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The University of Arizona, 1990

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STUDIES IN ASYMMETRIC SYNTHESIS: DIASTEREOSELECTIVE MANIPULATION OF CHROMATOGRAPHICALLY RESOLVED PYRANOSIDES FOR THE SYNTHESES OF NATURAL PRODUCTS

by

Jeffrey Burton Arterburn

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF CHEMISTRY

in Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

in the Graduate College

THE UNIVERSITY OF ARIZONA

1990

THE UNIVERSITY OF ARIZONA
GRADUATE COLLEGE

As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Jeffrey Burton Arterburn entitled STUDIES IN ASYMMETRIC SYNTHESIS: DIASTEREOSELECTIVE MANIPULATION OF CHROMATOGRAPHICALLY RESOLVED PYRANOSIDES FOR THE SYNTHESES OF NATURAL PRODUCTS and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

Eugene A. Mash	10/23/90 Date
Cornelius Steelink	10/23/90 Date
Robert B. Bates	10/23/90 Date
David E. Wigley	10/23/90 Date
William A. Remers	10/23/90 Date

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

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ACKNOWLEDGMENTS

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Many faces and events come to mind while pausing for this brief moment of retrospection. My esteem and affection is warmly extended to the close friends with whom I've experienced the comedy and drama of graduate school and life in Arizona. I especially thank Professor Eugene Mash, who has contributed much to my personal and scientific development. I could not be here today without the solid foundation provided by my family and their continuous support and understanding. Closest to my heart I thank my wife Michelle for her invaluable perspective and opinions, her ability to heighten my shortcomings to help me to strive, and most of all for sharing her love and life with me.

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ABSTRACT

Chromatographic resolution of diastereomeric pyranosides prepared from enantiomerically pure α-hydroxy esters was shown to be a reliable method of obtaining a variety of potentially useful chiral substrates. Several enantiomerically pure α-hydroxy esters are commercially available and lead to chromatographically separable pyranosides. The methyl esters of lactic and mandelic acid are inexpensive, available in both enantiomeric forms, and were easily incorporated into readily available racemic pyran substrates. The resolutions were performed on a preparative scale using gravity driven silica gel column chromatography. Phenylselenyl substituted tetrahydropyranosides were prepared using the alkoxy-selenation reaction and were subjected to elimination under mild oxidative conditions to afford dihydropyranosides. The resolved chirality of the anomeric center permitted diastereoselective functionalization of the alkene moiety in these compounds. The dihydropyranosides possessing lactate or mandelate ester appendages preferentially underwent epoxidation with peroxy acids and *cis*-dihydroxylation with catalytic osmium tetroxide on the face of the alkene anti to the appendage. Reduction of the ester with lithium aluminum hydride converted the sterically demanding ester appendage into a polar primary alcohol. This enabled the appendage to participate in the delivery of electrophilic reagents such as peroxy acids and mercuric acetate preferentially to the syn-face of the dihydropyranoside alkene. Utilization of these general principles permitted the asymmetric syntheses of 4-deoxyribose, (R)-mevalonolactone, a protected mevinic acid precursor, and the calicheamicin ethylamino sugar.

CHAPTER 1

DIHYDROPYRANOSIDE SUBSTRATES FOR CARBOHYDRATE SYNTHESIS

INTRODUCTION

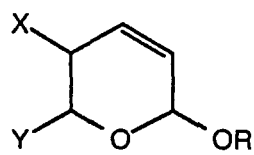
Organic chemists maintain a dynamic, productive relationship with the field of carbohydrate chemistry. Originally defined as "hydrates of carbon" with the empirical composition $C_n(H_2O)_m$, the term carbohydrate has been expanded to include deoxy and heteroatom substituted sugars. The stereoisomeric multiplicity and unique structure and reactivity relationships exhibited by carbohydrates provided an ideal environment for the evolution and application of stereochemical principles. In general the number of possible stereoisomers for a compound with *n* asymmetric carbon atoms is 2^n . From the vantage point of chemists interested in carbohydrates in the late 19th century, the assignment of relative and absolute stereochemistry within members of the "simple" aldohexoses with 4-asymmetric centers and 16 possible stereoisomers must have seemed a herculean task. However by utilizing the addition of cyanide to an aldose, followed by conversion of the nitrile to an aldehyde in the resulting diastereomeric cyanohydrins, E. Fischer was able to correlate the structures of 8 of the aldohexoses to D-glyceraldehyde, and the other 8 to L-glyceraldehyde.[1] In addition to providing a foundation for the developing field of carbohydrate chemistry with this work, the concept of asymmetric synthesis was first introduced when he observed that the diastereomeric cyanohydrins were not formed in equal amounts. Upon consideration of the significance of carbohydrates in biological processes, their potential as therapeutic agents, and the challenging structural variety they offer synthetic chemists, one finds their study as rewarding now as at any point in the history of chemistry.

The assignment of absolute configuration in this ascent of the sugar series relative to D-glyceraldehyde was accomplished later upon the advent of X-ray analysis. The mutually beneficial interaction between the development of new synthetic techniques and physical methods of analysis continues to this day. More powerful

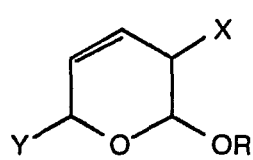
methods of structural determination made it possible to identify new compounds isolated in sub-milligram amounts, which in turn provide stimulus for the development of synthetic strategies to accomodate their individuality and provide useful quantities for further study. Chemical modification of available carbohydrates has been used extensively in synthesis. However the total synthesis of carbohydrates from non-sugar substrates is particularly suited for deoxy-, heteroatom-containing, branched, and uncommon substitution patterns, while challenging the state of the art in organic chemistry. The purpose of this chapter is to identify the salient features of such available strategies, with particular emphasis on approaches incorporating an intact pyran ring.

SYNTHESIS OF DIHYDROPYRANOSIDES

While linear alkenes and alkynes have been used extensively in racemic syntheses of carbohydrates, this approach is limited by the difficulty of performing stereoselective manipulations on acyclic substrates.[2, 3] Cyclic systems generally have more predictable conformations and are amenable to substituent directed functionalization. Both the 5,6-dihydropyranoside **1** and the 3,6-dihydropyranoside **2** have been used in carbohydrate syntheses.

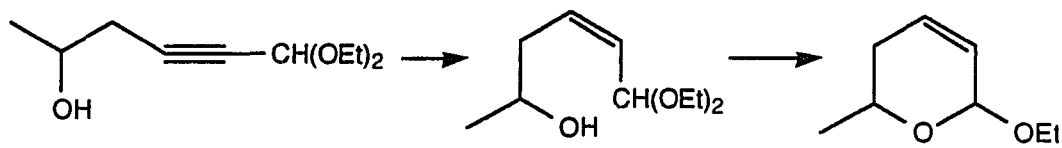


1



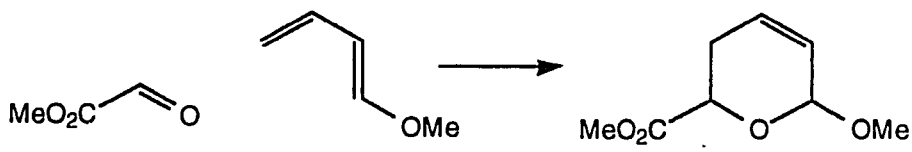
2

The triple bond of acetals of 5-hydroxy-2-pentyn-1-al **3** can be partially hydrogenated to the cis-alkene **4**, which undergoes acid catalyzed cyclization to afford the 5,6-dihydropyranoside **5**.[4]



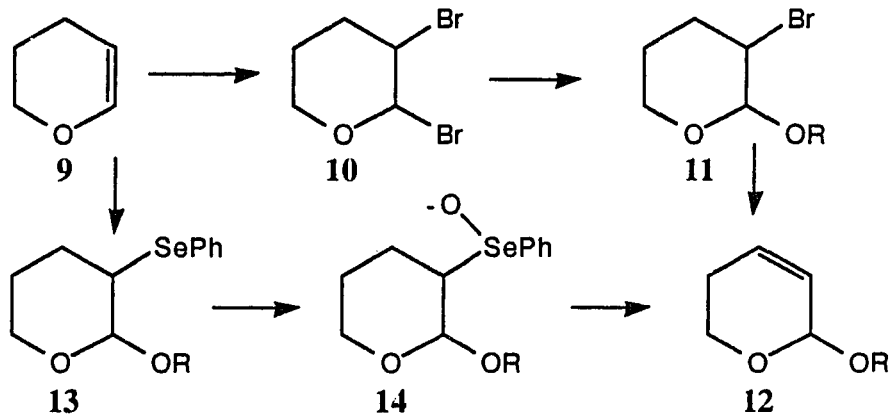
3 **4** **5**

Activated carbonyl conpounds such as ethyl glyoxalate **6** undergo cycloaddition reactions with 1-alkoxy-1,3-butadienes **7**, providing access to 6-substituted 5,6-dihydropyranosides **8**.[5, 6, 7, 8]

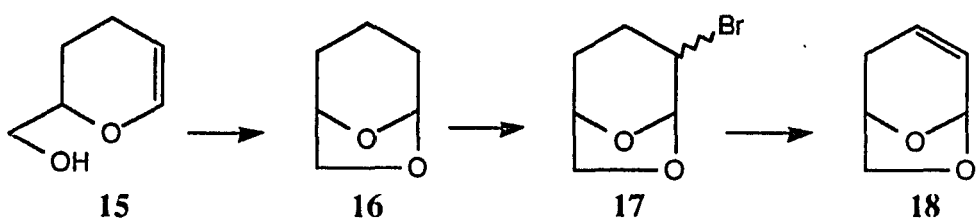


6 **7** **8**

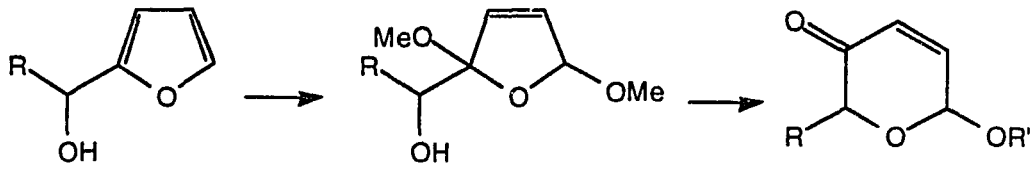
Bromination of 3,4-dihydro-2H-pyran **9** gives the dibrominated compound **10**. Substitution at the acetal occurs with alcohols under mildly basic conditions (e.g. trialkylamines) affording the 3-bromopyranoside **11**. Dehydrobromination occurs when heated with an alkoxide or amidine base and provides the 5,6-dihydropyranoside **12**.[9, 10, 11, 12] Alternatively, treatment with phenylselenyl chloride followed by substitution with an alcohol gives the 3-phenylselenylpyranoside **13**. Mild oxidation forms the selenoxide **14**, that then undergoes syn-elimination to afford the same 5,6-dihydropyranoside **12**.[13, 14]



The substituted 3,4-dihydro-2-(hydroxymethyl)-2H-pyran **15** was converted to the bicyclic acetal **16** by treatment with p-TsOH. Bromination in CCl_4 gave the bromo-acetal **17**. Elimination occurred upon treatment with NaOH in EtOH and afforded 6,8-dioxabicyclo[3.2.1]oct-3-ene **18** which is a useful precursor of racemic hexoses.[15, 16]

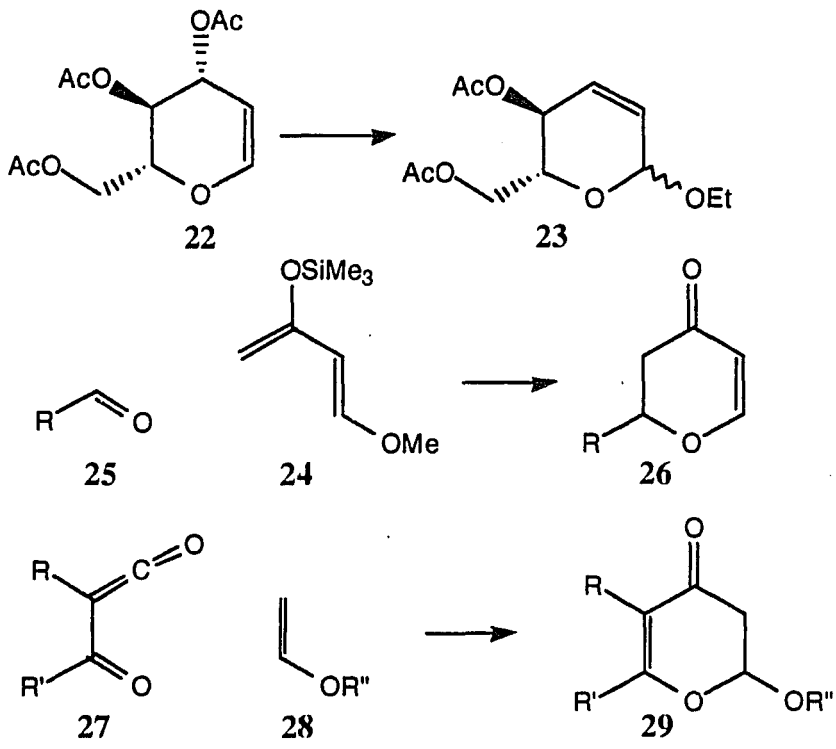


The oxidation of furyl alcohols **19** with bromine in methanol produces 2,5-dimethoxy-2,5-dihydrofurans **20**. Acid catalyzed rearrangement affords the alkyl or acetylated unsaturated pyranulosides **21**.[17, 18, 19, 20] Alternatively oxidation of **19** with m-CPBA[21] or pyridinium chlorochromate[22] provides the unsaturated pyranulose **21** (R'=OH) directly.

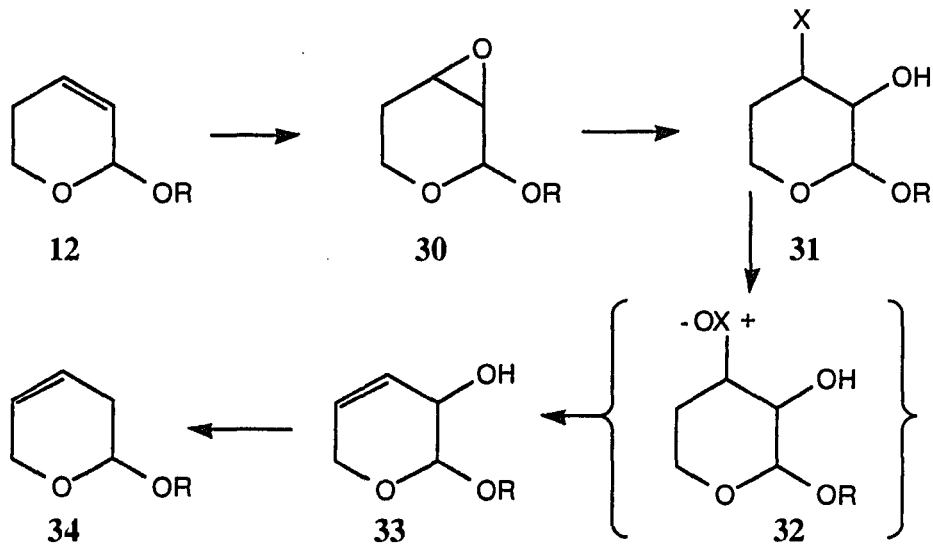


19 **20** **21**

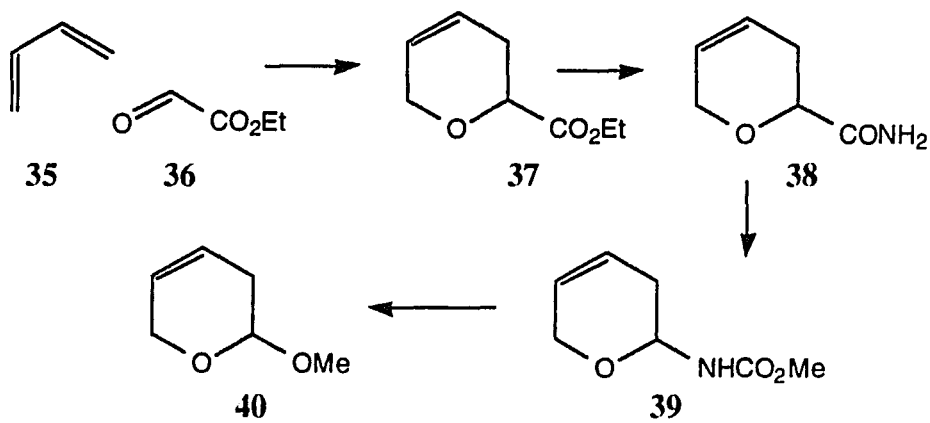
The Ferrier rearrangement of glycals converts a 3,4-dihydro-2H-pyran with an appropriate leaving group in the 4-position into a 5,6-dihydro-2H-pyranoside. This reaction has been widely used in carbohydrate synthesis; an example is the reaction of tri-O-acetyl-D-glucal **22** to give **23**.[23, 24] This reaction is of course applicable to non-carbohydrate precursors as well . Cycloaddition of silyloxy-dienes **24** and aldehydes **25** under Lewis acid catalysis affords dihydropyrones **26**, which can be a substrate for Ferrier rearrangement after conversion of the carbonyl to a suitable leaving group.[25, 26, 27] Acyl ketenes **27** react with enol ethers **28** to give 2-alkoxy-2,3-dihydro-4H-pyran-4-one derivatives **29** that should be suitable for carbohydrate syntheses.[28]



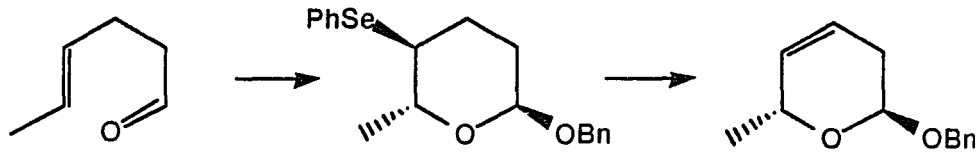
Fewer direct methods are available for the preparation of 3,6-dihydro-2H-pyranosides, although these substrates are ideal for the synthesis of 2-deoxy sugars. Epoxidation of the alkyl-5,6-dihydro-2H-pyranoside **12** gives a mixture of diastereomeric epoxides **30**. The major product is formed with the epoxide on the side of the ring opposite that of the anomeric appendage. This trans-epoxide undergoes nucleophilic attack at the 4-position with dimethylamine or phenylselenyl anion to give **31**. Mild oxidation generates the N- or Se-oxide respectively **32**, which then undergo syn-elimination to afford the allylic alcohol **33**. Tosylation followed by reduction with lithium aluminum hydride gives the 3,6-dihydro-2H-pyranoside **34**.[11, 29, 30]



The Diels-Alder reaction of butadiene **35** with ethyl glyoxalate **36** forms the substituted dihydropyran **37**. Treatment with aqueous ammonia produces the primary amide **38**. Hoffman degradation with methanolic sodium hypochlorite yields the N-substituted dihydropyranoside **39**. Conversion to the methyl dihydropyranoside **40** occurs upon treatment with boron trifluoride/methanol but the yields are low (~35%).[31]

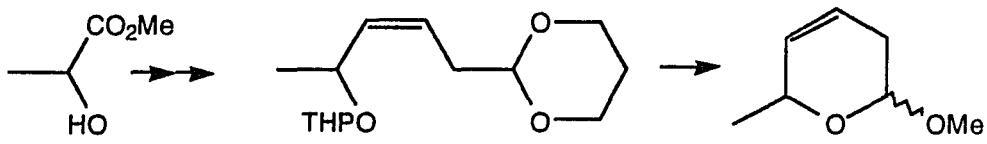


The reaction of trans-4-hexenal **41** with (p-chlorophenyl) selenyl bromide and benzyl alcohol under equilibrating conditions produces the pyranoside **42** in ~60% yield. In this compound the anomeric benzyloxy appendage is axial, and both the phenylselenyl and methyl substituents are equatorial. Oxidation to the selenoxide and subsequent syn-elimination affords the 6-substituted 3,6-dihydro-2H-pyranoside **43**.[32]



41 **42** **43**

Methyl lactate **44** was protected as the THP ether, the ester converted to an aldehyde and coupled via a Wittig reaction with a protected ylid to form the alkene **45**. Acid catalyzed methanolysis then afforded the 6-methyl-3,6-dihydro-2H-pyranoside **46** as a ~1:1 mixture of cis and trans isomers.[33]



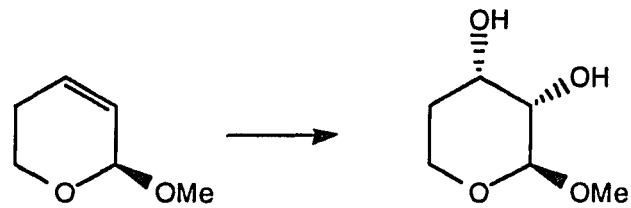
44 **45** **46**

REACTIONS OF DIHYDROPYRANOSIDES

A versatile approach to carbohydrates and derivatives utilizes stereoselective oxidation of the alkene moiety of dihydropyrans. The selectivity of these reactions depends upon the combination of steric interractions and conformational preferences which are inherent in the substrate. In this section several pertinent examples will be

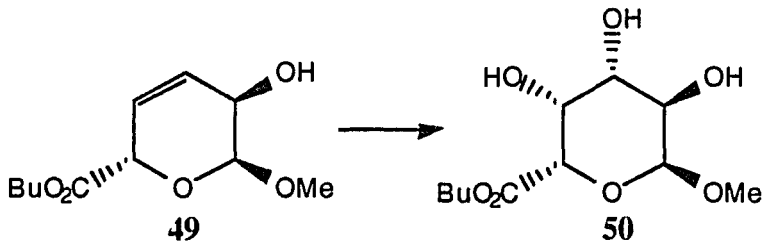
presented along with some general considerations that will permit extension to other systems.

Three general reagents have been used for the cis-dihydroxylation of dihydropyrans. With dilute, aqueous potassium permanganate[34, 35] or catalytic osmium tetroxide/hydrogen peroxide in t-butanol yields are generally 25-70%.[36, 37] Stoichiometric osmium tetroxide gives the diols in 70-100% yield, but the scale of these reactions is limited by the high cost of the oxidant (1 g, 3.9 mmol, $71).[38, 39] These reactions are generally subject to steric approach control and occur via delivery of the oxidizing agent to the face of the alkene that is opposite the anomeric appendage.[40] Stereoelectronic effects may also be involved.[124] Stoichiometric reaction of methyl 5,6-dihydro-2H-pyranoside **47** with OsO_4 in pyridine gives as a single product the diol **48** possessing the expected trans relationship to the anomeric substituent in 93% yield.[39]

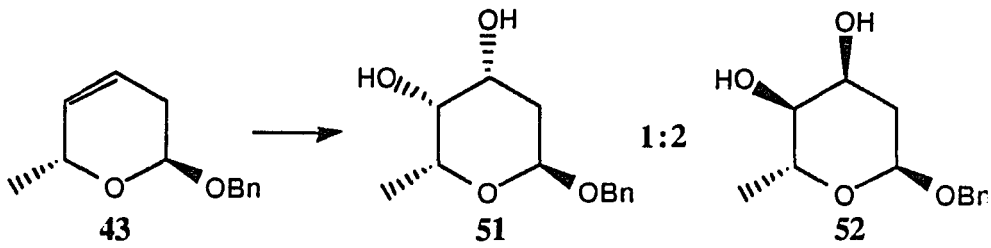


47 **48**

In the substituted 3,6-dihydropyranoside **49** anti-delivery of catalytic OsO_4 with hydrogen peroxide oxidant relative to the anomeric and hydroxyl substituent is observed, overcoming the steric impedance of the ^{t}butyl ester appendage, which provides as the sole product triol **50** in 48% yield.[30]

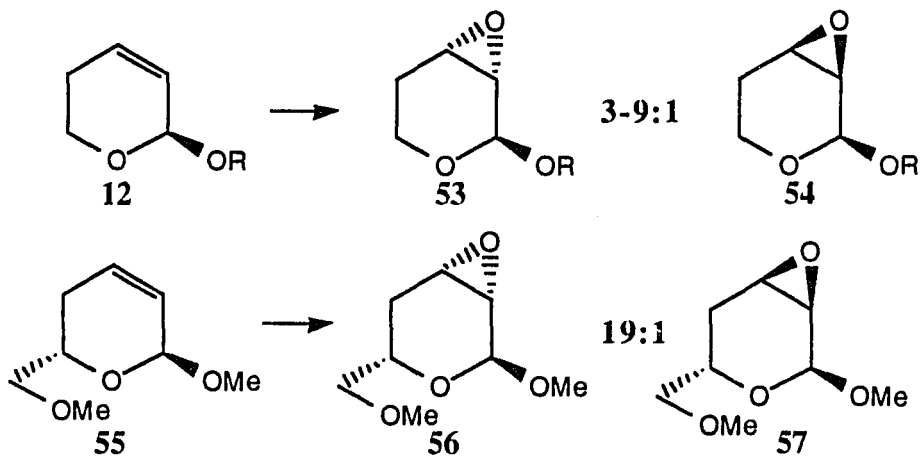


The reaction of 6-methyl-3,6-dihydro-2H-pyranoside **43** with catalytic OsO4/hydrogen peroxide affords the diol as a 2:1 mixture in 38% yield favoring the isomer with hydroxyl groups oriented syn to the anomeric appendage **52** relative to the "normal" anti-product **51**.[32] In this case the steric role of the anomeric substituent in reagent delivery may intuitively be expected to diminish with decreasing proximity to the alkene. However the formulation of mechanistic rationale from low-yielding reactions involving diastereomeric substrates must be tempered with consideration of differential conformer/reactivity relationships and the possibility of preferential decomposition of products. In general the results of dihydroxylation with dihydropyran substrates can be predicted by a comparison of substituent steric interactions.



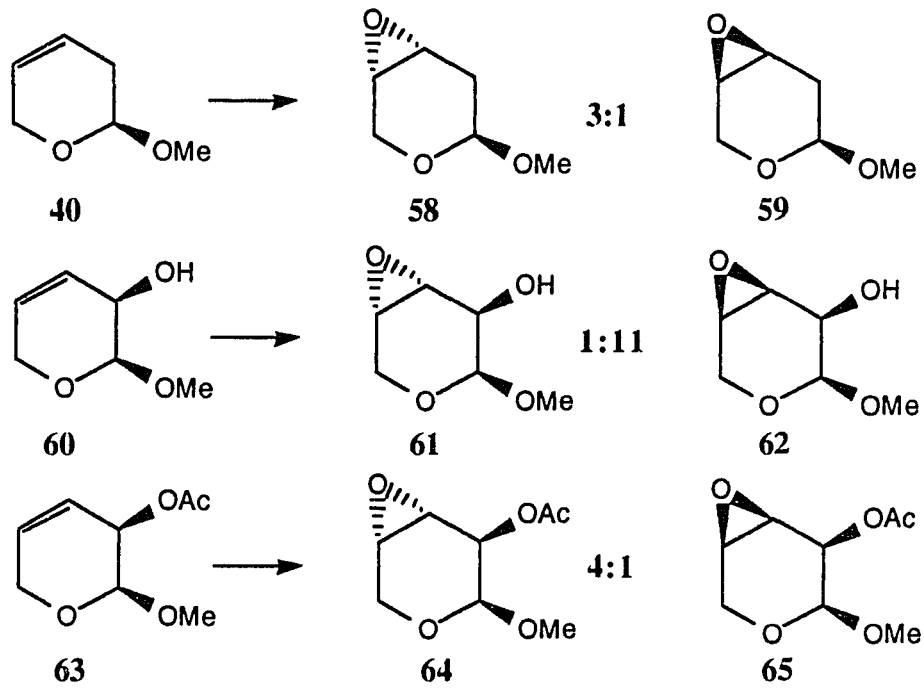
The epoxides derived from dihydropyrans are versatile intermediates in carbohydrate syntheses.[3, 30] Treatment of a dihydropyran with a peroxy acid or a mixture of 30% hydrogen peroxide and benzo- or acetonitrile generates the epoxide in 35-90% yield. The reaction rate is relatively slow and normally requires from one to seven days for completion. The epoxidation of simple dihydropyrans with

seven days for completion. The epoxidation of simple dihydropyrans with peroxy acids is subject to steric approach control. Thus 2-alkoxy-5,6-dihydro-2H-pyran **12** (R=Me, ^{t}Bu) is converted to a mixture of the favored "anti"- and "syn"-epoxides **53** & **54**, in 80-85% yield, with the product distribution ranging from 3:1 for the methyl pyranoside, to 9:1 for the tert-butyl appendage.[41] Similarly the 6-methoxymethyl-substituted dihydropyranoside **55** reacts with mCPBA to afford a mixture of epoxides in 80% yield favoring the anti- **56** to syn-product **57** in a ratio of 19:1.[9] In many instances the mixture of diastereomeric epoxides may be separated chromatographically.



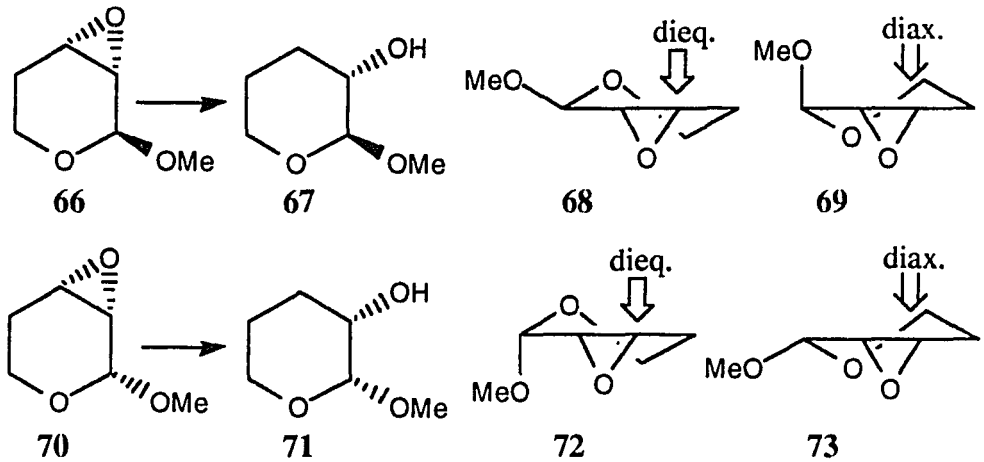
The 3,6-dihydro-2H-pyranoside **40** reacts with mCPBA to give a mixture favoring the anti- **58** over the syn-epoxide **59** in a 3:1 ratio, as expected from steric approach control.[42, 43] Polar substituents on the substrate that are capable of hydrogen-bonding with electrophilic peroxy acids may influence the epoxide product distribution.[44] The presence of the allylic hydroxyl in **60** overrides the steric opposition of the anomeric appendage and affords a mixture of anti- **61** and syn-epoxides **62** favoring the latter in a ratio of 1:11. The sterically demanding allylic

acetate appendage in **63** accentuates the effect of the anomeric appendage and forms the anti- **64** and syn-epoxides **65** in 64% yield with a ratio of 4:1. Epoxidation with the hydrogen peroxide/benzonitrile reagent may also form the syn-isomer via H-bonding of the intermediate peroxyiminobenzoic acid to the anomeric ether.[3]

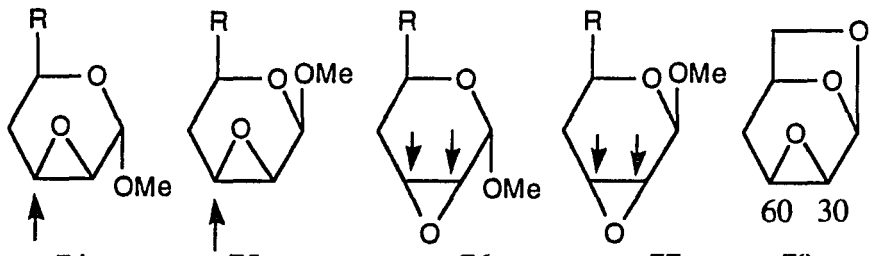


The course of the epoxidation of dihydropyranosides can be predicted by comparing the steric and polar effects of the substituents. The propensity for cleavage of the strained 3-membered epoxide ring makes these compounds versatile synthetic intermediates. The direction of nucleophilic opening depends on several factors: (a) attack resulting in trans-diaxial ring opening is normally favored in conformationally rigid systems, (b) participation of neighboring groups to stabilize or intercept reactive intermediates may occur, (c) conformational effects of the substrate may influence the approach of the nucleophile, and (d) different nucleophiles may behave individually.

The preferred conformation of simple 2-alkoxy-3,4-epoxytetrahydropyrans is that in which the alkoxy substituent is pseudo-axial due to the anomeric effect.[45, 46] However these conformers readily interconvert at ambient temperature. Nucleophilic attack of anti-epoxide **66** with $LiAlH_4$ ocurrs exclusively at the 4-position to afford 3-hydroxy-tetrahydropyranoside **67**. This result would be predicted via 1,3-diaxial opening if the more stable conformer **69** were also the reactive species. The syn-epoxide **70** also reacts with $LiAlH_4$ at the 4-position to give the 3-hydroxy-tetrahydropyranoside **71**. If diaxial opening is involved in this example then the conformer with the anomeric substituent pseudo-equatorial **73** would be the reactive partner. The alternative is diequatorial opening via attack at the epoxide carbon furthest away from the anomeric appendage and the non-bonding electrons of the ring oxygen atom in conformer **72**.[41]



Prediction of the site for nucleophilic attack on 6-substituted-2-alkoxy-3,4-epoxytetrahydropyrans generally follows the preferences indicated on **74** -**77**. Substituents (R) include CH_3, CH_2OH, $CO_2{}^tBu$, while the nucleophiles may be hydride, alkoxide, amine or phenylselenide.[3, 30, 36] An exception may be found in the reaction of the rigid bycyclic epoxide **78** with dimethylamine, which gives a 2:1 mixture of regioisomers that were isolated in the % yields indicated.[47]



74 **75** **76** **77** **78**

Combinations of these methods to functionalize dihydropyranosides, i.e. dihydroxylation, epoxidation, and nucleophilic epoxide opening, make it possible to prepare a variety of carbohydrates and derivatives. While the majority of these examples have utilized racemic pyranosides and concern relative stereochemistry, with an available source of enantiomerically pure dihydropyranosides these results could be adapted to asymmetric synthesis.

CHAPTER 2

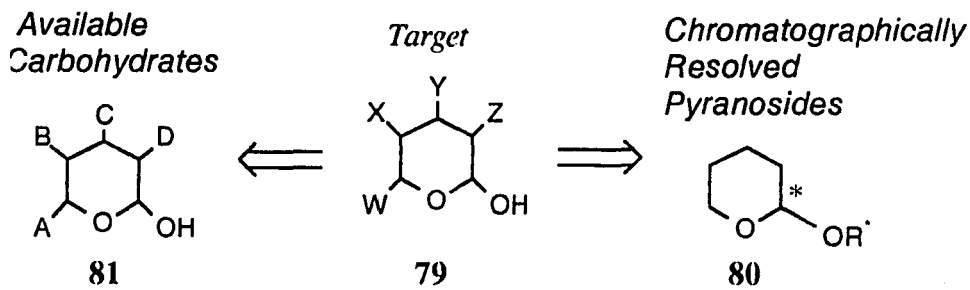
CHROMATOGRAPHIC RESOLUTION OF DIASTEREOMERIC PYRANOSIDES

Introduction

The pyran structural unit is one of the most important building blocks in nature. With structures ranging from simple monosaccharides to macroscopic polysaccharides, pyrans as carbohydrates are involved in practically every aspect of cellular metabolism, provide structural integrity, and play an important role in intra- and extra-cellular molecular recognition processes. The isolation of rare deoxy-, branched and heteroatom-containing sugars and nucleotides from plant, animal, fungal and bacterial sources has direct relevance to human biology, since many exhibit antibiotic and antitumor activity. Numerous acetate- and isoprene-derived primary and secondary metabolites containing a pyran unit are also involved in biological processes. The structural diversity and significance of these compounds makes the development of synthetic methods for their preparation in enantiomerically pure form of immediate importance.

δ-Hydroxy-aldehydes exist in an equilibrium that usually favors the cyclic hemi-acetal form, because of the thermodynamic stability of the 6-membered pyran ring. These hemiacetals are converted into pyranosides by reaction with alcohols or other nucleophiles under acid catalysis. These cyclic acetals are generally stable under basic conditions but can be cleaved readily with acid. These qualities have been used to "protect" both alcohol and pyranose-aldehyde functional groups from undesired reactions during synthetic manipulations of other positions within the molecule. The simplest type of pyranoside is the tetrahydropyranyl-ether (THP). 3,4-Dihydro-2H-pyran is a convenient precursor that readily undergoes addition of alcohols under mild acid catalysis. Formation of the anomeric center is normally stereorandom, and with achiral alcohols enantiomeric products are obtained. When chiral alcohols are utilized

diastereomeric pyranosides are formed. In some instances when simple protection is required this may be a nuisance, because spectral data will reflect the diastereomeric mixture and may complicate interpretation. Alternatively, the unique physical properties of these diastereomers may permit their separation, resulting in an effective transfer of absolute chirality from the alcohol to the pyran moiety. The potential utility of these results for the development of synthetic approaches to pyranoid natural products **79** resides in the possibility that the resolved chirality of the anomeric center in **80** could permit diastereoselective functionalization at other sites within the molecule. Many traditional approaches to pyran derivatives have utilized available carbohydrates as chiral starting materials.[125] The efficacy of this "chiron" approach depends upon the stereochemical matching of target **79** and starting material **81**. The limitations of this approach can be that precursors are unavailable or exceedingly expensive, and/or an excessive number of steps are required. Methodology that relies on diastereoselective functionalization of pyranosides via the resolved chirality of the anomeric center should be particularly useful for the preparation of deoxy-, branched, and heteroatom-substituted systems and offers advantages that complement available strategies.



81 **79** **80**

Chromatographic techniques are among the most widely used methods of purification. Applications range from using a small plug of silica to remove inorganic salts, qualitative analysis of reaction mixtures using thin layer plates, multi-gram preparative scale columns, to the determination of enantiomeric purity by gas chromatography (GC) or high pressure liquid chromatography (HPLC) using a column packed with a chiral support. The versatility and low expense of column chromatography favor its routine use by synthetic organic chemists. We hoped to identify a chiral alcohol that would lead to chromatographically separable pyranosides that could serve as versatile starting materials for asymmetric synthesis. Desirable qualities for an auxilliary include availability, stability, removability, and ease of recovery or disposal.

Synthesis

The diastereomeric THP ethers prepared from (-)-menthol, (+)-isomenthol, (-)-borneol, (-)-isopinocampheol, (-)-nopol, and (-)-myrtenol were inseparable on silica gel 60 using various eluent combinations composed of ethyl ether, ethyl acetate, dichloromethane, and hexanes. Fortunately the diastereomeric (S)-(-)-methyl lactate tetrahydropyranyl (THP) and tetrahydrofuranyl (THF) ethers were readily separable on analytical thin layer plates and by preparative column chromatography (Tables 1 and 2). The steric and electronic properties of the functional groups comprising the chiral center of the lactate moiety are quite different (e.g. hydrogen, alkyl, carbonyl and ether) and translate into diastereomeric differences in the THP- and THF-ethers that lead to chromatographic separability. Other secondary alcohols such as 3-methyl-2-butanol, 1-methoxy-2-propanol, sec-phenethyl alcohol, and 2-pentanol were not separable, indicating that an α-carbonyl component is required. However the diastereomeric THP

ethers derived from (S)-methyl 3-hydroxybutyrate and (S)-dimethyl malate were also inseparable in the solvent systems investigated. Chromatographic separability was observed for other α-hydroxy esters including: (S)-methyl mandelate **100** and **101**, (S)-methyl 3-phenyl-lactate **102** and **103**, (S)-methyl isocaproate **104** and **105**, and (S)-pantolactone **106** and **107**, (Table 3). Varying the alkyl group of the lactate esters from methyl to ethyl, ^{i}propyl, and ^{t}butyl lactates was accompanied with corresponding decreasing ease of separability. The enantiomerically pure (S)-(-)- and (R)-(+)-methyl lactates (100 g/ $27 & 5 g/ $28, Aldrich), and also (S)-(+)- and (R)-(-)-mandelic acids (100 g/ $106 & 25 g/ $40, Aldrich) are available and proved to be useful auxilliaries (vide infra).

Table 1. Separation of Diastereomeric Pyranosides of (S)-Methyl Lactate

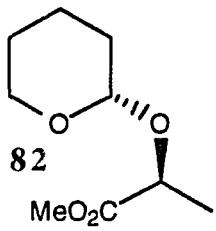
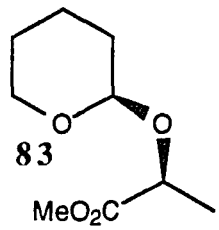
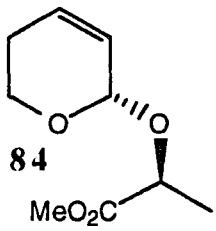
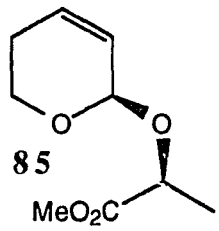
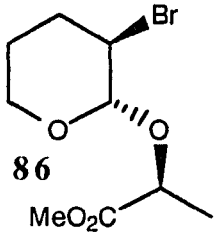
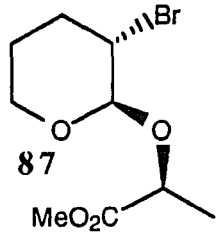
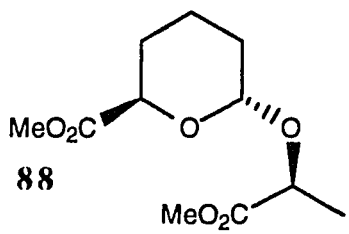
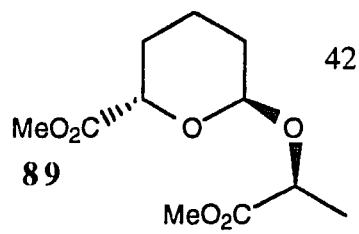
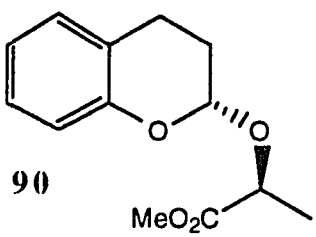
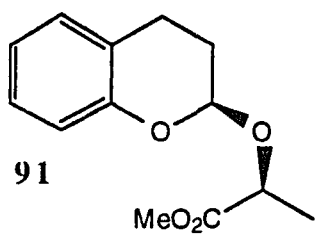
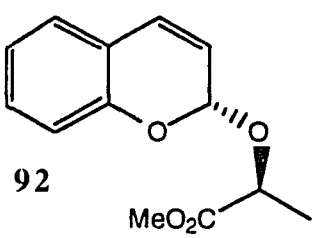
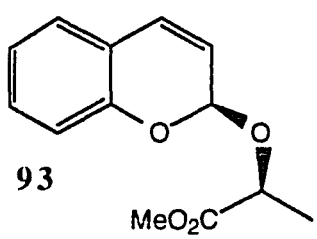
		Yields; α(% EtOAc /Hexanes)
 **82**	 **83**	49,49; 1.18 (20)
 **84**	 **85**	31,38; 1.34 (20)
 **86**	 **87**	42,42; 1.30 (20)
 **88**	 **89**	42,40; 1.09 (50)
 **90**	 **91**	48,23; 1.22 (10)
 **92**	 **93**	41,17; 1.58 (5)

Table 2. Separation of Diastereomeric Furanosides of (S)-Methyl Lactate

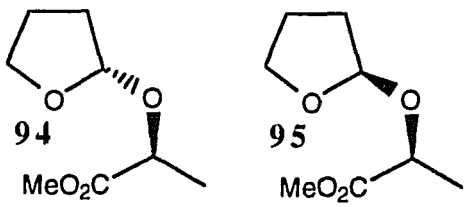
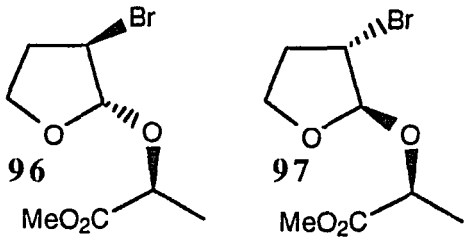
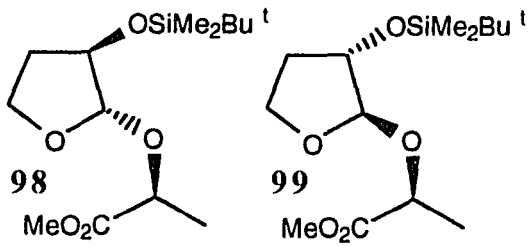
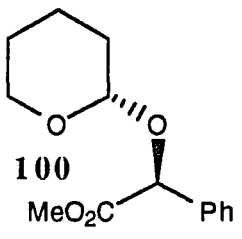
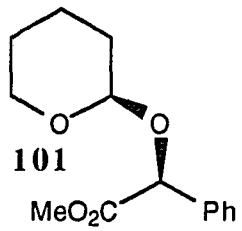
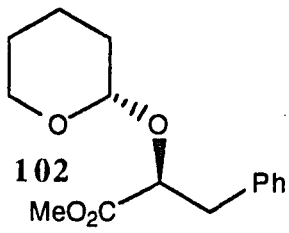
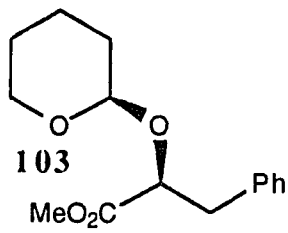
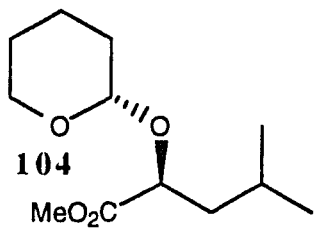
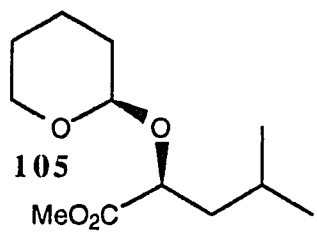
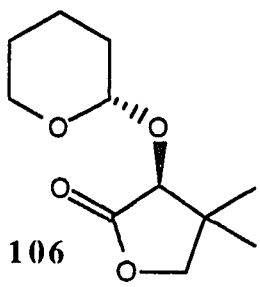
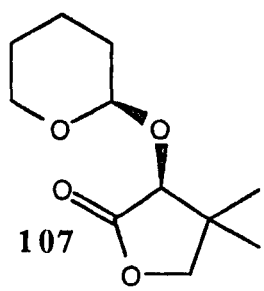
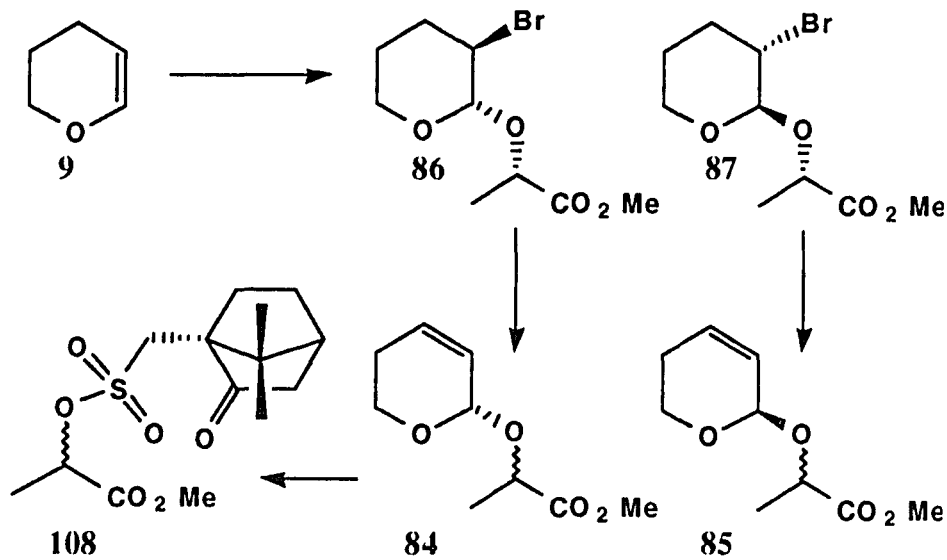
	Yields	α(% EtOAc /Hexanes)
 **94** **95**	45,48	1.25 (20)
 **96** **97**	43,44	1.10 (20)
 **98** **99**	36,36	1.19 (20)

Table 3. Separation of Diastereomeric THP Ethers of α-Hydroxy Esters

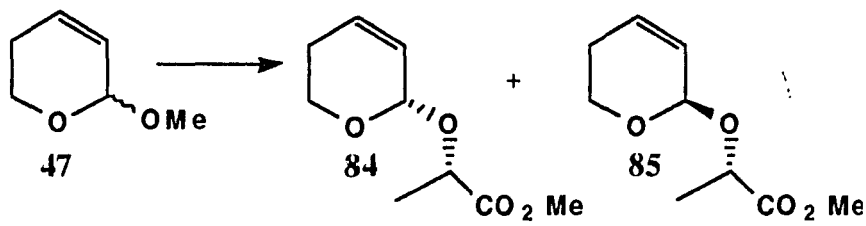
		Yields; α(% EtOAc /Hexanes)
 **100**	 **101**	42,49; 1.10 (20)
 **102**	 **103**	41,51; 1.11 (20)
 **104**	 **105**	33,42; 1.18 (20)
 **106**	 **107**	49,47; 1.40 (20)

With a general chromatographic resolution of pyranosides available we undertook the asymmetric synthesis of deoxy-carbohydrates and derivatives. Dihydropyranosides have been used in a variety of racemic syntheses of carbohydrates that provide a precedent for our asymmetric approach. Bromination of dihydropyran **9** gives the 2,3-dibromopyran which undergoes substitution at the anomeric center with (S)-(-)-methyl lactate /triethylamine to give the diastereomeric bromopyranosides **86**

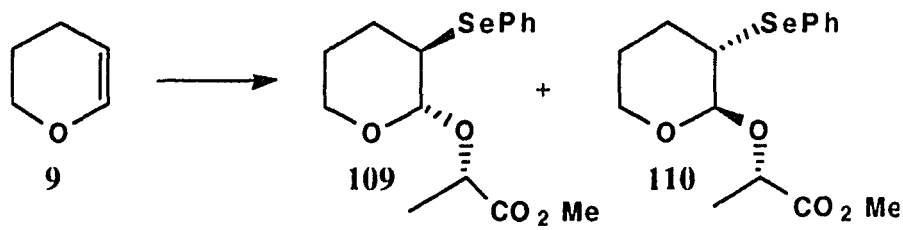
and **87** with the halogen and lactate substituents trans-related. These compounds are easily separated by gravity driven column chromatography. The isolated yields for the less polar **86** (R_f 0.33, 20% EtOAc/hexanes) and more polar diastereomer **87** (R_f 0.25, 20% EtOAc/hexanes) was 42% each. DBU in hot DMSO were the mildest conditions that would induce elimination of the bromide **86** and gave the 5,6-dihydropyran **84** in high yield. In order to determine if the chirality of the potentially epimerizable α-hydroxy ester in the lactate appendage was compromised under the basic elimination conditions, a sample was hydrolyzed in methanol and catalytic PPTS. Conversion of the hydrolyzed lactate to the camphorsulfonate **108** and NMR analysis showed that partial racemization had in fact occurred.



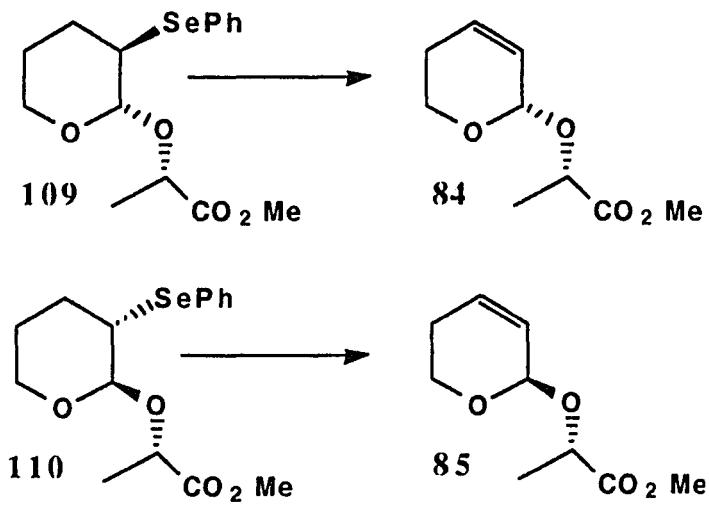
The racemic methyl 5,6-dihydropyranoside **47** was prepared from dihydropyran by the bromination /elimination pathway with MeOH and NaOMe, and then reacted with (S)-methyl lactate under mild acid catalysis in order to avoid base-induced epimerization of the lactate. This afforded the homogeneously chiral lactate pyranosides **84** and **85**, albeit in low yield (< 50%). Variation of the solvent, catalyst, and reaction temperature failed to improve this yield. The remaining mass balance consisted of acyclic decomposition and rearrangement products.



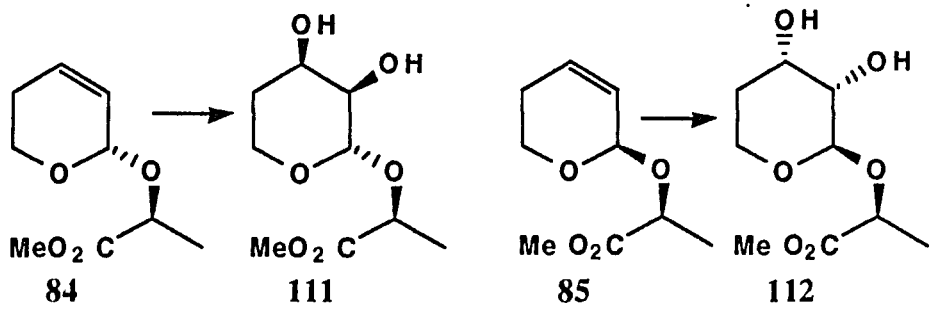
Aware of the thermodynamic instability of the dihydropyranosides,[48, 49] we hoped that a method of incorporating the lactate appendage under kinetic conditions would be more successful. The alkoxy-selenation reaction proved to be the method of choice.[13, 14] Phenylselenium bromide reacts rapidly with dihydropyran **9** to afford the 2-bromo-3-phenylselenyl-3,4,5,6-tetrahydro-2H-pyran. The acetal is formed trans to the phenylselenyl substituent upon addition of a solution of (S)-methyl lactate and triethylamine to give the pyranosides **109** and **110**.



This crude mixture of **109** and **110** could be subjected to oxidation with H_2O_2 at ambient temperature in a two-phase CH_2Cl_2 /H_2O, or alternatively the diastereomeric phenylselenyl-pyranosides could be separated and independently processed to obtain the dihydropyranosides **84** and **85**. Isolation of the selenated pyranosides requires one careful chromatography, followed by one clean-up column after independent oxidation. Separation of the mixture of dihydropyrans requires two careful chromatographies. Both methods give identical yields, with the less and more polar diastereomers **84** and **85** being obtained in 31 and 38% yields respectively.

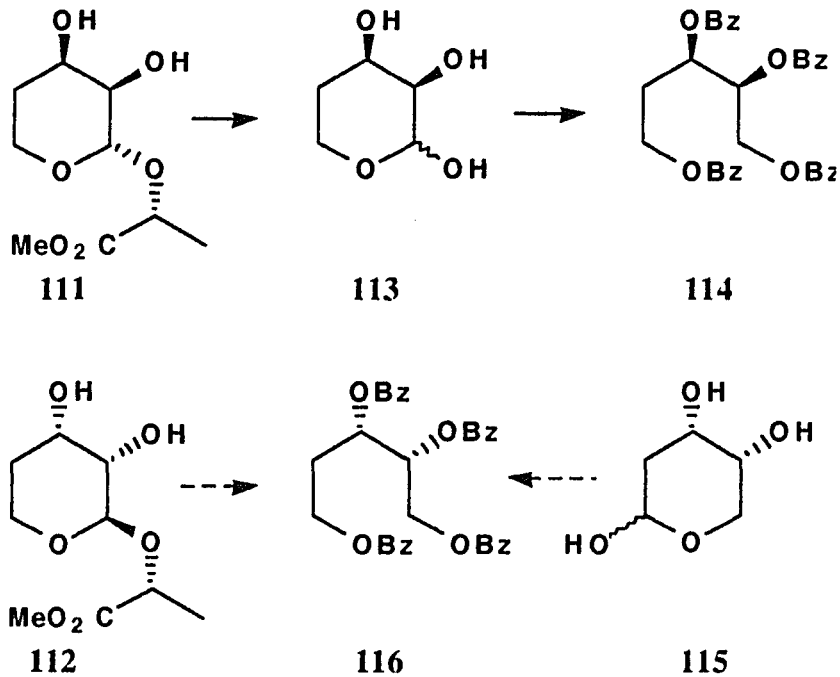


With the homogeneously chiral dihydropyranosides available, we were ready to enter the field of carbohydrate chemistry. The precedent for sterically directed cis-hydroxylation had been established in the racemic series. We were pleased to observe that dihydroxylation using catalytic osmium tetroxide/ N-methylmorpholine-N-oxide occurred exclusively on the face of the alkene opposite the anomeric appendage. The less polar dihydropyran **84** formed **111** in 61% yield, and more polar **85** gave **112** in 60% yield.



84 **111** **85** **112**

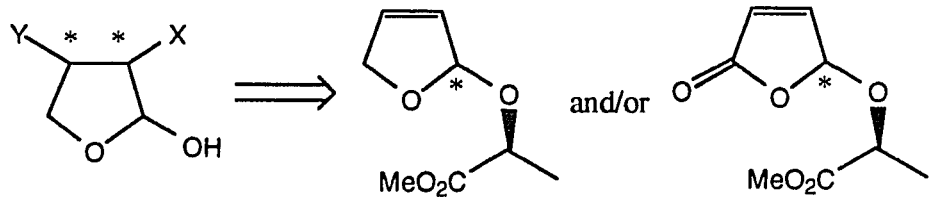
The potential for asymmetric functionalization of these chromatographically resolved dihydropyrans is clearly demonstrated with this rapid access to either enantiomer of 4-deoxyribose. The absolute configuration of the dihydroxylated pyranosides was established by conversion to the known perbenzoylated pentanetetrol **114** using the procedure of Verheyden and Moffatt.[126] Hydrolysis of the lactate appendage of **111** with 1N H_2SO_4 gave the corresponding lactol **113**. Reduction with $NaBH_4$ followed by reaction with excess benzoyl chloride gave the tetrabenzoate **114** in 89% yield, $[\alpha]_D$ +16.3 ^{o} (c 0.8, $CHCl_3$). Pyranoside **112** and natural 2-deoxyribose **115** were converted to identical tetrabenzoates **116** when subjected to the same reaction conditions, $[\alpha]_D$ -16.7 ^{o} (c 1.9, $CHCl_3$).



111 **113** **114**

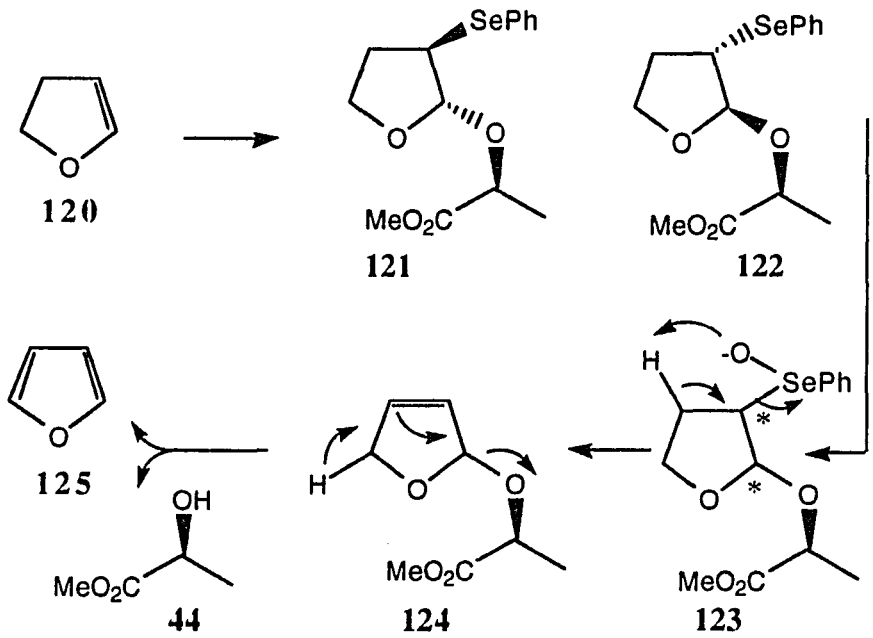
112 **116** **115**

At this point we were interested in the possibility of preparing and chromatographically resolving analogous dihydrofuranosides. A variety of tetroses and derivatives **117** could in principle be derived from a 2,5-dihydrofuranoside such as **118**, or from a substituted butenolide **119**.

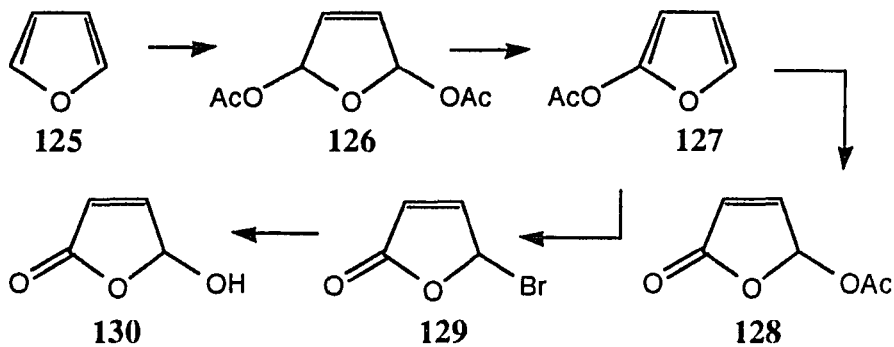


117 **118** **119**

The reaction of 2,3-dihydrofuran **120** with phenylselenyl bromide followed by (S)-methyl lactate and triethylamine gave the substituted tetrahydrofurans **121** and **122**, which were separable via chromatography (Rf 0.35, 0.27 respectively in 20% EtOAc/hexanes). Oxidation with hydrogen peroxide generates the selenoxide **123**, which eliminates phenylselenic acid to form the dihydrofuranoside **124** as an unstable intermediate that spontaneously eliminates methyl lactate **44** and furan **125**.



The route to butenolide **119** begins with the reaction of furan **125** and lead tetraacetate to produce 2,5-diacetoxy-2,5-dihydrofuran **126**.[50] Heating with catalytic 2-naphthylsulfonic acid in di-^{n}butyl phthalate causes elimination of acetic acid to afford 2-acetoxyfuran **127**.[51] Reaction with lead tetraacetate in acetic acid produces the acetate substituted butenolide **128**.[52] Unfortunately, the incorporation of methyl lactate did not occur under acidic, or neutral conditions and decomposition occurred under elevated temperatures and forcing conditions. Reaction of 2-acetoxyfuran **127** with bromine gave the bromo-substituted butenolide **129**.[52, 53] Attempts to introduce the methyl lactate appendage under basic conditions, e.g. trialkylamines, as the sodium salt, or with added bromophile $AgNO_3$ were unsuccessful. This compound reacts with water to give **130**, but again conditions that would permit the incorporation of methyl lactate were not discovered.[54] Although these initial studies were unsuccessful, further study is warranted and will almost certainly be productive.

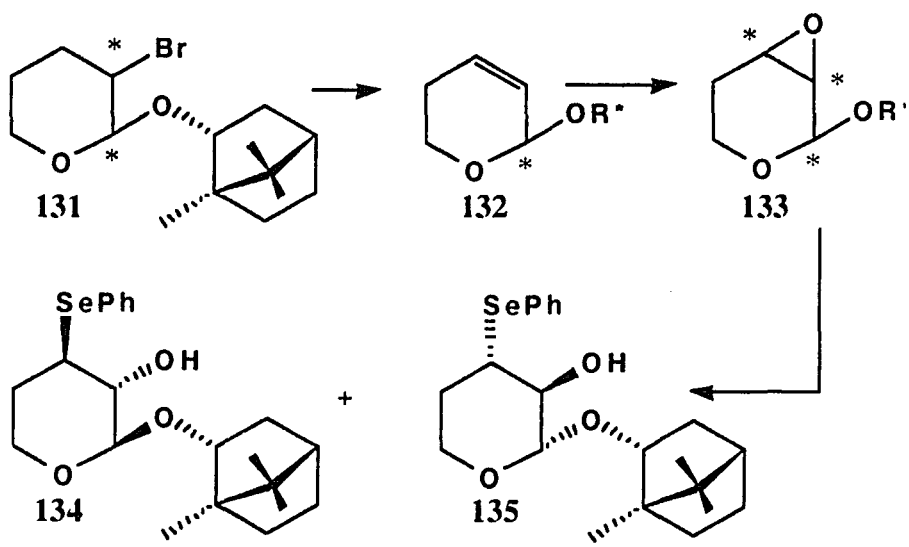


125 **126** **127** **130** **129** **128**

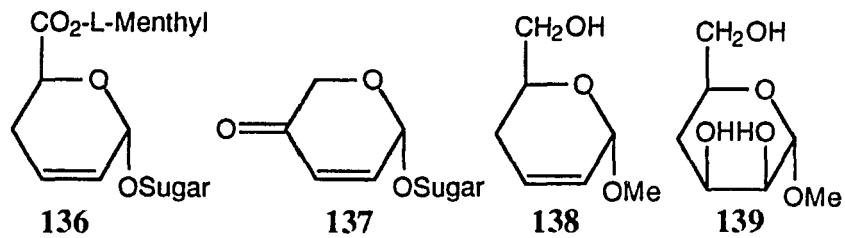
Conclusion

In this chapter a general method of chromatographic resolution of pyranosides is described. The homogeneously chiral dihydropyranosides made available with this methodology are precursors of deoxy-carbohydrates as demonstrated by a one-step preparation of both enantiomeric 4-deoxy-ribose derivatives. In this section a brief review of pertinent methodologies will be presented.

One example of an auxilliary-based diastereoselective functionalization of a dihydropentopyranoside substrate has been used in a synthesis of monic acid C.[11] Reaction of dihydropyran with bromine and (-)-1-borneol in the presence of N,N-dimethylaniline gave the diastereomeric bromotetrahydropyranyl ethers **131** in 82% combined yield as a 1:1 mixture. Attempts to achieve diastereoselective acetal formation with other chiral alcohols (i.e. nopinol, and 8-phenylmenthol) were unsuccessful as well. The diastereomeric bromides were not separable, so the mixture was subjected to elimination with DBU to afford the dihydropyrans **132** in 99% yield. These compounds were difficultly separable with HPLC, so again the mixture was subjected to sterically directed mCPBA epoxidation which afforded a 3:1 trans /cis ratio of **133**. Separation of the pair of trans epoxides by flash chromatography (61% yield) and reaction with sodium phenylselenide gave the hydroxy selenides **134** and **135**, that were at this point separable(48 and 49% yield). Subjecting these compounds to a parallel series of reactions allowed both to be incorporated in the total synthesis.

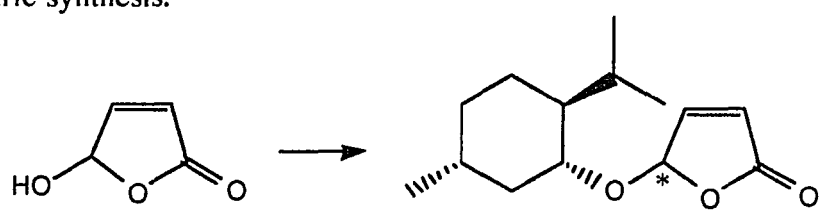


Various other approaches have provided access to chiral deoxyhexose derivatives. The cycloaddition of glyoxalate esters with 1-alkoxydiene substrates in which the alkoxy group is a sugar derivative gives a mixture of 4-diastereomeric pyranosides, which can be separated after conversion to their L-menthyl esters **136**.[5, 55, 56] Diastereomeric enones **137** can sometimes be separated and have been converted to disaccharides.[19] Racemic dihydrohexopyranoside **138** has been resolved as its 6-camphanyl ester.[7] 4-Deoxyhexopyranoside **139** was prepared from D-galactose in 6-steps.[57]



136 **137** **138** **139**

Enantiomerically pure butenolides were prepared from **130** by crystallization of the corresponding *d*- or *l*-menthyloxy derivatives **140**, and are useful compounds in asymmetric synthesis.[54]



130 **140**

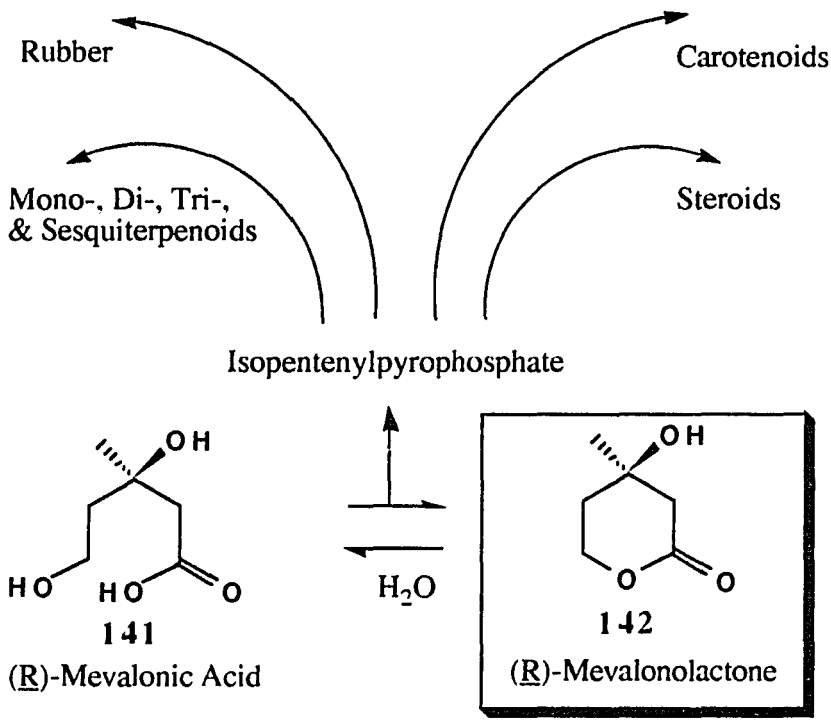
Our chromatographic resolution provides a rapid, general means of obtaining homogeneously chiral pyranosides that can be converted to a variety of substrates. In this chapter the ability of the anomeric appendage to sterically bias cis-hydroxylation of a dihydropyran was utilized to prepare 4-deoxyribose derivatives. This provided the foothold from which we explored the extension of this methodology to other systems.

CHAPTER 3

SYNTHESIS OF (R)-MEVALONOLACTONE

Introduction

(R)-Mevalonic acid **121** is an acetate-derived biogenetic precursor of the isoprenoid family of natural products.[58, 59, 60] (R)-Mevalonic acid, which exists in equilibrium with its δ-lactone form **142**, was shown to be the exclusive enantiomer that is enzymatically converted to mevalonate pyrophosphate. The biosynthetic pathway of mevalonate incorporation was elucidated by Cornforth and coworkers.[61] This pathway leads to an extremely diverse array of natural products including terpenes and steroids. Interest in the biosynthetic transformation of mevalonic acid in humans resides in the fact that more than one-half of the total body cholesterol is derived from *de novo* synthesis.[62] The rate-limiting step in cholesterol biosynthesis is the enzymatic reduction of hydroxymethylglutaryl coenzyme A to mevalonic acid.[63] Inhibitors of this enzymatic transformation are of great importance as potential hypocholesterolemic agents.[64]



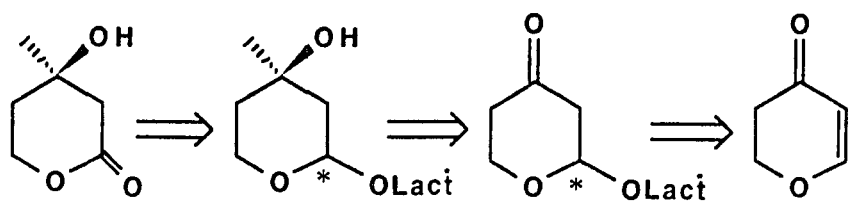
141
(R)-Mevalonic Acid

142
(R)-Mevalonolactone

We became interested in developing an efficient and versatile asymmetric synthesis of (R)-mevalonolactone that would make available a source of enantiomerically pure material and be readily amenable to the preparation of isotopically labelled derivatives. The structure of mevalonolactone can be conceptually related to a deoxygenated, branched pentopyranose. Its synthesis would illustrate the potential of our chromatographically resolved pyranosides as useful starting materials and provide a methodology that could possibly be extended to other systems.

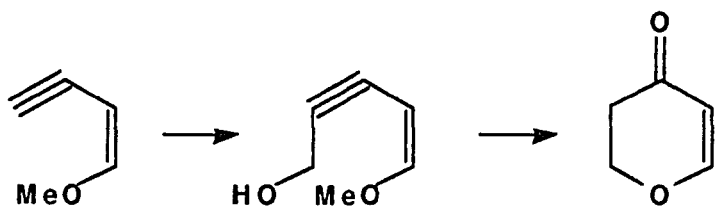
Synthesis

Our initial retrosynthetic analysis proceeded by the obvious formation of mevalonolactone **142** through hydrolysis and oxidation of pyranoside **143**. This tertiary alcohol would in turn result from delivery of a nucleophilic methyl group to the carbonyl of **144**, diastereofacially biased by 1,3-interactions with the anomeric appendage. We envisioned the possibility of isotopic- or radio-labelling in this step. Ketone **144** was anticipated to be chromatographically resolved as its (S)-methyl lactate pyranoside, in analogy to other pyranosides, and would be formed from the simple racemic starting material 2,3-dihydro-2H-pyran-4-one **145**.



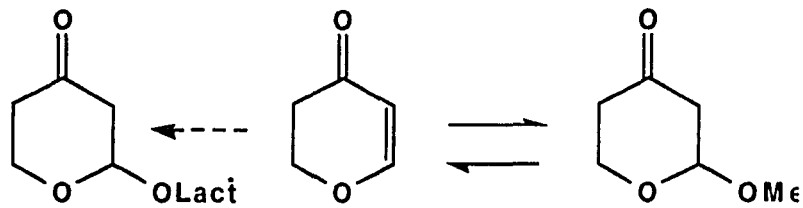
142 **143** **144** **145**

2,3-Dihydro-4H-pyran-4-one **145** had previously been prepared via cycloaddition of formaldehyde and substituted silyloxy-butadienes under Lewis acid catalysis, but no applications in synthesis have been reported.[25,27] The synthesis of a variety of substituted 2-alkyl-2,3-dihydro-γ-pyrones had been accomplished through addition of the lithium acetylide of readily available and inexpensive 1-methoxy-1-buten-3-yne to aliphatic aldehydes, followed by acid catalyzed cyclization to the pyrone.[65] We extended this methodology to prepare our desired unsubstituted pyrone. Formation of the lithium acetylide of **146** was followed by either direct introduction of gaseous formaldehyde, or a higher yield two-step procedure that involves addition to ethyl formate, followed by in situ DIBAL reduction which gave the propargylic alcohol **147**. This material was directly subjected to acid catalyzed cyclization and the product isolated by distillation under reduced pressure, affording **145** on a several gram scale.



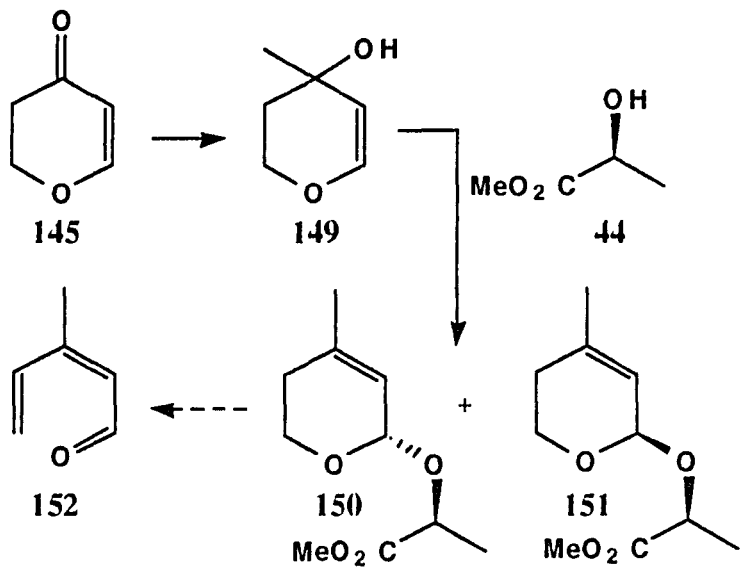
146 **147** **145**

Initial attempts to directly introduce the (S)-methyl lactate appendage under acid catalysis (PPTS, p-TsOH, TMS-OTf, BF_3-Et_2O), or under base catalyzed Michael addition (triethylamine, pyridine, sodium hydride) in a variety of solvents and in neat methyl lactate failed to provide **144** and resulted in decomposition under forcing conditions. This failure was confounded by the fact that the simple methanol adduct **148** could be formed under both acidic (TsOH) and basic conditions (NaOMe). However the precarious stability of this pyranoside was evident in the facile reversion to the thermodynamically favored pyrone **145**. The reluctance of the lactate moiety to add is attributed to steric congestion and a propensity for self condensation that is demonstrated with the results of a neat mixture of **145** and (S)-methyl lactate, pressurized to 6 atm, which gave **145** and lactate dimer as the only products.

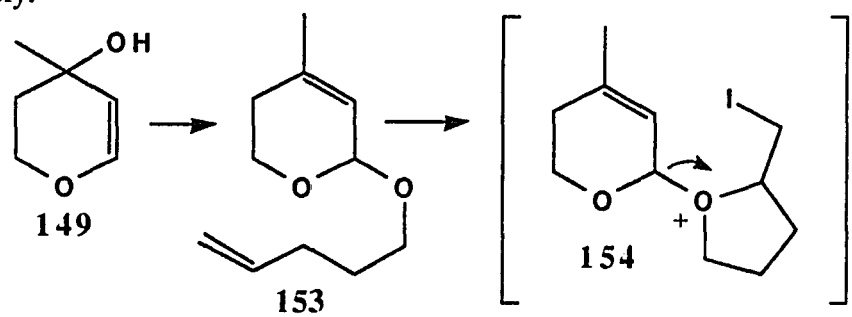


144 **145** **148**

These results forced us to alternate the order of synthetic steps. Reaction of **145** with methyllithium at -78°C proceeded with exclusive 1,2-carbonyl addition, affording the unstable tertiary allylic alcohol **149**. Direct introduction of the (α)-hydroxy ester via acid catalyzed expulsion of H_2O with concurrent rearrangement to the desired chromatographically separable 5,6-dihydropyranoses **150** and **151** proceeded in ~40% combined yield. A survey of reaction conditions varying solvents, catalysts, and dehydrating agents failed to improve this yield. Under all conditions the formation of acyclic ring cleavage products occurred and the thermodynamic decomposition product was the dienal **152**. These efforts recalled the poor results obtained during our earlier attempts to prepare dihydropyrans under thermodynamic conditions, and led us to look for a solution in a corresponding kinetically controlled pyranoside forming reaction.



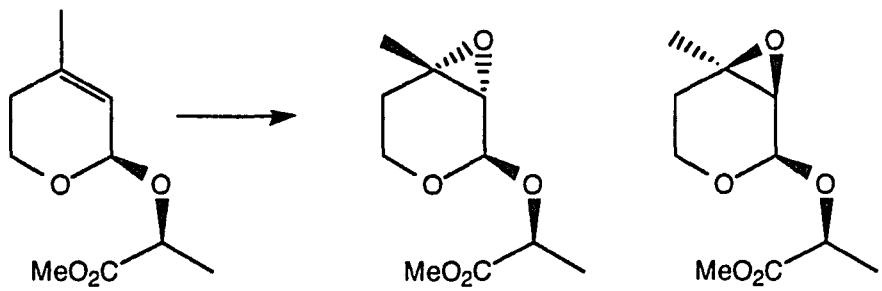
During a fortuitous discussion after presentation of a seminar, Professor B. Fraser-Reid suggested the use of a pentenyl-pyranoside activated by a halonium ion to generate the oxocation, as developed for use in oligosaccharide synthesis.[66] Reaction of **149** with an excess of 4-penten-1-ol afforded the "activated" pentenyl-pyranoside **153** in 91% yield over two steps. The effectiveness of this transformation reflects the comparative ease of forming a pyranoside with a simple primary alcohol. Reaction of **153** with iodonium bis-collidine perchlorate[127] presumably proceeds by initial formation of a halonium ion that is in equilibrium with the oxonium ion intermediate **154**. Elimination of the iodomethyltetrahydrofuran moiety generates the allylic oxocarbenium ion which then reacts with added (S)-methyl lactate or (S)-methyl mandelate to form the chromatographically separable less- and more-polar diastereomers of **150** and **151** (R=Me), or **155** and **156** (R=Ph), in 36% and 35% yields respectively.



150: R= Me
155: R= Me

151: R=Me
156: R=Me

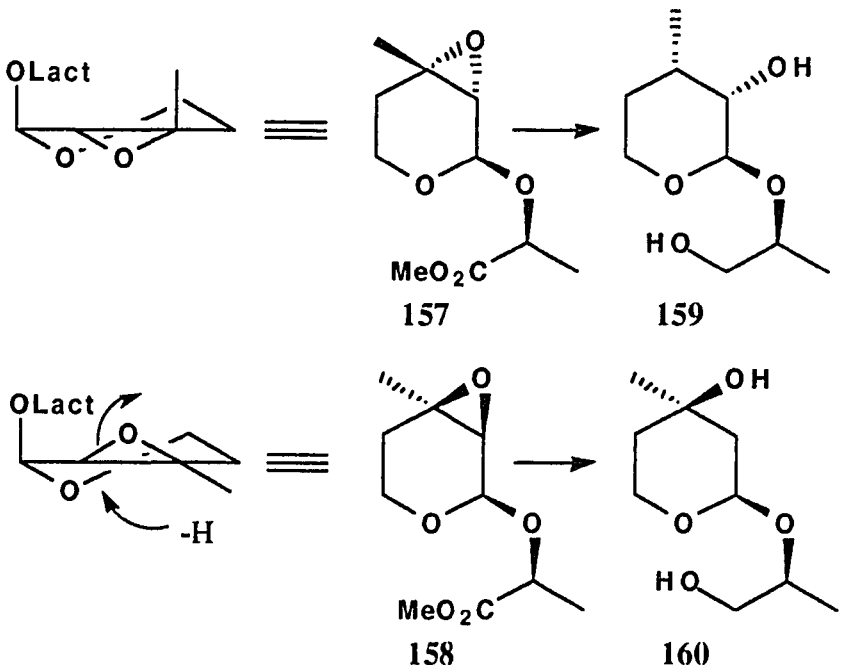
With the availability of the dihydropyran ensured, a method of selectively introducing the 4-hydroxyl was required. No reaction was observed when dihydropyranosides possesing an α-hydroxyester appendage were subjected to oxy-mercuration conditions. A two-step epoxidation/hydride ring opening seemed feasible for introduction of the tertiary alcohol. Previous work using racemic dihydropyrans of simple alcohols demonstrated selective (~3:1) formation of the anti-epoxide due to reagent delivery to the less sterically congested face of the alkene. Direct epoxidation of the methyl lactyl dihydropyran **151** with mCPBA gave a chromatographically separable mixture (~2.5 : 1) favoring the anti-diastereomer **157** over the syn-epoxide **158** as it was expected from simple steric considerations.



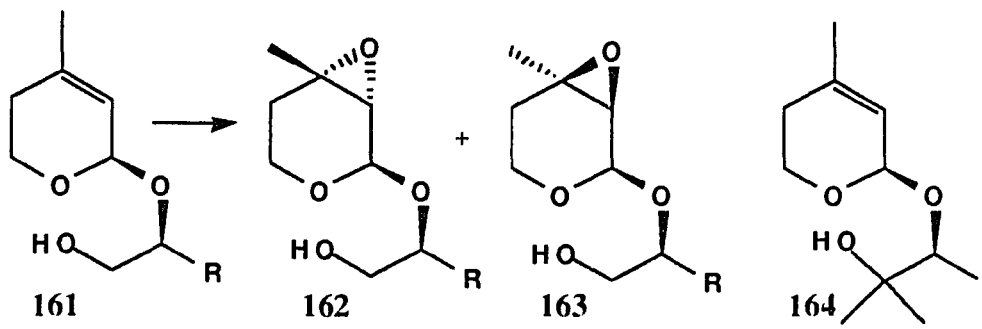
151 **157** **158**

The factors influencing nucleophilic opening of epoxy-tetrahydropyranosides and the preference for trans-diaxial ring opening were discussed in Chapter 1. One additional consideration is that nucleophilic attack at the less substituted position of the epoxide is normally favored due to fewer steric interactions. With our system the predominating anti-epoxide **157** should open trans-diaxially via attack at the tertiary epoxide position to give the undesired 3-hydroxyl substituted pyranoside **159**, while the minor syn-epoxide **158** would be expected to give the desired 4-hydroxyl compound **160**. These expectations were realized experimentally

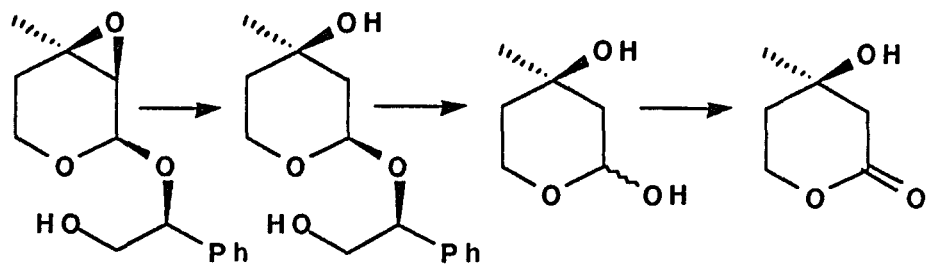
compound **160**. These expectations were realized experimentally as $LiAlH_4$ reduction caused rapid conversion of the syn-epoxide **158** exclusively to the 4-hydroxypyranoside **160**, while reaction of the anti-epoxide **157** was slow and favored the undesired regioisomeric product **159**. Attempts to hydrolyze the anomeric appendage of **157** prior to the reduction step instead resulted in diol formation from epoxide cleavage. At this point what we really required was a means to overcome the steric bias of the appendage that would allow us to preferentially form the syn-epoxide.



Peroxyacids are electrophilic reagents and susceptible to the directing influence of nearby polar functional groups.[44] We were able to prepare the desired syn-epoxides simply by converting the sterically demanding ester moiety into a hydrophilic alcohol, capable of hydrogen-bonding to assist in the delivery of the peroxy acid to the proximal syn-face of the alkene. Reduction of the lactate pyranoside **151** gave the alcohol **161** (R=Me), which underwent epoxidation with mCPBA and preferentially forming the desired syn-epoxide **163** over the anti-epoxide **162** in a ratio greater than 2:1. Lowering the temperature increased the selectivity, and using CH_2Cl_2 as solvent increased the rate of reaction relative to ether solvents. Attempted epoxidation with t-butyl hydroperoxide / $VO(AcAc)_2$ resulted in decomposition. Addition of two equivalents of methyllithium gave the tertiary alcohol **164** which also underwent epoxidation favoring the syn-isomer (3:1). Optimum results were realized with the reduced mandelate auxilliary **161** (R=Ph), which underwent highly selective syn-epoxidation with mCPBA in CH_2Cl_2 at 0°C (13:1). The resulting diastereomeric epoxides were easily separated by column chromatography.



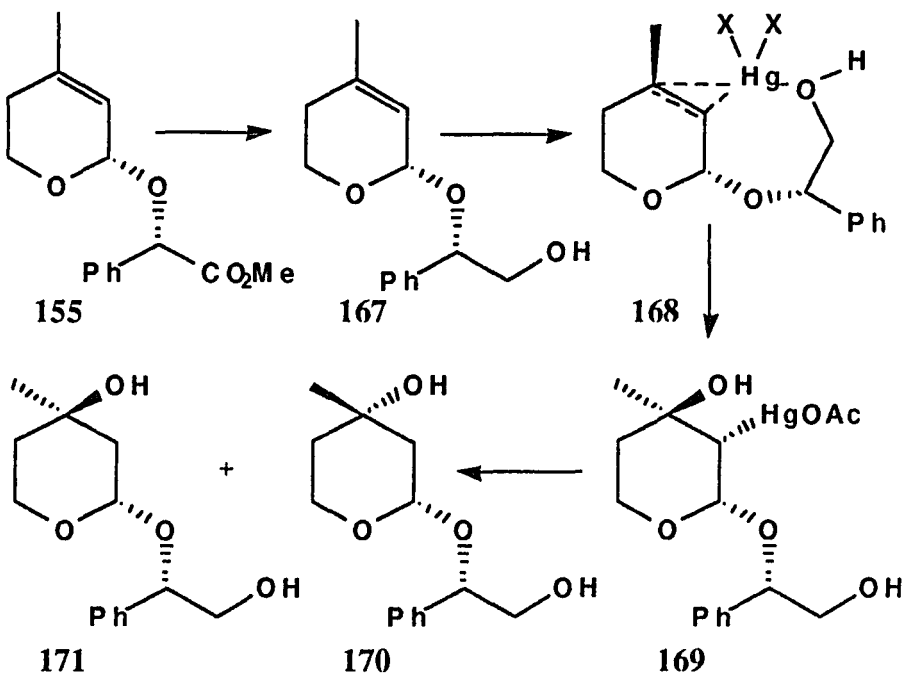
Chromatographic separation of the epoxides and subsequent reaction of the syn-epoxide **163** with $LiAlH_4$ afforded the tertiary alcohol with the desired (R)-configuration **165**. Ring opening with lithium aluminum deuteride or triteride would give material labelled stereospecifically at C-2. Our synthesis was completed by hydrolysis to the lactol **166** (10% aqueous HCl/ THF), followed by PCC oxidation to mevalonolactone **142** (73% yield over two steps). The absolute stereochemistry was confirmed by comparison of the optical rotation of our synthetic material to the maximum reported literature value; Synthetic: $[\alpha]^D$ -20.0° (c 0.4, EtOH), Lit.[67]: $[\alpha]^D$ -23° (c 0.85, EtOH). The enantiomeric excess is thus at least 87%. The observed rotation corresponds to that obtained by Eliel,[68] who performed NMR experiments with added Eu(hfc) which showed a single enantiomer. The enantiomeric purity of our starting (S)-methyl mandelate was 99%.



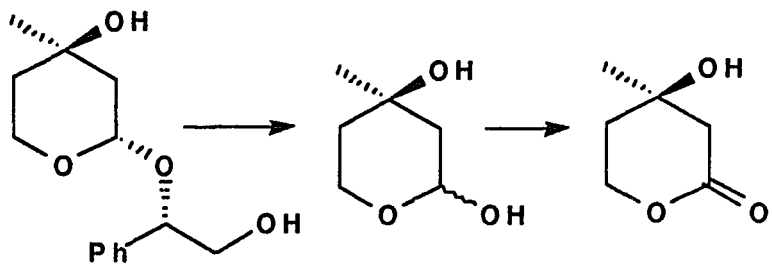
163 **165** **166** **142**

The overall yield of mevalonolactone obtained following the epoxidative synthetic pathway was 17%. A criticism of resolution based strategies is that up to one-half of the material is "wasted." Our unsaturated pyranosides are chromatographically resolved at the outset of a synthetic venture and once in hand, both can serve as useful chiral building blocks. This is in contrast to a "traditional resolution" where often both the material with the undesired configuration and the resolving agent remain in the mother liquor of a crystallization. An additional concern is that obtaining the other enantiomer, if it is desired, may not be straightforward if the enantiomeric resolving agent is not available, e.g. if an alkaloid is employed. The success of the reduced mandelate appendage for controlling epoxide formation in the more polar diastereomer challenged us to develop a chemo-complementary approach that would convert the less polar mandelate dihydropyranoside with (S)-anomeric configuration **155** to the desired 4-(R)-hydroxyl configuration. Accomplishing this would provide efficient use of both resolved pyranosides and demonstrate an additional synthetic protocol.

Consideration of the mechanism of oxymercuration suggested that while an ester appendage may sterically prevent reaction, conversion of **155** to the alcohol **167** may allow the appendage to participate in the delivery of the mercuric ion. The mercury (II) ion should be delivered preferentially syn to the appendage via **168**, and capture of water (or acetate) would occur by backside attack. The resulting organomercurial species **169** should have the desired (R)-hydroxyl configuration! This reaction indeed proceeded successfully in aqueous THF at 0°C, and upon reduction with $NaBH_4$ afforded an (8 : 1) mixture of chromatographically separable alcohols **170** and **171** favoring the desired product **171**.



The synthesis was completed by hydrolysis of **171** to the lactol **166** and oxidation with PCC as described previously, affording (R)-mevalonolactone **142** in 76% yield, that was identical in all aspects to material prepared by the epoxidative pathway. The yield of (R)-mevalonolactone obtained by following this oxymercuration pathway was 17%, which gives a combined yield of 34% over 9 steps from the pyrone **145**, and utilizes both resolved pyranosides.

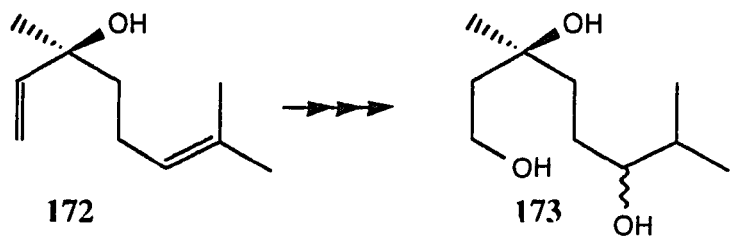


171 **166** **142**

Conclusion

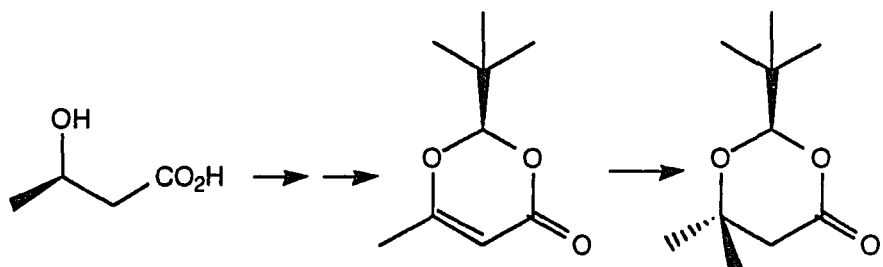
The previous section describes an efficient approach to (R)-mevalonolactone. Interest in this compound has initiated several asymmetric syntheses, and in this section a brief survey of these previous approaches will be presented for comparison.

(+)-Linalool **172** has been converted to (R)-mevalonolactone via **173**, in which the original chirality of the tertiary alcohol is preserved (21%, 5 steps, 100% ee).[67] Similarly the (S) enantiomer can be prepared from (-)-linalool.[69]



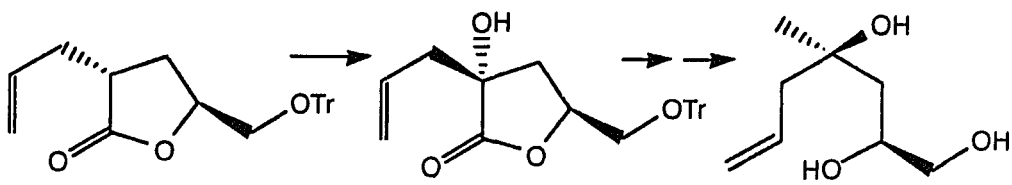
172 **173**

(R)-3-Hydroxybutanoic acid **174** was converted to (S)-mevalonolactone (10%, 8 steps, 91% ee) with the key asymmetric step being allylation of the chiral unsaturated dioxolane **175** to **176**, followed by ozonolysis, reduction and cyclization.[70]



174 **175** **176**

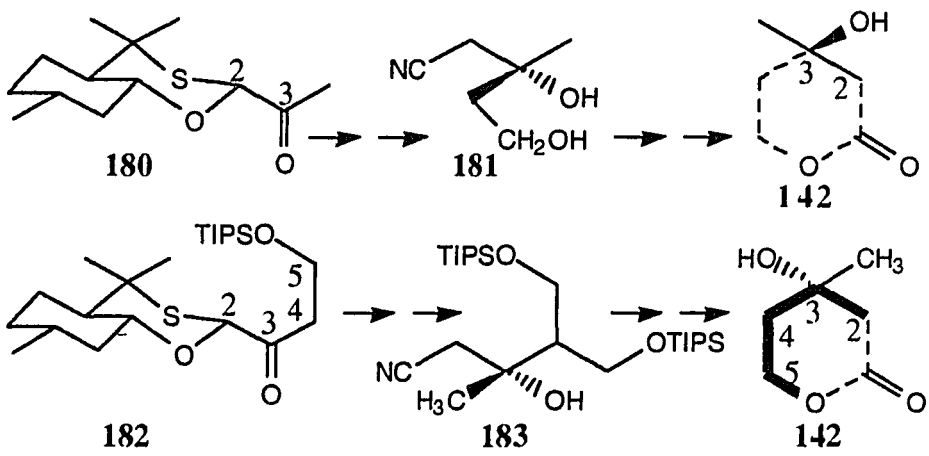
Chiral lactone **177**, derived from (S)-glutamic acid or (D)-mannitol, was converted to (R)-mevalonolactone (11%, 8 steps, 100% ee) and the (S)-enantiomer (20%, 9 steps, 100% ee).[71] The synthesis involves oxidation to **178** and conversion to alkene **179** that can be processed to either enantiomer depending upon the order of ozonolysis and periodate oxidation.



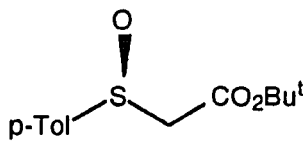
177 **178** **179**

Chiral oxathianes derived from (+)-pulegone have been used to prepare both (R) and (S)-mevalonolactone. The C-2, C-3, methyl-segment of the (R)-target **142** can be obtained from **180** Nucleophilic addition of the C-4, C-5 segment, reductive removal of the appendage and displacement with cyanide gives **181**, that was converted to **142** (40% yield, 10 steps, >87% ee).[68, 72] **182** Possesses the C-2 to

(40% yield, 10 steps, >87% ee).[68, 72] **182** Possesses the C-2 to C-5 backbone of target **142**. Nucleophilic addition of methyl to **182**, followed by reductive cleavage of the auxilliary and displacement with cyanide gives **183**, that could be converted to the (S)-product **142** (25% yield, 6-steps, >94% ee).[73, 74]



The enolate of chiral sulfoxide **184** possesses the C-1, C-2 segment and was converted to the (R)-product (39%, 4 steps, 17% ee).[75] Racemic anhydride **185** has been kinetically resolved with a cinchona alkaloid to give the mono-methyl ester, which was then reduced to (R)-mevalonolactone (73%, 2 steps, 31% ee),[76, 77] **185** was also kinetically resolved as the monoamide of a chiral binapthyl (44%, 4 steps, 58% ee).[78] The racemic monosodium salt **186** has been kinetically resolved with 0.1 equivalents of (+)-camphorsulfonic acid (CSA) to (R)-mevalonolactone (62% based on CSA, 1 step, 86% ee).[79]



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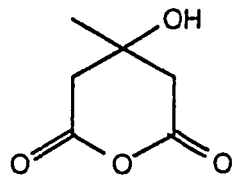

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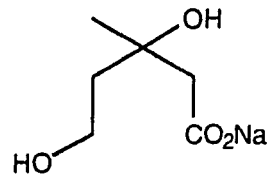
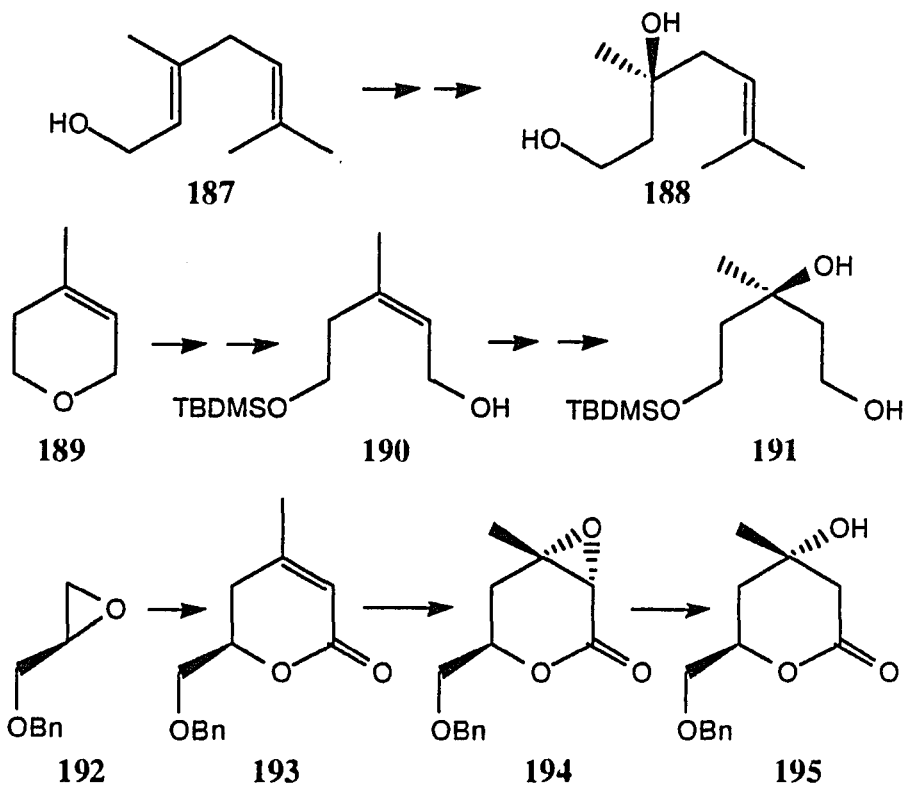


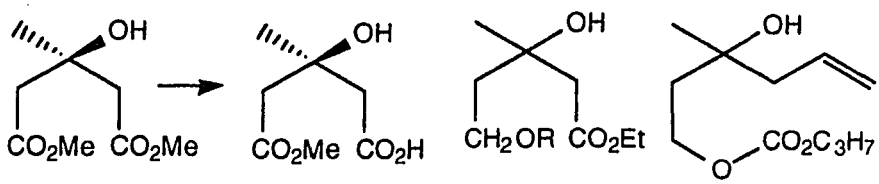
186

The Sharpless epoxidation has been used in two syntheses of mevalonolactone. Asymmetric mono-epoxidation of the allylic alcohol moiety in diene **187** and regioselective epoxide opening with $LiAlH_4$ gave **188**, which upon ozonolysis and further oxidation gave (R)-mevalonolactone (26% yield, 5 steps, 82% ee).[80] Another route converts 4-methyl-5,6-dihydropyran **189** to allylic alcohol **190**, epoxidation, opening with $LiBH_4$ gives **191**, which upon oxidation and ring-closure provides (R)-mevalonolactone (29%, 8 steps, >86% ee).[81] (S)-O-Benzylglycidol **192** has been used for the synthesis of both (R)- and (S)-mevalonolactone. Reaction with methyl lithiopropiolate followed by treatment with lithium dimethylcuprate and cyclization gave the unsaturated lactone **193**. Nucleophilic epoxidation gave epoxide **194** which was cleaved regioselectively with sodium phenylseleno(triisopropyloxy)borate to afford the

β-hydroxylactone **195**. This compound could be converted to (S)-mevalonolactone by sequential saponification, periodate cleavage and sodium borohydride reduction of the aldehyde (43%, 9 steps, 95% ee). Reduction of the lactone, periodate oxidation, and then Jones oxidation gave (R)-mevalonolactone (38%, 9 steps, 95% ee).[82]



Enzymatic methods have been applied to mevalonolactone syntheses. Pig liver esterase (PLE) converts the meso-diester **196** to mono-ester **197**; selective reduction of the ester and cyclization provides (R)-mevalonolactone (50%, 3 steps, 71% ee).[83] PLE preferentially hydrolyzes esters **198** with (R)-configuration from a racemic mixture to afford (R)-mevalonolactone (0-45%, 3 steps, 0-55% ee).[84] Racemic carbonate **199** undergoes enzymatic kinetic resolution to afford (R)-mevalonolactone (10%, 3 steps, 52% ee).[85]

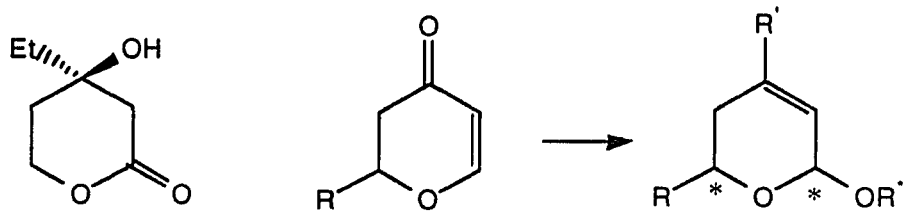


196 **197** **198** **199**

Oxidation of meso-diols has been used in mevalonolactone syntheses. Horse liver alcohol dehydrogenase converts diol **200** to the hemiacetal, which can be oxidized to (S)-mevalonolactone (21%, 2 steps, 14% ee).[86] This diol **200** was also converted to (S)-mevalonolactone by bacterial oxidation with strains of Gluconobacter (17-34%, 1 step, 27-79% ee).[87]

200

Our synthesis of (R)-mevalalonolactone uniquely involves diastereoselective functionalization of an intact pyranose ring. Each of the other syntheses proceeds through an acyclic intermediate at some point. The advantage of our approach is that we can easily extend it to prepare similar systems. The possibility of isotopic labelling was mentioned earlier and could be conveniently accomplished stereospecifically at C-2 during the epoxide opening or organomercurial reduction with a deuterated or tritiated metal hydride reagent. [88, 89] By switching the synthetic protocol applied to the resolved dihydropyrans, the enantiomeric (S)-mevalalonolactone would be obtained. (R)-Homo-mevalonolactone **201** is the biogenetic precursor of insect juvenile hormone, which is converted into an extremely diverse array of natural products.[90, 91] We can prepare this compound by substituting methyllithium with ethylmagnesium bromide in the addition to the pyrone. By starting with substituted pyrones **202** the chirality of the anomeric center can be used to resolve an additional stereocenter via **203**, and should provide access to other highly functionalized pyranosides.



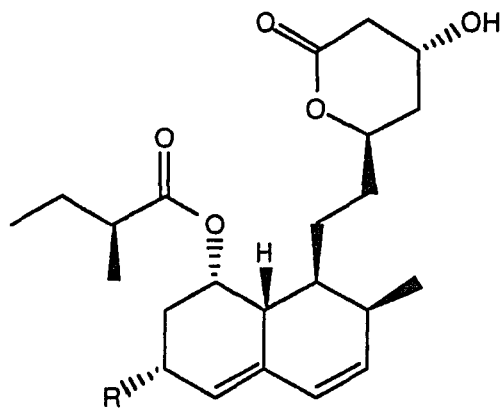
201 **202** **203**

CHAPTER 4

ASYMMETRIC SYNTHESIS OF A MEVINIC ACID PRECURSOR

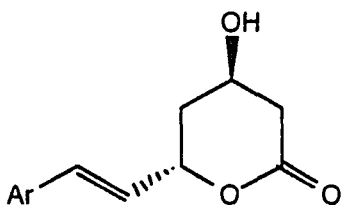
Introduction

In 1976 a potent competitive inhibitor of hydroxymethylglutaryl coenzyme A reductase (HMG CoA reductase) was isolated independently from the metabolites of *Penicillium citrinum* and *P. breviicompactum* by Endo et al. at the Sankyo Co. and Brown et al. at Beecham Pharmaceuticals respectively.[92, 93] The new compound called ML236B and compactin by the two groups respectively was shown to have structure **204**. A related compound named mevinolin was isolated in 1980 by Alberts et al. at Merck, Sharp & Dohme and shown to have the absolute stereostructure **205**.[94]

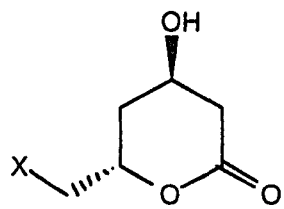


204: R = H, Compactin
205: R = Me, Mevinolin

Compounds distinguished by a β-hydroxy-δ-lactone unit attached by an ethylene bridge to a highly functionalized hexalin or octalin portion are collectively referred to as mevinic acids. The potent inhibitory activity of these compounds aroused considerable interest as possible hypocholesteremic agents. More than one-half of the total body cholesterol in humans is derived from *de novo* synthesis [62] and the rate limiting step in cholesterol biosynthesis is the reduction of HMG CoA to mevalonic acid.[63] Compactin has been shown to lower serum cholesterol levels in humans [95] and extensive biological studies have led to structurally simpler synthetic analogues possessing in common a chiral β-hydroxy-δ-lactone portion. Anologues of type **206** exhibit increased activity up to a factor of 2.8 relative to natural compactin.[96] The biological activity of analogues substituted with simple phenol **207** and thiophenol **208** moieties is largely retained.[97]



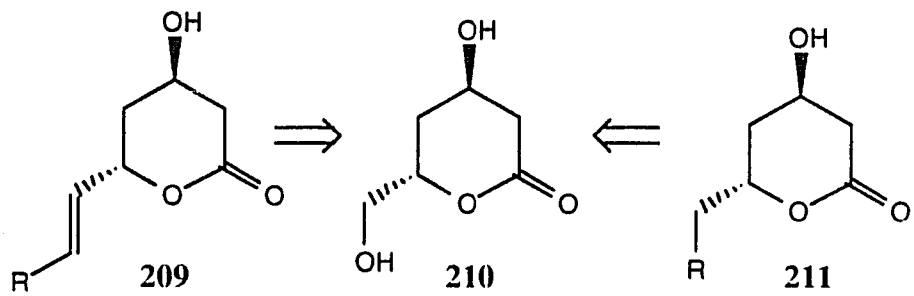
206



207: X = OAr
208: X = SAr

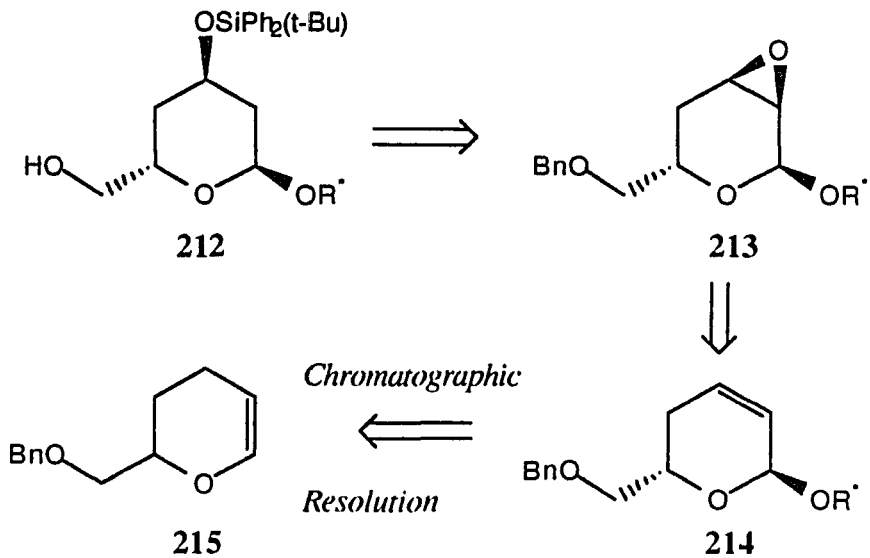
The importance of hypocholesterolemic agents for the health care industry coupled with the fact that the chiral lactone portion of mevinic acids and analogues is necessary for biological activity provides incentive for the development of efficient syntheses of chiral intermediates that can be utilized in a total synthesis or elaborated into new and potentially more effective agents. Our experiences with the versatility of unsaturated pentopyranose systems prompted an investigation of the potential for similar manipulations of unsaturated hexopyranoses.

Since compounds with either an ethyl or an ethylene bridge connecting the lactone moiety are known to exhibit biological activity we chose to prepare a penultimate chiral precursor that could be elaborated easily to both. The primary alcohol of a suitably protected pyranoside **210** could be converted to an unsaturated system **209** by successive oxidation and olefination, while the ethyl linkage of **211** could be formed by first conversion of the hydroxyl to a suitable leaving group followed by nucleophilic displacement.

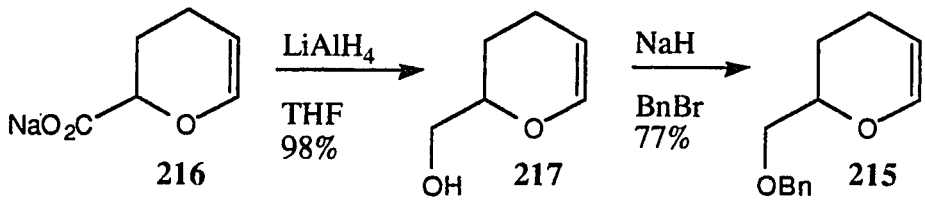


Synthesis

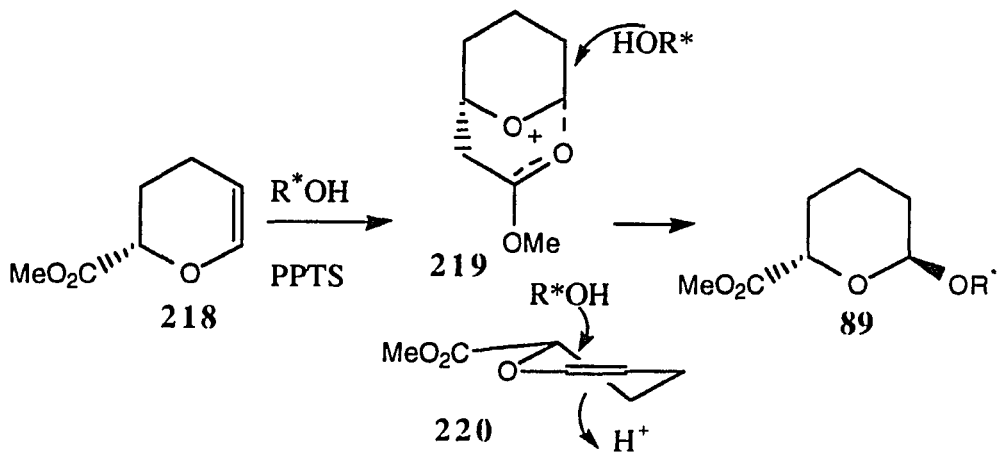
Our retrosynthetic analysis proceeds by introduction of the requisite 4(R)-hydroxyl substituent in **212** by hydride induced epoxide opening of **213**. This epoxide **213** would be obtained from a homogeneously chiral 5,6-dihydropyranoside **214** available via chromatographic resolution of the diastereomeric pyranosides formed from an appropriate enantiomerically pure α-hydroxy ester and racemic 3,4-dihydropyran **215**. The salient features of this synthetic plan are the formation of the required trans stereochemical relationship of appendages at the anomeric and 6-position of the dihydropyran ring and reliance on the anomeric appendage to control further functionalization of the alkene.



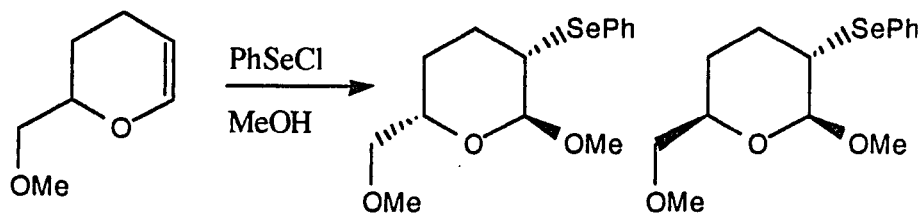
Our synthesis begins with the readily available and inexpensive sodium salt **216** (5 g, $18.80, Aldrich). Reduction with $LiAlH_4$ gave **217** which was then benzylated to provide the racemic starting material **215** in 77% yield over 2 steps. This compound possesses all six carbons required for the mevinic acid precursor. This reaction can be performed on a large scale and the product purified by distillation .



Previous experience with the 6-carbomethoxydihydropyran **218** had auspiciously demonstrated the potential for stereochemical linking of substituents at the anomeric and 6-position in **89**, presumably either via direct stabilization of the intermediate **219** formed under thermodynamic conditions, or by preferential reaction of the half-chair conformer **220** with the substituent pseudo-equatorial leading to the addition product in a chair conformation. We considered the possibility of preparing a racemic dihydropyranoside and introducing the α - hydroxy ester under thermodynamic conditions. Our early experience with the low yields that resulted from attempts to introduce lactate and mandelate auxiliaries into unsaturated pyranosides prompted us to investigate the alkoxyselenation reaction.

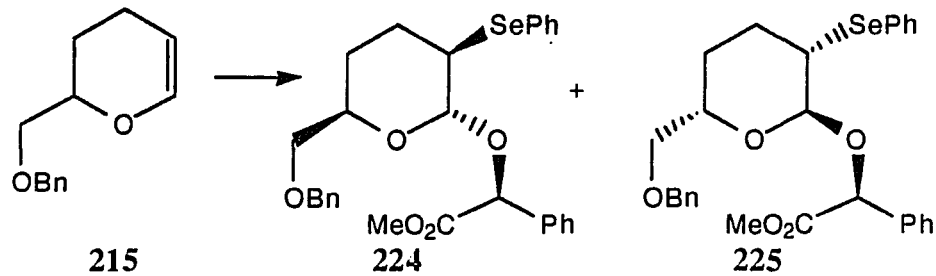


Kozikowski had investigated the racemic alkoxyselenation of **221** and observed formation of both diastereomers **222** and **223**, with a combined yield of 62%. The trans relationship of alkoxy and selenium substituents was generated in both products. The correlation of the anomeric methoxy appendage to the 6-substituent was solvent dependant. In CCl_4 the ratio of **222** to **223** was 1 : 2.3, while using tetrahydrofuran as solvent reversed the preferred product ratio to 1.9 : 1.[13]



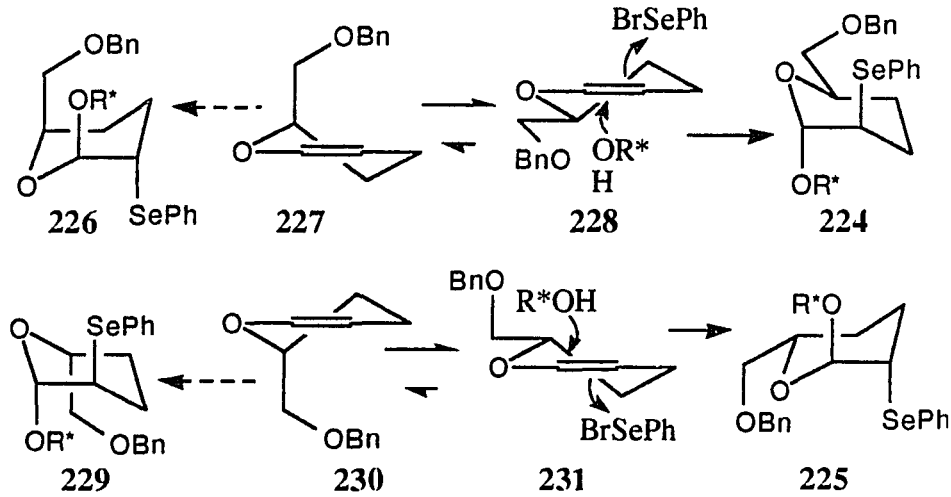
221 **222** **223**

Upon reaction of **215** with phenylselenyl bromide followed by (S) - methyl mandelate and triethylamine we were delighted to observe selective formation of exclusively the phenylselenyl-(S)-methyl mandelate derivatives **224** and **225** possessing a trans relationship of the anomeric appendage to both selenium- and benzyloxymethyl- substituents. Chromatographic resolution of the diastereomeric phenylselenyl-pyranosides required only one passage through silica gel 60 (column loading 1g per 100g silica, α = 1.54, 10% EtOAc/hexanes). The isolated yields of **224** and **225** were 34% and 39% respectively. The assignment of absolute stereochemistry was first assumed in analogy to the unsubstituted pyranosides, and later corroborated by conversion to a known mevinic acid precursor (vide infra).

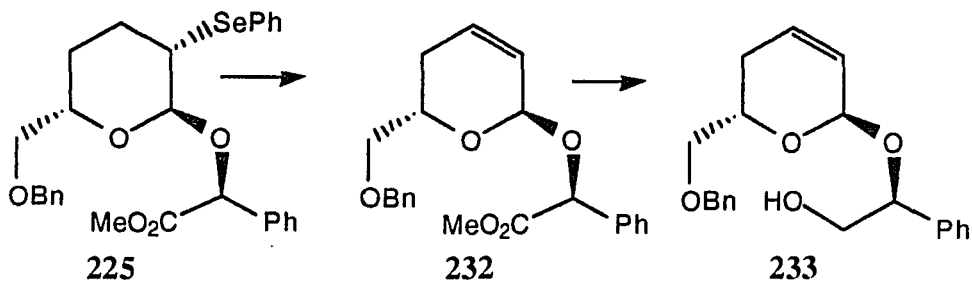


215 **224** **225**

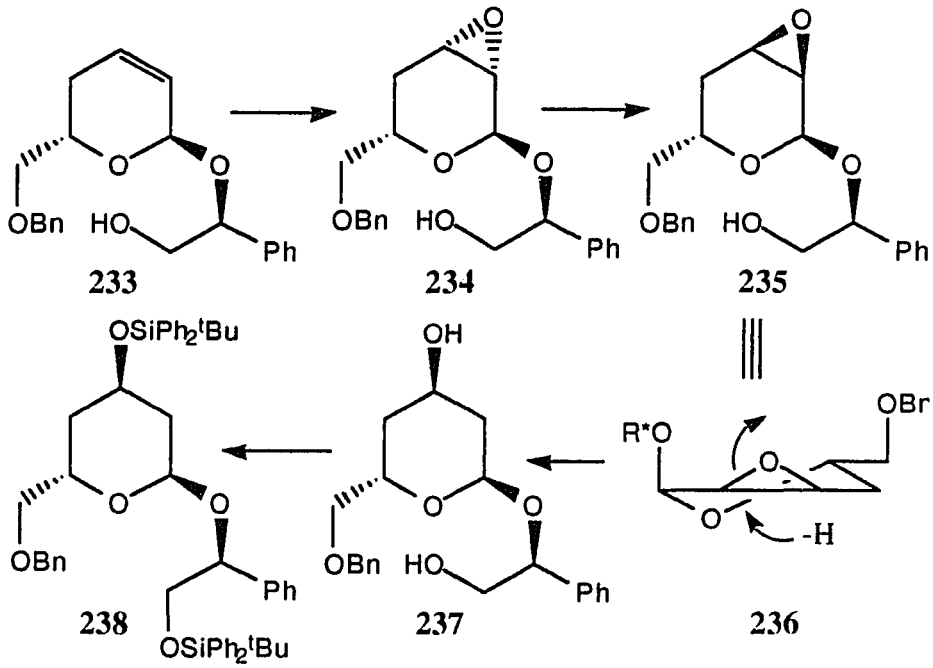
The reason for the observed trans-relationship of the anomeric and 6-substituents may be that incorporation of the bulky mandelate appendage occurs via the dihydropyran conformer with the benzyloxymethyl-substituent equatorial, e.g. **228** and **231** that lead to the chair conformers of **224** and **225** that limit 1,3-diaxial interractions. The alternative participation of pseudo-axial conformers **227** and **230** would lead to products **226** and **229** in which severe 1,3-diaxial interractions occur between the mandelate- and benzyloxymethyl-substituents.



Oxidation of the more polar diastereomer **225** with H_2O_2 generated the selenoxide that subsequently undergoes syn-elimination to afford the 5,6-dihydropyranoside **232** in 89% yield. Reduction of the mandelate ester with $LiAlH_4$ provided **233** in 95% yield, which is equipped with a primary alcohol capable of participating in delivery of a peroxy acid to the face of the alkene syn to the appendage, overriding the opposing steric bias of the 6-benzyloxymethyl appendage.

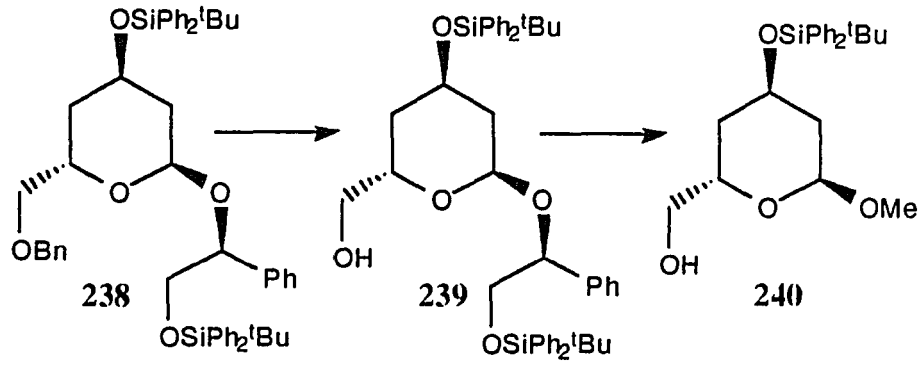


Treatment of **233** with mCPBA afforded a 12 : 1 mixture favoring syn-epoxide **235** over anti-epoxide **234** The epoxides were separated by column chromatography. Diaxial opening of the syn epoxide **235** occurs with $LiAlH_4$ via **236** and provides the desired 4-(R)-hydroxyl-substituted pyranoside **237** in 94% yield as the sole product. Protection of both free alcohols in **237** as the t-butyldiphenylsilyl ethers occurred quantitatively in dichloromethane with excess imidazole to afford **238.**



Compound **238** contains three differentially protected oxygen functionalities : benzyl ether, alcoholic silyl ether, and acetal. Removal of the benzyl ether by hydrogenation over 10% palladium on carbon catalyst afforded **239** in 99% yield. This compound is now available as an intermediate for the synthesis of mevinic acids. Saturated analogues can be obtained by conversion of the primary hydroxyl group to the iodide, which should undergo coupling with nucleophilic reagents. Unsaturated

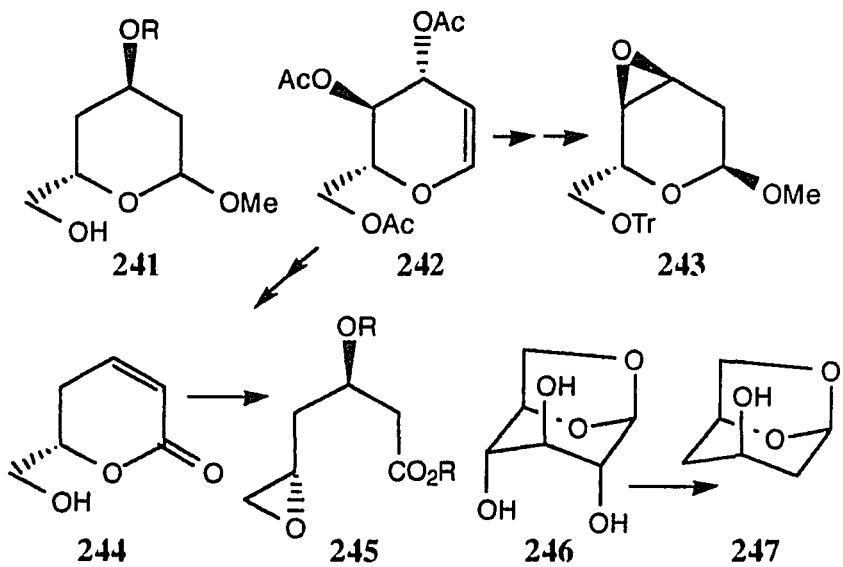
derivatives would be prepared by oxidation of the primary alcohol to the aldehyde, which would then be subjected to olefination. In order to confirm the absolute stereochemistry of **239** it was converted to **240** in 85% yield by methanolysis and separation of the resulting anomers. This compound had been prepared previously [98] and used for the synthesis of mevinic acid derivatives. Our synthetic material **240** exhibited corresponding NMR spectra, chromatographic mobility, and optical rotation to that reported.



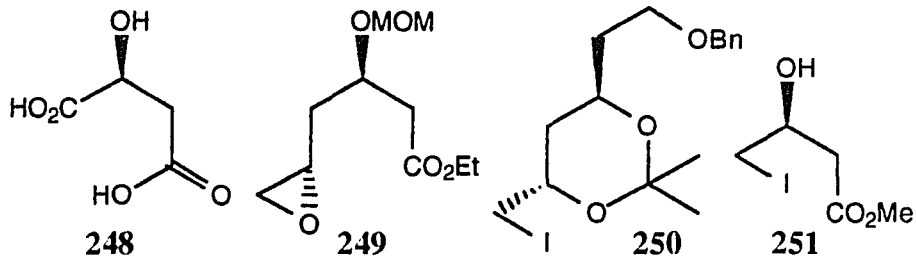
Conclusion

The synthesis described in this chapter provides a protected intermediate **239** for the synthesis of mevinic acids in 28% yield, requiring 7 steps from the starting achiral benzylated dihydropyran **215**. This example also demonstrates that our appendage-directed diastereoselective functionalization of dihydropyranosides can be extended to the synthesis of hexopyranoses in general. Several approaches to the lactone portion of mevinic acids have been described. This section will summarize previous asymmetric syntheses in order to define the context of our synthesis.

Carbohydrate precursors have been widely used to prepare mevinic acids. Methyl (α)-D-glucopyranoside has been converted to derivative **241** (R=Bn, 17%, 12 steps, ~100% ee).[99, 100] D-Glucose was converted to **241** (R=H, 29%, 10 steps, 100% ee),[101] and was used as a starting material for a saturated analogue (15%, 8 steps, ~100% ee).[102] Tri-O-acetyl-D-glucal **242** was converted to epoxide **243** (62%, 6 steps),[103] which has been extensively used to prepare protected intermediates **241** (R=Me, 48%, 9 steps, ~100% ee, removal of methyl ether <31% yield),[104] (R=^{t}BuMe$_2$Si-, 3%, 9 steps, ~100% ee),[105] (R=^{t}BuPh$_2$Si-, 33%, 11 steps, 100% ee).[97, 98] Tri-O-acetyl-D-glucal **242** was converted to enone **244**, which undergoes asymmetric Michael-addition with alkoxides to afford epoxide **245** (40-62%, 6 steps, ~100% ee), followed by reaction with nucleophiles with concommitant formation of the lactone.[106] D-Glucose was converted to the 1,6-anhydro-sugar **246** which can be di-deoxygenated to **247** (27%, 5 steps, ~100% ee), but requires inversion to obtain the natural configuration.[107]

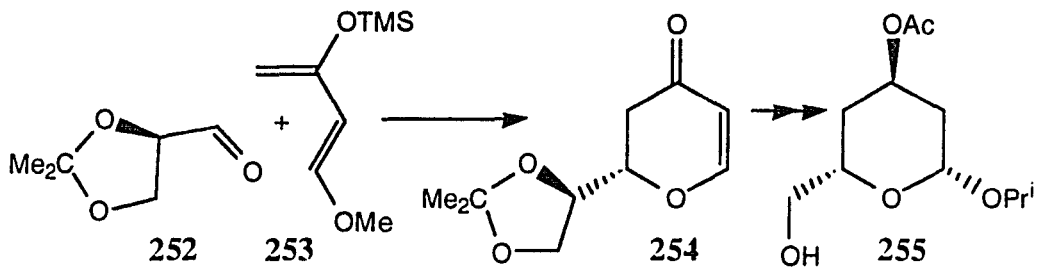


(S)-Malic acid **248** was converted to epoxide **249** (24% yield, 11 steps, >95% ee) which can be coupled to nucleophiles directly.[108] (S)-Malic diethyl ester was converted to iodide **250** (5%, 9 steps, >95% ee) and used in the total synthesis of compactin and mevinolin.[109, 110] Isoascorbic acid was converted to iodide **251** which contains C-1 to C-4 of the lactone, and was converted to an analogue by coupling with an allylic protected cyanohydrin anion (15%, 10 steps, >98% ee).[111]



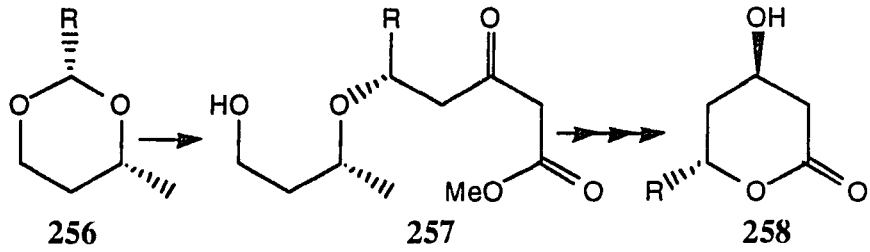
248 **249** **250** **251**

(R)-Isopropylidene glyceraldehyde **252** was transformed to the pyrone **254** via cyclcondensation with the siloxydiene **253**. Selective formation of the ^{i}propyl pyranoside, ketone reduction, hydrolysis of the acetonide followed by periodate cleavage and reductive workup gave **255** (26%, 7 steps, ~100% ee).[112]



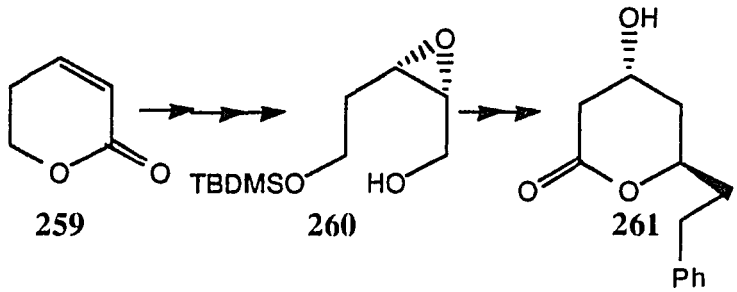
252 **253** **254** **255**

Acetals of 3-(R)-butane-1,3-diol **256** were condensed with trimethyl-silyl enol ethers forming the C-4 to C-5 bond and generating the C-5 stereocenter of **257**. Subsequent selective ketone reduction, hydrolysis and cyclization afforded mevinic acid analogues **258** (23%, 6 steps, ~100% ee).[113]



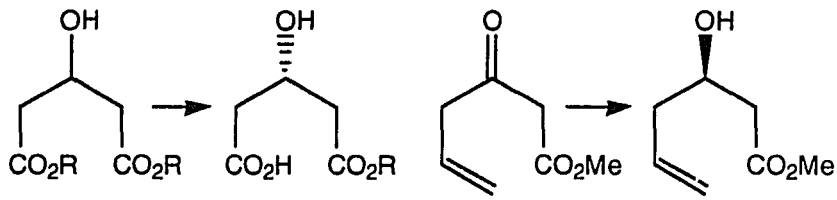
256 **257** **258**

Lactone **259** was hydrolyzed, protected, reduced, and subjected to Sharpless epoxidation to generate the C-3 stereocenter of **260**, further manipulation gave analogue **261** (8%, 12 steps, >93% ee).[114]



259 **260** **261**

Pig liver esterase selectively hydrolyzes the meso-diisopropyl ester **262** to **263** which has been converted to a lactone moiety that is enantiomeric to the naturally occurring stereochemistry (33%, 8 steps, 76% ee).[97] Reduction of prochiral ketone **264** with baker's yeast affords **265** (60-70% yield, 1 step, 76% ee) which can be subjected to iodolactonization or selenolactonization.[115, 116]



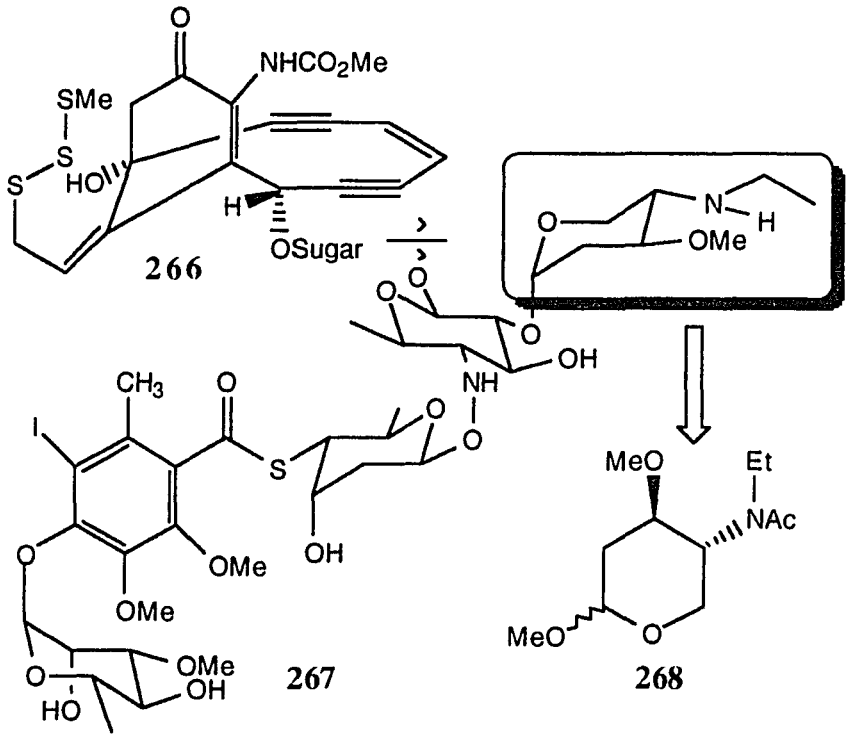
262 **263** **264** **265**

CHAPTER 5

SYNTHESIS OF THE 4-ETHYLAMINO SUGAR OF CALICHEAMICIN

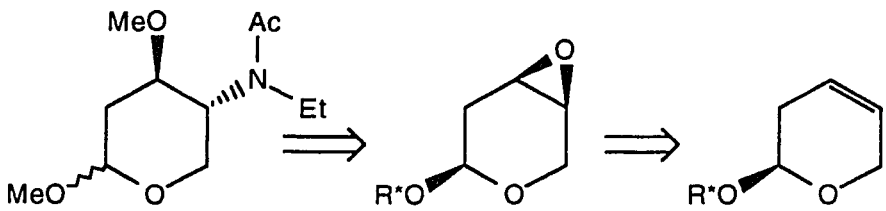
Introduction

Calicheamicin γ^1 **266** is an extremely selective and potent antitumor antibiotic that functions by cleaving DNA site specifically.[117, 118] The cleavage mechanism involves a thiol mediated Bergman cyclization of the ene-diyne moiety, producing a highly reactive phenylene diradical capable of abstracting hydrogen atoms from the DNA backbone. The oligosaccharide portion of calicheamicin γ^1 **267** plays a significant role in the specificity, as similar natural products are much less discriminating. As part of a larger strategy to construct the oligosacharide portion of calicheamicin γ^1 we identified the 4-ethylamino sugar **268** as a likely synthetic candidate for our approach using chromatographically resolved pyranosides. The absolute configuration of this sugar was not known at the outset of our synthesis and would be determined by comparison to our synthetic material.



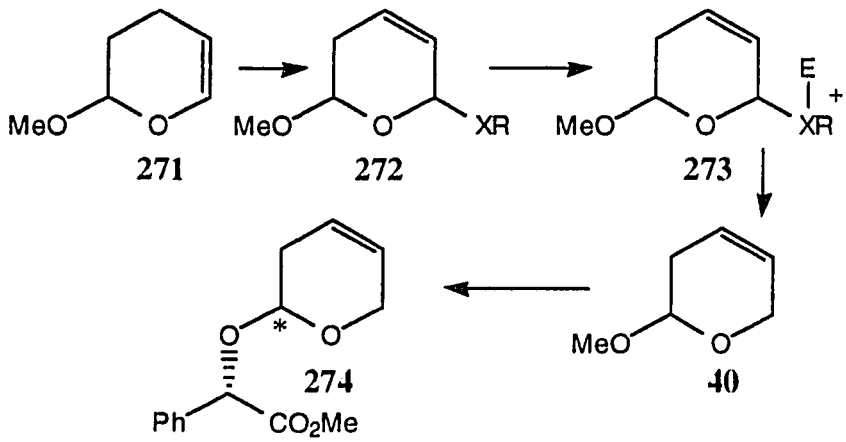
Synthesis

Using a direct disconnection approach the 4-ethylamino sugar **268** would be derived from the syn-4,5-epoxypyranoside **269**, itself prepared by epoxidation of the chromatographically resolved 4,5-unsaturated pyranoside **270**. The key issues addressed in this approach include obtaining a source of the dihydropyranoside, and the ability of the anomeric appendage to control remote functionalization of an alkene. While our previous work with 3,4-unsaturated pyranosides provides rapid access to 4-deoxy systems, expansion of this methodology to include members of 2-deoxypentopyranose natural products would be very useful.



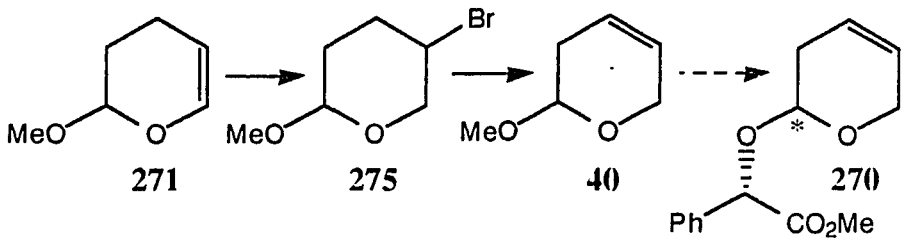
268 **269** **270**

Prior access to the racemic methyl pyranoside relies on either multi-step transformation of the 3,4-epoxypyranosides,[42] or cycloaddition of butadiene with an alkyl glyoxalate, followed by amide formation and finally Hoffman degradation.[31, 119] We designed an approach starting with readily available 3,4-dihydro-2-methoxy-2H-pyran **271** (100 g, $9.15, Aldrich). Bromination, followed by substitution with an appropriate nitrogen or sulfur nucleophile and finally elimination, would give the dihydropyranoside **272**. Generation of the cation **273** by electrophilic activation of the nucleophilic N or S-appendage with trimethyloxonium tetrafluoroborate, or some variant thereof, followed by hydride capture would afford the desired system **240**. Exchange of the anomeric appendage for an enantiomerically pure (α)-hydroxyester and chromatographic resolution would provide **274**.

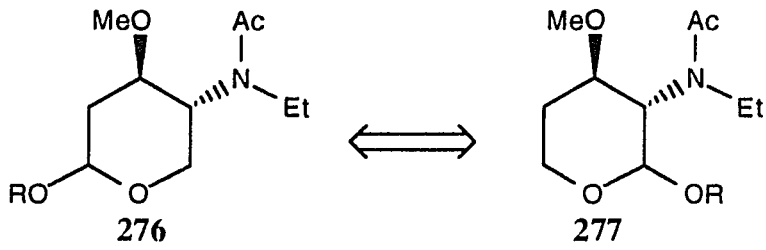


Generation of the bromo-substituted pyrrolidine or thiophenol pyranosides **273** proceeded as expected, but preliminary elimination attempts were problematic. In order to demonstrate that it would indeed be possible to incorporate the (α)-hydroxyester by exchanging for methanol, we rapidly prepared dihydropyranoside **40** from **271** by sequential bromination, DIBAL reduction of the resulting bromopyranoside to give

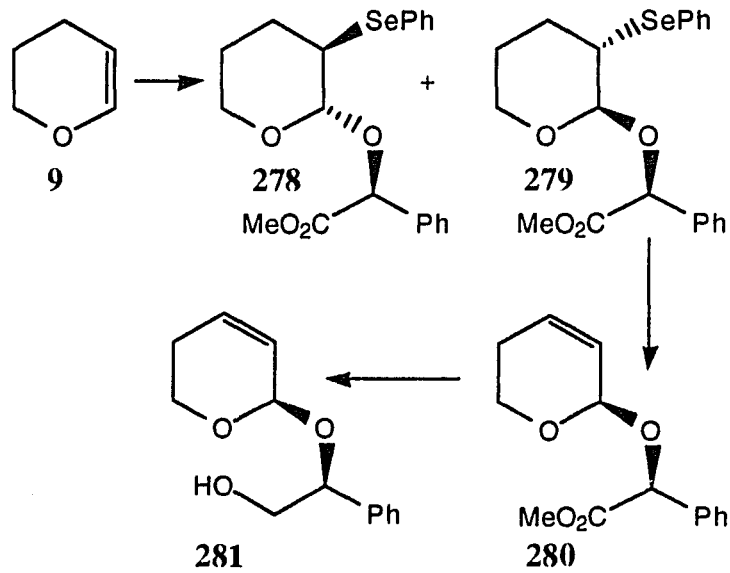
275, and finally elimination with DBU, producing a mixture of starting **271** and desired dihydropyranosides **40**. Separation and attempted acid catalyzed exchange for (S)-methyl lactate resulted in decomposition under forcing conditions. Our initial hope that this 3,6-dihydropyran, with the alkene out of "conjugation" with the acetal, would behave better than corresponding 5,6-dihydropyrans and undergo simple exchange was discouraged by the reactivity of the system.



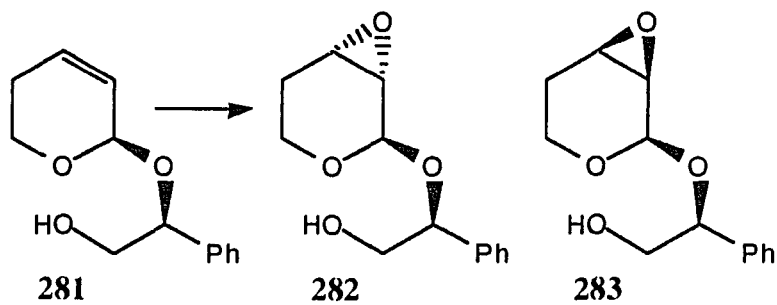
Rather than continue this strategy we elected to perform an end-switching step that would convert a 4-deoxy- to a 2-deoxy-pentopyranoside, i.e. **277** to **276**. This would enable us to expand upon the foundation of our previous results and increase the versatility of the method.



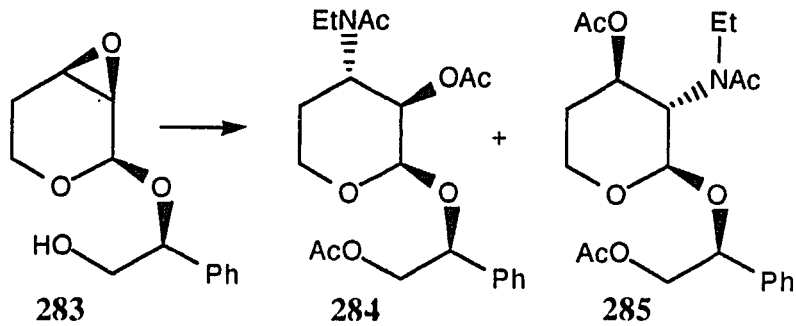
Reaction of dihydropyran **9** with phenylselenyl bromide and (S)-methyl mandelate gave the chromatographically separable selenides **278** and **279**. Separation of the the more polar selenide **279** and independent oxidation gave dihydropyranoside **280** in 47% yield. Reduction of the ester with $LiAlH_4$ gave alcohol **281** in 96% yield.



Epoxidation of **281** with mCPBA selectively produced chromatographically separable epoxides **282** and **283** in 96% yield, favoring the desired syn-diastereomer **283** (9 : 1).



We were now ready for the important epoxide opening reaction. Although we had previously observed nucleophilic attack of lithium aluminum hydride at the 3-position in the mevalonolactone and mevinic acid analogue syntheses, there is a possibility of abnormal diequatorial epoxide opening with amines. Examples of diaxial and diequatorial ring opening are reported for carbohydrate derived syn-epoxides, depending on conformational and steric factors. Reaction of syn-epoxide **283** with aqueous ethylamine at ambient temperature, followed by treatment with acetic anhydride in pyridine gave separable crystalline acetates **284** and **285** in 92-100% yield, favoring the desired product **285** (>6 : 1).



The ^{1}H- and ^{13}C-NMR spectra of the minor product **284** were observed as a ~1 : 1 mixture of conformers at ambient temperature, presumably due to competition between the anomeric and 3,4-substituents for an equatorial position, which determines the equilibrium of **286** and **287**. The major product **285** resulting from trans-diaxial epoxide opening **288** relaxes to the pyranoside ring conformer with all substituents equatorial **289** and exhibits simpler NMR spectra. Restricted rotation around the amide bond produced two sets of NMR signals in these compounds and in intermediates throughout the synthesis. The identity of the major product **285** was established by

homodecoupling (Table 4). The methylene protons of the ethylamine substituent occur between 2.9-3.5 ppm. The rotomeric CH(NAcEt) resonances occurred at 3.67 and 3.76 ppm. Characteristically the signal due to this hydrogen atom on the 3-position of the ring was observed as an apparent doublet of doublets (J= 6, 12 Hz), due to coupling with the adjacent anomeric and acetoxy-substituted hydrogen atoms. Decoupling this resonance collapses the region between 4.05-4.20 into a complex pattern, which is expected for the CH(OAc) at the 4-position in **285**.

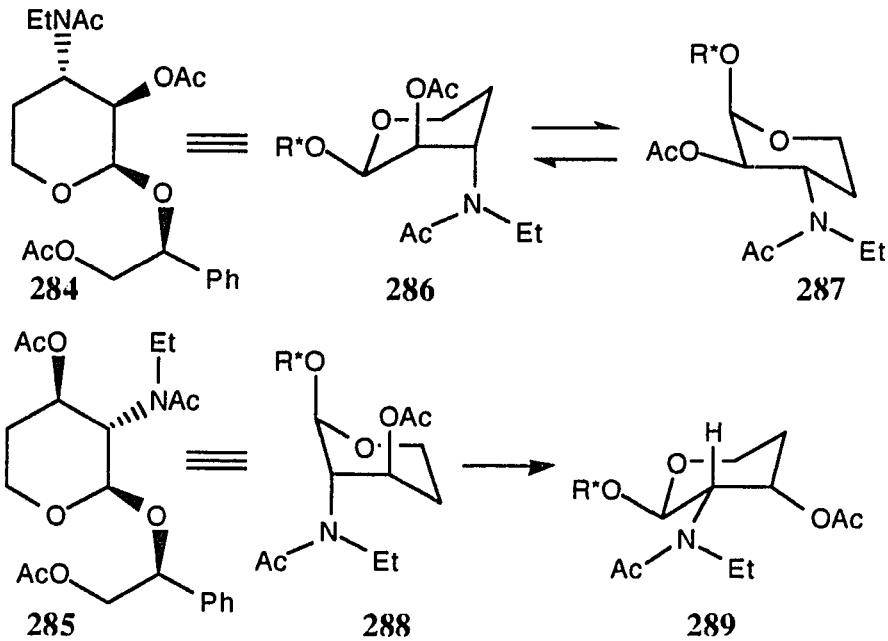
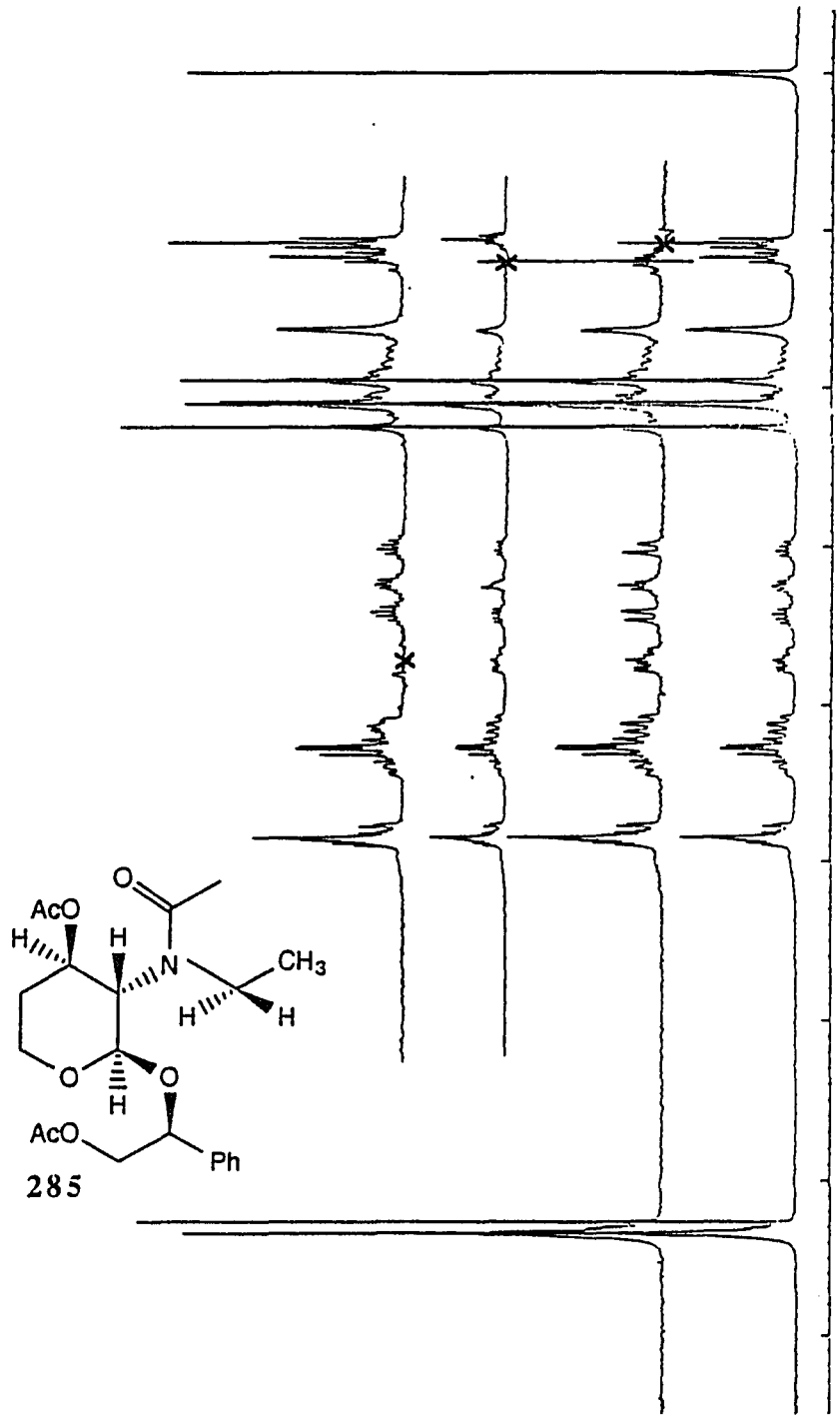
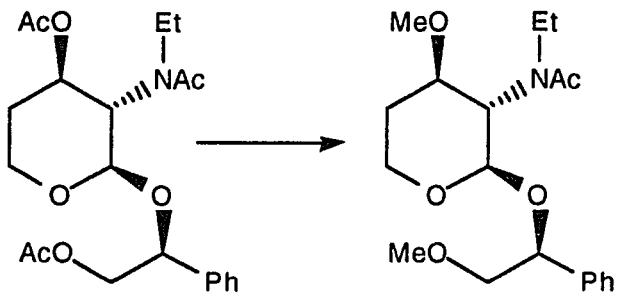


Table 4. ^{1}H-NMR Homodecoupling of Ethylamino Acetate Intermediate **285**



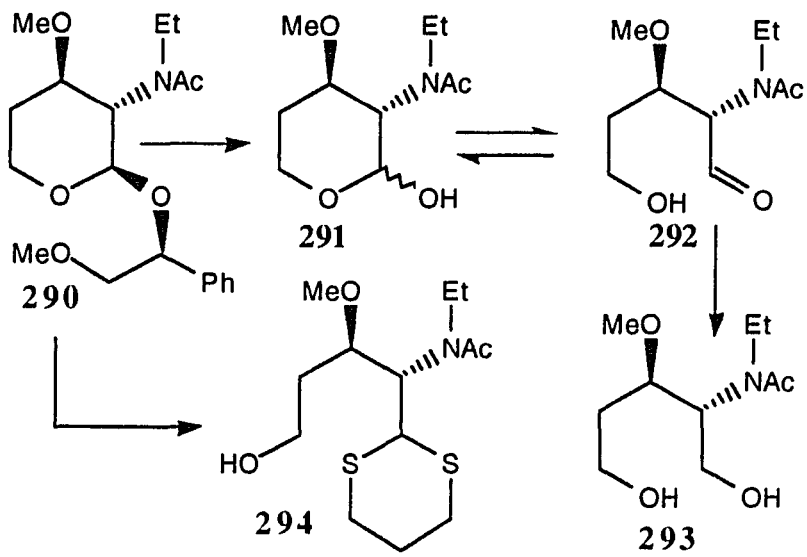
285

The major product **285** was converted to the bis-methyl ether **290** in 98% yield by cleavage of the ester groups with catalytic NaOMe in MeOH, followed by formation and methylation of the sodium salt with methyl iodide in THF.

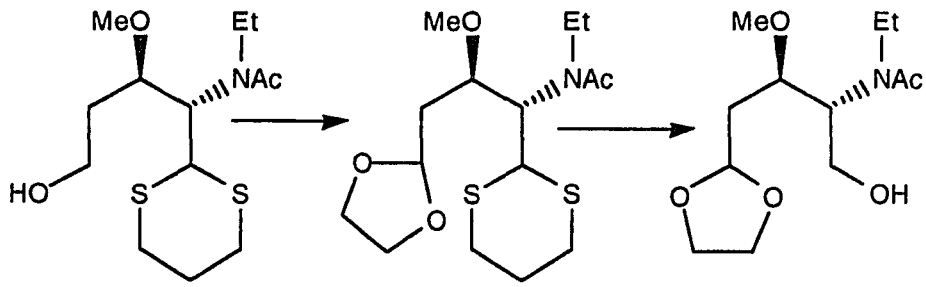


285 **290**

Hydrolysis of the anomeric appendage of **290** under acidic conditions gave lactol **291**, which exists in equilibrium with the acyclic alcohol **292.** Attempts to differentiate the ends by direct reaction of the primary alcohol of acyclic **292** were unsuccessful. Reduction to the diol **293** with $NaBH_4$ and attempted regioselective tosylation or silylation with one equivalent of reagent were also unsuccessful. One of the limited methods available to obtain the acyclic form of carbohydrates is conversion to a dithioacetal. Reaction of the pyranoside **290** with 1,3-propanedithiol and BF_3-Et_2O in CH_2Cl_2 gave the dithiane **294** in 71% yield.

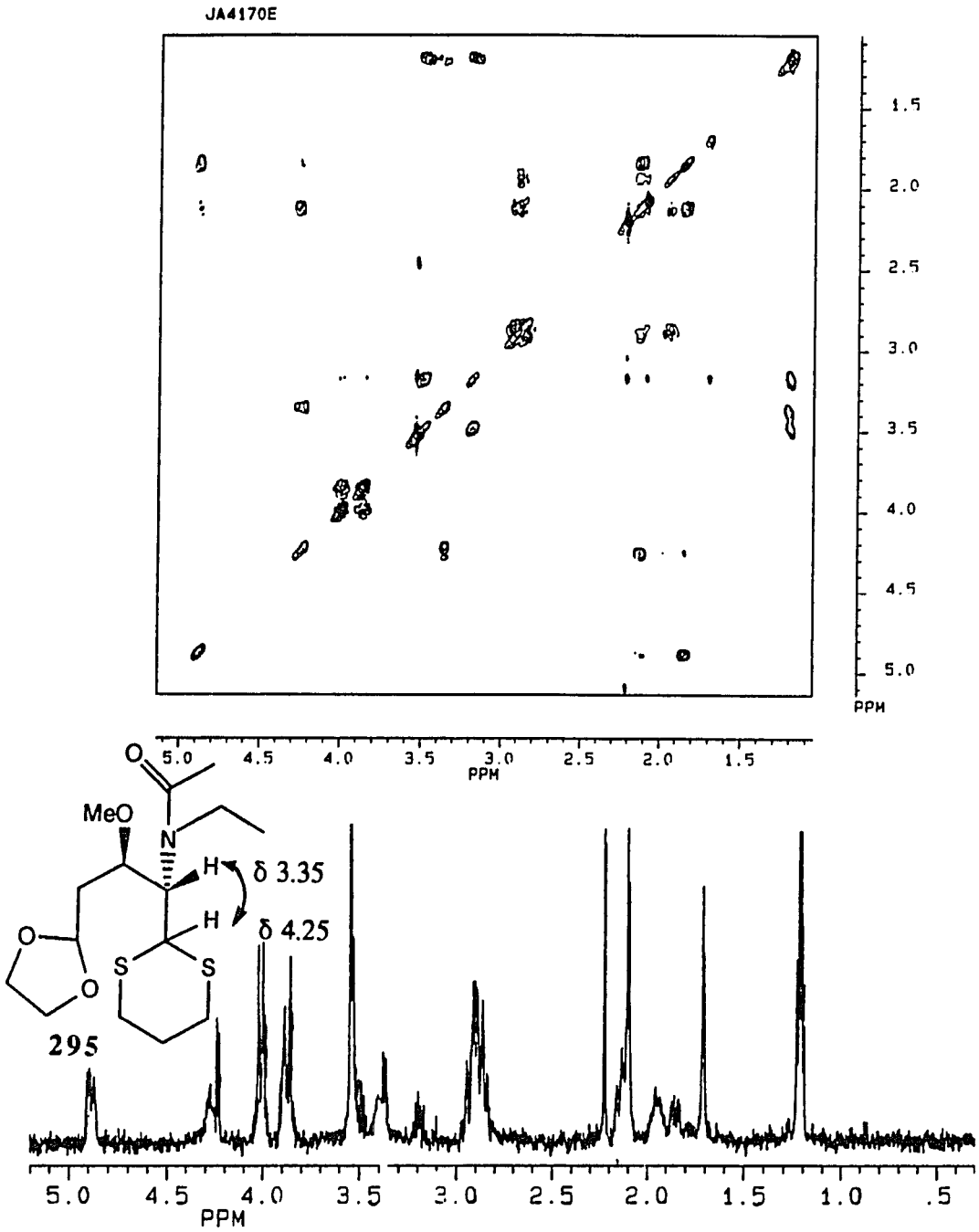


The primary alcohol of **294** was easily oxidized to the aldehyde using Swern conditions, and immediately protected as the dioxolane **295.** The structural assignment of **295** was confirmed using COSY 2D ^{1}H-NMR, which showed coupling of the dithiane proton at ~4.25 ppm to the resonance assigned to the CH(NAcEt) at ~3.35 ppm (Table 5). This compound possesses protected aldehyde oxidation states at both ends of the molecule. While the dioxolane acetal is sensitive to acidic conditions, the dithiane is susceptible to oxidative deprotection. Treatment with excess N-bromosuccinimide and silver nitrate in aqueous acetonitrile buffered with collidine rapidly cleaved the dithiane to the aldehyde,[120] which was reduced with $NaBH_4$ to afford the dioxolane alcohol **296** in 47% yield over 2 steps.

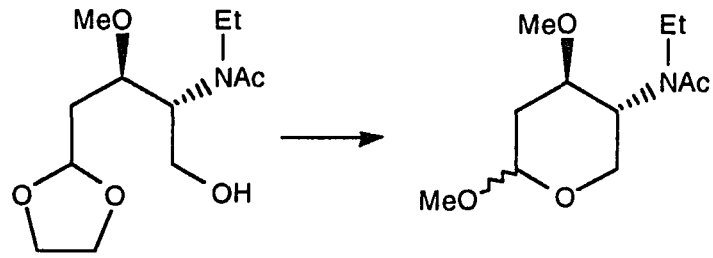


294 **295** **296**

Table 5. COSY 2D ^{1}H-NMR Spectrum of Dithiane **295**.



To complete the synthesis **296** was taken up in methanol acidified with p-TsOH, affording **268** in 83% yield, as an oil that was homogenous by TLC in a variety of eluents. The ^{1}H-NMR spectra indicates that the product with the anomeric methoxy substituent axial predominates. Final confirmation of the structure assigned **268** awaits comparison to authentic material. The absolute configuration of synthetic **268** should be 4(R),5(R), in analogy to our previous synthetic precedent.

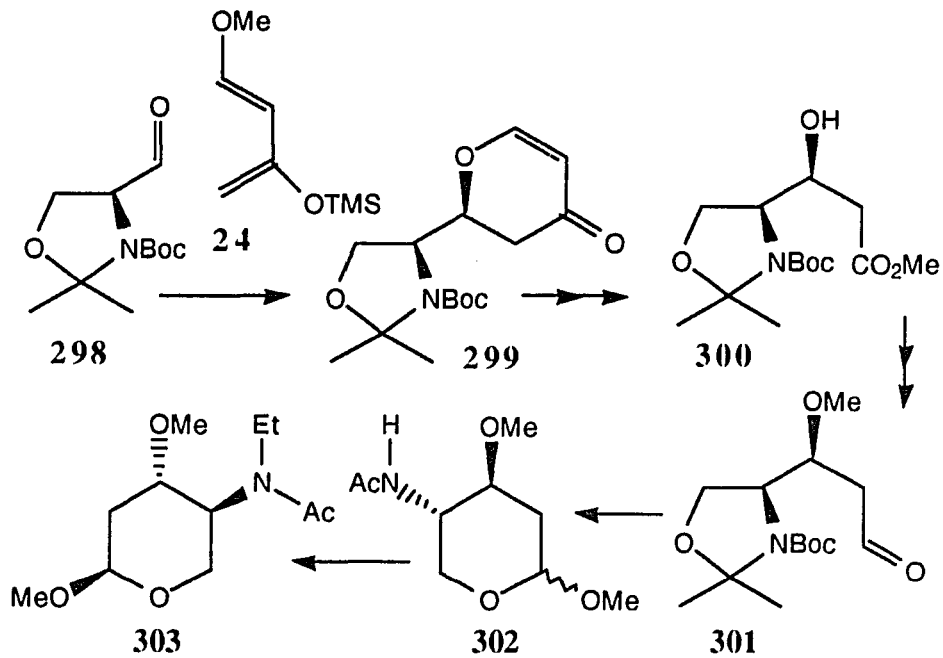


296 **268**

Conclusion

The synthesis described in this chapter affords the 4-ethylamino sugar of calicheamicin γ^1 in 17% yield over 12 steps from the chromatographically resolved (S)-methyl mandelate dihydropyranoside. This approach demonstrates the potential for the synthesis of heteroatom-containing sugars from enantiomerically pure, chromatographically resolved dihydropyranosides and should be useful for the synthesis of analogues. This synthesis also provides a method to interconvert 4- and 2-deoxypyranose substrates. Our synthesis could be adapted to the preparation of the enantiomeric 4(S),5(S)-amino sugar by using the equally available (R)-methyl mandelate in the alkoxy-selenation step. There is one recent communication describing the asymmetric synthesis of the natural amino sugar and in this section a brief review will be presented.

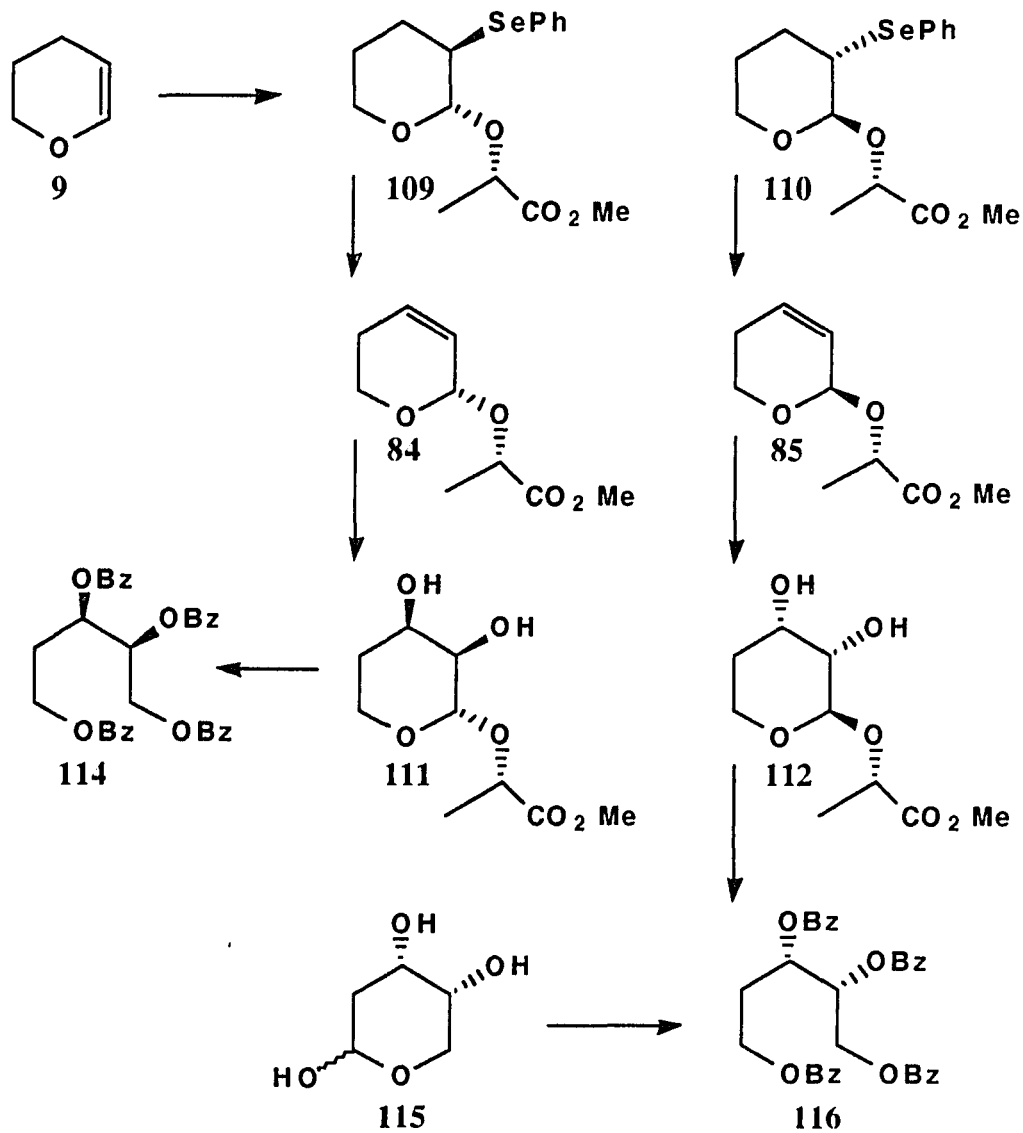
In the approach of Kahne et al. the required stereochemistry of the methyl ether is generated by hetero-Diels-Alder cycloaddition of a protected amino aldehyde **298** derived from L-serine and siloxy diene **24** to give dihydropyrone **299**.[121] This approach is patterned on the work of Danishefsky and Garner .[112, 122, 123] Oxidative degradation and esterification gave the β-hydroxy ester **300**. This compound was methylated, the ester reduced to the aldehyde **301**, which was deprotected and cyclized in methanol acidified with TsOH/$ZnCl_2$ affording methyl pyranoside **302**. At this point the α- and β-anomers were chromatographically separated and independently ethylated to produce the final ethylated amino sugar product **303**. The overall yield of this approach was 22% over 9 steps.



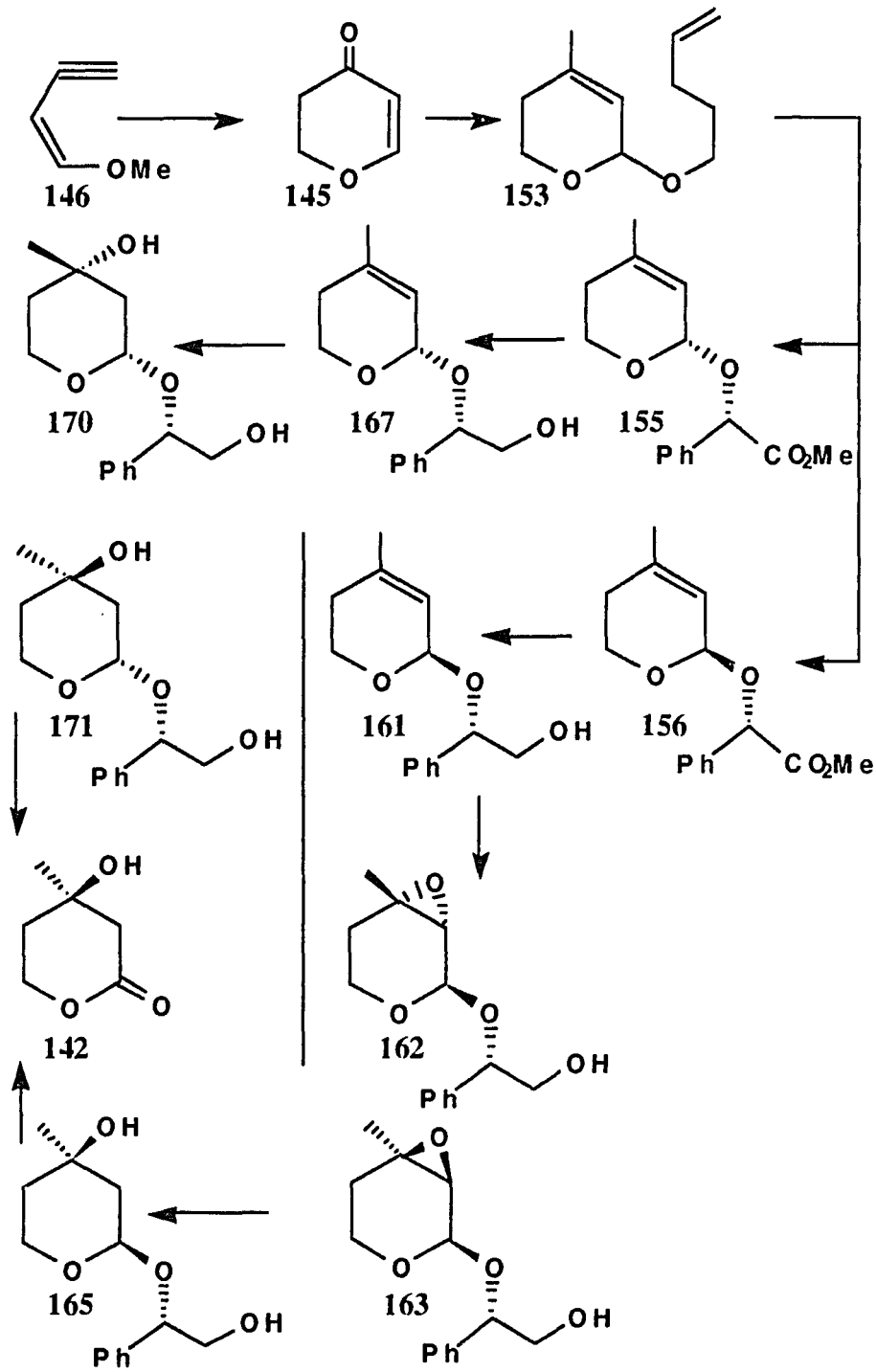
CHAPTER 6

EXPERIMENTAL

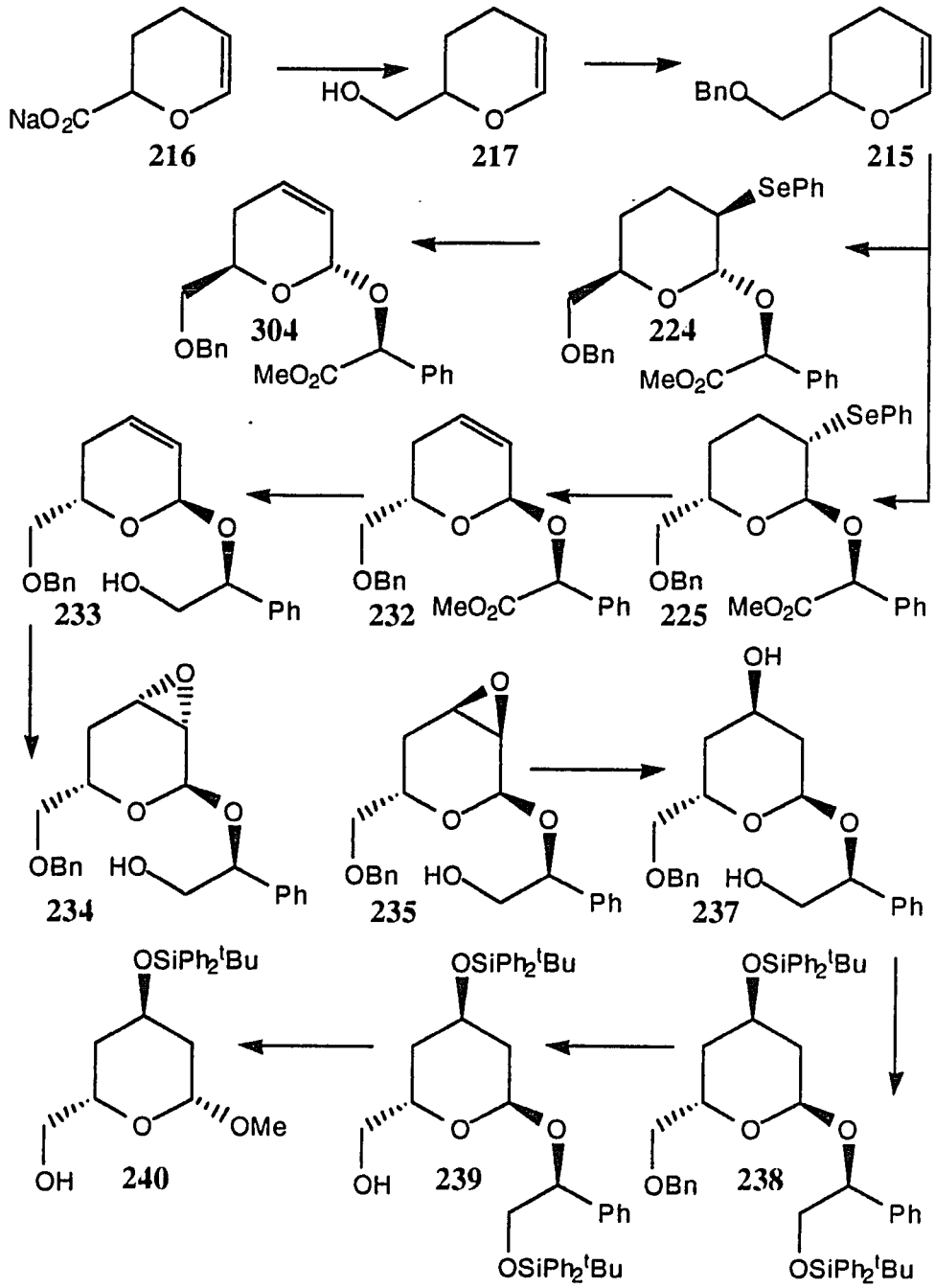
Scheme 1. Synthesis and Catalytic Osmylation of 5,6-Dihydropyranosides.



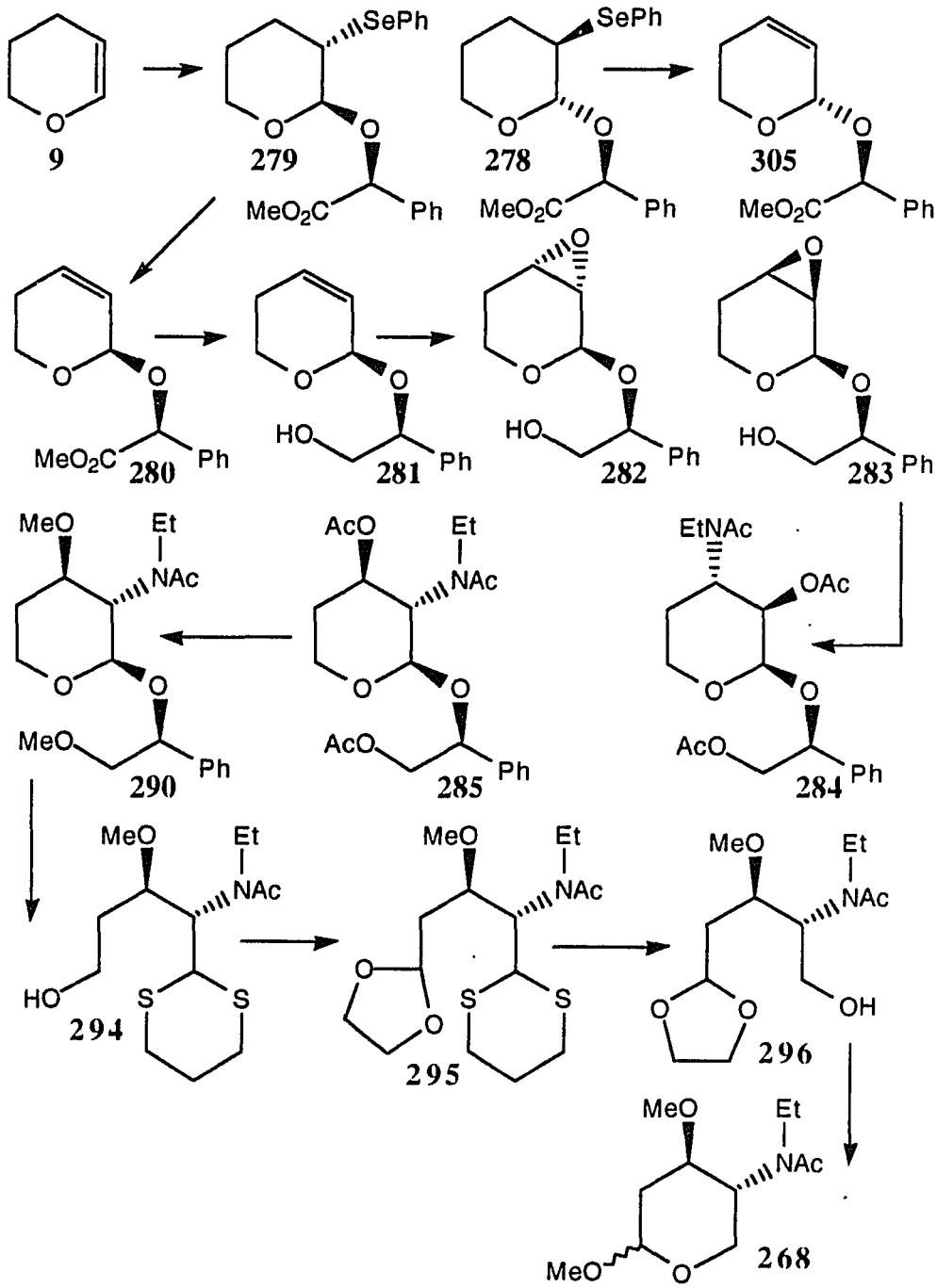
Scheme 2. Synthesis of (R)-Mevalonolactone



Scheme 3 Asymmetric Synthesis of a Mevinic Acid Precursor



Scheme 4 Synthesis of the 4-Ethylamino Sugar of Calicheamicin



2-[(S)-Methyl lactate]-5,6-dihydro-2H-pyran [84 & 85].

To a well-stirred solution of 3,4-dihydro-2H-pyran **9** (2.1 mL, 1.9 g, 23 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added dropwise a solution of phenylselenyl bromide that was prepared in situ by adding Br_2 (0.57 mL, 1.77 g, 11 mmol) to diphenyl diselenide (3.38 g, 10.8 mmol) in CH_2Cl_2 (10 mL). Decolorization occurred immediately. Next a solution of (S)-methyl lactate (2.1 mL, 2.3 g, 22 mmol) and triethylamine (3.3 mL, 2.4 g, 24 mmol) was added. The mixture was allowed to warm to room temperature slowly. After filtration the mixture was washed with water, saturated aqueous $NaHCO_3$, and brine (50 mL each), then dried (Na_2SO_4), filtered, and volatiles removed in vacuo leaving a yellow oil. At this point the selenyl-pyranosides **109** and **110** can be chromatographed (R_f 0.34 & 0.29, 20% EtOAc/hexanes, α = 1.17) and independently oxidized, or the crude mixture oxidized and the dihydropyranosides chromatographed with similar results.

To a solution of pyridine (2.9 mL, 2.8 g, 36 mmol) and the crude phenyl selenides **109** and **110** in CH_2Cl_2 (60 mL) at 0 °C was added dropwise an aqueous solution of H_2O_2 (1.62g, 47.5 mmol, 9.9 mL H_2O) while stirring vigorously. After stirring at room temperature for six days the mixture was diluted with CH_2Cl_2 (40 mL), washed with saturated $NaHCO_3$ (50 mL), and brine (50 mL), then dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (400g) eluted with 10% EtOAc/hexanes; the overlap fraction was similarly rechromatographed (200g) affording 1.233g (6.62 mmol, 31%) of the less polar diastereomer **84** (R_f 0.29, 20% EtOAc/hexanes) and 1.540g (8.27 mmol, 38%) of the more polar diastereomer **85** (R_f 0.22, 20% EtOAc/hexanes) as oils.

Spectral data for **84** : $[\alpha]_D$ -40.37° (c 2.72,$CHCl_3$); IR ($CHCl_3$) cm^{-1} 1746; ^1H NMR ($CDCl_3$) δ 1.45 (3, d, J=7 Hz), 1.90 (1, dm, J=17 Hz), 2.23-2.41 (1,m), 3.68-3.78 (1,m), 3.83 (3,s), 3.92 (1, dt, J=11.4 Hz), 4.47 (1,q, J=7 Hz), 5.00 (1,m), 5.82 (1, dm, J=10 Hz), and 6.07 (1,m); ^{13}C NMR ($CDCl_3$) δ 18.83 (CH_3), 24.51 (CH_2), 51.80 (CH_3), 57.32 (CH_2), 70.23 (CH), 92.77 (CH), 125.30 (CH), 129.15 (CH), and 173.51 (C).

Spectral data for **85** : $[\alpha]_D$ -77.4° (c 2.6, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1753; ^1H NMR ($CDCl_3$) δ 1.42 (3,d, J=6.8 Hz), 1.85-2.01 (1,m), 2.20-2.40 (1,m), 3.61 (1,dd, J=11.6 Hz, J=6.2Hz), 3.75 (3,s), 3.96 (1,dt, J=11.6, 3.5 Hz), 4.18 (1,q, J=6.8 Hz), 4.98 (1,m), 5.75 (1, dm, J=10.2 Hz), and 6.05-6.15 (1,m); ^{13}C NMR ($CDCl_3$) δ 18.40 (CH_3), 24.38 (CH_2), 51.71 (CH_3), 57.47 (CH_2), 73.12 (CH), 94.20 (CH), 124.78 (CH), 129.70 (CH), and 173.89 (C); mass spectrum (70 eV) m/z (rel. intensity) 186 (0.05), 185 (0.5), 156 (1), 142 (1), 127 (2), 115 (2), 100 (2), 99 (8), 84 (10), 83 (100), 55 (22); high resolution peak matching: calcd. for $C_9H_{14}O_4$ (M^+) 186.0892, obsd. 186.0882.

(S)-Methyl lactyl 4-deoxy-β-erythro-pentopyranosides [111 & 112].

To a solution of the more polar 5,6-dihydropyranoside **85** (516 mg, 2.77 mmol) and 4-methylmorpholine N-oxide (650 mg, 5.5 mmol) in THF (20 mL) at 0 °C was added 0.1M OsO_4 /THF (2.8 mL, 0.28 mmol). The mixture was stirred at ambient temperature for 12 h and then quenched with sodium bisulfite (600 mg, 5.8 mmol) in H_2O (1 mL), and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (200 g) eluted with ethyl acetate, affording 364 mg (1.65 mmol, 60%) of **112** (R_f 0.26, EtOAc). Spectral data for **112** : an oil, $[\alpha]_D$ +38.1° (c 1.15 , $CHCl_3$);

IR ($CHCl_3$) cm $^{-1}$ 3570, 3457, and 1740; ^1H NMR ($CDCl_3$) δ 1.42 (3, d, J=7 Hz), 1.65-1.97 (2, m), 3.54 (1,s), 3.62-3.89 (6, m), 3.99 (1, s), 4.06-4.18 (1, m), 4.28 (1, q, J=7 Hz), and 4.81 (1, d, J=4 Hz); ^{13}C NMR ($CDCl_3$) δ 17.48 (CH_3), 29.41 (CH_2), 51.97 (CH_3), 59.70 (CH_2), 66.03 (CH), 69.86 (CH), 72.15 (CH), 99.47 (CH), and 173.40 (C).

Similarly reaction of the less polar 5,6-dihydropyranoside **84** (625 mg, 3.35 mmol) afforded 448 mg (2.03 mmol, 61%) of dihydroxypyranoside **111** (R_f 0.31, EtOAc). Spectral data for **111** : an oil, $[\alpha]_D$ -98.3° (c 1.1 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 3561, and 1730; ^1H NMR ($CDCl_3$) δ 1.46 (3, d, J=7 Hz), 1.67-1.98 (2, m), 3.45-3.87 (7, m), 4.03-4.28 (2, m), 4.41 (1, q, J=7 Hz), and 4.70 (1, d, J=5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.46 (CH_3), 29.46 (CH_2), 51.98 (CH_3), 59.73 (CH_2), 65.74 (CH), 70.14 (CH), 71.26 (CH), 99.97 (CH), and 173.81 (C). Mass spectrum (70 eV) m/z (rel. intensity) 133 (28), 117 (86), 101 (53), 88 (39), 70 (66), 60 (100); (M+H) ion identified using FAB 221.1027; exact mass calcd. for $C_9H_{17}O_6$ 221.1049.

(2S,3R)-1,2,3,5-Tetra-O-benzoyl-1,2,3,5-pentanetetrol [114].

A solution of the diol **111** (106 mg, 0.481 mmol) in 1N H_2SO_4 (20 mL) was heated to 100 °C for 1.5 h. The mixture was cooled to room temperature, then neutralized with $Ba(OH)_2$ (6.3 g, 20 mmol) and bubbling CO_2 through the milky mixture. The volatiles were removed in vacuo (< 50°C) and the resulting white solid extracted with refluxing acetone in a Soxhlet apparatus for 8 h. The solvent was removed in vacuo, the residue taken up in H_2O (4 mL) and $NaBH_4$ (27 mg, 0.72mmol) added. The reaction was stirred 0.5 h and then quenched with Dowex 50 (H^+) ion exchange resin (~1 g). Filtration and concentration in vacuo gave a pale

yellow oil. The residue was taken up in pyridine (1 mL) and excess benzoyl chloride (0.5 mL, 0.6 g, 4 mmol) and then heated at 100 °C for 0.25 h. The mixture was cooled to room temperature, poured into H_2O (10 mL) and extracted with Et_2O (25 mL). The organic extract was washed with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl , 10% $CuSO_4$, and H_2O (25 mL each), dried ($MgSO_4$), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (50 g) eluted with 20% ethyl acetate/hexanes, affording 236 mg (0.428 mmol, 89%) of **114** (R_f 0.21, 20% EtOAc/hexanes). Spectral data for **114** : m.p. 129-130 °C, $[\alpha]_D$ +16.25° (c 0.8 , $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.30-2.58 (2, m), 4.37-4.90 (4, m), 5.81-5.98 (2, m), 7.25-7.65 (12, m), and 7.93-8.14 (8, m); ^{13}C NMR ($CDCl_3$) δ 29.77 (CH_2), 60.98 (CH_2), 62.55 (CH_2), 70.05 (CH), 72.30 (CH), 128.21 (CH), 128.42 (CH), 129.37 (C), 129.52 (CH), 129.67 (CH), 129.73 (CH), 132.84 (CH), 133.14 (CH), 133.30 (CH), 165.47 (C), 165.54 (C), 166.04 (C), and 166.27 (C).

For comparison the tetrabenzoate **116** was prepared similarly from **112** and 2-deoxy-D-ribose **115** : m.p. 129-130°C, $[\alpha]_D$ -16.7 ° (c 1.91 , $CHCl_3$), and exhibited identical spectral data.

5,6-Dihydro-4H-pyran-4-one [145].

To a solution of freshly distilled cis-1-methoxy-1-buten-4-yne **146** (5.0 mL, 5.4 g, 65.8 mmol) in THF (150 mL) at -78 °C was added a solution of n-BuLi in hexanes (1.6M, 38 mL, 61 mmol) dropwise via an addition funnel. After 0.25 h a cooled (-78 °C) solution of ethyl formate (4.9 mL, 4.5 g, 60.6 mmol) in THF (30 mL) was added rapidly via cannula and allowed to stir for 0.5 h. A solution of diisobutylaluminum hydride in toluene (1.5M, 44 mL, 66 mmol) was added dropwise.

The reaction was allowed to warm to 0 °C, then quenched with 3% aqueous HCl (200 mL) and the aqueous layer was extracted with Et_2O (200 mL, then 6 X 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil. The residue was taken up in 4 : 1 THF/H_2O (250 mL), acidified with para-toluenesulfonic acid monohydrate (300 mg, 1.58 mmol), and heated to reflux for 60 h. After cooling to room temperature the mixture was diluted with Et_2O (200 mL), washed with saturated aqueous $NaHCO_3$ (100 mL), and the aqueous layer extracted with Et_2O (500 mL) in a continuous extraction apparatus. The combined organic layers were dried (Na_2SO_4), filtered, and solvents removed by distillation at ambient pressure under argon. The residue was further distilled under vacuum to afford the product **145**, 2.64 g (26.9 mmol, 44%); a pale yellow liquid; b.p.$_{16mm}$ 89-92 °C; R_f 0.30, (50% EtOAc/hexanes); Spectral data for **145**: IR ($CHCl_3$) cm $^{-1}$ 1720, 1655, 1596, 1460, and 1403; ^1H NMR ($CDCl_3$) δ 2.61 (2, t, J=7 Hz), 4.51 (2, t, J=7 Hz), 5.42 (1, d, J=6 Hz), and 7.37 (1, d, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ 36.37 (CH_2), 68.03 (CH_2), 107.36 (CH), 163.36 (CH), and 191.66 (C).

4-Methyl-2-[1'-oxy-4'-penten]-5,6-dihydro-(2H)-pyran [153].

To a solution of CH_3Li in Et_2O (0.48M, 30 mL, 14.5 mmol) at -78 °C was added a solution of **145** (1.295 g, 13.2 mmol) in Et_2O (50 mL) dropwise via an addition funnel. The reaction was stirred for 0.25 h and then quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 X 15 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to a pale yellow liquid. The residue was taken up in CH_2Cl_2 (15 mL), 4-penten-1-ol (4.1 mL, 3.4 g, 39.7mmol) and PPTS (25 mg, 0.1 mmol) were added, and the mixture

stirred for 5 h. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL), the aqueous layer extracted with CH_2Cl_2 (3 X 15 mL), the combined organic layers were dried (Na_2SO_4), filtered, and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (200g) eluted with CH_2Cl_2, affording 2.195 g (12.0 mmol, 91%) of **153** as a colorless liquid homogenous by TLC (R_f 0.30, CH_2Cl_2); Spectral data for **153** : IR ($CHCl_3$) cm $^{-1}$ 1680, 1638, 1446, and 1421; ^1H NMR ($CDCl_3$) δ 1.63-1.82 (6, m), 2.15 (2, q, J=7 Hz), 2.26 (1, m), 3.45 (1, td, J=7, 10 Hz), 3.68-3.85 (2, m), 3.92 (1, dt, J=4, 11 Hz), 4.89 (1, s), 4.93-5.10 (2, m), 5.47 (1, s), and 5.83 (1, tdd, J=7, 10, 17 Hz); ^{13}C NMR ($CDCl_3$) δ 22.94 (CH_3), 28.98 (CH_2), 29.51 (CH_2), 30.36 (CH_2), 57.30 (CH_2), 67.09 (CH_2), 94.38 (CH), 114.64 (CH_2), 119.87 (CH), 137.44 (C), and 138.19 (CH).

4-Methyl-2-[(S)-methyl mandelyl]-5,6-dihydro-2H-pyran [155 & 156].

To a solution of **153** (500 mg, 2.74 mmol) and (S)-(-)-methyl mandelate (500 mg, 3.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added iodonium bis-collidine perchlorate[127] (1.29 g, 2.74 mmol). The mixture was stirred for 1 h and then poured into 10% aqueous $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 X 15 mL), the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine (15 mL each), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was chromatographed twice on silica gel 60 (200 g) eluted with 20% Et_2O/hexanes, affording 259 mg (0.987 mmol, 36%) of the less polar product **155** (R_f 0.22, 20% Et_2O/hexanes) and 252 mg (0.961 mmol, 35%) of the more polar product **156** (R_f 0.16, 20% Et_2O/hexanes).

Spectral data for **155** : a viscous oil, $[\alpha]_D$ +103.5° (c 1.15 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 1742, 1453, 1445, and 1435; ^1H NMR ($CDCl_3$) δ 1.64-1.82 (4, m), 2.26 (1, m), 3.66 (1, dt, J=6, 11 Hz), 3.71 (3, s), 3.79 (1, dt, J=3, 11 Hz), 5.13 (1, s), 5.36 (1, s), 5.63 (1, s), and 7.26-7.52 (5, m); ^{13}C NMR ($CDCl_3$) δ 22.92 (CH_3), 29.38 (CH_2), 52.15 (CH_3), 57.67 (CH_2), 76.39 (CH), 93.65 (CH), 119.42 (CH), 127.37 (CH), 128.35 (CH), 128.49 (CH), 136.87 (C), 137.90 (C), and 171.69 (C).

Spectral data for **156** : a viscous oil, $[\alpha]_D$ +52.8° (c 1.16 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 1747, 1493, 1453, and 1435; ^1H NMR ($CDCl_3$) δ 1.72-1.81 (4, m), 2.27 (1, m), 3.67-3.77 (4, m), 4.05 (1, dt, J=3, 11 Hz), 4.93 (1, s), 5.22 (1, s), 5.46 (1, s), and 7.27-7.52 (5, m); ^{13}C NMR ($CDCl_3$) δ 22.92 (CH_3), 29.36 (CH_2), 52.15 (CH_3), 57.83 (CH_2), 77.67 (CH), 93.48 (CH), 119.08 (CH), 127.28 (CH), 128.52 (CH), 136.31 (C), 138.23 (C), and 171.39 (C).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H,6.91. Found: C, 68.45; H, 6.80.

2-[(S)-1'-Ethoxy-2'-hydroxy-1'-phenyl]-4-methyl-5,6-dihydro-2H-pyran [167 & 161].

To a suspension of $LiAlH_4$ (35 mg, 0.92 mmol) in THF (2 mL) at 0 °C was added a solution of **155** (239 mg, 0.911 mmol) in THF (2 mL) dropwise via syringe. The reaction was stirred 0.5 h, then quenched by successive addition of H_2O (35 μL) , 10% NaOH (35 μL) and H_2O (105 μL) while stirring vigorously. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was chromatographed on silica gel 60 (75 g) eluted with 50% ethyl acetate/hexanes, affording 213 mg (0.911 mmol, 100%) of **167** as an oil that crystallized upon cooling (R_f 0.34, 50% EtOAc/hexanes). Spectral data for **167** : m.p. 45-46 °C, $[\alpha]_D$ +97.53°

(c 1.4 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 3590, 3458, 1492, 1452, and 1420; ^1H NMR ($CDCl_3$) δ 1.65-1.80 (4, m), 2.06-2.38 (2, m), 3.30-3.39 (1, m), 3.55-3.82 (3, m), 4.71 (1, dd, J=4, 8 Hz), 5.20 (1, s), 5.54 (1, s), and 7.20-7.42 (5, m); ^{13}C NMR ($CDCl_3$) δ 22.94 (CH_3), 29.37 (CH_2), 57.56 (CH_2), 66.79 (CH_2), 81.38 (CH), 95.88 (CH), 119.49 (CH), 126.56 (CH), 127.53 (CH), 128.16 (CH), 138.27 (C), and 140.22 (C).

Similarly reduction of **156** (220 mg, 0.839 mmol) gave 190 mg (0.811 mmol, 97%) of **161** as a colorless oil homogenous by TLC (R_f 0.33, 50% EtOAc/hexanes). Spectral data for **161** : $[\alpha]_D$ +54.85° (c 1.0, $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 3593, 3431, 1490, 1462, 1451, and 1420; ^1H NMR ($CDCl_3$) δ 1.76 (3, s), 1.84 (1, s), 2.27 (1, m), 2.76 (1, dd, J=5, 9 Hz), 3.61-3.88 (3, m), 4.03 (1, dt, J=4, 11 Hz), 4.89 (2, m), 5.43 (1, s), and 7.34 (5, m); ^{13}C NMR ($CDCl_3$) δ 22.93 (CH_3), 29.43 (CH_2), 57.88 (CH_2), 67.44 (CH_2), 79.99 (CH), 92.41 (CH), 119.67 (CH), 126.89 (CH), 127.99 (CH), 128.47 (CH), 137.87 (C), and 138.66 (C).

Oxy-Mercuration 2(S)-2-[(S)-1'-Ethoxy-2'-hydroxy-1'-phenyl]-4(R)-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2H-pyran [171].

Tetrahydrofuran (2 mL) was added to a solution of $Hg(OAc)_2$ (203 mg, 0.637 mmol) in H_2O (2 mL) and the bright yellow mixture was cooled to 0 °C. A solution of **167** (149 mg, 0.636 mmol) in THF (3 mL) was then added dropwise. The reaction was stirred at this temperature for 18 h and then quenched by adding successively 10% aqueous NaOH (0.8 mL), then $NaBH_4$ (12 mg, 0.32 mmol) in additional 10% aqueous NaOH (0.8 mL). The aqueous layer was saturated with NaCl, the mixture filtered, and extracted with EtOAc (5 X 10 mL). The combined organic extracts were dried

(Na_2SO_4), filtered and concentrated in vacuo. The residue was chromatographed on silica gel 60 (100 g) eluted with ethyl acetate, affording 110 mg (0.436 mmol, 69%) of the major diastereomer **171** as an oil that crystallized upon cooling (R_f 0.28, EtOAc), and 14 mg (0.055 mmol, 9%) of the minor diastereomer **170** as a viscous oil contaminated with (S)-2-hydroxy-2-phenylethanol (R_f 0.40, EtOAc); yield corrected by ^1H NMR.

Spectral data for **171** : m.p. 83-85 °C, $[\alpha]_D$ -7.07° (c 1.16 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 3596, 3458, 1493, and 1452; ^1H NMR ($CDCl_3$) δ 1.18-1.39 (4, m), 1.42-1.93 (4, m), 2.27 (1, m), 3.60-3.82 (4, m), 4.76 (1, t, J=6 Hz), 5.02 (1, dd, J=3, 7 Hz), and 7.25-7.44 (5, m); ^{13}C NMR ($CDCl_3$) δ 30.54 (CH_3), 38.21 (CH_2), 43.80 (CH_2), 60.97 (CH_2), 66.53 (CH_2), 69.02 (C), 80.64 (CH), 98.89 (CH), 126.49 (CH), 127.61 (CH), 128.24 (CH), and 139.48 (C).

Spectral data for **170** : ^1H NMR ($CDCl_3$) δ 1.19 (3, s), 1.24-2.07 (5, m), 3.27-3.85 (5, m), 4.10 (1, s), 4.68 (1, dd, J=4, 7 Hz), 5.26 (1, m), and 7.34 (5, s); ^{13}C NMR ($CDCl_3$) δ 29.89 (CH_3), 37.75 (CH_2), 40.90 (CH_2), 56.44 (CH_2), 66.30 (CH_2), 68.03 (C), 80.88 (CH), 98.79 (CH), 126.56 (CH), 128.15 (CH), 128.64 (CH), and 138.97 (C).

Epoxidation. 3(R),4(R)-3,4-Epoxy-2(R)-2-[(S)-1'-ethoxy-2'-hydroxy-1'-phenyl]-4-methyl-3,4,5,6-tetrahydro-2H -pyran [163].

To a solution of **161** (185 mg, 0.789 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added mCPBA (200 mg, 0.9 mmol). The reaction was stirred at this temperature for 18 h. The reaction mixture was poured into 10% aqueous Na_2CO_3 (15 mL), separated and the aqueous layer extracted with EtOAc (3 X 15 mL). The combined organic extracts

were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was chromatographed on silica gel 60 (100 g) eluted with 50% ethyl acetate/hexanes, affording 14 mg (0.056 mmol, 7%) of the less polar anti-epoxide **162** (R_f 0.20, 50% EtOAc/hexanes), and 183 mg (0.731 mmol, 93%) of the more polar syn-epoxide **163** (R_f 0.15, 50% EtOAc/hexanes).

Spectral data for **162** : an oil; ^1H NMR ($CDCl_3$) δ 1.42 (3, s), 1.75-1.89 (1, m), 1.98-2.12 (1, m), 2.95 (1, s), 3.41-3.53 (1, m), 3.66-3.88 (4, m), 4.83 (1, dd, J=4, 8 Hz), and 7.35 (5, m); ^{13}C NMR ($CDCl_3$) δ 23.36 (CH_3), 28.83 (CH_2), 55.98 (CH_2), 56.38 (C), 57.57 (CH), 67.23 (CH_2), 81.06 (CH), 94.29 (CH), 126.93 (CH), 128.35 (CH), 128.62 (CH), and 137.75 (C).

Spectral data for **163** : an oil, $[\alpha]_D$ +123.0° (c 1.1, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3663, 3475, 1491, 1452, and 1421; ^1H NMR ($CDCl_3$) δ 1.39 (3, s), 1.83-1.98 (2, m), 3.02 (1, s), 3.07 (1, d, J=3 Hz), 3.46-3.94 (4, m), 4.84-4.90 (2, m), and 7.27-7.40 (5, m); ^{13}C NMR ($CDCl_3$) δ 21.80 (CH_3), 29.80 (CH_2), 56.14 (C), 56.71 (CH_2), 58.30 (CH), 67.12 (CH_2), 79.32 (CH), 91.35 (CH), 127.08 (CH), 128.16 (CH), 128.51 (CH), and 138.16 (C).

Epoxide Opening: 2(R)-2-[(S)-1'-Ethoxy-2'-hydroxy-1'-phenyl]-4(R)-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2H-pyran [165].

To a suspension of $LiAlH_4$ (30 mg, 0.79 mmol) in THF (1.5 mL) at 0 °C was added a solution of **163** in THF (3 mL) dropwise via syringe. The reaction was allowed to stir at ambient temperature for 8 h. The reaction was then quenched by successive addition of H_2O (30 μL), 10% NaOH (30 μL), and H_2O (90 μL) while stirring vigorously. The reaction mixture was filtered through Celite and concentrated in

vacuo. The residue was chromatographed on silica gel 60 (100 g) eluted with ethyl acetate, affording 144 mg (0.571 mmol, 80%) of **165** as an oil that crystallized upon cooling (R_f 0.31, EtOAc). Spectral data for **165** : m.p. 83-84 °C, $[\alpha]_D$ +184.1° (c 1.4 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3435, 1491, 1452, and 1402; ^1H NMR ($CDCl_3$) δ 1.22 (3, s), 1.60-1.89 (4, m), 3.55-3.87 (4, m), 4.30 (1, dt, J=3, 12 Hz), 4.49 (1, s), 4.84 (2, s), and 7.33 (5, s); ^{13}C NMR ($CDCl_3$) δ 29.80 (CH_3), 37.89 (CH_2), 40.92 (CH_2), 56.38 (CH_2), 66.78 (CH_2), 67.03 (C), 78.41 (CH), 94.47 (CH), 127.10 (CH), 128.21 (CH), 128.55 (CH), and 137.58.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H,7.99. Found: C, 66.58; H, 7.88.

(4R)-4-Hydroxy-4-methyl-3,4,5,6-tetrahydro-2H-pyran-2-one (Mevalonolactone) [142].

To a solution of **171** (100 mg, 0.396 mmol) in THF (5 mL) was added 10% aqueous HCl (3 mL). The mixture was stirred for 0.5 h, then poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with hot EtOAc (10 X 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was chromatographed on silica gel 60 (75g) eluted with ethyl acetate, giving the lactol as a colorless liquid homogenous by TLC (R_f 0.25, EtOAc). This material was subjected to oxidation without further characterization.

To a suspension of PCC (215 mg, 1.00 mmol) and freshly ground 3 Å sieves (230 mg) in CH_2Cl_2 (1.5 mL) was added a solution of the above lactol in CH_2Cl_2 (2 mL). The mixture was stirred for 7 h at ambient temperature. Ether (10 mL) was added while stirring vigorously. Filtration of the mixture through silica gel 60 (15 g) eluted with Et_2O gave 39 mg (0.30 mmol, 76%) of (R)-mevalonolactone **142** (R_f 0.32,

EtOAc) which exhibited identical physical and spectral properties when compared to a sample of authentic racemic material (Aldrich). Spectral data for **142** : an oil, $[\alpha]_D$ -20.0° (c 0.85 , EtOH); Lit [67] $[\alpha]_D$ -23 ° (c 0.32 , EtOH); IR ($CHCl_3$) cm^{-1} 3431, and 1729; ^1H NMR ($CDCl_3$) δ 1.39 (3, s), 1.91 (2, m), 2.50 (1, d, J=17 Hz), 2.67 (1, d, J=17 Hz), 2.88 (1, s), 4.30-4.42 (1, m); ^{13}C NMR ($CDCl_3$) δ 29.53 (CH_3), 35.68 (CH_2), 44.54 (CH_2), 66.15 (CH_2), 67.93 (C), 171.04 (C).

Similarly, hydrolysis of pyranoside **165** (130 mg. 0.515 mmol) and oxidation with PCC (275 mg, 1.25 mmol) and 3Å sieves (300 mg) gave 49 mg (0.38 mmol, 74%) of **142**, $[\alpha]_D$ -20.1° (c 1.0 , EtOH).

6-Benzyloxymethyl-3,4-dihydro-2H-pyran [215].

To a suspension of $LiAlH_4$ (1.90g, 50 mmol) in dry THF (75mL) at 0 °C was added sodium 3,4-dihydro-2H-pyran-2-carboxylate **216** (10.0g, 66.6 mmol) in portions. The reaction was allowed to stir at ambient temperature for 2h and then quenched by successive addition of H_2O (1.9 mL), 10% NaOH (1.9 mL), and H_2O (5.7 mL) while stirring vigorously. Filtration through Celite and removing all of the volatiles in vacuo gave the product **217** as a pale yellow liquid (7.47g, 65.4 mmol, 98%) that was used without further purification. Spectral data for **217** : IR ($CHCl_3$) cm^{-1} 3590,3455, and 1648; ^1H NMR ($CDCl_3$) δ 1.60-1.86 (2, m), 1.91-2.20 (2, m), 2.62 (1, bs), 3.60-3.75 (2, m), 4.70 (1, m), and 6.39 (1, d, J=6Hz); ^{13}C NMR ($CDCl_3$) δ 19.25 (CH_2), 23.77 (CH_2), 65.18 (CH_2), 75.47 (CH), 100.70 (CH), and 143.17 (CH).

To a suspension of 50% NaH (3.46g, 72 mmol) in dry THF (75 mL) at 0 °C was added dropwise a solution of the alcohol **217** in THF (75 mL). The reaction was

stirred for 1h at room temperature, then benzyl bromide (7.8 mL, 65.4 mmol) was added and the mixture stirred further for 2h. The reaction was quenched by careful addition of H_2O (100 mL), extracted with ethyl ether (3 X 50 mL), the combined organic layers dried ($MgSO_4$), filtered and concentrated in vacuo. K_2CO_3 (1g) was added and the residue was distilled to afford the product **215** as a pale yellow liquid b.p. 2 mm 127-129 ^oC (9.56g, 50.25 mmol, 77% yield over two steps). Spectral data for **215** : IR ($CHCl_3$) cm^{-1} 1647, 1494, 1451, 1363, and 1240; ^1H NMR ($CDCl_3$) δ 1.59-2.17 (4, m), 3.48-3.63 (2, m), 3.97-4.07 (1, m), 4.58 (2, d, J=2.6Hz), 4.63-4.70 (1, m), 6.39 (1, d, J=6.2Hz), and 7.23-7.40 (5, m); ^{13}C NMR ($CDCl_3$) δ 19.30 (CH_2), 24.51 (CH_2), 72.39 (CH_2), 73.35 (CH_2), 74.00 (CH), 100.40 (CH), 127.58 (CH), 127.66 (CH), 128.32 (CH), 138.05 (C), and 143.54 (CH).

Alkoxy-selenation. 6-Benzyloxymethyl-2-[(S)-methyl mandelate] 3-Phenylselenyl-3,4,5,6-tetrahydro-2H-pyran [224 & 225].

Bromine (0.22 mL, 0.68g 4.25 mmol) was added dropwise to a solution of diphenyl diselenide (1.325g, 4.245 mmol) in dry CH_2Cl_2 (10 mL), and the resulting mixture was then added dropwise via cannula to a solution of 6-benzyloxymethyl-3,4-dihydro-2H-pyran **215** (1.617g, 8.50 mmol) in CH_2Cl_2 (10 mL) at - 78 ^oC. Decolorization occurred instantly. The reaction was stirred 0.5h followed by rapid addition of a cooled (-78 ^oC) solution of (S)-(+)-methyl mandelate (1.412g, 8.50 mmol) and triethylamine (1.30 mL, 0.94g, 9.35 mmol) in CH_2Cl_2 (10 mL). The reaction was allowed to warm to room temperature and stir for 24h. The reaction mixture was washed with H_2O, saturated $NaHCO_3$, saturated NaCl (50 mL each), dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was

chromatographed on silica gel 60 (300g) eluted with 10% ethyl acetate/hexanes, affording 1.525g (2.90 mmol, 34%) of the less polar diastereomer **224** (R_f 0.17, 10% EtOAc/hexanes), and 1.756g (3.34 mmol, 39%) of the more polar diastereomer **225** (R_f 0.11, 10% EtOAc/hexanes).

Spectral data for **224** : an oil, $[\alpha]_D$ -29.8° (c 0.7, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1744; ^1H NMR ($CDCl_3$) δ 1.25-1.98 (3, m), 2.41 (1, tt, J=13,4Hz), 3.38 (1, dd, J=4,10Hz), 3.50 (1, dd, J=6,10Hz), 3.62-3.70 (1, m), 3.63 (3, s), 3.84 (1, m), 4.53 (2, d, J=2Hz), 5.26 (1, s), 5.33 (1, s), and 7.24-7.61 (15, m); ^{13}C NMR ($CDCl_3$) δ 23.51 (CH_2), 23.80 (CH_2), 43.30 (CH), 52.18 (CH_3), 68.97 (CH), 73.03 (CH_2), 73.19 (CH_2), 75.59 (CH), 98.67 (CH), 127.29 (CH), 127.38 (CH), 127.46 (CH), 128.28 (CH), 129.11 (CH), 129.84 (C), 133.43 (CH), 136.34 (C), 138.35 (C), and 171.31 (C).

Spectral data for **225** : an oil, $[\alpha]_D$ +83.8° (c 0.7, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1749; ^1H NMR ($CDCl_3$) δ 1.60-2.10 (3, m), 2.62 (1, tt, J=4,13Hz), 3.50-3.67 (3, m), 3.71 (3, s), 4.26 (1, m), 4.67 (2, s), 5.03 (1, s), 5.28 (1, s), and 7.19-7.48 (15, m); ^{13}C NMR ($CDCl_3$) δ 23.62 (CH_2), 23.94 (CH_2), 29.63 (CH), 43.39 (CH), 52.21 (CH_3), 68.93 (CH), 73.09 (CH_2), 73.21 (CH_2), 76.73 (CH), 97.91 (CH), 127.24 (CH), 127.46 (CH), 128.27 (CH), 128.58 (CH), 128.70 (CH), 129.02 (CH), 129.61 (C), 133.33 (CH), 135.69 (C), 138.40 (C), and 170.77 (C).

Selenoxide elimination. 6-Benzyloxy-2-[(S)-methyl mandelate]-5,6-dihydro-2H-pyran [232 & 304].

To a solution of the more polar selenide **225** (1.449 g, 2.757 mmol) and pyridine (400 μL, 391 mg, 5 mmol) in CH_2Cl_2 (10 mL) was added dropwise 30%

H_2O_2 (680 μL, 755 mg, 6.62 mmol) diluted with additional H_2O (680 μL). The resulting mixture was stirred at ambient temperature for 48h, then diluted with CH_2Cl_2 (100 mL), washed with saturated $NaHCO_3$, saturated NaCl (50 mL each), dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (200g) eluted with 20% ethyl acetate/hexanes, affording 905 mg (2.456 mmol, 89%) of **232** (R_f 0.24, 20% EtOAc/hexanes). Spectral data for **232** : m.p. 57-58 °C, $[\alpha]_D$ +63.2° (c 1.3 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1747; ^1H NMR ($CDCl_3$) δ 1.92-2.06 (1, m), 2.16-2.34 (1, m), 3.54 (2, d, J=4Hz), 3.61 (3, s), 4.27 (1, m), 4.60 (2, d, J=4Hz), 5.04 (1, bs), 5.27 (1, s), 5.75 (1, dm, J=10Hz), 6.07 (1, dd, J=6, 10Hz), and 7.23-7.50 (10, m); ^{13}C NMR ($CDCl_3$) δ 26.59 (CH_2), 52.07 (CH_3), 66.11 (CH), 71.97 (CH_2), 73.18 (CH_2), 77.68 (CH), 94.02 (CH), 124.52 (CH), 127.29 (CH), 127.49 (CH), 128.26 (CH), 128.53 (CH), 128.66 (CH), 129.39 (CH), 136.22 (C), 138.19 (C), and 171.28 (C).

Similarly the less polar selenide **224** (1.443 g, 2.746 mmol) gave 887 mg (2.407 mmol, 88%) of **304** (R_f 0.10, 10% EtOAc/hexanes). Spectral data for **304** : an oil , $[\alpha]_D$ +108.3° (c 1.2 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1743; ^1H NMR ($CDCl_3$) δ 1.87 (1, dt, J=18, 4Hz), 2.15 (1, dd, J=11,18 HZ), 3.34-3.47 (2, m), 3.69 (3, s), 4.00 (1, m), 4.52 (2, s), 5.25 (1, bs), 5.44 (1, s), 5.90 (1, dm, J=10 Hz), 6.03 (1, dbd, J=5, 10 Hz), and 7.22-7.44 (10, m); ^{13}C NMR ($CDCl_3$) δ 26.56 (CH_2), 52.06 (CH_3), 66.09 (CH), 72.06 (CH_2), 73.14 (CH_2), 76.21 (CH), 93.83 (CH), 124.96 (CH), 127.47 (CH), 128.22 (CH), 128.29 (CH), 128.40 (CH), 128.87 (CH), 136.84 (C), 138.11 (C), and 171.50 (C).

Appendage ester reduction. 6(S)-6-Benzyloxymethyl-2(R)-2-[(S)-1'-ethoxy-2'-hydroxy-1'-phenyl]-5,6-dihydro-2H-pyran [233].

To a suspension of $LiAlH_4$ (92 mg, 2.4 mmol) in dry THF (5mL) at 0 °C was added a solution of **232** in THF (5 mL) dropwise via cannula. The reaction was stirred 0.5h, then quenched by successive addition of H_2O (92 μL), 10% NaOH (92 μL), and H_2O (276 μL) while stirring vigorously. The mixture was filtered through Celite, rinsed with EtOAc (100 mL), and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (100g) eluted with 30% ethyl acetate/hexanes, affording 747 mg (2.194 mmol, 95%) of **233** (R_f 0.22, 30% EtOAc/hexanes). Spectral data for **233** : an oil, $[\alpha]_D$ +58.8° (c 1.1 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3580, and 3472; ^1H NMR ($CDCl_3$) δ 1.88-2.18 (2, m), 2.96 (1, bs), 3.58 (2, d, J=5Hz), 3.68-3.80 (2, m), 4.32 (1, m), 4.63 (2, s), 4.91 (1, dd, J=4,7Hz), 5.01 (1, bs), 5.72 (1, dm, J=10 Hz), 6.03 (1, dd, J=5, 10Hz), and 7.22-7.45 (10, m); ^{13}C NMR ($CDCl_3$) δ 26.63 (CH_2), 66.44 (CH), 67.57 (CH_2), 72.18 (CH_2), 73.32 (CH_2), 80.99 (CH), 93.20 (CH), 125.52 (CH), 126.79 (CH), 127.66 (CH), 127.87 (CH), 128.35 (CH), 128.40 (CH), 128.58 (CH), 137.95 (C), and 138.89 (C).

Epoxidation. 6(S)-6-Benzyloxymethyl-3(R),4(R)-3,4-epoxy-2(R)-2-[(S)-1'-ethoxy-2'-hydroxy-1'-phenyl]-3,4,5,6-tetrahydro-2H-pyran [235].

To a solution of **233** (675 mg, 1.98 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added solid 50% mCPBA (821mg total, 2.38 mmol active) in portions. The reaction was maintained at 0-5 °C for 8 days then washed with 10% Na_2CO_3 (50 mL), the aqueous layer extracted with CH_2Cl_2 (3 X 25 mL), the combined organics dried

(Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (200g) eluted with 50% ethyl acetate/hexanes, affording 53 mg (0.15 mmol, 7%) of the less polar diastereomer **234** (R_f 0.21, 50% EtOAc/hexanes), and 624 mg (1.751 mmol, 88%) of the more polar diastereomer **235** (R_f 0.17, 50% EtOAc/hexanes).

Spectral data for the less polar anti-epoxide **234** : an oil, $[\alpha]_D$ +99.8° (c 2.4 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3477; ^1H NMR ($CDCl_3$) δ 1.72-1.98 (2, m), 2.90 (1, bs), 3.01 (1, d, J=4Hz), 3.32-3.50 (3, m), 3.66-3.78 (2, m), 4.27 (1, sextet, J=5Hz), 4.58 (2, d, J=3Hz), 4.89 (1, dd, J=4, 7Hz), 5.02 (1, s), and 7.24-7.40 (10, m); ^{13}C NMR ($CDCl_3$) δ 25.16 (CH_2), 49.15 (CH), 49.86 (CH), 63.89 (CH), 67.15 (CH_2), 71.84 (CH_2), 73.29 (CH_2), 80.94 (CH), 93.41 (CH), 126.86 (CH), 127.49 (CH), 127.64 (CH), 128.11 (CH), 128.34 (CH), 128.47 (CH), 137.72 (C), and 138.02 (C).

Spectral data for the more polar syn-epoxide **235**: an oil, $[\alpha]_D$ +121.5° (c 0.5 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3488, 1492, and 1452; ^1H NMR ($CDCl_3$) δ 1.76-2.05 (2, m), 2.98 (1, bs), 3.26 (1, t, J=4Hz), 3.38-3.85 (5, m), 4.19 (1, m), 4.59 (2, d, J=2Hz), 4.91 (1, dd, J=3, 8Hz), 5.03 (1, d, J=3Hz), and 7.24-7.42 (10, m); ^{13}C NMR ($CDCl_3$) δ 26.78 (CH_2), 50.67 (CH), 51.32 (CH), 64.26 (CH), 67.26 (CH_2), 71.91 (CH_2), 73.19 (CH_2), 80.14 (CH), 92.29 (CH), 126.96 (CH), 127.61 (CH), 128.04 (CH), 128.34 (CH), 128.44 (CH), 137.87 (C), and 138.34 (C).

Epoxide Opening. 6(S)-6-Benzyloxymethyl-2(R)-2-[(S)-1'-ethoxy-2'-hydroxy-1'-phenyl]-4(R)-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran [237].

To a suspension of $LiAlH_4$ (75 mg, 1.97 mmol) in dry THF (3 mL) at 0 °C was added a solution of **235** (600 mg, 1.683 mmol) in THF (3 mL) dropwise via cannula.

The reaction was stirred 4h at this temperature and then quenched by successive addition of H_2O (75 μL), 10% NaOH (75 μL), and H_2O (225 μL) while stirring vigorously. The mixture was filtered through Celite, rinsed with EtOAc (100 mL), and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (100g) eluted with 75% ethyl acetate/hexanes, affording 566 mg (1.579 mmol, 94%) of **237** (R_f 0.38, EtOAc). Spectral data for **237** : an oil, $[\alpha]_D$ +140.2° (c 1.2 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 3472; ^1H NMR ($CDCl_3$) δ 1.62-2.04 (4, m), 3.45-3.82 (5, m), 4.00 (1, bs), 4.13 (1, bs), 4.52-4.66 (3, m), 4.85 (1, dd, J=3, 8Hz), 4.93 (1, bs), and 7.22-7.37 (10, m); ^{13}C NMR ($CDCl_3$) δ 34.08 (CH_2), 34.94 (CH_2), 63.09 (CH), 63.81 (CH), 66.88 (CH_2), 72.94 (CH_2), 73.19 (CH_2), 79.15 (CH), 95.08 (CH), 126.91 (CH), 127.05 (CH), 127.52 (CH), 128.07 (CH), 128.27 (CH), 128.43 (CH), 137.74 (C), and 138.10 (C).

6(S)-6-Benzyloxymethyl-2(R)-2-[(S)-2'-^{t}butyldiphenylsilyloxy-1'-ethoxy-1'-phenyl]-4(R)-4-^{t}butyldiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran [238].

To a solution of **237** (565 mg, 1.576 mmol) and imidazole (452 mg, 6.636 mmol) in dry DMF (3 mL) was added t-butyldiphenylchlorosilane (822 μL, 869 mg, 3.161 mmol) dropwise. The reaction was stirred at ambient temperature for 72h, then diluted with ethyl ether (100 mL), washed with H_2O, brine (50 mL each), dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (100g) eluted with 10% ethyl acetate/hexanes, affording 1.316 g (1.576 mmol, 100%) of **238** (R_f 0.48, 20 % EtOAc/hexanes). Spectral data for **238** : an oil, $[\alpha]_D$ +57.4° (c 1.1 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 1470, 1426, and 1111; ^1H NMR

($CDCl_3$) δ 0.96 (8, s), 1.03 (8, s), 1.07 (2, s), 1.52-1.78 (4, m), 3.39 (1, dd, J=5, 10Hz), 3.49 (1, dd, J=4, 10Hz), 3.69 (1, dd, J=7, 10Hz), 4.05-4.16 (2, m), 4.54 (2, dd, J=12, 20Hz), 4.63 (1, m), 4.74 (1, d, J=4Hz), 4.89 (1, t, J=6Hz), and 7.22-7.78 (30, m); ^{13}C NMR ($CDCl_3$) δ 19.10 (C), 26.53 (CH_3), 26.78 (CH_3), 26.86 (CH_3), 34.89 (CH_2), 35.88 (CH_2), 63.30 (CH), 64.60 (CH), 68.21 (CH_2), 73.10 (CH_2), 73.23 (CH_2), 78.32 (CH), 94.55 (CH), 127.41 (CH), 127.52 (CH), 127.69 (CH), 127.75 (CH), 128.00 (CH), 128.26 (CH), 129.38 (CH), 129.46 (CH), 129.61 (CH), 133.46 (C), 133.60 (C), 134.13 (C), 134.49 (C), 134.76 (CH), 135.46 (CH), 135.58 (CH), 135.73 (CH), 135.94 (CH), 138.46 (C), and 140.30 (C).

2(R)-2-[(S)-2'-^{t}Butyldiphenylsilyloxy-1'-ethoxy-1'-phenyl]-4(R)-4-^{t}butyldiphenylsilyloxy-6(S)-6-hydroxymethyl-3,4,5,6-tetrahydro-2H-pyran [239].

A mixture of **238** (195 mg, 0.233 mmol) and 10% Pd/C catalyst (50 mg) in 100% ethanol (5 mL) was stirred at ambient temperature under 1 atm H_2 for 72h. Filtration through a plug of silica, removal of volatiles in vacuo, and chromatography of the residue on silica gel 60 (25 g) eluted with 20% EtOAc/hexanes afforded 173 mg (0.232 mmol, 99%) of **239** (R_f 0.18, 20% EtOAc/hexanes). Spectral data for **239** : a tacky solid, $[\alpha]_D$ +64.0° (c 0.5 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3590, 1470, and 1426; ^1H NMR ($CDCl_3$) δ 0.98 (8, s), 1.04 (8, s), 1.07 (2, s), 1.52-1.60 (3, m), 1.68-1.80 (2, m), 3.37-3.50 (1, m), 3.58-3.66 (1, m), 3.70 (1, dd, J=7, 10Hz), 4.04-4.13 (2, m), 4.56 (1, m), 4.72 (1, d, J=4Hz), 4.81 (1, t, J=6Hz), and 7.24-7.80 (25, m); ^{13}C NMR ($CDCl_3$) δ 19.13 (C), 26.81 (CH_3), 26.86 (CH_3), 34.20 (CH_2), 35.84 (CH_2), 64.35 (2xCH), 65.97 (CH_2), 68.21 (CH_2), 78.54 (CH), 94.36 (CH), 127.43 (CH),

127.49 (CH), 127.55 (CH), 127.64 (CH), 128.10 (CH), 129.49 (CH), 129.55 (CH), 133.49 (C), 133.55 (C), 134.08 (C), 134.46 (C), 135.62 (CH), 135.72 (CH), 135.96 (CH), and 140.08 (C).

4(R)-4-^{t}Butyldiphenylsilyloxy-6(S)-6-hydroxymethyl-2-methoxy-3,4,5,6-tetrahydro-2H-pyran [240].

To a solution of **239** (62 mg, .083 mmol) in dry methanol (2 mL) was added p-TsOH monohydrate (10 mg). The reaction was stirred at ambient temperature for 6h and then washed with satd $NaHCO_3$ (20 ml), extracted with ethyl ether (3 X 20 mL), dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (100g) eluted with 50% ethyl ether/hexanes, affording 3 mg (7.5 μmol, 9%) of the less polar anomer (R_f 0.25, ethyl ether/hexanes), and 25 mg (62.4 μmol, 76%) of the more polar anomer **240** (R_f 0.22, ethyl ether/hexanes). Spectral data for **240** : m.p.96-97 °C, $[\alpha]_D$ -15.9° (c 0.7 , $CHCl_3$), Lit.[98] m.p. 97-98 °C, $[\alpha]_D$ -11.2° (c 4.03 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 3593, and 3440; ^{1}H NMR ($CDCl_3$) δ 1.09 (9, s), 1.30-2.20 (5, m), 3.53 (3, s), 3.45-3.70 (2, m), 4.16 (1, m), 4.31 (1, m), 4.90 (1, dd, J=2, 10Hz), 7.27-7.46 (6, m), and 7.60-7.70 (4, m); ^{13}C NMR ($CDCl_3$) δ 19.13 (C), 19.18 (C), 26.81 (CH_3), 26.86 (CH_3), 34.18 (CH_2), 35.80 (CH_2), 64.35 (CH), 65.94 (CH_2), 68.21 (CH_2), 78.52 (CH), 94.35 (CH), 127.44 (CH), 127.49 (CH), 127.55 (CH), 127.64 (CH), 128.10 (CH), 129.50 (CH), 129.55 (CH), 133.47 (C), 133.52 (C), 134.06 (C), 134.44 (C), 135.61 (CH), 135.73 (CH), 135.96 (CH), and 140.08 (C).

2-[(S)-Methyl mandelyl]-3-phenylselenyl 3,4,5,6-tetrahydro-2H-pyran [278 & 279].

To a solution of dihydropyran **9** (2.1 mL,1.9 g, 23mmol) in CH_2Cl_2 (10 mL) cooled to -78 °C was added dropwise a solution of PhSeBr in CH_2Cl_2 (30 mL), generated by addition of bromine (570 µL, 1,768 mg, 11 mmol) to diphenyl diselenide (3,421 mg, 11 mmol). Decolorization occurred immediately. The mixture was stirred 0.5 at this temperature, then a solution of (S)-methyl mandelate (4,021 mg, 24 mmol) and triethylamine (3.4 mL, 2.5g, 24 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was allowed to warm to room temperature slowly over 2 h, and further stirred for 6 h. The mixture was washed with H_2O, saturated aqueous $NaHCO_3$, and brine (50 mL each), the organic extract dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (400 g) eluted with 10% ethyl acetate/hexanes, affording 3.010 g (7.425 mmol, 34%) of the less polar diastereomer **278** (R_f 0.36, 20% EtOAc/hexanes), and 4.236 g (10.450 mmol, 48%) of the more polar product **279** (R_f 0.26, 20% EtOAc/hexanes).

Spectral data for the less polar selenide **278** : an oil, $[\alpha]_D$ -51.6° (c 2.2, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1745, 1577, and 1435; ^1H NMR ($CDCl_3$) δ 1.38-1.52 (1, m), 1.74-2.02 (2, m), 2.24-2.40 (1, m), 3.50-3.63 (2, m), 3.65 (3, s), 3.68-3.81 (1, m), 4.99 (1, d, J=3 Hz), 5.31 (1, s), and 7.24-7.68 (10, m); ^{13}C NMR ($CDCl_3$) δ 22.89 (CH_2), 25.53 (CH_2), 43.57 (CH), 52.15 (CH_3), 61.86 (CH_2), 75.89 (CH), 99.55 (CH), 127.11 (CH), 127.26 (CH), 128.43 (CH), 129.00 (CH), 129.49 (C), 133.84 (CH), 136.22 (C), and 171.19 (C).

Spectral data for the more polar selenide **279** : an oil, $[\alpha]_D$ +96.5° (c 1.5, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1750, 1577, and 1435; ^1H NMR ($CDCl_3$) δ 1.48-1.93 (3,

m), 2.30-2.42 (1, m), 3.41 (1, m), 3.48-3.59 (1, m), 3.69 (3, s), 3.98 (1, m), 4.62 (1, d, J=4 Hz), 5.22 (1, s), and 7.12-7.48 (10, m); ^{13}C NMR ($CDCl_3$) δ 23.55 (CH_2), 26.54 (CH_2), 43.45 (CH), 52.23 (CH_3), 62.60 (CH_2), 77.20 (CH), 99.38 (CH), 127.30 (CH), 127.55 (CH), 128.53 (CH), 128.70 (CH), 128.87 (CH), 128.99 (C), 134.00 (CH), 135.57 (C), and 170.74 (C).

2-[(S)-Methyl mandelyl]- 5,6-dihydro-2H-pyran [280 & 305].

To a cooled (0 °C) solution of the more polar phenylselenyl pyranoside **279** (4.230 g, 10.4 mmol) and pyridine (1.5 mL, 1.5 g, 19 mmol) in CH_2Cl_2 (50 mL) was added 30% aqueous H_2O_2 (2.6 mL, 2.9 g, 25 mmol, diluted to 6mL with additional H_2O). The mixture was allowed to stir at ambient temperature for 96 h. The mixture was washed with saturated aqueous $NaHCO_3$, then brine (50 mL each), the organic extract dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (150 g) eluted with 20% ethyl acetate/hexanes, affording 2.325 g (9.36 mmol, 90%) of the dihydropyran **280** (R_f 0.16, 20% EtOAc/hexanes). Spectral data for **280** : m.p. 57-58 °C, $[\alpha]_D$ +64.3° (c 2.6 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1748; ^1H NMR ($CDCl_3$) δ 1.92 (1, dt, J=18, 4 Hz), 2.31 (1, m), 3.68-3.75 (4, m), 4.06 (1, dt, J=11, 4 Hz), 4.93 (1, s), 5.22 (1, s), 5.74 (1, dm, J=10 Hz), 6.09 (1, dbd, J=5, 10 Hz), and 7.30-7.52 (5, m); ^{13}C NMR ($CDCl_3$) δ 24.54 (CH_2), 52.19 (CH_3), 57.69 (CH_2), 77.79 (CH), 92.85 (CH), 124.93 (CH), 127.32 (CH), 128.59 (CH), 129.81 (CH), 136.20 (C), and 171.34 (C).

The less polar phenylselenyl pyranoside **278** (3.000 g, 7.40 mmol) was similarly reacted and worked up to afford (1.653 g, 6.66 mmol, 90%) of the dihydropyran **305** (R_f 0.22, 20% EtOAc/hexanes). Spectral data for **305** : an oil,

$[\alpha]_D$ +115.5° (c 1.1 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1745; ^1H NMR ($CDCl_3$) δ 1.85 (1, dt, J=18, 4 Hz), 2.30 (1, m), 3.60-3.86 (5, m), 5.13 (1, bs), 5.37 (1, s), 5.89 (1, dm, J=10 Hz), 6.07 (1, dbd, J=5, 10 Hz), and 7.26-7.54 (5, m); ^{13}C NMR ($CDCl_3$) δ 24.52 (CH_2), 52.18 (CH_3), 57.51 (CH_2), 76.27 (CH), 92.94 (CH), 125.28 (CH), 127.31 (CH), 128.38 (CH), 128.47 (CH), 129.40 (CH), 136.75 (C), and 171.62 (C).

Reduction of appendage ester. 2(R)-2-[(S)-1'-Ethoxy-2'-hydroxy-1'-phenyl]-5,6-dihydro-2H-pyran [281].

To a cooled (0 °C) suspension of $LiAlH_4$ (353 mg, 9.3 mmol) in THF (10 mL) was added dropwise a solution of mandelate pyranoside **280** (2.303 g, 9.27 mmol) in THF (20 mL). The mixture was stirred 0.5 h at this temperature, then quenched by successive addition of H_2O (350 μL), 10% NaOH (350 μL), and H_2O (1060 μL) while stirring vigorously. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was chromatographed on silica gel 60 (100 g) eluted with 50% ethyl acetate/hexanes, affording 1.960 g (8.898 mmol, 96%) of the alcohol **281** (R_f 0.25, 50% EtOAc/hexanes). Spectral data for **281** : an oil, $[\alpha]_D$ +86.5° (c 0.9 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3590, and 3429; ^1H NMR ($CDCl_3$) δ 1.88-2.02 (1, m), 2.22-2.30 (1, m), 2.77 (1, m), 3.62-3.88 (3, m), 4.03 (1, dt, J=4, 11 Hz), 4.83-4.96 (2, m), 5.70 (1, dm, J=10 Hz), 6.02-6.13 (1, m), and 7.34 (5, m); ^{13}C NMR ($CDCl_3$) δ 24.57 (CH_2), 57.74 (CH_2), 67.43 (CH_2), 80.08 (CH), 91.79 (CH), 125.61 (CH), 126.91 (CH), 128.05 (CH), 128.49 (CH), 129.26 (CH), and 138.52 (C).

Epoxidation. 3(R),4(R)-3,4-Epoxy-2(R)-2-[(S)-1'-ethoxy-2'-hydroxy-1'-phenyl]-3,4,5,6-tetrahydro-2H-pyran [283].

To a cooled (0 °C) solution of the dihydropyran **281** (468 mg, 2.12 mmol) in CH_2Cl_2 (50 mL) was added solid 50% mCPBA (880 mg total, 2.55 mmol active) in portions. The mixture was stirred at 0-5 °C for 168 h, then washed with 10% aqueous Na_2CO_3 (50 mL), the aqueous layer extracted with CH_2Cl_2 (3 X 25 mL), the combined organic extracts dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (200g) eluted with 80% ethyl acetate/hexanes, affording 436 mg (1.845 mmol, 87%) of the more polar syn-epoxide **283** (R_f 0.29, 80% EtOAc/hexanes), and 47 mg (0.199 mmol, 9%) of the less polar anti-epoxide **282** (R_f 0.38, 80% EtOAc/hexanes).

Spectral data for the more polar syn-epoxide **283** : an oil, $[\alpha]_D$ +160 9° (c 1.1 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 3588, 3486, 1491, and 1452; ^1H NMR ($CDCl_3$) δ 1.92-2.02 (2, m), 3.08 (1, bs), 3.22 (1, t, J=3 Hz), 3.34-3.40 (1, m), 3.49 (1, td, J=4, 11 Hz), 3.60-3.73 (1, m), 3.76-4.00 (2, m), 4.83-4.92 (2, m), and 7.28-7.42 (5, m); ^{13}C NMR ($CDCl_3$) δ 24.52 (CH_2), 49.92 (CH), 51.39 (CH), 55.63 (CH_2), 67.06 (CH_2), 79.27 (CH), 91.37 (CH), 127.08 (CH), 128.16 (CH), 128.50 (CH), and 138.09 (C).

Spectral data for the less polar anti-epoxide **282**: an oil, $[\alpha]_D$ +159.6° (c 2.4 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 3593, and 3454; ^1H NMR ($CDCl_3$) δ 1.84-2.16 (2, m), 2.79 (1, s), 3.03 (1, d, J=4 Hz), 3.32-3.50 (2, m), 3.63-3.92 (3, m), 4.78-4.92 (2, m), and 7.34 (5, m); ^{13}C NMR ($CDCl_3$) δ 23.31 (CH_2), 49.83 (CH), 50.16 (CH), 54.80 (CH_2), 67.00 (CH_2), 80.35 (CH), 93.09 (CH), 126.91 (CH), 128.26 (CH), 128.52 (CH), and 137.58 (C).

Ethylamine opening of epoxide and acetylation. 4(R)-4-Acetoxy-2(R)-2-[(S)-1'-ethoxy-2'-hydroxy-1'-phenyl]-3(S)-3-N-ethylacetamido-3,4,5,6-tetrahydro-2H-pyran [285].

The epoxide **283** (355 mg, 1.50 mmol) was taken up in an excess of 70 wt % aqueous ethylamine (5 mL, 4g, 62 mmol) and stirred at ambient temperature for 144 h. The volatiles were removed in vacuo leaving a white solid. The residue was taken up in pyridine (5 mL) and cooled in an ice bath. Acetyl chloride (530 μL, 585 mg, 7.5 mmol) was added dropwise. The mixture was stirred at ambient temperature for 2 h, then poured into H_2O (50 mL), extracted with CH_2Cl_2 (3 X 20 mL), the organic extract dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (150g) eluted with 80% ethyl acetate/hexanes, affording 520 mg (1.276 mmol, 85%) of the desired product **285** (R_f 0.20, 80% EtOAc/hexanes), and 91 mg (0.22 mmol, 15%) of **284** (R_f 0.32, 80% EtOAc/hexanes).

Spectral data for the more polar product **285** : m.p. 114-115 °C, $[\alpha]_D$ +126.6° (c 1.1 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1737, and 1630; ^1H NMR ($CDCl_3$) δ 1.08 &1.17 (3, t, J=7 Hz), 1.74-2.30 (11, m), 2.94-3.52 (2, m), 3.67 & 3.76 (1, dd, J= 6, 12Hz), 4.05-4.46 (4, m), 4.74-4.92 (3, m), and 7.34 (5, s); ^{13}C NMR ($CDCl_3$) δ 14.36 & 15.56 (CH_3), 20.34 & 20.51 (CH_3), 20.69 (CH_3), 22.10 (CH_3), 29.37 & 30.45 (CH_2), 35.68 (CH_2), 52.44 (CH), 58.24 (CH_2), 67.15 & 67.46 (CH_2), 69.36 & 69.61 (CH), 76.17 (CH), 93.79 & 94.03 (CH), 126.87 & 126.97 (CH), 128.23 & 128.33 (CH), 128.37 & 128.56 (CH), 136.81 & 137.22 (C), 169.37 & 169 83 (C), 170.25 & 170.42 (C), and 170.71 & 170.86 (C).

Anal. Calcd. for $C_{21}H_{29}NO_7$: C, 61.90; H, 7.17; N, 3.44. Found: C, 61.54; H, 7.24; N, 3.50.

Spectral data for the less polar product **284** : m.p. 93-94 °C, $[\alpha]_D$ +54.0° (c 1.0 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 1734, 1641, 1425, 1365; ^1H NMR ($CDCl_3$) δ 0.87 & 1.13 (3, t, J= 7 Hz), 1.54-2.52 (11, m), 3.18-4.36 (8, m), 4.76-4.99 (1, m), 5.14 (~0.5, d, J= 7 Hz), 5.76 (~0.5, bs), 7.21-7.42 (5, m); ^{13}C NMR ($CDCl_3$) δ 13.63 & 14.13 (CH_3), 20.99 & 20.83 (CH_3), 22.51 (CH_3), 22.35 (CH_3), 29.51, 31.16 & 31.74 (CH_2), 37.13 (CH_2), 60.92 & 61.20 (CH_2), 62.47 (CH), 66.88 & 67.04 (CH_2), 68.62 & 69.17 (CH), 76.92 & 78.49 (CH), 97.21 & 98.20 (CH), 127.05 (CH), 127.37 (CH), 128.30 (CH), 128.40 (CH), 128.66 (CH), 128.79 (CH), 136.58 & 137.66 (C), 169.66 (C), 170.12 (C), 170.66 (C).

Acetate ester cleavage and methylation. 2(R)-2-[(S)-1'-Ethoxy-2'-methoxy-1'-phenyl]-3(S)-3-N-ethylacetamido-4(R)-4-methoxy-3,4,5,6-tetrahydro-2H-pyran [290].

To a solution of **285** (515 mg, 1.264 mmol) in anhydrous methanol (5 mL) was added sodium methoxide (25 mg, 0.46 mmol) and the mixture stirred at ambient temperature for 5 h. The volatiles were removed in vacuo and the remainder coevaporated with benzene (5 x 5 mL) to remove methanol. The residue was taken up in THF (5 mL) and added dropwise to a suspension of 50% NaH (134 mg, 2.8 mmol) in THF (5 mL) cooled in an ice bath. The mixture was stirred for 0.5 h and then methyl iodide (174 μL, 397 mg, 2.8 mmol) was added. The reaction was stirred 2 h at ambient temperature, quenched by careful addition of H_2O (50 mL), extracted with CH_2Cl_2 (100 mL, then 3 x 25 mL), the organic extracts dried (Na_2SO_4), filtered and volatiles

removed in vacuo. The residue was chromatographed on silica gel 60 (50 g) eluted with ethyl acetate, affording 435 mg (1.238 mmol, 98%) of dimethylated product **290** (R_f 0.16, 80% EtOAc/hexanes). Spectral data for **290** : an oil, $[\alpha]_D$ +149.5° (c 0.95 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 1624; ^1H NMR ($CDCl_3$) δ 1.14 & 1.21 (3, t, J=7 Hz), 1.65-2.06 (2, m), 2.11 & 2.21 (3, s), 3.00-3.16 (1, m), 3.10 & 3.14 (3, s), 3.24-3.77 (5, m), 3.42 & 3.43 (3, s), 4.12 (1, bt, J=12 Hz), 4.28 (1, dt, J=4, 11 Hz), 4.86-4.92 (2,m), and 7.24-7.46 (5, m); ^{13}C NMR ($CDCl_3$) δ 14.58 & 15.13 (CH_3), 22.34 & 22.60 (CH_3), 29.51 & 30.56 (CH_2), 35.56 (CH_2), 53.94 (CH), 56.86 & 57.27 (CH), 58.17 & 58.44 (CH_2), 59.07 (CH_3), 76.05 & 76.22 (CH), 77.01 (CH_2), 78.26 (CH), 92.94 & 93.17 (CH), 127.27 & 127.40 (CH), 127.92 & 128.08 (CH), 128.20 & 128.28 (CH), 138.09 & 138.46 (C), and 170.64 & 171.43 (C).

Dithiane formation. 5-(1',3'-Dithiane)-4(S)-4-N-ethylacetamido-3(R)-3-methoxypentanol [294].

To a cooled (-78 °C) solution of the pyranoside **290** (164 mg, 0.467 mmol) in CH_2Cl_2 (5 mL) was added successively 1,3-propanedithiol (70 μL,75 mg, 0.7 mmol) and BF_3-Et_2O (344 μL, 397 mg, 2.8 mmol) dropwise via syringe. The reaction was stirred 0.25 h at this temperature, then the bath replaced with an ice bath and stirred 1h, then allowed to stir at ambient temperature for 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL), extracted with CH_2Cl_2 (3 x 25 mL), the organic extract dried ($MgSO_4$), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (50 g) eluted with ethyl acetate, affording 100 mg (0.325 mmol, 70%) of the dithiane **294** (R_f 0.17, EtOAc). Spectral data for **294** : an oil, $[\alpha]_D$ -5.04° (c 0.6 , $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 3415, 1620, and 1422;

^1H NMR ($CDCl_3$) δ 1.16 & 1.20 (3, t, J=7 Hz), 1.72-2.20 (5, m), 2.13 & 2.20 (3, s), 2.80-2.97 (4, m), 3.04-3.82 (6, m), 3.51 & 3.54 (3, s), and 4.23 & 4.26 (1, d, J=4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.93 (CH_3), 22.19 (CH_3), 25.81 (CH_2), 29.75 & 29.99 (CH_2), 30.63 & 31.61 (CH_2), 37.09 (CH_2), 50.54 (CH_3), 56.34 (CH), 58.03 & 58.46 (CH_2), 61.25 & 61.29 (CH), 84.91 (CH), and 172.84 (C).

Swern oxidation and dioxolane formation. 5-(1',3'Dioxolane)-1-(1',3'-dithiane)-2(S)-2-N-ethylacetamido-3(R)-3-methoxypentane [295].

To a cooled (-78 °C) solution of oxalyl chloride (31 μL, 45 mg, 0.36 mmol) in CH_2Cl_2 (780 μL) was added dropwise a solution of dimethylsulfoxide (55 μL, 60.5 mg, 0.78 mmol) in CH_2Cl_2 (330 μL). The reaction was stirred for 10 minutes and then a solution of the alcohol **294** (100 mg, 0.325 mmol) in CH_2Cl_2 (330 μL) was added dropwise. The mixture was stirred for 0.25 h, then triethylamine (227 μL, 165 mg, 1.63 mmol) was added and the cold bath removed. When the mixture reached room temperature H_2O (10 mL) was added and vigorously stirred for 10 minutes, then extracted with CH_2Cl_2 (3 x 20 mL), the organic extract dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was taken up in benzene (50 mL), with a large excess of ethylene glycol (1 mL, 1.1 g, 18 mmol), and PPTS (25 mg) added. The mixture was heated in a Dean-Stark apparatus, draining and replacing with fresh benzene (3 x 15 mL) over 2 h. After cooling to room temperature the mixture was washed with saturated aqueous $NaHCO_3$ (25 mL), the aqueous phase extracted with CH_2Cl_2 (3 x 20 mL), the combined organic extracts dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (25 g) eluted with ethyl acetate, affording 101 mg (0.289 mmol, 90%) of the dithiane-

dioxolane **295** (R_f 0.30, EtOAc). Spectral data for **295** : an oil, $[\alpha]_D$ +3° (c 0.5 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1626, and 1422; ^1H NMR ($CDCl_3$) δ 1.19 & 1.20 (3, t, J=7 Hz), 1.75-2.18 (4, m), 2.08 & 2.21 (3, s), 2.79-2.98 (4, m), 3.10-3.48 (4, m), 3.52 & 3.53 (3, s), 3.82-4.05 (4, m), 4.20-4.32 (1, m, J=5 Hz), and 4.87 (1, 2xdd, J=3, 7 Hz); ^{13}C NMR ($CDCl_3$) δ 13.98 (CH_3), 22.28 (CH_3), 25.78 & 26.07 (CH_2), 30.02 & 30.09 (CH_2), 30.54 & 31.28 (CH_2), 33.62 (CH_2), 37.44 (CH_2), 50.15 & 51.62 (CH_3), 55.89 (CH), 61.11 & 61.50 (CH), 64.57 & 64.68 & 64.77 (2xCH_2), 84.99 (CH), 101.68 & 102.44 (CH), and 172.24 (C).

Dithiane cleavage and reduction. 5-(1',3'-Dioxolane)-2(R)-2-N-ethylacetamido-3(R)-3-methoxypentanol [296].

To a solution of N-bromosuccinimide (519 mg, 2.916 mmol), silver nitrate (520 mg, 3.062 mmol), and 2,4,6-trimethylpyridine (771 μL, 707 mg, 5.83 mmol) in aqueous 80% acetonitrile (15 mL) was added rapidly a solution of the dithiane-dioxolane **295** (170 mg, 0.486 mmol) in acetonitrile (1 mL). Precipitate formed immediately. The reaction was stirred for 10 minutes and then treated successively at one-minute intervals with saturated solutions of Na_2SO_3 , Na_2CO_3 , and NaCl (500 μL each) while stirring vigorously, followed by CH_2Cl_2 (15 mL). The mixture was filtered through Celite, rinsed with CH_2Cl_2 (100 mL), the filtrate washed with saturated aqueous $NaHCO_3$ (25 mL), the organic extract dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was taken up in methanol (2 mL), $NaBH_4$ (20 mg, 53 mmol) added and the mixture refluxed for 1 h. After cooling to room temperature the mixture was poured into H_2O (20 mL), extracted with CH_2Cl_2 (3 x 20 mL), the organic extract dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue

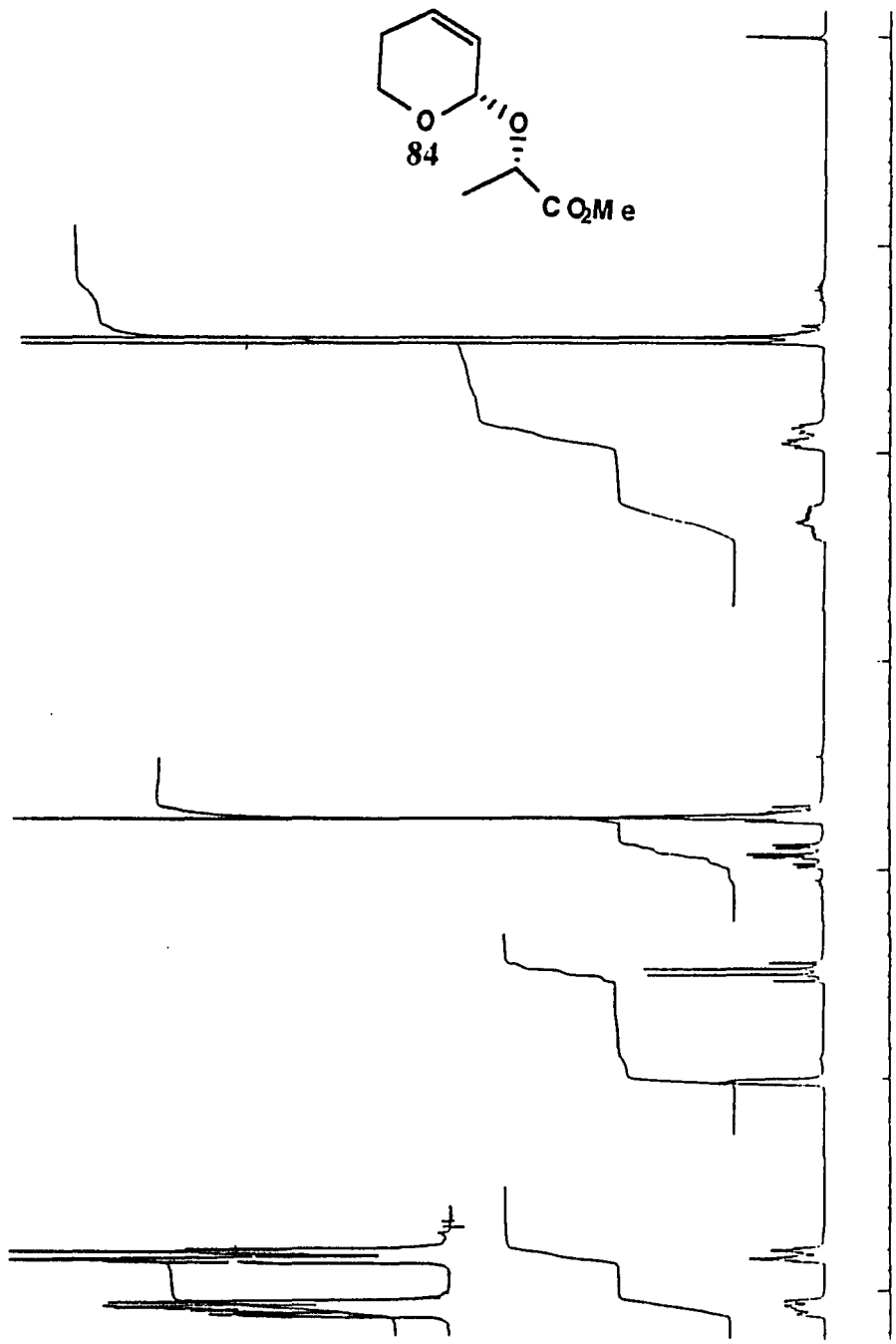
was chromatographed on silica gel 60 (25g) eluted with ethyl acetate, affording 60 mg (0.229 mmol, 47%) of the dioxolane alcohol **296** (R_f 0.15, EtOAc). Spectral data for **296** : an oil, $[\alpha]_D$ -42.3° (c 1.3 , $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3405, and 1610; ^1H NMR ($CDCl_3$) δ 1.21 (3, t, J=7 Hz), 1.72-2.70 (2, m), 2.16 (3, s), 3.18-3.81 (7, m), 3.39 (3, s), 3.82-4.02 (4, m), and 4.88 (1, dd, J=4, 5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.95 & 15.02 (CH_3), 21.45 & 22.20 (CH_3), 28.95 & 29.99 (CH_2), 33.36 & 37.15 (CH_2), 55.12 (CH_3), 58.42 & 58.69 (CH), 59.22 & 59.60 (CH_2), 64.77 (CH_2), 82.53 & 83.20 (CH), 101.89 & 102.59 (CH), and 172.22 & 173.25 (C).

Formation of the methyl pyranoside of the calicheamicin γ^1amino sugar. 5(R)-5-N-Ethylacetamido-2-methoxy-4(R)-4-methoxy-3,4,5,6-tetrahydro-2H-pyran [268].

To a solution of the dioxolane alcohol **296** (35 mg, 0.134 mmol) in methanol (500 μL) was added p-toluenesulphonic acid monohydrate (10 mg, 0.05 mmol). The mixture was stirred at ambient temperature for 20 h, diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ (20 mL), the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL), the organic extracts dried (Na_2SO_4), filtered and volatiles removed in vacuo. The residue was chromatographed on silica gel 60 (25g) eluted with ethyl acetate, affording 26 mg (0.111 mmol, 83%) of the methyl pyranoside **268**. Spectral data for **268** : an oil, $[\alpha]_D$ -90.77 ^{o} (c 0.65, $CHCl_3$); IR ($CHCl_3$) cm $^{-1}$ 1626, 1427, and 1360; ^{1}H NMR ($CDCl_3$) δ 1.14 & 1.20 (3, t, J=7 Hz), 1.72-2.60 (2, m), 2.09 & 2.15 (3, s), 3.02-4.12 (12, m), and 4.71 & 4.76 (1, m); ^{13}C NMR ($CDCl_3$) δ 14.60 (CH_3), 22.38 & 22.94 (CH_3), 33.17 & 34.61 & 35.86 (CH_2), 54.41 & 54.63 & 55.17 (2xCH_3), 57.80 & 58.09 (CH), 60.51 & 60.99 (CH_2), 74.44 & 75.68 (CH), 97.59 & 98.11 (CH), and 170.69 & 171.45 (C).

APPENDIX A.

NMR SPECTRA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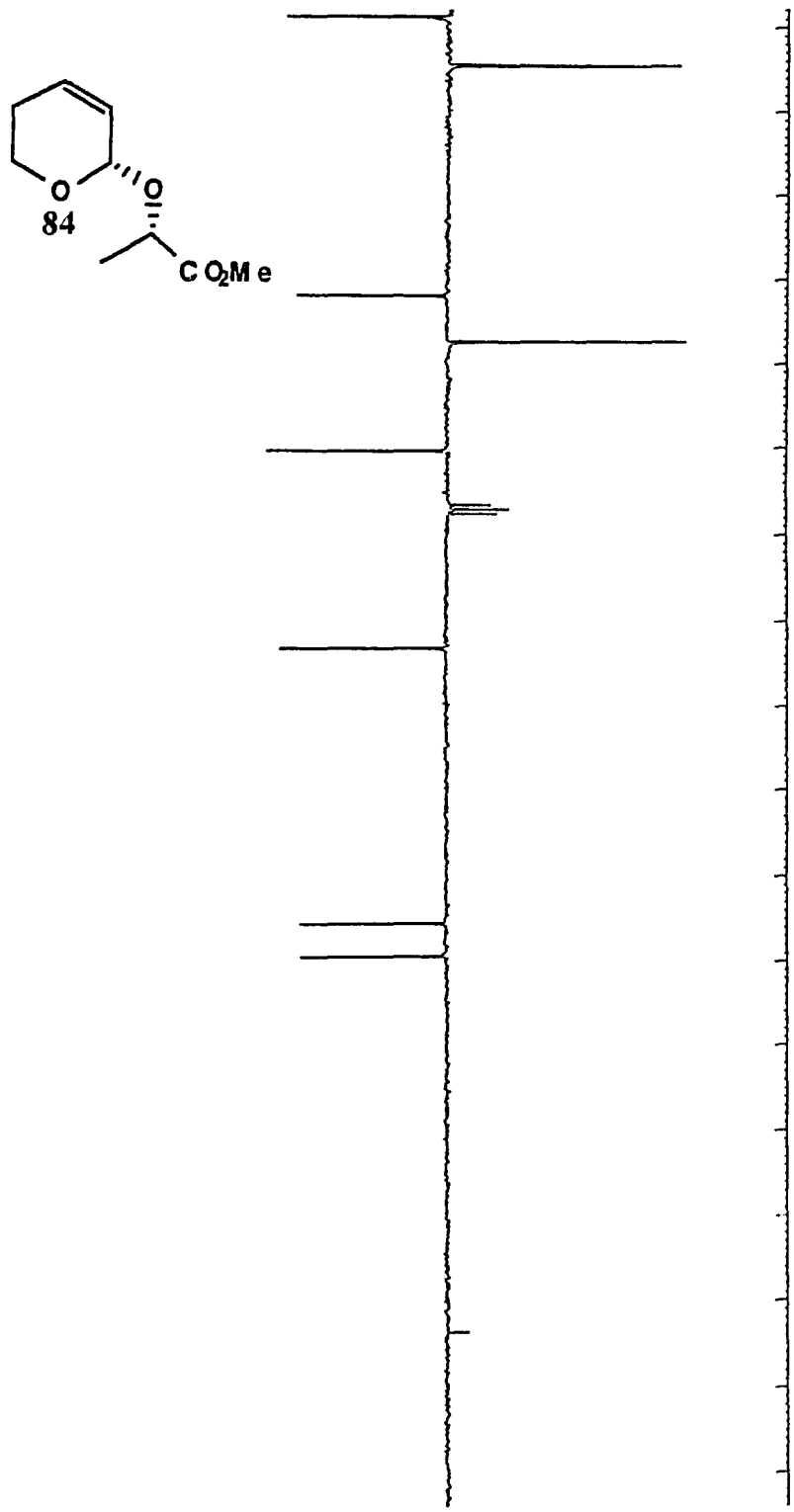
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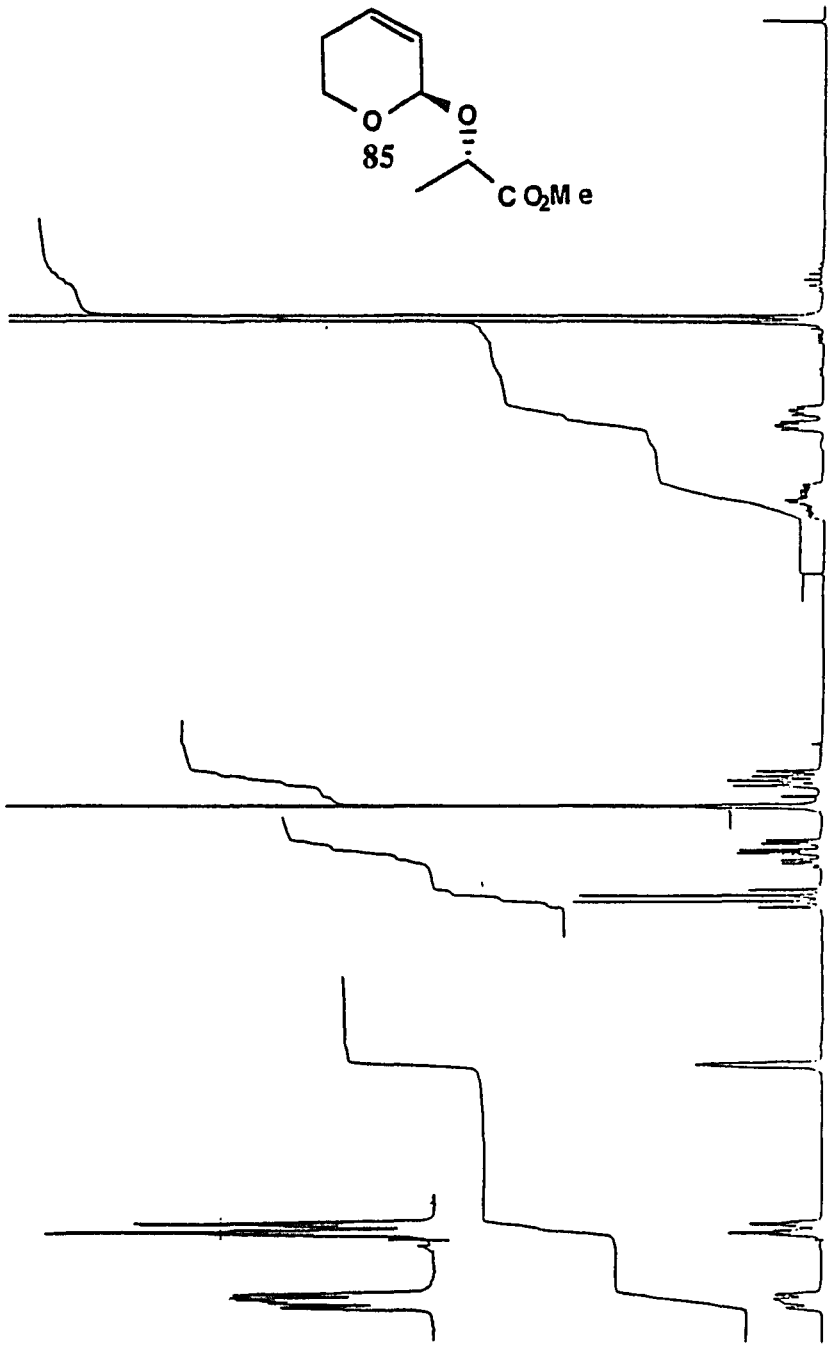
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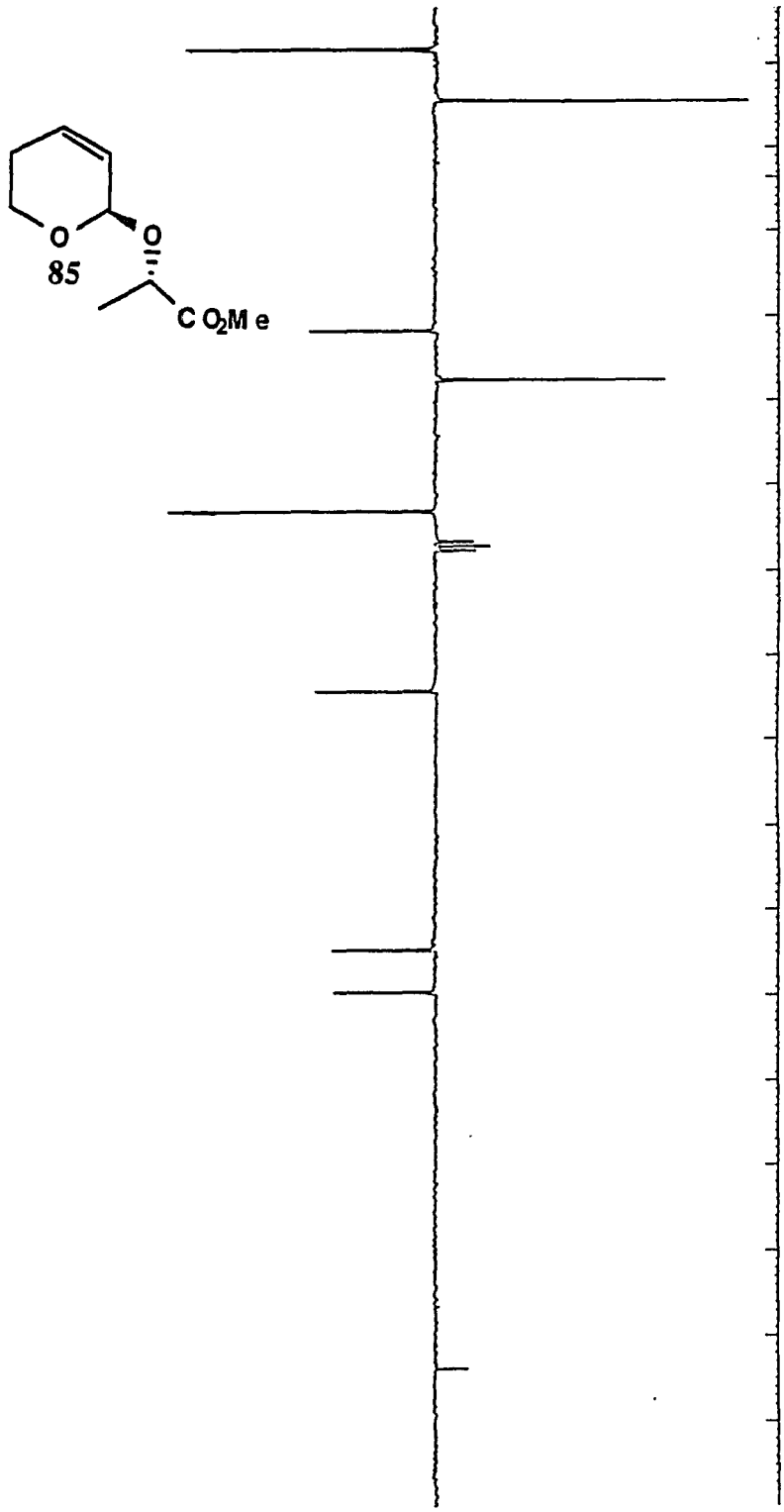
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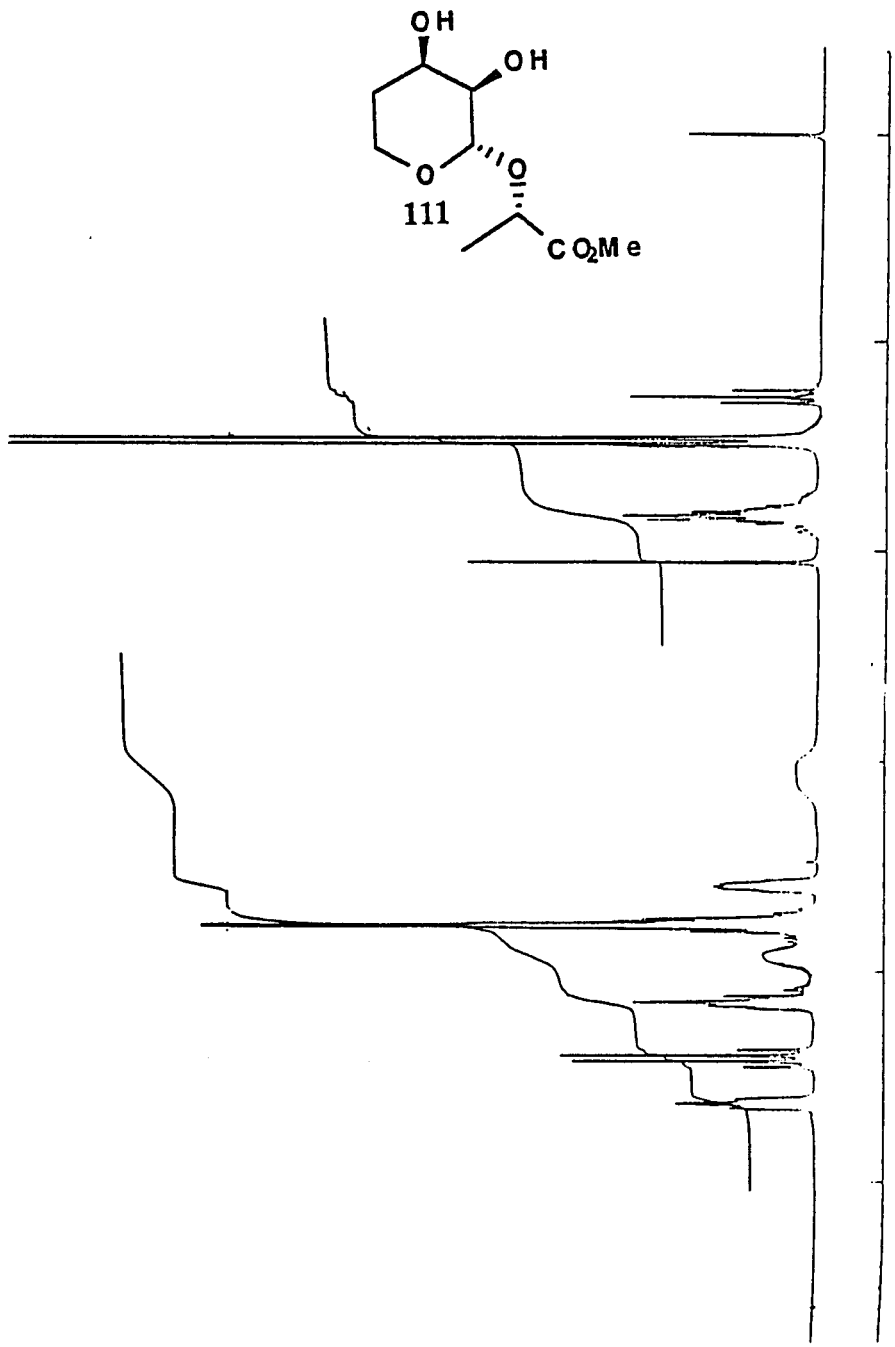
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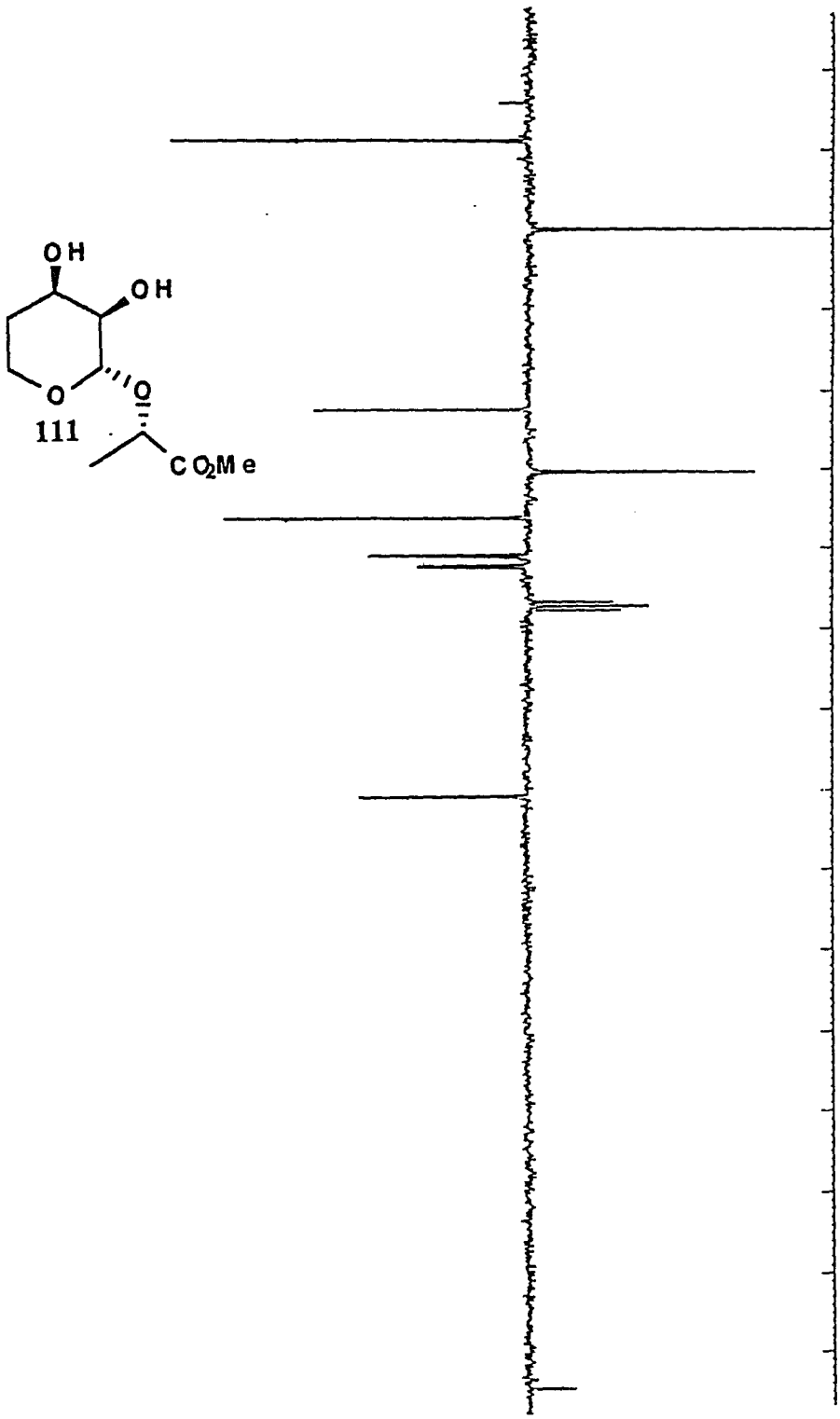

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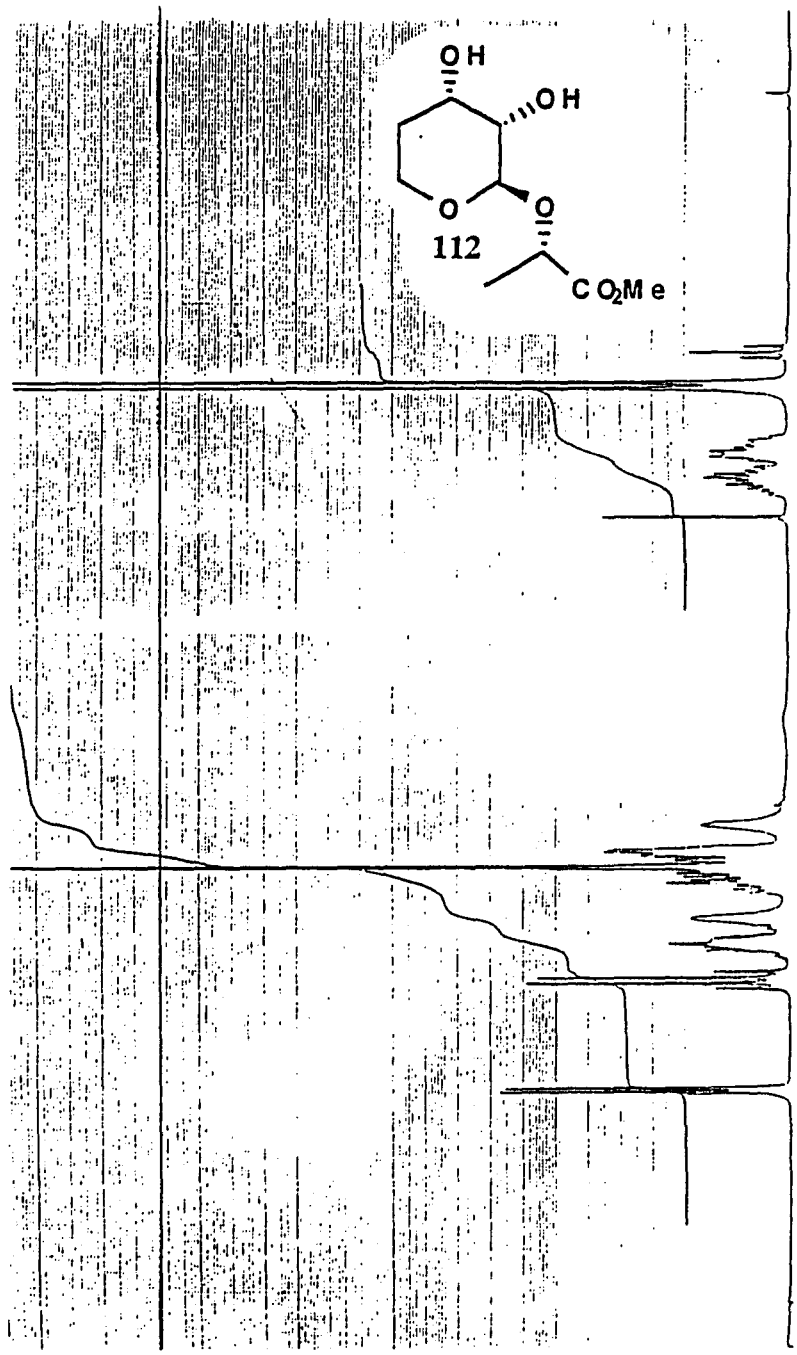
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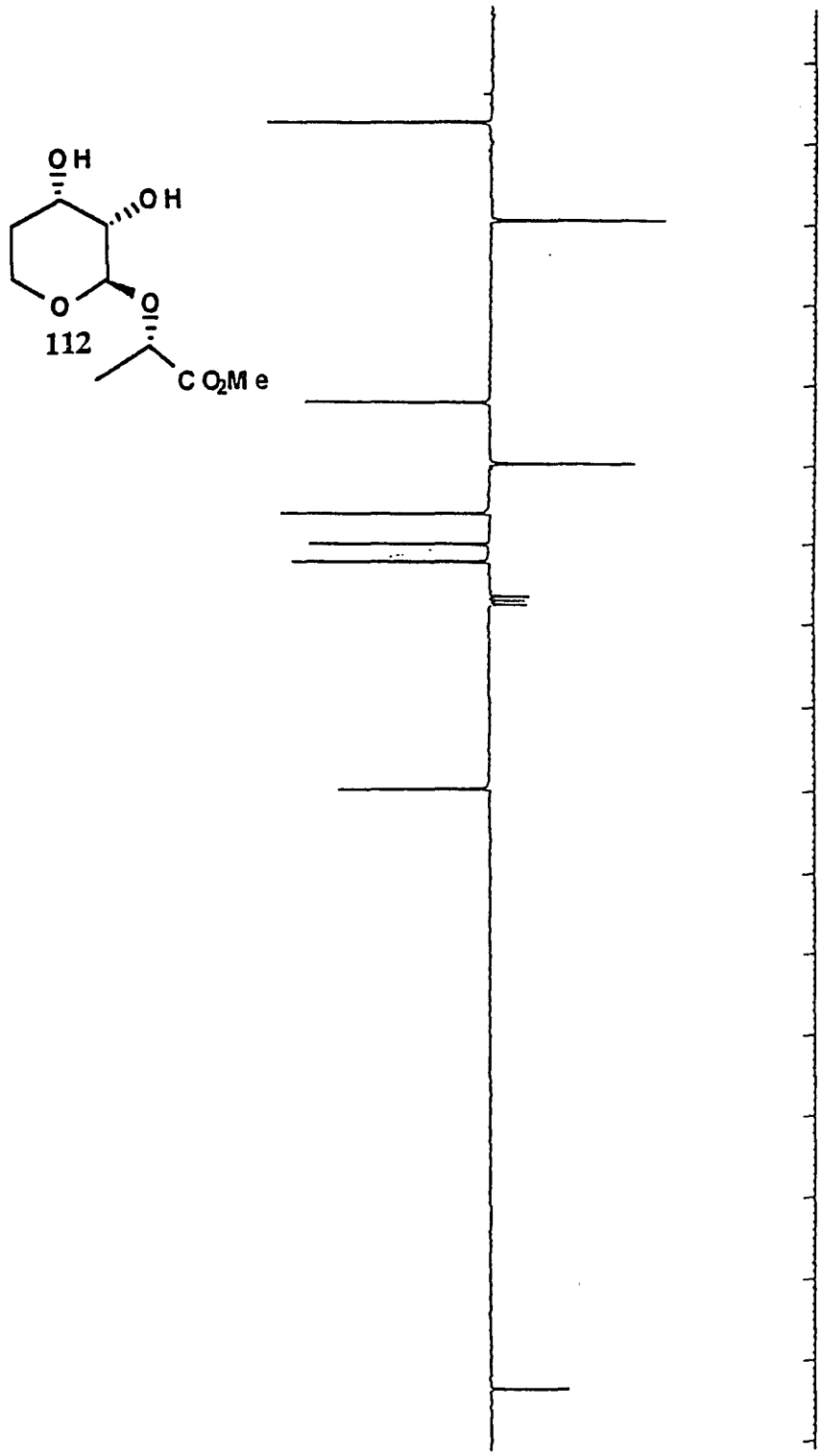
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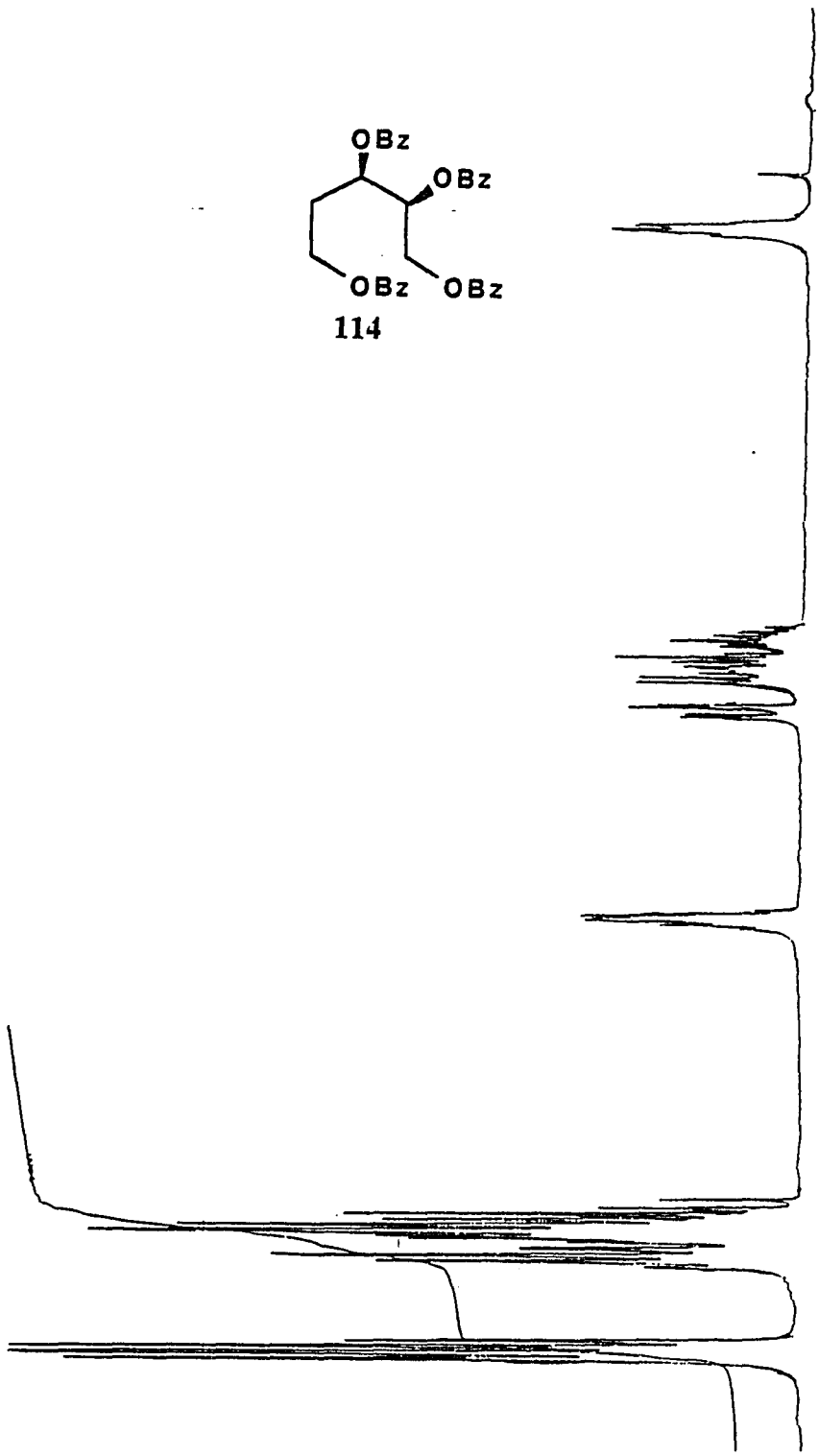

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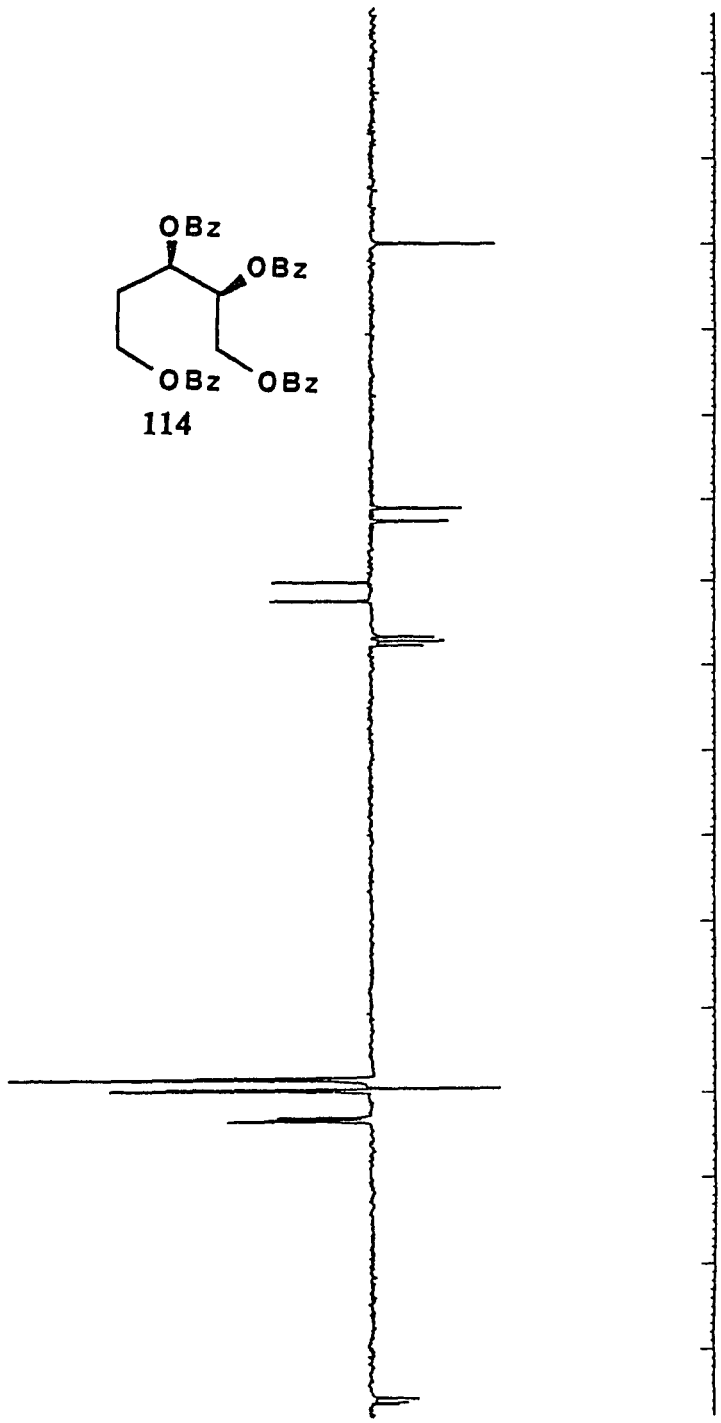

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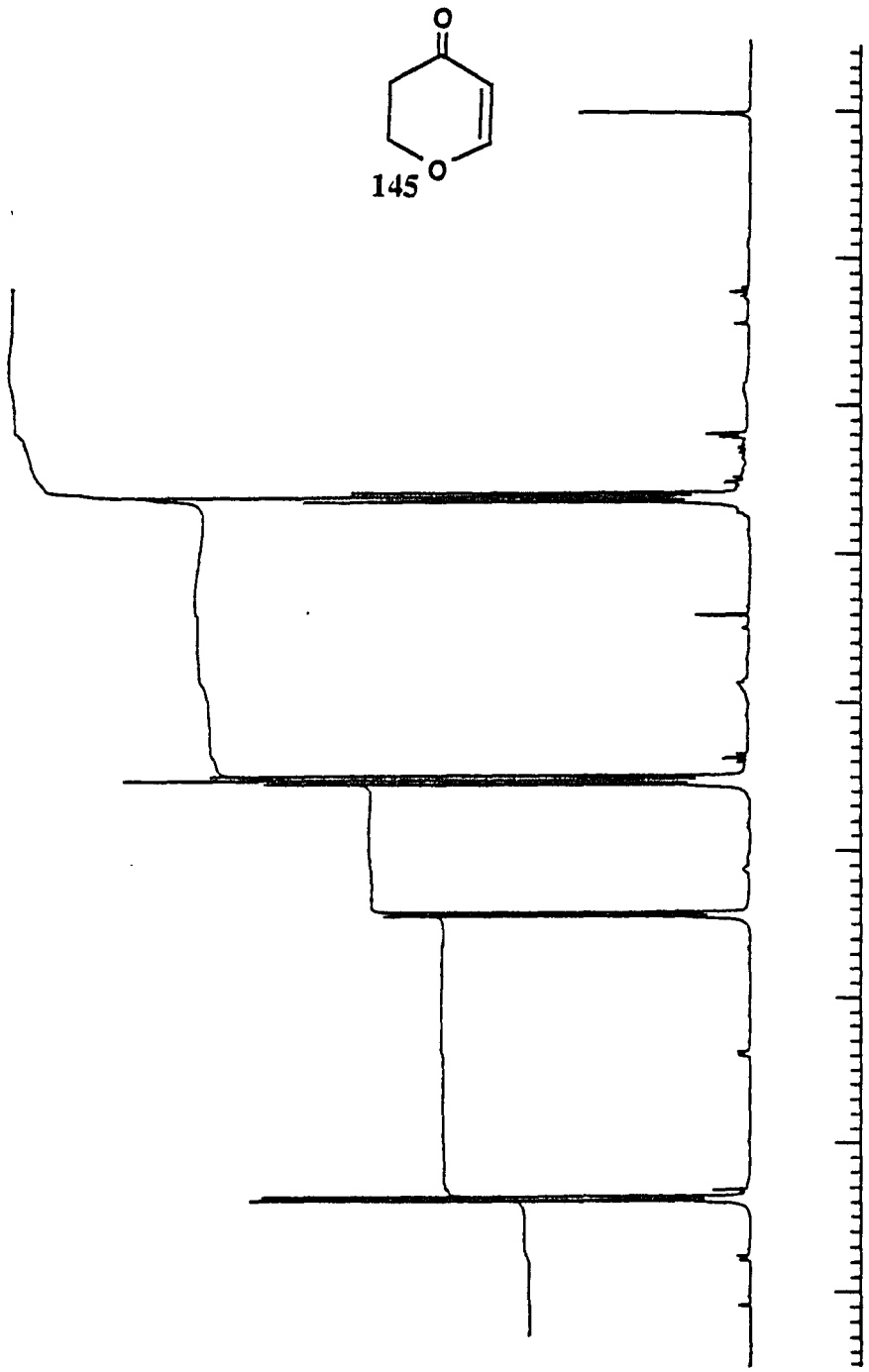
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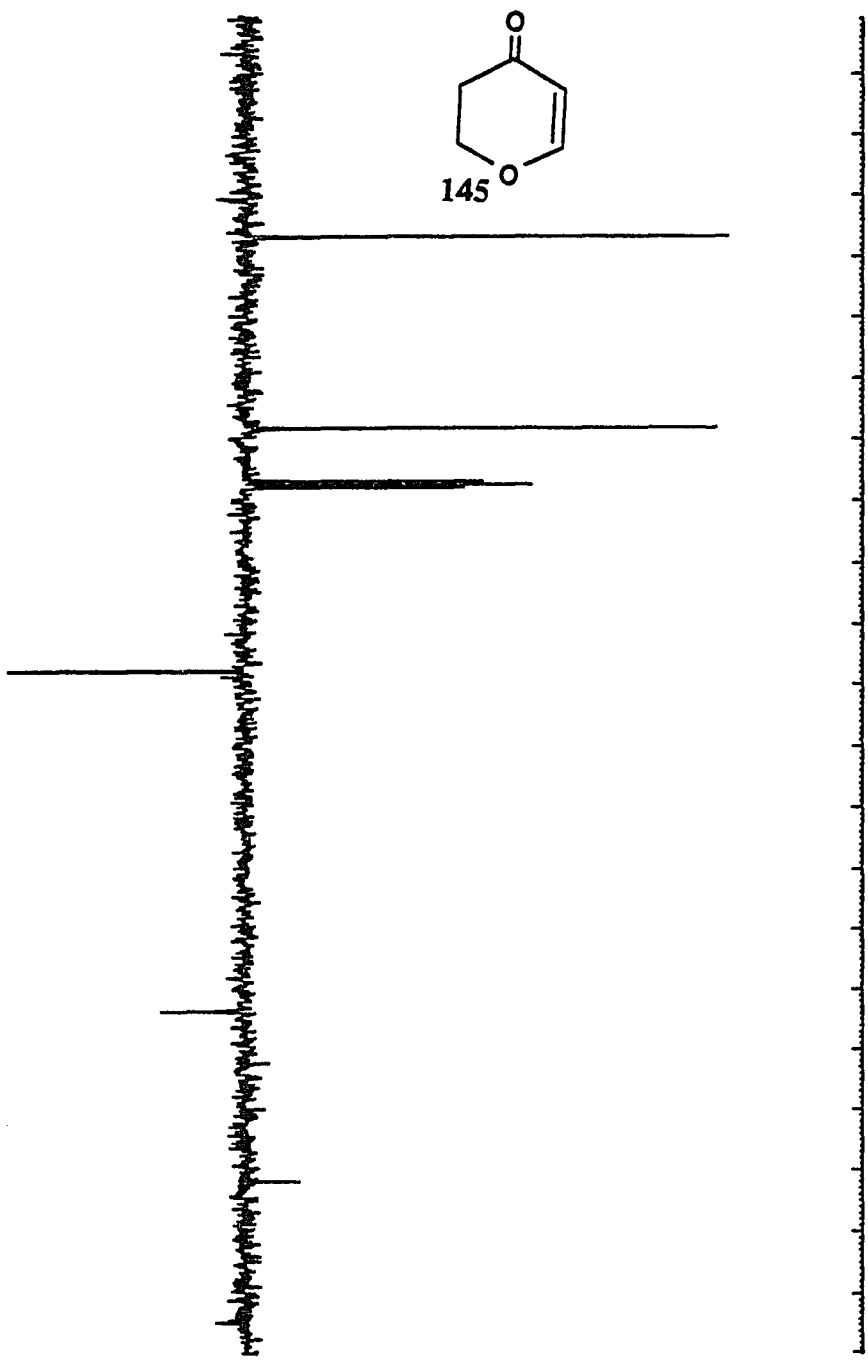
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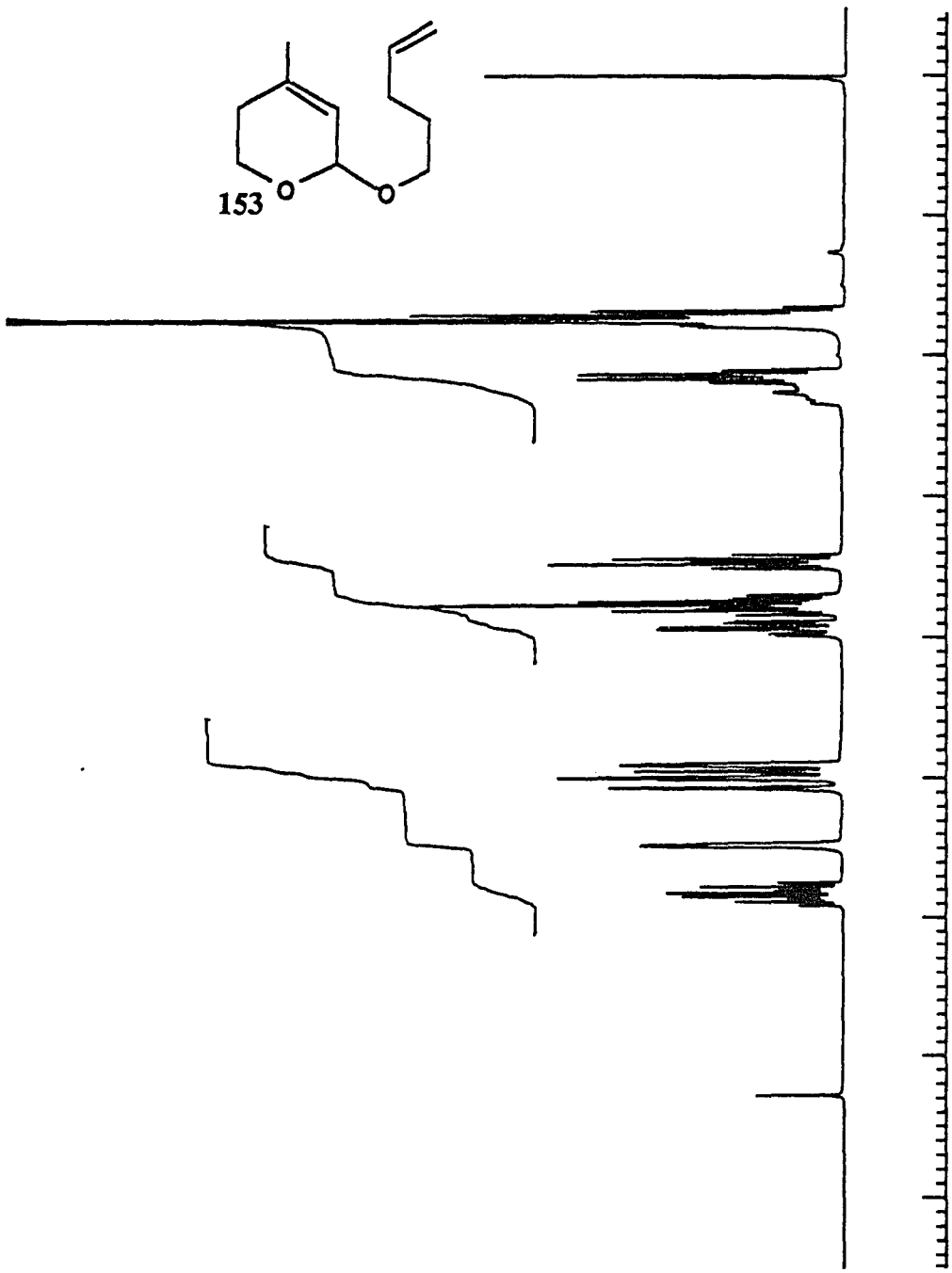
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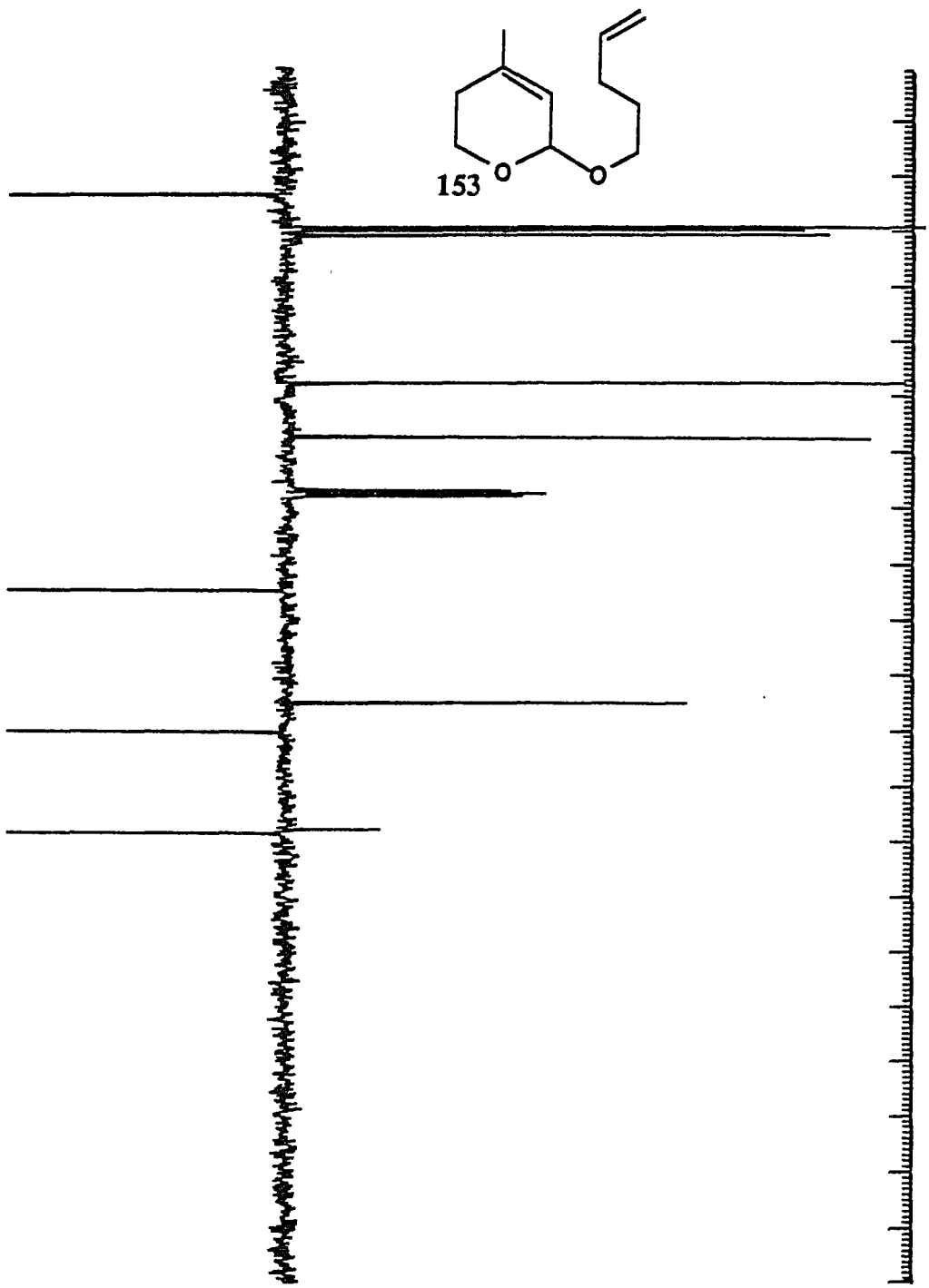
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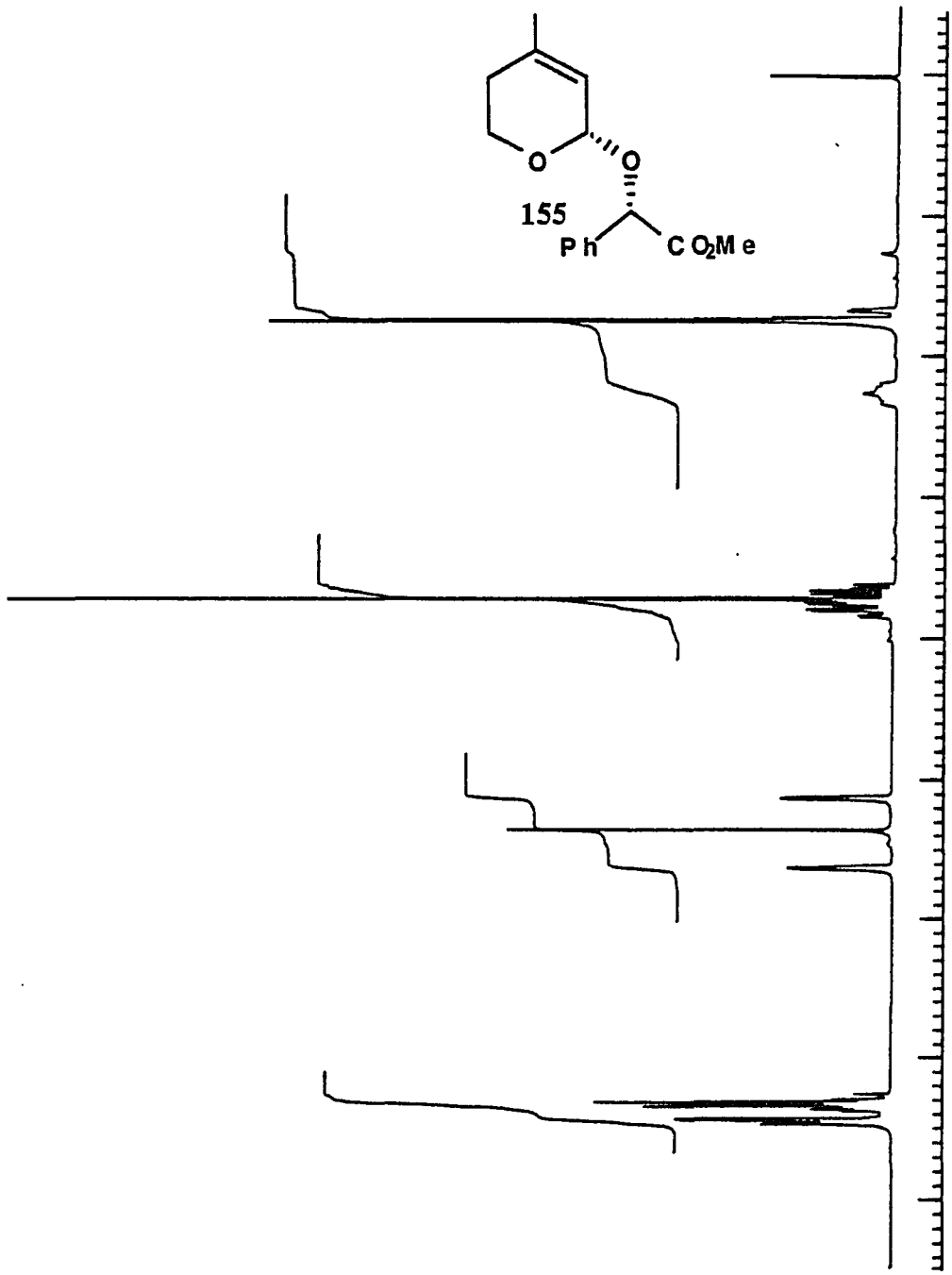
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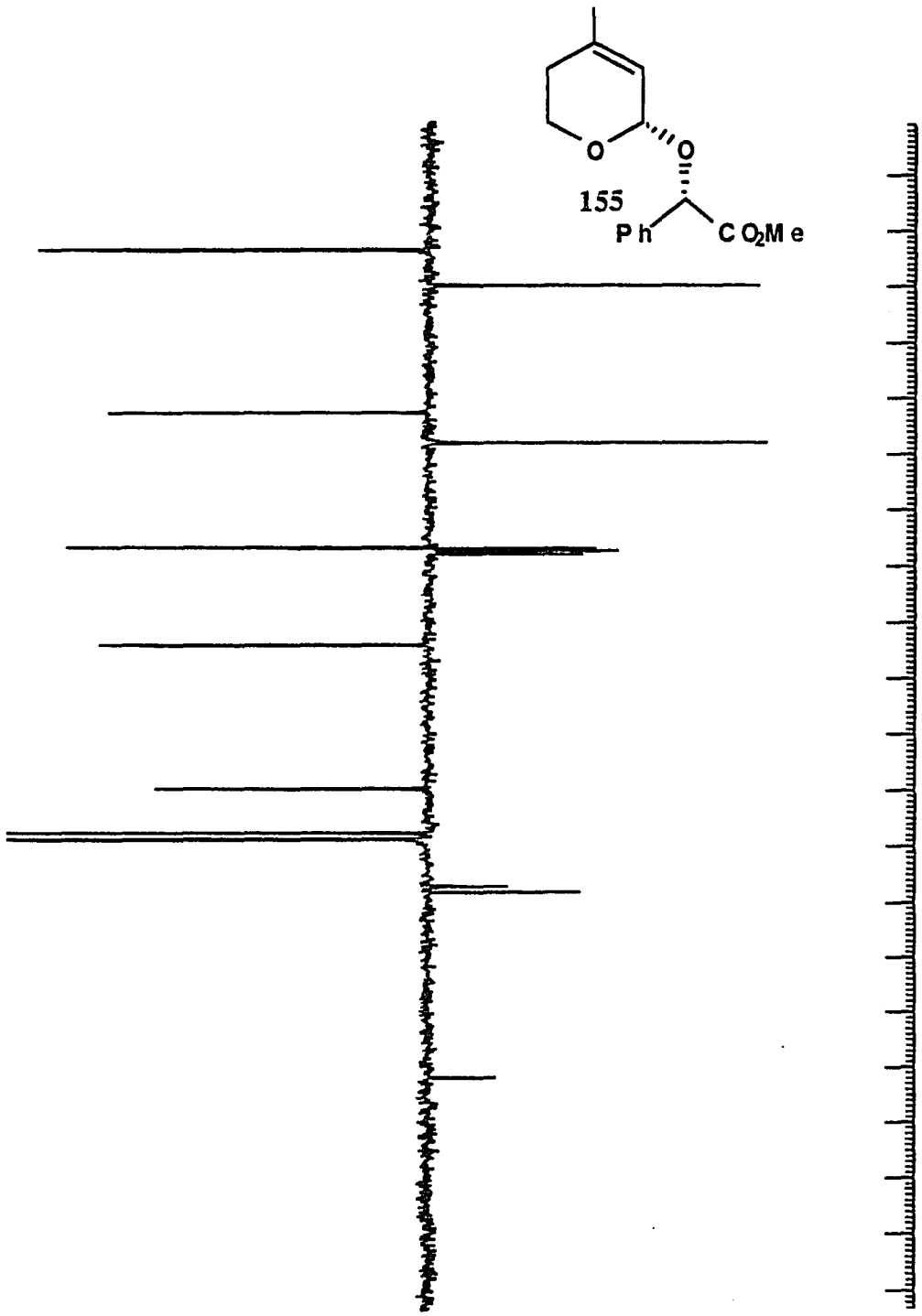
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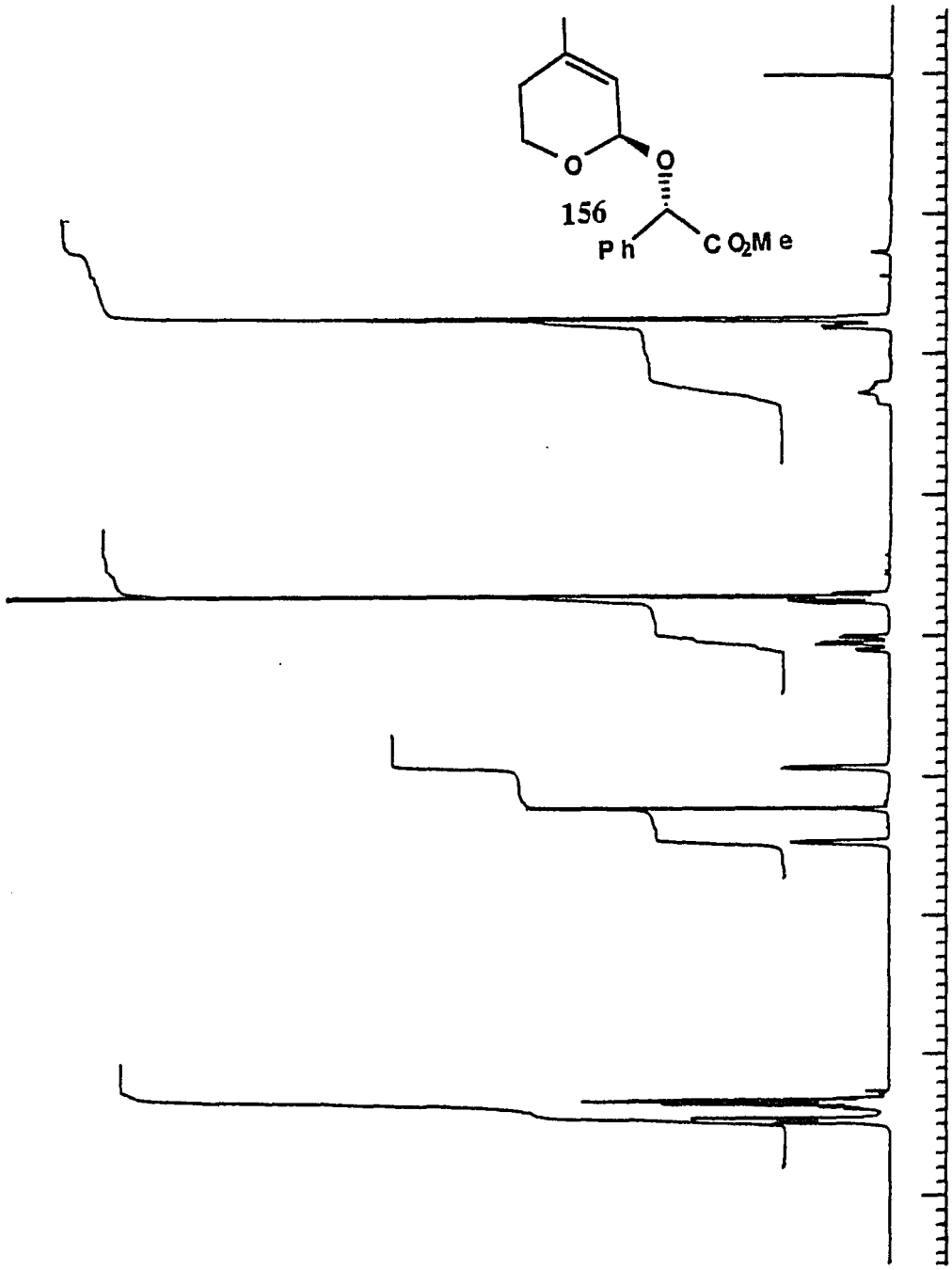
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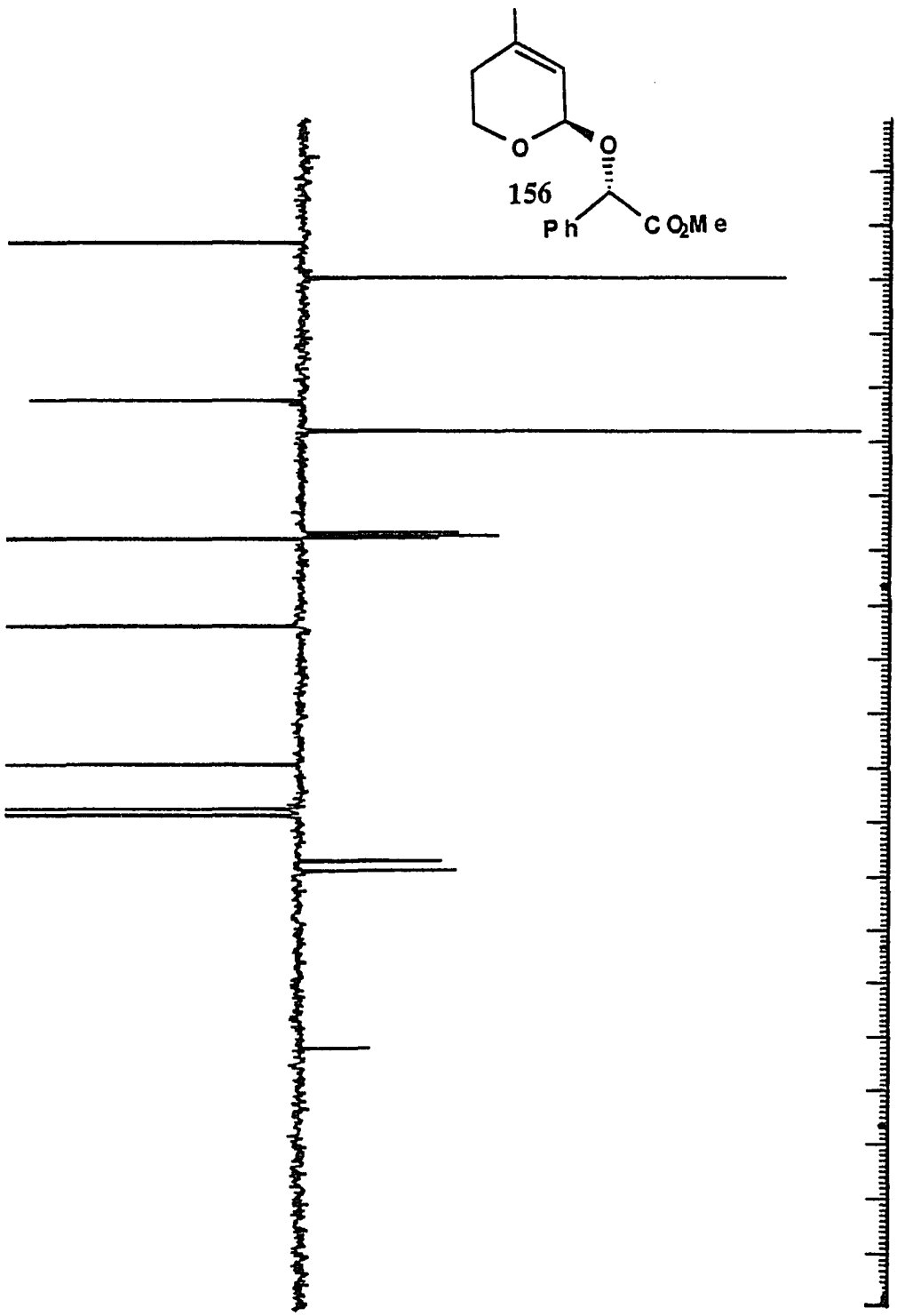
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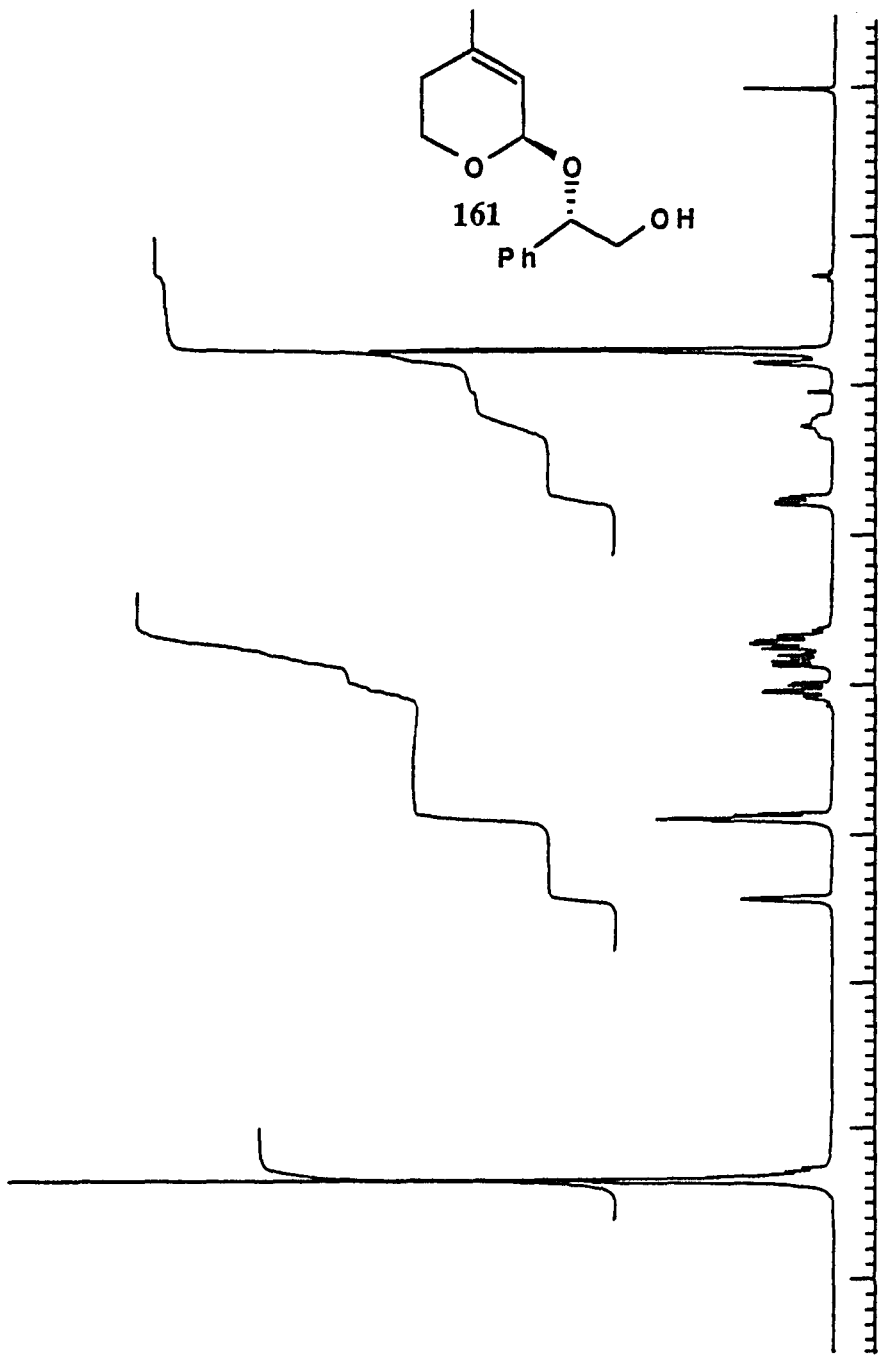

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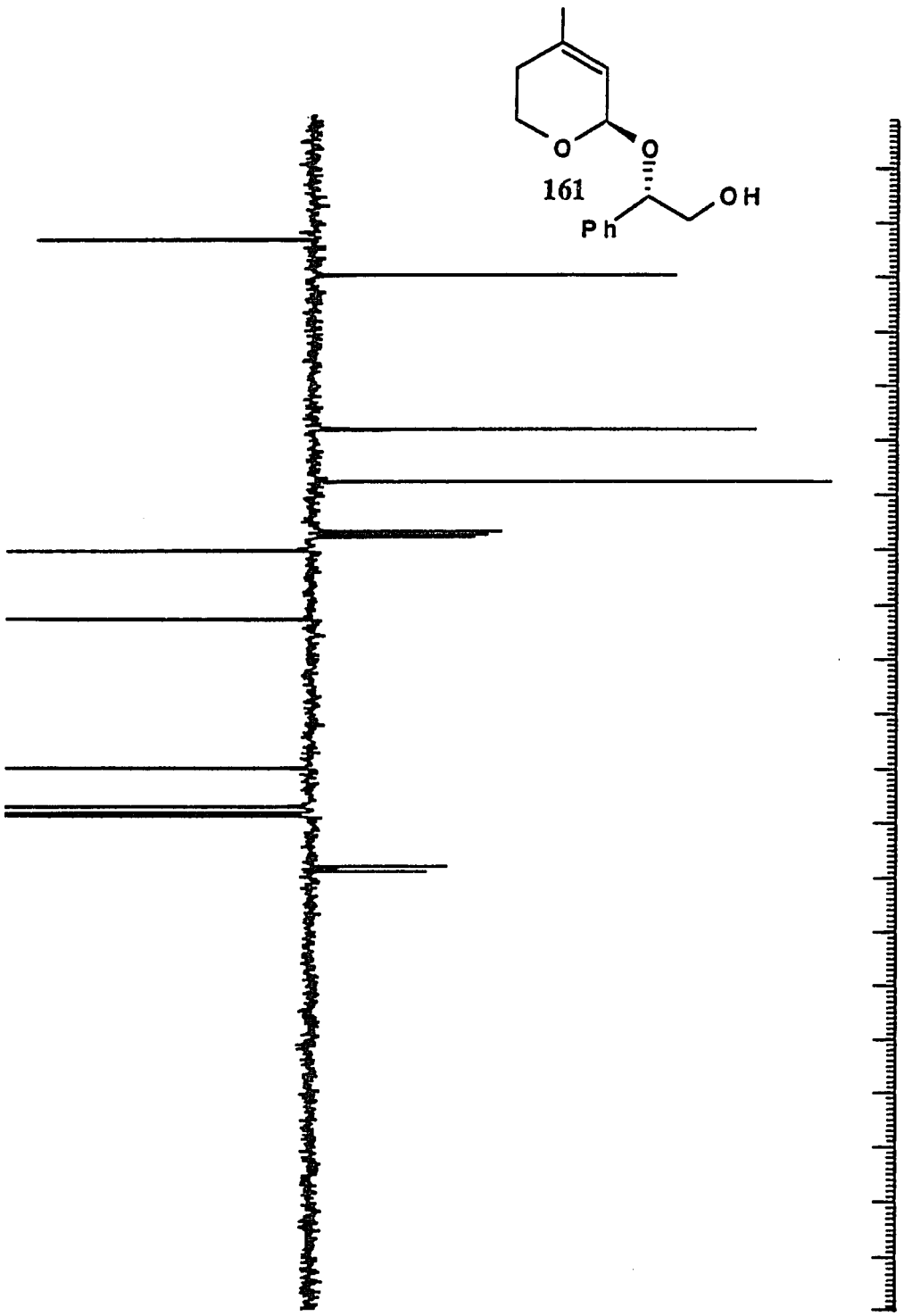

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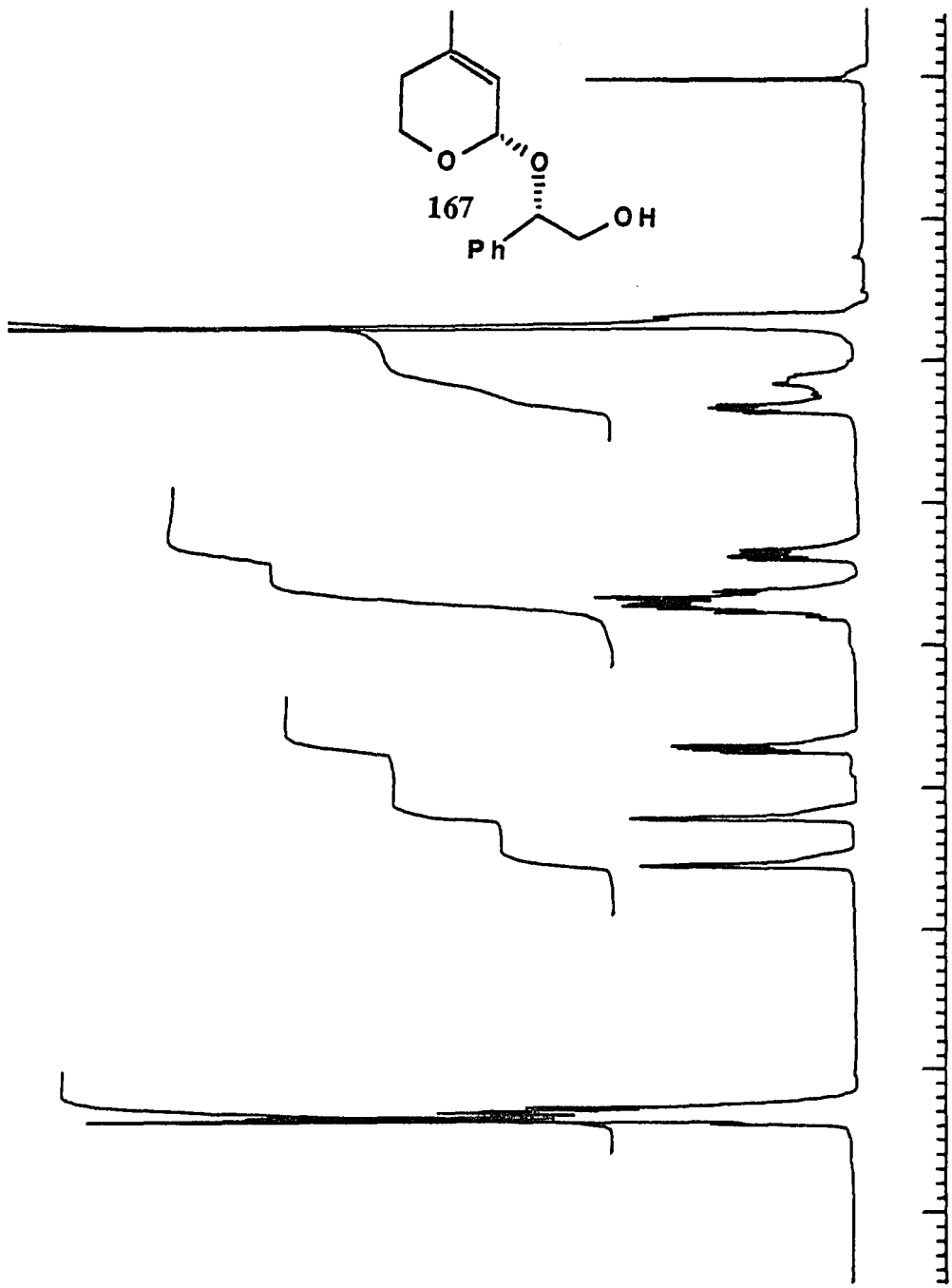

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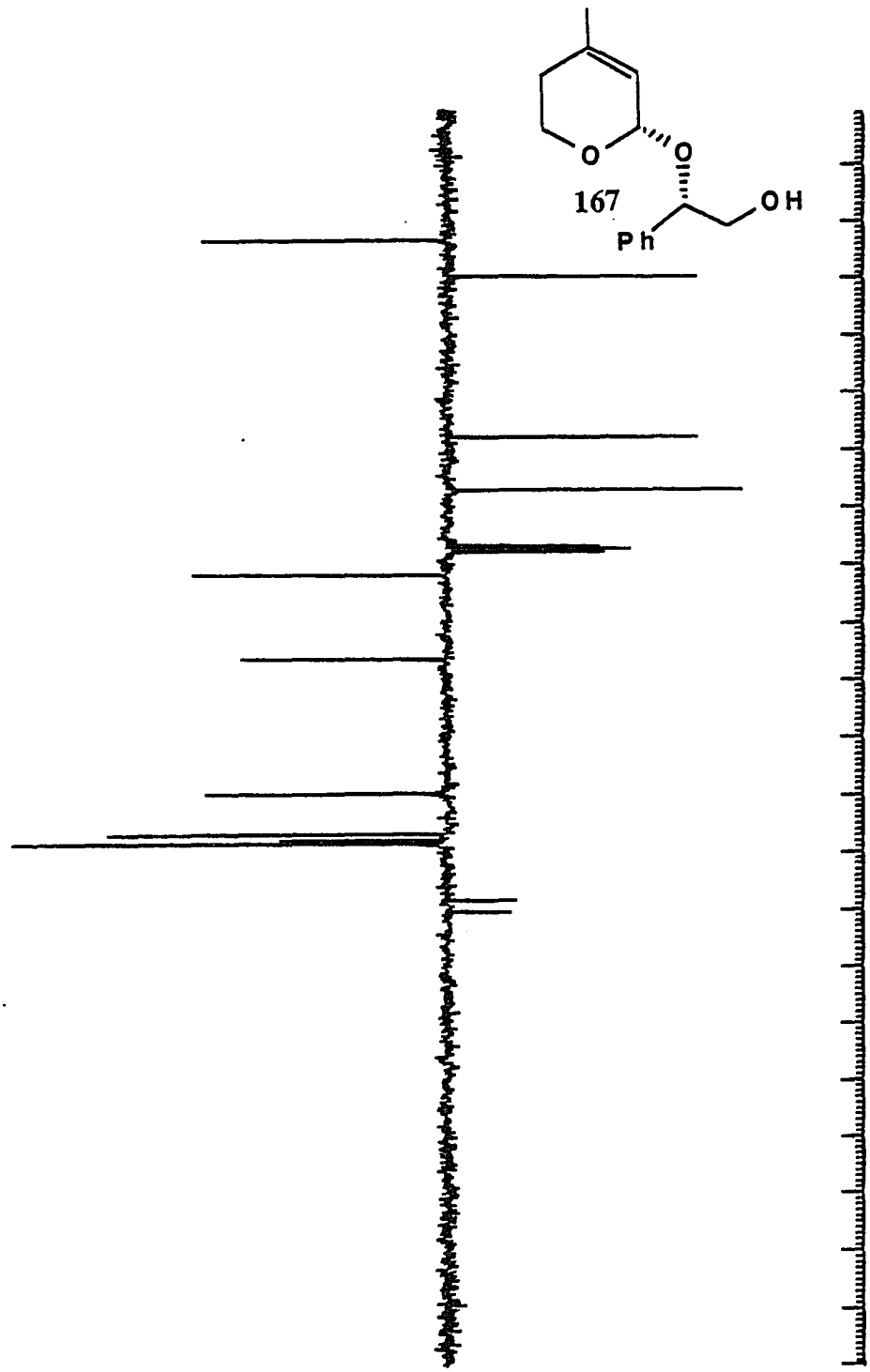

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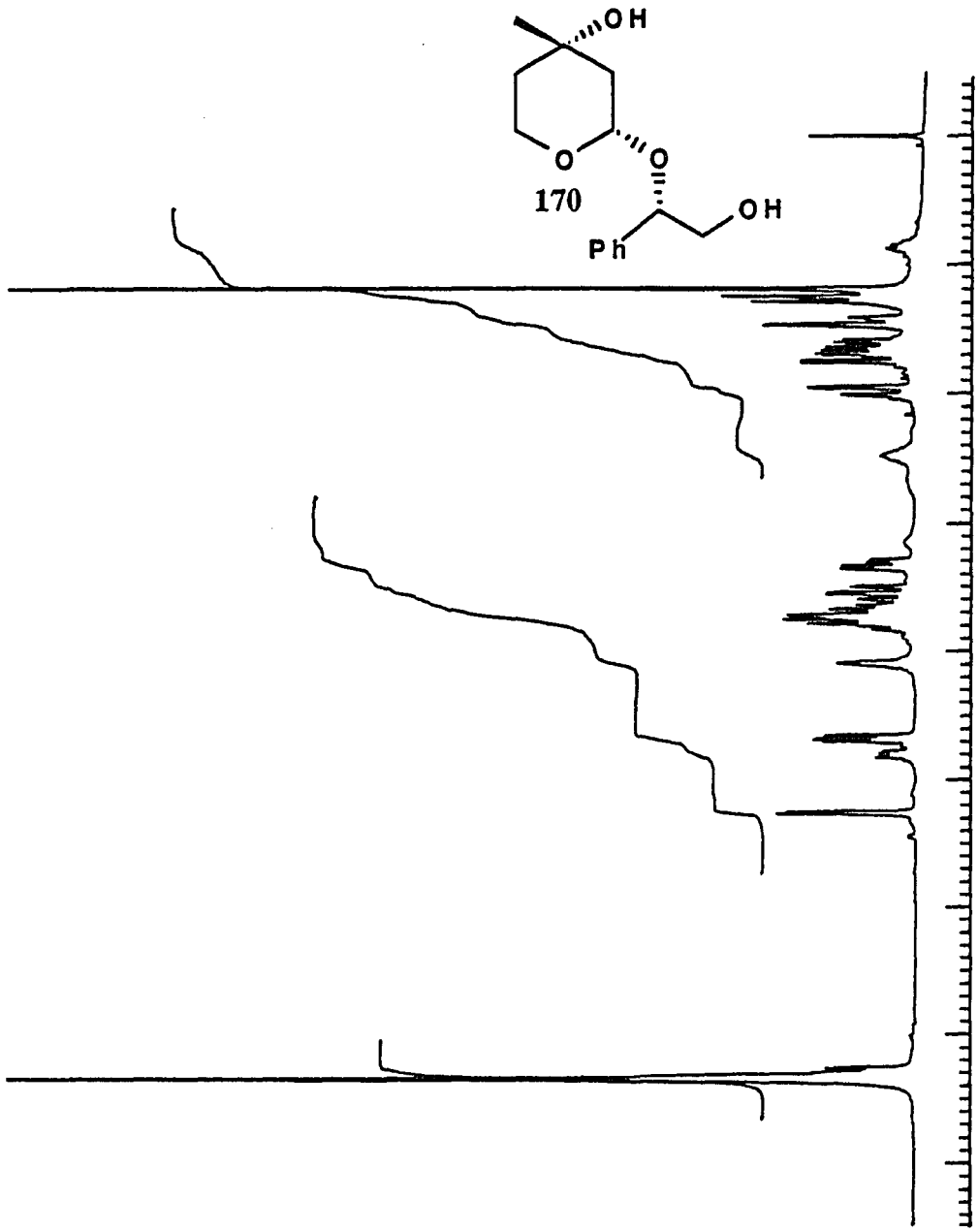

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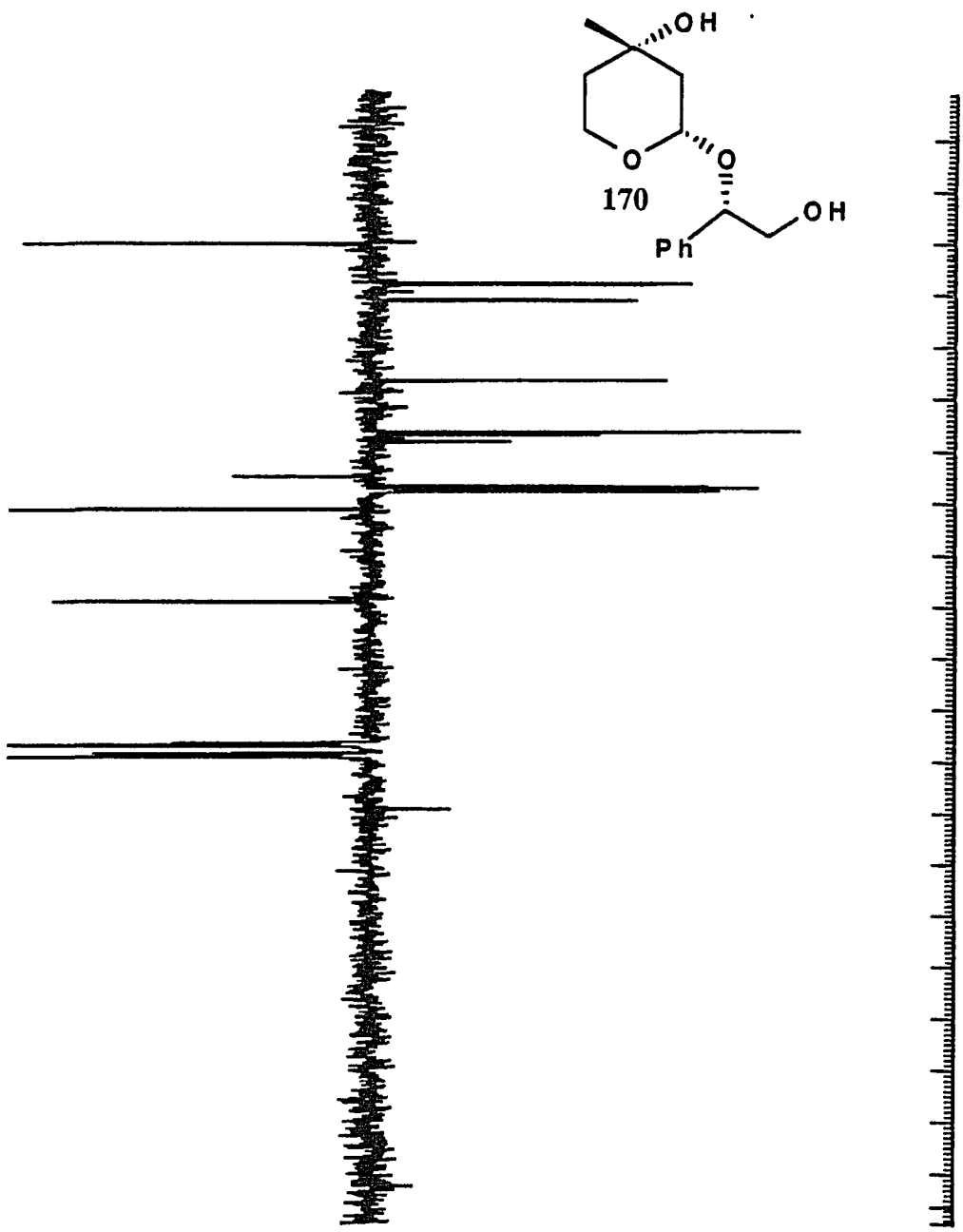

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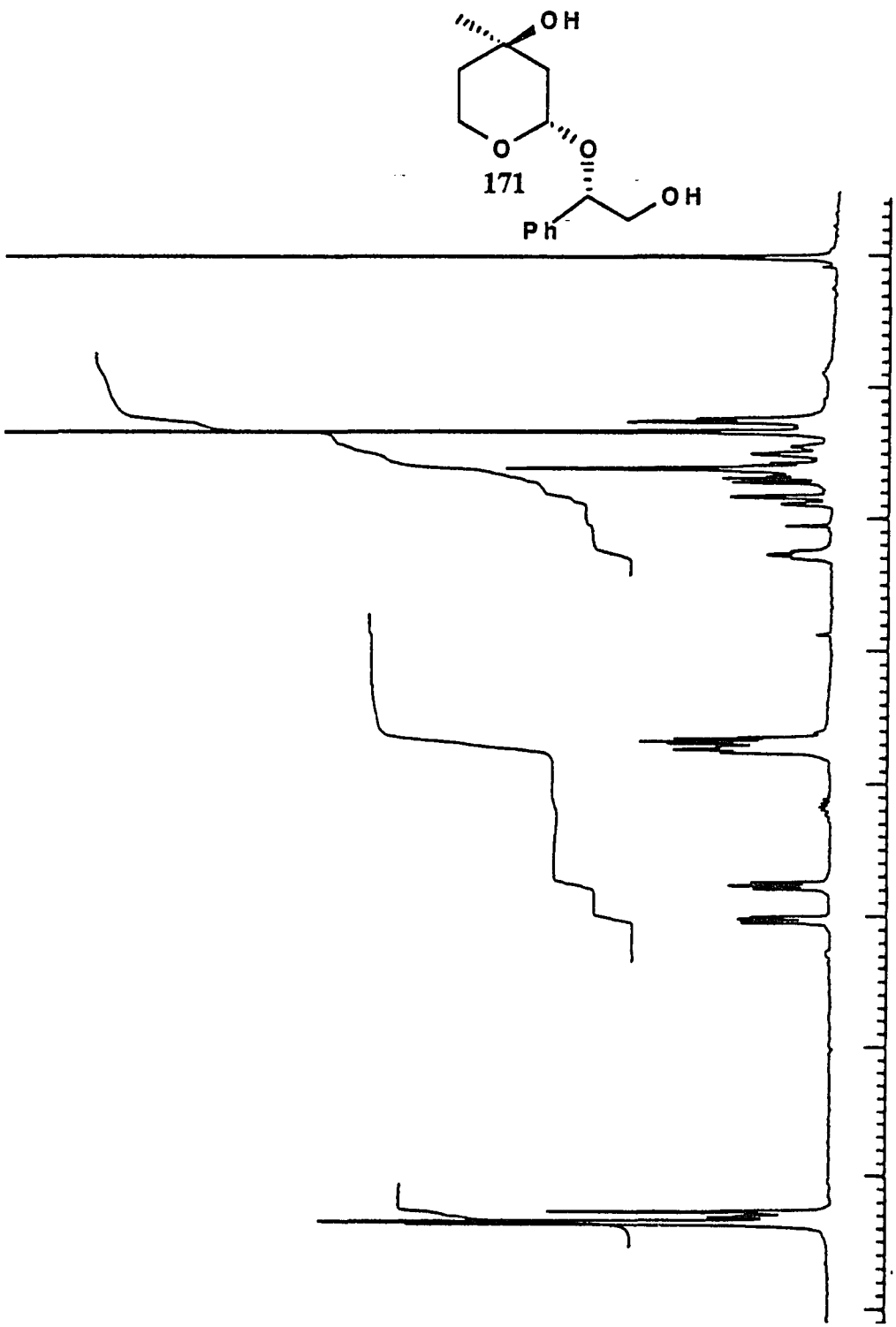

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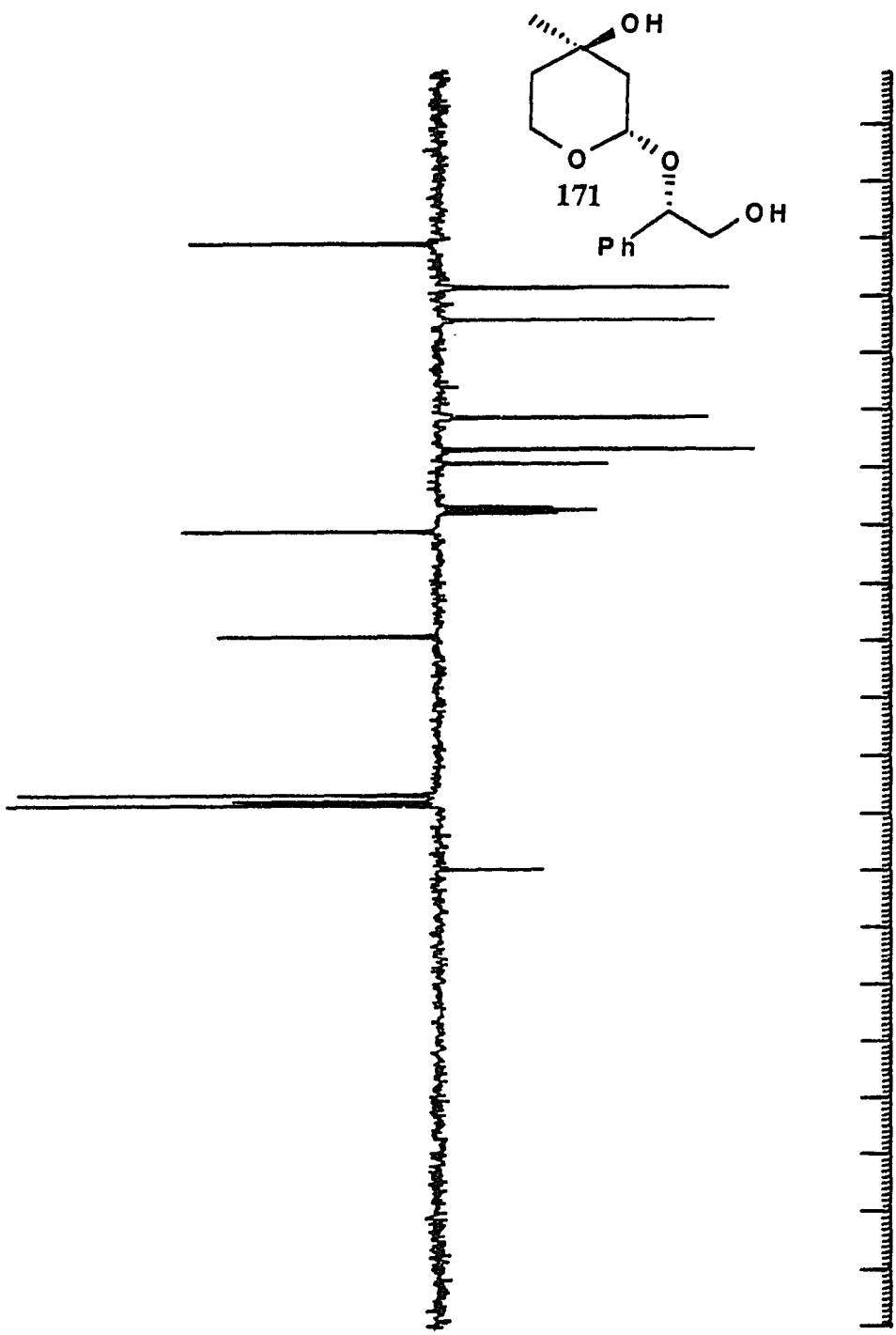

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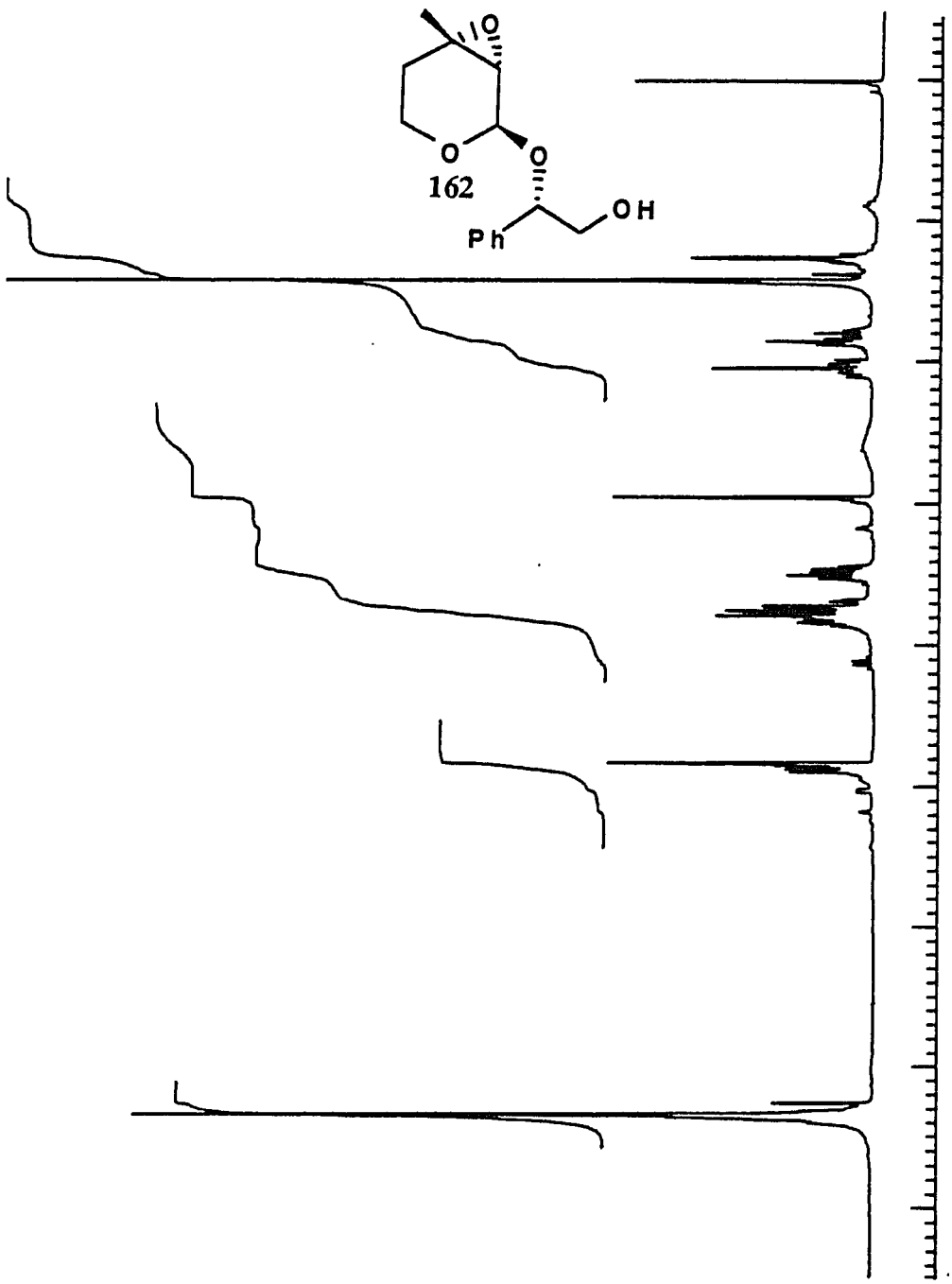

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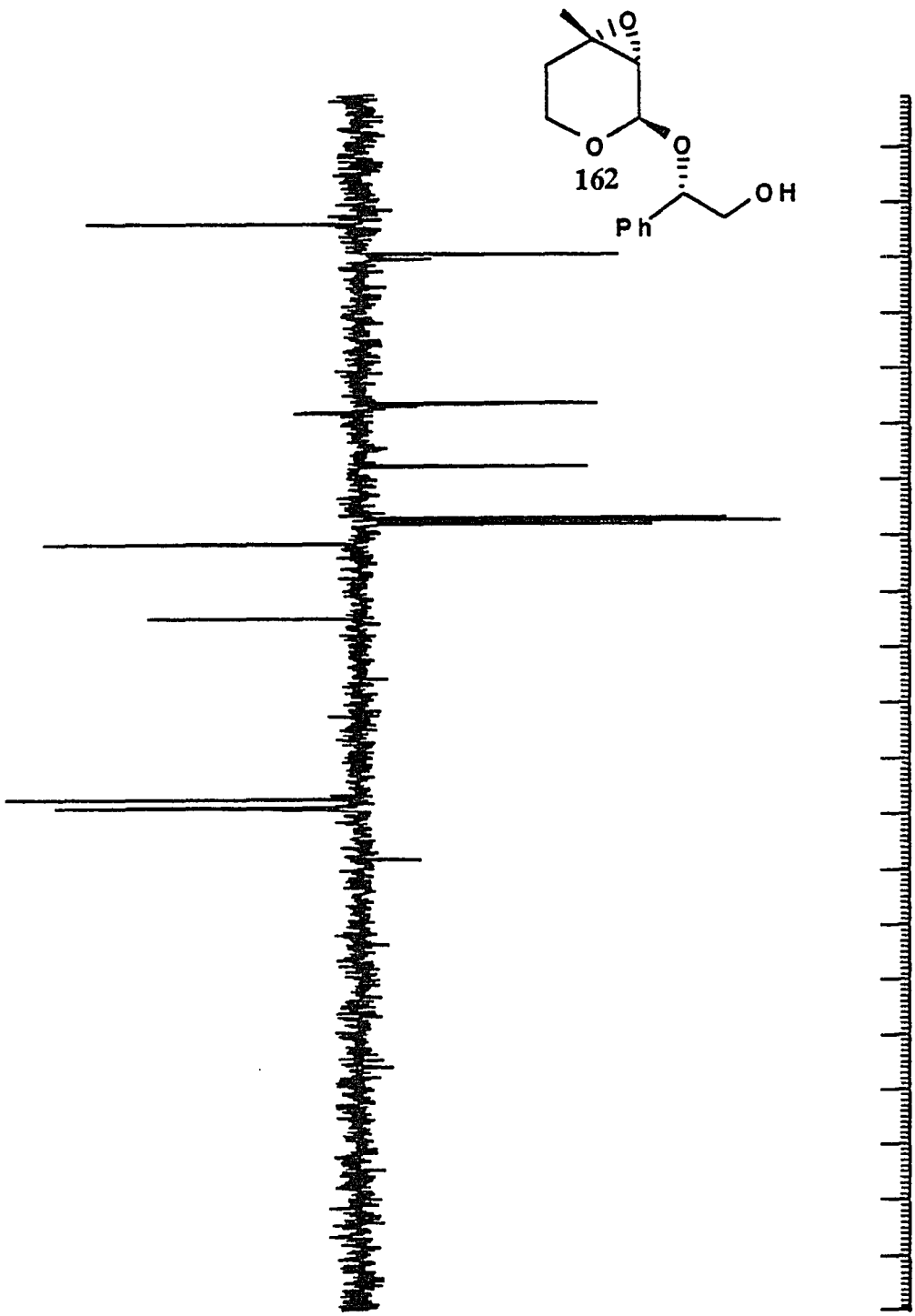

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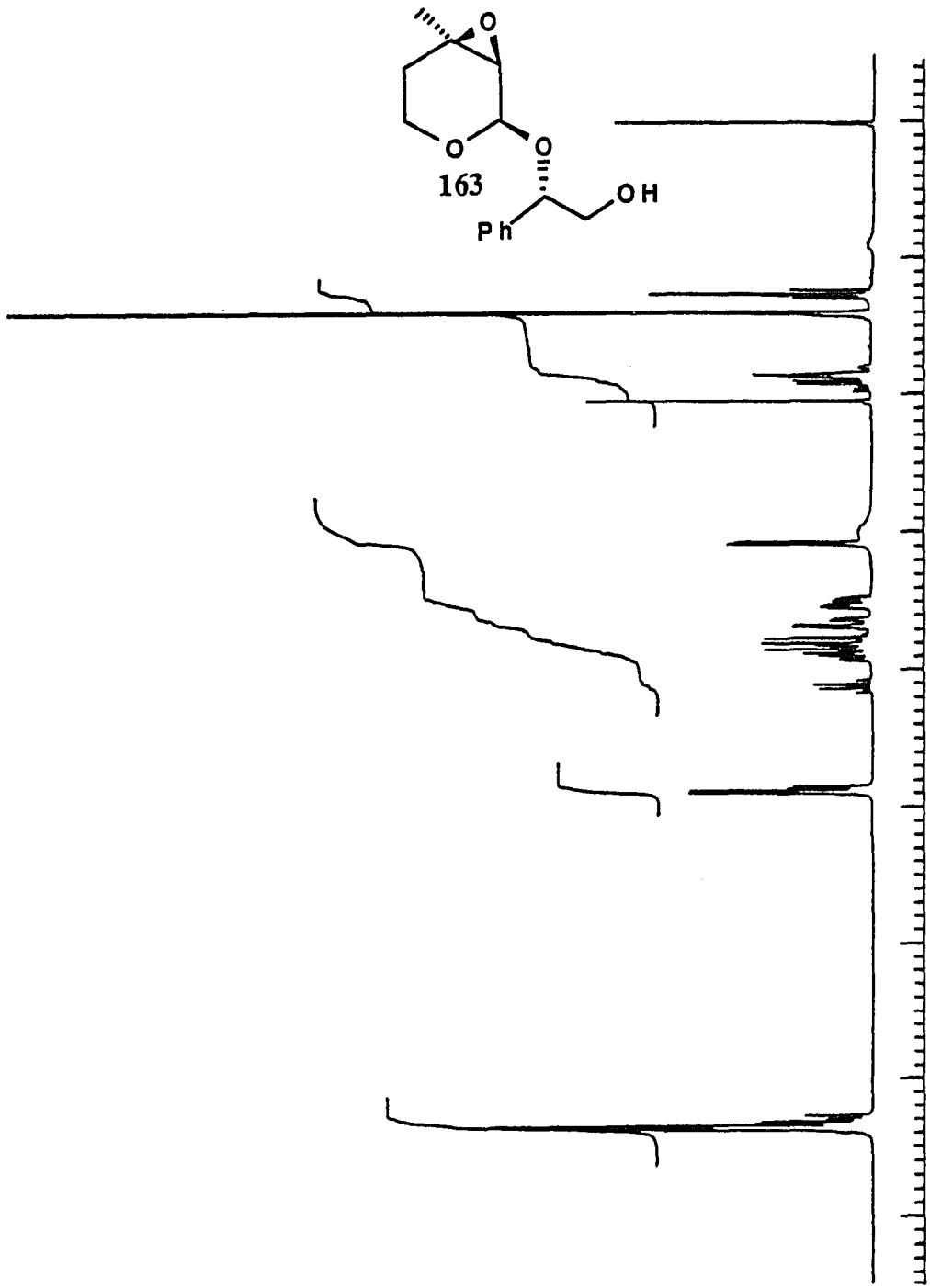
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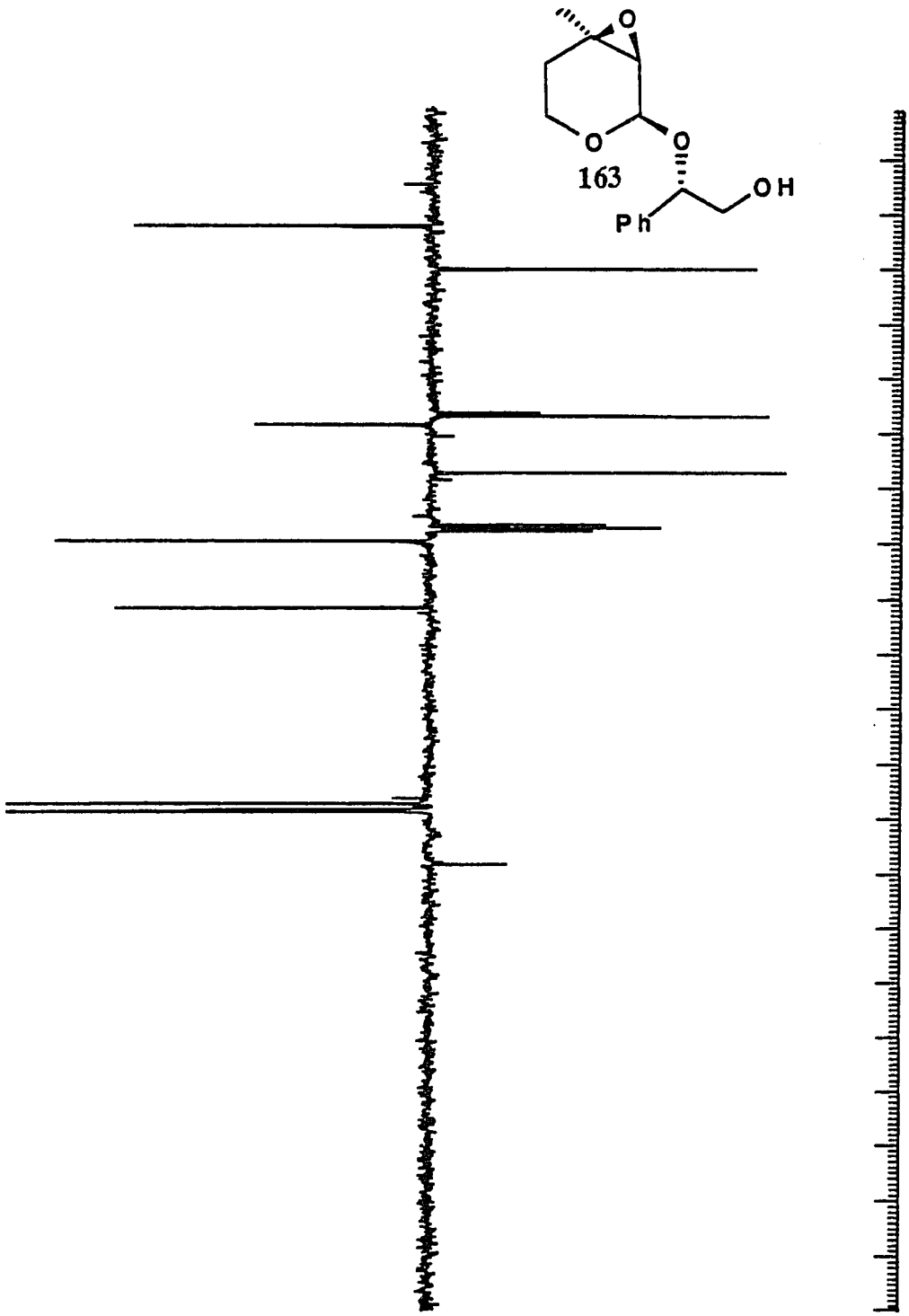

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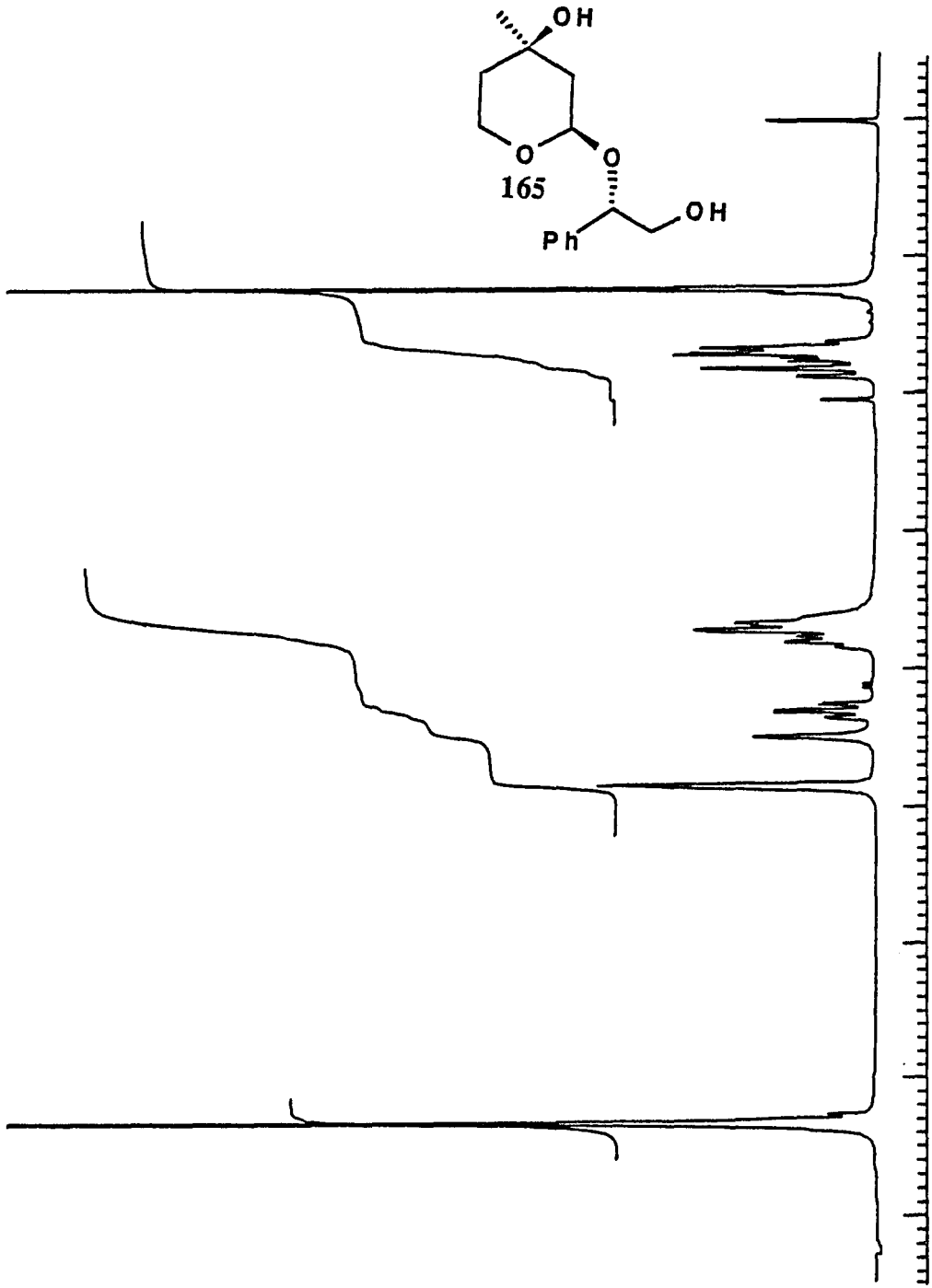

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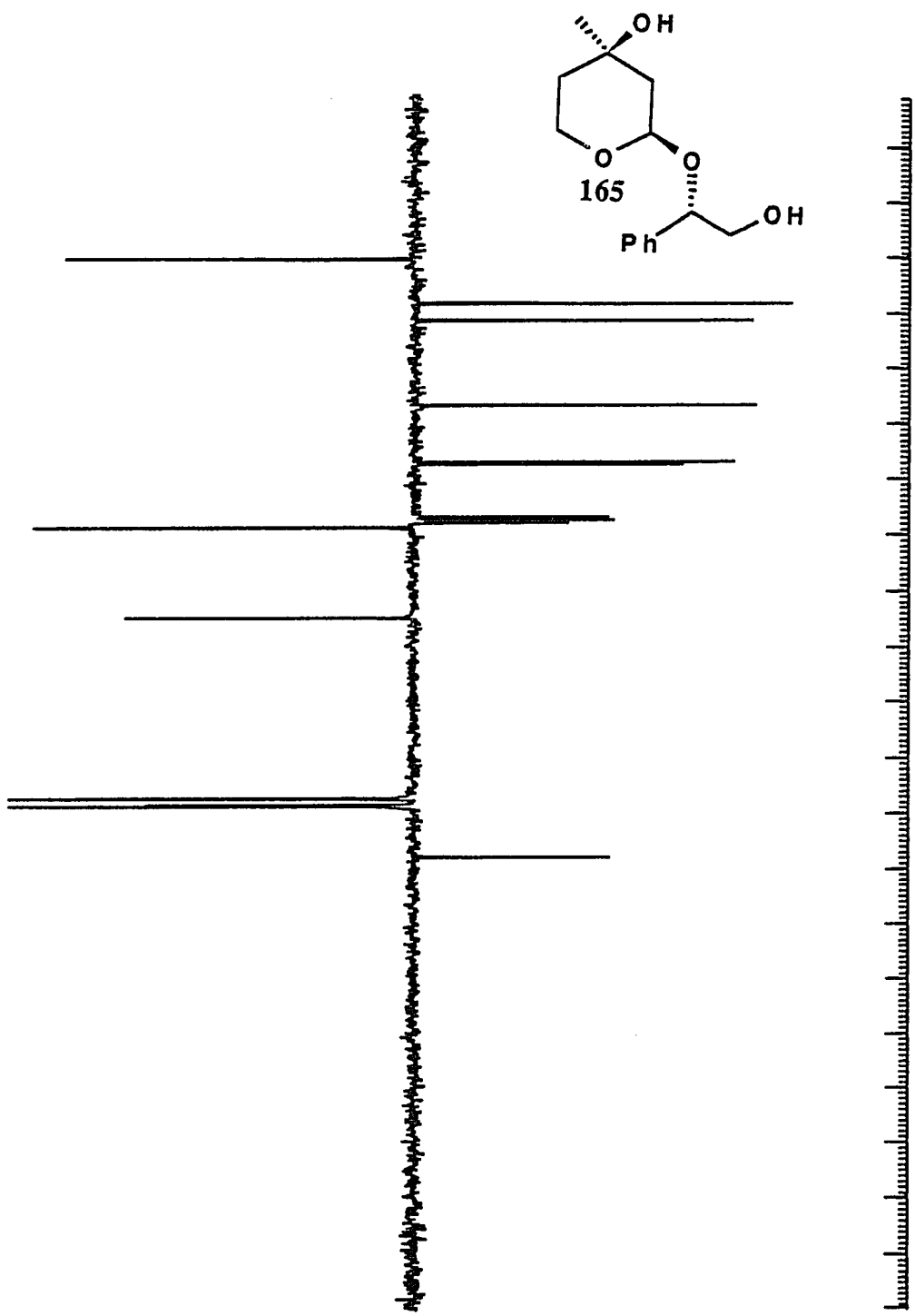

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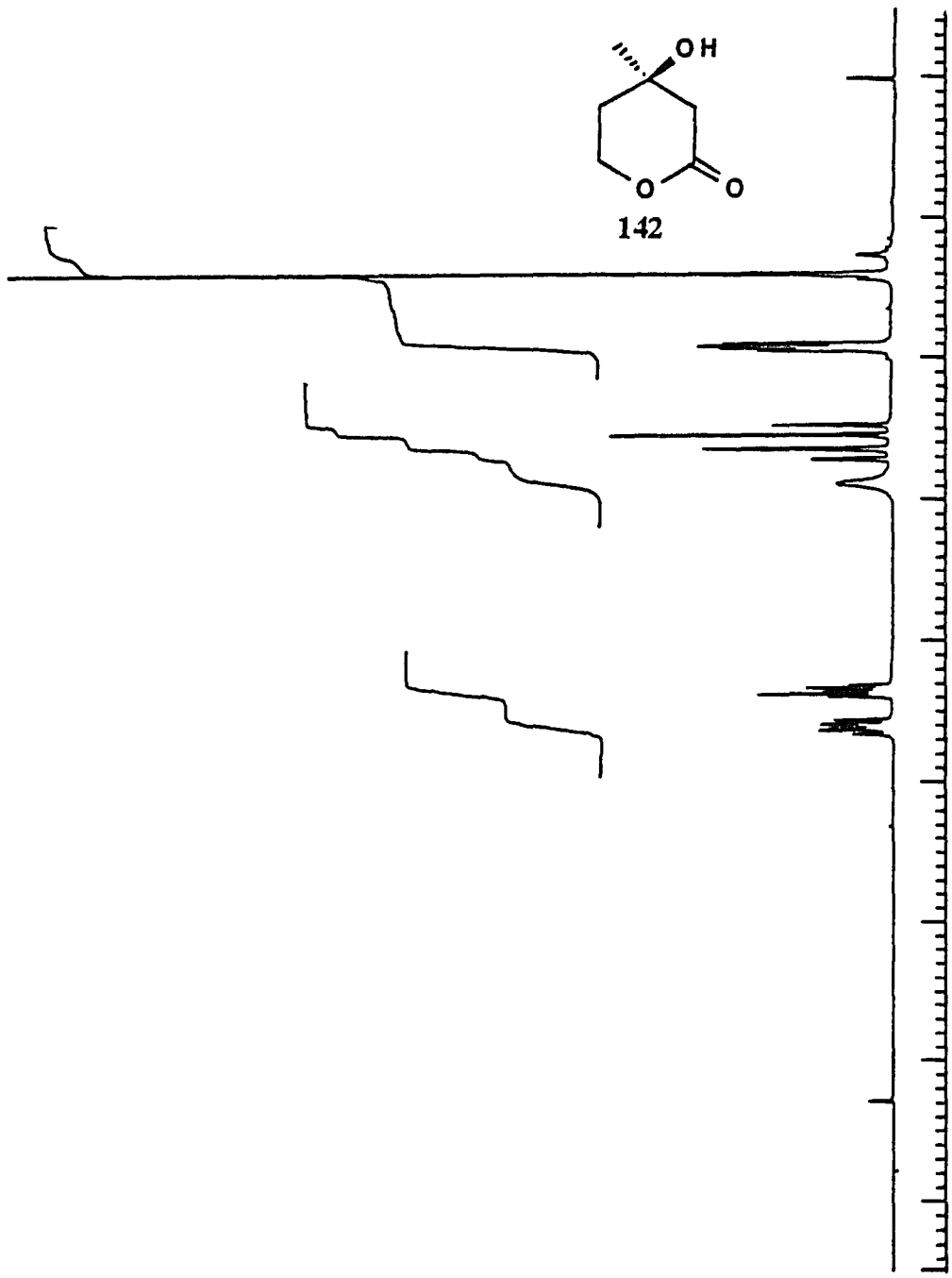

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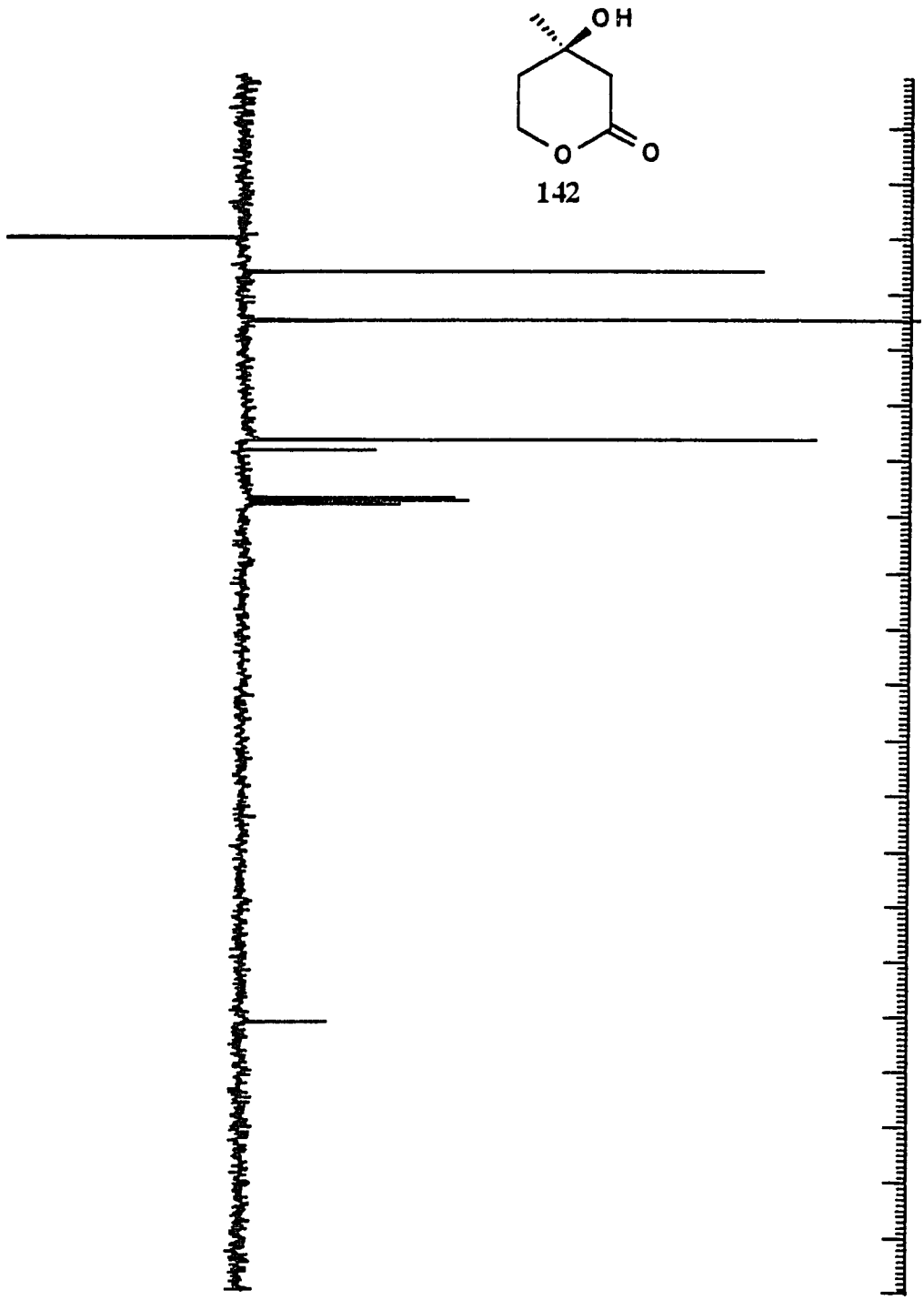

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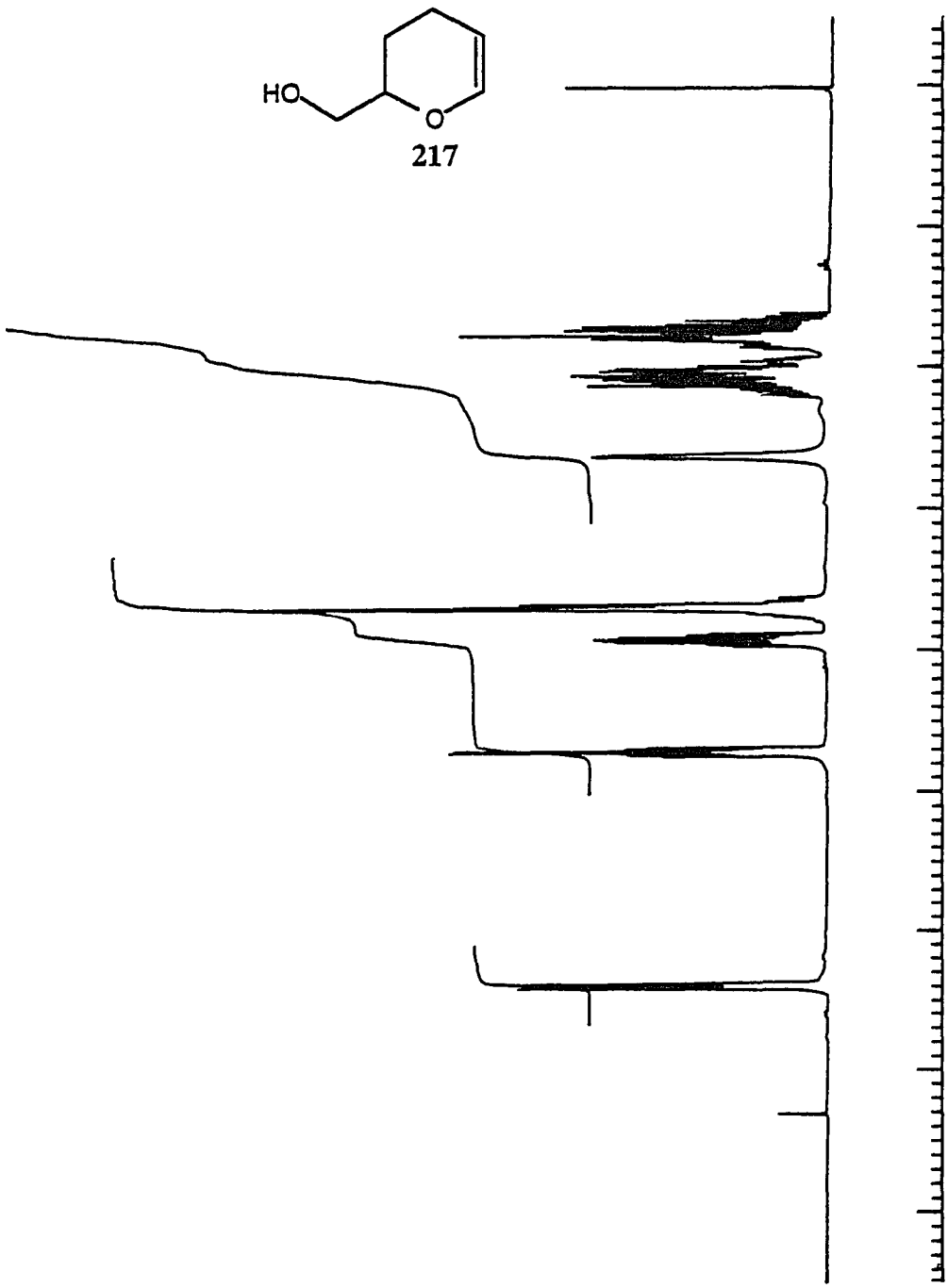

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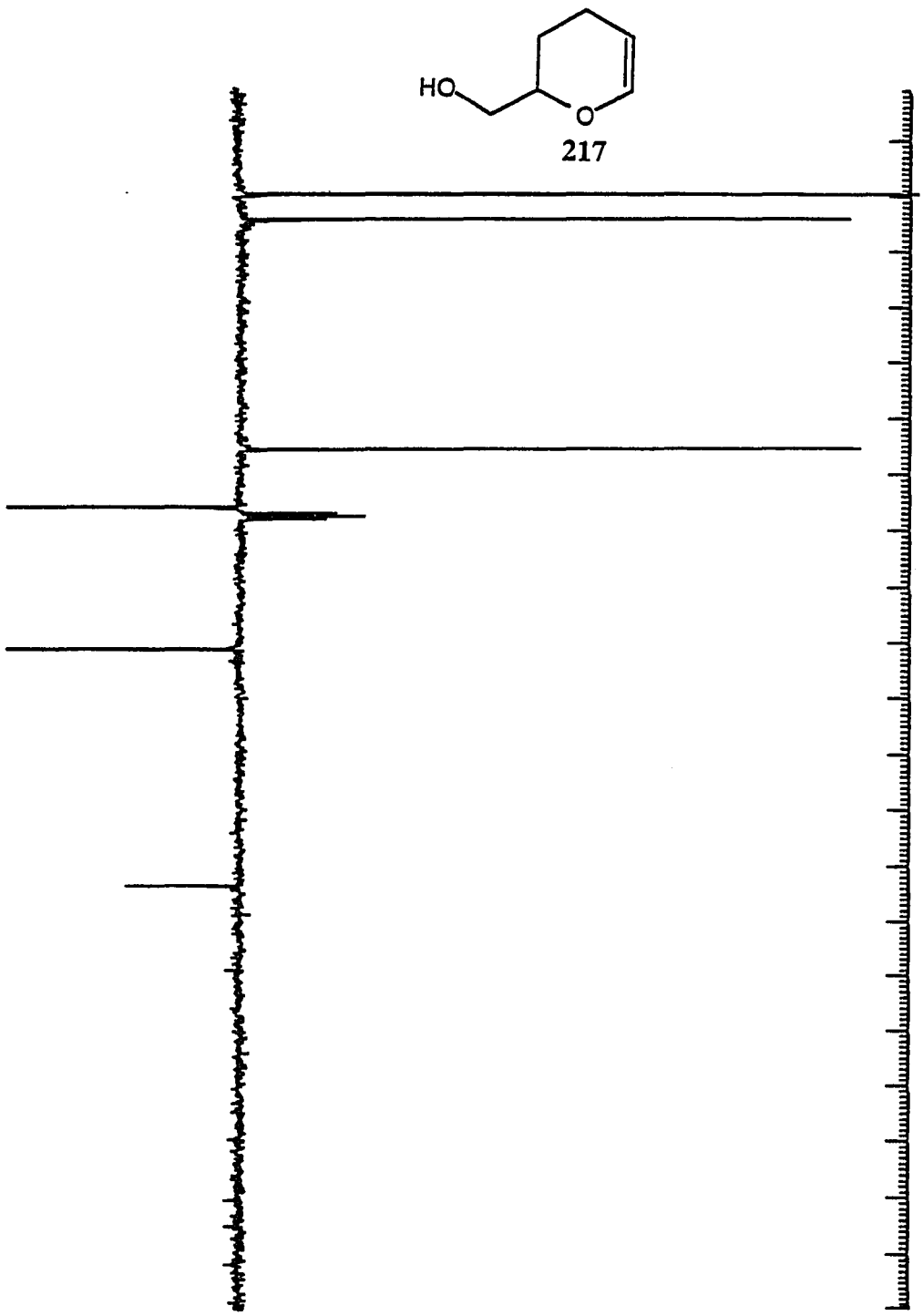

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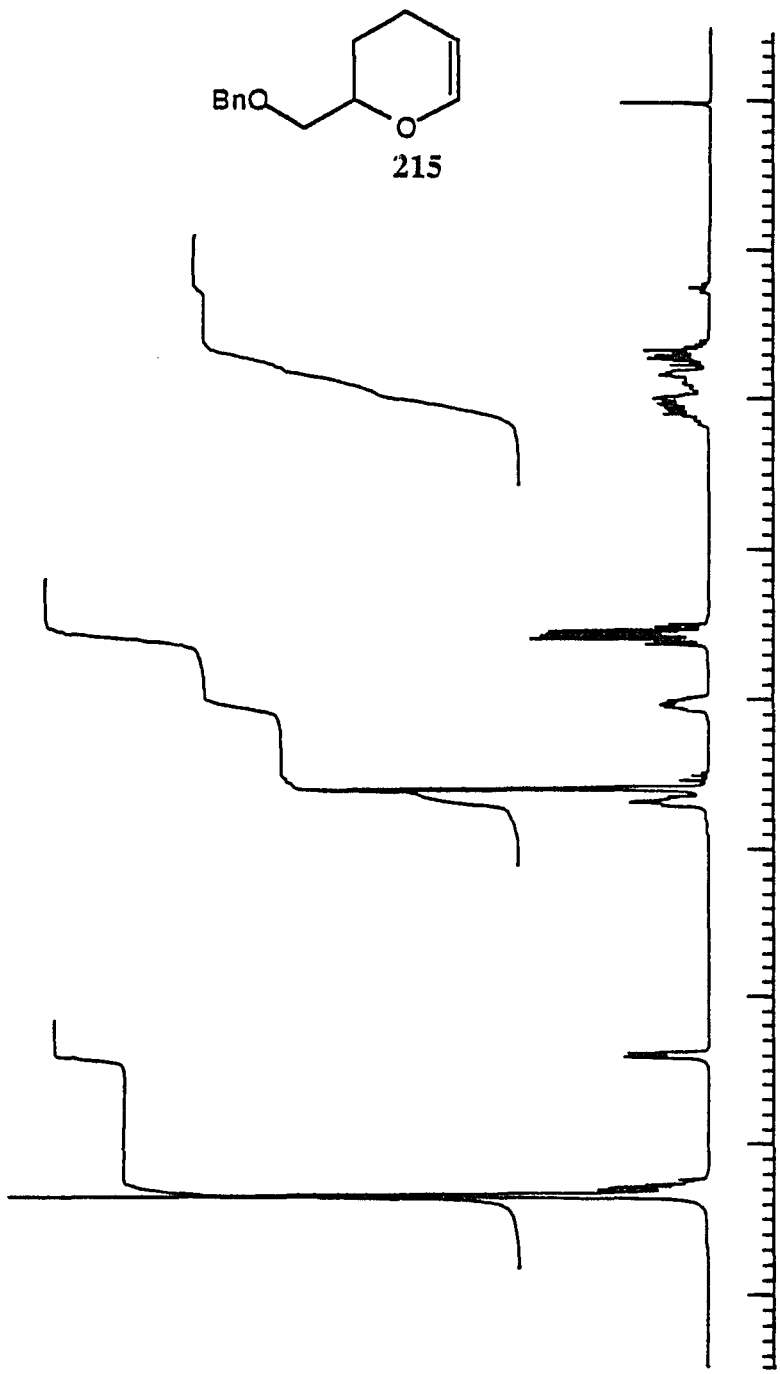

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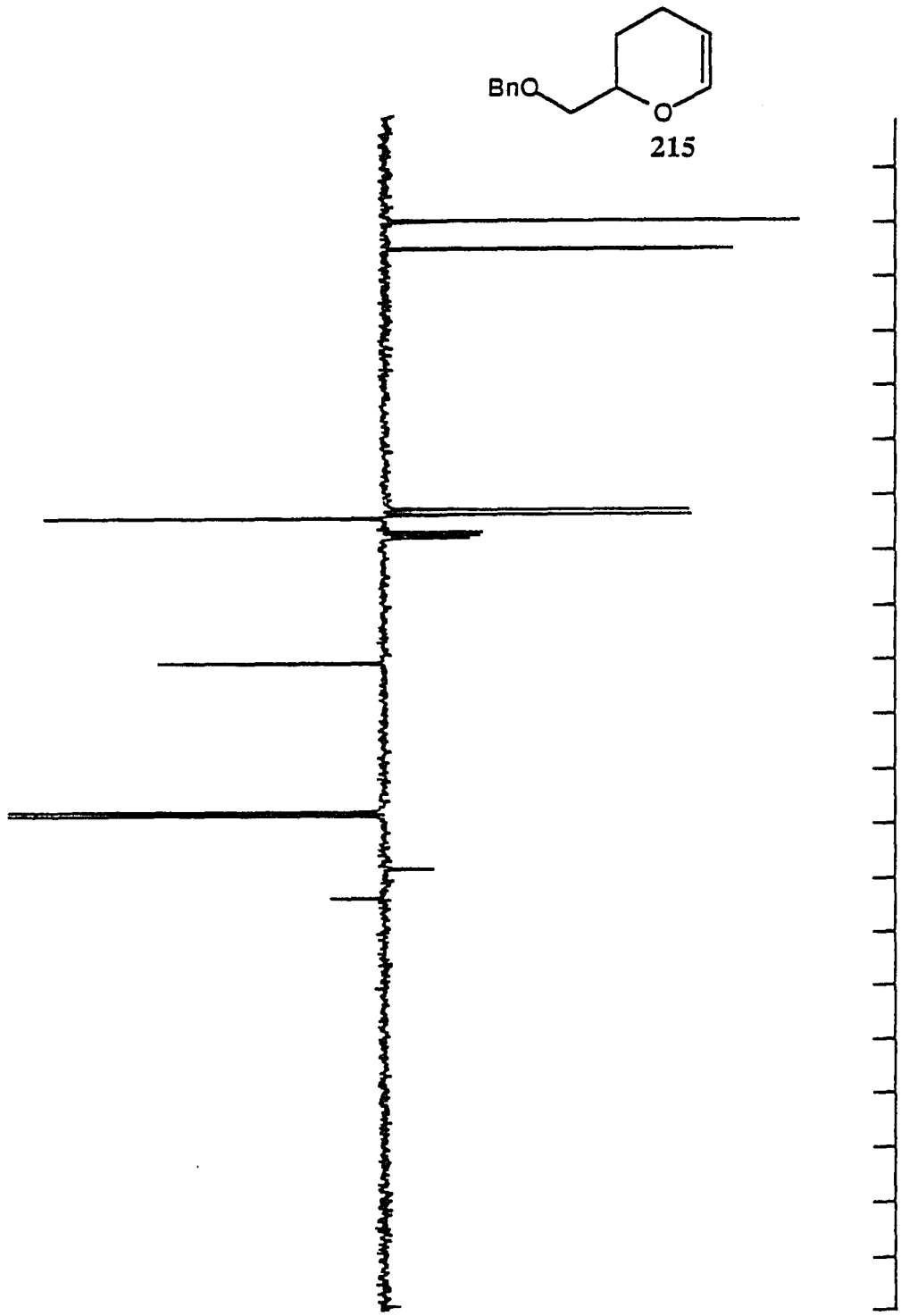

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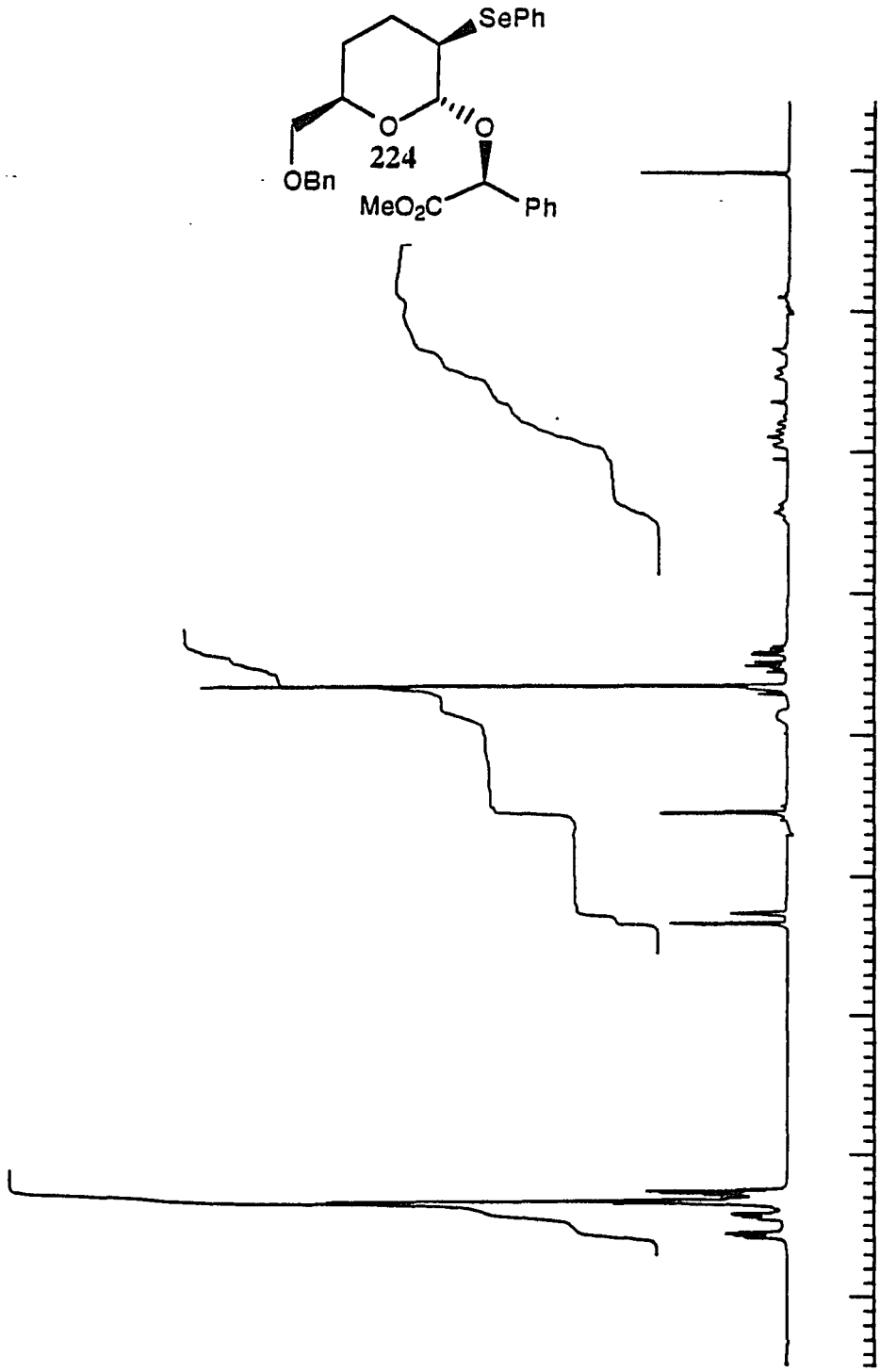
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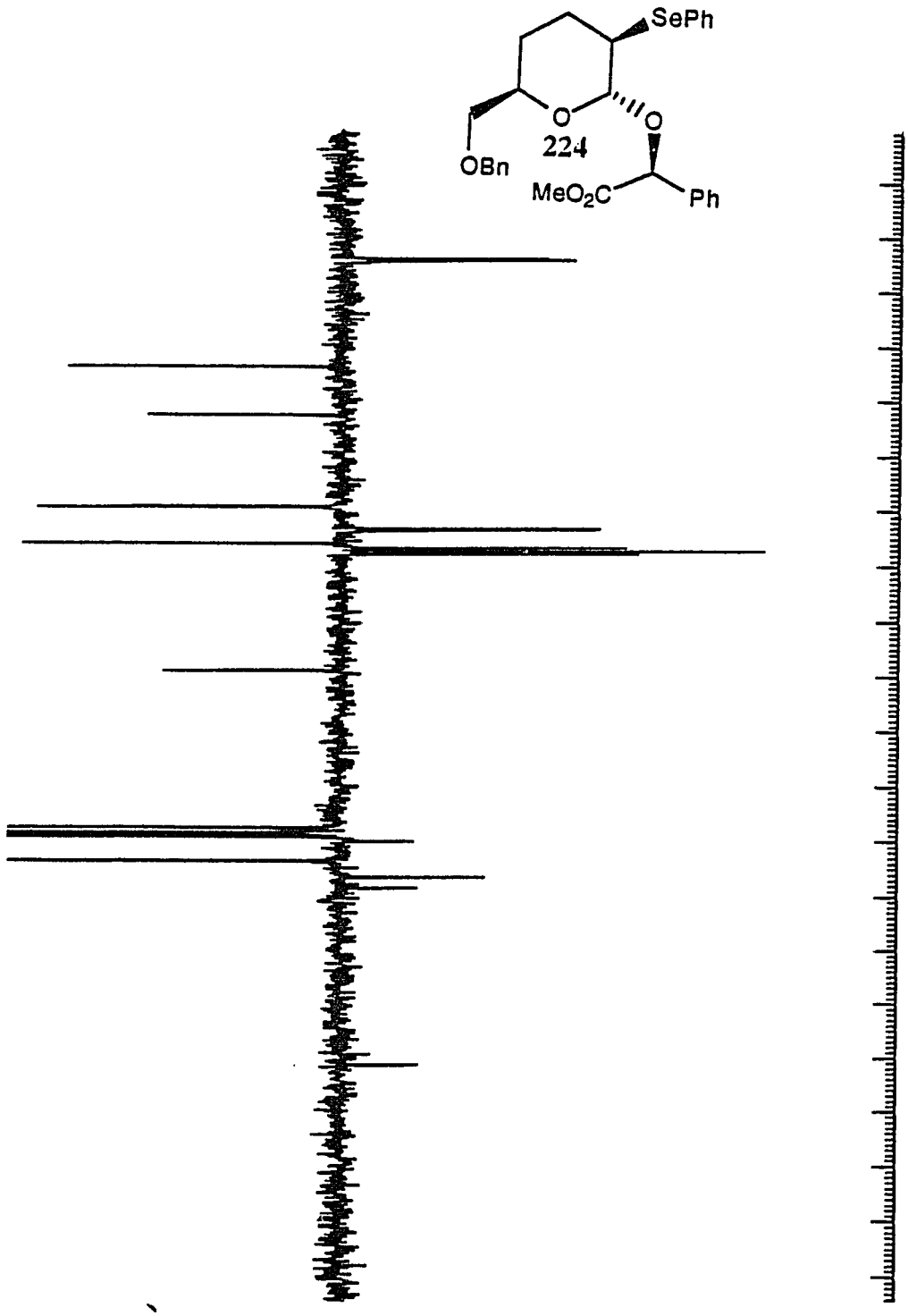
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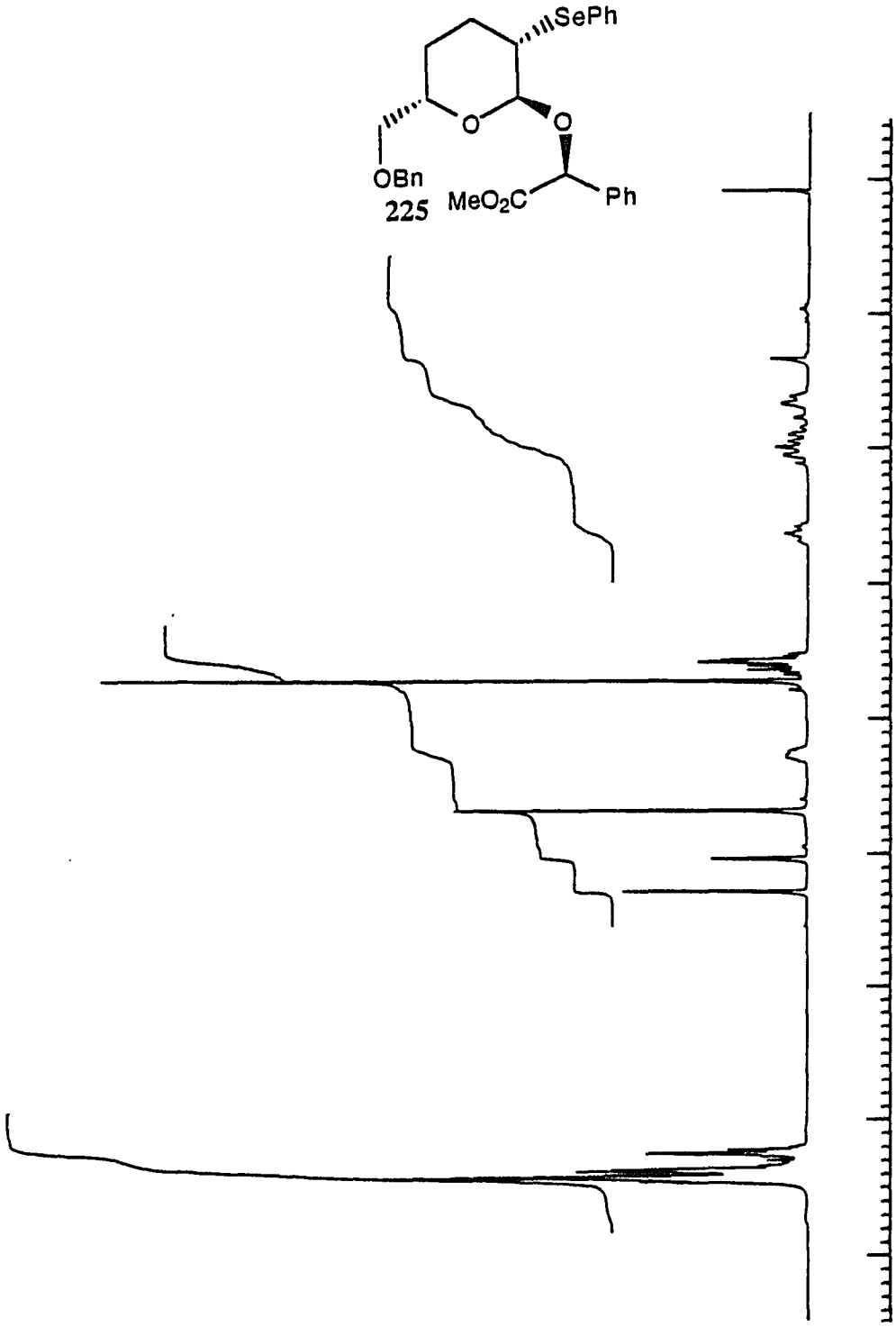
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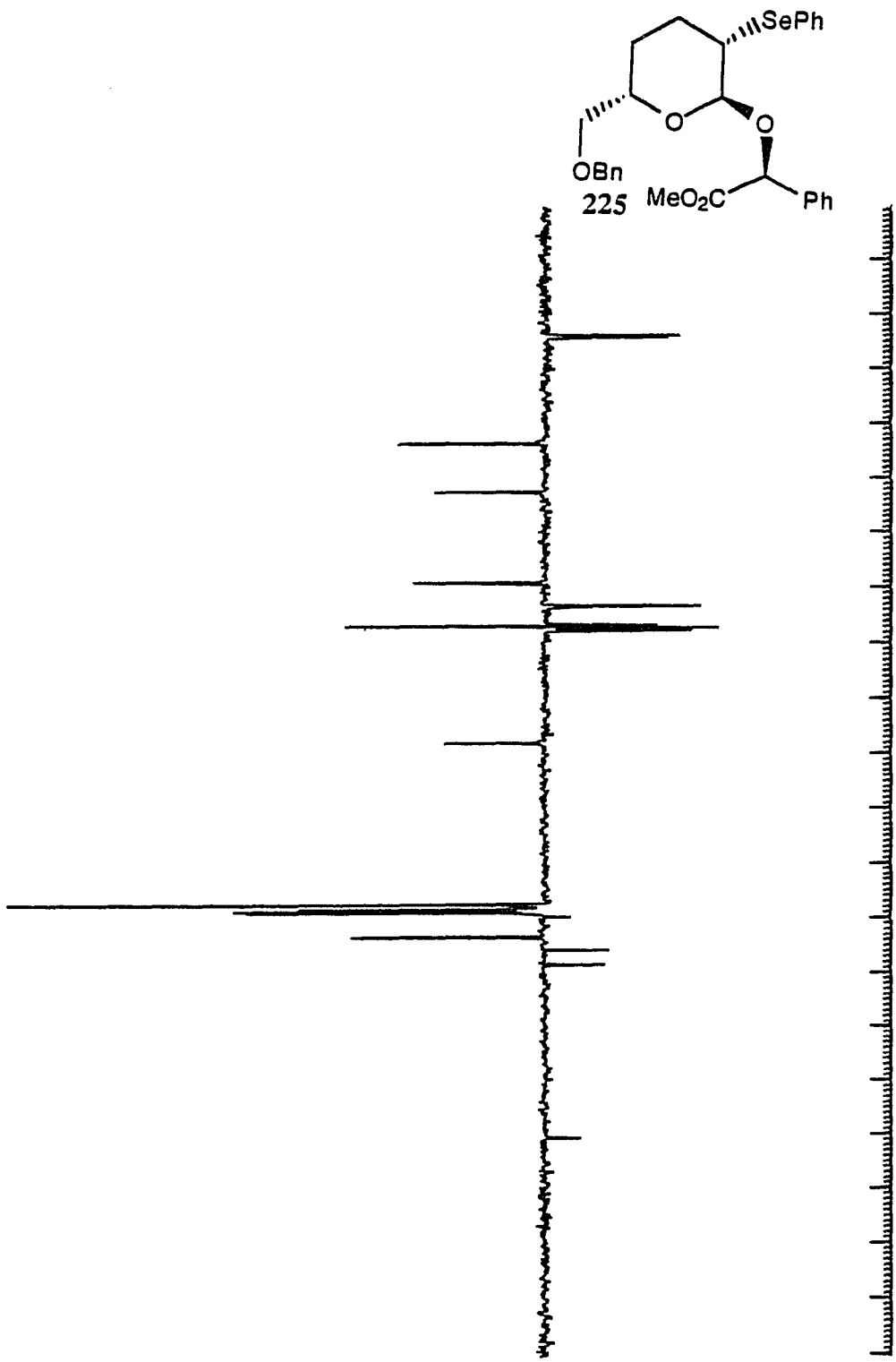
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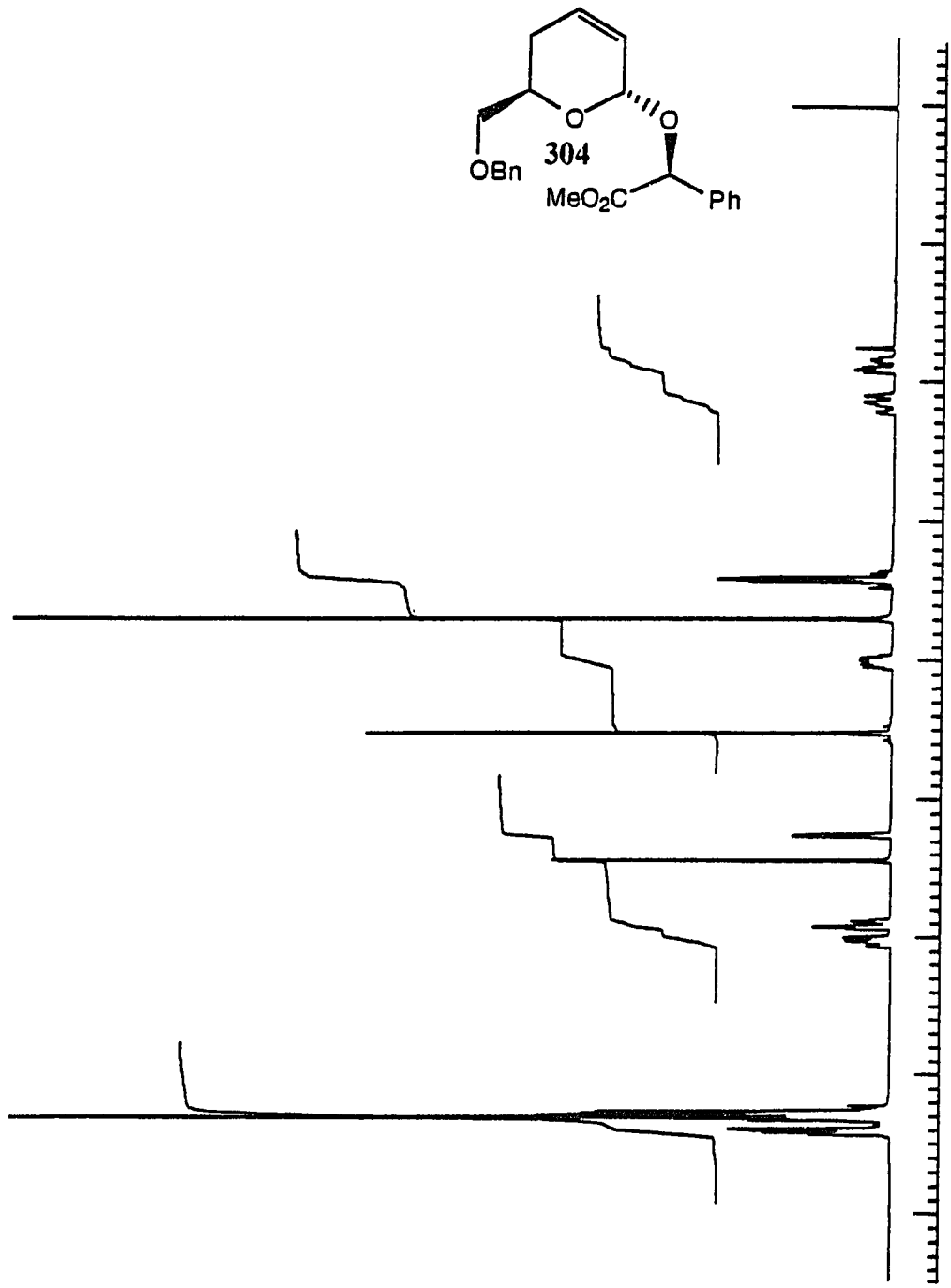
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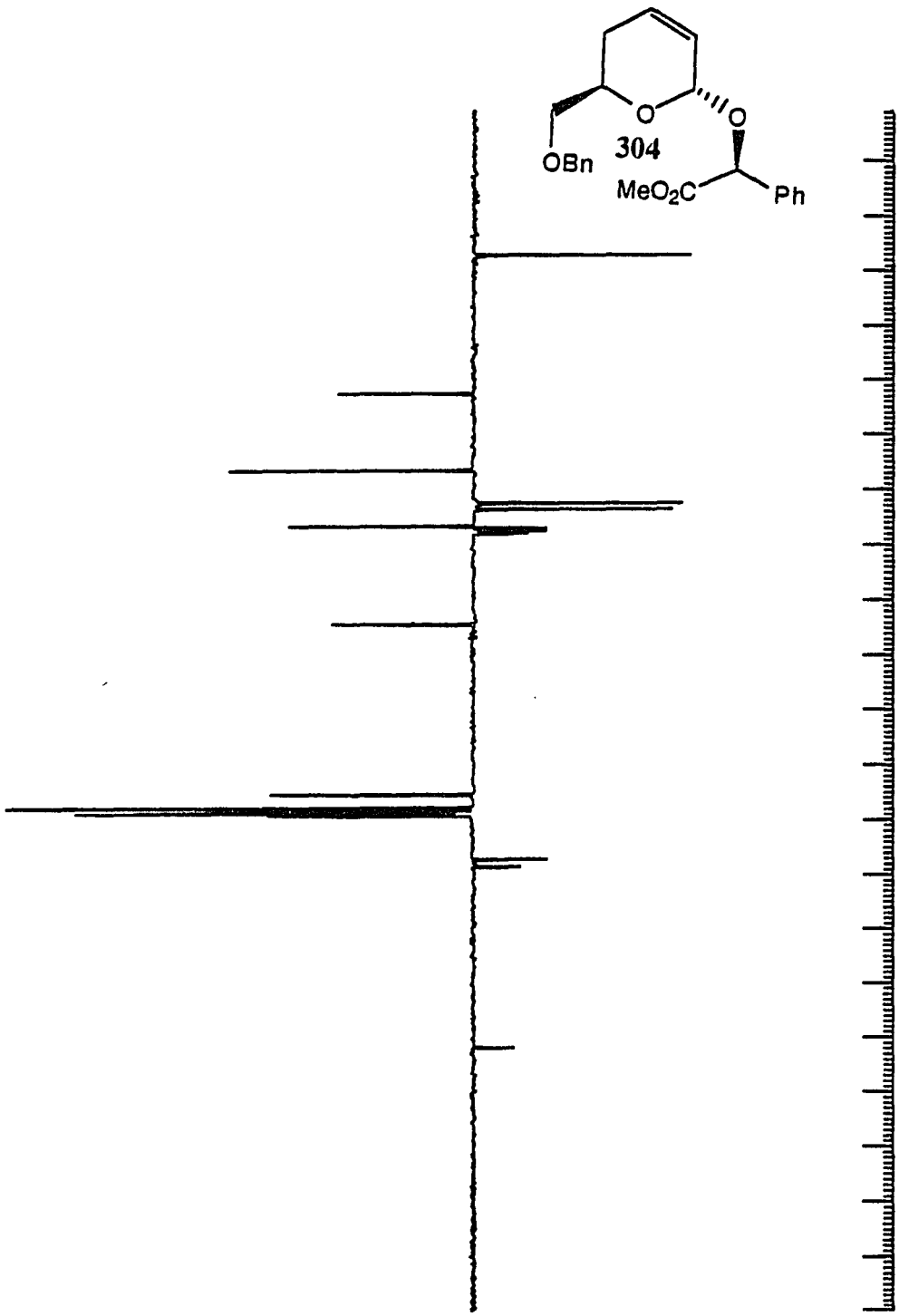
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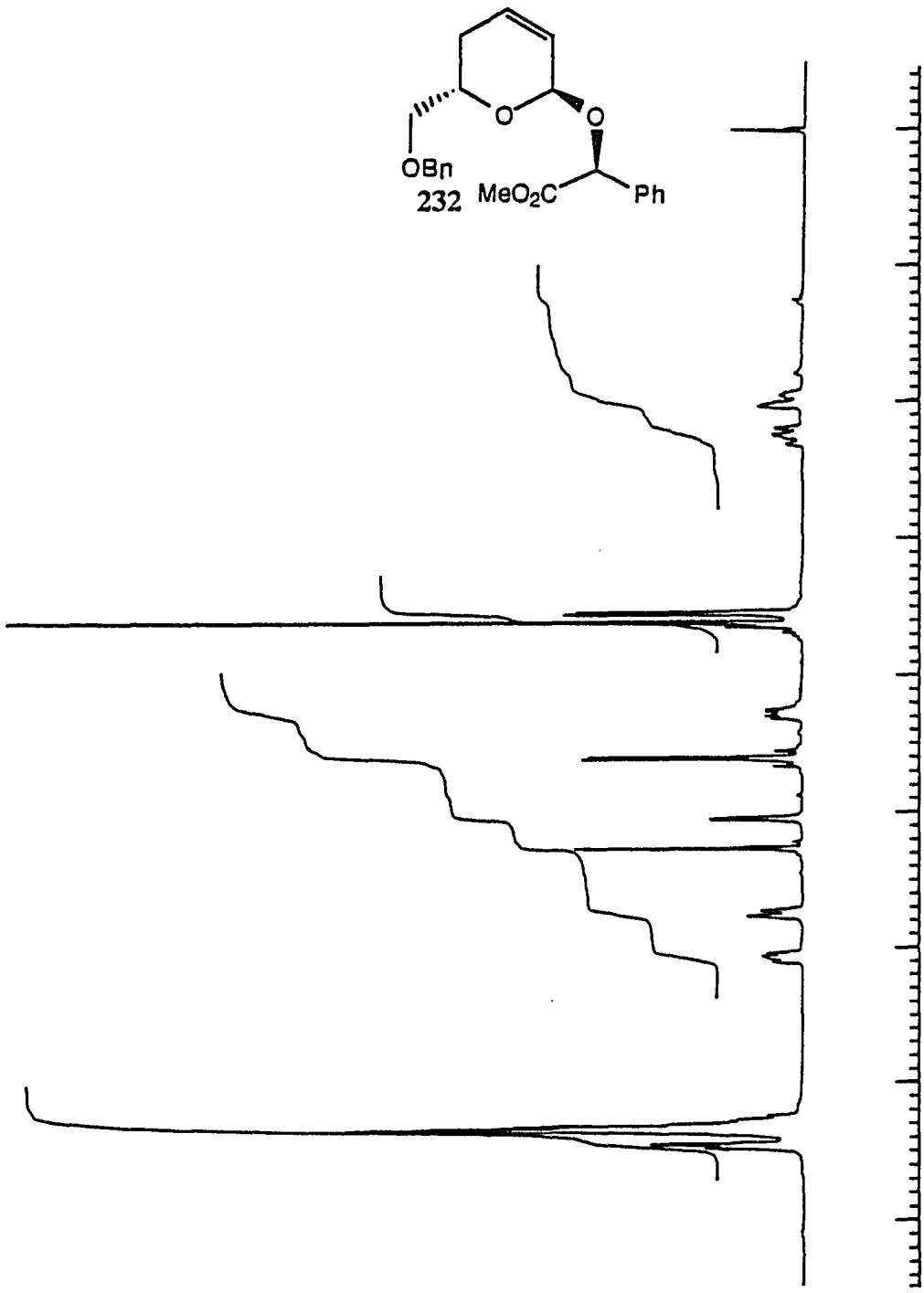
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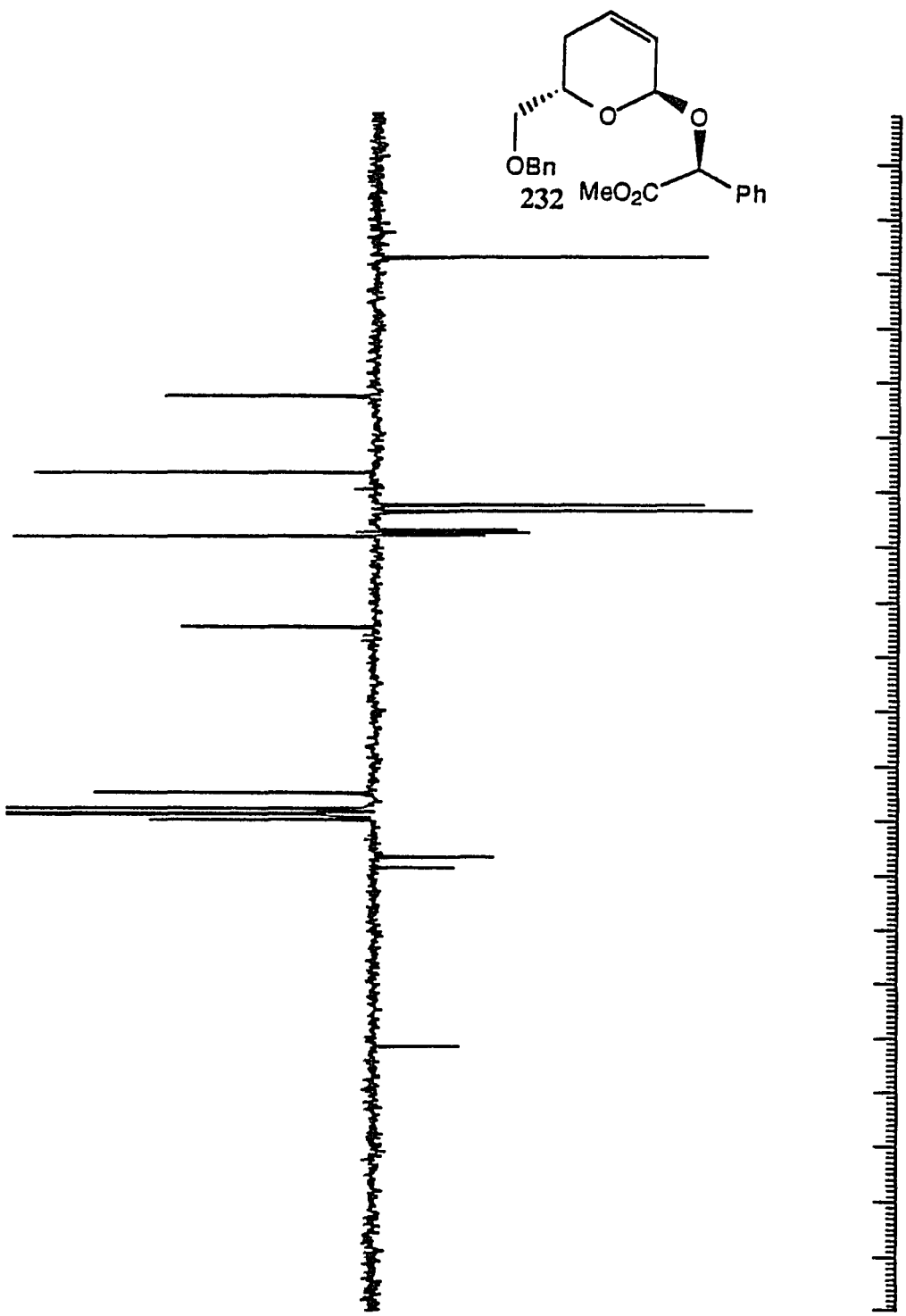
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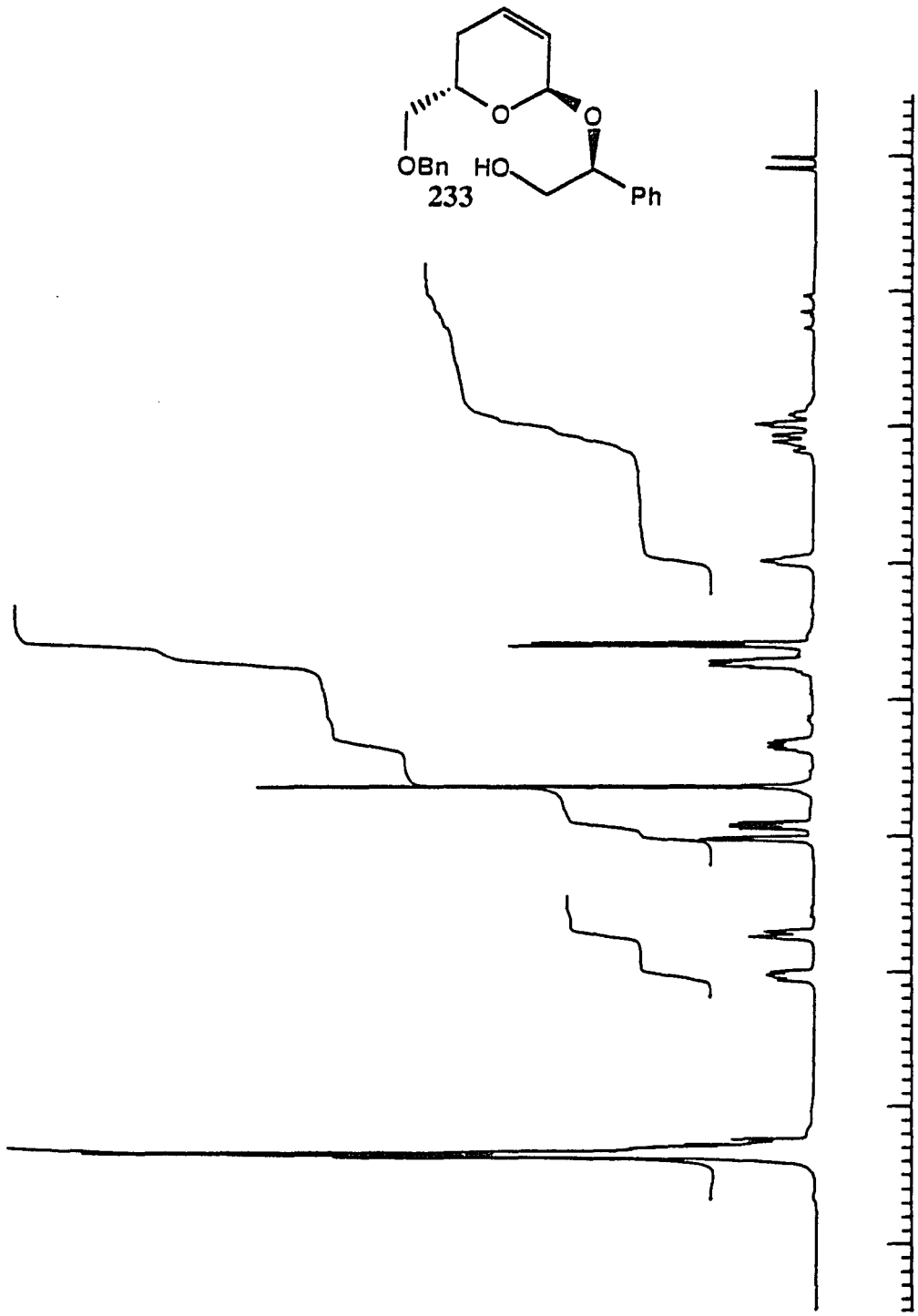
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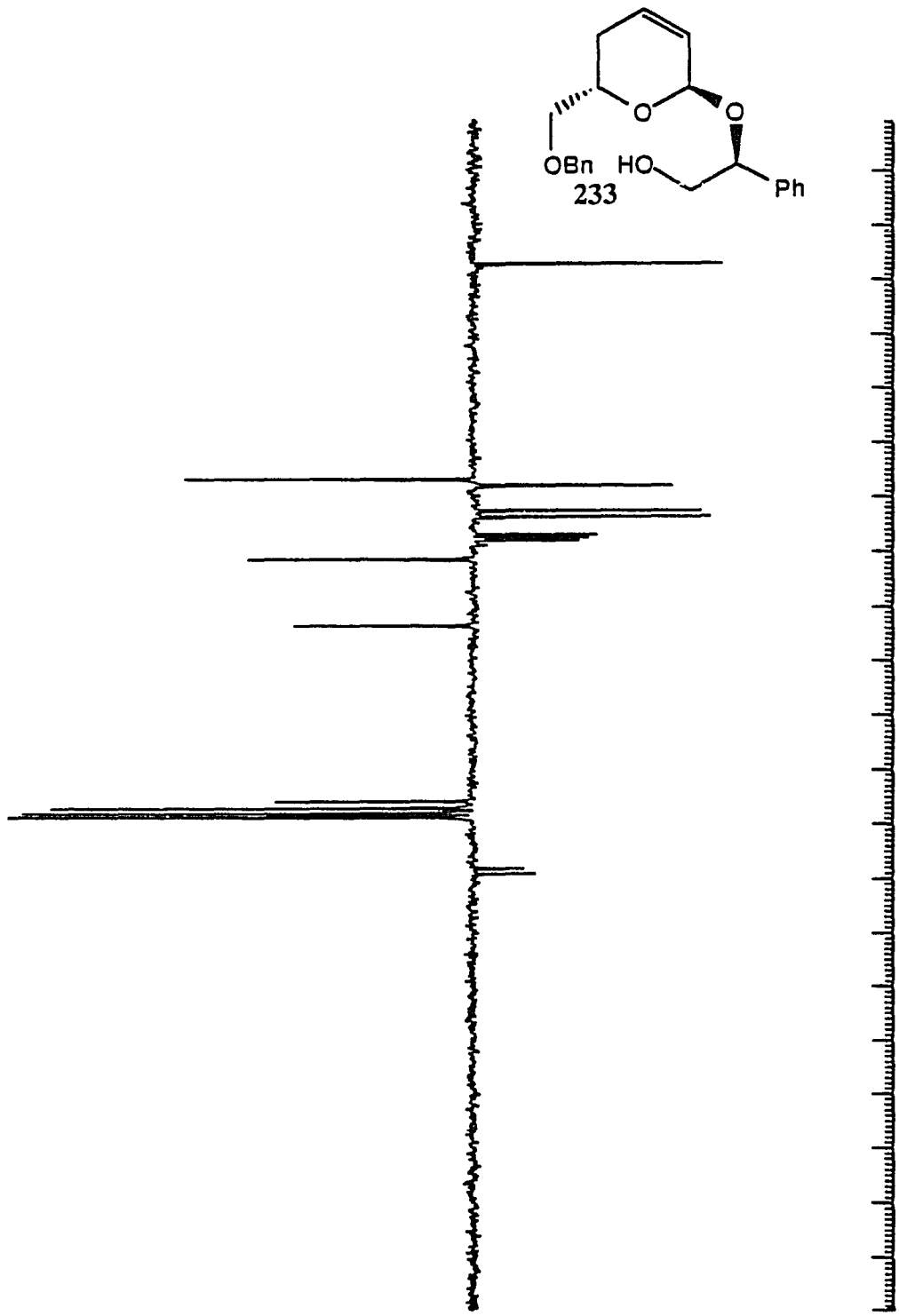
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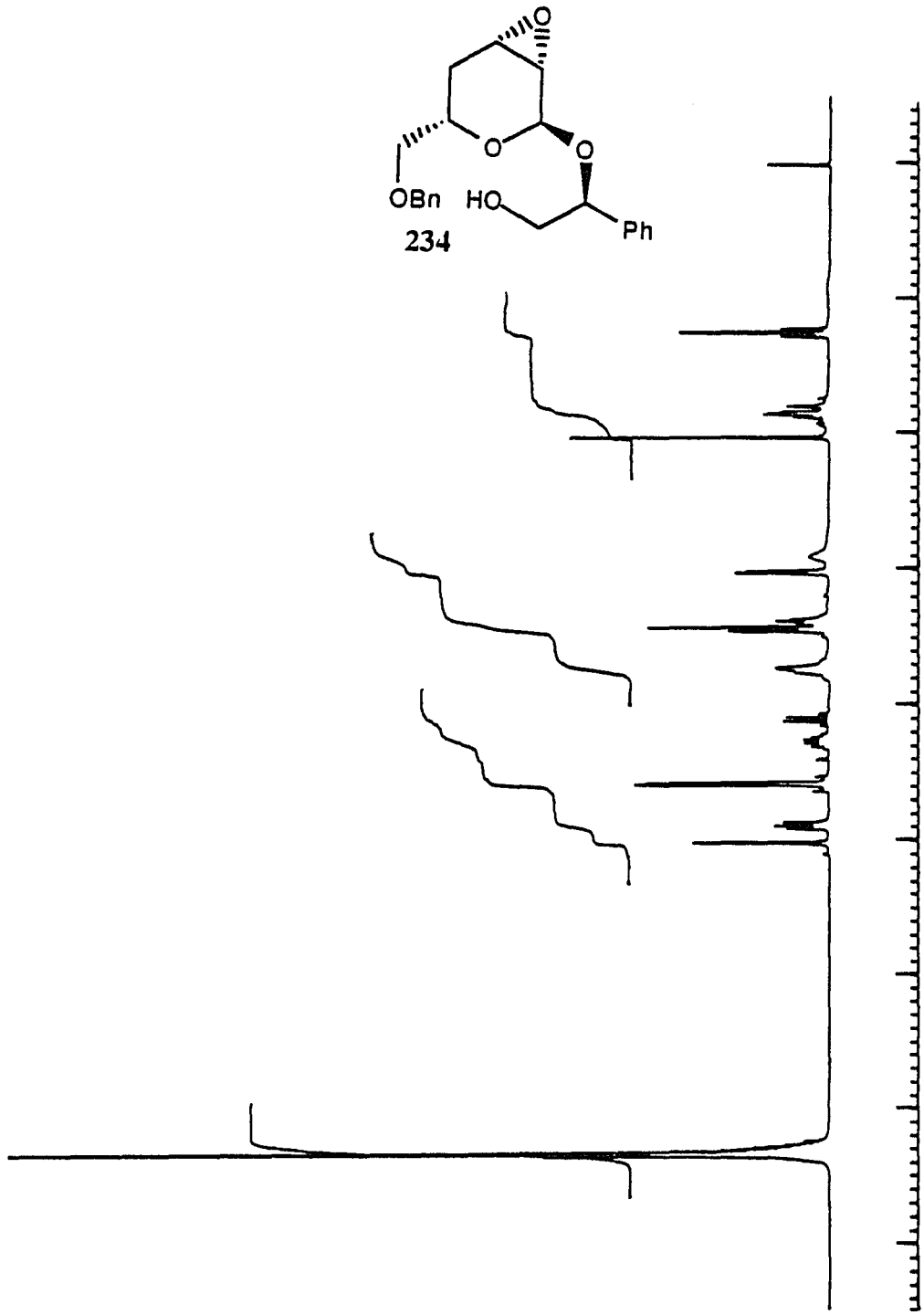
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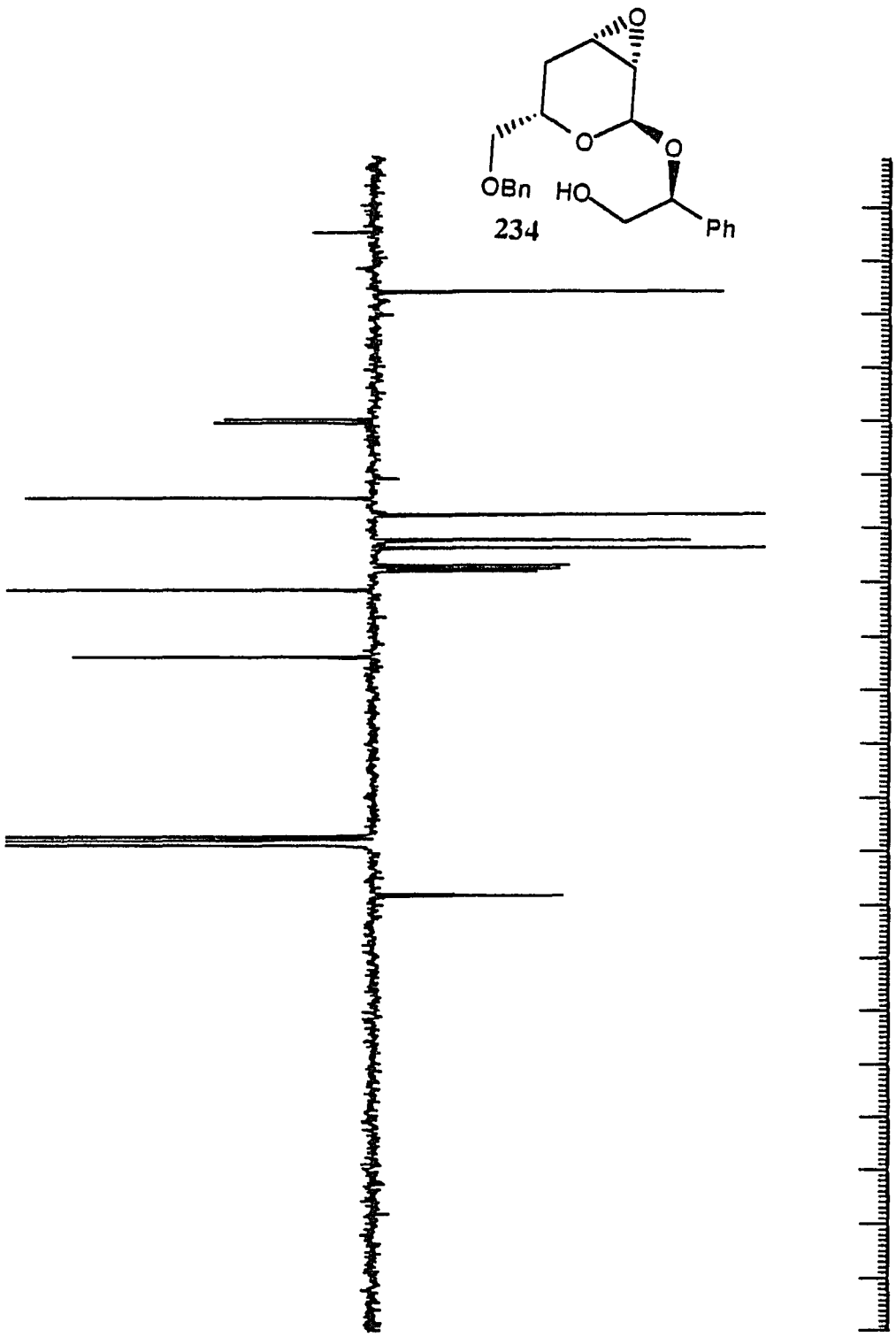
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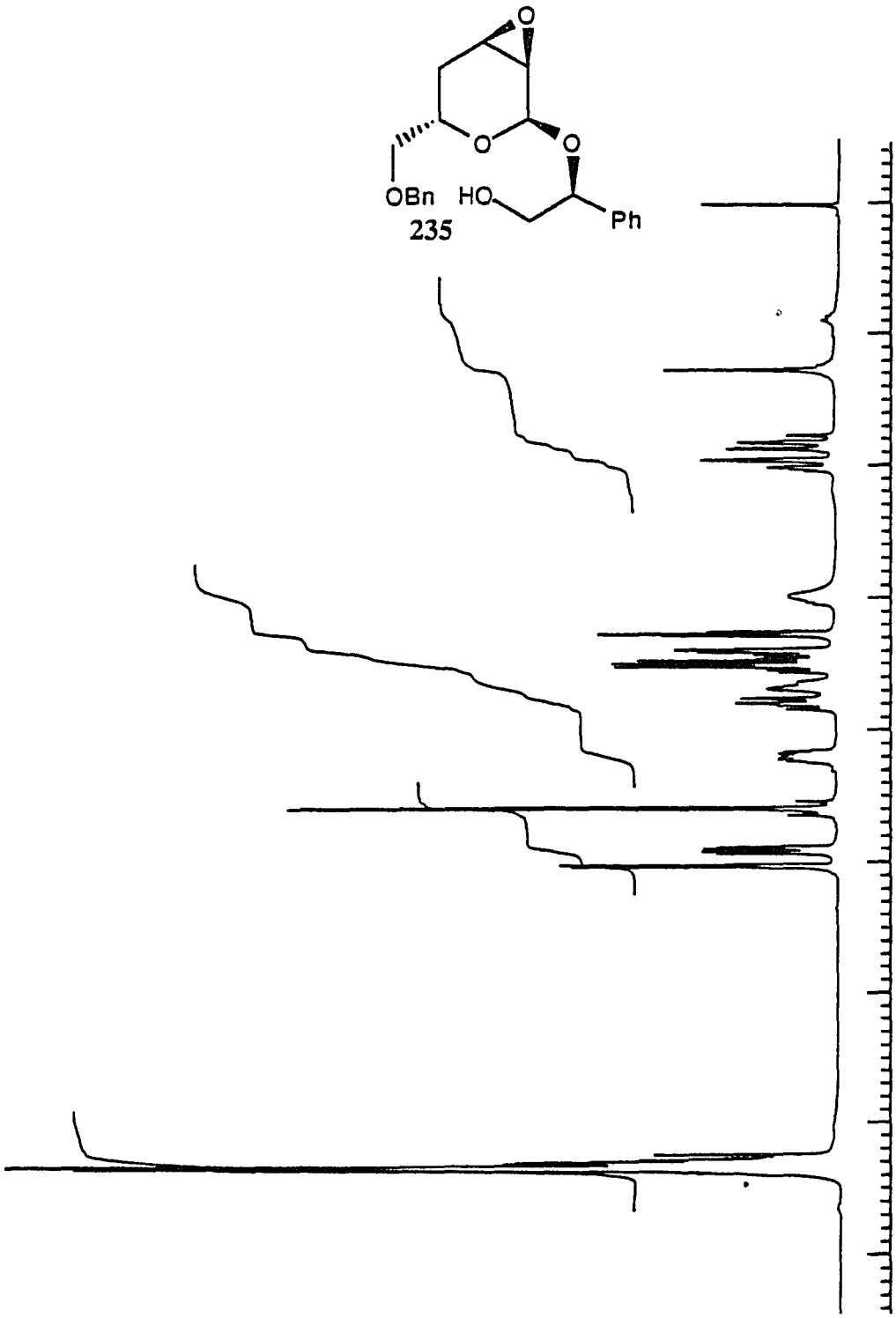
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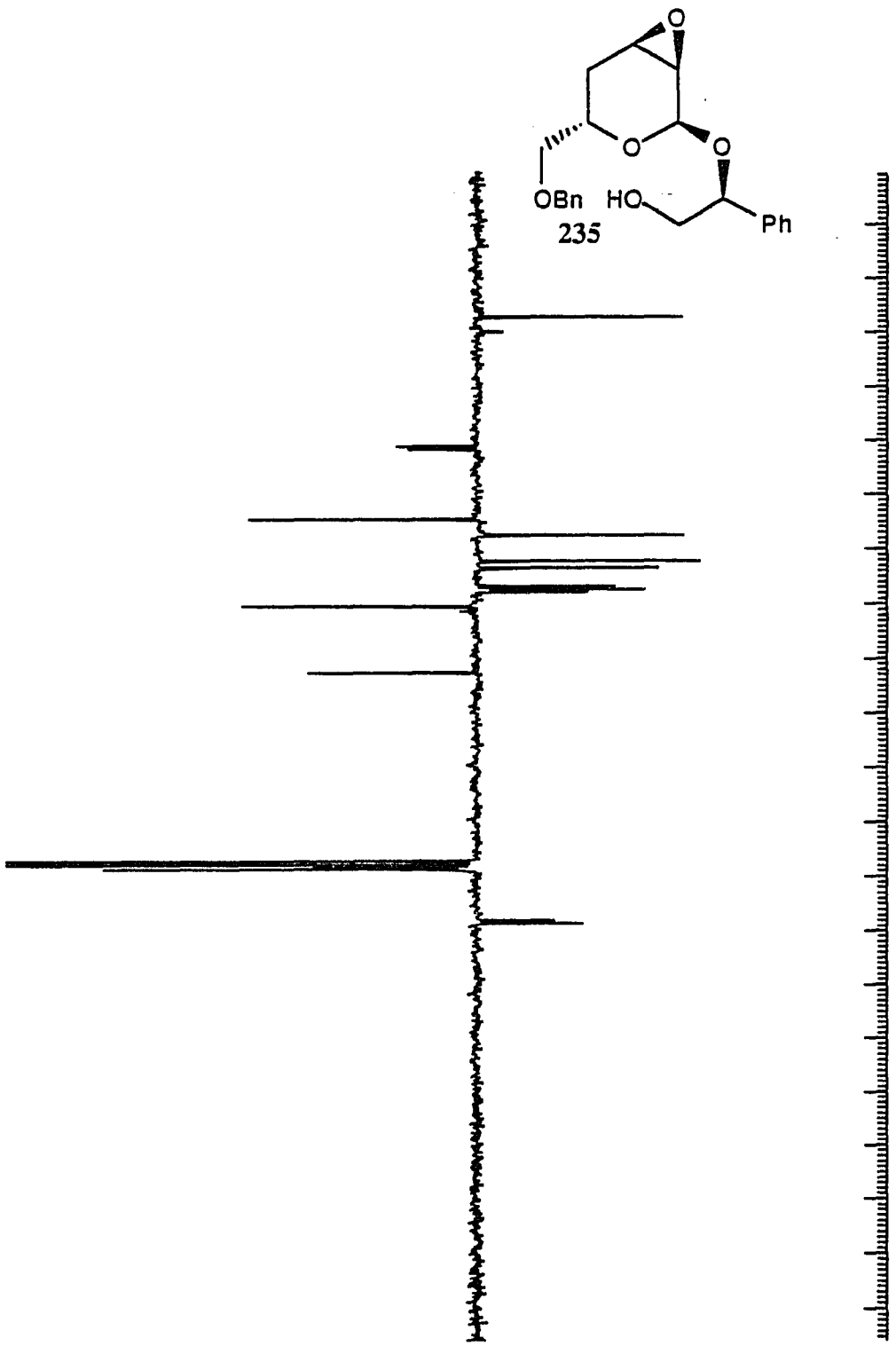
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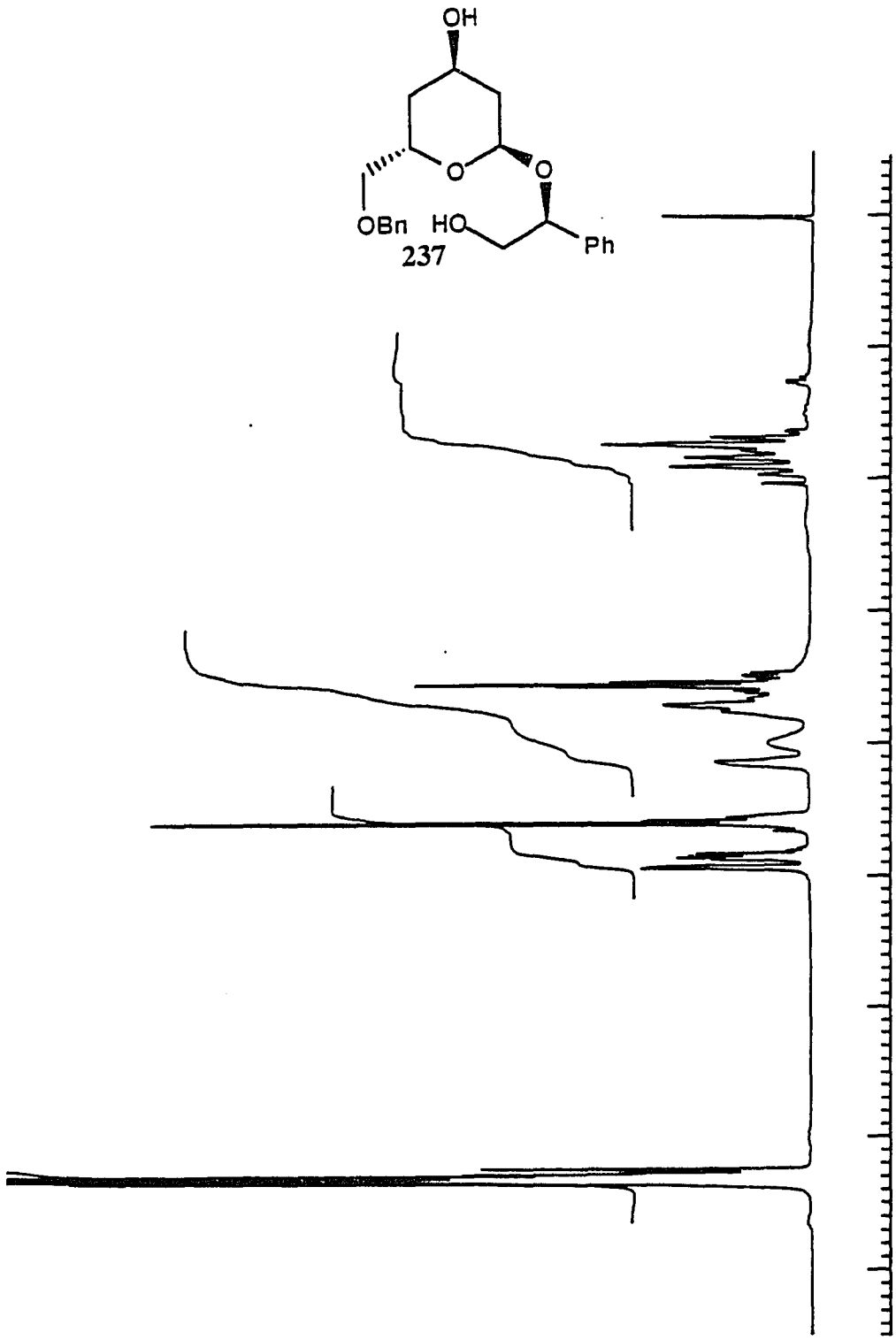

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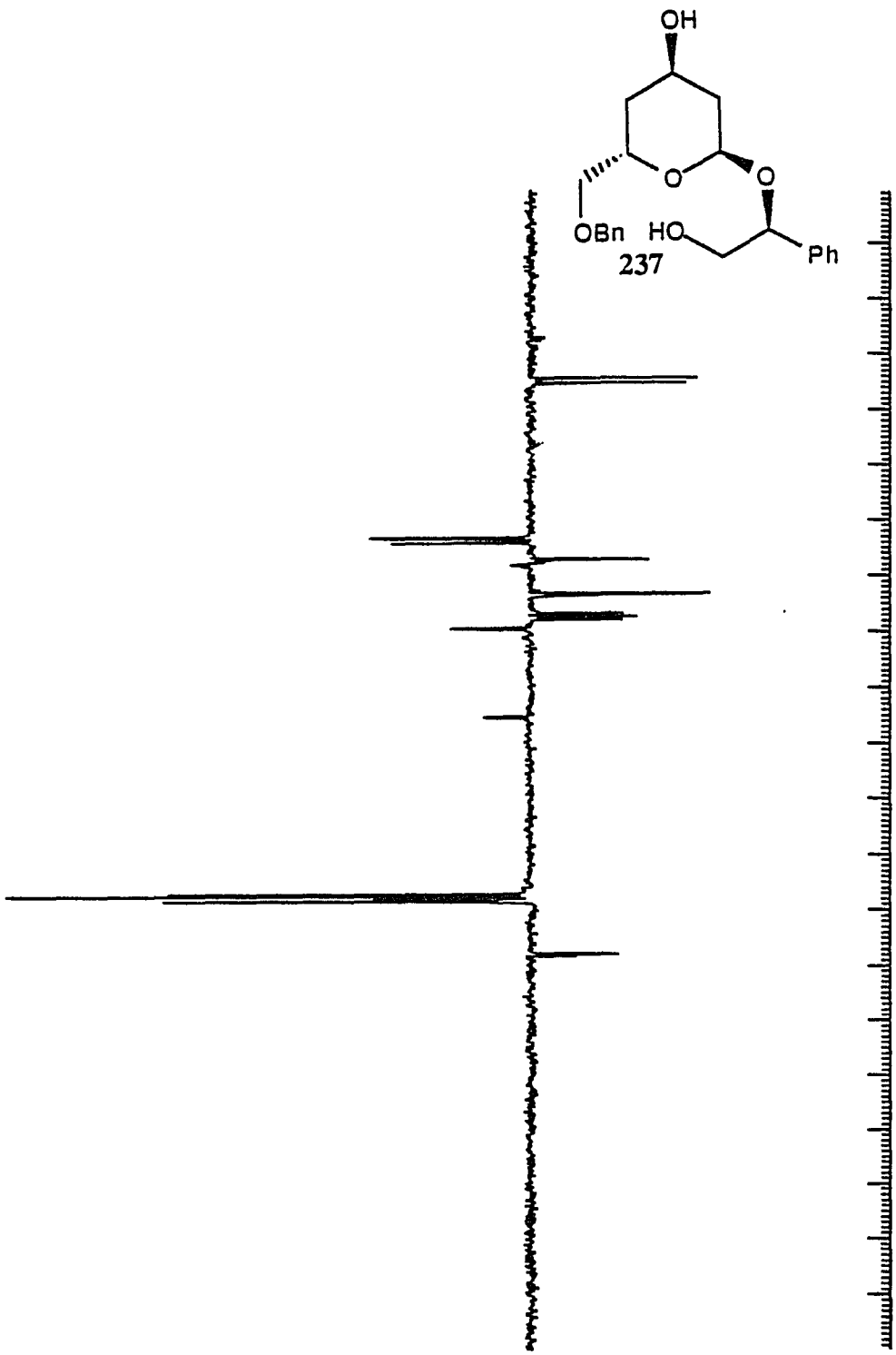
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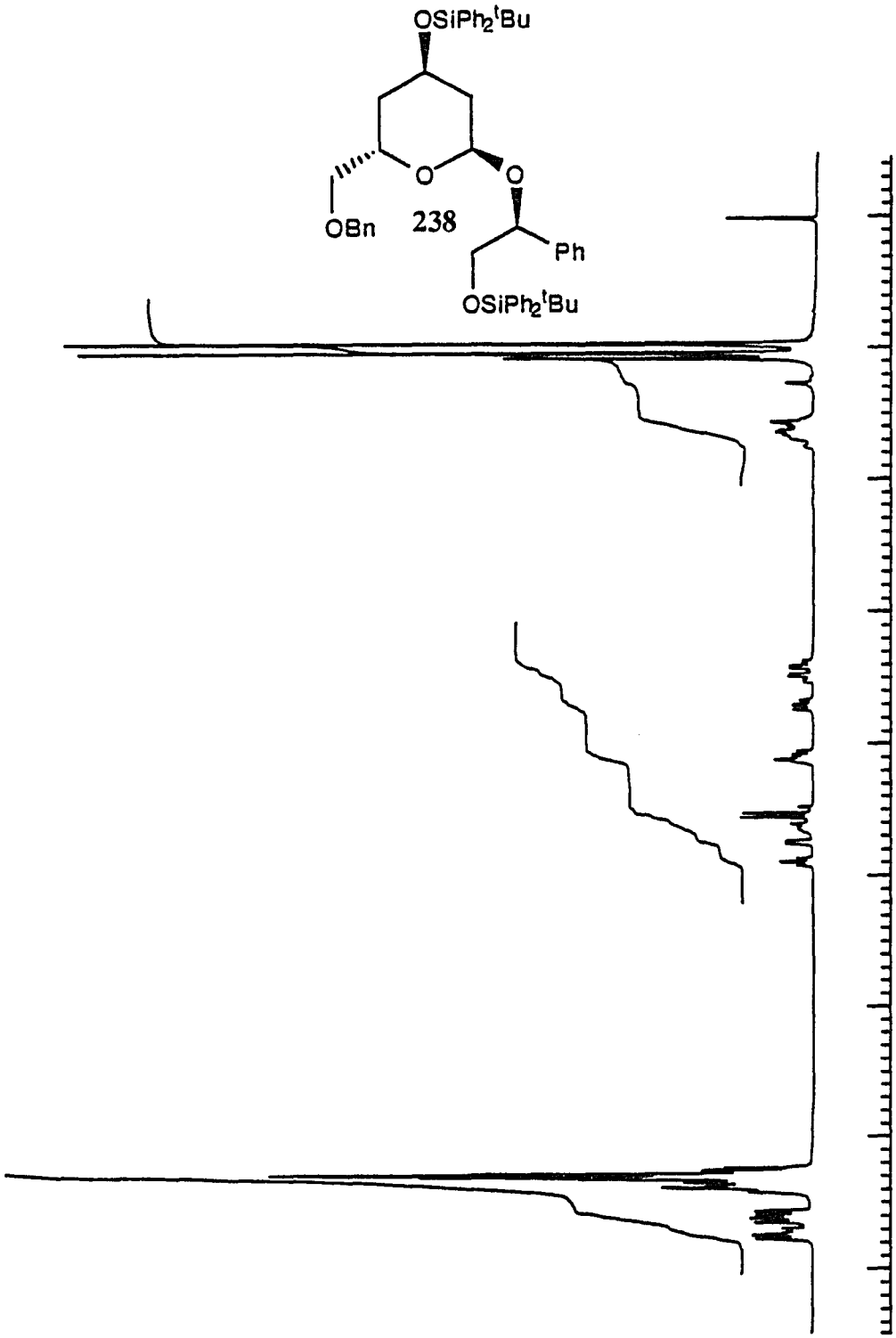
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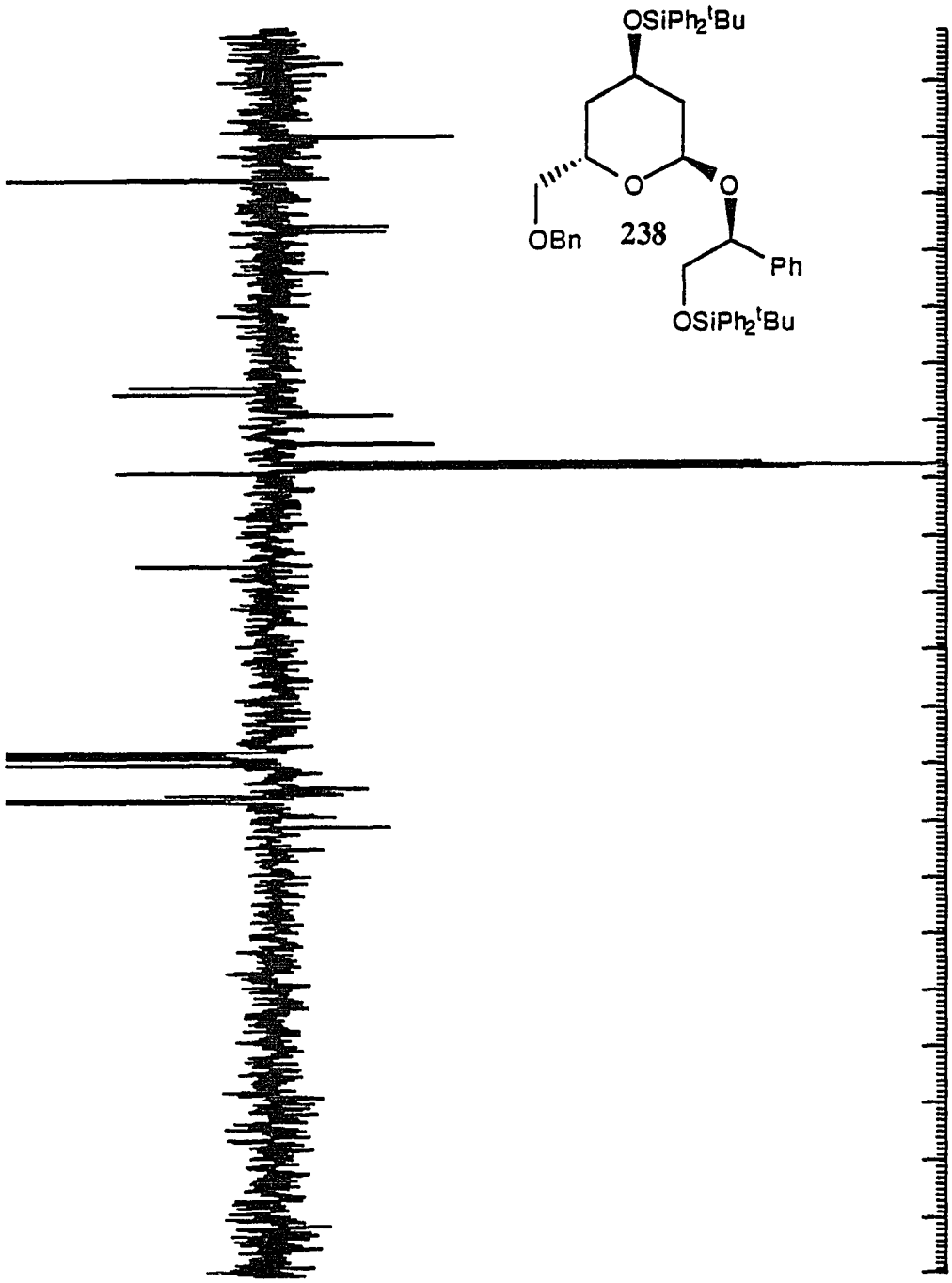
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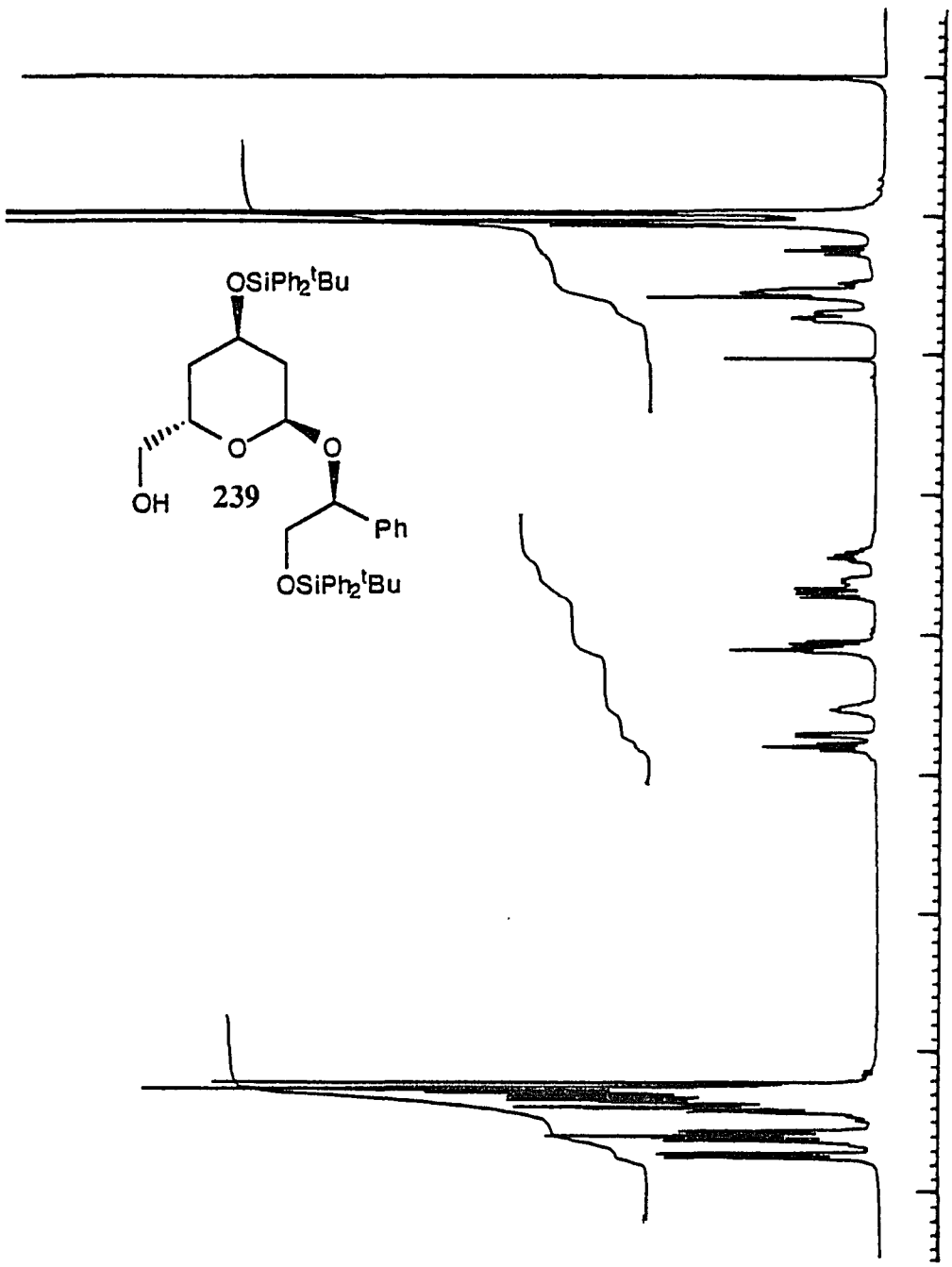
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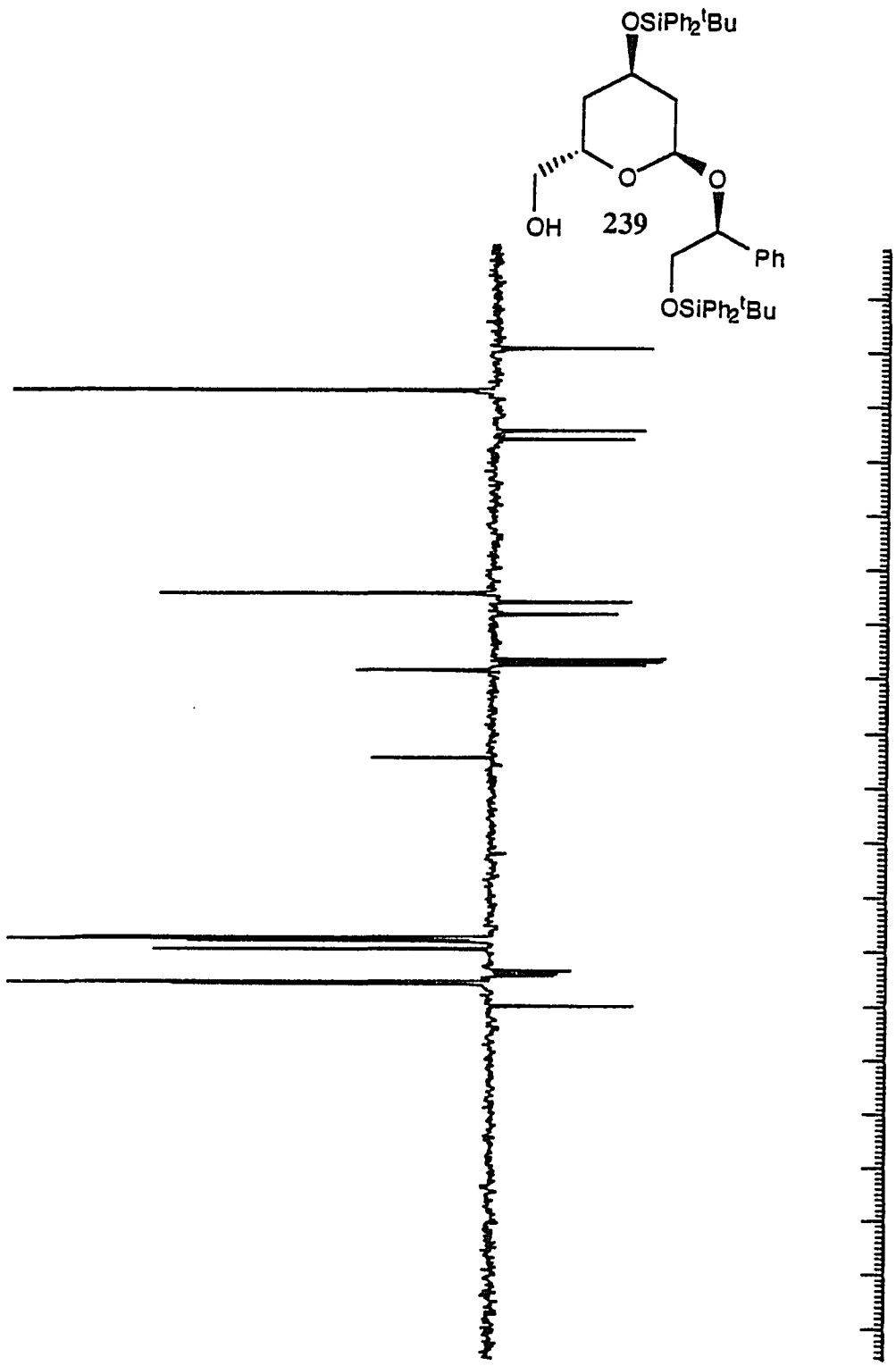
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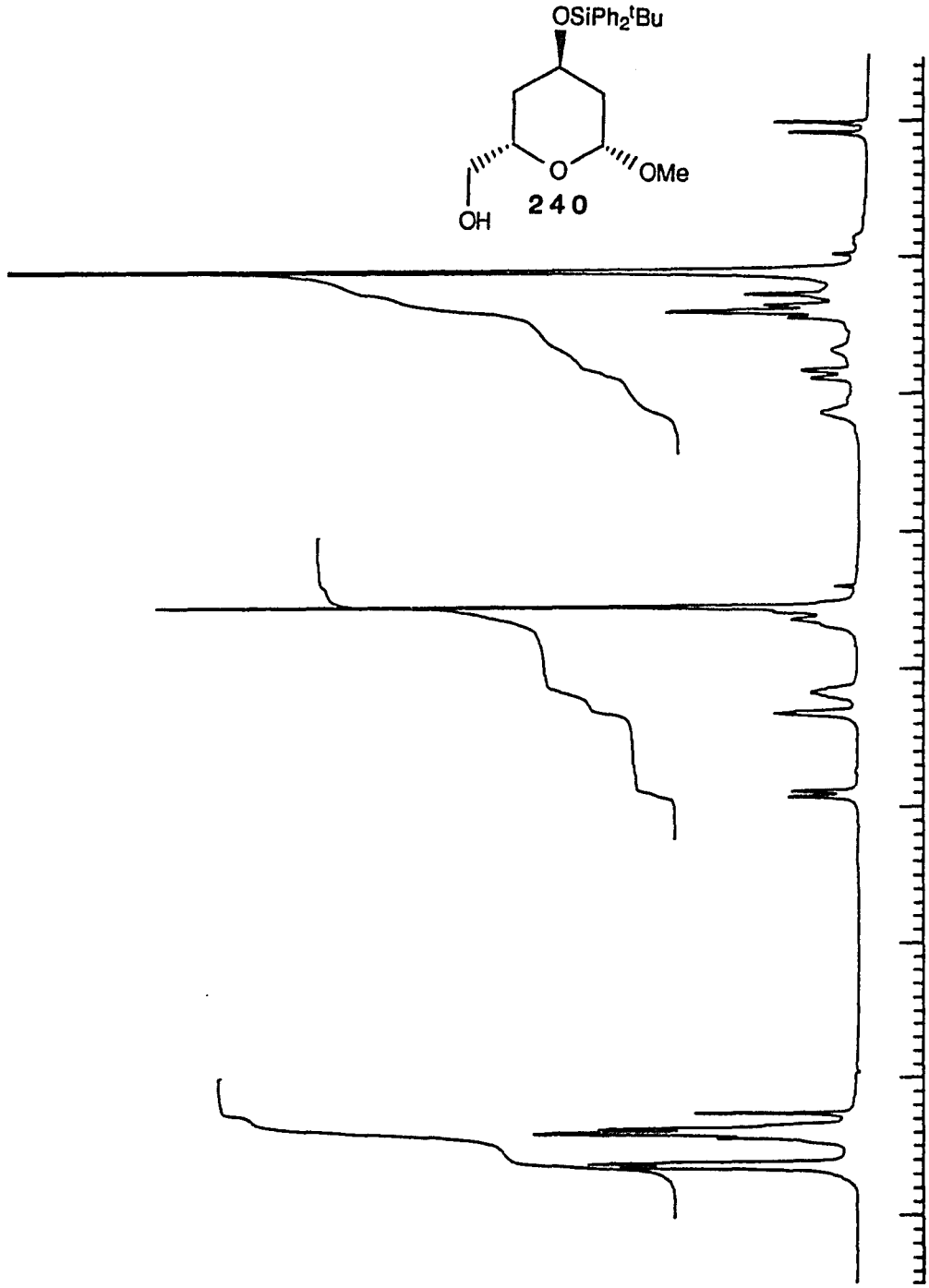
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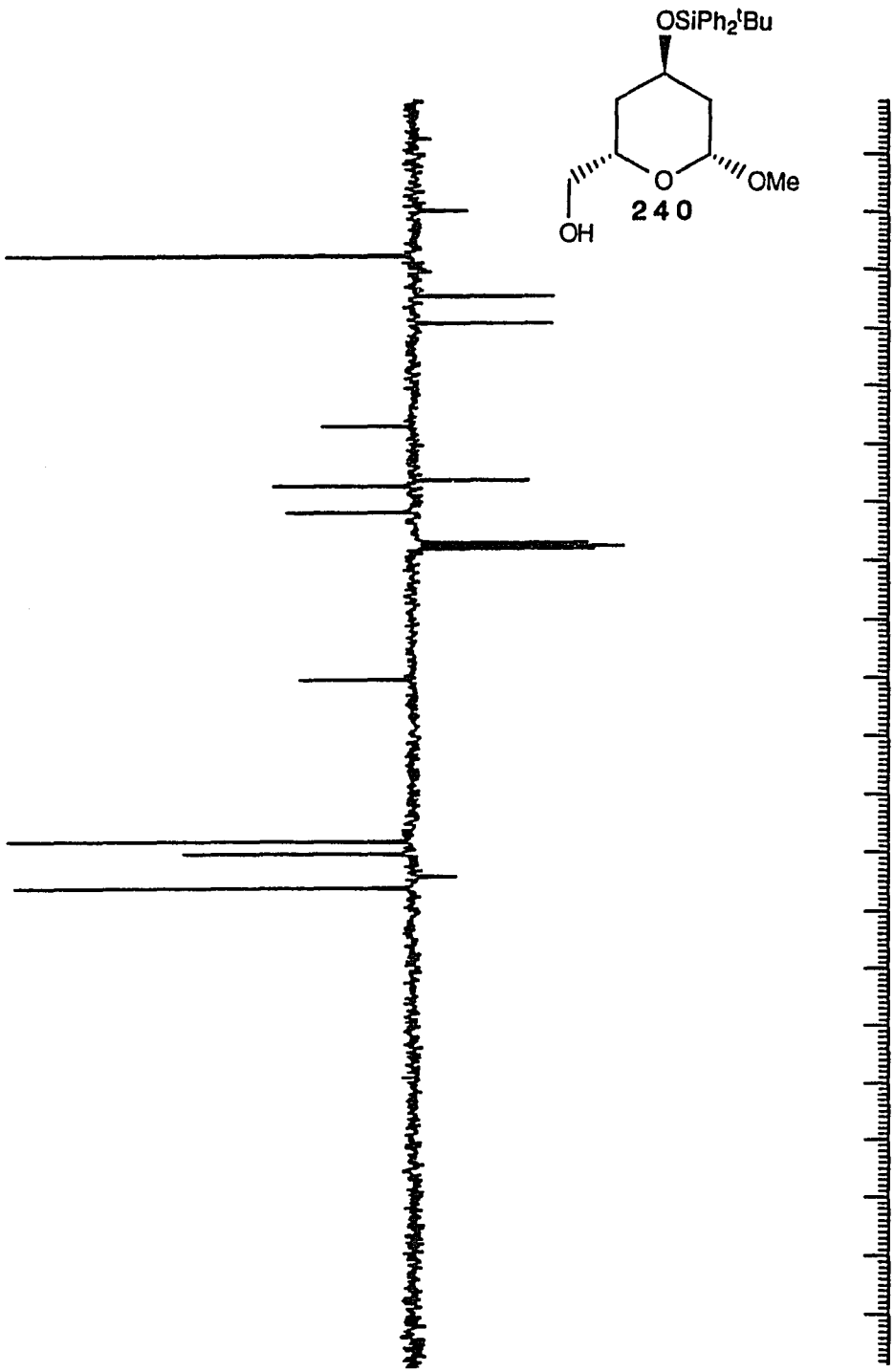
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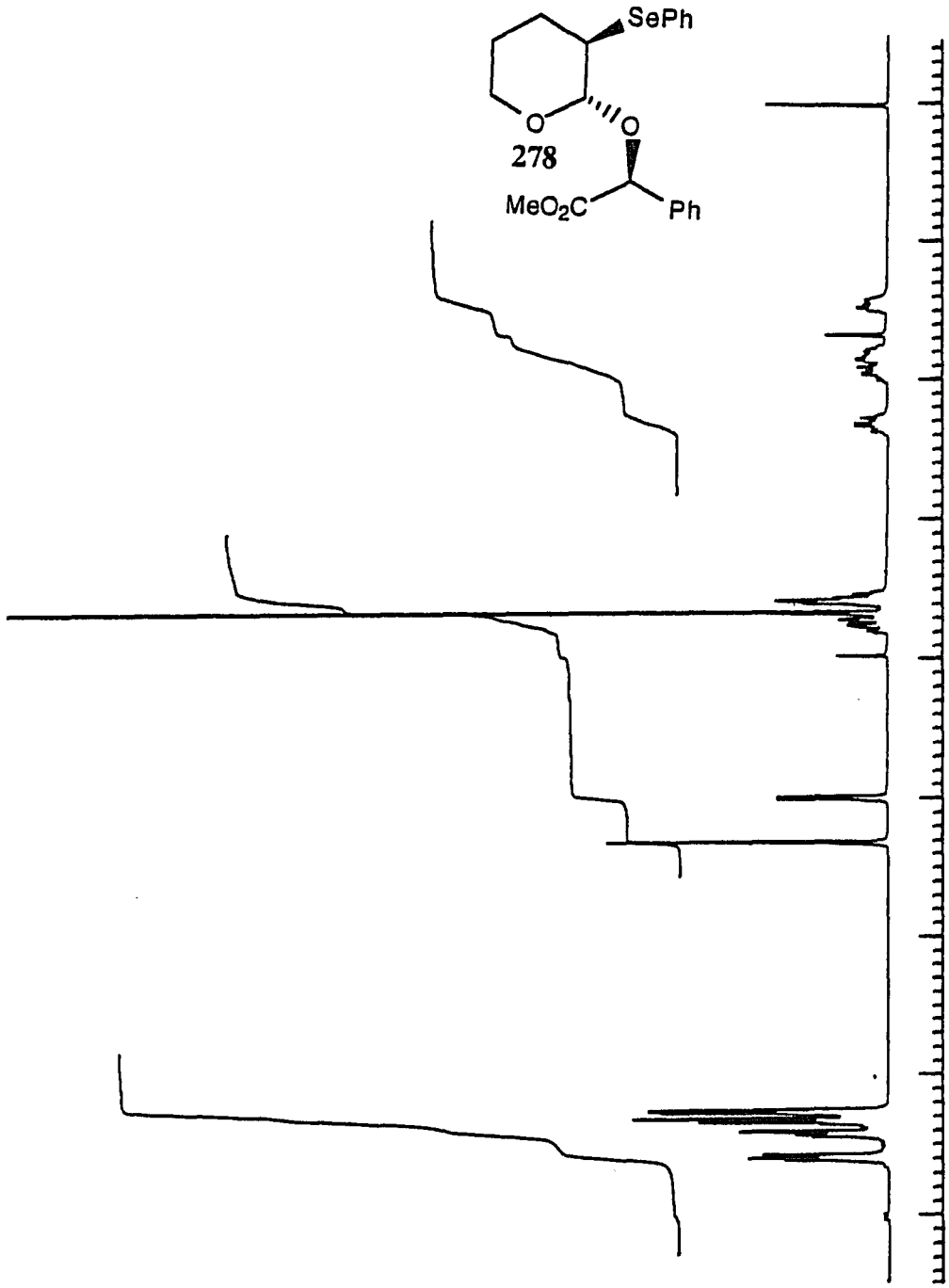
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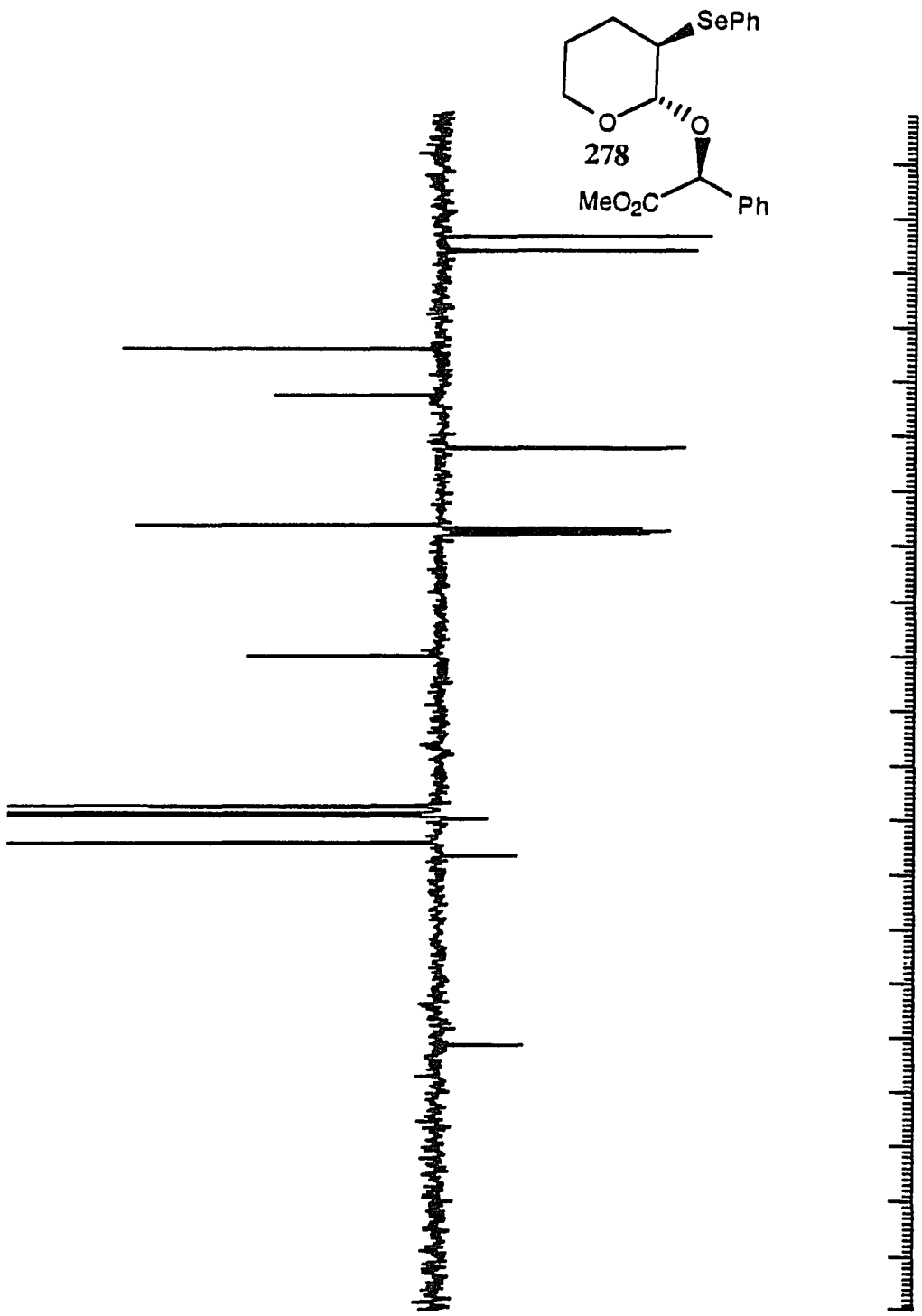
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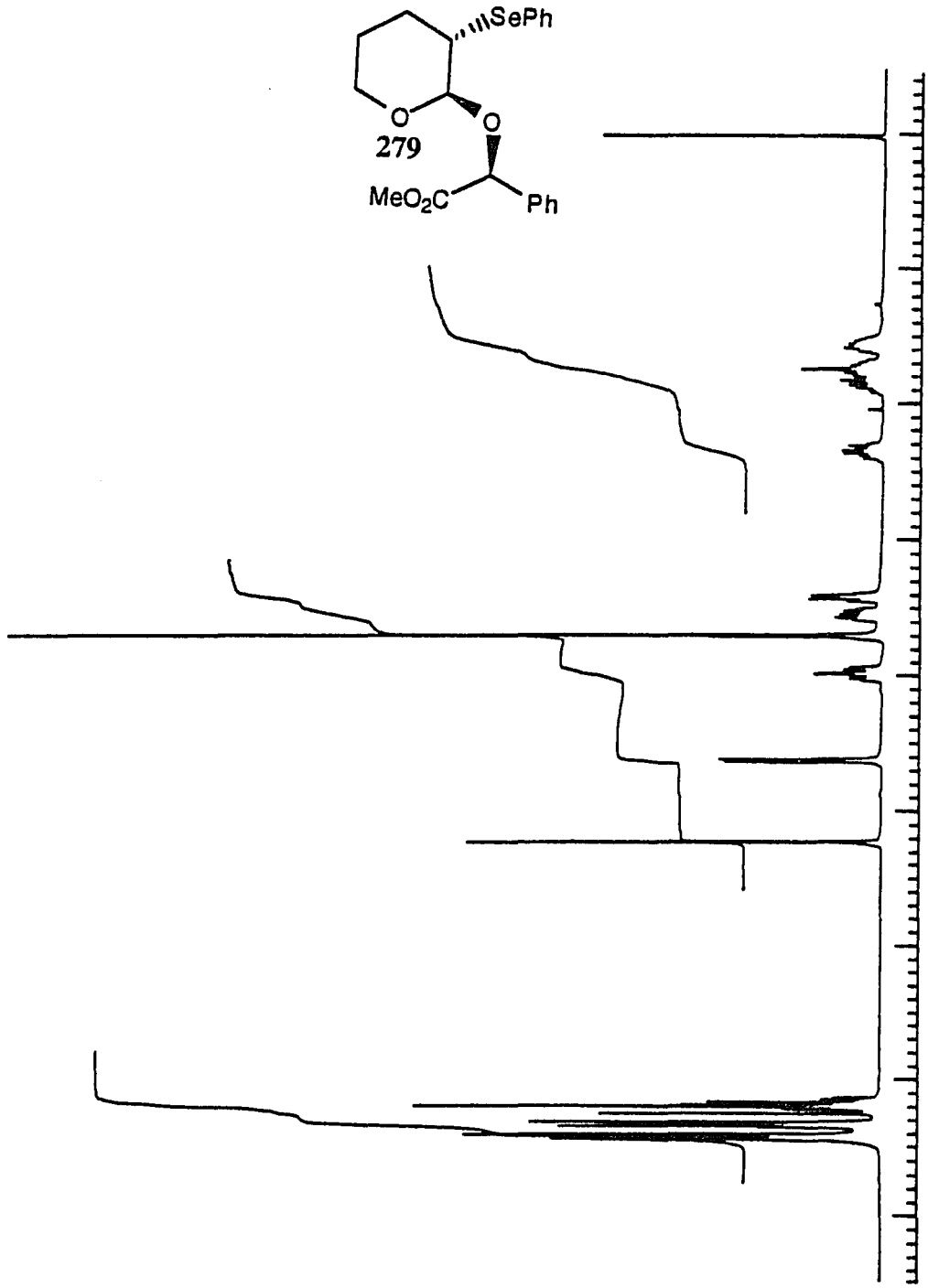
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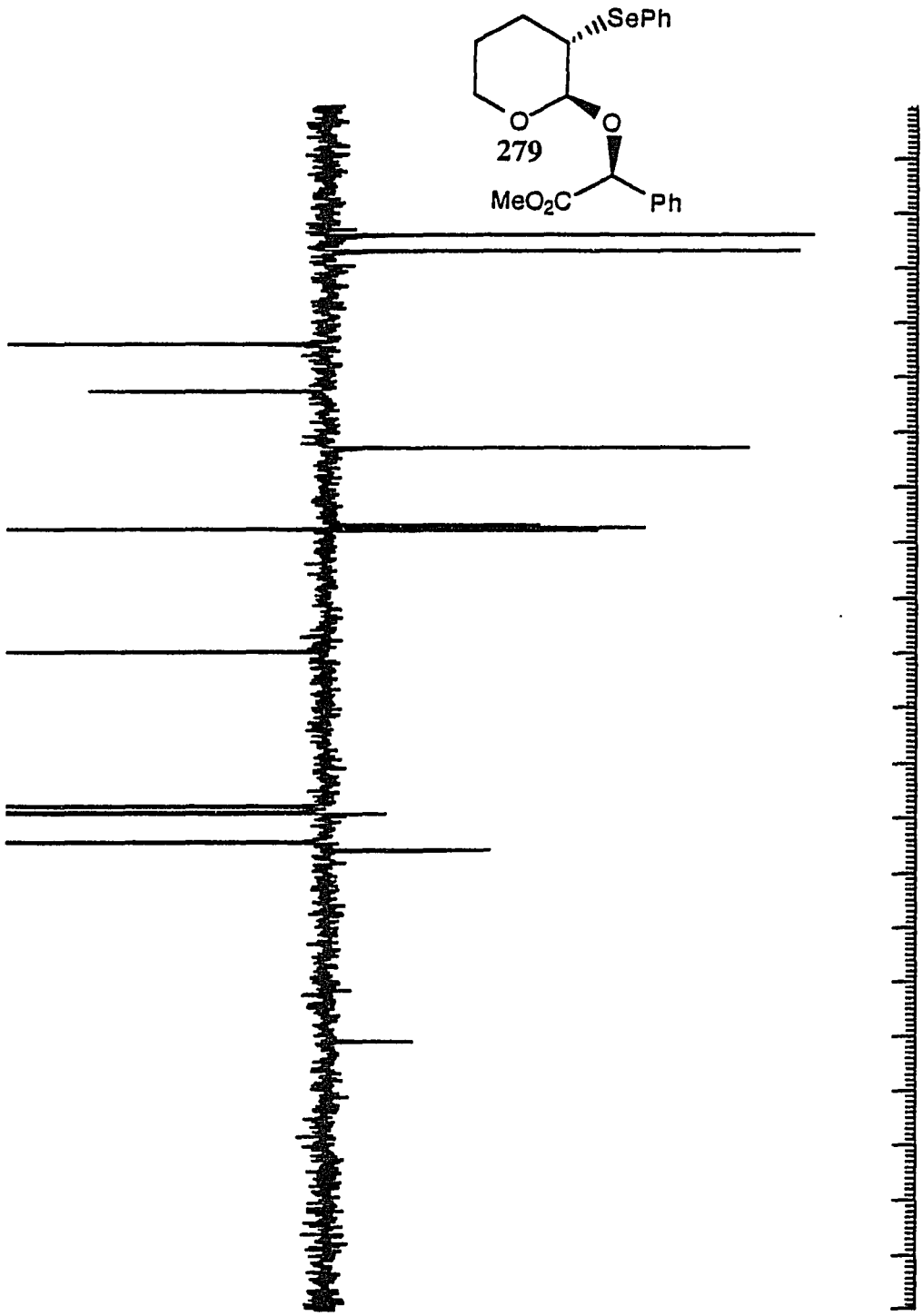
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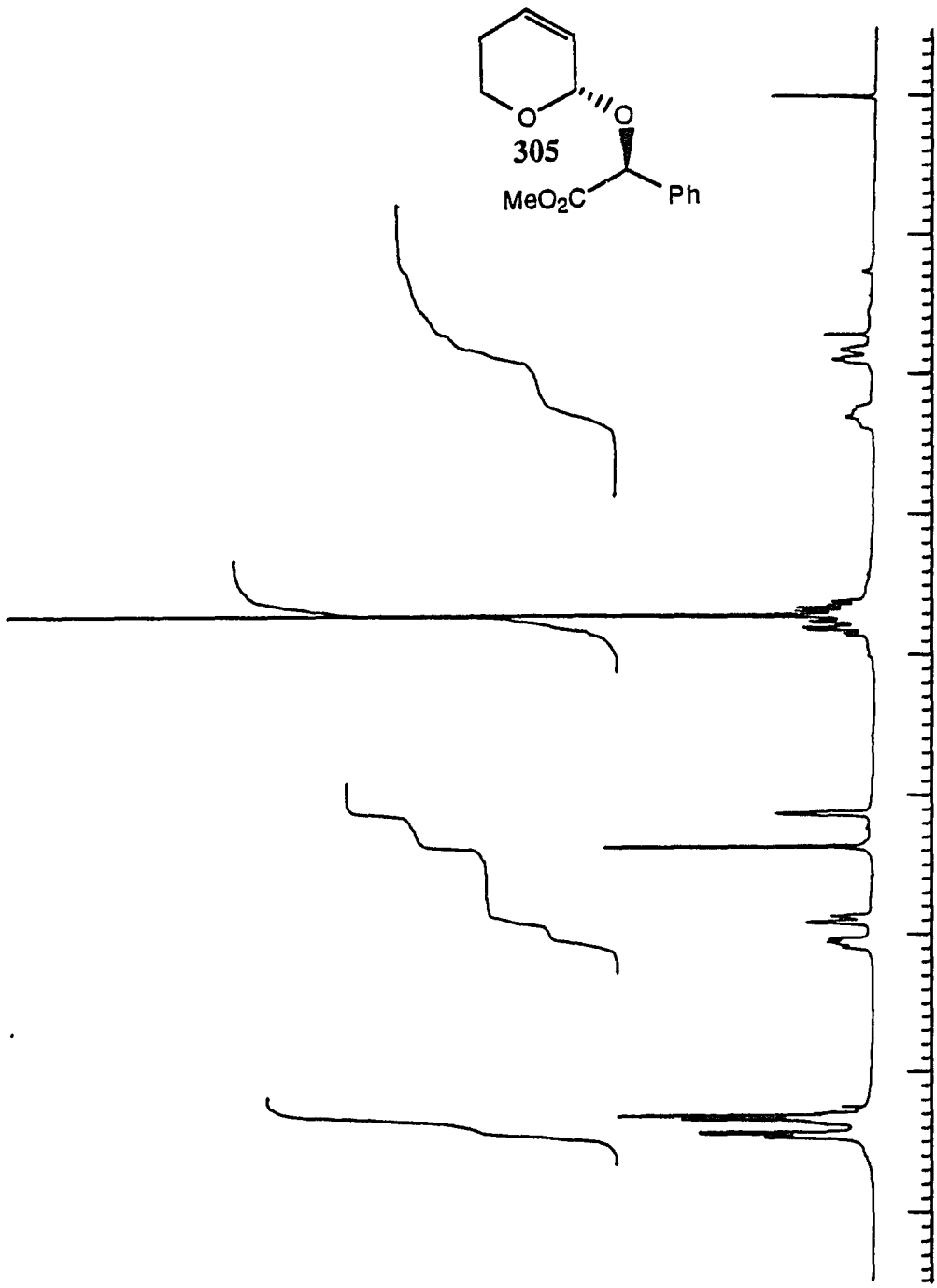
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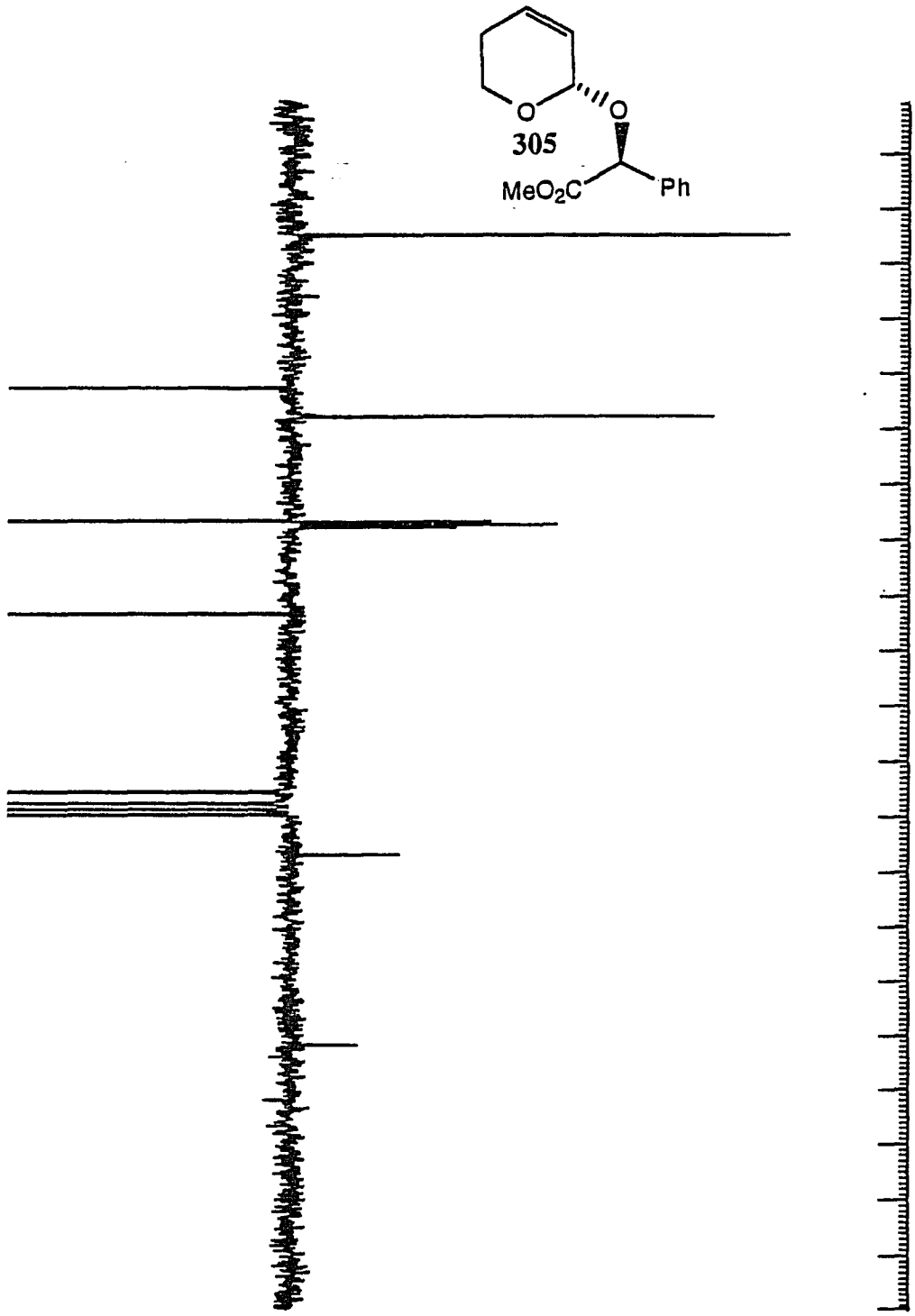
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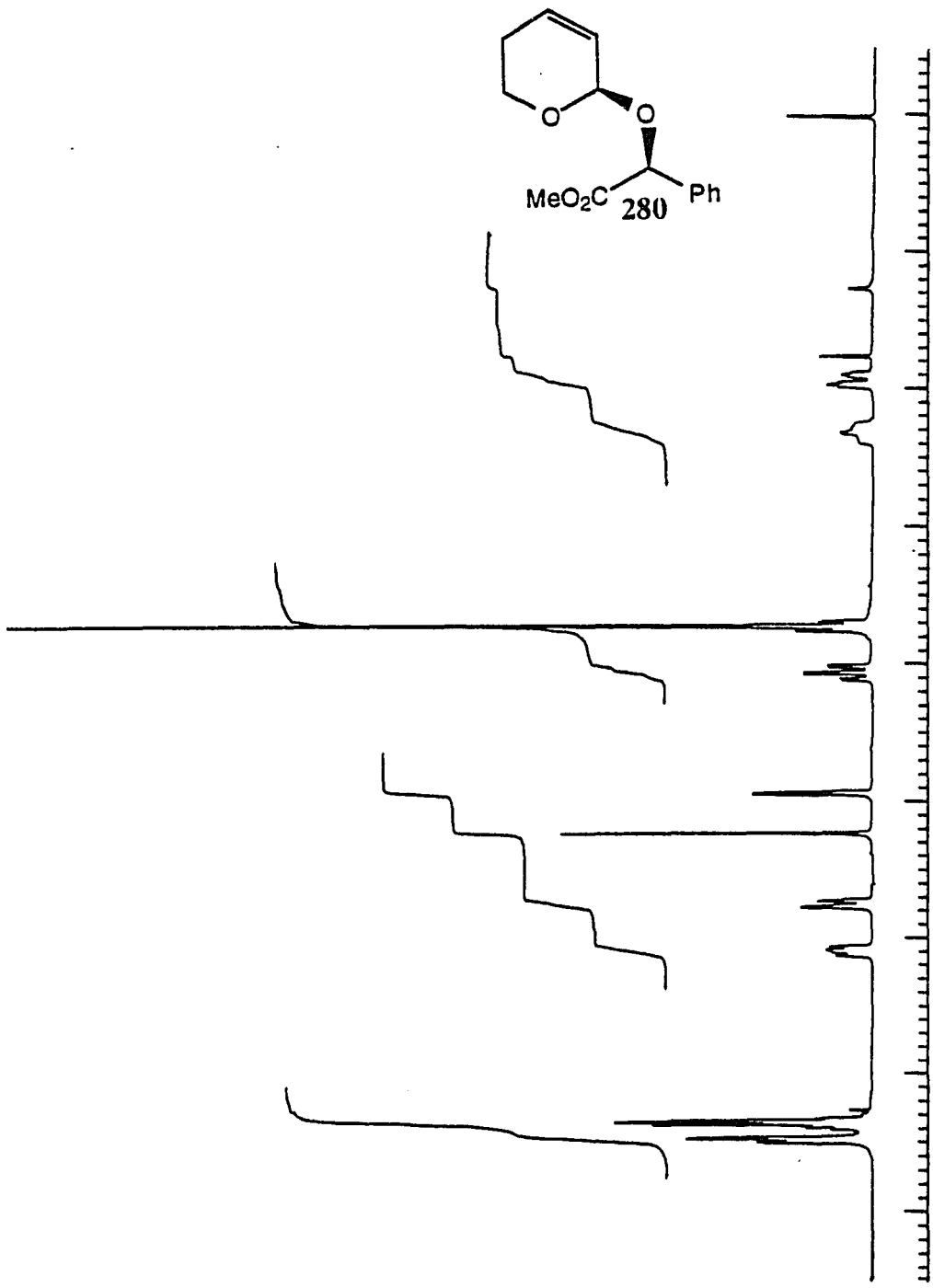
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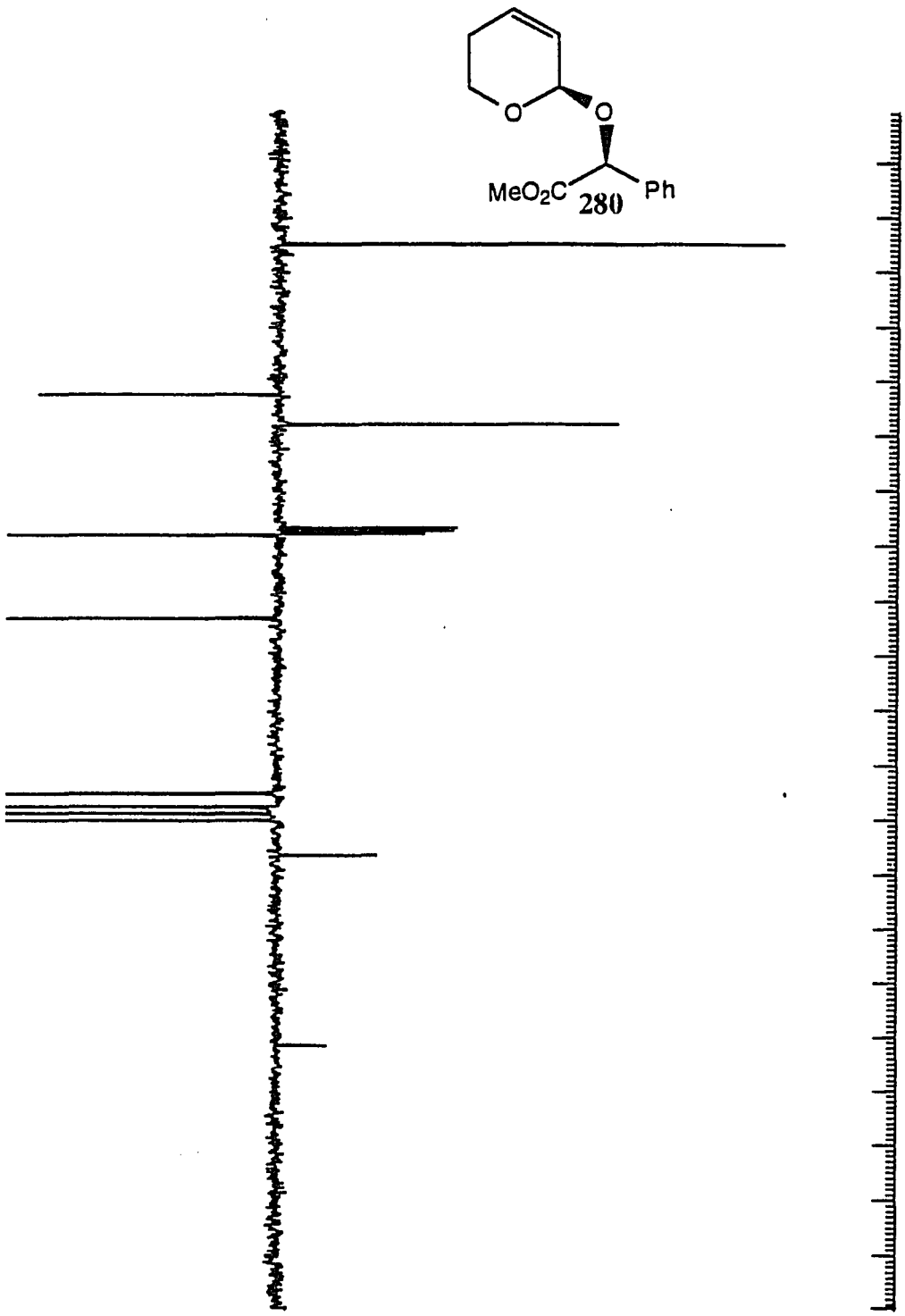
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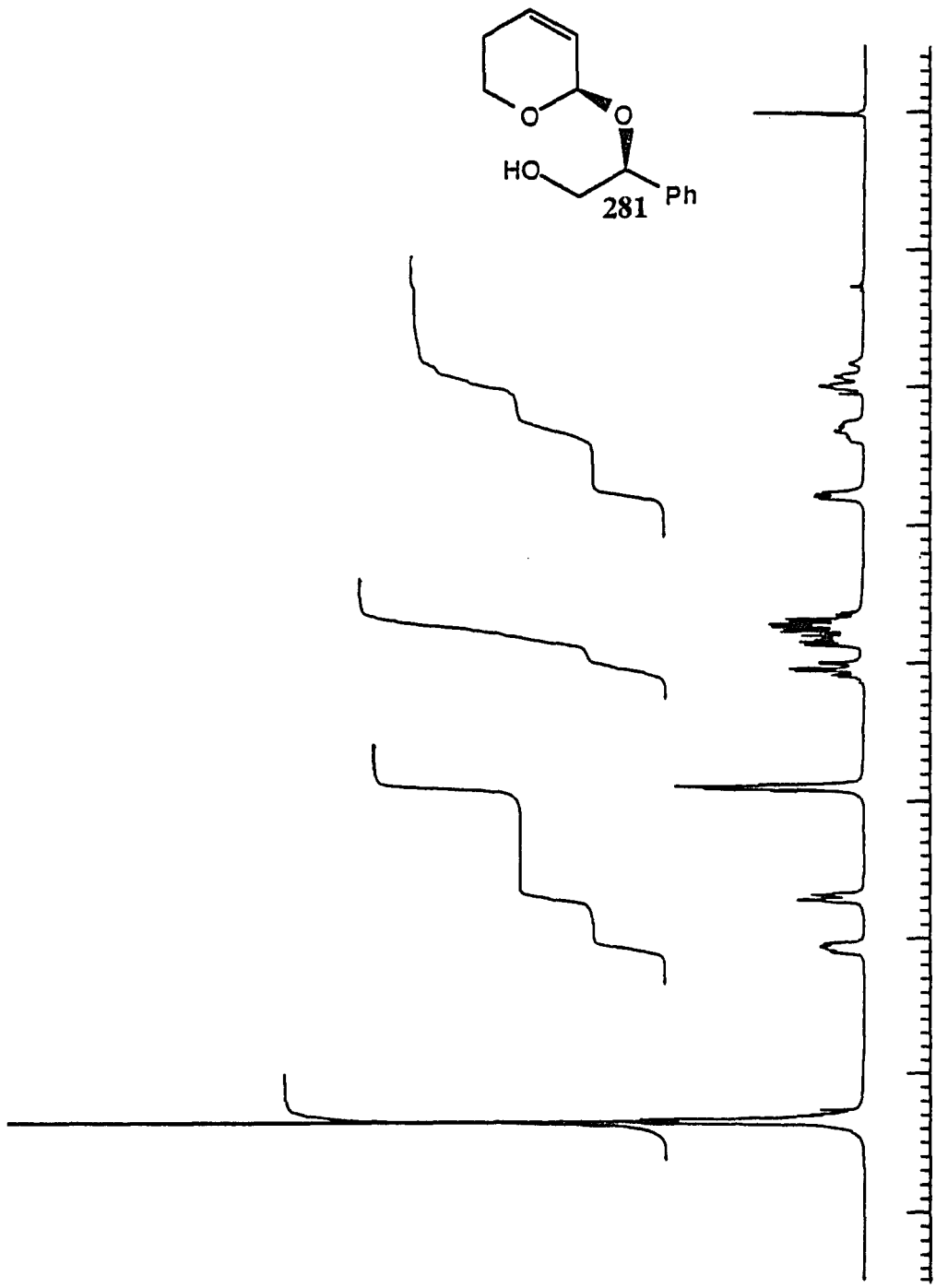
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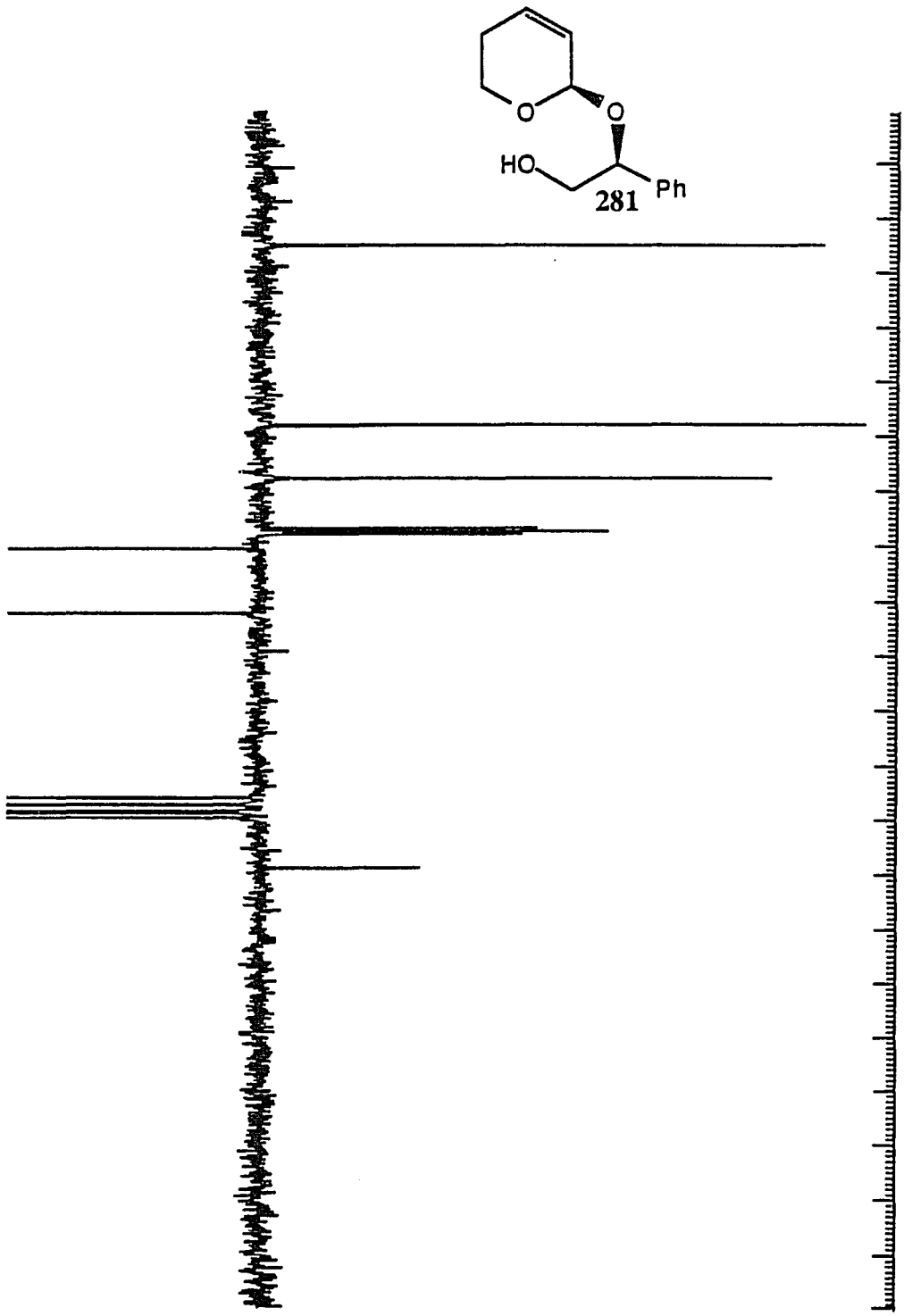
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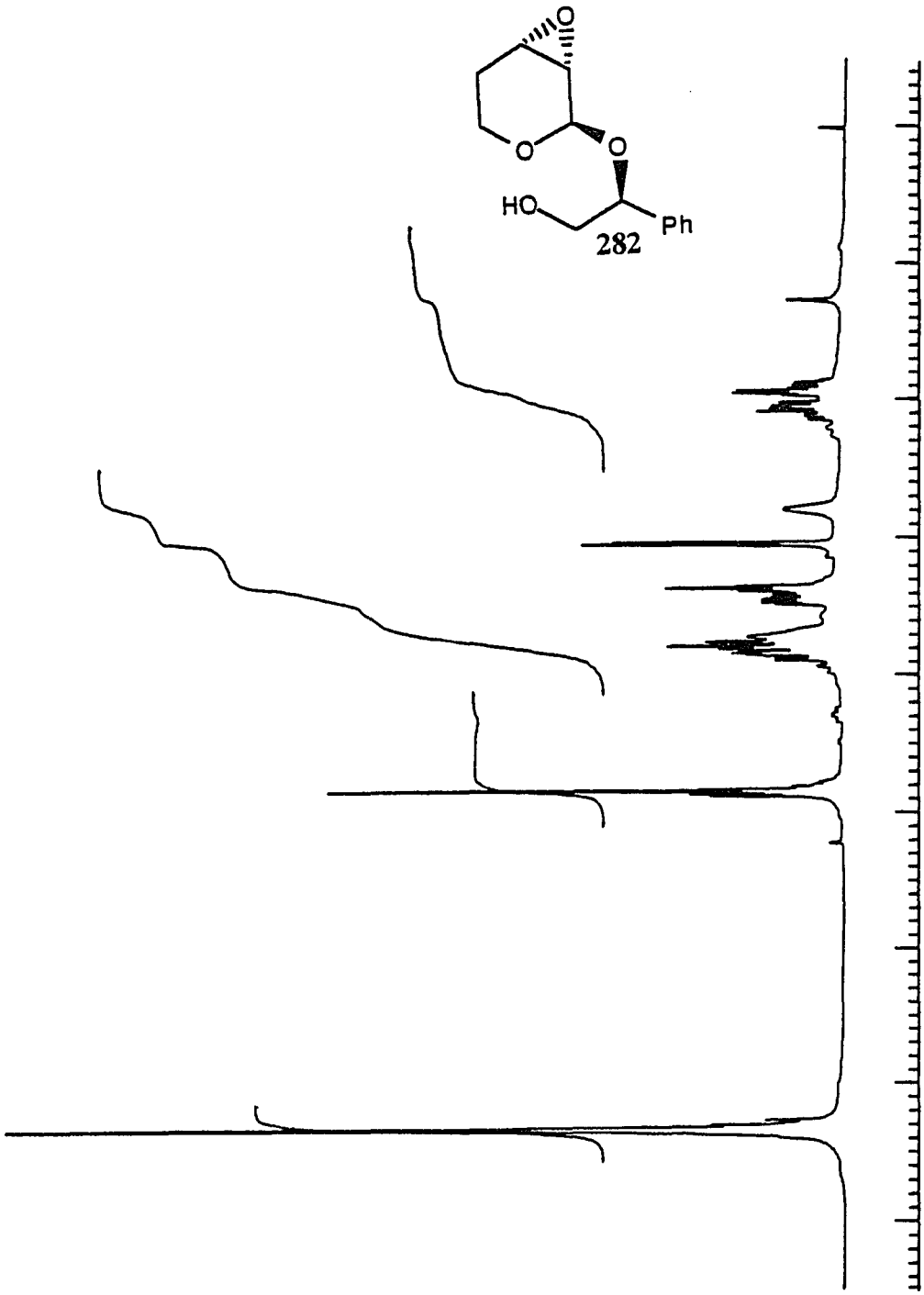

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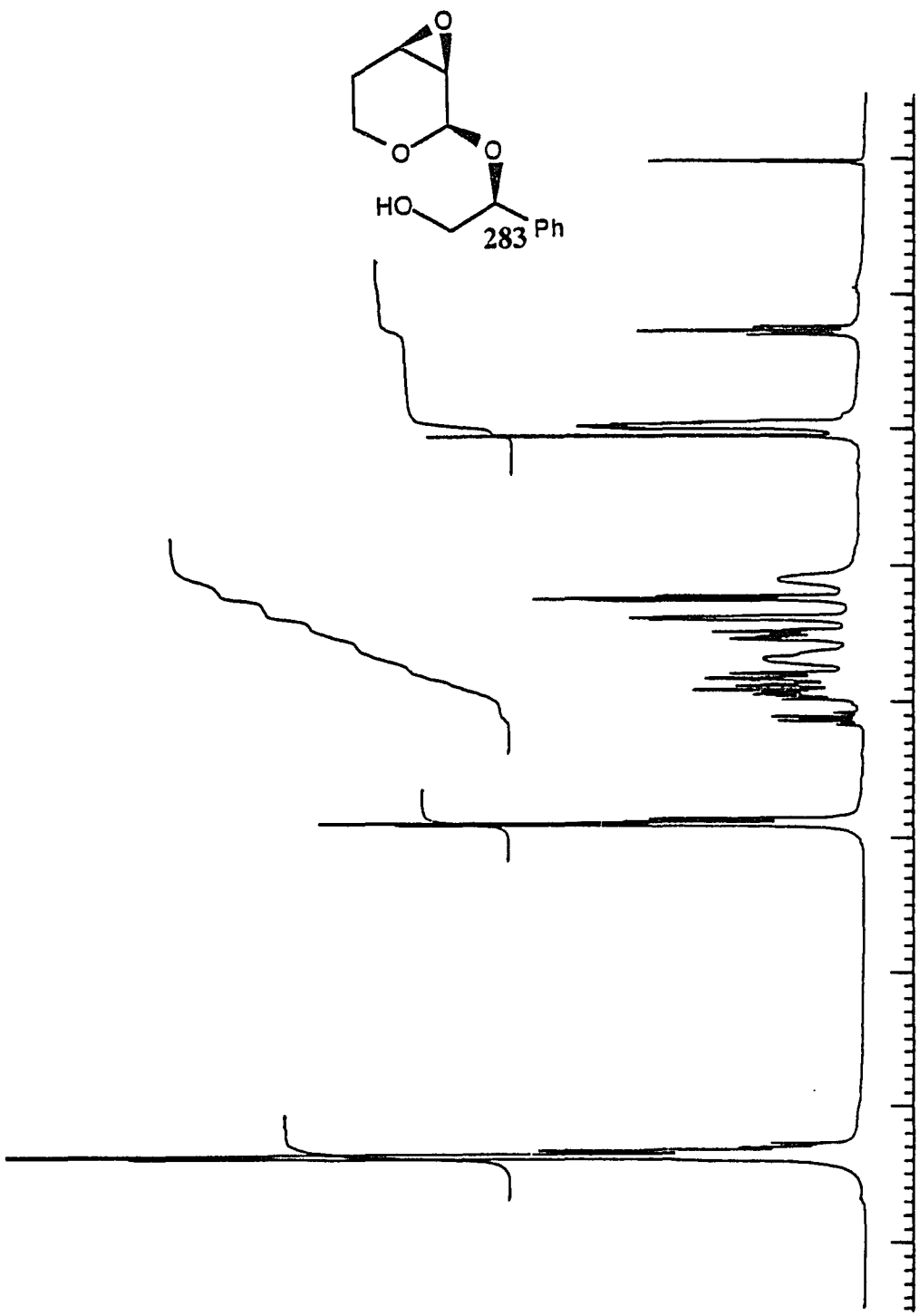
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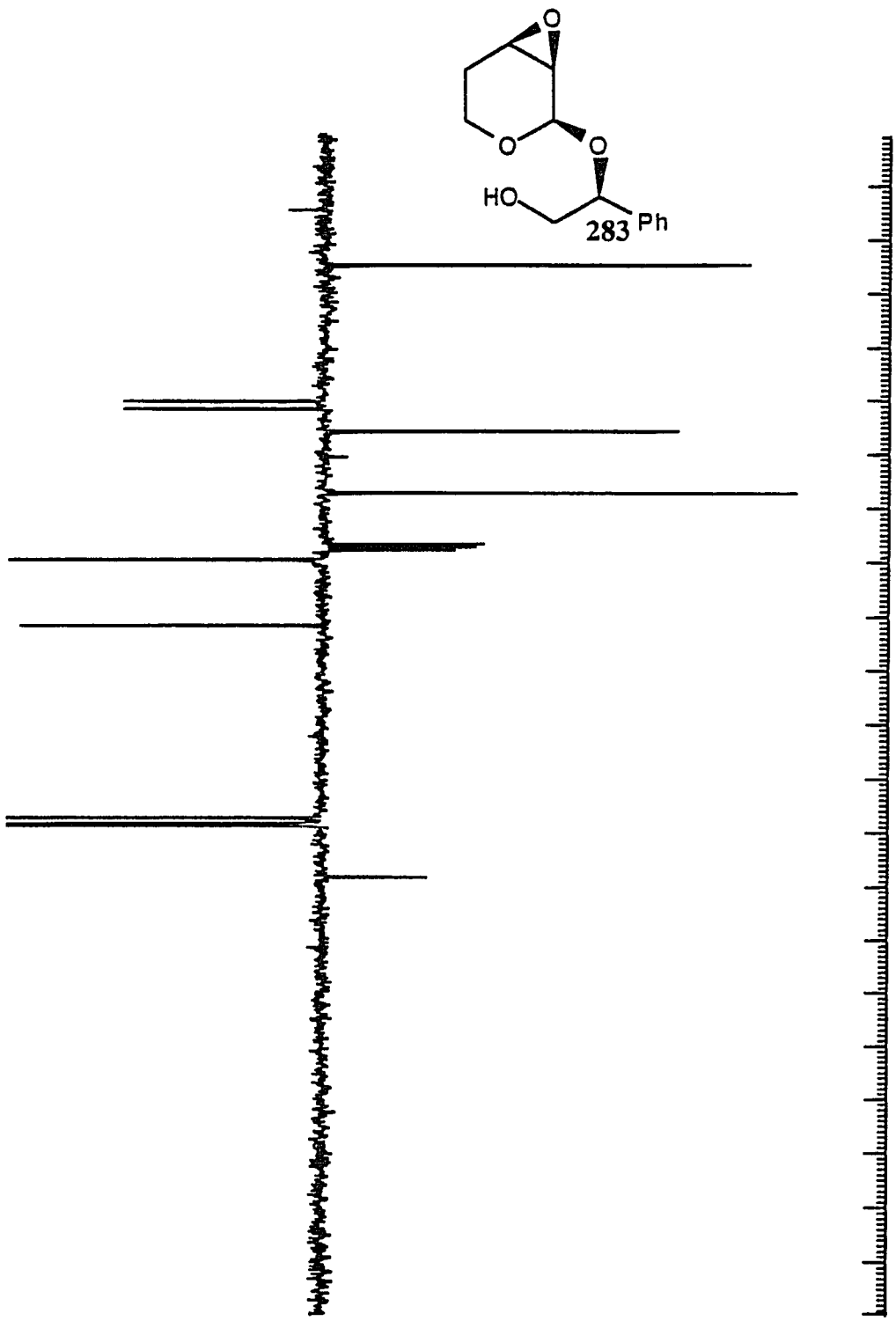
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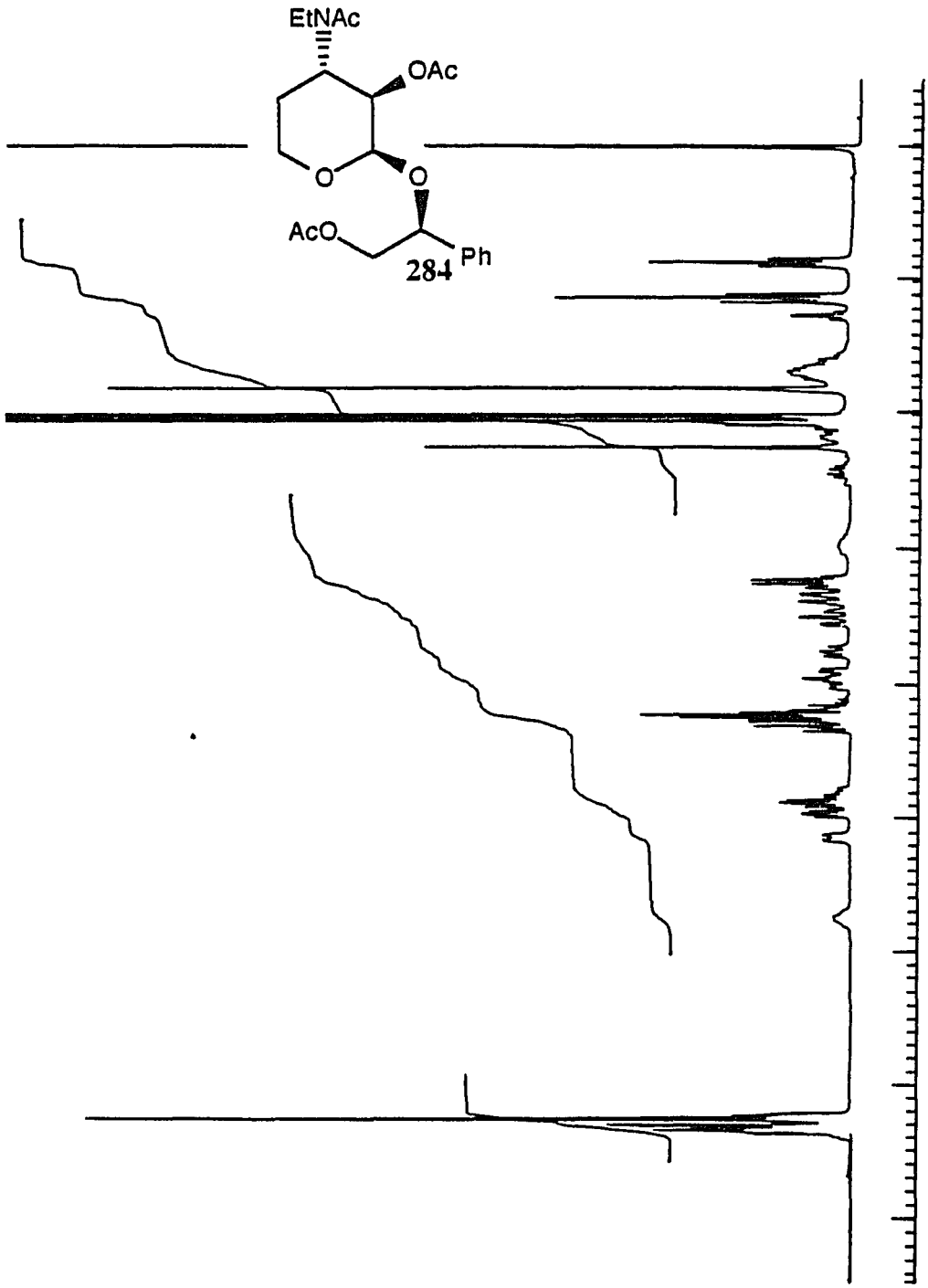
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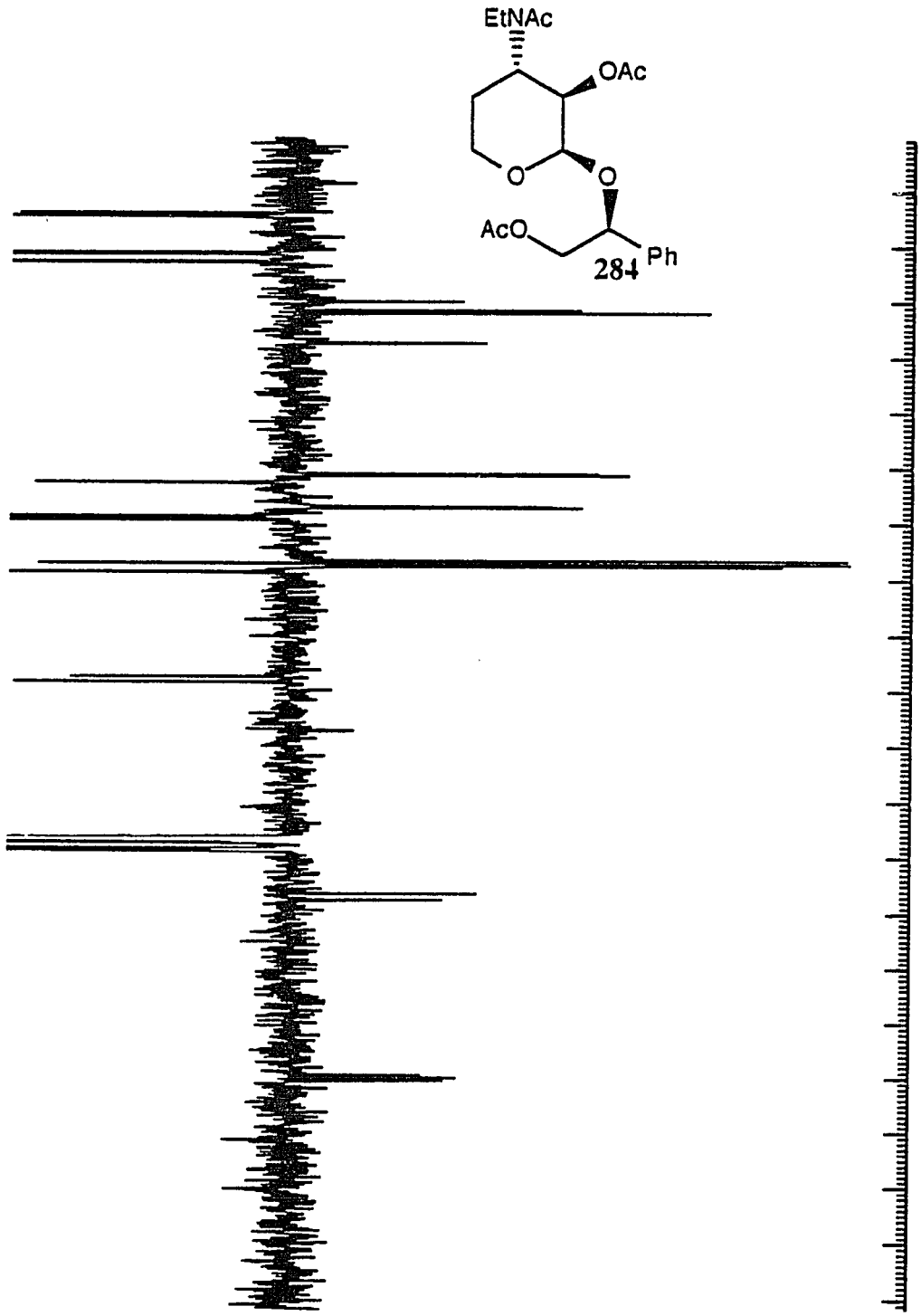
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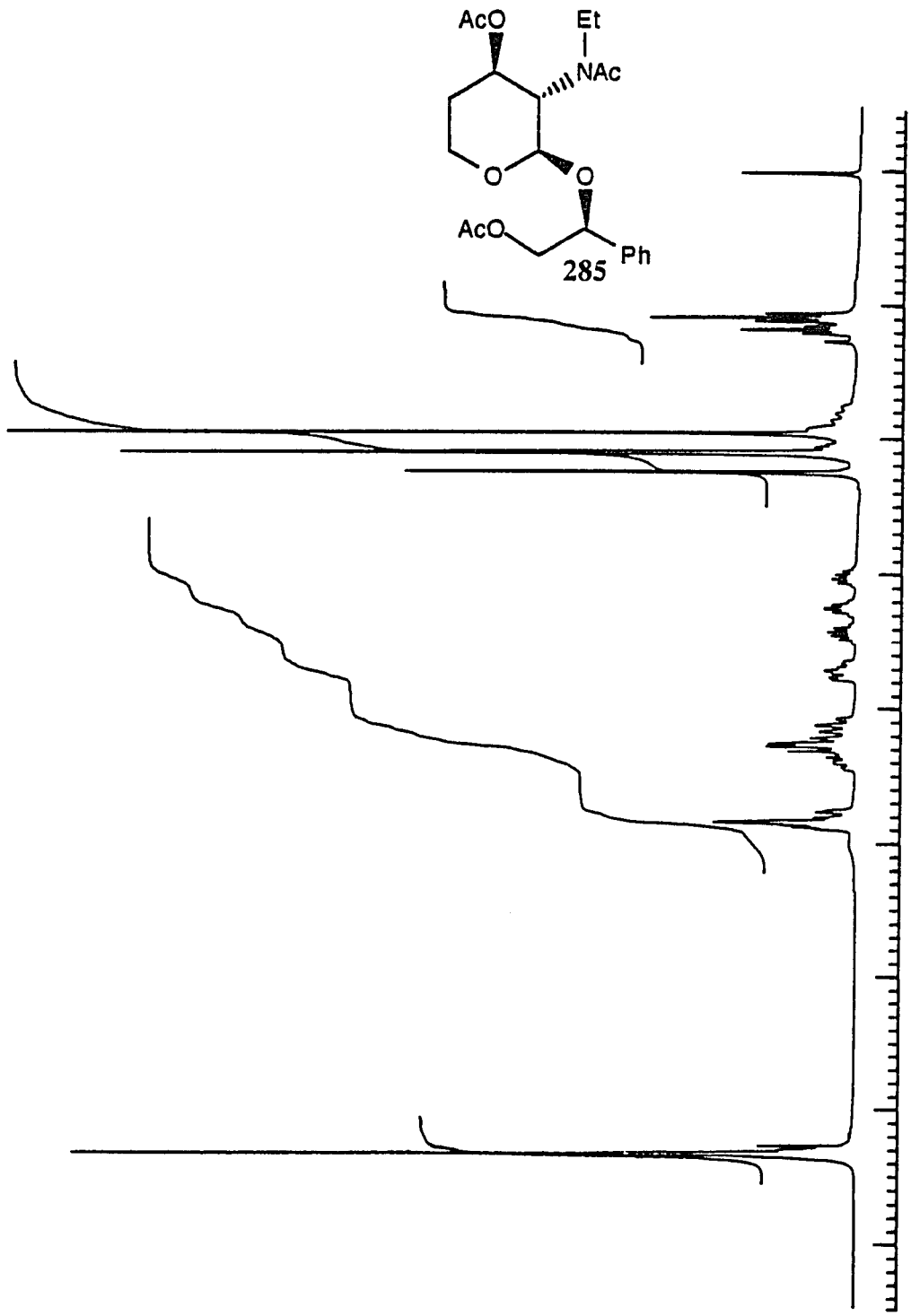
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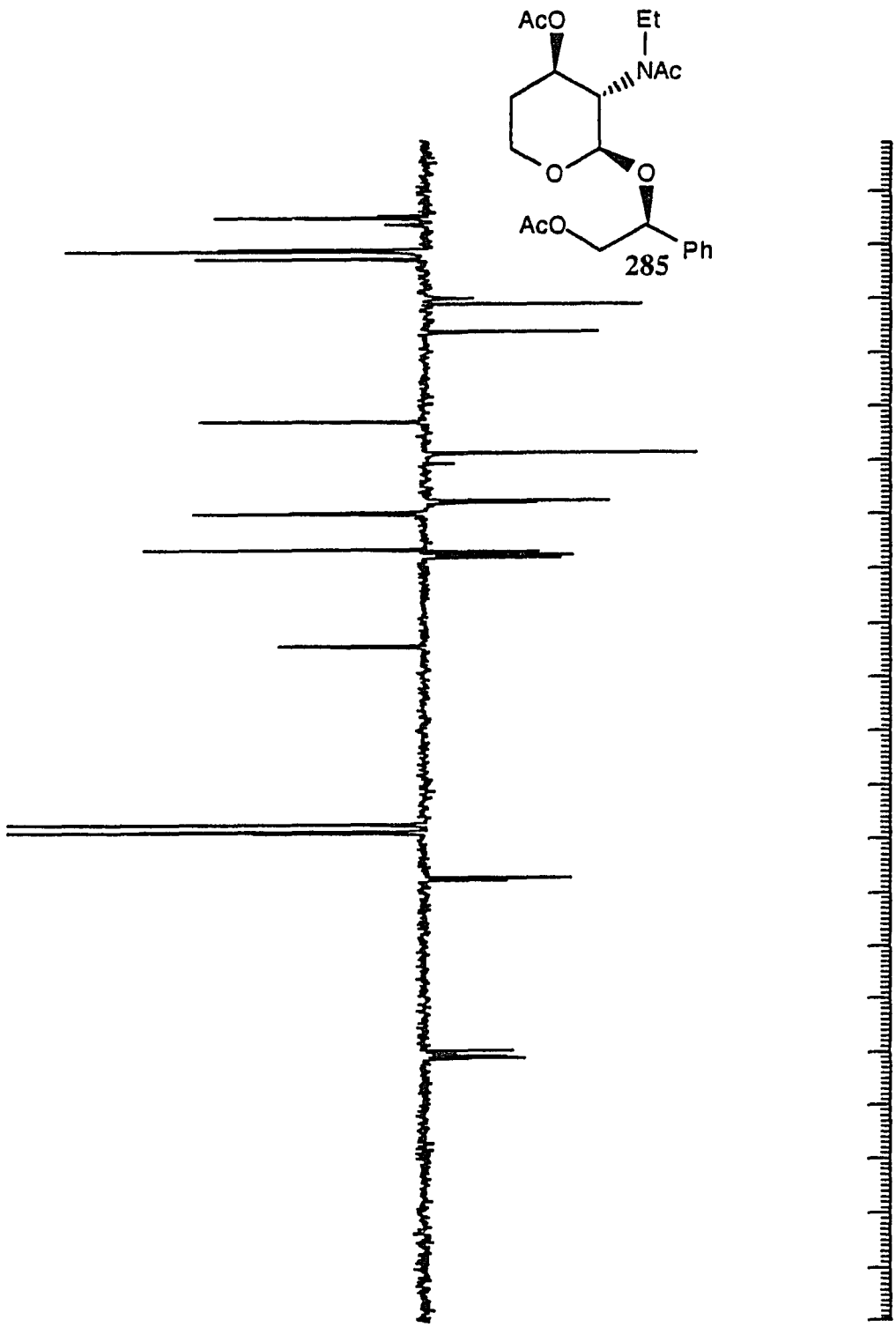
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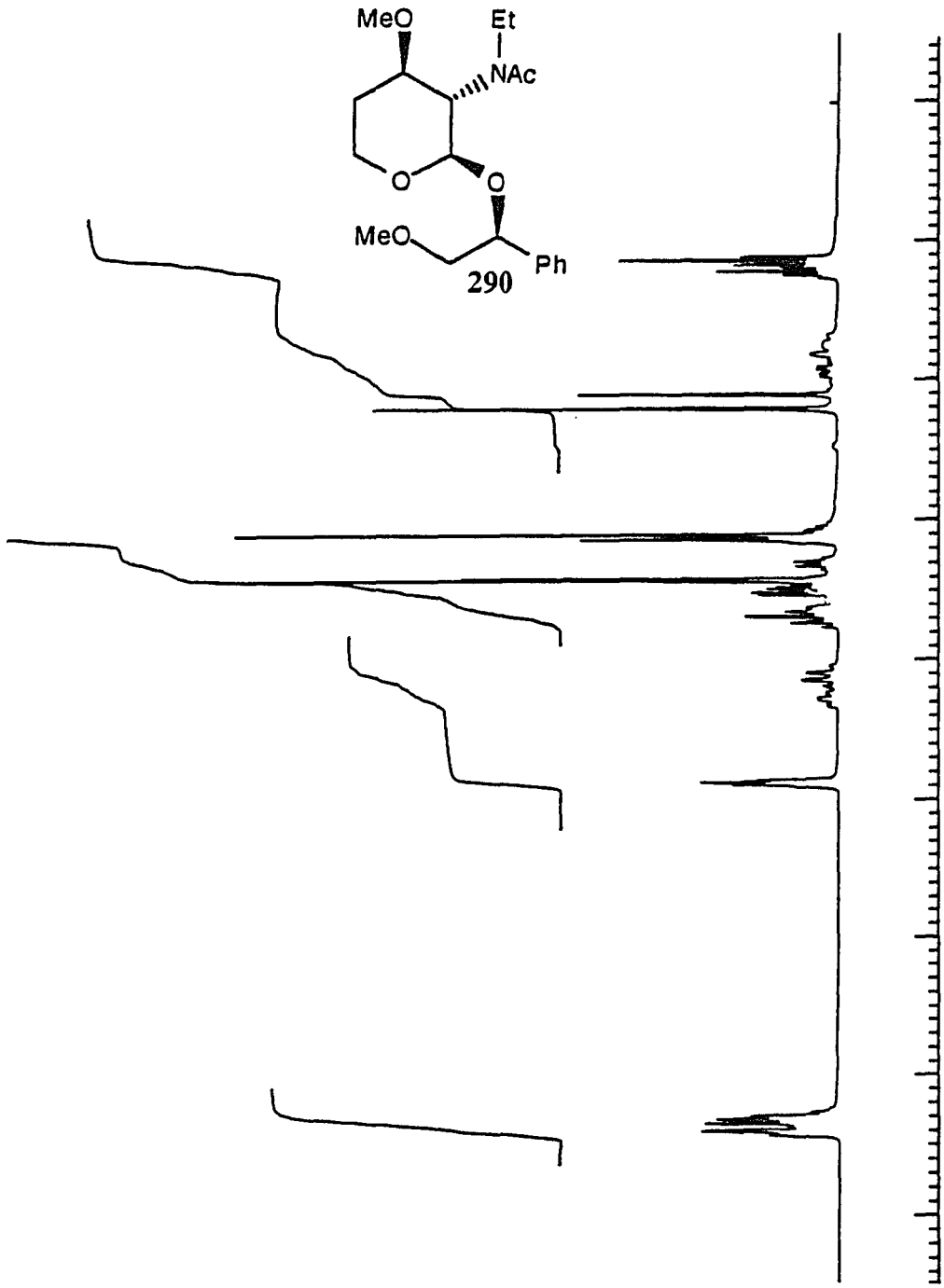

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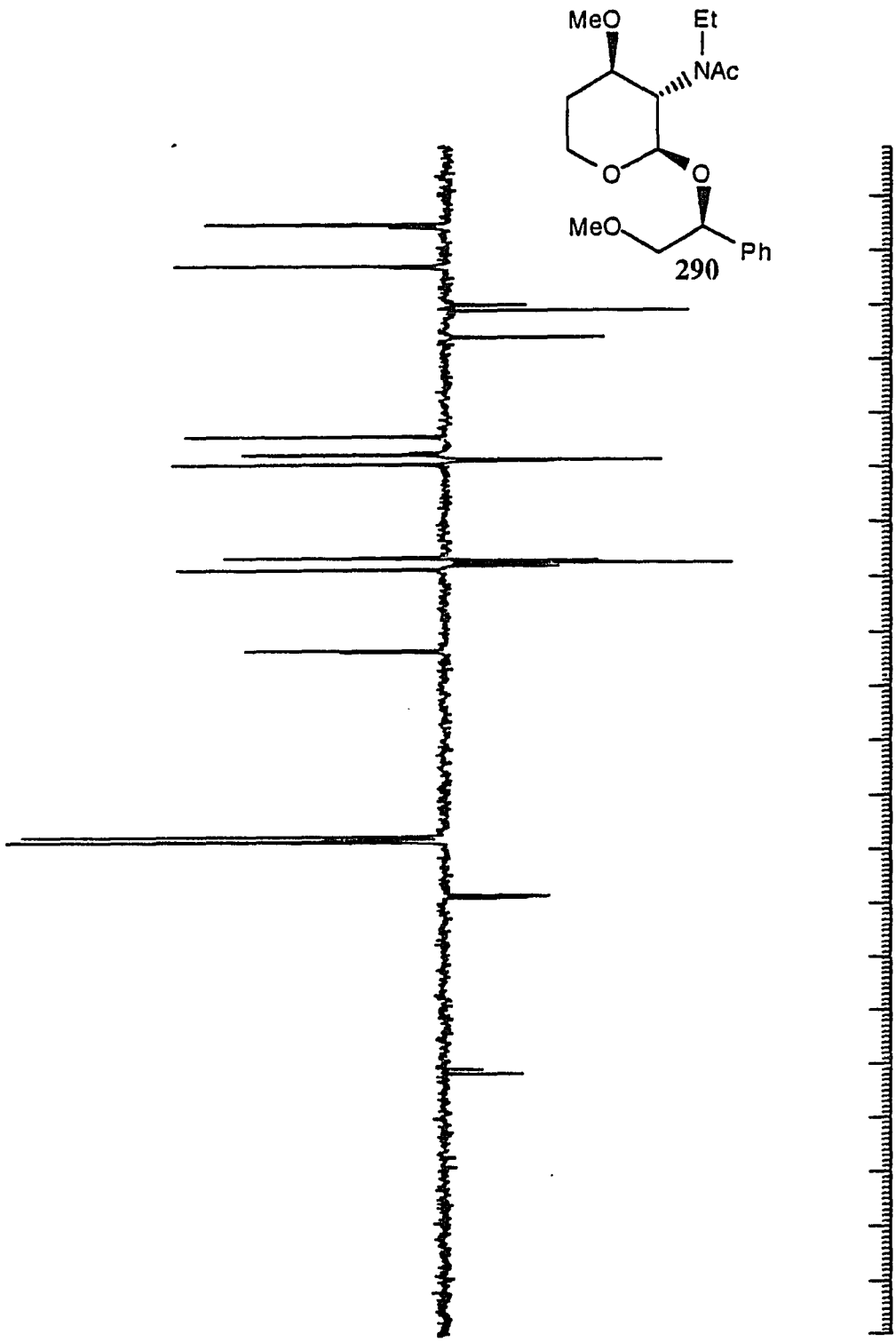

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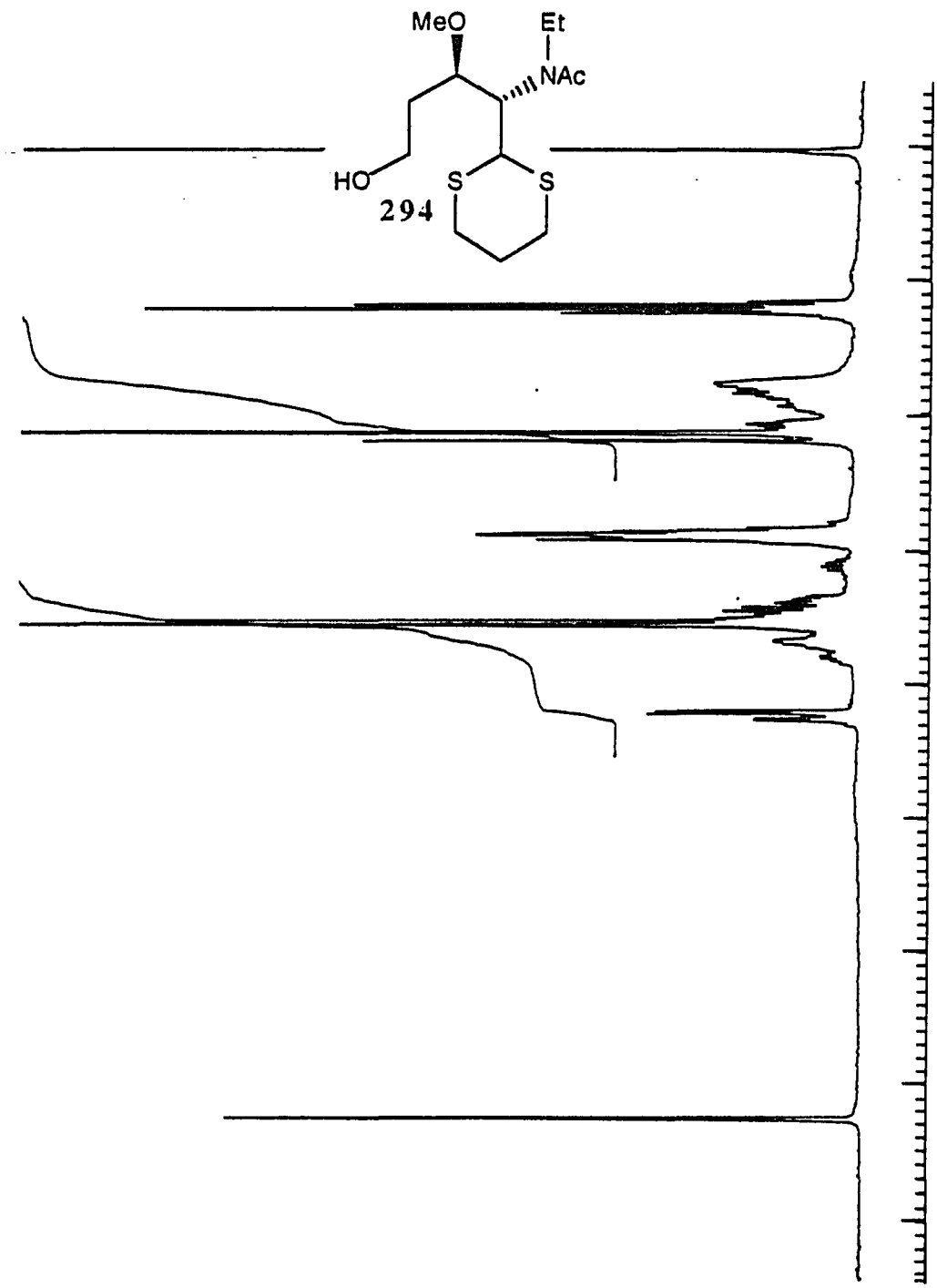
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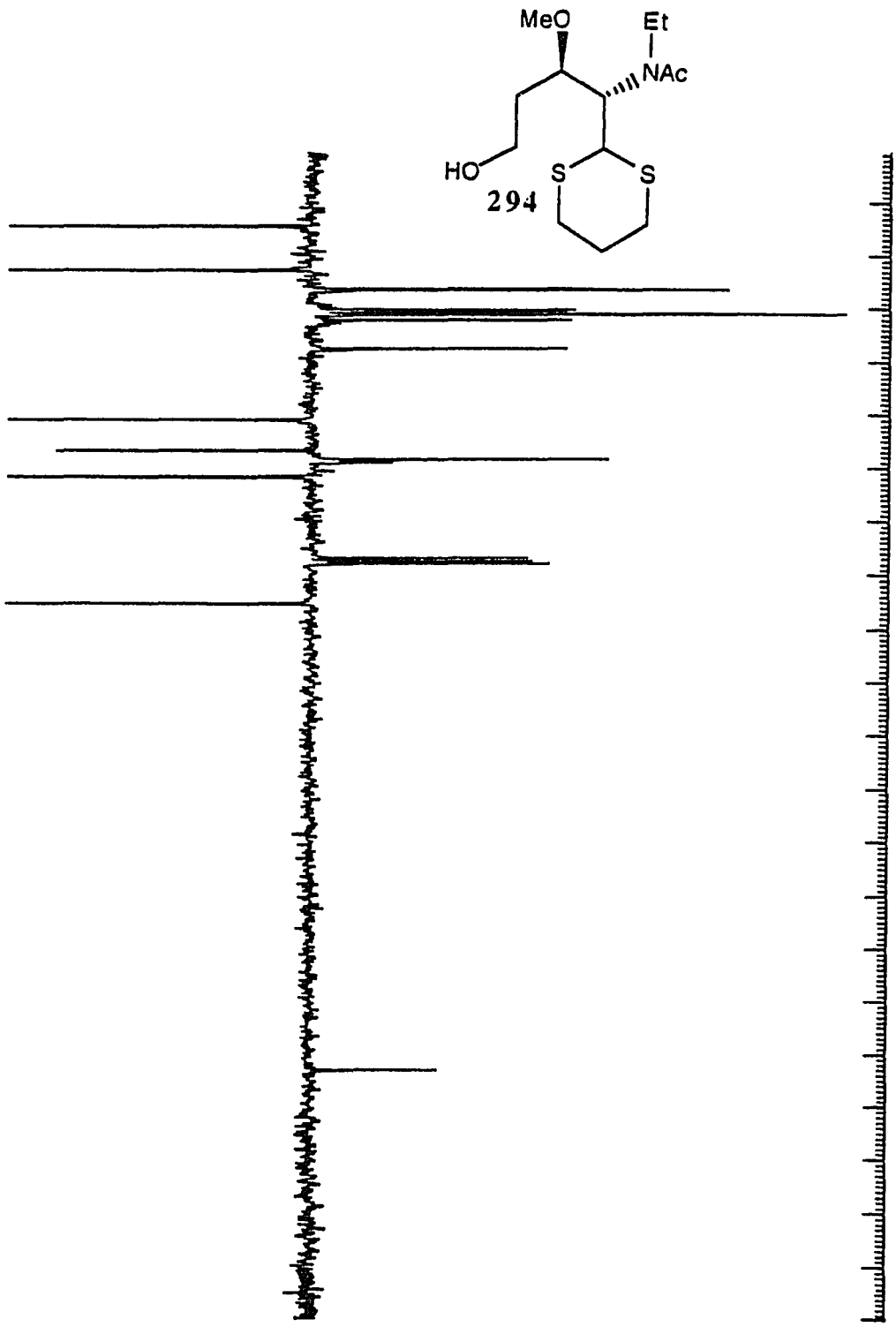
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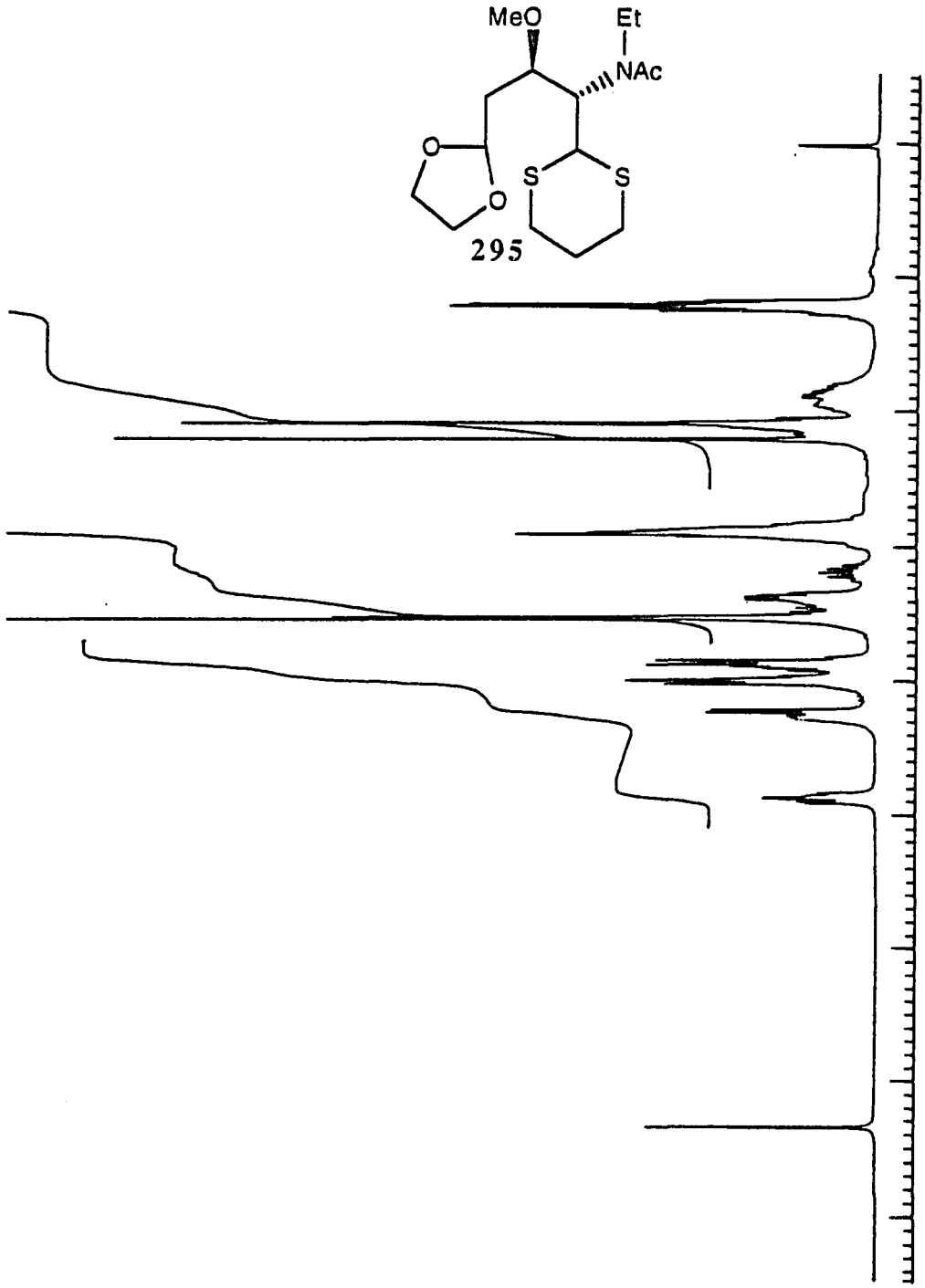
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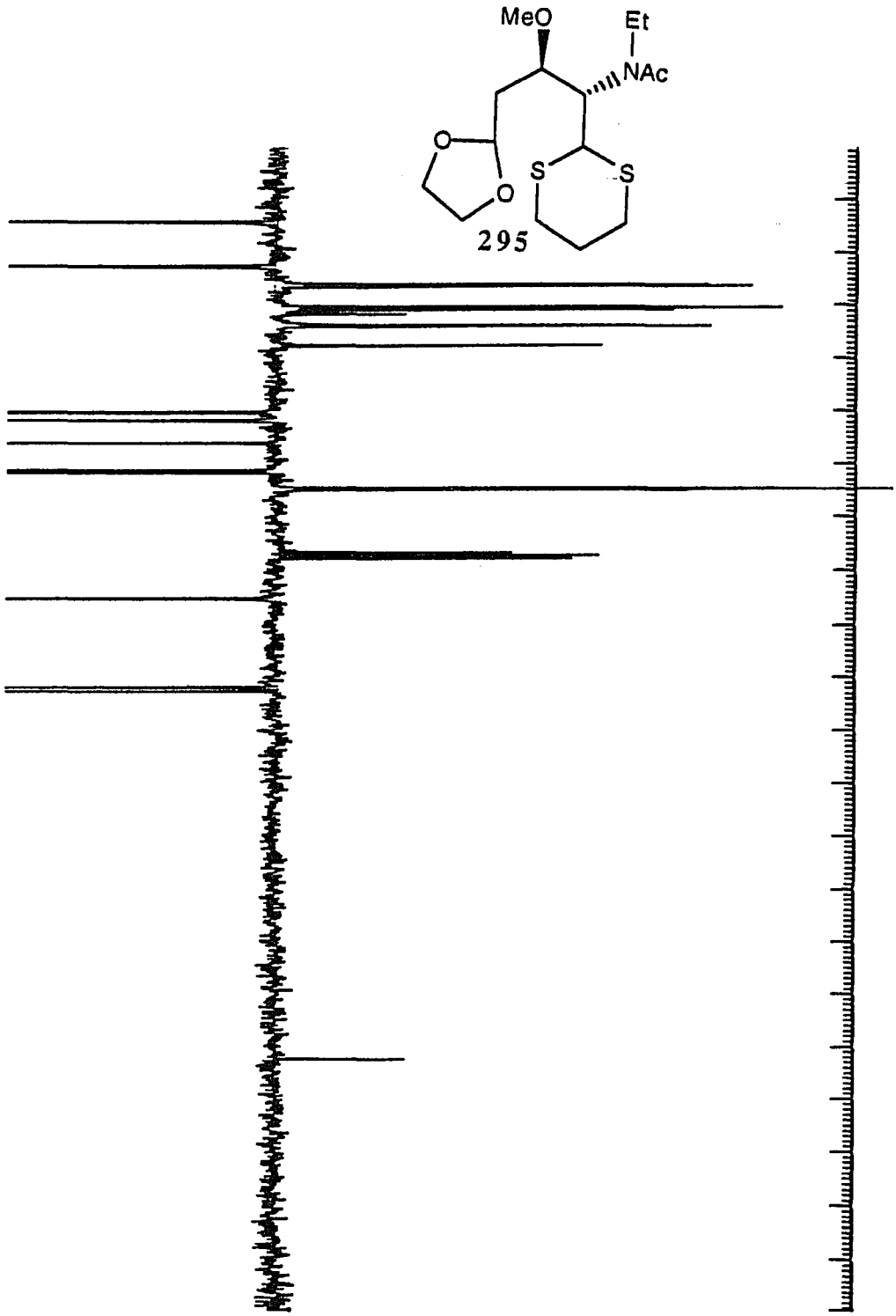
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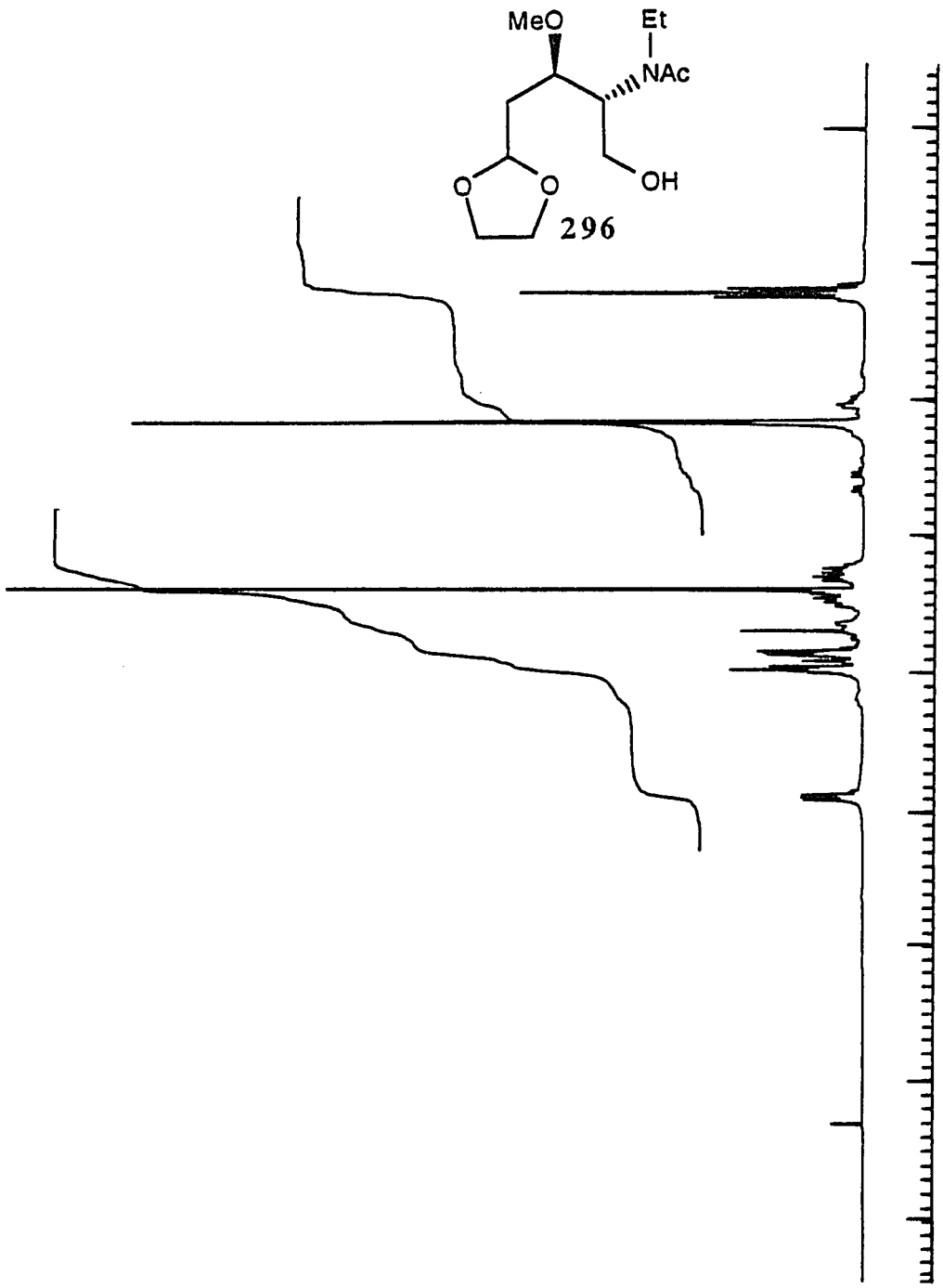
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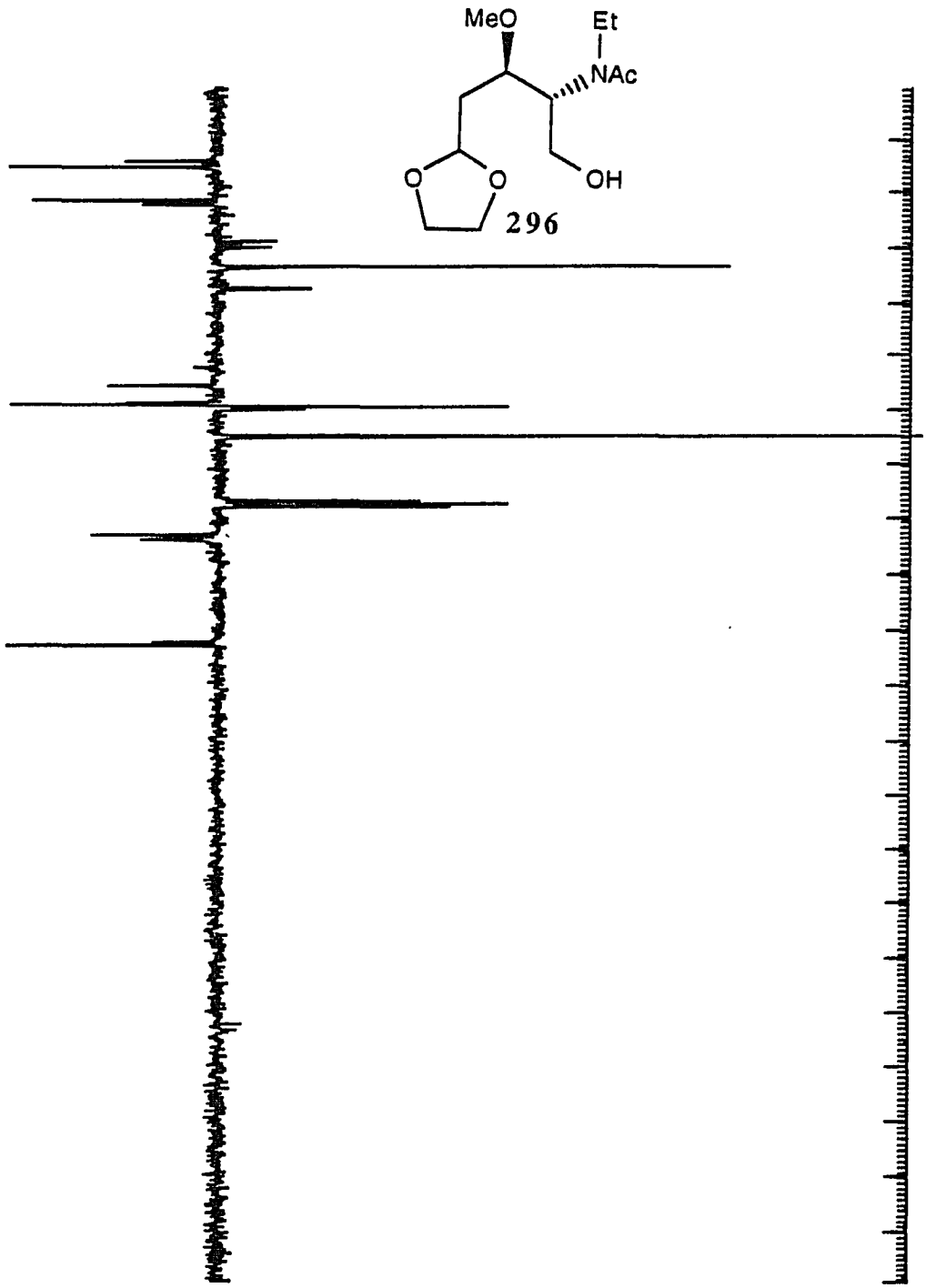
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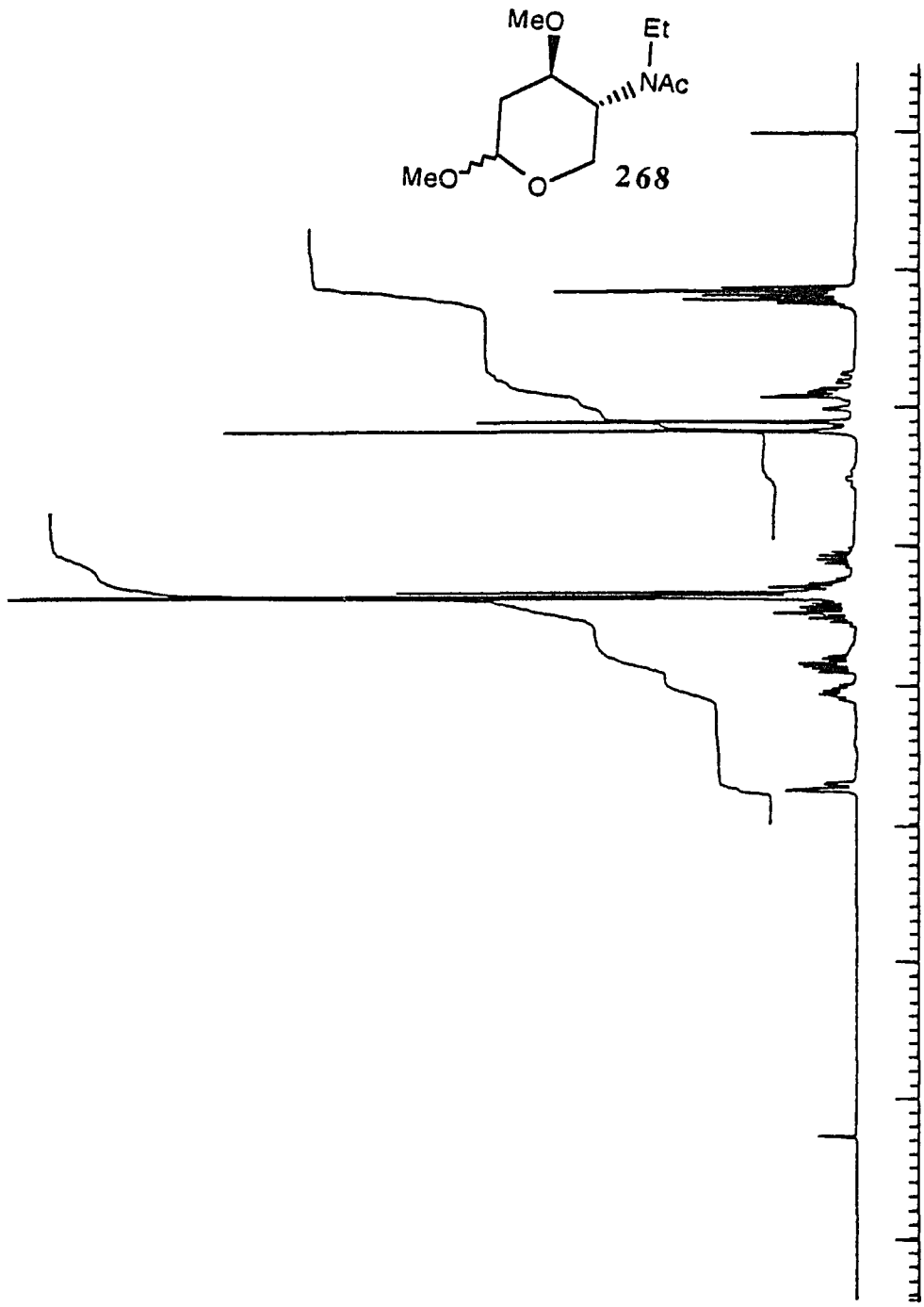
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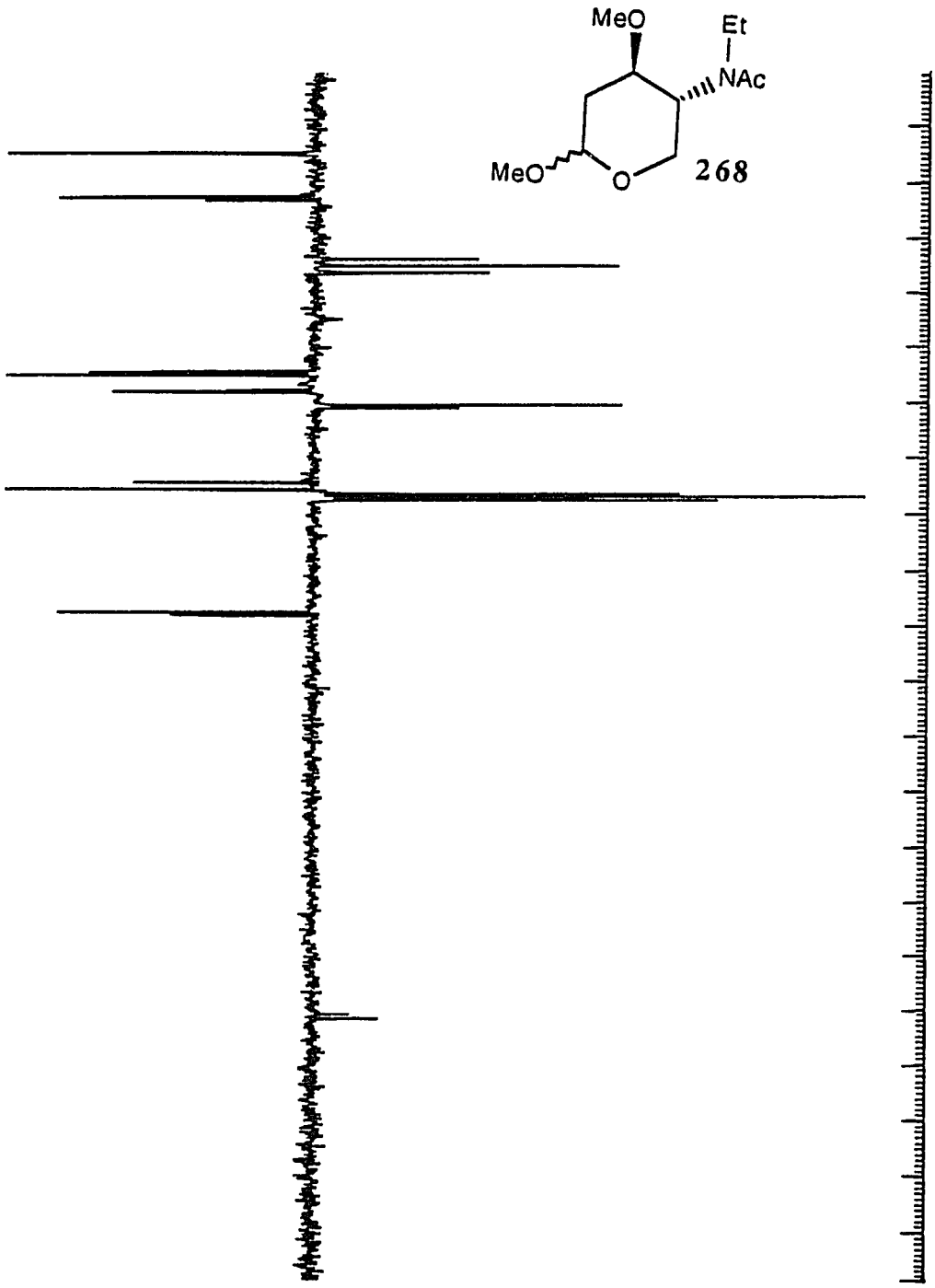

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