-carbon bond in one step. There are two alternative disconnections of either C-C bond at the amine stereogenic center to achieve this objective. We could make the choice depending on the different synthetic strategies, such as the availability of precursors and the presence of complicating structural features (Figure 50). Till now, the requirements for mild reaction conditions limit tolerance of complex multifunctional precursors. Thus, development of general methods for acyclic stereocontrol is a significant challenge.

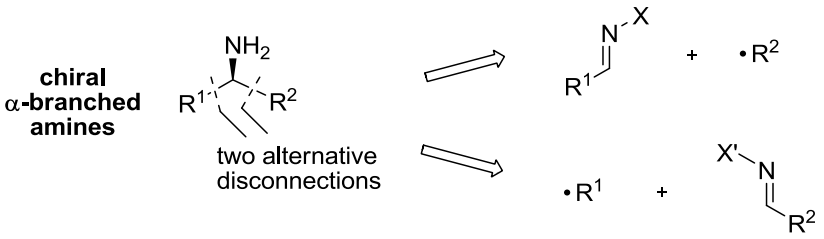


Figure 50. Radical synthetic strategies.

Stereocontrolled intermolecular radical addition[143-146] to imino compounds is an attractive approach to asymmetric amine synthesis.[147,148] Additions of basic organometallic reagents often cause aza-enolization[149-151] or are not tolerant of

multifunctional groups. In contrast, alkyl radicals are nonbasic, produced under mild conditions and undergo reactions without aza-enolization. The intermolecular addition reactions to π systems can allow the presence of additional functionality in both precursors because they have good chemoselectivity for addition to C=N bond. The neutral reaction conditions are typical and improve the flexibility. The radical intermediates are usually stable in the presence of Lewis acids or bases. Compared to reactions of traditional organometallic nucleophiles, these neutral conditions exhibit significant advantages.[152-166] However, the use of primary alkyl radicals remains uncommon; most general methods are more effective with secondary and tertiary radicals.

We were looking for such new radical addition conditions, which can use primary iodides (Figure 51). It would dramatically open the range of potential synthetic applications of radical additions to C=N bonds. We have developed suitable conditions to achieve this goal: photolysis of manganese carbonyl mediates highly stereoselective intermolecular radical addition of primary alkyl halides to *N*-acylhydrazones.[167]

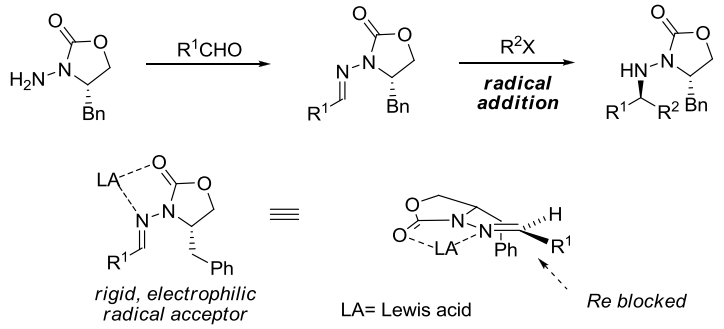
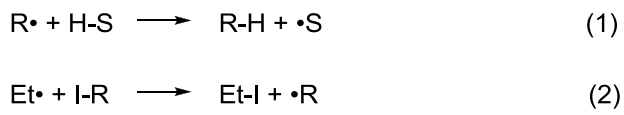


Figure 51. Intermolecular radical synthetic strategies.

We have prepared novel chiral *N*-acylhydrazones as chiral imino acceptors activated by Lewis acid,[168] which can restrict rotation of N-N bond. The methods for efficient preparation of *N*-acylhydrazones from *N*-amino-2-oxazolidinones are reliable and versatile.[169] We have made many such *N*-acylhydrazones from different aldehydes.

Our initial studies of radical[170,171] and allylsilane[172] additions disclosed the excellent synthetic potential of these novel chiral hydrazones. Further, several other related additions have since been reported.[173,174] Our earlier studies on these chiral hydrazones were related to secondary and tertiary radicals.[170,171] As noted above, this is a routine limitation to intermolecular radical addition reactions.

In our earlier studies, unchanged hydrazones were typically isolated back under addition condition of primary iodide in the presence of Bu_3SnH, whereas Et• addition (from Et_3B/O_2 initiation)[175] was the major product in the absence of Bu_3SnH. The latter is a common problem when triethylborane or diethylzinc are used as radical initiators. Based on this, there are some significant problems when applying intermolecular additions of primary alkyl radicals using existing methods: first, 1° radicals (vs 2° or 3°) are less-stable and might not live long enough to avoid reduction by hydrogen-atom abstraction from solvent (H-S, eq 1). Second, in most cases, the iodide atom transfer between the primary Et• and a primary alkyl iodide is thermoneutral and more unfavorable than side reactions of Et• (addition reactions of Et• or quenching by H-atom transfer from solvent, eq 2).



We therefore considered photolytic initiation. Kim has developed nonreductive radical conditions using photochemical initiation and hexamethylditin to mediate addition-elimination reactions of *C*-sulfonyl oxime ethers, a very special example of the successful intermolecular addition of various functionalized primary alkyl halides.[176-182] Though his procedures were different from our desired process, and did not generate a new chiral center, it was still encouraging, and we attempted to use Kim‟s conditions in our earlier study of tin- and boron-mediated radical additions.[170,171] Ethyl iodide addition to *N*-acylhydrazone provided the corresponding adduct. However, the reaction was not

general and was complicated by exchange of the carbonyl component with the acetone sensitizer. This suggested another alternative of these photochemical nonreductive conditions by a reagent similar to $Me_3SnSnMe_3$ without a sensitizer.

Dimanganese decacarbonyl [$Mn_2(CO)_{10}$] attracted our attention and might give a solution to the problem of primary alkyl radical addition to *N*-acylhydrazones. This commercially available yellow solid has a molecular structure containing two $Mn(CO)_5$ units, each with octahedral coordination, linked by a weak manganese-manganese single bond (38 kcal mol^{-1}).[183,184] $Mn_2(CO)_{10}$ is UV active; its λ_{max} is 324 nm (cyclohexane), associated with the $\sigma \rightarrow \sigma^*$ transition of the Mn-Mn bond, which may be broken by thermal or photochemical conditions (eq 3).[185,186] The resulting $\bullet Mn(CO)_5$ has been detected using EPR spectroscopy and spin-trapping techniques.[187,188]

$$(CO)_5Mn\text{-}Mn(CO)_5 \xrightarrow{h\nu} 2(CO)_5Mn\bullet \qquad (3)$$

$$(CO)_5Mn\bullet + I\text{-}R \longrightarrow (CO)_5Mn\text{-}I + \bullet R \qquad (4)$$

$Mn(CO)_5$ can undergo hydrogen-[189,190] or halogen-atom[191-194] abstraction reactions (eq 4); the latter behavior is quite similar to that of tin radicals. Halogen-atom abstraction from alkyl halides by $\bullet Mn(CO)_5$ generates alkyl radicals along with products of the type $X\text{-}Mn(CO)_5$. The formation rates (C-I > C-Br > C-Cl) are inversely proportional to the strength of the C-X bond. The rates are also decreased by steric hindrance reported by Brown:[192] the halogen-atom abstraction is inhibited when bulky phosphines replace carbonyl ligands on the Mn.

Application of $Mn_2(CO)_{10}$ in organic synthesis are just starting compared to the well-established oxidative radical reagent $Mn(OAc)_3$.[195,196] There are some interesting explorations of this reagent by Parsons and others with Wurtz-type homocoupling,[197,198] radical cyclizations,[199-202] TEMPO trapping,[198] and polymerization.[203,204] It is encouraging that high concentrations of the carbon-centered radicals were produced in the photolysis with $Mn_2(CO)_{10}$ in the case of homocoupling. Interestingly, Parsons found

that reaction of •$Mn(CO)_5$ with 1° halides was much more facile that with 2° or 3° halides. This is contrary to the usual order of reactivity for generation of alkyl radicals. However, Brown‟s observation gave the same order of reactivity in the halogen-atom transfer reactions of Mn(0)-centered radicals.

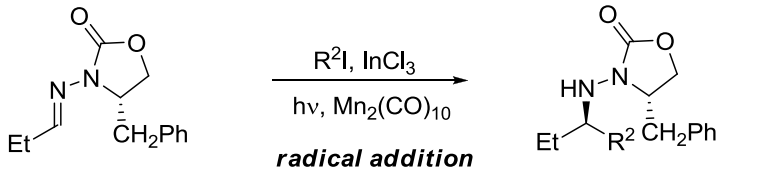
The practical concerns have also received some attention. Unlike the organotin reagents, $Mn_2(CO)_{10}$ is a solid; it may be easily handled for short periods in an ambient laboratory atmosphere (e.g., for measurement and transfer) and stored for long periods under an inert atmosphere in the freezer without decomposition. In contrast to tin halides such as Bu_3SnBr, the manganese(I) halide byproducts obtained from atom abstraction reactions with alkyl halides are relatively easy to remove.

Based on the above considerations, dimanganese decacarbonyl was considered a promising candidate for improving the synthetic potential of radical additions to imino compounds. In the photolytic Mn-Mn homolysis of manganese carbonyl [$Mn_2(CO)_{10}$], it does not require any sensitizer and could be applied for intermolecular addition to C=N bonds.

In 2001, we reported that manganese carbonyl mediates stereoselective photolytic radical addition of alkyl iodides to chiral *N*-acylhydrazones with tolerance of additional functionality in both coupling partners and excellent flexibility for synthetic planning (Table 1, Table 2).[167] Furthermore, we began to pay careful attention to mechanistic questions. Control experiments told us some basic information on the roles of the reaction components. In the absence of $Mn_2(CO)_{10}$, there was no reaction after irradiation for 24 h. Similarly, without irradiation, no adduct was observed. However, in the absence of $InCl_3$, the addition adduct was furnished in low yield, although the reaction was slow. This indicates that the indium chloride is not necessary to make the radical reaction work; rather, it appears to speed up the reaction and provide higher diastereoselectivity. In ambient light, the addition proceeded but was much less efficient than the reaction employing UV irradiation. Large quantities of galvinoxyl were required to completely

shut down the reaction, which suggests a non-chain radical process or a very short chain length.[205]

Table 1. Metal-Mediated Radical Addition to Propionaldehyde Hydrazone **186a**



186a **187, 188S, 189R-197R**

entry	mediator (equiv)	alkyl halide R^2X	adduct, yield[b]	dr
1	Et_3B (5)[a]	CH_3CH_2I	**187**, 33%	-
2	Me_6Sn_2 (1.2)	CH_3CH_2I	**187**, 56%	-
3	$Mn_2(CO)_{10}$ (1.0)	CH_3CH_2I	**187**, 85%	-
4	$Mn_2(CO)_{10}$ (2.0)	CH_3I	**188S**, 48%[c,d]	95:5[e]
5	$Mn_2(CO)_{10}$ (2.0)	$CH_3CH_2CH_2I$	**189R**, 66%	94:6[e]
6	$Mn_2(CO)_{10}$ (2.0)	$CH_3(CH_2)_3I$	**190R**, 78%	95:5[e]
7	$Mn_2(CO)_{10}$ (2.0)	$CH_3(CH_2)_4I$	**191R**, 79%	96:4[e]
8	$Mn_2(CO)_{10}$ (2.0)	$(CH_3)_2CHCH_2I$	**192R**, 54%[e]	95:5[f]
9	$Mn_2(CO)_{10}$ (2.0)	$(CH_3)_2CHI$	**193R**, 75%, 94%[g]	95:5[f]
10	$Mn_2(CO)_{10}$ (2.0)	$ClCH_2I$	**194R**, 63%	93:7[e]
11	$Mn_2(CO)_{10}$ (2.0)	$Cl(CH_2)_3I$	**195R**, 52%	96:4[f]
12	$Mn_2(CO)_{10}$ (2.0)	$Cl(CH_2)_4I$	**196R**, 55%	96:4[e]
13	$Mn_2(CO)_{10}$ (2.0)	Cl_2CHBr	**197R**, 38%[c,d]	98:2[f]

*Reaction conditions: To a deoxygenated solution of $InCl_3$ (2.2 equiv) and hydrazone **186a** in CH_2Cl_2 (0.1 M) was added the mediator and R^2X (10 equiv) followed by irradiation (300nm, Pyrex for 1-2 days at ca. 35 °C under N_2. [a] Irradiation was omitted. [b] Isolated yields of purified diastereomer mixture. R or S denotes the configuration of the new stereogenic center. Addition of methyl iodide gives *S* configuration due to the lower priority of the methyl ligand. [c] 20 equiv of R^2X was used. [d] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used in the removal of Mn byproducts. [e] Ratio by HPLC (Chiralcel OD, 2-PrOH/hexane). [f] Ratio by by ^1H NMR. [g] $InCl_3$ and hydrazone were stored under vacuum (ca. 1 mmHg) overnight prior to use, and a smaller amount of *i*-PrI (3 equiv) was used.

During investigation, besides expected addition product, an interesting side product, dichloromethyl adduct was detected; which was generated from the solvent. The

most reasonable explanation for this result is H-atom transfer from CH_2Cl_2. Besides, this latter alkyl radical and the *N*-centered radical may undergo the H-atom abstraction. And we also has the evidence that a solvent less prone (10:1 PhMH/MeCN) to H-atom abstraction would minimize consumption of alkyl iodide.[205]

Table 2. Preparation and $Mn_2(CO)_{10}$-Mediated Iodoethane Addition to Aldehyde Hydrazones

entry	Aldehyde R^1CHO (or acetal)	hydrazone, yield[a]	Et • adduct, yield[b]	dr
1	CH_3CHO	**186b**,66%	**188R**, 66%	95:5[d]
2	$CH_3(CH_2)_2CHO$	**186c**,87%	**189S**, 63%	95:5[d]
3	$CH_3(CH_2)_3CHO$	**186d**,89%	**190S**, 72%	97:3[d]
4	$CH_3(CH_2)_4CHO$	**186e**,88%	**191S**, 77%	97:3[d]
5	$(CH_3)_2CHCH_2CHO$	**186f**,85%	**192S**, 65%;83%[f]	95:5[e]
6	$ClCH_2CH(OMe)_2$	**186g**,85%	**194S**, 57%	93:7[d]
7	$Cl(CH_2)_3CHO$	**186h**,95%	**195S**, 60%	93:7[e]
8	$Cl(CH_2)_4CHO$	**186i**,89%	**196S**, 62%	97:3[d]
9	$Cl_2CHCH(OEt)_2$	**186j**,54%	**197S**, 34[c]	89:11[e]

*Reaction conditions for hydrazone formation: Aldehyde (5-10 equiv), ***N*-amino-2-oxazolidinones,** *p*-toluenesulfonic acid, CH_2Cl_2, rt. For radical addition conditions, see table 1. [a]Isolated yield. [b] Isolated yields of diastereomer mixture. [c] 1,8-Diazabi-cyclo[5.4.0]undec-7-ene (DBU) was used in the removal of Mn byproducts. [d] Ratio by HPLC. [e] Ratio by by ^1H NMR. [f] $InCl_3$ and hydrazone were stored under vacuum (ca. 1 mmHg) overnight prior to use, and a smaller amount of EtI (3 equiv) was used.

Interestingly, addition of 3-chloro-1-iodopropane to propionaldehyde hydrazone **186a** led to pyrrolidine **198R**, presumably via 3-chloropropyl radical addition and *in situ* nonradical cyclization (Figure 52). When the 3-chloropropyl group was in the C=N moiety in hydrazone **186h**, the pyrrolidine **198S** was furnished by ethyl addition. These are two examples of a potentially useful hybrid radical-ionic annulation.[205]

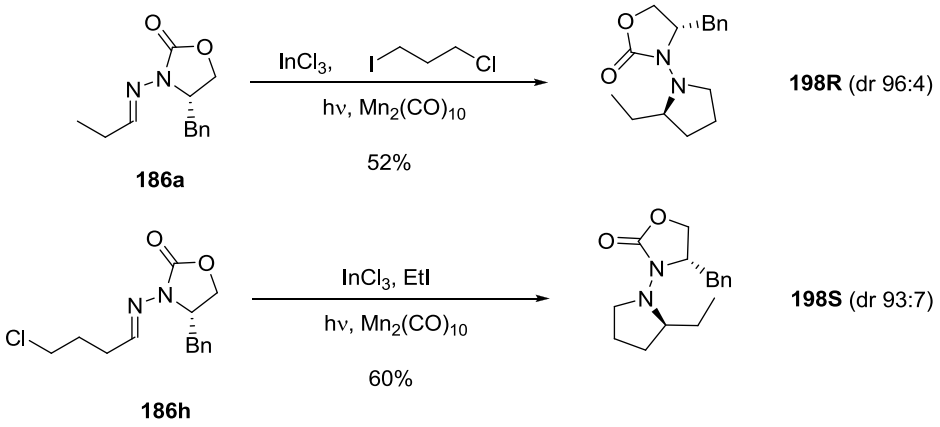


Figure 52. Hybrid radical-ionic annulation for pyrrolidine derivatives.

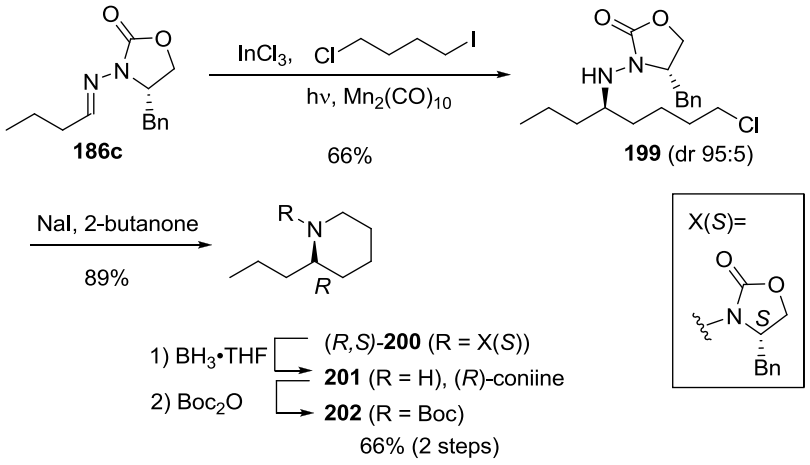


Figure 53. Hybrid radical-ionic annulation for (*R*)-coniine.

To examine its potential in asymmetric amine synthesis, we prepared the simple piperidine alkaloid coniine by Mn-mediated radical addition (Figure 53 and Figure 54). Mn-Mediated radical addition of 4-chlorobutyl iodide to **186c** produced **199** with high

diastereoselectivity. Cyclization happened under Finkelstein conditions, giving piperidine derivative (*R,S)*-**200**. Reduction with BH_3•THF afforded (*R*)-coniine. It was converted to the *tert*-butyl carbamate (*N*-Boc) and the absolute configuration was determined by comparison of its optical rotation. Additional information of the configuration was collected by an alternative route to *N*-benzoyl (*R*)-coniine. Benzoylation of hydrazine and N-N bond cleavage by SmI_2 gave **203**. Finkelstein reaction and base treatment of the iodide furnished *N*-benzoyl (*R*)-coniine and the configuration was examined by comparison of its optical rotation. The conversion of **199** to (*R*)-coniine by two routes proved that our Mn-mediated radical addition has practical potential in asymmetric amine synthesis.

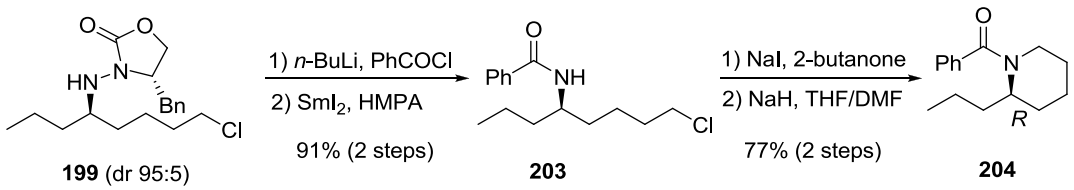


Figure 54. Hybrid radical-ionic annulation for *N*-benzoyl (*R*)-coniine.

Various reactions can use the photolysis of dimanganese decacarbonyl in the presence of alkyl iodides to generate alkyl radicals. The mechanistic questions for our process become more interesting. We proposed one alternative, a one-electron free-radical process (Figure 55). Alkyl radical addition provides the corresponding aminyl radical, which recombines with a pentacarbonyl-manganese radical or H-atom abstraction from solvent (path A). This photolysis chemistry also produces alkylmanganese species from iodides by radical-radical coupling. So, another possibility is a two-electron carbometalation-type reaction leading to the same adduct (path B). Further, photolysis of R-$Mn(CO)_5$ is known to generate R• species.[187,188,206] If the photolysis conditions used in our radical additions could permit a reversible homolysis and recombination of R-

$Mn(CO)_5$, these alkylmanganese species could adjust the reactivity of radicals via the persistent radical effect (PRE).[207-215] Specifically, a small excess of persistent metal-centered radicals could inhibit the destructive homocoupling of transient alkyl radicals. On the other hand, it is also known that photolysis of R-$Mn(CO)_5$ generates $Mn_2(CO)_{10}$, which differentiates this system from ideal examples of PRE wherein the homocoupling of the persistent radical is not observed to any significant extent. We investigated these issues further, by probing the reactivity of alkylmanganese species toward *N*-acylhydrazone **186a**.

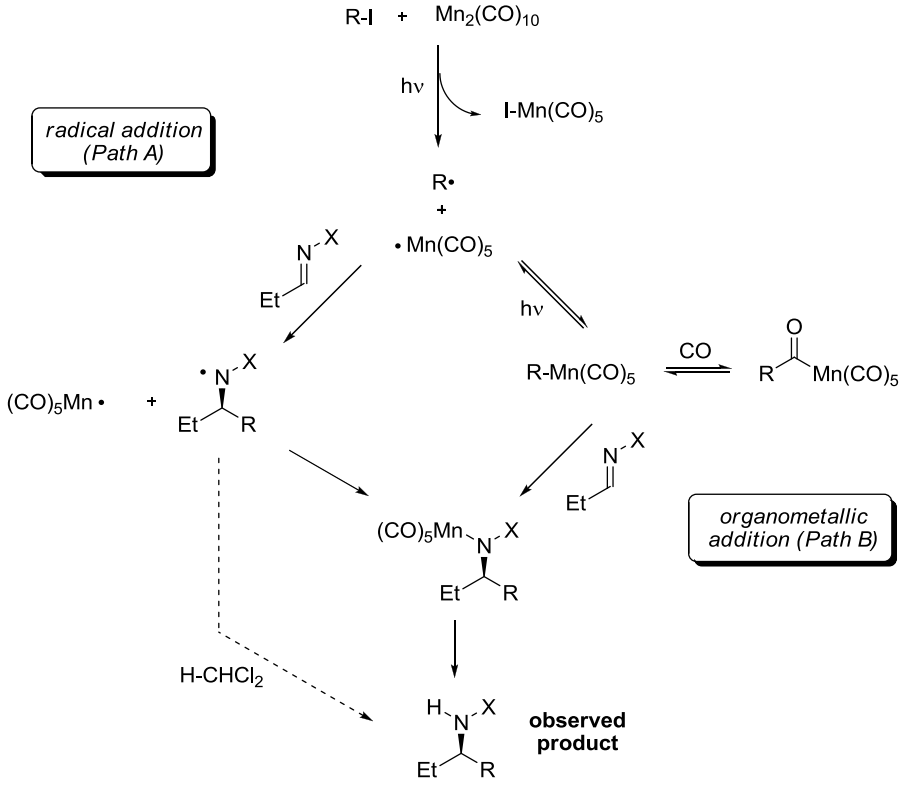


Figure 55. Mechanistic possibilities.

Alkylmanganese compounds were prepared and their reactivity was examined with *N*-acylhydrazones for evaluation of alkylmanganese intermediates (Figure 56).

Tridecyl analogues $(C_{13}H_{27})Mn(CO)_5$ and $(C_{13}H_{27}CO)Mn(CO)_5$ were prepared and exhibited the expected types of reactivity. These pairs of compounds interconverted thermally and photochemically, with the latter conditions leading to decomposition to alkane. Photolysis in CH_2Cl_2 in the absence of *N*-acylhydrazone gave tridecane, and the alkyl dimer ($C_{26}H_{54}$) was detected. Apparently, H-atom abstraction from CH_2Cl_2 occurs under these conditions.[205]

Next, we combined $(C_5H_{11})Mn(CO)_5$ and $(C_5H_{11}CO)Mn(CO)_5$ with the propionaldehyde-derived *N*-acylhydrazone (Figure 56). No reaction occurred in the dark or in ambient light, with or without Lewis acid. This means the organomanganese compounds do not react directly with the *N*-acylhydrazones (e.g., via a two-electron carbometalation or migratory insertion of the C=N bond). By photolysis of $(C_5H_{11})Mn(CO)_5$ with *N*-acylhydrazone at 300 nm in the presence of $InCl_3$, the *n*-pentyl radical adduct was formed in a small amount, along with some dimanganese decacarbonyl. When $(C_5H_{11}CO)Mn(CO)_5$ was used in the latter experiment, no addition took place, although formation of $(C_5H_{11})Mn(CO)_5$ from decarbonylation of $(C_5H_{11}CO)Mn(CO)_5$ was observed.[205]

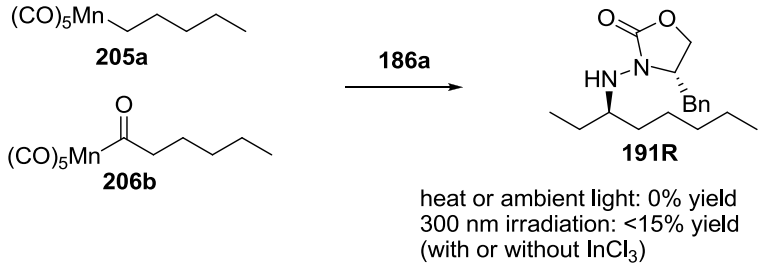


Figure 56. Mechanism examination.

We wondered if the possible Mn-containing components could provide some reactivity which would not be duplicated by the isolated alkylmanganese compound. We

prepared mixtures of R-$Mn(CO)_5$ and I-$Mn(CO)_5$ or R-$Mn(CO)_5$, R(CO)-$Mn(CO)_5$, I-$Mn(CO)_5$, and $Mn_2(CO)_{10}$ separately, which then were mixed with *N*-acylhydrazone and submitted to the standard photolysis conditions in the presence of $InCl_3$. No significant amount of addition product was found.[205]

Finally, the role of the alkyl iodide was examined by a crossover experiment. When $C_{13}H_{27}COMn(CO)_5$ was used in the photolysis, no observable addition reaction (TLC) was produced by irradiation for several hours. During this period, our group found a significant amount of $Mn_2(CO)_{10}$, detected qualitatively by TLC and visual inspection (yellow solid on the upper walls of the reaction vessel). At this point, iodopentane was added to the flask, and upon further irradiation, the addition reaction appeared to take its normal course. The only addition product contained the pentyl group; no tridecyl group was detected. This clarified the origin of the alkyl group; it must have come from pentyl iodide without the intervention of an alkylmaganese species.[215]

Based on the above result, we can conclude the nonradical reactions of alkyl- or acylmanganese species do not play a significant role under our radical conditions. The free-radical addition appears to either be nonchain or have a short chain length, and it requires generation of radicals from the alkyl iodide. All results suggest that effectiveness of the Mn-mediated additions may come from relatively high radical concentrations. It is interesting that the alkyl- and acylmanganese compounds can undergo photolytic reduction to alkane and do not form addition to any great extent. A solvent cage effect is one explanation. The alkyl- or acylmanganese homolysis produces a caged radical pair, kinetically distinguishing its alkyl radical component from the free alkyl radical produced by bimolecular halogen-atom abstraction. In the latter case, intermolecular addition to the *N*-acylhydrazone is favorable; in-cage recombination is prevented because the Mn-containing component in the solvent cage is I-$Mn(CO)_5$, not •$Mn(CO)_5$.[215]

In summary, we have developed manganese carbonyl mediated stereoselective photolytic radical addition of alkyl iodide to chiral *N*-acylhydrazones. Qualitative

mechanistic studies prove the importance of free radicals, indicate that this is a nonchain (or short chain length) free-radical process, and discover that organomanganese compounds are not a source of alkyl radical for the addition reactions under the conditions used in these reactions.[215]

Previous Studies on Synthetic Quinine

In this section, the background for Chapter 4 (FOMAL SYNTHESIS OF QUININE) will be introduced. Since 1600‟s, quinine has been well-known as the antimalarial drug. Malaria is a mosquito-borne infectious disease producing a debilitating condition which is caused by several species of the parasite *Plasmodium*. These parasites go into red blood cells, feed upon the protein, and destroy them. It is widespread in tropical and subtropical regions, including parts of the Americas, Asia, and Africa. Even today, malaria is still a major disease, which affects approximately 40 percent of the world‟s population. Each year, there are more than 250 million cases of malaria, killing between one and three million people, the majority of whom are young children in sub-Saharan Africa.[216,217]

In 1633, an Augustinian monk named Calancha of Lima in Peru, first wrote that a powder of cinchona “given as a beverage, cures the fevers and tertianas.” This powder from cinchona bark revealed its antimalarial properties. In the same centuries, this remedy was spread in Europe and then the cinchona bark was widely accepted as an antimalarial substance.

During the middle of the 18th century, cinchona bark began to attract the attention of chemists. They believed that powdered herb contained an “active principle”, which was responsible for the valuable properties. In this age of discovery, some scientists of several European laboratories started to extract and concentrate the active principle of the bark. Unfortunately, only the inactive calcium salt of quininic acid or cinchotannic acid was obtained. In 1820, Pelletier and Caventou, experts in the isolation of alkaloids,

successfully isolated quinine, which is the active principle in the yellow bark of cinchona. This allowed the quantitative evaluation of the quality of quina bark. After isolation of quinine and demonstration of its active antimalarial principle, both the alkaloid and the bark were always in short supply, since they were the only effective treatment against malaria at that time. By the middle of the 19th century, the discovery of synthetic quinine was heated. However, we still did not know the synthetic way and the structure of quinine at that time.

Today the three most important techniques to clarify the structure of natural products are mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy, and X-ray crystallography. The first two techniques can clarify the structure of most natural products. Though X-ray crystallography is a more powerful tool, it requires good-quality crystals of the target compounds. With these techniques, it may take only a few days for organic chemists to determine the structure of a natural product accurately. However, during the late 19th and early 20th century analytical methods were limited and "wet" chemical analysis was used routinely. The whole effort toward the structural confirmation of quinine lasted more than 50 years. Many prominent European chemists took very intense activity in the laboratories to explore quinine structure. After a series of papers, Königs consolidated the structural knowledge on quinine in 1906. Two years later, Rabe suggested the correct connectivity of quinine (Figure 57). However, some stereochemical issues were still not clarified.[15,16,218] The C8 and C9 configuration were rationalized in 1932. In 1944, Vladimir Prelog degraded the quinuclidine derivative to simple hydrocarbons by several steps and succeeded in establishing absolute and relative configuration at C3 and C4 of the alkaloid.[219,220]

At the beginning of the 20th century many research groups were making progress toward the synthesis of quinine. Rabe published the most important results in this area.[15,16,218] His key procedure is the reduction of quininone to quinine with aluminum

powder, which suggested that the total synthesis of quinine could be accomplished from quinotoxine, though his claims were not fully substantiated because of wartime pressure.

Toward total synthesis of quinine, we should remember one of the preeminent organic chemists of the 20th century, Robert Burns Woodward. He made great contributions to the strategy of synthesis, to the deduction of complicated structures, to the development of new chemical methods and theoretical aspects. He received the 1965 Nobel Prize for Chemistry according to his outstanding achievements in the art of organic chemistry. In his time, he provided the elegant solutions and simplicity of the methods involved in synthesis of natural products including quinine [(±)-homomeroquinene or (+)-quinotoxine, 1944], patulin (1950),[221] cholesterol and cortisone (1952),[222] lanosterol (1954),[223] lysergic acid and strychnine (1954),[224-226] reserpine (1958),[227-229] ellipticine (1959),[230] chlorophyll *a* (1960),[231,232] tetracycline (1962),[233] colchicine (1965), cephalosporin C (1966),[234,235] prostaglandin F_{2a} (1973),[236] and his paramount achievement: the synthesis of vitamin B_{12} (1973, with A. Eschenmoser).[237-240] The total synthesis of erythromycin A was published in 1981,[241-243] after his death.

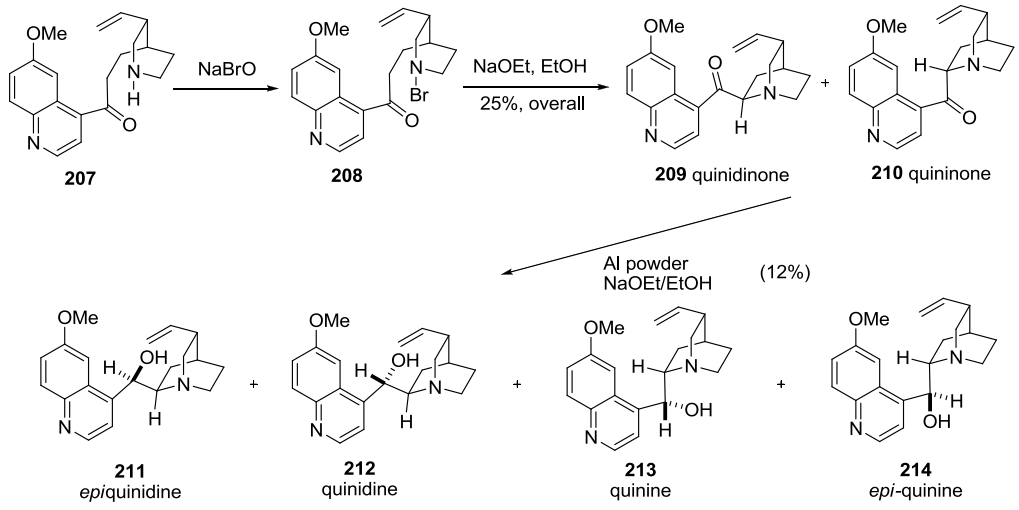


Figure 57. Quinine configuration analysis.

Guided by Woodward‟s deep knowledge of chemistry and the chemical literature, his contribution to the homomeroquinene/quinine synthesis challenge was in his unusual and novel treatment of that problem to install an extra ring for the appropriate configuration of adjacent centers (Figure 58). He proved that the basic homomeroquinene skeleton could be accessed from an isoquinoline. Synthetic routes and protocols for the preparation of such compounds were available from the beginning of the century, but they were not applied to the total synthesis. Therefore, practically, these basic ideas needed more effort than initially thought and a considerable number of synthetic steps. It was done by William von Eggers Doering.

In Doering‟s synthesis, 3-hydroxybenzaldehyde **215** was converted into isoquinolin-7-ol **216** via Schiff base by Pomerantz-Fritsch isoquinoline synthesis. This isoquinoline was transformed into its 8-methyl derivative **219** through the intermediacy of piperidine.[244] The methyl derivative was partially catalytically hydrogenated to the tetrahydroisoquinoline **220**, which was isolated as its *N*-acetyl derivative **221**.

A second catalytic hydrogenation provided **222** as a diastereomeric mixture.[245] The mixture was simplified by oxidation to the ketones **223** with concomitant epimerization of the tertiary carbon center next to the carbonyl group. The diastereomers were separated by the formation of the hydrate of compound with a *cis* ring junction. Ring opening and nitrosation of the tertiary carbon atom next to the carbonyl group furnished the oxime **224**, which was reduced to amine **225**.

Exhaustive methylation of **225** afforded **226** and then Hoffmann elimination was employed to form the vinyl moiety and make the intermediate product protected as an uramido derivative for isolation. The uramido derivative finally underwent an acid hydrolysis to regenerate homomeroquinene **228**.[246] Since Prelog had earlier prepared quinotoxine **230** from homomeroquinene, and assuming the success of Rabe‟s protocol to synthesize quinine **213** from quinotoxine **230**, Woodward‟s synthesis of

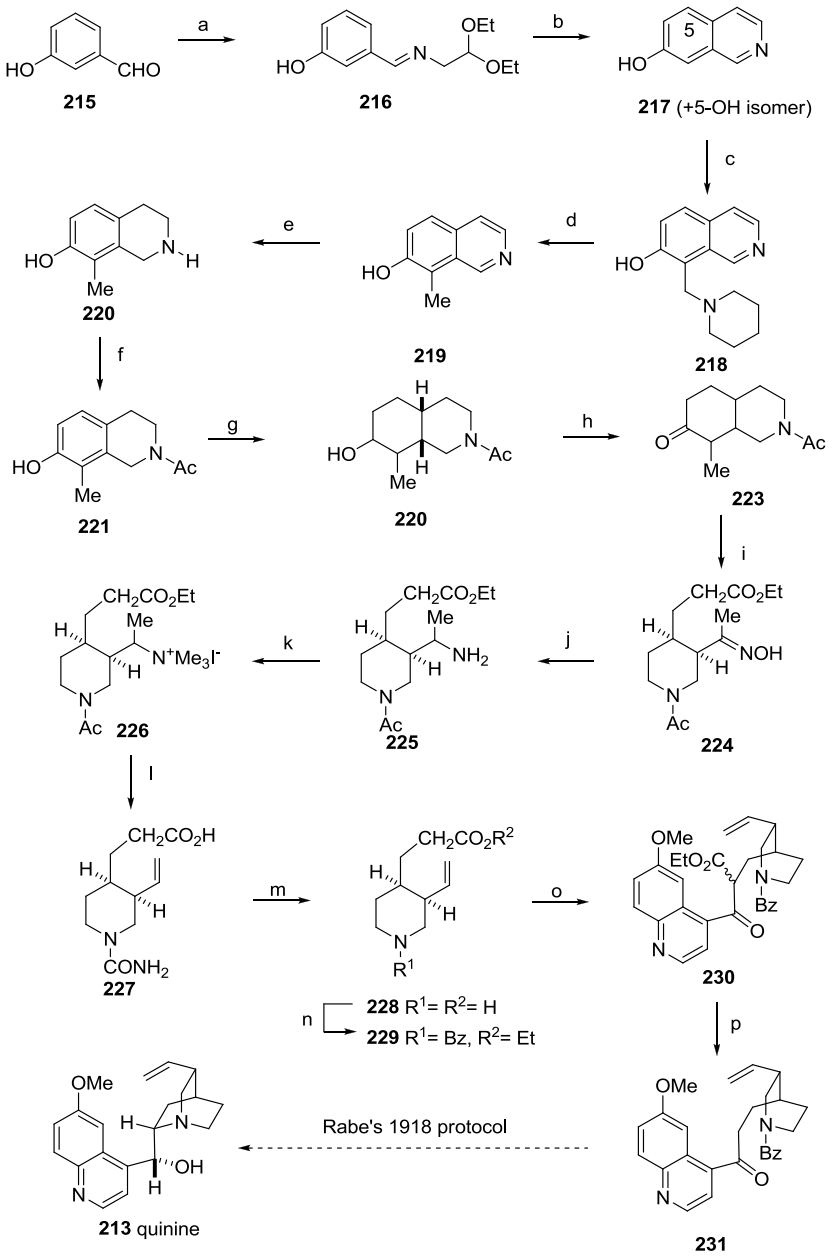
homomeroquinene appeared to be a formal total synthesis. However, his synthetic homomeroquinene was racemic.

Procedure then went one step further, which was achieved by conveniently protecting intermediate **228** as its known *N*-benzoyl ethyl ester **229**. Later, Rabe condensation with ethyl quininate was employed, obtaining furnish β-ketoester **230**.[247,248]

Subsequent hydrolysis and decarboxylation of the resultant β-ketoester gave *dl*-quinotoxine derivative, which was hydrolyzed to *dl*-quinotoxine and then resolved with *d*-dibenzoyl tartaric acid.[249,250] After a little over one year‟s hard work, on April 11, 1944 Woodward and Doering gained a precious 30 mg of synthetic *d*-quinotoxine which could be the compound used into the synthesis of quinine by Rabe‟s procedure. In the middle of World War II, and with natural quinine supplies cut by enemy forces, this breaking news went out from university laboratory to the national press, though Woodward‟s synthesis of quinine was not amenable to large-scale commercial production (Figure 58).

Quinine has five stereogenic centers. The Woodward-Doering synthetic scheme successfully generated two of them selectively by laborious diastereomer separations and chemical resolution. The route was carried out with conventional reactions and reagents that were available to any chemist of that time, protecting groups were hardly used, and one third of the reactions were run at room temperature. Although the synthesis suffered from low yields and lacked stereocontrol at every center, Woodward‟s first total synthesis of quinine was completed in a few months, which attracted great public attention, and remained a scientific milestone.[14]

Woodward‟s synthesis of quinine was published in 1944. The Woodward-Doering synthesis was actually a “formal” total synthesis of quinine, based on a seminal publication in 1918 by Paul Rabe and Karl Kindler, in which *d*-quinotoxine, the final product in the Woodward-Doering work, was transformed into quinine by a three-step sequence.[14,251]



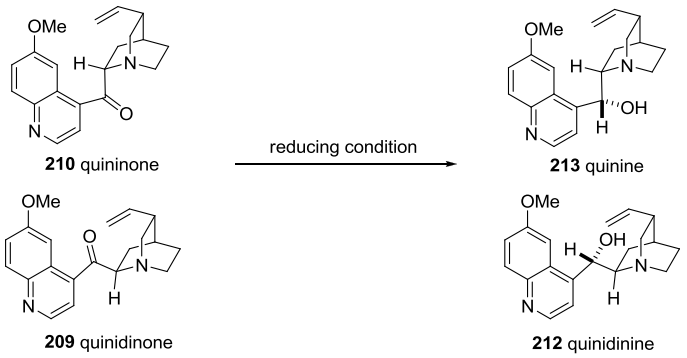
The approach to quinine by Woodward and Doering. Reagents and conditions: a) $H_2NCH(OEt)_2$ (94%); b) 1. 80% H_2SO_4; 2) NaOH, crystallization then H^+ (64%); c) piperidine, HCHO, EtOH (61%); d) NaOMe, MeOH,220°C, 16 h (65%); e) H_2, Pt, AcOH; f) Ac_2O (95%); g) H_2, Raney nichel, EtOH, 150°C, 205 bar, 16 h [1:1 *cis(*crystalline)/*trans(*oil)]; h) $H_2Cr_2O_7$, AcOH; Et_2O/H_2O, diastereomer separation (28%); i) EtO-N=O, NaOEt, EtOH (68%); j) H_2, Pt, AcOH, 1-3 bar; k) MeI, K_2CO_3 (91% overall); l) 1. 60% KOH, 180°C, 1 h; 2. KCNO (40%); m) 1. dilute HCl, EtOH, reflux (100%); n) PhCOCl, K_2CO_3 (96%); o) ethyl quininate, NaOEt, 80°C; p) 1.6N HCl, reflux (50%); 2. resolution with *d*-dibenzoyl tartrate (11%). Bz=benzoyl.

Figure 58. Approach reported by Woodward and Doering.

This sequence included 1) *d*-quinotoxine was oxidized with sodium hypobromite to generated "*N*-bromoquinotoxine"; 2) *N*-bromoquinotoxine underwent base-mediated cyclizaiton to produce "quininone"; 3) "quininone" was reduced to furnish quinine and quinidine (as a minor product) by aluminum-powder. The 1918 paper provided only a terse summary of this three-step process. In 1932, experimental details for the reduction protocol were published. After that, no one has reported efforts to simply attempt to repeat the Rabe-Kindler conversion of *d*-quinotoxine into quinine. Thus, Gilbert Stork and co-workers raised some possible doubts about the validity of this conversion, referring to Woodward and Doering‟s "total synthesis" as a "widely believed myth". Recently, Seeman reported his research on all the available data in the literature and in archival materials entitled: "*The Woodward-Doering/Rabe-Kindler Total Synthesis of Quinine: Setting the Record Straight*".[252] In his analysis, Dr. Seeman stated: "*I conclude that Paul Rabe and Karl Kindler did convert d-quinotoxine into quinine as they reported in 1918.*" and: "*I therefore also conclude that the Woodward-Doering/Rabe-Kindler total synthesis of quinine is a valid achievement*." This conclusion is insightful, based on a painstaking and careful review of a large number of published and unpublished materials.[252] However, it still lacked unambiguous experimental data to support the Rabe-Kindler conversion.

Williams and co-workers were really interested in confirming of Rabe-Kindler protocol of *d*-quinotoxine into quinine by experiments (Table 3). Finally, they have demonstrated that original conversion of quinotoxine to quinine reported by Rabe and Kindler in 1918 is readily repeatable and can be conducted under laboratory conditions, with literature available to Woodward and Doering in the early 1940s without the use of any modern separation, purification, analytical or spectroscopic methods or techniques. The procedure can go through on crude material and analytically pure quinine can be isolated from the final reaction mixture by crystallization of the corresponding tartrate salt.

Table 3. Rabe-Kindler Protocol Optimized by Williams and Co-workers



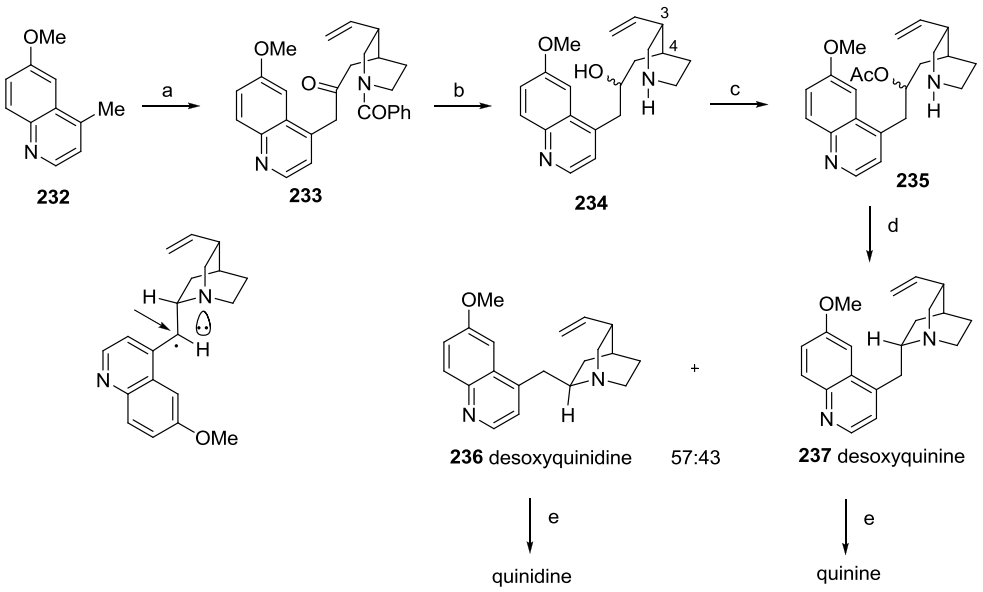
entry	reducing condition	T [°C]	yield of isolated quinine/quinidine	yield of quinine
1	DIBAL-H benzene	20	72%	33%
2	$NaBH_4$, EtOH	0	11%	4%
3	Al powder (new) NaOEt, EtOH	reflux	trace	trace
4	Al powder (new) NaOEt, EtOH	reflux	30% (1.1:1)	16%
5	Al powder (new) +Al_2O_3 NaOEt, EtOH	reflux	26% (1.1:1)	14%
6	Al powder (aerated) NaOEt, EtOH	reflux	24% (1.1:1)	13%
7	Al powder MeOH, NaOMe	reflux	8% (1.2:1)	4%
8	Al powder (sonication) NaOEt, EtOH	reflux	22% (1.1:1)	12%
9	Al powder Na(O*i*Pr), *i*PrOH	reflux	32% (1:1.2)	15%
10	Al(O*i*Pr)$_3$, *i*PrOH	reflux	28%	16%
11	$LiAlH_4$, ether	-78	45%	trace
12	$LiAlH_4$, ether	0	59%	trace
13	$LiAlH_4$, ether	20	56%	trace
14	$LiAlH_4$, ether	0	40% (1:1.5)	16%

This isolation was disclosed by Rabe and Kindler in 1939 and worked for Woodward and Doering in 1944. Williams and co-workers have discovered that the aluminum-power reduction by fresh reagent only gives trace amounts of quinine, while "aged" aluminum powder containing Al^{III} surface impurities gives "synthetically meaningful" yields. Further, they have provided solid experimental support that Woodward and Doering could have had difficulty reproducing the reported 12.3% yield of quinine from last step, while other reducing agents known in 1944, such as lithium aluminum hydride or the Meerwein-Ponndorf-Verley reduction, could have been used in the approach to quinine.

Finally, the conclusion by Seeman on the validity of the Rabe-Kindler work have solid experimental support which clears up any doubts initially raised by Stork in a letter to Woodward in 1944. Williams and co-workers stated at last: "*Our validation of the formal total synthesis of quinine as originally reported by Woodward and Doering in 1944 should serve to remove the blemish asserted on the reputations of Rabe and Kindler as well as those of Woodward and Doering.*"[17]

In the beginning of the 1960s, a group of Hoffman La Roche (Nutley, New Jersey) researchers under the leadership of Milan R. Uskokovic became interested in the synthesis of cinchona alkaloids. The initial strategies employed by Uskokovic and co-workers were similar to that of Woodward and Rabe (Figure 59). However, compared to Woodward's route, they had better steric control at key stages and overall yield. In the synthesis, the lithium anion of 6-methoxylepidine **232** was coupled with racemic *N*-benzoylmeroquinene methyl ester and the resultant ketone **233** was reduced to alcohol with DIBAL-H, which also removed the *N*-benzoyl protecting group. The diastereomeric alcohols were resolved with *d*-dibenzoyltartaric acid and the 3*R*,4*S* enantiomer was converted into the corresponding acetates **235** by a BF_3•Et_2O catalyzed acetylation. Then, the quinuclidine ring was formed by conjugate addition of the piperidine nitrogen atom to vinylquinoline intermediate, which was generated *in situ* by elimination of the acetate to

furnish a mixture of the previously known desoxyquinine **237** and desoxyquinidine **238** in a ratio of 57:43. The last step was interesting in that the hydroxyl group was introduced at C9 with the correct configuration (and a stereoselectivity of approximately 5:1) by an autooxidation with oxygen and potassium *tert*-butoxide.[20-22,253,254]



Synthesis of quinine by Uskokovic and co-worker in 1970. Reagents and conditions: a) 1.LDA, -78°C; 2. *N*-benzoylmeroquinene methyl ester (**233**; 78%); b) DIBAL-H (85%); c) BF_3•Et_2O, AcOH (96%); d) NaAcO, AcOH/benzene (79%); e) KO*t*Bu, O_2, *t*BuOH, DMSO (40%). LDA=lithium diisopropylamide.

Figure 59. Synthesis of quinine reported by Uskokovic and co-worker.

In 1974 Taylor and Martin approached quinine from 4-chloro-6-methxyquinoline **238**, via an olefin which was a nonisolable transient intermediate (Figure 60). Their method introduced alkyl and alkenyl groups into heterocyclic ring, involving the nucleophilic displacement of a leaving group by the transformation of the resultant hererocyclic ylide into alkyl- or alkenyl-substituted heterocycles. The olefin was converted into the mixture of desoxyquinine and desoxyquinidine by hydrolysis of the *N*-acetyl protecting group and spontaneous intramolecular Michael addition of the

piperidine nitrogen atom. The diastereomers of this mixture were oxidized using Uskokovic‟s procedure and the alkaloids isolated as the corresponding tartrates.[23,24]

In 1970 Gates and coworkers published a previous sequence (which was disclosed simultaneously with that of Gutzwiller and Uskokovic), which prepared the olefin from phosphorane **243** and aromatic aldehyde **242** (Figure 60). Then the olefin was transformed into the alkaloids in the same way as Uskokovic‟s approach.[25,255]

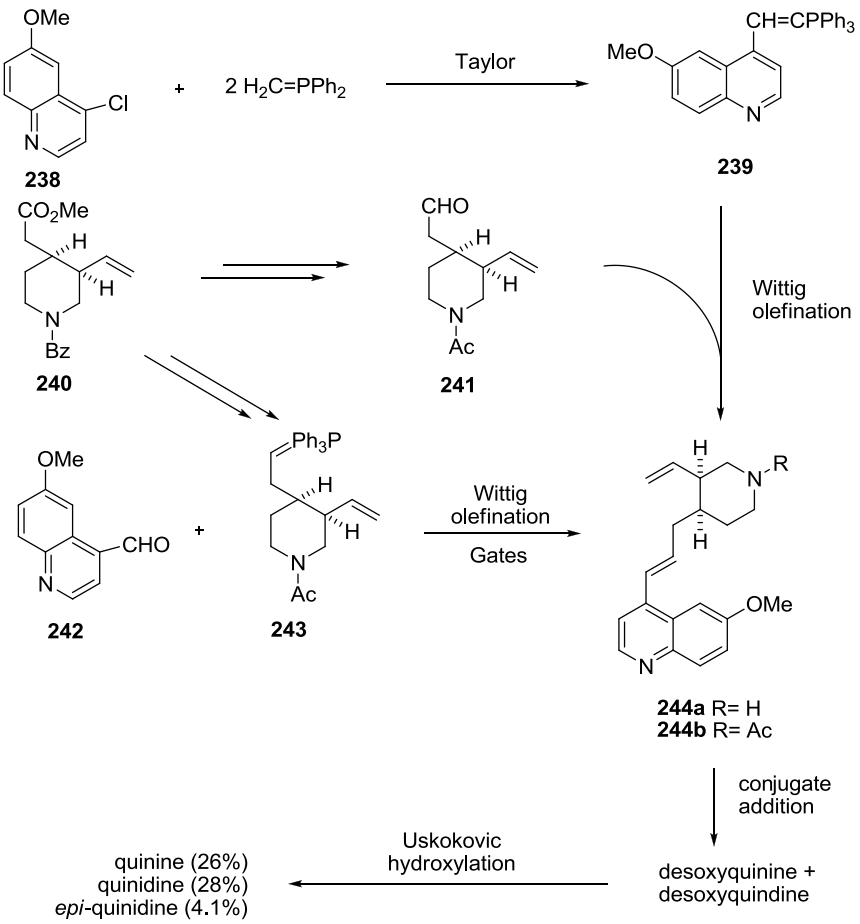
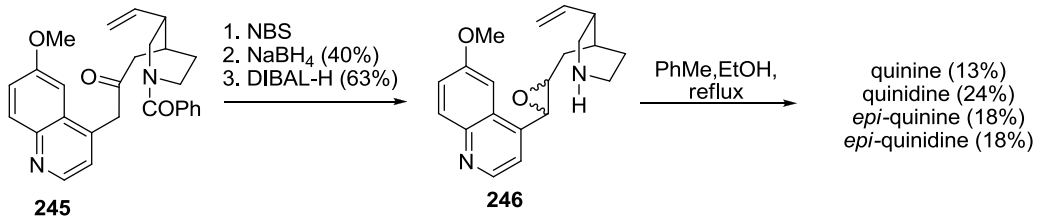


Figure 60. Synthesis of quinine reported by the research groups of Taylor and Gates.

In a modification of his previous synthesis, Uskokovic and co-workers also accomplished the key C8-N ring-closing reaction through the ring opening of an epoxide

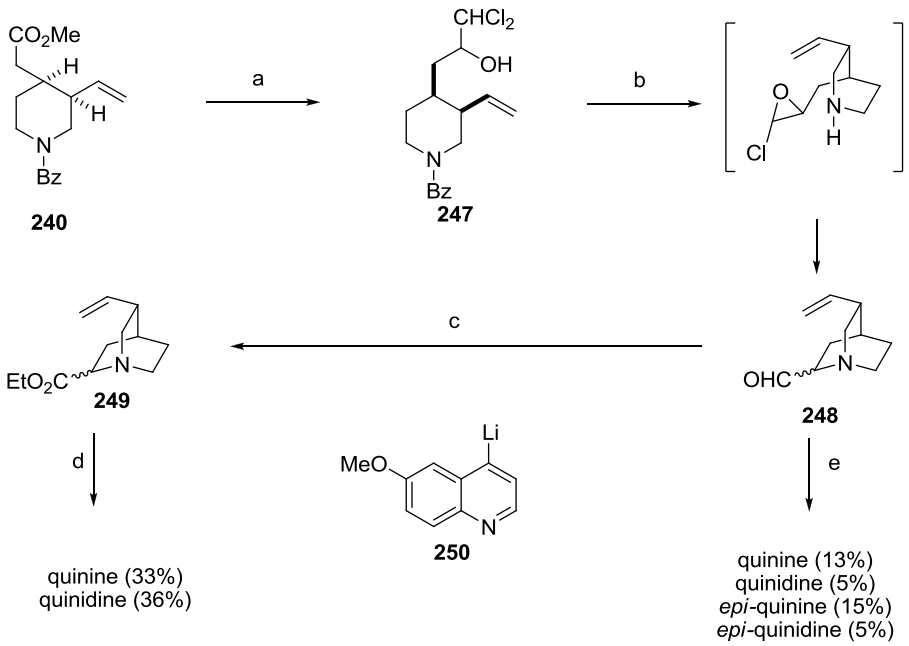
(Figure 61). This alternative sequence route would become a strategy for the fully controlled access to quinine two decades later. It started with known ketone **245**, which was prepared from active meroquinene. The epoxide was obtained by benzylic bromination with *N*-bromosuccinimde (NBS), followed by reduction of the α-bromoketone to a mixture of bromohydrins as well as spontaneous cyclization. The transform took place in 40% yield and all four possible epoxides were formed. Then, reductive removal of the *N*-benzoyl protecting group by DIBAL-H gave the desired epoxide **246**, which underwent nucleophilic ring opening and cyclization to give expected mixtures of the four possible diastereomers at C8 and C9.[22]



Synthesis of quinine by the amino epoxide ring closing approach by Uskokovic and co-worker in 1970.

Figure 61. Synthesis of quinine by Uskokovic and co-worker.

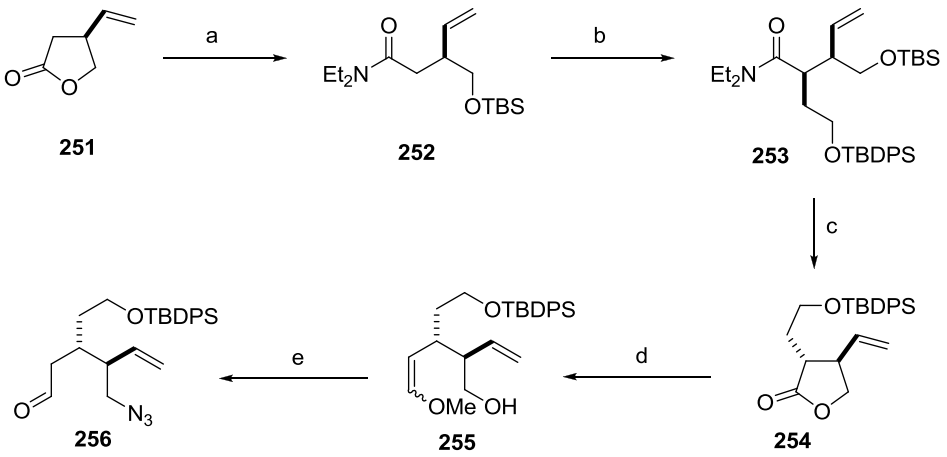
In 1978, Uskokovic and co-workers reported two slightly different syntheses of quinine using the novel C9-C4‟ approach (Figure 62). The key quinuclidine intermediates **248** and **249** were prepared by the aminochloroexpoxide cyclization. Aldehyde **248** was highly unstable and needed to be used immediately after its preparation, while ester **249** was more stable. The addition of organolithium **250** to aldehyde or ester furnished the mixture of alkaloids.[256,257]



Synthesis of quinine by the C9-C4' coupling approach by Uskokovic and co-worker(1978). Reagents and conditions: a) 1. DIBAL-H; 2. PhCOCl; 3. Cl_2HCLi (59%); b) KOH, benzene; c) 1. $AgNO_2$; 2. $EtOH/H^+$; d) 1. **250**, Et_2O, -78°C (30-40%); 2. DIBAL-H (59%); e) **250**, Et_2O, -78°C.

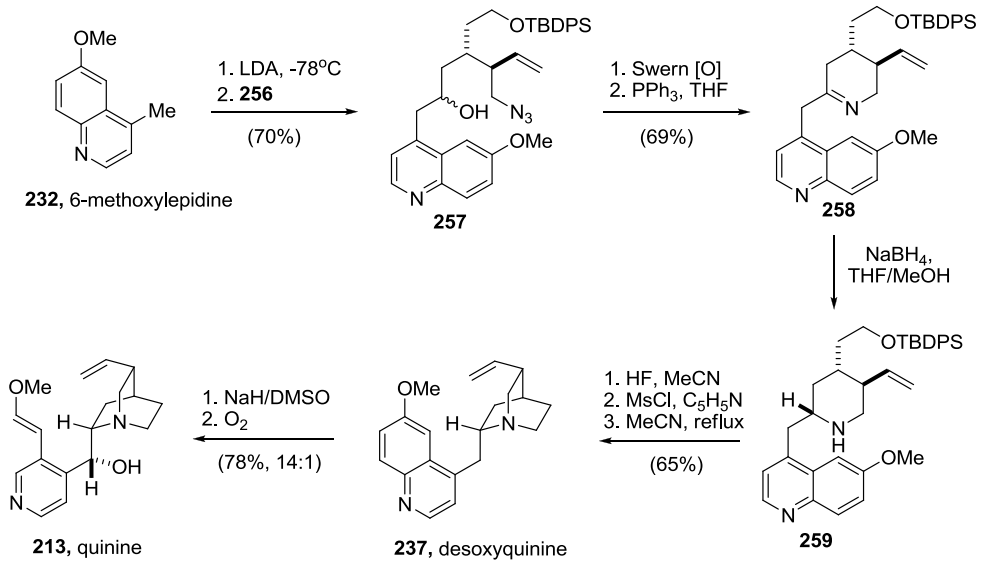
Figure 62. Synthesis of quinine by the C9-C4‟ coupling.

Professor Gilbert Stork of Columbia University has been one of the most prominent leaders in organic synthesis for over fifty years. He created a number of fundamental synthetic methods enriching the organic field, such as enamine and silyl enol ether carbon-carbon bond-forming methodologies and radical cyclizations. The starting material for his synthesis of the non-aromatic quinine framework was Taniguchi‟s lactone **251** (Figure 63).[26] The lactone was opened with a nucleophile to generate the related amide **252**. Then the C_2 side chain was introduced by enolate alkylation. Ring closure of **253** to generate lactone **254** was followed by reduction to the related lactols and subsequent Wittig homologation gave **255**. The primary alcohol underwent a Mitsunobu-type azidation.



Synthesis of quinine by Stork et al. by chemical manipulation of Taniguchi's lactone. Reagents and conditions: a) 1. Et_2NAlMe_2; 2. TBSCl, imidazole (79%); b) 1. LDA, -78°C; 2. $ICH_2CH_2OTBDPS$(79%, 20:1); c) 1. PPTS, EtOH; 2. xylene (93%); d) 1. DIBAL-H; 2. $Ph_3PCH(OMe)$ (93%); e) $(PhO)_2P(O)N_3$, PPh_3, DEAD; 2.5 N HCl (74%). DEAD=diethylazodicarboxlate, PPTS=pyridinium *p*-toluenesulfonate, TBS=*tert*-butyldimethylsilyl, TBDPS=*tert*-butyldiphenylsilyl.

Figure 63. Synthesis of compound **256** reported by Stork.



Synthesis of quinine by Stork et al.: The final steps. Ms=methanesulfonyl.

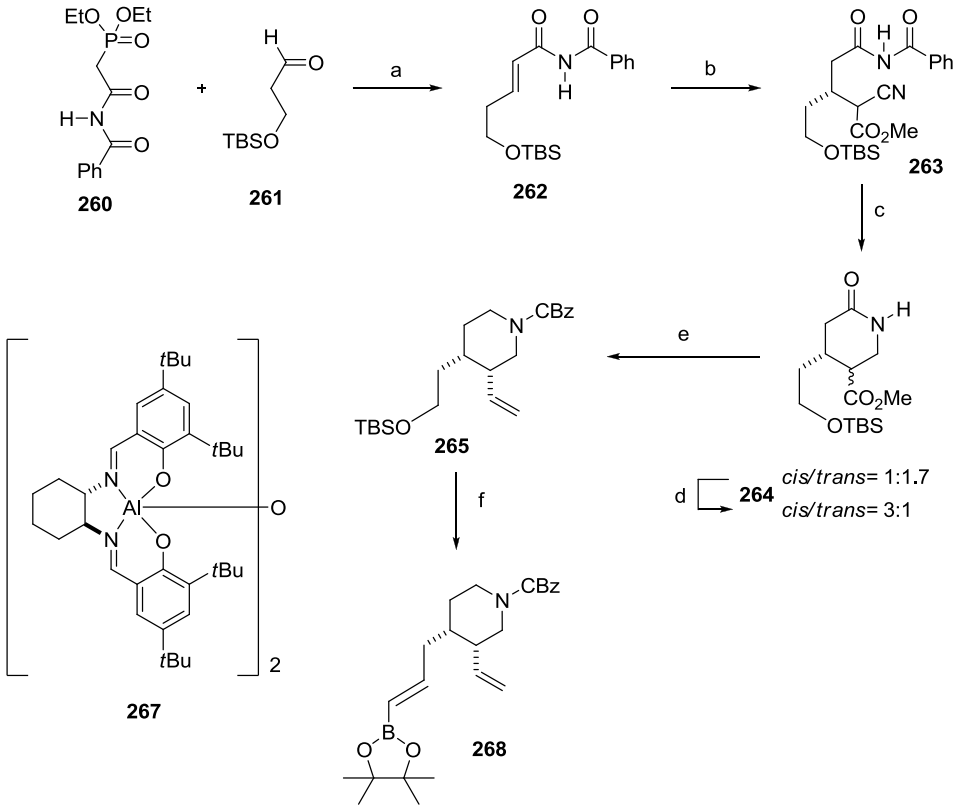
Figure 64. Synthesis of quinine reported by Stork.

Stork et al. coupled the 6-methoxylepidine anion with aldehyde **256** and oxidized the mixture of alcohols to the corresponding ketone (Figure 64). A Staudinger reaction with concomitant cyclization provided tetrahydropyridine derivative **258**. The key enantiospecific reduction of the tetrahydropyridine with sodium borohydride was employed. The silyl ether was then converted to mesylate followed by intramolecular cyclization to give, specifically and exclusively, desoxyquinine **237**, which was finally transformed into quinine by the autooxidation described by Uskokovic. More than 50 years after total synthesis by Woodward and Doering, Stork accomplished a modern stereocontrolled synthesis of quinine.[26]

Professor Eric N. Jacobsen from Harvard University is an outstanding chemist in the area of designing and discovering selective catalysts for use in organic synthesis. In 2004, his research led to a catalytic and highly stereocontrolled total synthesis of quinine and quinidine (Figure 65 and Figure 66).[27]

In their procedure, the protected aldehyde **261** underwent olefination with imidophosphonate **260** to give olefin **262** with high *trans* selectivity (Figure 65). Enantioselective conjugate addition of methyl cyanoacetate to **263** in the presence of (*S*,*S*)-(salen)-aluminum complex **267** (salen=*N*,*N*‘-bis(salicylidene) ethylenediamine dianion) gave **263**, and a hydrogenative lactamization with a Raney nickel catalyst furnished **264**. The *cis/trans* diastereomeric mixture (1:1.7) of esters was converted into a 3:1 *cis/trans* mixture by a selective deprotonation/reprotonation sequence. The Wittig olefination followed to install the vinyl group of compound **265**. The silyl protecting group was removed, followed by oxidation of the resultant alcohol to the corresponding aldehyde and olefination with dihalomethylboron pinacolate under Takai conditions to afford selectively the (*E*)-vinyl component **268**.

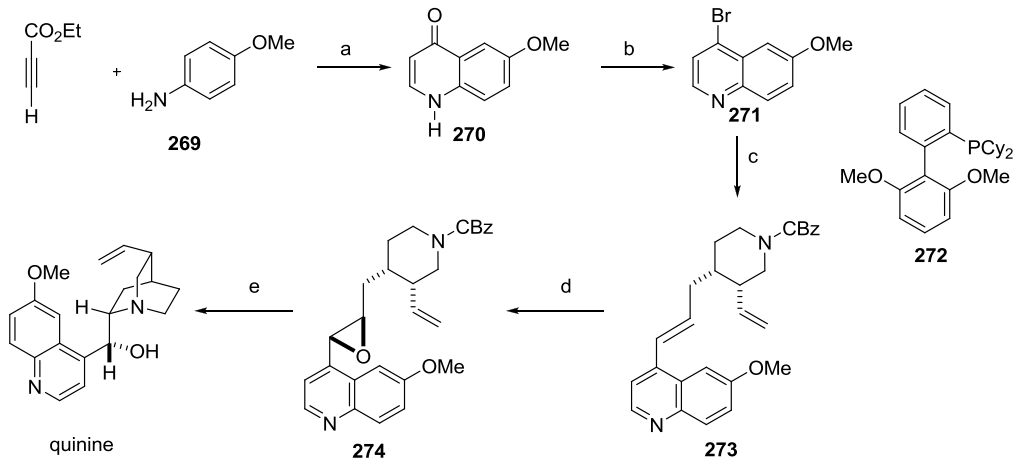
Bromoquinoline **271** and **268** were coupled through a Suzuki cross-coupling reaction in the presence of ligand **272** to produce vinyl quinolone **273** (Figure 66).



Synthesis of quinine by Jacobsen and co-wokers: Construction of the alicylcic fragment. Reagents and conditions: a) *n*BuLi, THF, -78°C->°C (84%, E/Z>50:1); b) $NCCH_2CO_2Me$, (*S,S*)-**267** (5 mol%), *t*BuOH, C_6H_{12}, RT(91%); c) Raney Ni, H_2, toluene/MeOH (3:1), 44 bar, 80°C, 12 h (89%); d) 1.LDA, THF, -78°C; 2.5% H_2O/THF, -78°C; e) 1. $LiAlH_4$, THF; 2. CBz_2O, Et_3N, CH_2Cl_2 (51%); 3. chromatographic separation of diastereomers; 4. TPAP, NMO, CH_2Cl_2; $Ph_3P^+MeBr^-$, KO*t*Bu, THF, 0°C (73%); f) 1. TBAF, THF; 2. TPAP, NMO, CH_2Cl_2 (86%); 3. Cl_2CHB (pinacolate), $CrCl_2$, LiI, THF (79%, E/Z>20:1). CBz_2O=dibenzyl dicarbonate, NMO=*N*-methylmorpholine-*N*-oxide, TBAF=tetra-butylammonium fluoride, TPAP=tetrapropylammonium perruthenate.

Figure 65. Synthesis of compound **268** reported by Jacobsen.

A Sharpless asymmetric dihydroxylation with the AD-mix-β reagent mixture and dehydrative cyclization gave the required epoxide **274** (Figure 66). Then microwave-assisted nucleophilic attack of the oxirane by the deprotected secondary amine accomplished the correct formation of the quinuclidine core and the synthesis of quinine.[27]



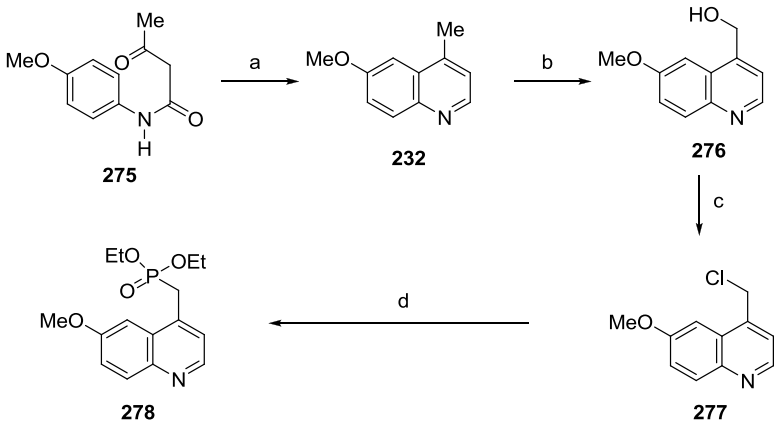
Syntheis of quinine by Jacobsen and co-workers. Reagents and conditions: a) 1. MeOH, RT, 12 h; 2. Dowtherm A, 250°C, 30 min (63%); b) Ph_3PBr_2, MeCN, microwaves, 170°C, 15 min (86%); c) **268**, $Pd(OAc)_2$, **272** (2.5 mol%), K_3PO_4, H_2O, THF, 16 h, RT (89%, E/Z>20:1); d) 1. AD-mix-β, $MeSO_2NH_2$, *t*BuOH, H_2O, 0°C (88%, dr > 96:4); 2. $MeCH(OMe)_3$, PPTS (cat.), CH_2Cl_2; 3. MeCOBr, CH_2Cl_2; 4. K_2CO_3, MeOH (81%); e) 1. Et_2AlCl, benzenethiol, 0°C->RT; 2. microwaves, 200°C, 20min (68%). Cy=cyclohexyl.

Figure 66. Synthesis of quinine reported by Jacobsen.

In the same year, a Japanese research group lead by Kobayashi disclosed another total synthesis of quinine (Figure 67 and Figure 68).[28] Their route is strongly based on previous experience from the research of Uskokovic, Taylor and Martin, and Jacobsen and co-workers.

Their novelty is in original and highly stereocontrolled synthesis of the meroquinene moiety. In this synthesis, allylic monoacetate **279** reacted with dimethyl malonate by palladium catalyst to give ester **280** a single enantiomer in almost quantitative yield (Figure 68). The ester was reduced, followed by the selective protection of the resultant primary alcohol to produce intermediate **282**. The vinyl ether **282** derived from **281** employed Claisen rearrangement and the resulting aldehyde **283** was reduced, followed by the protection with pivaloyl chloride to produce pivalate **284**. Ozonolysis of **284** with a reductive workup gave diol **285**. Then diol **285** was converted into the

diiodide **286** and treated with Mitsunobu conditions to construct the piperidine ring of **287** by dialkylation of benzylamine.



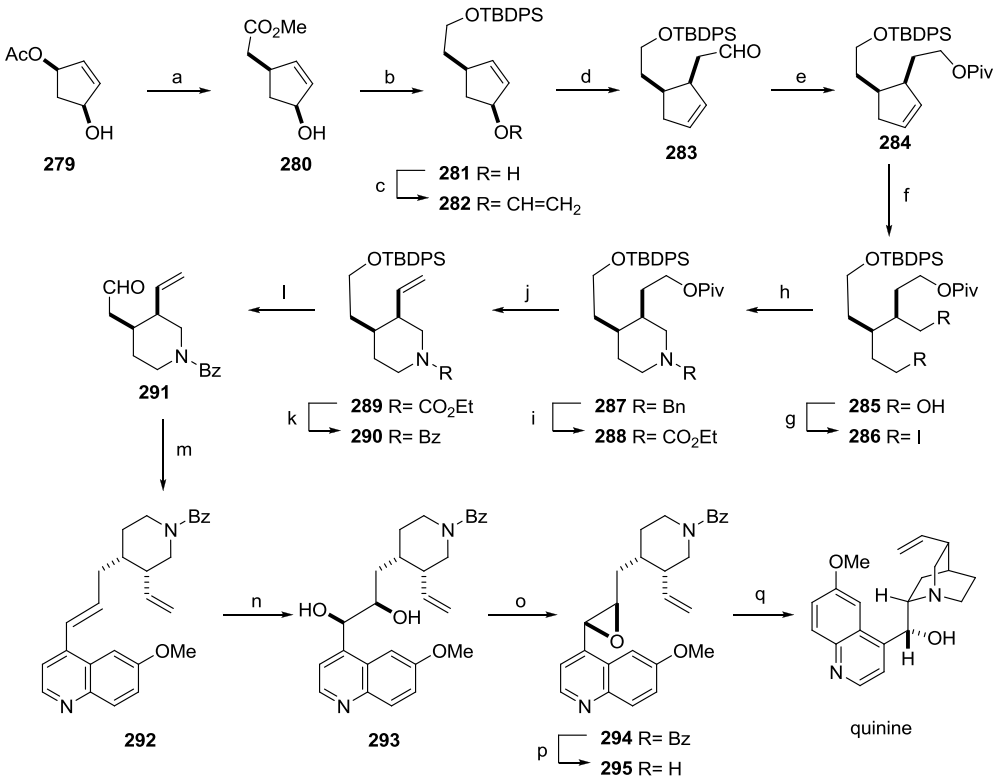
Synthesis of key imtermediate **278** by Kobayashi et al. Reagents and conditions: a) 1. H_2SO_4; 2. $POCl_3$; 3. Zn, AcOH (72%); b) *m*CPBA, CH_2Cl_2, RT; 2. Ac_2O, RT; 3. K_2CO_3, MeOH (43%); c) $SOCl_2$, CH_2Cl_2, reflux (71%); d) H-P(=O)$(OEt)_2$, *n*BuLi, THF (70%).

Figure 67. Synthesis of compound **278** reported by Kobayashi.

After replacement of the *N*-benzyl group of **287** with CO_2Et, it underwent selective deprotection of the pivalic acid ester, followed by phenylselenenylation of the free primary alcohol with Grieco‟s reagent and oxidative elimination of the corresponding selenoxide to furnish **289**. A second replacement of the *N*-protecting group to give **290** was completed by hydrolysis of the carbamate and benzoylation of the resultant free secondary amine. These changes in the nitrogen protecting group are necessary because selenoxide elimination cannot be successful on benzoyl derivatives. Then, desilylation of **290** and oxidation of the resulting primary alcohol provided the key intermediate **291**.

The aromatic component **278** was generated from keto amide **275** (Figure 67). The aldehyde **291** was reacted with the aromatic phosphonate **278** by using sodium hydride as the base and the product **292** treated with AD-mix-β to provide **293**. Diol **293**

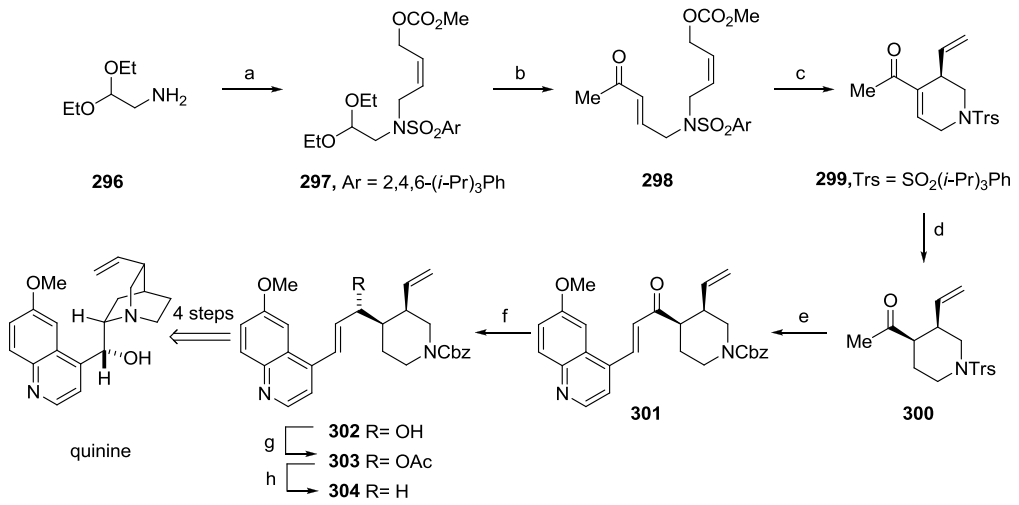
was transformed into the corresponding epoxide **294**, which was deprotected with DIBAL-H to furnish intermediate **295**. The last step was completed by nucleophilic ring opening of the epoxide under purely thermal conditions and furnished quinine.[28]



Synthesis of quinine by Acharya and Kobayashi. Reagents and conditions: a) 1. $CH_2(CO_2Me)_2$, *t*BuOK, $[Pd(PPh_3)_4]$ (cat.); 2. KI, DMF, 125°C (70%); b) 1. $LiAlH_4$; 2. TBDPSCl, imidazole (63%); c) H_2C=CHOEt, $Hg(OAc)_2$ (cat.); d) 190°C; e) 1. $NaBH_4$; 2. *t*BuCOCl, Et_3N, CH_2Cl_2 (66%); f) 1. O_3, *n*PrOH, -78°C; 2. $NaBH_4$ (81%); g) I_2, PPh_3, imidazole (88%); h) $BnNH_2$, dioxane (98%); i) $ClCO_2Et$, PhMe (99%); j) 1. NaOEt, EtOH; 2 *o*-NO_2-C_6H_4SeCN; PBu_3, THF; 3) 35% H_2O_2, THF (77%); k) 1. MeLi, 0°C; 2. BzCl (61%); l) 1.TBAF; 2. PCC (80%); m) **278**, NaH, THF, RT (82%); n) AD-mix-β, 0°C; o) $MeC(OMe)_3$, PPTS (cat.), CH_2Cl_2, TMSCl, K_2CO_3, MeOH (95%); p) DIBAL-H, PhMe; q) DMF, 160°C (66% from **294**). PCC=pyridinium chloroformate, piv=pivaloyl, Bn=benzyl.

Figure 68. Synthesis of quinine reported by Kobayashi.

In 2008, Krische‟s group at University of Texas at Austin reported a concise formal synthesis of (±)-quinine (Figure 69).[29]

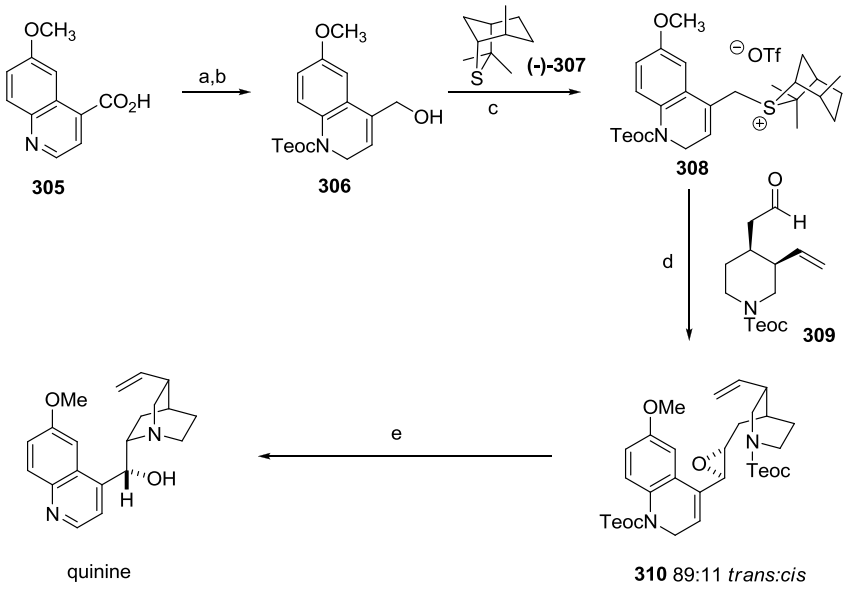


Formal synthesis of ( ) quinine by Krische and co-worker. Reagents and dconditions: a) 1. $ArSO_2Cl$, Et_3N, DCM, 0°C; 2. (*Z*)-4-hydroxy-2-butenyl methyl carbonate, DIAD, PPh_3, THF, 0°C (99% over 2 steps); b) 1. TFA, H_2O, $CHCl_3$,0°C; 2. Ph_3P=CHCOMe, DCM, RT (68% 2 steps); c) $Pd(PPh_3)_4$ (cat.), phosphine, *t*-AmOH, RT (68%); d) CuI, MeLi, DIBAL, THF-HMPA, -78°C (77%, dr>20:1); e) 1. Na, naphthalene, DME, -78°C; 2. CbzCl, Et_3N, DCM, 0°C (61% over 2 steps); 3) LHMDS, 6-methoxyquinoline-4-carbaldehyde, THF, -78°C; then Ac_2O, DMAP, DBU, -78°C to -40°C (64%); f) L-selectride, THF, -78°C (96%, dr > 20:1); g) Ac_2O, Et_3N, DMAP, DCM, 0°C (81%); h) $Pd(PPh_3)_4$, PBu_3, HCO_2H, Et_3N, THF, RT (78%). Cbz=carboxybenzyl.

Figure 69. Formal synthesis of quinine reported by Krische.

In his synthesis, sulfonylation of commercially available aminoacetaldehyde diethyl acetal **296** with 2,4,6-trisopropylbenzenesulfonyl chloride produced the sulfonamide, which was reacted with (*Z*)-4-hydroxy-2-butenyl methyl carbonate to furnish **297**. Hydrolysis of acetal **297** followed by Wittig olefination of the resulting aldehyde generated enone-allyl carbonate **298**. The merged Morita-Baylis-Hillman-Tsuji-Trost cycloallylation of the *N*-Trs protected enone-allyl carbonate **298** was completed with palladium catalyst and trimethyl phosphine to give *N*-Trs protected piperidine **299**. Diastereoselective conjugate reduction of **299** established the *cis*-piperidine **300** with the correct relative stereochemistry at C-3 and C-4. *N*-Trs protected *cis*-piperidine **300** was converted to the corresponding *N*-Cbz derivative, because reductive removal of the *N*-sulfonyl protecting group could not be performed in the presence of the quinolone. The *N*-Cbz derivative was transformed to enone **301** by aldol coupling-dehydration of 6-

methoxyquinoline-4-carbaldehyde. Enone **301** underwent 1,2-reduction under L-selectride in THF at -78 °C to produce allylic alcohol **302** as a single diastereomer. Conversion of allylic alcohol **302** to the corresponding acetate **303** followed by palladium-catalyzed, formate-mediated reduction provided the the C-7 deoxygenation **302** as a single alkene region and stereoisomer. Diene **304** was the key intermediate in Jacobsen"s synthesis of quinine. According to their strategy, quinine was accessible in 16 steps and 4% overall yield from commercial aminoacetaldehyde diethyl acetal.[29]



Synthesis of quinine by Aggarwal and co-workers. Reagents and conditions: a) BH_3•THF, RT 16 h (69%); b) TMS$(CH_2)_2$OH, triphosgene, K_2CO_3, THF, RT 1 h, followed by $NaBH_4$, H_2O, RT 4 h (79%); c) 2,6-di-*tert*-butylpyridine, Tf_2O, sulfide **(-)-307**, CH_2Cl_2, -45°C to RT 16 h (71%); d) KOH, CH_3CN/*t*-BuOH 15:1, 0°C, 24 h, (81%, 89:11 *trans*/*cis*); e) CsF, DMF, MW, 180°C, 15 min, then stir under O_2, RT 24 h (73%).

Figure 70. Synthesis of quinine by Aggarawal.

In 2010, Professor Aggarwal and co-workers at University of Bristol published the synthesis of quinine and quinidine through highly selective sulfur ylide mediated asymmetric epoxidation (Figure 70).[30] In the aromatic moiety, sulfonium salts are not

usually compatible with nucleophilic substituents within the same molecule because of a tendency toward polymerization. Thus, they masked the quinolone nitrogen as a carbamate and particularly chose trimethylsilylethyloxycarbamate (Teoc) group. In their synthesis, reduction of the known quinolone carboxylic acid **305** with BH_3•THF followed by carbamate formation and subsequent reduction with $NaBH_4$ provided alcohol **306**. The alcohol was activated with Tf_2O and treated with sulfide (-)-**307** to give sulfonium salt **308**. The sulfonium salt was reacted with aldehyde **309** (Although aldehyde has been prepared by Kobayashi, they obtained it more directly from quinine using known procedure.) under KOH in CH_3CN/*t*-BuOH to furnish epoxide **310** as an 89:11 separable mixture of *trans/cis* epoxides which were the only two diastereoisomers. Subsequent treatment with CsF in DMF for 15 min under microwave conditions caused the reaction cascade involving deprotection of the piperidine and quinolone rings and cyclization. Treatment of The crude reaction mixture with O_2 overnight completed oxidation of the quinoline ring and produce quinine in good yield.

Preparation of quinine has been a long-standing synthetic goal. Perhaps the most important reasons are to improve the organic field. Now organic chemistry has become well-established and advanced. It is still a high demanding area structures. Recently, atom economy, stereocontrol, overall simplicity, and environmental impact are becoming hot topics in the development of this field.

CHAPTER 3

A RADICAL ROUTE TO ALPHA, ALPHA-DISUBSTITUED ALPHA-AMINOESTERS

Retrosynthesis of α,α-Disubstituted α-Aminoesters

Recently, the carbon-carbon bond disconnection approach involving additions to imino compounds (Figure 71) has provided some notable accomplishments.[258] However, a significant obstacle to these additions, when strongly basic nucleophiles are used, is a competitive aza-enolization to form metalloenamines. Furthermore, the presence of other electrophilic functionality within such organometallic nucleophiles is often limited.

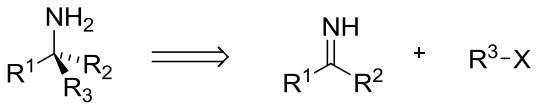


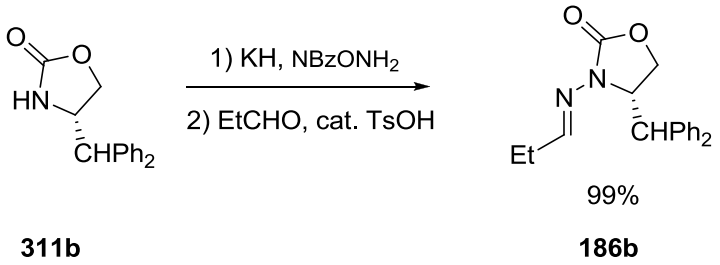
Figure 71. Retrosynthesis of chiral amines by C-C bond disconnection.

We have addressed this problem by developing Mn-mediated coupling of alkyl iodides with *N*-acylhydrazones,[167,205] exploiting conditions of notable versatility with respect to both coupling components.[259,260] Until now, these Mn-mediated coupling reactions have been limited to aldehyde-type acceptors.

In the Friestad group, we have made a great number of aldehyde-type acceptors in a successful and reliable way. It involves two steps: *N*-amination of commercially available chiral oxazolidinones and then condensation with aldehydes. In 2002, we reported the optimized methodology to prepare chiral *N*-acylhydrazones.[169]

The optimized procedure is that deprotonation of the commercially available chiral oxazolidinones by KH in dioxane was followed by treatment of O-(p-nitrobenzoyl)-hydroxylamine ($NbzONH_2$), giving *N*-amino-2-oxazolidinone. It was

condensed with aldehyde catalyzed by *p*-TsOH, affording the desired chiral *N*-acylhydrazones as single isomers. One example is showed in Figure 72.



311b **186b**

Figure 72. An example of preparation of chiral *N*-acylhydrazone.

Therefore, we have very efficient and reliable methodology to prepare aldimines and they are isolated as single isomers. There is no geometric isomerism issue on the C=N of aldehyde *N*-acylhydrazones, as they generally form as *E* isomers. Furthermore, wide studies have proved that aldehyde-type acceptors have high reactivity in different methodologies, such as addition of organometallic nucleophiles to C=N, Mannich reactions, Strecker reactions, radical additions, imine aziridination, Friedel-Crafts addition to imines, reduction of imine, and cycloadditions.[258]

Compared to aldehyde-type acceptors, ketimines are more challenging. We have only successfully prepared a few ketimines in our group (Table 7).[268] In that work, as a starting point for testing the configurational control in hydride additions of *N*-acylhydrazones, prochiral ketimine substrates were required. It is now well-documented that *N*-amino-2-oxazolidinones are reliably condensed with aldehydes to afford the corresponding *N*-acylhydrazones. It was expected that various ketones would condense with *N*-amino-4-benzyl-2-oxazolidinone under standard conditions.

One example is showed in Figure 73. Similar to the preparation of aldimines, *tert*-butyl ethyl ketone was condensed with *N*-amino-2-oxazolidinone in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene to obtain the ketone *N*-acylhydrazone. It has highly branched tertiary butyl substituent, and was isolated as a

single isomer (Figure 73). Ketones with less sterically demanding substituents would give the mixture of *E/Z* isomers, which can be difficult to separate by flash chromatography. We needed to explore an efficient and reliable way of preparation of our desired chiral ketimines.[268]

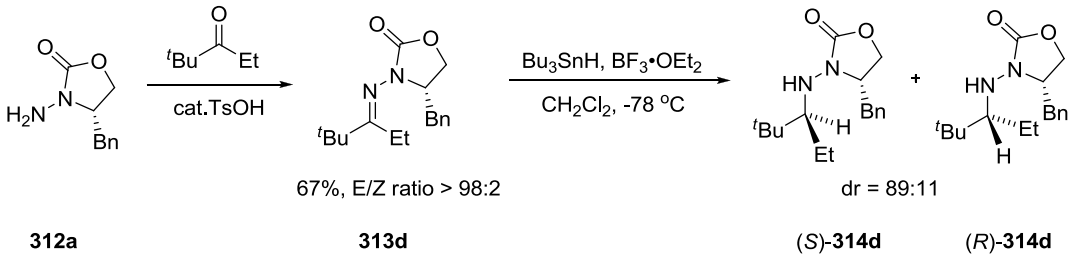


Figure 73. Preparation of ketone *N*-acylhydrazone.

Besides preparation of ketimines, their synthetic application has been limited by their reactivity. The reactions of ketimines have not been widely studied, especially intermolecular radical additons. Shono's group reported the electroreductive intermolecular coupling of ketoxime ethers with ketones.[283] In addition, the photoinduced intermolecular reaction of ketoxime ethers with α-alkoxy carbon radical was investigated by the group of Alonso.[157]

In our group, we have accomplished stereocontrol in hydride additions to ketone-derived chiral *N*-acylhydrazones.[268] Ketone hydrazones were reduced to diastereomeric mixtures of *N*-acylhydrazines (i.e. hydrazides) (Figure 73).

In 2005, nice work on ketimino radical acceptors was reported by the Takemoto group and has encouraged us.[163] The intermolecular carbon radical addition to ketimines was investigated using triethylborane as a radical initiator. The screening of reactive radical acceptors showed that methyl pyruvic hydrazone **315** and isatin hydrazone **317** exhibit good reactivities toward nucleophilic alkyl radicals. The reaction of **315** and **317** proceeded effectively even under aqueous reaction conditions. In the presence of

$BF_3 \cdot OEt_2$, the radical addition to the chiral ketimine **319** proceeded with good diastereoselectivities (Figure 74).

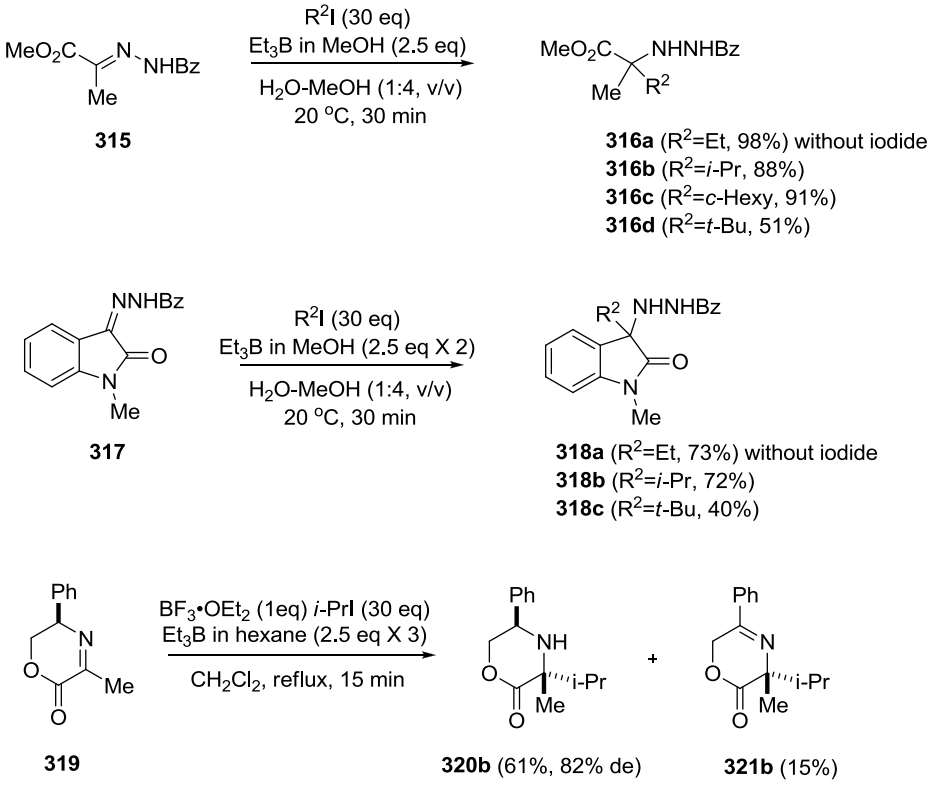


Figure 74. Intermolecular radical addition to **315, 317** and **319** by the Takemoto group.[163]

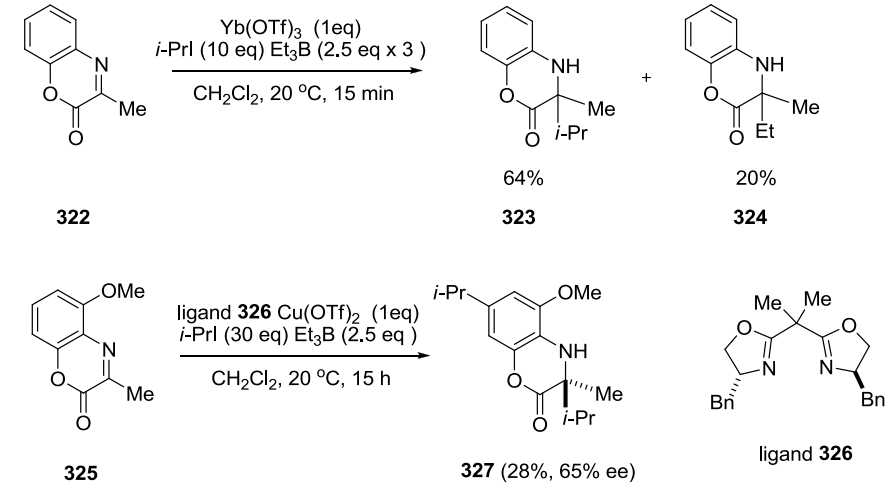


Figure 75. Intermolecular radical addition to **322** and **325** by the Takemoto group.[290]

In 2006, the Takemoto group also disclosed a chiral copper-mediated reaction of **325** with isopropyl radical under tin-free iodine atom-transfer conditions using *i*-PrI and Et_3B (Figure 75).[290] Although the competitive reaction with ethyl radical and isopropyl radical gave a complex mixture, 65% ee of diisopropylated product **327** was isolated in 28% yield.

Though we have exciting results from the Takemoto group, the reactivity of chiral ketimines with common auxiliaries in our group has not been widely studied. Besides, additions to ketone-derived imino compounds[261] have the potential to provide a diverse range of *tert*-alkyl amines not conveniently prepared by nucleophilic substitution. Here we exhibit the first examples of Mn-mediated coupling of diverse alkyl iodides with ketone-derived hydrazones in a route to α,α-disubstituted α-aminoesters (Figure 76).

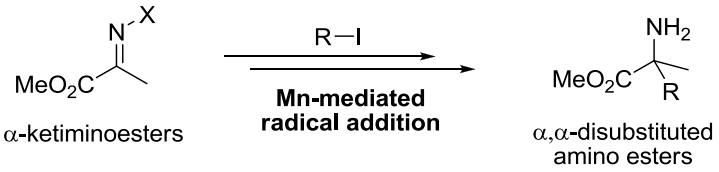


Figure 76. Our hypothesis on Mn-mediated radical route.

Intermolecular radical additions to aldehyde-derived imino acceptors have attracted growing attention, and a number of conditions may be used to achieve the additions.[147] However, radical additions to ketimine acceptors have not yet reached their full synthetic potential.[157,163] There were some examples involving addition of alkyl iodides (15-30 equiv) to ketimine acceptors in the presence of triethylborane (5.0-7.5 equiv) (Figure 77 and Figure 78).[163] Addition of simple commercial iodides (isopropyl, cyclohexyl, and *tert*-butyl) was accompanied by ethyl addition, N,C-dialkylation, and disproportionation side reactions (Figure 78). The ethylated imine **328a** would be obtained from intermediate **C**, as a result of a disproportionation reaction of the

intermediate radical **A** (Figure 78). Triethylborane worked as not only a radical initiator but also a radical chain terminator to trap the intermediate radical **A** to give adduct **B** and a chain-propagating ethyl radical. Therefore, a large amount of triethylborane is required for suppressing the formation of the ethylated imine **329a** (Figure 78). Then the reaction of hydrazones with an isopropyl radical was explored under iodine atom-transfer reaction conditions (Figure 74).

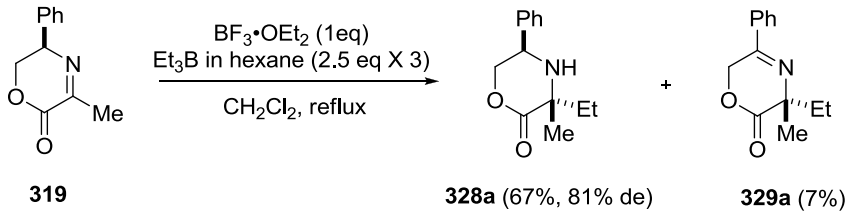


Figure 77. Intermolecular radical addition without iodides.

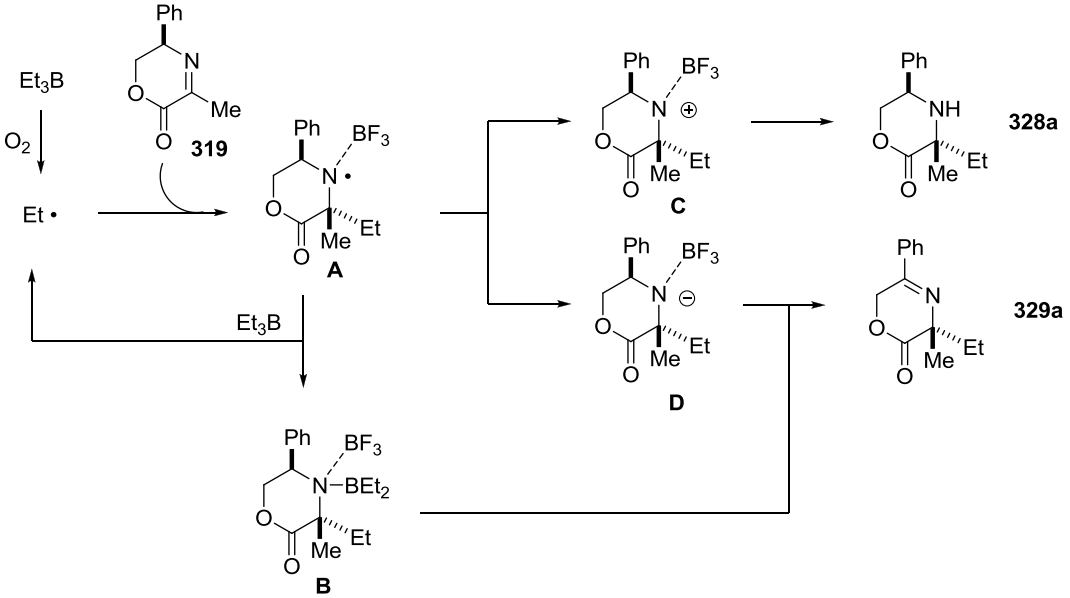


Figure 78. Proposed mechanism in the Takemoto group.[163]

During studies by Takemoto, Et_3B/O_2 were the initiators in their radical reactions and Et• was the radical produced from Et_3B/O_2 initiation. Thus, the competitive reaction with ethyl radical and isopropyl radical was observed. Though this was solved by addition of higher equiv (15 equiv) of isopropyl iodide, it is still our big concern. Furthermore, it may not be possible to use 15 equiv of a complicated alkyl iodide (Figure 97 in Chapter 4), especially if it takes a few steps to make.

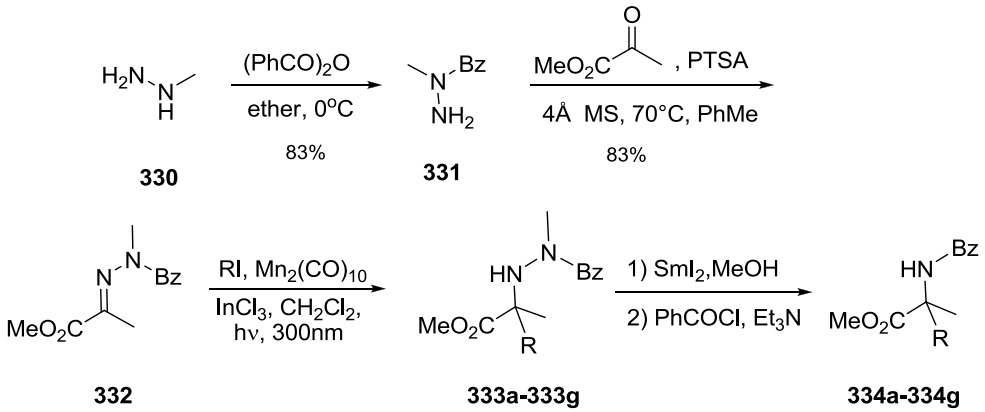
We hoped our Mn-mediated coupling method could broaden the scope with respect to the radical precursors (including primary and difunctional iodides), reduce the amount of iodide required, and avoid all of the side reaction noted in the earlier work.[163]

Addition to Achiral *N*-Acylhydrazone

For an initial examination of the radical addition to ketone hydrazones, a simple α-ketoester-derived *N*-acylhydrazone was prepared. Condensation of *N*-benzoyl-*N*-methylhydrazine **331** (Table 4) with methyl pyruvate afforded (*E*)-hydrazone **332** in 83% yield, with only trace amounts of the (*Z*)-hydrazone detected by ^{1}H NMR (*E*/*Z* > 99:1). In the ^{1}H NMR spectrum of **332**, the α-hydrogen of Me and γ-hydrogen of CO_2Me from (*Z*)-hydrazone were able to be assigned. Steric compression shifts (Δδ) of these two types of hydrogens are 0.32 and 0.04 ppm, which indicates (*E*)-hydrazone was favorable, according to our studies on the assignment of C=N geometry for *N*-acylhydrazones **340** (Table 6). With this radical acceptor in hand, Mn-mediated additions of various iodides to **332** were inspected (Table 4). Combining **332** with $InCl_3$ (2.2 equiv) in CH_2Cl_2, introduction of $Mn_2(CO)_{10}$ (1.1 equiv) and the iodide (5 equiv), and irradiation (300 nm, Rayonet) led to the alkyl adducts **333**. The N-H bond is likely formed by H-atom abstraction from solvent.[167,205] To examine the reactivity of **332** by our methodology, *i*-PrI was the preferred radical precursor. One reason is that it was commonly used in other radical methodologies, such as the Et_3B and O_2 initiation system (Figure 73), which will help us evaluate our radical system. The isopropyl radical is more stable than primary

radicals. Meanwhile, it worked very well on Mn-mediated radical addition to aldimines in our group (Table 1 in Chapter 2). Unsurprisingly, the isopropyl adduct **333b** was obtained in good yield (69%, Table 4, Entry 2).

Table 4. Mn-Mediated Addition of Alkyl Iodides to *N*-Acylhydrazone **332** and N-N Bond Cleavage



330 **331** **332** **333a-333g** **334a-334g**

Entry	R	yield of **333** (%)	yield of **334** (%)
1	Et	**333a,** 44	**334a,** 85
2	*i*-Pr	**333b,** 69	**334b,** 98
3	*n*-C_5H_{11}	**333c,** 63	**334c,** 79
4	*n*-$C_{12}H_{25}$	**333d,** 57	**334d,** 80
5	*i*-Bu	**333e,** 38[a] (51[b])	**334e,** 76
6	$TBSO(CH_2)_2$	**333f,** 49	**334f,** 95
7	$TBSO(CH_2)_4$	**333g,** 50[c] (73[b])	**334g,** 94

[a] Recovered **332**: 25%. [b] Yield in parentheses is corrected for recovered **332.**
[c] Recovered **332**: 32%.

One great advantage of our radical system is that various primary iodides (radical precursors) can be applied in addition to aldimine-type acceptors. Therefore, several alkyl iodides (EtI, *n*-$C_5H_{11}I$ and *n*-$C_{12}H_{25}I$) were investigated from short chain to long chain alkyl groups. The adducts were isolated in modest yields (Table 4, Entries 1, 3 and 4). β-Branched isobutyl radical was also able to be used under our reaction condition, though the yield was 38% (Table 4, Entry 5). To expand the potential synthetic use of Mn-

mediated radical addition to ketimines, we prepared functional iodides with *O*-TBS protecting groups. Addition products were isolated (Table 4, Entries 6 and 7), which gave us confidence to synthesize natural products in the future.

In our group, reductive N-N bond cleavage has been improved.[263] For synthetic access to chiral α-branched amines, cleavage of the N-N bond of the adduct hydrazines is required (Figure 79). According to our studies, N-N bond should be activated by acyl groups before reductive cleavage with SmI_2. There are two efficient options, trifluoroacetyl and benzoyl groups as shown in Figure 79. The hydrazine was acylated by lithiation and subsequent treatment of trifluoroacetic anhydride (TFAA) or benzoic anhydride. The *N*-benzoyl hydrazine or the *N*-trifluoroacetyl hydrazine was exposed to SmI_2 with MeOH as an additive to furnish the corresponding cleavage products (Figure 79).

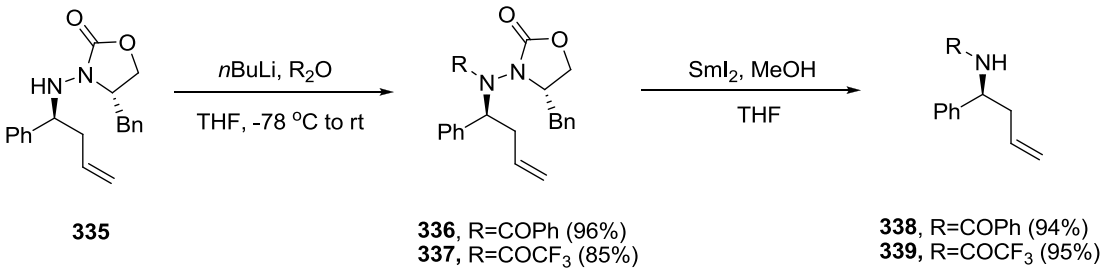


Figure 79. One example of N-N Bond cleavage of the adduct hydrazines.

Based on the studies of N-N bond cleavage in our group, we have already considered this step and had benzoyl group on achiral hydrazone that can activate N-N bond at the cleavage step. Subsequent treatment with SmI_2/MeOH in THF smoothly cleaved the N-N bonds of these adducts to provide the corresponding free amines.[262,263] We have tried to isolate those free amines, but, with the samarium residue, they are not able to be purified by flash chromatography. Fortunately, their *N*-benzoyl derivatives **334**

were well-suited for isolation (Table 4). The yields of this N-N bond cleavage reaction were consistently high, ranging from 76-98% for the two-step process.

Briefly speaking, Mn-mediated radical additions to achiral ketone-type acceptors gave moderate yields of adducts which could be smoothly converted to primary amines. The scope of our method could be extended to various iodides, including primary iodides and difunctional iodides.

Addition to Chiral *N*-Acylhydrazone

Asymmetric addition through this process was examined next. For this purpose we chose the chiral *N*-acylhydrazones derived from *N*-amino-2-oxazolidinones, which were successfully employed previously in a variety of reactions,[31] including stereocontrolled Mn-mediated radical additions to aldimine-type acceptors. We used a different amination reagent (monochloramine) to make *N*-amino-2-oxazolidinone, which is much cheaper than the $NbzONH_2$ we had used previously (Figure 72). Amination of the potassium salt of commercially available (*S*)-4-benzyl-2-oxazolidinone **311a** with a solution of monochloramine in methyl *tert*-butyl ether[284] gave a quantitative yield of the *N*-amino-2-oxazolidinone **312a**, which in turn was condensed with methyl pyruvate to give *N*-acylhydrazone **340** (*E/Z* 92:8). The *E/Z* ratio was measured by ^{1}H NMR. After removal of the minor (*Z*)-isomer via flash chromatography, the (*E*)-*N*-acylhydrazone **340** was obtained in 75% yield (Figure 80). Its purity was assessed by ^{1}H NMR.

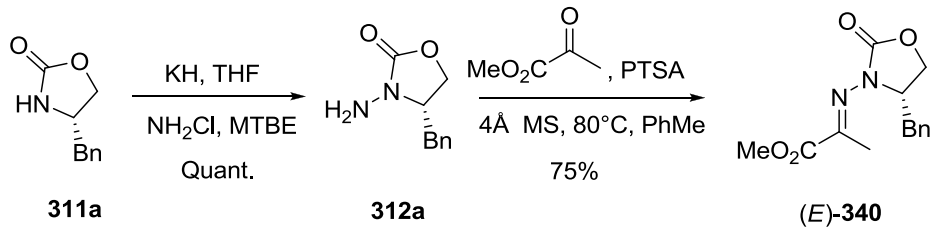


Figure 80. Preparation of (*E*)-**340**.

As we mentioned, assignment of C=N bond geometry was challenging for ketone-derived hydrazones. It can be achieved through comparison of ^{1}H NMR and ^{13}C NMR chemical shifts of the α-carbon of the *E* and *Z* isomers. Steric compression shifts are observed when a ketone is converted to ketone oxime or ketone hydrazone. Steric compression shifts in ^{13}C NMR spectroscopy arise from steric perturbations of carbon nuclei, and have been utilized in the studies of diverse organic compounds. Of relevance for this study is the ability of steric compression shifts to distinguish between carbons which have *cis* and *trans* relationships to the *N*-substituent of a C=N bond.[268]

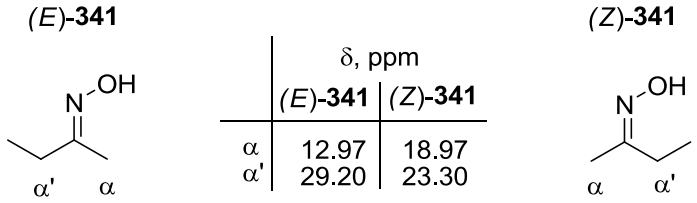


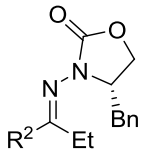
Figure 81. Example of an unsymmetrical ketone oxime.

One example of steric compression shifts in assignment of C=N bond geometry is presented in Figure 81. The *cis* α-carbon resonance is upfield from the *trans* α-carbon, and the difference of these chemical shifts is the steric compression shift.

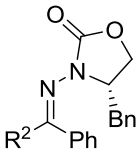
For ketone *N*-acylhydrazones obtained as mixtures of *E/Z* isomers, steric compression shifts (Δδ) could be observed clearly for one or both of the α-carbons. The key data used for assignment of C=N bond geometries of the hydrazones are found in Table 5. Upon assignment of structures **313a**-**313c** and **342a**-**342c** by ^{13}C chemical shifts according to the example above, the ^{1}H chemical shifts of the α-hydrogen within R^2 were also found to be reliable indicators of a *cis* or *trans* relationship of R^2 with the N-substituent on the C=N bond (i.e. the oxazolidinone). The *trans* methine (relative to the oxazolidinone) was found upfield of the *cis* methine in all compounds, with the differences in chemical shifts ranging from 0.45 to 0.84 ppm.

Table 5. Key NMR Data for Ketone *N*-Acylhydrazones

(R^2=^{i}Pr)
(R^2=^{c}C_5H_9)
(R^2=^{c}C_6H_{11})
(R^2=^{t}Bu)



313a-313d

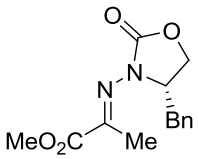


342a-342d

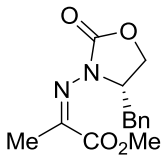
	α–Carbon of R^2 (δ, ppm)			α–Hydrogen of R^2 (δ, ppm)	
Hydrazone	R^2-*trans*[a]	R^2-*cis*[a]	Δδ (ppm)	R^2-*trans*[a]	R^2-*cis*[a]
313a	34.2 (*E*)	30.9 (*Z*)	3.3	2.68[b] (*E*)	3.24 (*Z*)
313b	45.4 (*E*)	42.2 (*Z*)	3.2	2.85 (*E*)	3.30 (*Z*)
313c	44.3 (*E*)	41.9 (*Z*)	2.4	2.36[c] (*E*)	3.13 (*Z*)
342a	37.3 (*Z*)	31.3 (*E*)	6.0	2.99[b] (*Z*)	3.52 (*E*)
342b	48.5 (*Z*)	42.5 (*E*)	6.0	3.12 (*Z*)	3.54 (*E*)
342c	47.6 (*Z*)	42.9 (*E*)	4.6	2.62[c] (*Z*)	3.46 (*E*)

[a] The designations *trans* and *cis* refers to the relationship between R^2 and the *N*-substituent. Therefore (*E*)-**313a-313c** and (*Z*)-**342a-342c** are designated here as *trans*.
[b] cf. corresponding aldehyde hydrazone (*E*): δ 2.60.
[c] cf. corresponding aldehyde hydrazone (*E*): δ 2.34.

Table 6. Key NMR Data for Ketone *N*-Acylhydrazones **340**



(*E*)-**340**
Major



(*Z*)-**340**
Minor

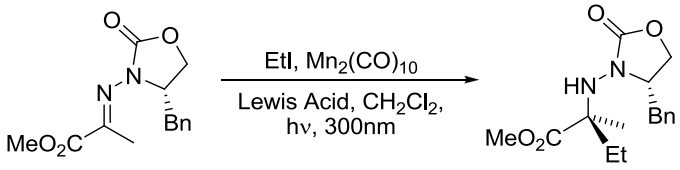
	α–Carbon of Me (δ, ppm)			α–Carbon of CO_2Me (δ, ppm)		
Hydrazone	Me-*trans*	Me-*cis*	Δδ (ppm)	CO_2Me-*trans*	CO_2Me-*cis*	Δδ (ppm)
340	21.8 (*Z*)	17.7 (*E*)	4.1	161.7 (*E*)	156.3 (*Z*)	5.4

	α–Hydrogen of Me (δ, ppm)			γ–Hydrogen of CO_2Me (δ, ppm)		
Hydrazone	Me-*trans*	Me-*cis*	Δδ (ppm)	CO_2Me-*trans*	CO_2Me-*cis*	Δδ (ppm)
340	2.30 (*Z*)	2.25 (*E*)	0.05	3.91 (*E*)	3.82 (*Z*)	0.09

According to our studies on assignment of C=N bond geometries of the hydrazones, the *cis* α-carbon resonance is upfield from the *trans* α-carbon (Table 6). In ^{13}C NMR, The *cis* methyl group (relative to the oxazolidinone) was found upfield of the *trans* methyl group, with a difference in chemical shift of 4.1 ppm. Similarly, the ^{13}C NMR data of CO_2Me indicated steric compression shift, which suggested the same configuration. ^{1}H NMR data is also a reliable indicator. Interestingly, hydrogens of both Me and CO_2Me groups indicated the same geometry. Fortunately, structures of *N*-acylhydrazones **340** were assigned by ^{1}H NMR and ^{13}C NMR and they can be separated by flash chromatography.

Addition of ethyl iodide to (*E*)-**340** using the Mn-mediated photolysis conditions as described above gave 66% yield of the ethyl adduct, with diastereomer ratio of 70:30 (Table 7, Entry 1). Screening a variety of Lewis acids showed that $InCl_3$, $Zn(OTf)_2$, $La(OTf)_3$, and $Mg(ClO_4)_2$ all led to similar yields of adduct **343a** (after correcting for recovered **340**), but interestingly, $La(OTf)_3$ and $Yb(OTf)_3$ inverted the diastereoselection (Table 7, Entries 2-7).

Table 7. Effect of Different Lewis Acids



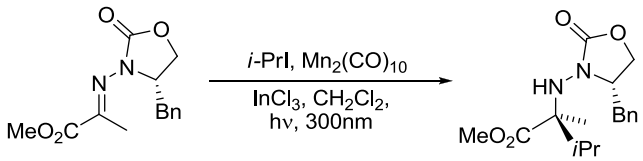
(*E*)-**340** **343a**

Entry	Lewis Acid	yield of **343a** (%)[a]	dr of **343a**
1	**$InCl_3$**	**66**	**70:30**
2	$In(OTf)_3$	25	51:49
3	$ZnCl_2$	<3	n.d.[b]
4	$Zn(OTf)_2$	53	63:37
5	$La(OTf)_3$	21 (58)	42:58
6	$Yb(OTf)_3$	25 (36)	34:66
7	$Mg(ClO_4)_2$	33 (57)	56:44
8	None	44 (49)	55:45

[a] Yield in parentheses is corrected for recovered (*E*)-**340.** [b] Not determined.

With stereocontrol at modest levels and subject to inversion with different Lewis acids, these observations were sharply in contrast to prior work involving additions to aldimines. Thus it was interesting to look at the role of the Lewis acid. Without Lewis acid, (*E*)-**340** exhibited low selectivity in ethyl addition (Table 7, Entry 8). Isopropyl addition occurred with much higher selectivity; in this case the absolute configuration of adduct **343b** was determined by crystallography (Table 8, Entry 1).[293] The stoichiometry of the Lewis acid was varied, illustrating the importance of at least 2 equiv of Lewis acid for effective stereocontrol (Table 8).

Table 8. Effect of the Amount of $InCl_3$



(*E*)-**340** **343b**

Entry	$InCl_3$ (equiv)	yield (%)	dr
1	**2.2**	**85**	**92:8**
2	1.2	70	82:18
3	0.5	54	80:20
4	0.2	50	74:26

The evidence above suggests the possibility of competitive binding of Lewis acids to the ester functionality of (*E*)-**340** (Figure 82, **A**) in addition to the two-point binding of the *N*-acylhydrazone. It is hard to say if either chelation **A** or **B** is favorable under our reaction condition. We may have both types of chelation in this system. In type **A**, Lewis acid chelated with the ester functionality and the N-N could rotate freely, which would provide species **C** (Figure 83). In **C**, *Si* face of C=N was blocked, which would produce the different configuration from Type **A** and **B** (Figure 82 and 83). Type **B** is the one that can control desired stereoselectivity (Figure 82**, B**) with Lewis acid chelated with

carbonyl group from chiral auxiliary and with the C=N nitrogen. In this type, N-N bond was locked and the acceptor was divided into two faces. The *Re* face was blocked by benzyl group from chiral auxiliary and radicals are allowed to attack C=N from *Si* face (Figure 82**, B**). In light of this, Lewis acids of higher coordination number might be expected to offer anomalous results. What may happen is that lanthanide Lewis acid could chelate with two or more *N*-acylhydrazone molecules by type **A**, which would adjust steric effects in space. That may force the rotation of N-N bond and block the *Si* face of C=N bond. Thus the inversion of stereocontrol with lanthanide Lewis acids is not surprising.

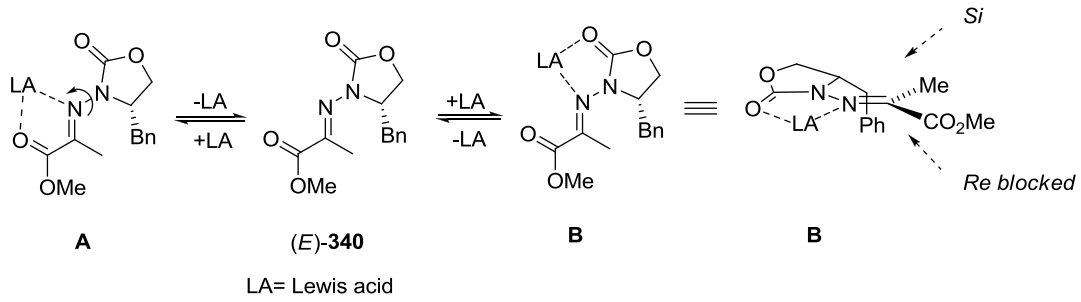


Figure 82. Two types of chelation.

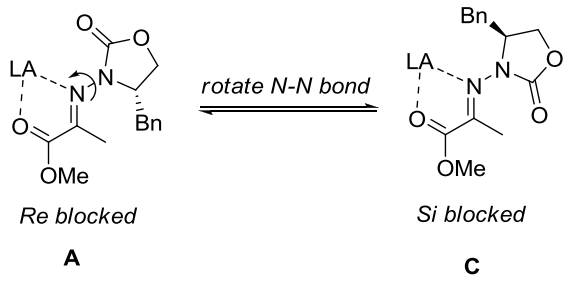
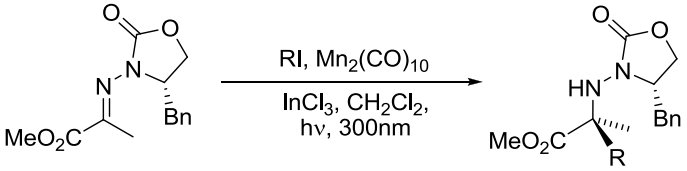


Figure 83. N-N Rotation of type **A** (Figure 82).

With this chiral radical acceptor in hand, Mn-mediated additions of various iodides to (*E*)-**340** were next examined. Only addition of isopropyl iodide provided the corresponding adduct in 85% yield with diastereomer ratio of 92:8 (Table 9, Entry 2). Additions of primary iodides and difunctional iodides gave the modest selectivity.

Table 9. Mn-Mediated Addition of Alkyl Iodides to Chiral *N*-Acylhydrazone.



(*E*)-**340** **343a-h**

Entry	R	yield of **343** (%)	dr of **343**
1	Et	**343a,** 66	70:30
2	***i*-Pr**	**343b, 85**	**92:8**
3	*n*-C_5H_{11}	**343c,** 60 (77)	68:32
4	*n*-$C_{12}H_{25}$	**343d,** 37 (58)	69:31
5	*i*-Bu	**343e,** 35 (49)	79:21
6	$TBSO(CH_2)_2$	**343f,** 36 (47)	69:31
7	$TBSO(CH_2)_4$	**343g,** 25 (32)	73:27
8	CH_2Cl	**343h,** 33 (48)	85:15

Yield in parentheses is corrected for recovered *(E)*-**340.**

The Hammond-Leffler postulate may help us explain our observation. The isopropyl radical is more stable than the ethyl radical. Thus, the postulated transition state from isopropyl radicals (Figure 84, line b) and the acceptor has the lower free energy than that from ethyl radicals (Figure 84, line a), by the facts (the persistent radical effect) that stabilize the secondary radicals. In isopropyl addition, the transition state showed in Figure 84 was favorable during the reaction, with **B** type chelation (Figure 82), which can control the diastereoselectivity. The diastereoselectivity would be expected to be enhanced in such a scenario because the transition state is later on the reaction coordinate, bringing the radical closer to the stereocontrol element. However, the transition state of ethyl addition might not be favorable. The other types of chelation

would have more chance to occur (Figure 82, **C**), which would decrease diastereoselectivity. The same situation happens to other different primary radical additions.

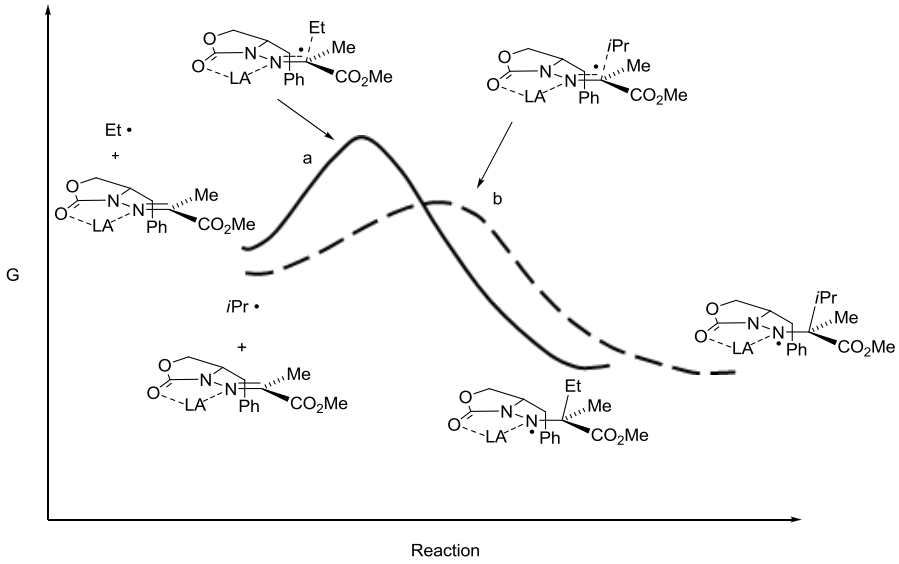


Figure 84. Hammond-Leffler postulate on our radical reaction.

As we discussed above, an acyl group was required to activate N-N bond before it was cleaved. Two options are trifluoroacetyl group and benzoyl group. However, benzoyl derived amino ester ((*S*)-(+)-**334b**) is a known compound, which allows us to identify the configuration easily.

Though there is an ester moiety in addition products, there is no α protons relative to ester moiety which is acidic enough to react with *n*-BuLi. In our case, only N-H hydrogen can be deprotonated by that strong base and furthermore, addition of butyl groups to the ester was not observed. The N-N bond cleavage was achieved upon sequential treatment of isopropyl adduct **343b** with *n*-BuLi, benzoic anhydride, and SmI_2/MeOH (Figure 85). This sequence afforded the known benzamide (*S*)-(+)-**334b** in good yield, confirming the assigned configuration. Although this N-N bond cleavage

employed the benzoyl group for purposes of chemical correlation of **334b**, the more synthetically useful trifluoroacetyl group can also be effective for N-N bond activation.

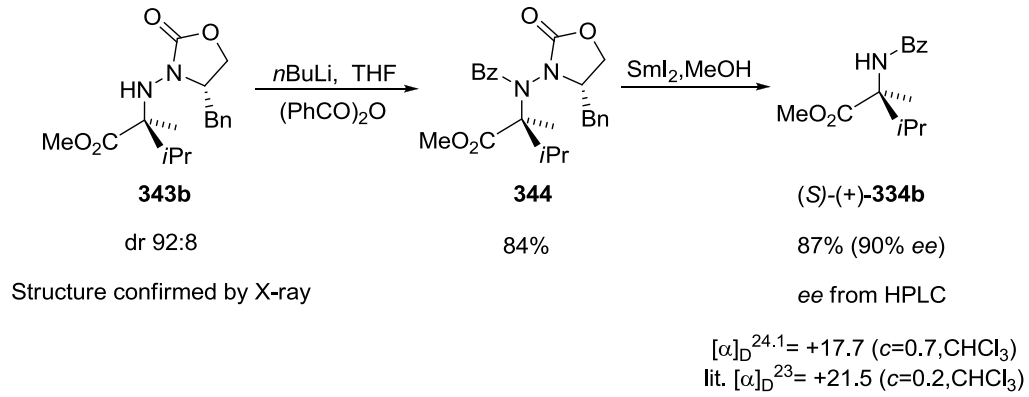


Figure 85. The N-N bond cleavage of **343b**.

Mechanism Discussion

According to the above observation and experience on additions to aldimine-type acceptors, we proposed a similar mechanism. The photolysis of $Mn_2(CO)_{10}$ in the presence of alkyl iodides generates alkyl radicals, which attacks the ketimine-type acceptor to afford the corresponding addition products. The difference from additions to aldimine-type acceptors is that when combining ketimines with $InCl_3$, there may be two possible types of chelation (Figure 82). The chelation on the right can control stereoselection (Figure 82, **B**), while the left one (Figure 82, **A**) can't restrain the rotation of N-N bond of (*E*)-**340**, which may decrease the stereoselectivity.

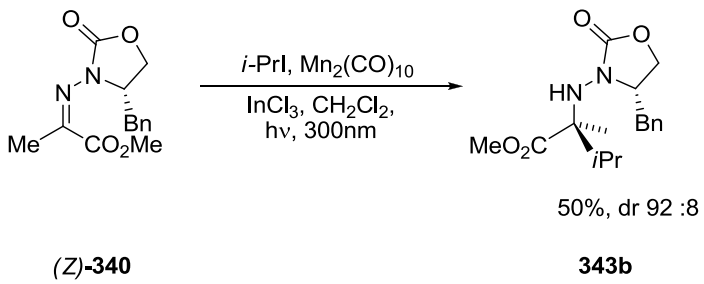


Figure 86. Isopropyl radical addition to (*Z*)-**340**.

Interesting, isopropyl radical addition to (*Z*)-**340** generated the same configuration (determined by ^{1}H NMR) of the new chiral center as (*E*)-**340** (Figure 86). This suggests that *Z* isomer could be interconverted to *E* isomer by rotation of C-N bond with Lewis acid. The *E* isomer is favorable since there is less steric demand by the Me group in comparison with CO_2Me (Figure 87). Then diastereoselectivity was controlled by chelation of type **B** showed on Figure 82. During the *E/Z* interconversion, some starting material would decompose, which can explain why the yield of addition to *Z* isomer is lower than *E* isomer.

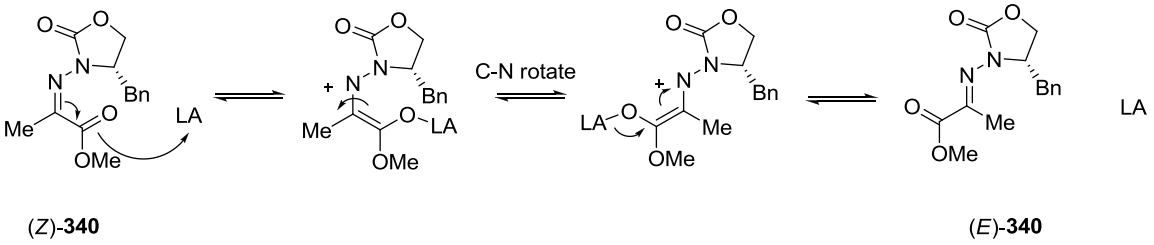


Figure 87. *E/Z* interconversion with Lewis acid.

In summary, we have exhibited the efficient radical route to synthesis of α,α-disubstituted α-aminoesters. Efforts are still needed to extend the scope of asymmetric additions to primary iodides and difunctional iodides. A future solution might be to change auxiliaries by more bulky groups, or to change the ester moiety of chiral *N*-acylhydrazone to other functional groups, which are precursors of carboxylic acids and retain the reactivity for C=N bond, or to apply chiral Lewis acids to additions with achiral ketimines.

CHAPTER 4

FORMAL SYNTHESIS OF QUININE

Retrosynthesis of Quinine

The well-known antimalarial properties of quinine have inspired synthetic efforts toward quinine since the very early days of natural product synthesis. We have reviewed those important synthetic accomplishments in Chapter 2.

Quinine attracted our interest in the course of our program to develop new C-C bond construction approaches to chiral amines.[31] Asymmetric preparation of amines presents challenges in the synthesis of nitrogen-containing natural products, particularly alkaloids and peptides derived from unusual amino acids. While numerous indirect methods involving C-N bond construction are available, an attractive alternative is a C-C bond construction via addition to the C=N of carbonyl imino derivatives,[32-39] which promises to efficiently introduce the stereogenic center and carbon-carbon in one step. Since two or three C-C bonds could be chosen for disconnection in the retrosynthetic direction, an ideal methodology for this bond construction would avoid limitations on the scope in both precursors. Developing such an ideal methodology, we have disclosed Mn-mediated free radical additions to chiral *N*-acylhydrazones, achieving excellent acyclic stereocontrol under mild reaction conditions compatible with complex multifunctional precursors. Quinine is an ideal challenge to exhibit the applicability of these Mn-mediated coupling reactions to synthetic problems in a multifunctional molecular setting.

We introduced novel chiral *N*-acylhydrazones[169] and their use in several types of addition reactions; they are good chiral imino acceptors for Lewis acid-promoted[168] addition of carbon-centered radicals,[170,171] allylsilanes, and trimethylsilylcyanide[172] under mild conditions. Recently, several accomplishments have been reported by using chiral *N*-acylhydrazone for asymmetric α-alkylation.[264] There were examples of highly stereoselective free radical coupling of alkyl iodides and chiral *N*-acylhydrazones.[169-

[174,265-268] However, applications to total synthesis have lagged because versatility of methods with respect to both radical and acceptor are limited.[147,152,163,165,173,269-273] One key problem which persists is the difficulty in achieving synthetically useful yields in the addition reactions of primary alkyl iodides.

Based on our studies, photolysis of dimanganese decacarbonyl has shown great promise for generating a broad range of alkyl radicals, and has expanded the synthetic potential of radical additions to imino compounds.[167,205,259] Few synthetic methods gain the trust of the bench chemist without demonstrations of the methodology in natural product synthesis, where multifunctional precursors challenge scope and versatility. Thus, an application of Mn-mediated coupling of alkyl halides and *N*-acylhydrazones to the preparation of a synthetically challenging alkaloid target became the next key goal in this program.

Our approach to quinine focuses on strategic application of our Mn-mediated hybrid radical-ionic annulation, a radical-polar crossover reaction,[271,274-279] which had previously been described for preparation of simple pyrrolidines and piperidines.[170,171]

For simple pyrrolidines, we have prepared them in two ways (Figure 52 in Chapter 2): addition of 3-chloro-1-iodopropane to propionaldehyde hydrazone **186b** via 3-chloropropyl radical addition and *in situ* nonradical cyclization, and ethyl radical addition to hydrazone **186h** with the 3-chloropropyl group. They gave us the pyrrolidines **198R** and **198S** (Figure 52 in Chapter 2), which have different configurations in five member ring. These suggested to us that radical-ionic annulation is potentially useful in chiral amine synthesis and we have flexible choices for the coupling partners to achieve desired configuration.

The simple piperidine alkaloid coniine was obtained by our Mn-mediated radical addition.[170,171] Radical addition of 4-chlorobutyl iodide to **186c** produced **199** with high diastereoselectivity (Figure 53 in Chapter 2). Though *in situ* annulation could not occur, we could still produce piperidine ring through two routes. The first is that cyclization was

accomplished under Finkelstein conditions, giving the piperidine derivative (*R,S)*-**200**, and reduction with BH_3•THF afforded (*R*)-coniine, which was isolated as the *tert*-butyl carbamate (*N*-Boc) derivative (Figure 53 in Chapter 2). The second is that, removal of the chiral auxiliary by benzoylation of hydrazine and treatment by SmI_2, then Finkelstein reaction and base treatment of the iodide furnished *N*-benzoyl (*R*)-coniine **204**. These results suggested to us that our Mn-mediated radical addition has practical potential in asymmetric amine synthesis.

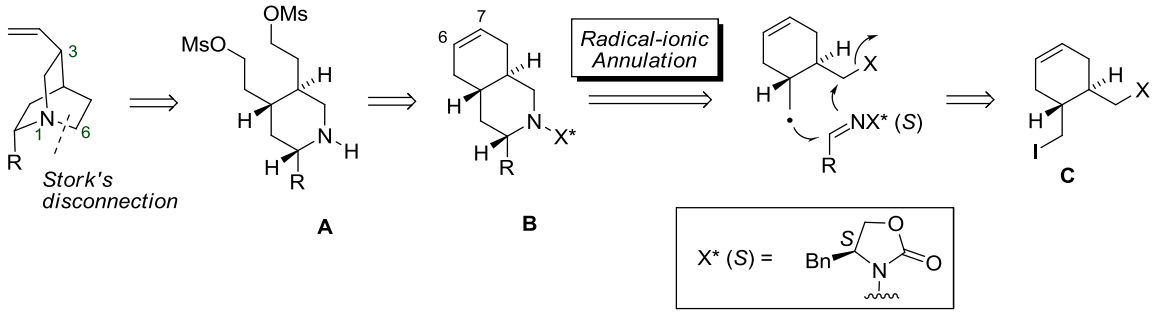


Figure 88. Initial synthetic strategy.

In our initial synthetic strategy, using Stork's disconnection of the *aza*-bicyclo[2.2.2]octane ring system suggested a 2,4,5-trisubstituted piperidine precursor **A** (Figure 88), which would be derived from oxidative cleavage of the C6–C7 bond of an octahydro-isoquinoline such as **B**. We envisaged an efficient access to the isoquinoline ring system through Mn-mediated radical addition to construct either of the two C–C bonds at the C3 stereogenic carbon. The stereoselective radical addition would be followed by closed-shell S_N2 displacement of a leaving group X by the imino nitrogen to complete the piperidine heterocycle.

Dr. Jun Qin in our group started to test these hypotheses with preparation of an iodide encompassing the structural features of **C**.[289] The multifunctional iodide was obtained from the diester **345** (ROH = (–)-menthol) which was acquired using the known enantioselective Diels-Alder reaction of dimenthyl fumarate[285] (Figure 89).

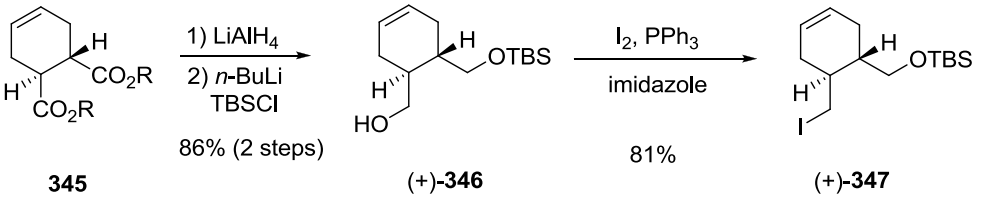


Figure 89. Preparation of the iodide coupling partner by Dr. Qin.

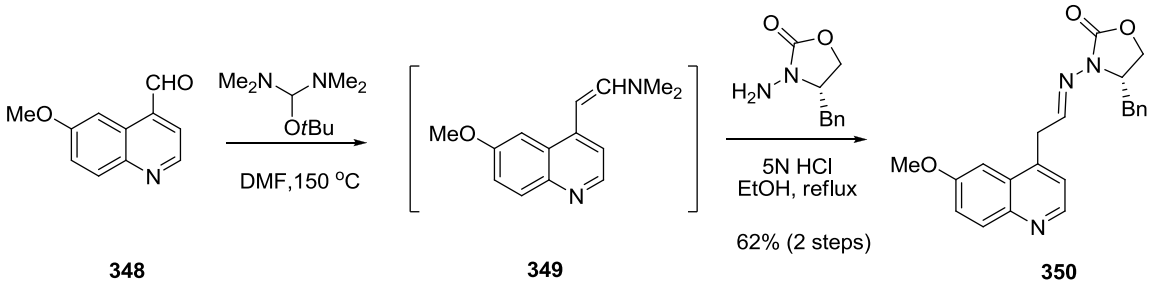


Figure 90. Preparation of the chiral *N*-acylhydrazone by Dr. Qin.

The radical acceptor, *N*-acylhydrazone **350**, was achieved by condensation of *N*-amino-2-oxazolidinone with enamine **349** derived from aldehyde **348** containing the 6-methoxyquinoline (Figure 90).

With hydrazone **350** now available, the stage was set to attempt the $Mn_2(CO)_{10}$-mediated coupling with iodide (-)-**347**. Unfortunately, there was no coupling product observed (Figure 91). Thus, Dr. Qin did a series of control experiments with different *N*-

acylhydrazones containing phenyl, *p*-methoxyphenyl, and 4-pyridyl substituents (Figure 92). The conclusion was that the basic nitrogen of the aromatic rings in hydrazones **350** and **352c** interfered with the Mn-mediated coupling reaction. Therefore, the 6-methoxyquinoline should be installed in the molecule at a later step.

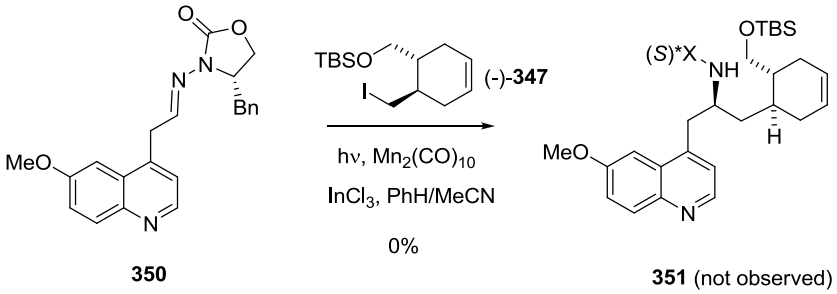


Figure 91. Initial radical coupling.

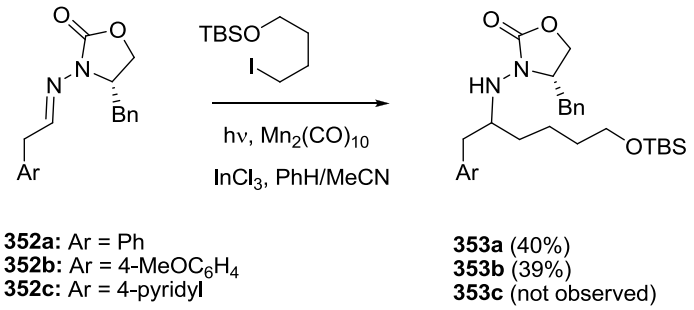


Figure 92. Control experiments for radical coupling step.

Right now, the construction of the azabicyclo[2.2.2]octane (quinuclidine) ring system was the key issue to be addressed. Dr. Chandra Sekhar Korapala made a great contribution on this key radical coupling step. During his investigation, wherever the cyclohexene moiety is (in the multifunctional iodide or the *N*-acylhydrazone), the yield never exceeded ca. 50% (Figure 93). Then, a saturated analog (±)-**359** was subjected to

our Mn-mediated radical coupling. Now without the alkene functionality, the yield was increased to 67% without any optimization (Figure 93).[260] The conclusion is that alkene moiety in (+)-**347** or **357** interfered with the Mn-mediated coupling reaction. We should use another functional group instead of alkene functionality.

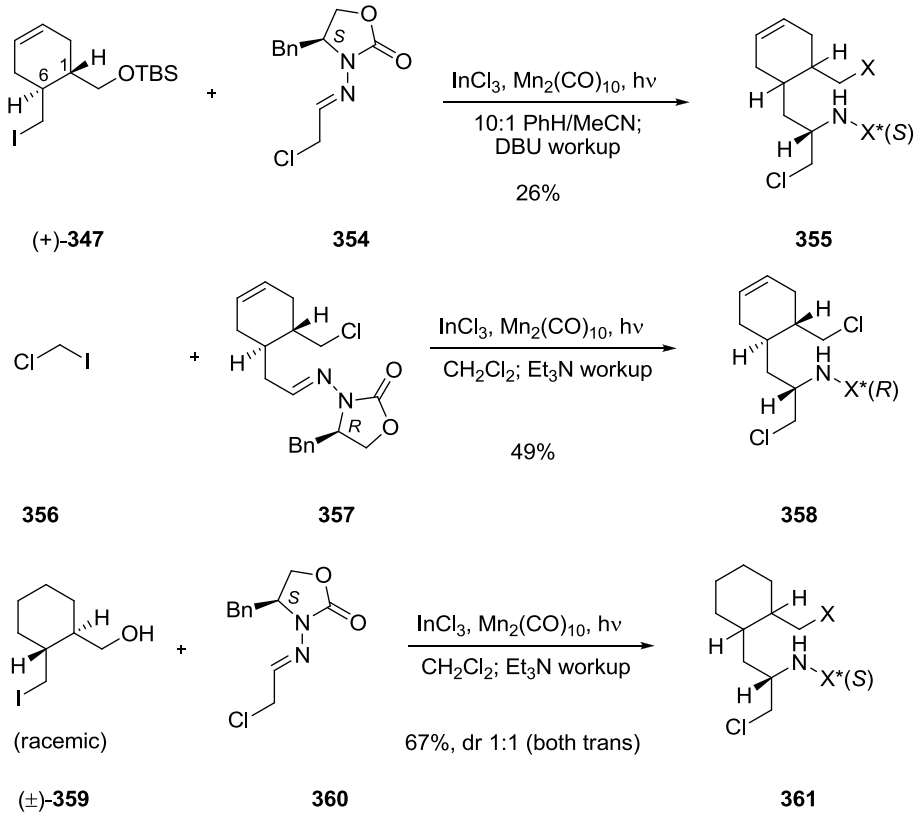


Figure 93. Intermolecular radical coupling studied by Dr. Korapala.

Based on the previous studies by Dr. Jun Qin and Dr. Chandra Sekhar Korapala, our revised strategy intended to do the first disconnection by two different ways (Figure 94). The first way is to disconnect C4‴-C9 of quinine by addition of quinolinylithium, which suggests 4-bromo-6-methoxyquinoline and quinuclidine aldehyde as logical precursors. The aldehyde could derive from quincorine. The second is to disconnect O-C9 by selective oxidation, which suggests deoxyquinine as the penultimate intermediate. Applying various sp^2-sp^3 C-C coupling methods, deoxyquinine can be disconnected to 4-

bromo-6-methoxyquinoline and halide with aza-bicyclo[2.2.2]octane ring system, which would also derive from quincorine (Figure 94).

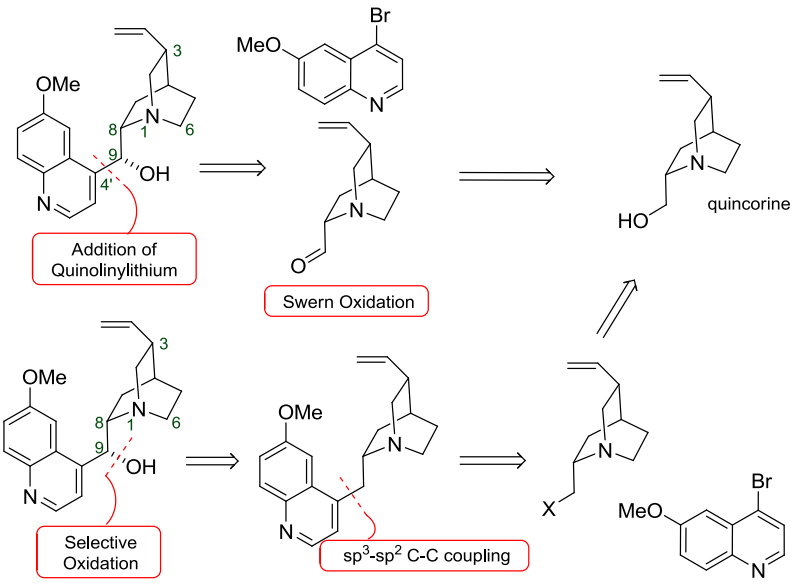


Figure 94.Revised retrosynthesis from quinine to quincorine.

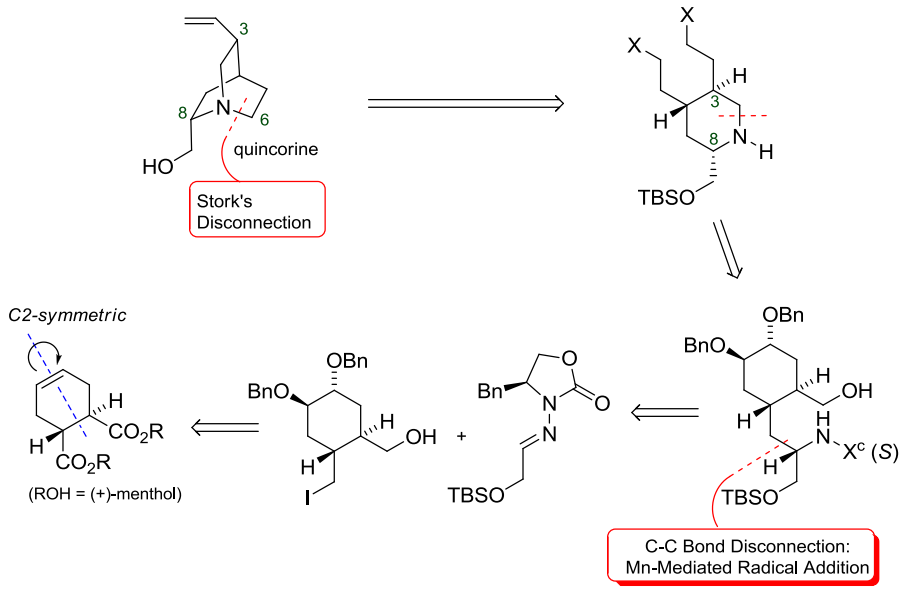


Figure 95. Revised retrosynthesis of quinine in our group.

Employing Stork‟s disconnection of the aza-bicyclo[2.2.2]octane ring system of quincorine suggests a 2,4,5-trisubstituted piperidine precursor (Figure 95), which in turn would derive from bis-benzyl ether with chiral auxiliary. The protected vicinal diol moiety would enable oxidative cleavage, which is necessary because the originally planned alkene interfered with the Mn-mediated coupling (Figure 93). We envisioned an efficient access to the bis-benzyl ether through Mn-mediated radical addition to construct C-C bonds at C8 stereogenic carbon, which suggests two coupling fragments. One is *N*-acylhydrazone. The other is functional iodide, which could derive from C_2-symmetric diesters (Figure 95).

In our synthetic strategy, there is a question in the cyclization of 2,4,5-trisubstituted piperidine derivative to produce the azabicyclic quinuclidine ring system (Figure 96). To exploit the latent C_2-symmetry, a group-selective cyclization is required. If it follows route a, we would have an aza-bicyclo[3.2.1]octane ring system that is not desired. If it goes through route b, we would make the corresponding aza-bicyclo[2.2.2]octane ring system (Figure 96).

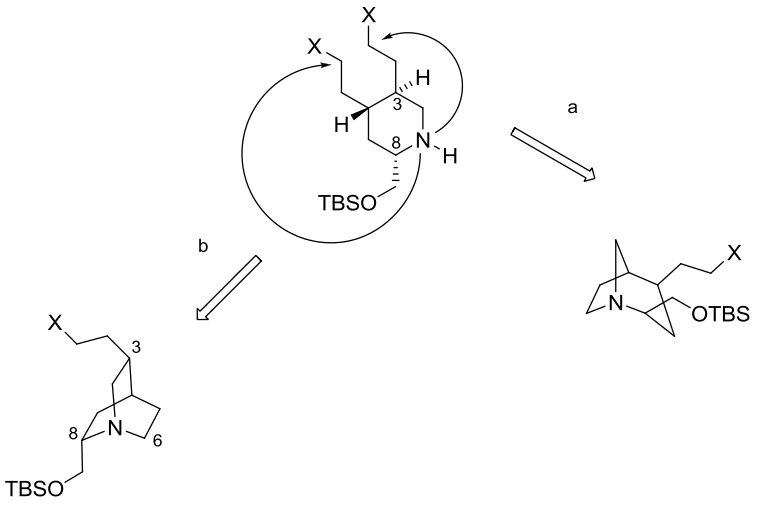


Figure 96. A group-selective cyclization.

Synthetic Approach to Quinine

With our quinine synthesis studies, we have improved the key C-C bond construction. Dr. Korapala began with preparation of functional iodide (Figure 96). For this purpose, the C_2-symmetric diester **345** (ROH = (+)-menthol) was acquired using the known enantioselective Diels-Alder reaction of dimethyl fumarate. The enantiopure diester *ent*-**345** was treated with m-CPBA, and the resulting epoxide was subjected to acidic alcoholysis with benzyl alcohol. Acid-catalyzed protection of the remaining free hydroxyl with benzyl trichloroacetimidate furnished bis-benzyl ether **363**. Reduction to the C_2-symmetric diol, monosilylation to **364**, conversion to iodide and desilylation provided the functional iodide **365**, which was one of our desired coupling fragments.[260] My contribution to this preparation of iodide is that the yield from **363** to **364** was optimized to 86% (2 steps) in 11.5 mmol scale and the yield from **364** to **365** was increased to 95% (2 steps) in 6.3 mmol scale (Figure 97).

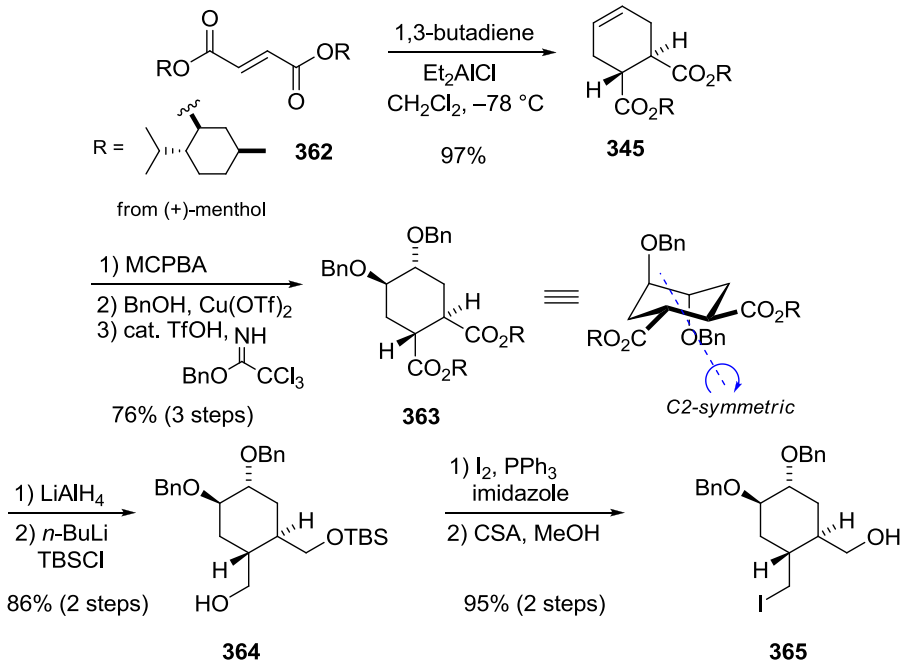


Figure 97. Preparation of our functional iodide.

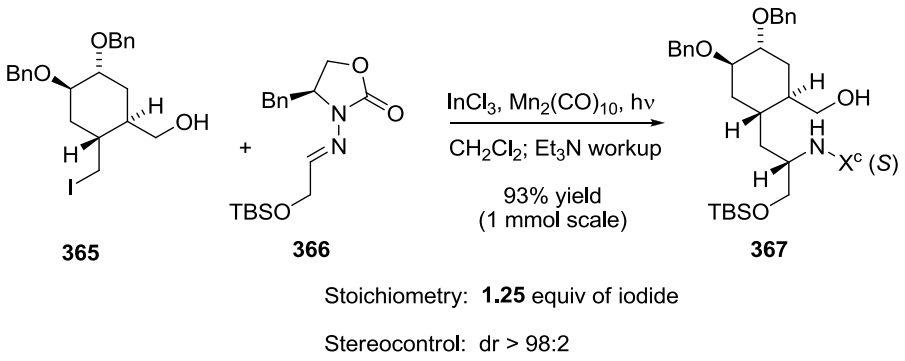


Figure 98. The key radical coupling step for our synthetic quinine.

In the key Mn-mediated coupling of **365** and **366**, first achieved by Dr. Chandra Sekhar Korapala, we were pleased to find quite remarkable yields (Figure 98). In most intermolecular radical additions to imino compounds, large excesses (10-20 equiv or more) of radical precursors are required. Clearly this would be a prohibitive stoichiometric requirement for an iodide such as **365**, prepared through several synthetic steps. To our great delight, the Mn-mediated coupling of **366** with only 1.25 equiv of **365** proceeded in 93% yield in 1 mmol scale, giving **367** as a single diastereomer.[260]

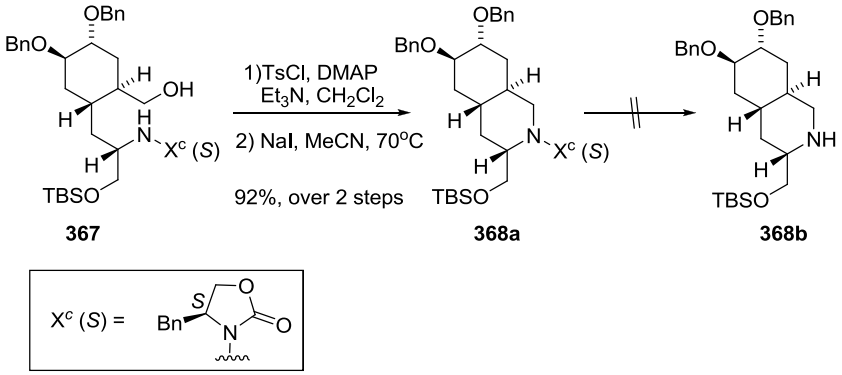


Figure 99. Hybrid radical-ionic annulation by Dr. Korapala.

Completion of the hybrid radical-ionic annulation would ideally occur *in situ* during the Mn-mediated coupling, but this has not yet been achieved. However, a stepwise radical-ionic annulation process proved efficient; successive treatment with TsCl and NaI provided decahydroisoquinoline **368a** in 92% yield. Thus the hybrid radical-ionic annulation sequence was accomplished by Dr. Korapala in overall 85% for the three steps (Figure 99).[260]

Cleavage of the N-N bond was required, and from piperidine **368a** this proved disappointing. Although Enders‟ procedure entailing heating with excess BH_3•THF is often successful for such tasks, when it was applied to **368a** it afforded a complex mixture. An extensive battery of catalytic hydrogenations on **368a**, with and without added acid, with a variety of catalysts (PtO_2, $Pd(OH)_2$, Pd/C), and with pressures up to 950 psi, met with no success (Figure 99).

Fortunately, preliminary results by Dr. Korapala showed that N-N bond cleavage could be addressed satisfactorily before piperidine ring construction. It was at this point that the new experimental studies described in this thesis began.

We applied trifluoroacetyl-activated nitrogen-nitrogen bond cleavage by SmI_2 to remove auxiliary of **367**, affording trifluoroacetamide **369** in overall yield of 72%. Subjection of **369** to Mitsunobu condition affected piperidine ring closure in an efficient fashion, furnishing piperidine **370** in 95% yield (Figure 100).

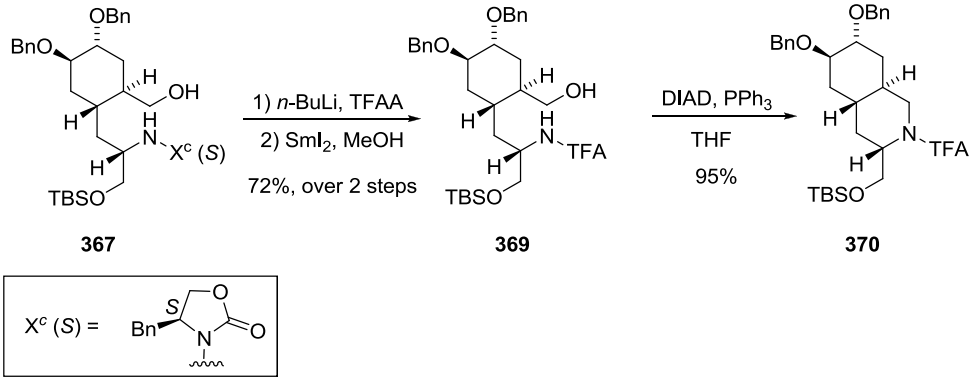


Figure 100. Removal of chiral auxiliary and the first annulation.

The next stage entailed oxidative cleavage of the vicinal diol to generate the precursors for a group-selective cyclization to forge the azabicyclo[2.2.2]octane ring system characteristic of the cinchona alkaloids.

Hydrogenative debenzylation of **370** provided the vicinal diol **371** (Figure 101). Silica gel-supported $NaIO_4$ efficiently opened the six membered ring at the diol moiety to afford an aldehyde **372**. This was not isolated due to instability, but was directly treated with $NaBH_4$ to prepare multifunctional piperidine **373** with two hydroxyl groups.

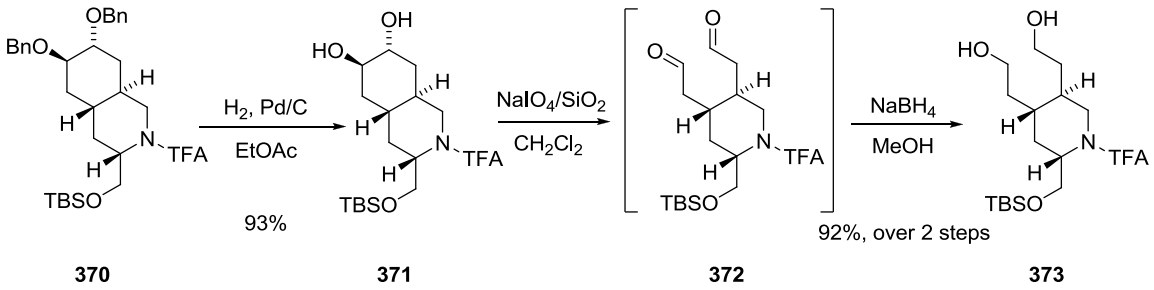


Figure 101. Preparation of diol by oxidative ring opening.

To set the stage for cyclization, diol **373** was converted to the corresponding diiodide **374** in quantitative yield (Figure 102). Fortunately, at the cyclization step, diiodide **374** was treated with methanolic ammonia, and the reaction proceeded in remarkable yield. However, cyclization occurred to afford two isomeric bicyclic ring systems assigned as azabicyclo[3.2.1]octane **375b** (major) and the desired azabicyclo[2.2.2]octane **375a** (minor). Upon dehydrohalogenation and desilylation (Figure 103), the products were not able to be isolated by flash chromatography. Since we had only ~20 mg of this mixture after workup, vacuum distillation was not practical. We distilled the mixture by cold finger at the different temperature range, and washed traces of condensate from the finger with $CDCl_3$ in every range to obtain several fractions. Then ^1H NMR and ^{13}C NMR were taken for every fraction. From the ^1H NMR spectra, it

is very hard to identify the peak of amino alcohol **376** because of impurity. However, by ^{13}C NMR, we can collect relatively clean data on compound **376**, although its separation as a pure substance was not possible at this point. From ^{13}C NMR, we found the peaks for the minor product assigned to quincorine (Figure 103). For the major product in **376**, there is no known azabicyclo[3.2.1]octane for comparison. Evidence for the structure is that **376b** (^{13}C NMR δ 62.5, 53.7, 47.0, 37.5, 31.0, 23.5 ppm) has the similar skeleton to **375** (δ 62.8, 53.8, 48.9, 38.0, 28.3, 21.6 ppm), which is different from quincorine (δ 57.2, 55.7, 40.1, 28.0, 27.3, 24.7 ppm). Because quincorine has previously been converted to quinine, this constituted a formal synthesis of quinine. However, dissatisfaction with the unfavorable selectivity in the cyclization led us to refine the route in a regio-convergent manner.

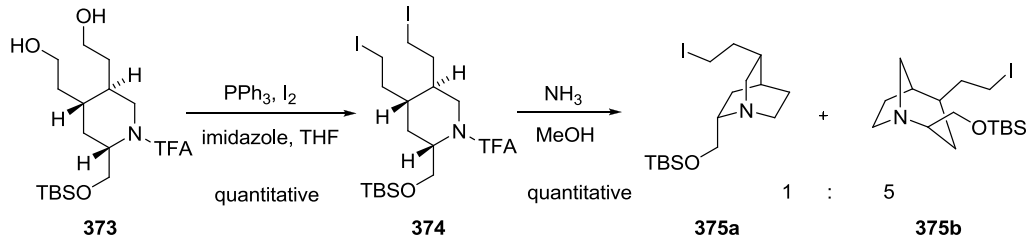


Figure 102. Cyclization of the diiodide.

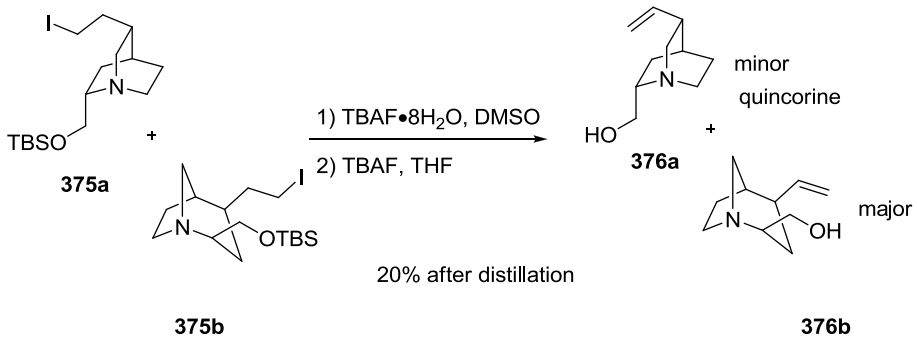


Figure 103. Elimination of the iodide.

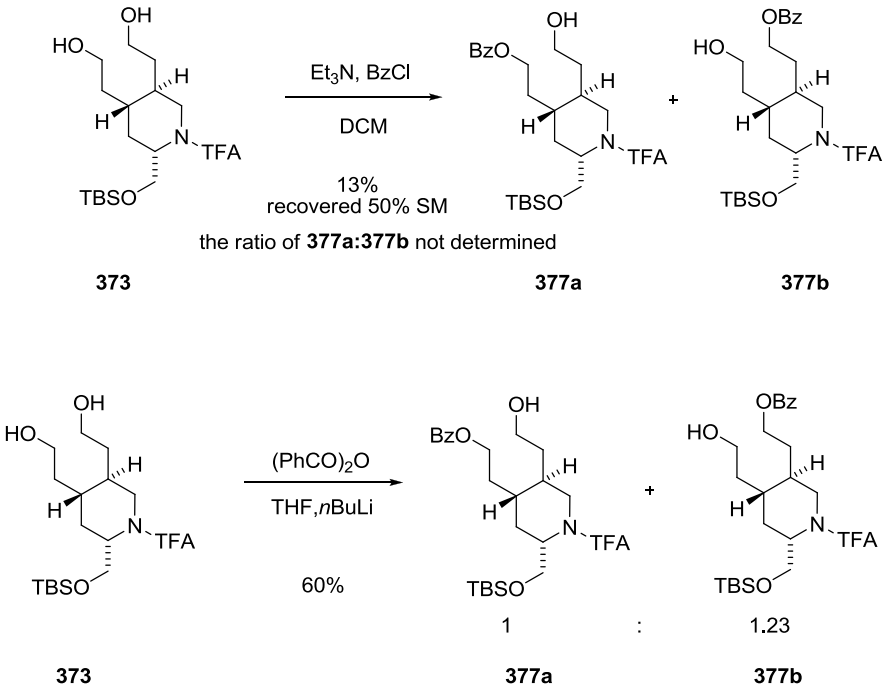


Figure 104. Monobenzoylation of the diol.

The solution we proposed was to differentiate the two hydroxyl groups of diol **373**. First, we attempted to do benzoylation with benzoyl chloride in the presence of triethylamine (Figure 104). Unfortunately, the yield of two monobenzoylate isomers was really low with recovery of 50% diol. Then, we have thought that 1.0 equiv of a strong base, such as *n*BuLi, may deprotonate one hydroxyl group of the diol moiety and react with benzoylation reagent. Monobenzoylation of **373** using *n*-BuLi and $(PhCO)_2O$ afforded two isomers in 60% yield with a ratio (**377a**/**377b**) of 1: 1.23 (Figure 104). This still suggests that the two hydroxyl group of the diol **373** have very similar reactivity.

The potential of biocatalytic transformation of diol to a single monoester attracted also our attention. We envisioned using an enzyme active site for regioselective esterification of two primary hydroxyl groups which are differentiated only by one atom located five bonds away from the oxygen. To our knowledge there are no prior examples of the use of an enzyme for reagent control in such a demanding regiocontrol problem.

Biocatalytic processes have been established as valuable methods to perform selective transformations in organic synthesis. Among the biocatalysts used in organic synthesis, lipases and other enzymes are applied in the synthesis of enantiomerically pure compounds.

One representative example has been done in Santaniello"s group (Figure 105). The prochiral diol **378** was treated with vinyl acetate in the presence of *Pseudomonas fluorescens lipase* (PFL) in chloroform at 30 ^{o}C and the reaction was stopped before the diacetate started to be formed. At this point, 40% of diol **378** was still present and 52% of the monoacetate **379** was isolated with 60% ee. When the reaction was carried out until the diol was consumed and 60% of the diacetate **380** was formed, the isolated acetate **379** (40% yield) exhibited >98% ee.[286]

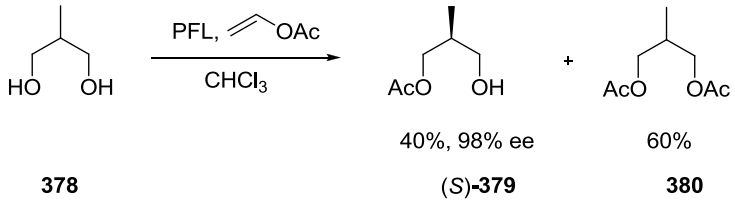


Figure 105. Lipase-catalyzed transesterification of 2-methyl-1,3-propanediol.

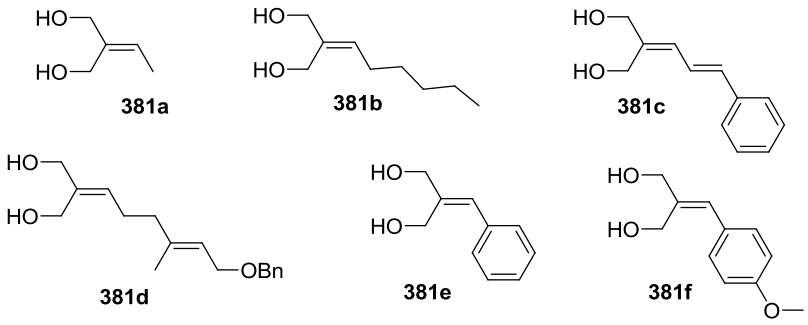
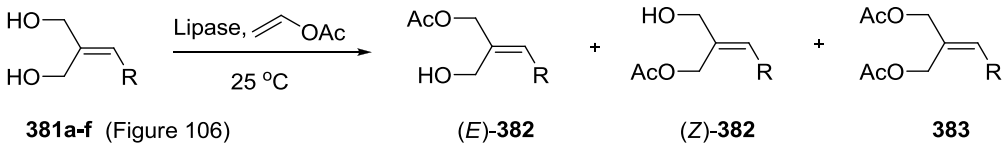


Figure 106. Screening of different α,α"-alkenediols.

Table 10. Lipase-Catalyzed Acetylation of α,α‟-Alkendiols



381a-f (Figure 106) (*E*)-**382** (*Z*)-**382** **383**

Entry[a]	Diol	Lipase	Time (h)	**382** Yield[b] (%)	E/Z ratio[c]	**383** Yield[b] (%)	**381** Yield[b] (%)
1	**381a**	---	24	0	---	---	Quant.
2	**381a**	Chirazyme	21	21	57:43	7	45
3	**381a**	AK	4	36	65:35	16	30
4	**381a**	PS-D	4	29	84:16	15	41
5	**381a**	AY	24	27	90:10	4	52
6	**381b**	PS-D	9	74	95:5	10	6
7	**381c**	PS-D	20	82	97:3	8	0
8	**381d**	PS-D	8	68	97:3	7	20
9	**381e**	PS-D	2	81	80:20	9	8
10	**381e**	AK	4	90	96:4	4	5
11	**381f**	PS-D	4	71	99:1	8	0

[a] The acetylation was carried out using vinyl acetate (1.0 equiv) and lipase (0.1 g equiv).
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis (entries 1-6) and HPLC analysis (entries 7-11).

The regioselective lipase-catalyzed acetylation of α,α‟-alkenediols **381** (Figure 106) was investigated in Takabe‟s group as shown in Table 10. Reactions were carried out in a shaking apparatus at 25 °C. After investigating different lipase catalyst, lipase PS-D (*Pseudomonas cepacia, Amano*) and AY (*Candida rugosa*, Amano) gave high regioselectivity (Entries 1-5). The acetylation of 2-ethylidenepropane-1,3-diol (**381a**) regioselectively provided the monoacetate **382a** in a *E*/*Z* ratio of 90/10 (entry 5). Alkyl and alkenyl substituents furnished higher regioselectivity using lipase PS-D (Entries 6-8). Similarly, aryl-substituted α,α‟-alkenediols **381e-f** were acetylated to afford the (*E*)-monoacetate **382e-f** with excellent regioselectivity (Entries 10-11). Using lipase, a significant change of regioselectivity was observed as well as chemical yield.[287]

The two great examples above have inspired us. However, in the first case, the two hydroxyl groups were at the α position relative to the prochiral center. The two hydroxyl groups in the second case were attached to the carbon next to alkene

functionality. Our diol, in which hydroxyl groups are two carbons away from the closest chiral center, is different from those two examples. Even if there were no selectivity observed, both isomeric monoesters could be cyclized to the [2.2.2] ring system in a convergent fashion.

Novozyme-435 (lipase from *Candida antarctica*, immobilized on a macroporous acrylic resin) used in our route is commercially available. Monoacetylation of diol **373** catalyzed by Novozyme-435 afforded two isomers **384** of monoacetate, in which the recovered diol can be reused (Figure 107).

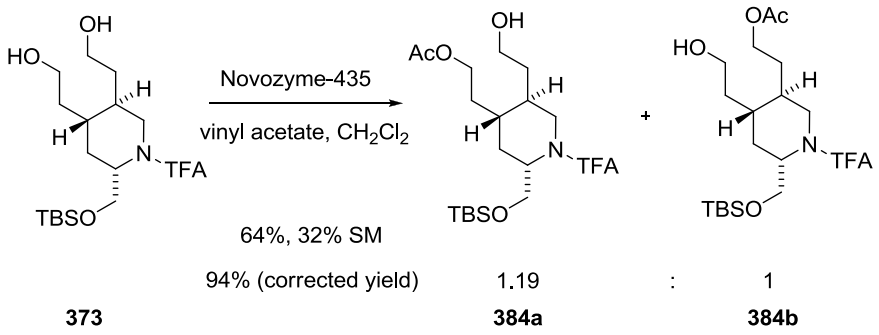


Figure 107. Lipase-catalyzed acetylation of the diol.

The acetate **384a** was converted to a selenide (Figure 108), followed by oxidative elimination to furnish olefin. Acetyl protecting group and trifluoroacetyl protecting group were both removed by using $Ba(OH)_2$, affording amine **385**. Subsequent treatment with iodination conditions furnished *O*-TBS-quincorine (**386**), unfortunately in < 50% yield (Figure 108). Similar results were observed using conditions which proceeded via the bromide (PPh_3, CBr_4). Thus, the route was revised. Dehydration via the selenide and selective removal of acetyl group in **384a** afforded alcohol **387**. This was followed by iodination and cyclization in methanolic ammonia (TFA protecting group can be

removed by methanolic ammonia) to afford *O*-TBS-quincorine **386** in good yield (Figure 108).

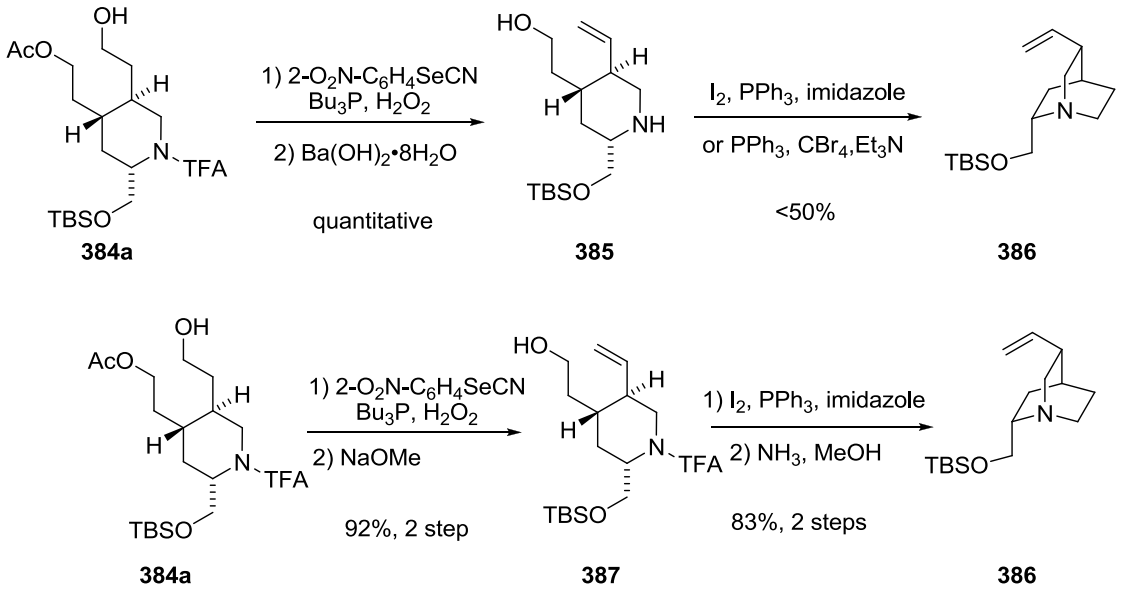


Figure 108. Synthesis of azabicyclo[2.2.2]octane moiety from **384a**.

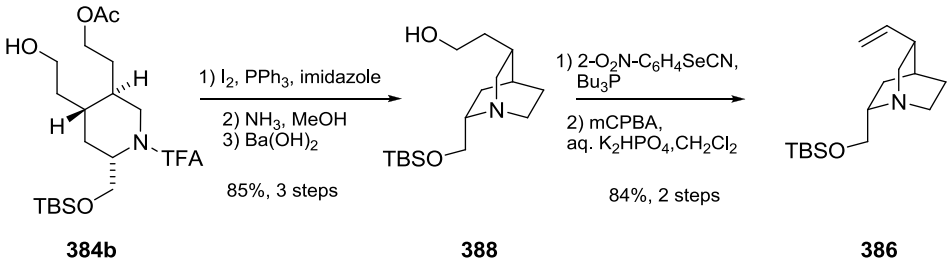


Figure 109. Synthesis of azabicyclo[2.2.2]octane moiety from **384b**.

Regioisomeric monoacetate **384b** underwent cyclization under the same two-stage protocol (Figure 109), and ester hydrolysis with $Ba(OH)_2$ gave amino alcohol **388**. Conversion to selenide and oxidative elimination furnished *O*-TBS-quincorine (**386**).

According to the reactions in Figure 108 and 109, both monoacetates from lipase-catalyzed acetylation of the diol could be converted into the same desired *O*-TBS-quincorine. The only difference between them is the order of steps involving cyclization and oxidative elimination. This has improved the overall efficiency of our synthetic route. The overall yield from the diol to *O*-TBS-quincorine is 67% based on the correct yield of lipase-catalyzed monoacetylation and conversion of two monoacetate isomers to *O*-TBS-quincorine, which is excellent for 5 steps in parallel.

O-TBS-quincorine **386** was treated with TBAF to accomplish our synthesis of quincorine **389**, which was found to be identical to commercially available quincorine (Figure 110). Two known transformations[257,280] close the synthetic pathway from **389** to quinine, and this route therefore completes a formal synthesis (Figure 111).

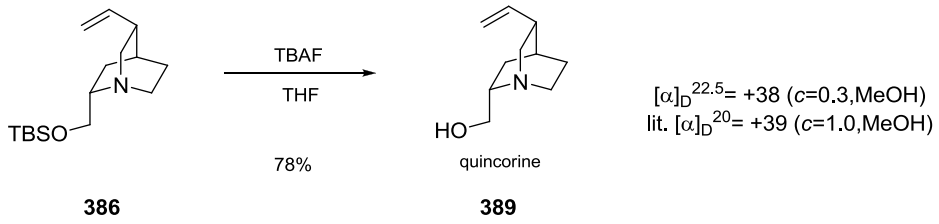


Figure 110. Deprotection of *O*-TBS-quincorine.

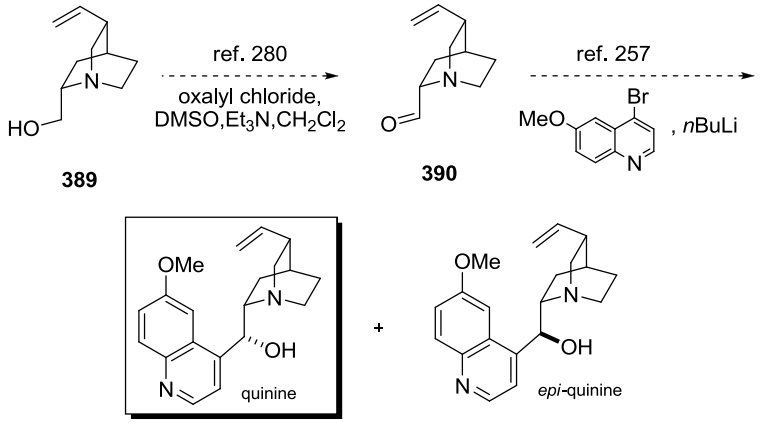


Figure 111. Synthetic route from quincorine to quinine.

In Dehmlow's group, qincorine was successfully converted to amino aldehyde **390** via Swern oxidation. The product was purified by distillation in a Kugelrohr apparatus on an 8 g scale. According to the addition condition applied by Uskokovic and co-workers, we would probably have two isomers. One of them is our target: quinine (Figure 111).

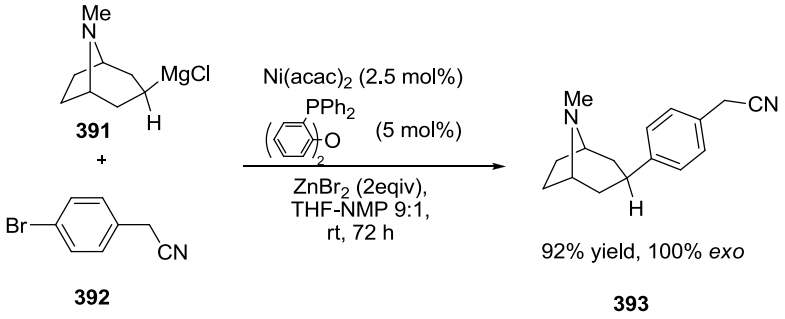


Figure 112. Direct aminoalkylation via Ni-catalyzed Negishi cross-coupling reactions.

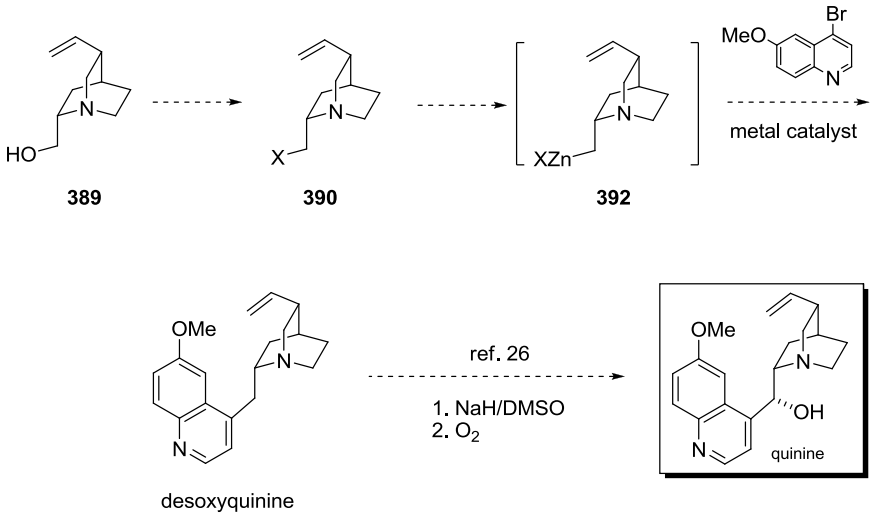


Figure 113. Proposed stereocontrolled coupling for total synthesis of quinine.

Thus, we are looking for a stereocontrolled methodology in this coupling step. Knochel‟s work has encouraged us that aminoalkyl chloride and aromatic bromide could be coupled by via Ni-catalyzed Negishi cross-coupling reaction (Figure 112).[288]

Based on Knochel‟s observation, in the future, we could convert the quincorine to aminoalkyl halide **390**. The aminoalkyl organozinc species from aminoalkyl halide would couple with aromatic bromide via Ni-catalyzed Negishi cross-coupling condition, affording desoxyquinine. The autooxidation of desoxyquinine **237**, which was finally transformed into quinine, has been successfully accomplished by Stork[26] (Figure 113).

CHAPTER 5

SUMMARY

In our group, we disclosed that manganese carbonyl mediates stereoselective photolytic radical addition of alkyl iodides to chiral imino acceptors, which is a powerful tool to form a new C-C bond and generate chiral center. In my thesis, we have extended the application of our methodology.

In Chapter 3, the couplings of iodides and *N*-acylhydrazones described the first applications of this Mn-mediated addition methodology to generation of quaternary carbon stereocenters by addition to ketimine acceptors and offer access to a variety of α-alkylated alanine analogs. With the feasibility of these Mn-mediated additions to ketimines now demonstrated, further studies are warranted. Notably, the numerous side reactions and large excesses of reagents found in the earlier work can be avoided by use of the Mn-mediated couplings presented here. These radical additions complement enolate alkylation methodologies, as they occur under nonbasic conditions and permit introduction of both primary and secondary alkyl groups with relative ease. The versatility with respect to the iodide is a distinguishing feature of the Mn-mediated coupling that foreshadows application to more complex targets.

In Chapter 4, a Mn-mediated radical–ionic annulation strategy was validated as a synthetic route to quinine. Structural features which interfere with the Mn-mediated radical addition were uncovered via a series of control experiments, which guided revision of the synthetic strategy. After completing the radical–ionic annulation in a stepwise fashion, a regio-convergent process for assembling the quinuclidine ring system established access to quincorine from either of two regioisomeric monoacetates, completing a formal synthesis of quinine. Intermolecular radical addition to C=N bonds has rarely been applied as a strategic bond construction in natural product synthesis; this

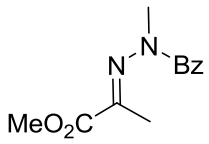
synthesis of quinine offers the strongest demonstration yet of the utility of such reactions in application toward complex multifunctional targets.

CHAPTER 6

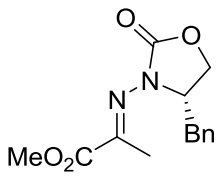
EXPERIMENTAL

Materials and Methods. Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. THF, diethyl ether, benzene and toluene were distilled from sodium/benzophenone ketyl under argon. CH_2Cl_2 was distilled from CaH_2 under argon or nitrogen. Alternatively, these solvents were purchased inhibitor-free and were sparged with argon and passed through columns of activated alumina prior to use dropwise addition of blue benzophenone ketyl solution revealed the THF purified in this manner sustained the blue color more readily than the control sample purified by distillation). Nitrogen was passed successively through columns of anhydrous $CaSO_4$ and R3-11 catalyst for removal of water and oxygen, respectively. All other materials were used as received from commercial sources unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator. Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in the initial elution solvent. Gradient flash chromatography was conducted by adsorption of product mixtures on silica gel, packing over a short pad of clean silica gel as a slurry in hexane, and eluting with a continuous gradient from hexane to the indicated solvent. Radial chromatography refers to centrifugally accelerated thin-layer chromatography performed with a Chromatotron using commercially supplied rotors. Melting points are uncorrected. Nuclear magnetic resonance (NMR) data were obtained at operating frequencies indicated in the text, and are reported in units of ppm. Infrared spectra were recorded using a single beam FT-IR spectrophotometer by standard transmission methods or by use of an attenuated total reflectance (ATR) probe. Optical rotations were determined using a digital polarimeter operating at ambient temperature. Low resolution mass spectra were obtained using sample introduction by dip, liquid chromatography or gas chromatography. High resolution mass spectra and combustion analyses were

obtained from external commercial and institutional services. Chromatographic diastereomer ratio analyses employed GCMS with 15 m x 0.25 mm x 0.25 μm (l x i.d. x f.t.) 5%-phenyl-95%-dimethylsiloxane column and helium as mobile phase or HPLC with Microsorb-MV Si 8um 100A or Chiralcel OD columns (2-propanol/hexane as mobile phase) or Chirex 3014 column (chloroform/hexane as mobile phase).

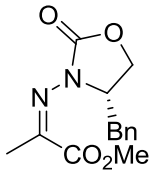


General Procedure A: Methyl 2-(2-benzoyl-2-methylhydrazono) propanoate (332). To a mixture of *N*-benzoyl-*N*-methylhydrazine **331** (2.794 g, 18.6 mmol), p-toluenesulfonic acid (60 mg) and activated 4Å molecular sieves (25 mg, powdered) in toluene was added methyl pyruvate (3.36 mL, 37.2 mmol, 2 equiv). The solution was heated at reflux for ca. 12 h. Filtration through Celite, concentration, and flash chromatography (hexane →1:1 hexane/EtOAc) afforded **332** (3.630 g, 83% yield) as a yellow oil; IR (film) 2953, 1725, 1659, 1441, 1359, 1290, 1146, 1051, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.58-7.55 (m, 2H), 7.48-7.38 (m, 3H), 3.87 (s, 3H), 3.46 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO, 90°C) 167.8, 163.9, 156.0, 134.4, 129.8, 127.9, 127.3, 51.8, 37.5, 16.2; MS (EI) m/z (relative intensity) 234 (M+, 0.03%), 175 ([M–CO_2Me]+, 77%), 105 ([Bz]+, 100%); Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.86; H, 6.25; N, 11.74.

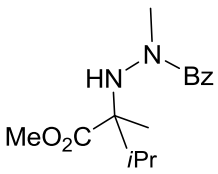


(*S,E*)-Methyl 2-(4-benzyl-2-oxooxazolidin-3-ylimino)propanoate ((*E*)-340). From (S)-3-amino-4-benzyloxazolidin-2-one **312a** (100 mg, 0.52 mmol) and methyl pyruvate (0.24 mL, 2.6 mmol, 5 equiv) by General Procedure A was obtained (*E*)-**340** (9 mg, 6%) and (*Z*)-**340** (108 mg, 75% yield) as a yellow oil; $[\alpha]_D^{24}$ –337.0 (c 0.5, $CHCl_3$); IR (film) 3027, 2949, 2913, 1772, 1723, 1441, 1327, 1196, 1147, 1098, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.35-7.26 (m, 3H), 7.15-7.13 (m, 2H), 4.61-4.51 (m, 1H), 4.32 (dd, *J* = 8.7, 7.7 Hz, 1H), 4.12 (dd, *J* = 9.1, 9.0 Hz, 1H), 3.91 (s, 3H), 3.21 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.82 (dd, *J* =

13.7, 8.9 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 164.0, 161.7, 152.3, 134.7, 129.1, 128.6, 127.1, 66.4, 60.8, 52.9, 38.0, 17.7; MS (EI) m/z (relative intensity) 276 (M+, 3%), 217 ([M–CO_2Me]+, 17%), 185 (100%); Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.98; H, 5.96; N, 10.09.

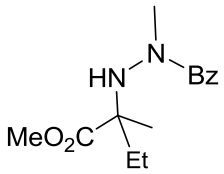


(*S,Z*)-methyl 2-(4-benzyl-2-oxooxazolidin-3-ylimino)propanoate ((*Z*)-340). ^{1}H NMR (300 MHz, $CDCl_3$) 7.35-7.26 (m, 3H), 7.15-7.13 (m, 2H), 4.40-4.29 (m, 1H), 4.24 (dd, *J* = 8.1, 7.7 Hz, 1H), 4.07 (dd, *J* = 8.4, 7.8 Hz, 1H), 3.82 (s, 3H), 3.30 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.86 (dd, *J* = 13.7, 8.9 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 162.6, 156.3, 154.0, 135.3, 129.2, 128.8, 127.1, 66.3, 60.6, 52.9, 38.0, 21.8.

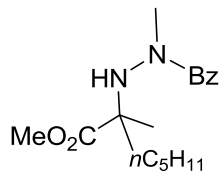


General Procedure B, Mn-Mediated Addition to N-Acylhydrazones: Methyl 2-(2-benzoyl-2-methylhydrazinyl)-2,3-dimethylbutanoate (333b). To a solution of hydrazone **332** (168 mg, 0.72 mmol) in CH_2Cl_2 (7.2 mL) in standard pyrex glassware was added $InCl_3$ (349 mg, 1.58 mmol, 2.20 equiv). The mixture was stirred for 0.5 h at room temperature, then 2-iodopropane (filtered through alumina, 0.08 mL, 0.79 mmol, 1.1 equiv) and $Mn_2(CO)_{10}$ (308 mg, 0.79 mmol, 1.10 equiv) were added successively. Using a Rayonet photochemical reactor, ultraviolet irradiation (300 nm) was supplied for 18–20 h; the ambient temperature inside the irradiation chamber reached 35 °C. Addition of NEt_3 (1 mL) and vigorous stirring for 1 h, followed by concentration and flash chromatography (hexane→3:1 hexane/EtOAc) afforded **333b** (139 mg, 69% yield). A similar result (65% yield) was obtained with 5 equiv 2-iodopropane; for other iodides 5 equiv was superior. 4b: Colorless solid; mp 88–90 °C; IR (film) 3289, 2965, 1727, 1641, 1632, 1447, 1372, 1248, 1144, 1123, 1064 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 90°C) 7.50-7.47 (m, 2H), 7.38-7.35 (m, 3H), 5.42 (br s, 1H), 3.67 (s, 3H), 3.01 (s, 3H), 1.78-

1.67 (m, apparent septet, J = 6.7 Hz, 1H), 0.91 (s, 3H), 0.63 (d, J = 6.8 Hz, 3H), 0.56 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO, 140°C) 174.8, 171.5, 136.0, 128.2, 127.1, 126.6, 66.2, 50.6, 36.7, 33.6, 16.0, 15.3, 12.6; MS (EI) m/z (relative intensity) 278 (M+, 3%), 235 ([M–i-Pr]+, 45%), 219 ([M–CO_2Me]+, 48%), 105 ([Bz]+, 100%); Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.85; H, 8.03; N, 9.96.

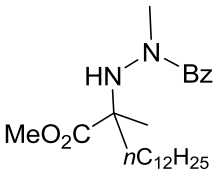


Methyl 2-(2-benzoyl-2-methylhydrazinyl)-2-methylbutanoate (333a). From hydrazone **332** (57 mg, 0.24 mmol) and iodoethane (0.10 mL, 1.20 mmol, 5 equiv) by General Procedure B was obtained **333a** (28 mg, 44% yield) as a colorless oil; IR (film) 3281, 2972, 2942, 1727, 1641, 1447, 1370, 1244, 1156, 1069 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 90°C) δ 7.53-7.50 (m, 2H), 7.41-7.38 (m, 3H), 5.62 (br s, 1H), 3.65 (s, 3H), 3.04 (s, 3H), 1.58 (dq, J = 14.6, 7.4 Hz, 1H), 1.42 (dq, J = 14.5, 7.4 Hz, 1H), 1.09 (s, 3H), 0.67 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO, 140°C) δ 174.1, 171.3, 135.6, 128.5, 127.1, 126.8, 63.6, 50.7, 38.2, 29.9, 17.8, 6.8; MS (EI) *m/z* (relative intensity) 264 (M^+, 4%), 205 ([M–CO_2Me]$^+$, 67%); Anal. Calcd. for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.40; H, 7.69; N, 10.38.

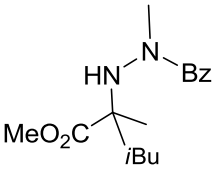


Methyl 2-(2-benzoyl-2-methylhydrazinyl)-2-methylheptanoate (333c). From hydrazone **332** (117 mg, 0.50 mmol) and 1-iodopentane (0.33 mL, 2.50 mmol, 5 equiv) by General Procedure B was obtained **333c** (97 mg, 63% yield) as a colorless oil; IR (film) 3285, 2950, 2860, 1728, 1638, 1446, 1364, 1250, 1201, 1062 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 90°C) δ 7.51-7.49 (m, 2H), 7.38-7.37 (m, 3H), 3.63 (s, 3H), 3.03 (s, 3H), 1.56-1.48 (m, 1H), 1.41-1.32 (m, 1H), 1.23-1.03 (m, 6H), 1.09 (s, 3H), 0.81 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO, 140°C) δ 174.2, 171.3, 135.6, 128.5, 127.1, 126.7, 63.2, 50.7, 38.1, 37.2, 30.6, 21.9, 20.7, 18.3, 12.4; MS (EI) *m/z* (relative intensity) 306 (M^+, 3%), 247

([M–CO_2Me]$^+$, 72%), 105 ([Bz]$^+$, 100%); Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.89; H, 8.71; N, 8.93.

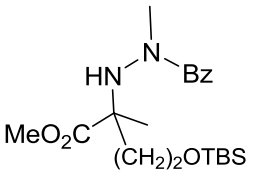


Methyl 2-(2-benzoyl-2-methylhydrazinyl)-2-methyltetradecanoate (333d). From hydrazone **332** (175 mg, 0.75 mmol) and 1-iodododecane (0.93 mL, 3.75 mmol, 5 equiv) by General Procedure B was obtained **340d** (174 mg, 57% yield) as a colorless oil; IR (film) 3285, 2925, 2848, 1728, 1638, 1463, 1360, 1242, 1160, 1062 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 90°C) δ 7.52-7.50 (m, 2H), 7.40-7.36 (m, 3H), 5.58 (br s, 1H), 3.64 (s, 3H), 3.04 (s, 3H), 1.56-1.48 (m, 1H), 1.40-1.33 (m, 1H), 1.27 (br s, 12H), 1.21-1.14 (m, 6H), 1.10 (s, 3H), 1.10-1.00 (m, 2H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO, 140°C) δ 174.2, 171.3, 135.6, 128.4, 127.1, 126.7, 63.2, 50.7, 38.1, 37.2, 30.3, 28.4, 28.01, 27.99, 27.97, 27.9, 27.8, 27.6, 22.3, 21.0, 18.3, 12.6; MS (EI) *m/z* (relative intensity) 404 (M$^+$, 1%), 345 ([M–CO_2Me]$^+$, 61%), 105 ([Bz]$^+$, 100%); Anal. Calcd for $C_{24}H_{40}N_2O_3$: C, 71.25; H, 9.97; N, 6.92. Found: C, 71.45; H, 10.06; N, 6.86.

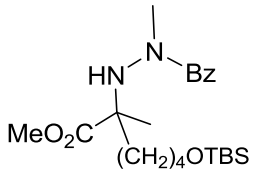


Methyl 2-(2-benzoyl-2-methylhydrazinyl)-2,4-dimethylpentanoate (333e). From hydrazone **332** (176 mg, 0.76 mmol) and 1-iodo-2-methylpropane (0.44 mL, 3.80 mmol, 5 equiv) by General Procedure B was obtained starting material **332** (44 mg, 25%) and **333e** (174 mg, 38% yield) as a colorless oil; IR (film) 3284, 2954, 2860, 1727, 1641, 1447, 1371, 1233, 1139, 1064 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 90°C) δ 7.52-7.50 (m, 2H), 7.41-7.38 (m, 3H), 5.61 (br s, 1H), 3.65 (s, 3H), 3.04 (s, 3H), 1.55-1.48 (m, 2H), 1.38-1.32 (m, 1H), 1.14 (s, 3H), 0.79 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO, 140°C) δ 174.4, 171.3, 135.6, 128.5, 127.0, 126.8, 63.2, 50.7, 46.6, 38.2, 23.2, 22.74, 22.67, 18.5; MS (EI) *m/z* (relative intensity) 292 (M$^+$, 2%), 233 ([M-CO_2Me]$^+$, 72%), 105 ([Bz]$^+$,

100%); Anal. Calcd. for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 66.04; H, 8.50; N, 9.25.

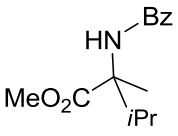


Methyl 2-(2-benzoyl-2-methylhydrazinyl)-4-(*tert*-butyldimethyl silyloxy)-2-methyl-butan-oate (333f). From hydrazone **332** (158 mg, 0.67 mmol) and 2-(*tert*-butyldimethylsilyloxy)-1-iodoethane (383 mg, 1.34 mmol, 2.00 equiv) by General Procedure B was obtained **333f** (130 mg, 49% yield) as a colorless oil; IR (film) 3280, 2953, 2925, 2855, 1727, 1642, 1462, 1368, 1249, 1122, 1090 cm^{-1}; ^1H NMR (400 MHz, DMSO, 120°C) δ 7.52-7.50 (m, 2H), 7.42-7.37 (m, 3H), 5.67 (br s, 1H), 3.66 (s, 3H), 3.53 (t, J = 6.8 Hz, 2H), 3.06 (s, 3H), 1.78 (ABX_2, Dn = 42.2 Hz, J_{AB} = 10.5 Hz, J_{AX} = 5.1 Hz, J_{BX} = 5.1 Hz, 2H), 1.19 (s, 3H), 0.87 (s, 9H), 0.01 (s, 3H), 0.006 (s, 3H); ^{13}C NMR (100 MHz, DMSO, 140°C) δ 174.0, 171.4, 135.6, 128.6, 127.2, 126.9, 62.0, 58.0, 56.1, 51.0, 38.1, 25.0, 18.7, 17.1, –4.0, –6.2; MS (EI) *m/z* (relative intensity) 394 (M^+, 1%), 337 ($[M–t\text{-}Bu]^+$, 19%), 335 ($[M–CO_2Me]^+$, 13%), 105 ($[Bz]^+$, 100%); Anal. Calcd. for $C_{20}H_{34}N_2O_4Si$: C, 60.88; H, 8.69; N, 7.10. Found: C, 61.25; H, 8.75; N, 6.92. Decomposition at 120°C in DMSO prevented acquisition of high quality ^{13}C NMR data for this compound.

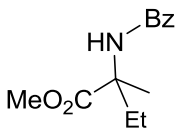


Methyl 2-(2-benzoyl-2-methylhydrazinyl)-6-(*tert*-butyldimethyl silyloxy)-2-methyl-hexanoate (333g). From hydrazone **332** (100 mg, 0.43 mmol) and 4-(*tert*-butyldimethylsilyloxy)-1-iodobutane (1.254 g, 3.99 mmol, 9.28 equiv) by General Procedure B was obtained starting material (32 mg, 32%) and **333g** (91 mg, 50% yield) as a colorless oil; IR (film) 3285, 2950, 2929, 2852, 1724, 1638, 1462, 1360, 1250, 1099 cm^{-1}; ^1H NMR (400 MHz, DMSO, 70°C) δ 7.53-7.50 (m, 2H), 7.40-7.36 (m, 3H), 5.67 (br s, 1H), 3.64 (s, 3H), 3.51-3.46 (m, 2H), 3.03 (s, 3H), 1.58-1.49 (m, 1H), 1.38-1.31 (m, 3H), 1.15-1.05 (m, 5H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, DMSO, 140°C) δ 174.4, 171.3,

135.6, 128.6, 127.2, 126.9, 63.3, 59.9, 50.8, 37.2, 32.1, 25.0, 19.2, 18.3, –4.1, –6.1; MS (EI) *m/z* (relative intensity) 422 (M^+, 0.9%), 365 ([M–*t*-Bu]$^+$, 40%), 363 ([M–CO_2Me]$^+$, 24%), 105 ([Bz]$^+$, 100%); Anal. Calcd. for $C_{22}H_{38}N_2O_4Si$: C, 62.52; H, 9.06; N, 6.63. Found: C, 62.94; H, 9.27; N, 6.46. Decomposition at 120°C in DMSO prevented acquisition of high quality ^{13}C NMR data for this compound.

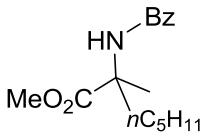


Procedure C, N–N Bond Cleavage: Methyl 2-benzamido-2,3-dimethylbutanoate[1] (334b). To a solution of **333b** (46 mg, 0.17 mmol) in THF (2 mL) and anhydrous MeOH (1 mL) at –78 °C under Ar was added SmI_2 (0.277 M in THF, 4.90 mL, 8 equiv) dropwise. The mixture was allowed to warm to ambient temperature over 2 h, then acetic acid (78 μL, 8 equiv) was added, followed by triethylamine (0.47 mL, 20 equiv) and benzoyl chloride (0.39 mL, 20 equiv). After removal of volatile materials, the residue was partitioned between dichloromethane and sodium carbonate solution, washed with water, dried, and concentrated. Flash chromatography (hexane → 3:1 hexane/EtOAc) afforded *N*-methylbenzamide (14 mg, 61%) and **334b**[281] (41 mg, 98% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.76 (m, 2H), 7.53-7.40 (m, 3H), 6.76 (br. s, 1H), 3.78 (s, 3H), 2.41 (septet, *J* = 6.9 Hz, 1H), 1.70 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H).

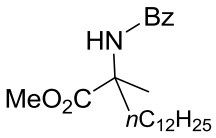


Methyl 2-benzamido-2-methylbutanoate (334a). From **333a** (31 mg, 0.12 mmol) by General Procedure C was obtained *N*-methylbenzamide (11 mg, 66%) and **334a** (24 mg, 85% yield) as a colorless oil ; IR (film) 3331, 2975, 2942, 1742, 1641, 1530, 1489, 1321, 1249, 1131cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.78 (m, 2H), 7.53-7.40 (m, 3H), 7.03 (br. s, 1H), 3.81 (s, 3H), 2.49 (dq, *J* = 13.9, 7.5 Hz, 1H), 1.93 (dq, *J* = 13.9, 7.5 Hz, 1H), 1.72 (s, 3H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 166.2, 134.8, 131.4, 128.5, 126.8, 61.3, 52.8, 29.3, 22.8, 8.6; MS (EI) *m/z* (relative intensity) 235 (M^+, 1%), 176 ([M-CO_2Me]$^+$, 19%), 105

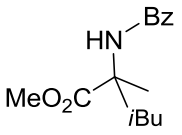
([Bz]$^+$, 100%); Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.62; H, 7.41; N, 5.89.



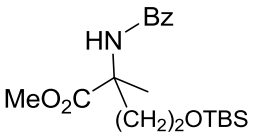
Methyl 2-benzamido-2-methylheptanoate (334c). From **333c** (48 mg, 0.16 mmol) by General Procedure C was obtained *N*-methylbenzamide (14 mg, 66%) and **334c** (34 mg, 79% yield) as a colorless solid; mp 82–84 °C; IR (film) 3332, 2954, 2861, 1742, 1641, 1530, 1489, 1451, 1329, 1260, 1207, 1134 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H), 7.53-7.40 (m, 3H), 7.05 (br s, 1H), 3.80 (s, 3H), 2.49-2.39 (m, 1H), 1.90-1.80 (m, 1H), 1.72 (s, 3H), 1.35-1.20 (m, 5H), 1.13-1.03 (m, 1H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 166.1, 134.7, 131.3, 128.4, 126.8, 60.7, 52.7, 36.3, 31.5, 23.9, 23.0, 22.3, 13.8; MS (EI) *m/z* (relative intensity) 277 (M$^+$, 2%), 218 ([M-CO_2Me]$^+$, 11%), 105 ([Bz]$^+$, 100%); Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.31; H, 8.31; N, 5.01.



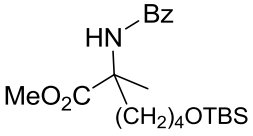
Methyl 2-benzamido-2-methyltetradecanoate (334d). From **333d** (49 mg, 0.12 mmol) by General Procedure C was obtained *N*-methylbenzamide (10 mg, 62%) and **334d** (36 mg, 80% yield) as a colorless solid; mp 57–59 °C; IR (film) 3346, 2924, 2853, 1743, 1641, 1529, 1451, 1072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.81-7.77 (m, 2H), 7.53-7.41 (m, 3H), 7.04 (br s, 1H), 3.80 (s, 3H), 2.48-2.39 (m, 1H), 1.88-1.80 (m, 1H), 1.72 (s, 3H), 1.32-1.18 (m, 19H), 1.15-1.00 (m, 1H), 0.87 (t, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 166.1, 134.8, 131.4, 128.5, 126.9, 60.9, 52.8, 36.37, 31.9, 29.61, 29.58, 29.55, 29.5, 29.39, 29.38, 29.3, 24.3, 23.1, 22.7, 14.1; MS (EI) *m/z* (relative intensity) 375 (M$^+$, 0.3%), 316 ([M–CO_2Me]$^+$, 7%), 105 ([Bz]$^+$, 100%); Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.72; H, 10.06; N, 3.62.



Methyl 2-benzamido-2,4-dimethylpentanoate (334e). From **333e** (84 mg, 0.29 mmol) by General Procedure C was obtained *N*-methylbenzamide (28 mg, 71%) and **334e** (58 mg, 76% yield) as a colorless solid; mp 114–116 °C; IR (film) 3265, 2953, 1738, 1630, 1577, 1547, 1241, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80-7.78 (m, 2H), 7.51-7.42 (m, 3H), 3.81 (s, 3H), 2.58 (dd, *J* = 14.1, 5.2 Hz, 1H), 1.78 (dd, *J* = 14.1, 7.7 Hz, 1H), 1.73 (s, 3H), 1.69-1.54 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 166.0, 134.9, 131.3, 128.5, 126.8, 60.3, 52.6, 44.4, 24.8, 24.2, 23.7, 22.5; MS (EI) *m/z* (relative intensity) 263 (M^+, 0.6%), 204 ($[M–CO_2Me]^+$, 13%), 105 ($[Bz]^+$, 100%); Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.36; H, 7.94; N, 5.26.

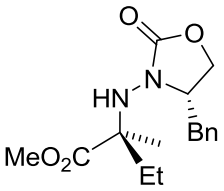


Methyl 2-benzamido-4-(*tert*-butyldimethylsilyloxy)-2-methylbutanoate (334f). From **333f** (44 mg, 0.11 mmol) by General Procedure C was obtained *N*-methylbenzamide (10 mg, 67%) and **334f** (38 mg, 95% yield) as a colorless oil; IR (film) 3377, 2953, 2925, 2856, 1741, 1666, 1529, 1485, 1451, 1324, 1254, 1128, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.80-7.78 (m, 2H), 7.51-7.38 (m, 3H), 3.82-3.75 (m, 2H), 3.76 (s, 3H), 2.30-2.16 (m, 2H), 1.72 (s, 3H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 166.5, 134.6, 131.4, 128.4, 127.0, 60.0, 59.4, 52.5, 39.4, 25.9, 22.8, 18.5, –5.47, –5.48; MS (ESI) *m/z* (relative intensity) 388 ($[M+Na]^+$, 17%), 366 ($[M+H]^+$, 100%); Anal. Calcd for $C_{19}H_{31}NO_4Si$: C, 62.43; H, 8.55; N, 3.83. Found: C, 62.61; H, 8.54; N, 3.77.

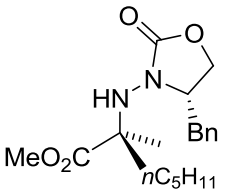


Methyl 2-benzamido-6-(*tert*-butyldimethylsilyloxy)-2-methylhexanoate (334g). From **333g** (44 mg, 0.11 mmol) by General Procedure C was obtained *N*-methylbenzamide (10 mg, 67%) and **334g** (38 mg, 95% yield) as a colorless solid; mp 86–88 °C; IR

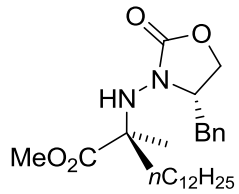
(film) 3346, 2952, 2930, 2857, 1742, 1658, 1642, 1529, 1488, 1462, 1256, 1128, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H), 7.53-7.40 (m, 3H), 7.07 (br. s, 1H), 3.80 (s, 3H), 3.62-3.49 (m, 2H), 2.45 (ddd, *J* = 13.5, 12.2, 4.6 Hz, 1H), 1.89 (ddd, *J* = 13.5, 11.8, 4.8 Hz, 1H), 1.72 (s, 3H), 1.55-1.45 (m, 2H), 1.45-1.10 (m, 2H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 166.2, 134.8, 131.5, 128.5, 126.9, 62.7, 60.9, 52.8, 36.1, 32.5, 25.9, 23.2, 20.8, 18.3, –5.3; MS (EI) *m/z* (relative intensity) 393 (M^+, 0.04%), 336 ([M–*t*-Bu]$^+$, 35%), 334 ([M–CO_2Me]$^+$, 2%), 105 ([Bz]$^+$, 100%); Anal. Calcd for $C_{21}H_{35}NO_4Si$: C, 64.08; H, 8.96; N, 3.56. Found: C, 64.28; H, 9.05; N, 3.50.



(*S*)-Methyl 2-((*S*)-4-benzyl-2-oxooxazolidin-3-ylamino)-2-methyl butanoate (343a). From hydrazone (*E*)-**340** (67 mg, 0.24 mmol) and iodoethane (0.10 mL, 1.20 mmol, 5 equiv) by General Procedure B was obtained **343a** (48 mg, 66% yield) as a colorless solid; mp 70–72℃ ; $[\alpha]_D^{28}$ +30.5 (*c* 0.5, $CHCl_3$); IR (film) 3295, 2950, 1765, 1727, 1453, 1398, 1238, 1149, 1093, 1030 cm^{-1}; major isomer ^1H NMR (300 MHz, $CDCl_3$) δ δ 7.35-7.25 (m, 3H), 7.19-7.16 (m, 2H), 4.09 (ABX, Δν= 17.2, J_{AB} = 8.7, J_{AX} = 7.5, J_{BX} = 3.0, 2H), 3.91 (dddd, *J* = 10.2, 6.6, 3.6, 3.3 Hz, 1H), 3.75 (s, 3H), 3.41 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.55 (dd, *J* = 13.3, 10.3 Hz, 1H), 1.78 (ABX_3, Δν= 35.5 Hz, J_{AB} = 13.8 Hz, J_{AX} = 7.5 Hz, J_{BX} = 7.5 Hz, 2H), 1.26 (s, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); minor isomer ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (m, 1H), 1.79 (m, 2H), 1.34 (s, 3H), 0.92 (*t*, *J* = 6.3 Hz, 3H); major isomer ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 159.0, 136.1, 129.2, 128.9, 127.0, 65.21, 65.20, 59.8, 52.2, 35.6, 30.6, 20.1, 8.5; minor isomer ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 158.7, 136.1, 129.2, 128.9, 127.0, 65.4, 65.2, 60.7, 52.2, 35.6, 30.7, 20.4, 8.6; MS (ESI) *m/z* (relative intensity) 329 ([M+Na]$^+$, 17%), 307 ([M+H]$^+$, 100%); Anal. Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.78; H, 7.48; N, 8.94.

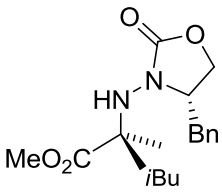


(*S*)-methyl 2-((*S*)-4-benzyl-2-oxooxazolidin-3-ylamino)-2-methyl heptanoate (343c). From hydrazone (*E*)-**340** (132 mg, 0.48 mmol) and 1-iodopentane (0.31 mL, 2.40 mmol, 5 equiv) by General Procedure B was obtained starting material (*E*)-**340** (29 mg, 20%) and **343c** (100 mg, 60% yield, dr 68: 32) as a colorless oil; $[\alpha]_D^{21}$ +25.4 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) major isomer δ 7.34-7.25 (m, 3H), 7.19-7.17 (m, 2H), 4.37 (s, 1H), 4.08 (ABX, Δν= 22.6 Hz, J_{AB} = 9.0 Hz, J_{AX} = 7.5 Hz, J_{BX} = 2.9 Hz, 2H), 3.90 (dddd, *J* = 10.3, 7.0, 3.5, 3.2 Hz, 1H), 3.75 (s, 3H), 3.41 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.54 (dd, *J* = 13.3, 10.4 Hz, 1H), 1.76 (m, 1H), 1.66 (m,1H), 1.38 (s, 3H), 1.30 (m, 6H), 0.89 (*t*, *J* = 7.0 Hz, 3H); minor isomer δ 7.34-7.25 (m, 3H), 7.17-7.14 (m, 2H), 4.55 (s, 1H), 4.10 (ABX, Δν= 17.8 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.1 Hz, J_{BX} = 2.4 Hz, 2H), 3.83 (dddd, *J* = 10.1, 6.8, 2.8, 2.8 Hz, 1H), 3.75 (s, 3H), 3.36 (dd, *J* = 13.5, 3.1 Hz, 1H), 2.56 (dd, *J* = 13.5, 10.3 Hz, 1H), 1.64 (m, 2H), 1.38 (s, 3H), 1.28 (m, 6H), 0.90 (*t*, *J* = 6.3 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 174.8, 159.0, 136.1, 129.2, 128.8, 126.9, 65.2, 64.8, 59.8, 52.2, 37.9, 35.6, 32.1, 23.7, 22.5, 20.5, 14.0; minor isomer δ 174.8, 158.9, 136.1, 129.2, 128.9, 127.0, 65.0, 60.8, 52.2, 37.3, 35.4, 32.1, 23.8, 22.5, 20.9, 14.0; HRMS (ESI) *m/z* calcd. for $C_{19}H_{29}N_2O_4$ ($[M+H]^+$) 349.2127; Found 349.2134.



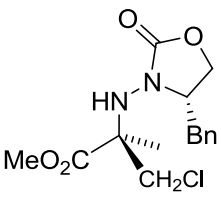
(*S*)-methyl 2-((*S*)-4-benzyl-2-oxooxazolidin-3-ylamino)-2-methyl tetradecanoate (343d). From hydrazone (*E*)-**340** (87 mg, 0.31 mmol) and 1-iododododecane (0.36 mL, 1.55 mmol, 5 equiv) by General Procedure B was obtained starting material (*E*)-**340** (31 mg, 36%) and **343d** (51 mg, 37% yield, dr 69: 31) as a colorless oil; $[\alpha]_D^{22}$ +19.6 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) major isomer δ 7.34-7.25 (m, 3H), 7.19-7.17 (m, 2H), 4.37 (s, 1H), 4.08 (ABX, Δν= 23.3 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.2 Hz, J_{BX} = 2.8 Hz, 2H), 3.90 (dddd, *J* = 10.3, 7.0, 3.2, 3.1 Hz, 1H), 3.75 (s, 3H), 3.41 (dd, *J* = 13.3, 3.0 Hz, 1H), 2.54 (dd, *J* = 13.2, 10.4 Hz, 1H), 1.76 (m, 1H), 1.66 (m,1H), 1.38 (s, 3H), 1.28 (s b,

20H), 0.87 (*t*, *J* = 6.7 Hz, 3H); minor isomer δ 7.34-7.26 (m, 3H), 7.16-7.14 (m, 2H), 4.10 (ABX, Δν= 28.7 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.0 Hz, J_{BX} = 2.3 Hz, 2H), 3.83 (dddd, *J* = 10.0, 6.9, 3.2, 2.7 Hz, 1H), 3.75 (s, 3H), 3.36 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.56 (dd, *J* = 13.4, 10.3 Hz, 1H), 1.68 (m, 2H), 1.37 (s, 3H), 1.28 (s b, 20H), 0.88 (*t*, *J* = 6.7 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 174.9, 159.0, 136.1, 129.2, 128.9, 127.0, 65.2, 64.8, 59.8, 52.2, 37.9, 35.6, 31.9, 29.9, 29.64, 29.62, 29.57, 29.5, 29.33, 24.0, 22.7, 20.5, 14.1; minor isomer δ 174.6, 158.9, 136.1, 129.2, 128.9, 127.0, 65.04, 64.96, 60.8, 52.3, 37.4, 35.4, 31.9, 29.97, 29.67, 29.64, 29.61, 29.5, 29.3, 24.2, 22.7, 21.0, 14.2; HRMS (ESI) *m/z* calcd. for $C_{26}H_{43}N_2O_4$ ($[M+H]^+$) 447.3223; Found 447.3222.

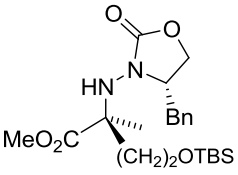


(*S*)-methyl 2-((*S*)-4-benzyl-2-oxooxazolidin-3-ylamino)-2,4-dimethylpentanoate (343e). From hydrazone (*E*)-**340** (103 mg, 0.37 mmol) and 1-iodo-2-methylpropane (0.21 mL, 1.85 mmol, 5 equiv) by General Procedure B was obtained starting material (29 mg, 28%) and **343e** (43 mg, 35% yield, dr 79: 21) as a colorless oil; $[\alpha]_D^{22}$ +19.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 7.34-7.25 (m, 3H), 7.20-7.18 (m, 2H), 4.24 (s, 1H), 4.08 (ABX, Δν= 21.3 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.4 Hz, J_{BX} = 2.8 Hz, 2H), 3.99 (dddd, *J* = 10.2, 6.8, 3.0, 3.0 Hz, 1H), 3.74 (s, 3H), 3.42 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.55 (dd, *J* = 13.3, 10.2 Hz, 1H), 1.78 (m, 1H), 1.74 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.66 (dd, *J* = 13.7, 5.8 Hz, 1H), 1.41 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H); minor isomer δ 7.34-7.25 (m, 3H), 7.17-7.13 (m, 2H), 4.65 (s, 1H), 4.10 (ABX, Δν= 31.5 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.3 Hz, J_{BX} = 2.3 Hz, 2H), 3.85 (dddd, *J* = 10.0, 7.0, 3.2, 3.2 Hz, 1H), 3.73 (s, 3H), 3.35 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.56 (dd, *J* = 13.5, 10.3 Hz, 1H), 1.85 (m, 1H), 1.72 (dd, *J* = 14.0, 6.1 Hz, 1H), 1.61 (dd, *J* = 14.0, 6.6 Hz, 1H), 1.39 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 175.1, 159.2, 136.2, 129.3, 128.8, 126.9, 65.1, 64.8, 59.7, 52.1, 47.1, 35.5, 24.4, 24.1, 23.7, 21.3; minor isomer δ 174.9, 158.7, 136.1, 129.2, 128.9, 127.0, 64.9, 64.5, 60.9, 52.1, 45.9, 35.4,

29.4, 24.0, 23.6, 20.8 HRMS (ESI) *m/z* calcd. for $C_{18}H_{27}N_2O_4$ ($[M+H]^+$) 335.1971; Found 335.1966.

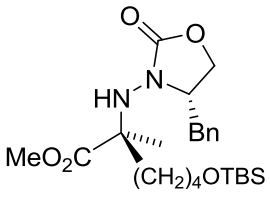


(*R*)-methyl 2-((*S*)-4-benzyl-2-oxooxazolidin-3-ylamino)-3-chloro-2-methylpropanoate (343h). From hydrazone (*E*)-**340** (67 mg, 0.24 mmol) and chloroiodomethane (0.17 mL, 2.4 mmol, 10 equiv) by General Procedure B was obtained starting material (*E*)-**340** (21 mg, 31%) and **343h** (27 mg, 33% yield, dr 85: 15) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 7.34-7.26 (m, 3H), 7.20-7.17 (m, 2H), 4.64 (s, 1H), 4.11 (ABX, Δν= 25.4 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.2 Hz, J_{BX} = 3.0 Hz, 2H), 3.98 (dddd, *J* = 10.3, 7.0, 3.3, 3.2 Hz, 1H), 3.84 (d, *J* = 11.5, 1H), 3.79 (s, 3H), 3.77 (d, *J* = 11.4, 1H), 3.43 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.53 (dd, *J* = 13.2, 10.4 Hz, 1H), 1.51 (s, 3H); minor isomer, 4.46 (s, 1H), 3.78 (s, 3H), 3.39 (dd, *J* = 13.3, 3.6 Hz, 1H), 2.63 (dd, *J* = 13.3, 10.0 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 172.1, 159.0, 135.8, 129.3, 128.9, 127.0, 65.4, 65.0, 60.1, 52.8, 47.9, 35.5, 19.2; minor isomer δ 171.7, 159.3, 135.8, 129.2, 128.9, 127.1, 65.8, 65.3, 60.5, 52.8, 47.8, 35.5, 20.5; HRMS (ESI) *m/z* calcd. for $C_{19}H_{20}N_2O_4Cl$ ($[M+H]^+$) 327.1112; Found 349.1117.

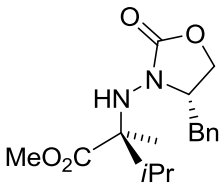


(*S*)-methyl 2-((*S*)-4-benzyl-2-oxooxazolidin-3-ylamino)-4-(*tert*-butyldimethylsilyloxy)-2-methylbutanoate (343f). From hydrazone (*E*)-**340** (85 mg, 0.31 mmol) and 2-(*tert*-butyldimethylsilyloxy)-1-iodoethane (443 mg, 1.55 mmol, 5 equiv) by General Procedure B was obtained starting material (*E*)-**340** (20 mg, 24%) and **343f** (49 mg, 36% yield, dr 69: 31) as a colorless oil; $[\alpha]_D^{22}$ +24.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 7.34-7.25 (m, 3H), 7.20-7.18 (m, 2H), 4.72 (s, 1H), 4.07 (ABX, Δν= 21.9 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.2 Hz, J_{BX} = 2.6 Hz, 2H), 3.96 (dddd, *J* = 9.9, 6.9, 3.2, 2.8 Hz, 1H), 3.78 (m, 2H), 3.74 (s, 3H), 3.42 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.54 (dd, *J* = 13.3, 10.2 Hz,

1H), 2.02 (m, 2H), 1.44 (s, 3H), 0.89 (s, 9H), 0.071 (s, 3H), 0.066 (s, 3H); minor isomer δ 7.34-7.25 (m, 3H), 7.17-7.15 (m, 2H), 4.70 (s, 1H), 4.10 (ABX, Δν= 31.0 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.3 Hz, J_{BX} = 2.4 Hz, 2H), 3.88 (dddd, *J* = 10.2, 6.9, 3.2, 3.1 Hz, 1H), 3.78 (m, 2H), 3.74 (s, 3H), 3.35 (dd, *J* = 13.5, 3.1 Hz, 1H), 2.56 (dd, *J* = 13.4, 10.2 Hz, 1H), 1.99 (m, 2H), 1.41 (s, 3H), 0.90 (s, 9H), 0.067 (s, 3H), 0.061 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 174.6, 159.0, 136.2, 129.3, 128.9, 126.9, 65.1, 64.0, 59.7, 59.1, 52.2, 40.2, 35.5, 25.9, 20.7, 18.3, -5.41, -5.47; minor isomer δ 174.2, 158.8, 136.0, 129.2, 128.9, 127.0, 65.1, 63.5, 60.7, 59.2, 52.3, 39.8, 35.4, 25.9, 21.2, 18.3, -5.35, -5.41; HRMS (ESI) *m/z* calcd. for $C_{22}H_{37}N_2O_5Si$ ($[M+H]^+$) 437.2472; Found 437.2465.

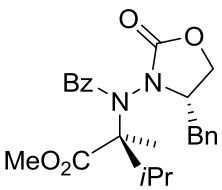


(*S*)-methyl 2-((*S*)-4-benzyl-2-oxooxazolidin-3-ylamino)-6-(*tert*-butyldimethylsilyloxy)-2-methylhexanoate (343g). From hydrazone (*E*)-**340** (62 mg, 0.22 mmol) and 4-(*tert*-butyldimethylsilyloxy)-1-iodobutane (346 mg, 1.10 mmol, 5 equiv) by General Procedure B was obtained starting material (*E*)-**340** (13 mg, 21%) and **343g** (26 mg, 25% yield, dr 73: 27) as a colorless oil; $[\alpha]_D^{22}$ +16.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 7.34-7.25 (m, 3H), 7.18-7.17 (m, 2H), 4.40 (s, 1H), 4.08 (ABX, Δν= 22.8 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.3 Hz, J_{BX} = 3.0 Hz, 2H), 3.91 (dddd, *J* = 10.2, 6.9, 3.3, 3.1 Hz, 1H), 3.74 (s, 3H), 3.61 (t, *J* = 6.2 Hz, 2H), 3.40 (dd, *J* = 13.3, 3.1 Hz, 1H), 2.55 (dd, *J* = 13.3, 10.3 Hz, 1H), 1.78 (m, 1H), 1.69 (m, 1H), 1.53 (m, 2H), 1.39 (s, 3H), 0.89 (s, 9H), 0.044 (s, 6H); minor isomer δ 3.63 (t, *J* = 6.2 Hz, 2H), 3.34 (dd, *J* = 13.3, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 174.7, 159.1, 136.1, 129.2, 128.9, 127.0, 65.2, 64.9, 62.7, 59.8, 52.2, 37.8, 35.6, 33.0, 25.9, 20.6, 20.5, 18.3, -5.3; minor isomer δ 174.5, 158.7, 136.0, 129.2, 128.9, 127.0, 65.01, 64.99, 62.8, 60.8, 52.3, 37.2, 35.5, 33.1, 25.9, 20.7, 20.6, 18.3, -5.3; HRMS (ESI) *m/z* calcd. for $C_{24}H_{41}N_2O_5Si$ ($[M+H]^+$) 465.2785; Found 465.2775.



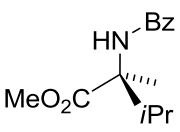
(*S*)-Methyl 2-((*S*)-4-benzyl-2-oxooxazolidin-3-ylamino)-2,3-dimethylbutanoate (343b). From hydrazone (*E*)-**340** (236 mg, 0.85 mmol) and 2-iodopropane (0.42 mL, 4.25 mmol, 5 equiv) by General Procedure B was obtained **343b** (231 mg, 85% yield) as a colorless oil, $[\alpha]_D^{22}$ +34.3 (*c* 0.6, $CHCl_3$); IR (film) 3293, 2963, 1765, 1728, 1453, 1391, 1252, 1123, 1095, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (m, 3H), 7.19-7.17 (m, 2H), 4.33 (s, 1H), 4.07 (ABX, Δν= 16.3 Hz, J_{AB} = 8.9 Hz, J_{AX} = 7.4 Hz, J_{BX} = 3.5 Hz, 2H), 3.89 (dddd, *J* = 10.5, 7.4, 3.5, 3.2 Hz, 1H), 3.75 (s, 3H), 3.42 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.54 (dd, *J* = 13.2, 10.5 Hz, 1H), 2.11 (septet, *J* = 6.9 Hz, 1H), 1.28 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 158.9, 136.1, 129.2, 128.9, 127.0, 67.5, 65.4, 59.3, 52.1, 35.9, 33.7, 17.5, 16.9, 15.6; MS (EI) *m/z* (relative intensity) 320 (M^+, 0.9%), 277 ($[M–i\text{-}Pr]^+$, 52%), 261 ($[M–CO_2Me]^+$, 48%); Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 64.01; H, 7.63; N, 8.62.

From hydrazone (*Z*)-**340** (36 mg, 0.13 mmol) and 2-iodopropane (0.07 mL, 0.65 mmol, 5 equiv) by General Procedure B was obtained **343b** (21 mg, 50% yield) as a colorless oil.

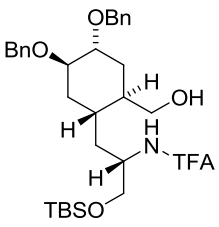


(*S*)-Methyl 2-(*N*-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)benzamido)-2,3-dimethyl-butanoate (344). To a solution of **343b** (58 mg, 0.18 mmol) in dry THF (1.2 mL) under Ar at –78 °C was added *n*-BuLi (2.3 M in hexanes, 0.16 mL, 0.36 mmol, 2 equiv) dropwise. After 1 h at –78 °C, benzoic anhydride (87 mg, 0.40 mmol, 2.2 equiv) in dry THF (0.6 mL) was added. The mixture was allowed to warm to ambient temperature, and after 2 h, was quenched with water. Concentration and flash chromatography (hexane → 1:1 hexane/EtOAc) afforded **344** (64 mg, 84% yield) as a colorless solid; mp 170–171°C; $[\alpha]_D^{23}$ +9.1 (*c* 0.7, $CHCl_3$); IR (film) 2926, 1777, 1726, 1666, 1449, 1351, 1267, 1220,

1083, 1030 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.04-8.01 (m, 2H), 7.03-6.92 (m, 8H), 4.43 (dddd, *J* = 11.4, 8.9, 8.4, 2.8 Hz, 1H), 3.56 (septet, *J* = 6.9 Hz, 1H), 3.49 (s, 3H), 3.48 (dd, *J* = 11.7, 3.0 Hz, 1H), 3.33 (ABX, Δν = 14.7 Hz, J_{AB} = 8.7 Hz, J_{AX} = 9.0 Hz, J_{BX} = 9.0 Hz, 2H), 1.57 (dd, *J* = 11.7, 11.7 Hz, 1H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.23 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 173.7, 156.9, 135.2, 134.6, 131.6, 128.9, 128.8, 128.41, 128.36, 127.2, 73.2, 67.1, 60.2, 52.6, 38.5, 30.4, 20.3, 18.7, 14.9; MS (ESI) *m/z* (relative intensity) 447 ($[M+Na]^+$, 100%), 425 ($[M+H]^+$, 9%); Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found: C, 68.04; H, 6.73; N, 6.42.

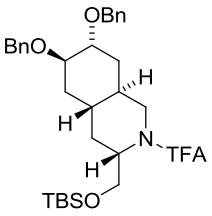


(*S*)-Methyl 2-benzamido-2,3-dimethylbutanoate ((*S*)-(+)-334b).[281] To a solution of **344** (48 mg, 0.11 mmol) in dry THF (1 mL) and dry MeOH (1 mL) under Ar was added SmI_2 (3.30 mL, 0.277 M in THF) dropwise. After ca. 12 h, the mixture was quenched with saturated aqueous NH_4Cl, concentrated, and partitioned between dichloromethane and saturated aqueous $NaHCO_3$. Concentration and flash chromatography gave **3112a** (21 mg, 85%) and (*S*)-(+)-**334b** (31 mg, 87% yield) as a colorless oil; HPLC (Chiral Pak OD-H, 5% *i*-PrOH/hexane, 1 mL/min) t_R 11.1 min (major), t_R 8.8 min (minor), er 95:5; $[\alpha]_D^{24}$ +17.7 (*c* 0.7, $CHCl_3$), lit.[281] $[\alpha]_D$ +21.5 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79-7.75 (m, 2H), 7.53-7.40 (m, 3H), 6.76 (br. s, 1H), 3.77 (s, 3H), 2.41 (septet, *J* = 6.9 Hz, 1H), 1.70 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H).



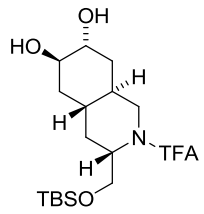
***N*-((*S*)-1-((1*R*,2*R*,4*R*,5*R*)-4,5-Bis(benzyloxy)-2-(hydroxymethyl)cyclohexyl)-3-(tert-butyldimethylsilyloxy)propan-2-yl)-2,2,2-trifluoroacetamide (369).** To a solution of **367**[260] (104 mg, 0.17 mmol) in THF (1.7 mL), was added *n*-BuLi (1.7 M in hexanes, 0.22 mL, 0.38 mmol) at –78 °C. After 1 h, trifluoroacetic anhydride (0.21 mL, 1.51 mmol) was added at –78 °C, and the mixture was allowed to warm to ambient temperature overnight. The reaction

was quenched by saturated NH_4Cl solution and the organic phase was washed with water, saturated $NaHCO_3$ solution and brine, then dried (Na_2SO_4) and concentrated to afford the trifluoroacetohydrazide. This material was taken up in MeOH (1 mL) and a solution of SmI_2 in THF (0.3 M, 4.33 mL) was added dropwise until the blue color remained. After 1 h, the reaction mixture was opened to the air. Concentration and flash chromatography (hexane/EtOAc 10:1 to 3:1) afforded **369** (66 mg, 72% yield) as a pale yellow oil; $[\alpha]_D^{24.1}$ –50.1 (*c* 0.9, $CHCl_3$); IR (film) 3424, 3317, 3088, 3063, 3030, 2925, 2855, 1711, 1551, 1462, 1253, 1182, 1161, 1095, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 6.94 (d, J = 8.4 Hz, 1H), 4.50 (ABq, Δν = 19.6 Hz, J_{AB} = 12.0 Hz, 2H), 4.48 (ABq, Δν = 54.2 Hz, J_{AB} = 12.0 Hz, 2H), 4.16-4.08 (m, 1H), 3.75 (dd, J = 11.2, 4.4 Hz, 1H), 3.68 (dd, J = 10.2, 4.4 Hz, 1H), 3.68-3.62 (m, 2H), 3.61 (dd, J = 10.2, 3.4 Hz, 1H), 3.51 (dd, J = 11.0, 3.0 Hz, 1H), 2.03-1.94 (m, 2H), 1.85-1.78 (m, 2H), 1.76-1.57 (m, 3H), 1.47 (ddd, J = 13.9, 11.7, 2.5 Hz, 1H), 1.29 (ddd, J = 13.9, 9.2, 4.3 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.1 ($^2J_{CF}$ = 36.4 Hz), 138.7, 138.6, 128.33, 128.27, 127.49, 127.46, 127.41, 127.36, 116.0 ($^1J_{CF}$ = 286.3 Hz), 75.0, 74.1, 70.8, 70.5, 64.9, 64.7, 49.5, 38.4, 33.9, 30.3, 28.9, 28.1, 25.8, 18.2, –5.5, –5.6; MS (ESI) *m/z* (relative intensity) 610.01 ($[M+H]^+$, 13%), 632.29 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{32}H_{47}F_3NO_5Si$ ($[M+H]^+$) 610.3176; Found 610.3180.

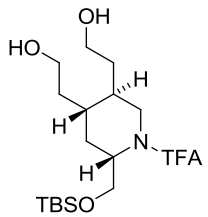


1-((3*S*,4a*R*,6*R*,7*R*,8a*R*)-6,7-Bis(benzyloxy)-3-((tert-butyldimethylsilyloxy)-methyl)octahydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (370). To a solution of trifluoroacetamide **369** (53 mg, 0.087 mmol) and PPh_3 (47 mg, 0.18 mmol) in THF (4.5 mL) at 0 °C was added diisopropyl azodicarboxylate (0.036 mL, 0.18 mmol). The mixture was allowed to warm to ambient temperature and stirred overnight. Concentration and flash chromatography (hexane to 5:1 hexane/EtOAc) afforded **370** (49 mg, 95% yield) as a pale yellow oil; $[\alpha]_D^{23.3}$ –52.0 (*c* 1.0, $CHCl_3$); IR (film) 3064, 3031,

2928, 2857, 1685, 1454, 1253, 1205, 1171, 1141, 1090, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 10H), 4.51 (ABq, Δν = 23.7 Hz, J_{AB} = 12.0 Hz, 2H), 4.50 (ABq, Δν = 24.9 Hz, J_{AB} = 12.0 Hz, 2H), 4.02-3.65 (br m, 6H), 3.17 (br s, 1H), 1.90-1.77 (m, 4H), 1.64-1.48 (m, 3H), 1.40-1.25 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 138.5, 138.4, 128.4 (2C), 127.6, 127.41, 127.39 (2C), 116.6 ($^1J_{CF}$ = 286.6 Hz), 74.2, 74.1, 70.8 (2C), 64.0, 31.9, 30.4, 25.8, 18.2, –5.51, –5.53, some peaks not observed due to line broadening related to TFA rotamers; MS (ESI) *m/z* (relative intensity) 592.00 ($[M+H]^+$, 52%), 614.19 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{32}H_{45}F_3NO_4Si$ ($[M+H]^+$) 592.3070; Found 592.3073.

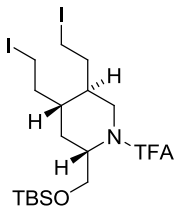


1-((3*S*,4a*R*,6*R*,7*R*,8a*R*)-3-((*tert*-Butyldimethylsilyloxy)methyl)-6,7-dihydroxy-octahydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (371). To a solution of bis-benzyl ether **370** (49 mg, 0.083 mmol) in EtOAc (2 mL) was added Pd/C (10% *w*/*w*, 0.21 mmol). The mixture was stirred under H_2 (balloon) for 2 days. Filtration, concentration and flash chromatography (hexane/EtOAc 3:1 to 1:1) afforded **371** (32 mg, 93% yield) as a colorless oil; $[\alpha]_D^{24.0}$ –53.3 (*c* 0.7, $CHCl_3$); IR (film) 3429, 2930, 2859, 1683, 1464, 1255, 1205, 1147, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94-3.80 (m, 6H), 3.20 (br s, 1H), 1.92-1.53 (m, 9H), 1.29 (br s, 1H), 0.87 (s, 9H), 0.039 (s, 3H), 0.038 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 116.5 ($^1J_{CF}$ = 286.6 Hz), 69.5, 63.9, 34.1, 32.9, 31.6, 25.8, 18.1, –5.5, –5.6, some peaks exhibited line broadening related to TFA rotamers; MS (ESI) *m/z* (relative intensity) 411.92 ($[M+H]^+$, 100%), 280.20 ($[M–OTBS]^+$, 58%); HRMS (ESI) *m/z* calcd. for $C_{18}H_{33}F_3NO_4Si$ ($[M+H]^+$) 412.2131; Found 412.2138.



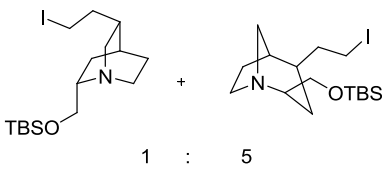
1-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4,5-bis(2-hydroxyethyl)-piperidin-1-yl)-2,2,2-trifluoroethanone (373). To a solution of vicinal diol **371** (144 mg, 0.35 mmol) in CH_2Cl_2 (3.5 mL)

was added silica gel-supported $NaIO_4$ (0.667 mmol/g, 577 mg, 0.385 mmol). After the mixture was stirred overnight, filtration and concentration afforded an unstable dialdehyde. This material was taken up in MeOH (35 mL), and to this solution was added $NaBH_4$ (26 mg, 0.69 mmol) at 0 °C. After 1 h the solution was concentrated and partitioned between CH_2Cl_2 and water, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography (hexane/EtOAc 1:1 to EtOAc) afforded diol **373** (133 mg, 92% yield) as a colorless oil; $[\alpha]_D^{25.0}$ –54.9 (*c* 0.5, $CHCl_3$); IR (film) 3366, 2930, 2859, 1683, 1472, 1451, 1256, 1202, 1143, 1114, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.13-4.05 (m, 1H), 3.98 (dd, *J* = 10.4, 3.9 Hz, 1H), 3.78-3.53 (m, 7H), 1.80-1.77 (m, 6H), 1.66-1.52 (m, 3H), 1.39-1.33 (m, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.6 ($^2J_{CF}$ = 34.9 Hz), 116.4 ($^1J_{CF}$ = 288.5 Hz), 62.1, 60.6, 60.0, 55.4, 43.9, 38.0, 36.1, 34.9, 33.8, 27.8, 25.8, 18.1, –5.7 (2C); MS (ESI) *m/z* (relative intensity) 414.02 ($[M+H]^+$, 100%), 436.15 ($[M+Na]^+$, 30%); HRMS (ESI) *m/z* calcd. for $C_{18}H_{35}F_3NO_4Si$ ($[M+H]^+$) 414.2287; Found 414.2287.

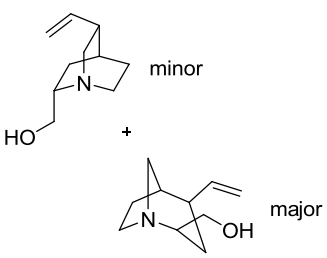


1-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4,5-bis(2-iodo ethyl)-piperidin-1-yl)-2,2,2-trifluoroethanone (374). To a solution of diol **373** (68 mg, 0.16 mmol), PPh_3 (173 mg, 0.66 mmol) and imidazole (56 mg, 0.82 mmol) in THF (10 mL) at 0 °C was added I_2 (168 mg, 0.66 mmol) in two portions over 15 min. After 1 h the mixture was quenched with sat. $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded the diiodide **374** (105 mg, quantitative) as a colorless oil; $[\alpha]_D^{24.2}$ –5.3 (*c* 0.4, $CHCl_3$); IR (film) 2953, 2928, 2857, 1679, 1449, 1198, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.13-4.07 (m, 1H), 4.02 (br d, *J* = 8.5 Hz, 1H), 3.67 (br, 1H), 3.58-3.52 (m, 2H), 3.38-3.30 (m, 2H), 3.18-3.05 (m, 2H), 2.14-2.06 (m, 1H), 1.88-1.72 (m, 5H), 1.66-1.58 (m, 1H), 1.34-1.25

(m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.1, 55.3, 42.9, 40.1, 38.4, 37.4, 35.5, 26.5, 25.8, 18.2, 3.9, 3.6, –5.6 (2C); HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{33}F_3I_2NO_2Si$ ($[M+H]^+$) 634.0322; Found 634.0336.

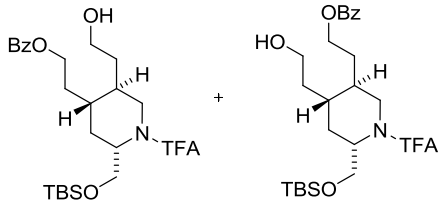


(2*S*,4*S*,8*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-8-(2-iodoethyl)-quinuclidine (375a) and (2*S*,4*R*,5*R*)-2-((*tert*-butyldimethylsilyloxy)-methyl)-4-(2-iodoethyl)-1-azabicyclo[3.2.1]octane (375b). To a solution of diiodide **374** (32 mg, 0.051 mmol) in MeOH (2 mL) was added NH_3/MeOH (7N, 2 mL). After ca. 12 h, the mixture was concentrated and purified by flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 10:1) to provide the tertiary amines **375a** and **375b** as an inseparable mixture of isomers (21 mg, quantitative, ratio 5:1) as colorless oil; IR (film) 2952, 2927, 2855, 1467, 1255, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 4.08 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.99-3.92 (m, 2H), 3.50-3.53 (m, 2H), 3.48-3.40 (m, 1H), 3.22-3.10 (m, 2H), 3.08 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.55-2.50 (m, 1H), 2.36 (dddd, *J* = 13.2, 12.4, 6.8, 5.2 Hz, 1H), 2.11 (ddd, *J* = 15.6, 7.6. 7.2 Hz, 1H), 2.02-1.88 (m, 4H), 1.61 (ddd, *J* = 15.6, 3.6, 2.8 Hz, 1H), 0.91 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 63.8, 62.8, 53.8, 48.9, 38.4, 38.0, 36.3, 28.3, 26.1, 21.6, 18.4, 3.2, –5.0, –5.2; minor isomer: δ 62.1, 58.5, 54.7, 43.0, 36.5, 33.8, 25.8, 24.5, 24.3, 21.0, 18.1, 2.4, –5.3, –5.5; MS (ESI) *m*/*z* (relative intensity) 410.10 ($[M+H]^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{16}H_{33}NOISi$ ($[M+H]^+$) 410.1376; Found 410.1386.



((2S,4R,5R)-4-vinyl-1-azabicyclo[3.2.1]octan-2-yl)methanol (376). To a solution of iodide **375** (32 mg, 0.08 mmol) in DMSO (8 mL) was added TBAF•3H_2O (73 mg, 0.23 mmol) and stirred overnight. The mixture was washed with sat. $NaHCO_3$, extracted with CH_2Cl_2 and concentrated. The residue

was dissolved in THF (1 mL). Then TBAF/THF (1M, 0.13 mL, 0.13 mmol) was added. The mixture was stirred overnight. Then the reaction mixture was washed with sat. $NaHCO_3$, extracted with CH_2Cl_2 and concentrated. The residue was distilled by cold finger at the different temperature range (100 ^oC, 150 ^oC and 200 ^oC), and washed traces of condensate from the finger with $CDCl_3$ in every range to obtain several fractions. The fraction at about 150 ^oC was more pure and ~3 mg of **376** (< 20% yield); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 143.0, 113.8, 63.8, 62.5, 53.7, 47.0, 42.1, 37.5, 31.0, 23.5.

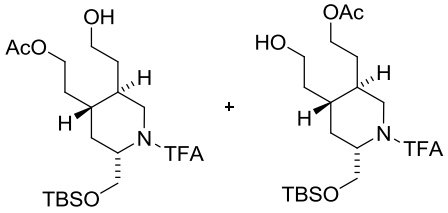


2-((2*S*,4*R*,5*R*)-2-((tert-butyldimethylsilyloxy)methyl)-5-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-4-yl)ethyl benzoate (377a) and 2-((3*R*,4*R*,6*S*)-6-((tert-butyldimethylsilyloxy)methyl)-4-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-3-yl)ethyl benzoate (377b). To a solution of diol **373** (16 mg, 0.039 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (2.2 M, 19 μL, 0.043 mmol). After 1 h, $(PhCO)_2O$ (9 mg, 0.041 mmol) was added and the mixture was allowed to warm to ambient temperature overnight. The mixture was partitioned between water and CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded **377a** (4.8 mg, 24%) and **377b** (5.9 mg, 29%) as colorless oils.

377a $[\alpha]_D^{23.2}$ –31.2 (*c* 0.2, $CHCl_3$); IR (film) 3435, 2955, 2927, 2855, 1722, 1680, 1462, 1275, 1203, 1144, 1113, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04-7.99 (m, 2H), 7.59-7.53 (m, 1H), 7.47-7.41 (m, 2H), 4.49-4.35 (m, 2H), 4.15-3.99 (m, 2H), 3.77-3.50 (m, 4H), 2.10-1.98 (m, 1H), 1.90-1.80 (m, 3H), 1.80-1.68 (m, 2H), 1.68-1.56 (m, 2H), 1.43-1.26 (m, 2H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 133.1, 130.1, 129.5, 128.4, 62.7, 62.2, 60.0, 55.6, 43.9, 43.9, 36.4, 35.0, 34.4, 34.0, 27.6, 25.8, 18.1, –5.7 (2C); MS (ESI) *m/z* (relative intensity) 540 ($[M+Na]^+$,

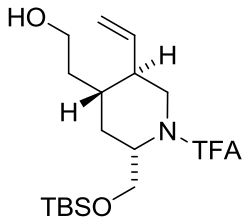
26%), 518 ([M+H]$^+$, 100%), 386 ([M–OBz]$^+$, 80%); HRMS (ESI) *m/z* calcd. for $C_{25}H_{39}F_3NO_5Si$ ([M+H]$^+$) 518.2550; Found 518.2570.

377b $[\alpha]_D^{23.2}$ –18.3 (*c* 0.3, $CHCl_3$); IR (film) 3434, 2949, 2927, 2856, 1722, 1679, 1451, 1275, 1203, 1142, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.99 (m, 2H), 7.58-7.53 (m, 1H), 7.48-7.41 (m, 2H), 4.42-4.32 (m, 2H), 4.16-4.08 (m, 1H), 4.05-3.97 (m, 1H), 3.77-3.55 (m, 4H), 2.03-1.54 (m, 8H), 1.43-1.25 (m, 2H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 133.0, 130.1, 129.5, 128.4, 62.5, 62.2, 60.5, 55.6, 43.8, 37.9, 37.1, 33.9, 31.2, 27.7, 25.8, 18.2, –5.6 (2C); MS (ESI) *m/z* (relative intensity) 540.24 ([M+Na]$^+$, 40%), 518 ([M+H]+, 100%), 386 ([M–OBz]$^+$, 10%), 308 (60%); HRMS (ESI) *m/z* calcd. for $C_{25}H_{39}F_3NO_5Si$ ([M+H]$^+$) 518.2550; Found 518.2558.



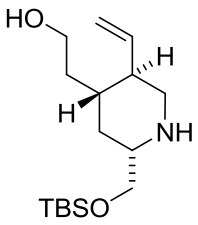
2-((3*R*,4*R*,6*S*)-6-((tert-butyldimethylsilyloxy)methyl)-4-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-3-yl)ethyl acetate (384a) and 2-((2*S*,4*R*,5*R*)-2-((tert-butyldimethylsilyloxy)methyl)-5-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-4-yl)ethyl acetate (384b). To a solution of diol **373** (155 mg, 0.38 mmol) in CH_2Cl_2 (16 mL) was added vinyl acetate (0.038 mL, 0.41 mmol) and lipase acrylic resin (*Candida antarctica*, 31 mg, 0.012 mmol). After 7 days, filtration, concentration and radial chromatography (hexane/EtOAc 10:1 to 1:1) afforded starting material (49 mg, 32%), which can be reused, **384a** (60 mg, 35%) and **384b** (50 mg, 29%) as colorless oils. **384a:** $[\alpha]_D^{24.0}$ –50.7 (c 0.6, $CHCl_3$); IR (film) 3466, 2955, 2929, 2861, 1739, 1683, 1471, 1367, 1252, 1193, 1143, 1052 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19-4.01 (m, 3H), 3.99 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.73 (ddd, *J* = 10.8, 5.5, 5.5 Hz, 1H), 3.69-3.53 (m, 4H), 2.05 (s, 3H), 1.92-1.86 (m, 1H), 1.82-1.76 (m, 1H), 1.70-

1.45 (m, 6H), 1.28-1.20 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7 ($^2J_{CF}$ = 35.2 Hz), 116.4 ($^1J_{CF}$ = 286.0 Hz), 62.2, 62.1, 59.9, 55.5, 43.8, 36.2, 34.8, 34.1, 33.7, 27.4, 25.8, 21.0, 18.1, –5.7 (2C); HRMS (ESI) *m/z* calcd. for $C_{20}H_{37}F_3NO_5Si$ ($[M+H]^+$) 456.2393; Found 456.2396. **384b:** $[\alpha]_D^{23.1}$ –42.4 (c 0.5, $CHCl_3$); IR (film) 3469, 2949, 2928, 2857, 1741, 1678, 1462, 1366, 1249, 1202, 1142, 1110, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15-4.02 (m, 3H), 3.99 (dd, *J* = 10.0, 3.4 Hz, 1H), 3.77-3.51 (m, 5H), 2.05 (s, 3H), 1.81-1.45 (m, 8H), 1.33-1.27 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5 ($^2J_{CF}$ = 34.0 Hz), 116.4 ($^1J_{CF}$ = 285.9 Hz), 62.1, 60.5, 55.5, 43.7, 37.9, 37.2, 33.9, 30.9, 27.6, 25.8, 20.9, 18.1, –5.7; MS (ESI) *m/z* (relative intensity) 456.05 ($[M+H]^+$, 41%), 478.26 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{20}H_{37}F_3NO_5Si$ ($[M+H]^+$) 456.2393; Found 456.2402.

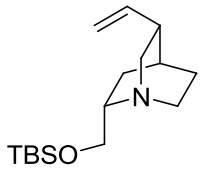


1-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4-(2-hydroxyethyl)-5-vinylpiperidin-1-yl)-2,2,2-trifluoroethanone (387). To a solution of monoester alcohol **384a** (22 mg, 0.048 mmol) in THF (0.48 mL) was added 2-$O_2NC_6H_5SeCN$ (22 mg, 0.096 mmol) and Bu_3P (24 μL, 0.096 mmol). The reaction mixture was heated at 60 °C overnight. The mixture was concentrated and the residue was dissolved in THF (1 mL). To this solution was added aqueous H_2O_2 (30% *w*/*w*, 0.09 mL, 0.82 mmol). After ca. 12 h, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography afforded an olefinic ester (21 mg, quantitative). To a solution of the olefinic ester (10 mg, 0.023 mmol) in MeOH (1 mL) was added NaOMe/MeOH solution (0.1 M, 0.23 mL, 0.023 mmol) in five portions over 5 h with TLC monitoring. Concentration and flash chromatography (hexane/EtOAc 10:1 to 3:1) afforded **387** (8.3 mg, 92%) as a colorless oil; $[\alpha]_D^{25.5}$ –60.3 (c 0.4, $CHCl_3$); IR (film) 3448, 2954, 2929, 2858, 1685, 1463, 1255, 1204, 1145, 1117, 1054 cm^{-1}; ^{1}H NMR (400

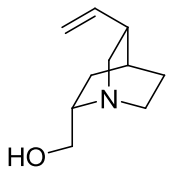
MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 17.1, 9.7, 9.2 Hz, 1H), 5.09-5.04 (m, 2H), 4.13-4.08 (m, 1H), 3.99-3.91 (m, 1H), 3.76-3.60 (m, 5H), 2.10 (m, apparent q, *J* = 8.2 Hz, 1H), 1.89 (dd, *J* = 11.4, 4.0 Hz, 1H), 1.83-1.67 (m, 2H), 1.53-1.46 (m, 2H), 1.26-1.20 (m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 116.5 ($^1J_{CF}$ = 286.6 Hz), 116.1, 63.0 (br), 60.9, 56.1, 46.3 (br), 46.0, 37.2, 33.1, 28.0, 26.1, 18.3, –5.5 (2C); HRMS (ESI) *m/z* calcd. for $C_{18}H_{33}F_3NO_3Si$ ($[M+H]^+$) 396.2182; Found 396.2188.



2-((2*S*,4*R*,5*R*)-2-((tert-butyldimethylsilyloxy)methyl)-5-vinylpiperidin-4-yl)ethanol (385). To a solution of alcohol **387a** (22 mg, 0.048 mmol) in THF (0.48 mL) was added 2-$O_2NC_6H_5SeCN$ (22 mg, 0.096 mmol) and Bu_3P (24 μL, 0.096 mmol). The reaction mixture was heated at 60 °C overnight. The mixture was concentrated and the residue was dissolved in THF (1 mL). To this solution was added aqueous H_2O_2 (30% w/w, 0.09 mL, 0.082 mmol). After ca. 12 h, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography afforded olefin (21 mg, quantitative). To a solution of olefin above (5.8 mg, 0.013 mmol) in MeOH/H_2O (5:1, 0.6 mL) at 0 °C was added $Ba(OH)_2$•$8H_2O$ (33 mg, 0.10 mmol), and the mixture was allowed to warm to ambient temperature. After 2 h, the mixture was diluted with CH_2Cl_2, filtered, and concentrated to afford **385** (4.0 mg, quantitative) as a colorless oil; $[\alpha]_D^{24.1}$ +28.2 (*c* 0.4, $CHCl_3$); IR (film) 3318, 3076, 2954, 2928, 2856, 1462, 1256, 1086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (ddd, *J* = 17, 10, 10 Hz, 1H), 5.10-5.04 (m, 2H), 3.73-3.60 (m, 2H), 3.58 (dd, *J* = 9.7, 3.8 Hz, 1H), 3.42 (dd, *J* = 9.6 Hz, 7.8 Hz, 1H), 3.02 (dd, *J* = 11.8, 4.2 Hz, 1H), 2.67-2.60 (m, 1H), 2.50 (dd, *J* = 11.6, 11.3 Hz, 1H), 1.92-1.82 (m, 2H), 1.72-1.65 (m, 3H), 1.45-1.35 (m, 1H), 1.32-1.25 (m, 2H), 0.89 (s, 9H), 0.052 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.5, 67.6, 60.3, 57.8, 52.3, 48.3, 37.0, 36.7, 33.5, 25.9, 18.3, –5.4 (2C); MS (ESI) *m/z* (relative intensity) 300.20 ($[M+H]^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{16}H_{34}NO_2Si$ ($[M+H]^+$) 300.2359; Found 300.2364.

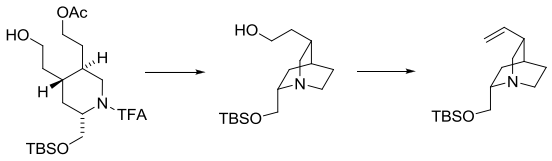


***O*-(*tert*-Butyldimethylsilyl)quincorine (386).** To a solution of alcohol **387** (5.2 mg, 0.013 mmol) was added PPh_3 (6.8 mg, 0.026 mmol) and imidazole (2.2 mg, 0.032 mmol) in THF (0.5 mL) at 0 °C was added I_2 (7 mg, 0.028 mmol) in two portions over 15 min. The mixture was stirred for 1 h, quenched with sat. $Na_2S_2O_3$, and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded the iodide, which was dissolved in MeOH (0.4 mL). To this solution was added NH_3/MeOH (7N, 0.4 mL). After ca. 12 h, concentration and flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 10:1) afforded *O*-TBS-quincorine (**386**, 3 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.24 (d, *J* = 10.8 Hz, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 4.37 (br d, *J* = 10.4 Hz, 1H), 3.76 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.72-3.62 (m, 1H), 3.45 (dd, *J* = 13.3, 10.8 Hz, 1H), 3.36-3.28 (m, 1H), 3.18-3.03 (m, 2H), 2.72-2.64 (m, 1H), 2.13-2.09 (m, 1H), 2.03-1.90 (m, 2H), 1.90-1.79 (m, 1H), 0.92 (s, 9H), 0.90-0.84 (m, 1H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 117.3, 62.3, 58.3, 53.9, 43.1, 36.9, 27.1, 25.9, 24.5, 21.0, 18.2, –5.3, –5.6; HRMS (ESI) *m/z* calcd. for $C_{16}H_{32}NOSi$ ($[M+H]^+$) 282.2253; Found 282.2266.



Quincorine (389). To a solution of **386** (8 mg, 0.028 mmol) in THF (1 mL) was added TBAF (1 M in THF, 37 μL, 0.037 mmol) at 0 °C. The solution was allowed to warm to ambient temperature. After ca. 12 h, concentration and preparative TLC (CH_2Cl_2/MeOH 2:1) afforded quincorine (**386**, 5.1 mg, 78%) as a colorless oil; $[\alpha]_D^{22.5}$ +38 (*c* 0.3, MeOH) [lit. $[\alpha]_D^{20}$ +39 (*c* 1.0, MeOH)[282]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 17.3, 10.4, 7.6 Hz, 1H), 5.07-5.01 (m, 2H), 3.46-3.43 (m, 2H), 3.17 (dd, *J* = 14.0 Hz, *J* = 6.0 Hz, 1H), 2.98-2.90 (m, 3H), 2.70-2.57 (m, 2H), 2.34-2.29 (m, 1H), 1.85-1.79 (m, 1H), 1.75-1.71 (m, 1H), 1.57-1.41 (m, 2H), 0.80-0.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 114.3,

63.0, 57.2, 55.7, 40.3, 40.1, 28.0, 27.3, 24.7; HRMS (ESI) *m/z* calcd. for $C_{10}H_{18}NO$ ($[M+H]^+$) 168.1388; Found 168.1388.



Alternative Preparation of 386. To a solution of alcohol **384b** (18 mg, 0.053 mmol), PPh_3 (28 mg, 0.11 mmol) and imidazole (9 mg, 0.13 mmol) in THF (0.5 mL) at 0 °C was added I_2 (27 mg, 0.11 mmol) in two portions over 15 min. After 1 h the mixture was quenched with sat. $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded the iodide. This material was dissolved in MeOH (1.5 mL). To this solution was added NH_3/MeOH (7N, 1.5 mL). After ca. 12 h, the mixture was concentrated to provide the tertiary amine (18 mg). To a solution of the tertiary amine (13 mg) in MeOH/H_2O (5:1, 0.6 mL) was added $Ba(OH)_2$•$8H_2O$ (60 mg, 0.19 mmol) at 0 °C. The mixture was allowed to warm to ambient temperature. After 2 h, the mixture was diluted with CH_2Cl_2, filtered and purified by flash chromatography (CH_2Cl_2/MeOH 3:1 to 1:1) to afford **388** (11 mg, 85% over 3 steps) as a colorless oil; $[\alpha]_D^{25.4}$ +5.8 (*c* 0.3, $CHCl_3$); IR (film) 3352, 2950, 2927, 2857, 1463, 1254, 1117, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, *J* = 10.8, 6.0, 1H), 3.72-3.66 (m, 3H), 3.33 (dd, *J* = 13.6, 10.8 Hz, 1H), 3.27-3.17 (m, 1H), 3.12-3.04 (m, 1H), 2.88-2.78 (m, 1H), 2.68 (ddd, *J* = 13.2, 5.2, 2.4 Hz, 1H), 2.5 (br, 1H), 1.93-1.81 (m, 2H), 1.69 (m, apparent q, *J* = 6.8 Hz, 2H), 1.66-1.53 (m, 1H), 1.40 (br dd, *J* = 13.2, 6.8 Hz, 1H), 1.33-1.28 (br, 1H), 0.93-0.88 (m, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 60.8, 57.7, 57.1, 42.3, 37.3, 31.5, 27.0, 26.0, 23.5, 18.4, –5.2, –5.3, one carbon is not resolved; ^{13}C NMR (100 MHz, C_6D_6) δ 65.5, 61.0, 57.6, 57.4, 42.2, 37.1, 32.2, 30.2, 26.7, 26.2, 24.4, 18.6, –5.1, –5.3; MS (ESI) *m/z* (relative intensity) 300.30 ($[M+H]^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{16}H_{34}NO_2Si$ ($[M+H]^+$) 300.2359; Found 300.2369. To a solution of alcohol **388** (10 mg, 0.034 mmol)

in THF (0.34 mL) was added 2-$O_2NC_6H_5SeCN$ (15 mg, 0.068 mmol) and Bu_3P (16 μL, 0.068 mmol). The reaction mixture was heated at 60 °C overnight. The mixture was concentrated and the residue (11 mg, 0.023 mmol) was dissolved in CH_2Cl_2 (0.6 mL). To this solution was added aq. K_2HPO_4 (2.4 M, 30 μL) and mCPBA (6 mg, 0.024 mmol). After ca. 12 h, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 10:1) afforded *O*-TBS-quincorine (**386**, 5.4 mg, 84%) as a colorless oil. This material was identical to that produced as described above.

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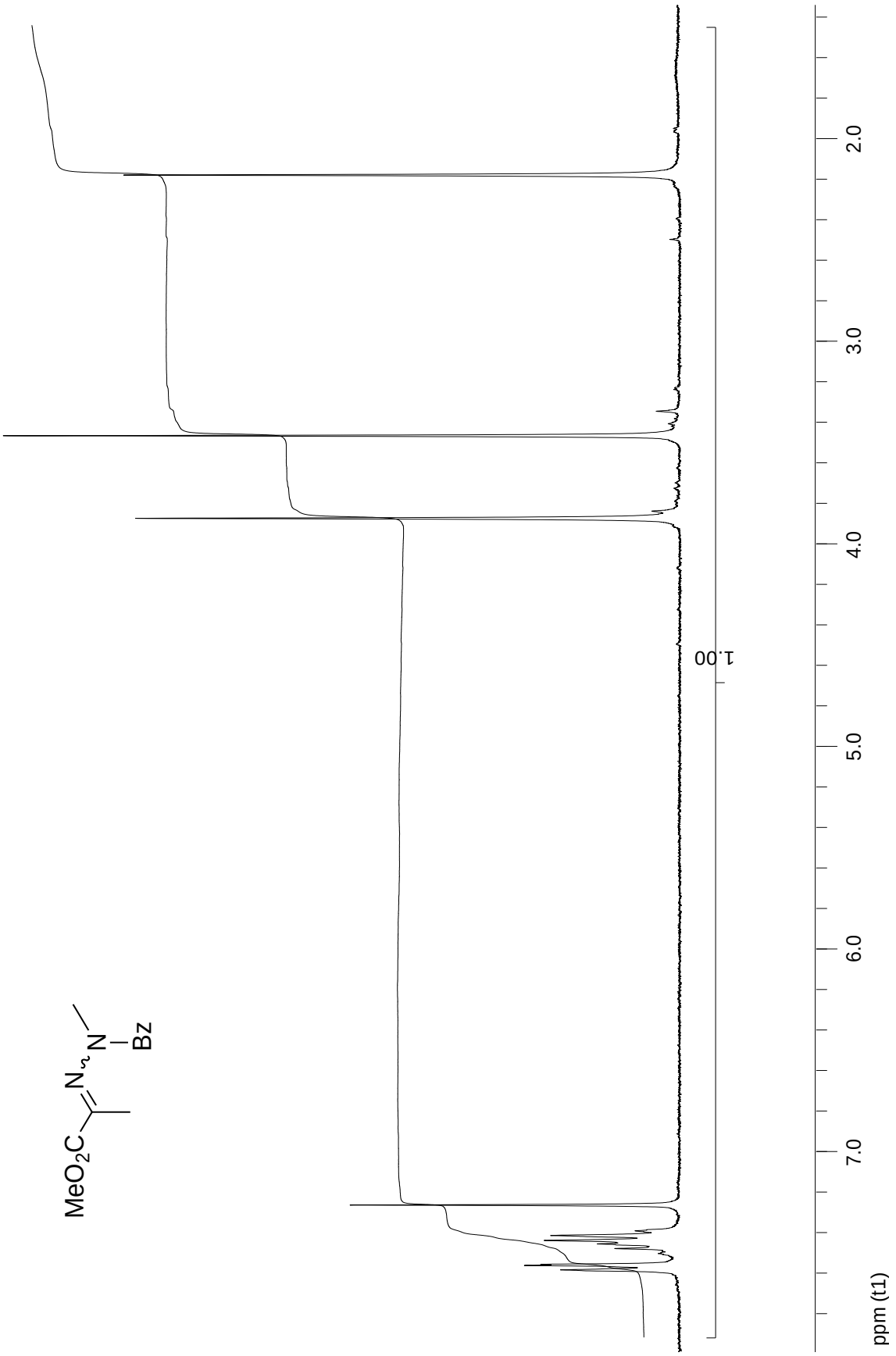
APPENDIX

SELECTED NMR SPECTRA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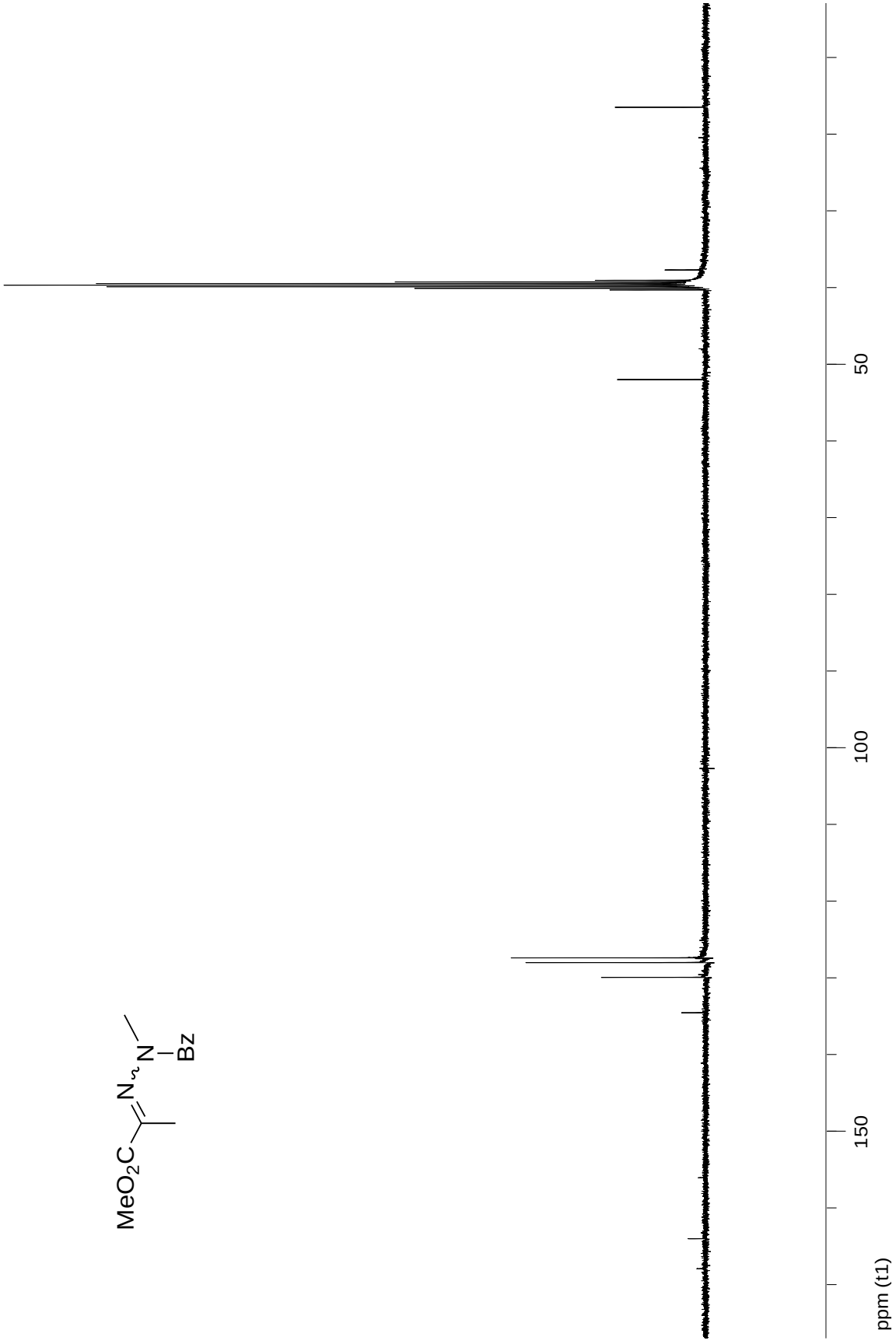
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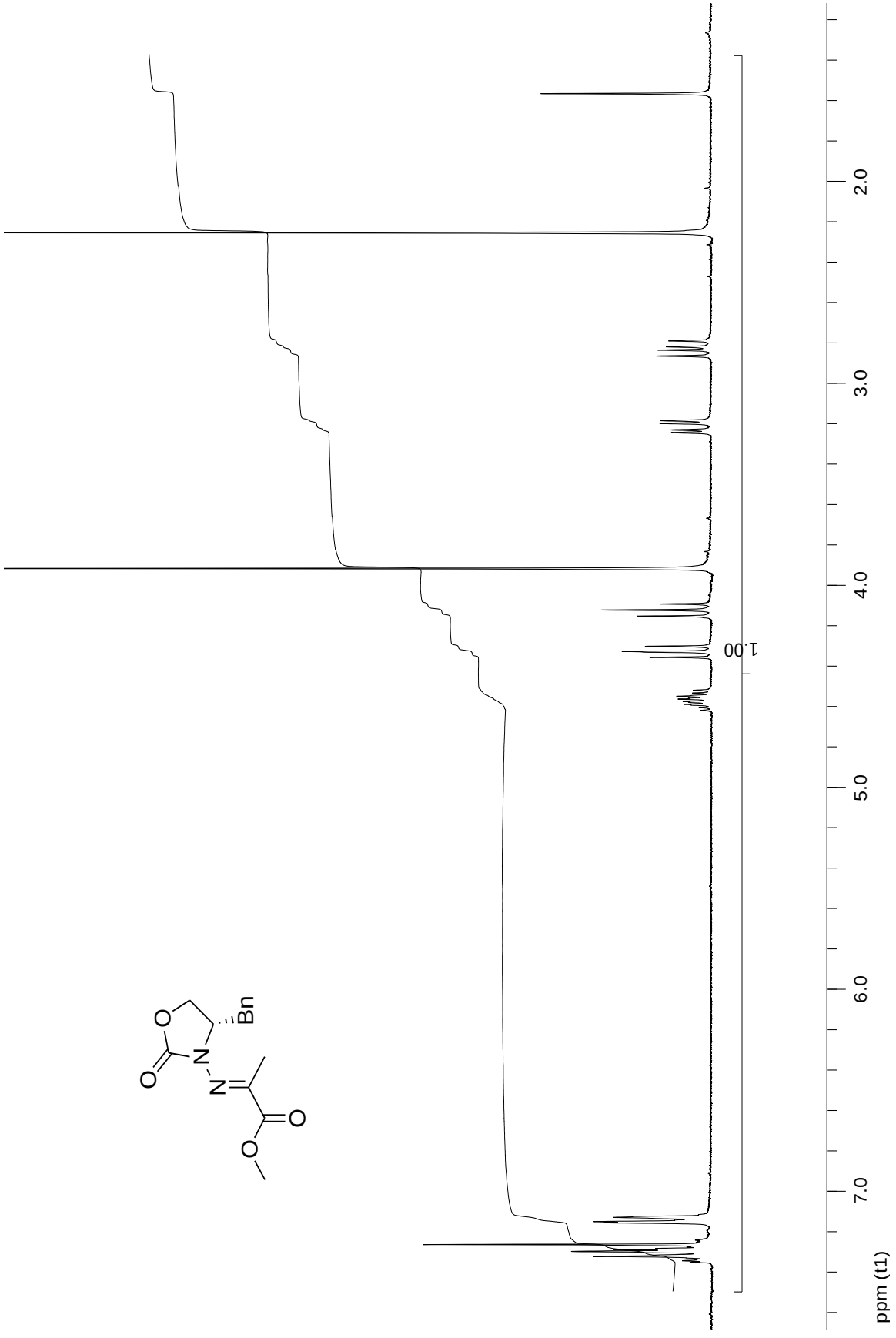
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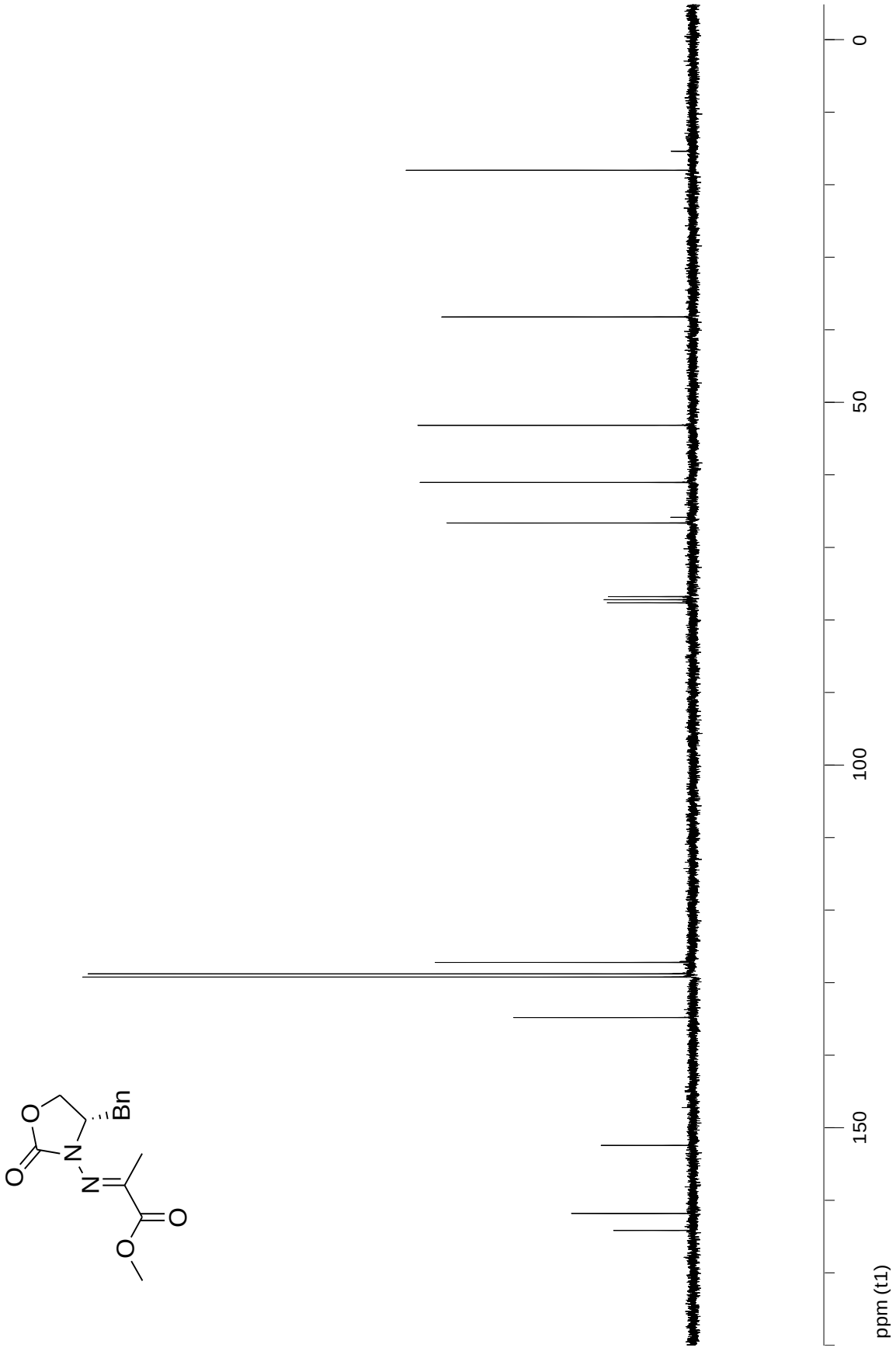
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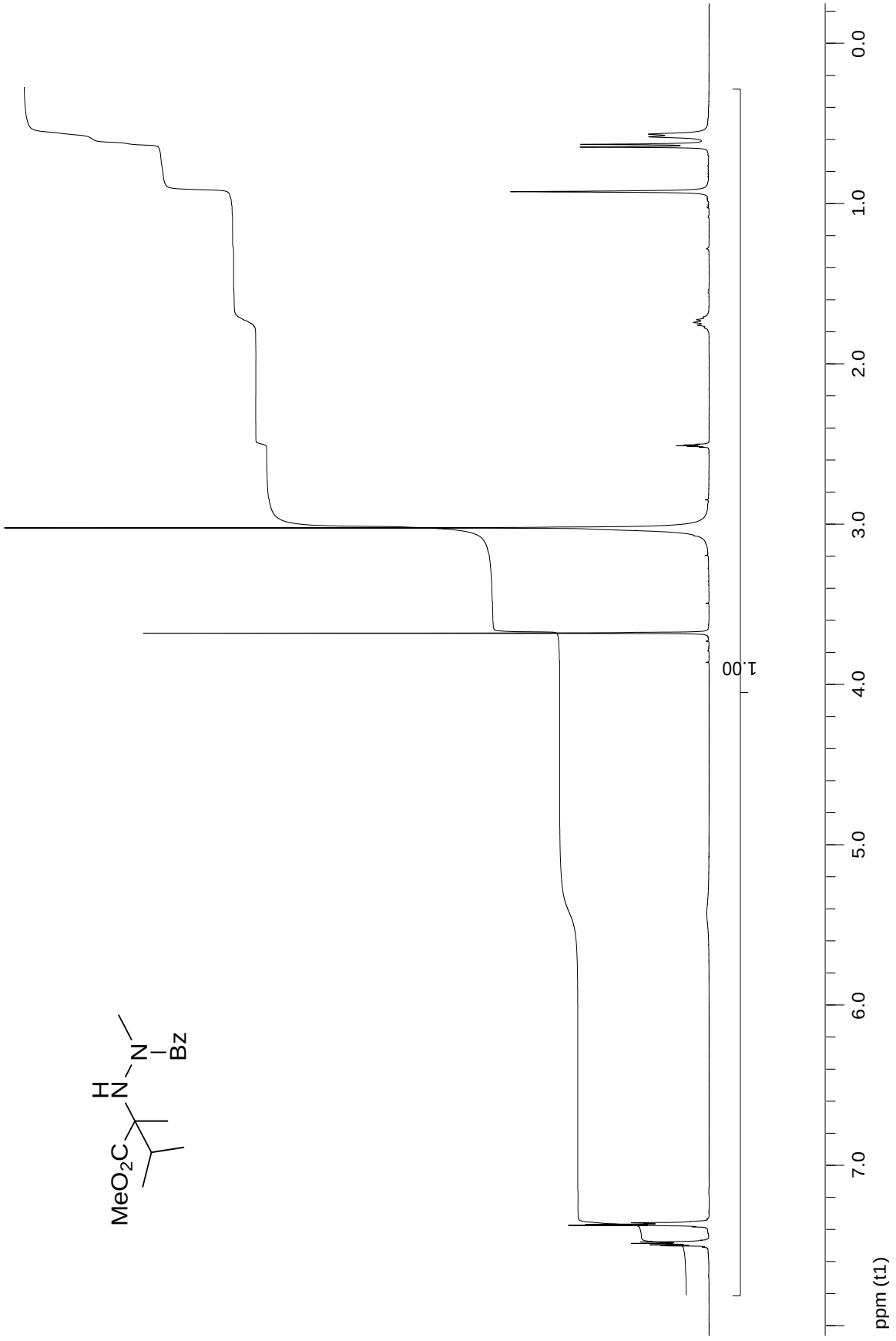
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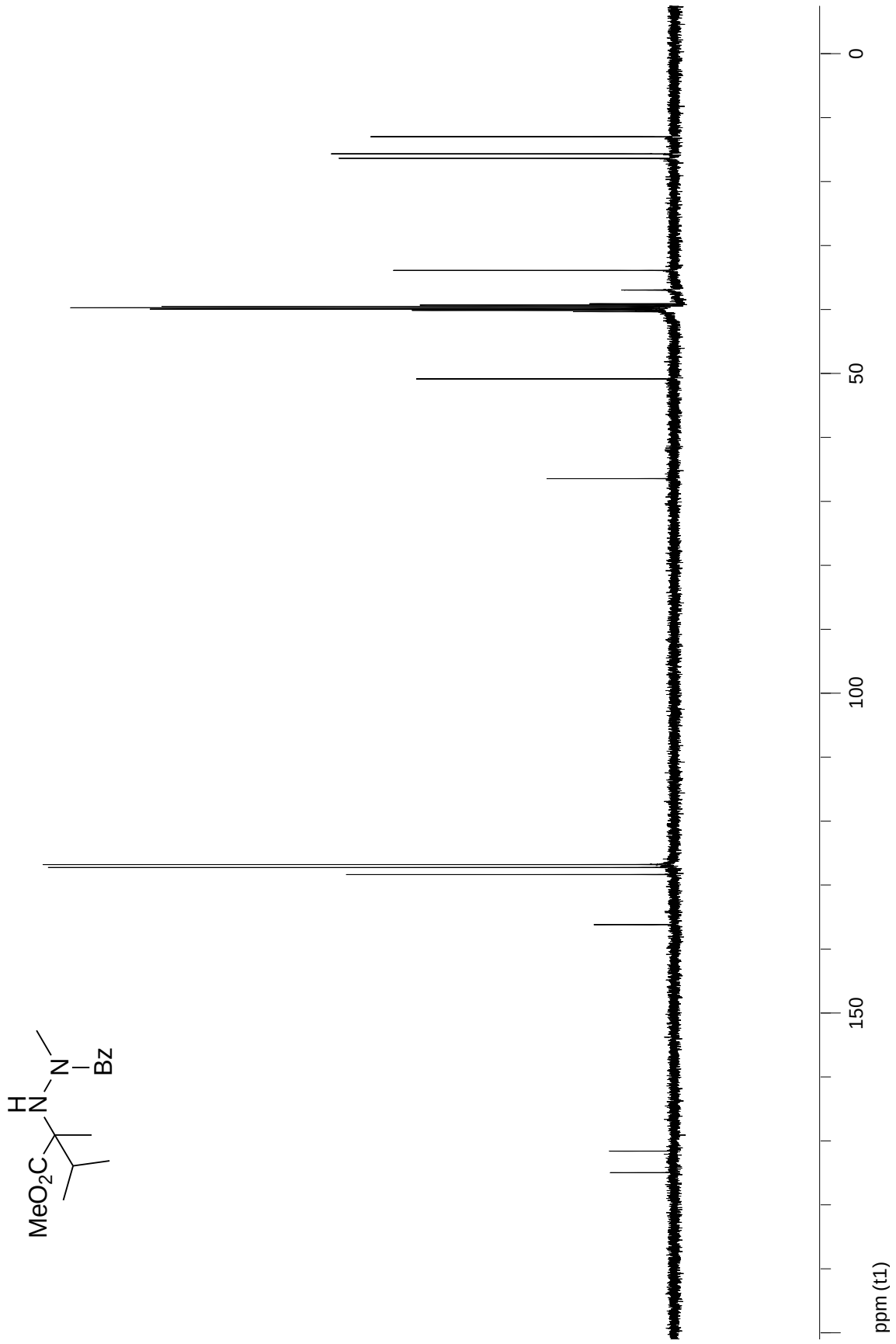
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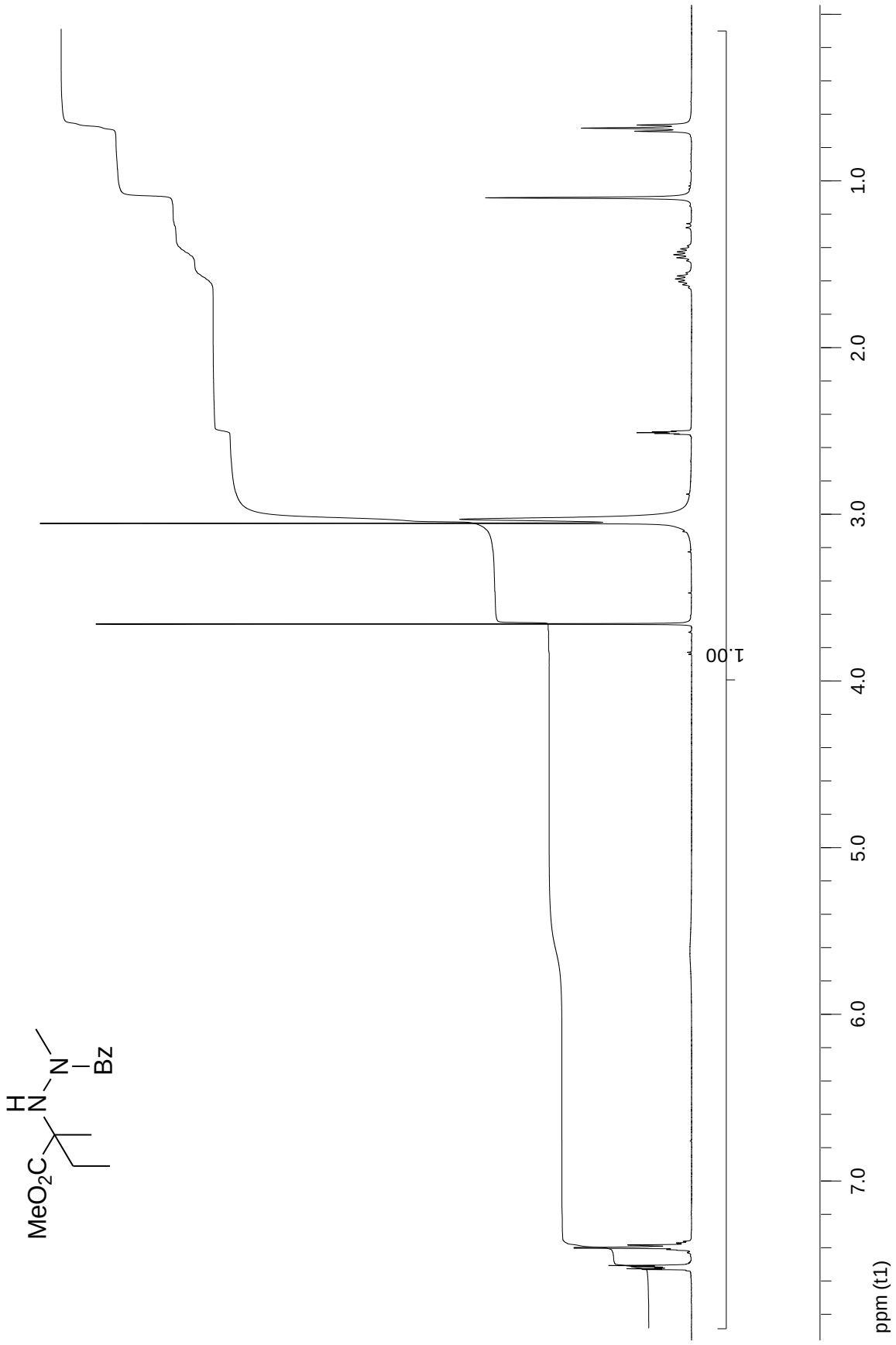
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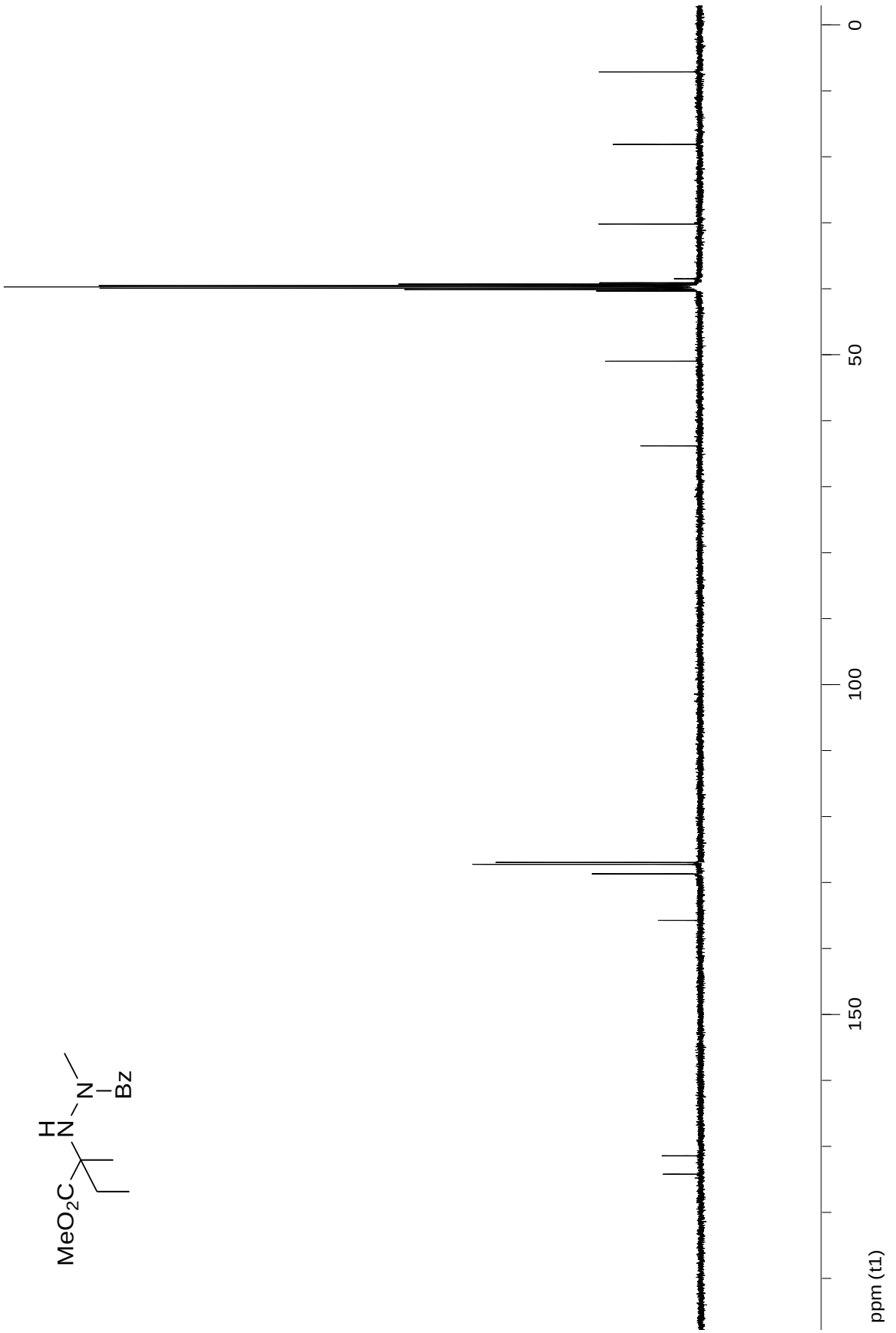
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)


MeO2C
H
N
N
Bz
0
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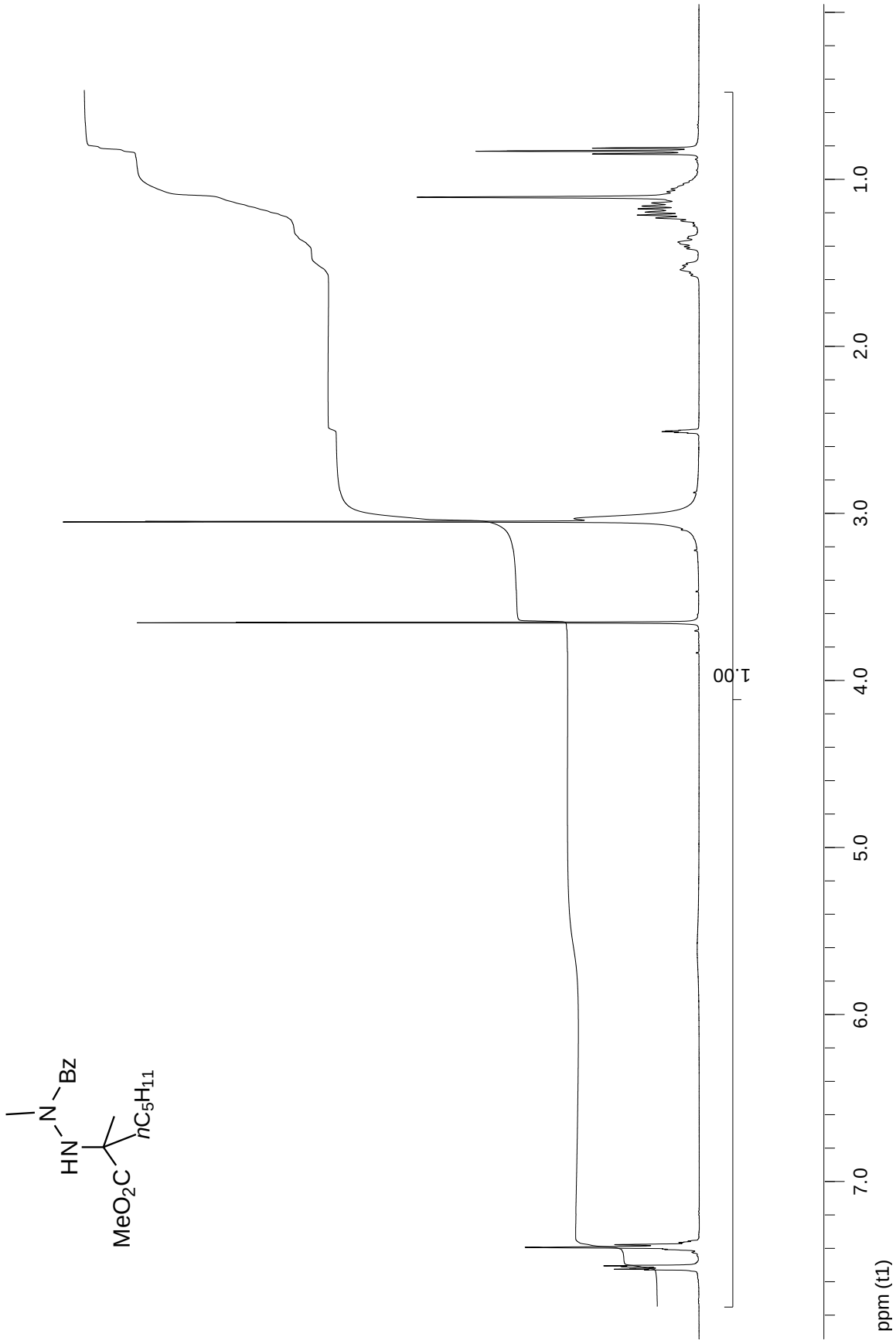
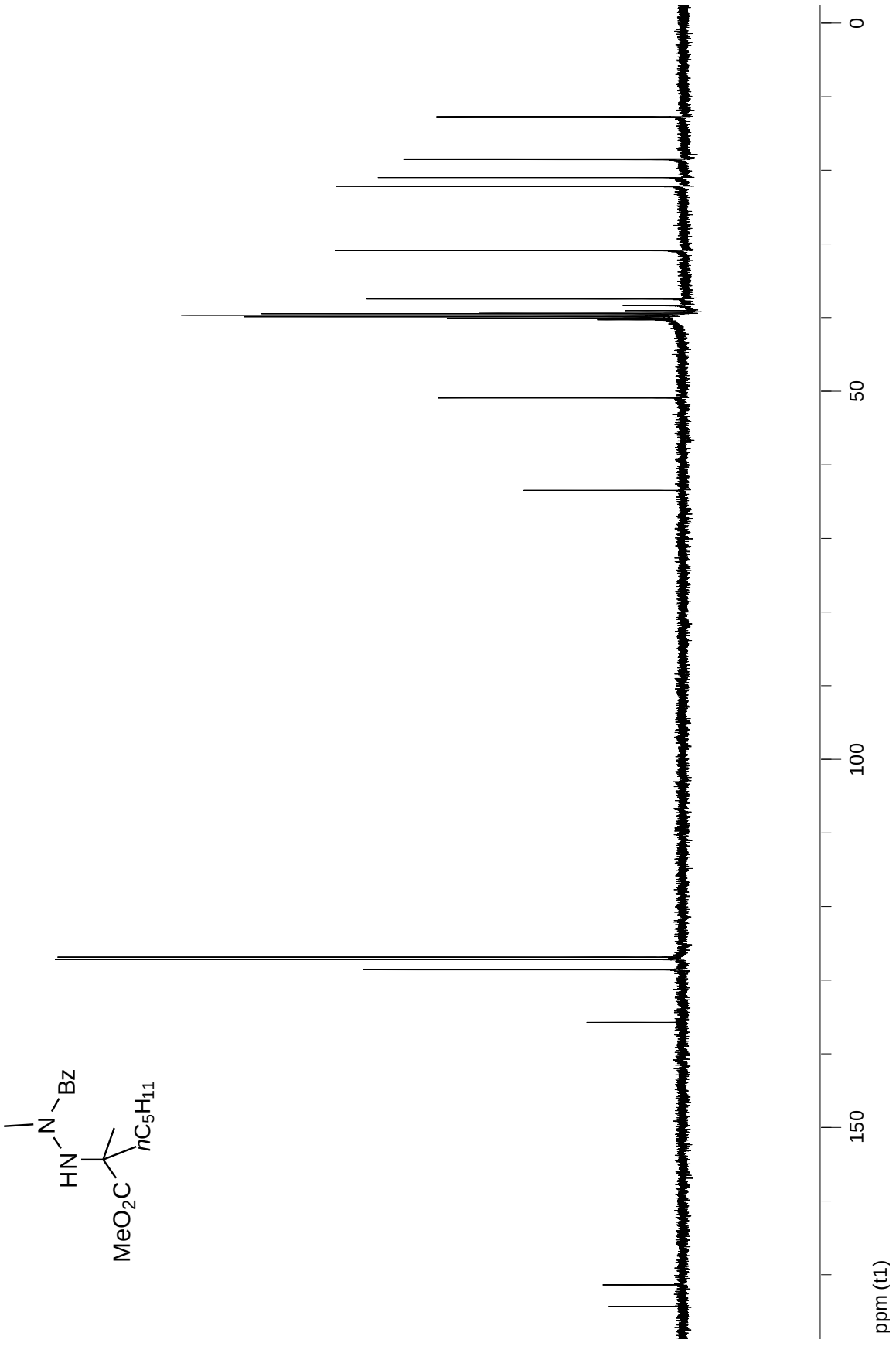
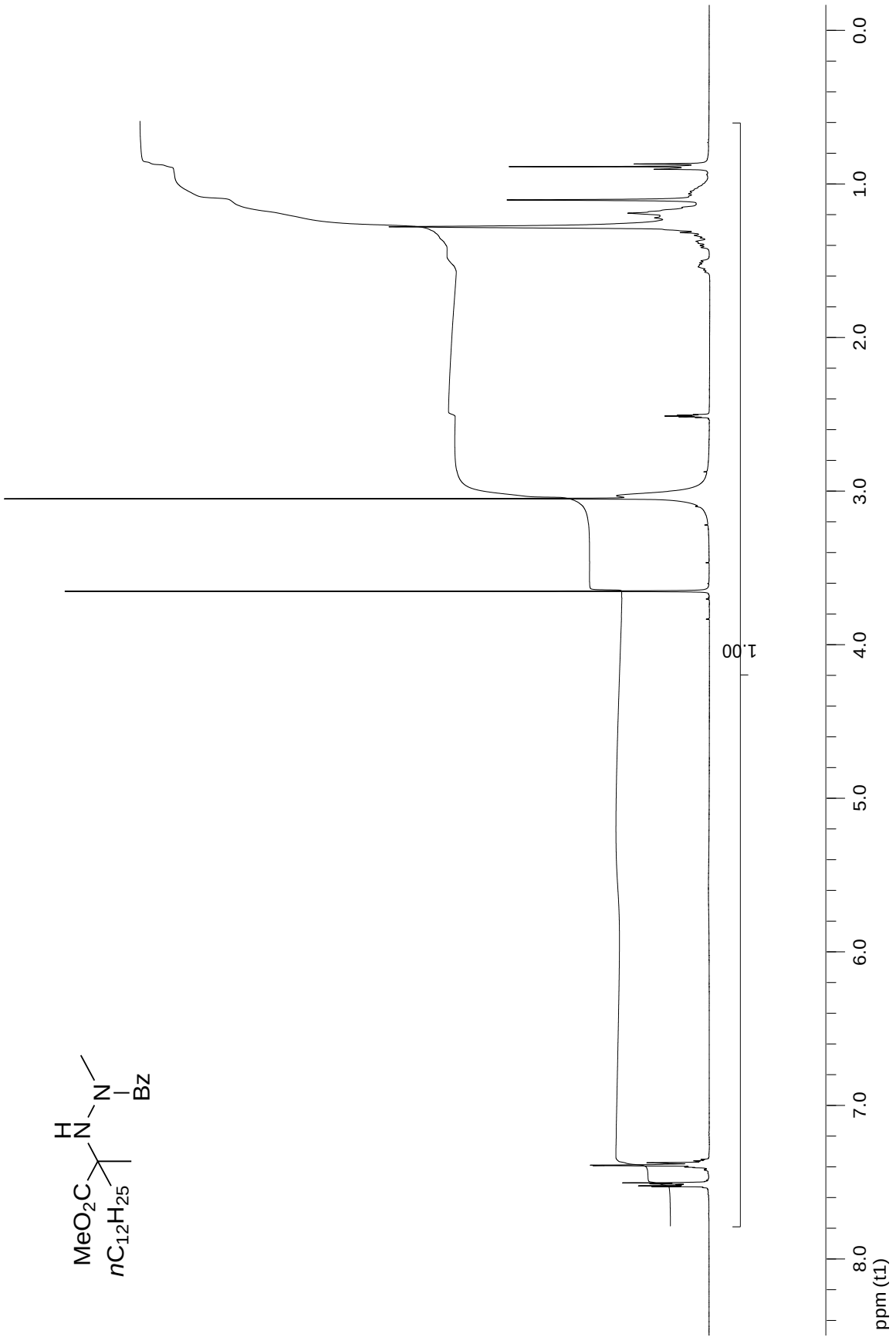
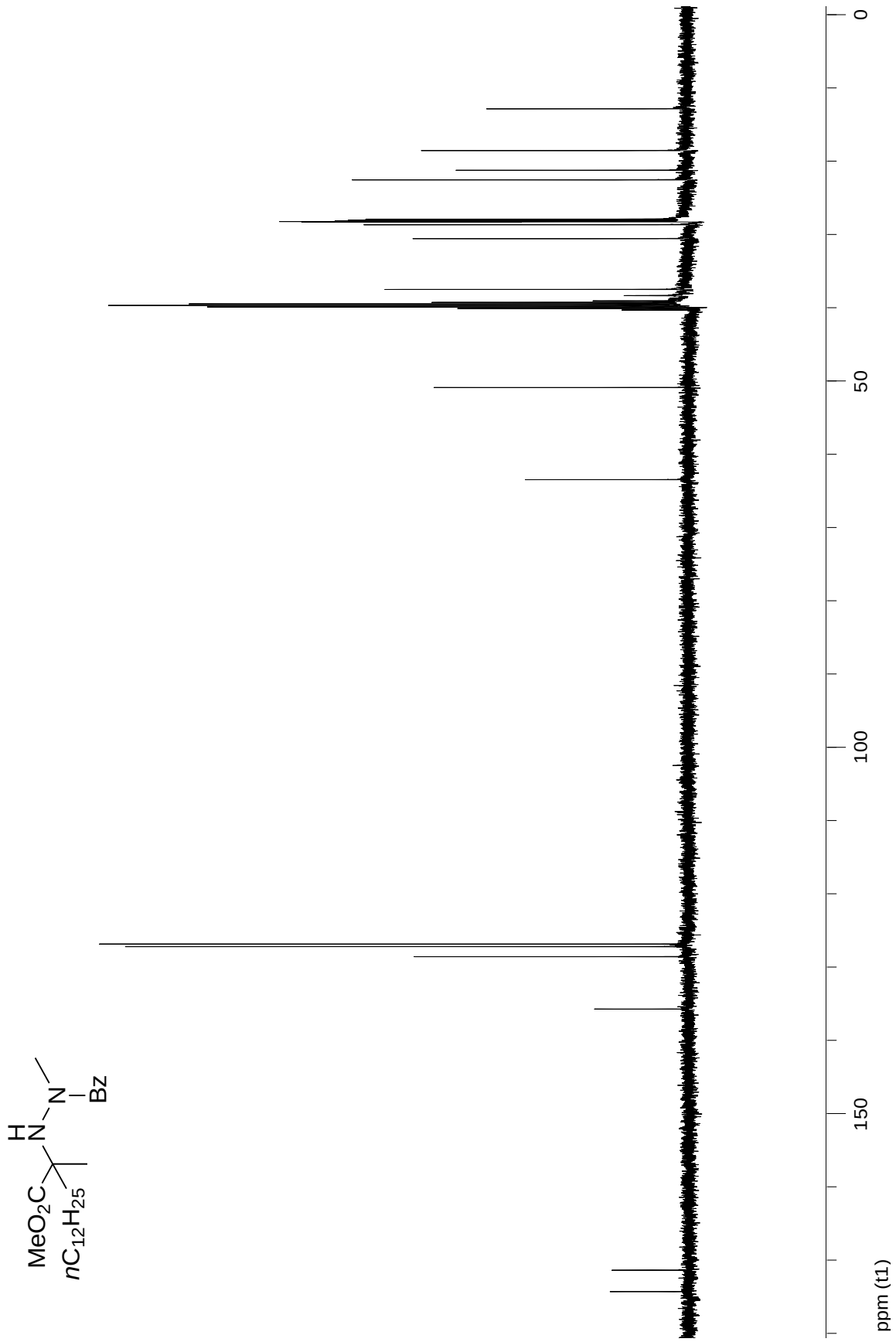
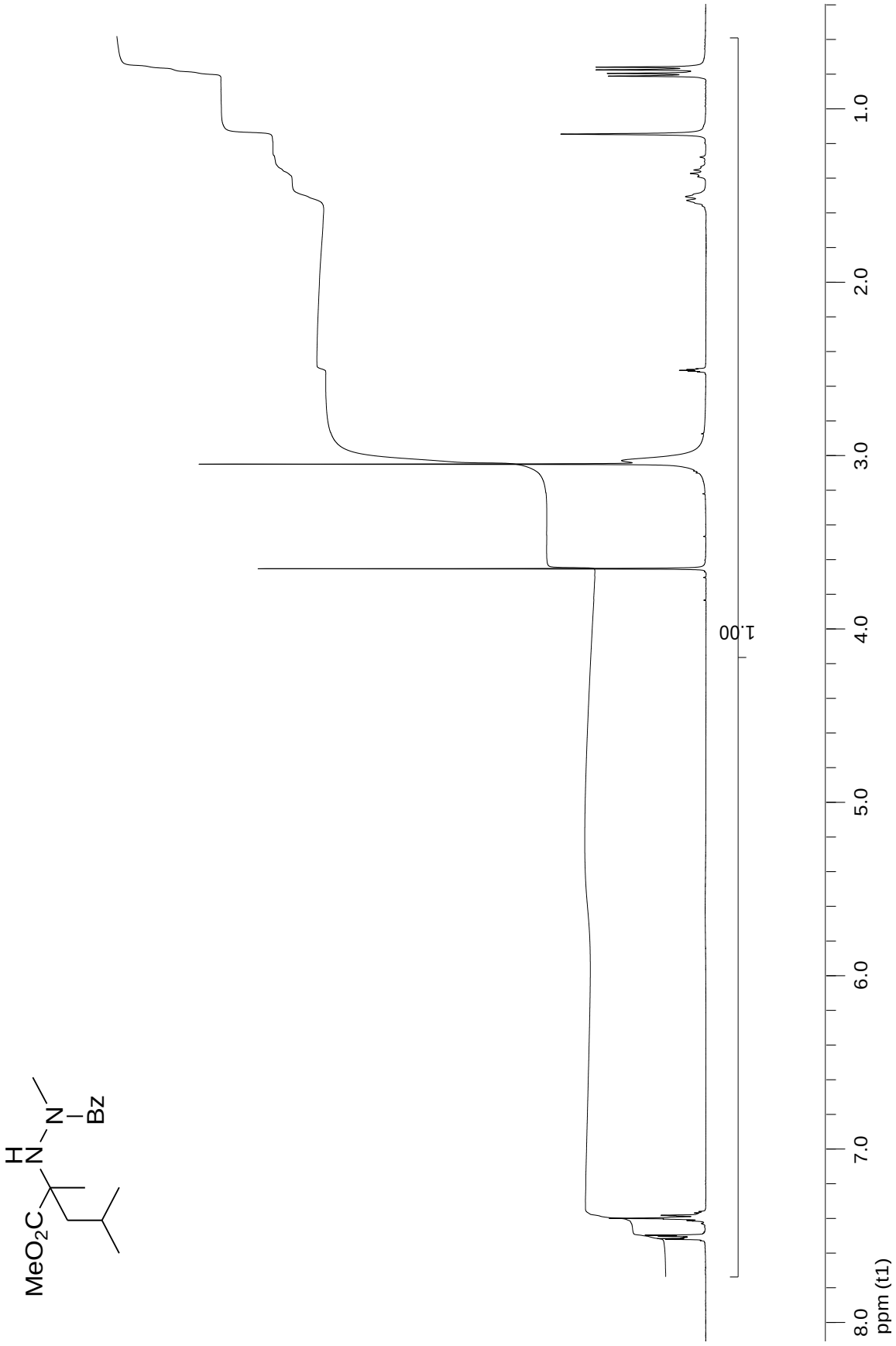
100
150
ppm (t1)

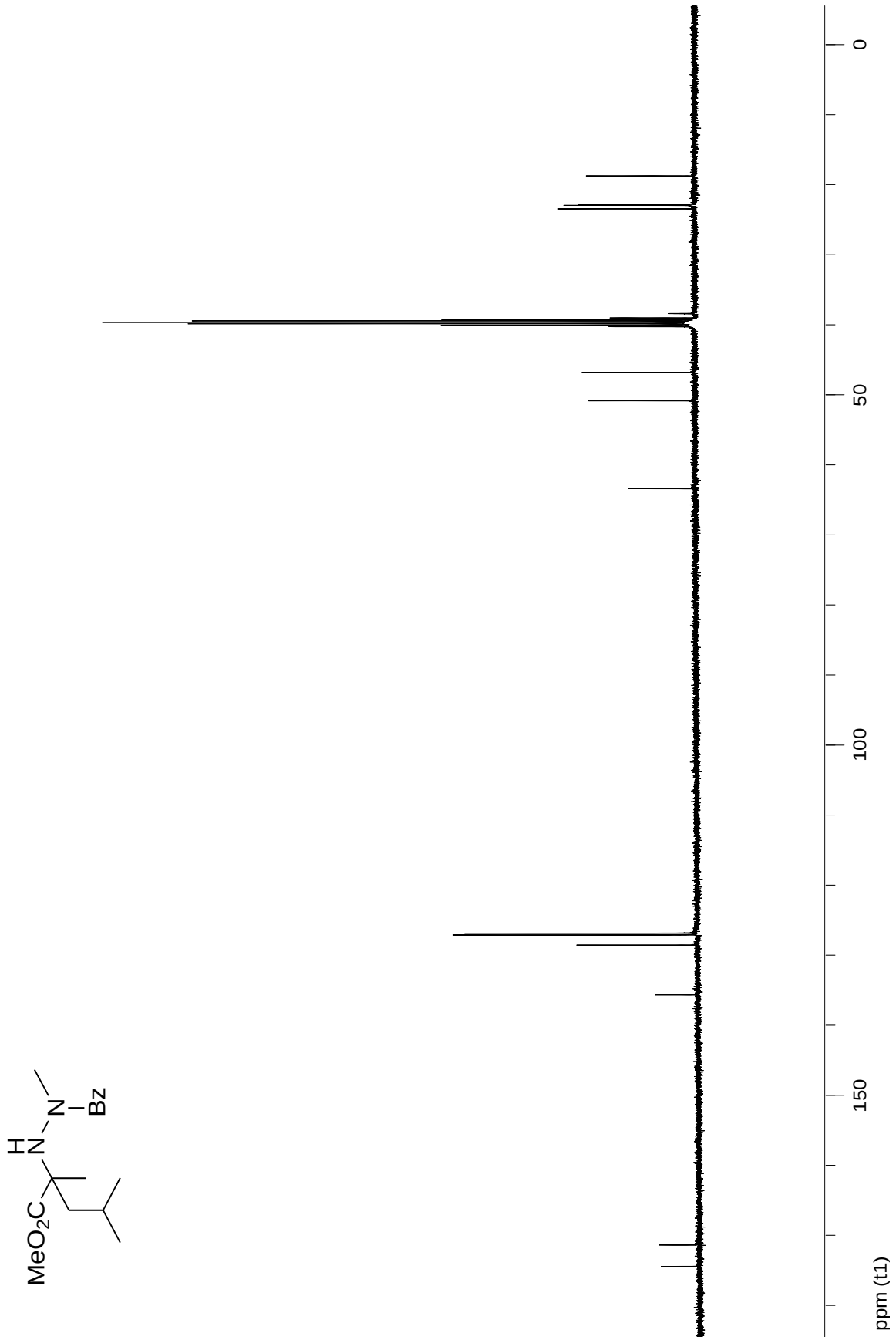

Bz
N
HN
MeO2C
nC5H11
1.00
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

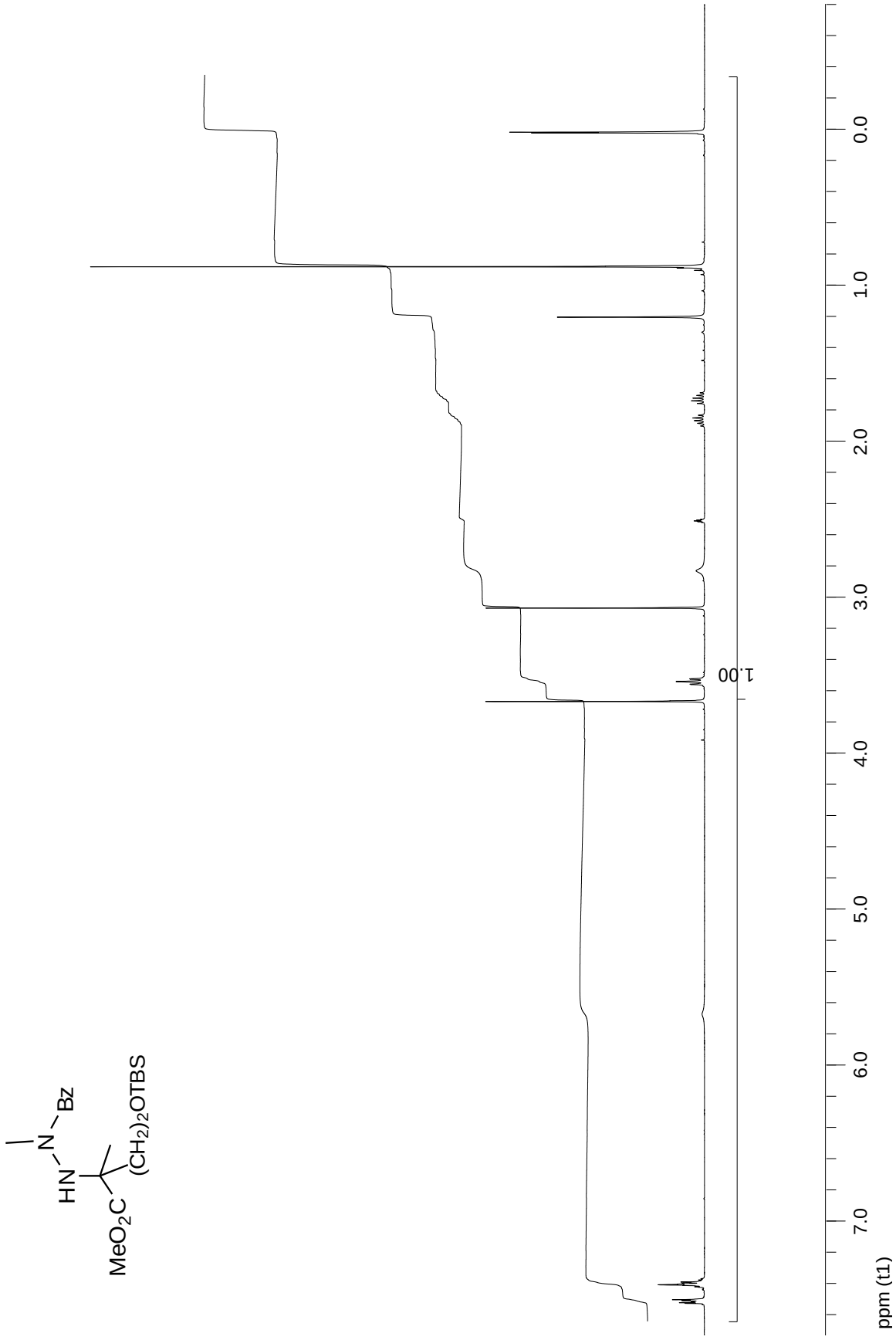

Bz
N
HN
MeO2C
nC5H11
0
50
100
150
ppm (t1)

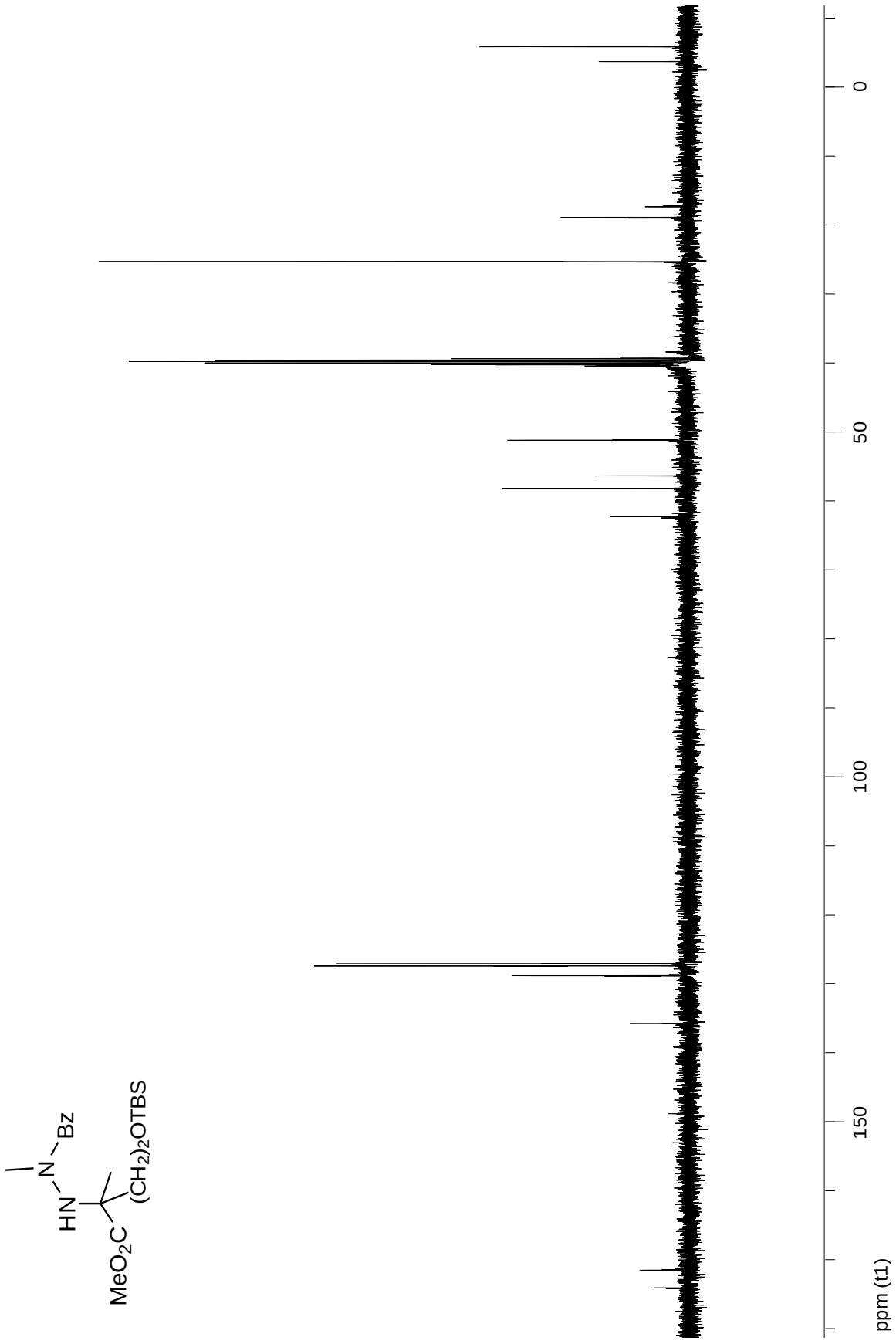

MeO2C
nC12H25
H
N
N
Bz
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

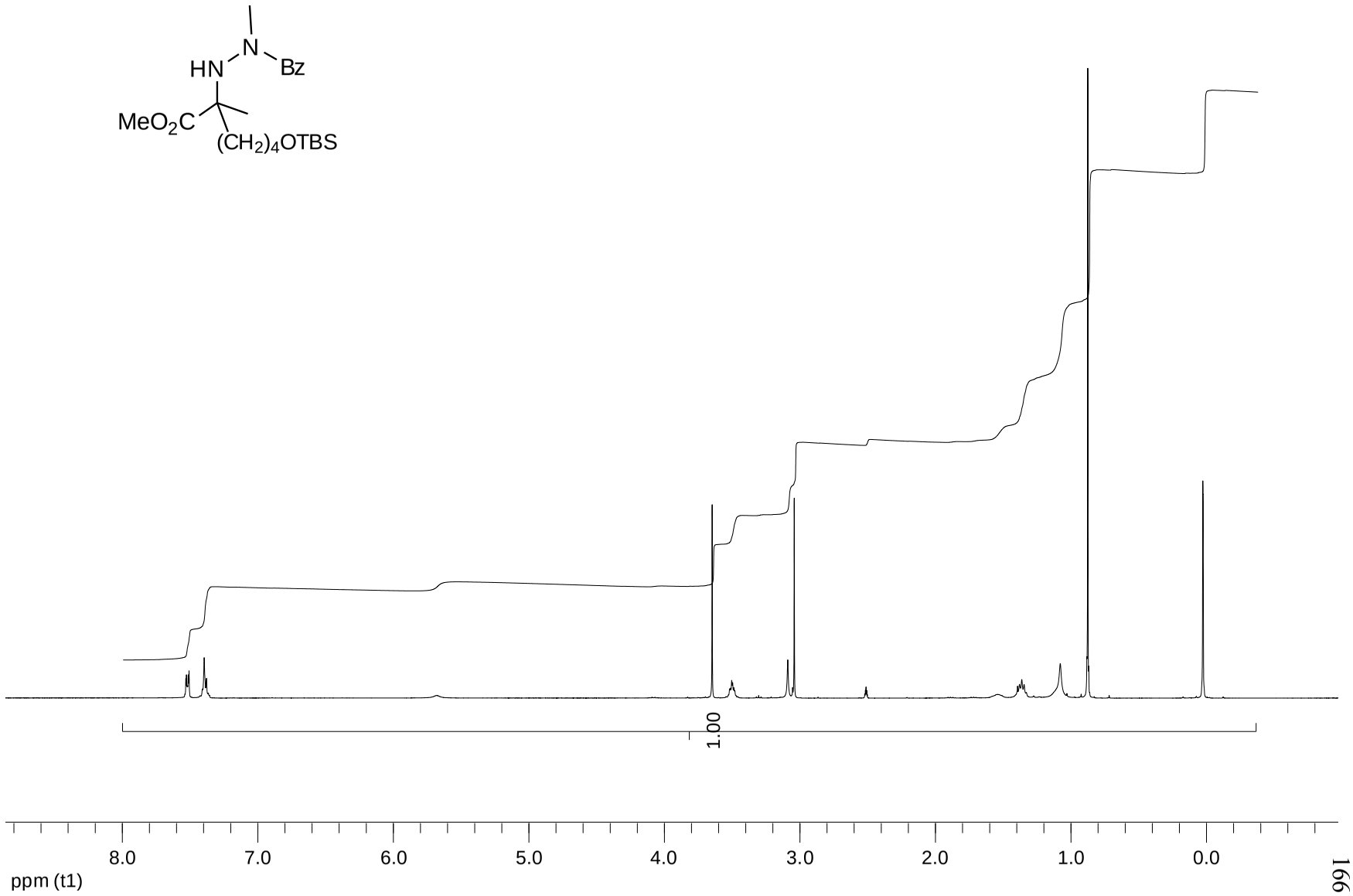

MeO2C
nC12H25
H
N
N
Bz
0
50
100
150
ppm (t1)


MeO2C
H
N
N
Bz
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


MeO2C
H
N
N
Bz
0
50
100
150
ppm (t1)


Bz
N
HN
MeO2C
(CH2)2OTBS
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)


Bz
N
HN
MeO2C
(CH2)2OTBS
0
50
100
150
ppm (t1)


HN
N
Bz
MeO2C
(CH2)4OTBS
1.00
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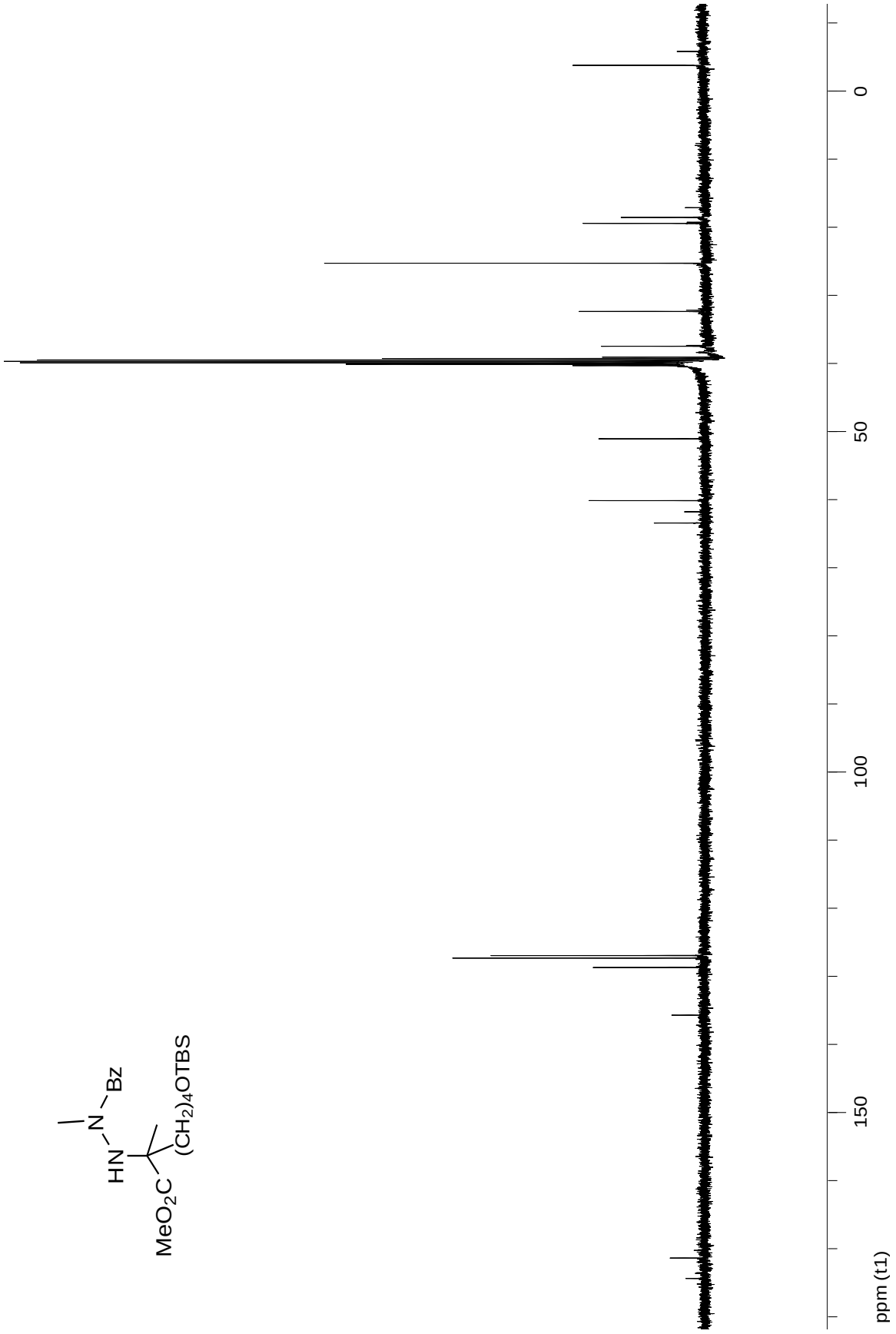
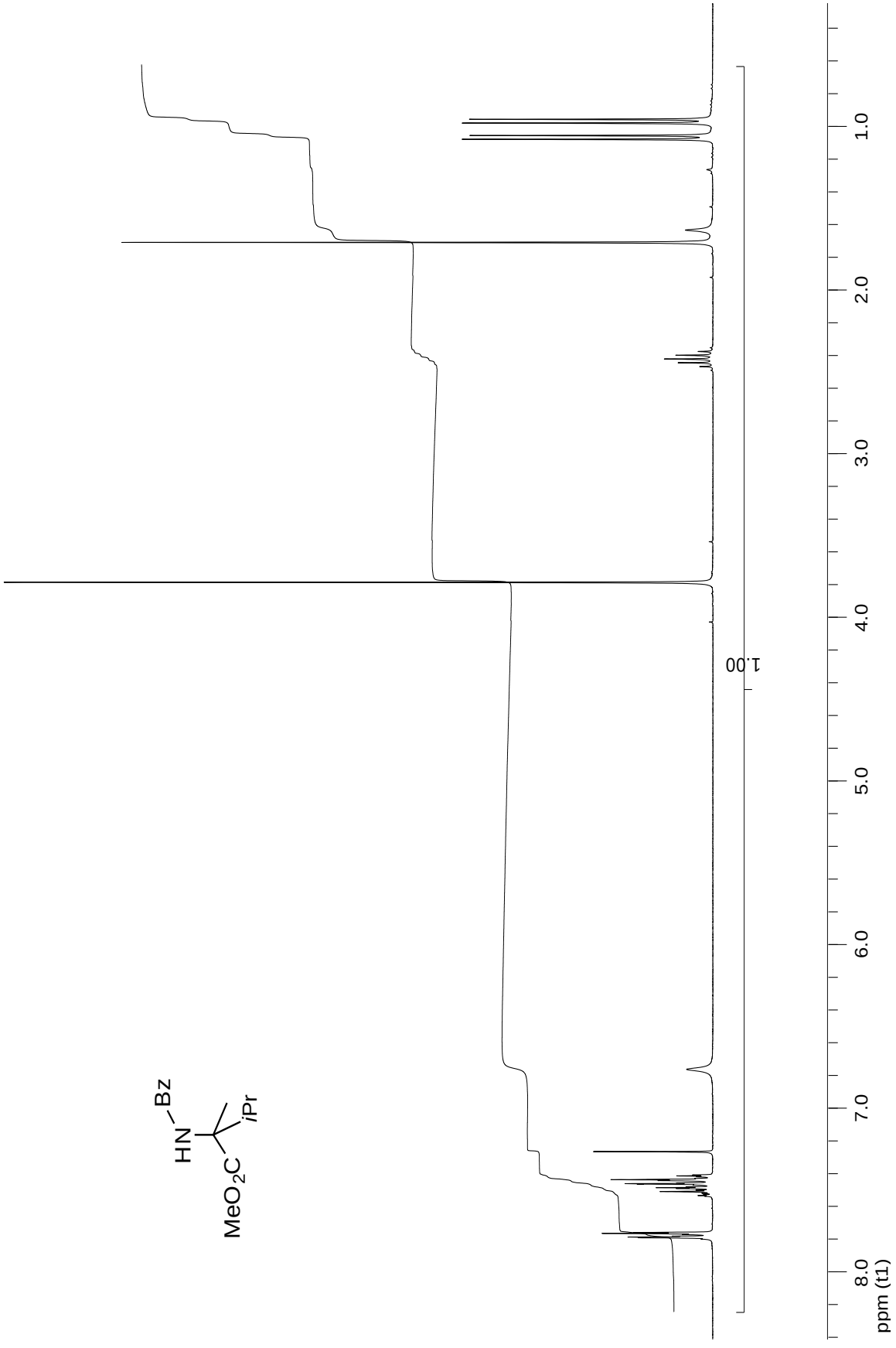
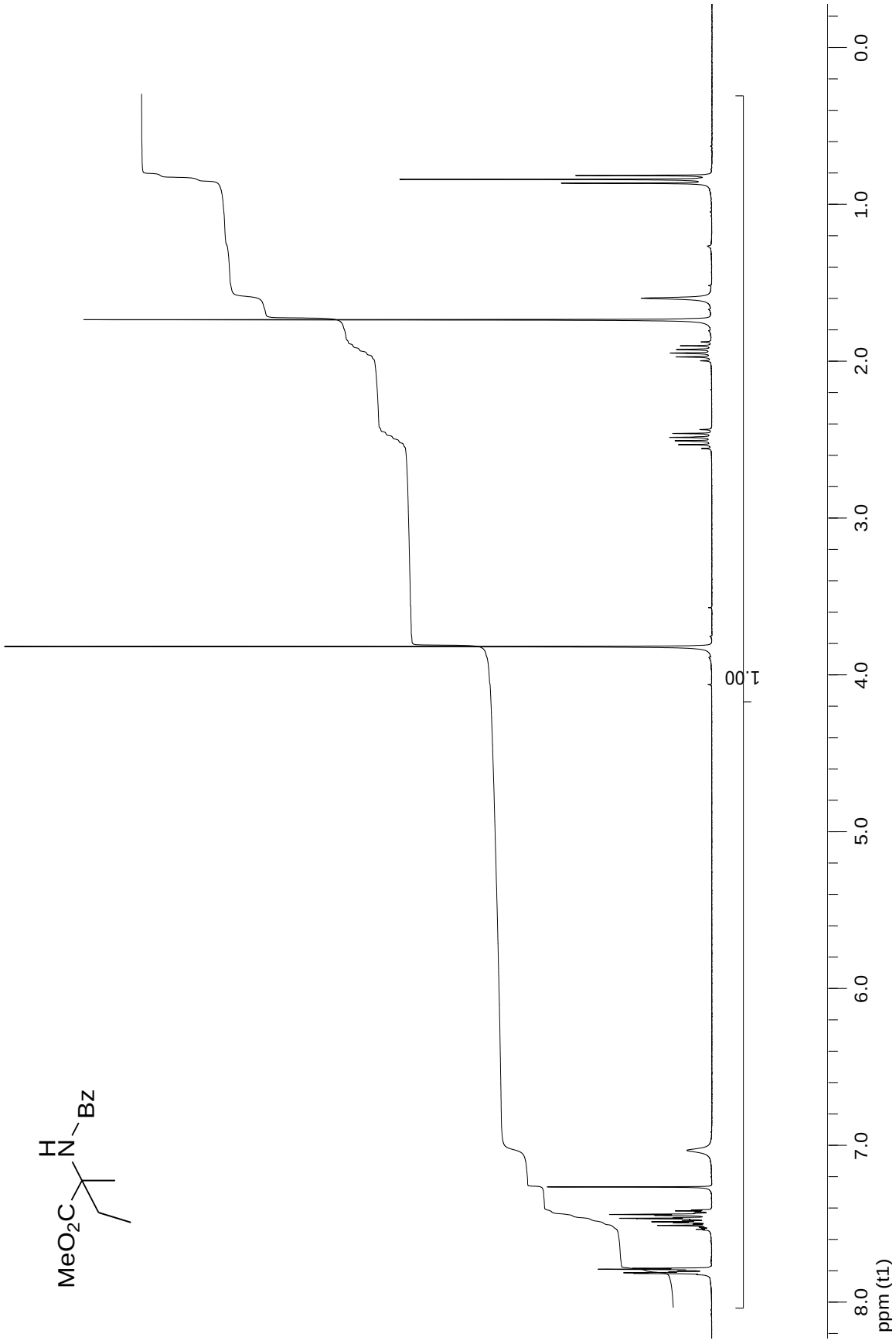
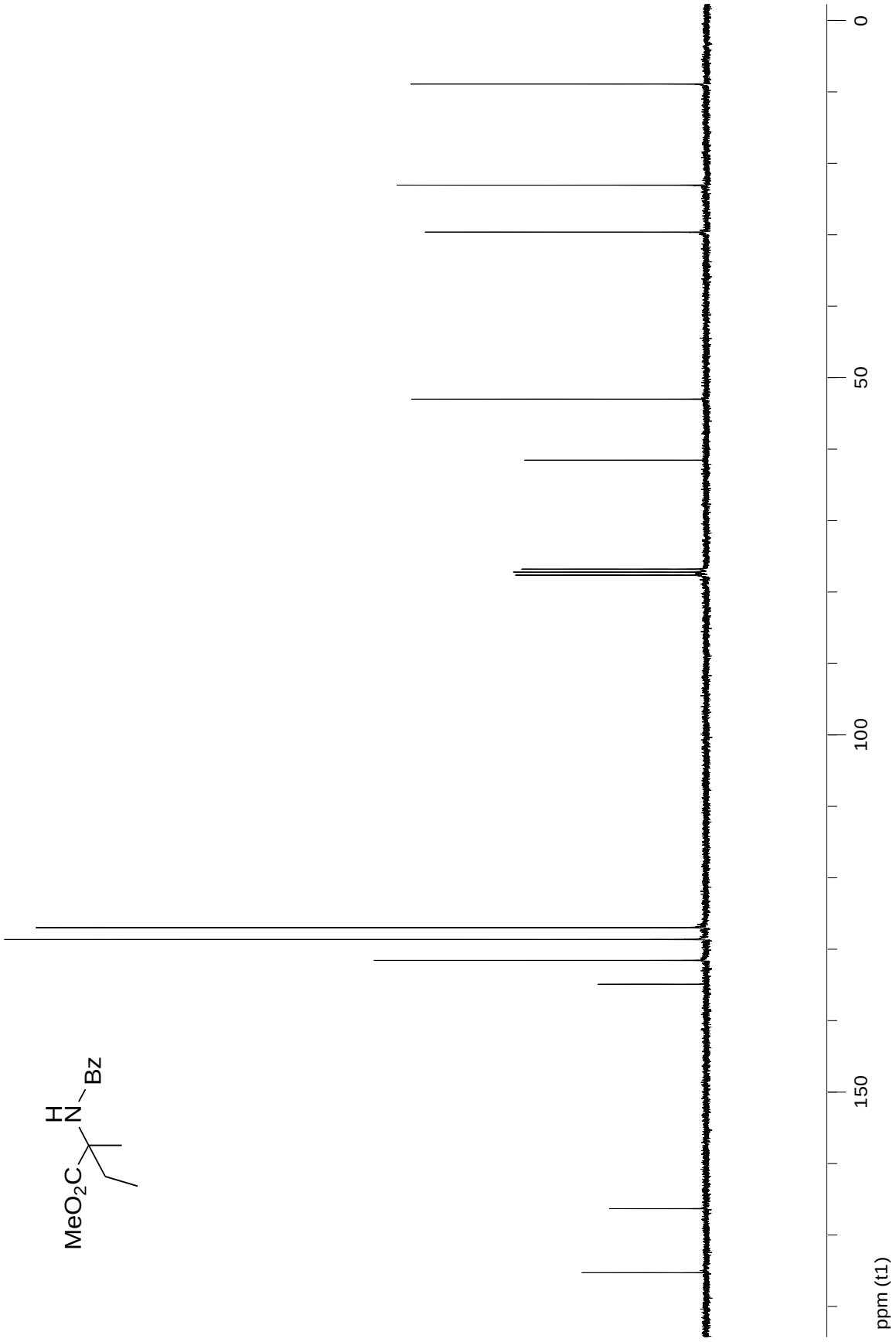
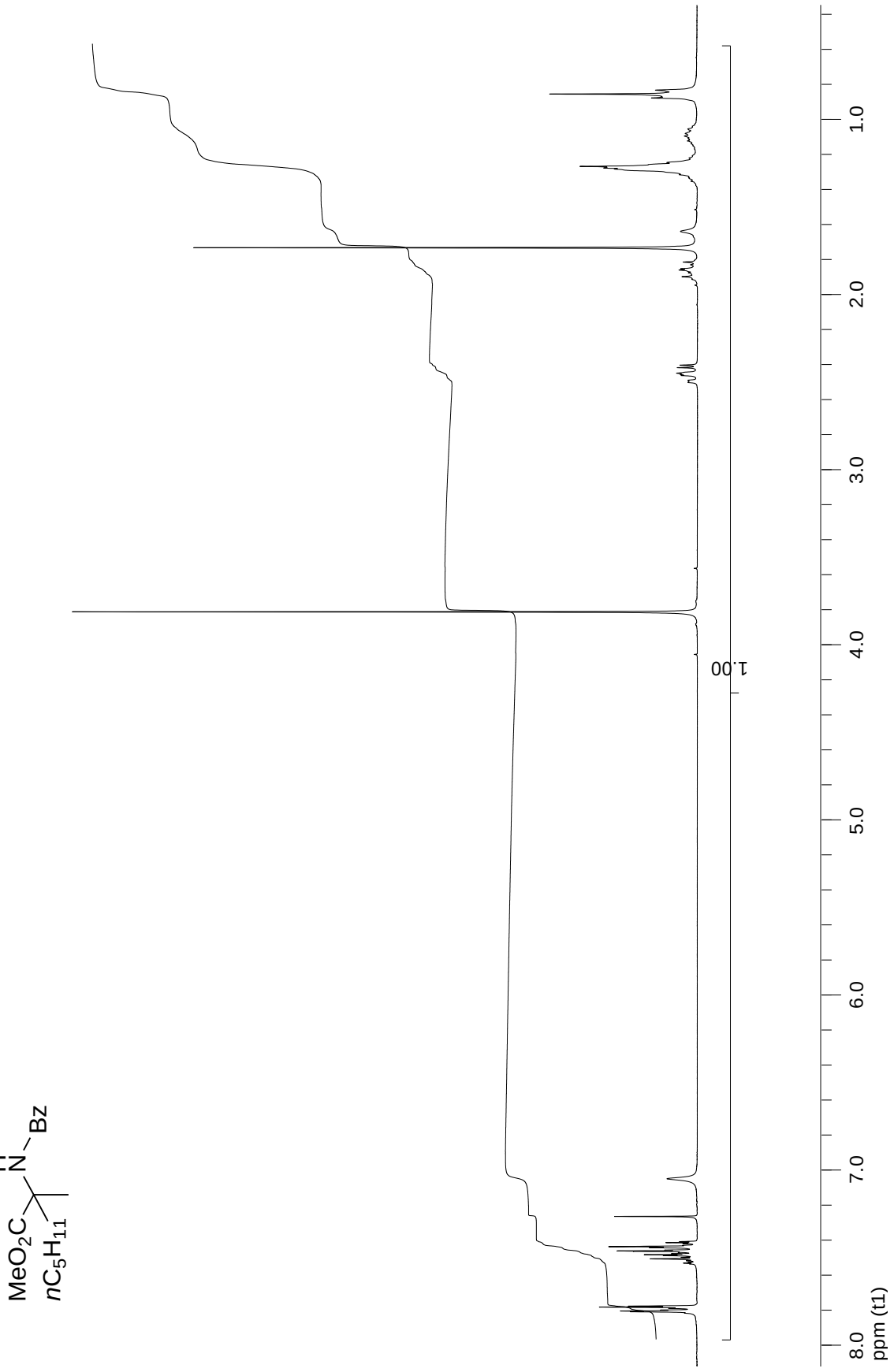
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

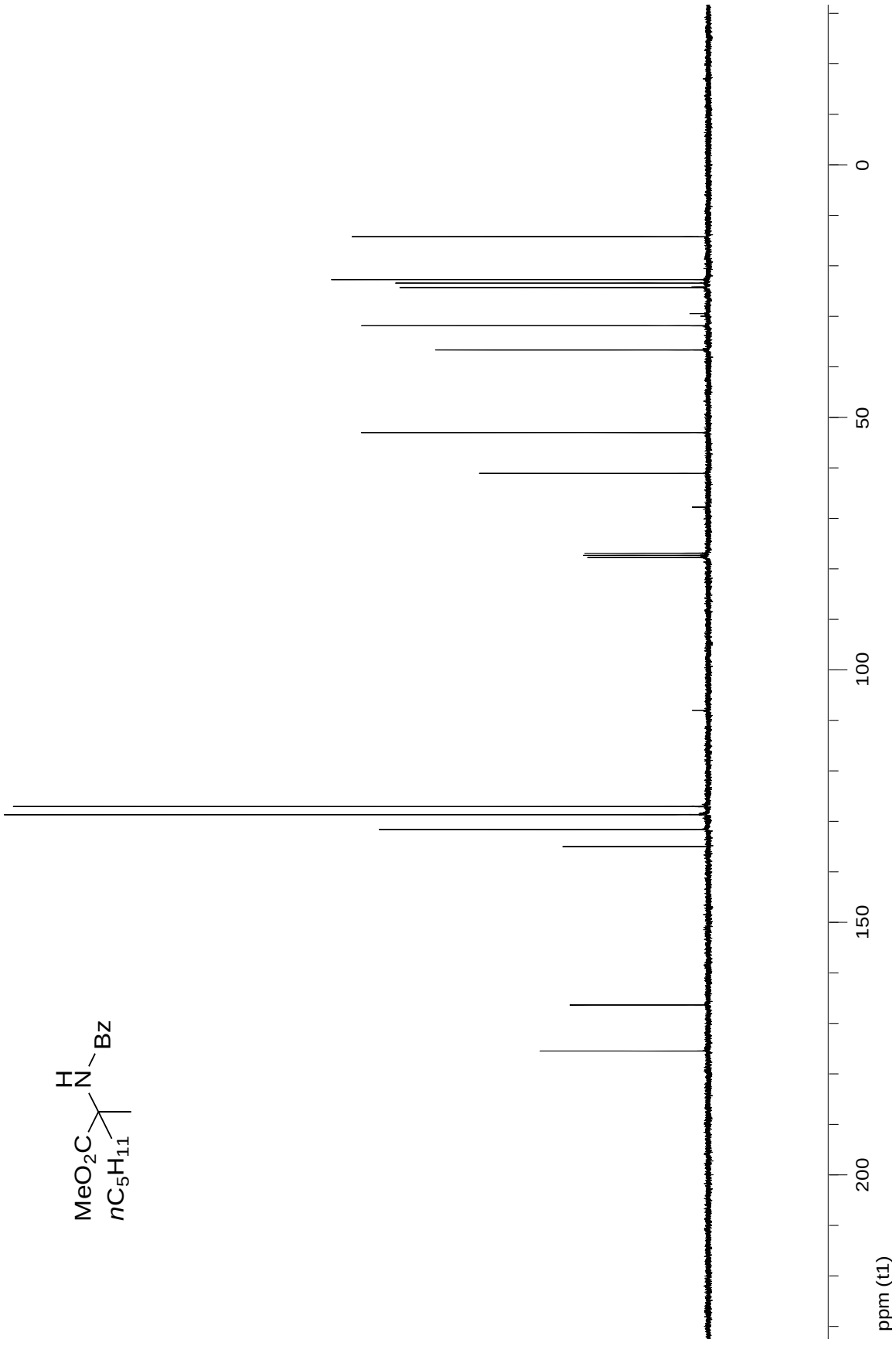

Bz
N
HN
MeO2C
(CH2)4OTBS
0
50
100
150
ppm (t1)

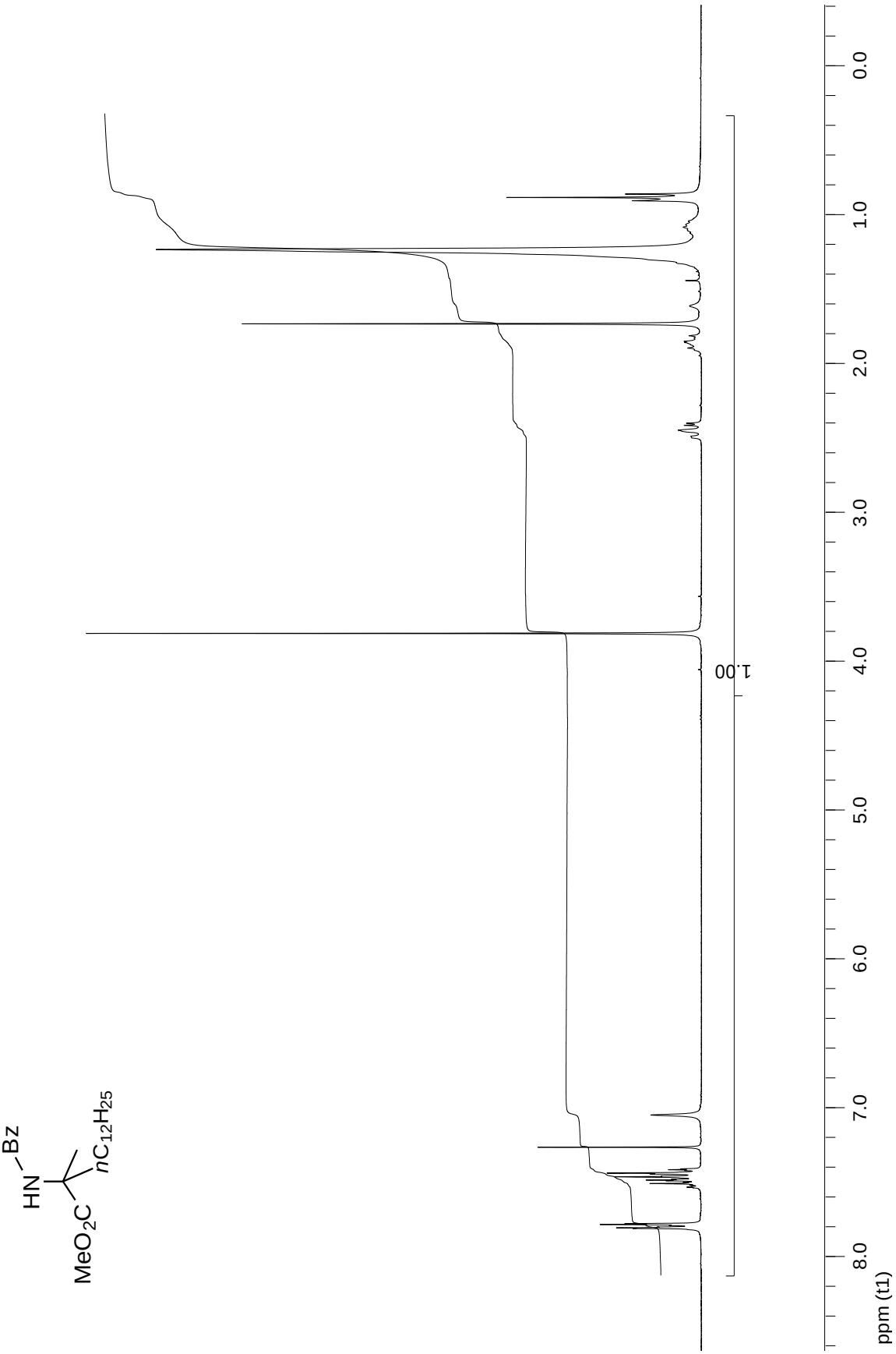

Bz
HN
iPr
MeO2C
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

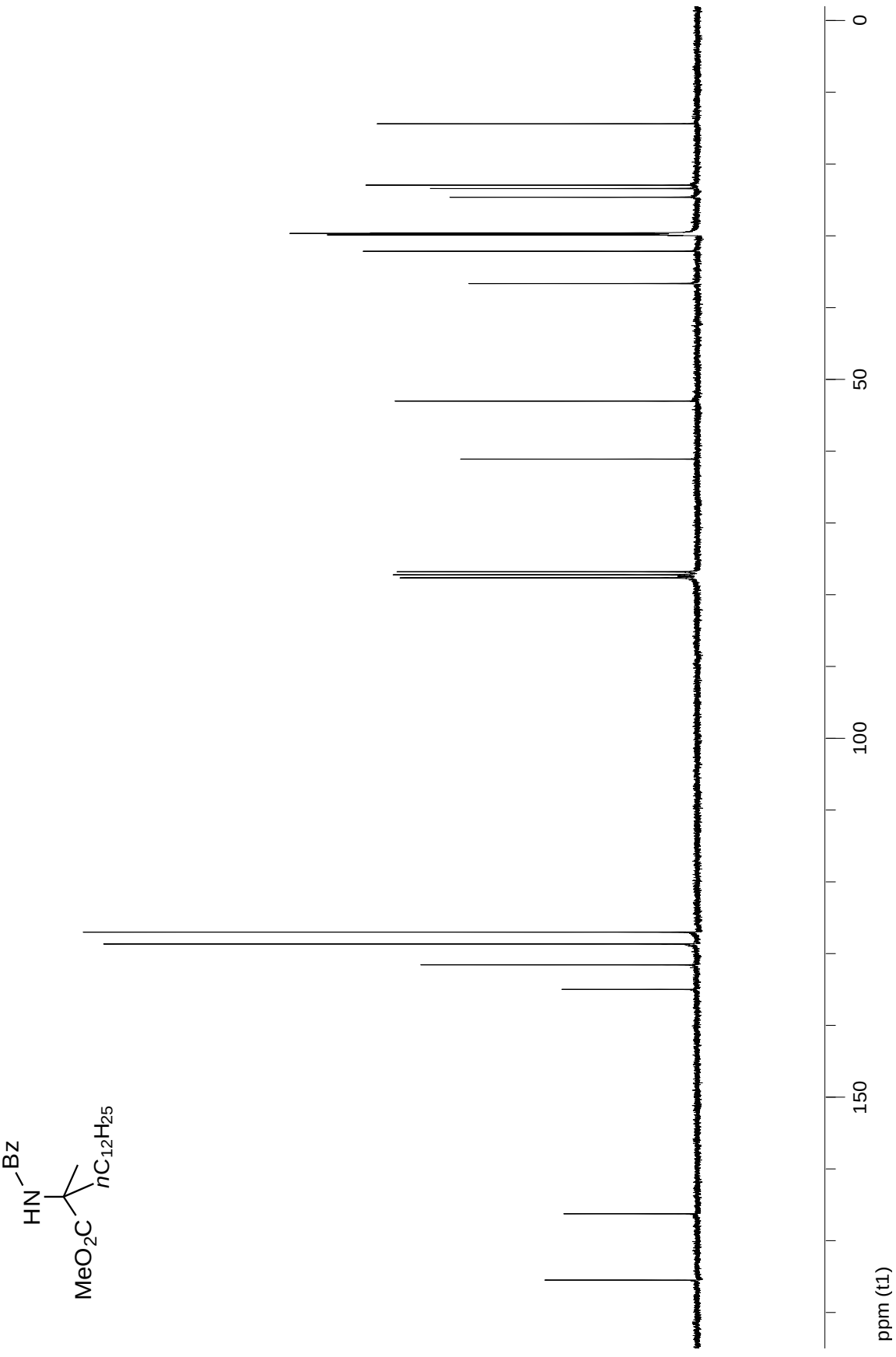

MeO2C
H
N
Bz
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

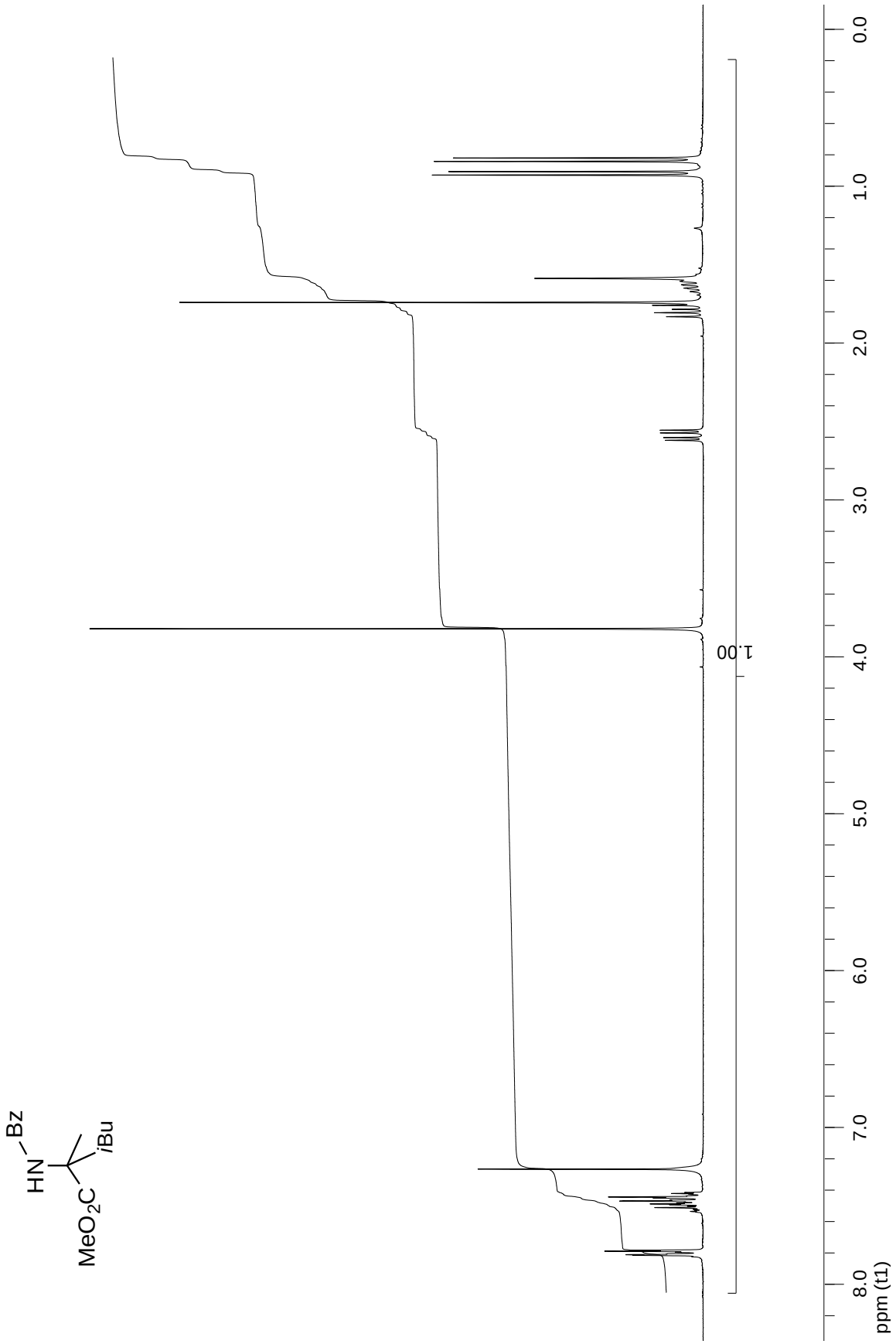

H
N
Bz
MeO2C
0
50
100
150
ppm (t1)

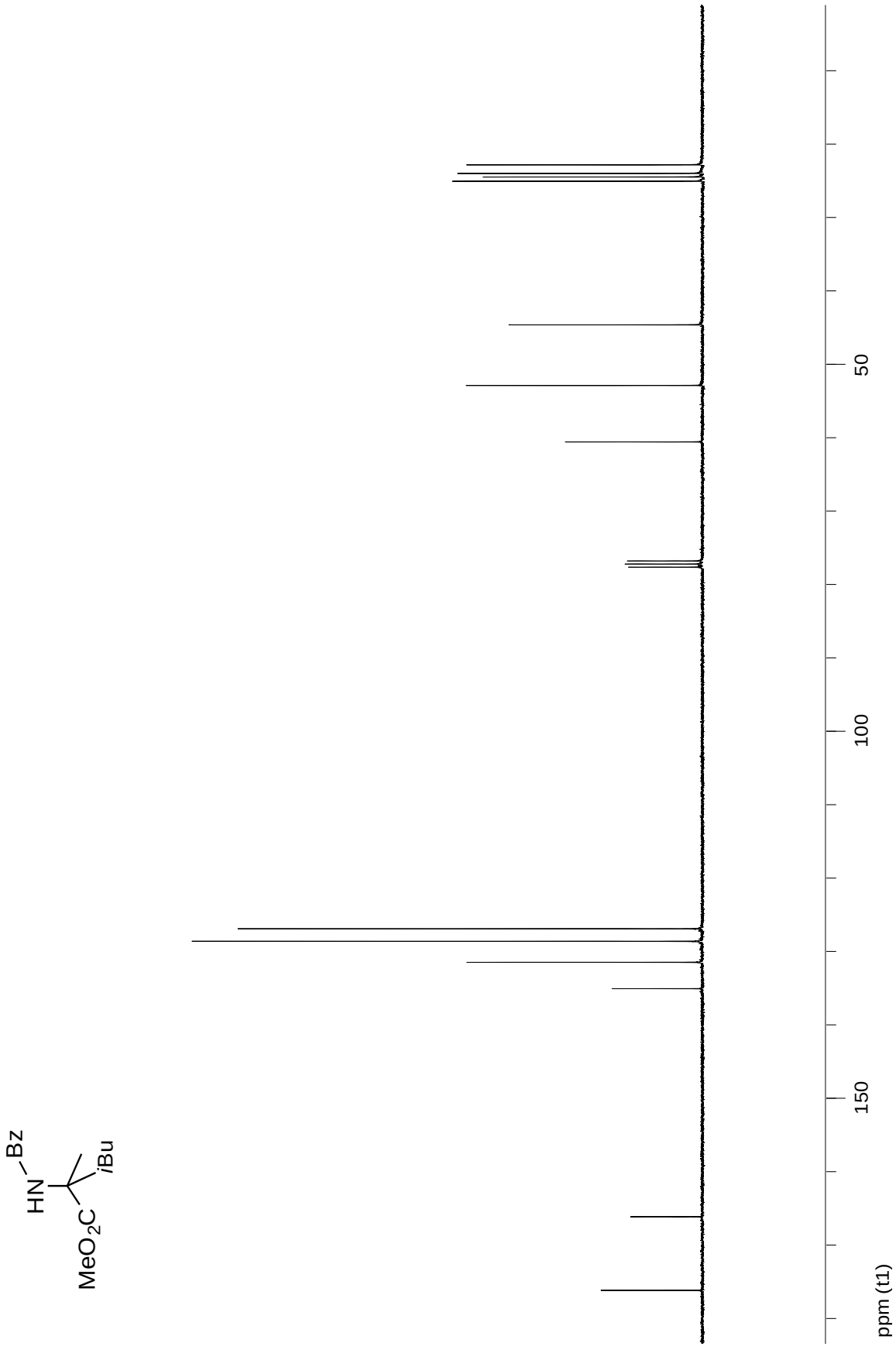

MeO2C
nC5H11
H
N
Bz
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

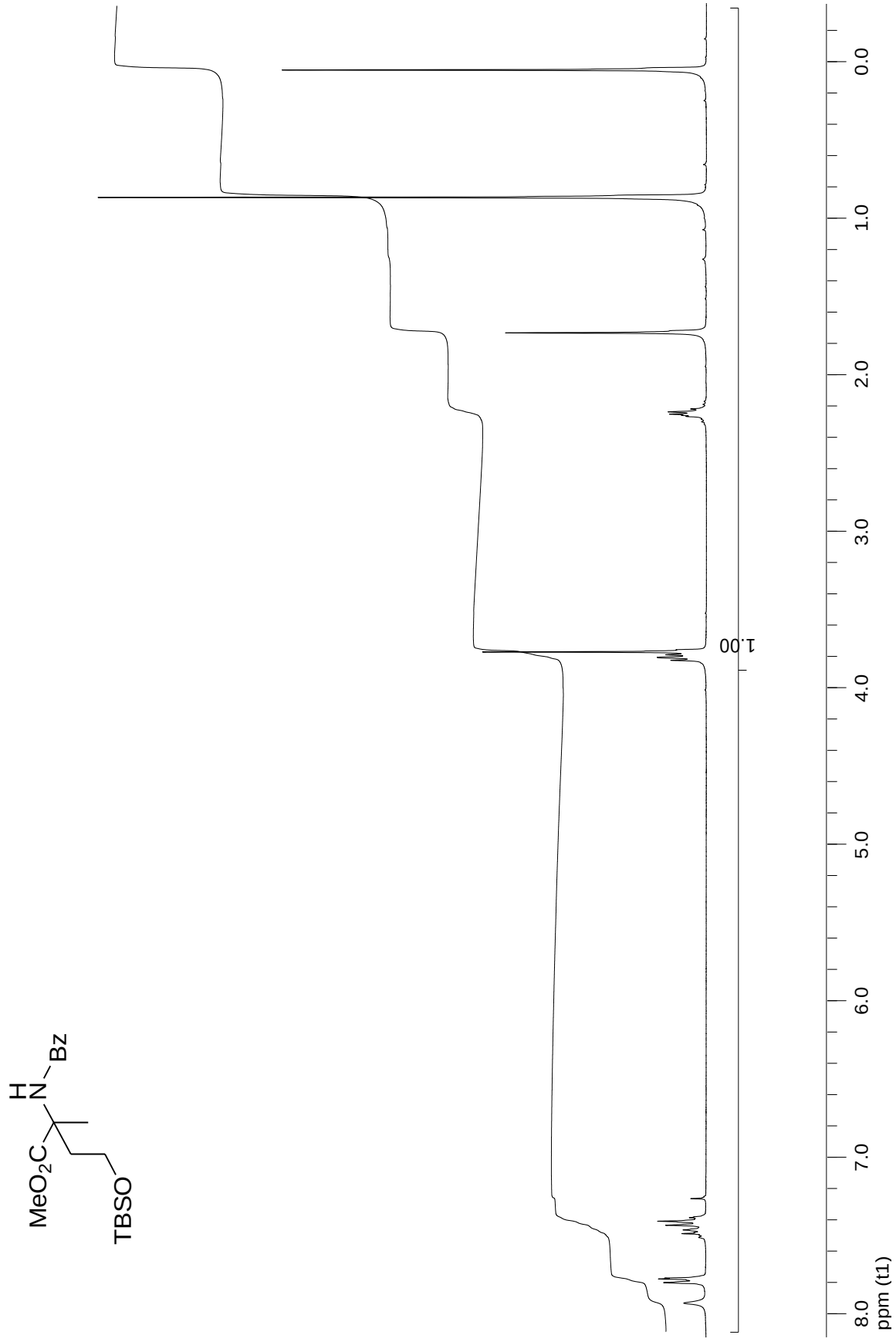

H
N
Bz
MeO2C
nC5H11
0
50
100
150
200
ppm (t1)

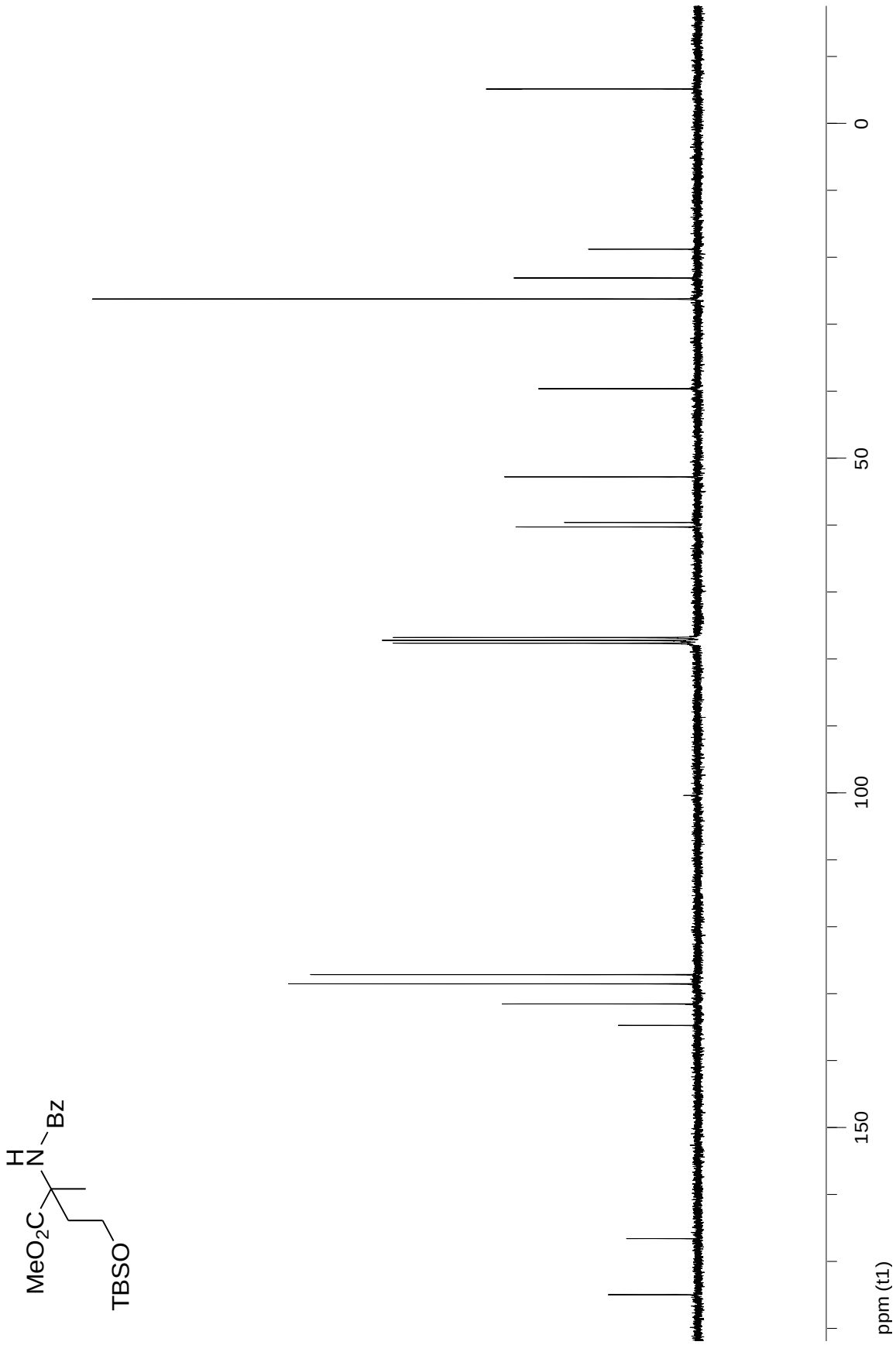

Bz
HN
MeO2C
nC12H25
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

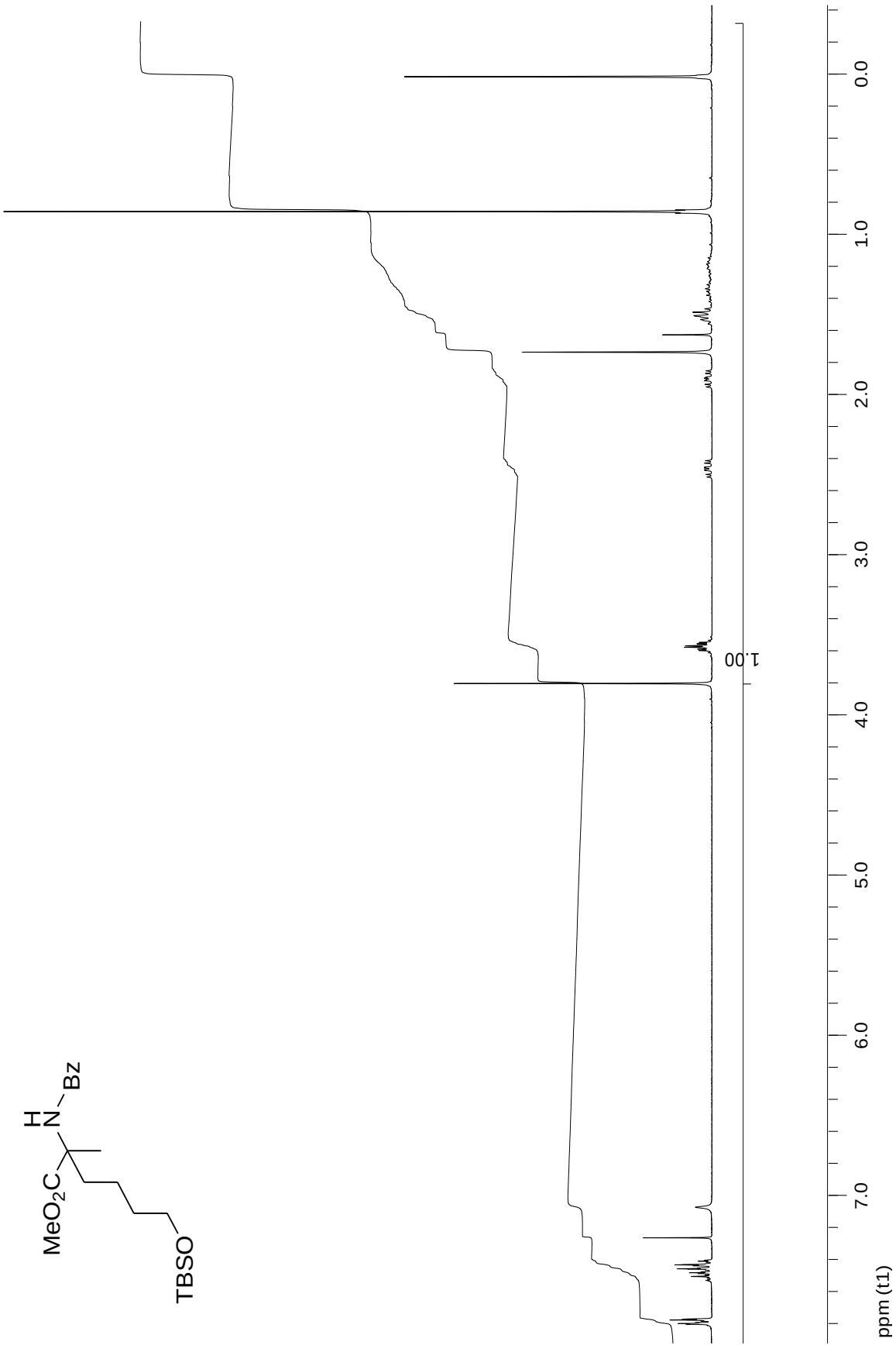

Bz
HN
nC12H25
MeO2C
0
50
100
150
ppm (t1)

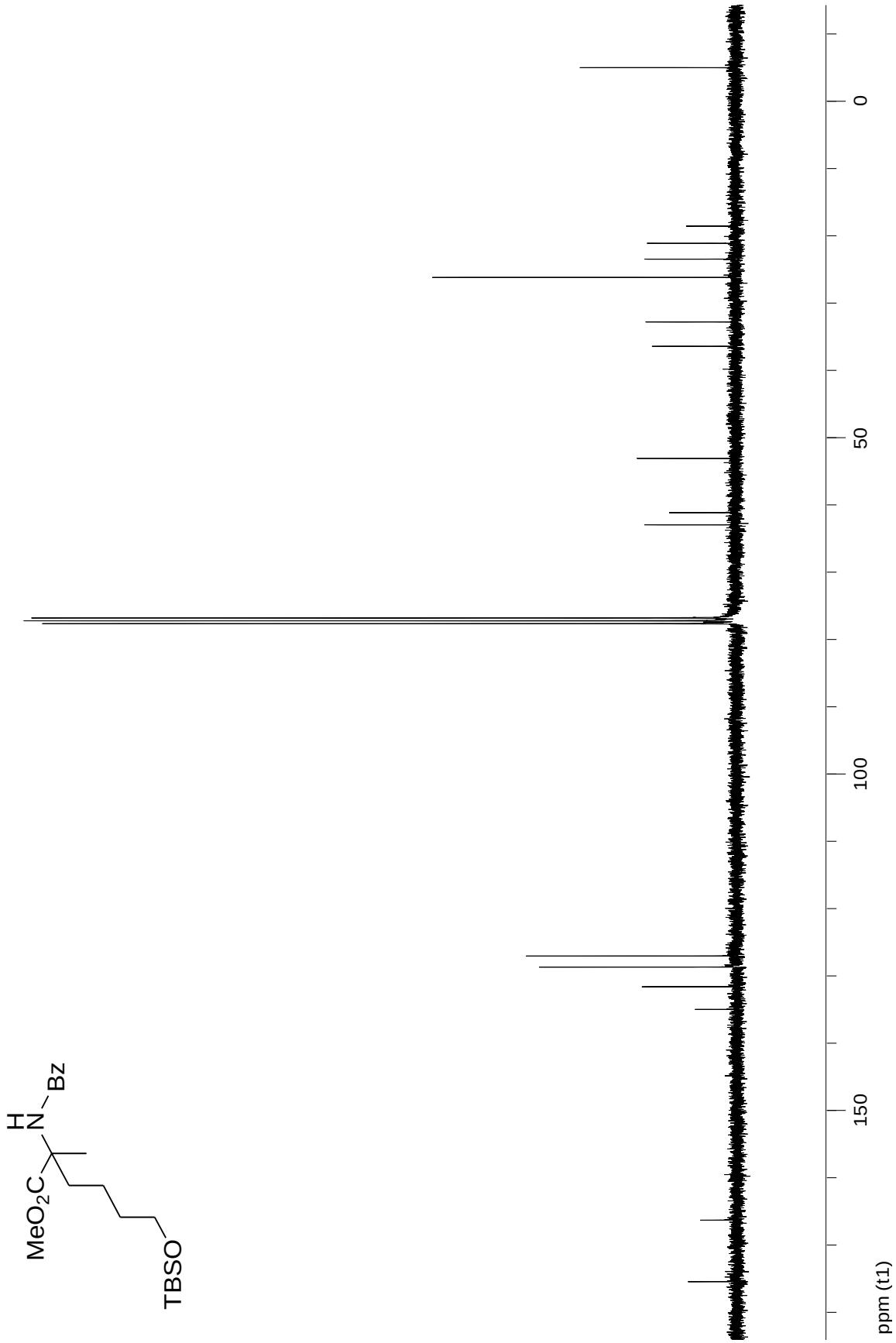

Bz
HN
MeO2C
iBu
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

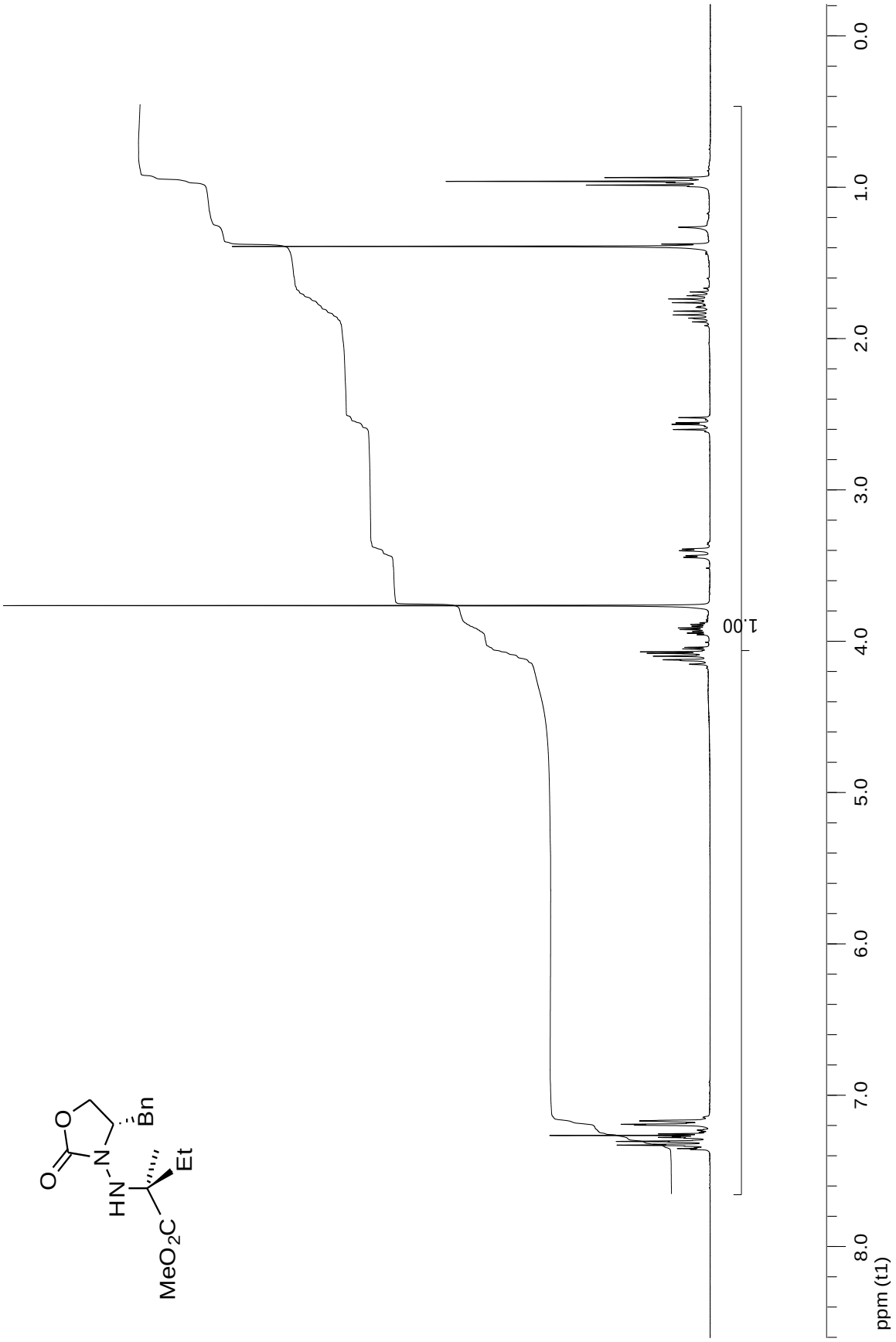

Bz
HN
MeO2C
iBu
50
100
150
ppm (t1)

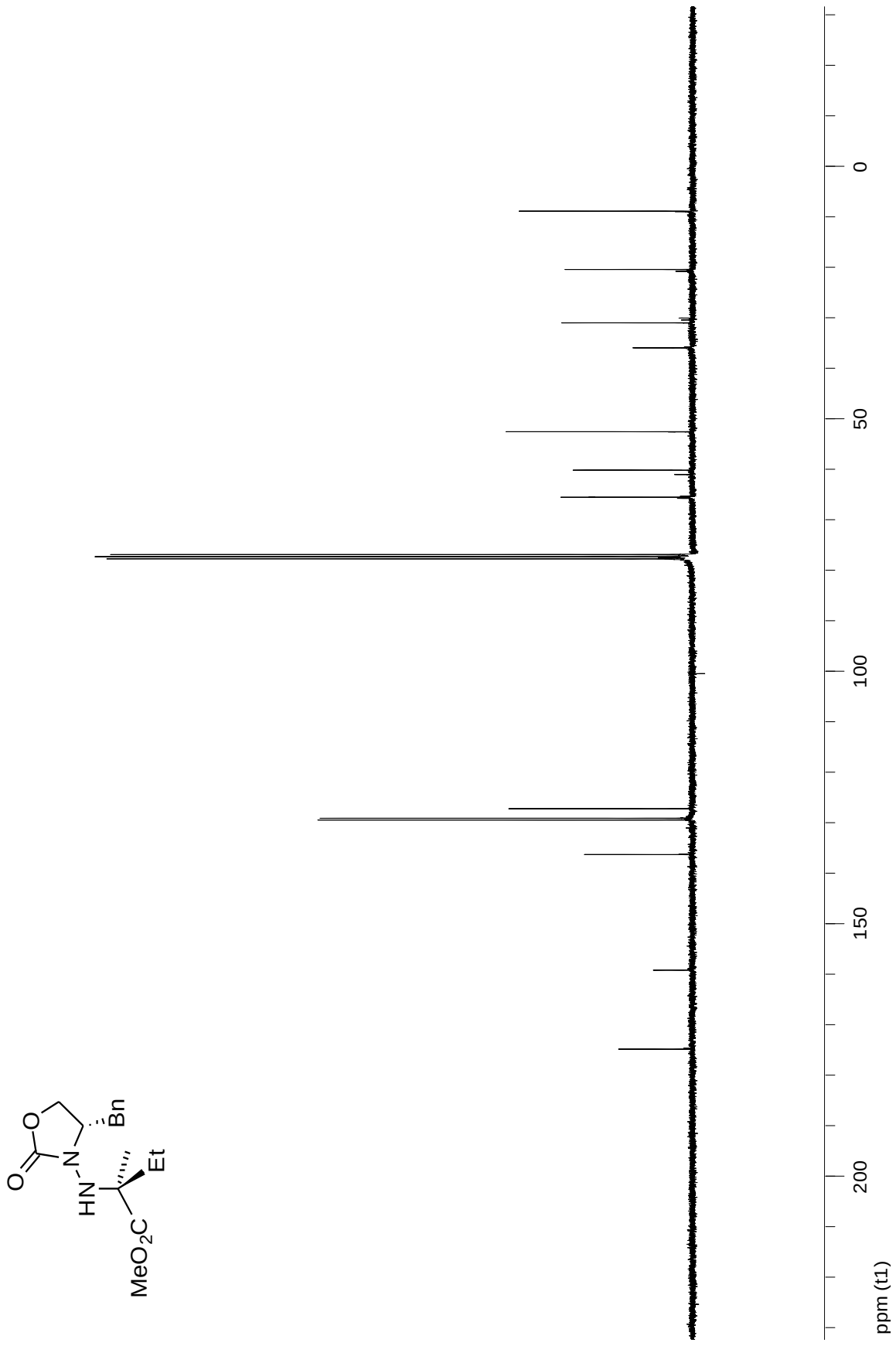

H
N
Bz
MeO2C
TBSO
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

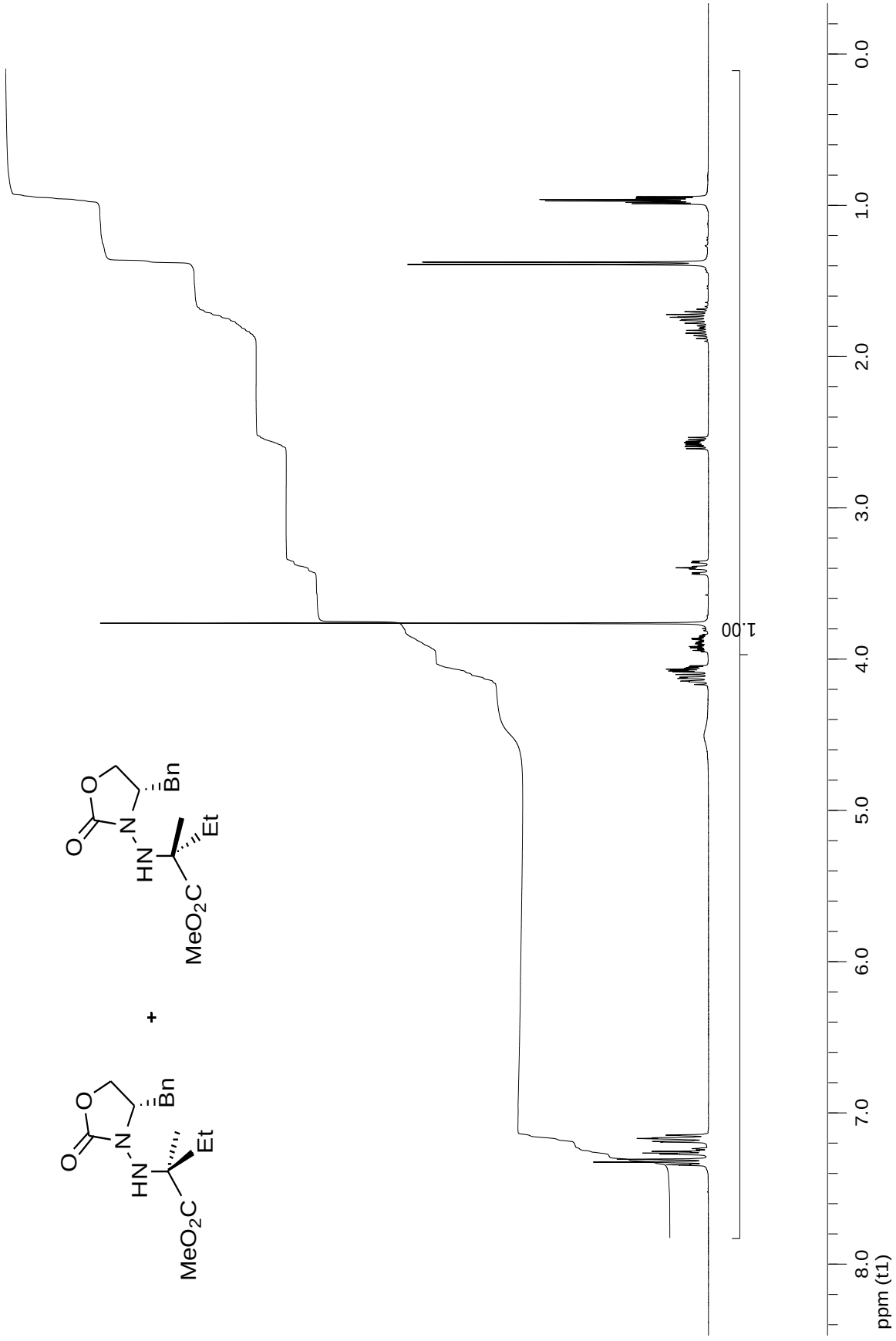

H
N
Bz
MeO2C
TBSO
0
50
100
150
ppm (t1)

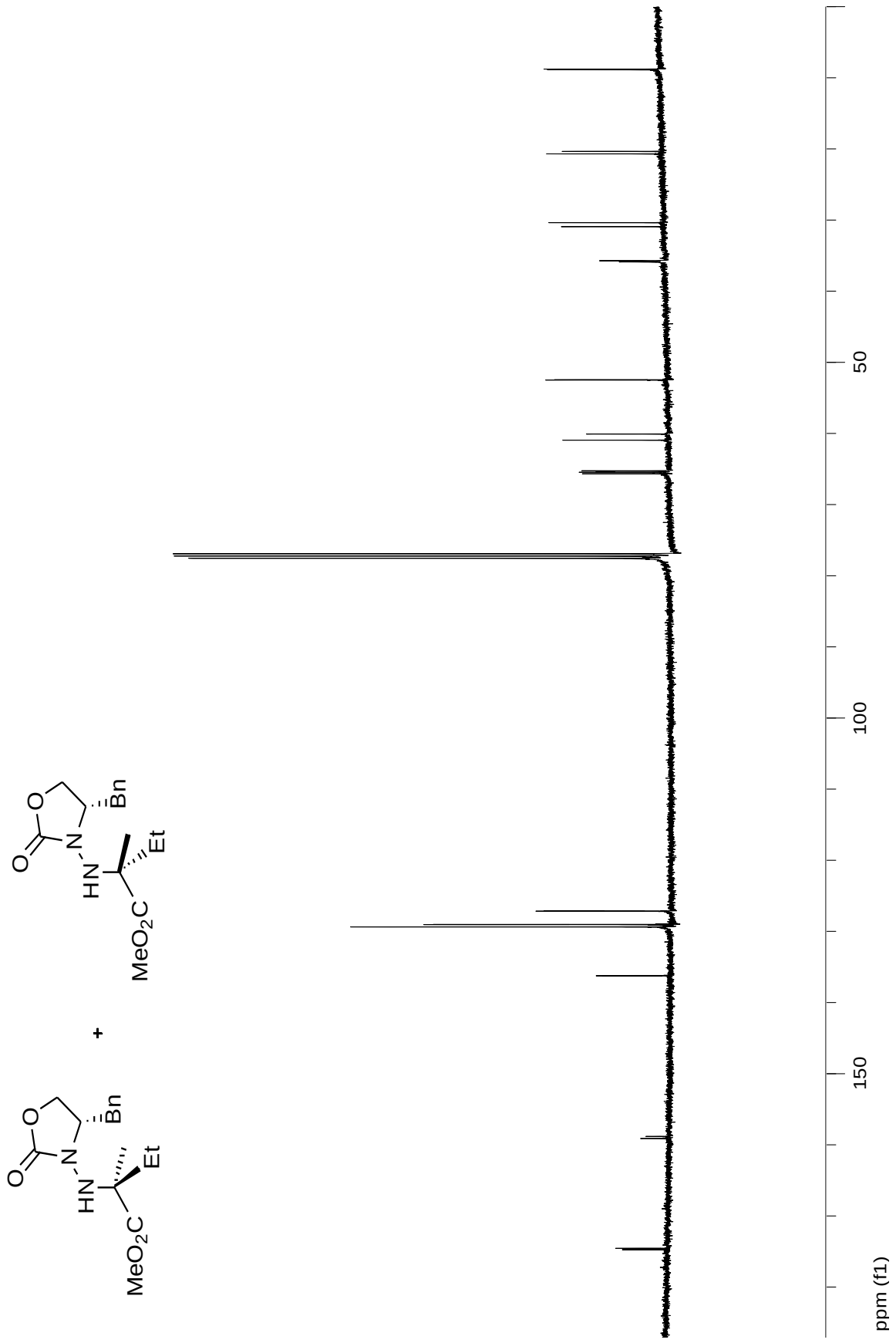

TBSO
MeO2C
H
N
Bz
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

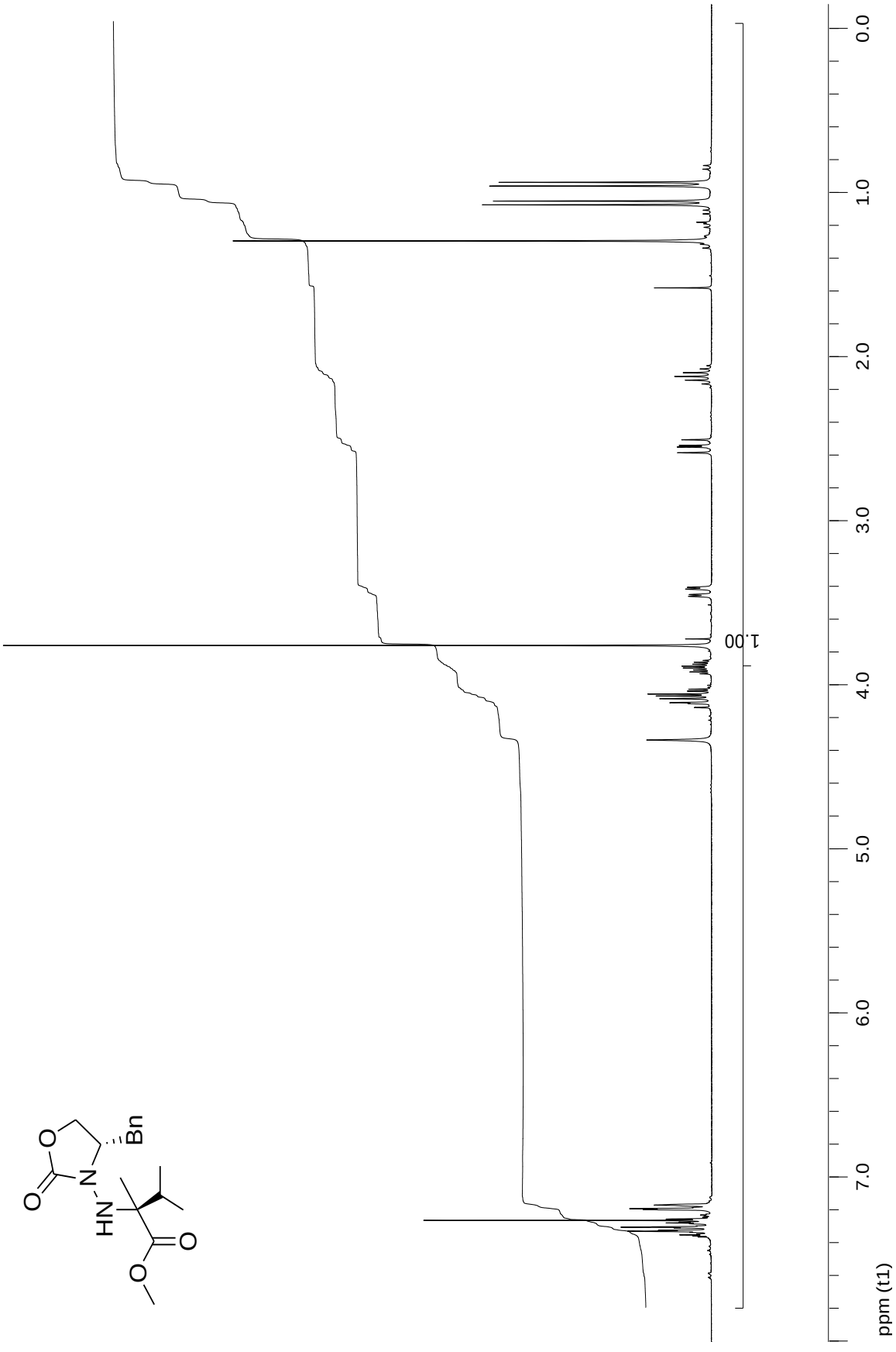

H
N
Bz
MeO2C
TBSO
0
50
100
150
ppm (t1)

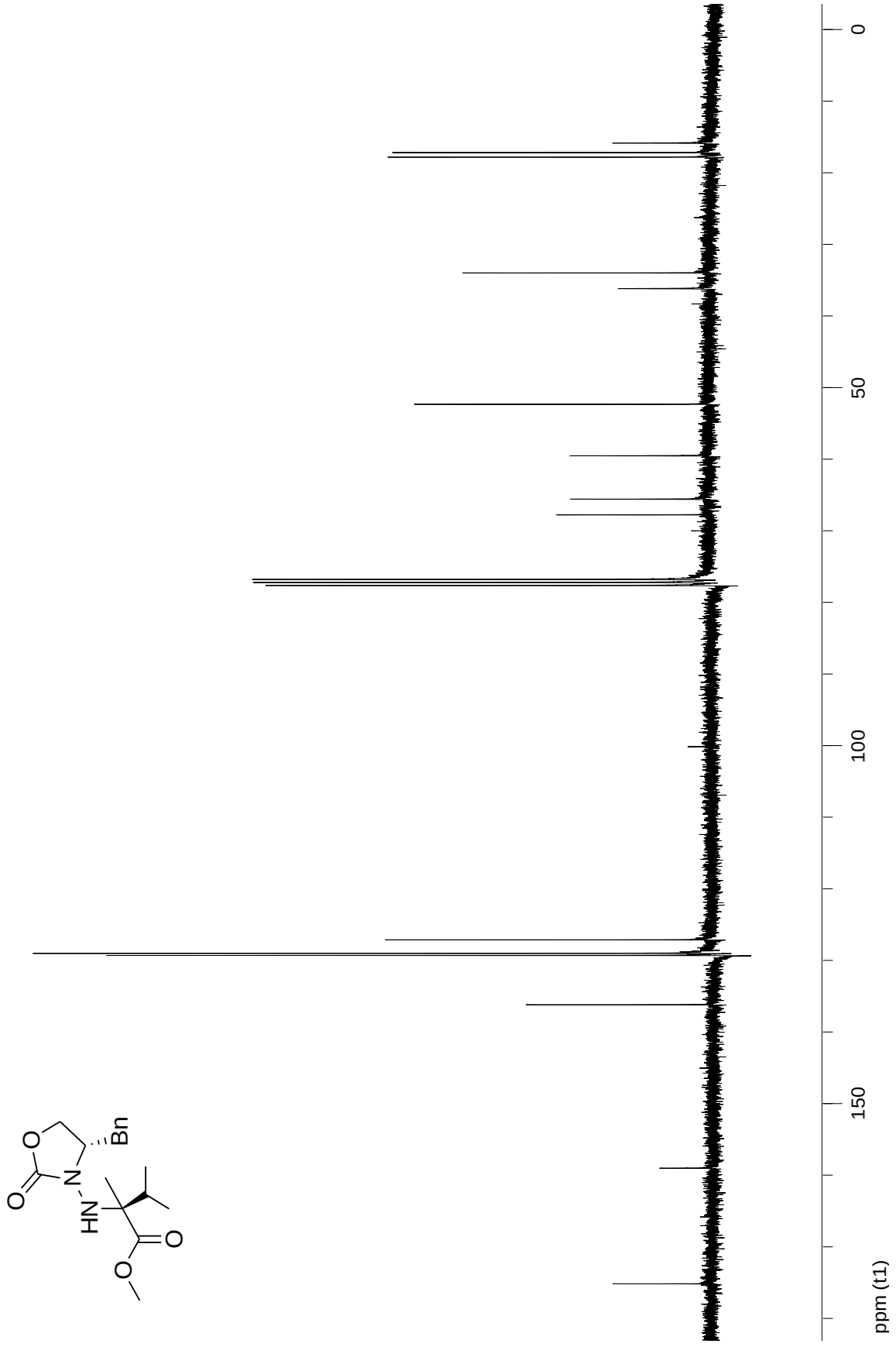

O
O
N
HN
Bn
Et
MeO2C
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

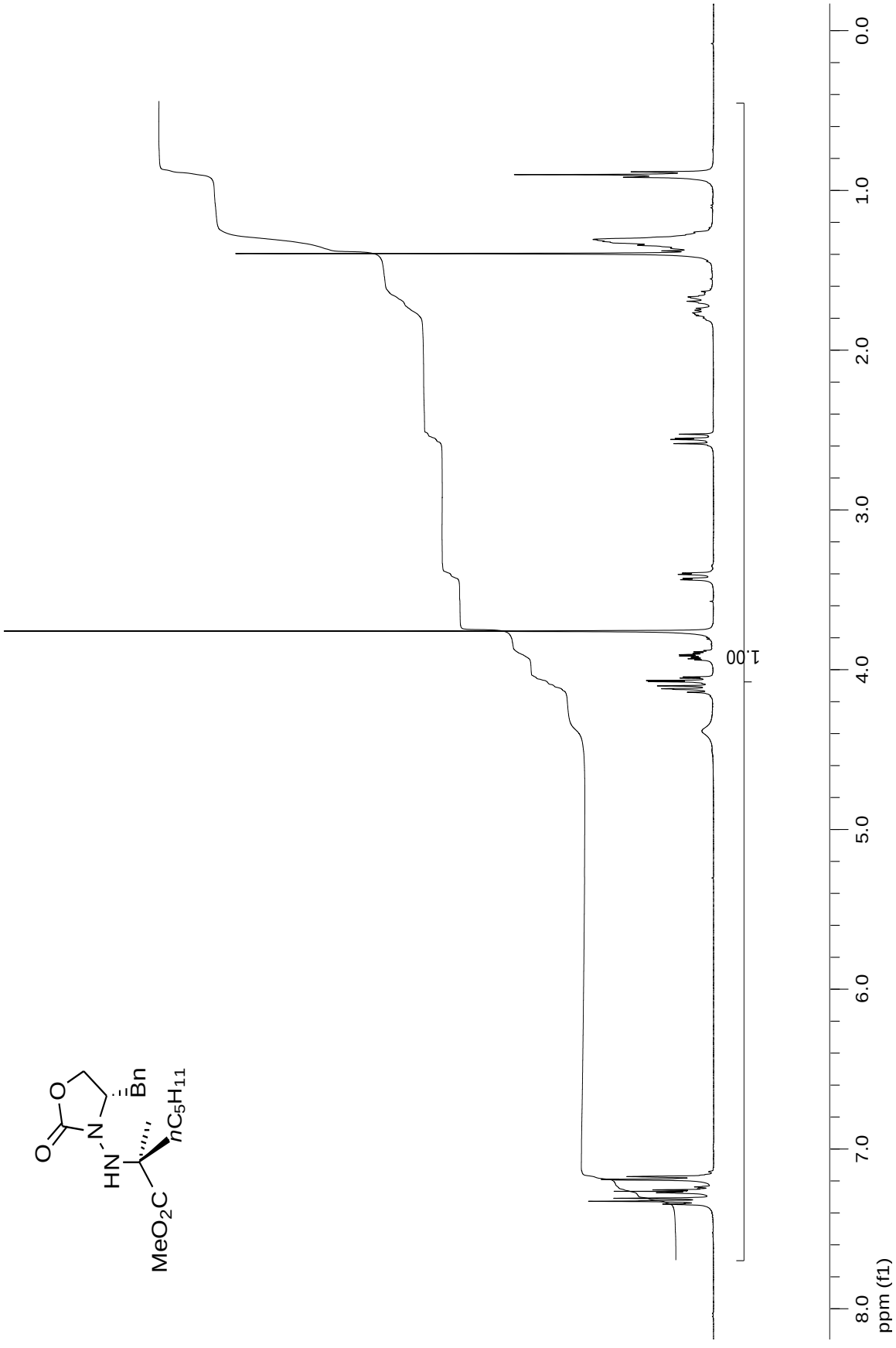

O
O
N
HN
Bn
Et
MeO2C
0
50
100
150
200
ppm (t1)

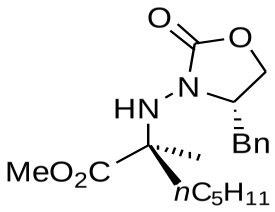

1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)
Bn
Et
HN
N
O
O
MeO2C
+
Bn
Et
HN
N
O
O
MeO2C


O
O
N
HN
Bn
Et
MeO2C
+
O
O
N
HN
Bn
Et
MeO2C
50
100
150
ppm (f1)

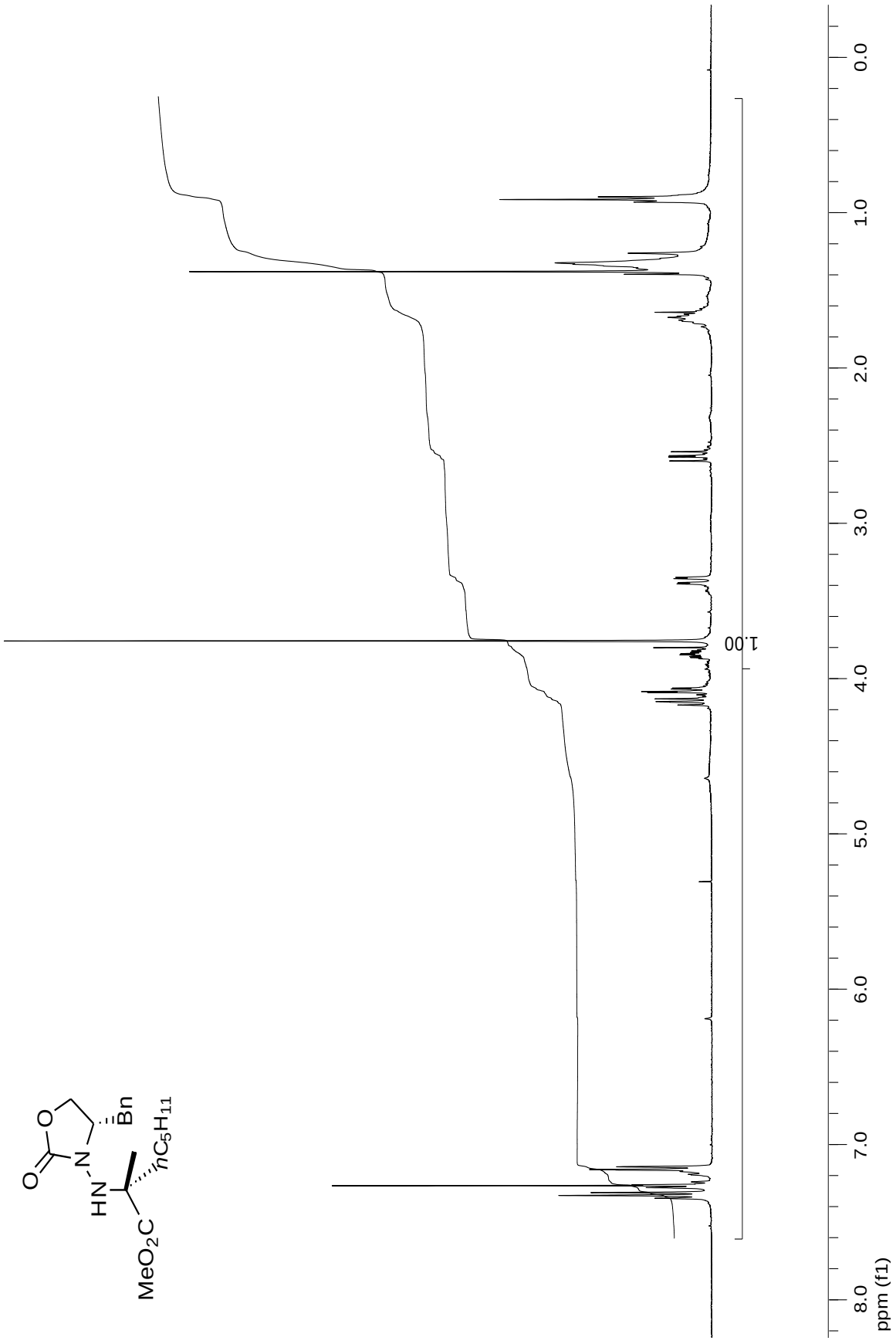

O
O
N
HN
Bn
O
O
O
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

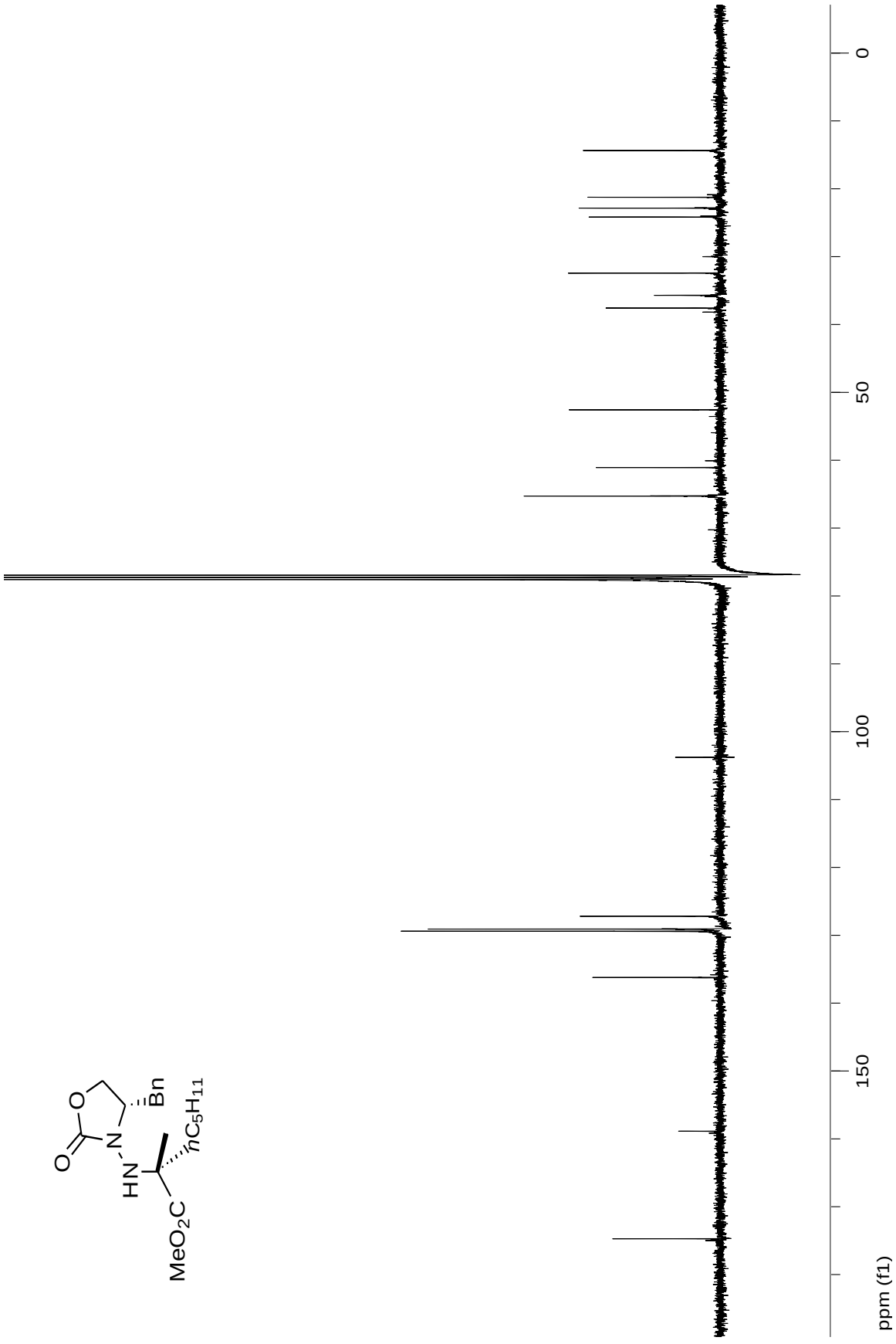

O
Bn
O
N
HN
O
O
O
150
100
50
0
ppm (t1)

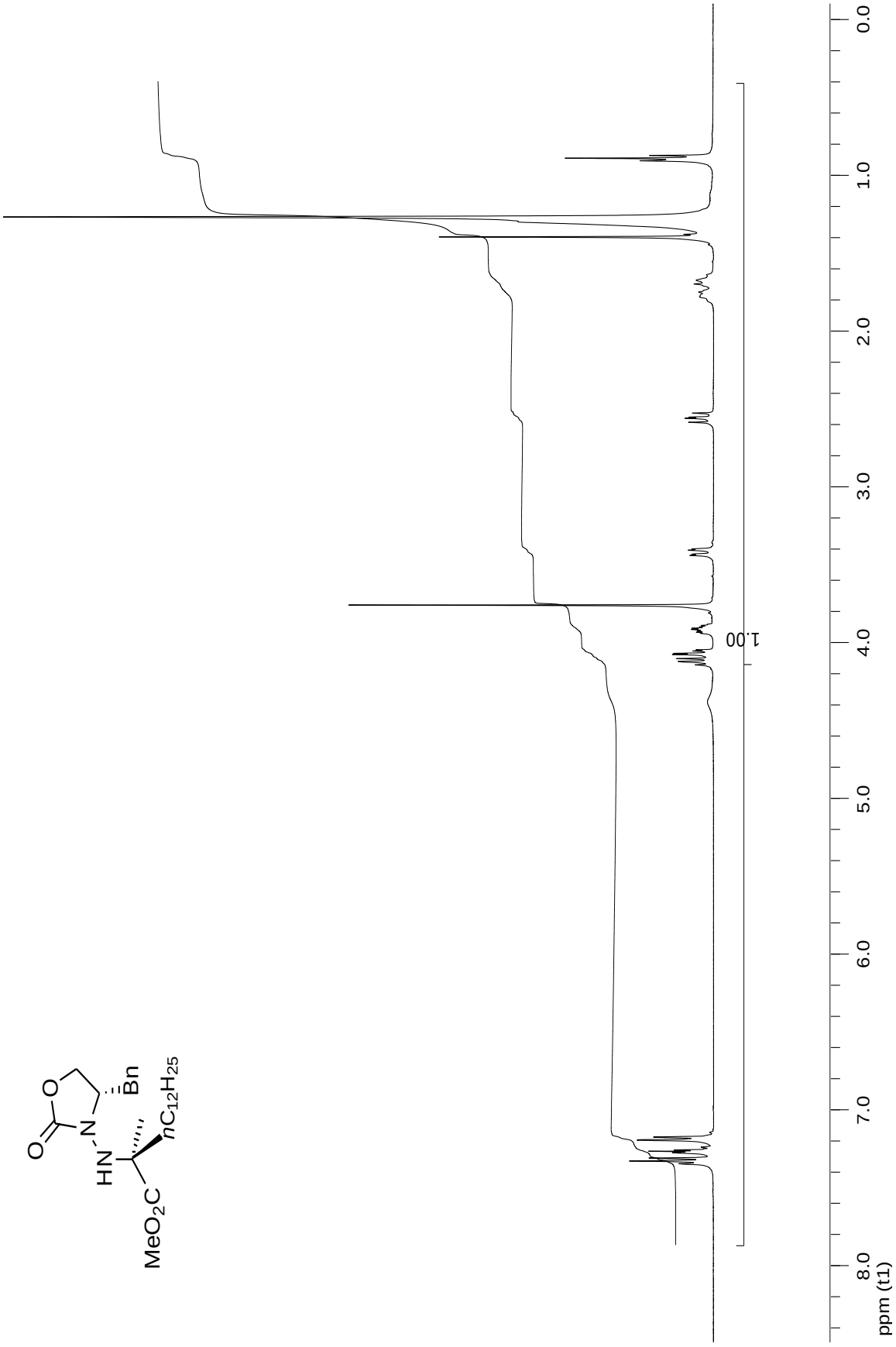

O
O
N
Bn
HN
nC5H11
MeO2C
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

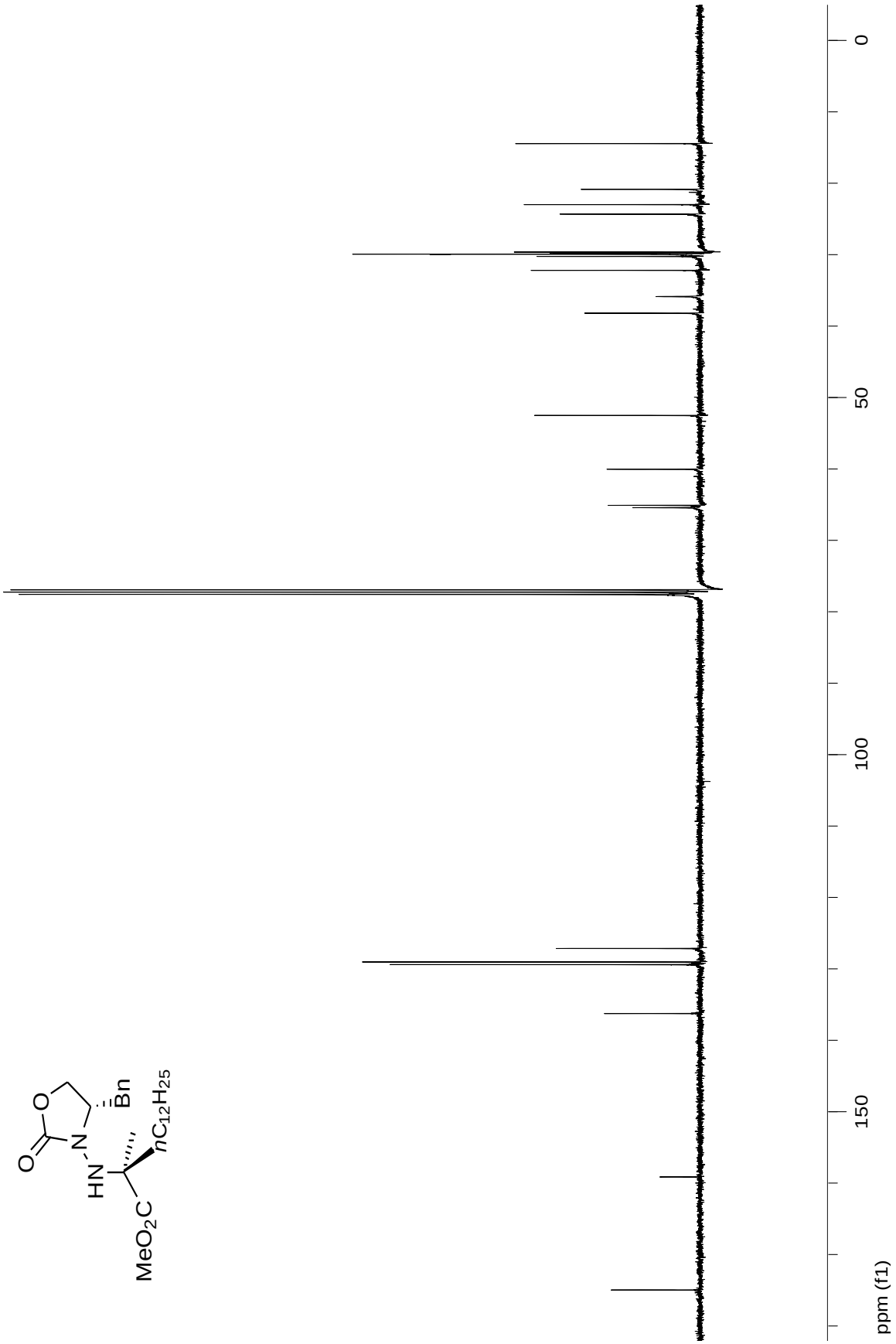

O
O
N
HN
Bn
MeO2C
nC5H11

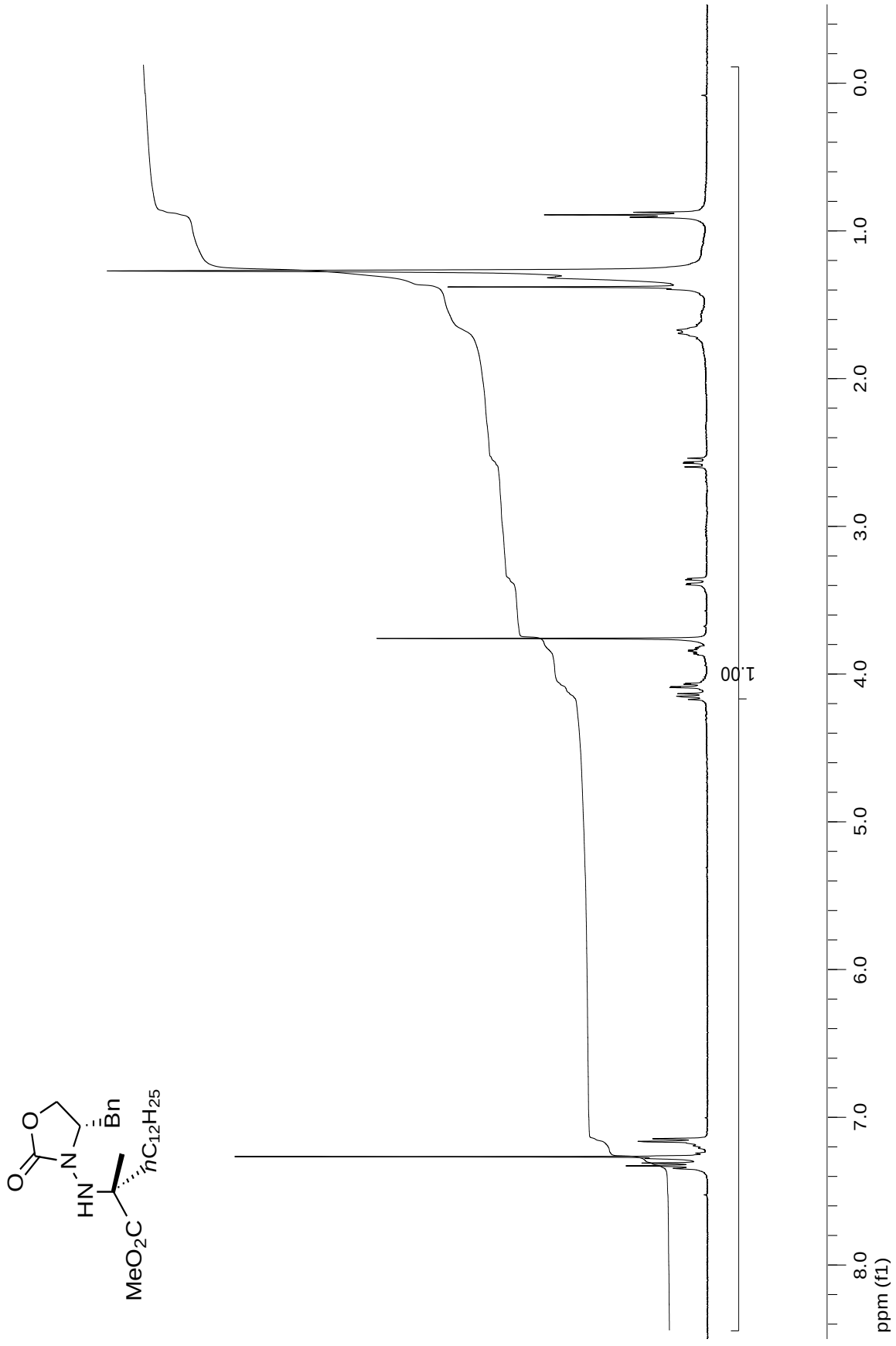
150
100
50
0
ppm (f1)

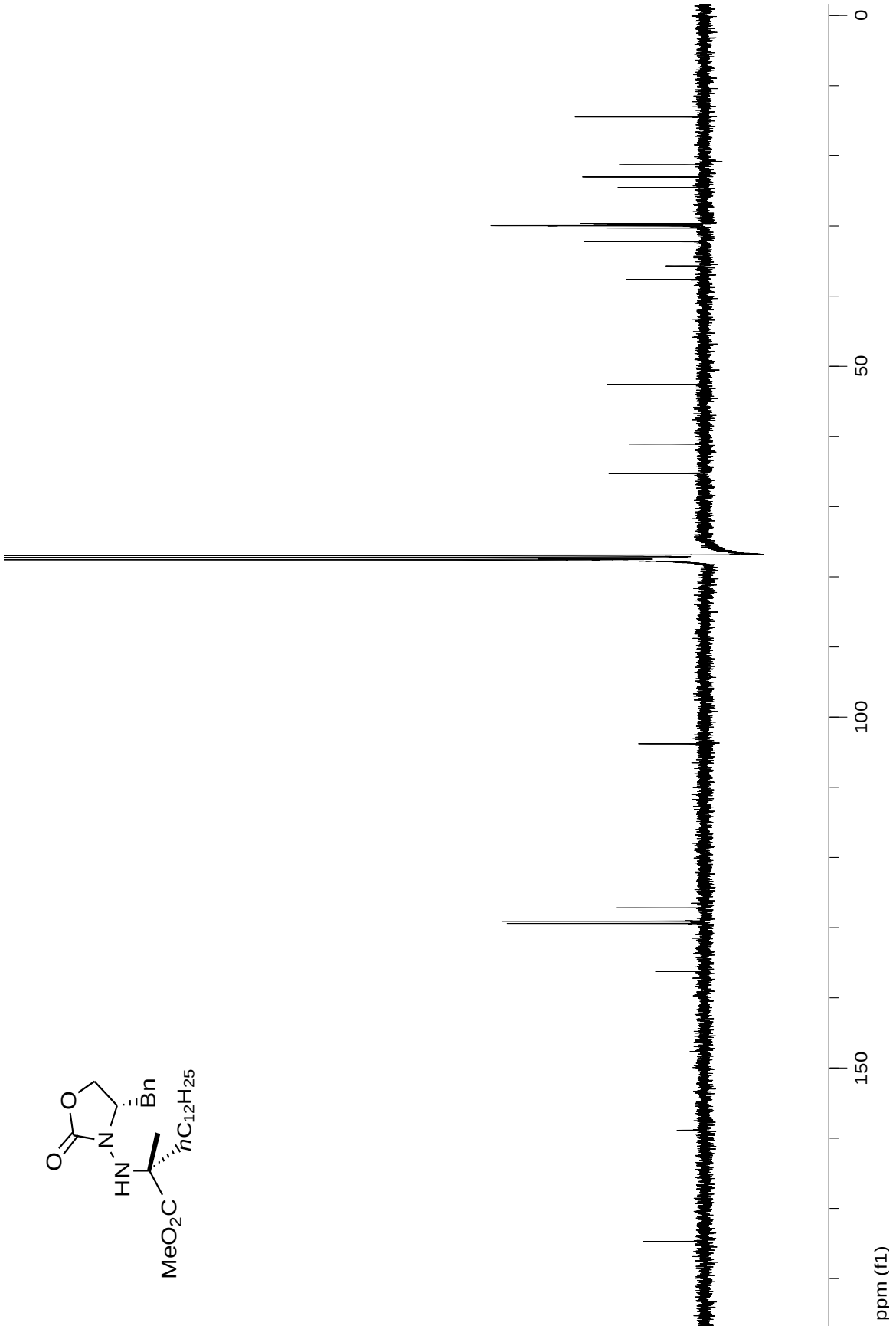

O
O
N
Bn
HN
nC5H11
MeO2C
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

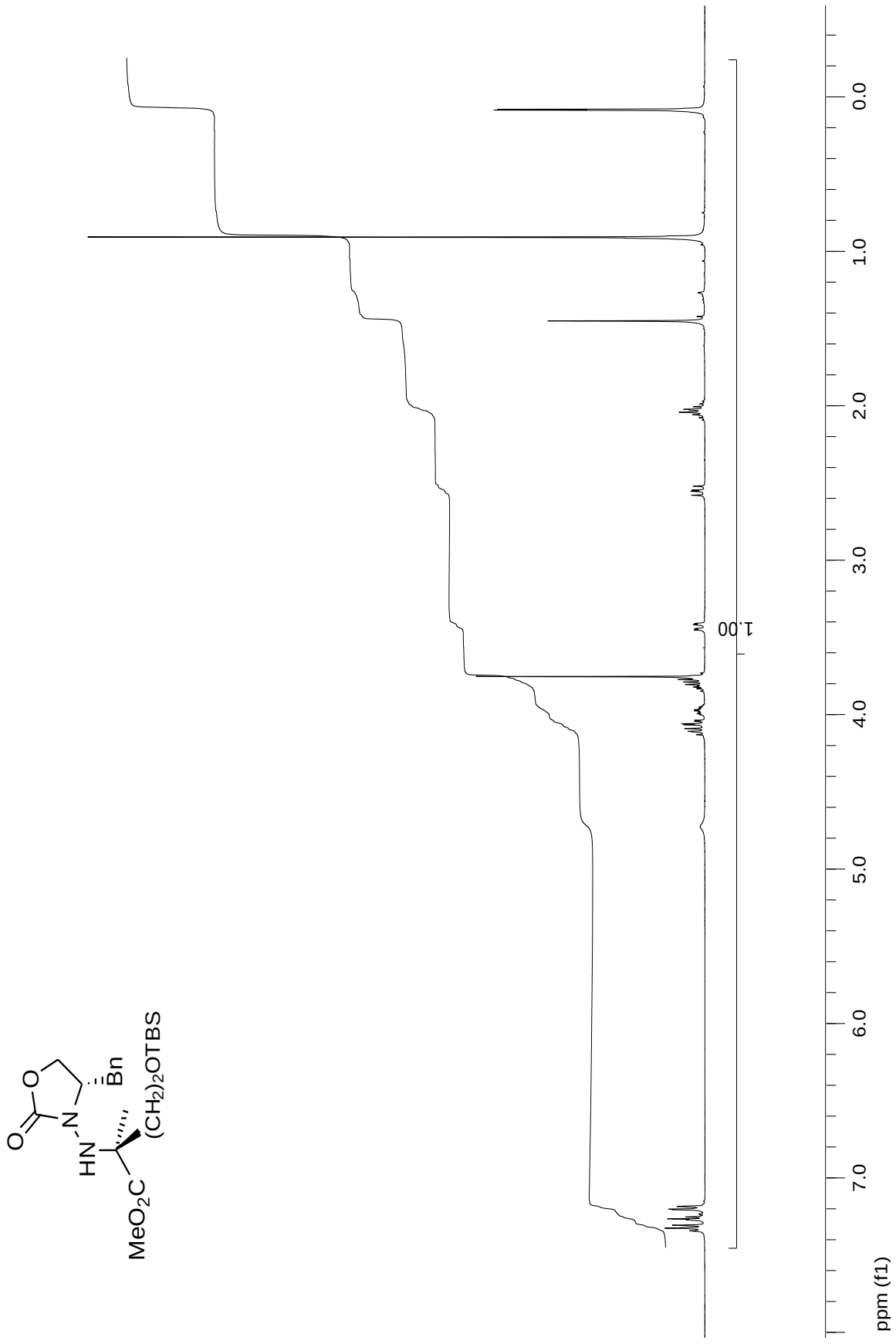

O
O
N
HN
Bn
nC5H11
MeO2C
0
50
100
150
ppm (f1)

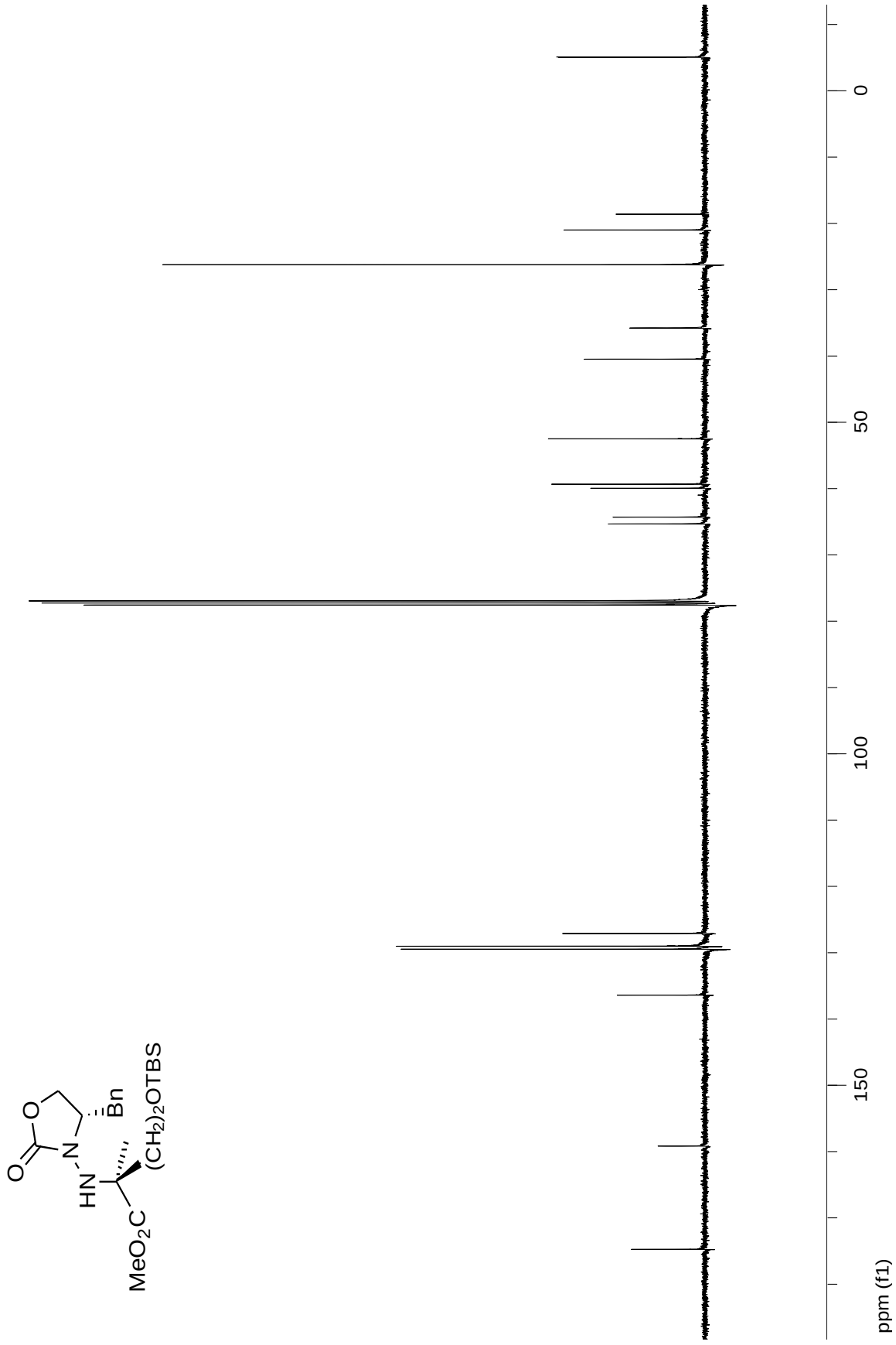

O
O
N
HN
Bn
MeO2C
nC12H25
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

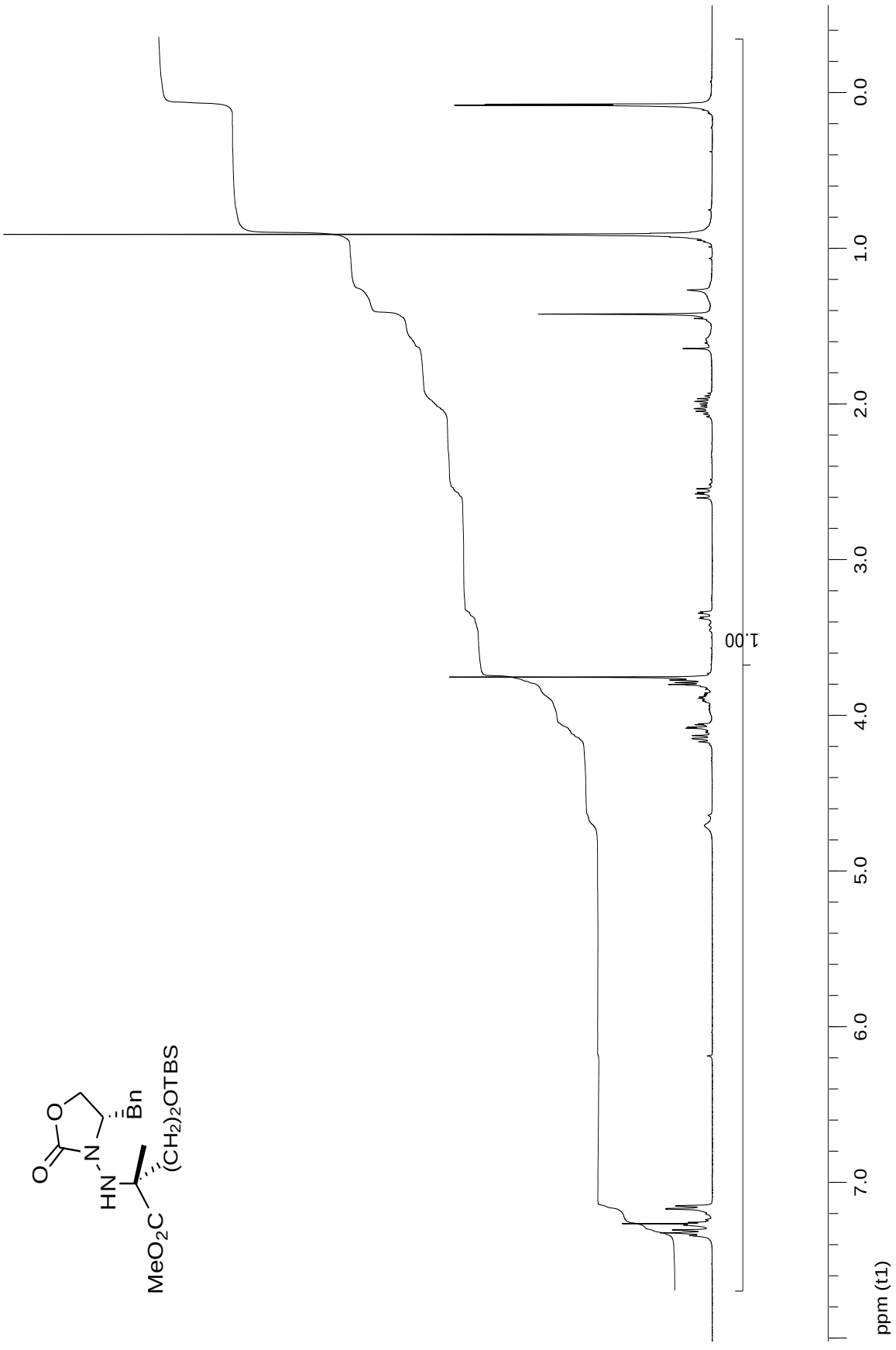

O
O
N
HN
Bn
MeO2C
nC12H25
0
50
100
150
ppm (f1)

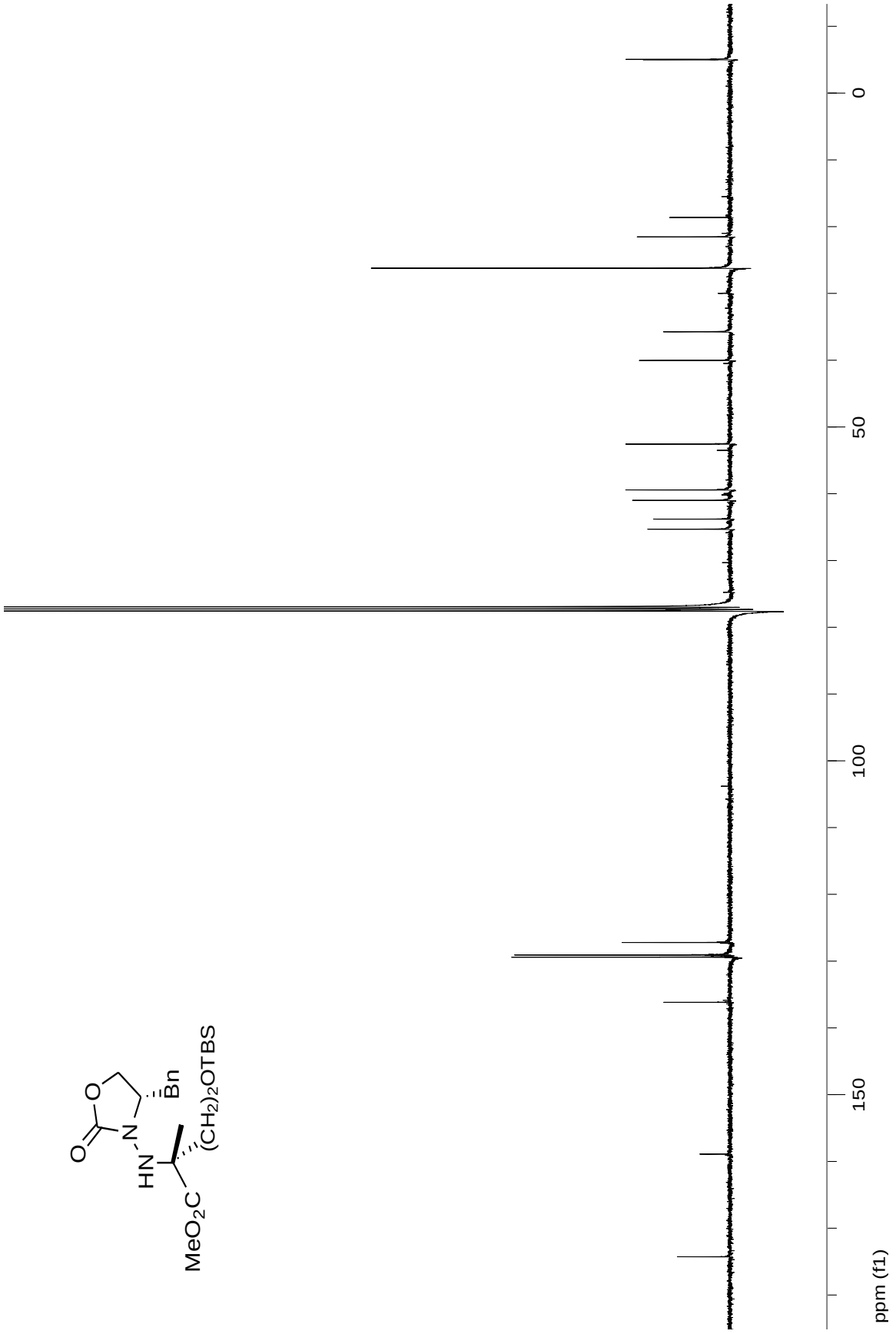

O
O
N
HN
Bn
nC$_{12}$H$_{25}$
MeO$_2$C
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

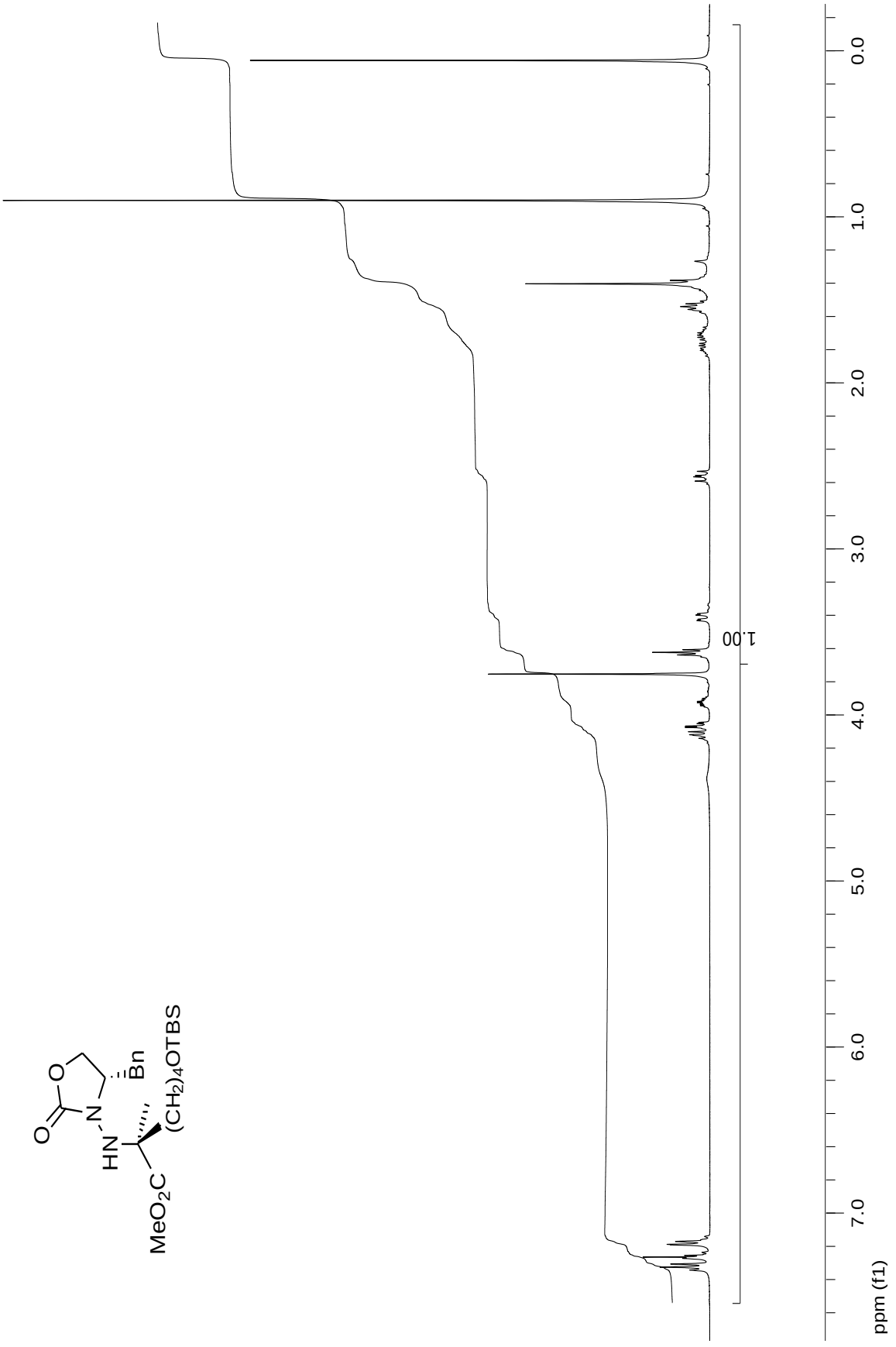

O
O
N
HN
Bn
nC12H25
MeO2C
0
50
100
150
ppm (f1)

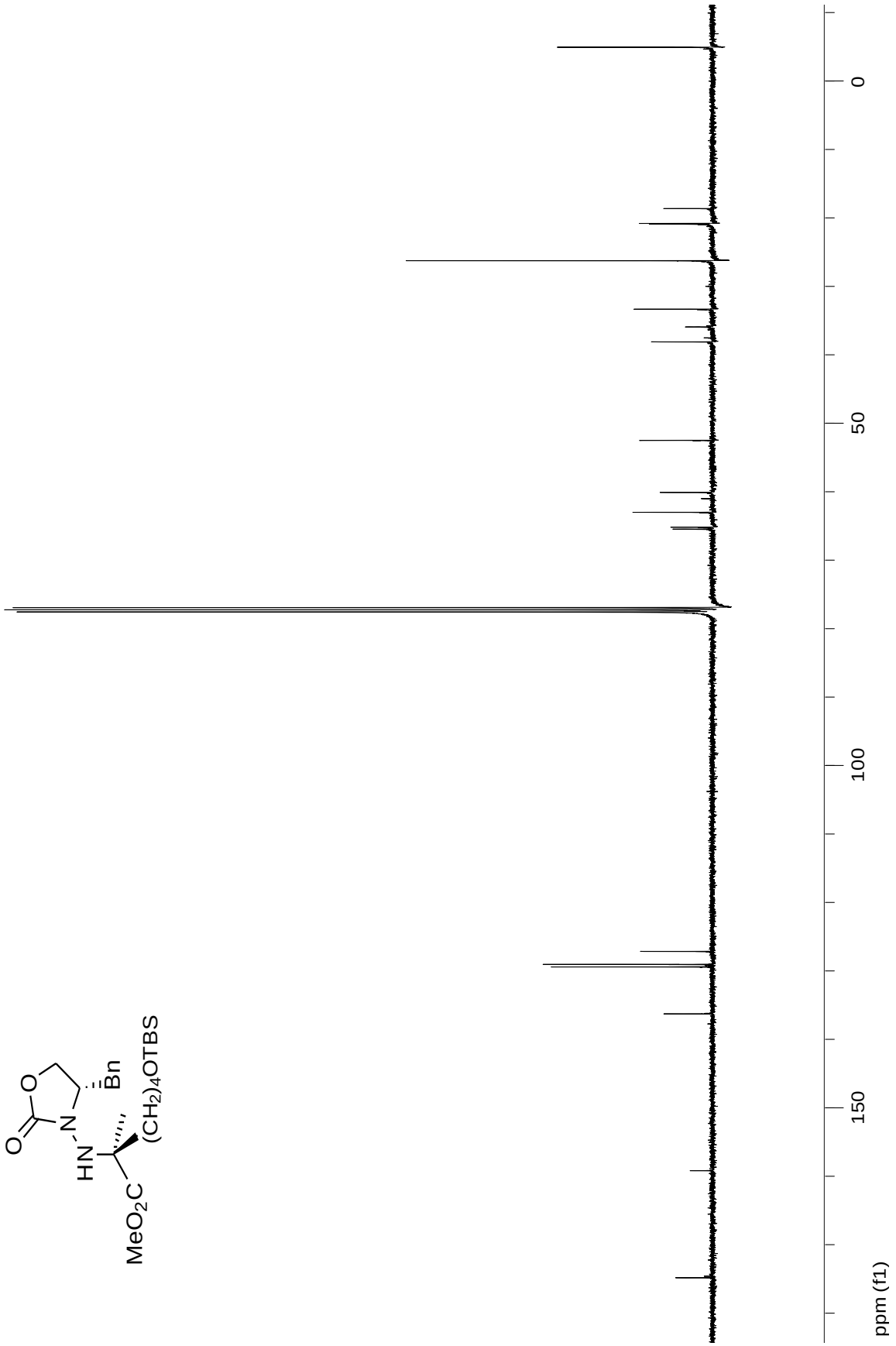

O
O
N
Bn
HN
MeO2C
(CH2)2OTBS
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)

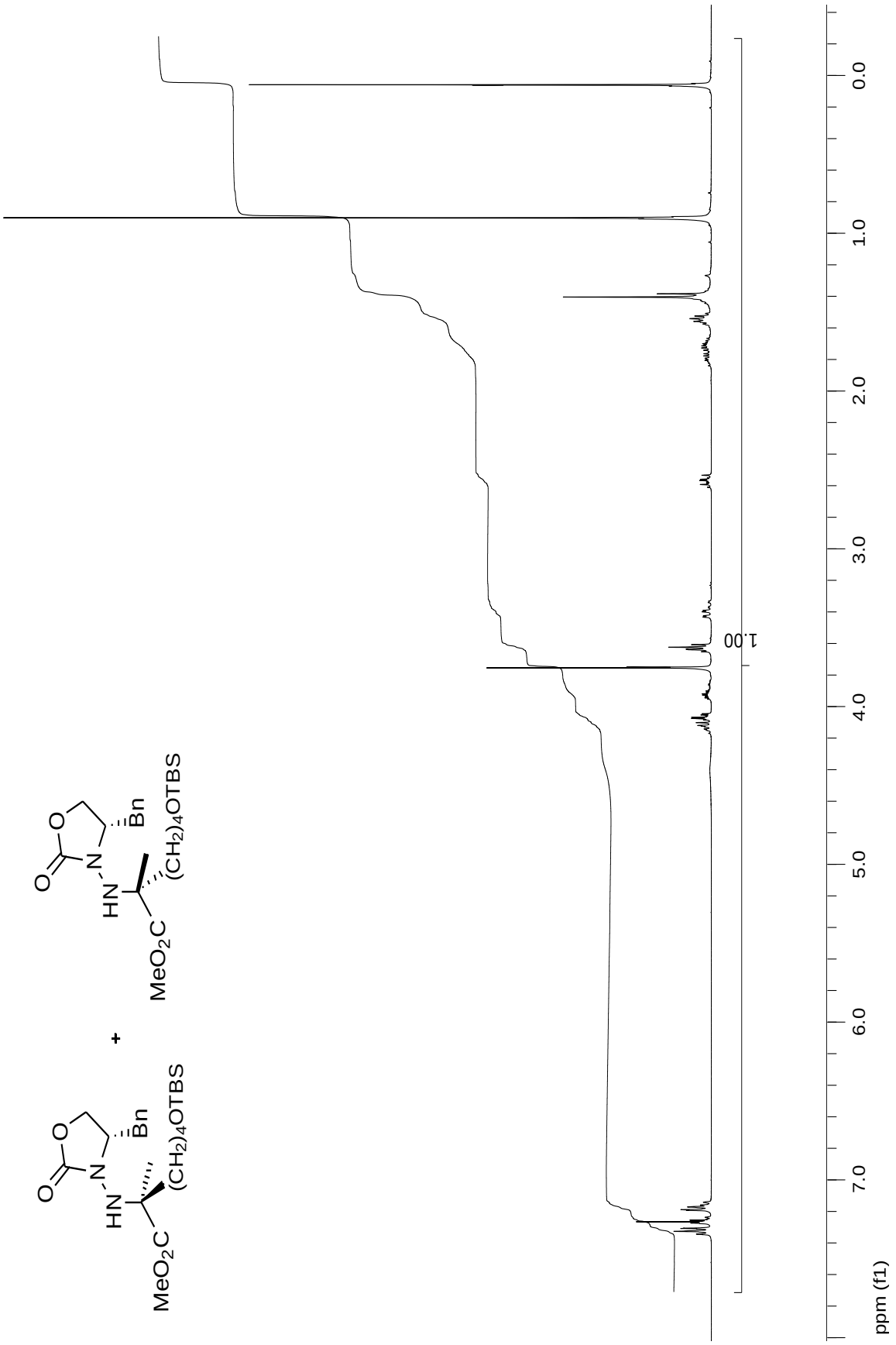

O
O
N
Bn
HN
MeO2C
(CH2)2OTBS
0
50
100
150
ppm (f1)

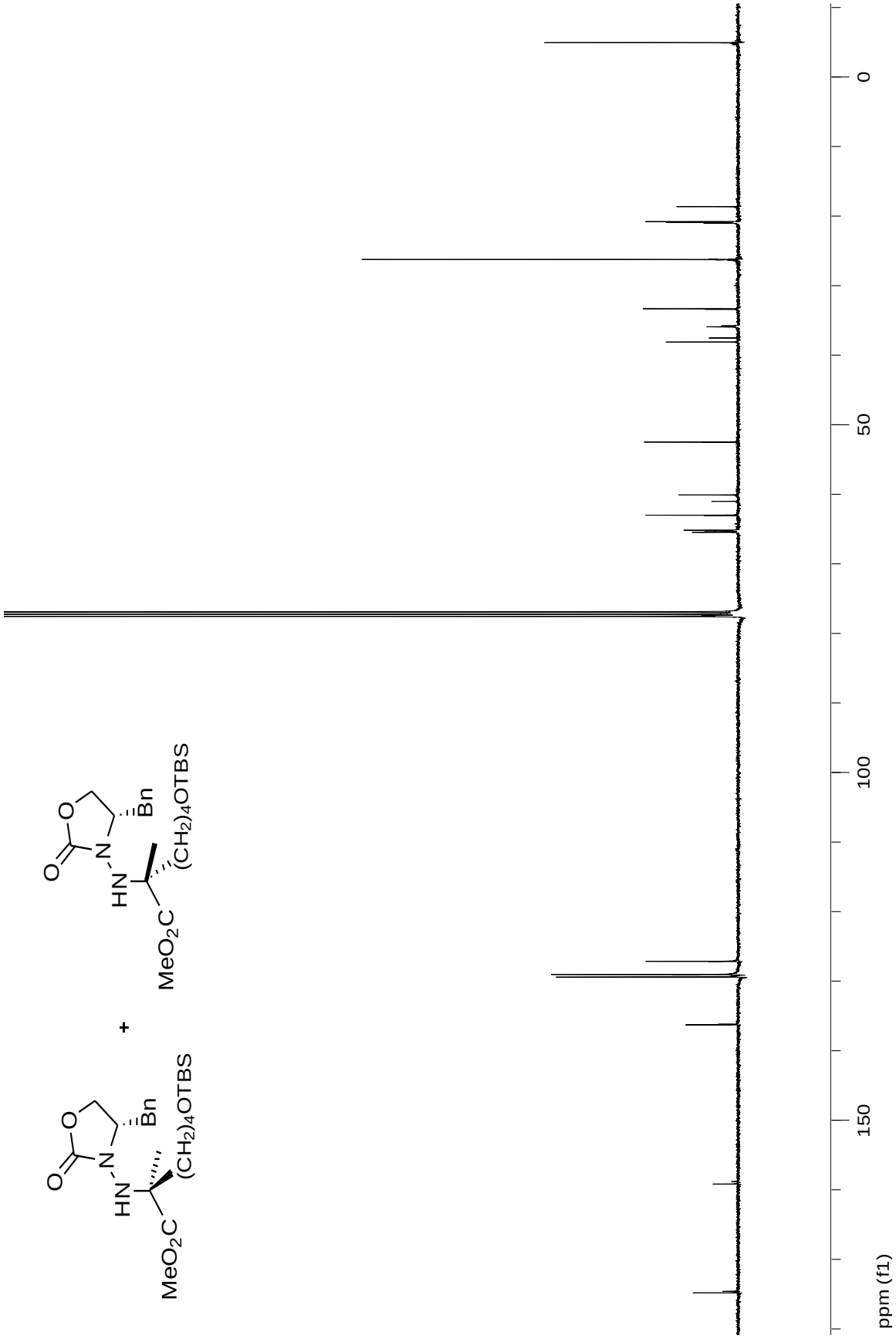

O
O
N
HN
Bn
MeO2C
(CH2)2OTBS
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

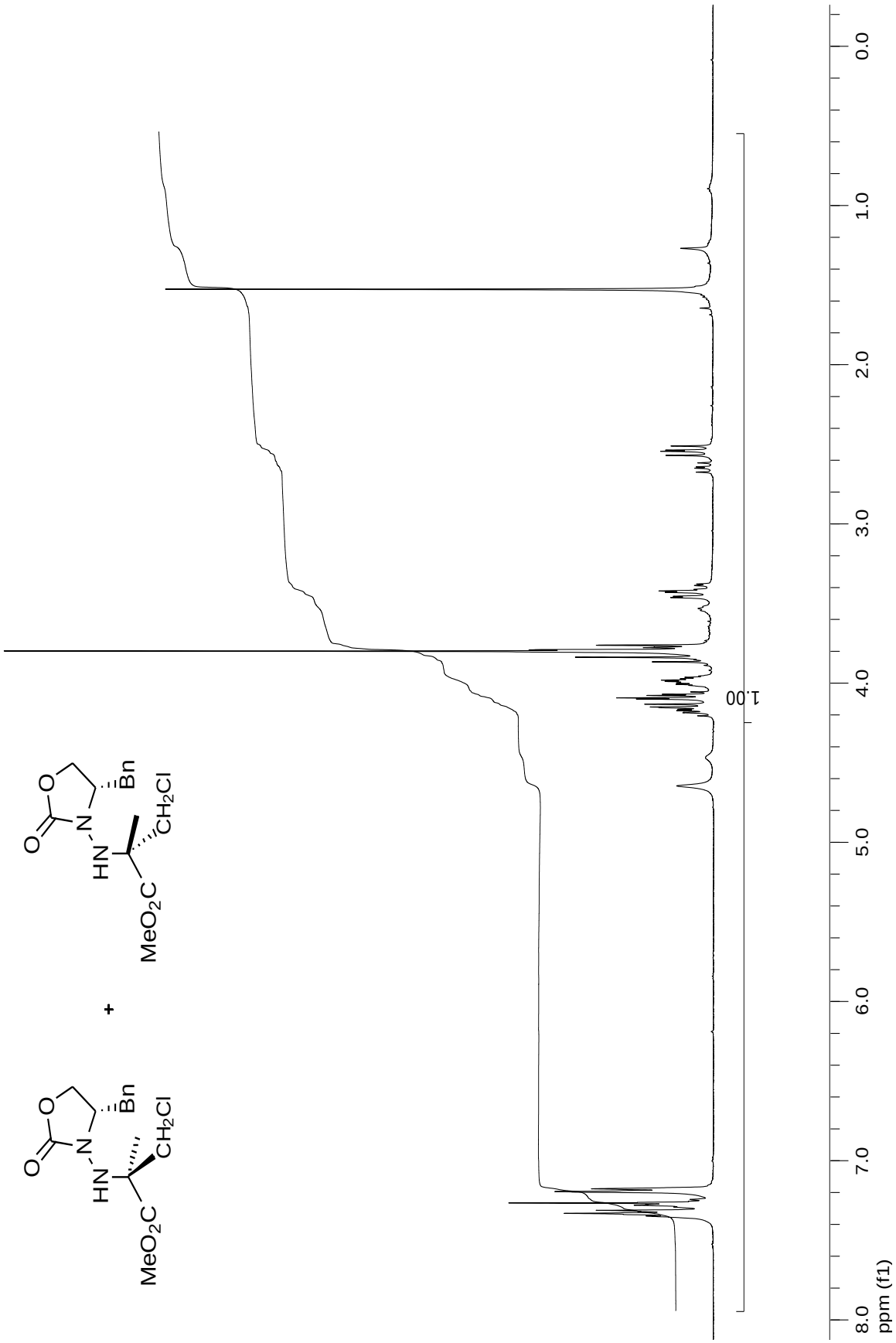

O
O
N
Bn
HN
(CH2)2OTBS
MeO2C
0
50
100
150
ppm (f1)

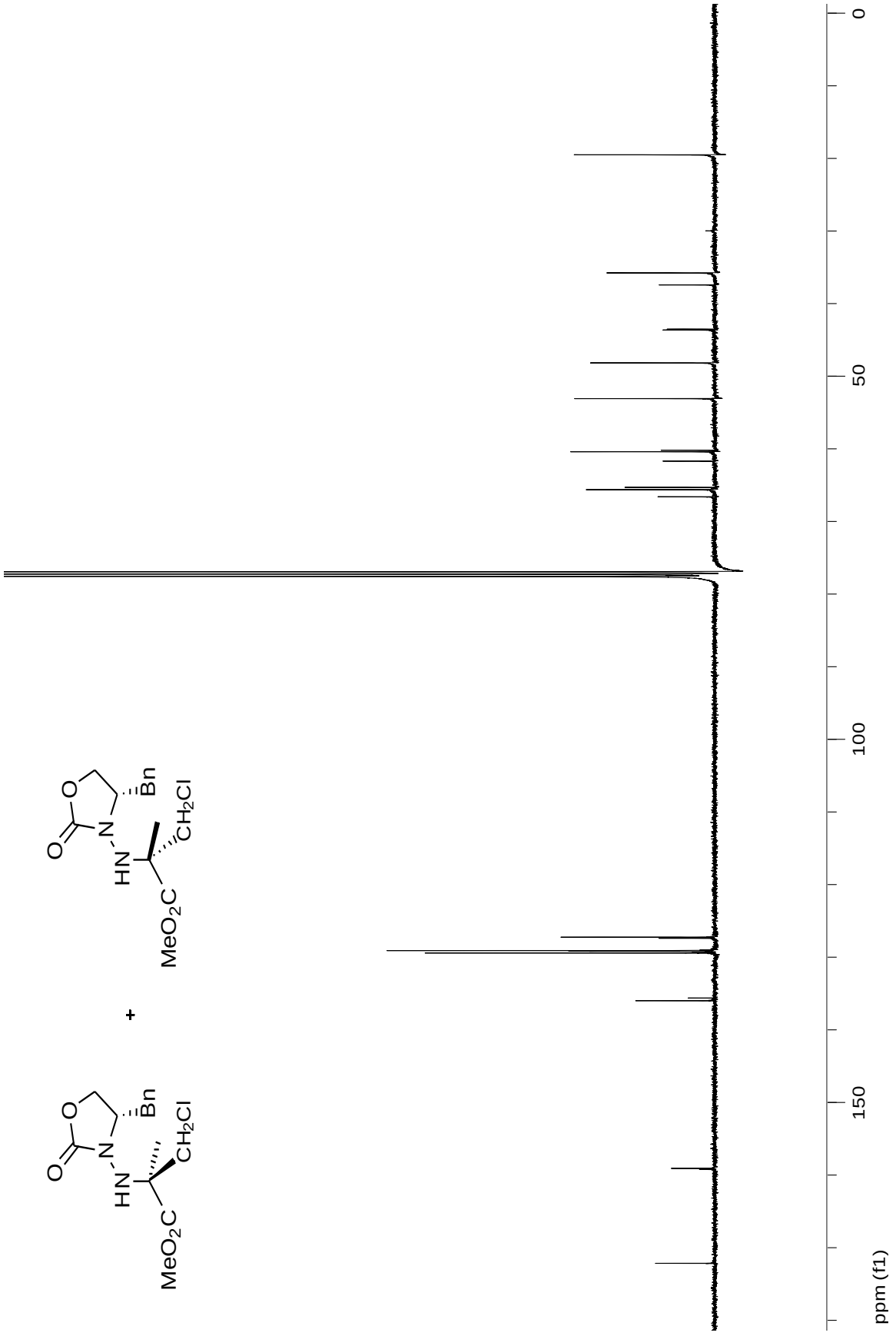

O
O
N
Bn
HN
MeO2C
(CH2)4OTBS
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)

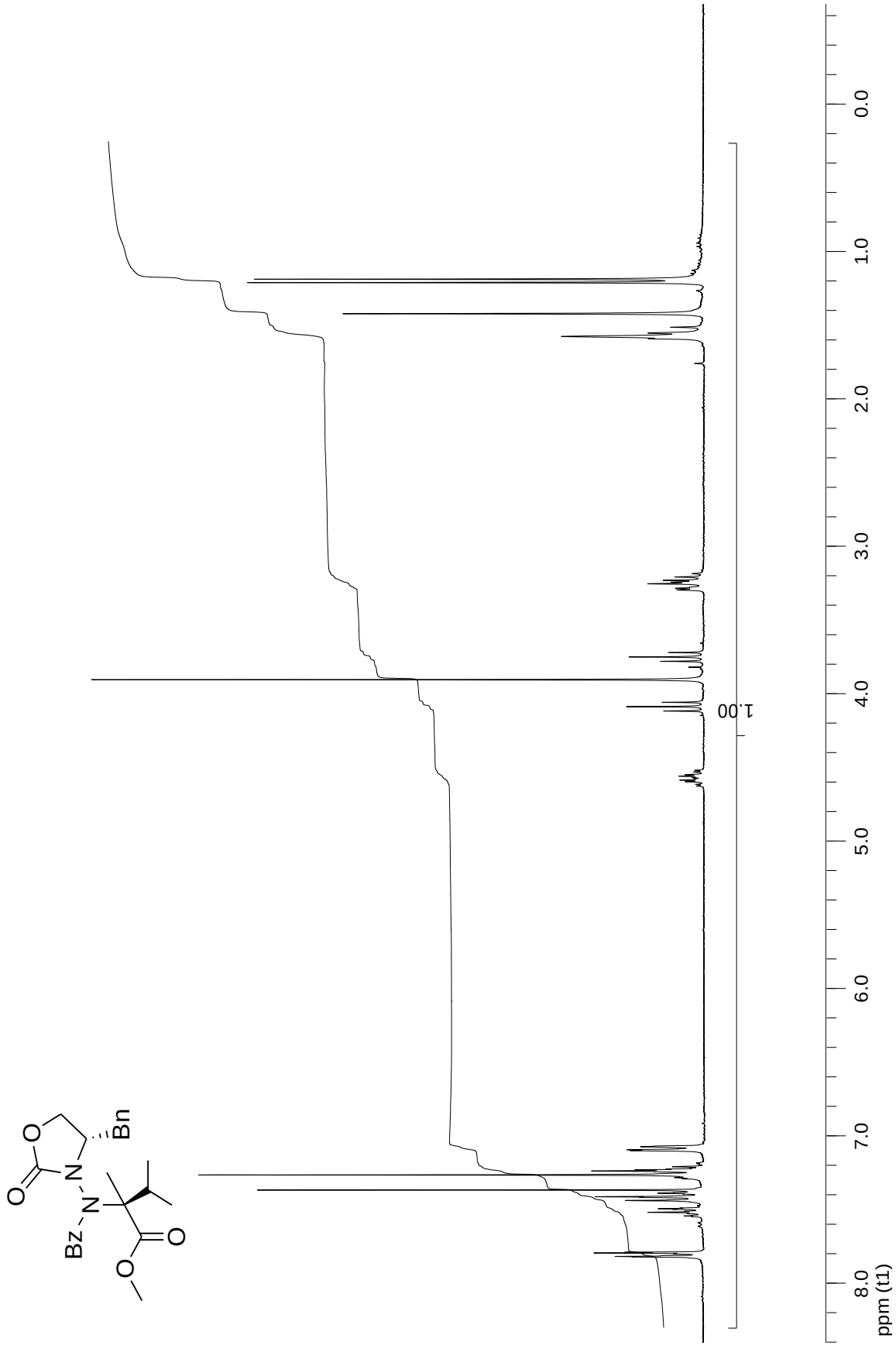

O
O
N
HN
Bn
MeO2C
(CH2)4OTBS
0
50
100
150
ppm (f1)

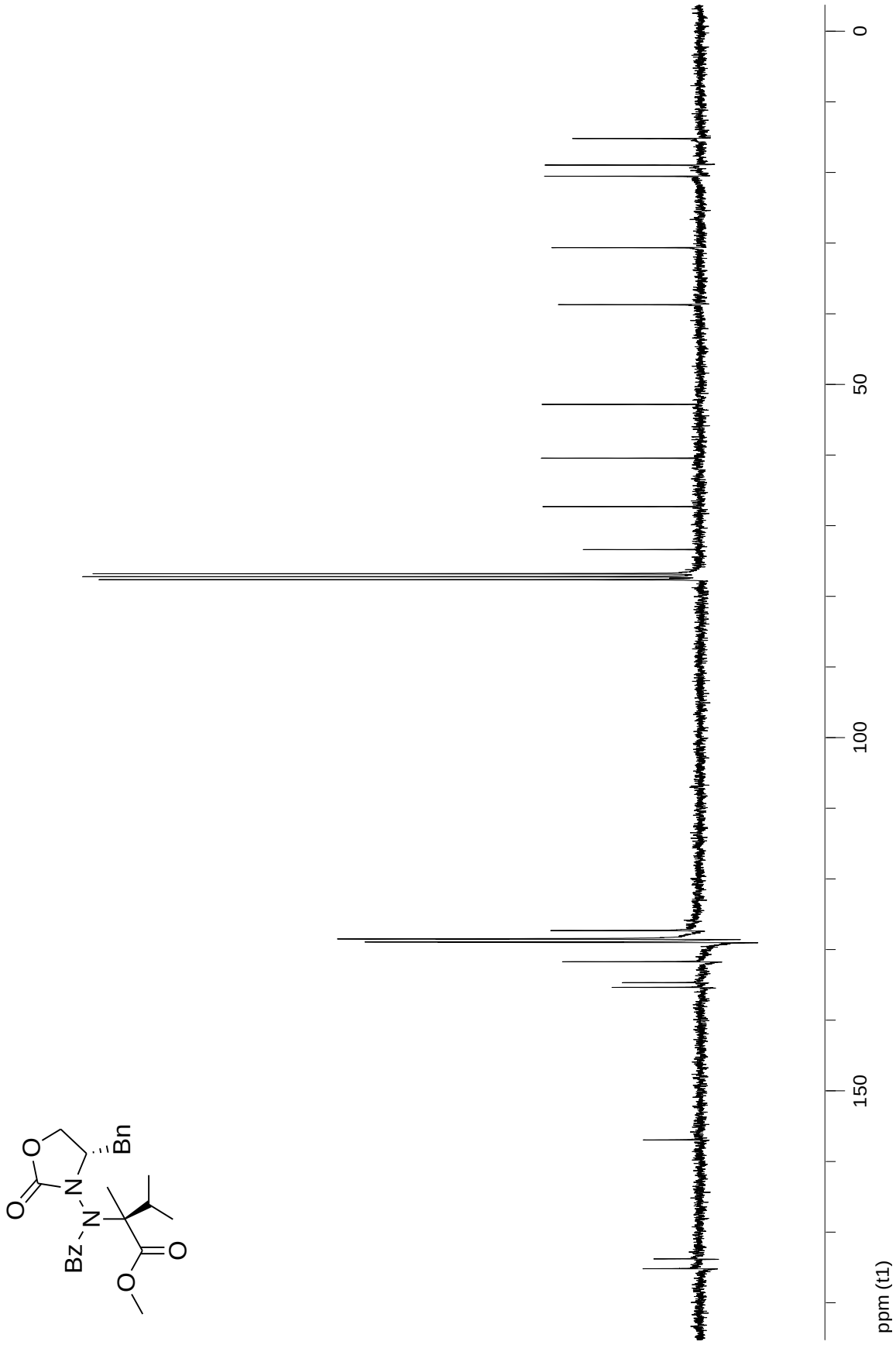

1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)
O
O
N
HN
Bn
MeO2C
(CH2)4OTBS
+
O
O
N
HN
Bn
MeO2C
(CH2)4OTBS

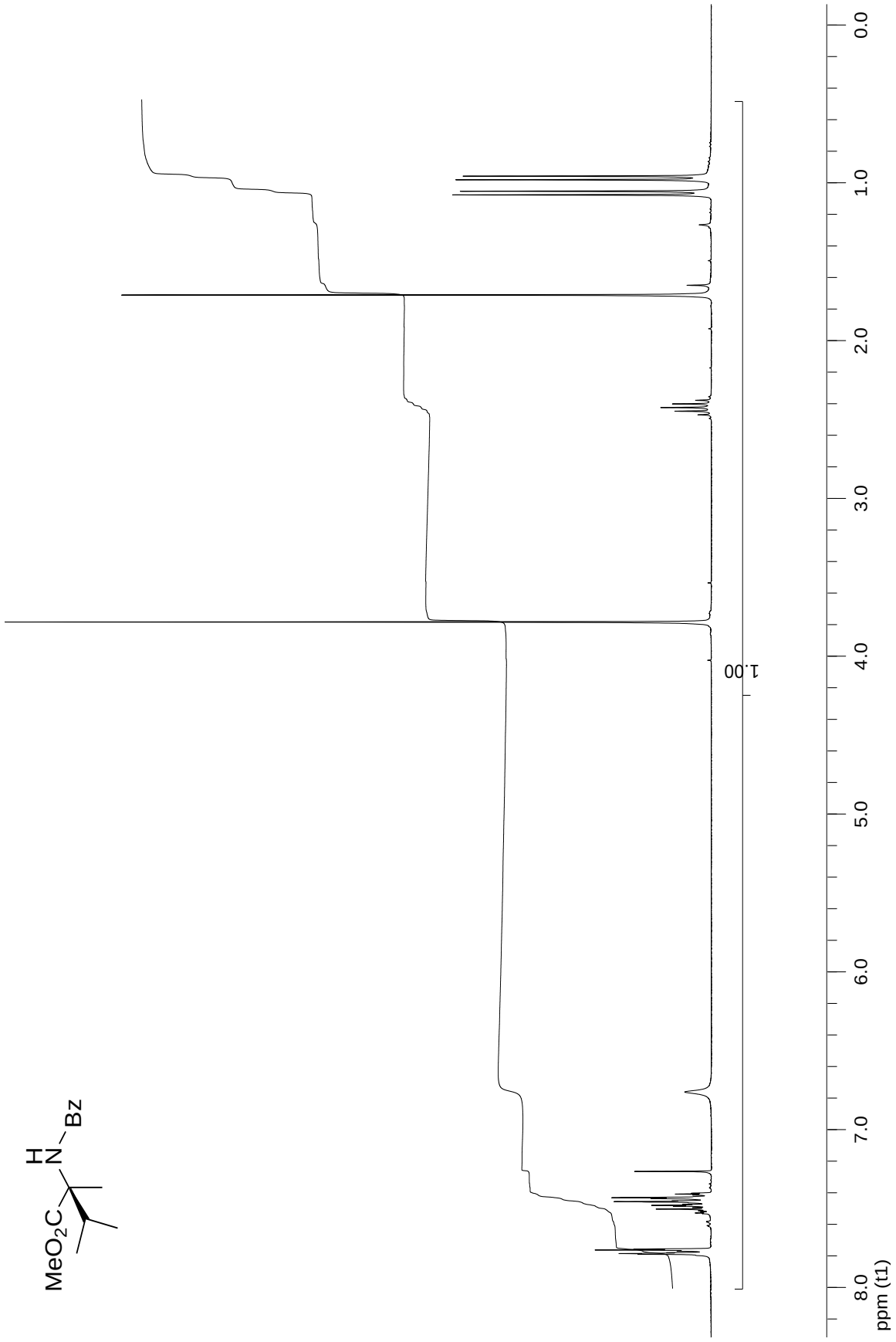

O
O
N
HN
Bn
MeO2C
(CH2)4OTBS
+
O
O
N
HN
Bn
MeO2C
(CH2)4OTBS
0
50
100
150
ppm (f1)

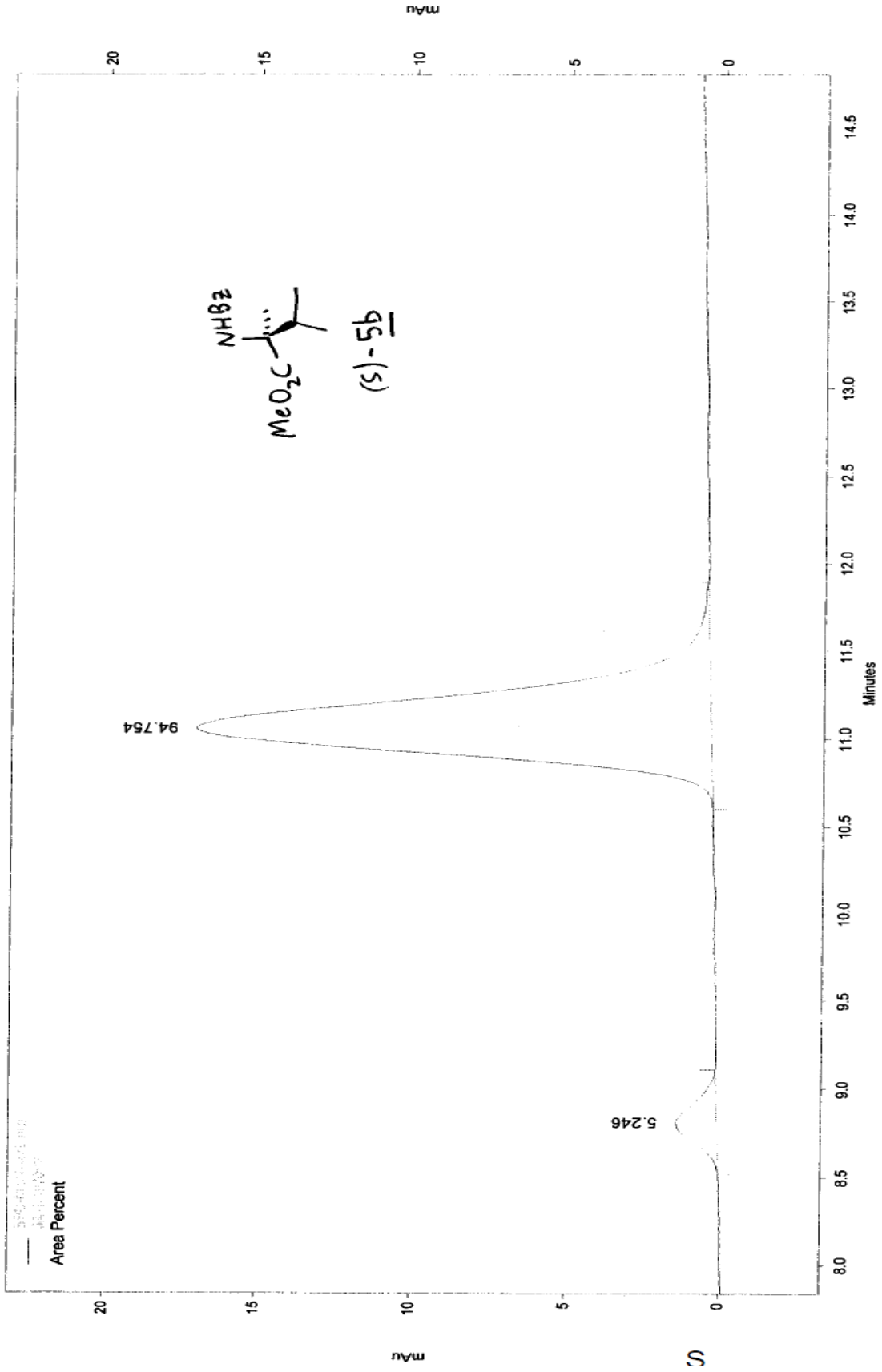

O
O
N
HN
Bn
CH2Cl
MeO2C
+
O
O
N
HN
Bn
CH2Cl
MeO2C
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

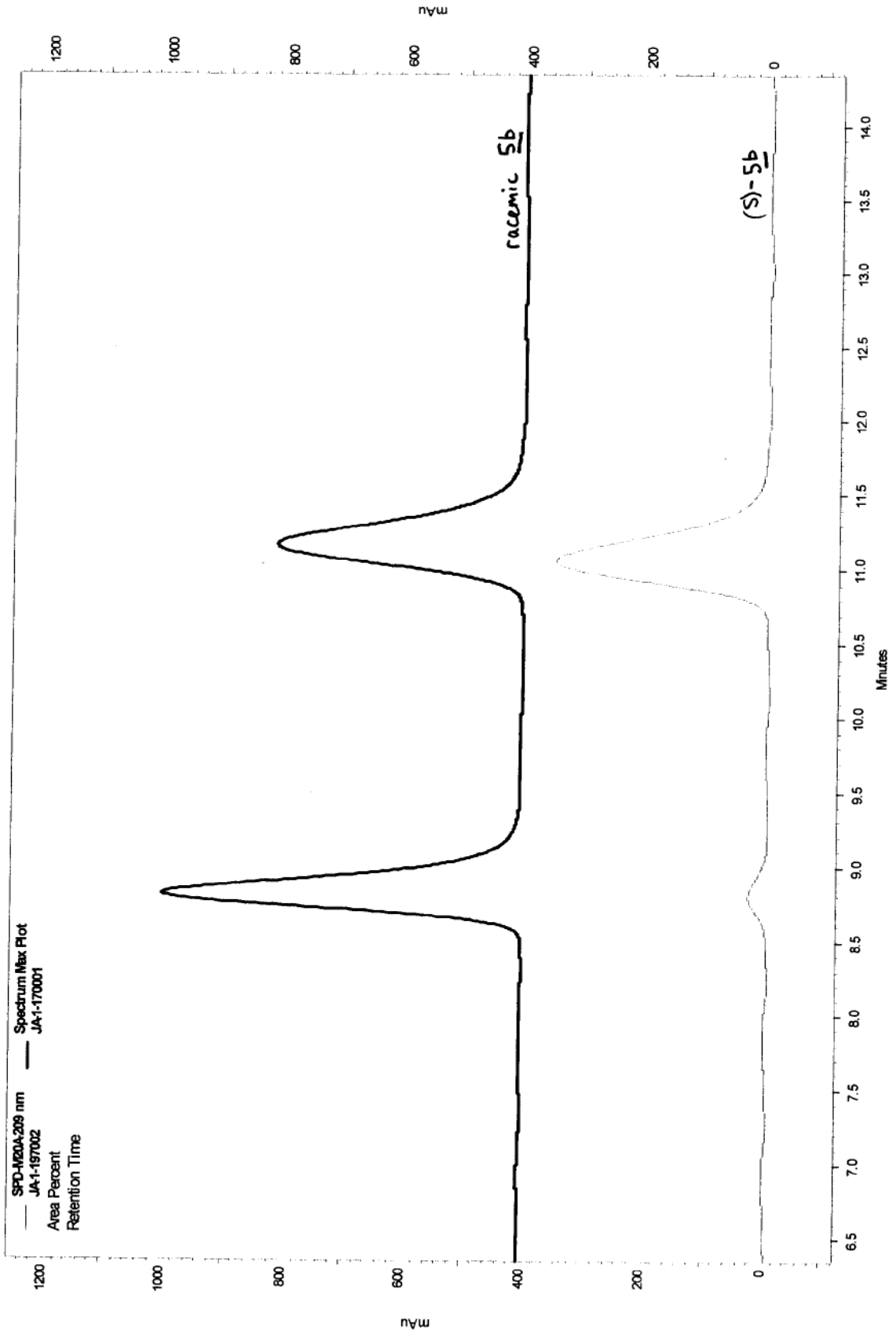

O
O
N
HN
Bn
CH2Cl
MeO2C
+
O
O
N
HN
Bn
CH2Cl
MeO2C
0
50
100
150
ppm (f1)

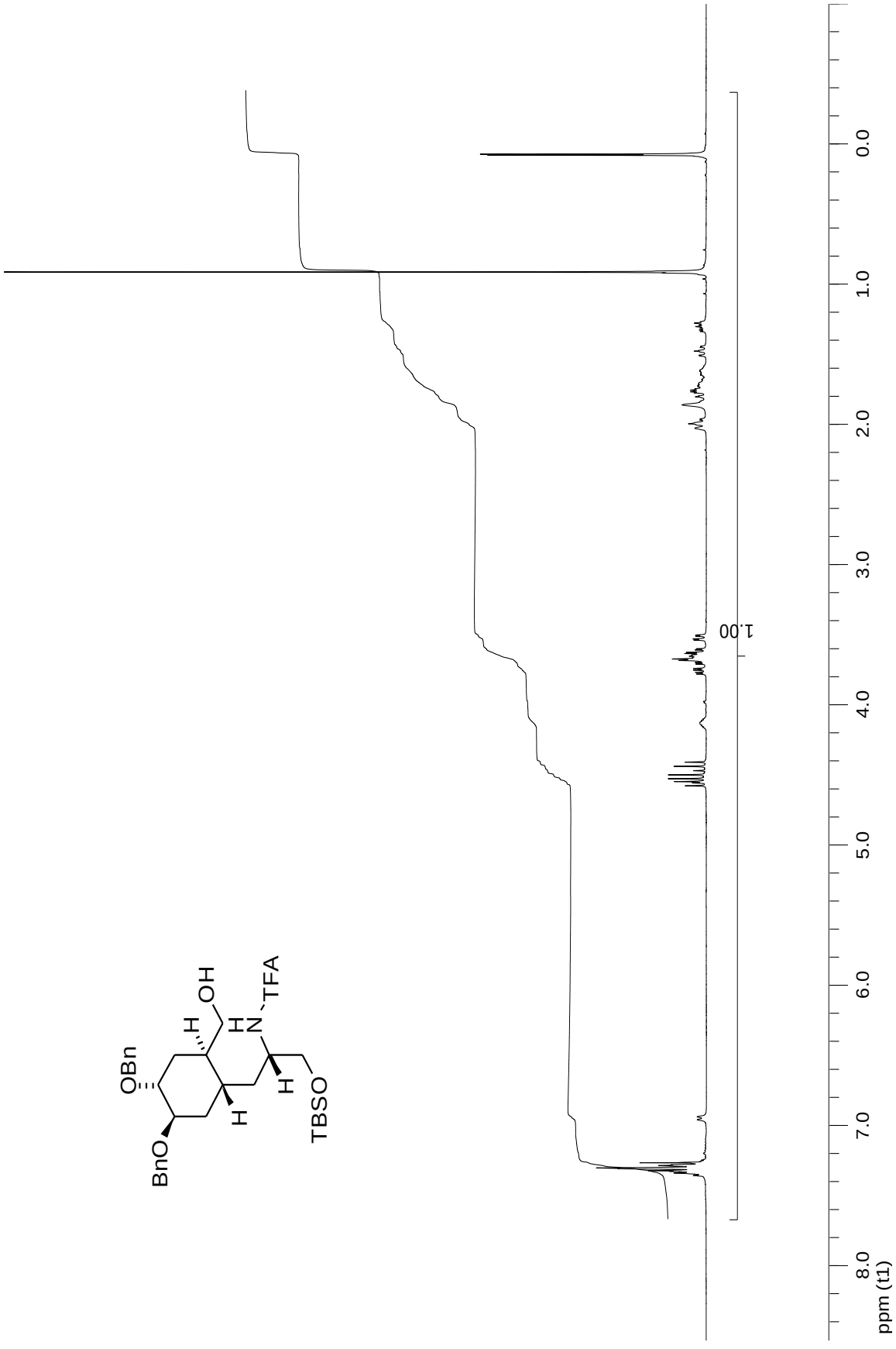

O
O
N
Bn
N
Bz
O
O
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

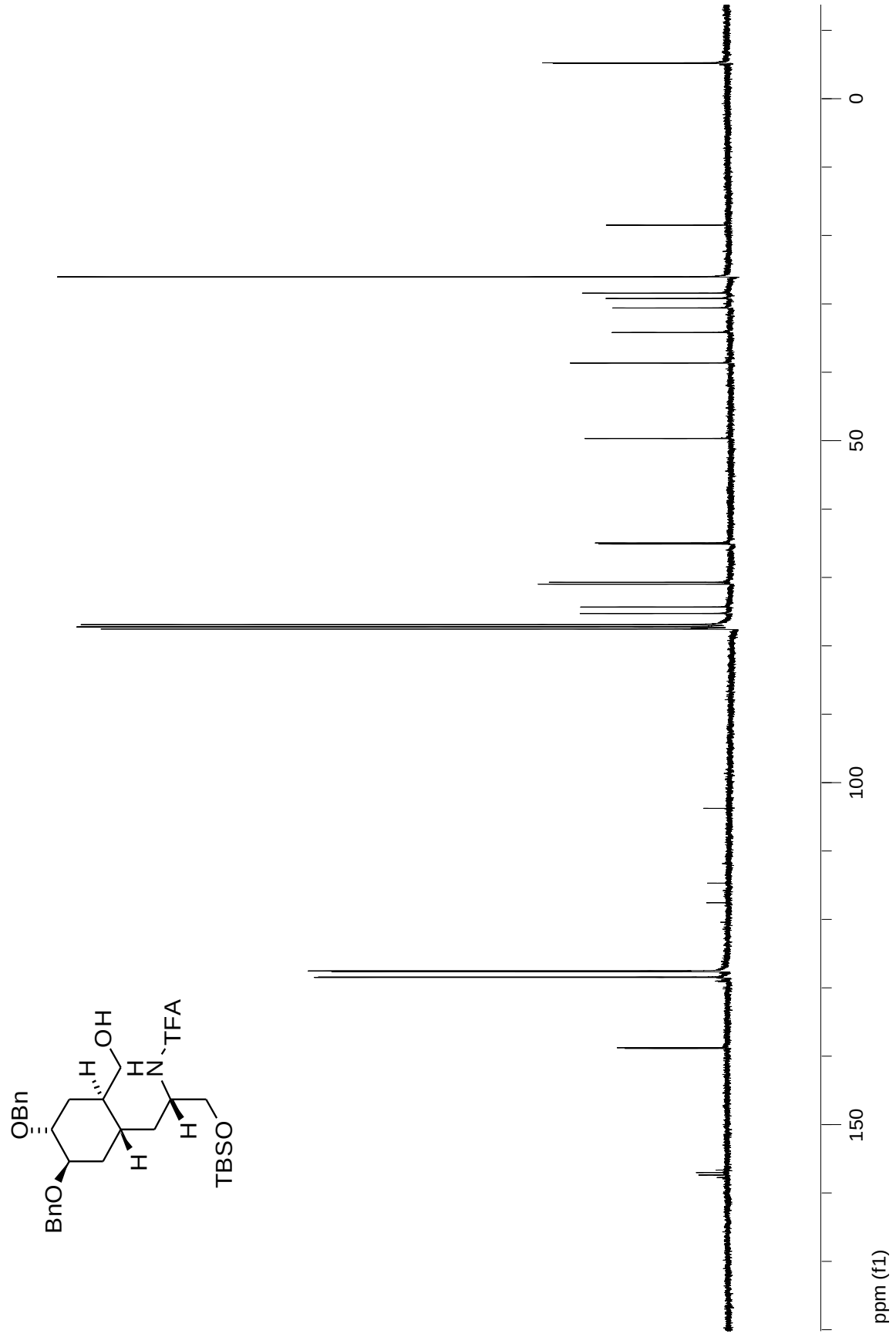

O
O
N
N
Bz
Bn
O
O
O
0
50
100
150
ppm (t1)

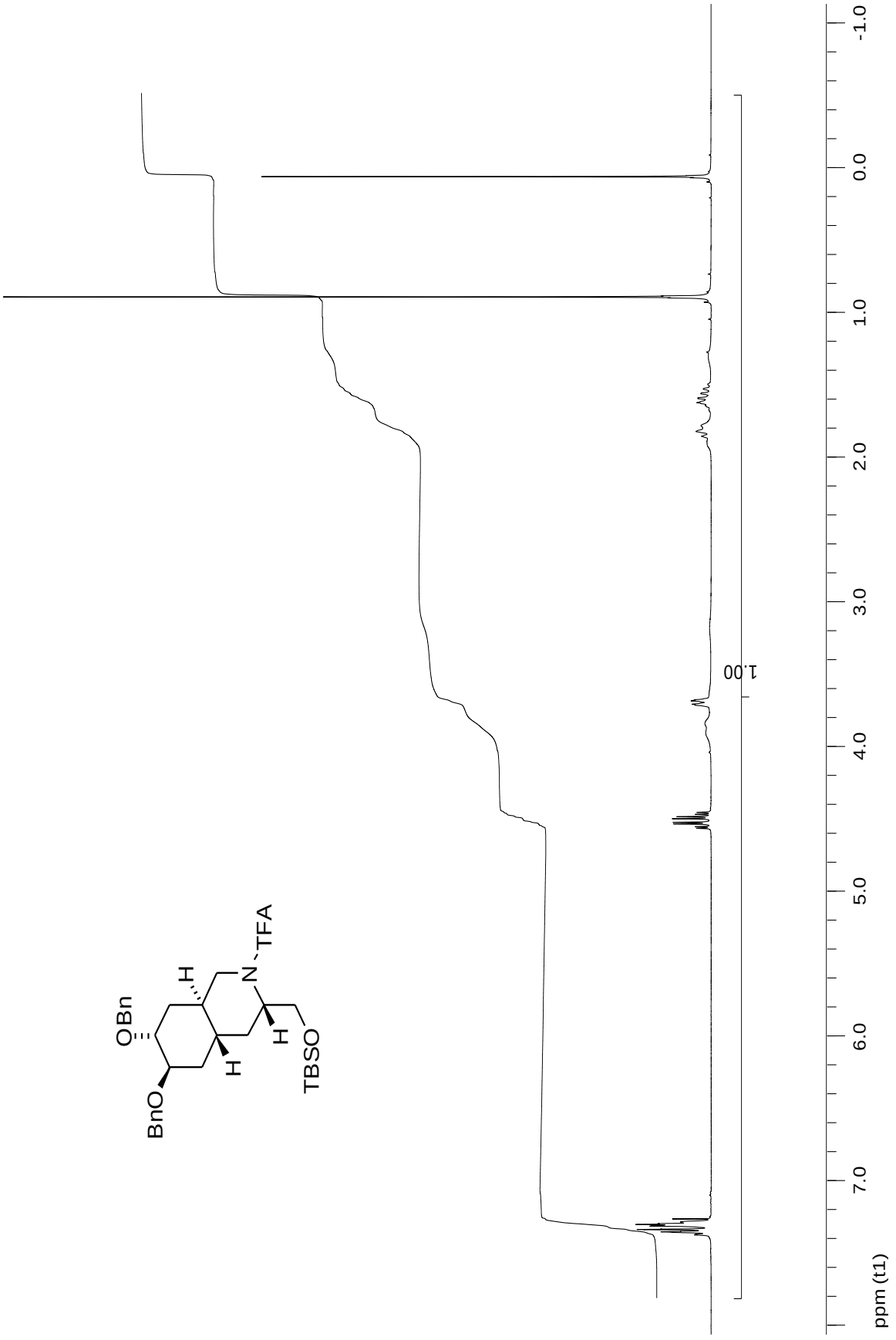

MeO2C
H
N
Bz
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

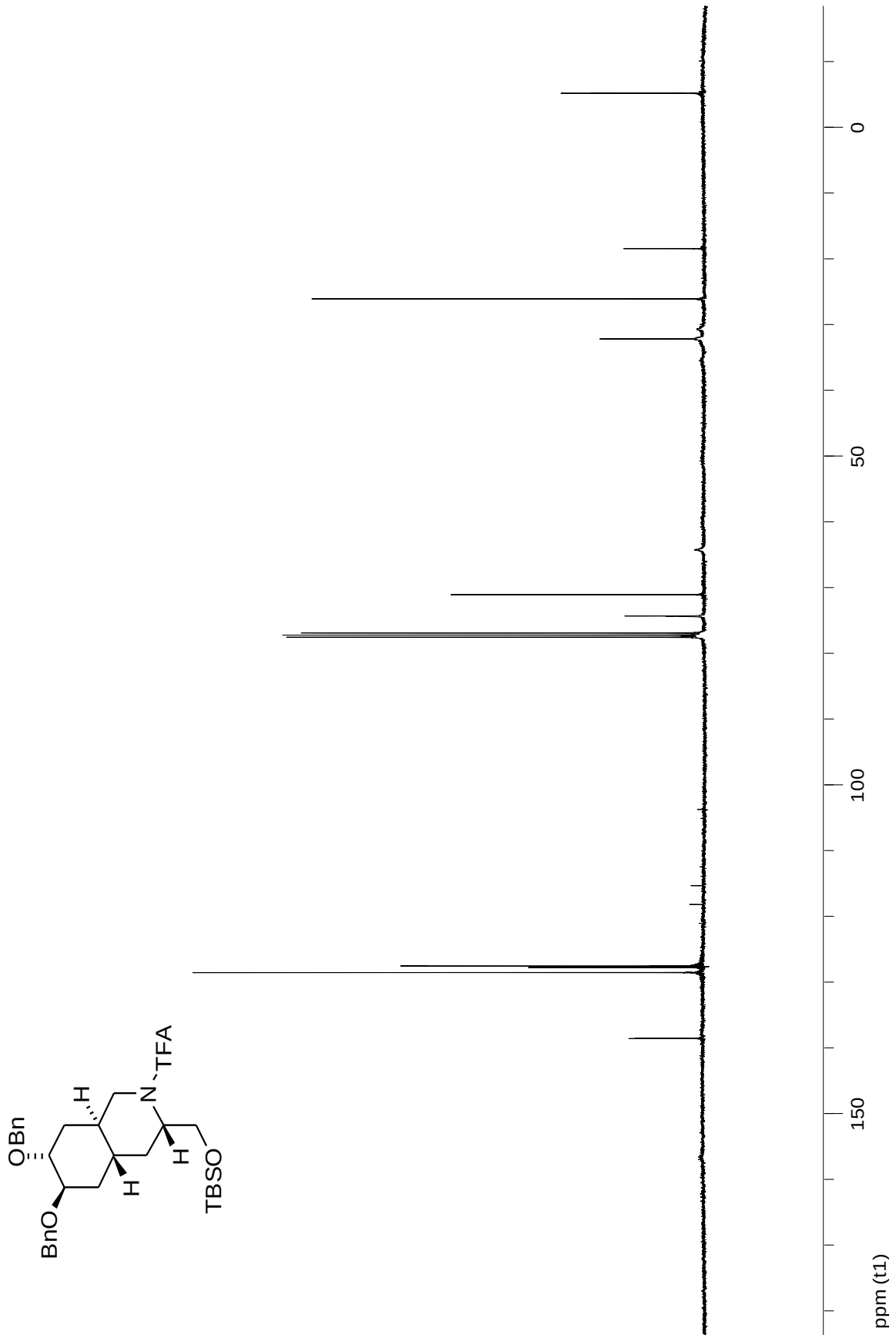

S
mAu
Area Percent
5.246
94.754
Minutes
NHBz
MeO2C
(S)-5b

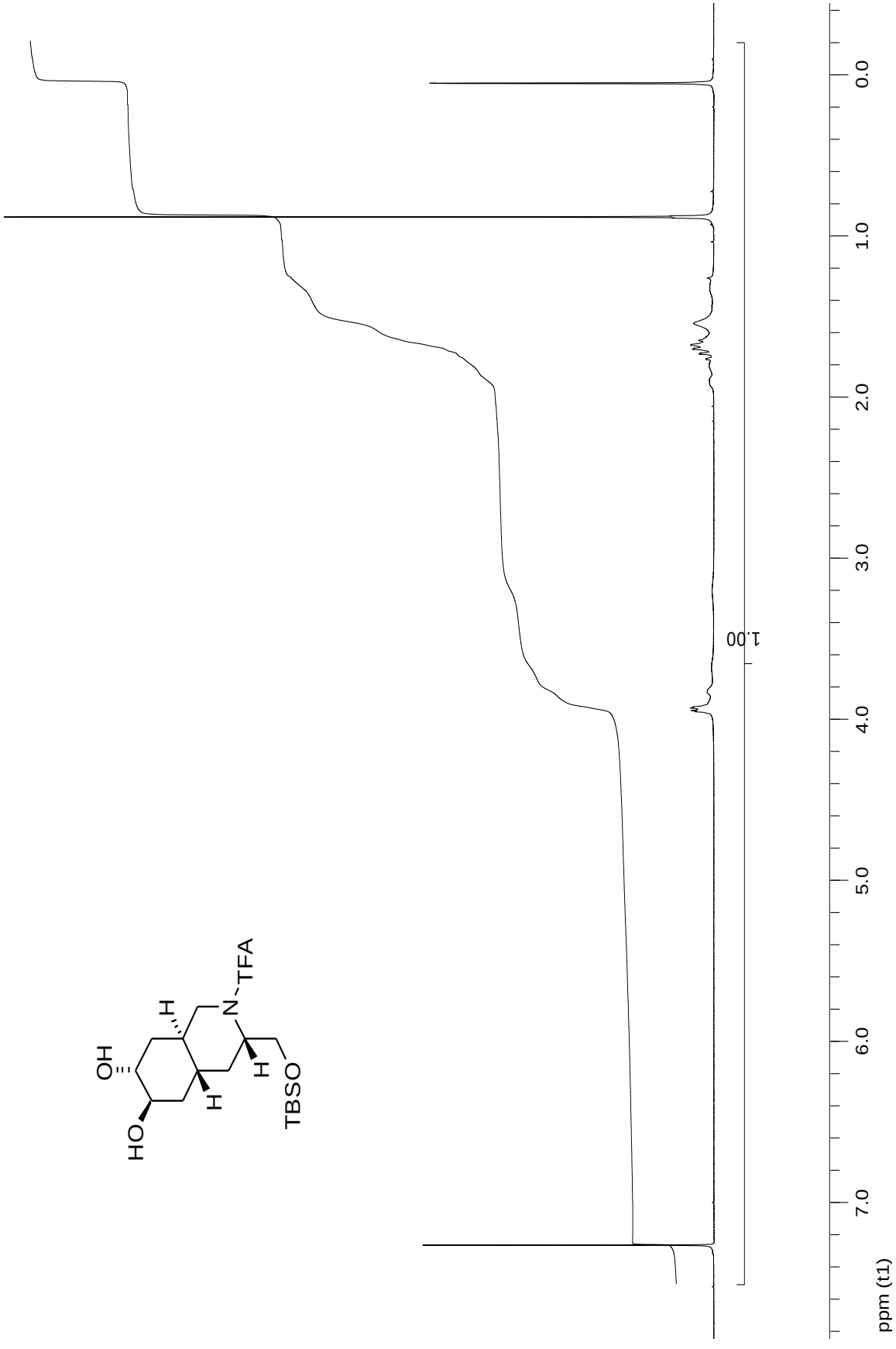

SPD-M20A:209 nm
JA-1-197002
Area Percent
Retention Time
Spectrum Max Plot
JA-1-170001
racemic 5b
(S)-5b
mAu
Minutes

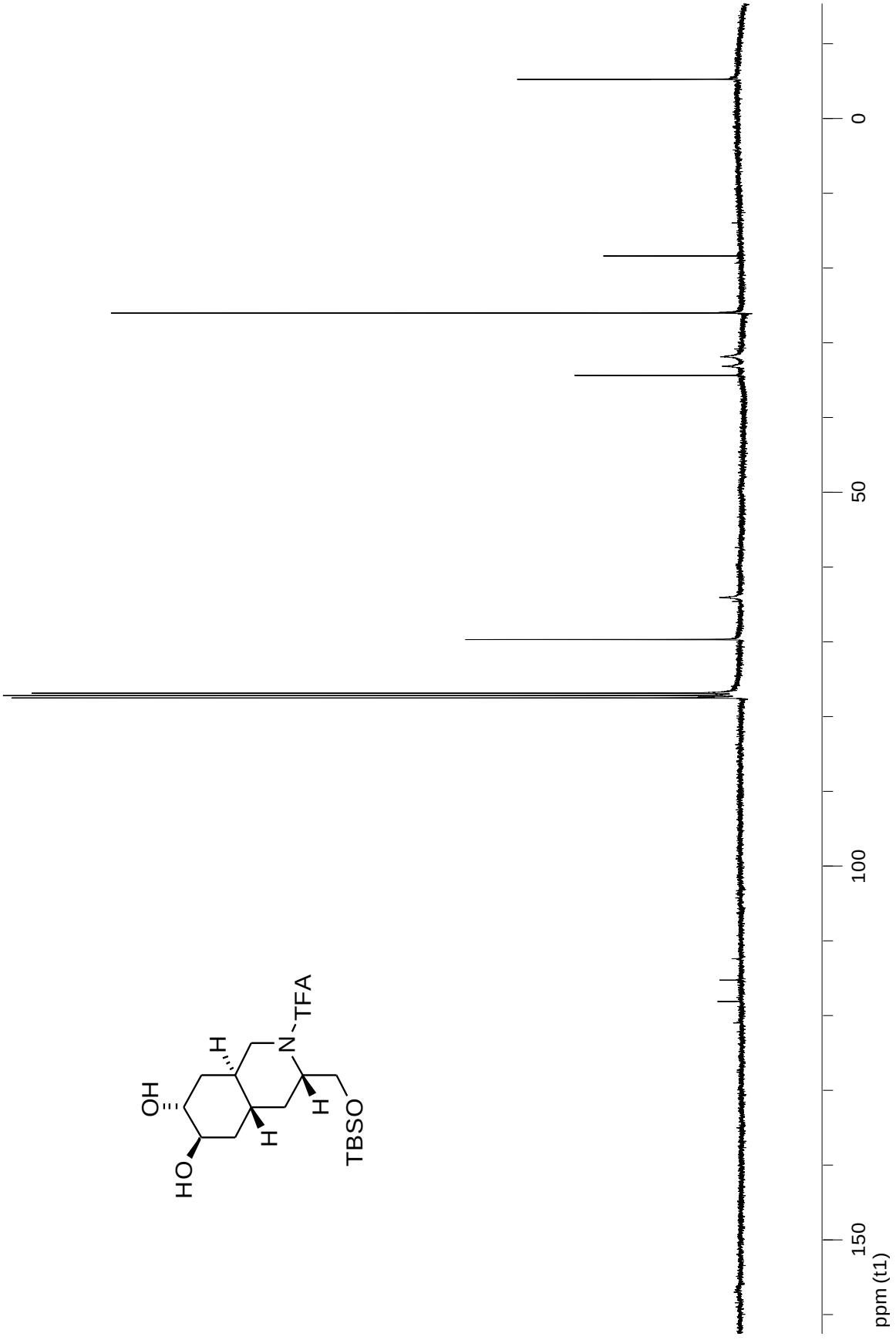

OBn
BnO
H
OH
H
N
TFA
H
H
TBSO
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

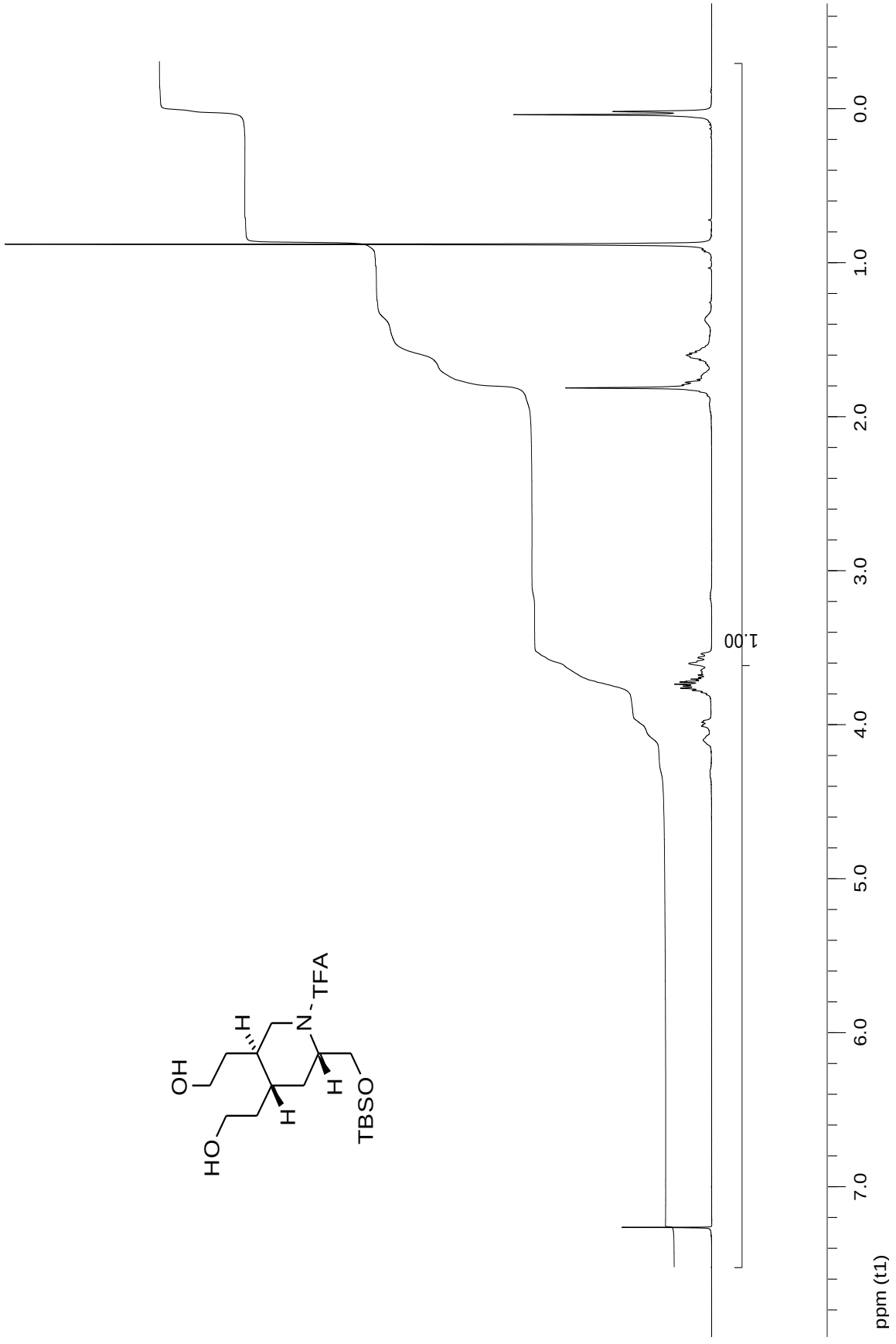

OBn
BnO
H
OH
H
N
TFA
H
H
TBSO
0
50
100
150
ppm (f1)

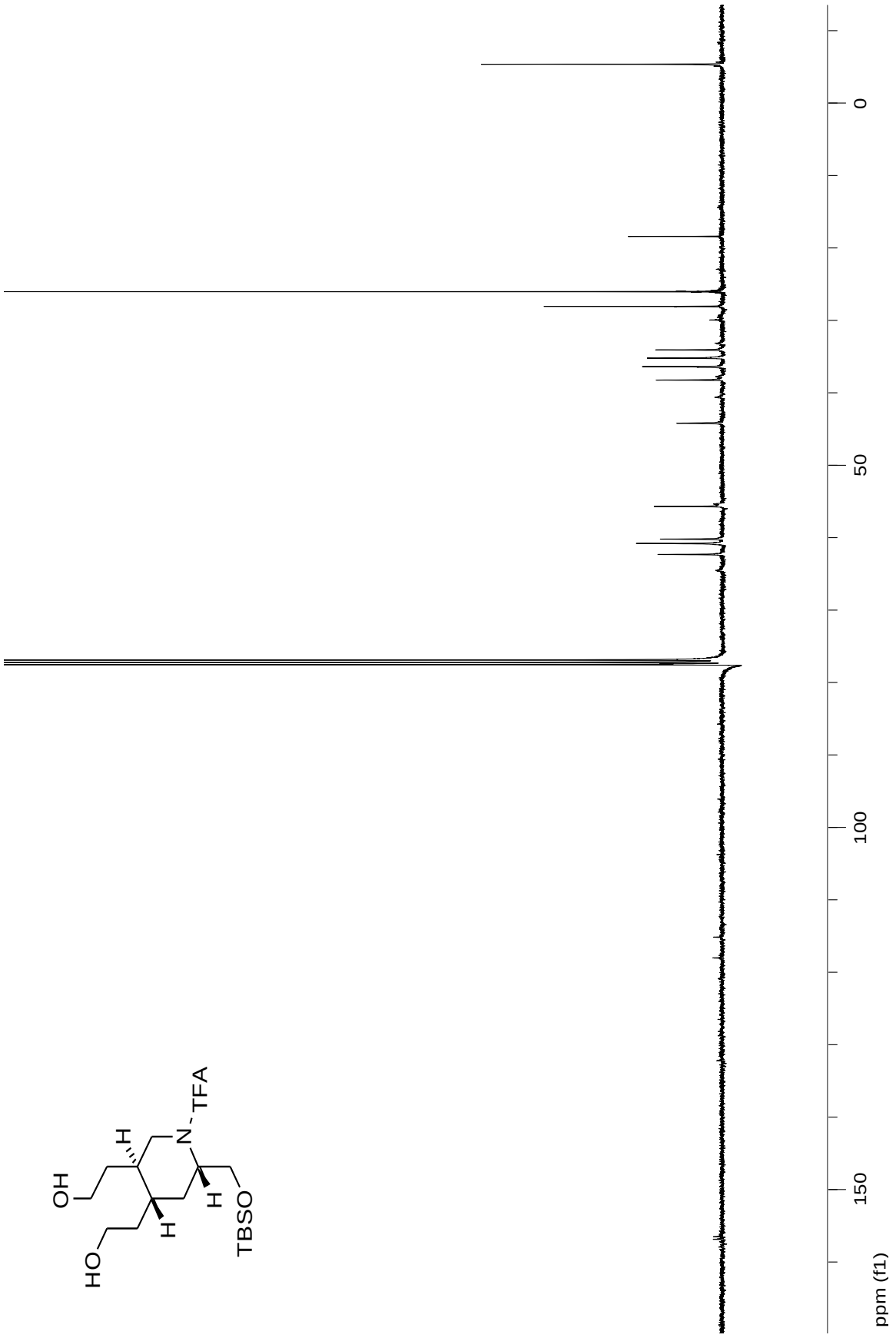

OBn
BnO
H
H
N
TFA
H
TBSO
1.00
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

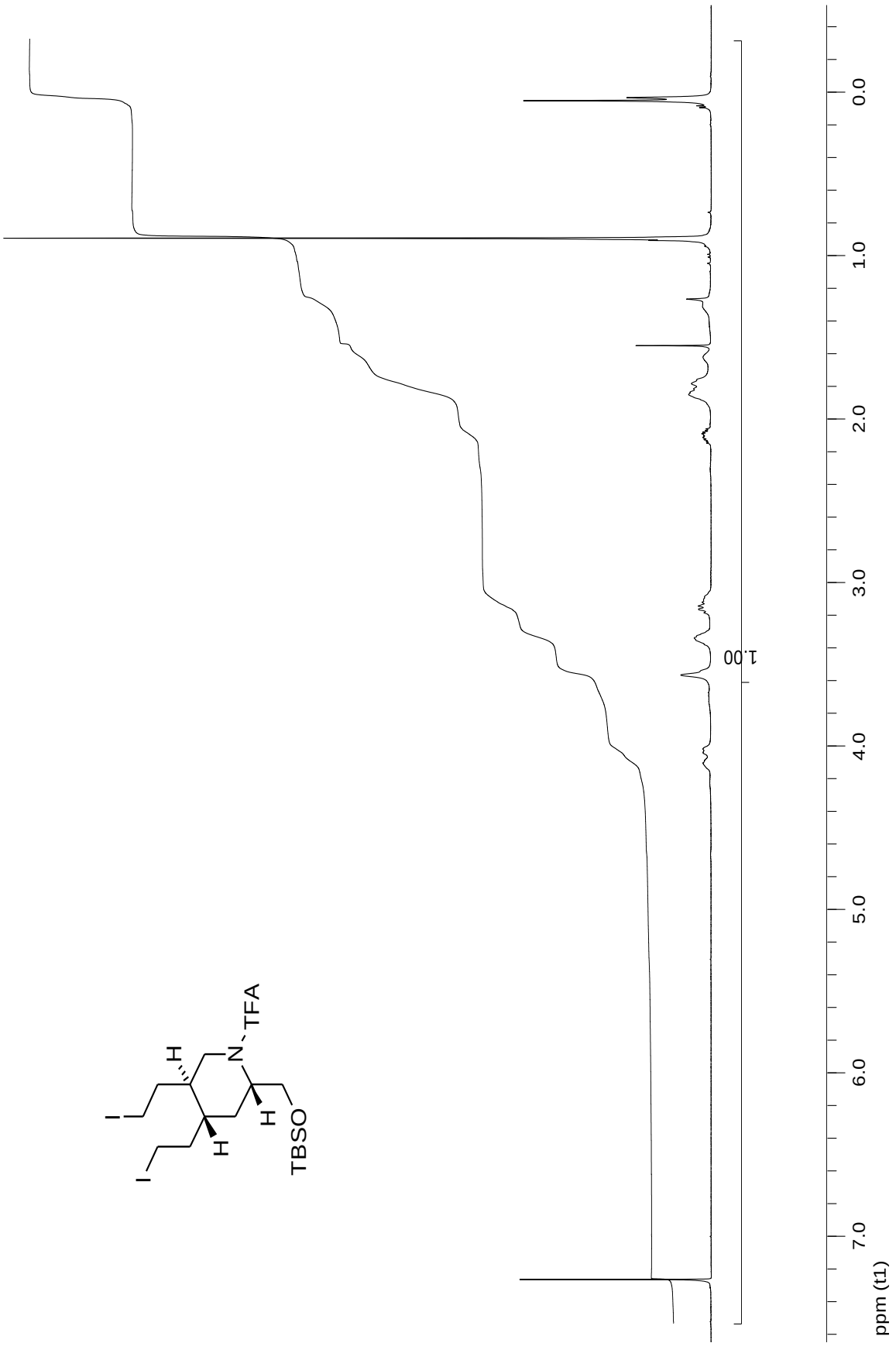

OBn
BnO
H
H
N
TFA
H
TBSO
0
50
100
150
ppm (t1)

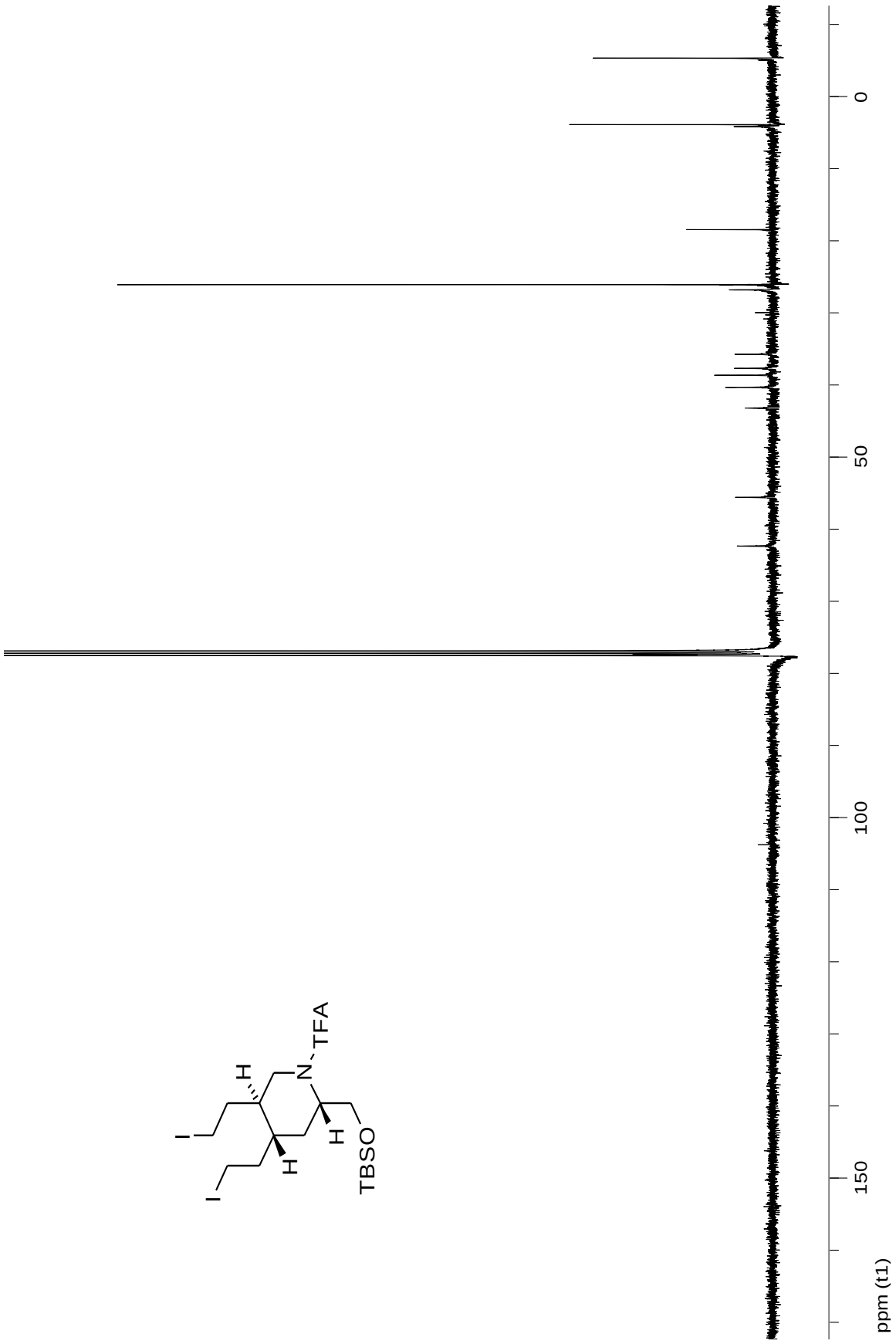

OH
HO
H
H
H
N
TFA
TBSO
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

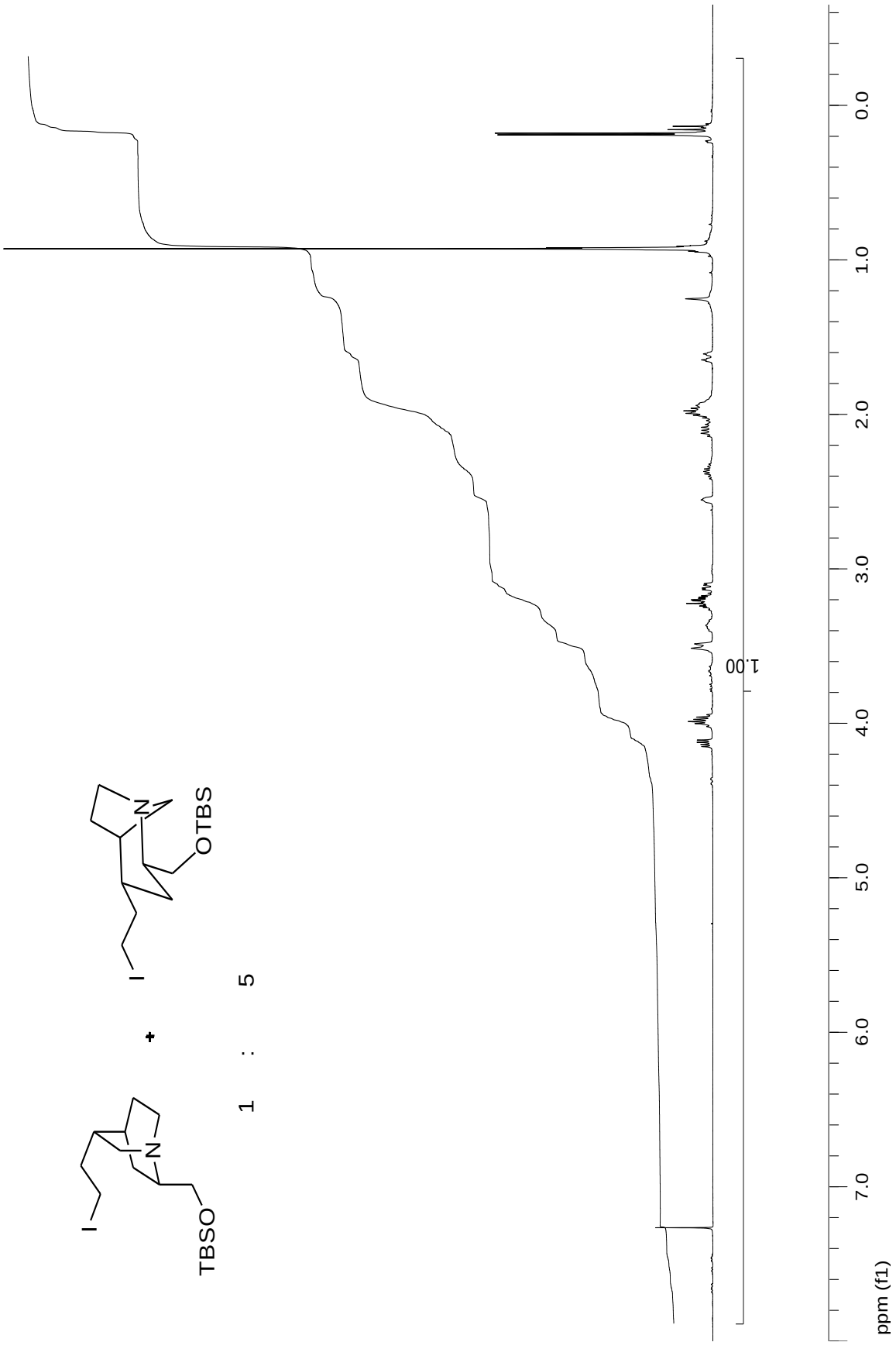

OH
HO
H
H
N
TFA
H
TBSO
0
50
100
150
ppm (t1)

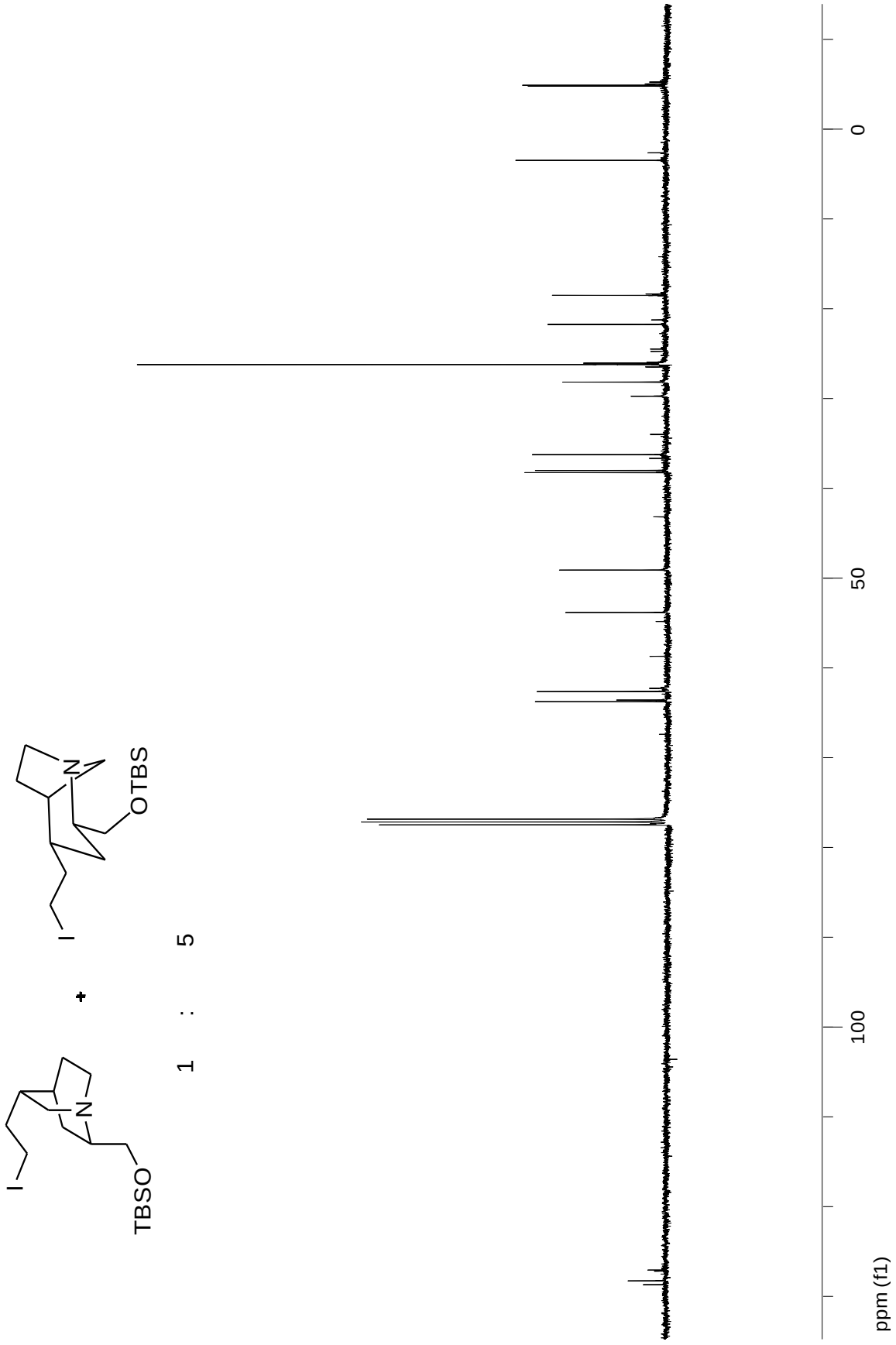

OH
HO
H
H
N
TFA
TBSO
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

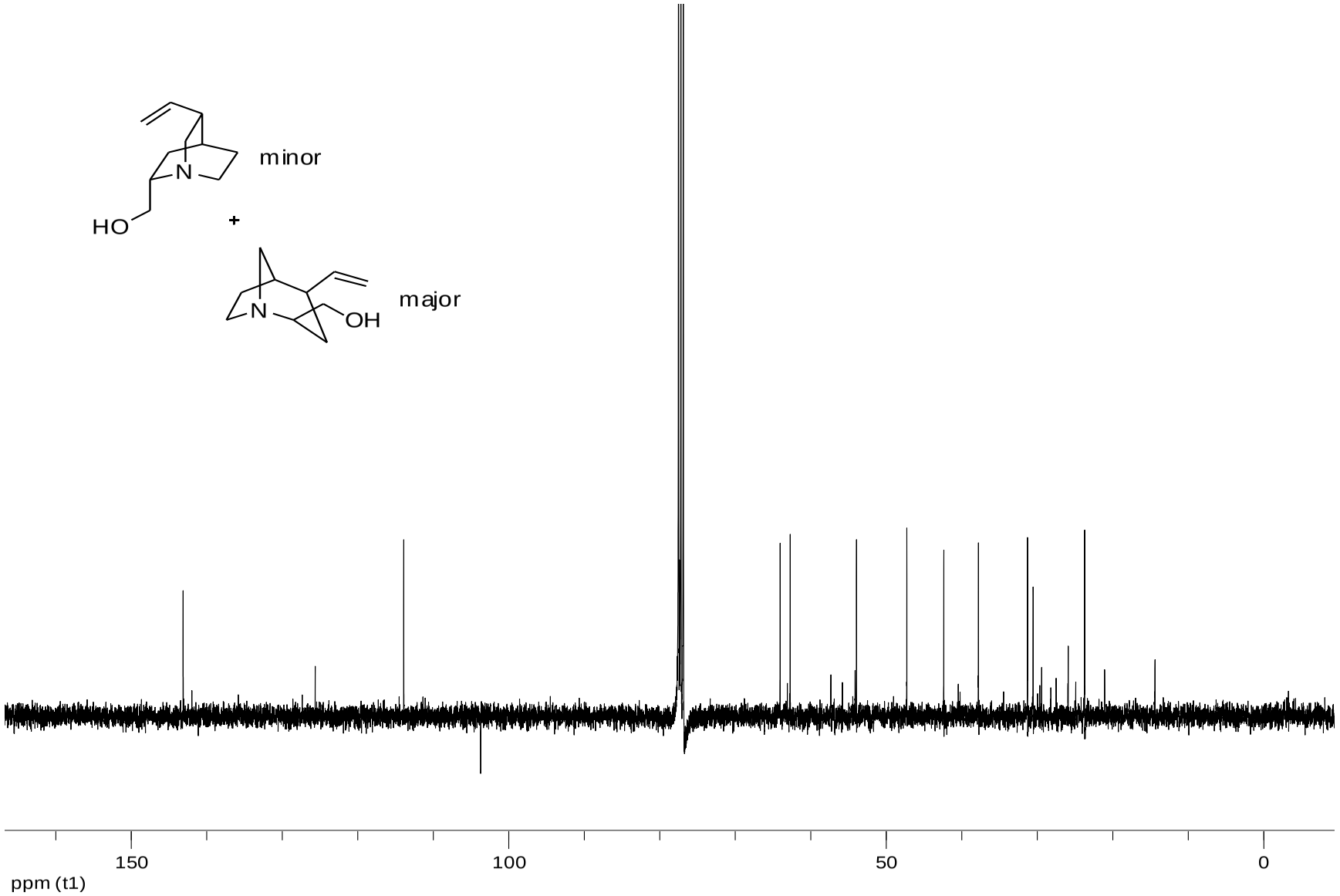

OH
HO
H
H
N
TFA
H
TBSO
0
50
100
150
ppm (f1)

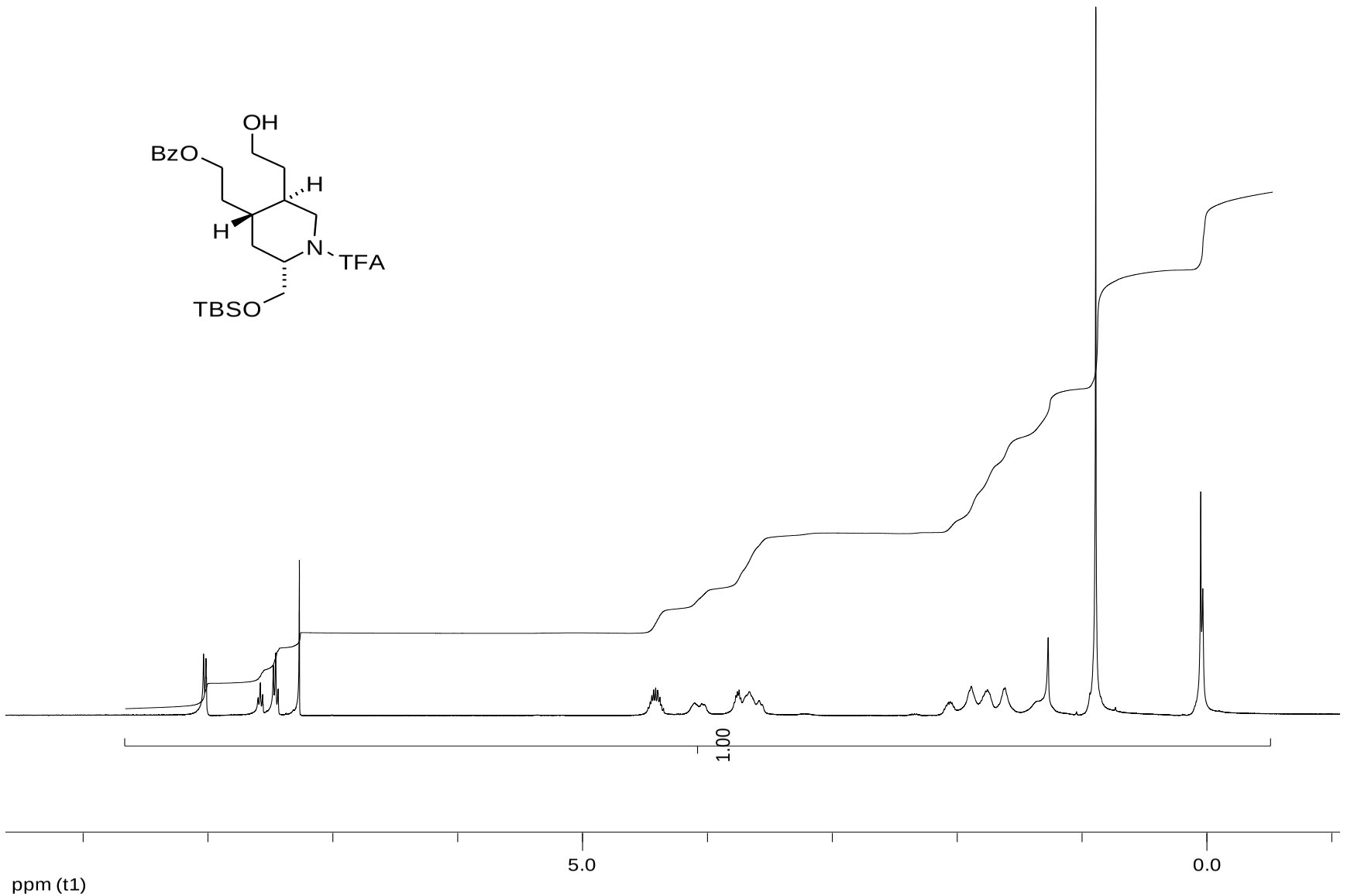

TFA
N
H
H
H
I
I
TBSO
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

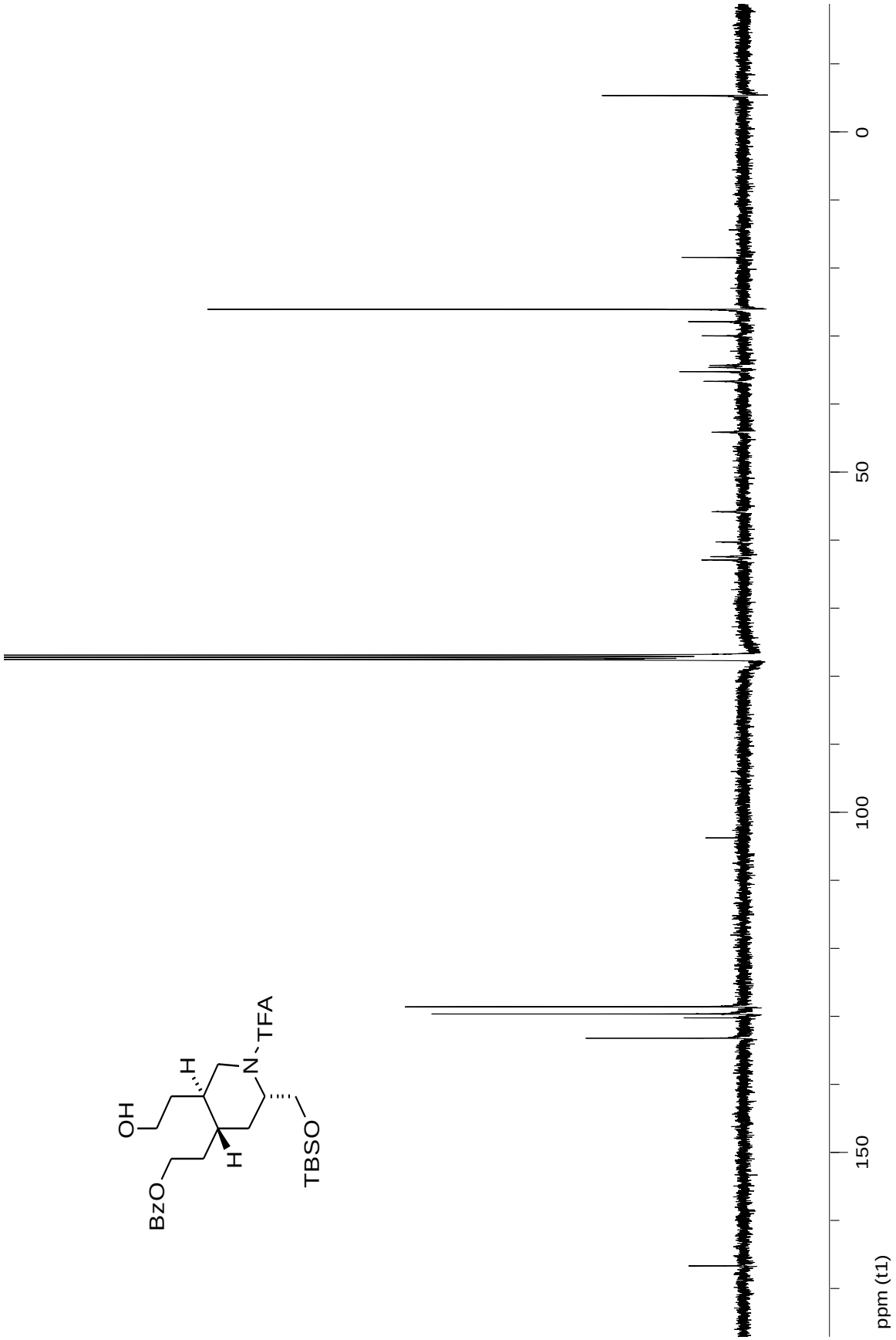

TFA
N
H
H
H
I
I
TBSO
0
50
100
150
ppm (t1)

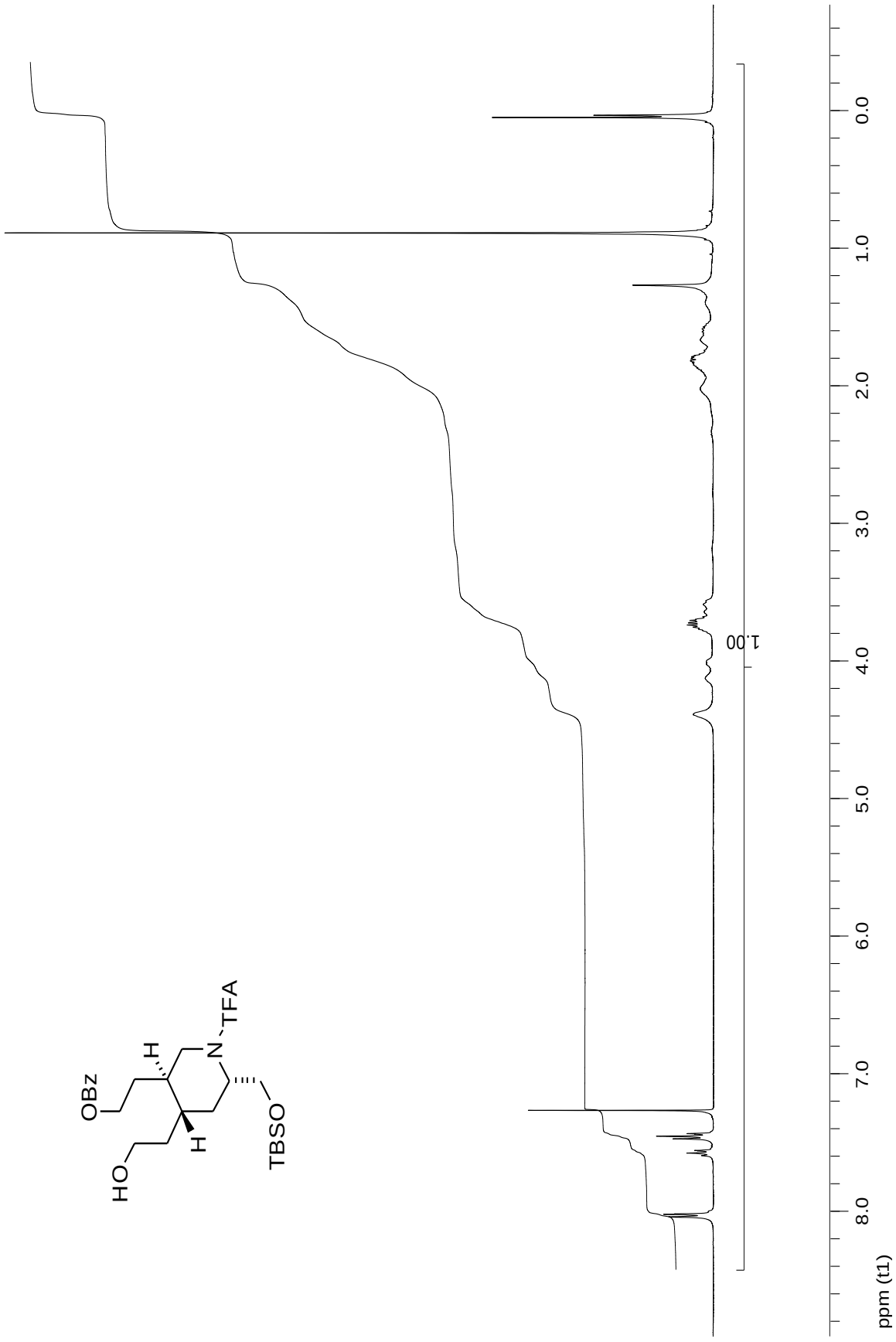

TBSO
I
N
+
I
N
OTBS
1 : 5
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)

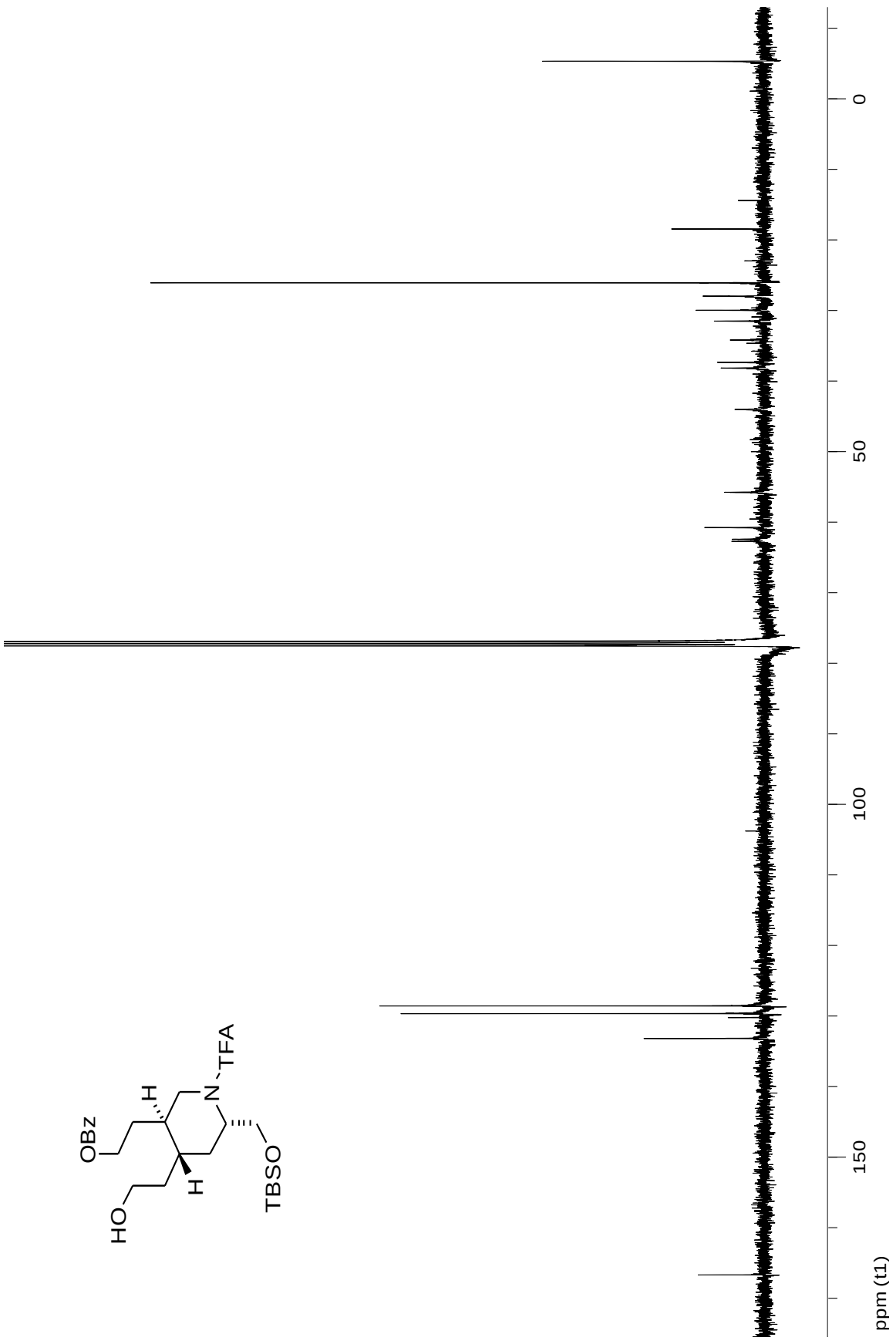

TBSO
I
N
+
1 : 5
N
OTBS
I
ppm (f1)
0
50
100

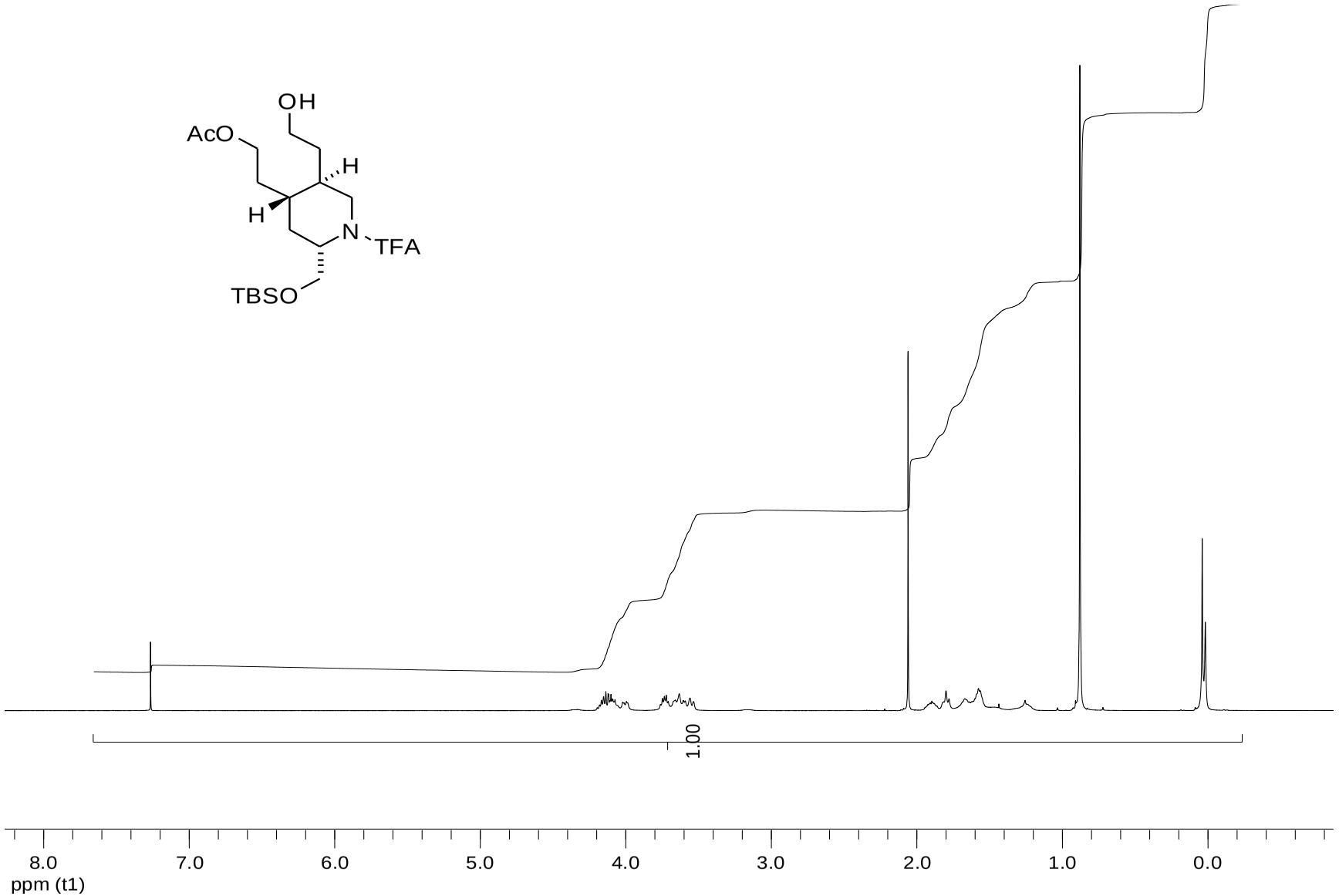

minor
HO
N
+
major
N
OH
150
100
50
0
ppm (t1)

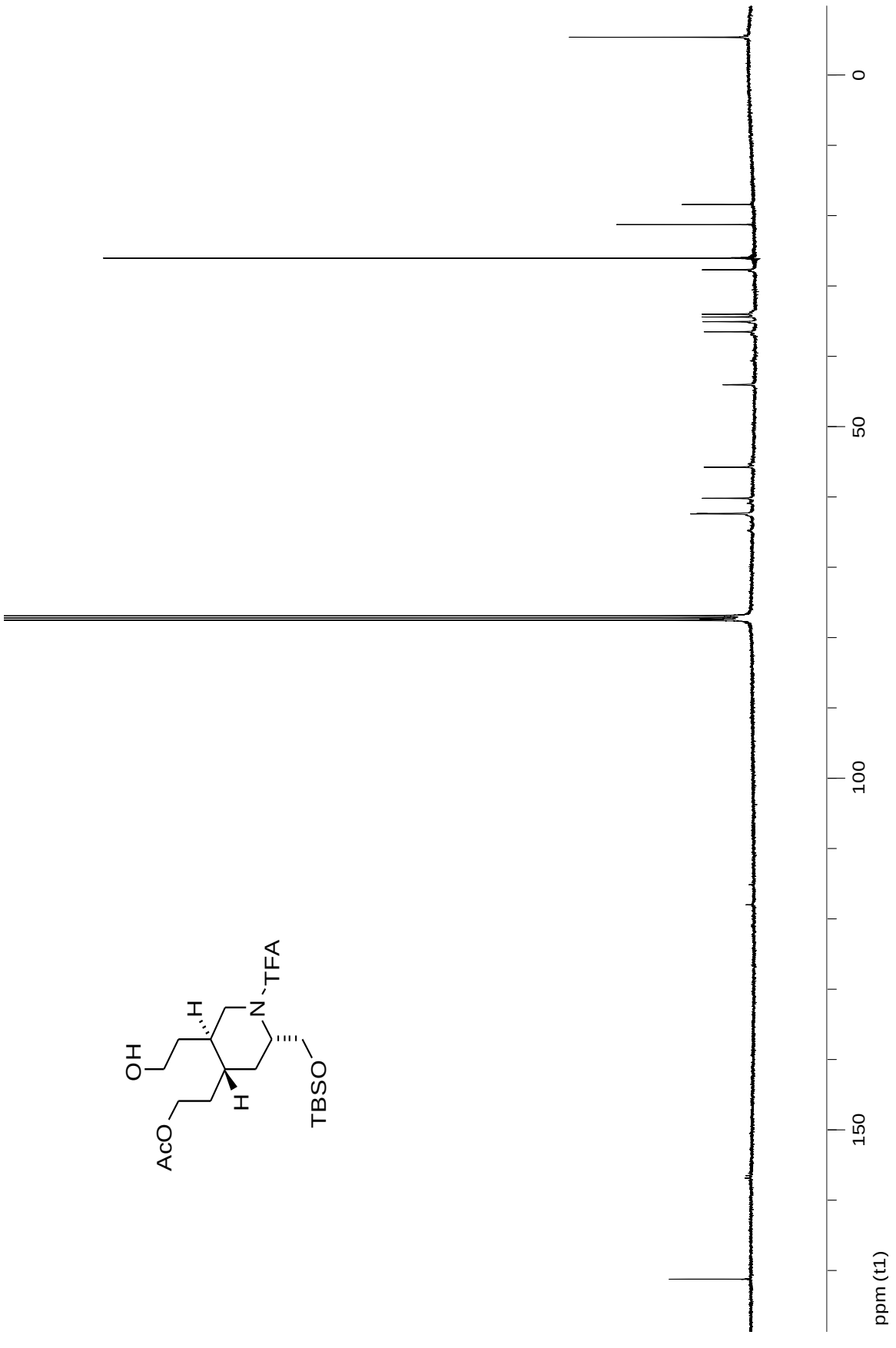

OH
BzO
H
H
N
TFA
TBSO
1.00
5.0
0.0
ppm (t1)

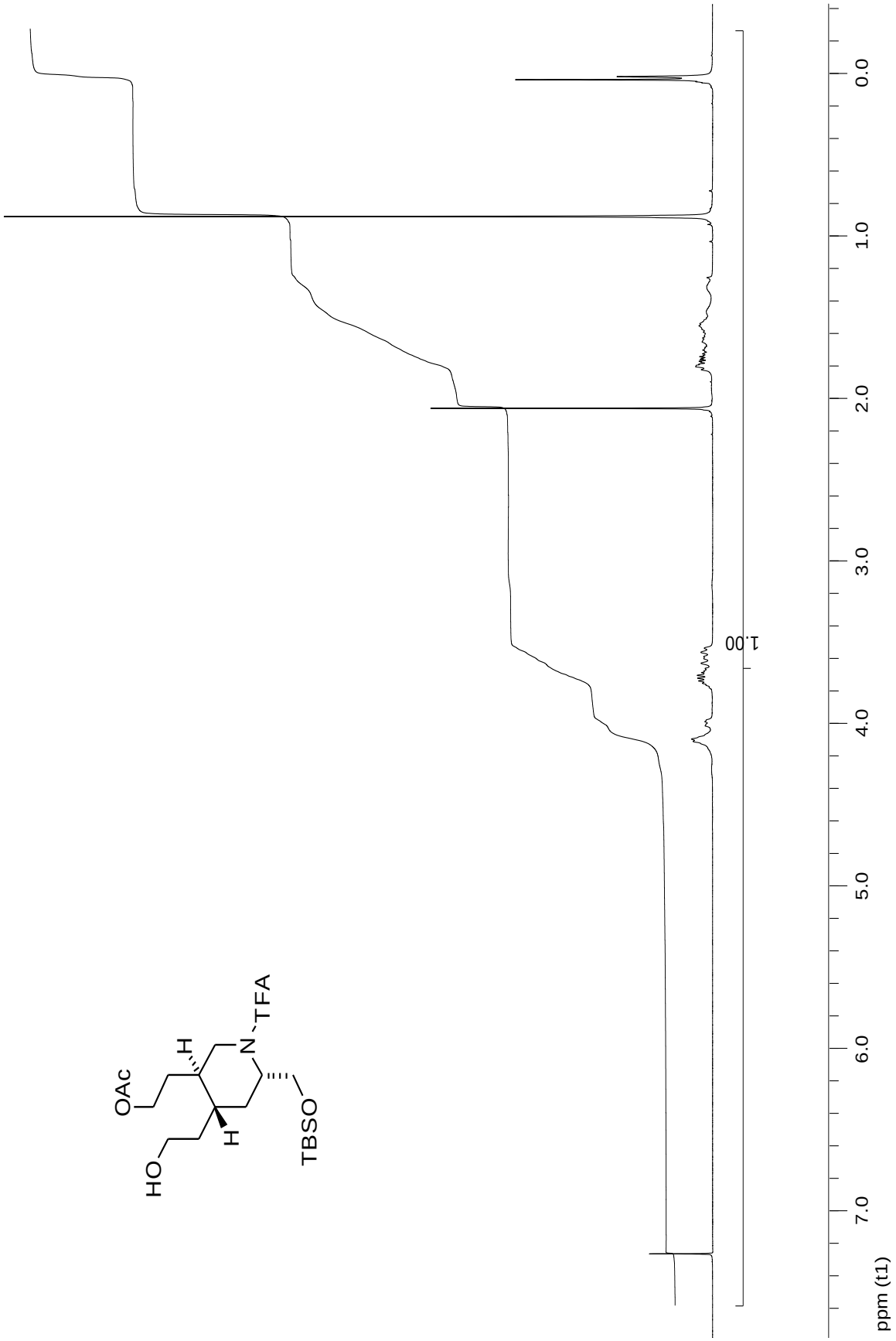

OH
H
N
TFA
H
TBSO
BzO
150
100
50
0
ppm (t1)

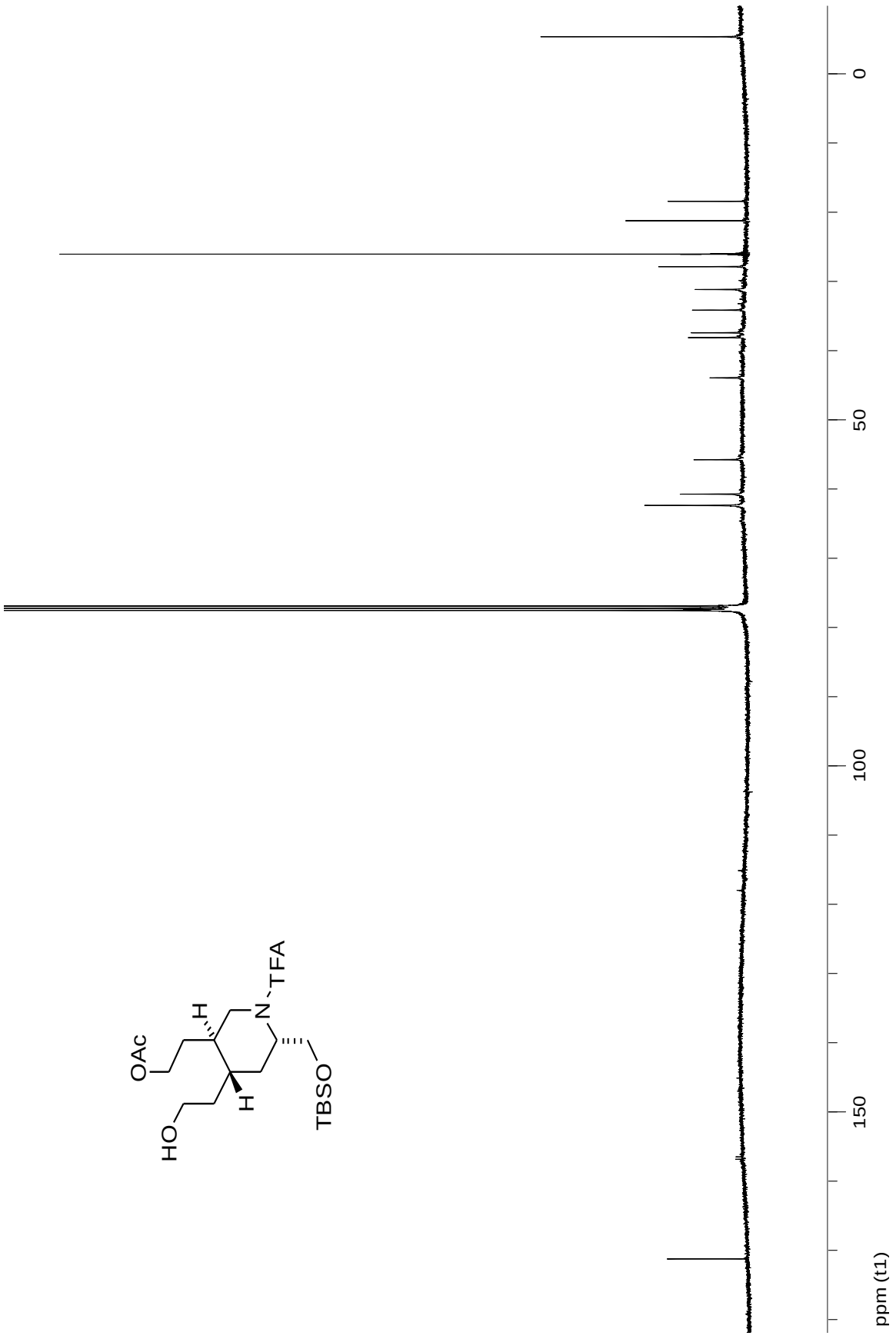

OBz
H
N
TFA
HO
H
TBSO
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

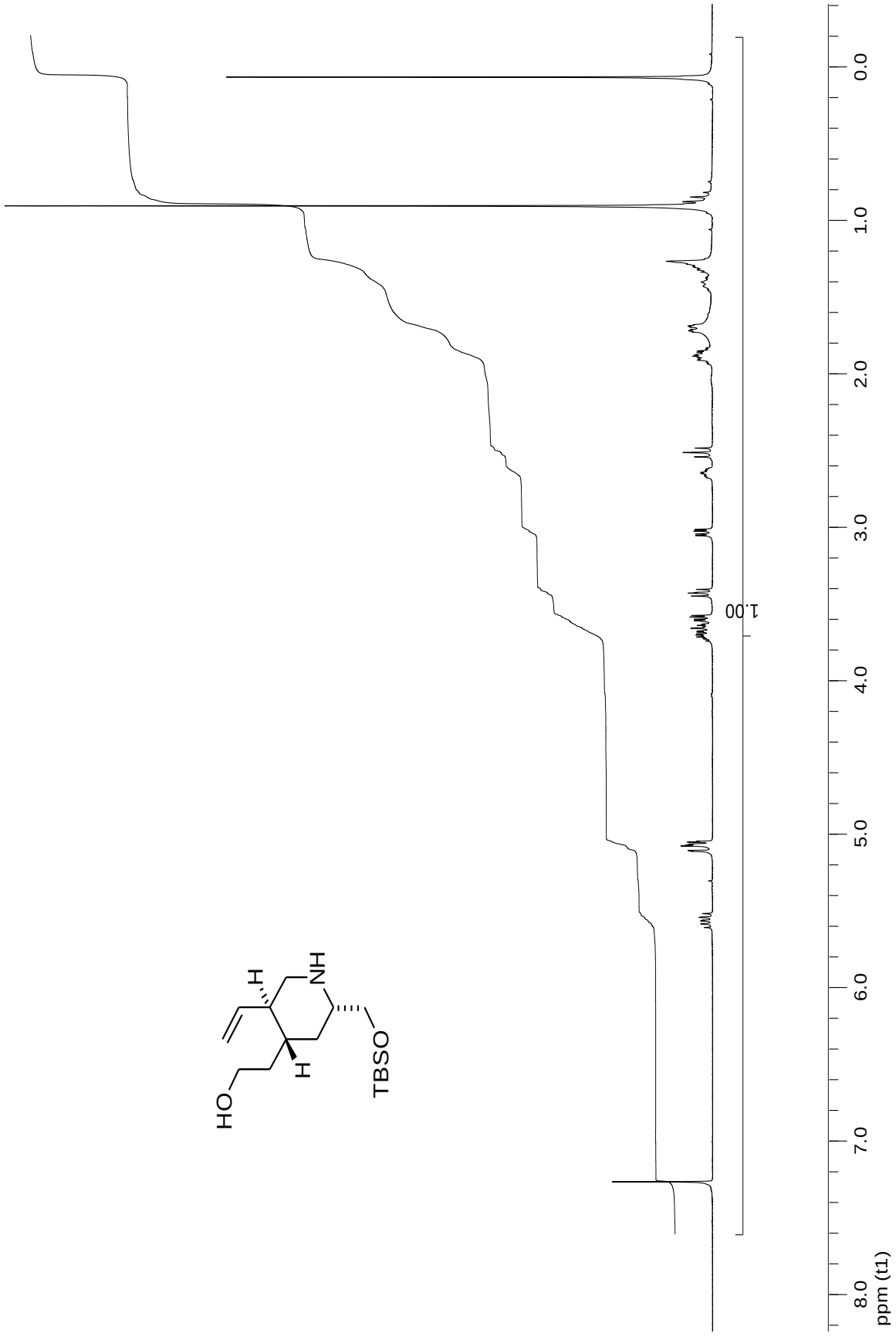

OBz
H
N
TFA
H
HO
TBSO
0
50
100
150
ppm (t1)

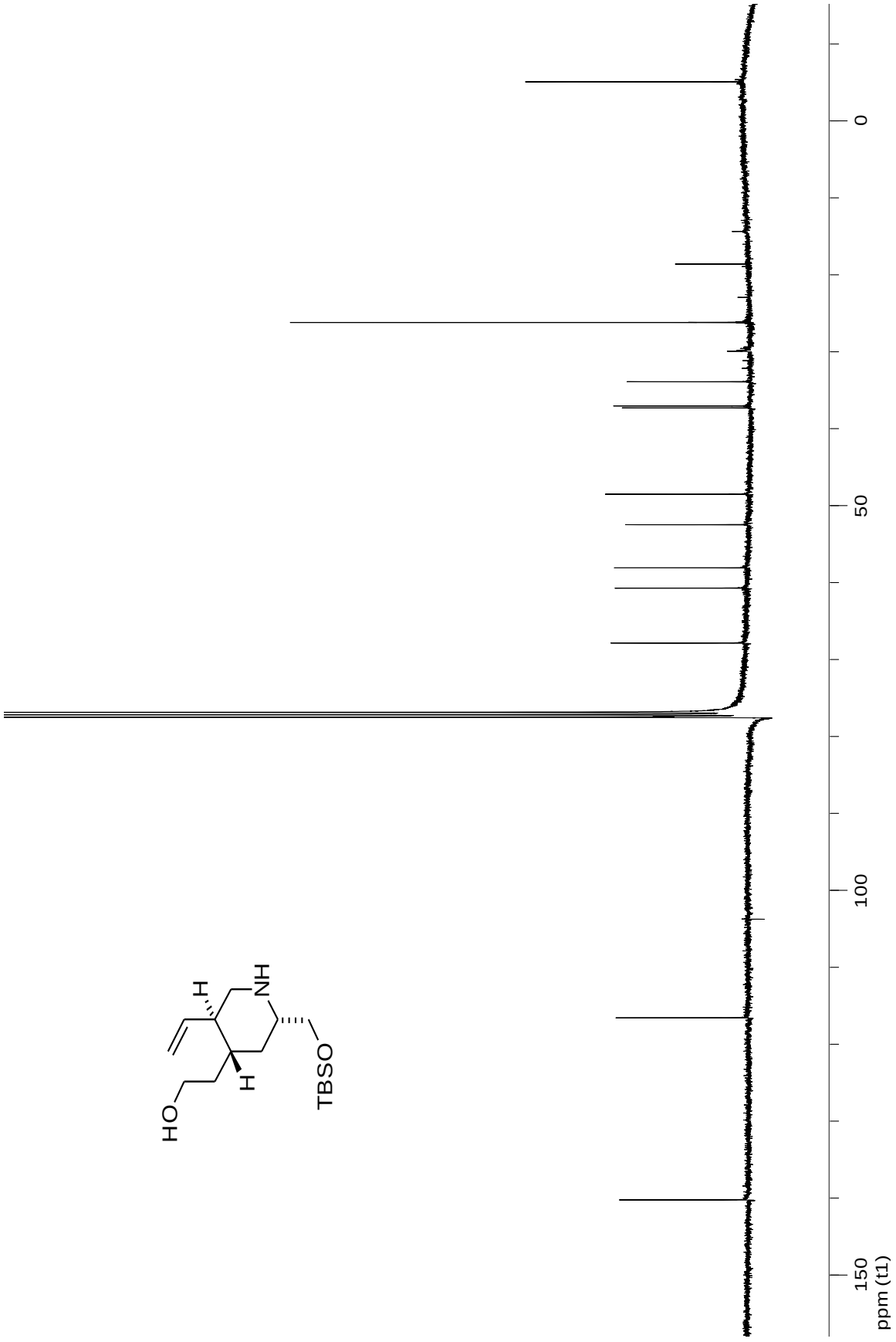

OH
AcO
H
H
N
TFA
TBSO
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

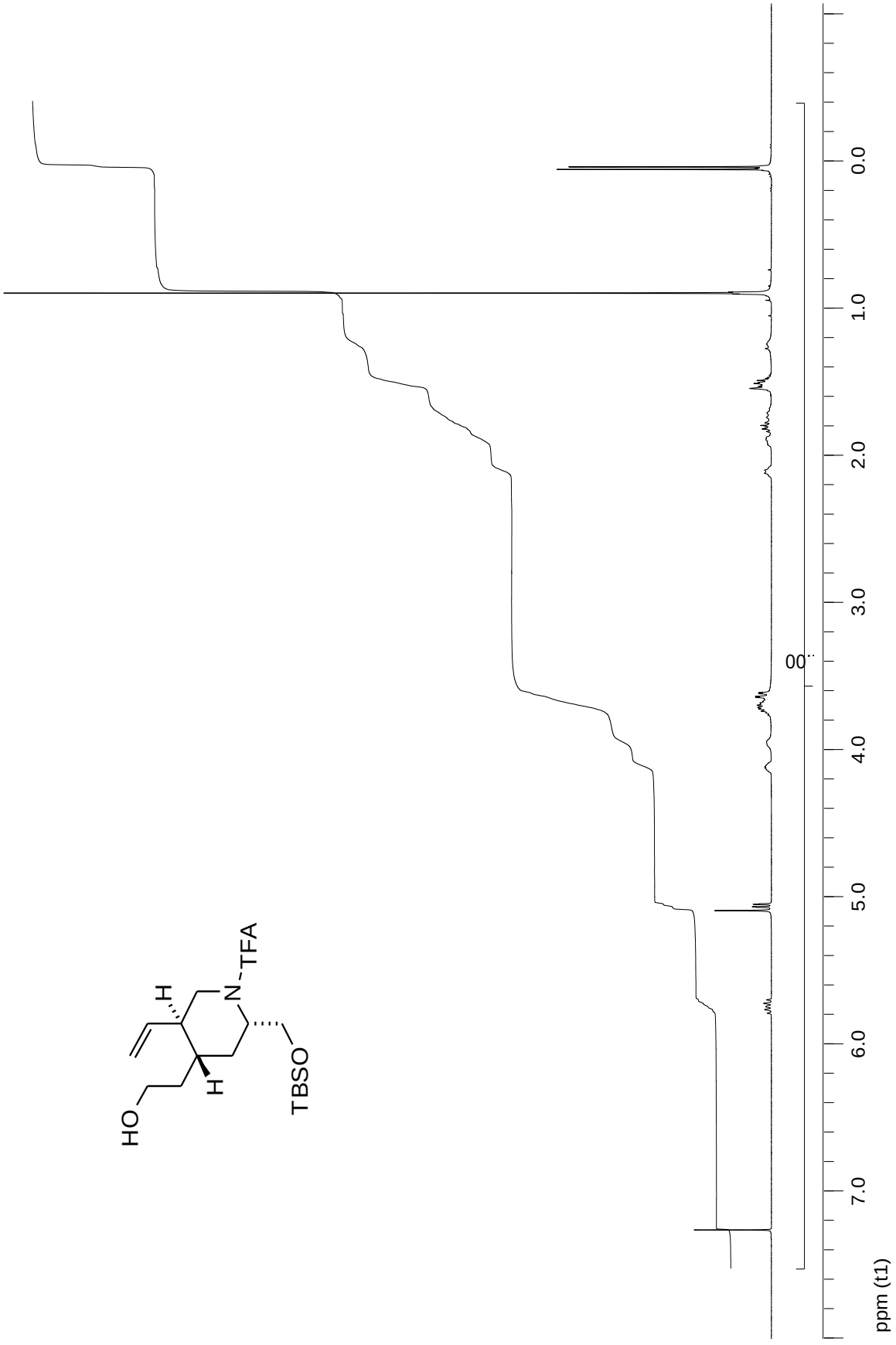

OH
AcO
H
H
N
TFA
TBSO
0
50
100
150
ppm (t1)

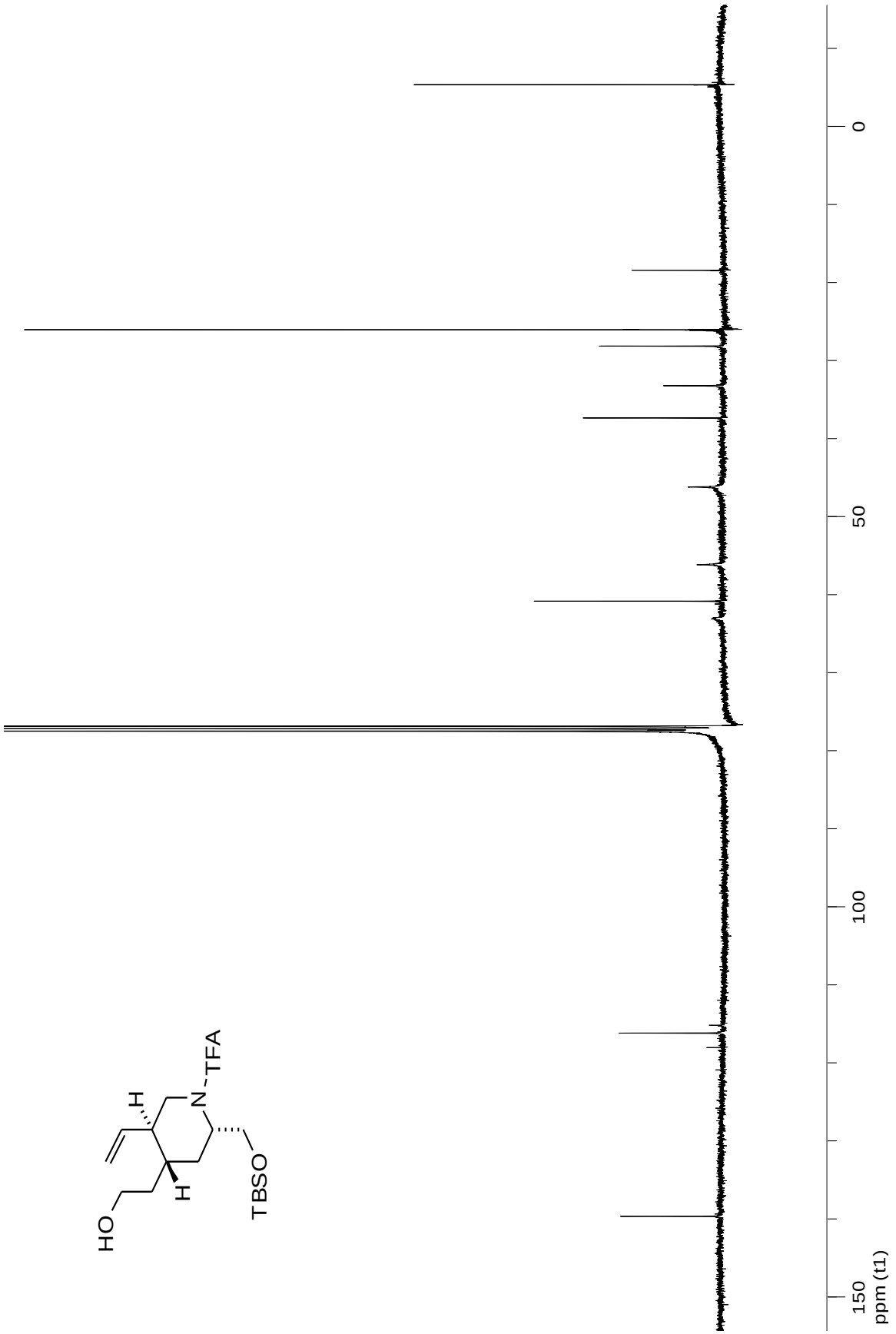

OAc
H
N
TFA
H
HO
TBSO
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

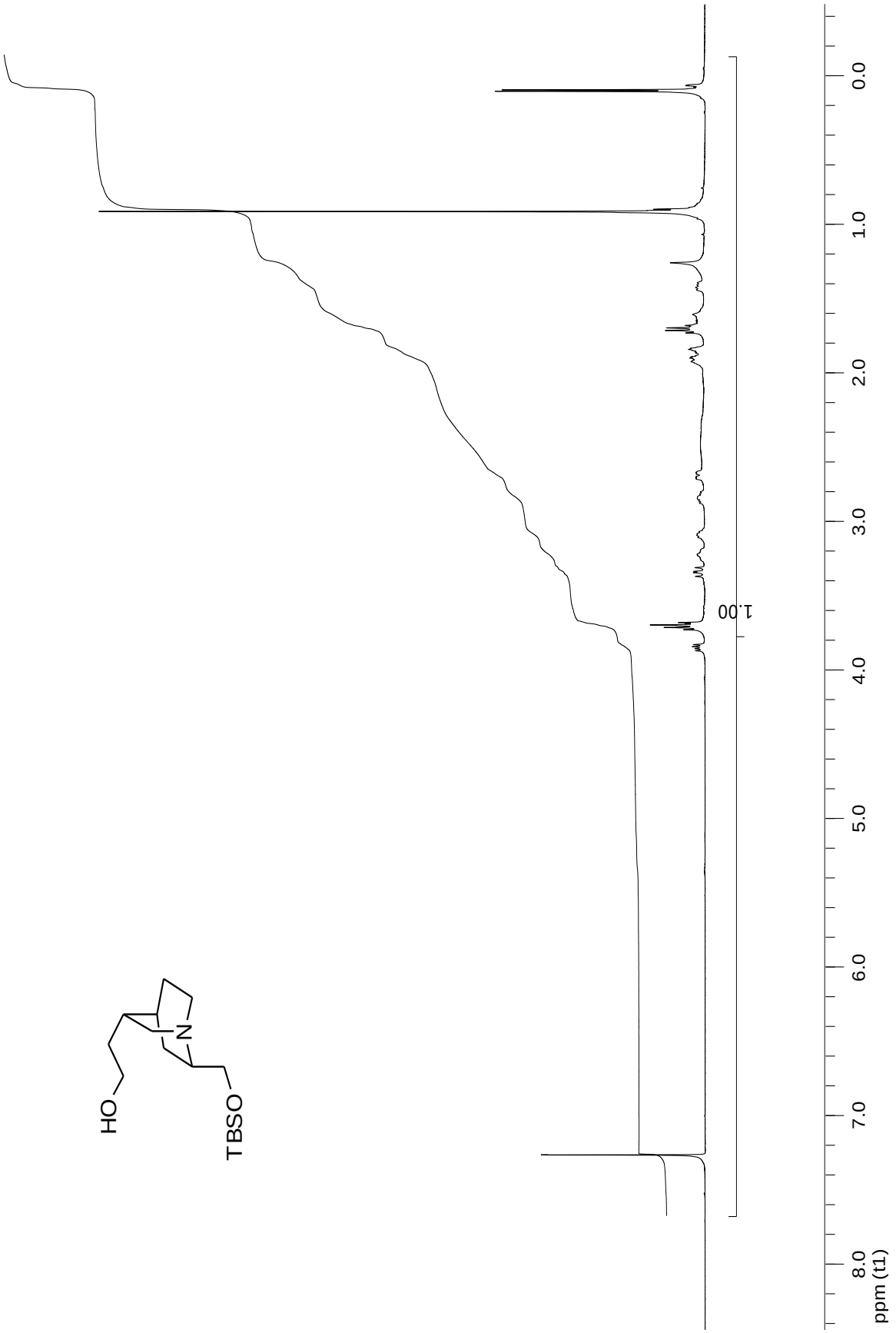

OAc
H
N
TFA
H
HO
TBSO
0
50
100
150
ppm (t1)

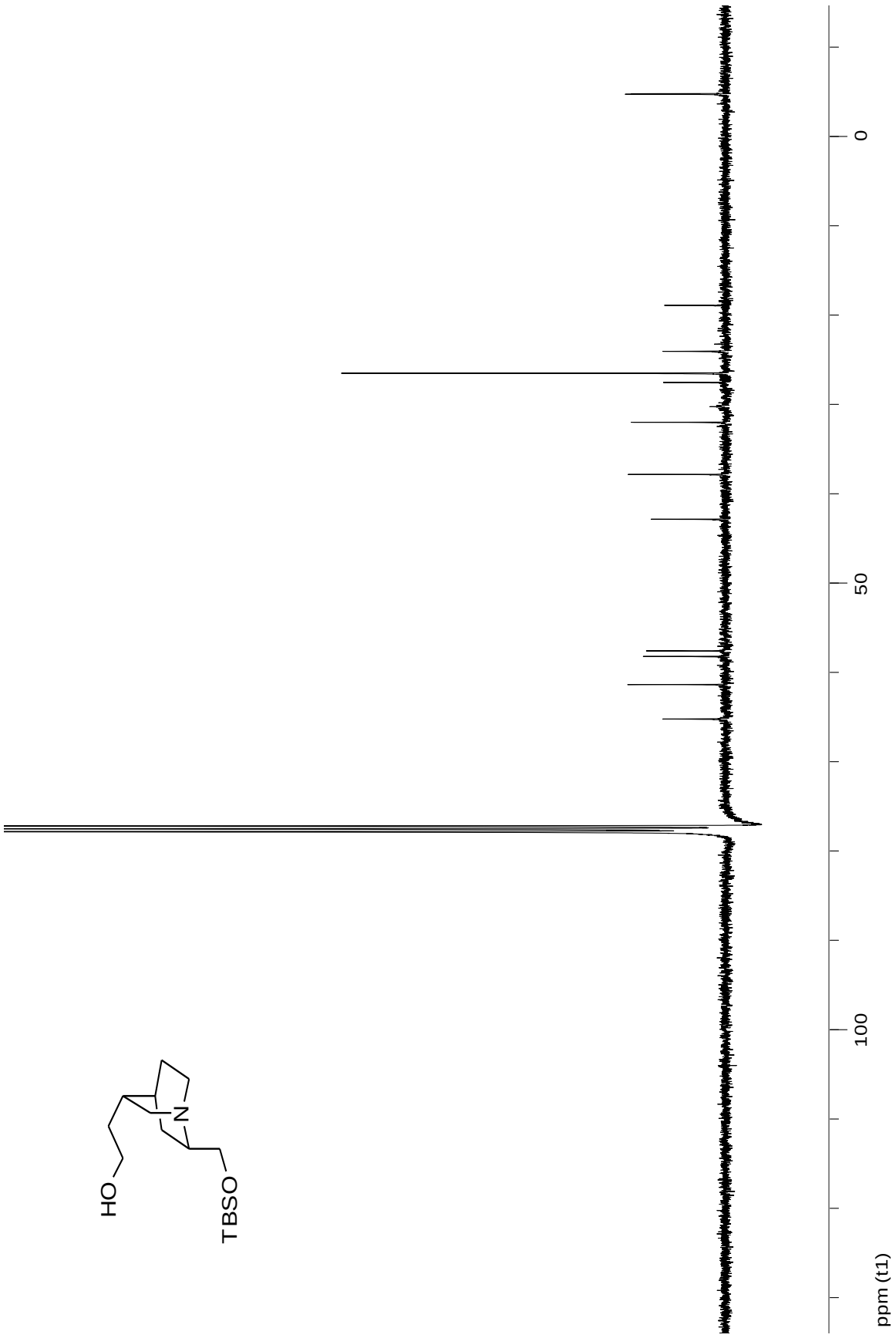

HO
H
H
NH
TBSO
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

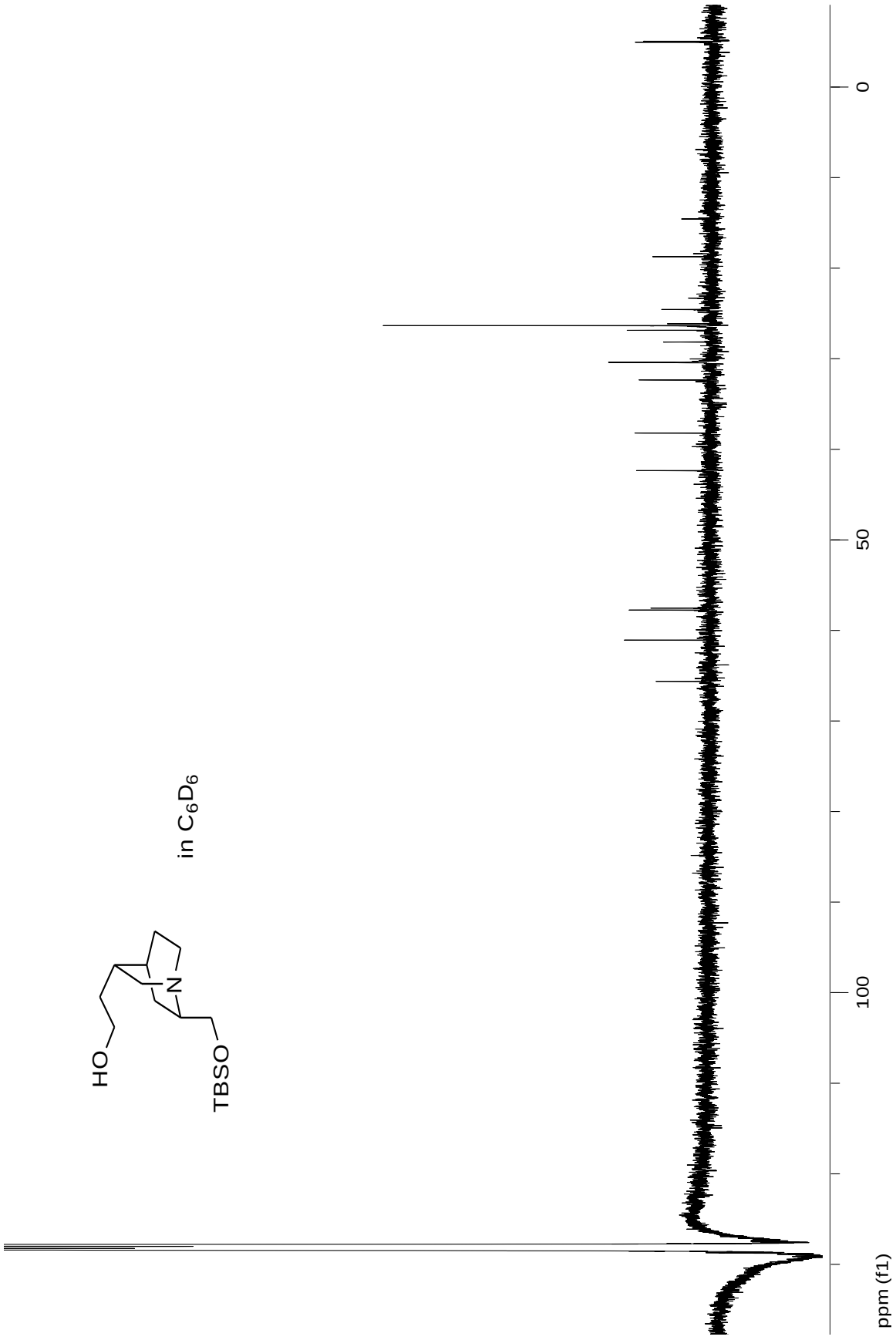

HO
H
H
HN
TBSO
150
100
50
0
ppm (t1)

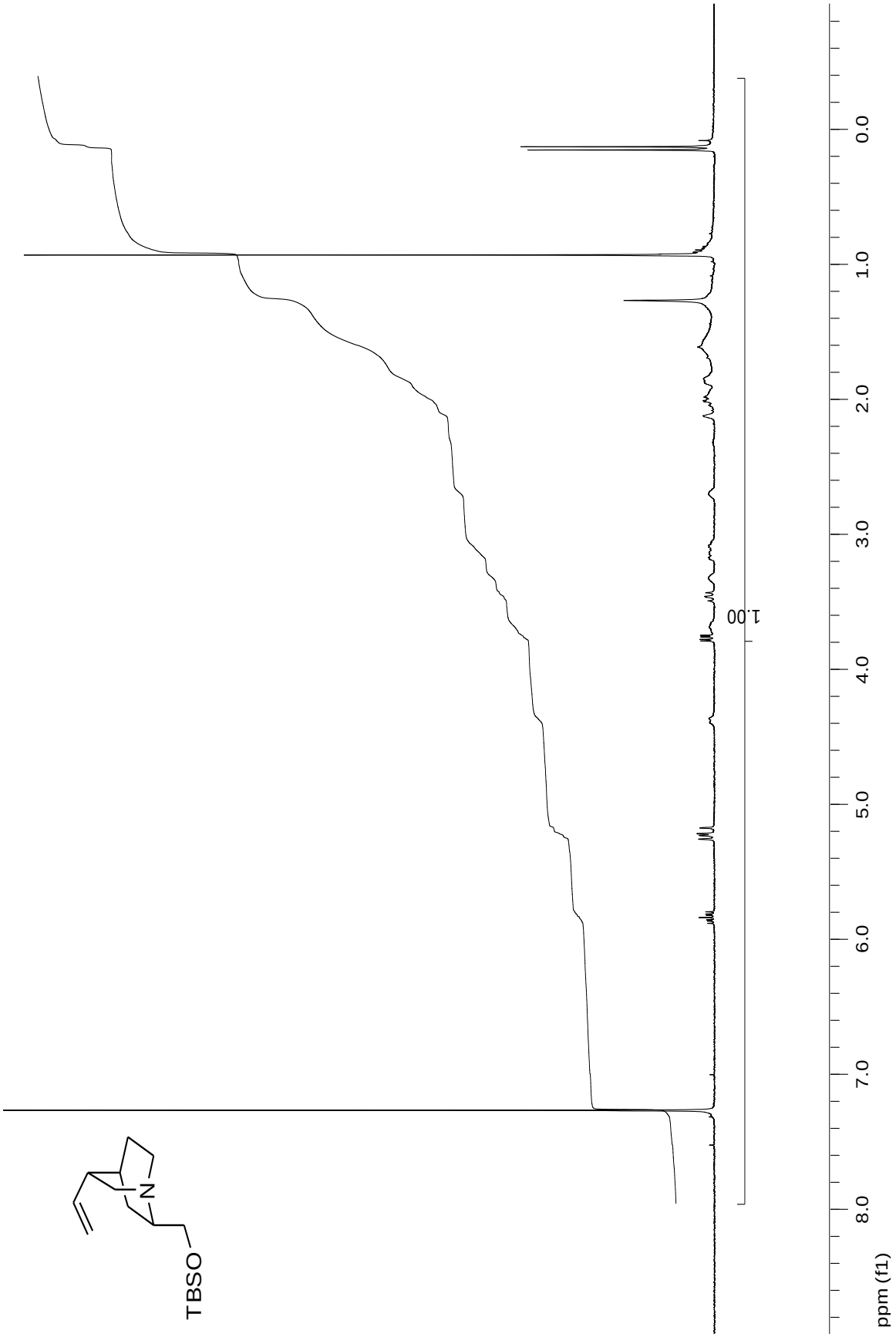

HO
H
H
N
TFA
TBSO
00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1)

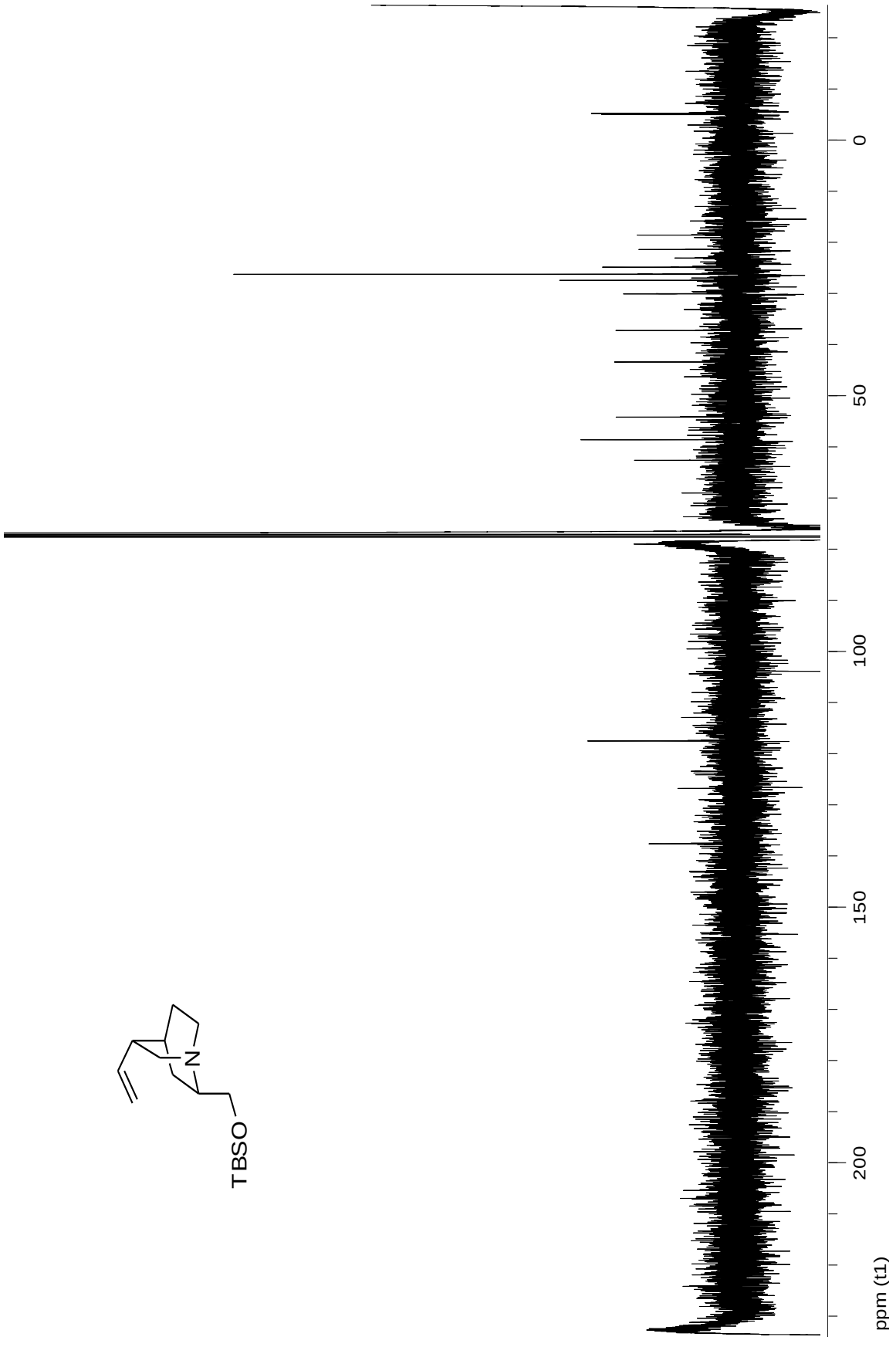

HO
H
H
N
TFA
TBSO
150
100
50
0
ppm (t1)

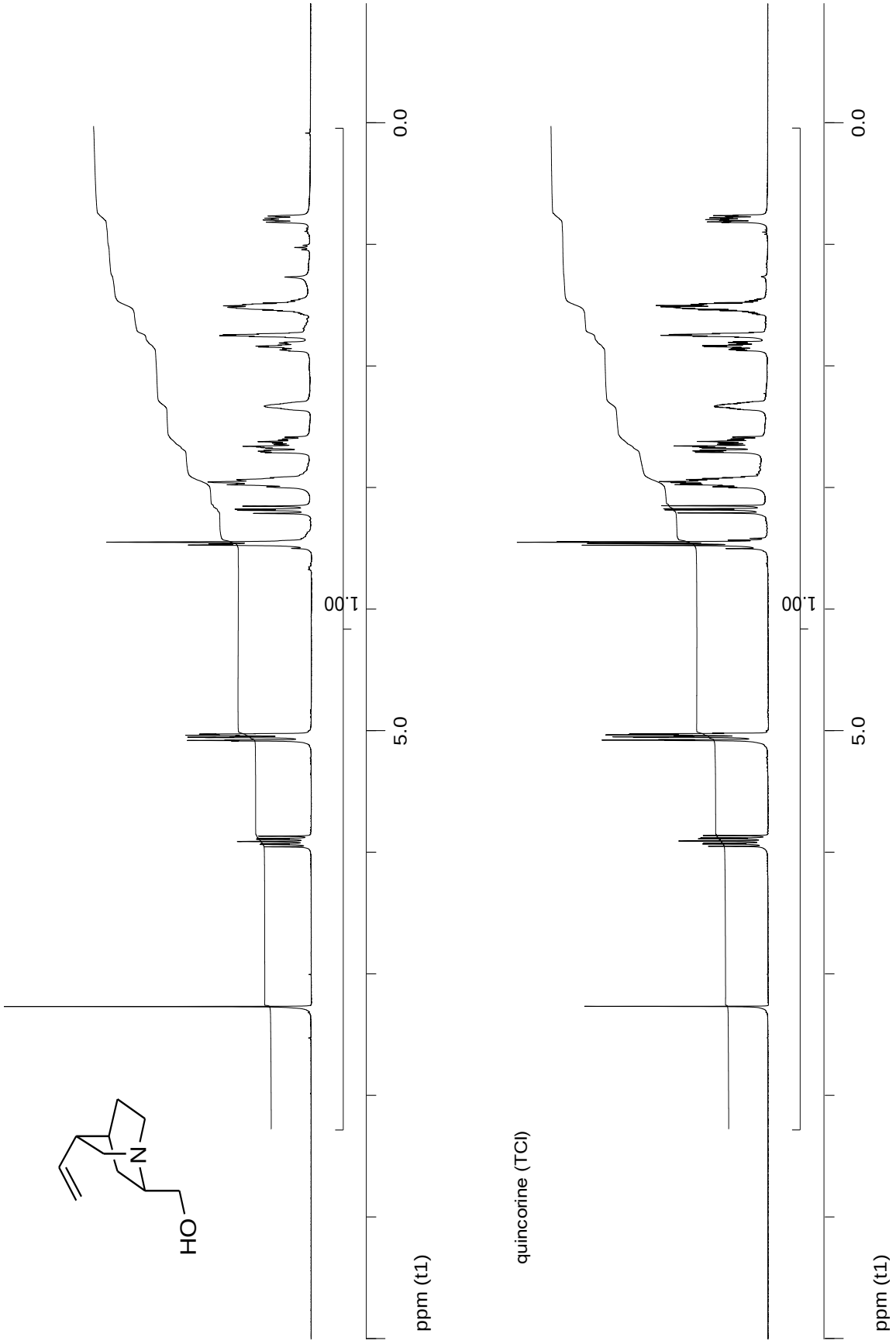

HO
N
TBSO
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

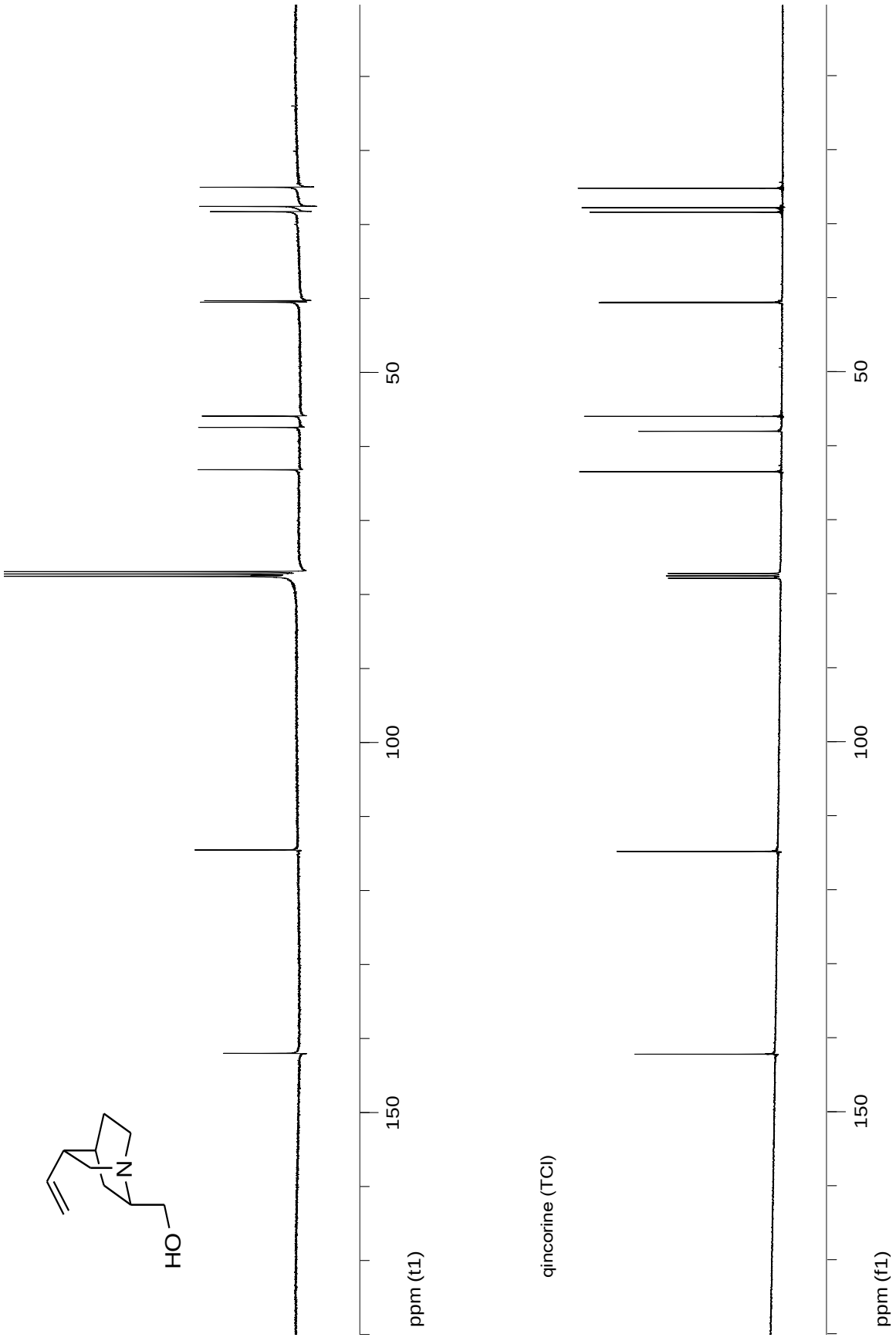

HO
N
TBSO
0
50
100
ppm (t1)


HO
N
TBSO
in C_6D_6
ppm (f1)
0
50
100


TBSO
N
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


TBSO
N
0
50
100
150
200
ppm (t1)


HO
N
1.00
5.0
0.0
ppm (t1)
quincorine (TCI)
1.00
5.0
0.0
ppm (t1)


HO
N
150
100
50
ppm (t1)
qincorine (TCI)
150
100
50
ppm (f1)