Scaffolding Catalysis: Towards Regioselective Hydroformylation of Alkenes and Site-Selective Functionalization of Polyhydroxylated Molecules

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Scaffolding Catalysis: Towards Regioselective Hydroformylation of Alkenes and Site-Selective Functionalization of Polyhydroxylated Molecules

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Thesis Advisor: Professor Kian L. Tan

Abstract

Chapter 1. We reported the first synthesis of all-carbon quaternary centers via hydroformylations using a catalytic directing group. With the ability of reversibly and covalently binding to a substrate, and coordinating to a metal center, scaffolding catalyst **1.1** is able to direct the branch-selective hydroformylation of 1,1-disubstituted olefins under mild temperature.

Chapter 2. We have designed and synthesized a chiral organocatalyst **2.11**. This catalyst is able to covalently bind to one hydroxyl, and utilize the induced intramolecularity to stereoselectively functionalize the other hydroxyl within a *cis*-1,2-diol via electrophile transfer. Catalyst **2.11** was used in the desymmetrization of *meso*-1,2-diols under mild conditions (4 °C to room temperature), leading to high yields and selectivities for a broad substrate scope.

Chapter 3. Catalyst **3.1** and **3.6** were demonstrated to selectively bind to primary

hydroxyls over secondary hydroxyls. By combining the binding selectivity with asymmetric catalysis, these scaffolding catalysts were shown to promote the selective silylation of secondary hydroxyls within terminal (*S*)-1,2-diols. The reversal of substrate bias was further applied to a regiodivergent kinetic resolution of racemic terminal 1,2-diols, producing secondary protected products in synthetically practical levels of enantioselectivity (>95:5 er) and yields (≥40%). Time course studies of this reaction further revealed the optimal condition to form the primary silylated product in high s-factor.

Chapter 4. Based on the previous understanding of catalyst **4.5** and **4.6**, the exclusive catalyst recognition of *cis*-1,2-diols within polyhydroxylated molecules was further discovered. This unique functional group display recognition was further allied with the catalyst's ability to stereoselectively differentiate hydroxyls within *cis*-1,2-diols, enabling the site-selective protection, functionalization, and activation of the inherently less reactive axial hydroxyl groups within carbohydrates. This methodology also enables the selective functionalization of multiple complex molecules, including digoxin, mupirocin, and ribonucleosides, demonstrating the potential power of scaffolding catalysis in the rapid access to valuable synthetic derivatives of polyhydroxylated compounds.

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Acknowledgements

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Last and most, to my wife Nanjun Liu, I thank you for your love, which encouraged me to go through hard times and achieve every successful step. You are the greatest thing ever happened to me, and I believe the best part is still waiting for us in our journey together.

List of Abbreviations

Ac	Acetyl
ACS	American Chemical Society
Bn	Benzyl
br	Broad
Bu	Butyl
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet
dd	Doublet of doublets
DIBAL-H	Di-isobutyl aluminum hydride
DIPEA	Diisopropylethylamine
DMF	N,N-Dimethylformamid
DMPS	Dimethyl phenyl silyl
dr	Diastereomer ratio
dt	Doublet of triplets
ee	Enantiomeric excess
Et	Ethyl
GC	Gas chromatography

HRMS	High resolution mass spectrometry
i-	Iso
IR	Infrared
m	Multiplet
Me	Methyl
Ms	Mesyl
n-	Normal
NMI	*N*-Methylimidazole
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMP	1,2,2,6,6-Pentamethylpiperidine
PPTS	Pyridinium *para*-toluene sulfonic acid
Pr	Propyl
p-TsOH	*para*-Toluenesulfonic acid
q	Quartet
rr	Regio-isomeric ratio
s	Singlet
t	Triplet
t-	Tertiary

TBDPS	*tertiary*-Butyl diphenyl silyl
TBS	*tertiary*-Butyl dimethyl silyl
TES	Triethyl silyl

Chapter 1

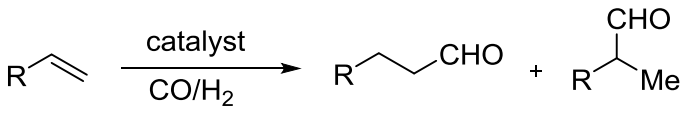
Hydroformylation of 1,1-Disubstituted Alkenes

Chapter 1. Hydroformylation of 1,1-Disubstituted Alkenes

1.1 Hydroformylation

First discovered in 1938 by Roelen,[1] hydroformylation has become one of the largest industrial processes today, with approximately 9 million tons of products manufactured every year.[2] Besides its industrial importance, this atom-economical addition of CO and H_2 to an alkene provides an opportunity to add a versatile aldehyde functional group through the formation of a carbon-carbon bond,[3] and therefore is recognized as a valuable synthetic tool in organic chemistry (Scheme 1.1).

Scheme 1.1. Hydroformylation.



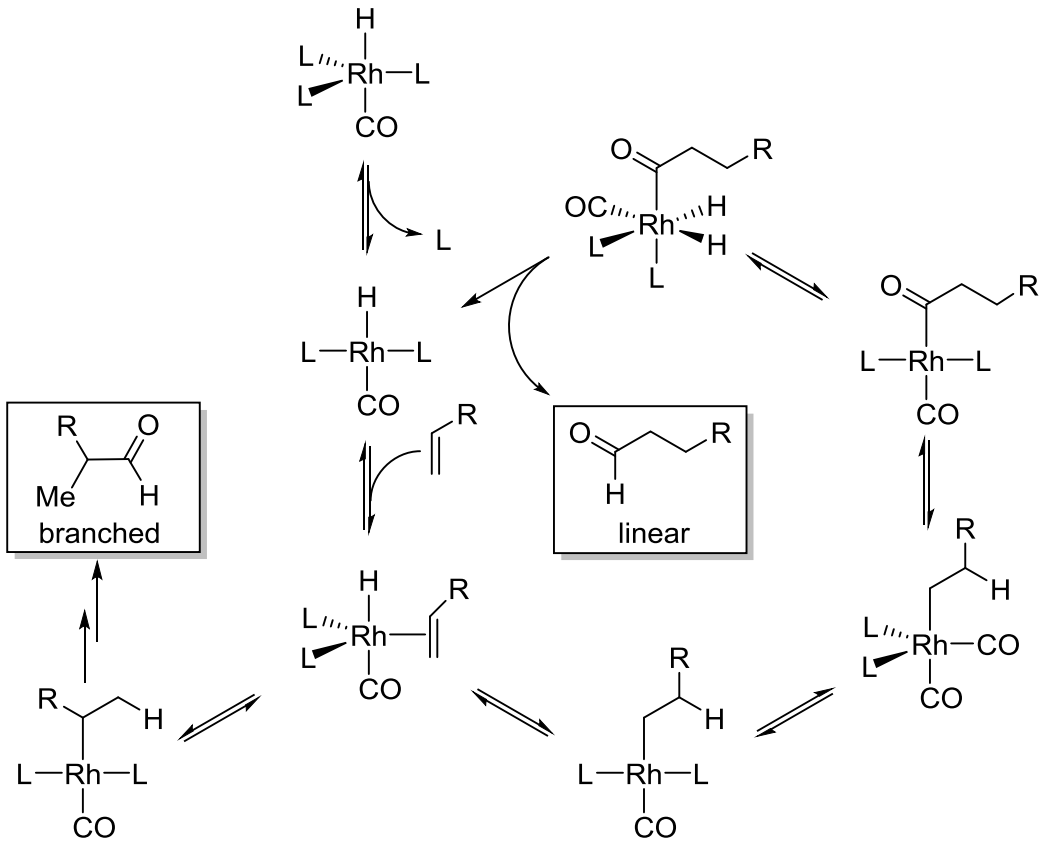
1.2 Challenges in Regioselective Hydroformylation

Despite its great value in industry and appealing synthetic advantages, the use of hydroformylation in organic synthesis is still limited due to the difficulty in controlling all aspects of reaction selectivities.

One field that has been the focus of intensive research efforts is controlling regioselectivity of hydroformylation. Traditionally, the regioselectivity is determined by intrinsic substrate preferences. In the hydroformylation of terminal alkenes, the linear

product is favored, where the aldehyde is formed on the less hindered terminal carbon. This bias results from the metal-carbon bond formation on the less hindered terminal carbon atom following hydride insertion, due to the steric effect between the substrate and the metal catalyst (Figure 1.1).

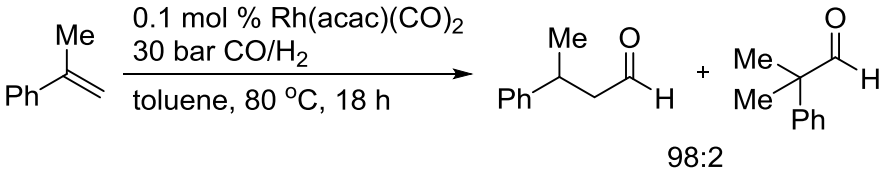
Figure 1.1. Mechanism of hydroformylation



One of the most significant challenges in regioselective hydroformylation is the use of 1,1-disubstituted alkenes to yield products containing all-carbon quaternary centers. Due to the substrate's strong favorability to bond metal with a primary carbon over a

tertiary carbon, the formation of linear product is dominant (Scheme 1.2). This observation was summarized as Keulemans' rule,[4] which stated that "addition of the formyl group to a tertiary C atom does not occur, so that no quaternary C atoms are formed".

Scheme 1.2. Hydroformylation of 1,1-disubstituted alkene.

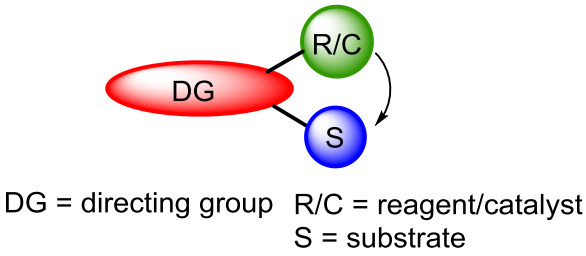


The challenges of regioselective hydroformylation limit its potential applications in organic synthesis. Thus general and efficient methods to enrich, and more importantly, to reverse the inherent regioselectivities of substrates are highly desired.

1.3 Directing Groups in Hydroformylation.

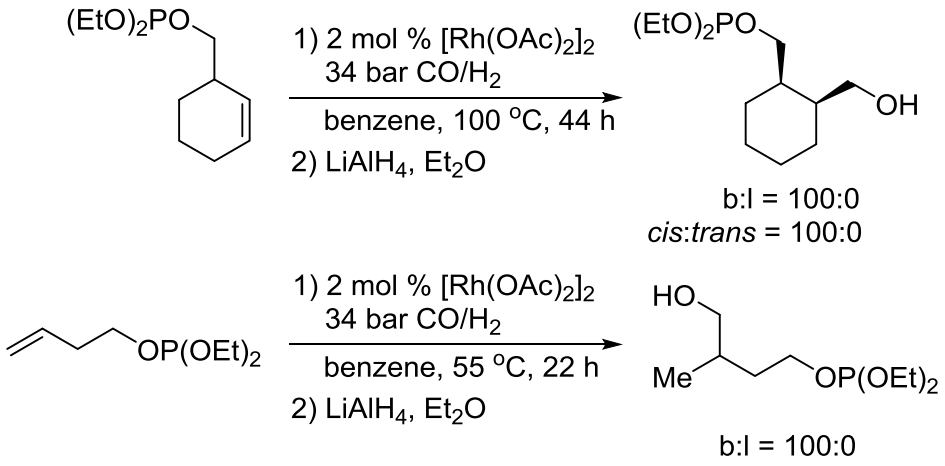
The use of directing group has been widely recognized as a powerful method to control selectivities in a variety of reactions.[5] By incorporating the directing group into the substrate, an attractive substrate-reagent interaction can be achieved through covalent or noncovalent interactions. The resulting cyclic transition state can then accelerate the directed reaction by reducing the activation entropy. As a consequence, the directed reaction is able to out compete other non-directed reaction pathways (Figure 1.2).

Figure 1.2. Concept of directing group.



In the area of regioselective hydroformylation, the use of directing groups is a proven strategy.[6] While linear products can be obtained via hydroformylations controlled by various methods, the access to branched aldehyde products generally relies on the use of phosphorus-based directing groups.

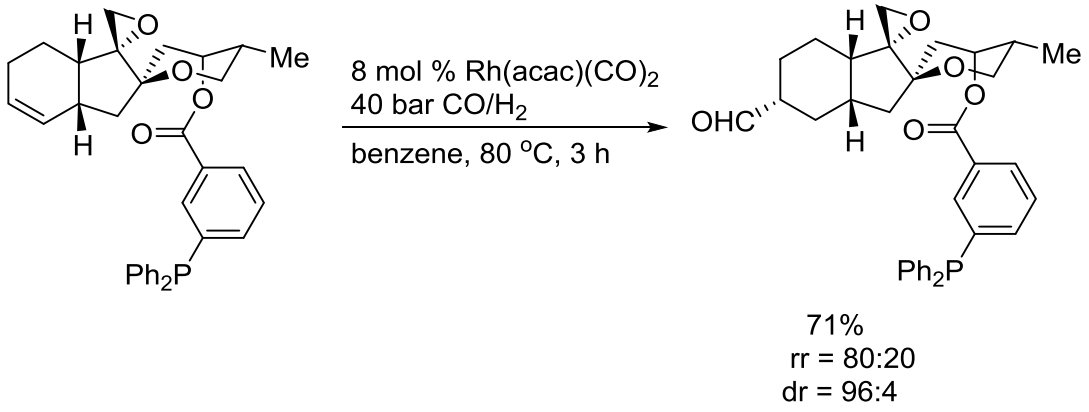
Scheme 1.3. Phosphite directed hydroformylation of homoallylic olefins



In 1990, Jackson reported the first use of phosphites to direct the branch-selective

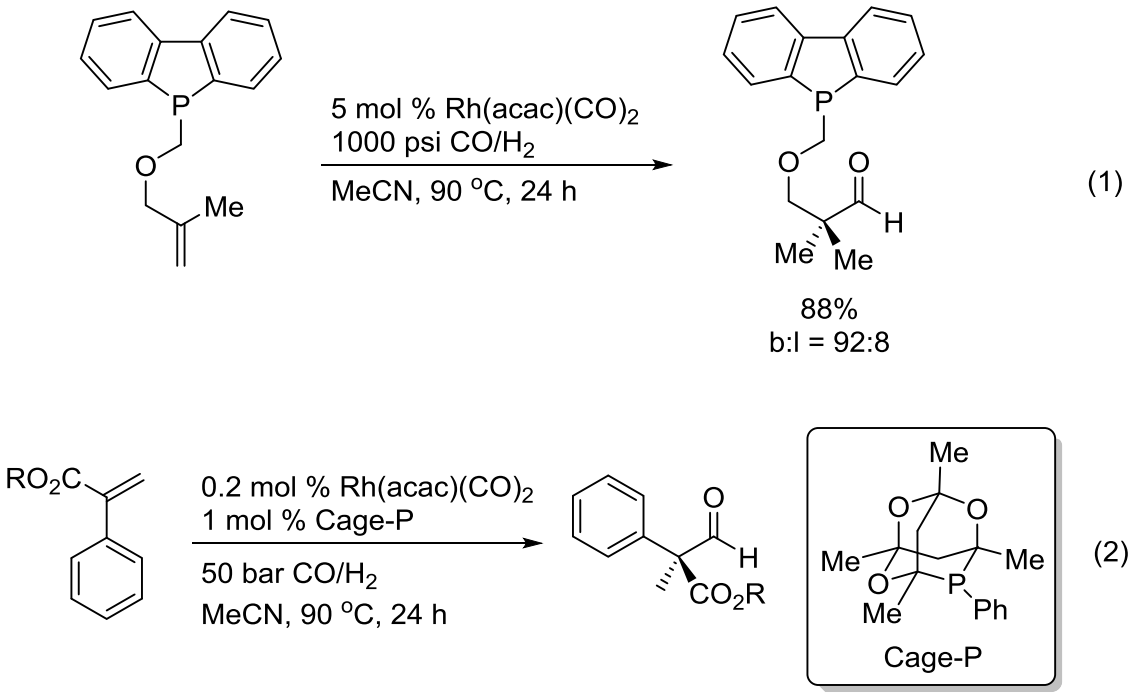
hydroformylation of cyclic and acyclic homoallylic olefins (Scheme 1.3).[7] Burke also employed a triphenylphosphine group to remotely induce a regio- and diastereoselective hydroformylation on a 1,2-disubstituted alkene, leading to the synthesis of (+)-phyllanthocin (Scheme 1.4).[8] Subsequently, Leighton[9] and Breit[10] demonstrated that similar directing groups can be used in the regio- and diastereoselective hydroformylations of terminal alkenes.

Scheme 1.4. Triphenylphosphine directed hydroformylation



In the hydroformylation of 1,1-disubstituted alkene, successful application of directing groups has been rare. In 2001, Leighton reported a single example of a directed hydroformylation of a 1,1-disubstituted allylic olefin to form the branched aldehyde product (Scheme 1.5, equation 1).[9] Esters were also shown to direct hydroformylation giving aldehydes containing all-carbon quaternary center by Clarke (Scheme 1.5, equation 2).[11]

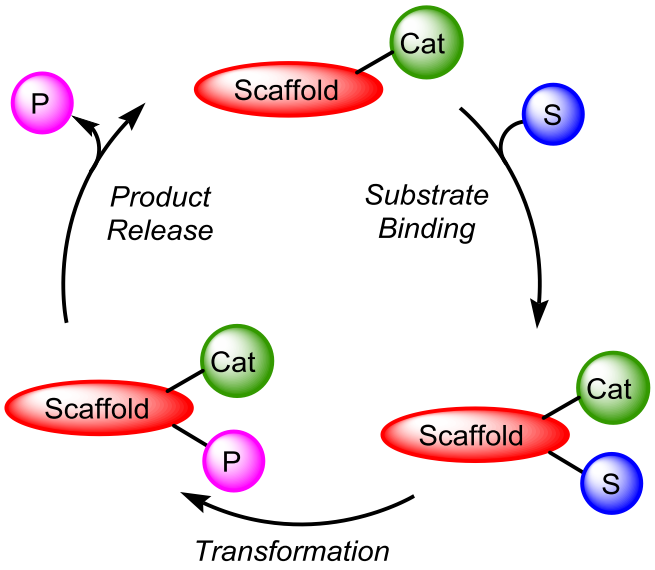
Scheme 1.5. Directed Hydroformylations of 1,1-disubstituted olefins.



1.4 Catalytic Directing Groups in Hydroformylation.

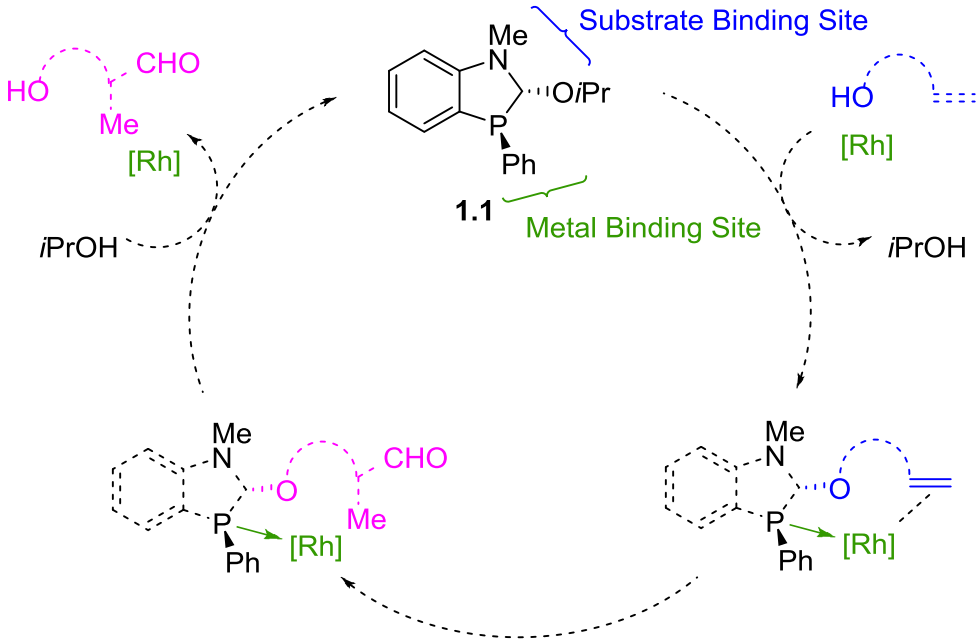
One critical disadvantage of directing groups is their use in stoichiometric quantities. Additionally, synthetic steps are required to install and remove directing groups. Development of a catalytic directing group would largely expand the practical scope of this concept. To achieve this goal, directing groups utilizing reversible covalent bonds with substrates have been developed (Figure 1.3).[6]

Figure 1.3. Concept of catalytic directing group.



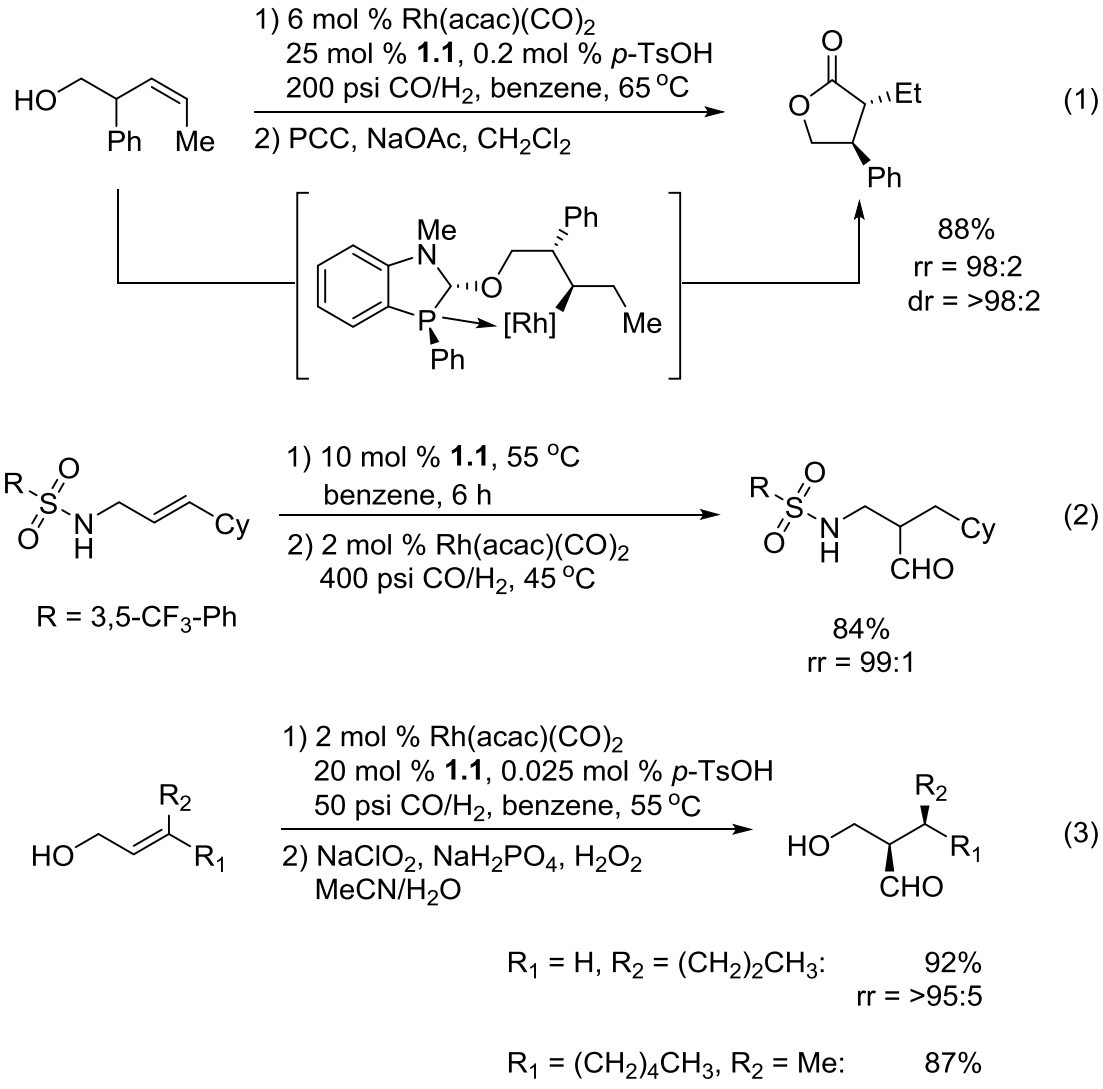
In 2008, Tan reported scaffolding catalyst **1.1** as the first catalytic directing group in hydroformylation.[12] In the design of this catalyst, a 1,3-azaphospholidine is employed to enable the formation of a reversible covalent bond between the catalyst and alcohol substrates. Simultaneously, the phosphine center in catalyst **1.1** is able to coordinate to the metal catalyst. As a result, a transient tether between substrate and metal catalyst is created, allowing a directed hydroformylation of the olefin with high selectivity (Figure 1.4).

Figure 1.4. Design of scaffolding catalyst **1.1**.



Catalytic amounts (20-25 mol %) of **1.1** were demonstrated to efficiently direct branch-selective hydroformylation of homoallylic alcohols. After hydroformylation and oxidation, products were isolated in the form of γ-lactones in high regio- and diastereoselectivities (Scheme 1.6, equation 1).[12] The substrate scope was further expanded to allylic sulfonamides (Scheme 1.6, equation 2),[13] as well as allylic alcohols (Scheme 1.6, equation 3),[14] in which case the loading of **1.1** can be dropped to as low as 5 mol %. Trisubstituted olefins, which are generally considered difficult substrates due to their higher activation barriers, also underwent scaffolding catalysed hydroformylation in high yields and regioselectivities (Scheme 1.6, equation 3).

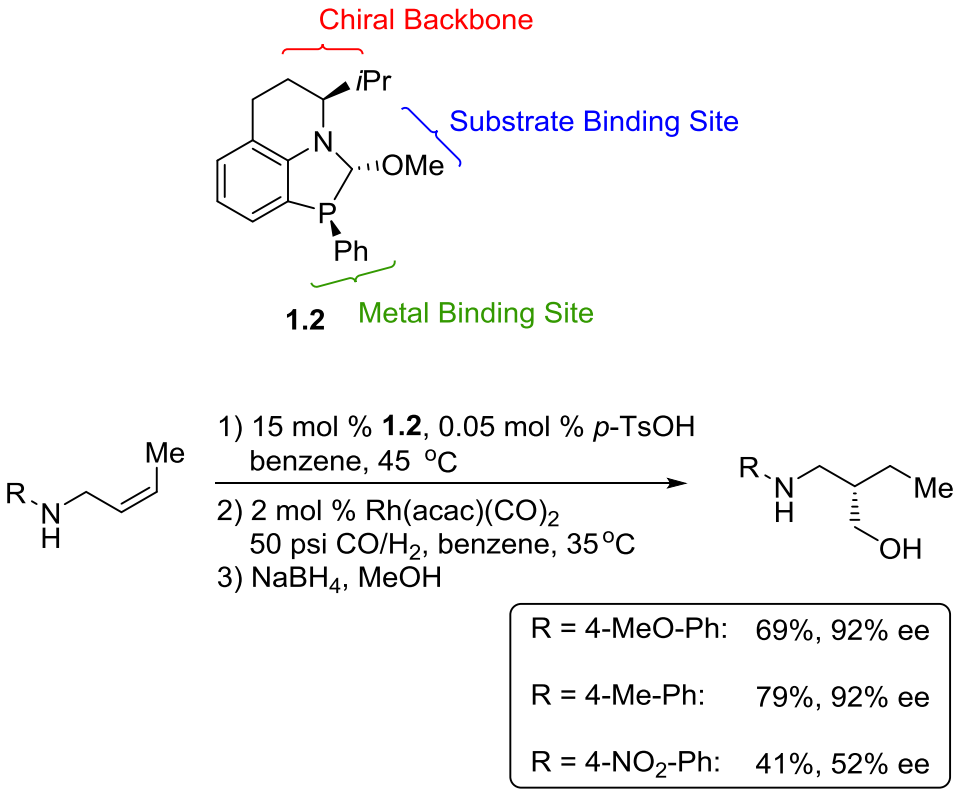
Scheme 1.6. Regio- and diastereoselective hydroformylations directed by catalyst **1.1**.



Similar to **1.1**, a chiral scaffolding catalyst **1.2** was also developed by Tan, facilitating the control of both regio- and enantioselectivity in the hydroformylation of allylic anilines.[15] Modifications of the aniline revealed that electron-donating groups promote the reaction in high yields and selectivities.[16] Through hydroformylation and reduction, a variety of chiral γ-amino alcohols were synthesized with high

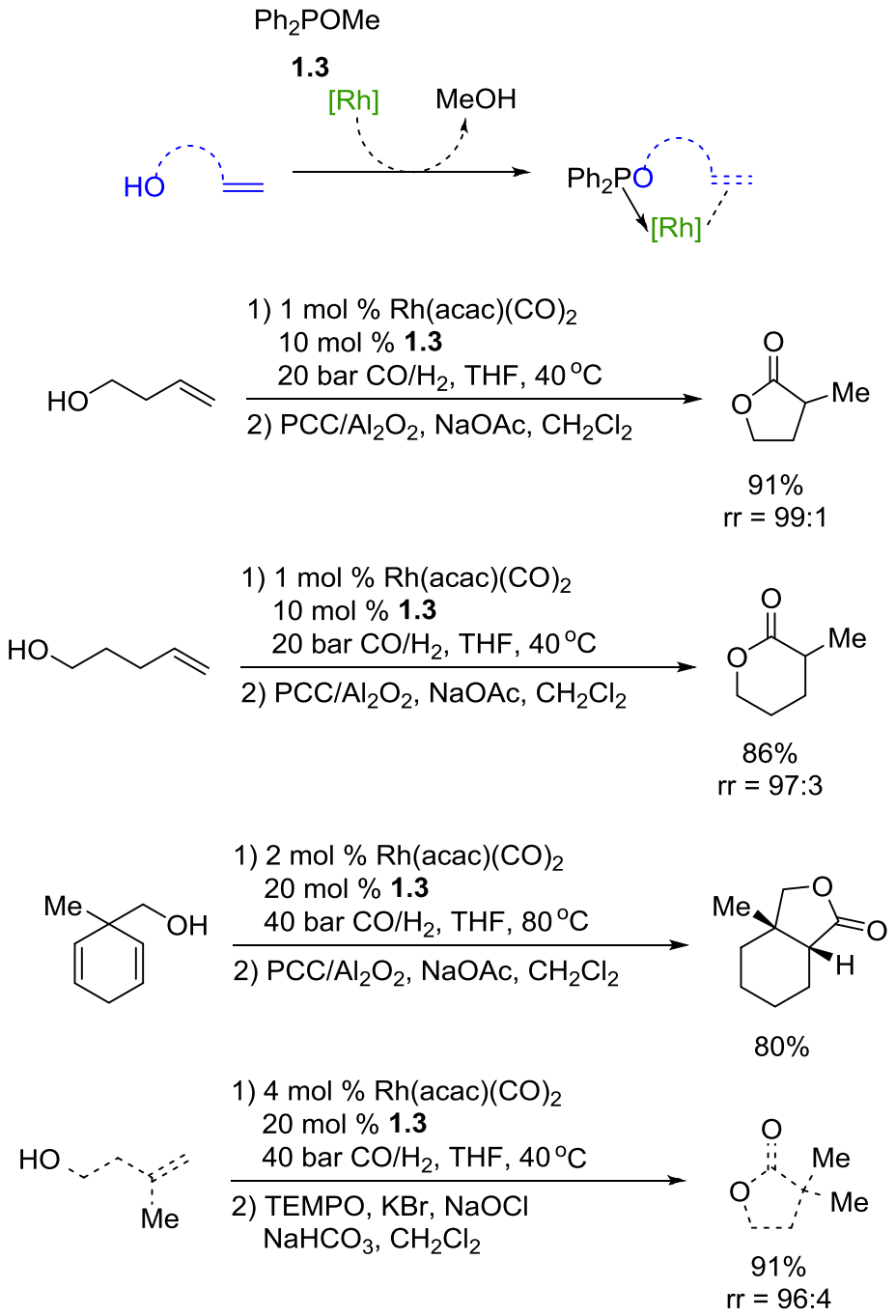
enantioselectivities (Scheme 1.7).

Scheme 1.7. Regio and enantioselective hydroformylations directed by chiral catalyst **1.2**.



Breit also introduced a phosphinite **1.3** as a catalytic directing group in hydroformylation (Scheme 1.8).[17] Under a similar principle as the scaffolding catalysis, phosphinite **1.3** reversibly bonds to homoallylic alcohols, and directs hydroformylation to form branched aldehydes. A remote control of regioselectivity by **1.3** was also demonstrated in the hydroformylation and oxidation of bishomoaalylic alcohols to form δ-lactones.[18] Later, the same catalyst was also applied to hydroformylation towards aldehydes containing quaternary centers.[19]

Scheme 1.8. Regio- and enantioselective hydroformylations directed by phosphinite **1.3.**



The developments of supramolecular catalysts to direct regioselective

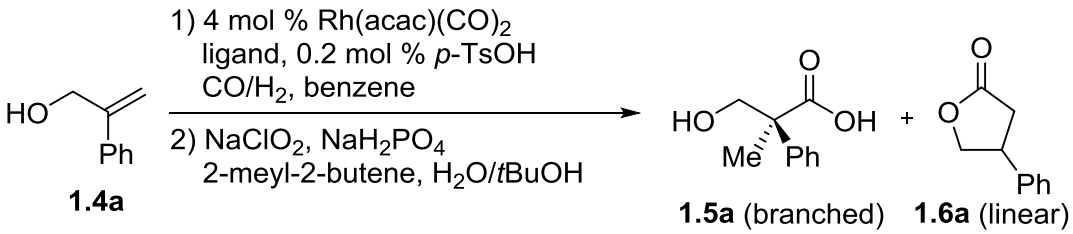
hydroformylations were also reported by Breit[20a-b] and Reek[20c]. Mimicking the enzymes, the functionalized supramolecular catalysts are able to recognize and coordinate to the substrate via multiple non-covalent bonds, and direct the regioselective hydroformylations. Even though attempts to form quaternary centers were not successful, these methods opened an important pathway to achieve regioselectivity in hydroformylations through supramolecular chemistry.

1.5 Synthesis of Quaternary Carbon Centers via Hydroformylations

Encouraged by previous successes with scaffolding catalyst **1.1**, we attempted synthesis of quaternary carbon centers via hydroformylation of 1,1-disubstituted olefins. We began by investigating the hydroformylation of allylic alcohol **1.4a**. Though styrenes are known to electronically promote branch-selective hydroformylation[21], previous attempts to hydroformylate α-substituted styrenes afforded only linear aldehyde products[22]. Applying Ph_3P as ligand, hydroformylation of **1.4a** at 75 ℃ was found to only yield the linear product (Table 1.1, entry 1). In contrast to the background reaction, using 20 mol % of catalyst **1.1**, the branched aldehyde containing a quaternary carbon center was obtained as the major product (Table 1.1, entry 2), indicating a reversal of the substrate inherent selectivity. Due to the unstable nature of the branched aldehyde and its tendency to dimerize to a cyclic acetal, we oxidized the crude mixture to isolate the carboxylic acid. Further optimization revealed that when performed at 45 ℃, the reaction forms the branched product in 64% yield and b:l = 95:5 regioselectivity (Table 1.1, entry

3). Interestingly, increasing the pressure of CO/H_2 to 400 psi further elevates the regioselectivity to b:l = 97:3, suggesting that higher pressure may change the selectivity-determining step, or mitigate the competing pathways (Table 1.1, entry 7). In addition, a control reaction with Ph_3P performed at the same temperature (45 ℃) resulted in no product formation, indicating that the directed reaction is accelerated dramatically compared to the background (Table 1.1, entry 8).

Table 1.1. Optimization for hydroformylations of **1.4a**.



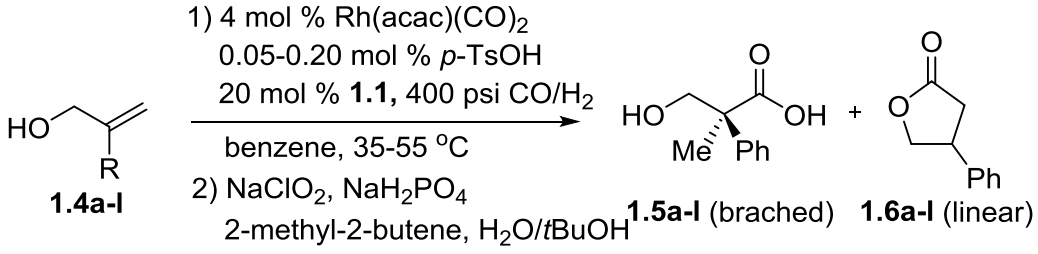
entry	ligand	pressure (psi)	temperature (°C)	b:l[a]	yield (%)[b]
1	Ph_3P[c]	400	75	<2:98	66[e]
2	**1.1**[d]	200	35	96:4	54
3	**1.1**[d]	200	45	95:5	64
4	**1.1**[d]	200	55	95:5	50
5	**1.1**[d]	50	45	89:11	38
6	**1.1**[d]	100	45	94:6	53
7	**1.1**[d]	400	45	97:3	70 (73)[f]
8	Ph_3P[c]	400	45	-	0

[a] Regioselectivities determined by ^1H NMR of crude reaction mixtures. [b] Yields of the branched product determined by ^1H NMR with internal standard. [c] 8 mol % Ph_3P. [d] 20 mol % **1.1**. [e] Isolated yield of lactone. f Isolated yield of branched product.

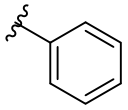
In our exploration of the substrate scope, both electron-deficient and electron-rich modifications on the substrate provided the branched product in good yields and high

regioselectivities (Table 1.2, **1.5b-c**). Bromo- or chloro-substituted aromatic rings also formed the quaternary aldehydes (Table 1.2, **1.5d-f**). Further examination revealed that incorporation of π-electron-withdrawing groups (Table 1.2, **1.5g-h**), naphthalene (Table 1.2, **1.5i**), and heterocyles (Table 1.2, **1.5j-k**) in the substrates were well tolerated. Hydroformylation of 2-methyl-propen-1-ol produced the branched product with promising regioselectivity (Table 1.2, **1.5l**). To improve regioselectivities of aliphatic substituted substrates, modifications of the catalyst will be needed.

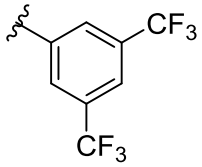
Table 1.2. Investigation of substrate scope.



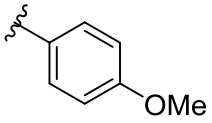
R =



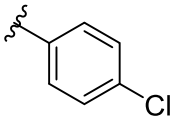
1.5a
73% yield[a]
b:l[b] = 97:3



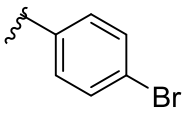
1.5b
80% yield[a]
b:l[b] > 98:2



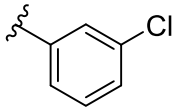
1.5c
66% yield[a]
b:l[b] > 98:2



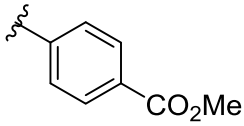
1.5d
60% yield[a]
b:l[b] = 97:3



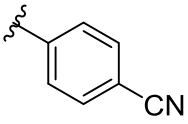
1.5e
71% yield[a]
b:l[b] = 94:6



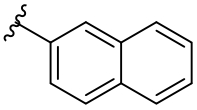
1.5f
77% yield[a]
b:l[b] > 98:2



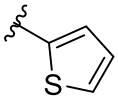
1.5g
74% yield[a]
b:l[b] > 98:2



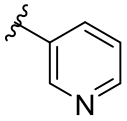
1.5h
67% yield[a]
b:l[b] > 98:2



1.5i
85% yield[a]
b:l[b] = 95:5



1.5j
70% yield[a]
b:l[b] = 95:5



1.5k
68% yield[a,c]
b:l[b] = 98:2

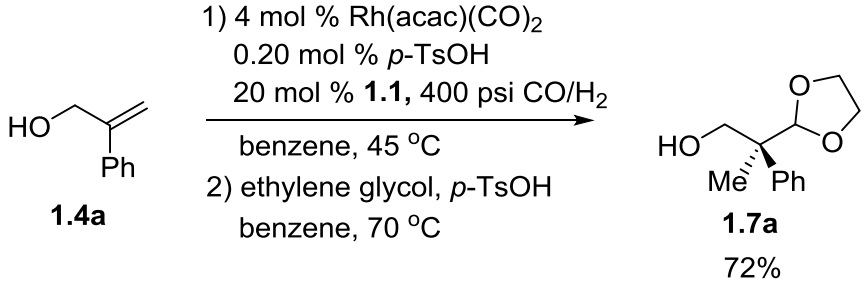
1.5l
49% yield[a]
b:l[b] = 76:24

[a] Isolated yield of branched product. [b] Regioselectivities determined by ^{1}H NMR of crude reaction mixture. [c] Reduction to the diol with $NaBH_4$ was performed instead of oxidation.

Since the required oxidation after hydroformylation limits the potential applications of this methodology, we also performed an acetal protection of the crude reaction mixture. The branched product was successfully isolated in the aldehyde

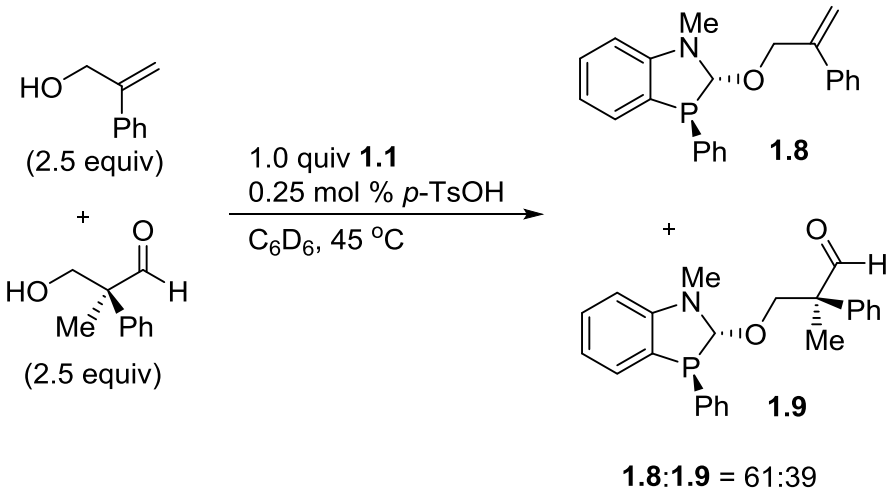
oxidation state with comparable yields (72%, Scheme 1.9).

Scheme 1.9. Acetal protection of the hydroformylation product.



Next, we studied a binding experiment of the scaffolding catalyst **1.1**. By adding 2.5 equivalents of substrate and 2.5 equivalents of the aldehyde product to catalyst **1.1** under acidic condition, the substrate was found to form a favored binding to **1.1** over the product (**1.8**:**1.9** = 61:39, Scheme 10). Therefore, the product inhibition can be mitigated during the reaction due to the catalyst's preference for binding to the starting material over the product.

Scheme 1.10. Binding study of catalyst **1.1**.



1.6 Conclusions

In summary, we have achieved the first synthesis of quaternary carbon centers via branch-selective hydroformylation with a catalytic directing group. The induced temporary intramolecularity allows this challenging reaction to be carried out under modest temperatures. We are currently developing catalysts to further expand the substrate scope of this method towards other disubstituted and trisubstituted olefins, as well as to achieve challenging selectivities in other organic transformations.

1.7 Experimental

General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher

Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringes, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). ^{1}H and ^{13}C NMR's were performed on either a Varian Unity INOVA 400 MHz or a Varian 500 MHz instrument. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C. Coupling constants are reported in Hz. Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet), br s (broad singlet). All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm^{-1}. HRMS data were generated in Boston College facilities. Hydroformylation was performed in an Argonaut Technologies Endeavor Catalyst Screening System using 1:1 H_2/CO supplied by Airgas, Inc.

Scaffolding catalyst **1.1** was synthesized following the previously reported procedures.[12]

Optimization of Branch Selective Hydroformylation

General Hydroformylation Procedure A. The oven dried glass reaction vial was placed in the Endeavor, and 2-phenylprop-2-en-1-ol (20 mg, 0.15 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of

dicarbonylacetylacetonato rhodium (I) (1.6 mg, 6.0×10^{-3} mmol, 4.0 mol %), **1.1** (8.6 mg, 3.0×10^{-2} mmol, 20 mol %), *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol, 0.20 mol %) and benzene (to total volume of 1 mL) was injected, followed by injection of additional benzene (0.5 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at the corresponding temperature (see below) for 10 minutes. Stirring was stopped, the Endeavor was charged with corresponding pressure (see below) of H_2/CO, stirring was re-initiated at 700 rpm., and the Endeavor was maintained at a constant temperature (see below) and pressure (see below) of H_2/CO for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction mixture was removed from the Endeavor and concentrated. The residue was redissolved in t-butanol (0.75 mL) and 2-methyl-2-butene (0.16 mL, 1.5 mmol, 10.0 eq.) followed by addition of a solution of $NaClO_2$ (80%, 68 mg, 0.60 mmol, 4.0 eq.) and NaH_2PO_4 (72 mg, 0.60 mmol, 4.0 eq.) in H_2O (0.4 mL). The solution was stirred at room temperature overnight. The resulting mixture was concentrated and redissolved in EtOAc (0.75 mL), followed by addition of 10% HCl (0.18 mL) and brine (0.18 mL). The solution was extracted with EtOAc (3 × 5 mL). Combined organic layers were dried over $MgSO_4$, filtered and solvent was removed. 1,3,5-Trimethoxybenzene (100 μL of 0.15 M in $CDCl_3$, 0.015 mmol) was added as standard and ^{1}H NMR was measured to analyze yields and selectivities.

General Hydroformylation Procedure B. The oven dried glass reaction vial was

placed in the Endeavor, and 2-phenylprop-2-en-1-ol (80 mg, 0.60 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium (I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol %), triphenylphosphine (13 mg, 4.8×10^{-2} mmol, 8.0 mol %) and benzene (to a total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 45 ℃ for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature and pressure of 45 ℃ and 400 psi H_2/CO for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction was removed from the Endeavor and concentrated. 1,3,5-Trimethoxybenzene (400 μL of 0.15 M in $CDCl_3$, 0.060 mmol) was added as standard and ^{1}H NMR was measured to analyze conversion.

General Hydroformylation Procedure C. The oven dried glass reaction vial was placed in the Endeavor, and 2-phenylprop-2-en-1-ol (80 mg, 0.60 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium (I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol %), triphenylphosphine (13 mg, 4.8×10^{-2} mmol, 8.0 mol %) and benzene (to a total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 75℃ for 10 minutes. Stirring

was stopped, the Endeavor was charged with 400 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature and pressure of 75℃ and 400 psi H_2/CO for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction was removed from the Endeavor and concentrated. The residue was redissolved in *t*-butanol (3 mL) and 2-methyl-2-butene (0.64 mL, 6.0 mmol, 10.0 eq.) followed by addition of a solution of $NaClO_2$ (80%, 270 mg, 2.4 mmol, 4.0 eq.) and NaH_2PO_4 (290 mg, 2.4 mmol, 4.0 eq.) in H_2O. The solution was stirred at room temperature overnight. The resulting mixture was concentrated and redissolved in EtOAc (3 mL), followed by addition of 10% HCl (0.75 mL) and brine (0.75 mL). The solution was extracted with EtOAc (3 × 20 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. ^{1}H NMR was measured to analyze selectivity. Flash column chromatography (Hex/EtOAc = 8/1) was performed to determine isolated yields.

Table 1.1, Entry 1. 2-Phenylprop-2-en-1-ol was hydroformylated using General Procedure C. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of < 2:98. Linear product was isolated as a white solid (64.0 mg, 66%).

Table 1.1, Entry 2. 2-Phenylprop-2-en-1-ol was hydroformylated using General Procedure A with 200 psi CO/H_2 at 35 ℃. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 96:4 and yield of 54%.

Table 1.1, Entry 3. 2-Phenylprop-2-en-1-ol was hydroformylated using General Procedure A with 200 psi CO/H_2 at 45 ℃. Analysis of crude mixture after oxidation by

^{1}H NMR showed a b:l selectivity of 95:5 and yield of 64%.

Table 1.1, Entry 4. 2-Phenylprop-2-en-1-ol was hydroformylated using General Procedure A with 200 psi CO/H_2 at 55 ℃. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 95:5 and yield of 50%.

Table 1.1, Entry 5. 2-Phenylprop-2-en-1-ol was hydroformylated using General Procedure A with 50 psi CO/H_2 at 45 ℃. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 89:11 and yield of 38%.

Table 1.1, Entry 6. 2-Phenylprop-2-en-1-ol was hydroformylated using General Procedure A with 100 psi CO/H_2 at 45 ℃. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 94:6 and yield of 53%.

Table 1, Entry 7. 2-Phenylprop-2-en-1-ol was hydroformylated using General Procedure A with 400 psi CO/H_2 at 45 ℃. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 97:3 and yield of 70%.

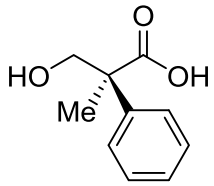
Table 1, Entry 8. 2-Phenylprop-2-en-1-ol was hydroformylated using General Procedure B. Analysis of crude mixture after hydroformylation by ^{1}H NMR showed 0% conversion.

*Hydroformylation Using Catalyst **1.1** and Product Characterizations*

General Hydroformylation Procedure. The oven dried glass reaction vial was placed in the Endeavor, and corresponding alcohol substrate (0.60 mmol, see below) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of

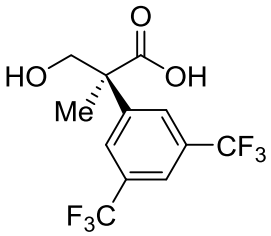
dicarbonylacetylacetonato rhodium (I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol %), **1.1** (34 mg, 0.12 mmol, 20 mol %), p-toluenesulfonic acid (see below) and benzene (to total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 35 °C (or 45 ℃ , see below) for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature (see below) and pressure (see below) of H_2/CO for 12 h (or 16 h, see below). The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction was removed from the Endeavor and concentrated. The residue was redissolved in t-butanol (3 mL) and 2-methyl-2-butene (0.64 mL, 6.0 mmol, 10.0 eq.) followed by addition of a solution of $NaClO_2$ (80 %, 270 mg, 2.4 mmol, 4.0 eq.) and NaH_2PO_4 (290 mg, 2.4 mmol, 4.0 eq.) in H_2O. The solution was stirred at room temperature overnight. The resulting mixture was concentrated and redissolved in EtOAc (3 mL), followed by addition of 10 % HCl (0.75 ml) and brine (0.75 mL). The solution was extracted with EtOAc (3 × 20 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated. ^{1}H NMR was measured to analyze selectivities. Flash column chromatography (Hex/EtOAc = 4/1) afforded pure branched products.

3-Hydroxy-2-methyl-2-phenylpropanoic acid (**1.5a**). 2-Phenylprop-2-en-1-ol (80 mg, 0.60 mmol) was hydroformylated with 0.20 mol % *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 45 ℃ for 12 h. Analysis of crude mixture



after oxidation by ^{1}H NMR showed selectivity (b:l = 97:3). Branched product was isolated as a white solid (79 mg, 73%)**. ^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36-7.24 (m, 5H), 6.98 (br s, 1H), 4.09 (d, 1H, *J* = 11.6), 3.66 (d, 1H, *J* = 11.2), 1.67 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 181.2, 139.5, 128.7, 127.6, 126.3, 69.1, 52.4, 20.0; **IR**: 2982, 1701, 1239, 1026, 698 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{16}NO_3$ $[M+NH_4]^+$: 198.11302, found: 198.11247.

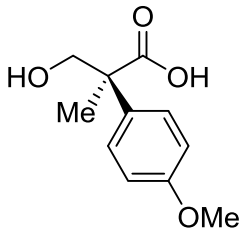
2-(3,5-Bis(trifluoromethyl)phenyl)-3-hydroxy-2-methylpropanoic acid (**1.5b**).



2-(3,5-Bis(trifluoromethyl)phenyl)prop-2-en-1-ol (160 mg, 0.60 mmol) was hydroformylated with 0.05 mol % *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 45 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of > 98:2. Branched product was isolated as a white solid (152 mg, 80%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.86 (s, 3H), 4.06 (d, 1H, *J* = 11.5), 3.89 (d, 1H, *J* = 11.5), 1.75 (s, 3H); **^{13}C NMR** (Acetone d-6, 125 MHz) δ 174.6, 145.3, 130.9 (q, *J* = 32.9), 127.9, 123.7 (q, *J* = 270.1), 120.6, 67.6, 52.5, 20.1; **IR**: 2924, 1711, 1373, 1287, 1187, 1132 cm^{-1}; **HRMS** (DART-TOF) calcd. For $C_{12}H_{14}F_6NO_3$ $[M+NH_4]^+$: 334.08779, found: 334.08865.

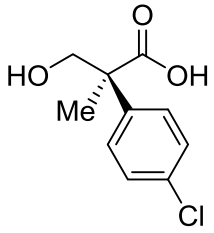
3-Hydroxy-2-(4-methoxyphenyl)-2-methylpropanoic acid (**1.5c**).

2-(4-Methoxyphenyl)-prop-2-en-1-ol (98 mg, 0.60 mmol) was hydroformylated with 0.20 mol % p-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 35 ℃ for 16 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l



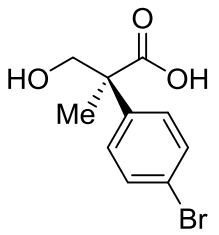
selectivity of > 98:2. Branched product was isolated as a white solid (83 mg, 66%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.21 (d, 2H, *J* = 8.5), 6.99 (br s, 1H), 6.81 (d, 2H, *J* = 8.5), 4.00 (d, 1H, *J* = 11.5), 3.72 (s, 3H), 3.56 (d, 1H, *J* = 11.5), 1.58 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 181.3, 158.9, 131.5, 127.4, 114.1, 69.1, 55.2, 51.6, 20.1; **IR**: 2937, 1703, 1514, 1253, 1187, 1029, 829 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{18}NO_4$ $[M+NH_4]^+$: 228.12358, found: 228.12384.

2-(4-Chlorophenyl)-3-hydroxy-2-methylpropanoic acid (**1.5d**). 2-(4-Chlorophenyl)-



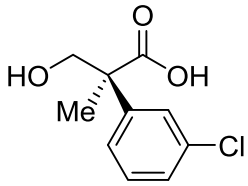
prop-2-en-1-ol (100 mg, 0.60 mmol) was hydroformylated with 0.05 mol % *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 35 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 97:3. Branched product was isolated as a white solid (78 mg, 60%)**. ^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33-7.24 (m, 4H), 6.54 (br s, 1H), 4.04 (d, 1H, *J* = 11.2), 3.66 (d, 1H, *J* = 11.6), 1.64 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 180.6, 138.1, 133.6, 128.8, 127.8, 68.9, 52.0, 20.1; **IR**: 2941, 1702, 1494, 1260, 1098, 1034, 1013, 824 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{15}Cl_1NO_3$ $[M+NH_4]^+$: 232.07405, found: 232.07432.

2-(4-Bromophenyl)-3-hydroxy-2-methylpropanoic acid (**1.5e**). 2-(4-Bromophenyl)-prop-2-en-1-ol (130 mg, 0.60 mmol) was hydroformylated with 0.05 mol % *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 35 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of



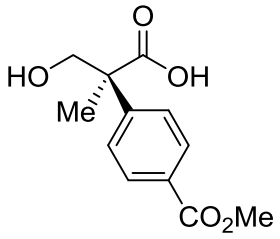
94:6. Branched product was isolated as a white solid (110 mg, 71%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48 (d, 1H, *J* = 8.8), 7.22 (d, 1H, *J* = 8.8), 7.05 (br s, 1H), 4.03 (d, 1H, *J* = 11.6), 3.66 (d, 1H, *J* = 11.6), 1.64 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 180.7, 138.5, 131.8, 128.1, 121.8, 68.8, 52.0, 20.0; **IR**: 2938, 1703, 1491, 1398, 1241, 1034, 1009, 820 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{15}Br_1NO_3$ $[M+NH_4]^+$: 276.02353, found: 276.02357.

2-(3-Chlorophenyl)-3-hydroxy-2-methylpropanoic acid (**1.5f**).



2-(3-Chlorophenyl)prop-2-en-1-ol (100 mg, 0.60 mmol) was hydroformylated with 0.20 mol % *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 35 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of > 98:2. Branched product was isolated as a white solid (99 mg, 77%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33 (s, 1H), 7.27-7.20 (m, 3H), 7.25 (br s, 1H), 4.04 (d, 1H, *J* = 11.2), 3.66 (d, 1H, *J* = 11.6), 1.63 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 180.3, 141.6, 134.6, 129.9, 127.8, 126.7, 124.6, 68.7, 52.2, 20.0; **IR**: 2982, 1703, 1244, 1035, 698 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{12}Cl_1O_3$ $[M+H]^+$: 215.04750, found: 215.04853.

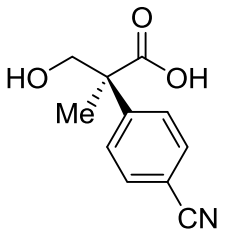
3-Hydroxy-2-(4-(methoxycarbonyl)phenyl)-2-methylpropanoic acid (**1.5g**). Methyl



4-(3-hydroxyprop-1-en-2-yl)benzoate (120 mg, 0.60 mmol) was hydroformylated with 0.05 mol % *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 45 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of > 98:2.

Branched product was isolated as a white solid (106 mg, 74%). **^{1}H NMR** (acetone d-6, 400 MHz) δ 7.96 (d, 2H, *J* = 8.6), 7.53 (d, 2H, *J* = 8.6), 4.10 (d, 1H, *J* = 10.8), 3.86 (s, 3H), 3.84 (d, 1H, *J* = 10.8), 1.62 (s, 3H); **^{13}C NMR** (Acetone d-6, 100 MHz) δ 175.2, 166.1, 147.3, 129.2, 128.7, 126.7, 67.9, 52.5, 51.4, 20.2; **IR**: 2952, 1719, 1437, 1282, 1194, 1115, 1018, 707 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{15}O_5$ $[M+H]^+$: 239.09195, found: 239.09209.

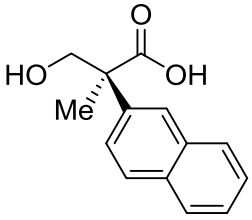
2-(4-Cyanophenyl)-3-hydroxy-2-methylpropanoic acid (**1.5h**).



4-(3-Hydroxy-prop-1-en-2-yl)-benzonitrile (96 mg, 0.60 mmol) was hydroformylated with 0.20 mol % *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 45 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of > 98:2. Branched product was isolated as a white solid (82 mg, 67%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40 (br s, 1H), 7.64 (d, 2H, *J* = 8.4), 7.48 (d, 2H, *J* = 8.4), 4.02 (d, 1H, *J* = 11.2), 3.76 (d, 1H, *J* = 11.2), 1.66 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 179.5, 145.0, 132.4, 127.4, 118.3, 111.6, 68.5, 52.6, 20.2; **IR**: 3362, 2240, 1721, 1220, 1034, 836, 677, 558 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{12}NO_3$ $[M+H]^+$: 206.08172, found: 206.08261.

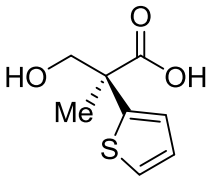
3-Hydroxy-2-methyl-2-(naphthalen-2-yl)propanoic acid (**1.5i**).

2-(Naphthalen-2-yl)-prop-2-en-1-ol (110 mg, 0.60 mmol) was hydroformylated with 0.05 mol % *p*-toluenesulfonic acid (500 μL of 6.0×10^{-4} M in benzene, 3.0×10^{-4} mmol) at 35 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l



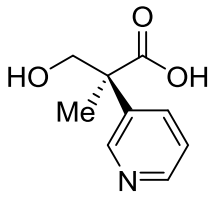
selectivity of 95:5. Branched product was isolated as a white solid (117 mg, 85%). **^{1}H NMR** (Acetone d-6, 500 MHz) δ 7.94-7.87 (m, 4H), 7.61-7.59 (m, 1H), 7.51-7.49 (m, 2H), 5.15-3.23 (br s, 1H), 4.28 (d, 1H, *J* = 10.5), 4.19 (br s, 1H), 3.95 (d, 1H, *J* = 11.0), 2.81 (s, 1H), 1.77 (s, 3H); **^{13}C NMR** (Acetone d-6, 125 MHz) δ 175.9, 139.4, 133.5, 132.5, 128.0, 127.8, 127.4, 126.0, 125.9, 125.0, 125.0, 68.2, 52.4, 20.4; **IR**: 2921, 1697, 1027, 816, 751, 477 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{14}H_{18}NO_3$ $[M+NH_4]^+$: 248.12867, found: 248.12972.

3-Hydroxy-2-methyl-2-(thiophen-3-yl)propanoic acid (**1.5j**). 2-(Thiophen-3-yl)-



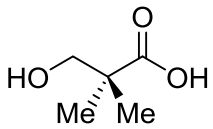
prop-2-en-1-ol (84 mg, 0.60 mmol) was hydroformylated with 0.20 mol % *p*-toluenesulfonic acid (2.0 mL of 6.0 × 10^{-4} M in benzene, 1.2 × 10^{-3} mmol) at 45 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 95:5. Branched product was isolated as a white solid (78 mg, 70%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.32-7.31 (m, 1H), 7.24 (d, 1H, *J* = 1.5), 7.13-7.12 (m, 1H), 6.87 (br s, 1H), 4.11 (d, 1H, *J* = 11.2), 3.72 (d, 1H, *J* = 11.2), 1.67 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 180.3, 140.5, 126.3, 125.9, 121.7, 68.7, 50.1, 20.6; **IR**: 2925, 1698, 1222, 1029, 871, 782, 684 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_8H_{10}O_3S$ $[M+NH_4]^+$: 204.06944, found: 204.07035.

2-methyl-2-(pyridin-3-yl)propane-1,3-diol (**1.5k**). 2-(pyridin-3-yl)-prop-2-en-1-ol (20 mg, 0.15 mmol) was hydroformylated with 0.20 mol % *p*-toluenesulfonic acid (500 μL of 6.0 × 10^{-4} M in benzene, 0.30 × 10^{-3} mmol) at 45 ℃ for 12 h. Reduction with



$NaBH_4$ (17 mg, 0.45 mmol) and MeOH (3.0 mL) at rt for 2h was performed instead of oxidation. Analysis of crude mixture after reduction by ^{1}H NMR showed a b:l selectivity of 98:2. Branched product was isolated as a white solid (17 mg, 68%). **^{1}H NMR** (Methanol d-4, 500 MHz) δ 8.65 (d, 1H, *J* = 1.7), 8.39 (dd, 1H, *J* = 1.5, 4.9), 7.96-7.94 (m, 1H), 7.43-7.40 (m, 1H), 3.84 (d, 2H, *J* = 11.0), 3.75 (d, 2H, *J* = 11.0), 1.37 (s, 3H); **^{13}C NMR** (Methanol d-4, 125 MHz) δ 147.7, 146.0, 140.7, 135.9, 123.4, 77.0, 43.8, 18.8; **IR**: 3346, 2812, 1416, 1020, 820, 713, 632 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_9H_{14}NO_2$ $[M+H]^+$: 168.10245, found: 168.10277.

3-hydroxy-2,2-dimethylpropanoic acid (**1.5l**). 2-methylprop-2-en-1-ol (43 mg, 0.60 mmol) was hydroformylated with 0.20 mol % *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M in benzene, 1.2×10^{-3} mmol) at 45 ℃ for 12 h. Analysis of crude mixture after oxidation by ^{1}H NMR showed a b:l selectivity of 76:24. Branched product was isolated as a white solid (35 mg, 49%). **^{1}H NMR** (acetone d-6, 500 MHz) δ 3.57 (s, 2H), 1.16 (s, 6H); **^{13}C NMR** (Acetone d-6, 125 MHz) δ 117.8, 68.8, 43.8, 21.4; **IR**: 2933, 1692, 1236, 1044 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_5H_{14}NO_3$ $[M+NH_4]^+$: 136.09737, found: 136.09743.

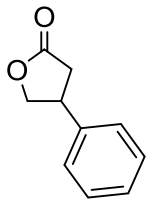


Linear Product Syntheses and Characterizations

General Procedure. The oven dried glass reaction vial was placed in the Endeavor, and corresponding alcohol substrates (0.60 mmol) was added. The Endeavor was sealed

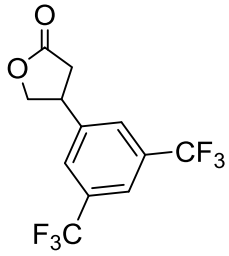
and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium (I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol %), triphenylphosphine (13 mg, 4.8×10^{-2} mmol, 8.0 mol %) and benzene (to total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 75 ℃ for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature and pressure of 75 ℃ and 400 psi H_2/CO for 16 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The sample was removed and concentrated. The crude residue was dissolved in CH_2Cl_2 (9 mL) and pyridinium chlorochromate (390 mg, 1.8 mmol, 3.0 eq.), sodium acetate (25 mg, 0.30 mmol, 0.50 eq.), and 3Å molecular sieves (1.2 g, 4-8 mesh) were added and the solution was agitated on an orbital shaker for 12 hours. Flash column chromatography (Hex/EtOAc = 8/1) afforded pure products.

4-Phenyldihydrofuran-2(3H)-one (**1.6a**, 83 mg, 85%). **^{1}H NMR** ($CDCl_3$, 500 MHz)



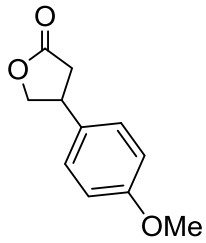
δ 7.39 (t, 2H, *J* = 7.6), 7.31 (t, 1H, *J* = 7.3), 7.25 (d, 2H, *J* = 7.6), 4.69 (dd, 1H, *J* = 7.8, 9.1), 4.28 (dd, 1H, *J* = 8.1, 9.1), 3.80 (m, 1H), 2.94 (dd, 1H, *J* = 8.8, 17.6), 2.69 (dd, 1H, *J* = 9.0, 17.4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 176.3, 139.4, 129.2, 127.7, 126.7, 74.0, 41.1, 35.7; **IR** 1759, 1156, 1007, 760, 702 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{11}O_2$ $[M+H]^+$: 163.07590, found 163.07652.

4-(3,5-Bis(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one (**1.6b**, 130 mg, 72%).

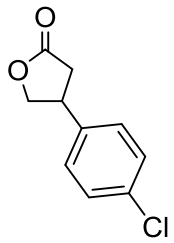


^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (s, 1H), 7.28 (s, 2H), 4.77 (dd, 1H, *J* = 8.1, 9.0), 4.34 (dd, 1H, *J* = 8.1, 9.3), 3.98 (m, 1H), 3.06 (dd, 1H, *J* = 8.8, 17.6), 2.73 (dd, 1H, *J* = 8.8, 17.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 174.9, 142.1, 132.7 (q, *J* = 34.4), 127.1, 123.0 (q, *J* = 271.1), 121.9, 72.9, 40.8, 35.3; **IR** 1786, 1374, 1276, 1170, 1110, 1030, 899, 842, 707, 682 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_9F_6O_2$ $[M+H]^+$: 299.05067, found 299.05024.

4-(4-Methoxyphenyl)dihydrofuran-2(3H)-one (**1.6c**, 74 mg, 64%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.13 (d, 2H, *J* = 8.8), 6.90 (d, 2H, *J* = 8.8), 4.62 (dd, 1H, *J* = 8.1, 9.1), 4.20 (dd, 1H, *J* = 8.1, 9.1), 3.79 (s, 3H), 3.72 (m, 1H), 2.88 (dd, 1H, *J* = 8.6, 17.4), 2.61 (dd, 1H, *J* = 9.3, 17.4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 176.4, 159.0, 131.3, 127.7, 114.5, 74.2, 55.3, 40.4, 35.9; **IR** 1765, 1511, 1454, 1254, 1164, 1014, 838, 602, 554 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{13}O_3$ $[M+H]^+$: 193.08647, found 193.08682.



4-(4-Chlorophenyl)dihydrofuran-2(3H)-one (**1.6d**, 73 mg, 62%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31 (d, 2H, *J* = 8.6), 7.29 (d, 2H, *J* = 8.4), 4.63 (dd, 1H, *J* = 7.8, 9.2), 4.20 (dd, 1H, *J* = 7.6, 9.0), 3.79-3.70 (m, 1H), 2.90 (dd, 1H, *J* = 8.8, 17.6), 2.60 (dd, 1H, *J* = 8.8, 17.4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 176.0, 138.0, 133.5, 129.3, 128.1, 73.7, 40.5, 35.6; **IR** 1774, 1485, 1425, 1161, 1093, 1011, 832, 680, 511, 496 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{10}ClO_2$



$[M+H]^+$: 197.03693, found 197.03745.

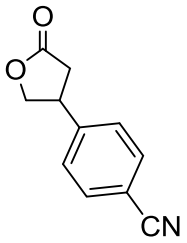
4-(4-Bromophenyl)dihydrofuran-2(3H)-one (**1.6e**, 110 mg, 76%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.49 (d, 2H, *J* = 8.6), 7.12 (d, 2H, *J* = 8.3), 4.66 (dd, 1H, *J* = 7.8, 9.0), 4.23 (dd, 1H, *J* = 7.6, 9.1), 3.76 (m, 1H), 2.92 (dd, 1H, *J* = 8.6, 17.4), 2.62 (dd, 1H, *J* = 8.8, 17.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 175.9, 138.6, 132.3, 128.4, 121.6, 73.7, 40.6, 35.6; **IR** 1764, 1486, 1422, 1154, 1010, 825, 539, 491 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{10}BrO_2$ $[M+H]^+$: 240.98642, found 240.98681.

4-(3-Chlorophenyl)dihydrofuran-2(3H)-one (**1.6f**, 95 mg, 81%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.31 (m, 1H), 7.24 (s, 1H), 7.14 (d, 2H, *J* = 8.3), 4.68 (dd, 1H, *J* = 7.8, 9.0), 4.27 (dd, 1H, *J* = 7.6, 9.0), 3.79 (m, 1H), 2.95 (dd, 1H, *J* = 8.5, 17.3), 2.66 (dd, 1H, *J* = 8.8, 17.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 175.9, 141.6, 135.0, 127.9, 127.1, 124.9, 73.6, 40.7, 35.5; **IR** 1773, 1598, 1480, 1164, 1083, 1019, 907, 785, 729, 693, 441 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{10}ClO_2$ $[M+H]^+$: 197.03693, found 197.03729.

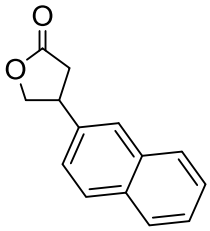
Methyl 4-(5-oxotetrahydrofuran-3-yl)benzoate (**1.6g**, 63 mg, 48%)**. ^{1}H NMR** ($CDCl_3$, 500 MHz) δ 8.01 (d, 2H, *J* = 8.5),7.30 (d, 2H, *J* = 8.5), 4.67 (dd, 1H, *J* = 7.8, 9.0), 4.26 (dd, 1H, *J* = 7.8, 9.3), 3.89 (s, 3H), 3.86-3.83 (m, 1H), 2.94 (dd, 1H, *J* = 8.8, 17.6), 2.66 (dd, 1H, *J* = 8.8, 17.4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 175.9, 166.5, 144.7, 130.4, 129.6, 126.8, 73.5, 52.2, 41.0, 35.4; **IR** 1778, 1717, 1280, 1168, 1109, 1019 cm^{-1}; **HRMS**

(DART-TOF) calcd. for $C_{12}H_{13}O_4$ $[M+H]^+$: 221.08138, found 221.08169.

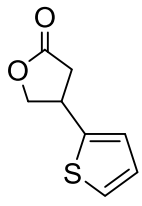
4-(5-Oxotetrahydrofuran-3-yl)-benzonitrile (**1.6h**, 82 mg, 72%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.65 (d, 2H, *J* = 8.2), 7.34 (d, 2H, *J* = 8.4), 4.67 (dd, 1H, *J* = 7.8, 9.2), 4.25 (dd, 1H, *J* = 7.4, 9.2), 3.84 (m 1H), 2.96 (dd, 1H, *J* = 8.8, 17.4), 2.63 (dd, 1H, *J* = 8.4, 17.6); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 175.4, 145.0, 133.0, 127.6, 118.3, 111.8, 73.2, 41.0, 35.4; **IR** 2225, 1763, 1609, 1507, 1166, 1013, 832, 729, 561 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{10}NO_2$ $[M+H]^+$: 188.07115, found 188.07101.



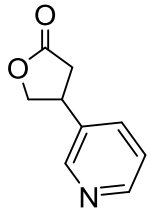
4-(Naphthalen-2-yl)dihydrofuran-2(3H)-one (**1.6i**, 97 mg, 76%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.87 (m, 3H), 7.69 (s, 1H), 7.54 (m, 2H), 7.35 (d, 1H, *J* = 8.3), 4.74 (dd, 1H, *J* = 7.8, 9.0), 4.38 (dd, 1H, *J* = 7.8, 9.0), 3.95 (m, 1H), 3.01 (dd, 1H, *J* = 8.8, 17.6), 2.80 (dd, 1H, *J* = 9.0, 17.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 176.4, 136.8, 133.4, 132.7, 129.1, 127.7, 126.7, 126.3, 125.5, 124.5, 73.9, 41.2, 35.7; **IR** 1759, 1158, 1006, 831, 749, 477 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{14}H_{13}O_2$ $[M+H]^+$: 213.09155, found 213.09151.



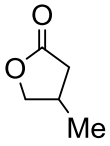
4-(Thiophen-3-yl)dihydrofuran-2(3H)-one (**1.6j**, 50 mg, 50%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.38-7.36 (m, 1H), 7.11-7.10 (m, 1H), 7.00-6.99 (m, 1H), 4.64 (dd, 1H, *J* = 7.8, 9.0), 4.26 (dd, 1H, *J* = 7.8, 9.0), 3.90-3.86 (m, 1H), 2.91 (dd, 1H, *J* = 8.6, 17.4), 2.64 (dd, 1H, *J* = 8.6, 17.4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 176.2, 140.1, 127.2, 125.8, 121.0, 73.5, 36.8, 35.6; **IR** 1770, 1167, 1017, 783 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_8H_9O_2S$ $[M+H]^+$: 169.03232, found 169.03152.



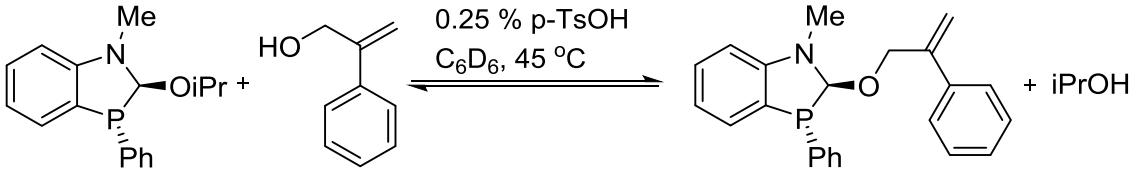
2-(pyridin-3-yl)butane-1,4-diol (**1.6k**, 19 mg, 75%). 2-(pyridin-3-yl)prop-2-en-1-ol (20 mg, 0.15 mmol) was hydroformylated. Reduction with $NaBH_4$ (17 mg, 0.45 mmol) and MeOH (3.0 mL) at rt for 2h was performed instead of oxidation. **^{1}H NMR** (Methanol d-4, 500 MHz) δ 8.46 (s, 1H), 8.41(d, 1H, J = 3.7), 7.80-7.78 (m, 1H), 7.43-7.40 (m, 1H), 3.78-3.72 (m, 2H), 3.55-3.51 (m, 1H), 3.45-3.40 (m, 1H), 3.03-2.99 (m, 1H), 2.10-2.03 (m, 1H), 1.87-1.80 (m, 1H); **^{13}C NMR** (Methanol d-4, 125 MHz) δ 149.0, 146.7, 139.3, 136.3, 123.8, 65.7, 59.1, 42.3, 34.3; **IR** 3260, 2925, 2855, 1427, 1050, 1028, 713 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_9H_{13}NO_2$ $[M+H]^+$: 168.10245, found 168.10230.



4-methyldihydrofuran-2(3H)-one (**1.6l**, 37 mg, 62%). Characterization data of this compound was previously reported.[23]



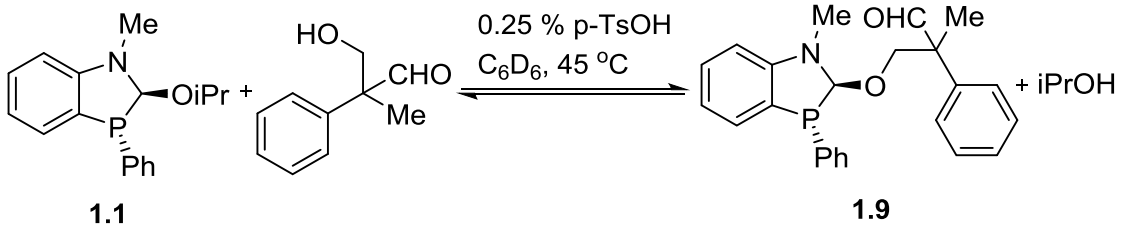
<u>*Binding Study of Catalyst **1.1***</u>



1.1 **1.8**

Catalyst **1.1** (5.7 mg, 2.0×10^{-2} mmol) was dissolved in C_6D_6 (1 mL) in an NMR tube under N_2. *p*-Toluenesulfonic acid (0.10 mL of 5.0×10^{-4} M in C_6D_6, 5.0×10^{-5} mmol) was added to the solution, followed by addition of 2-phenylprop-2-en-1-ol (13 mg, 0.10 mmol) and *i*PrOH (46 μL, 0.60 mmol). The solution was heated at 45 ℃ overnight.

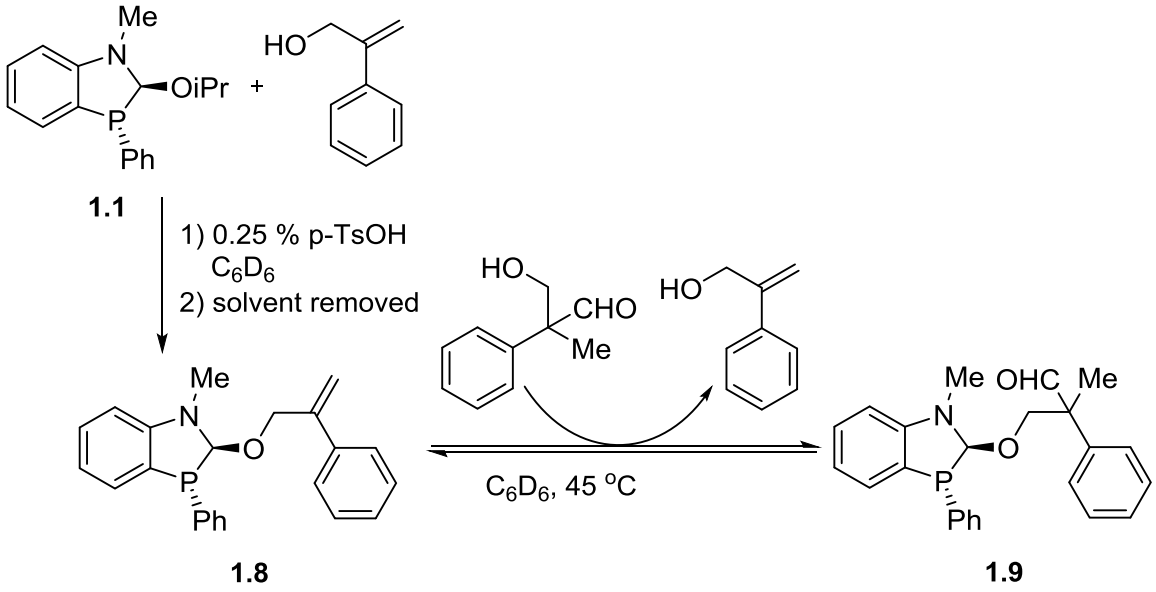
Analysis of the reaction by ^{1}H NMR showed **1.8**:**1.1** = 38:62, leading to Keq_1= 4.0.



1.1 **1.9**

Catalyst **1.1** (5.7 mg, 2.0 × 10^{-2} mmol) was dissolved in C_6D_6 (1 mL) in an NMR tube under N_2. p-Toluenesulfonic acid (0.10 mL of 5.0 × 10^{-4} M in C_6D_6, 5.0 × 10^{-5} mmol) was added to solution, followed by addition of 3-hydroxy-2-methyl-2-phenylpropanal (16 mg, 0.10 mmol, isolated from hydroformylation) and *i*-PrOH (23 μL, 0.30 mmol). Solution was heated at 45 ℃ overnight. Analysis of the reaction by ^{1}H NMR showed **1.9**:**1.1** = 41:59.

Note: Ignoring minor aldehyde dimerization, Keq_2 was calculated to be 2.3.



1.1 **1.8** **1.9**

Catalyst **1.1** (11 mg, 4.0 × 10^{-2} mmol), 2-phenylprop-2-en-1-ol (13 mg, 0.10

mmol) and p-toluenesulfonic acid (0.20 mL of 5.0×10^{-4} M in benzene d-6, 1.0×10^{-4} mmol) were dissolved in benzene d-6 (1 mL) under N_2. The solution was allowed to stand at room temperature for 10 min, and then solvent was removed under vacuum. The residue was redissolved in benzene d-6 (1 mL), and ^{1}H NMR analysis of solution showed **1.8** was formed (> 99%). 3-hydroxy-2-methyl-2-phenylpropanal (16 mg, 0.10 mmol, isolated from hydroformylation) was added, and mixture was heated at 45 ℃ overnight. Analysis of the reaction by ^{1}H NMR showed **1.9**:**1.8** = 39:61.

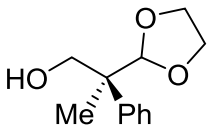
Note: Ignoring minor aldehyde dimerization, Keq_3 was calculated to be 0.57. This result matches the calculated Keq from binding study experiments 1 and 2 (Keq_2 / $Keq_1 = Keq_3$; 2.3 / 4.0 = 0.58).

*Hydroformylation using Catalyst **1.1** and Acetal Protection*

The oven dried glass reaction vial was placed in the Endeavor, and 2-phenylprop-2-en-1-ol (80 mg, 0.60 mmol) was added. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). A solution of dicarbonylacetylacetonato rhodium (I) (6.2 mg, 2.4×10^{-2} mmol, 4.0 mol %), **1.1** (34 mg, 0.12 mmol, 20 mol %), *p*-toluenesulfonic acid (2.0 mL of 6.0×10^{-4} M, 1.2×10^{-3} mmol, 0.20 mol %) and benzene (to a total volume of 4 mL) was injected, followed by injection of additional benzene (2 mL) to wash the injection port. The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 45 ℃ for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi

H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant temperature and pressure of 45 ℃ and 400 psi H_2/CO respectively for 12 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction was removed from the Endeavor and concentrated. The residue was redissolved in benzene (0.6 mL). Ethylene glycol (74 μL, 1.3 mmol) and a few crystals of p-toluenesulfonic acid were added. The reaction was refluxed for 3 h. The resulting mixture was cooled to room temperature and solvent was removed. Flash column chromatography (Hex/EtOAc = 6/1) afforded the pure product as colorless liquid.

2-(1,3-Dioxolan-2-yl)-2-phenylpropan-1-ol (**1.7a**, 90.2 mg, 72%). **^{1}H NMR**



($CDCl_3$, 500 MHz) δ 7.49-7.47 (m, 2H), 7.38-7.35 (m, 2H), 7.28-7.25 (m, 1H), 5.16 (s, 1H), 4.03-3.85 (m, 6H), 2.31 (t, 1H, J = 6.2), 1.42 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 141.8, 128.4, 127.0, 126.8, 108.5, 68.2, 65.3, 65.0, 46.5, 17.1; **IR**: 3458, 2884, 1107, 1028, 767, 699 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{17}O_3$ $[M+H]^+$: 209.11777, found: 209.11798.

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Chapter 2

Desymmetrization of *meso*-1,2-Diols

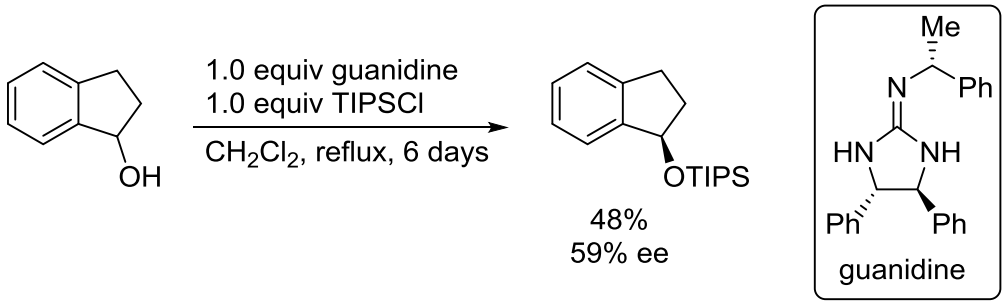
Chapter 2. Desymmetrization of *meso*-1,2-Diols

2.1 Selective Silyl Transfers

Protecting groups serve as a temporary shield for functionalities in a molecule, allowing the advance manipulation of sites with less inherent activities[1,2] Although in an ideal synthesis masking functional groups should be avoided, the strong advantage of protecting groups retains them as a practical and critical strategy in current organic syntheses.[2]

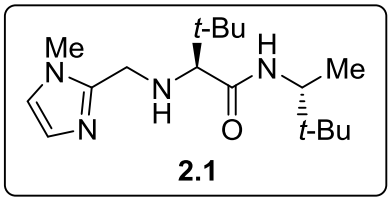
The robust nature and chemical orthogonality of silyl groups make them ideal choices for temporarily masking protic functionalities such as alcohols.[3] While the formation of silyl ether has been traditionally used for protections, new methods merging this transformation with enantio- and site-selective processes add significant synthetic value to silyl protection by introducing asymmetry and functional group differentiation to readily available achiral substrates.

Scheme 2.1. Modified guanidine promotes asymmetric silylation of indanol.



Early work by Ishikawa showed modified guanidines can promote asymmetric silylation of indanol in moderate enantioselectivities (Scheme 2.1).[4] In 2006, Hoveyda and Snapper developed an organic catalyst **2.1** for the desymmetrization of 1,2- and 1,3-diols via silyl transfer (Scheme 2.2).[5a] This catalyst was also shown to promote the resolution of racemic 1,2-diols[5b, 5c] and desymmetrization of *meso*-1,2,3-triols[5d]. Later, addition of 5-ethylthiotetrazole as the co-catalyst was demonstrated to dramatically increase the efficiency of this catalytic system. Aided by computational study, the observation was proposed to occur with a bi-catalyst mechanism; catalyst **2.1** serves as a chiral Brønsted base to selectively deprotonate the diol via multiple hydrogen bonds, while the deprotonated tetrazole activates the nucleophile for the transfer (Figure 2.1).[5e] Subsequently, several metal[6a-d] and non-metal catalysts[6e] have been reported to effectively promote enantio- and stereoselective silyl transfer to alcohols.

Scheme 2.2. Organic catalyst **2.1** for desymmetrization of 1,2 and 1,3-diols.



2.1

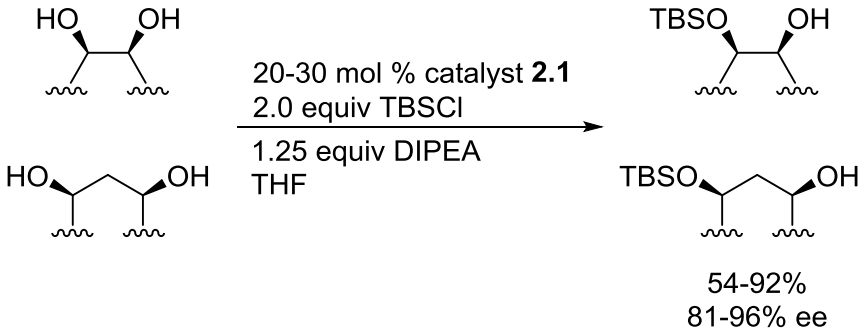
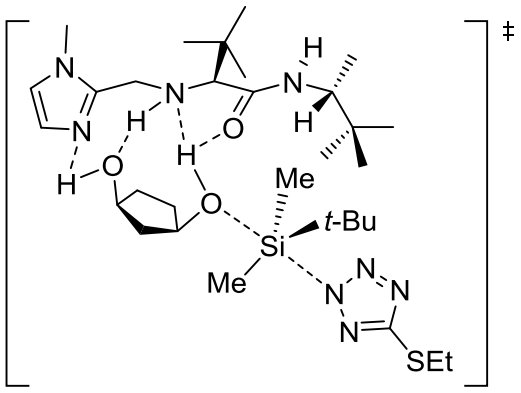


Figure 2.1. Proposed activation mode of bi-catalyst system with **2.1** and 5-ethylthiotetrazole.



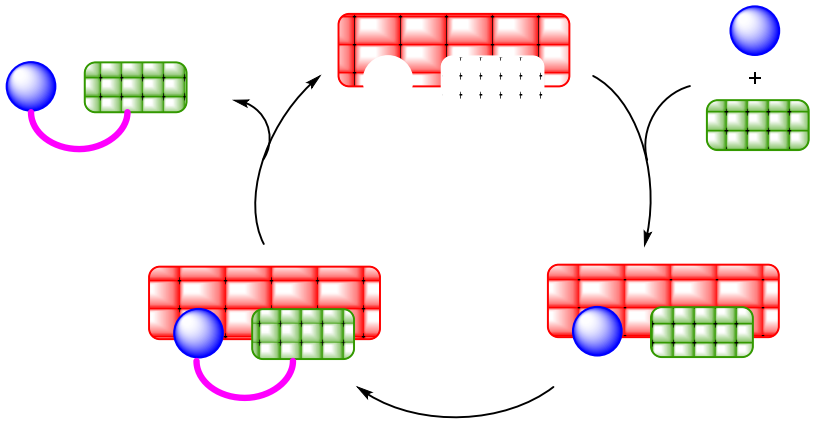
Previous advances in asymmetric silylation have showed its prominent utility in building block preparation and complex molecule synthesis. We thus decided to expand scaffolding catalysis and contribute to this valuable field. Different from the prior examples, we aimed to design an organic catalyst that takes advantage of an induced intramolecularity to enable a selective activation of substrates.

2.2 Induced Intramolecularity in Organocatalysis

The development of new catalysts represents a continuing focus of modern organic chemistry. As a fundamental understanding of previous catalyst designs, the activation of an organic transformation can be summarized as creating reactive pathways with lower energetic requirements, therefore allowing previously unfeasible reactions to proceed.[7] This process is widely proven achievable with the formation of intermediates where the target site of substrate is electronically activated by the catalyst towards the subsequent steps of a reaction (e.g., Lewis acid or base activation, hydrogen bond activation,

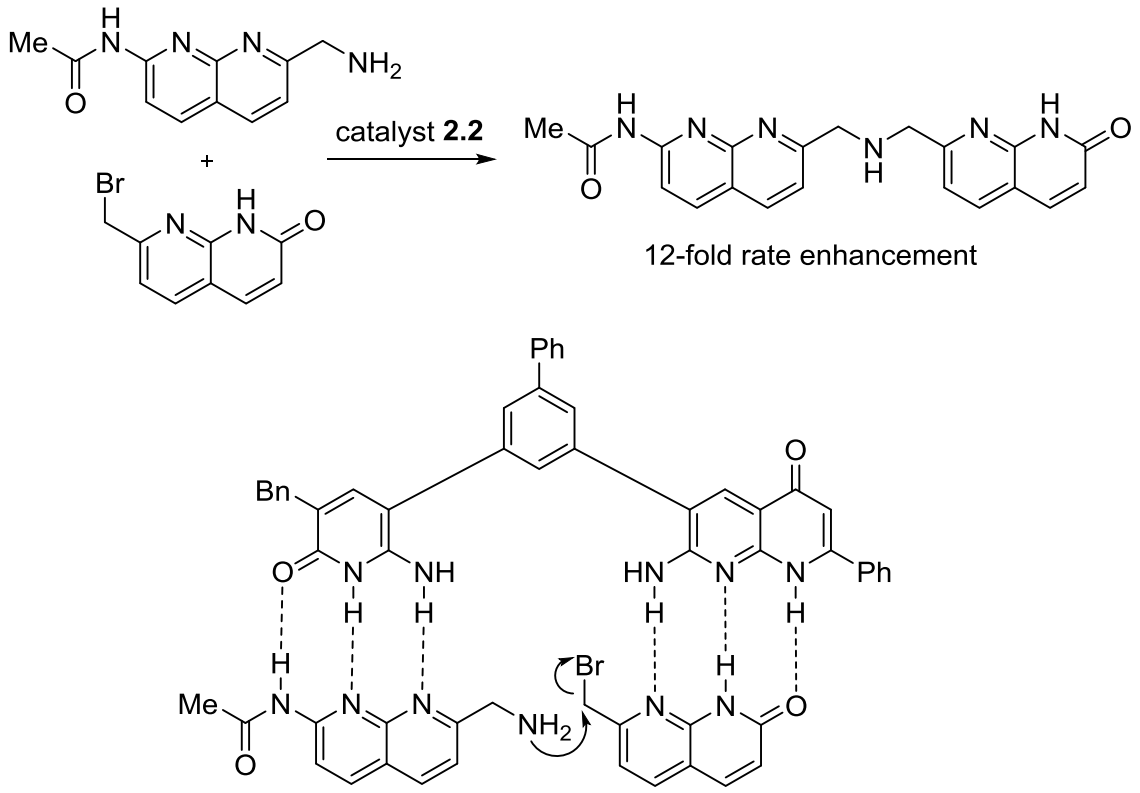
enamine formation, iminium formation, metal complexation, etc.).[8]

Figure 2.2. Concept of reactant preorganization.



An alternative and less explored strategy to enable difficult organic reactions is the preorganization of reactants (Figure 2.2).[9] This type of acceleration is best represented by enzymatic[10] and supramolecular catalysis[11]. By forming an intermediate wherein the substrate and reagent are positioned in a reactive arrangement in the substrate binding pocket, an enzyme effectively establishes an intramolecular transformation. This mode of activation can lead to a rate enhancement of a factor of 10^4-10^8 for 1.0 M reactants at room temperature. This dramatic acceleration has been demonstrated in a paragon report by Kelly,[12] in which a templating catalyst **2.2** accelerates an S_N2 reaction solely by constraining substrates to the proper orientation in the necessary proximity (Scheme 2.3).

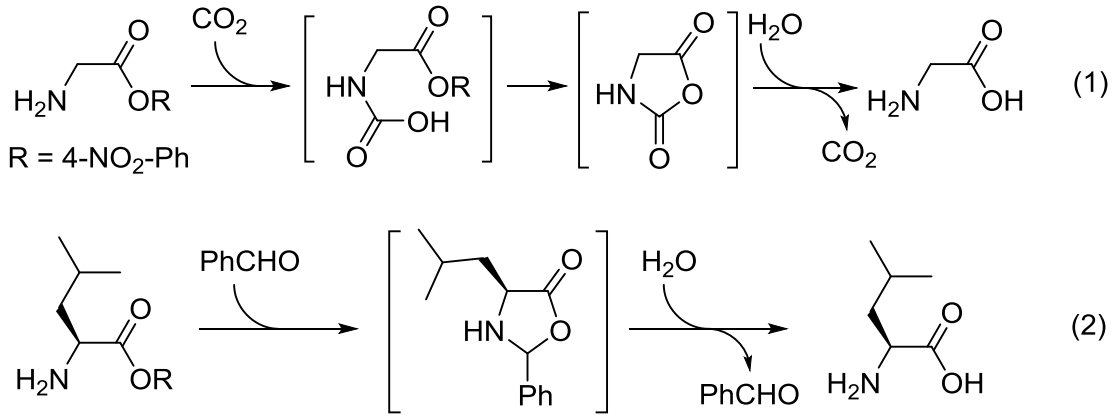
Scheme 2.3. Templating catalyst acceleratates S_N2 reaction.



Inspired by the successful application of reactant preorganization in other fields, small synthetic catalysts have been developed to achieve the same activation mode. In an early report of glycine ester hydrolysis with carbon dioxide as a catalyst, Wieland proposed the formation of a carbamic acid intermediate from the free amine group and CO_2, which accelerated the reaction through intramolecular esterification (Scheme 2.4, equation 1).[13] Subsequently, a number of aldehyde and ketone catalysts were reported by several groups to promote hydrolysis and alcoholysis of esters,[14] amides,[15] and nitriles.[16] Acting in the same manner as the carbon dioxide, these catalysts were able to covalently bond to the substrate's α-hydroxyl or amine, and promote an intramolecular hydrolysis

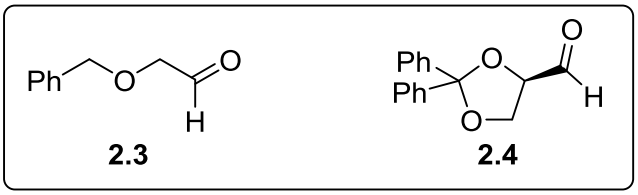
(Scheme 2.4, equation 2).

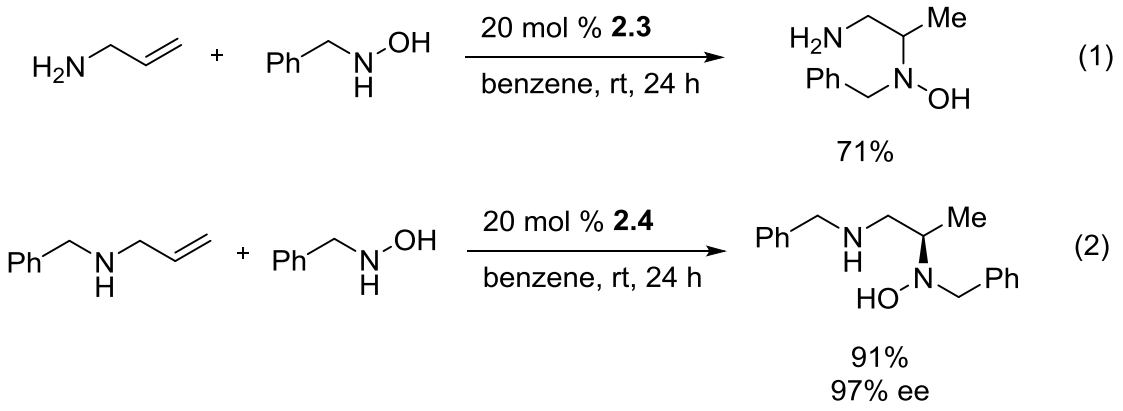
Scheme 2.4. CO_2 and aldehyde-promoted α-amino ester hydrolysis.



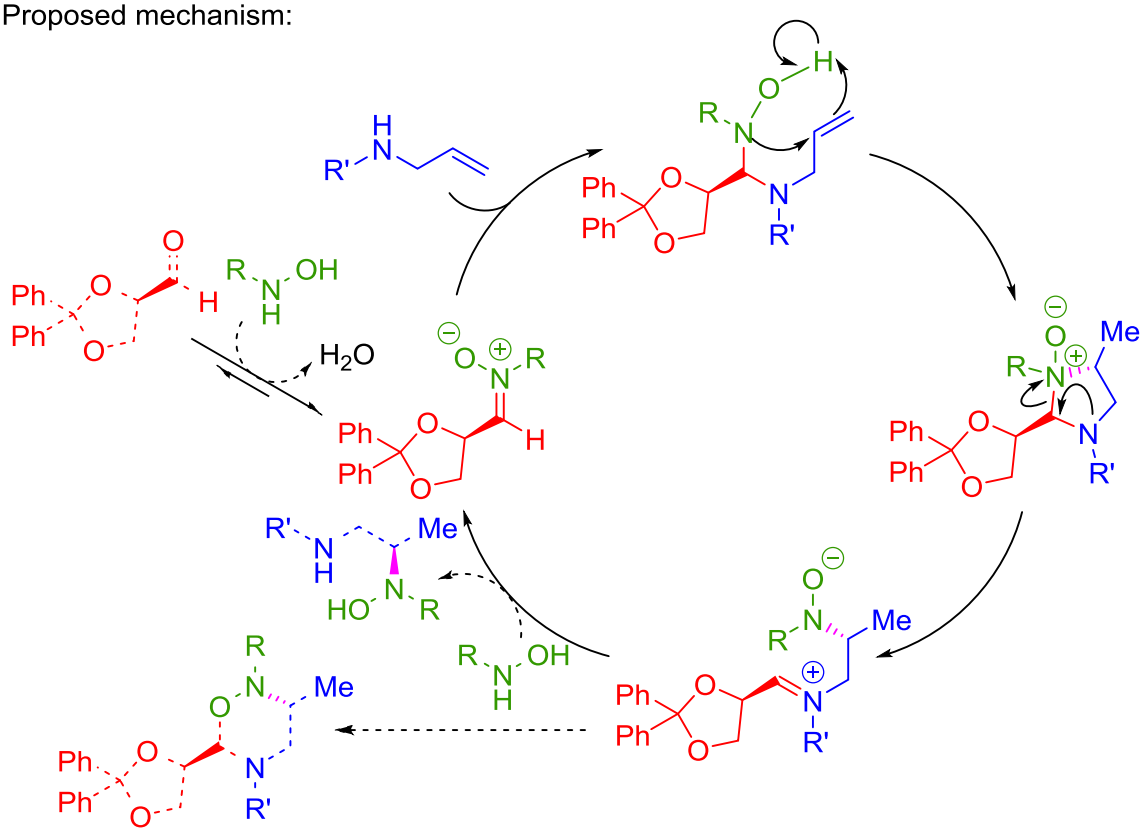
More recently, Beauchemin has employed alkyl aldehydes as catalysts for a traditionally challenging intermolecular hydroamination between hydroxylamines and allylic amines (Scheme 2.5).[17] In the proposed mechanism, the aldehyde catalyst covalently binds to both reactants, enabling the intramolecular addition of the hydroxylamine to the olefin. Subsequent development of chiral aldehyde **2.4** enabled this reaction to proceed in high enantioselectivity.[18]

Scheme 2.5. Aldehyde-promoted intermolecular hydroaminations.



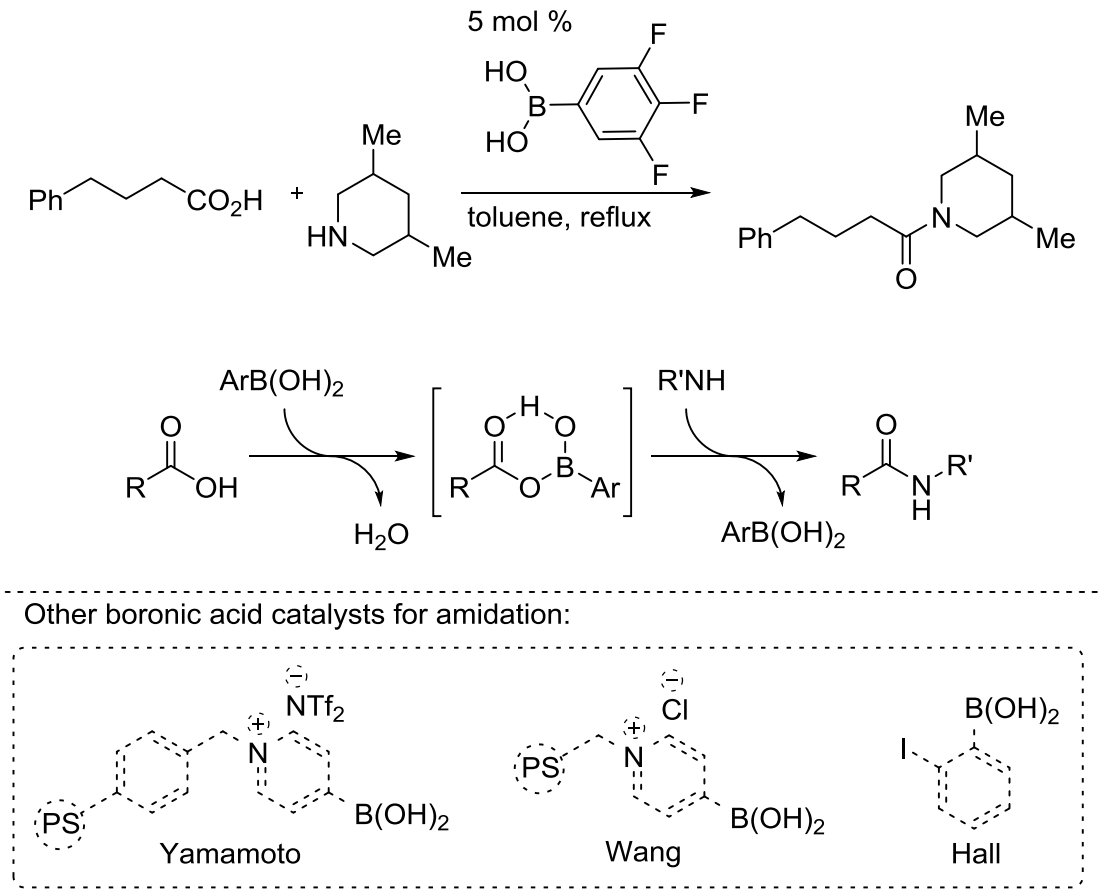


Proposed mechanism:



Boronic acids and esters are known to both covalently exchange with carboxylic acids and intramolecularly activate them via additional hydrogen bonding (Scheme 2.6). In 1996, Yamamoto reported the use of aryl boronic acids to activate carboxylic acids in amidation reactions.[19a, 19b] Incorporation of a pyridinium group by Yamamoto and Wang further enhanced the practicality of these catalysts by allowing for recycling.[19c-e] Later, Hall founded 2-iodophenyl boronic acid to efficiently catalyze the amidation of carboxylic acids at room temperature. The catalytic activity of boronic acids was further expanded to site-selective esterification of α-hydroxycaboxylic acids, transesterification of β-keto esters, and other carbon-carbon bond forming reactions.[20] More recently, borinate catalysts have also been applied by Taylor in the site-selective functionalization of carbohydrates and other complex molecules (discussed in Chapter 4).[21]

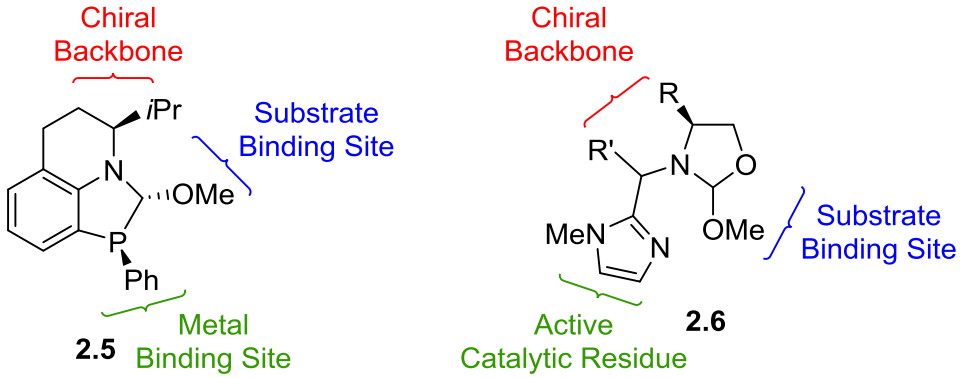
Scheme 2.6. Boronic acid catalyzed amidation of carboxylic acids.



2.3 Development of a Scaffolding Catalyst for Electrophile Transfer.

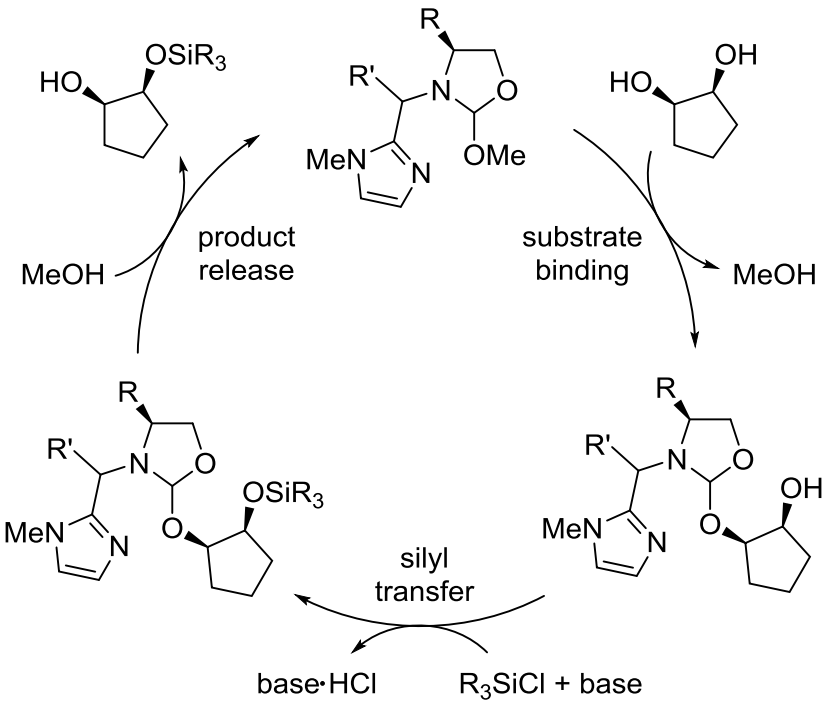
We sought to develop a new organic catalyst that would desymmetrize *meso*-1,2-diols, and would use induced intramolecularity as the predominant form of catalysis.[22] We envisioned that binding the substrate to the catalyst with a single rigid covalent bond would efficiently transfer asymmetry into the product of this reaction.

Figure 2.3. Organic catalyst design.



In order to design an effective desymmetrization catalyst we drew inspiration from our work in hydroformylation as well as the recently reported silyl transfer catalyst developed by Hoveyda and Snapper. Using ligand **2.5** as a template we retained the substrate-binding site as an oxazolidine ring, but replaced the metal-binding phosphine with *N*-methylimidazole, which could either serve to activate incoming electrophiles or act as a general base. Additionally, to increase the synthetic practicality of the catalyst, a chiral backbone that derives from commercial available amino alcohols was installed. We hypothesized that catalyst **2.6** would bind to one hydroxyl within a *meso*-1,2-diol, and selectively functionalize the other free hydroxyl (Figure 2.4).

Figure 2.4. Proposed catalytic cycle for desymmetrization.

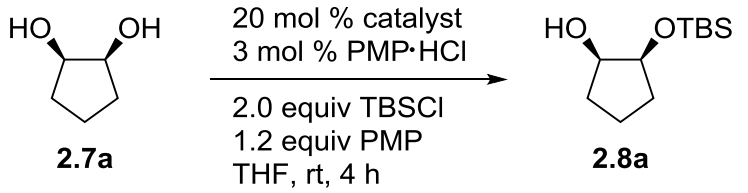


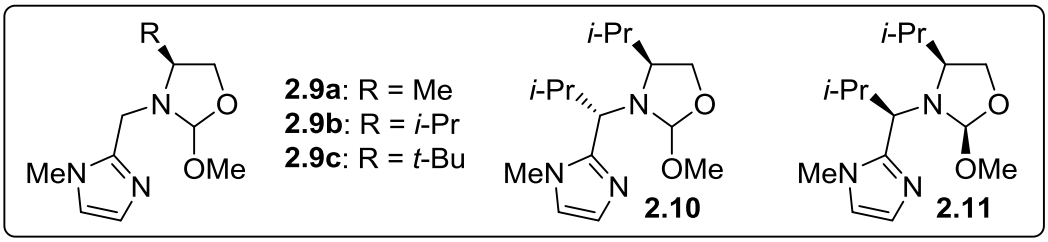
2.4 Desymmetrization of *meso*-1,2-Diols

The modular design of **2.6** allowed a family of catalysts to be synthesized and tested in the desymmetrization of *cis*-cyclopentane-1,2-diol (Table 2.1). Initial experiments with catalyst **2.9a** formed the mono-protected product in 17% yield and -9% ee (Table 2.1, entry 1). Increasing the steric hindrance of the substituents on the oxazolidine backbone led to improved enantioselectivity (Table 2.1, entry 2 and 3). Based on the less expensive valinol core, analogues with a substitutent adjacent to the imidazole ring were prepared and examined. Addition of a second stereocenter **(2.11)** dramatically increased both the yield and the enantioselectivity of the desymmetrization (Table 2.1, entry 5). Interestingly **2.10**, a diastereomer of **2.11**, promotes the formation opposite

enantiomer product in low ee (Table 2.1, entry 4), consistent with a strong matched mismatched relationship between the stereocenters.

Table 2.1. Catalyst optimization for desymmetrization.





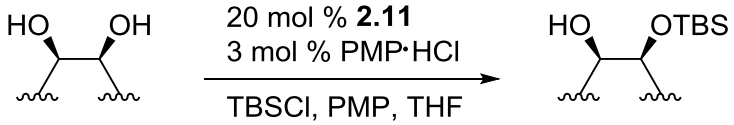
entry	catalyst	yield (%)[a]	ee (%)[b]
1	**2.9a**	17	-9
2	**2.9b**	19	34
3	**2.9c**	20	40
4	**2.10**	25	-16
5	**2.11**	84 (92)[c]	97 (94)[c]

[a]Reaction performed using 0.20 mmol substrate (0.40 M). Yields determined by GLC analysis with internal standard (1,3,5-trimethoxybenzene). [b]Enantiometic excess (ee) determined by chiral GLC analysis. [c]Reaction performed using 0.40 mmol substrate.

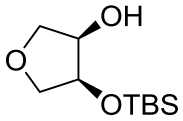
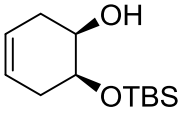
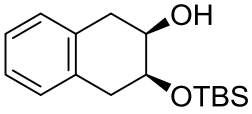
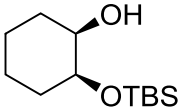
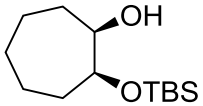
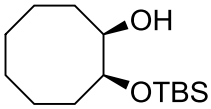
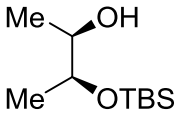
With optimal catalyst **2.11** identified, an investigation of the desymmetrization substrate scope revealed a broad tolerance of *meso*-1,2-diols at mild temperatures (4 °C to room temperature, Table 2.2). Introduction of oxygen heterocycle into the five-membered ring substrate was successful (Table 2.2, entry 1). Substrates with six-membered rings such as cyclohexene, 1,2,3,4-tetrahydro-2,3-napthalene, and cyclohexane are well

tolerated and provide high yields and ee's (Table 2.2, entry 2-4). Medium-sized ring diols, as well as acyclic diols also enantioselectively furnish the desired products (Table 2.2, entry 5-7).

Table 2.2. Substrate scope with TBSCl.



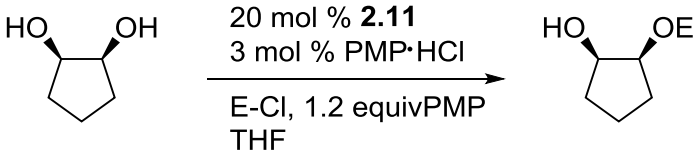
2.7b-h **2.8b-h**

entry[a]	product	yield (%)	ee (%)
1[b]		79	89
2[c]		87	90
3[b]		88	95
4[c]		86	92
5[d]		82	90
6[e]		93	86
7[f]		78	90

[a] All yields and ee values are an average of two runs. [b] TBSCl (4.0 equiv), PMP (1.2 equiv), rt, 24 h. [c] TBSCl (2.0 equiv), PMP (1.2 equiv), rt, 12 h. [d] TBSCl (4.0 equiv), PMP (2 equiv), 4 ^{o}C, 24 h. [e] TBSCl (4.0 equiv), PMP (2.0 equiv), rt, 24 h. [f] TBSCl (4.0 equiv), PMP (2.0 equiv), 4 ^{o}C, 36 h.

Multiple different silyl reagents were also selectively transferred by catalyst **2.11** (Table 2.3). High yields and ee's were obtained with the uses of both sterically less hindered triethylsilyl chloride and larger *tert*-butyldiphenylsilyl chloride (Table 2.3, entry 1 and 2). The transfer of significantly reactive dimethylphenylsilyl chloride led to a decrease in enantioselectivity (79% ee), which may due to the acceleration of the background reaction (Table 2.3, entry 3).

Table 2.3. Silyl reagent scope.



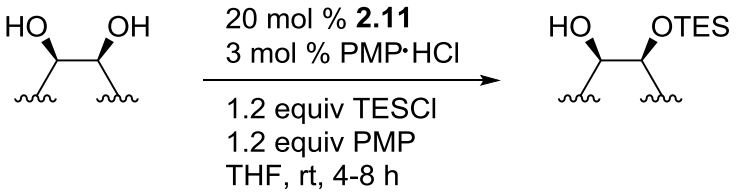
entry	electrophile	yield (%)[a]	ee (%)[a]
1[b]	TESCl	94	90
2[c]	TBDPSCl	75 (76)[d]	90 (86)[d]
3[e]	DMPSCl	71	79

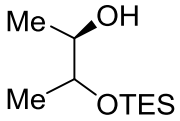
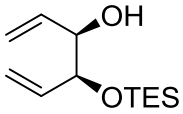
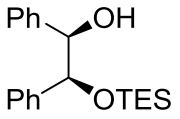
[a] Yields and ee values are an average of two runs. [b] TESCl (1.2 equiv), 0.20 M, rt, 1 h. [c] TBDPSCl (4.0 equiv), rt, 48 h. [d] 1.0 M, rt, 24 h. [e] DMPSCl (1.2 equiv), 0.20 M, rt, 1 h.

Acyclic *meso*-1,2-diols had previously been competent substrates in the desymmetrization; however, extended reaction time (36 h) is required for transferring *tert*-butyldimethylsilyl chloride (Table 2.2, entry 7). The use of triethylsilyl chloride dramatically lowered the reaction time (4 h) for *meso*-2,3-butanediol, while maintaining high enantioselectivity (Table 2.4, entry 1). In addition, we explored challenging

substrates that electronically deactivate hydroxyl groups towards *tert*-butyldimethylsilyl chloride, which were previously inaccessible with our catalysts. These substrates were also effectively desymmetrized with triethylsilyl chloride in 4-8 hours (Table 2.4, entry 2 and 3).

Table 2.4. Desymmetrization with TESCl.



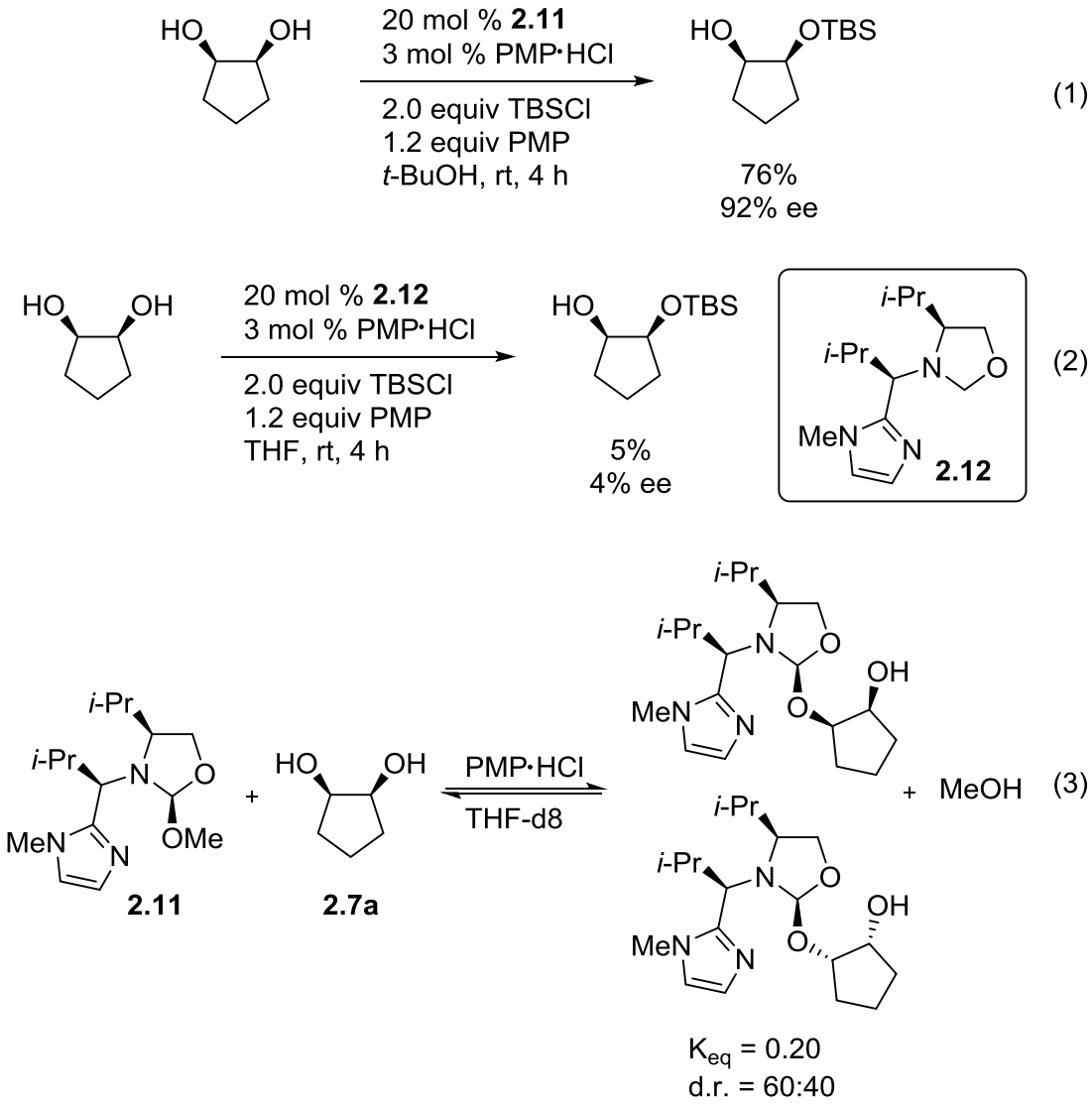
entry	product	yield (%)	ee (%)
1[a]		84	92
2[a]		82	92
3[b]		82	90

[a] Reaction was run for 4 h. [b] Reaction was run for 8 h.

We then turned to study the mechanism of catalysis in the desymmetrization of *meso*-1,2-diols. A protic solvent *tert*-butanol was tested in the reaction. The product was obtained in high enantioselectivity (92% ee), inconsistent with a possible hydrogen bond catalysis (Scheme 2.7, equation 1). Moreover, a control catalyst **2.12** that is unable to covalently bind to substrate was synthesized, and does not promote the selective silyl

transfer, highlighting the necessity of substrate binding to the catalyst in order to achieve the rate acceleration (Scheme 2.7, equation 2).

Scheme 2.7. Mechanistic study of catalyst **2.11**.

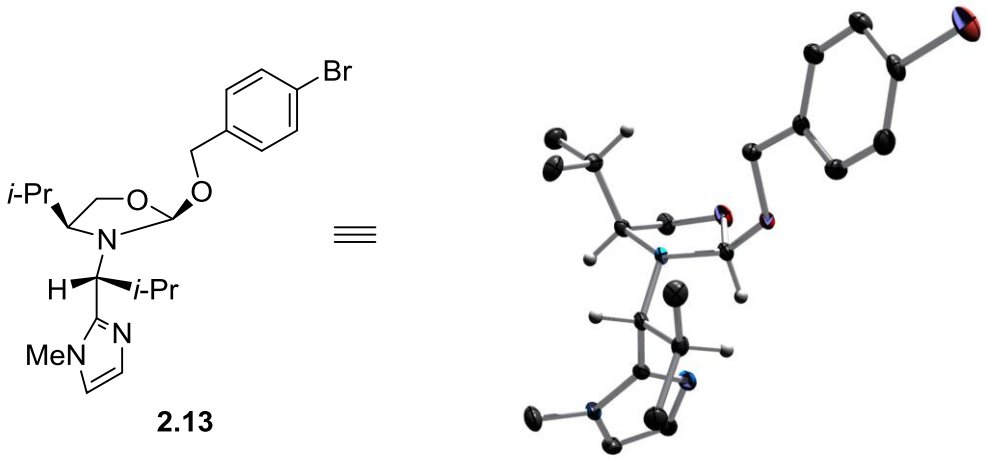


To further understand the mechanistic step that generates the selectivity during this reaction, we performed a binding experiment between diol **2.7a** and catalyst **2.11**

(Scheme 2.7 equation 3). ^{1}H NMR analysis of the crude mixture showed that two binding products are formed as diastereomers (d.r. = 60:40). This observation suggested that the binding event provides minimal discrimination between the two hydroxyl groups. Thus, the origin of the reaction selectivity should lie in the silyl transfer step.

This conclusion directed us to obtain an X-ray structure of catalyst **2.11** binding to 4-bromobenzyl alcohol (Figure 2.4). The X-ray structure confirmed our assignment of the stereocenters in **2.11**, and more importantly, showed that the two isopropyl groups conformationally arrange the substrate binding site, as well as the substrate backbone, which may be responsible for the selectivity during the silyl transfer step.

Figure 2.4. X-ray structure of catalyst **2.13**.



2.13

2.5 Conclusions

We have successfully developed an organic catalyst that applies a single reversible

covalent bond to bind to substrates. Through the rigid mode of binding, the catalyst is able to preorganize the substrate to achieve both a rate enhancement and a high selectivity of the reaction. This catalyst has been shown to facilitate a highly enantioselective desymmetrization of *meso*-1,2-diols via silyl transfer. The potential applications of this new catalytic system could be further expanded with new catalysts selectively functionalizing other diols (*trans*-1,2-diols, *cis*-1,3-diols, and *trans*-1,3-diols), as well as catalyzing other electrophile transfers, to be developed.

2.6 Experimental

General Considerations

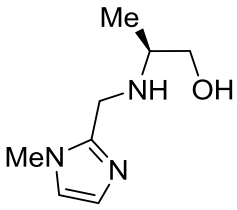
Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lithium reagents were titrated against 2-pentanol using 1,10-phenanthroline as the indicator. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe and cannula techniques, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). ^{1}H and ^{13}C NMR were performed on a Varian Gemini 400 MHz, Varian Gemini 500 MHz, or a Varian Unity Inova 500 MHz spectrometer. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. C_6D_6 was degassed by

three successive freeze-pump-thaw cycles and stored over 3Å molecular sieves in a dry box under a nitrogen atmosphere. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C NMR. Coupling constants are reported in Hz. All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm^{-1}. All GC analyses were performed on an Agilent Technologies 7890A GC System. HRMS and X-ray crystal structure data were generated in Boston College facilities. Analytical chiral high-performance liquid chromatography (HPLC) was performed on a Shimadzu-LC-2010A HT.

Catalyst Synthesis

N-methyl-imidazole-2-carboxaldehyde was made following literature procedures[23] and matched reported spectra.

(S)-2-((1-Methyl-1H-imidazol-2-yl)methylamino)propan-1-ol.[24] To a solution of



N-methyl-imidazole-2-carboxaldehyde (650 mg, 8.7 mmol) in methanol (17 mL) was added (*S*)-alaninol (960 mg, 8.7 mmol) and 4Å molecular sieves (1.7 g). After heating at reflux for 24 hours, the reaction was cooled to room temperature, and $NaBH_4$ (340 mg, 8.7 mmol) was added. The reaction was stirred at room temperature for 2 hours, followed by quenching with dropwise addition of concentrated HCl (0.44 mL). The resulting mixture was further neutralized with Na_2CO_3 (1.4 g). The precipitated salts were filtered off, and the filtrate was concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 10:1) afforded pure

product as a colorless oil (1.0 g, 70%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.86 (d, 1H, *J* = 1.2), 6.77 (d, 1H, *J* = 1.2), 3.91 (d, 1H, *J* = 14.4), 3.76 (d, 1H, *J* = 14.4), 3.60 (s, 3H), 3.53 (dd, 1H, *J* = 11.0, 3.9), 3.26-3.30 (m, 1H), 2.82 (qt, 1H, *J* = 10.3, 3.9), 1.04 (d, 3H, *J* = 6.4); **^{13}C NMR** (C_6D_6, 126 MHz) δ 147.0, 126.9, 121.2, 65.5, 54.9, 42.9, 32.7, 17.3; **IR**: 3201, 2872, 1636, 1499, 1452, 1283, 1048, 736, 662 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_8H_{16}N_3O$ $[M+H]^+$: 170.1293, found: 170.1292. **$[\alpha]_D^{25}$** = +33.0 (*c* = 1.10, $CHCl_3$, *l* = 50 mm).

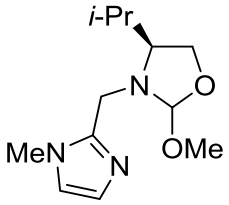
(4S)-2-Methoxy-4-methyl-3-((1-methyl-1H-imidazol-2-yl)methyl)oxazolidine (**2.9a**, d.r = 66:34). To a solution of (*S*)-2-(((1-methyl-1H-imidazol-2-yl)-methyl)-amino)-propan-1-ol (1.0 g, 6.0 mmol) in anhydrous methanol (24 mL) under argon was added *N,N*-dimethylformamide dimethyl acetal (0.80 mL, 6.0 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (24 mL), and the reaction was stirred at room temperature for another 2 hours, at which time, ^{1}H NMR analysis showed that all the substrate was consumed and product had formed. The solvent was removed under vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentane. The pentane was removed under vacuum, and Kugelrohr distillation (170 °C @ 0.05 mmHg) afforded pure product as a colorless oil (330 mg, 26%). **^{1}H NMR** (C_6D_6, 500 MHz) δ 7.15 (s, 0.34H), 7.12 (d, 0.66H, *J* = 0.1), 6.37 (s, 0.34H), 6.36 (s, 0.34H), 5.24 (s, 0.66H), 5.17 (s, 0.34H), 3.98 (t, 0.34H, *J* = 7.3),

3.78 (t, 0.66H, *J* = 6.8), 3.68-3.72 (m, 2H), 3.36-3.43 (m, 0.66H), 3.32-3.34 (m, 0.34H), 3.28 (s, 0.66H), 3.23 (s, 0.66H), 3.14 (s, 0.34H), 3.07 (s, 0.34H), 2.94-2.96 (m, 1H), 0.735 (d, 1H, *J* = 6.1), 0.705 (d, 2H, *J* = 5.9); **^{13}C NMR** (C_6D_6, 126 MHz) δ 145.7, 145.4, 121.8, 121.7, 114.7, 111.7, 109.0, 73.1, 72.6, 57.9, 54.9, 53.1, 51.4, 47.1, 43.4, 38.3, 32.7, 17.5, 16.8; **IR**: 2928, 1501, 1458, 1284, 1162, 1113, 1066, 1017, 975, 742 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{19}H_{14}N_3O$ [M-OMe]: 180.1137, found: 180.1142. **$[\alpha]_D^{24}$** = +11.6 (*c* = 1.09, C_6H_6, *l* = 50 mm).

*(S)-3-Methyl-2-((1-methyl-1H-imidazol-2-yl)methylamino)butan-1-ol***.**[24] To a solution of *N*-methyl-imidazole-2-carboxaldehyde (2.1 g, 20 mmol) in methanol (40 mL) was added (*S*)-valinol (2.2 g, 20 mmol) and 4Å molecular sieves (4.0 g). After heating at reflux for 24 hours, the reaction was cooled to room temperature, and $NaBH_4$ (760 mg, 20 mmol) was added. The reaction was stirred at room temperature for 2 hours, followed by quenching with dropwise addition of concentrated HCl (1.0 mL). The resulting mixture was further neutralized with Na_2CO_3 (3.3 g). The precipitated salts were filtered off, and the filtrate was concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 10:1) afforded the pure product as a colorless oil (2.3 g, 58%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.86 (d, 1H, *J* = 1.5), 6.77 (d, 1H, *J* = 1.2), 3.90 (d, 1H, *J* = 14.7), 3.78 (d, 1H, *J* = 14.9), 3.62 (dd, 1H, *J* = 11.2, 3.7), 3.58 (s, 3H), 3.39 (dd, 1H, *J* = 11.0, 7.3), 2.42 (m, 1H), 1.74 (m, 1H), 0.92 (d, 3H, *J* = 6.8), 0.87 (d, 3H, *J* = 6.8); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 147.4, 126.9, 121.3, 65.1, 61.6, 44.0, 32.6, 30.0, 19.5, 19.0; **IR**: 3199, 2955, 2871, 1500, 1465, 1283, 1043,

734, 705, 661 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{20}N_3O$ $[M+H]^+$: 198.1606, found:198.1606. $\mathbf{[\alpha]_D^{25}}$ = +19.0 (*c* = 1.0, CH_2Cl_2, *l* = 50 mm).

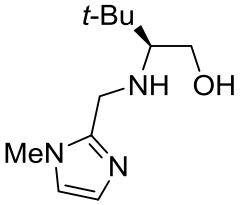
(4S)-4-Isopropyl-2-methoxy-3-((1-methyl-1H-imidazol-2-yl)methyl)oxazolidine



(**2.9b**, d.r. = 70:30). To a solution of (*S*)-3-methyl-2-(((1-methyl-1H-imidazol-2-yl)methyl)amino)butan-1-ol (860 mg, 4.4 mmol) in anhydrous methanol (18 mL) under argon was added *N,N*-dimethylformamide dimethyl acetal (580 μL, 4.4 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (18 mL), and the reaction was further stirred at room temperature for 2 more hours until ^{1}H NMR analysis showed that all of the substrate was consumed and product had formed. The solvent was removed under vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentane. The pentane was removed under vacuum, and Kugelrohr distillation (130 °C @ 0.05 mmHg) afforded pure product as colorless oil (490 mg, 47%). **^{1}H NMR** (C_6D_6, 500 MHz) δ 7.15 (d, 0.3H, *J* = 1.2), 7.12 (d, 0.7H, *J* = 1.0), 6.36 (d, 0.3H, *J* = 1.0), 6.35 (d, 0.7H, *J* = 1.2), 5.34 (s, 0.3H), 5.21 (s, 0.7H), 4.02 (d, 0.3H, *J* = 13.9), 3.895 (t, 0.6H, *J* = 8.1), 3.84 (d, 0.3H, *J* = 13.9), 3.79 (t, 0.7H), 3.74 (d, 0.7H, *J* = 13.4), 3.67-3.70 (m, 0.7H), 3.65 (d, 0.7H, *J* = 13.7), 3.17 (s, 0.9H), 3.09 (s, 2.1H), 3.07 (s, 2.1H), 2.98 (s, 09H), 2.82-2.86 (m, 1H), 1.67 (dt, 0.7H, *J* = 20.5, 6.8), 1.58 (ddd, 0.3H, *J* = 13.9, 6.8, 3.7), 0.715 (d, 0.3H, *J* = 6.8), 0.685 (d, 0.7H, *J* = 6.8), 0.645 (d, 0.7H, *J* = 6.8), 0.58 (d, 0.3H, *J* = 7.1); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 145.9,

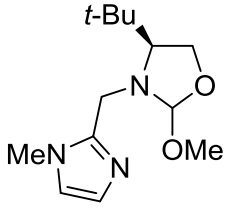
145.5, 128.7, 128.2, 121.6, 121.3, 115.1, 111.9, 68.3, 67.1, 65.6, 64.7, 53.0, 51.8, 49.3, 43.9, 32.5, 32.4, 30.7, 28.7, 20.1, 19.9, 17.5, 15.4; **IR**: 2956, 1500, 1466, 1284, 1158, 1123, 1080, 1062, 986, 741 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{18}N_3O$ [M-OMe]: 208.1450, found: 208.1459. $[\alpha]_D^{25}$ = -7.09 (*c* = 0.71, $CDCl_3$, *l* = 50 mm).

(S)-3,3-Dimethyl-2-((1-methyl-1H-imidazol-2-yl)methylamino)butan-1-ol.[24] To a



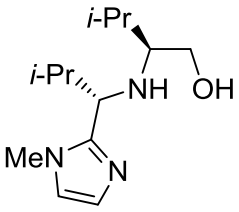
solution of *N*-methyl-imidazole-2-carboxaldehyde (750 mg, 6.8 mmol) in methanol (14 mL) was added (*S*)-*tert*-leucinol (0.80 g, 6.8 mmol) and 4Å molecular sieves (1.4 g). After heating at reflux for 24 hours, the reaction was cooled to room temperature, and $NaBH_4$ (260 mg, 6.8 mmol) was added. The reaction was stirred at room temperature for 2 hours, followed by quenching with dropwise addition of concentrated HCl (0.34 mL). The resulting mixture was further neutralized with Na_2CO_3 (1.1 g). The precipitated salts were filtered off, and the filtrate was concentrated. Flash column chromatography (CH_2Cl_2:MeOH = 10:1) afforded the pure product as a colorless oil (720 mg, 50%). ^{1}**H NMR** ($CDCl_3$, 500 MHz) δ 6.97 (d, 1H, *J* = 1.5), 6.88 (d, 1H, *J* = 1.0), 4.20 (br s, 2H), 4.15 (d, 1H, *J* = 15.9), 3.97 (d, 1H, *J* = 15.6), 3.82 (dd, 1H, *J* = 11.2, 3.7), 3.45 (s, 3H), 3.51 (dd, 1H, *J* = 11.2, 8.1), 2.45 (dd, 1H, *J* = 8.1, 3.7), 0.94 (s, 9H); ^{13}**C NMR** ($CDCl_3$, 125 MHz) δ 147.7, 126.0, 121.6, 68.7, 62.1, 46.0, 35.1, 32.9, 27.2; **IR**: 3333, 2950, 2868, 1501, 1476, 1283, 1110, 1045, 736 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{22}N_3O$ $[M+H]^+$: 212.17629, found: 212.17638. $[\alpha]_D^{25}$ = +5.0 (*c* = 1.0, CH_2Cl_2, *l* = 50 mm).

(4S)-4-tert-Butyl-2-methoxy-3-((1-methyl-1H-imidazol-2-yl)methyl)oxazolidine



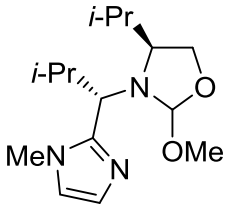
(**2.9c**, d.r. = 85:15). To a solution of (*S*)-3,3-dimethyl-2-(((1-methyl-1H-imidazol-2-yl)methyl)amino)butan-1-ol (0.70 g, 3.3 mmol) in anhydrous methanol (13 mL) under argon was added *N,N*-dimethylformamide dimethyl acetal (0.40 mL, 3.3 mmol). The reaction was stirred at room temperature for 2 hours, and the solvent was removed under vacuum. The residue was redissolved in anhydrous methanol (13 mL), and the reaction was again stirred at room temperature for 2 hours until ^{1}H NMR analysis showed all the substrate was consumed and product had formed. The solvent was removed under vacuum. The flask was brought into a dry glove box under nitrogen atmosphere, and the residue was extracted with degassed pentane. The pentane was removed under vacuum, and Kugelrohr distillation (180 °C @ 0.05 mmHg) afforded the pure product as a colorless oil (190 mg, 23%). **^{1}H NMR** (C_6D_6, 500 MHz) δ 7.21 (s, 1H), 6.38 (s, 1H), 5.55 (s, 0.85H), 5.28 (s, 0.15H), 3.95 (d, 1H, *J* = 13.4), 3.85-3.89 (m, 1H), 3.78-3.81 (m, 1H), 3.65 (d, 1H, *J* = 13.4), 3.15 (s, 0.5H), 3.13 (s, 2.5H), 3.01 (s, 2.5H), 3.00 (s, 0.5H), 2.65-2.68 (m, 1H), 0.85 (s, 1.4H), 0.83 (s, 7.6H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 145.2, 127.3, 121.7, 120.9, 114.9, 111.0, 72.3, 68.8, 66.3, 65.1, 53.2, 52.5, 51.8, 38.1, 34.6, 33.5, 33.3, 26.7, 26.4; **IR**: 2955, 2905, 1499, 1477, 1285, 1147, 1132, 1082, 1066, 993, 740 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{20}N_3O$ [M-OMe]: 222.1606, found: 222.1612. **$[\alpha]_D^{25}$** = -7.09 (*c* = 0.71, $CDCl_3$, *l* = 50 mm).

(S)-3-Methyl-2-((S)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propylamino)butan-1-ol.[24] *N*-methyl-2-imidazolecarboxaldehyde (1.62 g, 14.7 mmol) and (*S*)-valinol (1.52 g,



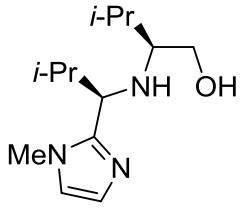
14.7 mmol) were heated at reflux in toluene for 3 hours. The solution was concentrated in vacuo. The resulting crude oxazolidine was dissolved in tetrahydrofuran (86 mL) and cooled to –78 °C. Isopropyl magnesium chloride (22.8 mL, 45.6 mmol, 2.0M in THF) was added dropwise. After stirring for 16 hours and allowing the solution to warm to room temperature, the reaction was quenched by slowly adding H_2O (5 mL). The layers were separated, and the organic layer was washed with H_2O (100 mL) and brine (100 mL). The organic layers were concentrated. Column chromatography (1% NEt_3 and 10% MeOH in CH_2Cl_2) yielded slightly yellow oil (86:14 diastereomer ratio). Rapid stirring of the oil with hexanes (3 mL) resulted in the precipitation of a slightly yellow solid that was one diastereomer (1.50 g, 43%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.98 (d, 1H, *J* = 1.0), 6.76 (d, 1H, *J* = 1.2), 3.61 (s, 3H), 3.57 (dd, 1H, *J* = 11.0, 3.9), 3.42 (d, 1H, *J* = 7.6), 3.34-3.37 (m, 1H), 3.17-3.21 (bs, 1H), 2.06 (dd, 1H, *J* = 11.0, 4.2), 1.99 (dt, 1H, *J* = 21.0, 6.8), 1.55-1.62 (m, 2H), 1.07 (d, 3H, *J* = 6.8), 0.86 (d, 3H, *J* = 6.8), 0.79-0.87 (m, 6H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 150.7, 127.5, 120.3, 63.2, 60.3, 58.4, 34.6, 32.8, 29.7, 19.8, 19.0; **IR**: 3219, 2958, 2198, 1467, 1281, 1047, 724, 439 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{13}H_{26}N_3O$ $[M+H]^+$: 240.2076, found: 240.2079. **$[\alpha]_D^{24}$** = -27.9 (*c* = 1.0, $CHCl_3$, *l* = 50 mm).

(4S)-4-Isopropyl-2-methoxy-3-((S)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propyl)-oxazolidine (**2.10**, d.r. = 95:5). (*S*)-3-methyl-2-((*S*)-2-methyl-1-(1-methyl-1H-imidazol-2-



yl)propylamino)butan-1-ol (1.01g, 4.18 mmol) was dissolved in methanol (17 mL) and sparged with nitrogen for 5 minutes. *N,N*-dimethylformamide dimethylacetal (2.79 mL, 20.9 mmol) was added in one portion, and the solution was stirred 13 hours at 50 °C. The solution was concentrated under high vacuum. The yellow residue was dissolved in methanol (17 mL) and another portion (2.79 mL, 20.9 mmol) of *N,N*-dimethylformamide dimethylacetal was added. After 3 hours, the solution was concentrated and stored in a dry glovebox. The yellow residue was distilled (150 °C at 0.25 torr) to yield a slightly yellow oil (994 mg, 84%). **^{1}H NMR** (C_6D_6, 500 MHz) δ 7.20 (s, 1H), 6.37 (s, 0.05H), 6.30 (s, 0.95H), 5.41 (s, 0.05H), 5.35 (s, 0.95H), 3.97 (ddd, 1H, *J* = 13.2, 5.6, 1.2), 3.79 (dd, 1H, *J* = 7.8, 2.2), 3.65 (d, 0.08H, *J* = 10.8), 3.51 (t, 1H, *J* = 7.8), 3.43 (d, 0.92H, *J* = 10.3), 3.33 (s, 2.83H), 3.10 (s, 0.17H), 3.08 (s, 0.17H), 2.88 (s, 2.83H), 2.58-2.65 (m, 1H), 2.16-2.22 (m, 1H), 1.32 (d, 2.7H, *J* = 6.6), 1.24 (d, 0.3H, *J* = 6.6), 1.08 (d, 0.3H, *J* = 6.8), 1.03 (d, 2.7H, *J* = 6.6), 0.94 (d, 2.7H, *J* = 6.9), 0.90-0.92 (m, 0.3H), 0.81 (d, 2.7H, *J* = 6.6), 0.74 (d, 0.3H, *J* = 6.4); **^{13}C NMR** (C_6D_6, 126 MHz) δ 147.5, 128.9, 120.4, 114.9, 66.7, 62.5, 61.6, 51.4, 32.7, 32.3, 31.8, 21.8, 21.0, 20.7, 17.6; **IR**: 2955, 2871, 1473, 1383, 1366, 1282, 1168, 1136, 1054, 959, 727 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{14}H_{24}N_3O$ [M-OMe]: 250.1919, found: 250.1920. **$[\alpha]_D^{26}$** = -12.5 (*c* = 1.20, $CDCl_3$, *l* = 50 mm).

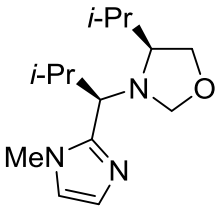
(S)-3-Methyl-2-((R)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propylamino)butan-1-ol.[24] To a stirring solution of L-valinol (25.3 g, 250 mmol) in anhydrous THF (188 mL)



under nitrogen atmosphere was added a solution of isobutyraldehyde (18.1 g, 250 mmol). $MgSO_4$ (15.1 g, 125 mmol) was added, and the reaction was stirred at room temperature for 3 hours (^{1}H NMR analysis showed oxazolidine formed). In another oven-dried glass reaction flask, to a solution of *N*-methylimidazole (45.2 g, 550 mmol) in anhydrous THF (250 mL) under nitrogen atmosphere was added butyllithium (55 mL of 10 M in hexanes, 550 mmol) slowly at -78 ℃ . The solution was stirred at -78 °C for 30 minutes, and the formed oxazolidine solution was slowly cannula transferred into the N-methylimidazolium lithium solution at -78 °C. The resulting mixture was stirred overnight and gradually warmed to room temperature. Aqueous NH_4Cl (50 mL) was added slowly to quench the reaction at 0 °C. $MgSO_4$ (15 g) was added. The mixture was stirred at room temperature for 15 minutes, filtered and concentrated. Excess *N*-methylimidazole was distilled off (150 °C @ 1.0 mmHg). Flash column chromatography (Hex/EtOAc = 2:1 to pure EtOAc) afforded the pure product **1a** as colorless oil (32.8 g, 55%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 6.93 (d, 1H, *J* = 1.2), 6.78 (d, 1H, *J* = 1.2), 3.56 (m, 4H), 3.35 (d, 1H, *J* = 1.2), 3.34 (d, 1H, *J* = 3.9), 2.15 (m, 1H), 1.90 (m, 1H), 1.64 (m, 1H), 0.98 (d, 3H, *J* = 6.8), 0.93 (d, 3H, *J* = 6.8), 0.88 (d, 3H, *J* = 2.9), 0.87 (d, 3H, *J* = 2.9); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 151.7, 127.0, 121.3, 64.2, 62.9, 60.4, 34.0, 32.9, 31.7, 20.2, 19.5, 19.4, 17.7; **IR**: 2956, 2871, 1488, 1468, 1280, 1045, 725 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{13}H_{26}N_3O$ $[M+H]^+$: 240.2076, found: 240.2087. $[\alpha]_D^{25}$ = +40.0 (*c* = 1.0, CH_2Cl_2, *l* = 50 mm).

(4S)-4-Isopropyl-2-methoxy-3-((R)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)-propyl)oxazolidine (**2.11**). To a solution of (S)-3-methyl-2-((R)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propylamino)butan-1-ol (8.4 g, 35 mmol) in anhydrous methanol (70 mL) under nitrogen atmosphere was added *N*,*N*-dimethylformamide dimethyl acetal (24 mL, 175 mmol). The reaction was stirred at 50 °C overnight (^{1}H NMR analysis showed all substrate consumed and product formed). Solvent was removed under vacuum, and the residue was redissolved in anhydrous methanol (70 mL). The reaction was stirred at 50 °C for 2 hours, and solvent was removed under vacuum. Impurities were distilled off (100 °C @ 0.05 mmHg). Kugelrohr distillation (130 ℃ @ 0.05 mmHg), followed by recrystallization with pentane (20 mL, 3 mL/g) at -40 ℃ overnight afforded the pure product **2.11** as white solid (5.6 g, 57 %).**^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.12 (d, 1H, *J* = 1.2), 6.80 (s, 1H), 6.20 (d, 1H, *J* = 1.2), 3.70 (dd, 1H, *J* = 9.0, 8.1), 3.52 (dd, 1H, *J* = 7.8, 7.1), 3.29 (s, 3H), 3.22 (d, 1H, *J* = 10.8), 2.78 (s, 3H), 2.60 (m, 2H), 1.68 (m, 1H), 1.34 (d, 3H, *J* = 6.4), 0.85 (d, 3H, *J* = 6.8), 0.66 (d, 3H, *J* = 6.8), 0.63 (d, 3H, *J* = 6.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 148.8, 128.7, 120.1, 112.4, 66.1, 65.8, 60.5, 52.7, 33.7, 32.2, 29.5, 21.6, 21.0, 20.2, 16.9; **IR**: 2956, 1470, 1281, 1052, 964 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{14}H_{24}N_3O$ [M-OMe]: 250.1919, found: 250.1926. $[\alpha]_D^{26}$ = -57.0 (*c* = 1.0, CH_2Cl_2, *l* = 50 mm).

(S)-4-isopropyl-3-((R)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propyl)oxazolidine (**2.12**). To a stirring solution of

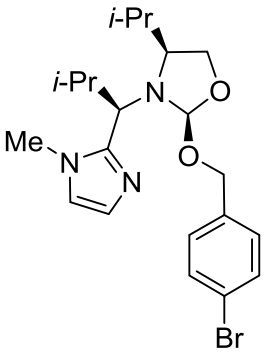


(*S*)-3-methyl-2-(((*R*)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propyl) amino)butan-1-ol (720 mg, 3.0 mmol) and paraformaldehyde (90 mg, 3.0 mmol) in anhydrous toluene (30 mL), *p*-toluenesulfonic acid monohydrate (5.7 mg, 3.0×10^{-2} mmol) was added. After heating at reflux overnight, the reaction was cooled to room temperature, and CH_2Cl_2 (30 mL) was added. The resulting solution was concentrated. Flash column chromatography (100% EtOAc) afforded the product as colorless oil (520 mg, 68%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.00 (d, 1H, *J* = 1.2), 6.73 (d, 1H, *J* =1.2), 5.01 (d, 1H, *J* = 4.6), 4.34 (d, 1H, *J* = 4.4), 3.61 (s, 3H), 3.41 (m, 3H), 2.57 (dd, 1H, *J* = 12.7, 6.6), 2.22 (m, 1H), 1.70 (m, 1H), 1.12 (d, 3H, *J* = 6.6), 0.93 (d, 3H, *J* = 6.8), 0.86 (d, 3H, 6.6), 0.66 (d, 3H, 6.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 147.9, 127.9, 120.3, 81.8, 67.6, 67.2, 62.8, 33.1, 33.0, 31.0, 21.1, 20.2, 20.0, 18.1; **IR**: 2955, 2868, 1468, 1279, 1140, 1084, 945, 724 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{14}H_{26}N_3O$: $[M+H]^+$: 252.2076, found: 252.2075. $\mathbf{[\alpha]_D^{26}}$ = +32.0 (*c* = 1.0, CH_2Cl_2, *l* = 50 mm).

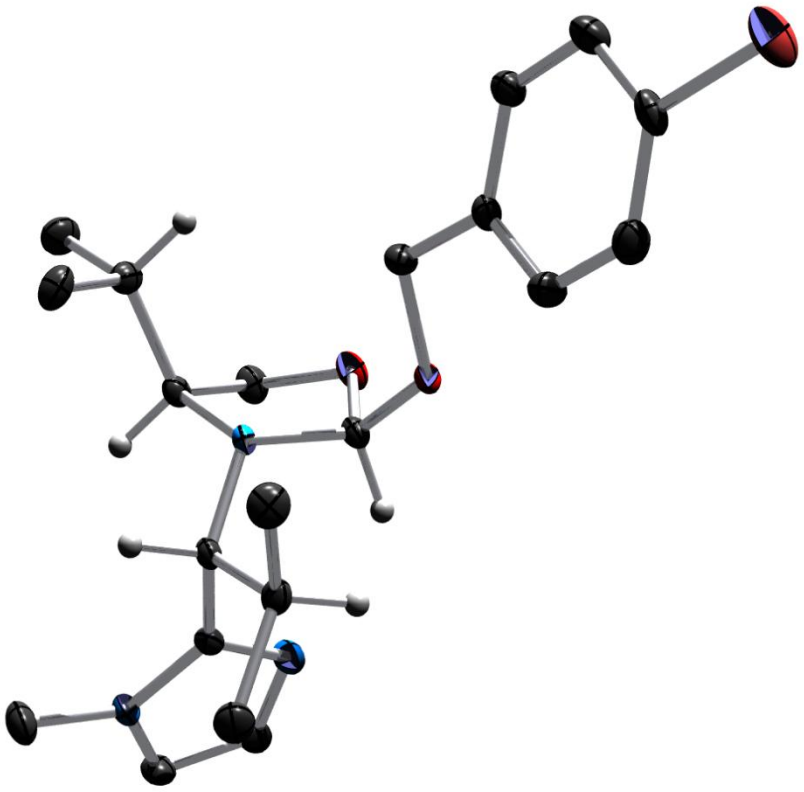
*Crystal Structure of **2.13***

In order to confirm the relative stereochemistry, **2.11** was converted to the more crystalline compound **2.13**.

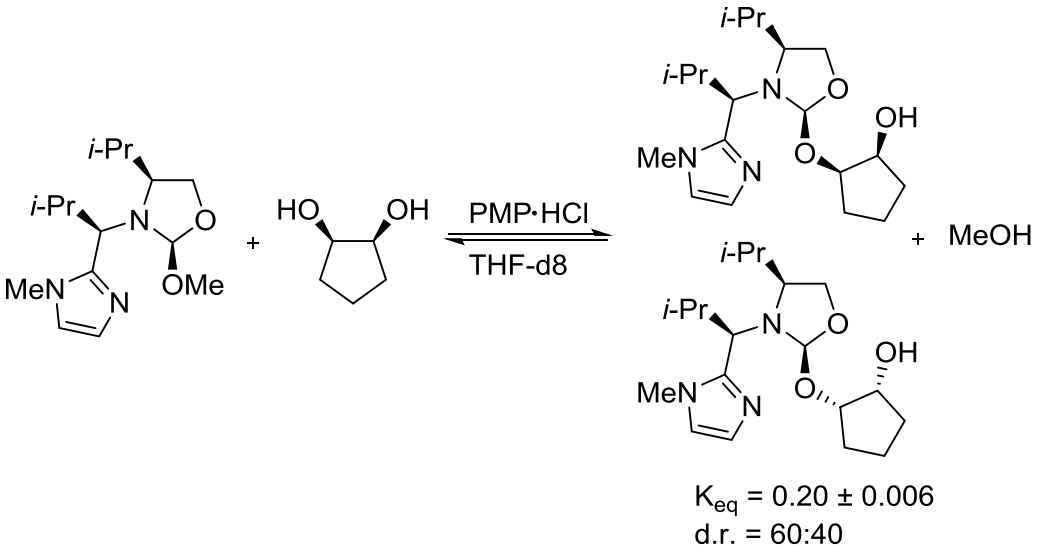
(2R,4S)-2-((4-Bromobenzyl)oxy)-4-isopropyl-3-((R)-2-methyl-1-(1-methyl-1H-imid azol-2-yl)propyl)oxazolidine (**2.13**). To an oven-dried reaction vial was added solution of (*4S*)-4-isopropyl-2-methoxy-3-((*R*)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propyl)oxaz



olidine **2.11** (56 mg, 0.20 mmol), 4-bromobenzyl alcohol (41 mg, 0.22 mmol, 1.1 eq.), and 1,2,2,6,6-pentamethylpiperidine hydrochloride (1.2 mg, 6.0 x 10^{-3} mmol, 3 mol %) in 1.0 mL anhydrous THF. After stirring at room temperature for 8 hours, solvent was removed under vacuum, and the residue was redissolved in 1.0 mL anhydrous THF. Removal and addition of solvent was repeated every 8 hours, until ^{1}H NMR showed that reaction was completed. Recrystallization of the crude product with Et_2O at 4°C afforded pure product **2.13**.



Catalyst Equilibrium Experiment with Substrate:



K_{eq} = 0.20 ± 0.006
d.r. = 60:40

In a glovebox, catalyst **2.11** (5.6 mg, 0.020 mmol), 1,2,2,6,6-pentamethylpiperidine hydrochloride (0.60 mg, 3.0 x 10^{-3} mmol), and *cis*-1,2-cyclopentanediol (10.2 mg, 0.10 mmol) were dissolved in THF-d_8 (0.45 mL) and added to a NMR tube. Trimethoxybenzene, as an internal standard, (0.050 mL, 0.010 mmol, 0.20 M solution in THF) was added to the NMR tube. The exchange reaction was followed by ^{1}H NMR. The reaction reached equilibrium in 3 hours with 40% starting catalyst **2.11** remaining and a 60:40 ratio of diastereomers. The K_{eq} was determined to be 0.193. This reaction was repeated to give a K_{eq} of 0.205. The average K_{eq} is 0.199 ± 0.006.

Catalyst Optimization of Silyl Ttransfer Reaction

To an oven-dried glass reaction vial, a solution of *cis*-1,2-cyclopentanediol (20.0 mg, 0.20 mmol), catalyst (0.040 mmol, 20 mol %), and 1,2,2,6,6-pentamethylpiperidine hydrochloride (1.2 mg, 6.0 x 10^{-3} mmol, 3 mol %) in anhydrous THF (0.25 mL) was

added. The reaction was stirred at room temperature for 10 minutes. 1,2,2,6,6-pentamethylpiperidine (44 μL, 0.24 mmol, 1.2 eq.) was added, followed by addition of a solution of *tert*-butylchlorodimethylsilane (60.0 mg, 0.40 mmol, 2.0 eq.) in anhydrous THF (0.25 mL). After stirring at room temperature for 4 hours, the reaction was quenched by addition of *N,N*-diisopropylethylamine (100 μL) and methanol (30 μL). The mixture was stirred at room temperature for 10 minutes and filtered through a Pasteur pipette packed with silica gel, followed by flushing with EtOAc (15 mL). To the combined filtrate, 1,3,5-trimethoxybenzene (50 μL of 0.40M in EtOAc, 0.020 mmol) was added as internal standard. Chiral GLC Analysis (Supelco Beta Dex 120 (30 × 0.15 mm × 0.25 μm film thickness), 78 °C for 100 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi.) of the crude product afforded yields and enantioselectivities.

	Major Product Enantiomer	Minor Product Enantiomer	Diol Substrate	Internal Standard[b]
GLC Ret. Time	91.7 min	94.0 min	103.9 min	109.5 min
Response Factor[a]	0.62	0.62	1.79	1.00

[a] Response factors were calculated against internal standard on GLC. [b] 1,3,5-trimethoxybenzene was used as internal standard.

Table 2.1, entry 1. Reaction was performed with **2.9a** using the general procedure. Chiral GLC analysis afforded yield (17%) and enantioselectivity (-9% ee).

Table 2.1, entry 2. Reaction was performed with **2.9b** using the general procedure. Chiral GLC analysis afforded yield (19%) and enantioselectivity (34% ee).

Table 2.1, entry 3. Reaction was performed with **2.9c** using the general procedure. Chiral GLC analysis afforded yield (20%) and enantioselectivity (40% ee).

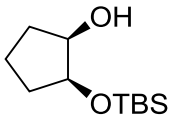
Table 2.1, entry 4. Reaction was performed with **2.10** using the general procedure. Chiral GLC analysis afforded yield (25%) and enantioselectivity (-16% ee).

Table 2.1, entry 5. Reaction was performed with **2.11** using the general procedure. Chiral GLC analysis afforded yield (84%) and enantioselectivity (97% ee).

Substrate Scope with TBSCl

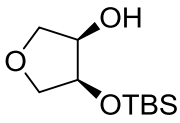
To an oven-dried glass reaction vial, a solution of *cis*-1,2-cyclopentanediol (41 mg, 0.40 mmol), catalyst **2.11** (22 mg, 0.080 mmol, 20 mol %), and 1,2,2,6,6-pentamethylpiperidine hydrochloride (2.3 mg, 0.012 mmol, 3 mol %) in anhydrous THF (0.50 mL) was added. The reaction was stirred at room temperature for 10 minutes. 1,2,2,6,6-pentamethylpiperidine (87 μL, 0.48 mmol, 1.2 eq.) was added, followed by addition of a solution of *tert*-butylchlorodimethylsilane (120 mg, 0.80 mmol, 2.0 eq.) in anhydrous THF (0.50 mL). After stirring at room temperature for 4 hours, the reaction was quenched by addition of *N,N*-diisopropylethylamine (200 μL) and methanol (60 μL). The mixture was stirred at room temperature for 10 minutes and was concentrated. Flash column chromatography (Hex/EtOAc = 20/1) afforded pure product as a colorless oil (80 mg, 92 %, 94% ee) (Chiral GLC Analysis (Supelco Beta Dex 120 (30 × 0.15 mm × 0.25 μm film thickness), 78 °C for 100 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi.)).

(1R,2S)-2-(tert-butyldimethylsilyloxy)cyclopentanol (Table 2.1, entry 5). The



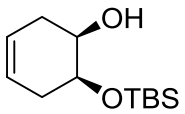
general procedure was followed to yield a colorless oil (79.5 mg, 92%, 94% ee). **GLC** (Supelco Beta Dex 120 (30 x 0.15 mm x 0.25 μm film thickness), 78 °C for 100 min, 20 °C/min to 180 °C, 180 °C for 20 min, 15 psi., t_{rmajor} = 91.6 min, t_{rminor} = 94.4 min); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.02-4.06 (m, 1H), 3.89-3.93 (m, 1H), 2.605 (d, 1H, *J* = 3.9), 1.59-1.88 (m, 5H), 1.42-1.51 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 75.4, 73.7, 31.6, 31.1, 26.0, 20.2, 18.3, -4.4, -4.8; **$[\alpha]_D^{26}$** = +18.7 (*c* = 0.52, $CHCl_3$, *l* = 50 mm).

(3R,4S)-4-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-3-ol (Table 2, entry 1).



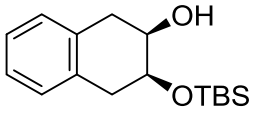
The general procedure was followed using 4 equivalents of *tert*-butylchlorodimethylsilane at 0.2 M and running 24 hours to yield a colorless oil (32 mg, 73%, 92% ee). The reaction was repeated to afford the product in 85% yield and 85% ee. **GLC** (Supelco Beta Dex 120 (30 × 0.15 mm × 0.25 μm film thickness), 75 °C for 260 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi., t_{rmajor} = 223.3 min, t_{rminor} = 229.7 min); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.26 (dd, 1H, *J* = 11.5, 5.9), 4.08-4.12 (m, 1H), 3.87-3.92 (m, 2H), 3.71 (dd, 1H, *J* = 9.5, 3.7), 3.57 (dd, 1H, *J* = 9.0, 5.6), 2.81 (d, 1H, *J* = 4.6), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 73.6, 72.5, 72.4, 71.2, 26.0, 18.3, -4.5, -4.8; **IR**: 2953, 2930, 2858, 1254, 1131, 1069, 836, 779 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{23}O_3Si$: $[M+H]^+$: 219.14165, found: 219.14213. **$[\alpha]_D^{26}$** = +21.0 (*c* = 1.1, CH_2Cl_2, *l* = 50 mm).

(1R,6S)-6-(tert-butyldimethylsilyloxy)cyclohex-3-enol (Table 2.2, entry 2). The

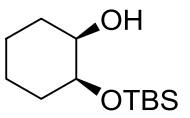


general procedure was followed running at 0.2 M in THF for 12 hours to yield a colorless oil (80.1 mg, 88%, 90% ee). The reaction was repeated to afford the product in 85% yield and 90% ee. **GLC** (Supelco Beta Dex 120 (30 x 0.15 mm x 0.25 μm film thickness), 95 °C for 70 min, 20 °C/min to 180 °C, 180 °C for 20 min, 15 psi., t_{rmajor} = 73.9 min, t_{rminor} = 74.1 min); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.55-5.55 (m, 2H), 3.86-3.92 (m, 2H), 2.28-2.30 (m, 2H), 2.18-2.22 (m, 3H), 0.90 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100) δ 124.0, 123.7, 70.0, 69.3, 31.5, 30.7, 26.0, 18.3, -4.3, -4.6; **$[\alpha]_D^{24}$** = +24.2 (*c* = 1.0, $CHCl_3$, *l* = 50 mm).

(2R,3S)-3-((tert-butyldimethylsilyl)oxy)-1,2,3,4-tetrahydronaphthalen-2-ol (Table 2.2, entry 3). The general procedure was followed with (2R,3S)-1,2,3,4-tetrahydronaphthalene-2,3-diol (99 mg, 0.60 mmol) at 0.2 M in THF for 8 hours to yield a colorless oil (142 mg, 85%, 95% ee). The reaction was repeated to afford the product in 90% yield and 94% ee. **Chiral HPLC Analysis** (Chiracel AS-H, hexanes/iPrOH = 99/1, 1.0 mL/min, 220 nm, t_{rmajor} = 4.9 min and t_{rminor} = 5.4 min); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.04-7.26 (m, 4H), 4.08-4.12 (m, 1H), 4.05-4.06 (m, 1H), 3.02 (t, 2H, *J* = 4.2), 2.99 (t, 1H, *J* = 8.3), 2.87 (dd, 1H, *J* = 16.1, 5.4), 2.24 (d, 1H, *J* = 3.4), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 133.8, 133.4, 129.2, 129.0, 126.3, 126.1, 70.5, 69.8, 34.9, 34.5, 26.0, 18.3, -4.2, -4.5; **IR**: 2928, 1253, 1083, 980, 918, 831, 775, 742 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{16}H_{27}O_2Si$: $[M+H]^+$: 279.1780, found:279.1781. **$[\alpha]_D^{25}$** = +27.0 (*c* = 1.0, MeOH, *l* = 50 mm).

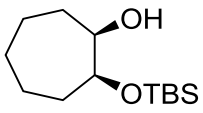


(1R,2S)-2-(tert-butyldimethylsilyloxy)cyclohexanol (Table 2, entry 4). The general



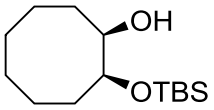
procedure was followed at 0.2 M in THF for 12 hours to yield a colorless oil (80.0 mg, 87%, 92% ee). The reaction was repeated to afford the product in 85% yield and 91% ee. **GLC** (Supelco Beta Dex 120 (30 x 0.15 mm x 0.25 μm film thickness), 80 °C for 190 min, 20 °C/min to 180 °C, 180 °C for 20 min, 15 psi, t_{rmajor} = 167.4 min, t_{rminor} = 172.7 min); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 3.73-3.76 (m, 1H), 3.63-3.65 (m, 1H), 2.18-2.19 (m, 1H), 1.72-1.79 (m, 2H), 1.65-1.72 (m, 2H), 1.56-1.62 (m, 2H), 1.44-1.51 (m, 1H), 1.21-1.31 (m, 1H), 0.91 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 72.2, 70.9, 30.7, 30.3, 26.0, 22.2, 21.3, 18.3, -4.3, -4.7; **$[\alpha]_D^{26}$** = +12.1 (*c* = 1.1, MeOH, *l* = 50 mm).

(1R,2S)-2-(tert-butyldimethylsilyloxy)cycloheptanol (Table 2, entry 5). The general



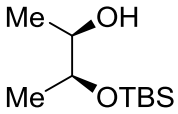
procedure was followed using 4 equivalents of *tert*-butylchlorodimethylsilane and 2 equivalents of 1,2,2,6,6-pentamethylpiperidine at 4 °C for 24 hours to yield a colorless oil (39.2 mg, 80%, 90% ee). The reaction was repeated to afford the product in 83% yield and 90% ee. **GLC** (Supelco Beta Dex 120 (30 x 0.15 mm x 0.25 μm film thickness), 95 °C for 70 min, 20 °C/min to 180 °C, 180 °C for 20 min, 15 psi, t_{rmajor} = 63.4 min, t_{rminor} = 63.7 min); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 3.80-3.82 (m, 1H), 3.73-3.75 (m, 1H), 2.55 (d, 1H, *J* = 4.4), 1.69-1.84 (m, 4H), 1.44-1.62 (m, 4H), 1.26-1.36 (m, 2H), 0.91 (s, 9H), 0.083 (s, 3H), 0.081 (s, 3H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 75.8, 73.7, 31.2, 31.1, 28.1, 26.0, 22.6, 21.4, 18.3, -4.3, -4.8; **$[\alpha]_D^{24}$** = +6.5 (*c* = 0.87, $CHCl_3$, *l* = 50 mm).

(1R,2S)-2-(tert-butyldimethylsilyloxy)cyclooctanol (Table 2, entry 6). The general



procedure was followed using 4 equivalents of *tert*-butylchlorodimethylsilane and 2 equivalents of 1,2,2,6,6-pentamethylpiperidine for 24 hours to yield a colorless oil (48.8 mg, 94%, 87% ee). The reaction was repeated to afford the product in 91% yield and 85% ee. **GLC** (Supelco Beta Dex 120 (30 x 0.15 mm x 0.25 μm film thickness), 150 °C for 30 min, 20 °C/min to 180 °C, 180 °C for 20 min, 15 psi, t_{rmajor} = 23.2 min, t_{rminor} = 23.9 min); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 3.92 (dt, 1H, *J* = 9.0, 3.2), 3.71-3.73 (m, 1H), 2.67-2.68 (m, 1H), 1.97-2.04 (m, 1H), 1.40-1.80 (m, 11H), 0.90 (s, 9H), 0.093 (s, 3H), 0.087 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 74.7, 73.7, 30.9, 29.2, 27.0, 26.0, 25.7, 25.4, 22.8, 18.3, -4.3, -4.7; **$[\alpha]_D^{24}$** = +2.88 (*c* = 0.83, $CHCl_3$, *l* = 50 mm).

(2R,3S)-3-(tert-butyldimethylsilyloxy)butan-2-ol (Table 2, entry 7). The general

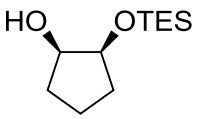


procedure was followed using 4 equivalents of *tert*-butylchlorodimethylsilane and 2 equivalents of 1,2,2,6,6-pentamethylpiperidine at 4 °C for 36 hours to yield a colorless oil (31.7 mg, 78%, 91% ee). The reaction was repeated to afford the product in 77% yield and 88% ee. **GLC** (Supelco Beta Dex 120 (30 x 0.15 mm x 0.25 μm film thickness), 80 °C for 35 min, 20 °C/min to 180 °C, 180 °C for 20 min, 15 psi, t_{rmajor} = 28.1 min, t_{rminor} = 29.1 min); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.68-3.78 (m, 2H), 2.12-2.13 (m, 1H), 1.085 (d, 3H, *J* = 5.7), 1.07 (d, 3H, *J* = 5.7), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 72.1, 71.3, 26.0, 18.2, 17.4, 17.2, -4.2, -4.7; **$[\alpha]_D^{26}$** = +14.7 (*c* = 0.19, CH_2Cl_2, *l* =

50 mm).

Silyl Reagent Scope

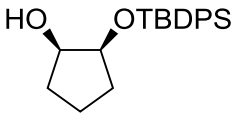
(1R,2S)-2-((triethylsilyl)oxy)cyclopentanol (Table 2.3, entry 1). To an oven-dried



glass reaction vial, a solution of *cis*-1,2-cyclopentanediol (61 mg, 0.60 mmol), catalyst **2.11** (34 mg, 0.12 mmol, 20 mol %), and 1,2,2,6,6-pentamethylpiperidine hydrochloride (3.4 mg, 0.018 mmol, 3 mol %) in anhydrous THF (3.0 mL) was added. The reaction was stirred at room temperature for 10 minutes. 1,2,2,6,6-pentamethylpiperidine (130 μL, 0.72 mmol, 1.2 eq.) was added, followed by addition of triethylchlorosilane (120 μL, 0.72 mmol, 1.2 eq.). After stirring at room temperature for 1 hour, the reaction was concentrated. Flash column chromatography (Hex/EtOAc = 20/1) afforded pure product as colorless oil (125 mg, 96%, 90% ee). A duplicate reaction of cis-1,2-cyclopentanediol (20 mg, 0.20 mmol) with the same procedure afforded the pure product as colorless oil (40 mg, 92%, 90% ee). **Chiral GLC Analysis** (Supelco Beta Dex 120 (30 × 0.15 mm × 0.25 μm film thickness), 80 °C for 180 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rmajor} = 160.5 min, t_{rminor} = 164.2 min). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.01 (dt, 1H, *J* = 8.3, 4.9), 3.89 (dt, 1H, *J* = 8.3, 3.7), 2.65 (d, 1H, *J* = 3.4), 1.55-1.85 (m, 5H), 1.44 (m, 1H), 0.95 (t, 9H, *J* = 8.0), 0.60 (q, 6H, *J* = 8.0); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 75.1, 73.7, 31.7, 31.2, 20.2, 6.9, 5.0; **IR**: 2955, 2876, 1123, 1096, 1005, 742, 728 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{11}H_{25}O_2Si$: $[M+H]^+$: 217.1624, found: 217.1629. **$[\alpha]_D^{24}$** = +18.0 (c = 1.0, CH_2Cl_2, *l* =

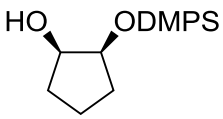
50 mm).

(1R,2S)-2-((tert-butyldiphenylsilyl)oxy)cyclopentanol (Table 2.3, entry 2). To an



oven-dried glass reaction vial, a solution of *cis*-1,2-cyclopentanediol (61 mg, 0.60 mmol), catalyst **2.11** (34 mg, 0.12 mmol, 20 mol %), and 1,2,2,6,6-pentamethylpiperidine hydrochloride (3.4 mg, 0.018 mmol, 3 mol %) in anhydrous THF (1.5 mL) was added. The reaction was stirred at room temperature for 10 minutes. 1,2,2,6,6-pentamethylpiperidine (130 μL, 0.72 mmol, 1.2 eq.) was added, followed by addition of *tert*-butyl(chloro)diphenylsilane (620 μL, 2.40 mmol, 4.0 eq.). After stirring at room temperature for 48 hours, the reaction was concentrated. Flash column chromatography (Hex/EtOAc = 80/1) afforded pure product as colorless oil (146 mg, 71%, 88% ee). A duplicate reaction of cis-1,2-cyclopentanediol (20 mg, 0.20 mmol) with the same procedure afforded the pure product as colorless oil (53 mg, 78%, 92% ee). **Chiral HPLC Analysis** (Chiracel OD-H, hexanes/iPrOH = 99/1, 1.0 mL/min, 220 nm, t_{rminor} = 4.9 min and t_{rmajor} = 5.7 min). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.67 (m, 4H), 7.44 (m, 2H), 7.38 (m, 4H), 4.05 (m, 1H), 3.88 (m, 1H), 2.73 (d, 1H, *J* = 2.9), 1.54-1.83 (m, 5H), 1.25 (m, 1H), 1.08(s, 9H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 136.0, 135.8, 133.9, 133.6, 130.1, 130.0, 128.0, 127.9, 76.7, 73.6, 31.1, 31.0, 27.2, 20.0 19.4; **IR**: 2931, 1105, 821, 740, 700, 611, 504 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{21}H_{27}OSi$: $[M\text{-}OH]^+$: 323.1831, found: 323.1822. $[\alpha]_D^{26}$ = +12.0 (c = 1.0, CH_2Cl_2, *l* = 50 mm).

(1R,2S)-2-((dimethyl(phenyl)silyl)oxy)cyclopentanol (Table 2.3, entry 3). To an oven-dried glass reaction vial, a solution of *cis*-1,2-cyclopentanediol (20 mg, 0.20 mmol),



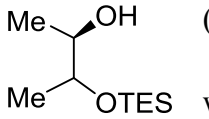
catalyst **2.11** (11 mg, 4.0 × 10^{-2} mmol, 20 mol %), and 1,2,2,6,6-pentamethylpiperidine hydrochloride (1.2 mg, 6.0 × 10^{-3} mmol, 3 mol %) in anhydrous THF (2.0 mL) was added. The reaction was stirred at room temperature for 10 minutes. 1,2,2,6,6-pentamethylpiperidine (44 μL, 0.24 mmol, 1.2 eq.) was added, followed by dropwise addition of a solution of chloro(dimethyl)phenylsilane (40 μL, 0.24 mmol, 1.2 eq.) in anhydrous THF (2.0 mL) over 2 hours by syringe pump. The reaction was concentrated. Flash column chromatography (Hex/EtOAc = 20/1) afforded the pure product as colorless oil (34 mg, 72%, 79% ee). A duplicate reaction of cis-1,2-cyclopentanediol (20 mg, 0.20 mmol) with the same procedure afforded pure product as colorless oil (33 mg, 70 %, 79 % ee). **Chiral HPLC Analysis** (Chiracel OD-H, hexanes/iPrOH = 99.8/0.2, 0.50 mL/min, 220 nm, t_{rminor} = 10.9 min and t_{rmajor} = 11.4 min). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.55-7.57 (m, 2H,), 7.35-7.40 (m, 3H), 3.98-4.02 (m, 1H), 3.85-3.88 (m, 1H), 2.575 (dd, 1H, J = 3.7, 0.5), 1.44-1.82 (m, 5H), 1.35-1.44 (m, 1H), 0.40 (s, 3H), 0.39 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 137.8, 133.6, 130.0, 128.2, 75.7, 73.7, 31.3, 31.0, 20.1, -1.0, -1.1; **IR**: 2961, 1253, 1117, 1093, 891, 830, 787, 741, 700 cm^{-1}; **$[\alpha]_D^{26}$** = +14.0 (c = 1.0, CH_2Cl_2, l = 50 mm).

Desymmetrization with TESCl

General procedure. To an oven-dried glass reaction vial, a solution of substrate (0.20 mmol), catalyst **2.11** (11 mg, 0.040 mmol, 20 mol %), and 1,2,2,6,6-pentamethylpiperidine hydrochloride (1.2 mg, 0.0060 mmol, 3 mol %) in

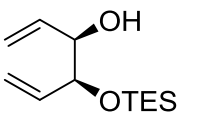
anhydrous THF (4.0 mL) was added. The reaction was stirred at room temperature for 10 minutes. 1,2,2,6,6-pentamethylpiperidine (44 μL, 0.24 mmol, 1.2 eq.) was added, followed by addition of triethylchlorosilane (40 μL, 0.24 mmol, 1.2 eq.). After stirring at room temperature for 4 hours, the reaction was concentrated. Flash column chromatography (Hex/EtOAc = 20/1) afforded pure product.

(2R,3S)-3-((triethylsilyl)oxy)butan-2-ol (Table 2.4, entry 1). *meso*-2,3-Butanediol



(18 mg, 0.20 mmol) was silylated using general procedure. Pure product was isolated as colorless oil (34 mg, 83%, 92% ee). A duplicate reaction of *meso*-2,3-butanediol (54 mg, 0.60 mmol) with the same procedure afforded the pure product as colorless oil (104 mg, 85%, 92% ee). **Chiral GLC Analysis** (Supelco Beta Dex 120 (30 × 0.15 mm × 0.25 μm film thickness), 85 °C for 50 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rmajor} = 41.4 min, t_{rminor} = 42.5 min). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 3.68-3.87 (m, 2H), 2.20 (d, 1H, *J* = 3.9), 1.08 (d, 6H, *J* = 6.1), 0.96 (t, 9H, *J* = 7.8), 0.60 (q, 6H, *J* = 7.8); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 71.8, 71.3, 17.6, 17.1, 7.0, 5.1; **IR**: 2956, 2877, 1239, 1106, 1003, 908, 725 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{25}O_2Si$: $[M+H]^+$: 205.1624, found: 205.1626. **$[\alpha]_D^{24}$** = +12.2 (c = 1.0, CH_2Cl_2, *l* = 50 mm).

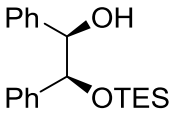
(3R,4S)-4-((triethylsilyl)oxy)hexa-1,5-dien-3-ol (Table 2.4, entry 2).



meso-1,5-Hexadiene-3,4-diol (23 mg, 0.20 mmol) was silylated using general procedure. Pure product was isolated as colorless oil (38 mg, 83%, 91% ee). A duplicate reaction of *meso*-1,5-Hexadiene-3,4-diol (69 mg, 0.60 mmol)

was silylated using general procedure. Pure product was isolated as colorless oil (110 mg, 80%, 92% ee). **Chiral GLC Analysis** (Supelco Beta Dex 120 (30 × 0.15 mm × 0.25 μm film thickness), 90 °C for 100 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rmajor} = 85.4 min, t_{rminor} = 87.4 min). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.77-5.84 (m, 2H), 5.28 (dt, 1H, *J* = 17.4, 1.5), 5.23 (dt, 1H, *J* = 17.4, 1.5), 5.19-5.20 (m, 1H), 5.16-5.18 (m, 1H), 4.10-4.12 (m, 1H), 4.04-4.08 (m, 1H), 2.32 (d, 1H, *J* = 4.4), 0.94 (t, 9H, *J* = 8.1), 0.60 (q, 6H, *J* = 8.1); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 136.9, 136.6, 117.3, 116.8, 77.1, 76.2, 7.0, 5.1; **IR**: 2955, 2877, 1459, 1416, 1238, 1003, 922, 829, 725 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{23}OSi$: $[M\text{-}OH]^+$: 211.15182, found: 211.15265. **$[\alpha]_D^{24}$** = +4.1 (c = 1.0, CH_2Cl_2, *l* = 50 mm).

(1R,2S)-1,2-diphenyl-2-((triethylsilyl)oxy)ethanol (Table 2.4, entry 3).



meso-1,2-Diphenylethane-1,2-diol (43 mg, 0.20 mmol) was silylated for 8 hours using general procedure. Pure product was isolated as colorless oil (53 mg, 81%, 92% ee). A duplicate reaction of *meso*-1,2-Diphenylethane-1,2-diol (129 mg, 0.60 mmol) was silylated using general procedure. Pure product was isolated as colorless oil (163 mg, 83%, 87% ee). **Chiral HPLC Analysis** (Chiracel OJ-H, hexanes/iPrOH = 99/1, 1.0 mL/min, 220 nm, t_{rmajor} = 7.3 min and t_{rminor} = 8.6 min). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.16-7.27 (m, 10H), 4.75 (dd, 1H, *J* = 5.9, 2.9), 4.70 (d, 1H, *J* = 5.9), 2.33 (d, 1H, *J* = 3.2), 0.77 (t, 9H, *J* = 7.8), 0.39 (q, 6H, *J* = 7.8); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 140.9, 140.7, 127.98, 127.96, 127.90, 127.7, 127.6, 127.4, 79.3, 78.9, 6.8, 4.8; **IR**: 2953, 2876, 1097, 1005, 837, 740, 700 cm^{-1}; **HRMS** (DART-TOF) calcd. for

$C_{10}H_{25}O_2Si$: $[M+H]^+$: 329.1937, found: 329.1926. $[\alpha]_D^{24}$ = +6.6 (c = 1.0, CH_2Cl_2, *l* = 50 mm).

Absolute Stereochemical Proof

The absolute stereochemistry of the products was determined by comparing the optical rotations to known values. The optical rotations of the silylated products in this paper were determined to be opposite in sign to the optical rotations of the products reported by the Hoveyda and Snapper groups[5]. The absolute stereochemistry of (*1R,2S*)-2-((triethylsilyl)oxy)cyclopentanol, (*1R,2S*)-2-((*tert*-butyldiphenylsilyl)-oxy)-cyclopentanol, and (*1R,2S*)-2-((dimethyl(phenyl)silyl)oxy)cyclopentanol was assigned by analogy.

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Chapter 3

Regiodivergent Resolution of Terminal 1,2-Diols

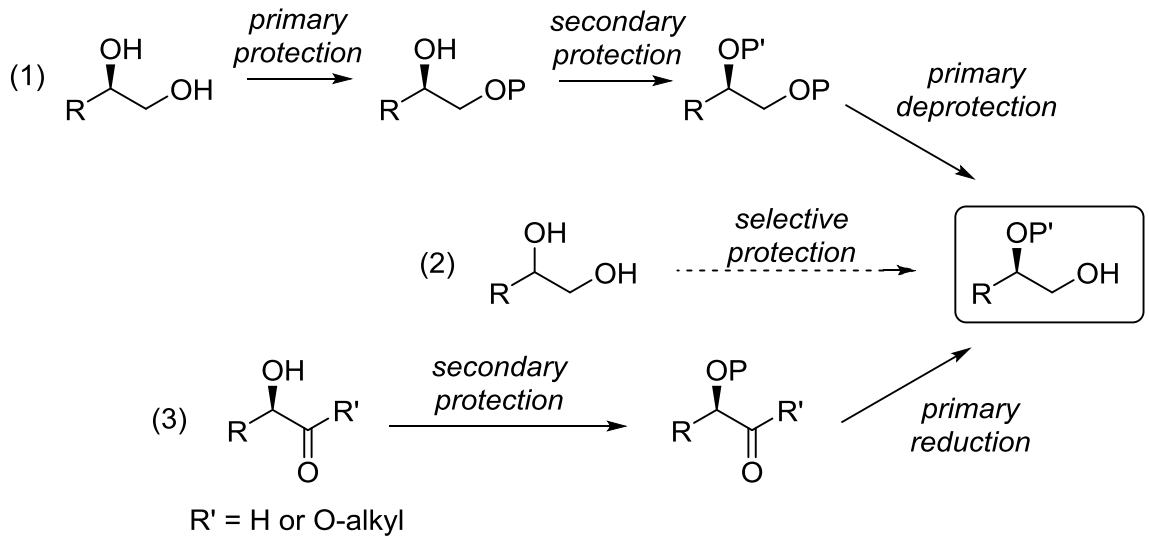
Chapter 3. Regiodivergent Resolution of Terminal 1,2-Diols

3.1 Synthesis of Secondary Protected Terminal Diols

With two versatile hydroxyl groups that are inherently differentiated by steric hindrance, terminal 1,2-diols serve as important building blocks in organic synthesis.[1] Owing to this importance, multiple methods have been developed to selectively modify terminal 1,2-diols. Since there is a large inherent reactivity difference (8 to 50 fold), this synthetic challenge is often addressed by employing reaction sequences wherein the primary hydroxyl is functionalized prior to the manipulation of the secondary hydroxyl.[2]

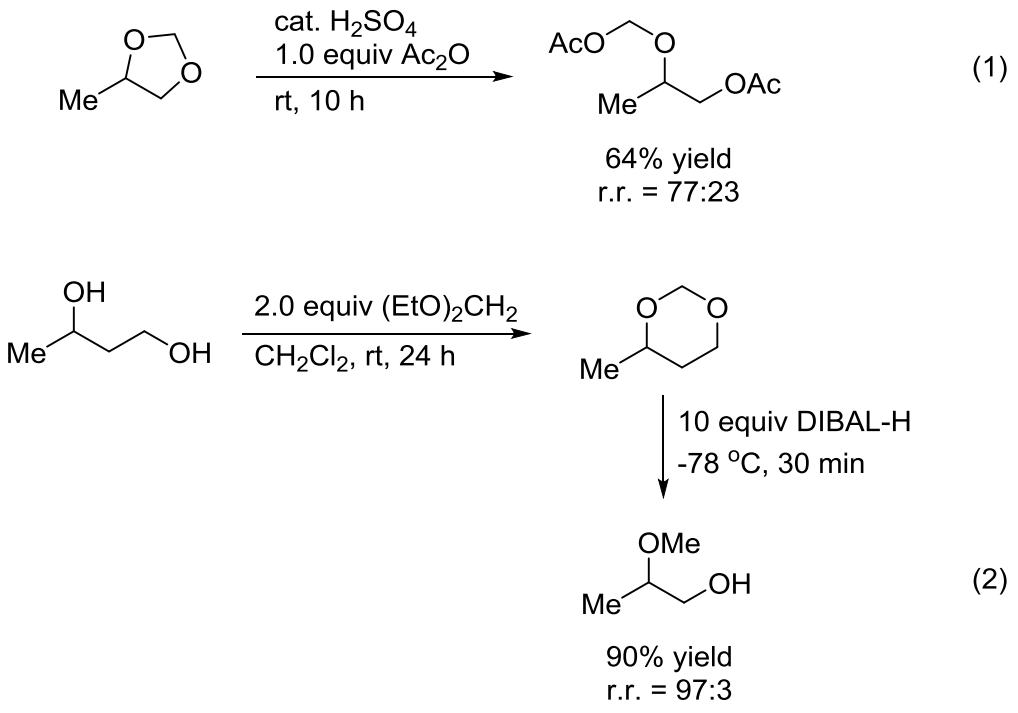
As a result of this reactivity paradigm, the traditional preparation of secondary hydroxyl mono-protected terminal 1,2-diols is usually achieved in a 3 step procedure where the primary and secondary hydroxyls are protected sequentially and orthogonally followed by deprotection of the primary hydroxyl (Scheme 3.1, route 1).[3] This strategy is inherently inefficient both in terms of atom and step economy.

Scheme 3.1. Synthese of secondary hydroxyl protected terminal 1,2-diols



To overcome this drawback, multiple methods have been developed with shortened synthetic routes. Early discovery by Bailey suggested the protection of the secondary hydroxyl in 1,n-diols could be achieved through acetolysis of their cyclic acetal derivatives (Scheme 3.2, equation 1).[4a] Later, Yamamoto demonstrated a reduction of cyclic acetals and orthoformates to furnish secondary protected 1,n-diols with free primary hydroxyls (Scheme 3.2, equation 2).[4b] Consequently, several successes using cyclic acetal and orthoformate as starting materials have been reported.[4c-f] This strategy was also expanded by methods using organotin complex[5] and silyl reagents[6] to form cyclic intermediates with terminal diols, which then lead to the protection of secondary hydroxyls.

Scheme 3.2. Access to secondary protected terminal diols via cyclic acetal and orthoformate.



Certain alternative strategies employ α-hydroxy aldehydes or esters as starting materials; with the primary hydroxyl temporarily masked in a higher oxidation state, the secondary hydroxyl group can be appropriately functionalized in advance of forming the final desired diol product (Scheme 3.1, route 3).[7] However, this sequence still requires an additional reduction step, and the necessary aldehyde and ester substrates can often prove less accessible than the equivalent diols.

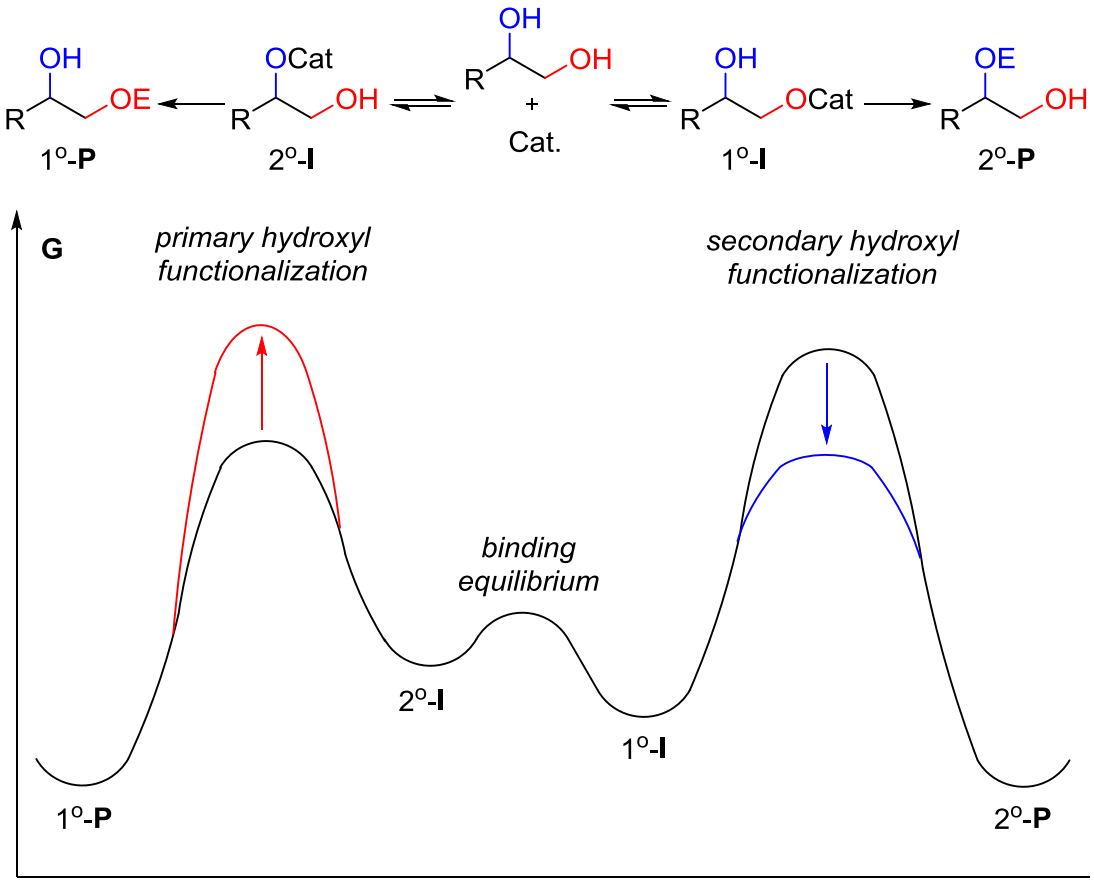
An ideal means of achieving this transformation would facilitate direct functionalization of the secondary hydroxyl group in the presence of a free primary hydroxyl via a reversal of the substrate's inherent selectivity (Scheme 3.1, route 2). This method should also be applicable to inexpensive and easily accessible starting materials.

We envisioned that the scaffolding catalyst previously developed in our group would meet all the standards, and grant direct access to the secondary protected products.

3.2 Design of Scaffolding Catalysis for Terminal Diols

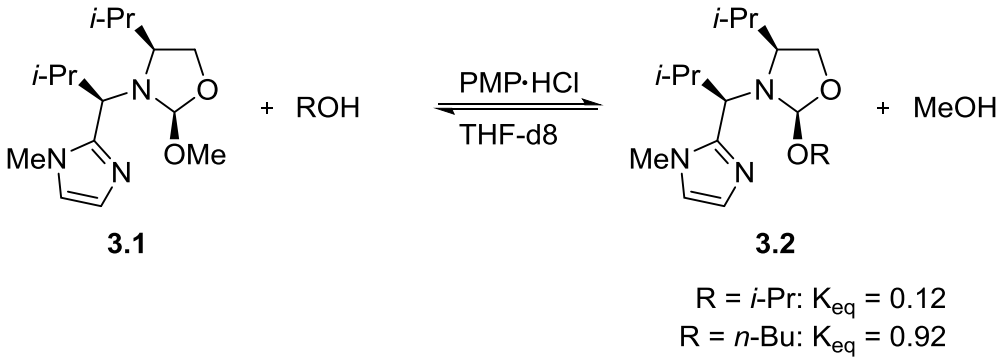
The successful employment of catalyst **3.1** in desymmetrization of *meso*-1,2-diols encouraged us to test it in the selective functionalization of the secondary hydroxyl within terminal 1,2-diols. Considering the mechanism of scaffolding catalysis, this reaction can be controlled by two distinct steps: the binding of the catalyst to one hydroxyl in the substrate and the activation of the non-bound hydroxyl. Such a situation can be represented using Curtin–Hammett principle (Figure 3.1); the site-selectivity is attributed to both the ratio of 1^{o}-**I**:2^{o}-**I** and the difference of energetic requirements in the subsequent functionalizations. Therefore, to reverse the substrate's inherent bias, the catalyst must not just prefer the formation of 1^{o}-**I** in the binding step, but also efficiently promote the secondary functionalization and impede the primary functionalization.

Figure 3.1. Scaffolding catalysis mechanism represented using Curtin-Hammett principle.



Previously, we have studied the binding selectivity of catalyst **3.1** towards different alcohols (Scheme 3.3).[8] Adding isopropanol to catalyst **3.1** results in an equilibrium with K_{eq} = 0.12, while a much higher K_{eq} = 0.92 was observed with 1-butanol under the same conditions. These data clearly demonstrated the catalyst's ability to preferentially bind to less hindered primary hydroxyls over secondary hydroxyls. We thus hypothesized that this selectivity leveraged with terminal 1,2-diol, the scaffolding catalyst would bind to the primary hydroxyl and activate the adjacent secondary hydroxyl towards the transfer of electrophiles.

Scheme 3.3. Binding study of scaffolding catalyst

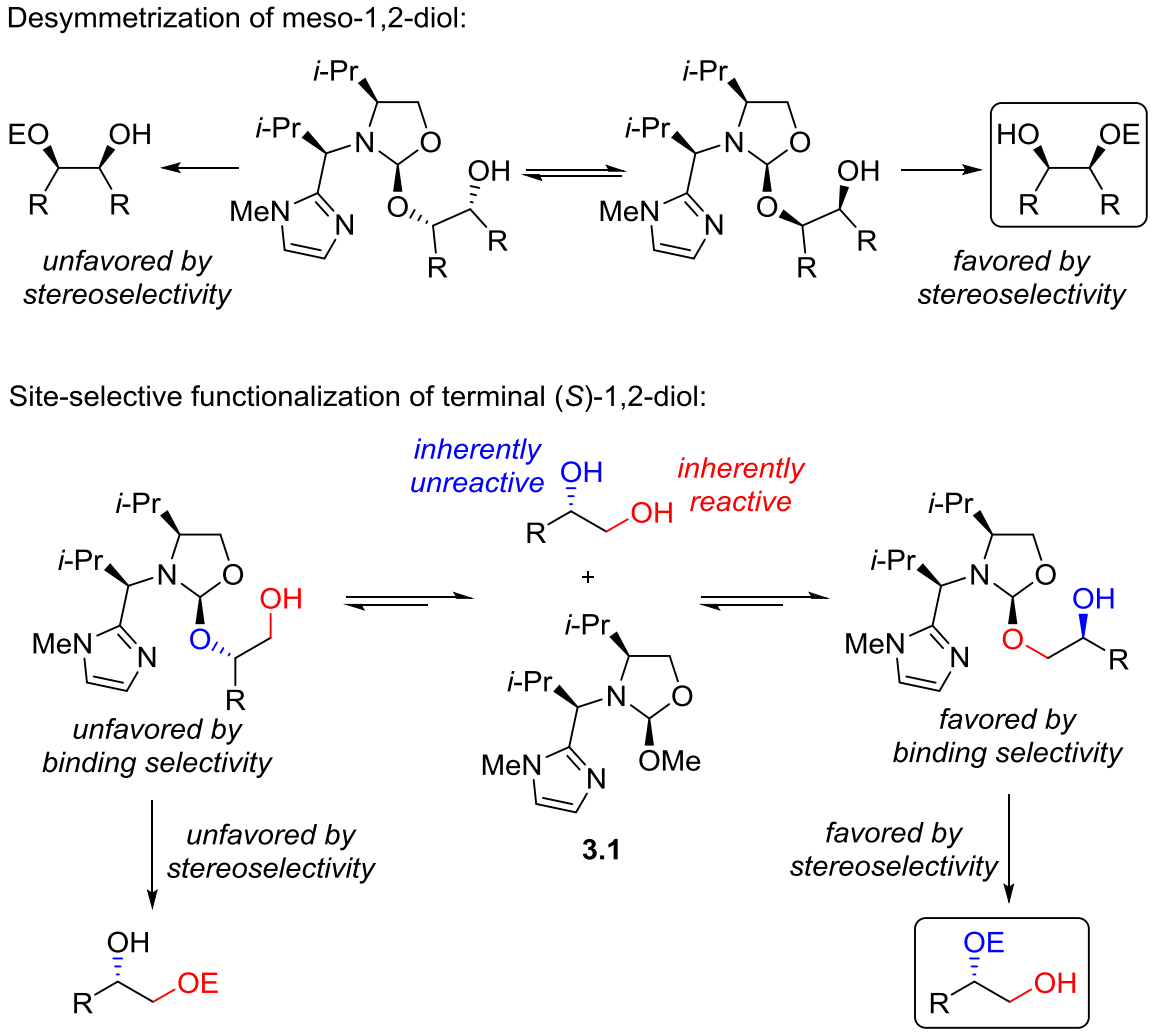


3.1 **3.2**

R = *i*-Pr: K_{eq} = 0.12
R = *n*-Bu: K_{eq} = 0.92

If the rate limiting step was functionalization of the hydroxyl, the site selectivity could be further improved by generating a matched stereochemical relationship between enantiopure diol substrates and the chiral catalyst (Scheme 3.4). In the previous desymmetrization of *meso*-1,2-diols, catalyst **3.1** was found to functionalize the pro-(*S*)-hydroxyl group. Therefore, we anticipated that the use of terminal (*S*)-1.2-diol would benefit from a synergy of both binding and stereoselectivity, allowing for the direct functionalization of the secondary hydroxyl.[9]

Scheme 3.4. Combine binding selectivity and stereoselectivity of scaffolding catalyst

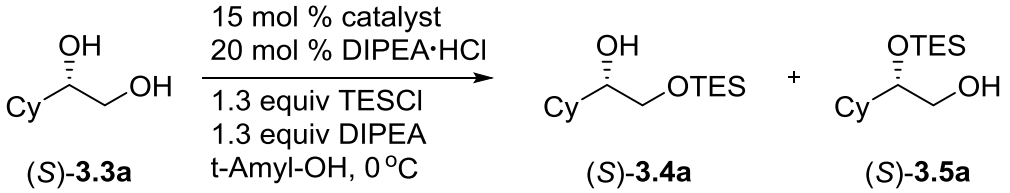


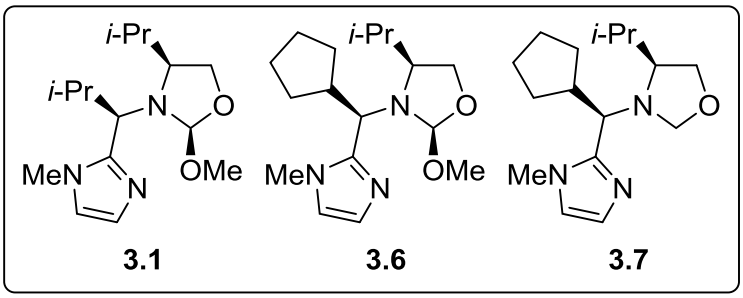
3.3 Selective Functionalization of Enantiopure Terminal 1,2-Diols

We began by investigating the site-selective silylation of (*S*)-**3.3a**. Using *N*-methylimidazole as a background catalyst, the inherent selectivity of the substrate was determined to strongly favor the primary hydroxyl functionalization ((*S*)-**3.4a**: (*S*)-**3.5a** = 98:2, Table 3.1, entry 1). This selectivity was dramatically reversed by the employment of

catalyst **3.1** ((*S*)-**3.4a**: (*S*)-**3.5a** = 18:82, Table 3.1, entry 2). Optimization of the catalyst structure also revealed that replacement of the isopropyl group adjacent to the imidazole ring with a cyclopentyl group (catalyst **3.6**) further enhanced the selectivity ((*S*)-**3.4a**: (*S*)-**3.5a** = 12:88), with (*S*)-**3.5a** isolated in 74% yield (Table 3.1, entry 3).

Table 3.1. Site-selective silylation of terminal (*S*)-1,2-diol





entry	catalyst	**3.4a**:**3.5a**[a]	yield of **3.5a** (%)[a]
1	**NMI**	98:2	<2
2	**3.1**	18:82	58
3	**3.6**	12:88	76 (74[b])
4	**3.7**	91:9	<1
5[c]	**3.6**	>98:2	<2

[a]Yields and selectivities determined by GC with an internal standard (1,3,5-trimethoxybenzene). [b]Isolated yield of (*S*)-**3.5a**. [c](*R*)-3.3a was used as the substrate.

With a successful initial attempt, we then performed experiments to support our initial hypothesis. Control catalyst **3.7**, which lacks a substrate-binding site, was

synthesized and subjected to the same conditions. This reaction afforded a selectivity similar to that of the background experiment, which strongly suggested the formation of covalent bond between the substrate and the catalyst was necessary to achieve the protection of the secondary hydroxyl (Table 3.1, entry 4). To demonstrate the importance of stereochemistry of the substrate, the opposite enantiomer diol, (*R*)-**3.3a**, was functionalized with catalyst **3.6**. As expected, silylation of primary hydroxyl was exclusively observed, because the stereoselectivity and inherent substrate reactivity are matched (Table 3.1, entry 5).

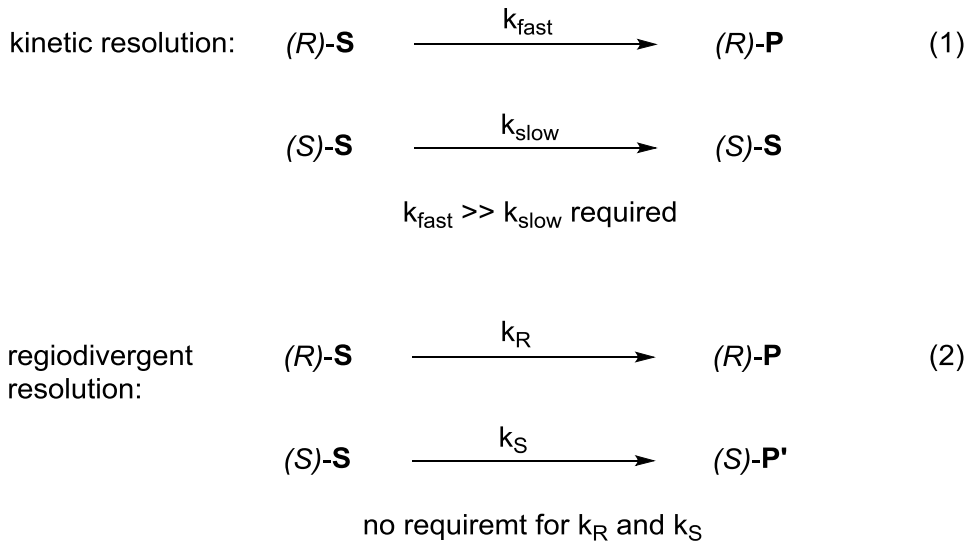
With the successful initial examination, we have demonstrated the effectiveness of scaffolding catalysts in the selective transfer of silyl groups to both enantiomers of terminal 1,2-diol, yet towards different constitutional isomers of the products (Table 3.1, entry 3 and 5). This observation indicates that by using a racemic mixture of the diol, our catalyst system could promote a regiodivergent resolution that leads to two separable enantioenriched products.

3.4 Regiodivergent Resolutions

Kinetic resolutions are widely applied methods for the synthesis of optically pure compounds from racemic starting materials (Scheme 3.5, equation 1).[10] The efficiency of the resolution is determined by the selectivity factor ($s = k_{fast}/k_{slow}$). Generally, high enantiopurity in a kinetic resolution is achieved with high conversion and reisolation of starting material. In order for the product to be isolated in high yield and ee, catalysts

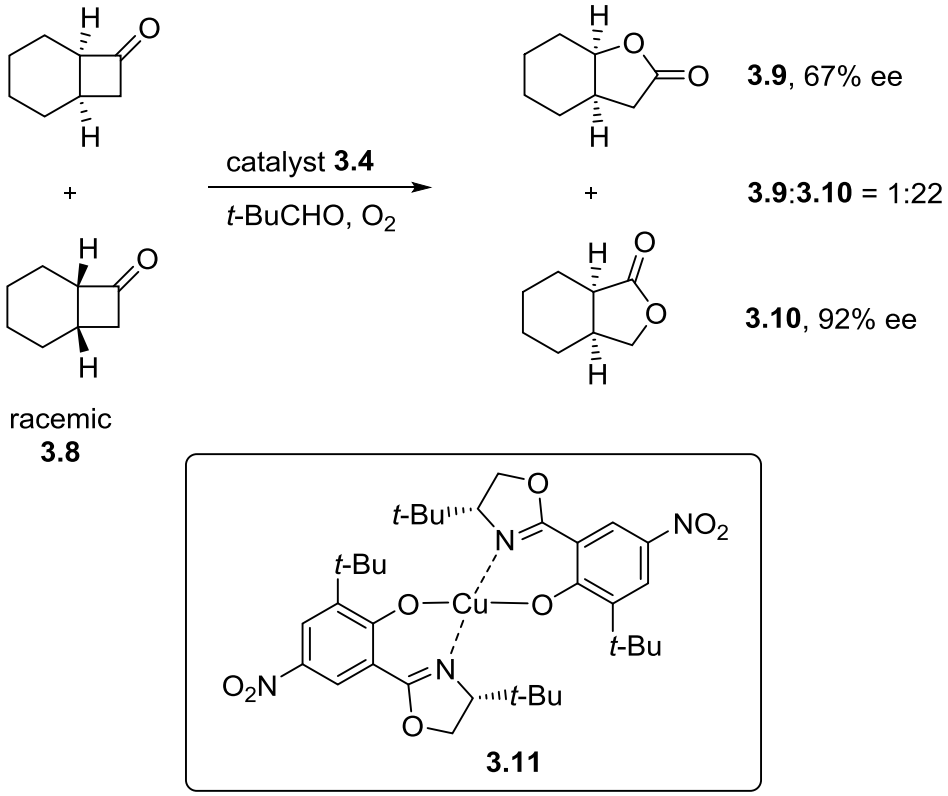
with exquisite selectivity are necessary. A classic example can be found in the hydrolytic kinetic resolution of racemic epoxides; a highly selective (salen)Co^{III} catalyst has been employed in order to obtain both the diol product and the recovered epoxide in practical yields and excellent enantiopurities.[11]

Scheme 3.5. Concepts of kinetic resolution and regiodivergent resolution



An alternative strategy for obtaining the products in high enantiopurity and yield is to perform a regiodivergent resolution, wherein the two enantiomers of starting material are converted into structurally isomeric products that can usually be separated by conventional methods (Scheme 3.5, equation 2).[12] Since the conversions of both substrate enantiomers have similar rates over the entire reaction time course, the use of divergent resolution avoids the requirement of a high selectivity factor.

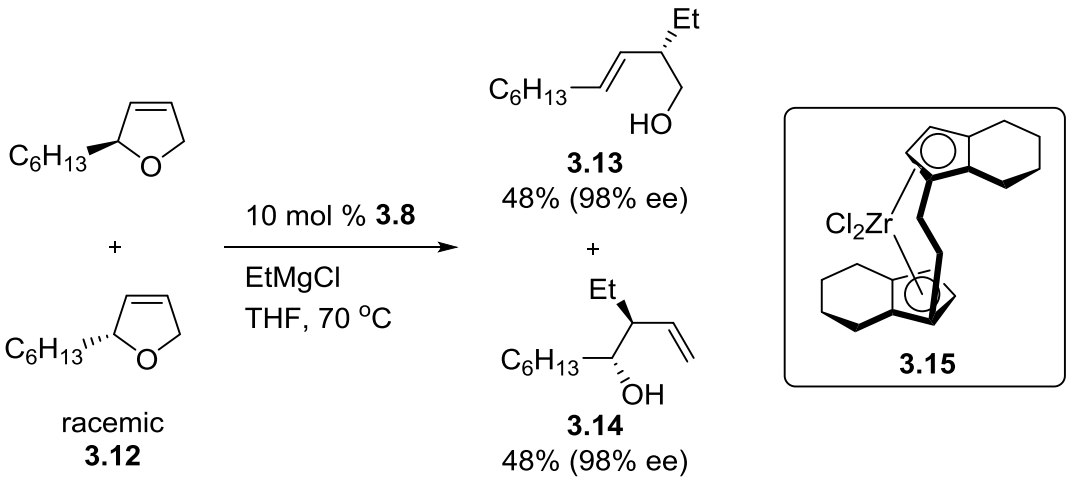
Scheme 3.6. Regiodivergent Baeyer-Villiger oxidation of a racemic ketone



Early studies have demonstrated that enzymes can be used to resolve racemic substrate through regiodivergent oxidations.[13] More recently, synthetic catalysts have been successfully developed to achieve the same goal. Bolm introduced a chiral copper **3.11** to convert racemic cyclobutanone into enantioenriched lactone regioisomers via a Bayer-Villiger oxidation (Scheme 3.6).[14] Hoveyda showed that a zirconium complex **3.15** perfectly controlled a regiodivergent ring opening of racemic dihydrofurans triggered by a Grignard reagent addition (Scheme 3.7).[15] Consequently, multiple examples of regiodivergent resolutions involving C-O bonding cleavages,[16] as well as other types of reactions such as Sharpless epoxidations,[17] diazo insertions and cyclopropanations,[18] and

a ynal cyclization[19] have been reported.

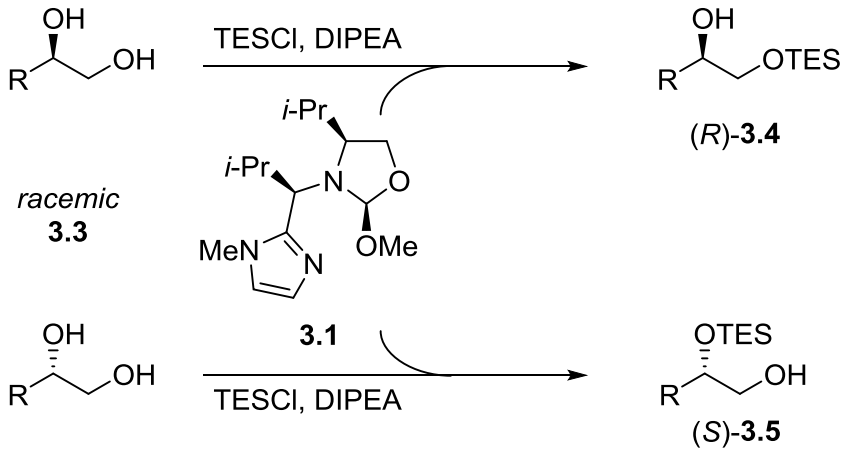
Scheme 3.7. A catalyst-controlled regiodivergent ring opening of racemic dihydrofurans



Enantioselective electrophile transfer provides an efficient access to enantiopure terminal 1,2-diols from inexpensive racemic starting materials.[20] The robust nature and chemical orthogonality of silyl protecting groups[21] has also made asymmetric silyl transfer particularly synthetically valuable in the resolution of alcohols. Recently, Hoveyda and Snapper disclosed the kinetic resolution of 1,2-diols via silylation with an organic catalyst.[22] Later, the same catalyst was applied to a highly effective regiodivergent resolution of 1,2-diols.[23] However, to the best of our knowledge, no successful regiodivergent resolution of terminal 1,2-diols has been reported, presumably due to the difficulty to control the silylation of one enantiomer substrate on the less reactive secondary hydroxyl group.

3.5 Regiodivergent Resolution of Racemic Terminal 1,2-Diols

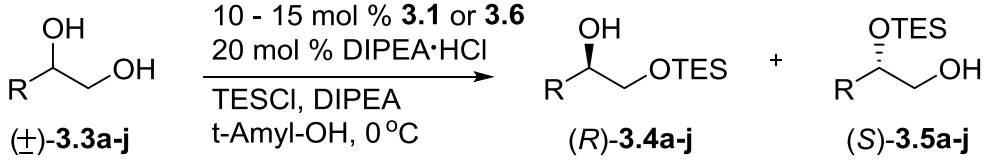
Scheme 3.8. Design of a regiodivergent resolution



With our promising results with enantiopure diols, we envisioned if selectivities were maintained, the scaffolding catalyst could enable a regiodivergent resolution of a racemic diol mixture (Scheme 3.8). Since the (*R*)-diol would exclusively furnish the primary protected product (*R*)-**3.4**, the only resource to form secondary silylated diol **3.5** would be the (*S*)-substrate, thereby high enantioselectivity in (*S*)-**3.5** could be expected. To our delight, the scaffolding catalysts exhibited a broad substrate scope, with high yields (>40% yields) and excellent enantioselectivities (>95% ee's) for the secondary silylated products (Table 3.2, (*S*)-**3.5a-j**). Sterically hindered alkyl substituents are well tolerated, yielding secondary functionalized products in high ee's (Table 3.2, entry 1-3). Small substituents methyl and vinyl lead to decreased yields (Table 3.2, entry 4 and 8), which can result from a drop in the binding selectivity of the catalyst that causes more

(*S*)-**3.3** converted to (*S*)-**3.4**. Similar results were also observed with groups known to deactivate the adjacent secondary hydroxyls such as CH_2OPh and vinyl (Table 3.2, entry 7 and 8). However, consistent to our anticipation, in all cases the ee's of secondary protected products (*S*)-**3.5** were still high. Finally, substrates with halogen groups, which offer additional synthetic value, provide excellent yields and enantioselectivities (Table 3.2, entry 9 and 10).

Table 3.2. Regiodivergent resolution of terminal 1,2-diols



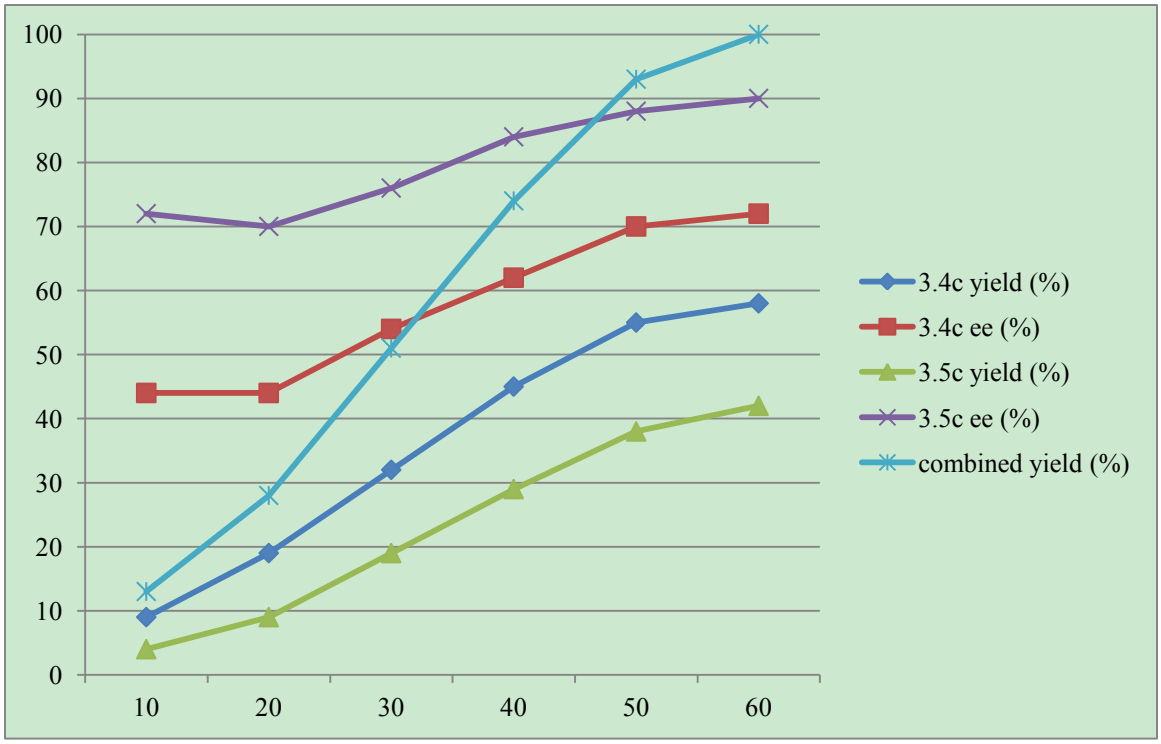
		3.4[a]		**3.5**[a]	
entry	R	yield (%)	ee (%)	yield (%)	ee (%)
1[b]	Cy	52	81	41	97
2[c]	*n*-Bu	54	79	40	98
3[b]	*i*-Bu	53	82	40	98
4[d]	Me	48	70	36	92
5[e]	Bn	46	80	40	96
6[c]	CH_2OBn	56	74	40	99
7[f]	CH_2OPh	44	78	32	96
8[d]	$CH{=}CH_2$	53	57	37	91
9[b]	CH_2Cl	52	90	45	97
10[b]	CH_2Br	50	91	41	98

[a]Yields and ee's are averages of two runs, ee's were determined by GC or HPLC analysis. **3.4** and **3.5** were separated by column chromatography to obtain isolated yields. [b]15 mol % **3.6**, 1.3 equiv TESCl, 1,3 equiv DIPEA, 1.5 h. [c]10 mol % **3.1**, 1.2 equiv TESCl, 1,2 equiv DIPEA, 1.5 h. [d]15 mol % **3.6**, 1.2 equiv TESCl, 1,2 equiv DIPEA, 25 min. [e]10 mol % **3.6**, 1.2 equiv TESCl, 1,2 equiv DIPEA, 45 min. [f]15 mol % **3.1**, 1.4 equiv TESCl, 1,4 equiv DIPEA, 45 min.

3.6 Time Course Study of Reaction Kinetics

While the optimal conditions to yield secondary protected products in high yields and enantioselectivities have been disclosed, the primary protected products were formed in only modest ee's under these conditions. We thus sought to reevaluate this reaction in order to maximize the yields and selectivities in the silylation of the primary hydroxyls.[24]

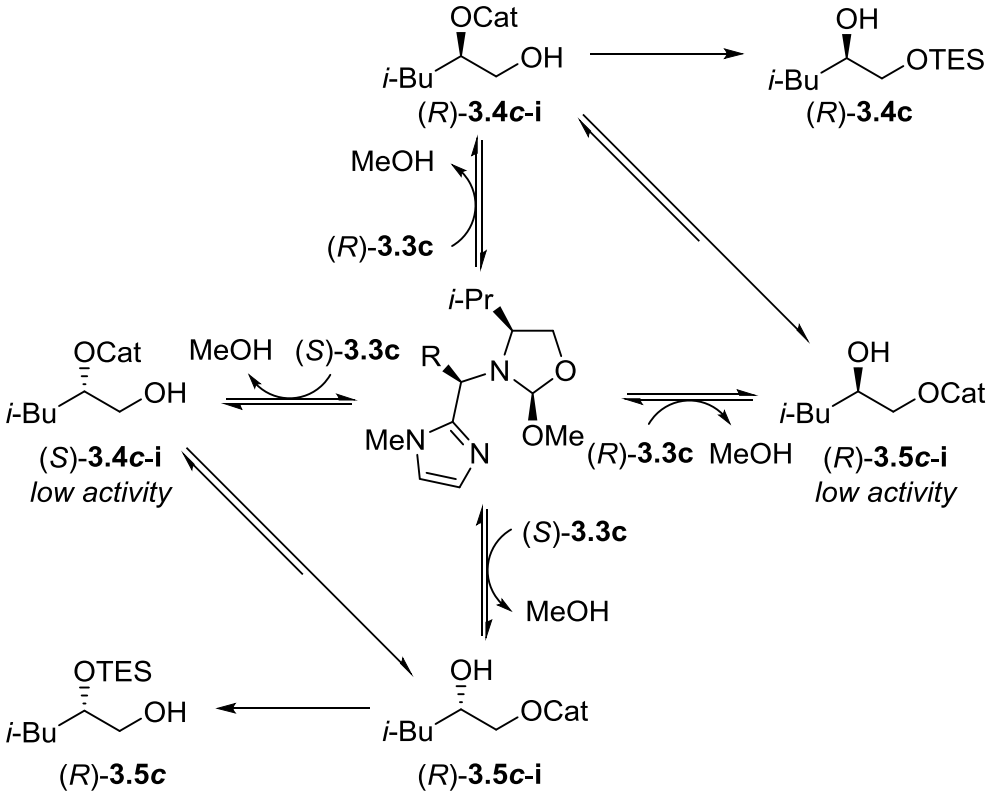
Figure 3.2. Time course study at 0 °C with a single addition of TESCl



To improve the divergent resolution, a time course study of the reaction at a reduced catalyst loading was carried out (10 mol % **3.6**, Figure 3.2). Intriguingly, the ee's of both products increased over time; moreover, their formation also accelerated during the course of the reaction. This observation can be rationalized by considering a kinetic

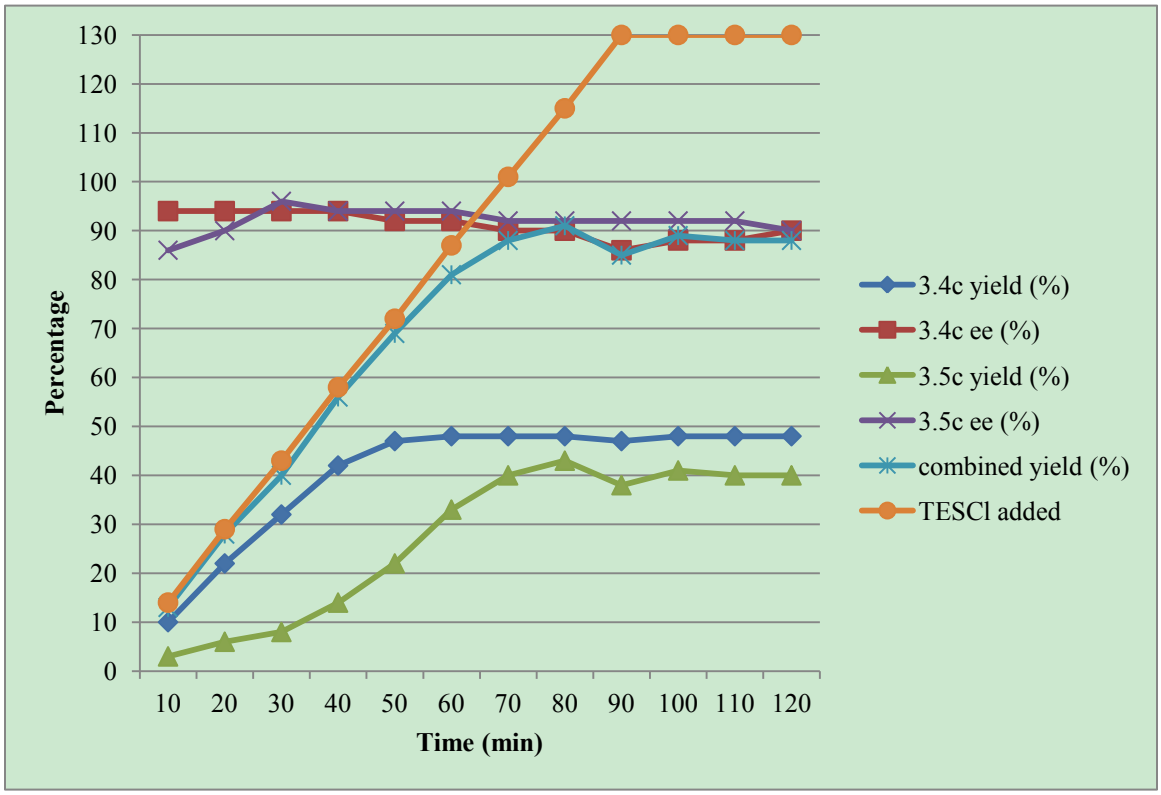
model of the reaction (Scheme 3.9). Since the majority of secondary protected product **3.5c** is obtained from (*S*)-**3.3c**, the opposite substrate enantiomer (*R*)-**3.3c** serves as an inhibitor for the formation of (*S*)-**3.5c** by majorly binding to the catalyst with the primary hydroxyl, thereby forming an inactive intermediate (*R*)-**3.5c-i** with a mismatched catalyst-substrate relationship. As (*R*)-**3.3c** is gradually converted to (*R*)-**3.4c** during the course, the concentration of catalyst bound to (*S*)-**3.3c** consequently increases, leading to the accelerating formation of (*S*)-**3.5c**. Additionally, the lower ee's in the early stage of the reaction can result from the limited exchange rate between catalyst **3.6** and diol **3.3c**, which allows the unselective background silylation to be competitive in the presence of excess silyl chloride.

Scheme 3.9. Proposed kinetic model.



To test this hypothesis we performed a slow addition of silyl chloride in order to suppress the rate of the silylation step (Figure 3.3). We also raised the reaction temperature to facilitate the exchange between catalyst **3.6** and the substrate. This time course showed a synchronized conversion with the silyl chloride addition rate, indicating only a limited amount of excess electrophile in solution during the process. To our delight, the enantioselectivities of both products remained high during the course, presumably due to the minimized unselective background silylation. In addition, the regulated TESCl addition further allowed the formation of **3.4c** in a constant high rate, while the formation of **3.5c** was effectively inhibited and remained slow during the first 30 minutes. This rate difference allowed us to obtain **3.4c** with 47% yield and 92% ee at the consumption of ~0.70 equiv TESCl.

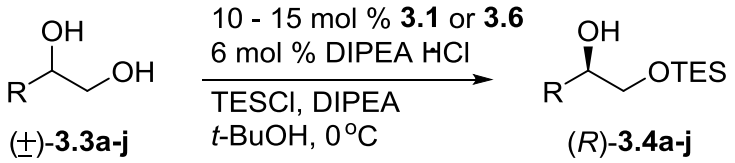
Figure 3.3. Time course study at room temperature with a syringe pump addition of TESCl



Based on the time course data, we employed 0.7 equiv of electrophile in order to obtain the primary protected product in high yield and enantioselectivity. To improve the practicality of the reaction we performed it at room temperature with portion-wise addition of TESCl. Application of the new conditions to the previous substrate scope of divergent resolution allowed the isolation of a variety of primary silylated diol **3.4** in the synthetically practical level of yields and ee's (Table 3.3). Alkyl groups with different steric hindrance were well tolerated in the new conditions (Table 3.3, entry 1-3). Primary protected products were also obtained in high enantiopurities with benzyl, CH_2OBn, and

groups containing halogens (Table 3.3, entry 5, 6, 9 and 10). A decrease of yield and ee was observed with methyl, CH_2OPh, and vinyl substituents, which were known to provide more undesired (*S*)-**3.4** from the (*S*)-diol substrate (Table 3.3, entry 4).

Table 3.3. Regiodivergent resolution towards primary protected terminal diols



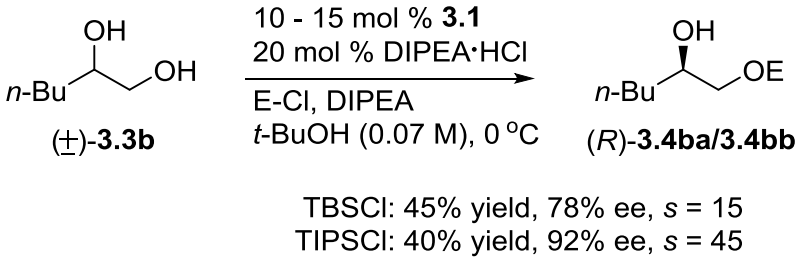
entry	R	catalyst	yield (%)[g]	ee (%)
1[a]	*Cy*	**3.6**	43	91
2[b]	*n*-Bu	**3.1**	46	93
3[c]	*i*-Bu	**3.6**	44	92
4[d]	Me	**3.6**	37	88
5[b]	Bn	**3.6**	41	92
6[c]	CH_2OBn	**3.1**	40	90
7[e]	CH_2OPh	**3.1**	36	89
8[b]	$CH{=}CH_2$	**3.6**	41	78
9[b]	CH_2Cl	**3.6**	40	95
10[b]	CH_2Br	**3.6**	41	95

[a]0.60 equiv TESCl and 0.70 equiv DIPEA were used, *t*-Amyl-OH was used as solvent, reaction was run at 4 °C for 2 h. [b]0.70 equiv TESCl and 0.80 equiv DIPEA were used. [c]0.60 equiv TESCl and 0.70 equiv DIPEA were used. [d]0.80 equiv TESCl and 0.90 equiv DIPEA were used. [e]0.70 equiv TESCl and 0.80 equiv DIPEA were used, reaction time was 2 h. [f]0.50 equiv TESCl and 0.60 equiv DIPEA were used, *t*-Amyl-OH was used as solvent. [g]Isolated yields.

Finally, the tolerance of silyl reagent range in this method was also explored (Scheme 3.10). Previous tests of bulky silyl chlorides resulted in no functionalization of the secondary hydroxyls. However, a traditional kinetic resolution can still be achieved if

the scaffolding catalyst provides a high selectivity factor. Using TBSCl in the resolution of 1,2-hexanediol provided (*R*)-**3.4ba** in 45% yield and 78% ee (s = 15). Increasing the steric bulk of the silyating reagent to TIPSCl afforded the product in 40% yield and 92% ee (s = 45). This level of selectivity provides a practical method for either isolating the product or starting diol in high enantioselectivity and yield.

Scheme 3.10. Silyl reagent scope



3.7 Conclusions

Through the synergy of the binding selectivity and stereoselectivity of our scaffolding catalysis design, we have demonstrated a method to directly functionalize the less reactive site of a molecule. Such reversal of substrate's inherent selectivity has been achieved in the context of terminal 1,2-diols, leading to a regiodivergent resolution towards the secondary silylated product in high isolated yields and ee's. With an understanding of the reaction kinetics based on time course studies, we have also modified conditions to obtain primary protected product in practical yields and enantiopurities with a range of silyl reagents.

3.8 Experimental

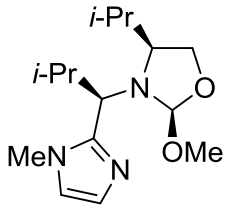
General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lithium reagents were titrated against 2-pentanol using 1,10-phenanthroline as the indicator. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe and cannula techniques, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). *tert*-amyl alcohol and *tert*-butanol were distilled over CaH_2 and stored over 3Å molecular sieves in a dry box under a nitrogen atmosphere. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. C_6D_6 was degassed by three successive freeze-pump-thaw cycles and stored over 3Å molecular sieves in a dry box under a nitrogen atmosphere. Column chromatography was performed using an ISCO automatic purification system (model: Combiflash RF 75 PSI) and RediSep Rf Gold pre-packed columns. Hydroformylation was performed in an Argonaut Technologies Endeavor® Catalyst Screening System using 1:1 H_2/CO supplied by Airgas, Inc. ^{1}H and ^{13}C NMR were performed on either a Varian Gemini 400 MHz, Varian Gemini 500 MHz or a Varian Unity Inova 500 MHz spectrometer. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C NMR. Coupling constants are reported in

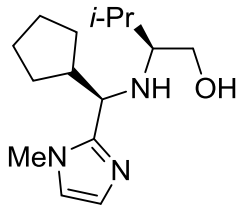
Hz. All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm^{-1}. All GC analyses were performed on an Agilent Technologies 7890A GC System. HRMS and X-ray crystal structure data were generated in Boston College facilities. Analytical chiral high-performance liquid chromatography (HPLC) was performed on a Shimadzu-LC-2010A HT.

<u>*Catalyst Synthesis*</u>

(4S)-4-isopropyl-2-methoxy-3-((R)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)-propyl) oxazolidine (**3.1**). The catalyst is synthesized following the previous reported procedure (Chapter 2, experimental)



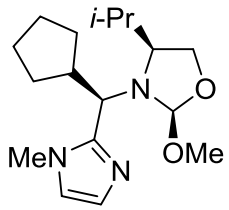
(S)-2-(((R)-cyclopentyl(1-methyl-1H-imidazol-2-yl)methyl)amino)-3-methylbutan-1-ol. Cyclopentene (68.1 g, 1.00 mol), tris(2,4-di*tert*-butyl-phenyl)phosphite (8.41 g, 13.0 mmol), and $Rh(acac)(CO)_2$ (903 mg, 3.50 mmol) were dissolved in anhydrous benzene (200 mL) in a pressure vessel. The pressure vessel was purged 3 times with 1:1 H_2/CO, pressurized to 150 psi, and heated to 80 °C. The reactions were stirred for 20 hours maintaining constant temperature and pressure. The concentration of the resulting crude cyclopenatanecarboxaldehyde solution was determined by ^{1}H NMR with internal standard (1,3,5-trimethoxybenzene) added to aliquot. The crude product solution was then used in the next step without purification. To a stirring solution of (*S*)-valinol (20.6 g,



200 mmol) in anhydrous THF (150 mL) under nitrogen atmosphere was added a solution of crude cyclopentanecarboxaldehyde (200 mmol) in benzene (100 mL). $MgSO_4$ (12.0 g, 100 mmol) was added, and the solution was stirred at room temperature for 3 hours to form the imine which closes to the oxazolidine in situ. In another oven-dried glass reaction flask, to a solution of *N*-methylimidazole (36.1 g, 440 mmol) in anhydrous THF (200 mL) under nitrogen atmosphere was added *n*-butyllithium (40 mL, 11 M in hexanes, 440 mmol) slowly at -78 °C. The solution was stirred at -78 °C for 30 minutes, and the formed oxazolidine solution was slowly cannula transferred into the N-methylimidazolium lithium solution at -78 °C. The resulting mixture was stirred overnight and gradually warmed to room temperature. Saturated aqueous NH_4Cl (40 mL) solution was added slowly to quench the reaction. $MgSO_4$ (12 g) was added. The mixture was stirred at room temperature for 15 minutes, filtered and concentrated. Excess *N*-methylimidazole was distilled off (150 °C @ 1.0 mmHg). Flash column chromatography (CH_2Cl_2/MeOH = 100:1 to 10:1) afforded the pure product as colorless oil (40.4 g, 76 %, d.r. = 92:8). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.77 (d, 0.18H, *J* = 6.8), 0.82 (d, 0.18H, *J* = 6.8), 0.87 (d, 2.82H, *J* = 6.8), 0.91 (d, 2.82H, *J* = 6.8), 1.20-1.32 (m, 0.54H), 1.33-1.74 (m, 8.46H), 2.13-2.22 (m, 1.88H), 2.24-2.27 (m, 0.12H), 3.26 (d, 0.06H, *J* = 7.1), 3.28 (d, 0.94H, *J* = 5.9), 3.30 (d, 0.94H, *J* = 2.9), 3.32 (d, 0.06H, *J* = 4.4), 3.61 (s, 2.82H), 3.62 (s, 0.18H), 3.72 (d, 1H, *J* = 7.6), 6.72 (d, 0.06H, *J* = 1.2), 6.76 (d, 0.94H, *J* = 1.2), 6.93 (d, 0.94H, *J* = 1.2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 38.1, 38.3, 38.4, 38.6, 44.4, 44.5, 44.6, 48.6, 48.7, 48.9, 49.8, 50.1, 52.1, 65.0, 77.7, 78.0, 79.3, 81.6, 82.0,

82.7, 139.7, 140.2, 146.1, 146.2, 169.8, 170.6; **IR**: 3201, 2952, 2868, 1486, 1467, 1280, 1107, 1047, 835, 724 cm^{-1}; **HRMS** (ESI+) calcd. for $C_{15}H_{28}N_3O$ $[M+H]^+$: 266.2227, found: 266.2247. $[\alpha]_D^{20}$ = +46.7 (c = 1.0, CH_2Cl_2, *l* = 50 mm).

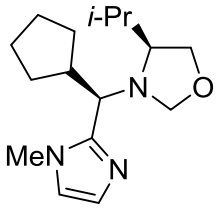
(2R,4S)-3-((R)-cyclopentyl(1-methyl-1H-imidazol-2-yl)methyl)-4-isopropyl-2-meth



oxyoxazolidine (**3.6**). To a solution of (S)-2-(((R)-cyclopentyl(1-methyl-1H-imidazol-2-yl)methyl)amino)-3-methylbutan-1-ol (7.4 g, 28 mmol) in anhydrous MeOH (56 mL) under nitrogen atmosphere was added *N,N*-dimethylformamide dimethyl acetal (19 mL, 140 mmol). The reaction was stirred at 50 °C overnight. The solvent was removed under vacuum, and the residue was redissolved in anhydrous MeOH (56 mL) in order to convert the small amount of dimethylamine bound catalyst to methanol bound catalyst. The reaction was stirred at 50 °C for 2 hours, and the solvent was removed under vacuum. The residue was moved into a dry box and was dissolved in anhydrous pentane (250 mL). The solution was cooled to -40 °C overnight, and dark yellow oil formed on the bottom of the flask. The top clear organic layer was decanted off and was concentrated to approximately 100 mL. The solution was cooled to -40 °C overnight during which the product precipitated as a white solid. The solid was filtered and washed with a small portion of cold pentane to afford pure product (−)-**2** (3.9 g, 46%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.69 (d, 3H, *J* = 7.1), 0.73-0.80 (m, 1H), 0.87 (d, 3H, *J* = 6.9), 1.46-1.78 (m, 7H), 2.33-2.40 (m, 1H), 2.75 (ddd, 1H, *J* = 8.8, 6.9, 5.1), 2.92 (s, 3H), 2.97-3.06 (m, 1H), 3.34 (s, 3H), 3.48 (d, 1H, *J* = 11.0), 3.59 (t, 1H, *J* = 7.8), 3.75 (t, 1H, *J* = 8.3), 6.27 (d, 1H, *J* =

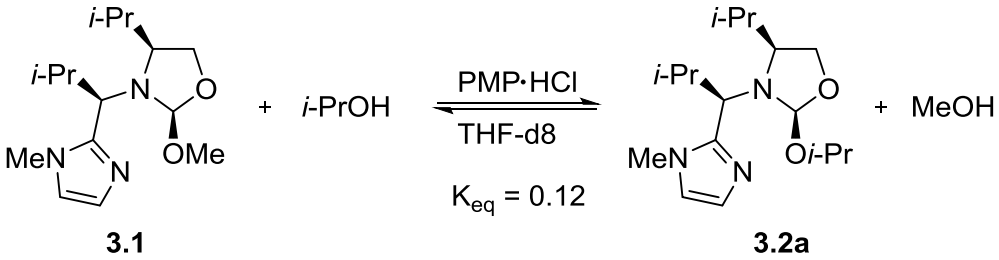
1.2), 6.72 (s, 1H), 7.16 (d, 1H, J = 1.2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 16.8, 20.1, 25.6, 26.0, 29.5, 31.8, 32.2, 32.3, 45.1, 52.3, 58.8, 65.4, 66.0, 112.6, 120.2, 128.5, 149.1; **IR**: 2952, 2870, 1650, 1482, 1192, 1174, 1122, 1074, 1052, 962 cm^{-1}**. Elemental Anaylsis**: $C_{17}H_{29}N_3O_2$ requires: C = 66.42%, H = 9.51%, N = 13.67%, found: C = 66.51%, H = 9.28%, N = 13.82%. **$[\alpha]_D^{20}$** = -37.3 (c = 1.0, CH_2Cl_2, l = 50 mm).

(S)-4-isopropyl-3-((R)-2-methyl-1-(1-methyl-1H-imidazol-2-yl)propyl)oxazolidine



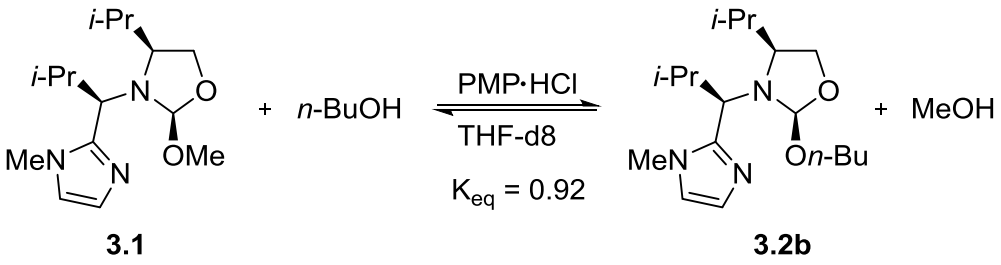
(**3.7**)**.** To a stirring solution of (S)-2-(((R)-cyclopentyl(1-methyl-1H-imidazol-2-yl)methyl)amino)-3-methylbutan-1-ol (0.50 g, 1.9 mmol) and paraformaldehyde (57 mg, 1.9 mmol) in anhydrous toluene (19 mL), *p*-toluenesulfonic acid monohydrate (3.6 mg, 1.9×10^{-2} mmol) was added. After refluxing overnight, reaction was cooled to room temperature, and CH_2Cl_2 (30 mL) was added. The resulting solution was concentrated. Flash column chromatography (100% EtOAc) afforded the product as colorless oil (280 mg, 54%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.88 (d, 3H, J = 6.8), 0.92 (d, 3H, J = 6.6), 1.51-1.73 (m, 8H), 2.02-2.07 (m, 1H), 2.57-2.60 (m, 1H), 2.70-2.73 (m, 1H), 3.47 (d, 2H, J = 6.3), 3.61 (d, 1H, J = 10.5), 3.68 (s, 3H), 4.42 (d, 1H, J = 4.6), 5.06 (d, 1H, J = 4.4), 6.78 (d, 1H, J = 1.0), 7.02 (d, 1H, J = 1.2); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 18.1, 19.8, 25.1, 25.4, 30.9, 31.0, 31.7, 33.1, 44.4, 61.5, 66.5, 67.6, 82.3, 120.3, 127.6, 148.4; **IR**: 2953, 2867, 1650, 1479, 1279, 1171, 1133, 1082, 943, 724 cm^{-1}; **$[\alpha]_D^{20}$** = +24.4 (c = 0.98, CH_2Cl_2, l = 50 mm).

Catalyst Equilibrium Experiments



3.1 **3.2a**

In a glovebox, a solution of catalyst **3.1** (35 mg, 0.13 mmol) and *N,N*-diisopropylethylamine hydrochloride (2.1 mg, 1.3×10^{-2} mmol) in anhydrous C_6D_6 (500 μL) was made. 200 μL of the solution was added to a NMR tube. iPrOH (0.25 mmol, 130 μL, 2M solution in C_6D_6) and MeOH (5.0×10^{-2} mmol, 25 μL, 2M solution in C_6D_6) was added to the NMR tube. C_6D_6 (150 μL) was added to the NMR tube to reach a total volume of 0.5 mL. The reaction was monitored by ^{1}H NMR. After 24 hours, equilibrium was reached. A ratio of **3.1**:**3.2a** = 68:32 gave a K_{eq} of 0.11. Another 200 μL of the catalyst and acid solution was added to another NMR tube. iPrOH (5.0×10^{-1} mmol, 250 μL, 2M solution in C_6D_6) and MeOH (5.0×10^{-2} mmol, 25 μL, 2M solution in C_6D_6) was added to the NMR tube. C_6D_6 (25 μL) was added to the NMR tube to reach a total volume of 0.5 mL. The reaction was monitored by ^{1}H NMR. After 24 hours, equilibrium was reached. A ratio of **3.1**:**3.2a** = 57:43, gave a K_{eq} of 0.12. The average K_{eq} for the two runs is 0.12 ± 0.01.



3.1 **3.2b**

In a glovebox, a solution of catalyst **3.1** (35 mg, 0.13 mmol) and *N,N*-diisopropylethylamine hydrochloride (2.1 mg, 1.3×10^{-2} mmol) in anhydrous C_6D_6 (500 μL) was made. 200 μL of the solution was added to a NMR tube. *n*BuOH (0.15 mmol, 75 μL, 2M solution in C_6D_6) and MeOH (5.0×10^{-2} mmol, 25 μL, 2M solution in C_6D_6) was added to the NMR tube. C_6D_6 (200 μL) was added to the NMR tube to reach a total volume of 0.5 mL. The reaction was monitored by ^{1}H NMR. After 24 hours, equilibrium was reached. A ratio of **3.1**:**3.2b** = 67:33 gave a K_{eq} of 0.98. Another 200 μL of the catalyst and acid solution was added to another NMR tube. *n*BuOH (5.0×10^{-2} mmol, 25 μL, 2M solution in C_6D_6) and MeOH (5.0×10^{-2} mmol, 25 μL, 2M solution in C_6D_6) was added to the NMR tube. C_6D_6 (250 μL) was added to the NMR tube to reach a total volume of 0.5 mL. The reaction was monitored by ^{1}H NMR. After 24 hours, equilibrium was reached. A ratio of **3.1**:**3.2b** = 43:57 gave a K_{eq} of 0.86. The average K_{eq} for the two runs is 0.92 ± 0.06.

Site-Selective Silylation of (S)-Cyclohexylethane-1,2-Diol (Table 3.1)

General Procedure. In a dry box, a solution of (*S*)-1-cyclohexylethane-1,2-diol (29

mg, 0.20 mmol), catalyst **3.6** (8.3 mg, 3.0 x 10^{-2} mmol, 15 mol %), and *N,N*-diisopropylethylamine hydrochloride (6.6 mg, 4.0 x 10^{-2} mmol, 20 mol %) in anhydrous *tert*-amyl alcohol (2.9 mL) was prepared in an oven-dried glass reaction vial. The reaction was stirred at 0 °C for 10 minutes. *N,N*-diisopropylethylamine (45 μL, 0.26 mmol, 1.3 equiv) was added, followed by addition of chlorotriethylsilane (44 μL, 0.26 mmol, 1.3 equiv). The reaction was stirred at 0 °C for 30 minutes. MeOH (100 μL) was added to quench the reaction. The solvent was removed under reduced pressure. Chiral GLC analysis of crude mixture with 1,3,5-trimethoxybenzene as internal standard afforded yields of products and the selectivity of the reaction (Supelco Gamma Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 115 °C for 180 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi; t_{sdantard} = 18.6 min, $t_{\mathbf{3.3a}}$ = 22.6 min, $t_{\mathbf{3.4a}}$ = 40.4 min, $t_{\mathbf{3.5a}}$ = 44.0 min; Response factors (standard: 1.0, **3.3a**: 1.3, **3.4a**: 0.56, **3.5a**: 0.65)).

Table 1, entry 1. Reaction was performed with *N*-methylimidazole (2.4 μL, 3.0 x 10^{-2} mmol) as catalyst using the general procedure. Chiral GLC analysis of the crude mixture afforded <2% yield of **3.5a** and a selectivity of **3.4a**:**3.5a** = 98:2.

Table 1, entry 2. Reaction was performed with **3.1** (8.4 mg, 3.0 x 10^{-2} mmol) as catalyst using the general procedure. Chiral GLC analysis of the crude mixture afforded 58% yield of **3.5a** and a selectivity of **3.4a**:**3.5a** = 18:82.

Table 1, entry 3. Reaction was performed using the general procedure. Chiral GLC analysis of the crude mixture afforded 76% yield of **3.5a** and a selectivity of **3.4a**:**3.5a** = 12:88. Column chromatography (0-20% EtOAc in Hexanes) afforded the pure product as

colorless oil (38 mg, 74%).

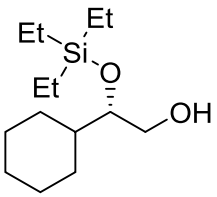
Table 1, entry 4. Reaction was performed with **7** (8.3 mg, 3.0 x 10^{-2} mmol) using the general procedure. Chiral GLC analysis of the crude mixture afforded <1% yield of **3.5a** and a selectivity of **3.4a**:**3.5a** = 91:9.

Table 1, entry 5. Reaction was performed with (*R*)-1-cyclohexylethane-1,2-diol (29 mg, 0.20 mmol) using the general procedure. Chiral GLC analysis of the crude mixture afforded <2% yield of **3.5a** and a selectivity of **3.4a**:**3.5a** > 98:2.

Regiodivergent Resolution of Racemic Terminal 1,2-Diols (Table 3.2)

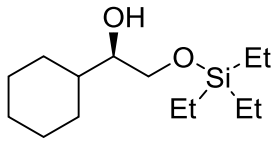
General Procedure. In a dry box, a solution of 1-cyclohexylethane-1,2-diol (140 mg, 1.0 mmol), catalyst **3.6** (46 mg, 0.15 mmol, 15 mol %), and *N,N*-diisopropylethylamine hydrochloride (33 mg, 0.20 mmol, 20 mol %) in anhydrous *tert*-amyl alcohol (14 mL) was prepared in an oven-dried glass reaction vial. The reaction was stirred at 0 °C for 10 minutes. *N,N*-diisopropylethylamine (230 μL, 1.3 mmol, 1.3 equiv) was added, followed by addition of chlorotriethylsilane (220 μL, 1.3 mmol, 1.3 equiv). The reaction was stirred at 0 °C for 45 minutes. MeOH (500 μL) was added to quench the reaction. The solvent was removed under reduced pressure. Column chromatography (0-20% EtOAc in Hexanes, using an ISCO automated purification system) afforded **3.4a** (145 mg, 56%) and **3.5a** (105 mg, 41%) as colorless oils.

(S)-2-cyclohexyl-2-(triethylsilyloxy)ethanol (*Table 3.2, entry 1,* **3.5a**). The general



procedure was followed to yield colorless oil (105 mg, 41%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 145 °C for 100 min, 10 °C/min to 200 °C, 200°C for 10 min, 15 psi., t_{rmajor} = 44.4 min, t_{rminor} = 45.0 min) 97% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.63 (q, 6H, *J* = 8.1), 0.98 (t, 9H, *J* = 8.1), 1.10-1.25 (m, 4H), 1.46-1.53 (m, 1H), 1.65-1.84 (m, 7H), 3.49 (dt, 1H, *J* = 6.1, 3.7), 3.53-3.59 (m, 2H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 5.3, 7.1, 26.5, 26.6, 26.8, 29.0, 29.3, 41.4, 64.2, 77.4; **IR**: 3421, 2924, 2876, 1450, 1238, 1118, 1006, 739 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{14}H_{31}O_2Si_1$: $[M+H]^+$: 259.2093, found: 259.2099. $[\alpha]_D^{20}$ = +8.7 (*c* = 1.1, CH_2Cl_2, *l* = 50 mm).

(R)-1-cyclohexyl-2-((triethylsilyl)oxy)ethanol (*Table 3.2, Entry 1,* **3.4a**). The general



procedure was followed to yield the product as a colorless oil (123 mg, 47%). **Chiral GC Analysis** (Supelco Gamma Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 115 °C for 180 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rmajor} = 172.2 min, t_{rminor} = 169.2 min) 81% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.59 (q, 6H, *J* = 7.8), 0.94 (t, 9H, *J* = 7.8), 0.98-1.06 (m, 2H), 1.10-1.25 (m, 3H), 1.33-1.40 (m, 1H), 1.57-1.65 (m, 2H), 1.69-1.75 (m, 2H), 1.87-1.91 (m, 1H), 2.48 (d, 1H, *J* = 2.9), 3.34-3.38 (m, 1H), 3.44 (dd, 1H, *J* = 9.8, 8.3), 3.67 (dd, 1H, *J* = 9.8, 3.2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.6, 6.9, 26.3, 26.4, 26.7, 29.0, 29.1, 40.7, 65.2, 76.0; **IR**: 2921, 2875, 2852, 1450, 1112, 1079, 1004, 817, 726 cm^{-1}; **HRMS** (ESI+) calcd. for $C_{14}H_{30}O_2NaSi$: $[M+Na]^+$: 281.1907, found: 281.1915. $[\alpha]_D^{20}$ =

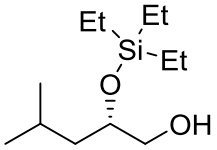
-6.4 (c = 1.3, CH_2Cl_2, *l* = 50 mm).

(S)-2-(triethylsilyloxy)hexan-1-ol (*Table 2, entry 2,* **3.5b**). The general procedure was followed using 1.2 equiv chlorotriethylsilane, 1.2 equiv *N,N*-diisopropylethylamine, 10 mol % **3.1**, and a reaction time of 1.5 hours to yield a colorless oil (88 mg, 38%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 95 °C for 120 min, 20 °C/min to 200 °C, 200°C for 20 min, 15 psi., t_{rmajor} = 106.1 min, t_{rminor} = 109.4 min) 98% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.63 (q, 6H, *J* = 7.8), 0.88-0.91 (m, 3H), 0.98 (t, 9H, *J* = 7.8), 1.23-1.34 (m, 4H), 1.47-1.52 (m, 2H), 1.91 (t, 1H, *J* = 6.4), 3.42-3.46 (m, 1H), 3.54-3.59 (m, 1H), 3.71-3.76 (m, 1H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 5.3, 7.0, 23.0, 23.3, 24.7, 43.5, 66.8, 71.4; **IR**: 3408, 2955, 2876, 1459, 1239, 1097, 1007, 727 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{29}O_2Si_1$: $[M+H]^+$: 233.1937, found: 233.1934. **$[\alpha]_D^{20}$** = +11.4 (*c* = 1.1, CH_2Cl_2, *l* = 50 mm).

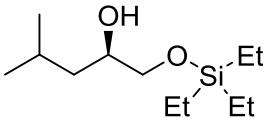
(R)-1-((triethylsilyl)oxy)hexan-2-ol (Table 3.2, entry 2, **3.4b**). The general procedure was followed using 1.2 equiv of chlorotriethylsilane, 1.2 equiv *N,N*-diisopropylethylamine, 10 mol % **3.1**, and a reaction time of 1.5 hours to yield a colorless oil (129 mg, 55%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 95 °C for 120 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rmajor} = 103.2 min, t_{rminor} = 102.1 min) 78% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.60 (q, 6H, *J* = 7.8), 0.89 (t, 3H, *J* = 7.1), 0.94 (t, 9H, *J* = 7.8), 1.22-1.45 (m, 6H), 2.44

(d, 1H, *J* = 3.2), 3.36 (dt, 1H, *J* = 2.0, 8.8), 3.59-3.64 (m, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.6, 6.9, 14.2, 23.0, 28.0, 32.7, 67.2, 72.1; **IR**: 2955, 2934, 2913, 2876, 1459, 1095, 1004, 803, 726 cm^{-1}; **HRMS** (ESI+) calcd. for $C_{12}H_{28}O_2NaSi$: $[M+Na]^+$: 255.1751, found: 255.1745. **$[\alpha]_D^{20}$** = -3.6 (c = 1.1, CH_2Cl_2, *l* = 50 mm).

(S)-4-methyl-2-(triethylsilyloxy)pentan-1-ol (Table 3.2, entry 3, **3.5c**). The general procedure was followed to yield colorless oil (94 mg, 40%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 95 °C for 120 min, 20 °C/min to 200 °C, 200°C for 20 min, 15 psi., t_{rmajor} = 80.4 min, t_{rminor} = 86.1 min) 98% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.63 (q, 6H, *J* = 8.1), 0.90 (d, 3H, *J* = 6.6), 0.91 (d, 3H, *J* = 6.6) 0.98 (t, 9H, *J* = 8.1), 1.38 (t, 2H, *J* = 6.8), 1.59-1.67 (m, 1H), 1.92 (t, 1H, *J* = 6.4), 3.39-3.44 (m, 1H), 3.57 (ddd, 1H, *J* = 11.0, 6.1, 3.7), 3.82 (ddt, 1H, *J* = 9.8, 5.4, 1.2); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 5.2, 7.0, 14.2, 23.0, 27.7, 40.0, 66.5, 73.1; **IR**: 3418, 2955, 2876, 1466, 1087, 1046, 742 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{29}O_2Si_1$: $[M+H]^+$: 233.1937, found: 233.1943. **$[\alpha]_D^{20}$** = +10.3 (*c* = 1.1, CH_2Cl_2, *l* = 50 mm).

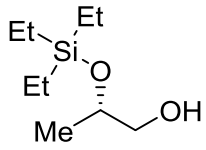


(R)-4-methyl-1-((triethylsilyl)oxy)pentan-2-ol (Table 3.2, entry 3, **3.4c**). The general procedure was followed to yield the product as colorless oil (125 mg, 54%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 95 °C for 90 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rmajor} = 75.9 min, t_{rminor} = 75.1 min) 82% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.60 (q, 6H, *J* = 7.8), 0.90 (d, 3H, *J* = 6.6), 0.92 (d, 3H,

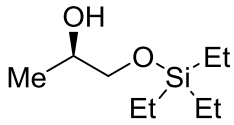


J = 6.6), 0.95 (t, 9H, *J* = 7.8), 1.11 (ddd, 1H, *J* = 13.5, 8.5, 4.2),1.36 (ddd, 1H, *J* = 14.2, 8.8, 5.9), 1.74-1.82 (m, 1H), 2.40 (d, 1H, *J* = 3.2), 3.33 (dd, 1H, *J* = 9.8, 7.8), 3.58 (dd, 1H, *J* = 9.8, 3.2), 3.71 (ddd, 1H, *J* = 16.4, 7.8, 3.2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.6, 6.9, 22.4, 23.6, 24.8, 42.0, 67.6, 70.3; **IR**: 2954, 2912, 2876, 1096, 1049, 1004, 789, 726 cm^{-1}; **HRMS** (ESI+) calcd. for $C_{12}H_{28}O_2NaSi$: $[M+Na]^+$: 255.1751, found: 255.1763. **$[\alpha]_D^{20}$** = +0.94 (c = 1.2, CH_2Cl_2, *l* = 50 mm).

(S)-2-(triethylsilyloxy)propan-1-ol (Table 3.2, entry 4, **3.5d**). The general procedure was followed using 1.2 equiv chlorotriethylsilane and 1.2 equiv *N,N*-diisopropylethylamine with a reaction time of 25 minutes. Column chromatography (3-20% Et_2O in Hexanes) yielded colorless oil (69 mg, 36%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 80 °C for 100 min, 20 °C/min to 200 °C, 200°C for 20 min, 15 psi., t_{rmajor} = 45.2 min, t_{rminor} = 46.8 min) 93% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.63 (q, 6H, *J* = 7.8), 0.97 (t, 9H, *J* = 7.8), 1.14 (d, 3H, *J* = 6.4), 1.96 (dd, 1H, *J* = 7.6, 5.1), 3.37 (ddd, 1H, *J* = 11.7, 6.6, 1.5), 3.48-3.53 (m, 1H), 3.89-3.95 (m, 1H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 5.1, 7.0, 20.1, 68.4, 69.1; **IR**: 3408, 2955, 2877, 1459, 1238, 1005, 741 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{12}H_{29}O_2Si_1$: $[M+H]^+$: 233.1937, found: 233.1934. **$[\alpha]_D^{20}$** = +18.6 (*c* = 1.0, CH_2Cl_2, *l* = 50 mm).

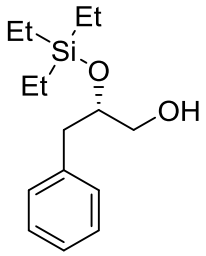


(R)-1-((triethylsilyl)oxy)propan-2-ol (Table 3.2, entrty 4, **3.4d**). The general procedure was followed using 1.2 equiv chlorotriethylsilane and 1.2 equiv *N,N*-diisopropylethylamine with a reaction time of 25 minutes. Column chromatography



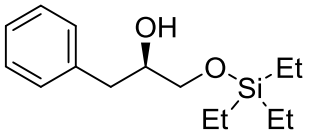
(3-20% Et_2O in Hexanes) yielded a colorless oil (97 mg, 51%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 80 °C for 45 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rmajor} = 36.8 min, t_{rminor} = 35.6 min) 70% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.60 (q, 6H, *J* = 7.8), 0.94 (t, 9H, *J* = 7.8), 1.10 (d, 3H, *J* = 6.4), 2.48 (d, 1H, *J* = 3.0), 3.32 (dd, 1H, *J* = 9.8, 7.8), 3.57 (dd, 1H, *J* = 9.8, 3.4), 3.77-3.84 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.6, 6.9, 18.4, 68.2, 68.4; **IR**: 2955, 2911, 2877, 1459, 1239, 1087, 1006, 801, 724 cm^{-1}; **HRMS** (ESI+) calcd. for $C_9H_{22}O_2NaSi$: $[M+Na]^+$: 213.1281, found: 213,1271. **$[\alpha]_D^{20}$** = -8.2 (c = 1.1, CH_2Cl_2, *l* = 50 mm).

(S)-3-phenyl-2-(triethylsilyloxy)propan-1-ol (Table 3.2, entry 5, **3.5e**). The general



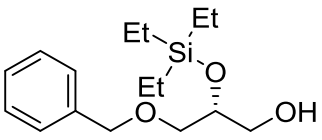
procedure was followed with 1.2 equiv of chlorotriethylsilane, 1.2 equiv *N,N*-diisopropylethylamine, and 10 mol % **3.1** to yield a colorless oil (116 mg, 44%). **Chiral HPLC Analysis** (OD-H, 1.0 mL/min, 10% *i*PrOH: 90% Hexanes, 220 nm, t_{rmajor} = 4.1 and t_{rminor} = 7.8 min) 96% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.53 (dq, 6H, *J* = 16.1, 3.4), 0.90-0.93 (m, 9H), 1.91 (dd, 1H, *J* = 7.0, 5.6), 2.80 (ddd, 2H, *J* = 19.6, 13.5, 6.1), 3.40-3.45 (m, 1H), 3.48-3.53 (m, 1H), 3.92 (dddd, 1H, *J* = 13.7, 7.3, 4.6, 0.98), 7.16-7.20 (m, 3H), 7.24-7.28 (m, 2H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 5.1, 7.0, 40.8, 65.8, 79.2, 126.5, 128.6, 129.8, 138.4; **IR**: 2953, 2912, 2876, 1455, 1238, 1103, 1004, 724, 698, 505 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{15}H_{27}O_2Si_1$: $[M+H]^+$: 267.1780, found: 267.1777. **$[\alpha]_D^{20}$** = -12.6 (*c* = 1.0, CH_2Cl_2, *l* = 50 mm).

(R)-1-phenyl-3-((triethylsilyl)oxy)propan-2-ol (Table 3.2, entry 5, **3.4e**). The



general procedure was followed using 1.2 equiv chlorotriethylsilane, 1.2 equiv *N,N*-diisopropylethylamine, and 10 mol % **3.1** to yield the product as a colorless oil (133 mg, 50%). **Chiral HPLC Analysis** (OD-H, 1.0 mL/min, 2% *i*PrOH: 98% Hexanes, 220 nm, t_{rmajor} = 5.50 min and t_{rminor} = 6.12 min) 80% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.59 (q, 6H, *J* = 7.8), 0.94 (t, 9H, *J* = 7.8), 2.42 (d, 1H, *J* = 3.9), 2.74 (dd, 1H, *J* = 13.7, 6.4), 2.78 (dd, 1H, *J* = 13.7, 7.1), 3.46 (dd, 1H, *J* = 9.8, 6.8), 3.60 (dd, 1H, *J* = 10.0, 3.7), 3.85-3.90 (m, 1H), 7.18-7.22 (m, 3H), 7.27-7.30 (m, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.6, 6.9, 39.8, 66.2, 73.0, 126.5, 128.6, 129.5, 138.5; **IR**: 2953, 2911, 2876, 1239, 1111, 1031, 792, 727, 698 cm^{-1}; **HRMS** (ESI+) calcd. for $C_{15}H_{26}O_2NaSi$: $[M+Na]^+$: 289.1594, found: 289.1600. $\mathbf{[\alpha]_D^{20}}$ = +2.6 (c = 1.0, CH_2Cl_2, *l* = 50 mm).

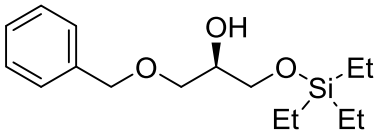
(R)-3-(benzyloxy)-2-(triethylsilyloxy)propan-1-ol (Table 3.2, entry 6, **3.5f**). The



general procedure was followed using 1.2 equiv chlorotriethylsilane, 1.2 equiv *N,N*-diisopropylethylamine, 10 mol % **3.1**, and a reaction time of 1.5 hours to yield a colorless oil (118 mg, 40%).**Chiral HPLC Analysis** (OD-H, 1.0 mL/min, 0.5% *i*PrOH: 99.5% Hexanes, 240 nm, t_{rmajor} = 23.2 and t_{rminor} = 30.5 min) 99% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.57-0.63 (q, 6H, *J* = 8.0), 0.91-0.95 (m, 9H), 2.04-2.08 (m, 1H), 3.44-3.51 (m, 2H), 3.57-3.68 (m, 2H), 3.88-3.93 (m, 1H), 4.51 (s, 2H), 7.25-7.35 (m, 5H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 4.8, 6.7, 64.9, 71.0, 71.9, 73.5, 127.6, 127.7, 128.4, 138.0; **IR**:

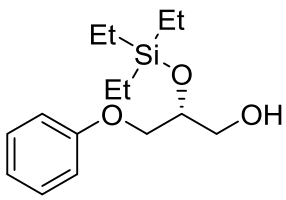
3439, 2954, 2876, 1455, 1239, 1098, 1005, 739, 698 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{16}H_{29}O_3Si_1$: $[M+H]^+$: 297.1886, found: 297.1881. $\mathbf{[\alpha]_D^{20}}$ = +21.4 (*c* = 1.1, CH_2Cl_2, *l* = 50 mm).

(R)-1-(benzyloxy)-3-((triethylsilyl)oxy)propan-2-ol (Table 3.2, entry 6, **3.4f**). The



general procedure was followed using 1.2 equiv chlorotriethylsilane, 1.2 equiv *N,N*-diisopropylethylamine, 10 mol % **3.1**, and a reaction time of 1.5 hours to yield product as a colorless oil (174 mg, 59%). **Chiral HPLC Analysis** (OD-H, 1.0 mL/min, 5% *i*PrOH: 95% Hexanes, 220 nm, t_{rmajor} = 7.87 min and t_{rminor} = 6.95 min) 73% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.59 (q, 6H, *J* = 7.8), 0.94 (t, 9H, *J* = 7.8), 2.48 (d, 1H, *J* = 4.9), 3.49 (dd, 1H, *J* = 9.5, 5.9), 3.53 (dd, 1H, *J* = 9.5, 4.9), 3.62 (dd, 1H, *J* = 10.0, 5.9), 3.66 (dd, 1H, *J* = 10.0, 4.9), 3.82-3.87 (m, 1H), 4.54 (s, 2H), 7.26-7.35 (m, 5H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.6, 6.9, 64.0, 71.0, 71.3, 73.7, 127.9, 128.0, 128.6, 138.4; **IR**: 2953, 2910, 2875. 1089, 1004, 804, 728, 696 cm^{-1}; **HRMS** (ESI+) calcd. for $C_{16}H_{28}O_3NaSi$: $[M+Na]^+$: 319.1700, found: 319.1697. $\mathbf{[\alpha]_D^{20}}$ = 0.53 (c = 1.1, CH_2Cl_2, *l* = 50 mm).

(R)-3-phenoxy-2-(triethylsilyloxy)propan-1-ol (Table 3.2, entry 7, **3.5g**). The

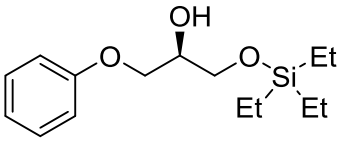


general procedure was followed using 1.4 equiv chlorotriethylsilane, 1.4 equiv *N,N*-diisopropylethylamine, and 15 mol % **3.1** to yield a colorless oil (87 mg, 31%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.68 (q, 6H, *J* = 7.8), 0.99 (t, 9H, *J* = 7.8), 2.00 (dd, 1H, *J* = 7.6, 5.4), 3.69 (dd, 1H, *J* = 11.3, 7.3), 3.75 (ddd, 1H, *J* = 11.2, 5.4, 4.2), 3.94 (dd, 1H, *J* = 9.3,

6.1), 3.99 (dd, 1H, *J* = 9.3, 5.9), 4.11-4.15 (m, 1H), 6.90 (dt, 2H, *J* = 8.8, 0.98), 6.96 (tt, 1H, *J* = 7.3, 0.98), 7.26-7.30 (m, 2H); **^{13}C NMR** ($CDCl_3$, 120 MHz) δ 5.1, 7.0, 64.6, 69.2, 71.3, 114.6, 121.1, 129.7, 158.5; **IR**: 3415, 2954, 2876, 1600, 1497, 1244, 1130, 1048, 749, 690 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{15}H_{27}O_2Si_1$: $[M+H]^+$: 283.1730, found: 283.1730. $\mathbf{[\alpha]_D^{20}}$ = +15.4 (*c* = 0.99, CH_2Cl_2, *l* = 50 mm).

Derivitization for ee. The product (15 mg, 9.0 x 10^{-2} mmol) was dissolved in 300 μL of CH_3CN and treated with 100 μL of hydrogen fluoride in pyridine. After 12 hours, column chromatography (1-10% MeOH in CH_2Cl_2) gave the known diol, (*R*)-3-phenoxypropane-1,2-diol. **Chiral HPLC Analysis** (OD-H, 1.0 mL/min, 15% *i*PrOH: 85% Hexanes, 240 nm) t_{rmajor} = 10.5 and t_{rminor} = 20.0 min) 96% ee (as diol).

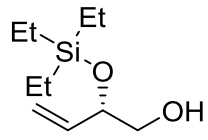
(R)-1-phenoxy-3-((triethylsilyl)oxy)propan-2-ol (Table 3.2, entry 7, **3.4g**). The



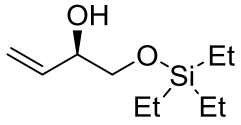
general procedure was followed using 1.4 equiv chlorotriethylsilane, 1.4 equiv *N,N*-diisopropylethylamine, and 15 mol % **3.1** to yield product as a colorless oil (131 mg, 47%). **Chiral HPLC Analysis** (OD-H, 1.0 mL/min, 10% *i*PrOH: 90% Hexanes, 220 nm, t_{rmajor} = 10.5 min and t_{rminor} = 5.09 min) 78% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.61 (q, 6H, *J* = 7.8), 0.94 (t, 9H, *J* = 7.8), 2.55 (d, 1H, *J* = 5.1), 3.74 (dd, 1H, *J* = 10.3, 5.1), 3.78 (dd, 1H, *J* = 10.3, 4.6), 3.99-4.05 (m, 3H), 6.89-6.91 (m, 2H), 6.92-6.96 (m, 1H), 7.25-7.28 (m, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.6, 6.9, 63.7, 68.7, 70.5, 114.8, 121.2 129.7, 158.9; **IR**: 2953, 2876, 1599, 1495, 1458, 1242, 1079, 1043, 1005, 802, 745, 727, 689 cm^{-1}; **HRMS** (ESI+) calcd. for $C_{15}H_{26}O_3NaSi$: $[M+Na]^+$: 305.1543, found: 305.1552.

$[\alpha]_D^{20}$ = -0.19 (c = 1.1, CH_2Cl_2, *l* = 50 mm).

(S)-2-(triethylsilyloxy)but-3-en-1-ol (Table 3.2, entry 8, **3.5h**). The general procedure was followed with 1.2 equiv chlorotriethylsilane, 1.2 equiv *N,N*-diisopropylethylamine, and a reaction time of 25 minutes to yield a colorless oil (71 mg, 35%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 90 °C for 100 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi., t_{rmajor} = 41.4 min, t_{rminor} = 43.1 min) 93% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.63 (q, 6H, *J* = 7.8), 0.97 (t, 9H, *J* = 7.8), 1.96-1.99 (m, 1H), 3.43-3.55 (m, 2H), 4.20-4.24 (m, 1H), 5.17 (ddd, 1H, *J* = 10.5, 2.9, 1.2), 5.28 (ddd, 1H, *J* = 17.4, 2.9, 1.7), 5.81 (dddd, 1H, *J* = 23.5, 10.5, 6.4, 1.7); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 5.1, 6.9, 67.0, 74.6, 116.5, 138.2; **IR**: 3415, 2955, 2877, 1459, 1098, 1007, 925, 743 cm^{-1}; **HRMS** (DART-TOF) calcd. for $C_{10}H_{23}O_2Si_1$: $[M+H]^+$: 203.1467, found: 203.1475. $[\alpha]_D^{20}$ = +7.4 (*c* = 0.82, CH_2Cl_2, *l* = 50 mm).

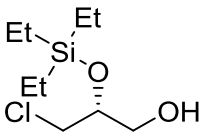


(R)-1-((triethylsilyl)oxy)but-3-en-2-ol (Table 3.2, entry 8, **3.4h**). The general procedure was followed using 1.2 eq of chlorotriethylsilane, 1.2 equiv *N,N*-diisopropylethylamine, and a reaction time of 25 minutes to yield product as a colorless oil (115 mg, 57%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 90 °C for 50 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rmajor} = 44.7 min, t_{rminor} = 43.0 min) 57% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.60 (q, 6H, *J* = 7.8), 0.95 (t, 9H, *J* = 7.8), 2.57 (d, 1H, 3.4), 3.42 (dd, 1H, *J* = 10.0, 7.8), 3.64 (dd, 1H, *J* = 10.0, 3.7), 4.13-4.18 (m,

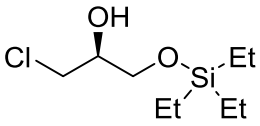


1H), 5.17 (dt, 1H, *J* = 10.5, 1.5), 5.33 (dt, 1H, *J* = 17.4, 1.5), 5.80 (ddd, 1H, *J* = 17.1, 10.5, 5.6); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.6, 6.9, 66.9, 73.3, 116.7, 136.8; **IR**: 2955, 2912, 2877, 1238, 1102, 1004, 923, 795, 725 cm^{-1}; **HRMS** (ESI+) calcd. for $C_{10}H_{22}O_2NaSi$: $[M+Na]^+$: 225.1281, found: 225.1285. **$[\alpha]_D^{20}$** = +0.84 (c = 1.2, CH_2Cl_2, *l* = 50 mm).

(R)-3-chloro-2-(triethylsilyloxy)propan-1-ol (Table 3.2, entry 9, **3.5i**). The general procedure was followed with a reaction time of 50 minutes to yield product as colorless oil (99 mg, 44%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 110 °C for 105 min, 20 °C/min to 200 °C, 200°C for 20 min, 15 psi, t_{rmajor} = 56.4 min, t_{rminor} = 57.9 min) 97% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.65 (q, 6H, *J* = 7.8), 0.98 (m, 9H), 1.85 (t, 1H, *J* = 6.4), 3.46 (dd, 1H, *J* = 10.8, 5.1), 3.58 (dd, 1H, *J* = 11.0, 7.1), 3.68-3.70 (m, 2H), 3.89-3.93 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 5.0, 6.9, 44.7, 64.0, 72.8; **IR**: 3397, 2956, 2878, 1459, 1240, 1120, 1046, 1006, 742 cm^{-1}; **HRMS** (ESI+) calcd. for $C_9H_{22}ClO_2Si$: $[M+H]^+$: 225.1078, found: 225.1071. **$[\alpha]_D^{20}$** = +8.3 (c = 1.1, CH_2Cl_2, *l* = 50 mm).

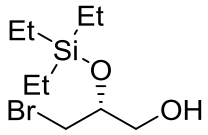


(S)-1-chloro-3-(triethylsilyloxy)propan-2-ol (Table 3.2, entry 9, **3.4i**). The general procedure was followed with a reaction time of 50 minutes to yield product as colorless oil (118 mg, 52%). **Chiral GC Analysis** (Supelco Gamma Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 110 °C for 50 min, 20 °C/min to 200 °C, 200°C for 20 min, 15 psi, t_{rmajor} = 45.1 min, t_{rminor} = 44.3 min) 90% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.61 (q, 6H, *J* = 8.1), 0.93-0.96 (m, 9H), 2.54 (d,

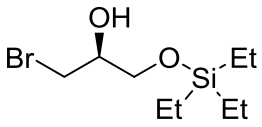


1H, *J* = 6.4), 3.54-3.61 (m, 2H), 3.66-3.72 (m, 2H), 3.80-3.86 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.5, 6.9, 45.6, 63.3, 71.6; **IR**: 3425, 2955, 2877, 1459, 1240, 1111, 1006, 804, 740 cm^{-1}; **HRMS** (ESI+) calcd. for $C_9H_{22}ClO_2Si$: $[M+H]^+$: 225.1070, found:225.1078. **$[\alpha]_D^{20}$** = -1.5 (c = 1.1, CH_2Cl_2, *l* = 50 mm).

(R)-3-bromo-2-(triethylsilyloxy)propan-1-ol (Table 3.2, entry 10, **3.5j**). The general procedure was followed to yield product as colorless oil (109 mg, 41%). **Chiral GC Analysis** (Supelco Beta Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 110 °C for 105 min, 20 °C/min to 200 °C, 200°C for 20 min, 15 psi, t_{rmajor} = 94.7 min, t_{rminor} = 97.2 min) 98% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.65 (q, 6H, *J* = 8.1), 0.96-0.99 (m, 9H), 1.85 (t, 1H, *J* = 6.4), 3.30-3.33 (m, 1H), 3.43-3.64 (m, 1H), 3.71 (dd, 2H, *J* = 6.1, 4.2), 3.92-3.96 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 4.8, 6.7, 33.0, 64.3, 72.2; **IR**: 3382, 2955, 2971, 2877, 1459, 1240, 1118, 1006, 969, 742, 728 cm^{-1}; **HRMS** (ESI+) calcd. for $C_9H_{22}BrO_2Si$: $[M+H]^+$: 269.0572, found: 269.0573. **$[\alpha]_D^{20}$** = +6.1 (c = 1.1, CH_2Cl_2, *l* = 50 mm).



(S)-1-bromo-3-(triethylsilyloxy)propan-2-ol (Table 3.2, entry 10, **3.4j**). The general procedure was followed to yield product as colorless oil (135 mg, 50%). **Chiral GC Analysis** (Supelco Gamma Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness), 110 °C for 80 min, 20 °C/min to 200 °C, 200°C for 20 min, 15 psi, t_{rmajor} = 74.8 min, t_{rminor} = 73.6 min) 90% ee. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 0.61 (q, 6H, *J* = 7.8), 0.93-0.96 (m, 9H), 2.56 (d, 1H, *J* = 6.4), 3.41-3.49 (m, 2H), 3.68 (dd, 1H, *J* = 10.0, 4.9), 3.72 (dd, 1H, *J* = 10.0, 4.9), 3.80-3.85 (m,



1H); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 4.5, 6.9, 34.7, 64.0, 71.3; **IR**: 2955, 2876, 1459, 1240, 1108, 1006, 799, 727, 671 cm^{-1}; **HRMS** (ESI+) calcd. for $C_9H_{22}BrO_2Si$: $[M+H]^+$: 269.0572, found: 269.0576. $[\alpha]_D^{20}$ = -0.99 (c = 1.2, CH_2Cl_2, *l* = 50 mm).

Time Course at 0 °C with a Single Addition of TESCl (Figure 3.1)

In a dry box, a solution of diol **3.3c** (24 mg, 0.20 mmol), catalyst **3.6** (6.2 mg, 0.02 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (2.0 mg, 1.2×10^{-2} mmol, 6 mol %) in anhydrous *tert*-butanol (3 mL) was prepared in an oven-dried glass reaction vial. A solution of 1,3,5-trimethoxybenzene as internal standard (50 μL, 2.0×10^{-2} mmol, 10 mol %, 0.40 M in $CDCl_3$,) was added. The reaction was brought out of the dry box, and was stirred at 4 °C for 15 minutes. *N,N*-diisopropylethylamine (49 μL, 0.28 mmol, 1.4 equiv) was added, followed by addition of chlorotriethylsilane (44 μL, 0.26 mmol, 1.2 equiv). The reaction was stirred at room temperature for 1 hour. Aliquots (0.5 mL) were taken at every 10 min. Methanol (5 μL) was added to quench the aliquot. The solvent was removed under reduced pressure. Chiral GLC analysis of the crude mixture afforded the yield and selectivity. Chiral GLC Analysis (Beta Dex 120 (30 m × 0.15 mm × 0.25 mm film thickness), 90 °C for 135 min, 20 °C/min to 160 °C, 160 °C for 20min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, $t_{(S)\text{-}\mathbf{3.4b}}$ = 96.2 min, $t_{(R)\text{-}\mathbf{3.4b}}$ = 97.4 min, $t_{(S)\text{-}\mathbf{3.5b}}$ = 104.2 min, $t_{(R)\text{-}\mathbf{3.5b}}$ = 110.9 min, t_{standard} = 143.7 min), Response Factors (*(S)*-**3.4c**: 0.59, *(R)*-**3.4c**: 0.59, *(S)*-**3.5c**: 0.66, *(R)*-**3.5c**: 0.66, standard: 1.0).

Time Course at Room Temperature with a Syringe Pump Addition of TESCl (Figure 3.2)

In a dry box, a solution of diol **3.3c** (240 mg, 2.0 mmol), catalyst **3.6** (61 mg, 0.20 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (20 mg, 0.12 mmol, 6 mol %) in anhydrous *tert*-butanol (30 mL) was prepared in an oven-dried glass reaction vial. The solution brought out of the dry box, and a solution of 1,3,5-trimethoxybenzene as internal standard (0.50 mL, 0.20 mmol, 10 mol %, 0.40 M in $CDCl_3$,) was added. The reaction was stirred at room temperature for 15 minutes. *N,N*-diisopropylethylamine (490 μL, 2.8 mmol, 1.4 equiv) was added, followed by addition of chlorotriethylsilane (440 μL, 2.6 mmol, 1.2 equiv) in 2 mL THF via syringe pump over 1.5 hours. The reaction was stirred at room temperature for 2 hour. Aliquots (0.5 mL) were taken every at 10 min. Methanol (5 μL) was added to quench the aliquot. The solvent was removed under reduced pressure. Chiral GLC analysis of the crude mixture afforded the yield and selectivity.

Regiodivergent Resolution towards Primary Protected Terminal 1,2-Diols

*General Procedure***.** In a dry box, a solution of diol substrate (1.0 mmol), catalyst **3.6** (31 mg, 0.10 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (10 mg, 6.0×10^{-2} mmol, 6 mol %) in anhydrous *tert*-butanol (15 mL) was prepared in an oven-dried glass reaction vial. The reaction was brought out of the dry box, and was stirred at room temperature for 15 minutes. *N,N*-diisopropylethylamine (120 μL, 0.70 mmol, 0.70 equiv) was added, followed by addition of chlorotriethylsilane (100 μL, 0.60

mmol, 0.60 equiv) in 4 portions every 15 minutes (dropwise addition was performed for each portion added). The reaction was stirred at room temperature for 1 hour (starting from the first addition of chlorotriethylsilane). Methanol (150 μL) was added to quench the reaction. The solvent was removed under reduced pressure, and flash column chromatography (hexanes:EtOAc = 60:1) afforded pure product. Chiral GLC or HPLC analysis of the product afforded the selectivity.

(R)-1-cyclohexyl-2-((triethylsilyl)oxy)ethanol (Table 3.3, entry 1, **3.4a**). The general procedure was followed using 10 mol % catalyst **3.6**, 0.70 equiv *N,N*-diisopropylethylamine, and 0.60 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 123 mg, 48%, er = 95:5, Run 2: 46%, er = 96.5:3.5).

(R)-1-((triethylsilyl)oxy)hexan-2-ol (Table 3.3, entry 2, **3.4b**).The general procedure was followed using 10 mol % catalyst **3.1**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 108 mg, 46%, er = 96.5:3.5, Run 2: 46%, er = 96:4).

(R)-4-methyl-1-((triethylsilyl)oxy)pentan-2-ol (Table 3.3, entry 3, **3.4c**). The general procedure was followed using 10 mol % catalyst **3.6**, 0.70 equiv *N,N*-diisopropylethylamine, and 0.60 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 101 mg, 43%, er = 96:4, Run 2: 44%, er = 95.5:4.5).

(R)-1-((triethylsilyl)oxy)propan-2-ol (Table 3.3, entry 4, **3.4d**). The general procedure was followed using 15 mol % catalyst **3.6**, 0.90 equiv *N,N*-diisopropylethylamine, and 0.80 equiv chlorotriethylsilane to yield product as

colorless oil (Run 1: 72 mg, 36%, er = 94.5:5.5, Run 2: 38%, er = 93.5:6.5).

(R)-1-phenyl-3-((triethylsilyl)oxy)propan-2-ol (Table 3.3, entry 5, **3.4e**). The general procedure was followed using 10 mol % catalyst **3.6**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane to yield product as a colorless oil (Run 1: 107 mg, 41%, er = 96:4, Run 2: 40%, er = 96:4).

(R)-1-(benzyloxy)-3-((triethylsilyl)oxy)propan-2-ol (Table 3.3, entry 6, **3.4f**). The general procedure was followed using 15 mol % catalyst **3.1**, 0.70 equiv *N,N*-diisopropylethylamine, and 0.60 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 122 mg, 41%, er = 95:5, Run 2: 40%, er = 95:5).

(R)-1-phenoxy-3-((triethylsilyl)oxy)propan-2-ol (Table 3.3, entry 7, **3.4g**). The general procedure was followed using 15 mol % catalyst **3.1**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane. The reaction was stirred for 2 hours to yield product as colorless oil (Run 1: 98 mg, 35%, er = 95:5, Run 2: 37%, er = 94:6).

(R)-1-((triethylsilyl)oxy)but-3-en-2-ol (Table 3.3, entry 8, **3.4h**). The general procedure was followed using 15 mol % catalyst **3.6**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane to yield product as colorless oil (Run 1: 84 mg, 42%, er = 89:11, Run 2: 40%, er = 89:11).

(S)-1-chloro-3-((triethylsilyl)oxy)propan-2-ol (Table 3.3, entry 9, **3.4i**). The general procedure was followed using 10 mol % catalyst **3.6**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane, to yield product as

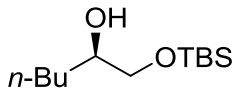
colorless oil (Run 1: 94 mg, 42%, er = 97.5:2.5, Run 2: 40%, er = 97.5:2.5).

(S)-1-bromo-3-((triethylsilyl)oxy)propan-2-ol (Table 3.3, entry 10, **3.4j**). The general procedure was followed using 10 mol % catalyst **3.6**, 0.80 equiv *N,N*-diisopropylethylamine, and 0.70 equiv chlorotriethylsilane, to yield product as colorless oil (Run 1: 110 mg, 41%, er = 97.5:2.5, Run 2: 40%, er = 97.5:2.5).

Kinetic Resolution Using tert-Butyldimethylsilyl Chloride (Scheme 3.7).

In a dry box, a solution of hexane-1,2-diol (120 mg, 1.0 mmol), catalyst **3.1** (42 mg, 0.15 mmol, 15 mol %), and *N,N*-diisopropylethylamine hydrochloride (10 mg, 0.060 mmol, 6 mol %) in anhydrous *tert*-butanol (15 mL) was prepared in an oven-dried glass reaction vial. The reaction was brought out of the dry box, and was stirred at room temperature for 45 minutes. *N,N*-diisopropylethylamine (140 μL, 0.80 mmol) was added, followed by addition of *tert*-butyldimethylsilyl chloride (110 mg, 0.70 mmol). The reaction was stirred at 4 °C for 24 hours. Methanol (150 μL) was added to quench the reaction. The solvent was removed under reduced pressure, and flash column chromatography (hexanes:EtOAc = 60:1) afforded pure product as colorless oil (Run 1: 106 mg, 46%, er = 89:11, Run 2: 101 mg, 43%, er = 89:11). Chiral GLC Analysis (Beta Dex 120 (30 m × 0.15 mm × 0.25 mm film thickness), 95 °C for 80 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rminor} = 56.9 min, t_{rmajor} = 57.8 min).

(R)-1-((tert-butyldimethylsilyl)oxy)hexan-2-ol (**3.4ba**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.59-3.63 (m, 2H), 3.37 (dd, 1H, *J* = 10.5, 8.3), 2.38 (d, 1H, *J* = 3.4), 1.24-1.43

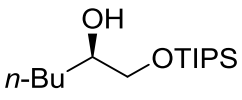


(m, 6H), 0.86-0.90 (m, 12H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 72.1, 67.5, 32.7, 28.0, 26.1, 23.0, 18.5, 14.2, -5.1, -5.2; IR: 2955, 2929, 2858, 1463, 1254, 1098, 835, 775 cm^{-1}; HRMS (ESI+) calcd. for $C_{12}H_{29}O_2Si$: $[M+H]^+$: 233.1937, found: 233.1938. $[\alpha]_D^{20} = -4.6$ (c = 1.0, CH_2Cl_2, *l* = 50 mm).

Kinetic Resolution Using Triisopropylsilyl Chloride (Scheme 3.7).

In a dry box, a solution of hexane-1,2-diol (120 mg, 1.0 mmol), catalyst **3.1** (42 mg, 0.15 mmol, 15 mol %), and *N,N*-diisopropylethylamine hydrochloride (10 mg, 0.060 mmol, 6 mol %) in anhydrous *tert*-butanol (15 mL) was prepared in an oven-dried glass reaction vial. The reaction was brought out of the dry box, and was stirred at room temperature for 45 minutes. *N,N*-diisopropylethylamine (140 μL, 0.80 mmol) was added, followed by addition of triisopropylsilyl chloride (150 μL, 0.70 mmol). The reaction was stirred at 4 °C for 48 hours. Methanol (150 μL) was added to quench the reaction. The solvent was removed under reduced pressure, Flash column chromatography (hexanes:EtOAc = 60:1) afforded pure product as colorless oil (Run 1: 115 mg, 42%, er = 95:5, Run 2: 105 mg, 38%, er = 97:3). Chiral GLC Analysis (Gamma Dex 120 (30 m × 0.15 mm × 0.25 mm film thickness), 110 °C for 150 min, 20 °C/min to 180 °C, 180°C for 20 min, 15 psi, t_{rminor} = 137.4 min, t_{rmajor} = 140.7 min).

(R)-1-((triisopropylsilyl)oxy)hexan-2-ol (**3.4bb**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.64 (dd, 1H, *J* = 9.5, 3.2), 3.56-3.61 (m, 1H), 3.40 (dd, 1H, *J* = 9.5, 7.6), 2.47 (d, 1H, 3.2), 1.25-1.39 (m, 6H), 0.95-1.07 (m, 21H), 0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz)



δ 72.2, 67.8, 32.7, 28.0, 23.0, 18.2, 14.2, 12.1; IR: 2940, 2865, 1463, 1103, 882, 797, 681, 660 cm^{-1}; HRMS (ESI+) calcd. for $C_{15}H_{35}O_2Si$: $[M+H]^+$: 275.2406, found: 275.2415. $[\alpha]_D^{20} = -4.2$ (c = 1.0, CH_2Cl_2, *l* = 50 mm).

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Chapter 4

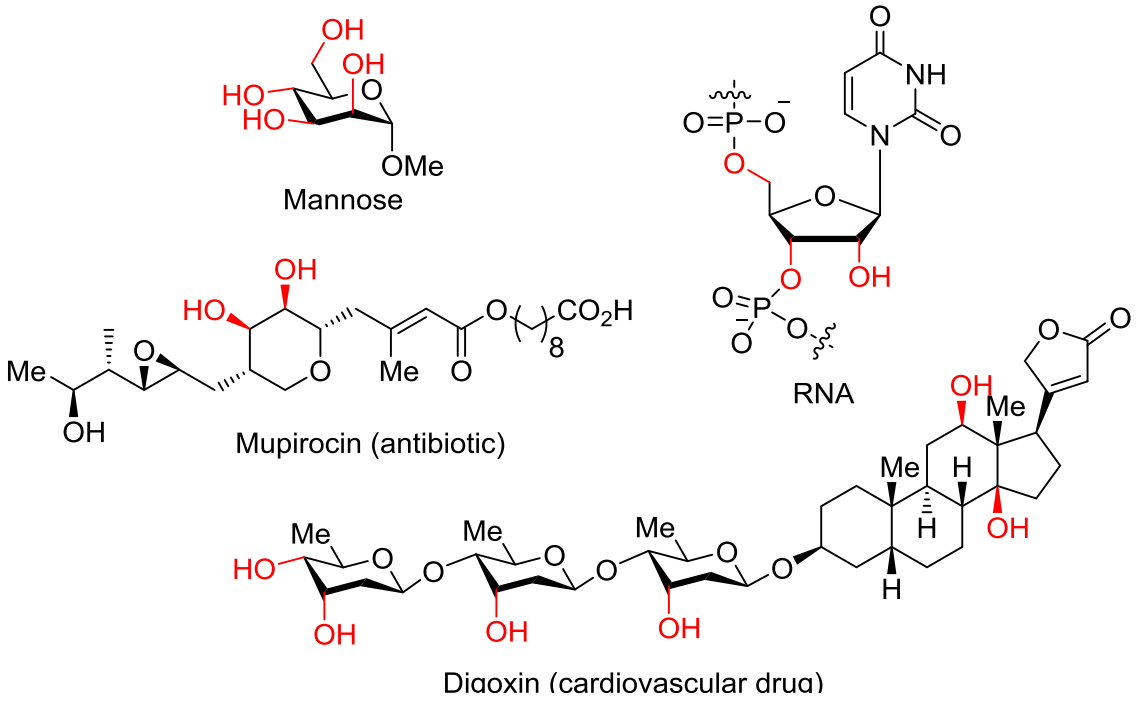
Site-Selective Functionalization of Complex Molecules

Chapter 4. Site-Selective Functionalization of Complex Molecules

4.1 Polyhydroxylated Molecules

Carbohydrates are commonly found in metabolic pathways and as structural building block in complex molecules. Besides their abundance, carbohydrates serve essential roles in biology as mediators of intercellular and intracellular processes, including cell-cell recognition, cell signaling regulation, cellular differentiation, and immune response.[1] These diverse functions have long suggested the potential of carbohydrates as therapeutics, leading to their increased use as core scaffolds in drug and vaccine discovery (Figure 1).[2]

Figure 4.1. Carbohydrates.



The significant biological importance of carbohydrates has led to intensive efforts focused on their synthesis.[3] However, their polyhydroxylated nature generates a large degree of complexity, imposing synthetic challenges to their selective functionalization and synthesis. Although significant progress has been made in this field, such as the development of automated oligosaccharide synthesis,[4] current methods to selectively modify carbohydrates heavily rely on elaborate protecting group strategies to ensure the appropriate spatial and temporal shielding of undesired reactive sites.

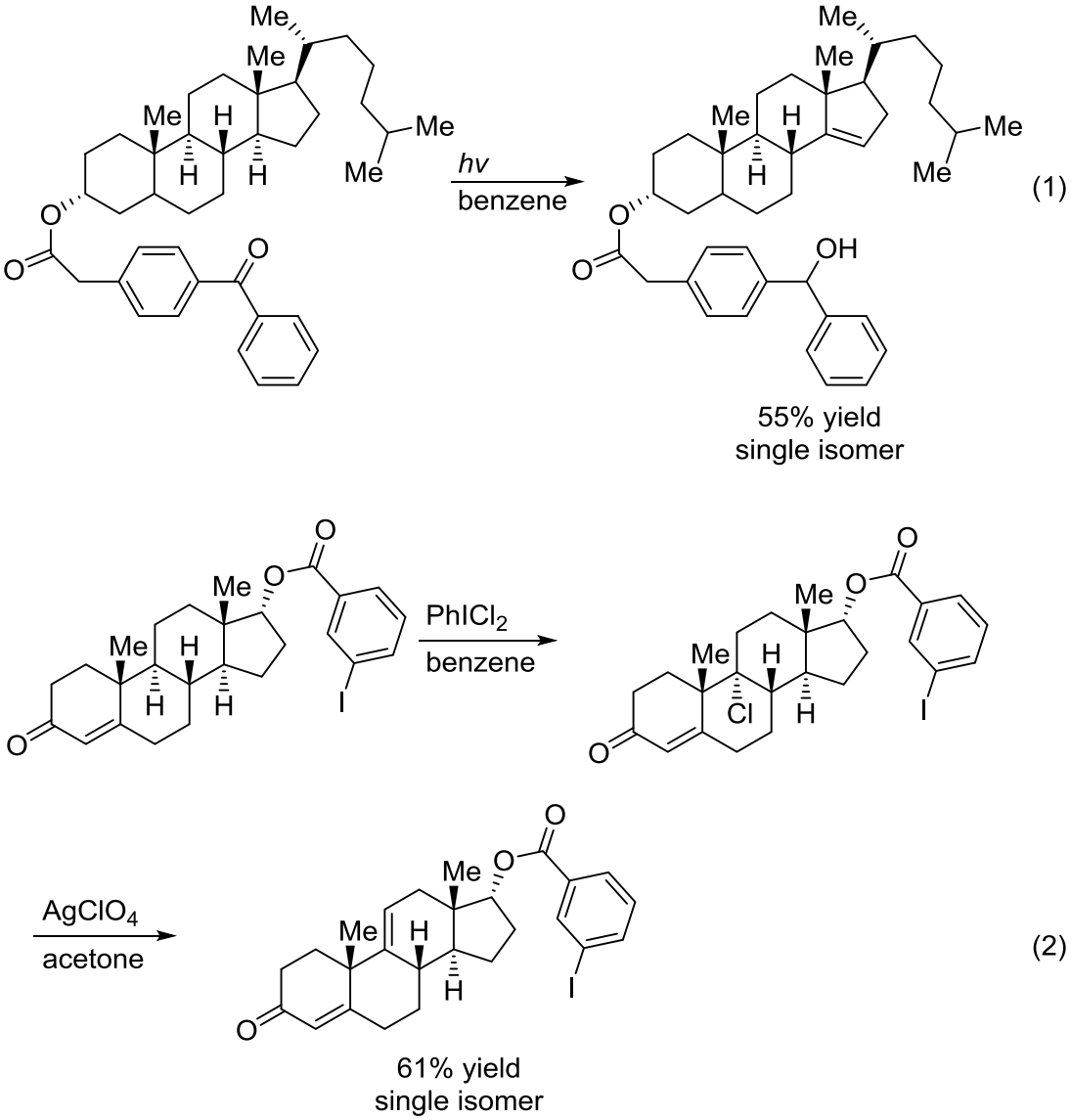
In a broader context, the same synthetic challenge also impedes the derivatization of numerous complex molecules containing polyhydroxylated frameworks. A growing desire has arisen for new methods that differentiate and selectively functionalize hydroxyl groups within a polyol structure. The ability to site-selectively funcationalize complex molecules would allow chemists to access new derivatives of natural products in efficient synthetic routes, as well as consequently expand the scope of biological studies in this area.

4.2 Selective Functionalization of Natural Products.

Given the increasing complexity and diversity of synthetic targets in modern organic synthesis, research efforts have been intensely focused on the development of new strategies to elevate the efficiency of synthetic routes. New methods to functionalize complex molecules with high and predictable site-selectivity could allow rapid access to

a diverse range of analogues from advanced common precursors, thereby are highly desired.

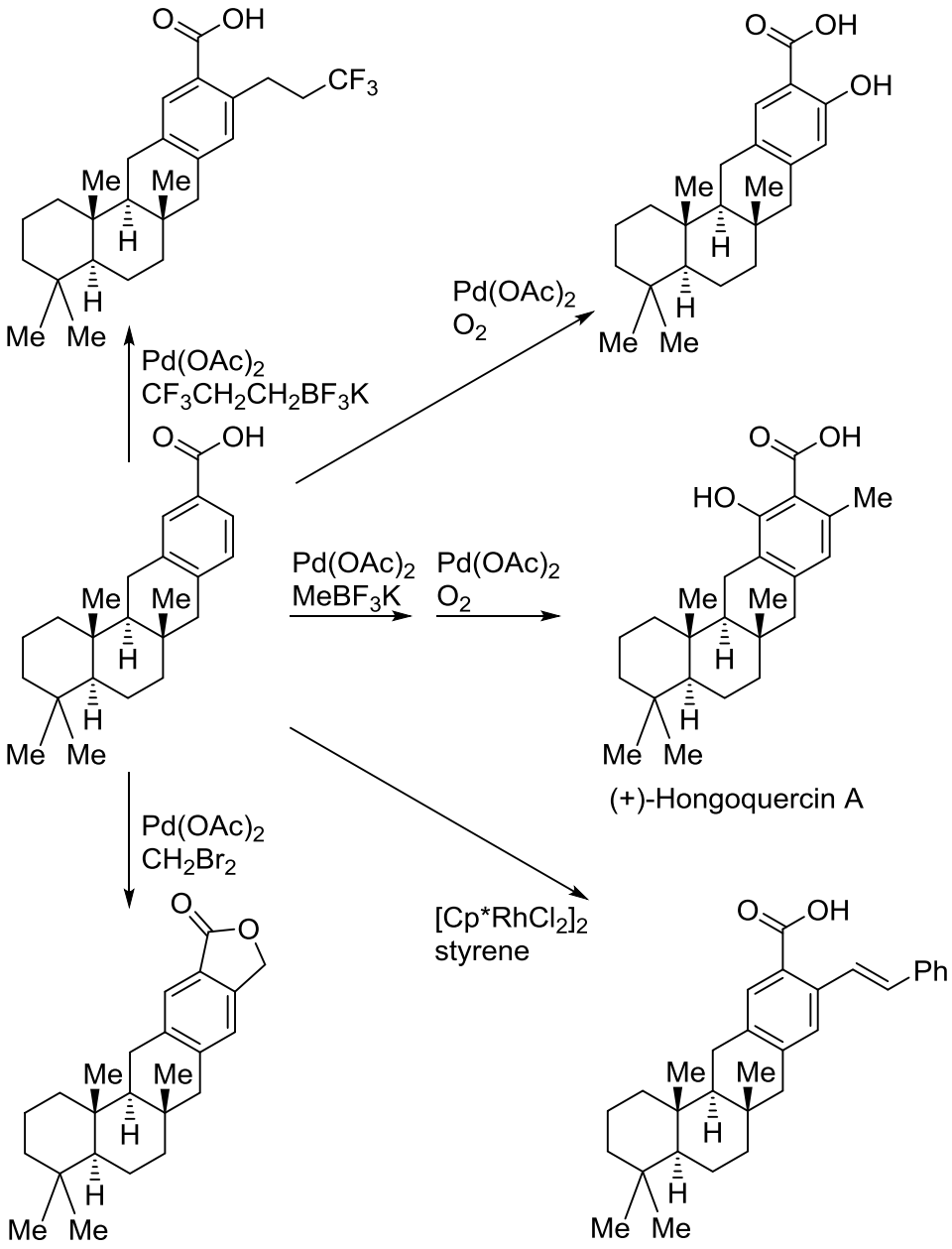
Scheme 4.1. Site-selective oxidation and halogenation of steroids with directing groups.



Such selective functionalization has been achieved with the stoichiometric use of directing groups. Early works by Breslow demonstrated that directed by benzophenone,

steroids can be selectively oxidized (Scheme 4.1, equation1).[5a] Later, aryl iodide has also been shown to remotely control the halogenation of steroids (Scheme 4.1, equation 2).[5b,5c] More recently, based on a carboxylic acid directed selective C-H functionalization, Yu and Baran reported a synthesis of (+)-Hongoquercin A and related analogues via selective derivatizations of a common precursor, demonstrating the high efficiency in synthetic designs delivered by site-selective functionalization (Scheme 4.2).[5d]

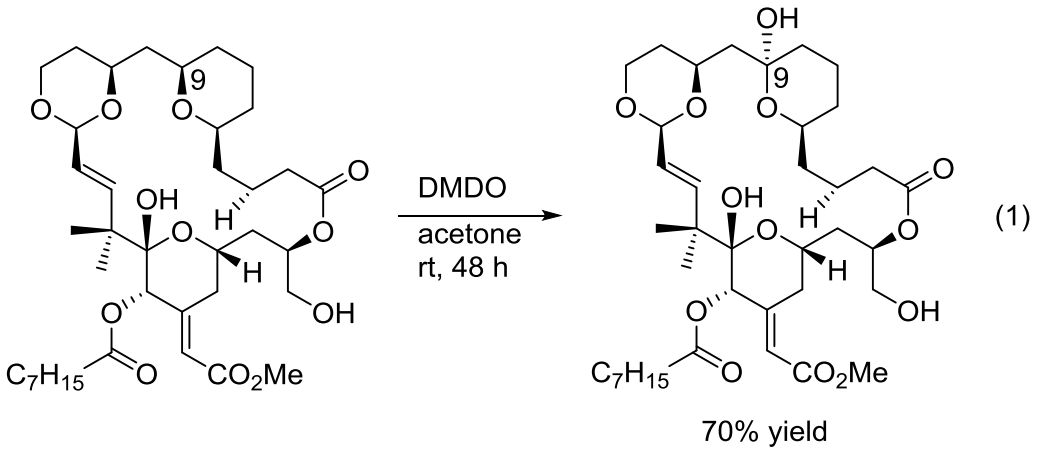
Scheme 4.2. Synthesis of (+)-hongoquercin A and related compounds via C-H functionalization.



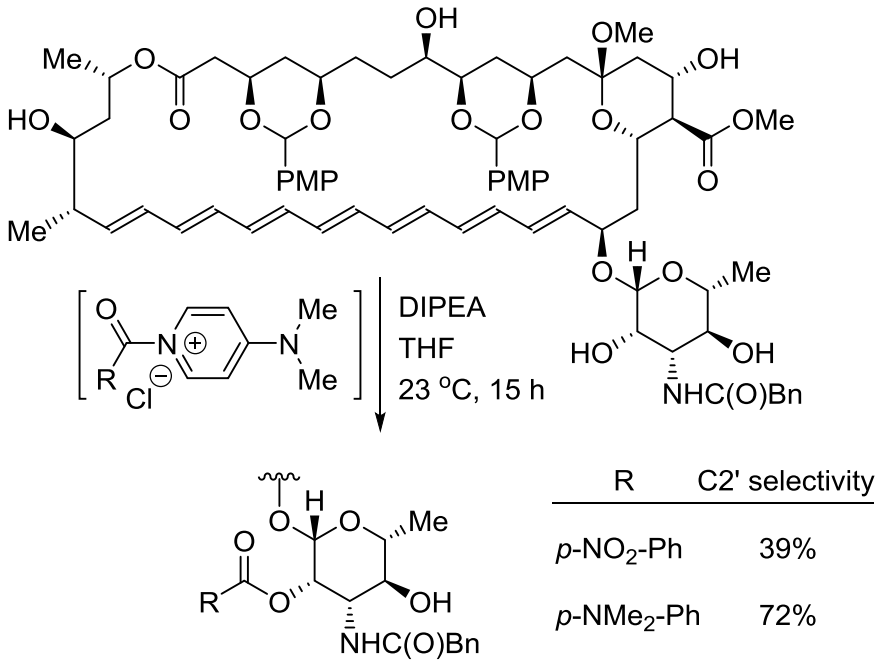
Multiple reagents and catalysts have also been successfully applied in the functionalization of a range of natural products.[6] In 2005, Wender reported a highly selective C-H oxidation enabled by dimethyldioxirane to install a hydroxyl group to the

C9 position of bryostatin analogues (Scheme 4.3, equation 1).[6a] Later, an iron complex was demonstrated by White to selectively oxidize aliphatic tertiary C-H bonds in complex molecules with high predictability based solely on their electronic and steric properties (Scheme 4.3, equation 2).[6b] In, 2007, a reagent control approach has also been used by Snyder in the programmable synthesis of resveratrol oligomers, allowing the access to a variety of natural and unnatural analogues.[6c] More recently, Burke showed that modification of C2'-OH in the polyhydroxylated molecule AmB can be achieved through proper electronic tuning of the electrophiles employed (Scheme 4.4).[6d]

Scheme 4.3. Reagent and catalyst enabled site-selective functionalization of complex molecules.



Scheme 4.4. Site-selective acylation of AmB via electronic runing of electrophiles.



R	C2' selectivity
p-NO_2-Ph	39%
p-NMe_2-Ph	72%

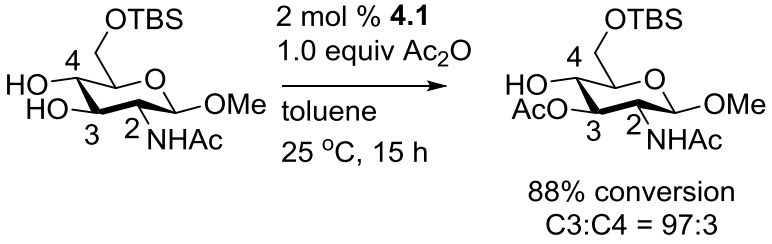
4.3 Site-Selective Catalysis in Natural Product Derivatizations.

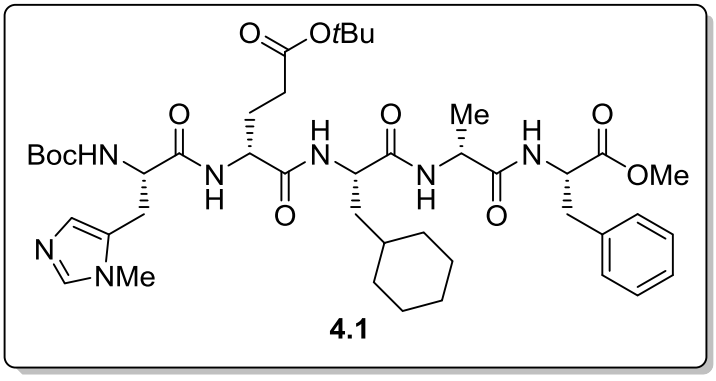
The use of a catalyst to control selectivitiy in an organic transformation is a widely appreciated strategy in synthesis.[7] This field has experienced significant progress over the last 30 years, especially in the development of new enantioselective reactions.[8] Alternatively, a less developed aspect of synthetic chemistry is site-selective catalysis, wherein a precise and selective modification of a complex molecule is enabled by a catalyst.[9-11] Achieving this goal is often magnified by the substrate's elevated complexity, requiring the catalyst to differentiate multiple accessible sites and to perform a single activation of the desired position. An added challenge is the selective modification of a site with little or no innate reactivity; the site-selective catalyst must be able to reverse the substrate bias, either by decreasing the activation energy for the target site, or by

increasing the energetic requirement for the activation of the other undesired sites within the molecule.

Owing to their high density of hydroxyl groups and strong preference for the functionalization of equatorial over axial sites, carbohydrates represent one of the most challenging substrate classes in site-selective catalysis. Traditionally, enzymes were considered as the primary tool to address this challenge.[12]. However, their strict recognition of the full substrate conformation usually led to narrow substrate scope. To explore alternative methods without these limitations, particular attention has been devoted to the development of new synthetic catalysts.

Scheme 4.5. Site-selective acylation of monosaccharides with peptide based catalyst.

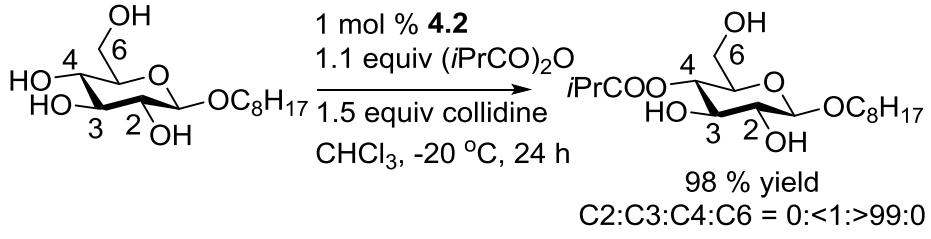


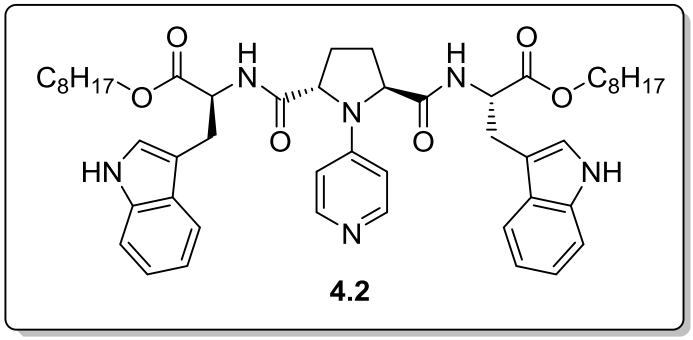


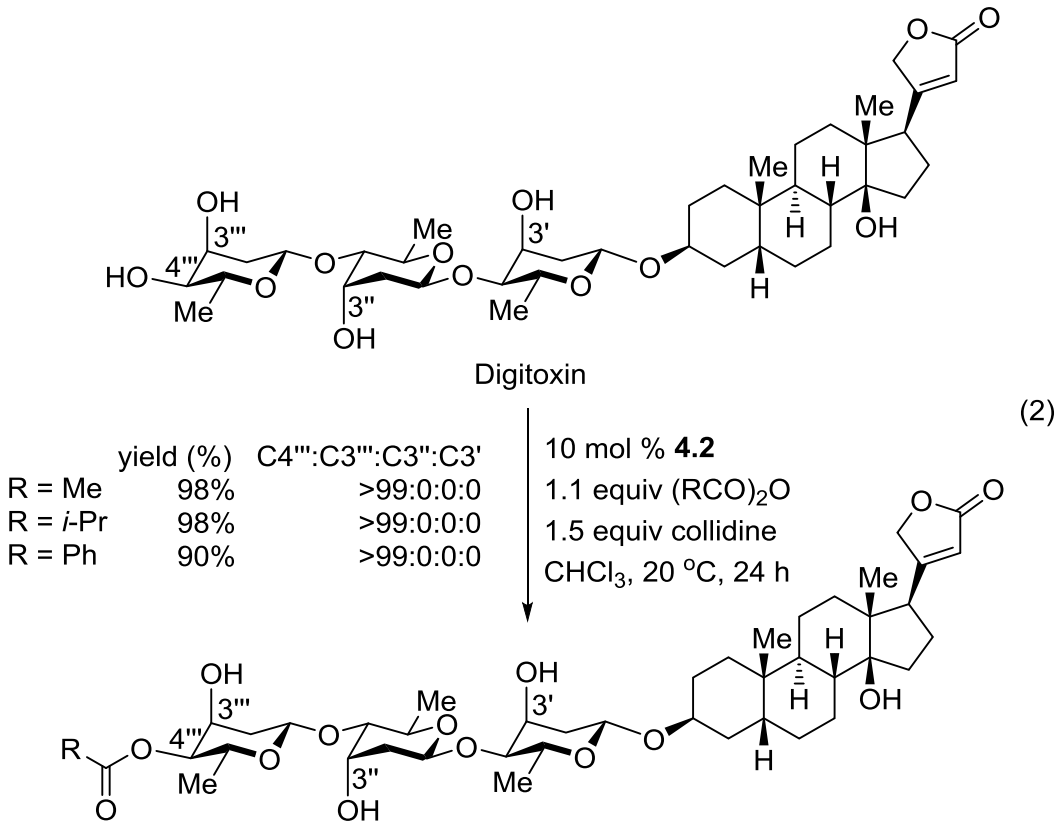
In 1998, Miller developed a library of peptide-based catalysts designed to mimic

the active site of enzymes.[9] These substrate-specific catalysts were proposed to interact with carbohydrates and other complex molecules via multiple non-covalent bonds, and facilitate site-selective functionalizations, such as the acyl transfer to C3 hydroxyl of *N*-acetylglucosamine derivative controlled by catalyst **4.1** (Scheme 4.5). Later, Kawabata reported a catalyst **4.2** containing 4-pyrrolidinopyridine as the active center. Catalyst **4.2** is able to form a hydrogen bond with the free primary hydroxyl group in a monosaccharide, and direct acylation of the adjacent C4-OH (Scheme 4.6, equation 1).[10a-d] This catalyst was also used to selectively acylate cardiac glycoside digitoxin by amplifying the intrinsic reactivity for the C4'-OH (Scheme 4.6, equation 2).[10e]

Scheme 4.6. Site-selective acylation of monosaccharides with Kawabata Catalyst.

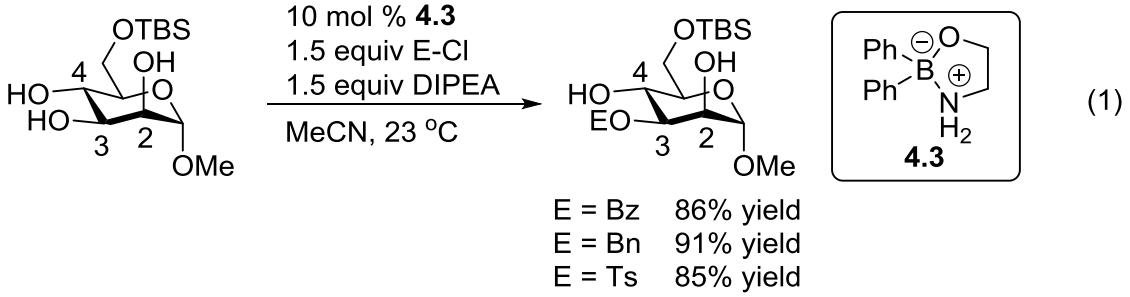


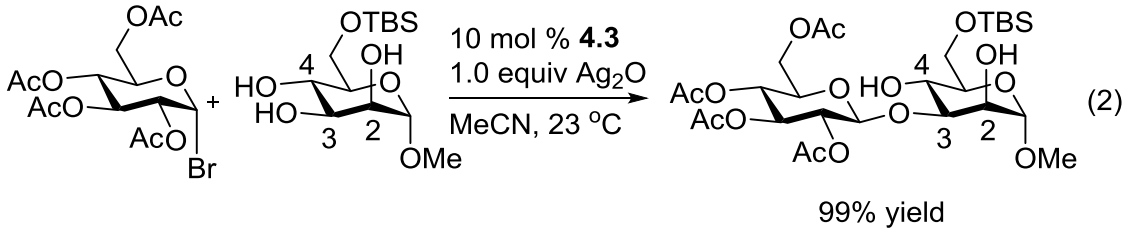


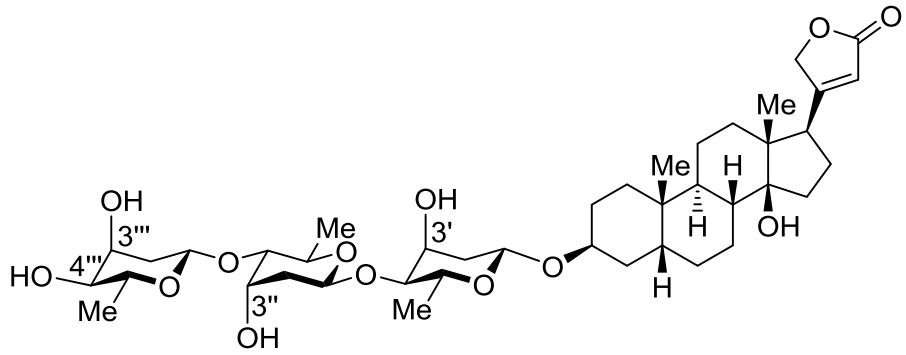


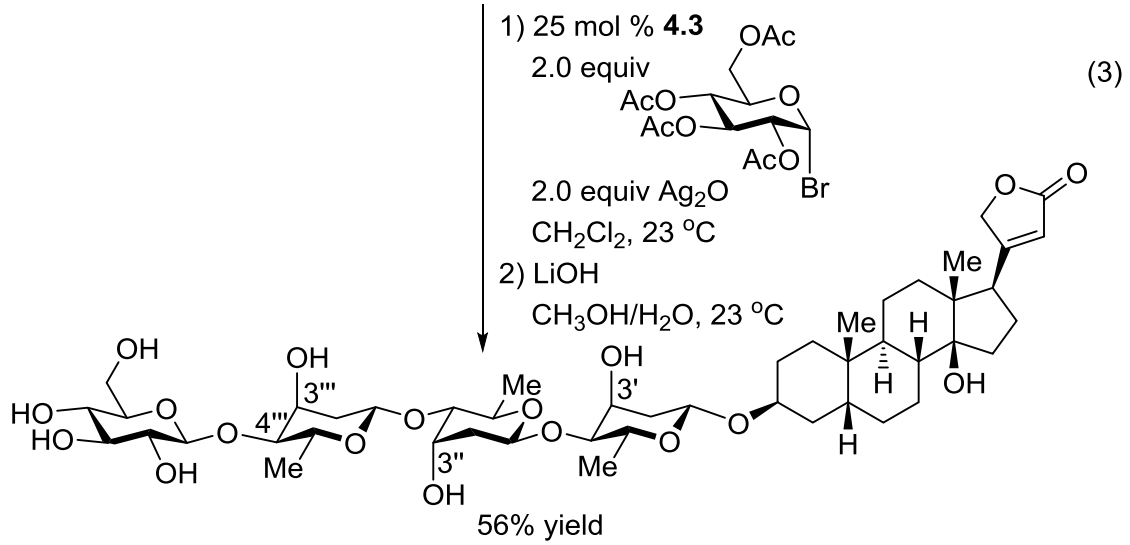
In addition to the use of non-covalent interactions, temporary covalent bonds have been recently employed in designing site-selective functionalization of carbohydrates. In 2011, a borinate catalyst **4.3** was developed by Taylor to covalently bind to a *cis*-1,2-diol unit within a monosaccharide, and selectively activate the equatorial hydroxyl for the transfer of a broad range of electrophiles (Scheme 4.7, equation 1 and 2), including acyl chlorides[11a], alkyl halides[11b], sulfonyl chlorides[11c], and glycosyl donors[11d]. This method was further expanded to allow the preparation of cardiac glycoside analogs of digitoxin through selective glycosylation of C4'-OH (Scheme 4.7, equation 3).[11e]

Scheme 4.7. Site-selective functionalization of monosaccharides with borinate catalyst







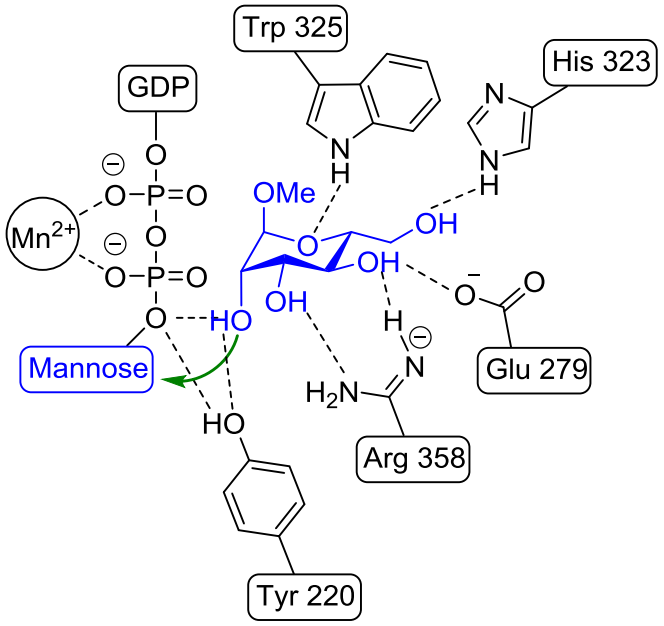


Despite these notable successes in the selective functionalization of carbohydrates and other natural products, the direct modification of the axial hydroxyl group within six-membered cyclic polyols had not been demonstrated with synthetic catalysts. Due to significant steric effects, axial hydroxyl groups are often rendered among the least reactive sites within carbohydrates; their functionalization thus generally requires the prior protection of other hydroxyls groups present. A potent catalyst that enables selective manipulation of axial hydroxyls within carbohydrates could effectively shorten syntheses, and open new avenues to a broad range of synthetic analogues thereby benefiting both chemical and biological research.

4.4 Catalyst Concept

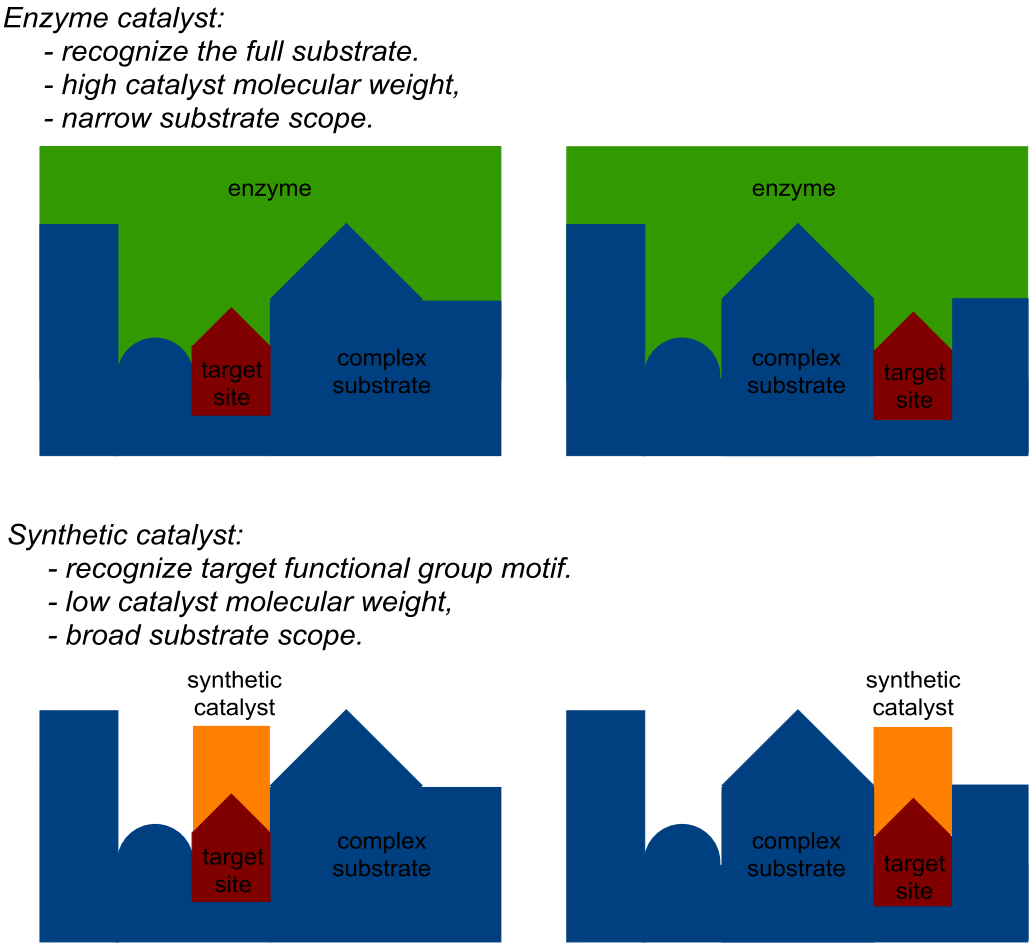
We decided to design an organic catalyst that enables selective activation of axial hydroxyl groups within carbohydrates. In addition, we aimed to develop predictable selectivity over a broad substrate scope, maximizing the synthetic potential of this method. Previously, direct activation of axial hydroxyl groups has been only achieved with enzymes. Studies of active enzymes revealed that proximity effects stand as a powerful means of accessing less reactive sites,[12] and widely determine the extraordinary selectivities in enzymatic catalysis. A demonstrative example has been reported by Howell to show the active site of α-1,2-mannosyltransferase Kre2p/Mnt1p, which catalyzes the mannosylation of the axial C2-hydroxyl of mannose through the application of multiple non-covalent interactions binding and orienting the substrate (Figure 4.2).[13]

Figure 4.2. Elucidated structure between Kre2p/Mnt1p a-1,2-mannosyltransferase and mannose.



We hypothesized that a synthetic catalyst utilizing reversible covalent bonding could produce similar site-selectivities for a broad substrate scope and with consistent predictability. This alternative mode of catalyst-substrate interaction would rely on recognition of a single functional group display in order to activate the desired target site.[14] Such a catalyst would require much less orienting structural features, thereby allowing a reduction of its molecular weight and complexity. Moreover, by recognizing a minimal functional group motif rather than the entire structure the catalyst would be applicable to any substrate that contained that substructure (Figure 4.3).

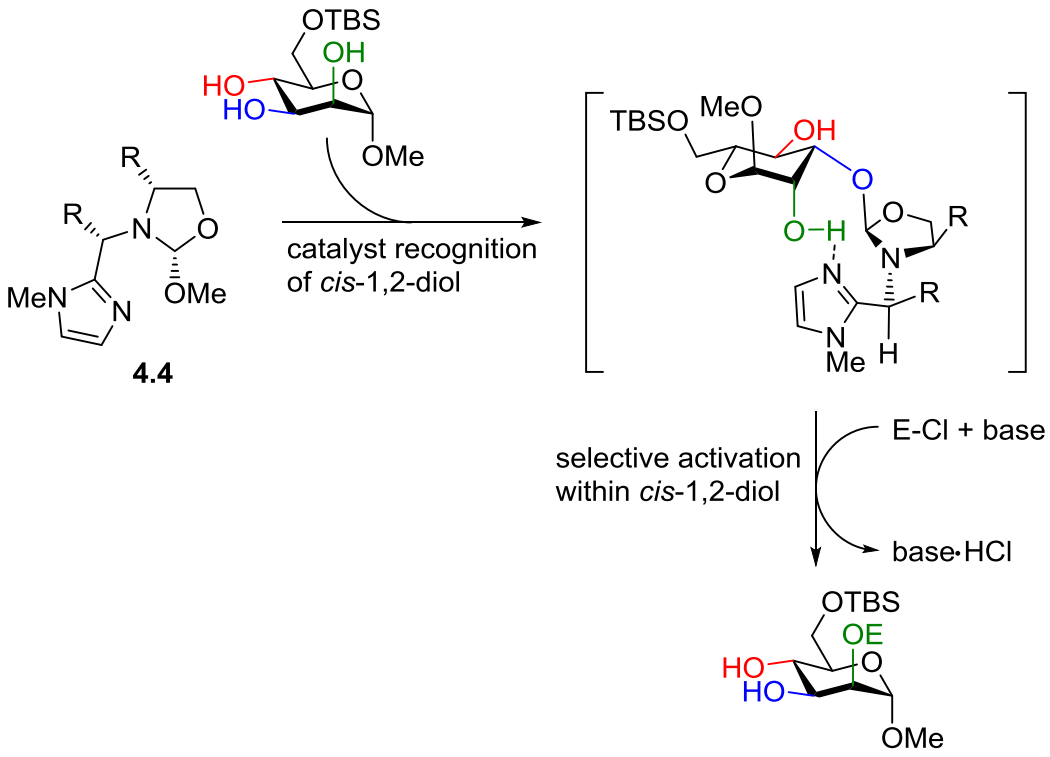
Figure 4.3. Concept of functional group display recognition enabled by synthetic catalyst.



A survey of polyhydroxylated molecules revealed that the majority of their axial hydroxyl groups exist within a *cis*-1,2-diol motif. Catalysts recognizing this specific diol could serve as valuable candidates towards axial hydroxyl modifications. Previously developed by our group, scaffolding catalyst **4.4** employs a single reversible-formed covalent bond to bind to hydroxyl substrates,[15-17] and shows excellent activity in the enantioselective functionalization of *cis*-1,2-diols. Although the substrate exchange mechanism of **4.4** could lead to unselective binding to multiple sites in carbohydrates, we

envisioned that only specific sites with proper proximity to the imidazole residue could be activated. In addition, the previously demonstrated stereocontrol of catalyst **4.4** suggested its potential to further differentiate the two sites within the *cis*-1,2-diol. Thus, the selection of correct catalyst enantiomers could enable a switchable and predictable modification between the equatorial, and more importantly, axial hydroxyl groups within six-membered rings (Scheme 4.8).

Scheme 4.8. Scaffolding catalyst enabling selective functionalization of axial hydroxyl groups.

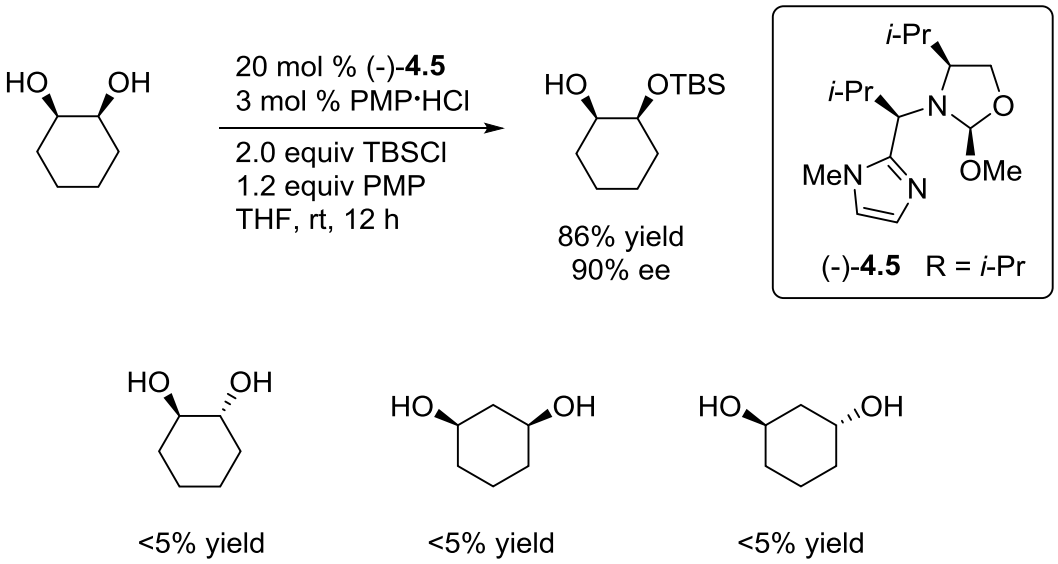


4.5 Site-Selective Functionalization of Monosaccharides

To assure the successful transfer of scaffolding catalyst's ability to distinguish *cis*-1,2-diol in the presence of other functional group motifs, we began by probing this

quality using cyclohexanediols as model substrates (Scheme 4.9).[15] Catalyst (−)-**4.5** has been demonstrated to promote the desymmetrization of meso-1,2-cyclohexanediol. However, replacing the *cis*-1,2-diol in the substrate with a *trans*-1,2-diol led to a dramatic drop of the yield (< 5%). Similarly, both *cis*- and *trans*-1,3-diols afforded minimal amounts of silylated product. Based on these observations, we expected these scaffolding catalysts to maintain their selective activation of *cis*-1,2-diol in polyol structures.

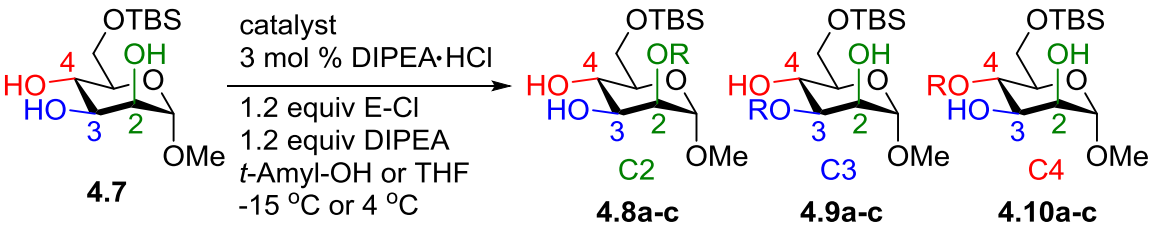
Scheme 4.9. Probing scaffolding catalyst's ability to recognize *cis*-1,2-diols.

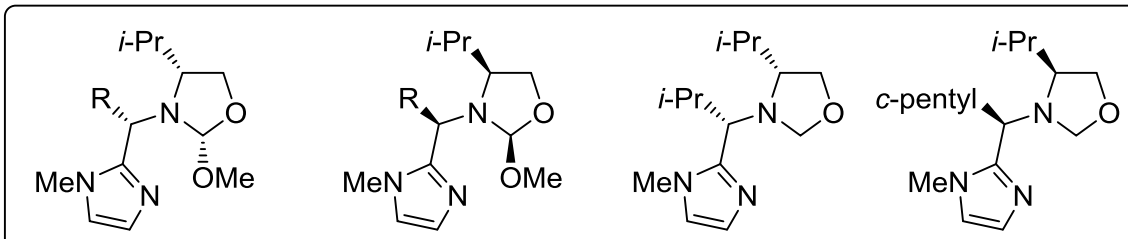


We then tested the effectiveness of the scaffolding catalysts in the context of a methyl-α-D mannose derivative **4.7** (Table 4.1). Using *N*-methylimidazole as the background catalyst, the inherent bias was observed in a transfer of triethylsilyl group, indicating the C2 axial hydroxyl is significantly less reactive than the other sites (C2:C3:C4 = 5:78:17, Table 4.1, entry 1). The use of scaffolding catalyst (+)-**4.5**

dramatically reversed this bias, with the silylation C2 hydroxyl now favored (76% yield, C2:C3:C4 = 90:10:<1, Table 4.1, entry 2). Notably, the absence of a *cis* relationship between C3-OH and C4-OH precluded the functionalization C4 hydroxyl, exactly as predicted. The lack of *cis*-1,2-diol in C2 protected product **4.8a** also suppressed the second silyl transfer, minimizing the amount of bis-silylated product (9%) obtained at high conversion (95%).

Table 4.1. Site-selective functionalization of mannose derivative.





entry	electrophile	catalyst	C2:C3:C4[a]	yield (%)[b,c]
1	TESCl[d]	20 mol % NMI	5:78:17	77
2	TESCl[d]	20 mol % (+)-**4.5**	90:10:<1	84 (76/74[f])
3	TESCl[d]	5 mol % (-)-**4.6**	<1:100:<1	(>98/>98[f])
4	TESCl[d]	20 mol % (+)-**4.5a**	3:92:5	7
5	TESCl[d]	20 mol % (-)-**4.6a**	2:92:6	9
6	AcCl[d]	20 mol % NMI	9:84:7	39
7	AcCl[d]	20 mol % (+)-**4.5**	84:15:1	74
8	AcCl[d]	5 mol % (-)-**4.6**	1:99:<1	(96)
9	MsCl[e]	20 mol % NMI	22:56:22	68
10	MsCl[e]	20 mol % (+)-**4.5**	91:8:1	(80)
11	MsCl[e]	5 mol % (-)-**4.6**	<1:100:<1	(97)

[a]A '<1' indicates the isomer was not observed by the mode of detection used. [b]Isolated yield of isomeric mixture. [c]Yields in parentheses are of the isolated major isomer. [d]Selectivity determined by ^{1}H NMR. [e]Selectivity determined by gas chromotography (GC). [f]Reaction performed on a 4.0 mmol scale (1.2 g) of substrate.

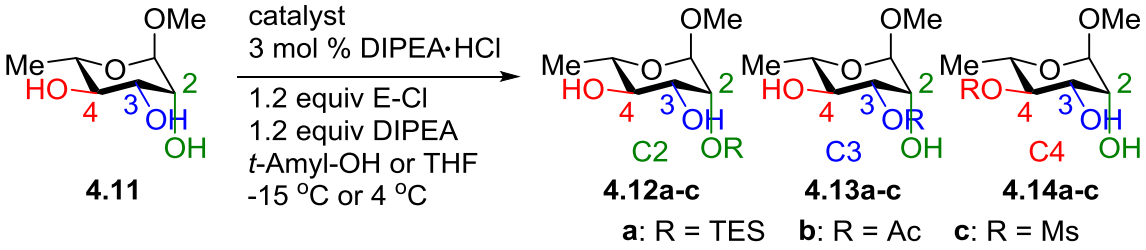
Since the site-selectivity of the scaffolding catalyst is dependent on its stereochemical configuration, replacing catalyst (+)-**4.5** with its opposite

pseudo-enantiomer (−)-**4.6** enabled a switch of the silylation selectivity to exclusively afford C3-protected regioisomer (Table 4.1, entry 3). The lower catalyst loading and excellent site selectivity are partially ascribed to the C3 hydroxyl being inherently most reactive site in mannose.

To demonstrate that our scaffolding catalysis was operating as proposed, we performed two control experiments with catalysts (+)-**4.5a** and (−)-**4.6a**, which lack the ability to covalently bind to mannose. Both catalysts favored the protection of C3 hydroxyl in dramatically diminished yields (<10% yields, Table 4.1, entry 4 and 5). These observations were consistent with our proposed mechanism, wherein reversible covalent bonding is necessary for both acceleration and selectivity.

Following the initial success in silylation, we explored the transfer of acyl and sulfonyl groups. To our delight, high yields and site-selectivities were achieved for both equatorial and axial hydroxyl functionalization with appropriate choice of catalyst (−)-**4.6** and (+)-**4.5**, respectively (Table 4.1, entry 6-11). The success of these reactions are of particular value as acylation offers both an orthogonal protection and a functionalization of carbohydrates, while mesyl groups can serve to activate hydroxyl group towards a variety of further chemical manipulations. We thus demonstrated scaffolding catalysis to constitute a broad method for electrophile transfer with predictable selectivity.

Table 4.2. Site-selective functionalization of rhamnose.



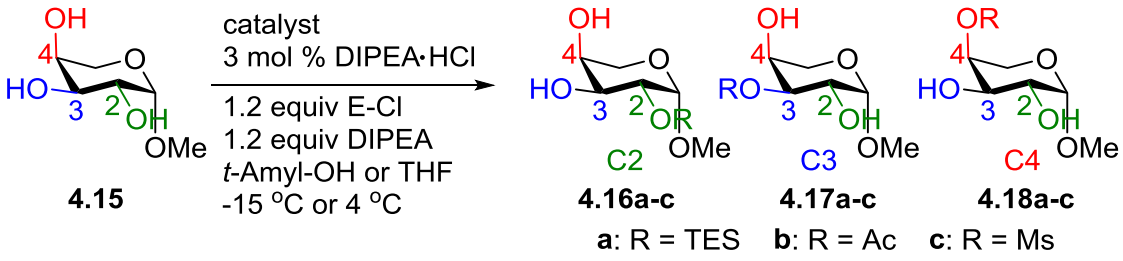
entry	electrophile	catalyst	C2:C3:C4[a]	yield (%)[b,c]
1	TESCl	20 mol % NMI	7:79:14	78
2	TESCl	20 mol % (-)-**4.6**	89:11:<1	88
3[d]	TESCl	5 mol % (+)-**4.5**	<1:100:<1	(>98)
4	AcCl	20 mol % NMI	12:79:9	83
5	AcCl	20 mol % (-)-**4.6**	84:14:2	73
6	AcCl	5 mol % (+)-**4.5**	1:99:<1	(98)
7[e]	MsCl	20 mol % NMI	24:57:19	72
8[e]	MsCl	20 mol % (-)-**4.6**	92:8:<1	(82)
9[e]	MsCl	5 mol % (+)-**4.5**	1:99:<1	(>98)

[a]A '<1' indicates the isomer was not observed by the mode of detection used. Selectivities were determined by ^{1}H NMR. [b]Isolated yield of isomeric mixture. [c]Yields in parentheses are of the isolated major isomer. [d]Reaction time of 20 h. [e]Selectivity determined by gas chromotography (GC).

A proposed advantage of our functional group display recognition strategy is its potentially broad substrate scope. To evaluate this feature, selective functionalizations of other monosaccharides containing *cis*-1,2-diol were investigated (Table 4.2). In contrast to the previous mannose derivative, Methyl-α-L-rhamnose **4.11** consist a *cis*-1,2-diol with opposite stereochemistry. Therefore the use of catalyst (−)-**4.6** and (+)-**4.5** was predicted to result in a reversed selectivity in this case. Consistent with this prediction, the scaffolding catalysts allowed the toggling of selective manipulation between C2 and

C3 hydroxyls with all three electrophiles (Table 4,2, entry 2, 3, 5, 6, 8 and 9). Similarly, a switchable functionalization between C3 and C4 hydroxyls of methyl-β-L-arabinaose **4.15** was achieved with (+)-**4.5** and (−)-**4.5**, while reaction at the C2 hydroxyl was minimized (Table 4.3).

Table 4.3. Site-selective functionalization of arabinose.



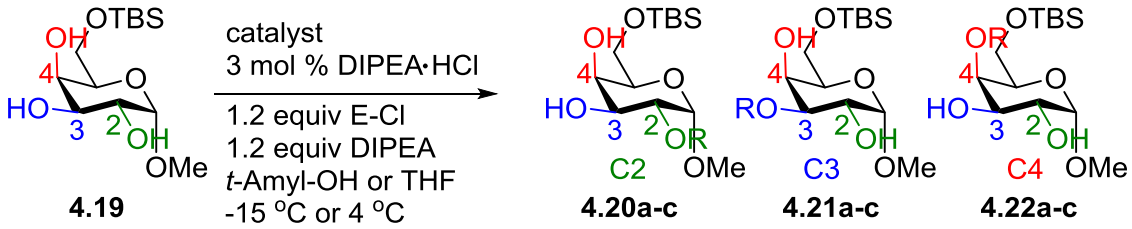
entry	electrophile	catalyst	C2:C3:C4[a]	yield (%)[b,c]
1	TESCl	20 mol % NMI	27:14:59	39
2	TESCl	20 mol % (-)-**4.5**	<1:3:97	(92)
3	TESCl	5 mol % (+)-**4.5**	<1:98:2	(97)
4	AcCl	20 mol % NMI	22:72:6	6
5[d]	AcCl	20 mol % (-)-**4.5**	5:9:86	61
6	AcCl	5 mol % (+)-**4.5**	3:96:1	(83)
7	MsCl	20 mol % NMI	68:23:9	27
8	MsCl	20 mol % (-)-**4.5**	3:10:87	93
9	MsCl	5 mol % (+)-**4.5**	1:92:7	(91

[a]A '<1' indicates the isomer was not observed by the mode of detection used. Selectivities were determined by ^{1}H NMR. [b]Isolated yield of isomeric mixture. [c]Yields in parentheses are of the isolated major isomer. [d]Reaction time 8 h.

Further expansion of substrate scope to galactose derivative **4.19** enabled a reversal of inherent selectivity which favors the C2-OH. Selective electrophile transfers onto C3

hydroxyl were achieved with catalyst (+)-**4.5** (Table 4.4, entry 2, 4 and 6). However, attempts to functionalize the axial C4 hydroxyl were unsuccessful, suggesting a further enlarged inherent bias in this substrate that may arise from an elevated steric hindrance of C4 position with the presence of the adjacent C6 methylene group.

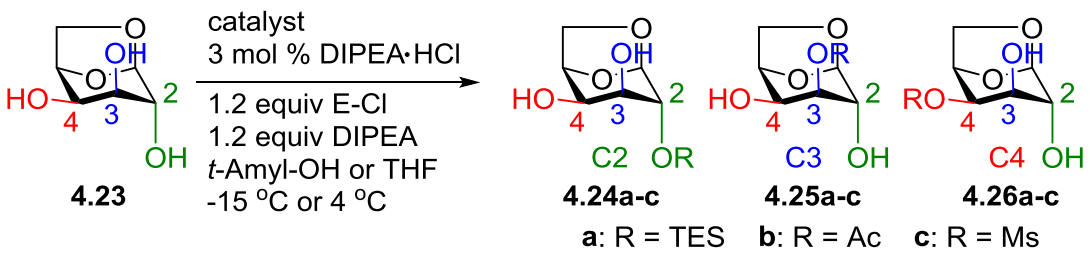
Table 4.4. Site-selective functionalization of galactose derivative.



entry	electrophile	catalyst	C2:C3:C4[a]	yield (%)[b,c]
1	TESCl	20 mol % NMI	86:14:<1	77
2	TESCl	20 mol % (+)-**4.5**	6:94:<1	95
3	AcCl	20 mol % NMI	42:58:<1	26
4	AcCl	20 mol % (+)-**4.5**	19:81:<1	96
5	MsCl	20 mol % NMI	76:24:<1	62
6	MsCl	20 mol % (+)-**4.5**	<1:100:<1	(74)

[a]A '<1' indicates the isomer was not observed by the mode of detection used. Selectivities were determined by ^{1}H NMR. [b]Isolated yield of isomeric mixture. [c]Yields in parentheses are of the isolated major isomer.

Table 4.5. Site-selective functionalization of 1,6-anhydro-β-D-galactose.



entry	electrophile	catalyst	C2:C3:C4[a]	yield (%)[b,c]
1	TESCl	20 mol % NMI	91:<1:9	51
2	TESCl	5 mol % (-)-**4.6**	1:<1:99	(98)
3	AcCl	20 mol % NMI	75:8:17	53
4	AcCl	5 mol % (-)-**4.6**	<1:3:97	(93)
5	AcCl	20 mol % (+)-**4.6**	2:81:17	(73)
6	MsCl	20 mol % NMI	75:6:19	50
7	MsCl	5 mol % (-)-**4.6**	<1:1:99	(88)
8	MsCl	20 mol % (+)-**4.6**	<1:75:25	(69)

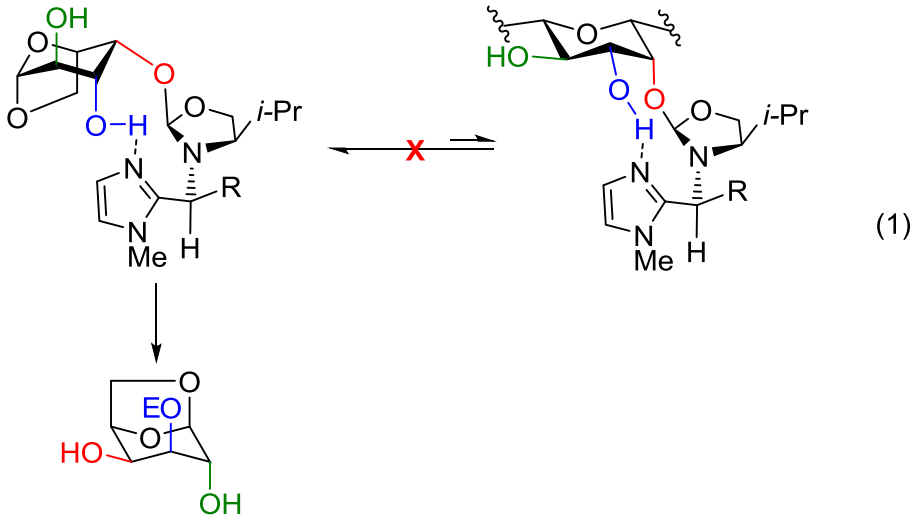
[a]A '<1' indicates the isomer was not observed by the mode of detection used. Selectivities were determined by ^{1}H NMR. [b]Isolated yield of isomeric mixture. [c]Yields in parentheses are of the isolated major isomer.

To access the C4 hydroxyl of galactose, we turned to examining its interconvertible bicyclic derivative 1,6-anhydro-β-D-galactose **4.23**. The resulted equatorial C4-OH was successfully functionalized with catalyst (−)-**4.6** (Table 4.5, entry 2, 4 and 7). Notably, the selectivity of acyl and mesyl transfers was also switched by catalyst (+)-**4.6** to favor the functionalization of the axial hydroxyl group in C3 position (Table 4.5, entry 5 and 8). Since 1,6-Anhydro-galactose cannot undergo a ring flip given its geometric constraints, the efficient transfer of both electrophiles to its axial hydroxyl is consistent with the scaffolding catalyst covalently bonding to the equatorial hydroxyl and consequently

activating the axial hydroxyl within the *cis*-1,2-diol motif (Scheme 4.10, equation 1). However, this observation cannot rule out the possibility of a ring flip occurring in the cases of unconstrained monosaccharides, which converts the targeting axial hydroxyl group into more reactive equatorial position prior to its functionalization (Scheme 4.10, equation 2).

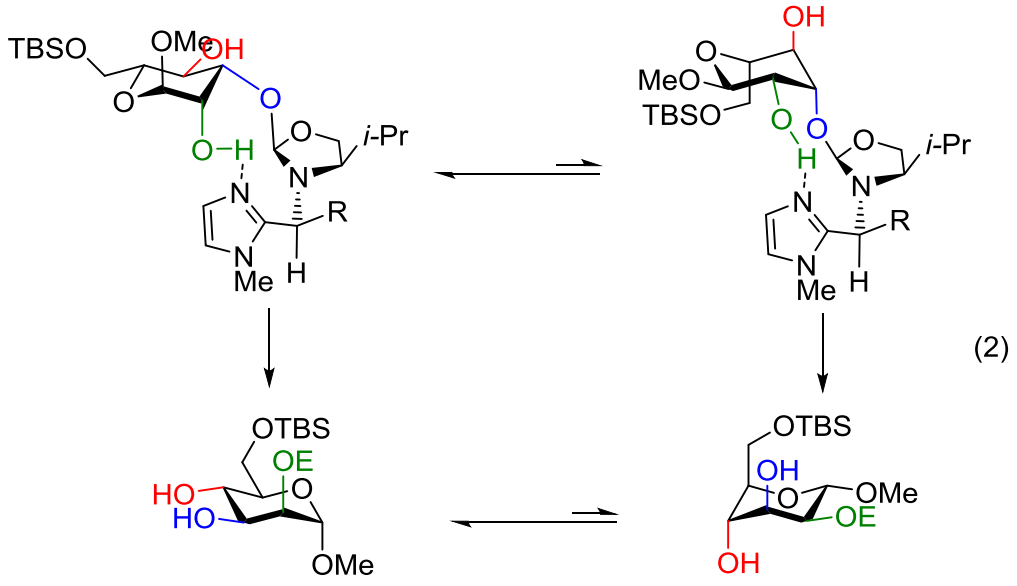
Scheme 4.10. Proposed mechanism for axial hydroxyl functionalizations

1,6-Anhydro-Galactose: Fixed Chair Conformation



(1)

Mannose: Potential Mechanisms

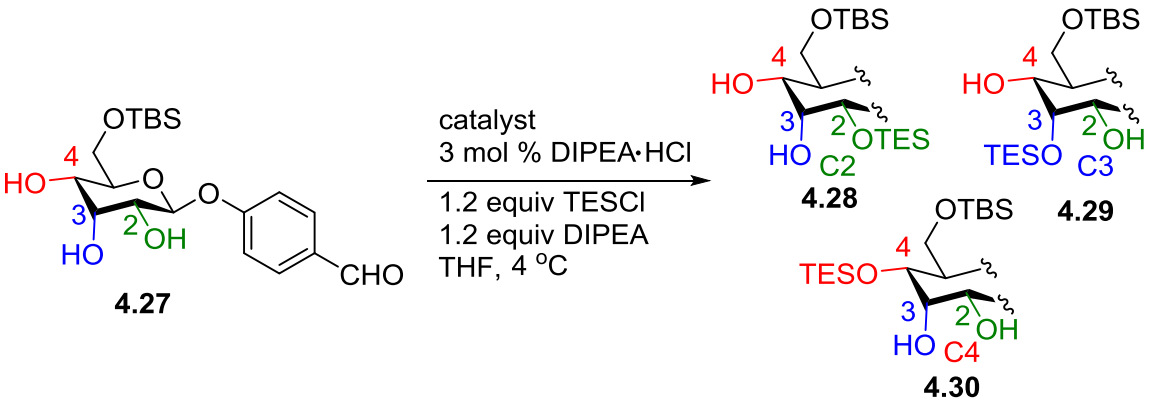


(2)

4.6 Site-Selective Functionalization of Complex Molecules

To fully demonstrate the potential synthetic utility of our catalytic system, we applied it to the functionalizations of other biologically and therapeutically valuable molecules containing *cis*-1,2-diols. Helicid is a monosaccharide bearing a *cis*,*cis*-1,2,3-triol that has been found to affect neurological activity.[18] Catalyst (−)-**4.6** and (+)-**4.6** afforded selective silylation of the C2 and C4 hydroxyls within the triol, respectively (Table 4.6), showing a good tolerance of the tethered aldehyde on C1 position. Notably, although the activation of the axial C3-OH could be enabled by the catalysts, the equatorial hydroxyls were preferentially functionalized in both cases presumably due to their higher intrinsic activities. Moreover, since *cis*,*cis*-1,2,3-triol is a common motif in multiple important compounds such as *myo*-inositol, this reaction suggested a potential application of scaffolding catalysts towards their selective derivatizations.

Table 4.6. Site-selective functionalization of Helicid derivative.

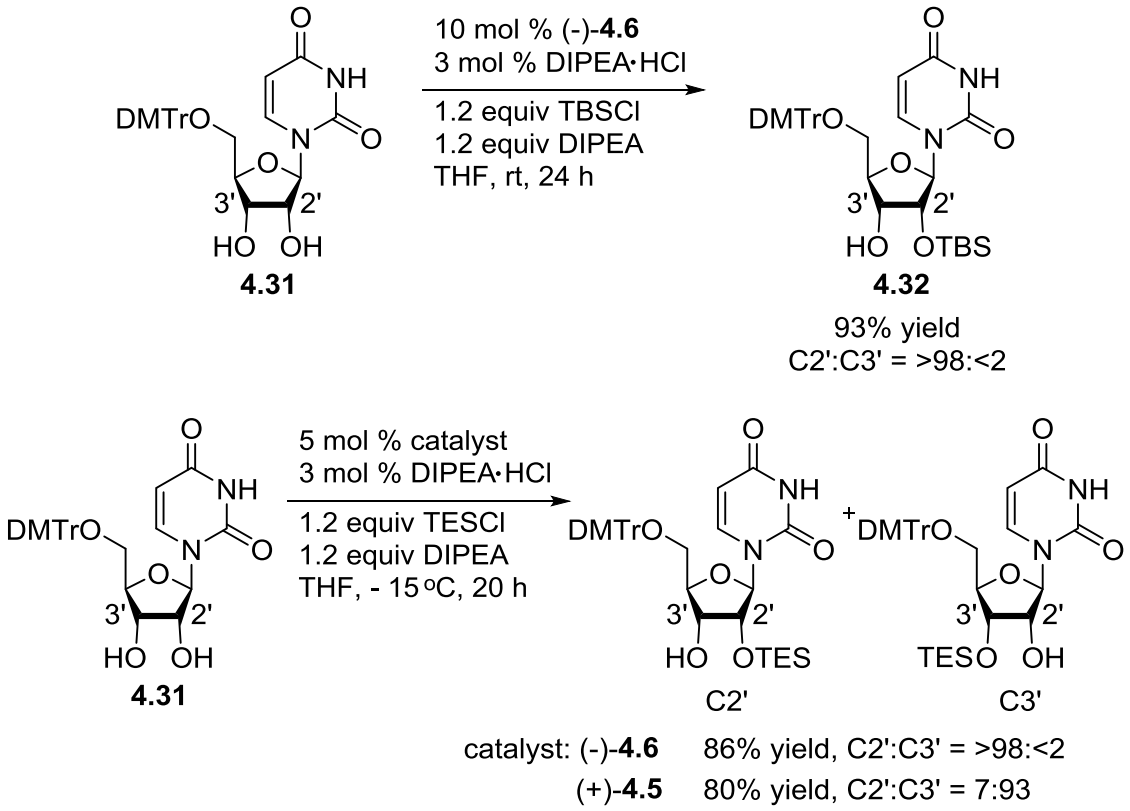


entry	catalyst	C2:C3:C4[a]	yield (%)[b,c]
1	5 mol % NMI	65:3:32	29
2	5 mol % (-)-**4.6**	95:5:<1	(90)
3	5 mol % (+)-**4.6**	10:13:77	(63)

[a]A '<1' indicates the isomer was not observed by the mode of detection used. Selectivities were determined by ^{1}H NMR. [b]Isolated yield of isomeric mixture. [c]Yields in parentheses are of the isolated major isomer.

We further tested our method on ribonucleosides derivatives, which contain a *cis*-1,2-diol in a five-membered ring. These compounds often require protection of the C2'-OH for their uses in automated RNA synthesis.[19] Traditional methods relied on unselective protections of C2' and C3' hydroxyls, followed by column separations to obtain the desired products. With (−)-**4.6**, we selectively transferred a TBS group to the C2'-OH of uridine (Scheme 4.11), showing the possibility of direct access to this category of molecules. The site-selectivity was also switched by our catalysts using more reactive TESCl.

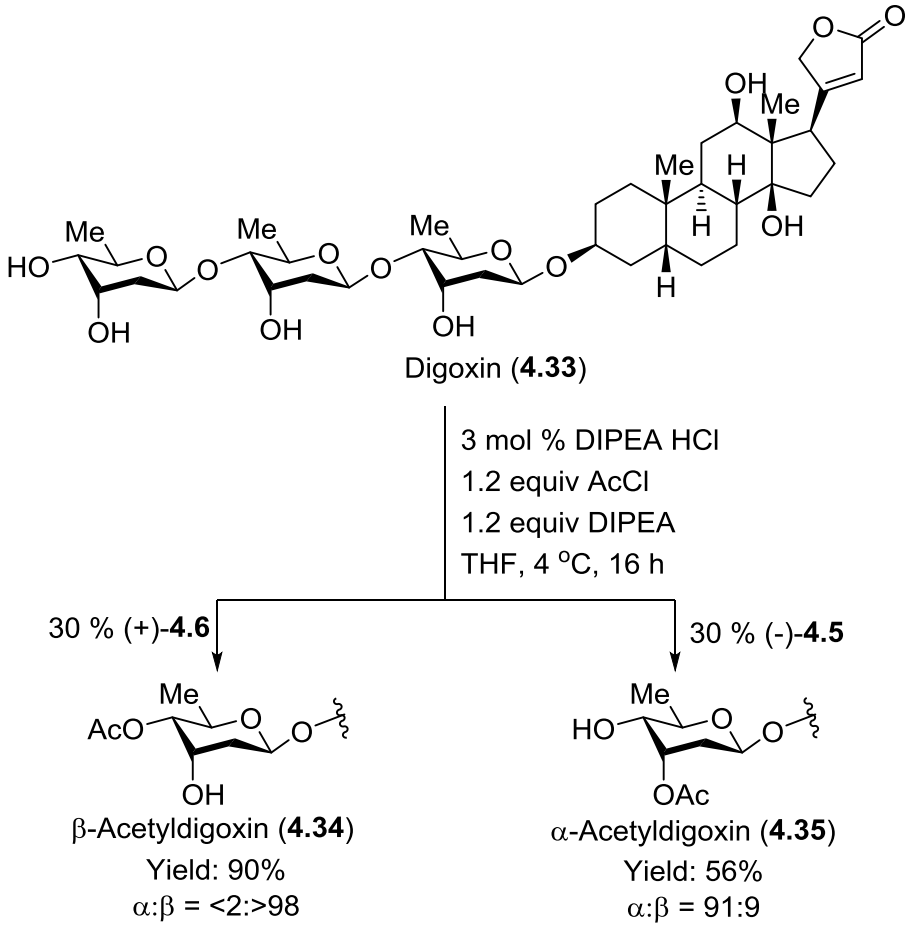
Scheme 4.11. Selective Silylation of uridine derivative.



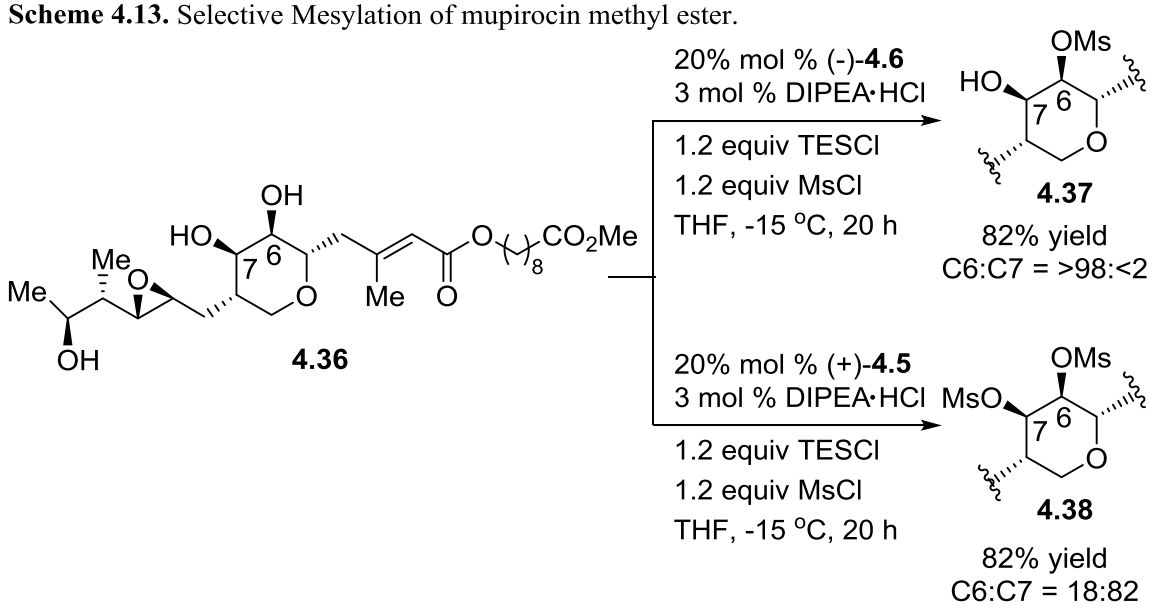
Finally, we demonstrated the power of the scaffolding catalysis by targeting the predictable derivatizations of complex molecules. Digoxin, a natural product isolated from *Digitalis lanta*, is a cardiac glycoside used in the treatment of congestive heart failure.[20] Two acetyl derivatives of digoxin, α-acetyldigoxin and β-acetyldigoxin, are also current cardiac drugs with significant higher costs. With a differentiation of six hydroxyl groups required, a single-step site-selective acylation of the target site in digoxin could be a highly rewarding synthetic route, facilitating our access to its valuable therapeutic derivatives. Gratifying, attempt to acylate the equatorial β-OH with catalyst (+)-**4.6** resulted in excellent selectivity and isolated yield (90% yield, α:β = <2:>98, Scheme

4.12). This selectivity was then overturned through the use of catalyst (−)-**4.5**, allowing a transfer of acyl group to the less reactive axial hydroxyl and yielding α-acetyldigoxin in 56 % yield (α:β = 91:9, Scheme 4.12). The success of this strategy was further strengthened by the mesylation of C6-OH and C7-OH of mupirocin methyl ester[21], which were enabled by catalyst (−)-**4.6** and (+)-**4.5**, respectively (Scheme 4.13). This mesylation methodology offers a new route to the rapid and selective derivatize of antibiotics containing *cis-1,2*-diols..

Scheme 4.12. Selective Acylation of digoxin.



Scheme 4.13. Selective Mesylation of mupirocin methyl ester.



4.7 Future Directions and Conclusions

We have demonstrated that functional group motif recognition is a powerful approach to enable site-selective functionalization of complex molecules. With a suite of chiral scaffolding catalysts targeting *cis*-1,2-diols via a reversible covalent bonding, high and switchable site-selectivities were consistently achieved in the transfer of electrophiles to a broad scope of monosaccharides, ribonucleosides, and other complex polyol structures. The selectivity offered by this catalytic system has also been proven highly predictable, thereby providing additional values for its application towards new substrates.

We envision that this strategy could further benefit from the development of catalysts towards other common diol relationship (*trans*-1,2-diol, *cis*- and *trans*-1,3-diols etc.), which would enable the activation of other previously inaccessible sites in

polyhydroxylated frameworks, therefore further empowering synthetic chemists in the rapid derivatization and selective manipulation of these complex molecular architectures.

4.8 Experimental

General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. *N,N*-Diisopropylethylamine, chlorotriethylsilane, acetyl chloride, and methanesulfonyl chloride were purchased from Sigma Aldrich and distilled over CaH_2 before use. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe techniques, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC).

^{1}H, ^{13}C, and gCOSY NMR were performed on a Varian Gemini 400 MHz, Varian Gemini 500 MHz or a Varian Unity Inova 500 MHz spectrometer. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C NMR. Signals are quoted as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (br s). Coupling constants are reported in Hz. All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module

and values are reported in cm^{-1}. All GC analyses were performed on an SHIMADZU GC-2014 System. HRMS data were generated in Boston College facilities.

Methyl α-L-rhamnose, methyl β-L-arabinose, and 1,6-anhydro-β-D-galactose were purchased from Carbosynth and used as received. Digoxin was purchased from Carbosynth and dried under vacuum at 100 °C overnight before use. The following compounds were prepared following the previously reported procedures: Methyl-6-(*tert*-butyldimethylsilyloxy)-α-D-mannose (**4.7**)[22], methyl-6-(*tert*-butyldimethylsilyloxy)-α-D-galactose (**4.19**)[22], 6-(*tert*-butyldimethylsilyloxy)-helicid (**4.27**)[22], 5-dimethoxytrityloxy-uridine[23] and mupirocin methyl ester[24].

All authentic minor products were prepared according to previous procedures.[14]

Catalyst Synthesis

Catalysts (−)-**4.5** was prepared according to previous procedures (Chapter 2, **2.11**) and can be purchased from Strem (Product Number: 07-1222). Catalysts (+)-**4.5** was prepared with same procedures from *D*-valinol and can be purchased from Strem (Product Number: 07-1223).

Catalysts (−)-**4.6** was prepared according to previous procedures (Chapter 3, **3.6**) and can be purchased from Strem (Product Number: 07-1226). Catalysts (+)-**4.6** was prepared with same procedures from *D*-valinol and can be purchased from Strem (Product Number: 07-1227).

Control catalyst (+)-**4.5a** was prepared according to previous procedures (Chapter 2,

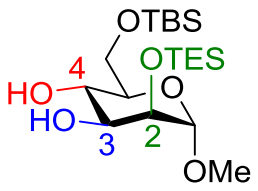
2.12) from D-valinol.

Control catalyst (−)-**4.6a** was prepared according to literature procedures (Chapter 3, **3.7**).

Site-Selective Functionalization of Mannose (Table 4.1)

General procedure A (Table 4.1, entry1). In a dry box, a solution of **4.7** (62 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous *tert*-amyl alcohol (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of chlorotriethylsilane (40 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 2 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography (Hexane/EtOAc = 20:1 to 5:1) afforded a mixture of mono-functionalized products (65 mg, 77%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 5:78:17).

Table 4.1, entry 2. The general procedure A was followed using (+)-**4.5** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. Column chromatography (Hexane/EtOAc = 20:1 to 1:1) afforded the bis-silylated product (10 mg, 9%), the substrate **4.7** (3 mg, 5%), and a

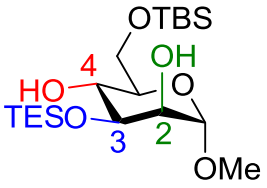


mixture of mono-functionalized products (71 mg, 84%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 90:10:-). A second column chromatography was performed to isolate the pure product **4.8a** (64 mg, 76%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.57 (d, 1H, *J* = 1.5), 3.90 (dd, 1H, *J* = 2.9, 1.7), 3.88 (dd, 1H, *J* = 10.5, 5.1), 3.85 (dd, 1H, *J* = 9.0, 3.2), 3.72-3.69 (m, 2H), 3.53-3.50 (m, 1H), 3.43 (s, 3H), 2.88 (br s, 1H), 2.11 (br s, 1H), 0.96 (t, 9H, *J* = 8.1), 0.90 (s, 9H), 0.63 (q, 6H, *J* = 7.8), 0.089 (s, 3H), 0.086 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 106.9, 83.0, 82.7, 82.4, 75.8, 69.9, 60.4, 31.5, 23.9, 12.4, 10.6, 0.3, 0.2. **IR**: 3428, 2953, 2927, 2878, 1251, 1139, 1110, 1048, 1005, 833, 776, 728 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{19}H_{42}O_6Si_2$: $[M+H]^+$: 423.2598, found: 423.2591.

Scale-up experiment. In a dry box, a solution of **3** (1.23 g, 4.0 mmol), (+)-**1** (225 mg, 0.80 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (20 mg, 0.12 mmol, 3 mol %) in anhydrous *tert*-amyl alcohol (20 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, *N,N*-diisopropylethylamine (836 μL, 4.8 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 °C for 20 minutes, followed by dropwise addition of chlorotriethylsilane (806 μL, 4.8 mmol, 1.2 eq). The reaction was stirred at 4 °C for 2 hours. MeOH (1.0 mL) was added to quench the reaction. The mixture was filtered through a column packed with silica gel, followed by flush with EtOAc (300 mL). The solvent was removed under reduced pressure. Column chromatography (Hexane/EtOAc = 20:1 to 1:1) afforded a mixture of

mono-functionalized products (1.39 g, 82%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 90:10:-). A second column chromatography was performed to isolate the pure product **4.8a** (1.25 g, 74%).

Table 4.1, entry 3. The general procedure A was followed using (−)-**4.6** (3.1 mg, 0.010 mmol, 5 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = -:100:-). Column chromatography afforded the pure product **4.9a** (84 mg, >98%).



^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.71 (d, 1H, *J* = 1.5), 3.87 (d, 1H, *J* = 1.0), 3.86 (d, 1H, *J* = 0.5), 3.84 (dd, 1H, *J* = 8.8, 3.7), 3.75-3.73 (m, 1H), 3.70 (td, 1H, *J* = 9.5, 2.0), 3.58-3.54 (m, 1H), 3.56 (s, 3H), 2.69 (d, 1H, *J* = 2.0), 2.57 (d, 1H, *J* = 1.5), 0.98 (t, 9H, *J* = 8.1), 0.90 (s, 9H), 0.67 (qd, 6H, *J* = 7.3, 2.5), 0.089 (s, 3H), 0.087 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 106.7, 83.9, 83.6, 83.2, 79.4, 71.4, 61.3, 32.4, 24.8, 13.3, 11.4, 1.1, 1.0. **IR**: 3506, 2953, 2929, 2878, 1252, 1137, 1106, 1054, 977, 834, 778, 742, 729 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{19}H_{42}O_6Si_2$: $[M+NH_4]^+$: 440.2864, found: 440.2874.

Scale-up experiment. In a dry box, a solution of **4.7** (1.23 g, 4.0 mmol), (-)-**4.6** (62 mg, 0.20 mmol, 5 mol %), and *N,N*-diisopropylethylamine hydrochloride (20 mg, 0.12 mmol, 3 mol %) in anhydrous *tert*-amyl alcohol (20 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, *N,N*-diisopropylethylamine (836 μL, 4.8 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 °C for 20 minutes, followed by dropwise addition of chlorotriethylsilane (806 μL, 4.8 mmol, 1.2 eq). The reaction was

stirred at 4 °C for 2 hours. MeOH (1.0 mL) was added to quench the reaction. The mixture was filtered through a column packed with silica gel, followed by flush with EtOAc (300 mL). The solvent was removed under reduced pressure. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = -:99:1). Column chromatography (Hexane/EtOAc = 20:1 to 1:1) afforded the pure product **4.9a** (1.69 g, >98%).

Table 4.1, entry 4. The general procedure A was followed using (+)-**4.5a** (10 mg, 0.040 mmol, 20 mol %) as the catalyst. Column chromatography (Hexane/EtOAc = 20:1 to 5:1) afforded a mixture of mono-functionalized products (6 mg, 7%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 3:92:5).

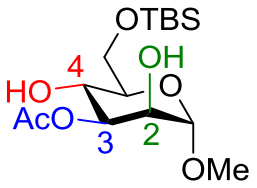
Table 4.1, entry 5. The general procedure A was followed using (-)-**4.6a** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. Column chromatography (Hexane/EtOAc = 20:1 to 5:1) afforded a mixture of mono-functionalized products (8 mg, 9%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 2:92:6).

General procedure B (Table 4.1, entry 6). In a dry box, a solution of **4.7** (62 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (3.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of acetyl chloride (17 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the

reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. 1,3,5-trimethoxybenzene (50 μL of 0.40 M in $CDCl_3$, 0.020 mmol, 10 mol %) was added as standard. ^{1}H NMR of the crude mixture afforded yield (39%) and selectivity (C2:C3:C4 = 9:84:7).

Table 4.1, entry 7. The general procedure B was followed using (+)-**4.5** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded selectivity (C2:C3:C4 = 84:15:1). Column chromatography (Hexane/EtOAc = 5:1 to 2:1) afforded the mixture of mono-functionalized products with **4.8b** as the major product (52 mg, 74%, C2:C3:C4 = 84:15:1). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.07 (dd, 1H, *J* = 3.4, 1.5), 4.68 (d, 1H, *J* = 1.5), 3.99 (d, 1H, *J* = 9.0), 3.92 (dd, 1H, *J* = 10.8, 4.9), 3.85 (dd, 1H, *J* = 10.5, 5.4), 3.81 (t, 1H, *J* = 9.5), 3.60-3.56 (m, 1H), 3.36 (s, 3H), 3.15 (br s, 1H), 2.44 (br s, 1H), 2.11 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 171.0, 87.8, 72.0, 71.0, 70.5, 70.2, 64.5, 55.2, 26.0, 21.1, 18.4, -5.23, -5.25. **IR**: 3412, 2952, 2929, 2856, 1748, 1725, 1375, 1251, 1237, 1139, 1078, 1048, 836, 777 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{15}H_{30}O_7Si$: $[M-OH]^+$: 333.1733, found: 333.1743.

Table 4.1, entry 8. The general procedure B was followed using (−)-**4.6** (3.1 mg, 0.010 mmol, 5 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = -:100:-). Column chromatography (Hexane/EtOAc = 5:1 to 2:1) afforded the pure product **4.9b** (67 mg, 96%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.08 (dd,



1H, *J* = 9.8, 3.2), 4.68 (d, 1H, *J* = 1.7), 4.00-3.98 (m, 1H), 3.96 (t, 1H, *J* = 9.5), 3.91 (dd, 1H, *J* = 10.5, 4.9), 3.86 (dd, 1H, *J* = 10.5, 5.6), 3.67-3.63 (m, 1H), 3.38 (s, 3H), 3.07 (br s, 1H), 2.18 (br s, 1H), 2.15 (s, 3H), 0.89 (s, 9H), 0.090 (s, 3H), 0.088 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 171.2, 100.8, 74.6, 71.5, 69.3, 68.2, 64.7, 55.2, 26.0, 21.3, 18.4, -5.3. **IR**: 3438, 2953, 2929, 1716, 1369, 1249, 1107, 1048, 969, 833, 776, 732 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{15}H_{30}O_7Si$: $[M+H]^+$: 351.1839, found: 351.1844.

General procedure C (Table 4.1, entry 9). In a dry box, a solution of **4.7** (62 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at -15 ℃ for 10 minutes, followed by dropwise addition of methanesulfonyl chloride (19 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at -15 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography (Hexane/EtOAc = 5:1 to 2:1) afforded a mixture of mono-functionalized products (53 mg, 68%). GC Analysis (Shimazu SHRXI-5MS 15 m, 150 °C for 3 min, 10 °C/min to 200 °C, 200°C for 6 min, 15 psi., t_{C2} = 10.50 min, t_{C3} = 11.04 min, t_{C4} = 9.50 min) of the mixture afforded selectivity

(C2:C3:C4 = 22:56:22).

Table 4.1, entry 10. The general procedure C was followed using (+)-**4.5** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. GC Analysis of the crude mixture afforded selectivity (C2:C3:C4 = 91:8:1). Column chromatography (Hexane/EtOAc = 5:1 to 2:1) afforded the pure product **4.8c** (62 mg, 80%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.81 (d, 1H, *J* = 1.7), 4.78 (dd, 1H, *J* = 3.2, 1.7), 4.00 (dd, 1H, *J* = 9.5, 3.2), 3.91 (dd, 1H, *J* = 10.3, 4.9), 3.83 (dd, 1H, *J* = 10.5, 6.4), 3.78 (t, 1H, 9.3), 3.60-3.56 (m, 1H), 3.38 (s, 3H), 3.13 (s, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 99.2, 7.5, 71.0, 70.6, 69.6, 65.0, 55.4, 38.6, 26.0, 18.4, -5.3. **IR**: 3457, 2928, 2856, 1352, 1175, 1138, 1069, 962, 907, 833, 777, 523 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{14}H_{30}O_8SSi$: $[M+H]^+$: 387.1509, found: 387.1510.

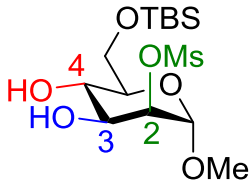
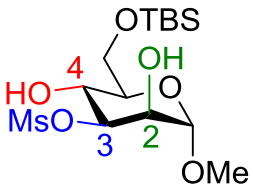


Table 4.1, entry 11. The general procedure C was followed using (−)-**4.6** (3.1 mg, 0.010 mmol, 5 mol %) as the catalyst. GC Analysis of the crude mixture afforded selectivity (C2:C3:C4 = -:100:-). Column chromatography (Hexane/EtOAc = 5:1 to 2:1) afforded the pure product **4.9c** (75 mg, 97%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.79 (dd, 1H, *J* = 9.5, 3.2), 4.72 (d, 1H, *J* = 1.7), 4.14-4.12 (m, 1H), 4.07 (td, 1H, *J* = 9.5, 2.0), 3.95 (dd, 1H, *J* = 10.3, 4.9), 3.85 (dd, 1H, *J* = 10.0, 7.1), 3.68-3.63 (m, 1H), 3.49 (d, 1H, *J* = 2.2), 3.38 (s, 3H), 3.18 (s, 3H), 2.57 (d, 1H, *J* = 4.7), 0.90 (s, 9H), 0.111 (s, 3H), 0.107 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 100.7, 82.7, 70.5, 10.1, 68.9, 65.5, 55.3, 38.6, 26.0, 18.4, -5.3, -5.4.

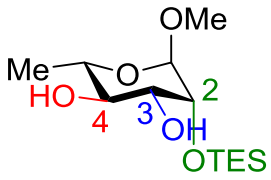


IR: 3497, 2930, 2857, 1350, 1253, 1175, 1135, 1109, 1058, 963, 837, 779 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{14}H_{30}O_8SSi$: $[M+H]^+$: 387.1509, found: 387.1500.

Site-Selective Functionalization of Rhamnose (Table 4.2).

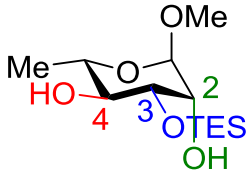
*General procedure D (Table 4.2, entry 1).*In a dry box, a solution of **4.11** (36 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous *tert*-amyl alcohol (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of chlorotriethylsilane (40 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flushing with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography (Hexane/EtOAc = 10:1 to 3:1) afforded a mixture of mono-functionalized products (46 mg, 78%). Selectivity of the mixture was determined by ^{1}H NMR (C2:C3:C4 = 7:79:14).

Table 4.2, entry 2. The general procedure D was followed using (−)-**4.6** (12 mg, 0.040 mmol, 20 mol %) as the catalyst. Column chromatography (Hexane/EtOAc = 10:1 to 3:1) afforded a mixture of mono-functionalized products with **4.12a** as the major product (52 mg, 88%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 =



89:11:-). A second column chromatography was performed for characterization of the pure product. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.54 (d, 1H, *J* = 1.5), 3.91 (dd, 1H, *J* = 3.7, 1.7), 3.62-3.58 (m, 2H), 3.38 (t, 1H, *J* = 9.3), 3.34 (s, 3H), 2.29 (br s, 1H), 2.03 (d, 1H, *J* = 10.5), 1.31 (d, 3H, *J* = 6.4), 0.97 (t, 9H, *J* = 6.0), 0.64 (q, 6H, *J* = 8.1). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 101.4, 74.0, 72.2, 72.1, 67.9, 55.0, 17.8, 6.9, 5.1. **IR**: 3416, 2953, 2877, 2831, 1458, 1239, 1052, 1005, 829, 727, 630 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{13}H_{28}O_5Si$: $[M+NH_4]^+$: 310.2050, found: 310.2049.

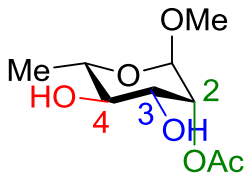
Table 4.2, entry 3. The general procedure D was followed using (+)-**4.5** (2.8 mg, 0.010 mmol, 5 mol %) as the catalyst. The reaction was stirred at 4 °C for 20 hours. Selectivity was determined by ^{1}H NMR of the crude reaction mixture (C2:C3:C4 = -:100:-). Column chromatography (Hexane/EtOAc = 10:1 to 3:1) afforded the pure product **4.13a** (59 mg, >98%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.68 (d, 1H, *J* = 1.2), 3.80 (dd, 1H, *J* = 8.8, 3.7), 3.78 (dd, 1H, *J* = 3.7, 1.5), 3.65-3.62 (m, 1H), 3.46 (td, 1H, *J* = 9.1, 2.9), 3.36 (s, 3H), 2.54 (d, 1H, *J* = 1.5), 2.04 (d, 1H, *J* = 3.4), 1.32 (d, 3H, *J* = 6.4), 0.98 (t, 9H, *J* = 8.1), 0.67 (q, 6H, *J* = 8.1). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 100.4, 73.4, 73.3, 71.8, 67.5, 55.0, 17.8, 6.9, 5.1. **IR**: 3477, 2954, 2911, 2833, 1458, 1238, 1107, 972, 852, 727, 616 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{13}H_{28}O_5Si$: $[M+ H]^+$: 293.1784, found: 293.1780.



General procedure E (Table 4.2, entry 4). In a dry box, a solution of **4.11** (36 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and

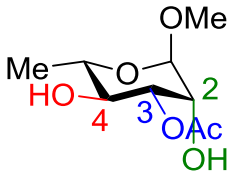
N,N-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of acetyl chloride (17 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flushing with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography (Hexane/EtOAc = 5:1 to 1:1) afforded a mixture of mono-functionalized products (37 mg, 83%). Selectivity of the mixture was determined by ^{1}H NMR (C2:C3:C4 = 12:79:9).

Table 4.2, entry 5. The general procedure E was followed using (−)-**4.6** (12 mg, 0.040 mmol, 20 mol %) as the catalyst in anhydrous THF (3.0 mL). Column chromatography (Hexane/EtOAc = 5:1 to 1:1) afforded the mixture of mono-functionalized products (32 mg, 73%) with **4.12b** as the major product. Selectivity was determined by ^{1}H NMR of the isolated mixture (C2:C3:C4 = 84:14:2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.08 (dd, 1H, *J* = 3.4, 1.5), 4.63 (d, 1H, *J* = 1.5), 3.92 (dd, 1H, *J* = 9.5, 3.4), 3.67-3.63 (m, 1H), 3.45 (t, 1H, *J* = 9.5), 3.37 (s, 3H), 3.16 (br s, 2H), 2.14 (s, 3H), 1.34 (d, 3H, *J* = 6.1). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 171.3, 98.7, 73.3, 72.6, 70.3, 68.1, 55.2, 21.2, 17.7. **IR**: 3409, 2934, 2837, 1747, 1726, 1376, 1237, 1135, 1076, 1054, 973, 838, 803 cm^{-1}. **HRMS** (DART-TOF) calcd. for



$C_9H_{16}O_6$: $[M+NH_4]^+$: 238.1291, found: 238.1294.

Table 4.2, entry 6. The general procedure E was followed using (+)-**4.5** (2.8 mg, 0.010 mmol, 5 mol %) as the catalyst in anhydrous THF (3.0 mL). ^{1}H NMR of the crude reaction mixture afforded the selectivity (C2:C3:C4 = 1:99:-). Column chromatography (Hexane/EtOAc = 5:1 to 1:1) afforded the pure product **4.13b** (43 mg, 98%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.04 (dd, 1H, *J* = 9.8, 3.2), 4.68 (d, 1H, *J* = 1.7), 4.05-4.03 (m, 1H), 3.74-3.71 (m, 1H), 3.64 (td, 1H, *J* = 9.5, 5.4), 3.41 (s, 3H), 2.21 (d, 1H, *J* = 5.6), 2.19 (s, 3H), 2.04 (d, 1H, *J* = 5.1), 1.37 (d, 3H, *J* = 6.1). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 171.6, 100.6, 75.2, 71.7, 69.9, 68.6, 55.2, 21.4, 17.8. **IR**: 3437, 2922, 2837, 1717, 1450, 1372, 1249, 1132, 1056, 987, 973, 805 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_9H_{16}O_6$: $[M+NH_4]^+$: 238.1291, found: 238.1283.



General procedure F (Table 4.2, entry 7). In a dry box, a solution of **4.11** (36 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of methanesulfonyl chloride (19 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica

gel, followed by flushing with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography (Hexane/EtOAc = 5:1 to 1:1) afforded a mixture of mono-functionalized products (37 mg, 72%). Selectivity of the mixture was determined by GC analysis (Shimazu SHRXI-5MS 15 m, 120 °C for 2 min, 1 °C/min to 140 °C, 10 °C/min to 200 °C, 200°C for 2 min, 15 psi., t_{C2} = 15.07 min, t_{C3} = 16.30 min, t_{C4} = 14.46 min) (C2:C3:C4 = 24:57:19).

Table 4.2, entry 8. The general procedure F was followed using (−)-**4.6** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. The reaction was stirred at -15 °C for 4 hours. Selectivity was determined by GC analysis of the crude reaction mixture (C2:C3:C4 = 92:8:-). Column chromatography (Hexane/EtOAc = 5:1 to 1:1) afforded the pure product **4.12c** (42 mg, 82%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.82 (dd, 1H, *J* = 3.2, 1.7), 4.79 (d, 1H, *J* = 1.7), 3.93 (d, 1H, *J* = 9.5), 3.68-3.62 (m, 1H), 3.44 (t, 1H, *J* = 9.5), 3.38 (s, 3H), 3.15 (s, 3H), 3.03 (br s, 1H), 2.74 (br s, 1H), 1.33 (d, 3H, *J* = 6.4). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 99.0, 79.0, 73.2, 69.8, 68.3, 55.3, 38.7, 17.6. **IR**: 3454, 2935, 2842, 1451, 1346, 1173, 1133, 1051, 963, 907, 855, 637, 529 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_8H_{16}O_7S$: $[M+NH_4]^+$: 274.0961, found: 274.0974.

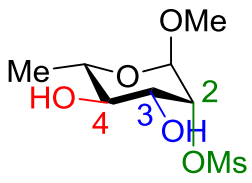
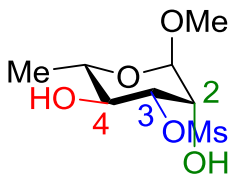


Table 4.2, entry 9. The general procedure F was followed using (+)-**4.5** (2.8 mg, 0.010 mmol, 5 mol %) as the catalyst. Selectivity was determined by GC analysis of the crude reaction mixture (C2:C3:C4 = 1:99:-). Column chromatography (Hexane/EtOAc = 5:1 to 1:1) afforded the pure product **4.13c** (51 mg, >98%). **^{1}H NMR** ($CDCl_3$, 500 MHz)



δ 4.76 (dd, 1H, *J* = 9.1, 3.2), 4.70 (d, 1H, *J* = 1.7), 4.19 (br s, 1H), 3.77-3.70 (m, 2H), 3.40 (s, 3H), 3.18 (s, 3H), 2.73 (br s, 1H), 2.71 (br s, 1H), 1.38 (d, 3H, *J* = 5.9). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 100.6, 82.8, 70.8, 70.5, 68.4, 55.2, 38.6, 17.8. **IR**: 3462, 2936, 2839, 1452, 1348, 1198, 1150, 1055, 959, 860, 799, 530, 513 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_8H_{16}O_7S$: $[M+NH_4]^+$: 274.0961, found: 274.0964.

Site-Selective Functionalization of Arabinose (Table 4.3).

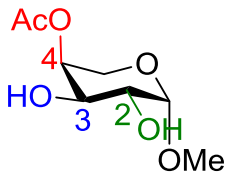
General procedure G (Table 4.3, entry 1). In a dry box, a solution of **4.15** (33 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous *tert*-amyl alcohol (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of chlorotriethylsilane (40 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. 1,3,5-trimethoxybenzene (50 μL of 0.40 M in $CDCl_3$, 0.020 mmol, 10 mol %) was added as standard. ^{1}H NMR of the crude mixture afforded the yield (39%) and selectivity (C2:C3:C4 = 27:14:59).

Table 4.3, entry 2. The general procedure G was followed using (−)-**4.5** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. Reaction was performed in anhydrous *tert*-amyl alcohol (3.0 mL). ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = -:3:97).Column chromatography (Hexane/EtOAc = 4:1 to 3:1) afforded the pure product **4.18a** (51 mg, 92%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.75 (d, 1H, *J* = 3.2), 4.00 (dd, 1H, *J* = 5.6, 3.4), 3.79-3.78 (m, 1H), 3.74-3.72 (m, 2H), 3.57 (dd, 1H, *J* = 12.2, 3.4), 3.42 (s, 3H), 2.27 (d, 1H, *J* = 6.1), 2.23 (br s, 1H), 0.97 (t, 9H, *J* = 8.1), 0.63 (q, 6H, *J* = 7.8). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 100.0, 70.8, 70.3, 69.8, 63.6, 55.9, 6.9, 5.1. **IR**: 3422, 2952, 2911, 2875, 1070, 1045, 1002, 890, 877, 798, 725 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{12}H_{26}O_5Si$: $[M+H]^+$: 279.1628, found: 279.1625.

Table 4.3, Entry 3. The general procedure G was followed using (+)-**4.5** (2.8 mg, 0.010 mmol, 5mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = -:98:2).Column chromatography (Hexane/EtOAc = 4:1 to 3:1) afforded the pure product **4.17a** (54 mg, 97%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.75 (d, 1H, *J* = 3.7), 3.82 (dd, 1H, *J* = 8.8, 3.7), 3.79 (t, 1H, *J* = 1.5), 3.75 (td, 1H, *J* = 8.6, 3.4), 3.72 (d, 2H, *J* = 1.7), 3.41 (s, 3H), 2.65 (s, 1H), 1.93 (d, 1H, *J* = 8.3), 0.98-0.95 (m, 9H), 0.68-0.63 (m, 6H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 100.2, 71.9, 70.0, 69.9, 61.7, 55.7, 6.9, 5.1. **IR**: 3458, 2952, 2911, 2875, 1062, 998, 848, 742 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{12}H_{26}O_5Si$: $[M+H]^+$: 279.1628, found: 279.1624.

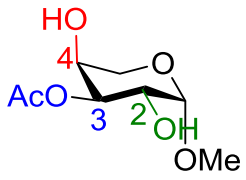
General procedure H (Table 4.3, entry 4). In a dry box, a solution of **4.15** (33 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (3.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of acetyl chloride (17 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. 1,3,5-trimethoxybenzene (50 μL of 0.40 M in $CDCl_3$, 0.020 mmol, 10 mol %) was added as standard. ^{1}H NMR of the crude mixture afforded the yield (6%) and selectivity (C2:C3:C4 = 22:72:6).

Table 4.3, entry 5. The general procedure H was followed using (−)-**4.5** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. Reaction was stirred for 8 hours. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = 5:9:86).Column chromatography (CH_2Cl_2/MeOH = 100:1 to 20:1) afforded the mixture of mono-functionalized products with **4.18b** as the major product (25 mg, 61%). **^{1}H NMR** (acetone-d6, 500 MHz) δ 5.08-5.07 (m, 1H), 4.69 (d, 1H, *J* = 3.4), 3.88 (dd, 1H, *J* = 9.8, 3.4), 3.80 (dd, 1H, *J* = 12.7, 1.5), 3.72 (dd, 1H, *J* = 9.8, 2.9), 3.57 (dd, 1H, *J* = 12.7, 2.4), 3.35 (s, 3H), 2.04 (s, 3H). **^{13}C NMR** (acetone-d6,



125 MHz) δ 170.9, 101.6, 72.7, 70.8, 69.1, 61.4, 55.8, 21.1. **IR**: 3429, 2937, 1734, 1241, 1077, 1038, 997 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_8H_{14}O_6$: $[M+H]^+$: 207.0869, found: 207.0861.

Table 4.3, entry 6. The general procedure H was followed using (+)-**4.5** (2.8 mg, 0.010 mmol, 5 mol %) as the catalyst. ^1H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = 3:96:1). Column chromatography (Hex/EtOAc = 2:1 to 1:2) afforded the pure product **4.17b** (34 mg, 83%). **^1H NMR** (acetone-d6, 500 MHz) δ 4.96 (dd, 1H, *J* = 10.3, 3.4), 4.70 (d, 1H, *J* = 3.7), 4.12 (d, 1H, *J* = 3.2), 4.00 (s, 1H), 3.98-3.96 (m, 1H), 3.79 (dd, 1H, *J* = 12.5, 1.5), 3.56 (dd, 1H, *J* = 12.2, 2.4), 3.52 (d, 1H, *J* = 8.8), 3.37 (s, 3H), 2.02 (s, 3H). **^{13}C NMR** (acetone-d6, 125 MHz) δ 171.1, 101.8, 74.0, 68.2, 67.6, 63.7, 55.6, 21.1. **IR**: 3436, 2927, 1737, 1716, 1240, 1141, 1057, 997cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_8H_{14}O_6$: $[M+H]^+$: 207.0869, found: 207.0878.



General procedure I (Table 4.3, entry 7). In a dry box, a solution of **4.15** (33 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of methanesulfonyl chloride (19 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to

quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography (Hex/EtOAc = 1:1 to 1:3) afforded the mixture of mono-functionalized products (13 mg, 27%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 68:23:9).

Table 4.3, entry 8. The general procedure I was followed using (−)-**4.5** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. Column chromatography (Hex/EtOAc = 1:1 to 1:3) afforded the mixture of mono-functionalized products (45 mg, 93%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 3:10:87). A second column chromatography (Hex/EtOAc = 1:1 to 1:3) afforded **4.18c** for characterizations. **^{1}H NMR** (acetone-d6, 500 MHz) δ 4.88-4.87 (m, 1H), 4.71 (d, 1H, *J* = 3.4), 3.96 (dd, 1H, *J* = 10.0, 3.4), 3.91 (dd, 1H, *J* = 13.0, 1.0), 3.74 (dd, 1H, *J* = 13.0, 2.2), 3.69 (dd, 1H, *J* = 10.0, 3.7), 3.36 (s, 3H), 3.15 (s, 3H). **^{13}C NMR** (acetone-d6, 125 MHz) δ 101.5, 81.5, 70.3, 69.0, 62.2, 55.9, 38.6. **IR**: 3439, 2939, 1337, 1173, 1076, 975, 925, 895 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_7H_{14}O_7S$: $[M+NH_4]^+$: 260.0804, found: 260.0809.

Table 4.3, entry 9. The general procedure I was followed using (+)-**4.5** (2.8 mg, 0.010 mmol, 5 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = 1:92:7). Column chromatography (Hex/EtOAc = 1:1 to 1:3) afforded the pure product **4.17c** (44 mg, 91%). **^{1}H NMR** (acetone-d6, 500 MHz) δ 4.75 (d, 1H, *J* = 3.2),

4.66 (dd, 1H, *J* = 9.0, 3.2), 4.47 (d, 1H, *J* = 2.7), 4.13 (s, 1H), 4.04-4.02 (m, 2H), 3.82 (dd, 1H, *J* = 12.2, 1.2), 3.61 (dd, 1H, *J* = 12.5, 2.2), 3.38 (s, 3H), 3.14 (s, 3H). **^{13}C NMR** (acetone-d6, 125 MHz) δ 72.1, 52.8, 39.8, 38.0, 34.1, 26.0, 9.0. **IR**: 3460, 1334, 1171, 1140, 1061, 1018, 972, 860 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_7H_{14}O_7S$: $[M+NH_4]^+$: 260.0804, found: 260.0802.

Site-Selective Functionalization of Galactose (Table 4.4).

General procedure J (Table 4.4, entry 1). In a dry box, a solution of **4.19** (62 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous *tert*-amyl alcohol (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of chlorotriethylsilane (40 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. 1,3,5-trimethoxybenzene (50 μL of 0.40 M in $CDCl_3$, 0.020 mmol, 10 mol %) was added as standard. ^{1}H NMR of the crude mixture afforded yield (77%) and selectivity (C2:C3:C4 = 86:14:-).

Table 4.4, entry 2. The general procedure J was followed using (+)-**4.5** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded selectivity (C2:C3:C4 = 6:94:-). Column chromatography (Hexane/EtOAc = 20:1 to 5:1) afforded the pure product **4.21a** (80 mg, 95%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.78 (d, 1H, *J* = 3.2), 3.88-3.84 (m, 2H), 3.80-3.74 (m, 3H), 3.41 (s, 3H), 2.58 (s, 1H), 1.87 (dd, 1H, *J* = 5.1, 3.7), 0.97 (t, 9H, *J* = 8.1), 0.89 (s, 9H), 0.66 (qd, 6H, *J* = 7.6, 3.4), 0.08 (s, 6H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 99.8, 72.7, 70.4, 70.0, 69.9, 62.5, 55.4, 26.0, 18.5, 7.0, 5.1, -5.1, -5.3. **IR**: 3566, 2953, 2930, 2877, 1250, 1086, 1053, 835, 744 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{19}H_{42}O_6Si_2$: $[M+H]^+$: 423.2598, found: 423.2612.

General procedure K (Table 4.4, entry 3. In a dry box, a solution of **4.19** (62 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (3.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of acetyl chloride (17 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. 1,3,5-trimethoxybenzene (50 μL of 0.40 M in $CDCl_3$, 0.020 mmol, 10 mol %) was added

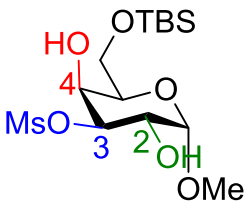
as standard. ^{1}H NMR of the crude mixture afforded yield (26%) and selectivity (C2:C3:C4 = 42:58:-).

Table 4.4, entry 4. The general procedure K was followed using (+)-**4.5** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded selectivity (C2:C3:C4 = 19:81:-). Column chromatography (Hexane/EtOAc = 5:1 to 2:1) afforded the mixture of mono-functionalized products with **4.21b** as the major product (67 mg, 96%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.03 (dd, 1H, *J* = 10.0, 2.9), 4.84 (d, 1H, *J* = 3.9), 4.18 (s, 1H), 4.06 (td, 1H, *J* = 10.8, 3.9), 3.91 (dd, 1H, *J* = 10.8, 4.9), 3.87 (dd, 1H, *J* = 10.8, 4.2), 3.76 (t, 1H, *J* = 4.6), 3.43 (s, 3H), 3.25 (d, 1H, *J* = 2.0), 2.16 (s, 1H), 1.99 (d, 1H, *J* = 11.0), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 171.3, 100.0, 73.7, 69.6, 69.3, 67.5, 64.0, 55.6, 26.0, 21.4, 18.4, -5.3, -5.4. **IR**: 3428, 2953, 2929, 2856, 1739, 1721, 1248, 1146, 1083, 1050, 836, 776 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{15}H_{30}O_7Si$: $[M-OH]^+$: 333.1733, found: 333.1743.

General procedure L (Table 4.4, entry 5). In a dry box, a solution of **4.19** (62 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at -15 ℃ for 10 minutes, followed by dropwise addition of methanesulfonyl chloride (19 μL, 0.24

mmol, 1.2 eq). The reaction was stirred at -15 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography (Hexane/EtOAc = 5:1 to 2:1) afforded the mixture of mono-functionalized products (48 mg, 62%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 76:24:-).

Table 4.4, entry 6. The general procedure L was followed using (+)-**4.5** (11 mg, 0.040 mmol, 20 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded selectivity (C2:C3:C4 = -:100:-). Column chromatography (Hexane/EtOAc = 5:1 to 2:1) afforded the pure product **4.21c** (57 mg, 74%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 4.85 (d, 1H, *J* = 4.2), 4.73 (dd, 1H, *J* = 10.0, 2.9), 4.30 (s, 1H), 4.12 (td, 1H, *J* = 10.0, 4.2), 3.89 (dd, 1H, *J* = 10.8, 5.4), 3.85 (dd, 1H, *J* = 10.8, 4.9), 3.76 (t, 1H, *J* = 5.1), 3.43 (s, 3H), 3.25 (d, 1H, *J* = 2.4), 3.18 (s, 3H), 2.39 (d, 1H, *J* = 10.3), 0.88 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 99.8, 82.3, 70.0, 69.7, 67.3, 63.3, 55.6, 39.0, 26.0, 18.4, -5.31, -5.32. **IR**: 3468, 2952, 2929, 2856, 1350, 1172, 1084, 1047, 961, 834, 776, 731, 526, 489 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{14}H_{30}O_8SSi$: $[M+H]^+$: 387.1509, found: 387.1505.



Site-Selective Functionalization of 1,6-Anhydro-Galactose (Table 4.5).

General procedure M (Table 4.5, entry 1). In a dry box, a solution of **4.23** (32 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and

N,N-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous *tert*-amyl alcohol (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of chlorotriethylsilane (40 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. 1,3,5-trimethoxybenzene (50 μL of 0.40 M in $CDCl_3$, 0.020 mmol, 10 mol %) was added as standard. ^{1}H NMR of the crude mixture afforded the yield (51%) and selectivity (C2:C3:C4 = 91:-:9).

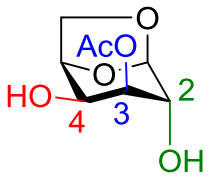
Table 4.5, entry 2. The general procedure M was followed using (−)-**4.6** (3.1 mg, 0.010 mmol, 5 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = 1:-:99). Column chromatography (Hexane/EtOAc = 3:1) afforded the pure product **4.26a** (54 mg, 98%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.36 (t, 1H, *J* = 1.5), 4.24 (d, 2H, *J* = 7.1), 4.06 (t, 1H, *J* = 4.7), 3.86-3.85 (m, 1H), 3.83 (d, 1H, *J* = 8.3), 3.63 (dd, 1H, *J* = 6.4, 5.9), 2.88 (s, 1H), 2.32 (d, 1H, *J* = 8.6), 0.96 (t, 9H, *J* = 8.1), 0.65 (q, 6H, *J* = 7.7). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 101.6, 74.7, 71.6, 71.2, 65.8, 63.9, 6.8, 4.9. **IR**: 3430, 2956, 2878, 1240, 1136, 1099, 1051, 1011, 938, 847, 809, 765, 744, 456 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{12}H_{24}O_5Si$: $[M+H]^+$: 277.1471, found: 277.1474.

General procedure N (Table 4.5, entry 3). In a dry box, a solution of **4.23** (32 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (3.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of acetyl chloride (17 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. 1,3,5-trimethoxybenzene (50 μL of 0.40 M in $CDCl_3$, 0.020 mmol, 10 mol %) was added as standard. ^{1}H NMR of the crude mixture afforded the yield (53%) and selectivity (C2:C3:C4 = 75:8:17).

Table 4.5, entry 4. The general procedure N was followed using (−)-**4.6** (3.1 mg, 0.010 mmol, 5 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = -:3:97). Column chromatography (Hexane/EtOAc = 1:1 to 1:2) afforded the pure product **4.26b** (38 mg, 93%). **^{1}H NMR** (acetone-d6, 500 MHz) δ 5.26 (s, 1H), 5.00 (br s, 1H), 4.41 (dd, 2H, *J* = 6.9, 3.2), 4.25 (d, 1H, *J* = 6.9), 4.07 (t, 2H, *J* = 1.0), 3.68 (d, 1H, *J* = 6.9), 3.54 (t, 1H, *J* = 5.9), 2.04 (s, 3H). **^{13}C NMR** (acetone-d6, 125 MHz) δ 170.4, 103.1, 73.9, 73.1, 70.8, 68.9, 64.8, 20.9. **IR**: 3432, 2961, 2905, 1727, 1432, 1373, 1238,

1132, 1050, 975, 928, 852, 700, 463 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_8H_{12}O_6$: $[M+H]^+$: 205.0712, found: 205.0717.

Table 4.5, entry 5. The general procedure N was followed using (+)-**4.6** (12 mg, 0.040 mmol, 20 mol %) as the catalyst. ^1H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = 2:81:17). Column chromatography (Hexane/EtOAc = 1:1 to 1:2) afforded the pure product **4.25b** (30 mg, 73%, C2:C3:C4 = 2:81:7). **^1H NMR** ($CDCl_3$, 500 MHz) δ 5.22 (t, 1H, *J* = 1.2), 5.03 (dq, 1H, *J* = 5.1, 1.2), 4.39 (d, 1H, *J* = 7.1), 4.32 (d, 2H, *J* = 6.4), 4.24 (d, 1H, *J* = 7.1), 4.15-4.12 (m, 1H), 3.56-3.53 (m, 2H), 2.03 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 170.7, 102.2, 75.7, 73.4, 71.5, 64.8, 64.1, 21.1. **IR**: 3418, 2963, 2904, 1723, 1435, 1240, 1137, 1066, 1040, 971, 852, 696, 438 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_8H_{12}O_6$: $[M+H]^+$: 205.0712, found: 205.0721.



General procedure O (Table 4.5, entry 6). In a dry box, a solution of **4.23** (32 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous THF (3.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at -15 ℃ for 10 minutes, followed by dropwise addition of methanesulfonyl chloride (19 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at -15 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with

silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. 1,3,5-trimethoxybenzene (50 μL of 0.40 M in $CDCl_3$, 0.020 mmol, 10 mol %) was added as standard. ^{1}H NMR of the crude mixture afforded the yield (50%) and selectivity (C2:C3:C4 = 75:6:19).

Table 4.5, entry 7. The general procedure O was followed using (−)-**4.6** (3.1 mg, 0.010 mmol, 5 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = -:1:99). Column chromatography (Hexane/EtOAc = 1:1 to 1:2) afforded the pure product **4.26c** (42 mg, 88%). **^{1}H NMR** (acetone-d6, 500 MHz) δ 5.28 (t, 1H, *J* = 1.5), 4.88 (t, 1H, *J* = 4.4), 4.56 (t, 1H, *J* = 4.2), 4.44 (d, 1H, *J* = 7.1), 4.38-4.37 (m, 2H), 4.15 (br s, 1H), 3.75 (br s, 1H), 3.60 (td, 1H, *J* = 5.1, 0.5), 3.22 (s, 3H). **^{13}C NMR** (acetone-d6, 125 MHz) δ 103.3, 75.0, 74.5, 74.0, 71.8, 64.9, 38.8. **IR**: 3458, 2937, 1340, 1172, 1132, 1055, 1000, 970, 901, 818, 525, 459 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_7H_{12}O_7S$: $[M+NH_4]^+$: 258.0648, found: 258.0652.

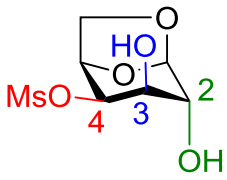
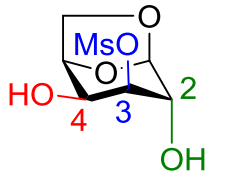


Table 4.5, entry 8. The general procedure O was followed using (+)-**4.6** (12 mg, 0.040 mmol, 20 mol %) as the catalyst. ^{1}H NMR of the crude mixture afforded the selectivity (C2:C3:C4 = -:75:25). Column chromatography (Hexane/EtOAc = 1:1 to 1:2) afforded the pure product **4.25c** (33 mg, 69%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.26 (s, 1H), 4.74 (dd, 1H, *J* = 2.9, 1.5), 4.62 (d, 1H, *J* = 6.9), 4.37 (t, 1H, *J* = 4.4), 4.24 (d, 1H, *J* = 7.3), 4.22 (dd, 1H, *J* = 6.4, 4.4), 3.83 (d, 1H, *J* = 6.9), 3.56 (t, 1H, *J* = 6.4), 3.13 (s, 3H). **^{13}C NMR** ($CDCl_3$,

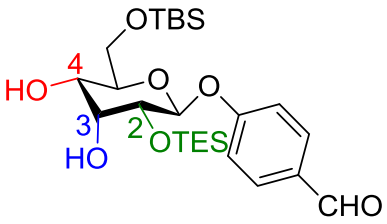


125 MHz) δ100.9, 81.2, 75.6, 72.2, 64.7, 64.1, 38.3. **IR**: 3462, 2939, 1333, 1171, 1138, 1068, 1001, 937, 849, 760, 527, 468 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_7H_{12}O_7S$: $[M+NH_4]^+$: 258.0648, found: 258.0651.

Site-Selective Functionalization of Helicid (Table 4.6).

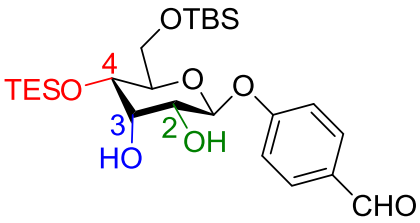
General procedure P (Table 4.6, entry 1). In a dry box, a solution of **4.27** (80 mg, 0.20 mmol), catalyst (*N*-methylimidazole, 3.2 μL, 0.040 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.0 mg, 0.0060 mmol, 3 mol %) in anhydrous *tert*-amyl alcohol (1.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of chlorotriethylsilane (40 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at 4 °C for 4 hours. MeOH (50 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flush with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography (Hexane/EtOAc = 20:1 to 3:1) afforded a mixture of mono-functionalized products (30 mg, 29%). ^{1}H NMR of the mixture afforded the selectivity (C2:C3:C4 = 65:3:32).

Table 4.6, entry 2. The general procedure P was followed using (−)-**4.6** (3.1 mg, 0.010 mmol, 5 mol %) as the catalyst. Column chromatography (Hexane/EtOAc = 20:1 to 3:1) afforded a mixture of mono-functionalized products. ^{1}H NMR of the mixture



afforded the selectivity (C2:C3:C4 = 95:5:-). A second column chromatography (Hexane/EtOAc = 20:1 to 3:1) afforded the pure product **4.28** (92 mg, 90%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.90 (s, 1H), 7.82 (d, 2H, *J* = 8.3), 7.20 (d, 2H, *J* = 8.8), 5.28 (d, 1H, *J* = 7.3), 4.2 (t, 1H, *J* = 2.9), 3.96-3.90 (m, 2H), 3.81-3.79 (m, 2H), 3.64 (s, 1H), 2.97 (d, 1H, *J* = 7.8), 2.89 (s, 1H), 0.96 (t, 9H, *J* = 7.8), 0.88 (s, 9H), 0.69 (q, 6H, *J* = 7.3), 0.04 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 191.1, 162.3, 132.0, 131.3, 116.6, 98.0, 74.5, 71.9, 71.7, 69.2, 64.2, 26.0, 18.5, 6.9, 5.0, -5.2, -5.3. **IR**: 3440, 2954, 2929, 2878, 1693, 1601, 1245, 1161, 1066, 834, 745 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{25}H_{44}O_7Si_2$: $[M+NH_4]^+$: 530.2969, found: 530.3001.

Table 4.6, entry 3. The general procedure P was followed using (+)-**4.6** (3.1 mg, 0.010 mmol, 5 mol %) as the catalyst. Column chromatography (Hexane/EtOAc = 20:1 to 3:1) afforded **4.28** (8 mg, 8%), **4.29** (11 mg, 11%), and **4.30** (65 mg, 63%), indicating the selectivity (C2:C3:C4 = 10:13:77). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.89 (s, 1H), 7.81 (d, 2H, *J* = 8.3), 7.15 (d, 2H, *J* = 8.3), 5.40 (d, 1H, *J* = 6.9), 4.18 (s, 1H), 3.89-3.83 (m, 3H), 3.74 (d, 2H, *J* = 3.4), 3.66-3.62 (m, 1H), 3.02 (s, 1H), 2.74 (s, 1H), 0.98 (t, 9H, *J* = 7.8), 0.85 (s, 9H), 0.67 (q, 6H, *J* = 8.3), -0.03 (s, 3H), -0.06 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 191.1, 162.3, 131.9, 131.3, 116.9, 98.6, 76.0, 71.1, 70.2, 68.6, 62.6, 26.0, 18.5, 6.9, 5.0, -5.1, -5.3. **IR**: 3431, 2953, 2929, 2878, 1687,



1601, 1243, 1132, 1058, 861, 832, 778, 744, 729 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{25}H_{44}O_7Si_2$: $[M+NH_4]^+$: 530.2969, found: 530.2986.

Site-Selective Silylation of Uridine and Characterization of Products:

*2'-O-TBS-5'-O-DMTr-uridine (**27**).* In a dry box, a suspension of 5'-*O*-DMTr-Uridine **4.31** (168 mg, 0.30 mmol), catalyst (-)-**4.6** (8.4 mg, 0.03 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.5 mg, 0.009 mmol, 3 mol %) in anhydrous THF (0.2 mL) was prepared in an oven-dried round-bottom flask. The suspension was brought out of the dry box, and *N,N*-diisopropylethylamine (78 μL, 0.45 mmol, 1.5 eq) was added to the stirring reaction at room temperature, followed by dropwise addition of *tert*-butyldimethylsilyl chloride (90 mg, 0.60 mmol, 2.0 eq) in THF (0.1 mL). The reaction was stirred at room temperature for 24 hours. DIPEA (30 μL) and MeOH (50 μL) was added to quench the reaction. The solvent was removed under reduced pressure. Column chromatography (Ethyl acetate/Hexane = 1:2 to 1:1) afforded the pure product 2'-*O*-TBS-5'-*O*-DMTr-uridine **4.32** (184 mg, 93%, 2':3' = >98:<2). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 9.28 (br s, 1H), 7.94 (d, 1H, *J* = 8.5), 7.38 (d, 1H, *J* = 7.0), 7.32-7.23 (m, 7H), 6.85 (d, 1H, *J* = 9.0), 5.96 (d, 1H, *J* = 3.0), 5.30 (d, 1H, *J* = 8.5), 4.37-4.34 (m, 2H), 4.11-4.10 (m, 1H), 3.80 (s, 6H), 3.54-3.48 (m, 2H), 2.59 (d, 1H, *J* = 6.0), 0.93 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 163.5, 159.0, 158.9, 150.5, 144.5, 140.4, 135.4, 135.2, 130.4, 130.3, 128.3 128.2, 127.4, 113.5, 113.5, 102.5, 88.9, 87.4, 83.7, 76.5, 70.6, 62.5, 55.4, 25.9, 18.2, -4.4, -5.0 **IR**: 3534, 2951, 2929,

1680, 1508, 1460, 1250, 1175, 1115, 1034, 908, 829, 728 cm^{-1}. **HRMS** (DART-ESI+) calcd. for $C_{36}H_{44}N_2O_8Si$: $[M+H]^+$: 661.29452, found: 661.29258.

Site-Selective Acylation of Digoxin and Characterization of Products.

*β-Acetyldigoxin (**4.34**).* In a dry box, a suspension of digoxin **4.33** (39 mg, 0.050 mmol), catalyst (+)-**4.6** (4.6 mg, 0.015 mmol, 30 mol %), and *N,N*-diisopropylethylamine hydrochloride (0.3 mg, 0.0015 mmol, 3 mol %) in anhydrous THF (2.5 mL) was prepared in an oven-dried round-bottom flask. The suspension was brought out of the dry box, and *N,N*-diisopropylethylamine (11 μL, 0.060 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at 4 ℃ for 10 minutes, followed by dropwise addition of acetyl chloride (4.3 μL, 0.060 mmol, 1.2 eq). The reaction was stirred at 4 °C for 16 hours. MeOH (12 μL) was added to quench the reaction. The solvent was removed under reduced pressure. Column chromatography (CH_2Cl_2/MeOH = 50:1 to 30:1) afforded the pure product β-acetyldigoxin **4.34** (37 mg, 90%, no α-acetyldigoxin observed). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.95 (s, 1H), 5.05-5.00 (m, 2H), 4.98-4.93 (m, 3H), 4.47 (dd, 1H, *J* = 9.8, 2.9), 4.31-4.28 (m, 3H), 4.24-4.22 (m, 1H), 4.10-4.05 (m, 2H), 3.91-3.82 (m, 2H), 3.43 (dd, 1H, *J* = 12.0, 4.2), 3.38 (d, 1H, *J* = 9.5, 6.1), 3.31 (dd, 1H, *J* = 9.5, 2.9), 3.27 (dd, 1H, *J* = 9.5, 2.9), 2.22-2.14 (m, 1H), 2.13 (s, 3H), 2.09-1.61 (m, 19H), 1.56-1.48 (m, 4H), 1.27 (d, 3H, *J* = 6.1), 1.25 (d, 3H, *J* = 6.4), 1.21 (d, 3H, *J* = 6.4), 1.00 (s, 3H), 0.83 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 178.6, 177.4, 172.2, 117.9, 100.8, 100.7, 97.1, 86.9, 83.9, 83.8, 76.8, 75.8, 75.6, 74.6, 69.6, 68.6,

68.5, 66.4, 57.4, 47.2, 42.4, 39.4, 39.1, 38.7, 38.1, 36.3, 33.8, 33.7, 31.6, 31.1, 31.0, 28.5, 27.9, 27.6, 24.4, 22.9, 21.0, 18.63, 18.60, 18.4, 10.0 **IR**: 3433, 2932, 2880, 1734, 1370, 1239, 1164, 1084, 1069, 1016, 866 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{43}H_{66}O_{15}$: $[M+Na]^+$: 845.4294, found: 845.4280.

*α-Acetyldigoxin (***4.35***).* The same procedure to produce β-acetyldigoxin was followed using (−)-**4.5** (4.2 mg, 0.015 mmol, 30 mol %) as the catalyst. Column chromatography (CH_2Cl_2/MeOH = 50:1 to 30:1) afforded the mixture of mono-acylated products with α-acetyldigoxin **4.35** as the major product (23 mg, 56%, α:β = 91:9). ^1H NMR and ^{13}C NMR spectra of the product matched with the corresponding spectra of α-acetyldigoxin obtained from Novartis. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.94 (s, 1H), 5.26 (d, 1H, *J* = 3.2), 5.03-4.89 (m, 6H), 4.30-4.27 (m, 2H), 4.05 (d, 1H, *J* = 2.2), 3.90-3.80 (m, 3H), 3.42 (dd, 1H, *J* = 11.7, 4.2), 3.37 (dd, 1H, *J* = 9.0, 5.6), 3.31 (dd, 1H, *J* = 9.5, 2.9), 3.26 (dd, 1H, *J* = 9.5, 2.9), 2.19-2.15 (m, 1H), 2.12-1.63 (m, 20H), 1.52-1.50 (m, 3H), 1.34-1.32 (m, 2H), 1.30 (d, 3H, *J* = 6.4), 1.29-1.27 (m, 2H), 1.24 (d, 3H, *J* = 1.7), 1.23 (d, 3H, *J* = 1.5), 0.99 (s, 3H), 0.82 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 179.2, 178.0, 173.0, 118.4, 101.3, 101.2, 97.6, 87.5, 84.5, 84.2, 76.4, 76.2, 75.2, 73.4, 72.9, 72.3, 70.2, 69.2, 69.0, 58.0, 47.8, 42.9, 39.6, 39.2, 38.7, 37.8, 36.9, 34.3, 34.2, 32.1, 31.7, 31.6, 29.1, 28.5, 28.2, 24.9, 23.5, 21.8, 19.3, 19.2, 10.6. **IR**: 3412, 2931, 2882, 1736, 1371, 1241, 1163, 1068, 1017m 866 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{43}H_{66}O_{15}$: $[M+Na]^+$: 845.4294, found: 845.4303.

Site-Selective Mesylation of Mupirocin and Characterization of Products.

*6-Mesyl mupirocin methyl ester (***4.37***).* In a dry box, a solution of mupirocin methyl ester **4.36** (51 mg, 0.10 mmol), catalyst (−)-**4.6** (6.1 mg, 0.020 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (0.5 mg, 0.0030 mmol, 3 mol %) in anhydrous THF (0.5 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (21 μL, 0.12 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at -15 ℃ for 10 minutes, followed by dropwise addition of methanesulfonyl chloride (9.3 μL, 0.12 mmol, 1.2 eq). The reaction was stirred at -15 °C for 20 hours. MeOH (25 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flushing with EtOAc (8 mL). The solvent was removed under reduced pressure. Selectivity of the reaction was determined by ^{1}H NMR in the crude reaction mixture (C6:C7 = >98:<2). Column chromatography (Hexane/EtOAc = 1:1 to 1/2) afforded the pure product **4.37** (49 mg, 82%). **^{1}H NMR** δ 5.73 (s, 1H), 4.53 (dd, 1H, *J* = 7.8, 2.5), 4.23-4.22 (m, 1H), 4.09-4.03 (m, 3H), 3.92 (dd, 1H, *J* = 12, 3.4), 3.84-3.81 (m, 1H), 3.67 (s, 3H), 3.59 (dd, 1H, *J* = 12, 3.4), 3.11 (s, 3H), 2.80-2.78 (m, 1H), 2.72 (dd, 1H, *J* = 7.8, 2.0), 2.56 (d, 1H, *J* = 3.9), 2.44 (dd, 1H, *J* = 14, 3.4), 2.36-2.30 (m, 3H), 2.24 (d, 1H, *J* = 3.4), 2.20 (d, 3H, *J* = 1.0), 2.13-2.11 (m, 1H), 1.85-1.80 (m, 1H), 1.69 (q, 1H, *J* = 7.4), 1.64-1.60 (m, 4H), 1.36-1.31 (m, 9H), 1.21 (d, 3H, *J* = 6.4), 0.95 (d, 3H, *J* = 7.3). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 174.5, 166.7, 154.9, 118.6, 79.2, 72.4, 71.5, 69.3, 65.8, 64.1, 61.5, 55.7, 51.7, 43.1, 42.6, 39.8, 39.1, 34.3, 31.9,

29.4, 29.3, 29.2, 28.9, 26.2, 25.1, 20.9, 19.0, 13.0. **IR**: 3500, 2933, 2858, 1714, 1649, 1455, 1438, 1353, 1226, 1175, 1152, 1116, 965, 942, 856, 529 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{28}H_{48}O_{11}S$: $[M+H]^+$: 593.2996, found: 593.2977.

*7-Mesyl mupirocin methyl ester (***4.38***)*. In a dry box, a solution of mupirocin methyl ester **4.36** (618 mg, 1.2 mmol), catalyst (+)-**4.5** (68 mg, 0.24 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (6.0 mg, 0.036 mmol, 3 mol %) in anhydrous THF (6.0 mL) was prepared in an oven-dried glass reaction vial. The solution was brought out of the dry box, and *N,N*-diisopropylethylamine (251 μL, 1.44 mmol, 1.2 eq) was added to the stirring reaction at room temperature. The reaction was stirred at -15 ℃ for 10 minutes, followed by dropwise addition of methanesulfonyl chloride (111 μL, 1.44 mmol, 1.2 eq). The reaction was stirred at -15 °C for 20 hours. MeOH (300 μL) was added to quench the reaction. The mixture was filtered through a Pasteur pipette packed with silica gel, followed by flushing with EtOAc (90 mL). The solvent was removed under reduced pressure. Selectivity of the reaction was determined by ^{1}H NMR in the crude reaction mixture (C6:C7 = 18:82). Column chromatography (Hexane/EtOAc = 1:1 to 2/5) afforded the pure product **4.38** (403 mg, 57%). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 5.75 (s, 1H), 5.04 (br s, 1H), 4.07 (t, 2H, *J* = 6.9), 3.86-3.82 (m, 2H), 3.70-3.3.65 (m, 5H), 3.61-3.59 (m, 1H), 3.15 (s, 3H), 2.81 (td, 1H, *J* = 5.9, 2.0), 2.78 (dd, 1H, *J* = 7.3, 2.5), 2.65 (d, 1H, *J* = 14), 2.36 (d, 1H, *J* = 6.8), 2.32-2.26 (m, 4H), 2.21 (s, 3H), 1.85-1.81 (m, 1H), 1.79-1.74 (m, 1H), 1.65-1.60 (m, 4H), 1.45 (q, 1H, *J* = 6.8), 1.38-1.28 (m, 9H), 1.24 (d, 3H, *J* = 6.4), 0.93 (d, 3H, *J* = 6.9). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 174.5, 166.8,

156.1, 118.1, 81.4, 75.4, 71.6, 67.6, 65.8, 64.1, 61.0, 54.8, 51.7, 42.9, 42.6, 39.6, 38.8, 34.3, 32.0, 29.3, 29.2, 29.1, 29.0, 26.2, 25.1, 21.3, 19.5, 12.6. **IR**: 3496, 2401, 2930, 2861, 1736, 1714, 1649, 1457, 1352, 1225, 1174, 1151, 1112, 968, 874, 548 cm^{-1}. **HRMS** (DART-TOF) calcd. for $C_{28}H_{48}O_{11}S$: $[M+H]^+$: 593.2996, found: 593.2980.

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Appendix 1

Spectras for Compound Characterizations.

HO
Me
O
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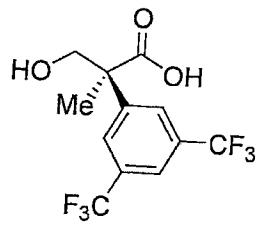
1
ppm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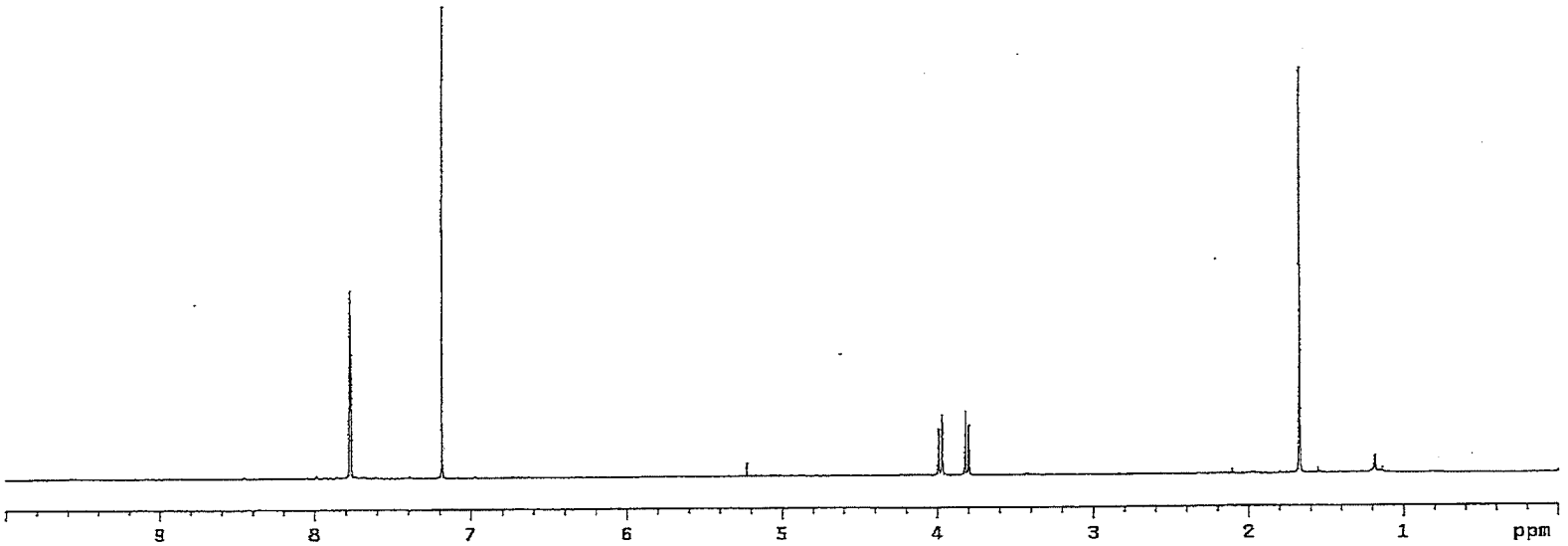
HO
OH
Me
CF3
F3C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8
7
6
5
4
3
2
1
ppm

ppm
1
2
3
4
5
6
7
8
9

HO
Me
O
OH
OMe

9
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6
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4
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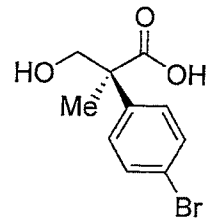
2
1
ppm

HO
Me
O
OH
Cl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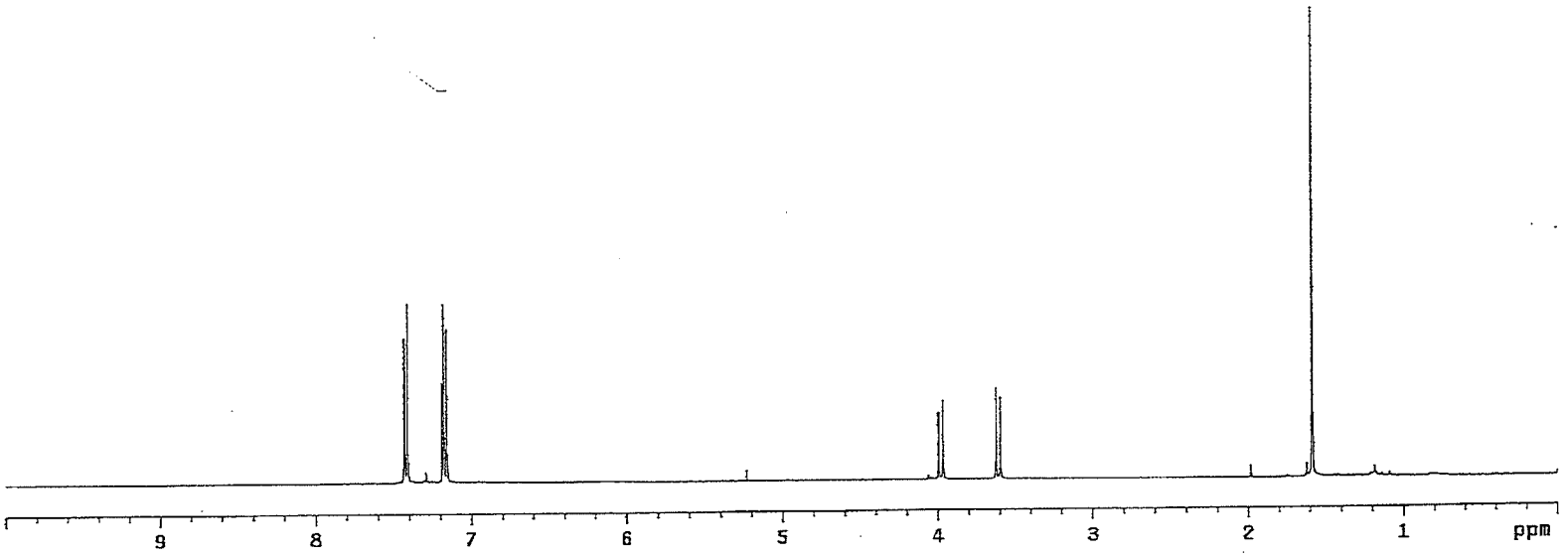
Me
Br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ppm

HO
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O
OH
Cl

9
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7
6
5
4
3
2
1
ppm

HO
Me
O
OH
CO2Me

9
8
7
6
5
4
3
2
1
ppm

9
8
7
6
5
4
3
2
1
ppm

HO
Me
O
OH
CN

ppm
1
2
3
4
5
6
7
8
9

HO
Me
O
OH

ppm
1
2
3
4
5
6
7
8
9

HO
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OH

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HO
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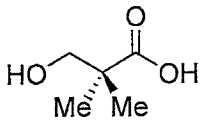
N
O
OH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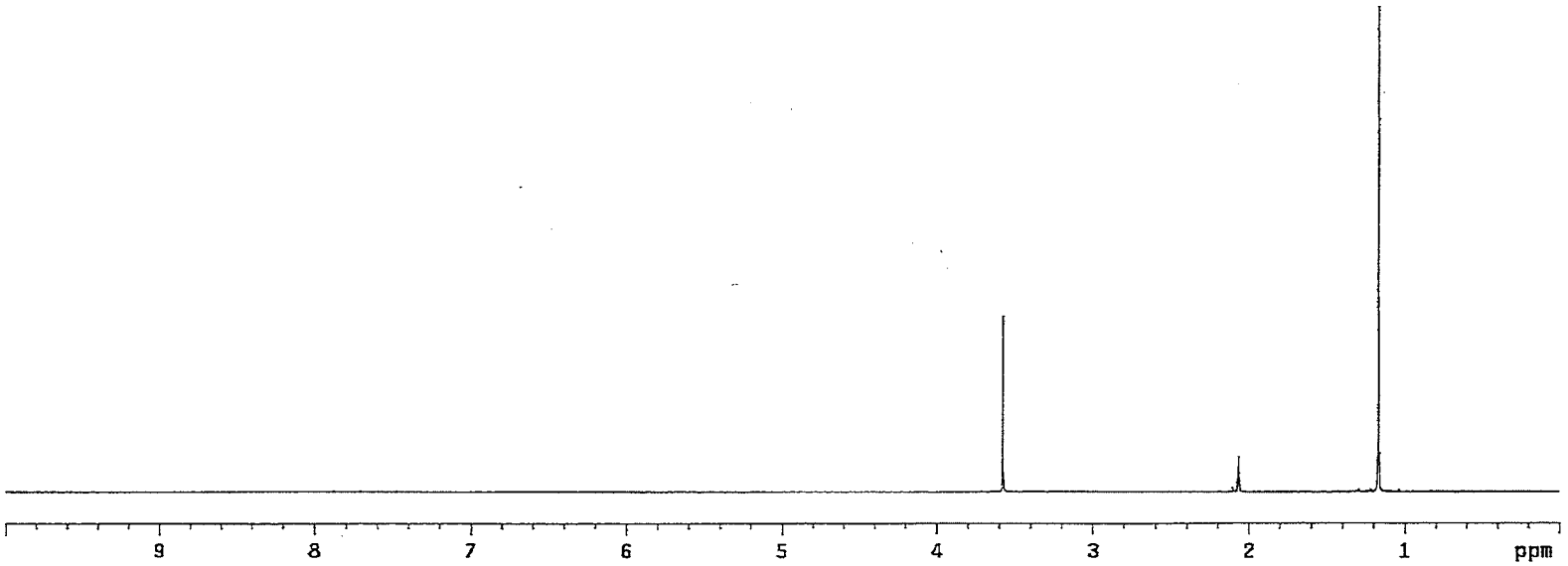
HO
OH
Me
Me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ppm

ppm
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2
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6
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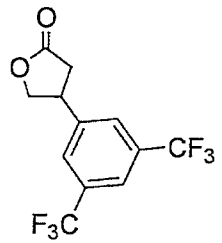
8
9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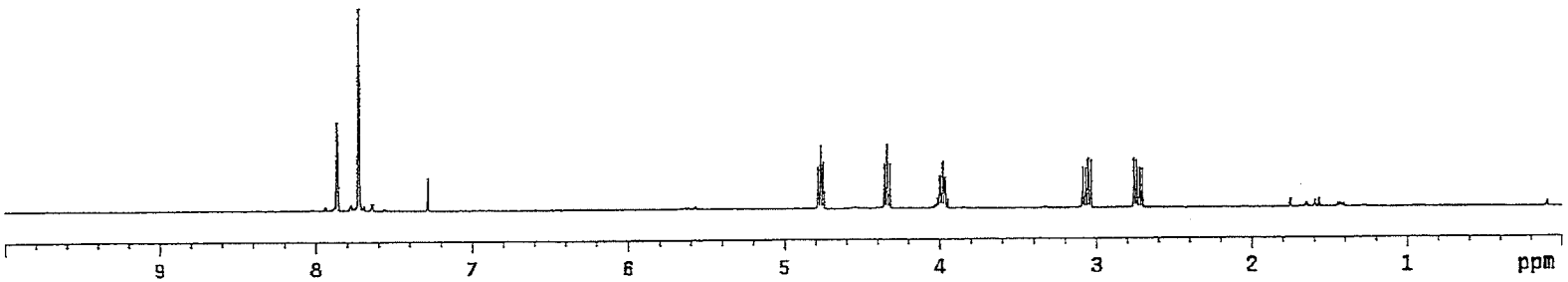
O
CF3
F3C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4
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ppm

9
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7
6
5
4
3
2
1
ppm
OMe
O
O

9
8
7
6
5
4
3
2
1
ppm

O
O
Cl

ppm
1
2
3
4
5
6
7
8
9

O
O
Br

ppm
1
2
3
4
5
6
7
8
9

O
O
Cl

ppm
1
2
3
4
5
6
7
8
9

O
O
CO2Me

9
8
7
6
5
4
3
2
1
ppm

O
O
CN

9
8
7
6
5
4
3
2
1
ppm

O
O

ppm
9
8
7
6
5
4
3
2
1

O
O
S

9
8
7
6
5
4
3
2
1
ppm

O
O
N

HO
Me
Ph
O
O
9
8
7
6
5
4
3
2
1
ppm

7
6
5
4
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1
ppm

MeN
N
NH
OH

140
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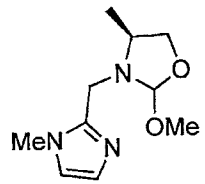
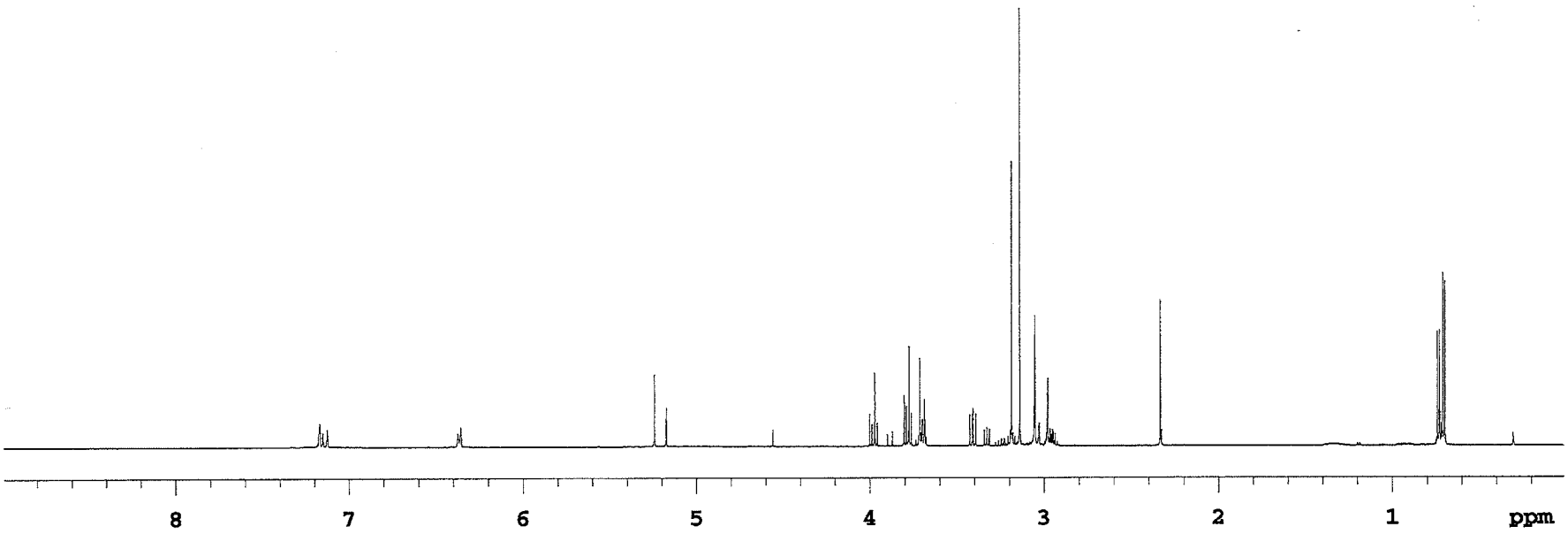
100
80
60
40
20
ppm

MeN
N
NH
OH


N
O
OMe
MeN
N

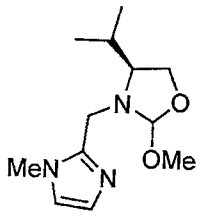

8
7
6
5
4
3
2
1
ppm

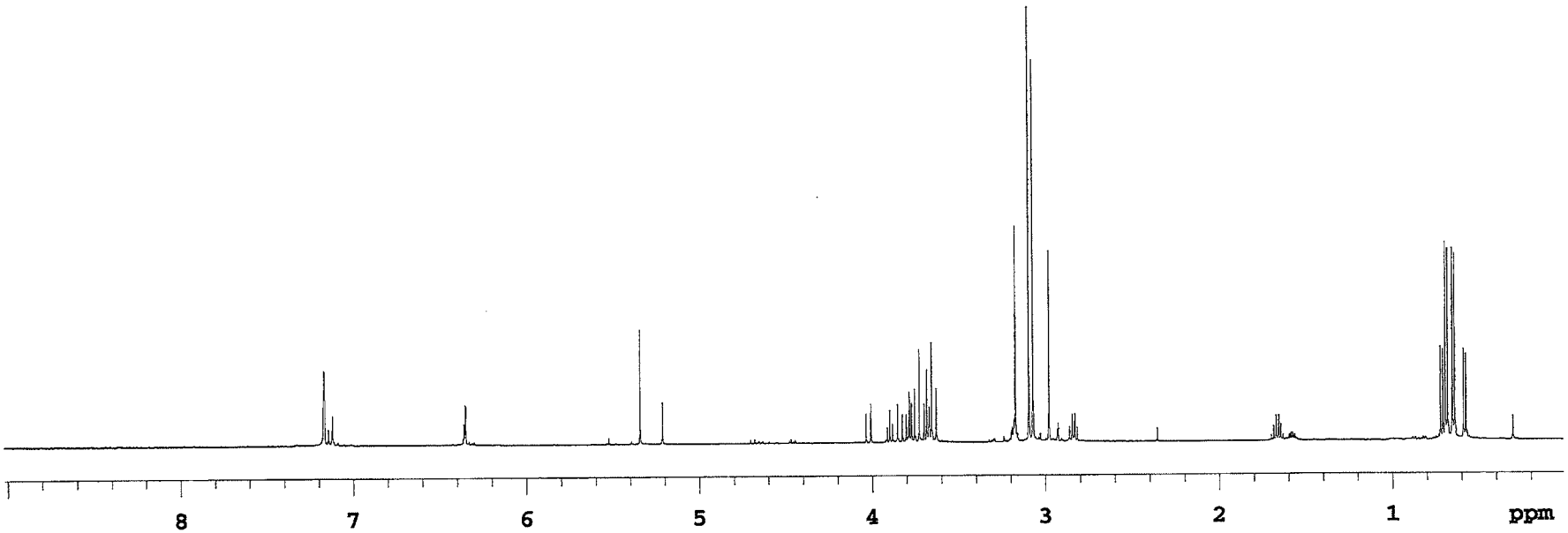
140
120
100
80
60
40
20
ppm
MeN
N
N
OMe
O

9
8
7
6
5
4
3
2
1
ppm

MeN
N
NH
OH

147.425
126.902
121.325
77.485
77.230
76.975
65.068
61.645
44.005
32.658
29.978
19.512
19.012
220
200
180
160
140
120
100
80
60
40
20
0
ppm
MeN
N
NH
OH


MeN
N
N
O
OMe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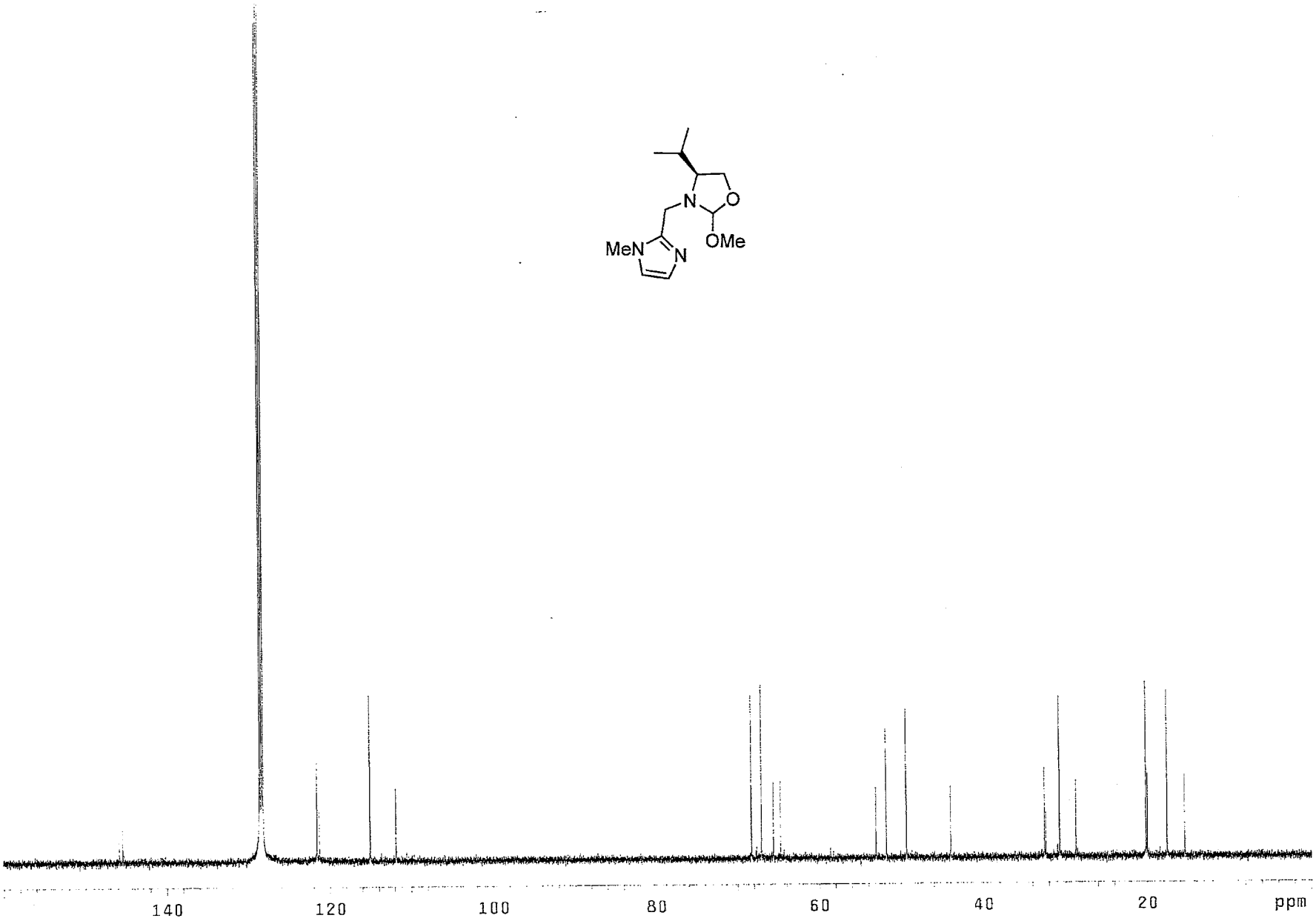
7
6
5
4
3
2
1
ppm


N
O
OMe
MeN
N
140
120
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80
60
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20
ppm

MeN
N
NH
OH

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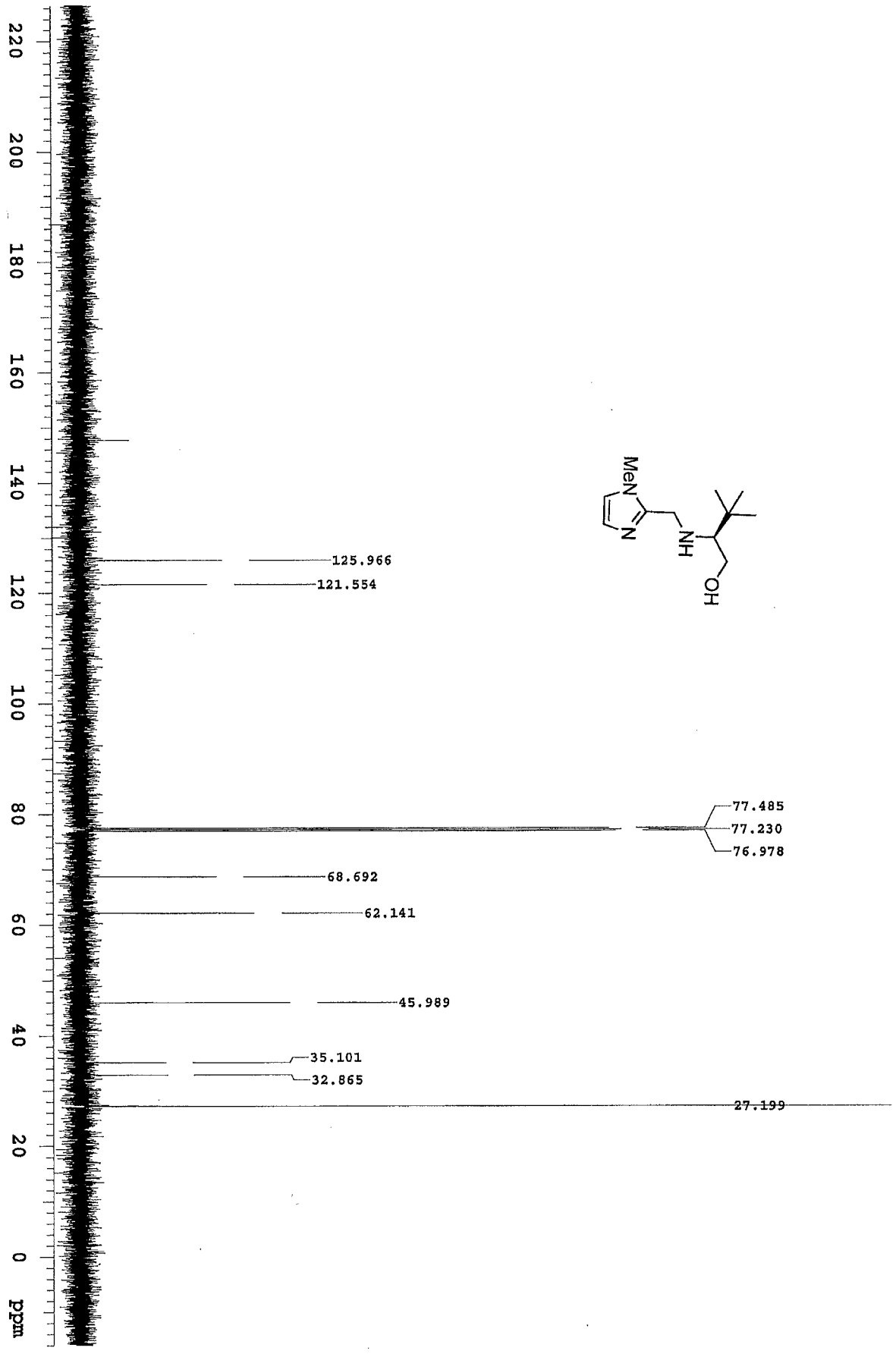
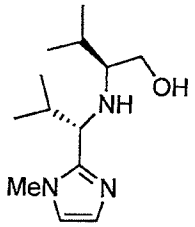
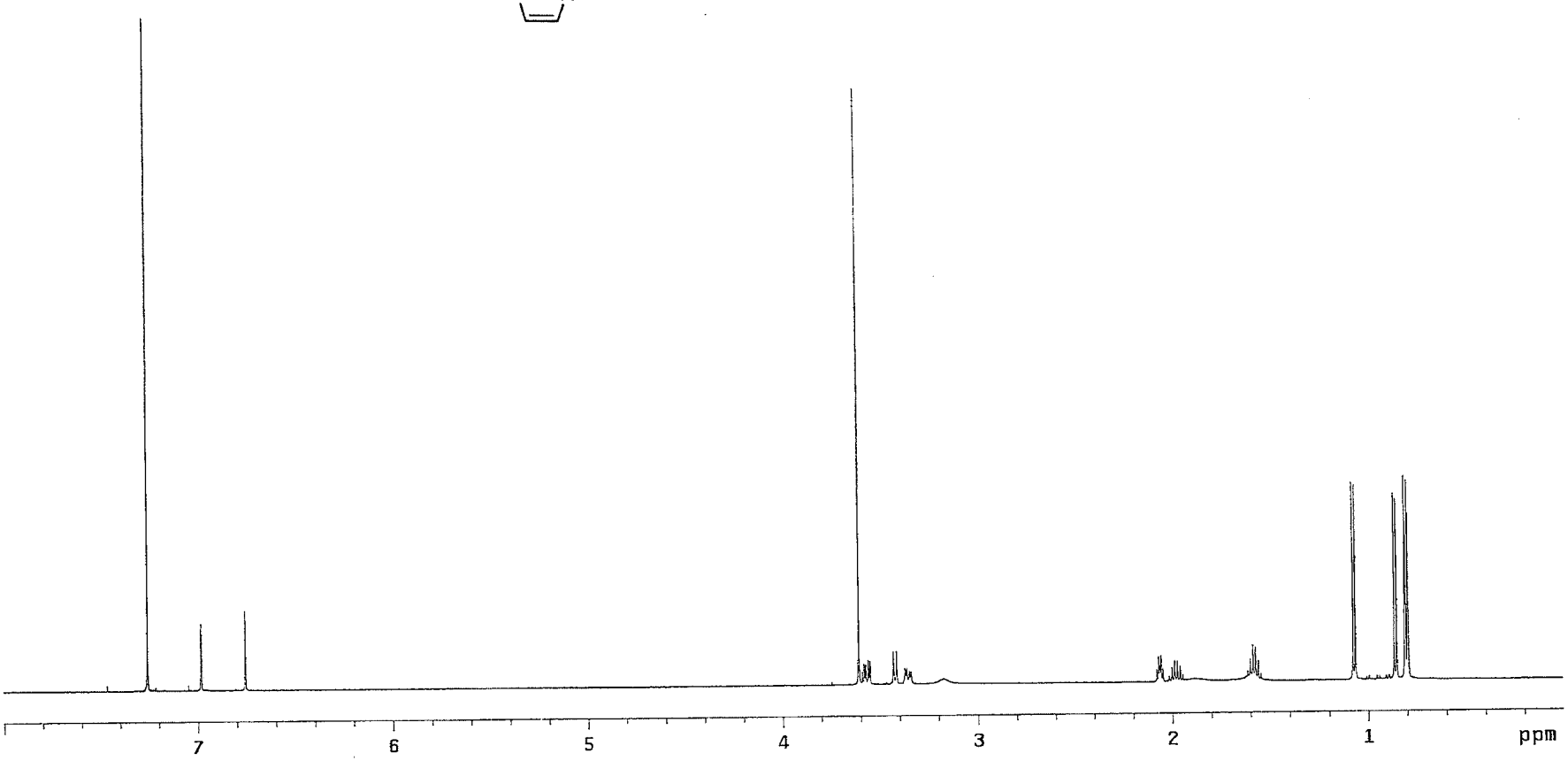
8
7
6
5
4
3
2
1
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm
125.966
121.554
77.485
77.230
76.978
68.692
62.141
45.989
35.101
32.865
27.199
MeN
N
NH
OH

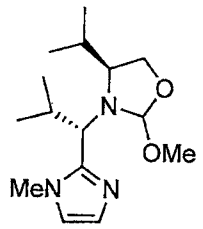
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

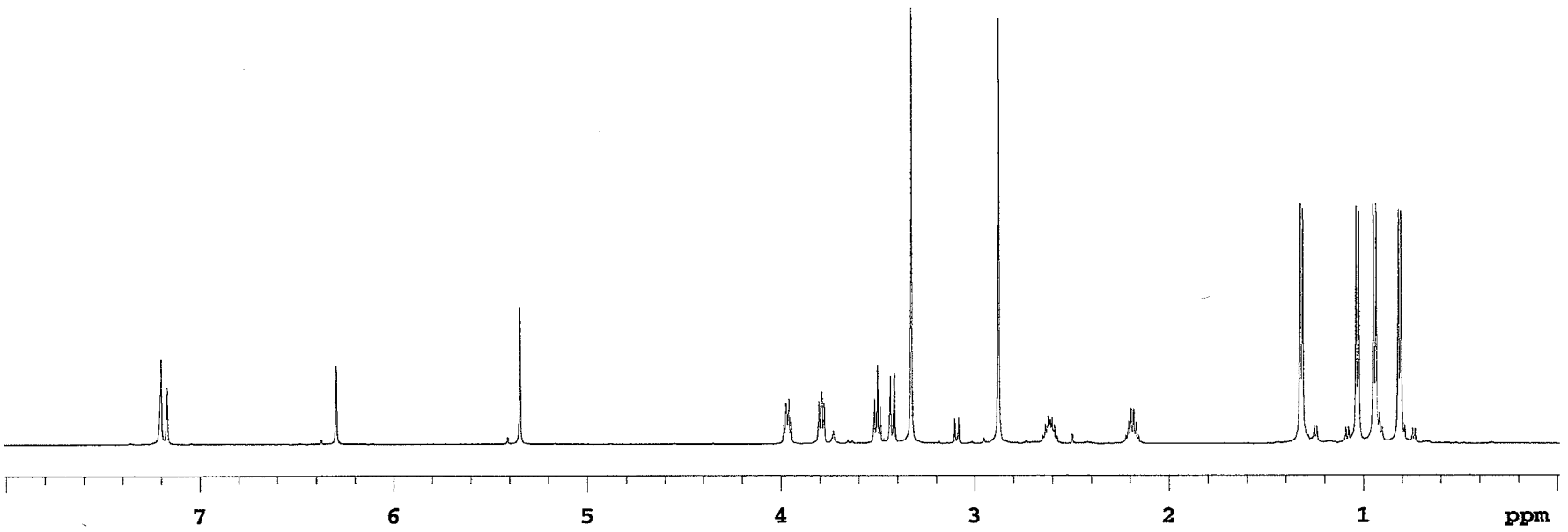
MeN
N
N
O
OMe

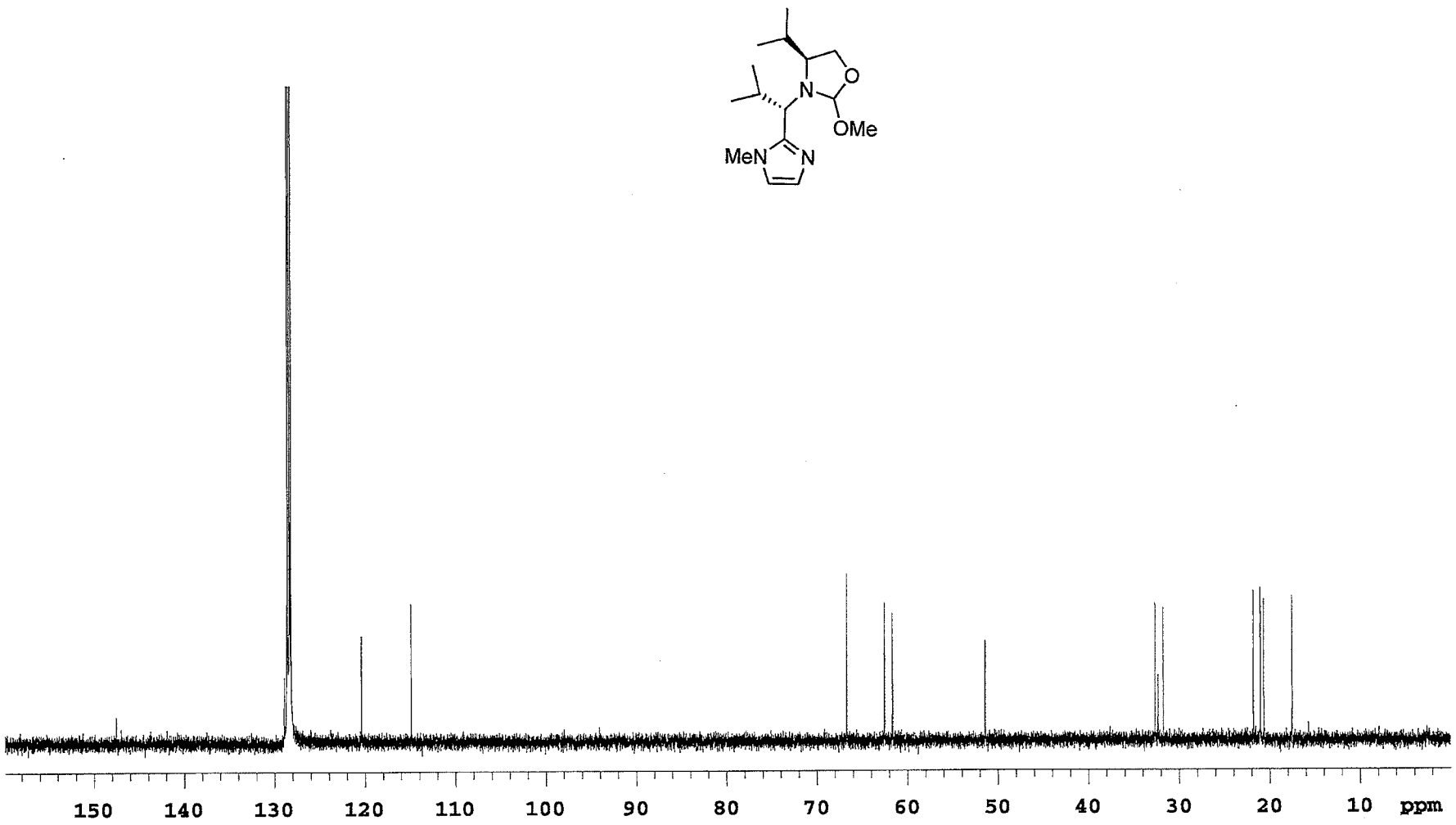

OH
NH
MeN
N


7
6
5
4
3
2
1
ppm

140
120
100
80
60
40
20
0
ppm
MeN
N
NH
OH

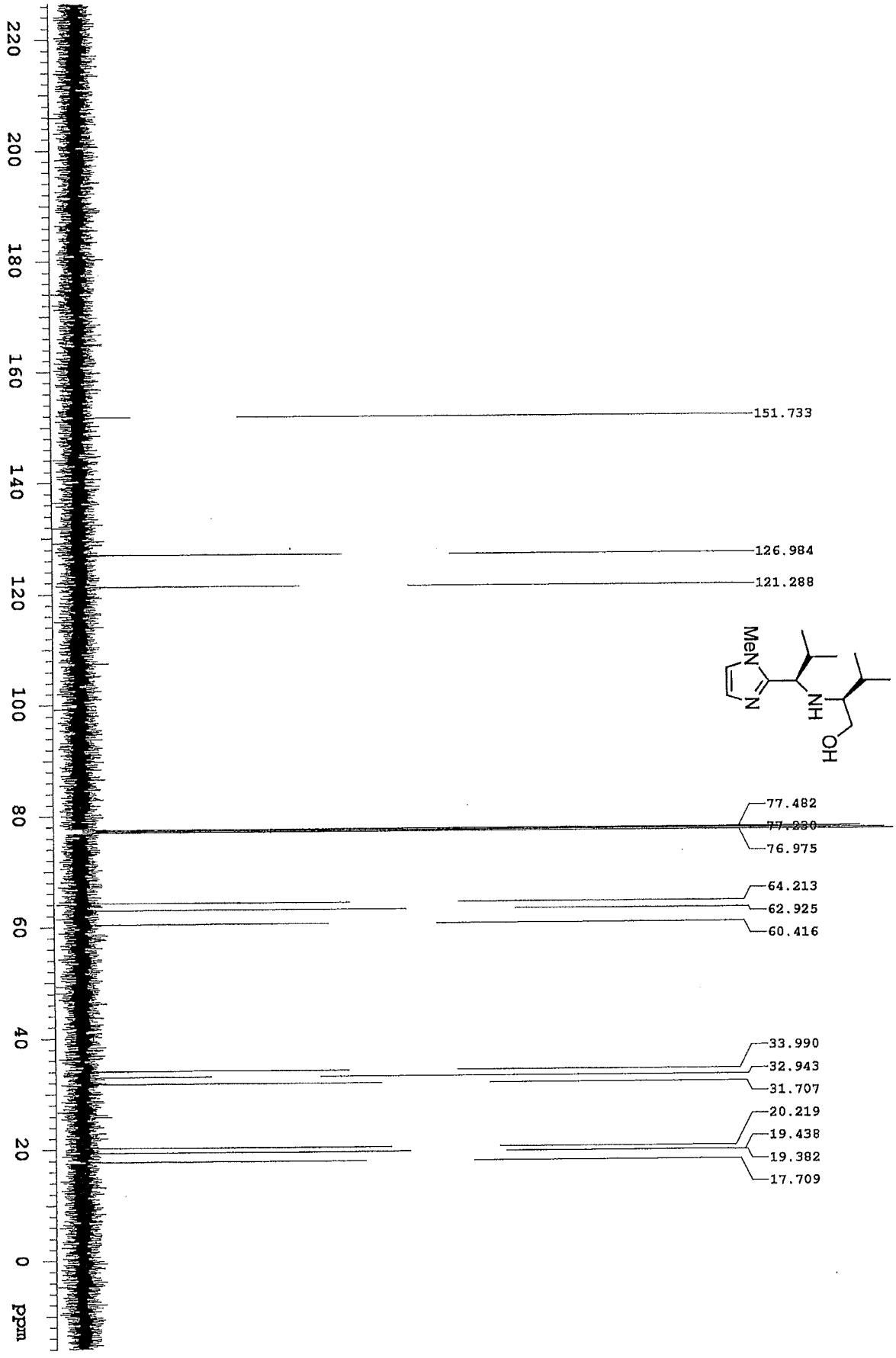

O
N
OMe
MeN
N


7
6
5
4
3
2
1
ppm


N
O
OMe
MeN
N
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

9
8
7
6
5
4
3
2
1
ppm

MeN
N
NH
OH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140
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100
80
60
40
20
0
ppm
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126.984
121.288
MeN
N
NH
OH
77.482
77.280
76.975
64.213
62.925
60.416
33.990
32.943
31.707
20.219
19.438
19.382
17.709

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8
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6
5
4
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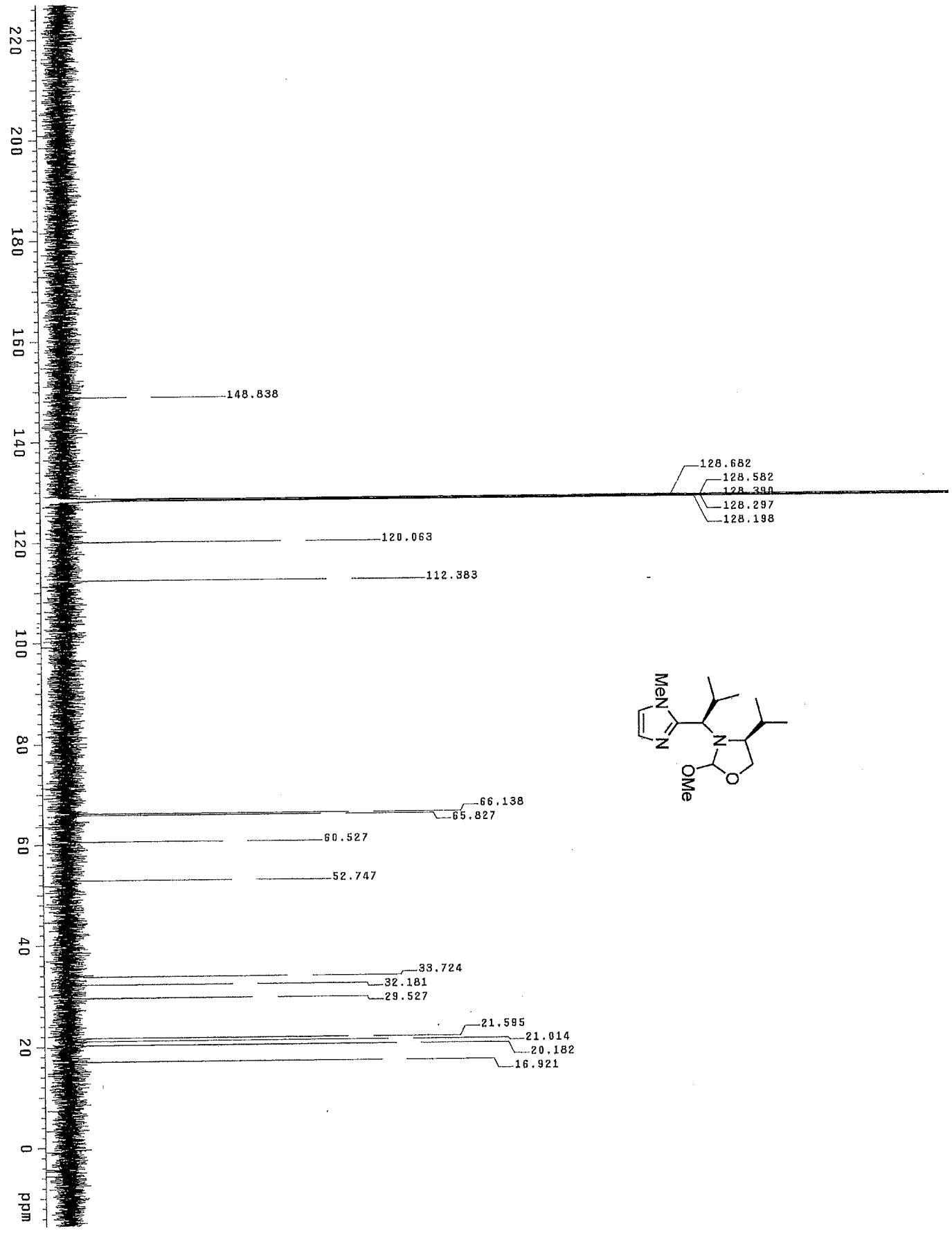
2
1
ppm

MeN
N
N
O
OMe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128.682
128.582
128.390
128.297
128.198
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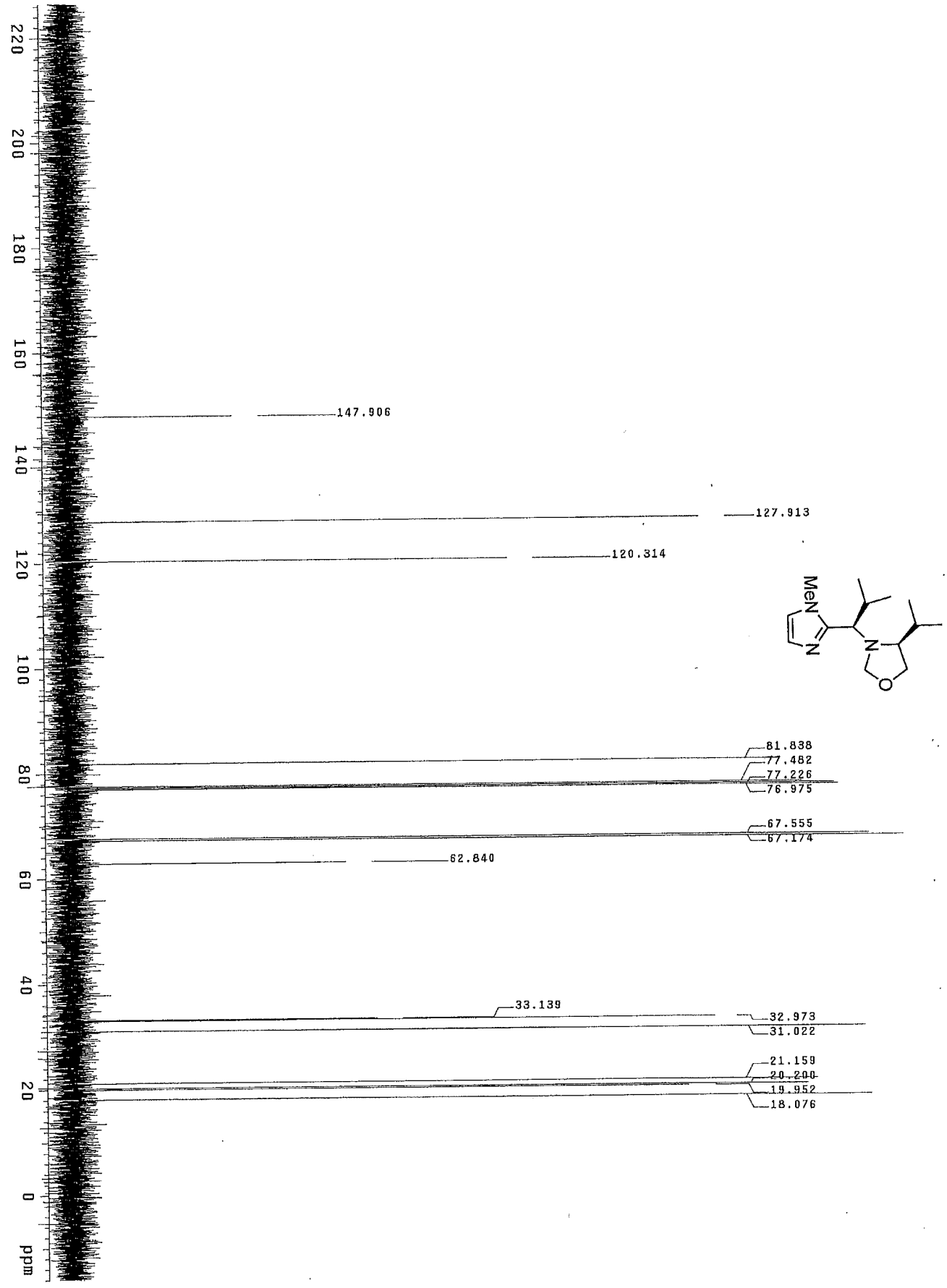
112.383
66.138
65.827
60.527
52.747
33.724
32.181
29.527
21.595
21.014
20.182
16.921
MeN
N
N
O
OMe
220
200
180
160
140
120
100
80
60
40
20
0
ppm

ppm
1
2
3
4
5
6
7
8
9
MeN
N
N
O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120.314
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77.482
77.226
76.975
67.555
67.174
62.840
33.139
32.973
31.022
21.159
20.200
19.952
18.076
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N
N
O
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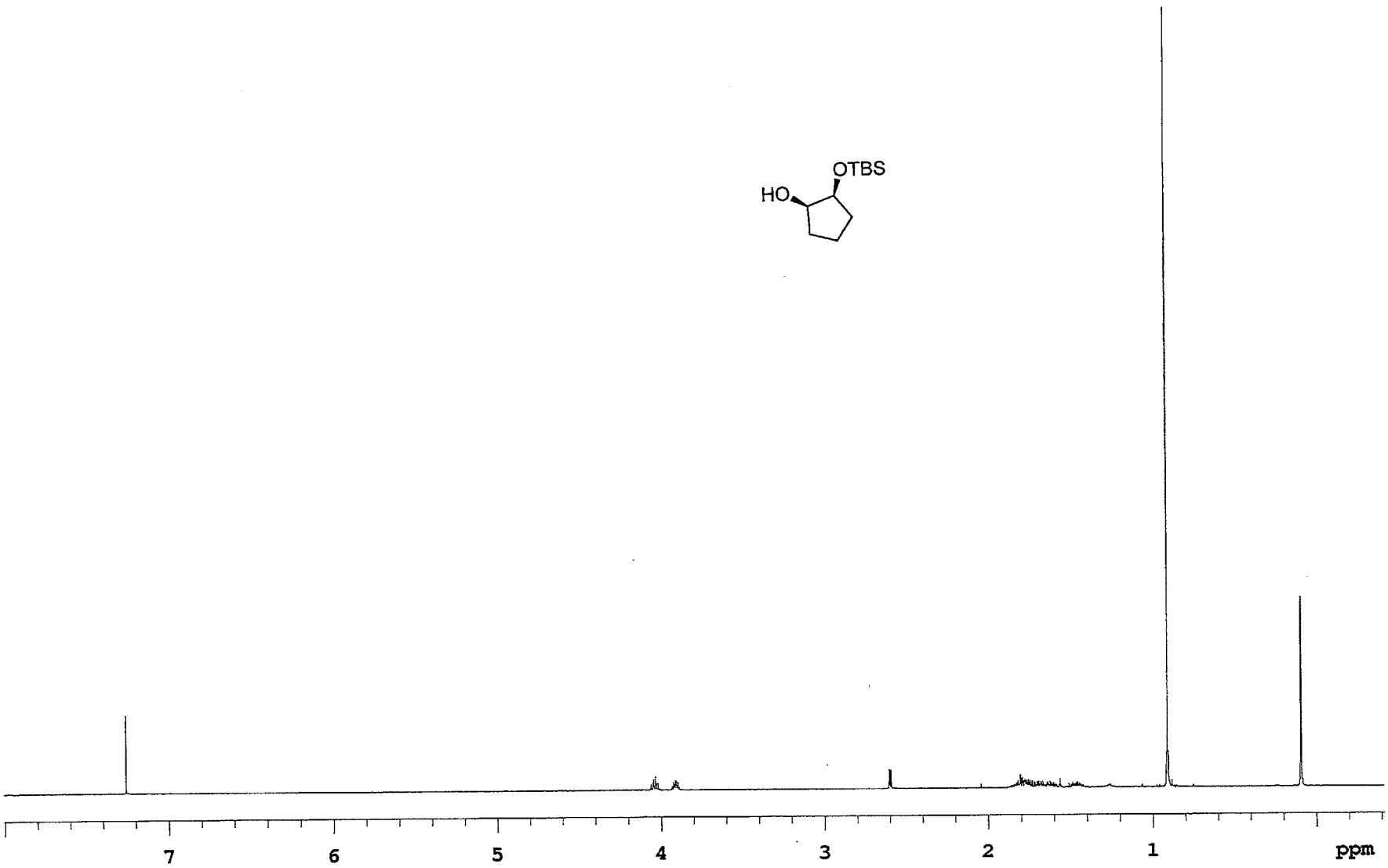
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
HO
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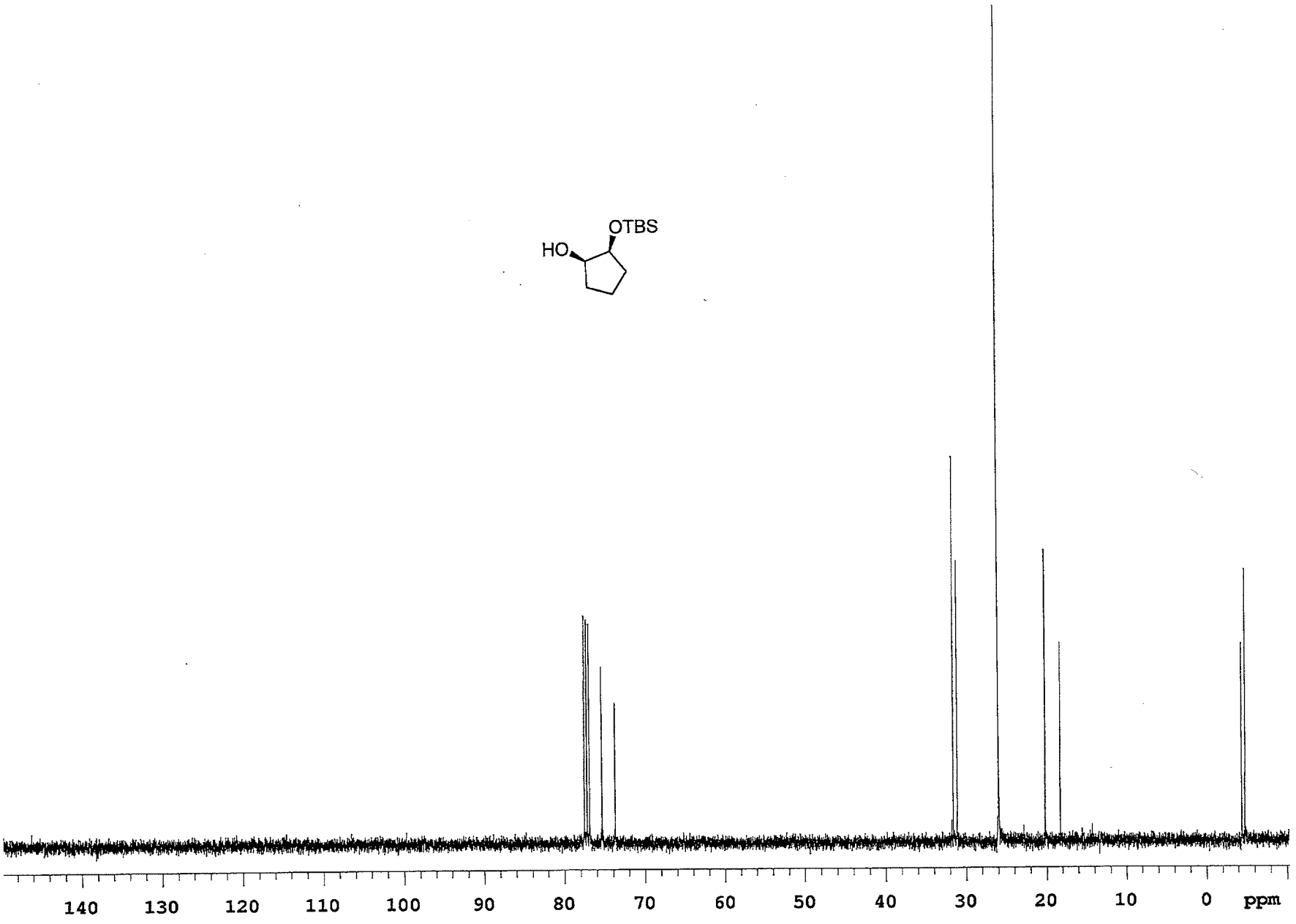
6
5
4
3
2
1
ppm


OTBS
HO
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110
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90
80
70
60
50
40
30
20
10
0
ppm

ppm
1
2
3
4
5
6
7
8
9

HO
OTBS
O

220
200
180
160
140
120
100
80
60
40
20
0
ppm
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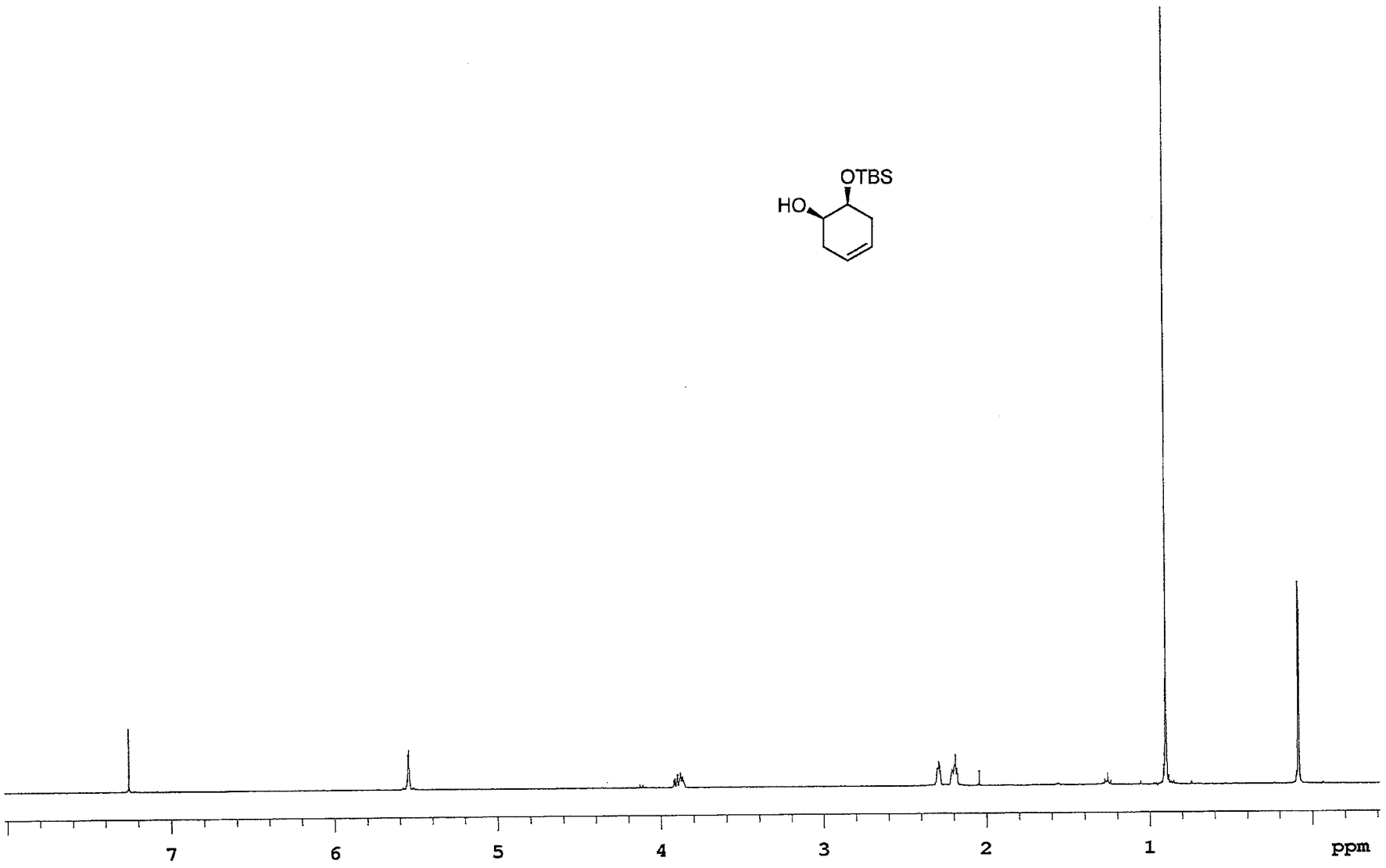
HO
OTBS
O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HO
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6
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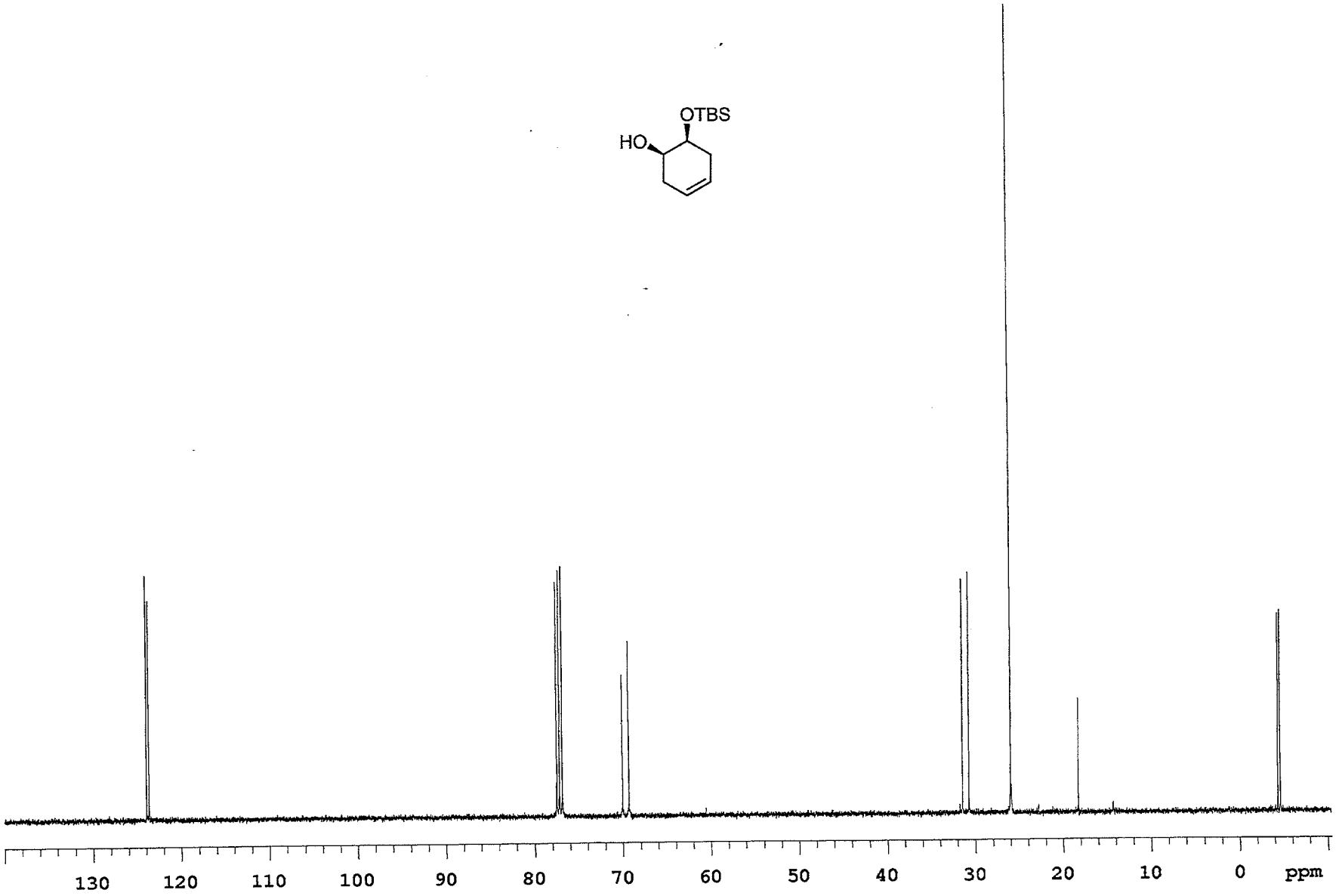
3
2
1
ppm


OTBS
HO
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120
110
100
90
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50
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30
20
10
0
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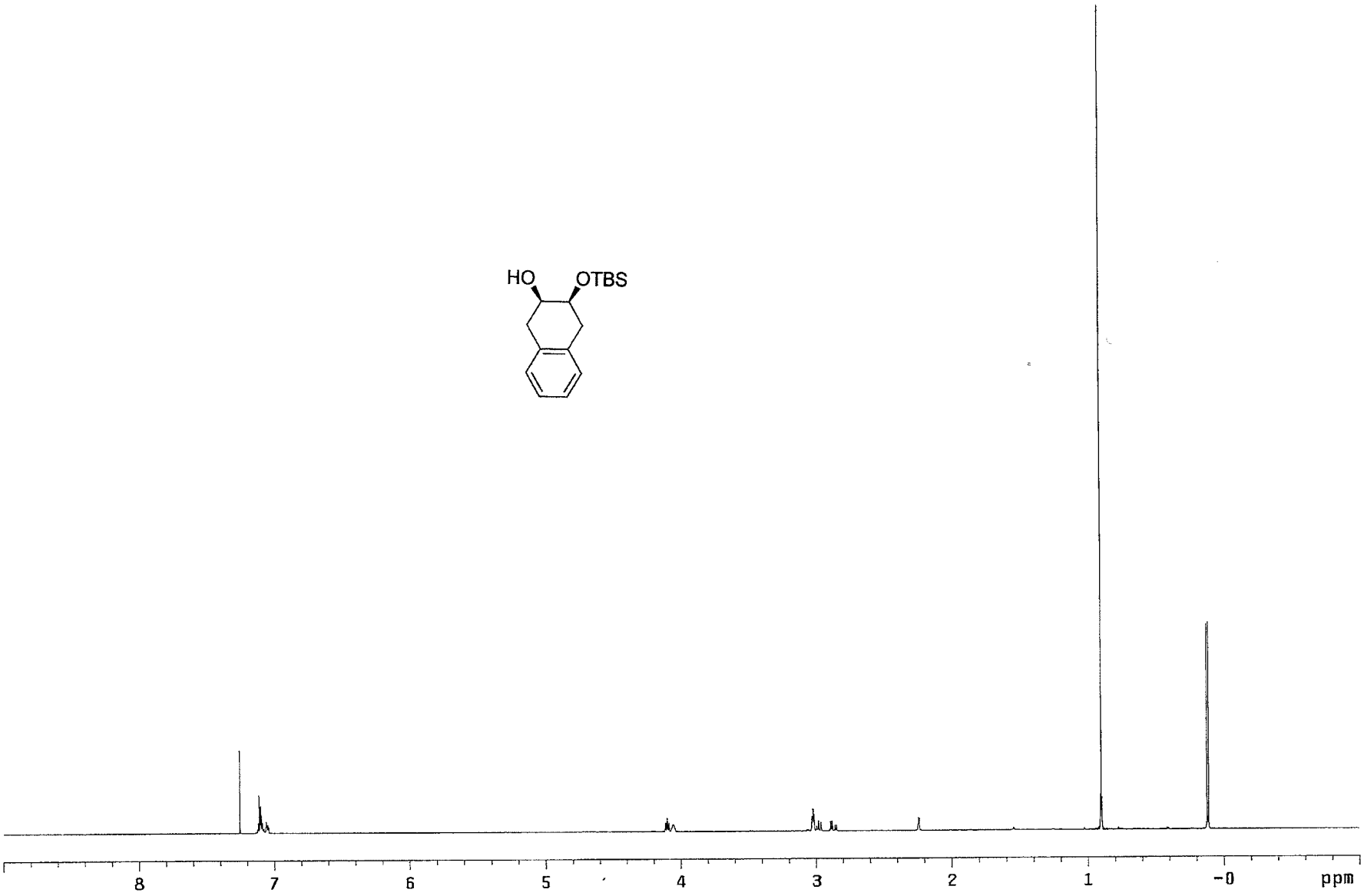
HO
OTBS
8
7
6
5
4
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1
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ppm

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200
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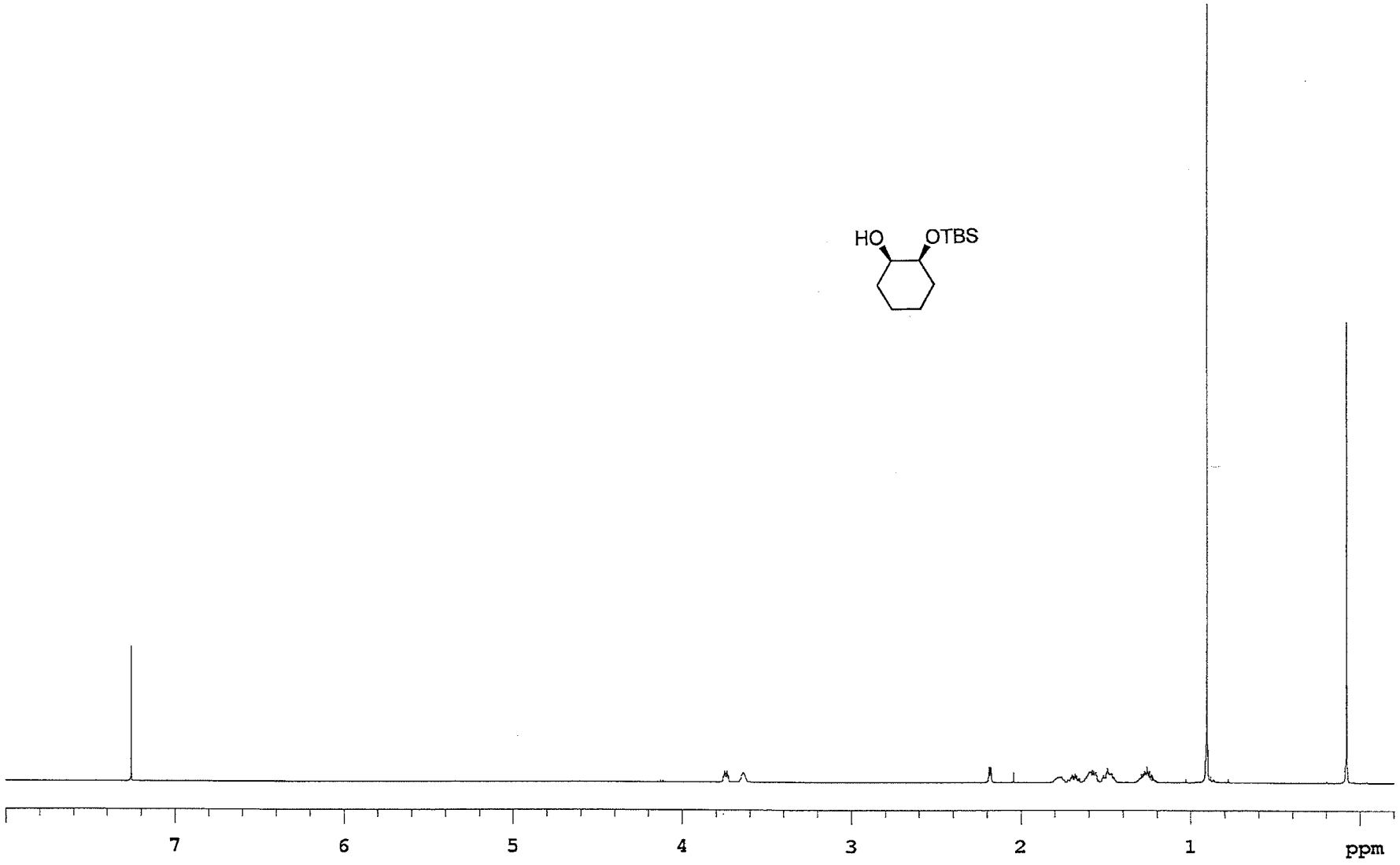
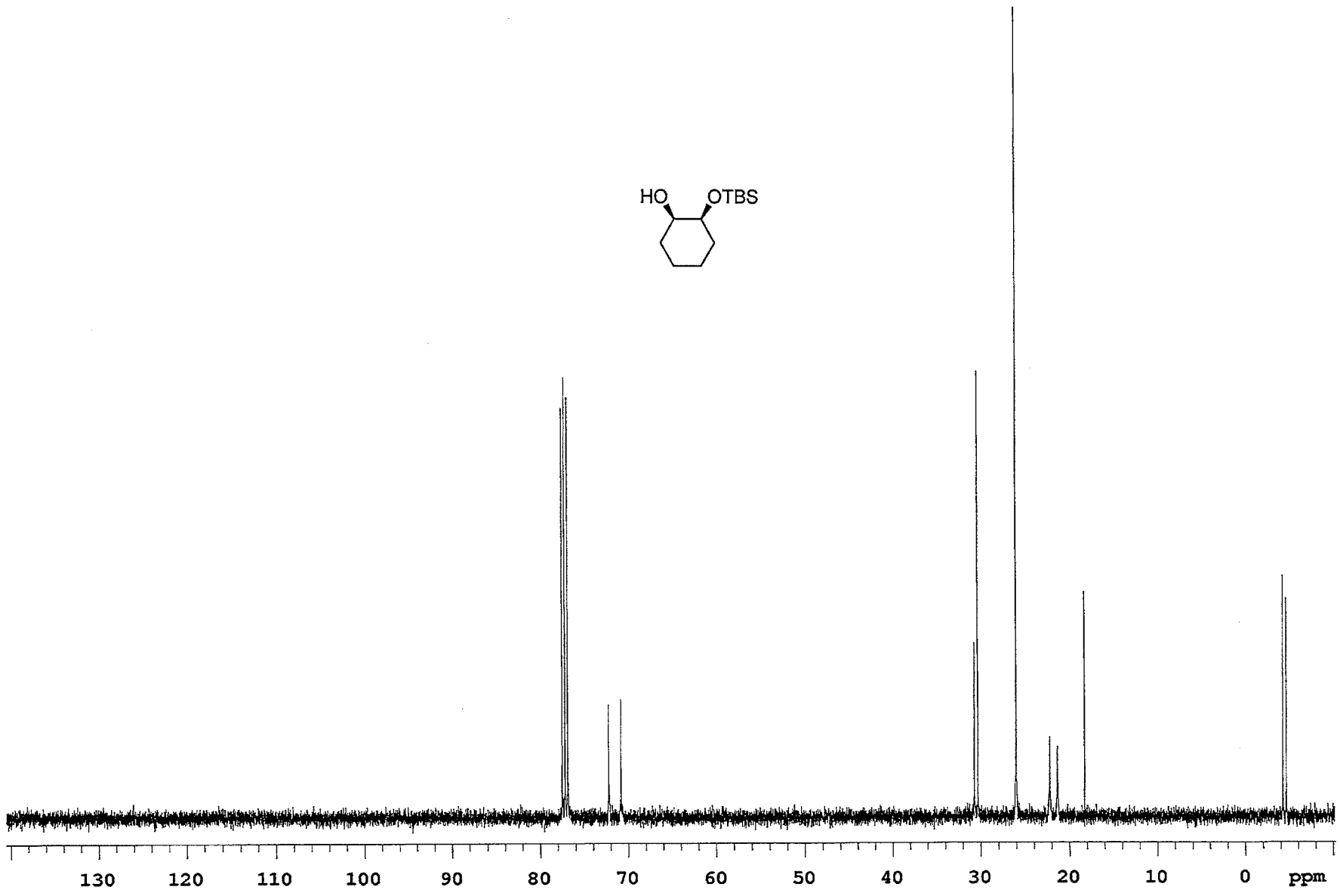
160
140
120
100
80
60
40
20
0
ppm
HO
OTBS


HO
OTBS
7
6
5
4
3
2
1
ppm


HO
OTBS
130
120
110
100
90
80
70
60
50
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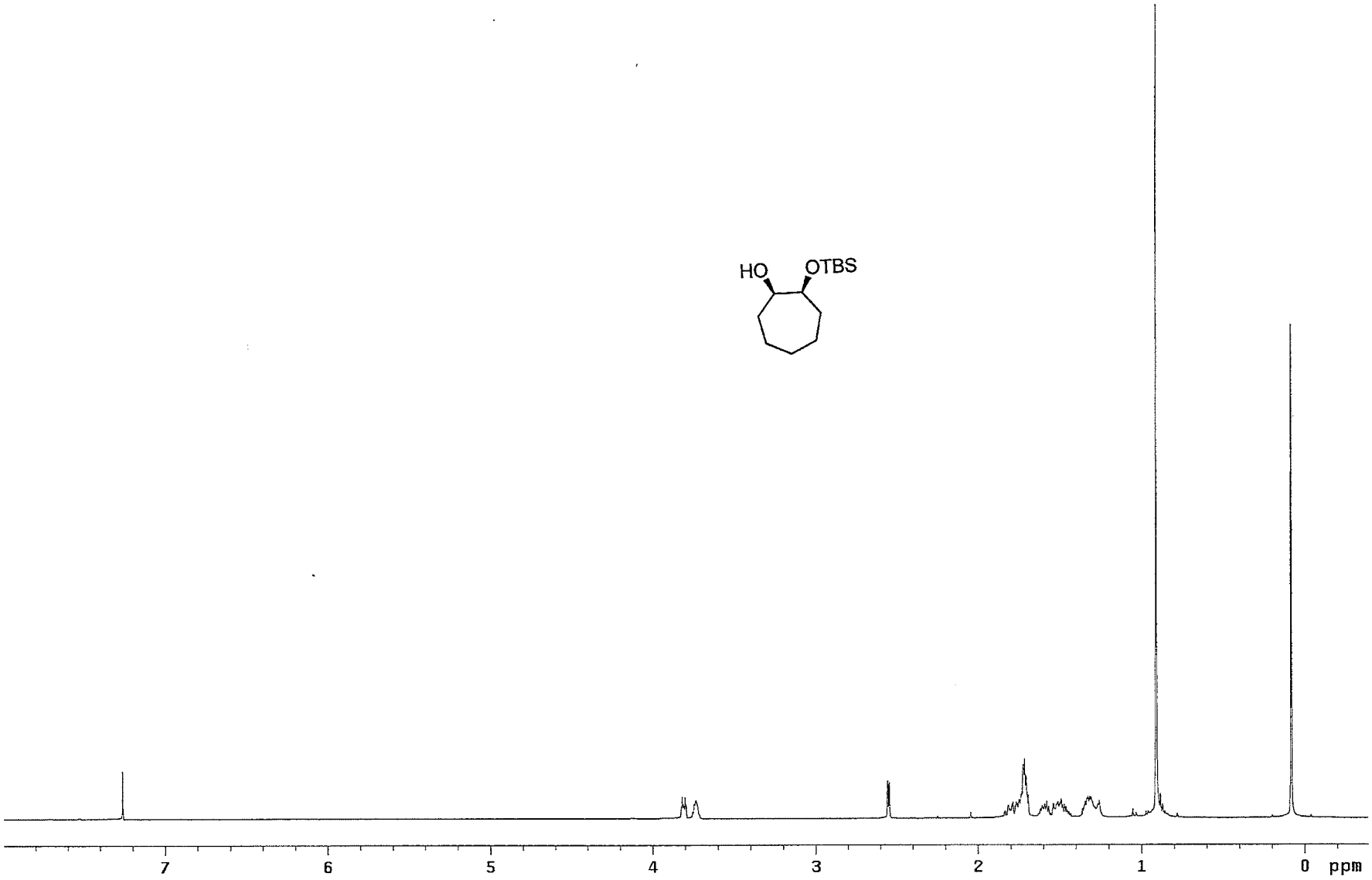
30
20
10
0
ppm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OTBS
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6
5
4
3
2
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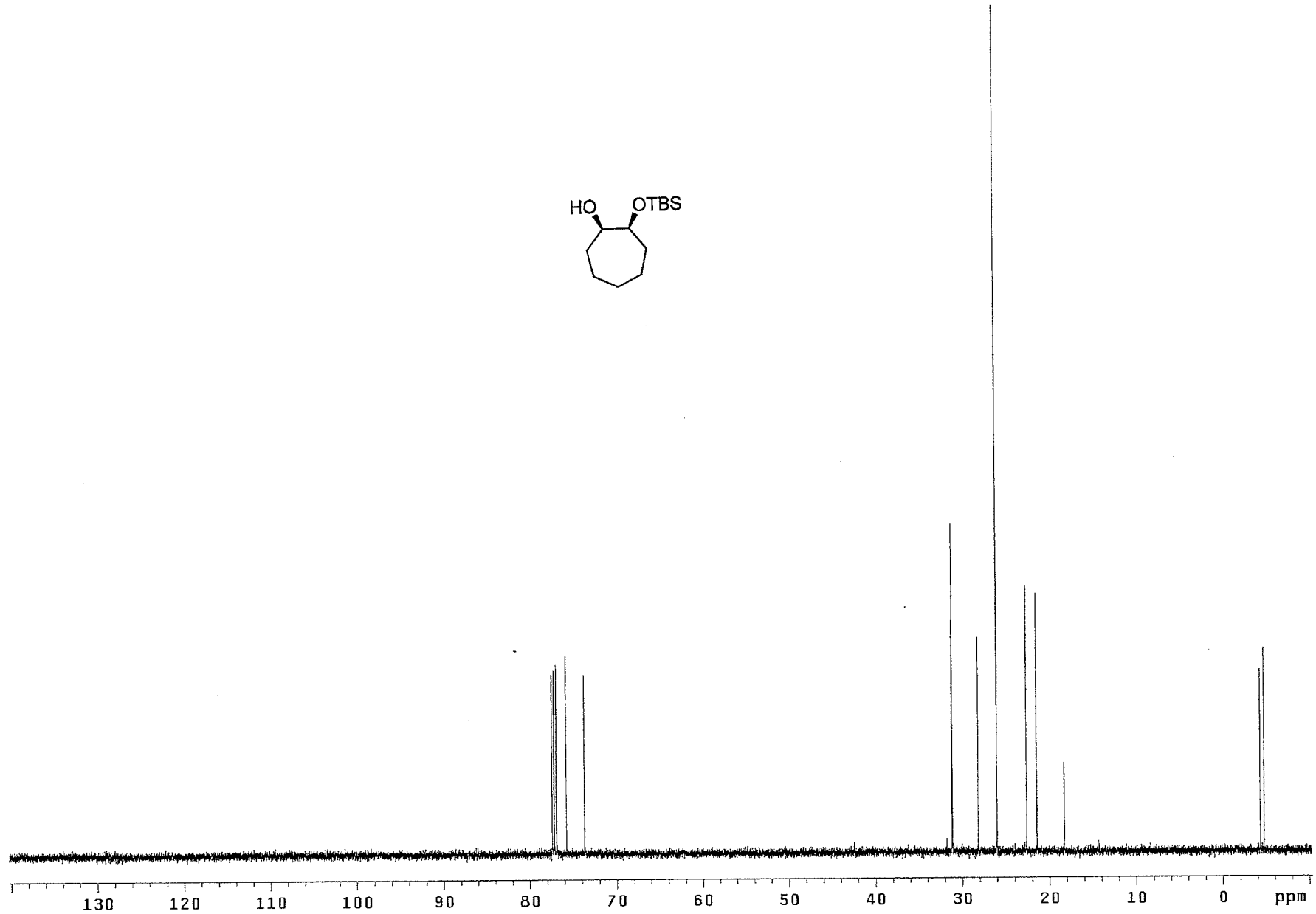
0
ppm


HO
OTBS
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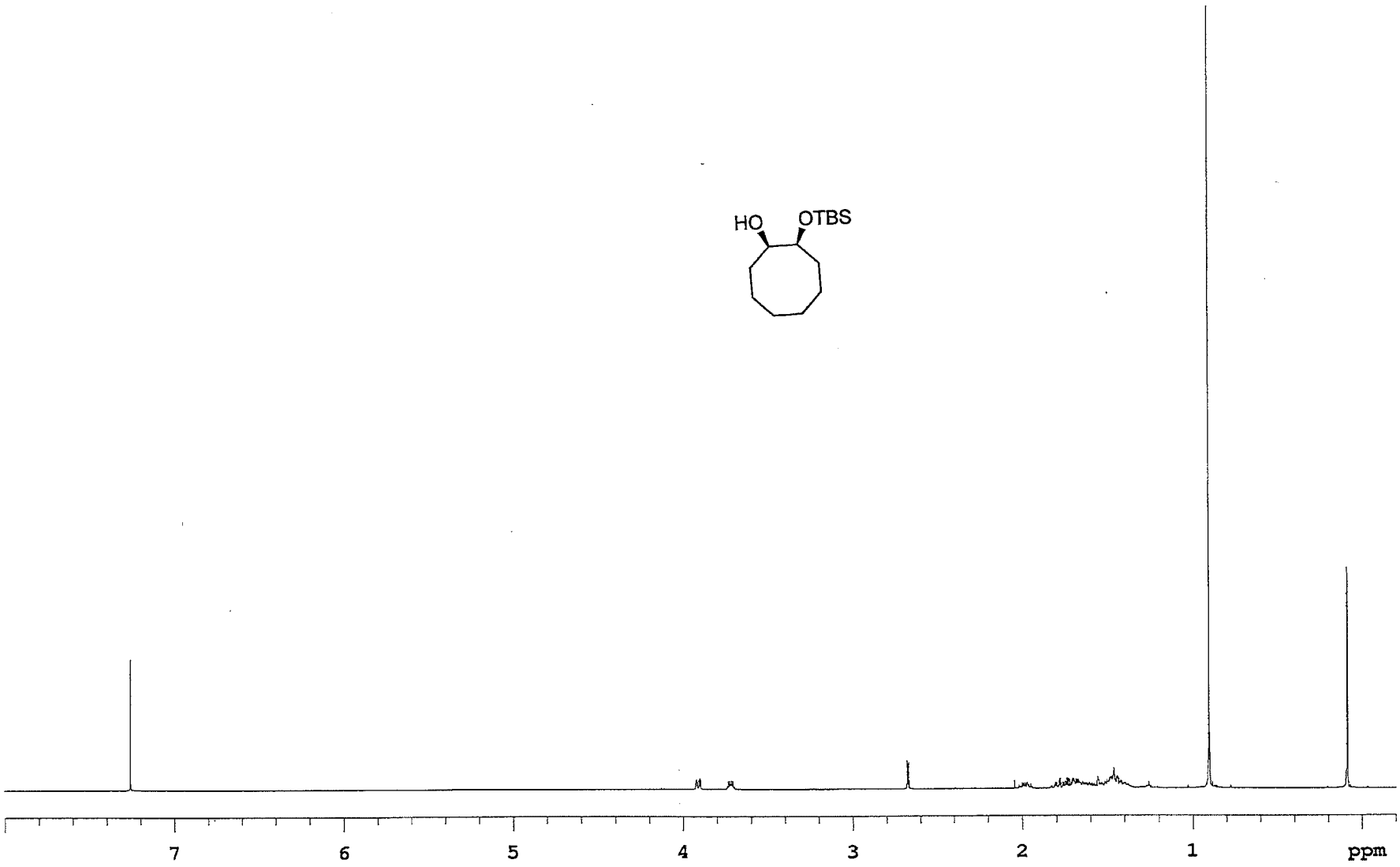
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


HO
OTBS
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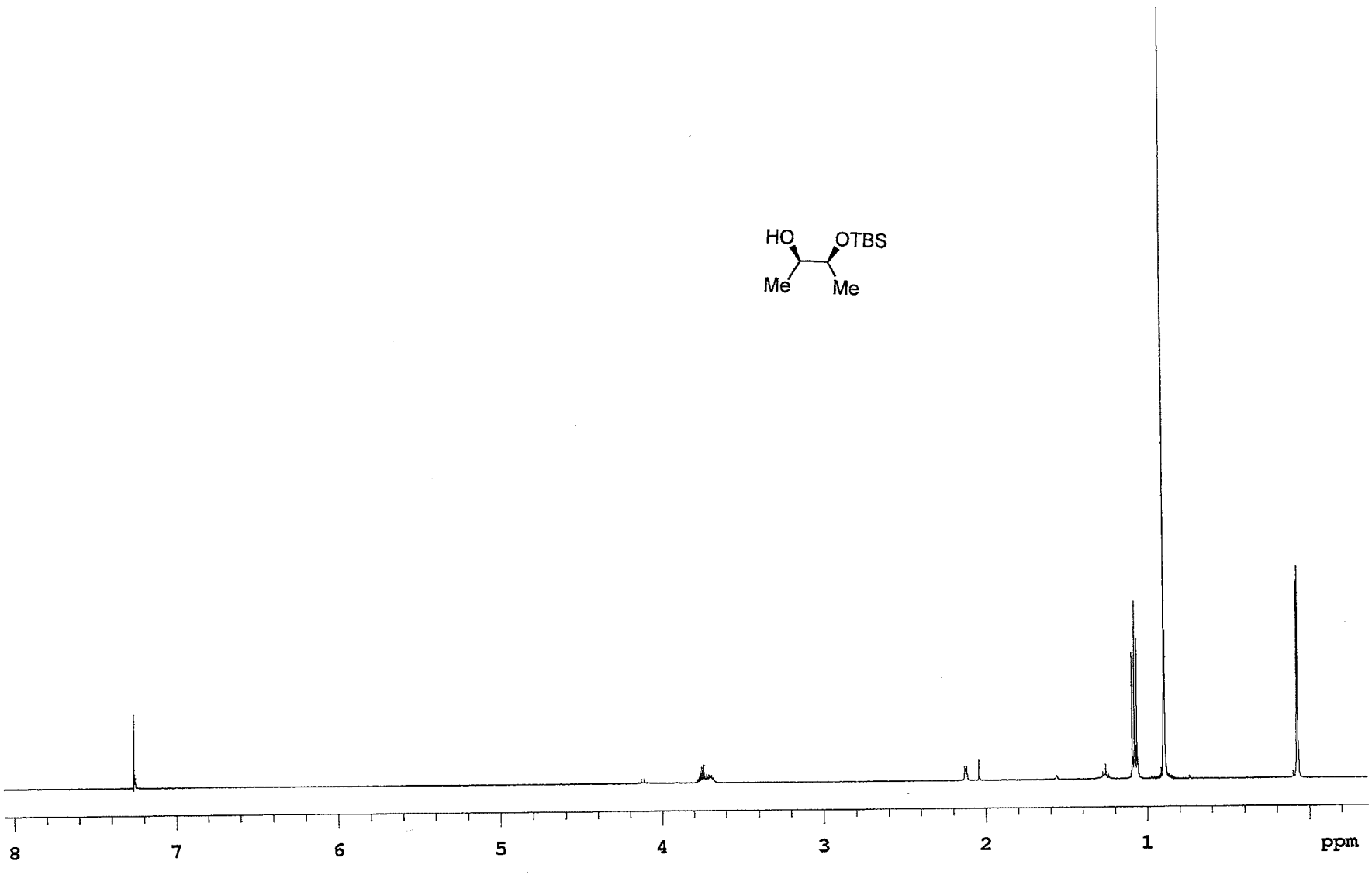
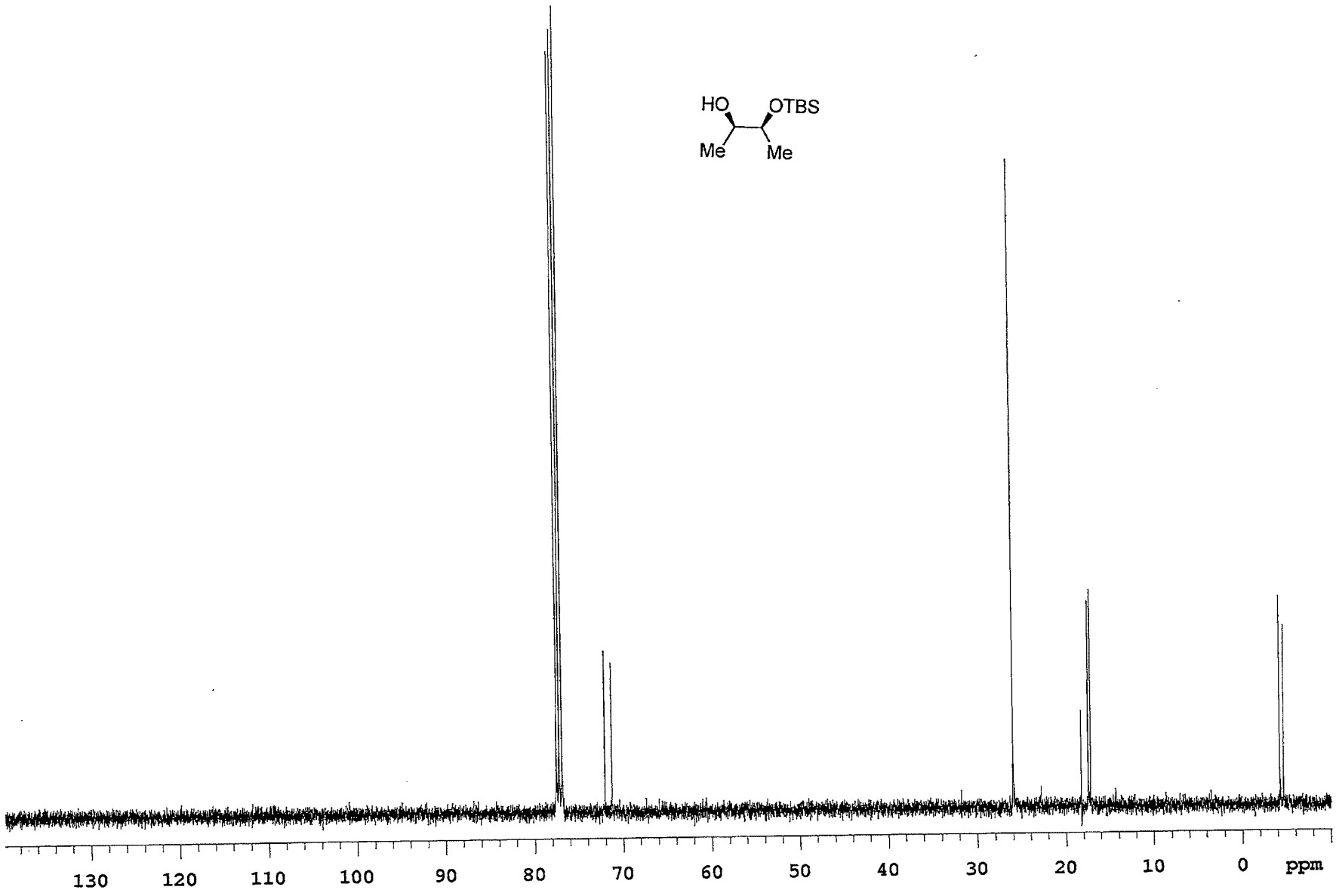
6
5
4
3
2
1
ppm


HO
OTBS
Me
Me
8
7
6
5
4
3
2
1
ppm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OTBS
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Me
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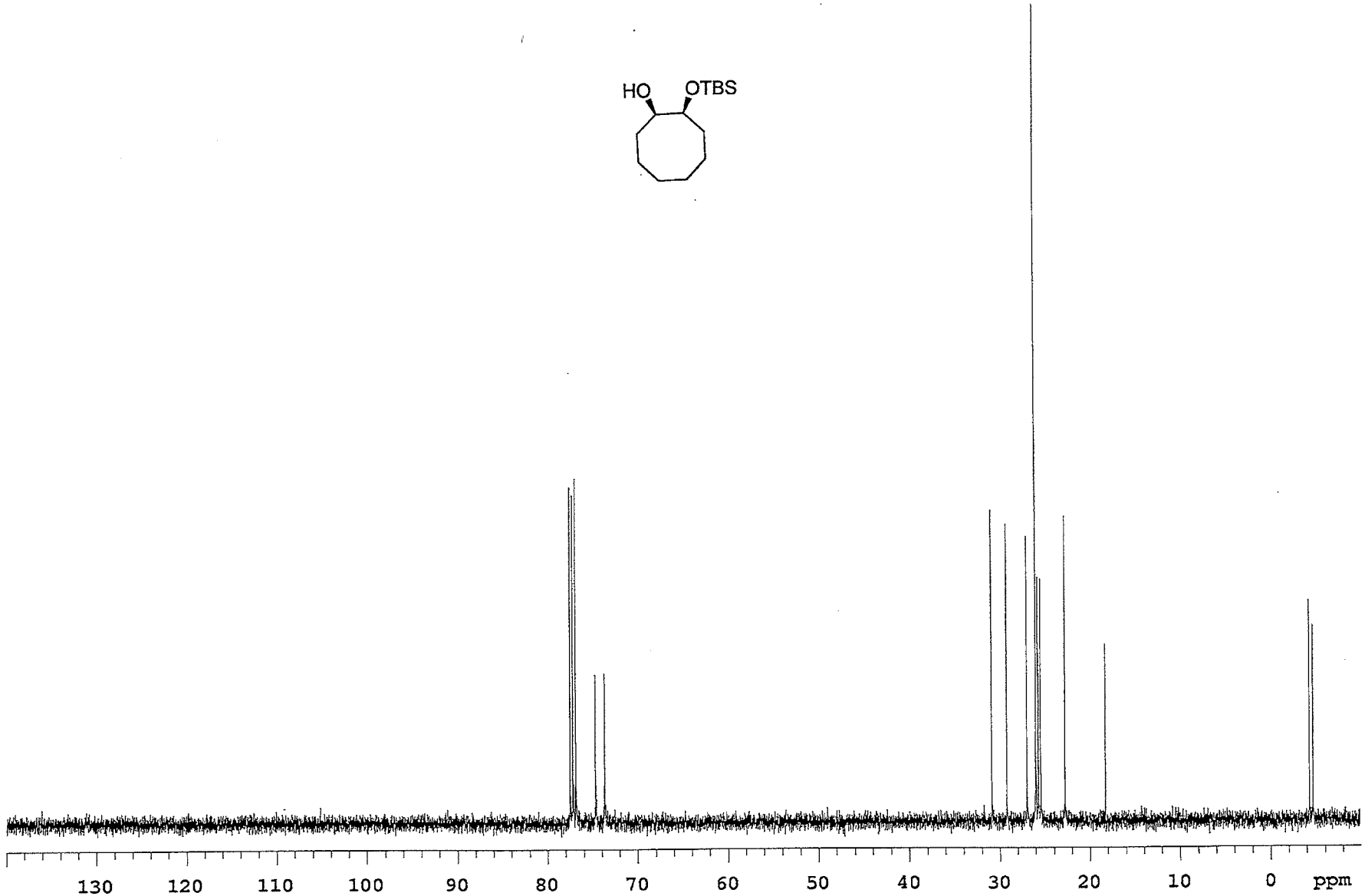
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OTBS
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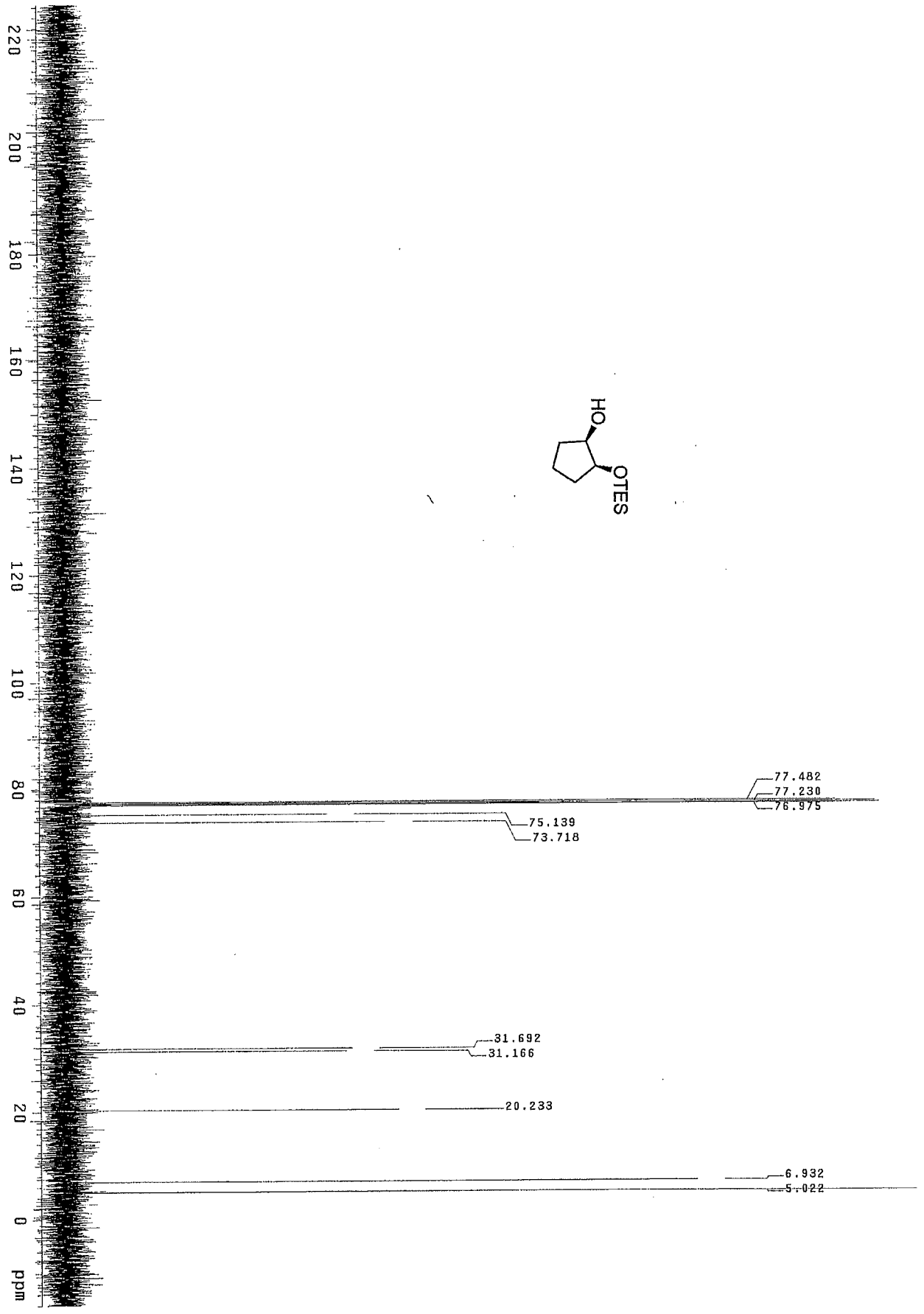
5
4
3
2
1
ppm

HO
OTES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OTES
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77.230
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75.139
73.718
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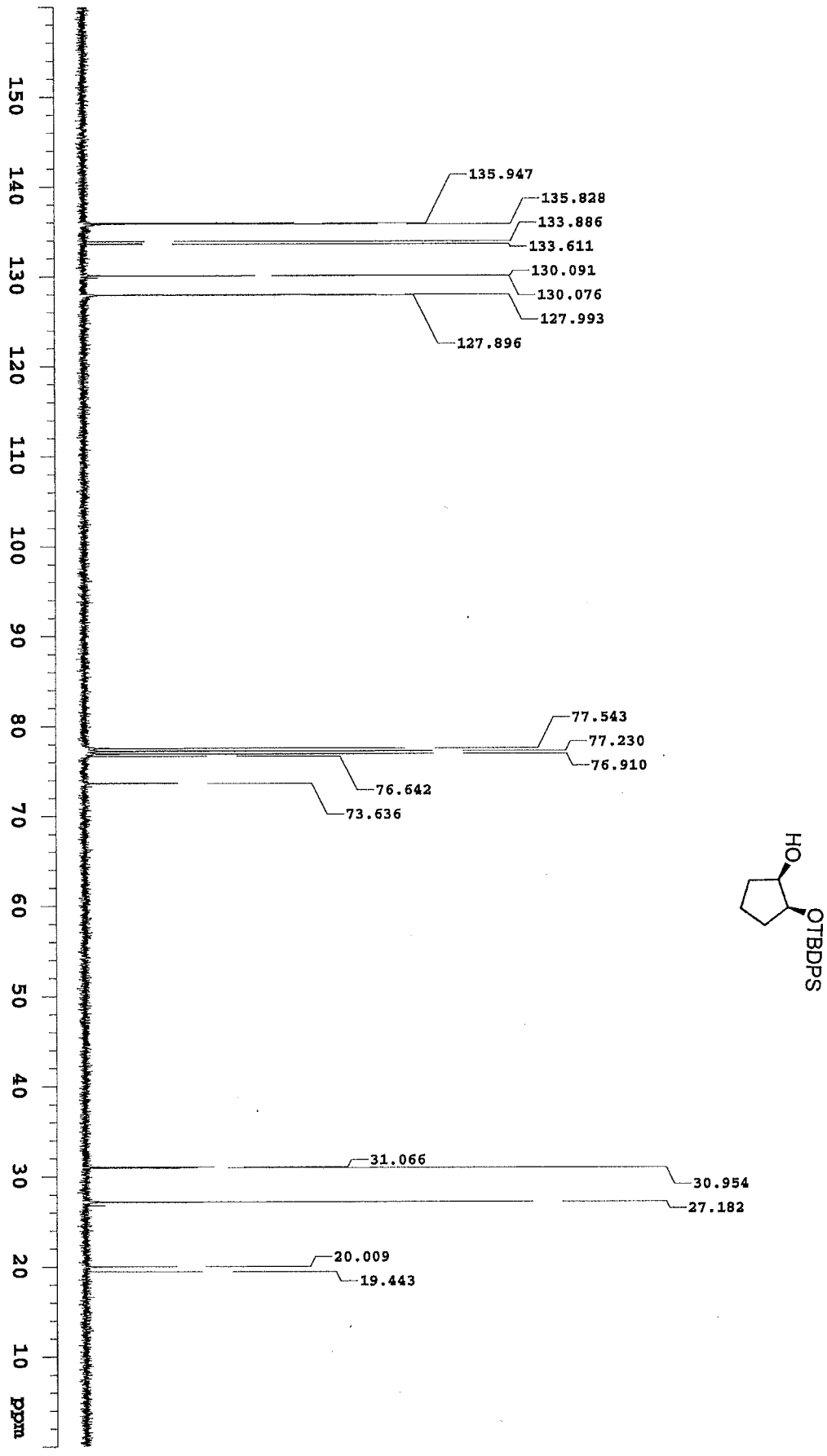
31.166
20.233
6.932
5.022
220
200
180
160
140
120
100
80
60
40
20
0
ppm

HO
OTBDPS

ppm
1
2
3
4
5
6
7
8
9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133.886
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130.076
127.993
127.896
77.543
77.230
76.910
76.642
73.636
31.066
30.954
27.182
20.009
19.443
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120
110
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90
80
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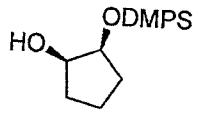
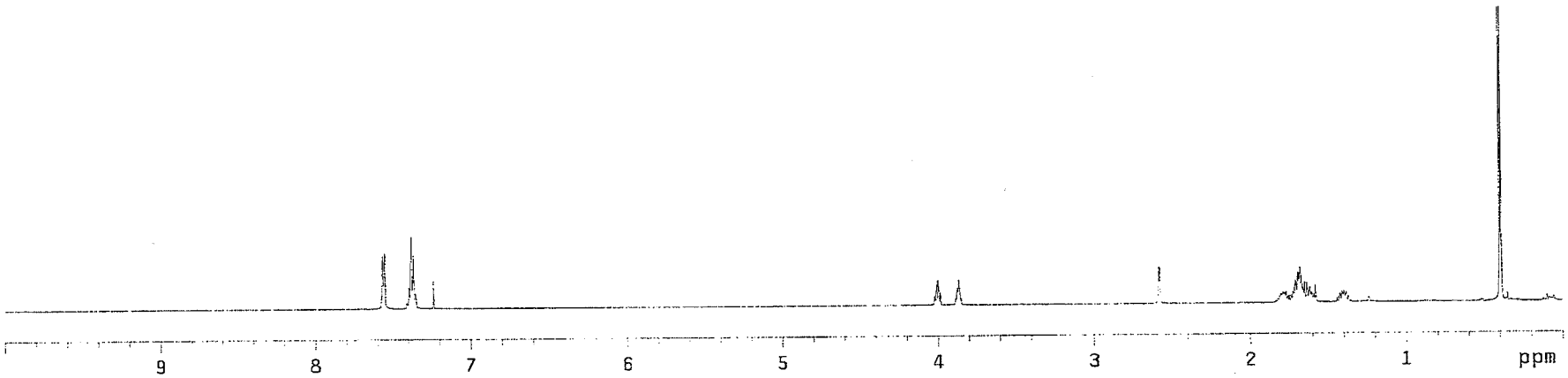
40
30
20
10
ppm
HO
OTBDPS


ODMPS
HO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8
7
6
5
4
3
2
1
ppm

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133.618
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128.156
77.550
77.230
76.910
75.653
73.651
31.297
30.969
20.105
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HO
ODMPS
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200
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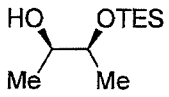
120
100
80
60
40
20
0
ppm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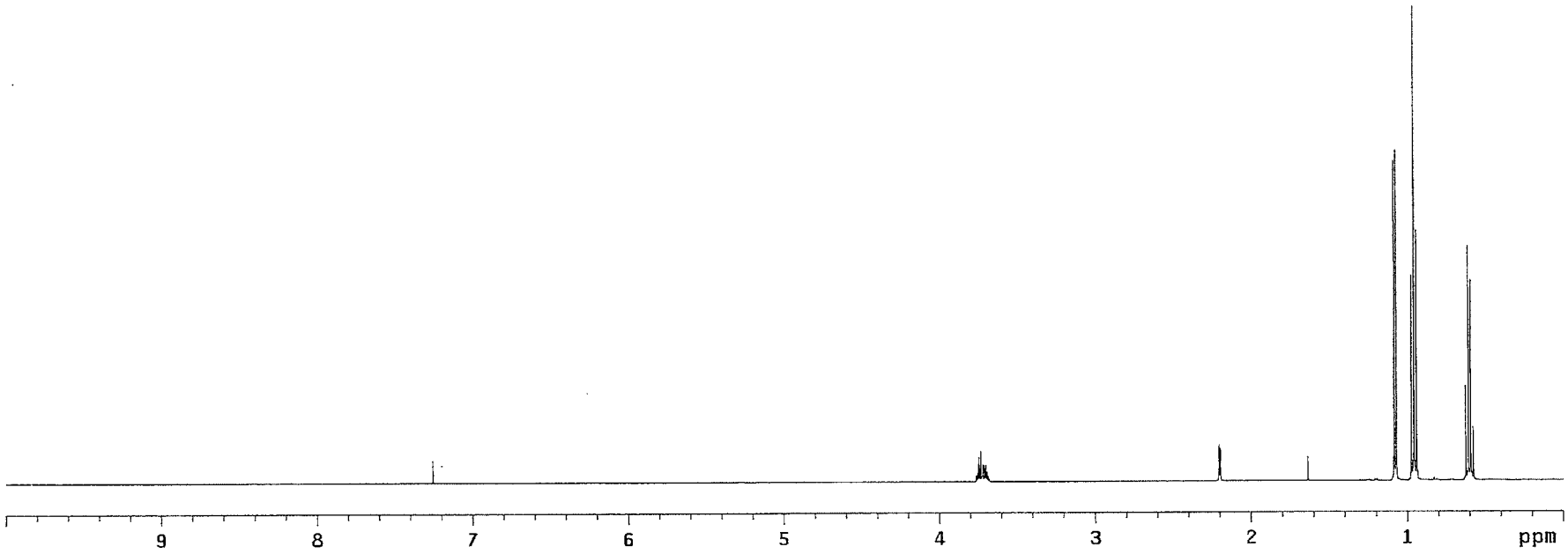
OTES
Me
Me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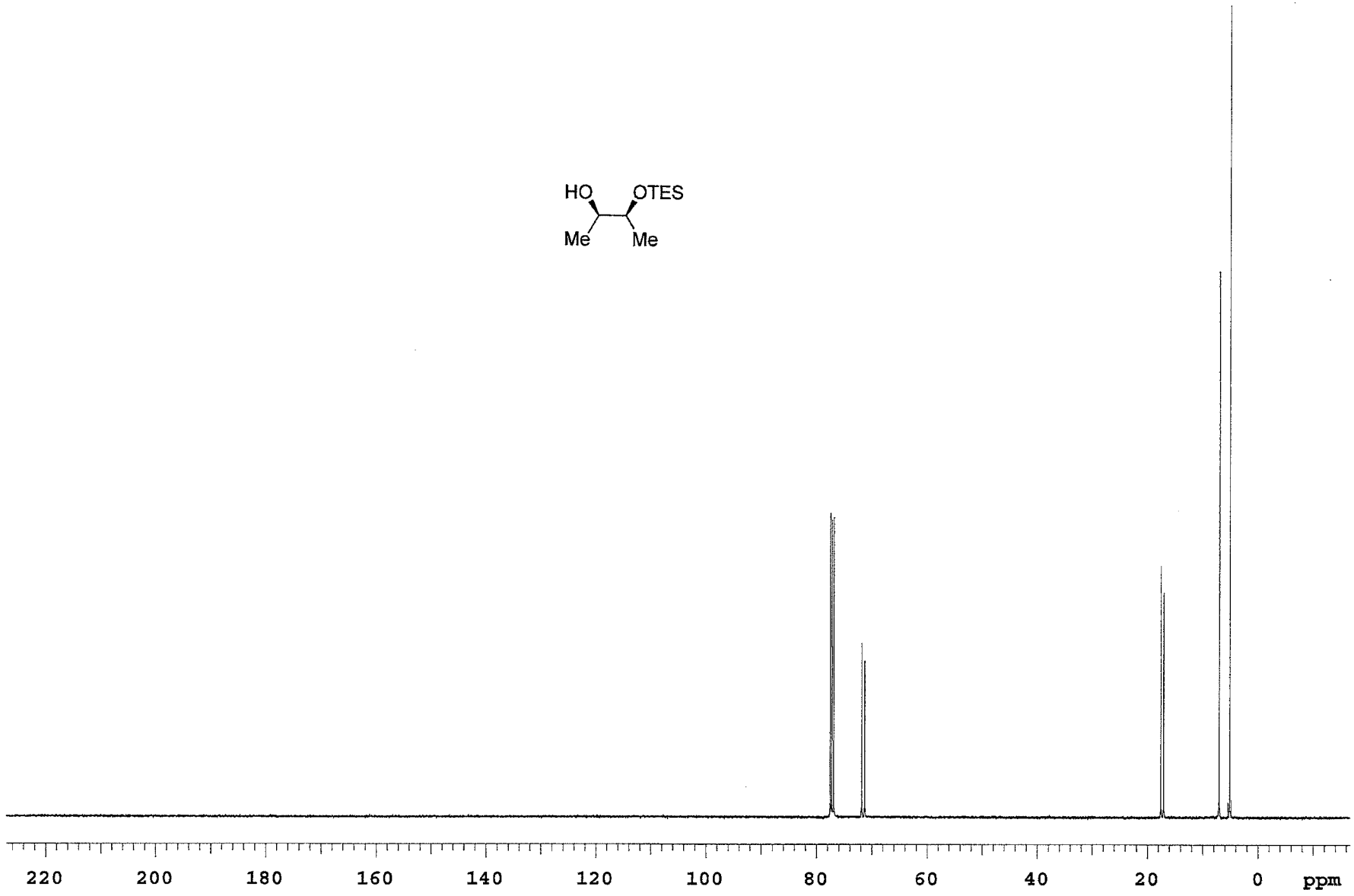
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OTES
Me
Me
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200
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60
40
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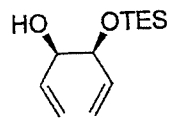
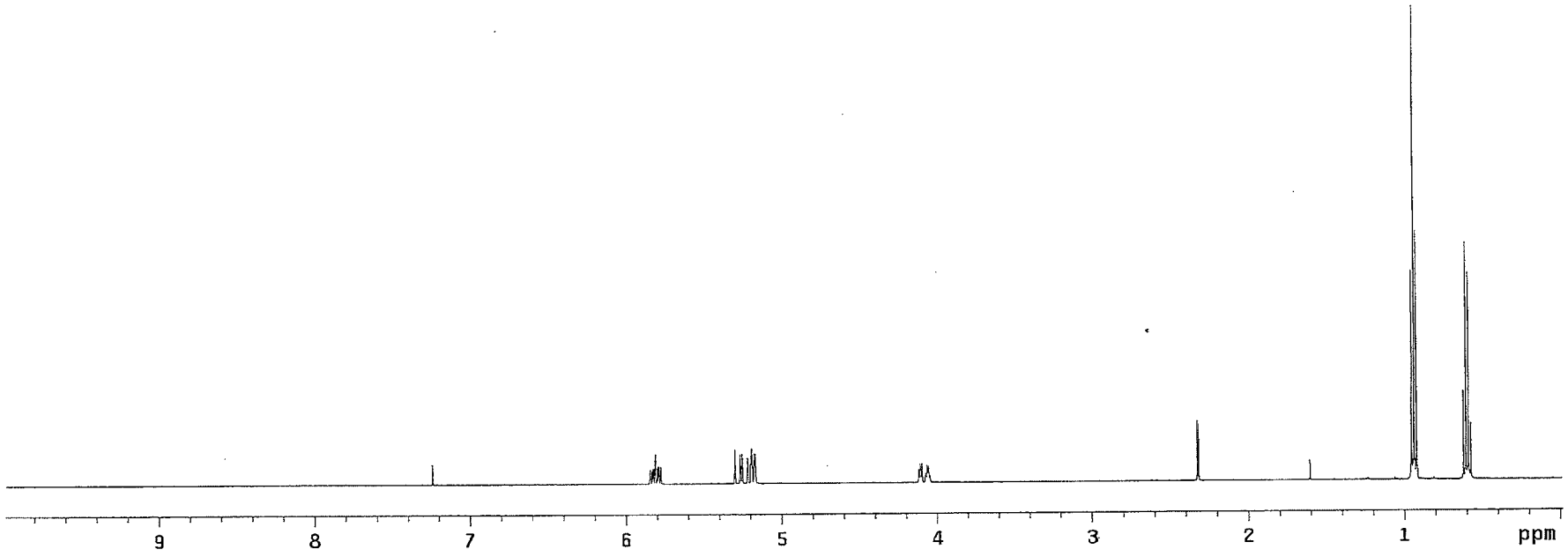
0
ppm


HO
OTES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8
7
6
5
4
3
2
1
ppm

220
200
180
160
140
120
100
80
60
40
20
0
ppm
136.922
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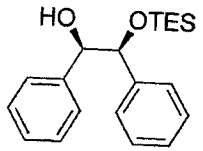
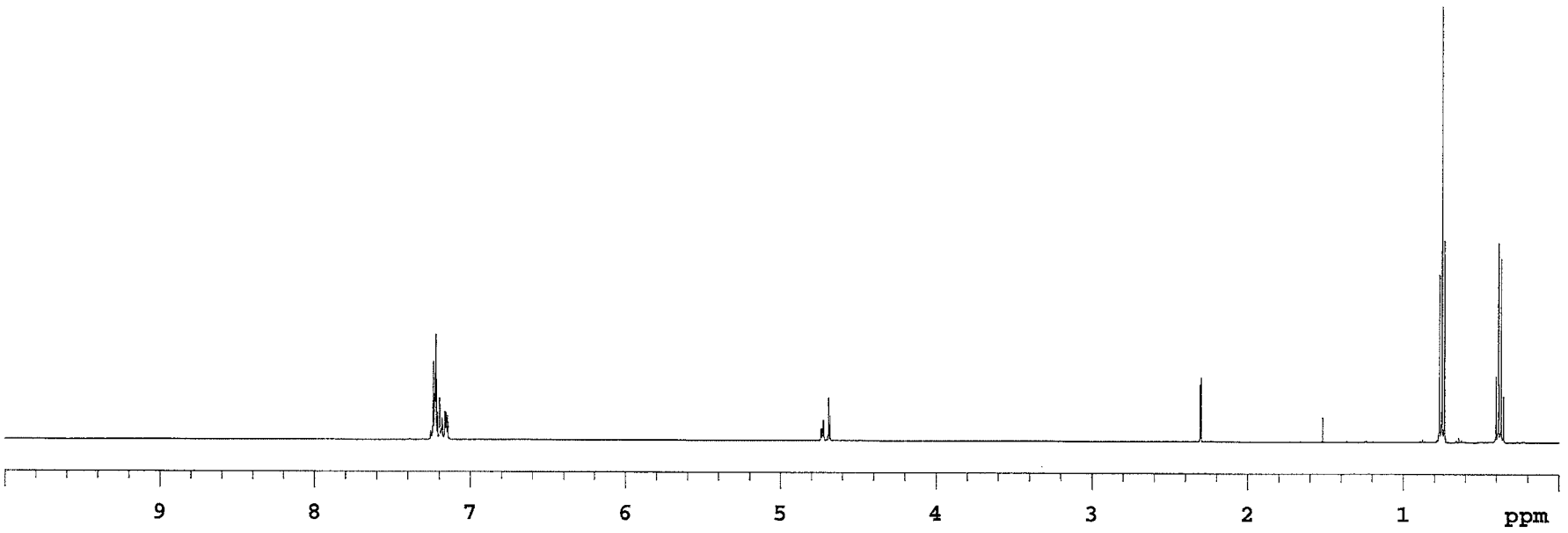
116.854
HO
OTES
77.543
77.231
77.119
76.911
76.256
6.973
5.105


HO
OTES


9
8
7
6
5
4
3
2
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ppm

HO
OTES
220
200
180
160
140
120
100
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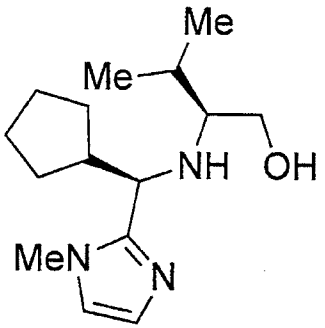
40
20
0
ppm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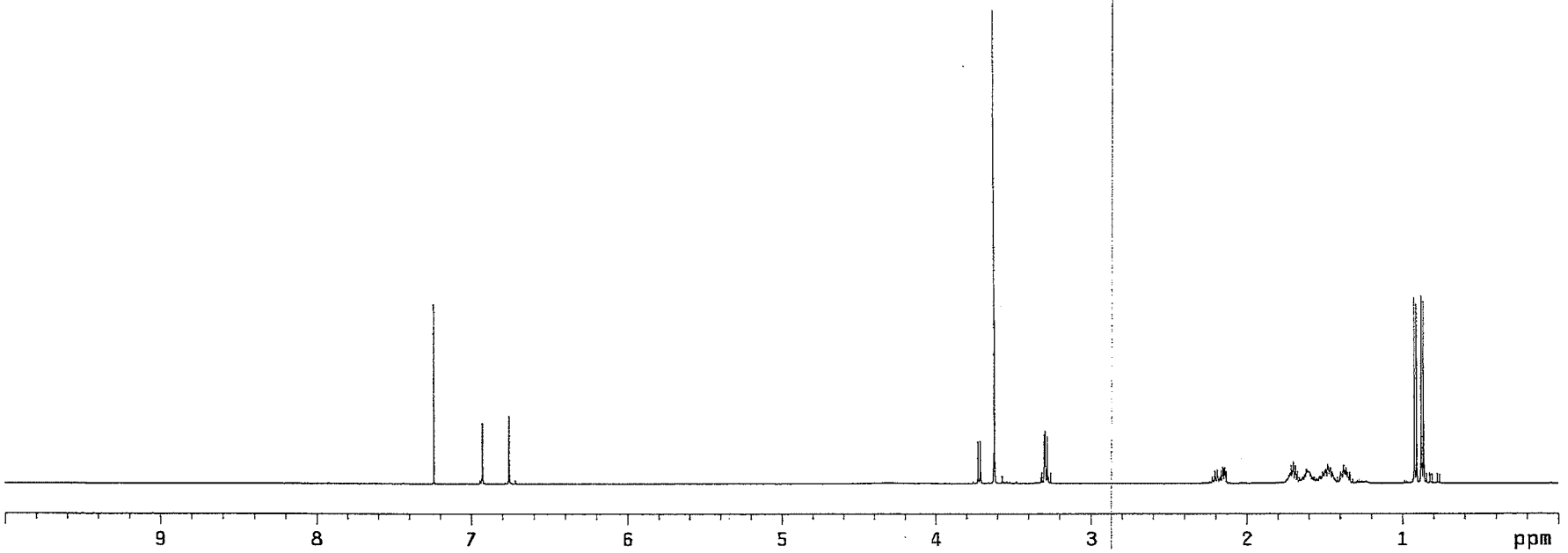
Me
NH
OH
MeN
N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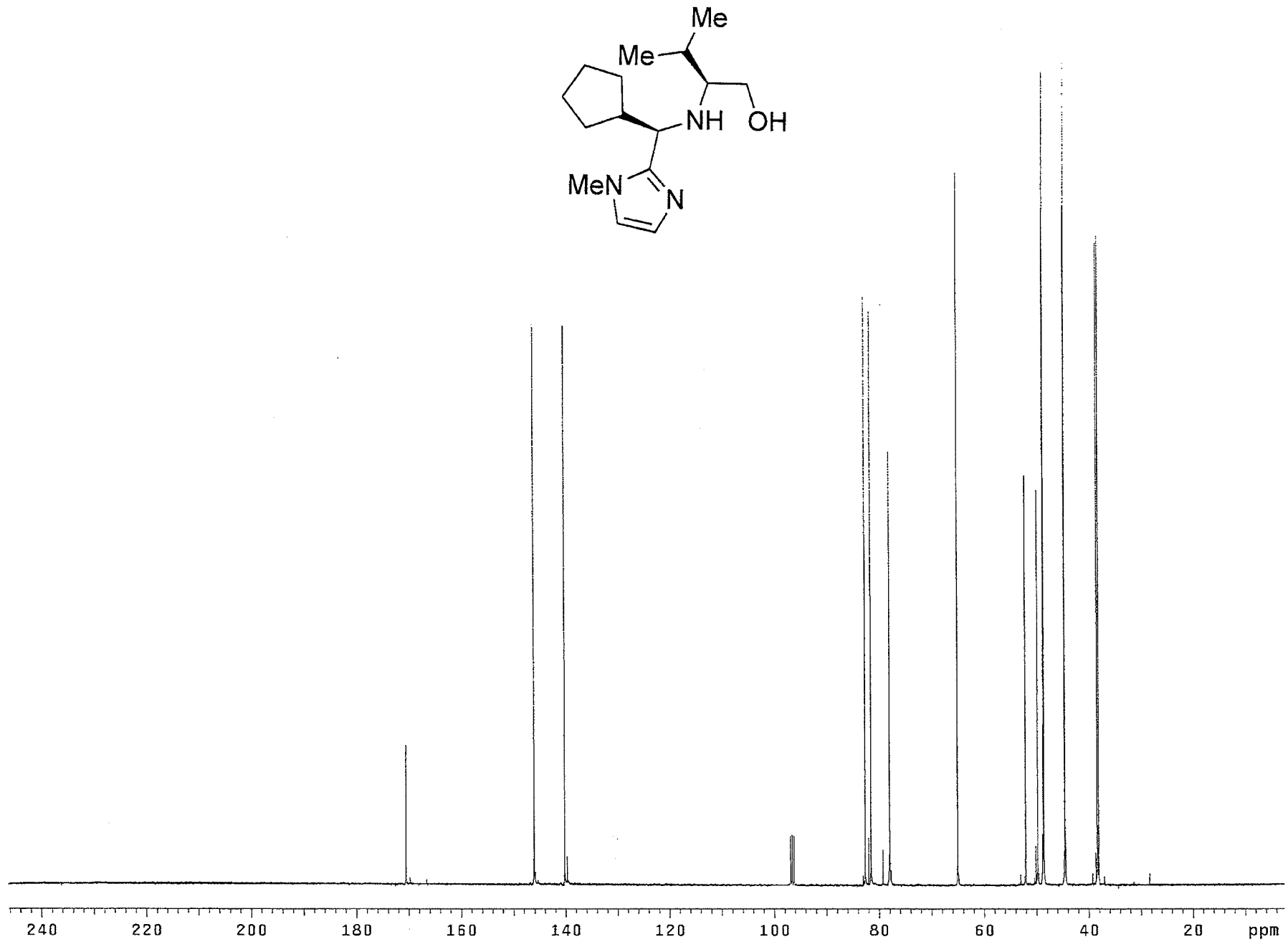
6
5
4
3
2
1
ppm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Me
NH
OH
MeN
N
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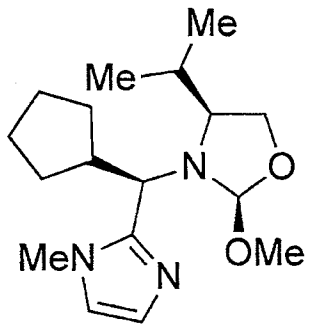
200
180
160
140
120
100
80
60
40
20
ppm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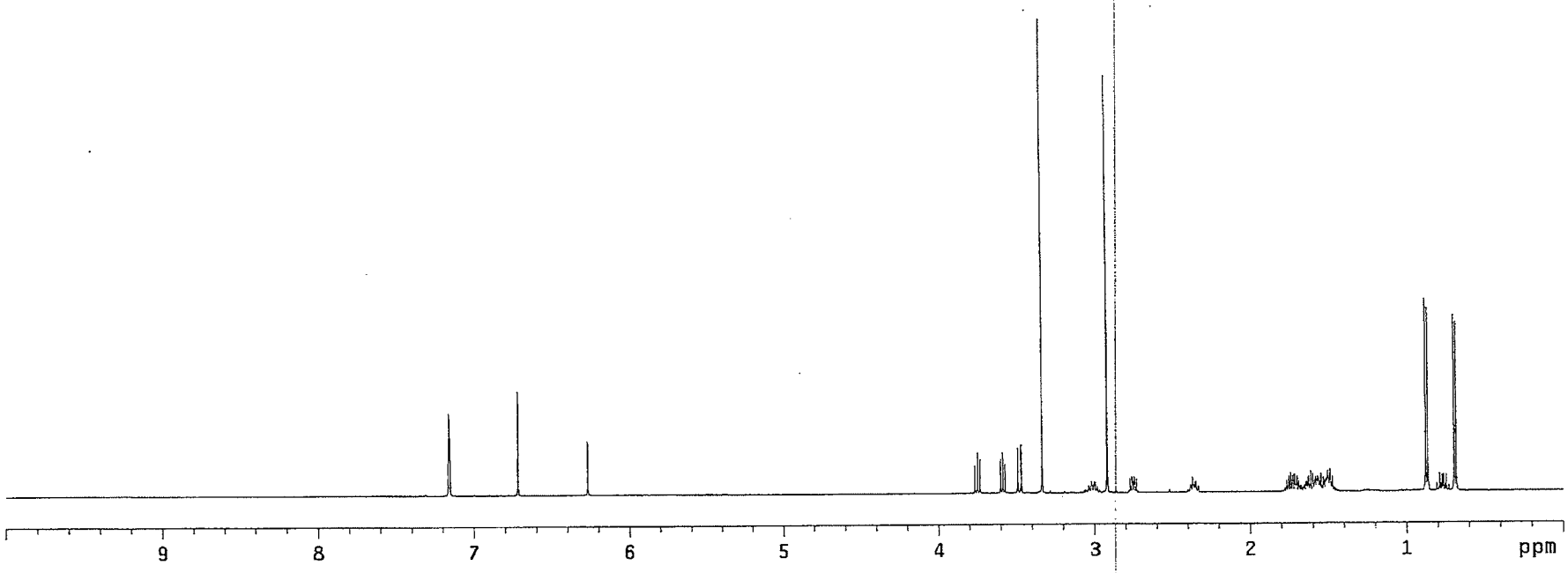
Me
N
O
MeN
N
OMe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2
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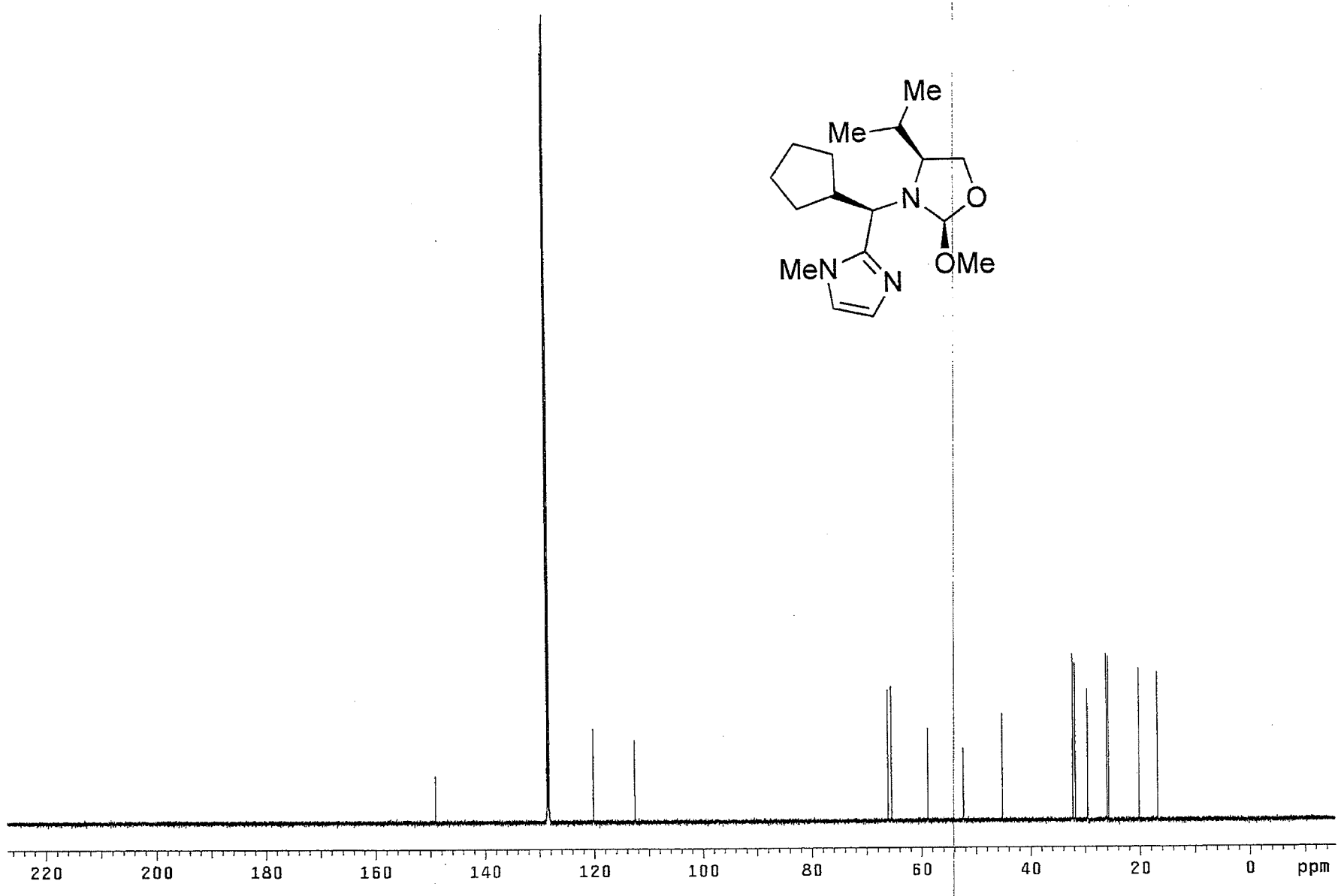
ppm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Me
N
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N
OMe
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200
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120
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40
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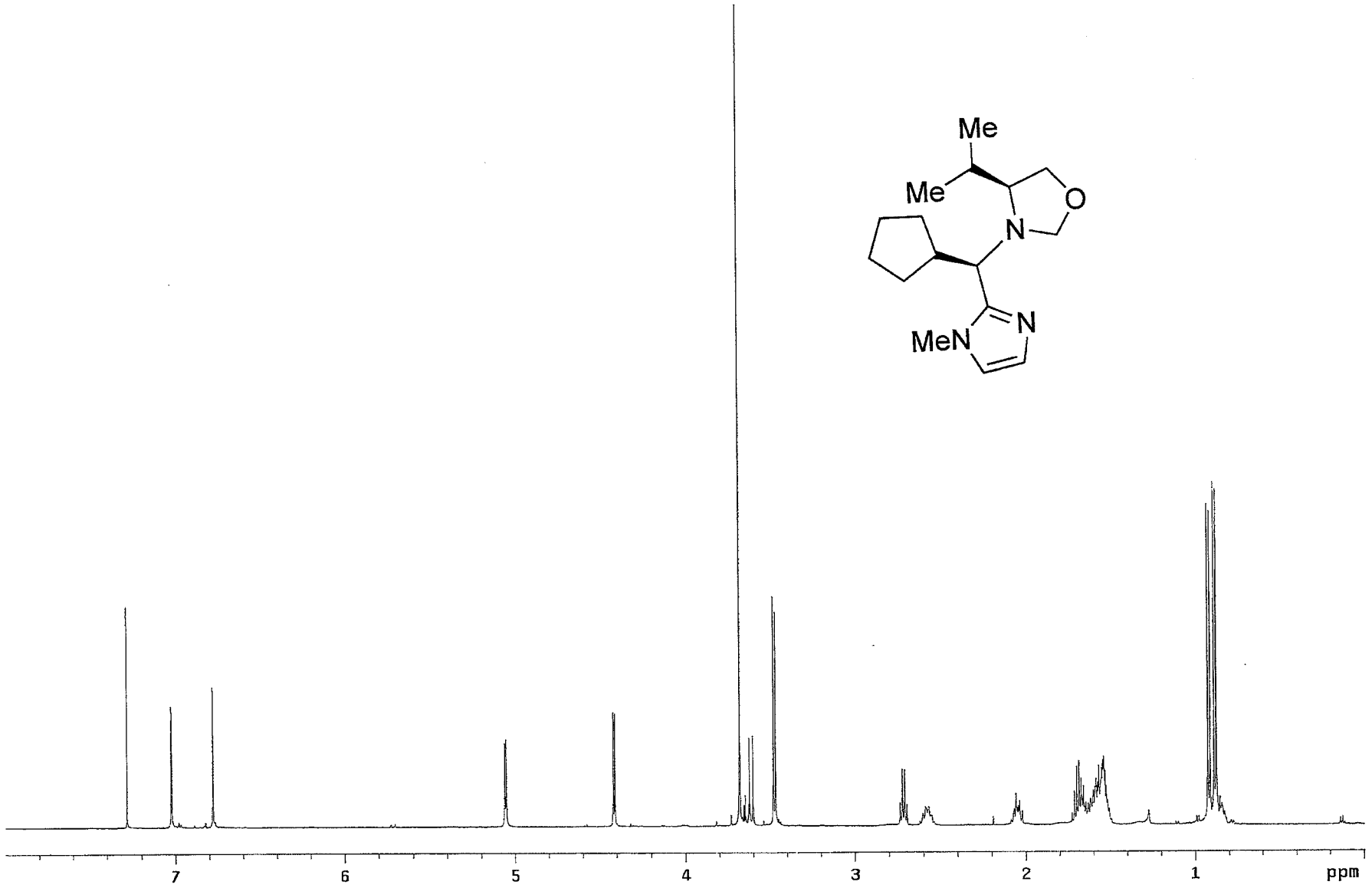
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Me
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N
MeN
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ppm

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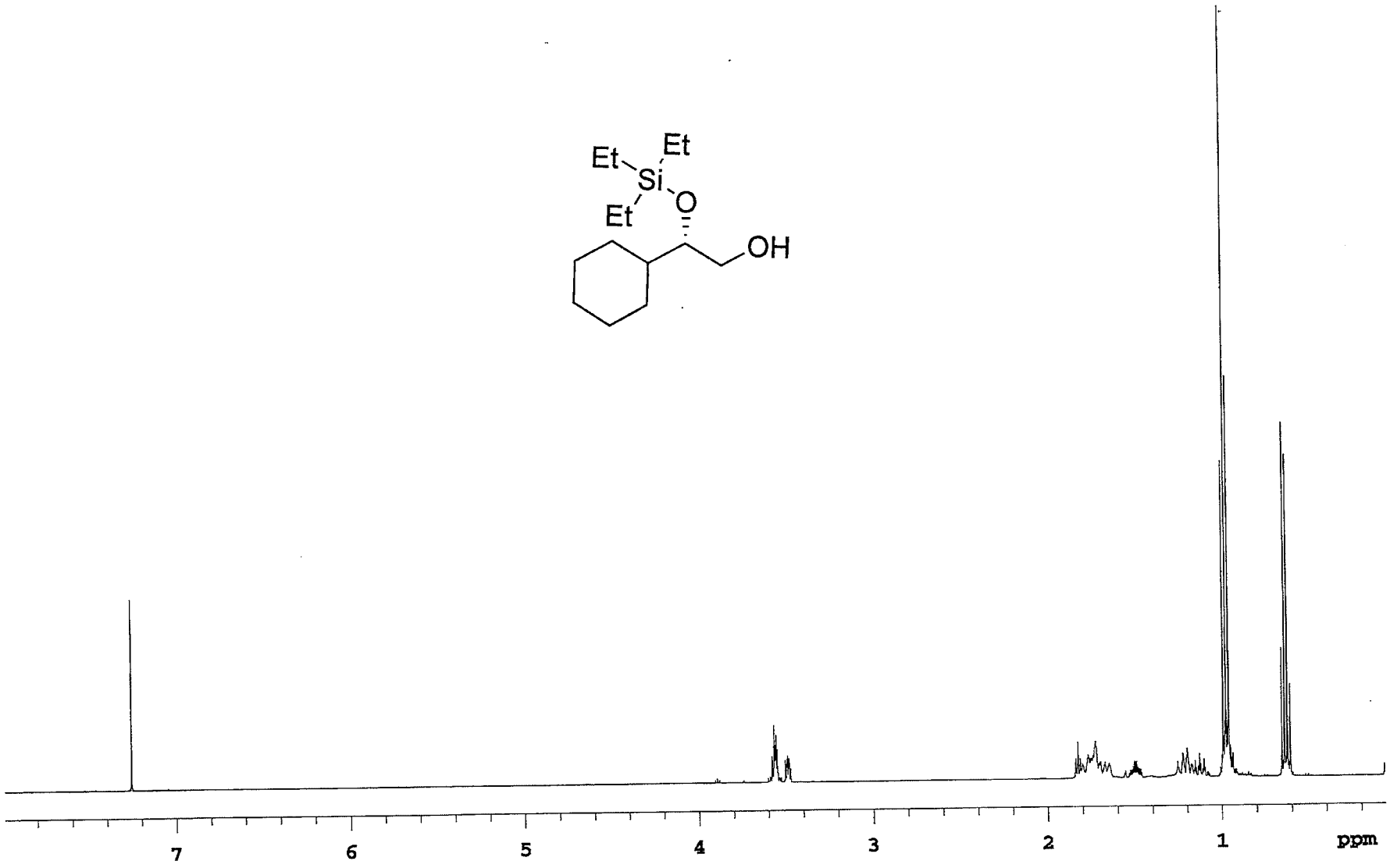
Et
Et
Si
Et
O
OH
7
6
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ppm

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Et
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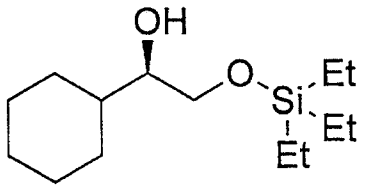
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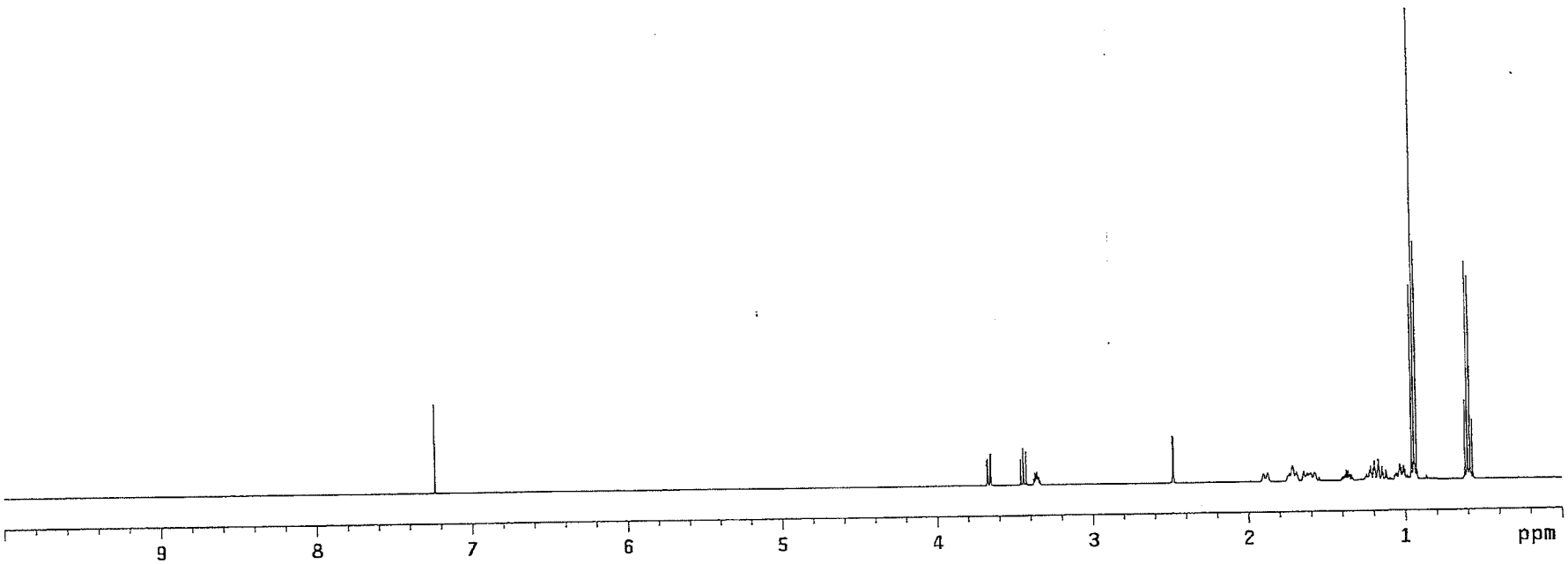
O
Si
Et
Et
Et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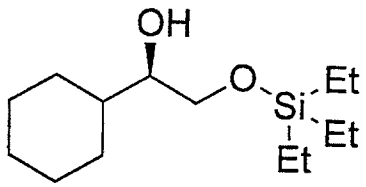
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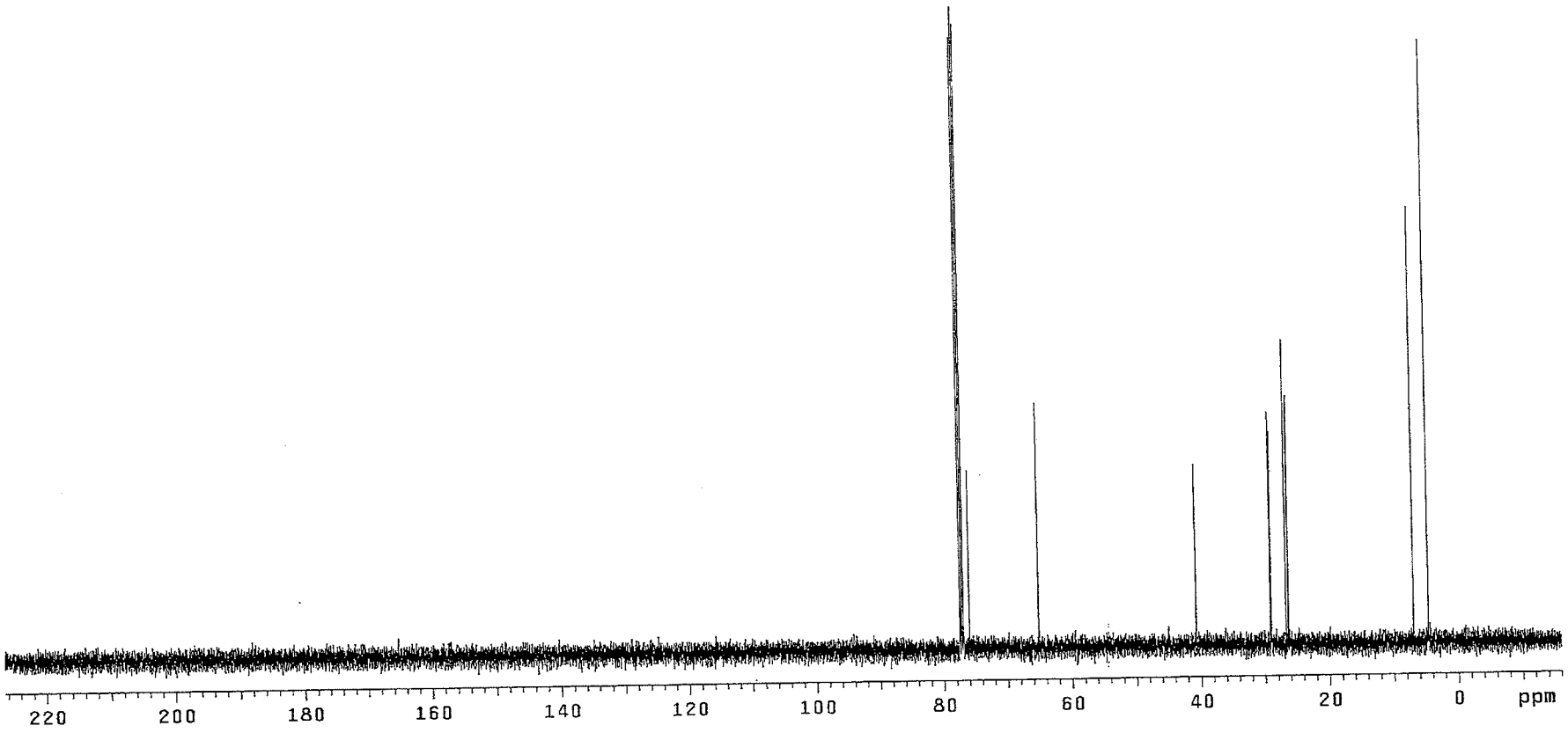
Si
Et
Et
Et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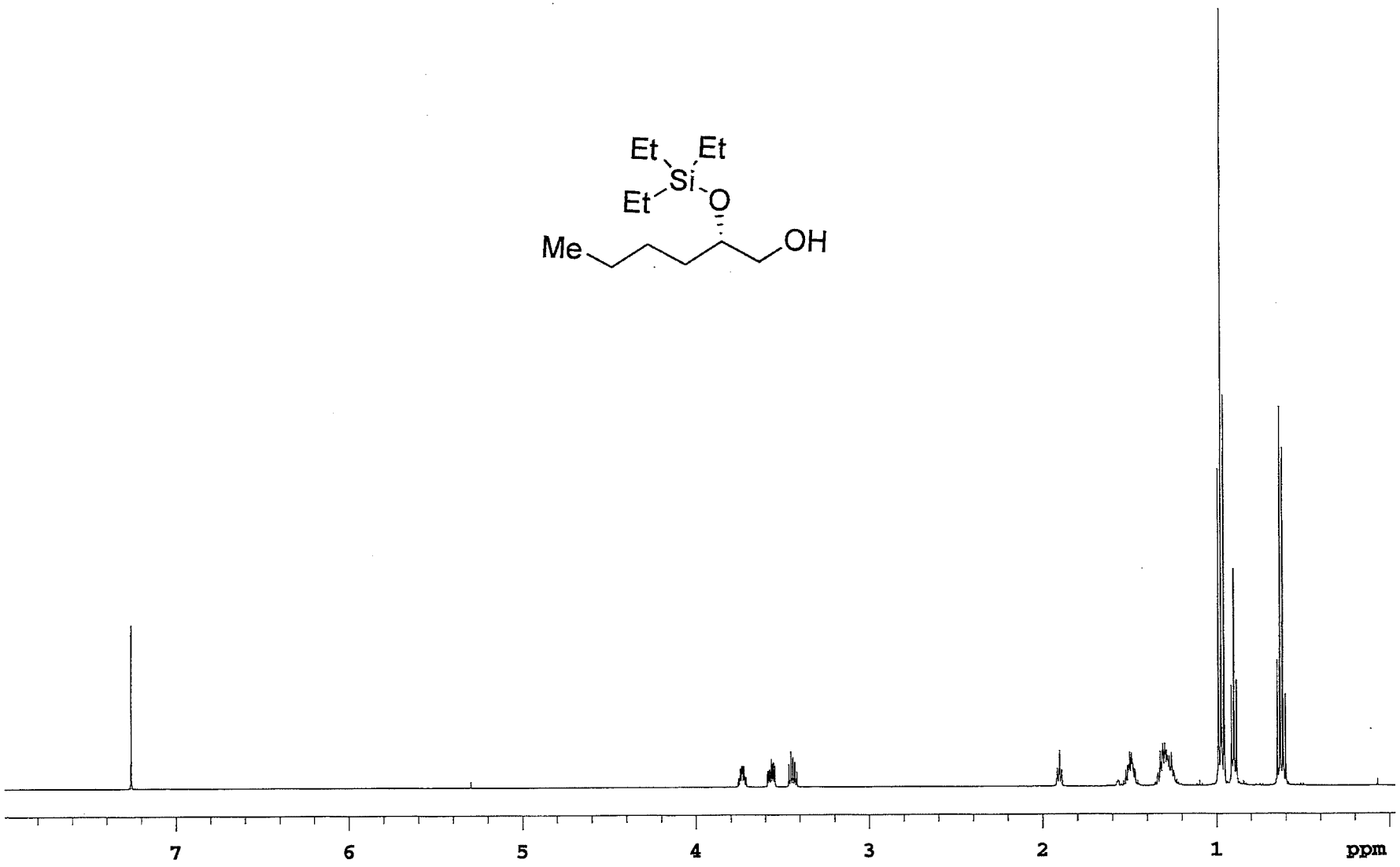
Et
Et
Si
Et
O
Me
OH
7
6
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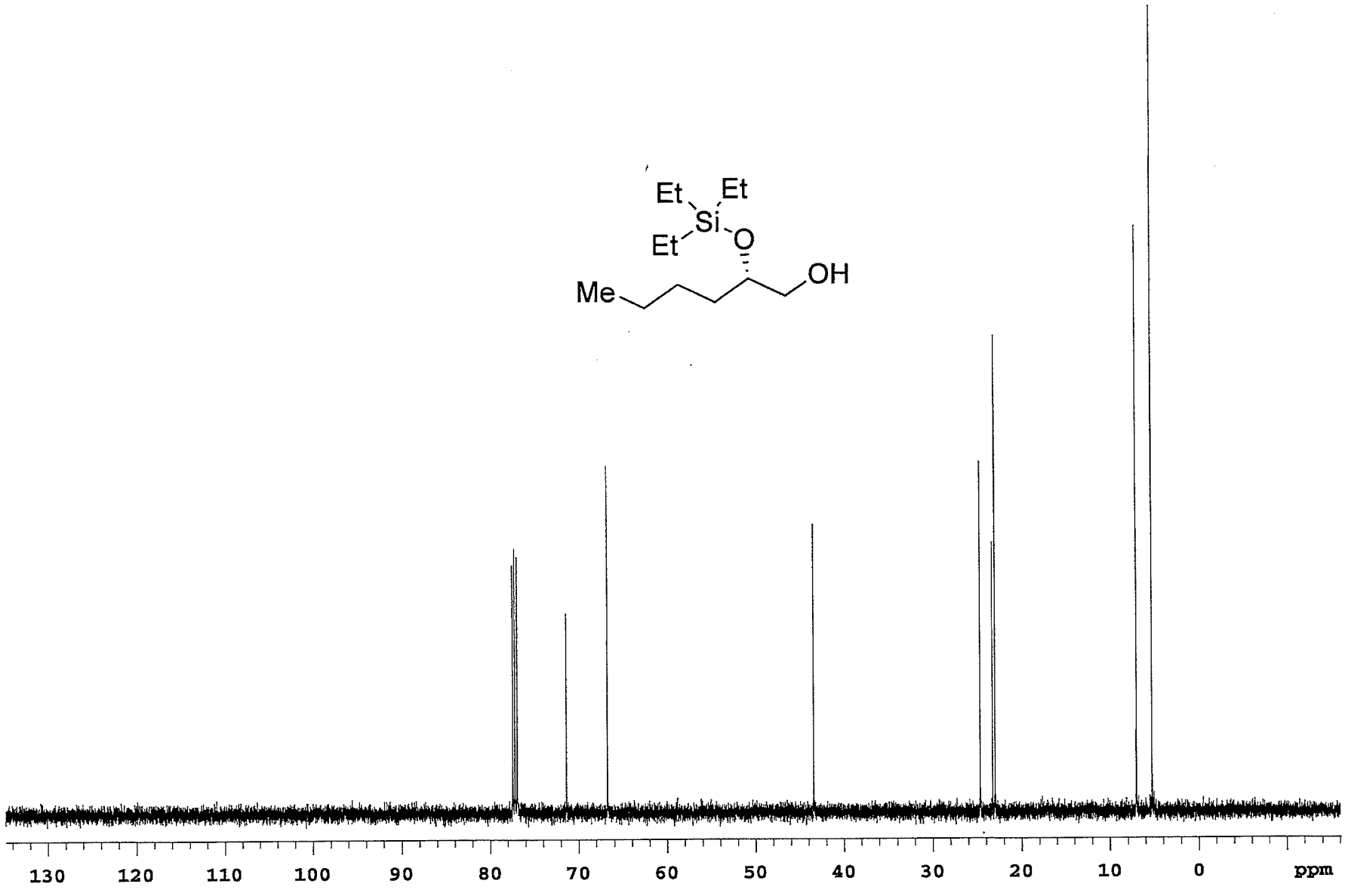
4
3
2
1
ppm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Et
Si
Et
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OH
Me
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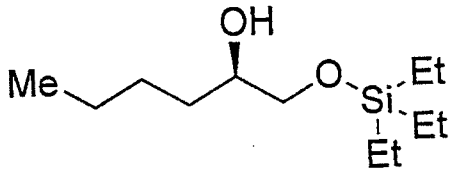
20
10
0
ppm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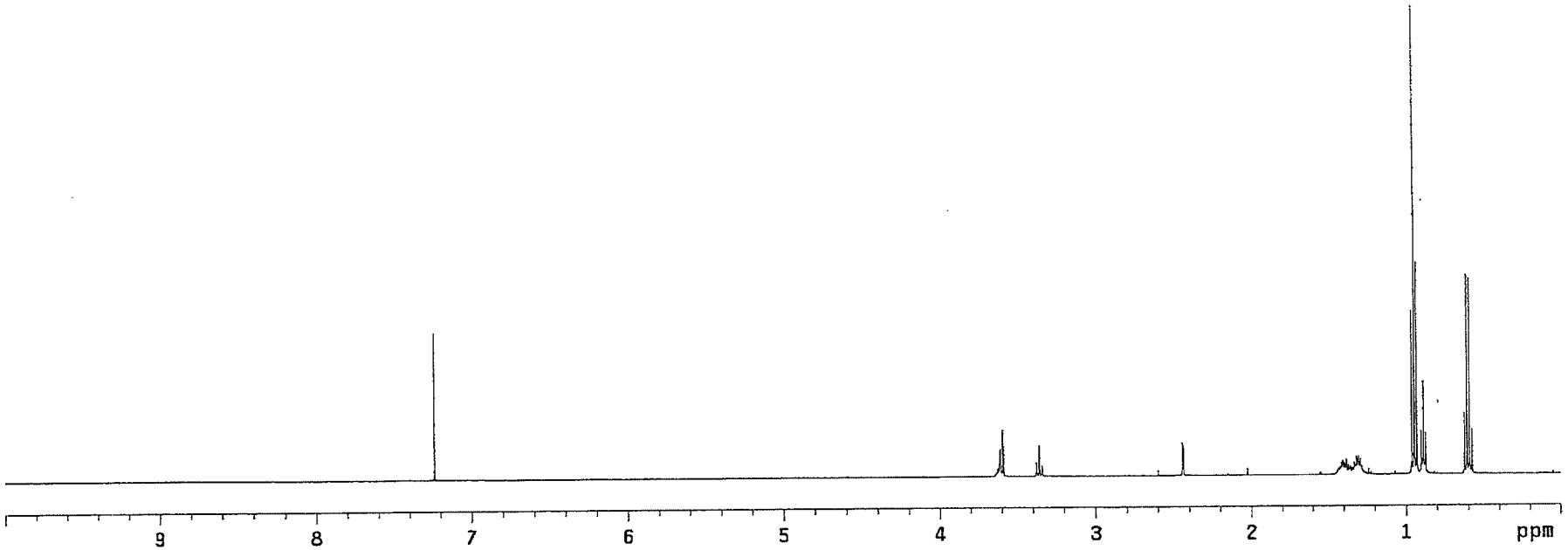
O
Si
Et
Et
Et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5
4
3
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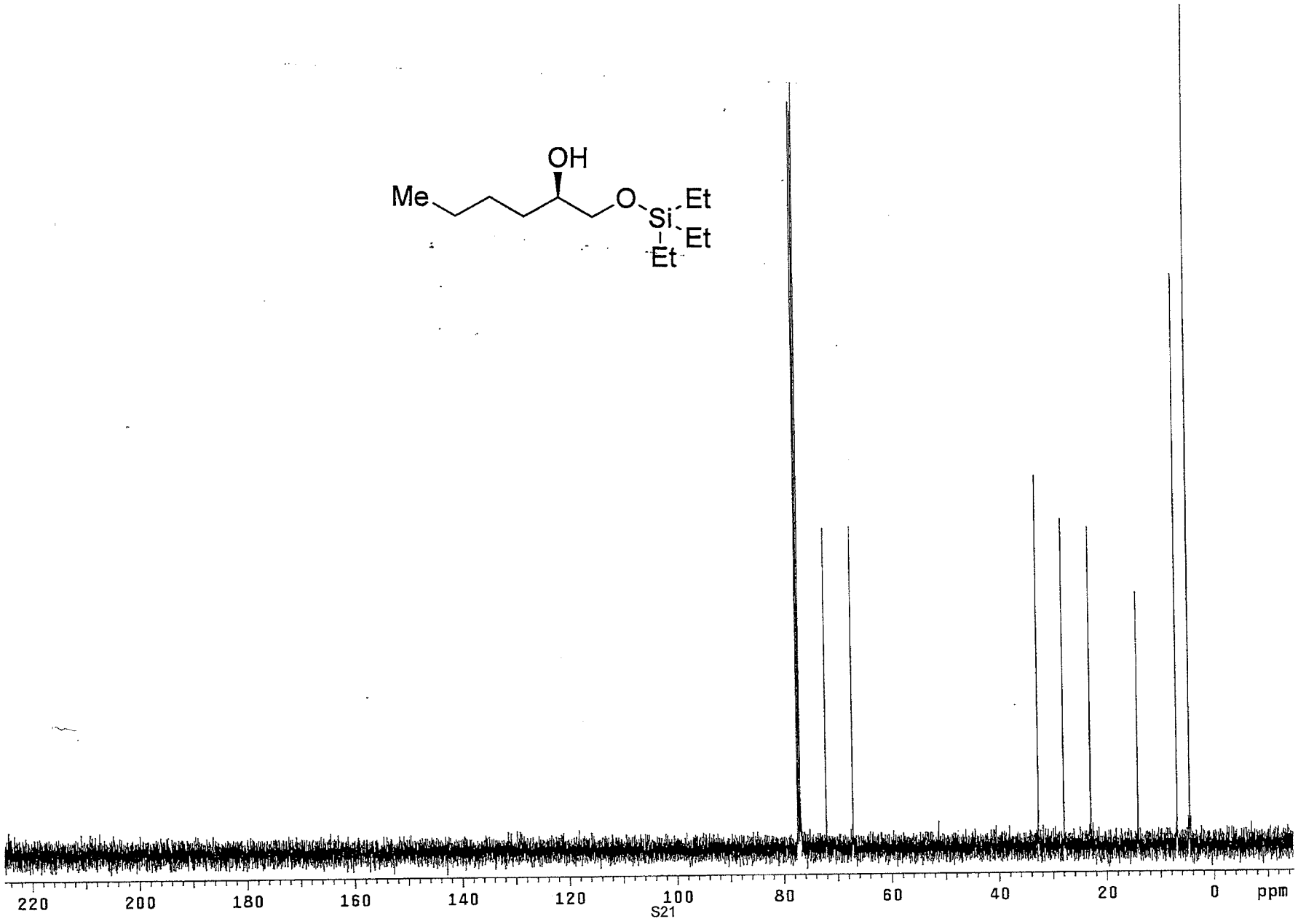
1
ppm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Si
Et
Et
Et
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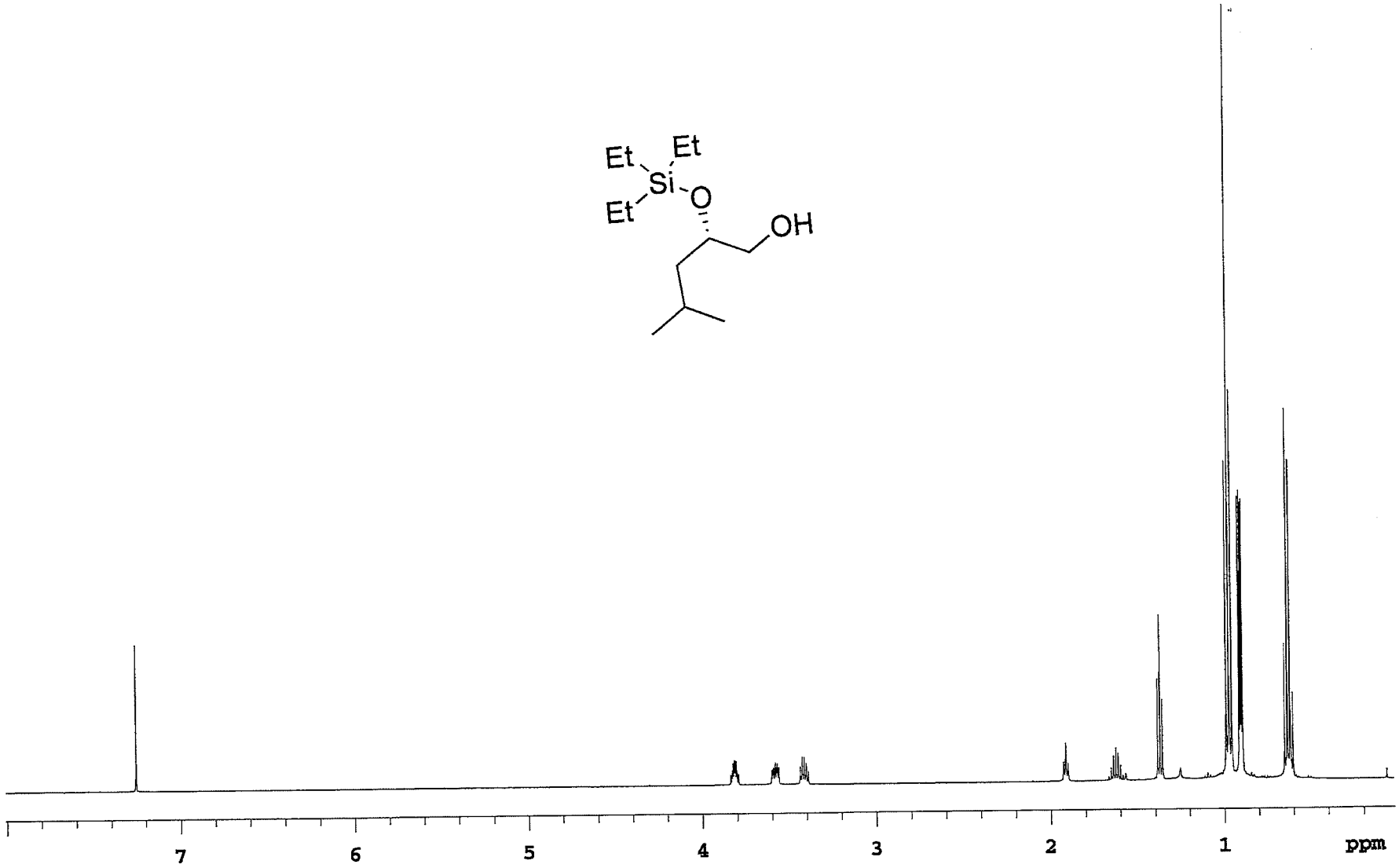
ppm


Et
Et
Si
Et
O
OH
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4
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2
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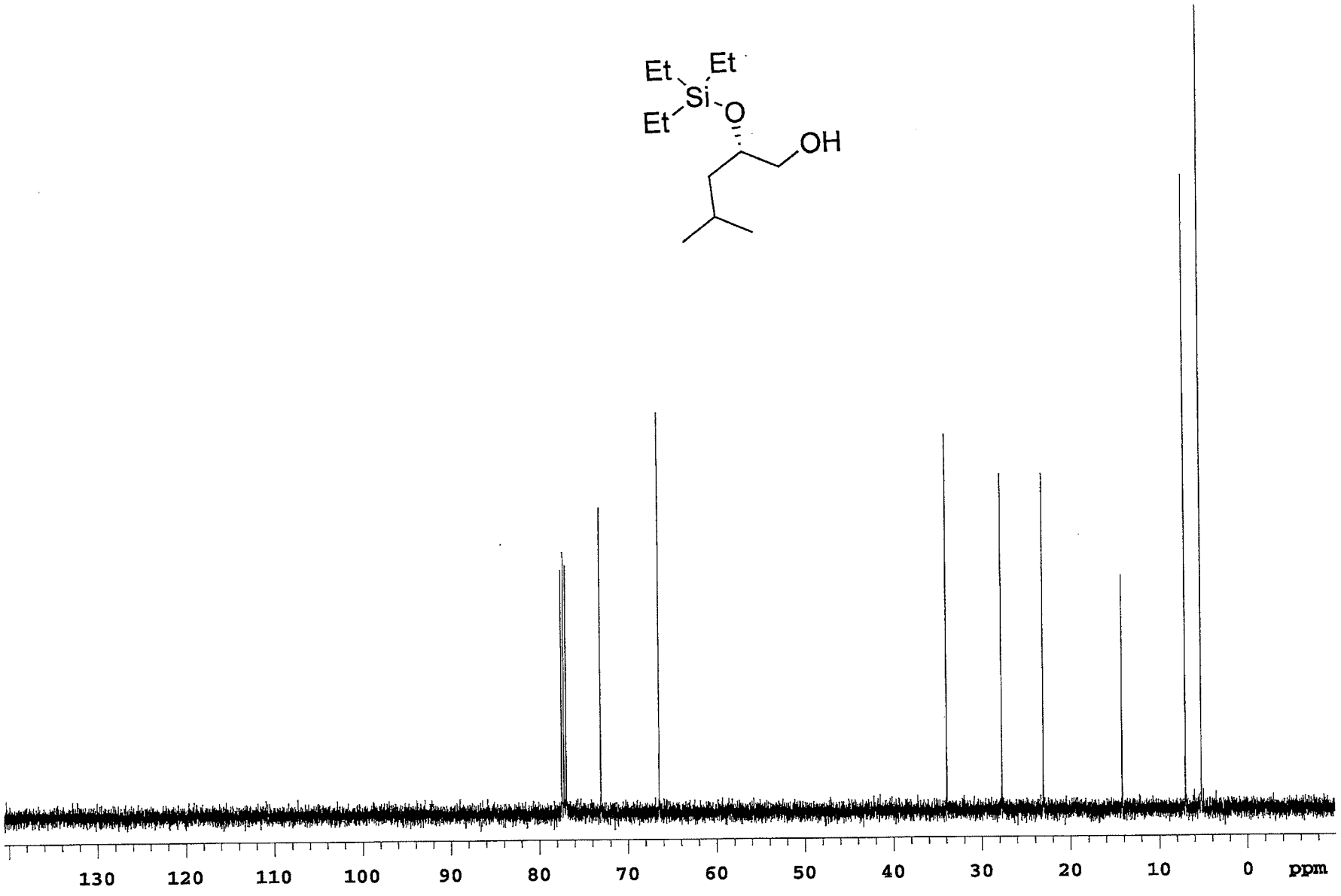
ppm


Et
Et
Si
Et
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OH
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20
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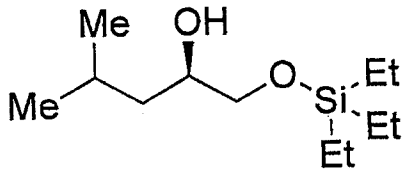
ppm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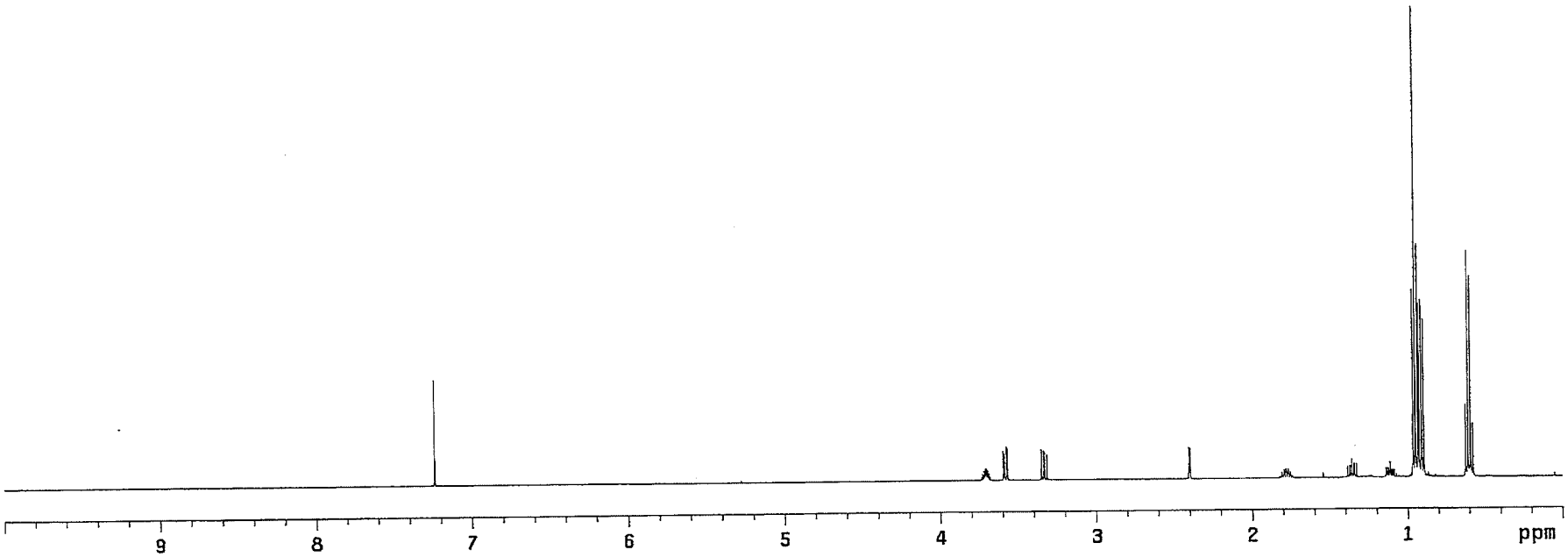
Me
O
Si
Et
Et
Et


9
8
7
6
5
4
3
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1
ppm

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OH
Me
O
Si
Et
Et
Et
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120
100
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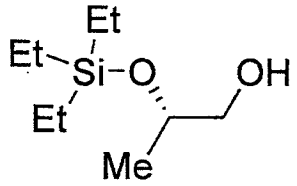
60
40
20
0
ppm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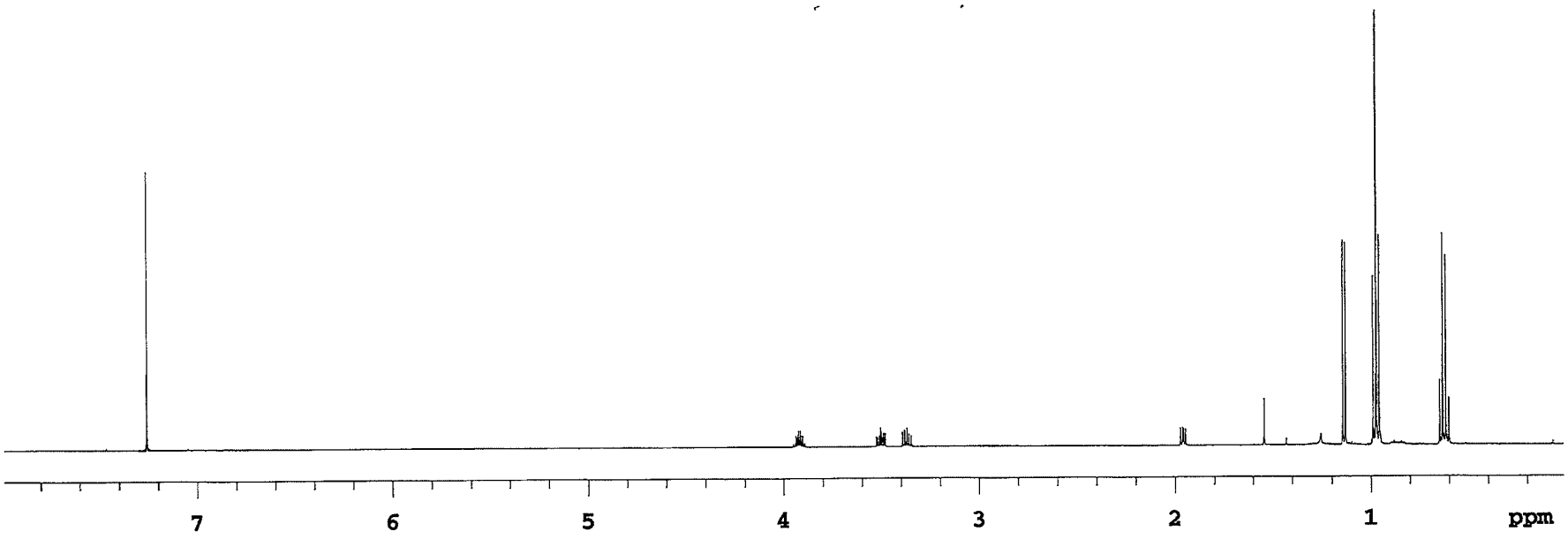
Et
Si
O
OH
Et
Me


7
6
5
4
3
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1
ppm

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120
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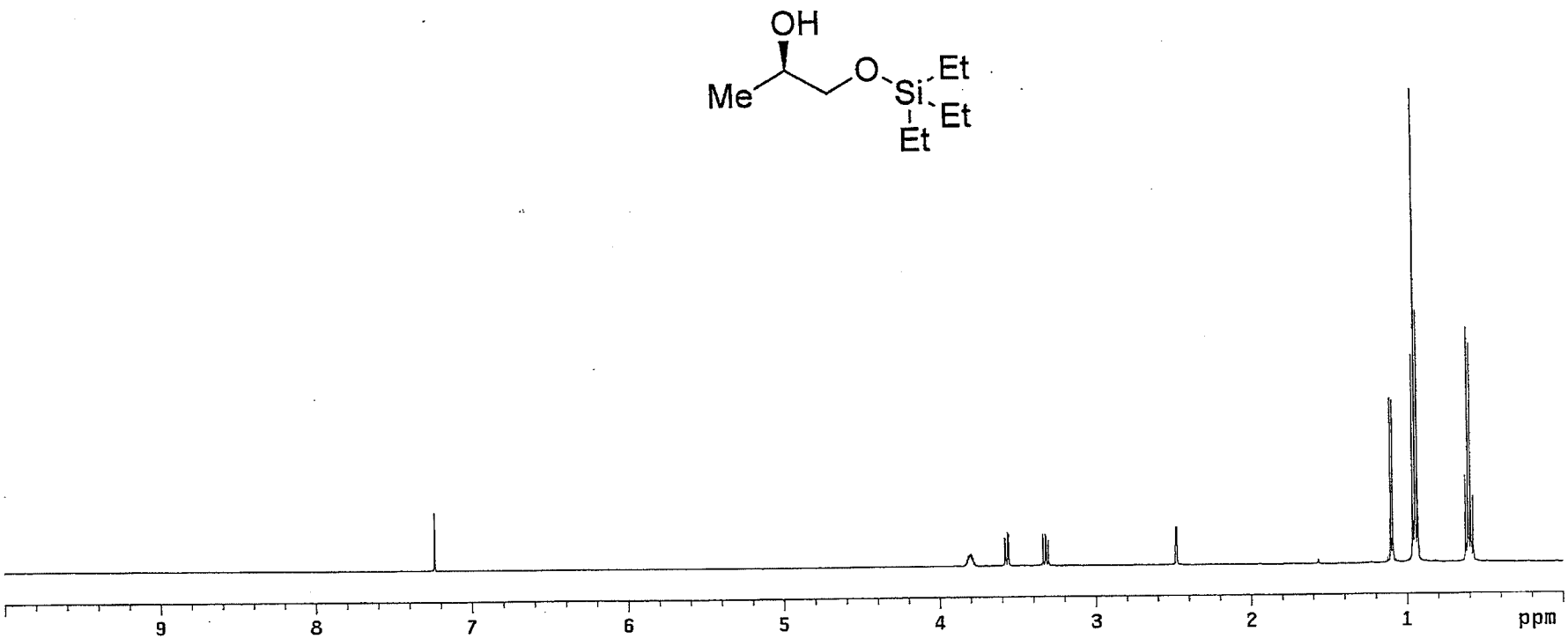
80
60
40
20
0
ppm
Et
Et
Si
O
Et
Me
OH


OH
Me
O
Si
Et
Et
Et
9
8
7
6
5
4
3
2
1
ppm

Me
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O
Si
Et
Et
Et
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120
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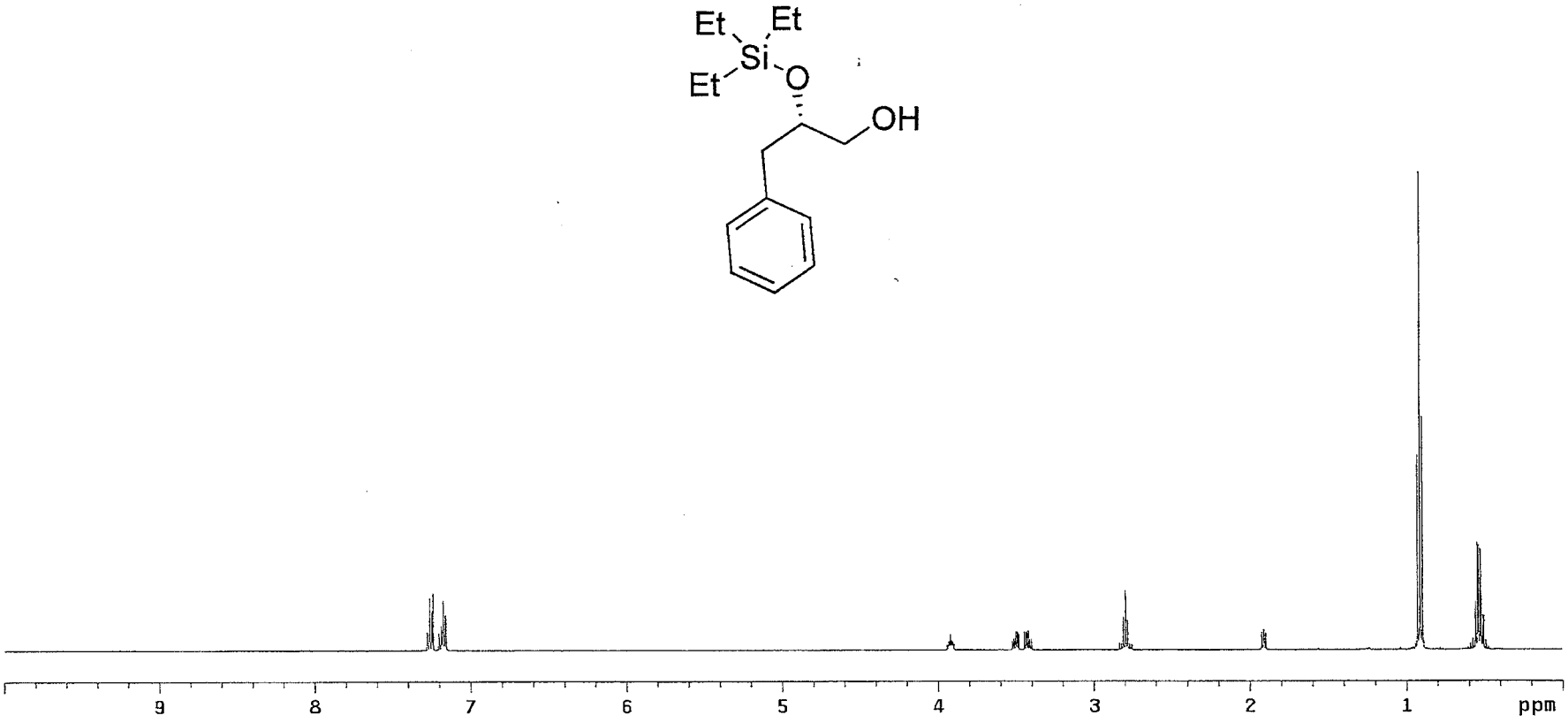
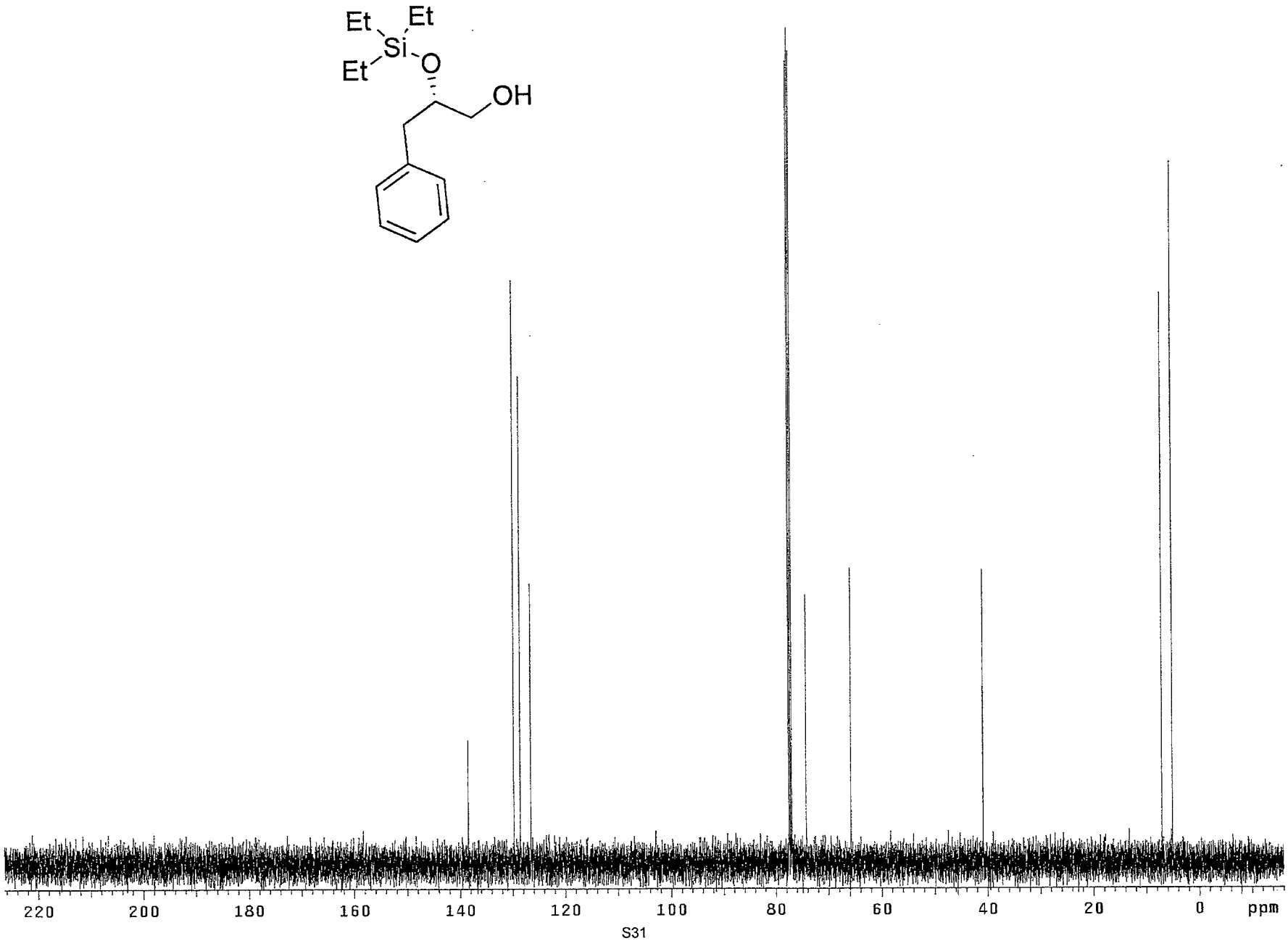
0
ppm


Et
Et
Si
Et
O
OH
9
8
7
6
5
4
3
2
1
ppm


Et
Et
Si
Et
O
OH
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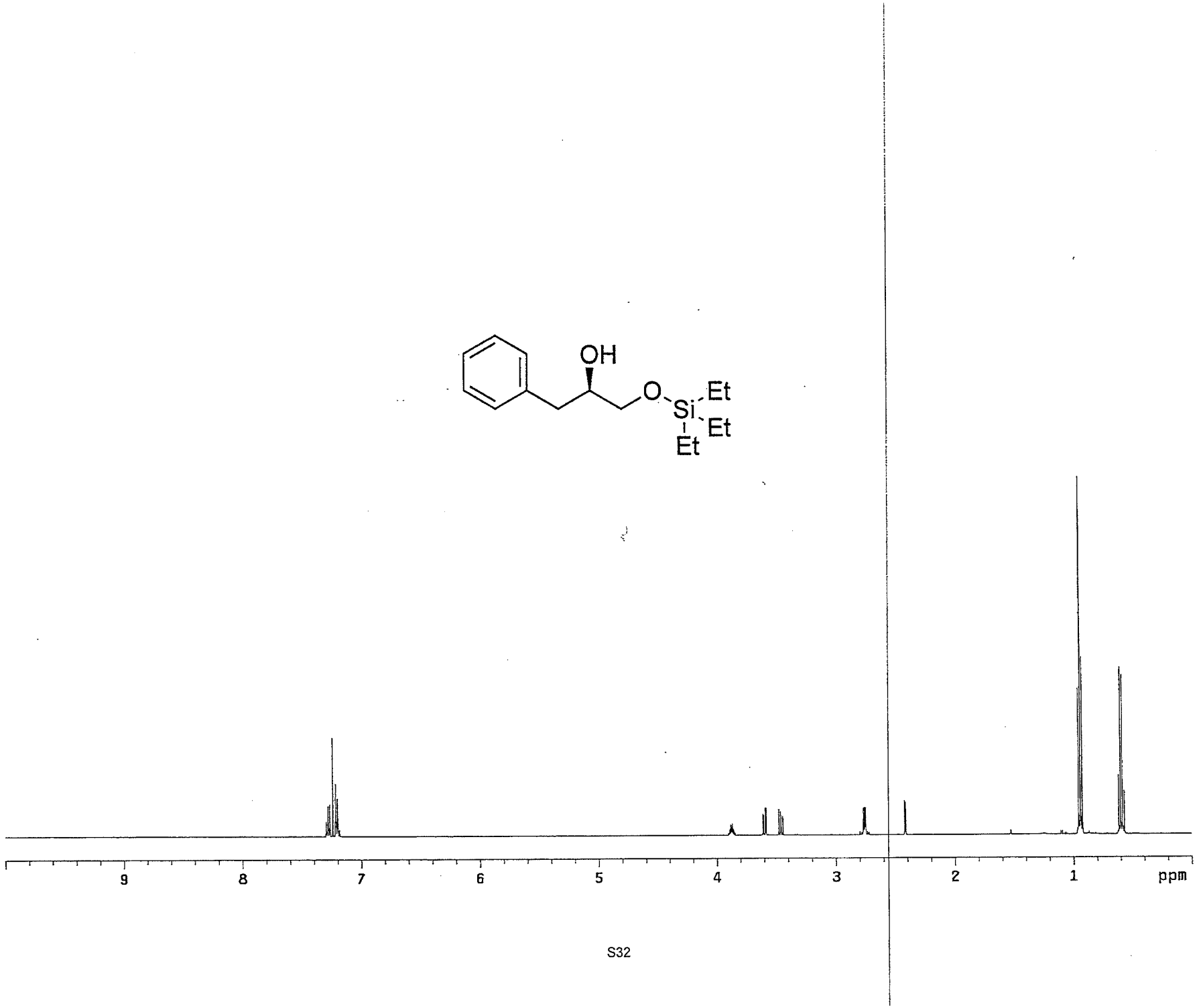
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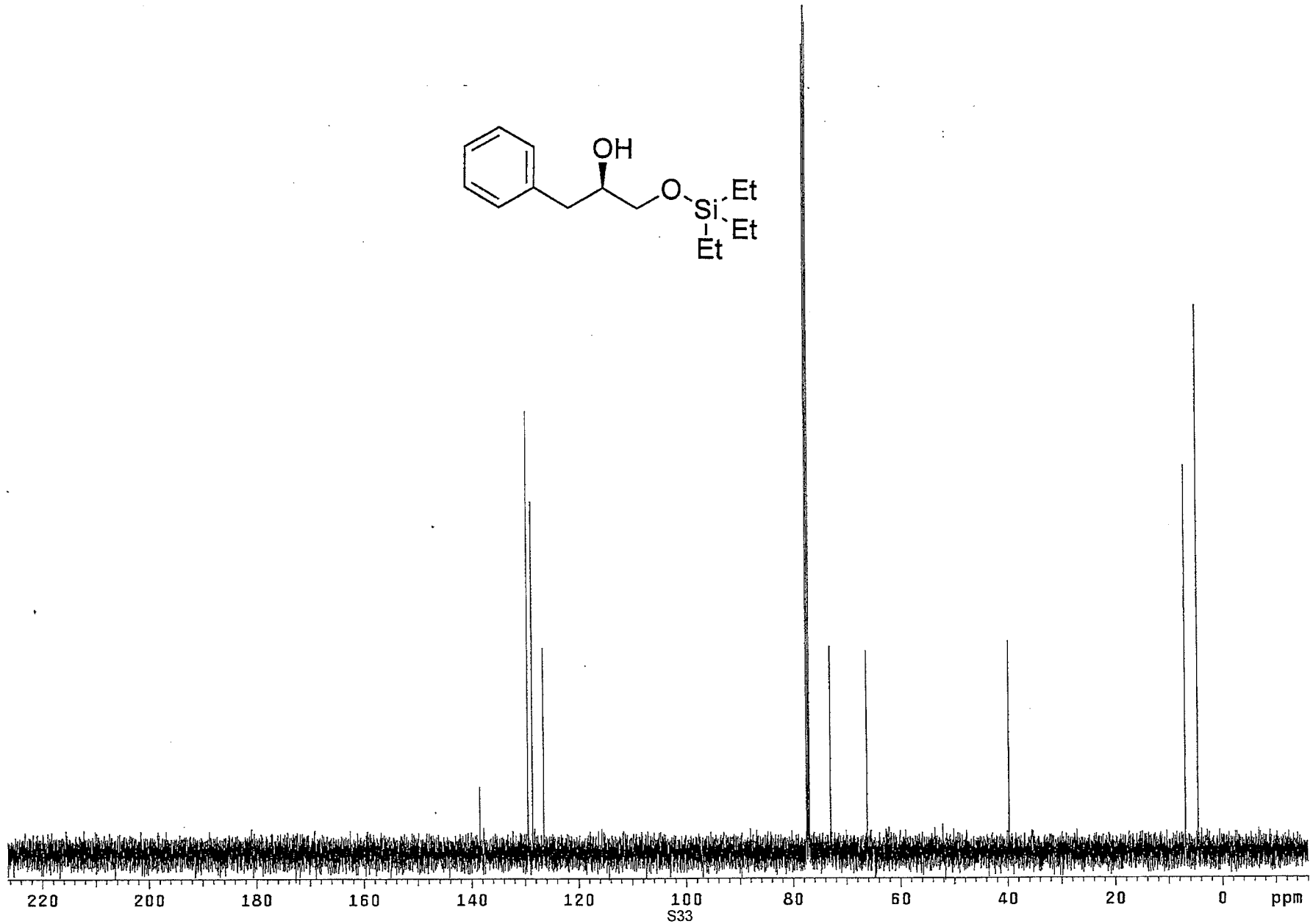
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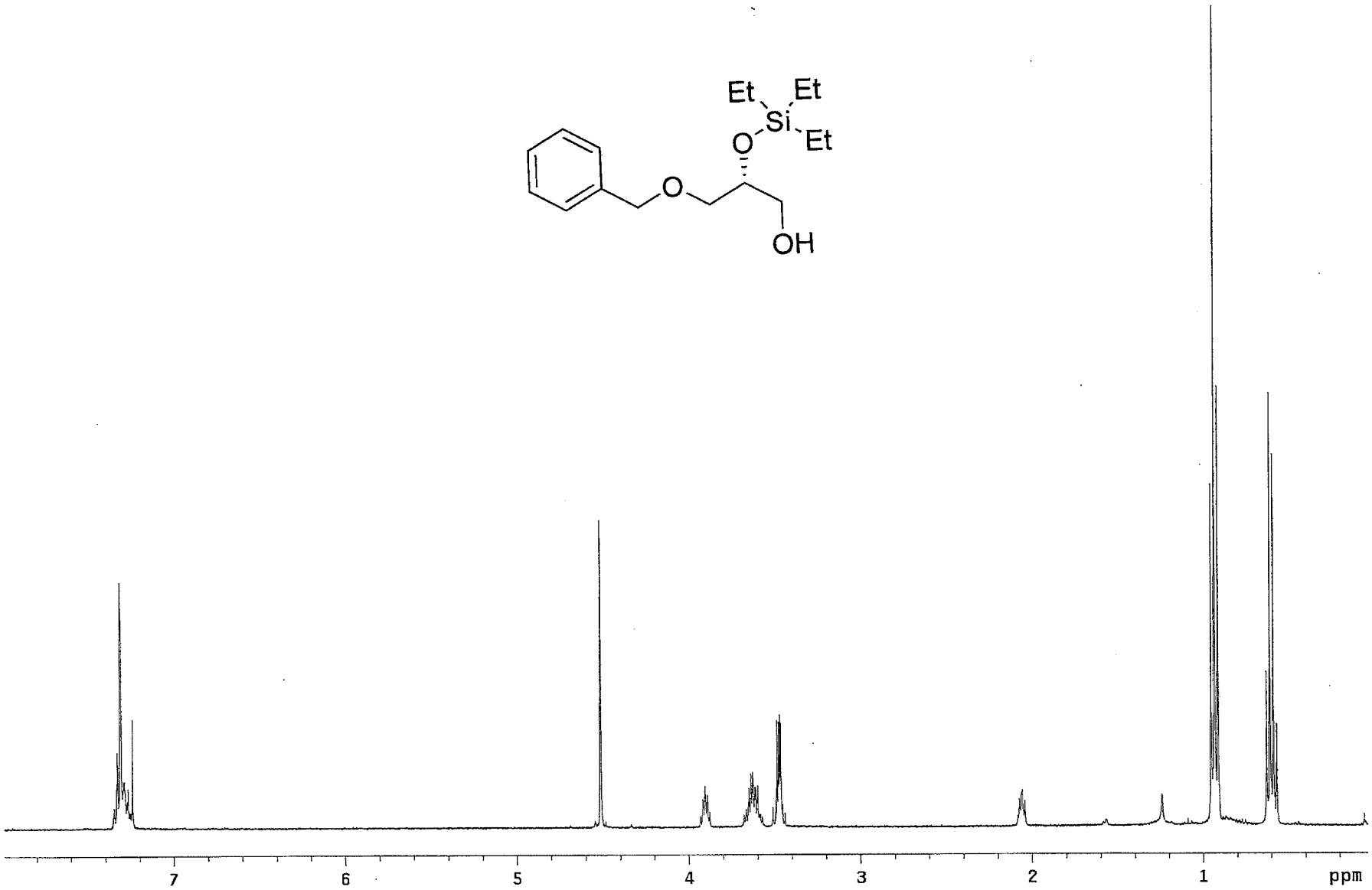
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ppm

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80
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0
ppm
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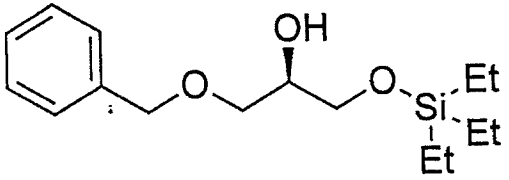
Et
Si
Et
Et
OH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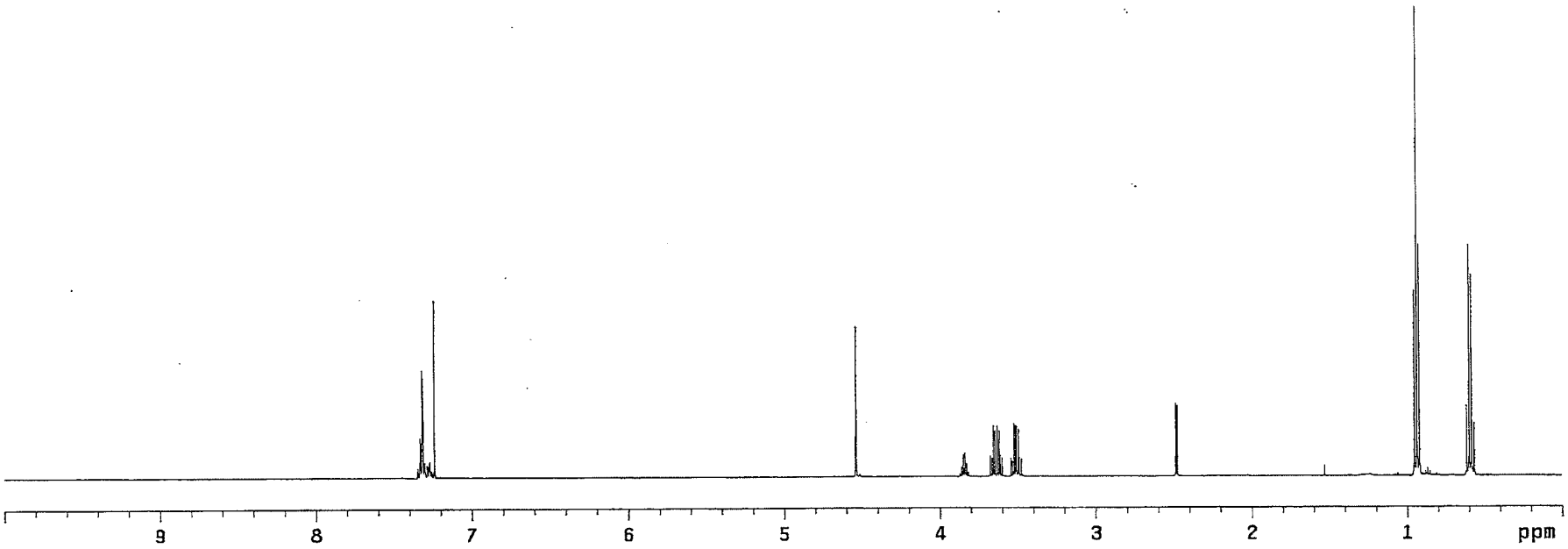
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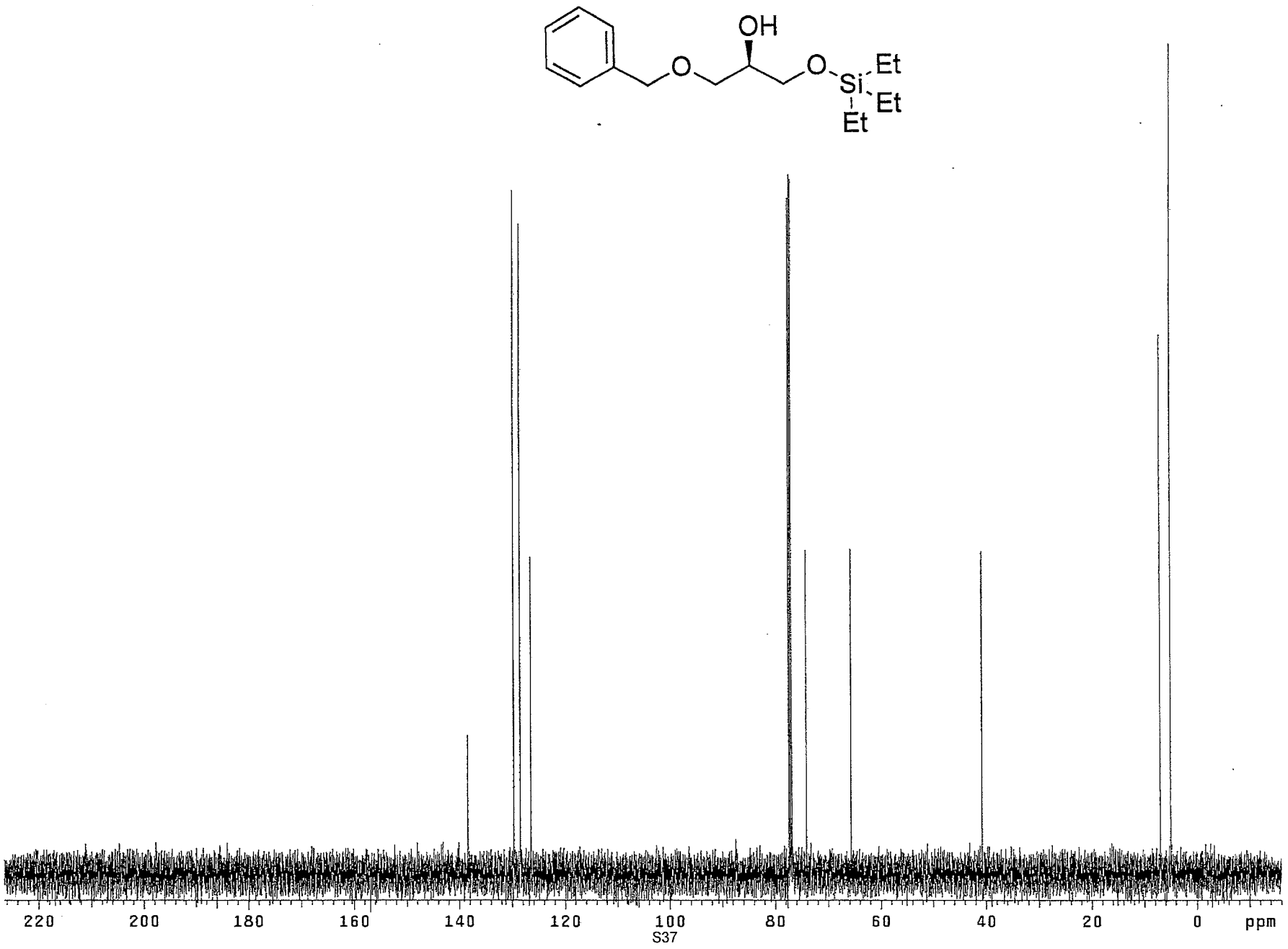
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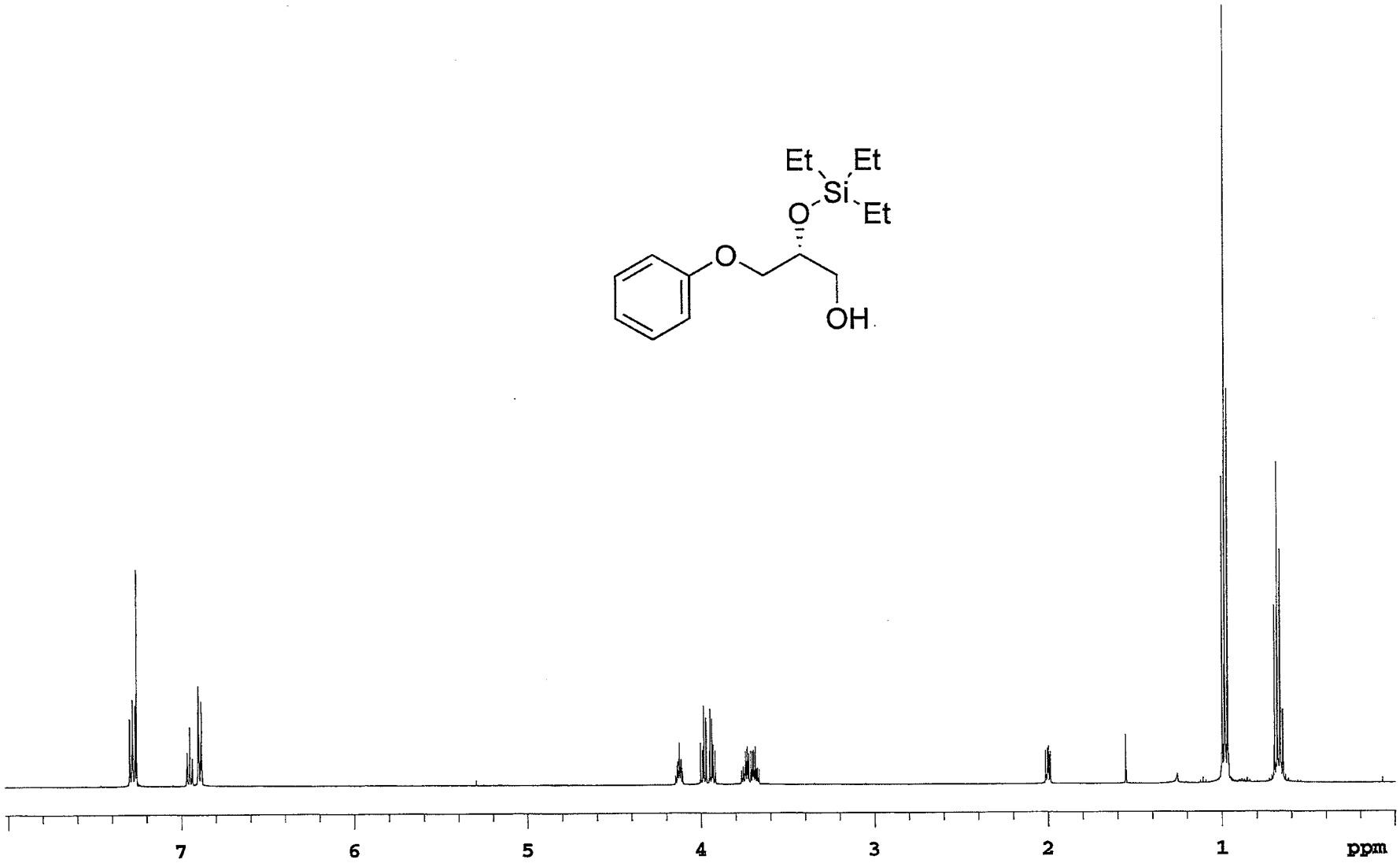
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Et
Si
Et
O
O
OH
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6
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4
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ppm
OH
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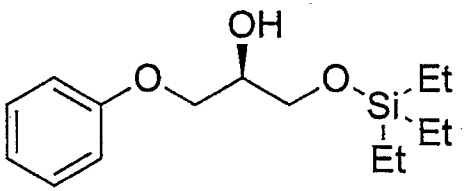
Si
Et
Et
Et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Et
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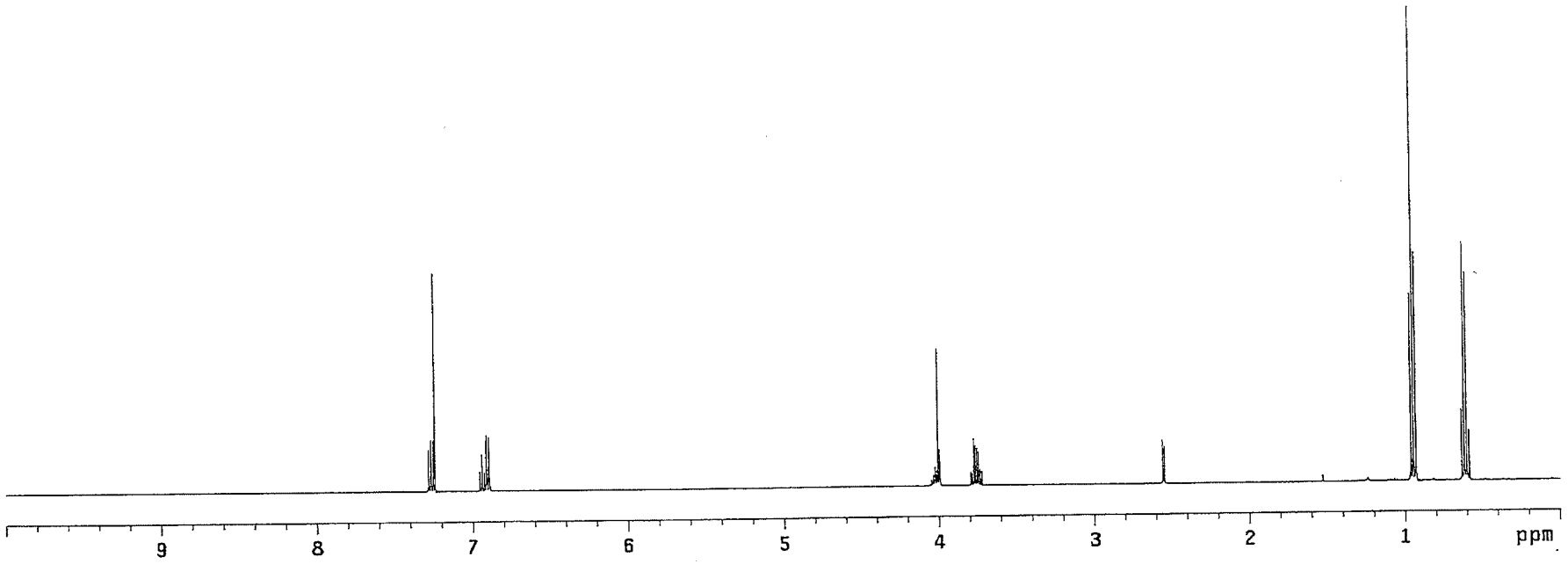
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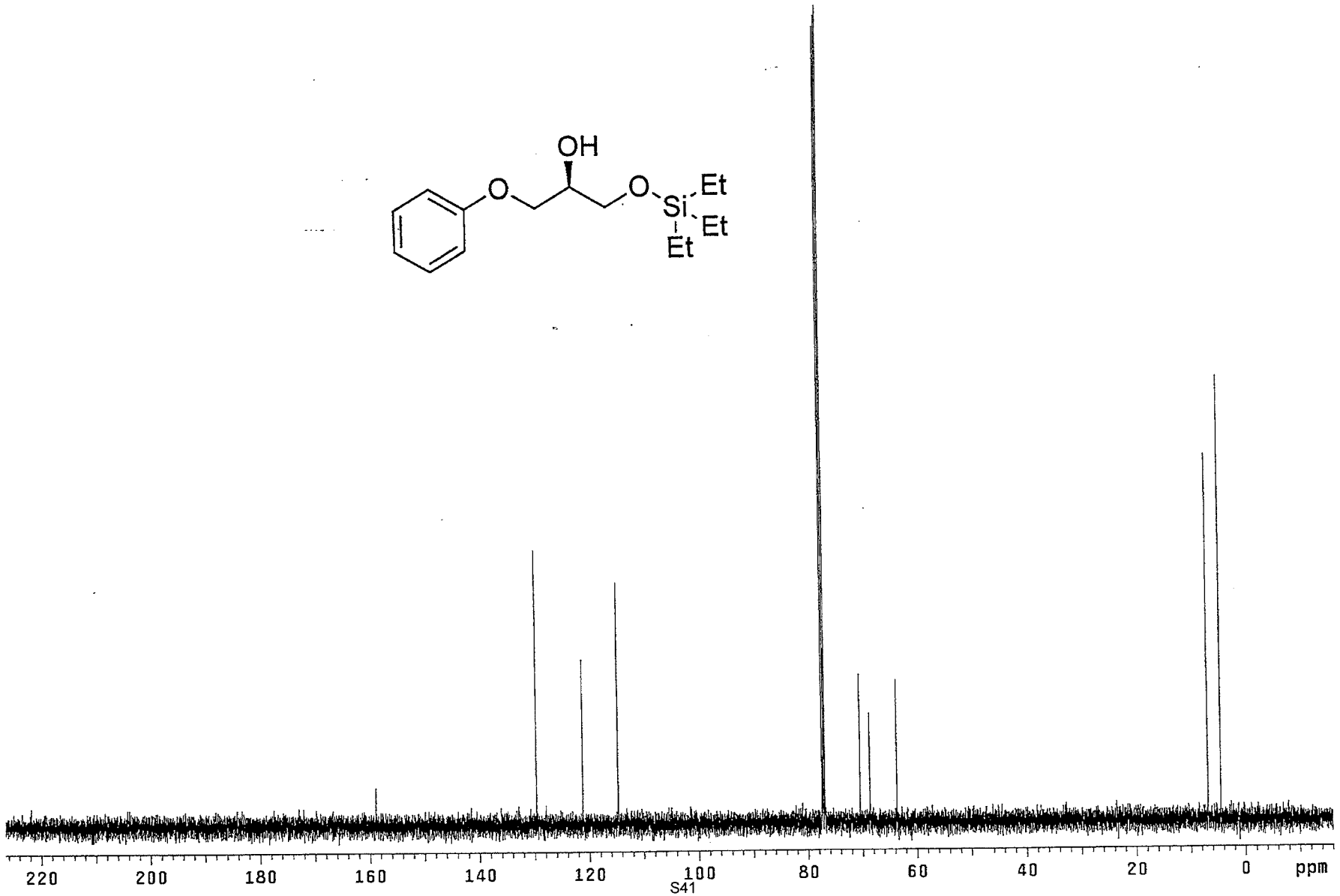
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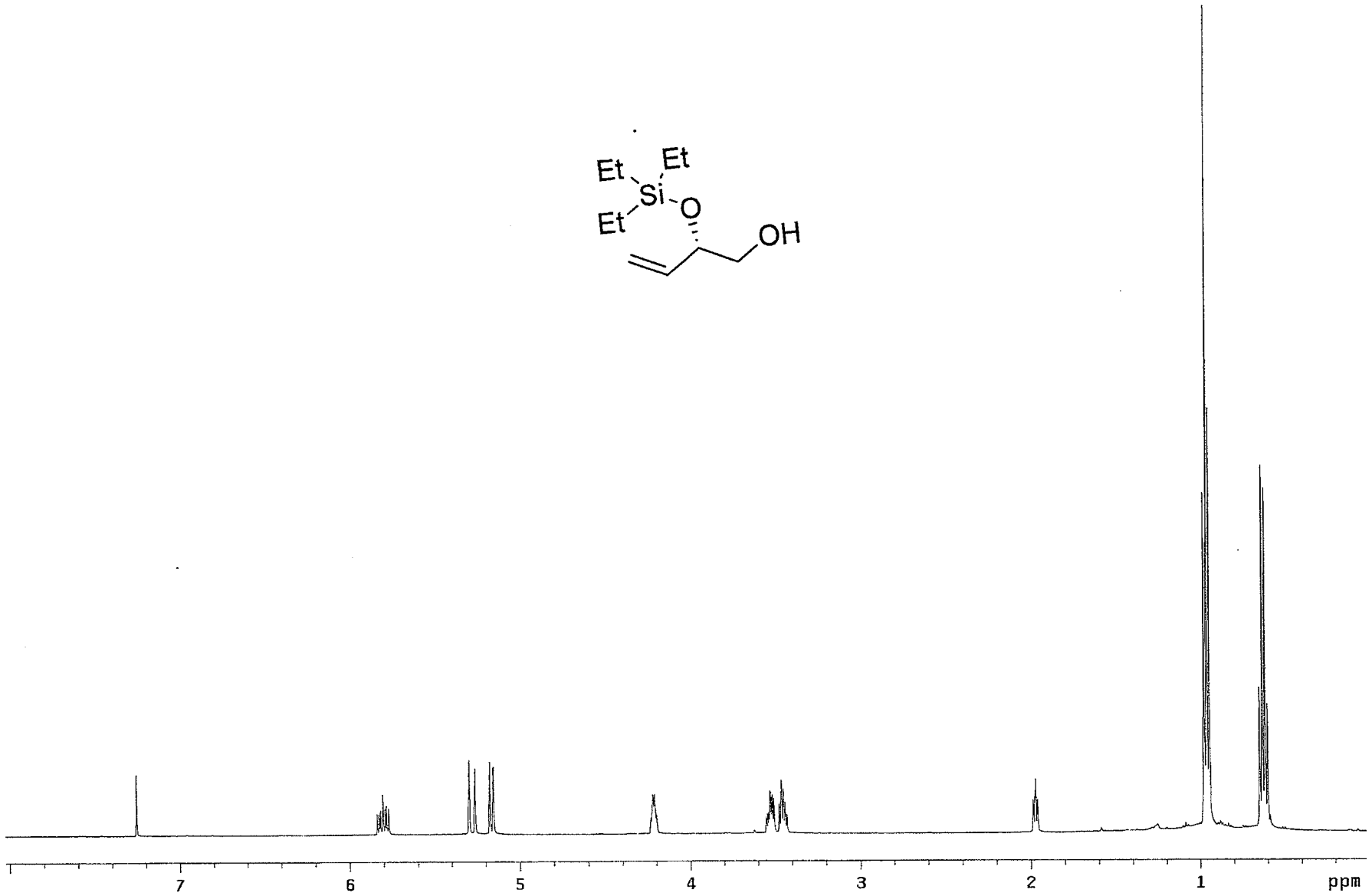
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Et
Si
Et
O
OH
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4
3
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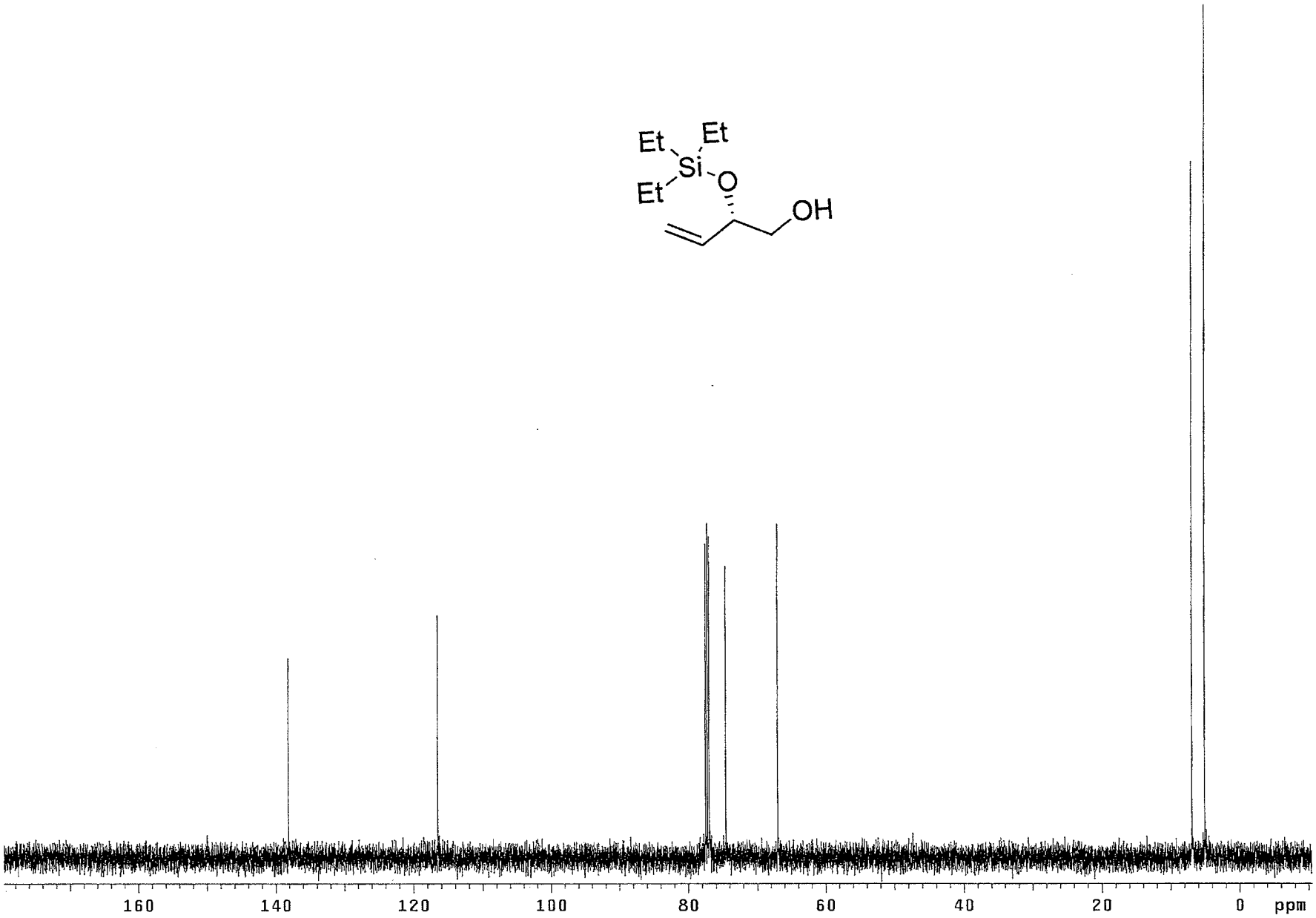
1
ppm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Et
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Et
O
OH
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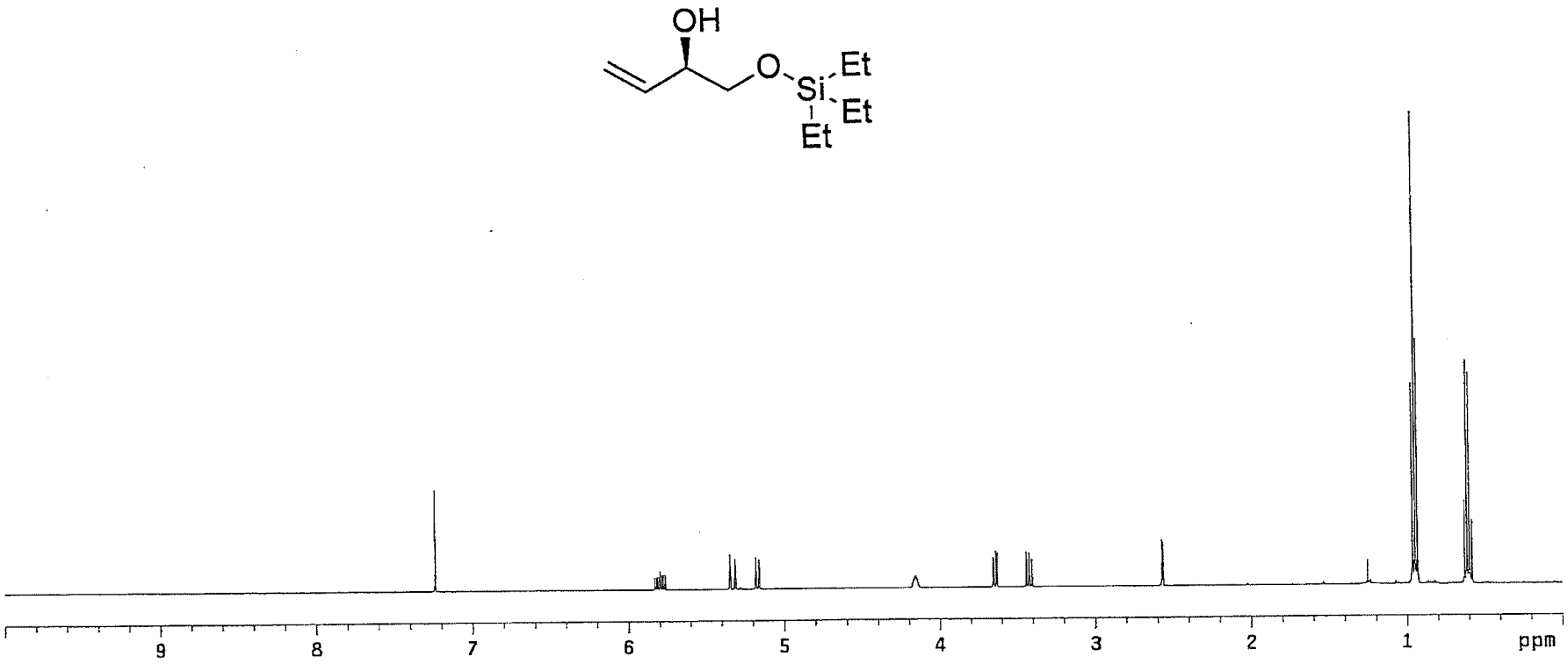
OH
O
Si
Et
Et
Et
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8
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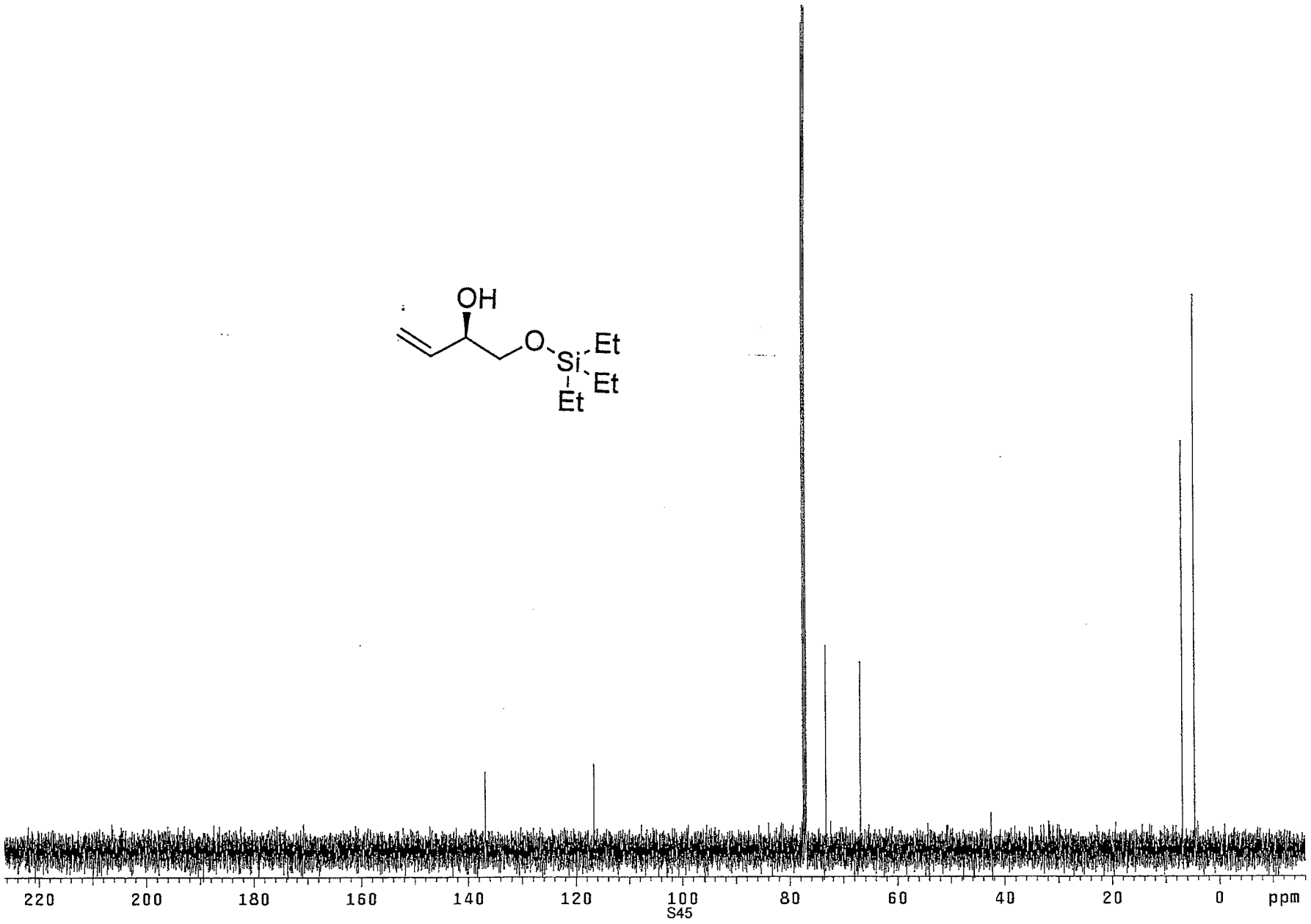
5
4
3
2
1
ppm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Si
Et
Et
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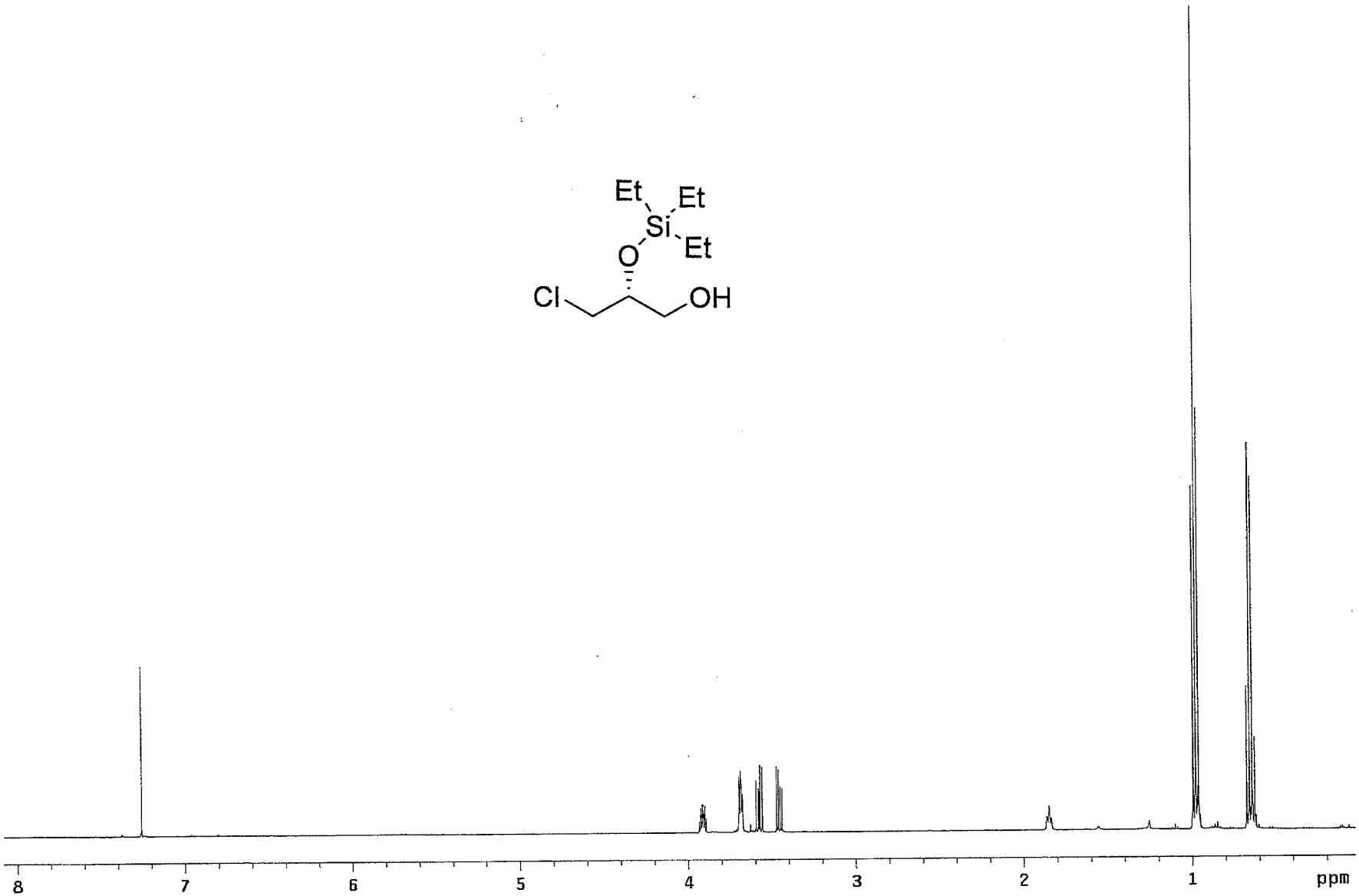
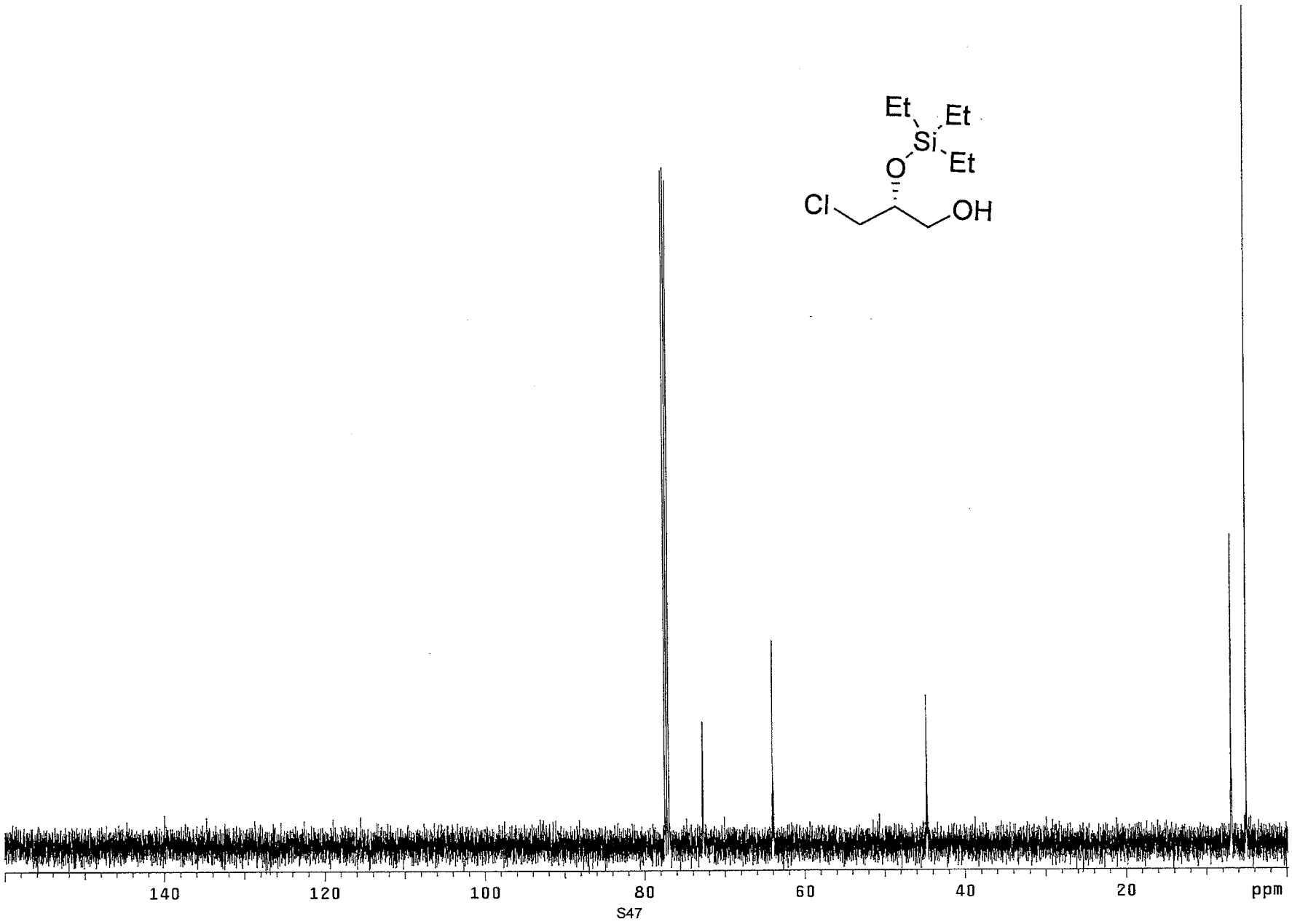

Et
Et
Si
Et
O
Cl
OH
8
7
6
5
4
3
2
1
ppm


Et
Et
Si
Et
O
Cl
OH
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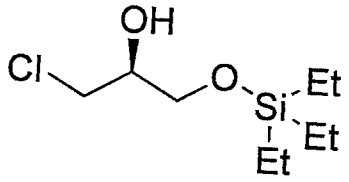
20
ppm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Cl
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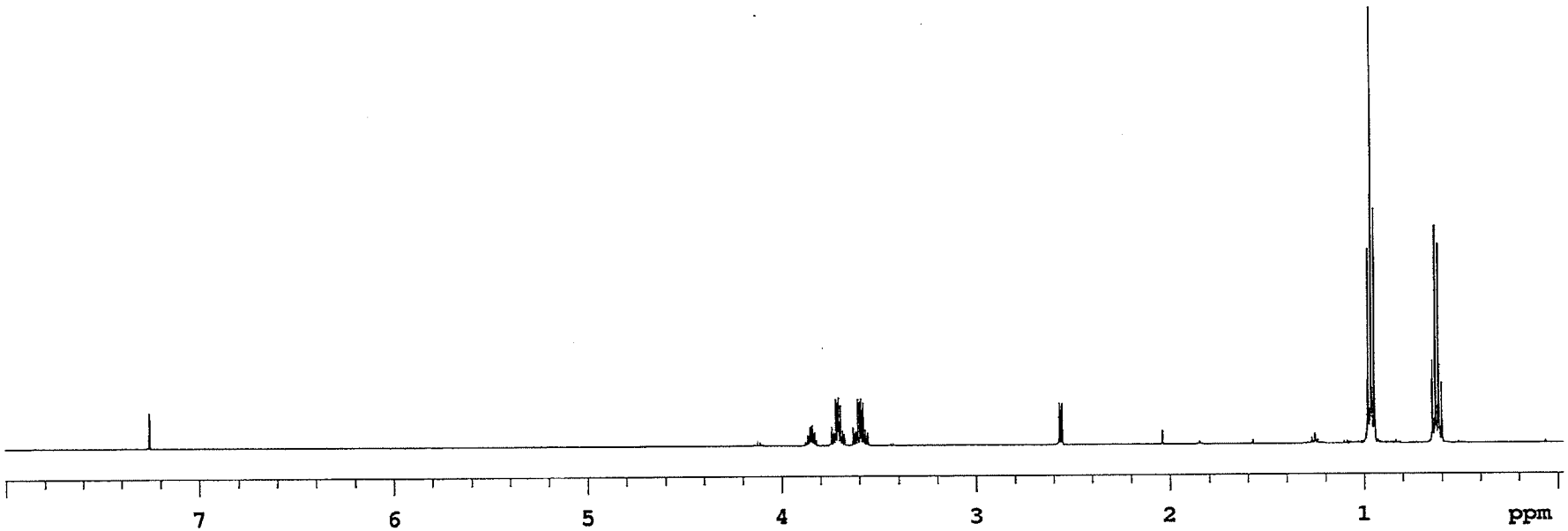
Si
Et
Et
Et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6
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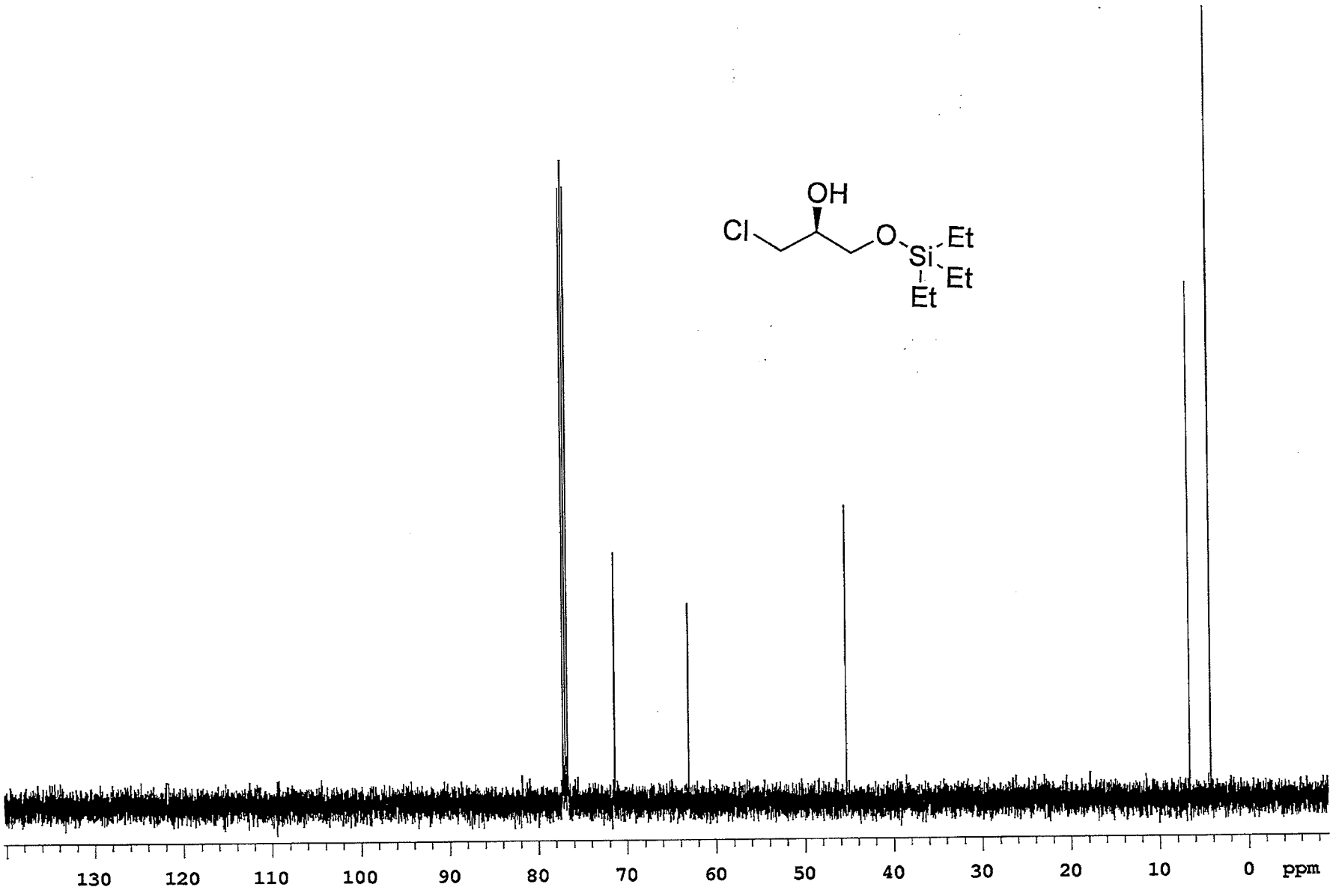
4
3
2
1
ppm


OH
Cl
O
Si
Et
Et
Et
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100
90
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30
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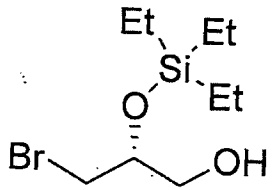
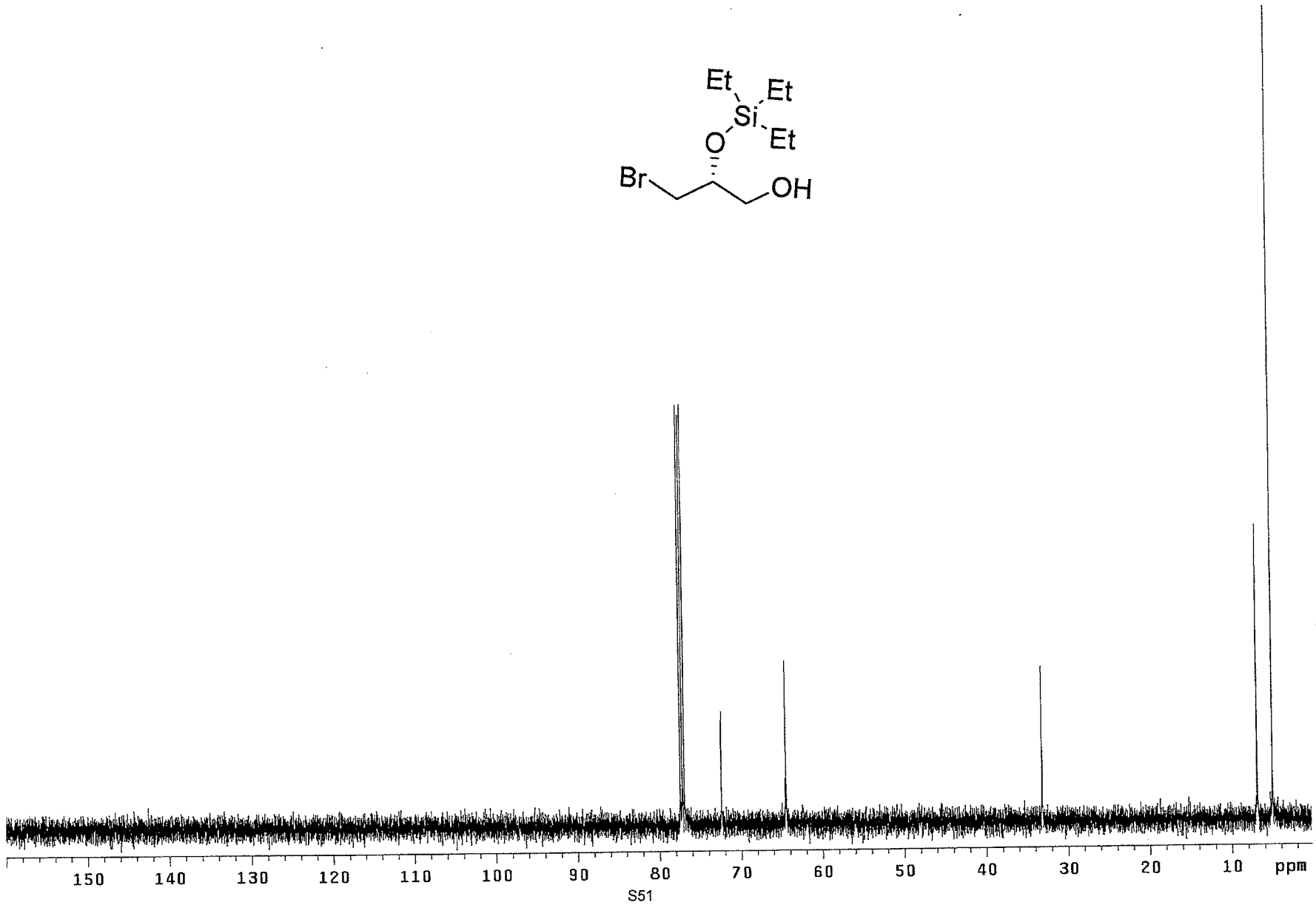
0
ppm


Et
Et
Si
Et
O
Br
OH

7
6
5
4
3
2
1
ppm


Et
Et
Si
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Br
OH
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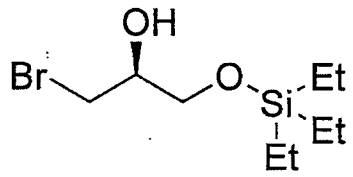
10
ppm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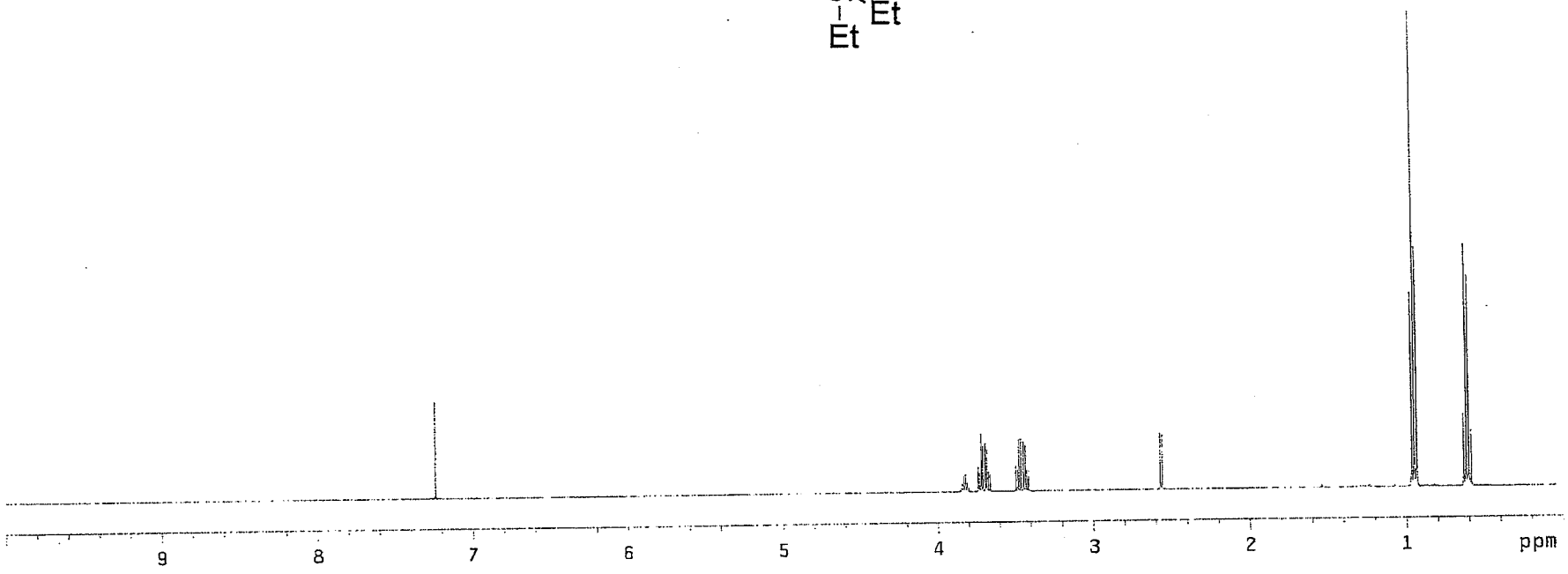
Si
Et
Et
Et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1
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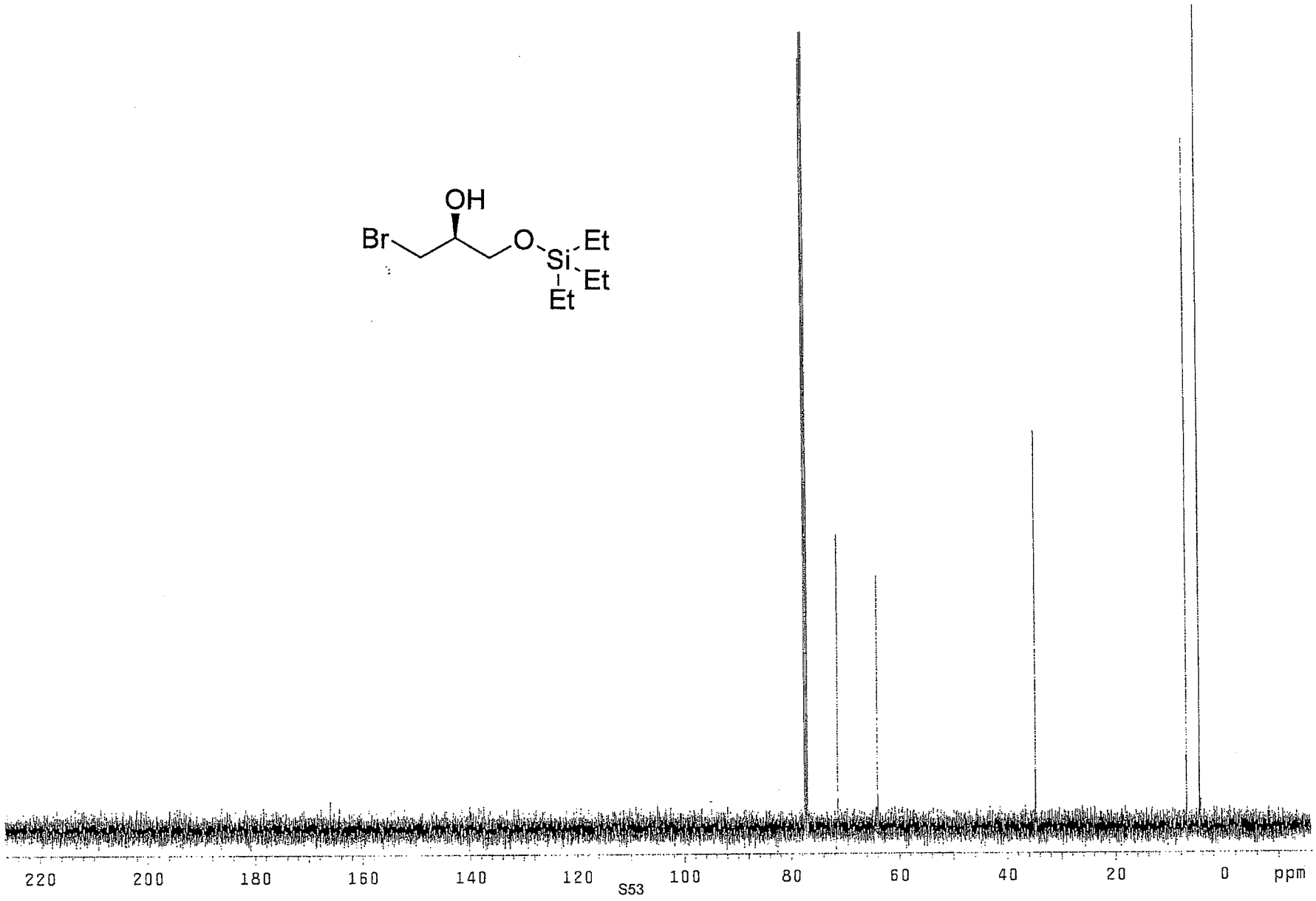
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Br
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Si
Et
Et
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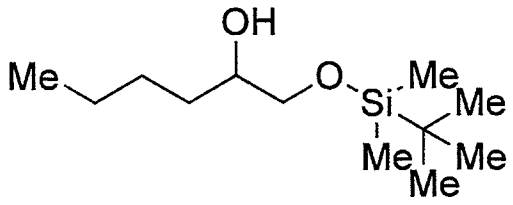
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Si
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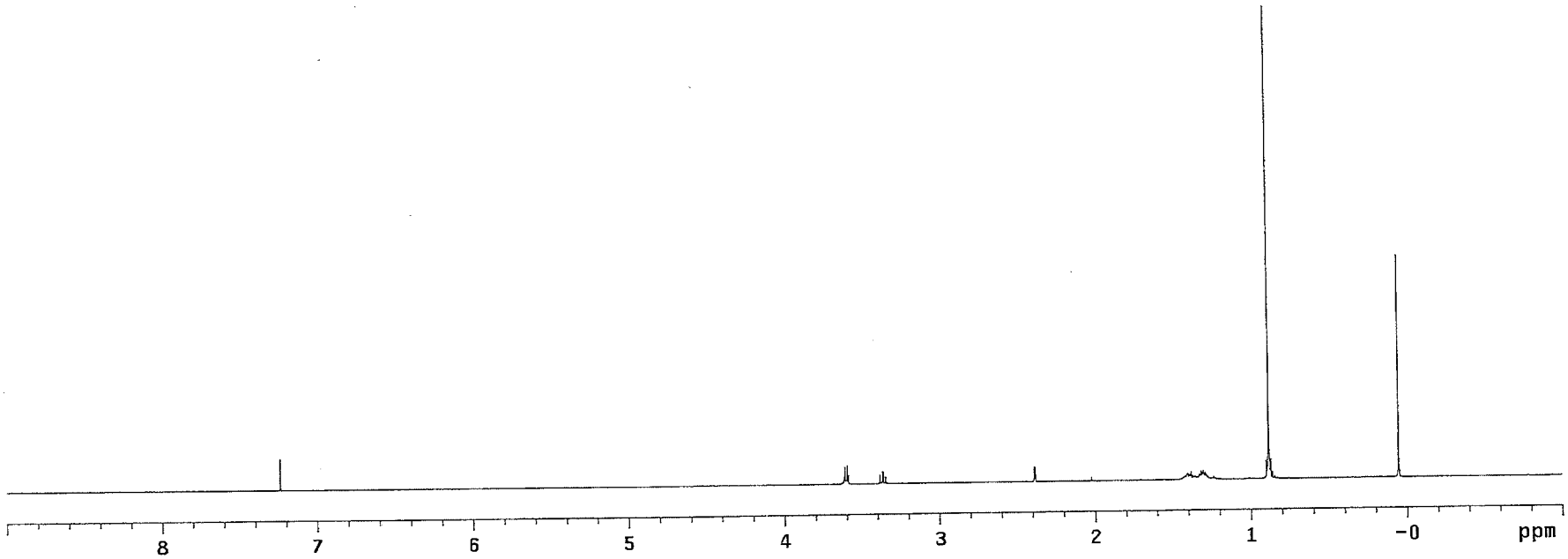
Me
Me
Me
Me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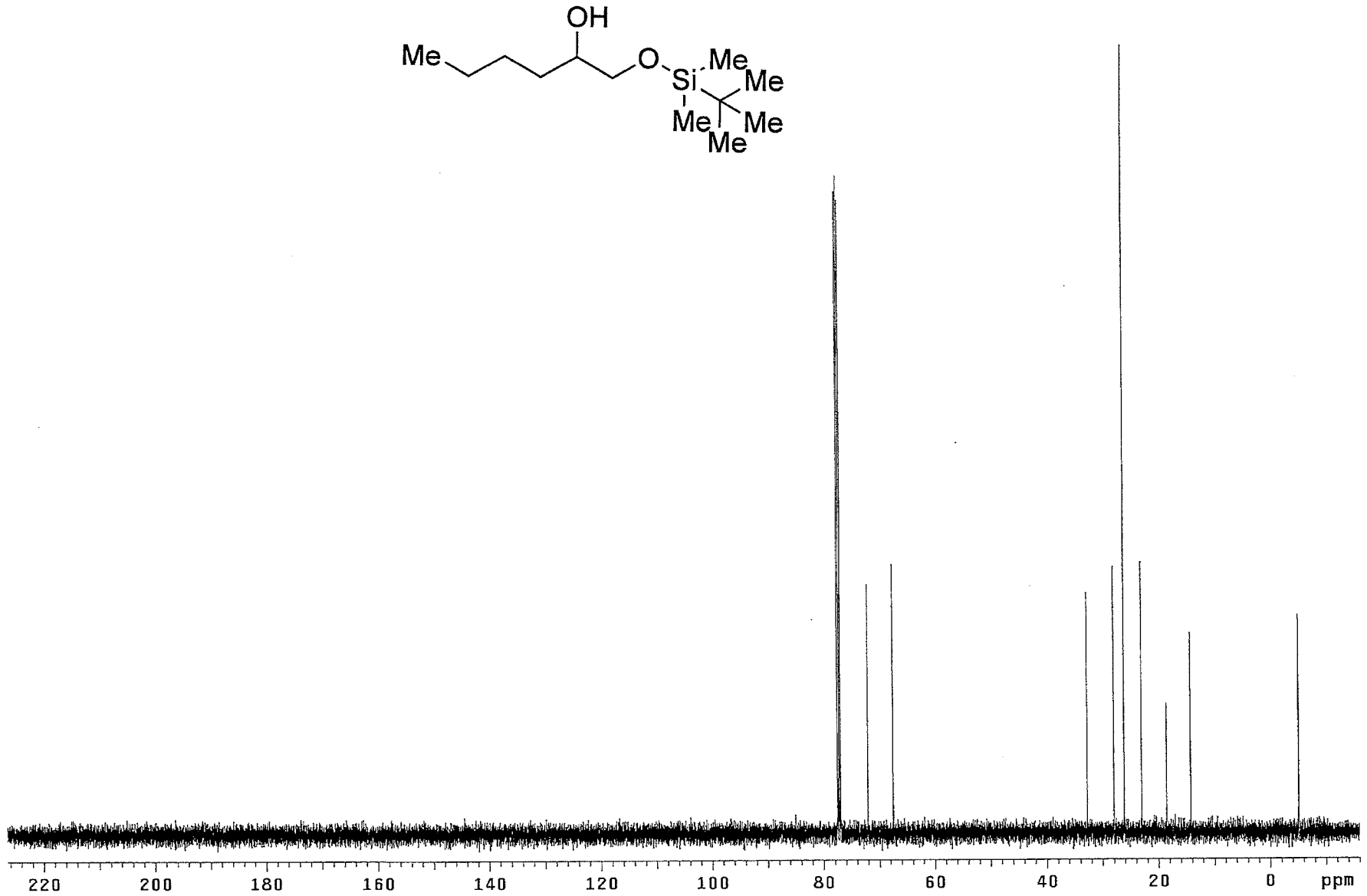
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O
Si
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Me
Me
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200
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160
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100
80
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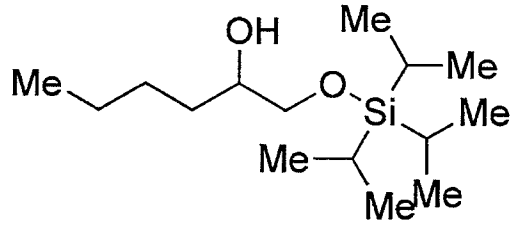
0
ppm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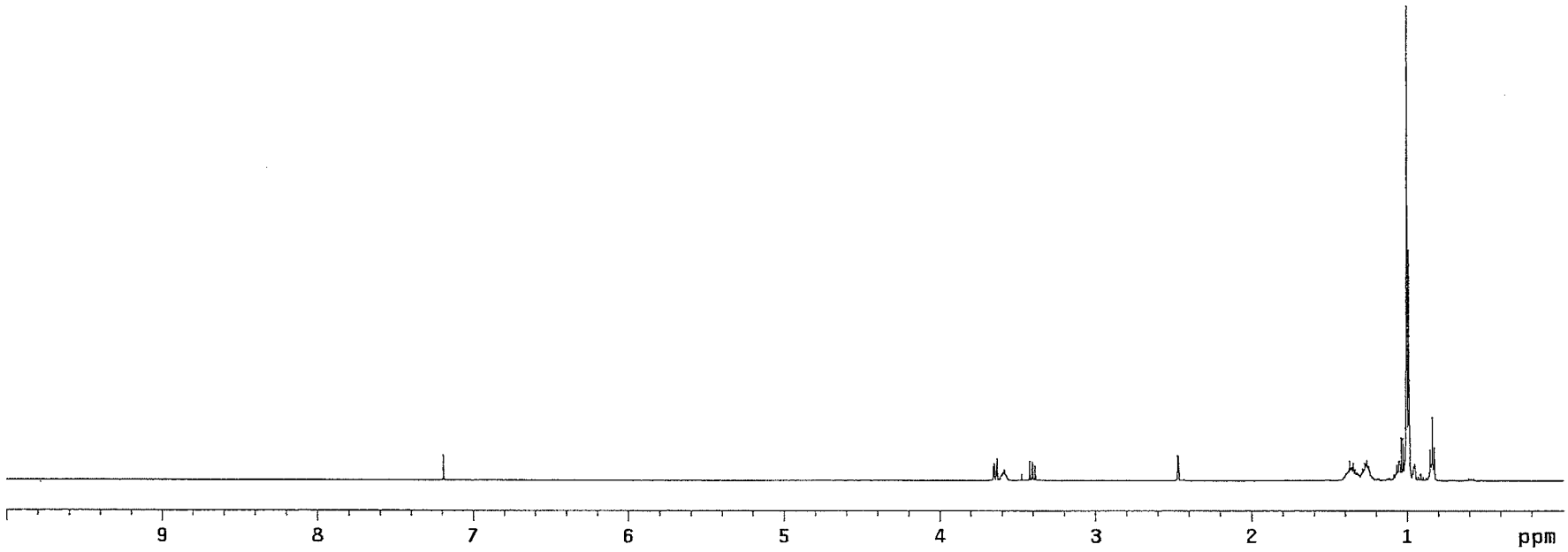
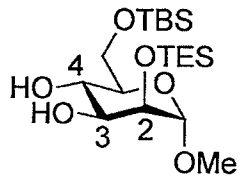
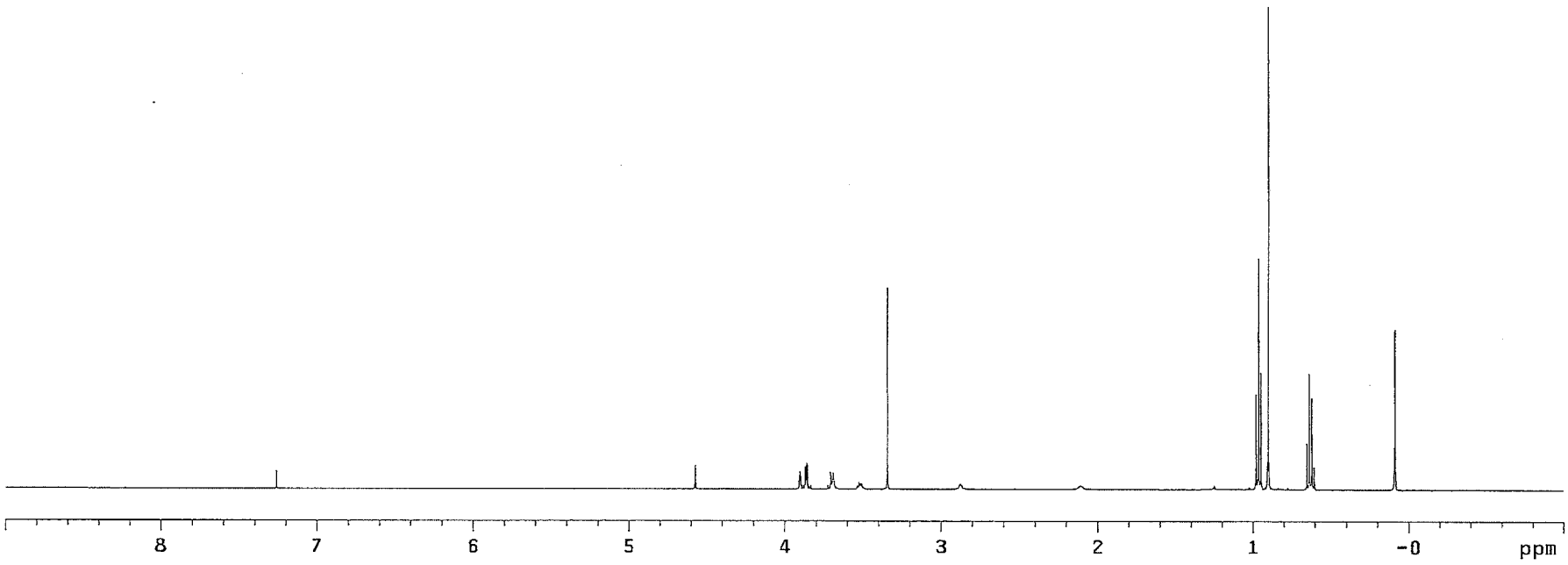
Me
O
Si
Me
Me
Me
Me

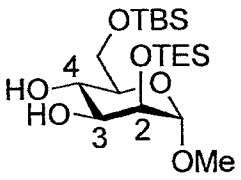

9
8
7
6
5
4
3
2
1
ppm

220
200
180
160
140
120
100
80
60
40
20
0
ppm

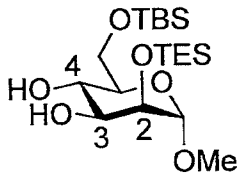
Me
OH
Me
O
Si
Me
Me
Me
Me
Me
Me

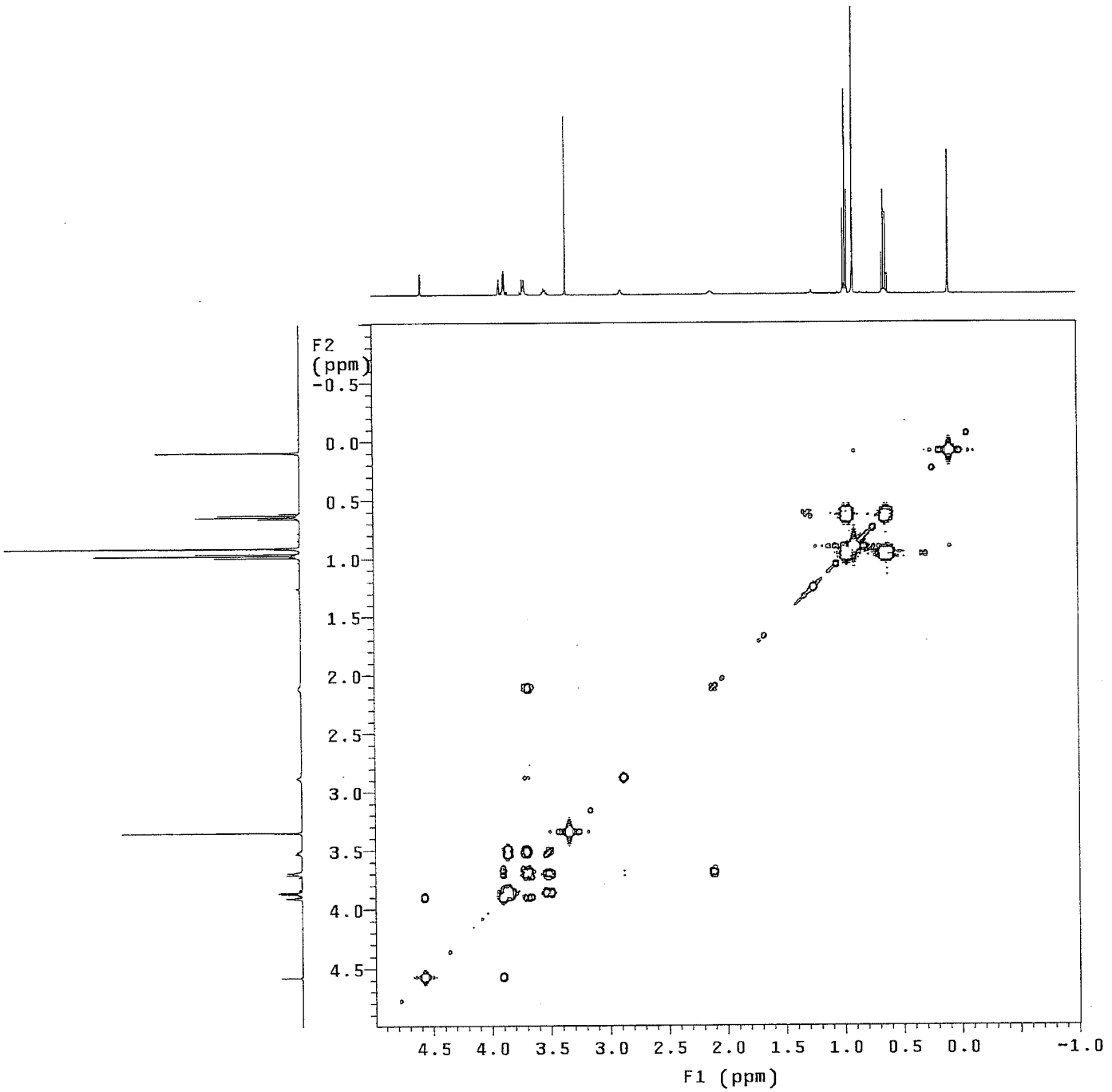

OTBS
OTES
4
HO
HO
O
3
2
OMe

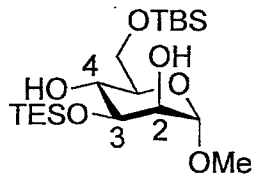

8
7
6
5
4
3
2
1
-0
ppm

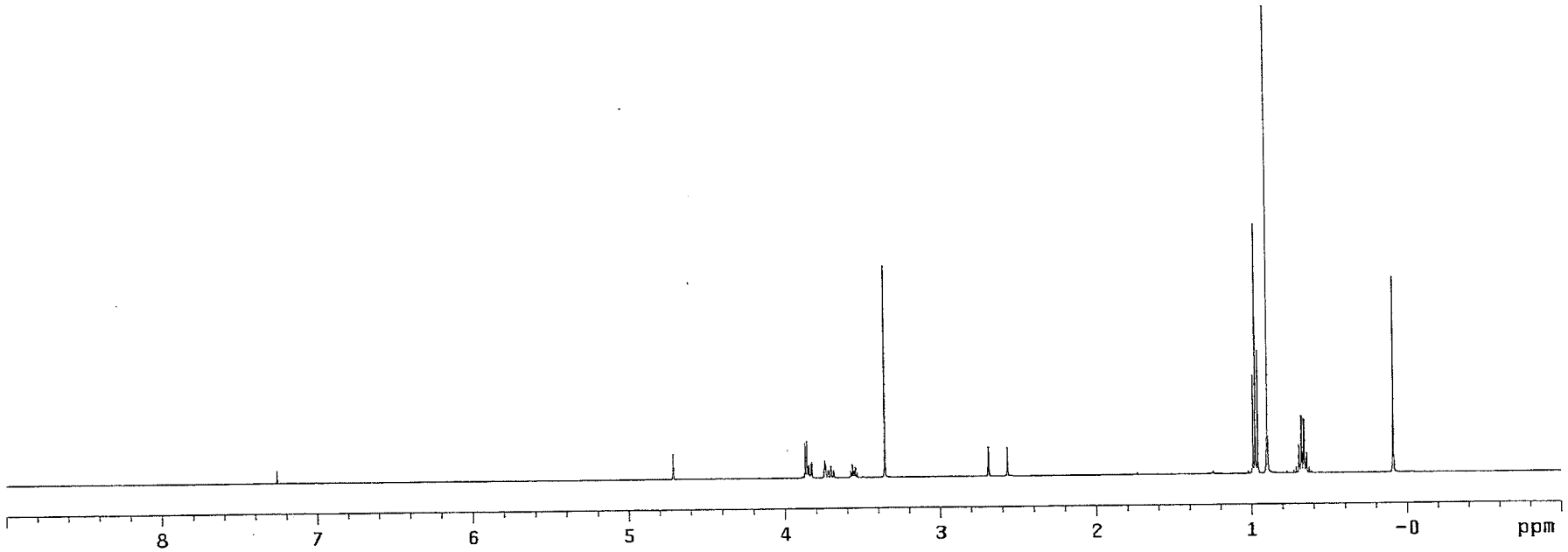

OTBS
OTES
4
HO
HO
3
2
O
OMe

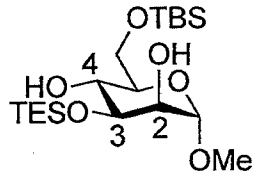
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
OTES
4
HO
HO
3
2
O
OMe

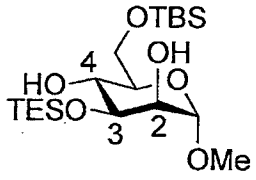

F2
(ppm)
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -1.0
F1 (ppm)

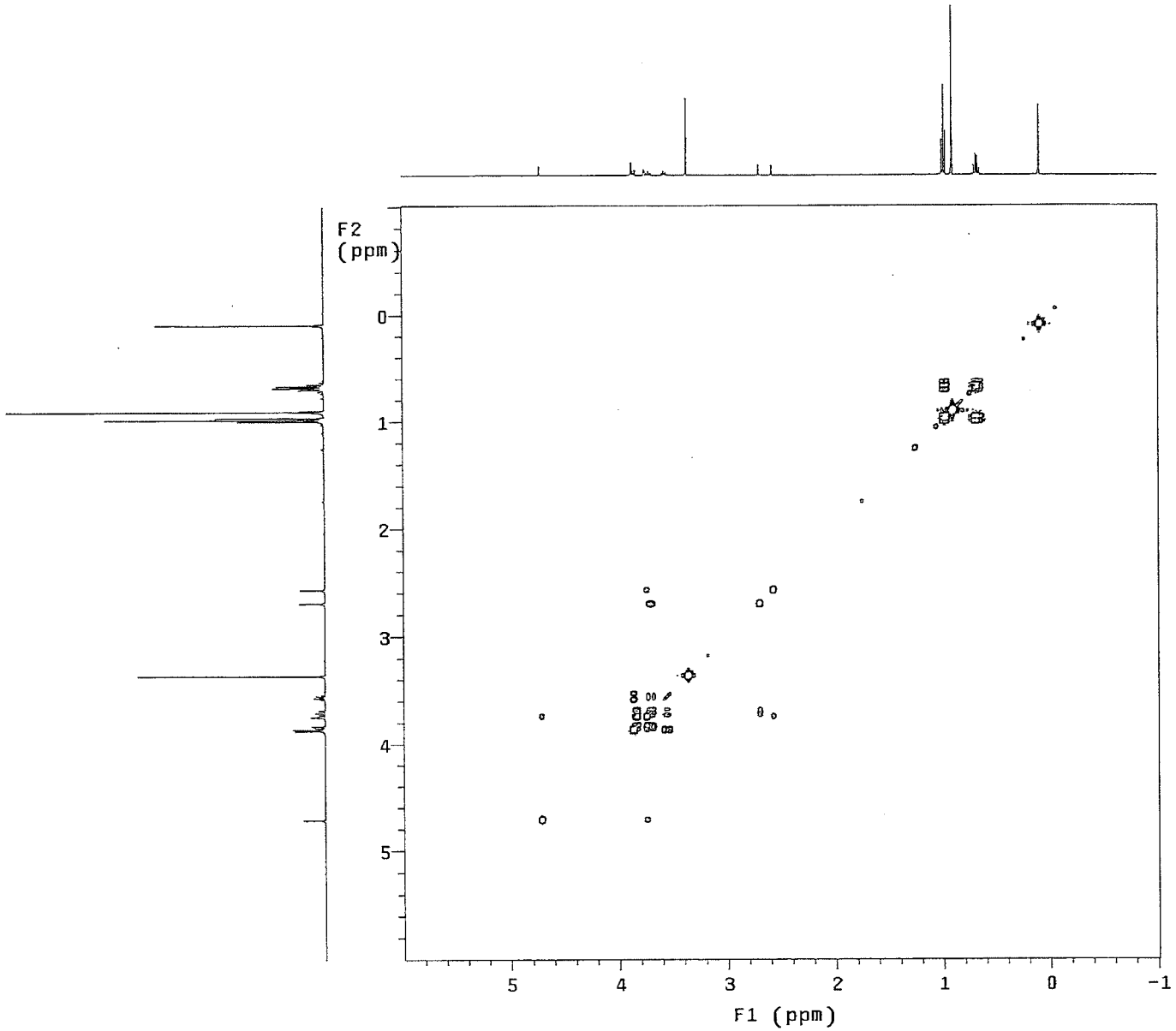

OTBS
OH
4
HO
O
TESO
3
2
OMe


8
7
6
5
4
3
2
1
-0
ppm


OTBS
OH
4
HO
O
TESO
3
2
OMe

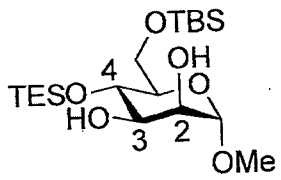
220
200
180
160
140
120
100
80
60
40
20
0 ppm


OTBS
OH
4
HO
O
TESO
3
2
OMe


F2
(ppm)
0
1
2
3
4
5
5
4
3
2
1
0
-1
F1 (ppm)

TESO
HO
4
3
2
OTBS
OH
O
OMe

ppm
8
7
6
5
4
3
2
1
0


OTBS
OH
4
TESO
O
HO
3
2
OMe

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100
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0
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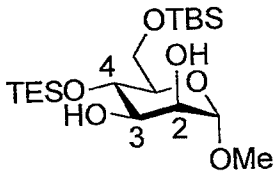
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OH
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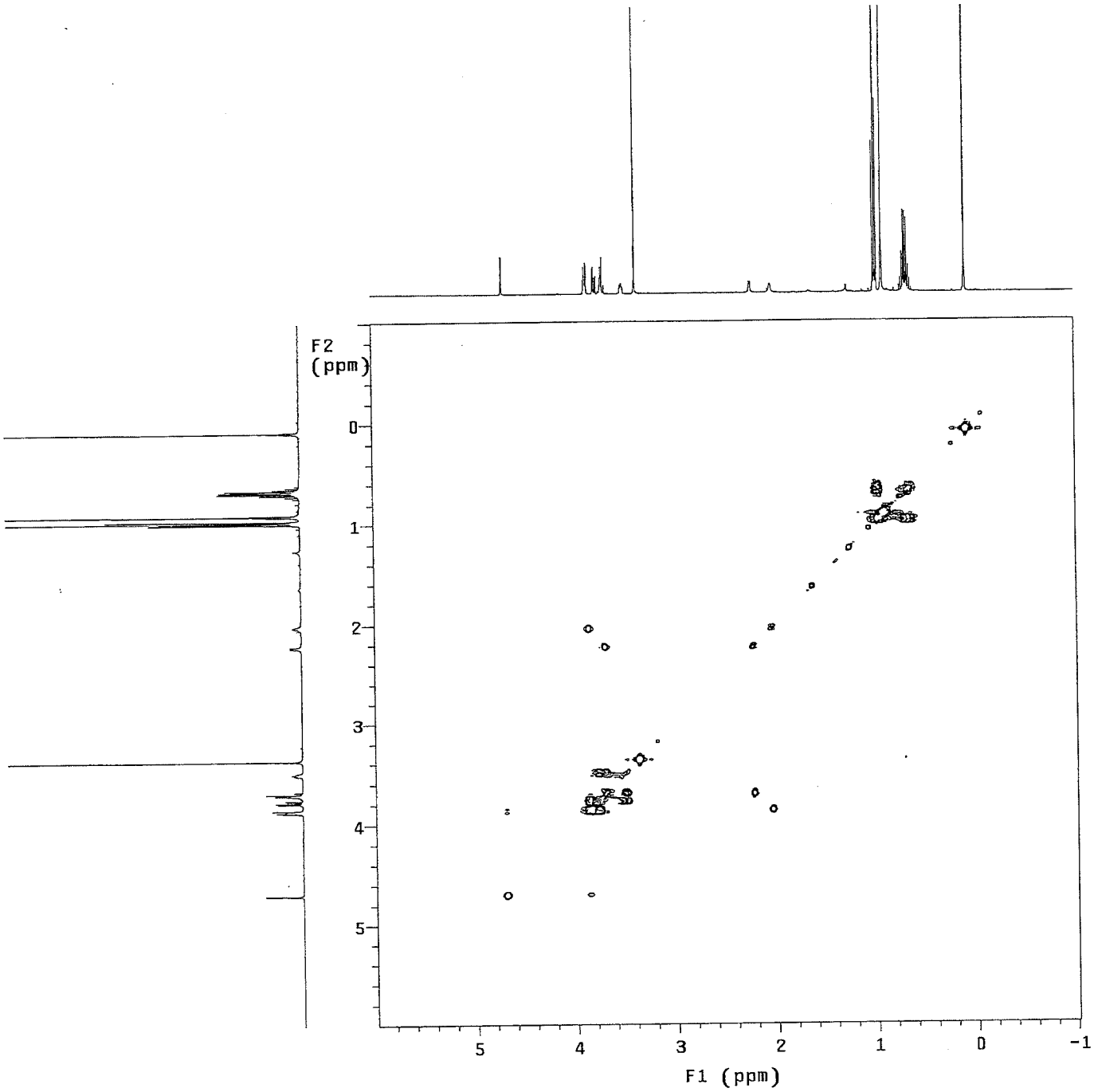
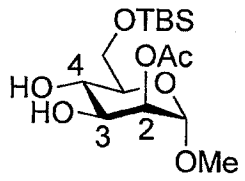
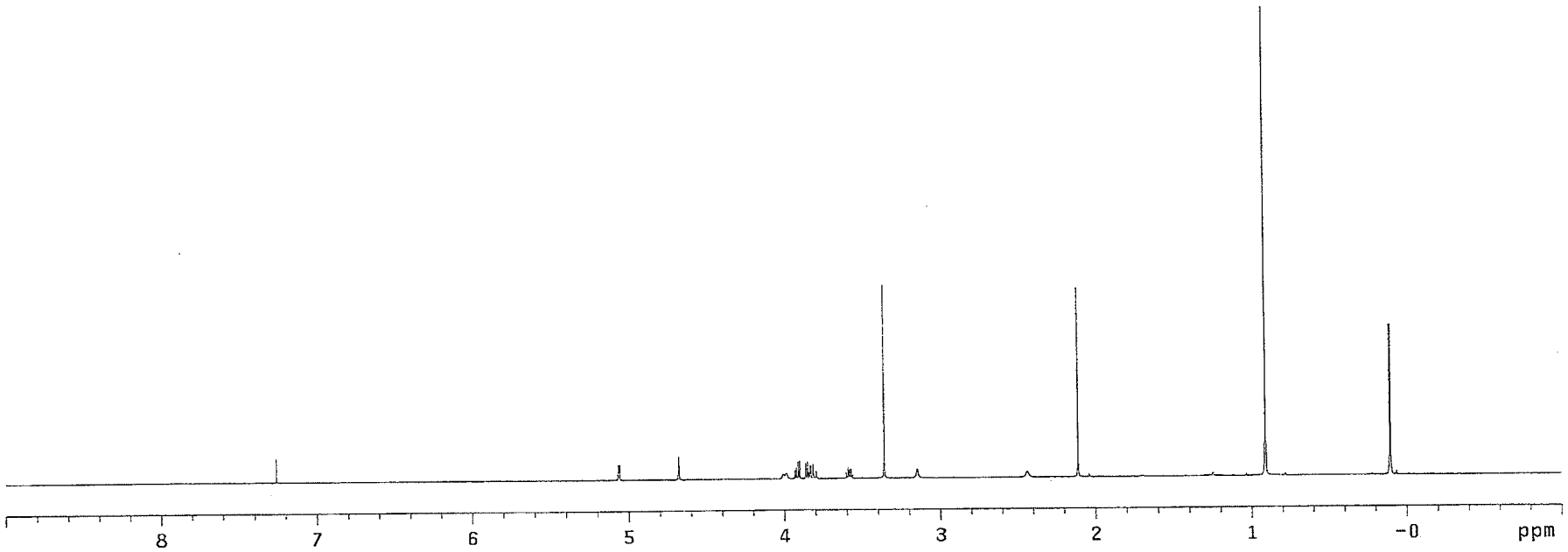
TESO
O
HO
3
2
OMe


F2
(ppm)
0
1
2
3
4
5
5
4
3
2
1
0
-1
F1 (ppm)


OTBS
OAc
4
HO
HO
3
2
O
OMe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7
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5
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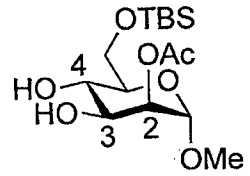
3
2
1
-0
ppm


OTBS
OAc
4
HO
HO
3
2
O
OMe

220
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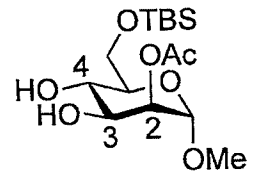
0
ppm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OAc
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HO
HO
3
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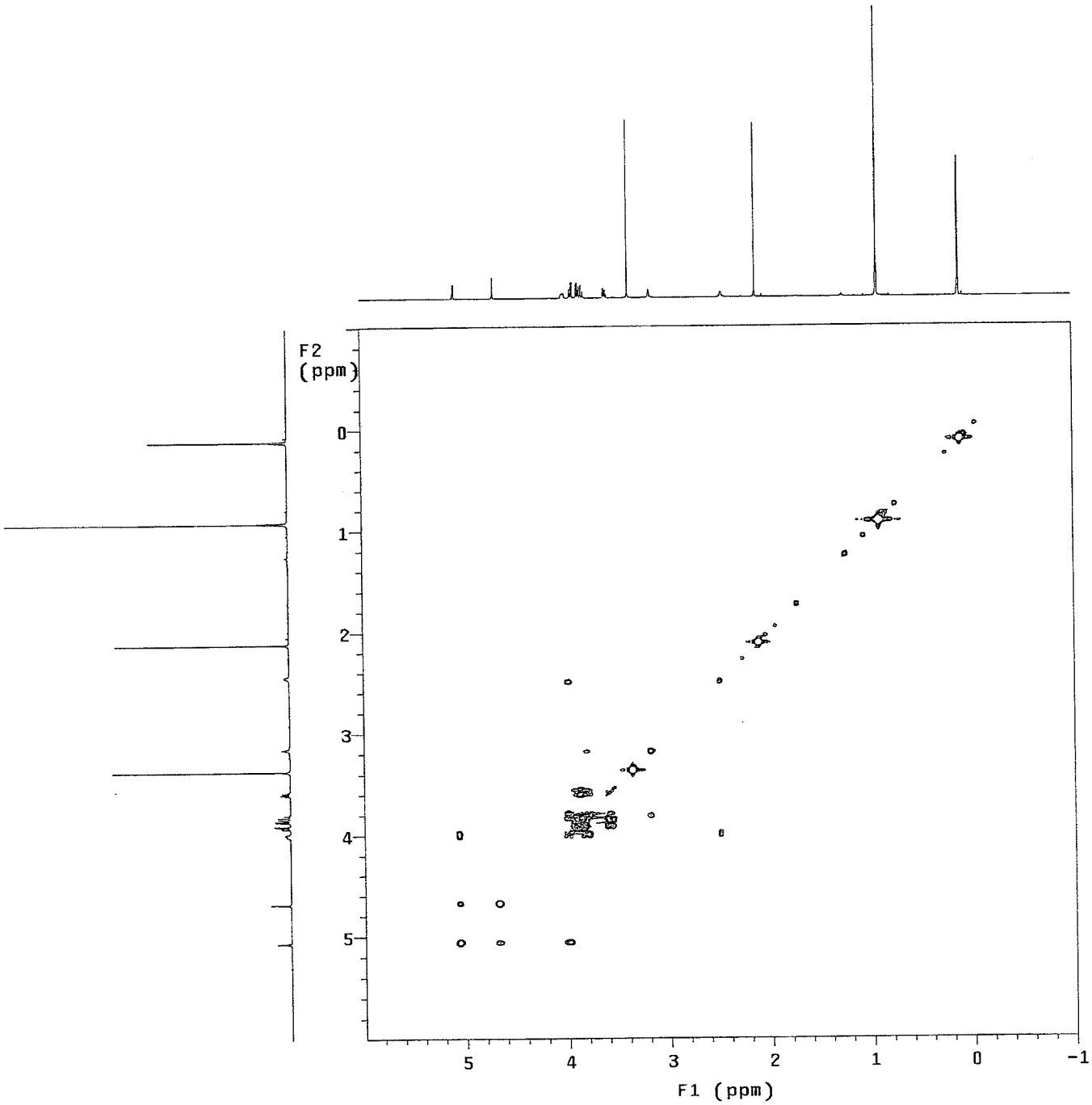
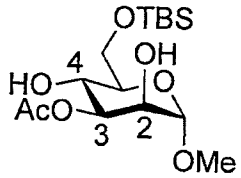
O
OMe


F2
(ppm)
0
1
2
3
4
5
5
4
3
2
1
0
-1
F1 (ppm)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AcO
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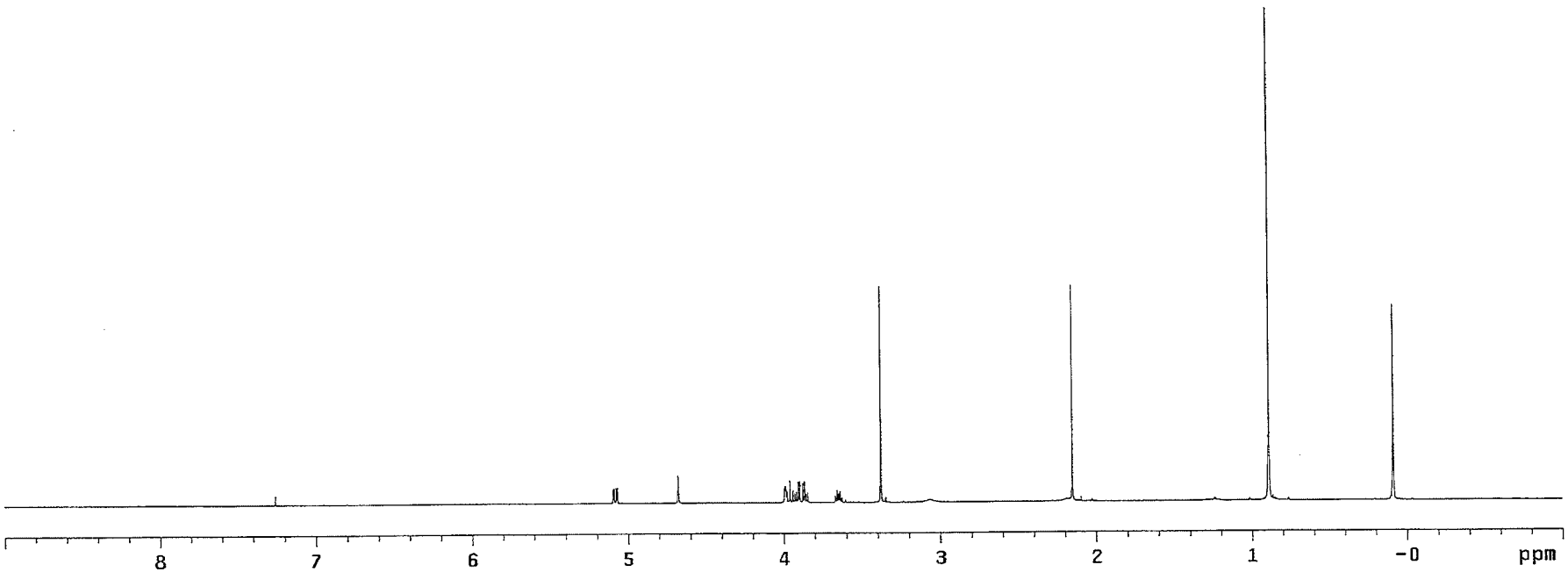
2
OMe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2
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-0
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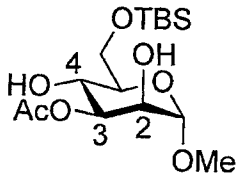
OTBS
OH
4
HO
O
AcO
3
2
OMe

220
200
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140
120
100
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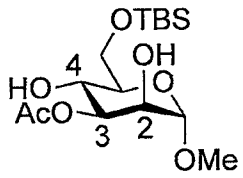
60
40
20
0
ppm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OH
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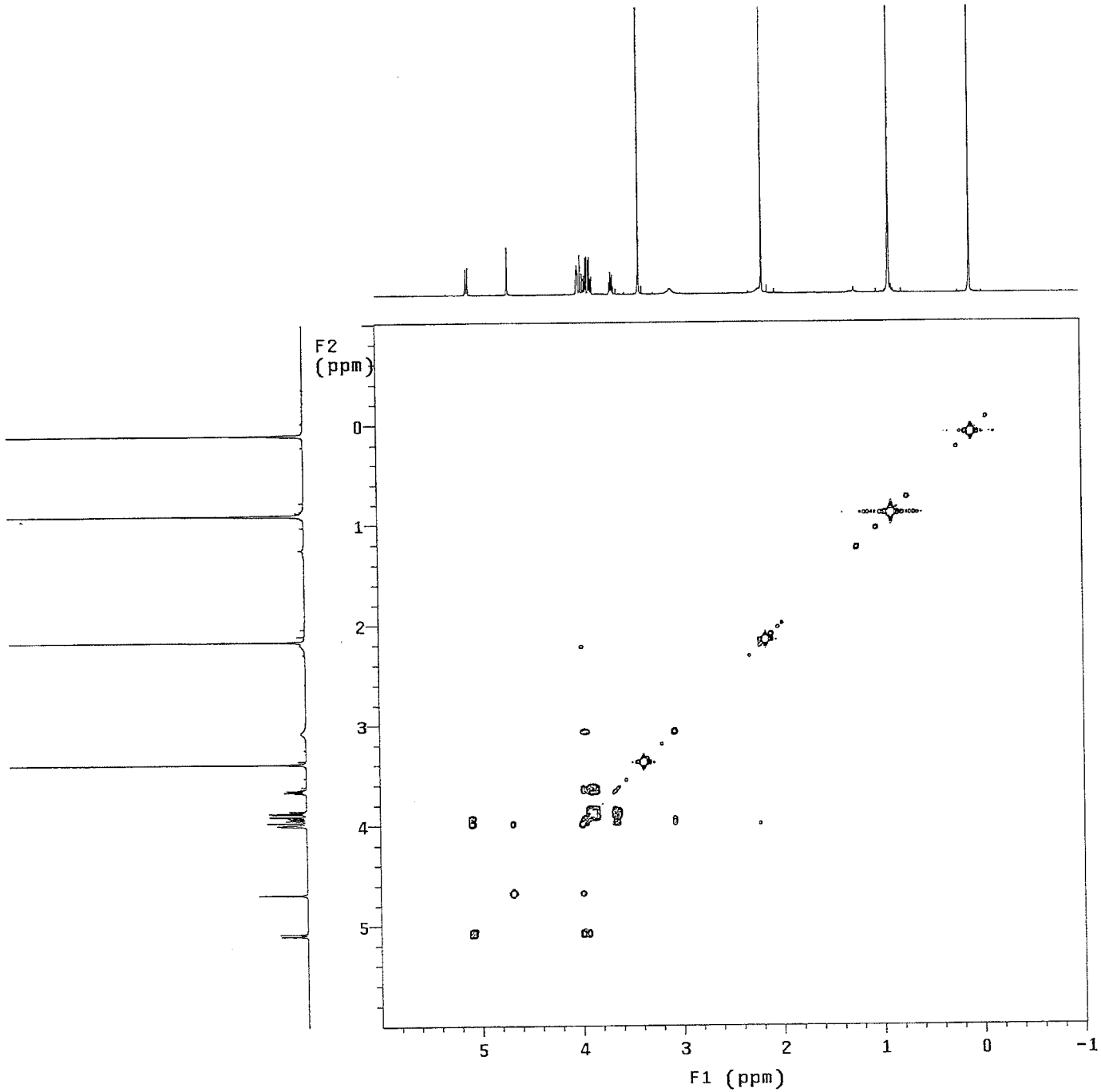
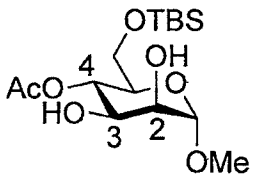
HO
O
AcO
3
2
OMe


F2
(ppm)
0
1
2
3
4
5
5
4
3
2
1
0
-1
F1 (ppm)


OTBS
OH
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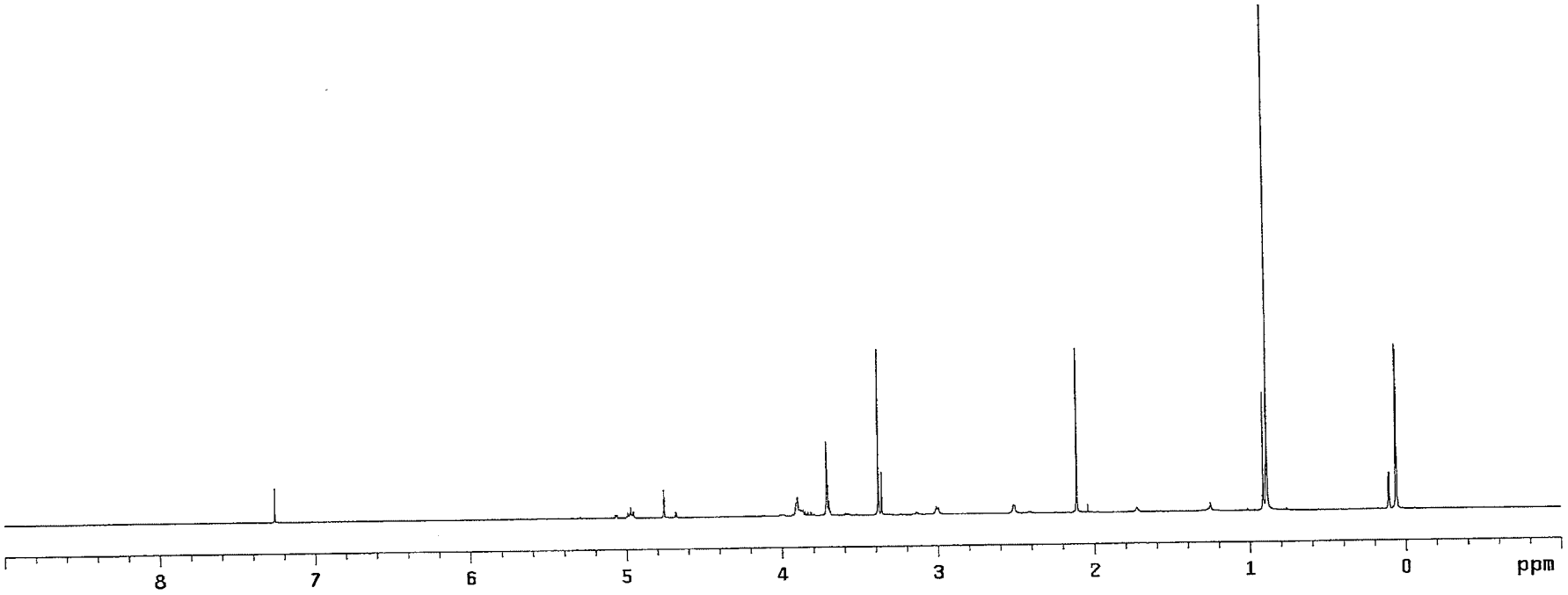
AcO
O
HO
3
2
OMe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7
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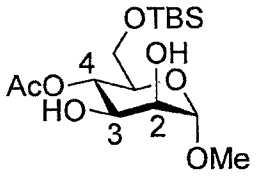
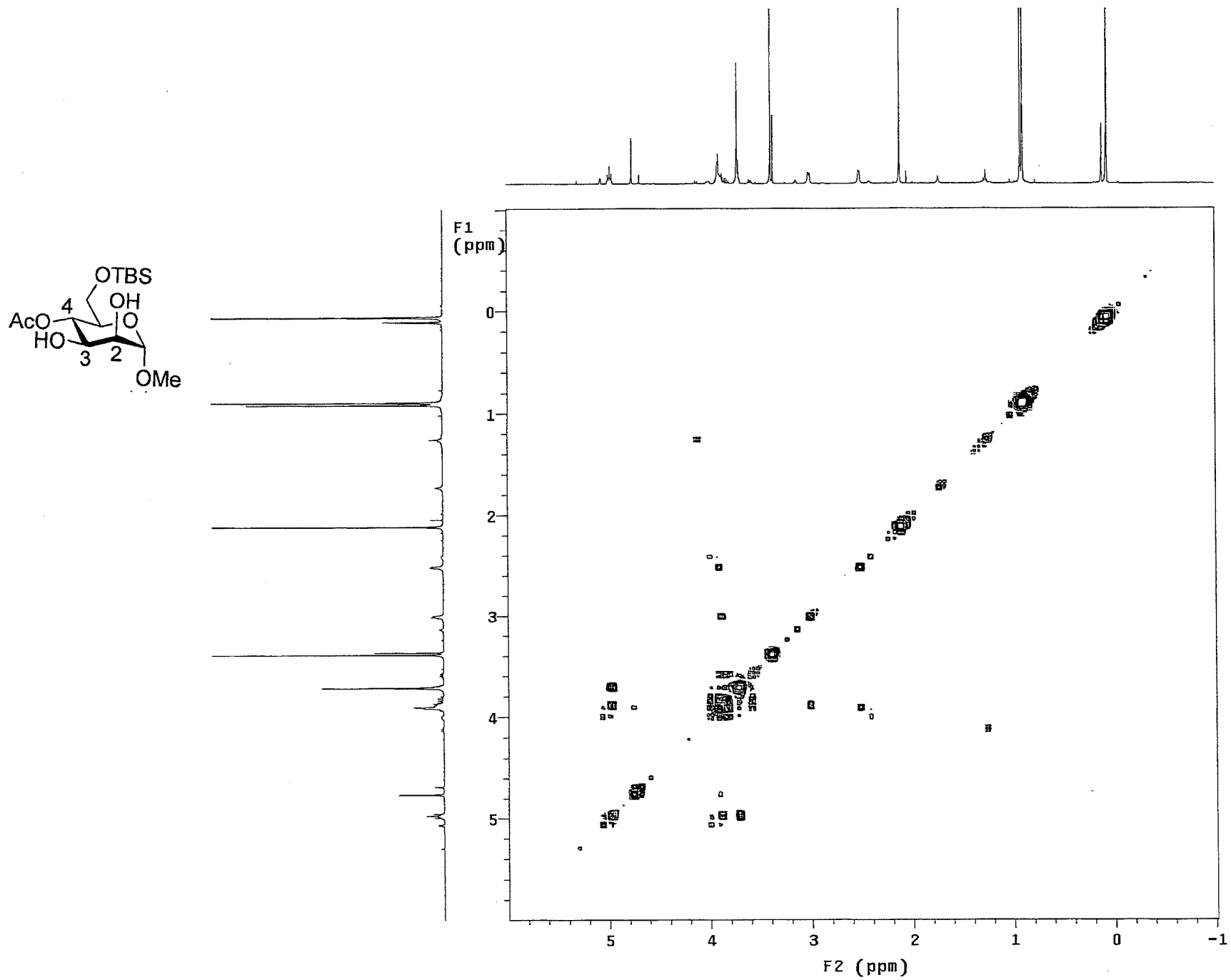
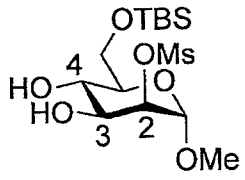
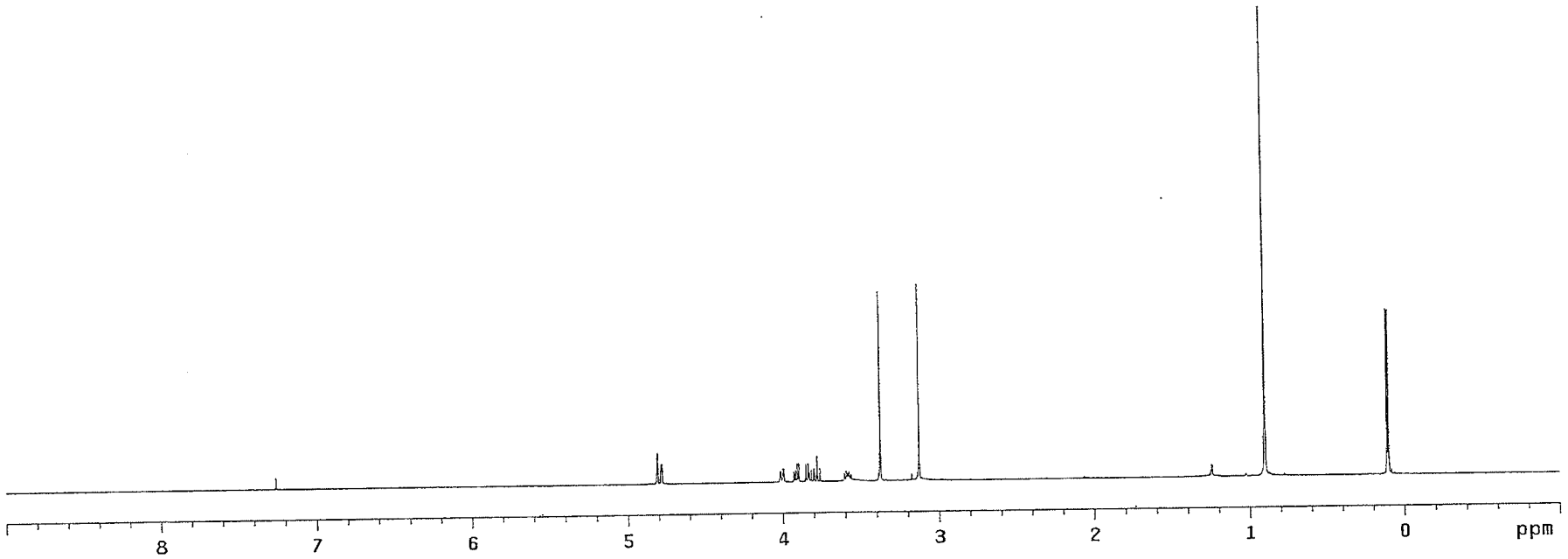
5
4
3
2
1
0
ppm

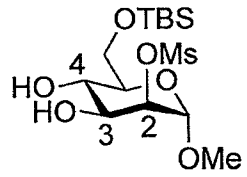

OTBS
OH
4
AcO
O
HO
3
2
OMe

220
200
180
160
140
120
100
80
60
40
20
0
ppm

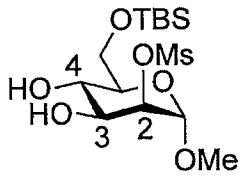

OTBS
OH
4
AcO
O
HO
3
2
OMe
F1
(ppm)
0
1
2
3
4
5
5
4
3
2
1
0
-1
F2 (ppm)

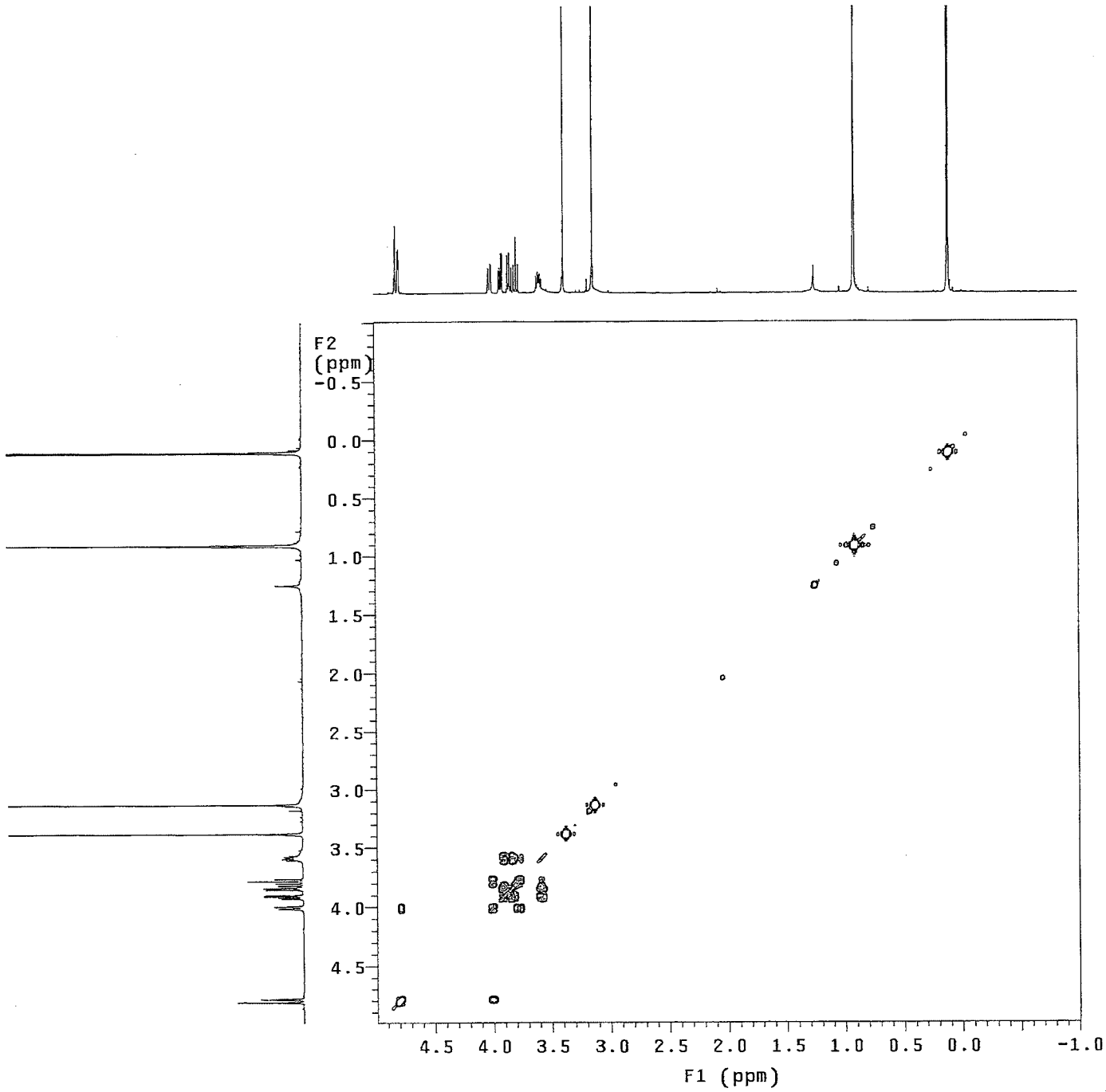

OTBS
OMs
4
HO
HO
3
2
O
OMe


8
7
6
5
4
3
2
1
0
ppm


OTBS
OMs
4
HO
O
HO
3
2
OMe

220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
OMs
4
HO
HO
3
2
O
OMe


F2
(ppm)
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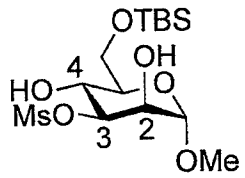
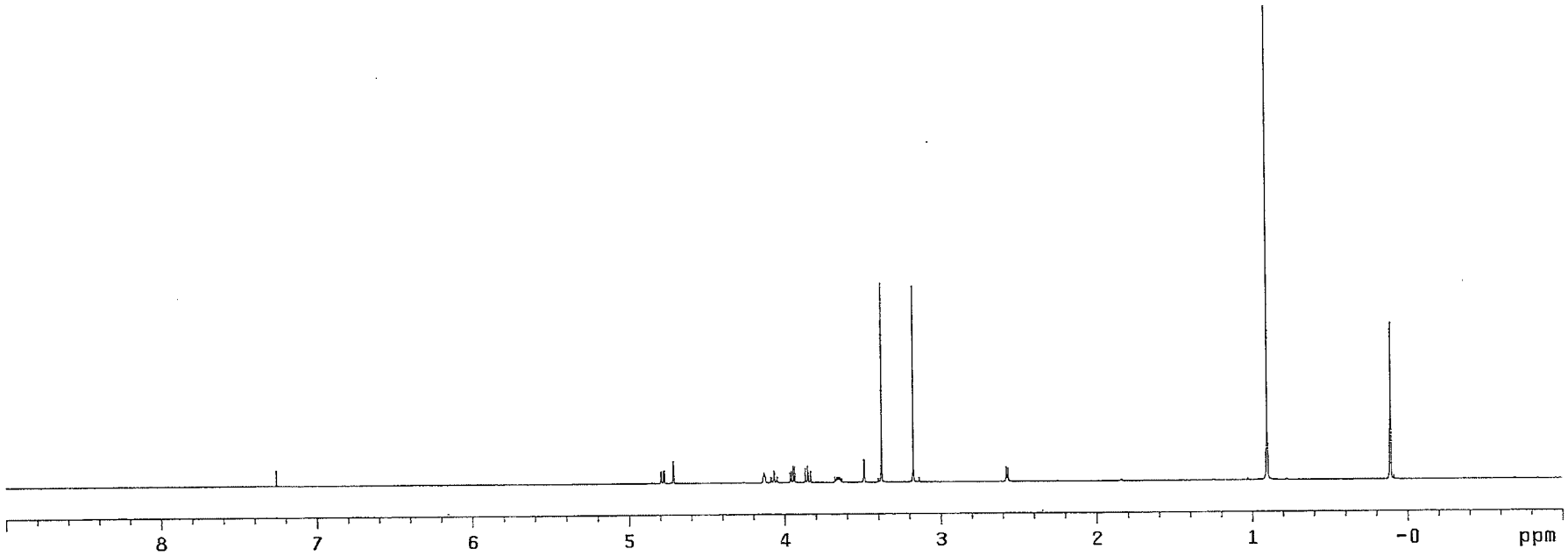
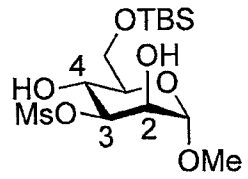
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-1.0
F1 (ppm)


OTBS
OH
4
HO
O
MsO
3
2
OMe


8
7
6
5
4
3
2
1
-0
ppm


OTBS
OH
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HO
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MsO
3
2
OMe

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200
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120
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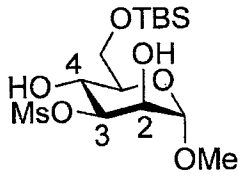
OTBS
OH
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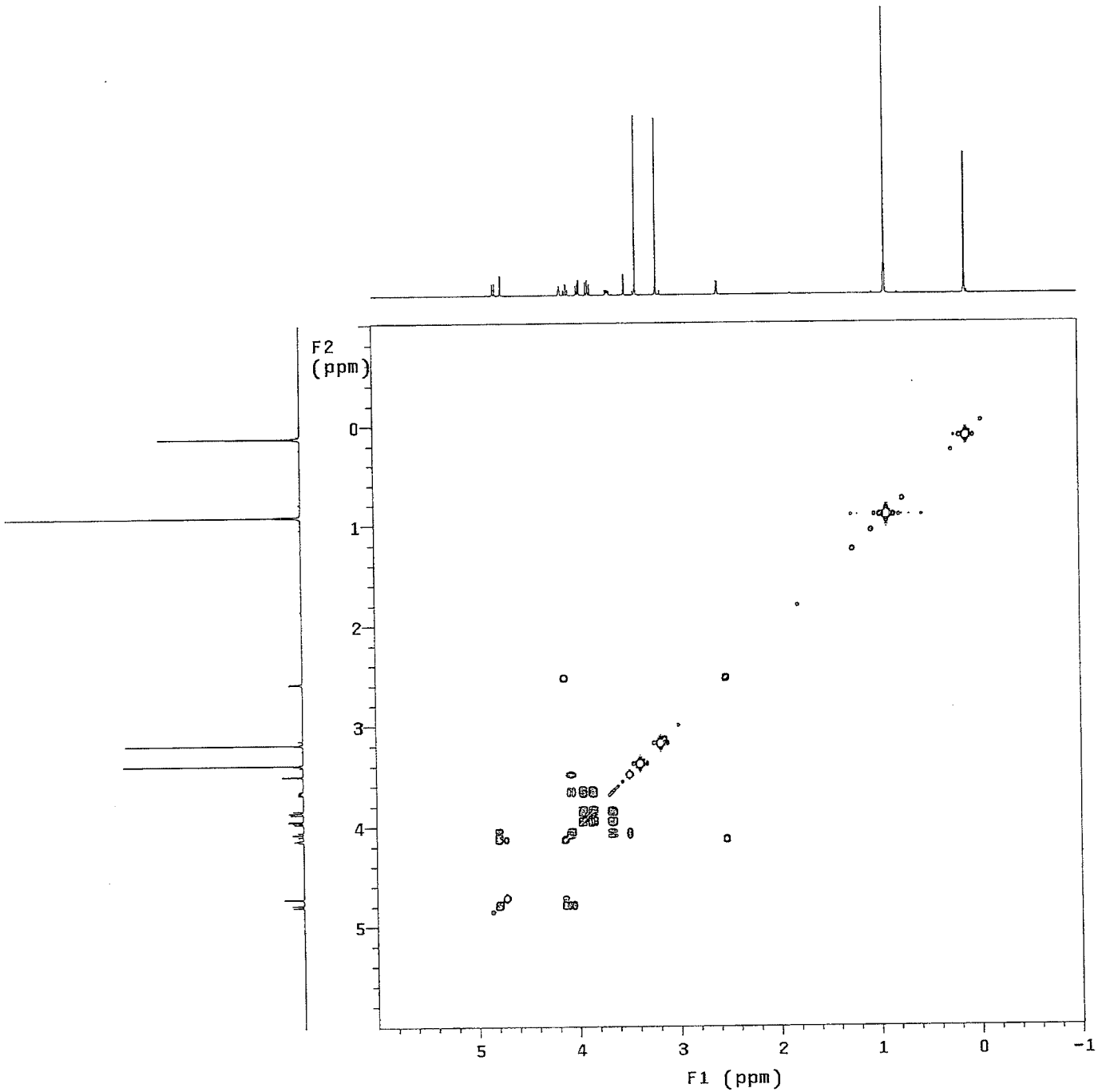
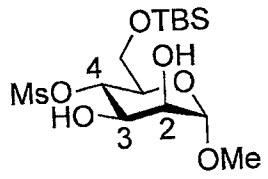
HO
O
MsO
3
2
OMe


F2
(ppm)
0
1
2
3
4
5
5
4
3
2
1
0
-1
F1 (ppm)


OTBS
OH
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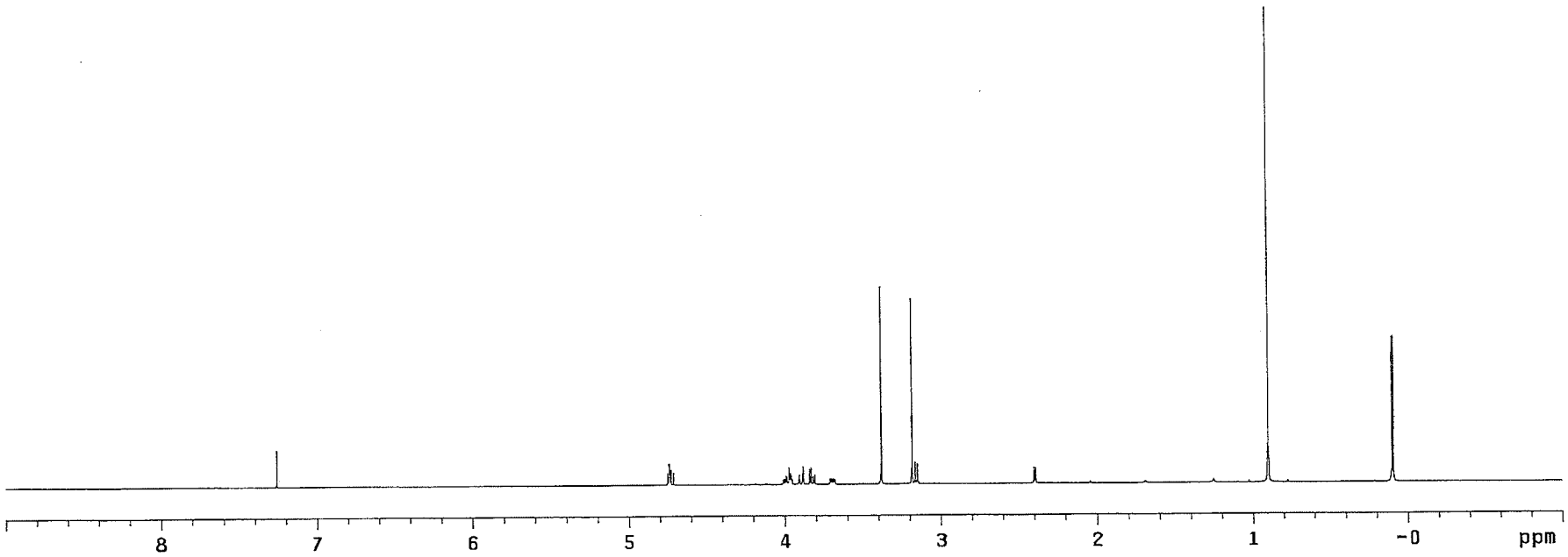
MsO
O
HO
3
2
OMe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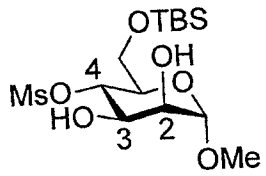
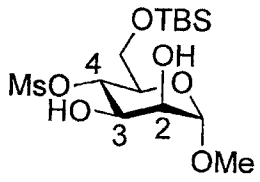
5
4
3
2
1
-0
ppm


OTBS
OH
4
MsO
O
HO
3
2
OMe

220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
OH
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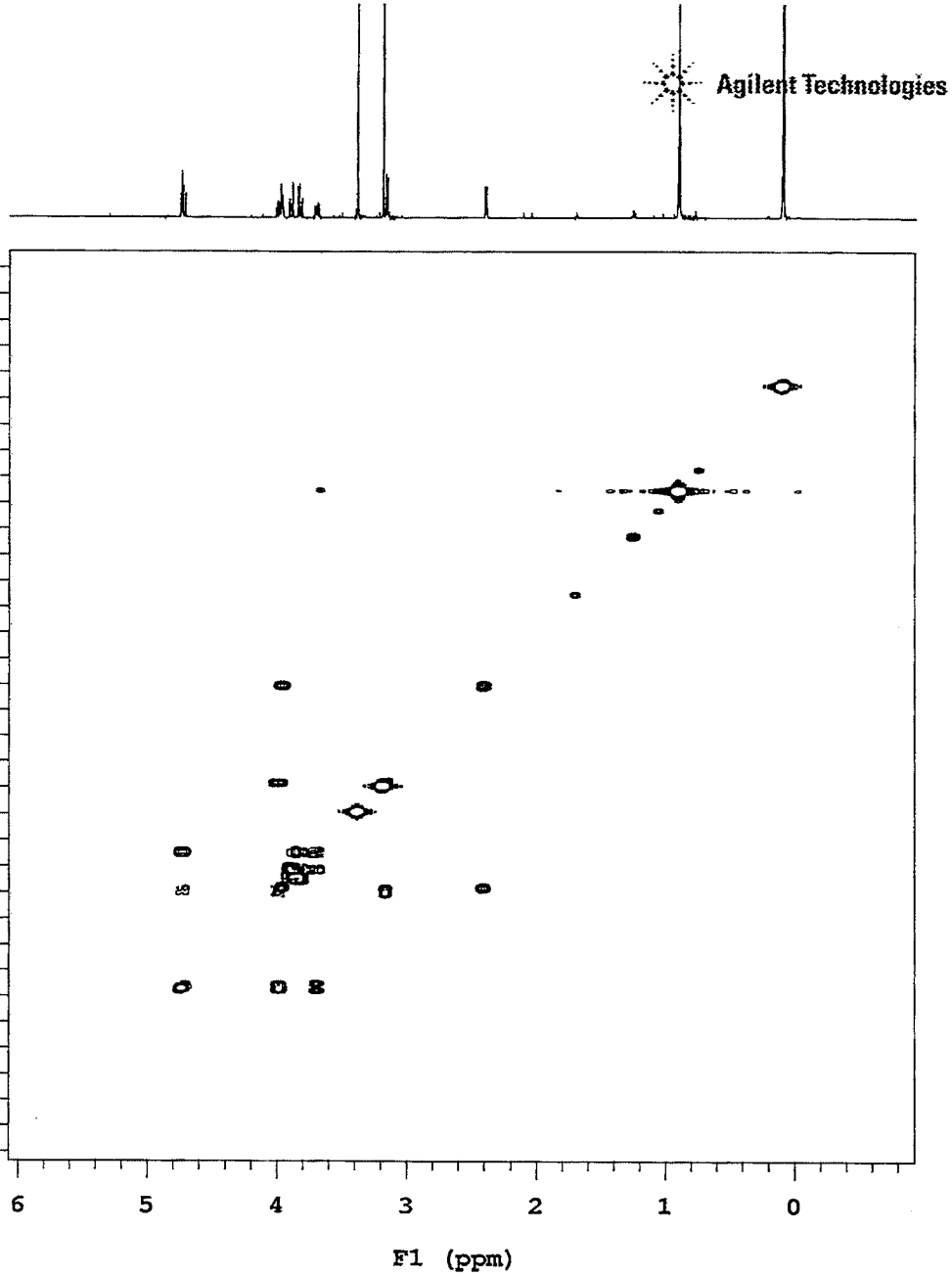
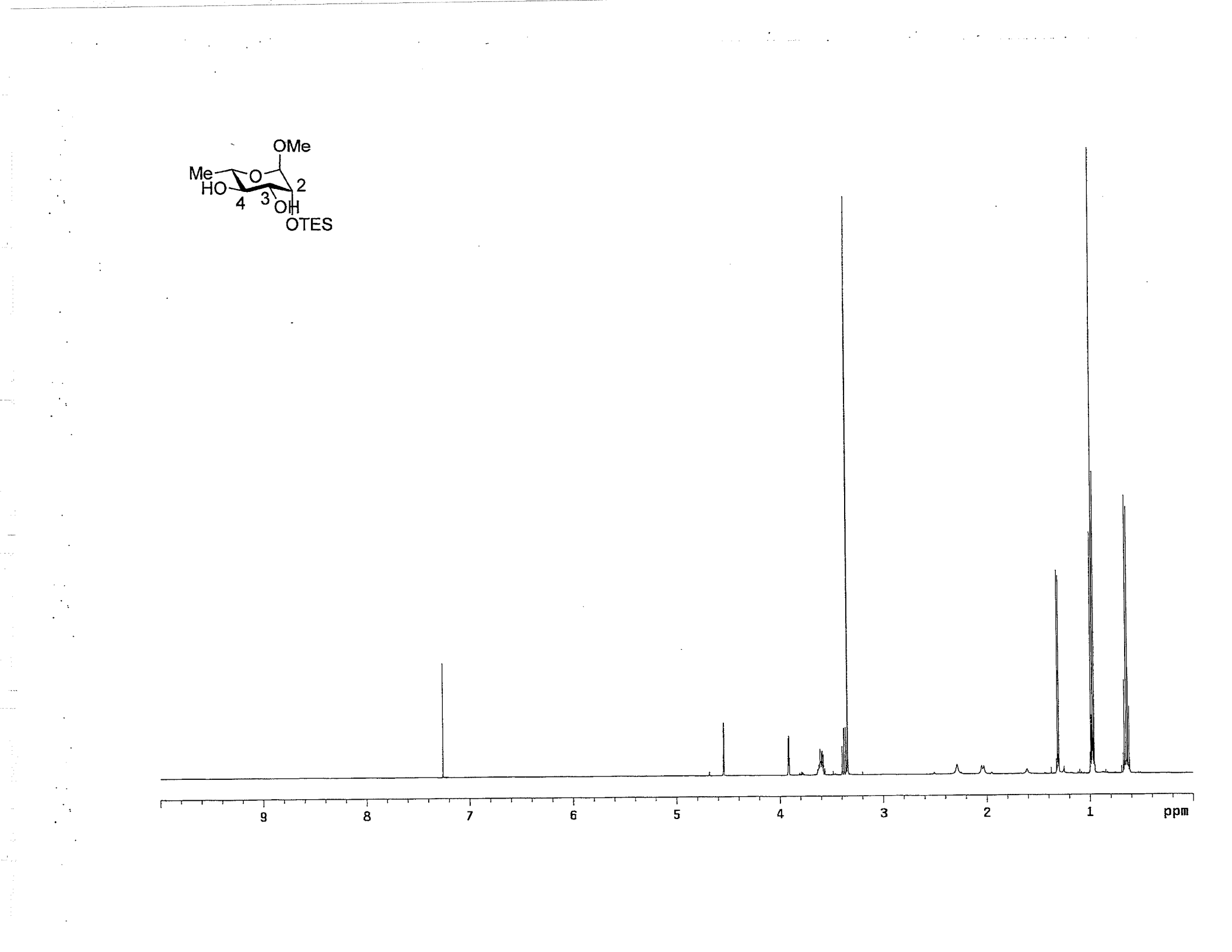
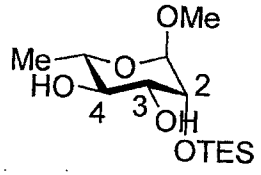
MsO
O
HO
3
2
OMe


Agilent Technologies
F2
(ppm)
0
1
2
3
4
5
6
6
5
4
3
2
1
0
F1 (ppm)


OMe
Me
O
HO
2
4
3
OH
OTES
9
8
7
6
5
4
3
2
1
ppm


OMe
Me
O
HO
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3
OH
OTES

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120
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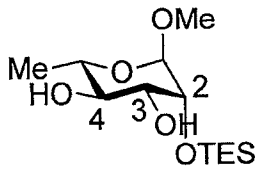
20
0
ppm


OMe
Me
O
HO
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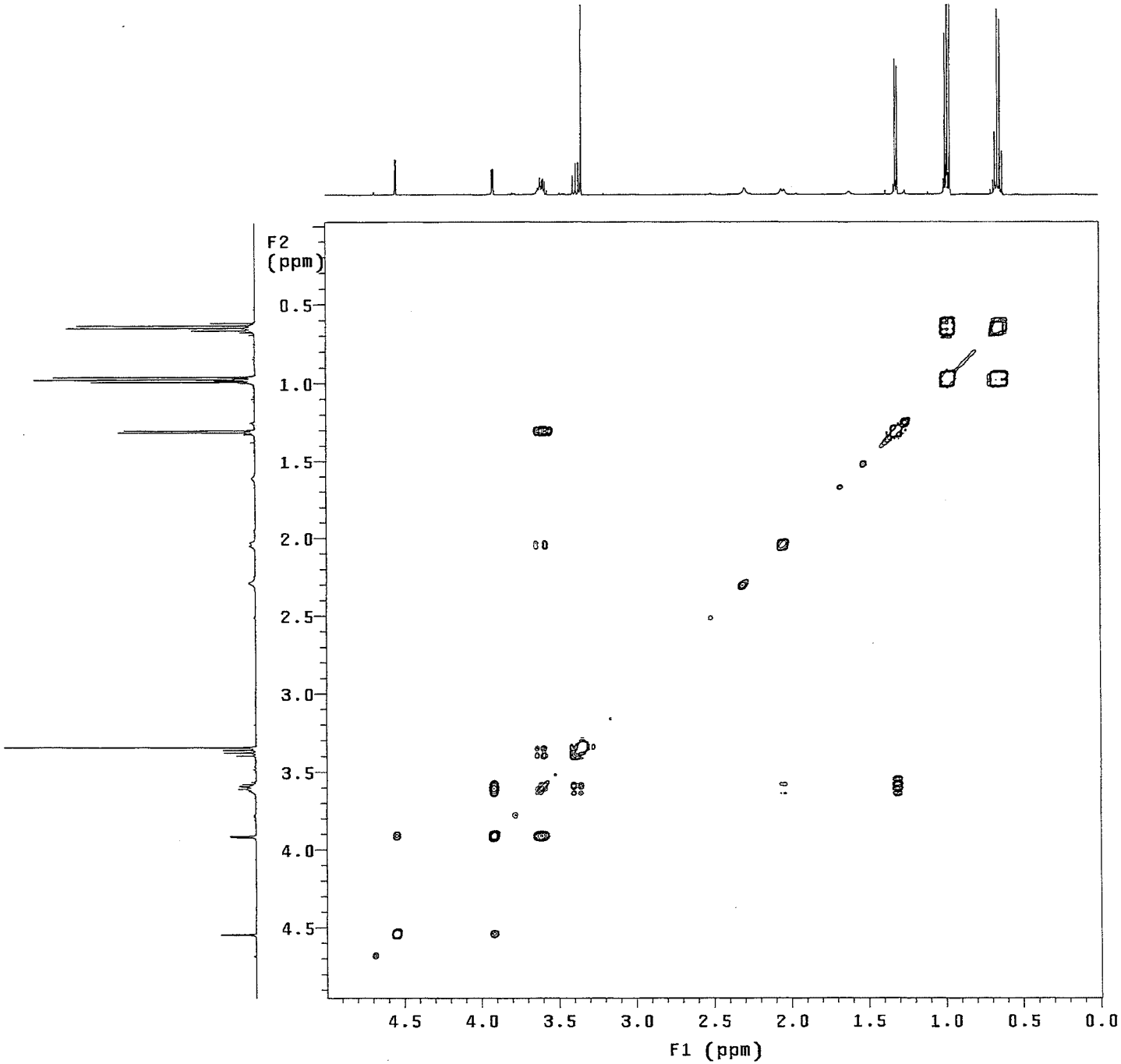
4
3
OH
OTES


F2 (ppm)
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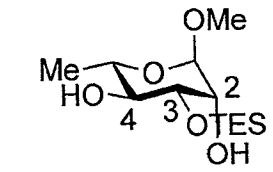
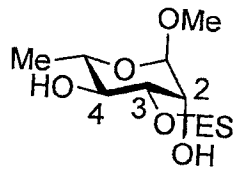
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
F1 (ppm)


OMe
Me
O
HO
2
4
3
OTES
OH

9
8
7
6
5
4
3
2
1
ppm


OMe
Me
O
HO
2
4
3
OTES
OH

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120
100
80
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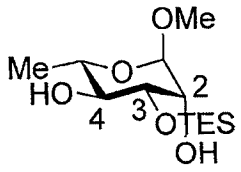
40
20
0
ppm


OMe
Me
O
HO
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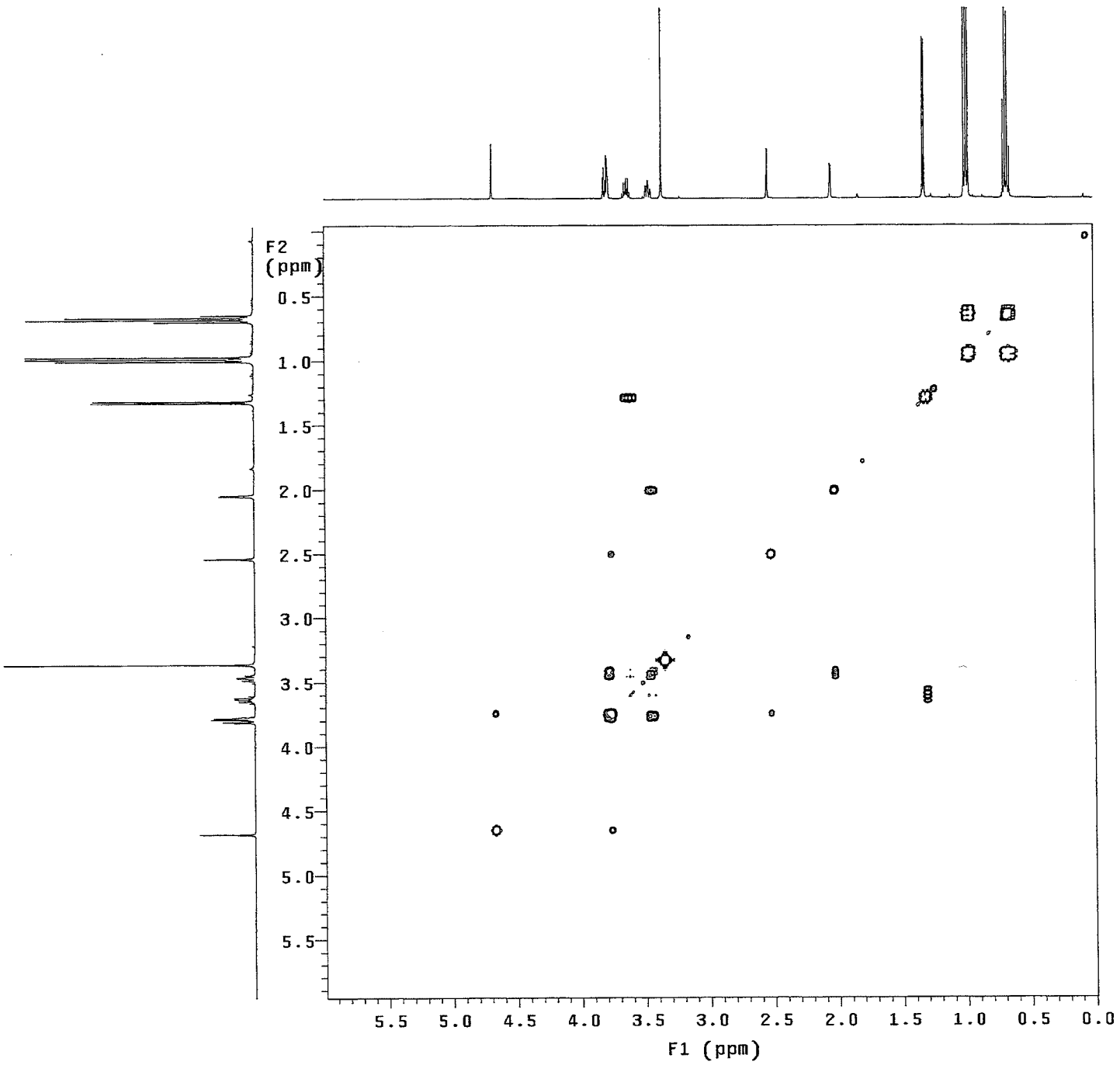
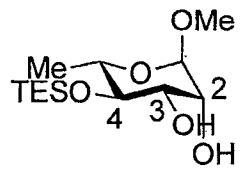
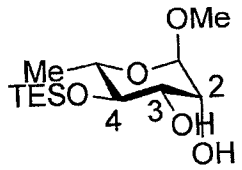
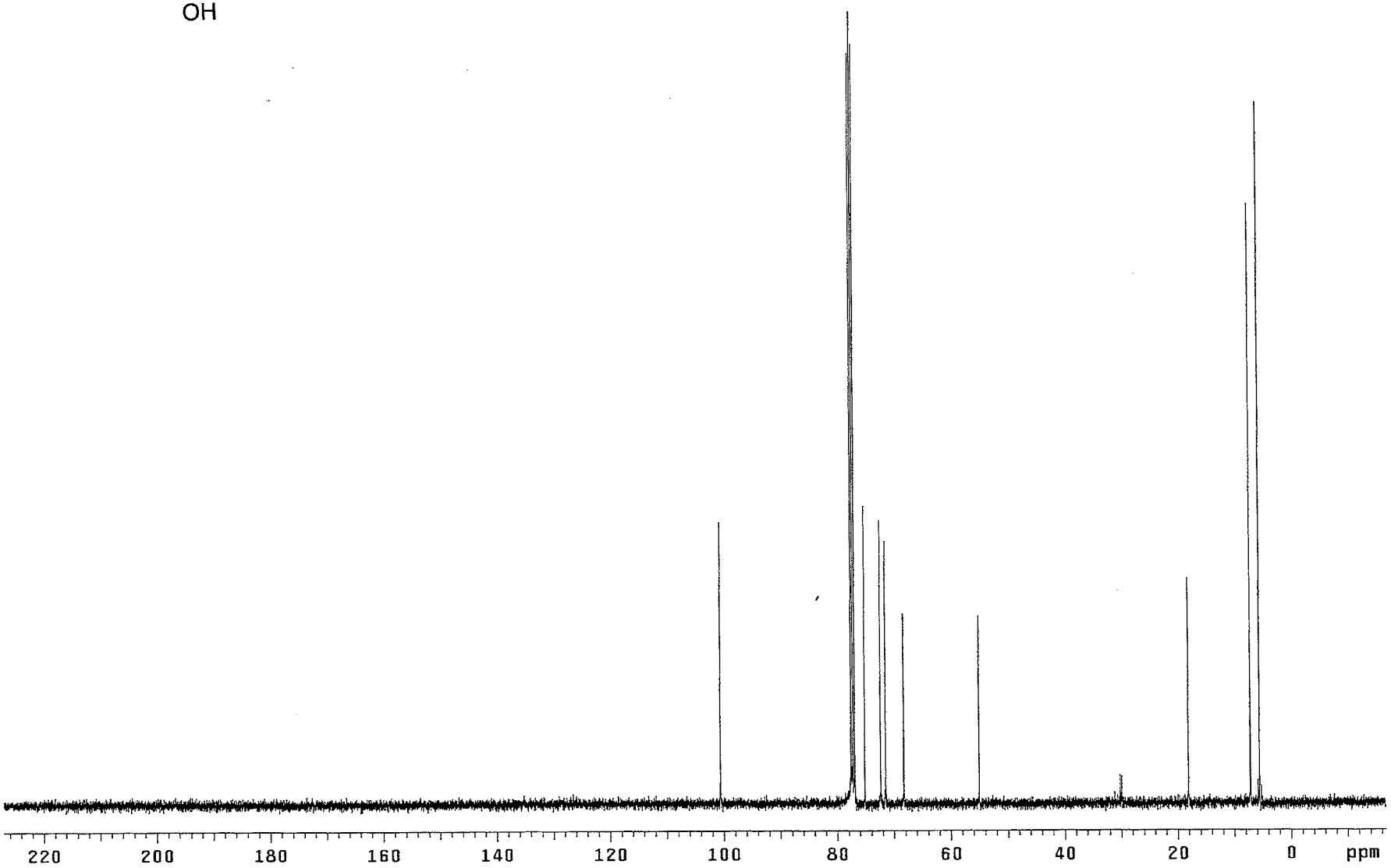
4
3
OTES
OH

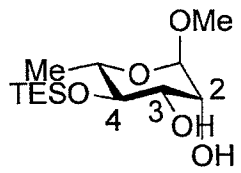

F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
F1 (ppm)

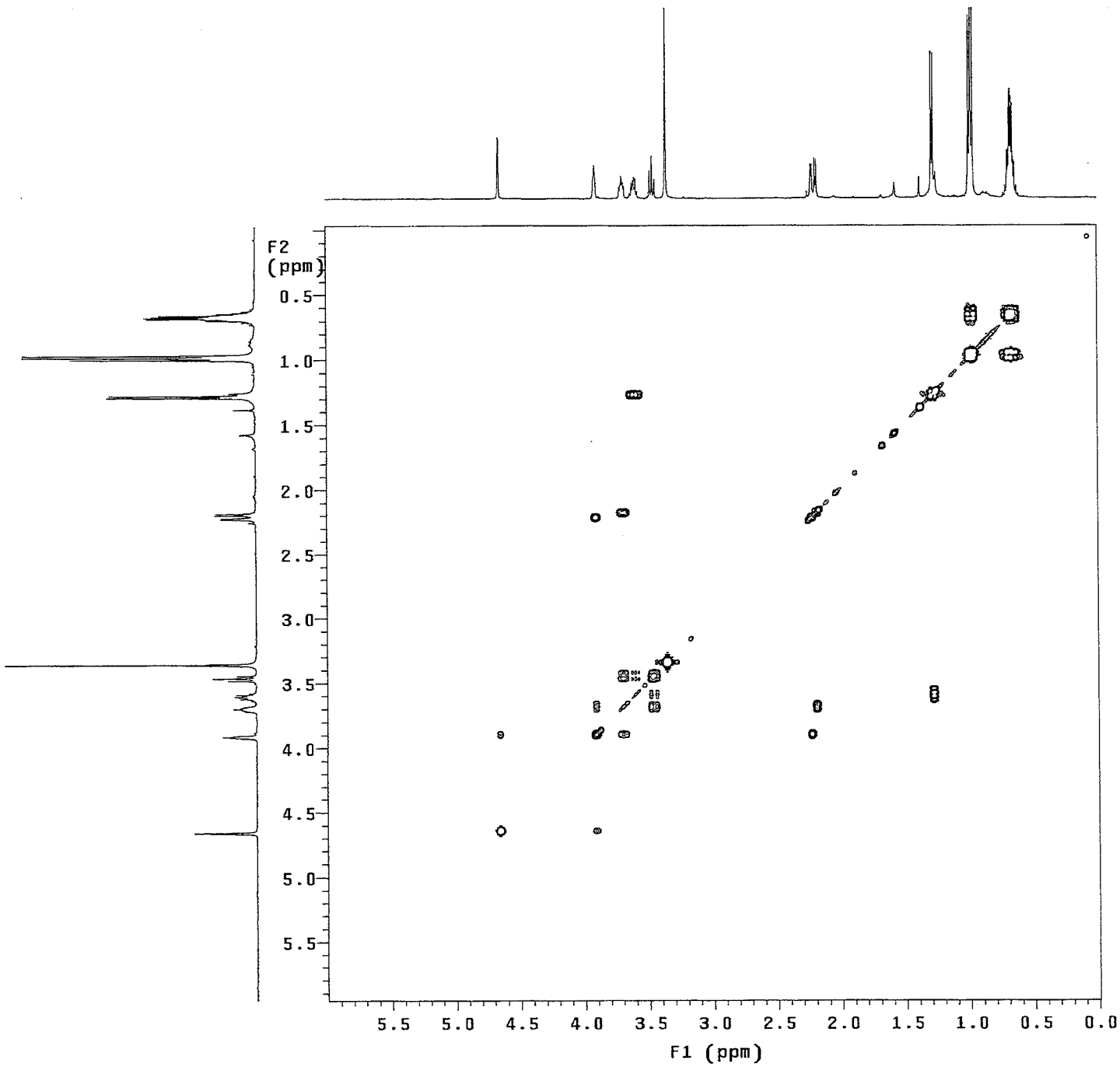

OMe
Me
O
TESO
2
4
3
OH
OH

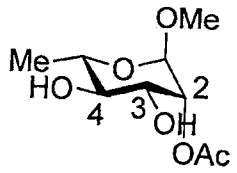
9
8
7
6
5
4
3
2
1
ppm


OMe
Me
O
TESO
2
4
3
OH
OH

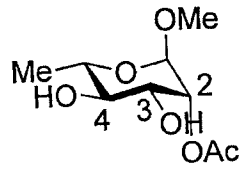

220
200
180
160
140
120
100
80
60
40
20
0
ppm


OMe
Me
O
TESO
2
4
3
OH
OH

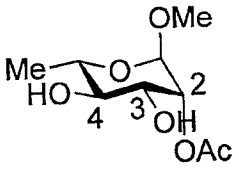

F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
F1 (ppm)

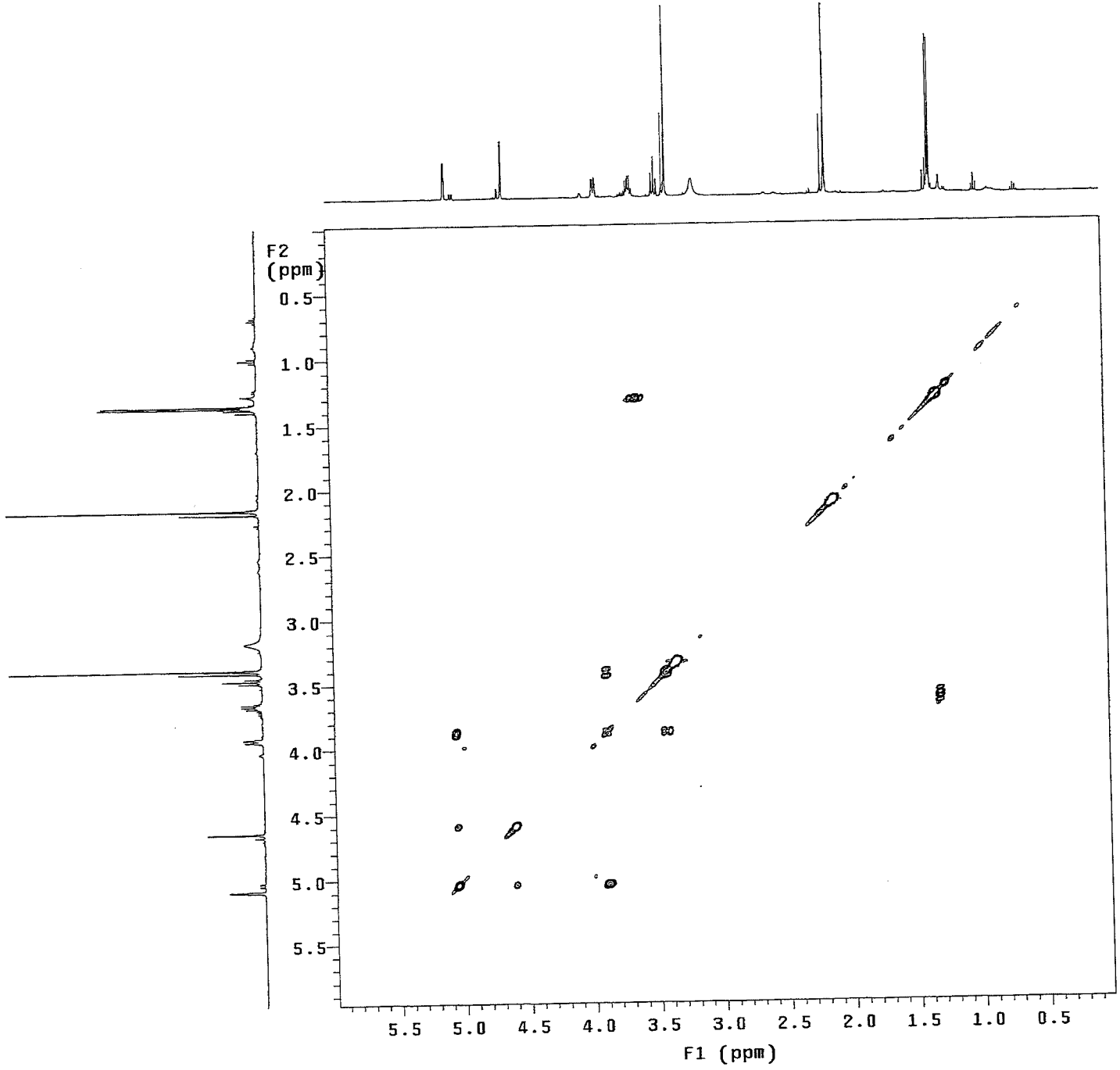

OMe
Me
O
HO
2
4
3
OH
OAc

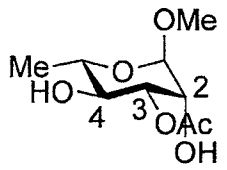
9
8
7
6
5
4
3
2
1
ppm


OMe
Me
O
HO
2
4
3
OH
OAc

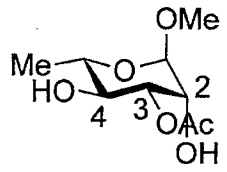
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OMe
Me
O
HO
2
4
3
OH
OAc

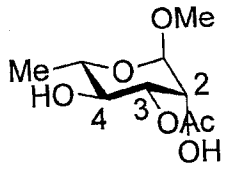

F2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
F1 (ppm)

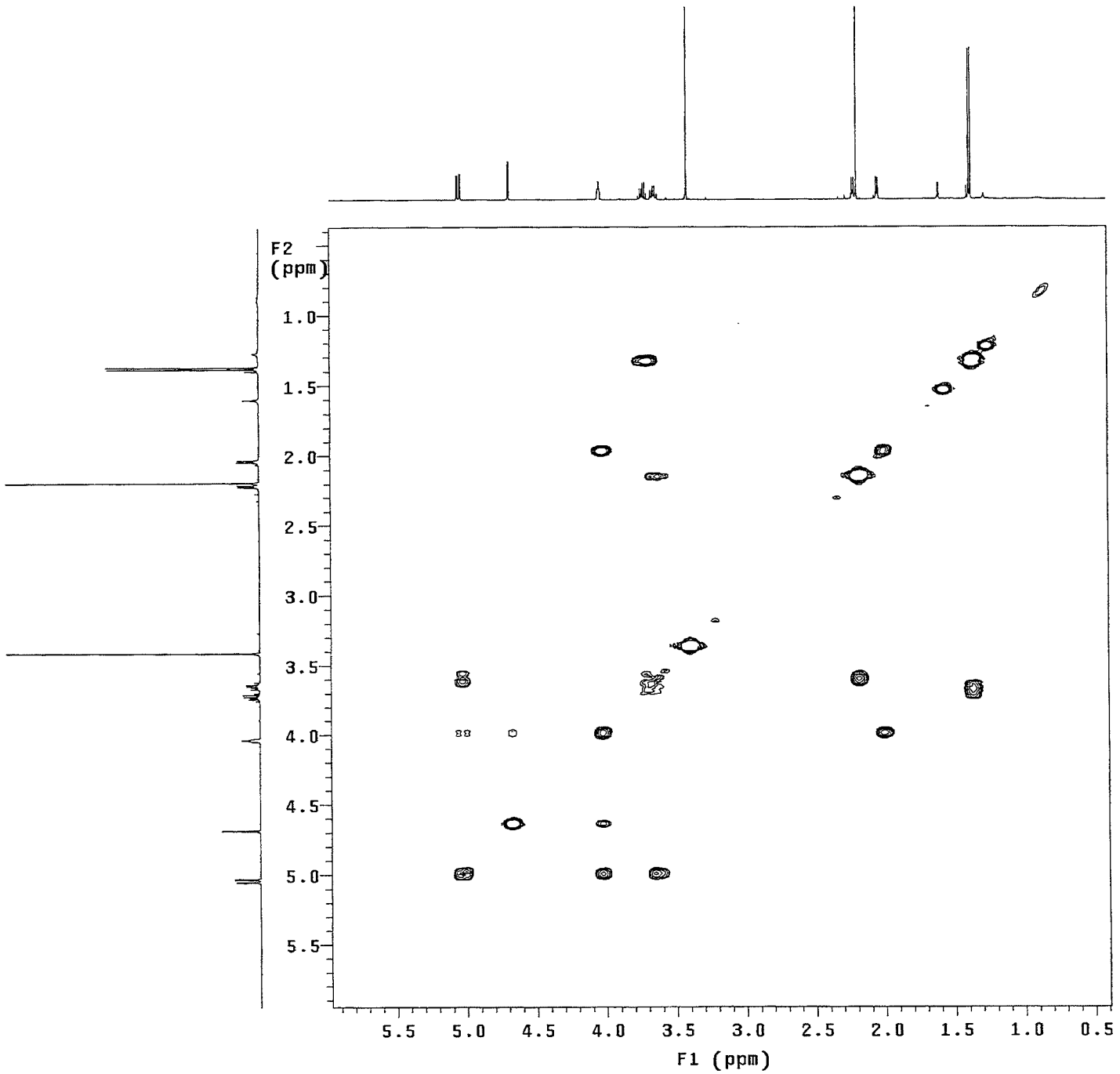

OMe
Me
O
HO
2
4
3
OAc
OH

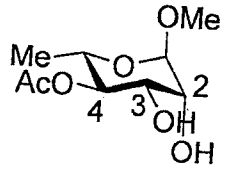
9
8
7
6
5
4
3
2
1
ppm


OMe
Me
O
HO
2
4
3
OAc
OH

220
200
180
160
140
120
100
80
60
40
20
0
ppm


OMe
Me
O
HO
2
4
3
OAc
OH

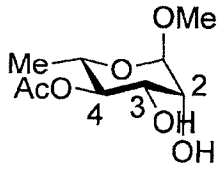

F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F1 (ppm)

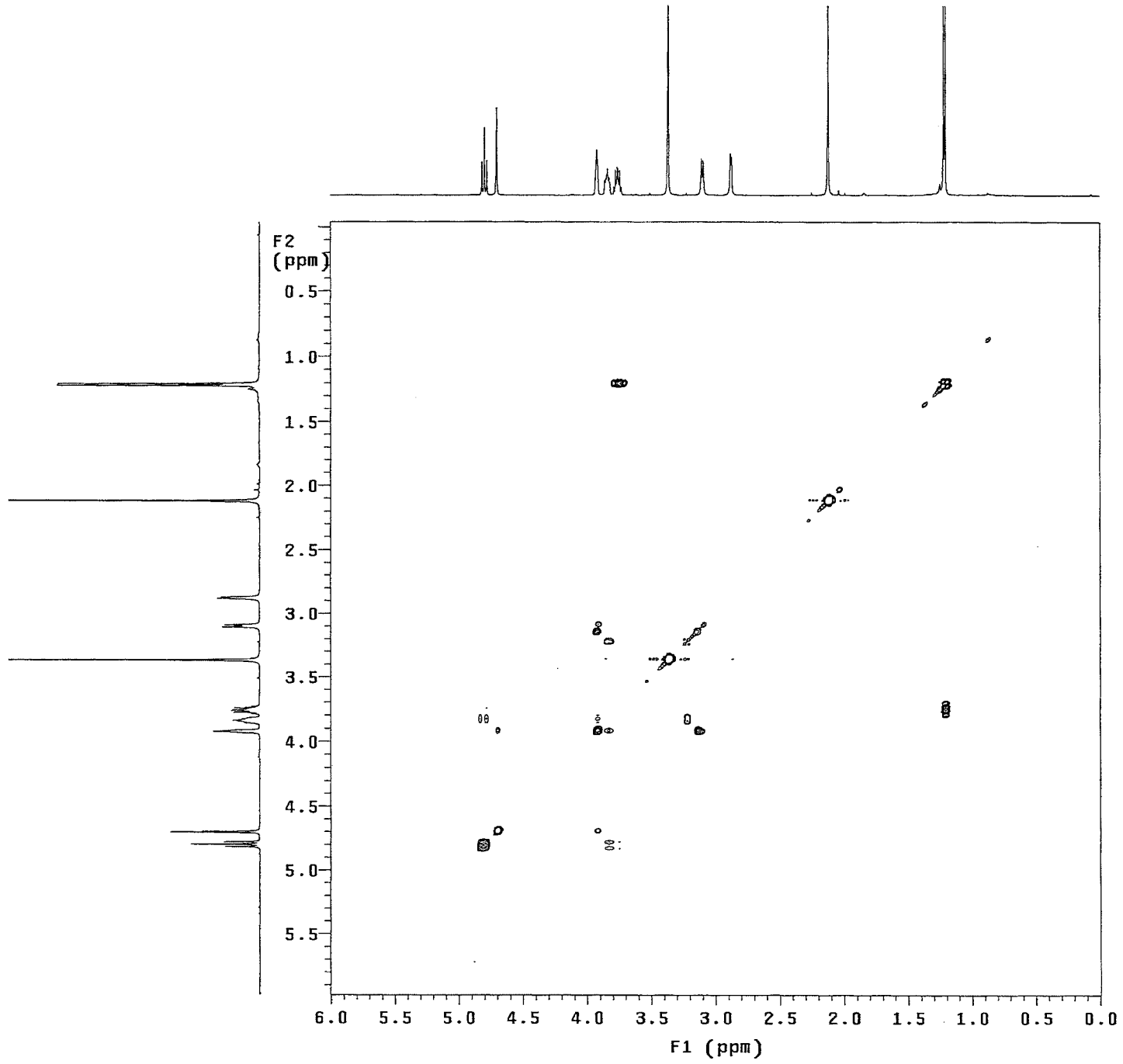

OMe
Me
O
AcO
2
4
3
OH
OH

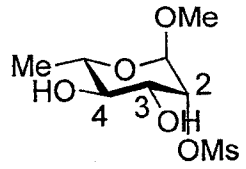
9
8
7
6
5
4
3
2
1
ppm

Me
AcO
O
OMe
4
3
2
OH
OH

220
200
180
160
140
120
100
80
60
40
20
0
ppm


OMe
Me
O
AcO
2
4
3
OH
OH

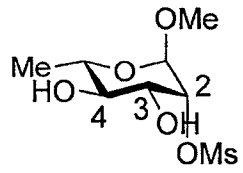

F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
F1 (ppm)

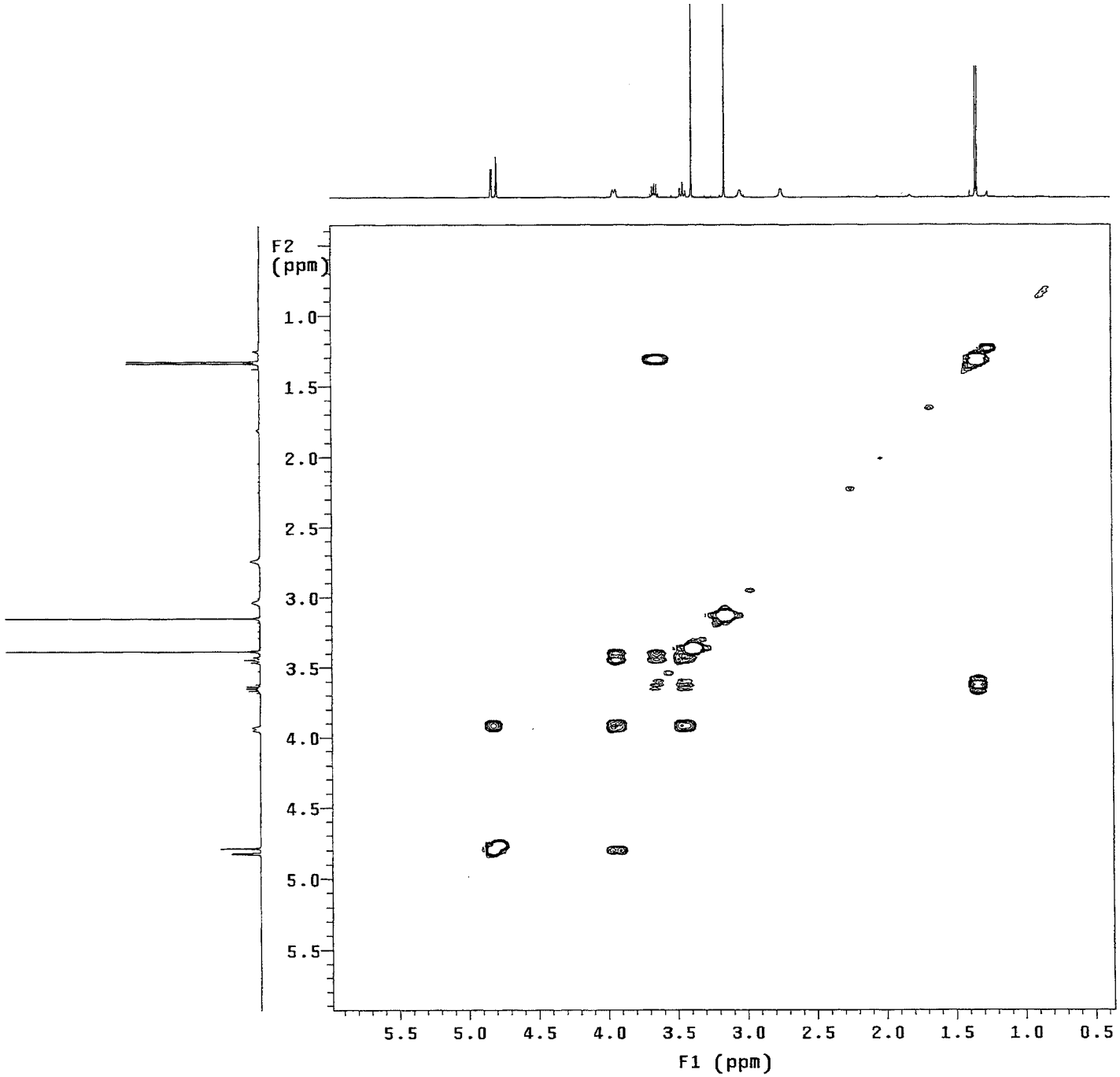

OMe
Me
O
HO
2
4
3
OH
OMs

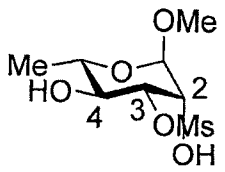
9
8
7
6
5
4
3
2
1
ppm

Me
HO
O
4
3
OH
2
OMe
OMs

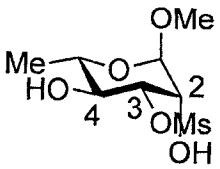
220
200
180
160
140
120
100
80
60
40
20
0
ppm

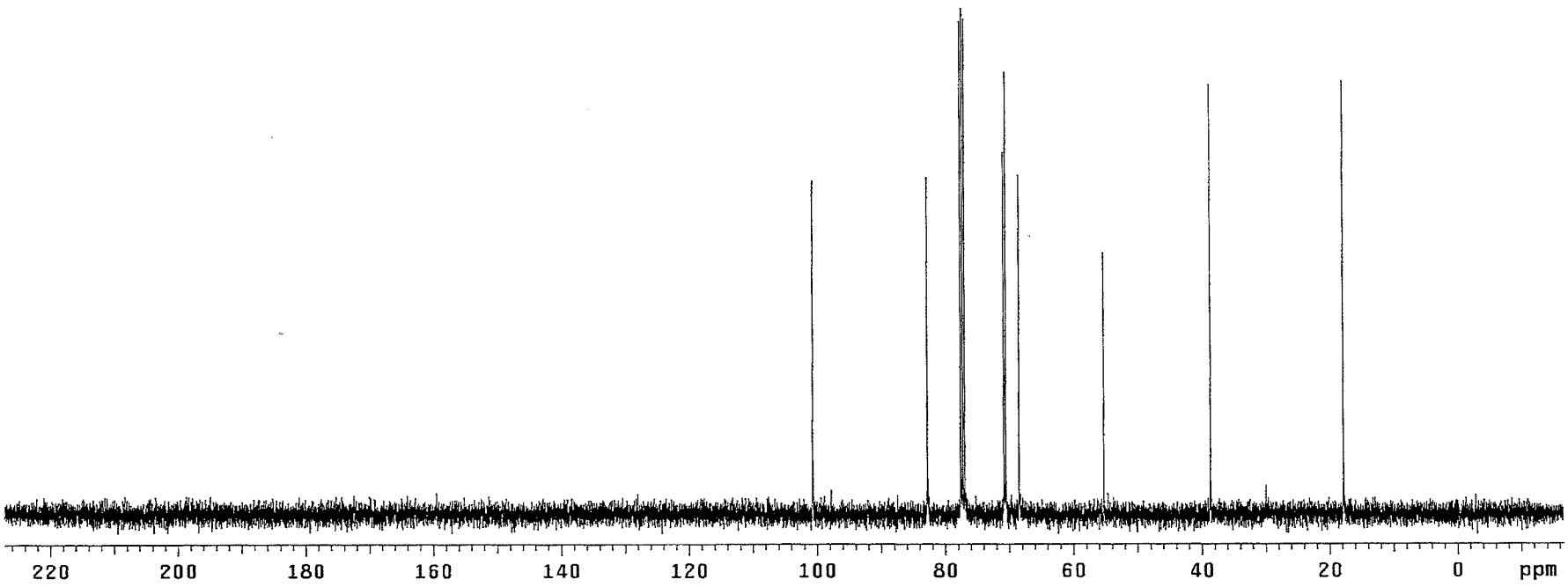

OMe
Me
O
HO
2
4
3
OH
OMs

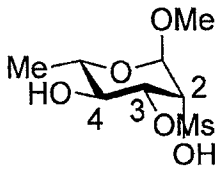

F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F1 (ppm)

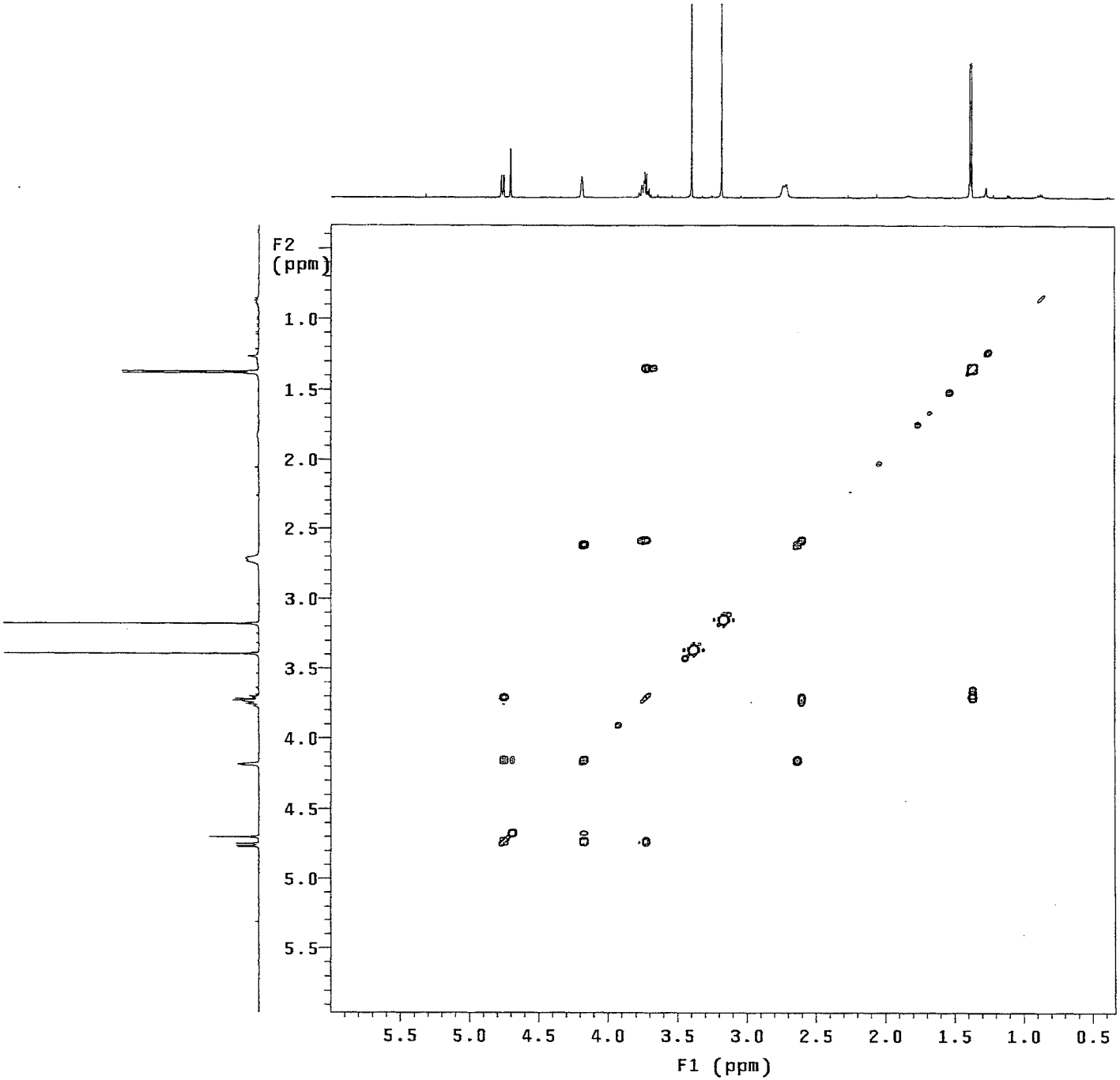

OMe
Me
O
HO
2
4
3
OMs
OH

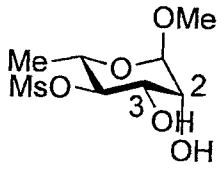
9
8
7
6
5
4
3
2
1
ppm


OMe
Me
O
HO
2
4
3
OMs
OH


220
200
180
160
140
120
100
80
60
40
20
0
ppm


OMe
Me
O
HO
2
4
3
OMs
OH

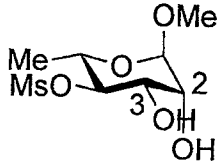

F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F1 (ppm)

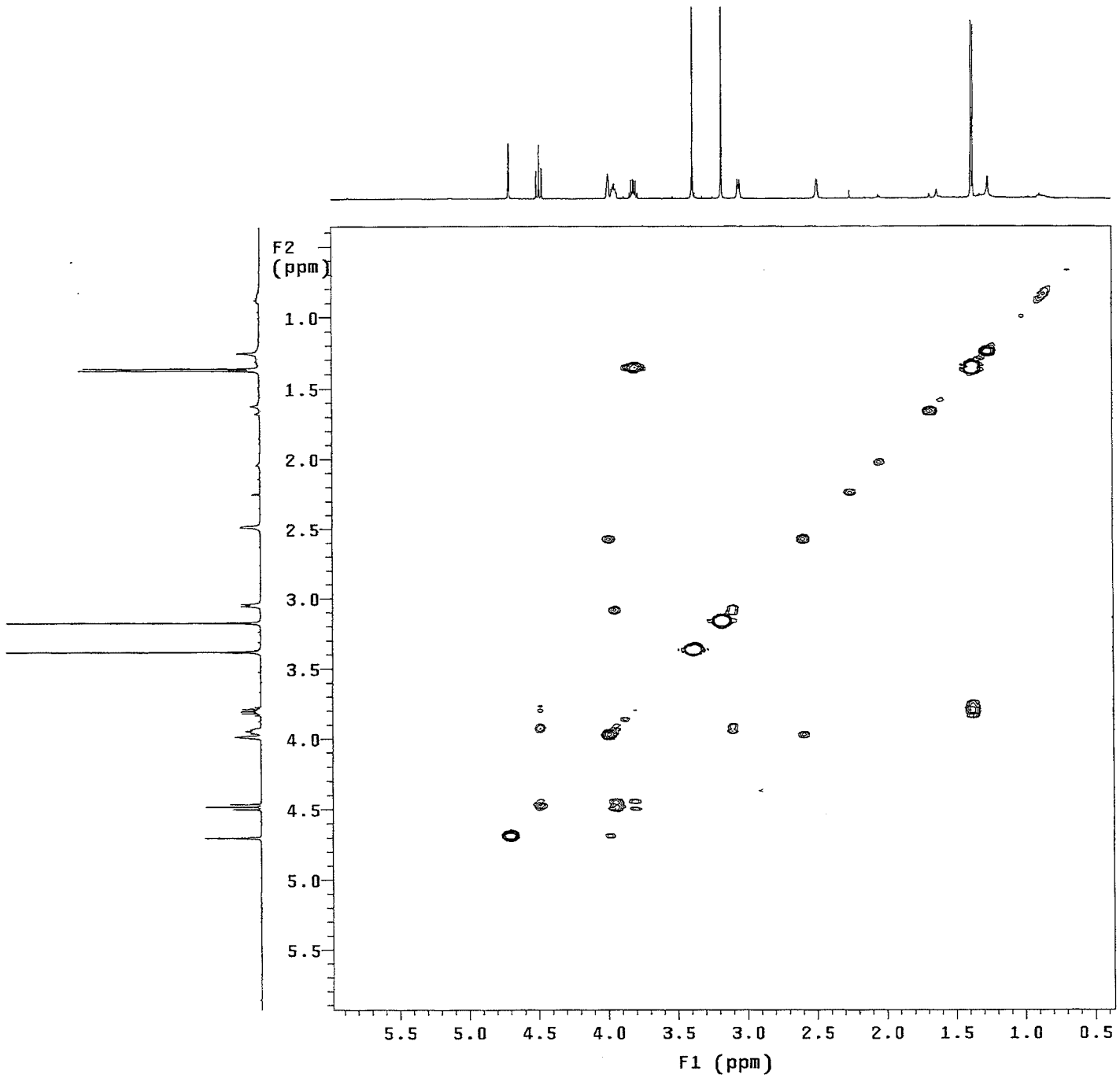

OMe
Me
O
MsO
2
3
OH
H
OH

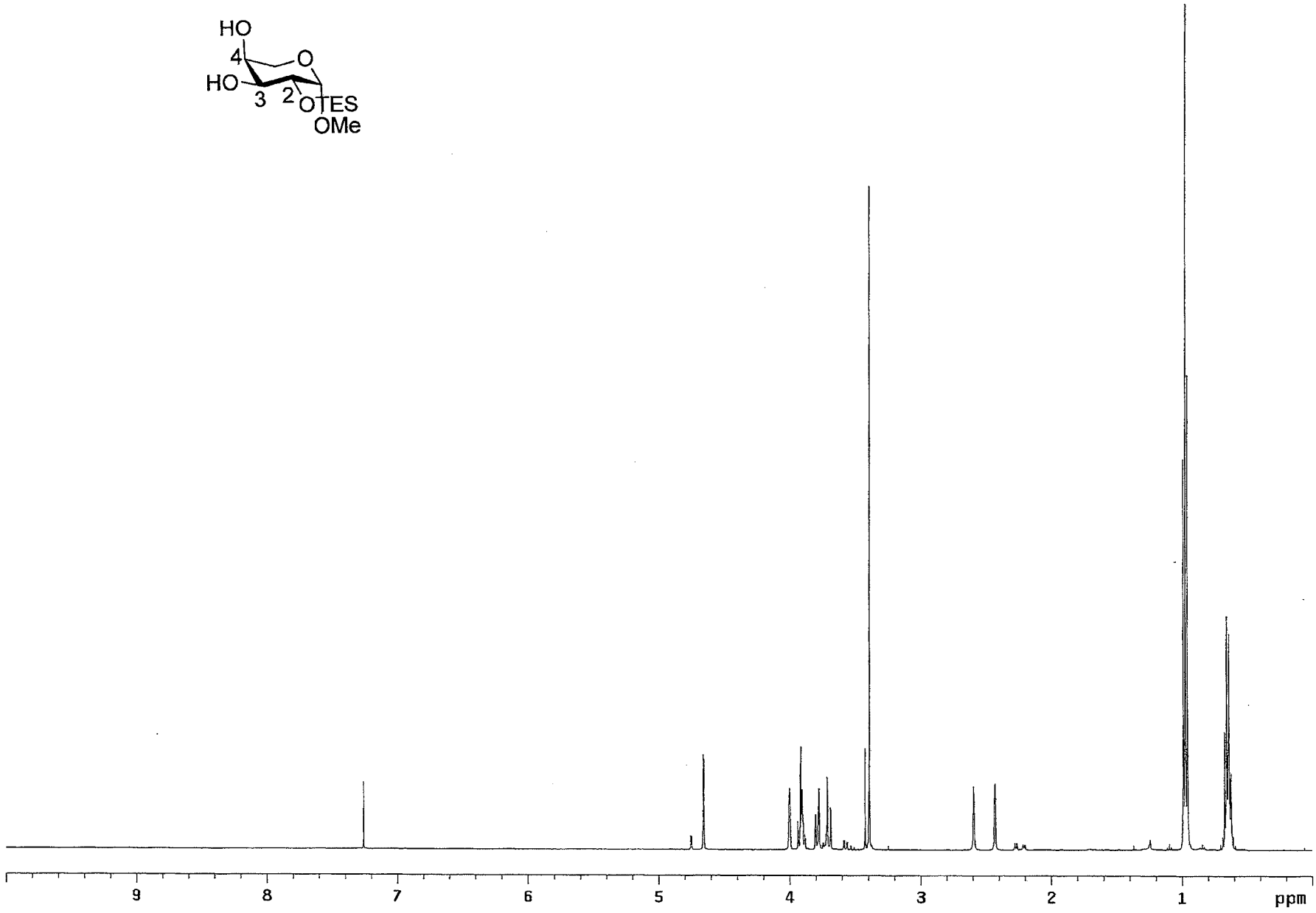
9
8
7
6
5
4
3
2
1
ppm

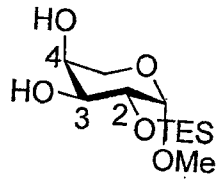
Me
MsO
O
OMe
3
OH
2
H
OH

220
200
180
160
140
120
100
80
60
40
20
0
ppm

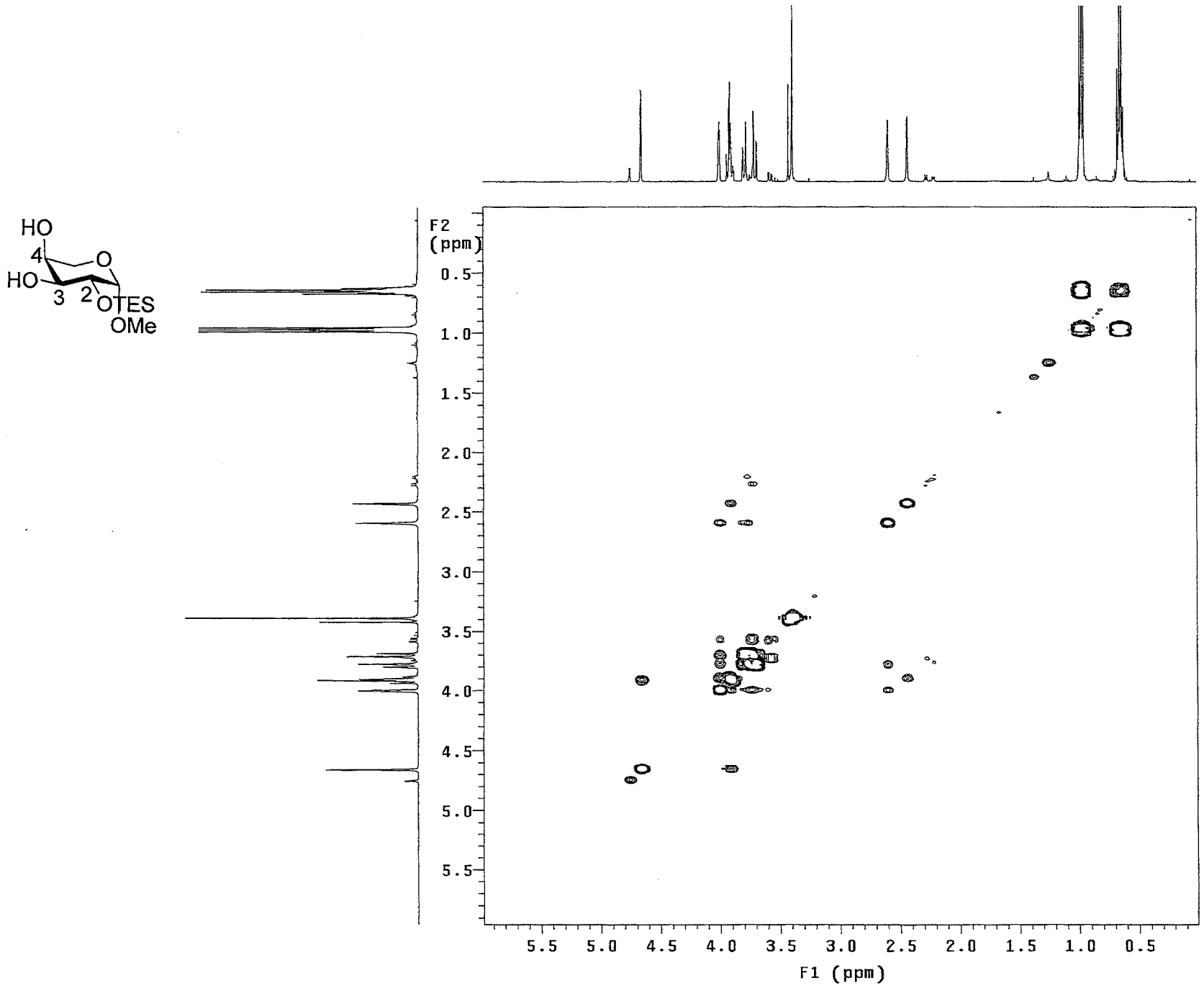

OMe
Me
O
MsO
2
3
OH
OH

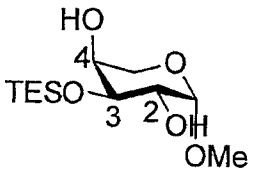

F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F1 (ppm)

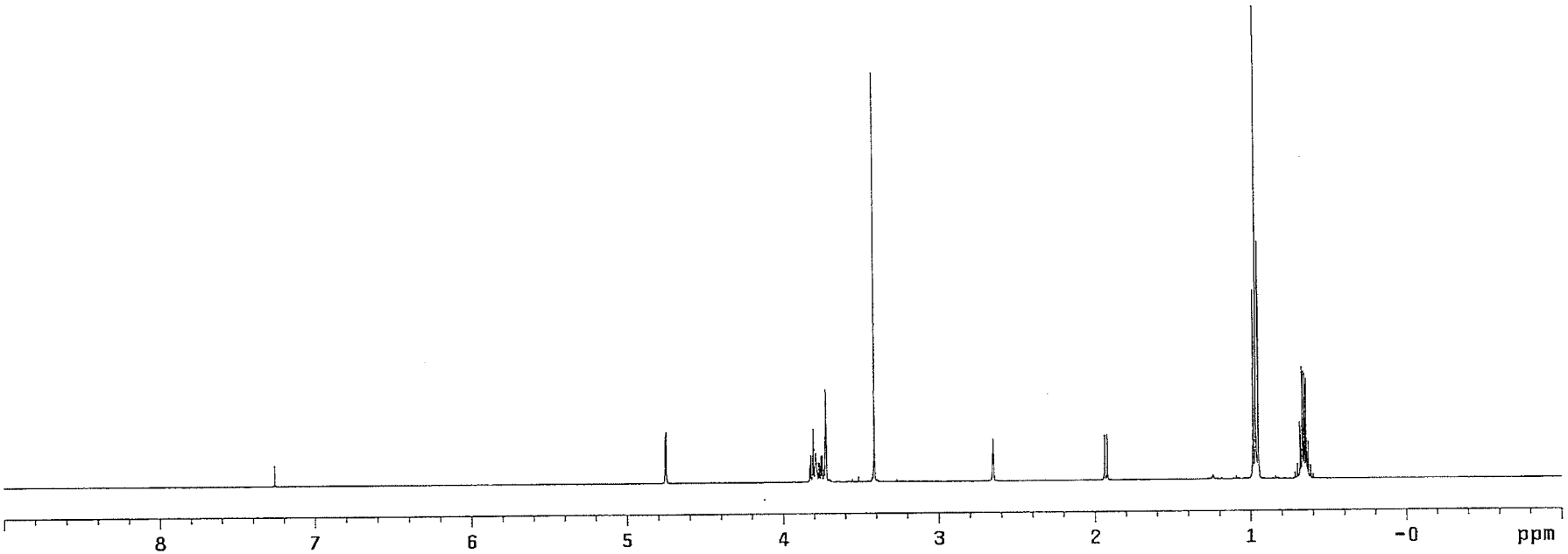

HO
4
O
HO
3
2
OTES
OMe
9
8
7
6
5
4
3
2
1
ppm

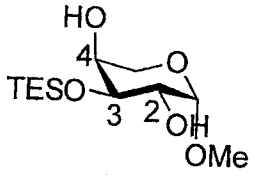

HO
4
O
HO
3
2
OTES
OMe

200
180
160
140
120
100
80
60
40
20
0
ppm

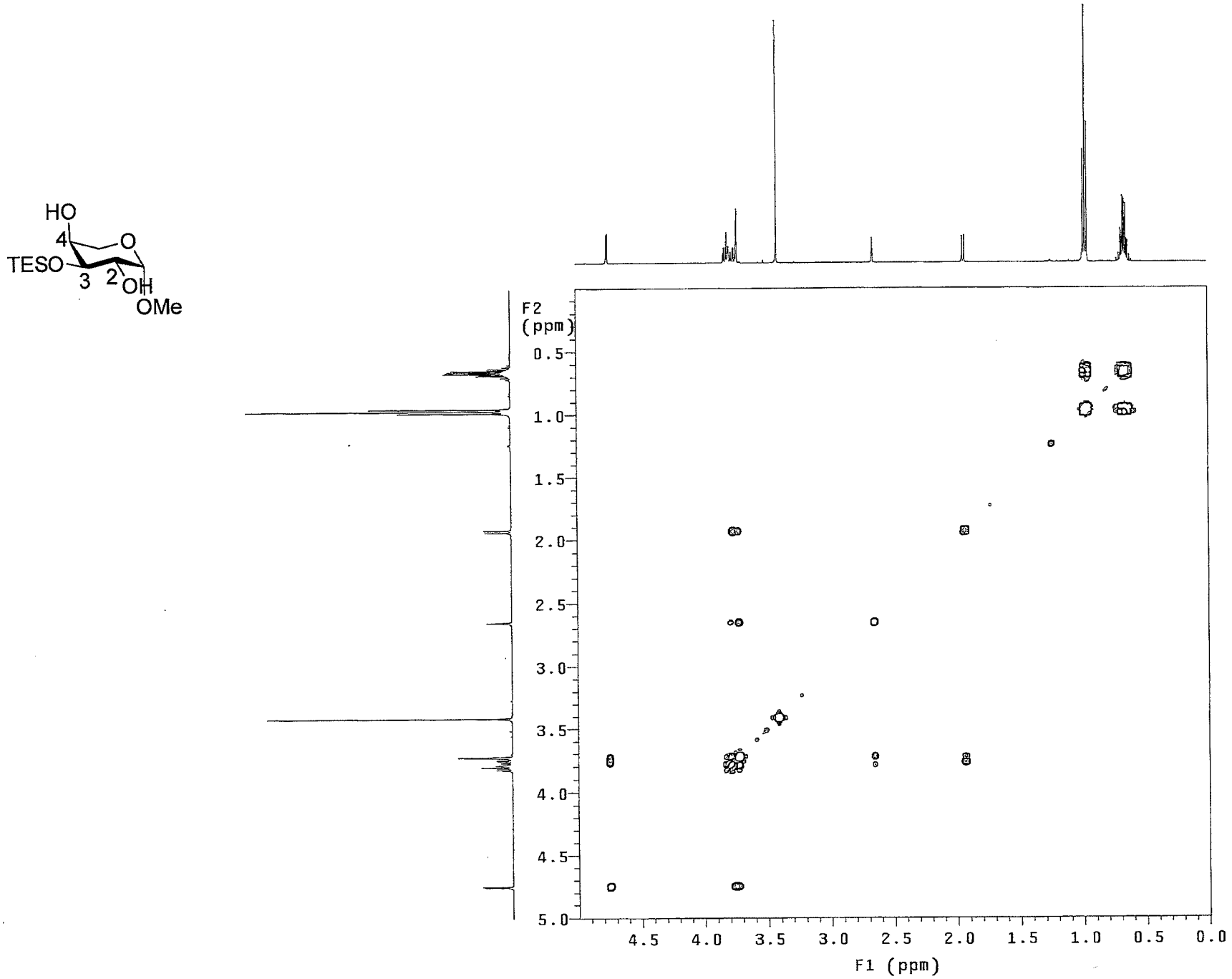

HO
4
O
HO
3
2
OTES
OMe
F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F1 (ppm)

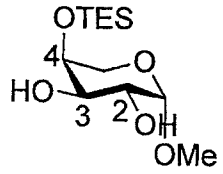

HO
4
O
TESO
3
2
OH
OMe

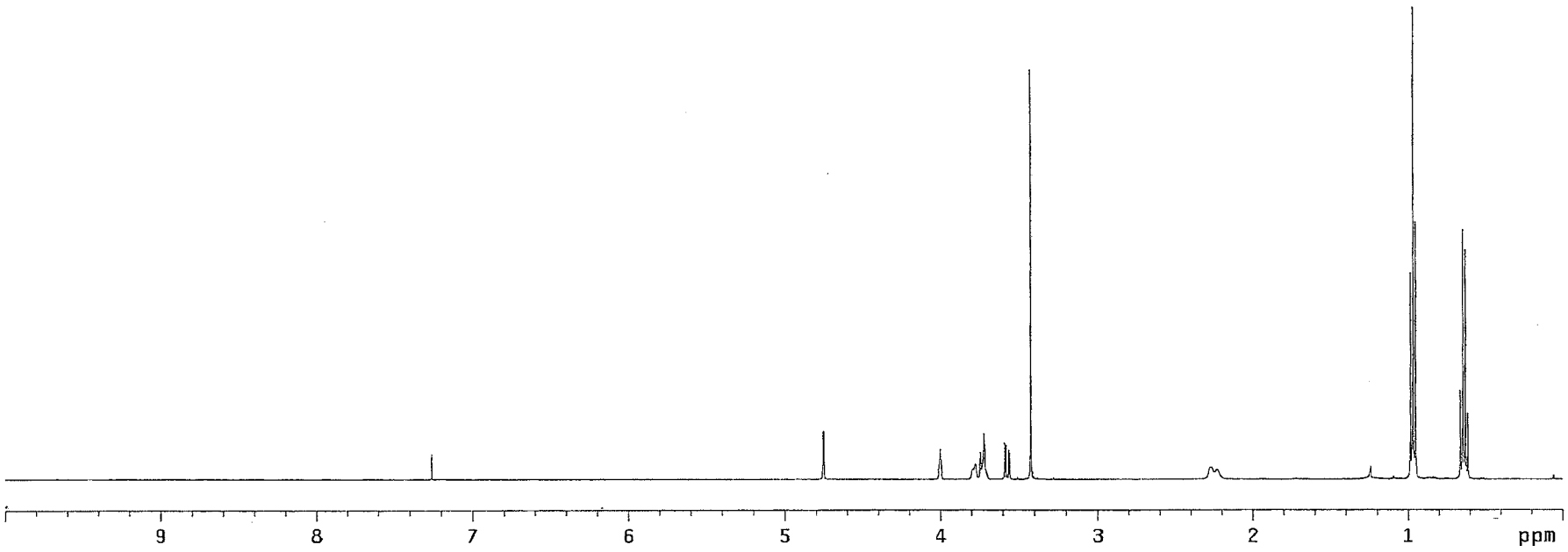

8
7
6
5
4
3
2
1
-0
ppm

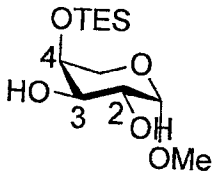

HO
4
O
TESO
3
2
OH
OMe

220
200
180
160
140
120
100
80
60
40
20
0
ppm

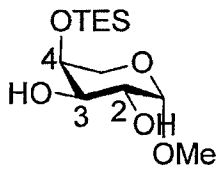

HO
4
O
TESO
3
2
OH
OMe
F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
F1 (ppm)

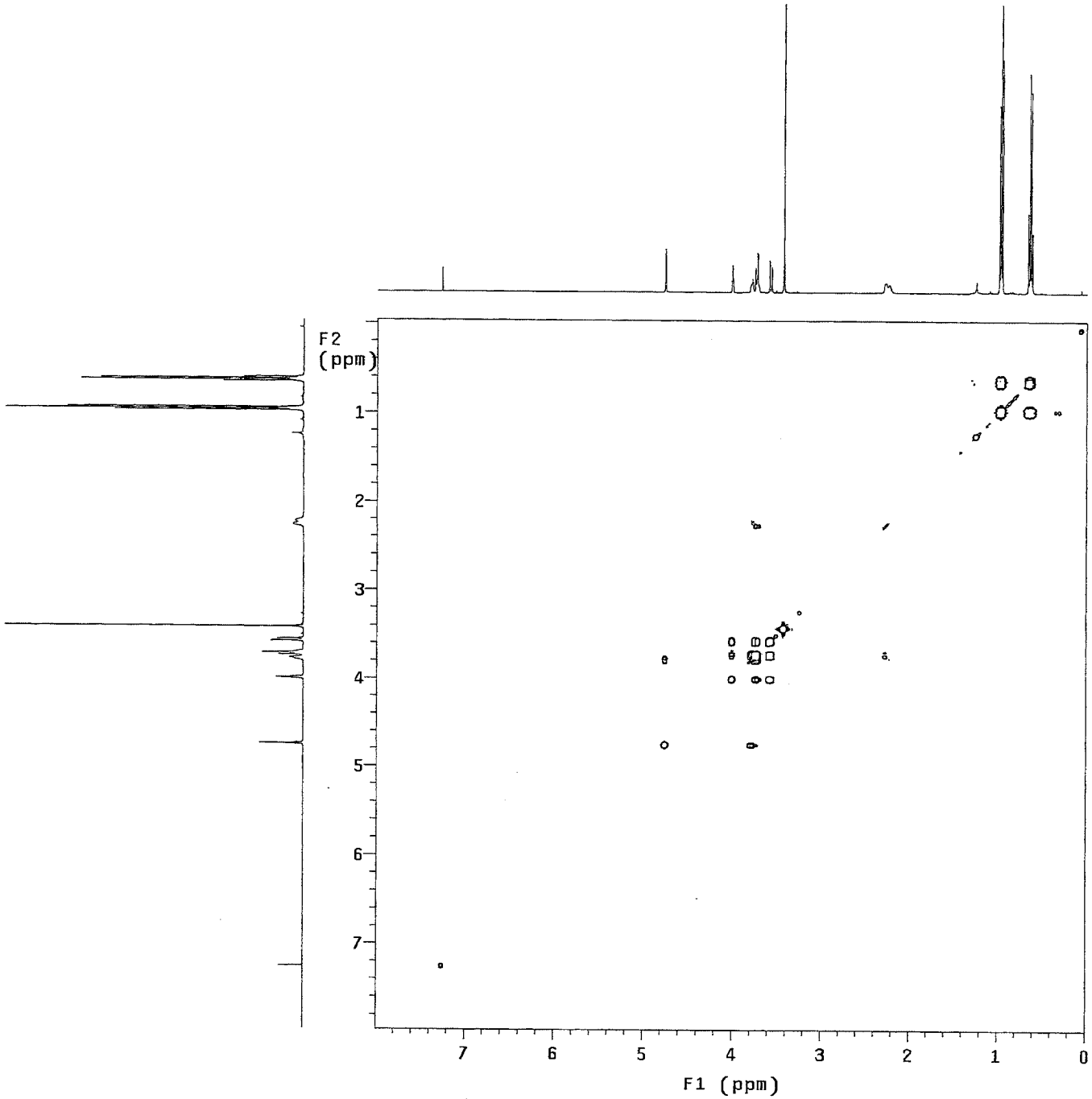

OTES
4
O
HO
3
2
OH
OMe

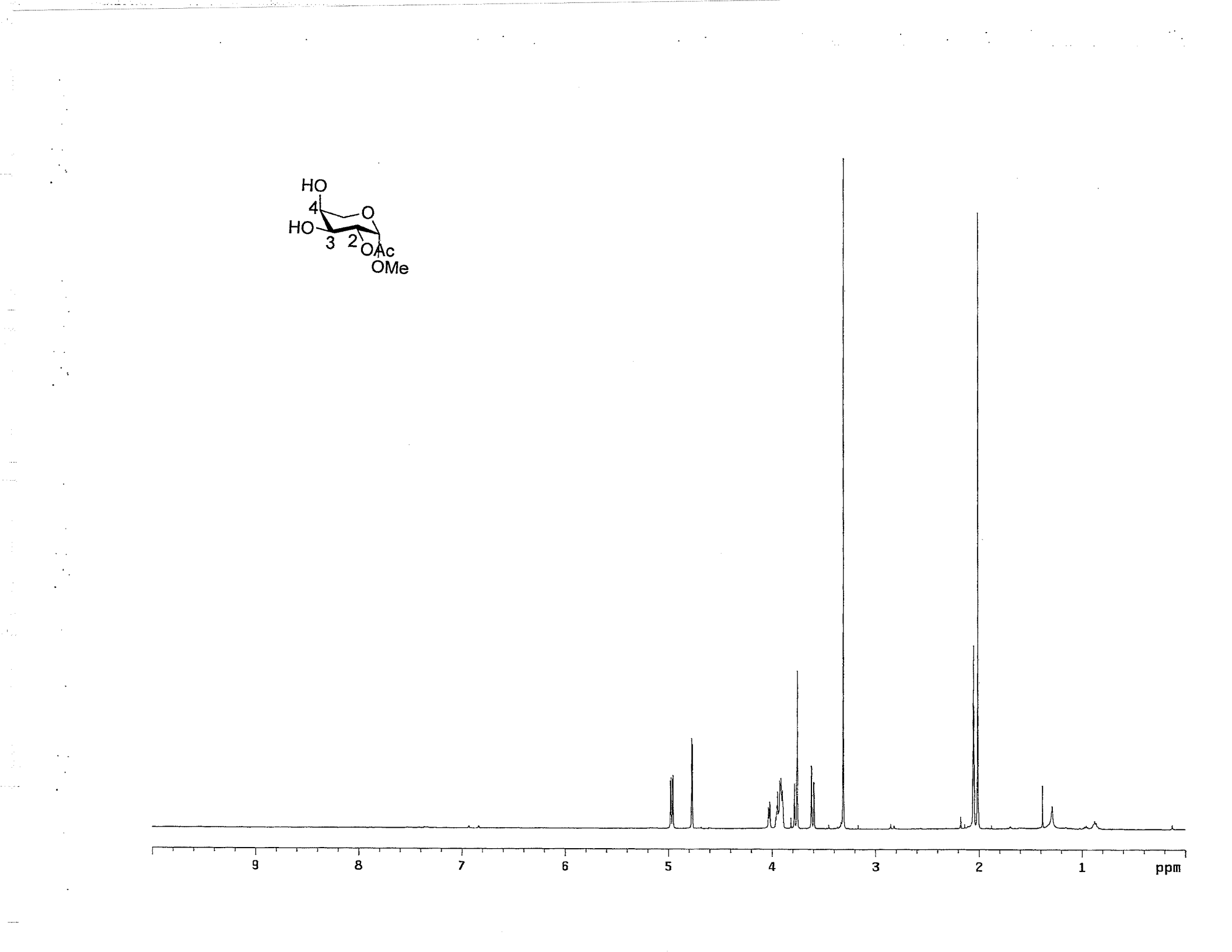

9
8
7
6
5
4
3
2
1
ppm

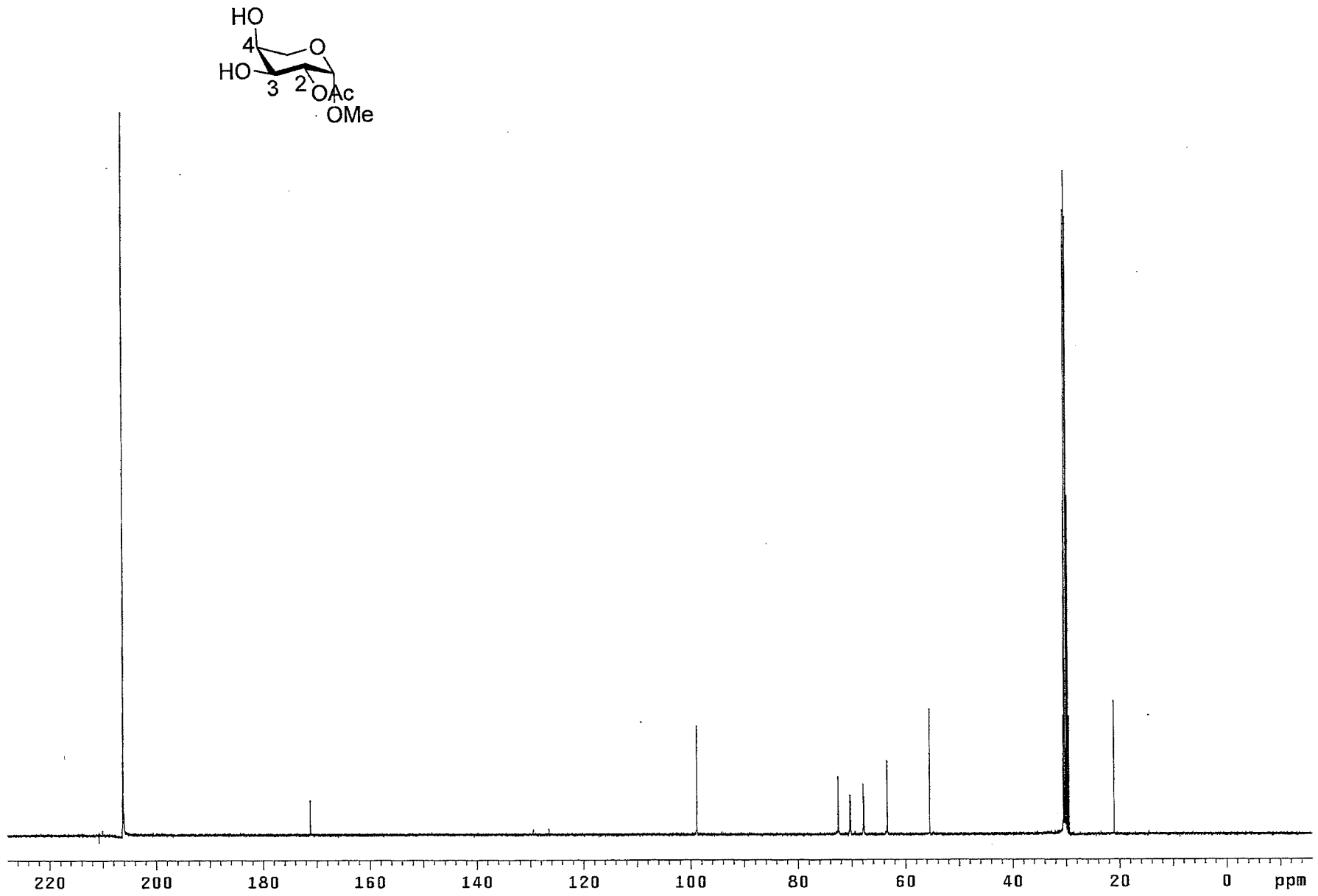

OTES
4
O
HO
3
2
OH
OMe

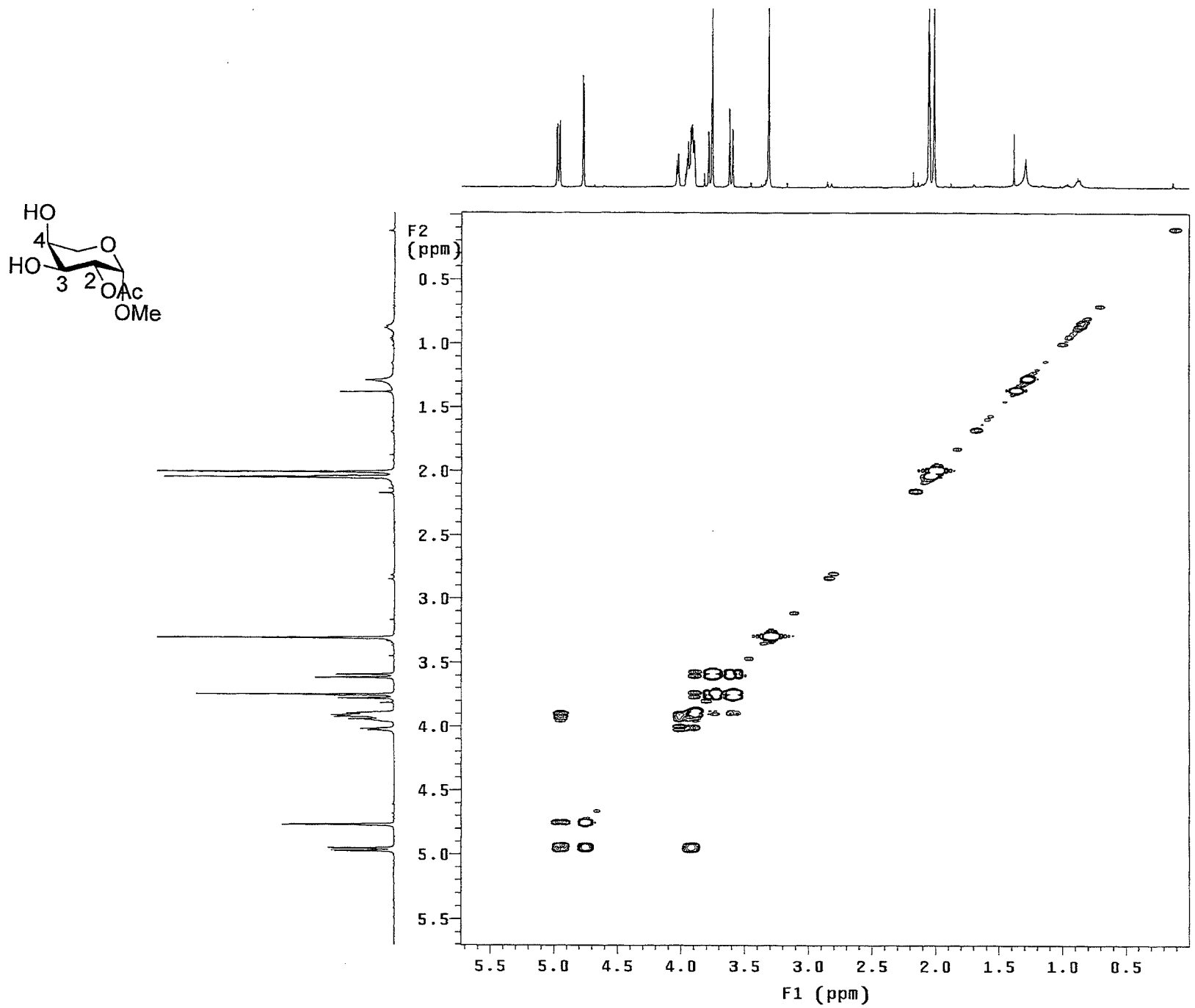
220
200
180
160
140
120
100
80
60
40
20
0
ppm

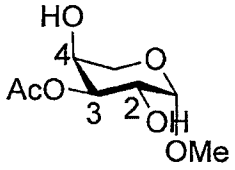

OTES
4
O
HO
3
2
OH
OMe

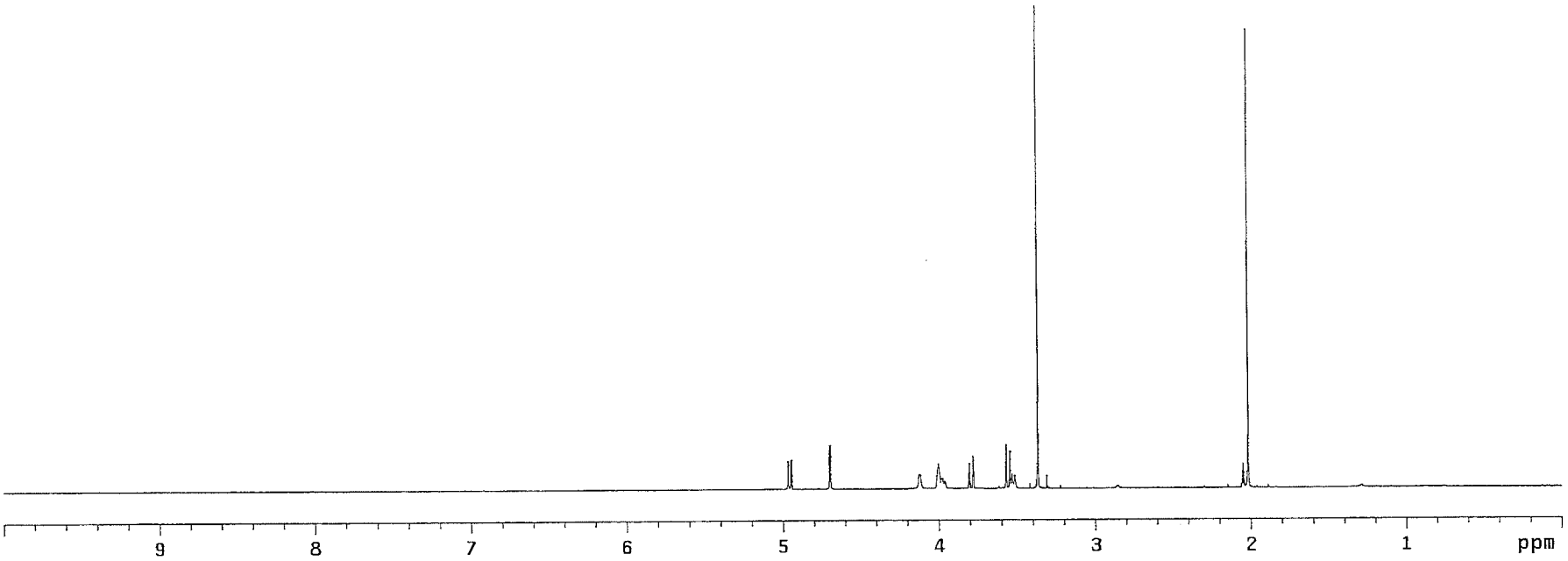

F2
(ppm)
1
2
3
4
5
6
7
7
6
5
4
3
2
1
0
F1 (ppm)

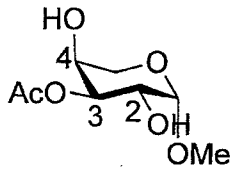

HO
4
O
HO
3
2
OAc
OMe
9
8
7
6
5
4
3
2
1
ppm


HO
4
O
HO
3
2
OAc
OMe
220
200
180
160
140
120
100
80
60
40
20
0
ppm

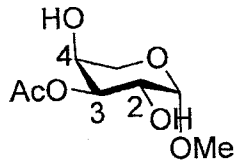

HO
4
O
HO
3
2
OAc
OMe
F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F1 (ppm)

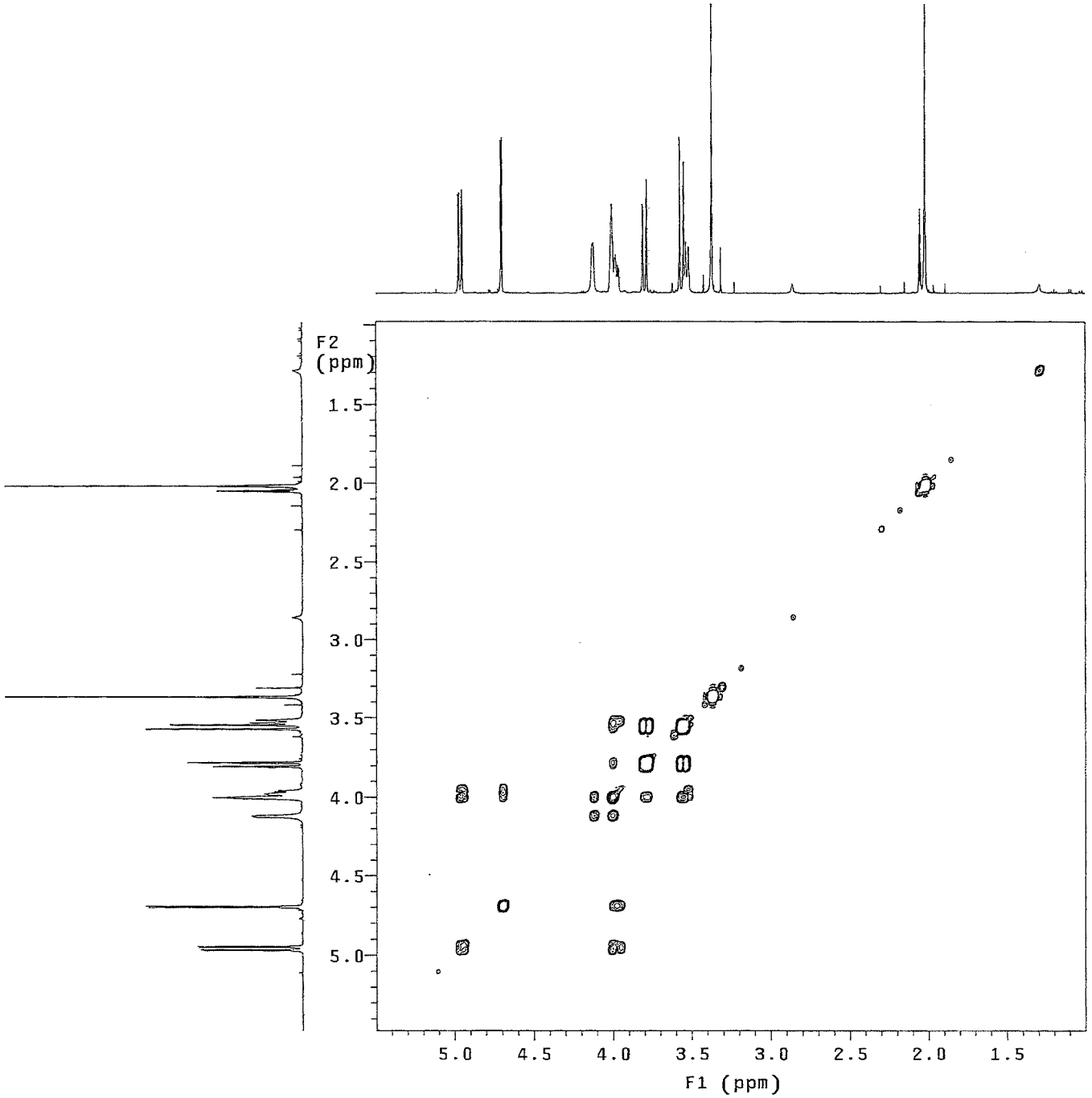

HO
4
O
AcO
3
2
OH
OMe

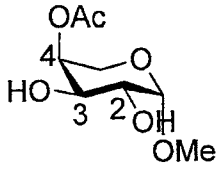

9
8
7
6
5
4
3
2
1
ppm

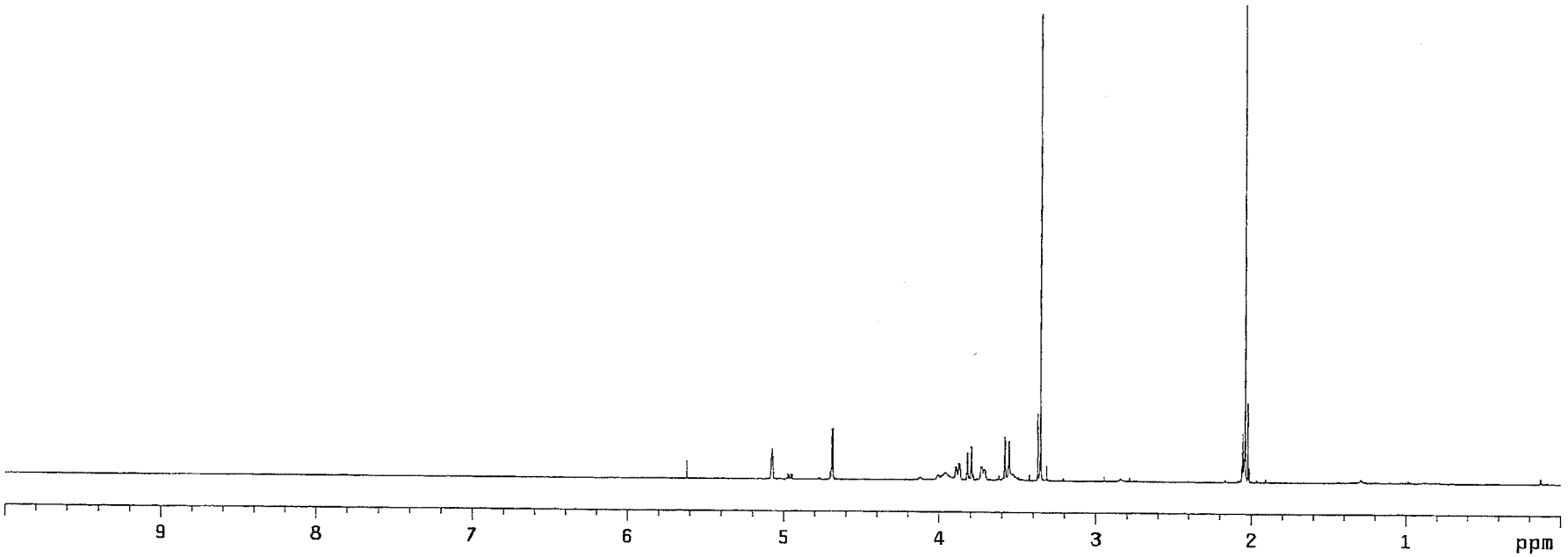

HO
4
O
AcO
3
2
OH
OMe

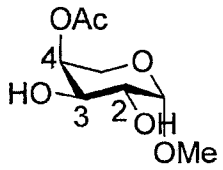
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
4
O
AcO
3
2
OH
OMe

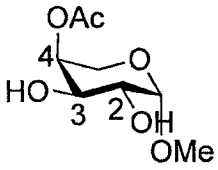

F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
F1 (ppm)

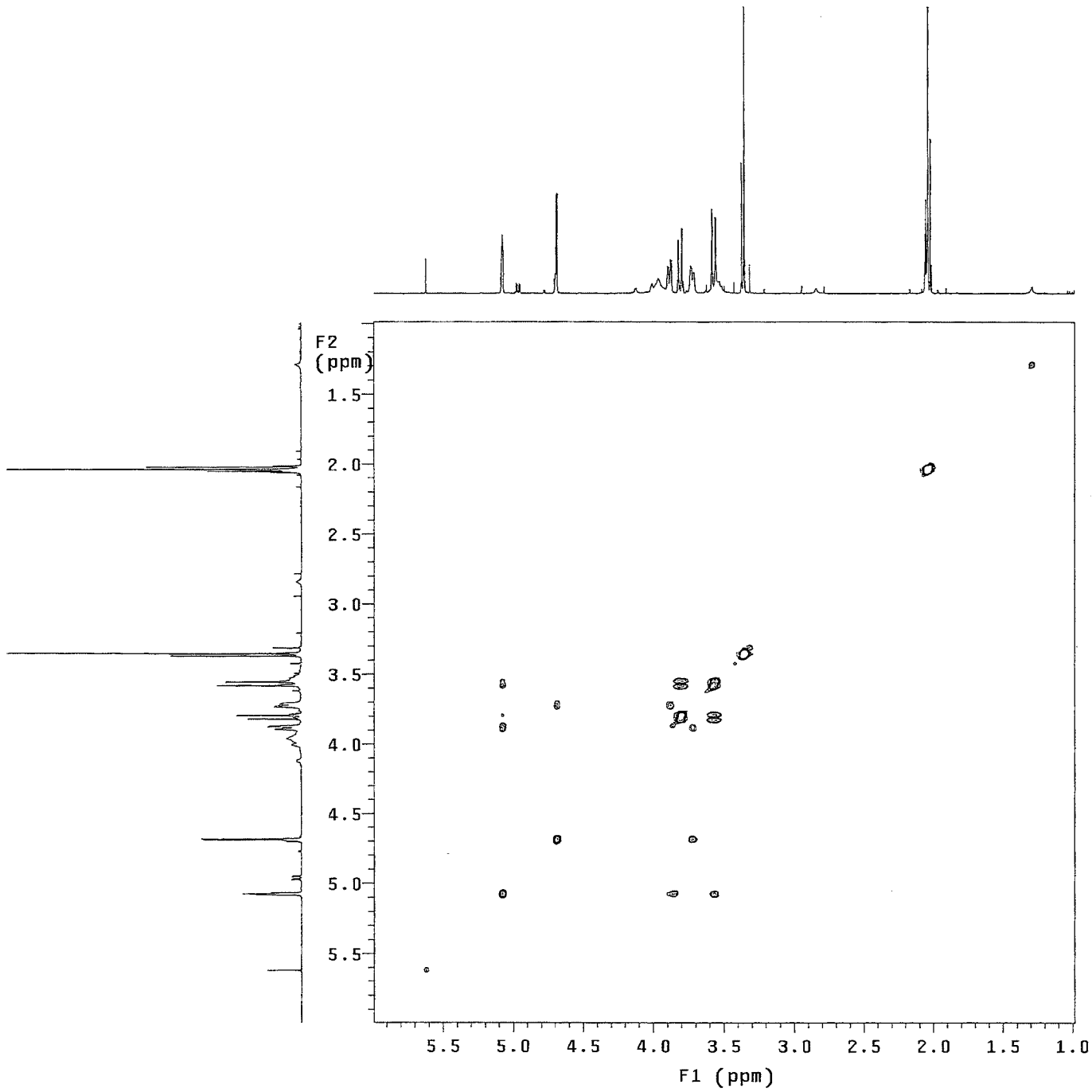

OAc
4
O
HO
3
2
OH
OMe

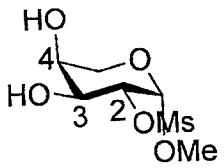

9
8
7
6
5
4
3
2
1
ppm


OAc
4
O
HO
3
2
OH
OMe

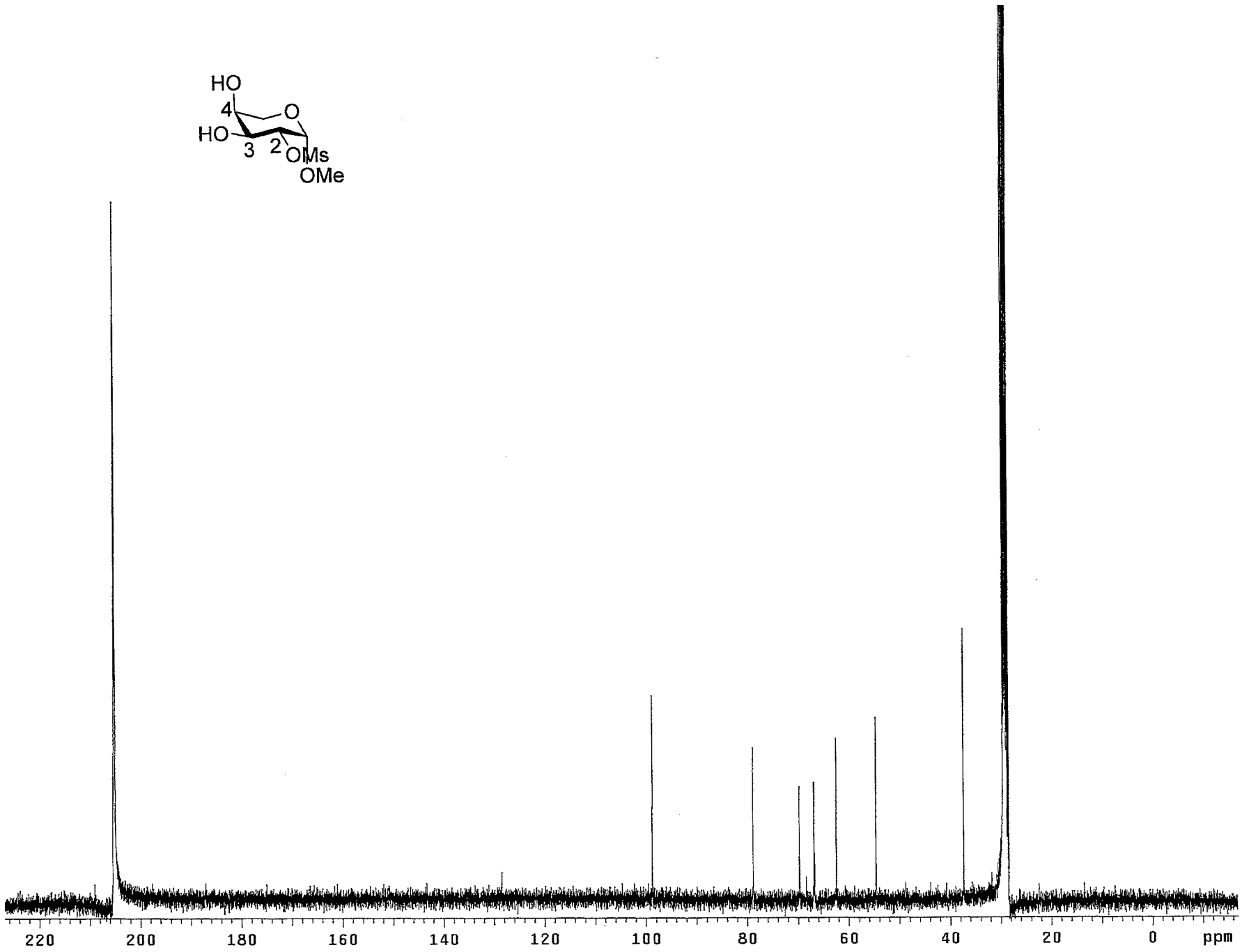
220
200
180
160
140
120
100
80
60
40
20
0
ppm

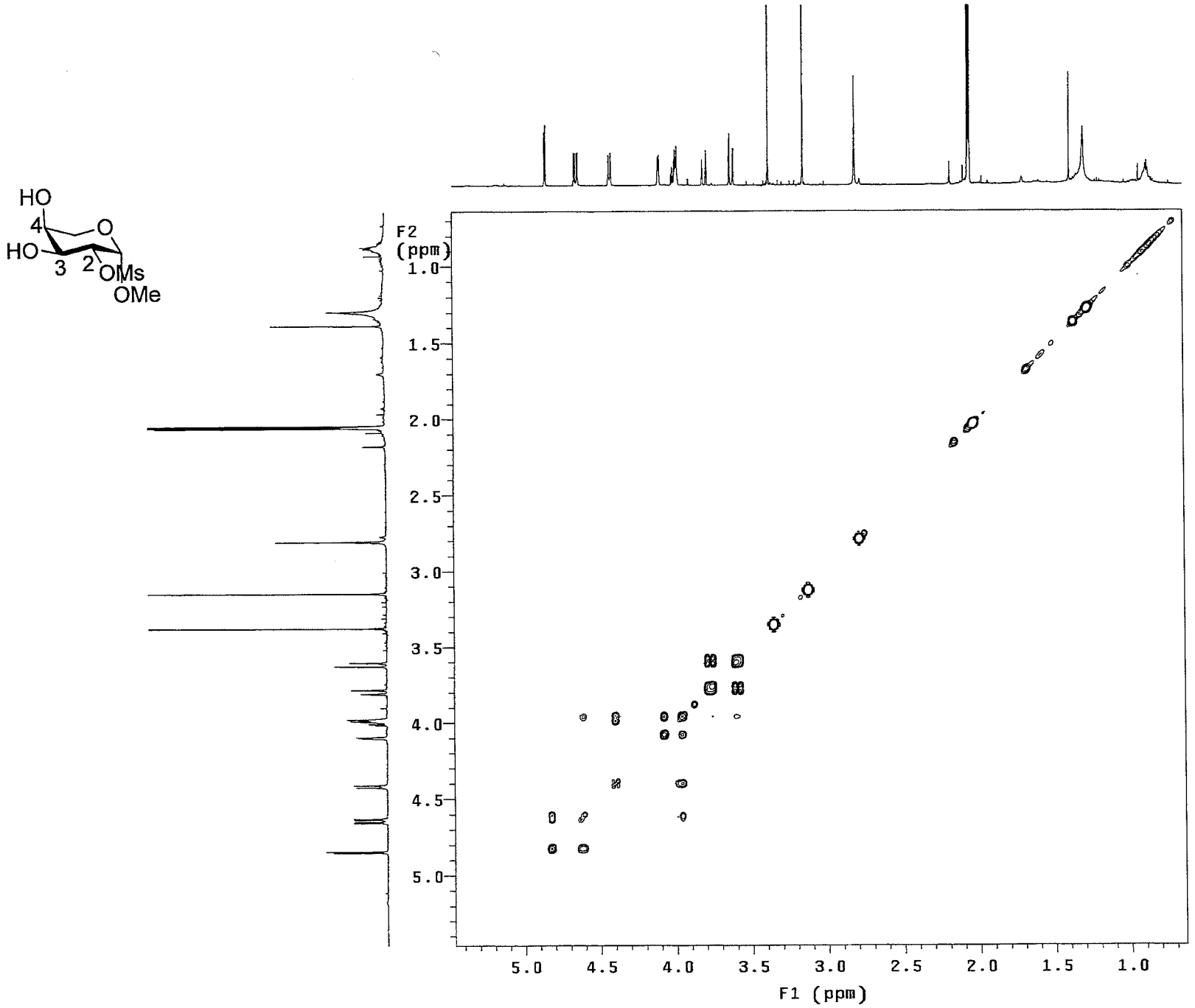

OAc
4
O
HO
3
2
OH
OMe

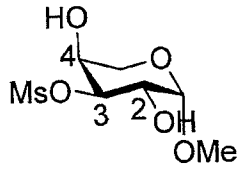

F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

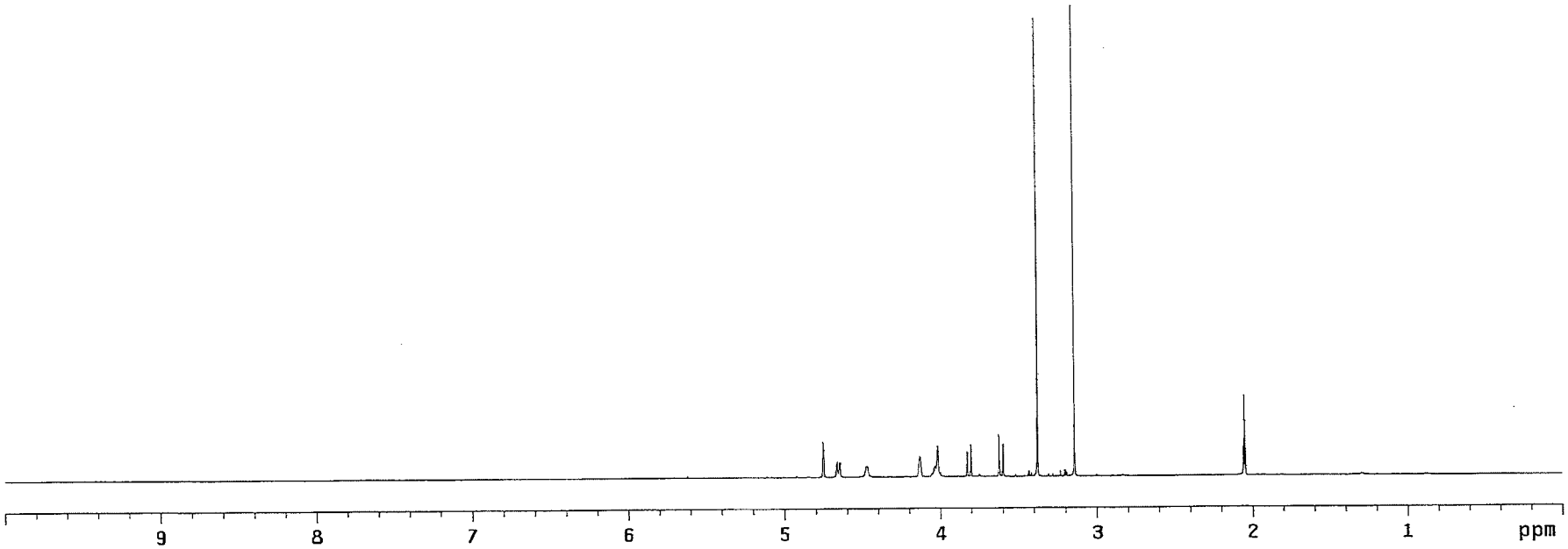

HO
4
O
HO
3
2
OMs
OMe

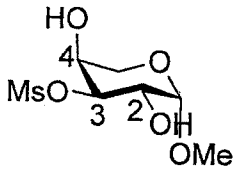
9
8
7
6
5
4
3
2
1
ppm


HO
4
O
HO
3
2
OMs
OMe
220
200
180
160
140
120
100
80
60
40
20
0
ppm

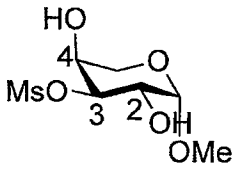

HO
4
O
HO
3
2
OMs
OMe
F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

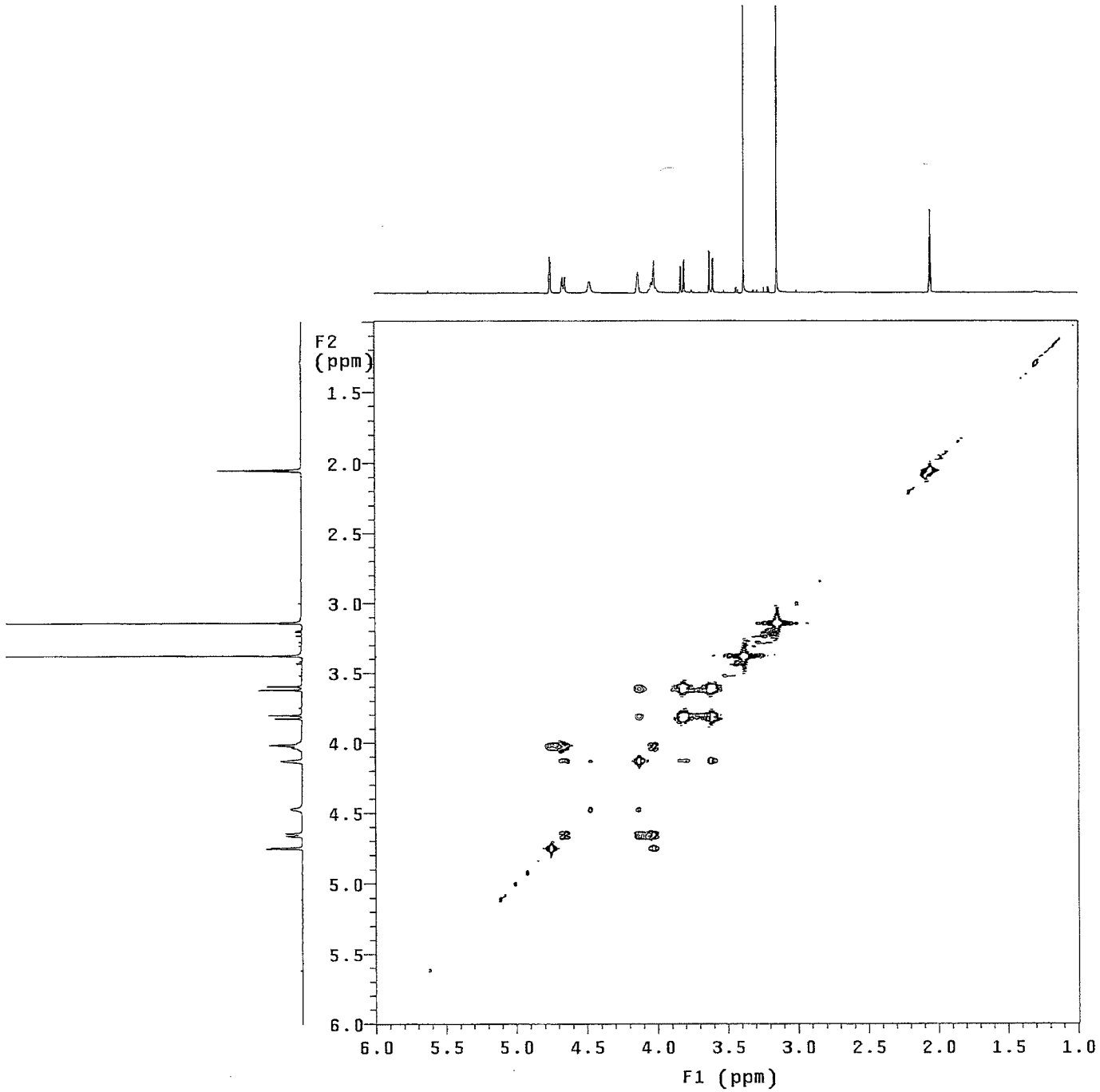

HO
4
O
MsO
3
2
OH
OMe

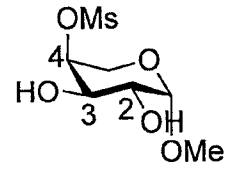

9
8
7
6
5
4
3
2
1
ppm

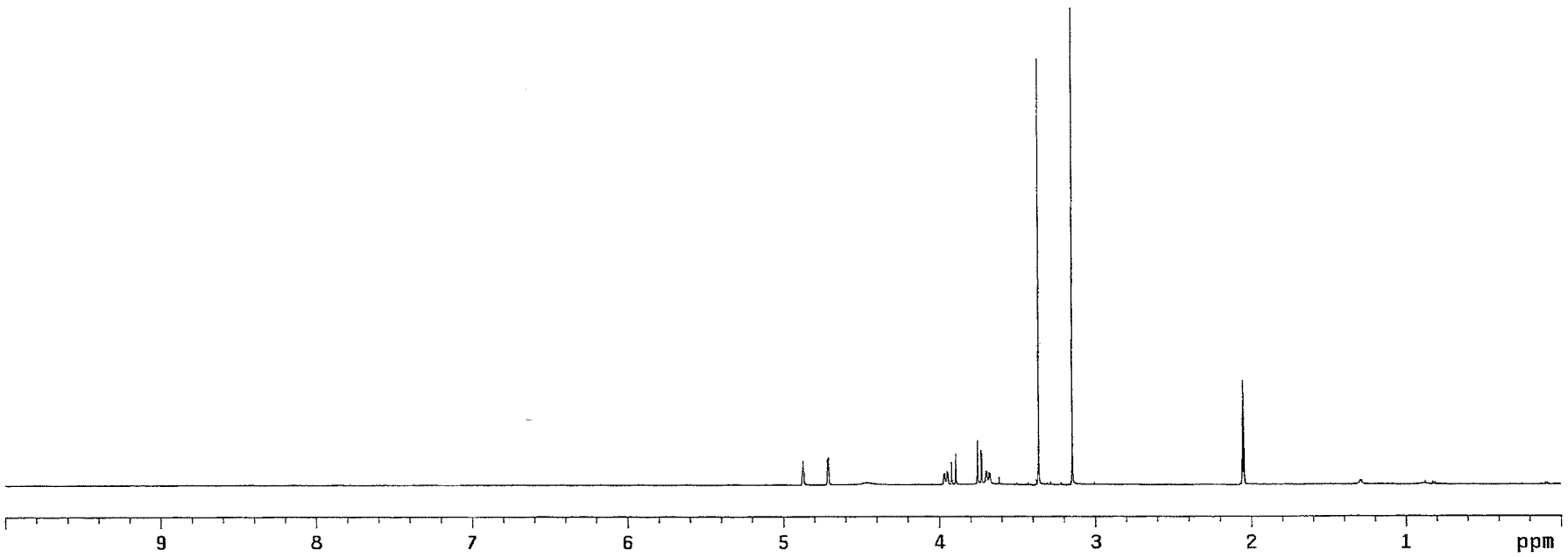

HO
4
O
MsO
3
2
OH
OMe

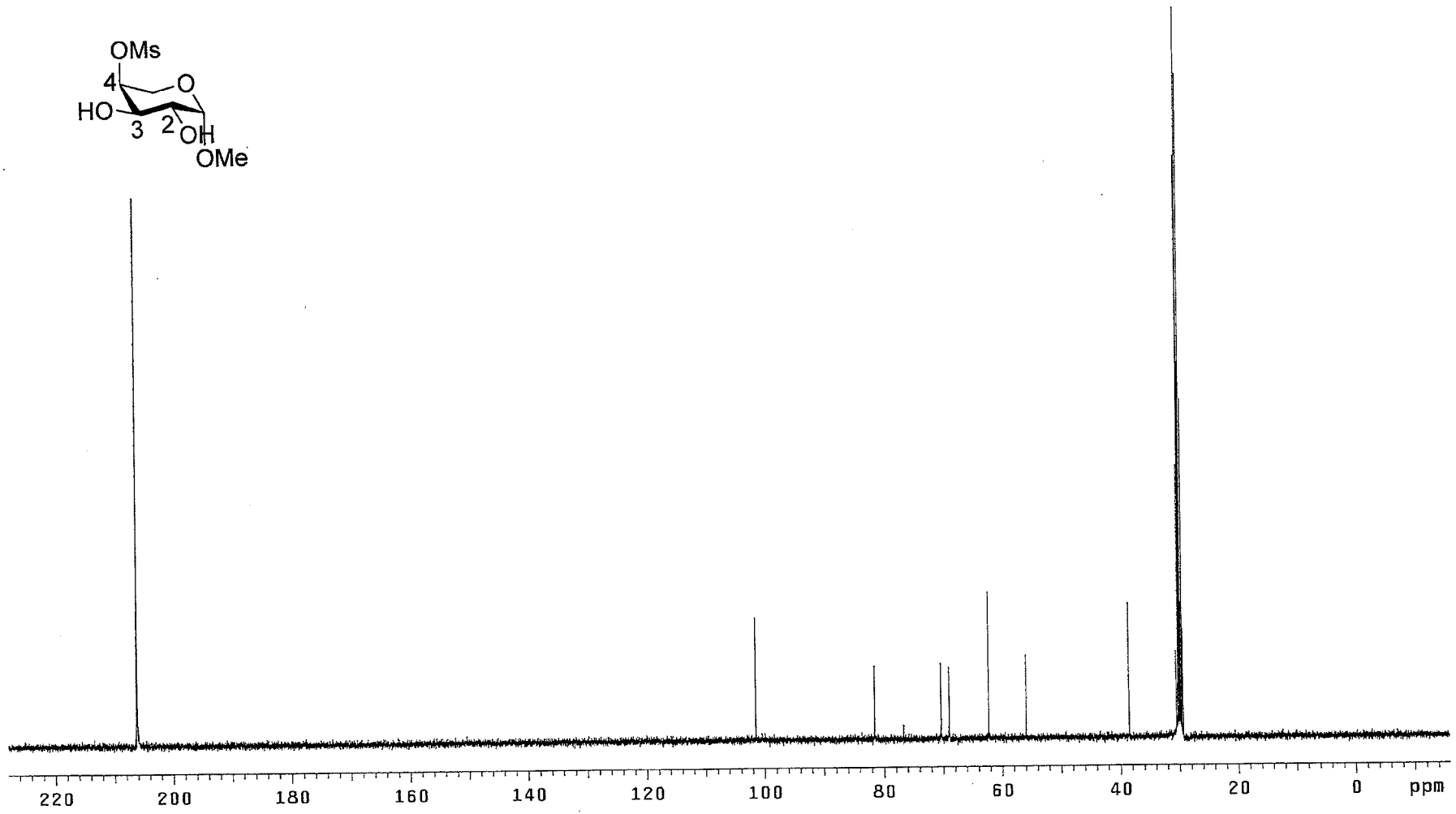
180
160
140
120
100
80
60
40
20
0
-20
ppm

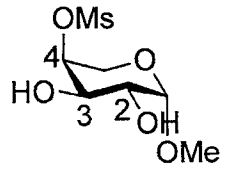

HO
4
O
MsO
3
2
OH
OMe

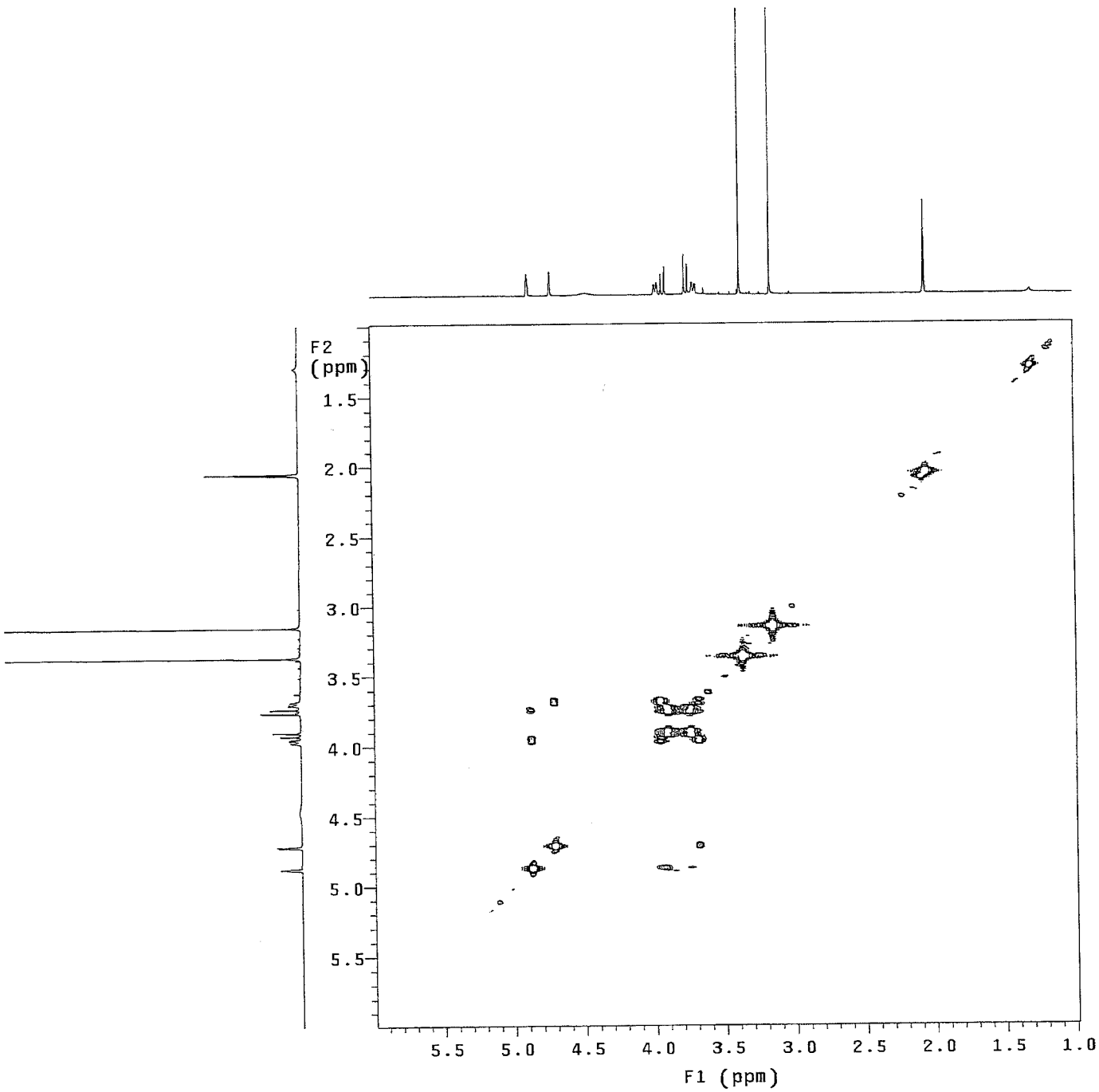

F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

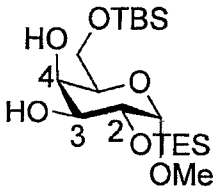

OMs
4
O
HO
3
2
OH
OMe

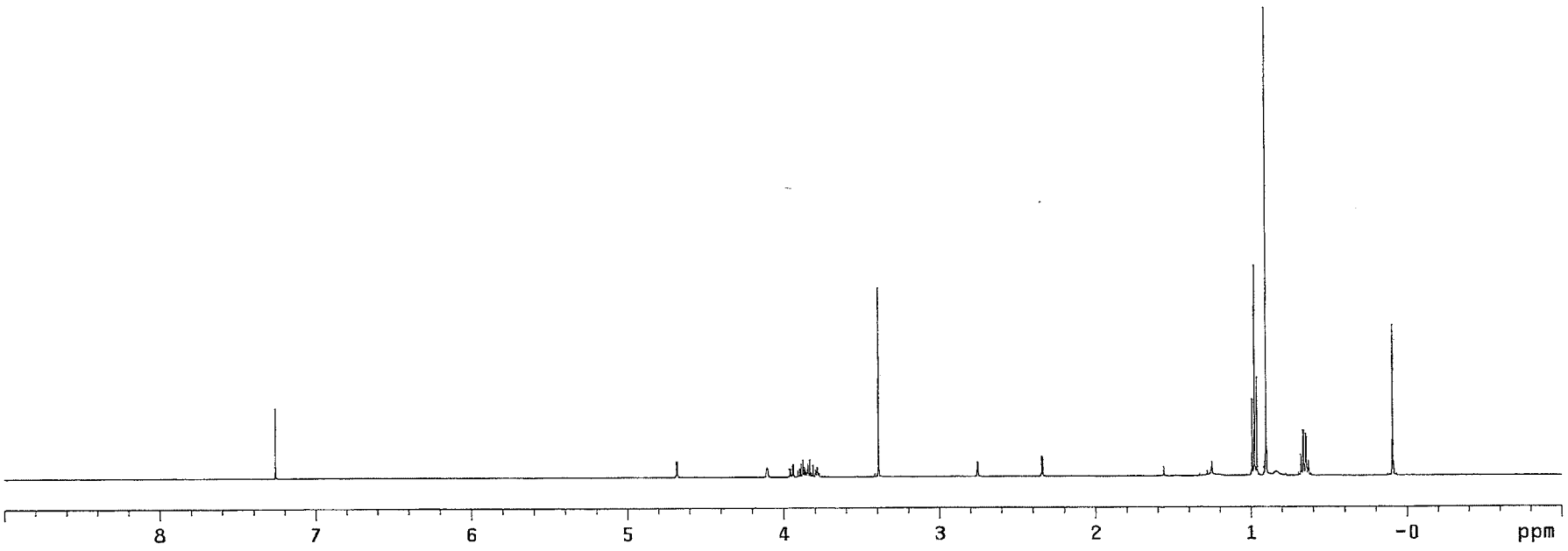

9
8
7
6
5
4
3
2
1
ppm

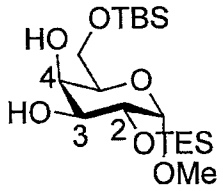

OMs
4
O
HO
3
2
OH
OMe
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OMs
4
O
HO
3
2
OH
OMe

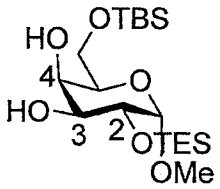

F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

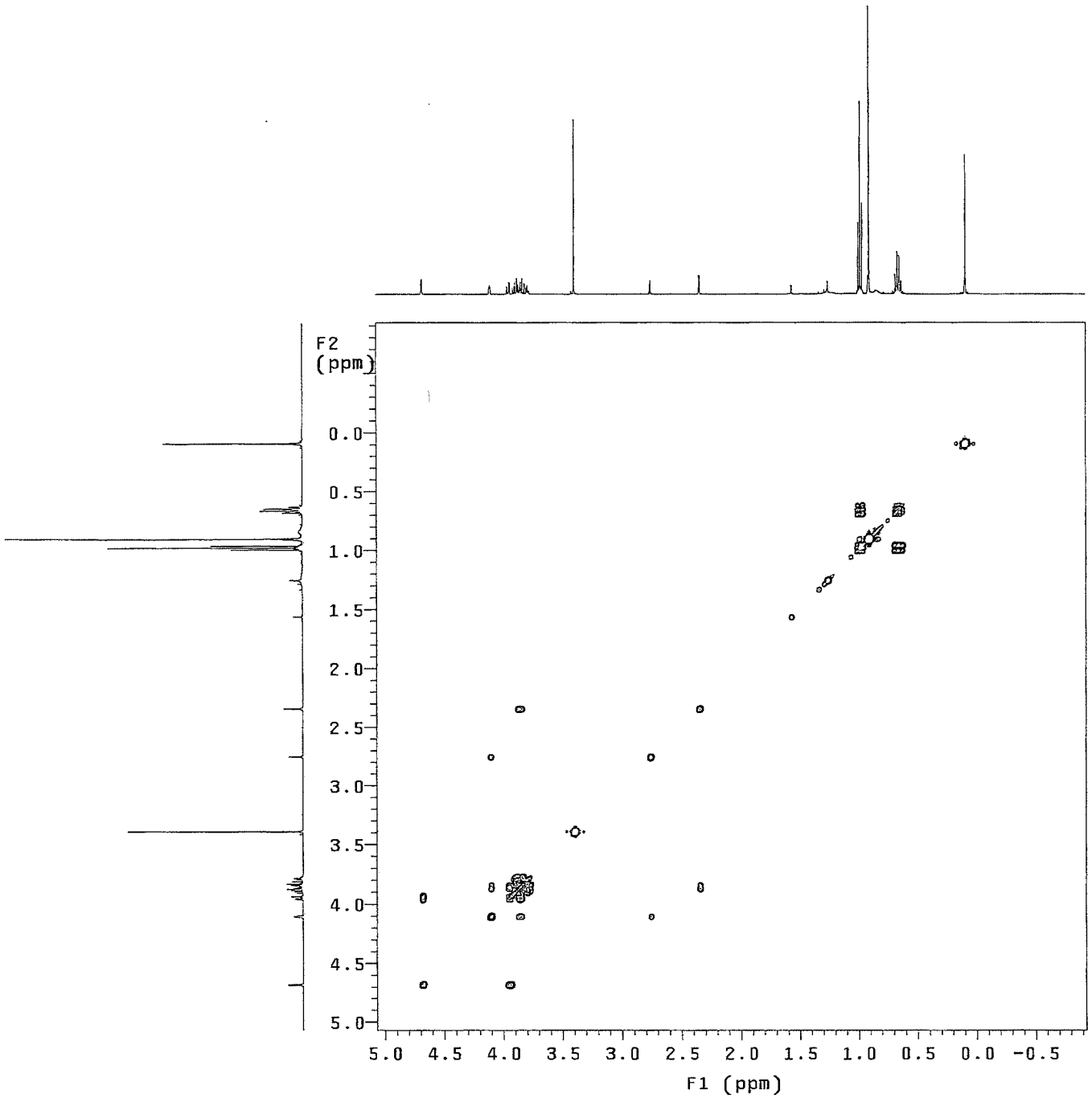

OTBS
HO
4
O
HO
3
2
OTES
OMe

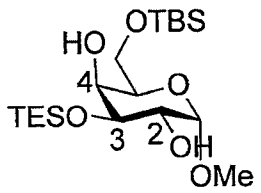

8
7
6
5
4
3
2
1
-0
ppm

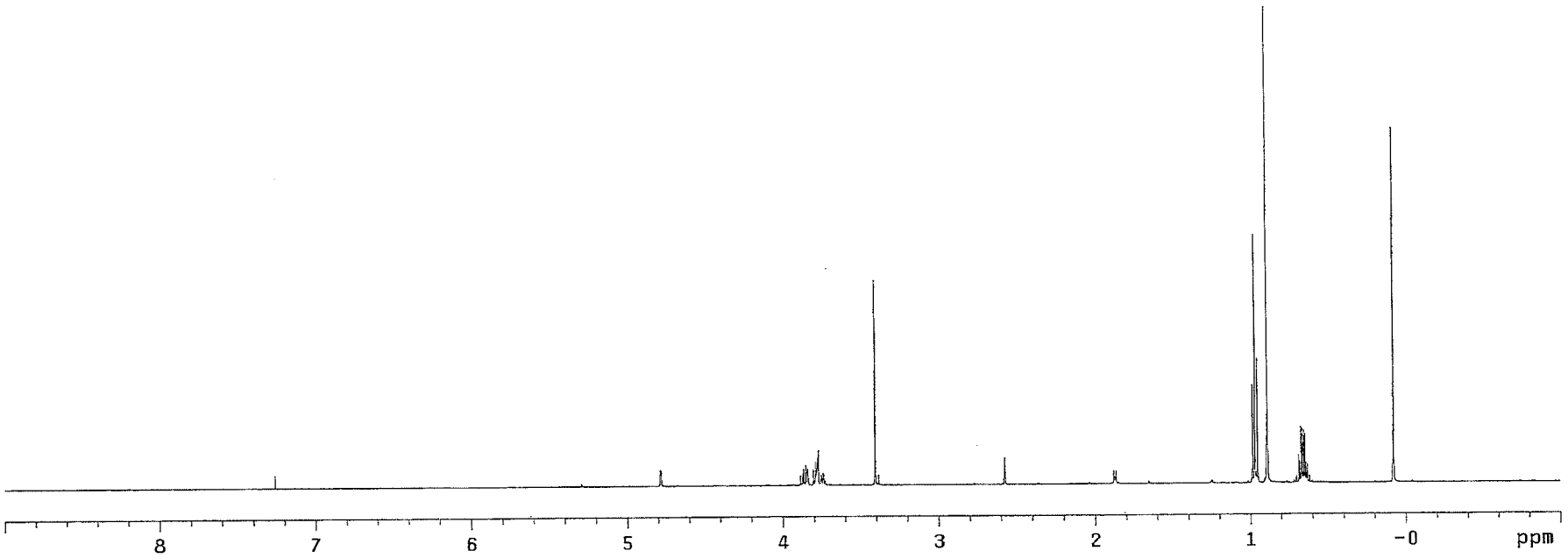

OTBS
HO
4
O
HO
3
2
OTES
OMe

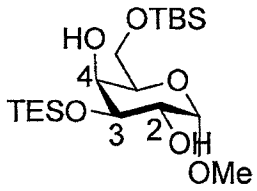
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
OTBS
4
O
HO
3
2
OTES
OMe

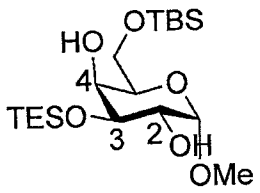

F2 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
F1 (ppm)

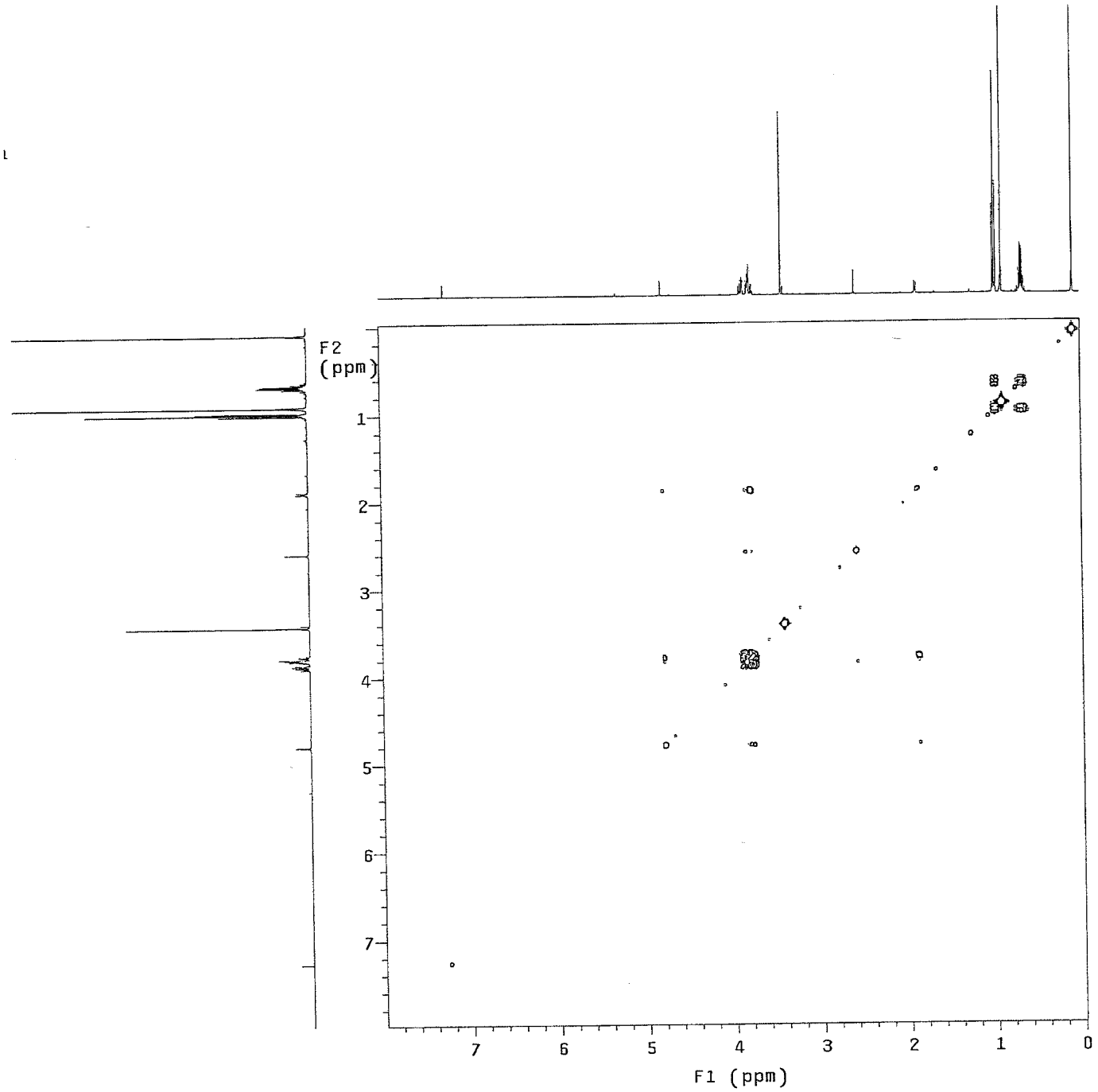

OTBS
HO
4
O
TESO
3
2
OH
OMe

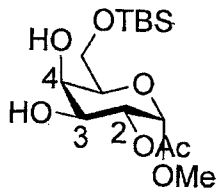

8
7
6
5
4
3
2
1
-0
ppm

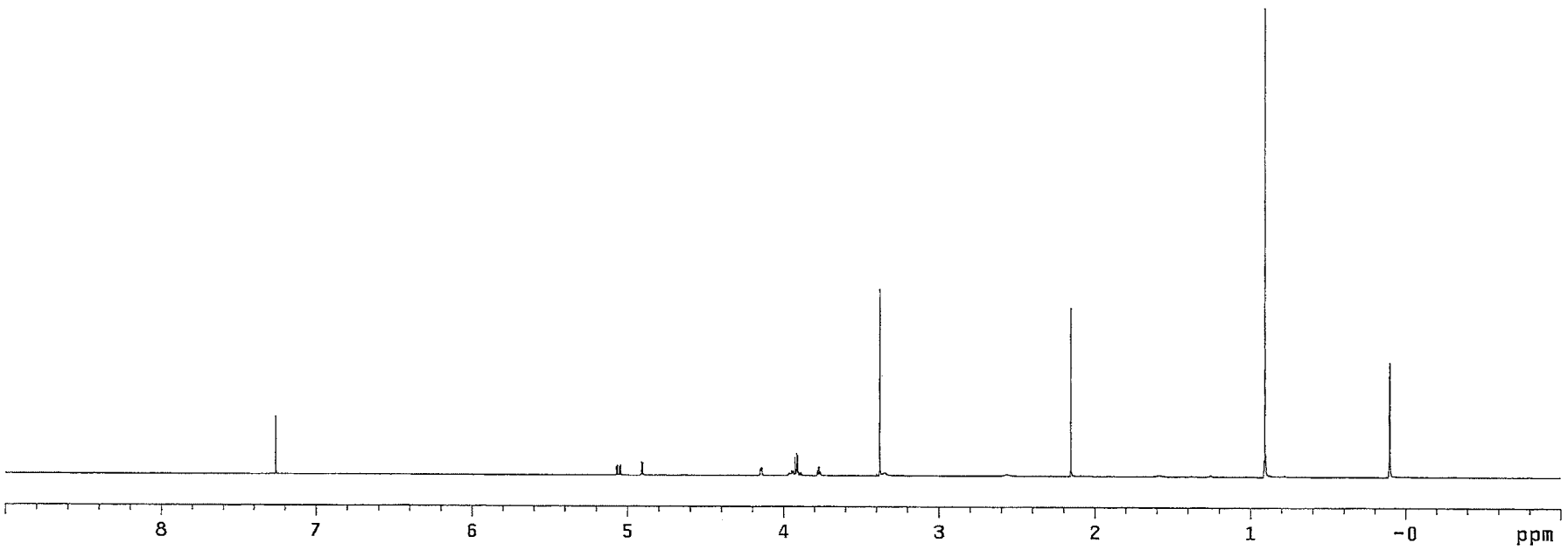

OTBS
HO
4
O
TESO
3
2
OH
H
OMe

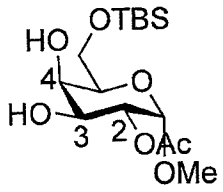
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
OTBS
4
O
TESO
3
2
OH
OMe

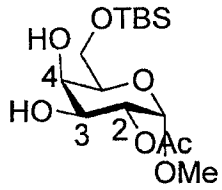

F2
(ppm)
1
2
3
4
5
6
7
7
6
5
4
3
2
1
0
F1 (ppm)

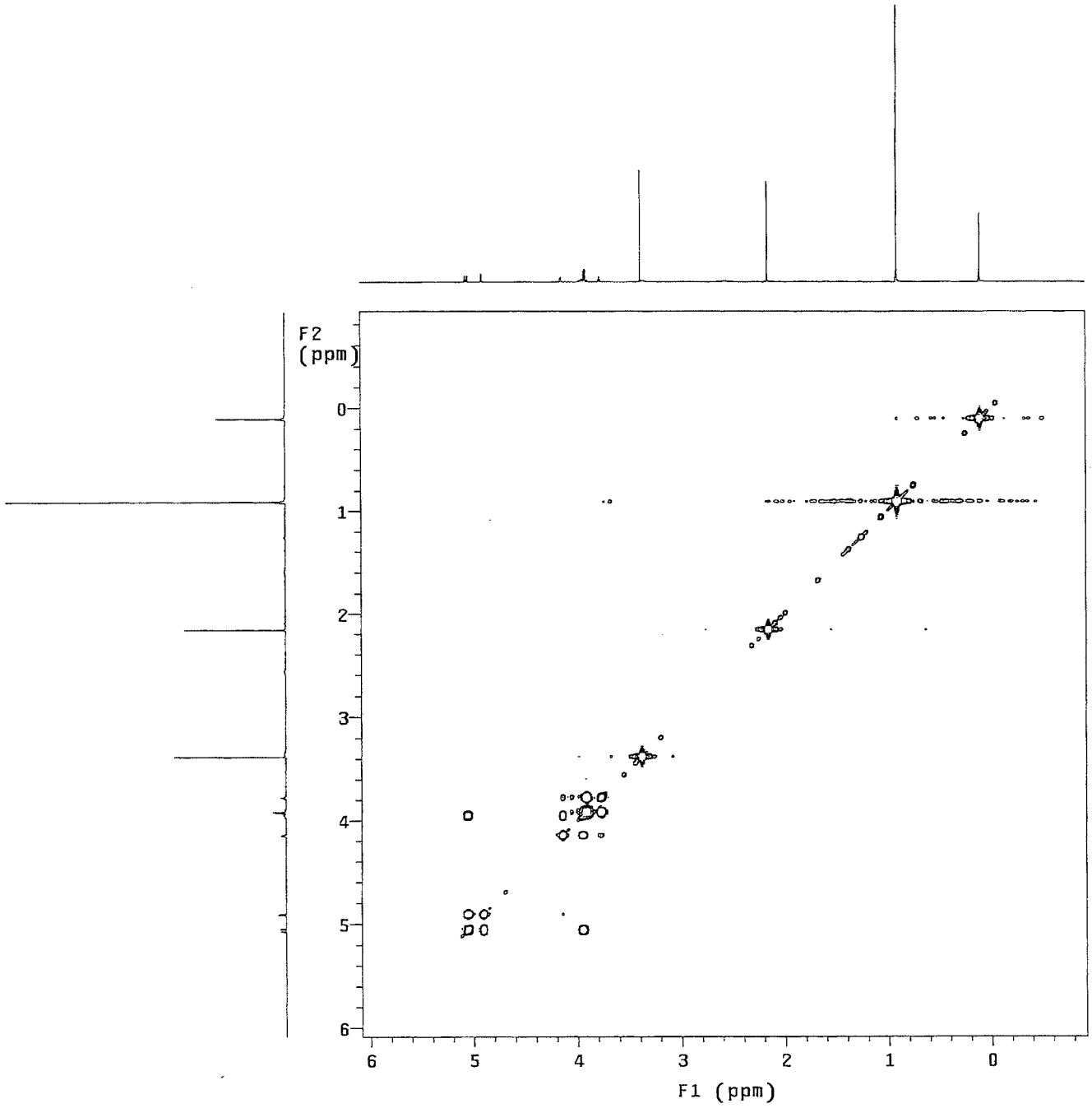

OTBS
HO
4
O
HO
3
2
OAc
OMe

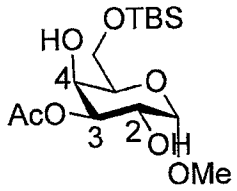

8
7
6
5
4
3
2
1
-0
ppm

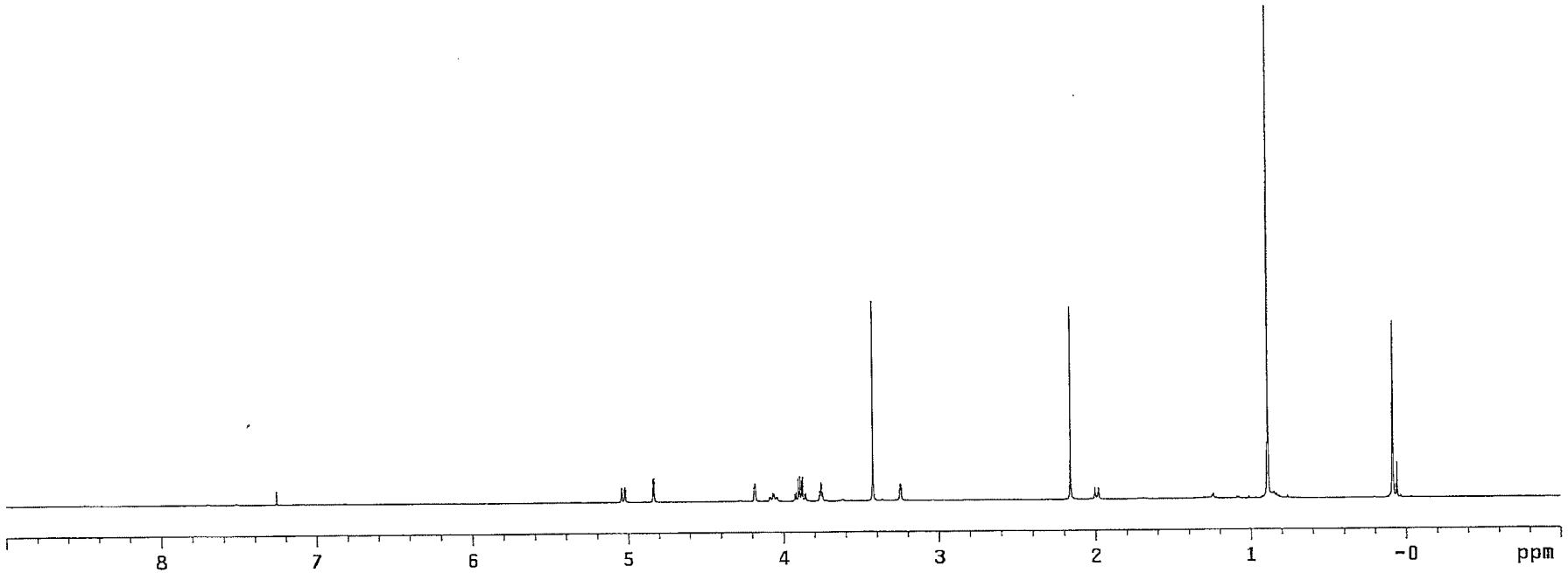

OTBS
HO
4
O
HO
3
2
OAc
OMe

220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTBS
HO
4
O
HO
3
2
OAc
OMe


F2
(ppm)
0
1
2
3
4
5
6
6
5
4
3
2
1
0
F1 (ppm)


OTBS
HO
4
O
AcO
3
2
OH
OMe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7
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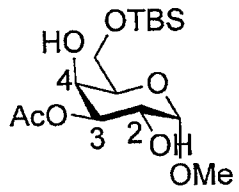
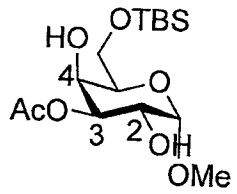
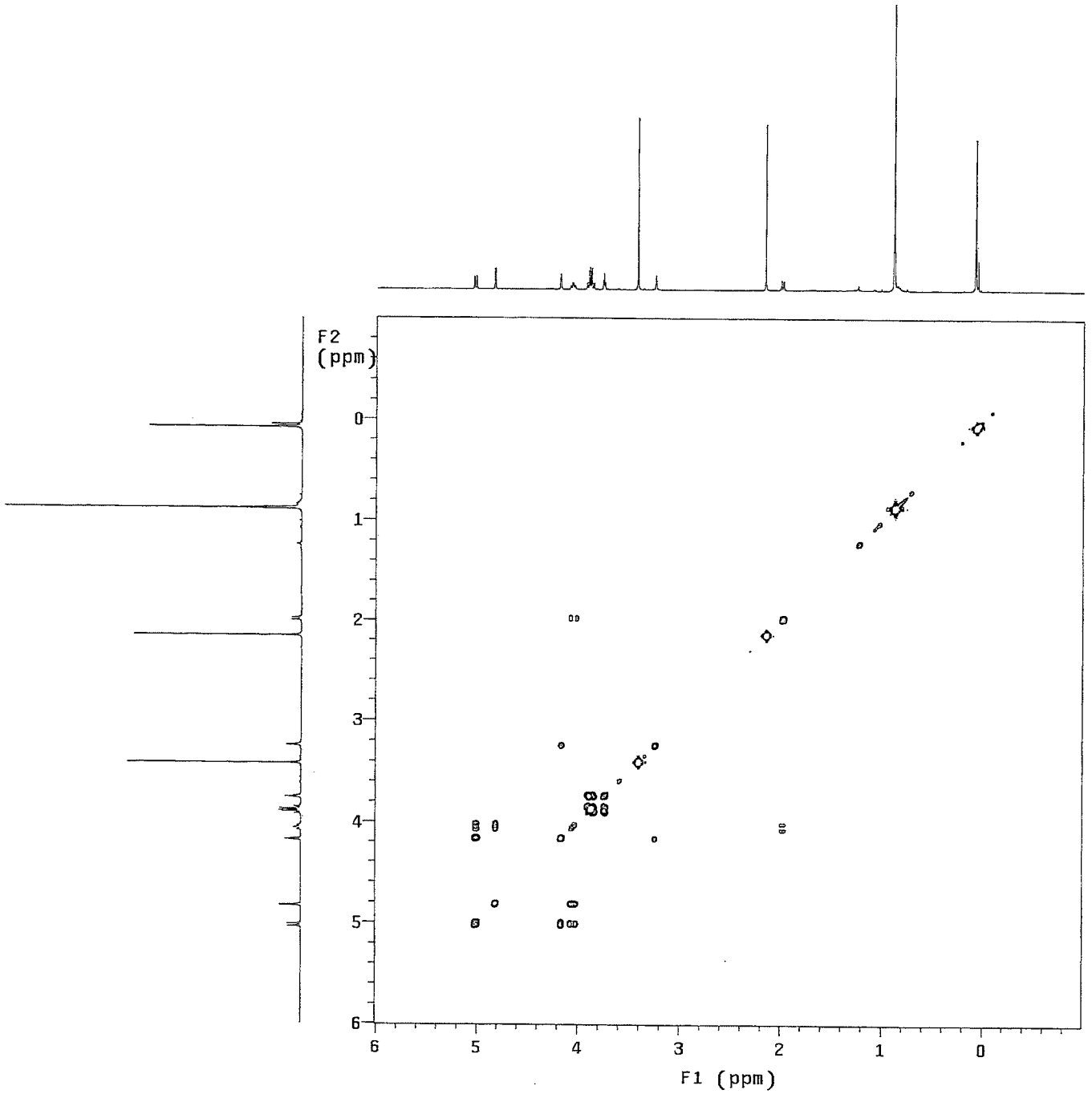
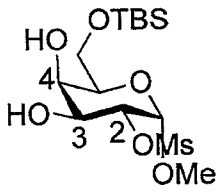
5
4
3
2
1
-0
ppm

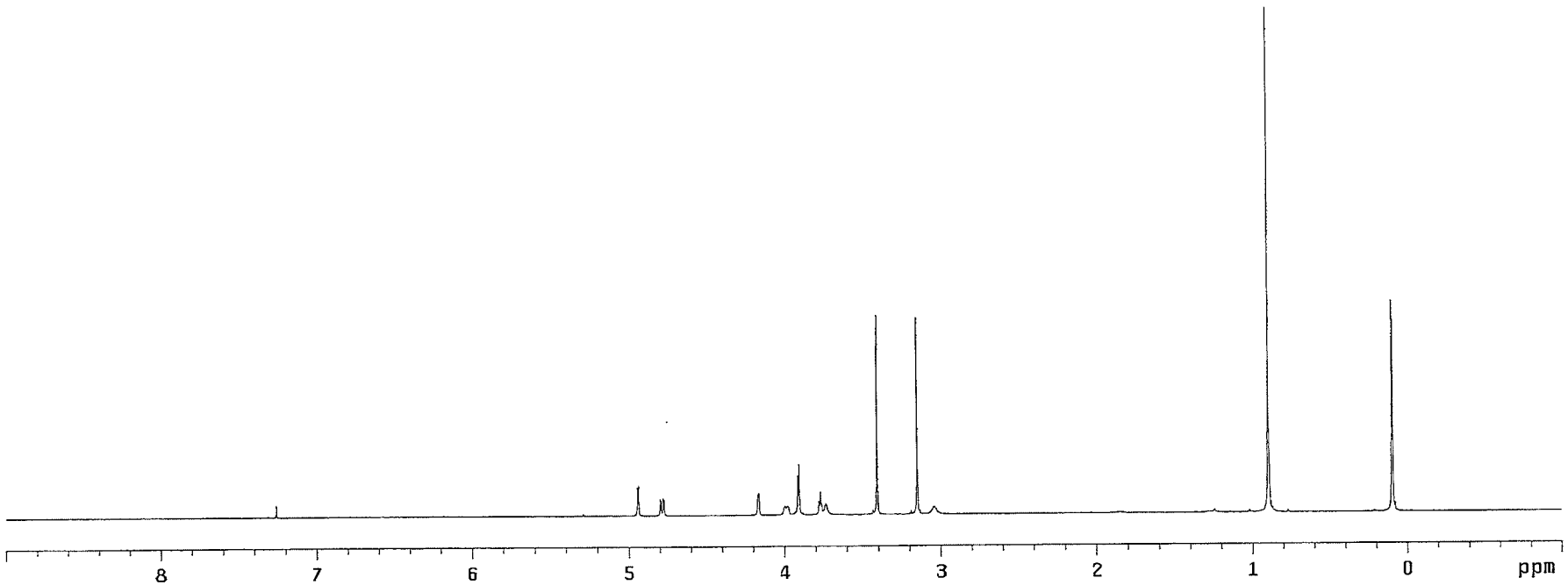

OTBS
HO
4
O
AcO
3
2
OH
OMe

220
200
180
160
140
120
100
80
60
40
20
0
ppm

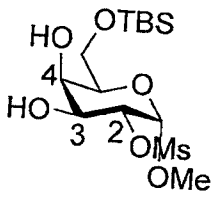

HO
OTBS
4
O
AcO
3
2
OH
OMe

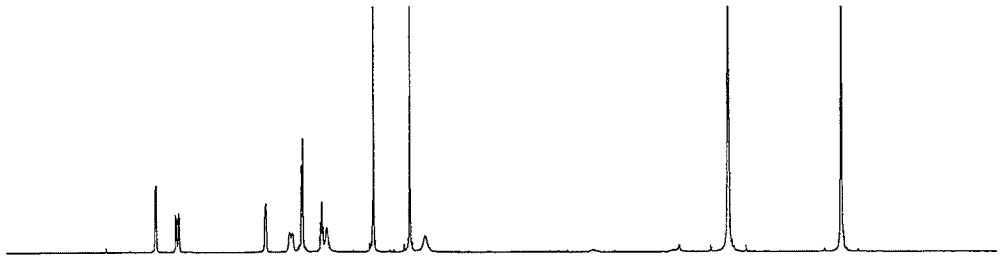

F2
(ppm)
0
1
2
3
4
5
6
6
5
4
3
2
1
0
F1 (ppm)

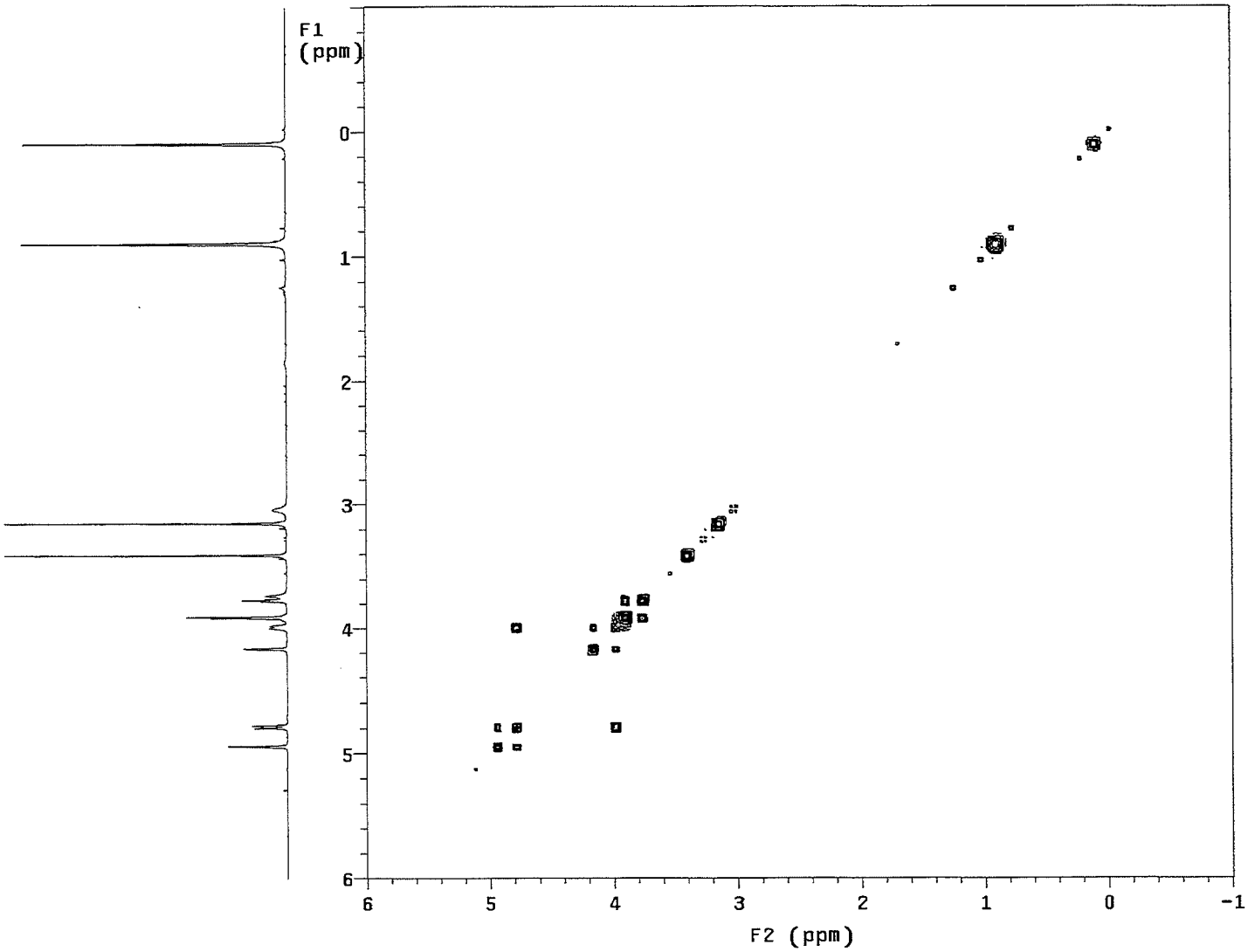

OTBS
HO
4
O
HO
3
2
OMs
OMe

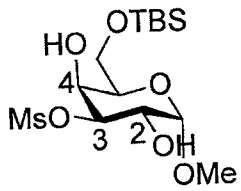

8
7
6
5
4
3
2
1
0
ppm

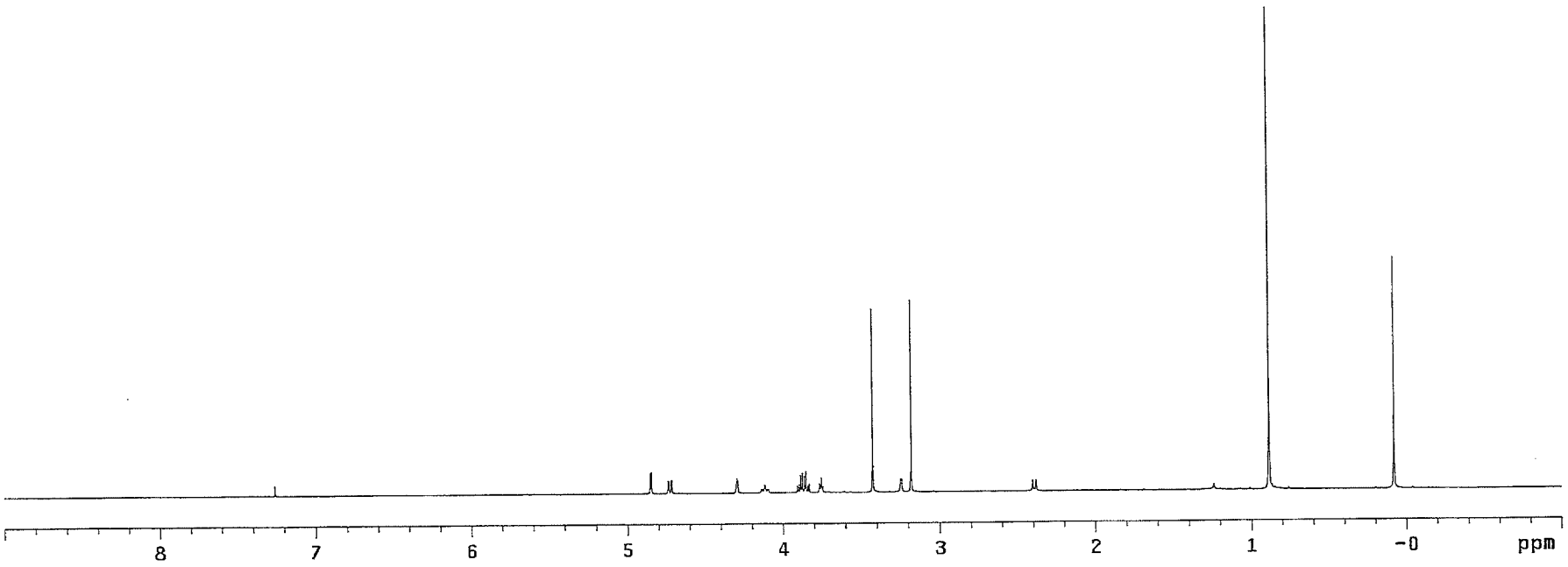
HO
OTBS
4
HO
3
2
O
OMs
OMe
220
200
180
160
140
120
100
80
60
40
20
0
ppm

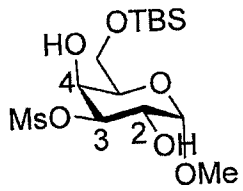

HO
OTBS
4
O
HO
3
2
OMs
OMe



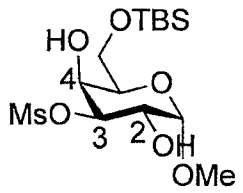

F1
(ppm)
0
1
2
3
4
5
6
6
5
4
3
2
1
0
-1
F2 (ppm)

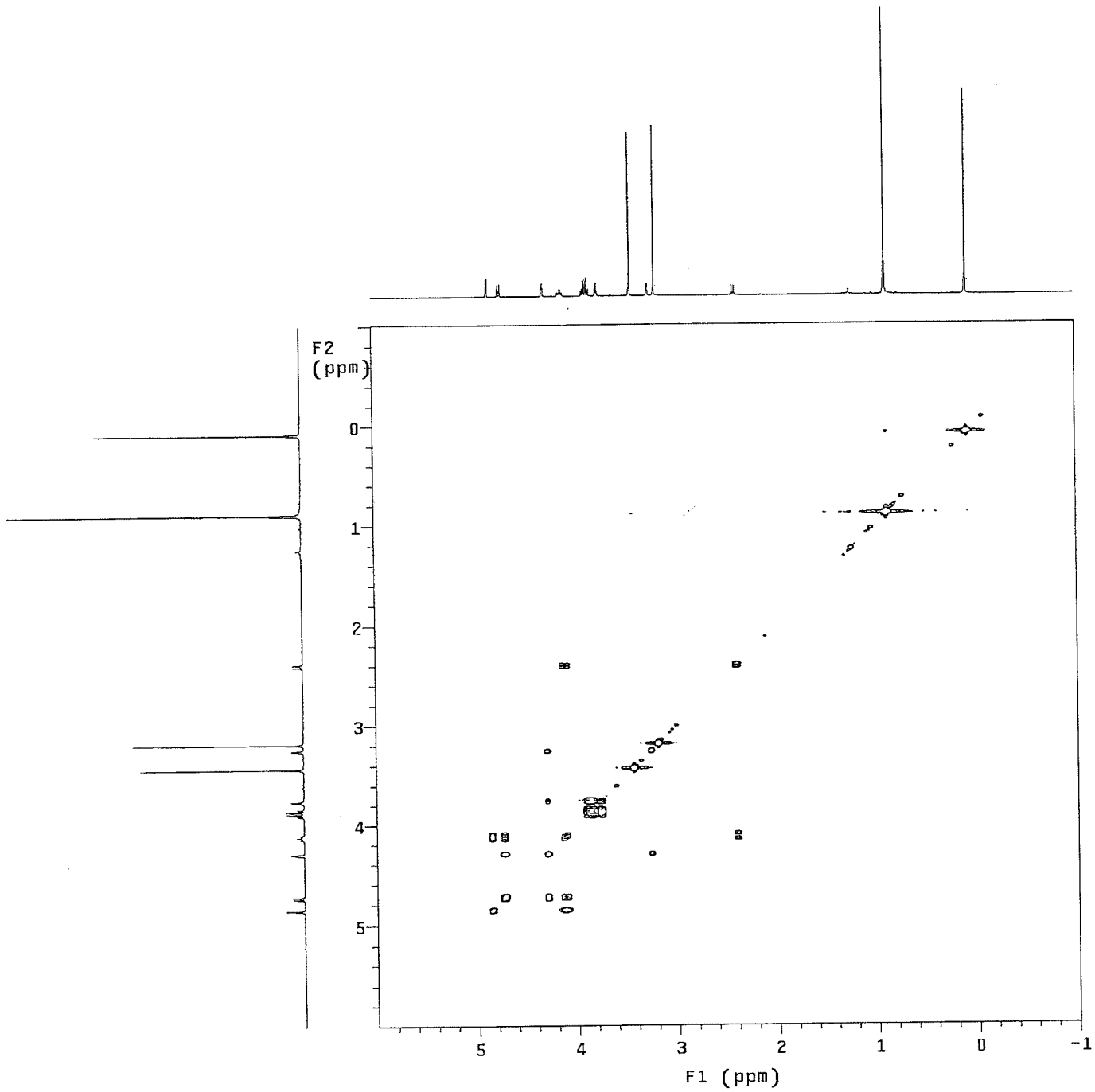

OTBS
HO
4
O
MsO
3
2
OH
OMe

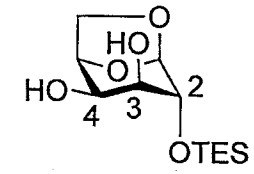

8
7
6
5
4
3
2
1
-0
ppm


OTBS
HO
4
O
MsO
3
2
OH
OMe

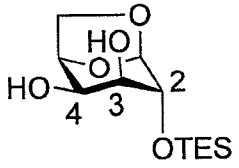
220
200
180
160
140
120
100
80
60
40
20
0
ppm

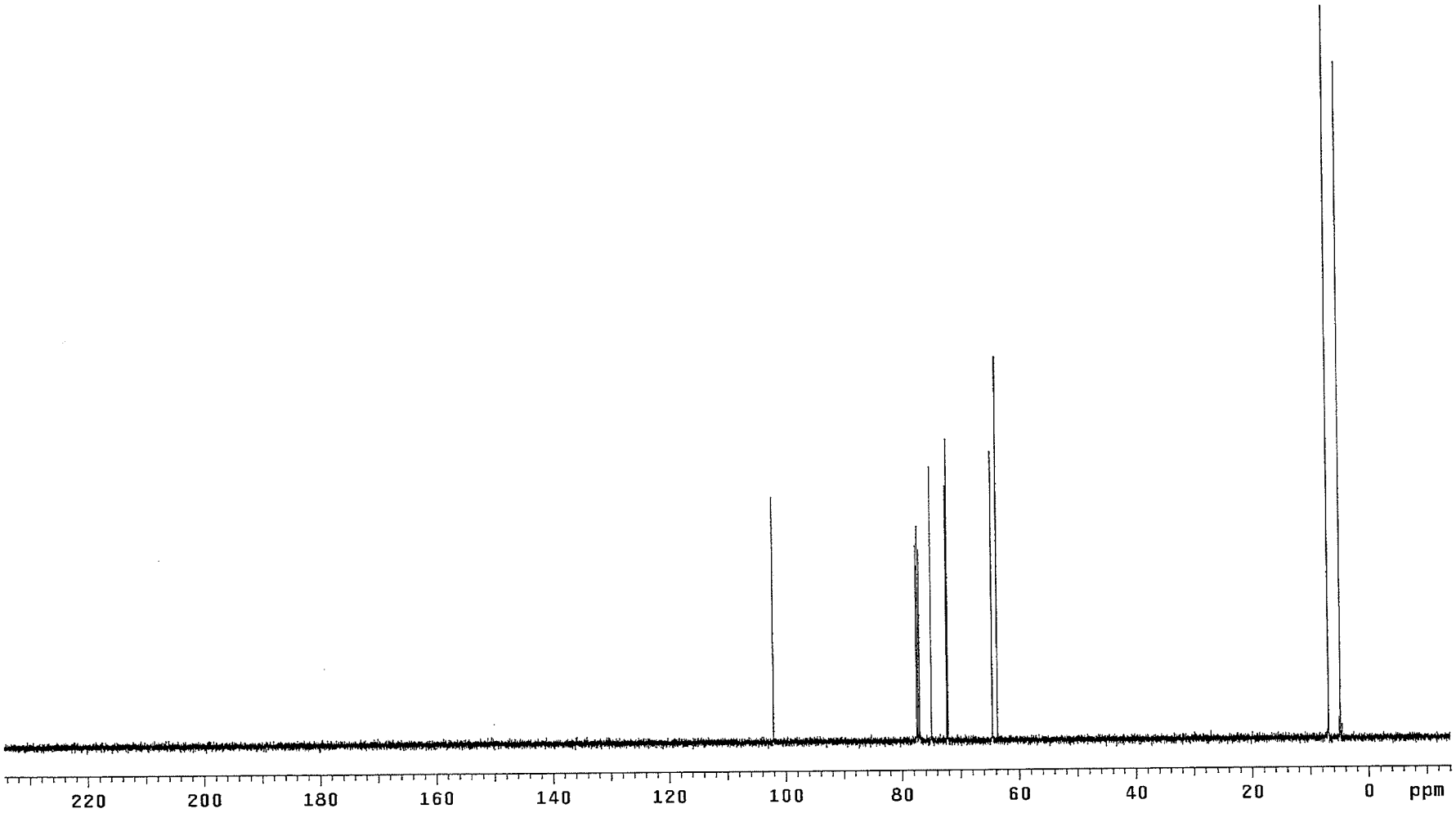

OTBS
HO
4
O
MsO
3
2
OH
OMe

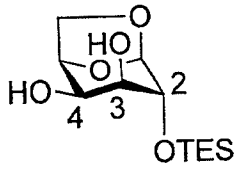

F2
(ppm)
0
1
2
3
4
5
5
4
3
2
1
0
-1
F1 (ppm)

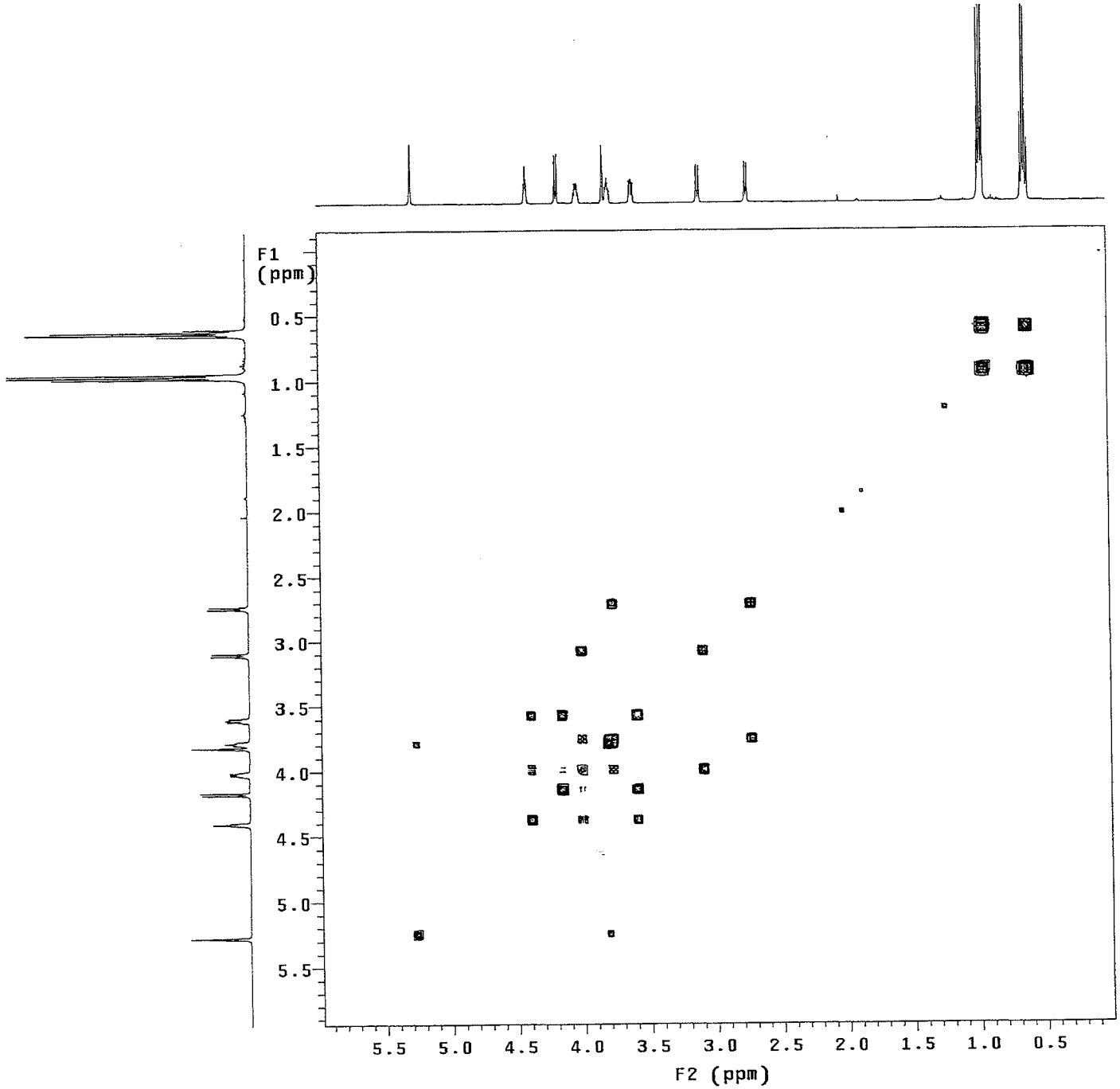

O
HO
O
HO
2
4
3
OTES

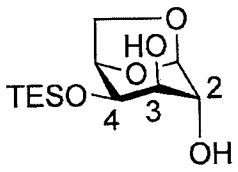
9
8
7
6
5
4
3
2
1
ppm

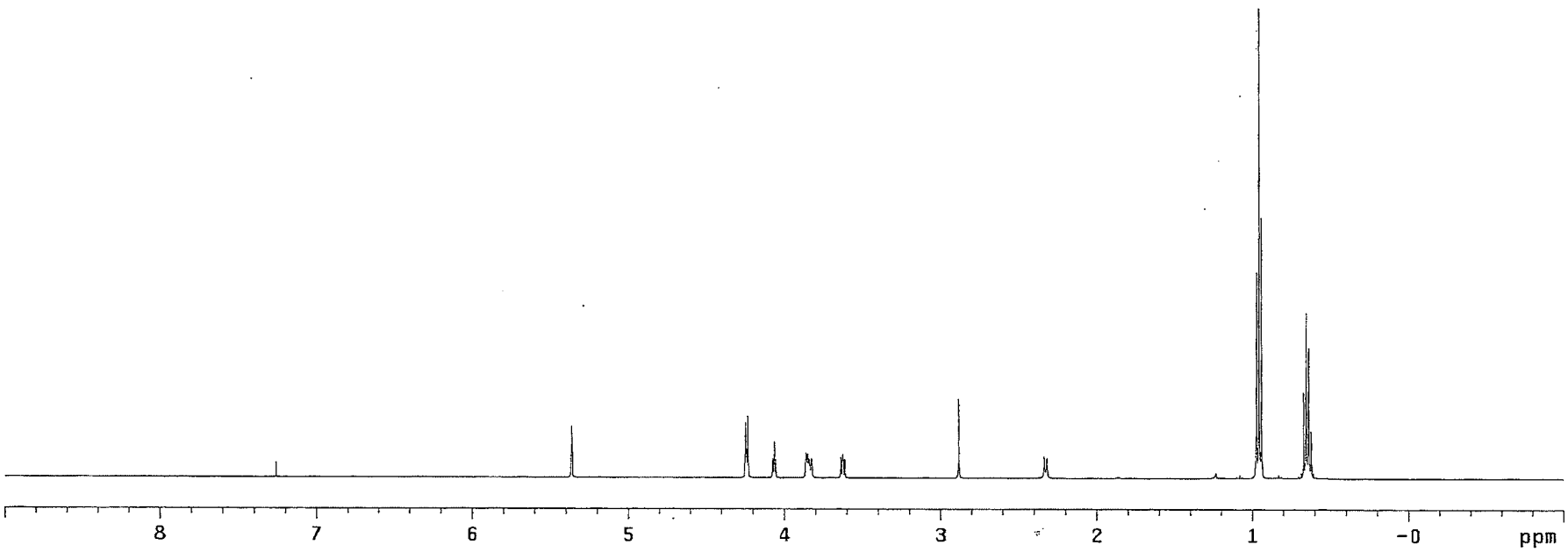

O
HO
O
HO
2
4
3
OTES

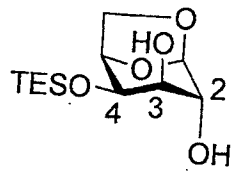

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
HO
O
HO
2
4
3
OTES

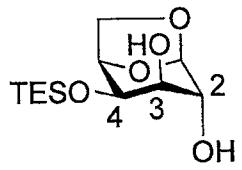

F1
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F2 (ppm)

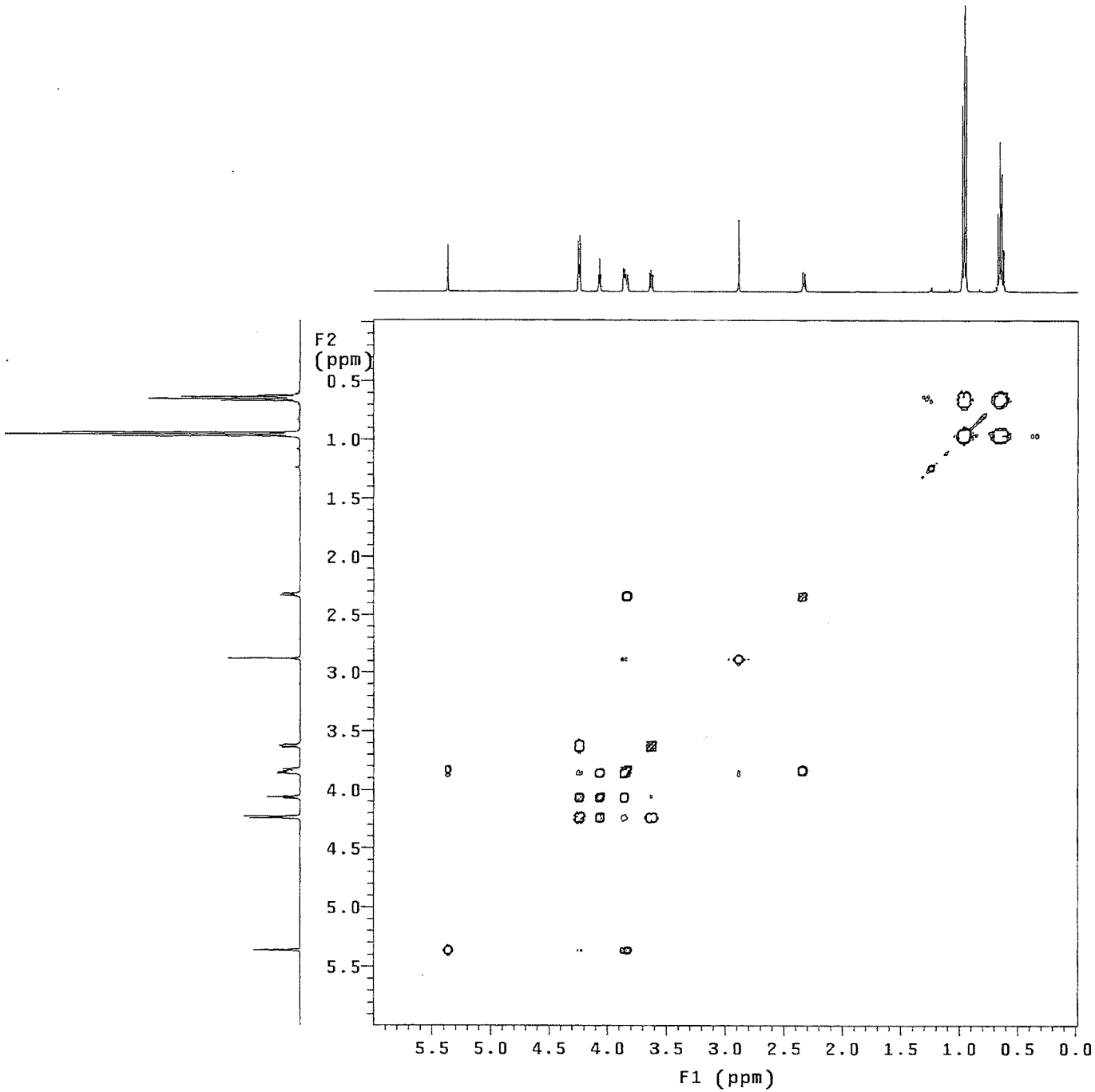

O
HO
O
TESO
2
4
3
OH

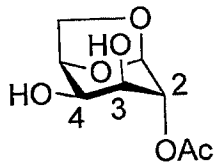

8
7
6
5
4
3
2
1
-0
ppm

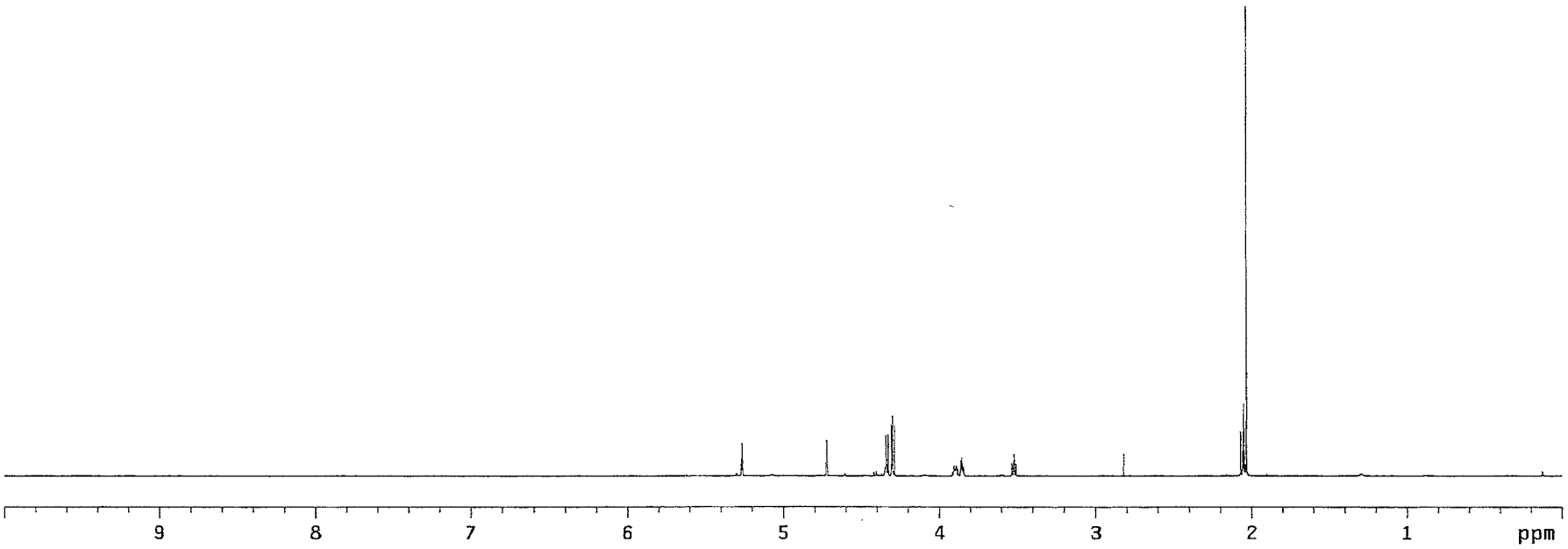

HO
O
TESO
4
3
2
OH

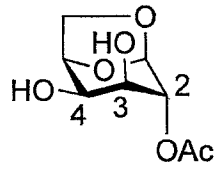
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
HO
O
TESO
2
4
3
OH

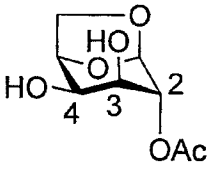

F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
F1 (ppm)

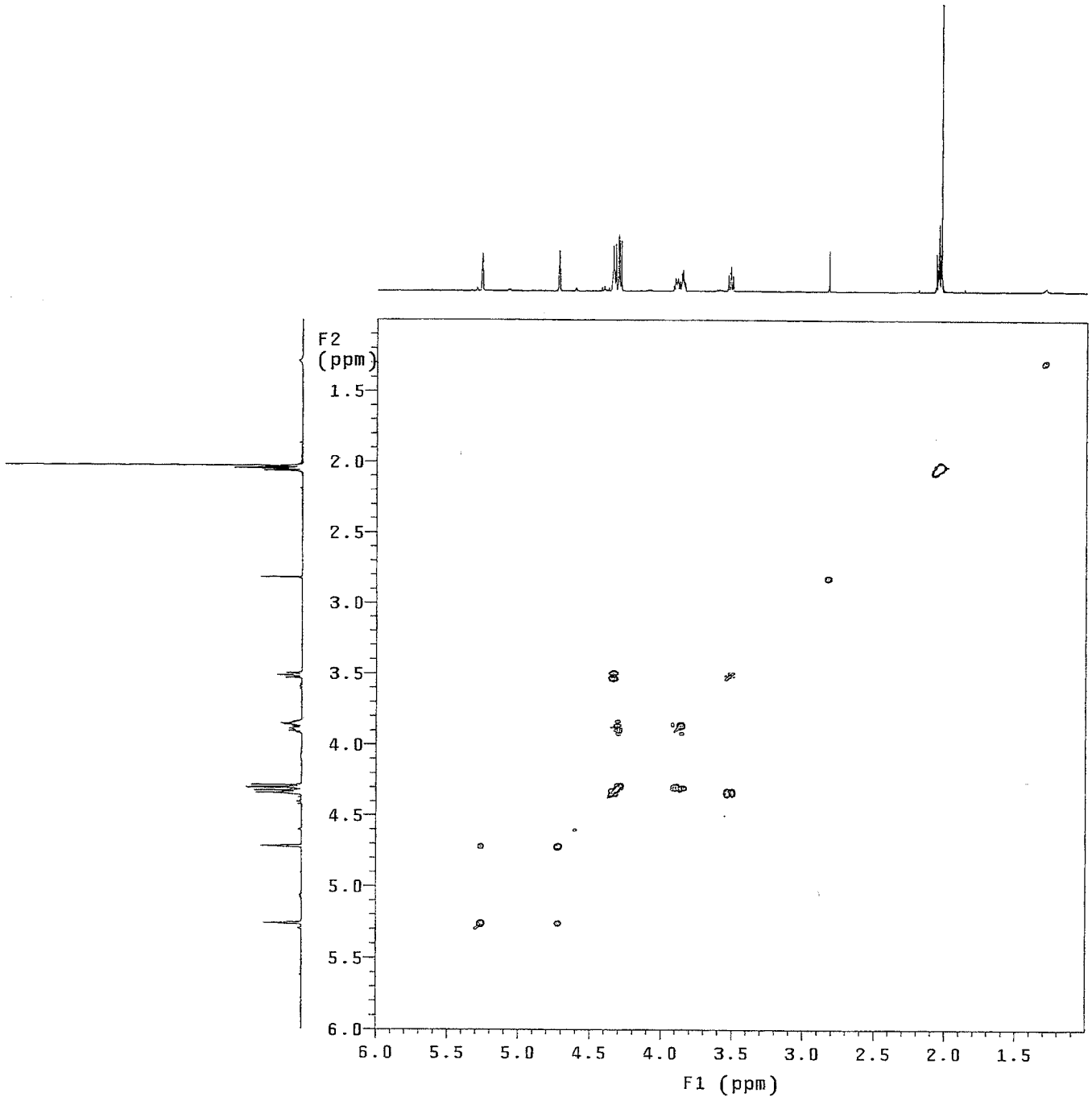

O
HO
O
HO
4
3
2
OAc

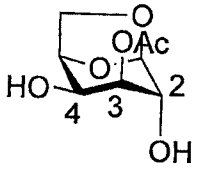

9
8
7
6
5
4
3
2
1
ppm

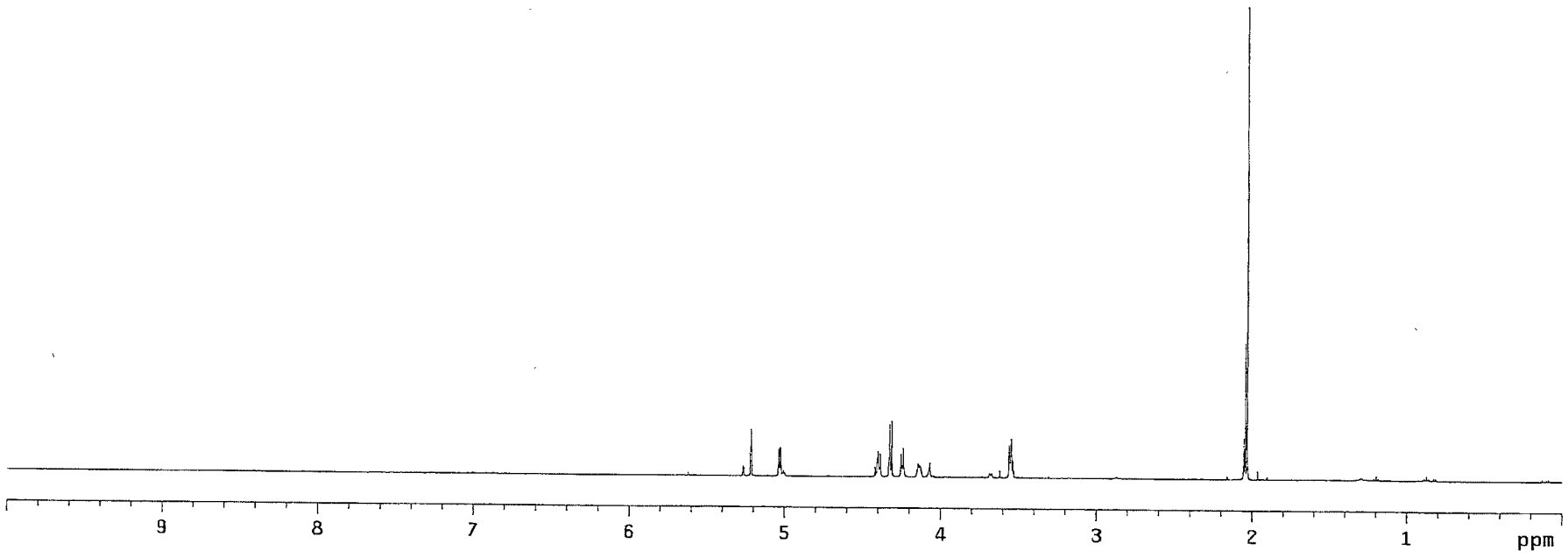

O
HO
O
HO
4
3
2
OAc

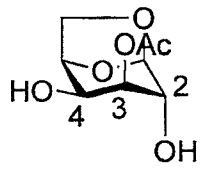
220
200
180
160
140
120
100
80
60
40
20
0
ppm

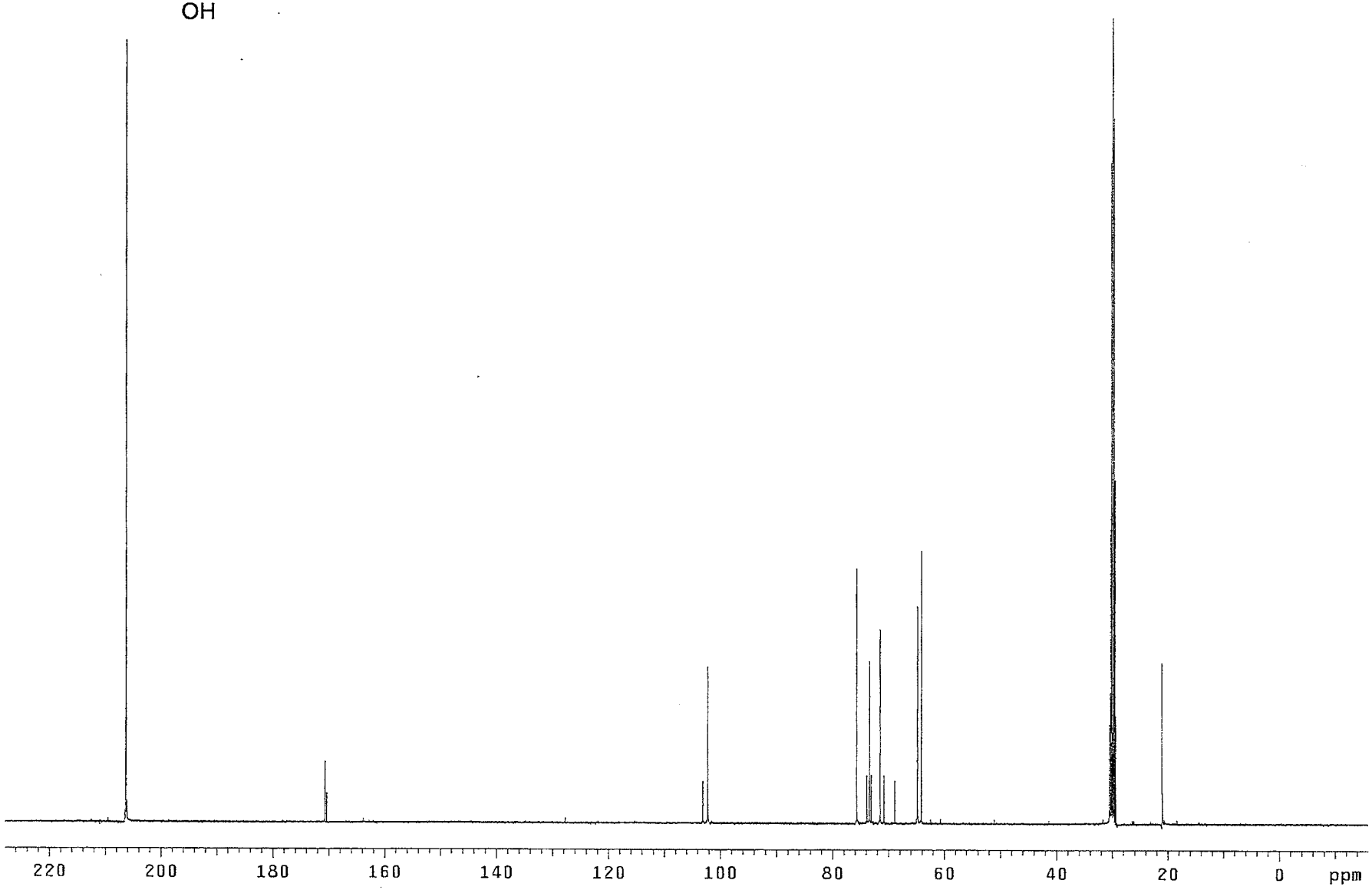

O
HO
O
HO
2
4
3
OAc

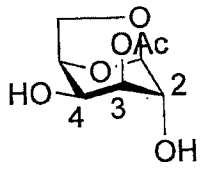

F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
F1 (ppm)

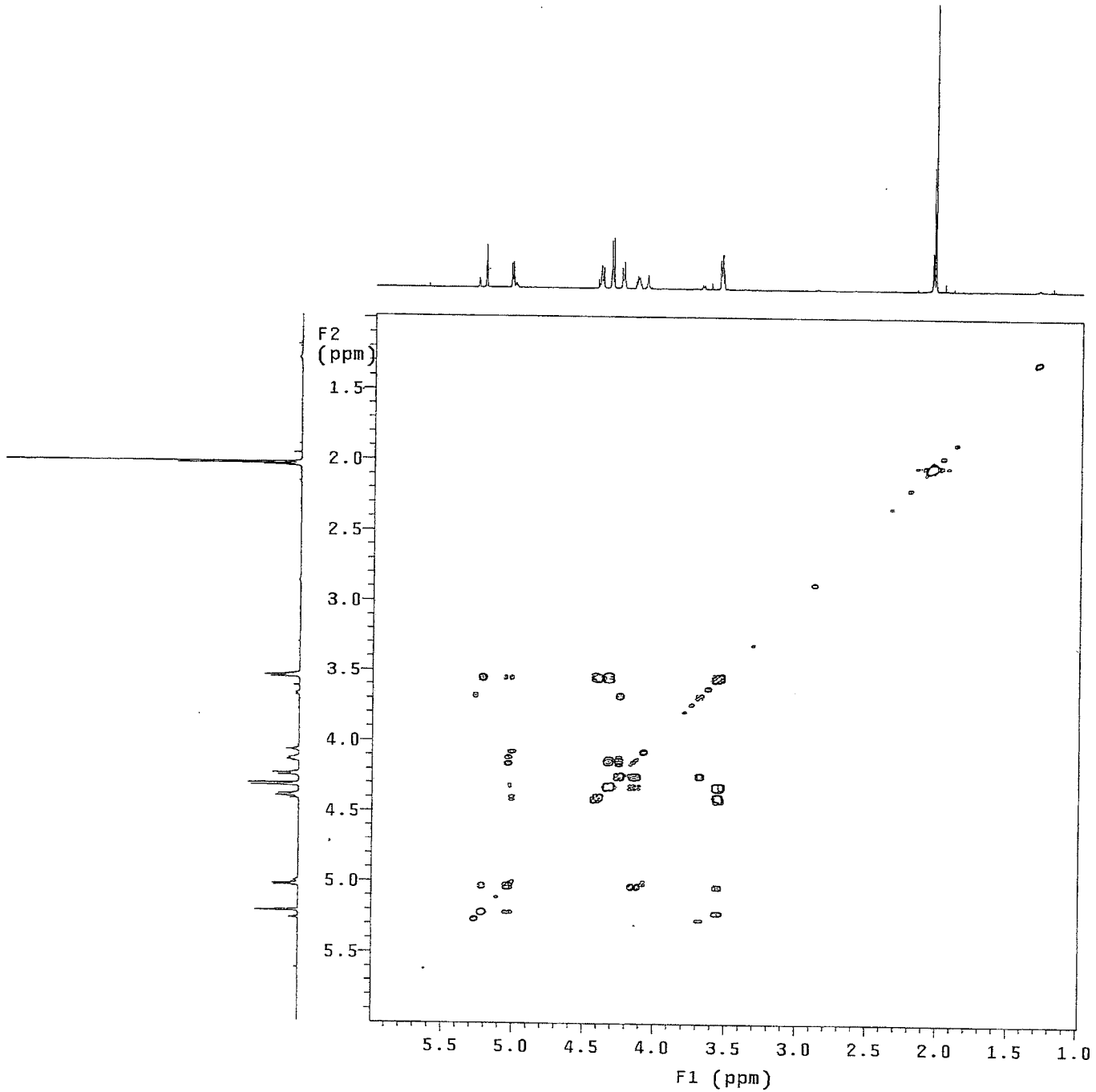

O
OAc
O
HO
2
4
3
OH


9
8
7
6
5
4
3
2
1
ppm


O
OAc
O
HO
2
4
3
OH

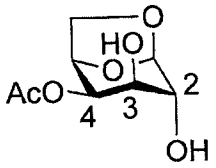

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
OAc
O
HO
2
4
3
OH

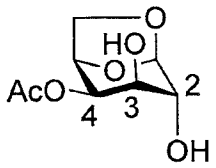

F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

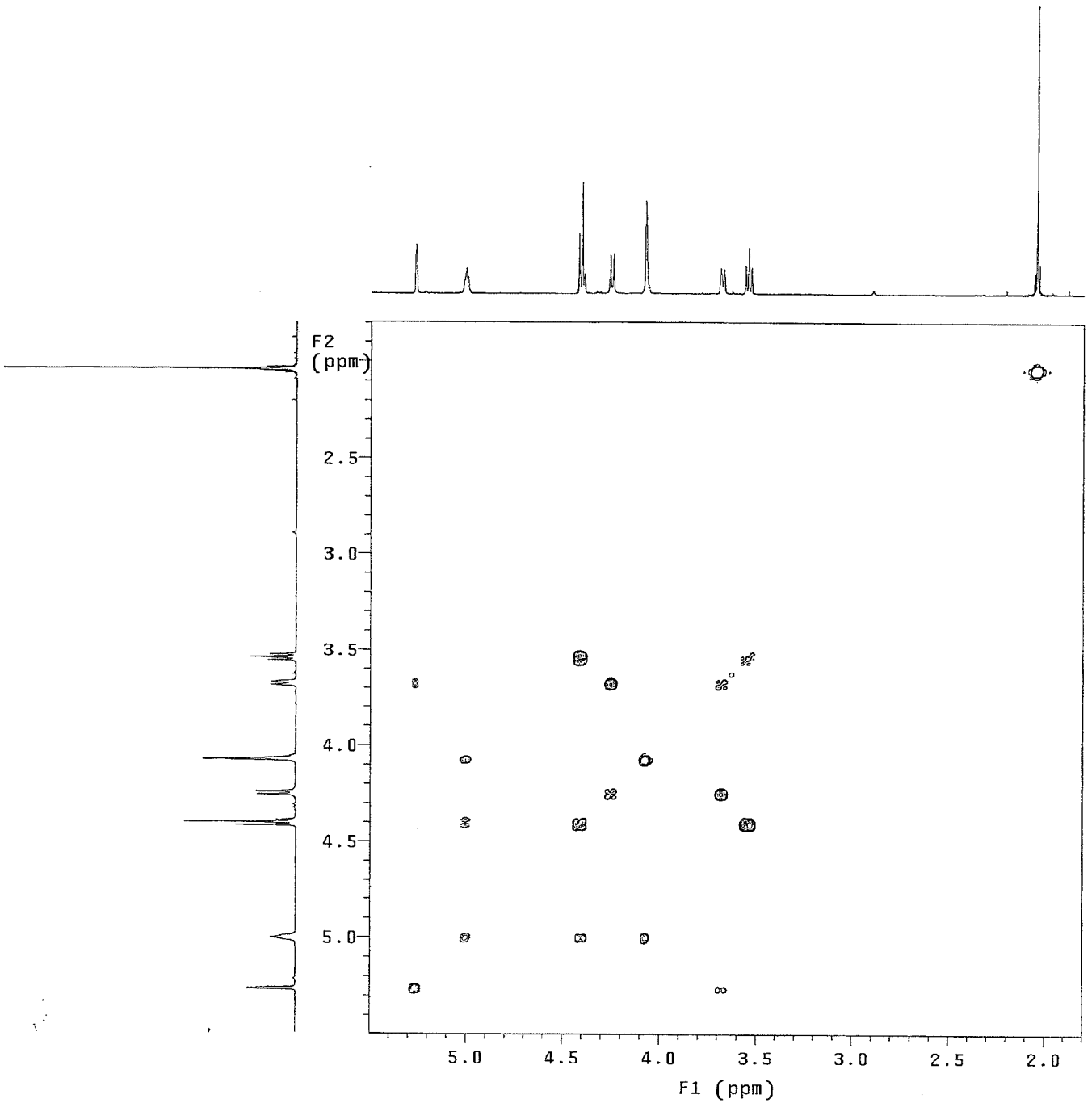
AcO
4
3
O
HO
O
2
OH

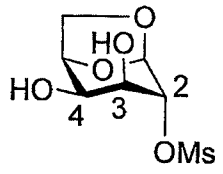
9
8
7
6
5
4
3
2
1
ppm

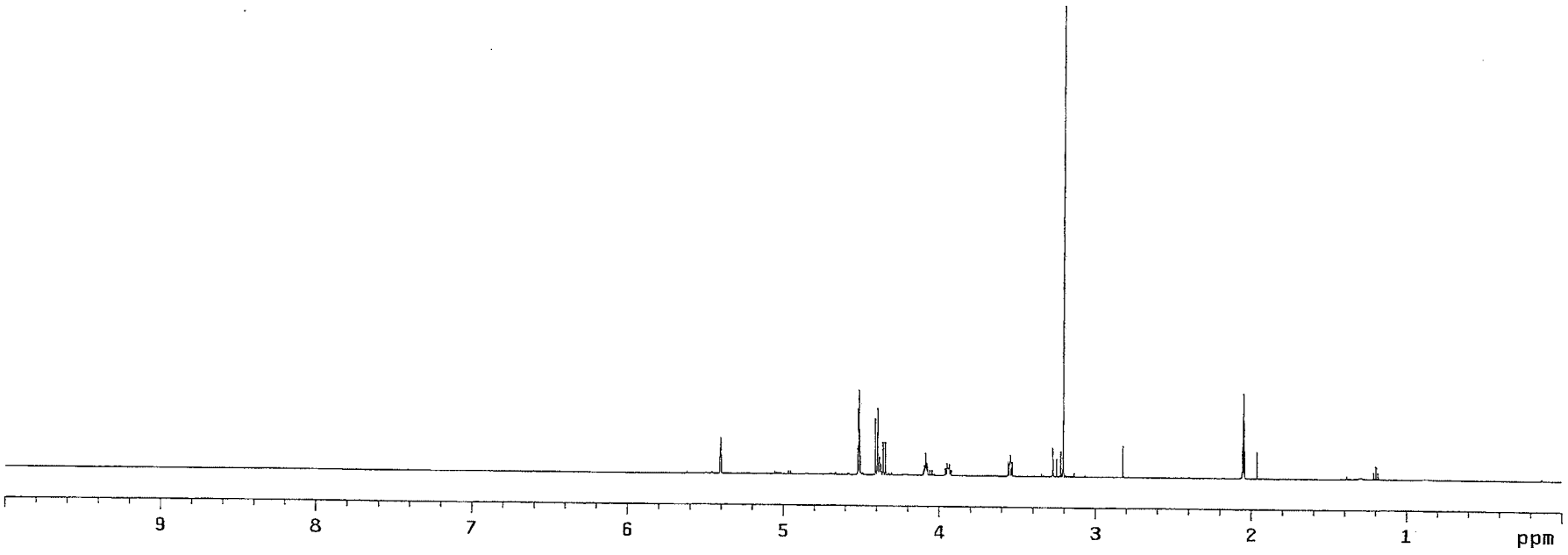

O
HO
O
AcO
2
4
3
OH

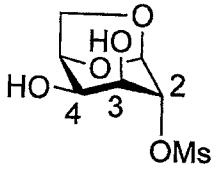
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
HO
O
AcO
2
4
3
OH

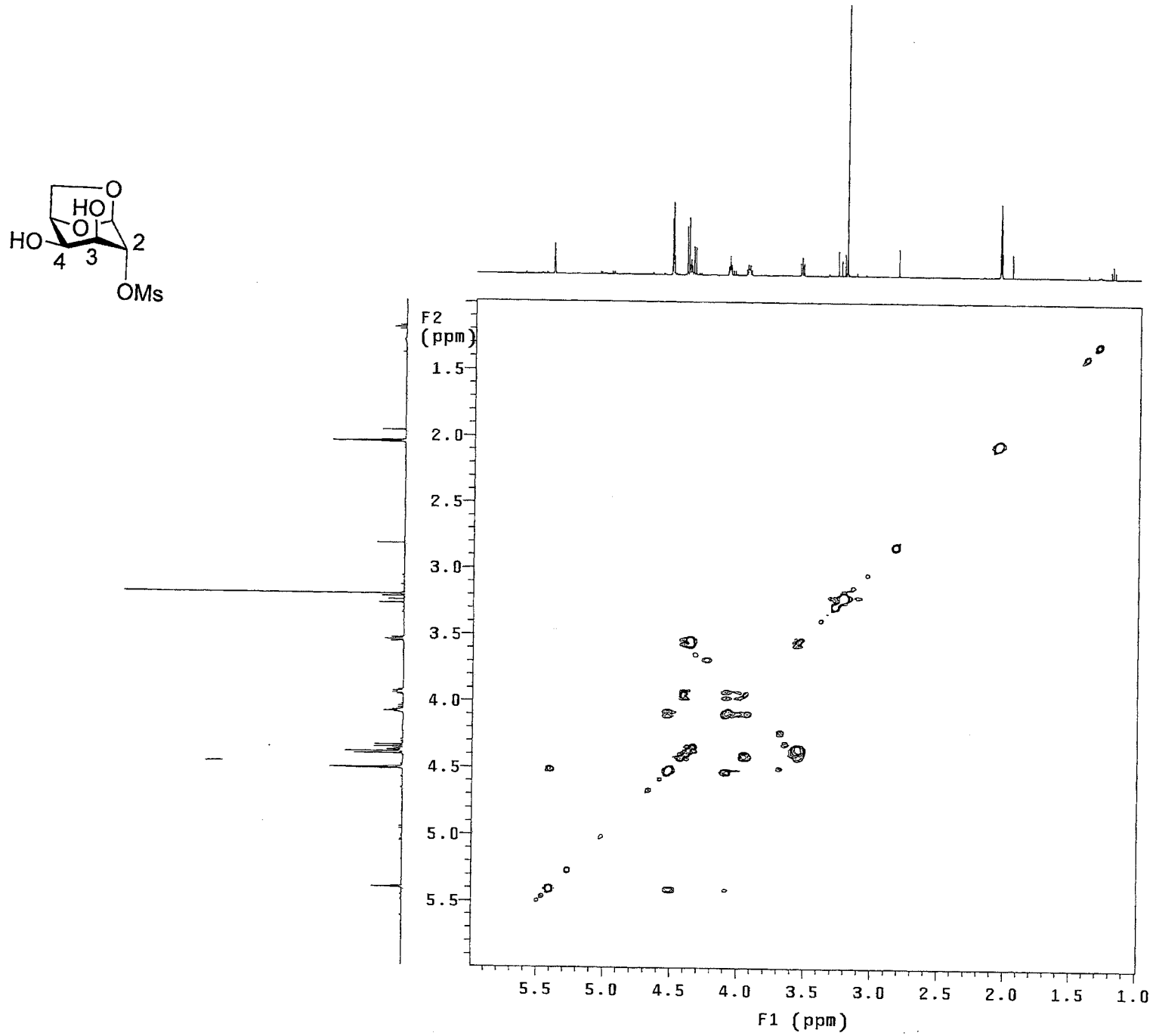

F2
(ppm)
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
F1 (ppm)

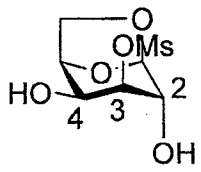

O
HO
O
HO
2
4
3
OMs

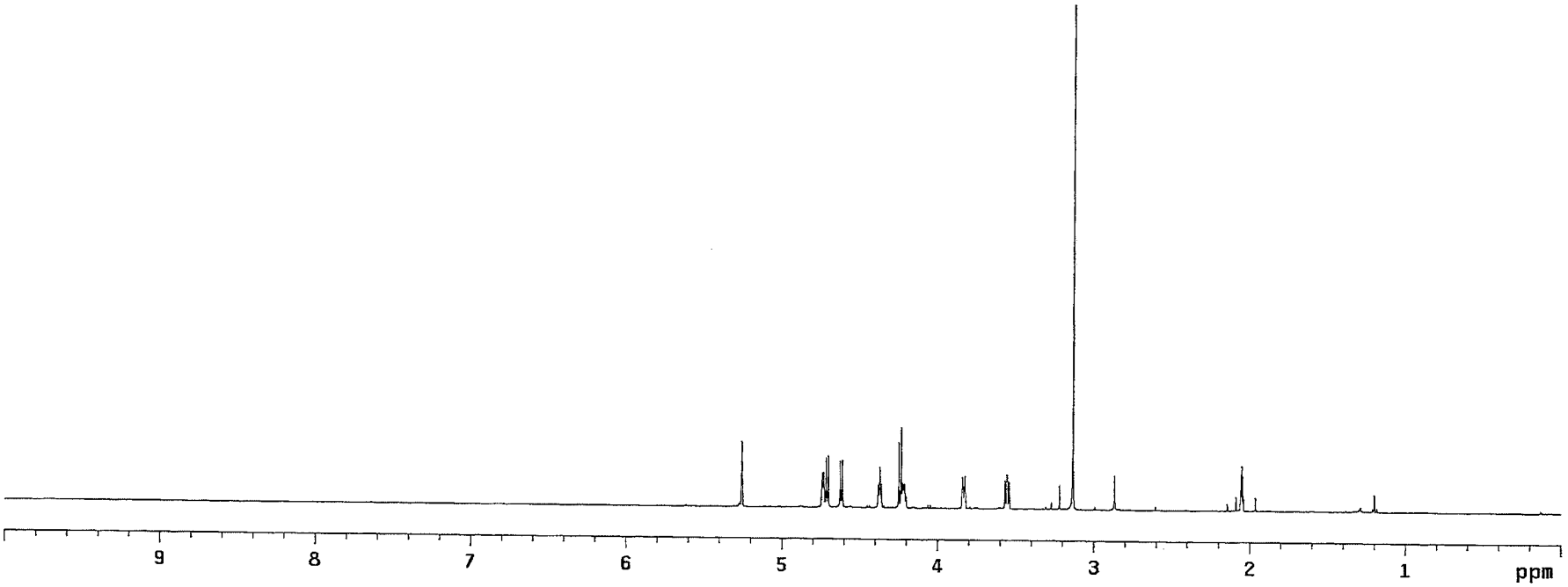

9
8
7
6
5
4
3
2
1
ppm

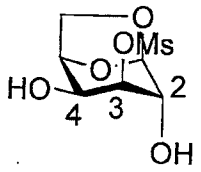

O
HO
O
HO
2
4
3
OMs

220
200
180
160
140
120
100
80
60
40
20
0
ppm

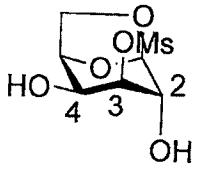

HO
O
HO
O
2
4
3
OMs
F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

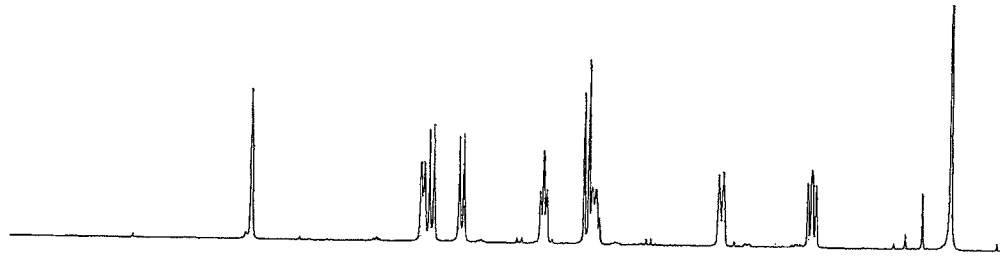

O
OMs
O
HO
2
4
3
OH

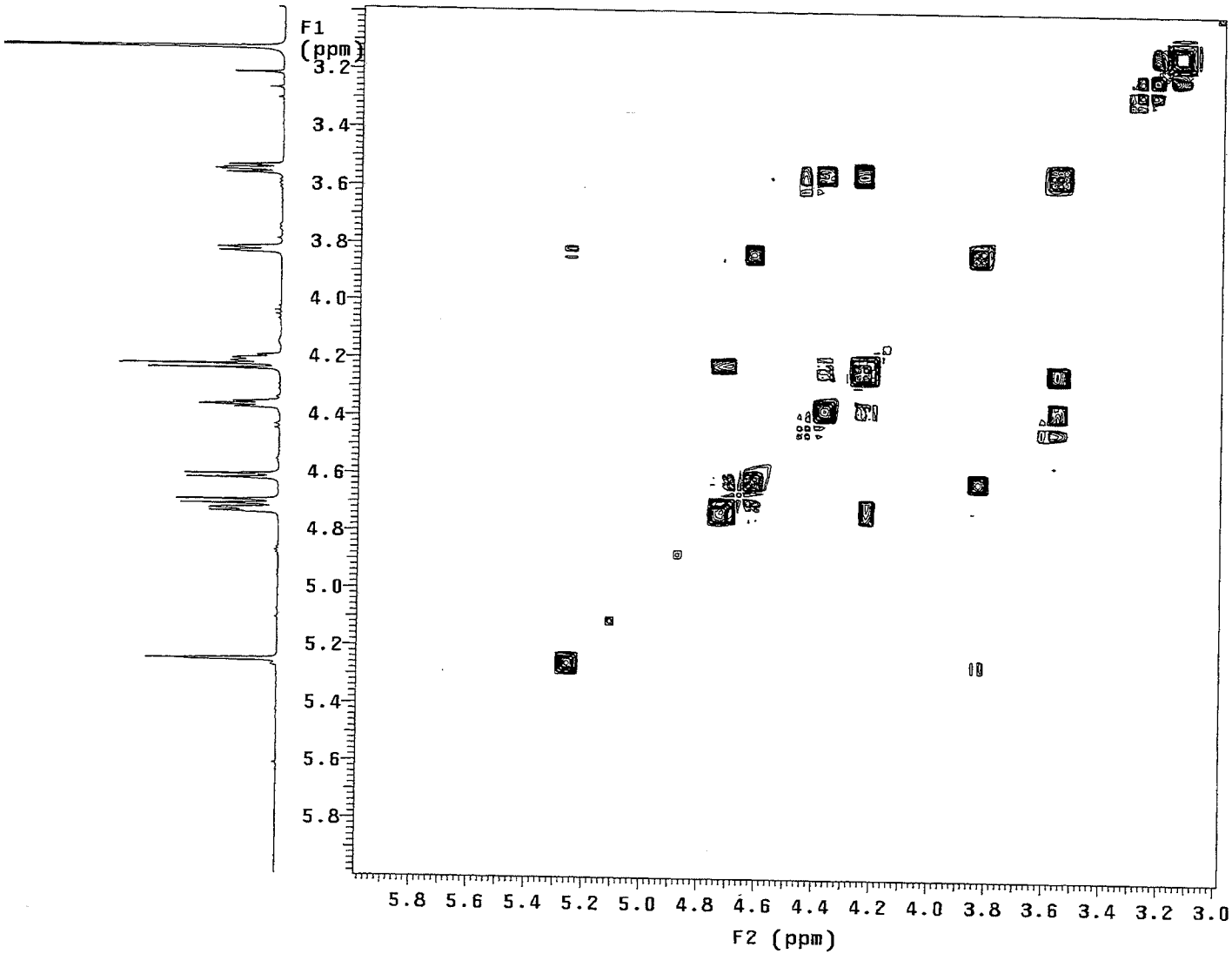

9
8
7
6
5
4
3
2
1
ppm

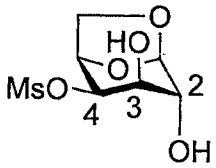

O
OMs
O
HO
2
4
3
OH

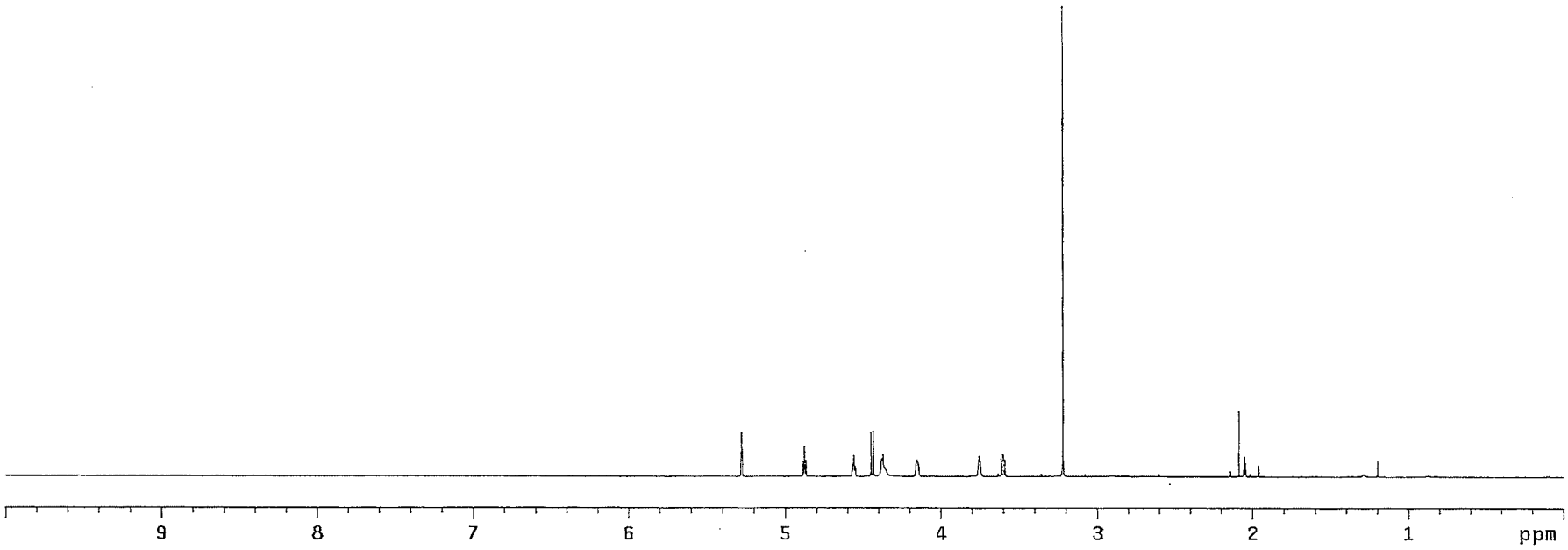
220
200
180
160
140
120
100
80
60
40
20
0
ppm

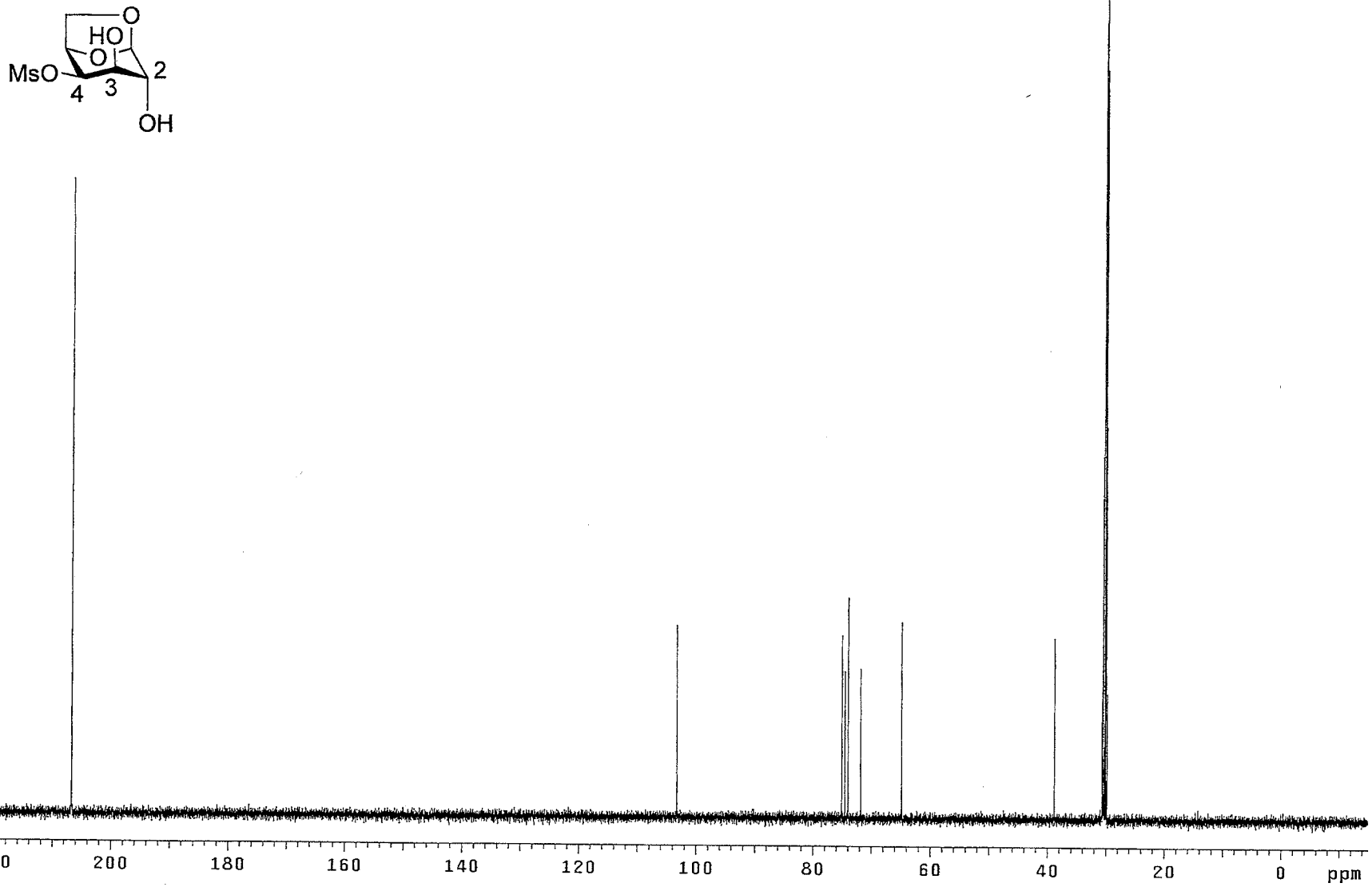

O
OMs
O
HO
4
3
2
OH

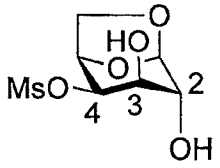


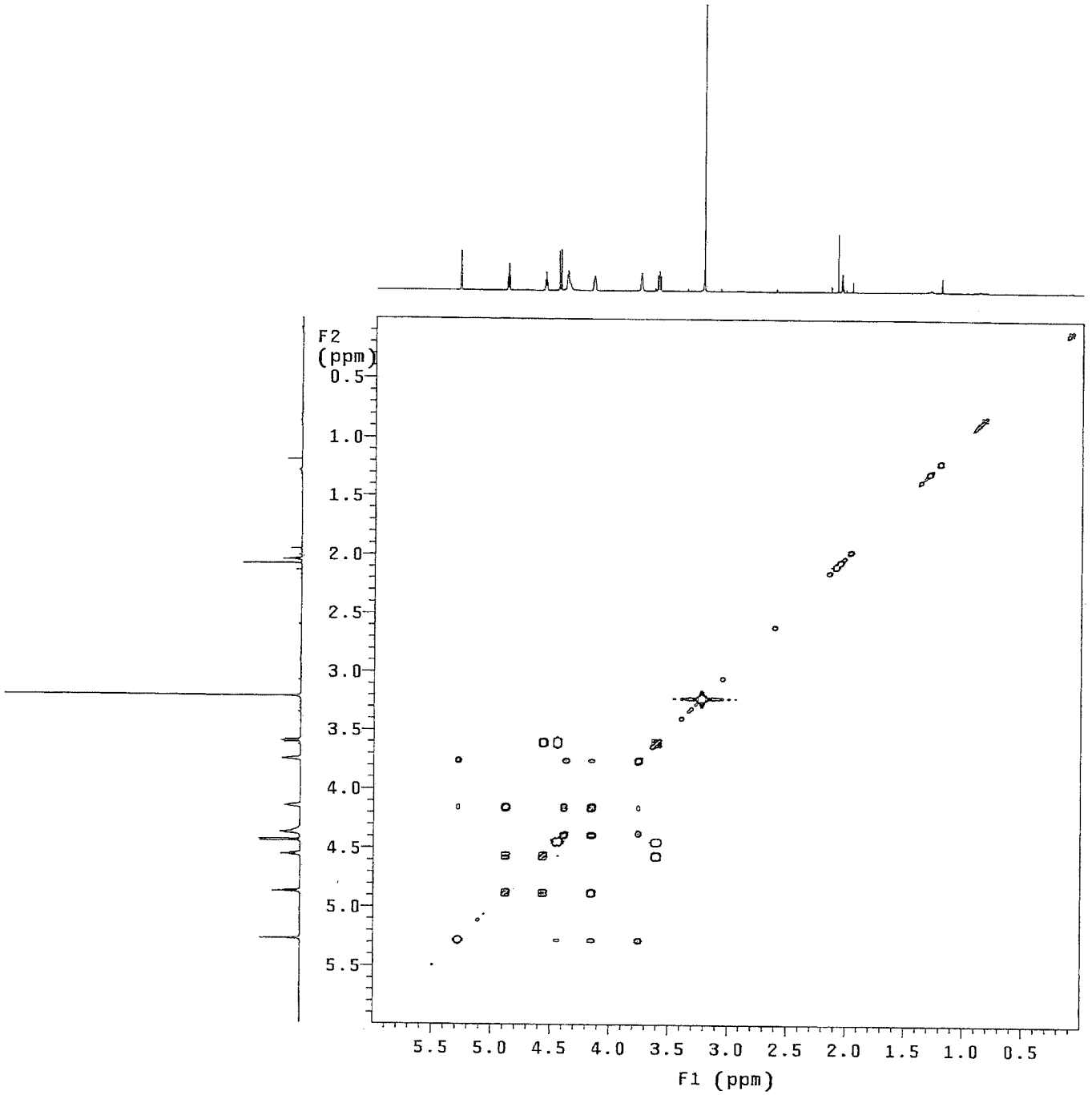

F1
(ppm)
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.6
5.8
5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0
F2 (ppm)

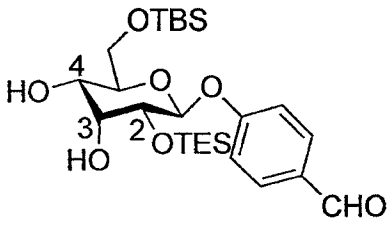

O
HO
O
MsO
2
4
3
OH

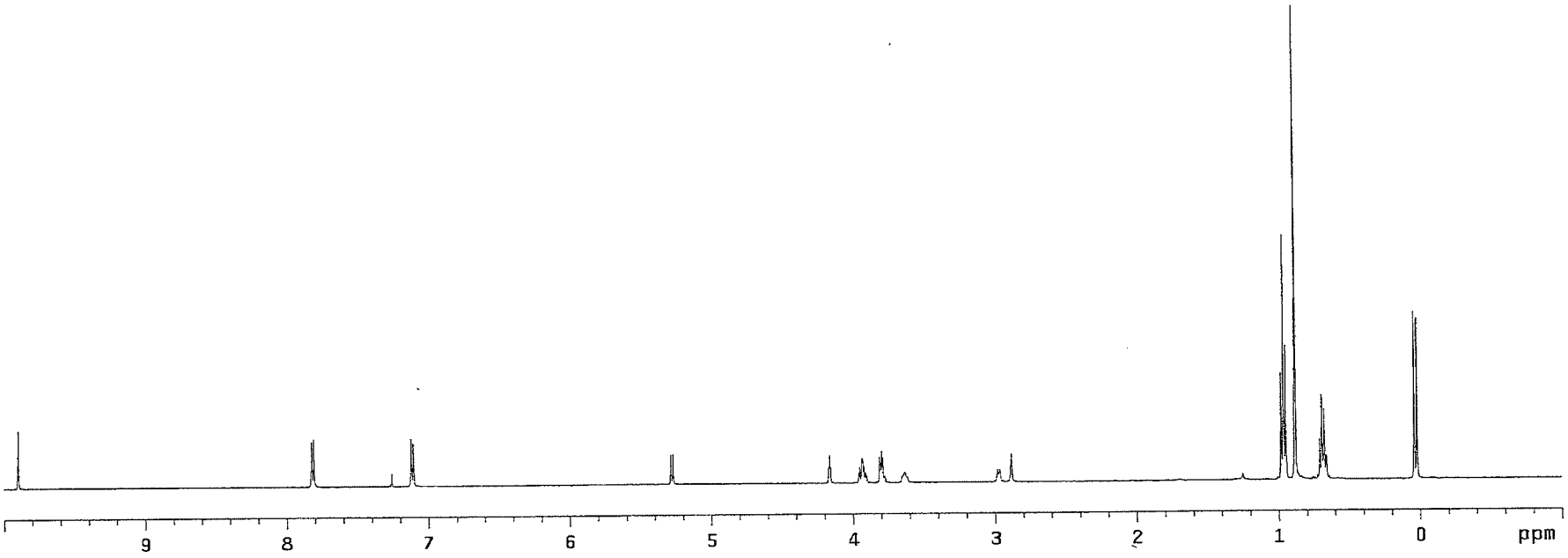

9
8
7
6
5
4
3
2
1
ppm

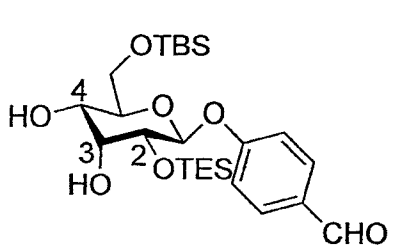

O
HO
O
MsO
2
4
3
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
HO
O
MsO
2
4
3
OH

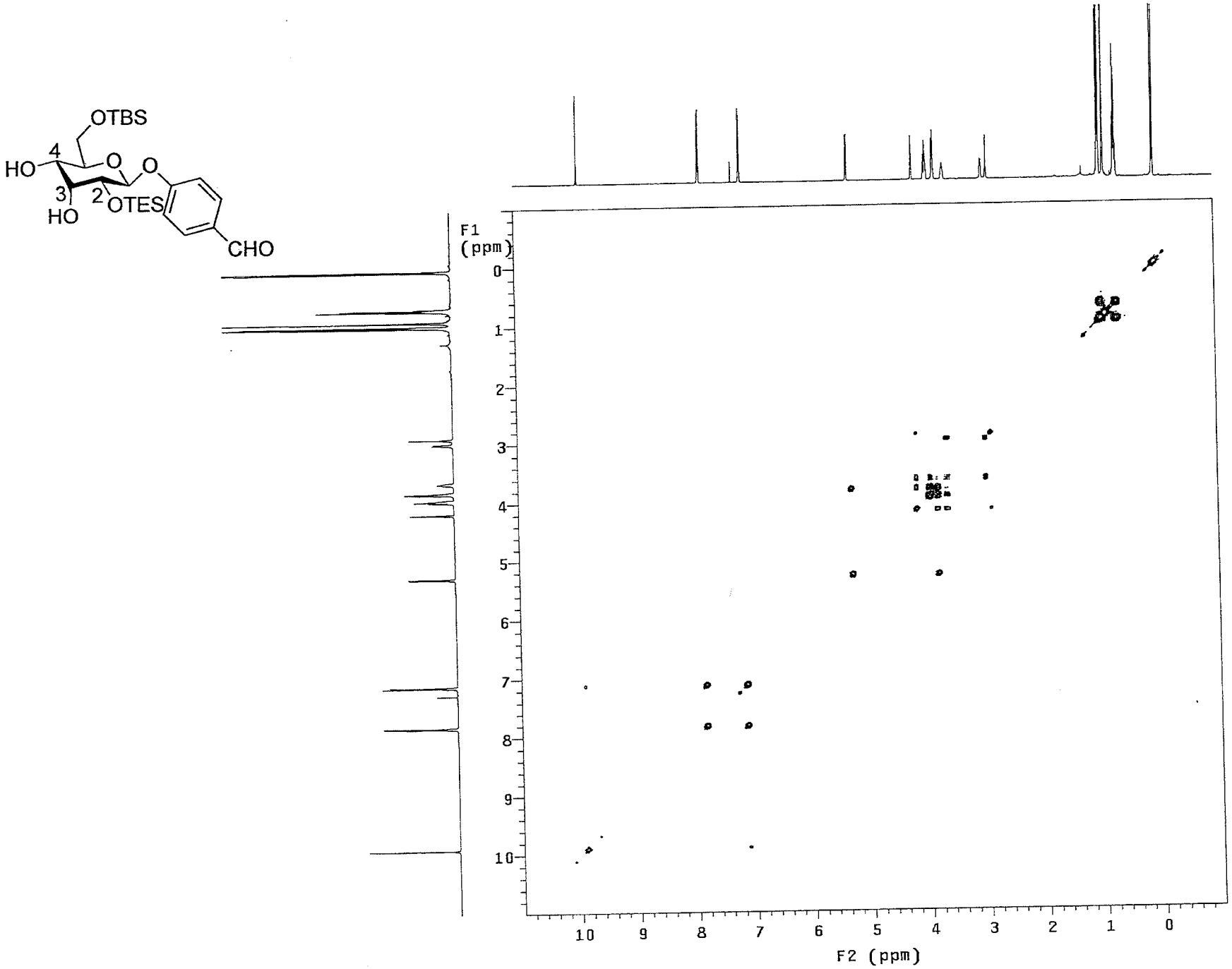

F2
(ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
F1 (ppm)

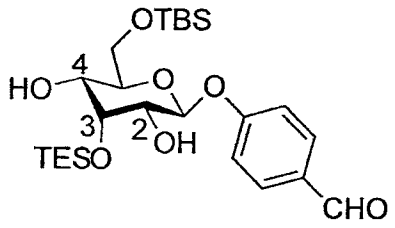

OTBS
4
HO
O
O
3
2
OTES
HO
CHO

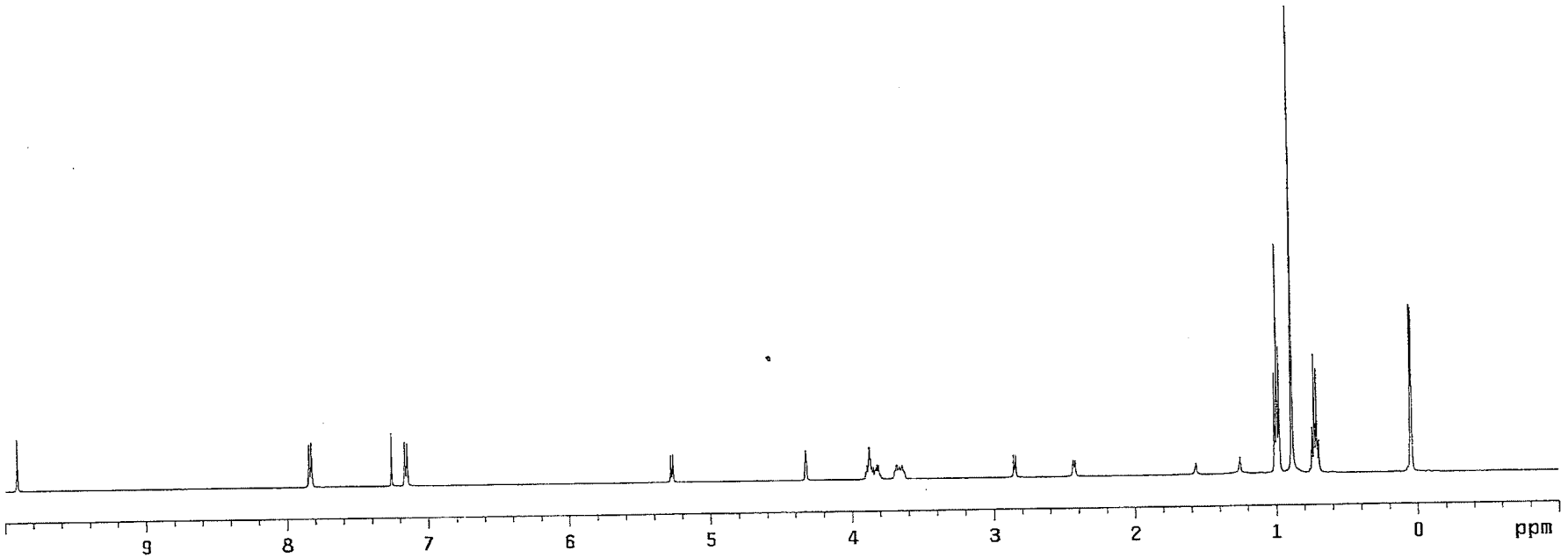

9
8
7
6
5
4
3
2
1
0
ppm

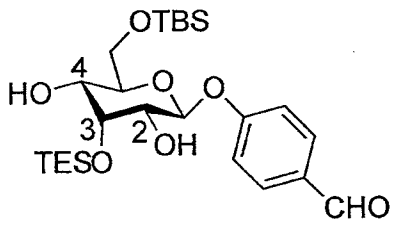

OTBS
4
HO
O
O
3
2
OTES
HO
CHO

220
200
180
160
140
120
100
80
60
40
20
0
ppm

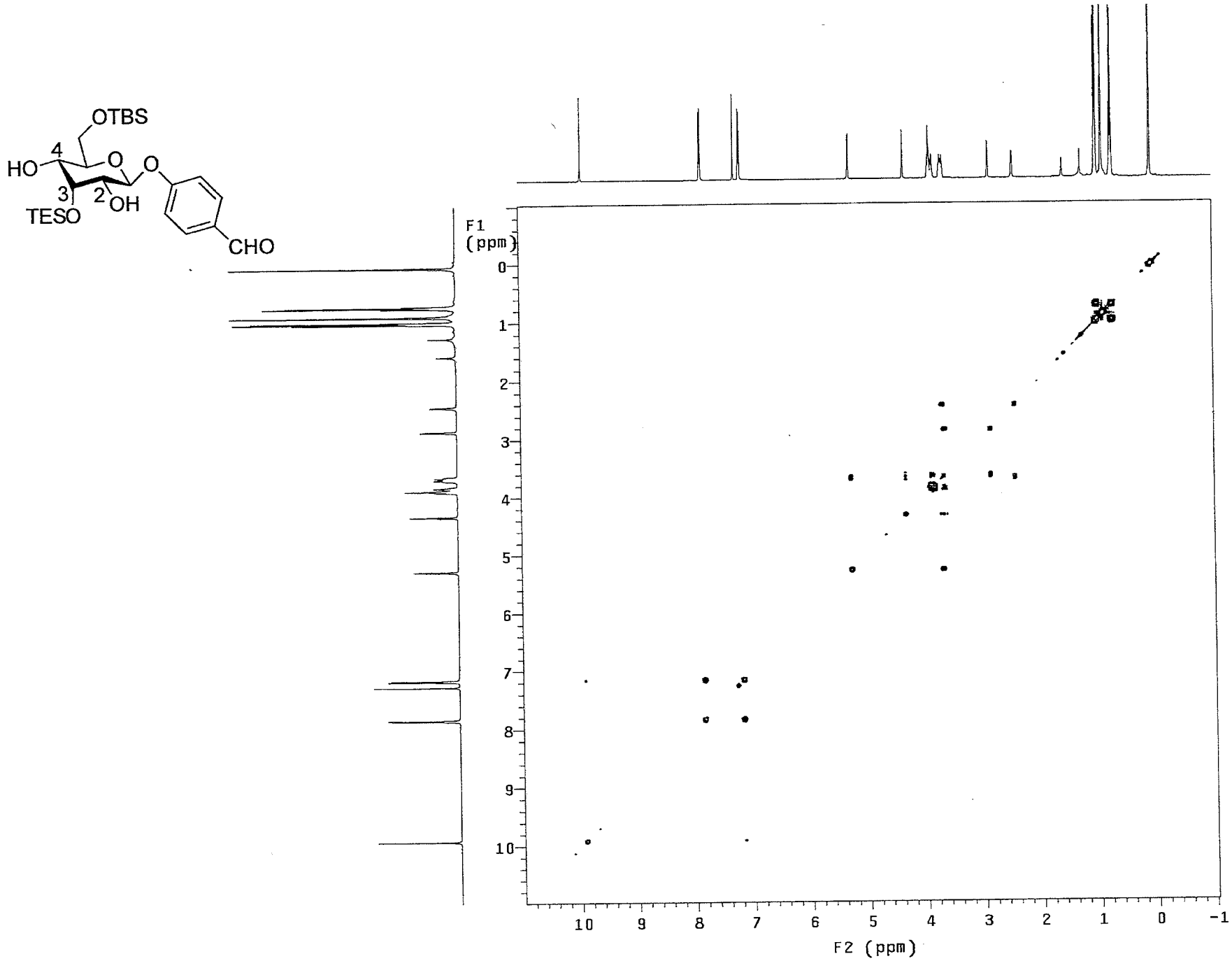

OTBS
HO
4
O
O
3
2
OTES
HO
CHO
F1
(ppm)
0
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
0
F2 (ppm)

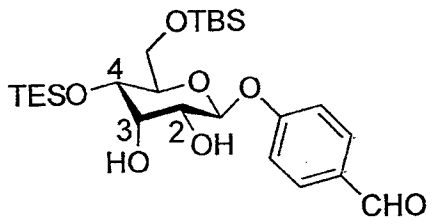

OTBS
4
HO
O
O
3
2
OH
TESO
CHO

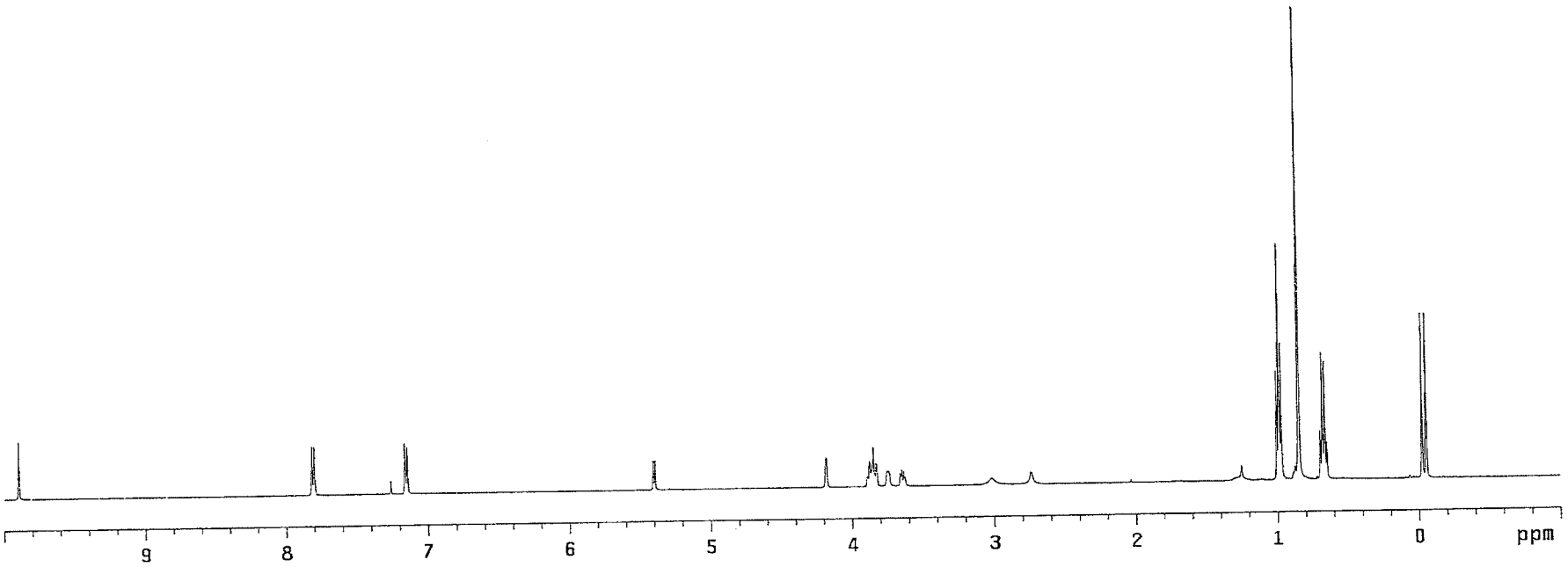

9
8
7
6
5
4
3
2
1
0
ppm

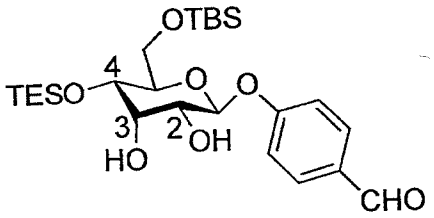

OTBS
4
HO
O
O
3
2
OH
TESO
CHO

220
200
180
160
140
120
100
80
60
40
20
0
ppm

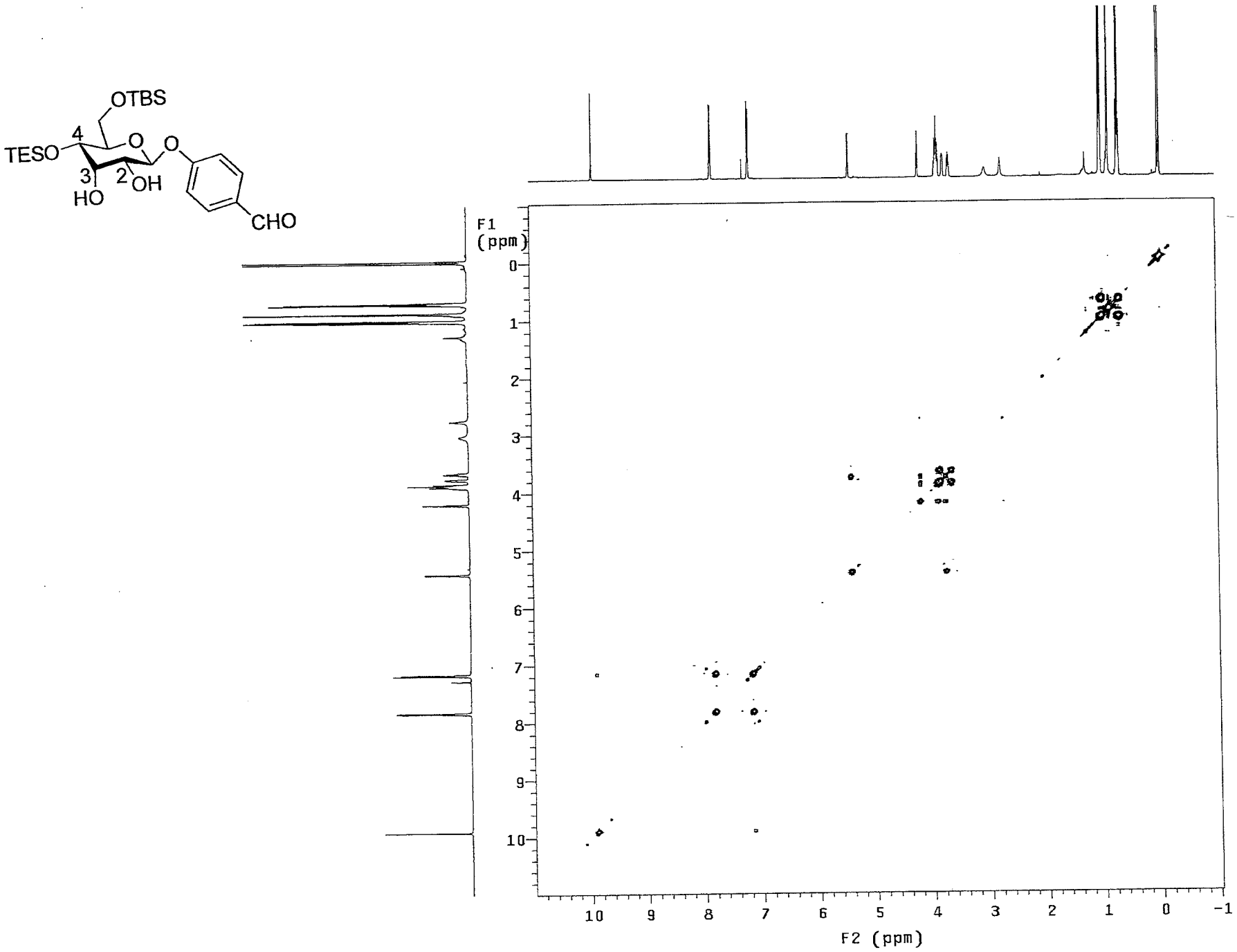

OTBS
4
HO
O
O
3
2
OH
TESO
CHO
F1
(ppm)
0
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
0
-1
F2 (ppm)

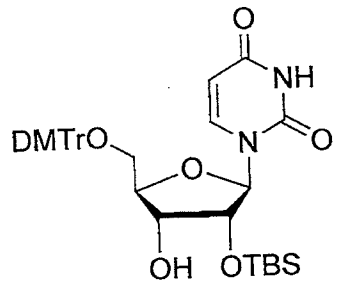

OTBS
4
TESO
O
O
3
2
OH
HO
CHO

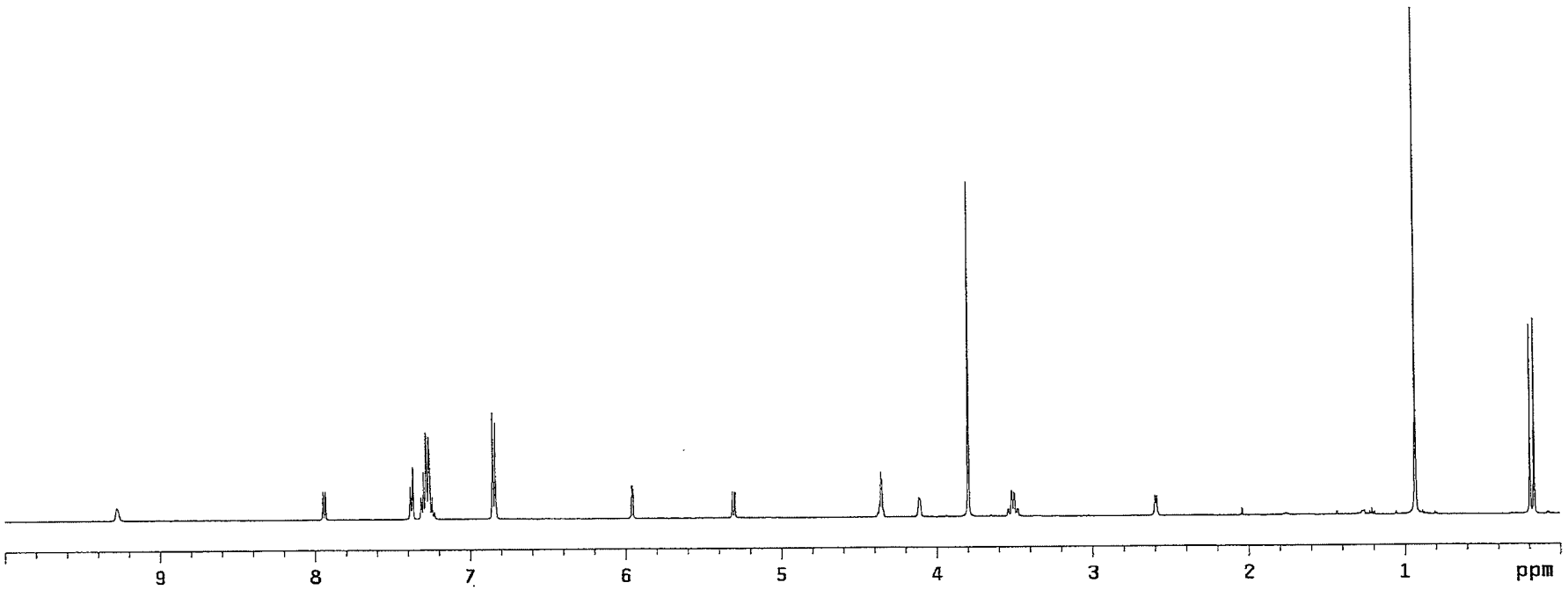

9
8
7
6
5
4
3
2
1
0
ppm

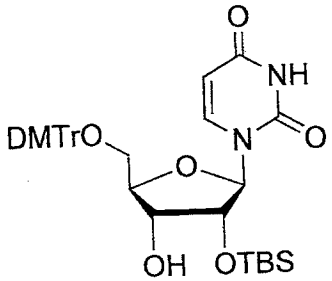

OTBS
4
TESO
O
O
3
2
OH
HO
CHO

220
200
180
160
140
120
100
80
60
40
20
0
ppm

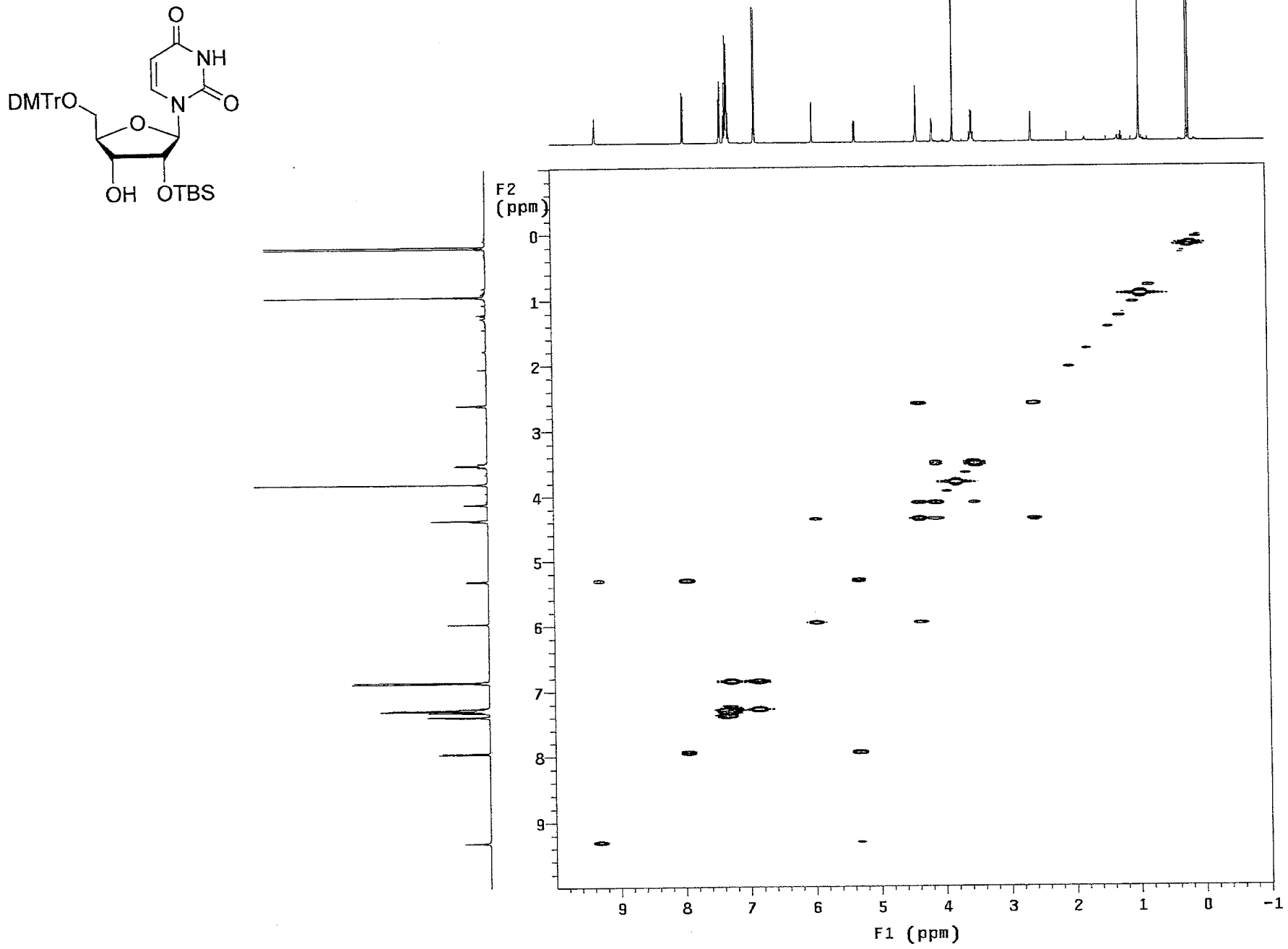

OTBS
TESO
4
O
O
3
2
OH
HO
CHO
F1
(ppm)
0
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
0
-1
F2 (ppm)

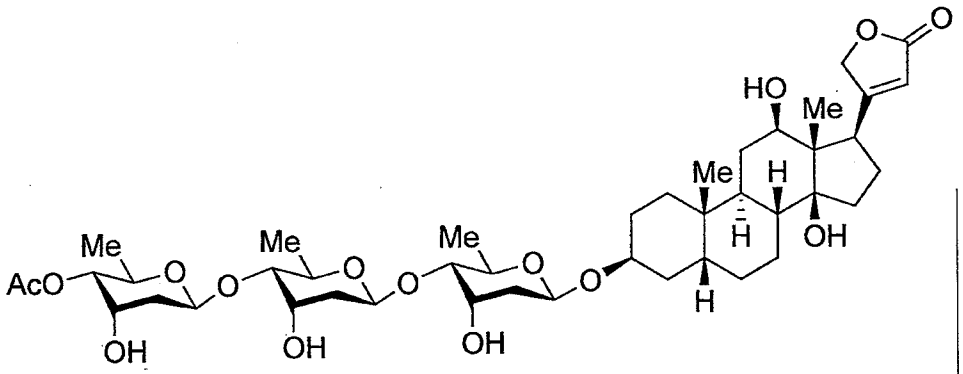

O
NH
DMTrO
N
O
O
OH
OTBS


9
8
7
6
5
4
3
2
1
ppm

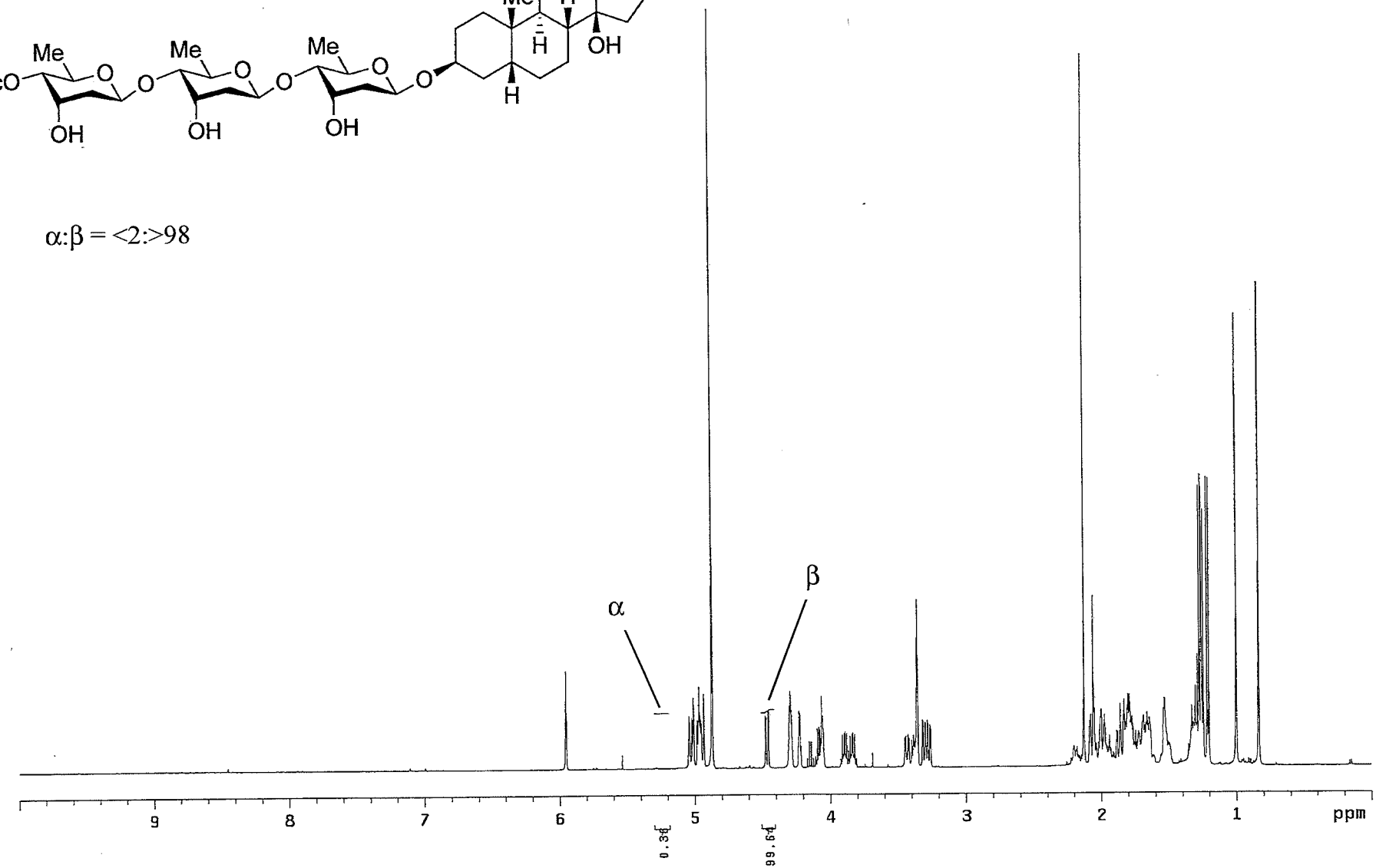

O
NH
DMTrO
N
O
O
OH
OTBS

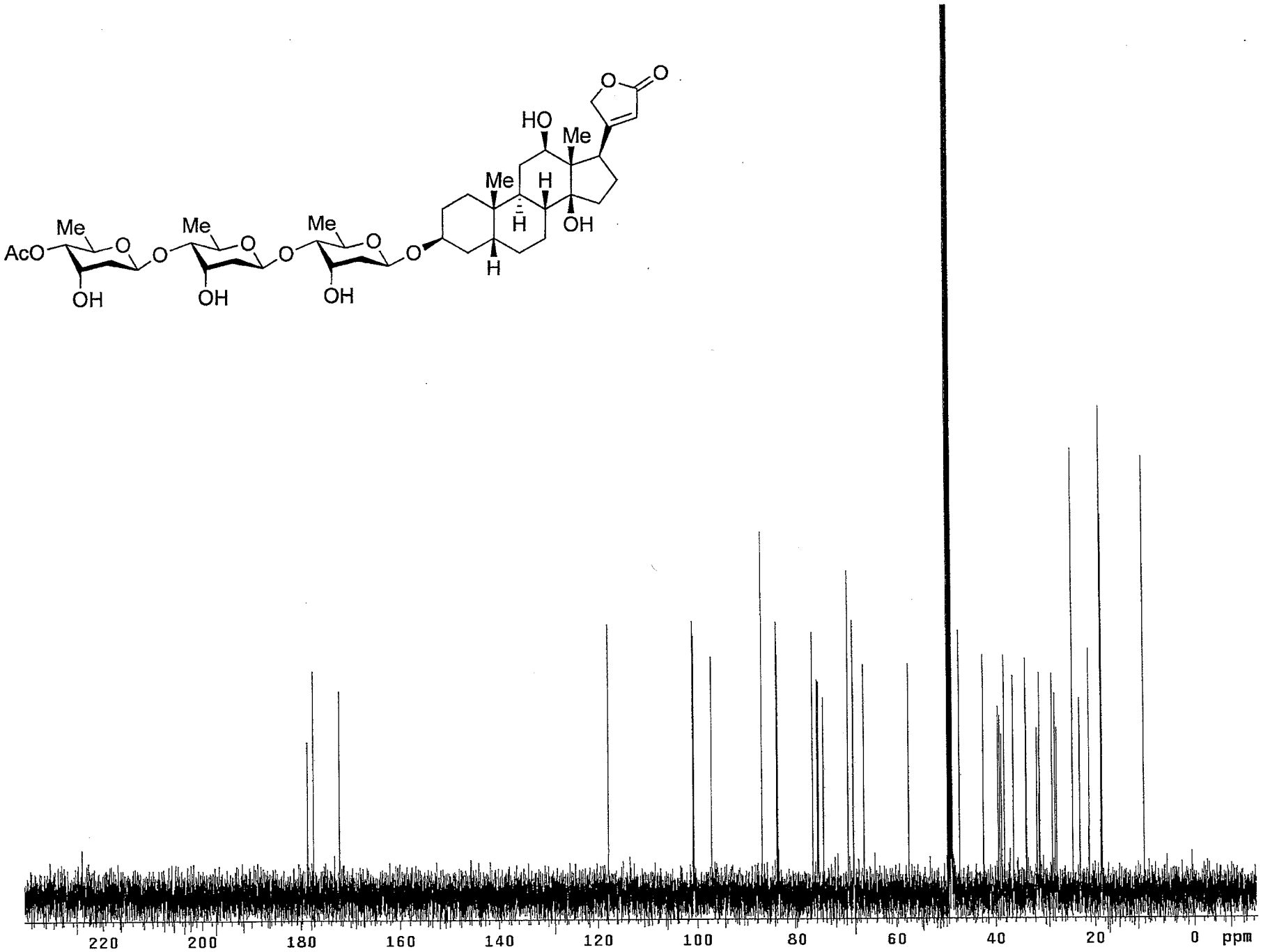
220
200
180
160
140
120
100
80
60
40
20
0
ppm

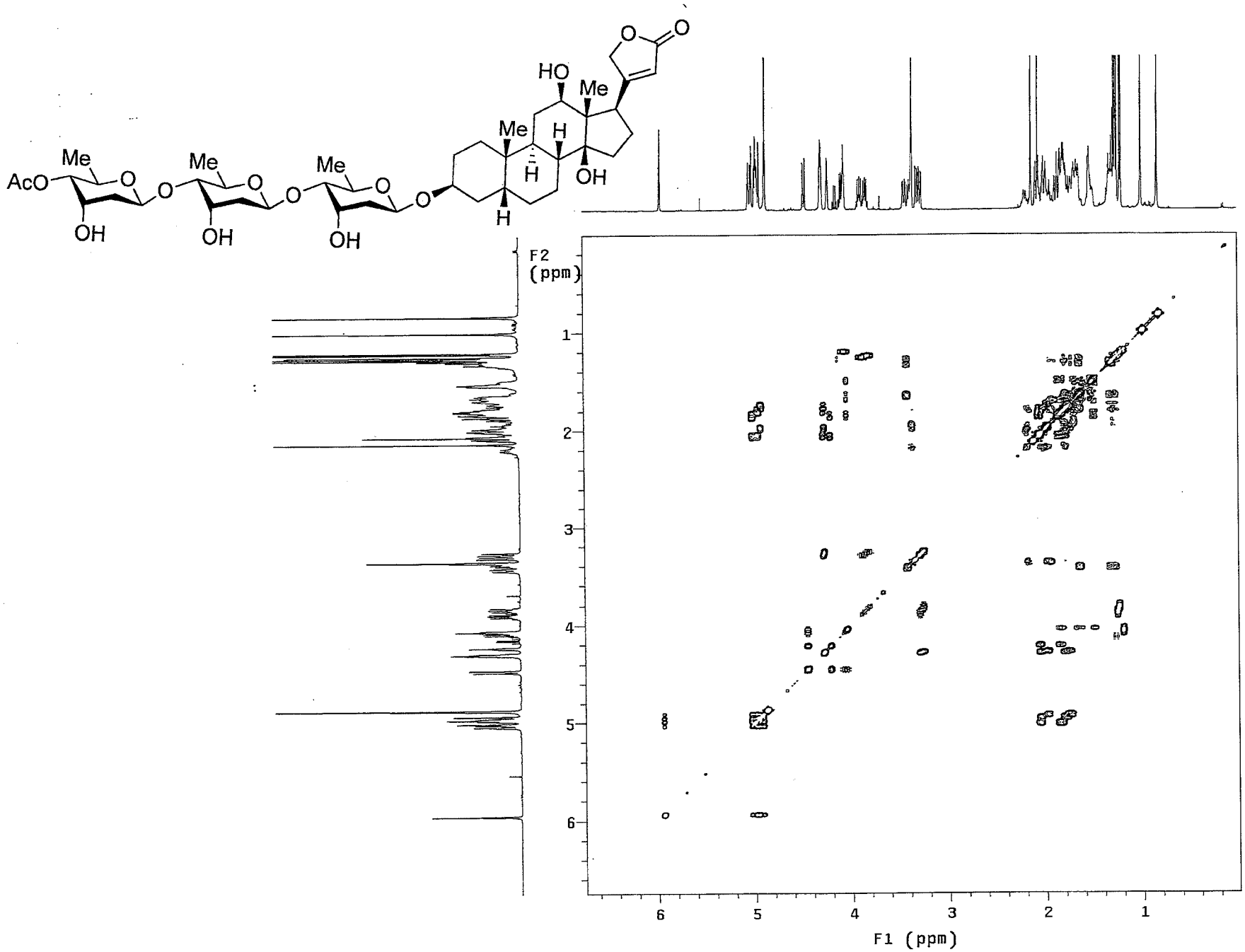

O
NH
DMTrO
N
O
O
OH
OTBS
F2
(ppm)
0
1
2
3
4
5
6
7
8
9
9
8
7
6
5
4
3
2
1
0
-1
F1 (ppm)

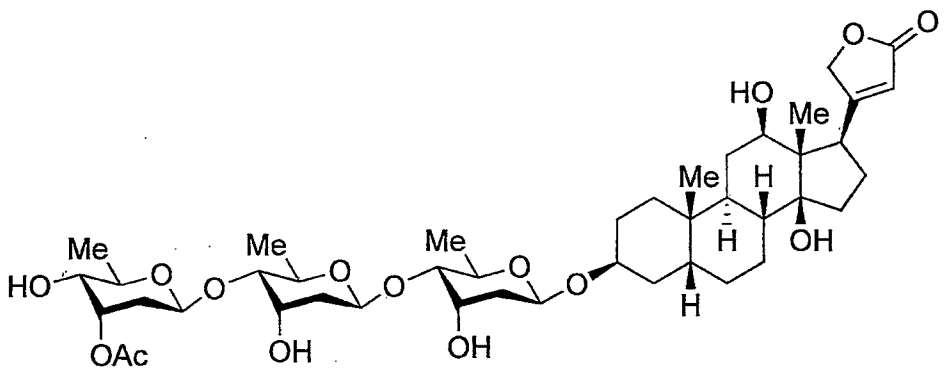

AcO
Me
O
OH
Me
O
OH
Me
O
OH
O
HO
Me
Me
H
H
H
OH
O
O

α:β = <2:>98


α
β
9
8
7
6
5
4
3
2
1
ppm
0.36
99.64

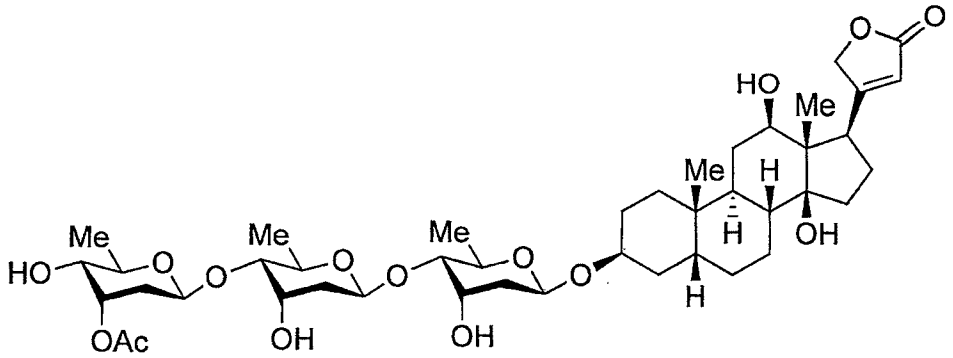

AcO
Me
O
OH
Me
O
OH
Me
O
OH
O
HO
Me
Me
H
H
H
OH
O
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm


AcO
Me
OH
HO
Me
H
OH
O
F2
(ppm)
F1 (ppm)
1
2
3
4
5
6

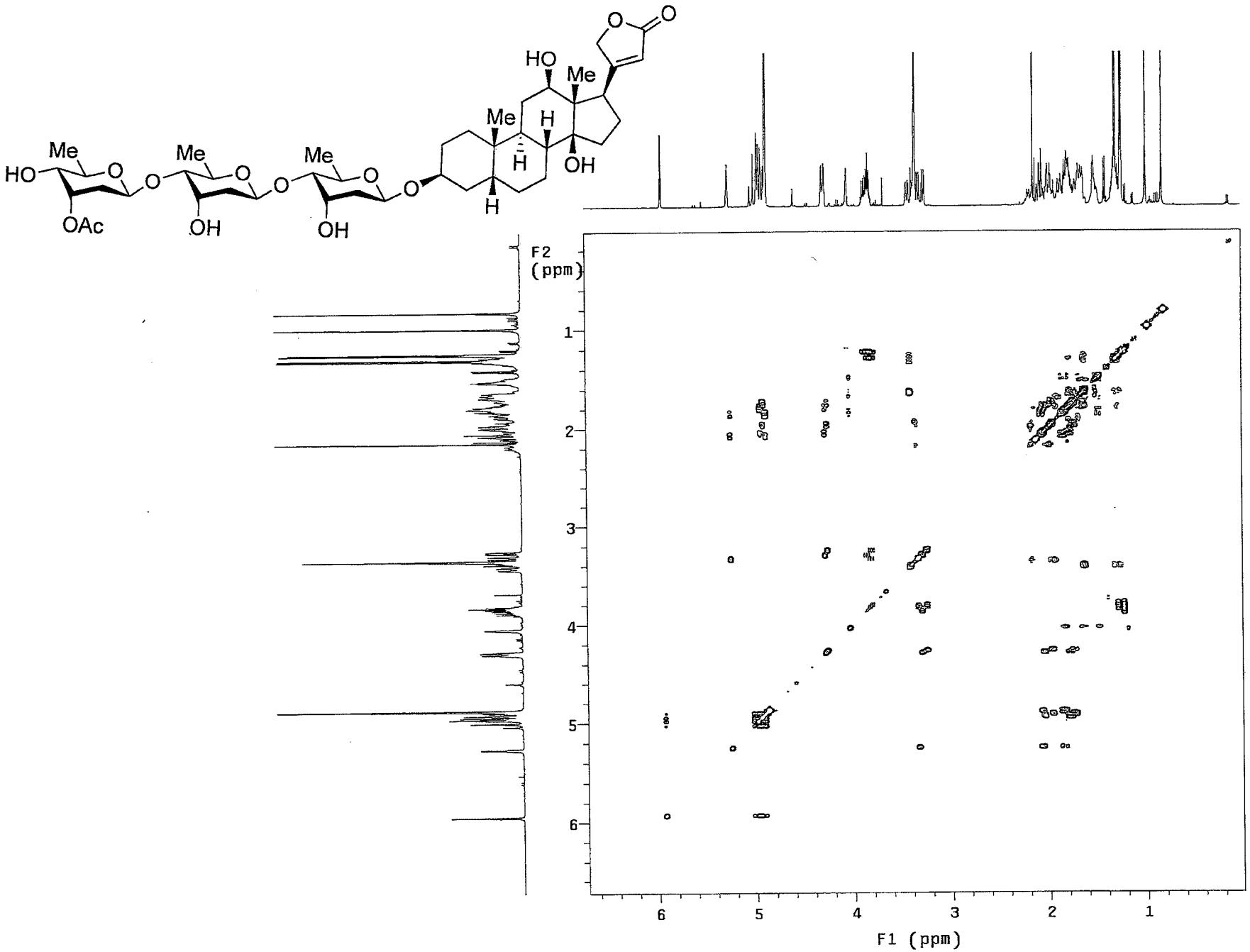

HO
Me
Me
H
H
OH
O
O
Me
HO
O
Me
O
Me
O
O
O
O
OAc
OH
OH

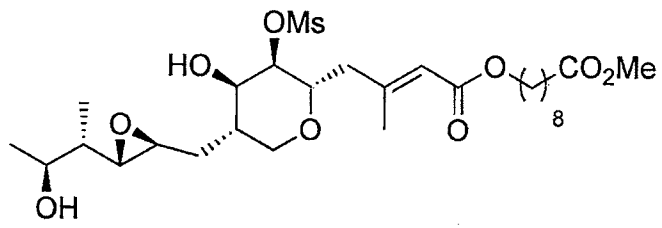
α:β = 91:9

α
β
9
8
7
6
5
4
3
2
1
ppm
91.04
8.96

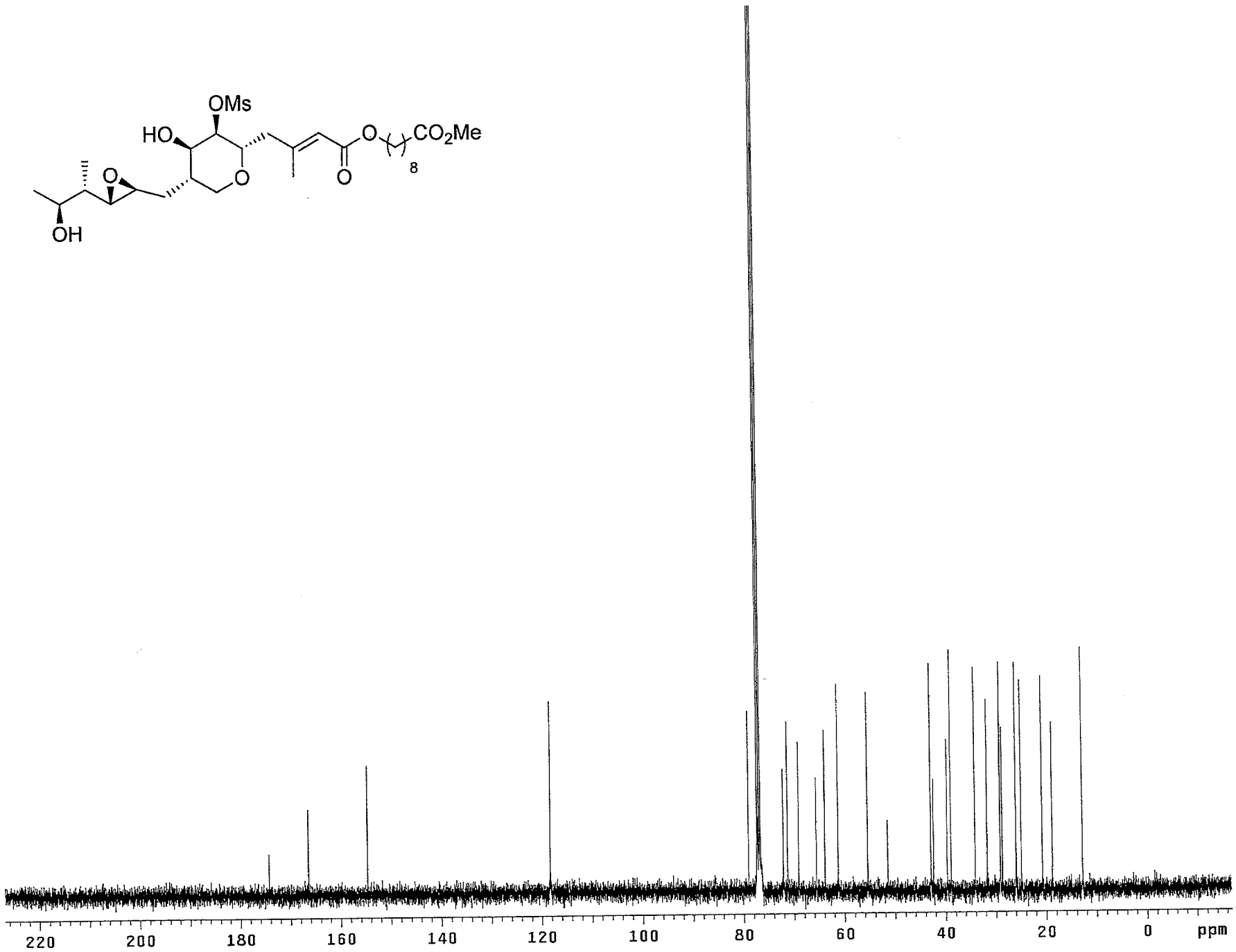

HO
Me
Me
H
H
OH
O
O
Me
HO
O
OAc
Me
O
OH
Me
O
OH

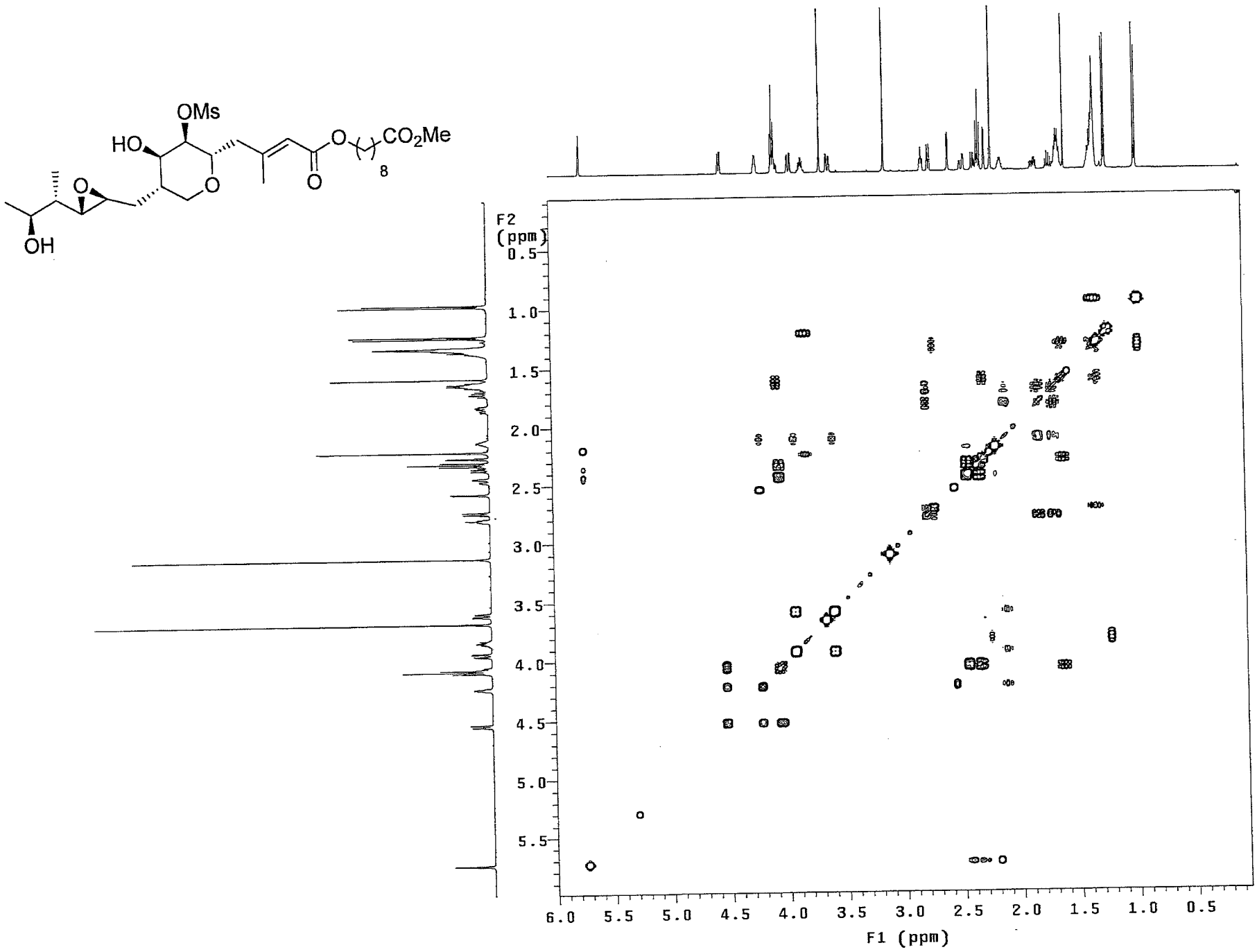
220
200
180
160
140
120
100
80
60
40
20
0
ppm

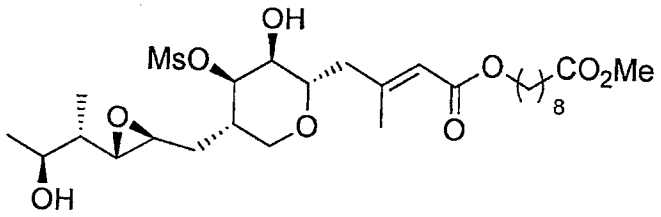

HO
Me
O
OAc
OH
OH
HO
Me
Me
H
H
OH
O
O
F2
(ppm)
1
2
3
4
5
6
6
5
4
3
2
1
F1 (ppm)


OMs
HO
O
O
O
O
8
CO2Me
OH

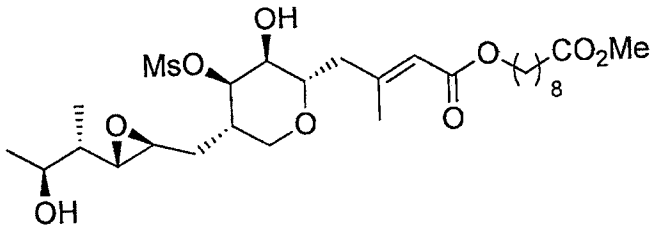
9
8
7
6
5
4
3
2
1
ppm


OMs
HO
O
O
O
CO2Me
8
O
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

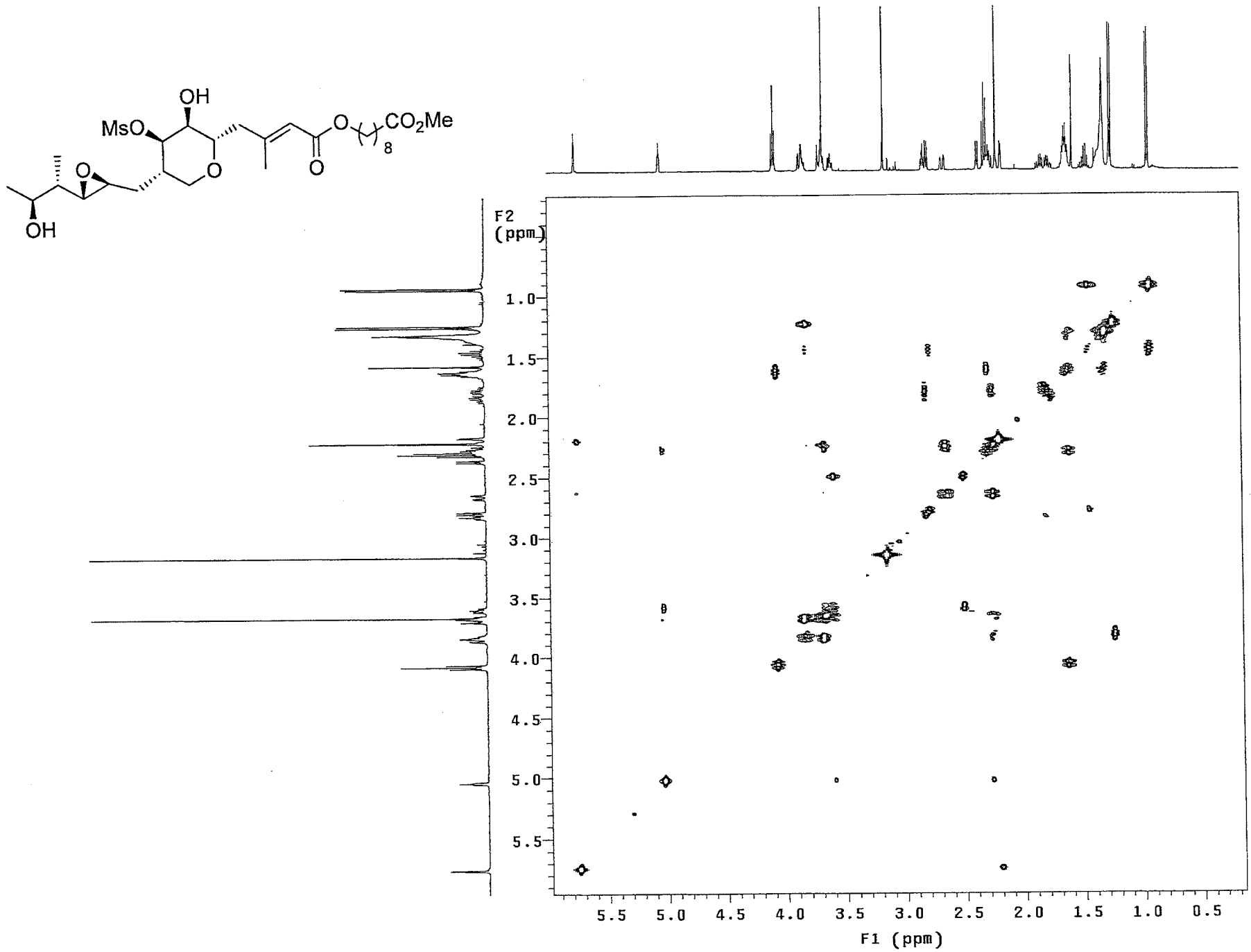

OMs
HO
O
O
O
O
8
CO2Me
OH
F2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F1 (ppm)


OH
MsO
O
O
O
O
8
CO2Me
O
OH

9
8
7
6
5
4
3
2
1
ppm


OH
MsO
O
O
O
O
8
CO2Me
O
OH

220
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
MsO
O
O
O
8
CO2Me
O
OH
F2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F1 (ppm)