I. Total Synthesis of Galbulimima Alkaloids

II. Resin-bound Glycosyl Phosphates As Glycosyl Donors

III. A Modular Synthesis of FGF-2 Binding Heparin Pentasaccharide

by

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Professor Timothy F. Jamison ________________________________ Chairman

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Professor Timothy M. Swager ________________________________

To my parents, Ann and Tom Hunt,

to my sisters, JenniferAnn and Susan Elizabeth Hunt

and in memory of my brother,

David Spencer Hunt.

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Preface

Portions of this work have been adapted from the following articles that were co-written by the author and are reproduced in part with permission from:

Hunt, D. K.; Seeberger, P. H. "Linker Influence on the Stereochemical Outcome of Glycosylations Utilizing Solid Support-Bound Glycosyl Phosphates"*Org. Lett.* **2002,** *4*, 2751. Copyright 2002 American Chemical Society.

Lohman, G. J. S.; Hunt, D. K.; Högermeier, J. A.; Seeberger, P. H. "Synthesis of Iduronic Acid Building Blocks for the Modular Assembly of Glycosaminoglycans" *J. Org. Chem.* **2003,** *68*, 7559. Copyright 2003 American Chemical Society.

Movassaghi, M.; Hunt, D. K.; Tjandra, M. "Total Synthesis and Absolute Stereochemical Assignment of (+)- and (–)-Galbulimima Alkaloid 13" *J. Am. Chem. Soc.* **2006,** *in press*. Copyright 2006 American Chemical Society.

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ABSTRACT

I. Total Synthesis of Galbulimima Alkaloids

The total synthesis of enantiomerically enriched (+)- and (–)-galbulimima alkaloid 13 is outlined. Sequential use of catalytic cross-coupling and cross-metathesis reactions followed by an intramolecular Diels-Alder reaction provided the required *trans*-decalin AB ring system and masked the C16-carbonyl as an *N*-vinyl carbamate for late stage oxidative unveiling as the corresponding C16-enone. Completely diastereoselective introduction of the C-ring via radical cyclization chemistry followed by an enamine-ketone addition for construction of the CDE-ring system allowed rapid entry to the pentacyclic core of these alkaloids. The absolute stereochemistry of natural (–)-galbulimima alkaloid 13 is now unambiguously revised to 2*S*.

Thesis Supervisor: Mohammad Movassaghi
Title: Firmenich Assistant Professor of Chemistry

II. Resin-bound Glycosyl Phosphates As Glycosyl Donors

Resin-bound glycosyl phosphates were readily accessed on solid support via a three step procedure from support-bound glycals. These resin-bound glycosyl phosphates were successfully used as glycosylating agents for coupling with a series of solution based nucleophiles. The stereochemical outcome of disaccharide formation was dependent on the nature of the linker connecting the saccharide to the polymer. Interestingly, other glycosyl donors such as thioglycosides and trichloroacetimidates did not exhibit this dependence, indicating a different reaction mechanism for glycosylation.

III. A Modular Synthesis of FGF-2 Binding Heparin Pentasaccharide

A modular synthesis of FGF-2 binding heparin pentasaccharide is outlined. The synthetic strategy utilizes a disaccharide trichloroacetimidate donor and a uronic acid acceptor as building blocks designed for later application to a fully automated synthesis.

Thesis Supervisor: Peter H. Seeberger
Title: Firmenich Assistant Professor of Chemistry (2003)

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Abbreviations

Ac	acetyl
All	allyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
Cy	cyclohexyl
DIPC	*N,N'*diisopropylcarbodiimide
DMAP	dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
Et	ethyl
g	grams
h	hours
IBX	2-iodoxybenzoic acid
^{i}Pr	isopropyl
Lev	levulinoyl
Me	methyl
Mes	mesityl
mg	milligram
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
nOe	nuclear Overhauser effect
Piv	pivaloyl
TBS	*tert*-butyldimethylsilyl
TDS	dimethylthexylsilyl
TBAF	tetrabutylammonium fluoride
Z	benzylcarbamate

Chapter 1

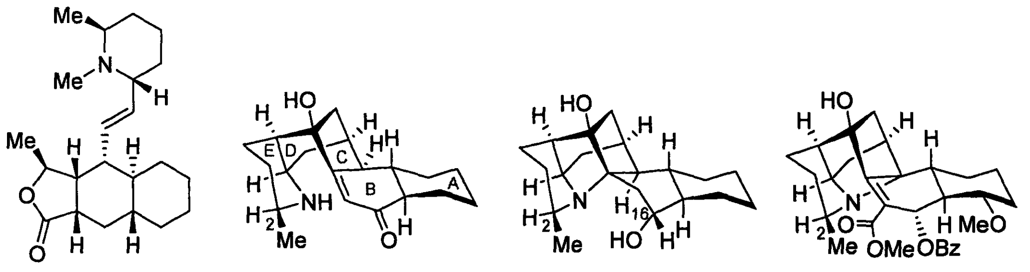
Total Synthesis of Galbulimima Alkaloids

Thesis Advisor: Mohammad Movassaghi

Introduction and Background

Organic synthesis has long provided access to biologically relevant but naturally scarce polycyclic alkaloids, facilitating the development of new therapeutic agents and improving our understanding of their essential activity. In addition, consideration of the biogenesis of structurally related alkaloids often suggests biomimetic approaches to their synthesis, frequently simplifying the construction of complex structural motifs.[1] The challenges presented by these synthetic targets also provide an excellent arena for the application of emergent chemical transformations.

In 1956, Ritchie and Taylor reported the isolation of a group of fascinating alkaloids from the bark of *Galbulimima belgraveana*, a tree native to northern Australia and Papua New Guinea.[2] Isolation of 28 distinct components followed, resulting in the identification of three discrete classes, exemplified by himbacine (**1**), galbulimima alkaloid 13 (GB 13, **2**), himgaline (**3**) and himandrine (**4**) (Figure 1).[3] The tetracyclic lactones such as himbacine (**1**) represent the major isolates, while the pentacyclic and hexacyclic bases such as GB 13 (**2**) and amine himgaline (**3**), and the highly oxygenated ester alkaloids such as himandrine (**4**) are found in varying amounts depending on the source. Relative stereochemistry for each member was determined using elegant chemical modification studies and via analysis of their UV, IR, and ^{1}H NMR spectra. Initial X-ray crystal data for himbacine hydrobromide indicated the absolute stereochemistry of **1** as depicted in Figure 1, including a 2*S* configuration of the stereocenter at C2.[5] This original assignment was later confirmed by stereoselective total synthesis.[6] Early structural analyses and X-ray data of the more complex polycycles indicated absolute configurations enantiomeric to those shown in Figure 1,[3a]



Himbacine (**1**) Galbulimima Alkaloid 13 (**2**) Himgaline (**3**) Himandrine (**4**)

Figure 1. Representative galbulimima alkaloids.[3,4]

however recent X-ray data for himandrine hydrogen bromide has suggested a reversal of this original assignment.[4,7]

Early biochemical evaluation of himbacine **1** indicated anti-spasmodic activity,[8] while recent studies have demonstrated its potential as a selective muscarinic antagonist in the cholergenic treatment of Alzheimer's disease.[9] Pharmacological data on the remaining galbulimima alkaloids, particularly the penta- and hexacyclic compounds, remains sparse, although spasmolytic activity and central and peripheral cardiovascular effects have been observed.[10] *Galbulimima* bark has also been reported to have psychoactive properties on ingestion.[10]

Biogenetic analysis of the *Galbulimima* alkaloids.

A compelling hypothesis by Mander, Ritchie and Taylor in 1967 linked various galbulimima alkaloids to a common polyacetate derived precursor.[3c] Atom mapping suggests a combination of nine acetate units and one pyruvate unit, with incorporation of ammonia to provide the necessary amine (Figure 2). Presumably the core skeletal structure of the Class I lactones would arise from AB ring bicycle formation followed by lactonization involving the incorporated pyruvate unit, and subsequent piperidine formation. For the more complex penta- and hexacyclic alkaloids, backbone construction would require

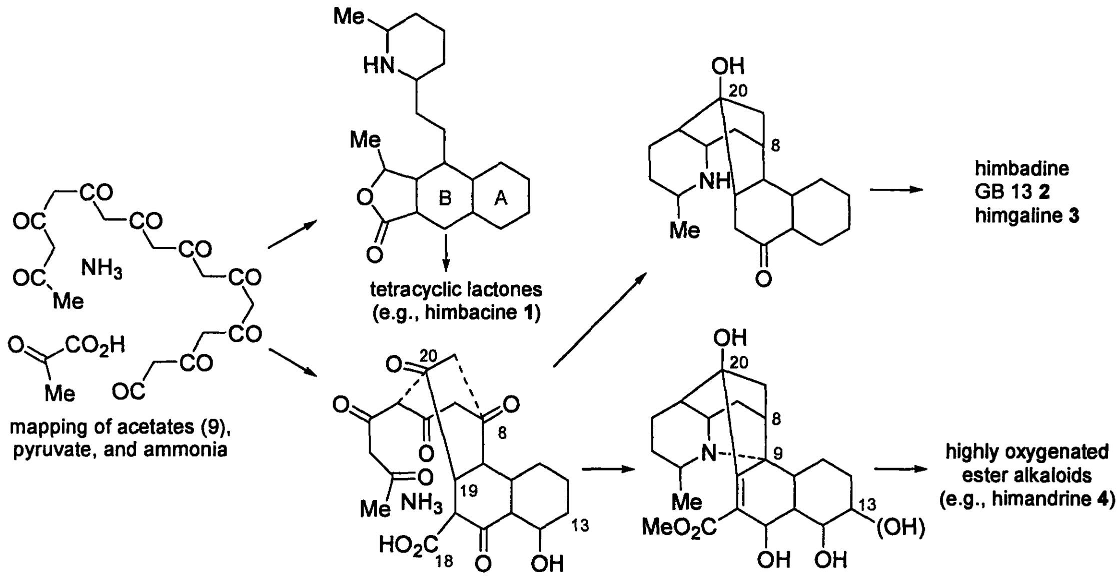


Figure 2. Mander, Ritchie and Taylor's biogenetic analysis of the galbulimima alkaloids.[3c]

connection of the C20-acetate unit to both C8 and the nascent piperidine ring. Subsequent decarboxylation of C18 would provide access to the Class III bases such as GB 13 (**2**), while N-C9 bond formation and oxidation at C13 would afford the skeleton of the highly oxygenated ester alkaloids of Class II.

Building on this initial analysis, in 2003 we developed a biogenetic proposal for the penta- and hexacyclic galbulimima alkaloids (Figure 3),[11] particularly the captivating

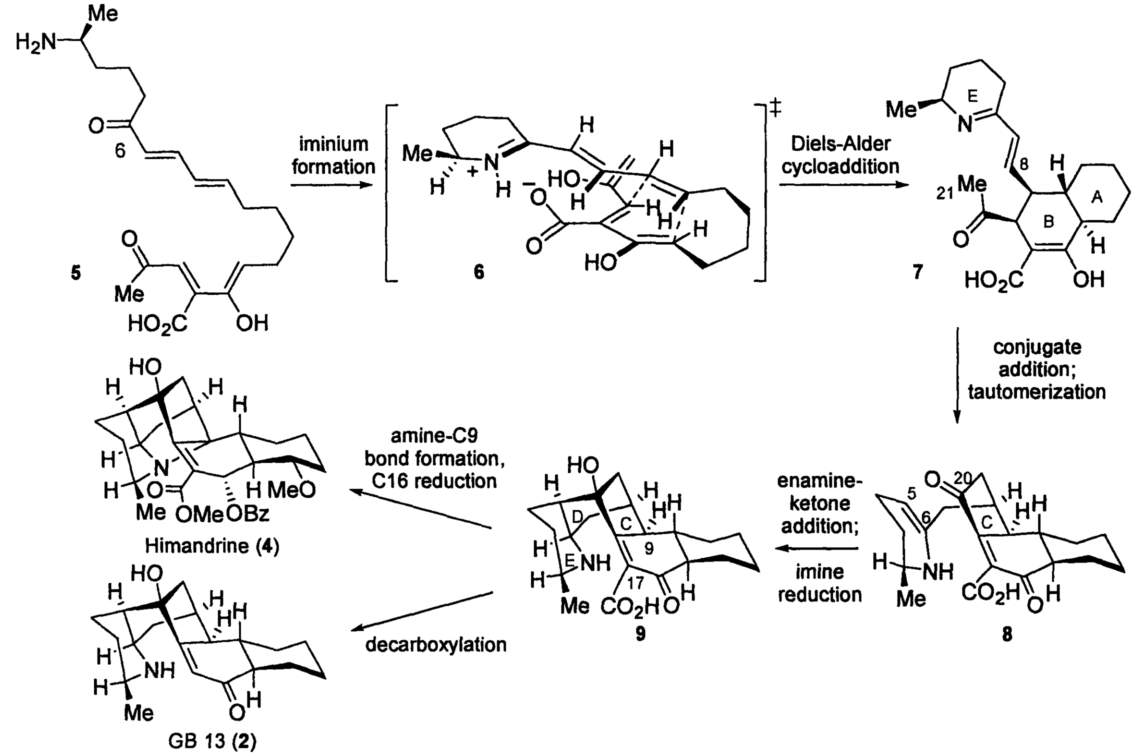
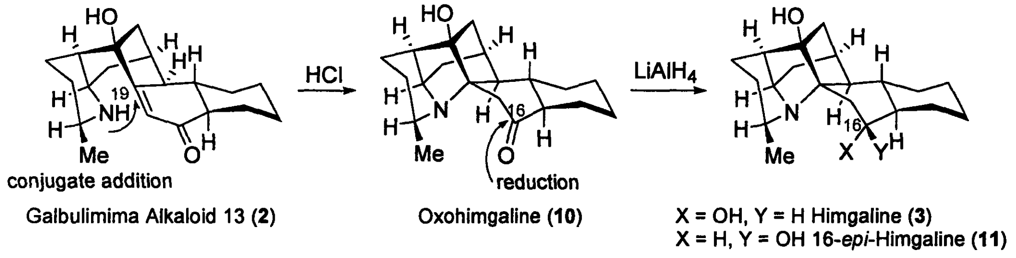


Figure 3. Our biogenetic analysis of the penta- and hexacyclic galbulimima alkaloids.[12,12]

CDE ring structure unique to these compounds.[12] In particular we sought a strategy that would obviate the need for late-stage oxidation state adjustment. A combination of the acetate, pyruvate, and ammonia building blocks may give rise to an unsaturated linear structure such as **5**. Iminium formation at C6 would provide the E ring and an intramolecular Diels-Alder cycloaddition of the resulting activated α,β-unsaturated iminium **6** would provide the AB ring system common to all members of the family. Stereocontrol of this cyclization to provide the required absolute stereochemistry and the *trans*-decalin may be substrate-derived or rely on enzymatic catalysis. We hypothesized that the bicyclic framework thus installed would afford the structure necessary to direct subsequent transformations in a diastereoselective manner. In examining the remaining framework, we envisioned that C-ring construction would result from conjugate addition of the C20-C21 enol of tricycle **7** to C8 of the α,β-unsaturated piperidine imine; tautomerization to the enamine would then provide tetracyclic ketone **8**. Addition at the C20-ketone of the C5-C6 enamine and subsequent diastereoselective reduction of the resulting imine would complete construction of the bridged CDE ring system and provide the tertiary alcohol at C20 (**9**). With this major framework established, conversion to the various alkaloids would be straightforward. For example, GB 13 (**2**) would result from decarboxylation of pentacycle **9**. Similarly, himandrine (**4**) would result from an amine addition to a conjugated enol at C9, followed by reduction at C16 and benzoylation.[12] Conversion of GB 13 (**2**) to hexacyclic himgaline (**3**) would result from the conjugate addition of the amine onto the enone at C19 and subsequent C16-ketone reduction to provide the secondary alcohol (Scheme 1). This



Scheme 1. Interconversion of GB 13 (**2**) and himgaline (**3**).[3c]

hypothesis is supported by the conjugate addition observed during Ritchie and Taylor's initial structure determination studies, where treatment with mild protic acid produced oxohimgaline (**10**), although initial reduction attempts provided the undesired C16-epimer of himgaline (**11**).[3c] It is noteworthy that several years after we began this work, Baldwin reported an interesting and biomimetically relevant synthesis of tetracyclic (+)-himbacine utilizing an iminium mediated transformation for diastereoselective formation of the AB ring system.[13] This work supports the viability of our independent proposal for substrate-directed formation of the AB bicycle en route to the more complex penta- and hexacyclic *Galbulimima* alkaloids.

Prior Synthetic Studies

The demonstrated biological activity of himbacine (**1**) has prompted a number of total syntheses of the tetracyclic lactone[14] as well as various derivatives for biological testing.[15] To date, construction of the AB-ring *trans*-decalin fragment has relied on a Diels-Alder reaction of various diene-dienophile pairs as outlined in Figure 4. In most cases subsequent coupling with the piperidine ring fragment has completed the total synthesis.

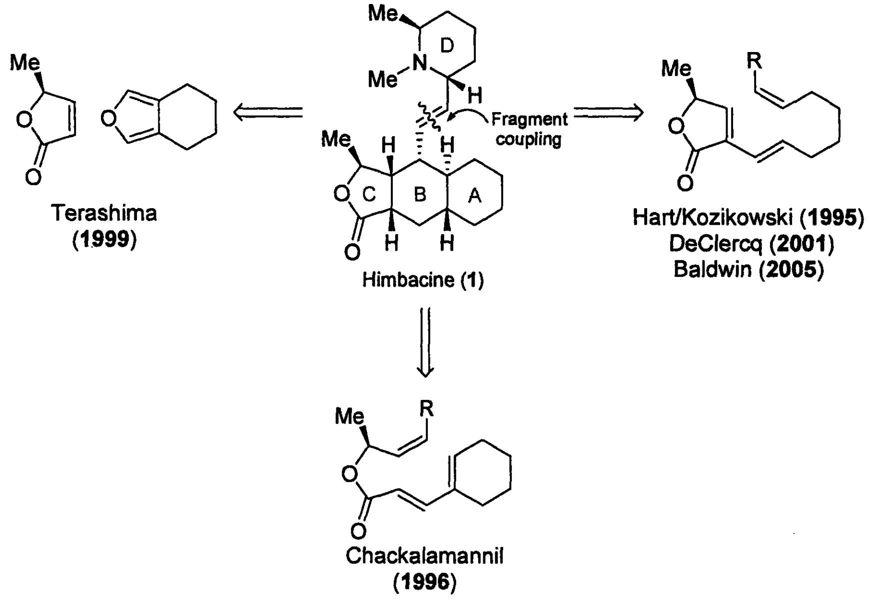
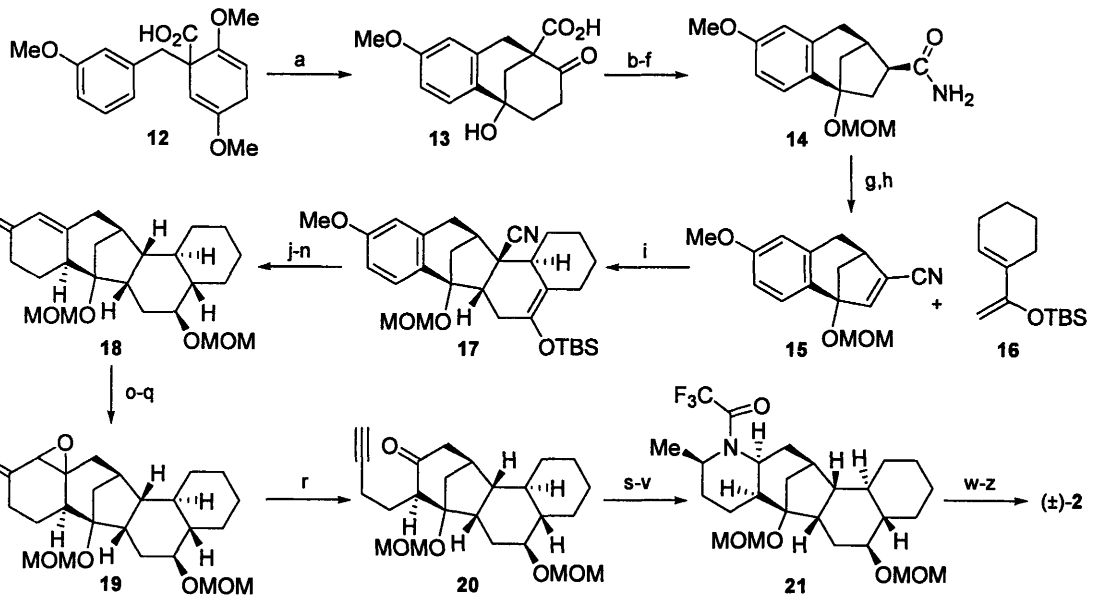


Figure 4. Previous syntheses of himbacine **1**.[14]

Despite the considerable interest shown in the galbulimima alkaloids and their intriguingly unique molecular framework, when we initiated our studies only a single report existed concerning synthesis of the more complex members of the family containing the CDE bridged tricyclic moiety. Work by Mander and McLachlan in 2003 outlined the first total synthesis of (±)-GB 13 (**2**).[16] Key steps in this original report include cycloaddition for construction of the AB decalin and subsequent elaboration of the benzenoid moiety of **17** to provide the piperidine E ring of the target structure (Scheme 2). In the event, acid-catalyzed cyclization of 2-(3- methoxybenzyl)-1,3-dienol ether **12** produced tricycle **13**, which on protection, diazoketone formation, and Wolff ring contraction afforded amide **14** as a mixture of *endo*:*exo* products with the desired *endo* compound as the major component (Scheme 2). Amide conversion to the nitrile and dehydrogenation using a α-selenation, oxidation, elimination sequence provided dienophile **15**, which smoothly underwent cycloaddition with diene **16** in the presence of ytterbium tris(2,2,6,6-tetramethyl-3,5-heptane-dionate) ($Yb(thd)_3$) at 110 °C to produce the desired endo-adduct **17** in excellent yield. Reduction of the unmasked C16 ketone and protection as the corresponding methoxymethyl ether and subsequent decyanation and Birch reduction of the benzenoid afforded enone **18**. Formation

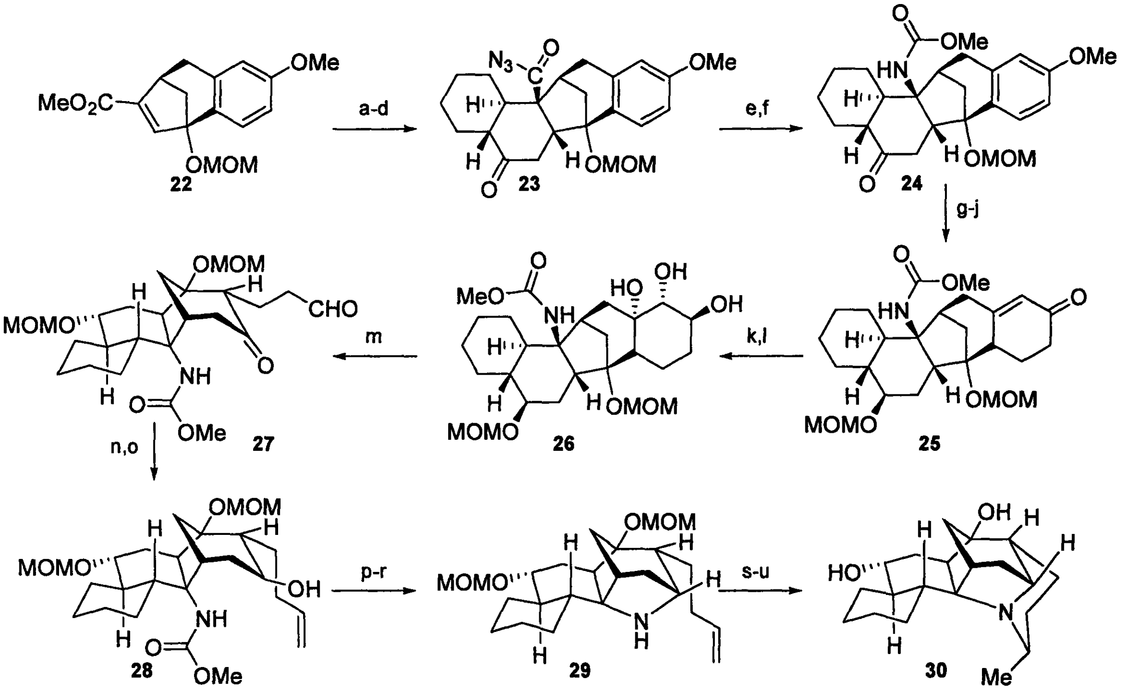


(a) 60% H_2SO_4, acetone, 80%. (b) AcOH, H_2O, 89%. (c) MOMCl, DMAP, $^iPr_2NEt$, CH_2Cl_2, 97%. (d) NaH, EtOCHO. (e) NEt_3, CH_3CN, $pNO_2C_6H_4SO_2N_3$. (f) *hv*, THF, $((CH_3)_3Si)_2NH$, O °C; aq. HCl, 68%. (g) Cl_3CCOCl, NEt_3, 98%. (h) potassium diisopropylamide, Ph_2Se_2, H_2O_2, THF, 74%. (i) **16**, $Yb(thd)_3$, 110 °C, 87%. (j) TBAF, THF, 74%. (k) $LiAlH_4$, THF, 94%. (l) MOMCl, DMAP, $^iPr_2NEt$, CH_2Cl_2, 96%. (m) Li, NH_3. (n) 10M HCl (cat), MeOH, THF, 55% (2 steps). (o) $LiAlH_4$, THF. (p) *m*CPBA, CH_2Cl_2. (q) DMP, $NaHCO_3$, 77% (3 steps). (r) $pNO_2ArSO_2NHNH_2$, pyridine, EtOH, THF, 76%. (s) H_2NOH HCl, pyridine, 100 °C. (t) $ZrCl_4$, $NaBH_4$. (u) Zn, AcOH, Et_2O. (v) TFAA, NEt_3, CH_2Cl_2, 32% (4 steps). (w) aq. HCl, acetone, 50 °C. (x) DMP, CH_2Cl_2. (y) MOMCl, DMAP, $^iPr_2NEt$, CH_2Cl_2, 57% (3 steps). (y) LDA, TMSCl, THF; $Pd(OAc)_2$, DMSO, CH_3CN, 82%. (z) K_2CO_3, H_2O, THF, MeOH, 55 °C; aq. HCl, acetone, 55 °C, 37% (2 steps).

Scheme 2. Mander's synthesis of (±)-GB13 (**2**).[16]

of the epoxy ketone **19** via a three step procedure was followed by Eschenmoser fragmentation to provide alkyne **20**. Condensation to the bis-oxime, reductive cyclization, further reduction of the resulting hydroxylamine and protection provided the trifluoroacetamide **21** as the major product. Reconstitution of the C16 ketone, installation of the required enone via silyl enol ether formation and Saegusa dehydrosilylation followed by final deprotection completed the synthesis of (±)-GB 13 (**2**).

Subsequent work out of the Mander group outlined construction of the hexacyclic himandrine skeleton **30** utilizing a similar strategy to that for GB 13.[17] Inclusion of methanol during the photo-Wolff rearrangement sequence and dehydrogenation provided unsaturated ester **22** for the cycloaddition with diene **16** (Scheme 3). Conversion of the Diels-Alder adduct to the carboxylic acid and isomerization to the trans-decalone was followed by acyl azide formation. Methyl carbamate **24** was accessed via methanolysis of the isocyanate obtained from thermal rearrangement of acyl azide **23**. Birch reduction of the aromatic ring



(a) **16**,100 °C, 48 h. (b) AcOH, THF, H_2O, 87% (2 steps). (c) HMPA, NaH, $CH_3(CH_2)_2SH$, 97%. (d) $(COCl)_2$, DMF, pyridine, Δ, NaN_3, 23 °C, THF, 5 h, 77%. (e) Δ, toluene, 20 min, ~100%. (f) MeOH, NaOMe, ~100%. (g) Li, NH_3, MeOH. (h) AcOH, THF, H_2O. (i) MOMCl, ^{i}Pr$_2$NEt. DMAP, CH_2Cl_2. (j) HCl, $CHCl_3$, 32% (4 steps). (k) 9-BBN, THF, MeOH, H_2O_2, 87%. (l) OsO_4, pyridine, THF, ~75%. (m) $Pb(OAc)_4$, MeOH, 0 °C, 2 h, ~70%. (n) $(MeO)_2POC(N_2)COMe$, K_2CO_3, MeOH, 0 °C, 4 h, 91%. (o) Li, NH_3, MeOH, 20 s, ~95%. (p) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0 °C, 2 h, 93%. (q) NaH, DMF, 97%. (r) HMPA, NaH, $CH_3(CH_2)_2SH$, 90%. (s) $PdCl_2$, CuCl, O_2, ^{n}Bu$_4$NCl, K_2CO_3, CH_3CN, Δ, 16 h, 85%. (t) Rh, Al_2O_3, $(CF_3)_2CHOH$, 95%. (u) Dowex 50W, MeOH: H_2O, 5:1, Δ, 8 h, ~60%.

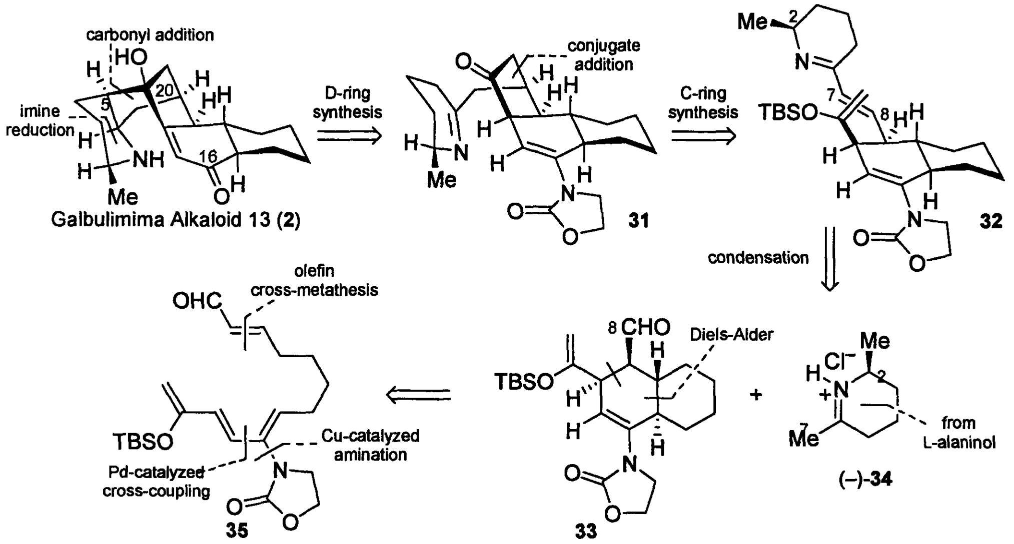
Scheme 3. Mander's synthesis of model himandrine skeleton (±)-**30**.[17]

also reduced the decalone to provide the enone **25** on isomerization of the anisole-derived methyl enol ether. Fragmentation of the enone to keto-aldehyde **27** required a multistep sequence via triol **26**. Subsequent conversion of the aldehyde to the alkyne and dissolving metal reduction provided β-carbinol **28** as a single diastereomer with concomitant reduction to the alkene. Pyrrolidine ring closure was effected by mesylation and carbamate cleavage with subsequent nucleophilic displacement by the unmasked amine. Final ring closure was achieved via an oxidative amination with subsequent hydrogenation and deprotection to provide the desired model system **30** of the himandrine skeleton.

Intrigued by the unique structure of these alkaloids and the paucity of studies directed at complex members possessing the fused CDE-ring system (i.e., **2**–**4**, Figure 1), we initiated our studies in this area. In particular we sought to design a synthetic strategy that would capitalize on our biogenetic analysis of the galbulimima alkaloids and hence allow access to multiple members of the family while minimizing the number of protecting group and oxidation state manipulations required. The resulting synthetic strategy has culminated in the first total synthesis of both (+)- and (–)-galbulimima alkaloid 13 (**2**), allowing the unambiguous absolute stereochemical assignment of the natural isomer.[11]

Retrosynthetic Analysis

Motivated by our biogenetic analysis of these interesting alkaloids, we composed a synthetic strategy for galbulimima alkaloid 13 **2** that incorporated several biomimetically inspired key steps. We envisioned a strategic C5-C20 bond disconnection to greatly simplify the structure of **2** to the tetracyclic precursor **31** (Scheme 4). As proposed in our initial biosynthetic analysis, addition of a C5-C6 enamine at the C20 ketone would provide the required bridged CDE ring system. In turn, imino-ketone **31** was expected from conjugate addition to α,β-unsaturated imine **32** of the C20 enol tautomer. In practice, we discovered that incorporation of a silyl enol ether at C20 in **32** was advantageous for effective C-ring closure, AB bicycle generation, and provided an appropriately masked ketone during fragment condensation. Ultimately, application of this endgame strategy to a tricycle



Scheme 4. Our retrosynthesis of galbulimima alkaloid 13 (**2**).

obtained from a linear precursor related to **5** (Figure 3) would allow examination of the practicality of our biomimetic hypothesis. Alternatively, fragment coupling to produce tricycle **32** was envisioned via condensation of aldehyde **33** with iminium chloride salt **34** (Scheme 4). Given the uncertainty concerning the absolute stereochemistry of naturally occurring **2**, incorporation of either hand of the readily available optically active iminium salt[18] with a racemic bicycle **33** would provide an expedient route to both enantiomers of advanced intermediates and the target compound. Rapid access to the tricycle **32** would also allow timely exploration of the unique CDE ring system and implementation of our biomimetic proposal for its formation. To this end, construction of the linear tetraene **35** for an *endo*-selective intramolecular Type I Diels-Alder cycloaddition was anticipated via sequential cross-coupling and cross-metathesis reactions. Introduction of a vinyl oxazolidinone to linear tetraene **35** installed the desired C16 oxidation state, effectively masked the C16-carbonyl during subsequent transformations and was readily removed for late-stage conversion to the required enone of the target compound. Incorporation of the vinyl amide also provided a reactive *N*-acyl-2-aminodiene for the intramolecular cycloaddition,

Results and Discussion

Synthesis of the AB ring bicycle.

Our first challenge in implementing our synthetic strategy toward galbulimima alkaloid 13 (**2**) lay in preparing the required substituted AB ring system. Construction of the *trans*-decalin framework and installation of four new stereocenters was envisioned via an intramolecular Diels-Alder reaction of linear precursor **35** (Figure 5). Elaboration

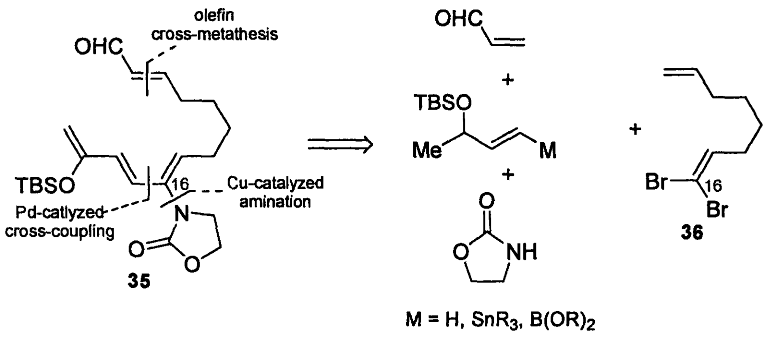
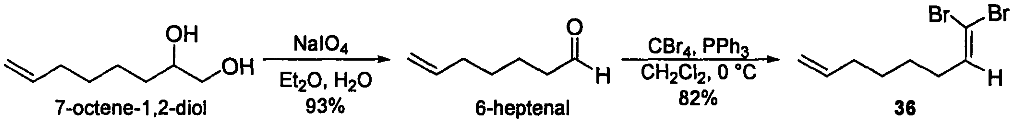


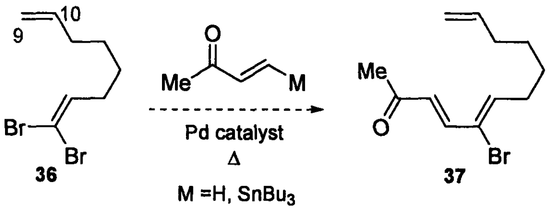
Figure 5. Retrosynthetic analysis of tetraene **35**.

of dibromoalkene **36** via sequential cross-coupling would provide the required diene. Installation of a vinyl oxazolidinone was proposed for introduction of a masked C16-carbonyl. The vinyl enamide should be stable to base and mild acid treatment, fluoride ion, and hydride, yet reactive toward oxidative functionalization or hydrolysis with strong acid for late-stage unveiling of the C16-ketone and conversion to the required α,β-enone of **2**. Following diene formation, the dienophile may be installed via olefin cross-metathesis with acrolein as the coupling partner (Figure 5).

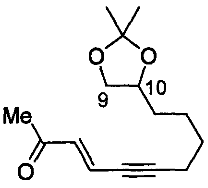
Synthesis of tetraene **35** began with dibromoalkene **36**, readily prepared from commercially available 7-octene-1,2-diol via oxidation to known 6-heptenal[19] followed by dibromomethylenation (Scheme 5).[20] Elaboration of the dihaloalkene to the *Z*,*E*-bromodiene was then undertaken. A number of palladium-catalyzed cross coupling strategies have taken advantage of the steric and electronic difference between the *cis*- and *trans*-bromide of dibromoalkenes such as **36** to effect stereoselective coupling with the more accessible *trans*-carbon-bromide bond, among them selective Suzuki,[21] Stille,[22] and Sonogashira,[23] and Heck reactions.[24] Our initial efforts focused on the use of palladium-catalyzed Heck and Stille conditions as outlined in Scheme 6. Early work with a C9-C10 acetonide model system exhibited adequate reactivity only at elevated temperatures and was accompanied by dehydrobromination to produce undesired alkyne **38** (Figure 6).[25] The desired vinyl bromide **37** was not observed, suggesting initial



Scheme 5. Synthesis of dibromoalkene **36**.



Scheme 6. Strategy for selective Heck or Stille cross-coupling with dibromoalkene **36**.

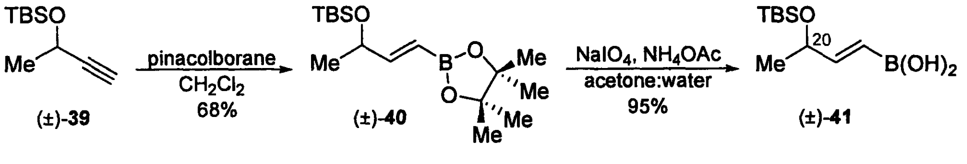


(±)-38

Figure 6. Dehydrobrominated alkyne product x.[25]

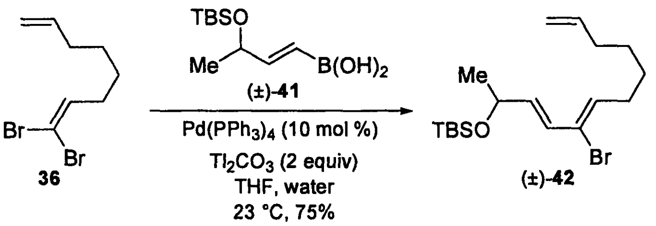
dehydrobromination to the bromoalkyne at elevated temperature with subsequent cross-coupling, a pathway that may result from a slow rate of transmetalation.[22]

In preparation for Suzuki cross-coupling,[26] boronate **40** and boronic acid **41** were prepared from silyl ether alkyne **39** via hydroboration[27] and subsequent hydrolysis[28] (Scheme 7). Use of the silyl ether allowed straightforward modification at C20 for



Scheme 7. Synthesis of boronate (±)-**40** and boronic acid **41**.

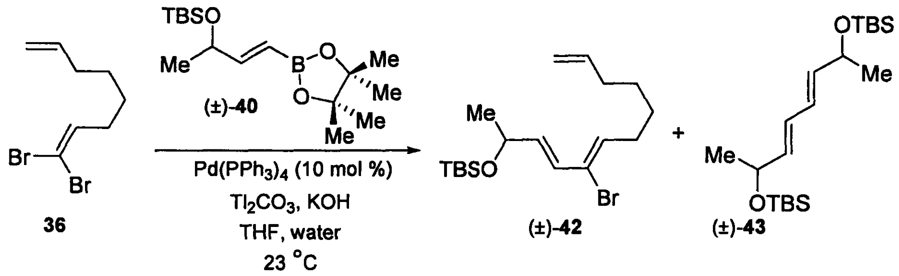
optimization of diene reactivity in the planned Diels-Alder cyclization. A variety of basic additives including potassium carbonate, potassium hydroxide, and thallium ethoxide were screened for a related model system, however these conditions generally required a large excess of the boronic acid and only produced moderate yields (15-50%). Ultimately, the Suzuki coupling of dihalide **36** with boronic acid **41** (1.1 equiv) utilizing tetrakis(triphenylphosphine) palladium with thallium carbonate (2 equiv) as the base in tetrahydrofuran-water smoothly provided desired vinyl bromide **42** in 75% yield (Scheme 8).[29,30] Later work performed by Meiliana Tjandra, in an effort to reduce the amount of



Scheme 8. Synthesis of bromodiene **42** via thallium carbonate mediated Suzuki cross-coupling.

thallium reagent required in favor of the less toxic potassium hydroxide, provided no overall improvement in reaction yield and also produced unwanted dimerization of the boronate (Table 1).[18] Use of the highly reactive catalyst system recently reported by Buchwald employing the SPhos ligand and palladium acetate likewise produced a 1:1 mixture of the desired vinyl bromide **42** and dimer **43**.[18,31]

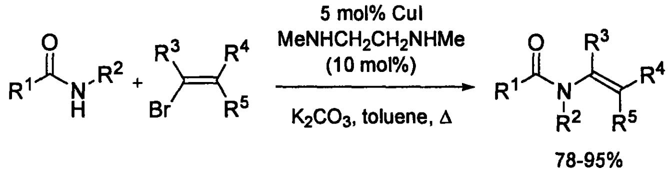
Table 1. Suzuki coupling optimization for reduction of thallium carbonate (Meiliana Tjandra).[18]



entry	Tl_2CO_3	KOH	yield, ratio, **42**:**43**[a]
1	1	none	70%, 3:1
2	0.5	1.5	59%, 2:1
3	0.25	1.75	39%, 1:1
4	0.1	1.9	19%, 1:1
5	0.1	4	38%, 1:1

[a] Ratios determined by ^1H NMR.

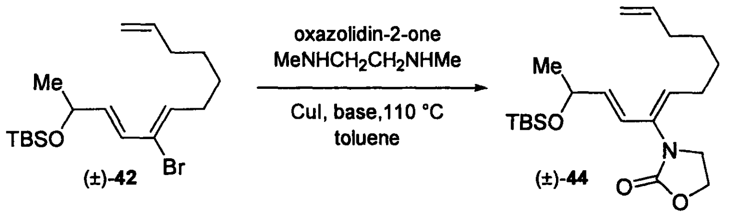
With vinylhalide **42** in hand, installation of the desired *N*-acyl group to the diene was addressed. While there is precedent for successful Diels-Alder cycloaddition in the presence of 2-bromo-1,3-dienes,[30] early Diels-Alder studies utilizing this functional group resulted in decomposition of the starting triene. In the event, successful introduction of a vinyl carbamate served a critical role in not only providing a robust *N*-acyl 2-aminodiene for the planned intramolecular type I Diels-Alder reaction, but also proved a highly effective strategy for masking the C16-carbonyl during subsequent manipulations. Recent work by Buchwald has outlined an efficient method for copper–catalyzed coupling of vinyl halides with various amide derivatives as outlined in Scheme 9.[32] Amination of vinyl bromides was optimal with cyclic amides, catalytic copper iodide with *N*,*N*-dimethylethylenediamine



Scheme 9. Buchwald's copper-catalyzed amination of vinyl halides.[32]

as the ligand at high concentration and elevated temperature. Our examination of the amidation of bromodiene **42** with excess oxazolidin-2-one is outlined in Table 2. Early work

Table 2. Optimization of the copper-catalyzed amination of bromodiene **42** with oxazolidin-2-one.

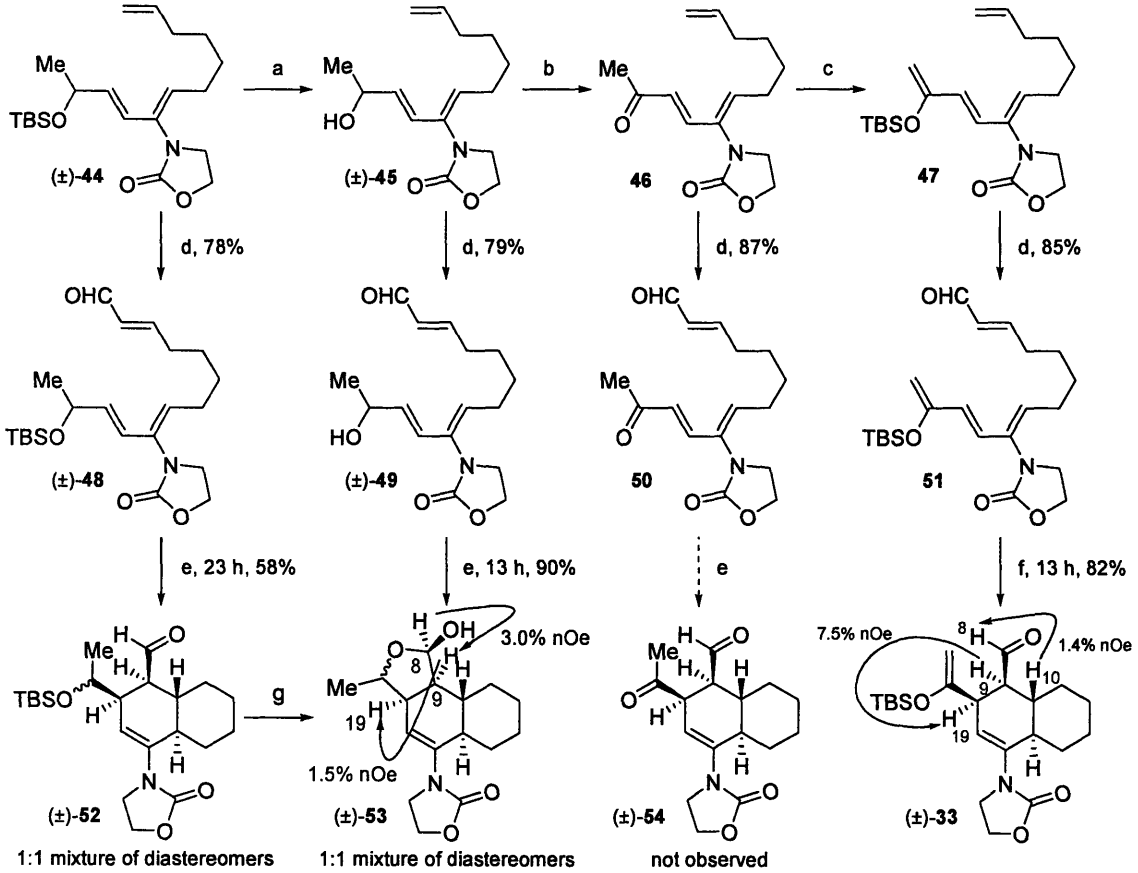


entry	oxazolidinone	concentration	base, equiv	equiv CuI	equiv diamine	time, yield
1	5.0	0.1 M	K_2CO_3, 8.0	0.2	0.4	no reaction
2	5.0	0.1 M	Cs_2CO_3, 8.0	0.2	0.4	no reaction
3	1.2	1 M	K_2CO_3, 2.0	0.2	1.0	18 h, 17%
4	2.2	0.25 M	Cs_2CO_3, 1.5	1.0	2.0	42 h, 37%
5	4.0	0.25 M	Cs_2CO_3, 4.0	1.0	2.0	42 h, 52%
6	3.0	0.5 M	K_2CO_3, 3.2	1.0	2.0	6 h, 12%
7	1.2	1 M	K_2CO_3, 2.0	1.0	5.0	1 h, alkyne
8	1.2	1 M	K_2CO_3, 2.0	0.5	2.5	20 h, 71% (<5%, alkyne)
9	1.2	0.25 M	K_2CO_3, 2.0	0.5	2.5	21 h, 95%

indicated that lower levels of copper iodide (20 mol%) provided low conversion, even at high concentration (Table 2, entries 1-3). Stoichiometric amounts of copper iodide improved the reactivity of the system, however extended reaction times produced only moderate yields (12-52%, Table 2, entries 4-6). Performing the reaction at higher concentration resulted in dehydrobromination to form the corresponding alkyne (Table 2, entry 7). Ultimately, use of 50 mol% of copper iodide with 250 mol% of the diamine ligand and potassium carbonate as the base was found to produce the desired product in reasonable yield (Table 2, entry 8).

Given the heterogeneous nature of the reaction mixture, slightly more dilute conditions were found to be optimal, allowing for better mixing and preventing unwanted alkyne formation to afford the desired *N*-acyl 2-aminodiene **44** in 95% yield (Table 2, entry 9).

Successful installation of the *N*-acyl group was followed by modification of the functional group at C20 moiety in order to optimize diene reactivity for *trans*-decalin formation via an intramolecular Diels-Alder cyclization.[33] Incorporation of the dieneophile would then allow access to various Diels-Alder precursors, where the desired oxidation state at C20 would be obtained via conversion of the cyclized products. Desilylation of C20-silyl ether **44** to the corresponding C20-alcohol and subsequent conversion to the C20-ketone and C20-silyl enol ether proceeded in excellent yield to produce *N*-acyl 2-aminodienes



(a) TBAF, THF, 95%. (b) MnO_2, CH_2Cl_2, 92%, (c) TBSOTf, NEt_3, CH_2Cl_2, -78 °C, 93%. (d) acrolein, 4,5-DihydroIMesCl_2Ru=CH(*o*-O^{i}Pr)Ph (10 mol%), CH_2Cl_2, 23 °C, (>20:1 *E/Z*). (e) benzene, 90 °C, (>20:1 *endo:exo*). (f) toluene, 90 °C, (>20:1 *endo:exo*). (g) TBAF, THF, not isolated (^{1}H NMR analysis).

Scheme 10. Synthesis and thermal Diels-Alder cycloaddition of trienes **48-50** and tetraene **51**.

45, **46**, and **47**, respectively (Scheme 10). Generation of the activated dienophile was achieved via olefin cross-metathesis of the terminal C9-C10 alkene with acrolein. External activation of the dienophile should selectively provide the desired *trans*-fused decalin system on cycloaddition.[34] The recent development of well-defined, air-stable, highly reactive ruthenium catalysts such as **55**, **56**, and **57** has provided an expedient route to functionalized alkenes from simple alkenes via cross-metathesis (Figure 7).[35] Recent work by Grubbs has demonstrated the successful, *E*-selective installation of α,β-unsaturated carbonyl compounds via cross metathesis with terminal alkenes.[36] Of the metathesis catalysts examined for the cross metathesis of terminal alkenes **44-47**, the Grubbs-Hoveyda G2 catalyst **57**[37] proved the most effective, providing the desired enals **48-51** in good yield with excellent *E*:*Z* selectivity (>20:1) (Scheme 10). The exceptional reactivity of catalyst **57** allowed the metathesis to proceed rapidly at ambient temperature, a feature vital for successful formation of the highly air- and temperature-sensitive silyl enol ether tetraene product **51**.

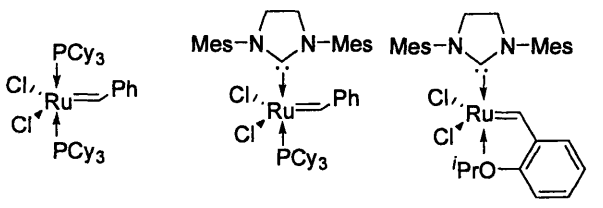
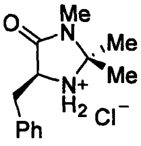


Figure 7. Representative ruthenium alkylidene catalysts for cross-metathesis.

In approaching the planned intramolecular Diels-Alder cycloaddition, we initially envisioned eventual application of chiral catalysis for enantioselective formation of the desired bicycle.[38] Thus far, efforts for Lewis acid catalysis of triene **48** cycloaddition with lanthanide triflates (scandium ($Sc(OTf)_3$ and ytterbium ($Yb(OTf)_3$)) have resulted in low yields of the desired products and decomposition of the precursor. Fortunately, heating the C20-silyl ether and C20-alcohol trienes **48** and **49** in benzene at 90 °C cleanly effected the desired cyclization in moderate to good yield (Scheme 10). In each case the desired *endo* cyclization was observed exclusively to provide the required *trans*-decalin system as a 1:1 mixture of diastereomers at C20. The slower reaction rate of silyl ether diene **48**, compared to that of alcohol **49**, likely results from steric congestion due to the bulky silyl alkyl substituents. Cyclization of triene **49** directly afforded the corresponding tricyclic hemiacetal

53 formed from the proximal C20-alcohol and C8-aldehyde. Deprotection of bicycle **52** en route to keto-aldehyde **54** via subsequent oxidation also produced acetal **53**. High diastereoselectivity for acetal formation was observed in both cases, providing (8*R*,9*S*) relative stereochemistry about the acetal center (Scheme 10), however further conversion to the keto-aldehyde **54** failed. Direct access to the keto-aldehyde bicycle was then envisioned via cyclization of the trienal **50**. Monitoring of the thermal Diels-Alder cyclization of ketodiene **50** by ^{1}H NMR suggested initial cycloaddition accompanied by further reaction, possibly due to internal aldol condensation with the C8-aldehyde. Extended exposure to the reaction conditions resulted in the decomposition, and neither the keto-aldehyde nor the putative tricyclic aldol product could be successfully isolated. Alternatively, analysis of triene **50** suggested the use of an organocatalyst such as MacMillan's imidazolidinone **58** for formation of an intermediate chiral iminium ion and subsequent diastereoselective synthesis of the desired ketone bicycle **54** (Figure 8).[39] Unfortunately, use of organocatalyst **58** as well as the achiral lanthanide scandium triflate resulted in decomposition and polymerization of triene **50**.

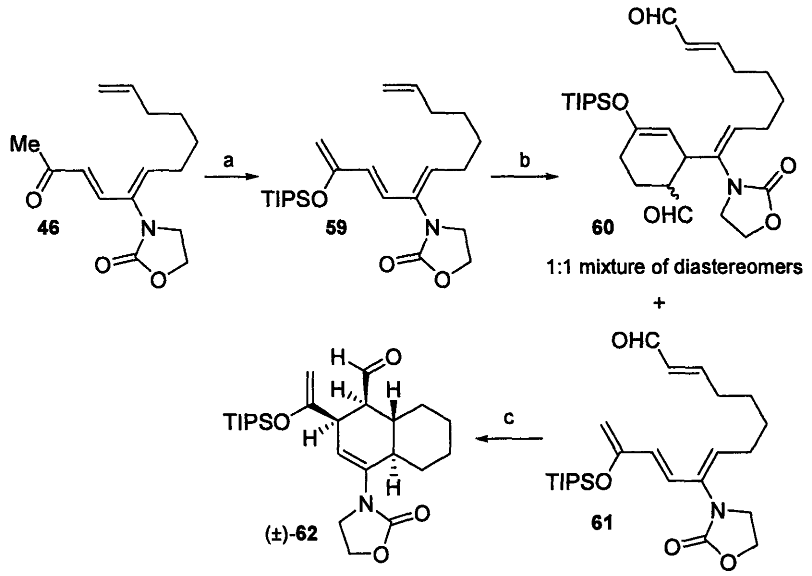


58

Figure 8. MacMillan's imidazolidinone organocatalyst **58**.

Ultimately, a silyl enol ether at C20 was found to provide the required diene reactivity for the cycloaddition and prevent undesired interaction with the neighboring C8-aldehyde. Heating a solution of tetraenal **51** in toluene at 90 °C afforded the desired *trans*-decalin aldehyde **33** with high *endo*-selectivity (>20:1 *endo*:*exo*), providing gram–quantities of this key building block in racemic form. The relative stereochemistry of the bicycle was indicated by nOe correlations between the C10-C8 and C9-C19 methines (Scheme 10), and later confirmed by X-ray crystal analysis of an advanced derivative, *vide infra*. Additionally, the silyl enol ether thus installed effectively masked the ketone from undesired reactivity during fragment coupling and provided a reactive handle for later formation of the C ring.

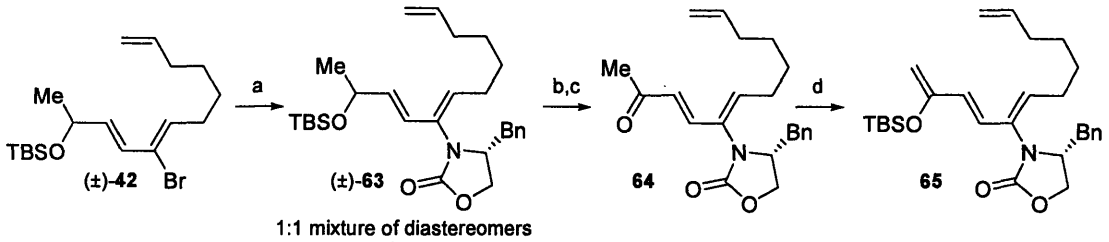
Access to optically active bicycle **33** was envisioned via asymmetric catalysis, however the sensitivity of the ^{t}butyl dimethylsilyl enol ether tetraenal **51** to polymerization and decomposition has thus far precluded the use of chiral catalysts. Preparation of the more bulky triisopropyl silyl enol ether at C20 was undertaken in an attempt to circumvent this sensitivity by providing a more stable tetraenal (Scheme 11). Interestingly, olefin cross-metathesis of precursor tetraene **59** also resulted in an unexpected Diels–Alder cycloaddition of the silyl enol ether diene with acrolein to produce the substituted cyclohexene **60** as a mixture of diastereomers. Unfortunately, the triisopropylsilyl enol ether tetrenal **61** did not provide the desired decalin with the same level of efficiency as the ^{t}butyldimethylsilyl enol ether **51** (Scheme 11).



(a) TIPSOTf, NEt_3, CH_2Cl_2, -78 °C, 83%. (b) acrolein, 4,5-DihydroIMesCl_2Ru=CH(*o*-^{i}PrO)Ph (10 mol%), CH_2Cl_2, 23 °C, 70% **61**, 5% **60**. (c) 90 °C, toluene, 26%, (>20:1 endo:exo).

Scheme 11. Synthesis of triisopropylsilyl enol ether tetraene **61** and bicycle **62**.

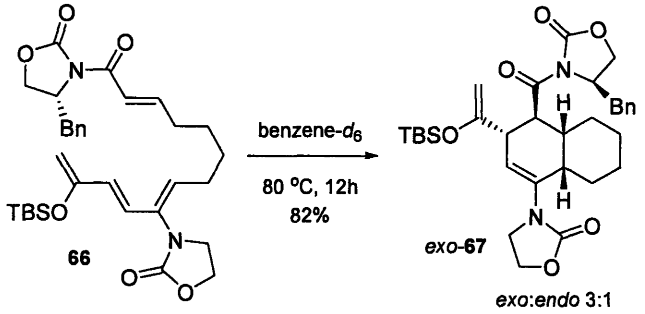
Further efforts to produce optically active bicycle **33** were focused on the incorporation of chiral auxiliaries.[40] Examination of the synthetic strategy immediately suggests incorporation of a chiral oxazolidinone during diene construction. Amination of bromodiene **42** with (*R*)-(+)-benzyloxazolidin-2-one according to our developed protocol provided the desired *N*-acyl diene **63** as a mixture of diastereomers at C20, albeit in low yield (Scheme 12). While access to C20-ketone **64** from this triene was straightforward,



(a) (R)-(+)-benzyloxazolidin-2-one, $MeNHCH_2CH_2NHMe$, CuI, K_2CO_3,110 °C, toluene, 21 h, 29%. (b)TBAF, THF, 76%. (c) MnO_2, CH_2Cl_2, 99%, (d) TBSOTf, NEt_3, CH_2Cl_2, -78 °C, <20%.

Scheme 12. Attempted synthesis of chiral tetraene **65**.

formation of the required C20-silyl enol ether **65** returned primarily unreacted ketone. Examination of ketone **64** suggests that the steric bulk of the benzyl substituent may force the oxazolidinone carbonyl out of diene conjugation, resulting in competing reactivity during formation of the silyl enol ether. Installation of a chiral oxazolidinone at C8 was also undertaken by Meiliana Tjandra in an effort to provide enantioenriched bicycle (Scheme 13).[18,40d,e] Unfortunately, catalysis of the cycloaddition was unsuccessful,

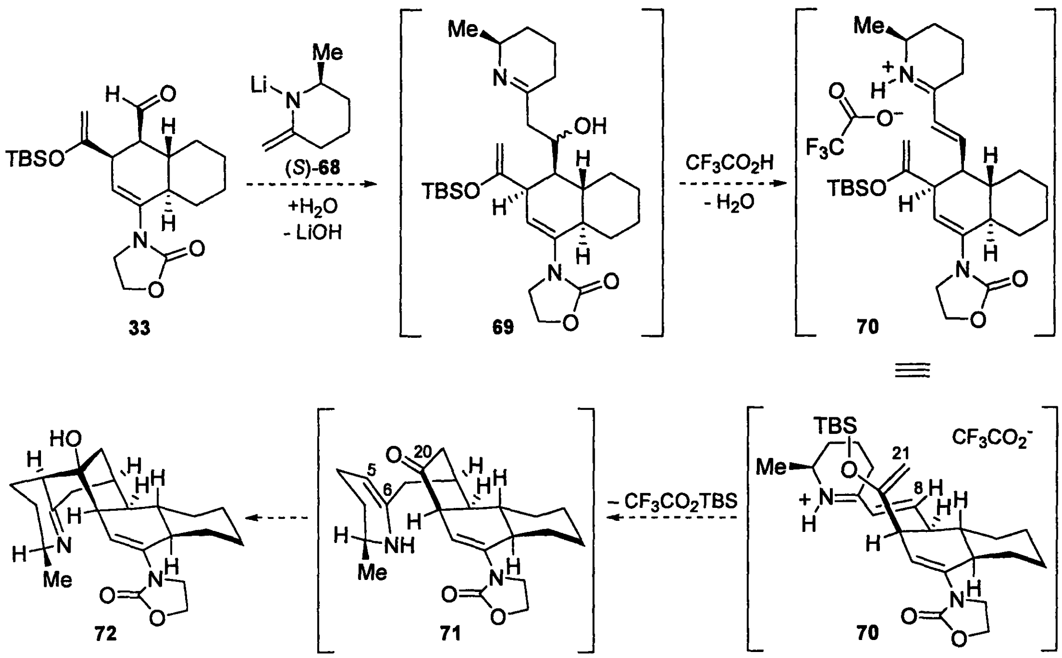


Scheme 13. Diels-Alder cycloaddition with chiral dienophile **66** (Meiliana Tjandra).[18]

while heating tetraene **66** at 90 °C in toluene produced a mixture of *exo*- and *endo*-products, with the undesired *exo*-product **67** predominating. Although an optically active bicycle would allow direct access to a single enantiomer of future intermediates, ultimately future work focused on the fragment coupling of the readily prepared racemic bicycle **33** with an optically active chiral E ring. Subsequent diastereomer separation provided the optically active target compound, while use of either hand of the chiral fragment proved an expedient route to both enantiomers of advanced intermediates and target alkaloid **2**.

Exploration of CDE ring synthesis: A C2 desmethyl model system.

With racemic bicycle **33** in hand, fragment coupling with the piperidine E ring was addressed. Inspired by possible biomimetic transformations, we envisioned a potential cascade cyclization for formation of the pentacyclic ring system as described in Scheme 14.

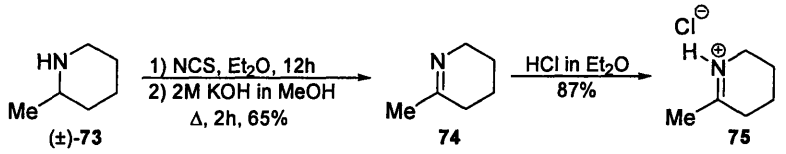


Scheme 14. Our proposed cascade mechanism for the condensation of bicycle **33** and metalloenamine **68** and acid-catalyzed formation of pentacycle **72**.

Addition of chiral metalloenamine **68** to the bicycle would provide β-hydroxyimine **69**, which would then undergo acid-catalyzed elimination to provide the α,β-unsaturated iminium **70**.[41] Conjugate addition of the reactive C21-silyl enol ether at C8 of the iminium **70** would then provide the tetracyclic ketone **71**, which would provide the desired pentacycle **72** and its C2-*epi* enantiomer via C5-C6 enamine addition to the C20-ketone as proposed in the biogenetic analysis of the CDE ring system.

Although our final synthetic strategy involved incorporation of an optically active piperidine ring fragment, initial reaction optimization utilized a system lacking the C1 methyl group in order to simplify reaction monitoring and data analysis by avoiding mixtures of diastereomers at intermediate stages. 6-Methyl-2,3,4,5-tetrahydropyridine **74** was prepared according to literature procedure from 2-methyl-1-piperidine **73** via dehydrohalogenation of the corresponding *N*-chloropiperidine with potassium hydroxide in methanol at reflux

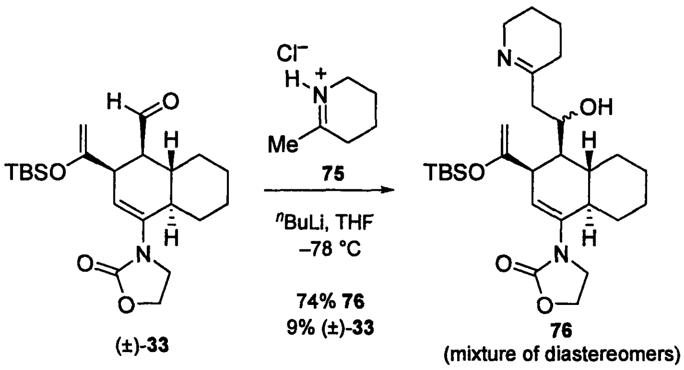
(Scheme 15).[42] While bulb-to-bulb distillation provided the pure imine **74**, polymerization



Scheme 15. Synthesis of iminium salt **75** (Dr. Bin Chen, Meiliana Tjandra, Diana K. Hunt).[18,43]

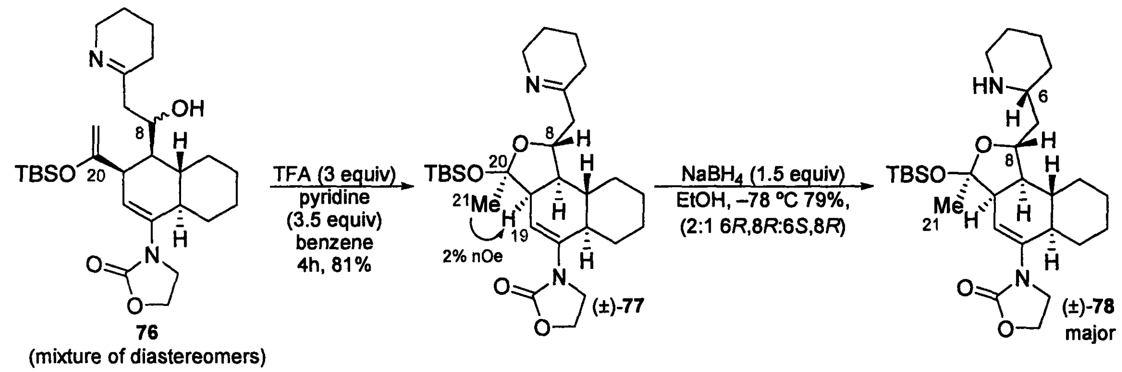
and decomposition was observed on storage. Dr. Bin Chen in our laboratory has successfully prepared the more robust chloride salt **75** on multi-gram scale by treatment of the free imine with hydrochloric acid, followed by trituration from tetrahydrofuran and rigorous drying.[43] Iminium chloride **75** was highly hygroscopic and required handling under inert atmosphere for optimal results.

Fragment coupling with bicycle **33** was achieved via condensation of the C8-aldehyde with the metalloenamine of imine salt **75**. Although lithiation and transmetalation routes involving cerium and magnesium were explored,[18] direct use of the lithiated imine at low temperature provided optimal results, affording the desired β-hydroxyimine **76** in 74% as a mixture of diastereomers at C8 (Scheme 16). Careful control of reaction temperature was



Scheme 16. Condensation of bicycle **33** with iminium salt **75**.

required to avoid undesired addition to the vinyl oxazolidinone carbonyl. With β-hydroxyimine **76** in hand, implementation of our proposed cascade cyclization for formation of the CDE ring system was undertaken. As outlined in Scheme 14, exposure of the β-hydroxyimine **76** to acidic conditions was expected to provide the α,β-unsaturated iminium ion, followed by cascade cyclization to provide the pentacyclic skeleton. Surprisingly, exposure of the diastereomeric mixture **76** to a mixture of trifluoroacetic acid and pyridine in benzene resulted in rapid cyclization of the C8-hydroxyl onto C21 of the silyl enol ether to give a single diastereomer of imine-acetal **77** (Scheme 17). The relative stereochemistry at



Scheme 17. Cyclization of β-hydroxyimine **76** to imine acetal **77** and reduction to amine acetal **78**.

C20 was obtained via nOe correlation of the C21 methyl protons and the C19 methine (Scheme 17). Subsequent reduction of imine-acetal **77** with sodium borohydride in ethanol[44] at low temperature provided the corresponding amino-acetal **78** as a mixture of diastereomers at C6 (2:1, relative stereochemistry: (6*R*,8*R*):(6*S*,8*R*), diastereomeric mixture, Scheme 17). X-ray crystallographic analysis of the major diastereomer established the relative stereochemistry of the acetal as shown and confirmed the *endo*-configuration of the *trans*-decalin system formed in the earlier Diels-Alder cyclization (Figure 9).

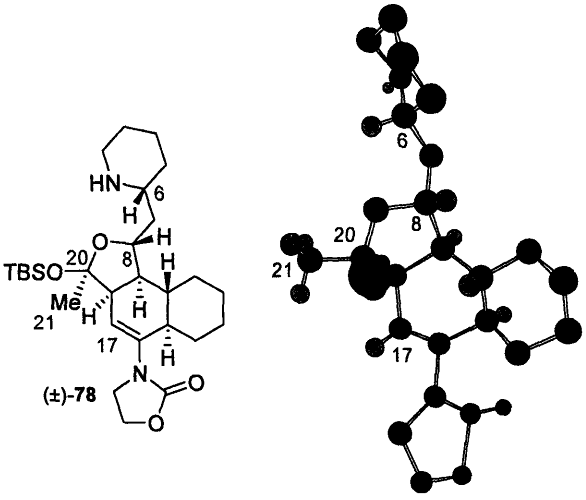
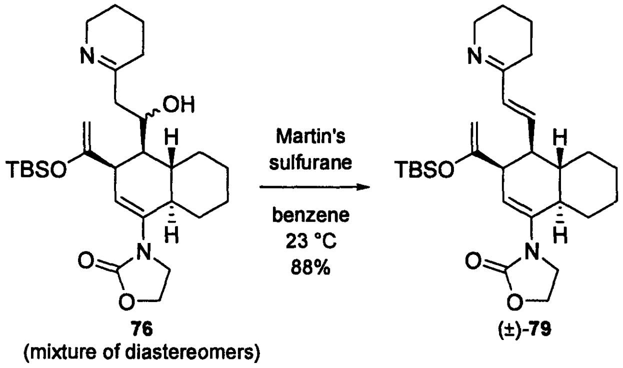


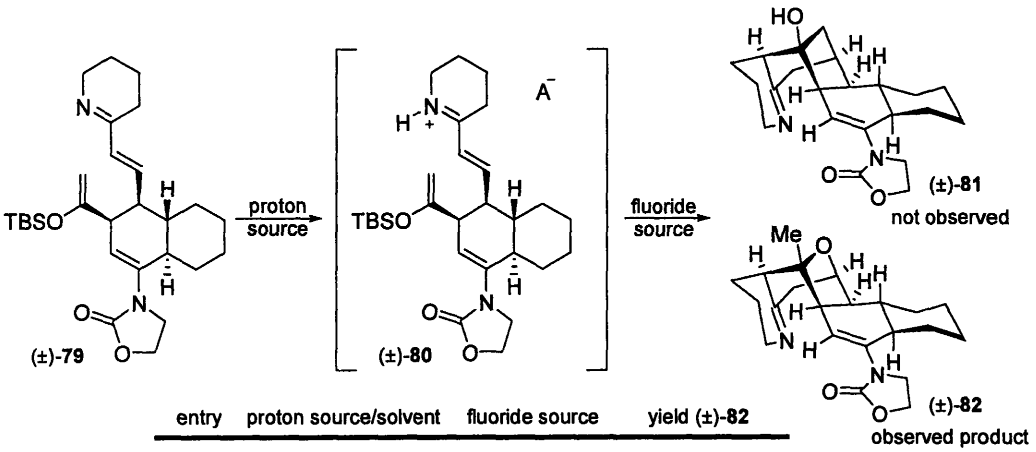
Figure 9. Chem3D representation of the X-ray crystal structure of amine acetal (±)-**78**. Silyl alkyl groups and methylene hydrogens have been omitted for clarity.

Subsequent efforts to obtain the α,β-unsaturated imine utilized chemical methods for the dehydration. While use of Burgess reagent[45] required elevated temperatures incompatible with the sensitive conjugated product, introduction of a benzene solution of Martin sulfurane[46] to the diastereomeric mixture of β-hydroxyimines **76** in benzene provided the desired *E*-alkene **79** cleanly in twenty minutes at ambient temperature (Scheme 18). Protonation of imine **79** was readily achieved with trifluoroacetic acid and pyridine in benzene,[47] however further reactivity was not observed, and heating of the mixture resulted in decomposition of the sensitive silyl enol ether. Subsequently, activation the silyl enol ether via nucleophilic catalysis was explored.[48] Where possible, deuterated solvent was used and reaction progress was monitored directly by ^{1}H NMR spectral analysis of the reaction mixture. Electophilic activation of the imine by protonation with either trifluoroacetic acid or nonafluoro ^{t}butyl alcohol was followed by addition of a fluoride source to effect the Mukaiyama aldol-Michael addition (Table 3). Work by Carriera has demonstrated the use of tetrabutylammonium triphenyldifluorosilicate (TBAT) for nucleophilic catalysis of Mukaiyama aldol reactions.[49] Unfortunately, exposure of silyl enol ether **79** to TBAT in the presence of either proton source resulted in decomposition of the substrate (Table 3, entries 1, 2). Surprisingly, silyl enol ether activation with triethylamine trihydrofluoride effected conjugate addition of the unmasked C20-oxygen, which was followed by C5-C6-enamine addition to the resulting C20-oxonium of intermediate **83** to



Scheme 18. Dehydrogenation of β-hydroxyimine **76** with Martin sulfurane.

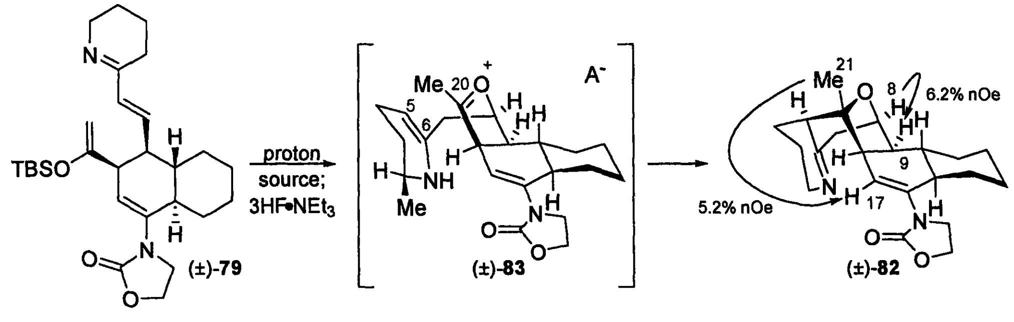
Table 3. Attempted electrophilic/nucleophilic activation of imine **79** for Mukaiyama-Michael reaction.



entry	proton source/solvent	fluoride source	yield (±)-**82**
1	TFA, pyridine-d^5 THF	TBAT*	decomposition
2	$(CF_3)_3COH$ benzene	TBAT*	decomposition
3	TFA, pyridine-d^5 benzene-d^6	$3HF \bullet NEt_3$	<10%
4	TFA, pyridine-d^5 THF	$3HF \bullet NEt_3$	60%
5	none/THF	$3HF \bullet NEt_3$	73%

*Tetrabutylammonium triphenydifluorosilicate

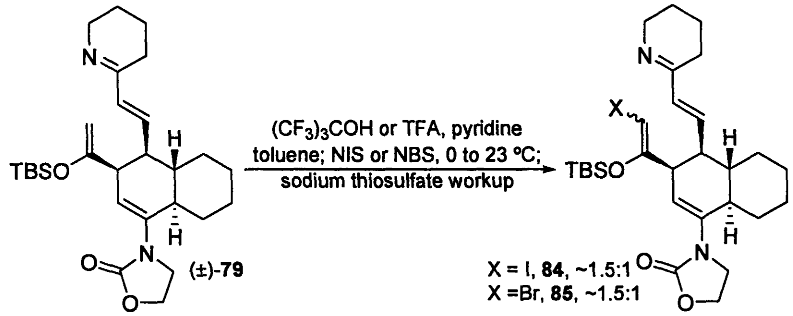
provide the air-sensitive ether imine **82** as a single diastereomer (Scheme 19; Table 3, entries 3-5). The presence of the methyl substituent was confirmed by ^{13}C DEPT-135 NMR and 2D-HSQC correlation spectra. The relative stereochemistry about the tetrohydrofuran ring was determined via nOe correlations for the C8-C9 and C21-C17 protons (Scheme 19).



Scheme 19. Formation of pentacyclic ether **82** from tricycle **79**.

This rapid cascade cyclization was observed with and without imine activation via an added proton source (Table 3, Entry 5). The preferred reactivity of the C20-oxygen to form oxonium **83** is likely due to a non-optimal orientation of the bulky C20-^{t}butyldimethylsilyl enol ether for conjugate addition (see **70**, Scheme 14). While disappointed at the failure to produce the desired carbocyclic C-ring, we were encouraged by the high diastereoselectivity of the transformation and the demonstrated reactivity of the enamine toward cyclization. These observations supported our proposal that the *trans*-decalin framework was capable of exerting stereocontrol in construction of the unique CDE ring system of the complex galbulimima alkaloids.

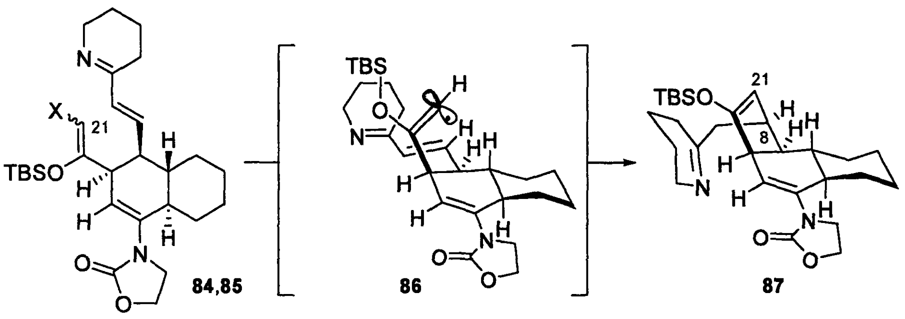
An alternative route for C ring formation via a radical cyclization strategy was then explored. We envisioned exploitation of the silyl enol ether of **79** to produce the corresponding α-halo ketone,[50] with subsequent free-radical cyclization onto the α,β-unsaturated imine to provide the desired five-membered carbocyclic C ring. Initial treatment of silyl enol ether **79** with *N*-iodosuccinimide (NIS) and sodium carbonate in tetrahydrofuran[51] resulted in *N*-iodination of the piperidine imine,[52] a process readily reversed by treatment with tributyltin hydride. Subsequent halogenation conditions relied on protonation of the imine with either nonafluoro-^{t}butyl alcohol or trifluoroacetic acid in the presence of pyridine to engage the imine prior to addition of either NIS or *N*-bromosuccinimide (NBS), respectively at 0 °C in toluene (Scheme 20). Interestingly, halogenation did not produce the corresponding α-halo ketone,[53] providing the silyl enol ether vinyl halides **84** and **85** as mixtures of regioisomers (~1.5:1). Excess halogenation, ostensibly at the imine nitrogen, occurred to a lesser extent. Reversion of the dihalo compounds to the C21-halogenated products was observed on exposure to a sodium thiosulfate workup or tributyltin hydride and gentle heating.[54] As attempted purification, extended storage, or exposure to light resulted in decomposition of the sensitive vinyl



Scheme 20. Formation of silyl enol ether vinyl halides **84** and **85**.

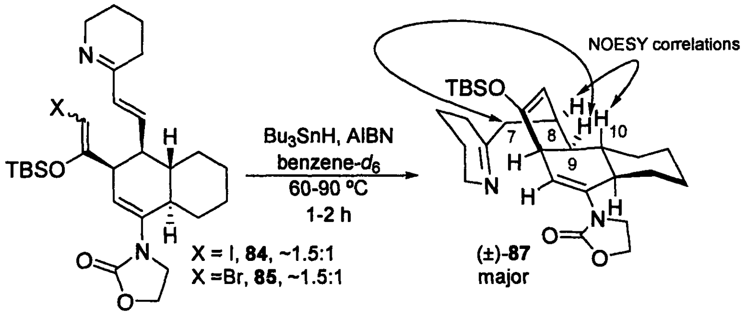
halides, crude iodide **84** and bromide **85** were treated to either a sodium thiosulfate workup or rapid filtration through silica gel to remove excess halosuccinimide and used immediately in the subsequent radical cyclization.

Despite a lack of precedent for the use of silyl enol ether vinyl halides for radical cyclization,[55] we envisioned that successful generation of a free-radical at C21 would result in rapid intramolecular 5-exo-trig vinyl-radical cyclization onto C8 of the α,β-unsaturated imine (Scheme 21).[56] Exposure of crude iodide **84** to tributyltin hydride with catalytic 2,2'-azobis(2-methylpropionitrile) (AIBN, 0.05-0.1 equiv) as the radical initiator and subsequent heating from 60 to 90 °C provided a single tetracyclic product **87**, albeit in low overall yield (two steps, Table 4, entries 1-3). Deuterated solvent was used to facilitate direct monitoring of the reaction mixture by ^{1}H NMR spectral analysis. NOESY experiments performed by my co-worker Meiliana Tjandra indicated key correlations between the C7-C9 and C8-C10 methines, indicating the desired 8*R*,9*S* relative stereochemistry about the newly formed C8 stereocenter (Table 4). Use of higher levels of initiator in an effort to improve the overall yield produced an inseparable and unidentified impurity (Table 4, entries 4, 5). Application of these catalytic conditions to vinyl bromide **85** failed to effect the radical cyclization (Table 4, entry 6,7). After some experimentation it was discovered that sequential addition of stoichiometric AIBN was required for effective cyclization of substrate **85** (Table 4, entries 8-10), while the quality of the crude vinyl halide influenced the overall yield. Ultimately, revisitation of the halogenation conditions revealed that bromination in the presence of excess sodium bicarbonate with freshly purified NBS, followed by exposure to tributyltin hydride (4.5 equiv) with portionwise addition of an excess of AIBN (1.5 equiv)



Scheme 21. Proposed 5-exo-trig vinyl radical cyclization of vinyl halides **84,85**.

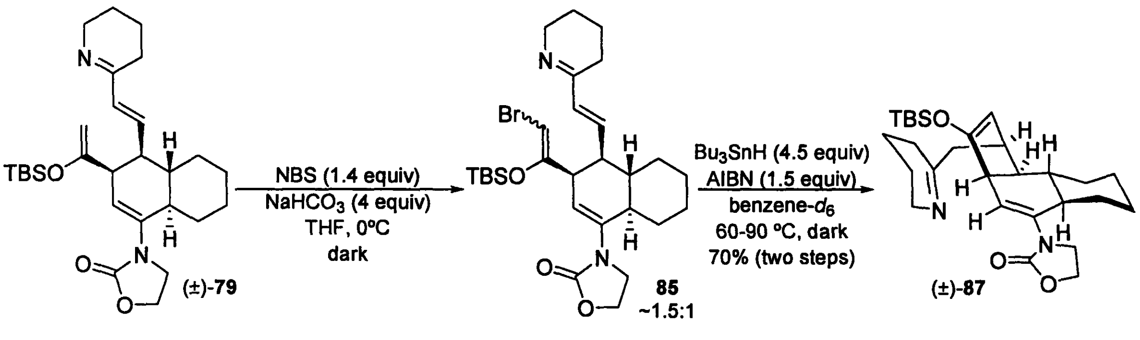
Table 4. Intramolecular vinyl radical cyclization with vinyl iodide **84** and vinyl bromide **85**.



X = I			X = Br		
Entry	equiv AIBN	yield (two steps)	Entry	equiv AIBN	yield (two steps)
1	0.1 (x2)	23%	6	0.1	decomposition
2	0.05	40%	7	0.1[c]	decomposition
3	0.1	30%	8	1.0	decomposition
4	0.2	~33%[a]	9	1.0[d]	35%
5	0.3	~50%[b]	10	1.0[e]	44%

[a] 3:1 **87**:unidentified diastereomer [b] 8:1 **87**:unidentified diastereomer [c] sequential addition, 2 portions. [d] sequential addition, 4 portions. [e] sequential addition, 2 portions.

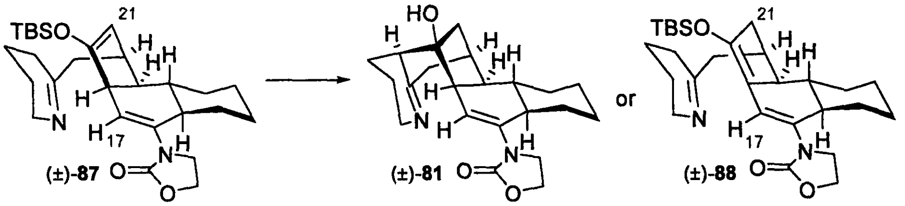
and heating at 90 °C over 1.5 hours provided a single diastereomer of tetracycle **87** in good yield over the two steps (Scheme 22).



Scheme 22. Optimized conditions for vinyl bromide formation and vinyl radical cyclization for construction of tetracycle **87** from tricycle **79**.

With successful diastereoselective introduction of the C-ring, final construction of the CDE-ring framework was undertaken. Earlier formation of pentacyclic ether **82** suggested that unmasking of the ketone at C20 of tetracycle **87** would result in the desired C5-C6 enamine addition, consistent with our proposed biosynthesis (Scheme 14). Treatment of silyl enol ether **87** with acetic acid in benzene or gentle heating with scandium triflate in methanol resulted in decomposition (Table 5, entries 1,2). Exposure to trifluoroacetic acid in benzene-d_6 produced the silyl enol ether tautomer **88** as observed by direct ^{1}H NMR spectral analysis of the reaction mixture (Table 5, entry 3). These data indicated the disappearance of the C21-vinyl methine resonance and a downfield shift of the C17-vinyl methine peak, consistent with the conjugated diene of **88**. Gratifyingly, we discovered that treatment of silyl enol ether **87** with either tetrabutylammonium fluoride or triethylamine-trihydrofluoride in tetrahydrofuran at ambient temperature smoothly effected the deprotection and addition, directly providing the pentacycle **81** as a single diastereomer (Table 5, entries 4,5).[54] Isolation of compound **81** was hampered by the extreme air-sensitivity of the strained cyclic imine. Direct diastereoselective reduction of the imine was then effected on the crude mixture with sodium borohydride in ethanol at 0 °C following removal of the volatiles from the cyclization reaction. While the resulting amine was air-stable, successful purification of the highly polar amino-alcohol was problematic. Ultimately, a four-step, one-pot synthesis was developed, wherein following reduction of the C6-imine the excess hydride was quenched with ethanolic hydrochloric acid, the mixture was neutralized with triethylamine,

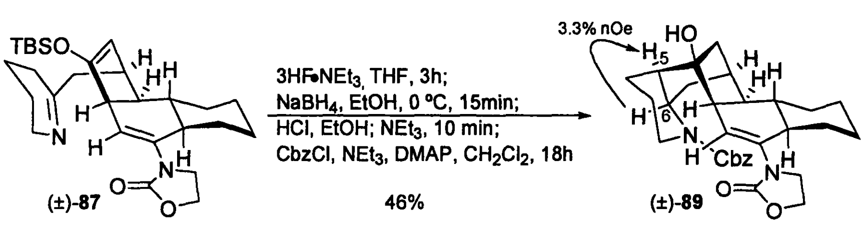
Table 5. Attempted formation of pentacycle **81**.



entry	conditions	temp, time	result
1	acetic acid-d_4, benzene-d_6	23 °C, 24h	decomposition
2	Sc(OTf)$_3$ (0.2 equiv) MeOH	23-50 °C, 21h	decomposition
3	TFA, benzene-d_6	23 °C, 1h	(±)-**88**, 67%
4	TBAF, THF	0-23 °C, 20min	(±)-**81** observed[a]
5	3HF•NEt$_3$ THF	23 °C, 3h	(±)-**81** observed[a]

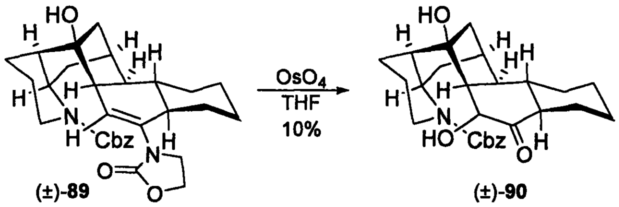
[a] Decomposed on attempted purification.

the volatiles were removed, and the crude amine exposed to benzylchloroformate in methylene chloride to provide the benzyl carbamate **89** as a single diastereomer in 46% overall yield (Scheme 23). A key nOe correlation between the C5 and C6 methines indicated that the required *cis*-stereochemistry at the piperidine ring juncture was achieved.



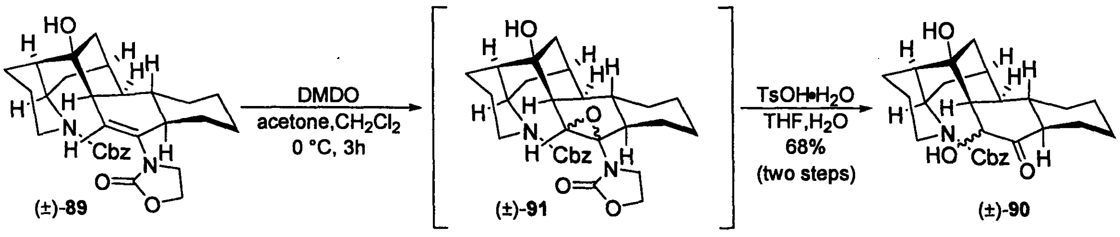
Scheme 23. One-pot synthesis of Cbz pentacycle **89** from tetracycle **87**.

With a robust route to pentacycle **89** in hand, final conversion of *N*-acyl alkene to the desired enone was addressed. Initial work exploited the reactivity of the C16-vinyl oxazolidinone to produce an α-hydroxy ketone, where subsequent dehydrogenation would provide the desired unsaturated carbonyl. Dihydroxylation of pentacycle **89** with osmium tetroxide[57] provided α-hydroxy ketone **90** as a single diastereomer, [58] however the yield was poor (Scheme 24). Alternatively, epoxidation with dimethyldioxirane(DMDO)[59] provided



Scheme 24. Oxidation of vinyl oxazolidinone **89** with osmium tetroxide.

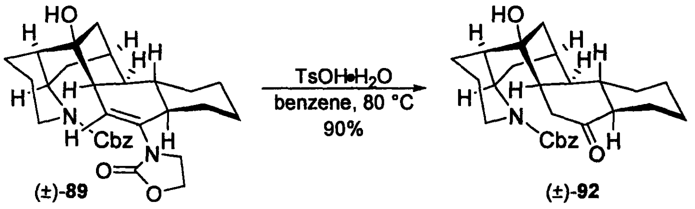
ketone **90** in moderate yield as a mixture of diastereomers following acid hydrolysis of the intermediate epoxide **91** (Scheme 25). Unfortunately, attempted dehydration of α-hydroxy



Scheme 25. Oxidation of vinyl oxazolidinone **89** with dimethydioxirane (DMDO).

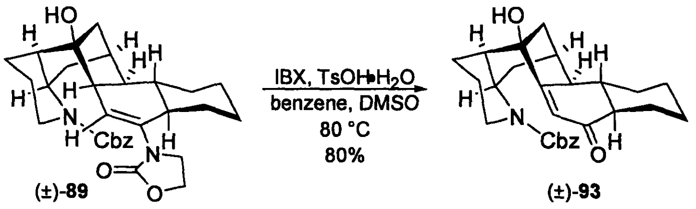
ketone **90** with either Martin sulfurane or via mesylation and elimination was unsuccessful. Subsequently, functionalization of the unmasked ketone was explored.

Recent work by Nicolau outlined a mild, efficient, one-pot conversion of unfunctionalized alcohols, aldehydes, and ketones to their α,β-unsaturated carbonyl counterparts with 2-iodoxybenzoic acid (IBX).[60] Addition of acid accelerated the process, supporting the hypothesis that the dehydrogenation proceeds through enolization followed by single electron transfer to IBX and subsequent rearrangement of the radical cation to provide the desired enone.[60b] Initial enone formation therefore takes place at the more enolizable site, although further unsaturation may be obtained through the use of excess reagent and extended reaction times. Hydrolysis of vinyl oxazolidinone **89** to the corresponding C16-ketone **92** was effected by gentle heating in the presence of *p*-toluenesulfonic acid (Scheme 26). While dehydrogenation of ketone **92** with IBX (2 equiv) in dimethylsulfoxide at 85 °C



Scheme 26. Hydrolysis of vinyl oxazolidinone **89**.

was sluggish,we were ultimately pleased to discover that direct conversion of the vinyl oxazolidinone **89** to enone **93** could be effected with a large excess of IBX (10-20 equiv) and *p*-toluenesulfonic acid (4 equiv) in a mixture of benzene and dimethylsulfoxide (3:4, [**89**] = 0.06 M) (Scheme 27). Direct ^{1}H NMR monitoring of the reaction in deuterated solvent

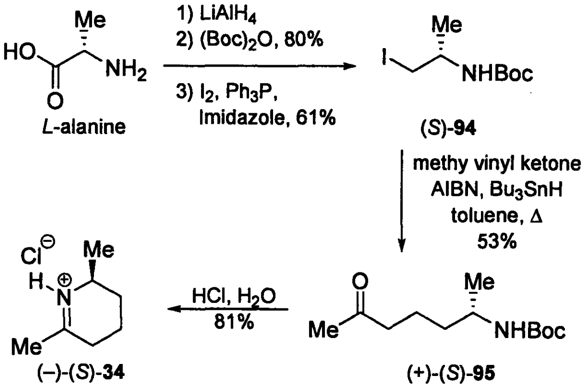


Scheme 27. One-pot hydrolysis and oxidation of vinyl oxazolidinone **89** to enone **93**.

indicated acid-assisted hydrolysis to the C16-ketone **92**, followed by oxidation to the desired enone.

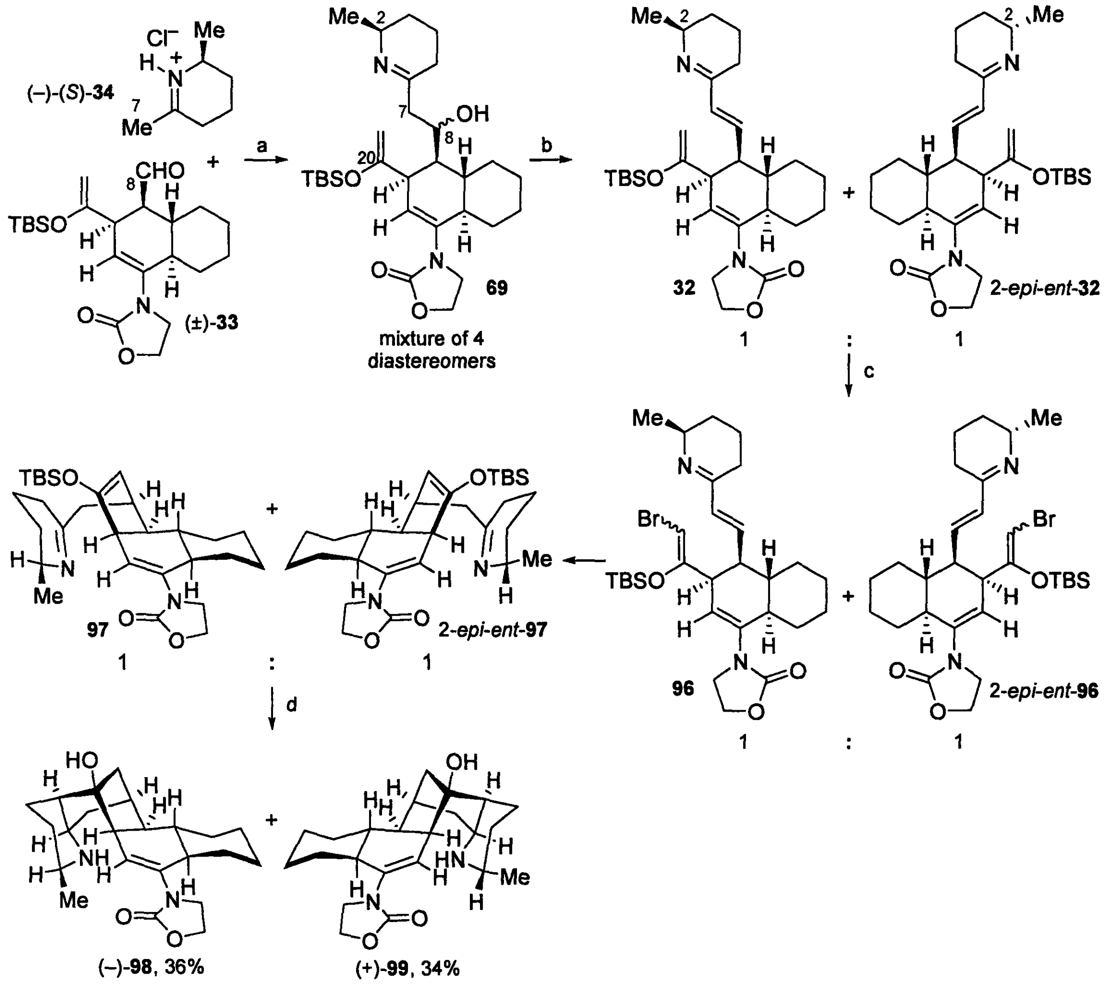
Synthesis of optically active (+)- and (–)-galbulimima alkaloid 13.

Having established a rapid and efficient route to racemic desmethyl pentacyclic model system **93**, application to the natural system was executed. Enantiomerically pure imine salts (*R*)- and (*S*)-**34** were prepared on multi-gram scale by Meiliana Tjandra from D- and L-alanine, respectively, via a five step procedure (Scheme 28).[18] Reduction of the acid and protection of the primary amine was followed by iodination to provide known alkyl halide **94**. Radical addition of methyl vinyl ketone introduced the remaining four carbon chain. Deprotection of linear ketone **95** to the primary amine with aqueous hydrochloric acid resulted in cyclization to produce the optically active piperidine imine salt (–)-(*S*)-**34** after trituration from tetrahydrofuran and rigorous drying. The optical activity of (–)-**34** was measured to be >99% ee by chiral HPLC analysis of the corresponding benzylated derivative. Use of either salt ((–)-(*S*)-**34** or (+)-(*R*)-**34**) in subsequent reaction sequences provided access to both enantiomers of the intermediates and target compounds.



Scheme 28. Synthesis of optically active imine salt 34 (Meiliana Tjandra).[18,61]

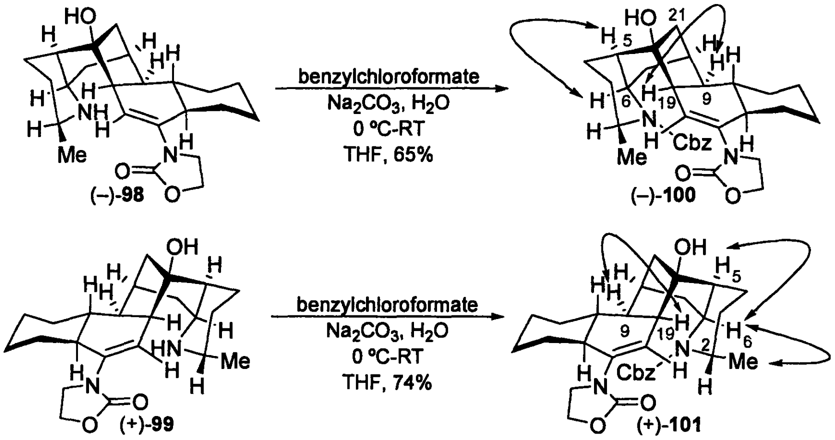
Following our optimized protocol, deprotonation of the iminium chloride (–)-(*S*)-**34** with ^{n}butyl lithium gave the corresponding lithiated enamine, which upon addition to a cold solution of racemic aldehyde **33** provided the corresponding β-hydroxy imine **69** in 85% yield as an inconsequential mixture of 4 diastereomers (Scheme 29). Dehydration using the Martin sulfurane reagent afforded the desired (7*E*)-α,β-unsaturated imine **32** and the



^{a}Conditions: (a) ^{n}BuLi, THF, –78 °C, 5 min, 85%. (b) Martin sulfurane, benzene, 23 °C, 81%. (c) NBS, NaHCO$_3$, THF, 0 °C; ^{n}Bu$_3$SnH, AIBN, benzene, 60 to 90 °C, 55% (2-steps). (d) Et$_3$N•(HF)$_3$, THF, 23 °C; NaBH$_4$, EtOH, 0 °C, 70% (2-steps).

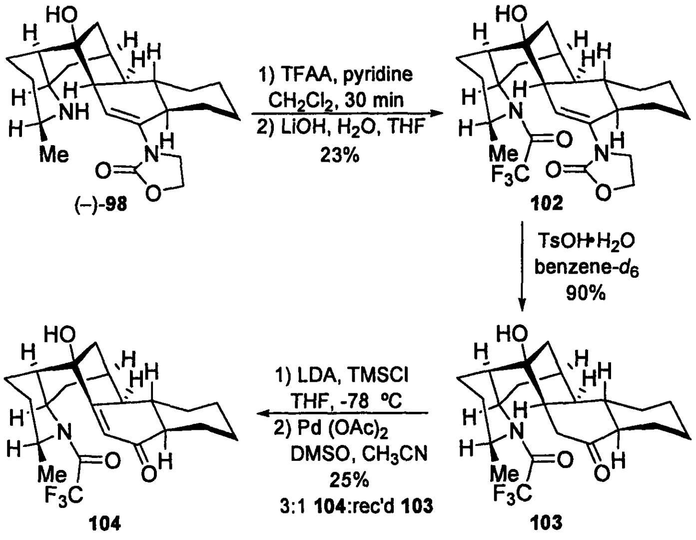
Scheme 29. Synthesis of pentacycles (–)-**98** and (+)-**99** from bicycle (±)-**33** and imine salt (–)-(*S*)-**34**.

corresponding 2-*epi*-enantiomer as an equal mixture of inseparable diastereomers in 81% yield. These diastereomers were carried forward together in the next two steps prior to their chromatographic separation. Conversion of the imines **32** and 2-*epi*-*ent*-**32** to the corresponding silyl enol ether vinyl bromides (Scheme 29, ~1:1.5 mixture of C20-olefin isomers) was followed by heating of the crude vinyl bromides with excess tributyltin hydride and sequential addition of AIBN to provide the desired tetracycle **97** along with the C2-*epi*-enantiomer in 55% yield over the two steps. Treatment of the enol ethers with triethylamine–trihydrofluoride, subsequent removal of the volatiles under reduced pressure, and introduction of sodium borohydride in ethanol resulted in the desired enamine-to-ketone addition and diastereoselective C6-imine reduction, cleanly affording the desired stable pentacyclic amines in a one-pot process (Scheme 29). At this stage the optically active pentacyclic amine (–)-**98** (36%) and the corresponding 2-*epi*-enantiomer, amine (+)-**99** (34%), were readily separated by flash column chromatography (Scheme 29). Formation of the corresponding benzyl carbamates (–)-**100** and (+)-**101** and detailed 2D-NMR analysis indicated that formation of the C8 stereocenter during the radical cyclization as well as the introduction of the three contiguous stereocenters (C20, C5, and C6) occurred with a high level of diastereoselection (Scheme 30). For (–)-**100**, NOESY correlations between H5-H6 and H9-H19 confirmed the *cis*-BC- and *cis*-DE-ring systems, respectively, while a correlation between H6-H21 was consistent with the correct relative stereochemistry for the CDE-ring system (Scheme 30). Observation of a NOESY correlation between C1-C6 for



Scheme 30. Formation of benzyl carbamates (–)-**100** and (+)-**101**. NOESY correlations are indicated with curved arrows (Diana K. Hunt, Meiliana Tjandra).[18]

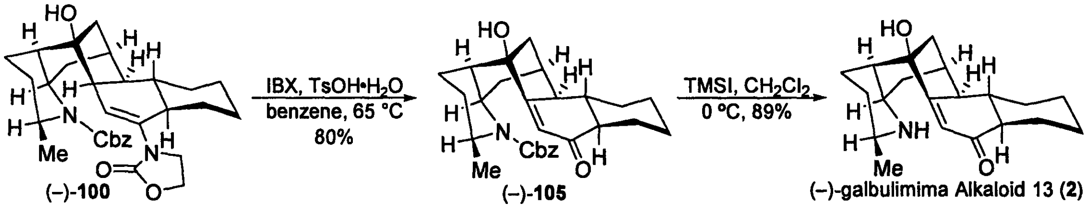
(+)-**101** identified this compound as the C2-epimer of the target intermediate (–)-**100**. Synthesis from (–)-**98** of an advanced intermediate from Mander's synthesis of (±)-GB 13 confirmed this assignment (Scheme 31).[16] Protection of the amine with trifluoroacetic acid and pyridine in methylene chloride occurred with concomitant acetylation of the tertiary hydroxyl at C20. Selective cleavage of this ester with lithium hydroxide in water-THF provided the desired trifluoroacetamide **102** in 23% yield over the two steps (unoptimized). Subsequent hydrolysis of the vinyl oxazolidinone by gentle heating in benzene with *p*-toluenesulfonic acid provided the corresponding ketone in excellent yield.



Scheme 31. Synthesis of advanced intermediate **104** from pentacycle (–)-**98**.[16]

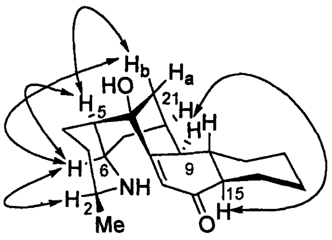
Ketone **103** was converted to the desired enone via formation of the trimethylsilyl enol ether followed by Saegusa dehydrosilylation.[62] Spectra for the trifluoroacetamide **104** matched published spectra.[16]

Direct conversion of *N*-vinyl carbamate (–)-**100** to the desired *N*-Cbz galbulimima alkaloid 13 (**105**) with IBX and *p*-toluenesulfonic acid proceeded smoothly in 80% yield (Scheme 32). We were pleased to discover that deprotection of *N*-Cbz **105** with trimethylsilyliodide (TMSI) followed by hydrolysis (1N HCl) and basic (1N NaOH) treatment provided synthetic galbulimima alkaloid 13 (**2**) in 89% yield (Scheme 32). It is of note that in the absence of base treatment trace C16-oxohimgaline (**10**) resulting from conjugate addition of the secondary amine at C19 was observed, as proposed for the biogenetic synthesis of these alkaloids (Scheme 1). All spectroscopic data for our enantiomerically enriched (–)-galbulimima alkaloid 13 matched those reported for the natural compound. Detailed analysis of 2D-NMR data identified key NOESY correlations between



Scheme 32. Synthesis of galbulimima alkaloid 13 (–)-**2**.

the protons at C2-C6 and C6-C5, indicating the all-*cis* configuration of these methines (Figure 10). Correlations between the C6 and C5 methines and one of the C21 methylene protons indicated the correct configuration of the bridged CDE ring system, while a correlation between the C9-C15 methines indicated the relative stereochemistry about the AB *trans*-decalin. Significantly, the sign of rotation for our synthetic **2** ($[\alpha]^{22}_{D}$ = –64 (*c* 0.06, CHCl$_3$)), was consistent with that reported for the natural galbulimima alkaloid 13 (**2**, Figure 1, [α] = –84 (CHCl$_3$)[3d]), unambiguously securing the absolute stereochemistry. Furthermore, synthesis of (+)-galbulimima alkaloid 13 (*ent*-**2**, $[\alpha]^{22}_{D}$ = +66 (*c* 0.07, CHCl$_3$)) using (+)-(*R*)-**34** (>99% ee) via the route described above with intermediacy of key pentacycle (+)-*ent*-**98** confirmed our absolute stereochemical assignment. Consideration of these data require that the previously reported absolute stereochemistry for natural GB 13 (**2**) be revised as shown in Figure 1.[4,7]

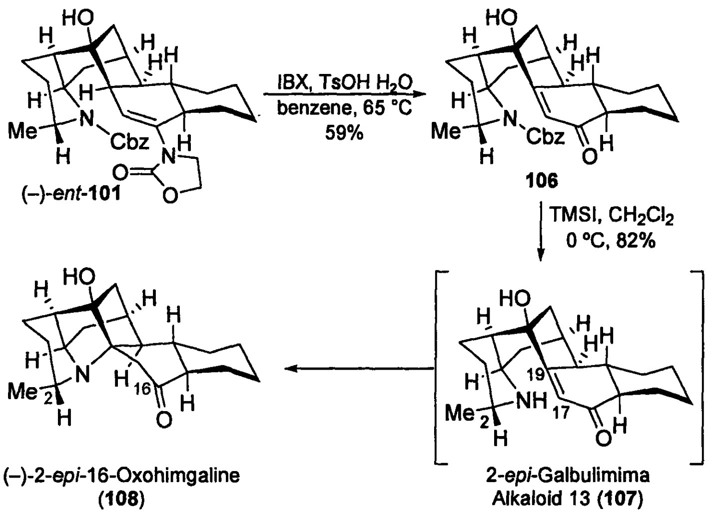


(–)-galbulimima Alkaloid 13 (**2**)

Figure 10. Key NOESY correlations for (–)-galbulimima alkaloid 13 **2**.

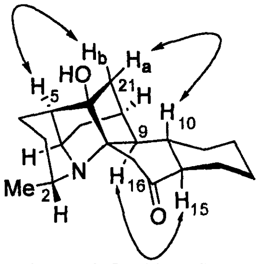
Synthesis of C2-*epi*-C16-oxohimgaline: Insight into the biogenesis of himgaline.

With access to pentacyclic amine (+)-**101** and (–)-*ent*-**101** via incorporation of either (*S*)- or (*R*)-**34** (Scheme 33), we attempted the synthesis of optically active 2-*epi*-galbulimima alkaloid 13 (i.e., **107**, Scheme 33). Interestingly, removal of the nitrogen-protective group of 2-*epi*-*N*-Cbz galbulimima alkaloid 13 (**106**, Scheme 33), under identical conditions to those described for compound **105** led to exclusive isolation of (–)-2-*epi*-16-oxohimgaline (**108**, Scheme 33, $[a]^{22}_{D}$ = –24 (*c* 0.085, CH$_2$Cl$_2$)). Formation of hexacyclic **108** was indicated by the disappearance of the ^{1}H NMR C17 vinylic methine resonance and an upfield shift in the ^{13}C NMR ketone resonance consistent with a saturated carbonyl. Detailed analysis of 2D-



Scheme 33. Synthesis of (−)-2-epi-16-oxohimgaline **108**.

NMR data identified key NOESY correlations between the protons at C5-C21b and C21a-C10, indicating the correct relative stereochemistry for the bridged CDE-ring system (Figure 11). Correlations between the C9 and C15 methines indicated the correct stereochemistry for the AB *trans*-decalin system. The corresponding enantiomer (+)-2-*epi*-*ent*-16-oxohimgaline was also prepared ($[a]^{22}{}_{D}$ = +24 (*c* 0.070, CH_2Cl_2), using the same procedure and starting with (+)-**101**. As previously noted, the amine-C19 conjugate addition was observed to a lesser extent for galbulimima alklaloid 13 (**2**), and was found to be subject to basic hydrolysis. The exclusive isolation of the cyclized product for the 2-*epi*-compounds is likely due to decreased steric interactions between the C2-methyl and the C17 methine. Significantly, this facile conjugate addition further supports the hypothesis for the biosynthesis of himgaline (**3**) via sequential conjugate addition and carbonyl reduction of galbulimima alkaloid 13 (**2**).



(−)-2-*epi*-16-Oxohimgaline
(**108**)

Figure 11. Key NOESY correlations for (−)-2-*epi*-16-oxohimgaline **108**.

Conclusion

We describe the first total synthesis of (–)- and (+)-galbulimima alkaloid 13 (**2** and *ent*-**2**, respectively, Figure 1). The previously reported absolute stereochemistry of natural (–)-galbulimima alkaloid 13 is now unambiguously revised to 2*S*. The diastereoselective introduction of the C-ring via radical cyclization chemistry followed by successful execution of our strategy for construction of the CDE-ring system of **98** (**33**→**98**, Scheme 29) allowed a rapid entry to the pentacyclic core of these alkaloids, while masking the C16-carbonyl as an *N*-vinyl carbamate enabled its late stage oxidative unveiling as the corresponding C16-enone. The completely diastereoselective conversion of tetracycle **97** to pentacycle **98** and the conjugate addition seen for both galbulimima alkaloid 13 (**2**) and 2-*epi*-galbulimima alkaloid 13 (**107**) provide strong experimental support for the hypothesis that the more complex galbulimima alkaloids derive from a common precursor. Indeed, many of the biosynthetic steps may rely on highly diastereoselective, non-enzymatically catalyzed transformations. Ongoing work in our laboratory is focused on the synthesis of other members of this intriguing family of alkaloids.

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Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 32–63 μm, standard grade, Sorbent Technologies).[1] Where necessary (so noted), silica gel was neutralized by treatment of the silica gel prior to chromatography with the eluent containing 1% triethylamine. Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Where necessary (so noted), silica gel plates were neutralized by treatment with a solution of 5% triethylamine in dichloromethane followed by heating on a hot plate (~250 °C). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an ethanolic phosphomolybdic acid (PMA), an acidic solution of *p*-anisaldehyde (anis), an aqueous solution of ceric ammonium molybdate (CAM), an aqueous solution of potassium permanganate ($KMnO_4$) or an ethanolic solution of ninhydrin followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~20 Torr at 25–35 °C, then at ~1 Torr unless otherwise indicated.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, and toluene were purchased from J.T. Baker (Cycletainer^{TM}) and were purified by the method of Grubbs et al. under positive argon pressure.[2] Triethylamine, diisopropylethylamine, and benzene were distilled over calcium hydride immediately before use. Acrolein was distilled over calcium sulfate immediately before use. Methyl vinyl ketone was distilled over potassium carbonate and calcium chloride immediately prior to use. Martin sulfurane was purchased from Aldrich and stored in a glove box under nitrogen atmosphere. *N*-Bromosuccinimide (NBS) was recrystallized from boiling water prior to use. 2-Iodoxybenzoic acid (IBX) was prepared according to literature procedure.[3] Activated γ-manganese dioxide (MnO_2) was prepared according to literature procedure.[4] The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).[5] Ammonia saturated dichloromethane was obtained by agitation of dichloromethane in the presence of ammonium hydroxide followed by drying over anhydrous sodium sulfate. Where necessary (so noted) solutions were deoxygenated by alternate freeze (liquid nitrogen)/evacuation/argon-flush/thaw cycles (FPT, three iterations) or degassed by purging with argon for several minutes.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with a Varian 300 Mercury or a Varian inverse probe 500 INOVA spectrometer or a Bruker inverse probe 600 Avance spectrometer. Chemical shifts are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the

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NMR solvent ($CHCl_3$: δ 7.27, C_6D_5H: δ7.16). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian 500 INOVA spectrometer or a Bruker 400 spectrometer with a Magnex Scientific superconducting magnet and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.2, benzene-d_6: δ 128.4). Infrared data were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. Gas chromatograpy was performed on an Agilent Technologies 6890N Network GC System with a HP-5 5% Phenyl Methyl Siloxane column (50 °C, 6 min; 25 °C/min to 250 °C; 250 °C, 6 min). We acknowledge the assistance of Dr. Peter Mueller and Mr. Michael Schmidt in obtaining the X-ray crystal structure of compound **78**. We are grateful to Dr. Li Li for obtaining the mass spectroscopic data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX 4.7 Tesler FTMS spectrometer using electronspray ion source (ESI) or electronspray (ES).

Compound Numbering. For compound **2** and compounds ≥ **52**, the atom numbering system used is consistent with correlated atoms in the final product as numbered in the isolation papers of the natural alkaloids.[6]

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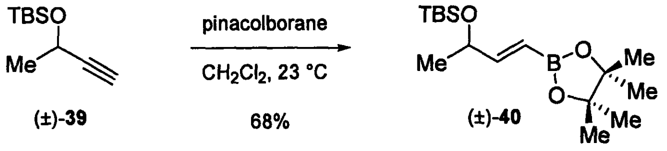
[6] Ritchie, E.; Taylor, W. C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, Chapter 14.



(±)-*trans*-2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-but-1-enyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (40):

Terminal alkyne **39**[7] (4.70 g, 25.5 mmol, 1 equiv) was added dropwise via syringe to a solution of freshly prepared pinacolborane[8] in dichloromethane (5 M, 10 mL, 50.2 mmol, 2.00 equiv) at 0°C. The solution was stirred and allowed to warm to ambient temperature. After 24 h, the solution was partitioned between diethyl ether (300 mL) and saturated aqueous ammonium chloride solution (150 mL). The aqueous phase was extracted with diethyl ether (2 × 150 mL) and the combined organic phases were washed with saturated aqueous ammonium chloride solution (100 mL), were washed with brine (80 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting oil by flash column chromatography (silica gel: diam. 9 cm, ht. 10 cm; eluent: hexanes:EtOAc [95:5] to hexanes:EtOAc [80:20]) provided boronate **(±)-40** (5.40 g, 68%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	6.60 (dd, *J* = 18, 4.0 Hz, 1H, **CH**=CHB), 5.63 (dd, *J* = 18, 1.7 Hz, 1H, CH=**CH**B), 4.37-4.32 (m, 1H, CH_3**CH**CH=CH), 1.28 (s, 6H, BOC(**CH$_3$**)CH_3), 1.28 (s, 6H, BOC(CH_3)**CH$_3$**), 1.22 (d, *J* = 6.7 Hz, 3H, CH**CH$_3$**), 0.91 (s, 9H, SiC(**CH$_3$**)$_3$), 0.05 (s, 6H, Si(**CH$_3$**)$_2$).
^{13}C NMR (125 MHz, $CDCl_3$, 20°C):	157.2 (B**C**=C), 83.3 (BC=**C**), 70.0 ((Me)$_2$**C**), 26.1, 25.0, 24.9, 23.9, 18.5, –4.5 ($SiCH_3$), –4.6 ($SiCH_3$).
FTIR (thin film) cm^{-1}:	2929 (m), 1996 (w), 1611 (w), 1370 (w), 1337 (w), 1146 (w).
HRMS (ESI)	calcd for $C_{16}H_{33}BNaO_3Si$ $[M+Na]^+$: 335.2184, found: 335.2177.
GC, t_R:	11.73 min
TLC (20% EtOAc in hexanes), *Rf*:	**40**, 0.63 ($KMnO_4$)

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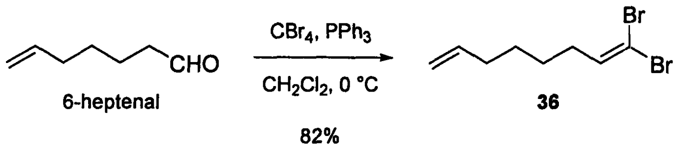
[7] Prepared from 3-butynol, *tert*-butyldimethylsilylchloride, imidazole, dimethylformamide, 23 °C, 12h; see: Cotterill, A. S.; Gill, M.; Gimenez, A.; Milanovic N. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, *22*, 3269.

[8] Pinacolborane was prepared according to Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.



1,1-Dibromo-octa-1,7-diene (9):

Triphenylphosphine (6.34 g, 24.2 mmol, 2.40 equiv) was added in three portions to a solution of carbon tetrabromide (4.00 g, 12.1 mmol, 1.20 equiv) in dichloromethane (30 mL) at 0°C in an ice bath to produce a yellow-orange solution. The solution was stirred at 0 °C for 10 min. A solution of 6-heptenal[9] (1.12 g, 10.0 mmol, 1 equiv) in dichloromethane (6 mL) was introduced via cannula to the cold reaction mixture. The transfer was completed using a second 4–mL portion of dichloromethane and the mixture was vigorously stirred at 0°C. The solution became dark orange and white solid precipitated. After 1 h, excess dibromophosphorane was quenched by sequential addition of triethylamine (3.4 mL, 24 mmol, 2.4 equiv) and methanol (1.0 mL, 25 mmol, 2.5 equiv). The solution was allowed to warm to room temperature, transferred to a separatory funnel and added dropwise to a solution of ^{n}pentane–diethyl ether (5:1, 300 mL), resulting in precipitation of triphenylphosphine oxide. The resulting light brown solid was removed by filtration and washed with ^{n}pentane (100 mL). The combined organic filtrate was concentrated and purified by flash column chromatography (silica gel: diam. 5 cm, ht. 10 cm; eluent: hexanes:EtOAc [90:10]) to yield dibromide **36** as a colorless oil (2.21 g, 82%).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	6.40 (t, *J* = 7.4 Hz, 1H, $Br_2C{=}C\mathbf{H}$), 5.85-5.76 (m, 1H, $\mathbf{H}C{=}CH_2$), 5.02 (app-dq, *J* = 17, 1.5 Hz, 1H, *trans*-$HC{=}C\mathbf{H_2}$), 4.97 (m, 1H, *cis*-$HC{=}C\mathbf{H_2}$), 2.14-2.05 (m, 4H, $Br_2C{=}CHC\mathbf{H_2}$, $H_2C{=}CHC\mathbf{H_2}$), 1.47-1.41 (m, 4H, $CH_2(C\mathbf{H_2})_2CH_2$).
^{13}C NMR (125 MHz, $CDCl_3$, 20°C):	138.9, 138.7, 114.9 ($HC{=}\mathbf{C}H_2$), 88.9 ($Br_2\mathbf{C}{=}CH$), 33.6, 33.0, 28.4, 27.4.
FTIR (thin film) cm^{-1}:	2928 (s), 2857 (m), 1641 (m), 911 (s), 804 (m), 780 (m).
HRMS–EI (*m/z*):	calcd for $C_8H_{13}Br_2$ $[M+H]^+$: 265.9300, found: 265.9324.
GC, t_R:	10.16 min
TLC (40% EtOAc in hexanes), *Rf*:	6-heptenal, 0.64 ($KMnO_4$) **36**, 0.75 (UV, $KMnO_4$)

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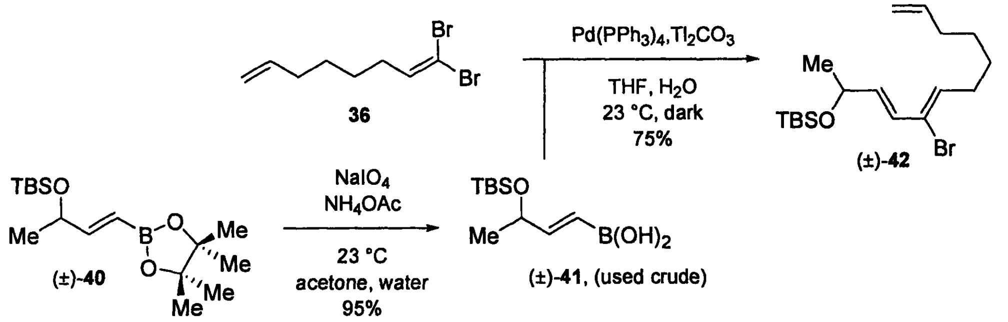
[9] 6-Heptenal was prepared from 7-octene-1,2-diol (commercially available), sodium metaperiodate, diethyl ether, water, 1h, 93%. Spectroscopic data matched published data; see: Taylor, R. E.; Galvin, G. M.; Hilfiker, K. A.; Chen, Y. *J. Org. Chem.* **1998**, *63*, 9580.



(±)-(2*E*,4*Z*)-(4-Bromo-1-methyl-undeca-2,4,10-trienyloxy)-*tert*-butyl-dimethyl-silane (42):

To a solution of boronate (±)-**40** (0.94 g, 3.0 mmol, 1 equiv) in acetone and water (30 mL, 2:1) was added sodium periodate (2.0 g, 9.4 mmol, 3.1 equiv) and ammonium acetate (0.71 g, 9.2 mmol, 3.0 equiv). The resulting cloudy solution was stirred at ambient temperature. After 48 h, the reaction mixture was placed under reduced pressure to remove acetone, was diluted with ethyl acetate (100 mL) and the phases separated. The aqueous layer was extracted with ethyl acetate (100 mL) and the combined organic layers were washed with brine (50 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to provide boronic acid (±)-**41** as a light brown oil (0.66 g, 95%). Dibromide **36** (150 mg, 0.56 mmol, 1 equiv) and crude boronic acid (±)-**41** (160 mg, 0.69 mmol, 1.2 equiv) were combined, dissolved in THF–water (3:1, 11 mL), and the solution was degassed thoroughly (FPT). Tetrakis(triphenylphosphine)palladium (33 mg, 0.028 mmol, 0.050 equiv) was added as a solid, light was excluded, and the resulting clear yellow solution was stirred for 5 min. Thallium carbonate (0.53 g, 1.1 mmol, 2.0 equiv) was added as a solid, and the resulting heterogeneous yellow-white mixture was stirred in the dark. After 25 h, the light tan reaction mixture was diluted with ethyl acetate and passed through a silica plug and the clear solution was concentrated. The resulting brown oil was purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 4 cm; eluent: hexanes:EtOAc [98:2] to hexanes:EtOAc [96:4]) to provide triene (±)-**42** as a yellow oil (156 mg, 75%).

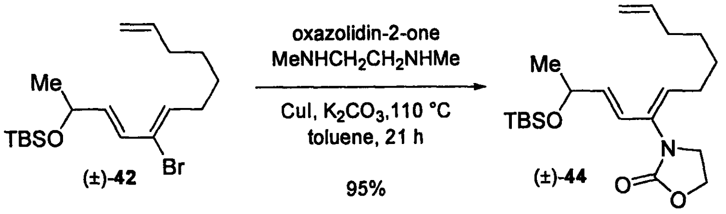
^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	6.19 (d, J = 14.6 Hz, 1H, BrCC**H**=CH), 6.03 (dd, J = 14.6, 4.8 Hz, 1H, BrCCH=C**H**), 5.91-5.75 (m, 2H, BrC=C**H**; CH_2=C**H**), 5.06-4.93 (m, 2H, **CH_2**=CH), 4.44 (m, 1H, TBSOC**H**CH_3), 2.35-2.28 (m, 2H, BrC=CHC**H_2**), 2.10-2.06 (m, 2H, CH_2=CHC**H_2**), 1.49-1.43 (m, 4H, (C**H_2**)$_2$), 1.25 (d, J = 6.4 Hz, 3H, C**H_3**), 0.92 (s, 9H, SiC(C**H_3**)$_3$), 0.08 (s, 3H, SiC**H_3**), 0.07 (s, 3H, SiC**H_3**).
^{13}C NMR (125 MHz, $CDCl_3$, 20°C):	138.9, 138.3, 133.7, 127.5, 125.2, 114.7, 68.5 (TBSOCH), 33.8, 31.6, 28.7, 28.1, 26.1

($C(CH_3)_3$), 24.8, 18.5, –4.4 ($SiCH_3$), –4.5 ($SiCH_3$).

FTIR (thin film) cm^{-1}: 2955 (s), 2929 (s), 2857 (s), 1472 (w), 1462 (w), 1255 (m), 1149 (m), 1089 (m), 835 (s), 776 (s).

HRMS (ESI): calcd for $C_{18}H_{33}NaBrOSi$ $[M+Na]^+$: 395.1376, found: 395.1365.

TLC (40% EtOAc in hexanes), *Rf*:
41, 0.26 ($KMnO_4$)
42, 0.83 (UV, KMnO4)

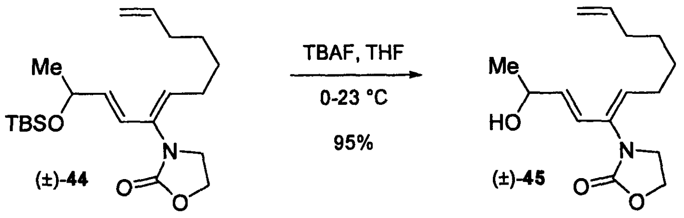


(±)-3-{(1*Z*)-1-[(*E*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-but-1-enyl]-octa-1,7-dienyl}-oxazolidin-2-one 44:

Vinyl bromide (±)-**42** (3.10 g, 8.30 mmol, 1 equiv) was transferred in dry toluene to a flame-dried Schlenk pressure vessel, the solvent was removed under reduced pressure, and the vessel filled with argon. Oxazolidin-2-one (869 mg, 9.96 mmol, 1.20 equiv), copper iodide (790 mg, 4.15 mmol, 0.500 equiv), and potassium carbonate (2.29 g, 16.6 mmol, 2.00 equiv) were added under argon, and the vessel was evacuated and back-filled with argon three times. Dimethylethylenediamine (2.23 mL, 20.8 mmol, 2.50 equiv) and toluene (33 mL) were added. The reaction vessel was sealed under argon atmosphere and the green-gray heterogeneous mixture was heated to 110 °C. The solution turned slate-blue after five minutes, then light yellow-green. After 21 h, the solution was cooled to ambient temperature and partitioned between ethyl acetate (200 mL) and water (100 mL). The blue aqueous layer was extracted with ethyl acetate (3 × 150 mL), and the combined yellow organic layers were washed with brine (50 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting brown oil was purified by flash column chromatography (silica gel: diam. 7 cm, ht. 10 cm; eluent: CH_2Cl_2:acetone [99:1] to CH_2Cl_2:acetone [96:4] to CH_2Cl_2:acetone [85:15]) to provide triene (±)-**44** as a light yellow oil (2.98 g, 95%).

^{1}H NMR (500 MHz, C_6D_6, 20°C):	6.09 (dd, J = 15.4, 1.0 Hz, 1H, (TBSO)CHCH=**CH**), 5.77-5.69 (m, 1H, **CH**=CH_2), 5.63 (dd, J = 15.6, 5.5 Hz, 1H, (TBSO)CH**CH**=CH), 5.46 (t, J = 7.4 Hz, 1H, (N)C=**CH**), 5.04-4.97 (m, 2H, CH=$\mathbf{CH_2}$), 4.27 (app-p, J = 6.1 Hz, 1H, (TBSO)**CH**), 3.55-3.51 (m, 2H, OCH_2CH_2N), 3.02-2.91 (m, 2H, $OCH_2\mathbf{CH_2}N$), 2.04-1.98 (m, 2H, $\mathbf{CH_2}CH=CH_2$), 1.94-1.90 (m, 2H, (N)C=CH$\mathbf{CH_2}$), 1.28-1.24 (m, 4H, $(\mathbf{CH_2})_2$), 1.21 (d, J = 6.3 Hz, 3H, TBSOCH$\mathbf{CH_3}$), 1.01 (s, 9H, SiC$(\mathbf{CH_3})_3$), 0.11 (s, 3H, Si$(\mathbf{CH_3})_2$), 0.10 (s, 3H, Si$(\mathbf{CH_3})_2$).
^{13}C NMR (125 MHz, C_6D_6, 20°C):	156.2 (O=**C**), 139.2, 134.5, 134.1, 134.0, 125.6, 115.1, 69.5, 61.9, 46.2, 34.3, 29.3, 28.8, 28.3, 26.5, (C$(\mathbf{CH_3})_3$), 25.2, 18.8, –4.0 ($SiCH_3$), –4.2 ($SiCH_3$).
FTIR (thin film) cm^{-1}:	2928 (w), 2856 (w), 1758 (s), 1414 (m), 1251 (w), 834 (m).

HRMS (ESI):	calcd for $C_{21}H_{37}NaNO_3Si$ $[M+Na]^+$: 402.2435, found: 402.2444.
TLC (3% acetone in CH_2Cl_2), *Rf*:	**42**, 0.89 (UV, CAM) **44**, 0.54 (UV, CAM)

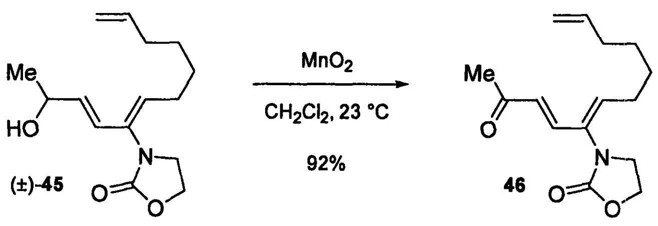


(±)-**44** → (±)-**45**

(±)-3-[(1*Z*)-1-((*E*)-3-Hydroxy-but-1-enyl)-octa-1,7-dienyl]-oxazolidin-2-one (45):

A solution of tetrabutylammonium fluoride in THF (1M, 1.9 mL, 1.9 mmol, 1.5 equiv) was added to a solution of silyl ether (±)-**44** (487 mg, 1.28 mmol, 1 equiv) in THF (10 mL) at 0 °C. The resulting light yellow solution was vigourously stirred and allowed to warm to ambient temperature. After 3.5 h, the reaction mixture was diluted with ethyl acetate (50 mL), water (5 mL), and saturated aqueous ammonium chloride solution (25 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 ml), and the combined organic layers were washed with brine (25 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 6.5 cm; eluent: CH_2Cl_2:acetone [95:5] to CH_2Cl_2:acetone [80:20] to CH_2Cl_2:acetone [50:50]) to provide the alcohol (±)-**45** as a clear oil (321 mg, 95%).

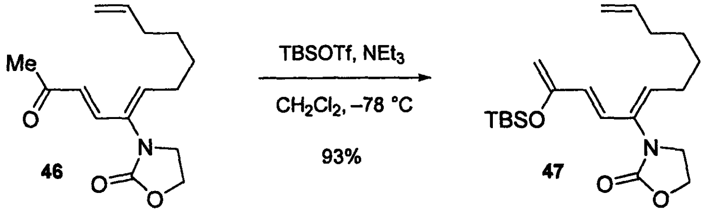
^1H NMR (500 MHz, C_6D_6, 20°C):	5.99 (d, J = 15.6 Hz, 1H, MeC(OH)CH=C**H**), 5.81-5.71 (m, 1H, C**H**=CH_2), 5.64 (dd, J = 15.6, 5.5 Hz, 1H, MeC(OH)C**H**=CH), 5.41 (t, J = 7.4 Hz, 1H, (N)C=C**H**), 5.07-4.97 (m, 2H, CH=$\mathbf{CH_2}$), 4.24 (br-s, 1H, C**H**OH), 3.67-3.57 (m, 2H, $O\mathbf{CH_2}CH_2N$), 2.97 (t, J = 8.0 Hz, 2H, $OCH_2\mathbf{CH_2}N$), 2.36-2.18 (br-s, O**H**), 2.03-1.91 (m, 4H, (allylic $\mathbf{CH_2}$), 1.32-1.25 (m, 4H, $(\mathbf{CH_2})_2$, 1.23 (d, J = 6.3 Hz, 3H, $\mathbf{CH_3}$).
^{13}C NMR (125 MHz, C_6D_6, 20°C):	156.7 (O=**C**), 139.2 (**C**=CN), 134.5, 134.1, 128.7, 126.1, 115.1 (HC=$\mathbf{CH_2}$), 68.3, 62.2, 46.2, 34.3, 29.3, 28.9, 28.2, 24.0.
FTIR (thin film) cm^{-1}:	3421 (br-m, OH), 2973 (w), 2927 (m), 2857 (w), 1741 (s, C=O), 1419 (s), 1247 (m), 1037 (m).
HRMS (ESI):	calcd for $C_{15}H_{23}NaNO_3$ $[M+Na]^+$: 288.1572, found: 288.1572.
TLC (10% acetone in CH_2Cl_2), *Rf*:	**44**, 0.75 (UV, CAM) **45**, 0.16 (UV, CAM)



(±)-3-[(1*Z*)-1-((*E*)-3-Oxo-but-1-enyl)-octa-1,7-dienyl]-oxazolidin-2-one (46):

γ-Manganese dioxide (1.21 g, 13.9 mmol, 11.7 equiv) was added under an argon atmosphere in one portion to a solution of alcohol (±)-**45** (317 mg, 1.20 mmol, 1 equiv) in dichloromethane (6 mL) and the mixture was stirred at ambient temperature. After 19.5 h, the reaction mixture was diluted with dichloromethane and passed through celite. The resulting solution was concentrated under reduced pressure to provide spectroscopically clean ketone **46** as a clear oil (289 mg, 92%). If desired, purification of ketone **46** could be achieved via flash column chromatography (silica gel, eluent: CH$_2$Cl$_2$:acetone [98:2] to CH$_2$Cl$_2$:acetone [90:10]).

^{1}H NMR (500 MHz, C$_6$D$_6$, 20°C):	6.77 (d, *J* = 15.8 Hz, 1H, MeCOCH=**CH**), 6.00 (d, *J* = 15.8 Hz, 1H, MeCO**CH**=CH), 5.78-5.70 (m, 1H, **CH**=CH$_2$), 5.52 (t, *J* = 7.6 Hz, 1H, (N)C=**CH**), 5.06-4.99 (m, 2H, CH=**CH$_2$**), 3.47 (app-t, *J* = 7.8 Hz, 2H, O**CH$_2$**CH$_2$N), 2.73 (app-t, *J* = 7.8 Hz, 2H, OCH$_2$**CH$_2$**N), 1.94-1.90 (m, 7H, allylic-**CH$_2$**, allylic-**CH$_2$**, Me), 1.21-1.20 (m, 4H, (**CH$_2$**)$_2$).
^{13}C NMR (125 MHz, C$_6$D$_6$, 20°C):	196.6 (ketone-C=O), 156.1 (carbamate-C=O), 143.7, 140.2, 139.0, 134.1, 126.6, 115.3, 62.2 (**O**CH$_2$CH$_2$N), 46.0 (OCH$_2$CH$_2$**N**), 34.2, 29.3, 28.8, 28.3, 27.9.
FTIR (thin film) cm^{-1}:	2924 (m), 1754 (s, C=O), 1746 (s, C=O), 1666 (m), 1631 (m), 1599 (m), 1414 (s), 1251 (m).
HRMS (ESI):	calcd for C$_{15}$H$_{21}$NaNO$_3$ [M+Na]$^+$: 286.1414, found: 286.1421.
TLC (10% acetone in CH$_2$Cl$_2$), *Rf*:	**45**, 0.16 (UV, CAM) **46**, 0.42 (UV, CAM)

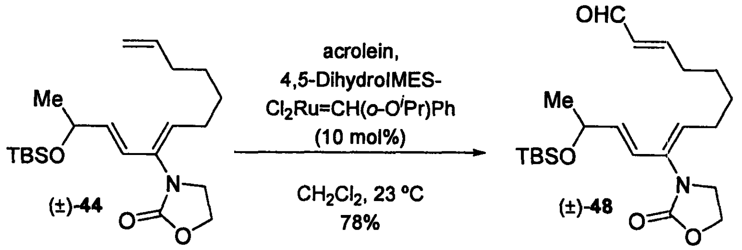


3-{(1*Z*)-1-[(*Z*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-but-1,3 dienyl]-octa-1,7-dienyl}-oxazolidin-2-one (47):

Triethylamine (860 µL, 6.12 mmol, 1.50 equiv) was added to a solution of ketone **46** (1.07 g, 4.08 mmol, 1 equiv) in dichloromethane (20 mL) at –78 °C, followed by dropwise addition of TBSOTf (1.12 mL, 4.89 mmol, 1.20 equiv). After 15 min, the excess silylating agent was quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL) and allowed to warm to ambient temperature. The reaction mixture was diluted with ethyl acetate (80 mL) and washed with saturated aqueous sodium bicarbonate solution (30 mL). The aqueous phase was extracted with ethyl acetate (4 × 75 mL), and the combined organic layers were washed with brine (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (neutralized silica gel: diam. 5 cm, ht. 9 cm; eluent: CH_2Cl_2:acetone [97:3]) to provide the silyl enol ether **47** as a white solid (1.44 g, 93%).

^{1}H NMR (500 MHz, C_6D_6, 20°C):	6.80 (d, *J* = 15.3 Hz, 1H, **HC**=CHCOTBS), 6.06 (d, *J* = 15.3 Hz, 1H, HC=**CH**COTBS), 5.76-5.68 (m, 1H, **CH**=CH_2), 5.60 (t, *J* = 7.4 Hz, 1H, (N)C=**CH**), 5.03-4.96 (m, 2H, CH=$\mathbf{CH_2}$), 4.42 (s, 1H, $\mathbf{CH_2}$=CHOTBS), 4.33 (s, 1H, $\mathbf{CH_2}$=CHOTBS), 3.51 (app-t, *J* = 7.6 Hz. 2H, O$\mathbf{CH_2}$$CH_2$N), 2.89 (app-t, *J* = 8.0 Hz, 2H, O$CH_2$$\mathbf{CH_2}$N), 2.03-1.99 (m, 2H, $\mathbf{CH_2}$CH=CH_2), 1.95-1.85 (m, 2H, (N)C=CH$\mathbf{CH_2}$), 1.24-1.21 (m, 4H, ($\mathbf{CH_2}$)$_2$), 1.02 (s, 9H, SiC($\mathbf{CH_3}$)$_3$), 0.18 (s, 6H, Si($\mathbf{CH_3}$)$_2$).
^{13}C NMR (125 MHz, C_6D_6, 20°C):	156.3, 155.6, 139.2, 136.1, 134.8, 127.3. 126.5, 115.1, 97.4, 62.1, 46.3, 34.2, 29.3, 28.7, 28.6, 26.4, 18.9, –4.2.
FTIR (thin film) cm^{-1}:	2930 (s), 2858 (s), 1759 (s, C=O), 1415 (m), 1316 (m), 1254 (m), 1030 (m), 840 (m).
HRMS (ESI):	calcd for $C_{21}H_{36}NO_3Si$ [M+H]$^+$: 378.2459, found: 378.2465.

TLC, *Rf*:
(10% acetone in CH_2Cl_2, neutralized plates): **46**, 0.58 (UV, CAM)
47, 0.79 (UV, CAM)



12-(tert-Butyl-dimethyl-silanyloxy)-9-(2-oxo-oxazolidin-3-yl)-trideca-2,8,10-trienal (48):

To a solution of silyl ether (±)-**44** (47.6 mg, 0.125 mmol, 1 equiv) in dichloromethane (625 μL) was added freshly distilled acrolein (34 μL, 0.50 mmol, 4.00 equiv, no stabilizer present), followed by Hoveyda–Grubbs G2 Ru-cat ((4,5-DihydroIMES)-(PCy_3)Cl_2Ru=CH(*o*-iPrO)Ph),[10] 8.5 mg, 0.014 mmol, 0.110 equiv). The green solution was stirred at ambient temperature for 10 minutes, then purified immediately without concentration via flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 8 cm; eluent: CH_2Cl_2:acetone [99:1] to CH_2Cl_2:acetone [98:2] to CH_2Cl_2:acetone [90:10]) to provide the triene (±)-**48** as a tan oil (40.1 mg, 78%). Additionally, the starting silyl ether (±)-**44** was recovered (6.5 mg, 14%).

^{1}H NMR (500 MHz, C_6D_6, 20 °C):	9.34 (d, *J* = 7.6 Hz, 1H, **CHO**), 6.12 (dd, *J* = 15.4, 1.2 Hz, 1H, (TBSO)CHCH=**CH**), 6.04 (dt, *J* = 15.5, 6.8 Hz, 1H, CHOCH=**CH**), 5.91 (ddt, *J* = 15.6, 7.6, 1.2 Hz, 1H, CHOC**H**=CH), 5.63 (dd, *J* = 15.6, 5.5 Hz, 1H, (TBSO)CHC**H**=CH), 5.42 (t, *J* = 7.3 Hz, 1H, (N)C=**CH**), 4.28 (app-p, *J* = 6.1 Hz, 1H, (TBSO)**CH**), 3.58-3.54 (m, 2H, O**CH$_2$**CH$_2$N), 3.03-2.91 (m, 2H, OCH$_2$**CH$_2$**N), 1.95-1.90 (m, 2H, **CH$_2$**CH=CHCHO), 1.71-1.67 (m, 2H, (N)C=CH**CH$_2$**), 1.20 (d, *J* = 6.3 Hz, 3H, TBSOCH**CH$_3$**), 1.15-1.03 (m, 4H, (**CH$_2$**)$_2$) 1.01 (s, 9H, SiC(**CH$_3$**)$_3$), 0.10 (s, 3H, Si(**CH$_3$**)$_2$), 0.10 (s, 3H, Si(**CH$_3$**)$_2$.
^{13}C NMR (125 MHz, C_6D_6, 20°C):	193.1 (**C**HO), 157.3, 156.2, 134.7, 134.5, 133.7, 133.3, 125.4, 69.4 (**C**(OSi), 62.0 (O**C**H$_2$CH$_2$N), 46.2 (OCH$_2$**C**H$_2$N), 32.6, 28.6, 28.1, 27.9, 26.5 (SiC(**C**H$_3$)$_3$), 25.2, 18.8, –4.0 (Si(**C**H$_3$)$_2$), –4.2 (Si(**C**H$_3$)$_2$).
FTIR (neat) cm^{-1}:	2929 (m), 1759 (s), 1690 (s), 1416 (m), 1251 (m), 836 (m).
HRMS (ESI)	calcd for $C_{22}H_{37}NNaO_4Si$ [M+Na]$^+$: 430.2384, found: 430.2374.
TLC (3% acetone in hexanes), *Rf*:	**44**, 0.42 (UV, CAM) **48**, 0.24 (UV, CAM)

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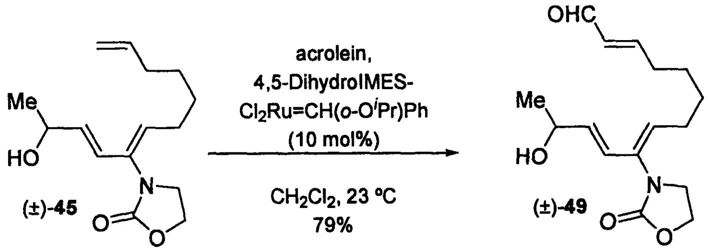
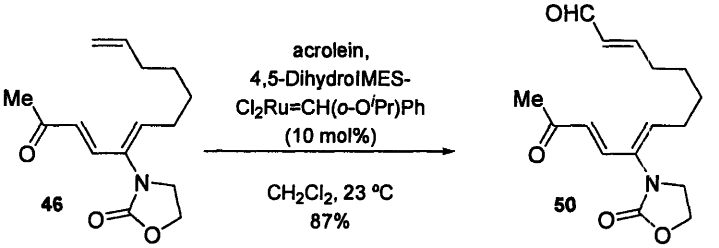
[10] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.



12-Hydroxy-9-(2-oxo-oxazolidin-3-yl)-trideca-2,8,10-trienal (49):

To a solution of alcohol (±)-**49** (43.0 mg, 0.162 mmol, 1 equiv) in dichloromethane (800 μL) was added freshly distilled acrolein (43 μL, 0.65 mmol, 4.00 equiv, no stabilizer present), followed by Hoveyda–Grubbs G2 Ru-cat ((4,5-DihydroIMES)Cl$_2$Ru=CH(*o*-iPrO)Ph)((4,5-DihydroIMES)-(PCy$_3$)Cl$_2$Ru=CHPh, 10.5 mg, 0.0168 mmol, 0.10 equiv). The green solution was stirred at ambient temperature for 10 minutes, then purified immediately without concentration via flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 8 cm; eluent: CH$_2$Cl$_2$:acetone [85:15] to CH$_2$Cl$_2$:acetone [75:25] to CH$_2$Cl$_2$:acetone [70:30]) to provide the triene (±)-**49** as a tan oil (37.6 mg, 79%). Additionally, the starting alcohol (±)-**45** was recovered (2.8 mg, 7%).

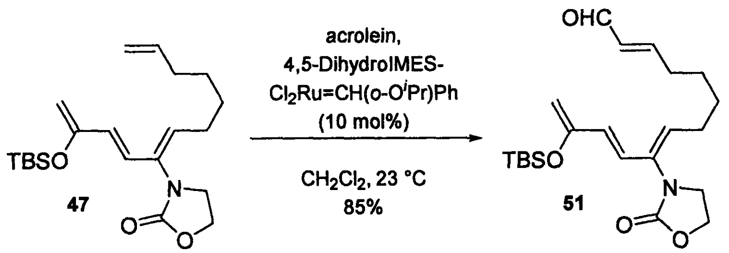
^{1}H NMR (500 MHz, C$_6$D$_6$, 20 °C):	9.38 (d, *J* = 7.7 Hz, 1H, C**H**O), 6.20 (dt, *J* = 15.6, 6,7 Hz, 1H, CHOCH=C**H**), 6.11 (d, *J* = 15.7 Hz, 1H, (HO)CHCH=C**H**), 5.98 (ddt, *J* = 15.6, 7.7, 1.0 Hz, 1H, CHOC**H**=CH), 5.73 (dd, *J* = 15.6, 5.8 Hz, 1H, (HO)CHC**H**=CH), 5.44 (t, *J* = 7.4 Hz, 1H, (N)C=C**H**), 4.40-4.33 (m, 1H, (HO)C**H**), 3.78 (td, *J* = 7.8, 2.1 Hz, 2H, OC**H**$_2$CH$_2$N), 3.19-3.14 (m, 1H, O**H**), 3.09 (app-t, *J* = 8.0 Hz, 2H, OCH$_2$C**H**$_2$N), 1.94 (app-q, *J* = 7.0 Hz, 2H, C**H**$_2$CH=CHCHO), 1.80 (app-q, *J* = 6.4 Hz, 2H, (N)C=CHC**H**$_2$), 1.31 (d, *J* = 6.4 Hz, 3H, HOCHC**H**$_3$), 1.21-1.09 (m, 4H, (C**H**$_2$)$_2$).
^{13}C NMR (125 MHz, C$_6$D$_6$, 20°C):	193.6 (**C**HO), 157.9, 156.9, 134.6, 134.6, 133.7, 133.6, 125.8, 68.2 (**C**(OH)), 62.5 (O**C**H$_2$CH$_2$N), 46.3 (OCH$_2$**C**H$_2$N), 32.7, 28.7, 28.0, 27.8, 24.1.
FTIR (neat) cm^{-1}:	3427 (br-m, OH), 2926 (m), 1750 (s), 1686 (s), 1418 (m), 1243 (br-w), 1036 (w), 972 (w).
HRMS (ESI)	calcd for C$_{16}$H$_{23}$NNaO$_4$ [M+Na]$^+$: 316.1519, found: 316.1512.
TLC (15% acetone in hexanes), *Rf*:	**45**, 0.24 (UV, CAM) **49**, 0.12 (UV, CAM)



12-Oxo-9-(2-oxo-oxazolidin-3-yl)-trideca-2,8,10-trienal (50):

To a solution of ketone alcohol **46** (37.3 mg, 0.142 mmol, 1 equiv) in dichloromethane (710 µL) was added freshly distilled acrolein (38 µL, 0.56 mmol, 4.00 equiv, no stabilizer present), followed by Hoveyda–Grubbs G2 Ru-cat ((4,5-DihydroIMES)Cl_2Ru=CH(*o*-iPrO)Ph)((4,5-DihydroIMES)-(PCy_3)Cl_2Ru=CHPh,[10] 9.1 mg, 0.0145 mmol, 0.10 equiv). The green solution was stirred at ambient temperature for 10 minutes, then purified immediately without concentration[\] via flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 8 cm; eluent: CH_2Cl_2:acetone [96:4] to CH_2Cl_2:acetone [94:6] to CH_2Cl_2:acetone [89:11] to CH_2Cl_2:acetone [80:20]) to provide the triene **50** as a tan oil (36.0 mg, 87%). Additionally, the starting ketone **46** was recovered (4.1 mg, 11%).

^{1}H NMR (500 MHz, C_6D_6, 20 °C):	9.39 (d, *J* = 8.7 Hz, 1H, **CHO**), 6.87 (d, *J* = 15.8 Hz, 1H, CH_3(O)CCH=**CH**), 6.17 (dt, *J* = 15.6, 6.7 Hz, 1H, CHOCH=**CH**), 6.06 (d, *J* = 15.8 Hz, 1H, CH_3(O)CC**H**=CH), 5.98 (ddt, *J* = 15.7, 7.8, 1.3 Hz, 1H, CHOC**H**=CH), 5.61 (t, J = 7.5 Hz, 1H, (N)C=**CH**), 3.68 (dd, *J* = 8.9, 7.7 Hz,, 2H, O**CH₂**CH_2N), 2.89 (dd, *J* = 8.0, 6.9 Hz, 2H, OCH_2**CH₂**N), 1.89 (aap-q, *J* = 7.2 Hz, 2H, **CH₂**CH=CHCHO), 1.77 (app-q, *J* = 6.3 Hz, 2H, (N)C=CH**CH₂**), 1.97 (s, 3H, **CH₃**), 1.15-1.03 (m, 4H, (**CH₂**)₂).
^{13}C NMR (125 MHz, C_6D_6, 20°C):	196.8 (**CO**(CH_3)) 193.3 (**CHO**), 157.4, 156.3, 143.3, 140.1, 134.2, 133.7, 126.7, 62.4 (**OCH₂**CH_2N), 46.0 (OCH_2**CH₂**N), 32.5, 28.6, 28.1, 28.0, 27.8.
FTIR (neat) cm^{-1}:	2928 (w), 1755 (s), 1687 (s), 1418 (s), 1254 (br-m), 1037 (w), 977 (w).
HRMS (ESI)	calcd for $C_{16}H_{21}NNaO_4$ $[M+Na]^+$: 314.1363, found: 314.1359.
TLC (10% acetone in hexanes), *Rf*:	**46**, 0.34 (UV, CAM) **50**, 0.16 (UV, CAM)



(2*E*,8*Z*,10*E*)-12-(*tert*-Butyl-dimethyl-silanyloxy)-9-(2-oxo-oxazolidin-3-yl)-trideca-2,8,10,12-tetraen-1-al (51):

To a solution of silyl enol ether **47** (500 mg, 1.32 mmol, 1 equiv) in dichloromethane (6.6 mL) was added freshly distilled acrolein (354 μL, 5.30 mmol, 4.00 equiv, no stabilizer present), followed by Hoveyda-Grubbs G2 cat (4,5-DihydroIMES(Cl_2Ru=CH(*o*-O^{i}Pr)Ph,[10] 82 mg, 0.13 mmol, 0.10 equiv). The green solution was stirred at ambient temperature for 10 minutes, then purified immediately without concentration[11] via flash column chromatography (neutralized silica gel: diam. 5 cm, ht. 8 cm; eluent: CH_2Cl_2:acetone:NEt_3 [98:1:1]) to provide the tetraene **51** as a tan solid (455 mg, 85%).

^{1}H NMR (500 MHz, C_6D_6, 20°C):	9.34 (d, *J* = 7.6 Hz, 1H, **CHO**), 6.71 (d, *J* = 15.3 Hz, 1H, **HC**=CHCOTBS) 6.07 (d, *J* = 15.3 Hz, 1H, HC=**CH**COTBS), 6.01 (dd, *J* = 15.6, 6.6 Hz, 1H, C**H**=CHCHO), 5.90 (dd, *J* = 15.6, 7.6 Hz, 1H, CH=**CH**CHO), 5.55 (t, *J* = 7.4 Hz, 1H, (N)C=**CH**), 4.43 (s, 1H, **CH**$_2$=CHOTBS), 4.34 (s, 1H, **CH**$_2$=CHOTBS), 3.55 (app-t, *J* = 7.9 Hz, 2H, O**CH**$_2$CH$_2$N), 2.90 (app-t, *J* = 7.4 Hz, 2H, OCH$_2$**CH**$_2$N), 1.93 (app-q, *J* = 7.2 Hz, 2H, **CH**$_2$CH=CH$_2$), 1.67 (app-q, *J* = 6.9 Hz, 2H, (N)C=CH**CH**$_2$), 1.11-0.94 (m, 13H, (**CH**$_2$)$_2$, SiC(**CH**$_3$)$_3$), 0.18 (s, 6H, Si(**CH**$_3$)$_2$).
^{13}C NMR (125 MHz, C_6D_6, 20°C):	193.2 (CHO), 157.5, 156.4, 155.5, 135.5, 135.0, 133.6, 127.0, 126.8, 97.5, 62.2, 46.3, 32.6, 28.5, 28.3, 27.9, 26.3, 18.8, –4.2.
FTIR (thin film) cm^{-1}:	2951 (s), 2930 (s), 2858 (m), 1753 (s), 1689 (s), 1414 (m), 1253 (m), 840 (m).
HRMS (ESI):	calcd for $C_{22}H_{35}NaNO_4Si$ [M+Na]$^+$: 428.2228, found: 428.2226.
TLC, *Rf*: (3% acetone in CH_2Cl_2, neutralized plates)	**47**, 0.63 (UV, CAM) **51**, 0.30 (UV, CAM)

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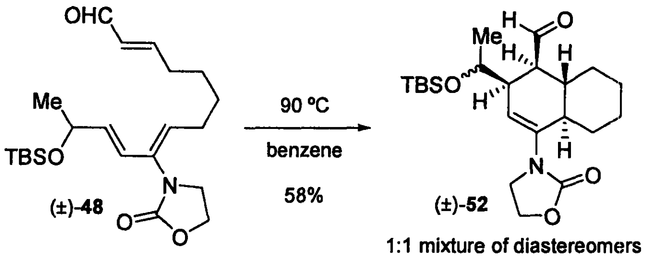
[11] Concentration of the reaction mixture of extended reaction times resulted in decomposition of the sensitive tetraene **51**.



Silyl ether bicycle 52:

Triene (±)-**48** (24.5 mg, 0.064 mmol, 1 equiv) was dissolved in benzene (750 μL) under argon atmosphere and the vessel was heated to 90 °C. After 23 h, the solvent was removed under reduced pressure and the resulting oil purified by flash column chromatography (silica gel: diam. 1 cm, ht. 5 cm; eluent: hexanes:acetone [85:15]) to provide the (±)-*trans*-decalin aldehyde **52** as a yellow oil (14.1 mg, 58%, 1:1 mixture of diastereomers).

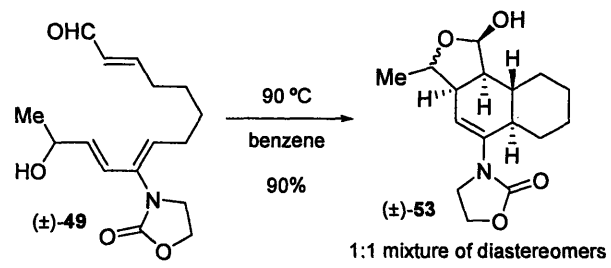
^{1}H NMR (500 MHz, C_6D_6, 20°C, mixture of two diastereomers, **52**:20-*epi*-**52**, ~1:1): 9.85 (d, J = 4.3 Hz, 1H, CHO), 9.74 (d, J = 3.6 Hz, 1H, CHO), 5.21 (dd, J = 5.2, 2.2 Hz, 1H, NC=C**H**), 5.04 (dd, J = 4.7, 2.1 Hz, 1H, NC=C**H**), 3.95-3.87 (m, 2H, C**H**COTBS, C**H**COTBS), 3.46-3.36 (m, 4H, OC**H**$_2$CH$_2$N, OC**H**$_2$CH$_2$N), 2.86 (app-p, J = 8.7 Hz, 2H), 2.61-2.54 (m, 2H), 2.50-2.41 (m, 2H), 2.37-2.25 (m, 2H), 2.25-2.16 (m, 2H), 2.09-1.93 (m, 4H), 1.84-1.78 (m, 1H), 1.76-1.56 (5H), 1.38-1.16 (m, 4H), 1.13 (d, J = 6.1 Hz, 3H, C**H**$_3$), 1.08 (d, J = 6.5 Hz, 3H, C**H**$_3$), 1.05-0.87 (m, 2H), 0.98 (s, 9H, SiC(C**H**$_3$)$_3$), 0.95 (s, 9H, SiC(C**H**$_3$)$_3$), 0.78 (app-dq, J = 13.0, 5.1 Hz, 2H), 0.08 (s, 3H, SiC**H**$_3$), 0.04 (s, 3H, SiC**H**$_3$), 0.04 (s, 3H, SiC**H**$_3$), 0.01 (s, 3H, SiC**H**$_3$).

^{13}C NMR (125 MHz, C_6D_6, 20°C mixture of two diastereomers, **52**:20-*epi*-**52**, ~1:1): 203.6 (**C**HO), 202.8 (**C**HO), 156.0 (carbamate-**C**=O), 155.9 (carbamate-**C**=O), 140.7, 140.3, 117.3, 117.3, 70.5, 70.3, 61.8, 61.8, 54.8, 53.6, 47.0, 46.7, 45.5, 44.4, 43.0, 42.7, 38.3, 38.3, 31.2, 30.8, 30.6, 30.3, 27.1, 27.0, 27.0, 27.0, 26.5, 26.5, 22.9, 22.7, 18.6, 18.6, –3.6 (SiCH$_3$), –3.7 (SiCH$_3$), –3.9(SiCH$_3$), –4.2 (SiCH$_3$).

FTIR (thin film) cm^{-1}: 3411 (br-w), 2929 (s), 2856 (m), 1754 (br-s), 1410 (m), 1254 (m), 836 (m).

HRMS (ESI): calcd for $C_{22}H_{37}NNaO_4Si$ [M+Na]$^+$: 430.2384, found: 430.2399.

TLC (40% acetone in hexanes), *Rf*: **48,** 0.53 (UV, CAM, $KMnO_4$)
52, 0.55 (UV, CAM, $KMnO_4$)



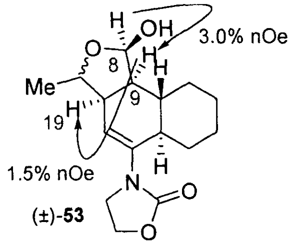
Hemiacetal bicycle 53:

Triene (±)-**49** (33.0 mg, 0.112 mmol, 1 equiv) was dissolved in benzene (750 µL) under argon atmosphere and the vessel was heated to 90 °C. After 13 h, the solvent was removed under reduced pressure and the resulting oil purified by flash column chromatography (silica gel: diam. 1 cm, ht. 5 cm; eluent: hexanes:acetone [70:30]) to provide the (±)-*trans*-decalin acetal **53** as a white solid (29.6 mg, 90%, 1:1 mixture of diastereomers).

^{1}H NMR (500 MHz, C_6D_6, 20°C, mixture of two diastereomers, **53**:20-*epi*-**53**, ~1:1): 5.47 (d, *J* = 2.6 Hz, 1H, HOC**H**), 5.43 (d, *J* = 3.3 Hz, 1H, HOC**H**), 5.13 (dd, *J* = 4.9, 2.2 Hz, 1H, NC=C**H**), 5.13 (dd, *J* = 4.7, 2.2 Hz, 1H, NC=C**H**), 4.56 (ddd, *J* = 13.1, 9.1, 6.1 Hz, 1H, **C**HCH_3), 3.88 (ddd, *J* = 12.1, 9.3, 6.1 Hz, 1H, **C**HCH_3), 3.66 (d, *J* = 3.5 Hz, 1H, O**H**), 3.52-3.45 (m, 5H, O**H**, OC**H**$_2$CH$_2$N, OC**H**$_2$CH$_2$N), 3.23 (tdd, *J* = 10.1, 4.7, 2.5 Hz, 1H, C=CHC**H**), 2.88 (qd, *J* = 8.7, 3.6 Hz, 2H, OCH$_2$C**H**$_2$N, OCH$_2$C**H**$_2$N), 2.68 (tdd, *J* = 9.3, 5.1, 2.2 Hz, 1H, C=CHC**H**), 2.55-2.48 (m, 2H, OCH$_2$C**H**$_2$N, OCH$_2$C**H**$_2$N), 2.38-2.31 (m, 1H, NCC**H**), 2.30-2.23 (m, 1H, NCC**H**), 2.08-1.99 (m, 4H, HOCHC**H**, HOCHC**H**), 1.80 (app-td, *J* = 12.9, 2.3 Hz, 2H), 1.71-1.57 (m, 4H), 1.40 (d, *J* = 6.0 Hz, 3H, C**H**$_3$), 1.34-1.22 (m, 3H), 1.22-1.01 (m, 3H), 1.14 (d, *J* = 6.6 Hz, 3H, C**H**$_3$), 0.94-0.79 (m, 4H).

^{13}C NMR (125 MHz, C_6D_6, 20°C mixture of two diastereomers, **53**:20-*epi*-**53**, ~1:1):156.4 (carbamate-C=O), 156.3 (carbamate-C=O), 140.1, 139.8, 117.2, 116.7, 100.9, 99.5, 81.7, 75.8, 62.0, 62.0, 51.0, 50.0, 47.2, 47.0, 44.8, 41.8, 41.3, 40.9, 39.8, 38.8, 32.1, 31.1, 30.4, 30.3, 27.0 26.9, 26.9, 26.9, 22.5, 20.6.

nOe data (500 MHz, C_6D_6, 20°C):



(±)-**53**

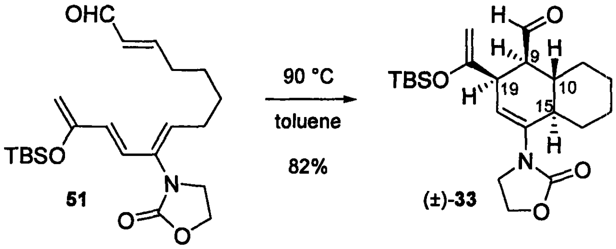
1:1 mixture of diastereomers

FTIR (thin film) cm^{-1}: 3406 (br-s, OH), 2926 (s), 2855 (m), 1747 (br-s), 1415 (s), 1279 (m), 1236 (m), 1082 (m), 994 (m).

HRMS (ESI): calcd for $C_{16}H_{23}NNaO_4$ $[M+Na]^+$: 316.1519, found: 316.1513..

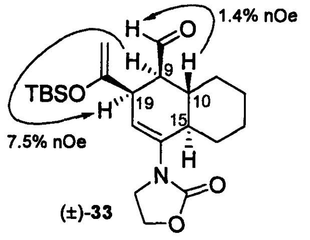
TLC, *Rf*:
(40% acetone in hexanes)

49, 0.18 (UV, CAM, $KMnO_4$)
53, 0.24 (UV, CAM, $KMnO_4$)

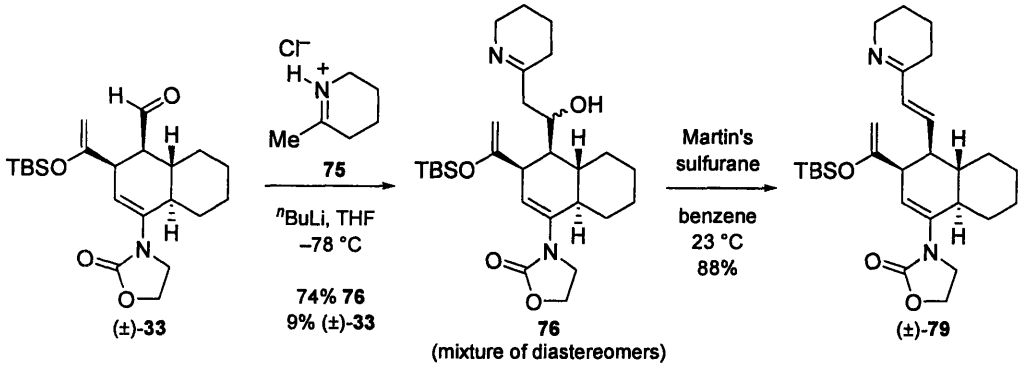


(±)-(9*S*, 10*R*, 15*R*, 19*S*)-*trans*-Decalin aldehyde 33:

A flame-dried Schlenk flask was charged with tetraene **51** (279 mg, 0.688 mmol, 1 equiv) and toluene (34 mL) and sealed under argon atmosphere. The vessel was heated to 90 °C. After 13 h, the solvent was removed under reduced pressure and the resulting oil was purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 8 cm; eluent: CH_2Cl_2:acetone:NEt_3 [94:5:1]) to provide the (±)-*trans*-decalin aldehyde **33** as a yellow oil (228 mg, 82%).

^{1}H NMR (500 MHz, C_6D_6, 20°C):	9.66 (d, J = 5.2 Hz, 1H, CHO), 5.01 (dd, J = 5.2, 2.1 Hz, 1H, NC=C**H**), 4.37 (d, J = 1.1 Hz, 1H, C=C**H**$_2$), 4.34 (d, J = 1.0 Hz, 1H, C=C**H**$_2$), 3.42-3.33 (m, 2H, OC**H**$_2$CH$_2$N), 2.98-2.95 (m, 1H, C**H**COTBS), 2.79 (q, J = 8.6 Hz, 1H, OCH$_2$C**H**$_2$N), 2.50-2.45 (m, 1H, OCH$_2$C**H**$_2$N), 2.33-2.28 (m, 1H, HCC(N)C**H**), 2.26-2.21 (m, 1H, CHOC**H**), 2.04-1.97 (m, 2H, CHOCHC**H**), 1.67-1.62 (m, 2H, (C**H**$_2$)$_4$), 1.54-1.52 (m, 1H, (C**H**$_2$)$_4$), 1.26 (qt, J = 13.2, 3.8 Hz, 1H, (C**H**$_2$)$_4$), 1.17-1.09 (m, 1H, (C**H**$_2$)$_4$), 1.03-0.92 (m, 1H, (C**H**$_2$)$_4$), 0.97 (s, 9H, SiC(C**H**$_3$)$_3$), 0.83 (qd, J = 3.8, 12.6 Hz, 1H, (C**H**$_2$)$_4$), 0.14 (s, 3H, SiC**H**$_3$), 0.12 (s, 3H, SiC**H**$_3$).
^{13}C NMR (125 MHz, C_6D_6, 20°C):	203.6 (CHO), 158.2 (carbamate-**C**=O), 156.2, 140.8, 117.8, 95.4, 62.0 (O**C**H$_2$CH$_2$N), 53.9, 46.7 (OCH$_2$**C**H$_2$N), 44.4, 42.7, 37.4, 30.9, 27.2, 27.0, 26.4 (SiC(**C**H$_3$)$_3$), 18.8, –3.9 (Si**C**H$_3$), –4.3 (Si**C**H$_3$).
nOe data (500 MHz, C_6D_6, 20°C):	
FTIR (thin film) cm^{-1}:	2929 (s), 2857 (m), 1756 (s), 1724 (s), 1408 (m), 1255 (m), 1220 (m), 837 (s).

HRMS (ESI):	calcd for $C_{22}H_{36}NO_4Si$ $[M+H]^+$: 406.2408, found: 406.2403.
TLC, *Rf*:	
(30% acetone in hexanes, pretreat NEt_3)	**51**, 0.26 (UV, CAM) **33**, 0.33 (CAM)



β–hydroxy imine 76 and α,β–unsaturated imine (±)-79:

To a suspension of iminium chloride **75** (68 mg, 0.51 mmol, 2.0 equiv) in THF (600μL) at –78 °C and sealed under argon[12] was added a solution of *n*-butyllithium in hexanes (2.53 M, 380 μL, 1.9 mmol, 3.9 equiv). The resulting brown solution was maintained at –78 °C for 30 min, was warmed to 0 °C for 10 min, then cooled to –78 °C. A sample of aldehyde (±)-**33** (101 mg, 0.25 mmol, 1 equiv) in a round-bottomed flask was azeotropically dried from toluene (2 x 2 mL), the flask was evacuated and backfilled with argon three times, charged with THF (600 μL), and cooled to –78 °C. The lithiated enamine solution was transferred cold via cannula to the cold aldehyde solution. After ten minutes excess anion was quenched at –78 °C by the addition of saturated aqueous ammonium chloride solution (1 mL) and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate (65 mL) and saturated aqueous ammonium chloride solution (25 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 60 mL) and the combined organic layers were washed with brine (25 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 6.5 cm; eluent: hexanes:acetone:NEt_3 [89:10:1] to hexanes:acetone:NEt_3 [74:25:1] to provide β–hydroxyimine (±)-**76** (92 mg, 74%, mixture of diastereomers) as a yellow foam. Additionally, the starting aldehyde (±)-**33** was recovered (9.5 mg, 9%).

To a solution of β–hydroxyimine (±)-**76** (92 mg, 0.18 mmol, 1 equiv, equal mixture of two diastereomers) in benzene (8 mL) at 23 °C was added a solution of Martin sulfurane (170 mg, 0.25 mmol, 1.4 equiv) in benzene (1 mL) via syringe. After 1 h the solution was concentrated under reduced pressure and the resulting orange residue purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 5 cm; eluent: acetone:hexanes:NEt_3 [79:10:1] to acetone:hexanes:NEt_3 [69:30:1] to acetone:hexanes:NEt_3 [64:35:1]) to provide the α,β-unsaturated imine (±)-**79** (78 mg, 88%). as a clear solid.

^{1}H NMR (500 MHz, C_6D_6, 20 °C):	6.43 (d, *J* = 16.1 Hz, 1H, C7-H), 6.08 (dd, *J* = 16.2, 10.3 Hz, 1H, C8-H), 5.14 (dd, *J* = 5.1, 2.1 Hz, 1H, C17-H), 4.29 (s, 1H, C21-H), 4.25 (s, 1H, C21-H), 3.75 (br-t, 2H, C2-H), 3.46-3.42

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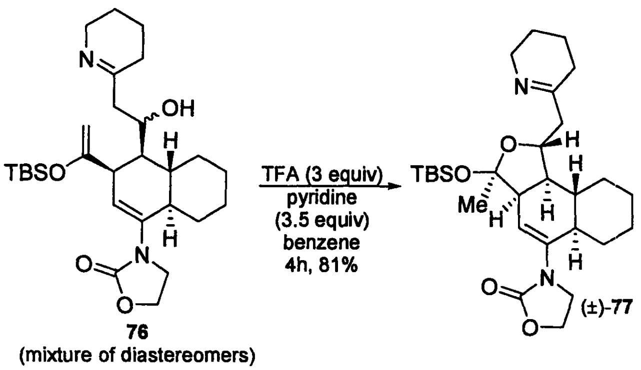
[12] Rigorous inert atmosphere and anhydrous conditions were required for optimal results.

	(m, 2H, $OC\mathbf{H}_2CH_2N$), 2.94 (app-q, *J* = 8.8 Hz, 1H, $OCH_2C\mathbf{H}_2N$), 2.77 (m, 1H, C19-H), 2.64 (dt, *J* = 8.3, 5.1 Hz, 1H, $OCH_2C\mathbf{H}_2N$), 2.42 (m, 1H, C15-H), 2.27 (br-dt, *J* = 11.5, 6.3 Hz, 1H, C5-H), 2.15 (td, *J* = 10.9, 6.3 Hz, 1H, C9-H), 2.12-2.03 (m, 2H, C14-H, C5-H), 1.84 (m, 1H, C10-H), 1.80-1.68 (m, 2H, C11-H, C12-H), 1.44-1.20 (m, 6H, C3-H, C3-H, C4-H, C4-H, C12-H, C13-H), 1.06 (app-dq, *J* = 12.3, 3.2 Hz, 1H, C14-H), 1.00-0.92 (m, 10H, $SiC(C\mathbf{H}_3)_3$, C13-H), 0.81 (aqd, *J* = 3.2, 12.6 Hz, 1H, C11-H), 0.18 (s, 3H, $SiC\mathbf{H}_3$), 0.17 (s, 3H, $SiC\mathbf{H}_3$).
^{13}C NMR (125 MHz, C_6D_6, 20 °C):	164.9, 159.0, 140.5, 137.6 (C8), 136.3 (C7), 119.3 (C17), 94.3 (C21), 61.8 (Ca), 50.4 (C19), 48.0 (C2), 46.8 (Cb), 46.6 (C9), 43.2 (C15), 40.3 (C10), 31.7 (C11), 30.6 (C14), 27.4 (C12), 27.1 (C13), 26.3 ($SiC(\mathbf{C}H_3)_3$), 26.2 (C5), 23.0 (C3), 20.2 (C4), 18.7 ($Si\mathbf{C}(CH_3)_3$), -4.1 ($SiCH_3$), -4.2 ($SiCH_3$).
FTIR (thin film) cm^{-1}:	2929 (s), 2856 (m), 1757 (s, C=O), 1619 (w), 1406 (m), 1216 (br-m), 836 (m).
TLC, *Rf*: (50% acetone in hexanes, neutralized plates)	**33**, 0.64 (UV, CAM) **76**, 0.55 (ninhydrin, green) **79**, 0.45 (UV, ninhydrin, yellow)
HRMS (ESI):	**76**, calcd for $C_{28}H_{47}N_2O_4Si$ $[M+H]^+$: 503.3300, found: 503.3312. **79**, calcd for $C_{29}H_{47}N_2O_3Si$ $[M+H]^+$: 485.3171, found: 485.3198

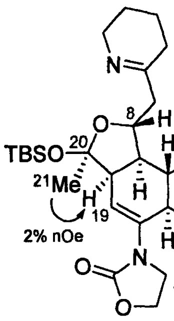


Imine-acetal (±)-77:

To a solution of β-hydroxyimine **76** (65.1 mg, 0.129 mmol, 1 equiv, equal mixture of two diastereomers) in benzene (12.9 mL) at 23 °C was added pyridine (36.5 μL, 0.451 mmol, 3.5 equiv), followed by dropwise addition of trifluoroacetic acid (30 μL, 0.388, 3.o equiv). After 4 h the solution was concentrated under reduced pressure and the resulting oil purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 9 cm; eluent: hexanes:acetone:NEt_3 [79:20:1] to hexanes:acetone:NEt_3 [69:30:1]) to provide the acetal (±)-**77** as an orange solid (51.4 mg, 81%).

^{1}H NMR (500 MHz, C_6D_6, 20°C):	5.15 (dd, J = 4.2, 2.5 Hz, 1H, C17-H), 4.48-4.43 (m, 1H, C8-H), 3.60 (br-s, 2H, C2-H), 3.50-3.44 (m, 2H, $O\mathbf{CH_2}CH_2N$), 3.07 (app-q, J = 8.6 Hz, 1H, $OCH_2\mathbf{CH_2}N$), 2.89-2.83 (m, 1H, $OCH_2\mathbf{CH_2}N$), 2.49-2.42 (m, 1H, C15-H), 2.42-2.37 (m, 1H, C7-H), 2.37-2.32 (m, 1H, C19-H), 2.23-2.17 (m, 1H, C10-H), 2.03-1.81 (m, 4H), 1.77-1.60 (m, 4H, C9-H), 1.43 (s, 3H, C21-H), 1.42-1.15 (m, 6H), 1.02-0.89 (m, 1H), 0.95 (s, 9H, $SiC(\mathbf{CH_3})_3$), 0.77 (qd, J = 12.8, 3.4 Hz, 1H), 0.26 (s, 3H, $Si\mathbf{CH_3}$), 0.22 (s, 3H, $Si\mathbf{CH_3}$).
^{13}C NMR (125 MHz, C_6D_6, 20°C):	167.2 (N=**C**), 156.0 (carbamate-**C**=O), 140.2 (NC=CH), 116.5, 106.5 (**C**CH_3), 81.1, 61.6 (OCH_2CH_2N), 50.2, 49.3, 47.9, 47.3, 46.3, 42.3, 41.3, 31.4, 30.6, 29.6, 27.0, 26.9, 26.8, 26.2 ($SiC(CH_3)_3$), 22.3, 20.0, 18.3, -2.6 ($SiCH_3$), -2.7 ($SiCH_3$).

nOe data (500 MHz, C_6D_6, 20°C):

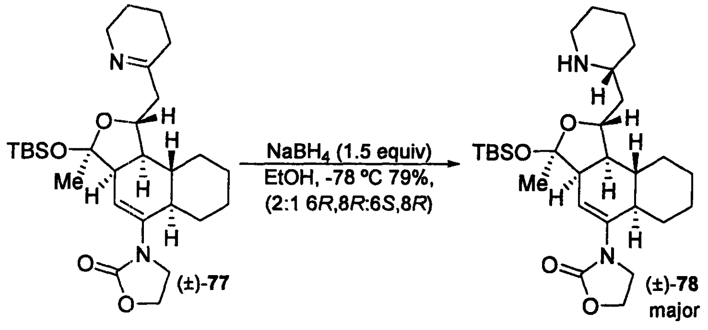


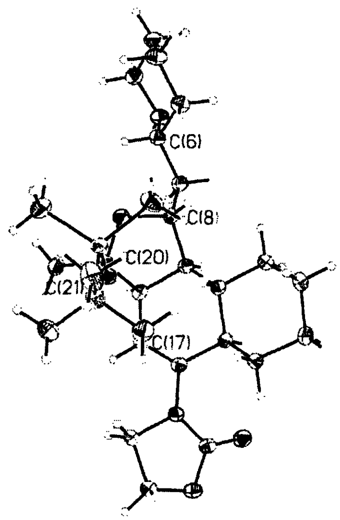
(±)-**77**

FTIR (thin film) cm^{-1}: 3424 (br-s), 2927 (m), 2854 (w), 1757 (m), 1659 (br-w), 1408 (w), 992 (m).

HRMS (ESI): calcd for $C_{28}H_{48}N_2O_4Si$ $[M+H]^+$: 503.3300, found:.503.3302.

TLC, *Rf*:
(30% acetone in hexanes, neutralized plates) **76**, 0.14 (ninhydrin, CAM)
77, 0.44 (ninhydrin, CAM)





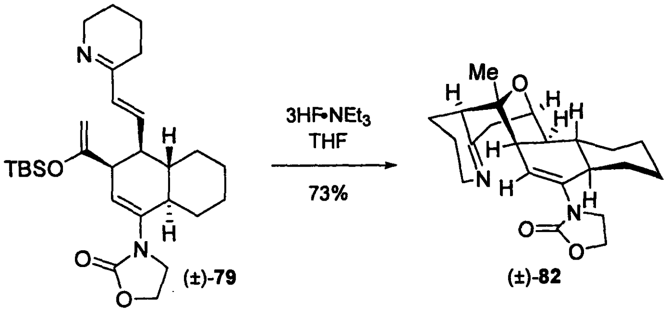
Amine acetal tetracycle 78:

To a solution of imine acetal (±)-**77** (1.9 mg, 3.9 μmol, 1 equiv) in ethanol (1 mL) at –78 °C was added a solution of sodium borohydride in ethanol (0.07M, 80 μL, 59 μmol, 1.5 equiv). After 1 h excess hydride was quenched at –78 °C by the addition of saturated aqueous ammonium chloride (1 mL) and the solution was allowed to warm to ambient temperature. The resulting heterogeneous solution was diluted with ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate (5 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (5 mL) and the combined organic layers were washed with brine (5 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (neutralized silica gel: diam. 0.5 cm, ht. 1.2 cm; eluent: hexanes:acetone:NEt$_3$ [54:45:1]) to provide the amine acetal tetracycles (±)-**78** (major) and (±)-6-*epi*-**78** (minor) as a mixture of diastereomers (1.5 mg, 79%, 2:1 **78**:6-*epi*-**78**).

^{1}H NMR (500 MHz, C$_6$D$_6$, 20°C):	(major diastereomer **78**): 5.16 (dd, J = 4.0, 2.3 Hz, 1H, C17-H), 4.16 (dt, J = 9.9, 3.8 Hz, 1H), 3.53-3.45 (m, 2H, OC**H$_2$**CH$_2$N), 3.11 (app-q, J = 8.6 Hz, OCH$_2$C**H$_2$**N), 3.04 (br-d, J = 11.8 Hz, 1H), 2.90-2.84 (m, 1H, OCH$_2$C**H$_2$**N), 2.77-2.70 (m, 1H), 2.52 (td, J = 12.0, 3.1 Hz, 1H), 2.47-2.39 (m, 1H, C15-H), 2.36-2.31 (m, 1H, C19-H), 2.25-2.19 (m, 1H, C10-H), 1.85-1.65 (m, 5H), 1.65-1.56 (m, 1H), 1.56-1.17 (m, ?H), 1.46 (s, 3H, C21-H), 1.01-0.90 (m, 1H), 0.93 (s, 9H, SiC(C**H$_3$**)$_3$), 0.82-0.72 (m, 1H), 0.21 (s, 3H, SiC**H$_3$**), 0.19 (s, 3H, SiC**H$_3$**).

TLC, *Rf*:

(70% acetone in hexanes, neutralized plates)	**77**, 0.58 (CAM)
	6-*epi*-**78** (minor), 0.22 (CAM)
	78 (major), 0.19 (CAM)



(±)-79 (±)-82

Pentacyclic ether (±)-82:

To a solution of α,β–unsaturated imine (±)-**79** (3.0 mg, 6.1 μmol, 1 equiv) in THF (610 μL) at 23 °C was added triethylamine trihydrogen fluoride (6 μL, 0.037 mmol, 6.0 equiv). After 15 hours, the reaction mixture was concentrated under reduced pressure[13] and purified by flash column chromatography (neutralized silica gel: diam. 0.5 cm, ht. 2.5 cm; eluent: hexanes:acetone:NEt_3 [69:30:1] to provide ether (±)-**82** (1.6 mg, 73%) as a yellow oil.

^{1}H NMR (500 MHz, C_6D_6, 20 °C) δ:	5.74 (d, *J* = 2.1 Hz, 1H, C17-H), 4.75 (ddd, *J* = 10.5, 8.0, 3.8 Hz, 1H, C8-H), 3.61 (br-t, 2H, C2-H), 3.45-3.42 (m, 2H, O**CH$_2$**CH$_2$N), 2.89 (app-q, *J* = 8.6 Hz, 1H, OCH$_2$**CH$_2$**N), 2.69 (m, 1H, C15-H), 2.59-2.52 (m, 3H, OCH$_2$**CH$_2$**N, C7-H, C19-H), 2.04 (dtt, *J* = 18.5, 5.6, 2.1 Hz 1H), 1.91 (dtt, *J* = 18.5, 5.6, 2.1 Hz 1H), 1.72 (app-d, *J* = 1.7 Hz, 3H, C21-H), 1.70-1.66 (m, 2H), 1.57 (m, 1H), 1.36-1.26 (m, 6H), 1.05 (app-qt, *J* = 13.2, 4.0 Hz, 1H), 0.93 (app-qd, *J* = 12.4, 3.4 Hz, 1H,), 0.83 (app-qd, *J* = 12.2, 3.8 Hz, 1H).
^{13}C NMR (100 MHz, C_6D_6, 20 °C) δ:	167.3, 156.1, 148.4, 135.3, 112.1, 110.2 (C17), 85.0 (C8), 61.8 (OCH$_2$CH$_2$N), 52.3 (C19), 49.7 (C19), 48.1 (C7), 47.0 (C9), 46.9 (OCH$_2$CH$_2$N), 43.5 (C15), 30.9 (C11), 30.8 (C13), 30.6 (C14), 27.3 (C12), 26.7, 22.6 (C3), 20.4 (C4), 12.1 (C21).
FTIR (neat) cm^{-1}:	2923 (s), 2852 (m), 1750 (s), 1411 (m), 1216 (m).

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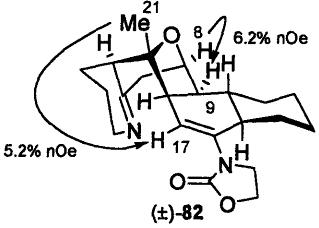
[13] The ether product was highly air-sensitive and must be handled under rigorous air-free conditions.

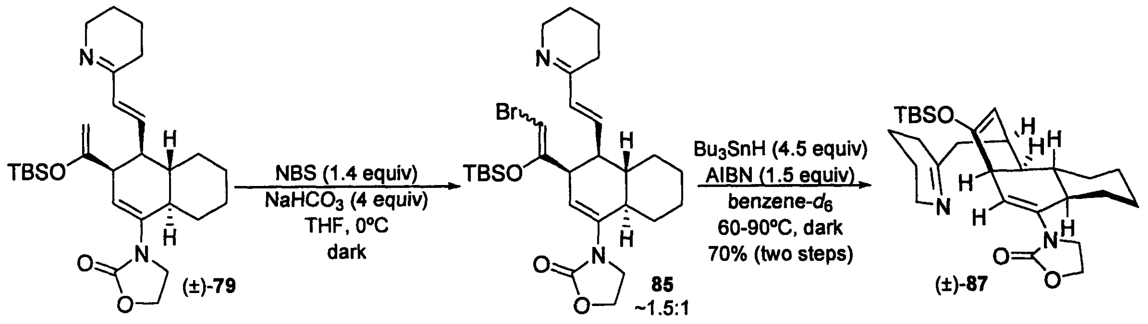
nOe data (500 MHz, C_6D_6, 20°C): Additional data: H8-H7 (5.8%).



(±)-**82**

FTIR (neat) cm^{-1}: 2923 (s), 2852 (m), 1750 (s, C=O), 1411 (m), 1216 (br-m), 1038 (w).

TLC, *Rf*:
(50% acetone in hexanes, neutralized plates) **79**, 0.45 (UV, ninhydrin, yellow)
82, 0.38 (ninhydrin)



Tetracycle (±)-87:

A solution of α,β–unsaturated imine (±)-**79** (37.8 mg, 0.0780 mmol, 1 equiv) in THF (4 mL) was degassed via an argon purge. To this solution was added solid sodium bicarbonate (35.0 mg, 0.417 mmol, 5.34 equiv) under argon. The reaction mixture was cooled to 0 °C, light was excluded, and NBS (17.5 mg, 0.098 mmol, 1.3 equiv) was added as a solid. The reaction mixture was maintained at 0 °C for ten minutes, then diluted with hexanes:acetone:NEt_3 ([50:50:1], 10 mL), was filtered cold through a silica plug (diam. 0.5 cm, ht. 2.5 cm) and the filtrate was concentrated under reduced pressure to produce an orange-brown foam. This residue was dissolved in benzene and filtered to remove excess insoluble succinimide, and the solution was then concentrated and placed under reduced pressure (~ 0.5 Torr) for 1 h. The resulting brominated product was used crude for the cyclization step.

The crude vinyl bromide was dissolved in benzene-d_6[14] (1.2 mL), was degassed via an argon purge, and was charged with tributyltin hydride (62 μL, 0.23 mmol, 3.00 equiv). A solution of AIBN in benzene-d_6 (0.30M) was prepared in a flame-dried flask, degassed via bubbling argon, and a portion[15] (66 μL, 0.0195 mmol, 0.25 equiv) was transferred to the reaction mixture. The reaction solution was placed in a pre-heated 60 °C oil bath and heated to 90 °C over 20 min. After 30 min, the reaction mixture was cooled, an additional portion of AIBN was added (66 μL, 0.0195 mmol, 0.25 equiv), and the mixture was returned to 90 °C. After a subsequent 20 min, the solution was cooled, additional tributyltin hydride (32 μL, 0.12 mmol, 1.5 equiv) and AIBN (132 μL, 0.039 mmol, 0.50 equiv) were added, and the reaction was returned to 90 °C. After 30 min, the reaction was cooled, a final portion of AIBN was added (132 μL, 0.039 mmol, 0.50 equiv), and the mixture was returned to 90 °C. After an additional 30 min at 90 °C, the reaction appeared complete by direct ^1H NMR spectral analysis. The reaction solution was cooled, triethylamine (300 μL) was added to neutralize adventitious hydrobromic acid, and the solution was concentrated to ~200 μL under reduced pressure. The resulting brown oil was purified via flash column chromatography (neutralized silica gel: diam. 1.0 cm, ht. 10 cm; eluent: hexanes:acetone:NEt_3 [97:2:1] to acetone:hexanes:NEt_3 [94:5:1] to acetone:hexanes:NEt_3 [91:8:1] to acetone:hexanes:NEt_3 [89:10:1]) to provide a tetracycle (±)-**87** as a tan foam (26.3 mg, 70% (two steps)).

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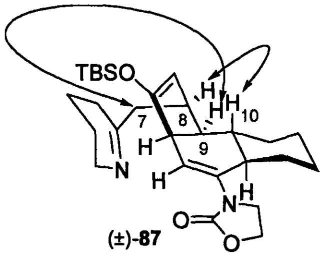
[14] Deuterated solvent was used to facilitate evaluation of reaction progress by direct ^1H NMR monitoring.

[15] Sequential addition of the reagents was necessary for optimal results.

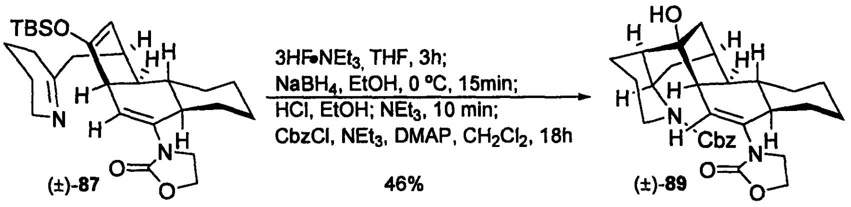
^{1}H NMR (500 MHz, C_6D_6, 20 °C): 5.65 (dd, *J* = 4.3, 2.4 Hz, 1H, C17-H), 4.75 (app-t, *J* = 2.7 Hz, 1H, C21-H), 3.61 (br-t, 2H, C2-H), 3.45-3.35 (m, 3H, $OC\mathbf{H}_2CH_2N$, C19-H), 3.08 (app-q, *J* = 8.5 Hz, 1H, $OCH_2C\mathbf{H}_2N$), 2.96 (m, 1H, C8-H), 2.71 (dt, *J* = 8.5, 4.9 Hz, 1H, $OCH_2C\mathbf{H}_2N$), 2.47 (m, 1H, C15-H), 2.17 (m, 3H, C7-H), 2.06 (m, 1H), 1.82-1.72 (m, 4H, C9-H), 1.42-1.25 (m, 6H), 1.17 (m, 1H C10-H), 1.00-0.92 (m, 10H, $SiC(C\mathbf{H}_3)_3$), 0.90 (m, 1H), 0.20 (s, 3H, $SiC\mathbf{H}_3$), 0.18 (s,3H, $SiC\mathbf{H}_3$).

TLC, *Rf*:
(50% acetone in hexanes, neutralized plates) **87**, 0.63 (ninhydrin)

NOESY correlations (600 MHz, C_6D_6, 20 °C): H7-H9, H8-H10.



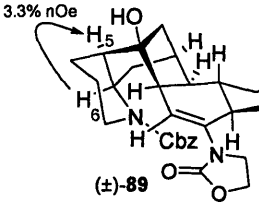
(±)-**87**



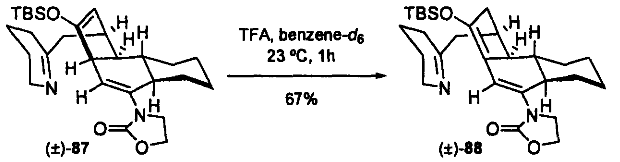
__Pentacycle (±)-89:*__

To a solution of tetracycle (±)-**87** (45.9 mg, 0.095 mmol, 1 equiv) in THF (5 mL) at 23 °C was added triethylamine trihydrogen fluoride (77 μL, 0.47 mmol, 5.0 equiv). After 3 h, the solution was cooled to 0 °C and the volatiles were removed under reduced pressure on a manifold and allowed to warm to ambient temperature (3 h). The crude reaction mixture was dissolved in ethanol (3.5 mL) and cooled to 0 °C. A suspension of sodium borohydride (5.5 mg, 0.14 mmol, 1.5 equiv) in ethanol (1.5 mL) was added dropwise to the cold reaction mixture under an argon atmosphere. The resulting solution was stirred at 0 °C for ten minutes, then excess hydride was quenched at 0 °C by the addition of ethanolic hydrochloric acid (0.5 M, 200 μL) and the solution was vigorously stirred for five minutes. The reaction mixture was neutralized by the addition of triethylamine (300 μL), was stirred for five minutes, and the volatiles were removed under reduced pressure on a manifold (2 h). The resulting white solid was dissolved in CH_2Cl_2 (1.9 mL), followed by the addition of triethylamine (66 μL, 0.48 mmol, 5.0 equiv), 4-dimethylaminopyridine (18 mg, 0.14 mmol, 1.5 equiv), and benzylchloroformate (27 μL, 0.19 mmol, 2.0 equiv). After 2 h, an additional portion of benzylchloroformate (27 μL, 0.19 mmol, 2 equiv) was added. After an additional 13 h, the reaction was diluted with ethyl acetate (25 mL), hexanes (25 mL), and saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (30 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow oil via flash column chromatography (silica gel: diam. 1 cm, ht. 10 cm; eluent: hexanes:acetone [85:15] to hexanes:acetone [80:20] to hexanes:acetone [70:30]) afforded pentacycle (±)-**89** (22.1 mg, 46%, three steps) as a clear oil.

^{1}H NMR (500 MHz, C_6D_6, 20 °C):	7.33-7.29 (m, 2H, ArH), 7.20-7.12 (m, 2H, ArH), 7.09-7.04 (m, 1H, ArH), 5.85 (br-s, 1H, C17-H), 5.25 (d, *J* = 12.4 Hz, 1H, CH_2Ph), 5.19 (d, *J* = 12.4 Hz, 1H, CH_2Ph), 4.70-4.62 (m, 1H, C6-H), 4.17 (br-d, *J* = 12.5 Hz, 1H, C2-H), 3.49-3.39 (m, 2H, OCH_2CH_2N), 2.94 (app-q, *J* = 8.6 Hz, 1H, OCH_2CH_2N), 2.70 (dt, *J* = 8.6, 5.9 Hz, 1H, OCH_2CH_2N), 2.66 (br-s, 1H, OH), 2.51-2.47 (m, 1H, C15-H), 2.44 (dt, *J* = 12.8, 2.3 Hz, 1H, C2-H), 2.12-1.91 (m, 2H, C10-H, C7-H), 1.81-1.52 (m, 4H, C4-H, C5-H, C8-H, C21-H), 1.38-1.28 (m, 2H, C3-H), 1.28-1.17 (m, 2H, C21-H), 1.15-0.89 (m, 4H, C3-H, C7-H, C19-H), 0.87-0.77 (m, 1H), 0.68 (app-q, *J* = 11.7 Hz, 1H, C9-H).

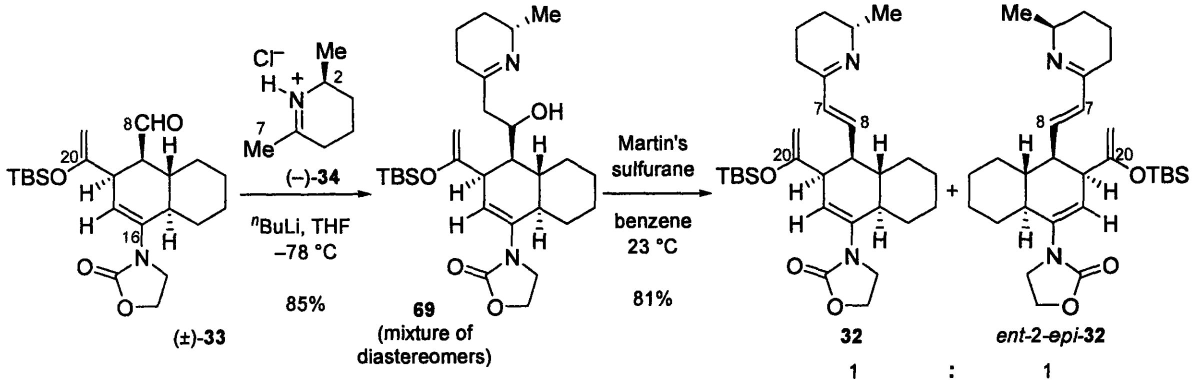
^{13}C NMR (125 MHz, C_6D_6, 20 °C):	157.2, 155.7, 139.7 (C16), 138.2, 129.1, 128.9, 123.5 (C17), 80.3 (C20), 67.5 ($BnCH_2$), 61.9 (Ca), 52.6 (C19), 48.0 (C6), 48.0 (Cb), 47.7 (C5), 46.2 (C9), 40.8 (C10), 40.5 (C2), 39.5 (C15), 34.6, 34.0 (C8), 33.3, 30.0 (C7), 29.4, 27.1, 27.0 (C21), 25.8 (C3), 23.5 (C4).
nOe data (500 MHz, C_6D_6, 20°C):	 (±)-89
FTIR (neat) cm^{-1}:	3428 (br-m, OH), 2926 (s), 1735 (s), 1691 (s), 1424 (s), 1267 (s), 1169 (w), 1097 (m), 735 (w).
HRMS (ESI):	calcd for $C_{30}H_{38}NaN_2O_5$ $[M+Na]^+$: 529.2673, found: 529.2671.
TLC (40% acetone in hexanes), *Rf*:	**89**: 0.27 ($KMnO_4$)

*A silyl enol ether tautomer was also obtained using acid treatment:



Silyl tetracycle (±)-88:

To a solution of tetracycle (±)-**87** (1.0 mg, 2.0 μmol, 1 equiv) in benzene-d_6 (700 μL) was added a solution of trifluoroacetic acid in benzene-d_6 (0.13M, 38.5 μL, 5.0 μmol, 2.5 equiv) at 23 °C. After 1.5 h, excess acid was quenched by the addition of triethylamine (15 μL), the solution was concentrated under reduced pressure to 200 μL, and purified immediately by flash column chromatography (neutralized silica gel: diam. 0.5 cm, ht. 1.2 cm; eluent: hexanes:acetone:NEt_3 [84:15:1]) to provide the tetracycle (±)-**88** as a clear film (0.5 mg, 67%). ^{1}H NMR (500 MHz, C_6D_6, 20°C): 6.11 (d, J = 1.6 Hz, 1H, C17-H), 3.57 (m, 2H, C2-H), 3.37 (app-q, J = 8.4 Hz, 1H, OCH_2CH_2N), 3.29 (td, J = 8.8 Hz, 4.1 Hz, 1H, OCH_2CH_2N), 3.05 (app-q, J = 8.8 Hz, 1H, OCH_2CH_2N), 2.96-2.86 (m, 1H, C15-H), 2.61-2.53 (m, 1H, OCH_2CH_2N), 2.49-2.40 (m, 1H), 2.27-2.22 (m, 1H), 2.17-2.06 (m, 1H), 1.94-1.88 (m, 1H), 1.78-1.60 (m, 4H), 1.51-1.40 (m, 1H), 1.40-1.28 (m, 6H), 1.28-1.20 (m, 2H), 1.07-0.87 (m, 4H), 1.04 (s, 9H, $SiC(CH_3)_3$), 0.18 (s, 3H, $SiCH_3$), 0.17 (s, 3H, $SiCH_3$). TLC, *Rf*: (50% acetone in hexanes, neutralized plates): **87**, 0.52 (CAM); **88**, 0.54 (UV, CAM).



3-{3-[1-*tert*-Butyl-dimethyl-silanyloxy)-vinyl]-4-[2-(6-methyl-3,4,5,6-tetrahydro-pyridin-2-yl)-vinyl]-3,4,4a,5,6,8,8s-octahydro-naphthalene-1-yl}-oxazolidin-2-one (32):

To a suspension of iminium chloride (–)-(2*S*)-**34**[16] (101 mg, 0.68 mmol, 2.00 equiv) in THF at –78 °C and sealed under argon[17] was added a solution of *n*-butyllithium in hexanes (2.53 M, 520 µL, 1.32 mmol, 3.87 equiv). The resulting brown solution was maintained at –78 °C for 30 min, was warmed to 0 °C for 10 min, then cooled to –78 °C. A sample of aldehyde (±)-**33** (137 mg, 0.34 mmol, 1 equiv) in a round-bottomed flask was azeotropically dried from toluene (2 x 4 mL), the flask was evacuated and backfilled with argon three times, charged with THF (700 µL), and cooled to –78 °C. The lithiated enamine solution was transferred cold via cannula to the cold aldehyde solution. After ten minutes excess anion was quenched at –78 °C by the addition of saturated aqueous ammonium chloride solution (2 mL) and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate (40 mL) and saturated aqueous ammonium chloride solution (15 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 40 mL) and the combined organic layers were washed with brine (15 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 10 cm; eluent: CH_2Cl_2:acetone:NEt_3 [98:1:1] to CH_2Cl_2:acetone:NEt_3 [97:2:1] to CH_2Cl_2:acetone:NEt_3 [96:3:1]) to provide β–hydroxyimine **69** (168 mg, 85%, equal mixture of 4 diastereomers) as a light yellow oil. Additionally, the starting aldehyde (±)-**33** was recovered (8.1 mg, 6%).

A solution of Martin sulfurane (219 mg, 0.326 mmol, 1.18 equiv) in benzene (2 mL) under argon atmosphere,[17] was transferred via cannula to a solution of β–hydroxyimine **69** (153 mg, 0.276 mmol, 1 equiv) in benzene (4 mL) at 23 °C. After 25 min, the reaction mixture was concentrated under reduced pressure and the resulting oil was purified by flash column chromatography (neutralized silica gel: diam. 5 cm, ht. 18 cm; eluent: hexanes:acetone:NEt_3 [89:10:1] to acetone:hexanes:NEt_3 [84:15:1] to acetone:hexanes:NEt_3 [74:25:1] to acetone:hexanes:NEt_3 [64:35:1]) to provide the α,β-unsaturated imines (119 mg, 81%, **32**:*ent*-2-*epi*-**32**, ~1:1) as a yellow oil.

The corresponding enantiomers of the β–hydroxyimine (203 mg, 70%, equal mixture of 4 diastereomers) and the α,β-unsaturated imine (167 mg, 85%, *ent*-**32**:2-*epi*-**32**, ~1:1) were prepared using the same procedure and the imine salt (+)-(2*R*)-**34**.

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[16] Meiliana Tjandra, Movassaghi group, Massachussetts Institute of Technology, Cambridge, MA, 2005, personal communication.

[17] Rigorous inert atmosphere and anhydrous conditions were required for optimal results.

^{1}H NMR (500 MHz, C$_6$D$_6$, 20°C, equal mixture of two diastereomers, **32**:*ent*-2-*epi*-**32**, ~1:1): 6.46 (d, *J* = 4.6 Hz, 1H, C7-H), 6.43 (d, *J* = 4.6 Hz, 1H, C7-H), 6.13-6.05 (m, 2H, C8-H, C8-H), 5.14-5.11 (m, 2H, C17-H, C17-H), 4.29 (br-s, 2H, C21-H, C21-H), 3.62-3.52 (m, 2H, C2-H, C2-H), 3.46-3.41 (m, 4H, OC**H**$_2$CH$_2$N, OC**H**$_2$CH$_2$N), 2.95-2.89 (m, 2H, OCH$_2$C**H**$_2$N, OCH$_2$C**H**$_2$N), 2.79-2.75 (m, 2H, C19-H, C19-H), 2.65-2.60 (m, 2H, OCH$_2$C**H**$_2$N, OCH$_2$C**H**$_2$N), 2.40-2.31 (m, 4H, C5-H, C5-H, C15-H, C15-H), 2.19-2.07 (m, 6H, C5-H, C5-H, C9-H, C9-H, **CH$_2$**, **CH$_2$**), 2.01-1.94 (m, 2H, C10-H, C10-H), 1.86-1.71 (m, 8H, **CH$_2$**, **CH$_2$**), 1.57-1.49 (m, 8H, C3-H, C3-H, C4-H, C4-H), 1.39 (br-s, 3H, C1-H), 1.38 (br-s, 3H, C1-H), 1.36-1.21 (m, 6H, **CH$_2$**, **CH$_2$**), 0.97 (br-s, 18H, SiC(**CH$_3$**)$_3$), 0.19 (br-s, 3H, Si(**CH$_3$**)$_2$), 0.18 (br-s, 3H, Si(**CH$_3$**)$_2$), 0.17 (br-s, 3H, Si(**CH$_3$**)$_2$), 0.17 (br-s, 3H, Si(**CH$_3$**)$_2$).

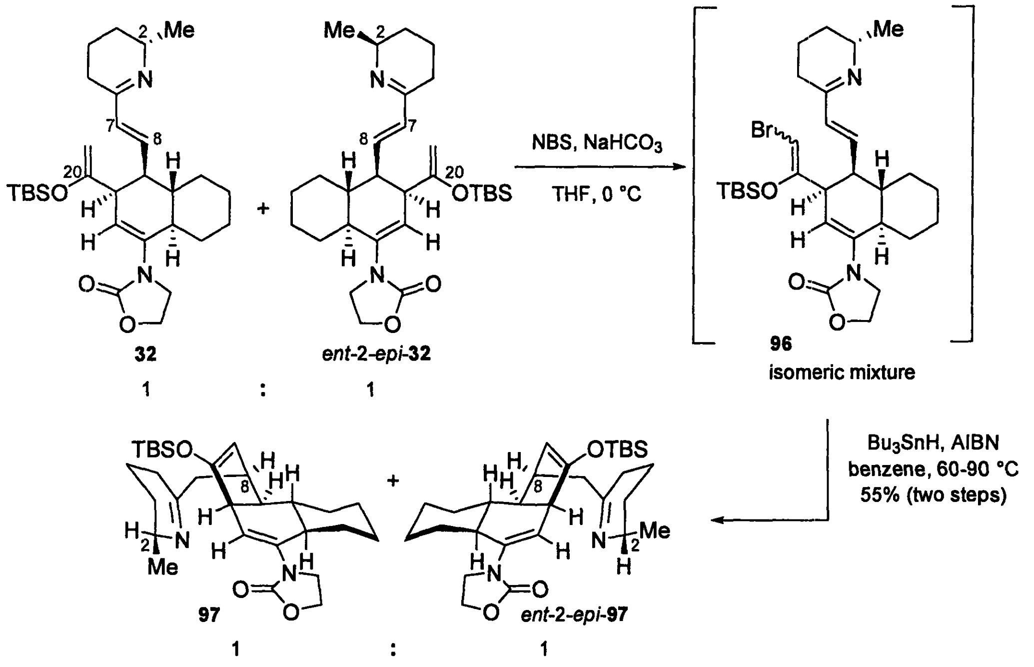
^{13}C NMR (125 MHz, C$_6$D$_6$, 20°C, equal mixture of two diastereomers, **32**:*ent*-2-*epi*-**32**, ~1:1): 163.99, 163.98, 159.64, 159.63, 156.01, 155.99, 140.46 (br-s, 2 carbons), 137.99 (C8), 137.95 (C8), 136.26 (C7), 136.19 (C7), 119.44 (C17), 119.25 (C17), 94.39 (C21), 94.34 (C21), 61.80 (br-s, 2 carbons, O**C**H$_2$CH$_2$N, O**C**H$_2$CH$_2$N), 54.53, 54.41, 48.05 (C19), 48.04 (C19), 46.82 (OCH$_2$**C**H$_2$N), 46.78 (OCH$_2$**C**H$_2$N), 46.63 (C9), 46.60 (C9), 43.21 (C15), 43.16 (C15), 40.39 (C10), 40.36 (C10), 31.74 (C11), 31.67 (C11), 30.65 (C14), 30.61 (C14), 30.42, 30.37, 27.39, 27.36, 27.11 (br-s, 2 carbons), 26.31, 26.29, 25.88, 25.85, 24.30, 24.26, 19.66, 19.47, 18.69 (SiC(**C**H$_3$)$_3$), –4.03 (Si(**C**H$_3$)$_2$), –4.05 (Si(**C**H$_3$)$_2$), –4.17 (Si(**C**H$_3$)$_2$), –4.23 (Si(**C**H$_3$)$_2$).

FTIR (thin film, equal mixture of two diastereomers, **32**:*ent*-2-*epi*-**32**, ~1:1) cm^{-1}: 2929 (s), 2856 (m), 1756 (s), 1615 (m), 1406 (m), 1259 (m), 1215 (m), 839 (s).

HRMS (ESI, **15**): calcd for C$_{29}$H$_{47}$N$_2$O$_4$Si [M+H]$^+$: 517.3456, found: 517.3464.

HRMS (ESI, **6**:*ent*-2-*epi*-**6**, ~1:1): calcd for C$_{29}$H$_{46}$N$_2$O$_3$Si [M]$^+$: 499.3351, found: 499.3354.

TLC Rf (neutralized plates):	
(CH_2Cl_2:acetone:NEt_3 [96:3:1])	**33**, 0.59 (CAM) **69**, 0.21 (CAM)
(hexanes:acetone:NEt_3 [69:30:1])	**69**, 0.40 (UV, CAM) **32** and *ent*-2-*epi*-**32,** 0.44 (UV, CAM)



3-[3-(*tert*-Butyl-dimethyl-silanyloxy)-1-(6-methyl-3,4,5,6-tetrahydro-pyridin-2-ylmethyl)-3a,5a,6,7,8,9,9a,9b-octahydro-1*H*-cyclopenta[*a*]naphthalen-5-yl]-oxazolidin-2-one (97 and *ent*-2-*epi*-97):

A solution of α,β–unsaturated imine **32** (119 mg, 0.238 mmol, 1 equiv, equal mixture of **32** and *ent*-2-*epi*-**32**) in THF (12 mL) was degassed via an argon purge. To this solution was added solid sodium bicarbonate (106 mg, 1.26 mmol, 5.29 equiv) under argon. The reaction mixture was cooled to 0 °C, light was excluded, and NBS (50.5 mg, 0.284 mmol, 1.19 equiv) was added as a solid. The reaction mixture was maintained at 0 °C for ten minutes, then diluted with hexanes:acetone:NEt$_3$ ([50:50:1], 10 mL), was filtered cold through a silica plug (diam. 1 cm, ht. 2.5 cm) and the filtrate was concentrated under reduced pressure to produce an orange-brown foam. This residue was dissolved in benzene and filtered to remove excess insoluble succinimide. It was then concentrated and placed under reduced pressure (~ 0.5 Torr) for 1 h. The resulting brominated product was used crude for the cyclization step.

The crude vinyl bromide was dissolved in benzene-*d*$_6$[18] (4.8 mL), was degassed via an argon purge, and was charged with tributyltin hydride (192 μL, 0.722 mmol, 3.00 equiv). A solution of AIBN in benzene-*d*$_6$ (0.30M) was prepared in a flame-dried flask, degassed via bubbling argon, and a portion[19] (200 μL, 0.060 mmol, 0.25 equiv) was transferred to the reaction mixture. The reaction solution was placed in a pre-heated 60 °C oil bath and heated to 90 °C over 20 min. After 30 min, the reaction mixture was cooled, an additional portion of AIBN was added (200 μL, 0.060 mmol, 0.25 equiv), and the mixture was returned to 90 °C. After a subsequent 20 min, the solution was cooled, additional tributyltin hydride (96 μL, 0.36 mmol, 1.5 equiv) and AIBN (400 μL, 0.030 mmol, 0.50 equiv) were added, and the reaction was returned to 90 °C. After 30 min, the reaction was cooled, a final portion of AIBN was added (400 μL, 0.030 mmol, 0.50 equiv), and the mixture was returned to 90 °C.

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[18] Deuterated solvent was used to facilitate evaluation of reaction progress by direct ^{1}H NMR monitoring.

[19] Sequential addition of the reagents was necessary for optimal results.

After an additional 30 min at 90 °C, the reaction appeared complete by direct ^{1}H NMR spectral analysis. The reaction solution was cooled, triethylamine (1 mL) was added to neutralize adventitious hydrobromic acid, and the solution was concentrated to ~400 μL under reduced pressure. The resulting brown oil was purified via flash column chromatography (neutralized silica gel: diam. 2.5 cm, ht. 10 cm; eluent: hexanes:acetone:NEt_3 [97:2:1] to acetone:hexanes:NEt_3 [95:4:1] to acetone:hexanes:NEt_3 [92:7:1] to acetone:hexanes:NEt_3 [84:15:1]) to provide an equal mixture of two diastereomeric **97** and *ent*-2-*epi*-**97** as a tan foam (65.7 mg, 55% (two steps)).

The corresponding enantiomers, tetracycles *ent*-**97** and 2-*epi*-**97** (90 mg, 54% (two steps), (~1:1)) were prepared using the same procedure and starting with α,β-unsaturated imines *ent*-**32**:2-*epi*-**32**, (~1:1)).

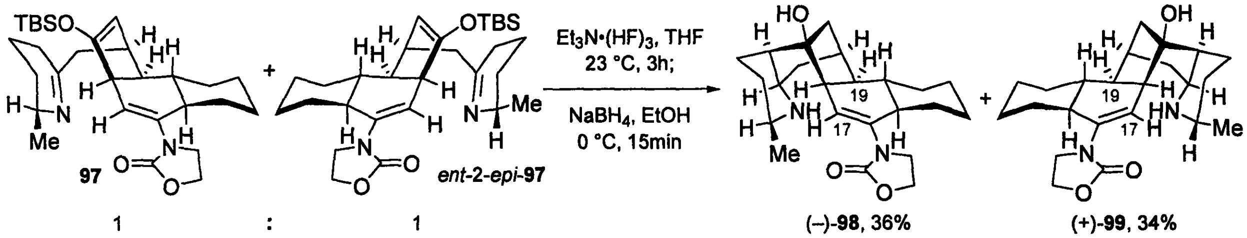
^{1}H NMR (500 MHz, C_6D_6, 20°C, equal mixture of two diastereomers, **97**:*ent*-2-*epi*-**97**, ~1:1): 5.66-5.63 (m, 2H, C17-H, C17-H), 4.83 (app-t, *J* = 2.9 Hz, 1H, C21-H), 4.70 (app-t, *J* = 2.9 Hz, 1H, C21-H), 3.46-3.35 (m, 8H, OC**H$_2$**CH$_2$N, OC**H$_2$**CH$_2$N, C2-H, C2-H, C19-H, C19-H), 3.11-3.05 (m, 2H, OCH$_2$C**H$_2$**N, OCH$_2$C**H$_2$**N), 2.99-2.94 (m, 1H, C8-H), 2.94-2.88 (m, 1H, C8-H), 2.74-2.69 (m, 2H, OCH$_2$C**H$_2$**N, OCH$_2$C**H$_2$**N), 2.50-2.44 (m, 2H, C15-H, C15-H), 2.21-2.15 (m, 4H, C7-H, C7-H, C**H$_2$**, C**H$_2$**), 2.15-2.09 (m, 2H, C**H$_2$**, C**H$_2$**), 2.09-2.02 (m, 2H, C**H$_2$**, C**H$_2$**), 1.79-1.65 (m, 8H, C9-H, C9-H, C**H$_2$**, C**H$_2$**), 1.56-1.43 (m, 4H, C**H$_2$**, C**H$_2$**), 1.43-1.26 (m, 4H, C10-H, C10-H, C**H$_2$**, C**H$_2$**), 1.36 (d, J = 6.7 Hz, 3H, C1-H), 1.35 (d, J = 6.7 Hz, 3H, C1-H), 1.24-1.11 (m, 4H, C**H$_2$**, C**H$_2$**), 1.01 (br-s, 18H, SiC(C**H$_3$**)$_3$), 0.99-0.83 (m, 8H, C**H$_2$**, C**H$_2$**), 0.21 (s, 3H, SiC**H$_3$**)$_2$), 0.20 (s, 3H, SiC**H$_3$**)$_2$), 0.19 (s, 3H, SiC**H$_3$**)$_2$), 0.18 (s, 3H, SiC**H$_3$**)$_2$).

^{13}C NMR (125 MHz, C_6D_6, 20°C, equal mixture of two diastereomers, **97**:*ent*-2-*epi*-**97**, ~1:1): 167.31, 167.16, 156.35 (br-s, 2 carbons), 155.48, 155.24, 139.62 (br-s, 2 carbons), 128.93 (br-s, 2 carbons), 118.02, 117.96, 105.25, 104.82, 61.89 (br-s, 2 carbons), 53.97, 53.84, 47.27, 47.24, 46.95, 46.82, 44.87, 44.76, 43.99, 43.95, 43.63 (br-s, 2 carbons), 32.10, 32.01, 30.36 (br-s, 2 carbons), 30.29, 30.24, 30.14, 30.05, 27.38 (br-s, 2 carbons), 27.36, 27.34, 26.34, 26.32, 24.42, 24.38, 19.84, 19.67, 18.76, 18.73, –4.17, –4.18, –4.20, –4.21.

FTIR (thin film, equal mixture of two diastereomers, **97**:*ent*-2-*epi*-**97**, ~1:1) cm^{-1}: 3397 (br-w), 2928 (s), 2856 (m), 1758 (s, C=O), 1650 (m), 1408 (m), 1254 (m), 1212 (w), 865 (m), 841 (m), 782 (w).

HRMS (ESI): calcd for $C_{29}H_{47}N_2O_3Si$ $[M+H]^+$: 499.3351, found: 499.3357.

TLC, *Rf*:
(30% acetone in hexanes, neutralized plates) **32**, 0.44 (UV, CAM)
ent-2-*epi*-**97**, 0.51 (UV, CAM)



Pentacyclic amines (–)-98 and (+)-99:

To a solution of tetracycle **97** (65.7 mg, 0.132 mmol, 1 equiv, equal mixture of **97** and *ent*-2-*epi*-**97**) in THF (13 mL) at 23 °C was added triethylamine trihydrogen fluoride (107 µL, 0.660 mmol, 5.00 equiv). After 3 h, the solution was cooled to 0 °C and the volatiles were removed under reduced pressure on a manifold and allowed to warm to ambient temperature (3 h). The crude reaction mixture was dissolved in ethanol (10 mL) and cooled to 0 °C. A suspension of sodium borohydride (10 mg, 0.26 mmol, 2.0 equiv) in ethanol (2 mL) was added dropwise to the cold reaction mixture under an argon atmosphere. The resulting solution was stirred at 0 °C for ten minutes, then excess hydride was quenched at 0 °C by the addition of ethanolic hydrochloric acid (0.5 M, 1.5 mL) and the solution was vigorously stirred for five minutes. The reaction mixture was neutralized by the addition of triethylamine (2 mL), was stirred for five minutes, and the volatiles were removed under reduced pressure on a manifold (1 h). The resulting white solid was dissolved in ethyl acetate (50 mL), saturated aqueous sodium bicarbonate solution (25 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (10 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow oil via flash column chromatography (neutralized silica gel: diam. 1 cm, ht. 10 cm; eluent: CH_2Cl_2:methanol [95:5] to ammonia saturated CH_2Cl_2:methanol [92:8]) afforded the readily separable pentacyclic amines (–)-**98** (18.4 mg, 36%, $[\alpha]^{22}_D = -29$ (*c* 0.44, CH_2Cl_2)) and (+)-**99** (17.3 mg, 34%, $[\alpha]^{22}_D = +65$ (*c* 0.43, CH_2Cl_2)).

The corresponding enantiomeric amines, (+)-**98** and (–)-**99** (20.0 mg and 25.0 mg, respectively, 66%), were obtained using the same procedure and starting with a mixture of *ent*-**97** and 2-*epi*-**97** (~1:1).

^{1}H NMR (500 MHz, C_6D_6, 20°C):	Pentacyclic amine (–)-**98**: 6.09 (br-s, 1H, C17-H), 3.85-3.80 (m, 1H, C19-H), 3.50 (app-q, *J* = 7.4 Hz, 1H, OCH_2CH_2N), 3.44 (app-q, *J* = 6.6 Hz, 1H, OCH_2CH_2N), 3.02-2.91 (m, 2H, OCH_2CH_2N), 2.79-2.71 (m, 2H, OCH_2CH_2N), 2.42-2.33 (m, 1H), 2.13 (t, *J* = 9.8 Hz, 1H), 2.00-1.94 (m, 1H), 1.90-1.84 (m, 2H), 1.74 (ddd, *J* = 14.0, 6.2, 3.6 Hz, 1H), 1.71-1.61 (m, 2H), 1.56-1.46 (m, 2H), 1.44-1.31 (m, 3H), 1.23-1.09 (m, 6H), 0.98-0.88 (m, 2H) 0.85 (d, *J* = 6.2 Hz, 3H, C1-H).

^{1}H NMR (500 MHz, C_6D_6, 20°C): Pentacyclic amine (+)-**99**: 6.00 (br-s, 1H, C17-H), 3.70-3.65 (m, 1H, C19-H), 3.56-3.46 (m, 2H, $OC\mathbf{H}_2CH_2N$), 3.26 (t, J = 6.1 Hz, 1H, C6-H), 3.07 (app-q, J = 6.3 Hz, 1H, C2-H), 3.04-2.96 (m, 1H, $OCH_2C\mathbf{H}_2N$), 2.77 (app-q, J = 6.5 Hz, 1H, $OCH_2C\mathbf{H}_2N$), 2.07-1.67 (m, 11H), 1.30-1.09 (m, 6H), 1.09-1.02 (m, 2H), 1.00-0.98 (m, 2H), 0.93 (d, J = 6.5 Hz, 3H, C1-H).

^{13}C NMR (125 MHz, C_6D_6, 20°C): Pentacyclic amine (–)-**98**: 157.4 (carbamate C=O), 137.5 (C16), 128.9 (C17), 80.6 (C20), 61.7 ($O\mathbf{C}H_2CH_2N$), 56.2, 53.8, 47.8, 47.6, 46.3, 45.8, 45.1, 42.1, 40.6, 40.1, 38.1, 33.8, 31.6, 29.4, 27.1, 26.9, 24.0, 23.4.

^{13}C NMR (125 MHz, C_6D_6, 20°C): Pentacyclic amine (+)-**99**: 157.5 (carbamate C=O), 138.0 (C16), 128.9 (C17), 81.1 (C20), 61.9 ($O\mathbf{C}H_2CH_2N$), 48.6, 48.0, 47.3, 46.2, 44.0 (br), 40.9, 40.6, 40.0 (br), 37.6, 33.9, 29.7, 28.2, 27.3, 27.1, 21.1, 20.6.

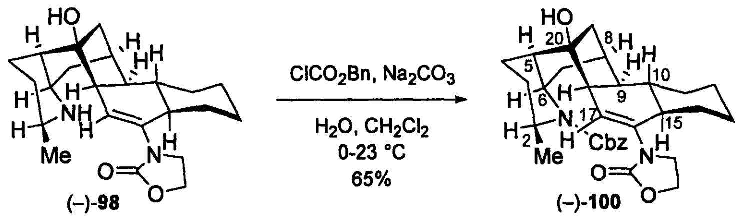
FTIR (thin film) cm^{-1}: Pentacyclic amine (–)-**98**: 3430 (br-s, OH), 2926 (s), 2855 (m), 1748 (s), 1662 (m), 1481 (w), 1447 (w), 1413 (m), 1279 (w), 1101 (m), 735 (m).

FTIR (thin film) cm^{-1}: Pentacyclic amine (+)-**99**: 3424 (br-s, OH), 2926 (s), 2856 (m), 1743 (s), 1666 (w), 1482 (w), 1446 (w), 1416 (m), 1280 (w), 1101 (w), 734 (m).

HRMS (ESI): Pentacyclic amine (–)-**98**: calcd for $C_{23}H_{35}N_2O_3$ $[M+H]^+$: 387.2642, found: 387.2635.

HRMS (ESI): Pentacyclic amine (+)-**99**: calcd for $C_{23}H_{35}N_2O_3$ $[M+H]^+$: 387.2642, found: 387.2636.

TLC, *Rf*:
(10% MeOH:NH_3 satd CH_2Cl_2)
98, 0.63 ($KMnO_4$)
99, 0.26 ($KMnO_4$)



Carbamate (–)-100:

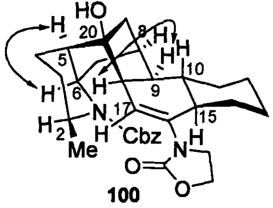
A solution of sodium carbonate (21 mg, 0.19 mmol, 10 equiv) in water (475 μL) was added to a solution of amine (–)-**98** (7.5 mg, 0.019 mmol, 1 equiv) in dichloromethane (600 μL) at 23 °C. The heterogeneous mixture was stirred vigorously and cooled to 0 °C. Benzylchloroformate (8.2 μL, 0.057 mmol, 3.0 equiv) was added dropwise and the resulting mixture was warmed to room temperature for 15 minutes. Two additional portions of benzylchloroformate (8.2 μL, 0.057 mmol, 3.0 equiv each) were added over 30 minutes, followed by dilution of the reaction mixture with dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (5 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow oil via flash column chromatography (silica gel: diam. 1 cm, ht. 2.5 cm; eluent: hexanes:acetone [90:10] to hexanes:acetone [80:20] to hexanes:acetone [75:25] to hexanes:acetone [70:30]) provided the carbamate (–)-**100** ($[\alpha]^{22}_{D} = -62$ (*c* 0.6, CH_2Cl_2)) as a clear film (6.6 mg, 65%).

The corresponding enantiomer, carbamate (+)-**98** (17.0 mg, 63%), was obtained using the same procedure and starting with amine (+)-**100**.

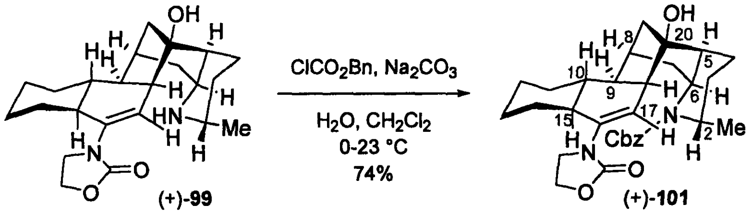
^1H NMR (500 MHz, C_6D_6, 20°C): 7.32 (d, *J* = 7.2 Hz, 2H, ArH), 7.18 (m, 2H, ArH), 7.07 (t, *J* = 7.4 Hz, 1H, ArH), 5.86 (bs, 1H, C17-H), 5.27-5.19 (m, 2H, $PhCH_2OC(O)N$), 4.66-4.57 (m, 1H, C6-H), 4.39 (br-s, 1H, C2-H), 3.55-3.43 (m, 2H, OCH_2CH_2N), 3.01 (app-q, *J* = 8.3 Hz, 1H, OCH_2CH_2N), 2.75 (td, *J* = 8.6, 5.9 Hz, 1H, OCH_2CH_2N), 2.66-2.61 (m, 1H, C19-H), 2.45-2.37 (m, 2H, OH, C7-H), 2.09-2.01 (m, 3H, C5-H, C15-H), 1.78-1.65 (m, 3H, C8-H), 1.64 (m, 2H, C21-H), 1.56-1.43 (m, 3H, C4-H, C4-H, C3-H), 1.37-1.28 (m, 2H, C3-H, C21-H), 1.26 (dt, *J* = 13.2, 3.2 Hz, 1H), 1.20 (app-t, *J* = 9.7 Hz, 1H, C9-H), 1.13 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 3H, C1-H), 1.04-0.95 (m, 2H, C7-H), 0.83-0.74 (m, 2H, C10-H).

^{13}C NMR (125 MHz, C_6D_6, 20°C): 157.3 (carbamate-C=O), 156.0 ($PhCH_2OC(O)N$), 139.3 (C16), 138.3 ($HC{=}CCH_2OC(O)N$), 129.1 (Ar-C), 128.9 (Ar-C), 128.6 (Ar-C), 127.9 (Ar-C), 123.6 (br, C17), 80.5 (C20), 67.4 ($PhCH_2OC(O)N$), 62.0

	(OCH_2CH_2N), 52.9 (C9), 48.1 (C5), 48.0 (OCH_2CH_2N), 47.9 (C6), 46.8 (C2), 45.0 (C10), 40.8 (C15), 39.4 (C19), 34.7 (C21), 34.4 (C4), 33.5 (C8), 33.0, 30.2 (C3), 29.6, 27.1, 27.0, 20.7 (C1), 17.8 (C4).
FTIR (thin film) cm^{-1}:	3427 (br-s, OH), 2928 (s), 2855 (w), 1733 (s), 1688 (s), 1415 (s), 1316 (s), 1093 (s).
HRMS (ESI):	calcd for $C_{31}H_{40}NaN_2O_5$ $[M+Na]^+$: 543.2829, found: 543.2808.
TLC, *Rf*: (50% acetone:hexanes)	**98**, <0.05 ($KMnO_4$) **100**, 0.31 ($KMnO_4$)
NOESY correlations (600 MHz, C_6D_6, 20°C):	Additional data: H2-H3, H3-H4, H4-H5, H4-H19, H3-H5, **H5-H6**, H6-H7a, H6-H21a, H7a-H8, H7b-H9, **H9-H19**, H17-H19, H19-H4a,b. Key correlations are shown in bold.



100



Carbamate (+)-101:

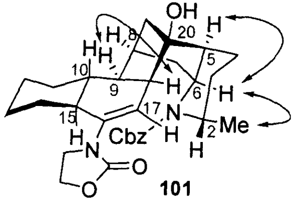
A solution of sodium carbonate (62 mg, 0.58 mmol, 10 equiv) in water (1 mL) was added to a solution of pentacyclic amine (+)-**99** (22.5.0 mg, 0.0580 mmol, 1 equiv) in dichloromethane (1.2 mL) at 23 °C. The heterogeneous mixture was stirred vigorously and cooled to 0 °C. Benzylchloroformate (25 µL, 0.18 mmol, 3.0 equiv) was added dropwise and the resulting solution was warmed to room temperature for 15 minutes. The reaction mixture was diluted with dichloromethane (15 mL) and saturated aqueous sodium bicarbonate solution (10 mL), and water (3 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 15 mL). The combined organic layers were washed with brine (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow oil via flash column chromatography (silica gel: diam. 1 cm, ht. 7.5 cm; eluent: hexanes:acetone [90:10] to hexanes:acetone [80:20] to hexanes:acetone [75:25] to hexanes:acetone [70:30]) provided the carbamate (+)-**101** ($[\alpha]^{22}_D = +63$ (*c* 0.7, CH_2Cl_2)) as a clear film (22.4 mg, 74%).

The corresponding enantiomer, carbamate (–)-**99** (18.2 mg, 54%), was obtained using the same procedure and starting with amine (–)-**101**.

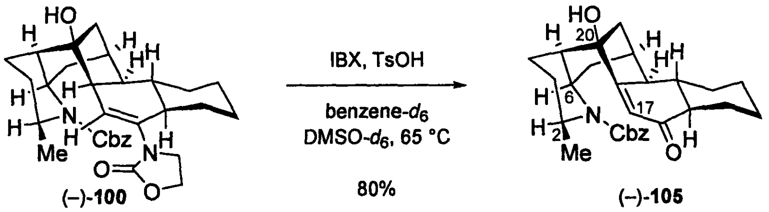
^1H NMR (500 MHz, C_6D_6, 20°C):	7.28 (d, *J* = 7.6 Hz, 2H, ArH), 7.08 (app-t, *J* = 8.1 Hz, ArH), 5.69 (br-s, 1H, C17-H), 5.21 (d, *J* = 12.4 Hz, 1H, $PhCH_2OC(O)N$), 5.11 (d, *J* = 12.4 Hz, 1H, $PhCH_2OC(O)N$), 4.13 (app-q, *J* = 8.2 Hz, 1H, C6-H), 4.05 (app-q, *J* = 6.0 Hz, 1H, C2-H), 3.53-3.43 (m, 2H, OCH_2CH_2N), 2.96 (app-q, *J* = 8.5 Hz, 1H, OCH_2CH_2N), 2.85-2.80 (m, 1H, C19-H), 2.73-2.67 (m, 1H, OCH_2CH_2N), 2.30-2.21 (m, 2H, C15-H, C5-H), 2.01-1.97 (m, 3H, C8-H, C10-H), 1.87-1.85 (m, 2H, C9-H, C4-H), 1.79 (br-d, *J* = 12.6 Hz, 1H, C7-H), 1.68-1.61 (m, 3H, C3-H), 1.58-1.53 (m, 2H, C4-H, C21-H), 1.38 (d, *J* = 11.4 Hz, 1H, C21-H), 1.27-1.24 (m, 2H), 1.16-1.14 (m, 2H), 1.15-1.13 (m, 3H, C1-H), 1.09 (m, 2H, C3-H), 0.86-0.85 (m, 2H, C7-H).
^{13}C NMR (125 MHz, C_6D_6, 20°C):	157.3 (carbamate-C=O), 156.4 ($PhCH_2OC(O)N$), 139.2 (C16), 138.3 ($HC{=}CCH_2OC(O)N$), 129.1 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 123.3 (br, C17), 81.3 (C20), 67.1 ($PhCH_2OC(O)N$), 62.0 (OCH_2CH_2N), 49.2 (C2), 49.1 (C9), 48.8 (C6), 47.6 (OCH_2CH_2N),

	46.9 (C15), 43.5, 40.9 (C10), 39.1 (C19), 34.2 (C5), 33.6 (C8), 32.4 (C7), 29.8, 29.7, 28.9 (C3), 27.1, 27.0, 20.1, 18.9 (C4).
FTIR (thin film) cm^{-1}:	3423 (br-s, OH), 2927 (s), 2855 (w), 1734 (s), 1691 (s), 1407 (m), 1297 (m), 1095 (w), 1039 (w).
HRMS (ESI):	calcd for $C_{31}H_{40}NaN_2O_5$ $[M+Na]^+$: 543.2829, found: 543.2817.
TLC, *Rf*: (50% acetone:hexanes)	**99**, <0.05 ($KMnO_4$) **101**, 0.31 ($KMnO_4$)

NOESY correlations (600 MHz, C_6D_6, 20°C): Additional data: **H1-H6**, **H5-H6**, **H9-H19**, H17-Hb, H17-H19, H19-H4, H15-H9, H4-H2, H4-H6. Key correlations are shown in bold.



101



(–)-*N*-Cbz-Galbulimima alkaloid 13 (105):

p-Toluenesulfonic acid monohydrate (12 mg, 60 μmol, 4.0 equiv) and IBX (47 mg, 0.16 mmol, 11 equiv) were added to a solution of vinyl oxazolidinone (–)-**100** (8.0 mg, 15 μmol, 1 equiv) in benzene-d_6 (300 μL) and DMSO-d_6[20] (400 μL) at 23 °C. The resulting suspension was sonicated (1.5 h) until it became homogeneous, then heated to 65 °C. ^{1}H NMR spectral analysis of the reaction mixture was used to monitor conversion to product. After 10 h, the solution was diluted with ethyl acetate (10 mL), saturated aqueous sodium bicarbonate solution (5 mL) and water (3 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (5 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow residue via flash column chromatography (silica gel: diam. 0.5 cm, ht. 3.5 cm; eluent: hexanes:acetone [85:15] to hexanes:acetone [70:30]) provided enone **105** (5.5 mg, 80%).

The corresponding enantiomer, enone *ent*-**105** (3.5 mg, 67%) was obtained using the same procedure and starting with vinyl oxazolidinone (+)-**100**.

^{1}H NMR (500 MHz, C_6D_6, 20°C):	7.32 (d, *J* = 7.2 Hz, 2H, ArH), 7.20-7.15 (m, 2H, ArH 7.09 (t, *J* = 7.2 Hz, 1H, ArH), 5.99 (d, *J* = 2.1 Hz, 1H, C17-H), 5.23 (m, 2H, Ph**CH**$_2$OC(O)N), 4.69 (app-q, *J* = 8.5 Hz, C6-H), 4.46-4.39 (m, 1H, C2-H), 2.67-2.52 (m, 2H), 1.97-1.90 (m, 1H), 1.75-1.64 (m, 4H), 1.55-1.44 (m, 3H), 1.38-1.24 (m, 3H), 1.21-1.13 (m, 2H), 1.12-1.04 (m, 5H, C1-H), 1.04-0.85 (m, 3H), 0.84 (dd, *J* = 11.6, 5.2 Hz, 1H), 0.61 (app-dq, *J* = 12.2, 3.3 Hz, 1H) .
^{13}C NMR (125 MHz, C_6D_6, 20°C):	199.0 (C16), 172.5 (C19), 155.8 (PhCH$_2$**O**C(O)N), 138.1 (HC=**C**CH$_2$OC(O)N), 129.1 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 119.3 (C17), 81.1 (C20), 67.5 (Ph**C**H$_2$OC(O)N), 56.7, 52.6, 47.4, 47.3, 46.2, 45.2, 36.1, 35.7, 31.7, 30.3, 30.2, 26.9, 26.5, 25.9, 20.4, 19.3.
FTIR (thin film) cm^{-1}:	3428 (br-s, OH), 2924 (s), 2852 (m), 1687 (m), 1666 (s), 1412 (w), 1314 (w).
HRMS (ESI):	calcd for $C_{28}H_{37}N_1O_4$ [M+H]$^+$: 450.2639,

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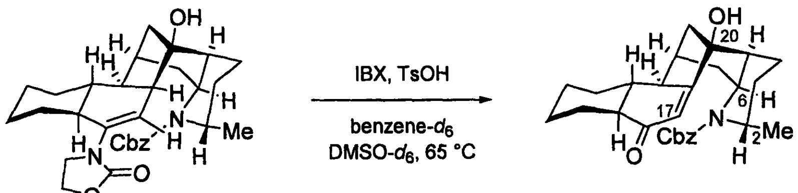
[20] Deuterated solvent was used to facilitate evaluation of reaction progress by direct ^{1}H NMR monitoring.

	found: 450.2639.
TLC, *Rf*: (50% acetone:hexanes)	**100**, 0.31 (KMnO$_4$) **105**, 0.57 (UV, CAM)



(+)-**101** 56% (+)-*ent*-**106**

<u>*N*-Cbz-2-*epi*-Galbulimima alkaloid 13 (106):</u>

p-Toluenesulfonic acid monohydrate (8.0 mg, 42 μmol, 4.6 equiv) and IBX (31 mg, 0.11 mmol, 12 equiv) were added to a solution of vinyl oxazolidinone (+)-**101** (4.8 mg, 9.2 μmol, 1 equiv) in benzene-d_6 (300 μL) and DMSO-d_6[21] (450 μL) at 23 °C. The suspension was sonicated (1 h) until it became homogeneous, then heated to 65 °C. ^{1}H NMR analysis of the reaction mixture was used to monitor conversion to product. After 10 h, the solution was diluted with ethyl acetate (8 mL), saturated aqueous sodium bicarbonate solution (8 mL) and water (3 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 8 mL). The combined organic layers were washed with brine (5 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting yellow residue via flash column chromatography (silica gel: diam. 1 cm, ht. 2 cm; eluent: hexanes:acetone [85:15] to hexanes:acetone [80:20]) provided enone *ent*-**106** (2.3 mg, 56%).

The corresponding enantiomer, enone **106** (4.8 mg, 59%) was obtained using the same procedure and starting with vinyl oxazolidinone (–)-**101**.

^{1}H NMR (500 MHz, C_6D_6, 20°C): 7.30-7.27 (m, 2H, ArH), 7.15-7.12 (m, 2H, ArH), 7.09-7.05 (m, 1H, ArH), 5.99-5.96 (m, 1H, C17-H), 5.18 (d, *J* = 12.4 Hz, PhC**H**$_2$OC(O)N), 5.14 (d, *J* = 12.4 Hz, PhC**H**$_2$OC(O)N), 4.50 (app-q, *J* = 9.2 Hz, 1H, C6-H), 3.71-3.64 (m, 1H, C2-H), 2.64-2.59 (m, 1H), 2.30 (dt, *J* = 13.8, 8.0 Hz, 1H), 2.23-2.16 (m, 1H), 1.77-1.65 (m, 3H), 1.64-1.43 (m, 6H), 1.36-1.27 (m, 2H), 1.22 (d, *J* = 6.5 Hz, 3H, C1-H), 1.18-1.04 (m, 4H), 1.04-0.96 (m, 1H), 0.96-0.86 (m, 2H), 0.74-0,65 (m, 1H).

^{13}C NMR (125 MHz, C_6D_6, 20°C): 199.0 (C16), 173.3 (C19), 156.6 (PhCH$_2$**O**C(O)N), 138.1 (HC=CCH$_2$OC(O)N), 129.1 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 119.6 (C17), 82.0 (C20), 67.3 (OCH$_2$CH$_2$N), 54.4, 52.4, 49.1, 48.5, 47.4, 43.1, 39.3, 35.6, 31.8, 30.6, 29.9, 27.0, 26.5, 26.0, 21.1, 21.0.

FTIR (thin film) cm^{-1}: 3423 (br-s, OH), 2929 (m), 2857 (w), 1687 (m), 1662 (s), 1300 (m), 1154 (w).

HRMS (ESI): calcd for $C_{28}H_{37}N_1O_4$ $[M+H]^+$: 450.2639,

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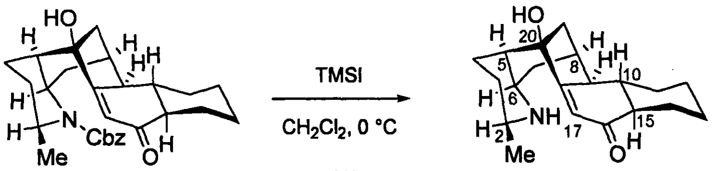
[21] Deuterated solvent was used to facilitate evaluation of reaction progress by direct ^{1}H NMR monitoring.

	found: 450.2644.
TLC, *Rf*: (50% acetone:hexanes)	**101**, 0.31 (KMnO$_4$) **106**, 0.57 (UV, CAM)



(−)-105

(−)-galbulimima alkaloid 13 (2)

(−)-Galbulimima alkaloid 13 (2):[22]

N-Cbz enone **105** (2.7 mg, 6.0 μmol, 1 equiv) was azeotropically dried from toluene (3 × 1 mL), was dissolved in dichloromethane (1.0 mL), and was cooled to 0 °C. Trimethylsilyliodide (TMSI, 1.2 μL, 9.0 μmol, 1.5 equiv) was added to the cooled solution, and the resulting yellow solution was stirred at 0 °C. Additional portions of TMSI were added at 20 minute intervals until complete consumption of **105** was observed by TLC analysis (70 min). The reaction mixture on completion was a cloudy yellow solution, with a brown residue. Excess silylated products were quenched at 0 °C by the addition of aqueous hydrochloric acid solution (1N, 1.5 mL) and the mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with hexanes (10 mL) and aqueous hydrochloric acid solution (1N, 2 mL) and the layers were separated. The organic layer was extracted with aqueous hydrochloric acid solution (1N, 4 mL). The combined acidic aqueous layers were washed sequentially with hexanes (2 × 10 mL), dichloromethane (10 mL), and hexanes (10 mL). The aqueous layer was then basified to pH 13 with aqueous sodium hydroxide solution (1N, 10 mL). The resulting solution was stirred at ambient temperature for 1 h. The aqueous solution was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed sequentially with water (18 mL) and brine (20 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to provide (−)-galbulimima alkaloid 13 (**2**, $[\alpha]^{22}_{D}$ = −34 (*c* 0.045, CH_2Cl_2)[23]) as a white film (1.7 mg, 89%).

The corresponding enantiomer, (+)-*ent*-galbulimima alkaloid 13 (**2**, 1.4 mg, 58%, $[\alpha]^{22}_{D}$ = +34 (*c* 0.090, CH_2Cl_2)[23]), was obtained.using the same procedure and starting with *N*-Cbz amine *ent*-**105**.

^1H NMR (500 MHz, C_6D_6, 20°C): 6.07 (d, *J* = 2.2 Hz, 1H, C17-H), 3.28 (dt, *J* = 11.4, 2.3 Hz, 1H, C9-H), 2.88 (app-t, *J* = 5.1 Hz, 1H, C6-H), 2.72-2.66 (m, 1H), 2.60-2.55 (m, 1H), 2.15 (app-qd, *J* = 6.1, 2.3 Hz, 1H, C2-H), 1.98 (m, 1H, OH), 1.91 (app-t, *J* = 4.4 Hz, 1H, C5-H), 1.84-1.81 (m, 1H, C8-H), 1.78 (dd,

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[22] a) For the prior synthesis of (±)-**2**, please see: Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2400. The Supporting Information of this same report contains copies of the NMR spectra of the natural (−)-**2** along with synthetic (±)-**2**. b) For isolation and optical rotation data, see: Ritchie, E.; Taylor, W. C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, Chapter 14 and references therein.

[23] Literature value: [α] = −84 ($CHCl_3$); see reference 22b. We have also measured the rotation of (−)-**2** in chloroform (2 sources): a) chloroform passed through basic alumina (Grade I) and dried over 4Å-MS, $[\alpha]^{22}_{D}$ = −51 (*c* 0.06, $CHCl_3$), and b) chloroform passed through basic alumina (Grade I) and distilled from P_2O_5, $[\alpha]^{22}_{D}$ = −64 (*c* 0.06, $CHCl_3$). Additionally, we have measured the rotation of (+)-**2** in chloroform: a) chloroform passed through basic alumina (Grade I) and dried over 4Å-MS, $[\alpha]^{22}_{D}$ = +51 (*c* 0.07, $CHCl_3$), and b) chloroform passed through basic alumina (Grade I) and distilled from P_2O_5, $[\alpha]^{22}_{D}$ = +66 (*c* 0.07, $CHCl_3$).

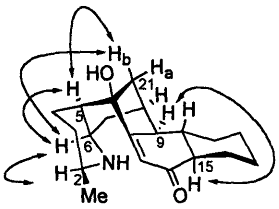
J = 11.2, 3.6 Hz, 1H, C15-H), 1.75-1.69 (m, 1H), 1.67-1.60 (m, 1H), 1.55 (app-dq, J = 13.9, 2.9 Hz, 1H, C7-Ha), 1.53-1.47 (m, 1H), 1.40 (ddd, J = 10.8, 5.6, 2.1 Hz, 1H, C21-Ha), 1.26 (dd, J = 5.6, 2.4 Hz, 1H, C21-Hb), 1.23-0.90 (m, 8H, C10-H, C7-Hb), 0.77 (m, 1H), 0.75 (d, J = 6.1 Hz, 3H, C1-H).

^{13}C NMR (125 MHz, C_6D_6, 20°C): 199.4 (C16), 178.9 (C19), 119.2 (C17), 79.7 (C20), 55.4 (C6), 53.3 (C15), 53.2 (C2), 51.2 (C9), 48.2 (C21), 47.6 (C10), 46.6 (C5), 41.0 (C7), 33.1 (C8), 31.9, 30.6, 27.3 (C3 or C4), 26.7, 26.1, 25.0 (C3 or C4), 23.6 (C1).

FTIR (thin film) cm^{-1}: 3403 (br-s, OH), 2921 (s), 2851 (m), 1708 (w), 1646 (s), 1447 (m), 1261 (m). (Literature values: 3406, 2929, 2854, 1705, 1646, 1446).[22]

HRMS (ESI): calcd for $C_{20}H_{30}N_1O_2$ [M+H]$^+$: 316.2271, found: 316.2280.

NOESY correlations (600 MHz, C_6D_6, 20°C): Additional data: H1-H2, **H2-H6, H5-H6, H5-H21b**, H6-H7a, **H6-H21b**, H7a-H8, H7a-H6, H8-H21a, **H9-H15**. Key correlations are shown in bold.

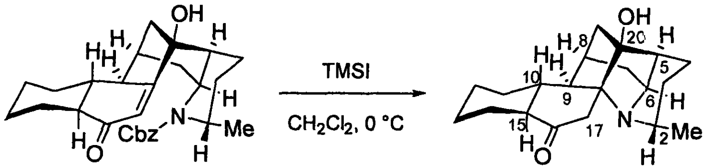


(–)-galbulimia alkaloid 13 (2)

Comparison of our (–)-GB 13 (2) assignments with prior assignments for (±)-2:

Assignment	Mander's report[22a] (±)-GB-13 (2) (^{1}H, 300 MHz, $CDCl_3$)	This work (–)-GB 13 (2) (^{1}H, 500 MHz, $CDCl_3$)	This work (–)-GB 13 (2) (^{1}H, 500 MHz, C_6D_6)	This work (–)-GB 13 (2) ^{13}C (125 MHz, C_6D_6)
C1	0.89, (d, J = 6.2 Hz)	0.89, (d, J = 6.1 Hz)	0.75, (d, J = 6.1 Hz)	23.6
C2			2.15, (app-qd, J = 6.1, 2.3 Hz)	53.2
C3,C4			2.72-2.66 (m); 2.60-2.55 (m)	27.3, 25.0
C5			1.91 (app-t, J = 4.4 Hz)	46.6
C6	3.34, (t, J = 5.1 Hz)	3.34, (t, J = 5.1 Hz)	2.88, (app-t, J = 5.1 Hz)	55.4
C7			1.55 (app-dq, J = 13.9, 2.9); 1.02 (m)	41.0
C8			1.84-1.81 (m)	33.1

C9	3.47, (dt, J = 11.3, 2.2 Hz)	3.47, (dt, J = 11.2, 2.1 Hz)	3.28, (dt, J = 11.4, 2.3 Hz)	51.2
C10			~1.13, m	47.6
C11-C14				31.9, 30.6, 26.7, 26.1
C15			1.78, dd, J = 11.2, 3.6 Hz	53.3
C16	–	–	–	199.4
C17	5.92, (d, J = 2.0 Hz)	5.93 (d, J = 2.1 Hz)	6.07, (d, J = 2.2 Hz)	119.2
C19	–	–	–	178.9
C20	–	–	–	79.7
C21			1.40 (ddd, J = 10.8, 5.6, 2.1 Hz); 1.26 (dd, J = 5.6, 2.4 Hz)	48.2



(+)-*ent*-**106** (+)-*ent*-**108**

(+)-*ent*-108:

N-Cbz enone *ent*-**106** (2.1 mg, 4.7 μmol, 1 equiv) was azeotropically dried from toluene (3 × 1 mL), was dissolved in dichloromethane (800 μL), and was cooled to 0 °C. Trimethylsilyliodide (TMSI, 1.5 μL, 11 μmol, 2.2 equiv) was added to the cooled solution, and the resulting yellow solution was stirred at 0 °C. Additional portions of TMSI were added at 20 minute intervals until complete consumption of *ent*-**106** was observed by TLC analysis (50 min). The reaction mixture on completion was a cloudy yellow solution, with a brown residue. Excess silylated products were quenched at 0 °C by the addition of aqueous hydrochloric acid solution (1N, 1.5 mL) and the reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with hexanes (10 mL) and aqueous hydrochloric acid solution (1N, 3 mL) and the layers were separated. The organic layer was extracted with aqueous hydrochloric acid solution (1N, 4 mL). The combined acidic aqueous layers were washed sequentially with hexanes (2 × 10 mL), dichloromethane (10 mL), and hexanes (10 mL). The aqueous layer was then basified to pH 13 with aqueous sodium hydroxide solution (1N, 11 mL). The resulting solution was stirred at ambient temperature for 1 h. The aqueous solution was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were washed sequentially with water (18 mL) and brine (10 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to provide (+)-*ent*-**108**, $[\alpha]^{22}_{D}$ = +24 (*c* 0.070, CH$_2$Cl$_2$)) as a white film (1.4 mg, 93%).

The corresponding enantiomer, (–)-**108**, 2.8 mg, 82%, $[\alpha]^{22}_{D}$ = –24 (*c* 0.085, CH$_2$Cl$_2$)), was obtained using the same procedure and starting with *N*-Cbz enone **106**.

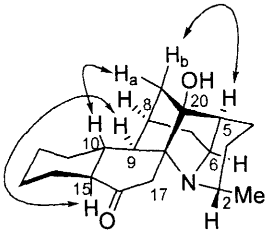
^{1}H NMR (500 MHz, C$_6$D$_6$, 20°C): 3.08-3.02 (m, 2H, C2-H, C6-H), 3.02 (d, *J* = 13.5 Hz, 1H, C17-Ha), 2.55 (br-d, *J* = 12.9 Hz, 1H, C17-Hb), 1.99-1.91 (m, 2H, C9-H, OH), 1.91-1.88 (m, 1H, C8-H), 1.87-1.81 (m, 1H), 1.80-1.72 (m, 2H, C15-H, C21-Ha), 1.68-1.48 (m, 7H, C5-H, C21-Hb, C7-Ha), 1.43-1.30 (m, 3H), 1.26 (br-d, *J* = 12.7 Hz, 1H, C7-Hb), 1.14 (qd, *J* = 11.4, 3.4 Hz, 1H, C10-H), 1.06 (d, *J* = 7.0 Hz, 3H, C1-H), 1.02-0.89 (m, 3H), 0.79 (dd, *J* = 13.6, 6.5 Hz, 1H), 0.73-0.63 (m, 1H).

^{13}C NMR (125 MHz, C$_6$D$_6$, 20°C): 212.3 (C16), 87.4 (C20), 75.7 (C19), 60.5 (C9), 57.3 (C6), 55.0 (C5), 52.8 (C15), 50.6 (C2), 47.9 (C21), 44.4 (C10), 40.9 (C17), 37.1 (C7), 36.2 (C8), 32.5, 30.3, 26.4, 25.7, 24.1, 22.4, 20.7 (C1).

FTIR (thin film) cm^{-1}: 3302 (br-m, OH), 2929 (s), 2853 (w), 1706 (m, C=O), 1314 (w), 1300 (w), 1182 (w).

HRMS (ESI): calcd for $C_{20}H_{30}N_1O_2$ $[M+H]^+$: 316.2271, found: 316.2270.

NOESY correlations (600 MHz, C_6D_6, 20°C): H6-H7b, H8-H7a, H8-H7b, **H9-H15**, **H5-H21b**, **H5-H7b**, **H10-H21a**. Key correlation shown in bold.



(+)-*ent*-**108**

Crystal data and structure refinement for imine acetal **78**:

Identification code	05056	
Empirical formula	C28 H48 N2 O4 Si	
Formula weight	504.77	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 13.2084(8) Å	α= 90°.
	b = 19.7724(16) Å	β= 91.735(2)°.
	c = 11.0439(9) Å	γ = 90°.
Volume	2882.9(4) $Å^3$	
Z	4	
Density (calculated)	1.163 Mg/m^3	
Absorption coefficient	0.115 mm^{-1}	
F(000)	1104	
Crystal size	0.20 x 0.20 x 0.20 mm^3	
Theta range for data collection	1.85 to 24.71°.	
Index ranges	-15<=h<=15, -23<=k<=23, -12<=l<=12	
Reflections collected	40426	
Independent reflections	4906 [R(int) = 0.0391]	
Completeness to theta = 24.71°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9773 and 0.9773	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4906 / 1 / 326	
Goodness-of-fit on F^2	1.021	
Final R indices [I>2sigma(I)]	R1 = 0.0376, wR2 = 0.0912	
R indices (all data)	R1 = 0.0454, wR2 = 0.0963	
Largest diff. peak and hole	0.410 and -0.222 e.$Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for imine acetal **78**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	7947(1)	388(1)	4155(1)	23(1)
O(4)	6964(1)	305(1)	3205(1)	21(1)
O(1)	7036(1)	-839(1)	2716(1)	25(1)
O(3)	4781(1)	2543(1)	-470(1)	24(1)
O(2)	5417(1)	1750(1)	-1686(1)	27(1)
N(2)	5521(1)	1649(1)	403(1)	20(1)
C(22)	5266(1)	1949(1)	-675(1)	21(1)
N(1)	7520(1)	-2781(1)	1554(1)	24(1)
C(20)	6403(1)	-269(1)	2817(1)	21(1)
C(15)	6867(1)	830(1)	-252(1)	20(1)
C(17)	5593(1)	555(1)	1305(1)	19(1)
C(27)	7986(1)	1330(1)	4402(1)	26(1)
C(21)	5587(1)	-432(1)	3705(1)	26(1)
C(23)	5000(1)	1978(1)	1391(2)	26(1)
C(6)	7836(1)	-2106(1)	1976(1)	21(1)
C(10)	7515(1)	267(1)	349(1)	20(1)
C(24)	4753(1)	2661(1)	830(1)	26(1)
C(16)	5959(1)	988(1)	510(1)	19(1)
C(8)	7482(1)	-854(1)	1533(1)	21(1)
C(19)	5996(1)	-142(1)	1517(1)	20(1)
C(2)	7771(1)	-3297(1)	2464(2)	27(1)
C(5)	8986(1)	-2103(1)	2134(2)	26(1)
C(30)	8001(2)	1687(1)	3166(2)	33(1)
C(7)	7433(1)	-1578(1)	1079(1)	22(1)
C(11)	8361(1)	65(1)	-494(2)	26(1)
C(29)	7034(1)	1553(1)	5061(2)	32(1)
C(26)	9150(1)	95(1)	3475(2)	32(1)
C(3)	8912(1)	-3338(1)	2652(2)	31(1)
C(14)	7554(1)	1442(1)	-469(1)	23(1)
C(4)	9338(1)	-2651(1)	3026(2)	32(1)
C(9)	6885(1)	-344(1)	726(1)	20(1)
C(28)	8927(1)	1542(1)	5159(2)	39(1)
C(12)	9039(1)	666(1)	-776(2)	32(1)
C(13)	8420(1)	1252(1)	-1288(2)	30(1)
C(25)	7775(2)	-85(1)	5592(2)	36(1)

Bond lengths [Å] and angles [°] for imine acetal **78**.

Si(1)-O(4)	1.6524(11)
Si(1)-C(25)	1.8624(17)
Si(1)-C(26)	1.8694(17)
Si(1)-C(27)	1.8838(17)
O(4)-C(20)	1.4151(18)
O(1)-C(20)	1.4090(18)
O(1)-C(8)	1.4503(18)
O(3)-C(22)	1.3607(19)
O(3)-C(24)	1.4565(19)
O(2)-C(22)	1.2068(19)
N(2)-C(22)	1.364(2)
N(2)-C(16)	1.4312(19)
N(2)-C(23)	1.4614(19)
N(1)-C(2)	1.463(2)
N(1)-C(6)	1.470(2)
C(20)-C(21)	1.514(2)
C(20)-C(19)	1.538(2)
C(15)-C(16)	1.519(2)
C(15)-C(14)	1.536(2)
C(15)-C(10)	1.542(2)
C(17)-C(16)	1.328(2)
C(17)-C(19)	1.492(2)
C(27)-C(28)	1.535(2)
C(27)-C(29)	1.536(2)
C(27)-C(30)	1.538(2)
C(23)-C(24)	1.518(2)
C(6)-C(5)	1.524(2)
C(6)-C(7)	1.524(2)
C(10)-C(11)	1.529(2)
C(10)-C(9)	1.532(2)
C(8)-C(7)	1.517(2)
C(8)-C(9)	1.545(2)
C(19)-C(9)	1.537(2)
C(2)-C(3)	1.517(2)
C(5)-C(4)	1.528(2)
C(11)-C(12)	1.526(2)
C(3)-C(4)	1.524(2)
C(14)-C(13)	1.527(2)
C(12)-C(13)	1.518(2)

O(4)-Si(1)-C(25)	112.17(7)
O(4)-Si(1)-C(26)	112.04(7)
C(25)-Si(1)-C(26)	108.30(9)
O(4)-Si(1)-C(27)	102.00(7)
C(25)-Si(1)-C(27)	112.12(8)
C(26)-Si(1)-C(27)	110.16(8)
C(20)-O(4)-Si(1)	131.79(9)
C(20)-O(1)-C(8)	110.26(11)
C(22)-O(3)-C(24)	109.15(11)
C(22)-N(2)-C(16)	123.93(13)
C(22)-N(2)-C(23)	110.38(12)
C(16)-N(2)-C(23)	122.87(12)
O(2)-C(22)-O(3)	121.86(14)
O(2)-C(22)-N(2)	128.48(15)
O(3)-C(22)-N(2)	109.66(13)
C(2)-N(1)-C(6)	111.10(12)
O(1)-C(20)-O(4)	110.98(12)
O(1)-C(20)-C(21)	108.46(12)
O(4)-C(20)-C(21)	110.59(12)
O(1)-C(20)-C(19)	104.38(12)
O(4)-C(20)-C(19)	108.42(12)
C(21)-C(20)-C(19)	113.86(13)
C(16)-C(15)-C(14)	113.83(12)
C(16)-C(15)-C(10)	110.32(12)
C(14)-C(15)-C(10)	108.28(12)
C(16)-C(17)-C(19)	124.36(14)
C(28)-C(27)-C(29)	109.02(13)
C(28)-C(27)-C(30)	109.04(14)
C(29)-C(27)-C(30)	108.78(14)
C(28)-C(27)-Si(1)	111.50(13)
C(29)-C(27)-Si(1)	109.43(11)
C(30)-C(27)-Si(1)	109.03(11)
N(2)-C(23)-C(24)	101.06(12)
N(1)-C(6)-C(5)	108.20(12)
N(1)-C(6)-C(7)	109.05(12)
C(5)-C(6)-C(7)	113.54(13)
C(11)-C(10)-C(9)	111.87(13)
C(11)-C(10)-C(15)	109.47(12)
C(9)-C(10)-C(15)	112.84(13)
O(3)-C(24)-C(23)	104.41(12)
C(17)-C(16)-N(2)	119.32(13)
C(17)-C(16)-C(15)	122.83(14)
N(2)-C(16)-C(15)	117.76(12)
O(1)-C(8)-C(7)	107.60(12)
O(1)-C(8)-C(9)	106.94(12)
C(7)-C(8)-C(9)	114.14(12)
C(17)-C(19)-C(9)	115.23(12)
C(17)-C(19)-C(20)	114.23(12)
C(9)-C(19)-C(20)	103.67(12)
N(1)-C(2)-C(3)	109.61(13)
C(6)-C(5)-C(4)	110.74(13)
C(8)-C(7)-C(6)	114.93(13)
C(12)-C(11)-C(10)	111.43(13)
C(2)-C(3)-C(4)	110.27(14)
C(13)-C(14)-C(15)	110.79(13)
C(3)-C(4)-C(5)	110.78(14)
C(10)-C(9)-C(19)	112.30(12)
C(10)-C(9)-C(8)	113.56(13)
C(19)-C(9)-C(8)	103.17(12)
C(13)-C(12)-C(11)	110.96(14)
C(12)-C(13)-C(14)	111.84(13)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters ($Å^2$x 10^3) for imine acetal **78**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	23(1)	26(1)	19(1)	-2(1)	-3(1)	4(1)
O(4)	24(1)	20(1)	20(1)	0(1)	-2(1)	1(1)
O(1)	35(1)	21(1)	18(1)	1(1)	3(1)	8(1)
O(3)	25(1)	21(1)	26(1)	1(1)	-4(1)	3(1)
O(2)	35(1)	27(1)	20(1)	0(1)	-4(1)	2(1)
N(2)	20(1)	21(1)	19(1)	1(1)	1(1)	3(1)
C(22)	18(1)	20(1)	24(1)	2(1)	-4(1)	-1(1)
N(1)	25(1)	20(1)	27(1)	-1(1)	-3(1)	0(1)
C(20)	24(1)	17(1)	22(1)	-1(1)	0(1)	1(1)
C(15)	21(1)	21(1)	17(1)	0(1)	0(1)	1(1)
C(17)	15(1)	22(1)	20(1)	-3(1)	-1(1)	0(1)
C(27)	26(1)	28(1)	25(1)	-6(1)	0(1)	-3(1)
C(21)	31(1)	25(1)	23(1)	2(1)	4(1)	-1(1)
C(23)	28(1)	25(1)	26(1)	-1(1)	6(1)	6(1)
C(6)	23(1)	20(1)	21(1)	-3(1)	0(1)	1(1)
C(10)	20(1)	22(1)	19(1)	1(1)	0(1)	2(1)
C(24)	26(1)	24(1)	26(1)	-1(1)	4(1)	5(1)
C(16)	19(1)	20(1)	17(1)	-2(1)	-3(1)	1(1)
C(8)	23(1)	22(1)	17(1)	0(1)	1(1)	1(1)
C(19)	21(1)	20(1)	19(1)	0(1)	0(1)	-3(1)
C(2)	32(1)	20(1)	29(1)	0(1)	0(1)	-1(1)
C(5)	24(1)	23(1)	33(1)	-1(1)	0(1)	-1(1)
C(30)	41(1)	26(1)	34(1)	-2(1)	3(1)	-4(1)
C(7)	24(1)	22(1)	21(1)	-2(1)	-1(1)	1(1)
C(11)	27(1)	27(1)	25(1)	3(1)	5(1)	8(1)
C(29)	33(1)	28(1)	34(1)	-8(1)	2(1)	2(1)
C(26)	24(1)	41(1)	32(1)	-7(1)	-7(1)	8(1)
C(3)	31(1)	25(1)	38(1)	5(1)	-1(1)	7(1)
C(14)	22(1)	22(1)	25(1)	3(1)	3(1)	1(1)
C(4)	24(1)	31(1)	39(1)	0(1)	-7(1)	3(1)
C(9)	23(1)	19(1)	18(1)	-2(1)	-2(1)	2(1)
C(28)	33(1)	51(1)	33(1)	-15(1)	1(1)	-8(1)
C(12)	25(1)	36(1)	34(1)	5(1)	11(1)	6(1)
C(13)	27(1)	31(1)	31(1)	7(1)	9(1)	0(1)
C(25)	41(1)	40(1)	25(1)	5(1)	-5(1)	5(1)

Hydrogen bonds for imine acetal **78** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(3)#1	0.889(15)	2.413(15)	3.2665(18)	160.9(16)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y,-z

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for imine acetal **78**.

	x	y	z	U(eq)
H(15)	6611	661	-1058	23
H(17)	5038	697	1769	23
H(21A)	5163	-802	3383	39
H(21B)	5166	-31	3826	39
H(21C)	5902	-570	4481	39
H(23A)	5446	2024	2123	31
H(23B)	4378	1730	1602	31
H(6)	7535	-2020	2781	25
H(10)	7841	461	1100	24
H(24A)	4074	2817	1063	31
H(24B)	5261	3004	1088	31
H(8)	8206	-708	1610	25
H(19)	5431	-468	1349	24
H(2A)	7504	-3741	2190	32
H(2B)	7455	-3181	3238	32
H(5A)	9214	-1655	2435	32
H(5B)	9295	-2182	1340	32
H(30A)	7381	1576	2697	50
H(30B)	8592	1535	2724	50
H(30C)	8039	2178	3288	50
H(7A)	7823	-1610	330	26
H(7B)	6719	-1688	863	26
H(11A)	8775	-297	-107	32
H(11B)	8060	-117	-1258	32
H(29A)	7022	1334	5856	47
H(29B)	6429	1421	4581	47
H(29C)	7042	2045	5165	47
H(26A)	9143	-399	3409	49
H(26B)	9727	237	3992	49
H(26C)	9209	294	2668	49
H(3A)	9223	-3487	1892	38
H(3B)	9081	-3676	3288	38
H(14A)	7150	1811	-850	28
H(14B)	7835	1609	317	28
H(4A)	10088	-2671	3055	38
H(4B)	9112	-2536	3847	38
H(9)	6616	-581	-16	24
H(28A)	8904	2030	5314	58
H(28B)	9538	1433	4715	58
H(28C)	8941	1297	5931	58
H(12A)	9406	813	-26	38
H(12B)	9547	527	-1369	38
H(13A)	8139	1127	-2099	35
H(13B)	8867	1649	-1386	35
H(25A)	7138	53	5951	53
H(25B)	8341	14	6159	53
H(25C)	7756	-572	5423	53
H(1)	6856(11)	-2786(10)	1401(16)	33(5)

Chapter 2

Resin-bound Glycosyl Phosphates As Glycosyl Donors

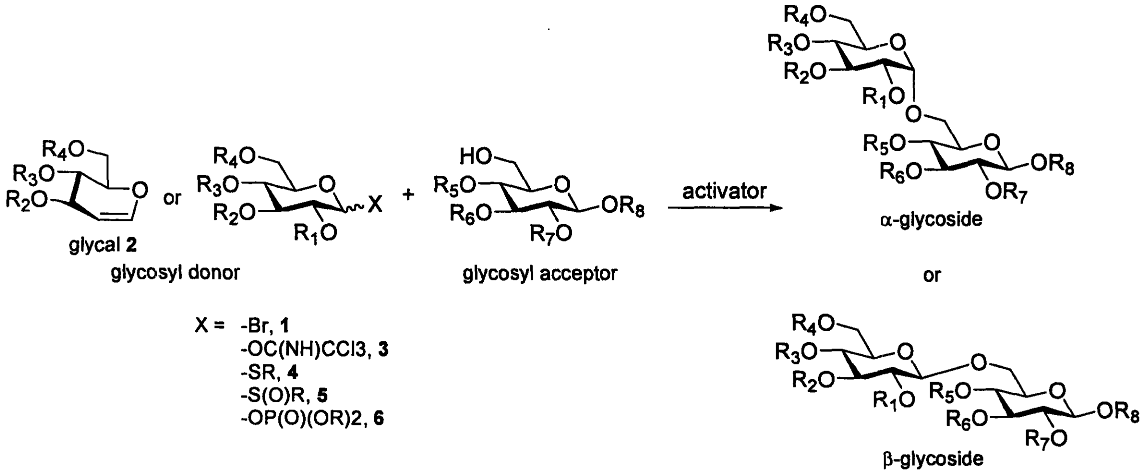
Thesis Advisor: Peter H. Seeberger

Introduction and Background

While the significance of oligosaccharides and glycoconjugates in biological signaling pathways and cell adhesion is generally appreciated, the difficulty associated with their isolation and identification has hindered detailed investigations. Unlike nucleic acid and protein biopolymers, which are biosynthesized under genetic control, complex carbohydrates are enzymatically generated, resulting in microheterogeneous mixtures that are difficult to characterize and purify.[1] Synthetic methodologies must take into consideration the specific challenges posed by oligosaccharides, particularly hydroxyl group differentiation, the generation of highly branched structures, and the stereospecific formation of each glycosidic linkage. Both enzymatic and chemical methods have been applied to these issues, each offering unique advantages.

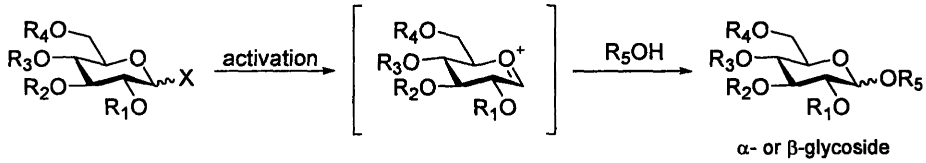
The application of natural glycosyltransferases and glycosidases to oligosaccharide construction offers the benefit of excellent stereo- and regiocontrol and eliminates the need for extensive protecting group manipulations.[2] The diversity of carbohydrates available by this method is limited, however, by enzyme specificity, precluding the use of non-natural substrates. Where unusual linkages or unnatural sugars would be advantageous for biological study or therapeutic application, chemical synthesis remains an invaluable tool.

Synthetic oligosaccharide formation requires a glycosyl donor which forms an electrophilic species on activation and couples with a nucleophilic acceptor hydroxyl (Scheme 1). Since the first report by Koenigs and Knorr involving glycosyl halides (**1**),[3]



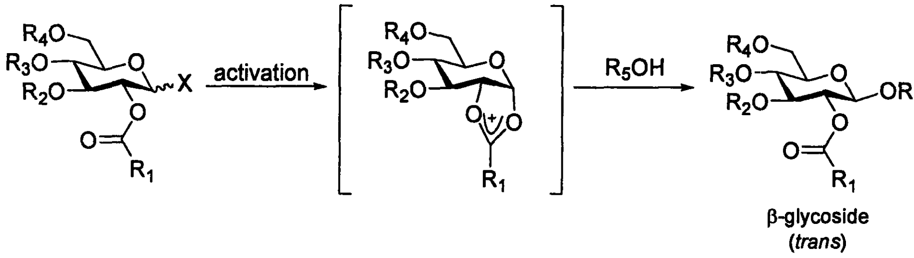
Scheme 1. The general strategy for chemical synthesis of oligosaccharides.

numerous glycosyl donors have been developed, among them 1,2-anhydrosugars (glycals, **2**),[4] glycosyl trichloroacetimidates (**3**),[5] thioglycosides (**4**),[6] glycosyl sulfoxides (**5**),[7] and glycosyl phosphates (**6**).[8] Although α-glycosidic linkages are favored due to the anomeric effect, stereoselectivity can depend on a number of factors, including leaving group identity, the electronic and steric nature of donor and acceptor substituents, the activator, the solvent, and the temperature. These variables are thought to affect the stability and conformation of the putative oxonium ion formed following the departure of the leaving group during activation (Scheme 2). Though the mechanisms of several donor types, such as sulfoxides,[9] trichloroacetimidates,[10] and phosphites,[11] have been investigated, a detailed general mechanism remains elusive and is often a matter of debate.[12]



Scheme 2. Proposed oxonium intermediate in the glycosylation reaction.

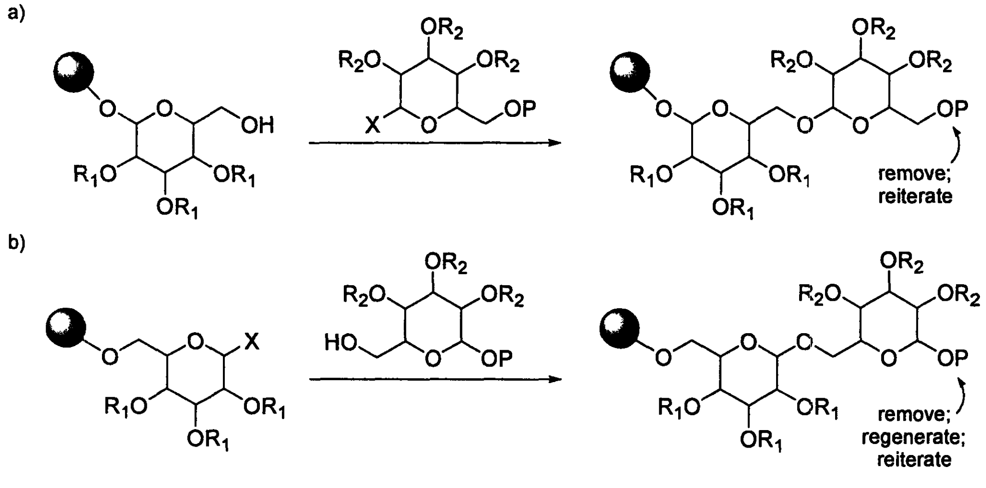
Various techniques have been developed to enhance the stereoselectivty of glycosylation reactions, particularly the formation of energetically-disfavored β-glucosidic linkages, which are prevalent in biological systems. Numerous methods have been employed to produce ß-linked sugars, including the use of participating solvents,[13,8] intramolecular aglycone delivery,[14] and glycal donors.[15] A common and general method for producing ß-linked glucosyl sugars utilizes anchimeric assistance from an ester or amide protecting group installed at C2. For a wide range of donor types and sugars, interaction of a C2-ester with the intermediate oxonium species formed on activation effectively blocks the *cis*-face such that the *trans*-product is formed exclusively (Scheme 3).[16]



Scheme 3. Use of a C2-participating group for stereospecific formation of β-glucosides.

Advances in the chemical synthesis of oligonucleotides and oligopeptides over the last several decades, particularly the exploitation of solid phase strategies,[17] have facilitated widespread exploration of their structure and function. As a result of this success, interest in the application of the solid phase paradigm to the construction of complex carbohydrates has intensified. Attractive features of the solid-phase approach include the elimination of intermediate purification steps, which allows the use of excess reagent to drive reactions to high conversion. Recent work has also demonstrated the applicability of the solid-phase paradigm to the automated synthesis of oligosaccharides.[18]

Solid-phase oligosaccharide synthesis may be approached from two different directions, through linker attachment at either a reducing or non-reducing site on the sugar, resulting in immobilized acceptor or donor, respectively (Scheme 4).[19] In the acceptor-bound paradigm, following glycosylation an orthogonal temporary protecting group is removed and the process repeated, while in the donor-bound strategy, a new donor is regenerated and the process repeated. A number of syntheses have employed the acceptor-



Scheme 4. Solid-phase oligosaccharide synthesis: a) acceptor-bound strategy; b) donor-bound strategy.[19]

bound method and a variety of donors to produce diverse and complex structures such as the phytoalexin elicitor (**7**),[18] Lewis blood determinants (**8**),[20] and heparin sulfate-like oligomers (**9**), as well as carbohydrate libraries (Figure 1).[19] In addition, a variety of polymer-supported glycosyl donors, attached to the solid phase at each of the four non-reducing positions, have been explored. While acceptor-bound methods often lead to inert anomeric moieties, efficient donor-bound synthesis may allow straight-forward access to peptide or lipid containing glycoconjugates by direct ligation on solid support at the available reducing sugar.[19] Effective glycosylations with resin-bound glycosyl fluorides, trichloroacetimidates, thioglycosides and glycals have been demonstrated, with the latter two methods providing the best yields and purity.[15,21] Several examples of oligosaccharides synthesized utilizing the donor-bound method are shown in Figure 2.[15,21c]

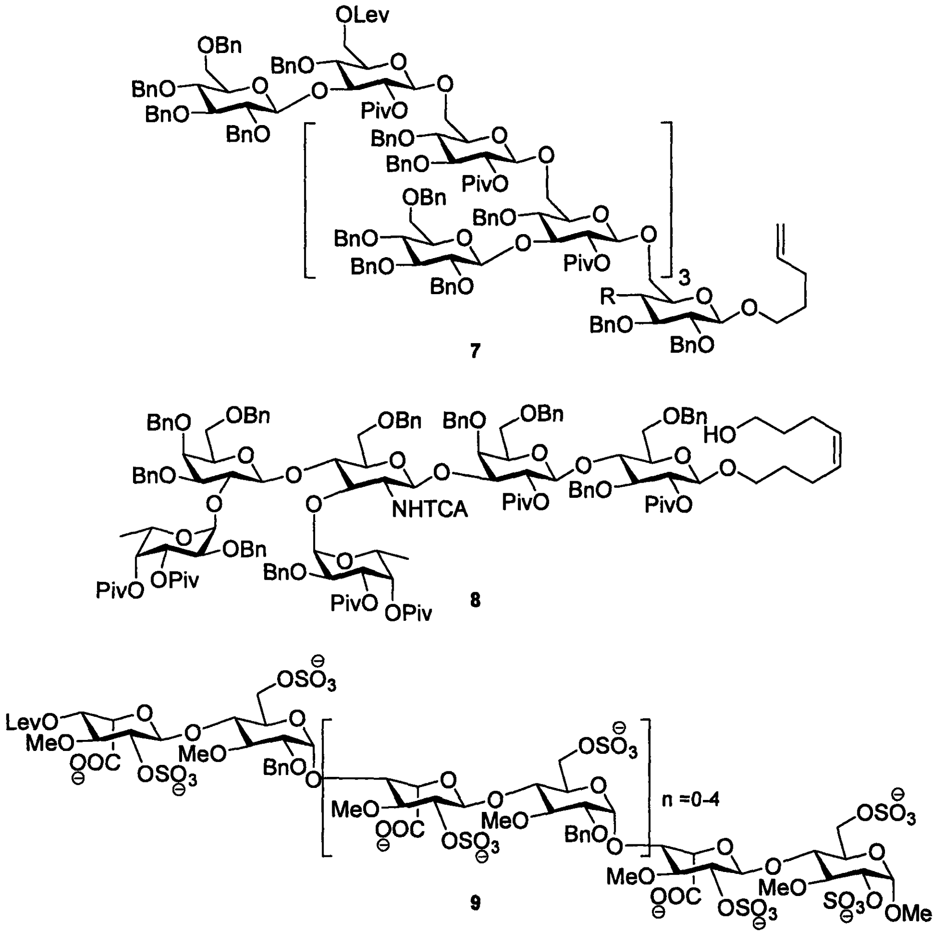


Figure 1. Representative structures synthesized using acceptor-bound solid-phase oligosaccharide synthesis: protected phytoalexin elicitor (**7**), protected Lewis Y (**8**), and a heparin sulfate-like oligomer **9**.

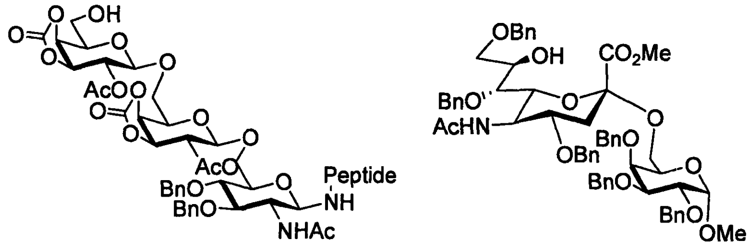
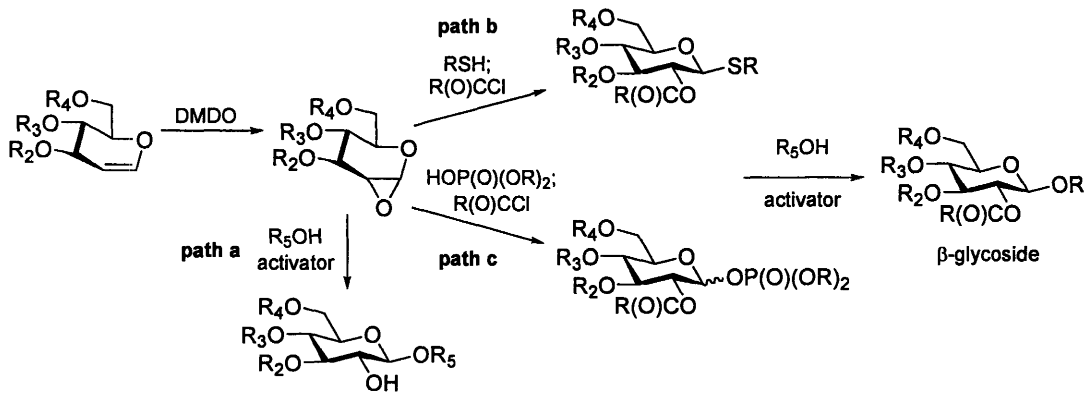


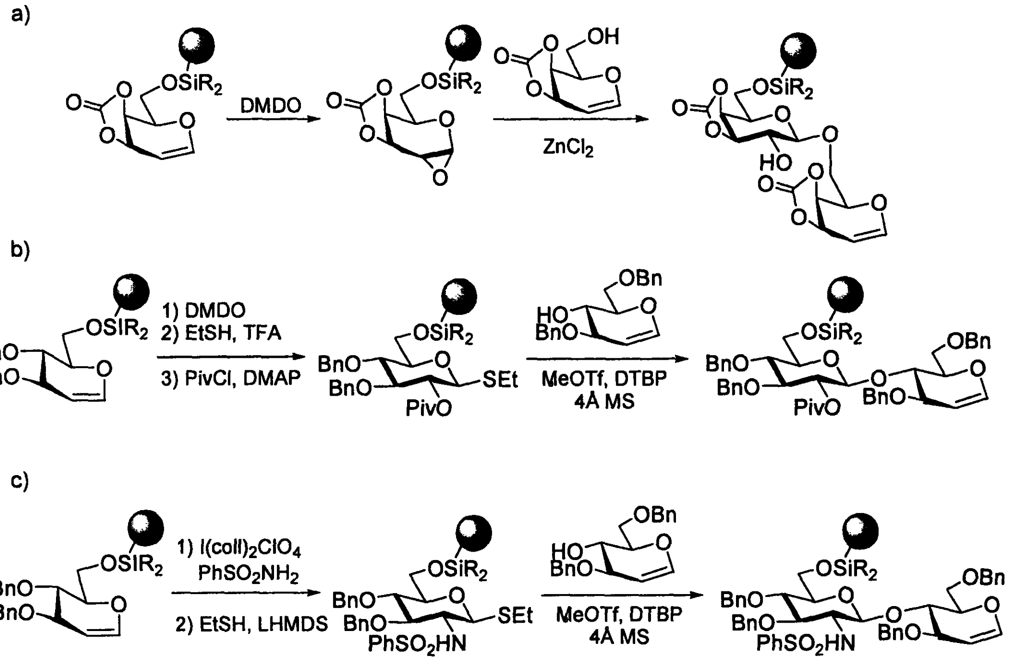
Figure 2. Representative structures synthesized using donor-bound solid-phase oligosaccharide synthesis.

The use of glycals as synthetic intermediates is particularly attractive as they simplify the manipulations required for hydroxyl differentiation. Glycals have been used both as donors[15] and as precursors to thioglycosides[22] and glycosyl phosphates[8] (Scheme 5). Use of



Scheme 5. Glycals as donors (path a) and precursors to thioglycosides (path b) or glycosyl phosphates (path c).

a C2-ester in thiodonor and phosphate formation generally insures β-linkages in the final products. Resin-bound glycals have been used to produce extended structures as well as resin-bound thioglycosides and thioethyl 2-amidoglucosyl donors (Scheme 6).[15] The high-



Scheme 6. Resin-bound oligosaccharide synthesis using glycals (a), glycal-derived thioglycosides (b), and thioethyl 2-amidoglucosyl donors (c).[15]

yielding one-pot synthesis of glycosyl phosphates from glycals and the high reactivity of these donors suggest they would be an attractive addition to donor-bound oligosaccharide synthesis.

Linker choice is an important consideration in any solid-phase synthesis. The linker should be inert to all required manipulations, yet easily installed and readily cleaved to release the desired product. Donor-bound strategies have employed assorted chemical anchors for resin attachment, including various trialkylsilyl[15,21a] and *p*-alkoxybenzyl groups,[21b,d] as well as base-labile succinate[21c] and succinamyl[21e] linkers. Linkers are chosen with the overall protecting scheme and chemical pathway in mind and are designed for generalized use. The work discussed in this chapter describes the synthesis and use of resin-bound glycosyl phosphates, where the succinate linker chosen was observed to influence the stereochemical outcome of the glycosylation reaction.[23]

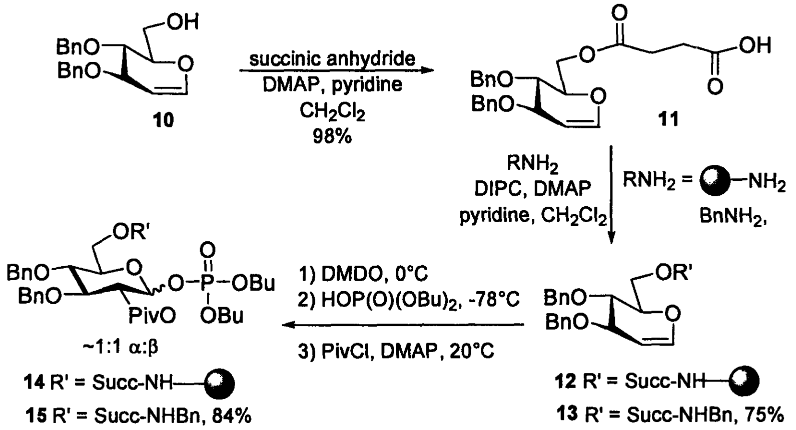
Results and Discussion

Preparation of resin-bound glycosyl phosphates.

Recent work has demonstrated the utility of anomeric phosphate donors, which couple rapidly and in high yield in both solution phase and acceptor-bound glycosylations upon activation with stoichiometric trimethylsilyl trifluoromethanesulfonate (TMSOTf). Successful application of glycals to the solution phase one-pot synthesis of glycosyl phosphates[8] suggested an efficient route to their resin-bound counterparts analogous to Danishefsky's synthesis of polymer supported thioglycosides (Scheme 6).[15]

Preparation of resin-bound glycosyl phosphates began with the selection of an appropriate support and linker system. Polystyrene resin was chosen for its excellent swelling properties in methylene chloride, the primary solvent for our planned resin-bound operations. An aminomethyl-functionalized resin coupled to succinate would provide a succinamyl linker[24] that could be readily cleaved through basic hydrolysis.[25]

Attachment to the resin was undertaken at the readily differentiated C6-hydroxyl of dibenzyl glycal **10**. Exposure of **10** to succinic anhydride and dimethylaminopyridine (DMAP) in pyridine and methylene chloride provided the C6-succinate **11** in excellent yield (Scheme 7). Immobilization of glycal **11** onto the aminomethyl resin via amide formation with diisopropylcarbodiimide provided resin-bound glycal **12**. In order to facilitate reaction analysis a solution-phase model system of the resin-bound donor system was also prepared. Analogous coupling of glycal **11** with benzylamine provided model system **13**.

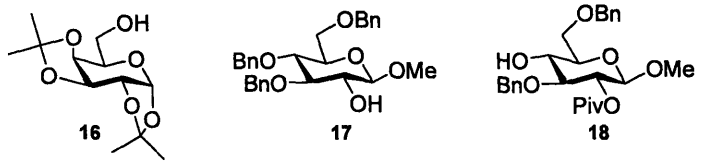


Scheme 7. Synthesis of resin-bound and solution-phase model glycosyl phosphates with a succinamyl linker.

Application of our previously developed solution-phase three-step, one-pot procedure for access to glycosyl phosphates from glycals provided resin-bound glycosyl phosphate **14** and model glycosyl phosphate **15** from glycals **12** and **13**, respectively. Initial epoxidation of each glycal was achieved by exposure to an acetone solution of dimethyldioxirane (DMDO) (Scheme 7). Removal of the volatiles was followed by epoxide opening with dibutylphosphate to provide the desired anomeric phosphate. Finally, installation of a pivaloyl ester at C2 provided the desired participating group, which was expected to ensure the desired β-selectivity for the glycosylation reaction. Epoxidation with dimethyldioxirane (DMDO) was performed twice for the resin-bound conversion as outlined for Danishefsky's thioglycoside preparation from the 1,2-anhydrosugar.[15] Comparative analysis of ^{31}P NMR and high resolution magic angle spinning (HR-MAS) ^{31}P NMR for compounds **15** and **14**, respectively, indicated a 1:1 mixture of α and β glycosyl phosphates was obtained in both cases.

Disaccharide synthesis with resin-bound glycosyl phosphates.

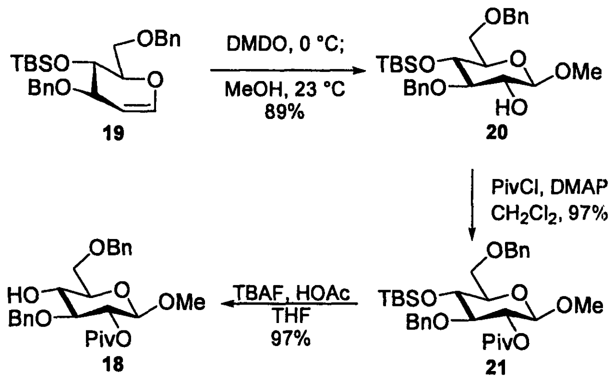
With glycosyl phosphates **14** and **15** in hand, activation of the support-bound donor for union with a series of nucleophiles was explored. Glycosyl acceptors displaying C6 (**16**),[26] C2 (**17**), and C4 (**18**) hydroxyl groups were investigated in glycosylations with both the resin-bound donor **14** and model system **15** (Figure 3). Acceptor **18** was synthesized from glycal **19** via epoxidation and ring opening with methanol to provide methyl glycoside **20**, subsequent pivaloyl protection at C2 (**21**), and fluoride-mediated silyl deprotection to reveal the desired C4-hydroxyl of **18** in good yield (Scheme 8).



16 **17** **18**

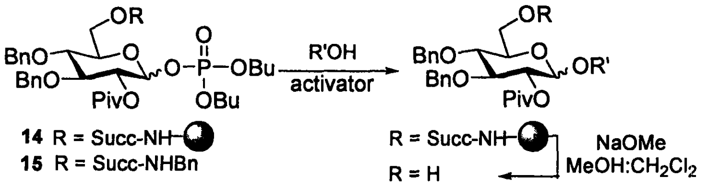
Figure 3. C6-, C2- and C4-OH acceptors for glycosylation.

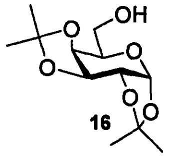
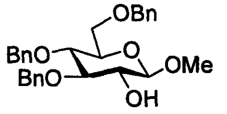
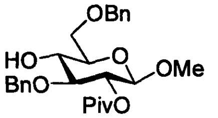
Glycosylation was effected by swelling of resin **14** in methylene chloride, followed by phosphate activation with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at low temperature in the presence of acceptor **16**, **17**, or **18** (Table 1). Cleavage of the disaccharides from the resin was achieved by exposure to sodium methoxide in a mixture of methanol and methylene chloride to provide glycosides **22**, **24** and **26**. The reported yields in Table 1 reflect the total yield over the four solid-phase operations. In several cases double glycosylations or excess activator were required for full conversion of the resin bound donor.



Scheme 8. Synthesis of C4-hydroxyl acceptor **18**.

Table 1. Disaccharide synthesis using resin-bound phosphate **14** and solution-phase model **15**.



entry	donor	R'OH	product	R	yield (%, α:β)
1	**14**		**22**	H	58%, α:β 1:2.2[a]
2	**15**	**16**	**23**	Succ-NHBn	85%, α:β 1:4[b]
3	**14**		**24**	H	26%, α:β 1:2[a]
4	**15**	**17**	**25**	Succ-NHBn	98%, α:β 1:1.1[c] (38%, α:β 1:1.4)[b]
5	**14**		**26**	H	27%, α:β 1:1.7[d]
6	**15**	**18**	**27**	Succ-NHBn	80% , α:β 1.1:1[c]

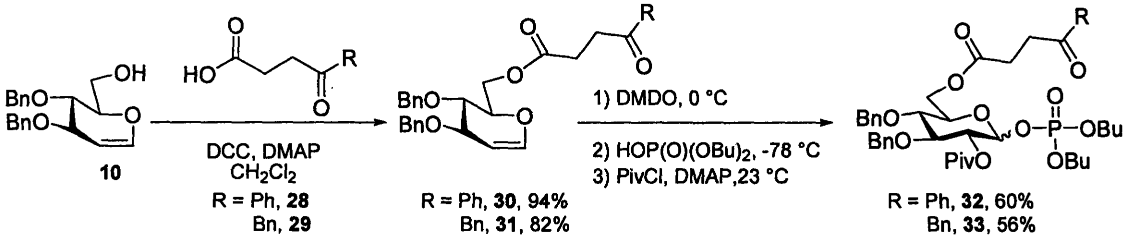
[a] Resin-bound phosphate **14** (1.0 equiv) was swelled in CH_2Cl_2, R'OH (2.5-6.5 equiv) was added, followed by TMSOTf (1.1 equiv) at -15 °C, and the reaction shaken for 2 h; the procedure was repeated twice. [b] Phosphate 6 (1.1 equiv) and R'OH (1.0 equiv) were dissolved in CH_2Cl_2, TMSOTf (1.3 equiv) added at -78 °C, and the reaction warmed to -10 °C over 2 h. [c] Phosphate 6 (1.1 equiv) and R'OH (1.0 equiv) were dissolved in CH_2Cl_2, TMSOTf (1.3 equiv) added at -78 °C , followed by another 1.3 equiv activator after warming to -30 °C over 1 h. [d] Resin-bound phosphate 5 (1.0 equiv) was swelled in CH_2Cl_2, R'OH (2.0 equiv) added, followed by slow warming from -78 °C with addition of 3 x 1.1 equiv of TMSOTf added on one hour delays at -78 °C, -30 °C, and -10 °C.

Surprisingly, despite the presence of a participating pivaloyl ester at C2 for the resin-bound donor **14**, the resulting disaccharides were obtained as anomeric mixtures that only slightly favored the expected ß-anomer (Table 1, entries 1, 3, and 5). Analogous solution phase glycosylation reactions employing glycosyl phosphate **15** also produced anomeric mixtures, suggesting the nature of the linker, rather than the solid-phase protocol, was responsible for these unexpected results (Table 1, entries 2, 4, and 6).

Investigation of C6-linker effects on reactions with glycosyl phosphates.

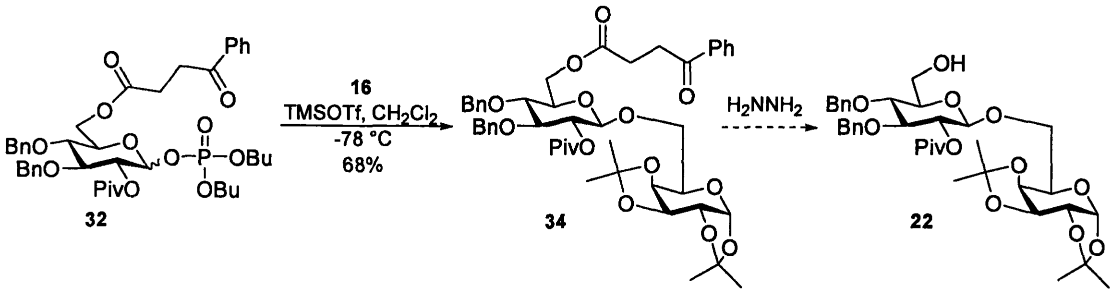
Previous work in our laboratory, including couplings with glycosyl phosphates containing a C6-levulinate ester, had not indicated any interference of the C6-hydroxyl protecting group with anomeric selectivity.[8,18] On the basis of these considerations, we reasoned that a levulinate-type linker would not affect glycosylation stereoselectivity, while hydrazine cleavage should allow rapid removal of the products from the resin under neutral conditions. A 3-benzoylpropionate ester linker, previously utilized at the anomeric position in an acceptor-bound strategy for the assembly of di-, tri-, and tetrasaccharides,[27] was selected to replace the succinamyl linker.

Investigations into the use of this new linker were performed on a solution-phase model system for expedient analysis of the chosen route. Glycosyl phosphate formation, subsequent glycosylations, and linker cleavage therefore utilized C6-3-benzoylpropionate ester **30** (Scheme 9). Union of glycal **10** and 3-benzoylpropionic acid **28** afforded protected



Scheme 9. Synthesis of 3-benzoylpropionic and 4-oxo-5-valeric linker model phosphates from glycal **10**.

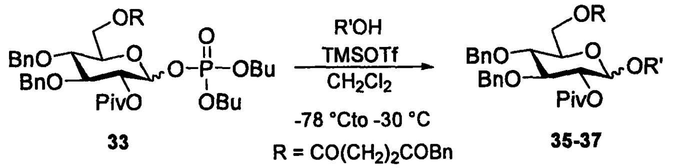
glycal **30** that was readily converted to the corresponding glycosyl phosphate **32** as described above. Subsequent coupling with acceptor **16** produced exclusively the β-disaccharide **34**, consistent with effective participation of the C2-pivaloate ester (Scheme 10). Unfortunately,

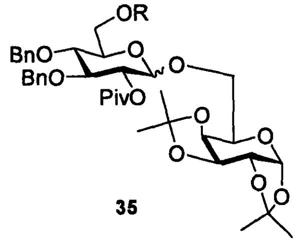
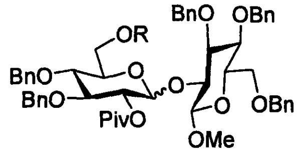
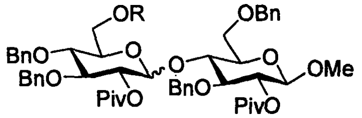


Scheme 10. Glycosylation with phosphate **32** and attempted linker cleavage.

cleavage of the 3-benzoylpropionic ester with either excess hydrazine or hydrazine acetate proved very slow, requiring prolonged reaction times (18 h) to produce 50-80% conversion even at elevated temperature (80°C). We hypothesized that addition of a methylene group to the linker would alter the electrophilicity of the benzylic carbonyl, alleviate steric crowding, and facilitate its removal with hydrazine. To assess this strategy, a 4-oxo-5-phenyl-valerate ester[28] model linker was installed at C6 of galactose **16**. We were pleased to find the linker was efficiently cleaved at ambient temperature in the presence of hydrazine (2 equiv) in 90 minutes. Encouraged by these initial observations, we investigated the use of this linker for glycosyl phosphate formation and glycosylation with acceptor **16**. Glycal **10** was equipped with the 4-oxo-5-phenyl-valeric ester at C6 and converted to the corresponding glycosyl phosphate **33** (Scheme 9). Surprisingly, subsequent coupling with the acceptors **16**, **17**, and **18** produced an anomeric mixture of disaccharides **35-37** as previously observed for the succinamyl glycosyl phosphates **14** and **15** (Table 2).

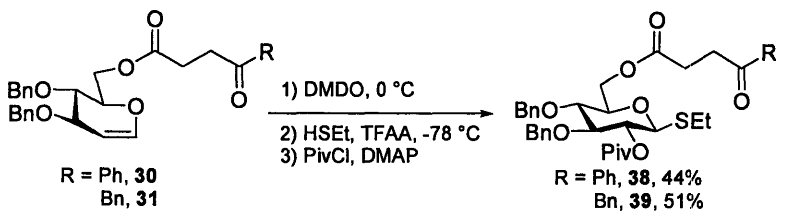
Table 2. Disaccharide synthesis using 4-oxo-5-phenylvaleric ester linker model phosphate **33**.



acceptor	product	yield (%, α:β)
16	 **35**	88% (α:β 1:1.6)
17	 **36**	94% (α:β 1:2.2)
18	 **37**	53% (α:β 1:1.8)

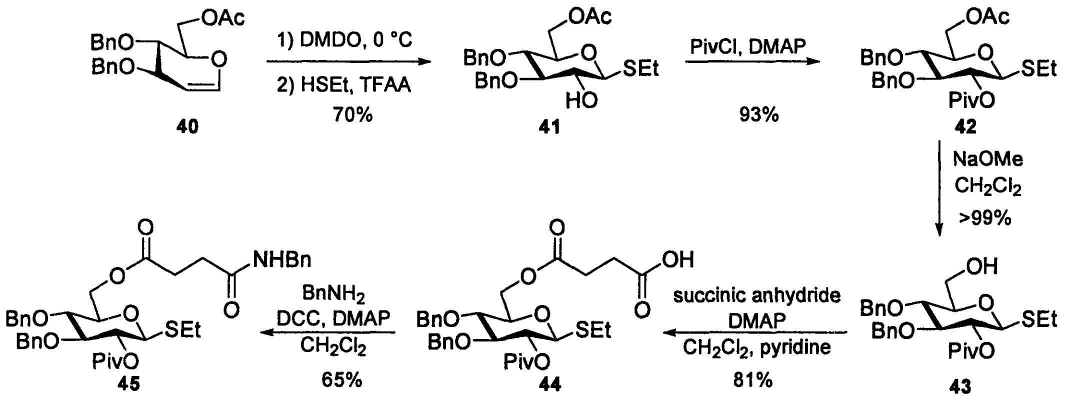
Exploring linker effects with thioglycosides and trichloroacetimidates.

In light of the observed erosion of glycosylation stereoselectivity for glycosyl phosphates **15** and **33**, we decided to explore the generality of the observed linker effect for different anomeric leaving groups. To this end, the corresponding thioglycoside and glycosyl trichloroacetimidate donors, each containing a C2-pivaloate ester and one of the three C6 model linkers, were prepared. 3-Benzoylpropionoate and 4-oxo-5-valerate ester glycals **30** and **31** were subjected to epoxidation and ring opening with ethanethiol to produce the corresponding phenyl and benzyl ketone thioglycosides, where installation of the C-2 pivaloate ester then provided thioglycosides **38** and **39** (Scheme 11). Application of this sequence to succinamyl glycal **13** failed to provide the desired thioglycoside **45**, and an



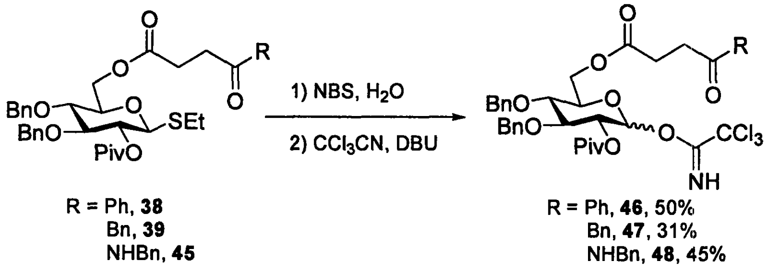
Scheme 11. Synthesis of C6-model linker thioglycosides **38** and **39** from glycals **30** and **31**.

alternate route was employed (Scheme 12). The C6-acetate thioglycoside **41** was obtained from glycal **40**, followed by pivaloate formation to provide C2-pivaloyl thioglycoside **42**.



Scheme 12. Synthesis of C6-succinamyl thioglycoside **45**.

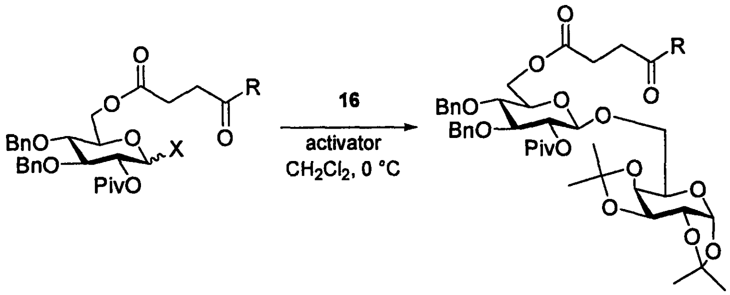
Basic hydrolysis of the acetate was then followed by introduction of the succinate at C6 and amide coupling with benzylamine to provide the desired succinamyl thioglycoside **45**. The required trichloroacetimidates **46-48** were synthesized from thioglycosides **38**, **39**, and **45** via the corresponding lactols (Scheme 13).

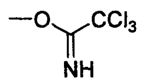


Scheme 13. Formation of C6-model linker trichloroacetimidates **46-48** from thioglycosides **38**, **39**, and **45**.

Thioglycosides **38**, **39**, and **45** and trichloroacetimidates **46-48** were then coupled with galactose acceptor **16** (Table 3). Both donor types exhibited complete β-selectivity for

Table 3. Glycosylations with thioglycosides and glycosyl trichloroacetimidates with various C6-linkers.



X	activator	donor	R	product	yield
—SEt	NIS TMSOTf (cat)	**38**	Ph	**34**	82%
		39	Bn	**35**	79%
		45	NHBn	**23**	73%
 $—OC(=NH)CCl_3$	TMSOTf (cat)	**46**	Ph	**34**	70%
		47	Bn	**35**	37%
		48	NHBn	**23**	69%

each of the three model linkers. The influence of a C6 linker on glycosylation stereoselectivity for glycosyl phosphates and the absence of a dependence for thioglycosides and glycosyl trichloroacetimidates suggest the presence of different intermediates along the reaction pathway. The exact nature of the linker interference during glycosylation is not understood at this time, but must be taken into consideration in the development of new linkers for the donor-bound approach to the synthesis of oligosaccharides and carbohydrate libraries on solid support.

Conclusion

We have demonstrated the preparation of glycosyl phosphates from support-bound glycals using a one-pot, three-step procedure. These glycosyl phosphates were used as resin-bound glycosyl donors in the formation several disaccharides with a variety of acceptors. The nature of the succinic-like linker connecting the C6 hydroxyl group to the support was found to fundamentally influence the stereoselectivity of glycosylations involving these donors, but not that of similar thioglycoside or trichloroacetimidate donors. These results suggest that protecting-group influence on glycosylation with glycosyl phosphates must be considered during synthetic planning, and illuminate the difficulty in proposing a general mechanism for chemical glycosylations.

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[26] Glycosyl acceptor **x** is commercially available (Aldrich).

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Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 400 mesh, Silicycle).[1] Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and by exposure an aqueous solution of ceric ammonium molybdate (CAM), followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~20 Torr at 25–35 °C, then at ~1 Torr.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, diethyl ether, and tetrahydrofuran were purchased from J.T. Baker (Cycletainer^{TM}) and were purified by the method of Grubbs et al. under positive argon pressure.[2] Trimethylsilyl trifluoromethanesulfonate (TMSOTf) purchased from Acros Chemicals. All solid-phase resin was purchased from Novabiochem and was prewashed six times with each of the following: tetrahydrofuran, tetrahydrofuran:methanol (95:5), and dichloromethane. Pyridine was distilled over calcium hydride immediately before use. *N*-Bromosuccinimide (NBS) was recrystallized from boiling water prior to use.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker-400 NMR spectrometer (400 MHz) or a Varian VXR-500 spectrometer (500 MHz). Chemical shifts are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent ($CHCl_3$: δ 7.27). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian 500 INOVA spectrometer or a Bruker 400 spectrometer with a Magnex Scientific superconducting magnet and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.2). Phosphorus-31 nuclear magnetic resonance spectra (^{31}P NMR) spectra were obtained on a Varian VXR-300 (120 MHz) or a Varian VXR-500 (200 MHz) and are reported in δ relative to H_3PO_4 (0.0 ppm) as an external reference. Infrared data were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 24 °C using a sodium lamp (589 λ). We are grateful to Dr. Li Li for obtaining the mass spectroscopic data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX 4.7 Tesler FTMS spectrometer using electronspray ion source (ESI) or electronspray (ES).

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[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

Solution phase phosphate synthesis. General Procedure A.[4] The protected glycal (1.0 equiv) was azeotropically dried with toluene (3 × 10 mL), dried under reduced pressure (~1 Torr) for 2 h. To a solution of the glycal in methylene chloride (1.5 mL/0.1 mmol glycal) at 0 °C was added a solution of dimethyldioxirane in acetone (0.08 M, 1.5 equiv) After 15 min, the volatiles were removed under reduced pressure (~1 Torr), the residue was dissolved in methylene chloride (2 mL/0.1 mmol glycal), and the solution cooled to –78 °C. Dibutylphosphate (1.1 equiv) was added drop wise to this solution, and the reaction stirred at –78 °C for 30 min. The solution was warmed to 0 °C and dimethylaminopyridine (4.0 equiv) was added, followed by pivaloyl chloride (2.0 equiv) and the reaction was warmed to room temperature. After 1 h, the mixture was concentrated under reduced pressure and the resulting white solid purified by flash column chromatography to provide the desired phosphate.

Solid phase phosphate coupling and disaccharide cleavage from the resin. General Procedure B. The acceptor (2.5-6.5 equiv) was azeotropically dried with toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 2 h. A solution of this acceptor in methylene chloride was transferred via cannula to the resin bound glycosyl phosphate (1.0 equiv) swelled in methylene chloride (10 mL/1.0 g resin). The reaction was cooled to –10 °C, trimethylsilyl trifluoromethane sulfonate was added, and the reaction shaken at –10 °C for 2 h. The solution phase was decanted, the resin was washed three times with methylene chloride (5 mL/g resin), and the reaction sequence repeated. Excess activator was quenched at –10 °C with methanol (10 mL/1.0 g resin), the resin as washed six times with each of tetrahydrofuran, tetrahydrofuran:methanol (95:5), and methylene chloride, then rigorously dried under reduced pressure (~1 Torr) over phosphorous pentaoxide. The resin (1.0 equiv) was swelled in CH_2Cl_2:methanol (10:1, 1.0 mL/g resin) and a solution of sodium methoxide in methanol (25% by weight, 2.0 equiv) was added and the reaction was shaken for 30 min at ambient temperature. The resin was washed with methylene chloride and the solution decanted six times. The solution phase was washed with dilute aqueous hydrochloric acid, water and brine, and the combined organic phases were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. Purification was accomplished by flash column chromatography on silica gel to provide the desired disaccharides.

Solution phase phosphate coupling. General Procedure C. Glycosyl phosphate (1.1 equiv) and acceptor (1.0 equiv) were combined, azeotropically dried with toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 2 h. To a solution of this mixture in methylene chloride (1 mL/0.1 mmol phosphate) at –78 °C was added trimethylsilyl trifluoromethane sulfonate (TMSOTf, 1.3 equiv), and the reaction was warmed to –30 °C. After 1 h, a second portion of TMSOTf (1.3 equiv) was added, and the reaction stirred for an additional 1 h. Excess activator was quenched at –30 °C with triethylamine (1 mL/0.1 mmol

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[4] Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545.

phosphate), the volatiles were removed under reduced pressure, and the resulting oil purified by flash column chromatography on silica gel to give the desired disaccharide.

Solution phase phosphate coupling. General Procedure D. Glycosyl phosphate (1.1 equiv) and acceptor (1.0 equiv) were combined, azeotropically dried with toluene (3 × 5 mL), and dried under reduced pressure (~1 Torr) for 2 h. To a solution of this mixture in dichloromethane (1 mL/0.1 mmol phosphate) at –78 °C was added trimethylsilyl trifluoromethane sulfonate (1.5 equiv), and the reaction mixture was warmed to –40 °C. After 45 min, the reaction mixture was warmed to –10 °C. After an additional 45 min, excess activator was quenched with triethylamine (1 mL/1 mL phosphate), the volatiles were removed under reduced pressure, and the resulting oil was purified by flash column chromatography on silica gel to give the desired disaccharide.

Solution phase thioglycoside coupling. General Procedure E.[5] Thioglycoside (1.1-1.2 equiv) and acceptor (1.0 equiv) were combined, azeotropically dried with toluene (3 × 5 mL), and dried under reduced pressure for 2 h. To a solution of this mixture in methylene chloride (3 mL/0.1 mmol donor), was added freshly activated 4 Å molecular sieves (1:1 sieves:donor, acceptor by weight). The reaction mixture was cooled to 0 °C, *N*-iodosuccinimide (NIS) (1.6 equiv) was added, light was excluded, and trimethylsilyl trifluoromethane sulfonate (0.5 equiv) was added dropwise. After 10 minutes, the reaction mixture was warmed to ambient temperature until the reaction appeared complete by analytical thin layer chromatography (0.5-12 h). The red reaction mixuture was diluted with ethyl acetate, was filtered through celite, and was washed sequentially with aqueous sodium thiosulfate solution and brine. The clear organic layer was then dried over anhydrous magnesium sulfate, was filtered, was concentrated under reduced pressure, and was purified via flash column chromatography on silica gel to provide the disaccharide.

Solution phase trichloroacetimidate coupling. General Procedure F.[6] Trichloroacetimidate (1.1-1.2 equiv) and acceptor (1.0 equiv) were combined, azeotropically dried with toluene (3 × 5 mL), and dried under reduced pressure (~1 Torr) for 2 h. To a solution of this mixture in methylene chloride (3 mL/0.1 mmol donor) at 0 °C was added trimethylsilyl trifluoromethane sulfonate (TMSOTf, 0.1 equiv). After 1 h, excess activator was quenched by addition of triethylamine (1:1 NEt_3:TMSOTf by volume). The volatiles were removed under reduced pressure and the residue was purified via flash column chromatography on silica gel to provide the disaccharide.

Thioglycoside formation from protected glycals. General Procedure G. The glucal (1.0 equiv) was azeotropically dried toluene (3 × 5 mL), dried under reduced pressure (~1 Torr) for 2 h. To a solution of this glycal in dichloromethane (0.5 mL/0.1 mmol glycal) at 0 °C was added a solution of dimethyldioxirane in acetone (0.08 M, 1.2-1.5 equiv) was After 15 min, the volatiles were removed under reduced pressure, the residue was dissolved in dichloromethane (1.5 mL/0.1 mmol glycal), and the solution cooled to –78 °C. Ethanethiol (30 equiv) was added dropwise to this solution, followed by a few drops of TFAA. The

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[5] Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.

[6] Schmidt, R. R. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

reaction was stirred at –78 °C for 30 minutes and then allowed to warm to ambient temperature until the reaction appeared complete by analytical thin layer chromatography (0.5-12 h). The volatiles were removed by evaporation under a nitrogen stream, and the resulting oil purified by flash column chromatography on silica gel. To a solution of this thioglyscoside in dichloromethane (0.5 mL/0.1 mmol glycal) and dimethylaminopyridine (4 equiv) and pivaloyl chloride (2 equiv) were added. When the reaction appeared complete by analytical thin layer chromatographyn (3-12 h), the reaction solution was diluted with ethyl acetate:hexanes (1:1), was filtered through a silica plug, was concentrated under reduced pressure, and was purified via flash column chromatography on silica gel to give the desired thioglycoside.

Glycosyl trichloroacetimidate synthesis from protected thioglycosides. General Procedure H.[7] To a solution of the thioglycoside (1.0 equiv) in acetone:water (4:1, 2.5 mL/0.2 mmol thiodonor) was added *N*-bromosuccinimide (NBS) (4.0 equiv). After 1-3 h, the solution was concentrated under reduced pressure and the resulting residue purified by flash column chromatography on silica gel. The resulting oil was azeotropically dried from toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 1 h. To a solution of this lactol in dichloromethane:trichloroacetonitrile (1:1, 1.0 ml/0.04 mmol thioglycoside) at 0 °C was added DBU (0.1 equiv) and the reaction warmed to ambient temperature. After 12 h, the solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel to give the provide the glycosyl trichloroacetimidate.

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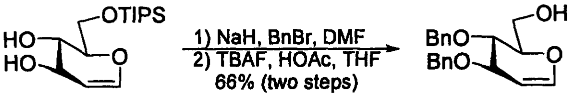
[7] Schmidt, R. R. *Adv. Carbohydr. Chem. Biochem.* **1994,** *50,* 21.



10

3,4-Di-*O*-benzyl-D-glucal (10):

To a solution of 6-*O*-Triisopropylsilyl-D-glucal[8] (8.07 g, 26.8 mmol) in dimethylformamide (DMF, 80 mL) was added benzylbromide (7.00 mL, 58.9 mmol), followed by slow addition of sodium hydride (60% suspension in oil, 2.36 g, 58.9 mmol). After 12 h, excess hydride was quenched by slow addition of methanol (10 mL). The resulting solution was diluted with water and extracted with ethyl acetate (3 × 100 mL). The organic layers were washed with saturated aqueous sodium bicarbonate solution and water, were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. The crude oil was then dissolved in THF (80 mL) and acetic acid (1.53 mL, 26.8 mmol) and a solution of tetrabutylammonium fluoride in THF (1M, 40 mL, 40 mmol) were added. After 4 h, the reaction mixture was diluted with ethyl acetate (300 mL) and washed sequentially with water (100 mL), saturated aqueous sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purfied by flash silica column chromatography (silica gel: eluent: hexames:ethyl acetate [80:20]) to afford glycal **10** as a clear oil (5.73 g, 66%). Characterization data were consistent with previously reported data.[3]

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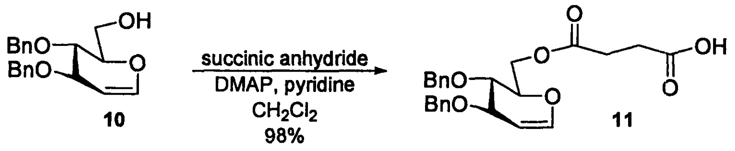
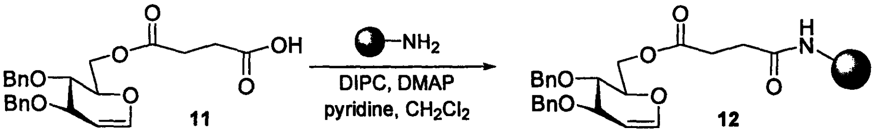
[8] Alonso, R. A; Vite, G. D.; McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 573.



3,4-Di-*O*-benzyl-6-*O*-succinoyl-D-glucal (11):

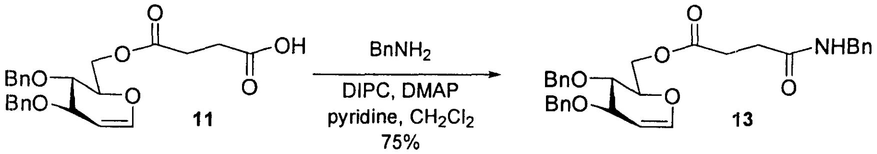
To a solution of glycal **10** (1.91 g, 5.84 mmol) in pyridine:methylene chloride (1:1, 40 mL) was added dimethylaminopyridine (1.21 g, 9.92 mmol) and succinic anhydride (0.88 g, 8.76 mmol). After 18 h, the reaction mixture was diluted with diethyl ether (500 ml) and washed with dilute aqueous acetic acid (pH 3), water, and brine. The combined organic phases were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash silica column chromatography (silica gel: eluent: hexanes:ethyl acetate [40:60]) to afford glucal **11** as a yellow oil (2.48 g, 98%).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	8.56 (br-s, 1H), 7.71 (m, 1H), 7.28-7.18 (m, 8H), 6.31 (app-d, J = 6.5 Hz, 1H), 5.07 (s, 1H), 4.85-4.82 (m, 1H), 4.77 (d, J = 11.0 Hz, 1H), 4.59 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 4.37-4.31 (m, 2H), 4.15-4.14 (m, 1H), 4.03-4.00 (m, 1H), 3.55 (dd, J = 6.5 Hz, 9.0 Hz, 1H), 2.61-2.52 (m, 4H).
^{13}C NMR (125 MHz, $CDCl_3$, 20°C):	177.4, 171.8, 144.3, 138.0, 127.7, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 100.0, 75.4, 74.9, 73.8, 73.6, 70.5, 62.9, 28.8, 28.7
FTIR (thin film) cm^{-1}:	3432 (br-m), 1735 (s), 1718 (s), 1648 (w), 1166 (m), 1098 (m).
HRMS–ESI (*m/z*):	calcd for $C_{24}H_{26}NaO_7$ $[M+Na]^+$: 449.1571, found: 449.1565.
$[\alpha]^{24}_D$:	–1.5 (c 1.00, CH_2Cl_2).



Resin-bound glycal 12:

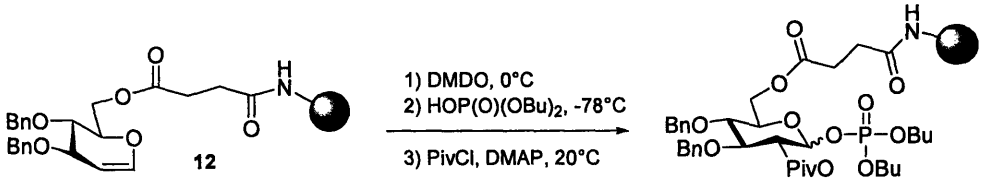
To a solution of glucal **11** (1.55 g, 3.64 mmol) in dichloromethane (10 mL) at 0 °C was added dimethylaminopyridine (0.142 g, 1.17 mmol) and diisopropylcarbodiimide (DIPC, 0.506 mL, 4.01 mmol). After 10 min, this solution was transferred via cannula to aminomethyl polystyrene resin (1.43 g, 1.46 mmol) swelled in pyridine (10 mL), and the reaction was shaken at room temperature for 20 h. Unreacted resin was capped by the addition of acetic anhydride (1.5 mL) and the suspension shaken for an additional 2 h. The solution decanted, and the resin was rinsed six times with each of tetrahydrofuran, tetrahydrofuran:methanol (95:5), and methylene chloride, then rigorously dried under reduced pressure (~1 Torr) over phosphorous pentaoxide. HR-MAS ^1H NMR indicated successful resin loading, with a theoretical resin loading 0.711 mmol/g (calculated from resin weight gain).



3,4-Di-*O*-benzyl-6-*O*-*N*-benzyl-succinamyl-D-glucal (13):

To a solution of glucal **11** (0.603 g, 1.41 mmol) in methylene chloride (20 mL) at 0 °C was added dimethylaminopyridine (0.190 g, 1.55 mmol) and diisopropylcarbodiiminde (0.243 mL, 1.55 mmol). After 10 min, benzylamine (0.309 mL, 2.83 mmol) was added and the reaction warmed to ambient temperature. After 19 h, the reaction mixture was diluted with ethyl acetate (200 mL) and run through a silica plug to remove excess urea. The resulting solution was concentrated under reduced pressure and purified by flash silica column chromatography (silica gel: eluent: hexanes:ethyl acetate [60:40]) to afford **13** as a white solid (0.55 g, 75%).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	7.28-7.18 (m, 11H), 6.29 (d, *J* = 6.0 Hz, 1H), 5.86 (br-s, 1H), 4.85-4.83 (m, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.59 (dd, *J* = 11.5, 5.5 Hz, 2H), 4.48 (d, *J* = 4.0 Hz, 1H), 4.35-4.29 (m, 4H), 4.15-4.13 (m, 1H), 4.04-4.00 (m, 1H), 3.69 (dd, *J* = 8.5, 6.0, Hz, 1H), 2.64 (t, *J* = 6.5 Hz, 2H), 2.42 (t, *J* = 6.5 Hz, 2H).
^{13}C NMR (125 MHz, CDCl$_3$, 20°C):	172.6, 171.0, 144.3, 138.1, 138.0, 137.8, 128.7, 128.4, 128.0, 127.9, 127.7, 127.5, 100.0, 75.3, 74.9, 73.8, 73.6, 70.5, 62.9, 43.7, 31.0, 29.5
FTIR (thin film) cm^{-1}:	3408 (br-s), 1735 (m), 1652 (s), 1237 (w), 1099 (m), 737 (m).
HRMS–ESI (*m/z*):	calcd for $C_{31}H_{33}NNaO_6$ [M+Na]$^+$: 538.2200, found: 538.2200.
$[\alpha]^{24}_{D}$:	–3.13 (c 0.99, CH$_2$Cl$_2$).

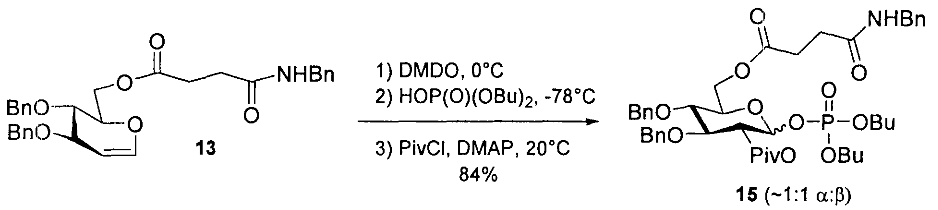


12

14 (~1:1 α:β)

Resin-bound phosphate 14:

To resin-bound glucal **12** (0.728 mmol/g, 1.80 g, 1.30 mmol) swelled in methylene chloride (30 mL) at 0 °C was added a solution of dimethyldioxirane in acetone (0.08 M, 24.3 mL, 1.95 mmol) the mixture was shaken at 0 °C for 30 min. The solution was decanted and the process repeated once. The solution was decanted and the resin rinsed three times with methylene chloride (10 mL each), then swelled in methylene chloride (30 mL) and the mixture cooled to -78 °C. Dibutyl phosphate (0.281 mL, 1.43 mmol) was added dropwise to this mixture and the vessel was shaken at –78 °C. After 30 min, the mixture was warmed to 0 °C,dimethylaminopyridine (0.633 g, 5.19 mmol) and pivaloyl chloride (0.320 mL, 2.60 mmol) were added, and the reaction was warmed to ambient temperature. The solution was decanted, and the resin was rinsed six times with each of tetrahydrofuran, tetrahydrofuran:methanol (95:5), and methylene chloride, then rigorously dried under reduced pressure (~1 Torr) over phosphorous pentaoxide to afford a tan resin with a theoretical loading of 0.585 mmol/g (calculated by resin weight gain). ^{31}P and ^{1}H HR-MAS NMR of the tan resin indicated phosphate formation.



Dibutyl 6-*O*-*N*-benzyl-succinamyl-3,4-di-*O*-benzyl-2-*O*-pivaloyl-α-D glucopyranoside phosphate (15):

General Procedure A using glucal **13** (0.232 g, 0.449 mmol), dimethyldioxirane (8.4 mL, 0.67 mmol), dibutylphosphate (97 μL, 0.49 mmol), pivaloyl chloride (0.193 mL, 0.898 mmol), and dimethylaminopyridine (0.219 g, 1.80 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [40:60]) afforded phosphate **15** as a colorless oil (0.311 g, 84%, 1:1 α:β).

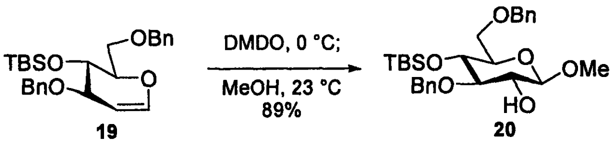
^{1}H NMR (500 MHz, CDCl$_3$, 20°C, equal mixture of diastereomers (α:β)): 7.37-7.25 (m, 30H), 6.30 (app-s, 1H), 5.56 (dd, *J* = 6.1, 2.1 Hz, 0.8H), 5.40 (t, *J* = 2.7 Hz, 0.8H), 5.13 (s, 0.4H), 5.04 (dd, *J* = 9.2, 7.9 Hz, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.78-4.59 (m, 6.1H), 4.52 (dd, *J* = 11.0, 3.7 Hz, 1.8H), 4.45-4.42 (m, 2H), 4.29 (dd, *J* = 7.6, 2.8 Hz, 2H), 4.26 (d, *J* = 2.1 Hz, 1H), 4.21 (dd, *J* = 14.7, 4.9 Hz, 1H), 4.09-3.93 (m, 8.4H), 3.75 (t, *J* = 9.8 Hz, 1H), 3.54 (t, *J* = 9.2, 1.1H), 3.46 (t, *J* = 10.1, 1H), 3.31-3.27 (m, 1.1H), 2.95-2.89 (m, 1.1H), 2.78 (t, *J* = 6.7 Hz, 0.6H), 2.66 (t, *J* = 6.7 Hz, 1.8H), 2.60-2.42 (m, 5H), 1.69-1.57 (m, 6.5H), 1.43-1.32 (m, 5.6H), 1.27-1.16 (m, 13.8H), 0.96-0.89 (m, 7.5H).

^{13}C NMR (125 MHz, CDCl$_3$, 20°C): 177.3, 172.7, 172.2, 171.6, 171.3, 139.4, 138.5, 137.8, 137.5, 128.9, 128.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.6, 127.6, 1277.5, 103.3, 96.5, 95.6, 82.7, 77.6, 77.6, 77.5, 75.3, 75.1, 73.8, 72.9, 72.8, 71.8, 71.5, 68.3, 68.2, 68.2, 68.1, 63.3, 63.0, 43.8, 43.8, 39.2, 39.0, 32.3, 32.3, 32.2, 32.1, 31.3, 31.2, 30.2, 29.8, 27.3, 27.3, 18.8, 18.8, 13.8, 13.8.

^{31}P NMR (120 MHz, CDC13, 20°C): -2.91, -2.93

FTIR (thin film) cm^{-1}: 2962 (m), 1739 (s), 1673 (m), 1275 (m), 1148 (s), 1029 (s).

HRMS–ESI (*m/z*): calcd for $C_{44}H_{60}NNaO_{12}P$ [M+Na]$^+$: 848.3745, found: 848.3719.



Methyl 3,6-di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (20):

Glycal **19** (1.1056 g, 2.509 mmol) was azeotropically dried from toluene (3 x 10 mL) and dried at ~1 Torr for 5 h. The glucal was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. A solution of dimethyldioxirane (DMDO) in acetone (0.08 M, 34.5 mL, 2.750 mmol) was added via cannula and the reaction was stirred for 15 min. The solvent was removed *in vacuo*, and the residue dissolved in CH_2Cl_2:methanol (3:2, 25 mL) and stirred vigorously. After 2.5 h, the volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) to afford **20** as a clear oil (1.0937 g, 89%).

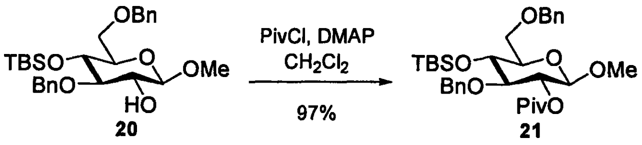
^{1}H NMR (500 MHz, $CDCl_3$, 20°C): 7.30-7.24 (m, 8H), 7.21-7.18 (m, 2H), 4.87 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.45 (d, *J* = 12.2 Hz, 1H), 4.13 (d, *J* = 7.6 Hz, 1H), 3.71 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.52-3.48 (m, 5H), 3.44-3.37 (m, 2H), 3.31 (app-t, *J* = 8.8 Hz, 1H), 2.18 (d, *J* = 2.4 Hz, 1H), 0.76 (s, 9H), –0.06 (s, 3H), –0.09 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 20°C): 139.0, 138.5, 128.5, 128.5, 127.8, 127.7, 127.6, 103.7, 84.8, 76.8, 75.1, 74.8, 73.6, 71.1, 69.7, 57.3, 26.1, 18.2, –3.6, –4.7.

FTIR (thin film) cm^{-1}: 2929 (w), 2856 (w), 1251 (w), 1114 (s), 1064 (s).

HRMS–ESI (*m/z*): calcd for $C_{27}H_{40}NaO_6Si$ $[M+Na]^+$: 511.2486, found: 511.2462.

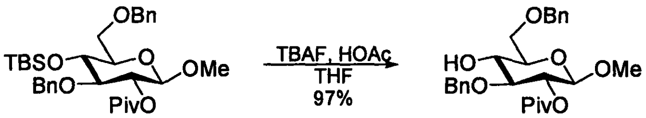
$[\alpha]^{24}_D$: –0.73 (c 0.96, CH_2Cl_2).



Methyl 3,6-di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-2-*O*-pivaloyl-β-D-glucopyranoside (21):

To a solution of methyl glycoside **20** (1.0318 g, 2.111 mmol) in dichloromethane (25 mL) was added dimethylaminopyridine (0.5268 g, 4.318 mmol) and pivaloyl chloride (0.520 mL, 4.222 mmol) and the reaction stirred vigorously at ambient temperature. After 24 h, the volatiles were removed under reduced pressure and the residue purified by flash column chromatography (silica gel: hexanes:ethyl acetate [80:20]) to provide **21** as a clear oil (1.1788 g, 97%).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	7.26-7.16 (m, 10H), 4.99 (dd, J = 9.2, 7.9 Hz, 1H), 4.63-4.56 (m, 3H), 4.46 (d, J = 12.5 Hz, 1H), 4.26 (d, J = 7.9 Hz, 1H), 3.70 (dd, J = 10.7, 1.8 Hz, 1H), 3.59 (dd, J = 9.5, 8.6 Hz, 1H), 3.53-3.50 (m, 1H), 3.45 (app-t, J = 8.5 Hz, 1H), 3.43-3.40 (m, 1H), 3.41 (s, 3H), 1.05 (s, 9H), 0.74 (s, 9H), –0.12 (s, 3H), –0.17 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, 20°C):	177.1, 138.5, 138.3, 128.5, 128.3, 127.8, 127.7, 127.4, 127.1, 102.3, 102.3, 83.4, 76.9, 74.7, 73.7, 73.6, 71.2, 69.5, 56.9, 39.0, 27.2, 26.1, 18.2, –3.7, –4.7.
FTIR (thin film) cm^{-1}:	2930 (m), 1740 (s), 1455 (w), 1135 (s), 1105 (s).
HRMS–EI (*m/z*):	calcd for $C_{32}H_{48}NaO_7Si$ $[M+Na]^+$: 595.3061, found: 595.3074.
$[\alpha]^{24}_D$:	+5.07 (c 0.75, CH_2Cl_2).

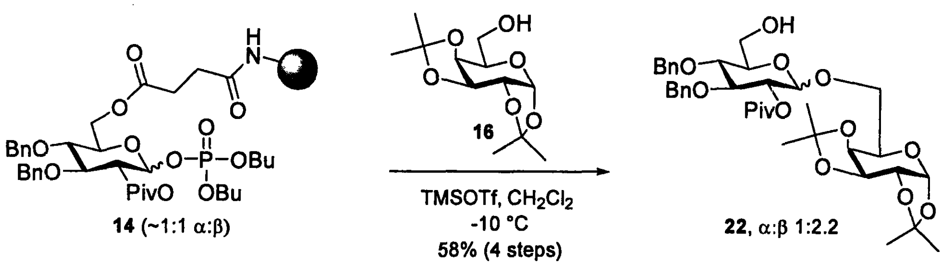


21 **18**

Methyl 3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside (18):

To a solution of glucopyranoside **21** (1.0987 g, 1.918 mmol) in THF (20 mL) was added acetic acid (0.110 mL, 1.918 mmol) and a solution of tetrabutylammonium fluoride in THF (1M, 2.88 mL, 2.877 mmol) and were added and the reaction stirred at ambient temperature (30 °C). After 14 h, an additional portion of TBAF (1M, 1.5 mL, 1.5 mmol) was added. After another 7 h, an additional portion of TBAF (1M, 1.5 mL, 1.5 mmol). After 14 h, the reaction mixture was diluted with ethyl acetate, washed with water, saturated aqueous sodium bicarbonate solution, and brine. The organic layer was dried anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) to afford **18** as a light yellow oil (0.8495 g, 97 %).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	7.36-7.28 (m, 10H), 5.02 (dd, *J* = 9.5, 7.9, Hz, 1H), 4.73 (d, *J* = 11.3 Hz , 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.32 (d, *J* = 7.9 Hz, 1H), 3.79-3.72 (m, 3H), 3.56 (app-t, *J* = 9.2 Hz, 1H), 3.52-3.50 (m, 1H), 3.48 (s, 3H), 2.67 (d, *J* = 2.4 Hz, 1H), 1.22 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, 20°C):	177.1, 138.4, 137.9, 128.7, 128.7, 128.0, 128.0, 127.8, 102.5, 82.8, 74.5, 74.3, 73.9, 72.8, 72.0, 70.5, 57.1, 27.3.
FTIR (thin film) cm^{-1}:	3485 (br-w, OH), 2969 (m), 1738 (s), 1135 (s), 1076 (s).
HRMS–EI (*m/z*):	calcd for $C_{26}H_{34}NaO_7$ $[M+Na]^+$: 481.2197, found: 481.2182.
$[\alpha]^{24}_D$:	–29.8 (c 1.85, CH_2Cl_2).



3,4-Di-*O*-benzyl-2-*O*-pivaloyl-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside 22.

General Procedure B using resin **14** (0.585 mmol/g, 0.149 g, 0.0872 mmol), acceptor **7** (0.153 g, 0.585 mmol; 0.140 g, 0.536 mmol), and TMSOTf (22 μL, 0.095 mmol, twice), and NaOMe (40 μL, 0.17 mmol), and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded disaccharide **22** (35 mg, 58%, 1:2.2 α:β).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C): (α isomer): 7.34-7.27 (m, 10H), 5.52 (d, *J* = 5.0, 1H), 5.41 (m, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.84 (s, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.64-4.61 (m, 2H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.33-4.31 (m, 1H), 4.24 (app-d, *J* = 8.0 Hz, 1H), 4.00 (app-d, *J* = 3.0 Hz, 1H), 3.95 (app-s, 1H), 3.83-3.71 (m, 5H), 1.53 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.22 (s, 9H).

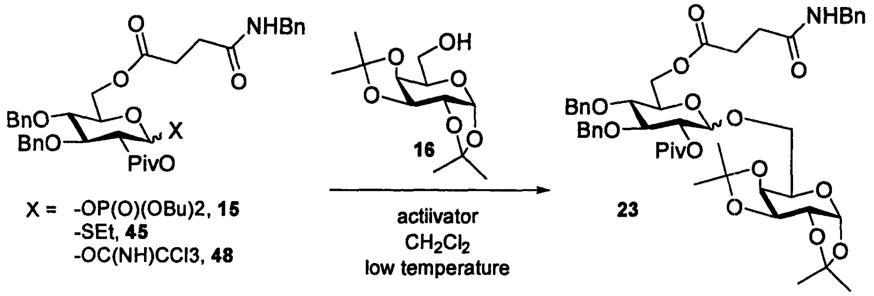
^{1}H NMR (500 MHz, $CDCl_3$, 20°C): (β isomer): 7.35-7.26 (m, 10H), 5.49 (d, *J* = 4.9 Hz, 1H), 5.05 (app-t, *J* = 7.9 Hz, 1H), 4.81-4.70 (m, 3H), 4.62-4.59 (m, 2H), 4.50 (d, *J* = 7.9 Hz, 1H) 4.30-4.27 (m, 2H), 4.02-3.99 (m, 1H), 3.93-3.86 (m, 2H), 3.73 (t, *J* = 9.2 Hz, 1H), 3.68-3.61 (m, 3H), 3.46-3.43 (m, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.21 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$, 20°C): (α isomer): 177.5, 138.1, 128.4, 128.2, 127.9, 127.8, 127.5, 109.4, 108.6, 98.2, 96.2, 78.2, 75.1, 73.7, 71.9, 71.4, 70.8, 70.6, 70.5, 68.0, 66.5, 65.9, 62.0, 38.9, 27.2, 26.1, 25.9, 24.9, 24.5

^{13}C NMR (125 MHz, $CDCl_3$, 20°C): (β isomer): 176.8, 138.0, 137.7, 128.5, 128.4, 128.0, 127.9, 127.6, 127.4, 109.3, 108.6, 101.2, 96.3, 83.0, 77.7, 75.3, 75.0, 74.9, 72.9, 70.9, 70.5, 70.5, 68.3, 66.6, 62.1, 38.8, 27.1, 26.1, 25.9, 24.9, 24.3, 14.2.

FTIR (thin film) cm^{-1}: (α isomer): 3464 (w), 2979 (m), 1733 (m), 1138 (m), 1072 (s).

FTIR (thin film) cm^{-1}:	(β isomer): 3464 (m), 2979 (m), 1741 (m), 1383 (m), 1072 (s).
HRMS–ESI (*m/z*):	(α isomer): calcd for $C_{37}H_{50}NaO_{12}$ $[M+Na]^+$: 709.3194, found: 709.3198.
HRMS–ESI (*m/z*):	(β isomer): calcd for $C_{37}H_{50}NaO_{12}$ $[M+Na]^+$: 709.3194, found: 709.3204.
$[\alpha]^{24}_{D}$:	(α isomer): –11.9 (c 0.91, CH_2Cl_2).
$[\alpha]^{24}_{D}$:	(β isomer): –47.5 (c 1.44, CH_2Cl_2).



3,4-di-*O*-benzyl-6-*O*-*N*-benzylsuccinamyl-2-*O*-pivaloyl-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside (23):

General Procedure C using phosphate **15** (81 mg, 0.098 mmol), acceptor **16** (22 mg, 0.083 mmol) and TMSOTf (24 μL, 0.090 mmol) and purification by flash column chromatography (silica gel: eluent: methylene chloride:acetone [95:5]) afforded **23** as a white solid (62 mg, 85%, 1:4 α:β).

General Procedure E using thiodonor **45** (0.219 g, 0.323 mmol), acceptor **16** (70 mg, 0.27 mmol), NIS (97 mg, 0.43 mmol), and TMSOTf (25 μL, 0.14 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [65:35]) afforded **23** as a white solid (0.161 g, 69%, β).

General Procedure F using trichloroacetimidate **48** (61 mg, 0.079 mmol), acceptor **16** (18 mg, 0.071 mmol), and TMSOTf (2 μL, 0.01 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [60:40]) afforded **23** as a white foam (45 mg, 73%, β).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C): (α isomer): 7.34-7.25 (m, 10H), 6.14 (app-s, 1H), 5.43 (d, *J* = 5.0 Hz, 1H), 5.40 (app-d, *J* = 3.0 Hz, 1H), 4.85 (d, *J* = 10.5 Hz, 1H), 4.78 (s, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.62-4.59 (m, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 6.0 Hz, 1H), 4.34 (app-d, *J* = 9.5 Hz, 1H), 4.21 (app-d, *J* = 10.0 Hz, 1H), 3.9 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.92-3.88 (m, 2H), 3.75-3.62 (m, 3H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.53-2.46 (m, 2H), 1.52 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 1.29 (s, 3H), 1.23 (s, 9H).

^{1}H NMR (400 MHz, $CDCl_3$, 20°C): (β isomer): 7.33-7.24 (m, 15H), 6.27 (br-s, 1H), 5.45 (d, *J* = 4.9 Hz, 1H), 5.07 (t, *J* = 9.1 Hz, 1H), 4.81 (d, *J* = 10.9 Hz, 1H), 4.76-4.72 (m, 2H), 4.57-4.55 (m, 2H), 4.46-4.36 (m, 4H), 4.27-4.18 (m, 3H), 3.97 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.92 (app-s, 1H), 3.73 (t, *J* = 9.2 Hz, 1H), 3.62-3.59 (m, 3H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.49

(app-t, J = 6.7 Hz, 2H), 1.50 (s, 3H), 1.43 (s, 3H), 1.31 (s, 6H), 1.22 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$, 20°C): (α isomer): 177.4, 172.5, 171.0, 138.2, 137.9, 137.8, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 109.4, 108.6, 97.7, 96.2, 78.4, 74.9, 73.3, 71.4, 70.7, 70.6, 70.5, 69.6, 67.8, 65.9, 63.5, 43.6, 38.9, 31.1, 29.6, 27.1, 26.1, 25.9, 24.8, 24.4.

^{13}C NMR (100 MHz, $CDCl_3$, 20°C): (β isomer): 176.9, 172.6, 171.2, 138.5, 138.0, 127.7, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8, 127.5, 127.5, 109.3, 108.6, 101.4, 96.2, 83.2, 77.4, 75.1, 73.1, 72.9, 71.2, 70.6, 70.5, 67.1, 43.7, 38.9, 31.0, 29.7, 27.2, 26.2, 26.1, 25.1, 24.4.

FTIR (thin film) cm^{-1}: (α isomer); 2918 (w), 1732 (s), 1210 (m), 1138 (s), 1069 (s).

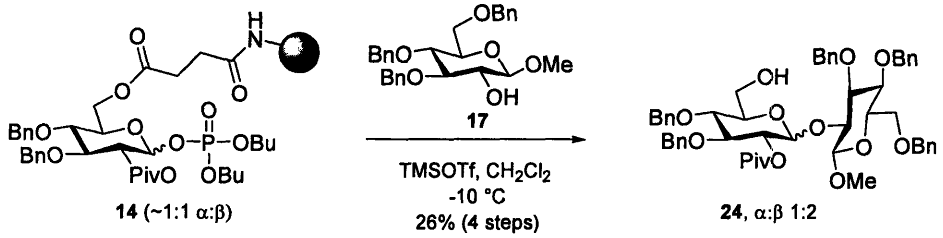
FTIR (thin film) cm^{-1}: (β isomer): 2978 (w), 2933 (w), 1739 (s), 1674 (m), 1166 (m), 1071 (s).

HRMS–ESI (*m/z*): (α isomer): calcd for $C_{48}H_{61}NNaO_{14}$ $[M+Na]^+$: 898.3984,
found: 898.3968.

HRMS–ESI (*m/z*): (β isomer): calcd for $C_{48}H_{61}NNaO_{14}$ $[M+Na]^+$: 898.3984,
found: 898.3998.

$[\alpha]^{24}_{D}$: (α isomer): –6.7 (c 0.18, CH_2Cl_2).

$[\alpha]^{24}_{D}$: (β isomer): –31.2 (c 2.04, CH_2Cl_2).



14 (~1:1 α:β)

17

24, α:β 1:2

Methyl 3,4-di-*O*-benzyl-2-*O*-pivaloyl-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (24):

General Procedure B using resin **14** (0.353 mmol/g, 0.327 g, 0.115 mmol), acceptor **17** (0.138 g, 0.309 mmol; 0.130 g, 0.293 mmol), TMSOTf (29 μL, 0.127 mmol, twice), and NaOMe (53 μL, 0.23 mmol), and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded disaccharide **24** as a clear oil (27 mg, 26%, 1:2 α:β).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	(α isomer): 7.39-7.10 (m, 25H), 5.42 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.31 (d, *J* = 1.8 Hz, 1H), 4.88 (d, *J* = 11 Hz, 1H), 4.78 (dd, *J* = 11.0, 7.1 Hz, 2H), 4.73-4.68 (m, 2H), 4.62 (app-t, *J* = 12.2 Hz, 2H), 4.55 (app-t, *J* = 12.2 Hz, 3H), 4.26 (d, *J* = 7.9 Hz, 1H), 3.98 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.90-3.81 (m, 2H), 3.75 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.71 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.67-3.60 (m, 2H), 3.58-3.51 (m, 6H), 3.49-3.45 (m, 1H), 1.23 (s, 9H).
^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	(β isomer): 7.33-7.22 (m, 23H), 7.09-7.07 (m, 2H), 5.07-5.06 (m, 2H), 4.85-4.70 (m, 6H), 4.65-4.59 (m, 2H), 4.51 (at, *J* = 12.2 Hz, 2H), 4.28 (d, *J* = 7.6 Hz, 1H), 3.89-3.81 (m, 2H), 3.75-3.65 (m, 4H), 3.61-3.56 (m, 3H), 3.52 (s, 3H), 3.46-3.41 (m, 2H), 1.07 (s, 9H).
^{13}C NMR (125 MHz, CDCl$_3$, 20°C):	(α isomer): 177.8, 138.8, 138.4, 138.3, 138.1, 138.0, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 104.7, 97.5, 83.6, 78.6, 78.0, 77.4, 76.8, 76.2, 75.3, 75.2, 74.0, 73.7, 72.0, 71.4, 68.8, 68.2, 61.8, 57.3, 39.2, 29.9, 27.4.
^{13}C NMR (125 MHz, CDCl$_3$, 20°C):	(β isomer): 177.0, 138.5, 138.3, 138.2, 138.1, 138.0, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 127.6, 102.8, 99.5, 85.4, 83.4, 78.8, 78.2, 77.0, 75.7, 75.2, 75.2, 75.1, 74.9, 74.1, 73.7, 73.3, 68.7, 61.8, 57.3, 38.9, 27.4, 27.3.

FTIR (thin film) cm^{-1}: (α isomer): 3428 (br-m), 2924 (m), 1731 (m), 1142 (s), 1061 (s).

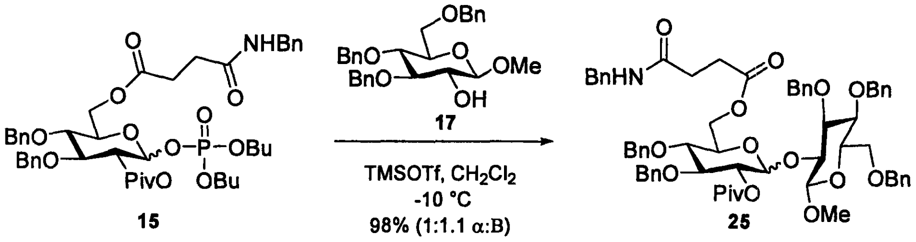
FTIR (thin film) cm^{-1}: (β isomer): 3483 (br-m), 2917 (m), 1738 (m), 1362 (w), 1074 (br-s).

HRMS–ESI (*m/z*): (α isomer): calcd for $C_{53}H_{62}NaO_{12}$ $[M+Na]^+$: 913.4133, found: 913.4117.

HRMS–ESI (*m/z*): (β isomer): calcd for $C_{53}H_{62}NaO_{12}$ $[M+Na]^+$: 913.4133, found: 913.4115.

$[\alpha]^{24}{}_D$: (α isomer): +23.1 (c 0.7, CH_2Cl_2).

$[\alpha]^{24}{}_D$: (β isomer): –8.05 (c 1.23, CH_2Cl_2).



Methyl 6-*O*-*N*-benzylsuccinamyl-3,4-di-*O*-benzyl-2-*O*-pivaloyl-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-β-D-galactopyranoside (25):

General Procedure C using phosphate **15** (0.118 g, 0.143 mmol), acceptor **17** (56 mg, 0.12 mmol), and TMSOTf (36 μL, 0.16 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes ethyl acetate [60:40]) afforded **25** as a white solid (0.127 g, 98%, 1:1.1 α:β).

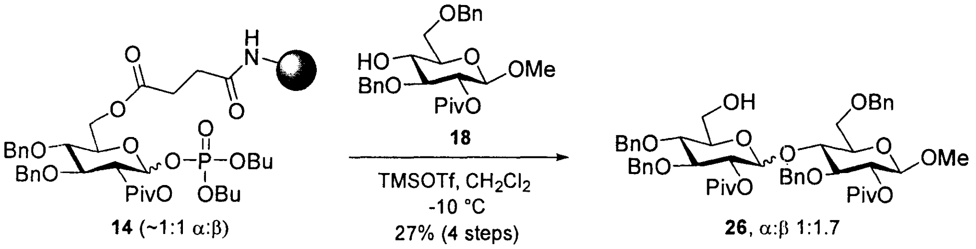
^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	(β isomer): 7.38-7.25 (m, 23H), 7.11-7.09 (m, 2H), 6.09 (br-t, *J* = 5.5 Hz, 1H), 5.13 (app-t, *J* = 7.9 Hz, 1H), 5.02 (d, *J* = 7.9 Hz, 1H), 4.91 (d, *J* = 11.6 Hz, 1H), 4.80-4.75 (m, 2H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.61-4.50 (m, 4H), 4.43-4.40 (m, 3H), 4.34 (d, *J* = 7.3 Hz, 1H), 4.26 (dd, *J* = 11.9, 5.2 Hz, 1H), 3.73-3.59 (m, 6H), 3.57-3.54 (m, 4H0, 3.45-3.43 (m, 1H), 2.74-2.70 (m, 2H), 2.49 (app-t, *J* = 6.7 Hz, 2H), 1.12 (s, 9H).
^{13}C NMR (125 MHz, CDCl$_3$, 20°C):	(α isomer): 177.7, 172.6, 171.3, 138.5, 138.4, 138.2, 138.1, 138.0, 137.9, 128.8, 128.7, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.6, 104.6, 97.1, 83.5, 78.6, 78.2, 77.5, 76.4, 76.1, 75.2, 75.1, 75.1, 73.7, 73.5, 71.3, 69.7, 68.8, 68.0, 63.4, 57.3, 43.8, 39.2, 31.4, 29.9, 27.4, 27.3.
^{13}C NMR (125 MHz, CDCl$_3$, 20°C):	(β isomer): 176.0, 172.8, 171.3, 138.8, 138.5, 138.2, 138.1, 137.7, 128.9, 128.6, 128.6, 128.4, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.5, 127.3, 103.1, 103.0, 99.5, 99.3, 85.1, 83.7, 79.7, 77.9, 77.7, 75.8, 75.6, 75.5, 75.2, 75.1, 75.1, 75.0, 74.8, 73.6, 73.4, 73.0, 68.8, 63.5, 63.4, 60.6, 57.0, 43.7, 39.0, 31.2.
FTIR (thin film) cm^{-1}:	(α isomer): 1733 (s), 1677 (w), 1141 (s), 1100 (s), 1059 (s).
FTIR (thin film) cm^{-1}:	(β isomer): 2870 (w), 1738 (s), 1659 (w), 1144 (s), 1071 (br-s).

HRMS–ESI (*m/z*): (α isomer): calcd for $C_{64}H_{73}NNaO_{14}$ $[M+Na]^+$: 1102.4928, found: 1102.4919.

HRMS–ESI (*m/z*): (β isomer): calcd for $C_{64}H_{73}NNaO_{14}$ $[M+Na]^+$: 1102.4928, found: 1102.4911.

$[\alpha]^{24}_{D}$: (α-isomer): +16.6 (c 1.07, CH_2Cl_2).

$[\alpha]^{24}_{D}$: (β-isomer): –8.5 (c 0.61, CH_2Cl_2).



Methyl 3,4-di-*O*-benzyl-2-*O*-pivaloyl-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside (26):

Acceptor **18** (91 mg, 0.20 mmol) was azeotropically dried with toluene (3 × 5 mL) and dried under reduced pressure for 2 h. A solution of this acceptor in dichloromethane (2 mL) was transferred via cannula to resin **14** (0.353 mmol/g, 0.272 g, 0.096 mmol) swelled in dichloromethane (2 mL). The reaction was cooled to –78 °C, trimethylsilyl trifluoromethane sulfonate (TMSOTf, 24 μL, 0.11 mmol) was added, and the reaction mixture was shaken and warmed slowly to –10 °C over 1 h. The reaction mixture was cooled to –30 °C and an additional portion of TMSOTf (24 μL, 0.11 mmol) was added, followed by warming of the reaction mixture to –15 °C over 45 min. An additional portion of TMSOTf (24 μL, 0.11 mmol) was added and the reaction shaken for 45 min at –15 °C. Excess activator was quenched at –15 °C with methanol (4 mL), the resin was washed six times with each of THF (5 mL ea.), THF:methanol (95:5, 5 mL ea.),, and CH_2Cl_2 (5 mL ea.), then rigorously dried under reduced pressure (~1 Torr) over phosphorous pentaoxide. The resin was swelled in CH_2Cl_2:MeOH (10:1, 4.2 mL), and a solution of sodium methoxide in methanol (43 μL, 0.19 mmol) was added and the reaction shaken for 30 min. The resin was washed with CH_2Cl_2 (5 × 6 mL), and the solution decanted. The solution phase was washed with dilute aqueous hydrochloric acid, water and brine, and the combined organic phases were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) to afford disaccharide **26** as a clear oil (23 mg, 27%, 1:1.7 α:β).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	(α isomer): 7.33-7.22 (m, 20H), 5.45 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.35 (d, *J* = 1.5 Hz, 1H), 5.10 (app-t, *J* = 7.9 Hz, 1H), 4.85 (d, *J* = 10.7 Hz, 1H), 4.73-4.66 (m, 3H), 4.60 (s, 2H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.31 (d, *J* = 7.9 Hz, 1H), 4.00 (app-t, *J* = 8.9 Hz, 1H), 3.87 (dd, *J* = 8.9, 3.1, Hz, 1H), 3.80 (app-t, *J* = 8.9 Hz, 1H), 3.74-3.66 (m, 5H), 3.62-3.58 (m, 2H), 3.51-3.49 (m, 4H), 1.19 (s, 9H), 1.09 (s, 9H).
^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	(β isomer): 7.40-7.21 (m, 10H), 5.02-4.95 (m, 2H), 4.93 (d, *J* = 11.3 Hz, 1H), 4.80 (d, *J* = 4.9 Hz, 1H), 4.77 (d, *J* = 4.3 Hz, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.61 (dd, *J* = 11.0, 6.1 Hz, 2H),

4.54 (d, J = 11.3 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.41 (d, J = 7.9 Hz, 1H), 4.30 (d, J = 8.23 Hz, 1H), 4.05 (app-t, J= 9.8 Hz, 1H), 3.78 (dd, J = 11.0, 3.4 Hz, 1H), 3.72 (dd, J = 11.0, 1.6 Hz, 1H), 3.62-3.58 (m, 2H), 3.51-3.45 (m, 5H), 3.37-3.35 (ddd, J = 10.0, 3.4, 1.8 Hz, 1H), 3.24-3.22 (m, 1H), 3.17-3.15 (m, 1H), 1.17 (s, 9H), 1.16 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$, 20°C): (α isomer): 177.3, 177.1, 138.3, 138.3, 138.1, 137.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.6, 102.3, 98.6, 83.4, 78.5, 75.5, 75.0, 74.1, 73.9, 73.6, 73.2, 73.1, 71.6, 68.6, 68.2, 62.1, 57.0, 57.0, 39.0, 39.0, 27.2.

^{13}C NMR (125 MHz, $CDCl_3$, 20°C): (β isomer): 177.1, 177.0, 138.8, 138.2, 138.1, 138.0, 128.8, 128.6, 128.6, 128.6, 128.5, 128.2, 128.0, 127.8, 127.7, 127.4, 126.8, 102.5, 99.6, 83.0, 80.9, 78.1, 77.6, 77.5, 75.5, 75.4, 75.2, 75.0, 74.9, 73.9, 73.5, 72.4, 67.8, 61.6, 57.1, 57.0, 39.0, 39.0, 27.5, 27.3.

FTIR (thin film) cm^{-1}: (α isomer): 1735 (s), 1640 (m), 1278 (w), 1138 (s), 1075 (s).

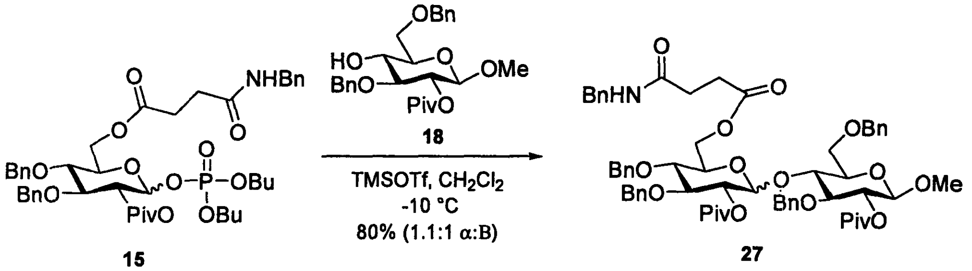
FTIR (thin film) cm^{-1}: (β isomer): 1739 (s), 1653 (m), 1277 (m), 1140 (s), 1075 (s).

HRMS–ESI (*m/z*): (α isomer): calcd for $C_{51}H_{64}NaO_{13}$ $[M+Na]^+$: 907.4239,
found: 907.4214.

HRMS–ESI (*m/z*): (β isomer): calcd for $C_{51}H_{64}NaO_{13}$ $[M+Na]^+$: 907.4239,
found: 907.4244.

$[\alpha]^{24}_{D}$: (α isomer): –2.4 (c 0.5, CH_2Cl_2).

$[\alpha]^{24}_{D}$: (β isomer): –26.9 (c 0.98, CH_2Cl_2).



Methyl 6-*O*-*N*-benzylsuccinamyl-3,4-di-*O*-benzyl-2-*O*-pivaloyl-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside (27):

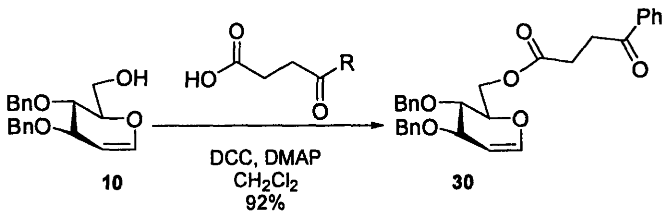
General Procedure C using phosphate **15** (0.138 g, 0.167 mmol), acceptor **18** (69 mg, 0.15 mmol), TMSOTf (42 μL, 0.18 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes ethyl acetate [60:40]) afforded **27** as a white solid (0.130 g, 80%, 1.1:1 α:β).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C, equal mixture of diastereomers, α:β): 7.36-7.14 (m, 39H), 6.49 (app-s, 1H), 5.97 (br-s, 1H), 5.34 (app-s, 1H), 5.28 (app-s, 1H), 5.08 (s, 1H), 5.02 (t, *J* = 8.9 Hz, 1H), 4.96-4.90 (m, 2H), 4.83-4.24 (m, 24H), 4.14-4.11 (m, 3H), 4.00 (t, *J* = 9.2 Hz, 1H), 3.95-3.93 (m, 1H), 3.87-3.83 (m, 2H), 3.75-3.60 (m, 6H), 3.52-3.37 (m, 10H), 3.29-3.27 (m, 1H), 2.72 (t, *J* = 6.7 Hz, 1H), 2.66 (s, 1H), 2.54-2.28 (m, 9H), 1.14-1.11 (m, 18H), 1.05, (s, 9H), 0.99 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$, 20°C, equal mixture of diastereomers, α:β): 177.5, 177.2, 177.1, 176.8, 172.6, 172.5, 171.4, 171.2, 139.1, 138.9, 138.4, 138.1, 138.0, 137.9, 137.7, 137.5, 128.9, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 127.3, 127.3, 102.3, 99.6, 99.4, 98.2, 83.2, 80.7, 78.7, 78.6, 75.4, 75.2, 75.0, 74.9, 74.6, 74.0, 73.7, 73.6, 73.4, 73.2, 73.0, 72.5, 71.5, 70.6, 69.3, 68.0, 67.8, 66.8, 63.5, 63.2, 57.0, 43.9, 43.7, 43.7, 39.0, 39.0, 38.9, 31.3, 31.2, 31.1, 29.9, 29.8, 27.5, 27.3, 27.2, 27.1.

FTIR (thin film) cm^{-1}: 2970 (m), 1737 (s), 1673 (m), 1143 (br-s), 1091 (s).

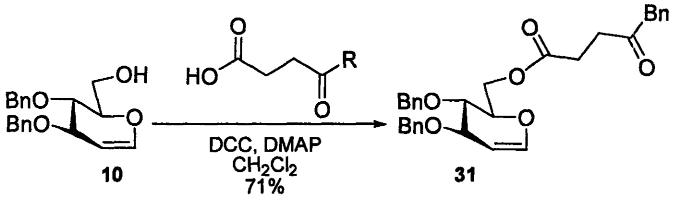
HRMS–ESI (*m/z*): calcd for $C_{62}H_{75}NNaO_{15}$ $[M+Na]^+$: 1096.5029, found: 1096.4999.



6-*O*-3'-benzoylpropionyl-3,4-di-*O*-benzyl-D-glucal (30):

To a solution of 3-benzoylpropionic acid (74 mg, 0.42 mmol) in dichloromethane (2 mL) at 0 °C was added dicyclohexylcarbodiimie (92 mg, 0.45 mmol) and dimethylaminopyridine (54 mg, 0.44 mmol). After 10 min, a solution of glucal **10** (91 mg, 0.28 mmol) in dichloromethane (2 mL) was transferred via cannula to this solution. and the reaction warmed to ambient temperature. After 1.5 h, the solution was diluted with hexanes:ethyl acetate (1:1, 40 mL), filtered through silica gel, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent hexanes:ethyl acetate [75:25]) to afford **30** as a white solid (0.125 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$, 20°C):	7.99-7.97 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.36-7.28 (m, 10H), 6.40 (d, *J* = 6.2 Hz, 1H), 4.92 (dd, *J* = 6.2, 2.7 Hz, 1H), 4.86 (d, *J* = 11.3 Hz, 1H), 4.71-4.65 (m, 2H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.48-4.40 (m, 2H), 4.23-4.22 (m, 1H), 4.15-4.11 (m, 1H), 3.81 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.37-3.27 (m, 2H), 2.80 (t, *J* = 6.6 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$, 20°C):	198.1, 172.9, 144.6, 138.3, 138.1, 136.7, 133.4, 128.8, 128.7, 128.3, 128.3, 128.1, 128.0, 127.9, 100.2, 77.4, 75.5, 75.2, 74.1, 73.9, 70.7, 63.1, 33.5, 29.9, 28.3.
FTIR (thin film) cm^{-1}:	2918 (w), 1736 (s), 1686 (s), 1215 (m), 1098 (s).
HRMS–EI (*m/z*):	calcd for $C_{30}H_{30}NaO_6$ $[M+Na]^+$: 509.1935, found: 509.1945.
$[\alpha]^{24}_D$:	–2.4 (c 1.05, CH_2Cl_2).



10 **31**

3,4-Di-*O*-benzyl-6-*O*-4'-oxo-5'-phenyl-valeryl-D-glucal (31):

To a solution of 4-Oxo-5-phenylvaleric acid[9] (0.151 g, 0.785 mmol) in dichloromethane (2 mL) at 0 °C was added dicyclohexylcarbodiimide (0.175 g, 0.848 mmol) and dimethylaminopyridine (0.111 g, 0.911 mmol). After 10 min, a solution of glucal **10** (0.123 g, 0.376 mmol) in dichloromethane (2 mL) was transferred via cannula to the reaction mixture, and mixture was allowed to warm to ambient temperature. After 14 h, the solution was diluted with hexanes:ethyl acetate (1:1, 150 mL), was filtered through silica gel, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15]) to afford **31** as a white solid (0.134 g, 71%).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	7.35-7.20 (m, 15H), 6.39 (dd, J = 6.1, 0.9 Hz, 1H), 4.92 (dd, J = 6.1, 2.8 Hz, 1H), 4.85 (d, J = 11.3 Hz, 1H), 4.67 (d, J = 11.8 Hz, 2H), 4.57 (d, J = 11.6 Hz, 1H), 4.39-4.38 (m, 2H), 4.23-4.21 (m, 1H), 4.10-4.07 (m, 1H), 3.78-3.74 (m, 3H), 2.79-2.73 (m, 2H), 2.58 (t, J = 6.7 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, 20°C):	206.4, 172.6, 144.6, 138.3, 138.0, 134.2, 129.7, 129.0, 128.7, 128.7, 128.3, 128.1, 128.0, 128.0, 127.3, 100.2, 75.6, 75.2, 74.0, 73.8, 70.7, 63.0, 50.2, 36.6, 29.9, 28.1.
FTIR (thin film) cm^{-1}:	2922 (m), 1734 (s), 1717 (s), 1099 (br-m), 740 (w).
HRMS–ESI (*m/z*):	calcd for $C_{31}H_{32}NaO_6$ $[M+Na]^+$: 523.2091, found: 523.2086.
$[\alpha]^{24}{}_D$:	+2.22 (c 0.63, CH_2Cl_2).

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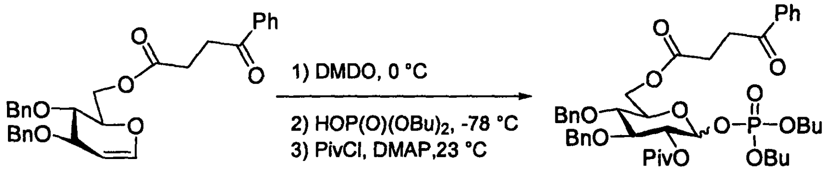
[9] Tschantz, M. A.; Burgess, L .E.; Meyers, A. I. *Org. Synth.* **1996**, *73*, 215.

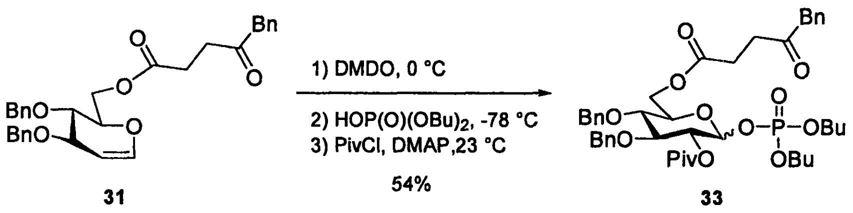


30 32

Dibutyl 6-*O*-3′-benzoylpropionyl-3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside phosphate (32):

General Procedure A using glucal **30** (0.350 g, 0.719 mmol), dimethyldioxirane (13.5 mL, 1.08 mmol), dibutylphosphate (0.156 mL, 0.791 mmol), pivaloyl chloride (0.177 mL, 1.44 mmol), DMAP (0.351 g, 2.88 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded **32** as a clear oil (0.340 g, 60%).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	7.97 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.34-7.24 (m, 10H), 5.24 (app-t, *J* = 7.6 Hz, 1H), 5.14 (app-t, *J* = 8.8 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 2H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 10.7 Hz, 1H), 4.44 (d, *J* = 12.5 Hz, 1H), 4.28 (dd, *J* = 11.9, 3.7 Hz, 1H), 4.07-3.99 (m, 5H), 3.75-3.69 (m, 2H), 3.33-3.30 (m, 2H), 2.78-2.76 (m, 2H), 1.68-1.61 (m, 4H), 1.41-1.36 (m, 4H), 1.21 (s, 9H), 0.96-0.89 (m, 6H).
^{13}C NMR (100 MHz, CDCl$_3$, 20°C):	197.9, 177.0, 172.7, 137.9, 137.6, 137.6, 133.5, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 127.5, 96.7, 96.6, 82.9, 76.9, 75.3, 75.3, 73.9, 73.0, 72.9, 68.3, 68.2, 68.1, 68.0, 62.7, 39.1, 33.4, 32.3, 32.3, 28.2, 27.3, 18.8, 18.8, 13.8, 13.8.
^{31}P (120 MHz, CDCl$_3$, 20 °C)	1.66.
FTIR (thin film) cm^{-1}:	2961 (m), 1738 (s), 1688 (m), 1151 (s), 1029 (s).
HRMS–ESI (*m/z*):	calcd for $C_{43}H_{57}NaO_{12}P$ [M+Na]$^+$: 819.3480, found: 819.3493.
$[\alpha]^{24}_D$:	+24.2 (c 1.49, CH$_2$Cl$_2$).



Dibutyl 3,4-di-*O*-benzyl-6-*O*-4'-oxo-5'-phenyl-valeryl-2-*O*-pivaloyl-D-glucopyranoside phosphate (33):

General Procedure A using glycal **31** (63 mg, 0.13 mmol), dimethyldioxirane (1.90 mL, 0.151 mmol), dibutylphosphate (0.027 mL, 0.139 mmol), pivaloyl chloride (0.031 mL, 0.252 mmol), DMAP (77 mg, 0.63 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded **33** as a clear oil (56 mg, 54%).

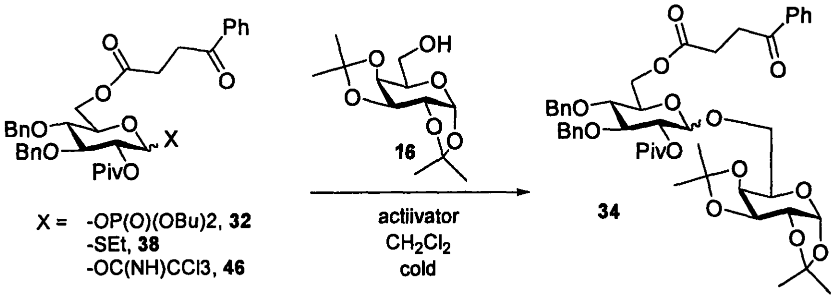
^{1}H NMR (400 MHz, $CDCl_3$, 20°C, mixture of diastereomers, α:β): 7.53-7.20 (m, 21H), 5.61-5.59 (m, 0.4H), 5.43-5.41 (m, 0.4H), 5.24-5.21 (m, 1H), 5.14 (app-t, *J* = 8.0 Hz, 1H), 4.81-4.70 (m, 4.2H), 4.60-4.51 (m, 2.8H), 4.38-4.32 (m, 1.4H), 4.25-4.12 (m, 2.8H), 4.07-3.96 (m, 5.6H), 3.74 (as, 2.8H), 3.72-3.66 (m, 1.4H), 2.82-2.66 (m, 2.8H), 2.59-2.48 (m, 2.8H), 1.78-1.56 (m, 5.6H), 1.46-1.32 (m, 5.6H), 1.27-1.21 (m, 12.6H), 0.97-0.88 (m, 8.4H).

^{13}C NMR (125 MHz, $CDCl_3$, 20°C, mixture of diastereomers, α:β): 206.2, 206.2, 177.2, 177.0, 172.6, 172.4, 137.9, 137.8, 137.5, 134.1, 134.1, 129.6, 129.6, 129.6, 128.9, 128.7, 128.6, 128.6, 128.6, 128.5, 128.3, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.7, 127.6, 127.5, 127.3, 127.3, 96.6, 96.6, 95.6, 95.6, 82.4, 77.6, 77.4, 76.9, 75.3, 75.2, 73.8, 72.9, 72.9, 72.7, 71.7, 71.4, 68.2, 68.2, 68.1, 68.1, 68.0, 68.0, 67.5, 67.4, 63.0, 62.7, 50.1, 50.1, 39.1, 39.0, 36.5, 36.5, 32.4, 32.4, 32.3, 32.3, 32.2, 32.2, 32.2, 29.9, 28.0, 27.8, 27.3, 27.3, 27.2, 27.2, 18.8, 18.8, 18.7, 13.7, 13.7.

^{31}P NMR (120 MHz, $CDCl_3$, 20°C, mixture of diastereomers, α:β): –2.52, –2.58.

FTIR (thin film) cm^{-1}: 2961 (m), 1739 (s), 1277 (m), 1144 (s), 1028 (s).

HRMS–EI (*m/z*): calcd for $C_{44}H_{59}NaO_{12}P$ [M+Na]$^+$: 833.3636, found: 833.3615.



6-O-3'-benzoylpropionyl-3,4-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-β-D-galactopyranoside (34):

Glycosyl phosphate **32** (0.129 g, 0.161 mmol) and acceptor **16** (38 mg, 0.15 mmol) were combined, azeotropically dried with toluene (3 × 5 mL) and dried under reduced pressure for 2 h. To a solution of this mixture in dichloromethane (3 mL) at –78 °C was added trimethylsilyl trifluoromethane sulfonate (40 μL, 0.18 mmol). After 45 min, excess activator was quenched at –78 °C with triethylamine (1 mL), the volatiles were removed under reduced pressure, and the resulting oil purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes ethyl acetate [60:40]) to afford disaccharide **34** as a white solid (84 mg, 68%).

General Procedure E using thiodonor **38** (0.123 g, 0.189 mmol), acceptor **16** (42 mg, 0.16 mmol), NIS (60 mg, 0.27 mmol), TMSOTf (15 μL, 0.088 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes ethyl acetate [67:33]) afforded **22** as a white foam (0.113 g, 82%, β).

General Procedure F using trichloroacetimidate **46** (37 mg, 0.049 mmol), acceptor **16** (11 mg, 0.043 mmol), TMSOTf (1 μL, 0.005 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] afforded **34** as a white foam (26 mg, 70%, β).

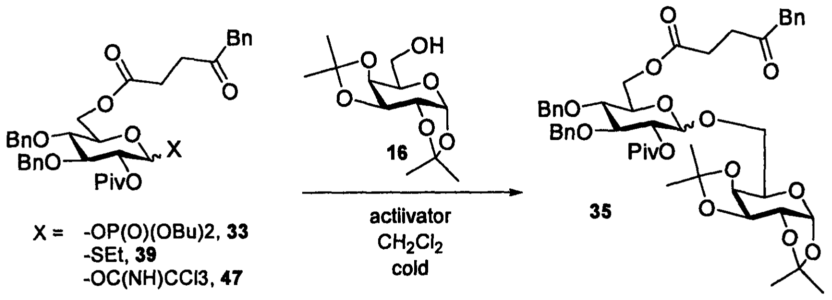
^{1}H NMR (500 MHz, CDCl$_3$, 20°C): 7.96 (d, J = 7.0 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.33-7.25 (m, 10H), 7.48 (d, J = 4.9 Hz, 1H), 5.07 (dd, J = 9.2, 7.9 Hz, 1H), 4.80 (d, J = 10.7 Hz, 1H), 4.75 (d, J = 11.0 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.60-4.57 (m, 2H), 4.47 (d, J = 7.9 Hz, 1H), 4.41 (dd, J = 11.9, 2.1 Hz, 1H), 4.32-4.27 (m, 2H), 4.23 (dd, J = 7.9, 1.8 Hz, 1H), 4.03 (dd, J = 10.7, 4.9 Hz, 1H), 3.93 (dt, J = 6.4, 1.5 Hz, 1H), 3.73 (t, J = 8.9 Hz, 1H), 3.67 (t, J = 9.4 Hz, 1H), 3.61-3.57 (m, 2H), 3.32 (td, J = 6.7,1.5 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 1.57 (s, 3H), 1.51 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.23 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, 20°C): 198.0, 176.9, 172.8, 138.2, 137.9, 136.6, 133.4, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.6, 109.4, 108.7, 101.7, 96.3, 83.4, 77.5, 75.2, 75.1, 73.3, 73.0, 71.3, 70.7, 70.7, 69.1, 67.3, 63.2, 39.0, 33.5, 28.3, 27.3, 26.3, 26.1, 25.2, 24.5.

FTIR (thin film) cm^{-1}: 2977 (w), 1739 (s), 1688 (m), 1382 (m), 1070 (s).

HRMS–ESI (*m/z*): calcd for $C_{47}H_{58}NaO_{14}$ $[M+Na]^+$: 869.3719, found: 869.3754.

$[\alpha]^{24}_{D}$: –29.8 (c 1.08, CH_2Cl_2).



3,4-di-*O*-benzyl-6-*O*-4'-oxo-5'-phenyl-valeryl-2-*O*-pivaloyl-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-D-galactopyranoside (35):

General Procedure D using phosphate **33** (80 mg, 0.099 mmol), acceptor **16** (22 mg, 0.085 mmol), TMSOTf (25 μL, 0.14 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded **35** as a white solid (64 mg, 88%, 1:1.6 α:β).

General Procedure E using thiodonor **39** (73 mg, 0.11 mmol), acceptor **16** (25 mg, 0.095 mmol), NIS (40 mg, 0.18 mmol), TMSOTf (9 μL, 0.05 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded **35** as a white foam (64 mg, 79%, β).

General Procedure F using trichloroacetimidate **47** (45 mg, 0.058 mmol), acceptor **16** (13 mg, 0.048 mmol), TMSOTf (1 μL, 0.006 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15]) afforded **35** as a clear oil (15 mg, 37%, β).

^{1}H NMR (400 MHz, $CDCl_3$, 20°C, mixture of diastereomers, 1:1.6 α:β): 7.37-7.20 (m, 21H), 5.51 (d, J = 5.0 Hz, 0.4H), 5.48 (d, J = 4.9 Hz, 1H), 5.40 (br-s, 0.4H), 5.08 (t, J = 8.2 Hz, 1H), 4.86-4.69 (m, 4.2H), 4.62 (dd, J = 8.0, 2.4 Hz, 0.4H), 4.58-4.49 (m, 4.2H), 4.46 (d, J = 7.9 Hz, 1H), 4.36-4.21 (m, 5.6H), 4.03-4.00 (m, 1.4H), 3.94-3.87 (m, 1.4H), 3.76-3.52 (m, 7H), 2.82-2.67 (m, 2.8H), 2.59-2.52 (m, 2.8H), 1.52 (s, 1.2H), 1.49 (s, 3H), 1.43 (s, 4.2H), 1.35-1.31 (m, 8.4H), 1.21 (s, 12.6H).

^{1}H NMR (400 MHz, $CDCl_3$, 20°C): (β isomer): 7.32-7.18 (m, 15H), 5.46 (d, J = 4.9 Hz, 1H), 5.06 (dd, J = 9.2, 8.0 Hz, 1H), 4.79-4.69 (m, 3H), 4.56-4.51 (m, 2H), 4.45 (d, J = 7.9 Hz, 1H), 4.32 (dd, J = 12.0, 2.2 Hz, 1H), 4.27-4.19 (m, 3H), 4.00 (dd, J = 10.5, 4.7 Hz, 1H), 3.93-3.90 (m, 1H), 3.73-3.69 (m, 3H), 3.65-3.50 (m, 3H), 2.76-2.70 (m, 2H), 2.55 (t, J = 6.6 Hz, 2H), 1.48 (s, 3H), 1.42 (s, 3H), 1.30 (s, 6H), 1.20 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, 20°C, mixture of diastereomers, 1:1.6 α:β):): 206.4, 206.3, 177.6, 177.0, 172.7, 172.6, 138.2, 138.2, 137.8, 134.2, 134.2, 129.6, 129.6, 128.9, 128.9, 128.6, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 109.6, 109.4, 108.8, 108.7, 101.7, 97.9, 96.4, 96.4, 83.4, 78.5, 77.5, 75.2, 75.2, 73.5, 73.3, 73.0, 71.6, 71.4, 71.0, 70.8, 70.7, 70.7, 69.9, 69.1, 68.1, 67.3, 66.4, 66.1, 63.5, 63.2, 50.2, 50.2, 39.1, 39.0, 36.6, 28.1, 27.9, 27.4, 27.3, 27.3, 27.2, 36.3, 26.3, 26.2, 25.2, 25.1, 24.7, 24.5.

^{13}C NMR (100 MHz, $CDCl_3$, 20°C): (β isomer): 206.4, 177.0, 172.6, 138.1, 137.8, 134.2, 129.6, 128.9, 128.6, 128.6, 128.3, 128.1, 127.9, 127.6, 127.3, 109.4, 108.7, 101.7, 96.4, 83.4, 77.4, 75.2, 73.2, 73.0, 71.3, 70.7, 70.7, 69.1, 67.3, 63.2, 50.2, 39.0, 36.6, 28.1, 27.3, 26.3, 26.1, 25.2, 24.5.

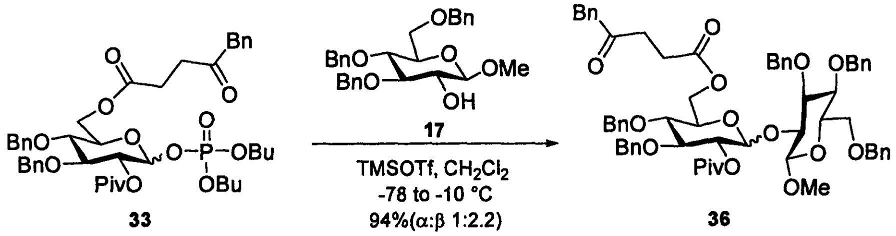
FTIR (thin film) cm^{-1}: 2978 (m), 1738 (s), 1095 (s), 1071 (s), 1008 (m).

FTIR (thin film) cm^{-1}: (β isomer): 2978 (w), 1739 (s), 1139 (m), 1070 (s), 1006 (m).

HRMS–ESI (*m/z*): calcd for $C_{48}H_{60}NaO_{14}$ $[M+Na]^+$: 883.3875, found: 883.3881.

HRMS–ESI (*m/z*): (β isomer): calcd for $C_{48}H_{60}NaO_{14}$ $[M+Na]^+$: 883.3875,
found: 883.3878.

$[\alpha]^{24}_{D}$: (β isomer): –37.0 (c 0.70, CH_2Cl_2).



Methyl 3,4-di-*O*-benzyl-6-*O*-4'-oxo-5'-phenyl-valeryl-2-*O*-pivaloyl-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-D-glucopyranoside (36):

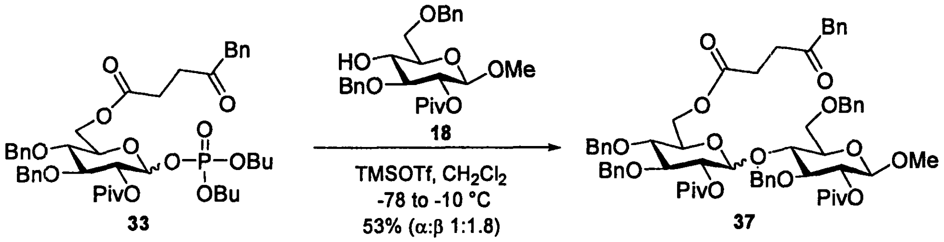
General Procedure D using glycosyl phosphate **33** (70 mg, 0.086 mmol), acceptor **17** (36 mg, 0.076 mmol), TMSOTf (22 μL, 0.12 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded **36** (76 mg, 94%, 1:2.2 α:β).

^{1}H NMR (400 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β): 7.38-7.07 (m, 46.8H), 5.41 (br-s, 0.6H), 5.31 (br-s, 0.6H), 5.13 (t, J = 8.1 Hz, 1H), 5.02 (d, J = 7.8 Hz, 1H), 4.93 (d, J = 11.7 Hz, 1H), 4.85-4.48 (m, 15.6H), 4.38-4.35 (m, 2.1H), 4.29-4.24 (m, 1.6H), 4.03-3.91 (m, 2H), 3.77-3.42 (m, 19.8H), 2.78-2.68 (m, 3.1H), 2.57 (t, J = 6.4 Hz, 2H), 2.50-2.47 (m, 1.1H), 1.23 (s, 5H), 1.10 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β): 206.4, 206.4, 177.7, 176.7, 172.7, 172.6, 138.9, 138.5, 138.3, 138.2, 138.2, 138.0, 137.9, 137.8, 134.2, 129.7, 129.0, 128.7, 128.6, 128.6, 128.6, 128.5, 128.4, 128.3, 128.1, 128.1, 128.1, 128.0, 127.9, 127.8, 127.4, 127.3, 104.6, 103.2, 99.6, 97.2, 85.0, 83.8, 83.5, 80.4, 78.6, 78.2, 77.9, 77.4, 76.0, 75.7, 75.1, 75.1, 74.8, 73.7, 73.7, 73.5, 73.1, 71.3, 69.9, 68.9, 68.8, 68.0, 63.6, 63.3, 57.3, 57.0, 50.2, 39.2, 39.0, 36.6, 36.6, 28.1, 27.9, 27.4, 27.3.

FTIR (thin film) cm^{-1}: 1736 (s), 1454 (m), 1141 (s), 1094 (s), 1070 (s).

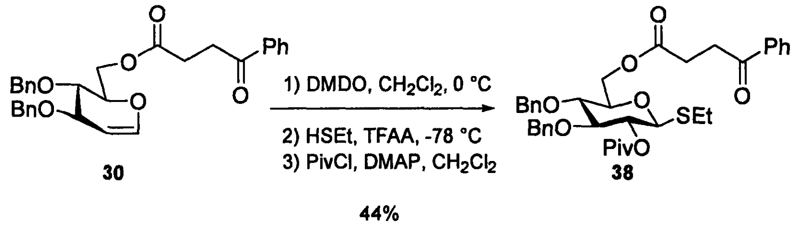
HRMS–ESI (*m/z*): calcd for $C_{64}H_{72}NaO_{14}$ [M+Na]$^+$: 1087.4814, found: 1087.4819.



Methyl 3,4-di-*O*-benzyl-6-*O*-4'-oxo-5'-phenyl-valeryl-2-*O*-pivaloyl-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside (37):

General Procedure D using glycosyl phosphate **33** (82 mg, 0.10 mmol), acceptor **18** (41 mg, 0.089 mmol), TMSOTf (26 µL, 0.14 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded **37** (49 mg, 53%, 1:1.6 α:β).

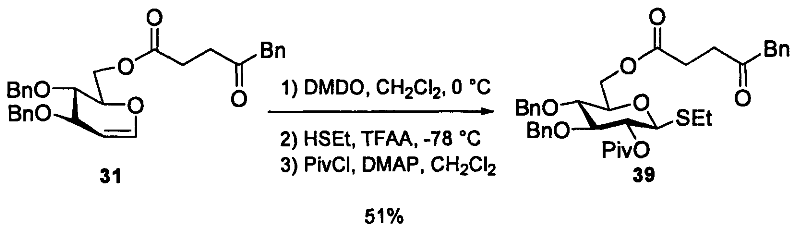
^{1}H NMR (400 MHz, $CDCl_3$, 20°C):	(β isomer): 7.42-7.17 (m, 25H), 5.03-4.96 (m, 2H), 4.83-4.61 (m, 4H), 4.54-4.47 (m, 3H), 4.28 (d, *J* = 8.0 Hz, 1H), 4.21-4.04 (m, 3H), 3.85-3.72 (m, 2H), 3.68 (s, 2H), 3.64-3.61 (m, 2H), 3.58-3.44 (m, 3H), 3.39-3.34 (m, 2H), 2.65-2.52 (m, 2H), 2.40-2.30 (m, 1H), 2.24-2.16 (m, 1H), 1.18 (s, 9H), 1.11 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$, 20°C):	(β isomer): 206.4, 177.0, 176.8, 172.5, 139.3, 138.1, 138.0, 137.8, 134.3, 129.7, 128.9, 128.6, 128.6, 128.4, 128.2, 128.2, 128.1, 128.1, 127.8, 127.3, 127.2, 127.2, 102.5, 99.5, 83.1, 81.0, 78.5, 78.0, 77.4, 75.4, 75.2, 75.1, 75.0, 74.3, 74.1, 73.9, 73.4, 73.0, 72.2, 68.0, 63.1, 57.0, 50.0, 39.0, 38.8, 36.5, 29.9, 27.8, 27.5, 27.1.
FTIR (thin film) cm^{-1}:	(β isomer): 2966 (w), 1739 (s), 1277 (w), 1141 (s), 1090 (s).
HRMS–ESI (*m/z*):	(β isomer): calcd for $C_{62}H_{74}NaO_{15}$ $[M+Na]^+$: 1081.4925, found: 1081.4912.
$[\alpha]^{24}_D$:	(β isomer): –18.7 (c 1.49, CH_2Cl_2).



Thioethyl 6-*O*-3′-benzoylpropionyl-3,4-di-*O*-benzyl-2-pivaloyl-β-D-glucopyranoside (38):

General Procedure G using glucal **30** (0.340 g, 0.698 mmol), dimethyldioxirane (13 mL, 1.05 mmol), ethanethiol (1.55 mL, 20.9 mmol), DMAP (69 mg, 0.57 mmol), pivaloyl chloride (0.035 mL, 0.29 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded **38** as a white solid (79 mg, 44%).

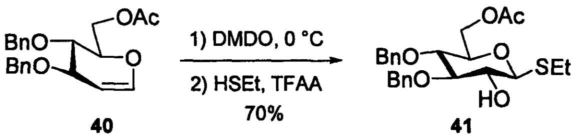
^{1}H NMR (400 MHz, $CDCl_3$, 20°C):	7.96 (app-d, J = 7.1 Hz, 2H), 7.57 (app-t, J = 7.4 Hz, 1H), 7.46 (app-t, J = 7.6 Hz, 2H), 7.34-7.25 (m, 10H), 5.08 (t, J = 9.7 Hz, 1H), 4.83-4.72 (m, 3H), 4.60 (d, J = 10.8 Hz, 1H), 4.44-4.40 (m, 2H), 4.27 (dd, J = 12.0, 4.7 Hz, 1H), 3.75 (t, J = 8.9 Hz, 1H), 3.64-3.59 (m, 2H), 3.31 (t, J = 6.5 Hz, 2H), 2.79 (t, J = 6.5 Hz, 2H), 2.78-2.62 (m, 2H), 1.27-1.17 (m, 12H).
^{13}C NMR (100 MHz, $CDCl_3$, 20°C):	198.0, 177.0, 172.7, 138.1, 137.8, 136.6, 133.4, 128.8, 128.7, 128.6, 128.6, 128.3, 128.2, 128.1, 127.9, 127.5, 84.8, 83.8, 77.5, 77.4, 75.4, 75.3, 71.6, 63.4, 38.9, 33.5, 28.3, 27.3, 24.0, 15.1.
FTIR (thin film) cm^{-1}:	2969 (w), 1737 (s), 1687 (m), 1157 (s), 1089 (m).
HRMS–ESI (*m/z*):	calcd for $C_{37}H_{44}NaO_8S$ $[M+Na]^+$: 671.2649, found: 671.2635.
$[\alpha]^{24}_D$:	–16.4 (c 1.39, CH_2Cl_2).



Thioethyl 3,4-di-*O*-benzyl-6-*O*-4'-oxo-5'-phenyl-valeryl-2-pivaloyl-β-D-glucopyranoside (39):

General Procedure G using glucal **31** (0.331 g, 0.661 mmol), dimethyldioxirane (10 mL, 0.79 mmol), ethanethiol (1.50 mL, 19.8 mmol), DMAP (0.186 g, 1.52 mmol), pivaloyl chloride (0.098 mL, 0.800 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded **39** as a clear oil (0.215 g, 51%).

^{1}H NMR (400 MHz, CDCl$_3$, 20°C):	7.35-7.20 (m, 15H), 5.09 (t, *J* = 9.3 Hz, 1H), 4.81-4.72 (m, 3H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.40 (d, *J* = 10.0 Hz, 1H), 4.37-4.34 (m, 1H), 4.22 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.77-3.72 (m, 3H), 3.63-3.55 (m, 2H), 2.77-2.65 (m, 4H), 2.56 (app-t, *J* = 6.6 Hz, 2H), 1.26-1.21 (m, 12H).
^{13}C NMR (100 MHz, CDCl$_3$, 20°C):	206.4, 177.1, 172.6, 138.1, 137.8, 134.2, 129.7, 129.0, 128.7, 128.6, 128.3, 128.2, 127.9, 127.6, 127.3, 84.9, 83.9, 77.6, 77.4, 75.5, 75.3, 71.6, 63.4, 50.2, 39.0, 36.6, 29.9, 28.1, 27.4, 24.2, 15.1, 14.4.
FTIR (thin film) cm^{-1}:	2924 (s), 1736 (s), 1454 (m), 1160 (br-s), 1090 (s).
HRMS–ESI (*m/z*):	calcd for $C_{38}H_{46}NaO_8S$ [M+Na]$^+$: 685.2806, found: 685.2812.
$[\alpha]^{24}_D$:	–14.0 (c 0.42, CH_2Cl_2).



Thioethyl 6-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranoside (41):

General Procedure G using 6-*O*-acetyl-3,4-dibenzyl-D-glucal **40**[10] (1.18 g, 3.20 mmol), dimethyldioxirane (48 mL, 3.84 mmol), ethanethiol (7.10 mL, 96 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15] to hexanes:ethyl acetate [75:25]) afforded **41** as a clear oil (0.994 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$, 20°C):	7.36-7.21 (m, 10H), 4.93 (d, J = 11.2 Hz, 1H), 4.83 (d, J = 10.3 Hz, 2H), 4.53 (d, J = 10.8 Hz, 1H), 4.30-4.26 (m, 2H), 4.15 (dd, J = 11.9, 2.2 Hz, 1H), 3.57-3.51 (m, 1H), 3.50-3.48 (m, 3H), 2.69-2.66 (m, 2H), 2.41 (br-s, 1H), 1.98 (s, 3H), 1.26 (t, J = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, 20°C):	171.0, 138.6, 137.8, 128.7, 128.3, 128.2, 128.0, 86.5, 86.1, 77.3, 77.2, 75.4, 75.3, 73.5, 63.5, 24.8, 21.1, 15.5.
FTIR (thin film) cm^{-1}:	3453 (br-w), 2922 (w), 1742 (s), 1237 (s), 1038 (s).
HRMS–ESI (*m/z*):	calcd for $C_{24}H_{30}NaO_6S$ [M+Na]$^+$: 469.1655, found: 469.1651.
$[\alpha]^{24}_D$:	–4.3 (c 0.61, CH_2Cl_2).

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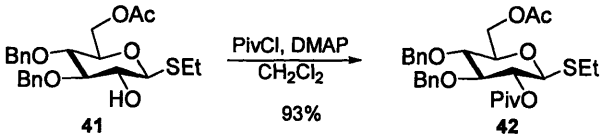
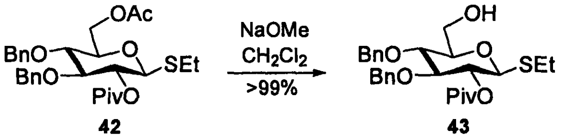
[10] Fischer, S.; Hamann, C. H. *J. Carbohydr. Chem.* **1995**, *14*, 327.



Thioethyl 6-*O*-acetyl-3,4-di-*O*-benzyl-2-pivaloyl-β-D-glucopyranoside (42):

To a solution of thioglycoside **41** (0.994 g, 2.24 mmol) in dichloromethane (20 mL) was added dimethylaminopyridine (1.08 g, 8.85 mmol) and pivaloyl chloride (0.551 mL, 4.47 mmol). After 1 h, the reaction solution was diluted with ethyl acetate:hexanes (1:1), was filtered through silica gel, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent hexanes:ethyl acetate [70:30]) to afford **42** as a clear oil (1.11 g, 93%).

^{1}H NMR (400 MHz, CDCl$_3$, 20°C):	7.36-7.23 (m, 10H), 5.11 (app-t, *J* = 9.3 Hz, 1H), 4.83-4.72 (m, 3H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.42 (d, *J* = 10.0 Hz, 1H), 4.37 (dd, *J* = 2.0, 12.0 Hz, 1H), 4.21 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.76 (t, *J* = 8.8 Hz, 1H), 3.64 (t, *J* = 9.8 Hz, 1H), 3.59-3.56 (m, 1H), 2.74-2.63 (m, 2H), 2.04 (s, 3H), 1.27-1.18 (m, 12H).
^{13}C NMR (100 MHz, CDCl$_3$, 20°C):	177.1, 171.0, 138.1, 137.7, 128.7, 128.6, 128.3, 128.3, 127.9, 127.6, 84.9, 83.9, 77.4, 77.3, 75.5, 75.3, 71.6, 63.3, 39.0, 27.4, 24.2, 21.1, 15.1.
FTIR (thin film) cm^{-1}:	2970 (w), 2928 (w), 1740 (s), 1233 (m), 1162 (m).
HRMS–ESI (*m/z*):	calcd for C$_{29}$H$_{38}$NaO$_7$S [M+Na]$^+$: 553.2230, found: 553.2238.
$[\alpha]^{24}_{D}$:	–12.1 (c 0.33, CH$_2$Cl$_2$).



Thioethyl 3,4-di-*O*-benzyl-2-pivaloyl-β-D-glucopyranoside (43):

To a solution of thioglycoside **42** (1.11 g, 2.08 mmol) in dichloromethane (20 mL) was added a solution of sodium methoxide in methanol (25% by weight, 0.147 mL, 0.716 mmol). After 2.5 h, the reaction solution was brought to pH 7 by addition of acidic Dowex resin. The solution was decanted and was concentrated under reduced pressure to provide a quantitative yield of **43**. Spectral data matched published data.[11]

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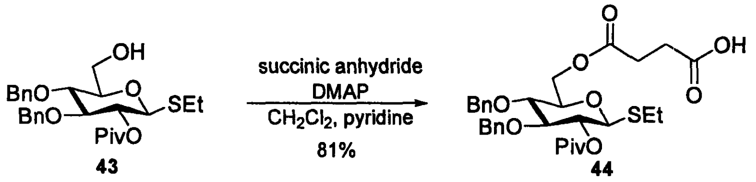
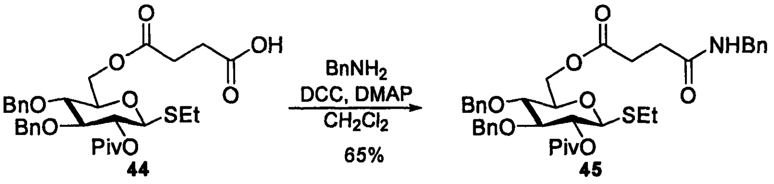
[11] Zheng, C.; Seeberger, P. H.; Danishefsky, S. J. *J. Org. Chem.* **1998**, *63*, 1126.



Thioethyl 3,4-di-*O*-benzyl-2-pivaloyl-6-*O*-succinoyl-β-D-glucopyranoside (44):

To a solution of compound **43** (0.895 g, 1.83 mmol) in pyridine:dichloromethane (1:1, 20 mL) was added dimethylaminopyridine (0.384 g, 3.15 mmol) and succinic anhydride (0.277 g, 2.77 mmol). After 17 h, the solution was diluted with diethyl ether (100 ml) and was washed sequentially with with dilute aqueous acetic acid (pH 3), water, and brine. The combined organic phases were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [60:40] to hexanes:ethyl acetate [40:60]) afforded **44** as a yellow oil (0.876 g, 81%).

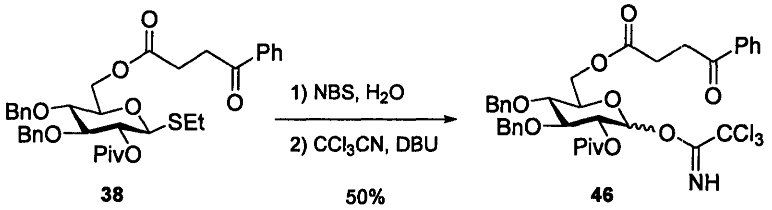
^{1}H NMR (400 MHz, $CDCl_3$, 20°C):	7.33-7.22 (m, 10H), 5.08 (t, *J* = 9.8 Hz, 1H), 4.80-4.76 (m, 2H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 4.41-4.37 (m, 2H), 4.23 (dd, *J* = 11.9, 4.7 Hz, 1H), 3.74 (t, *J* = 8.9 Hz, 1H), 3.60 (t, *J* = 9.2 Hz, 1H), 3.57-3.53 (m, 1H), 2.71-2.58 (m, 6H), 1.25-1.20 (m, 12H).
^{13}C NMR (100 MHz, $CDCl_3$, 20°C):	178.1, 177.0, 171.9, 138.0, 137.6, 128.7, 128.6, 128.3, 128.2, 127.9, 127.5, 84.8, 83.7, 77.4, 75.4, 75.2, 71.5, 63.5, 38.9, 28.9, 28.8, 27.3, 24.0, 15.1.
FTIR (thin film) cm^{-1}:	2970 (w), 1739 (s), 1714 (m), 1160 (s), 1090 (m).
HRMS–ESI (*m/z*):	calcd for $C_{31}H_{40}NaO_9S$ $[M+Na]^+$: 611.2285, found: 611.2273.
$[\alpha]^{24}_D$:	–18.7 (c 1.63, CH_2Cl_2).



Thioethyl 3,4-di-*O*-benzyl-6-*O*-*N*-benzylsuccinamyl-2-pivaloyl-β-D-glucopyranoside (45):

To a solution of compound **44** (0.685 g, 1.16 mmol) in dichlormethane (20 mL) at 0 °C was added dimethylaminopyridine (0.164 g, 1.35 mmol) and dicyclohexylcarbodiimide (0.265 mL, 1.28 mmol). After 10 min, benzylamine (0.254 mL, 2.33 mmol) was added and the reaction solution was warmed to ambient temperature. After 2 h, the reaction mixture was diluted with hexanes:ethyl acetate (1:1) and filtered through silica gel to remove excess urea. The reaction solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [50:50]) to afford **45** as a white solid (0.513 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$, 20°C):	7.35-7.24 (m, 15H), 5.95 (br-s, 1H), 5.09 (dd, *J* = 9.8, 9.3 Hz, 1H), 4.83-4.72 (m, 3H), 4.57 (d, *J* = 10.9 Hz, 1H), 4.43 (d, *J* = 5.7 Hz, 2H), 4.38 (d, *J* = 10.1 Hz, 2H), 4.21 (dd, *J* = 11.9, 4.8 Hz, 1H), 3.74 (t, *J* = 8.5 Hz, 1H), 3.62-3.56 (m, 2H), 2.73-2.64 (m, 4H), 2.49 (t, *J* = 6.7 Hz, 2H), 1.27-1.22 (m, 12H).
^{13}C NMR (100 MHz, $CDCl_3$, 20°C):	176.4, 172.8, 171.2, 138.4, 138.1, 137.7, 128.9, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 84.8, 83.9, 77.6, 75.4, 75.3, 71.6, 63.6, 43.9, 39.0, 31.2, 29.7, 27.4, 24.2, 15.1.
FTIR (thin film) cm^{-1}:	2922 (s), 1734 (s), 1456 (m), 1159 (m), 1088 (m).
HRMS–ESI (*m/z*):	calcd for $C_{38}H_{47}NNaO_8S$ $[M+Na]^+$: 700.2915, found: 700.2921.
$[\alpha]^{24}_D$:	–2.94 (c 0.17, CH_2Cl_2).



6-*O*-3'-Benzoylpropionyl-3,4-di-*O*-benzyl-2-pivaloyl-β-D-glucopyranosyl trichloroacetimidate (46):

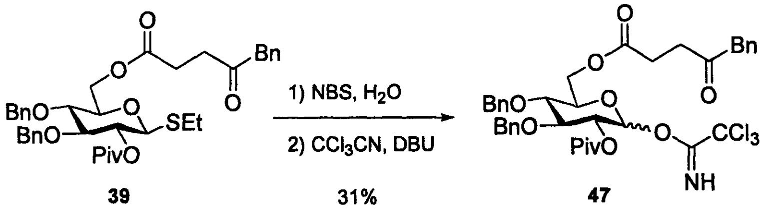
General Procedure H using thioglycoside **38** (64 mg, 0.099 mmol), NBS (74 mg, 0.41 mmol), DBU (1.5 μL, 0.010 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20]) afforded **46** (37 mg, 50%, α:β 1:2).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C, mixture of diastereomers, α:β): 8.60-8.59 (m, 1.5H), 7.90 (d, *J* = 7.3 Hz, 3H), 7.53 (app-t, *J* = 7.5 Hz, 1.5H), 7.43 (t, *J* = 7.8 Hz, 3H), 7.35-7.22 (m, 15H), 6.49 (d, *J* = 3.5 Hz, 0.5H), 5.87 (d, *J* = 7.5 Hz, 1H), 5.30 (app-t, *J* = 8.1 Hz, 1H), 5.04 (dd, *J* = 10.1, 3.7 Hz, 0.5H), 4.84-4.71 (m, 4.5 H), 4.60 (t, *J* = 9.5 Hz, 1.5H), 4.38-4.27 (m, 3H), 4.15-4.06 (m, 1H), 3.80-3.69 (m, 3.5H), 3.30-3.25 (m, 3H), 2.77-2.73 (m, 3H), 1.15-1.13 (m, 13.5H).

^{13}C NMR (125 MHz, $CDCl_3$, 20°C, mixture of diastereomers, α:β): 198.0, 198.0, 177.7, 176.8, 176.6, 172.7, 172.7, 161.3, 161.0, 138.2, 138.0, 137.7, 137.6, 136.6, 133.5, 128.8, 128.8, 128.7, 128.7, 128.7, 128.6, 128.6, 128.6, 128.4, 128.3, 128.2, 128.2, 128.2, 128.0, 127.9, 127.6, 127.6, 95.9, 93.6, 83.2, 79.9, 77.0, 76.7, 75.7, 75.6, 75.1, 74.8, 73.9, 72.4, 71.8, 71.7, 62.8, 62.6, 39.0, 33.5, 29.9, 28.4, 28.3, 27.3, 27.3, 27.3, 27.3.

FTIR (thin film) cm^{-1}: 1735 (s), 1685 (m), 1276 (m), 1145 (m), 750 (m).

HRMS–ESI (*m/z*): calcd for $C_{37}H_{40}Cl_3NaO_9$ $[M+Na]^+$: 770.1666, found: 770.1680.



3,4-Di-*O*-benzyl-6-*O*-4'-oxo-5'-phenyl-valeryl-2-pivaloyl-β-D-glucopyranosyl trichloroacetimidate (47):

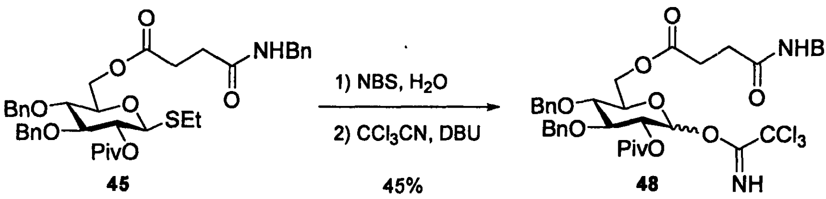
General Procedure H using thioglycoside **39** (0.193 g, 0.291 mmol), NBS (0.200 g, 1.12 mmol), DBU (3.8 μL, 0.025 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15]) afforded **47** (70 mg, 31%, α:β 1:1.3).

^{1}H NMR (400 MHz, $CDCl_3$, 20°C, mixture of diastereomers, α:β): 8.64 (s, 1H), 8.63 (s, 0.8H), 7.64-7.61 (m, 0.8H), 7.43-7.20 (m, 25.5H), 6.52 (d, *J* = 3.5 Hz, 0.8H), 5.90 (dd, *J* = 7.5, 2.6 Hz, 1H), 5.35 (t, *J* = 7.6 Hz, 1H), 5.10 (dd, *J* = 10.1, 3.5 Hz, 0.8H), 4.88-4.76 (m, 7H), 4.60-4.56 (m, 1.8H), 4.36-4.27 (m, 3.5H), 4.17 (app-t, *J* = 9.6 Hz, 0.8H), 4.09 (td, *J* = 10.1, 2.6 Hz, 1H), 3.83-3.70 (m, 5.3H), 3.02 (app-q, *J* = 6.9 Hz, 1H), 2.82-2.70 (m, 2.5H), 2.61-2.52 (m, 3.5H), 1.18 (s, 15.8H).

^{13}C NMR (100 MHz, $CDCl_3$, 20°C, mixture of diastereomers, α:β): 206.4, 206.4, 177.7, 176.6, 172.5, 161.3, 160.9, 138.1, 137.9, 137.6, 137.6, 134.2, 134.2, 130.2, 129.7, 129.6, 129.5, 129.3, 129.0, 128.9, 128.7, 128.7, 128.7, 128.6, 128.6, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.6, 127.6, 127.3, 127.0, 95.9, 93.6, 83.2, 79.9, 76.8, 76.6, 76.4, 75.7, 75.6, 75.0, 75.0, 74.8, 74.8, 73.9, 72.4, 71.8, 71.7, 71.7, 62.9, 62.8, 62.6, 50.2, 50.2, 39.0, 36.6, 31.0, 28.8, 28.1, 28.0, 27.3, 27.3.

FTIR (thin film) cm^{-1}: 2923 (w), 1738 (s), 1675 (w), 1281 (m), 1138 (s), 1066 (s).

HRMS–ESI (*m/z*): calcd for $C_{38}H_{42}Cl_3NNaO_9$ [M+Na]$^+$: 784.1822, found: 784.1831.



3,4-Di-*O*-benzyl-6-*O*-*N*-benzylsuccinamyl-2-pivaloyl-β-D-glucopyranosyl trichloroacetimidate 48):

General Procedure H using thioglycoside **45** (0.167 g, 0.246 mmol), NBS (0.186 g, 1.05 mmol), DBU (3.0 μL, 0.019 mmol) and purification by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25]) afforded **48** (70 mg, 45%, α:β 1:1.4).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β): 7.41-7.25 (m, 25.5H), 6.46 (d, J = 3.8 Hz, 0.7H), 6.08 (d, J = 2.9 Hz, 1H), 6.00-5.90 (m, 1.7H), 5.37 (at, J = 3.5 Hz, 1H), 5.08 (dd, J = 3.5, 9.9 Hz, 0.7H), 4.96-4.80 (m, 6.8H), 4.63-4.58 (m, 1.7H), 4.46-4.37 (m, 1.7H), 4.34-4.21 (m, 3.4H), 4.20-4.10 (m, 1.7H), 3.91-3.87 (m, 1H), 3.81-3.76 (m, 1H), 3.70-3.67 (m, 0.7H).

^{13}C NMR (125 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β): 178.1, 177.1, 172.8, 172.7, 171.4, 171.2, 138.4, 138.3, 138.2, 138.0, 137.6, 128.9, 128.9. 128.9, 128.9, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.7, 91.6, 90.4, 82.2, 79.9, 77.9, 75.6, 75..6, 75.5, 75.1, 74.1, 71.8, 71.6, 68.7, 66.8, 63.5, 44.0, 43.9, 39.5, 39.0, 31.3, 31.3, 29.9, 29.8, 29.8, 27.4, 27.3, 27.3, 27.3.

FTIR (thin film) cm^{-1}: 3352 (br-w), 1732 (s), 1657 (m), 1161 (s), 1122 (s).

HRMS–EI (*m/z*): calcd for $C_{38}H_{43}Cl_3N_2NaO_9$ [M+Na]$^+$: 799.1931, found: 779.1934.

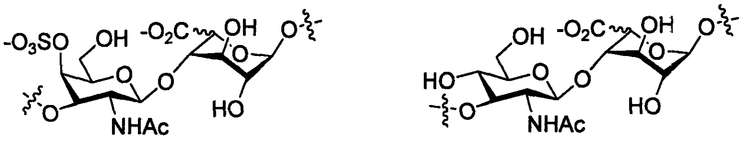
Chapter 3

A Modular Synthesis of FGF-2 Binding Heparin Pentasaccharide

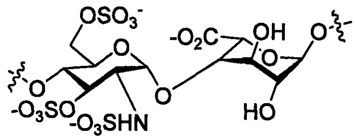
Thesis Advisor: Peter H. Seeberger

Introduction and Background

Glycosaminoglycans (GAGs) are a class of linear, negatively charged, highly functionalized oligosaccharides whose interactions with proteins and other biopolymers are essential to a number of biological processes including anticoagulation[1], cell-cell adhesion[2], and growth factor signaling.[3] Structurally, GAGs are extended polymer chains generally composed of repeating disaccharides of a 2-deoxy-2-amino sugar and an uronic acid. These structures are further elaborated through acetylation, epimerization, and *N*- and *O*-sulfation by various enzymes to produce a diversely functionalized set of molecules (Figure 1).



Dermatan sulfate   Chondroitin sulfate



Heparin

Figure 1. Representative glycosaminoglycan polysaccharides.

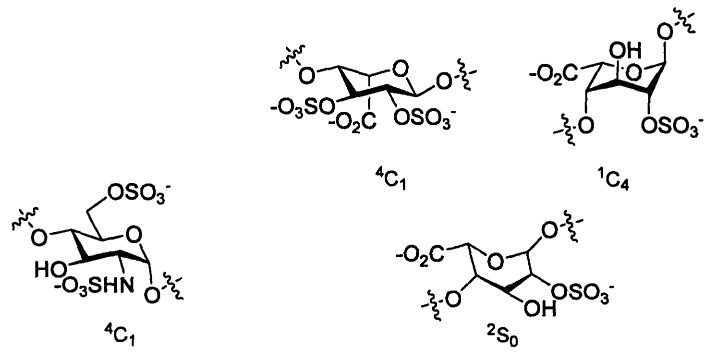
Although important for their incredible range of bioactivity, the microheterogeneity of GAGs intensifies the challenge associated with their purification and characterization.

Both heparin and heparan sulfate are biosynthesized as proteoglycans where the carbohydrate chain, consisting of repeating glucosamine and uronic acid disaccharides, is covalently linked to a protein core. They differ in the extent of their sulfation and uronic acid content. Heparin is found in mast cells, generally contains more L-iduronic acid and is more highly sulfated than heparan sulfate, which is produced by nearly all cells.[1,4] Although formed by the same pathway as heparin, heparan sulfate remains attached to its protein core, while heparin is ultimately processed into smaller GAG chains.[1] The differential action of heparin lyases on heparin and heparan sulfate may be used to differentiate the two oligosaccharide types.

While many protein-binding GAGs exist as proteoglycans, in some cases short specific sequences also bind and induce unique biological activity.[1,5] Numerous such heparin and heparan sulfate sequences have been identified, largely due to interest generated for possible biomedical applications. Heparin isolated from animal sources has been used medically as an anticoagulant for over sixty years.[6] Heparin and heparan sulfate sequences are also implicated in mast cell regulation,[7] herpes simplex virus infection,[8] and growth factor activation,[9] among other processes.

Commercial heparin is commonly isolated from porcine or bovine tissues containing high levels of mast cells, followed by proteolysis, ion exchange, and fractional precipitation.[5] Fractional precipitation allows isolation of low molecular weight heparin, which is easier to administer clinically than unfractionated heparin and produces fewer undesirable side effects, such as heparin-induced thrombocytopenia.[1] Biochemical studies concerning heparin generally rely on structurally defined sequences prepared by enzymatic degradation of these larger oligomers.

Investigation of heparin conformation has suggested a primarily helical molecule displaying charged sulfate and carboxylate groups in relatively rigid patterns associated with its specificity for protein binding.[2] Protein interaction appears to rely largely on charge orientation in the heparin structure, which in turn results from individual sugar conformation. Computational analysis indicates that configuration and placement of L-iduronic acid in particular may greatly affect this overall charge placement. While D-glucosamine and D-glucoronic acid adopt the $^4C_1$ chair conformation, L-iduronic acid is more flexible and data suggest three possible conformers: $^4C_1$ and $^1C_4$ chairs and the $^2S_0$ skew boat (Figure 2).[1,2]



glucosamine conformation

iduronic acid conformations

Figure 2. Conformations of individual glucosamine and iduronic acid residues found in heparin.[1,2]

The preferred conformation for iduronic acid depends on substituent identity (sulfation and acetylation) and its position in the chain, with the $^1C_4$ and $^2S_0$ preferred for a non-reducing sugar. Interchange between these conformers within larger chains may alter the position of key charged residues, and the low energy barrier between the two suggests that the ring may change conformation on binding to form favorable electrostatic interactions with the protein.[1] The prevalence of L-iduronic acid residues in regions responsible for protein binding supports this observation.[2]

Fibroblast growth factors (FGFs) make up a family of structurally related signaling polypeptides key to a number of developmental processes, including cell proliferation, differentiation, morphogenesis, and angiogenesis.[1,3] Signal transduction involves dimerization of the tyrosine kinase FGF receptors (FGFRs), a process promoted by simultaneous binding of FGF and FGFR to soluble or cell surface-bound heparin and heparan sulfate.[1] Acidic fibroblast growth factor (FGF-1) and basic fibroblast growth factor (FGF-2), have received much attention, resulting in high-resolution X-ray crystallographic data of FGF-FGFR-heparin complexes.[10,11]

The crucial relationship between fibroblast growth factor (FGF) heparin binding and FGF receptor activation offers an entry to promising therapeutic targets for the regulation of cell growth. Heparin-mediated dimer- and oligomerization of both acidic (FGF-1) and basic fibroblast growth factor (FGF-2) with FGF receptors (FGFR) appears critical to receptor activation.[12] Biochemical studies have indicated that small modifications of heparin oligomer length and sulfation pattern affect specificity for distinct FGF polypeptides.[13] In addition to work demonstrating higher FGF-2 affinity for heparin containing L-iduronic acid as the sole uronic acid,[14] preliminary studies suggest 2-*O*- and 6-*O*-sulfation of L-iduronic acid and *N*-sulfation of the D-glucosamine units are essential for binding. [1,2]

Several studies have investigated the minimum required length for heparin-FGF-FGFR binding. Analysis of binding by ultracentrifugation of FGF-2 with heparin oligosaccharides suggest that while a hexasaccharide is sufficient for binding, an octasaccharide is required for receptor activation.[1] Crystallographic work detailing an FGF-2:FGFR complex in the absence of heparin also indicates a minimum octasaccharide to adequately bridge the positively charged "binding canyon" observed between components.[16] Other reports suggest that a hexasaccharide[17] or even a tetrasaccharide[18] are sufficient to affect FGF-2 binding. In light of this disparity, in approaching a synthesis of FGF-2 binding oligosaccharide, a strategy for rapid access to heparins of varying length would be advantageous for the deconvolution of their biological activity.

Prior Synthetic Studies

Inspection of the repeating nature of FGF-2 binding heparin oligosaccharides suggests a disaccharide unit as a key synthetic building block. Use of a disaccharide donor incorporating a removable protecting group at C4 of a non-reducing L-iduronic acid or D-glucosamine would allow iterative synthesis of heparin structures of varying lengths. Possible repeating components may display either an uronic acid or a glucosamine at the disaccharide reducing end (Figure 3).

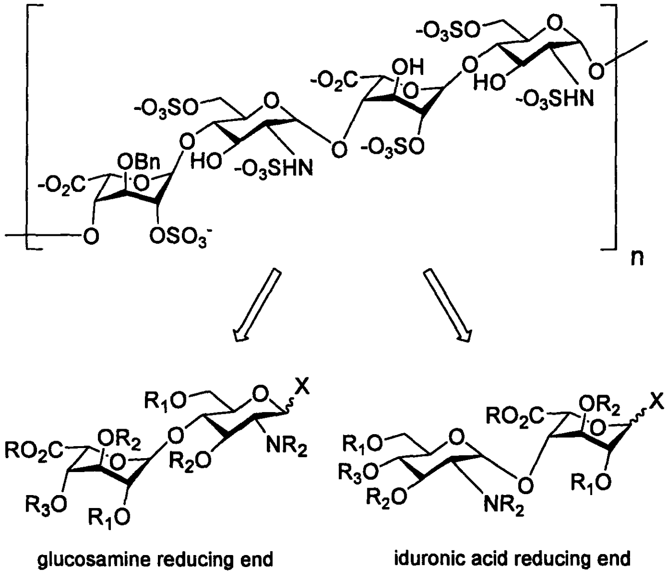
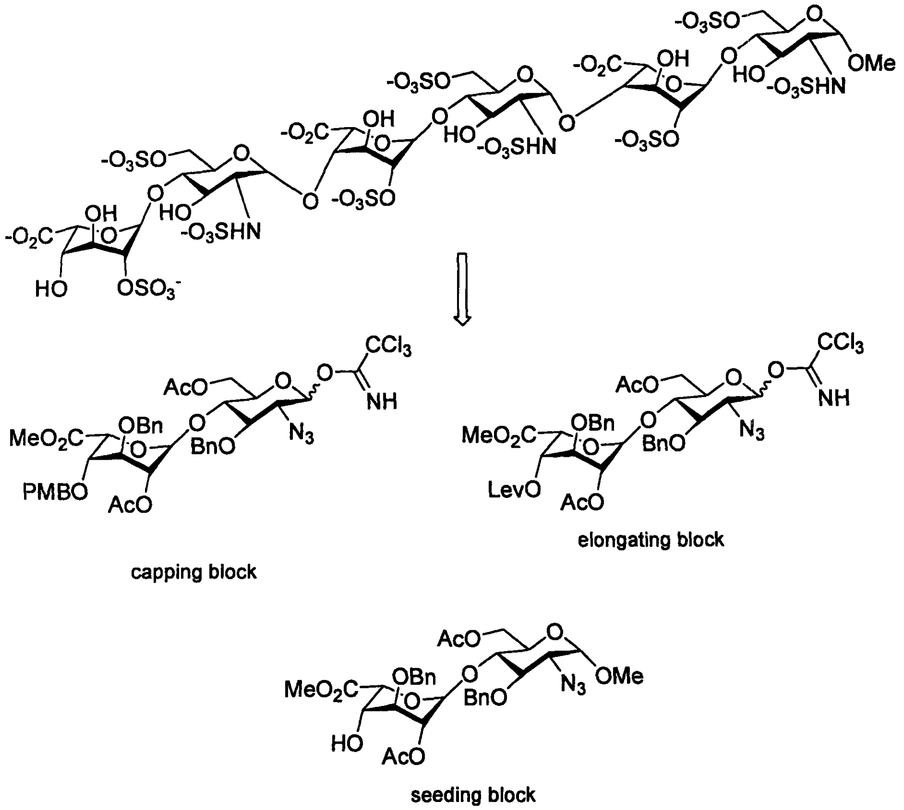


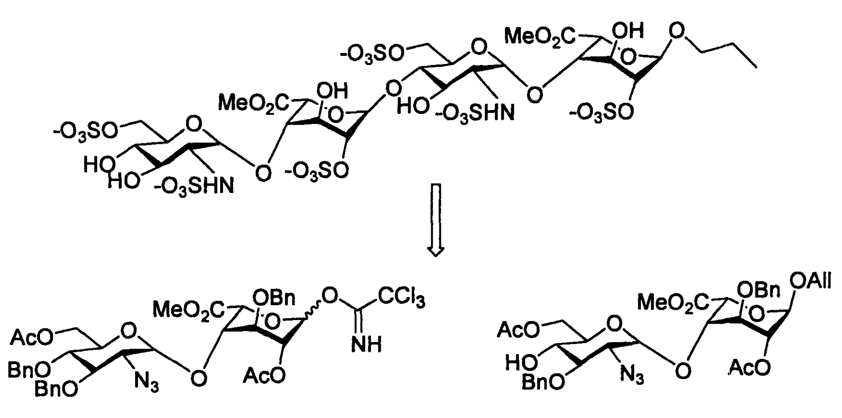
Figure 3. FGF-2 binding heparin oligosaccharide retrosynthesis. X=leaving group.

Several syntheses of FGF-2 binding heparin oligosaccharides have been reported, using both uronic acid and glucosamine reducing end strategies. Early work by Sinaÿ and coworkers utilized disaccharide trichloroacetimidates containing glucosamine moieties at the reducing end.[3,19] A number of pentasaccharides with both D-glucoronic and L-iduronic acids were synthesized and used in binding studies to determine the optimal uronic acid content for good binding to FGF-2. Subsequent work extended this strategy to the synthesis of related hexa- and octasaccharides (Scheme 1). Iterative glycosylation of a seeding block with an elongating disaccharide donor was followed by disaccharide capping provided a modular strategy for synthesis of the larger oligomers.[19]



Scheme 1. Retroynthesis of FGF-2 binding heparin hexasaccharide synthesized by Sinay and coworkers.

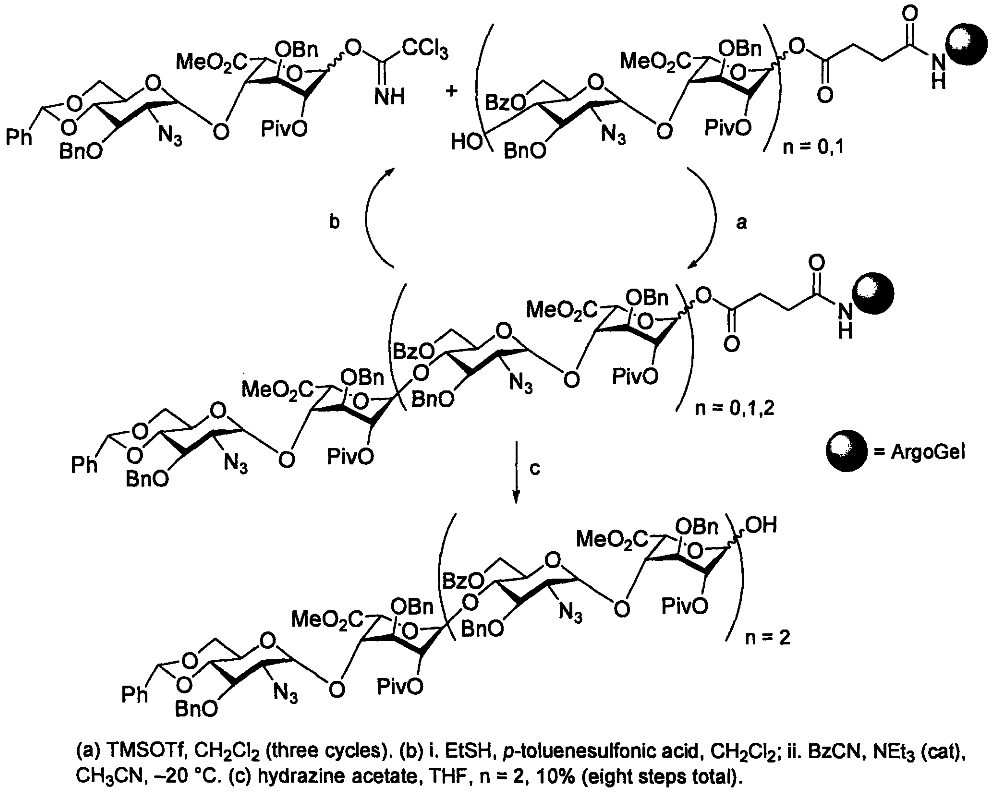
Later reports by Lay and coworkers outlined syntheses of tetra- and hexasaccharides utilizing uronic acid donors (Scheme 2).[13] Research by Martín-Lomas also employed



Scheme 2. Retrosynthesis of FGF-2 binding heparin tetrasaccharide synthesized by Lay and coworkers.[2]

reducing end L-iduronic acids in their syntheses of a related hexa- and octasaccharide.[20] In each case, placement of a participating ester at the uronic acid C2 of the trichloroacetimidate donor provided the necessary selectivity on glycosylation.

While these syntheses are impressive, overall they remain lengthy and require numerous purification steps. In addition, coupling yields tend to decrease as oligomer size and complexity increase. Analysis of the repeating heparin polymer suggests iterative synthesis, while the ability to use excess reagents to drive coupling yields and ease of purification recommend a solid-phase strategy. Indeed, after we began this work, the Martín-Lomas group successfully applied their modular approach to a polymer-supported synthesis of heparin-like oligosaccharides (Scheme 3).[21] Triple coupling cycles were used to increase glycosylation efficiency, providing the desired octasaccharide in 10% overall yield. Recent successes concerning the automated syntheses of complex oligosaccharides on solid support[22] indicate the feasibility of a correlated fully automated solid-phase heparin



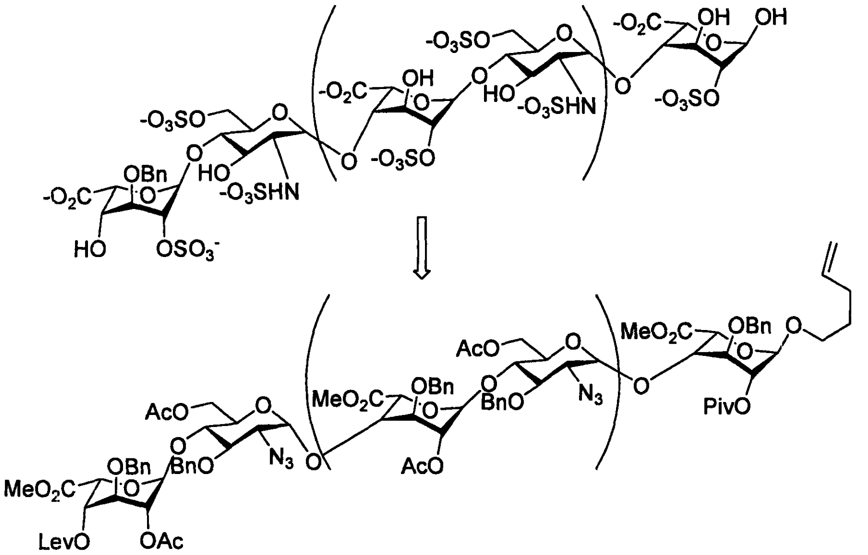
(a) TMSOTf, CH_2Cl_2 (three cycles). (b) i. EtSH, *p*-toluenesulfonic acid, CH_2Cl_2; ii. BzCN, NEt_3 (cat), CH_3CN, −20 °C. (c) hydrazine acetate, THF, n = 2, 10% (eight steps total).

Scheme 3. Polymer supported heparin synthesis.

synthesis. Efforts toward the iterative synthesis of FGF-2 binding heparin oligosaccharides and steps towards the automation of this sequence are discussed in this chapter.

Retrosynthetic Analysis

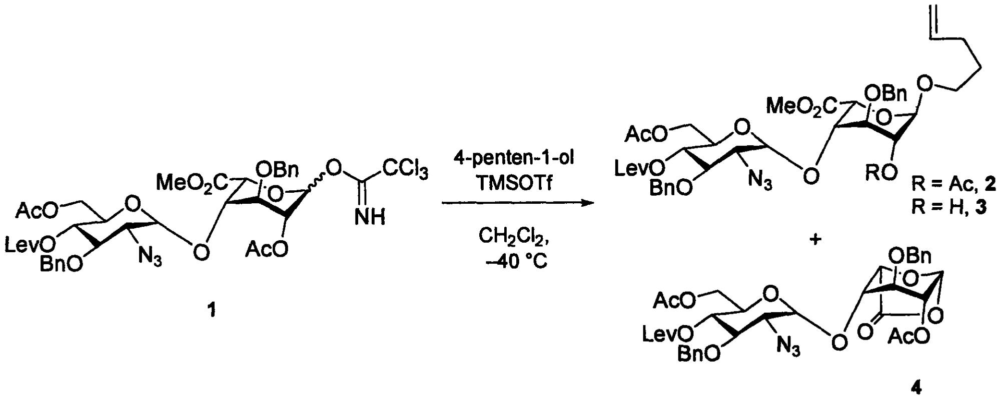
The synthetic work described herein details efforts toward the synthesis of FGF-2 binding heparin of various lengths. Initial solution-phase work was designed with consideration for ultimate application of the sequence to an automated solid-phase synthesis of the desired oligosaccharides. The orthogonal protection required for the sequential unmasking and introduction of the desired sulfation pattern led to the protecting group strategy outlined in Figure 4. Carboxylate moieties in the final structure were protected as methyl esters, *O*-sulfation sites were masked as acetate or pivaloate esters, *N*-sulfates were masked as azide groups, and free hydroxyls were protected as benzyl ethers. A levulinate ester was used as a temporary protecting group for sequence elongation. A pentenyl alcohol reducing end was used as a linker model and to facilitate spectral comparison with expected cleavage products for an automated solid-phase protocol utilizing an octenediol linker[23] for reducing end immobilization. Reduction of the installed azides was anticipated prior to resin cleavage due to their general incompatibility with the cross-metathesis procedure used to access the free oligosaccharides.[24]



methyl esters = carboxylates; acetates = *O*-sulfates; azides = *N*-sulfates; Bn = free OH; Lev = temporary

Figure 4. Retrosynthesis of FGF-2 binding heparin protecting group strategy.

Trichloroacetimidates were chosen as the preferred glycosyl donors based on previous success for automated syntheses of complex structures in our laboratory. [25] Prior work in our laboratory indicated a disaccharide donor containing a reducing end glucosamine as the optimal donor for sequence elongation.[26] Early work utilizing alternative uronic acid reducing end disaccharide donor **1** and a pentenyl alcohol acceptor resulted in the loss of the C2 acetate (**3**) and formation of cyclic lactone **4** along with the desired coupling product **2** (Scheme 4).[27] While in a solid-phase protocol the cyclic lactone would be readily removed during the washing cycle, the free hydroxyl of compound **3** could result in complex mixtures upon structure elongation. Glycosylation of pentenyl alcohol with a glucosamine disaccharide donor produced anomeric mixtures under all solid-phase compatible protocols. Ultimately, reducing end monosaccharide **6** was incorporated, with subsequent elongation utilizing disaccharide trichloroacetimidate **5** (Figure 5). While C2-acetates were used for the disaccharide uronic acids, a C2-pivaloyl ester was chosen for iduronic acid **6** as previous work by India Sietlaff in our group had demonstrated that the corresponding acetate produced the orthoester exclusively on glycosylation with pentenyl alcohol.[27] Additional work showed that disaccharide donor **5** gave the desired α selectivity under conditions amenable to solid-phase work and eventual automation.[26] Synthesis focused on building blocks—disaccharide **5** and monosaccharide **6**—and subsequent application of these components to our strategy for the construction of FGF-2 binding heparin oligosaccharides.



Scheme 4. Investigation of iduronic acid reducing end disaccharide donor **1** with linker model.

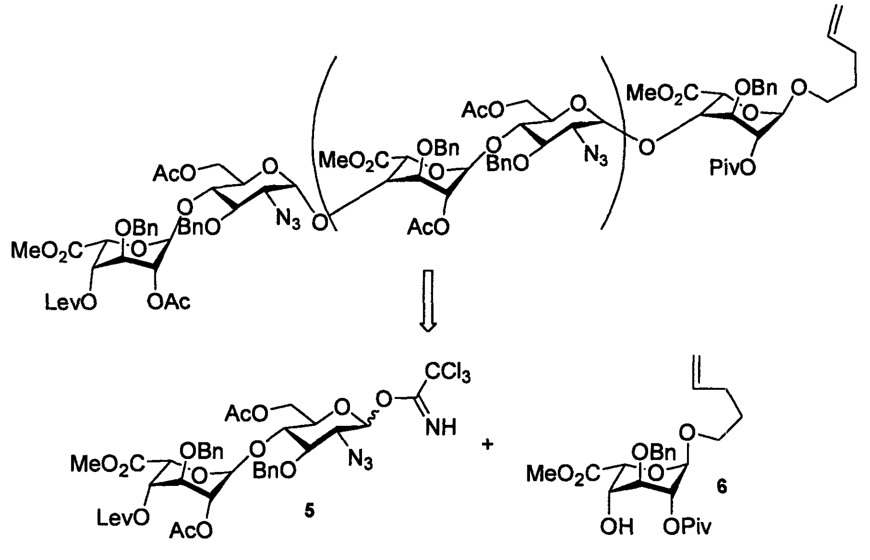


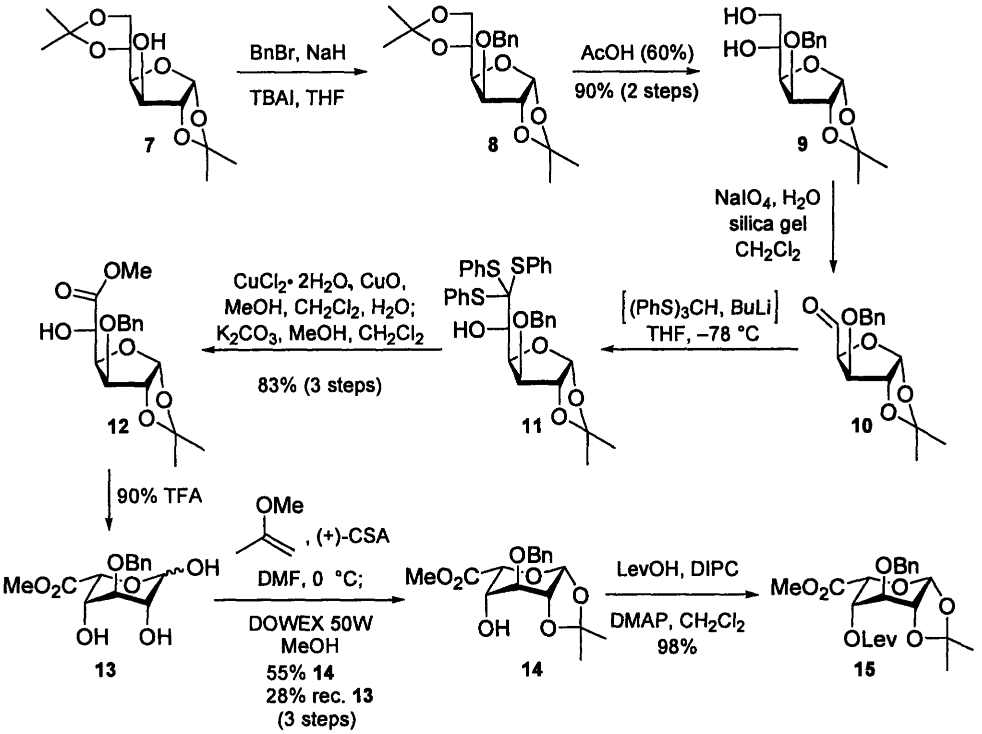
Figure 5. Our retrosynthesic analysis of protected FGF-2 binding heparin oligomers.

Results and Discussion

Iduronic acid donor synthesis.

The prevalence of L-iduronic acid in many heparin structures, including FGF-2 binding heparin, necessitates concise and efficient access to differentially protected iduronic acid synthons. While itself not commercially available, L-iduronic acid has been synthesized from a variety of starting materials including idose,[28] glucose,[29,30] glycals,[31] and glucoronic acid.[32] Commercially available L-idose is very costly, rendering it undesirable for large scale synthesis, while syntheses utilizing other starting materials require the inversion of the C-5 stereocenter on a D-gluco sugar. Few methods reported for this inversion have realized full selectivity for the desired configuration.

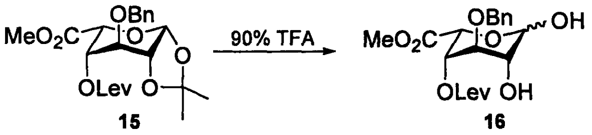
Previous work by the group[30] and work performed in conjunction with my colleague Greg Lohman outlined a concise, scalable synthetic route to differentially protected iduronic acid **15** from commercially available diacetone glucose (Scheme 5).[33] This sequence relies on selective introduction of the required L-idose-configuration of thioorthoester **11** via addition of trithiophenylmethyllithium to aldehyde **10**,[34] obtained from diacetone glucose **7** after benzylation, selective acetal cleavage, and diol oxidation (Scheme 5). Cleavage of the thioorthoester **11** to the furanose methyl ester **12** with copper chloride dihydrate and copper



Scheme 5. Synthesis of differentially protected L-iduronic ester **15** from diacetone glucose.

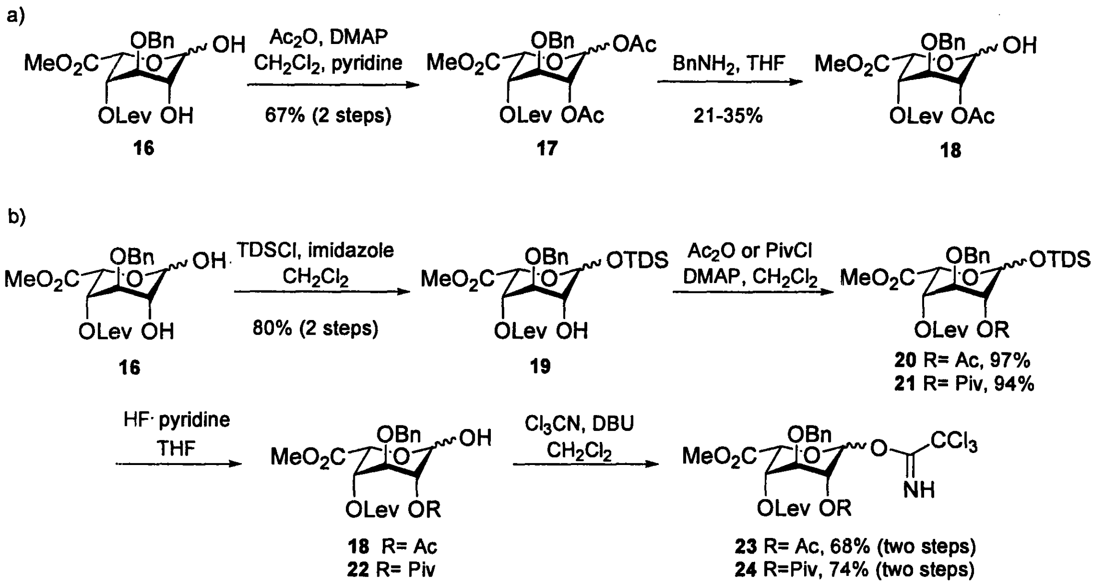
oxide in methanol followed by acidic removal of the isopropylidene provided crystalline triol **13** in its pyranose form.[35] Installation of a 1,2-isopropylidene[36] onto **13** locked the sugar in the $^1C_4$ pyranose form, providing key intermediate **15** after formation of the levulinate ester.[35]

Acidic cleavage of isopropylidene **15** provided diol **16**, prepared for differential protection of the C-1 and C-2 hydroxyls (Scheme 6). While selective cleavage of a 1,2-



Scheme 6. Isopropylidene cleavage of acetonide **15** to produce crude diol **16**.

diacetate[37] with benzylamine had been shown to provide the desired C2-acetate lactol for a corresponding system, in the presence of the C4-levulinate ester anomeric acetate cleavage of **17** proceeded was sluggish and produced low yields of the desired lactol **18** (Scheme 7a).

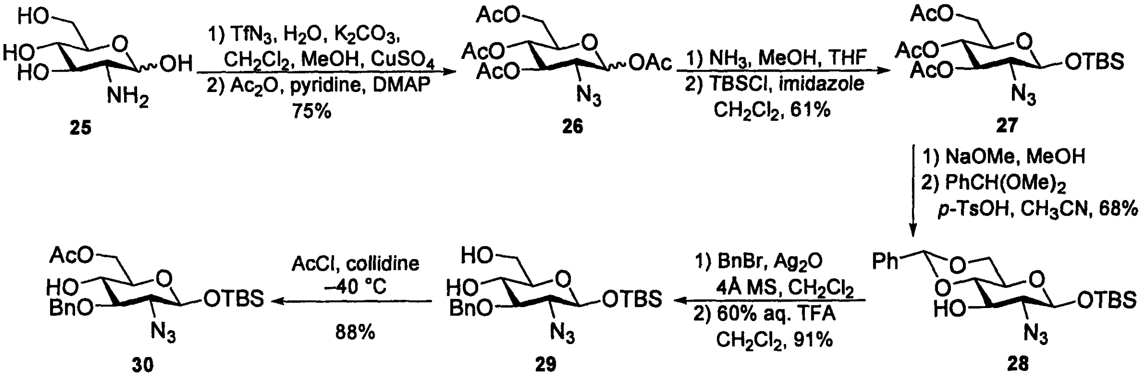


Scheme 7. Differentiation of diol **16** to produce trichloroacetimidates **23** and **24**.

Undesired reactivity at the C4-levulinate ester may be responsible for this result. As an alternative, differential silyl ether protection[38] was employed. This pathway was additionally attractive as it allowed ready access to both the C2-acetate and C2-pivaloate esters for incorporation into the disaccharide donor and the desired monosaccharide, respectively. While low temperature ether formation for related C4-benzyl ether iduronic acids with ^{t}butyldimethylsilyl (TBS) chloride produced the desired anomeric silyl ether, the less sterically demanding levulinate ester required the bulkier thexyldimethylsilyl (TDS) species and prolonged reaction at low temperature to achieve the desired selectivity (Scheme 7b). Protection of the C2-hydroxyl of **19** as either the acetate or levulinate ester then provided intermediates **20** and **21**. Exposure of TDS ethers **20** and **21** to hydrogen fluoride-pyridine in tetrahydrofuran at ambient temperature provided the desired lactols **18** and **22**, respectively, which were smoothly converted to the corresponding trichloracetimidate donors **23** and **24** in high yield with trichloroacetonitrile and catalytic 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU).

Disaccharide donor and reducing end iduronic acid synthesis.

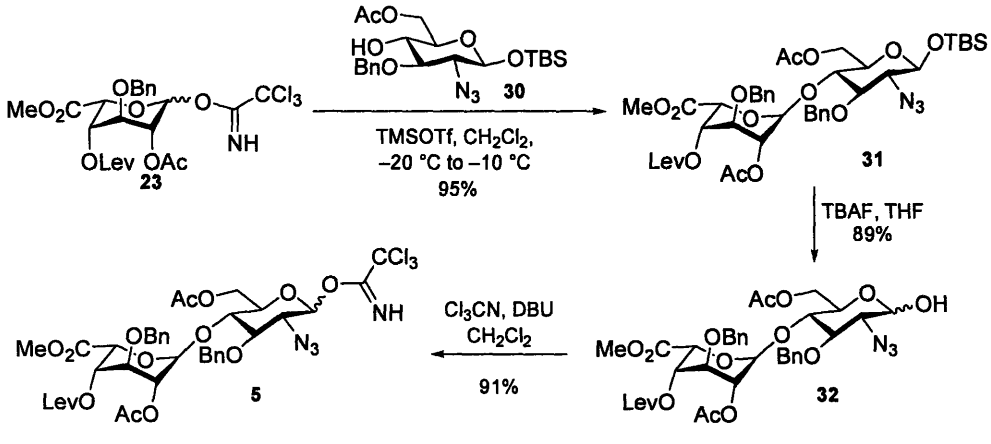
With the necessary iduronic acid donors in hand, construction of the disaccharide donor was undertaken. Glucosamine **30** was synthesized in nine steps on multi-gram scale from commercially available D-glucosamine **25** according to the Seeberger group protocol (Scheme 8).[30] Azide formation followed by peracetylation of the crude mixture produced



Scheme 8. Synthesis of glucosamine **30**.

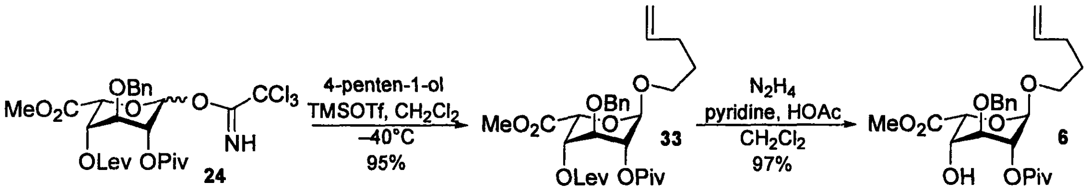
tetraacetate **26**. The anomeric acetate was cleaved selectively with ammonia and the resulting lactol protected as the TBS ether (**27**). Global deacetylation and protection as the cyclic benzylidene (**28**) allowed for selective benzylation of C4, which provided diol **29** on treatment with aqueous trifluoroacetic acid. Selective low-temperature acylation at C6 with acetyl chloride and collidine provided the desired acceptor **30** in excellent overall yield.

Preparation of the required trichloroacetimidate donor began with glycosylation of acceptor **30** with iduronic acid donor **23** in dichloromethane with catalytic trifluoromethanesulfonate (TMSOTf) from –20°C to –10°C to provide disaccharide **31** in excellent yield and selectivity (Scheme 9). Initial orthoester formation was observed



Scheme 9. Synthesis of disaccharide donor **5**.

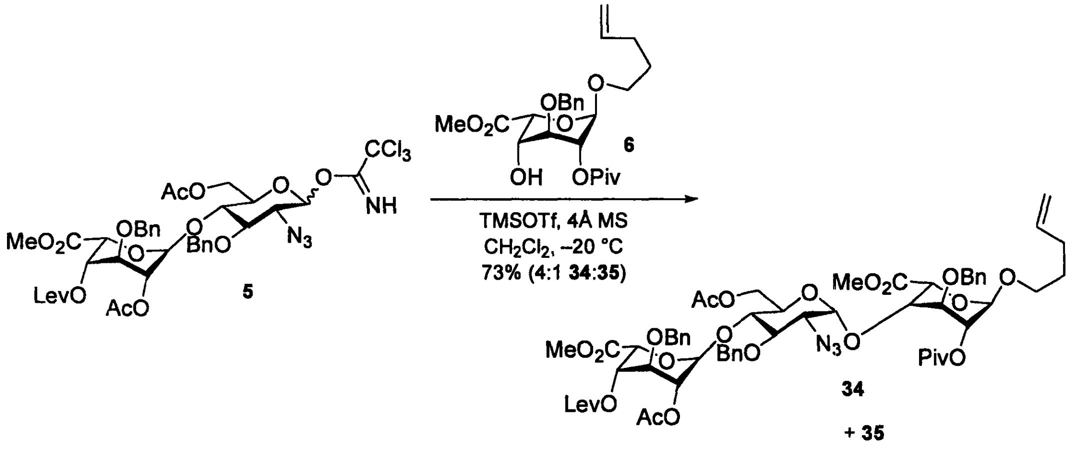
followed by rearrangement to the desired α-disaccharide on warming to –10°C. Silyl ether removal in buffered TBAF provided lactol **32**, which was readily converted to trichloroacetimidate **5**. In turn, the reducing end monosaccharide **6** was obtained via glycosylation of donor **24** with pentenyl alcohol, followed by levulinate ester cleavage with hydrazine in pyridine-acetic acid (Scheme 10).



Scheme 10. Synthesis of reducing end monosaccharide **6**.

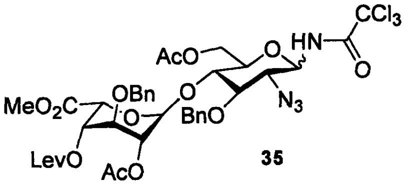
Pentasaccharide synthesis.

With access to gram quantities of our two building blocks **5** and **6**, our iterative strategy for heparin oligomer construction was implemented. Trisaccharide formation via glycosylation of acceptor **6** with donor **5** was undertaken (Scheme 11). Although activation with catalytic TMSOTf in methylene chloride at –20 °C over activated 4 Å molecular sieves produced trisaccharide **34** in good yield, an additional impurity **35** and several other minor side products were also observed. Impurity **35** was inseparable by standard chromatographic methods on silica gel, and its ^{1}H NMR spectrum was characterized by a pseudo triplet at 5.6 ppm and additional acetate, levulinate, and methyl ester-related peaks. Alternative coupling solvents such as diethyl ether and tetrahydrofuran produced lower product yields and failed



Scheme 11. Heparin trisaccharide synthesis.

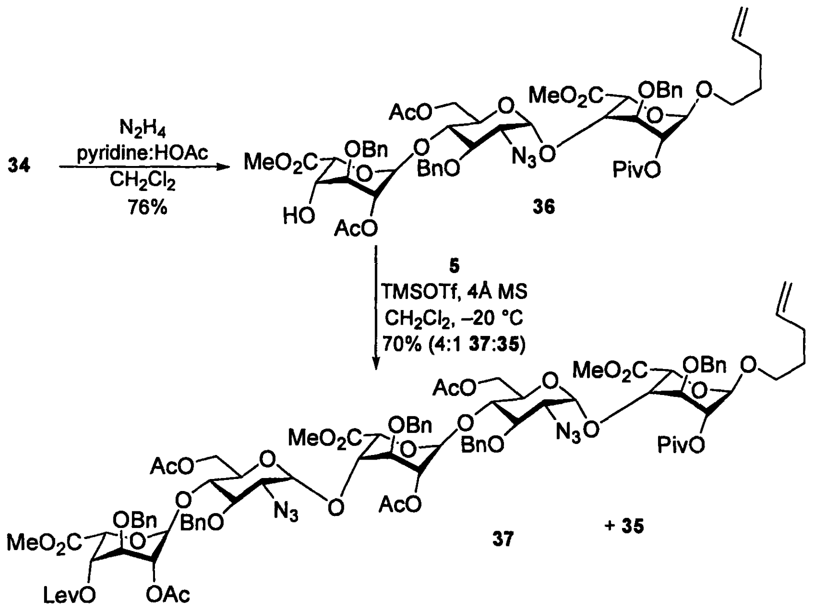
to eliminate this undesired side product. This impurity was also observed during pentasaccharide construction (*vide infra*) suggesting **35** was associated with the disaccharide donor common to both glycosylations. A sample enriched in by-product **35** was obtained via preparative high pressure liquid chromatographic purification of the trisaccharide glycosylation reaction mixture. ^{1}H NMR spectral analysis of this sample and associated mass spectral data identified **35** as the trichloroacetamide shown in Figure 6, probably obtained via reaction of the liberated trichloracetamide following donor activation.



35

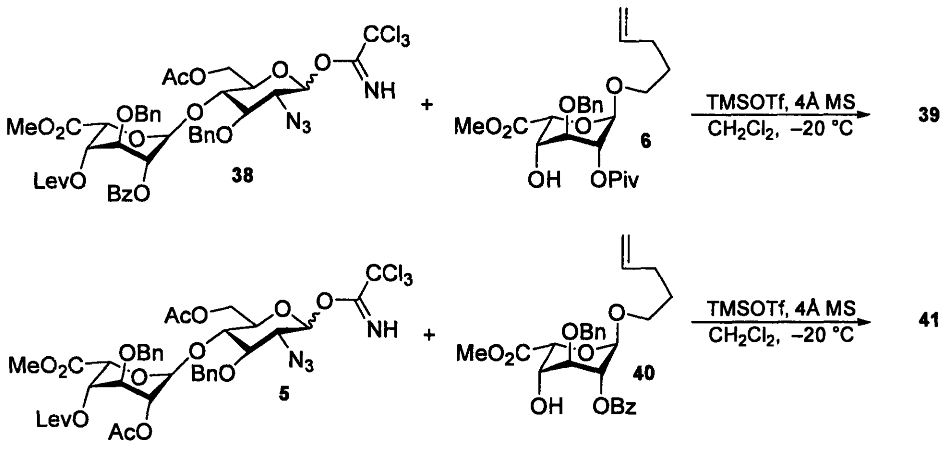
Figure 6. Trichloroacetamide side product **35** obtained on glycosylation with donor **5**.

Ultimately clean trisaccharide **34** was obtained on a small scale via size-exclusion chromatography. Removal of the C4-levulinate ester of **34** with hydrazine then provided trisaccharide acceptor **36** (Scheme 12). Iteration of the glycosylation step with this new acceptor **36** and disaccharide donor **5** then afforded pentasaccharide **37** along with trichloroacetamide **35** (Scheme 12). Although the major impurity resulting from glycosylation had been identified, close examination of the acetate region of the ^{1}H NMR spectra for both the tri- and pentasaccharides **34** and **37** between 2-3 ppm indicated apparent peak doubling; further analysis was hindered by the large number of resonances in the acetate region. In order to determine the nature of the doubling, disaccharide donor **38** and iduronic



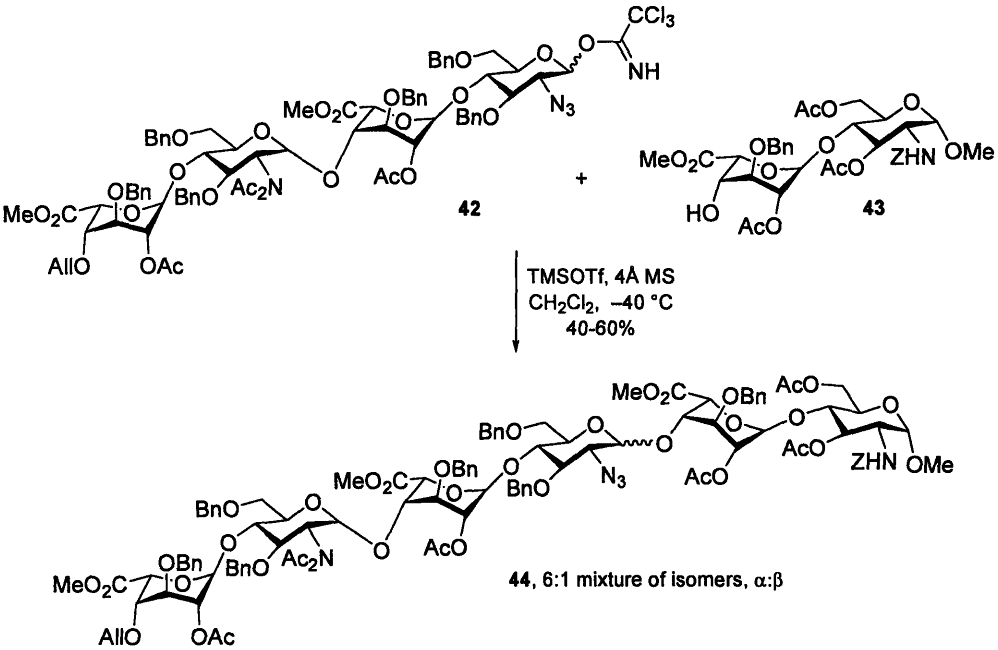
Scheme 12. Heparin pentasaccharide synthesis.

acid acceptor **40**, each containing a benzoate ester at the iduronic acid C2, were synthesized and coupled with acceptor **6** and donor **5**, respectively (Scheme 13). The downfield shift of



Scheme 13. Synthesis of benzoate-containing trisaccharides.

the benzoate methylene should allow more ready evaluation of the observed impurities. Assessment of the ^{1}H NMR spectra of both reaction mixtures indicated multiple products containing the benzoate methylene in the region from 7-8 ppm. Further analysis of mass spectral data of **39** and **41** suggests that these impurities are of the same molecular weight as the desired products and hence may represent the undesired ß-coupled products. While these findings contradict previously published results utilizing donor **5** and similar acceptors,[3,7,8] Greg Lohman in the Seeberger laboratory also observed the undesired β-coupled product for the glycosylation of tetrasaccharide trichloroacetimidate donor **42** and disaccharide acceptor **43** (Scheme 14).[39] An alternative explanation remains elusive.



Scheme 14. Previous work outlining an unexpected α,β-mixture for coupling of glucosamine donor **42** and uronic acid acceptor **43**.[39]

Early attempts to prepare heparin oligosaccharides via an automated solid-phase protocol were thwarted due to technical difficulties during the initial resin-loading cycle with iduronic acid donor **24**. The utility of the general strategy outlined in this chapter has been confirmed, however, by subsequent work by Christian Noti in the Seeberger lab utilizing a modified synthetic strategy with disaccharide donor **5** for the solution phase synthesis of a small library of heparin tetra- and hexasaccharides.[40] In addition, microarrays containing these heparin oligosaccharides were prepared.[41] Incubation of these carbohydrate microarrays with FGF-2 indicated that both the tetra-and hexasaccharide heparins were sufficient for binding. Ongoing work in the Seeberger laboratory is focused on the automation of these sequences for ready access to heparin libraries for biological testing.

Conclusion

A high-yielding method for the production of differentially protected iduronic acid trichloroacetimidates **23** and **24** via selective silylation was devised. Synthesis of disaccharide **31** and the corresponding trichloroacetimidate **5** was achieved in a manner amenable to large scale preparation. A method for the reduction and acetylation of azides was developed in solution with requirements for solid-phase application taken into account. Trisaccharide **34** and pentasaccharide **37** were synthesized using a solution-phase protocol designed for application to an automated synthesis on solid support. Early analysis of reaction side products suggested the possibililty of anomeric mixtures despite contradictory published work regarding donors such as **5**.

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Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 400 mesh, Silicycle). [1] Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and by exposure an aqueous solution of ceric ammonium molybdate (CAM), followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~20 Torr at 25–35 °C, then at ~1 Torr.

Materials. Commercial reagents and solvents were used as received with the following exceptions: dichloromethane, diethyl ether, and tetrahydrofuran were purchased from J.T. Baker (Cycletainer^{TM}) and were purified by the method of Grubbs et al. under positive argon pressure.[2] Trimethylsilyl trifluoromethanesulfonate (TMSOTf) purchased from Acros Chemicals. All solid-phase resin was purchased from Novabiochem and was prewashed six times with each of the following: tetrahydrofuran, tetrahydrofuran:methanol (95:5), and dichloromethane. Pyridine was distilled over calcium hydride immediately before use. *N*-Bromosuccinimide (NBS) was recrystallized from boiling water prior to use.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker-400 NMR spectrometer (400 MHz) or a Varian VXR-500 spectrometer (500 MHz). Chemical shifts are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent ($CHCl_3$: δ 7.27). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian 500 INOVA spectrometer or a Bruker 400 spectrometer with a Magnex Scientific superconducting magnet and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.2). Phosphorus-31 nuclear magnetic resonance spectra (^{31}P NMR) spectra were obtained on a Varian VXR-300 (120 MHz) or a Varian VXR-500 (200 MHz) and are reported in δ relative to H_3PO_4 (0.0 ppm) as an external reference. Infrared data were obtained with a Perkin-Elmer 2000 FTIR and are reported as follows: [frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 24 °C using a sodium lamp (589 λ). We are grateful to Dr. Li Li for obtaining the mass spectroscopic data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX 4.7 Tesler FTMS spectrometer using electronspray ion source (ESI) or electronspray (ES).

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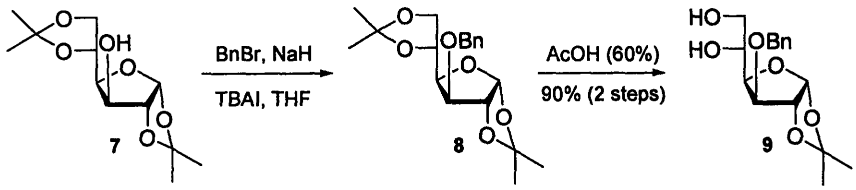

3-*O*-benzyl-1,2-isopropylidine-α-D-glucofuranoside (9):

Sodium hydride (60% in mineral oil, 3.1 g, 77 mmol) was added portionwise to a solution of commercially-available diacetone glucose **7** (16.6 g, 63.8 mmol) in tetrahydrofuran (160 mL). After evolution of hydrogen ceased, tetrabutylammonium iodide (160 mg, 0.43 mmol) and benzyl bromide (8 mL, 67.2 mmol) were added. After 14 h, excess hydride was quenched by slow addition of water followed by evaporation of the organic layer under reduced pressure. The aqueous phase was extracted with ethyl acetate (3 × 250 mL) and the combined organic phases were dried over anhydrous magnesium sulfate, were filtered through a silica plug, and were concentrated under reduced pressure.

Aqueous acetic acid (66%, 100 mL) was added to the resulting oil (**8**) and the solution was stirred vigorously at ambient temperature. After 16 h, the volatiles were evaporated under reduced pressure and the residue was partitioned between dichloromethane saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with dichloromethane (2 × 250 mL) and the combined organic phases were dried over anhydrous magnesium sulfate and were concentrated under reduced pressure. Purifiation of the resulting residue by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [90:10] to hexanes:ethyl acetate [1:1]) afforded **9** (17.8 g, 57.4 mmol, 90%). Spectra were consistent with previously reported data.[3,4]

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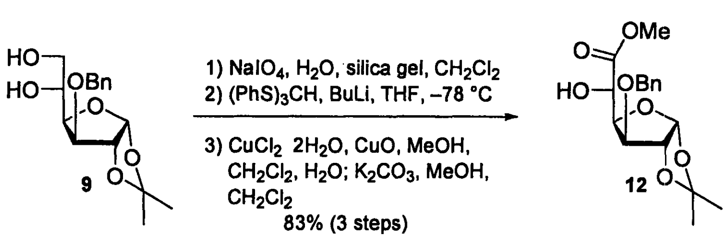

Methyl 3-*O*-benzyl-1,2-isopropylidene-α-L-idofuranosiduronate (12):

To a suspension of silica gel (38 g) in dichloromethane (320 mL) was added a solution of sodium metaperiodate (5.25 g, 24.5 mmol) in water (38 mL). The suspension was stirred vigorously for 30 minutes, followed by addition of a solution of **9** (5.87 g, 18.9 mmol) in dichloromethane (30 mL). The reaction was vigorously stirred for 1.5 h, followed by filtration through celite and concentration under reduced pressure. The residue (**10**) was dried under vacuum over P_2O_5 and used without further purification.

To a flame-dried three-necked flask was added tris(phenylthio)orthoformate (7.74 g, 22.7 mmol), followed by tetrahydrofuran (30 mL). The reaction vessel was cooled to –78 °C and ^{n}butyllithium (1.6 M in hexanes, 13.0 mL, 20.8 mmol) was added dropwise. The bright yellow solution was allowed to warm slowly to –50 °C over 1 h, then cooled to –78 °C and stirred for 30 minutes. A solution of the crude aldehyde **10** (5.26 g, 18.9 mmol) in tetrahydrofuran (20 mL) and added dropwise via cannula to the reaction flask at –78 °C over 15 min. After 1 h, the reaction solution was allowed to warm to room temperature over 30 min, when excess anion was quenched by addition of a saturated aqueous ammonium chloride solution (20 mL). The aqueous phase was extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were dried over anhydrous magnesium sulfate, were filtered, were concentrated under reduced pressure, and were dried under reduced pressure (~1 Torr). The crude thioorthoformate **11** was used without further purification.

To a suspension of copper chloride (1.38 g, 8.08 mmol) and copper oxide (0.263 g, 3.30 mmol) in methanol:water (12:1, 26 mL) was added a solution of crude **11** (1.08 g, 1.63 mmol) in dichloromethane (10 mL). After 5 min, the volatiles were removed under reduced pressure with gentle heat. The resulting green-white solid was dissolved in ethyl acetate (250 mL) and washed with aqueous hydrochloric acid (1 N, 2 × 24 mL), brine (2 × 50 mL), and saturated aqueous sodium bicarbonate solution (50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, were filtered, were concentrated under reduced pressure, and were dried under reduced pressure (~1 Torr) for 1 h. The resulting oil was dissolved in dichloromethane (23 mL) and methanol (4 mL) and potassium carbonate (60 mg, 0.43 mmol) was added. After 1.5 h, the reaction solution was filtered through celite and was concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [90:10] to hexanes:ethyl acetate [85:15] to hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [75:25] to hexanes:ethyl acetate [70:30]) afforded **12** as a light yellow oil (437 mg, 83%). Spectra were consistent with reported data.[5]

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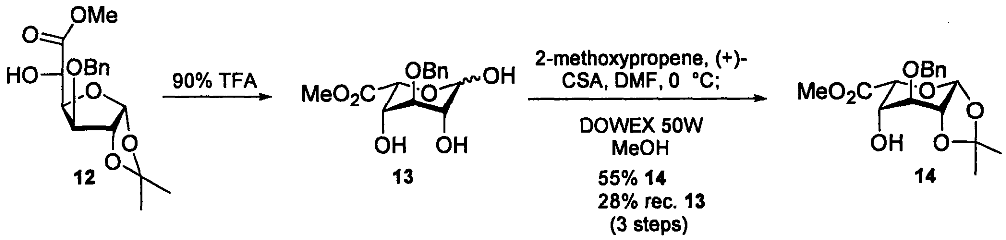

Methyl 3-*O*-benzyl-1,2-isopropylidene-α-L-idopyranosiduronate (14):

Compound **12** (7.52 g, 22.2 mmol) was dissolved in 90% aqueous trifluoroacetic acid (80 mL) and stirred at ambient temperature for 30 min. The reaction solvent was removed and the residue was azeotropically dried from toluene (5 × 30 mL), and dried under reduced pressure (~1 Torr) over phosphorous pentaoxide for 18 h. The resulting white solid **13** was dissolved in 2-methoxypropene (43 mL) and cooled to 0 °C. To the cooled reaction mixture was added a solution of (+)-camphorsulfonic acid (529 mg, 2.23 mmol) in dimethylformamide (4.3 mL). After 1 h, the reaction mixture was basified with triethylamine (5 mL) and allowed to warm to ambient temperature. The volatiles were removed under reduced pressure and the reaction mixture was dried under reduced pressure (~1 Torr) for 18 h. The crude product was dissolved in methanol (60 mL), and Dowex acidic resin (50 mg) was added. After 30 min, the resin was filtered off and rinsed with excess dichloromethane. The solution phase was concentrated under reduced pressure and purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [85:15] to hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [75:25] to hexanes:ethyl acetate [66:33] to hexanes:ethyl acetate [33:66] to ethyl acetate) to afford isopropylidene **14** (4.15 g, 55%) and recovered triol **13** (1.89 g, 28%). Spectra were in agreement with reported data.[6]

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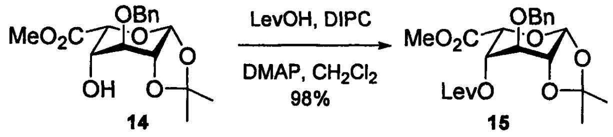
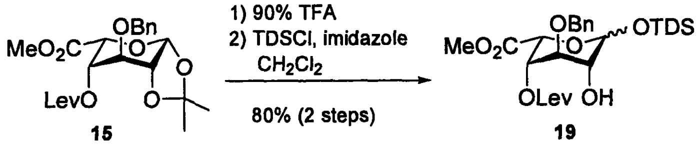


Methyl 3-*O*-benzyl-1,2-isopropylidene-4-O-levulinyl-α-L-idopyranosiduronate (15):

To a solution of **14** (2.69 g, 7.95 mmol) in dichloromethane (50 mL) at 0 °C were added levulinic acid (1.34 mL, 12.7 mmol), diisopropylcarbodiimide (DIPC, 1.87 mL, 11.9 mmol), and dimethylaminopyridine (1.56 g, 12.8 mmol), and light was excluded. The reaction was allowed to warm to ambient temperature and was stirred vigorously for 11 h. The reaction mixture was diluted with hexanes:ethyl acetate (1:1) and excess urea removed by filtration through a silica plug. The resulting solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [70:30] to hexanes:ethyl acetate [50:50]) to afford levulinate **15** as a yellow oil (3.44 g, 98%).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	7.39-7.33 (m, 5H), 5.37 (d, J = 2.61 Hz, 1H), 5.20 (m, 1H), 4.82 (d, J = 1.6 Hz, 1H), 4.68 (d, J = 1.6 Hz, 1H), 4.53 (d, J = 1.5 Hz, 1H), 4.08 (app-t, J = 2.1 Hz, 1H), 3.93 (m, 1H), 3.8 (s, 3H), 2.75 (m, 2H), 2.56 (t, J = 6.4 Hz, 2H), 2.18 (s, 3H), 1.62 (s, 3H), 1.38 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$, 20°C):	206.9, 172.5, 168.9, 137.7, 129.3, 128.9, 128.6, 112.7, 97.2, 75.8, 73.5, 72.8, 70.7, 67.8, 38.5, 30.4, 28.7, 28.6, 26.9.
FTIR (thin film) cm^{-1}:	2934, 1766, 1742, 1721
HRMS–EI (*m/z*):	calcd for $C_{22}H_{28}NaO_9$ $[M+Na]^+$: 459.1626, found: 459.1617.
$[\alpha]^{24}_D$:	–32.0 (c 1.00, CH$_2$Cl$_2$)



Methyl (dimethylthexylsilyl-3-*O*-benzyl-4-*O*-levulinoyl-L-idopyranosid)uronate (19):

Isopropylidene **15** (503 mg, 1.15 mmol) was dissolved in 90% aqueous trifluoroacetic acid (10 mL) and stirred at ambient temperature for 15 min. The volatiles were removed under reduced pressure and the resulting oil azeotropically dried from toluene (5 × 10 mL), and dried under reduced pressure (~1 Torr) for 18 h. The resulting brown oil was dissolved in dichloromethane (1.2 mL) and imidazole (304 mg, 4.4 mmol) was added. The solution was cooled to –20 °C and dimethylthexylsilyl chloride (0.290 mL, 1.5 mmol) was added. After 41 h, saturated aqueous sodium bicarbonate solution (1 mL) was added and the reaction mixture was allowed to warm to ambient temperature. The reaction mixture was partitioned between dichloromethane and brine, and the aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, were filtered, were concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [66:33] to hexanes:ethyl acetate [50:50]) to afford **19** as a clear oil (500 mg, 80%, α:β 1:2.5).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	(α isomer): 7.39-7.28 (m, 5H, ArH), 5.31 (s, 1H), 5.27 (app-t, *J* = 2.8 Hz, 1H), 4.97 (d, *J* = 2.4 Hz, 1H), 4.67 (dd, *J* = 11.6, 14.0 Hz, 2H), 3.78 (s, 3H), 3.76 (app-t, *J* = 2.4 Hz, 1H), 3.60 (br-d, *J* = 10.1 Hz, 1H), 2.73 (t, *J* = 10.0 Hz, 2H), 2.58-2.48 (m, 3H), 2.17 (s, 3H), 1.60-1.56 (m, 1H), 0.83-0.81 (m, 12H), 0.17 (s, 3H, SiC**H**$_3$), 0.14 (s, 3H, SiC**H**$_3$).
^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	(β isomer): 7.38-7.32 (m, 5H, ArH), 5.17 (s, 1H, C4-H), 5.04 (app-s, 1H, C1-H), 4.77 (d, *J* = 11.9 Hz, 1H, ArC**H**$_2$), 4.63 (d, *J* = 11.9 Hz, 1H, ArC**H**$_2$), 4.60 (app-s, 1H, C5-H), 3.92-3.91 (m,1H, C3-H), 3.80 (s, 3H, OC**H**$_3$), 3.58 (s, 1H, C2-H), 2.74-2.71 (m, 2H), 2.60-2.52 (m, 2H), 2.43 (d, *J* = 4.9 Hz, 1H, OH), 2.18 (s, 3H), 1.67-1.64 (m, 1H), 0.91-0.88 (m, 12H), 0.26 (s, 3H, SiC**H**$_3$), 0.19 (s, 3H, SiC**H**$_3$).
^{13}C NMR (125 MHz, CDCl$_3$, 20°C):	(α isomer): 206.4, 171.4, 169.4, 137.9, 128.4, 127.9, 127.7, 96.0, 75.0, 72.6, 69.3, 69.0, 66.5, 52.6, 38.0, 34.1, 29.8, 28.1, 25.0, 20.2, 20.1,18.6, 18.6, –2.3, –3.5.
^{13}C NMR (125 MHz, CDCl$_3$, 20°C):	(β isomer): 206.4, 171.9, 168.1, 137.5, 128.7, 128.3, 128.0, 94.3, 75.2, 72.9, 72.7, 68.8, 67.5,

52.6, 38.0, 34.2, 29.9, 28.3, 25.1, 20.4, 20.2, 18.8, 18.6, –1.7, –3.3.

FTIR (thin film) cm^{-1}: (α isomer): 1744 (s), 1719 (m), 1364 (w), 1153 (s), 1054 (s).

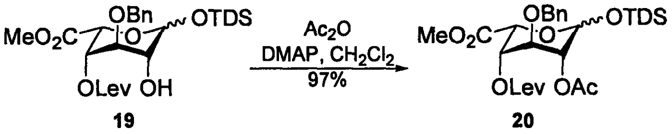
FTIR (thin film) cm^{-1}: (β isomer): 1768 (s), 1742 (s), 1721 (s), 1253 (m), 1154 (s), 1048 (s), 836 (m).

HRMS–EI (*m/z*): (α isomer): calcd for $C_{27}H_{42}NaO_9Si[M+Na]^+$: 561.2490,
found: 561.2488.

HRMS–EI (*m/z*): (β isomer): calcd for $C_{27}H_{42}NaO_9Si[M+Na]^+$: 561.2490,
found: 561.2473.

$[\alpha]^{24}_{D}$: (α isomer): –54.9 (c 2.35, CH_2Cl_2).

$[\alpha]^{24}_{D}$: (β isomer): +8.65 (c 1.90, CH_2Cl_2).



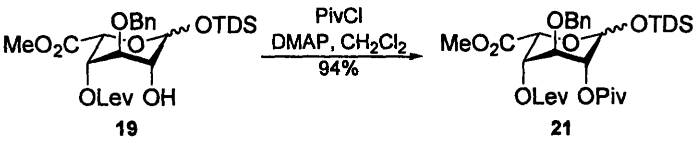
Methyl (dimethylthexylsilyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-L-idopyranosid)uronate (20):
To a solution of silyl ether **19** (345 mg, 0.641 mmol) in dichloromethane (6 mL) were added acetic anhydride (0.120 mL, 1.28 mmol) and dimethylaminopyridine (130 mg, 1.07 mmol). After 2 h, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [66:33]) to afford **20** as a clear oil (363 mg, 97%).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β, 1:2): 7.40-7.28 (m, 7.5H), 5.30 (s, 0.5H), 5.19 (app-s, 0.5H), 5.14 (app-s, 1H), 5.00-4.98 (m, 1.5H), 4.79-4.70 (m, 3.5H), 4.62 (d, J = 1.8 Hz, 1H), 3.87 (t, J = 2.8 Hz, 1H), 3.80-3.78 (m, 5H), 2.83-2.77 (m, 1.5H), 2.68-2.49 (m, 4.5H), 2.21-2.19 (m, 4.5H), 2.11-2.09 (m, 4.5H), 1.64-1.58 (m, 1.5H), 0.88-0.82 (m, 18H), 0.24-0.15 (m, 9H).

^{13}C NMR (125 MHz, CDCl$_3$, 20°C, mixture of diastereomers, α:β, 1:2): 206.3, 172.1, 172.0, 170.5, 170.2, 169.4, 168.1, 137.7, 137.3, 128.8, 128.5, 128.3, 128.0, 127.9, 127.7, 93.3, 93.2, 77.5, 74.2, 73.1, 72.9, 72.7, 72.6, 68.6, 68.3, 67.7, 67.4, 66.1, 52.7, 52.6, 37.8, 37.8, 34.2, 34.2, 30.0, 30.0, 28.1, 28.1, 25.1, 25.0, 21.2, 21.2, 20.4, 20.2, 20.1, 20.0, 18.8, 18.7, 18.7, 18.6, –1.7, –2.4, –3.4, –3.5.

FTIR (thin film) cm^{-1}: 1744 (s), 1720 (w), 1231 (br-m), 1156 (m), 1055 (m).

HRMS–EI (*m/z*): calcd for C$_{29}$H$_{44}$NaO$_{10}$Si [M+Na]$^+$: 603.2596, found: 603.2600.



Methyl (dimethylthexylsilyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-L-idopyranosid)uronate (21):

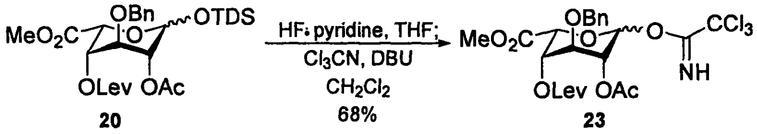
To a solution of silyl ether **19** (541 mg, 1.00 mmol) in dichloromethane (10 mL) were added pivaloyl chloride (0.250 mL, 2.01 mmol) and dimethylaminopyridine (227 mg, 1.86 mmol). After 48 h, the reaction mixture was diluted with ethyl acetate:hexanes (1:1) and filtered through a silica plug. The solution phase was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [50:50]) to afford **21** as a clear oil (588 mg, 94%).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C, mixture of diastereomers, α:β, 1:0.3): 7.39-7.32 (m, 6.5H), 5.26 (app-s, 0.3H), 5.24 (app-s, 0.3H), 5.07 (m, 1H), 4.99 (d, *J* = 2.0 Hz, 0.3H), 4.98-4.97 (m, 1H), 4.78-4.70 (m, 3.6H), 4.57 (app-s, 1H), 3.80-3.78 (m, 3.9H), 3.71 (app-s, 0.3H), 2.78-2.68 (m, 2.6H), 2.56-2.53 (m, 2.6H), 2.19 (app-s, 3.9H), 1.63-1.59 (m, 1.3H), 1.26-1.21 (m, 11.7H), 0.87-0.82 (m, 15.6H), 0.22-0.15 (m, 7.8H).

^{13}C NMR (125 MHz, $CDCl_3$, 20°C, mixture of diastereomers, α:β,): 206.2, 206.2, 177.8, 177.7, 172.2, 172.0, 169.3, 168.0, 137.7, 137.4, 128.7, 128.5, 128.3, 127.9, 127.7, 93.6, 93.4, 75.3, 73.7, 73.1, 72.8, 72.6, 68.5, 68.2, 67.3, 66.1, 52.7, 52.5, 39.1, 37.9, 37.9, 34.2, 34.1, 30.0, 29.9, 28.1, 28.1, 27.4, 27.3, 26.7, 25.1, 25.0, 20.2, 20.1, 18.7, 18.7, 18.7, 18.6, -1.7, -2.4, -3.4, -3.5.

FTIR (thin film) cm^{-1}: 1741 (s), 1368 (w), 1152 (s), 1053 (m), 837 (m).

HRMS–EI (*m/z*): calcd for $C_{32}H_{50}NaO_{10}Si$ $[M+Na]^+$: 645.3065, found: 645.3080.



Methyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-L-idopyranosiduronate trichloroacetimidate (23): To a solution of silyl ether **20** (890 mg, 1.53 mmol) in tetrahydrofuran (15 mL) was addded HF•pyridine (70% solution, 1.0 mL). After 28 h, the reaction solution was diluted with water and extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [65:35[to hexanes:ethyl acetate [40:60]) provided the deprotected lactol **18**. To a solution of this lactol in dichloromethane and trichloroacetonitrile (1:1, 10 mL) at $0^{\circ}C$ was added DBU (5 µL) and the reaction mixture was allowed to warm over 30 min. The volatiles were removed under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [50:50]) to afford trichloroacetimidate **23** as a white foam (662 mg, 74%). Spectra corresponded to published data.[7]

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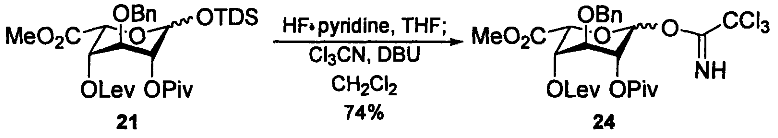
[7] Tabeur, C.; Machetto, F.; Mallet, J.; Duchaussoy, P.; Petitou, M., Sinaÿ, P. *Carbohydr. Res.* **1996**, *281*, 253.



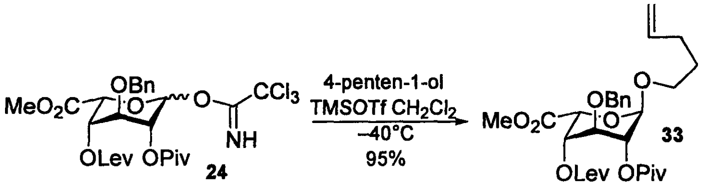
Methyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-L-idopyranosiduronate trichloroacetimidate (24):

To a solution of silyl ether **21** (588 mg, 0.94 mmol) in tetrahydrofuran (8 mL) was added HF•pyridine (70% solution, 0.7 mL). After 28 h, the reaction solution was diluted with water, was extracted with dichloromethane (3 × 40 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel: hexanes:ethyl acetate [50:50]) provided the deprotected lactol **22**. To a solution of this lactol in dichloromethane and trichloroacetonitrile (1:1, 7 mL) at 0 °C was added DBU (4 μL) and the reaction was allowed to warm to ambient temperature over 30 min. The volatiles were removed under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: hexanes:ethyl acetate [65:35]) to afford trichloroacetimidate **24** as a white foam (398 mg, 68%, equal mixture of diastereomers, α:β).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C, equal mixture of diastereomers, α:β): 8.72 (s, 1H), 8.70 (s, 1H), 7.38-7.29 (m, 10H), 6.38 (s, 1H), 6.23 (app-s, 1H), 5.32 (s, 1H), 5.28-5.26 (m, 2H), 5.13 (s, 1H), 5.04 (s, 1H), 4.84-4.72 (m, 5H), 3.94 (t, J = 3.0 Hz, 1H), 3.83-3.80 (m, 7H), 2.79-2.68 (m, 4H), 2.57-2.53 (m, 4H), 2.19 (app-s, 6H), 1.25-1.23 (m, 18H).

^{13}C NMR (125 MHz, $CDCl_3$, 20°C, equal mixture of diastereomers, α:β): 206.0, 177.5, 177.2, 171.9, 171.8, 168.1, 167.2, 160.6, 160.0, 137.2, 137.0, 128.7, 128.4, 128.3, 127.9, 127.9, 127.7, 95.1, 94.3, 74.6, 73.3, 73.2, 72.6, 72.3, 67.8, 67.5, 67.5, 65.8, 65.0, 52.8, 52.7, 39.1, 38.9, 37.8, 29.8, 28.0, 27.3, 27.1.

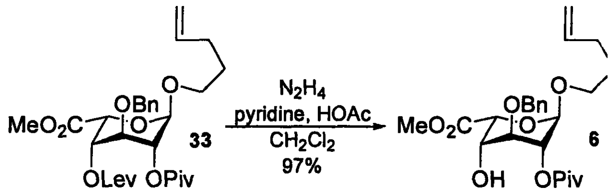
FTIR (thin film) cm^{-1}:	1769 (w), 1741 (s), 1722 (m), 1677 (w), 1144 (s), 1064 (s).
HRMS–EI (*m/z*):	calcd for $C_{26}H_{32}Cl_3NNaO_{10}Si$ $[M+Na]^+$: 646.0984, found: 646.0996.



n-Pentenyl methyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-L-idopyranosiduronate (33):

Iduronic trichloroacetimidate **24** (398 mg, 0.637 mmol, 1 equiv) was azeotropically dried from toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 3 h. To a solution of this donor in dichloromethane (5 mL) at –25 °C was added 4-pentenol (72 μL, 0.70 mmol, 1.1 equiv), followed by trimethylsilyl trifluoromethanesulfonate (TMSOTf, 12 μL, 0.1 equiv). After 10 min, excess acid was quenched at low temperature by addition of triethylamine (100 μL) and the reaction solution was allowed to warm to ambient temperature. The reaction solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [60:40]) to afford **33** as a clear oil (333 mg, 95%).

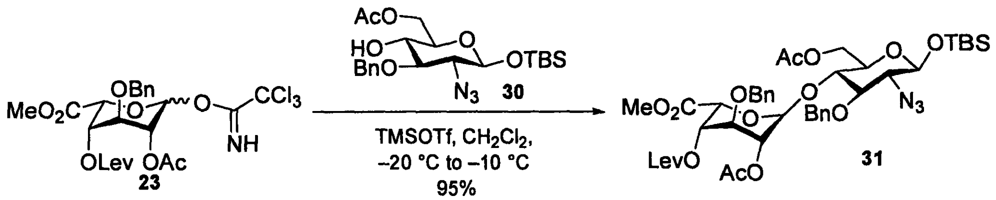
^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	7.38-7.28 (m, 5H), 5.81-5.76 (m, 1H), 5.23 (t, *J* = 4.5 Hz, 1H), 5.00 (dd, *J* = 3.5, 1.5 Hz, 1H), 4.97-4.93 (m, 2H), 4.92-4.91 (m, 1H), 4.88 (d, *J* = 2.0 Hz, 1H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 3.79 (s, 3H), 3.77-3.74 (m, 1H), 3.71 (dd, *J* = 4.0, 2.0 Hz, 1H), 3.52-3.49 (m, 1H), 2.77-2.70 (m, 2H), 2.55-2.52 (m, 2H), 2.18 (s, 3H), 2.18-2.11 (m, 2H), 1.73-1.67 (m, 2H), 1.20 (s, 9H).
^{13}C NMR (125 MHz, CDCl$_3$, 20°C):	206.2, 177.5, 171.9, 169.3, 138.2, 137.8, 128.5, 127.9, 127.7, 115.1, 98.7, 77.5, 77.2, 77.0, 73.3, 72.3, 68.3, 68.2, 66.7, 66.1, 52.7, 38.9, 37.9, 30.4, 29.9, 28.7, 28.1, 27.2.
FTIR (thin film) cm^{-1}:	2957 (w), 1741 (s), 1366 (w), 1149 (s), 1055 (m).
HRMS–EI (*m/z*):	calcd for $C_{29}H_{40}NaO_{10}$ [M+Na]$^+$: 571.2514, found: 571.2501.



n-Pentenyl methyl 3-*O*-benzyl-2-*O*-pivaloyl-L-idopyranosiduronate (6):

To a solution of levulinate ester **33** (333 mg, 0.606 mmol, 1 equiv) in dichloromethane (6 mL) was added a solution of hydrazine in pyridine:acetic acid (0.5 M, 3:2, 2.5 mL, 2 equiv). After 1 h the reaction mixture was diluted with acetone and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [70:30]) to afford acceptor **6** as a yellow oil (266 mg, 97%).

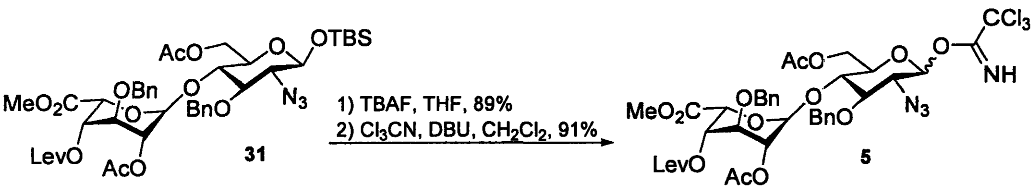
^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	7.37-7.24 (m, 5H), 5.84-5.71 (m, 1H), 5.01-4.99 (m, 1H), 4.97-4.93 (m, 2H), 4.86 (d, *J* = 1.8 Hz, 1H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.05 (d, *J* = 10.2 Hz, 1H), 3.82 (s, 3H), 3.81-3.74 (m, 1H), 3.70-3.68 (m, 1H), 3.50 (dt, *J* = 9.6, 7.8 Hz, 1H), 2.67 (d, *J* = 12.0 Hz, 1H), 2.13 (dd, *J* = 13.5, 6.9 Hz, 1H), 1.77-1.67 (m, 2H), 1.23 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, 20°C):	177.4, 170.7, 138.6, 138.3, 129.1, 128.5, 128.3, 115.7, 99.5, 74.9, 72.4, 68.9, 68.8, 68.2, 67.1, 53.1, 39.5, 30.9, 30.4, 29.3, 27.8, 1.7.
FTIR (thin film) cm^{-1}:	3582 (br-w), 2918 (s), 1739 (s), 1141 (s), 1210 (w), 1049 (s)
HRMS–EI (*m/z*):	calcd for $C_{24}H_{34}NaO_8$ $[M + Na]^+$: 473.2146, found: 473.2146.



tert-Butyldimethylsilyl (Methyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosiduronate)-(1→4)-2-azido-6-*O*-acetyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside (31):

Trichloroacetimidate **23** (1.390 g, 2.39 mmol, 1.3 equiv) and glucosamine **30** (832 mg, 1.84 mmol, 1 equiv) were combined and azeotropically dried from toluene (3 × 20 mL) and dried under reduced pressure (~1 Torr) over phosphorous pentaoxide for 18 h. To a solution of this mixture in dichloromethane (25 mL) at –25 °C was added trimethylsilyl trifluoromethanesulfonate (TMSOTf, 44 μL, 0.24 mmol, 0.1 equiv), and the reaction mixture was allowed to warm to –10 °C over 30 min. Excess triflic acid was quenched by addition of triethylamine (200 μL), and the reaction was allowed to warm to ambient temperature. The reaction solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [50:50]) to afford disaccharide **31** as a clear oil (1.548 g, 95%).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	7.39-7.21 (m, 10H), 5.10 (s, 1H), 5.08 (t, J = 3.0 Hz, 1H), 4.99 (d, J = 2.5 Hz, 1H), 4.85 (s, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.53 (d, J = 8.0 Hz, 1H), 4.52 (dd, J = 12.0, 2.5 Hz, 1H), 4.14 (dd, J = 11.5, 5.5 Hz, 1H), 3.85 (t, J = 9.5 Hz, 1H), 3.80 (t, J = 3.0 Hz, 1H), 3.50-3.47 (m, 1H), 3.44 (s, 3H), 3.36 (dd, J = 10.0, 7.5 Hz, 1H), 3.23 (t, J = 9.5 Hz, 1H), 2.81-2.74 (m, 1H), 2.67-2.61 (m, 1H), 2.58-2.52 (m, 1H), 2.49-2.43 (m, 1H), 2.17 (s, 3H), 2.08 (s, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, 20°C):	206.2, 171.9, 170.7, 170.1, 168.7, 138.1, 137.5, 128.6, 128.4, 128.3, 128.1, 127.6, 97.7, 97.4, 81.0, 74.8, 74.7, 73.6, 72.8, 7.27, 68.9, 68.1, 67.3, 66.8, 62.5, 52.3, 37.7, 30.0, 28.0, 25.8, 21.1, 21.1, 18.2, –4.2, –5.0.
FTIR (thin film) cm^{-1}:	2929 (m), 2111 (s), 1743 (s), 1367 (m), 1260 (s), 1231 (s), 1158 (m), 1107 (s), 1071 (s), 1043 (s). 840 (m).
HRMS–EI (*m/z*):	calcd for $C_{42}H_{57}N_3O_{15}NaSi$ $[M+Na]^+$: 894.3400, found: 894.3462.

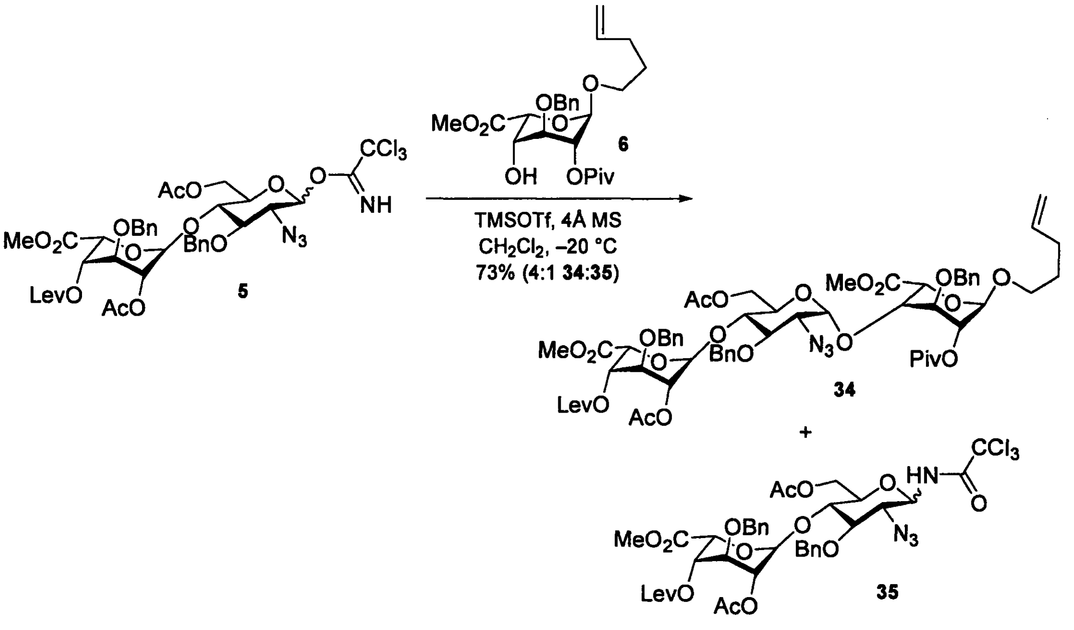


Methyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosiduronate-(1→4)-2-azido-6-*O*-acetyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside trichloroacetimidate (5):

To a solution of silyl ether **31** (1.663 g, 1.87 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added acetic acid, followed by a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 3.71 mL, 3.7 mmol, 2 equiv). After 3 h, the reaction solution was diluted with ethyl acetate (150 mL) and washed sequentially with aqueous sodium bicarbonate solution (1%) and brine. The combined aqueous layers were extracted with ethyl acetate (2 × 75 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, were concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [65:35] to hexanes:ethyl acetate [25:75]) to afford lactol **32** as a yellow foam (1.256 g, 89%).

To a solution of lactol **32** (88 mg, 0.12 mmol, 1 equiv) in dichloromethane: trichloroacetonitrile (1:1, 3 mL) at 0 °C was added DBU (3 drops). After 10 min, the reaction solution was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [50:50]) to afford trichlroacetimidate **5** (95 mg, 91%).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C):	8.77 (s, 1H), 7.43-7.19 (m, 10H, ArH), 6.42 (d, *J* = 3.7 Hz, 1H), 5.13 (s, 1H), 5.09-5.06 (m, 1H), 4.95-4.90 (m, 2H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.70 (d, *J* = 11 Hz, 1H), 4.67 (d, *J* = 11.0 Hz, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.49 (app-d, *J* = 12.2 Hz, 1H), 4.22 (dd, *J* = 12.5, 2.8 Hz, 1H), 4.07-4.04 (m, 1H), 3.87-3.81 (m, 2H), 3.73 (dd, *J* = 10.4, 3.7 Hz, 1H), 3.46 (s, 3H, OC**H**$_3$), 2.77 (ddd, *J* = 18.3, 8.2, 5.2 Hz, 1H), 2.65 (ddd, *J* = 18.6, 6.7, 4.9 Hz, 1H), 2.55 (ddd, *J* = 17.4, 8.2, 4.9 Hz, 1H), 2.47 (ddd, *J* = 17.4, 6.7, 5.2 Hz, 1H), 2.18 (s, 3H), 2.09 (s, 3H), 2.09 (s, 3H).



n-Pentenyl (Methyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosiduronate)-(1→4)-(2-azido-6-*O*-acetyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside)-(1→4) methyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-L-idopyranosiduronate (34):

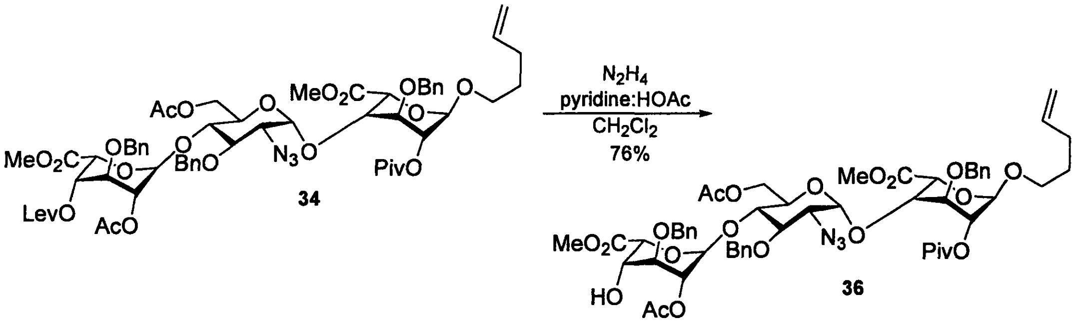
Trichloroacetimidate **5** (125 mg, 0.139 mmol, 1.3 equiv) and iduronic acid **6** (48.9 mg, 0.109 mmol, 1 equiv) were combined and azeotropically dried from toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 18 h. To a solution of this mixture in dichloromethane (1 mL) was added freshly activated 4 Å molecular sieves (100 mg) and the suspension was stirred vigorously. After 30 min, the reaction mixture was cooled to –20 °C. Trimethylsilyl trifluoromethane sulfonate (2.5 μL, 0.013 mmol, 0.1 equiv) was added and the reaction allowed to warm to –10 °C over 30 min. Excess acid was quenched by addition of triethylamine (50 μL) and the reaction was allowed to warm to ambient temperature. The reaction solution was filtered through celite to remove the molecular sieves and the resulting solution was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [80:20] to hexanes:ethyl acetate [50:50]) to afford trisaccharide **34** as a light yellow oil along with trichloroacetamide impurity **35** (93.7 mg, 73%, **34**:**35**, 4:1).

^{1}H NMR (500 MHz, $CDCl_3$, 20°C):	**34**: 7.39-7.24 (m, 15H), 5.82-5.76 (m, 1H), 5.16 (d, *J* = 3 Hz, 1H), 5.10 (t, *J* = 3.5 Hz, 1H), 5.04 (d, *J* = 3.5 Hz, 1H), 5.02 (d, *J* = 1.5 Hz, 1H), 4.99-4.94 (m, 2H), 4.87 (dd, *J* = 7.0, 3.5 Hz, 2H), 4.80 (dd, *J* = 10.5, 5.5 Hz, 2H), 4.75 (d, *J* = 4.0 Hz, 1H), 4.73 (d, *J* = 2.0 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 10.5 Hz, 1H), 4.47 (d, *J* = 12.5 Hz, 1H), 4.22 (dd, *J* = 12.5, 3.0 Hz, 1H), 4.12 (t, *J* = 4.5 Hz, 1H), 3.95-3.92 (m, 3H), 3.81-3.71 (m, 3H), 3.73 (s, 3H, OCH_3), 3.54-3.48 (m, 1H), 3.50 (s, 3H, OCH_3), 3.33 (dd, *J* = 10, 3.5 Hz, 1H), 2.78-2.71 (m, 1H), 2.70-2.63

(m, 1H), 2.56-2.44 (m, 2H), 2.18 (s, 3H), 2.13-2.03 (m, 2H), 2.10 (s, 3H), 2.08 (s, 3H), 1.72-1.66 (m, 2H), 1.21 (s, 9H).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C): **35**: 7.44-7.21 (m, 9H), 7.07-7.04 (m, 1H), 5.63 (app-t, *J* = 5.8 Hz, 1H), 5.18-5.06 (m, 2H), 4.91 (app-t, *J* = 2.7 Hz, 1H), 4.87 (d, *J* = 3.3 Hz, 1H), 4.86-4.84 (m, 1H), 4.82-4.79 (m, 1H), 4.78-4.65 (m, 1H), 4.55 (app-d, *J* = 3.2 Hz, 1H), 4.47-4.38 (m, 1H), 4.29-4.10 (m, 1H), 4.03-3.98 (m, 1H), 3.95-3.91 (m, 1H), 3.84-3.73 (m, 1H), 3.72-3.69 (m, 1H), 3.59 (s, 3H), 3.60-3.54 (m, 1H), 2.84-2.43 (m, 4H), 2.18 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H).

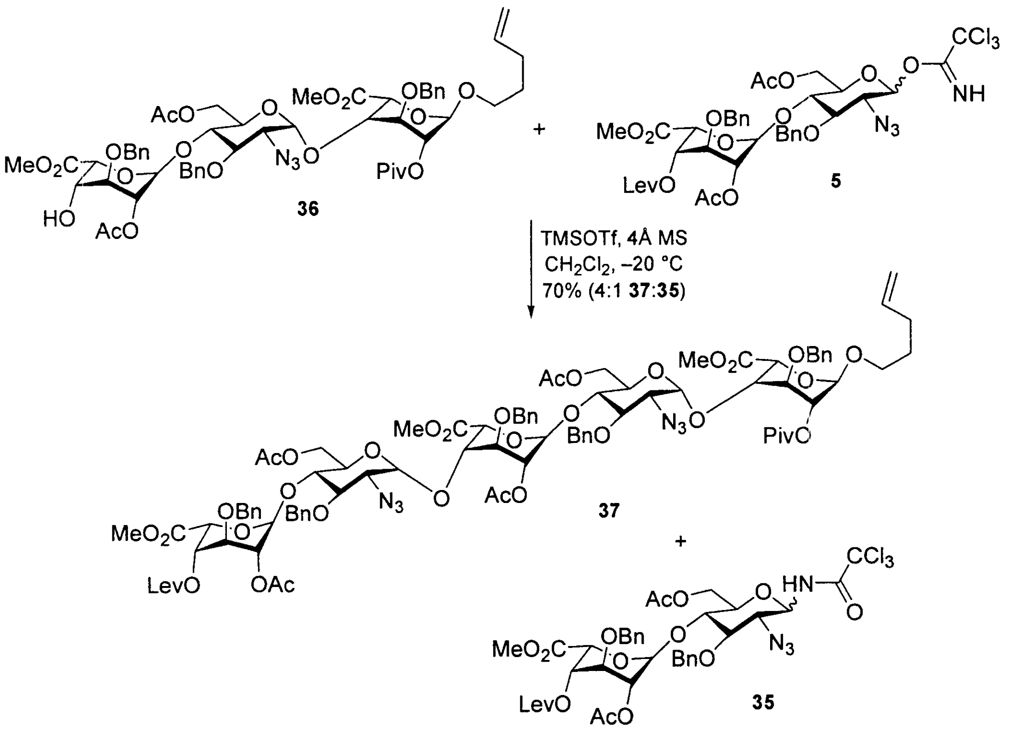
HRMS–EI (*m/z*): calcd for **34** C$_{60}$H$_{75}$N$_3$NaO$_{22}$ [M+H]$^+$: 1212.4734,
found: 1212.4766.



n-Pentenyl (methyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosiduronate)-(1→4)-(2-azido-6-*O*-acetyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside)-(1→4) methyl 3-*O*-benzyl-2-*O*-pivaloyl-L-idopyranosiduronate (36):

To a solution of trisaccharide **34** (93.7 mg, 0.078 mmol, 1 equiv) in dichloromethane (500 μL) was added a solution of hydrazine in pyridine:acetic acid (0.5 M, 3:2, 230 μL, 0.117 mmol, 1.5 equiv). After 1.5 h, excess hydrazine was quenched by addition of acetone (1 mL) and the reaction solution was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [60:40] to hexanes:ethyl acetate [50:50]) to afford acceptor **36** as a clear oil (64.4 mg, 76%).

^{1}H NMR (500 MHz, CDCl$_3$, 20°C): 7.42-7.25 (m, 15H, ArH), 5.84-5.75 (m, 1H), 5.10-4.61 (m, 15H), 4.49-4.43 (m, 2H), 4.24 (dd, *J* = 12.2, 3.4 Hz, 1H), 4.12 (app-t, *J* = 4.3 Hz, 1H), 4.00-3.91 (m, 3H), 3.90-3.82 (m, 1H), 3.80-3.69 (m, 2H), 3.73 (s, 3H), 3.55 (d, *J* = 4.0 Hz, 1H), 3.52 (s, 3H), 3.51-3.48 (m, 1H), 3.33 (dd, *J* = 10.4, 3.7 Hz, 1H), 2.62 (br-s, 1H, OH), 2.15-2.07 (m, 8H), 1.74-1.66 (m, 2H), 1.22 (s, 9H).



n-Pentenyl (Methyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosiduronate)-(1→4)-(2-azido-6-*O*-acetyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside)-(1→4) (Methyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-levulinoyl-α-L-idopyranosiduronate)-(1→4)-(2-azido-6-*O*-acetyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside)-(1→4) methyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-L-idopyranosiduronate (37):

Trichloroacetimidate **5** (70.2 mg, 0.078 mmol, 1.3 equiv) and trisaccharide **36** (64.4 mg, 0.059 mmol, 1 equiv) were combined and azeotropically dried from toluene (3 × 5 mL) and dried under reduced pressure (~1 Torr) for 18 h. To a solution of this mixture in dichloromethane (1 mL) was added freshly activated 4 Å molecular sieves (70 mg) and the suspension was stirred vigorously. After 30 min, the reaction mixture was cooled to –20 °C. Trimethylsilyl trifluoromethane sulfonate (5.0 μL, 0.027 mmol, 0.45 equiv). After 30 min, excess acid was quenched by addition of triethylamine (50 μL) and the reaction was allowed to warm to ambient temperature. The reaction solution was filtered through celite to remove the molecular sieves and the resulting solution was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel: eluent: hexanes:ethyl acetate [75:25] to hexanes:ethyl acetate [66:34] to hexanes:ethyl acetate [50:50]) to afford pentasaccharide **37** as a white foam along with trichloroacetamide **35** (75.8 mg, 70% (**37**:**35**, 4:1)).

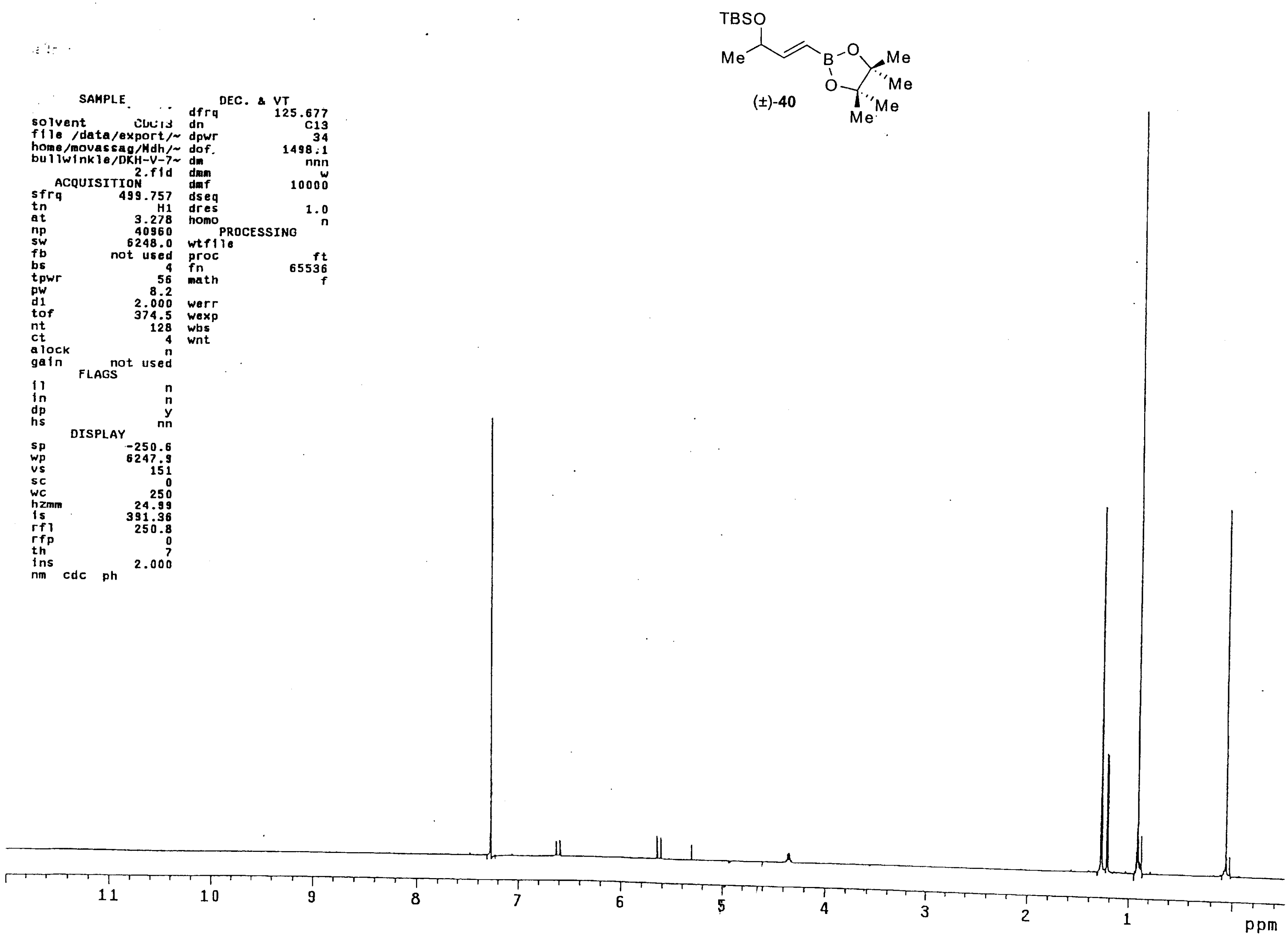
^{1}H NMR (500 MHz, CDCl$_3$, 20°C): 7.42-7.23 (m, 25H), 5.84-5.75 (m, 1H), 5.31 (d, J = 4.7 Hz, 1H), 5.16 (d, J = 2.9 Hz, 1H), 5.10-5.07 (m, 1H), 5.06-4.99 (m, 3H), 4.98-4.95 (m, 4H), 4.94-4.89 (m, 1H), 4.88-4.84 (m, 4H), 4.81-4.66 (m, 8H), 4.64-4.59 (m, 1H), 4.52-4.39 (m, 2H), 4.23 (dd, J = 12.6, 3.3 Hz, 1H), 4.19 (dd, J = 12.6, 2.9 Hz, 1H), 4.11 (t, J = 4.4 Hz, 1H), 4.02-3.99 (m, 1H), 3.97-3.79 (m, 5H), 3.76 (s, 3H, OC**H**$_3$), 3.63 (dd, *J* = 10.2, 9.1 Hz, 1H), 3.50 (s, 3H, OC**H**$_3$), 3.48 (s, 3H, OC**H**$_3$), 3.34-3.28 (m, 3H), 2.80-2.62 (m, 3H), 2.57-2.43 (m, 2H), 2.18 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 1.73-1.66 (m, 1H), 1.35-1.18 (m, 12H),

HRMS–EI (*m/z*): calcd for $C_{91}H_{110}N_6NaO_{34}$ $[M+H]^+$: 1853.6955, found: 1853.6989.

Appendix A

Spectra for Chapter 1

Thesis Advisor: Mohammad Movassaghi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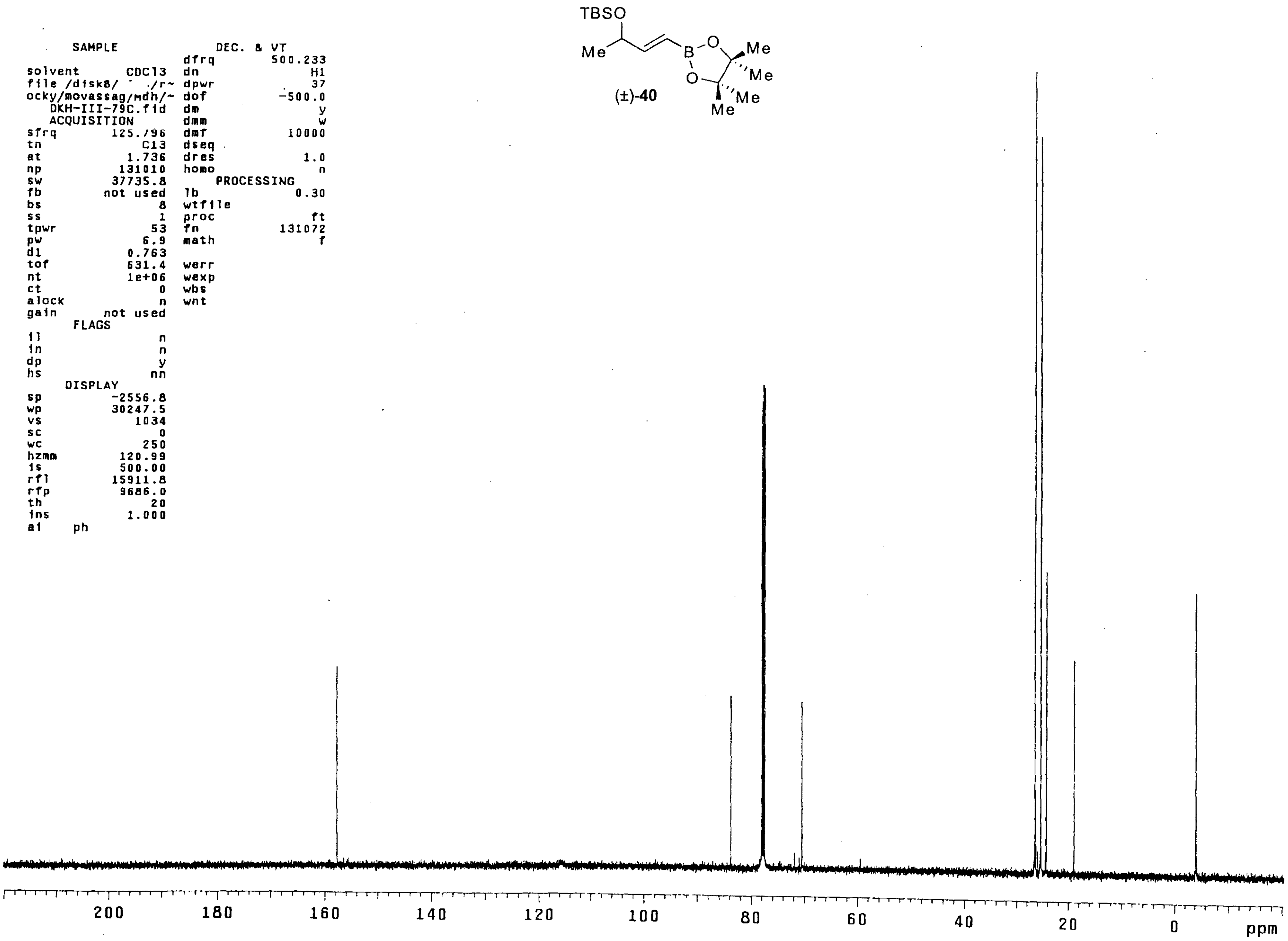

(±)-40

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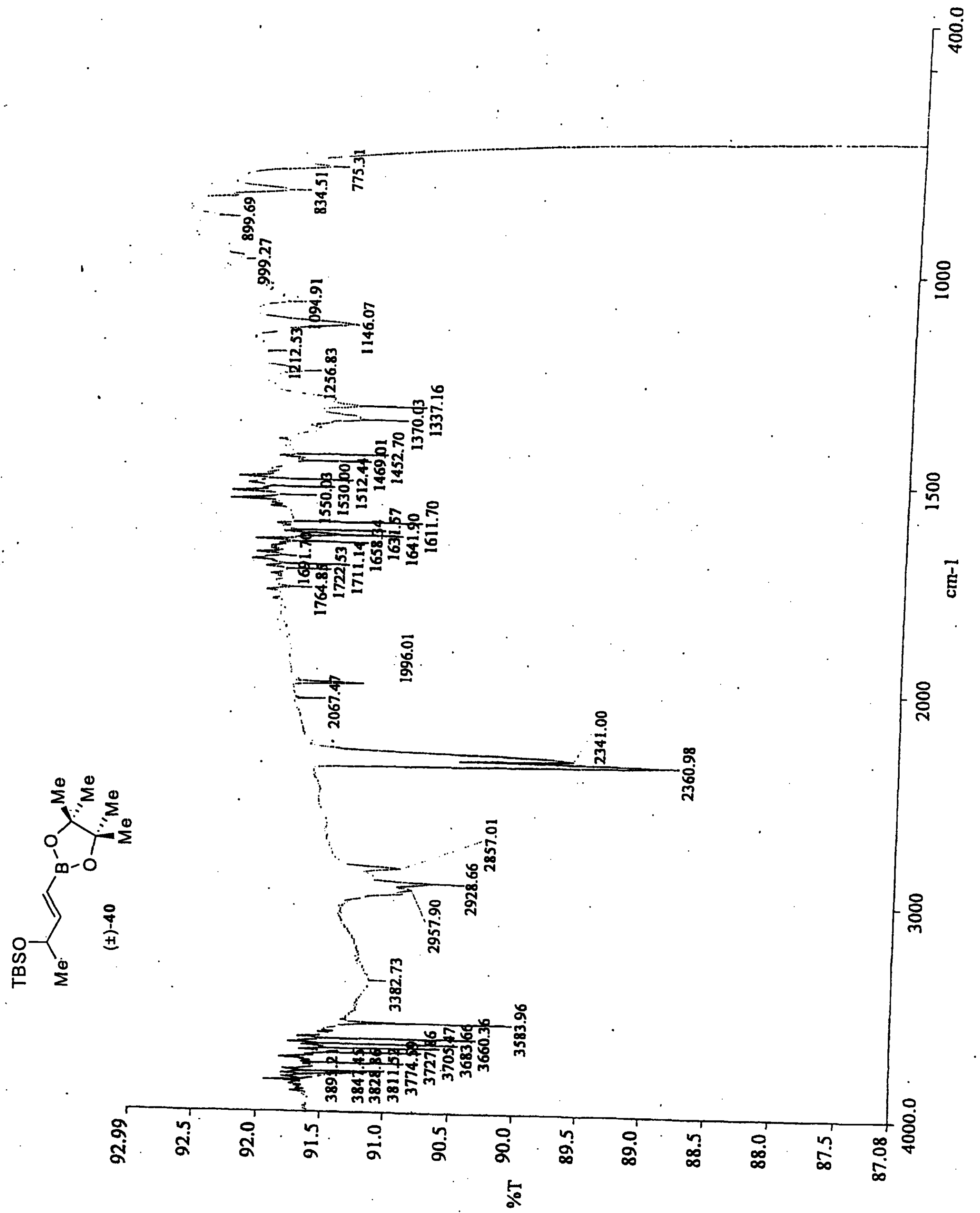
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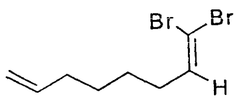

36

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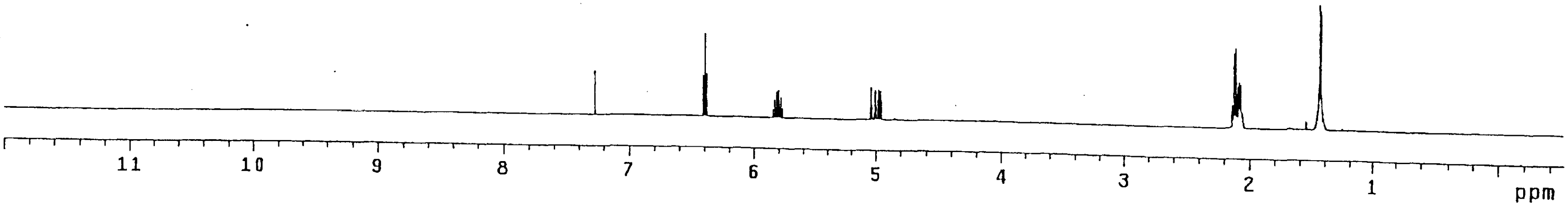

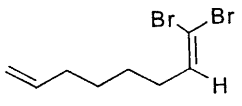

36

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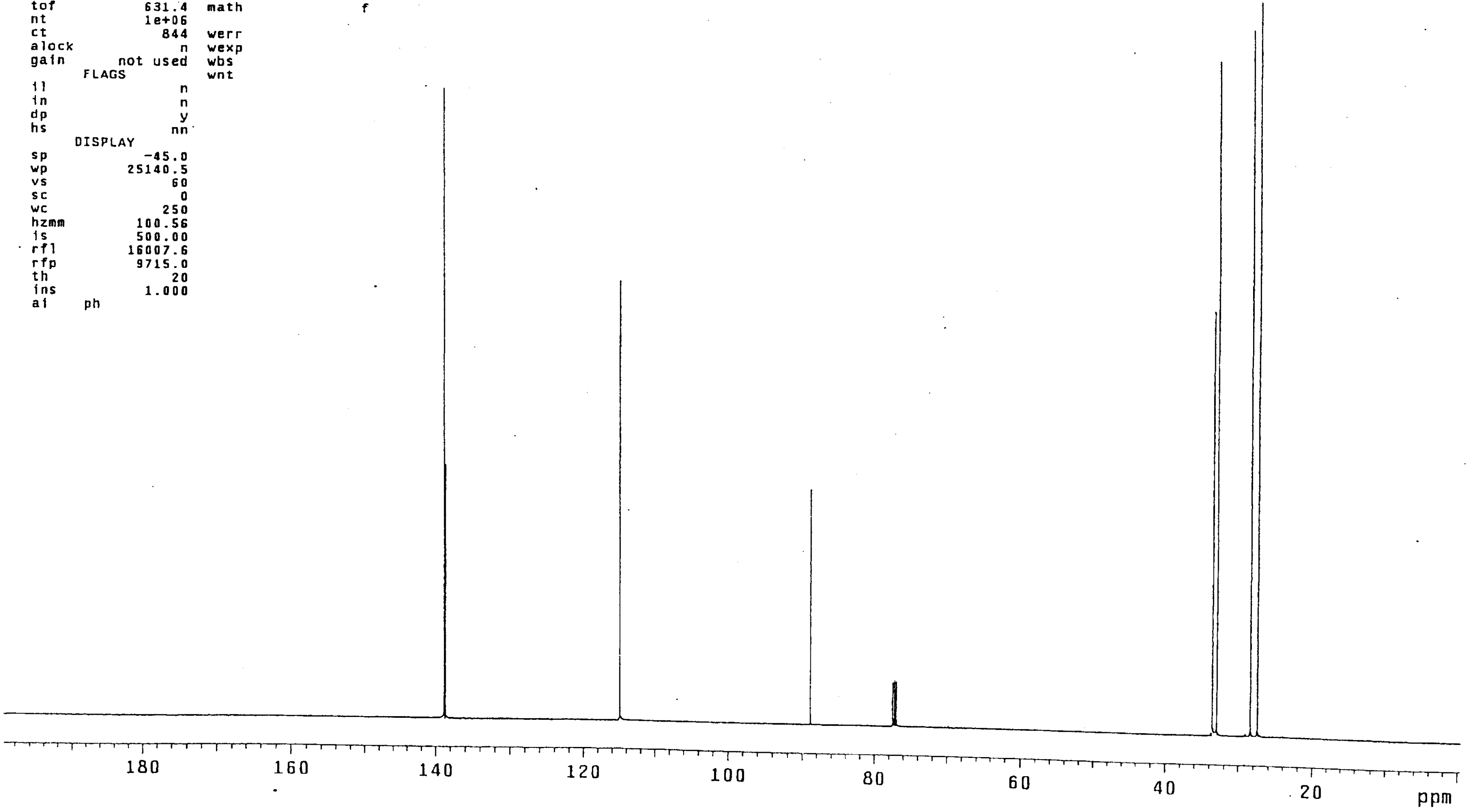

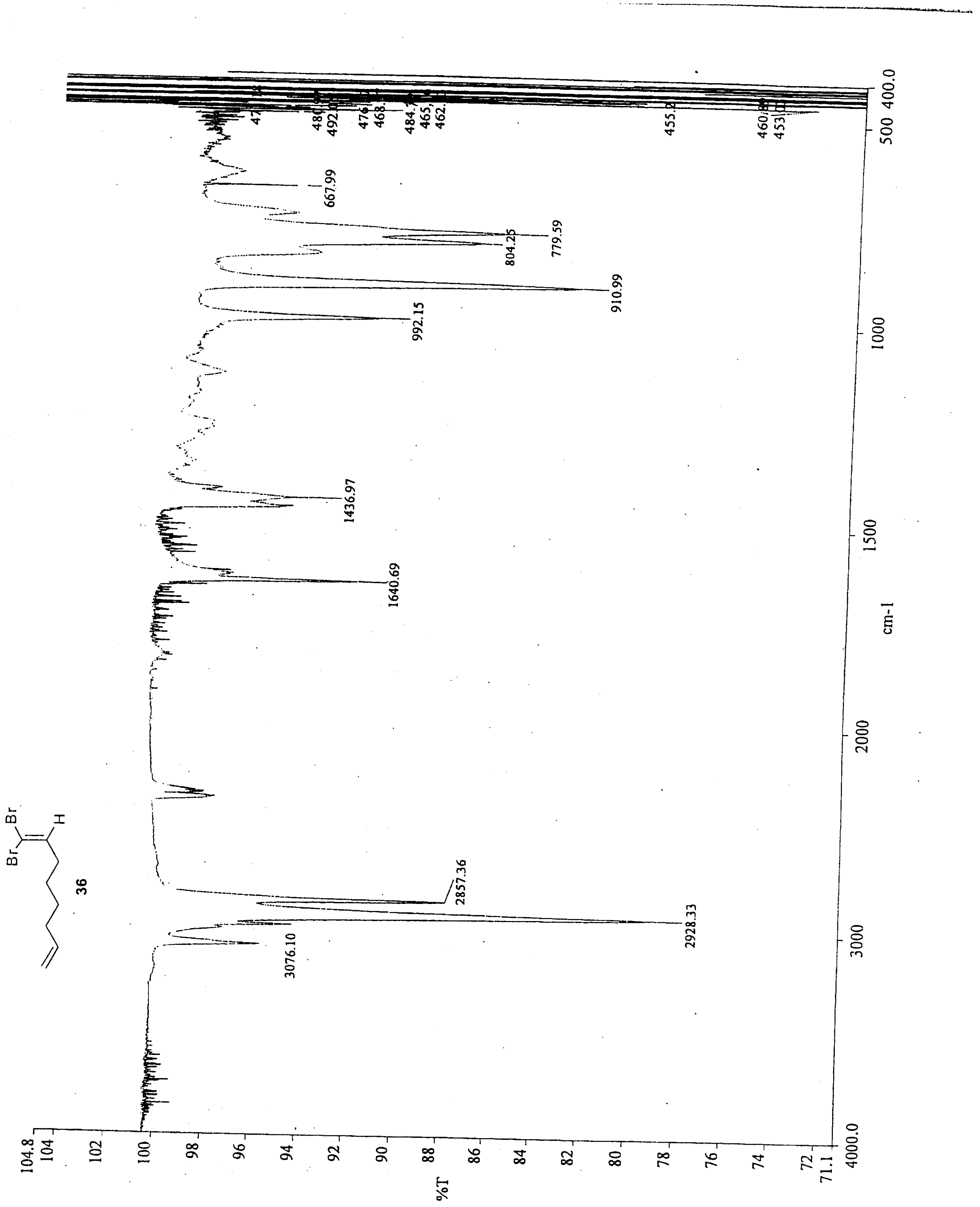

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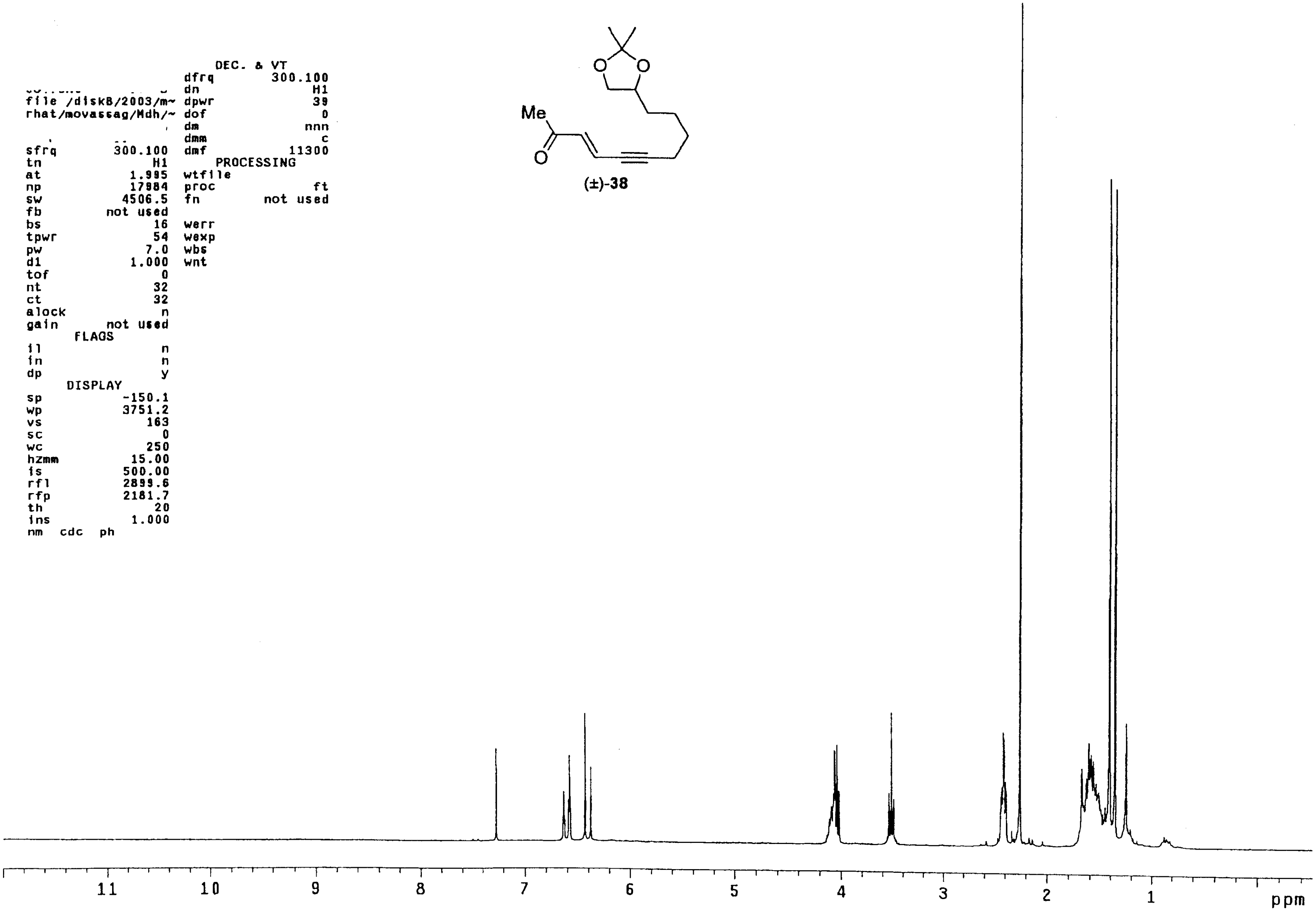

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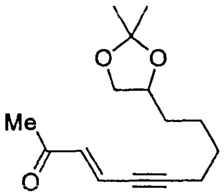
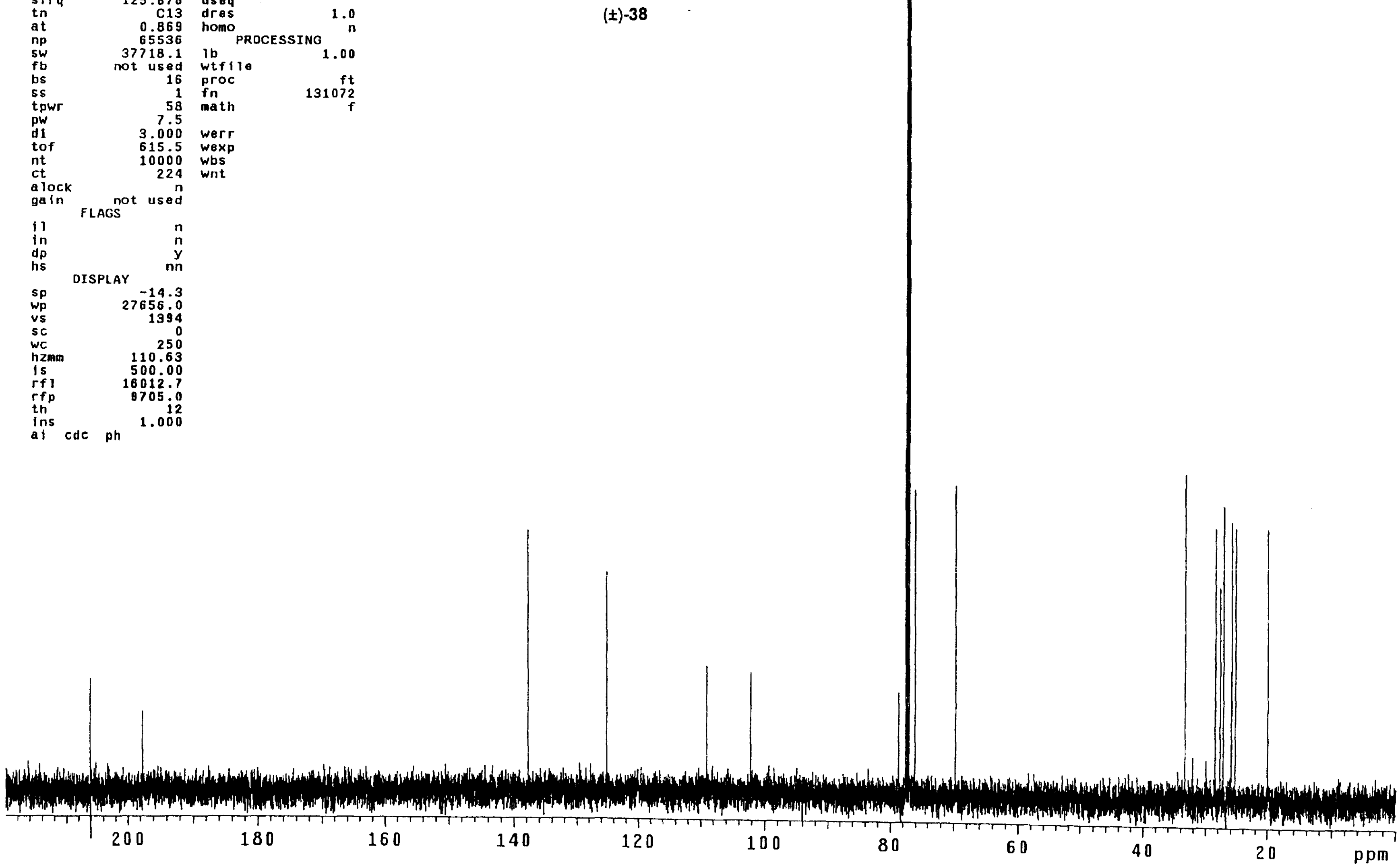
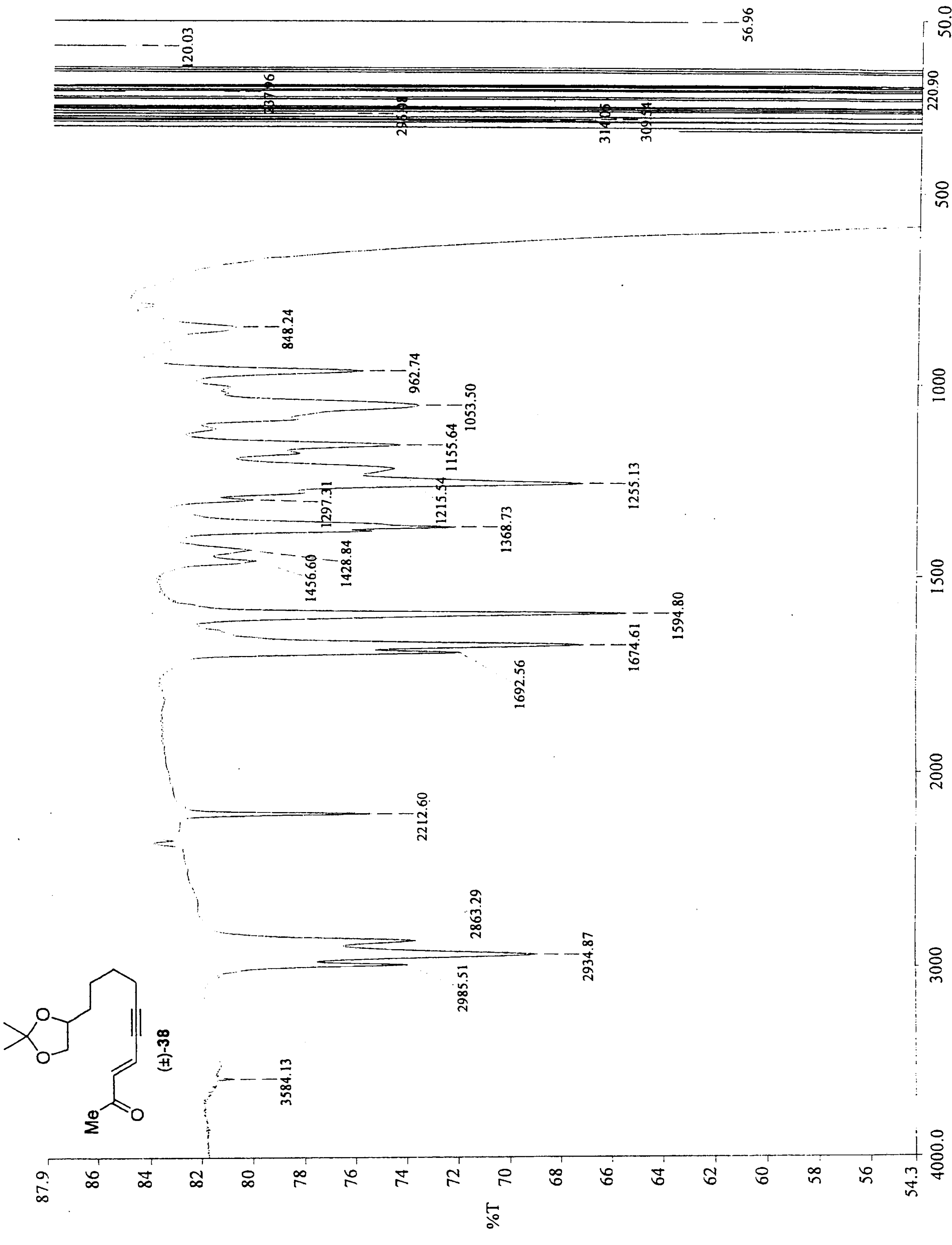
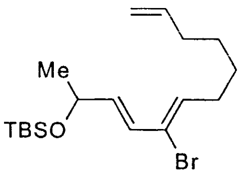


(±)-38

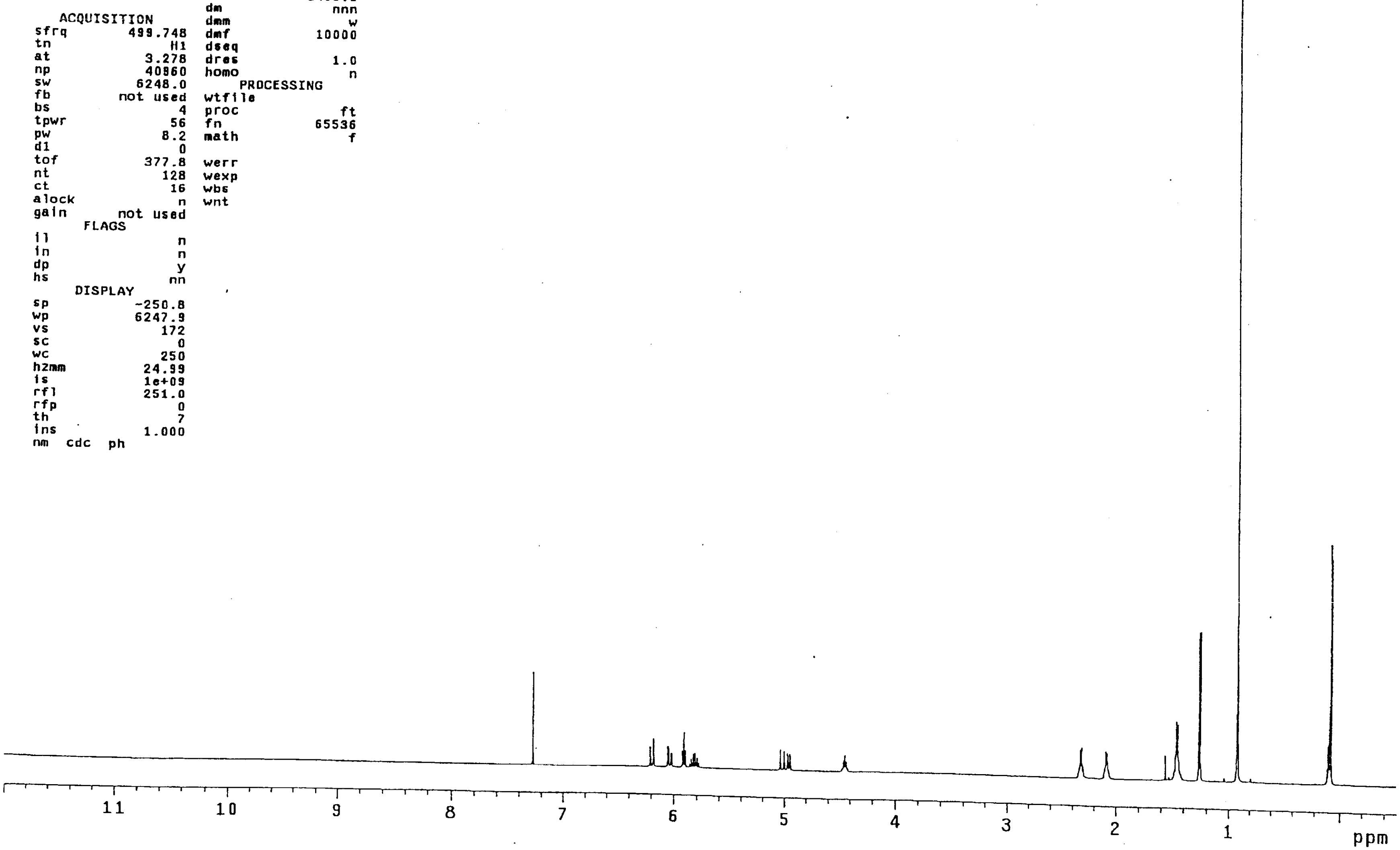


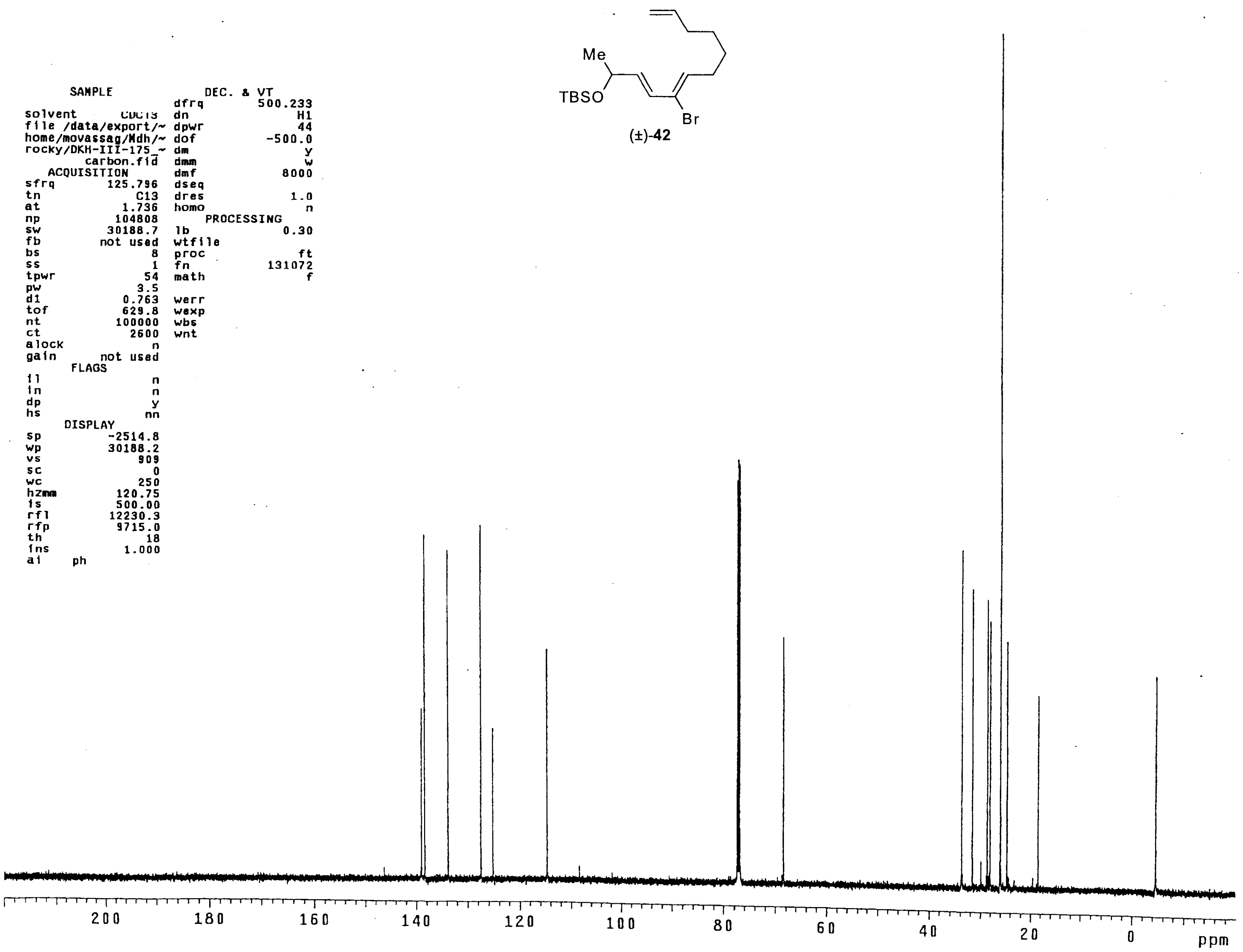

(±)-38
Me
O
O
O
%T
cm-1
87.9
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54.3
4000.0
3000
2000
1500
1000
500
50.0
3584.13
2985.51
2934.87
2863.29
2212.60
1692.56
1674.61
1594.80
1456.60
1428.84
1368.73
1297.31
1215.54
1255.13
1155.64
1053.50
962.74
848.24
120.03
56.96
237.96
220.90
296.98
314.06
309.54



(±)-**42**

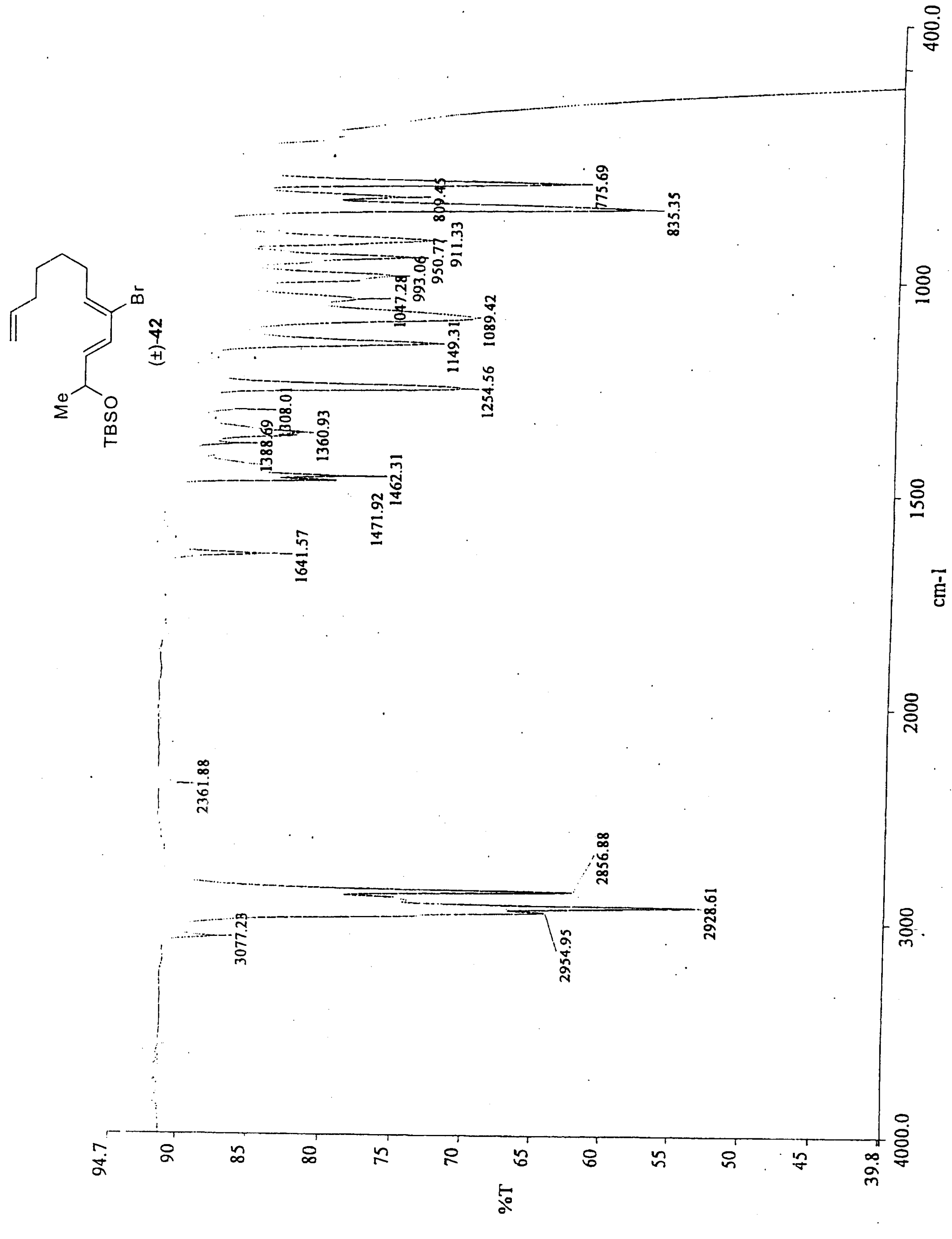
```
                                   DEC. & VT
                          dfrq         125.674
                          dn               C13
                          dpwr              34
                          dof           1498.1
   ACQUISITION            dm               nnn
                          dmm                w
sfrq        499.748       dmf            10000
tn               H1       dseq
at            3.278       dres             1.0
np            40960       homo               n
sw           6248.0           PROCESSING
fb         not used       wtfile
bs                4       proc              ft
tpwr             56       fn             65536
pw              8.2       math               f
d1                0
tof           377.8       werr
nt              128       wexp
ct               16       wbs
alock             n       wnt
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp           -250.8
wp           6247.9
vs              172
sc                0
wc              250
hzmm          24.99
is            1e+09
rfl           251.0
rfp               0
th                7
ins           1.000
nm  cdc  ph
```



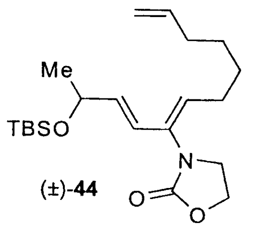


(±)-**42**

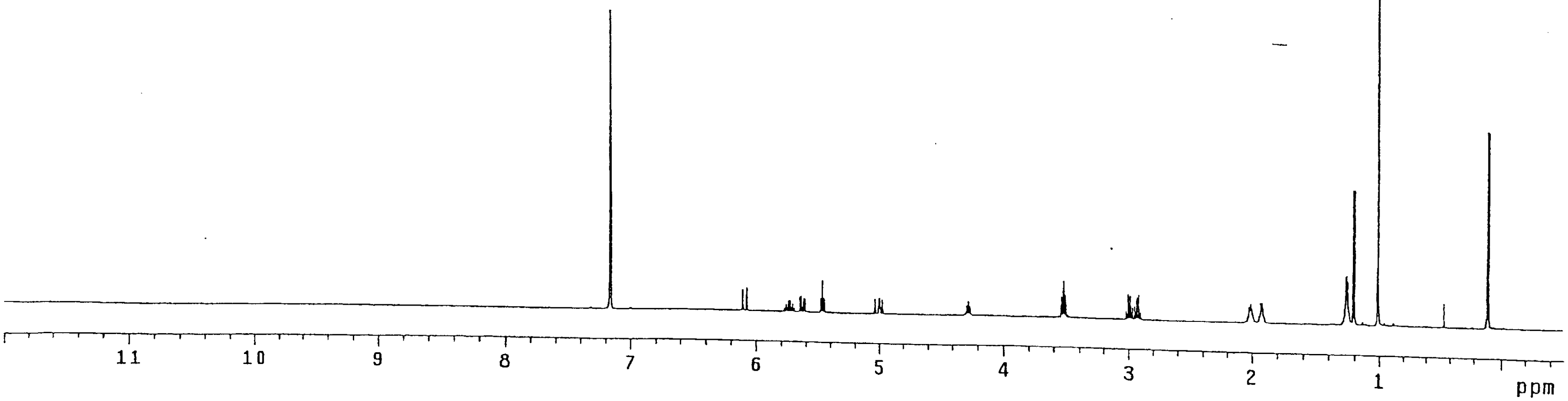
```
      SAMPLE              DEC. & VT
                         dfrq       500.233
solvent       CDCl3     dn              H1
file /data/export/~     dpwr            44
home/movassag/Mdh/~     dof         -500.0
rocky/DKH-III-175_~     dm               y
         carbon.fid     dmm              w
   ACQUISITION          dmf           8000
sfrq        125.796     dseq
tn              C13     dres           1.0
at            1.736     homo             n
np           104808         PROCESSING
sw          30188.7     lb            0.30
fb         not used     wtfile
bs                8     proc            ft
ss                1     fn          131072
tpwr             54     math             f
pw              3.5
d1            0.763     werr
tof           629.8     wexp
nt           100000     wbs
ct             2600     wnt
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp          -2514.8
wp          30188.2
vs              909
sc                0
wc              250
hzmm         120.75
is           500.00
rfl         12230.3
rfp          9715.0
th               18
ins           1.000
ai    ph
```


(±)-42
Me
TBSO
Br
%T
94.7
90
85
80
75
70
65
60
55
50
45
39.8
4000.0
3000
2000
1500
1000
400.0
cm-1
3077.23
2954.95
2928.61
2856.88
2361.88
1641.57
1471.92
1462.31
1388.69
1360.93
1308.01
1254.56
1149.31
1089.42
1047.28
993.06
950.77
911.33
835.35
809.45
775.69

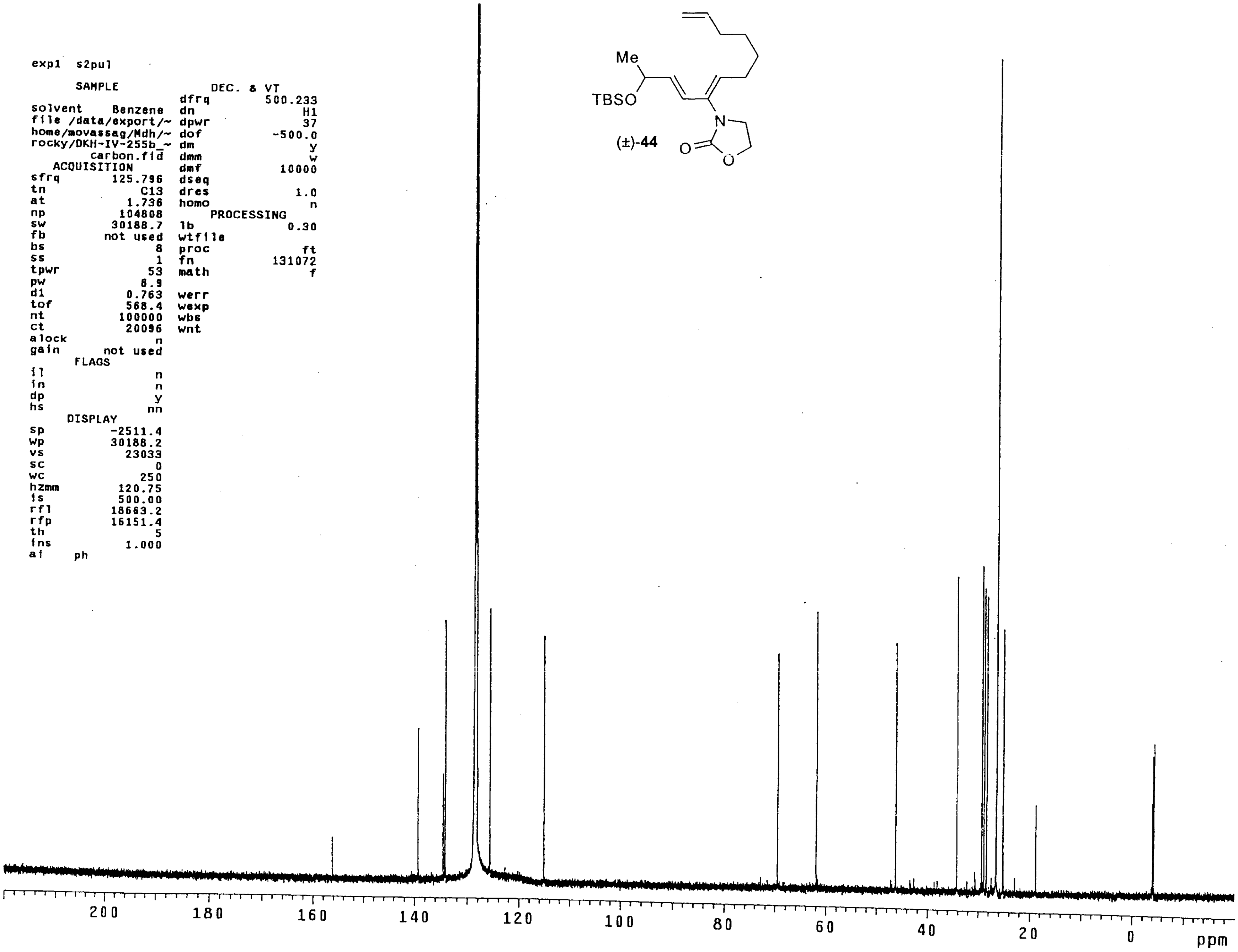
```
      SAMPLE              DEC. & VT
                        dfrq       125.677
solvent    Benzene      dn             C13
file /data/movassa~     dpwr            34
g/Mdh/DKH-III-299b~     dof         1498.1
             .fid       dm             nnn
   ACQUISITION          dmm              w
sfrq         499.757    dmf          10400
tn                H1    dseq
at             3.278    dres           1.0
np             40960    homo             n
sw            6248.0          PROCESSING
fb          not used    wtfile
bs                16    proc            ft
tpwr              56    fn           65536
pw               8.2    math             f
d1                 0
tof            358.1    werr
nt                 8    wexp
ct                 8    wbs
alock              n    wnt
gain        not used
      FLAGS
il                 n
in                 n
dp                 y
hs                nn
     DISPLAY
sp            -250.7
wp            6247.9
vs               151
sc                 0
wc               250
hzmm           24.99
is             33.57
rfl            250.9
rfp                0
th                14
ins            1.000
nm  cdc   ph
```



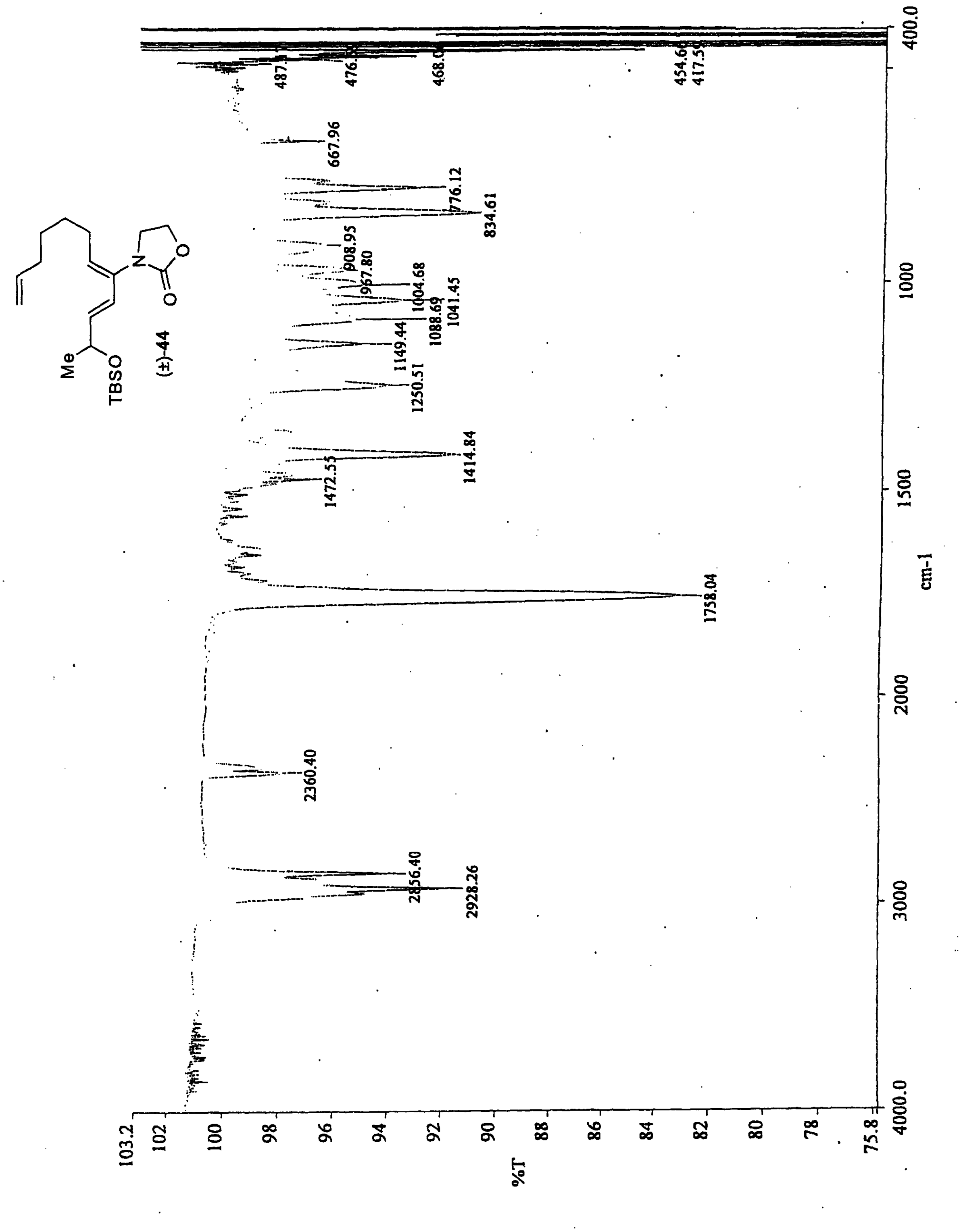
(±)-**44**



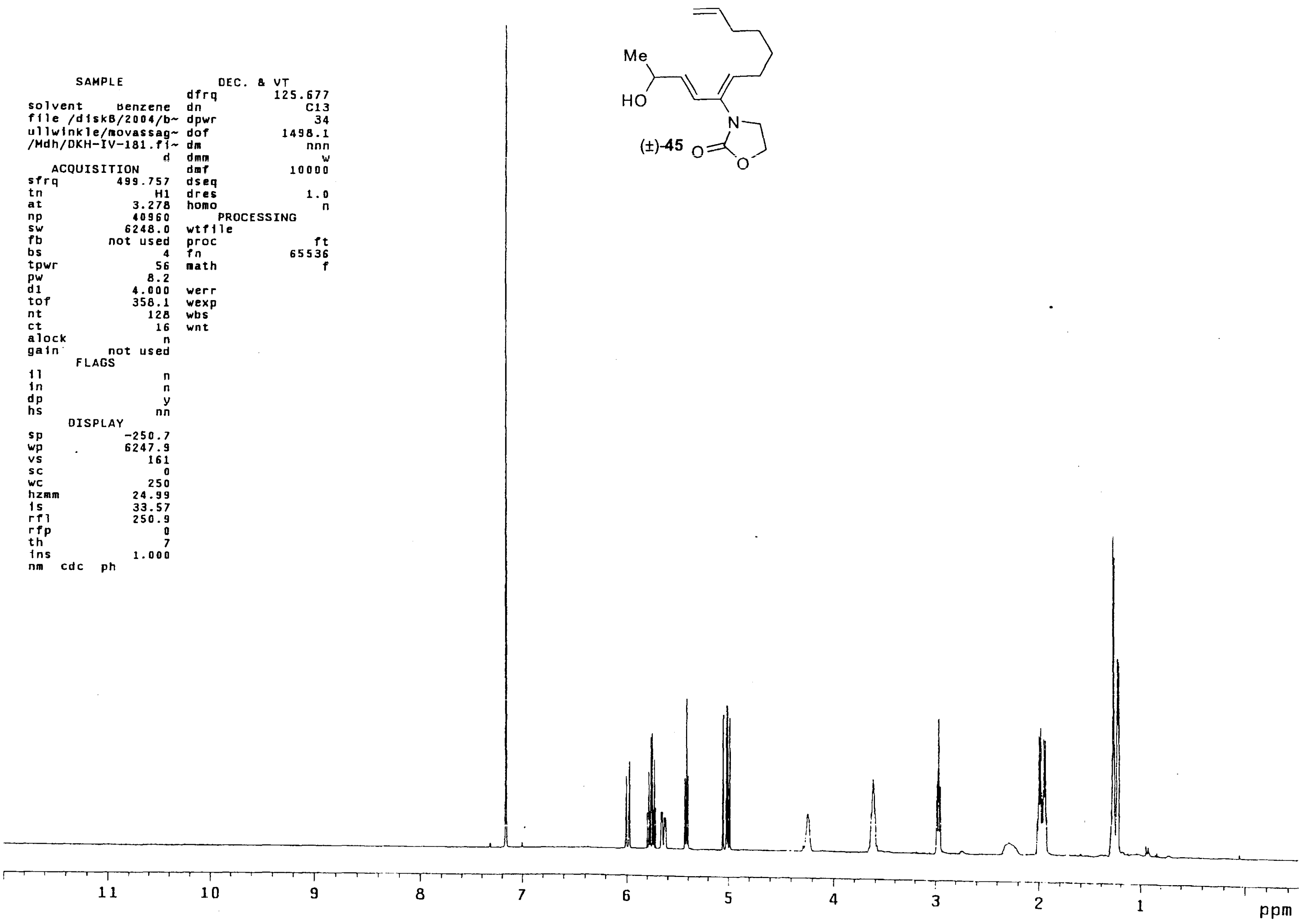
```
exp1  s2pul

      SAMPLE                 DEC. & VT
                      dfrq          500.233
solvent    Benzene    dn                 H1
file /data/export/~   dpwr               37
home/movassag/Mdh/~   dof            -500.0
rocky/DKH-IV-255b_~   dm                  y
         carbon.fid   dmm                 w
   ACQUISITION        dmf             10000
sfrq        125.796   dseq
tn              C13   dres              1.0
at            1.736   homo                n
np           104808      PROCESSING
sw          30188.7   lb               0.30
fb         not used   wtfile
bs                8   proc               ft
ss                1   fn             131072
tpwr             53   math                f
pw              8.9
d1            0.763   werr
tof           568.4   wexp
nt           100000   wbs
ct            20096   wnt
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp          -2511.4
wp          30188.2
vs            23033
sc                0
wc              250
hzmm         120.75
is           500.00
rfl         18663.2
rfp         16151.4
th                5
ins           1.000
ai    ph
```



(±)-44

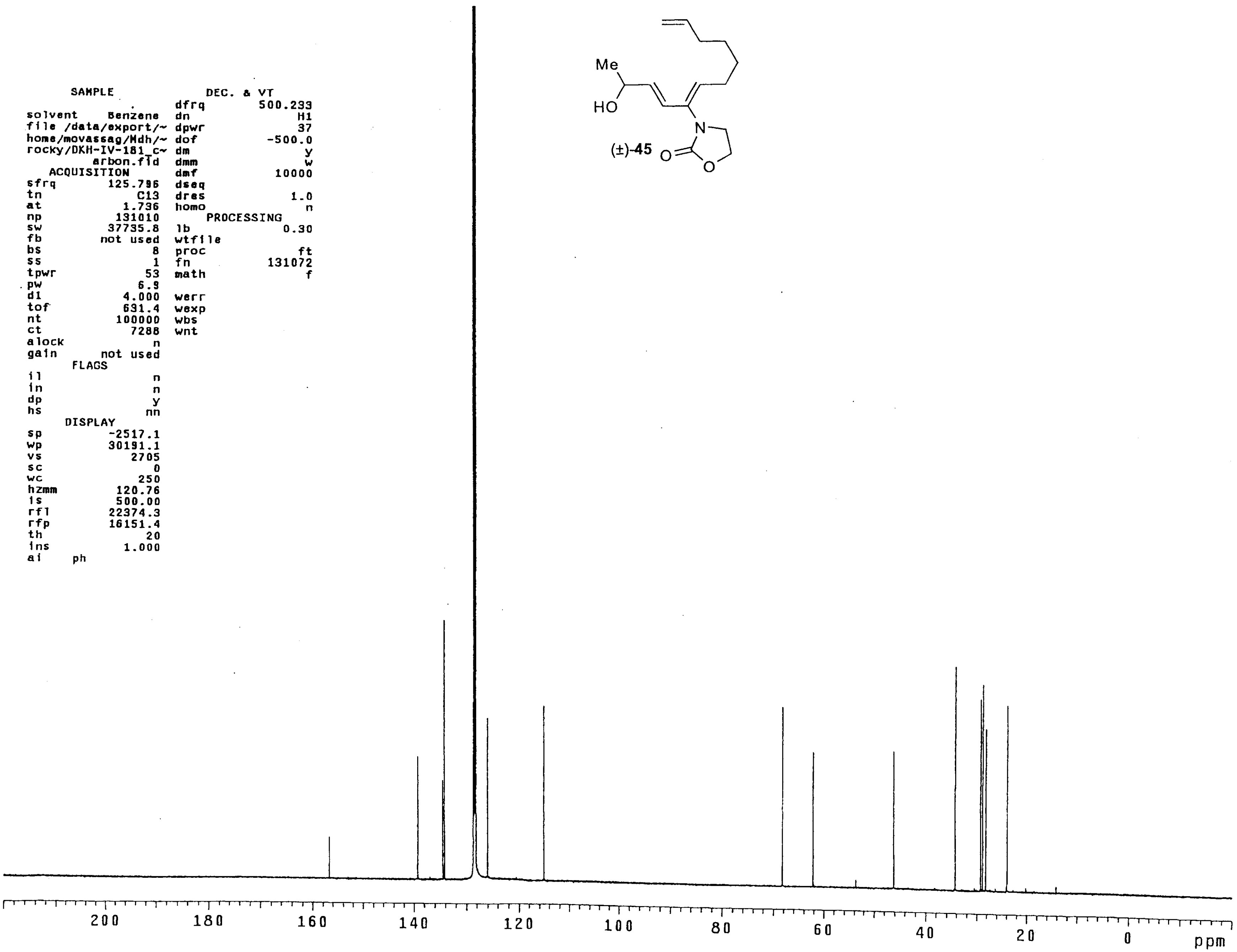


TBSO
Me
(±)-44
N
O
O
%T
103.2
102
100
98
96
94
92
90
88
86
84
82
80
78
75.8
4000.0
3000
2000
1500
1000
400.0
cm-1
2928.26
2856.40
2360.40
1758.04
1472.55
1414.84
1250.51
1149.44
1088.69
1041.45
1004.68
967.80
908.95
834.61
776.12
667.96
487.
476.
468.0
454.60
417.5



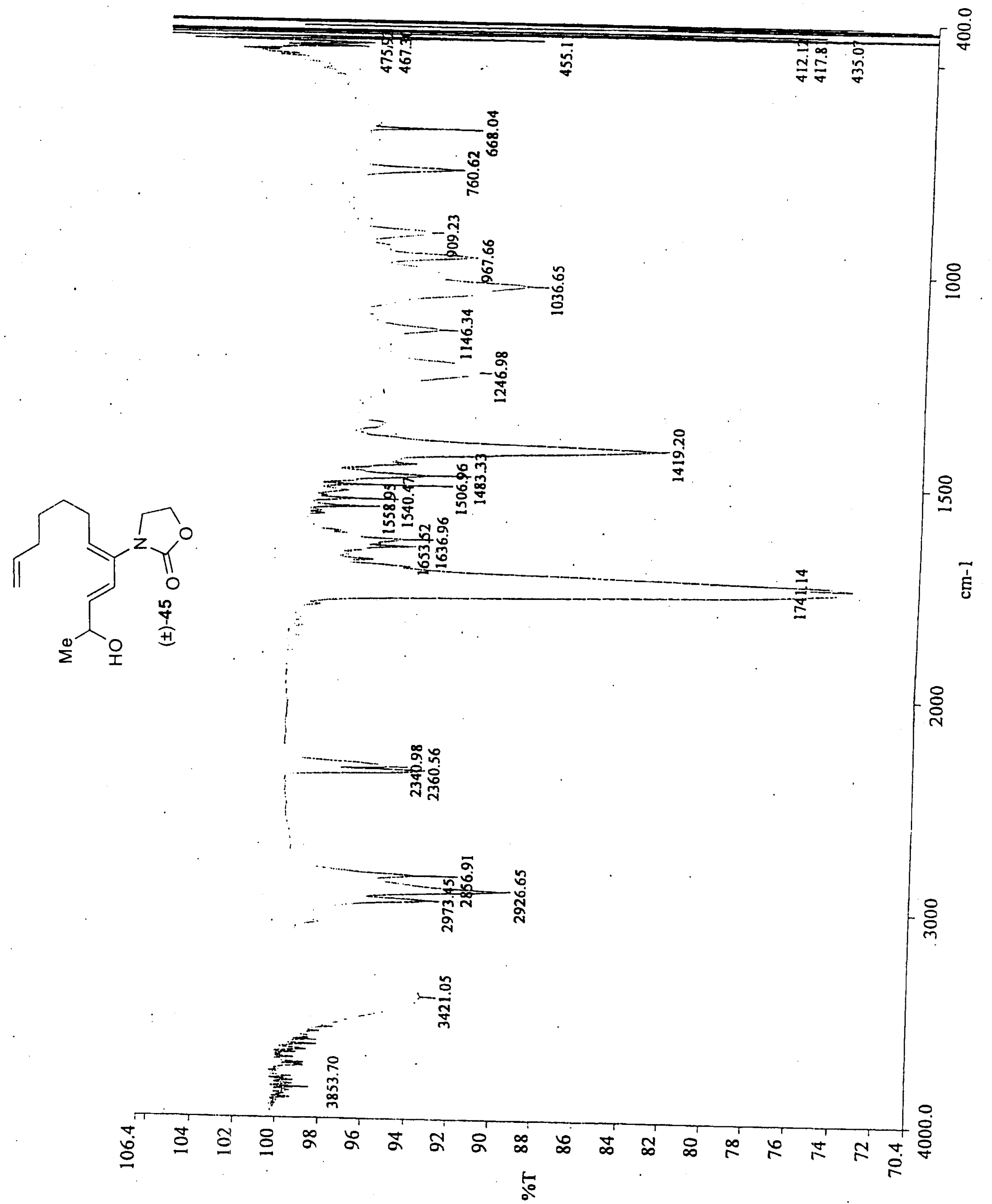
(±)-45

```
      SAMPLE             DEC. & VT
                      dfrq       125.677
solvent    benzene    dn             C13
file /disk8/2004/b~   dpwr            34
ullwinkle/movassag~   dof         1498.1
/Mdh/DKH-IV-181.fi~   dm             nnn
                  d   dmm              w
   ACQUISITION        dmf          10000
sfrq        499.757   dseq
tn               H1   dres           1.0
at            3.278   homo             n
np            40960       PROCESSING
sw           6248.0   wtfile
fb         not used   proc            ft
bs                4   fn           65536
tpwr             56   math             f
pw              8.2
d1            4.000   werr
tof           358.1   wexp
nt              128   wbs
ct               16   wnt
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp           -250.7
wp           6247.9
vs              161
sc                0
wc              250
hzmm          24.99
is            33.57
rfl           250.9
rfp               0
th                7
ins           1.000
nm  cdc  ph
```

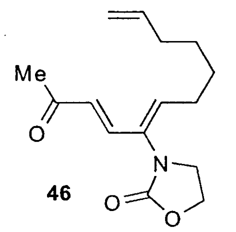


(±)-45

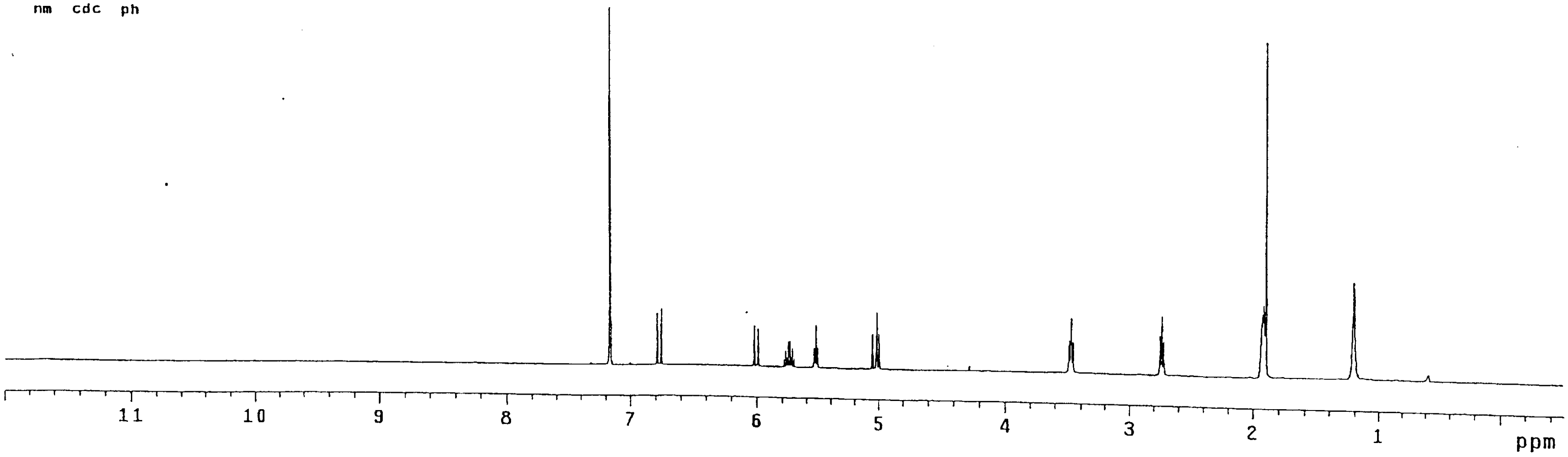
```
     SAMPLE                  DEC. & VT
                       dfrq         500.233
solvent    Benzene     dn                H1
file /data/export/~    dpwr              37
home/movassag/Mdh/~    dof           -500.0
rocky/DKH-IV-181_c~    dm                 y
          arbon.fid    dmm                w
   ACQUISITION         dmf            10000
sfrq        125.796    dseq
tn              C13    dres             1.0
at            1.736    homo               n
np           131010          PROCESSING
sw          37735.8    lb              0.30
fb         not used    wtfile
bs                8    proc              ft
ss                1    fn            131072
tpwr             53    math               f
pw              6.9
d1            4.000    werr
tof           631.4    wexp
nt           100000    wbs
ct             7288    wnt
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp          -2517.1
wp          30191.1
vs             2705
sc                0
wc              250
hzmm         120.76
is           500.00
rfl         22374.3
rfp         16151.4
th               20
ins           1.000
ai    ph
```

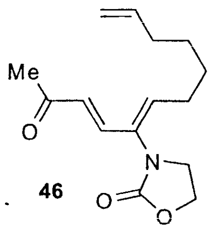

Me
HO
N
O
O
%T
106.4
104
102
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70.4
cm-1
4000.0
3000
2000
1500
1000
400.0
3853.70
3421.05
2973.45
2856.91
2926.65
2340.98
2360.56
1741.14
1741.14
1653.52
1636.96
1558.95
1540.47
1506.96
1483.33
1419.20
1246.98
1146.34
1036.65
967.66
909.23
760.62
668.04
475.52
467.30
455.1
412.12
417.8
435.07

(±)-45


46

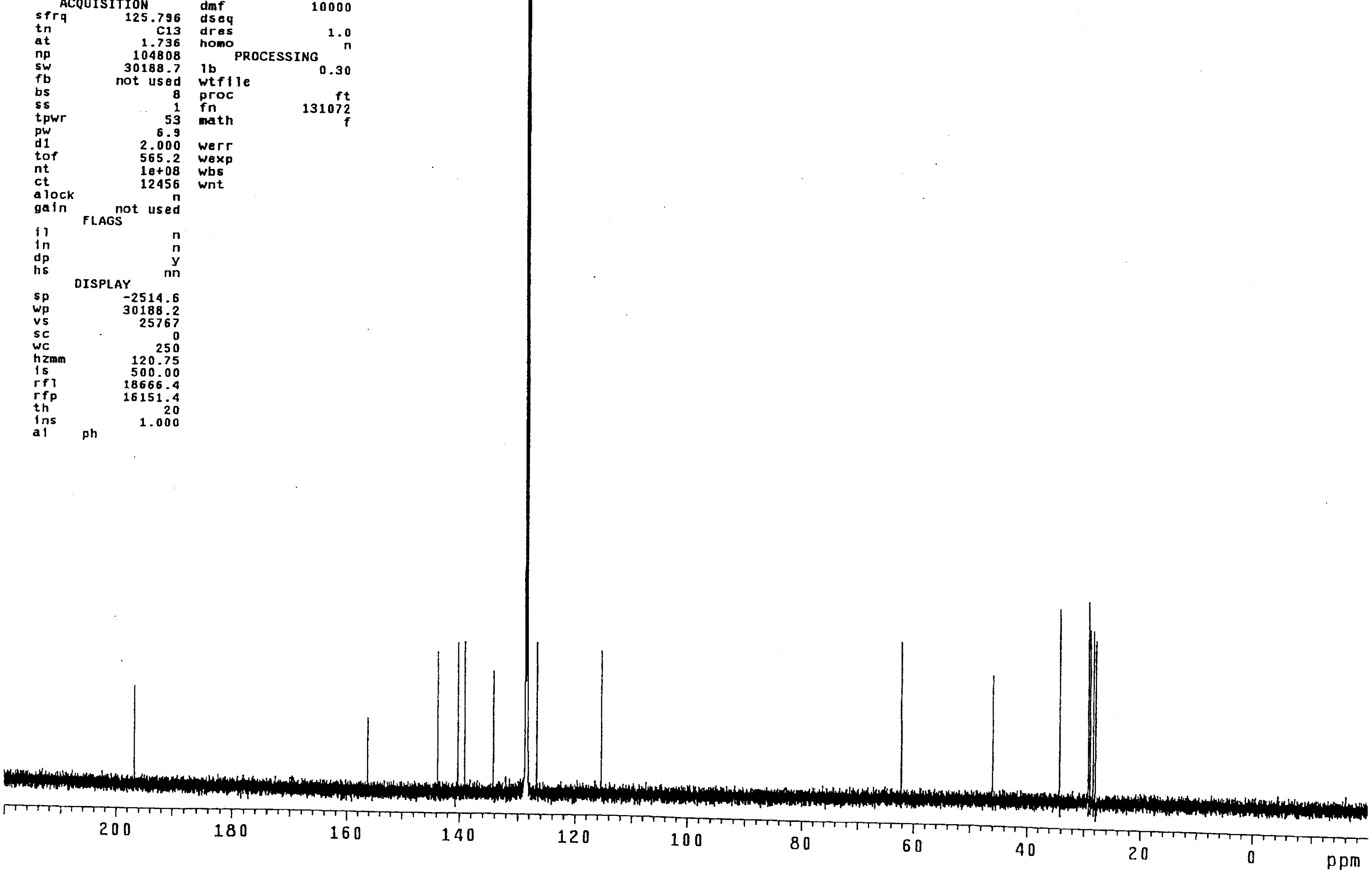
```
      SAMPLE              DEC. & VT
                      dfrq        125.677
solvent    Benzene    dn              C13
file /data/movassa~   dpwr             34
g/Mdh/DKH-IV-55cr.~   dof          1498.1
               fid    dm              nnn
    ACQUISITION       dmm               w
sfrq       499.757    dmf           10000
tn              H1    dseq
at           3.278    dres            1.0
np           40960    homo              n
sw          6248.0        PROCESSING
fb        not used    wtfile
bs              16    proc             ft
tpwr            56    fn            65536
pw             8.2    math              f
d1           2.000
tof          357.8    werr
nt              64    wexp
ct              32    wbs
alock            n    wnt
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -250.7
wp          6247.9
vs              58
sc               0
wc             250
hzmm         24.99
is           33.57
rfl          250.9
rfp              0
th               7
ins          1.000
nm  cdc  ph
```

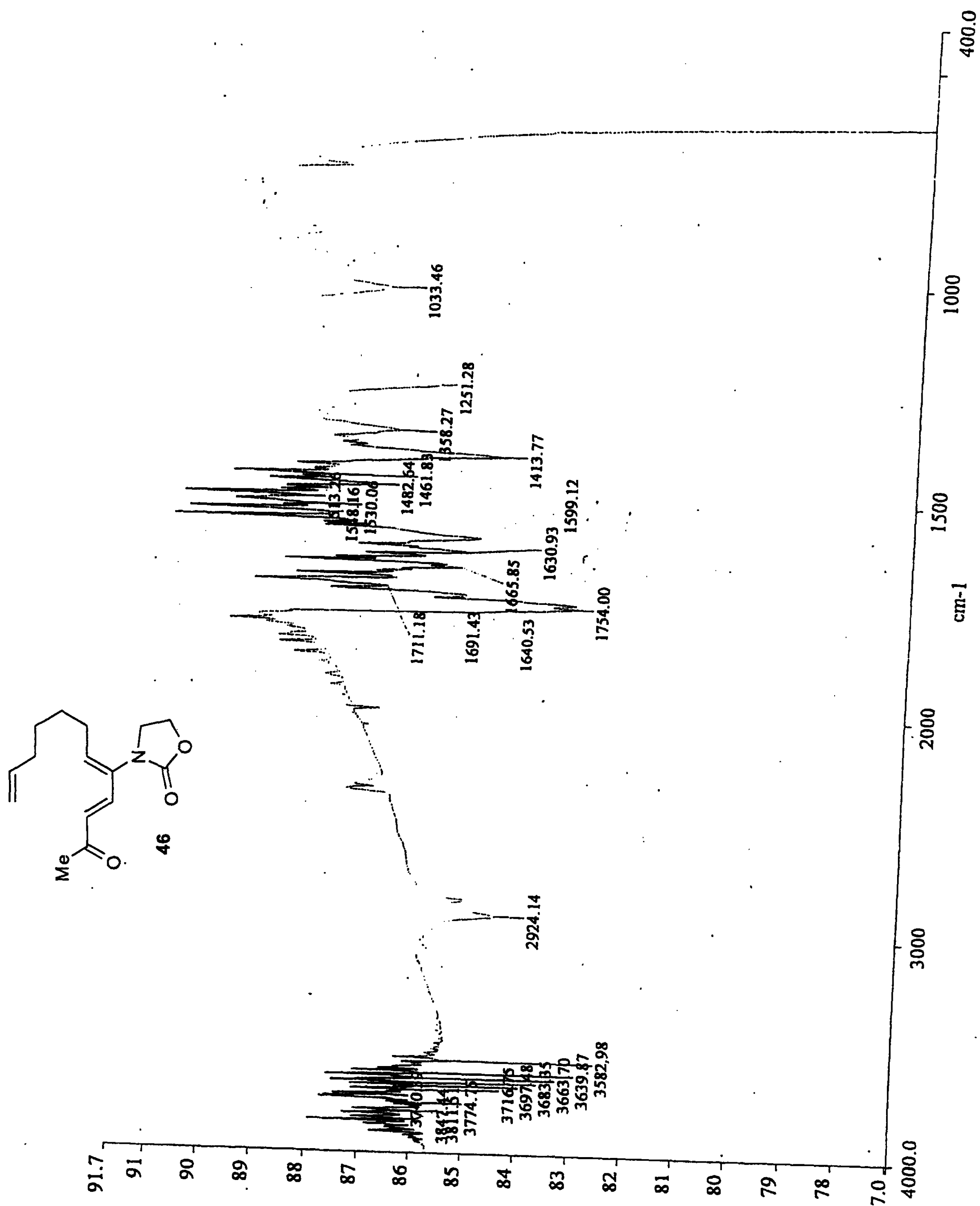




46

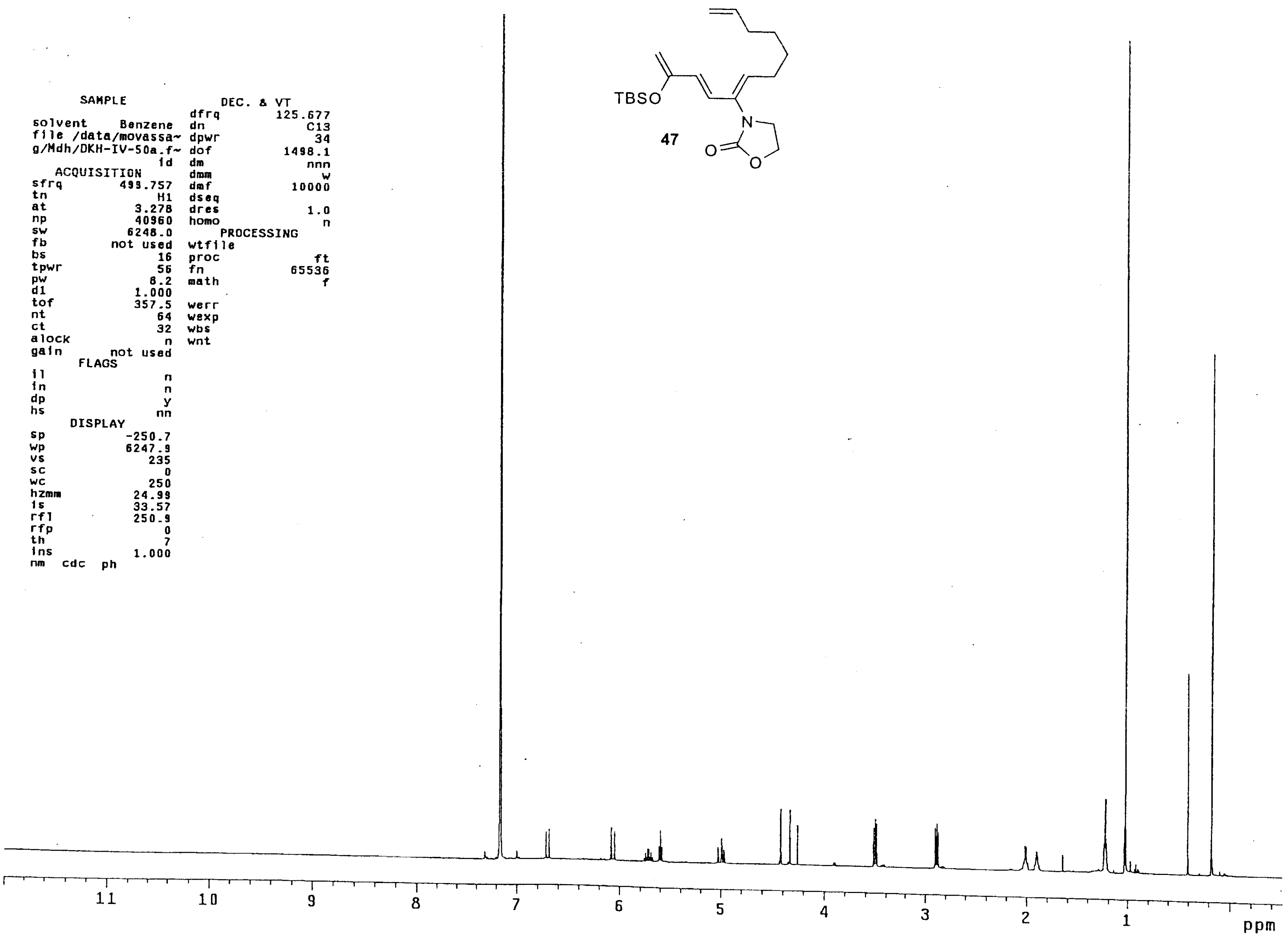
```
      SAMPLE                DEC. & VT
.                       dfrq         500.233
solvent     Benzene     dn                H1
file /data/export/~     dpwr              37
home/movassag/Mdh/~     dof           -500.0
rocky/DKH-IV-55_ca~     dm                 y
           rbon.fid     dmm                w
   ACQUISITION          dmf            10000
sfrq        125.796     dseq
tn              C13     dres             1.0
at            1.736     homo               n
np           104808          PROCESSING
sw          30188.7     lb              0.30
fb         not used     wtfile
bs                8     proc              ft
ss                1     fn            131072
tpwr             53     math               f
pw              6.9
d1            2.000     werr
tof           565.2     wexp
nt            1e+08     wbs
ct            12456     wnt
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp          -2514.6
wp          30188.2
vs            25767
sc                0
wc              250
hzmm         120.75
is           500.00
rfl         18666.4
rfp         16151.4
th               20
ins           1.000
ai    ph
```



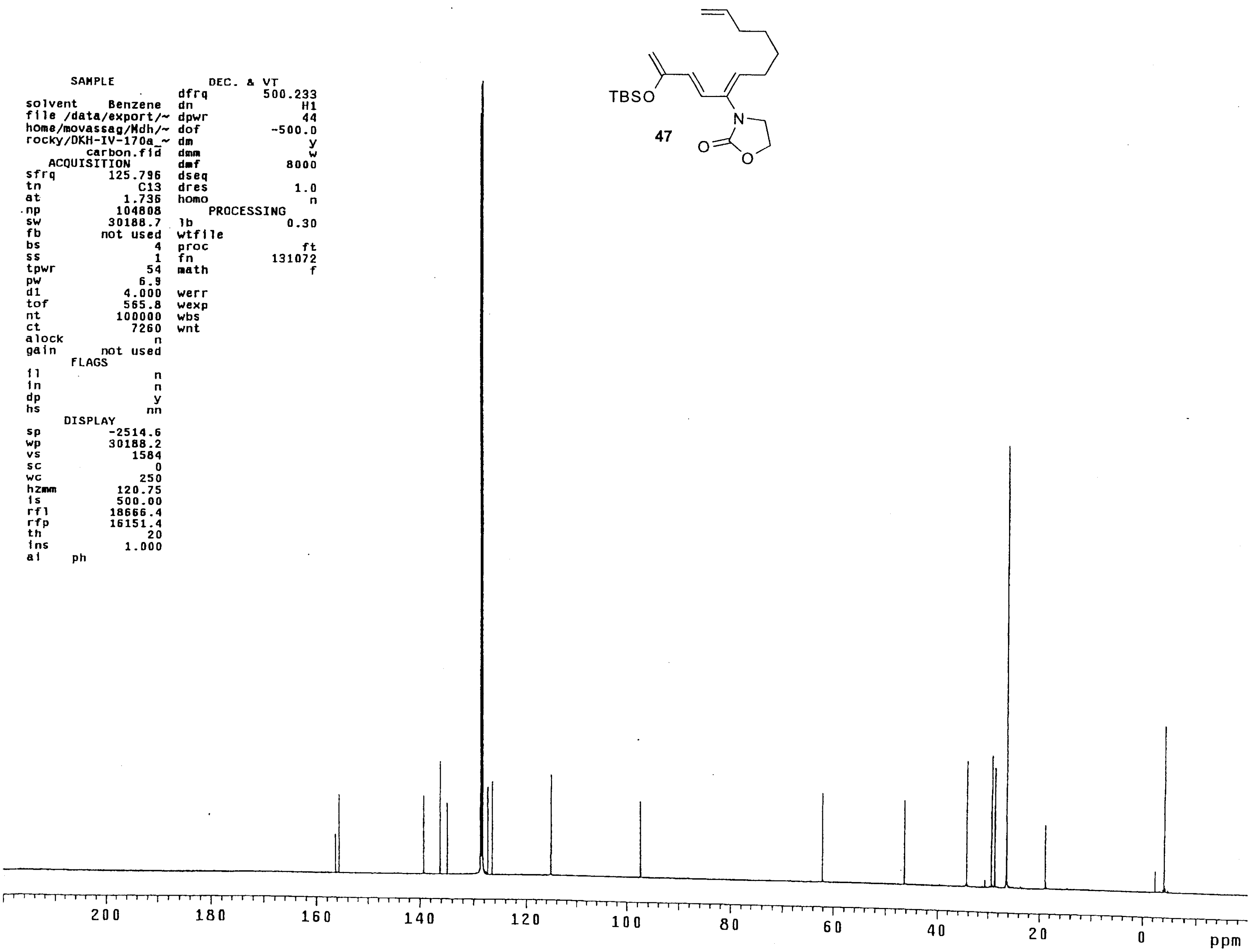

46

Me
O
N
O
O
%T
91.7
91
90
89
88
87
86
85
84
83
82
81
80
79
78
77.0
4000.0
3000
2000
1500
1000
400.0
cm-1
3847.14
3811.51
3774.75
3716.75
3697.48
3683.35
3663.70
3639.87
3582.98
2924.14
1754.00
1711.18
1691.43
1665.85
1640.53
1630.93
1599.12
1548.16
1530.06
1513.26
1482.64
1461.83
1413.77
1358.27
1251.28
1033.46

```
      SAMPLE                DEC. & VT
                      dfrq          125.677
solvent    Benzene    dn                C13
file /data/movassa~   dpwr               34
g/Mdh/DKH-IV-50a.f~   dof            1498.1
                id    dm                nnn
   ACQUISITION        dmm                 w
sfrq         499.757  dmf             10000
tn                H1  dseq
at             3.278  dres              1.0
np             40960  homo                n
sw            6248.0        PROCESSING
fb          not used  wtfile
bs                16  proc               ft
tpwr              56  fn              65536
pw               8.2  math                f
d1             1.000
tof            357.5  werr
nt                64  wexp
ct                32  wbs
alock              n  wnt
gain        not used
        FLAGS
il                 n
in                 n
dp                 y
hs                nn
       DISPLAY
sp            -250.7
wp            6247.9
vs               235
sc                 0
wc               250
hzmm           24.99
is             33.57
rfl            250.9
rfp                0
th                 7
ins            1.000
nm   cdc   ph
```

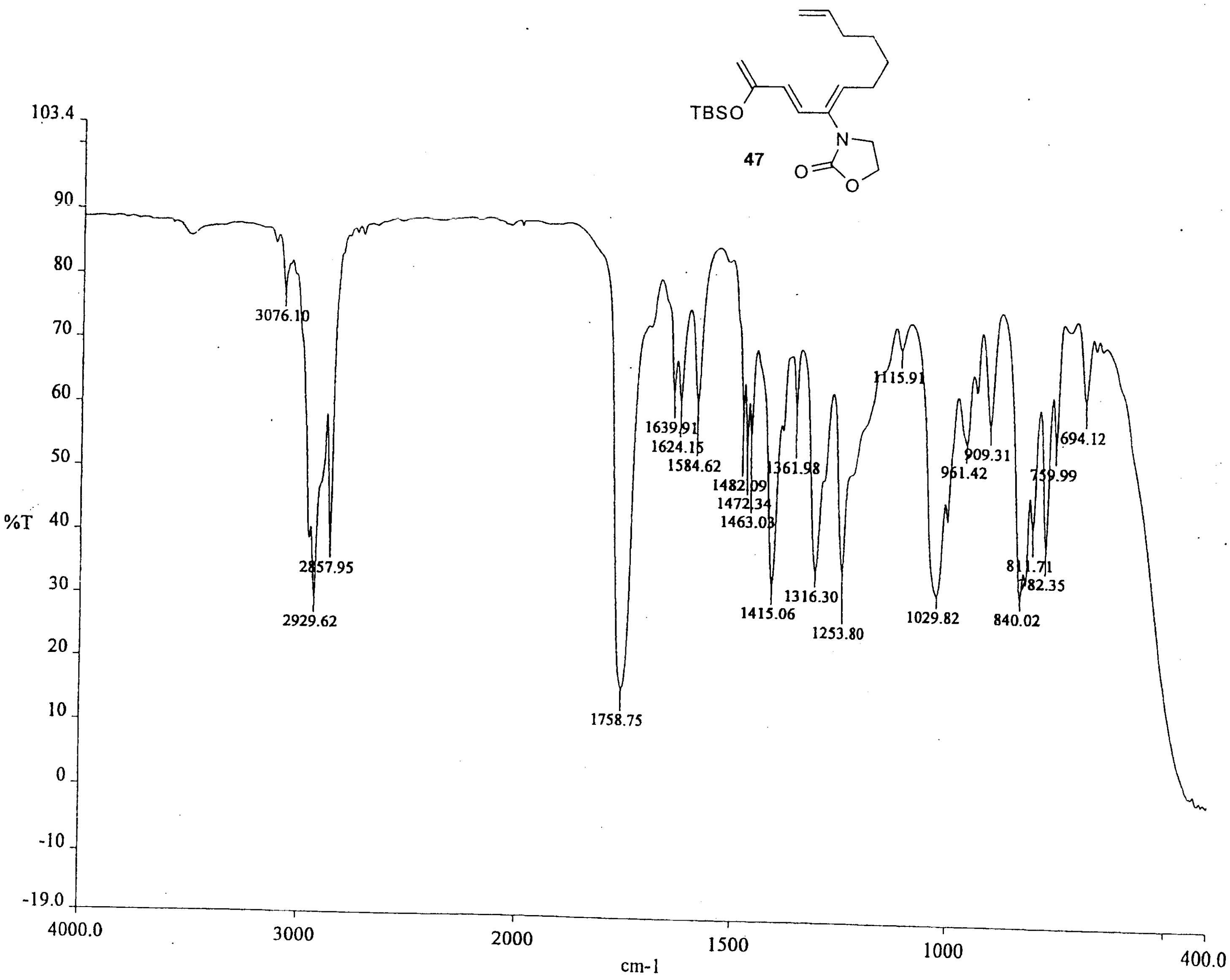


47



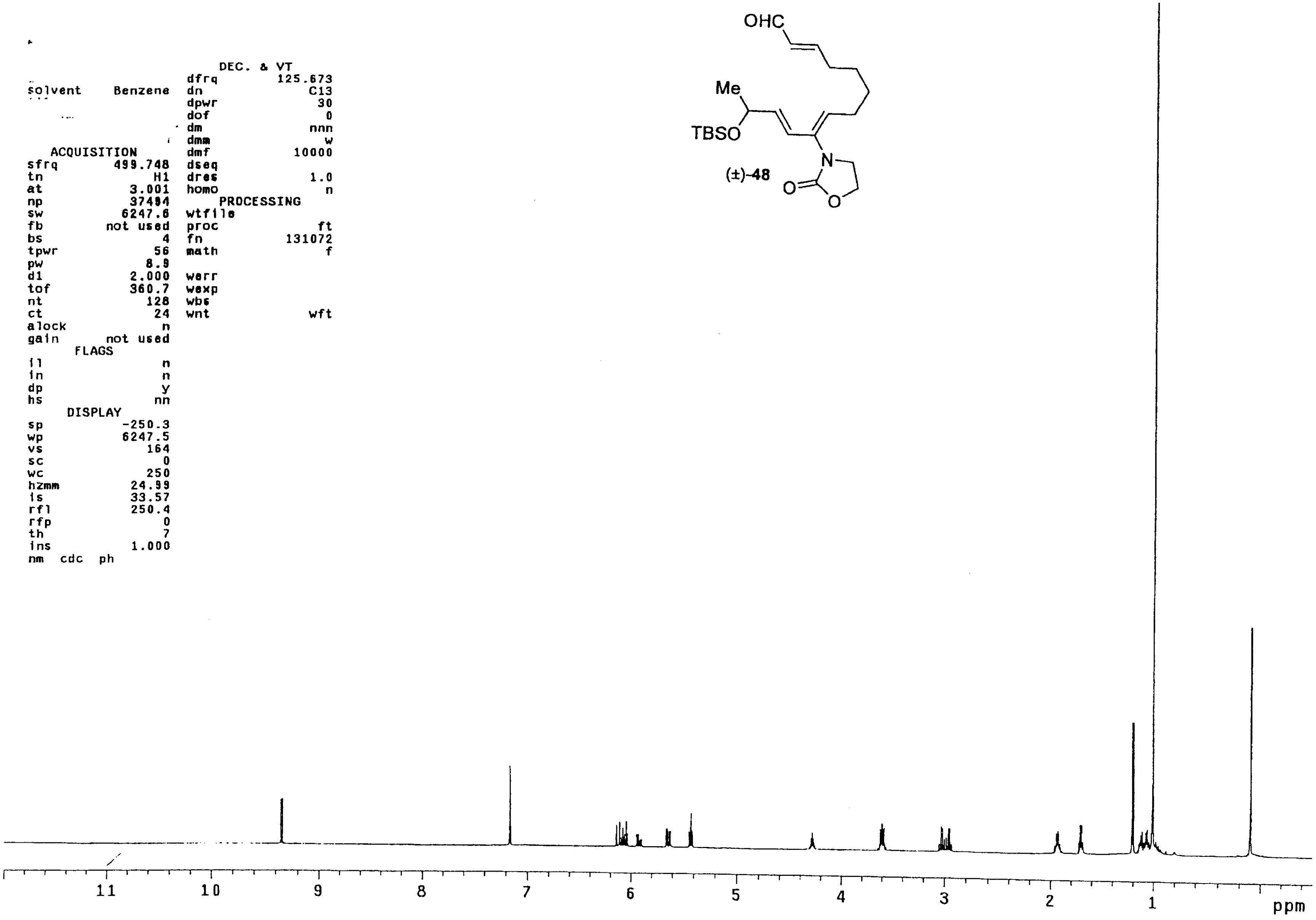
47

```
     SAMPLE                 DEC. & VT
                     dfrq         500.233
solvent    Benzene   dn                H1
file /data/export/~  dpwr              44
home/movassag/Mdh/~  dof           -500.0
rocky/DKH-IV-170a_~  dm                 y
       carbon.fid    dmm                w
   ACQUISITION       dmf             8000
sfrq       125.796   dseq
tn             C13   dres             1.0
at           1.736   homo               n
np          104808       PROCESSING
sw         30188.7   lb              0.30
fb        not used   wtfile
bs               4   proc              ft
ss               1   fn            131072
tpwr            54   math               f
pw             6.9
d1           4.000   werr
tof          565.8   wexp
nt          100000   wbs
ct            7260   wnt
alock            n
gain      not used
     FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp         -2514.6
wp         30188.2
vs            1584
sc               0
wc             250
hzmm        120.75
is          500.00
rfl        18666.4
rfp        16151.4
th              20
ins          1.000
ai     ph
```

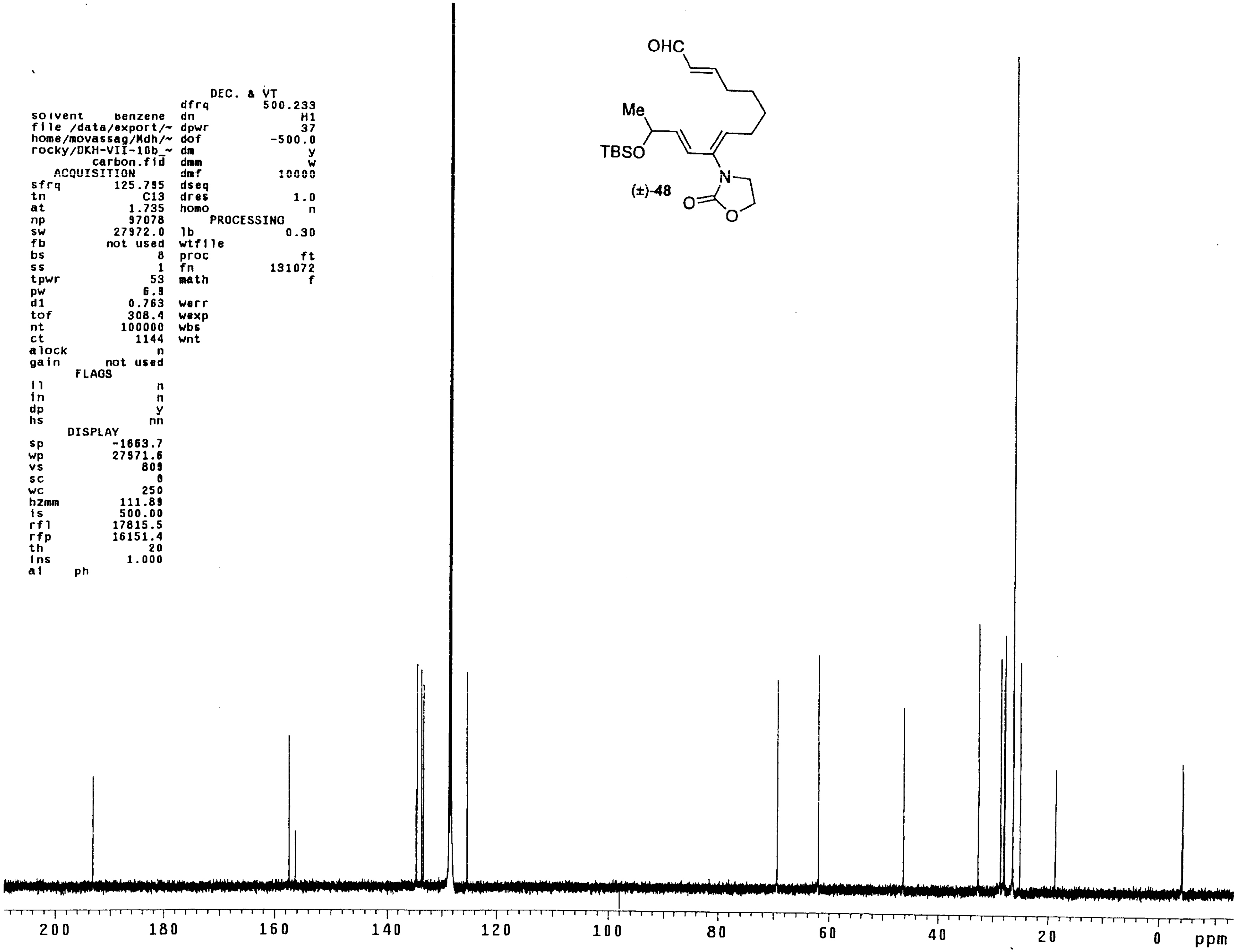

47

TBSO
N
O
O
%T
103.4
90
80
70
60
50
40
30
20
10
0
-10
-19.0
4000.0
3000
2000
1500
1000
400.0
cm-1
3076.10
2857.95
2929.62
1758.75
1639.91
1624.15
1584.62
1482.09
1472.34
1463.03
1361.98
1415.06
1316.30
1253.80
1115.91
1029.82
961.42
909.31
840.02
811.71
782.35
759.99
694.12

```
                                 DEC. & VT
                          dfrq         125.673
solvent     Benzene       dn               C13
                          dpwr              30
                          dof                0
                          dm               nnn
                          dmm                w
   ACQUISITION            dmf            10000
sfrq         499.748      dseq
tn                H1      dres             1.0
at             3.001      homo               n
np             37494         PROCESSING
sw            6247.6      wtfile
fb          not used      proc              ft
bs                 4      fn            131072
tpwr              56      math               f
pw               8.9
d1             2.000      werr
tof            360.7      wexp
nt               128      wbs
ct                24      wnt              wft
alock              n
gain        not used
        FLAGS
il                 n
in                 n
dp                 y
hs                nn
       DISPLAY
sp            -250.3
wp            6247.5
vs               164
sc                 0
wc               250
hzmm           24.99
is             33.57
rfl            250.4
rfp                0
th                 7
ins            1.000
nm   cdc   ph
```

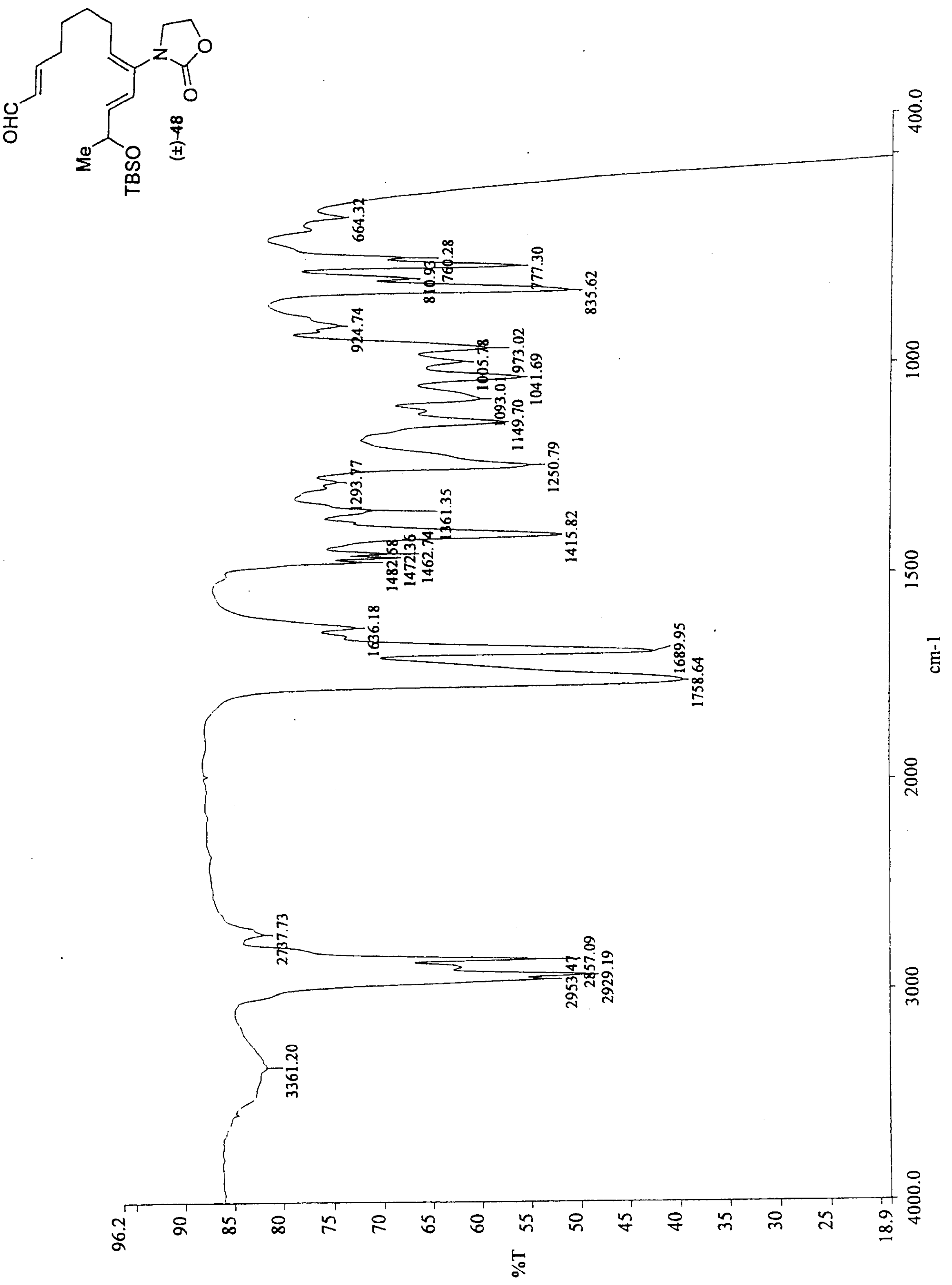


(±)-**48**

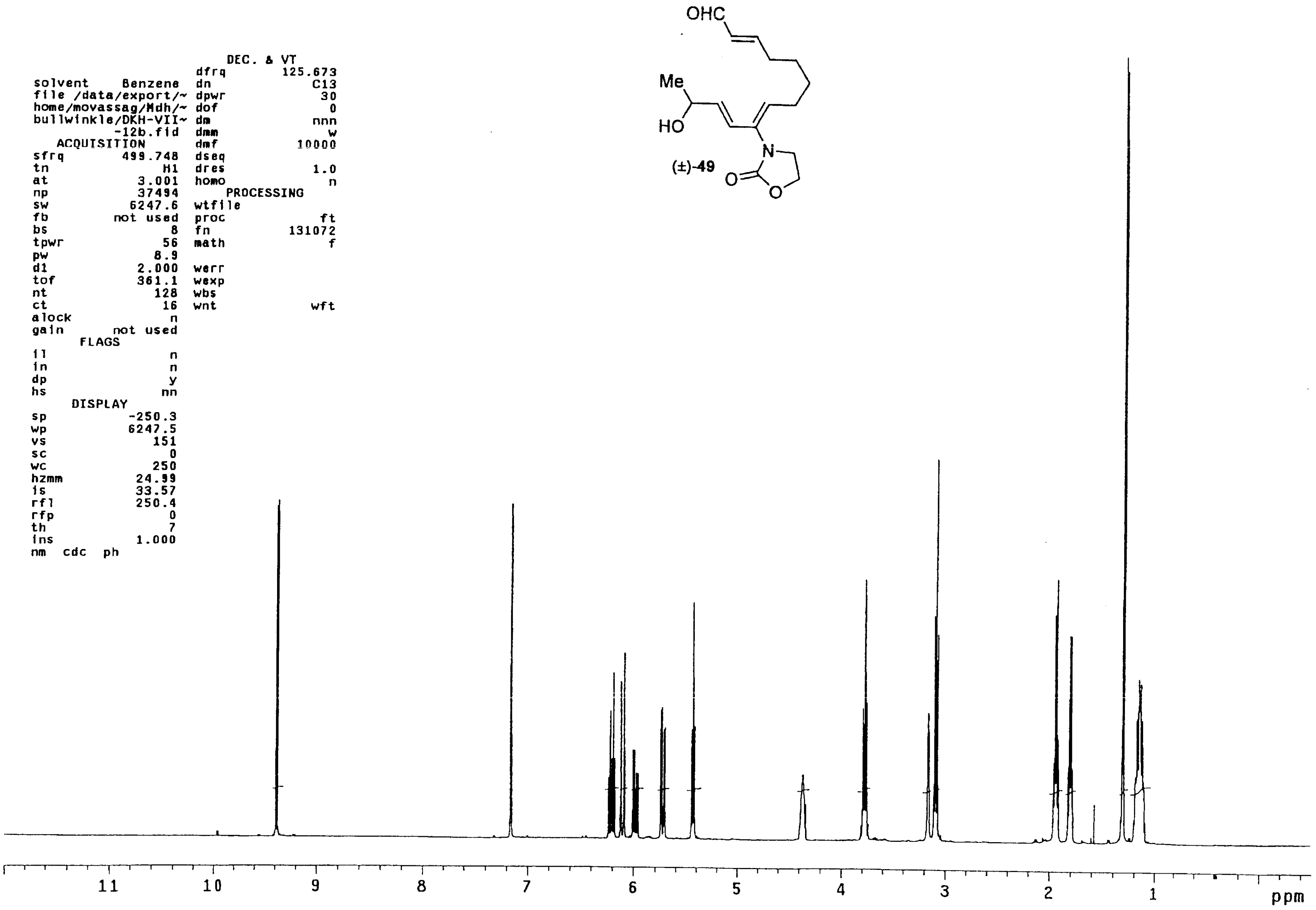


```
                                 DEC. & VT
                          dfrq          500.233
solvent    benzene        dn                 H1
file /data/export/~       dpwr               37
home/movassag/Mdh/~       dof            -500.0
rocky/DKH-VII-10b_~       dm                  y
       carbon.fid         dmm                 w
   ACQUISITION            dmf             10000
sfrq         125.795      dseq
tn               C13      dres              1.0
at             1.735      homo                n
np             97078          PROCESSING
sw           27972.0      lb               0.30
fb          not used      wtfile
bs                 8      proc               ft
ss                 1      fn             131072
tpwr              53      math                f
pw               6.9
d1             0.763      werr
tof            308.4      wexp
nt            100000      wbs
ct              1144      wnt
alock              n
gain        not used
       FLAGS
il                 n
in                 n
dp                 y
hs                nn
      DISPLAY
sp           -1663.7
wp           27971.6
vs               809
sc                 0
wc               250
hzmm          111.89
is            500.00
rfl          17815.5
rfp          16151.4
th                20
ins            1.000
ai    ph
```

(±)-48

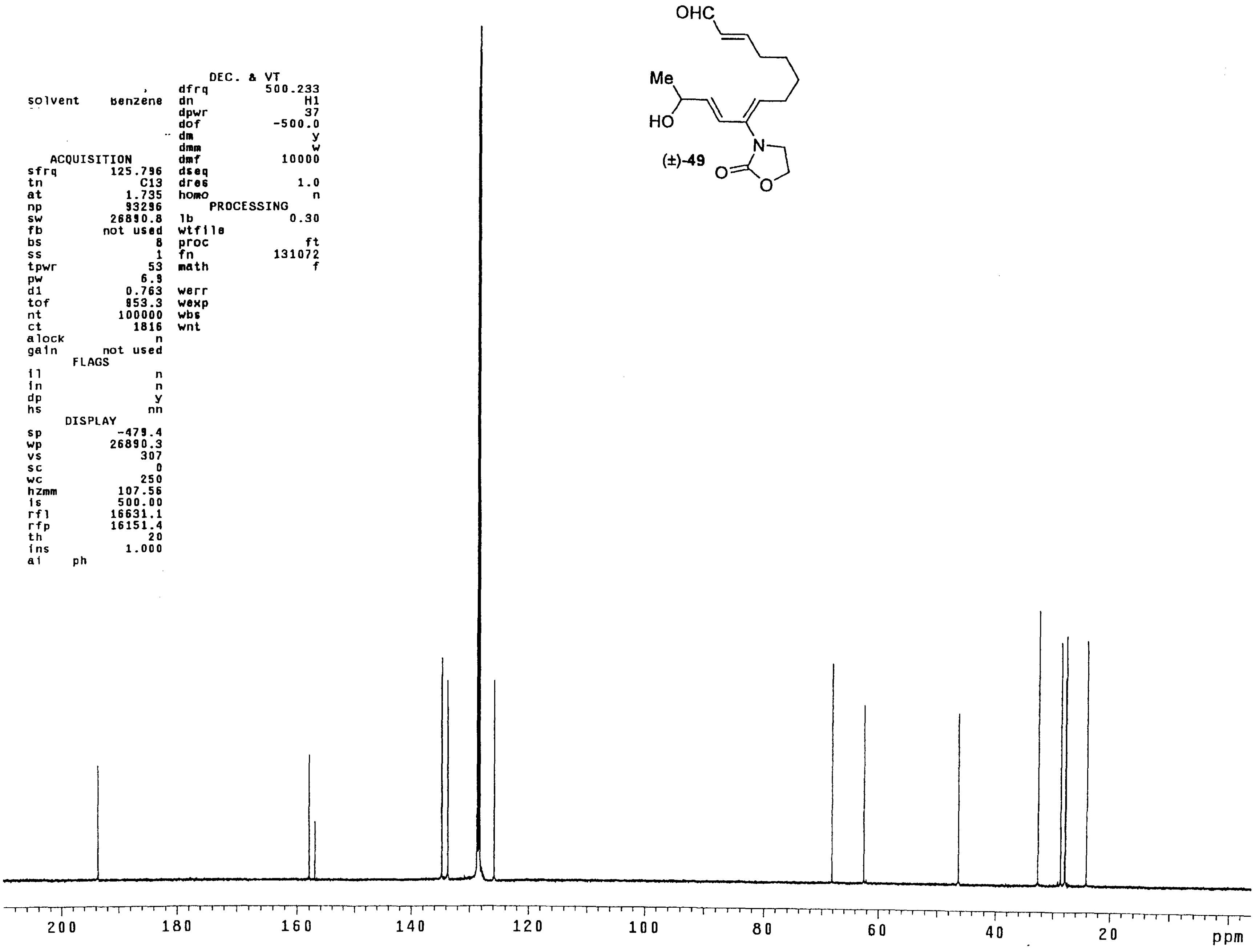

(±)-48

OHC
Me
TBSO
N
O
O
%T
96.2
90
85
80
75
70
65
60
55
50
45
40
35
30
25
18.9
4000.0
3000
2000
1500
1000
400.0
cm-1
3361.20
2953.47
2857.09
2929.19
2737.73
1758.64
1689.95
1636.18
1482.58
1472.36
1462.74
1415.82
1361.35
1293.77
1250.79
1149.70
1093.01
1041.69
1005.78
973.02
924.74
835.62
810.93
777.30
760.28
664.32



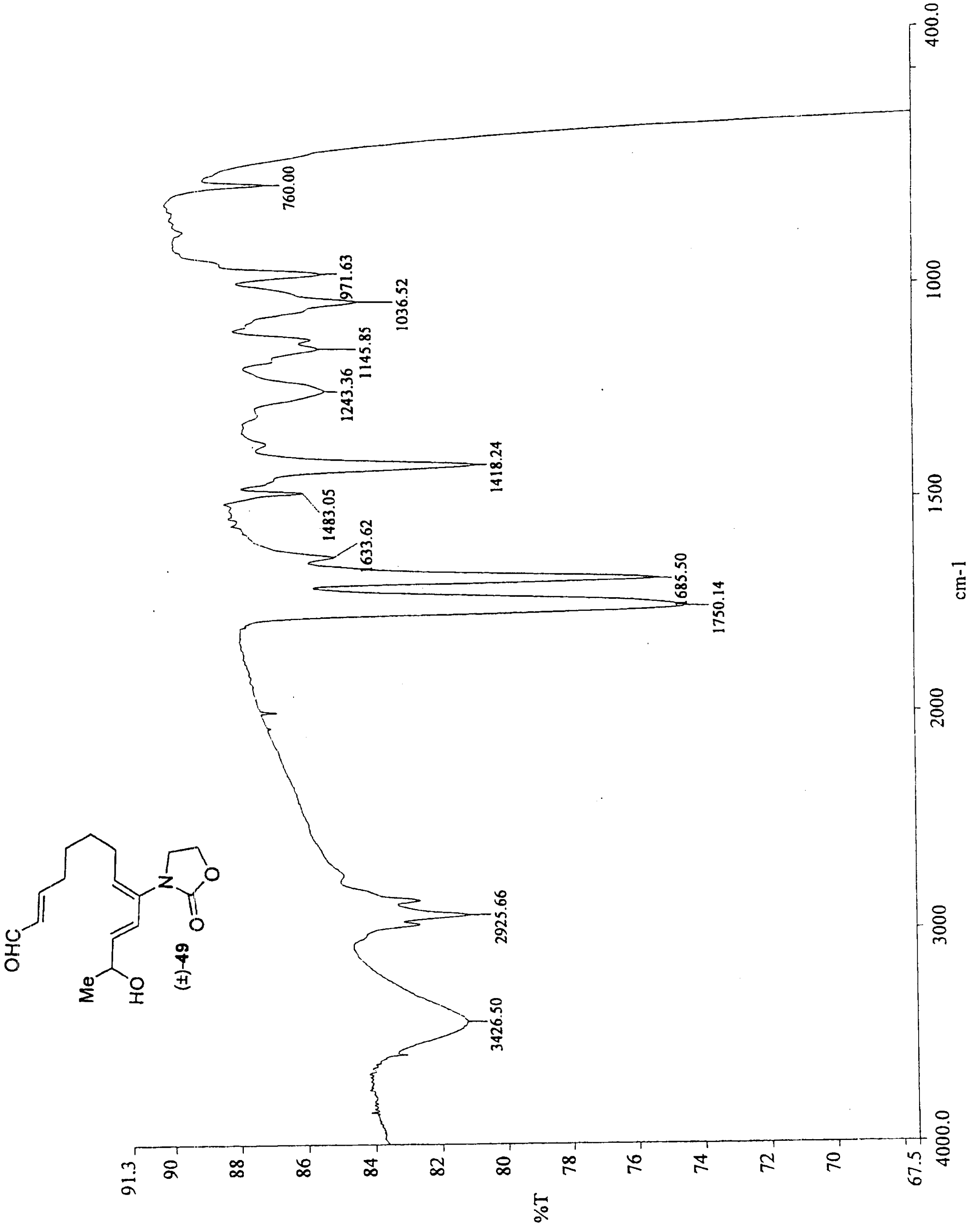
(±)-49

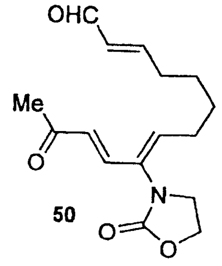
```
                         DEC. & VT
                        dfrq        125.673
solvent     Benzene     dn              C13
file /data/export/~     dpwr             30
home/movassag/Mdh/~     dof               0
bullwinkle/DKH-VII~     dm              nnn
          -12b.fid      dmm               w
   ACQUISITION          dmf           10000
sfrq        499.748     dseq
tn               H1     dres            1.0
at            3.001     homo              n
np            37494        PROCESSING
sw           6247.6     wtfile
fb         not used     proc             ft
bs                8     fn           131072
tpwr             56     math              f
pw              8.9
d1            2.000     werr
tof           361.1     wexp
nt              128     wbs
ct               16     wnt             wft
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp           -250.3
wp           6247.5
vs              151
sc                0
wc              250
hzmm          24.99
is            33.57
rfl           250.4
rfp               0
th                7
ins           1.000
nm  cdc  ph
```



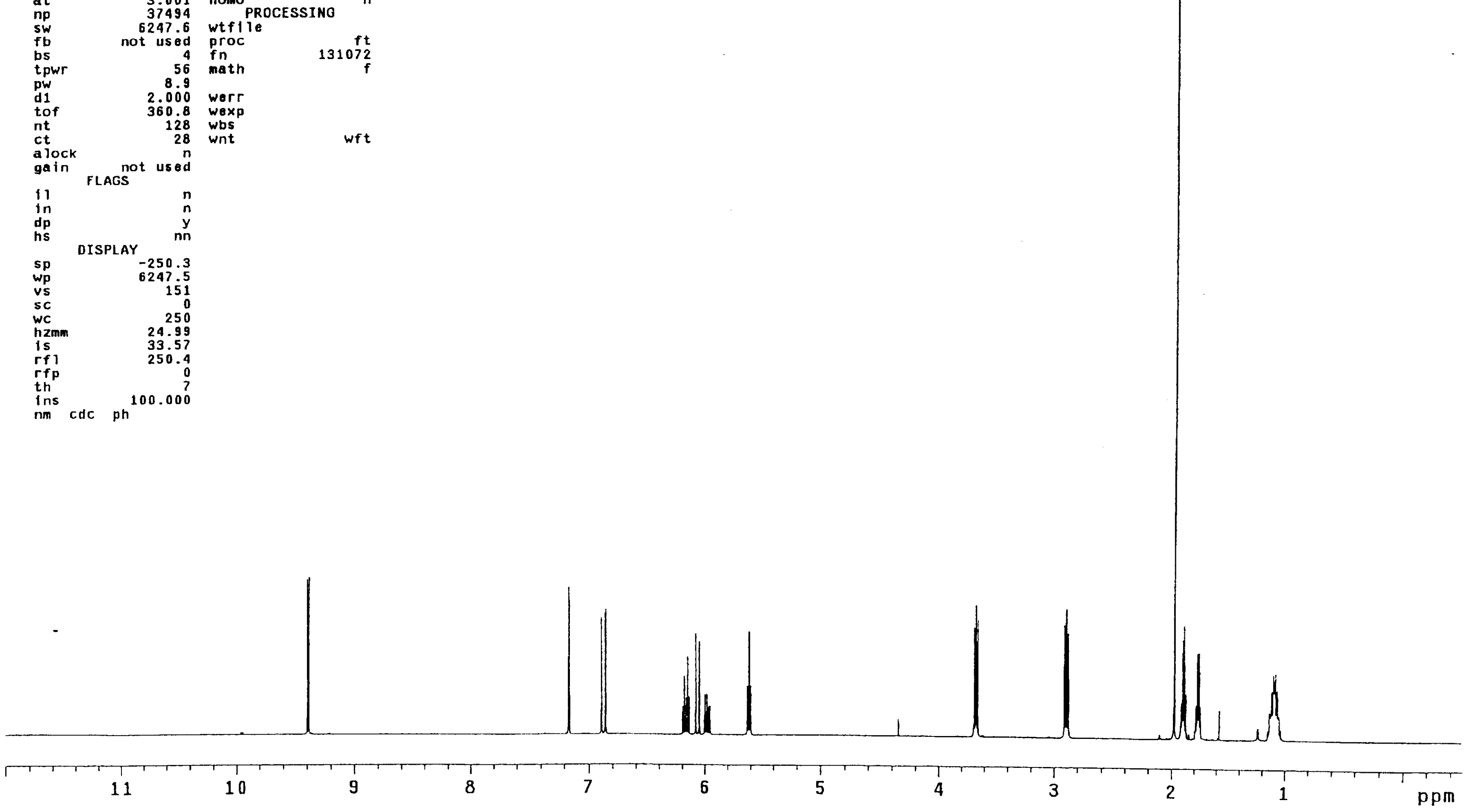
(±)-49

```
                        DEC. & VT
                        dfrq      500.233
solvent    benzene      dn             H1
                        dpwr           37
                        dof        -500.0
                        dm              y
                        dmm             w
  ACQUISITION           dmf         10000
sfrq       125.796      dseq
tn             C13      dres          1.0
at           1.735      homo            n
np           93296         PROCESSING
sw         26890.8      lb           0.30
fb        not used      wtfile
bs               8      proc           ft
ss               1      fn         131072
tpwr            53      math            f
pw             6.9
d1           0.763      werr
tof          953.3      wexp
nt          100000      wbs
ct            1816      wnt
alock            n
gain      not used
     FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -479.4
wp         26890.3
vs             307
sc               0
wc             250
hzmm        107.56
is          500.00
rfl        16631.1
rfp        16151.4
th              20
ins          1.000
ai    ph
```

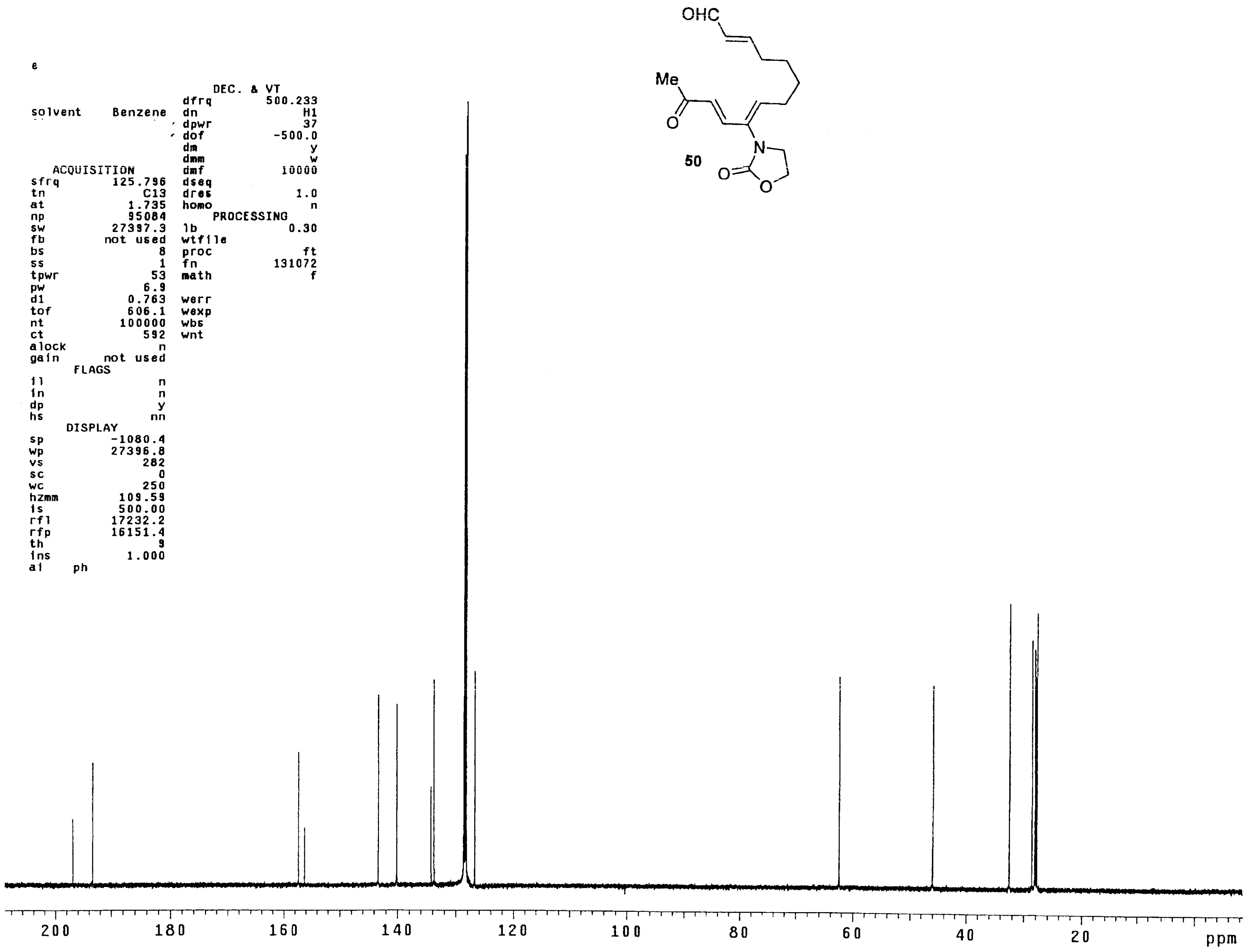

(±)-49
OHC
Me
HO
N
O
O
%T
cm-1
91.3
90
88
86
84
82
80
78
76
74
72
70
67.5
4000.0
3000
2000
1500
1000
400.0
3426.50
2925.66
1750.14
1685.50
1633.62
1483.05
1418.24
1243.36
1145.85
1036.52
971.63
760.00



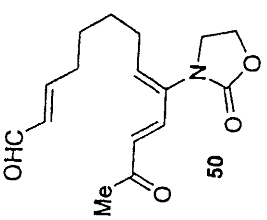
50



```
                             DEC. & VT
                        dfrq        125.673
solvent     Benzene     dn              C13
                        dpwr             30
                        dof               0
                        dm              nnn
                        dmm               w
    ACQUISITION         dmf           10000
sfrq        499.748     dseq
tn               H1     dres            1.0
at            3.001     homo              n
np            37494         PROCESSING
sw           6247.6     wtfile
fb         not used     proc             ft
bs                4     fn           131072
tpwr             56     math              f
pw              8.9
d1            2.000     werr
tof           360.8     wexp
nt              128     wbs
ct               28     wnt             wft
alock             n
gain       not used
       FLAGS
il                n
in                n
dp                y
hs               nn
      DISPLAY
sp           -250.3
wp           6247.5
vs              151
sc                0
wc              250
hzmm          24.99
is            33.57
rfl           250.4
rfp               0
th                7
ins         100.000
nm  cdc  ph
```

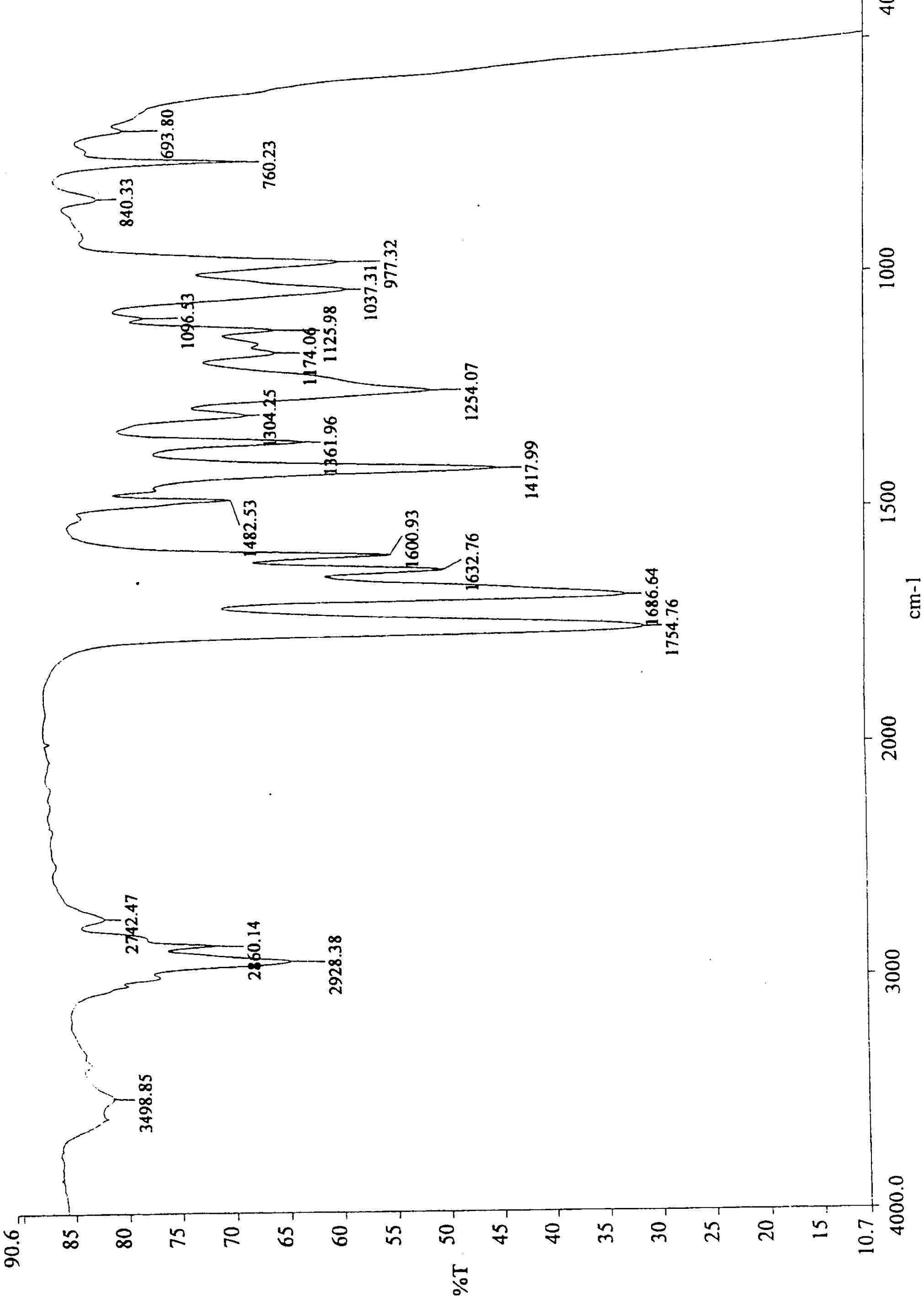


```
e
                          DEC. & VT
                    dfrq        500.233
solvent    Benzene  dn               H1
                    dpwr             37
                    dof          -500.0
                    dm                y
                    dmm               w
  ACQUISITION       dmf           10000
sfrq       125.796  dseq
tn             C13  dres            1.0
at           1.735  homo              n
np           95084      PROCESSING
sw         27397.3  lb             0.30
fb        not used  wtfile
bs               8  proc             ft
ss               1  fn           131072
tpwr            53  math              f
pw             6.9
d1           0.763  werr
tof          606.1  wexp
nt          100000  wbs
ct             592  wnt
alock            n
gain      not used
     FLAGS
il               n
in               n
dp               y
hs              nn
    DISPLAY
sp         -1080.4
wp         27396.8
vs             282
sc               0
wc             250
hzmm        109.59
is          500.00
rfl        17232.2
rfp        16151.4
th               9
ins          1.000
ai    ph
```

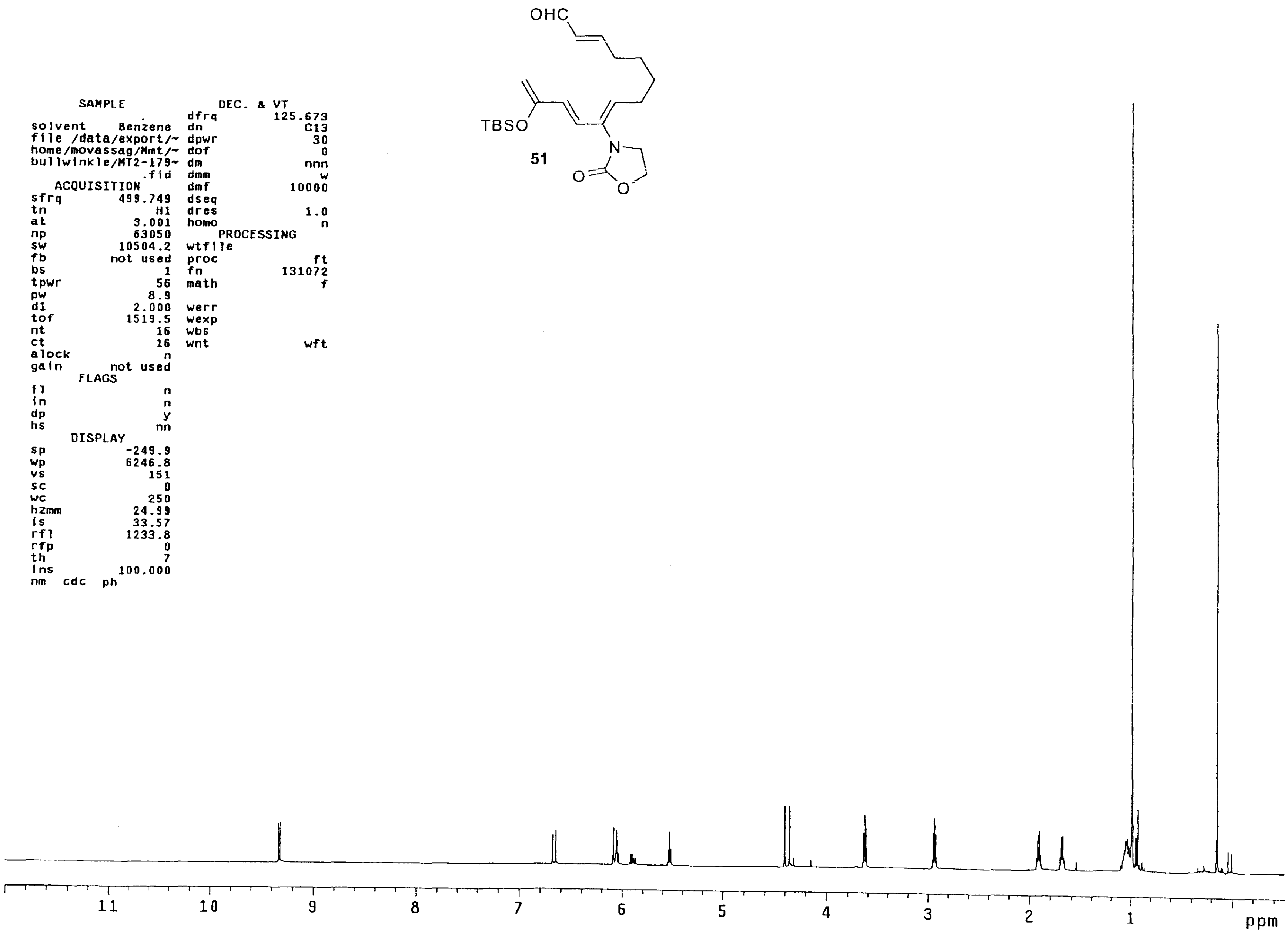


OHC
Me
O
N
O
O

50

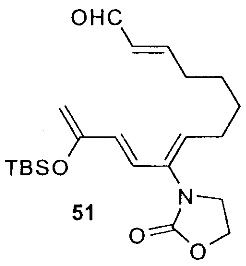


%T
cm-1
90.6
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10.7
4000.0
3000
2000
1500
1000
400.0
3498.85
2928.38
2860.14
2742.47
1754.76
1686.64
1632.76
1600.93
1482.53
1417.99
1361.96
1304.25
1254.07
1174.06
1125.98
1096.53
1037.31
977.32
840.33
760.23
693.80

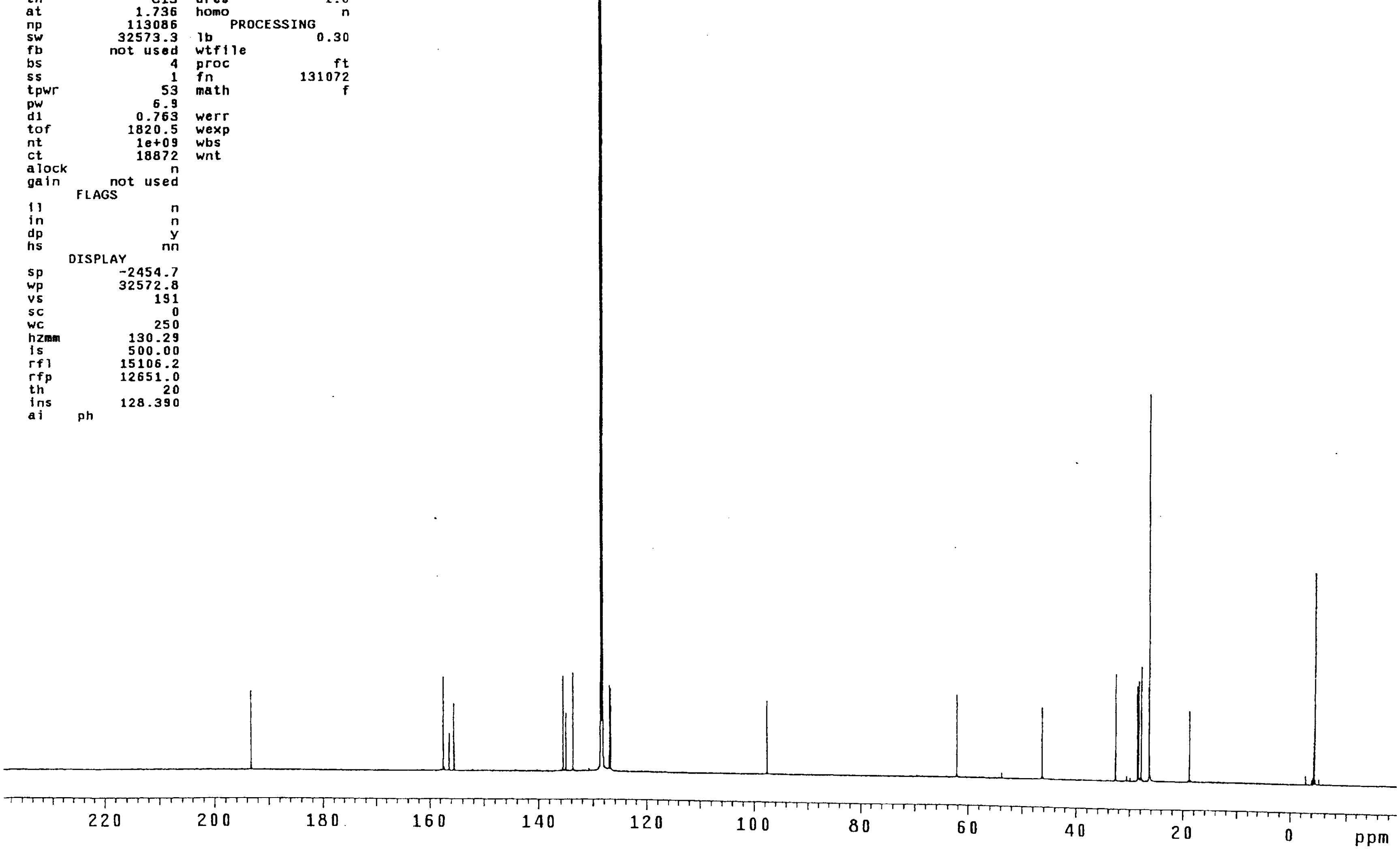


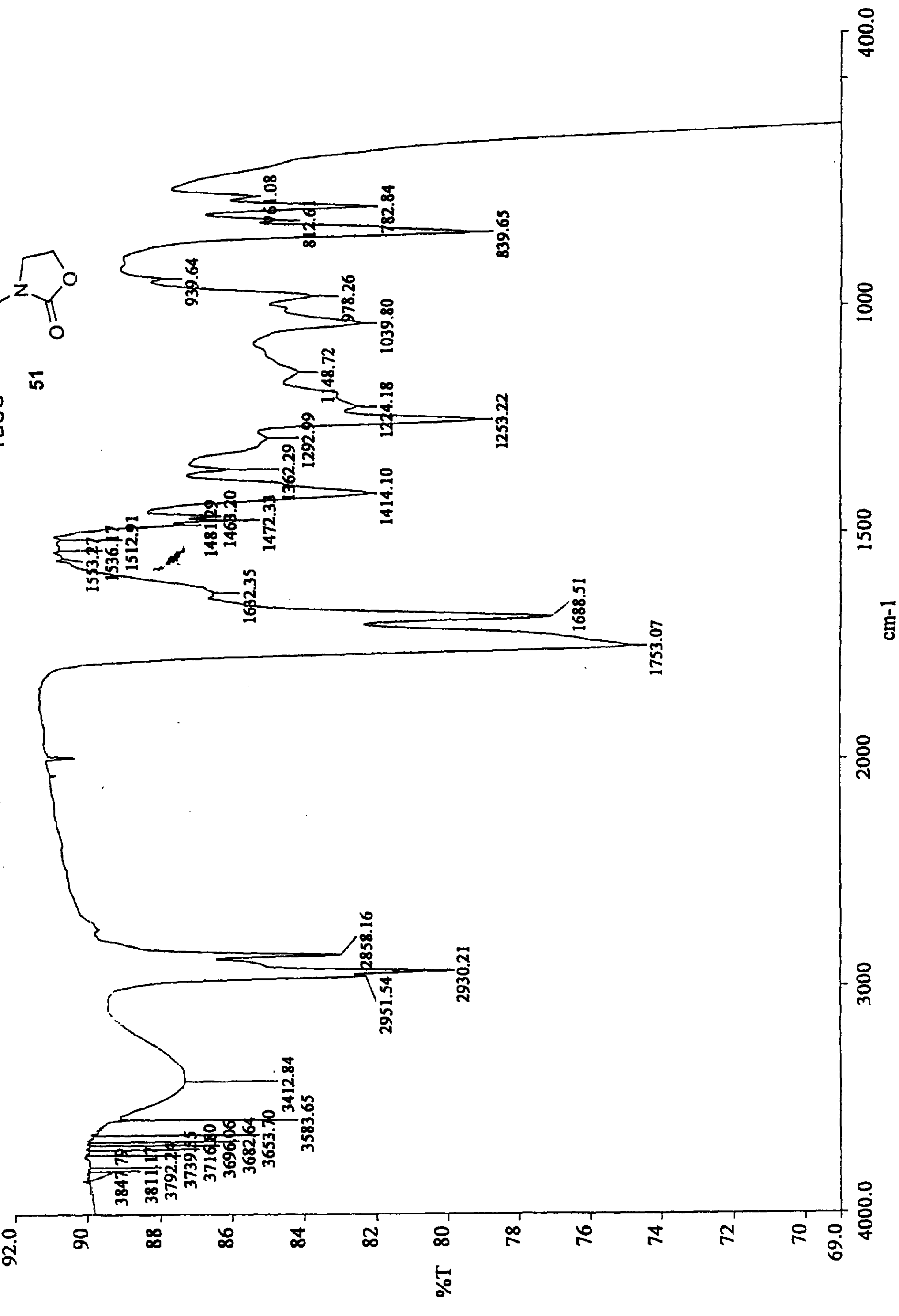
```
      SAMPLE            DEC. & VT
                     dfrq      125.673
solvent    Benzene   dn            C13
file /data/export/~  dpwr           30
home/movassag/Mmt/~  dof             0
bullwinkle/MT2-179~  dm            nnn
              .fid   dmm             w
   ACQUISITION       dmf         10000
sfrq       499.749   dseq
tn              H1   dres          1.0
at           3.001   homo            n
np           63050       PROCESSING
sw         10504.2   wtfile
fb        not used   proc           ft
bs               1   fn         131072
tpwr            56   math            f
pw             8.9
d1           2.000   werr
tof         1519.5   wexp
nt              16   wbs
ct              16   wnt           wft
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -249.9
wp          6246.8
vs             151
sc               0
wc             250
hzmm         24.99
is           33.57
rfl         1233.8
rfp              0
th               7
ins        100.000
nm   cdc   ph
```

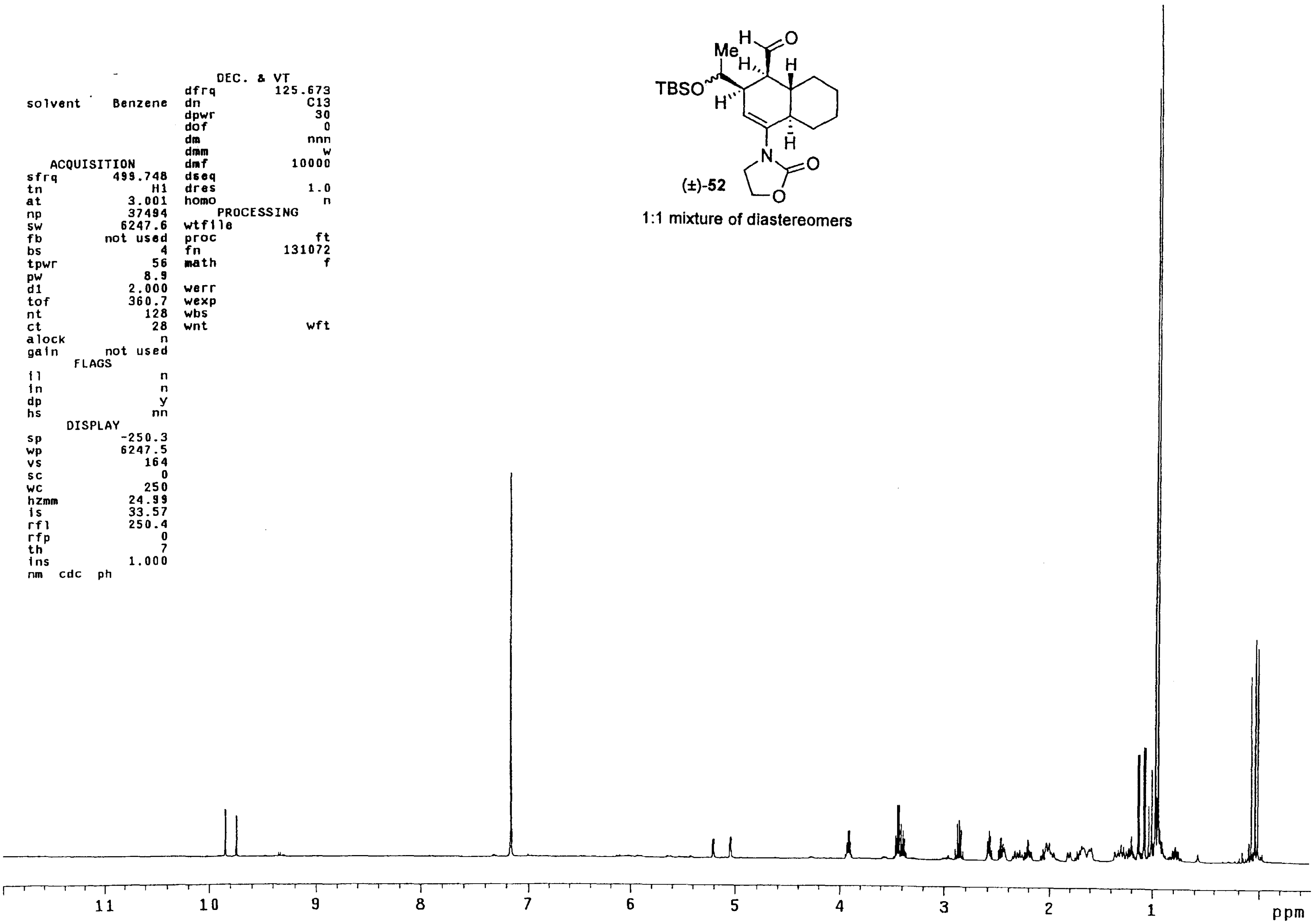
```
      SAMPLE              DEC. & VT
                     dfrq       500.233
solvent    Benzene   dn              H1
file /data/export/~  dpwr            37
home/movassag/Mmt/~  dof         -500.0
rocky/MT2-179_carb~  dm               y
            on.fid   dmm              w
   ACQUISITION       dmf          10000
sfrq       125.797   dseq
tn             C13   dres           1.0
at           1.736   homo             n
np          113086      PROCESSING
sw         32573.3   lb            0.30
fb        not used   wtfile
bs               4   proc            ft
ss               1   fn          131072
tpwr            53   math             f
pw             6.9
d1           0.763   werr
tof         1820.5   wexp
nt          1e+09    wbs
ct           18872   wnt
alock            n
gain      not used
       FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp         -2454.7
wp         32572.8
vs             191
sc               0
wc             250
hzmm        130.29
is          500.00
rfl        15106.2
rfp        12651.0
th              20
ins        128.390
ai    ph
```



51



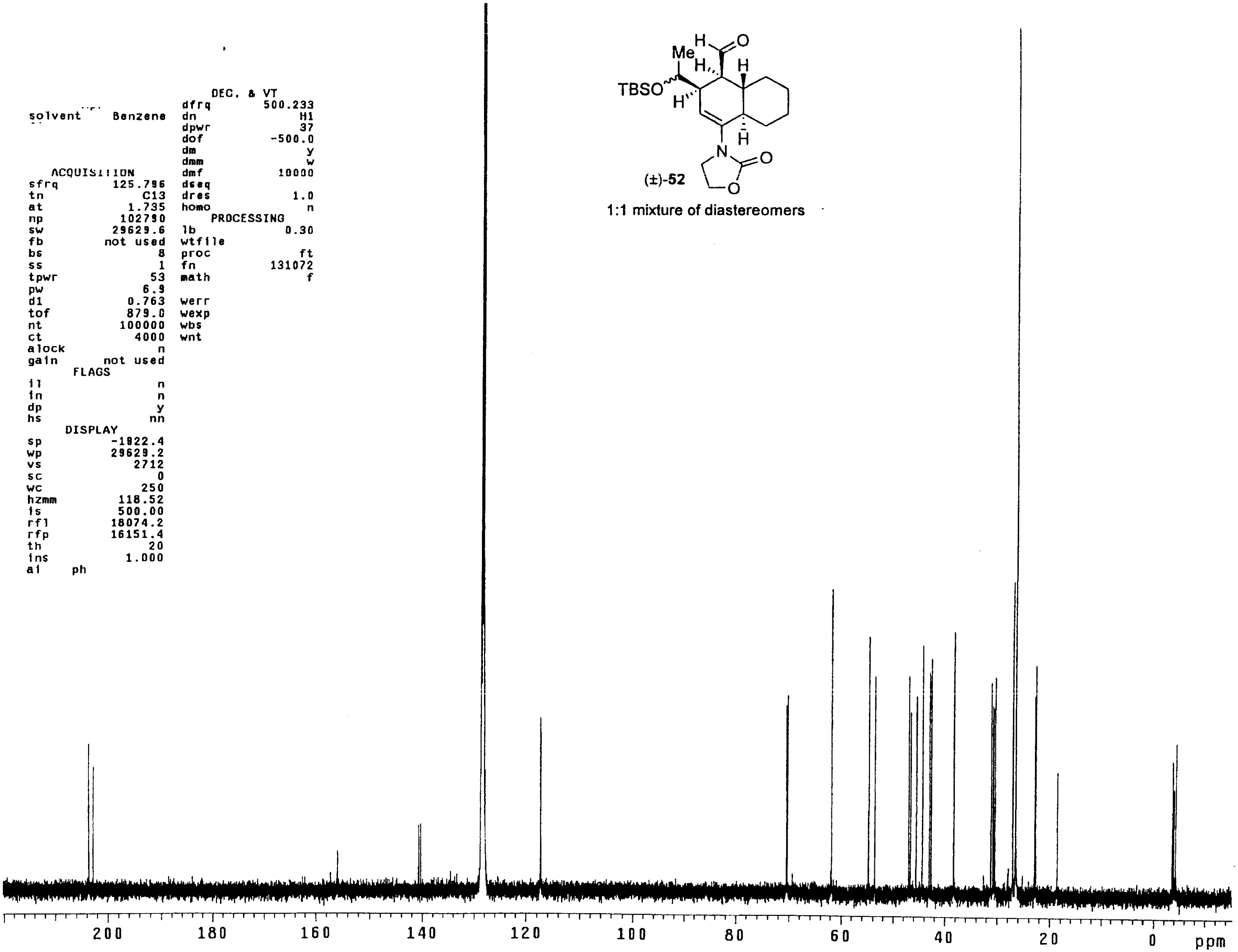

OHC
TBSO
N
O
O
51
%T
92.0
90
88
86
84
82
80
78
76
74
72
70
69.0
4000.0
3000
2000
1500
1000
400.0
cm-1
3847.79
3811.17
3792.24
3739.35
3716.80
3696.06
3682.64
3653.70
3583.65
3412.84
2951.54
2930.21
2858.16
1753.07
1688.51
1632.35
1553.27
1536.17
1512.91
1481.29
1468.20
1472.33
1414.10
1362.29
1292.99
1253.22
1224.18
1148.72
1039.80
978.26
939.64
839.65
812.61
782.84
761.08



(±)-52

1:1 mixture of diastereomers

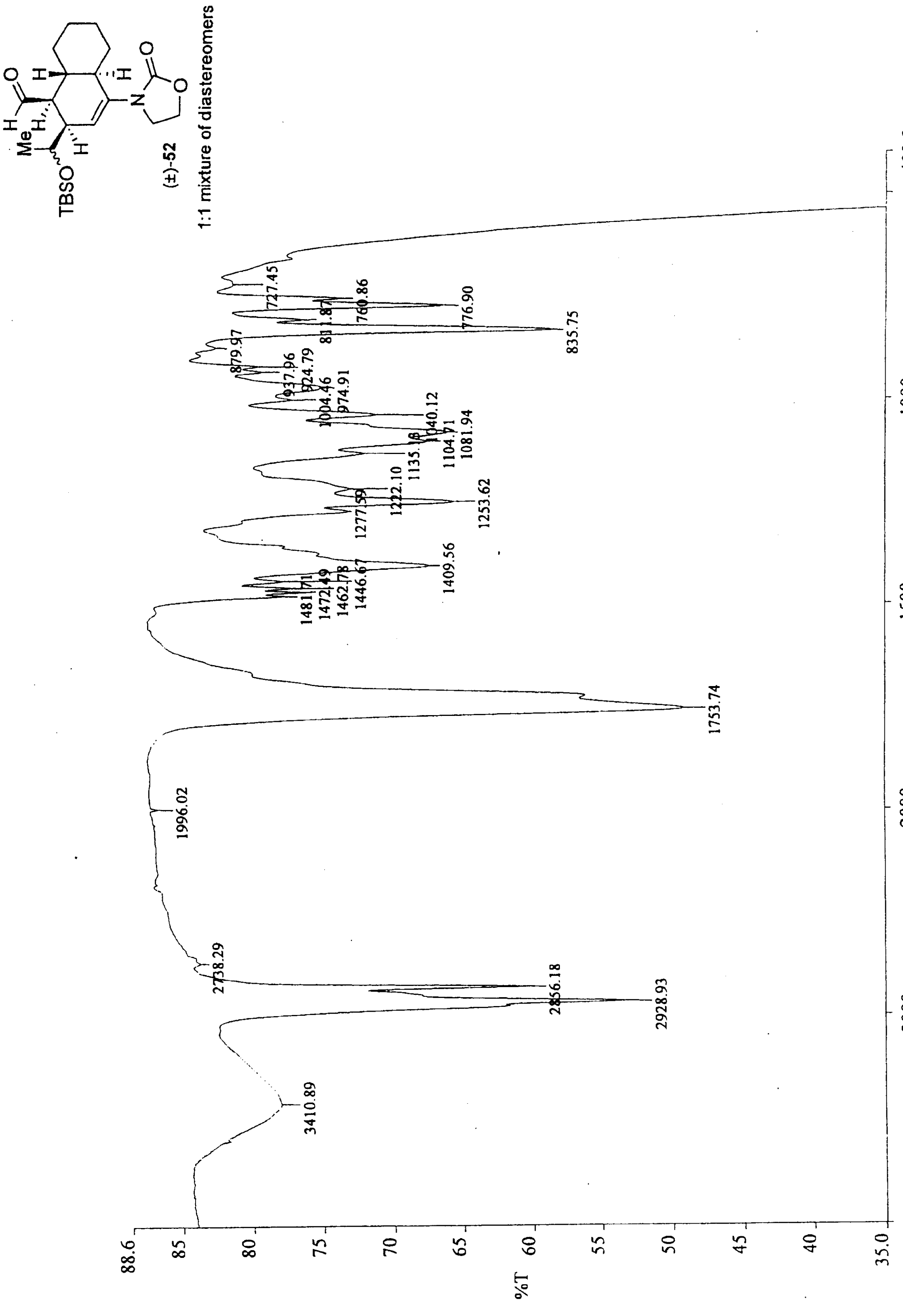
```
                             DEC. & VT
                         dfrq        125.673
solvent    Benzene       dn              C13
                         dpwr             30
                         dof               0
                         dm              nnn
                         dmm               w
   ACQUISITION           dmf           10000
sfrq        499.748      dseq
tn               H1      dres            1.0
at            3.001      homo              n
np            37494          PROCESSING
sw           6247.6      wtfile
fb         not used      proc             ft
bs                4      fn           131072
tpwr             56      math              f
pw              8.9
d1            2.000      werr
tof           360.7      wexp
nt              128      wbs
ct               28      wnt             wft
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp           -250.3
wp           6247.5
vs              164
sc                0
wc              250
hzmm          24.99
is            33.57
rfl           250.4
rfp               0
th                7
ins           1.000
nm  cdc  ph
```



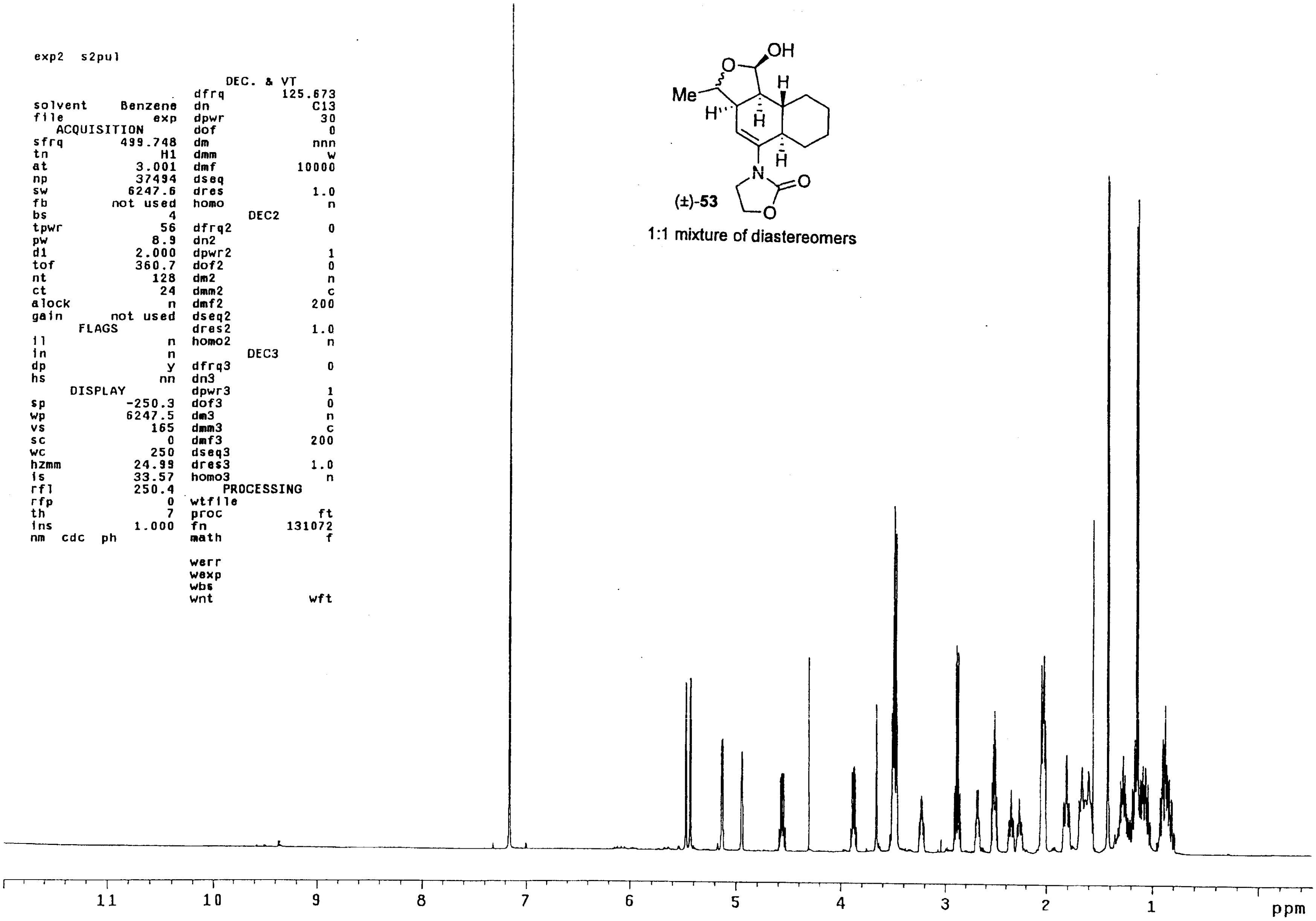
(±)-52

1:1 mixture of diastereomers

```
                        DEC. & VT
                        dfrq        500.233
solvent     Benzene     dn               H1
                        dpwr             37
                        dof          -500.0
                        dm                y
                        dmm               w
   ACQUISITION          dmf           10000
sfrq        125.796     dseq
tn              C13     dres            1.0
at            1.735     homo              n
np           102790        PROCESSING
sw          29629.6     lb             0.30
fb         not used     wtfile
bs                8     proc             ft
ss                1     fn           131072
tpwr             53     math              f
pw              6.9
d1            0.763     werr
tof           879.0     wexp
nt           100000     wbs
ct             4000     wnt
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp          -1822.4
wp          29629.2
vs             2712
sc                0
wc              250
hzmm         118.52
is           500.00
rfl         18074.2
rfp         16151.4
th               20
ins           1.000
ai    ph
```


(±)-52

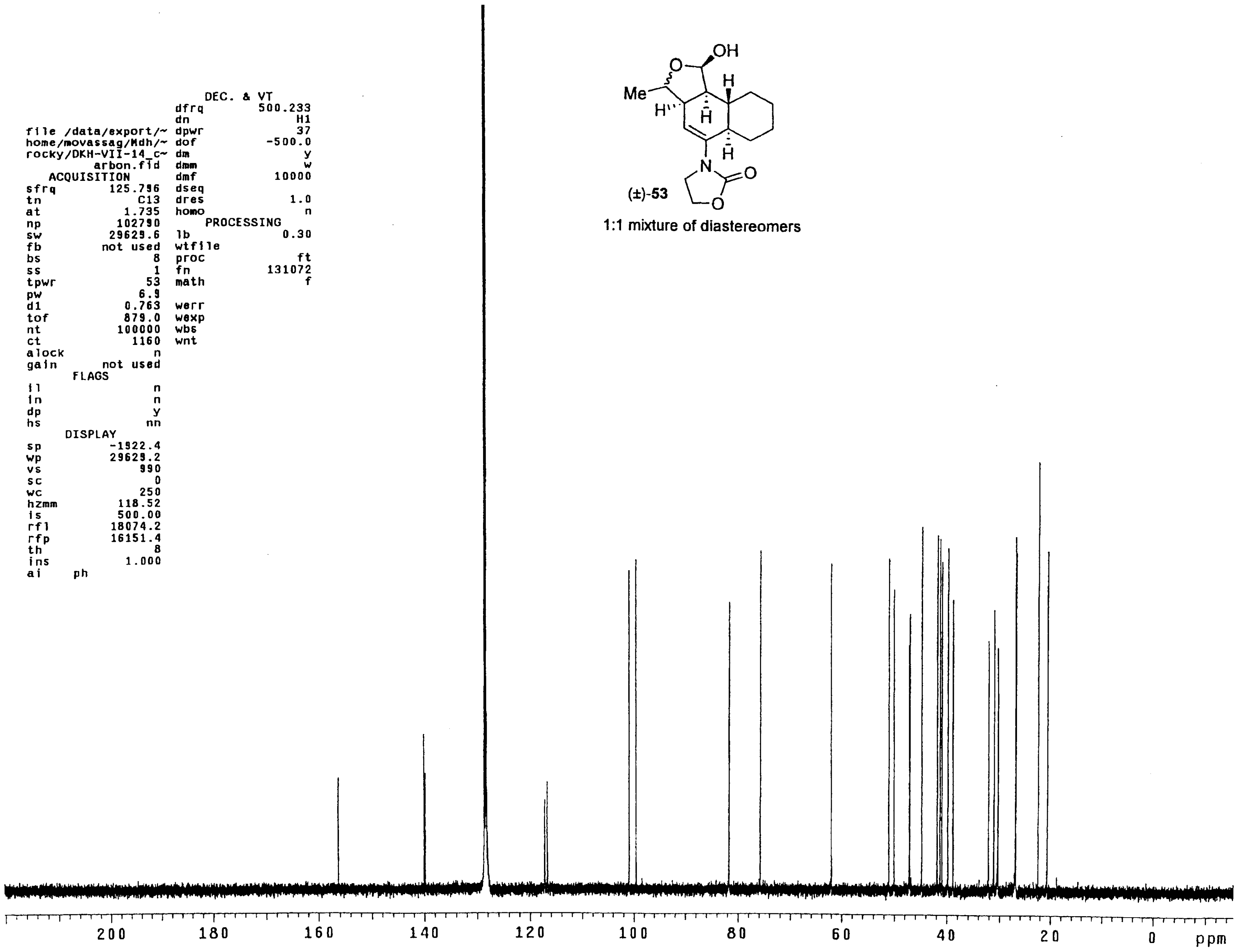
1:1 mixture of diastereomers



(±)-**53**

1:1 mixture of diastereomers

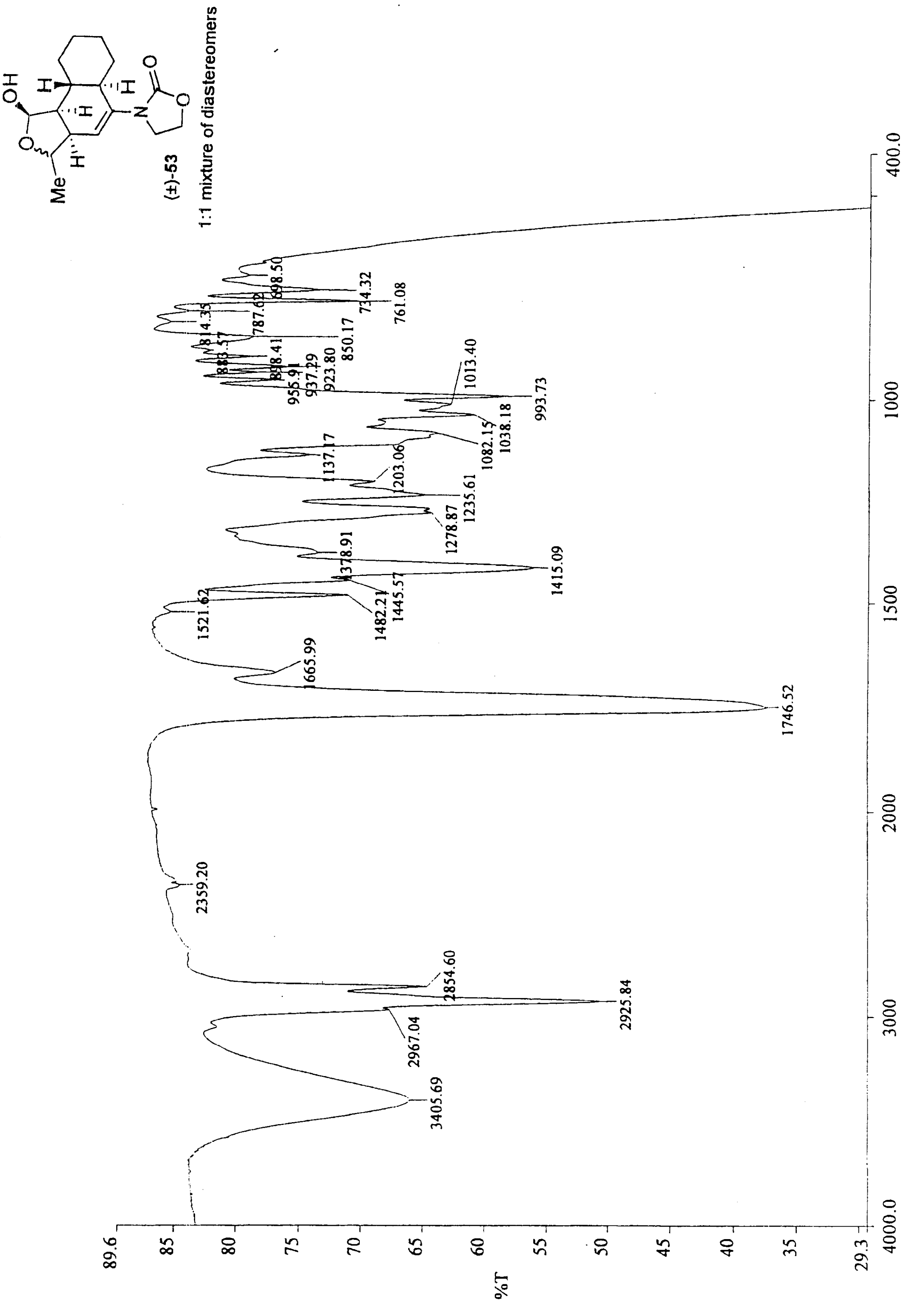
```
exp2  s2pul

                          DEC. & VT
                         dfrq        125.673
solvent     Benzene      dn              C13
file            exp      dpwr             30
   ACQUISITION           dof               0
sfrq        499.748      dm              nnn
tn               H1      dmm               w
at            3.001      dmf           10000
np            37494      dseq
sw           6247.6      dres            1.0
fb         not used      homo              n
bs                4            DEC2
tpwr             56      dfrq2             0
pw              8.9      dn2
d1            2.000      dpwr2             1
tof           360.7      dof2              0
nt              128      dm2               n
ct               24      dmm2              c
alock             n      dmf2            200
gain       not used      dseq2
      FLAGS              dres2           1.0
il                n      homo2             n
in                n            DEC3
dp                y      dfrq3             0
hs               nn      dn3
     DISPLAY             dpwr3             1
sp           -250.3      dof3              0
wp           6247.5      dm3               n
vs              165      dmm3              c
sc                0      dmf3            200
wc              250      dseq3
hzmm          24.99      dres3           1.0
is            33.57      homo3             n
rfl           250.4         PROCESSING
rfp               0      wtfile
th                7      proc             ft
ins           1.000      fn           131072
nm  cdc  ph              math              f

                         werr
                         wexp
                         wbs
                         wnt             wft
```



```
                              DEC. & VT
                          dfrq         500.233
                          dn                H1
file /data/export/~       dpwr              37
home/movassag/Mdh/~       dof           -500.0
rocky/DKH-VII-14_c~       dm                 y
          arbon.fid       dmm                w
   ACQUISITION            dmf            10000
sfrq        125.796       dseq
tn              C13       dres             1.0
at            1.735       homo               n
np           102790          PROCESSING
sw          29629.6       lb              0.30
fb         not used       wtfile
bs                8       proc              ft
ss                1       fn            131072
tpwr             53       math               f
pw              6.9
d1            0.763       werr
tof           879.0       wexp
nt           100000       wbs
ct             1160       wnt
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp          -1922.4
wp          29629.2
vs              990
sc                0
wc              250
hzmm         118.52
is           500.00
rfl         18074.2
rfp         16151.4
th                8
ins           1.000
ai    ph
```

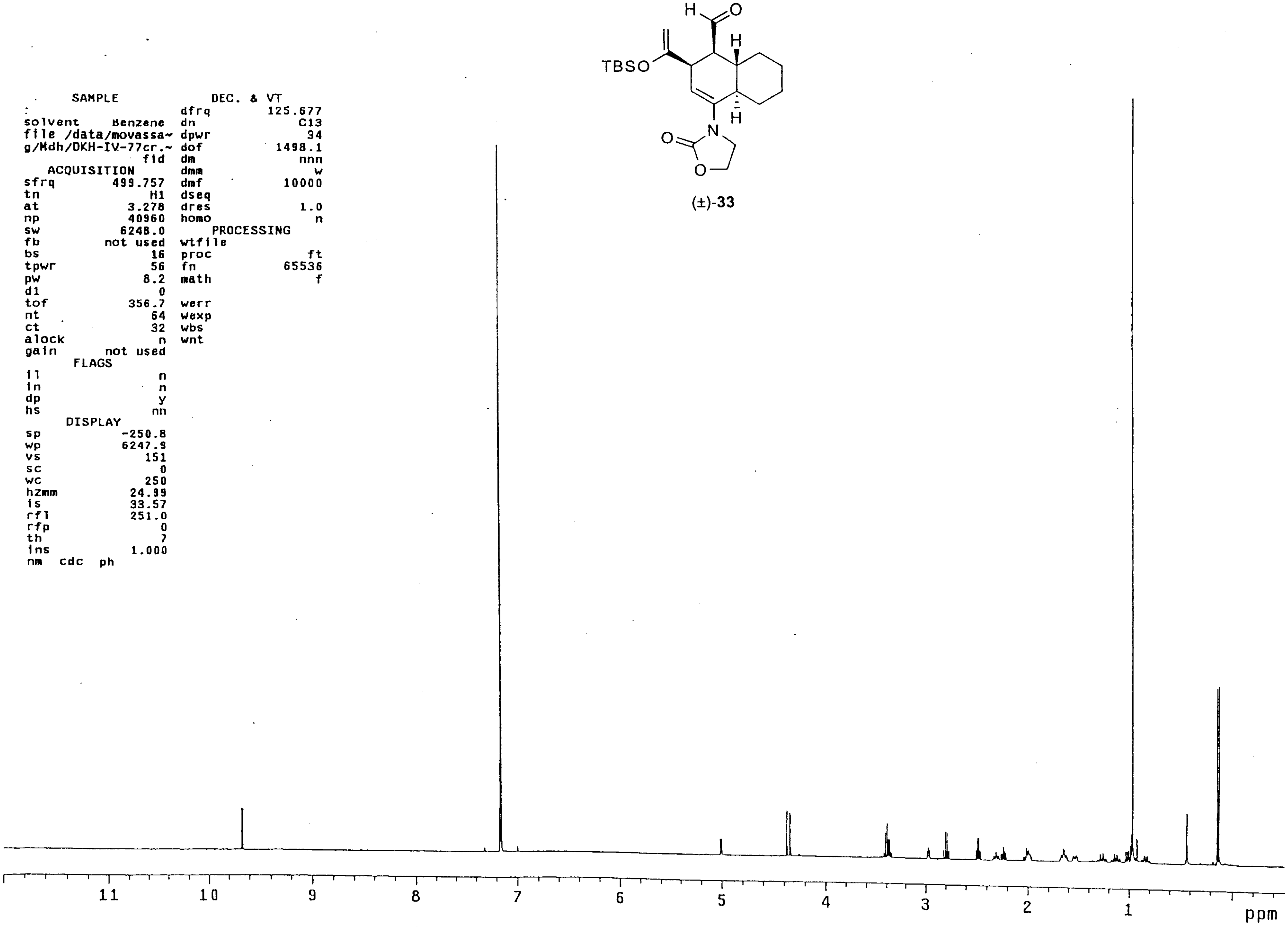
(±)-**53**

1:1 mixture of diastereomers



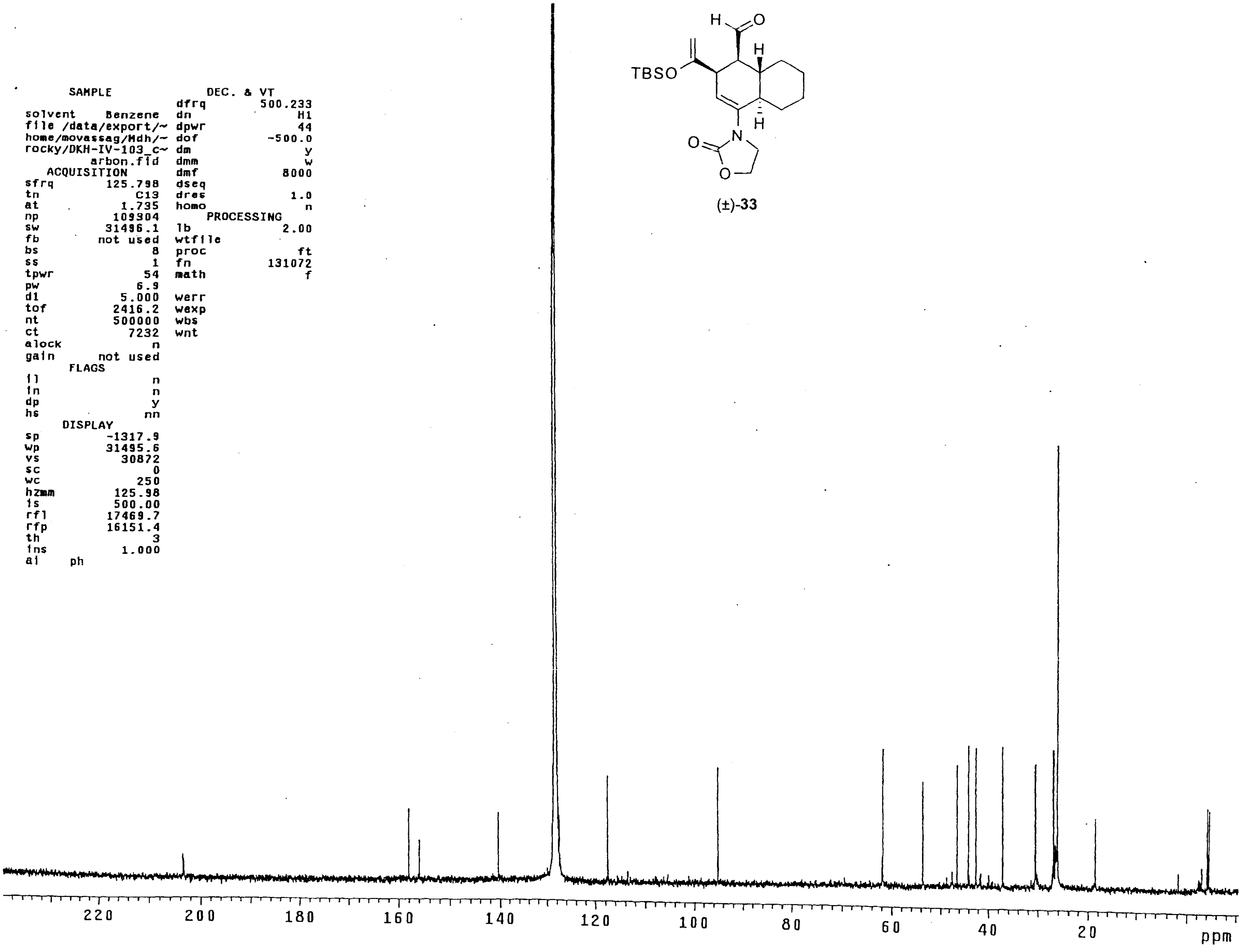
(±)-53

1:1 mixture of diastereomers



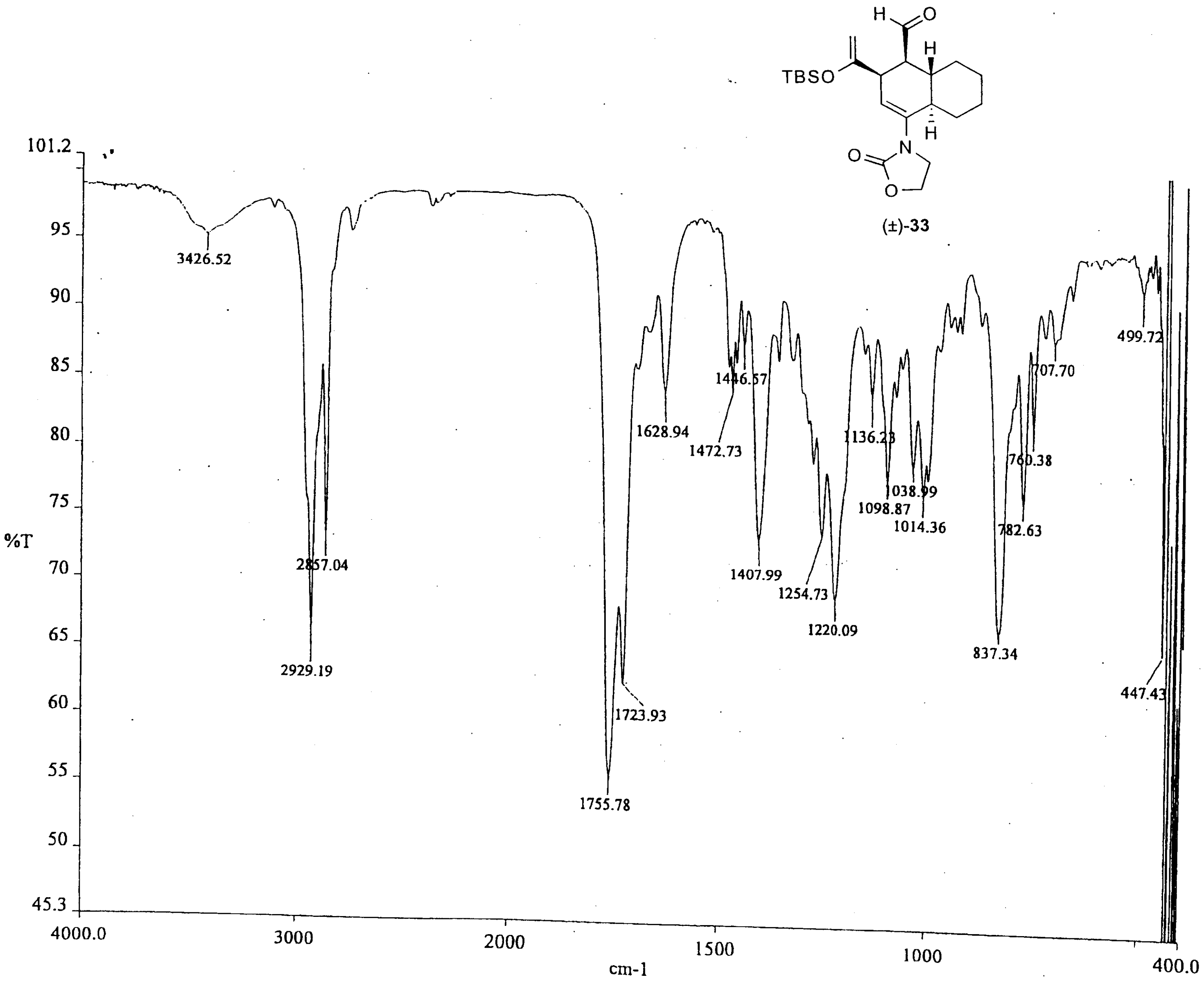
(±)-33

```
      SAMPLE              DEC. & VT
:                       dfrq         125.677
solvent     Benzene     dn               C13
file /data/movassa~     dpwr              34
g/Mdh/DKH-IV-77cr.~     dof           1498.1
                fid     dm               nnn
   ACQUISITION          dmm                w
sfrq        499.757     dmf            10000
tn               H1     dseq
at            3.278     dres             1.0
np            40960     homo               n
sw           6248.0        PROCESSING
fb         not used     wtfile
bs               16     proc              ft
tpwr             56     fn             65536
pw              8.2     math               f
d1                0
tof           356.7     werr
nt               64     wexp
ct               32     wbs
alock             n     wnt
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp           -250.8
wp           6247.9
vs              151
sc                0
wc              250
hzmm          24.99
is            33.57
rfl           251.0
rfp               0
th                7
ins           1.000
nm  cdc  ph
```

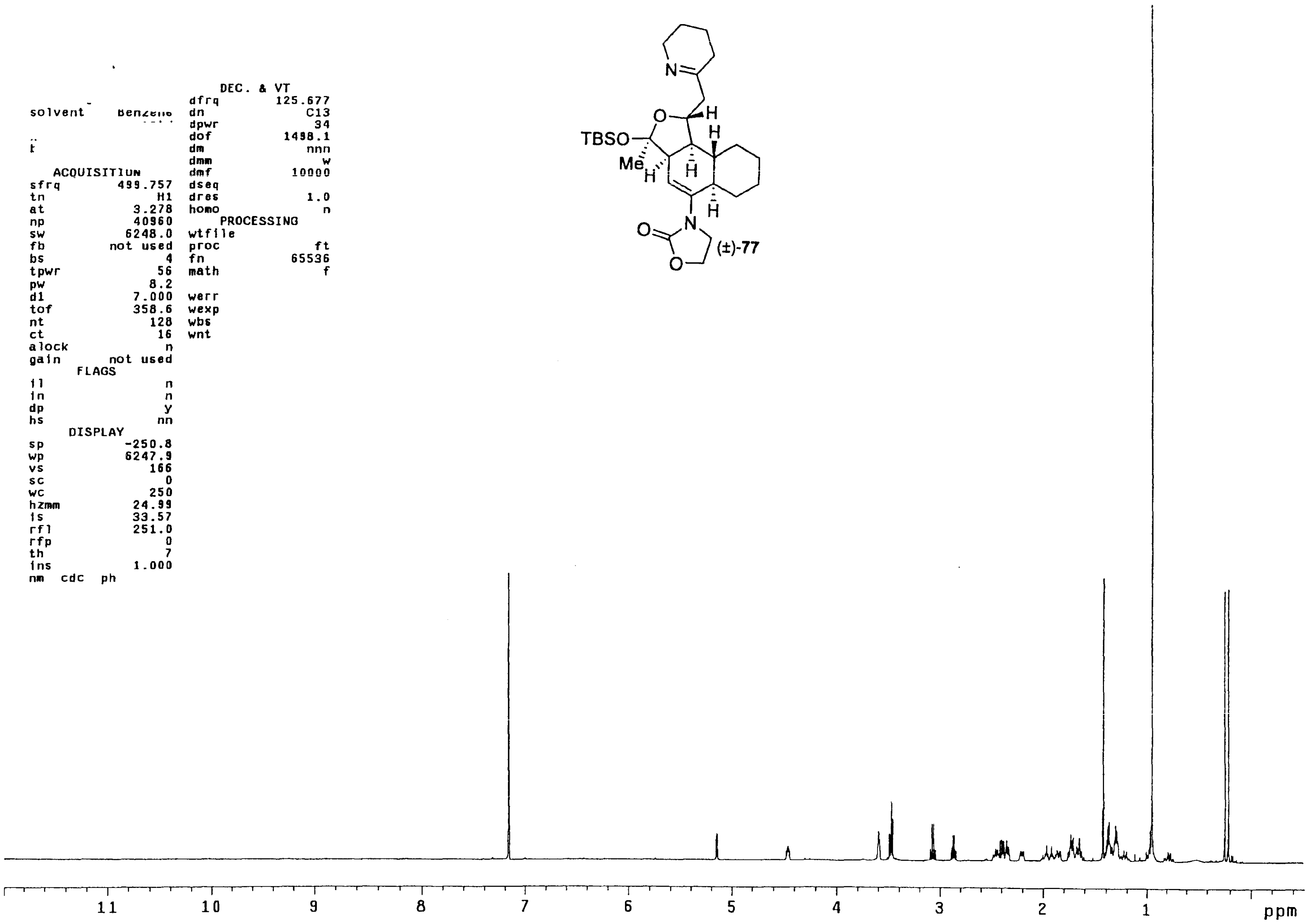


(±)-33

```
      SAMPLE              DEC. & VT
                     dfrq        500.233
solvent    Benzene   dn               H1
file /data/export/~  dpwr             44
home/movassag/Mdh/~  dof          -500.0
rocky/DKH-IV-103_c~  dm                y
         arbon.fid   dmm               w
    ACQUISITION      dmf            8000
sfrq       125.798   dseq
tn             C13   dres            1.0
at           1.735   homo              n
np          109304       PROCESSING
sw         31496.1   lb             2.00
fb        not used   wtfile
bs               8   proc             ft
ss               1   fn           131072
tpwr            54   math              f
pw             6.9
d1           5.000   werr
tof         2416.2   wexp
nt          500000   wbs
ct            7232   wnt
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp         -1317.9
wp         31495.6
vs           30872
sc               0
wc             250
hzmm        125.98
is          500.00
rfl        17469.7
rfp        16151.4
th               3
ins          1.000
ai    ph
```

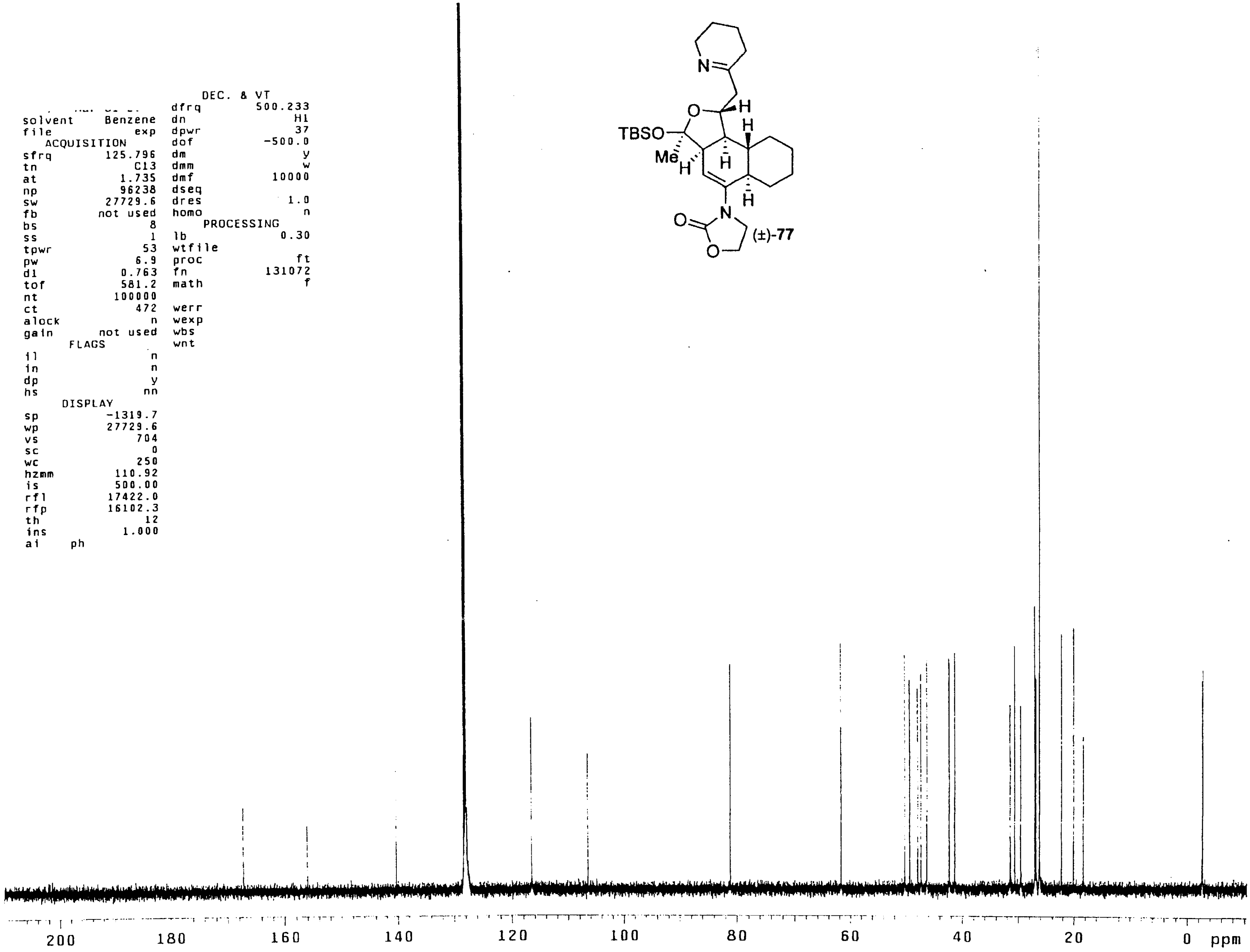

(±)-33

TBSO
H
O
H
H
N
O
O
101.2
95
90
85
80
75
70
65
60
55
50
45.3
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
3426.52
2929.19
2857.04
1755.78
1723.93
1628.94
1472.73
1446.57
1407.99
1254.73
1220.09
1136.23
1098.87
1038.99
1014.36
837.34
782.63
760.38
707.70
499.72
447.43

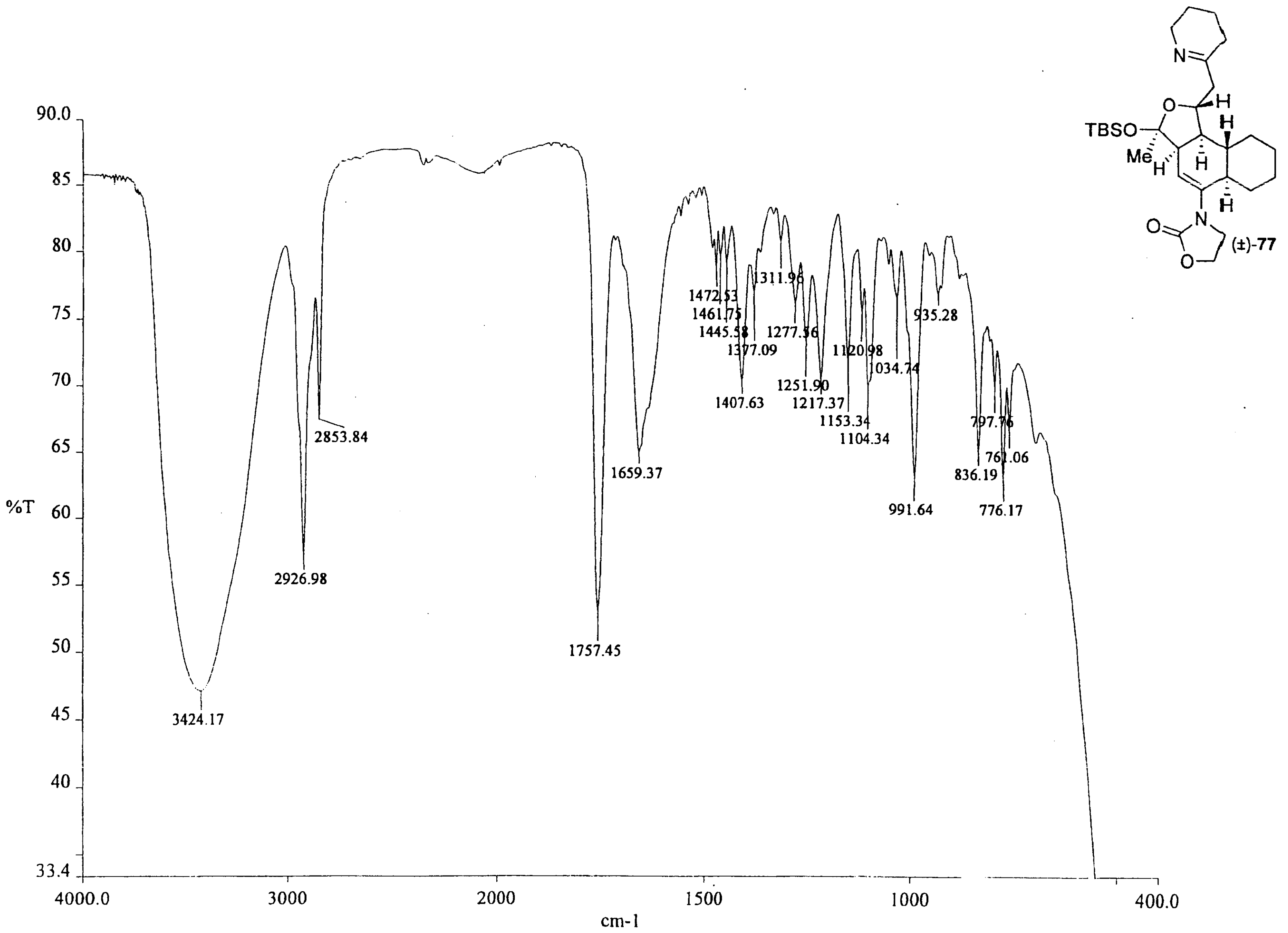


```
                              DEC. & VT
                         dfrq        125.677
solvent    Benzene       dn              C13
                         dpwr             34
                         dof          1498.1
t                        dm              nnn
                         dmm               w
   ACQUISITION           dmf           10000
sfrq         499.757     dseq
tn                H1     dres            1.0
at             3.278     homo              n
np             40960        PROCESSING
sw            6248.0     wtfile
fb          not used     proc             ft
bs                 4     fn            65536
tpwr              56     math              f
pw               8.2
d1             7.000     werr
tof            358.6     wexp
nt               128     wbs
ct                16     wnt
alock              n
gain        not used
      FLAGS
il                 n
in                 n
dp                 y
hs                nn
     DISPLAY
sp            -250.8
wp            6247.9
vs               166
sc                 0
wc               250
hzmm           24.99
is             33.57
rfl            251.0
rfp                0
th                 7
ins            1.000
nm  cdc  ph
```

```
[illegible]                   DEC. & VT
solvent    Benzene   dfrq         500.233
file           exp   dn                H1
   ACQUISITION       dpwr              37
sfrq       125.796   dof           -500.0
tn             C13   dm                 y
at           1.735   dmm                w
np           96238   dmf            10000
sw         27729.6   dseq
fb        not used   dres             1.0
bs               8   homo               n
ss               1       PROCESSING
tpwr            53   lb              0.30
pw             6.9   wtfile
d1           0.763   proc              ft
tof          581.2   fn            131072
nt          100000   math               f
ct             472
alock            n   werr
gain      not used   wexp
      FLAGS          wbs
il               n   wnt
in               n
dp               y
hs              nn
     DISPLAY
sp         -1319.7
wp         27729.6
vs             704
sc               0
wc             250
hzmm        110.92
is          500.00
rfl        17422.0
rfp        16102.3
th              12
ins          1.000
ai    ph
```



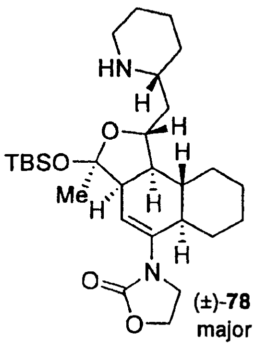
(±)-77


90.0
85
80
75
70
65
60
55
50
45
40
33.4
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
3424.17
2926.98
2853.84
1757.45
1659.37
1472.53
1461.75
1445.58
1407.63
1377.09
1311.96
1277.56
1251.90
1217.37
1153.34
1120.98
1104.34
1034.74
991.64
935.28
836.19
797.76
776.17
761.06
TBSO
Me
H
O
H
H
H
H
N
O
N
O

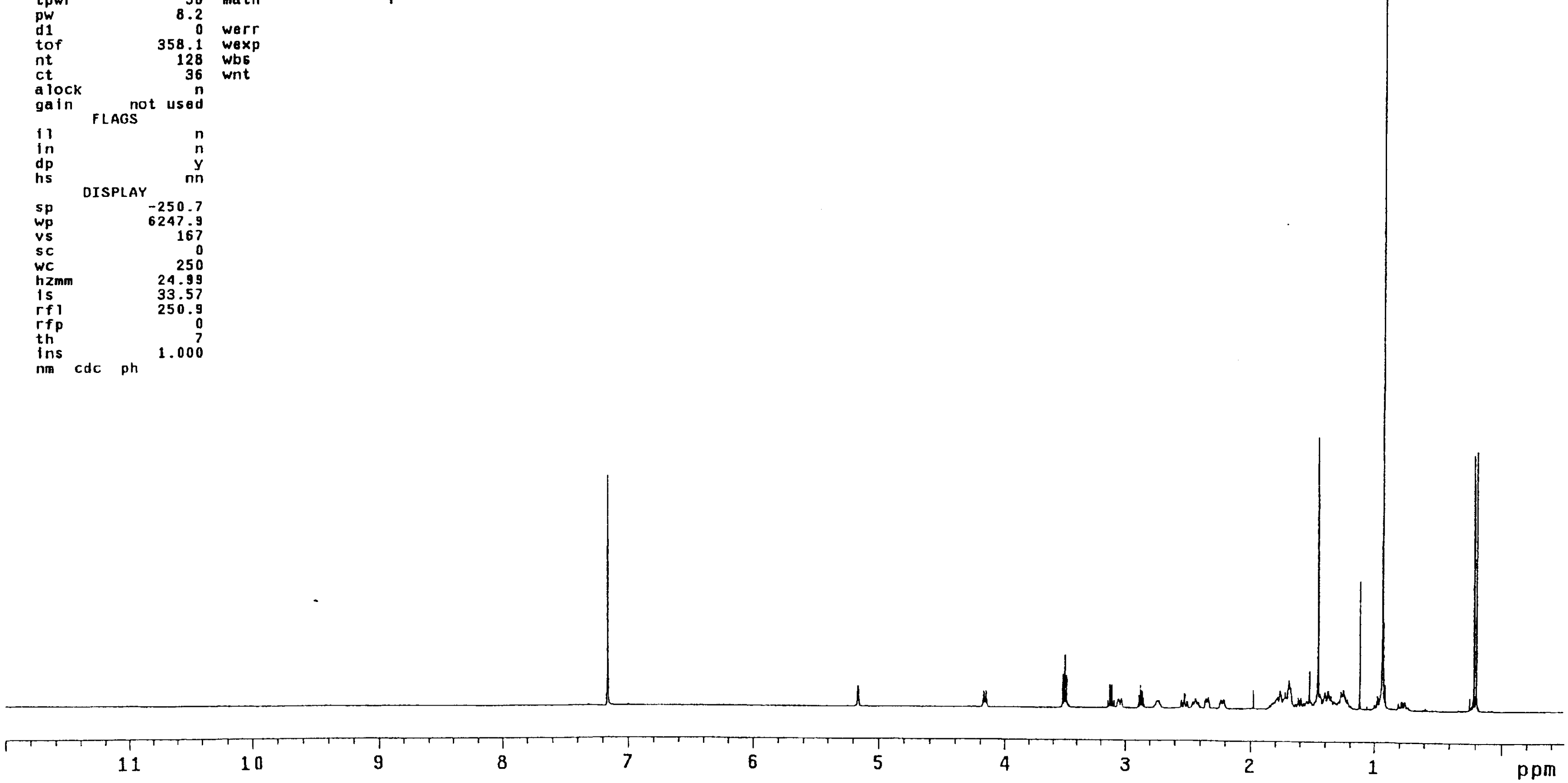
(±)-77

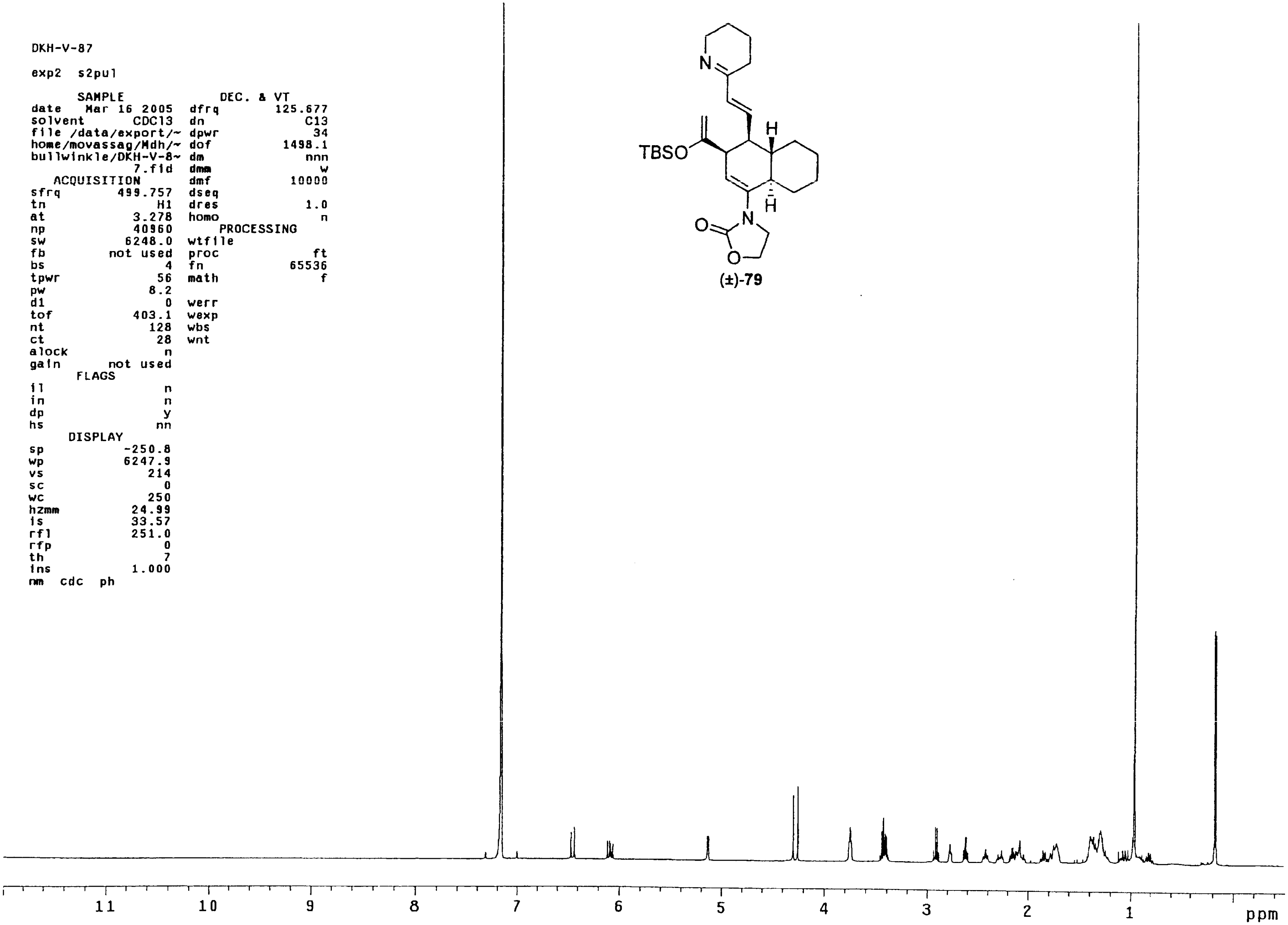
```
solvent    Benzene
  ACQUISITION
sfrq       499.757
tn              H1
at           3.278
np           40960
sw          6248.0
fb        not used
bs               4
tpwr            56
pw             8.2
d1               0
tof          358.1
nt             128
ct              36
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp          -250.7
wp          6247.9
vs             167
sc               0
wc             250
hzmm         24.99
is           33.57
rfl          250.9
rfp              0
th               7
ins          1.000
nm  cdc  ph
```

```
        DEC. & VT
dfrq       125.677
dn             C13
dpwr            34
dof         1498.1
dm             nnn
dmm              w
dmf          10000
dseq
dres           1.0
homo             n
      PROCESSING
wtfile
proc            ft
fn           65536
math             f

werr
wexp
wbs
wnt
```



(±)-**78**
major

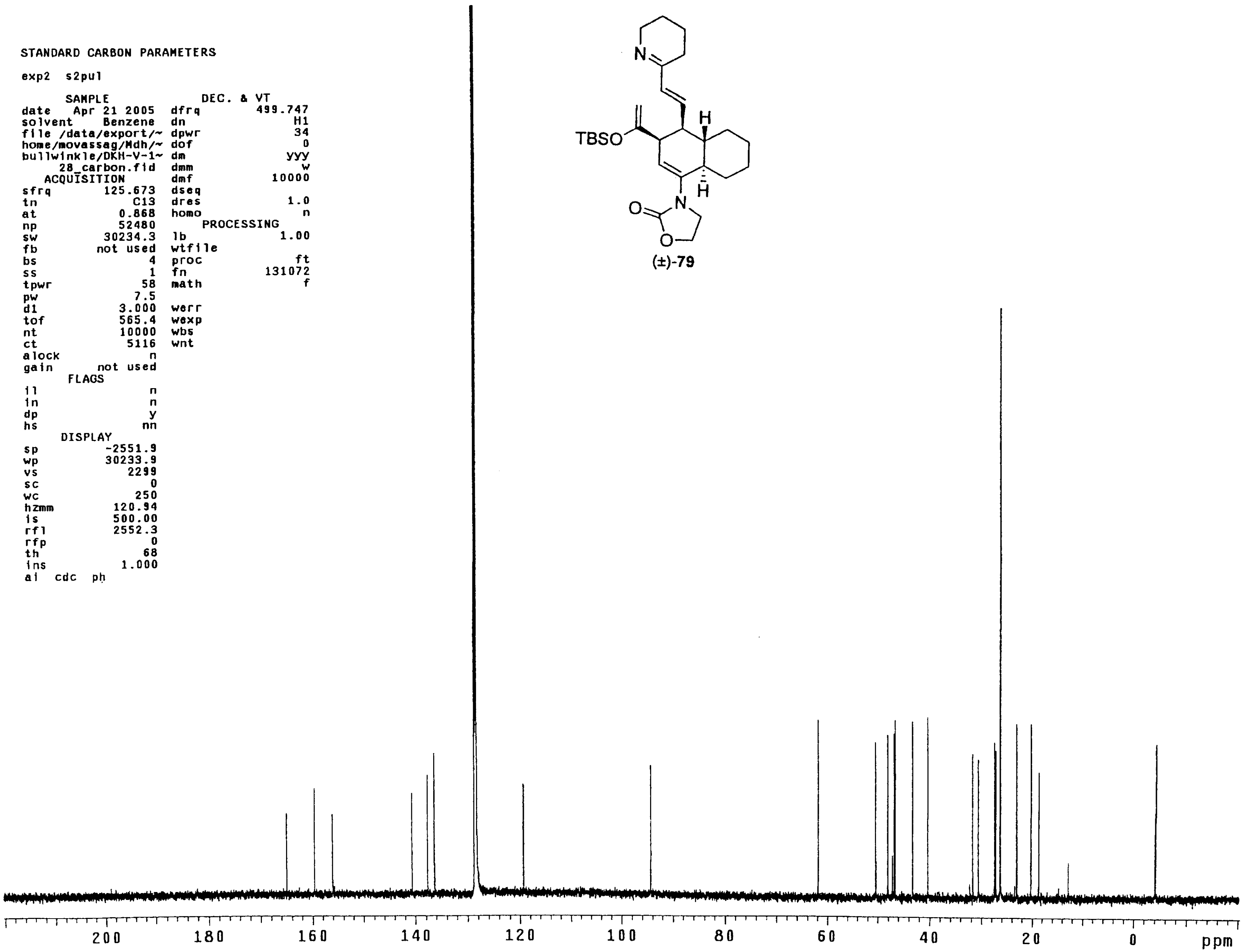




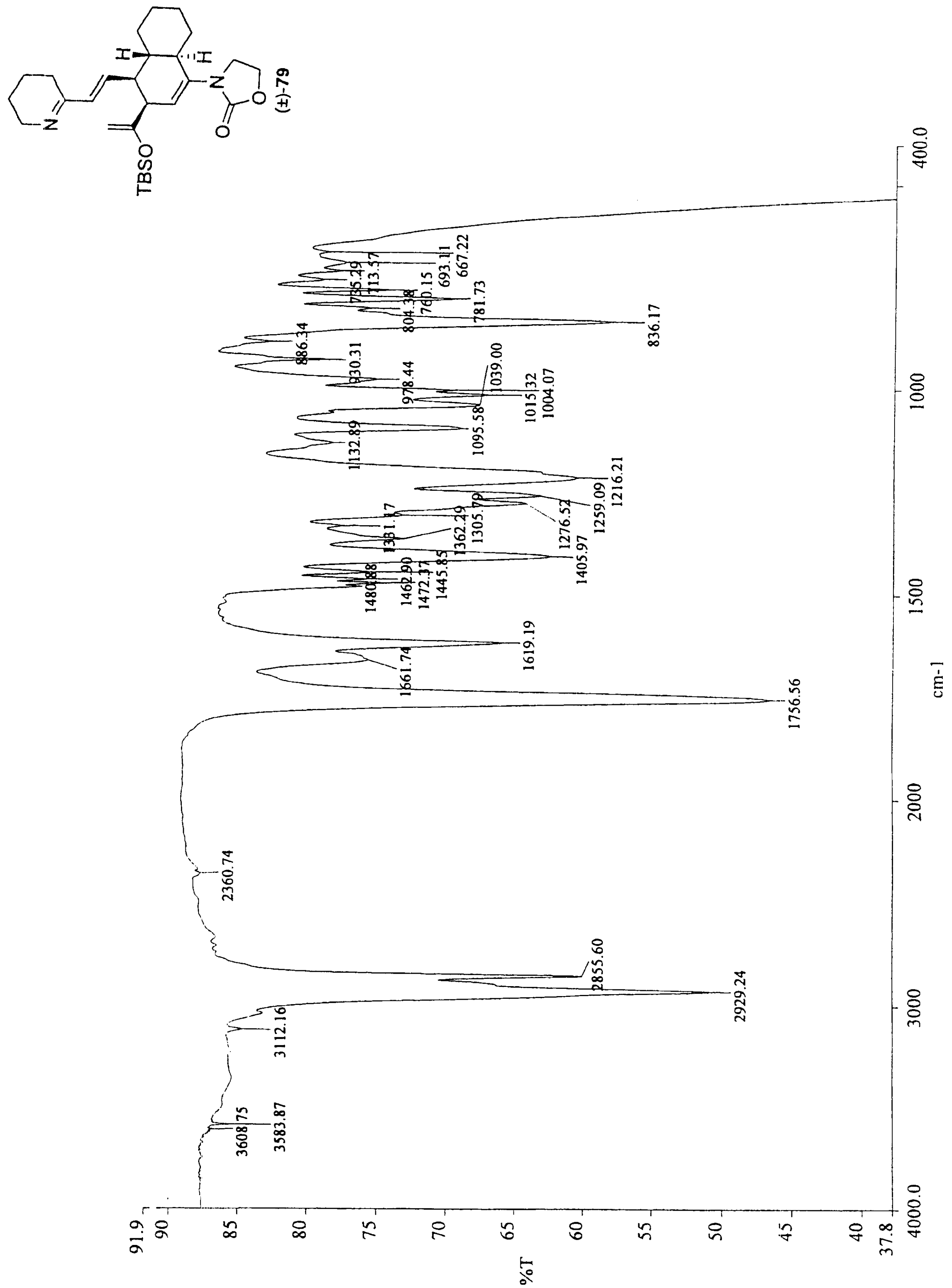
(±)-79

```
DKH-V-87

exp2  s2pul

        SAMPLE                 DEC. & VT
date   Mar 16 2005  dfrq         125.677
solvent      CDCl3  dn               C13
file /data/export/~ dpwr              34
home/movassag/Mdh/~ dof           1498.1
bullwinkle/DKH-V-8~ dm               nnn
             7.fid  dmm                w
   ACQUISITION      dmf            10000
sfrq       499.757  dseq
tn              H1  dres             1.0
at           3.278  homo               n
np           40960      PROCESSING
sw          6248.0  wtfile
fb        not used  proc              ft
bs               4  fn             65536
tpwr            56  math               f
pw             8.2
d1               0  werr
tof          403.1  wexp
nt             128  wbs
ct              28  wnt
alock            n
gain      not used
        FLAGS
il               n
in               n
dp               y
hs              nn
       DISPLAY
sp          -250.8
wp          6247.9
vs             214
sc               0
wc             250
hzmm         24.99
is           33.57
rfl          251.0
rfp              0
th               7
ins          1.000
nm  cdc  ph
```

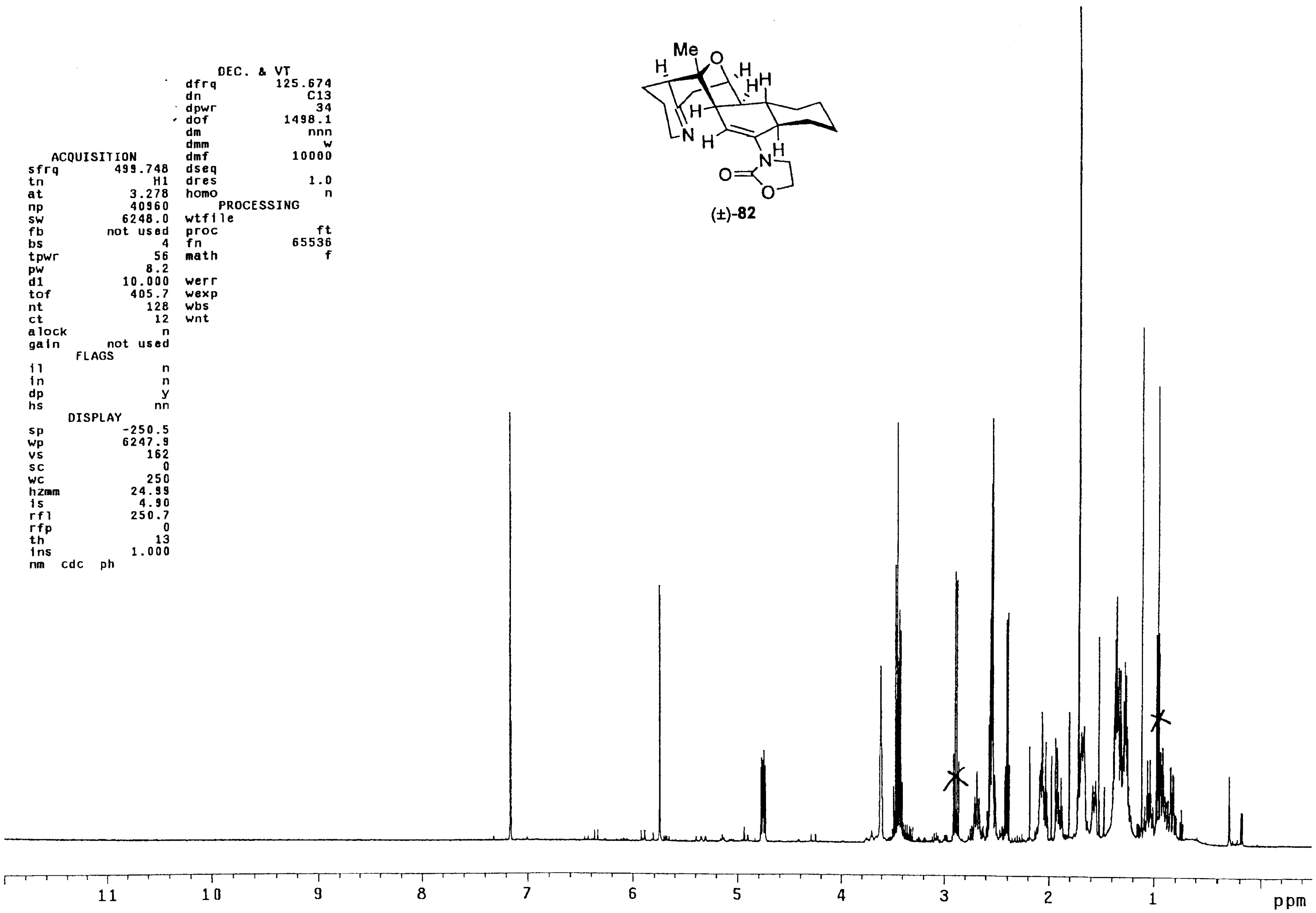
```
STANDARD CARBON PARAMETERS

exp2  s2pul

      SAMPLE              DEC. & VT
date   Apr 21 2005  dfrq       499.747
solvent    Benzene  dn              H1
file /data/export/~ dpwr            34
home/movassag/Mdh/~ dof              0
bullwinkle/DKH-V-1~ dm             yyy
    28_carbon.fid   dmm              w
   ACQUISITION      dmf          10000
sfrq       125.673  dseq
tn             C13  dres           1.0
at           0.868  homo             n
np           52480      PROCESSING
sw         30234.3  lb            1.00
fb        not used  wtfile
bs               4  proc            ft
ss               1  fn          131072
tpwr            58  math             f
pw             7.5
d1           3.000  werr
tof          565.4  wexp
nt           10000  wbs
ct            5116  wnt
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp         -2551.9
wp         30233.9
vs            2299
sc               0
wc             250
hzmm        120.94
is          500.00
rfl         2552.3
rfp              0
th              68
ins          1.000
ai  cdc  ph
```



(±)-79

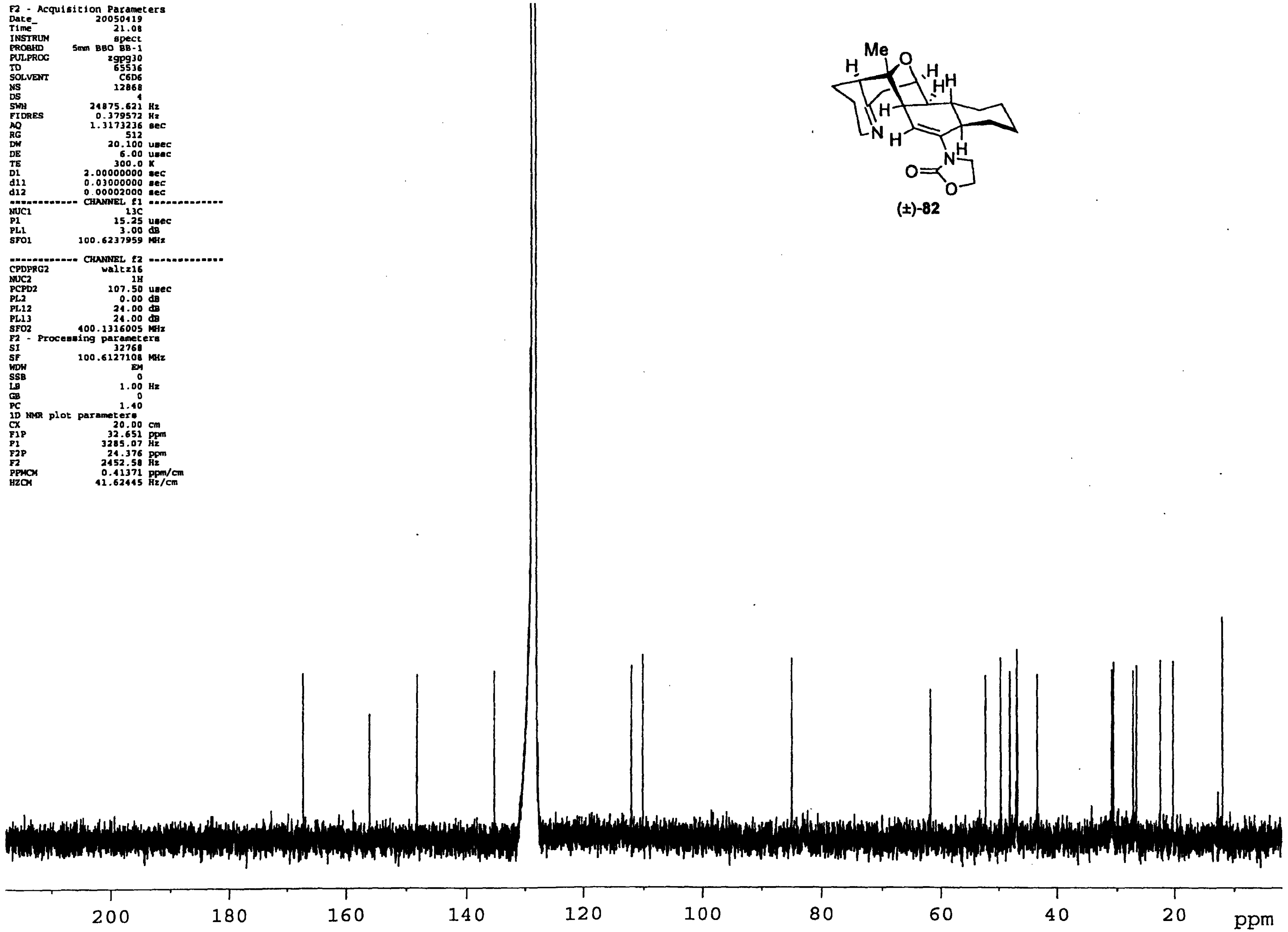

TBSO
N
H
H
N
O
O
91.9
90
85
80
75
70
65
60
55
50
45
40
37.8
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
3608.75
3583.87
3112.16
2929.24
2855.60
2360.74
1756.56
1661.74
1619.19
1480.88
1462.90
1472.37
1445.85
1405.97
1381.17
1362.29
1305.79
1276.52
1259.09
1216.21
1132.89
1095.58
1039.00
1015.32
1004.07
978.44
930.31
886.34
836.17
804.38
781.73
760.15
735.29
713.57
693.11
667.22

(±)-79



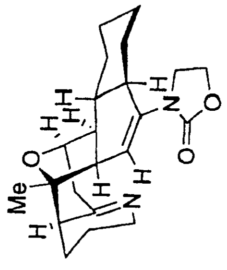
(±)-82

```
   ACQUISITION          DEC. & VT
sfrq     499.748   dfrq       125.674
tn            H1   dn             C13
at         3.278   dpwr            34
np         40960   dof         1498.1
sw        6248.0   dm             nnn
fb      not used   dmm              w
bs             4   dmf          10000
tpwr          56   dseq
pw           8.2   dres           1.0
d1        10.000   homo             n
tof        405.7      PROCESSING
nt           128   wtfile
ct            12   proc            ft
alock          n   fn           65536
gain    not used   math             f
      FLAGS
il             n   werr
in             n   wexp
dp             y   wbs
hs            nn   wnt
     DISPLAY
sp        -250.5
wp        6247.9
vs           162
sc             0
wc           250
hzmm       24.99
is          4.90
rfl        250.7
rfp            0
th            13
ins        1.000
nm  cdc  ph
```

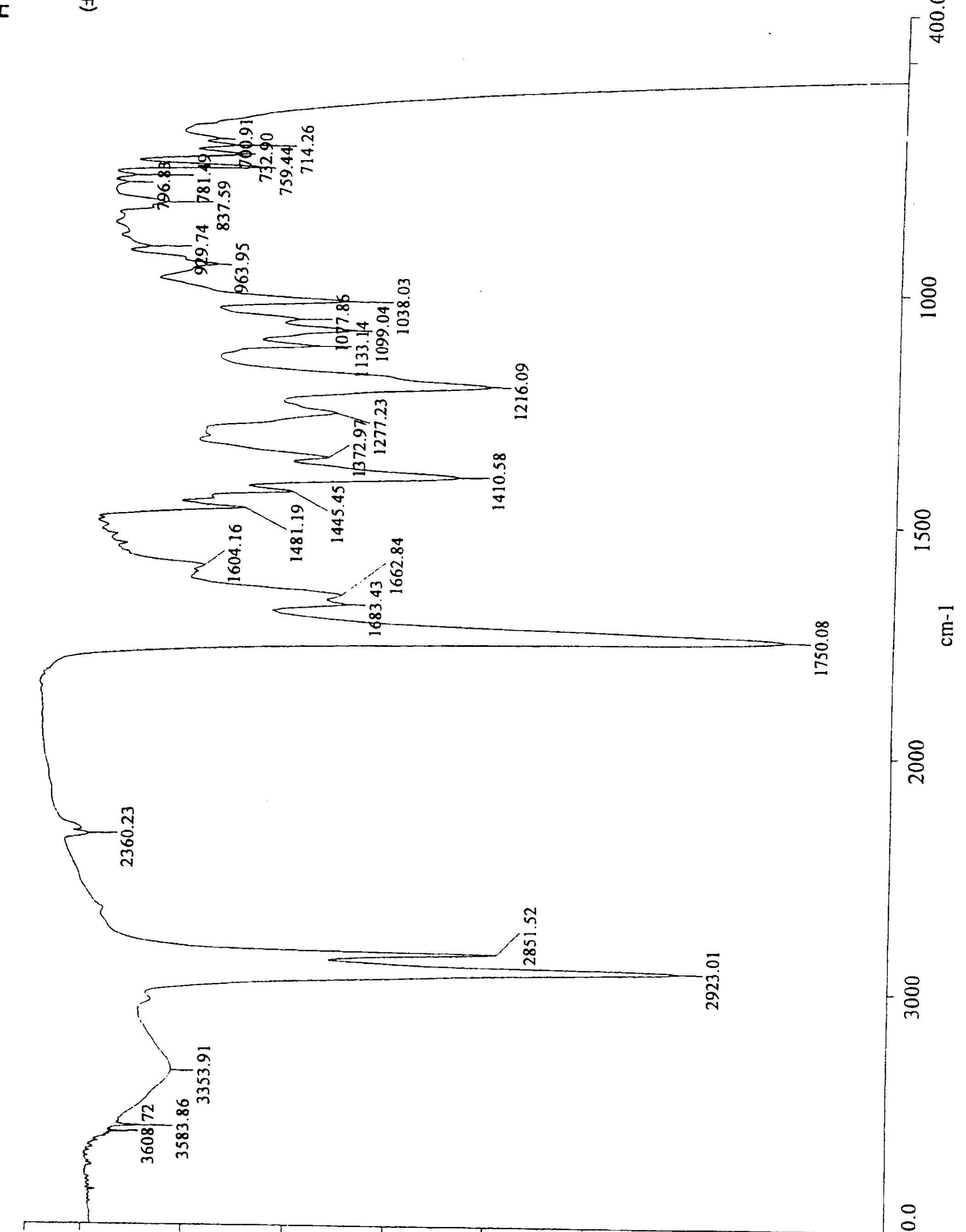


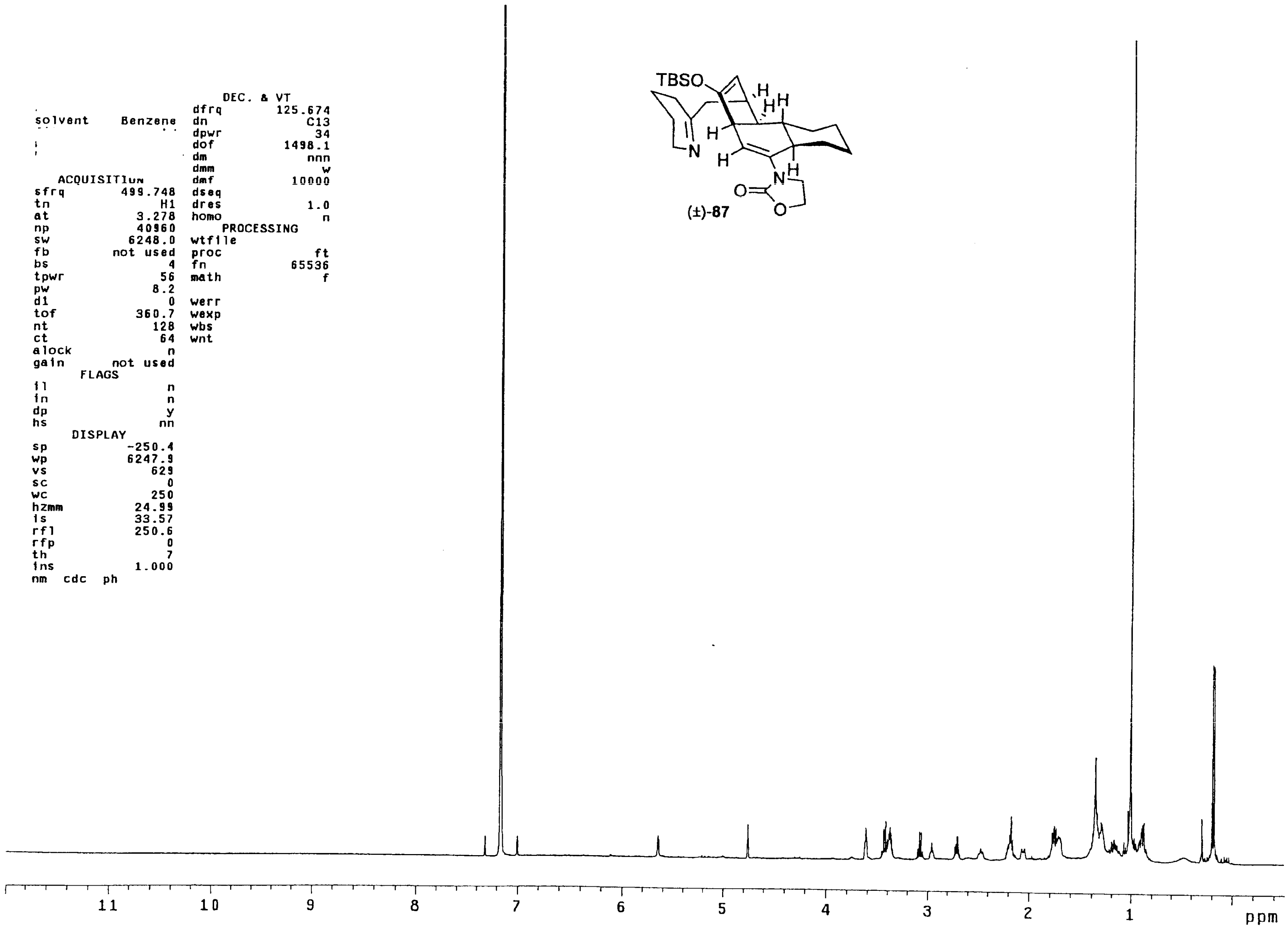
```
F2 - Acquisition Parameters
Date_           20050419
Time               21.08
INSTRUM            spect
PROBHD     5mm BBO BB-1
PULPROG           zgpg30
TD                 65536
SOLVENT             C6D6
NS                 12868
DS                     4
SWH            24875.621 Hz
FIDRES          0.379572 Hz
AQ             1.3173236 sec
RG                   512
DW                20.100 usec
DE                  6.00 usec
TE                 300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec
============= CHANNEL f1 =============
NUC1                 13C
P1                 15.25 usec
PL1                 3.00 dB
SFO1         100.6237959 MHz

============= CHANNEL f2 =============
CPDPRG2          waltz16
NUC2                  1H
PCPD2             107.50 usec
PL2                 0.00 dB
PL12               24.00 dB
PL13               24.00 dB
SFO2         400.1316005 MHz
F2 - Processing parameters
SI                 32768
SF           100.6127108 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
1D NMR plot parameters
CX                 20.00 cm
F1P               32.651 ppm
F1               3285.07 Hz
F2P               24.376 ppm
F2               2452.58 Hz
PPMCM            0.41371 ppm/cm
HZCM            41.62445 Hz/cm
```

(±)-82


Me
H
O
H
H
H
H
N
H
N
O
O

(±)-82


%T
87.8
85
80
75
70
65
60
55
50
45.2
4000.0
3000
2000
1500
1000
400.0
cm-1
3608.72
3583.86
3353.91
2923.01
2851.52
2360.23
1750.08
1683.43
1662.84
1604.16
1481.19
1445.45
1410.58
1372.97
1277.23
1216.09
1133.14
1099.04
1077.85
1038.03
963.95
929.74
837.59
796.83
781.49
759.44
732.90
714.26
700.91

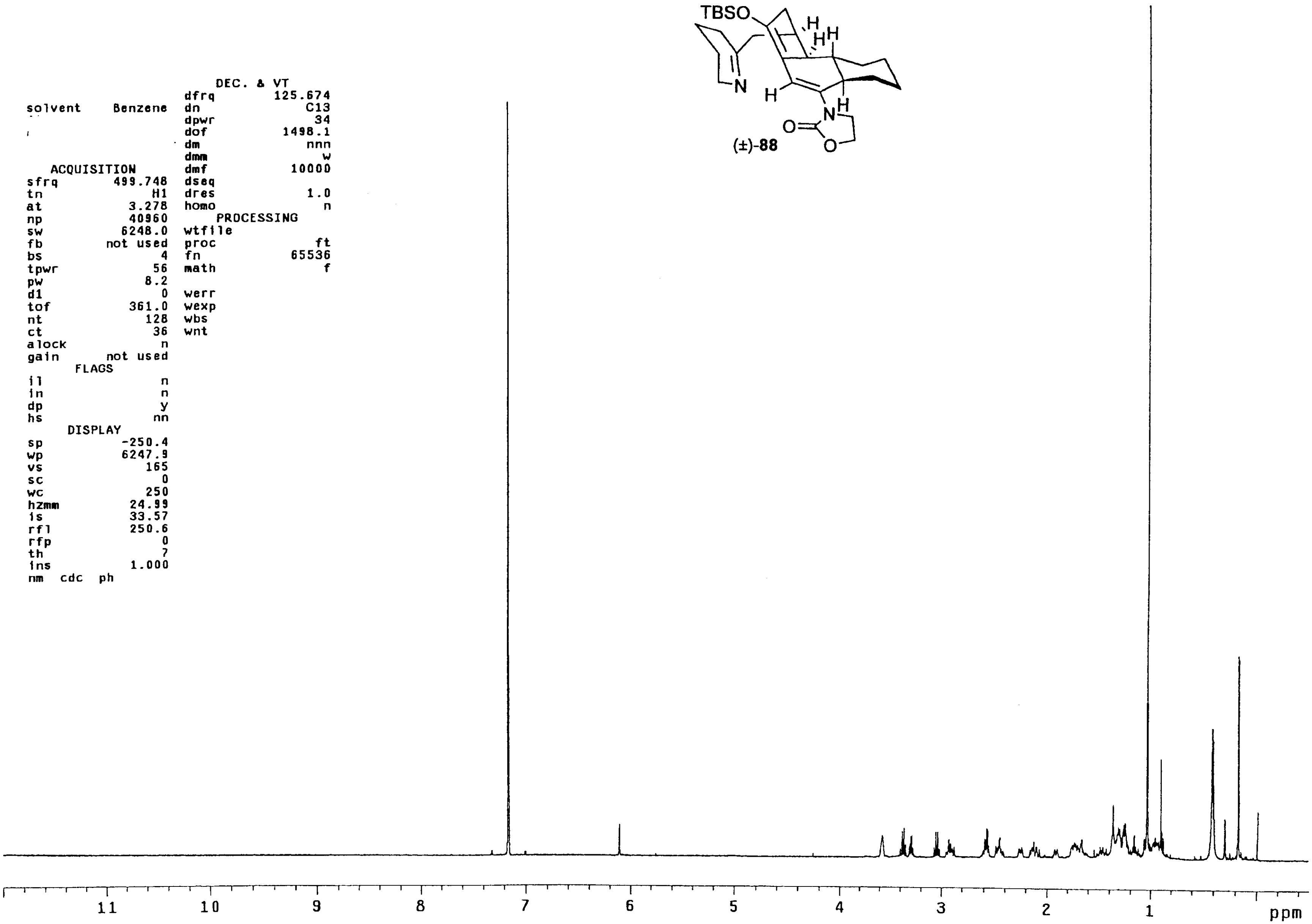


(±)-87

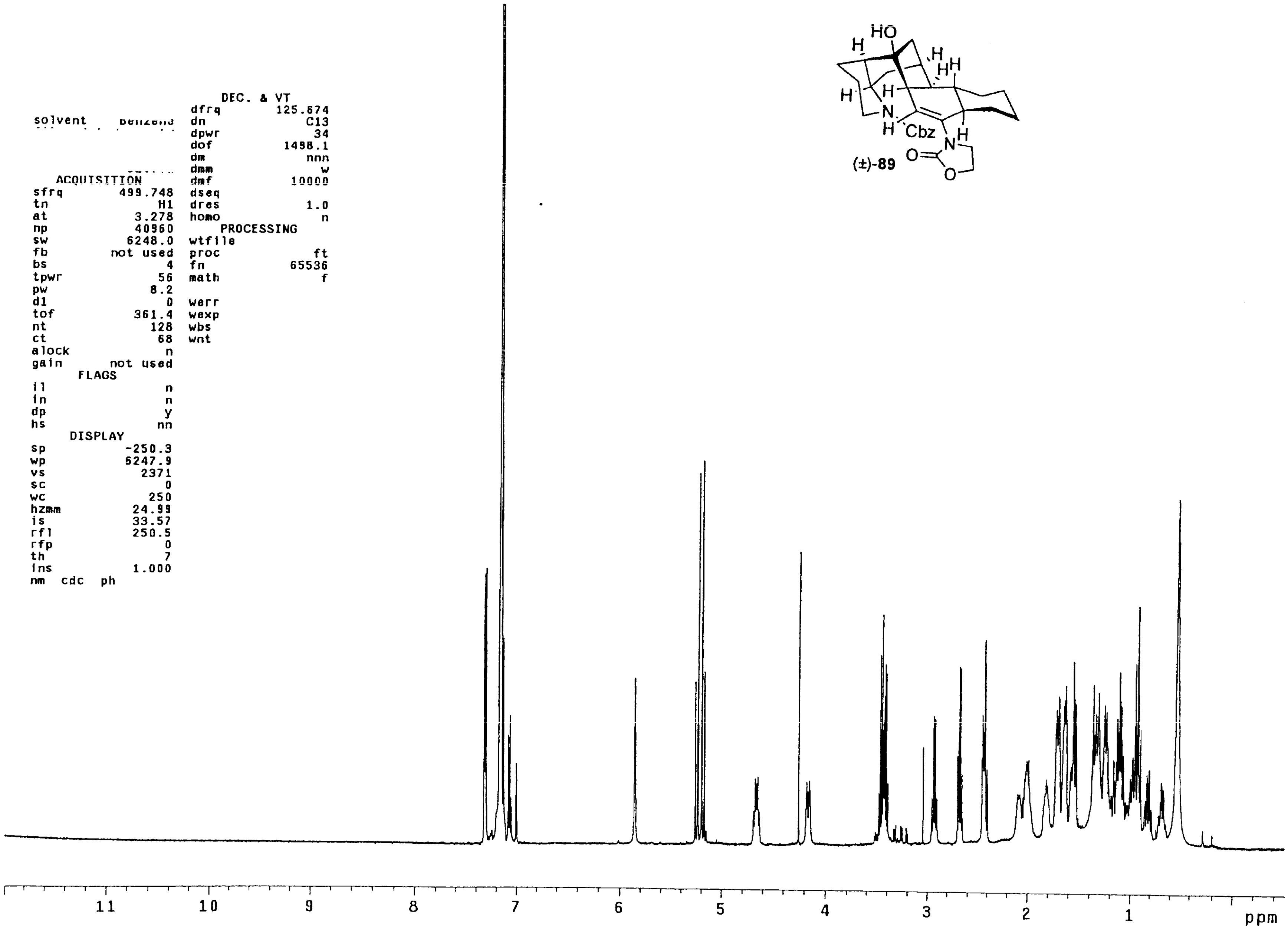
```
                            DEC. & VT
                         dfrq        125.674
solvent     Benzene      dn              C13
                         dpwr             34
                         dof          1498.1
                         dm              nnn
                         dmm               w
    ACQUISITIun          dmf           10000
sfrq          499.748    dseq
tn                 H1    dres            1.0
at              3.278    homo              n
np              40960        PROCESSING
sw             6248.0    wtfile
fb           not used    proc             ft
bs                  4    fn            65536
tpwr               56    math              f
pw                8.2
d1                  0    werr
tof             360.7    wexp
nt                128    wbs
ct                 64    wnt
alock               n
gain         not used
       FLAGS
il                  n
in                  n
dp                  y
hs                 nn
      DISPLAY
sp             -250.4
wp             6247.9
vs                629
sc                  0
wc                250
hzmm            24.99
is              33.57
rfl             250.6
rfp                 0
th                  7
ins             1.000
nm  cdc  ph
```

```
solvent    Benzene

   ACQUISITION
sfrq        499.748
tn               H1
at            3.278
np            40960
sw           6248.0
fb         not used
bs                4
tpwr             56
pw              8.2
d1                0
tof           361.0
nt              128
ct               36
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp           -250.4
wp           6247.9
vs              165
sc                0
wc              250
hzmm          24.99
is            33.57
rfl           250.6
rfp               0
th                7
ins           1.000
nm  cdc  ph
```

```
         DEC. & VT
dfrq        125.674
dn              C13
dpwr             34
dof          1498.1
dm              nnn
dmm               w
dmf           10000
dseq
dres            1.0
homo              n
      PROCESSING
wtfile
proc             ft
fn            65536
math              f

werr
wexp
wbs
wnt
```

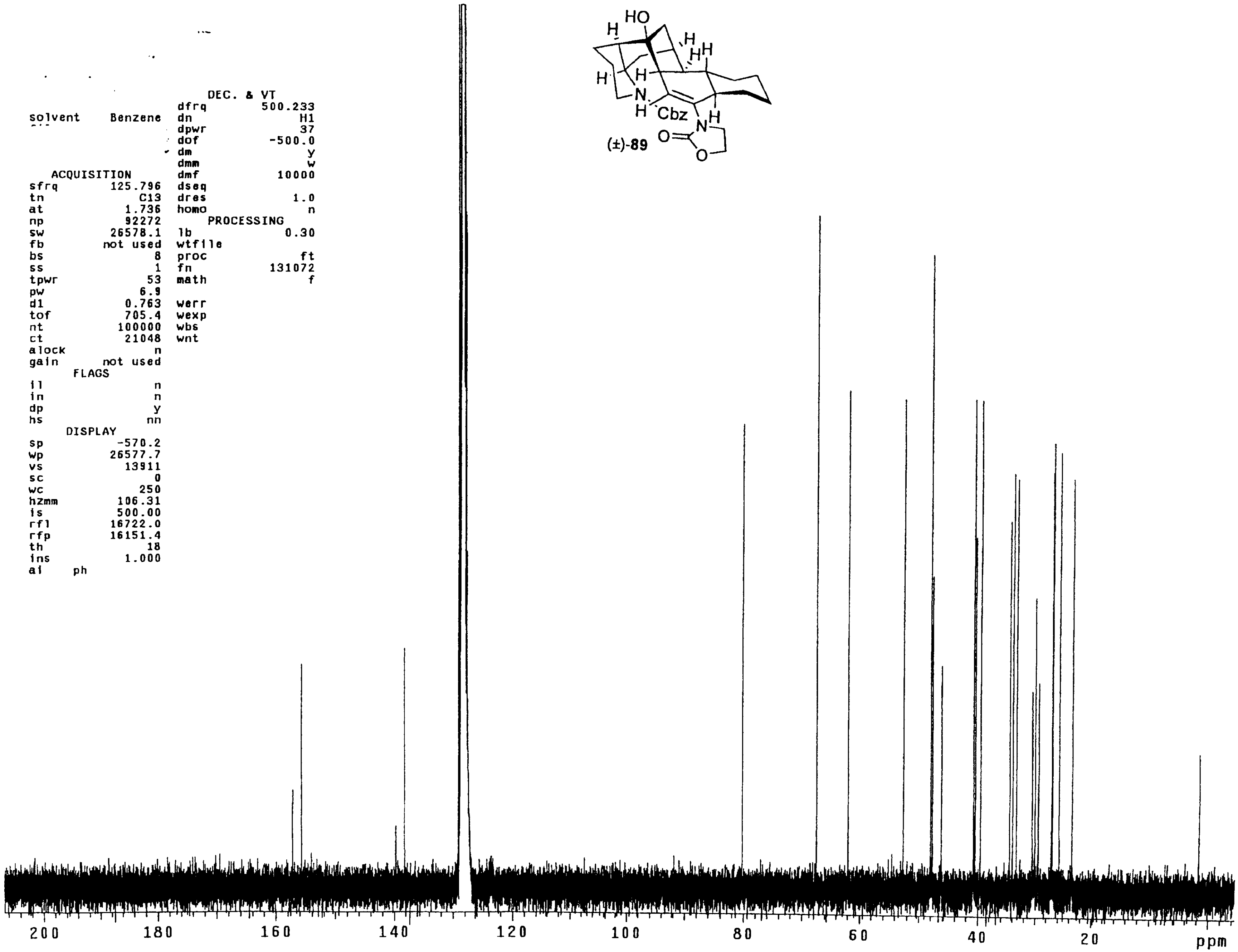


(±)-**88**

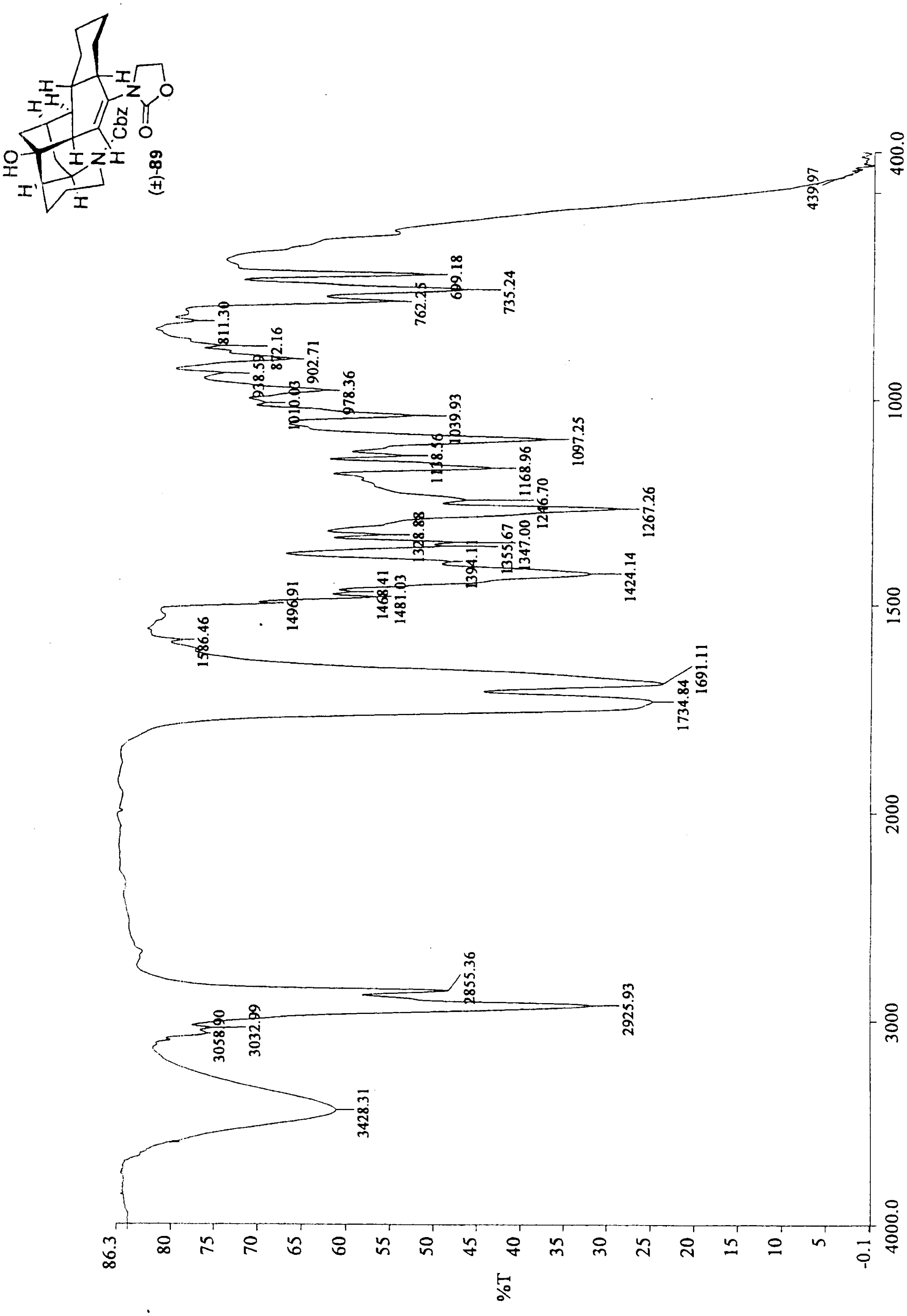


(±)-89

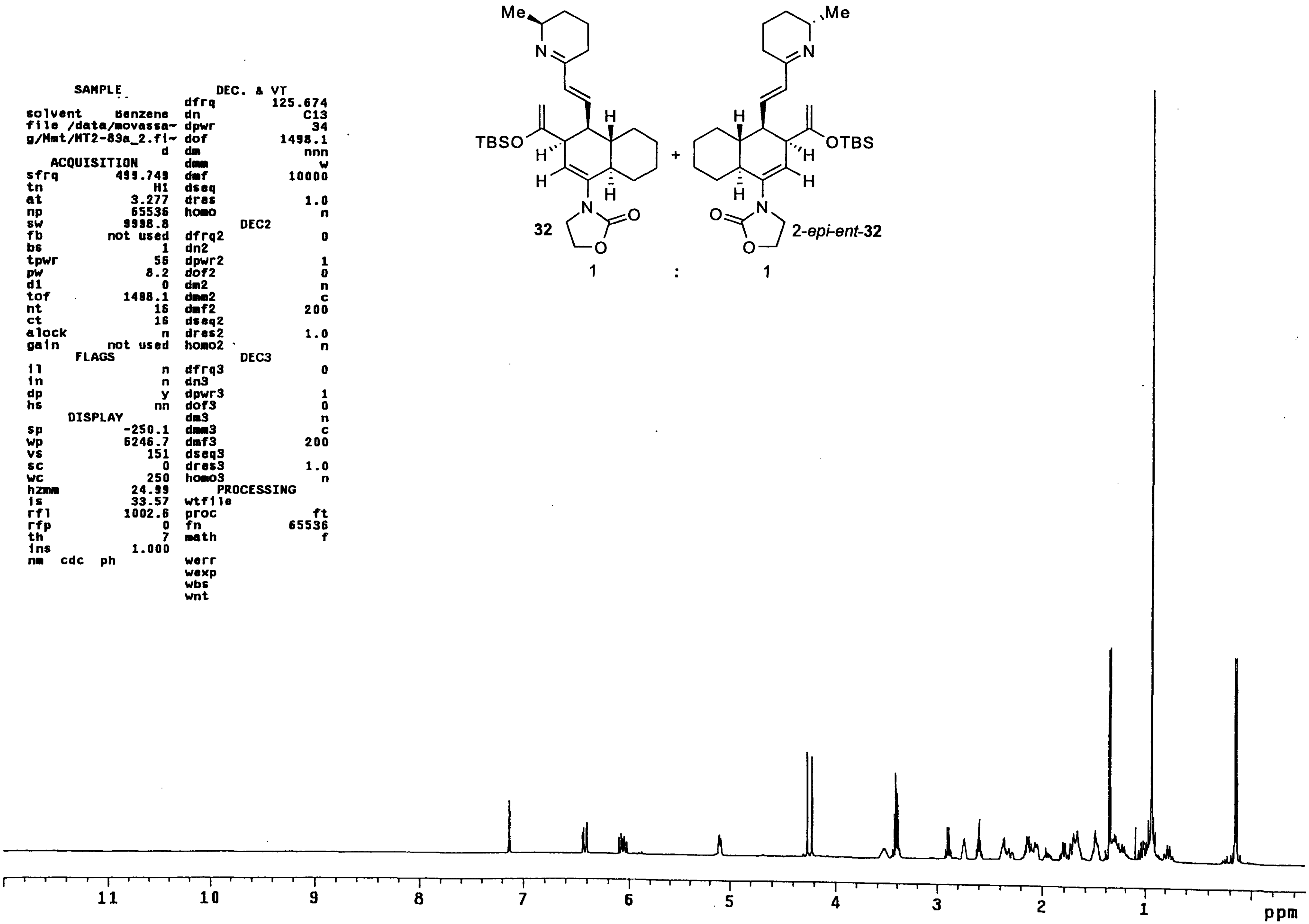
```
solvent    benzene
                        DEC. & VT
                     dfrq     125.674
                     dn           C13
                     dpwr          34
                     dof       1498.1
                     dm           nnn
                     dmm            w
   ACQUISITION       dmf        10000
sfrq      499.748    dseq
tn             H1    dres         1.0
at          3.278    homo           n
np          40960       PROCESSING
sw         6248.0    wtfile
fb       not used    proc          ft
bs              4    fn         65536
tpwr           56    math           f
pw            8.2
d1              0    werr
tof         361.4    wexp
nt            128    wbs
ct             68    wnt
alock           n
gain     not used
      FLAGS
il              n
in              n
dp              y
hs             nn
     DISPLAY
sp         -250.3
wp         6247.9
vs           2371
sc              0
wc            250
hzmm        24.99
is          33.57
rfl         250.5
rfp             0
th              7
ins         1.000
nm  cdc  ph
```



```
                                  DEC. & VT
                           dfrq          500.233
solvent    Benzene         dn                 H1
                           dpwr               37
                           dof            -500.0
                           dm                  y
                           dmm                 w
   ACQUISITION             dmf             10000
sfrq         125.796       dseq
tn               C13       dres              1.0
at             1.736       homo                n
np             92272          PROCESSING
sw           26578.1       lb               0.30
fb          not used       wtfile
bs                 8       proc               ft
ss                 1       fn             131072
tpwr              53       math                f
pw               6.9
d1             0.763       werr
tof            705.4       wexp
nt            100000       wbs
ct             21048       wnt
alock              n
gain        not used
      FLAGS
il                 n
in                 n
dp                 y
hs                nn
     DISPLAY
sp            -570.2
wp           26577.7
vs             13911
sc                 0
wc               250
hzmm          106.31
is            500.00
rfl          16722.0
rfp          16151.4
th                18
ins            1.000
ai    ph
```


HO
H
H
H
H
H
N
H
Cbz
N
O
O
(±)-89
%T
86.3
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
-0.1
4000.0
3000
2000
1500
1000
400.0
cm-1
3428.31
3058.90
3032.99
2925.93
2855.36
1734.84
1691.11
1586.46
1496.91
1468.41
1481.03
1424.14
1394.11
1355.67
1347.00
1328.88
1267.26
1246.70
1168.96
1138.56
1097.25
1039.93
1010.03
978.36
938.59
902.71
872.16
811.30
762.25
699.18
735.24
439.97

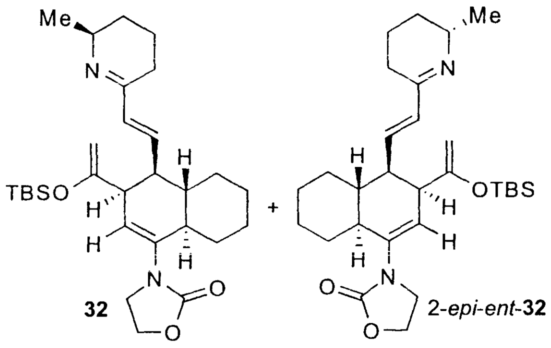
```
     SAMPLE              DEC. & VT
                    dfrq       125.674
solvent   Benzene   dn             C13
file /data/movassa~ dpwr            34
g/Mmt/MT2-83a_2.fi~ dof         1498.1
                  d dm             nnn
   ACQUISITION      dmm              w
sfrq        499.749 dmf          10000
tn               H1 dseq
at            3.277 dres           1.0
np            65536 homo             n
sw           9998.8          DEC2
fb         not used dfrq2            0
bs                1 dn2
tpwr             56 dpwr2            1
pw              8.2 dof2             0
d1                0 dm2              n
tof          1498.1 dmm2             c
nt               16 dmf2           200
ct               16 dseq2
alock             n dres2          1.0
gain       not used homo2            n
      FLAGS                  DEC3
il                n dfrq3            0
in                n dn3
dp                y dpwr3            1
hs               nn dof3             0
     DISPLAY        dm3              n
sp           -250.1 dmm3             c
wp           6246.7 dmf3           200
vs              151 dseq3
sc                0 dres3          1.0
wc              250 homo3            n
hzmm          24.99       PROCESSING
is            33.57 wtfile
rfl          1002.6 proc            ft
rfp               0 fn           65536
th                7 math             f
ins           1.000
nm  cdc  ph         werr
                    wexp
                    wbs
                    wnt
```



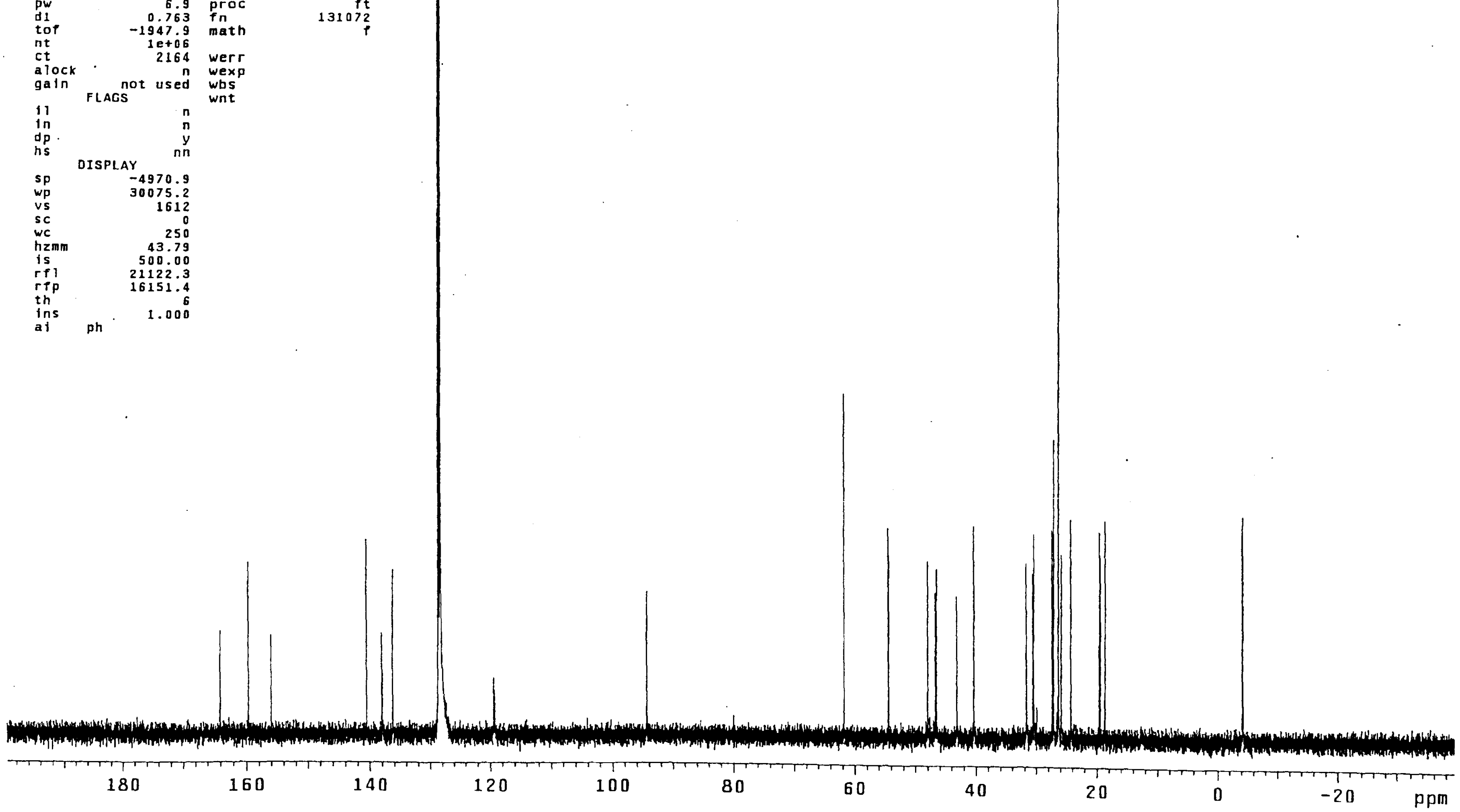
32 + 2-*epi*-*ent*-**32**

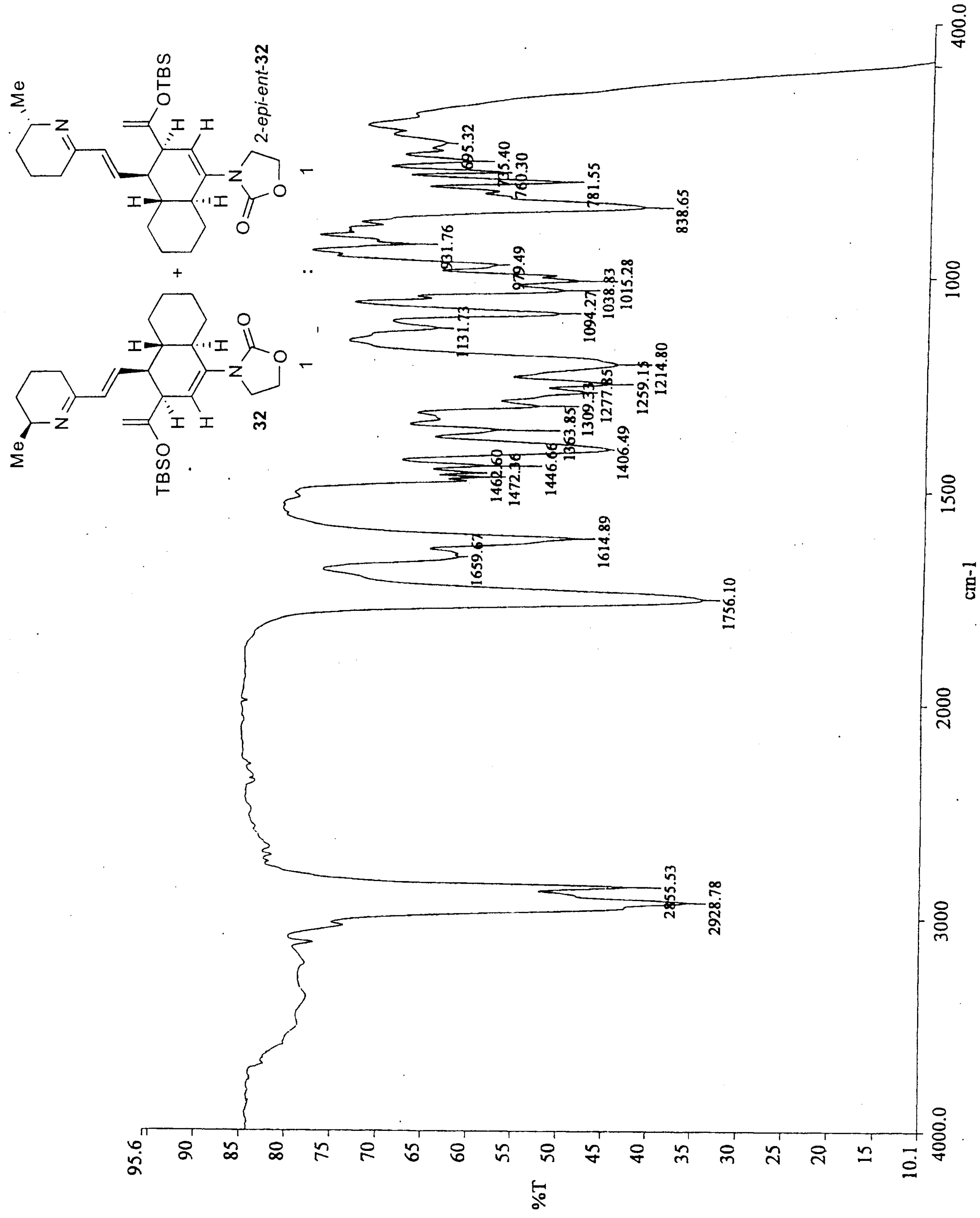
1 : 1

```
      SAMPLE                DEC. & VT
.                      dfrq         500.233
solvent    Benzene     dn                H1
file           exp     dpwr              37
   ACQUISITIQN         dof           -500.0
sfrq       125.793     dm                 y
tn             C13     dmm                w
at           1.737     dmf            10000
np          104492     dseq
sw         30075.2     dres             1.0
fb        not used     homo               n
bs               4         PROCESSING
ss               1     lb              0.30
tpwr            53     wtfile
pw             6.9     proc              ft
d1           0.763     fn            131072
tof        -1947.9     math               f
nt           1e+06
ct            2164     werr
alock            n     wexp
gain      not used     wbs
      FLAGS            wnt
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp         -4970.9
wp         30075.2
vs            1612
sc               0
wc             250
hzmm         43.79
is          500.00
rfl        21122.3
rfp        16151.4
th               6
ins          1.000
ai    ph
```



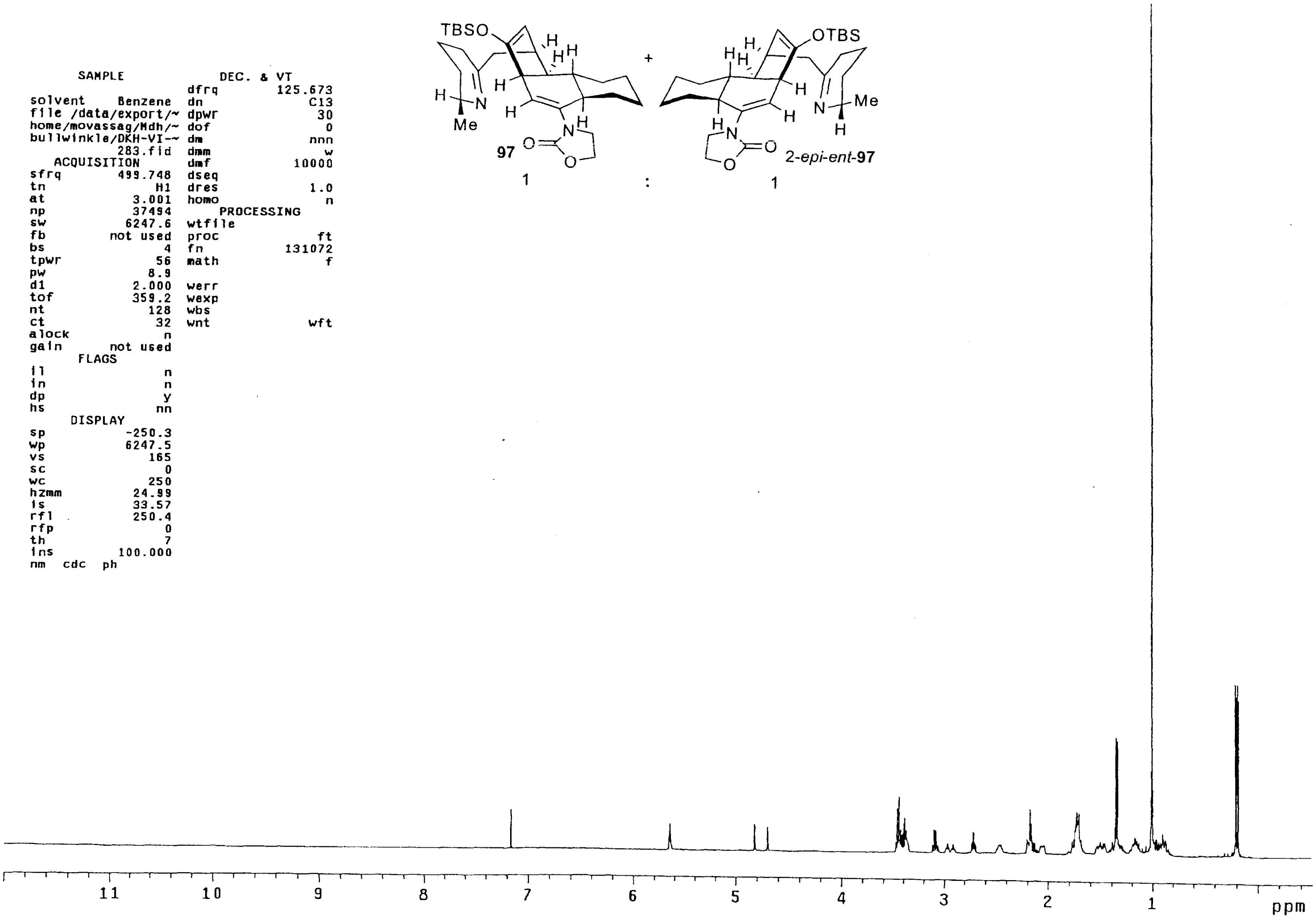
32 1 : 1 2-*epi*-*ent*-**32**




32 + *2-epi-ent-***32**

1 : 1

```
      SAMPLE                DEC. & VT
                         dfrq         125.673
solvent     Benzene      dn               C13
file /data/export/~      dpwr              30
home/movassag/Mdh/~      dof                0
bullwinkle/DKH-VI-~      dm               nnn
            283.fid      dmm                w
    ACQUISITION          dmf            10000
sfrq        499.748      dseq
tn               H1      dres             1.0
at            3.001      homo               n
np            37494          PROCESSING
sw           6247.6      wtfile
fb         not used      proc              ft
bs                4      fn            131072
tpwr             56      math               f
pw              8.9
d1            2.000      werr
tof           359.2      wexp
nt              128      wbs
ct               32      wnt              wft
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp           -250.3
wp           6247.5
vs              165
sc                0
wc              250
hzmm          24.99
is            33.57
rfl           250.4
rfp               0
th                7
ins         100.000
nm   cdc   ph
```



97

1

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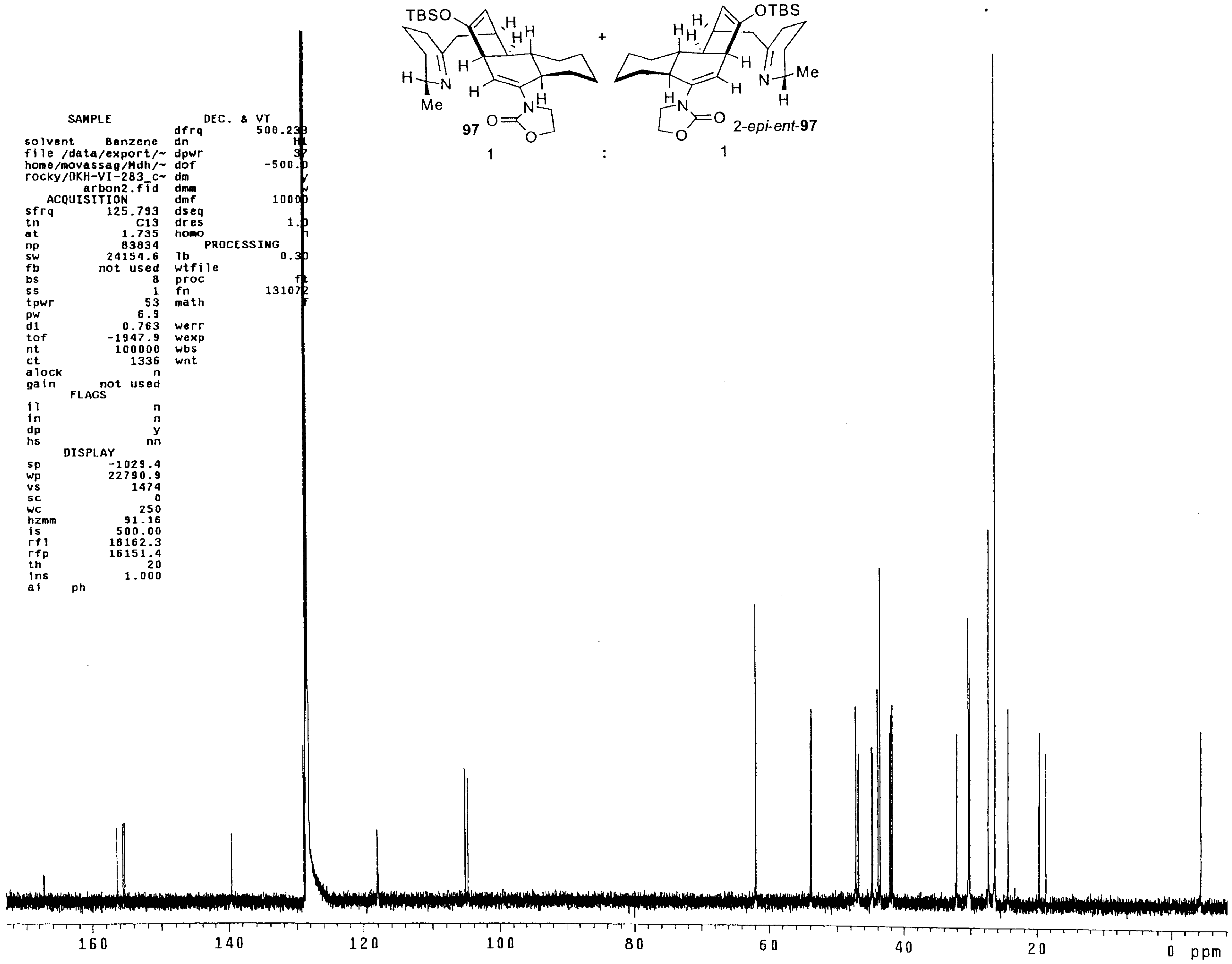
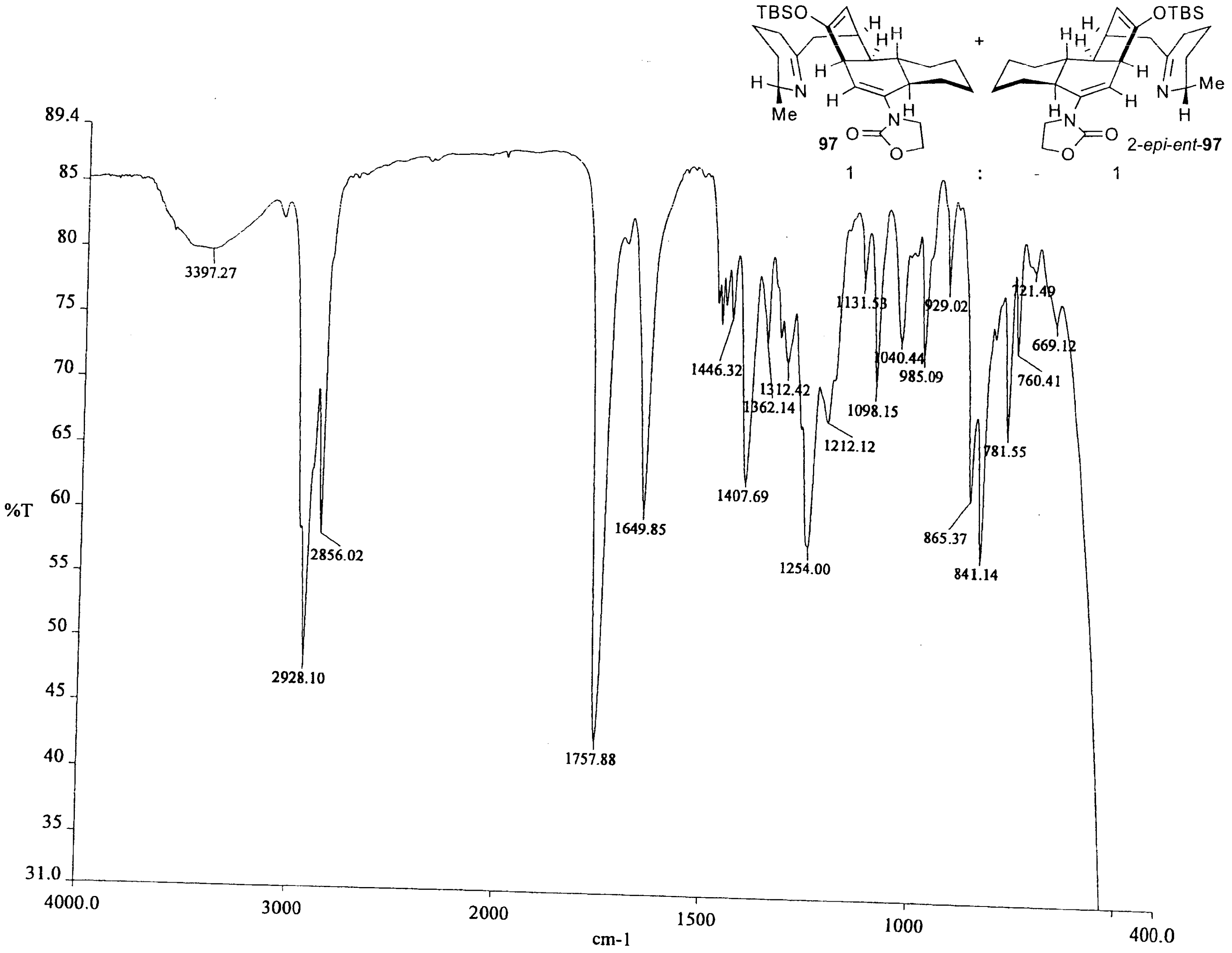
2-*epi*-*ent*-**97**

1

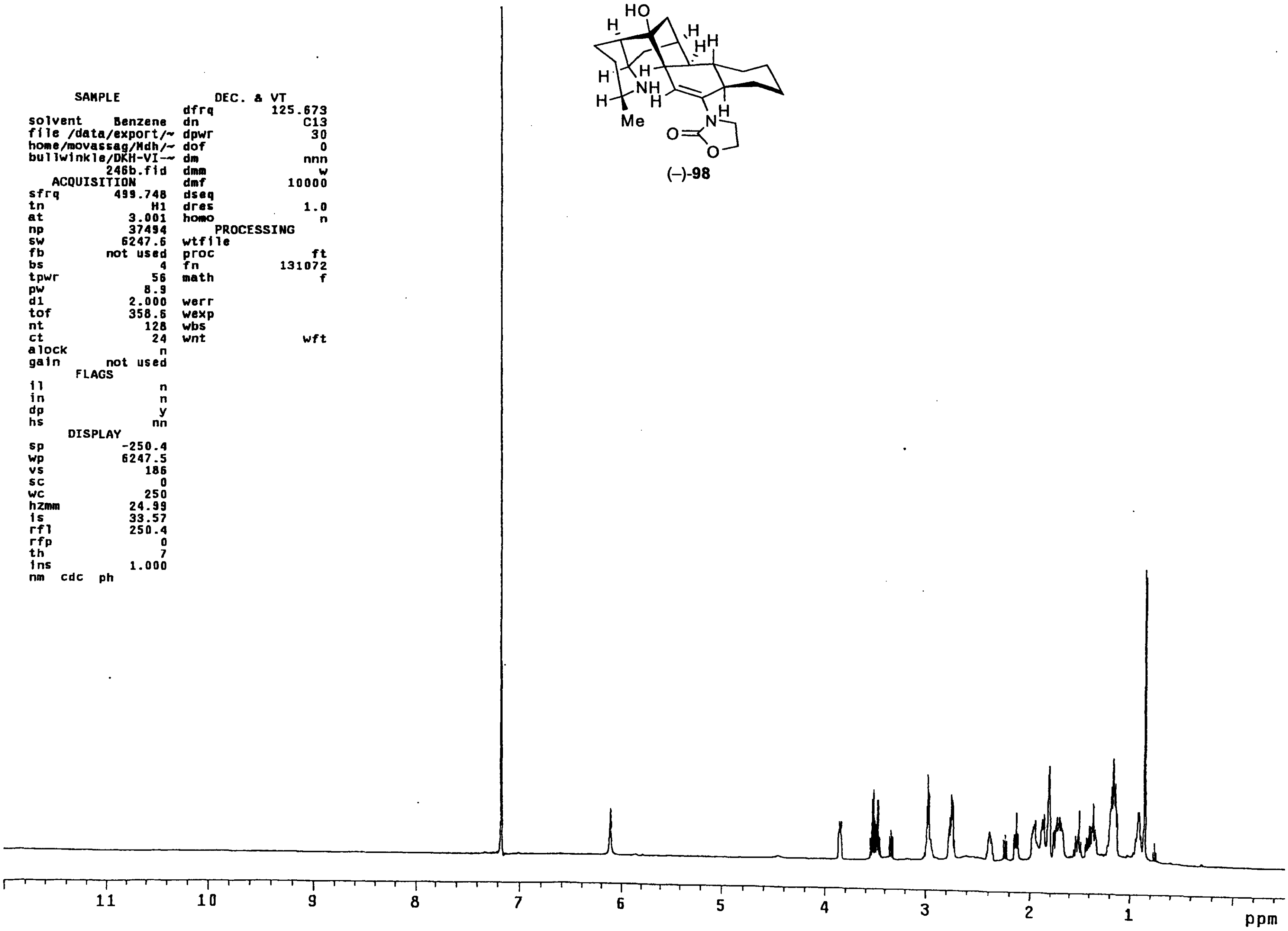


97 1 : 1 2-*epi*-*ent*-**97**

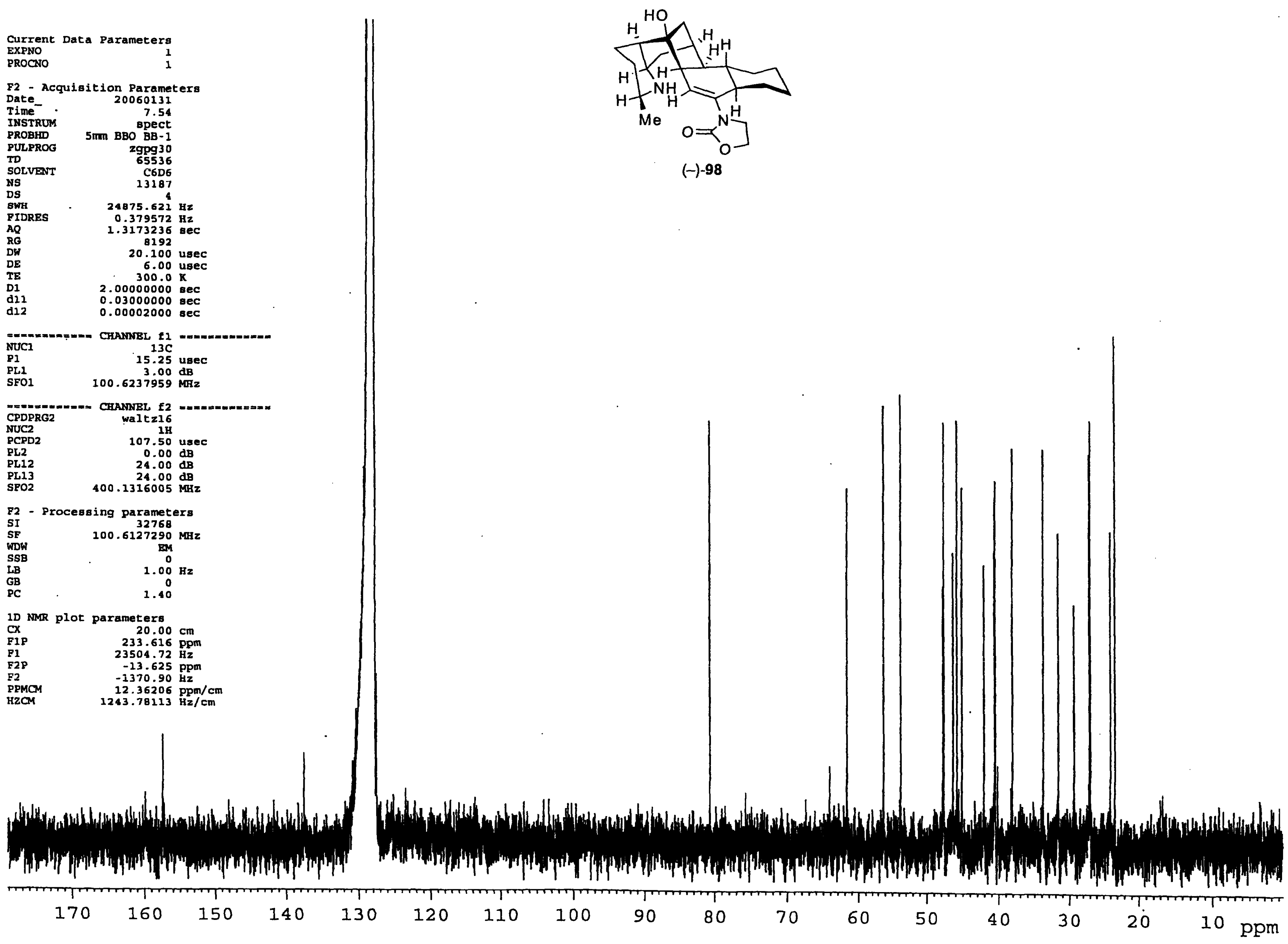
```
      SAMPLE             DEC. & VT
                        dfrq       500.233
solvent    Benzene      dn              H1
file /data/export/~     dpwr            37
home/movassag/Mdh/~     dof         -500.0
rocky/DKH-VI-283_c~     dm               y
         arbon2.fid     dmm              w
   ACQUISITION          dmf          10000
sfrq        125.793     dseq
tn              C13     dres           1.0
at            1.735     homo             n
np            83834        PROCESSING
sw          24154.6     lb            0.30
fb         not used     wtfile
bs                8     proc            ft
ss                1     fn          131072
tpwr             53     math             f
pw              6.9
d1            0.763     werr
tof         -1947.9     wexp
nt           100000     wbs
ct             1336     wnt
alock             n
gain       not used
       FLAGS
il                n
in                n
dp                y
hs               nn
      DISPLAY
sp          -1029.4
wp          22790.9
vs             1474
sc                0
wc              250
hzmm          91.16
is           500.00
rfl         18162.3
rfp         16151.4
th               20
ins           1.000
ai     ph
```


TBSO
OTBS
H
N
Me
O
+
97
2-epi-ent-97
1 : 1
%T
89.4
85
80
75
70
65
60
55
50
45
40
35
31.0
4000.0
3000
2000
1500
1000
400.0
cm-1
3397.27
2928.10
2856.02
1757.88
1649.85
1446.32
1407.69
1362.14
1312.42
1254.00
1212.12
1131.53
1098.15
1040.44
985.09
929.02
865.37
841.14
781.55
760.41
721.49
669.12

```
      SAMPLE            DEC. & VT
                     dfrq         125.673
solvent    Benzene   dn               C13
file /data/export/~  dpwr              30
home/movassag/Mdh/~  dof                0
bullwinkle/DKH-VI-~  dm               nnn
          246b.fid   dmm                w
    ACQUISITION      dmf            10000
sfrq       499.748   dseq
tn              H1   dres             1.0
at           3.001   homo               n
np           37494       PROCESSING
sw          6247.6   wtfile
fb        not used   proc              ft
bs               4   fn            131072
tpwr            56   math               f
pw             8.9
d1           2.000   werr
tof          358.6   wexp
nt             128   wbs
ct              24   wnt              wft
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -250.4
wp          6247.5
vs             186
sc               0
wc             250
hzmm         24.99
is           33.57
rfl          250.4
rfp              0
th               7
ins          1.000
nm  cdc  ph
```

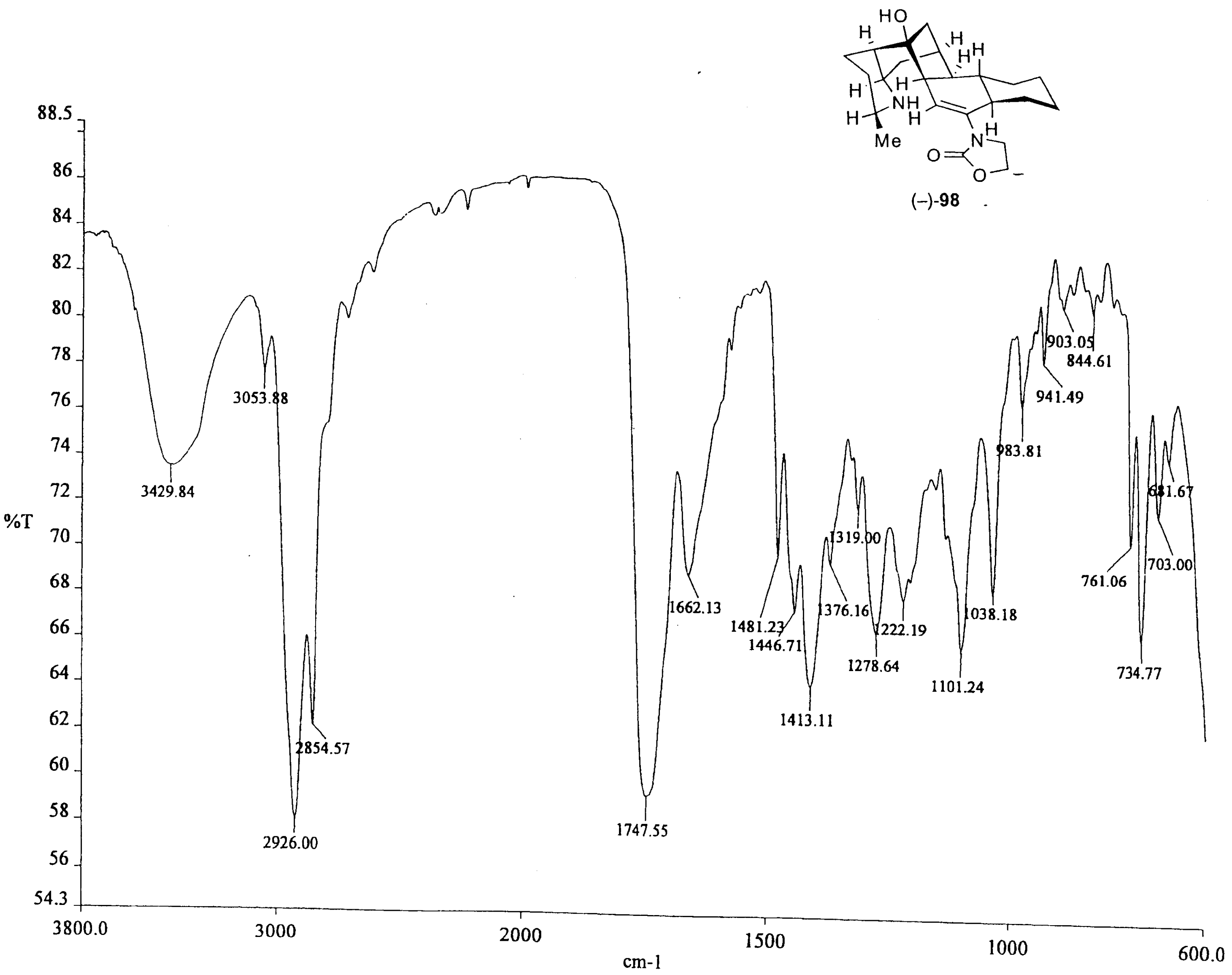


(–)-98



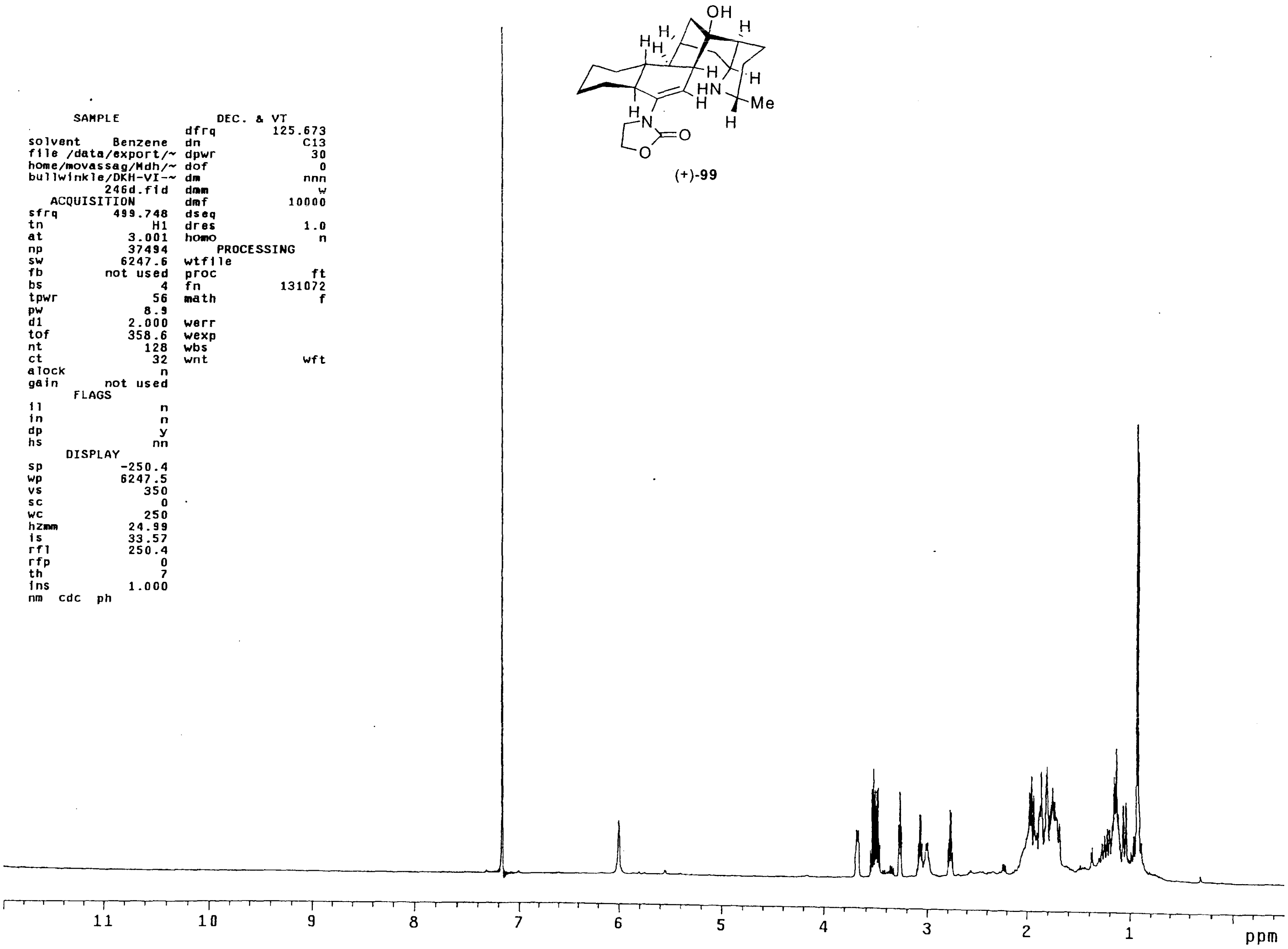
(–)-**98**

```
Current Data Parameters
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20060131
Time               7.54
INSTRUM           spect
PROBHD   5mm BBO BB-1
PULPROG          zgpg30
TD                65536
SOLVENT            C6D6
NS                13187
DS                    4
SWH           24875.621 Hz
FIDRES         0.379572 Hz
AQ            1.3173236 sec
RG                 8192
DW               20.100 usec
DE                 6.00 usec
TE                300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

============ CHANNEL f1 ============
NUC1                13C
P1                15.25 usec
PL1                3.00 dB
SFO1        100.6237959 MHz

============ CHANNEL f2 ============
CPDPRG2         waltz16
NUC2                 1H
PCPD2            107.50 usec
PL2                0.00 dB
PL12              24.00 dB
PL13              24.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127290 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
F1P             233.616 ppm
F1             23504.72 Hz
F2P             -13.625 ppm
F2             -1370.90 Hz
PPMCM          12.36206 ppm/cm
HZCM         1243.78113 Hz/cm
```



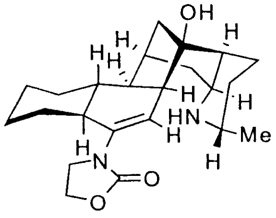
(−)-98

HO
H
H
H
H
H
NH
H
H
Me
H
N
O
O
88.5
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54.3
%T
3800.0
3000
2000
1500
1000
600.0
cm-1
3429.84
3053.88
2926.00
2854.57
1747.55
1662.13
1481.23
1446.71
1413.11
1376.16
1319.00
1278.64
1222.19
1101.24
1038.18
983.81
941.49
903.05
844.61
761.06
734.77
703.00
681.67

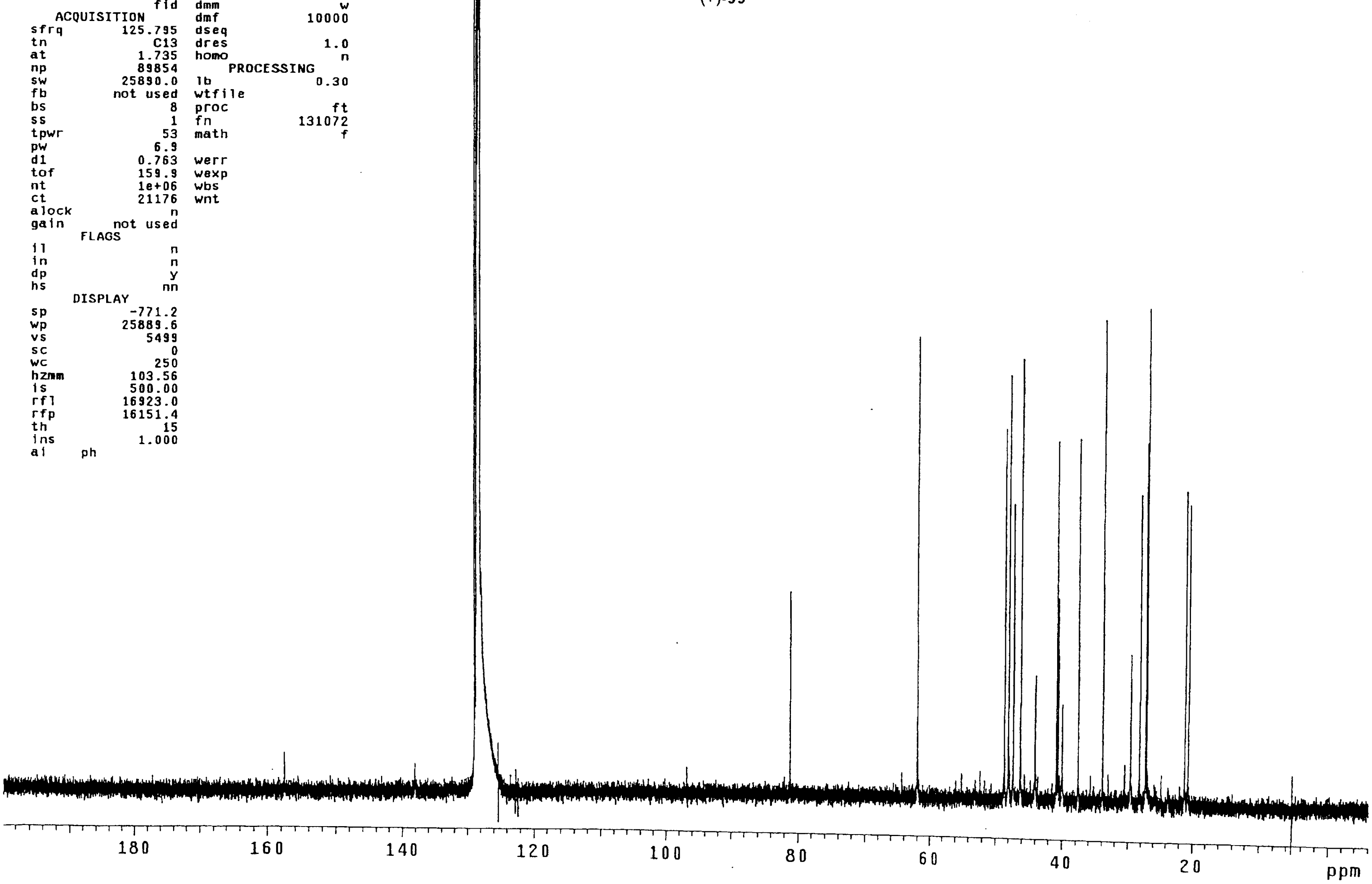


(+)-99

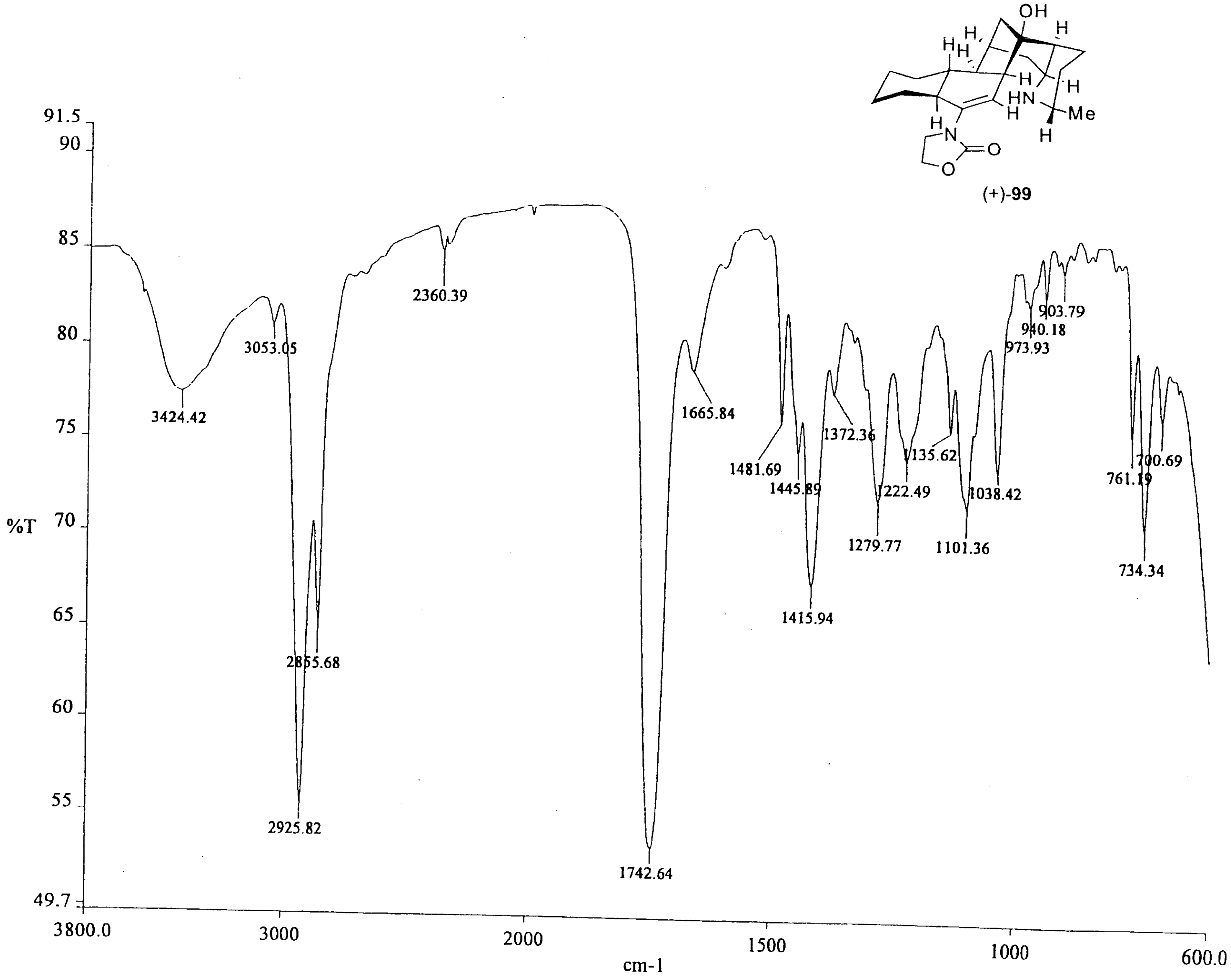
```
      SAMPLE              DEC. & VT
                     dfrq         125.673
solvent    Benzene   dn               C13
file /data/export/~  dpwr              30
home/movassag/Mdh/~  dof                0
bullwinkle/DKH-VI-~  dm               nnn
          246d.fid   dmm                w
   ACQUISITION       dmf            10000
sfrq       499.748   dseq
tn              H1   dres             1.0
at           3.001   homo               n
np           37494       PROCESSING
sw          6247.6   wtfile
fb        not used   proc              ft
bs               4   fn            131072
tpwr            56   math               f
pw             8.9
d1           2.000   werr
tof          358.6   wexp
nt             128   wbs
ct              32   wnt              wft
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -250.4
wp          6247.5
vs             350
sc               0
wc             250
hzmm         24.99
is           33.57
rfl          250.4
rfp              0
th               7
ins          1.000
nm  cdc  ph
```



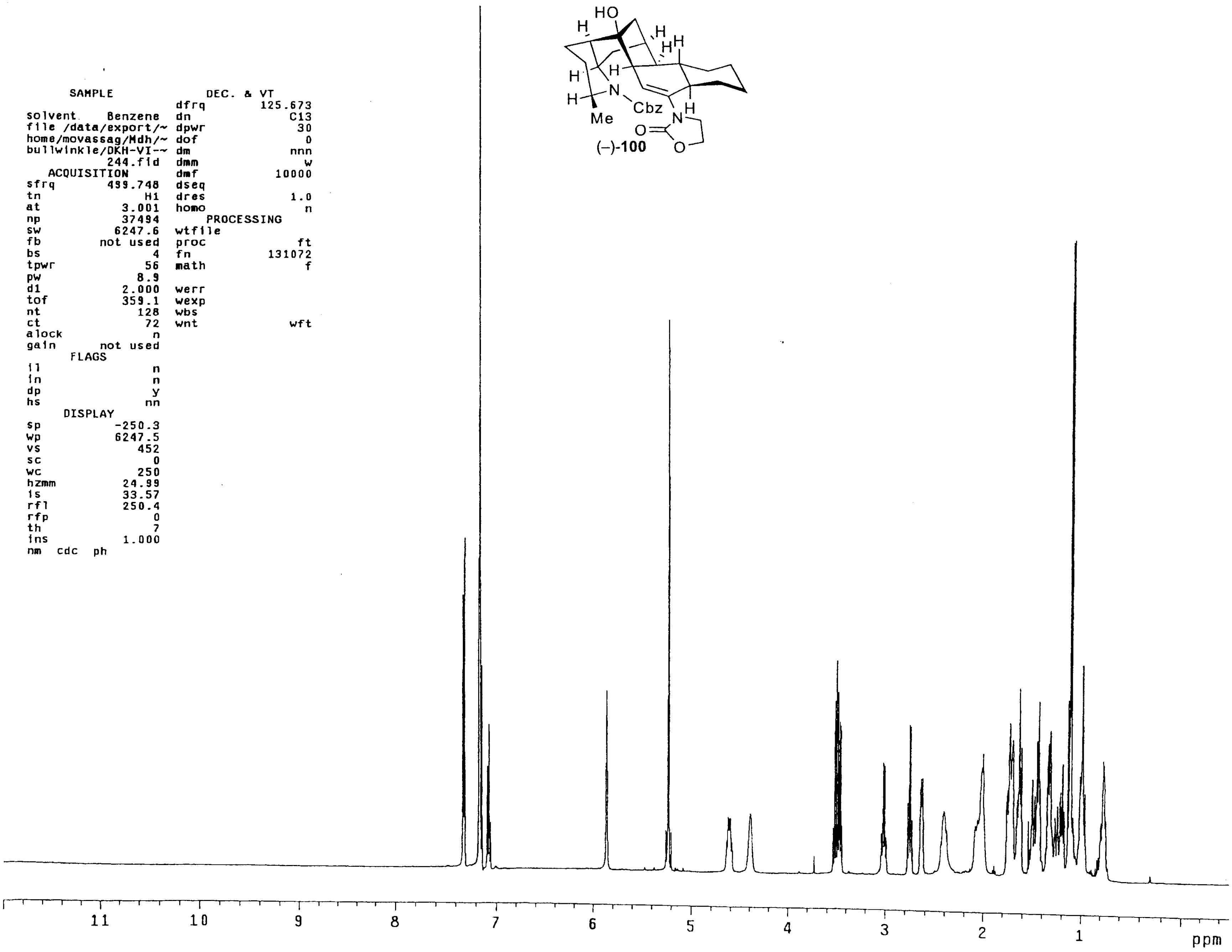
(+)-**99**



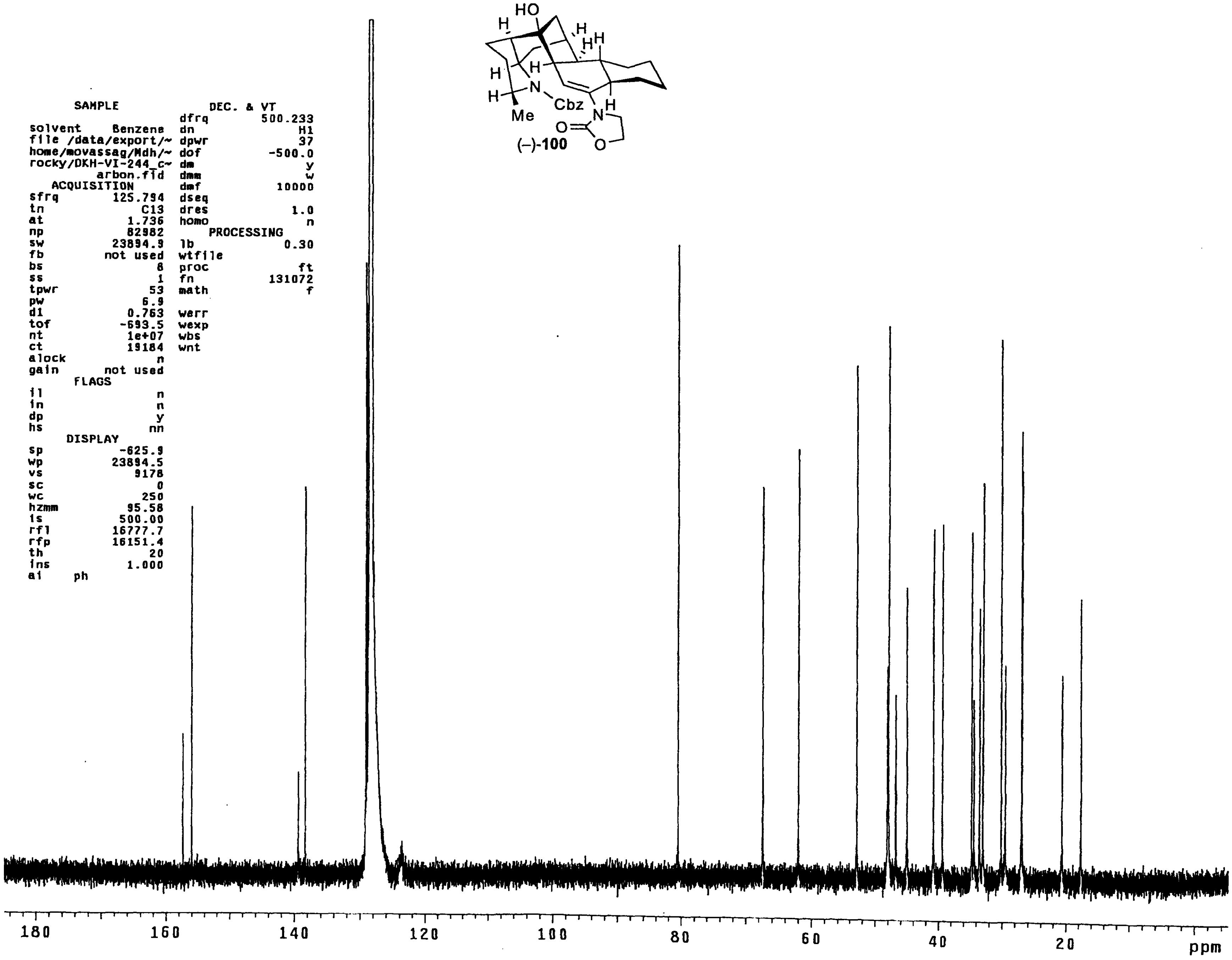
```
        SAMPLE              DEC. & VT
                          dfrq       500.233
solvent    Benzene        dn              H1
file /data/export/~       dpwr            37
home/movassag/Mdh/~       dof         -500.0
rocky/DKH-VI-246d.~       dm               y
               fid        dmm              w
    ACQUISITION           dmf          10000
sfrq       125.795        dseq
tn             C13        dres           1.0
at           1.735        homo             n
np           89854           PROCESSING
sw         25890.0        lb            0.30
fb        not used        wtfile
bs               8        proc            ft
ss               1        fn          131072
tpwr            53        math             f
pw             6.9
d1           0.763        werr
tof          159.9        wexp
nt          1e+06         wbs
ct           21176        wnt
alock            n
gain      not used
        FLAGS
il               n
in               n
dp               y
hs              nn
       DISPLAY
sp          -771.2
wp         25889.6
vs            5499
sc               0
wc             250
hzmm        103.56
is          500.00
rfl        16923.0
rfp        16151.4
th              15
ins          1.000
ai     ph
```


OH
H
H
H
H
H
H
HN
H
Me
H
H
N
O
O
91.5
90
85
80
75
70
65
60
55
49.7
%T
3800.0
3000
2000
1500
1000
600.0
cm-1
3424.42
3053.05
2925.82
2855.68
2360.39
1742.64
1665.84
1481.69
1445.89
1415.94
1372.36
1279.77
1222.49
1135.62
1101.36
1038.42
973.93
940.18
903.79
761.19
734.34
700.69

(+)-**99**



```
      SAMPLE               DEC. & VT
                      dfrq       125.673
solvent    Benzene    dn             C13
file /data/export/~   dpwr            30
home/movassag/Mdh/~   dof              0
bullwinkle/DKH-VI-~   dm             nnn
          244.fid     dmm              w
   ACQUISITION        dmf          10000
sfrq       499.748    dseq
tn              H1    dres           1.0
at           3.001    homo             n
np           37494       PROCESSING
sw          6247.6    wtfile
fb        not used    proc            ft
bs               4    fn          131072
tpwr            56    math             f
pw             8.9
d1           2.000    werr
tof          359.1    wexp
nt             128    wbs
ct              72    wnt            wft
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -250.3
wp          6247.5
vs             452
sc               0
wc             250
hzmm         24.99
is           33.57
rfl          250.4
rfp              0
th               7
ins          1.000
nm  cdc  ph
```



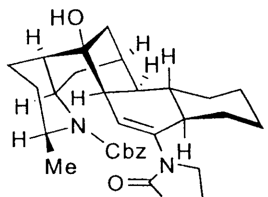
(–)-100

```
       SAMPLE            DEC. & VT
                       dfrq          500.233
solvent    Benzene     dn                 H1
file /data/export/~    dpwr               37
home/movassag/Mdh/~    dof            -500.0
rocky/DKH-VI-244_c~    dm                  y
         arbon.fid     dmm                 w
   ACQUISITION         dmf             10000
sfrq       125.794     dseq
tn             C13     dres              1.0
at           1.736     homo                n
np           82982        PROCESSING
sw         23894.9     lb               0.30
fb        not used     wtfile
bs               8     proc               ft
ss               1     fn             131072
tpwr            53     math                f
pw             6.9
d1           0.763     werr
tof         -693.5     wexp
nt           1e+07     wbs
ct           19184     wnt
alock            n
gain      not used
       FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp          -625.9
wp         23894.5
vs            9178
sc               0
wc             250
hzmm         95.58
is          500.00
rfl        16777.7
rfp        16151.4
th              20
ins          1.000
ai     ph
```

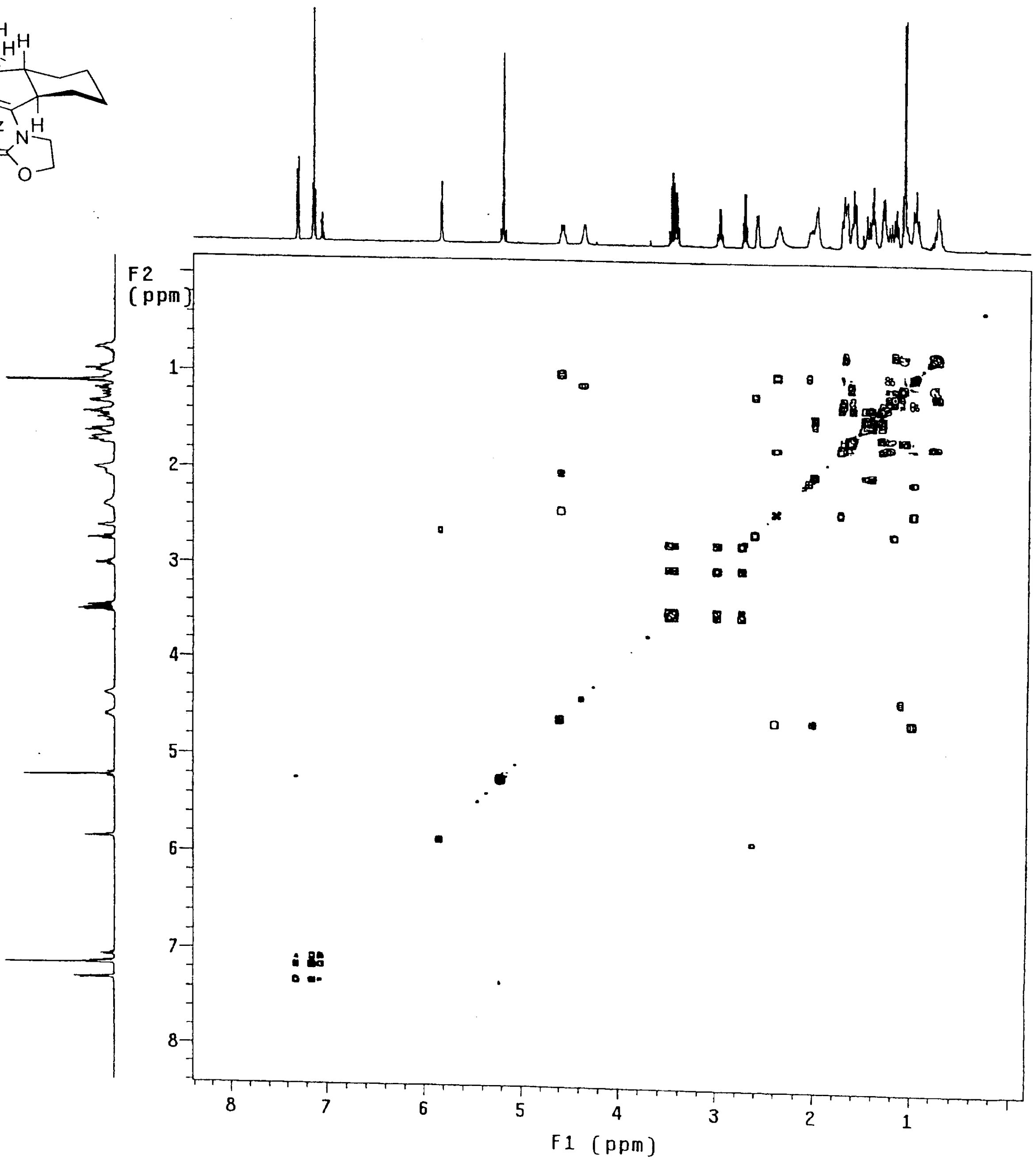
Pulse Sequence: gCOSY
Solvent: Benzene
Ambient temperature

INOVA-500 "zippy"

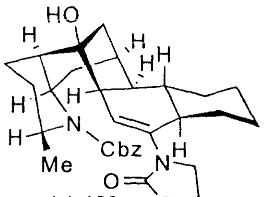
PULSE SEQUENCE: gCOSY
Relax. delay 1.000 sec
Acq. time 0.238 sec
Width 4293.7 Hz
2D Width 4293.7 Hz
26 repetitions
128 increments
OBSERVE H1, 499.7446815 MHz
DATA PROCESSING
Sq. sine bell 0.119 sec
F1 DATA PROCESSING
Sq. sine bell 0.030 sec
FT size 2048 x 2048
Total time 0 min, -1 sec



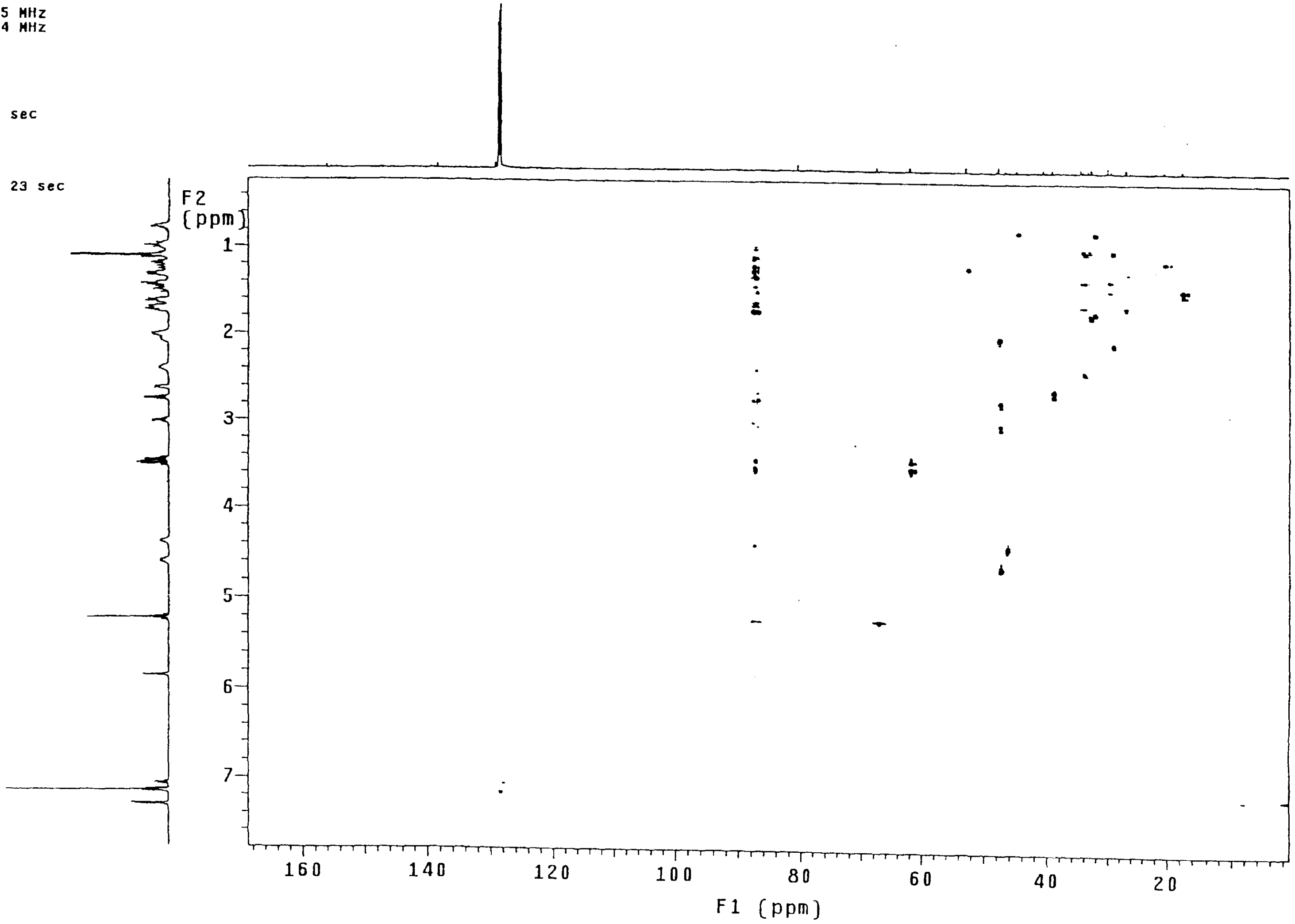
(–)-**100**

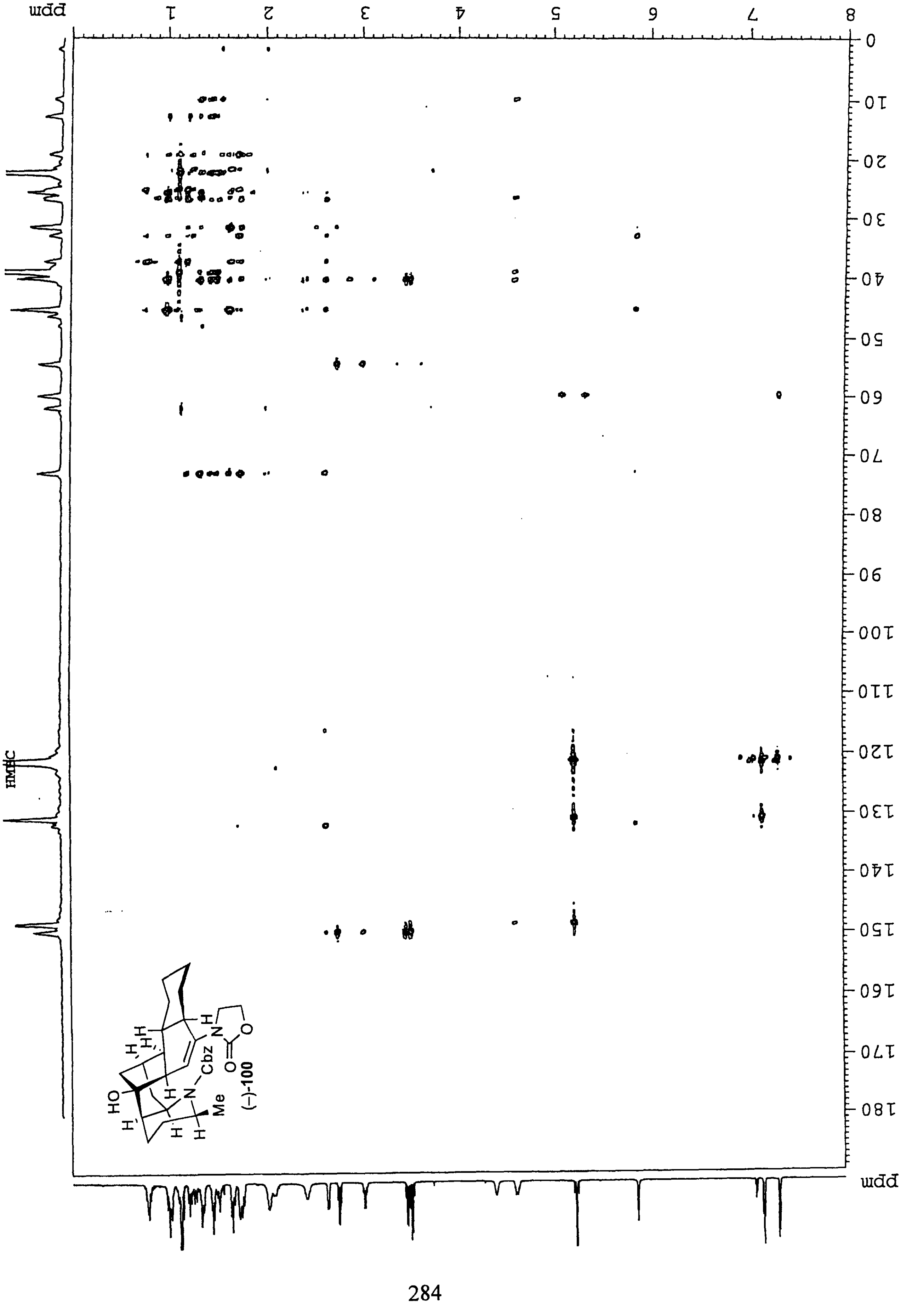


```
Pulse Sequence: HSQC
 Solvent: Benzene
 Ambient temperature
User:  1-14-87

INOVA-500  "zippy"

PULSE SEQUENCE: HSQC
 Relax. delay 1.000 sec
 Acq. time 0.099 sec
 Width     4186.7 Hz
 2D Width 23255.8 Hz
 32 repetitions
 2 x 256 increments
OBSERVE   H1, 499.7446815 MHz
DECOUPLE C13, 125.6718434 MHz
 Power 52 dB
 on during acquisition
 off during delay
 GARP-1 modulated
DATA PROCESSING
 Gauss apodization 0.113 sec
F1 DATA PROCESSING
 Sq. sine bell 0.022 sec
  Shifted by -0.022 sec
FT size 2048 x 2048
Total time 6 hr, 52 min, 23 sec
```

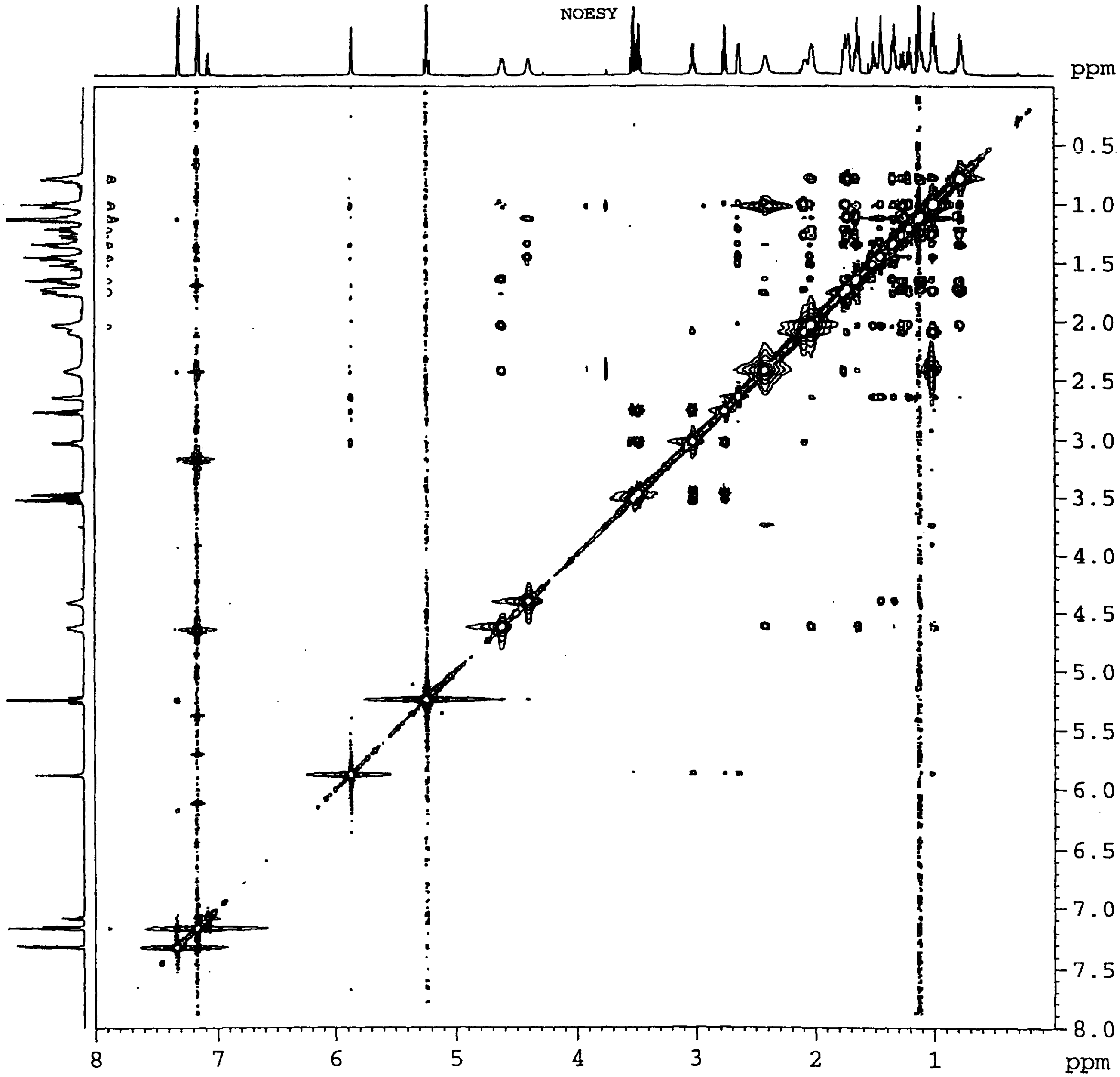


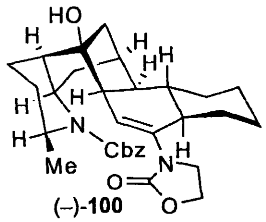
(–)-**100**




HMBC
ppm
1
2
3
4
5
6
7
8
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
ppm
HO
H
H
H
H
H
N
Cbz
Me
H
H
N
O
O
O

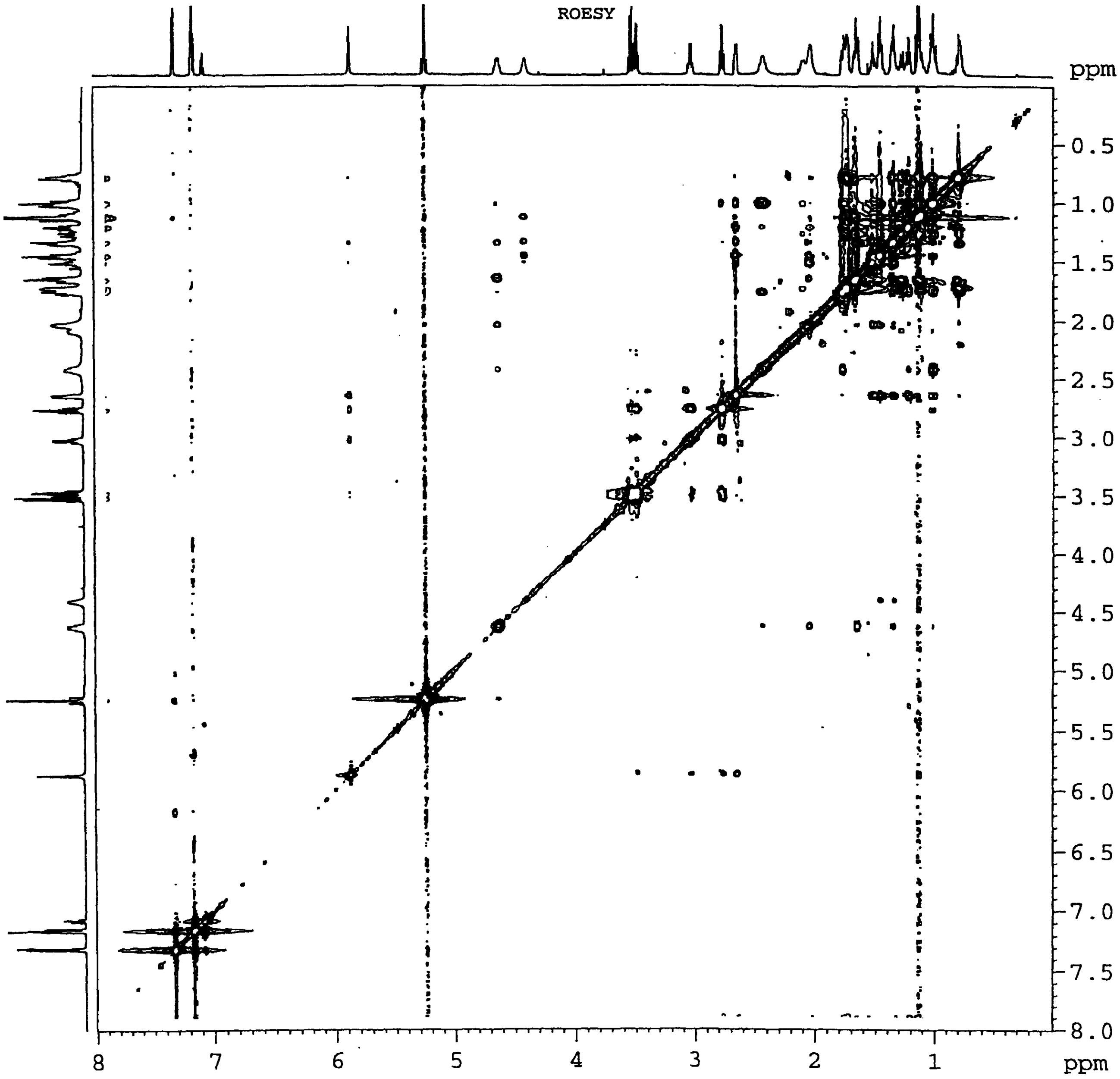
(–)-100

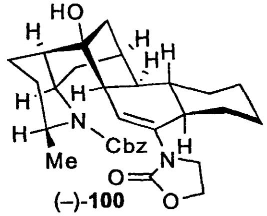




(–)-**100**

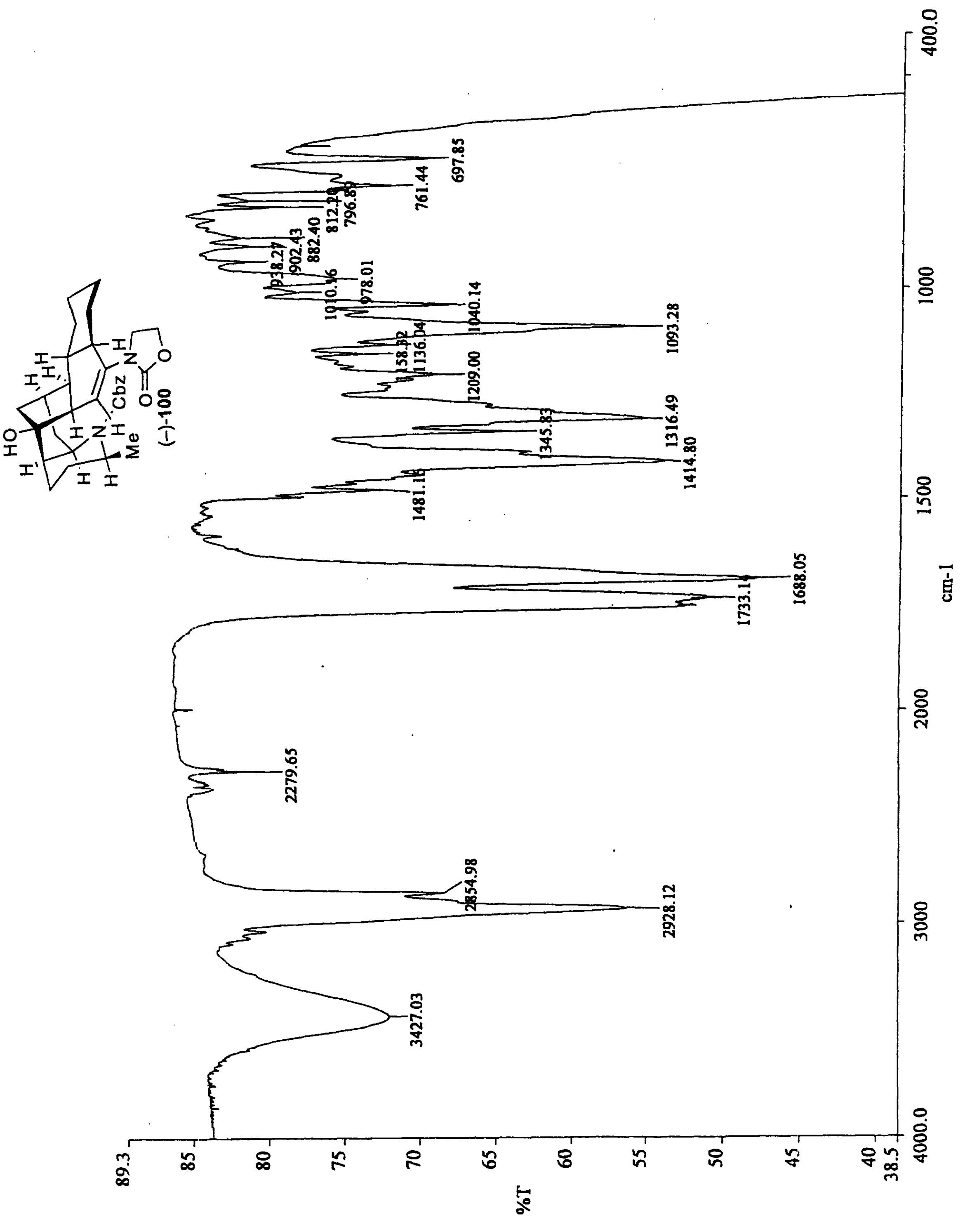
```
F2 - Acquisition Parameters
Date_           20060124
Time               11.39
INSTRUM            spect
PROBHD   5 mm CPTXI Z-G
PULPROG          noesyph
TD                  1024
SOLVENT             C6D6
NS                    32
DS                    16
SWH             4807.692 Hz
FIDRES          4.695012 Hz
AQ             0.1066500 sec
RG                    64
DW               104.000 usec
DE                  6.00 usec
TE                 295.0 K
d0            0.00009267 sec
D1            0.80000001 sec
D8            0.40000001 sec
IN0           0.00020800 sec
MCREST        0.00000000 sec
MCWRK         0.80000001 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  8.90 usec
PL1                -6.00 dB
SFO1         600.4674019 MHz

F1 - Acquisition parameters
ND0                    1
TD                   512
SFO1            600.4674 MHz
FIDRES          9.390024 Hz
SW                 8.007 ppm
FnMODE              TPPI

F2 - Processing parameters
SI                  2048
SF           600.4650000 MHz
WDW                 SINE
SSB                    2
LB                  0.00 Hz
GB                     0
PC                  1.00

F1 - Processing parameters
SI                  1024
MC2                 TPPI
SF           600.4650000 MHz
WDW                 SINE
SSB                    2
LB                  0.00 Hz
GB                     0
```

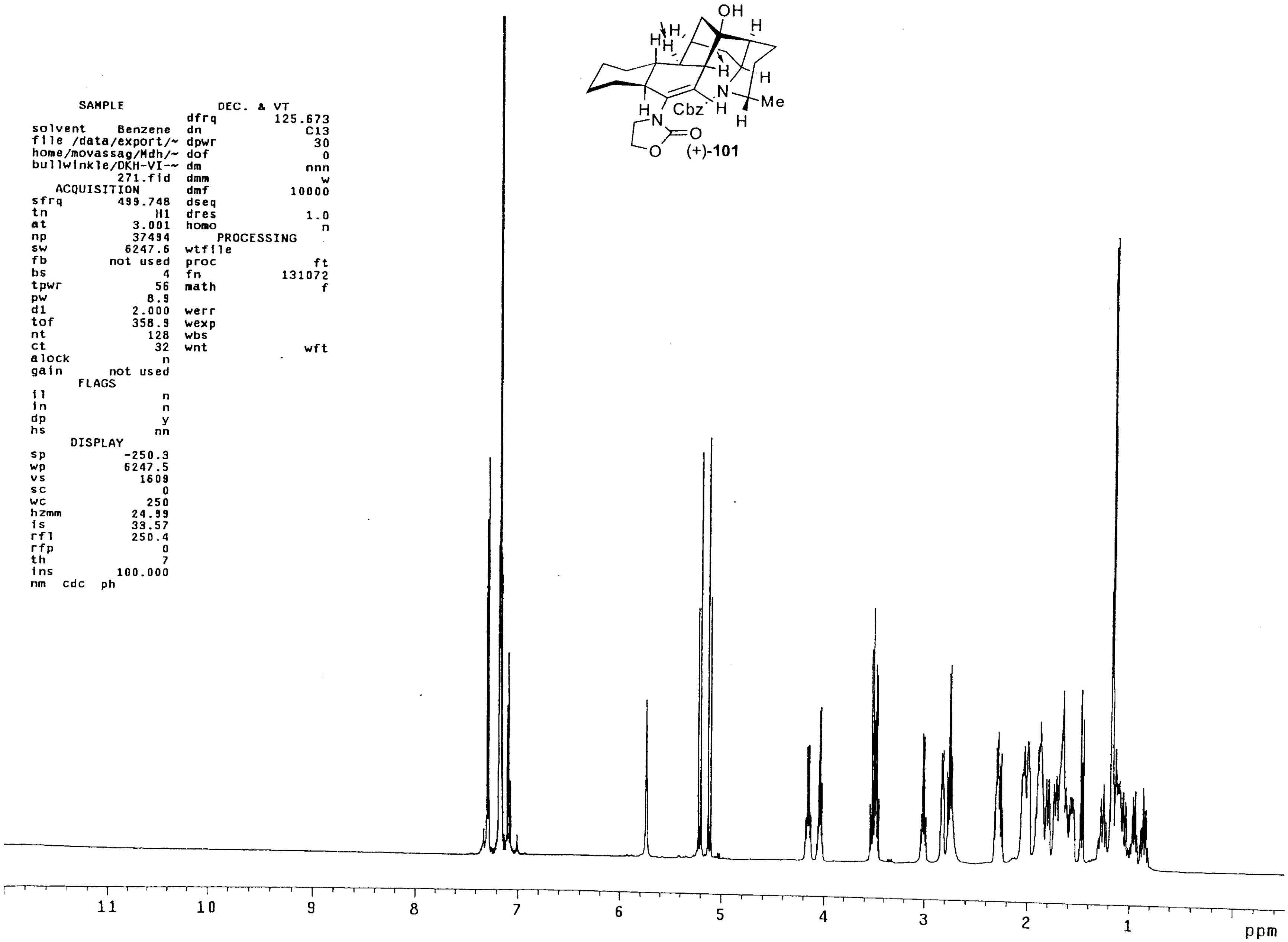




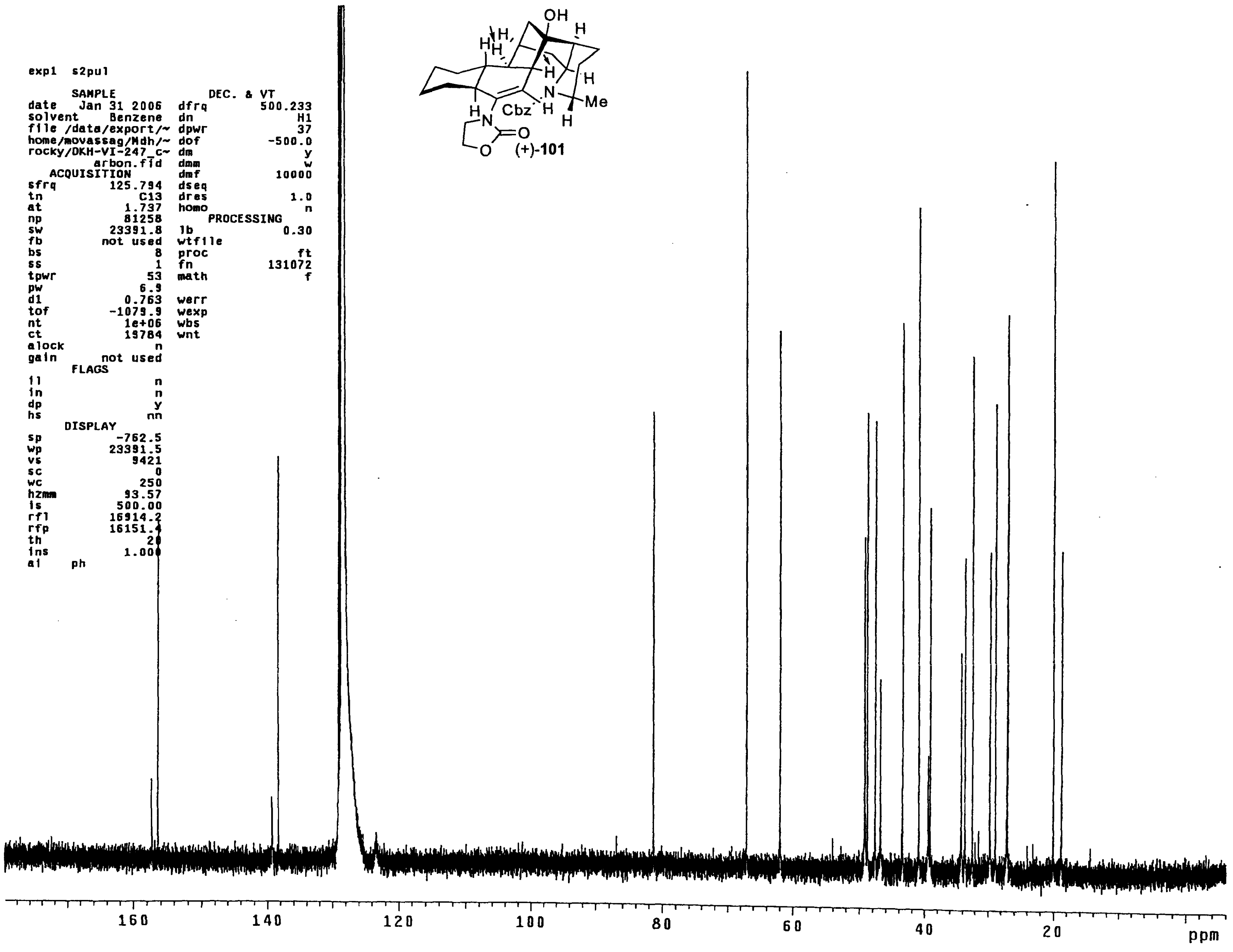
(–)-**100**

```
F2 - Acquisition Parameters
Date_            20060124
Time                17.45
INSTRUM             spect
PROBHD   5 mm CPTXI Z-G
PULPROG           roesyph
TD                   1024
SOLVENT              C6D6
NS                     32
DS                     16
SWH              4807.692 Hz
FIDRES           4.695012 Hz
AQ              0.1066500 sec
RG                     64
DW                104.000 usec
DE                   6.00 usec
TE                  295.0 K
d0             0.00009433 sec
D1             0.80000001 sec
d12            0.00002000 sec
IN0            0.00020800 sec
MCREST         0.00000000 sec
MCWRK          0.80000001 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   8.90 usec
P15             400000.00 usec
PL1                 -6.00 dB
PL11                15.20 dB
SFO1          600.4674019 MHz

F1 - Acquisition parameters
ND0                     1
TD                    512
SFO1             600.4674 MHz
FIDRES           9.390024 Hz
SW                  8.007 ppm
FnMODE               TPPI

F2 - Processing parameters
SI                   2048
SF            600.4650000 MHz
WDW                  SINE
SSB                     2
LB                   0.00 Hz
GB                      0
PC                   1.00

F1 - Processing parameters
SI                   1024
MC2                  TPPI
SF            600.4650000 MHz
WDW                  SINE
SSB                     2
LB                   0.00 Hz
GB                      0
```


HO
H
H
H
H
H
H
N
Cbz
H
Me
N
O
O
H
(–)-100
%T
89.3
85
80
75
70
65
60
55
50
45
40
38.5
4000.0
3000
2000
1500
1000
400.0
cm-1
3427.03
2928.12
2854.98
2279.65
1733.14
1688.05
1481.16
1414.80
1345.83
1316.49
1209.00
1158.32
1136.04
1093.28
1040.14
1010.96
978.01
938.27
902.43
882.40
812.79
796.89
761.44
697.85


(+)-101

```
       SAMPLE              DEC. & VT
                        dfrq         125.673
solvent    Benzene  dn              C13
file /data/export/~ dpwr              30
home/movassag/Mdh/~ dof                0
bullwinkle/DKH-VI-~ dm               nnn
          271.fid   dmm                w
   ACQUISITION      dmf            10000
sfrq       499.748  dseq
tn              H1  dres             1.0
at           3.001  homo               n
np           37494       PROCESSING
sw          6247.6  wtfile
fb        not used  proc              ft
bs               4  fn            131072
tpwr            56  math               f
pw             8.9
d1           2.000  werr
tof          358.9  wexp
nt             128  wbs
ct              32  wnt              wft
alock            n
gain      not used
       FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp          -250.3
wp          6247.5
vs            1609
sc               0
wc             250
hzmm         24.99
is           33.57
rfl          250.4
rfp              0
th               7
ins        100.000
nm  cdc  ph
```



(+)-101

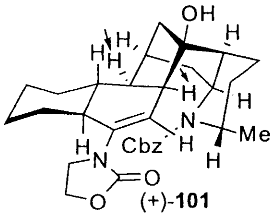
```
exp1  s2pul

      SAMPLE              DEC. & VT
date    Jan 31 2006  dfrq       500.233
solvent     Benzene  dn              H1
file /data/export/~  dpwr            37
home/movassag/Mdh/~  dof         -500.0
rocky/DKH-VI-247_c~  dm               y
         arbon.fid   dmm              w
   ACQUISITION       dmf          10000
sfrq        125.794  dseq
tn              C13  dres           1.0
at            1.737  homo             n
np            81258       PROCESSING
sw          23391.8  lb            0.30
fb         not used  wtfile
bs                8  proc            ft
ss                1  fn          131072
tpwr             53  math             f
pw              6.9
d1            0.763  werr
tof         -1079.9  wexp
nt           1e+06   wbs
ct            19784  wnt
alock             n
gain       not used
      FLAGS
il                n
in                n
dp                y
hs               nn
     DISPLAY
sp           -762.5
wp          23391.5
vs             9421
sc                0
wc              250
hzmm          93.57
is           500.00
rfl         16914.2
rfp         16151.4
th               20
ins           1.000
ai    ph
```

Pulse Sequence: gCOSY

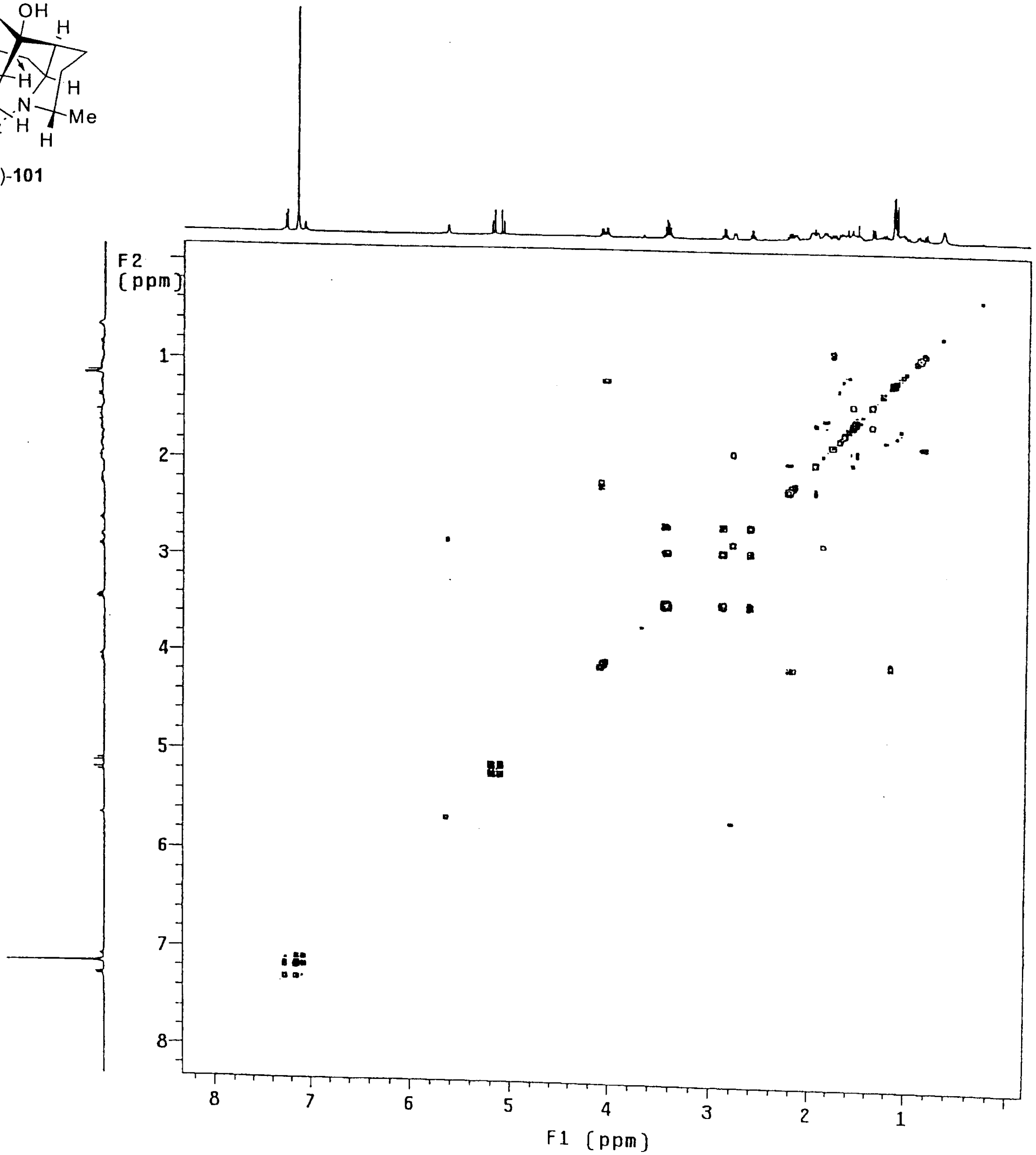
Solvent: Benzene
Ambient temperature

INOVA-500 "zippy"

PULSE SEQUENCE: gCOSY
Relax. delay 1.000 sec
Acq. time 0.241 sec
Width 4247.2 Hz
2D Width 4247.2 Hz
24 repetitions
128 increments
OBSERVE H1, 499.7446814 MHz
DATA PROCESSING
Sq. sine bell 0.120 sec
F1 DATA PROCESSING
Sq. sine bell 0.030 sec
FT size 2048 x 2048
Total time 0 min, -1 sec



(+)-**101**

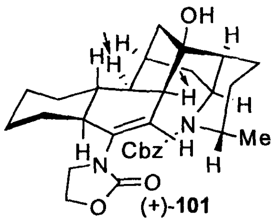


Pulse Sequence: HSQC

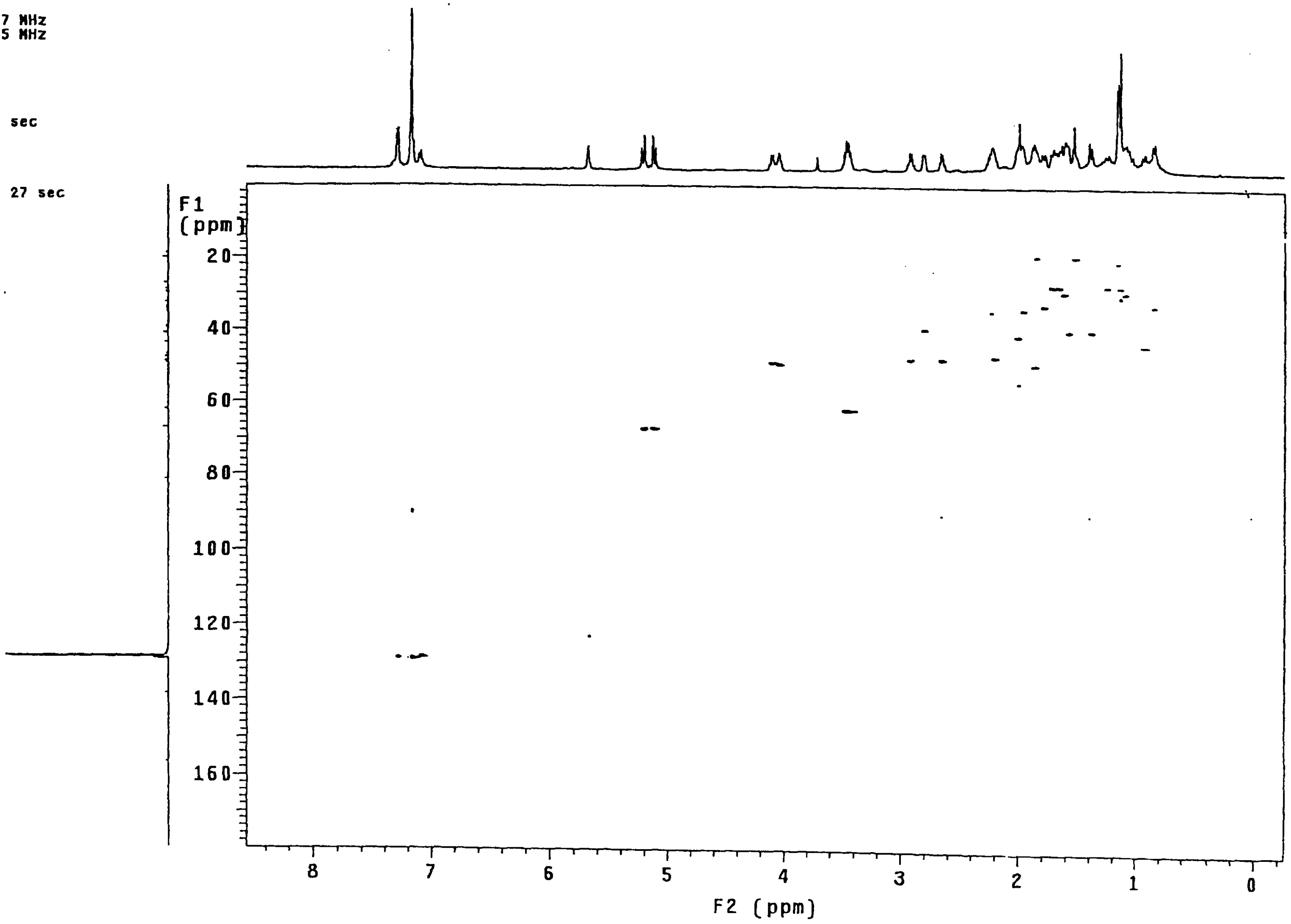
Solvent: Benzene
Ambient temperature
User: 1-14-87

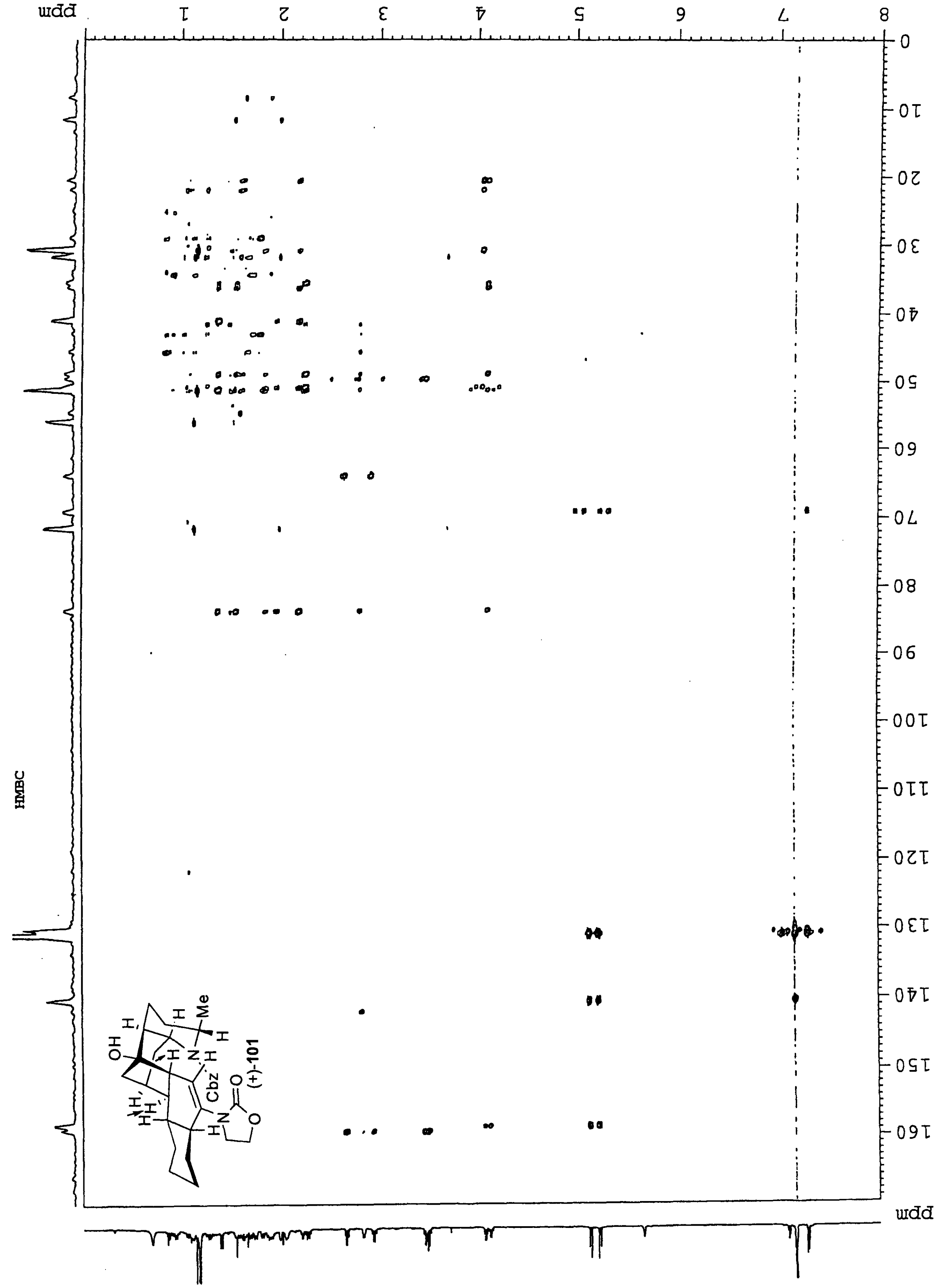
INOVA-500 "zippy"

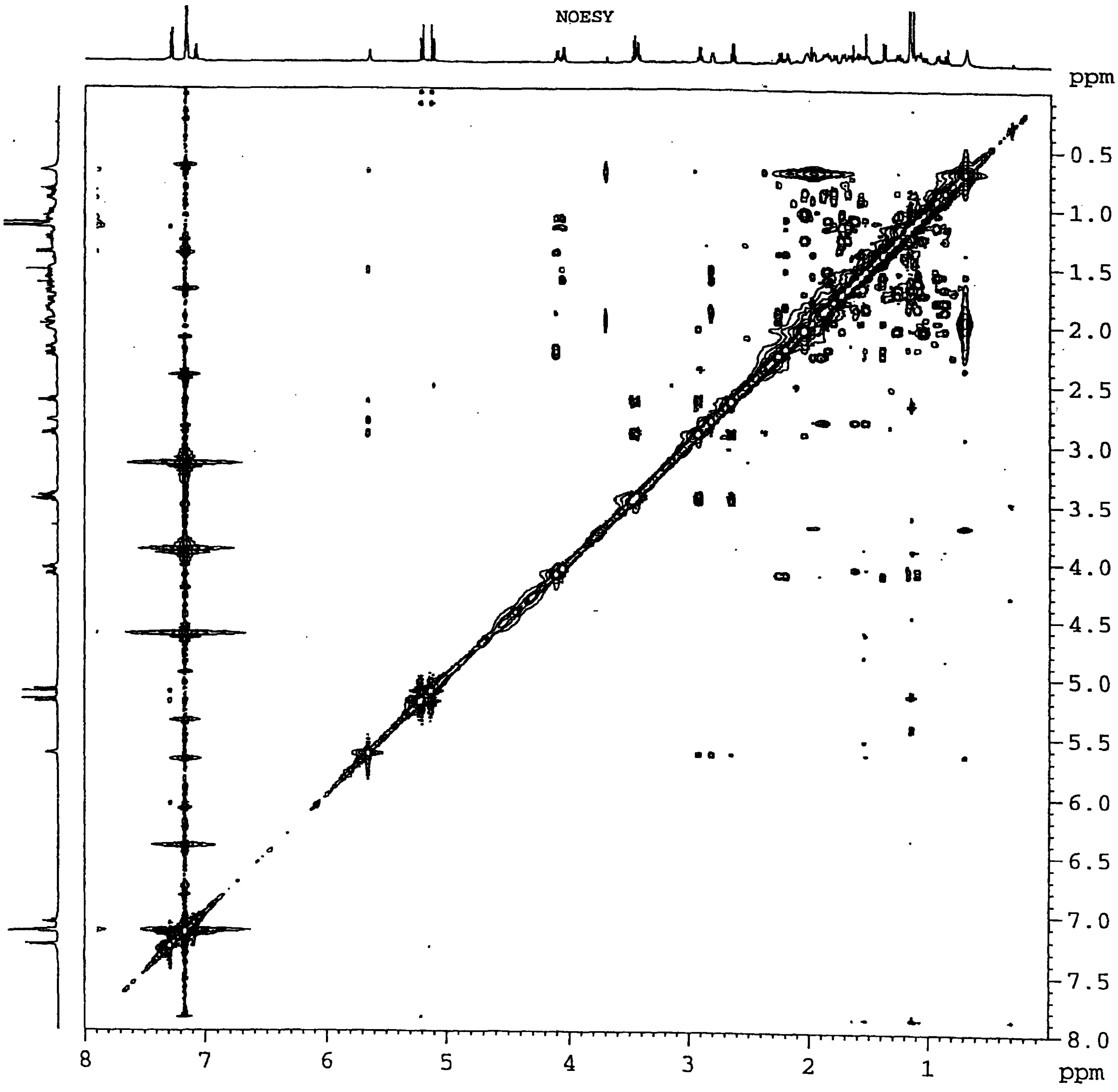
PULSE SEQUENCE: HSQC
Relax. delay 1.000 sec
Acq. time 0.099 sec
Width 4406.3 Hz
2D Width 22598.9 Hz
32 repetitions
2 x 256 increments
OBSERVE H1, 499.7446817 MHz
DECOUPLE C13, 125.6721325 MHz
Power 52 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.107 sec
F1 DATA PROCESSING
Sq. sine bell 0.023 sec
Shifted by -0.023 sec
FT size 2048 x 2048
Total time 6 hr, 52 min, 27 sec

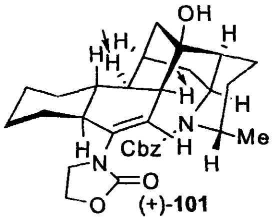


(+)-101



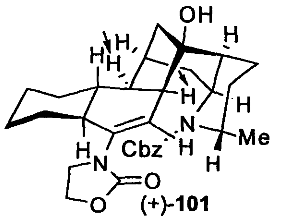

HMBC
ppm
1
2
3
4
5
6
7
8
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm
OH
H
H
H
Me
H
N
H
Cbz
H
H
H
N
O
O
(+)-101



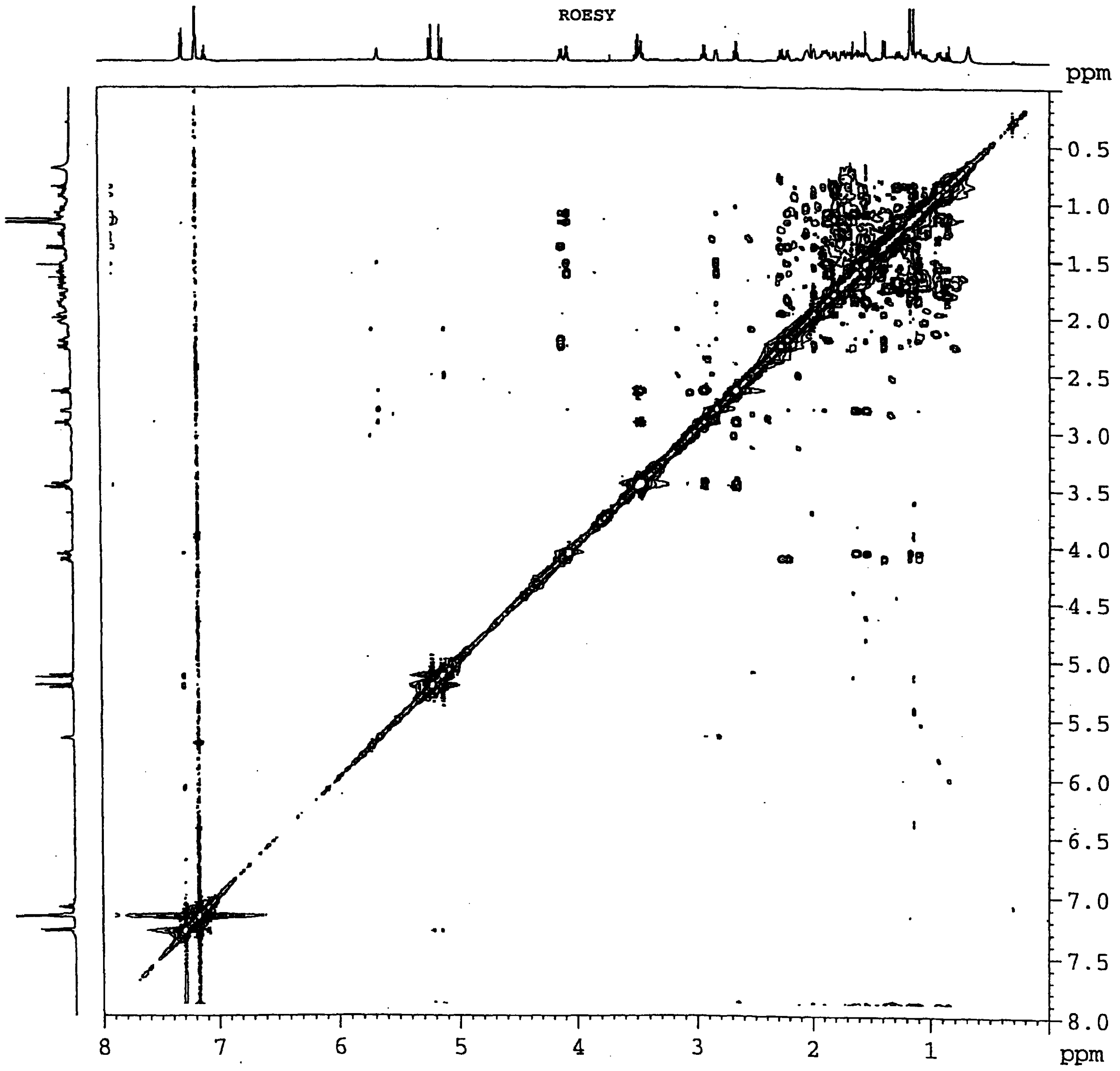


(+)-**101**

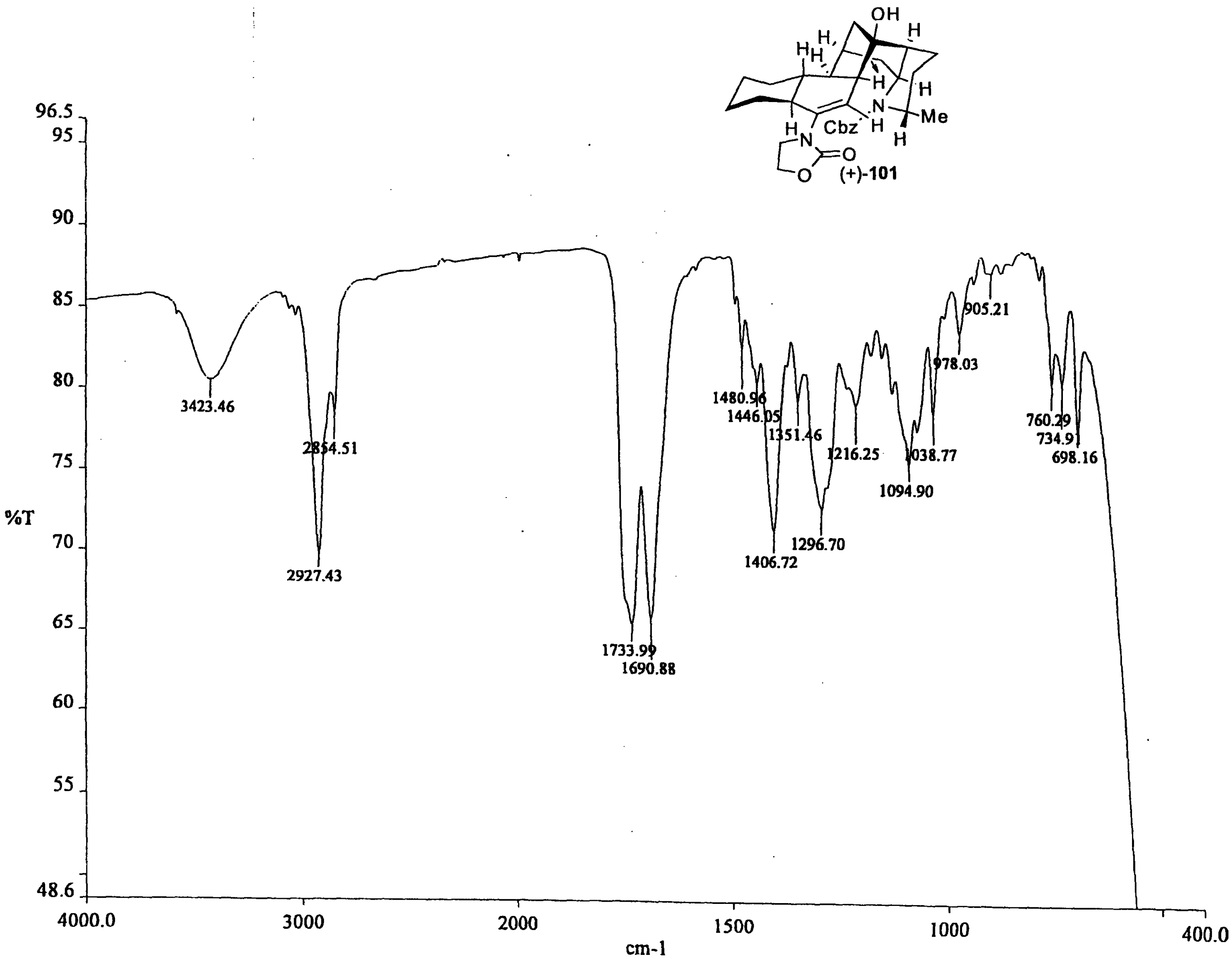
```
F2 - Acquisition Parameters
Date_          20060127
Time              15.57
INSTRUM           spect
PROBHD   5 mm CPTXI Z-G
PULPROG         noesyph
TD                 1024
SOLVENT             D2O
NS                   24
DS                   16
SWH            4807.692 Hz
FIDRES         4.695012 Hz
AQ            0.1066500 sec
RG                  128
DW              104.000 usec
DE                 6.00 usec
TE                295.0 K
d0           0.00009267 sec
D1           0.69999999 sec
D8           0.40000001 sec
IN0          0.00020800 sec
MCREST       0.00000000 sec
MCWRK        0.69999999 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 8.90 usec
PL1               -6.00 dB
SFO1        600.4674019 MHz

F1 - Acquisition parameters
ND0                   1
TD                  480
SFO1           600.4674 MHz
FIDRES        10.016026 Hz
SW                8.007 ppm
FnMODE             TPPI

F2 - Processing parameters
SI                 2048
SF          600.4650000 MHz
WDW                SINE
SSB                   2
LB                 0.00 Hz
GB                    0
PC                 1.00

F1 - Processing parameters
SI                 1024
MC2                TPPI
SF          600.4650000 MHz
WDW                SINE
SSB                   2
LB                 0.00 Hz
GB                    0
```

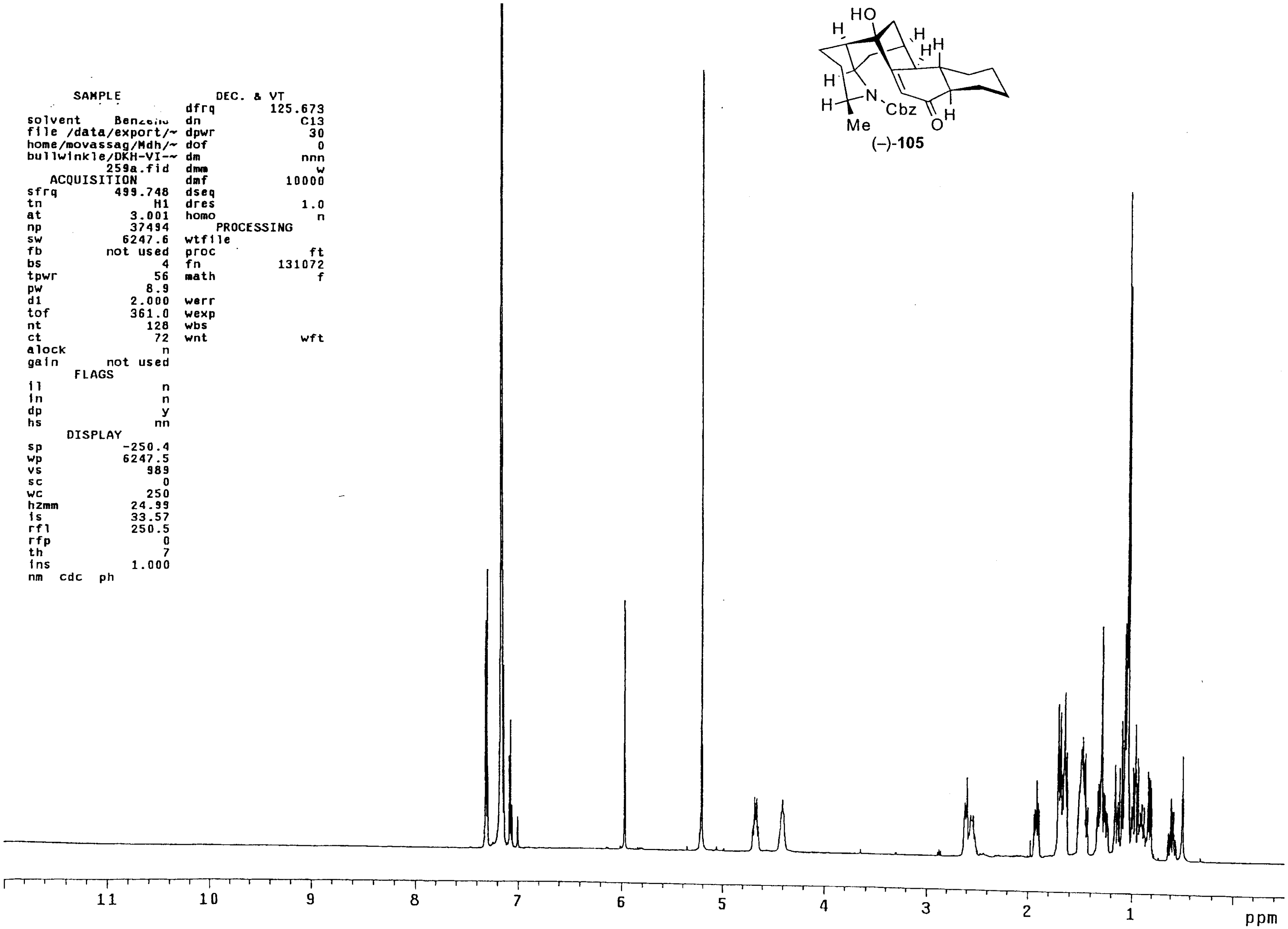


(+)-**101**



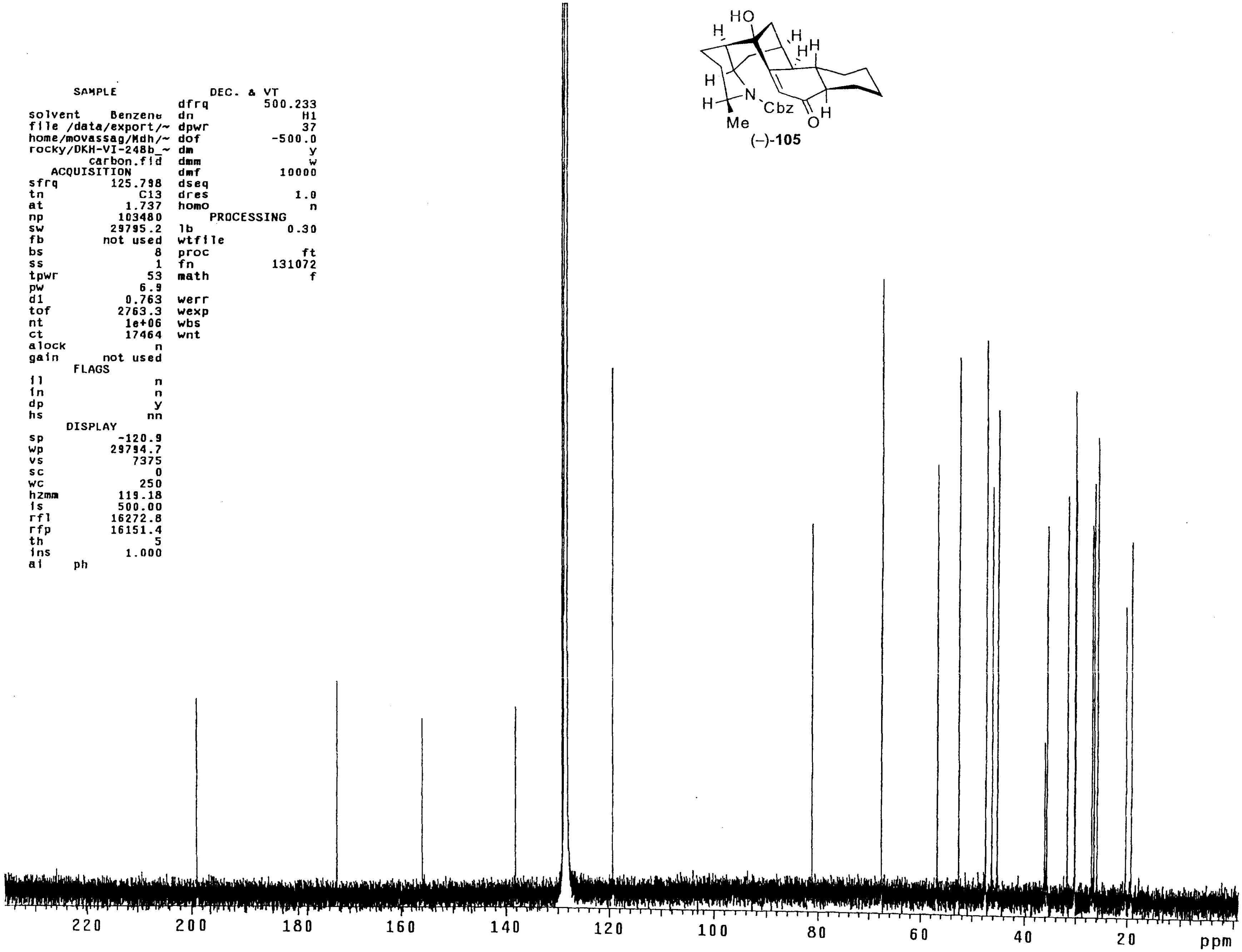
```
F2 - Acquisition Parameters
Date_             20060127
Time                 19.54
INSTRUM              spect
PROBHD    5 mm CPTXI Z-G
PULPROG            roesyph
TD                    1024
SOLVENT               C6D6
NS                      24
DS                      16
SWH             4807.692 Hz
FIDRES          4.695012 Hz
AQ             0.1066500 sec
RG                     128
DW                104.000 usec
DE                   6.00 usec
TE                  295.0 K
d0             0.00009433 sec
D1             0.69999999 sec
d12            0.00002000 sec
IN0            0.00020800 sec
MCREST         0.00000000 sec
MCWRK          0.69999999 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    8.90 usec
P15              400000.00 usec
PL1                  -6.00 dB
PL11                 15.20 dB
SFO1           600.4674019 MHz

F1 - Acquisition parameters
ND0                      1
TD                     480
SFO1              600.4674 MHz
FIDRES           10.016026 Hz
SW                   8.007 ppm
FnMODE                TPPI

F2 - Processing parameters
SI                    2048
SF             600.4650000 MHz
WDW                   SINE
SSB                      2
LB                    0.00 Hz
GB                       0
PC                    1.00

F1 - Processing parameters
SI                    1024
MC2                   TPPI
SF             600.4650000 MHz
WDW                   SINE
SSB                      2
LB                    0.00 Hz
GB                       0
```


OH
H
H,
HH
H
H
N
Me
H
Cbz
H
N
O
O
(+)-101
96.5
95
90
85
80
75
%T
70
65
60
55
48.6
4000.0
3000
2000
1500
1000
400.0
cm-1
3423.46
2854.51
2927.43
1733.99
1690.88
1480.96
1446.05
1351.46
1406.72
1296.70
1216.25
1094.90
1038.77
978.03
905.21
760.29
734.91
698.16



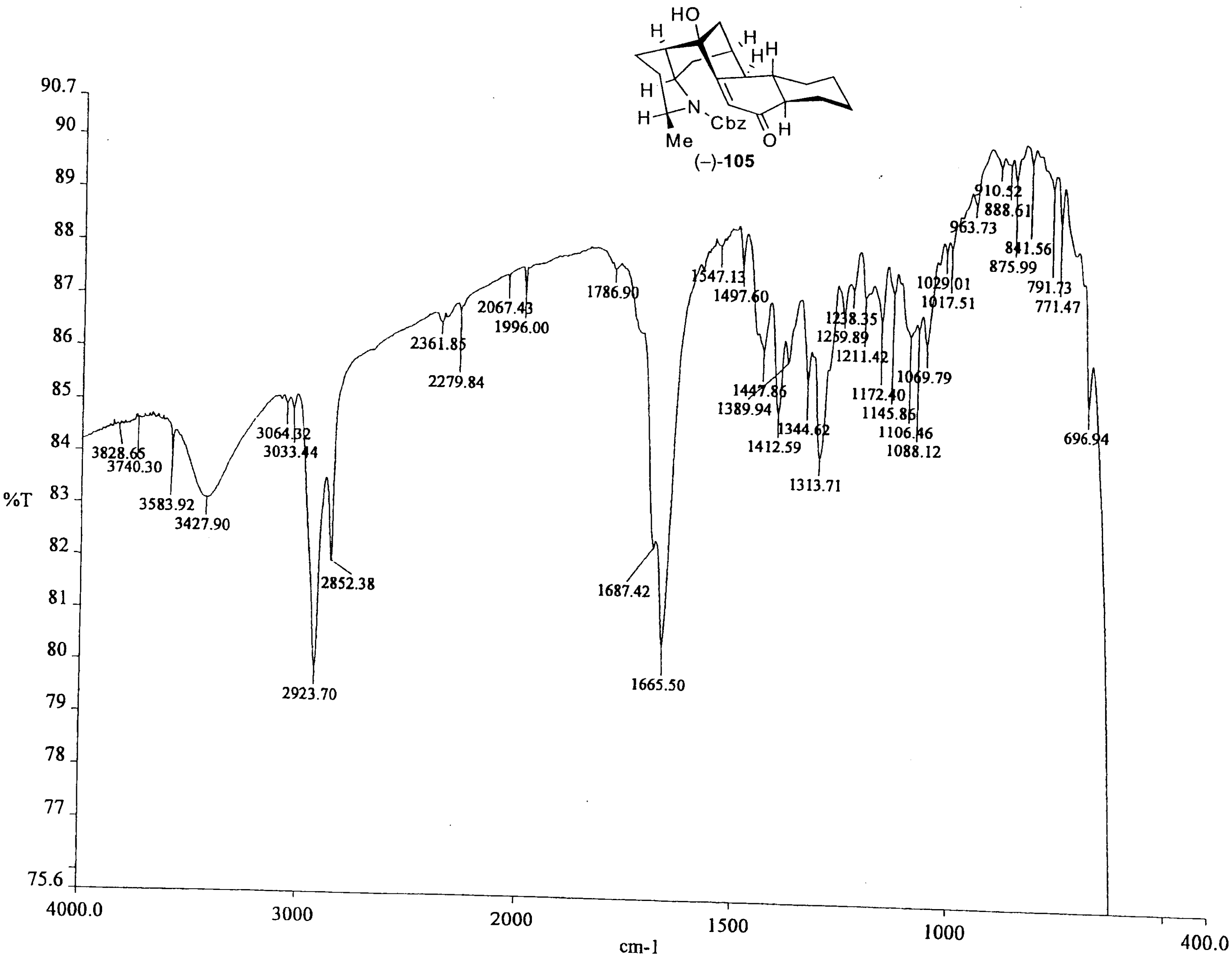
(–)-**105**

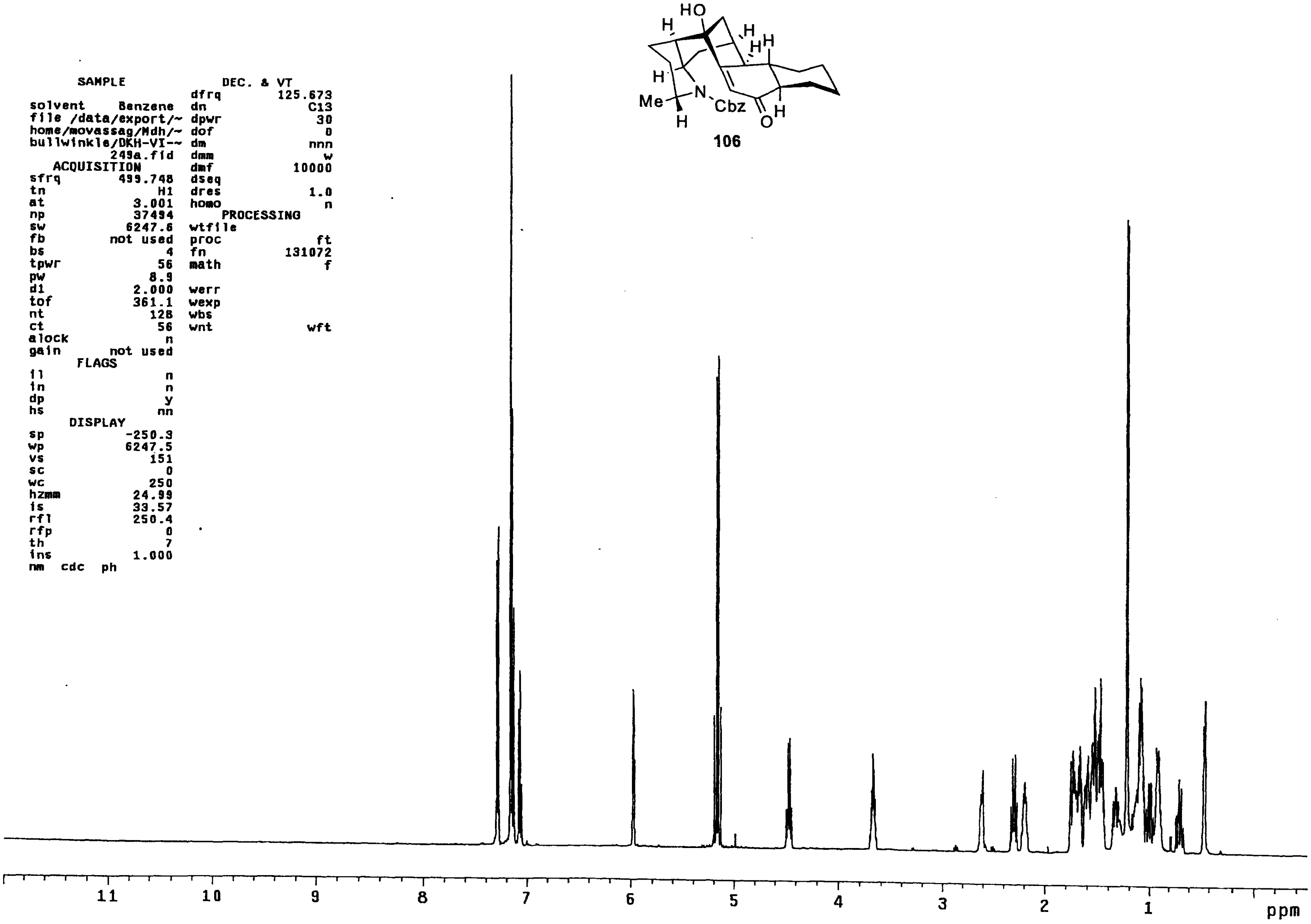
```
     SAMPLE              DEC. & VT
                     dfrq       125.673
solvent    Benzene   dn             C13
file /data/export/~  dpwr            30
home/movassag/Mdh/~  dof              0
bullwinkle/DKH-VI-~  dm             nnn
          259a.fid   dmm              w
   ACQUISITION       dmf          10000
sfrq       499.748   dseq
tn              H1   dres           1.0
at           3.001   homo             n
np           37494      PROCESSING
sw          6247.6   wtfile
fb        not used   proc            ft
bs               4   fn          131072
tpwr            56   math             f
pw             8.9
d1           2.000   werr
tof          361.0   wexp
nt             128   wbs
ct              72   wnt            wft
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -250.4
wp          6247.5
vs             989
sc               0
wc             250
hzmm         24.99
is           33.57
rfl          250.5
rfp              0
th               7
ins          1.000
nm  cdc  ph
```



(–)-**105**

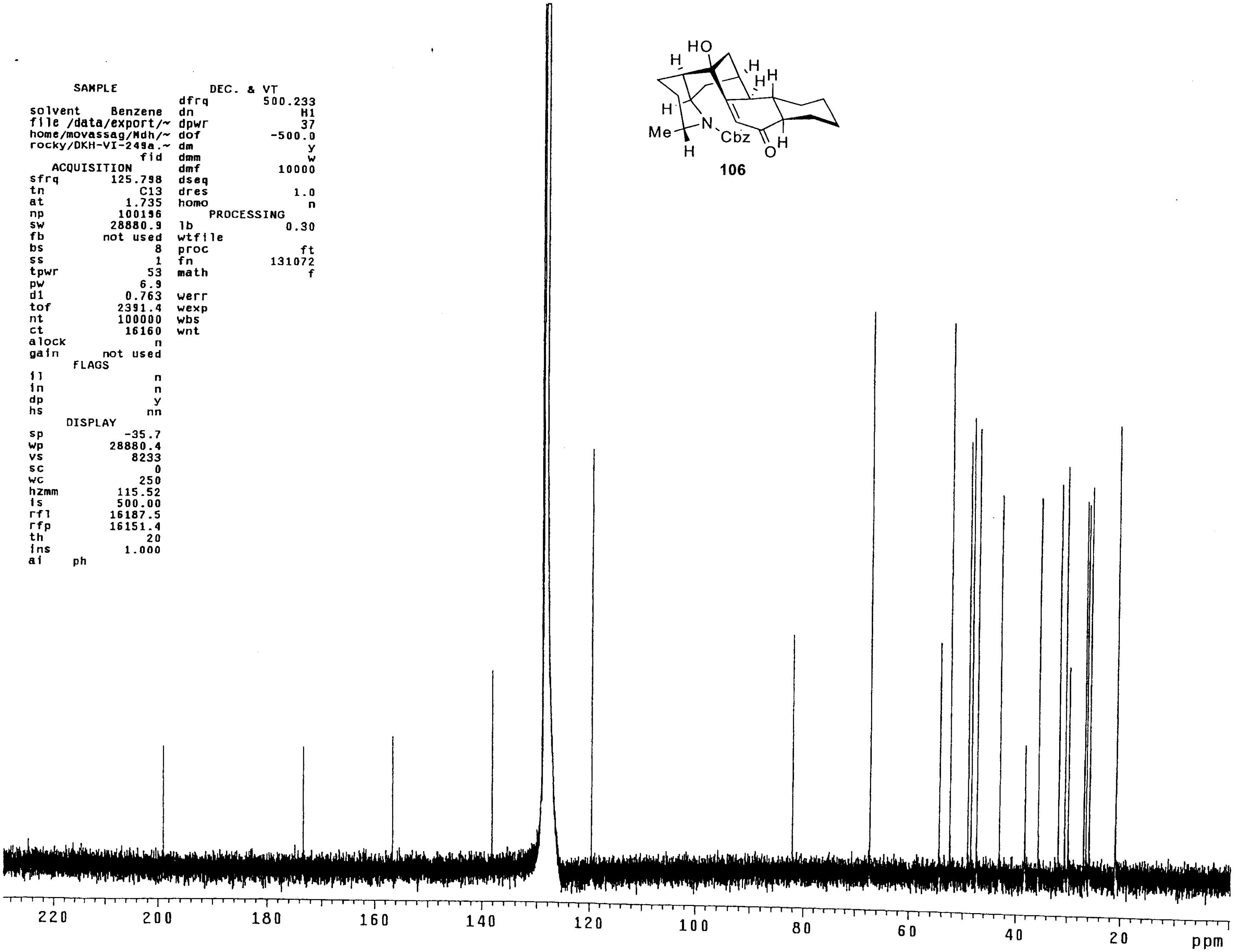
```
      SAMPLE               DEC. & VT
                       dfrq          500.233
solvent    Benzene     dn                 H1
file /data/export/~    dpwr               37
home/movassag/Mdh/~    dof            -500.0
rocky/DKH-VI-248b_~    dm                  y
         carbon.fid    dmm                 w
   ACQUISITION         dmf             10000
sfrq         125.798   dseq
tn               C13   dres              1.0
at             1.737   homo                n
np            103480       PROCESSING
sw           29795.2   lb               0.30
fb          not used   wtfile
bs                 8   proc               ft
ss                 1   fn             131072
tpwr              53   math                f
pw               6.9
d1             0.763   werr
tof           2763.3   wexp
nt             1e+06   wbs
ct             17464   wnt
alock              n
gain        not used
      FLAGS
il                 n
in                 n
dp                 y
hs                nn
     DISPLAY
sp            -120.9
wp           29794.7
vs              7375
sc                 0
wc               250
hzmm          119.18
is            500.00
rfl          16272.8
rfp          16151.4
th                 5
ins            1.000
ai    ph
```


(-)-**105**
HO
H
H
H
H
H
H
N
Cbz
Me
O
H
%T
90.7
90
89
88
87
86
85
84
83
82
81
80
79
78
77
75.6
4000.0
3000
2000
1500
1000
400.0
cm-1
3828.65
3740.30
3583.92
3427.90
3064.32
3033.44
2923.70
2852.38
2361.85
2279.84
2067.43
1996.00
1786.90
1687.42
1665.50
1547.13
1497.60
1447.86
1389.94
1412.59
1344.62
1313.71
1238.35
1259.89
1211.42
1172.40
1145.86
1106.46
1088.12
1069.79
1029.01
1017.51
963.73
910.52
888.61
875.99
841.56
791.73
771.47
696.94



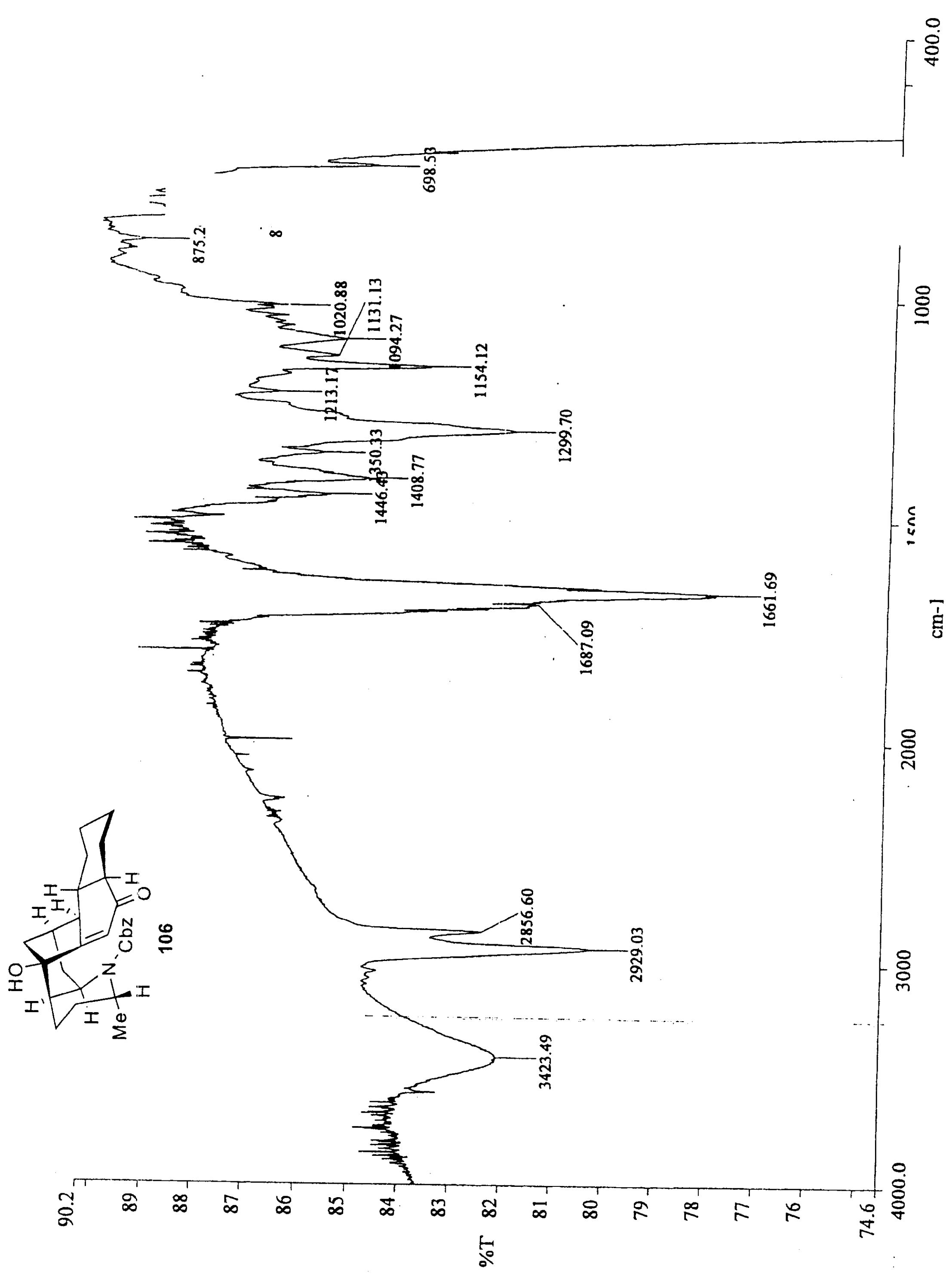
106

```
      SAMPLE              DEC. & VT
solvent    Benzene  dfrq       125.673
file /data/export/~ dn             C13
home/movassag/Mdh/~ dpwr            30
bullwinkle/DKH-VI--~ dof             0
          249a.fid  dmm            nnn
   ACQUISITION      dmm              w
sfrq       499.748  dmf          10000
tn              H1  dseq
at           3.001  dres           1.0
np           37494  homo             n
sw          6247.6      PROCESSING
fb        not used  wtfile
bs               4  proc            ft
tpwr            56  fn          131072
pw             8.9  math             f
d1           2.000
tof          361.1  werr
nt             128  wexp
ct              56  wbs
alock            n  wnt            wft
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp          -250.3
wp          6247.5
vs             151
sc               0
wc             250
hzmm         24.99
is           33.57
rfl          250.4
rfp              0
th               7
ins          1.000
nm  cdc  ph
```



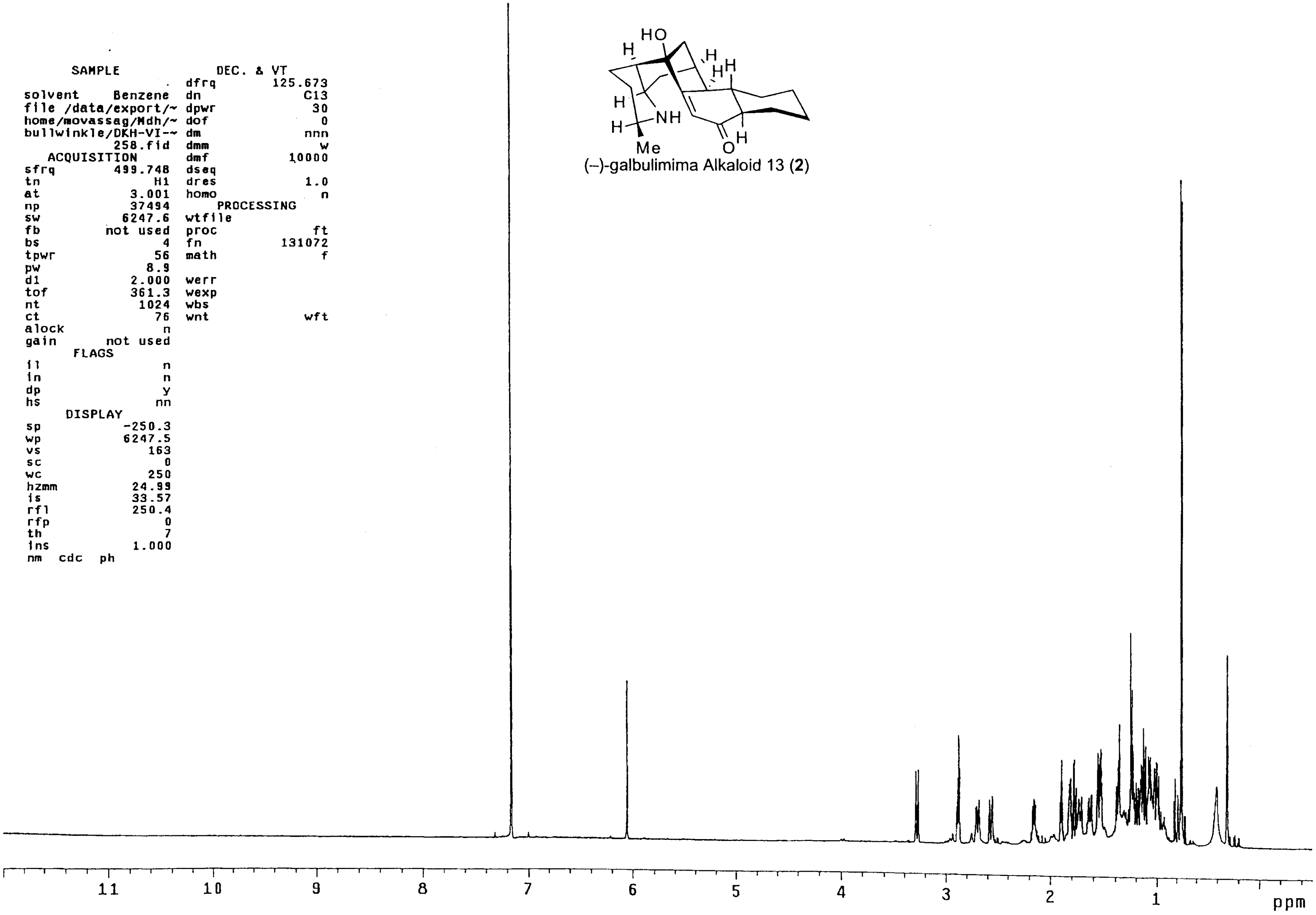
106

```
       SAMPLE              DEC. & VT
                          dfrq        500.233
solvent    Benzene        dn               H1
file /data/export/~       dpwr             37
home/movassag/Mdh/~       dof          -500.0
rocky/DKH-VI-249a.~       dm                y
                fid       dmm               w
   ACQUISITION            dmf           10000
sfrq       125.798        dseq
tn             C13        dres            1.0
at           1.735        homo              n
np          100196           PROCESSING
sw         28880.9        lb             0.30
fb        not used        wtfile
bs               8        proc             ft
ss               1        fn           131072
tpwr            53        math              f
pw             6.9
d1           0.763        werr
tof         2391.4        wexp
nt          100000        wbs
ct           16160        wnt
alock            n
gain      not used
       FLAGS
il               n
in               n
dp               y
hs              nn
      DISPLAY
sp           -35.7
wp         28880.4
vs            8233
sc               0
wc             250
hzmm        115.52
is          500.00
rfl        16187.5
rfp        16151.4
th              20
ins          1.000
ai    ph
```

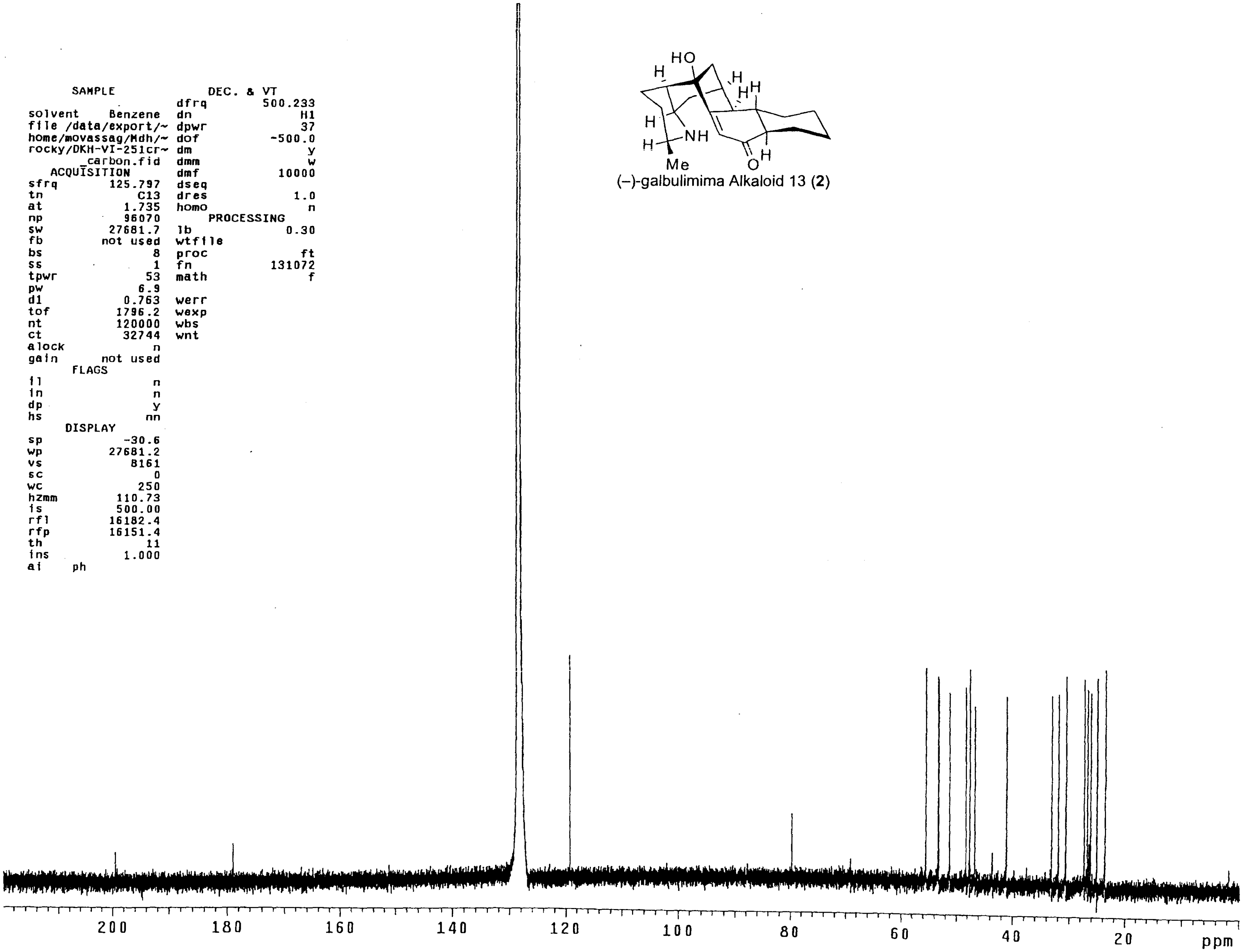

%T
90.2
89
88
87
86
85
84
83
82
81
80
79
78
77
76
74.6
4000.0
3000
2000
1500
1000
400.0
cm-1
3423.49
2929.03
2856.60
1687.09
1661.69
1446.43
1408.77
1350.33
1299.70
1213.17
1154.12
1131.13
1094.27
1020.88
875.2
698.53
HO
H
H
H
H
N
Cbz
O
H
Me
H
H

106

```
      SAMPLE             DEC. & VT
                    .  dfrq       125.673
solvent     Benzene    dn             C13
file /data/export/~    dpwr            30
home/movassag/Mdh/~    dof              0
bullwinkle/DKH-VI-~    dm             nnn
            258.fid    dmm              w
   ACQUISITION         dmf          10000
sfrq        499.748    dseq
tn               H1    dres           1.0
at            3.001    homo             n
np            37494       PROCESSING
sw           6247.6    wtfile
fb         not used    proc            ft
bs                4    fn          131072
tpwr             56    math             f
pw              8.9
d1            2.000    werr
tof           361.3    wexp
nt             1024    wbs
ct               76    wnt            wft
alock             n
gain       not used
       FLAGS
il                n
in                n
dp                y
hs               nn
      DISPLAY
sp           -250.3
wp           6247.5
vs              163
sc                0
wc              250
hzmm          24.99
is            33.57
rfl           250.4
rfp               0
th                7
ins           1.000
nm  cdc  ph
```



(–)-galbulimima Alkaloid 13 (**2**)

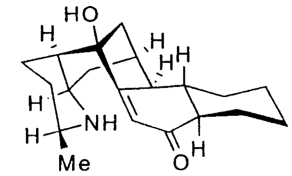


(–)-galbulimima Alkaloid 13 (**2**)

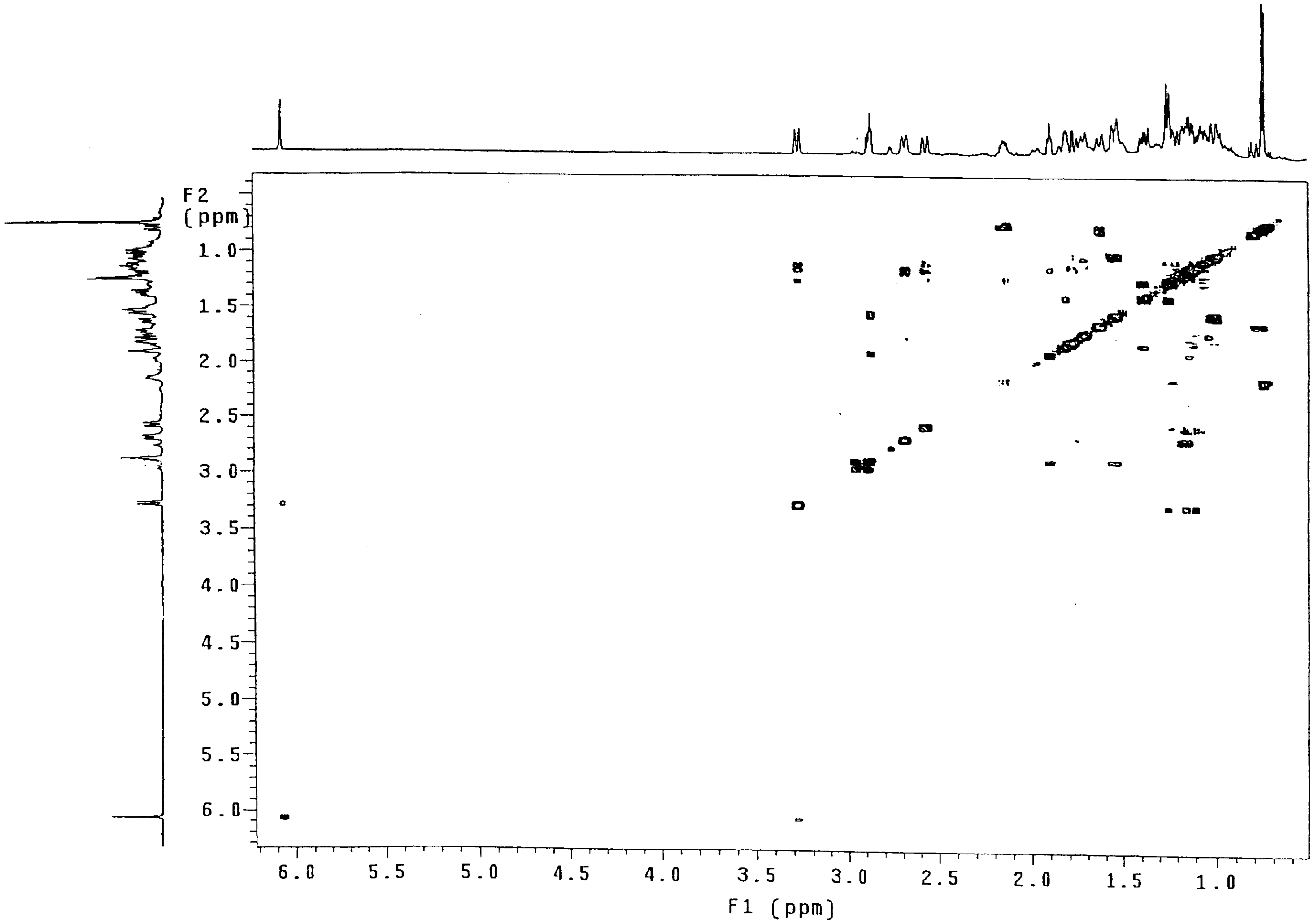
```
      SAMPLE            DEC. & VT
                      dfrq       500.233
solvent    Benzene   dn              H1
file /data/export/~  dpwr            37
home/movassag/Mdh/~  dof         -500.0
rocky/DKH-VI-251cr~  dm               y
     _carbon.fid     dmm              w
   ACQUISITION       dmf          10000
sfrq       125.797   dseq
tn             C13   dres           1.0
at           1.735   homo             n
np           96070      PROCESSING
sw         27681.7   lb            0.30
fb        not used   wtfile
bs               8   proc            ft
ss               1   fn          131072
tpwr            53   math             f
pw             6.9
d1           0.763   werr
tof         1796.2   wexp
nt          120000   wbs
ct           32744   wnt
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp           -30.6
wp         27681.2
vs            8161
sc               0
wc             250
hzmm        110.73
is          500.00
rfl        16182.4
rfp        16151.4
th              11
ins          1.000
ai    ph
```

Pulse Sequence: gCOSY

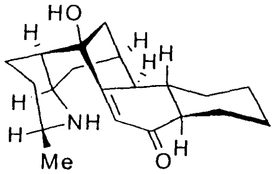
```
PULSE SEQUENCE: gCOSY
 Relax. delay 1.000 sec
 Acq. time 0.213 sec
 Width    4801.9 Hz
 2D Width 4801.9 Hz
 16 repetitions
 128 increments
OBSERVE   H1, 499.7446819 MHz
DATA PROCESSING
 Sq. sine bell 0.107 sec
F1 DATA PROCESSING
 Sq. sine bell 0.027 sec
FT size 2048 x 2048
Total time 0 min, -1 sec
```



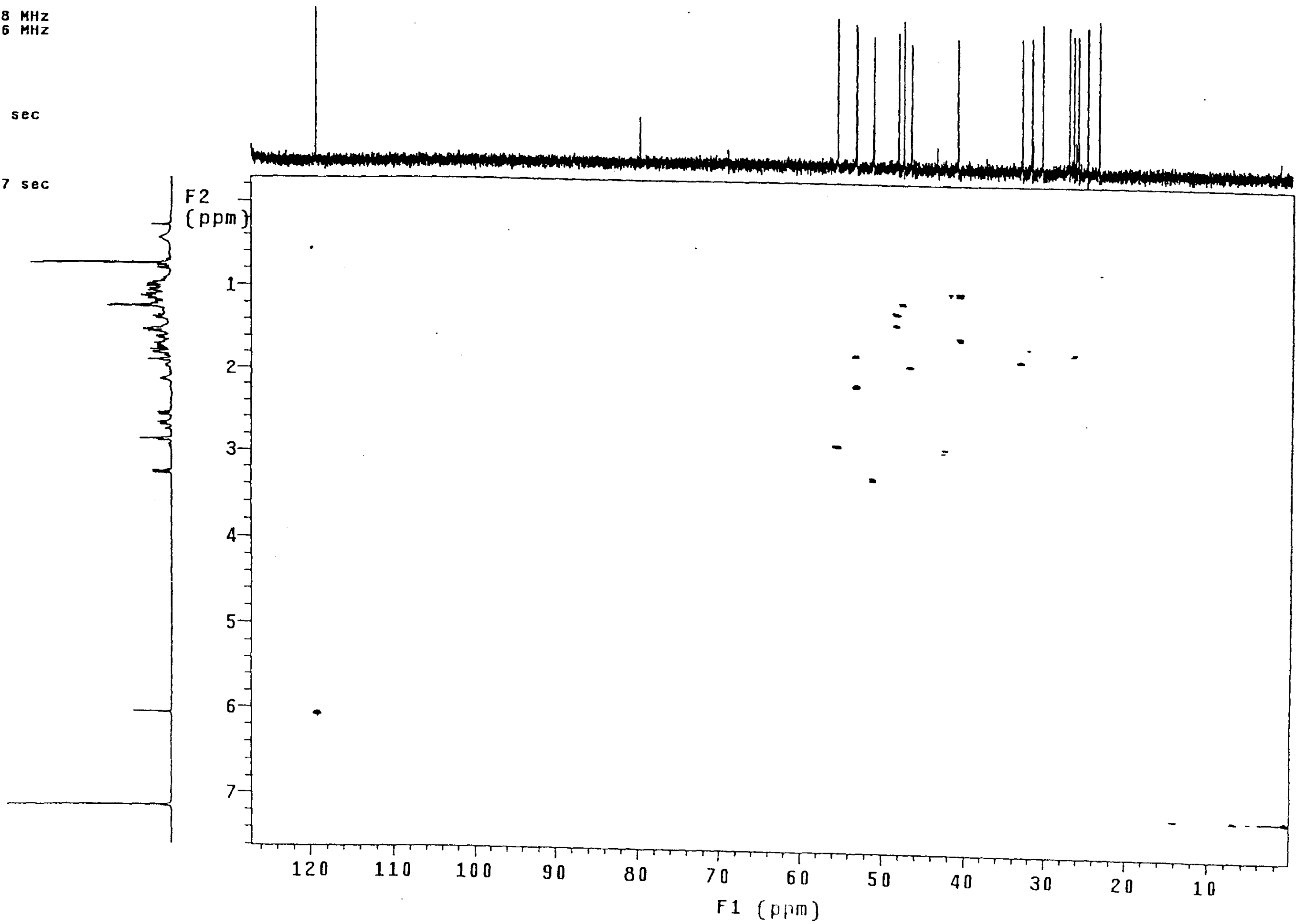
(–)-galbulimima Alkaloid 13 (**2**)

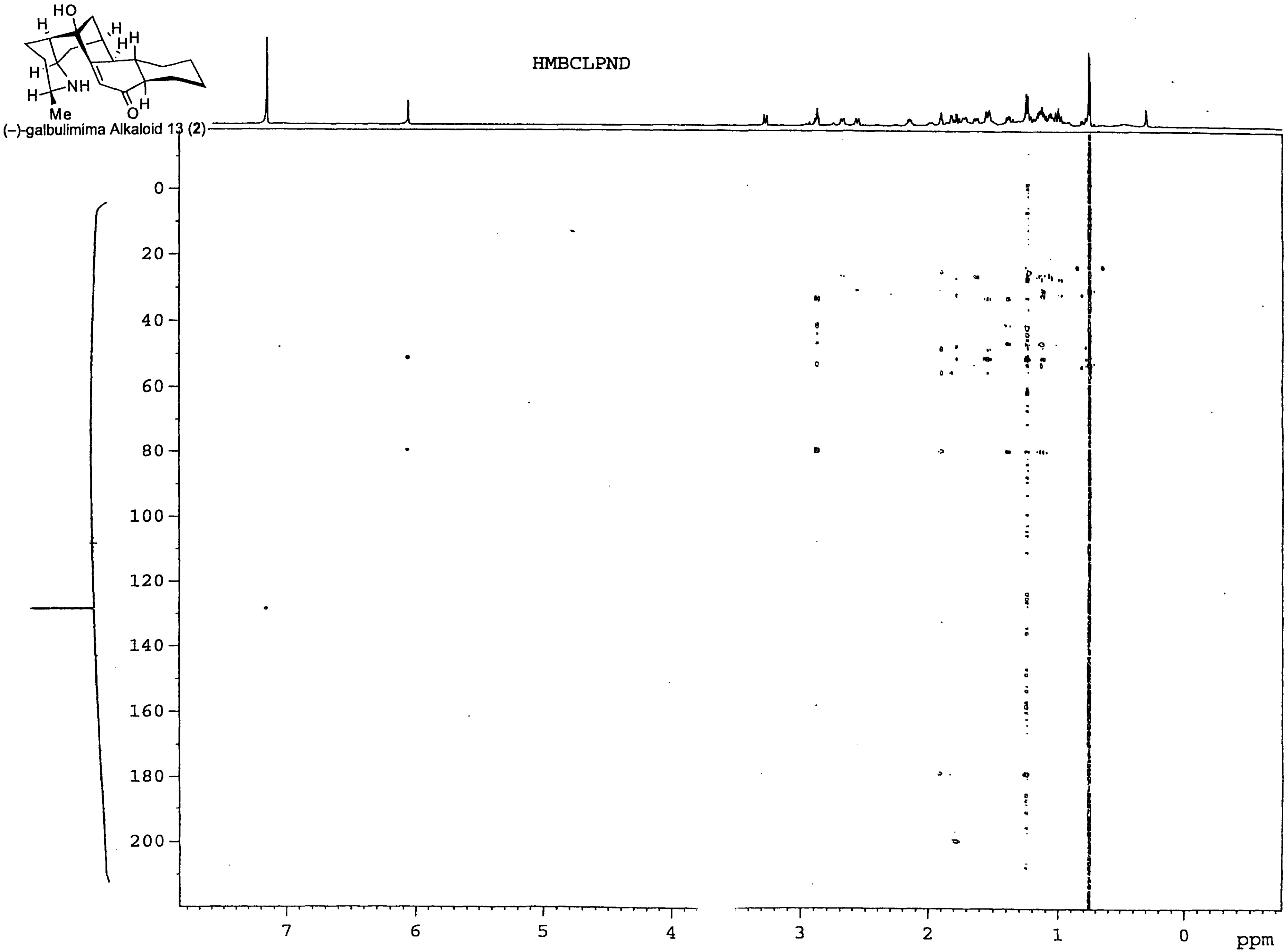


```
Pulse Sequence: HSQC
 Solvent: Benzene
 Ambient temperature
User:  1-14-87

PULSE SEQUENCE: HSQC
 Relax. delay 1.000 sec
 Acq. time 0.100 sec
 Width     4542.4 Hz
 2D Width 26490.1 Hz
 36 repetitions
 2 x 300 increments
OBSERVE   H1, 499.7446838 MHz
DECOUPLE C13, 125.6740716 MHz
 Power 52 dB
 on during acquisition
 off during delay
 GARP-1 modulated
DATA PROCESSING
 Gauss apodization 0.104 sec
F1 DATA PROCESSING
 Sq. sine bell 0.019 sec
  Shifted by -0.019 sec
FT size 2048 x 2048
Total time 9 hr, 2 min, 7 sec
```

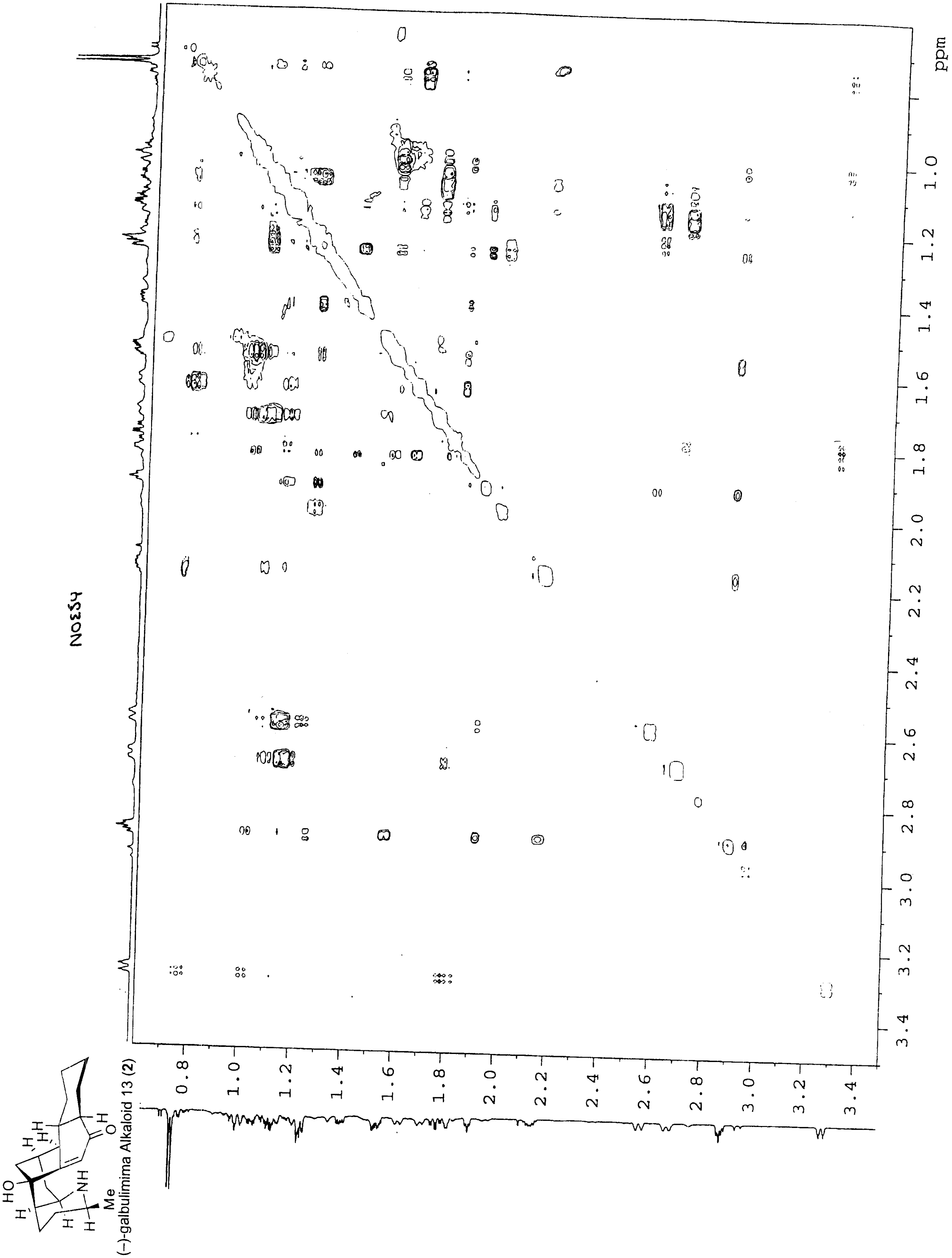


(−)-galbulimima Alkaloid 13 (**2**)



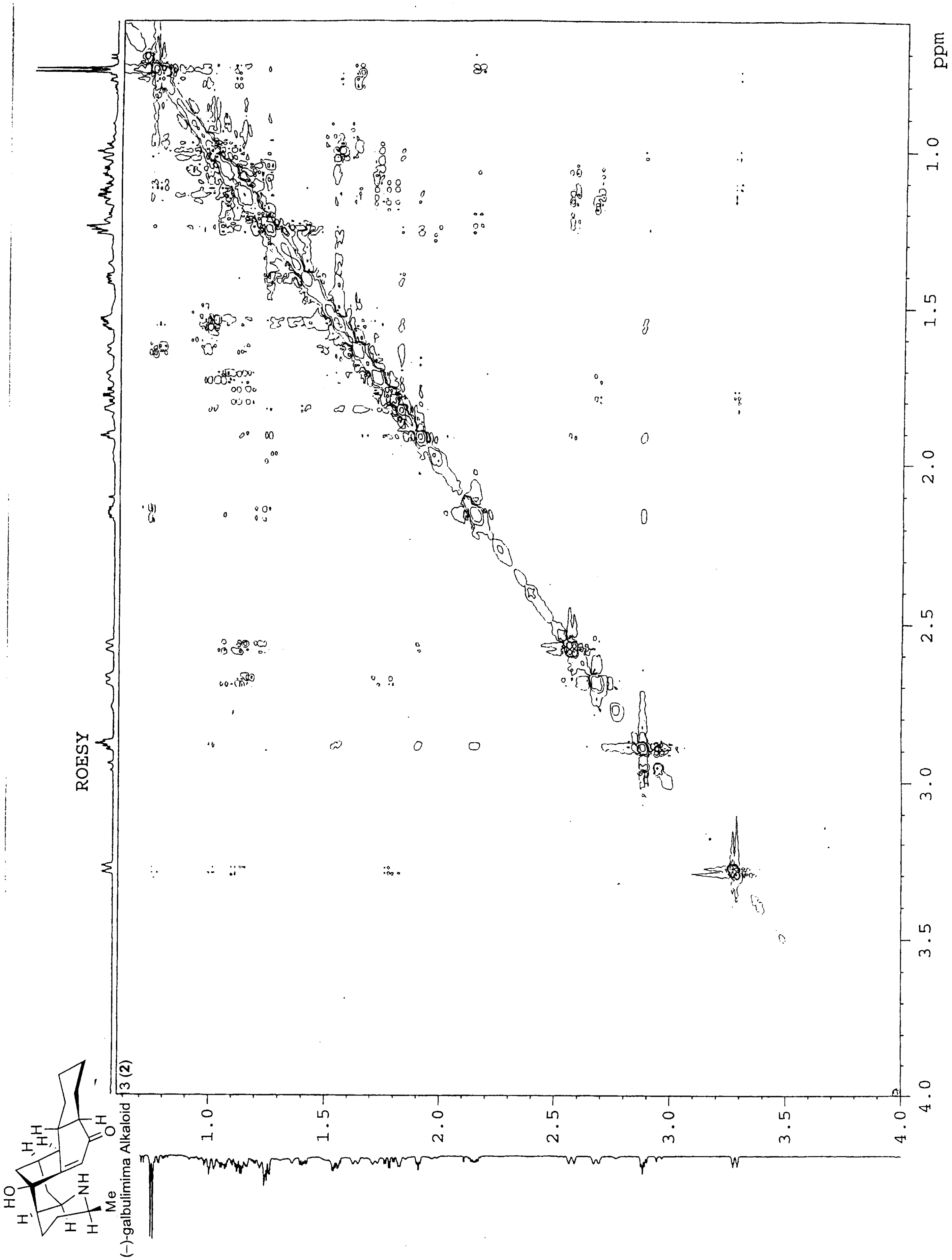


(–)-galbulimima Alkaloid 13 (**2**)

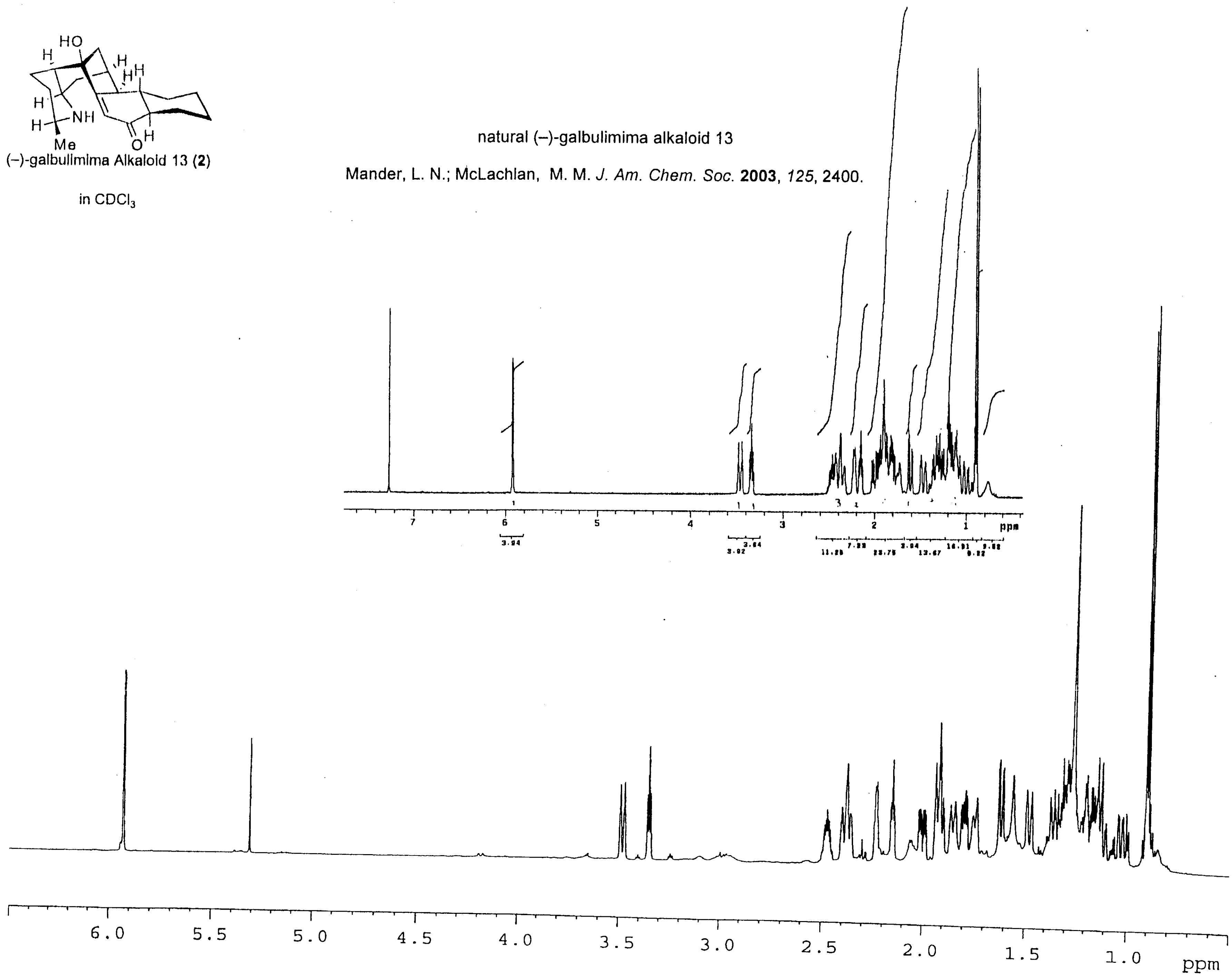


NOESY

(–)-galbulimima Alkaloid 13 (2)



ROESY
(–)-galbulimima Alkaloid 3 (2)
HO
H
H
H
H
NH
Me
H
H
O
H
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0

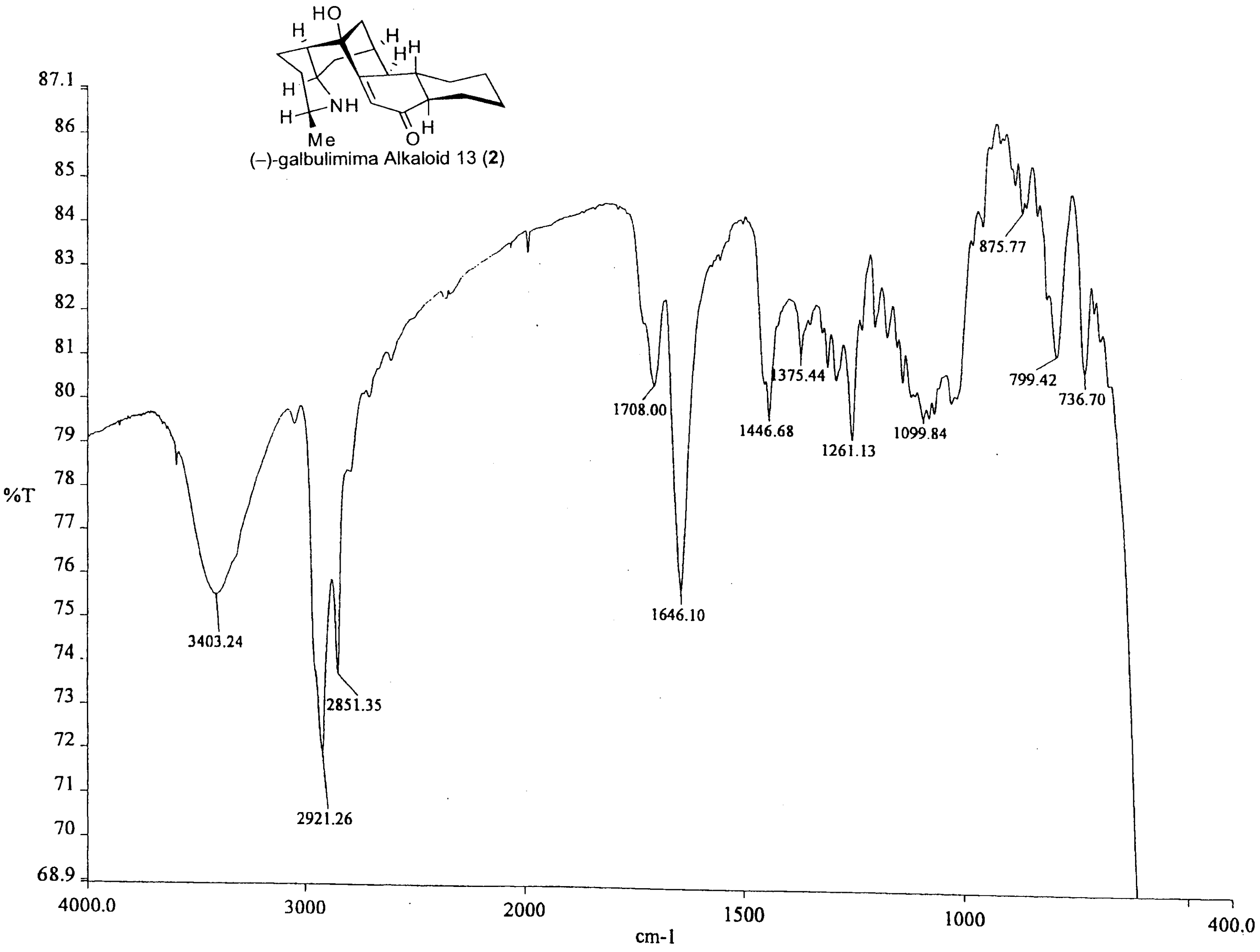


(−)-galbulimima Alkaloid 13 (**2**)

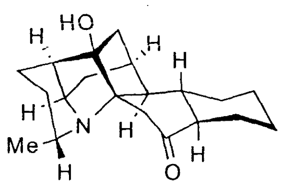
in $CDCl_3$

natural (−)-galbulimima alkaloid 13

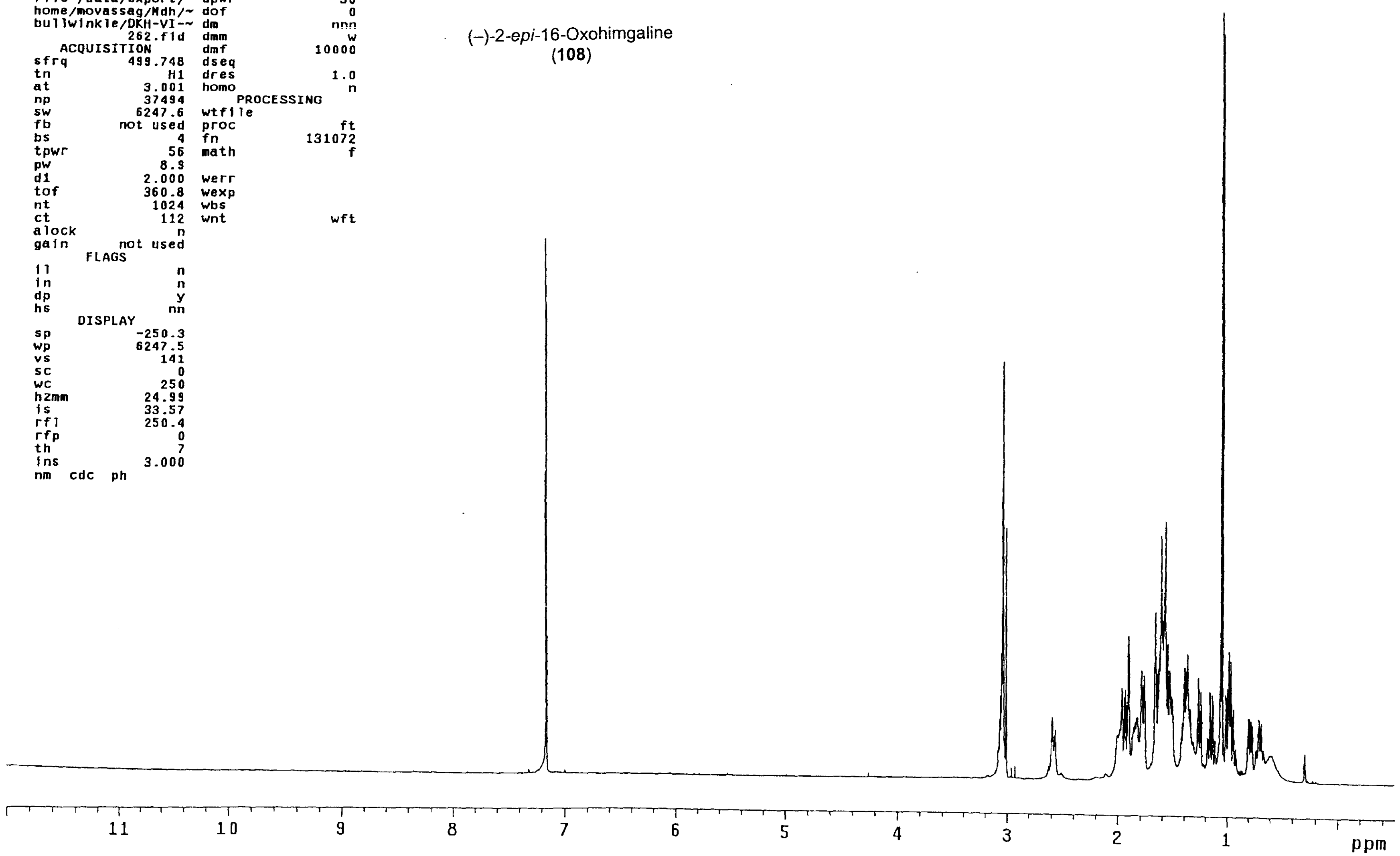
Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2400.


(−)-galbulimima Alkaloid 13 (**2**)

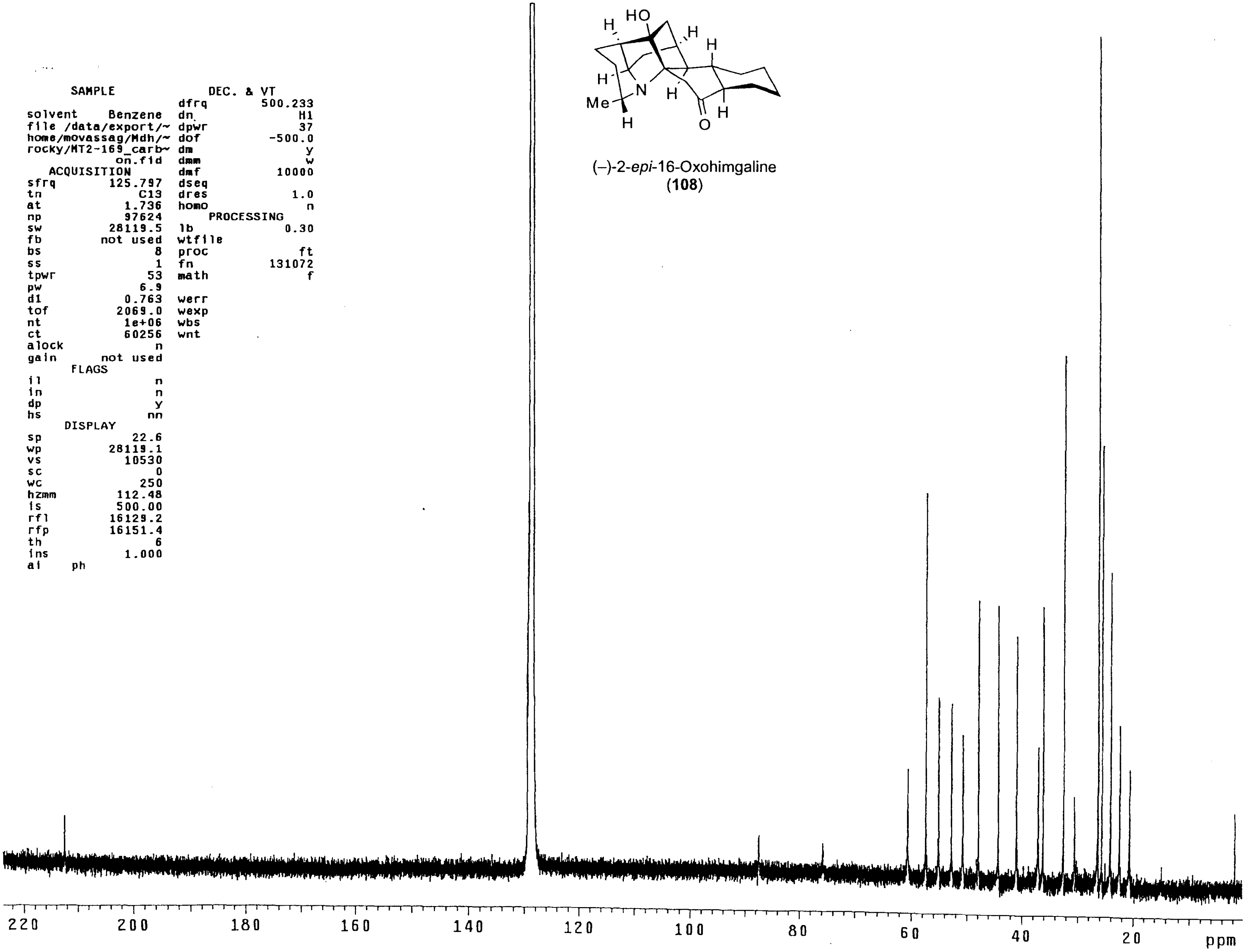
```
        SAMPLE              DEC. & VT
                         dfrq       125.673
solvent    Benzene       dn             C13
file /data/export/~      dpwr            30
home/movassag/Mdh/~      dof              0
bullwinkle/DKH-VI-~      dm             nnn
          262.fid        dmm              w
     ACQUISITION         dmf          10000
sfrq        499.748      dseq
tn               H1      dres           1.0
at            3.001      homo             n
np            37494         PROCESSING
sw           6247.6      wtfile
fb         not used      proc            ft
bs                4      fn          131072
tpwr             56      math             f
pw              8.9
d1            2.000      werr
tof           360.8      wexp
nt             1024      wbs
ct              112      wnt            wft
alock             n
gain       not used
        FLAGS
il                n
in                n
dp                y
hs               nn
       DISPLAY
sp           -250.3
wp           6247.5
vs              141
sc                0
wc              250
hzmm          24.99
is            33.57
rfl           250.4
rfp               0
th                7
ins           3.000
nm  cdc  ph
```



(–)-2-*epi*-16-Oxohimgaline
(**108**)

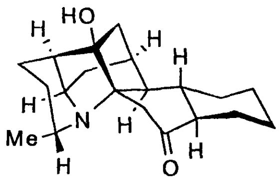


```
      SAMPLE           DEC. & VT
                       dfrq        500.233
solvent    Benzene     dn               H1
file /data/export/~    dpwr             37
home/movassag/Mdh/~    dof          -500.0
rocky/MT2-169_carb~    dm                y
            on.fid     dmm               w
   ACQUISITION         dmf           10000
sfrq       125.797     dseq
tn             C13     dres            1.0
at           1.736     homo              n
np           97624        PROCESSING
sw         28119.5     lb             0.30
fb        not used     wtfile
bs               8     proc             ft
ss               1     fn           131072
tpwr            53     math              f
pw             6.9
d1           0.763     werr
tof         2069.0     wexp
nt          1e+06      wbs
ct           60256     wnt
alock            n
gain      not used
      FLAGS
il               n
in               n
dp               y
hs              nn
     DISPLAY
sp            22.6
wp         28119.1
vs           10530
sc               0
wc             250
hzmm        112.48
is          500.00
rfl        16129.2
rfp        16151.4
th               6
ins          1.000
ai    ph
```

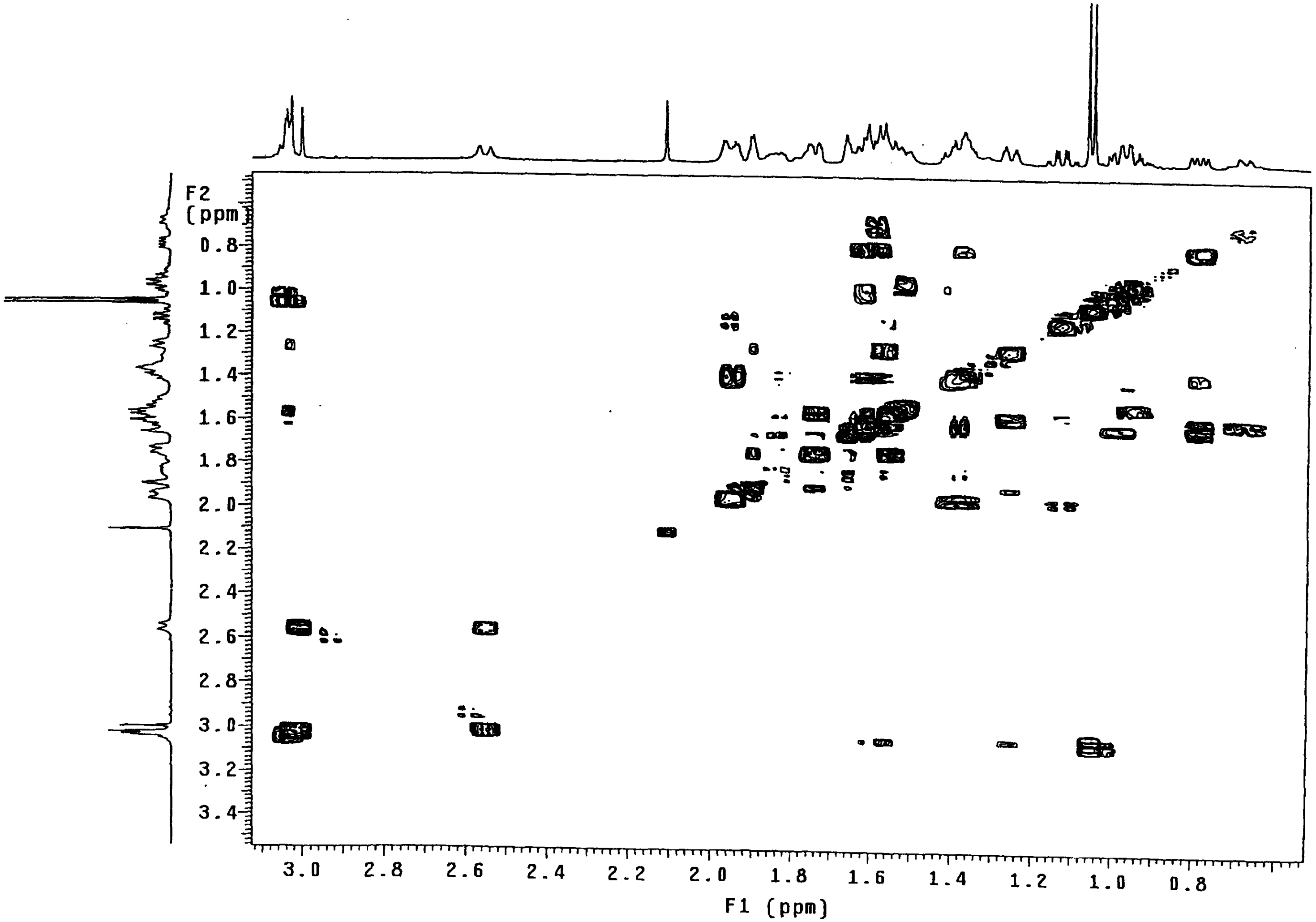


(–)-2-*epi*-16-Oxohimgaline
(**108**)

```
Pulse Sequence: gCOSY
 Solvent: Benzene
_Ambient temperature

PULSE SEQUENCE: gCOSY
 Relax. delay 1.000 sec
 Acq. time 0.227 sec
 Width     4507.6 Hz
 2D Width 4507.6 Hz
 64 repetitions
 128 increments
OBSERVE   H1, 499.7446840 MHz
DATA PROCESSING
 Sq. sine bell 0.113 sec
F1 DATA PROCESSING
 Sq. sine bell 0.028 sec
FT size 2048 x 2048
Total time 0 min, -1 sec
```



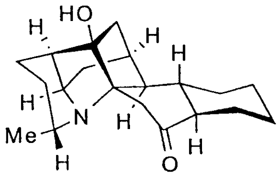
(–)-2-*epi*-16-Oxohimgaline
(108)



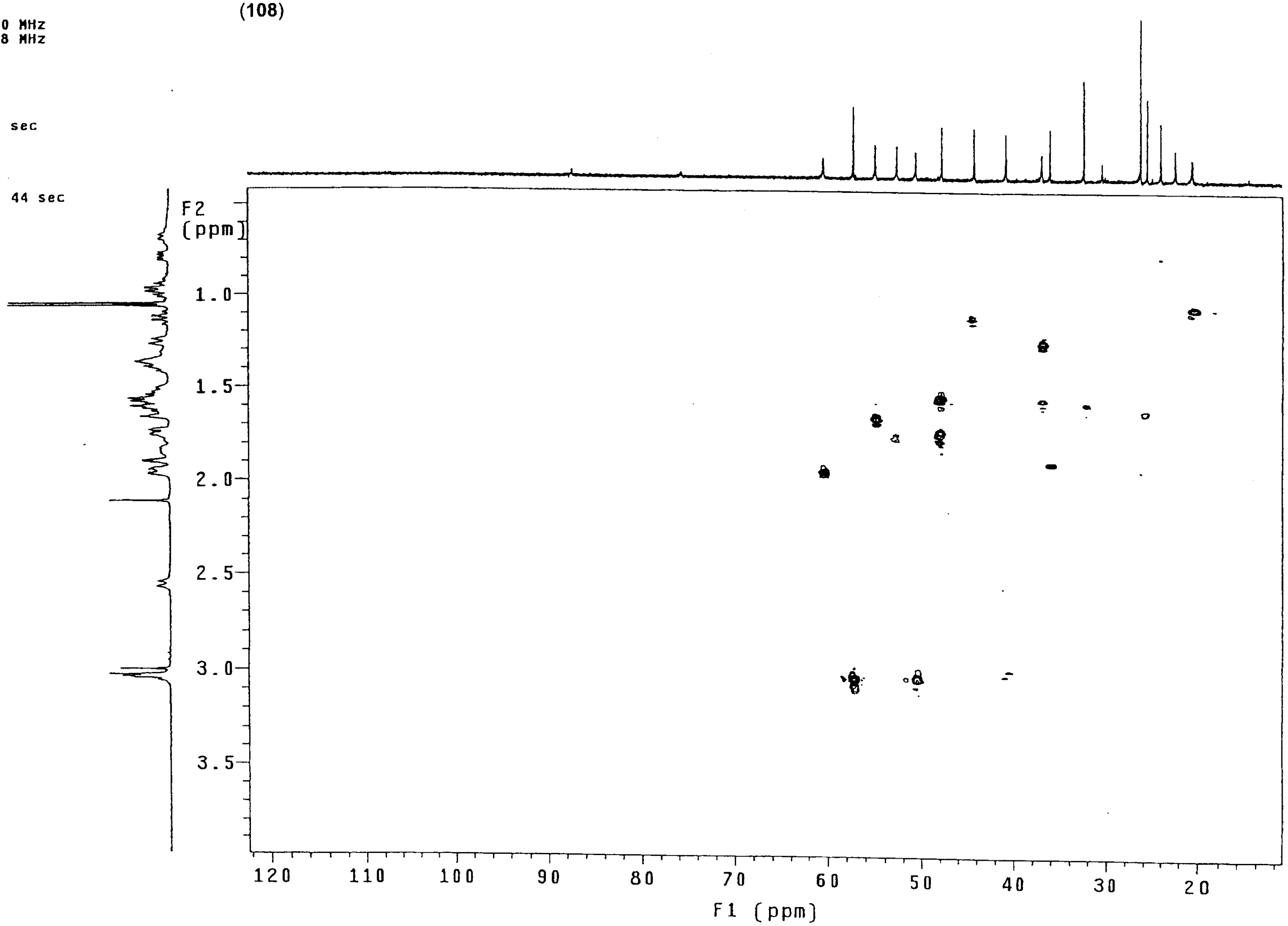
Pulse Sequence: HSQC

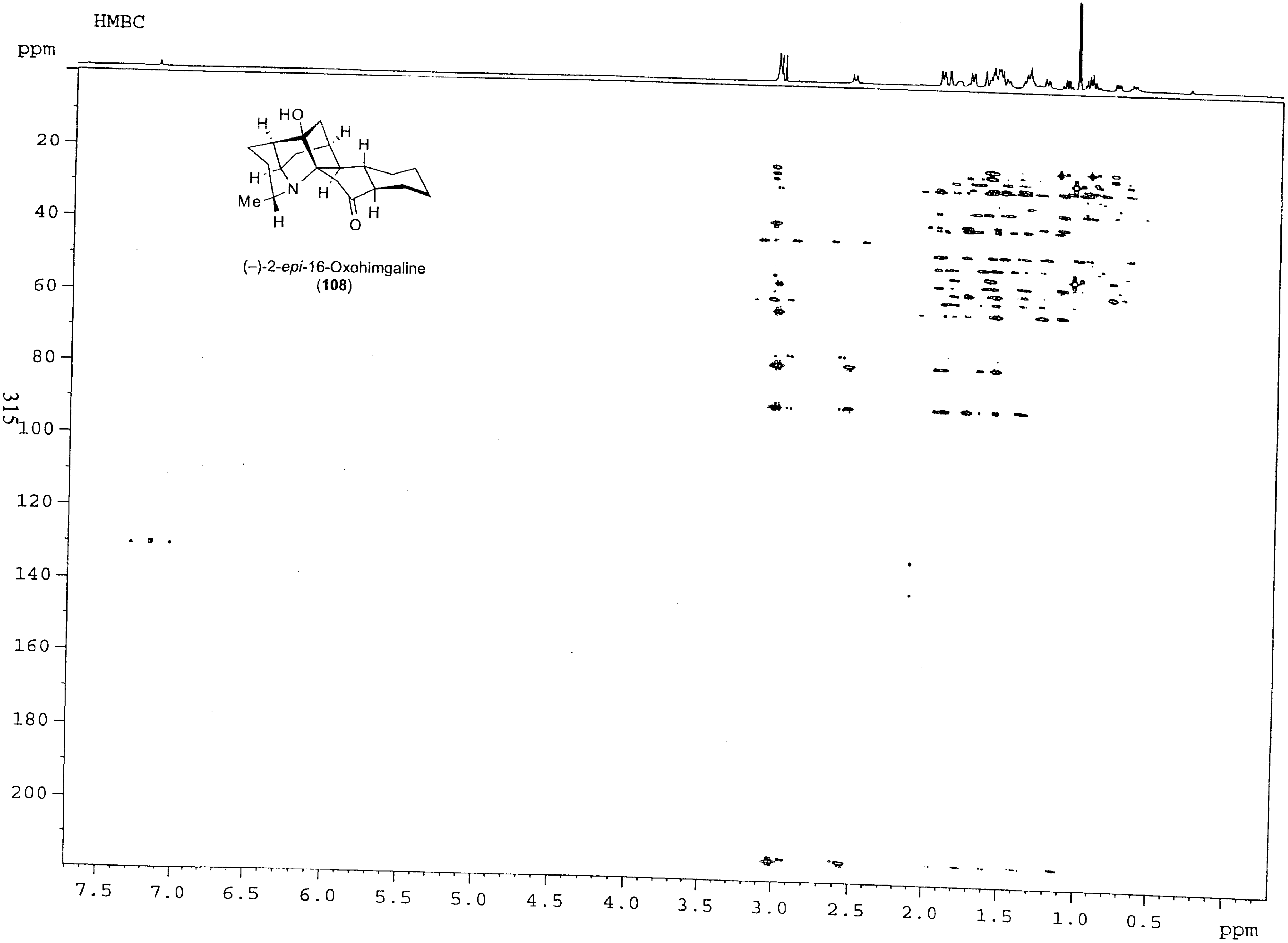
Solvent: Benzene
Ambient temperature

PULSE SEQUENCE: HSQC
Relax. delay 1.000 sec
Acq. time 0.227 sec
Width 4507.6 Hz
2D Width 27662.5 Hz
32 repetitions
2 x 256 increments
OBSERVE H1, 499.7446840 MHz
DECOUPLE C13, 125.6746698 MHz
Power 52 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.105 sec
F1 DATA PROCESSING
Sq. sine bell 0.019 sec
Shifted by -0.019 sec
FT size 2048 x 2048
Total time 7 hr, 27 min, 44 sec



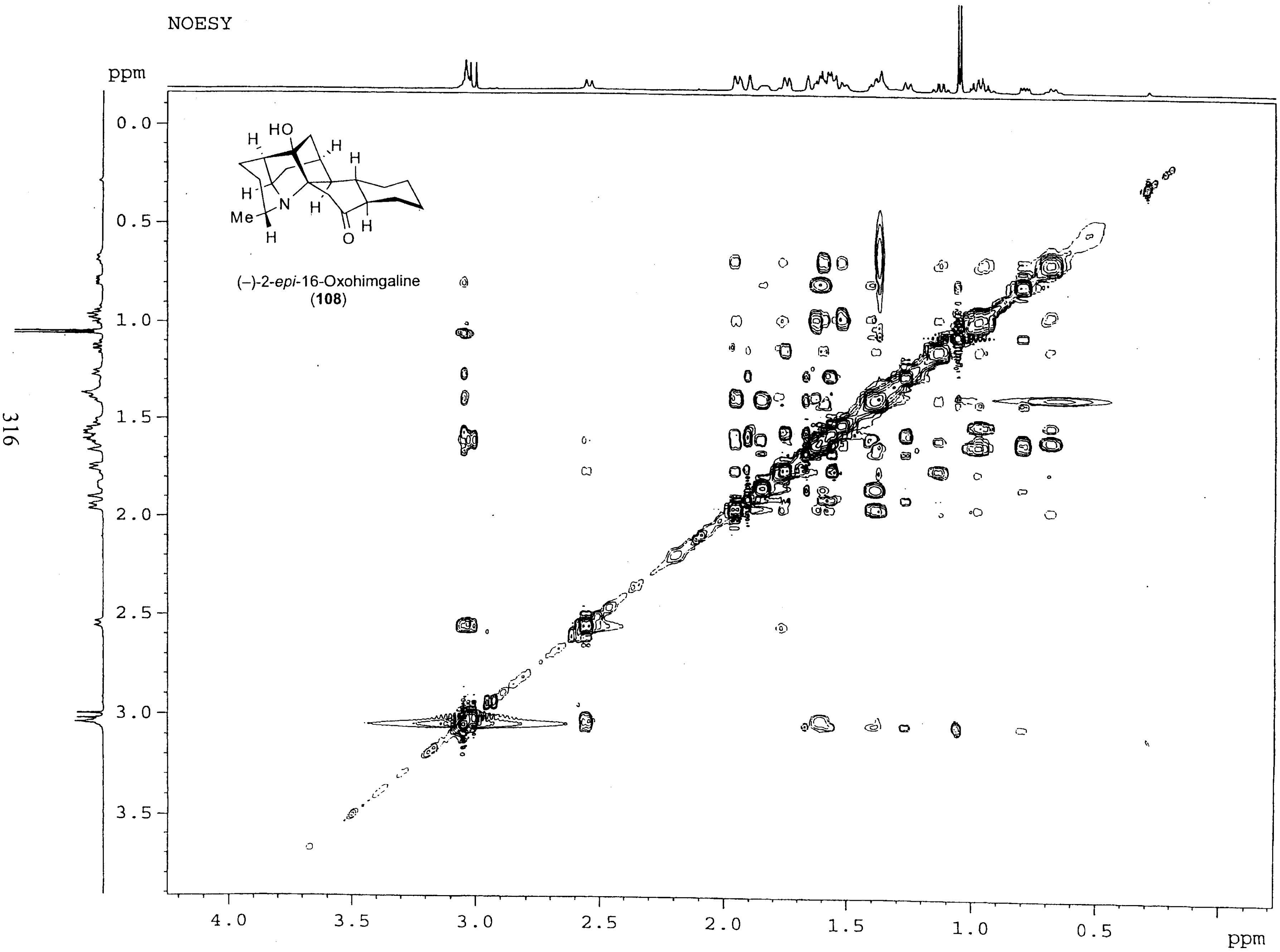
(–)-2-*epi*-16-Oxohimgaline
(**108**)





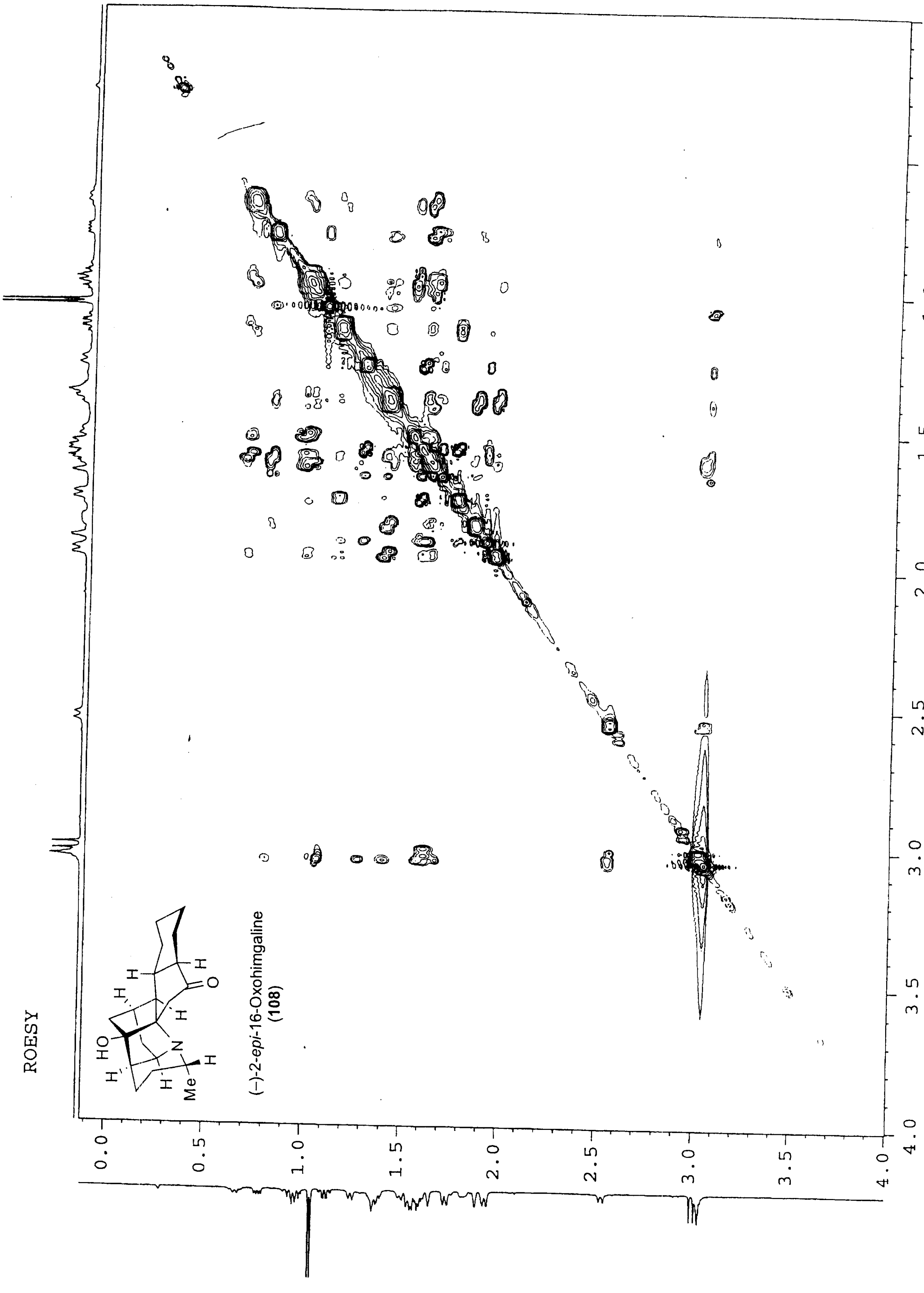
(−)-2-*epi*-16-Oxohimgaline
(**108**)

NOESY

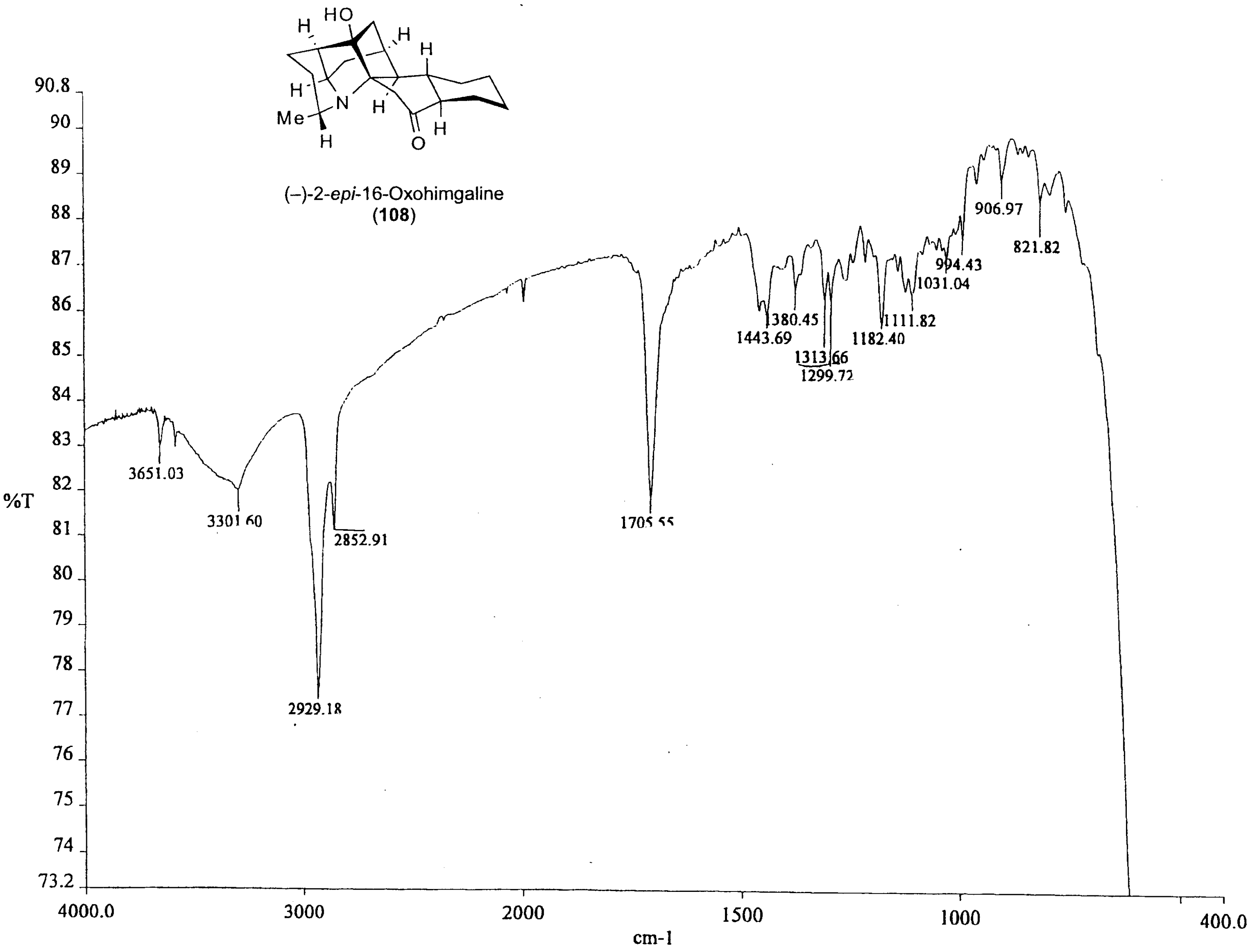


(−)-2-*epi*-16-Oxohimgaline

(**108**)



(−)-2-*epi*-16-Oxohimgaline
(**108**)

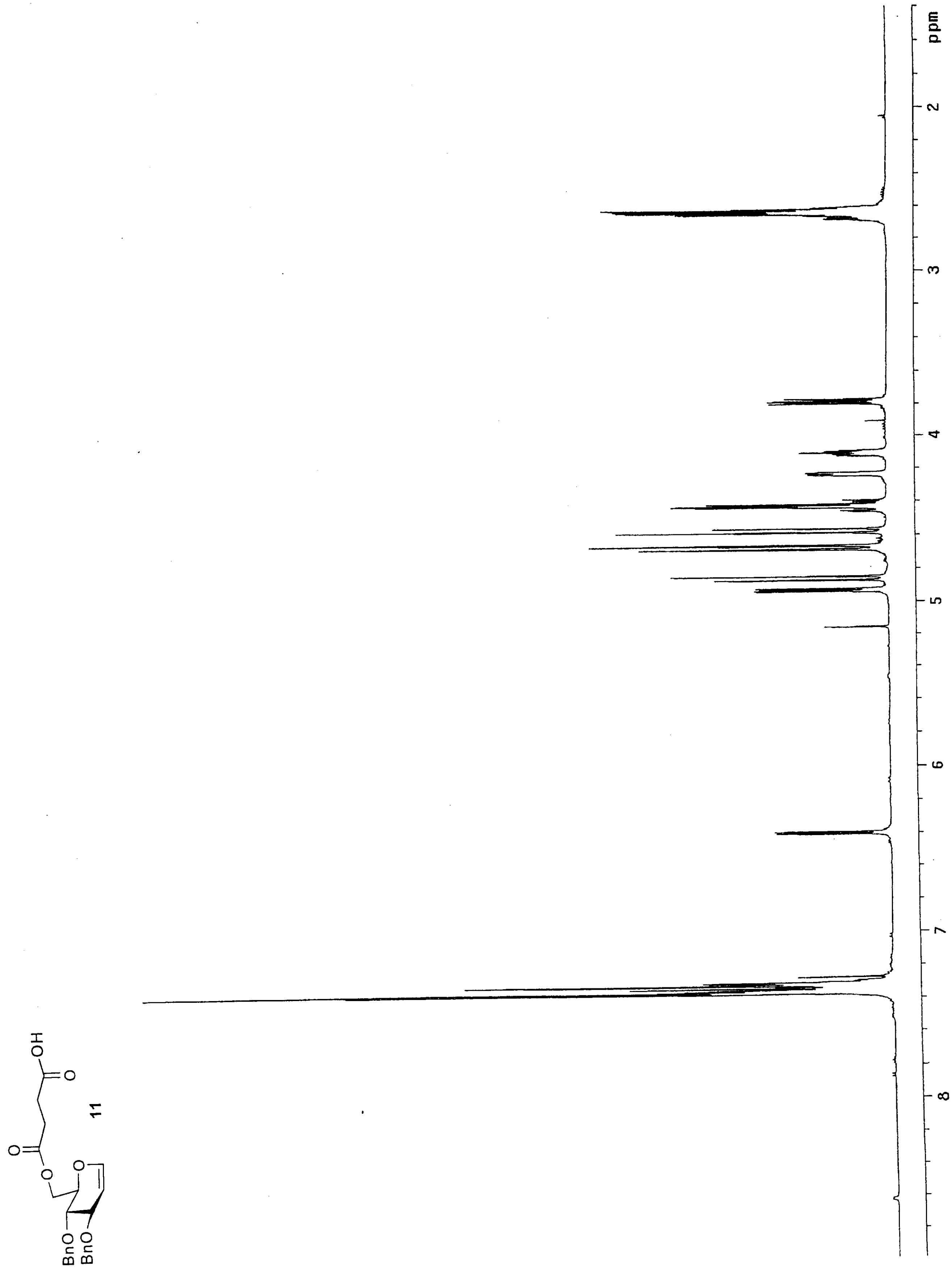


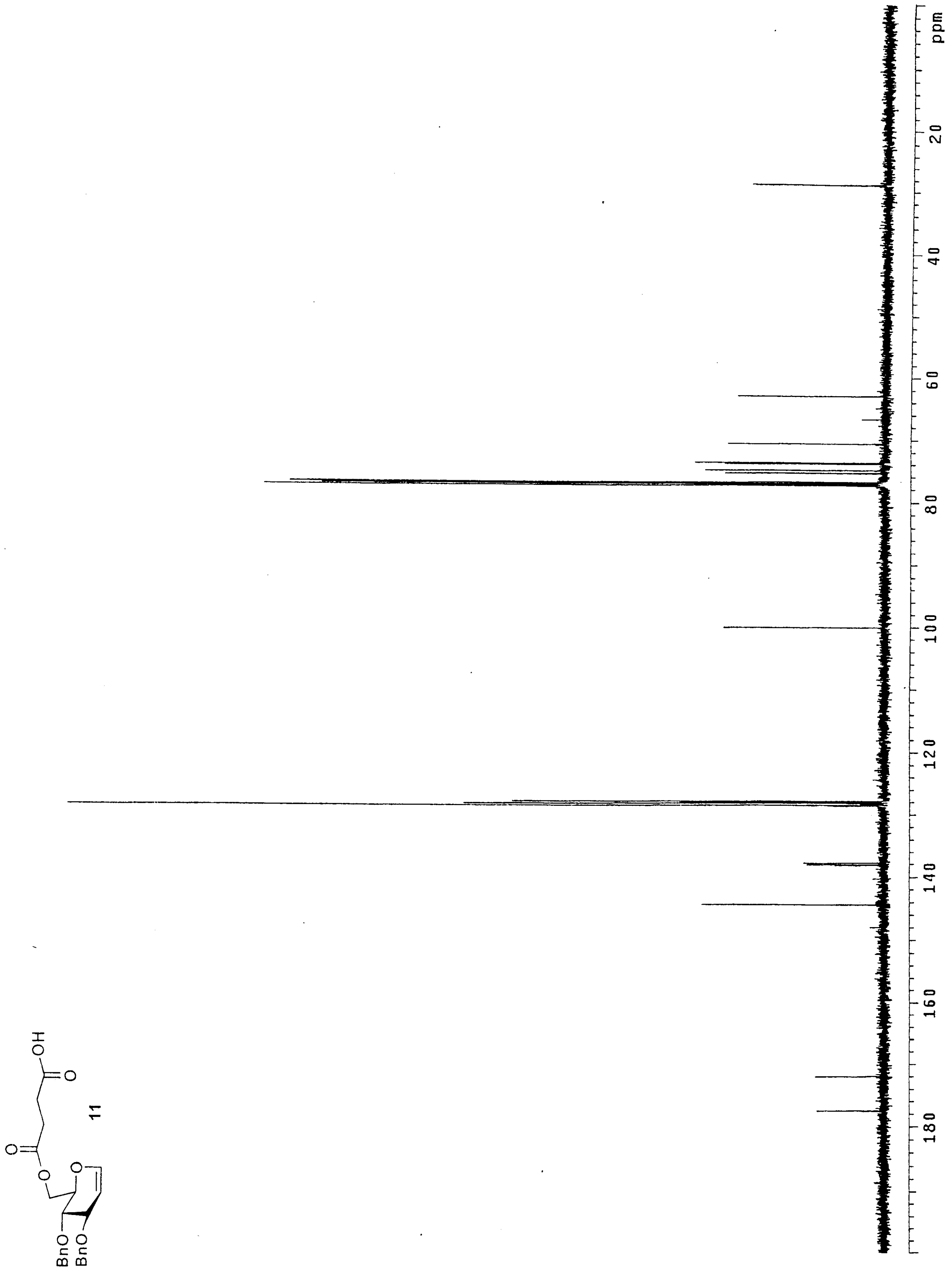
(–)-2-*epi*-16-Oxohimgaline
(108)

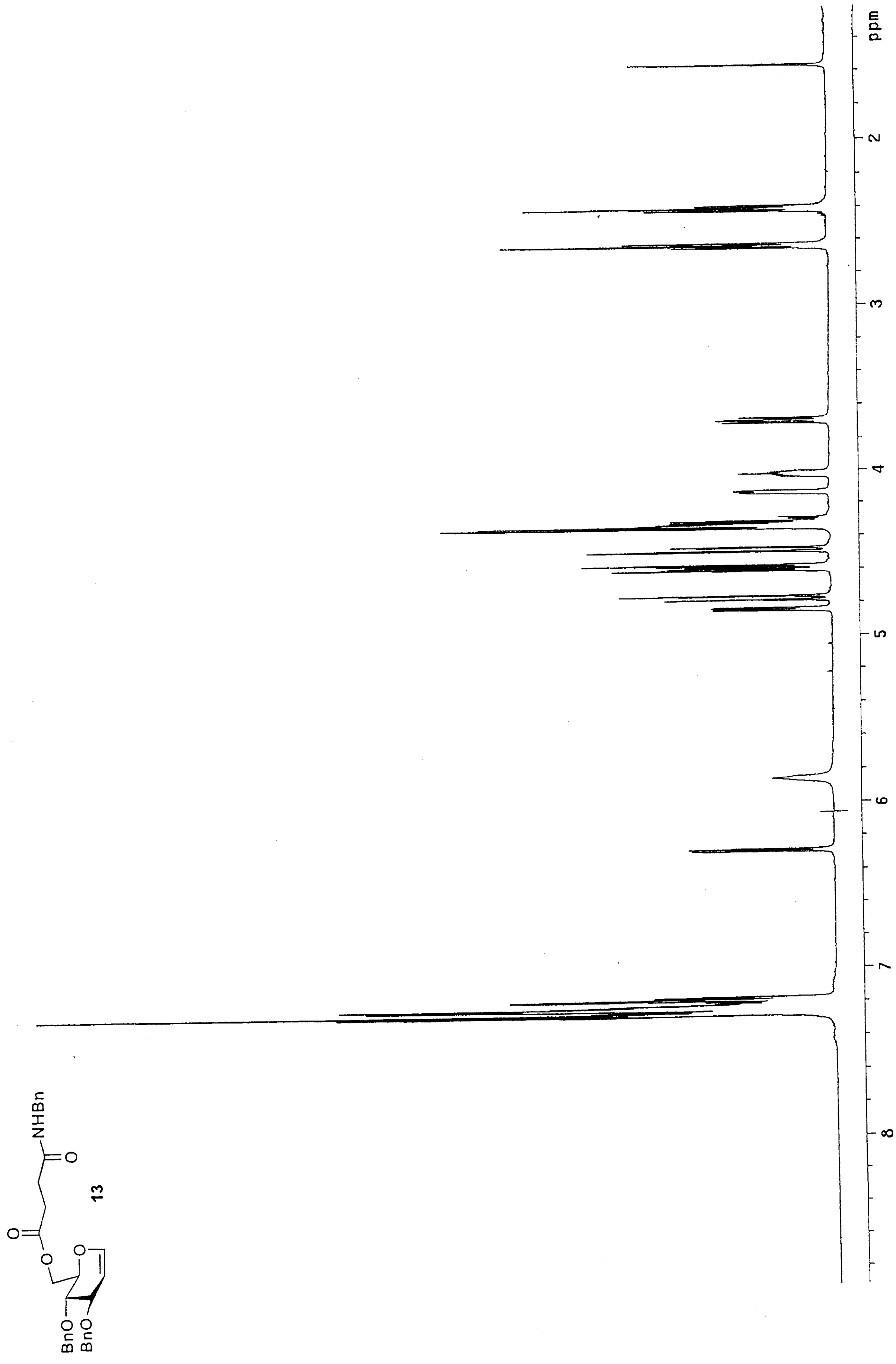
Appendix B

Spectra for Chapter 2

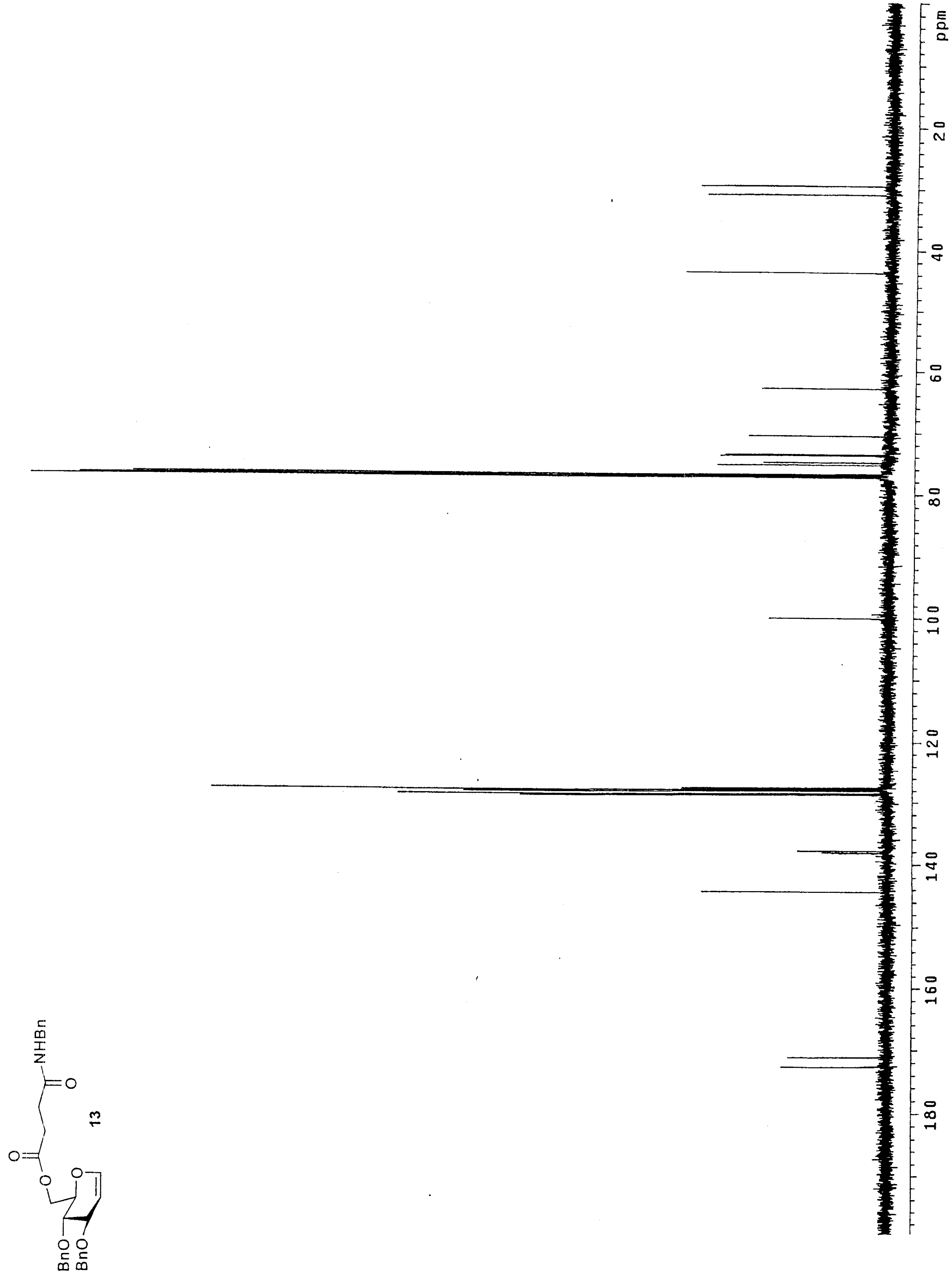
Thesis Advisor: Peter H. Seeberger


11


11



13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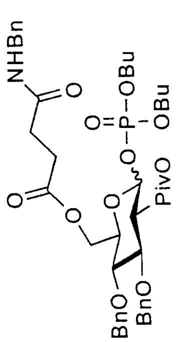
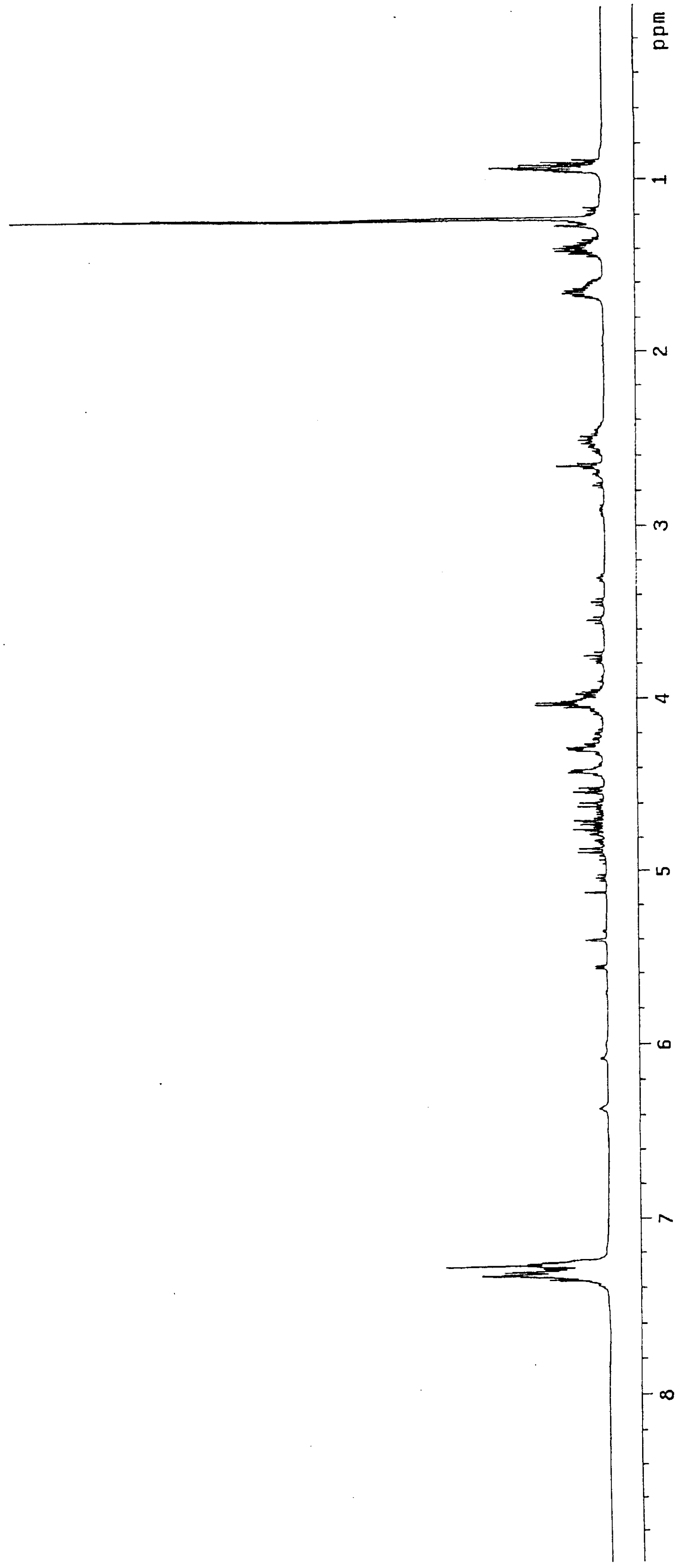
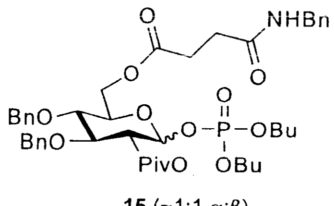
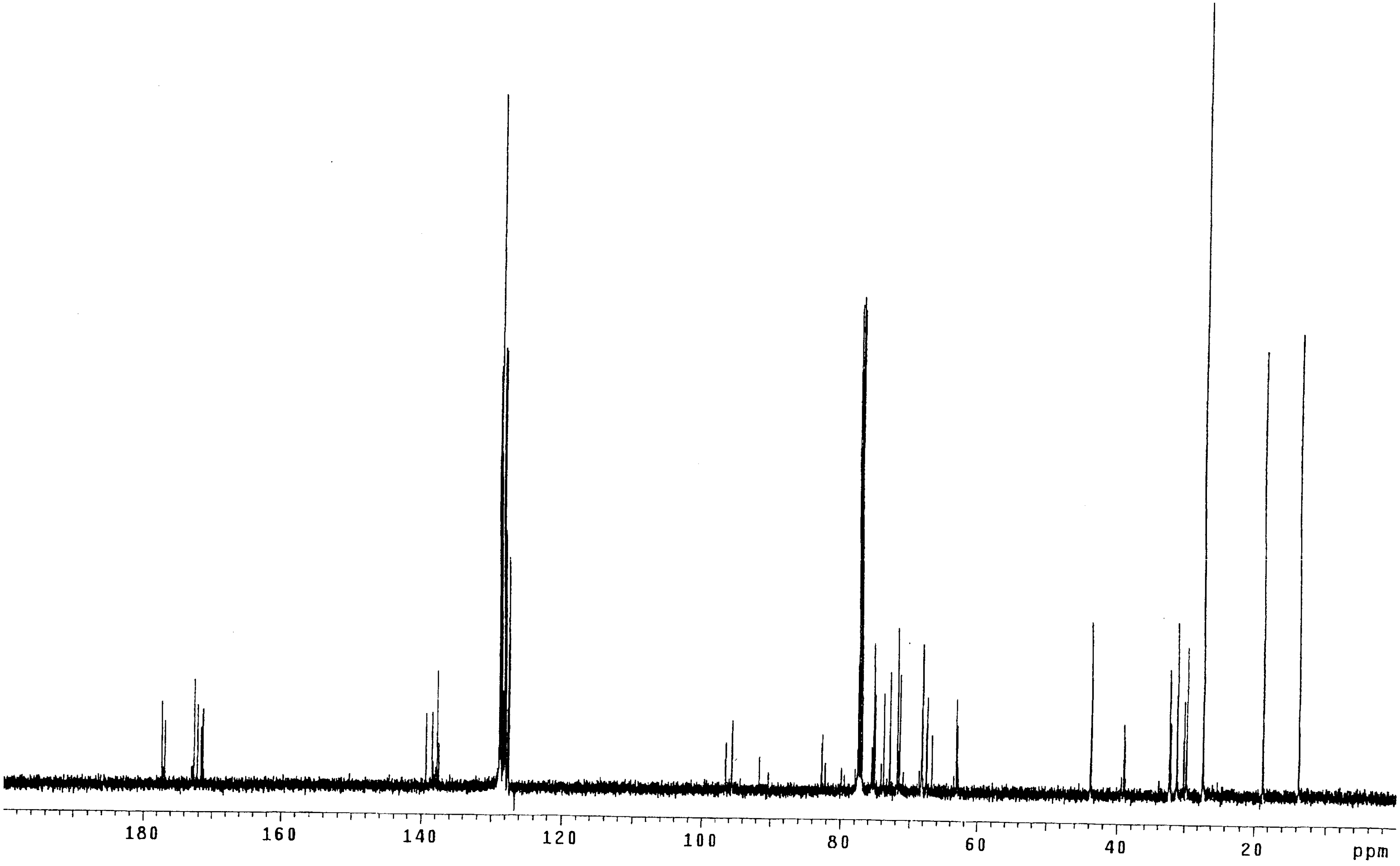


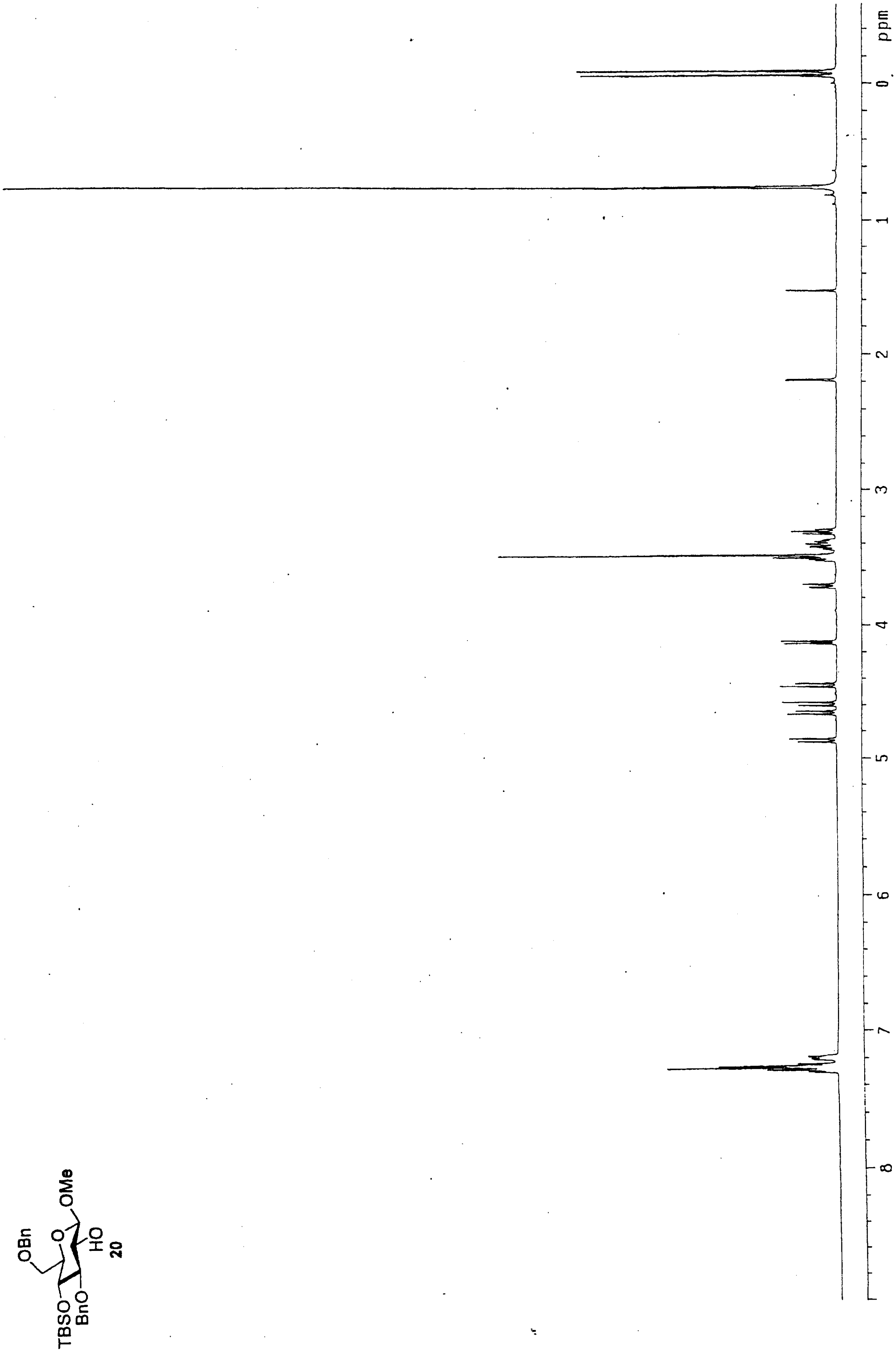
15 (~1:1 α:β)

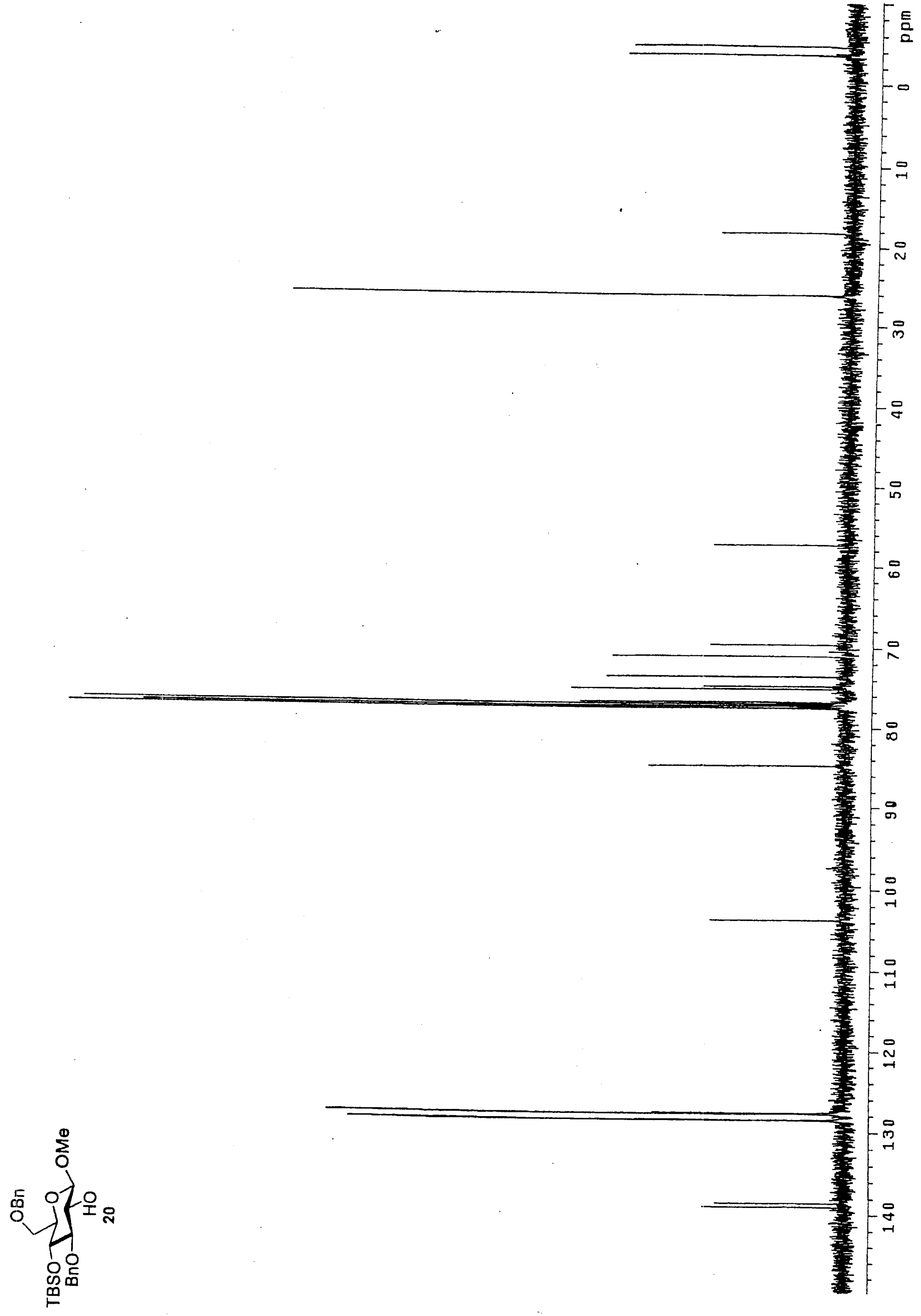



NHBn
O
O
O
BnO
BnO
O
O
P
OBu
PivO
OBu

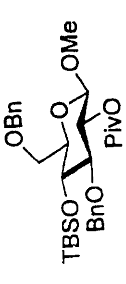
15 (~1:1 α:β)


180
160
140
120
100
80
60
40
20
ppm


OBn
O
OMe
TBSO
BnO
HO
20
ppm
0
1
2
3
4
5
6
7
8


OBn
O
OMe
TBSO
BnO
HO
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

20



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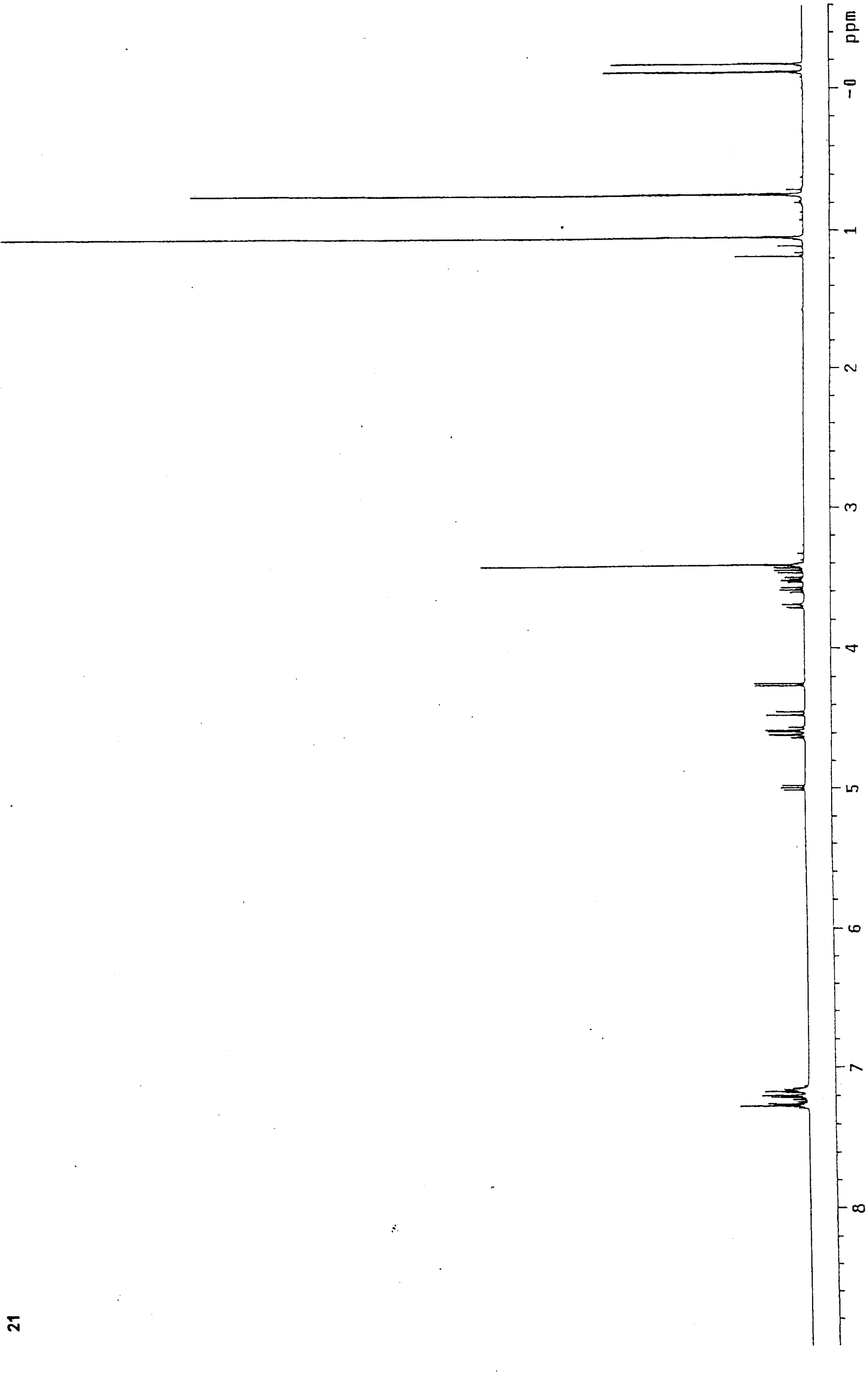

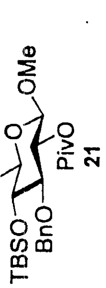

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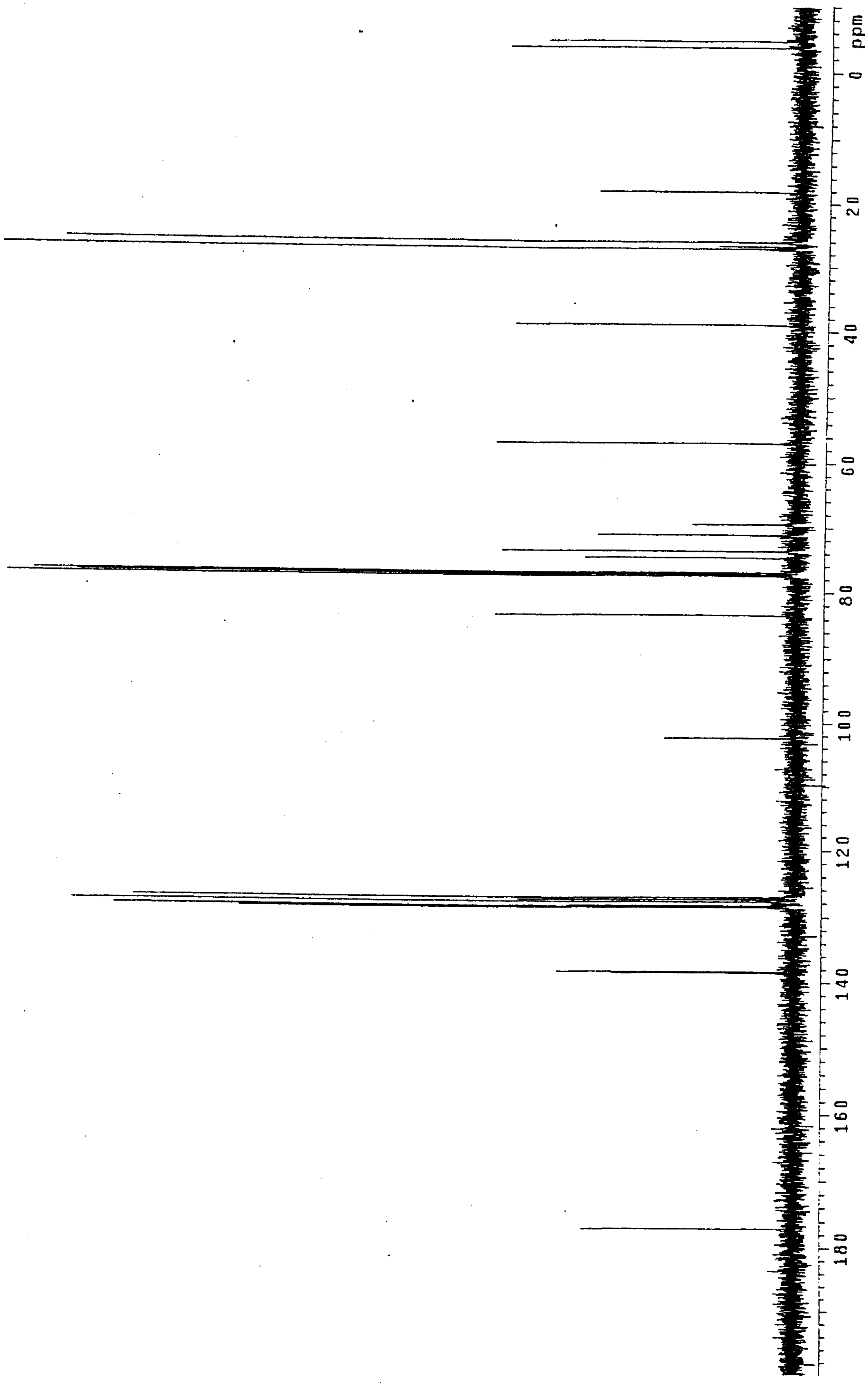

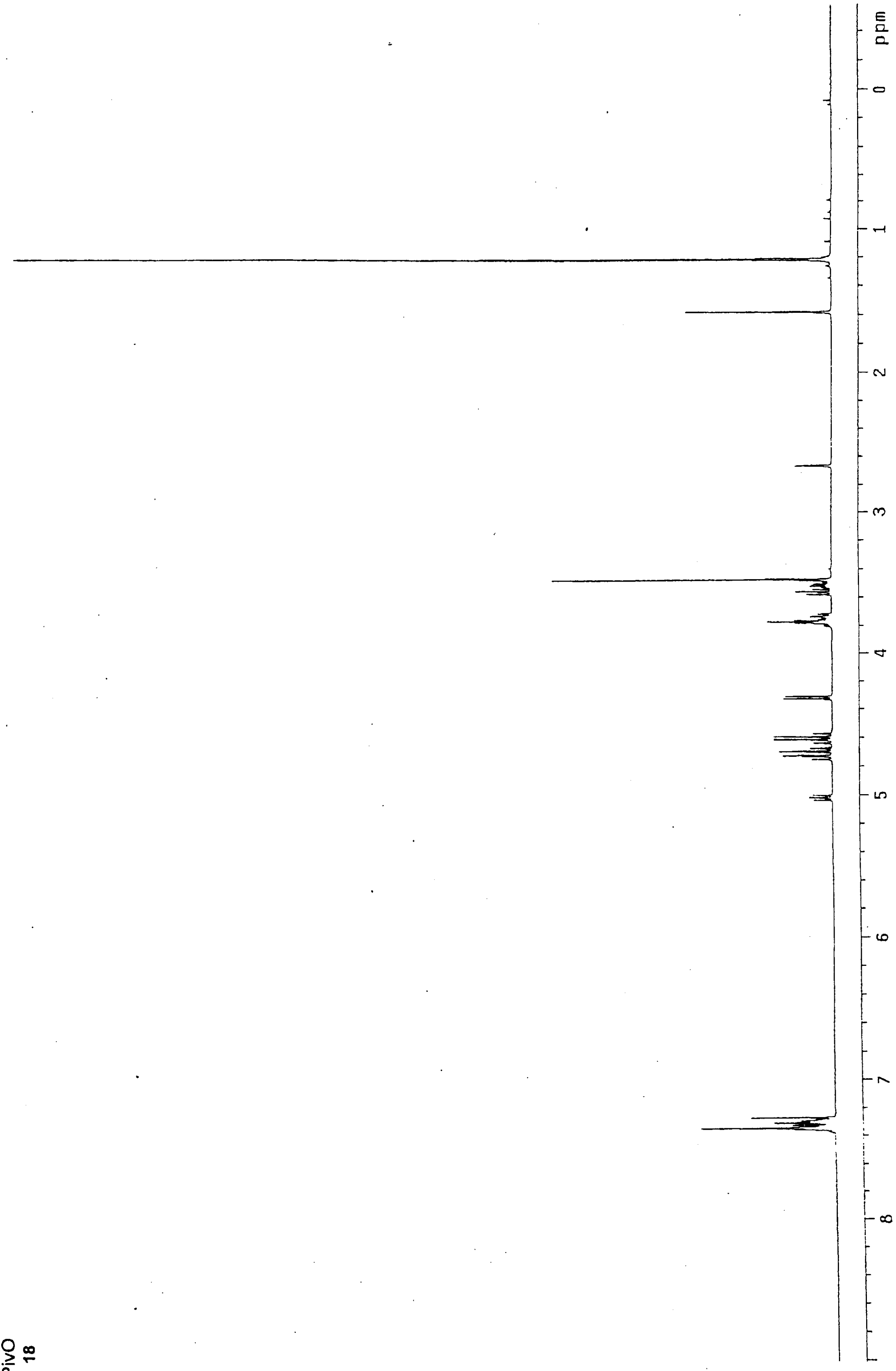

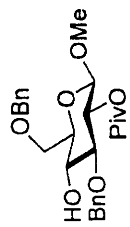

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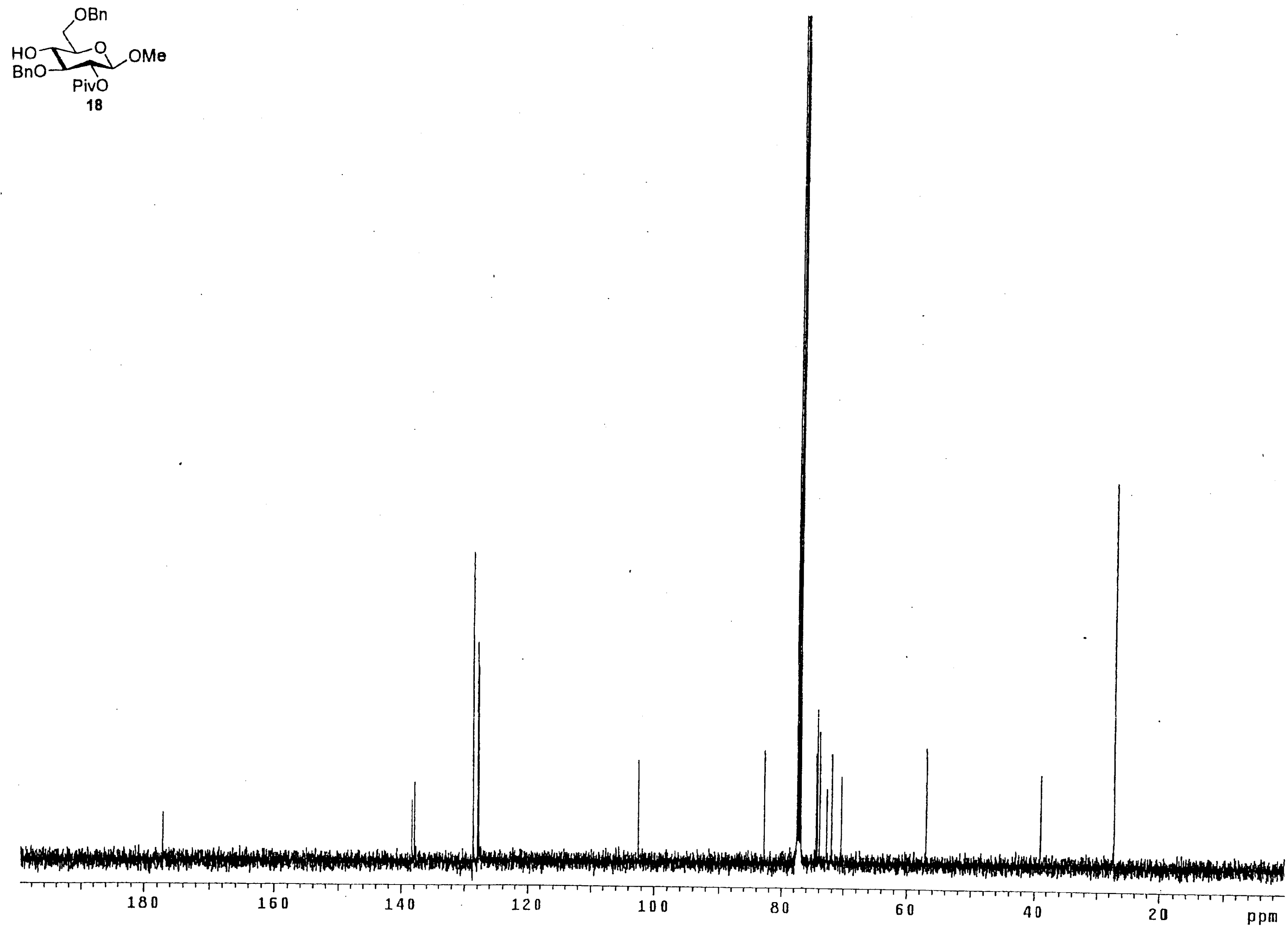

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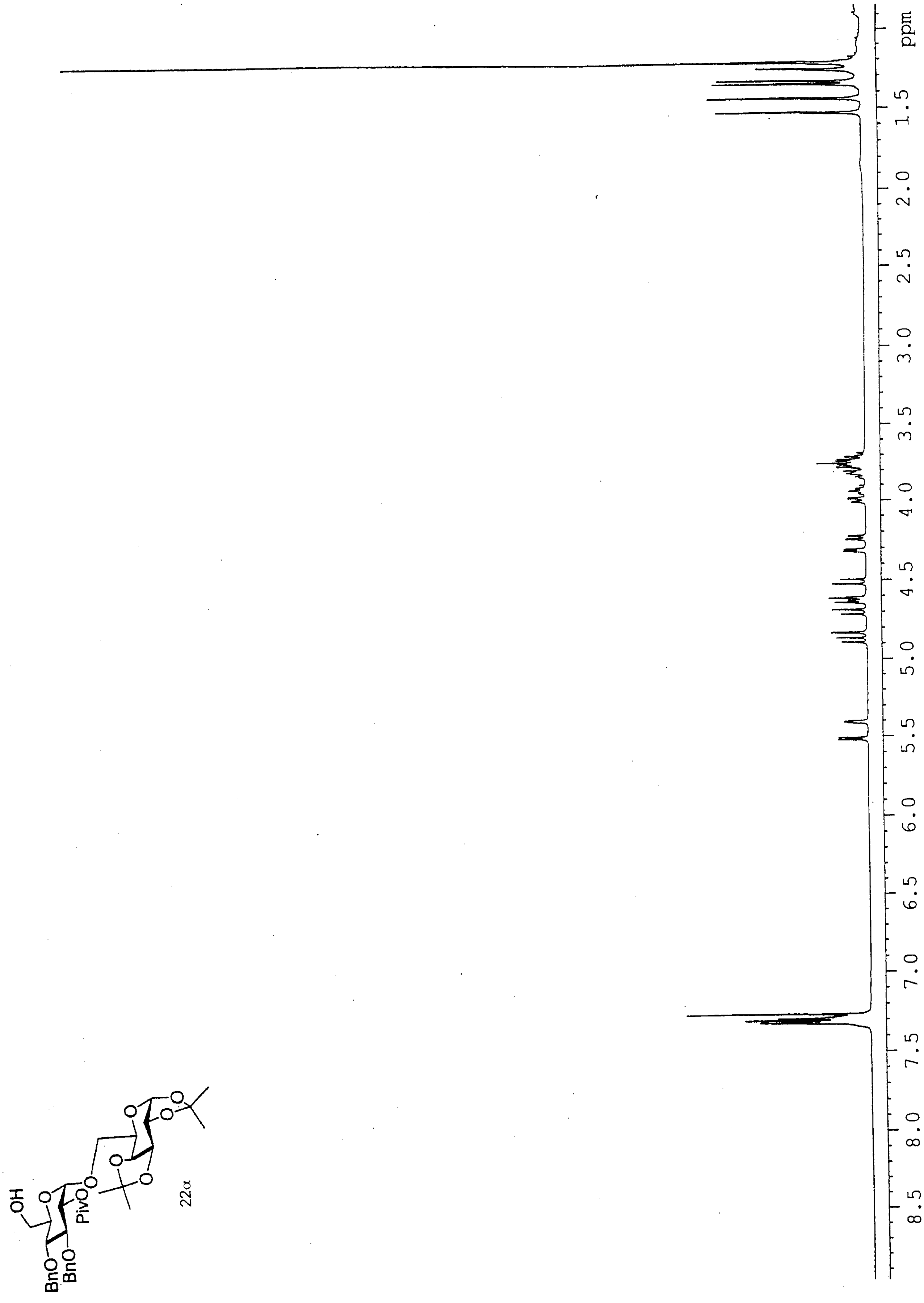
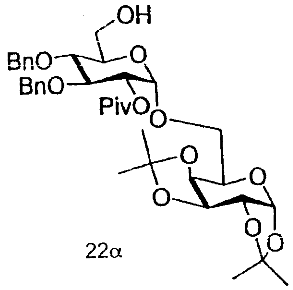
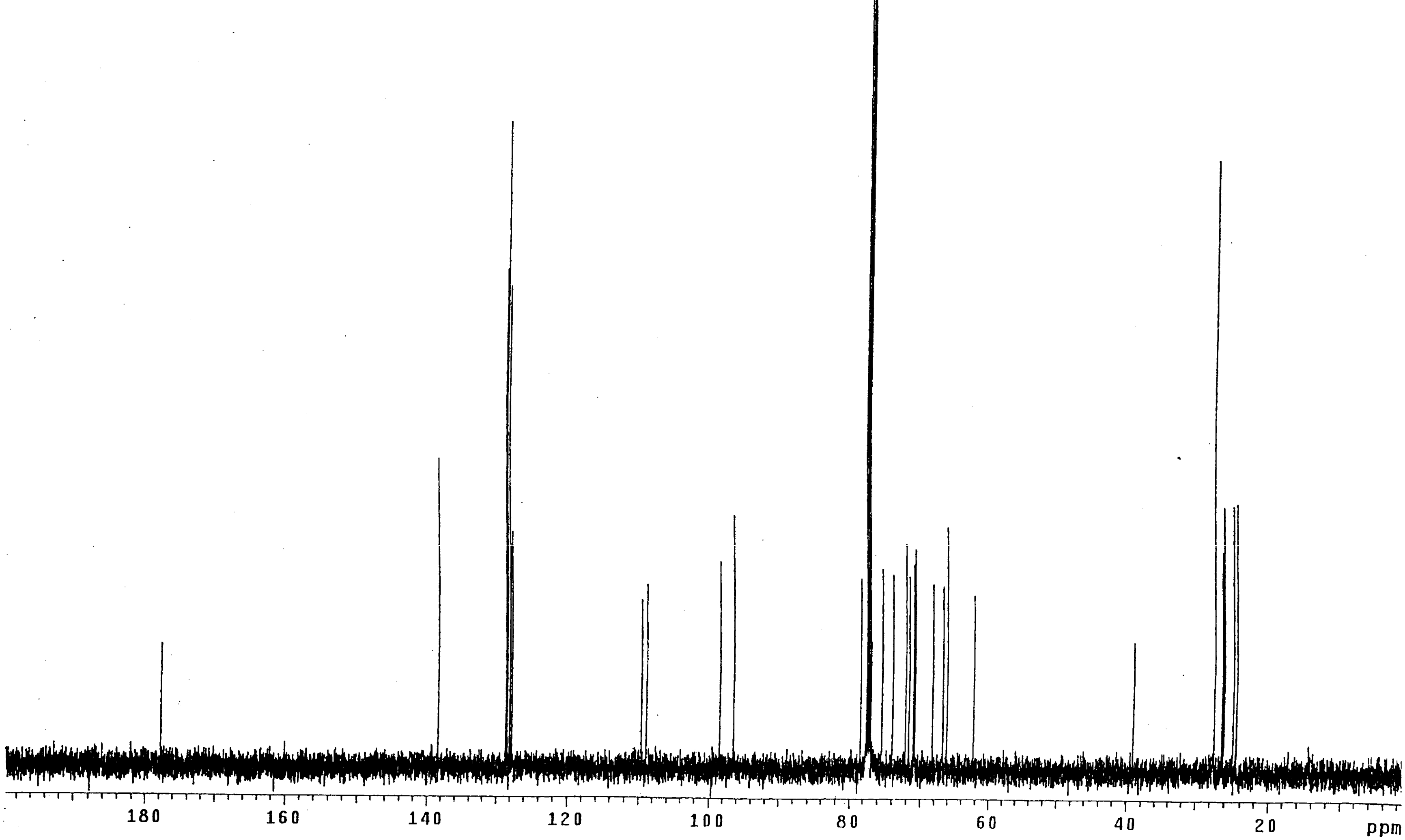
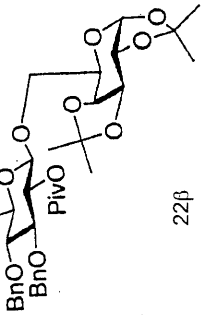


22α



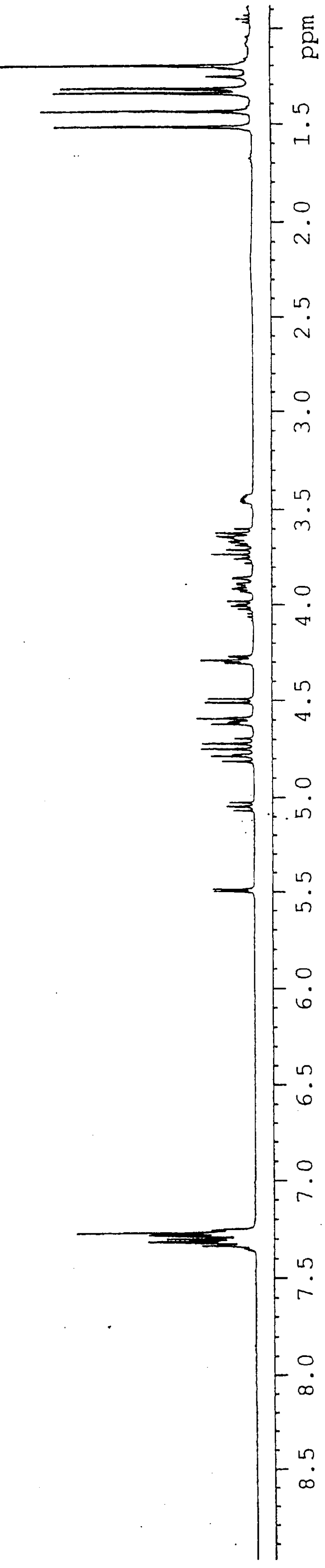
22α





OH
O
O
BnO
BnO
PivO
O
O
O
O

22β



ppm
1.5
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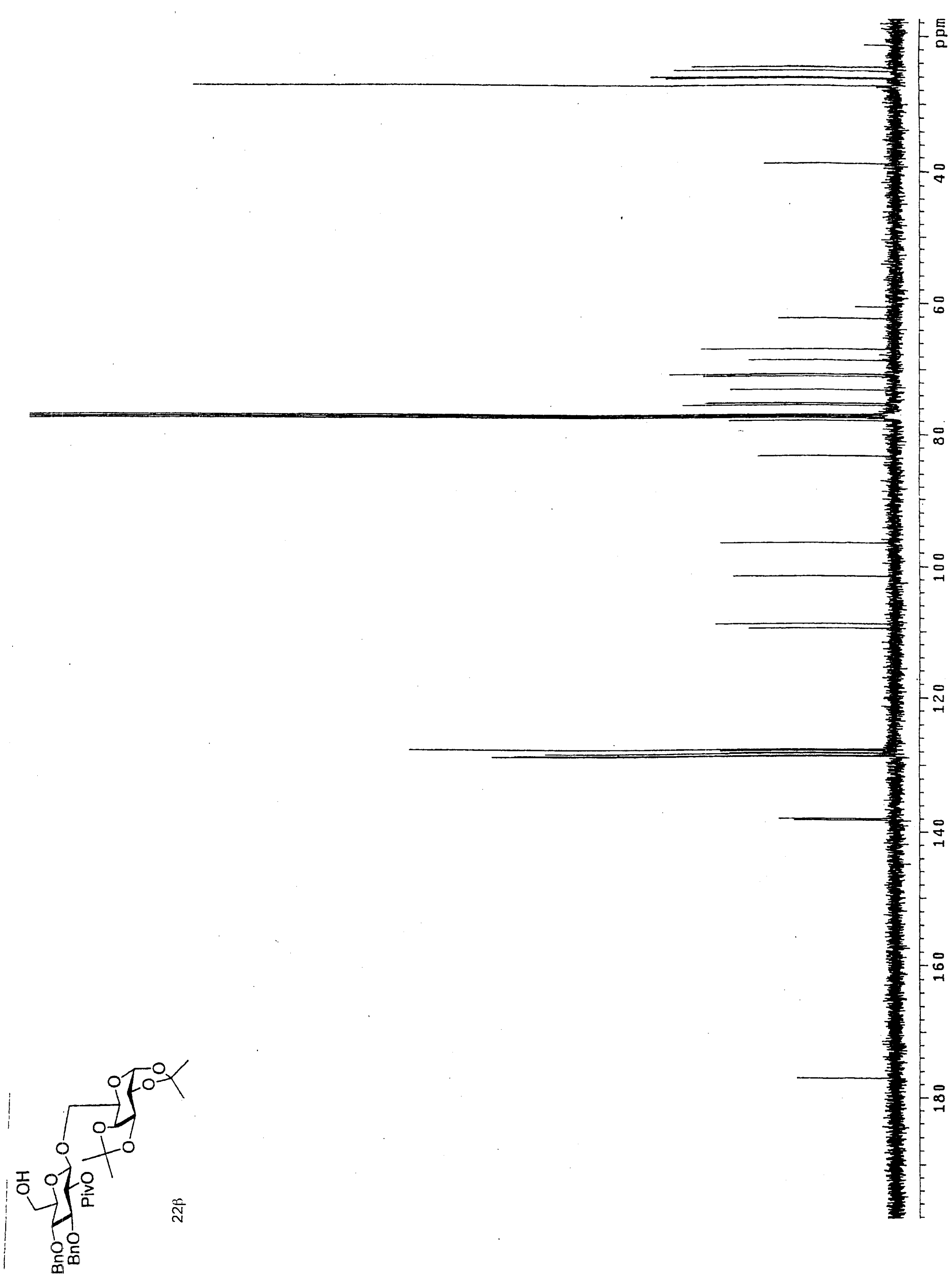
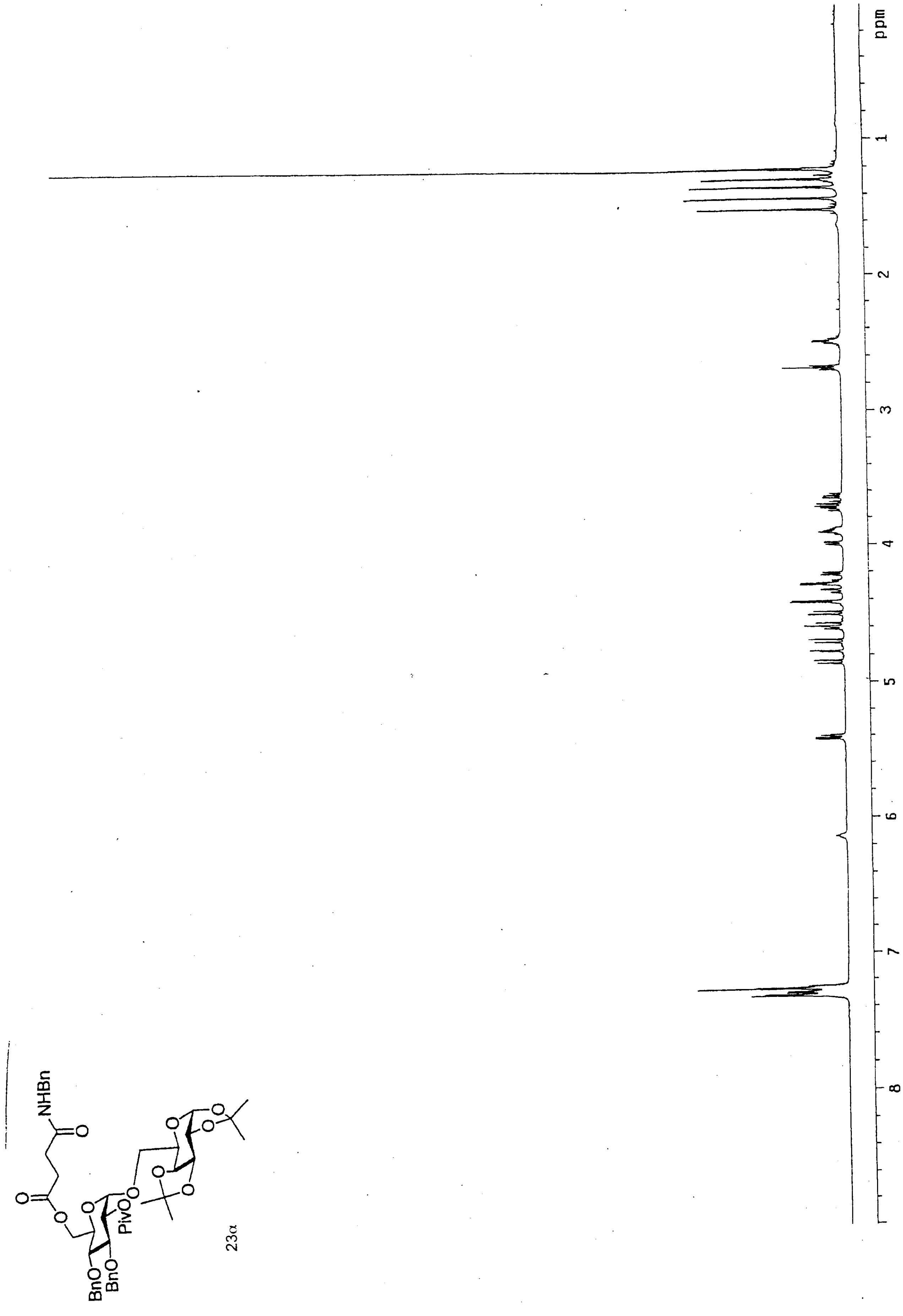
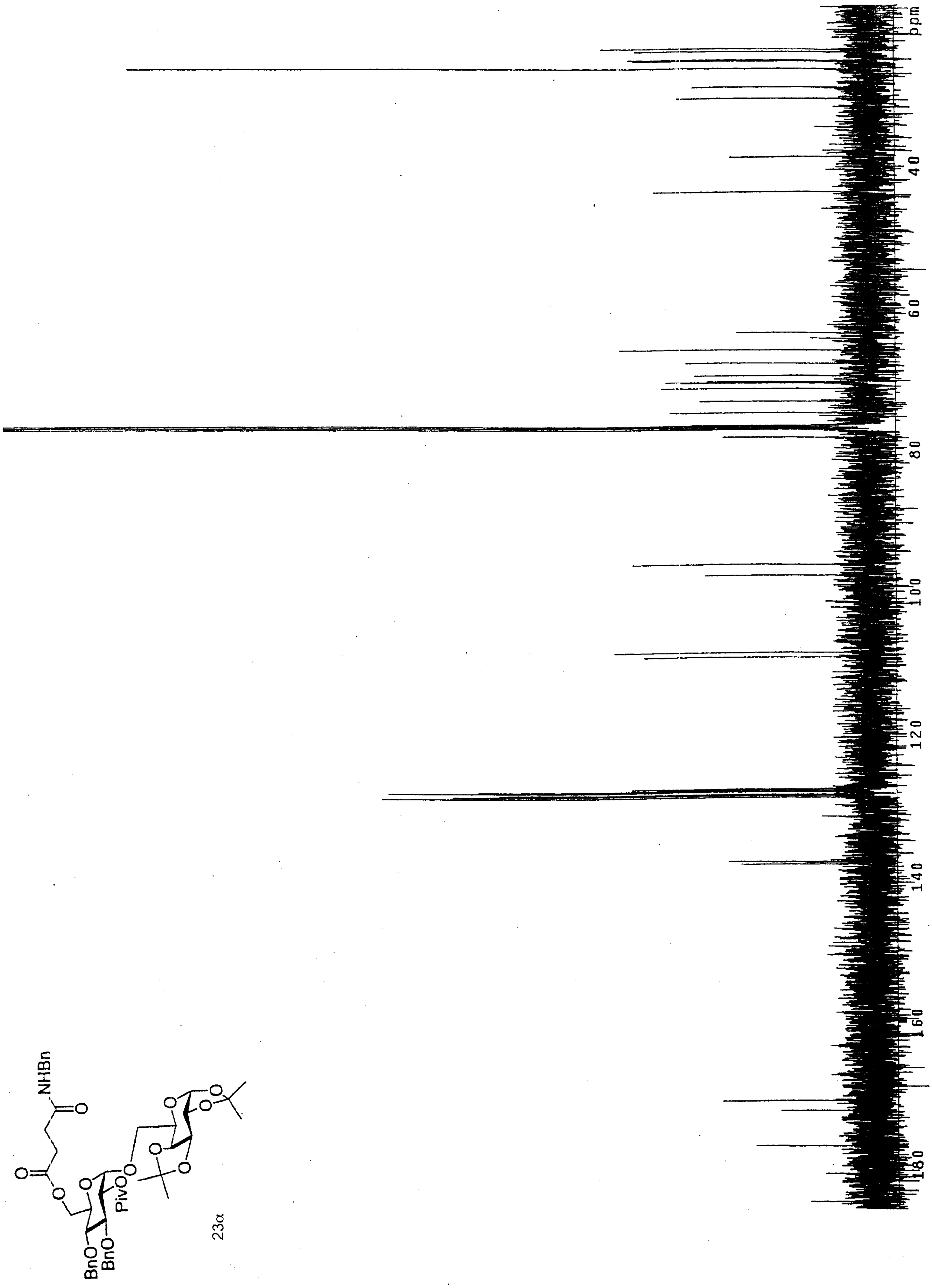
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5



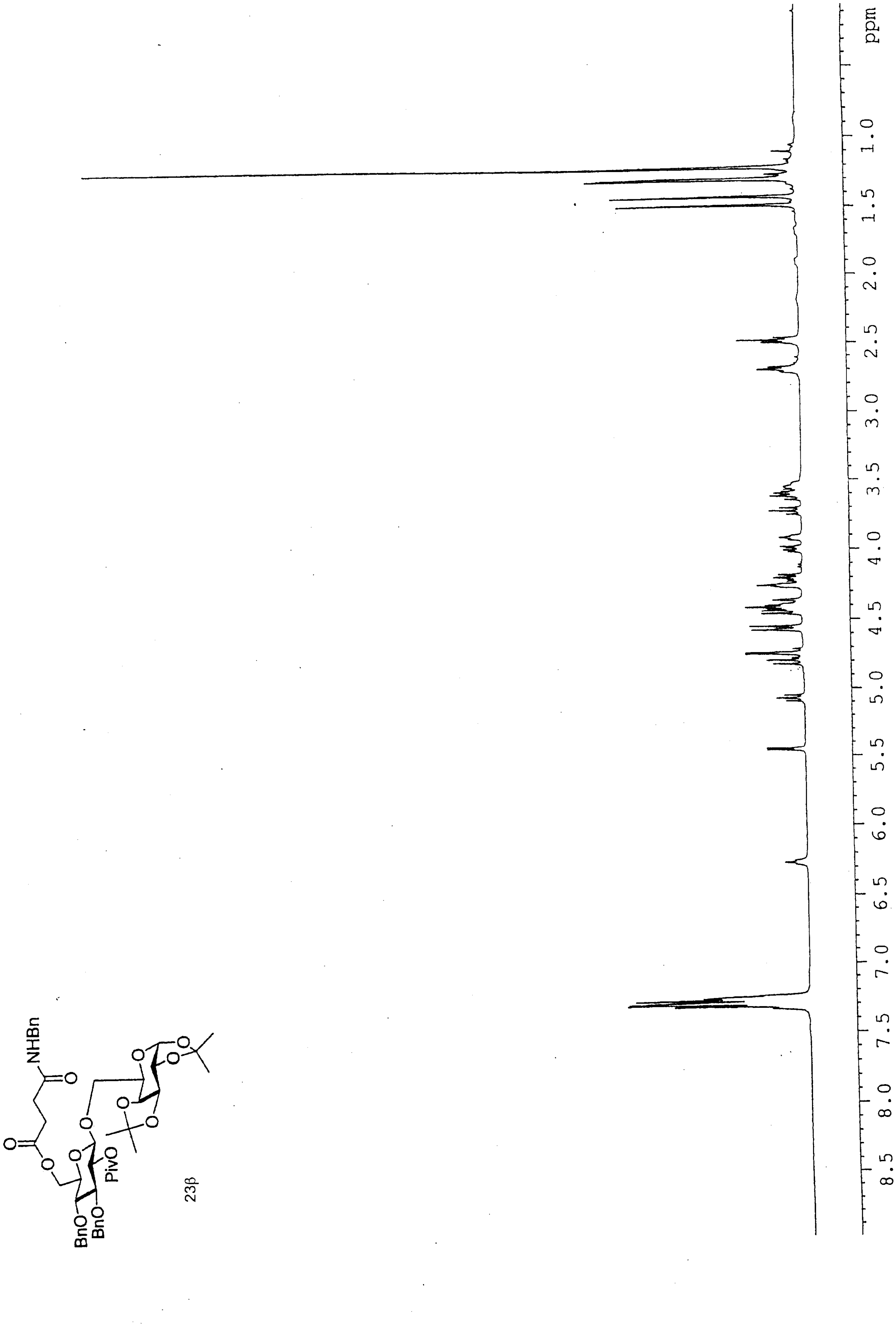
22β



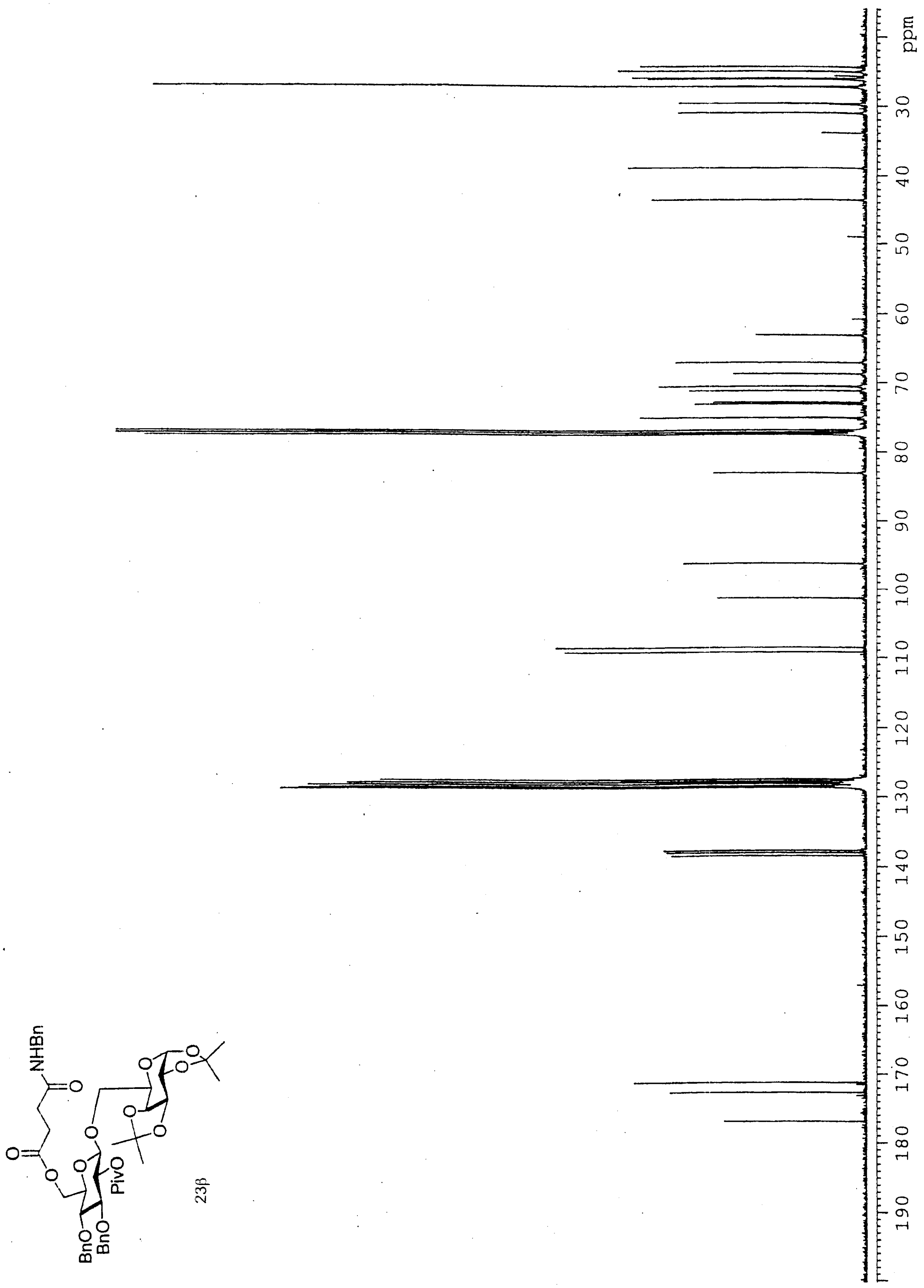
23α



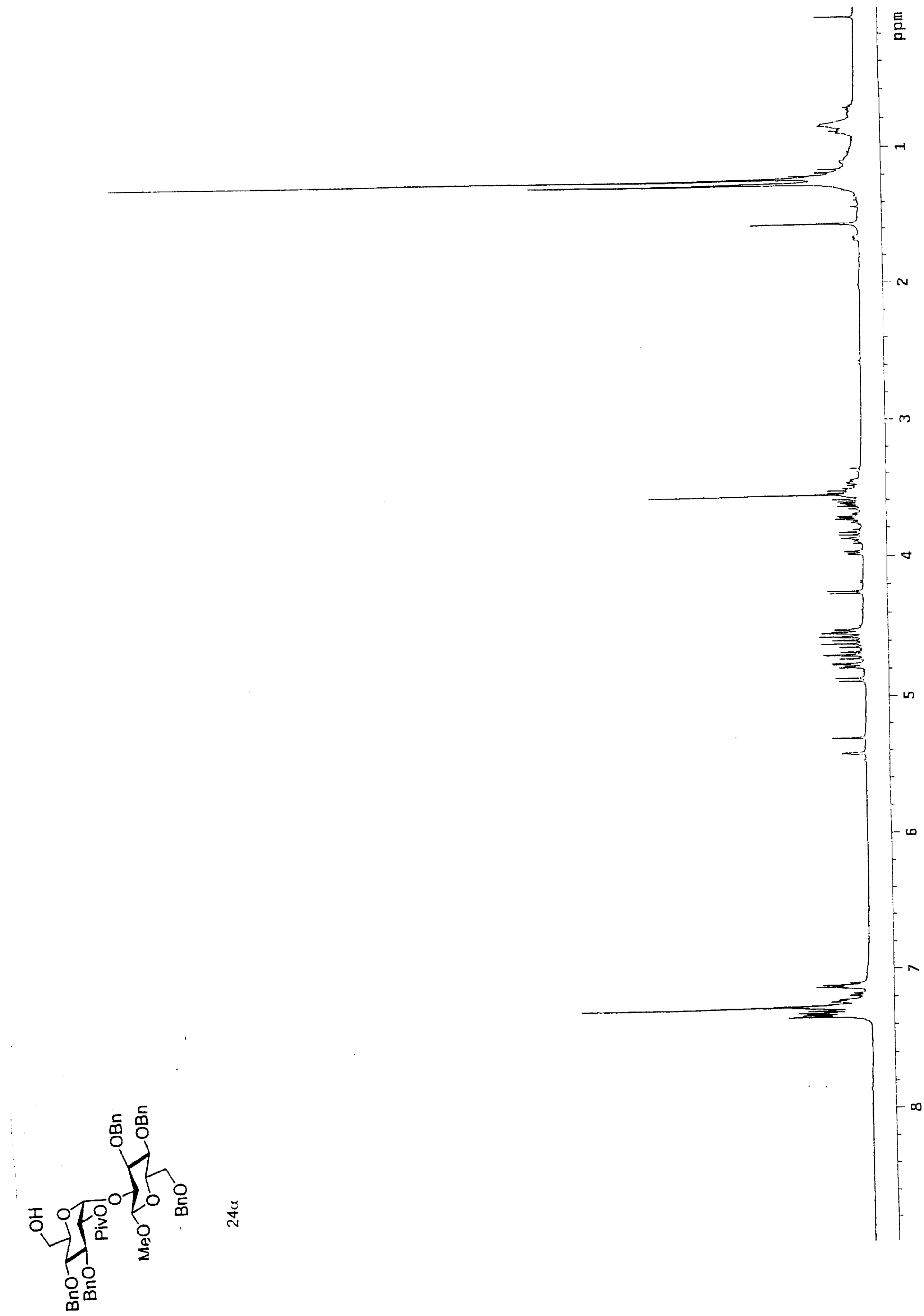
23α


NHBn
O
O
O
O
O
O
O
O
O
BnO
BnO
PivO
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5

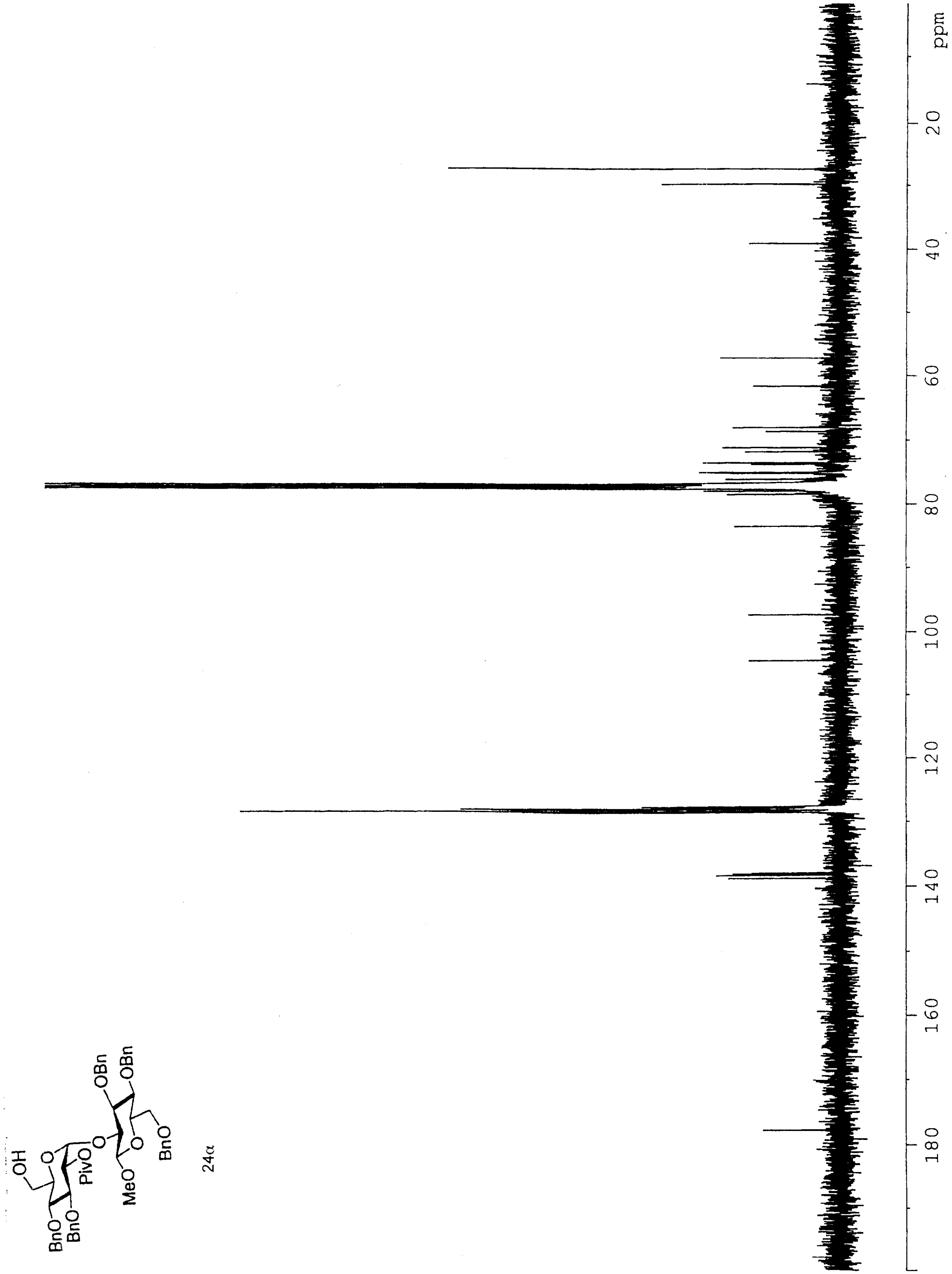
23β


ppm
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
NHBn
O
O
BnO
BnO
PivO
O
O
O
O
O
O

23β



24α


OH
O
BnO
BnO
PivO
O
OBn
OBn
O
MeO
BnO
ppm
20
40
60
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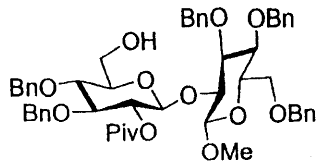
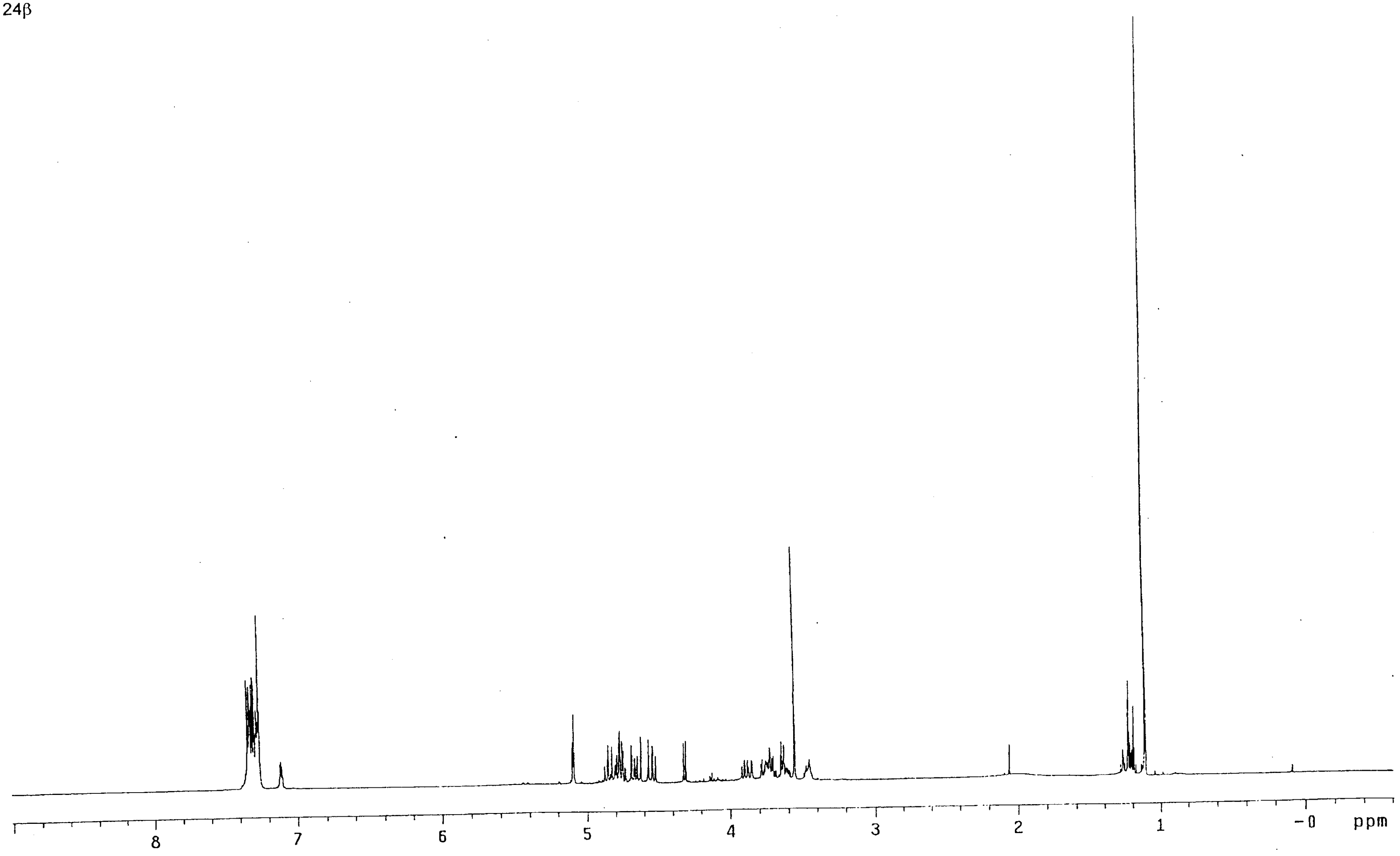
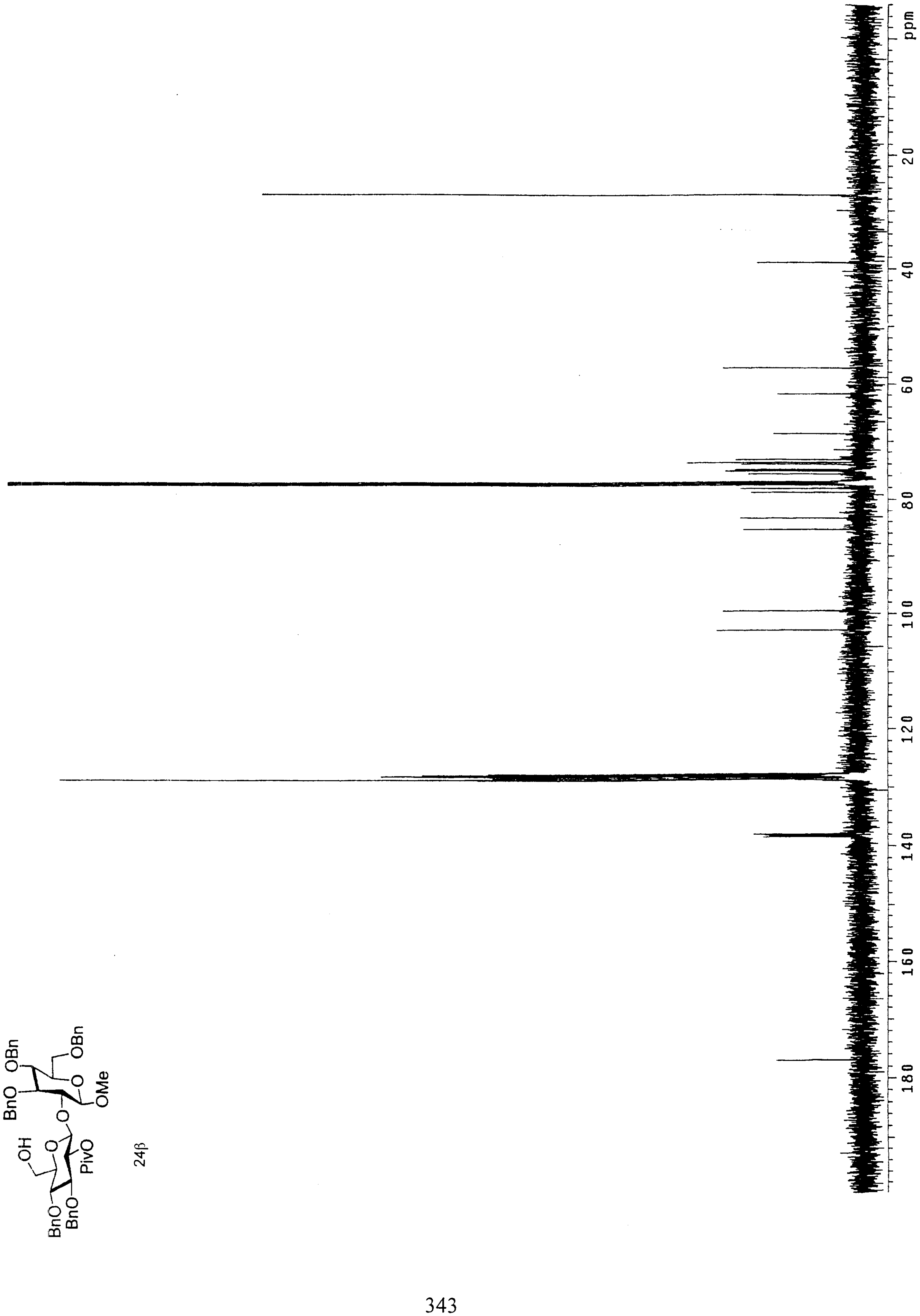
120
140
160
180

24α



24β




BnO
OBn
OBn
O
OMe
OH
O
O
BnO
BnO
PivO
24β
ppm
180
160
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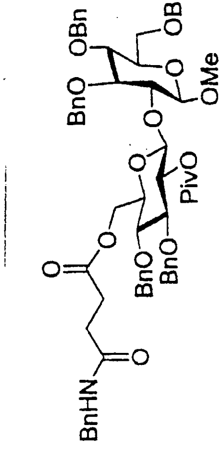
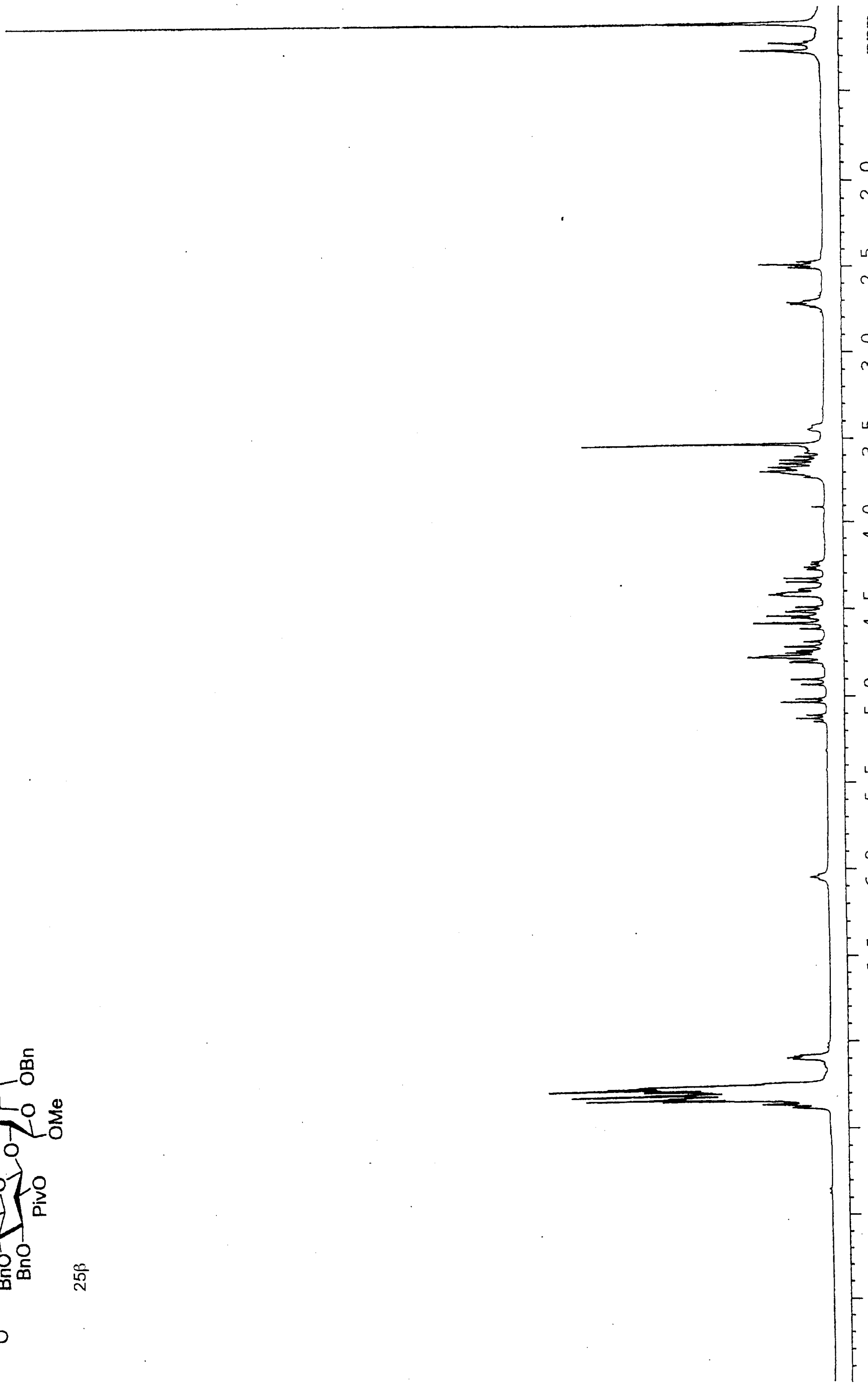
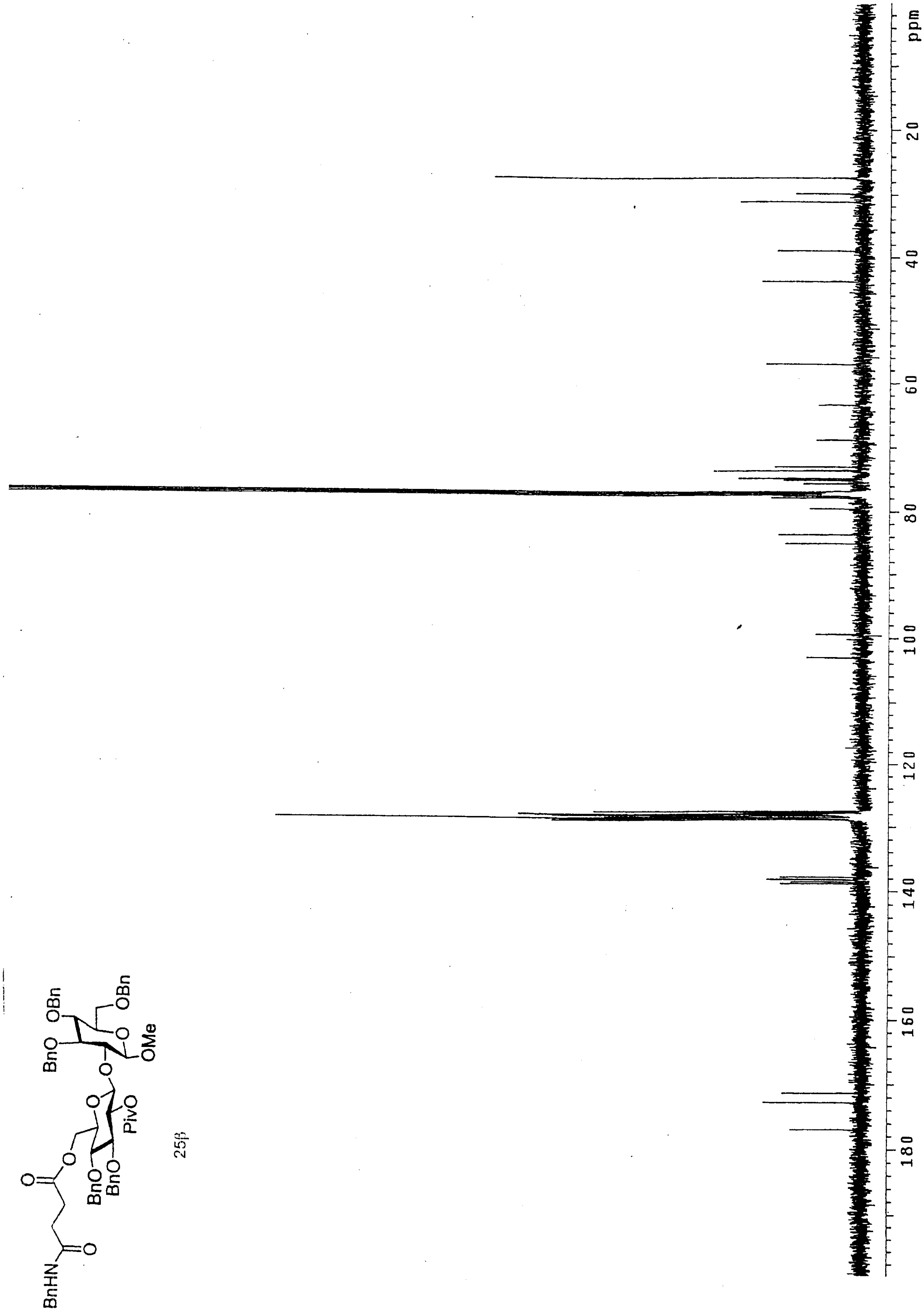
120
100
80
60
40
20

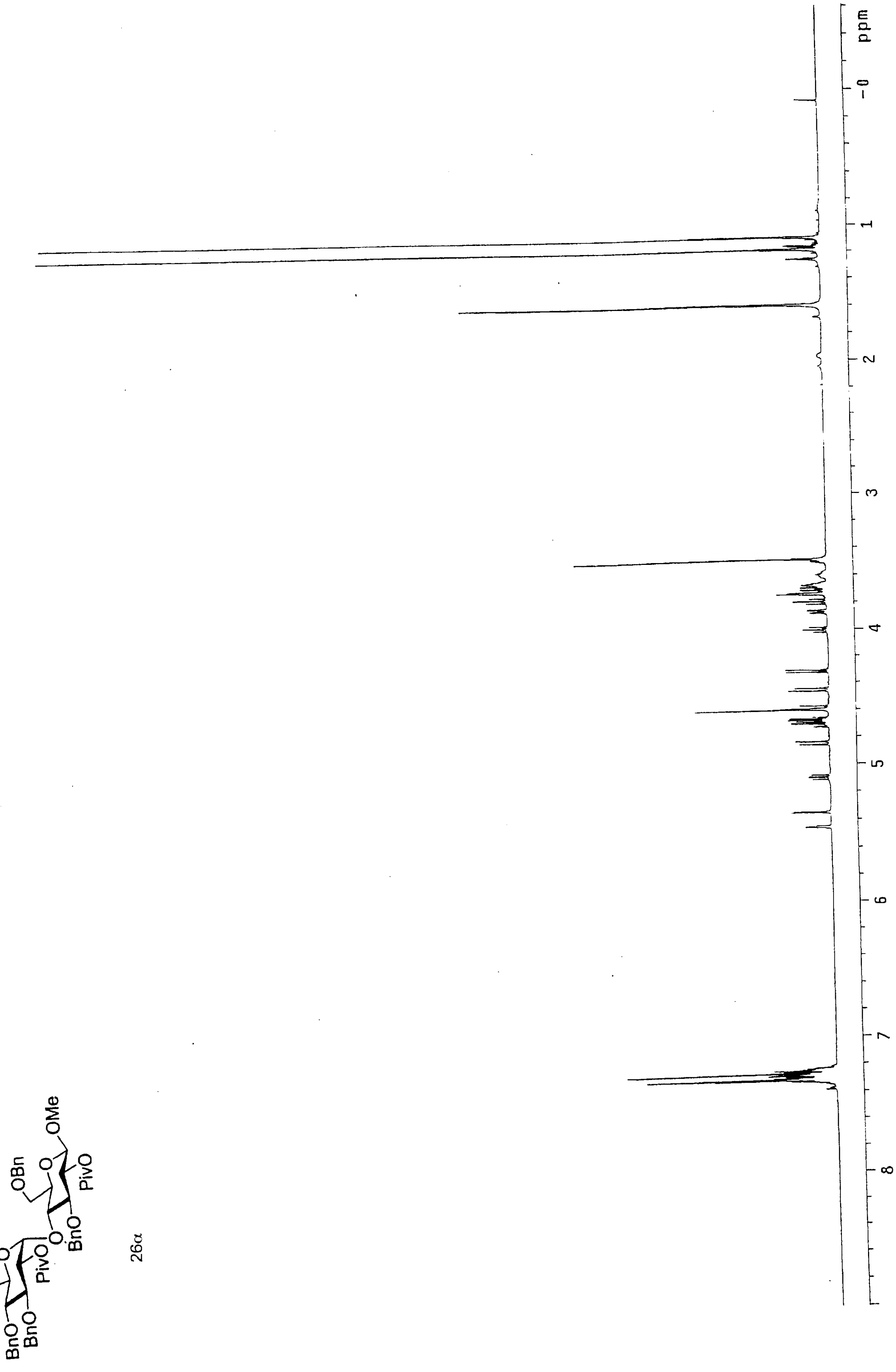

BnHN
O
O
O
BnO
BnO
O
PivO
O
BnO
OBn
O
OBn
OMe

25β


ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5


BnHN
O
O
O
BnO
BnO
PivO
O
O
BnO
OBn
O
OBn
OMe
ppm
20
40
60
80
100
120
140
160
180

25β



26α


BnO
BnO
OH
O
PivO
O
BnO
OBn
O
OMe
PivO
ppm
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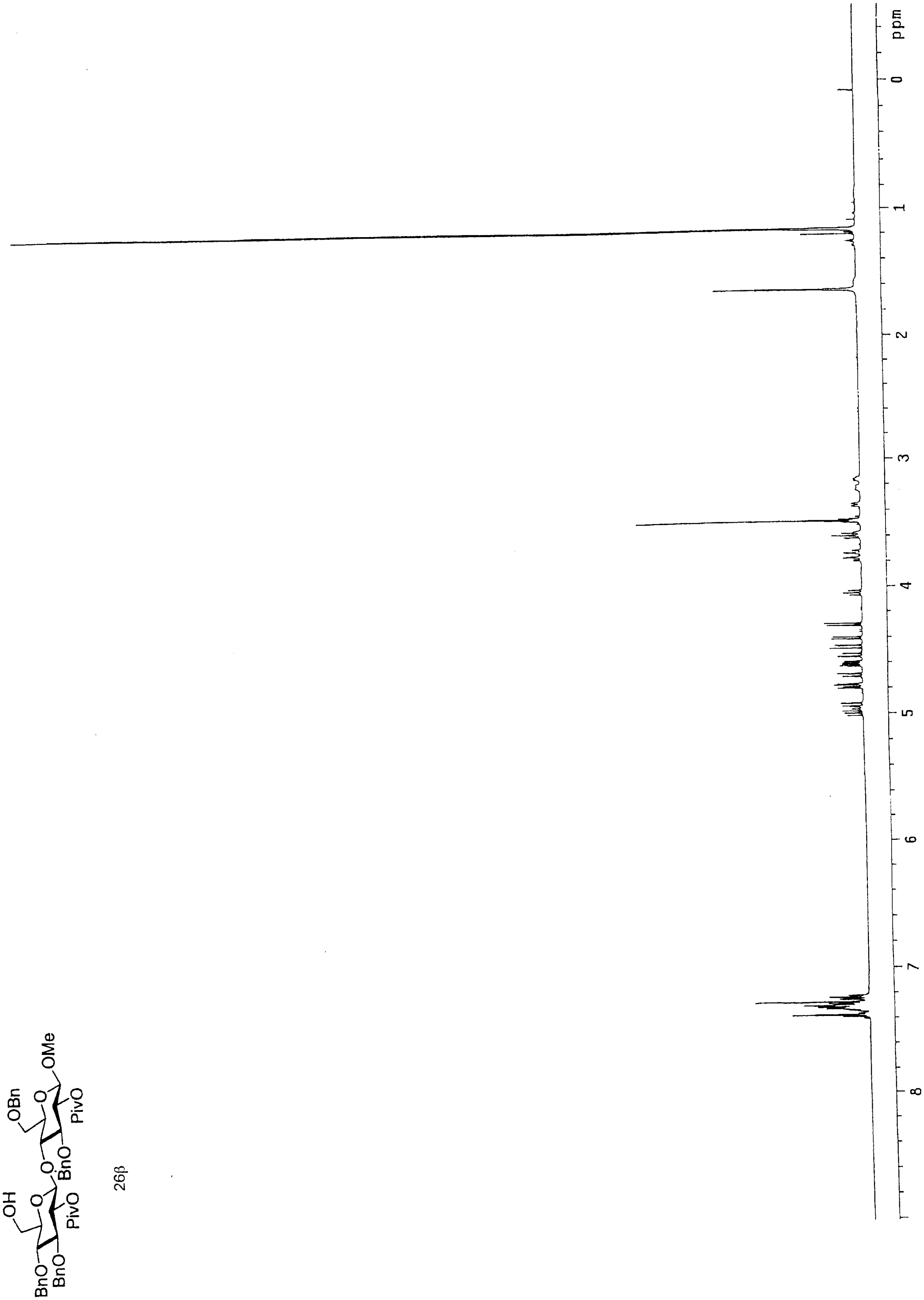
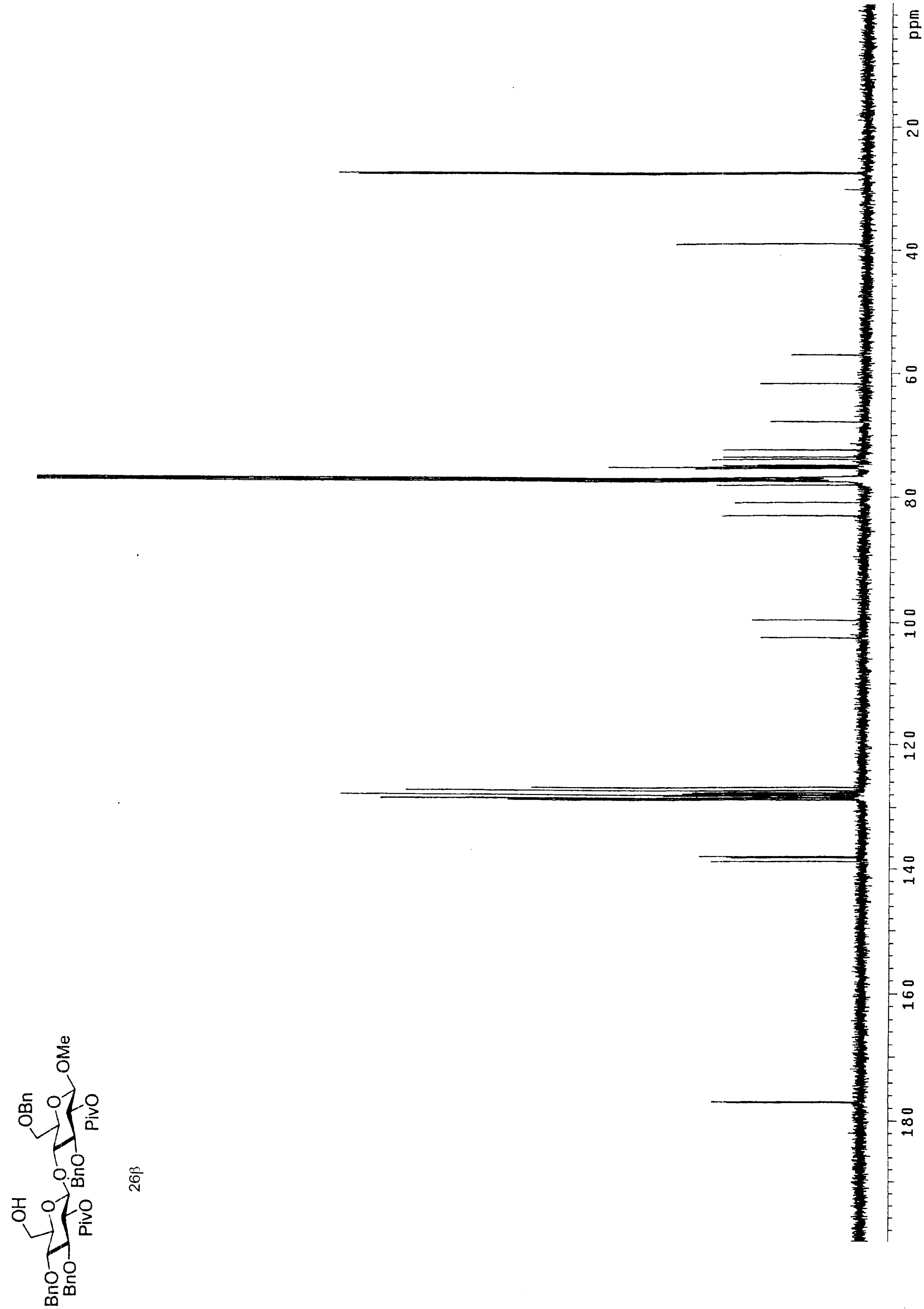
60
80
100
120
140
160
180

26α



26β


BnO
BnO
OH
O
PivO
O
BnO
OBn
O
PivO
OMe
ppm
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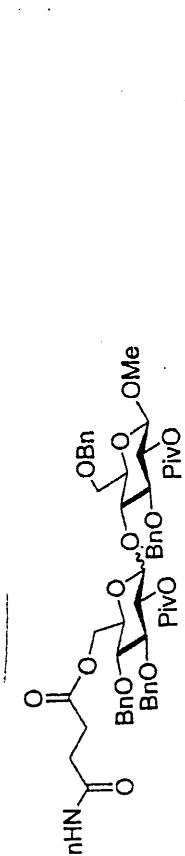
60
80
100
120
140
160
180

26β



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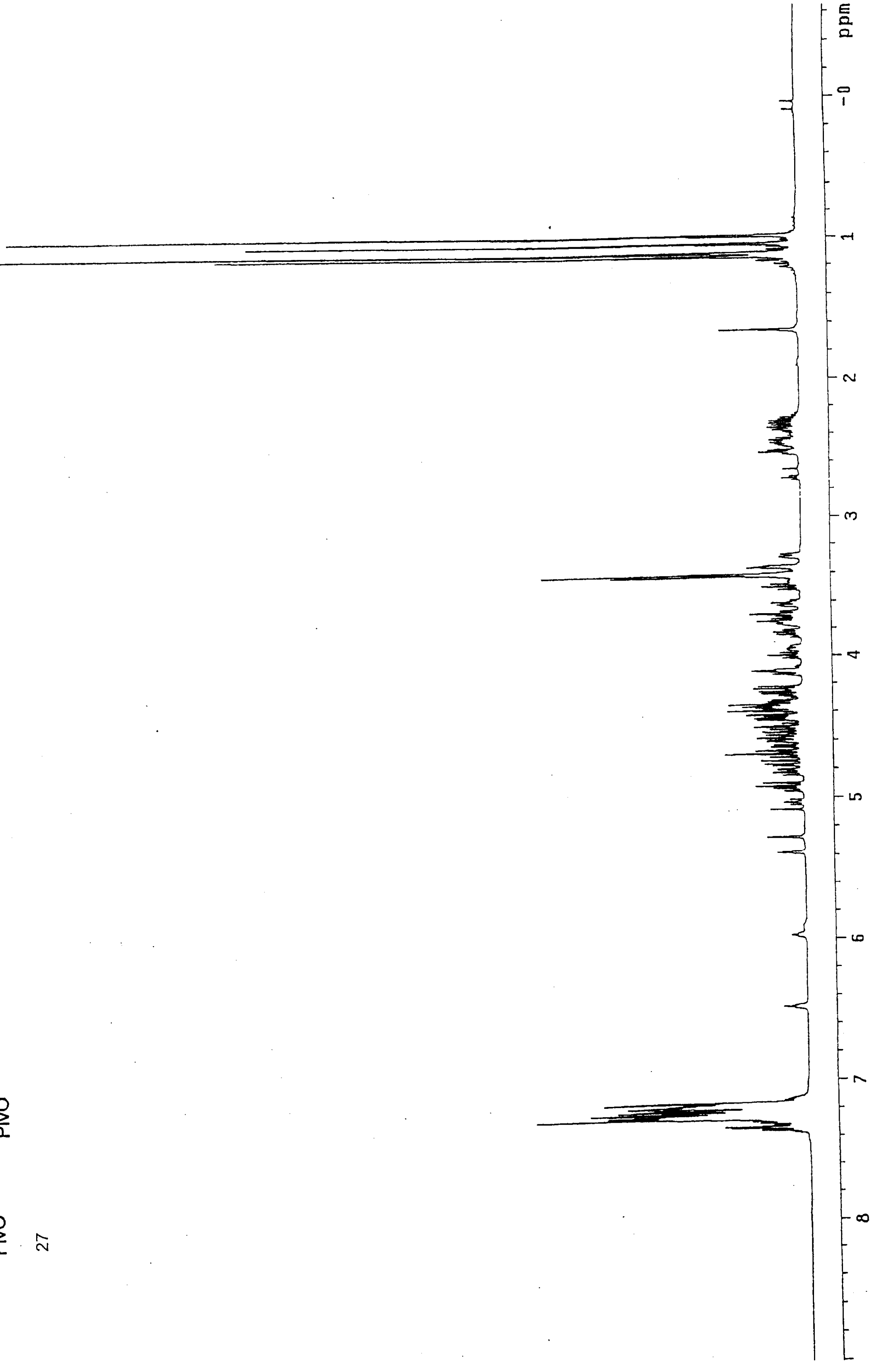
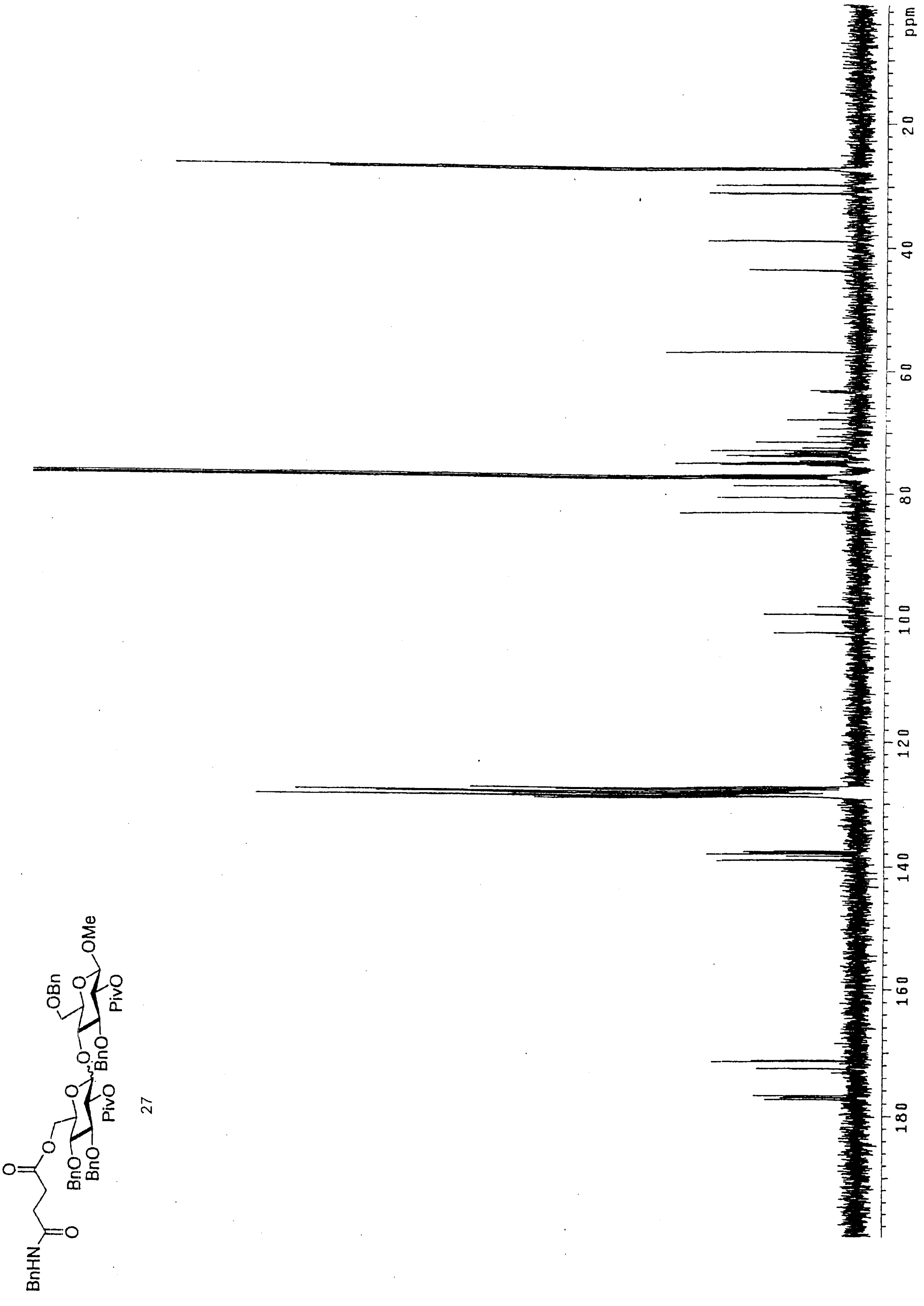


BnHN
O
O
O
BnO
BnO
O
PivO
O
BnO
O
OBn
O
PivO
OMe

27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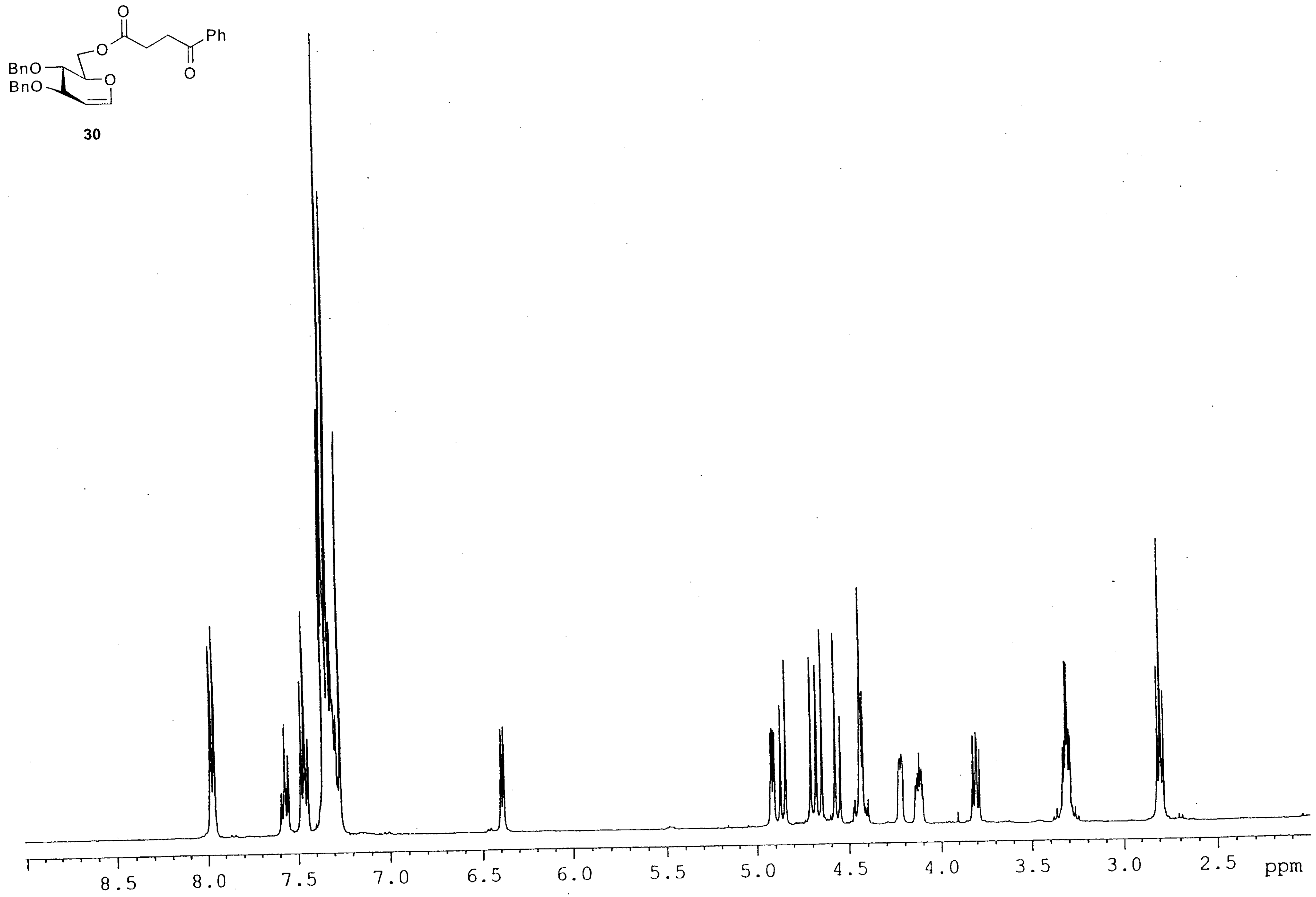
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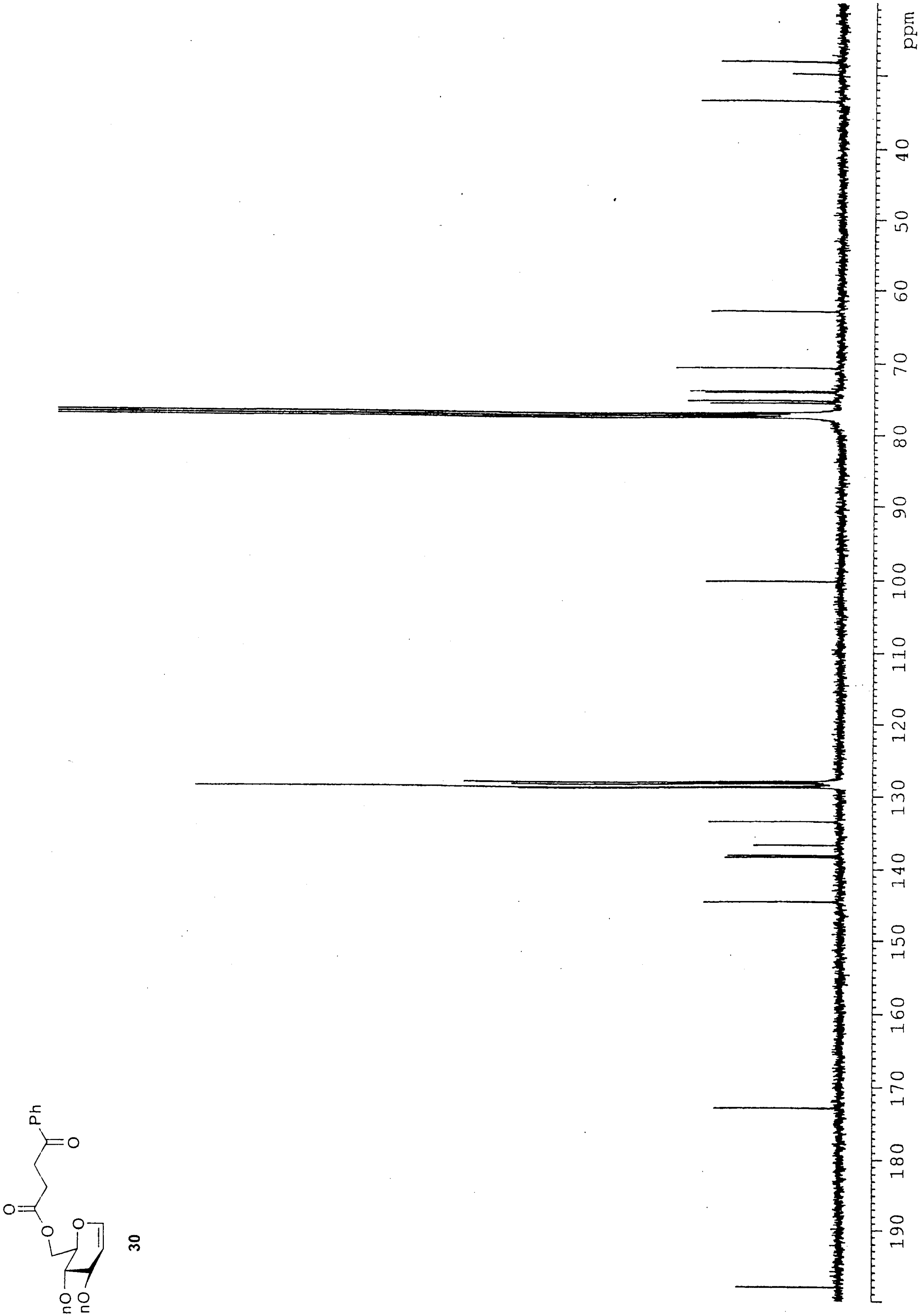
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40
50
60
70
80
90
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140
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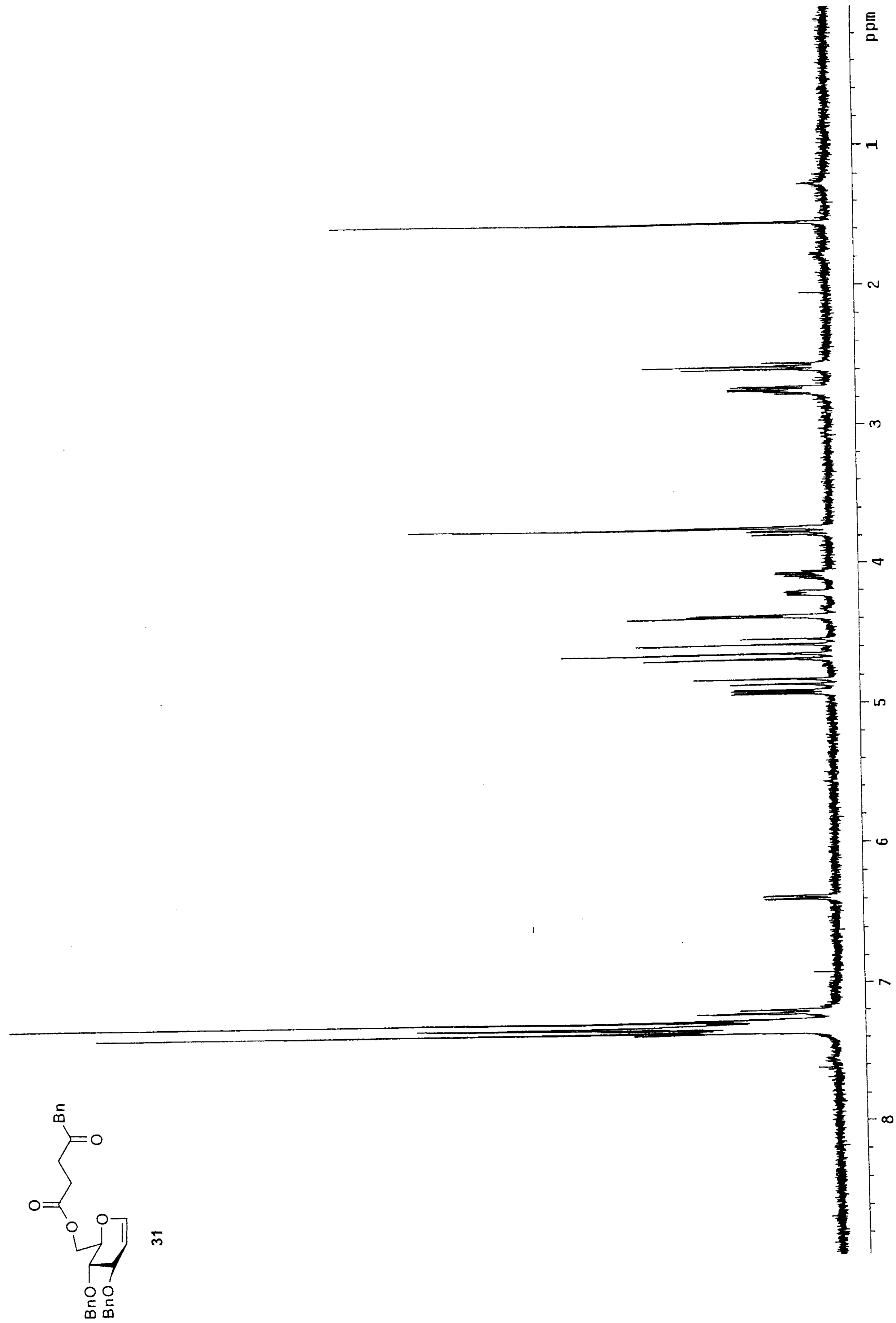
170
180
190
BnO
BnO
O
O
O
O
Ph

30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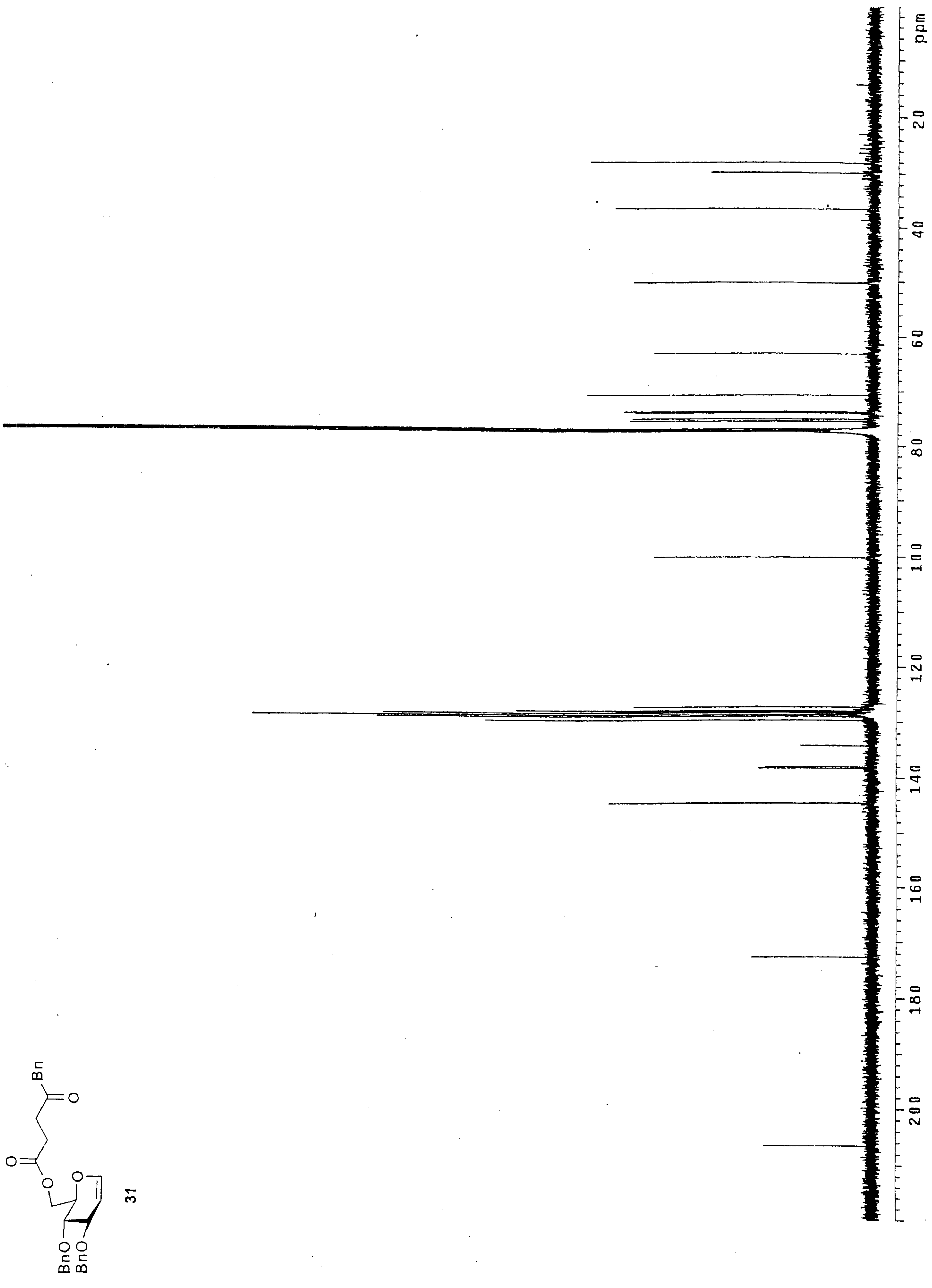

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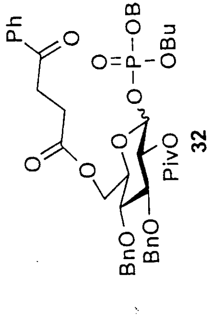
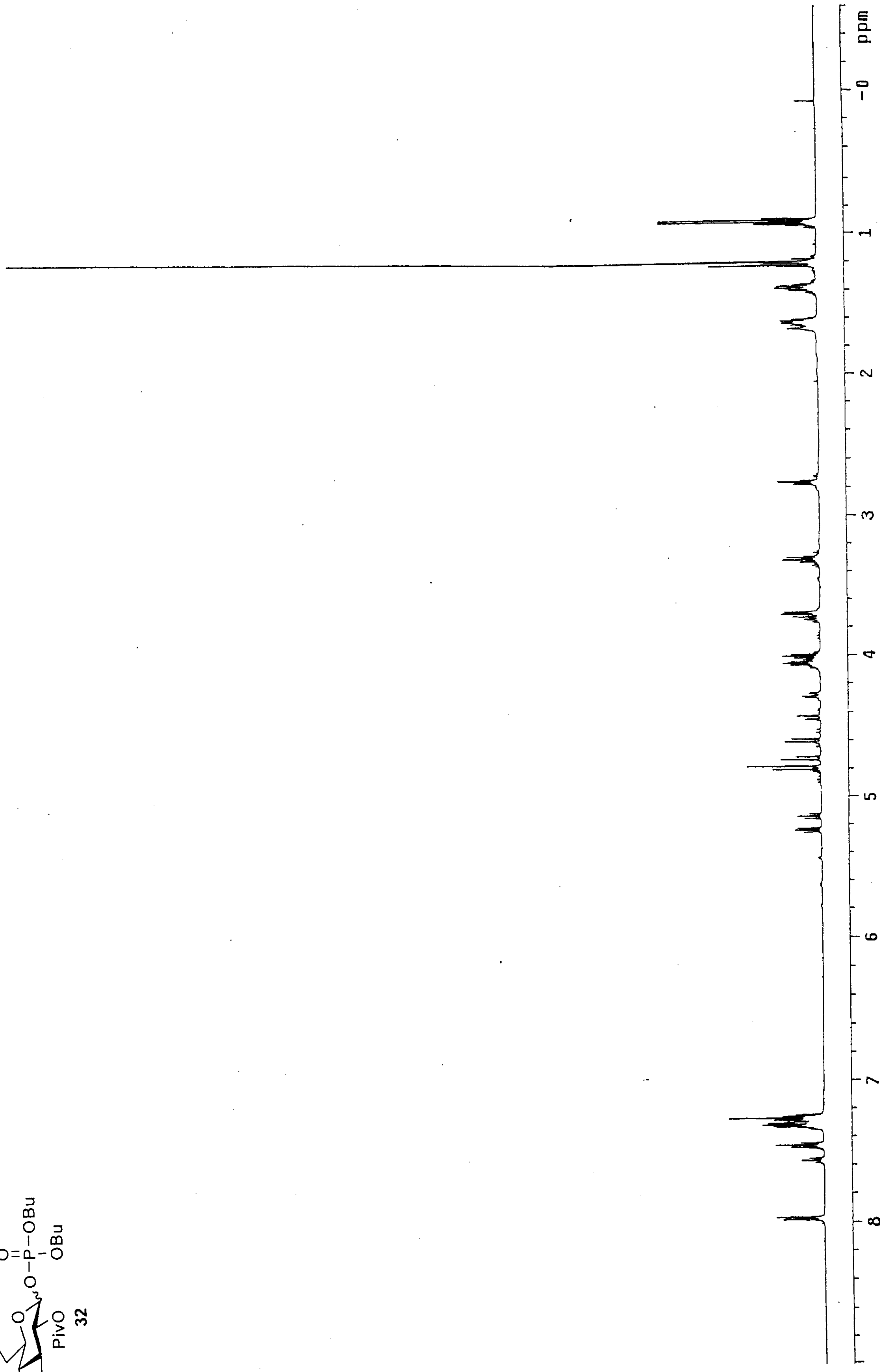
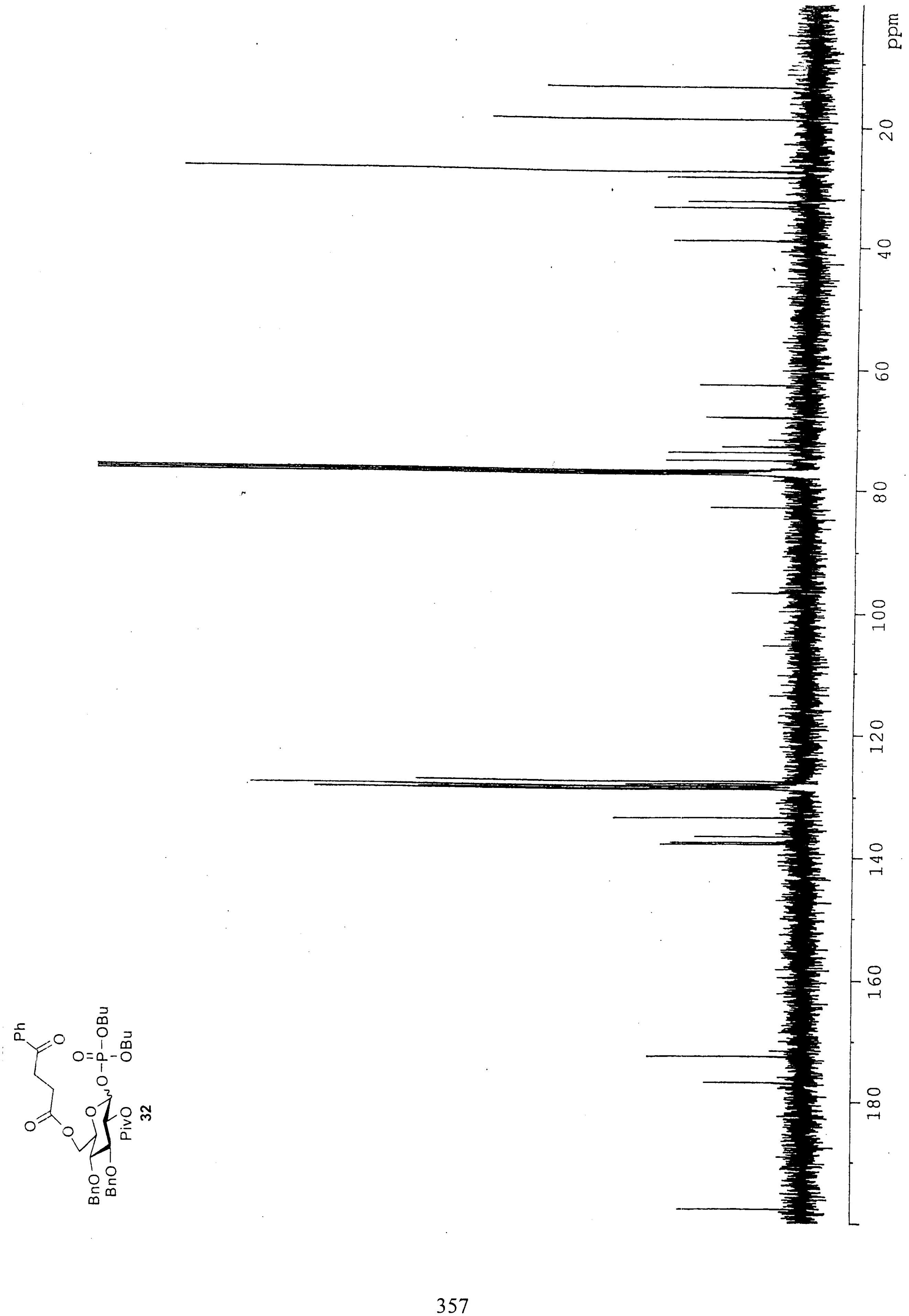


32

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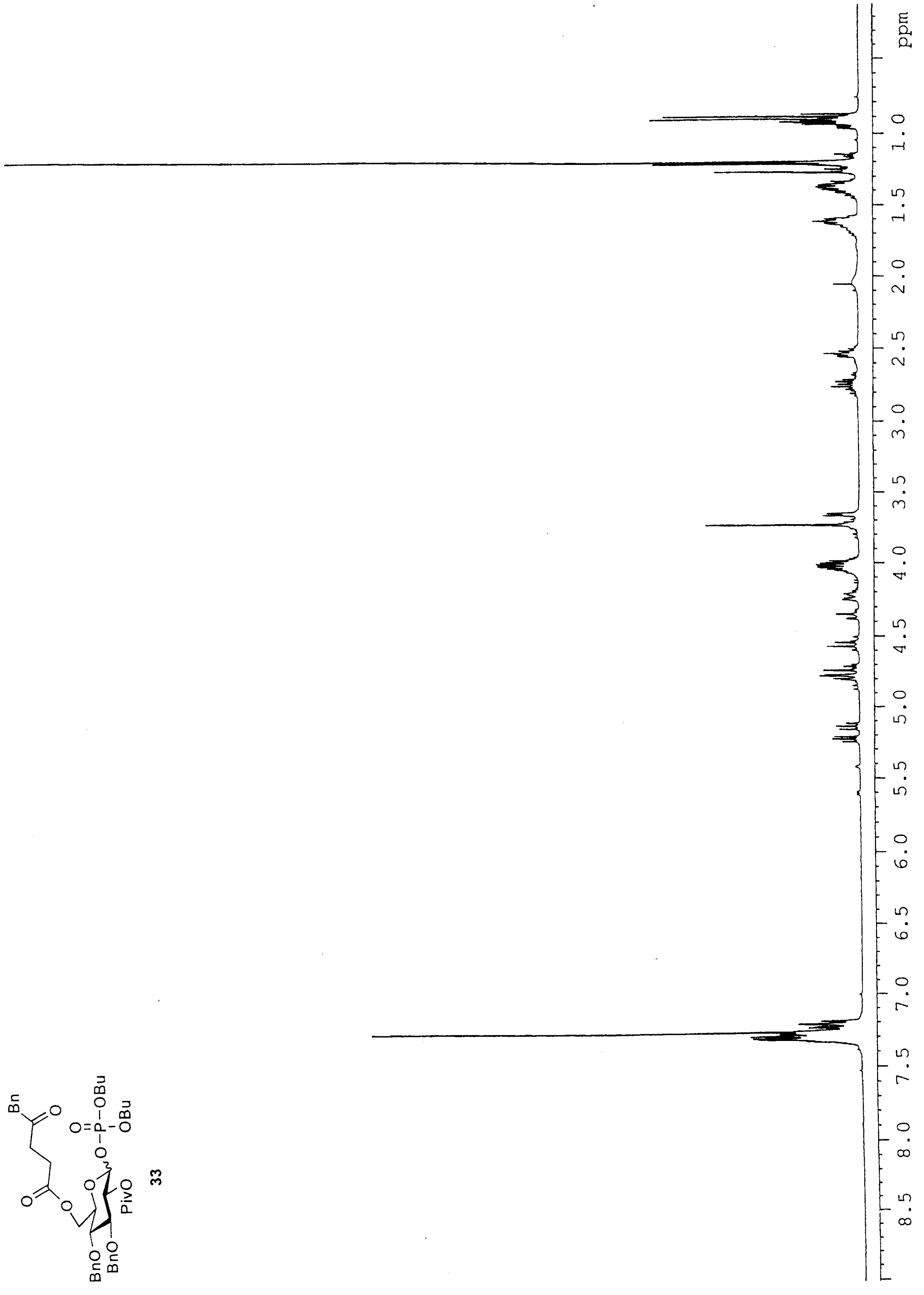

ppm
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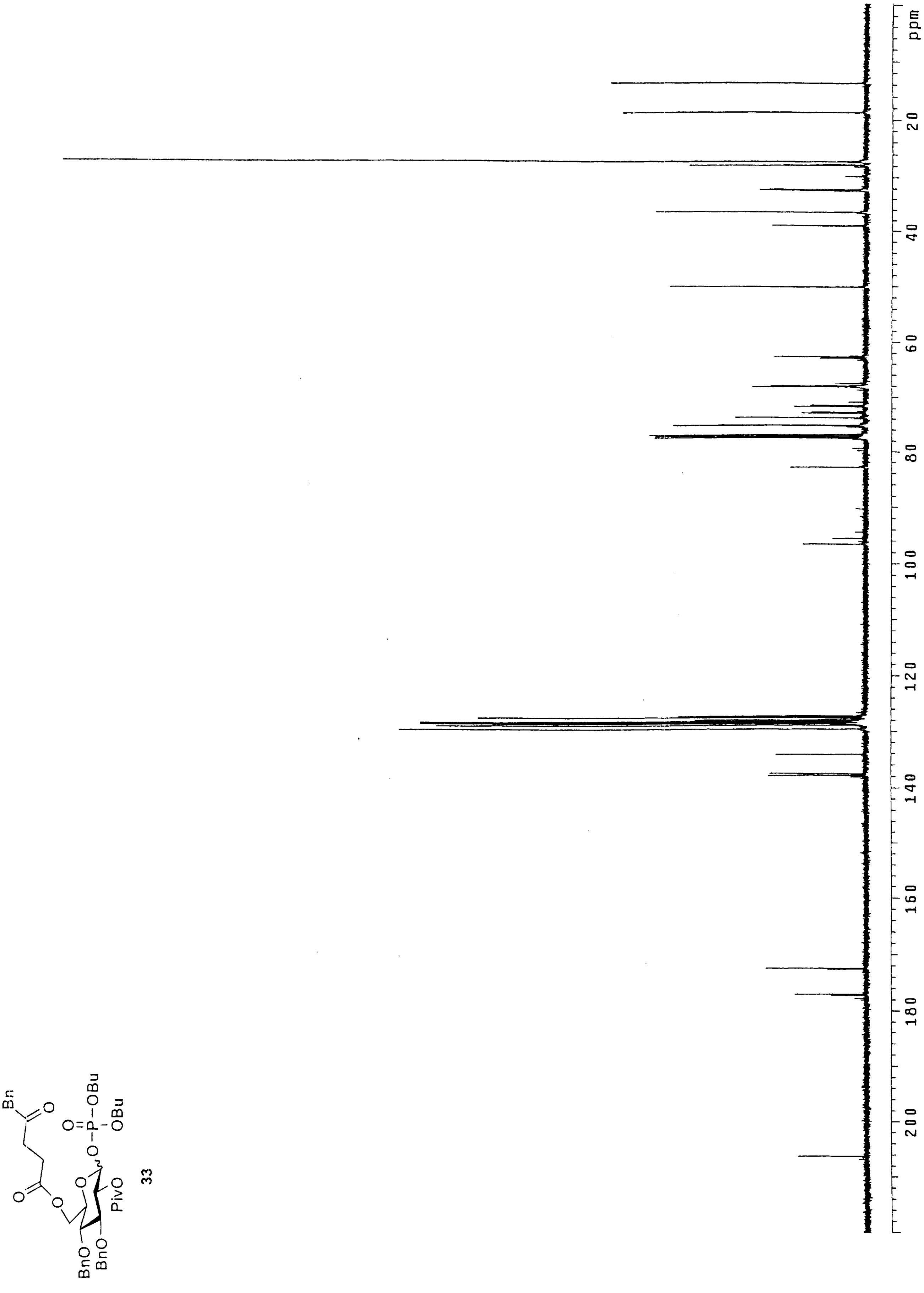
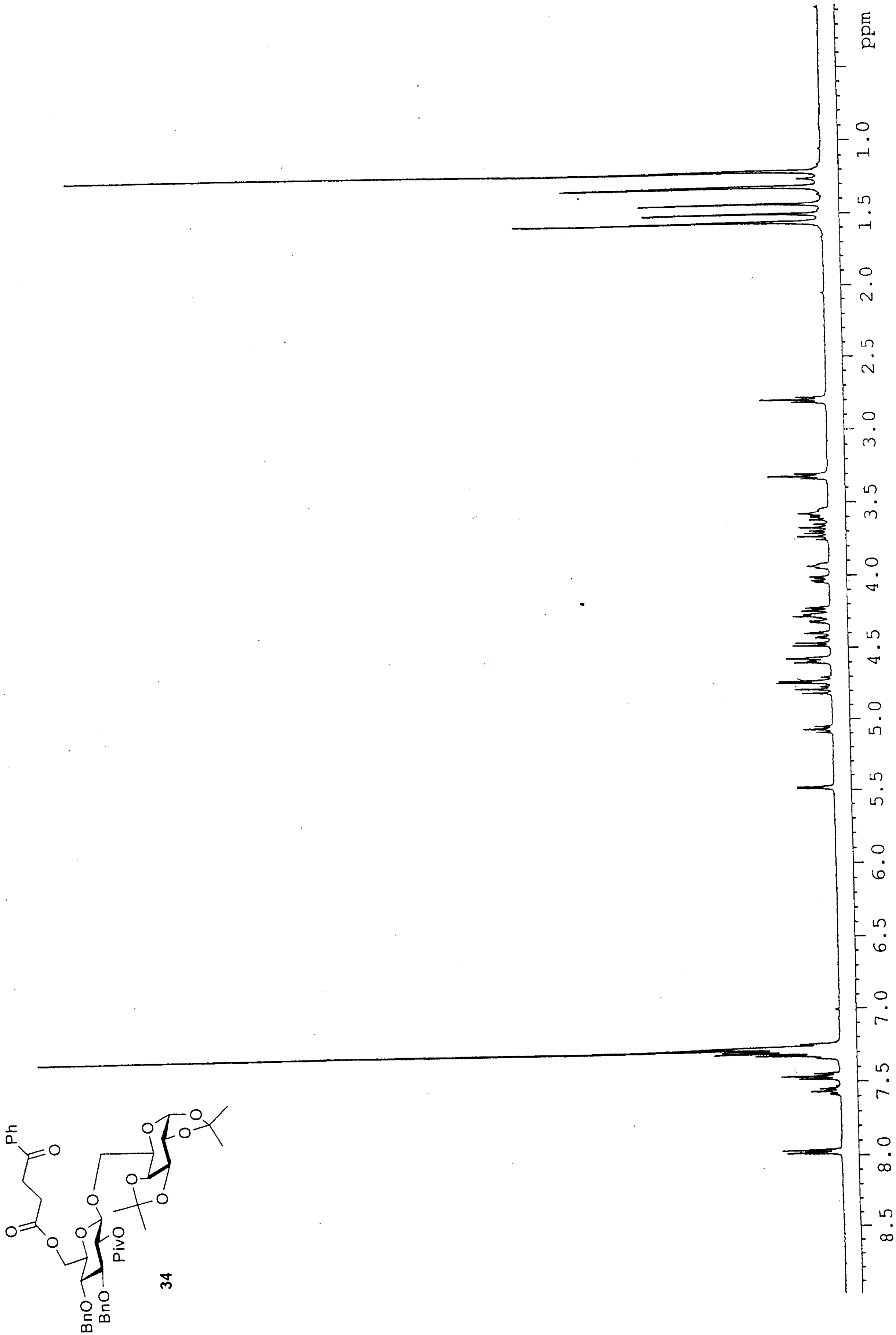
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
Bn
O
O
O
O
P
OBu
OBu
BnO
BnO
PivO

33


BnO
BnO
PivO
O
O
O
O
Bn
O
O
O
P
OBu
OBu
ppm
20
40
60
80
100
120
140
160
180
200

33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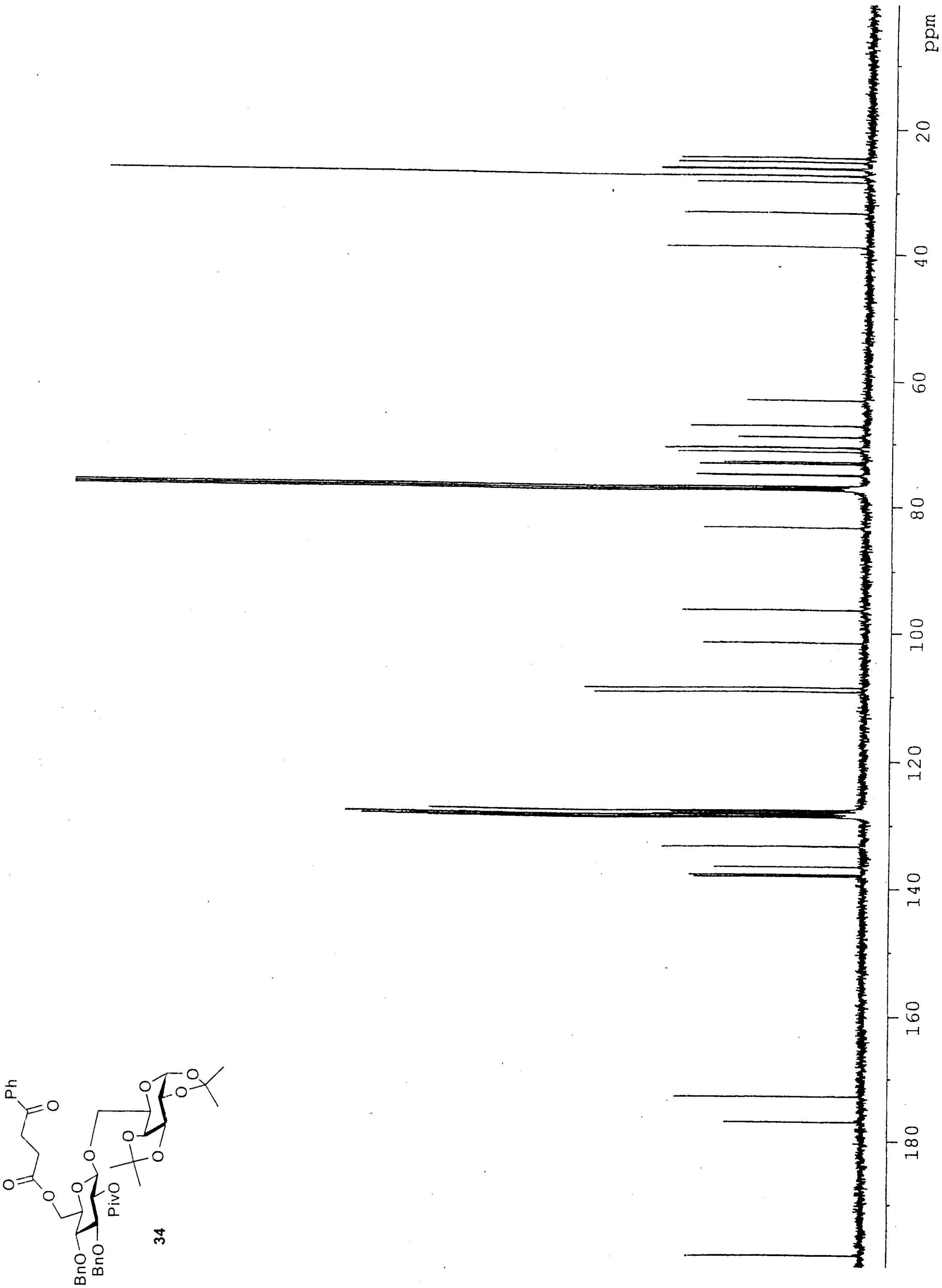
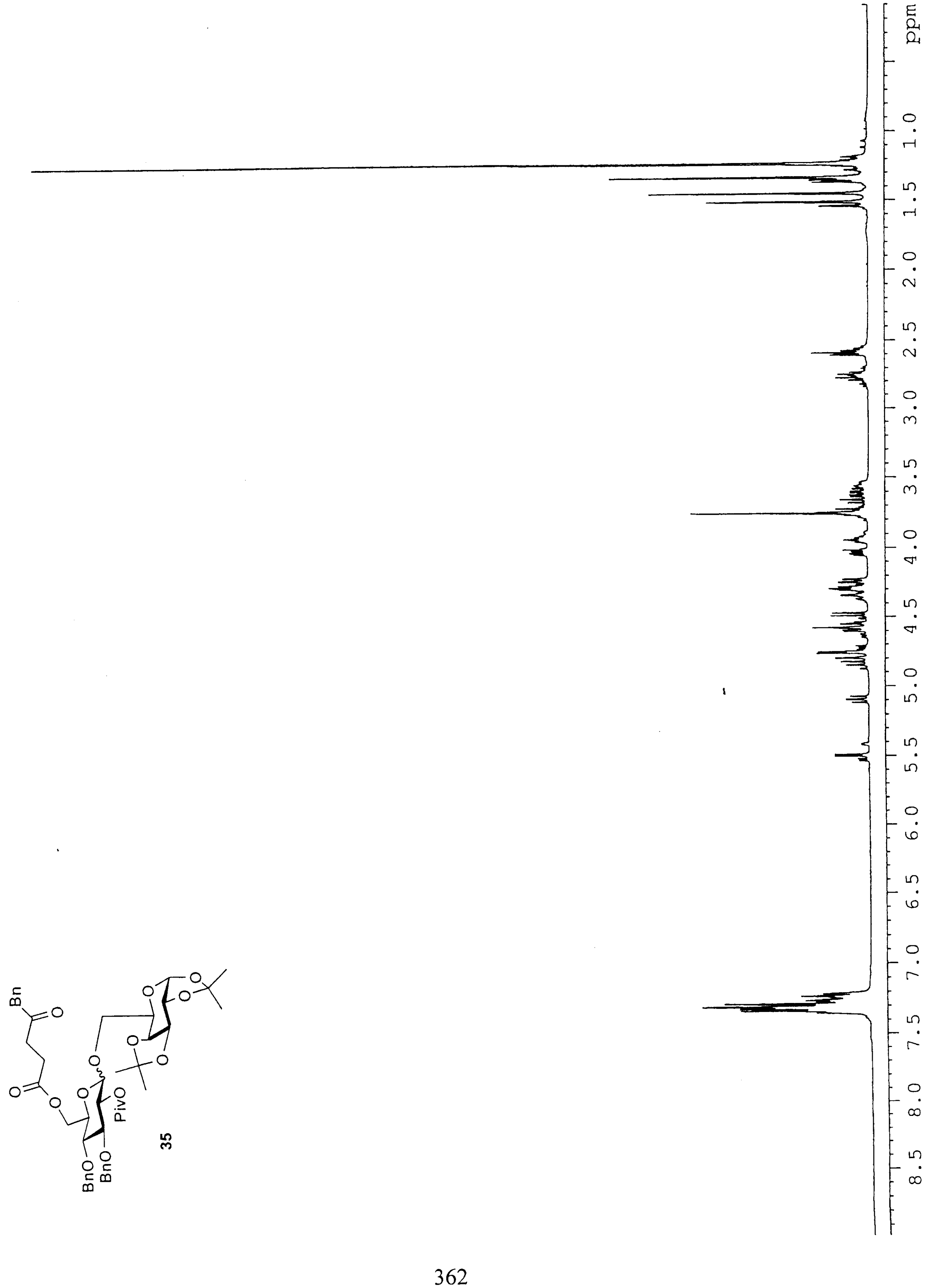
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
Ph
O
BnO
BnO
PivO
O
O
O
O
O
O
O

34



34



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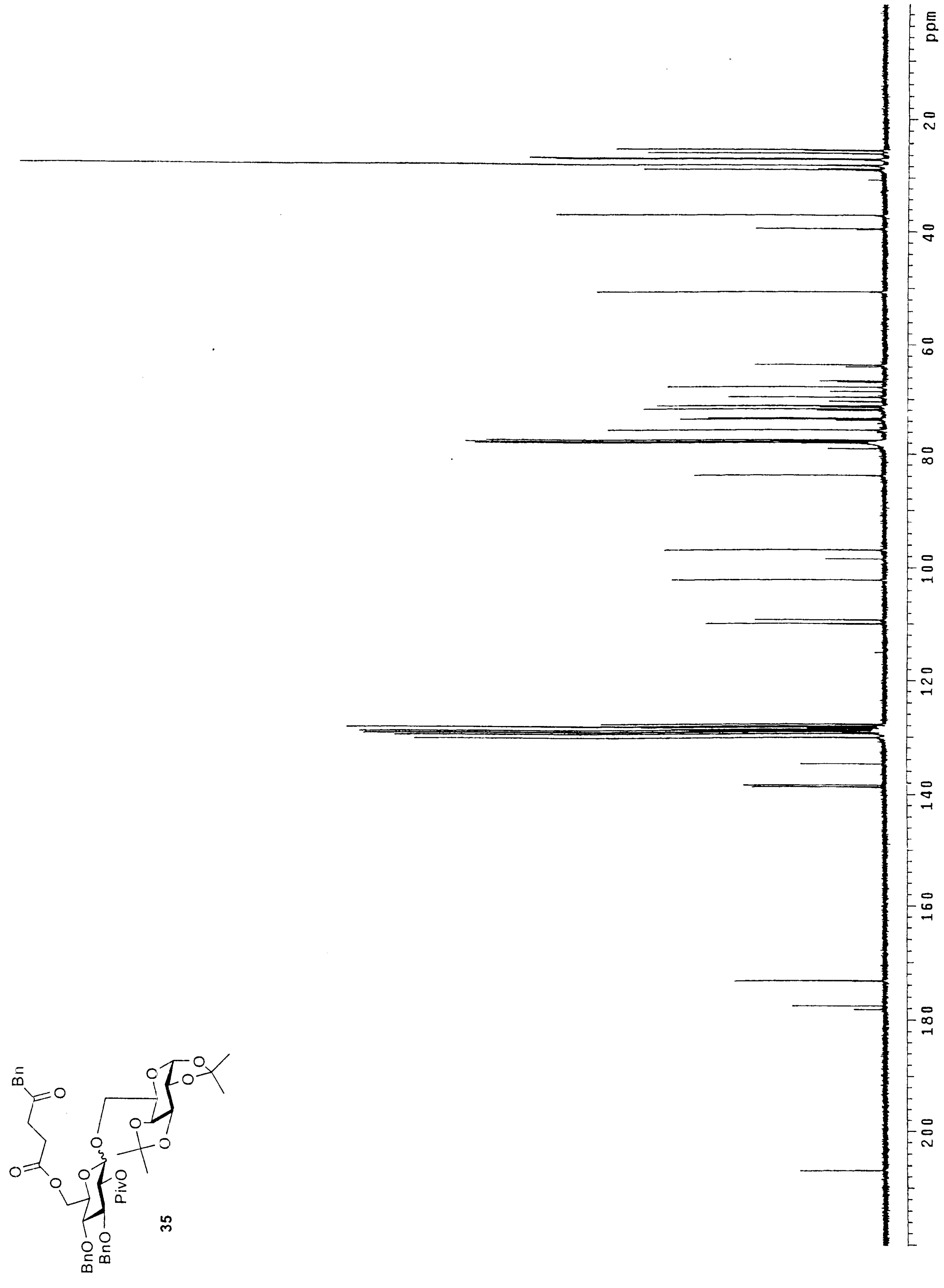
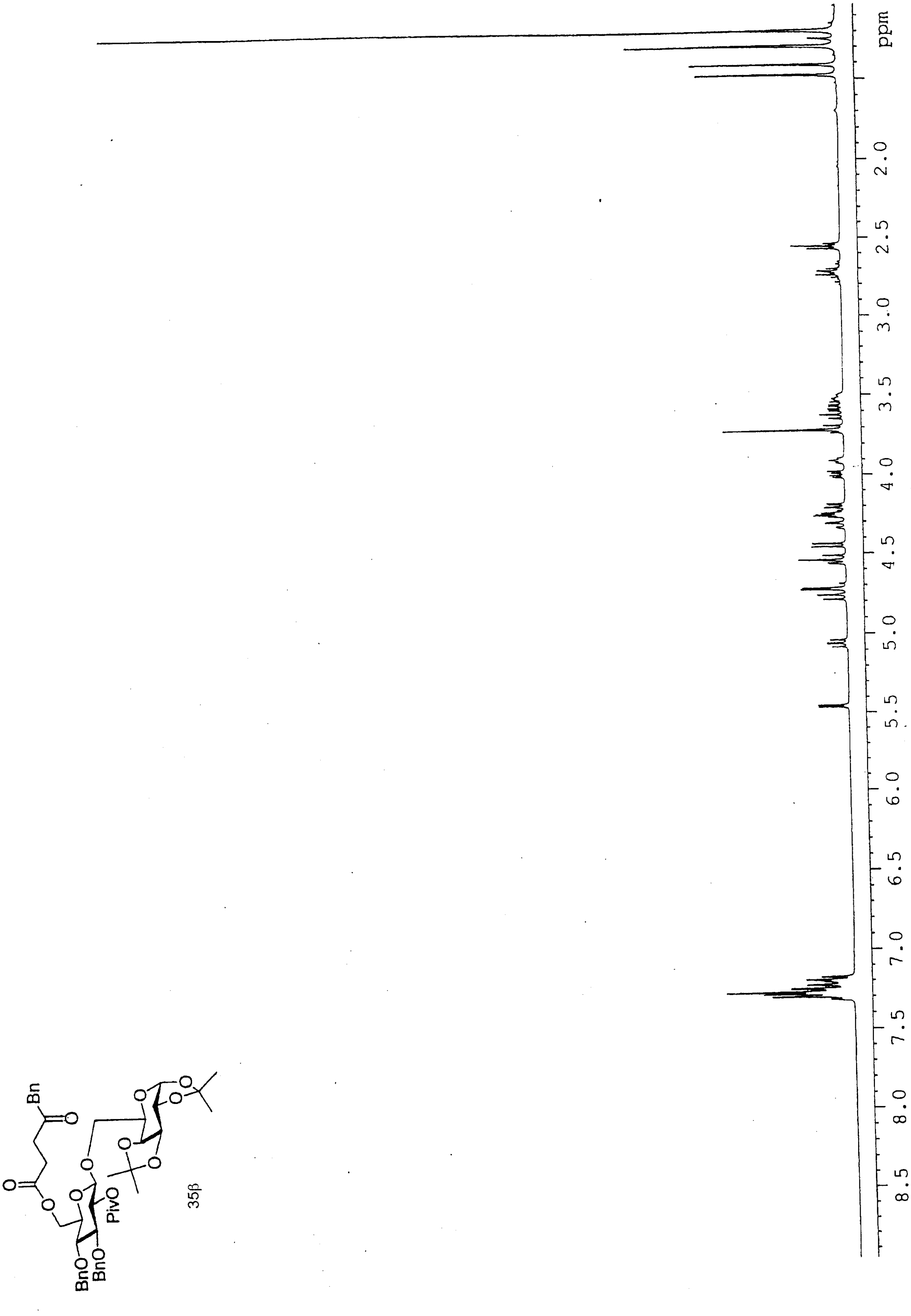
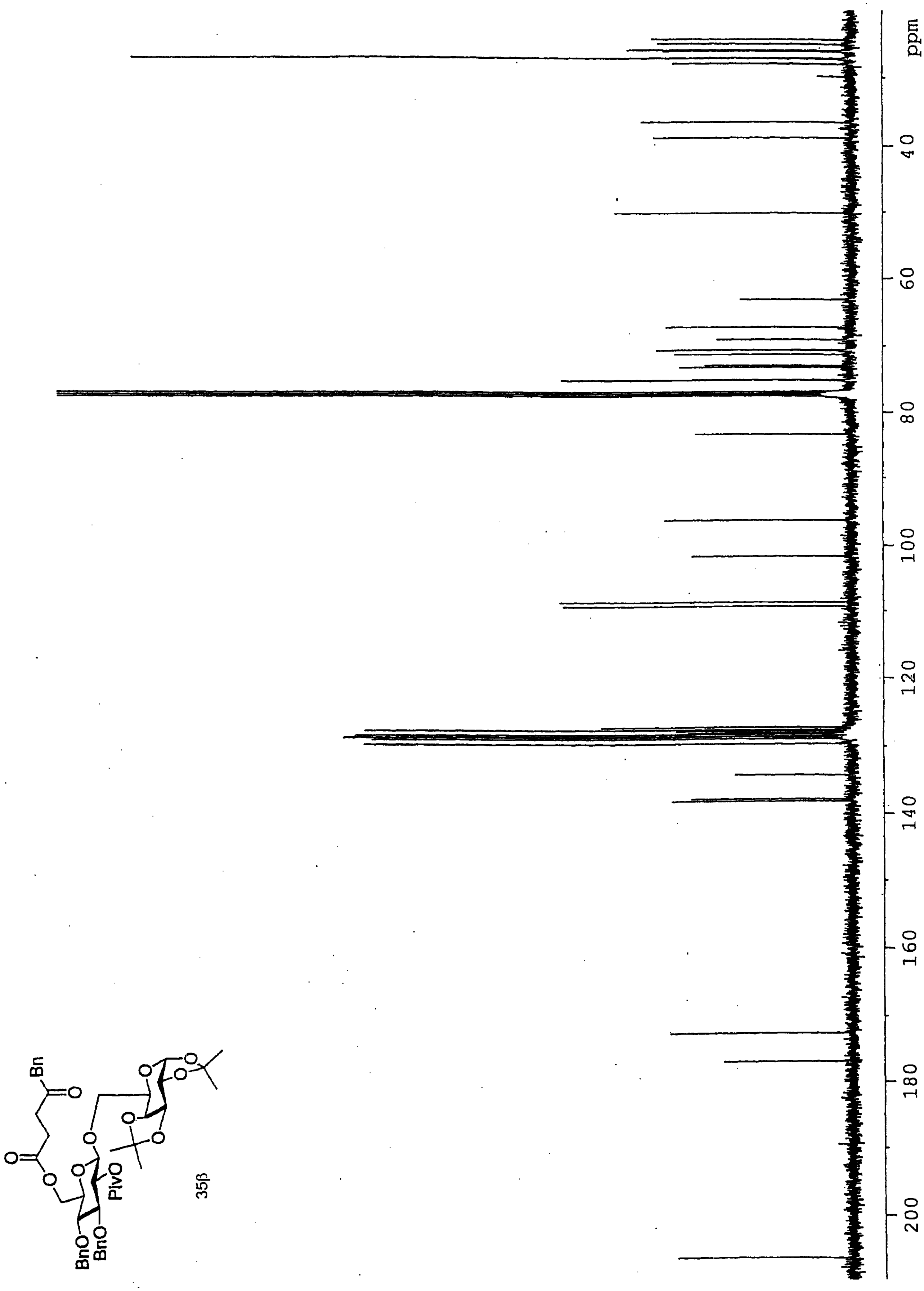


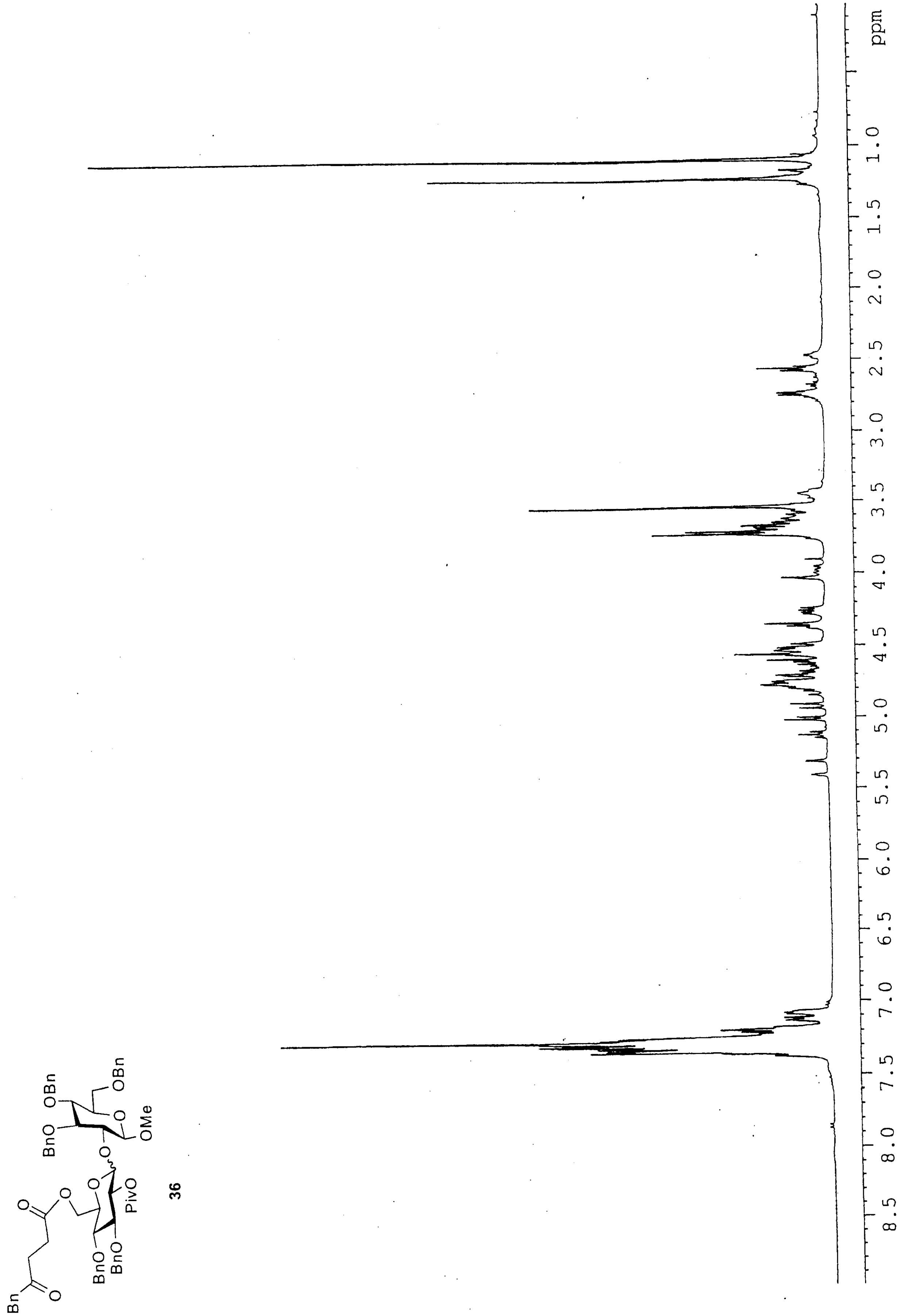
35



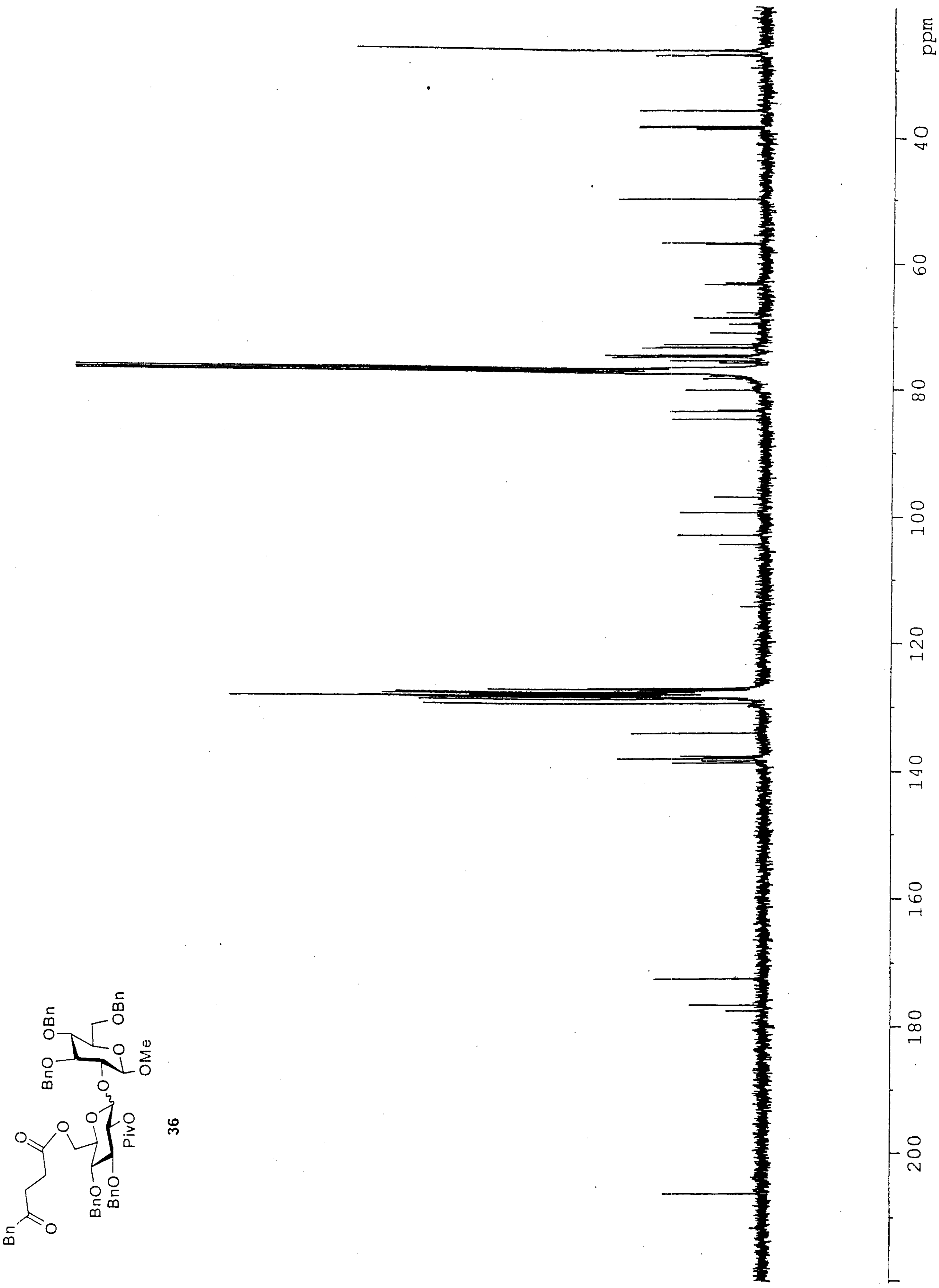
35β



35β


36

Bn
O
O
O
BnO
BnO
PivO
O
O
BnO
OBn
OBn
O
OMe
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5


ppm
40
60
80
100
120
140
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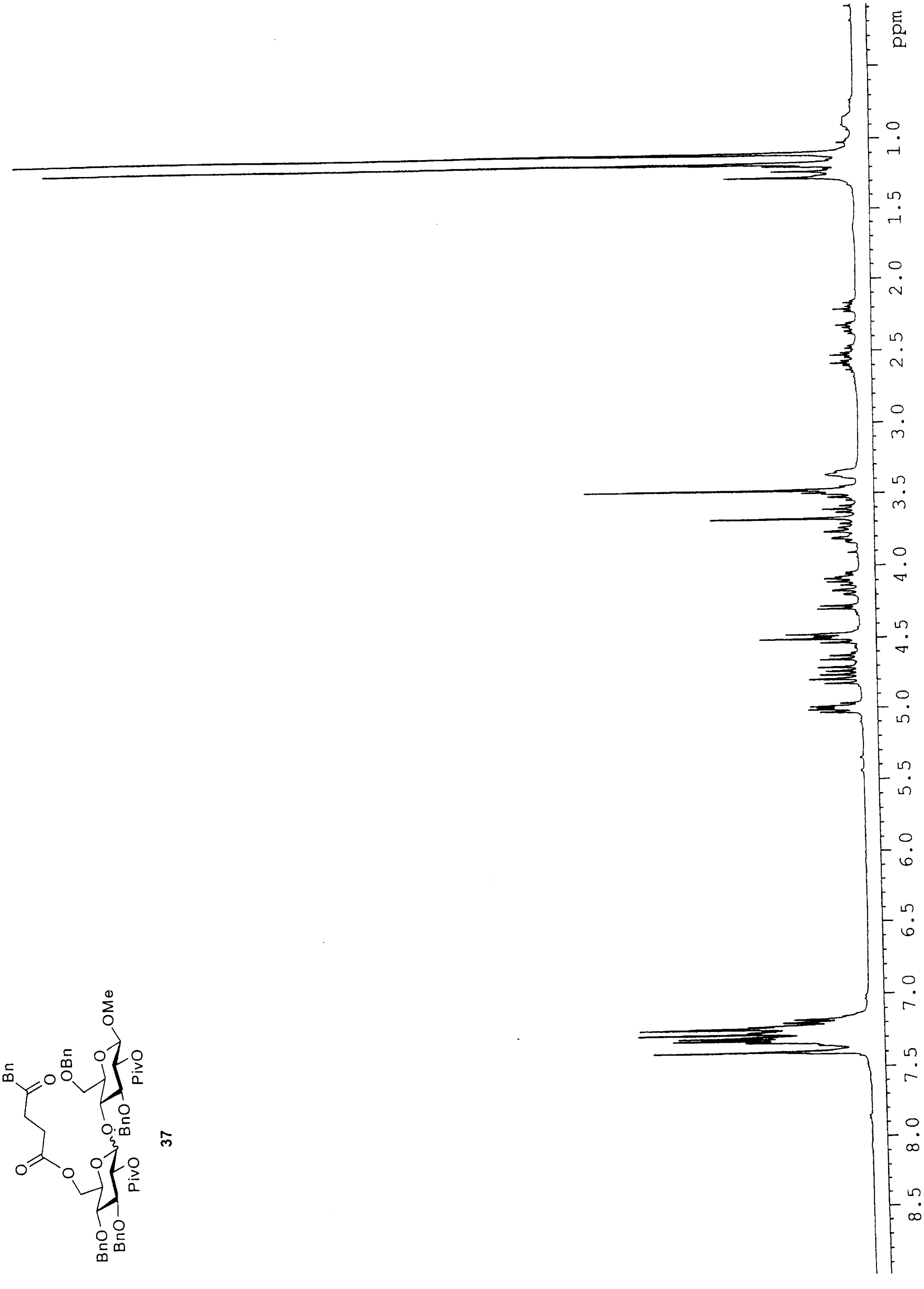
180
200
Bn
O
BnO
BnO
PivO
O
BnO
OBn
OBn
OMe

36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2.5
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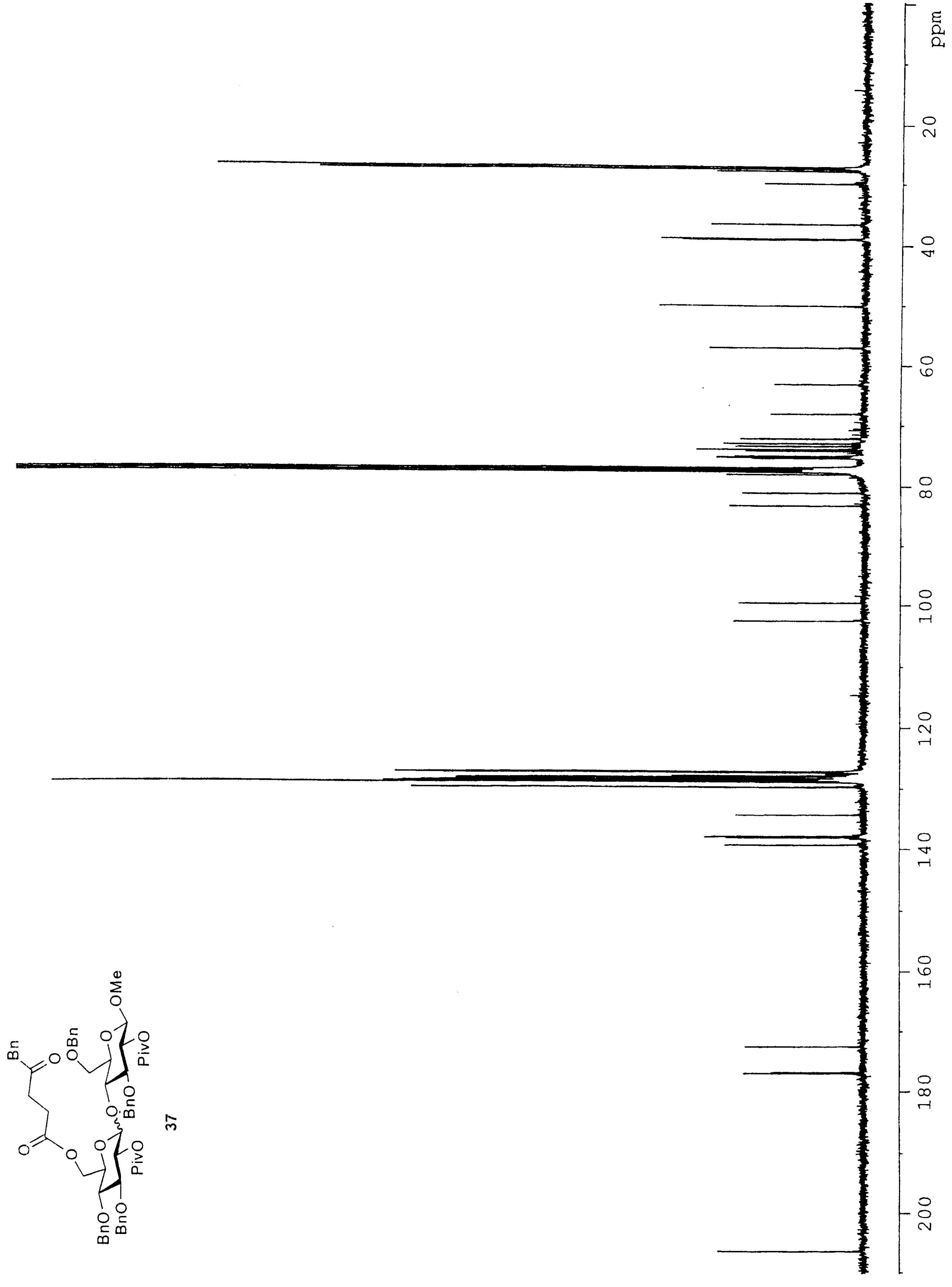
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
Bn
O
O
OBn
OMe
BnO
BnO
PivO
BnO
PivO

37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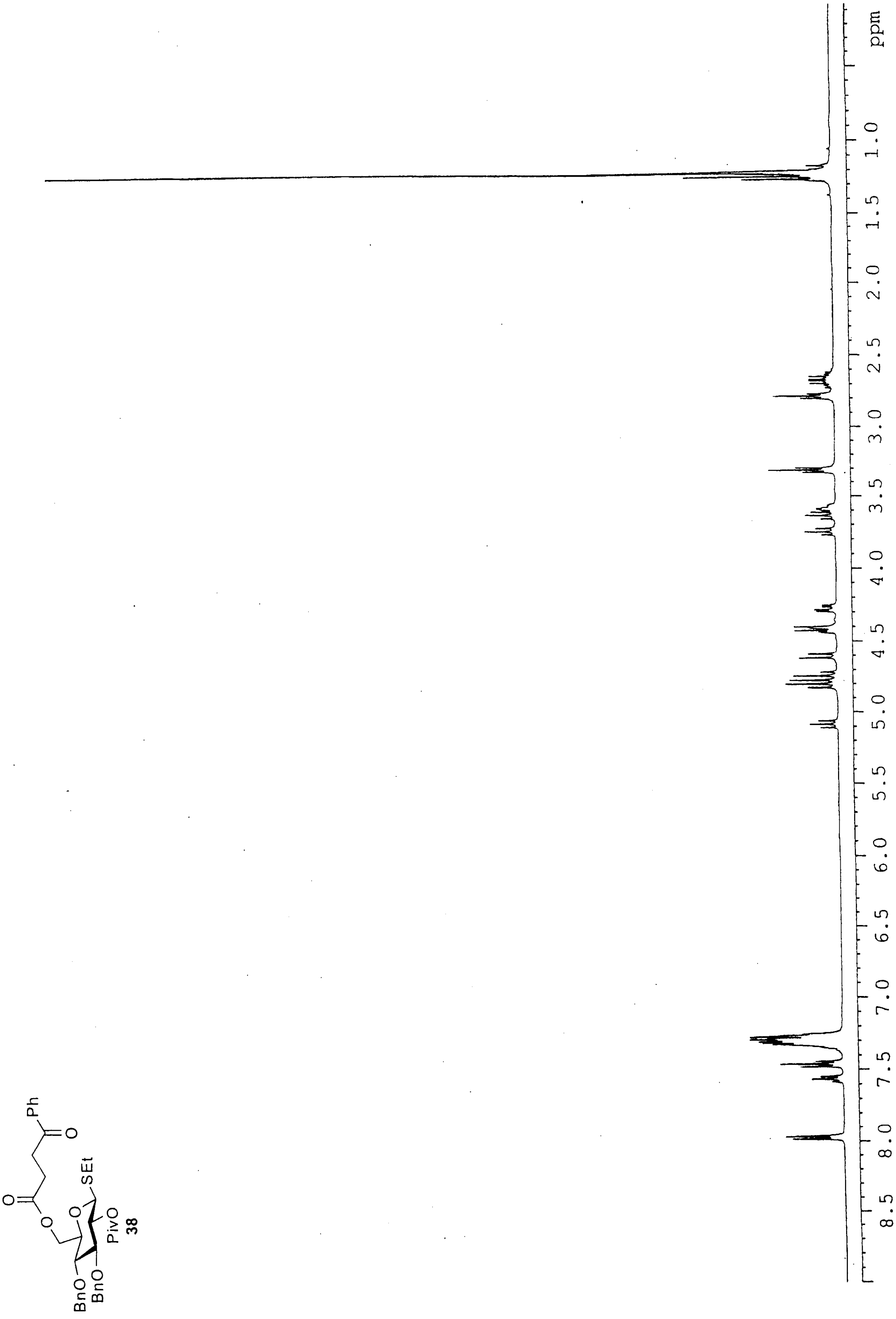
60
80
100
120
140
160
180
200
Bn
O
OBn
OMe
O
O
O
BnO
BnO
PivO
O
O
BnO
PivO
37


Ph
O
O
O
O
SEt
PivO
BnO
BnO

38

ppm
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1.5
2.0
2.5
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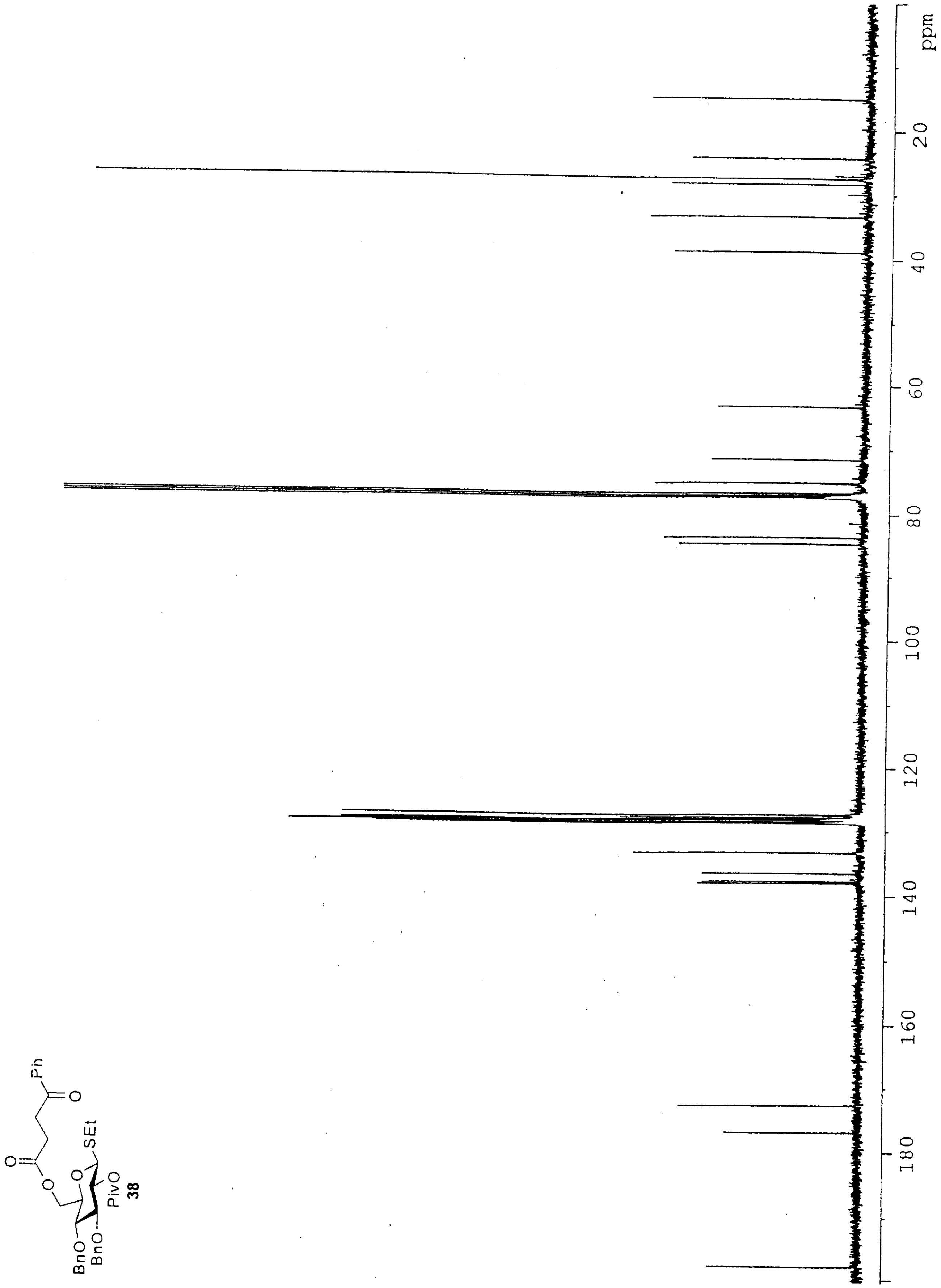
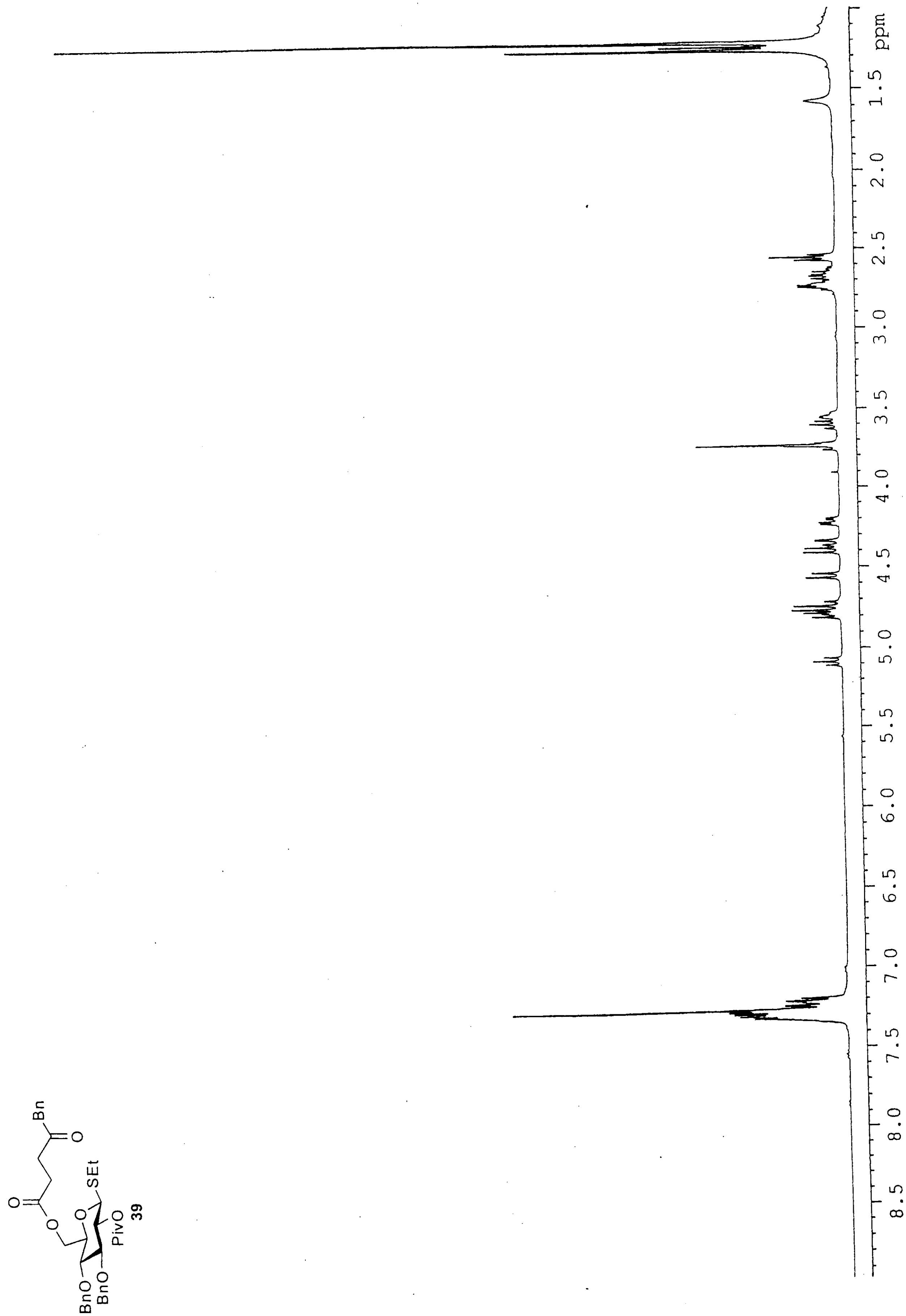
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5



38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2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
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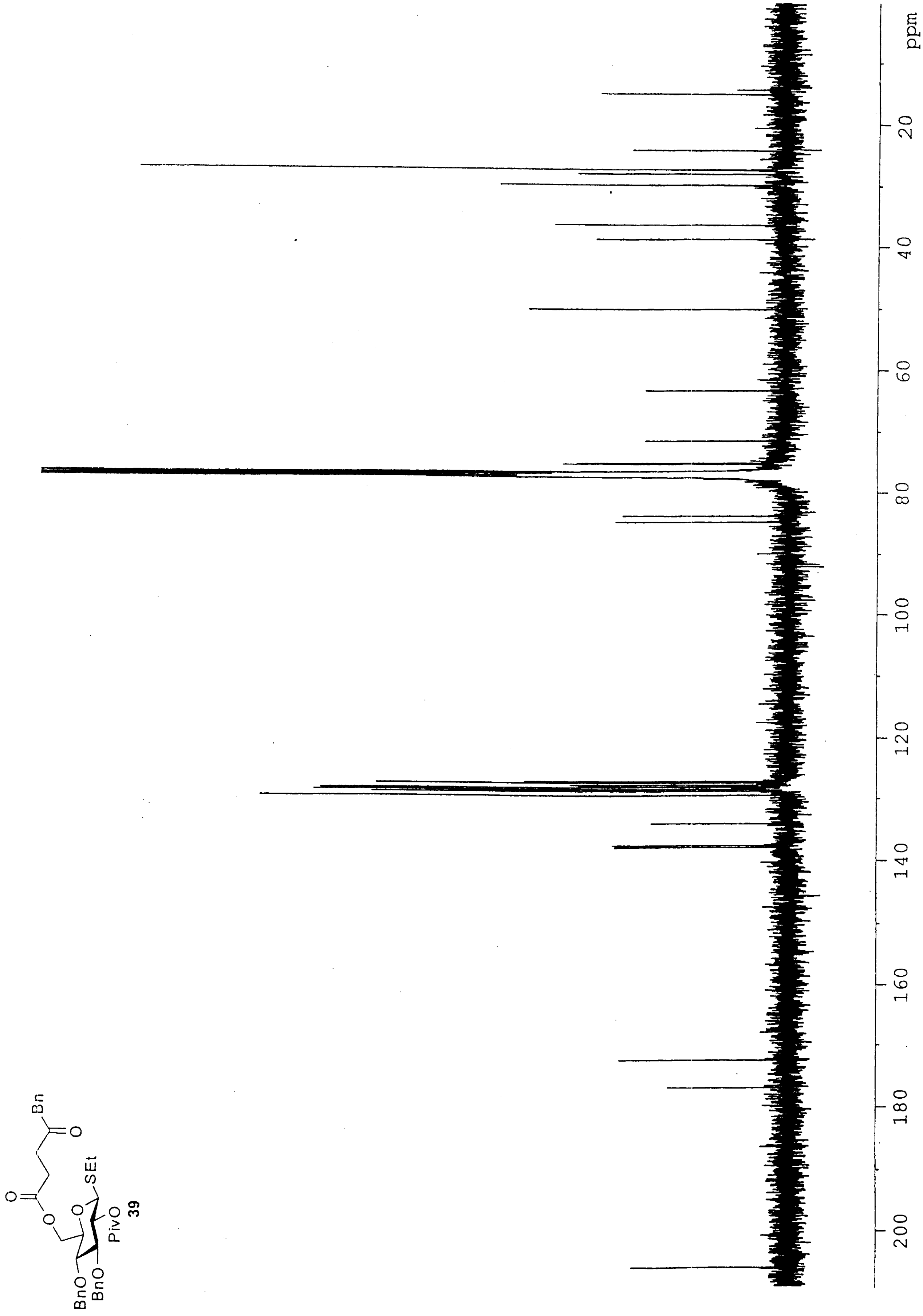
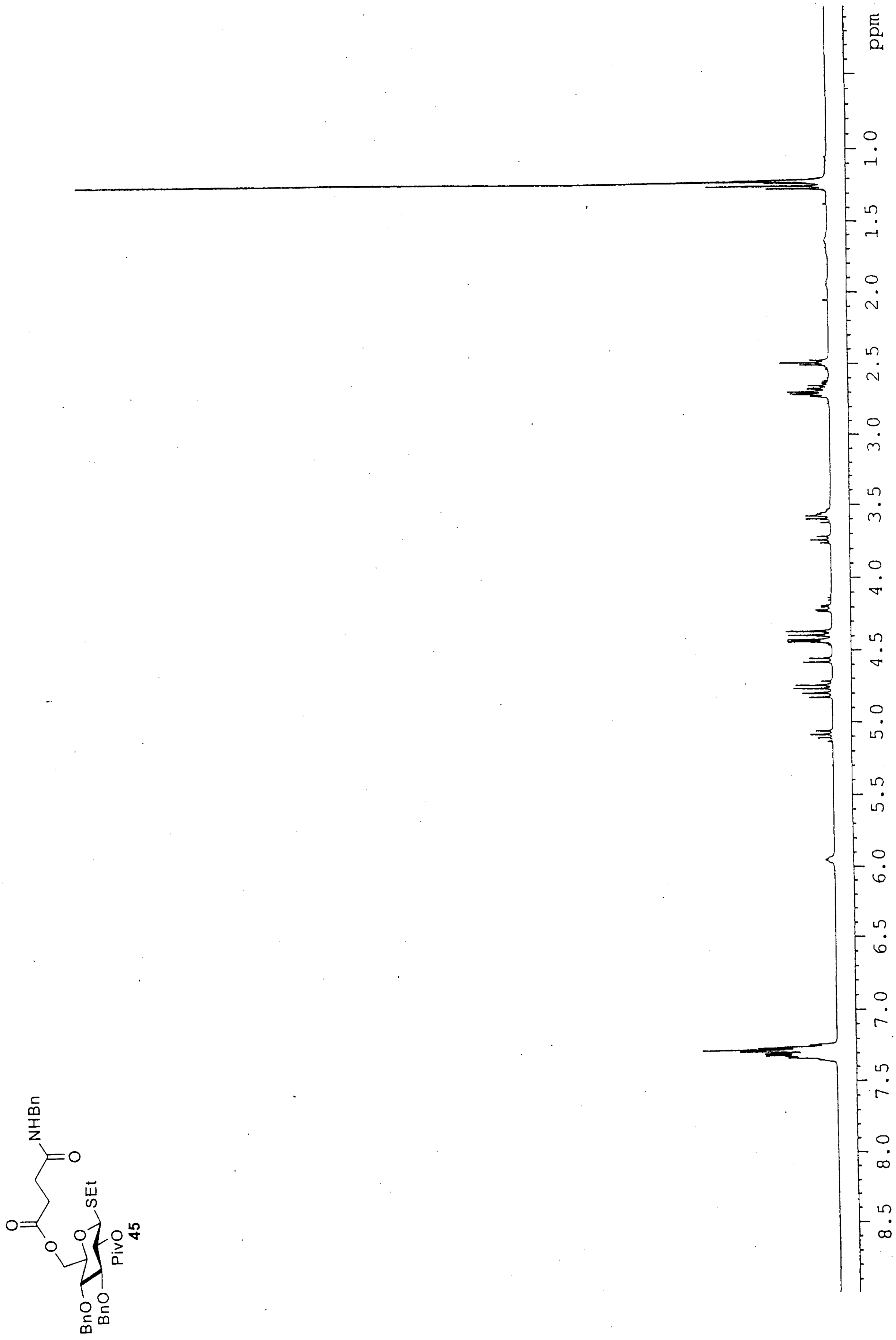
7.0
7.5
8.0
8.5
BnO
BnO
PivO
SEt
O
O
O
Bn

39



BnO
BnO
PivO
SEt
O
O
O
O
Bn
39
ppm
20
40
60
80
100
120
140
160
180
200


BnO
BnO
PivO
SEt
O
O
O
O
NHBn
O
ppm
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1.5
2.0
2.5
3.0
3.5
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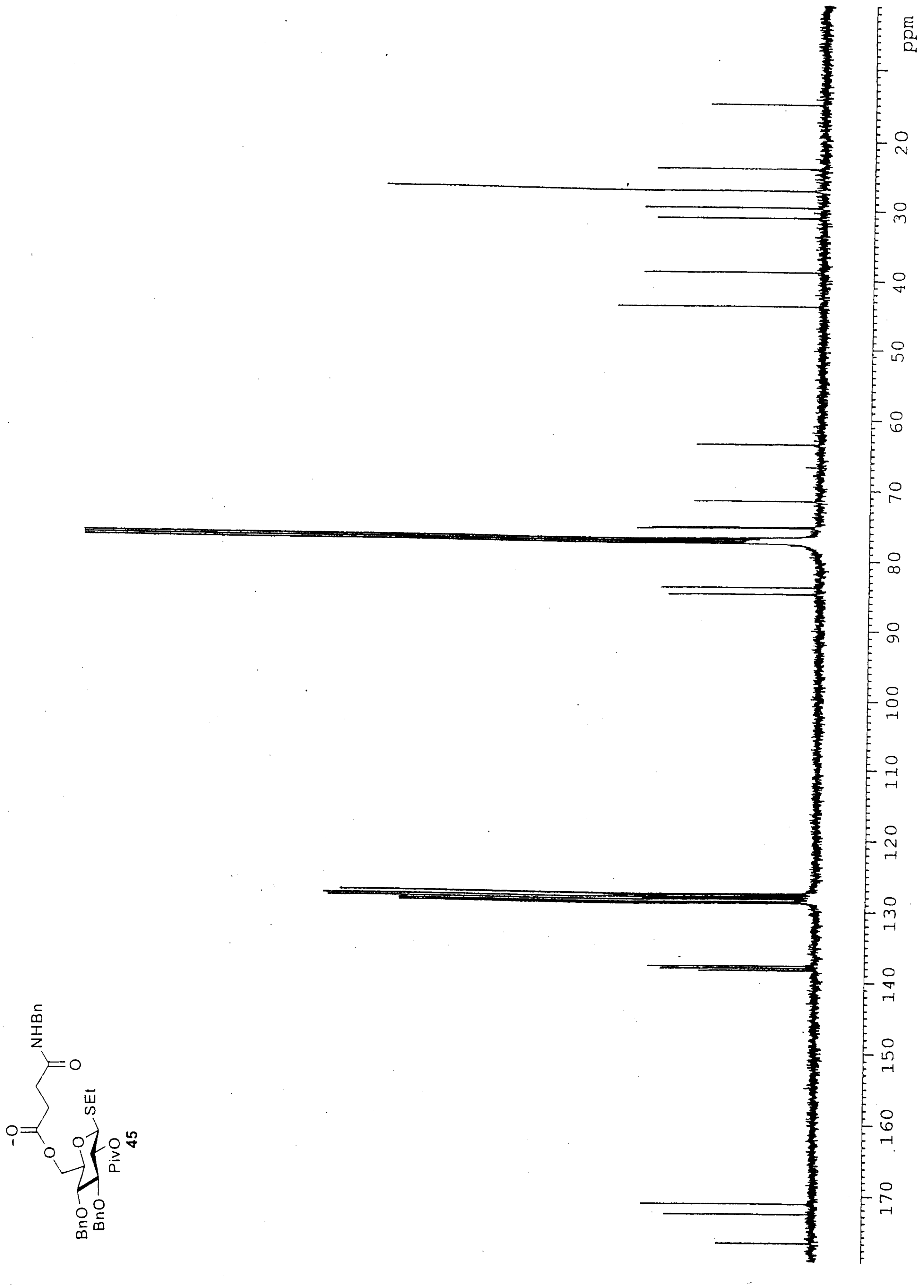
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5

45


NHBn
O
O
O
O
SEt
BnO
BnO
PivO
45
ppm
20
30
40
50
60
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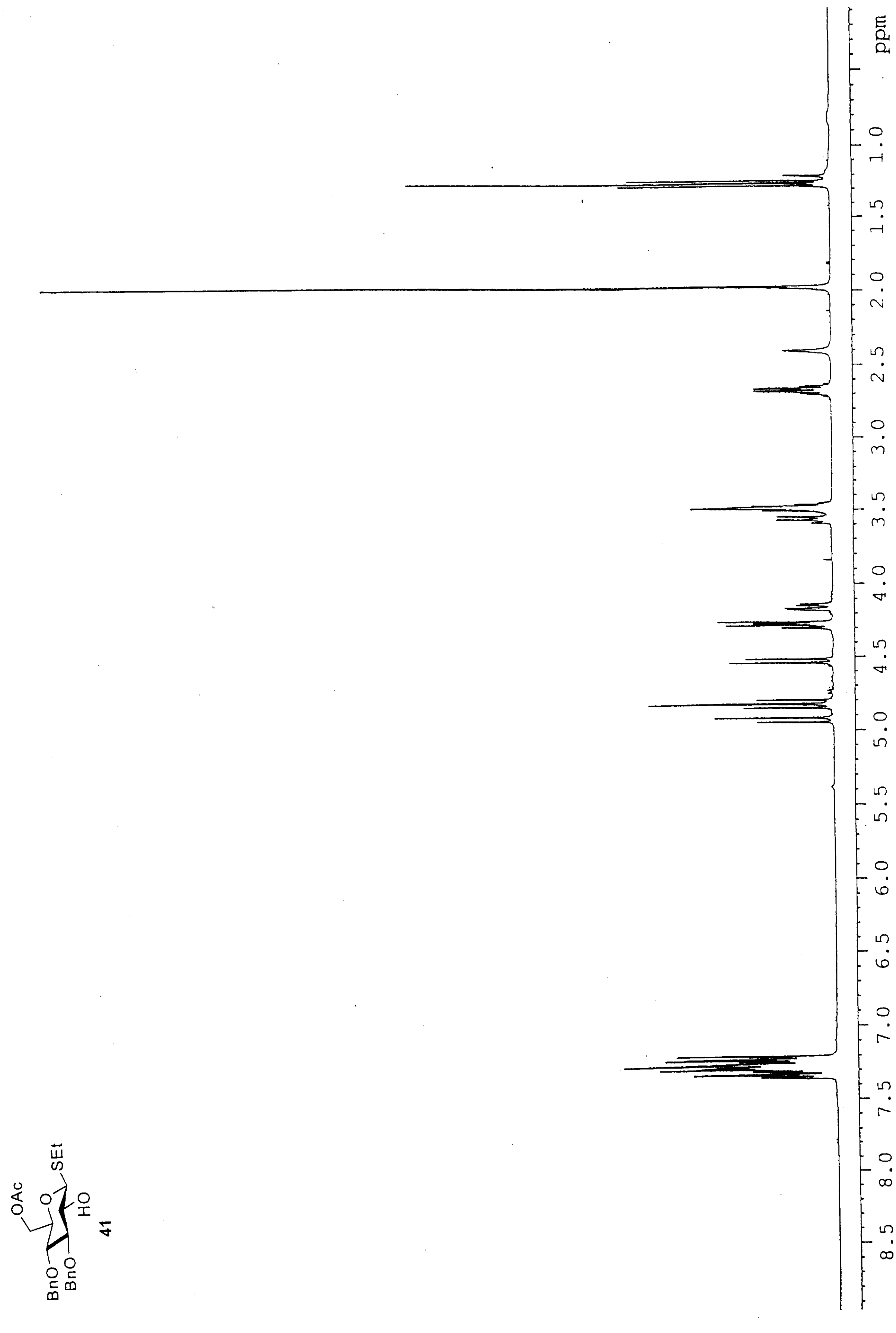
120
130
140
150
160
170


OAc
O
SEt
BnO
BnO
HO
41
ppm
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2.5
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3.5
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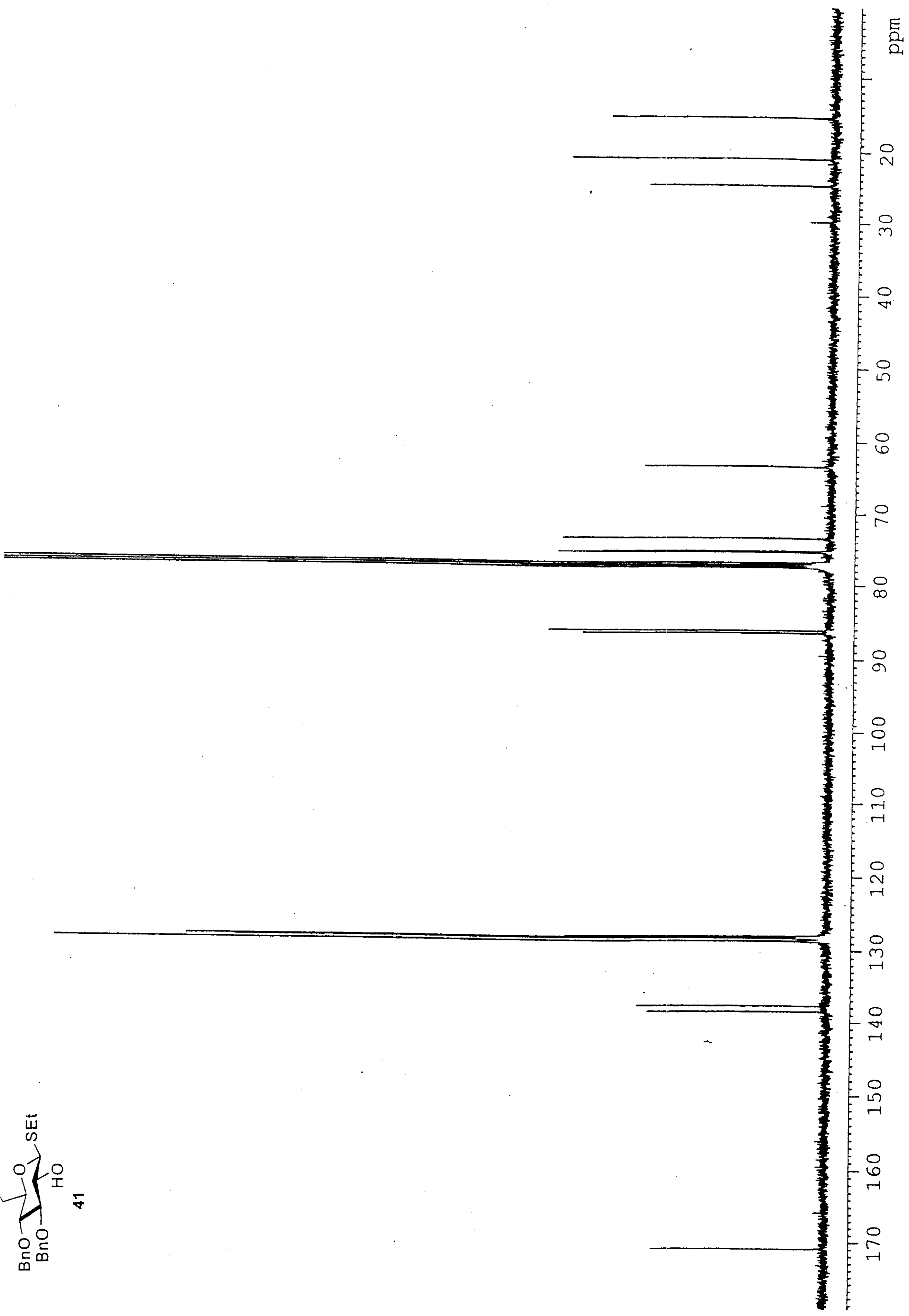
7.0
7.5
8.0
8.5


OAc
O
SEt
HO
BnO
BnO
ppm
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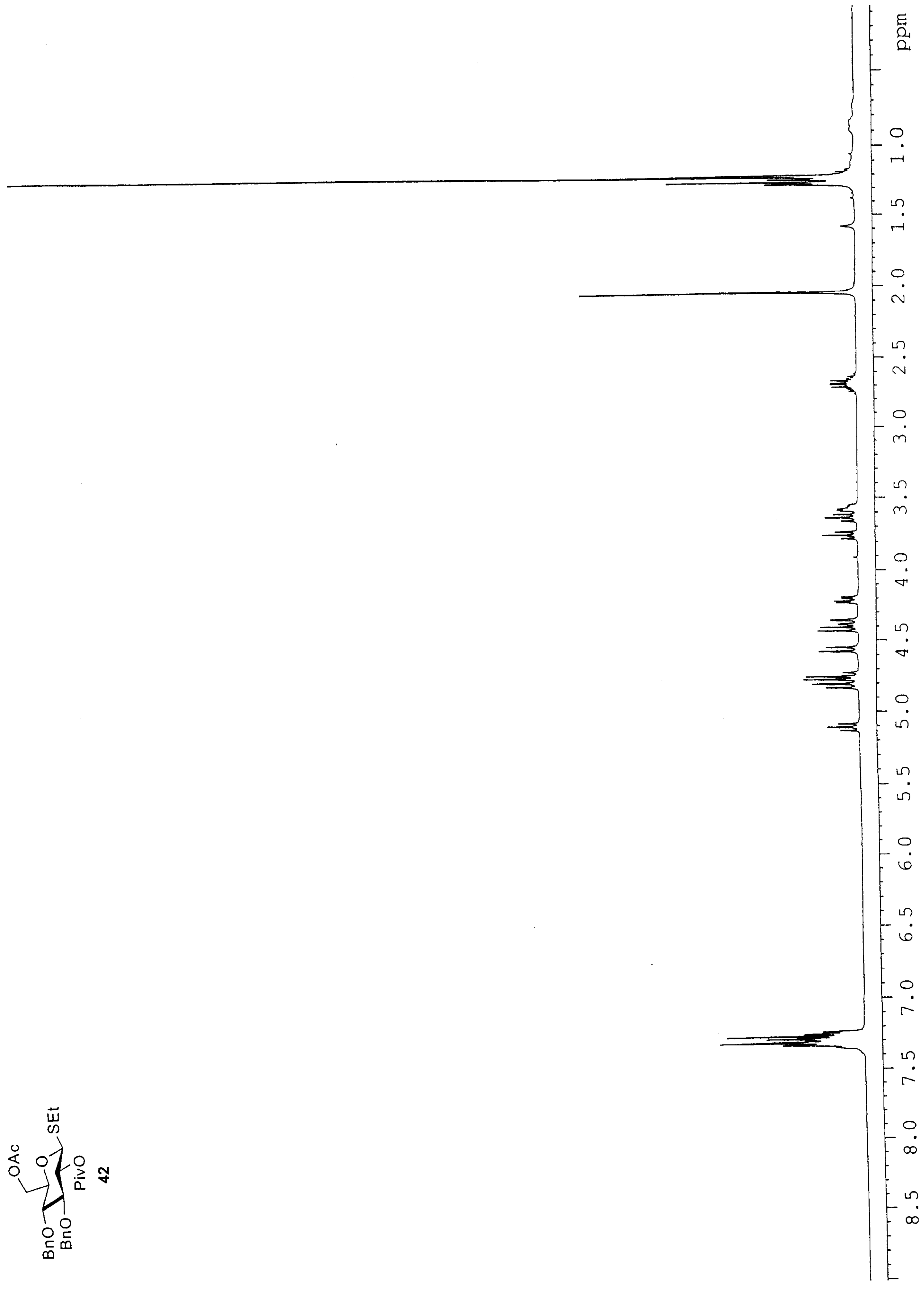
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

41



OAc
O
SEt
BnO
BnO
PivO
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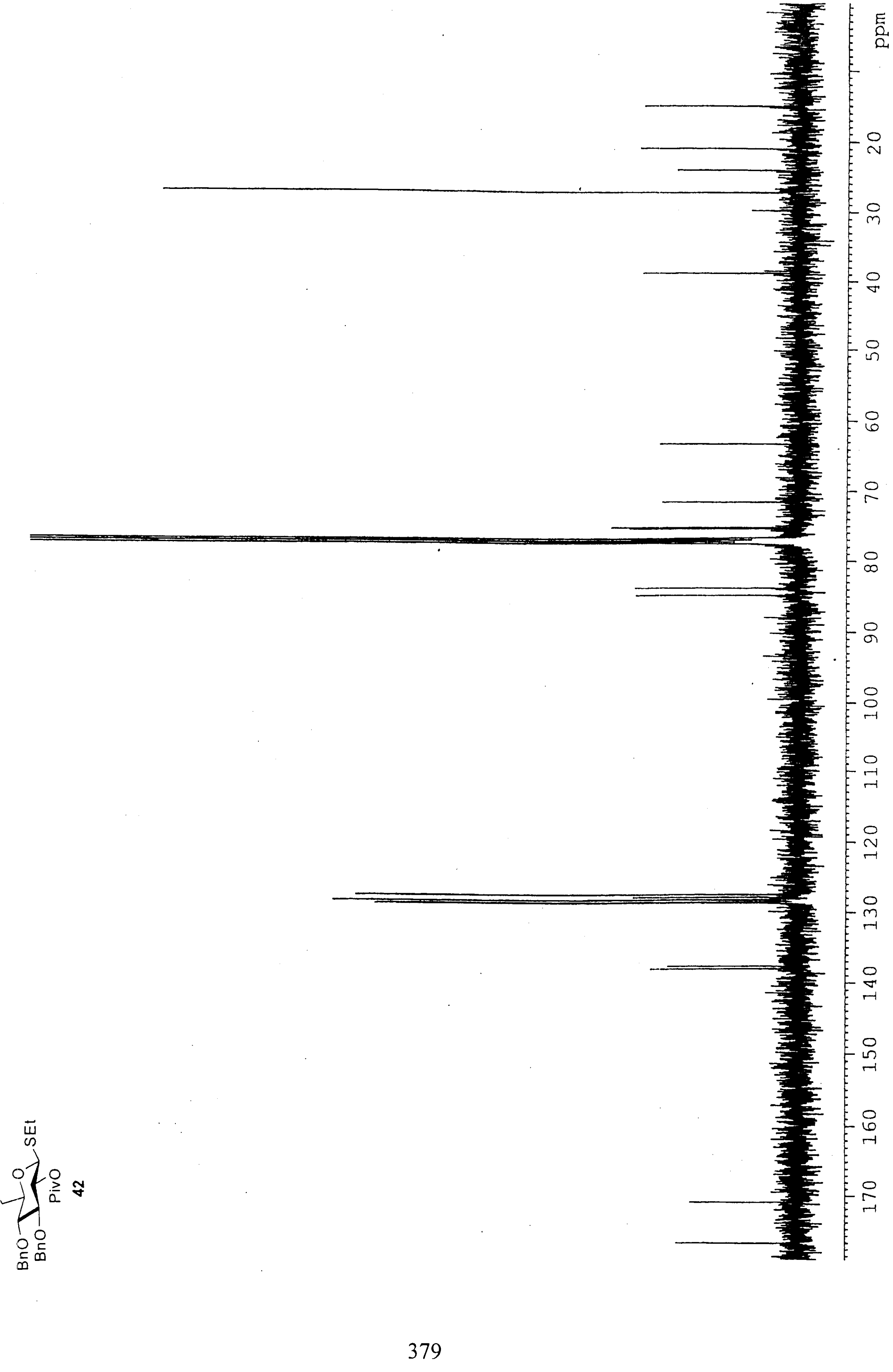
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

42


OAc
SEt
BnO
BnO
PivO
ppm
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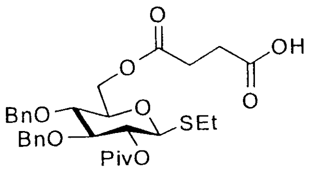
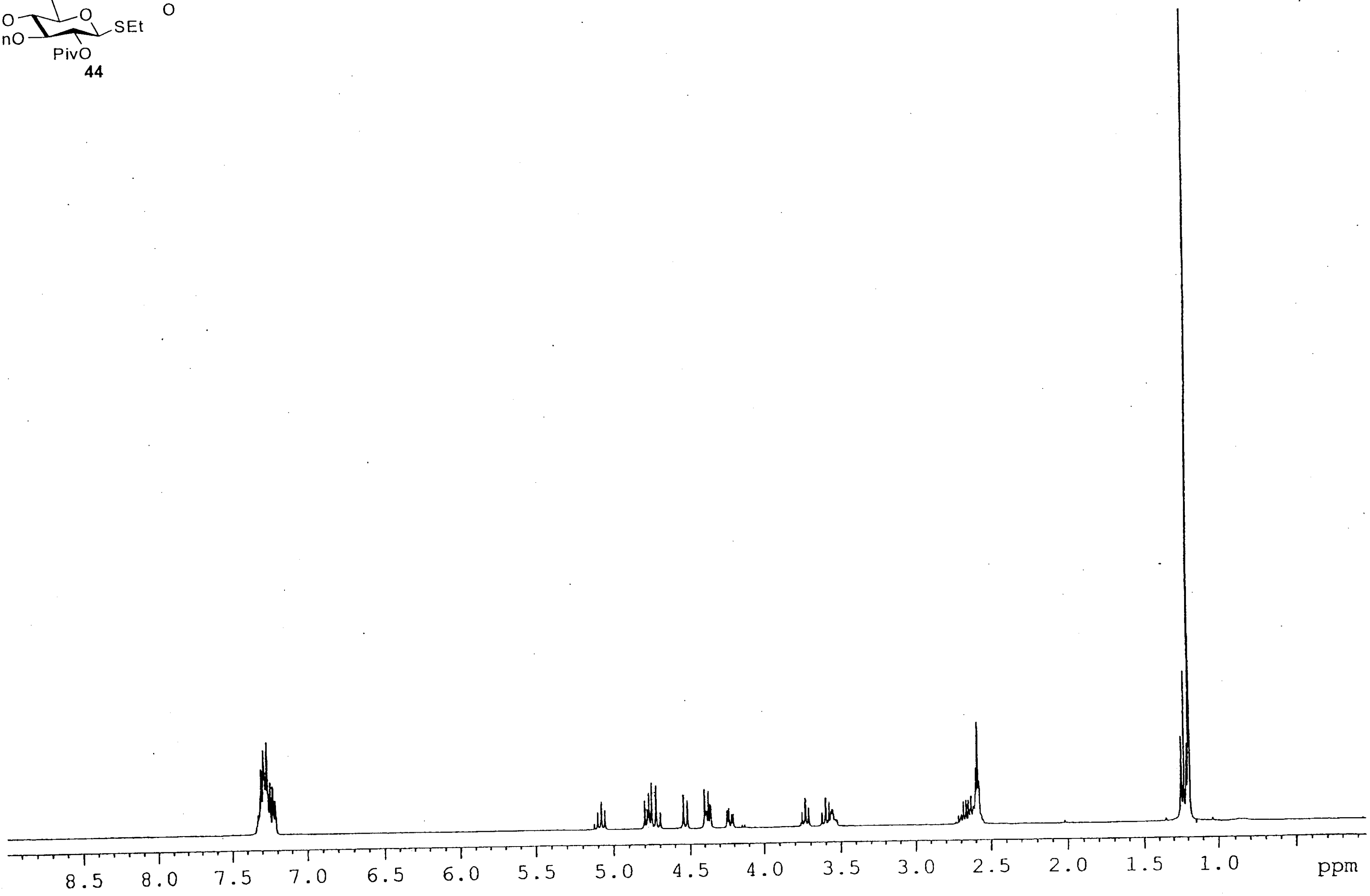
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

42


O
O
OH
O
BnO
BnO
O
SEt
PivO

44


8.5
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6.5
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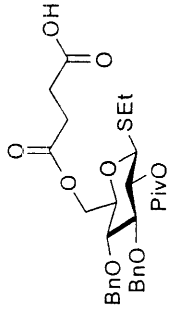
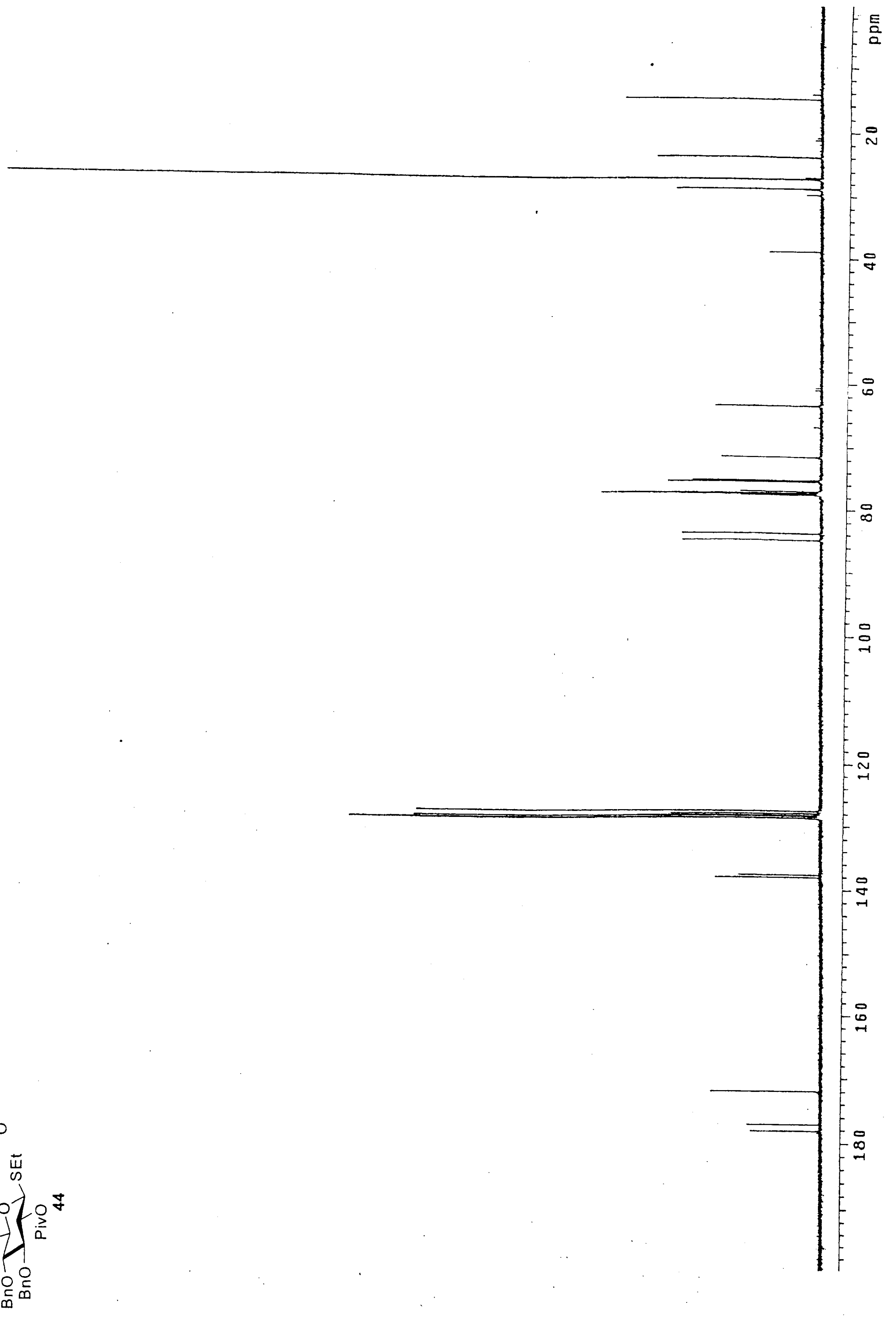
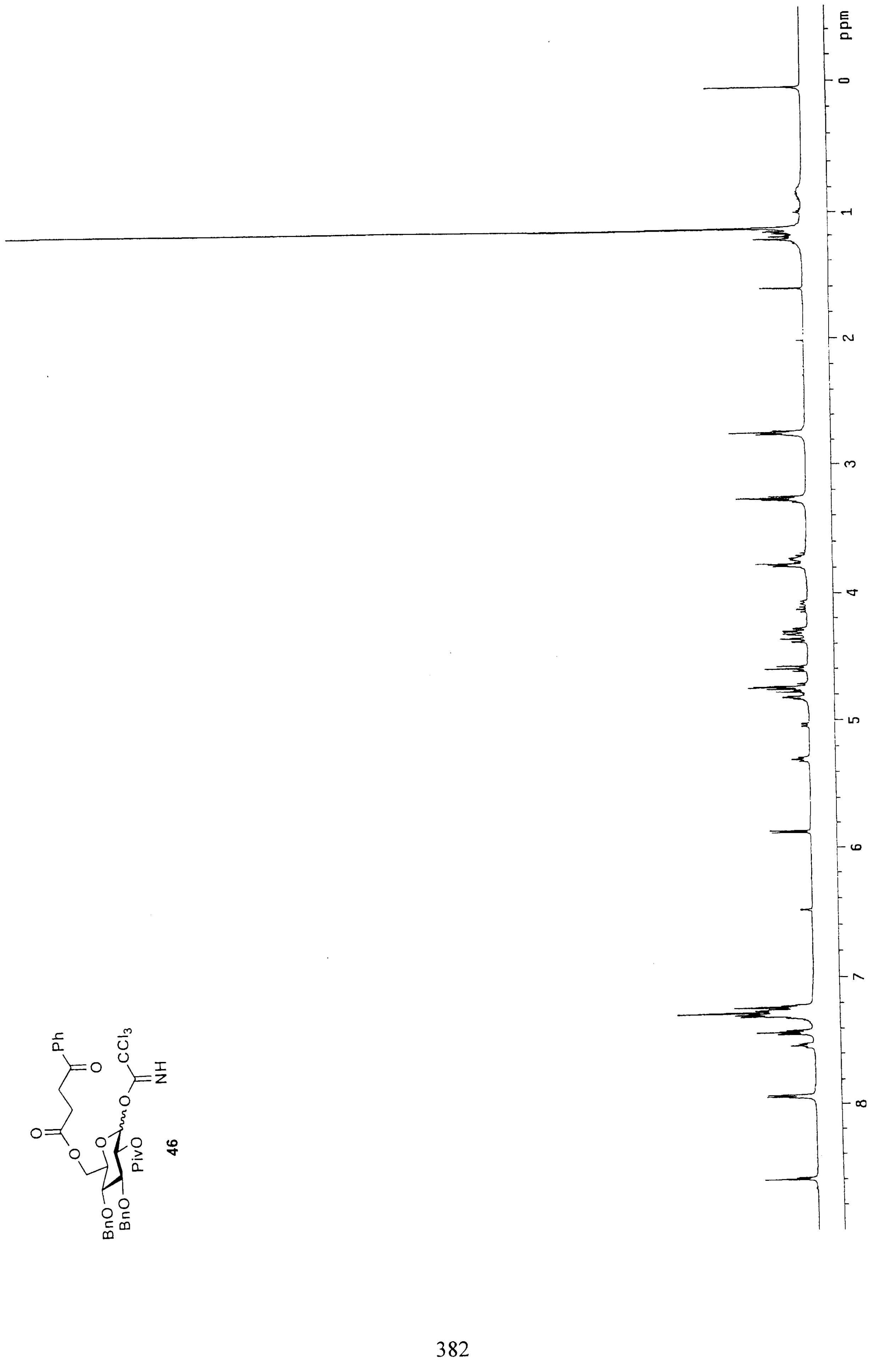
3.0
2.5
2.0
1.5
1.0
ppm

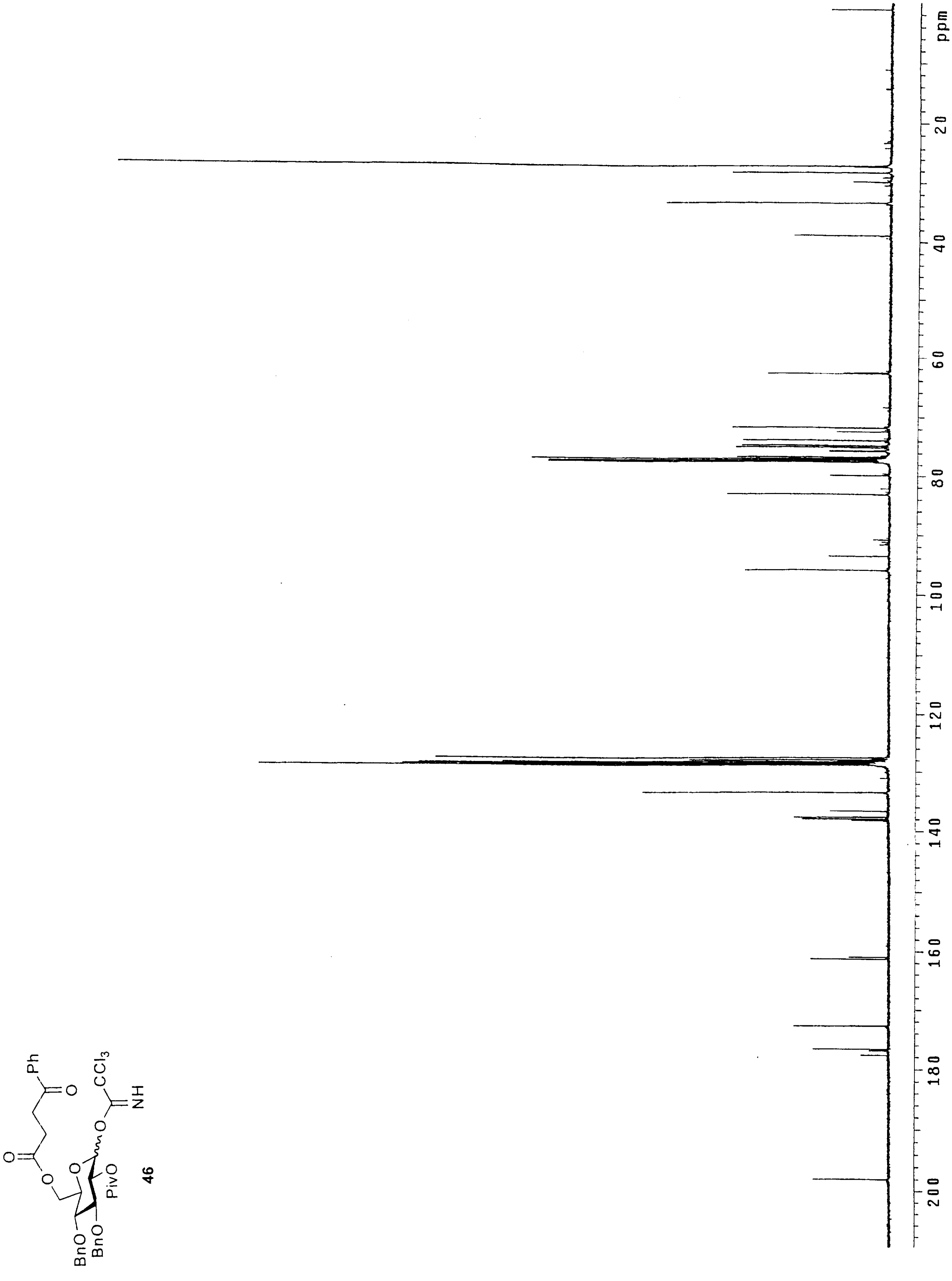


44

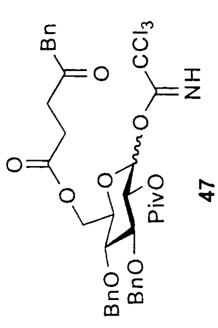




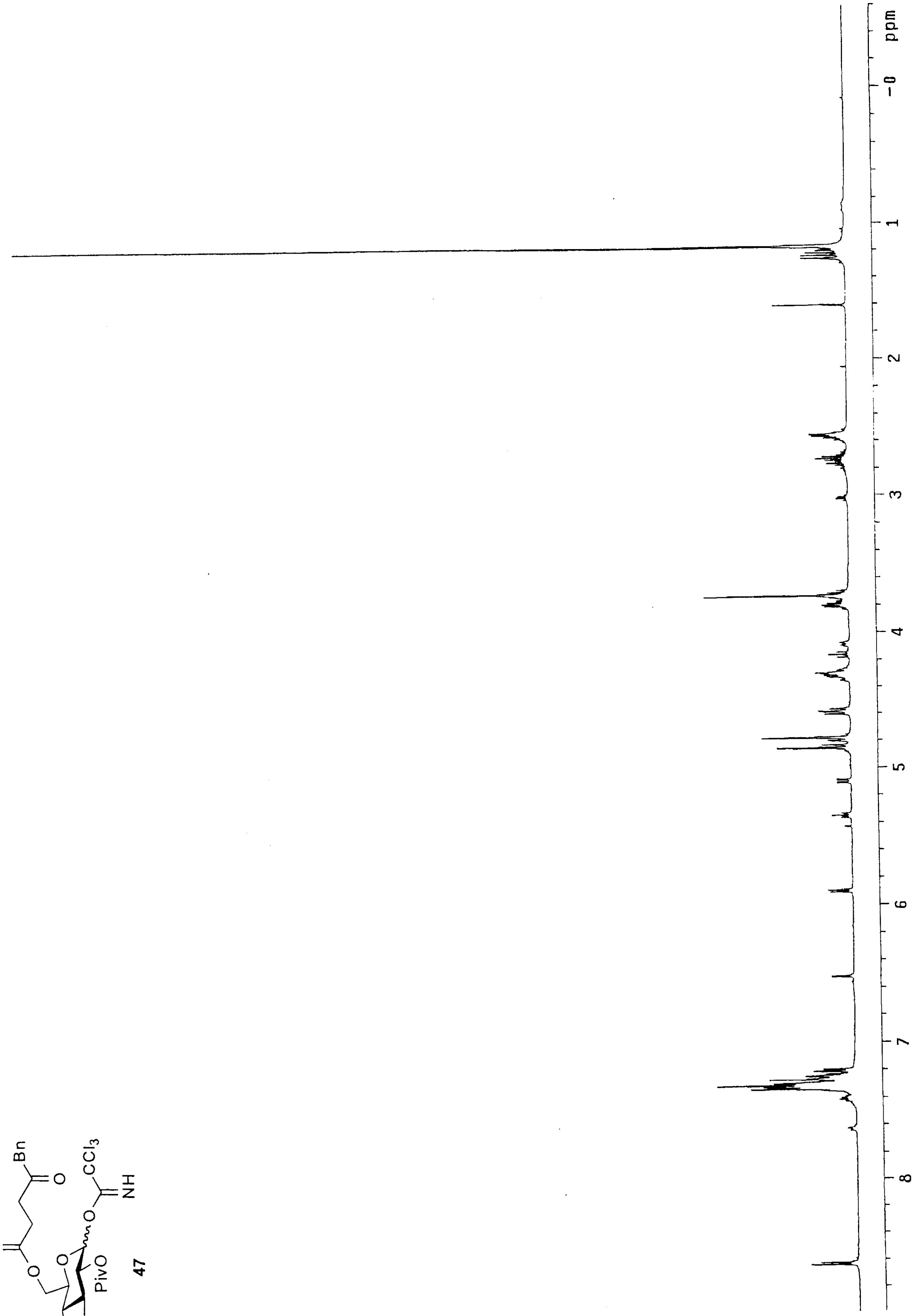
46


ppm
20
40
60
80
100
120
140
160
180
200
BnO
BnO
PivO
O
O
O
Ph
O
CCl$_3$
NH

46

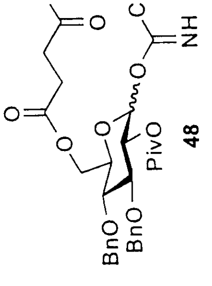


47

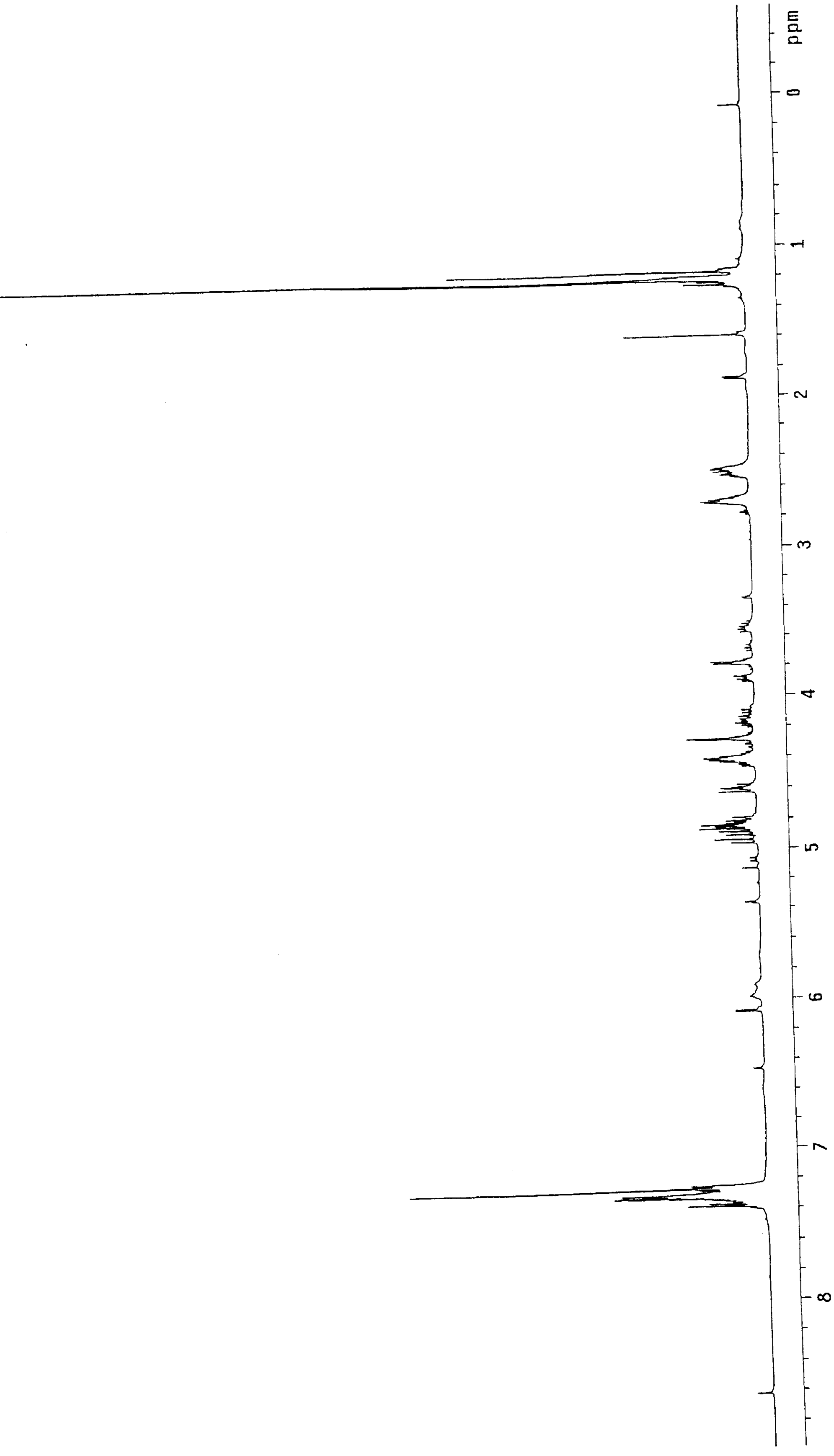


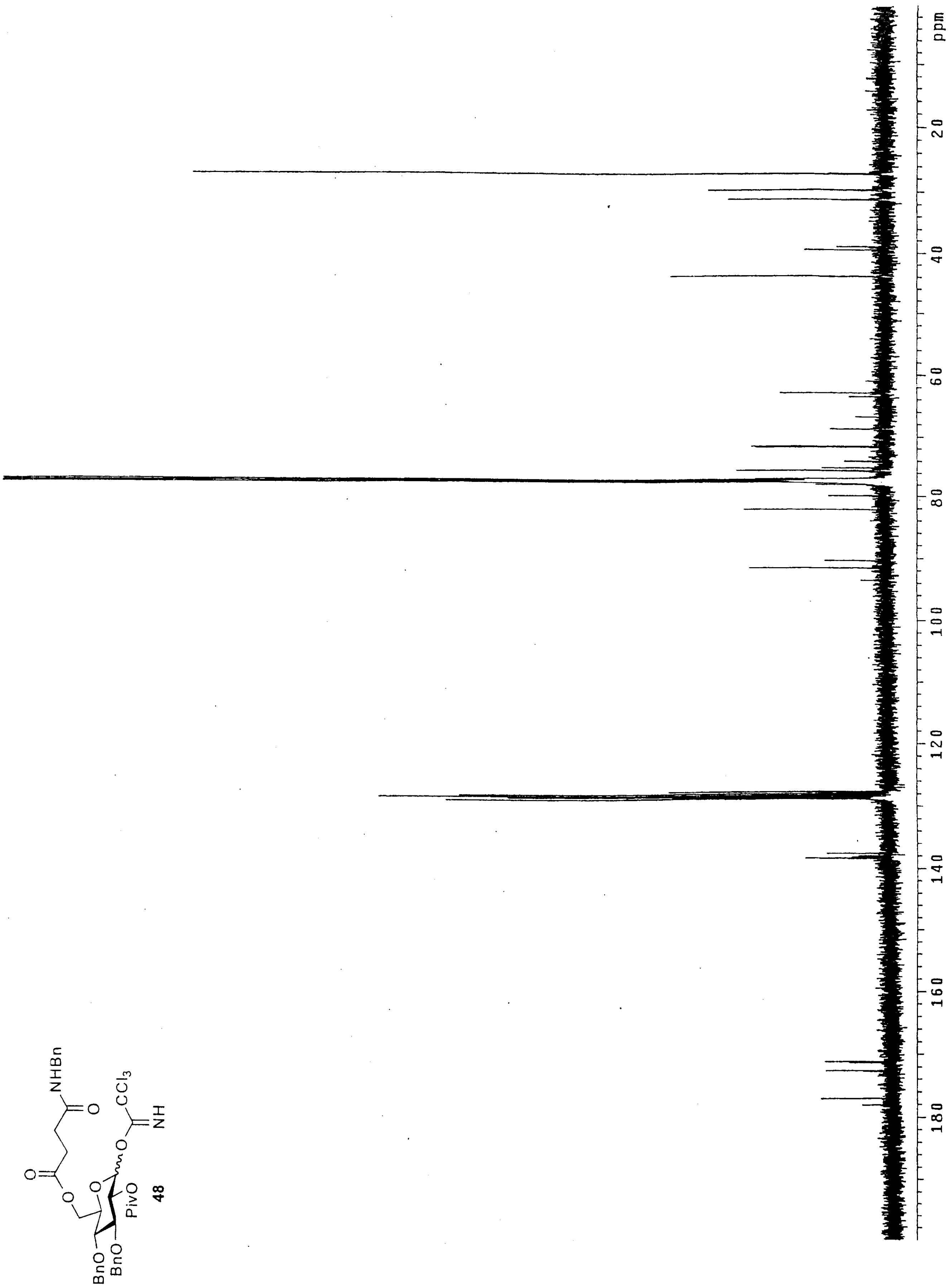

ppm
20
40
60
80
100
120
140
160
180
200
BnO
BnO
PivO
O
O
O
O
Bn
O
CCl3
NH

47



48





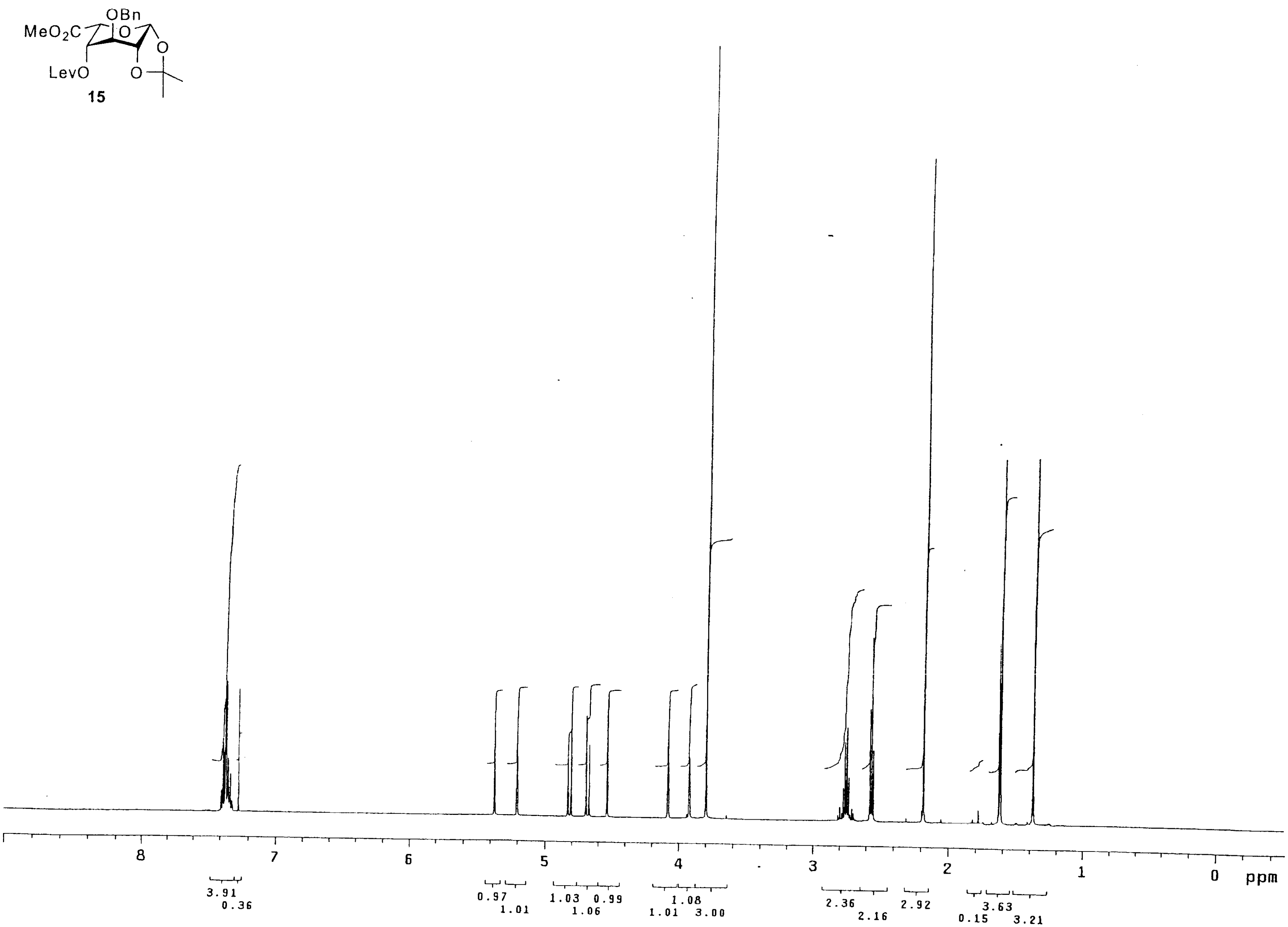
NHBn
O
O
O
O
O
BnO
BnO
PivO
O
CCl3
NH
ppm
20
40
60
80
100
120
140
160
180

48

Appendix C

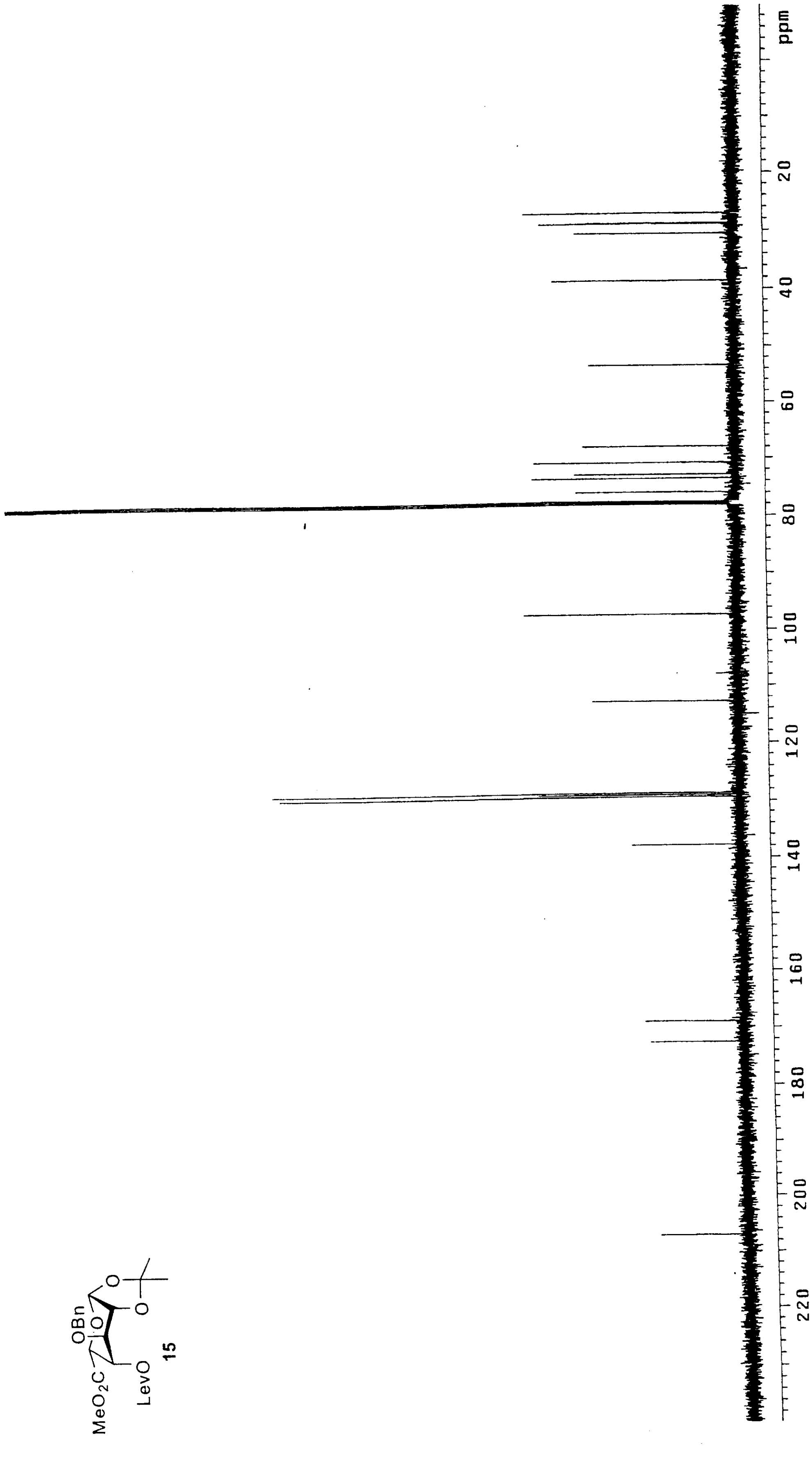
Spectra for Chapter 3

Thesis Advisor: Peter H. Seeberger

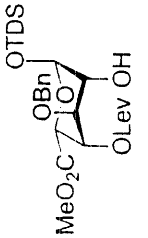


15

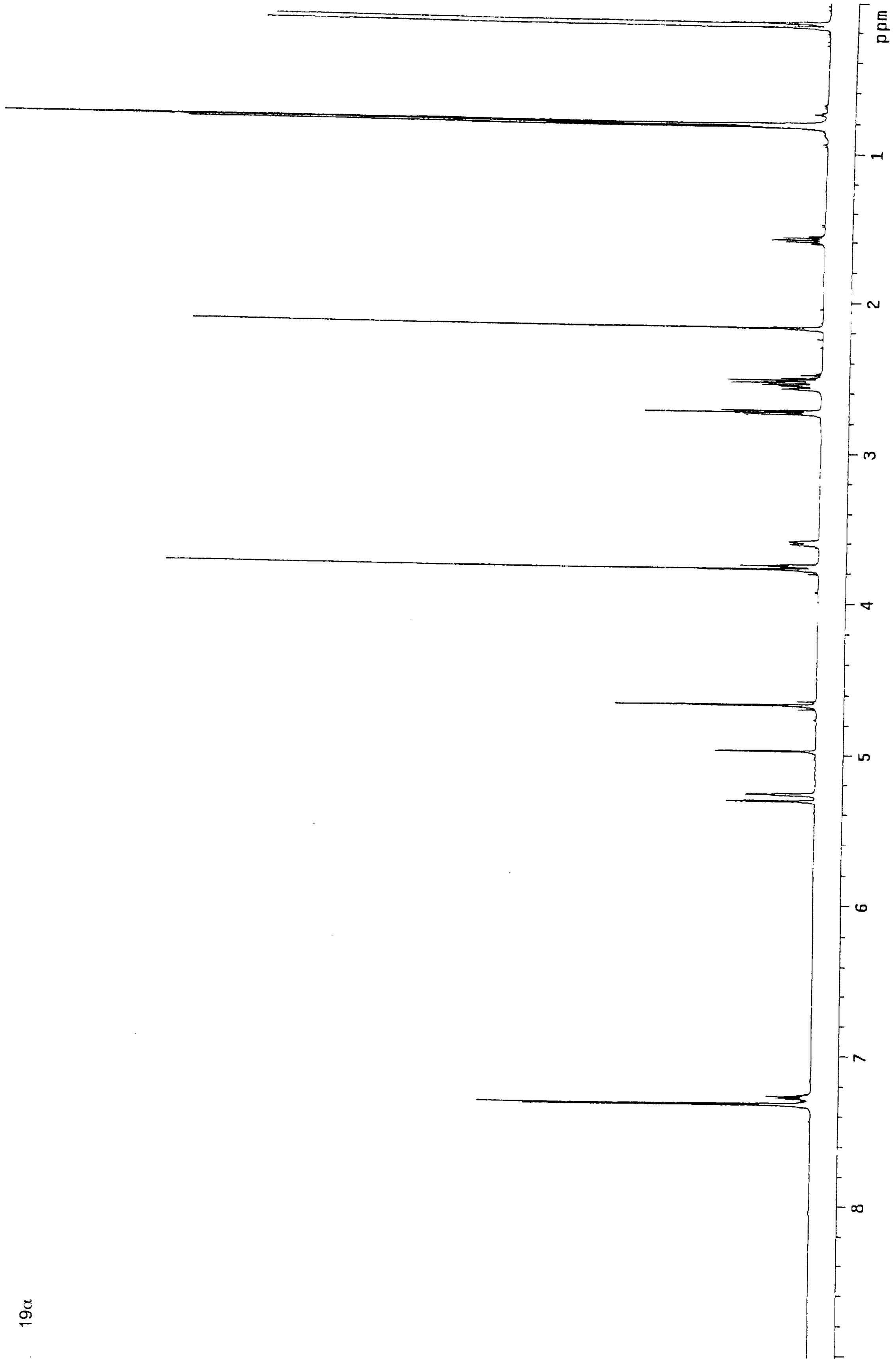
MeO₂C
OBn
O
O
LevO
O
8
7
6
5
4
3
2
1
0
ppm
3.91
0.36
0.97
1.01
1.03
1.06
0.99
1.08
1.01
3.00
2.36
2.16
2.92
0.15
3.63
3.21

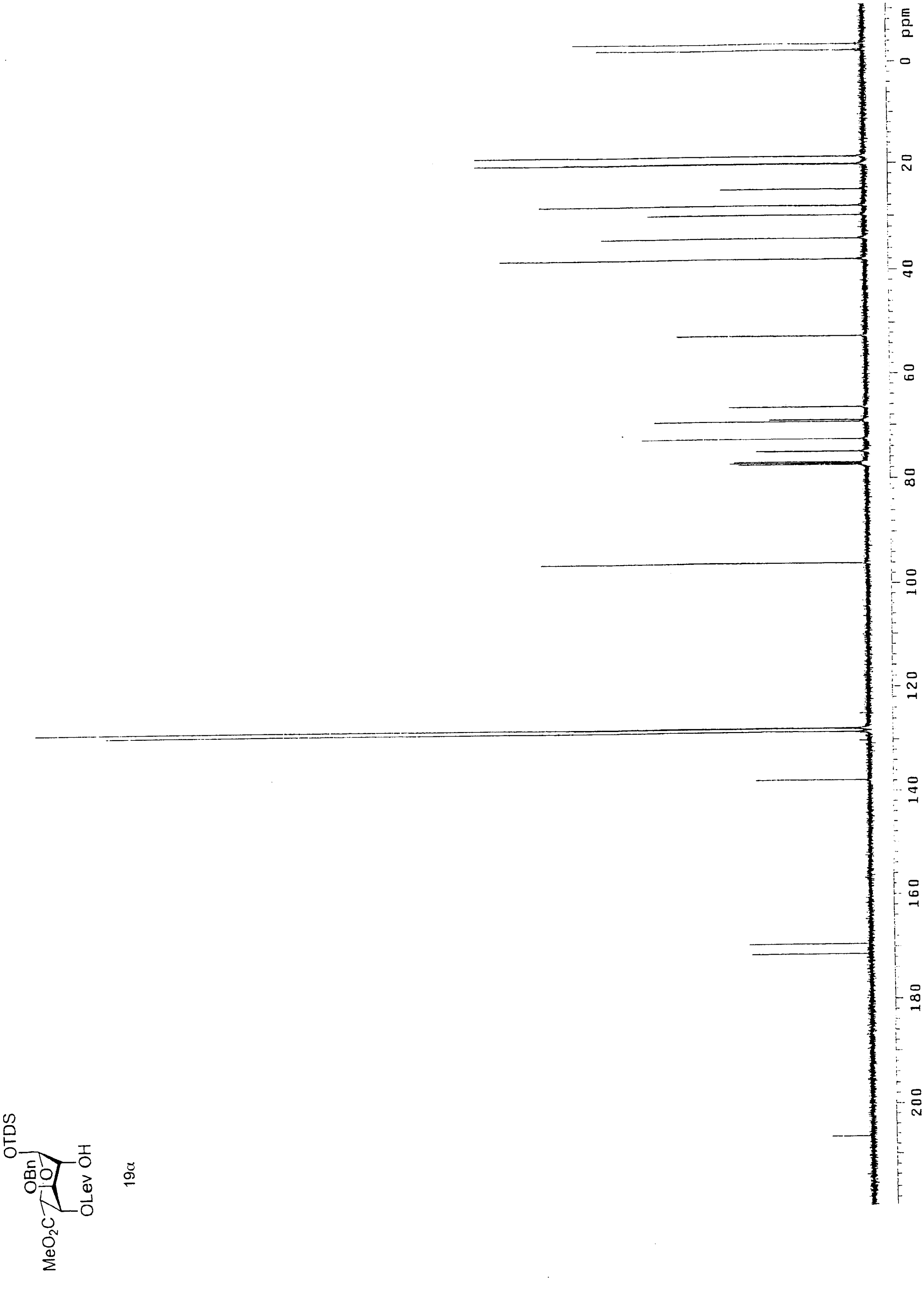


15

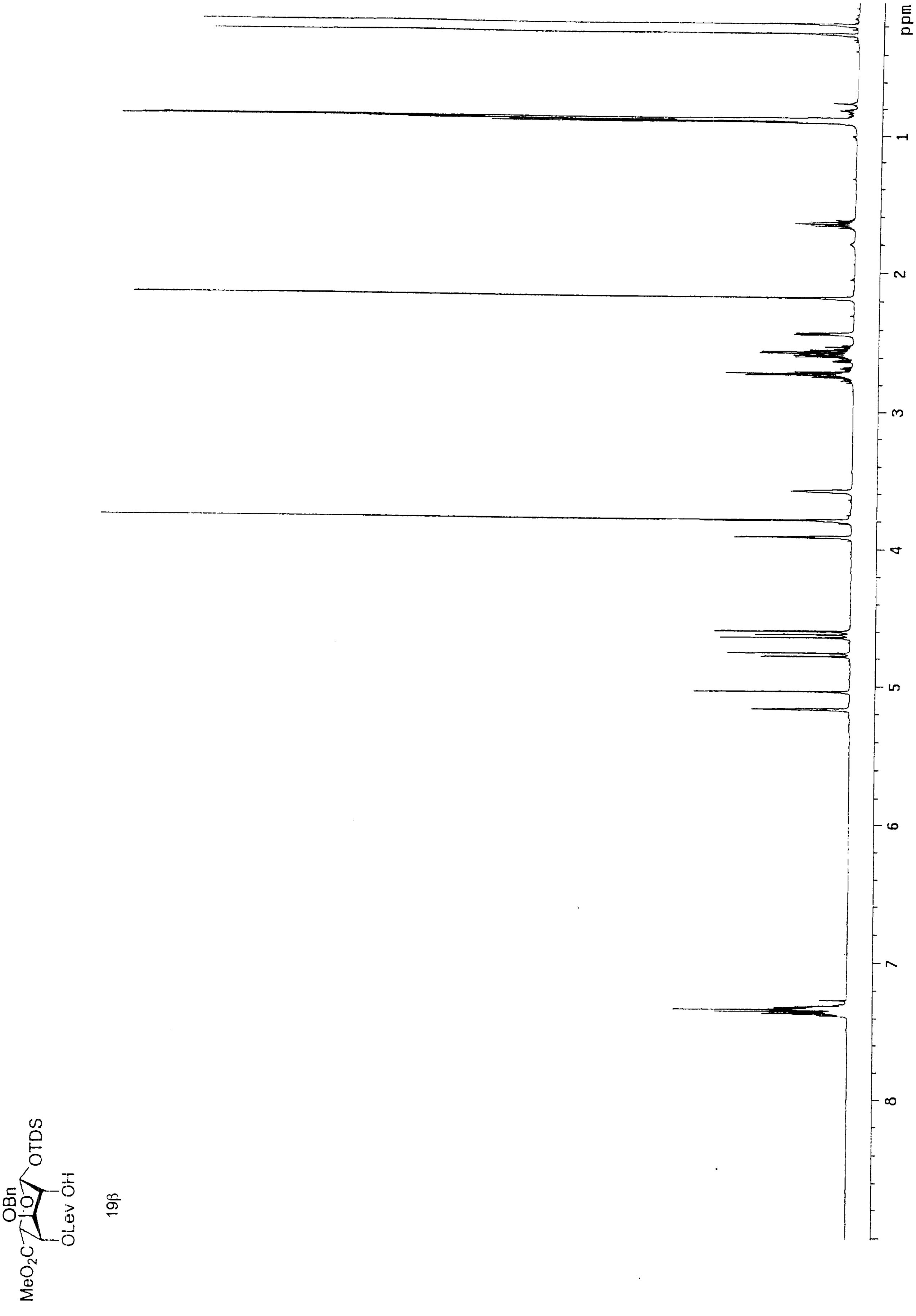


19α

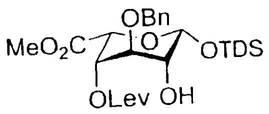




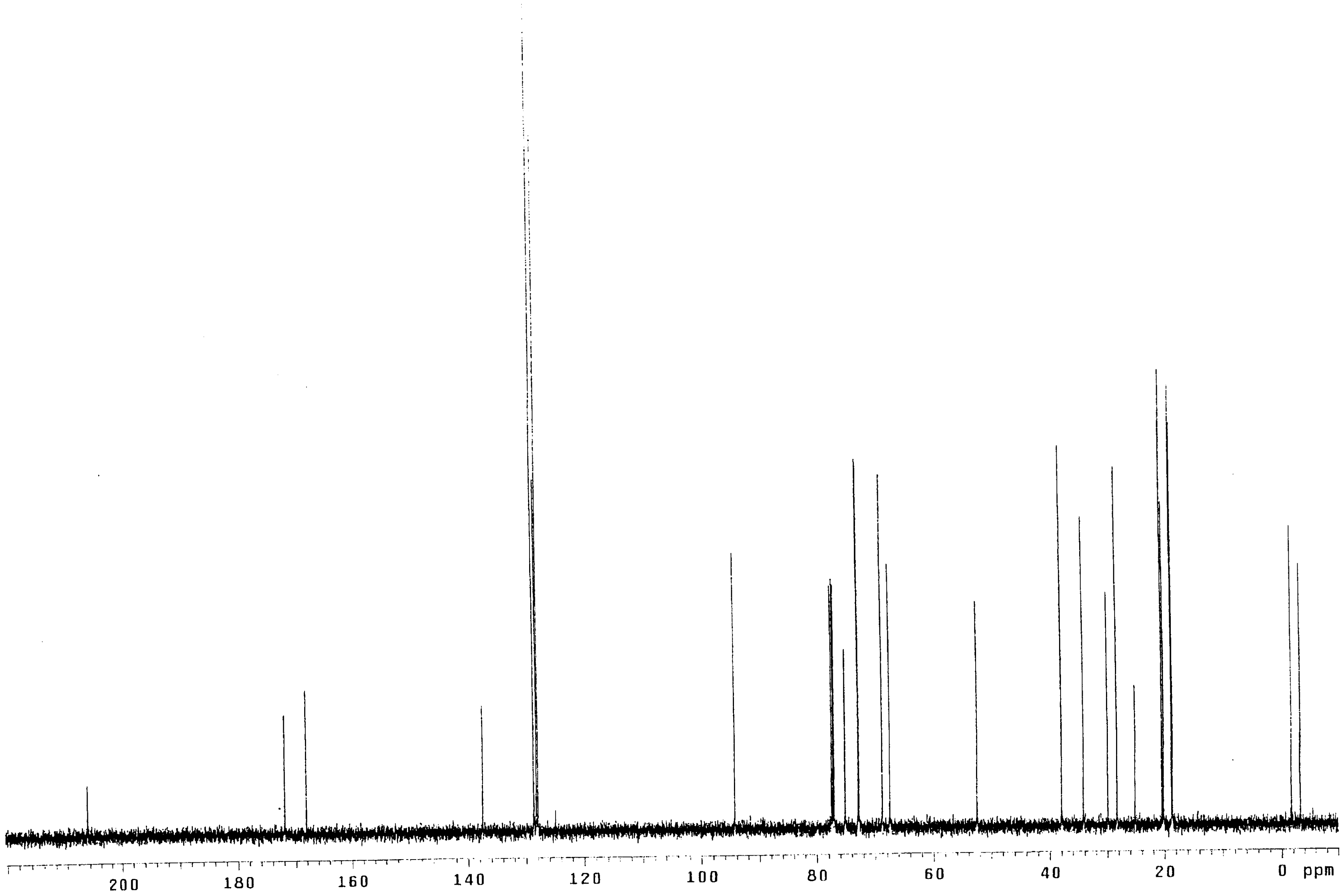
19α

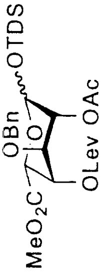


19β



19β





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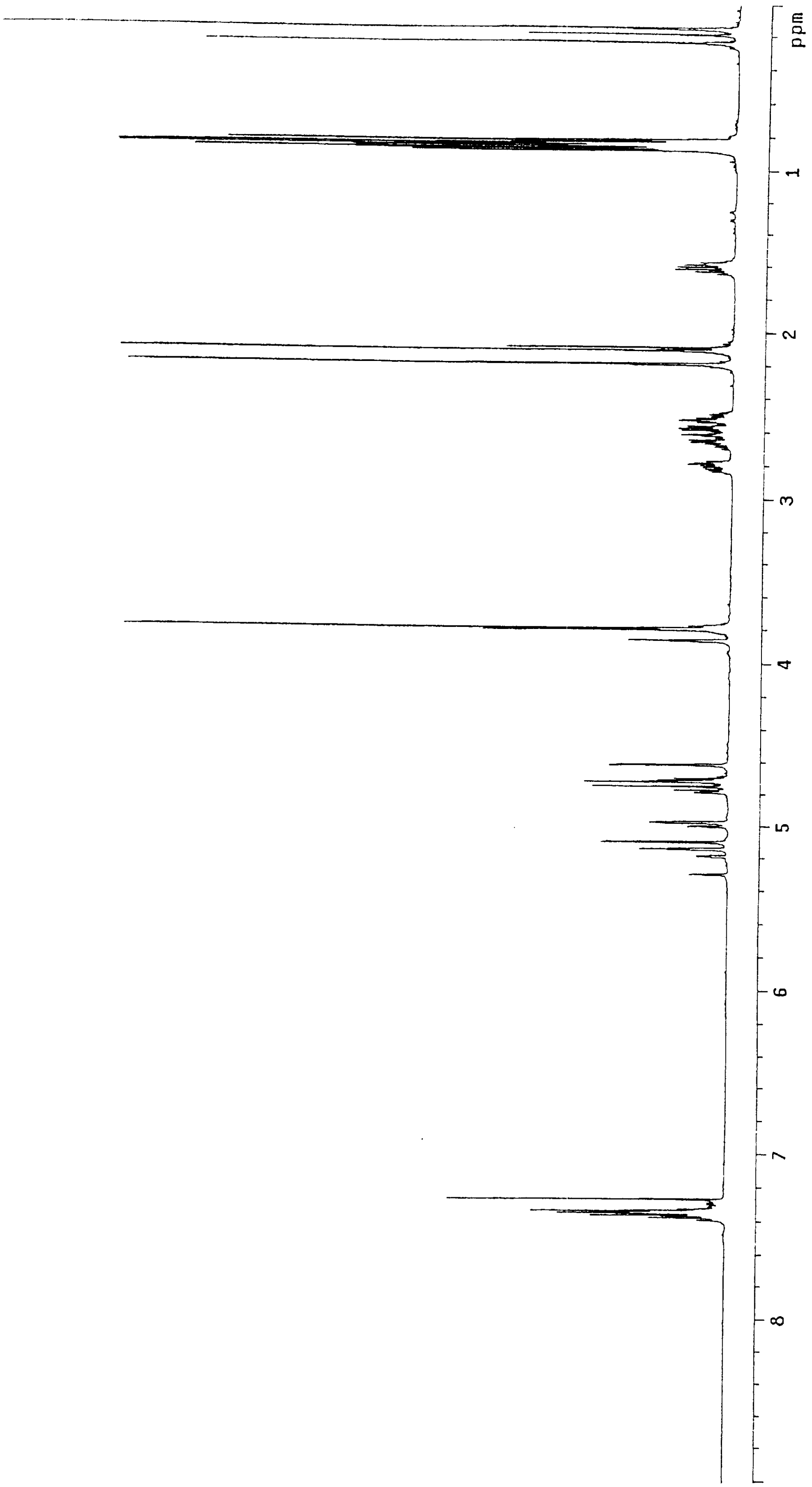

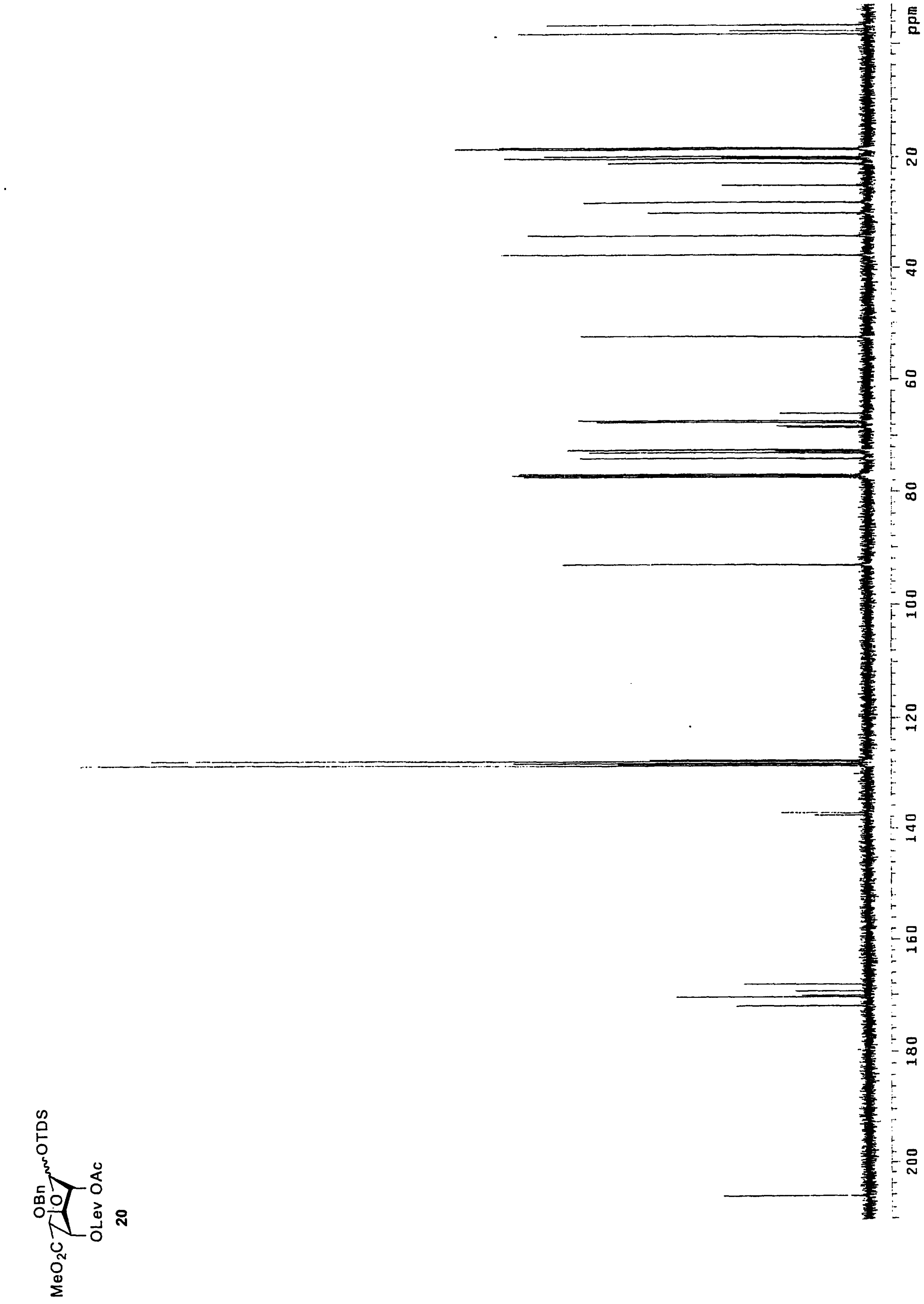

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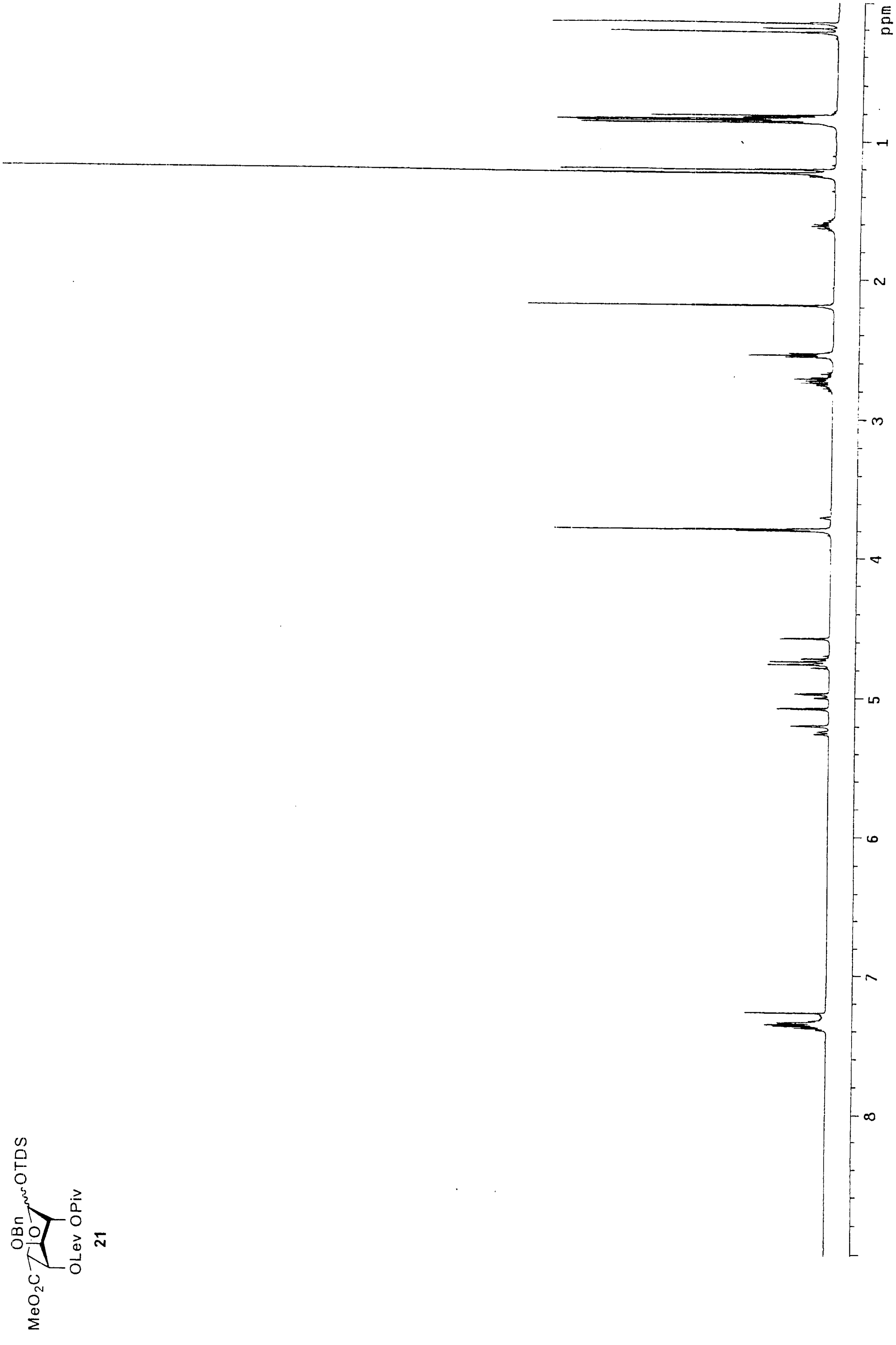

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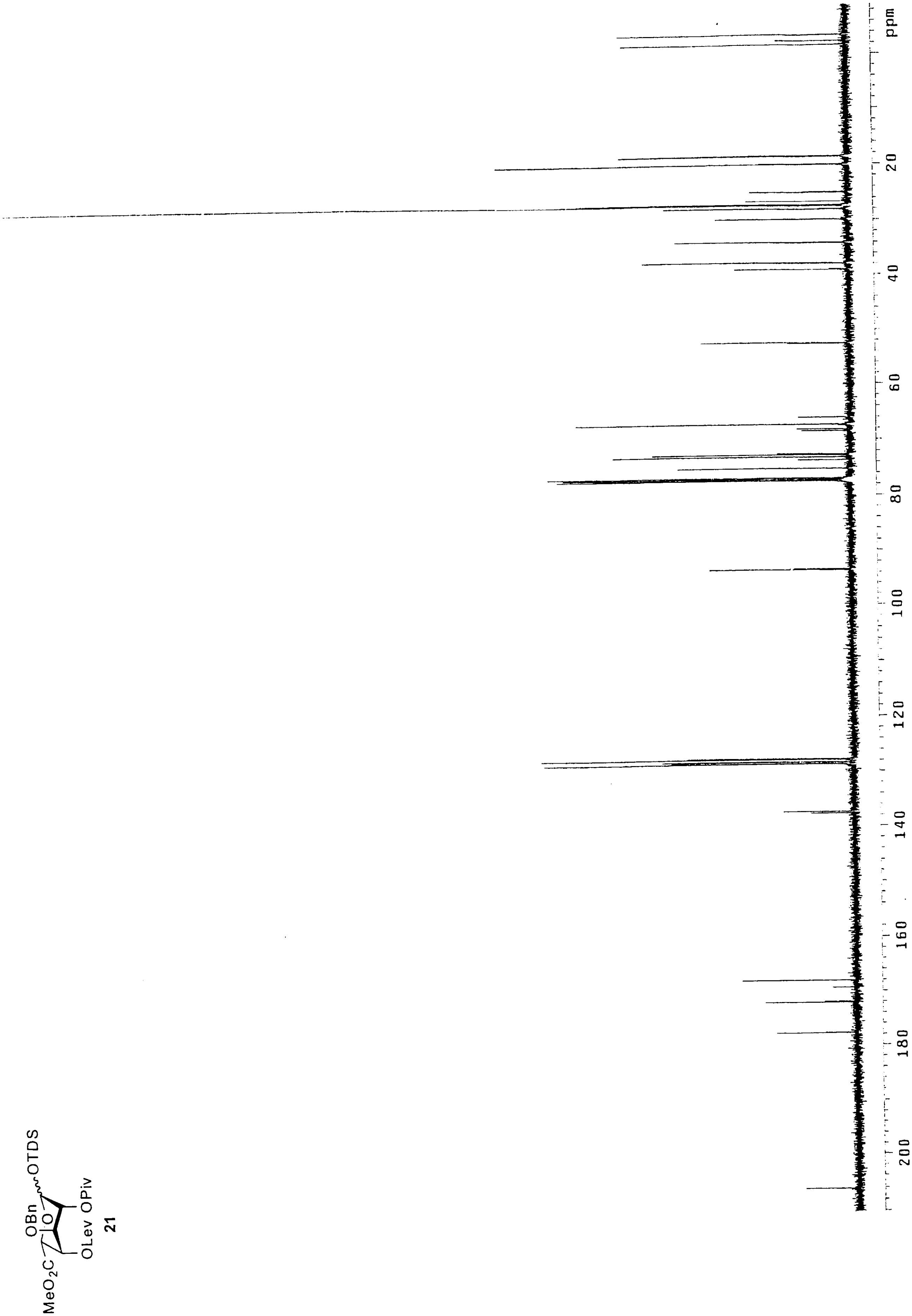
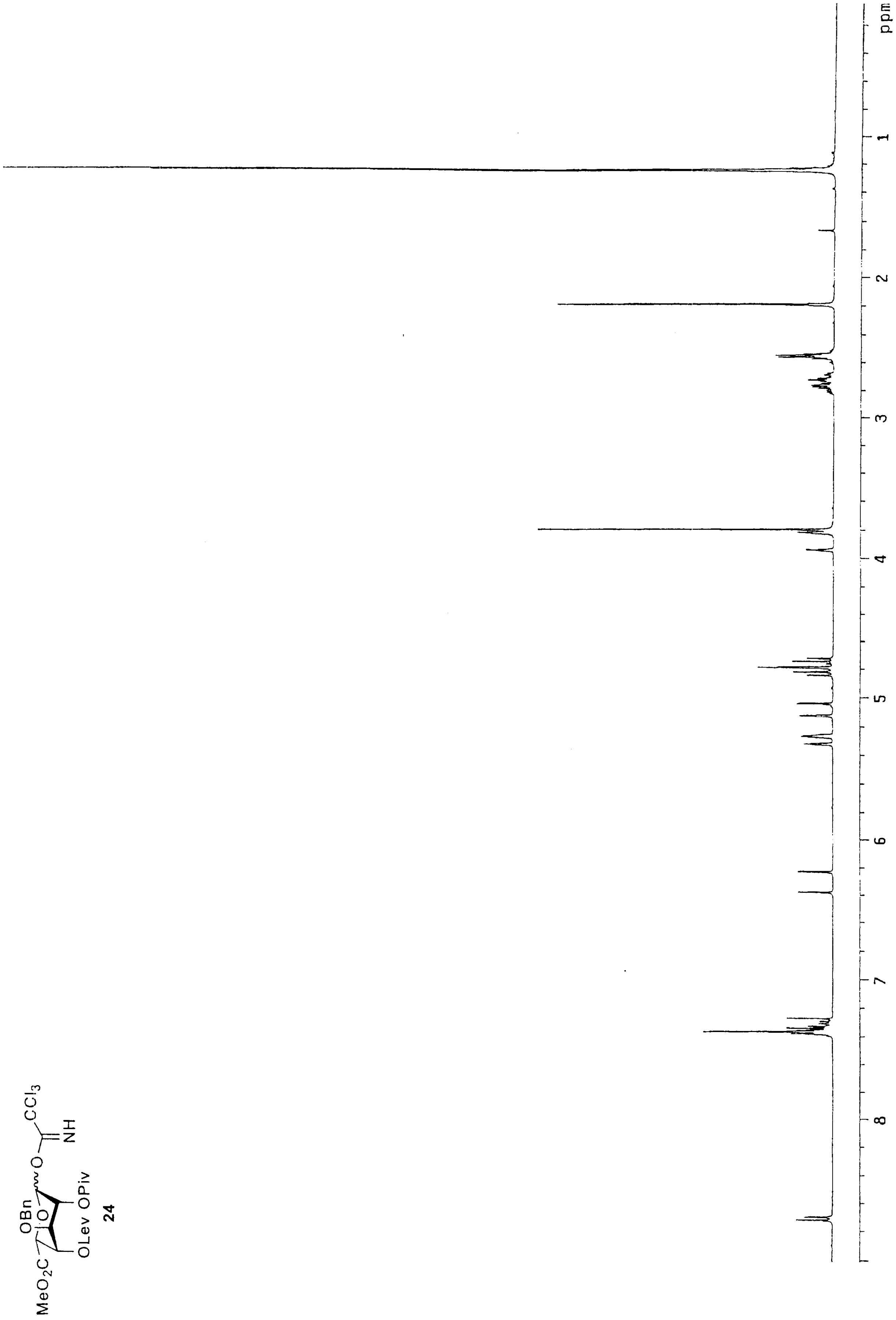
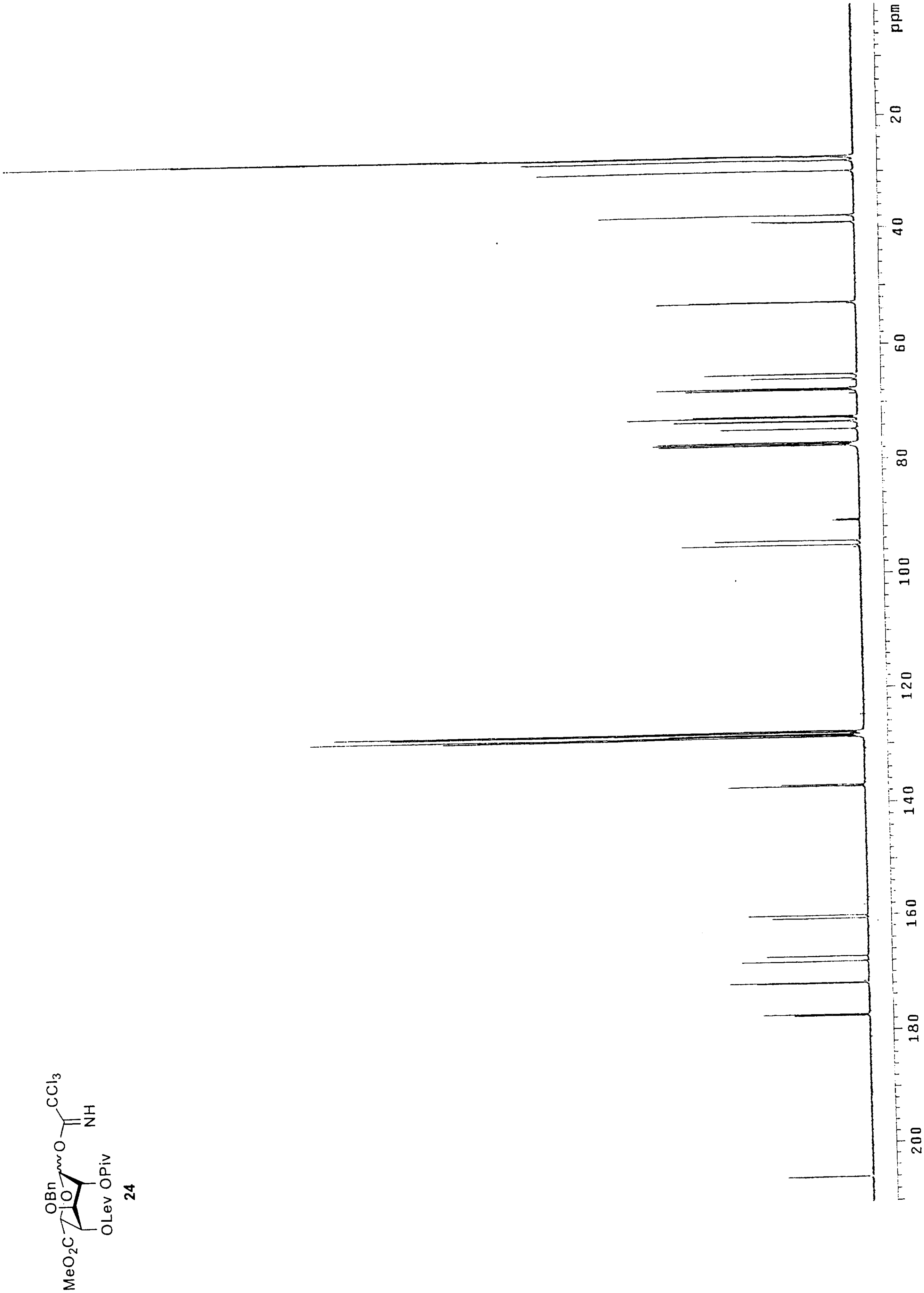


MeO2C
OBn
O
OTDS
OLev
OPiv
ppm
20
40
60
80
100
120
140
160
180
200

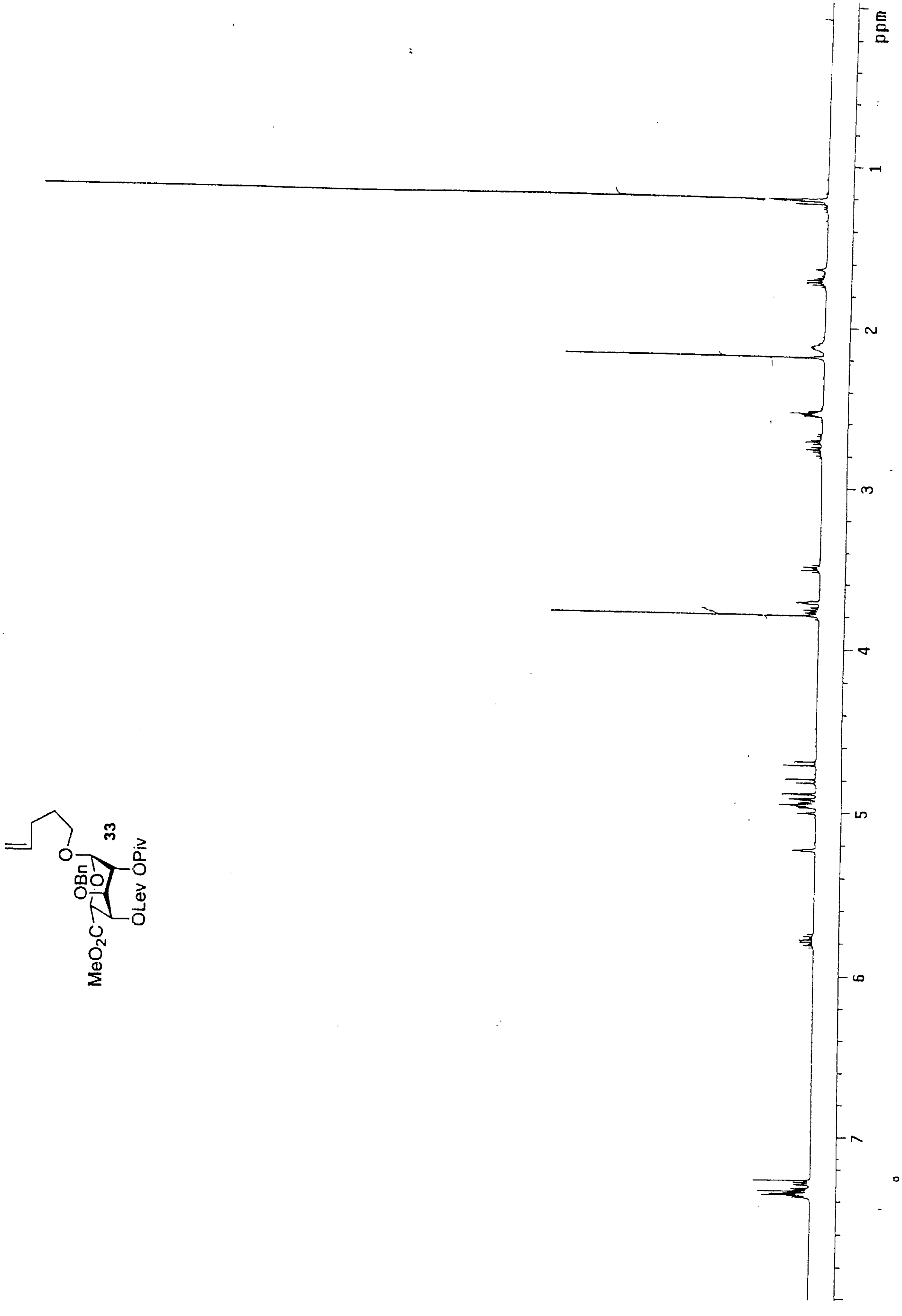
21



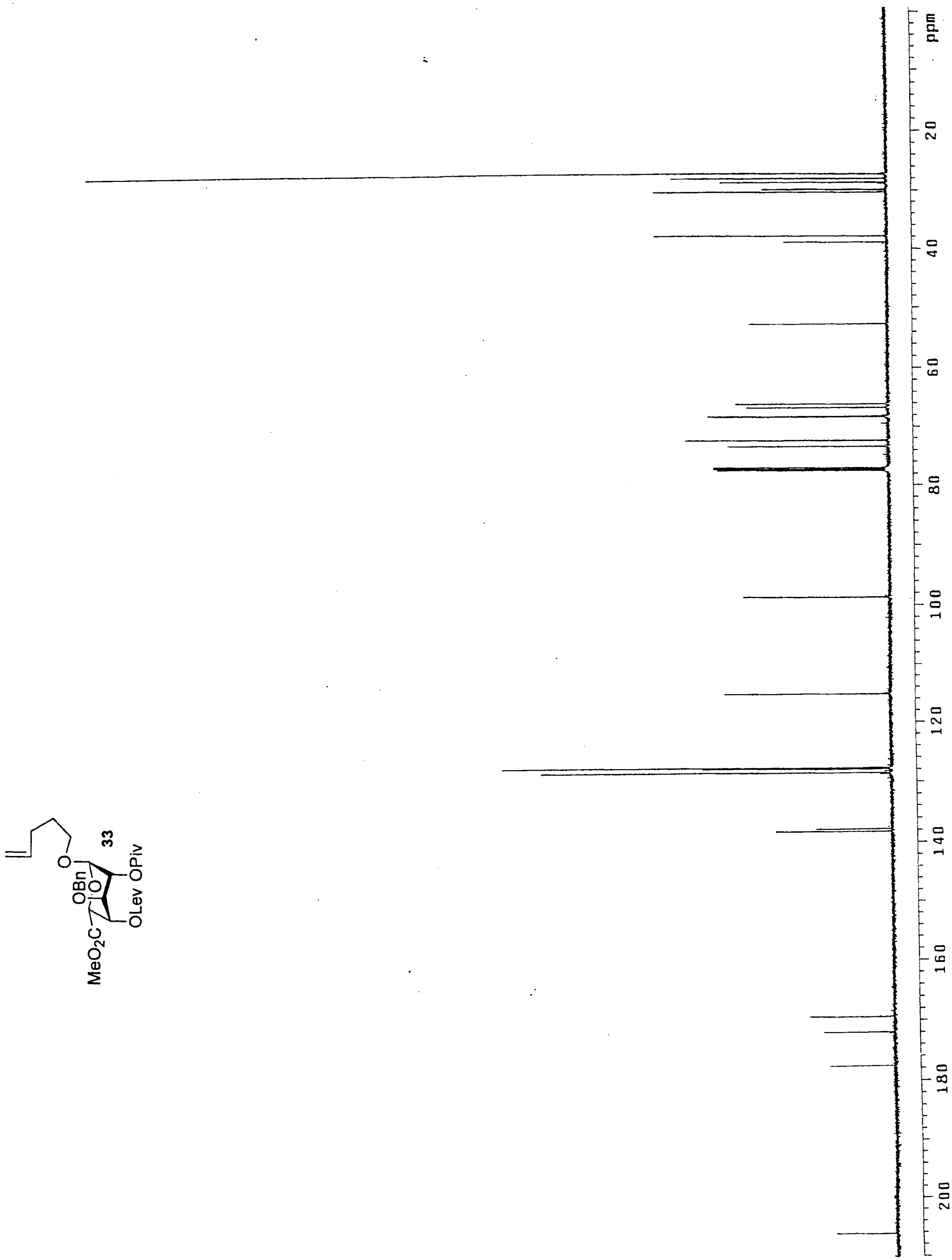
24


MeO2C
OBn
O
O
CCl3
NH
OLev
OPiv

24
ppm
20
40
60
80
100
120
140
160
180
200



33



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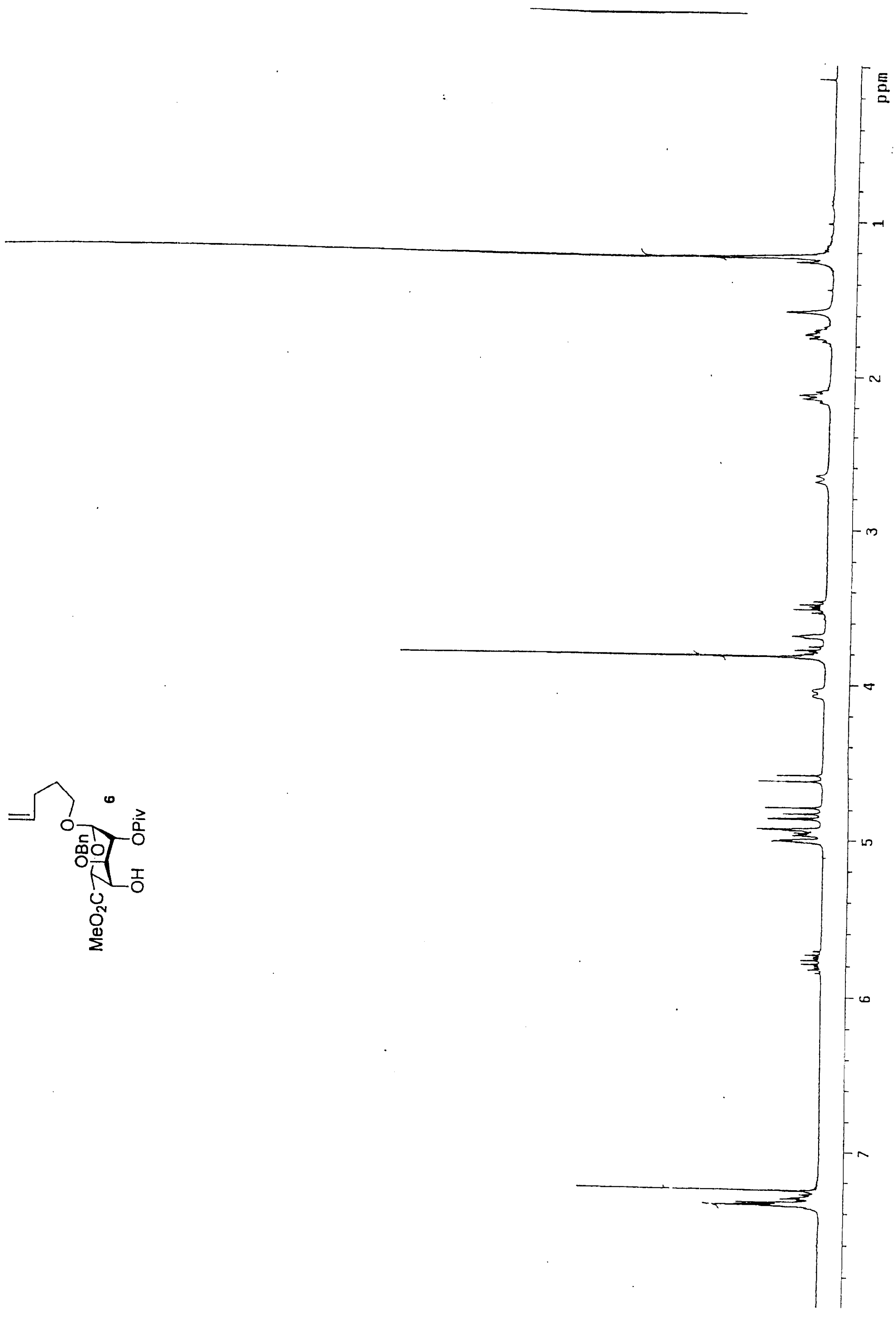

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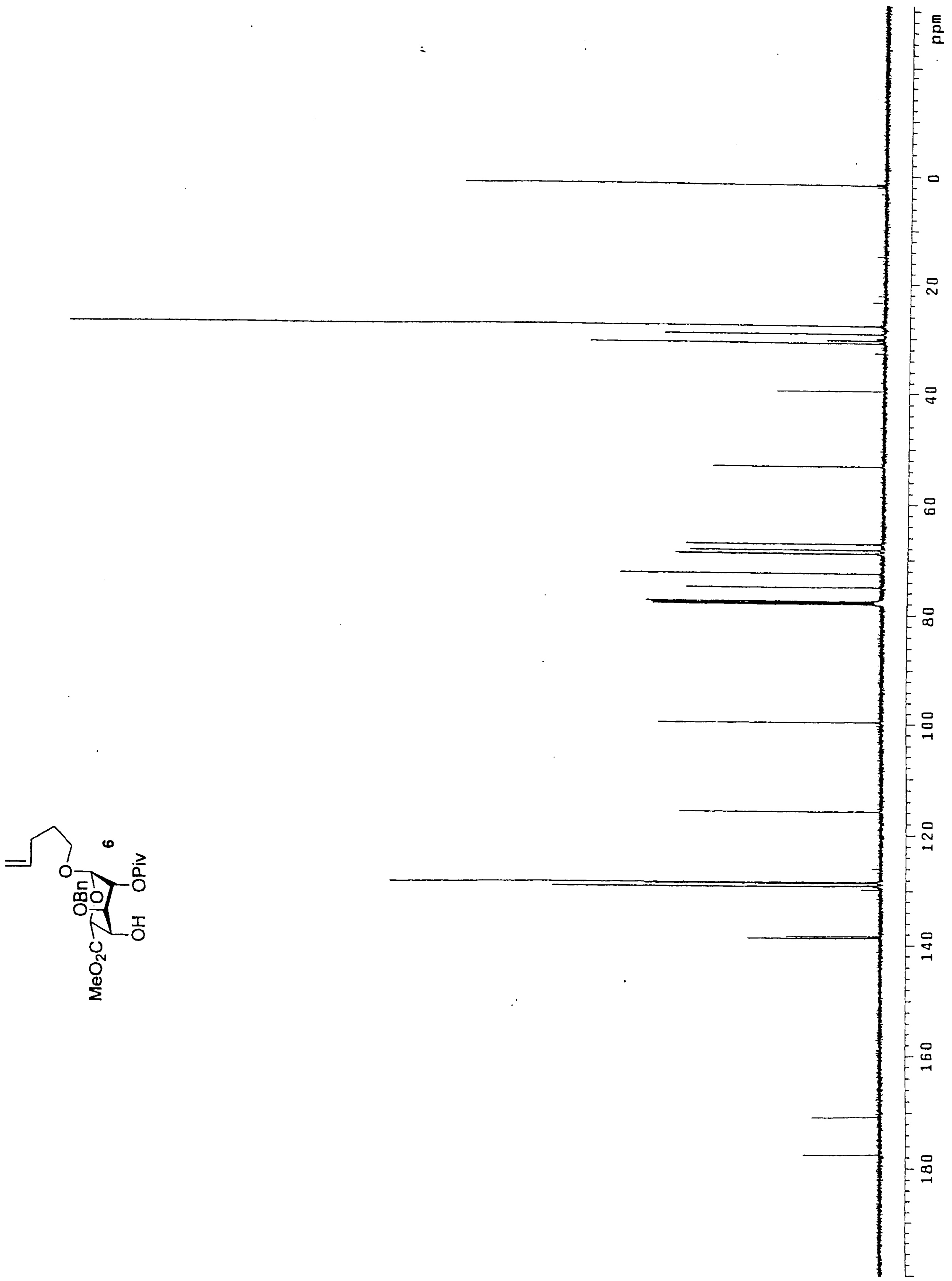

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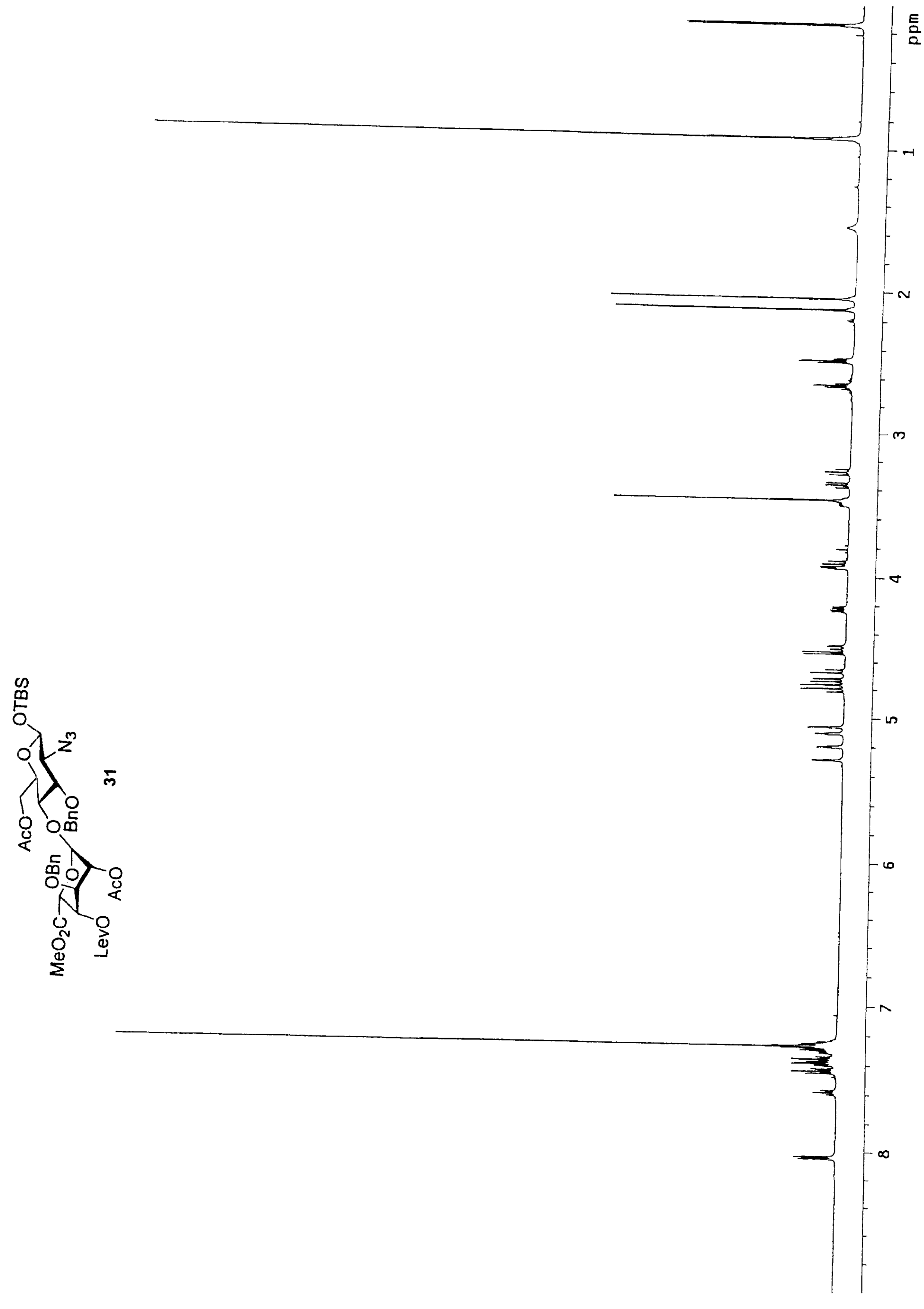

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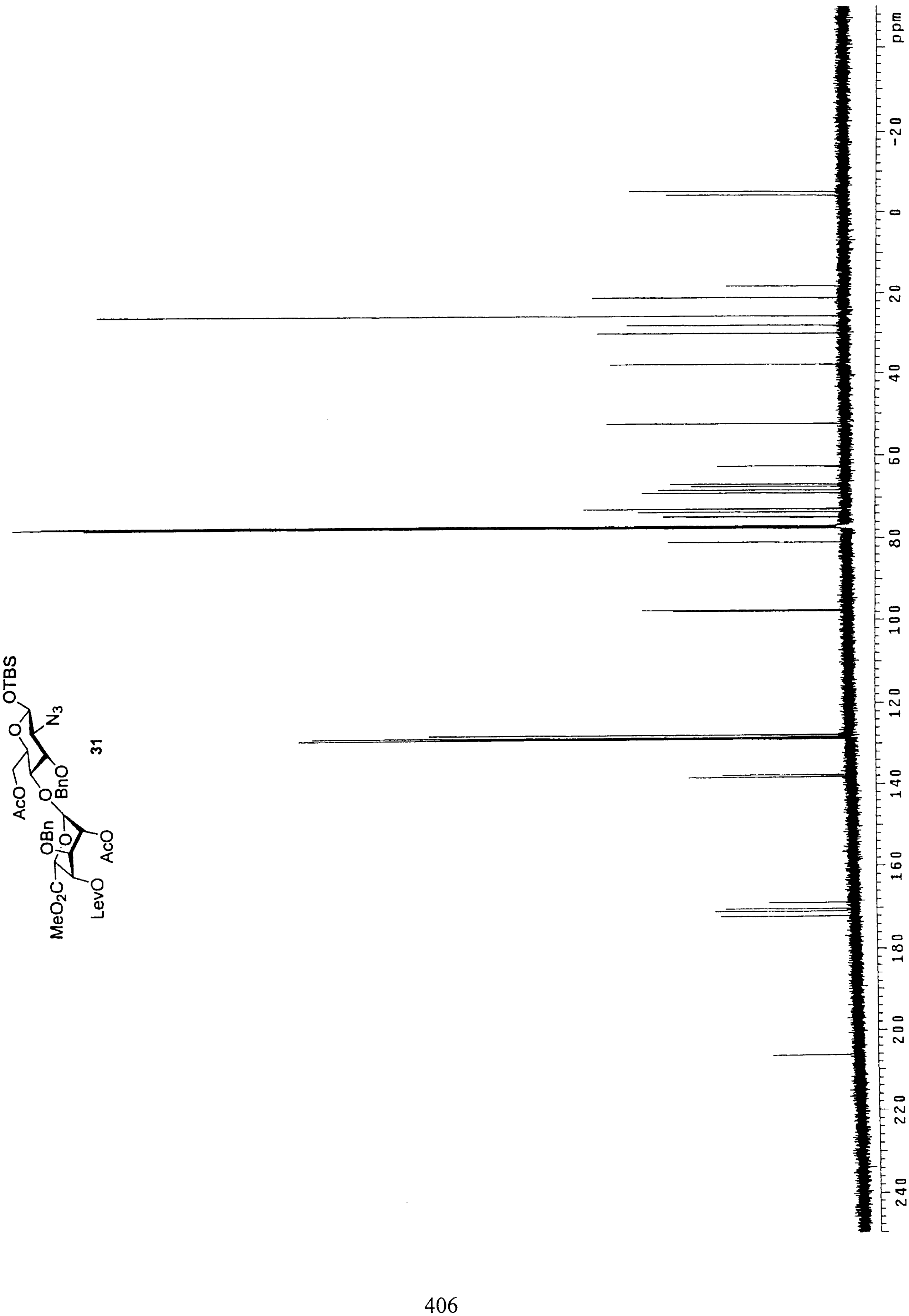
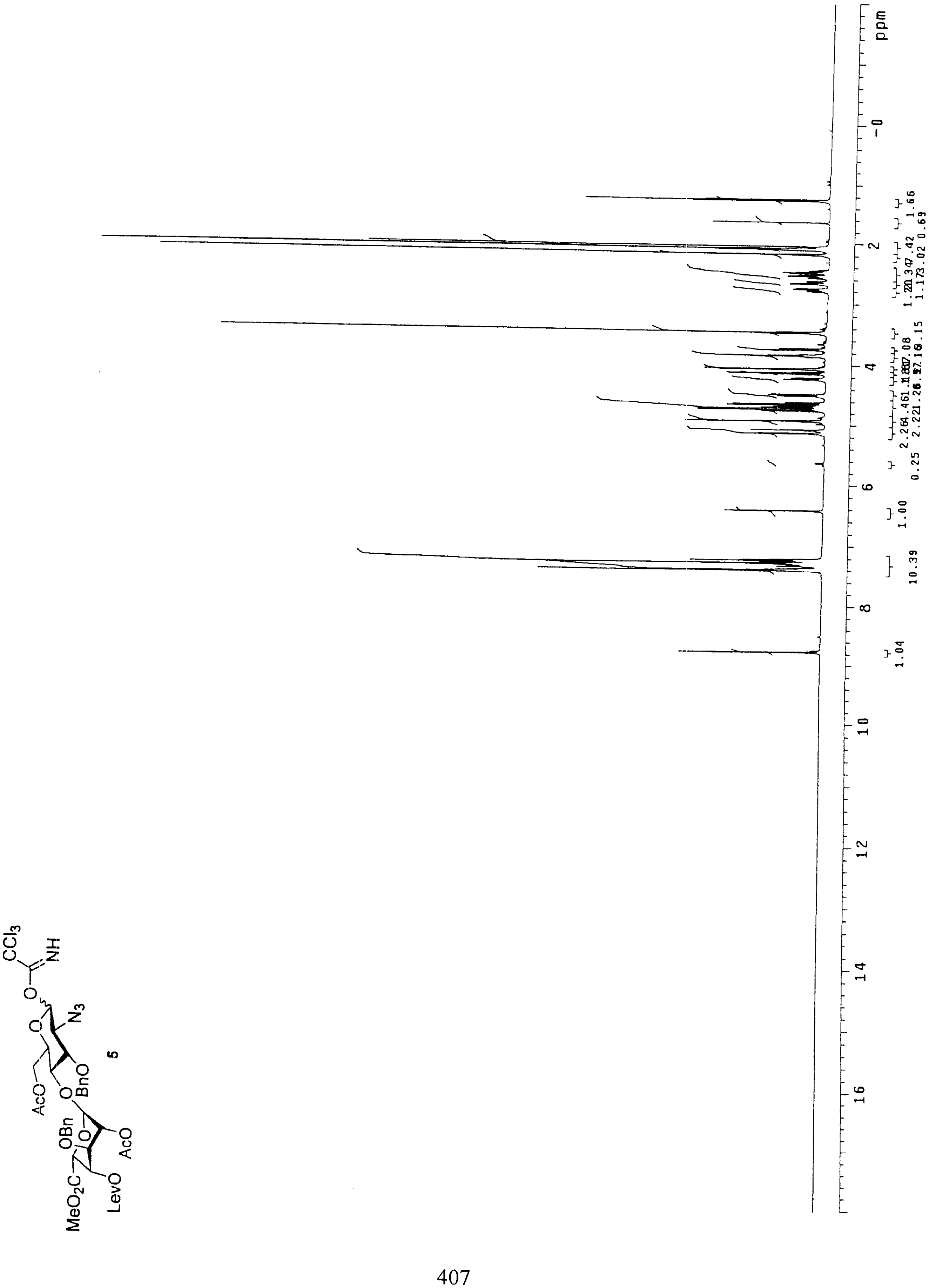
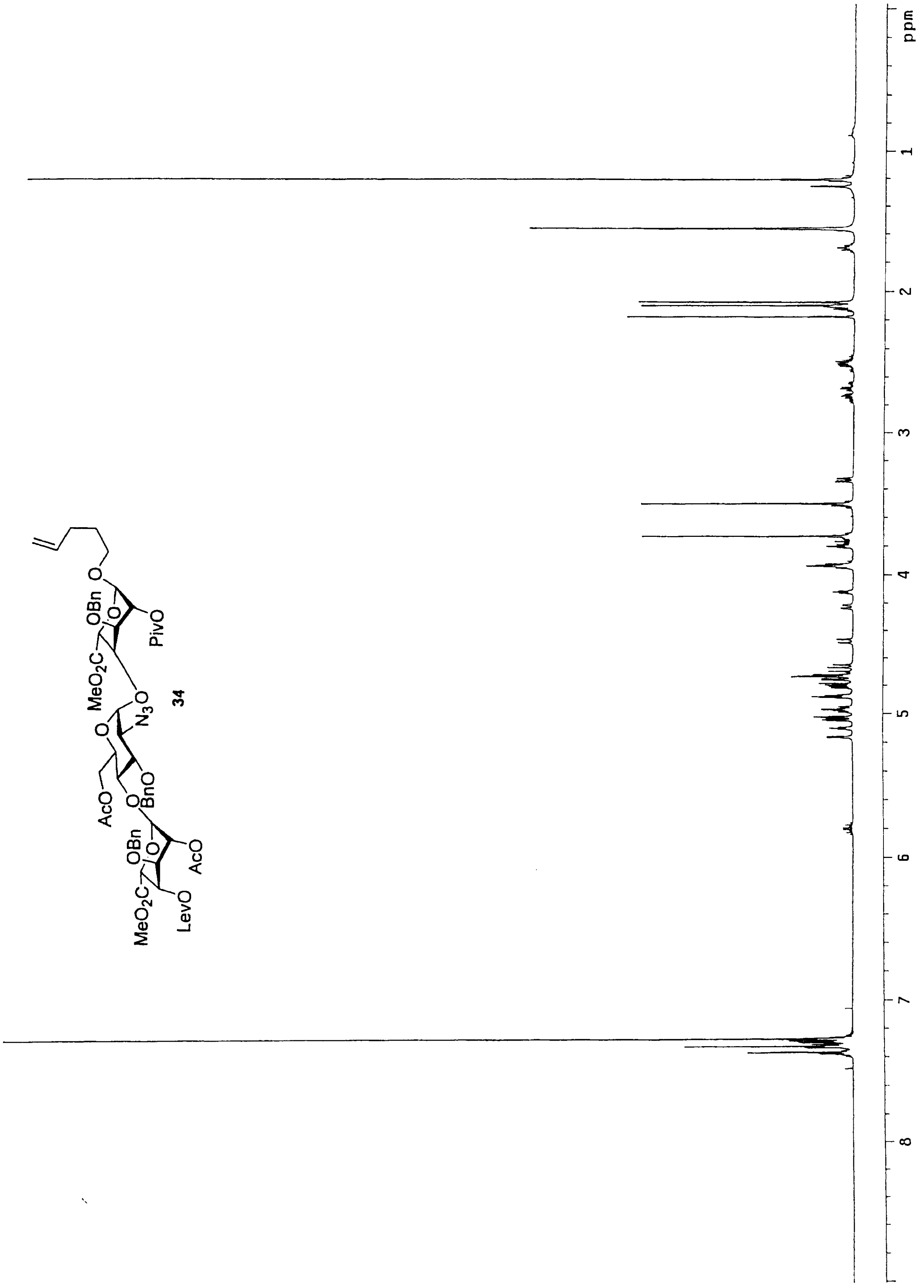

OTBS
N3
AcO
O
BnO
OBn
MeO2C
LevO
AcO
ppm
-20
0
20
40
60
80
100
120
140
160
180
200
220
240

31

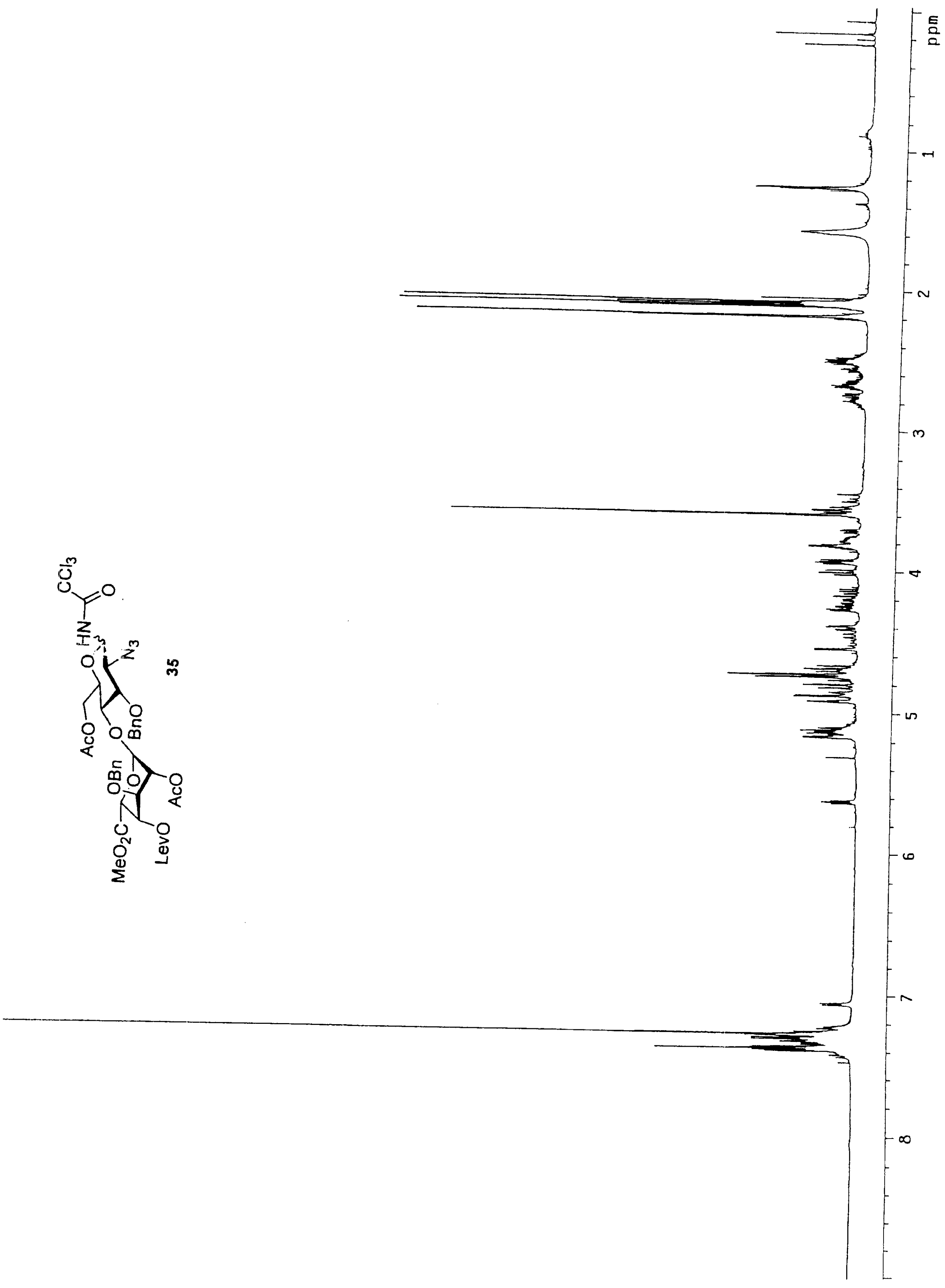

CCl3
NH
O
N3
AcO
BnO
OBn
MeO2C
LevO
AcO
ppm
16
14
12
10
8
6
4
2
0
1.04
10.39
1.00
0.25
1.66
0.69

5

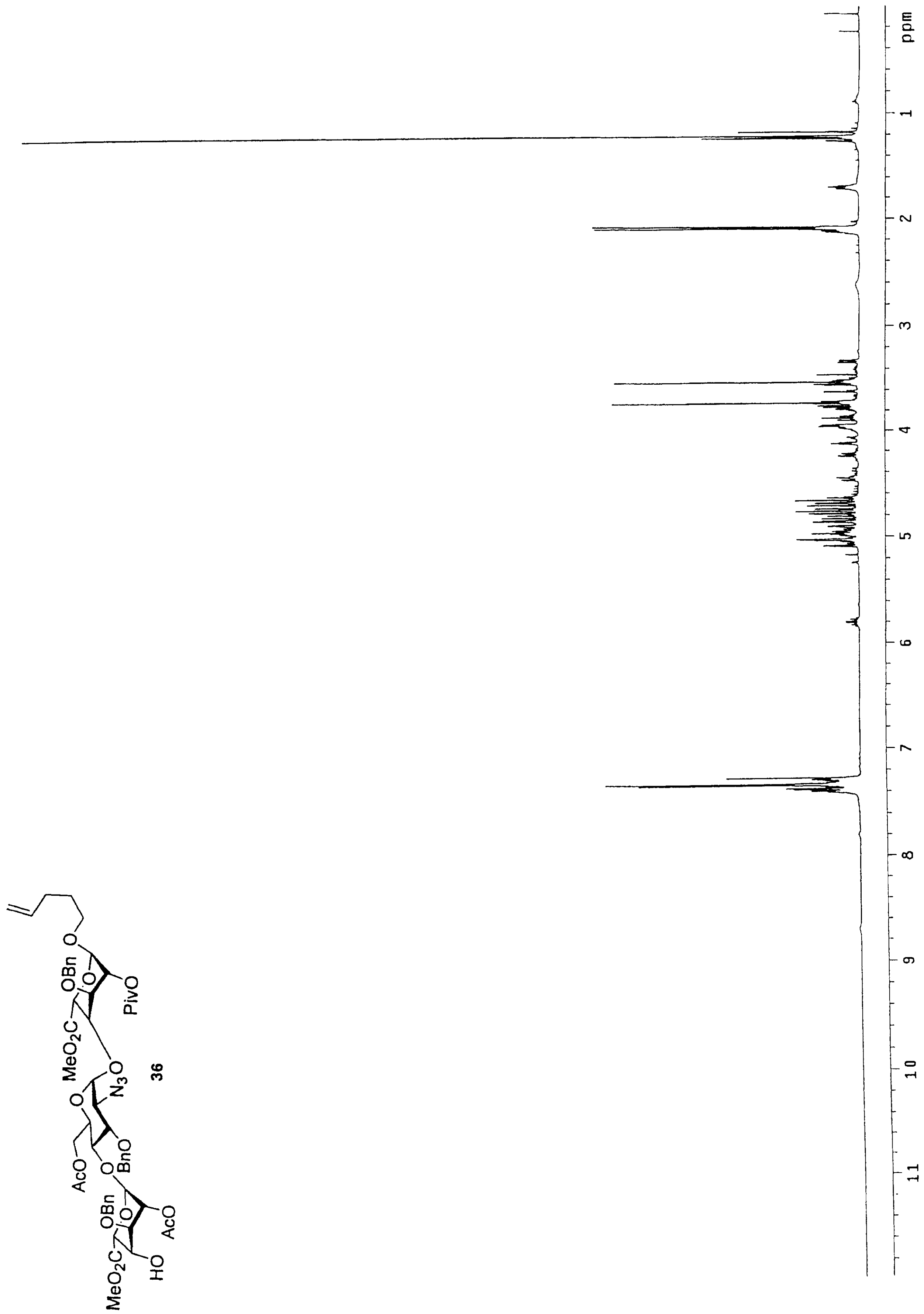


MeO$_2$C
OBn
O
LevO
AcO
O
BnO
AcO
O
N$_3$
O
MeO$_2$C
OBn
O
PivO
O
ppm
1
2
3
4
5
6
7
8

34

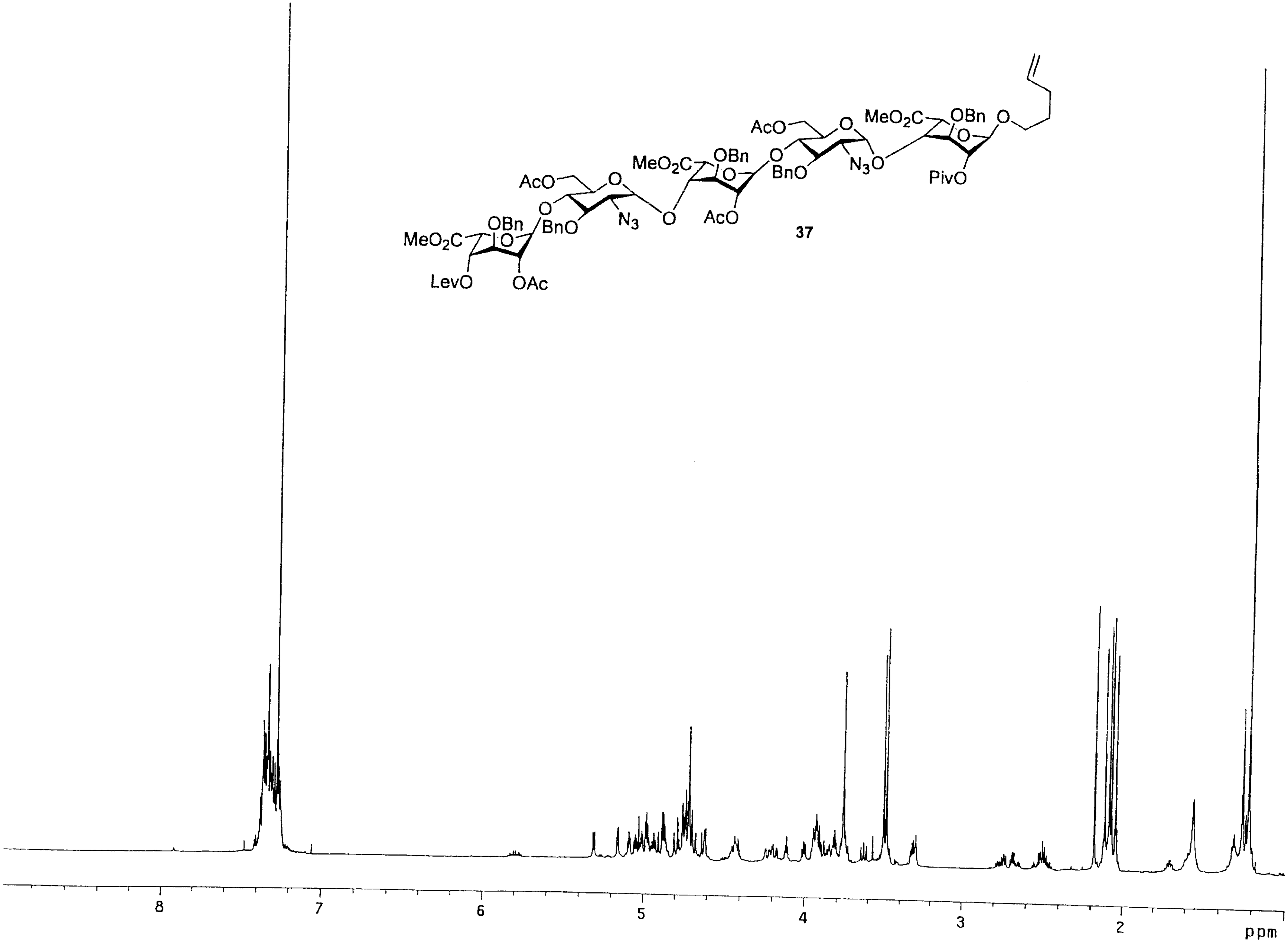


35



36

MeO2C
OBn
O
HO
AcO
AcO
O
BnO
O
N3
MeO2C
OBn
O
O
PivO
ppm
1
2
3
4
5
6
7
8
9
10
11



37

Diana Katharine Hunt

Curriculum Vitae

Education

Massachusetts Institute of Technology, Cambridge, MA.
Ph.D. Organic Chemistry (expected 2006)
Thesis title: "I. Total Synthesis of Galbulimima Alkaloids II. Resin-bound glycosyl phosphates as glycosyl donors. III. A modular synthesis of FGF-2 binding heparin pentasaccharide."

Swarthmore College, Swarthmore, PA.
BA, major in Chemistry, 1999
Thesis title: "Enantiopure Eight and Nine-Membered Carbocycle Synthesis via Transition Metal Catalyzed Ring-Closing Metathesis."

Research Experience

2003-present Graduate Research Associate, Massachussetts Institute of Technology
Dr. Mohammad Movassaghi, Advisor.

- Progress toward the total synthesis of galbulimima alkaloid 13 and himgaline.

2000-2003 Graduate Research Associate, Massachussetts Institute of Technology
Dr. Peter H. Seeberger, Advisor.

- Investigated the modular synthesis of FGF-2 binding heparin pentasaccharide in solution for application to automated solid phase synthesis.
- Investigated linker influence on the stereochemical outcome of glycosylations with resin-bound glycosyl phosphates.

1999-2000 Research Intern, Pfizer Research and Development (formerly Parke-Davis)

Dr. Charles Stankovic, Supervisor.

- Worked on a broad range of synthetic projects including large scale synthesis of intermediates and exploratory work for development of new routes.

1998-1999 Undergraduate Researcher, Swarthmore College
Dr. Robert S. Paley, Advisor.

- Prepared eight and nine-membered carbocycles via ring-closing metathesis of organometallic complexes.

1997 Undergraduate Researcher, University of Michigan
Dr. Coleen Pugh, Advisor.

- Investigated the effect of immiscible components on smectic layer induction in nematic liquid crystals.
- Preparation and purification of liquid crystals and analysis via differential scanning calorimetry.

Teaching Experience

2004-present	Volunteer docent, Museum of Science, Boston.
2003	Teaching assistant for graduate level organic synthesis course (one semester); MIT.
2000-2001	Teaching assistant for introductory organic chemistry (three semesters); MIT, Head TA Fall 2001.
1999	Student tutor, organic chemistry; Swarthmore College.
1997-1999	Laboratory teaching assistant for organic chemistry; Swarthmore College.
1997-1999	Writing Associate; Swarthmore College.

Awards

2004	Wyeth Scholar Travel Award, MIT.
2001	Excellence in Teaching Award, MIT.
1998	Stanley Adamson Award for Excellence in Chemistry, Swarthmore College.

Publications

Lohman, G. J .S.; Hunt, D. K.; Högermeier, J. A.; Seeberger, P. H. "Synthesis of Iduronic Acid Building Blocks for the Modular Assembly of Glycosaminoglycans" *J. Org. Chem.* **2003**, *68*, 7559-7561.

Hunt, D. K.; Seeberger, P. H. "Linker Influence on the Stereochemical Outcome of Glycosylations Utilizing Solid Support-Bound Glycosyl Phosphates" *Org. Lett.* **2002**, 4, 2751-2754.

Paley, R. S.; Estroff, L. A.; Gauguet, J. M.; Hunt, D. K.; Newlin, R. C. "Enantiopure η^4-(1-Sulfinyldiene)Iron(0) Tricarbonyl Complexes as Templates for Carbocycle Construction via Ring-Closing Metathesis" *Org. Lett.* **2000**, 2, 365-368.

Small, A. C.; Hunt, D. K.; Pugh, C. "Induction of Smectic Layering in Nematic Liquid Crystals using Immiscible Components. III. The Effect of Lateral *n*-Alkanoyl Substituents on the Thermotropic Behaviour of 2,5-bis[4'(*n*-Perfluoroheptyloctyloxy)benzoyloxy]toluene" *J. of Liquid Crystals* **1999**, 26, 849-857.

Presentations

Hunt, D. K.; Movassaghi, M. "Synthetic Studies of Galbulimima Alkaloids" Graduate Research Symposium, MIT, Cambridge, MA, May 2004.

Hunt, D. K.; Seeberger, P. H. "Linker Influence on the Stereochemical Outcome of Glycosylations Utilizing Solid Support-Bound Glycosyl Phosphates" Boehringer-Ingelheim Research Fellow Symposium, Ridgefield, CT, October 2002.

Affiliations

American Chemical Society
Sigma Xi Research Society